Benzoylpyruvates in Heterocyclic Chemistry

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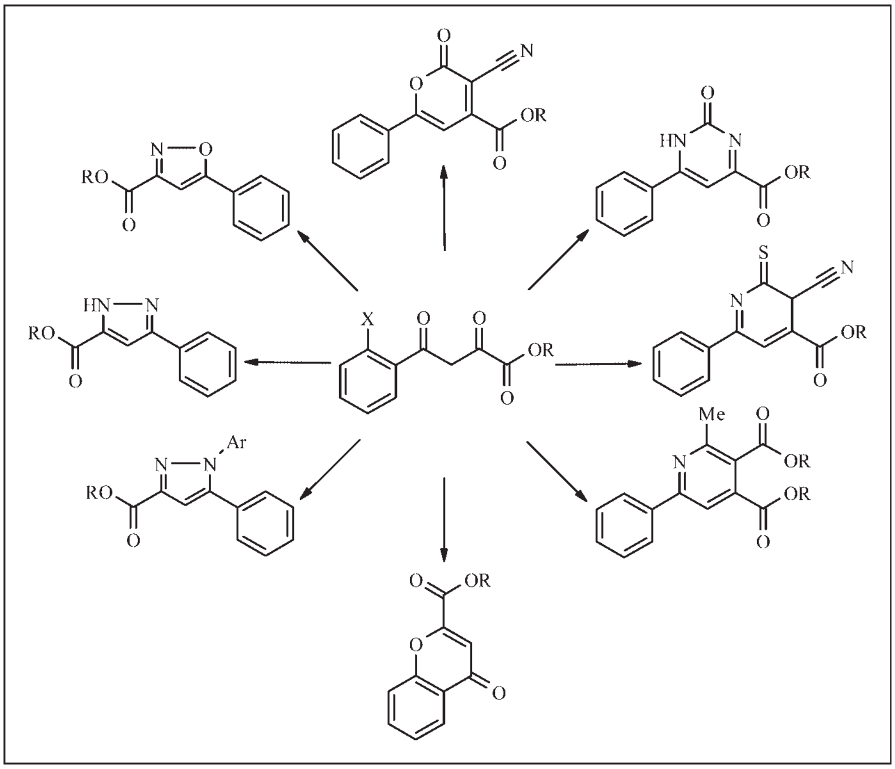

The present review covers the utility of benzoylpyruvates as a vehicle for the preparation of highly functionalized heterocycles. Regio- and chemoselective features are discussed with reference to the application of different nucleophilic species. In this context, the preparation of such rings as pyrazoles, isoxazoles, primidines, and pyridines are presented. As the means to establish a distinct functional pattern, the rendered strategy can be seen as an alternative to cross-coupling protocols.

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INTRODUCTION

4-Aryl-2,4-dioxobutyrates are formally derivatives of pyruvic acid and are as such trivially referred to as benzoylpyruvates. Being endowed with multiple functionalities, they are important synthetic precursors, capable of interacting with both electrophilic as well as nucleophilic reagents. In particular, in the latter case they offer a versatile scaffold on which to mould annulated rings carrying distinct structural features. This versatility draws its impetus from the conspicuous qualitative differences between the three carbonyl functionalities, which makes regio- and chemoselective discrimination possible. Through a judicious matching of the applied nucleophilic species, the mode of annulation may be predicted, rendering a powerful tool for the construction of a variety of heterocyclic compounds. For example, the approach has found its use in the preparation of pyrazoles, isoxazoles, pyrimidines, and pyridines carrying a γ-aryl ester motif.

From a pharmaceutical point of view, the spatial arrangement of substituents conferred on heterocycles *via* benzoylpyruvate chemistry is highly interesting, since it can give rise to pronounced biological activity. Within the compound classes covered by pyrazoles, isoxazoles, pyrimidines, and pyridines, such diverse effects are observed as GPCR antagonism [1–4], ion-channel modulation [5] and kinase inhibition [6,7].

GENERAL CONSIDERATIONS

The ambivalent electrophilic nature of benzoylpyruvates resides on the presence of three interrelated

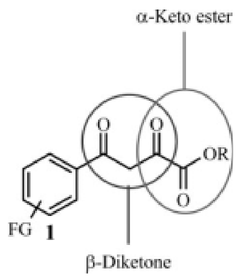


Figure 1. Dual nature of benzoylpyruvates.

carbonyl entities, capable of modulating and accentuating the individual electronic character through inductive and tautomeric effects. Embedded within the framework of the benzoylpyruvates are both the structural features of α-keto esters and β-diketones (Fig. 1). As a consequence, the chemistry of benzoylpyruvates may be expected to resonate this dual relationship.

In the case of α-keto esters **2**, the adjacent carboxyl moiety imparts the ketone with an enhanced electrophilic character due to its inductive withdrawal. However, this may be moderated by the presence of active protons due to keto/enol tautomerisation between **2** and **3** (Scheme 1).

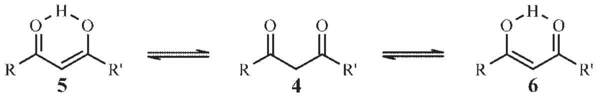
In the case of β-diketones **4**, sharing an active methylene group enables both carbonyl functionalities to undergo keto/enol tautomery between **4**, **5**, and **6**, effectively forming a Michael acceptor. To what extent the incipient groups are electronically distinguishable, *i.e.* the regiochemical preference leading to either **5** or **6**, depends on the peripheral substitution pattern (Scheme 2).

Combining the two features of the disseminated structure, yields a supposition on the reactivity of benzoylpyruvates, where the cooperative effect renders the position adjacent to the ester most susceptible to attack by nucleophiles (Scheme 3). Thus, in terms of regioselectivity, the outcome seems predictable.

If the applied nucleophile contains multiple activity, *i.e.* an ambident nucleophile like **10**, benzoylpyruvates can form rings *via* a formal cyclodehydration process. However, the annulation might either involve reaction on the ketone or on the ester, leading to **11** or **12**, thereby posing a chemoselective issue (Scheme 4). What is immediately evident is that the two reactive modes will result in different ring sizes and hence making allowance for kinetic versus thermodynamic control. In particular, the added stability originating from resonance energy, aromatization favors the formation of a γ-aryl ester motif **11**. Thus, the linker that joins the nucleophilic ‘‘warheads’’ and indeed the nature of the ‘‘warheads’’ themselves decide the direction of annulation.

Scheme 1. Keto/enol tautomery in α-keto esters.

Scheme 2. Keto/enol tautomery in β-diketones.



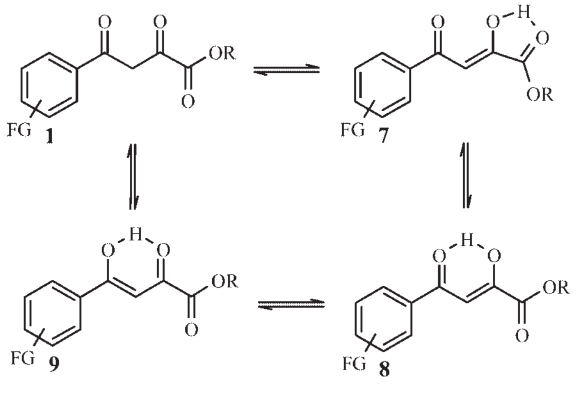
Because of the structural features exhibited by benzoylpyruvates, expectedly both acid and base catalysis may advance the cyclodehydration.

The benzoylpyruvates themselves are readily prepared by reacting enol ates of the corresponding acetophenone with a suitable oxalic diester [8–10]. In this respect, lithium enol ates offer a particular advantage by allowing the desired product to be isolated as a solid, shelf-stabile, 1:1 lithium complex. Generally, the protocol can be used to furnish benzoylpyruvates with an aryl moiety carrying either electron donating or electron withdrawing substituents [10]. Considering the number of commercially available acetophenones, benzoylpyruvates as a class do indeed constitute a diverse starting point for the preparation of heterocycles incorporating an aryl motif.

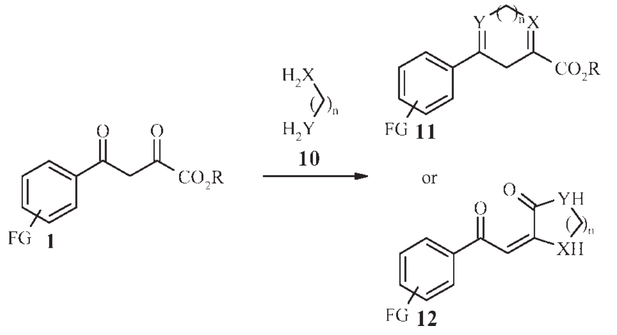
N,N′-DINUCLEOPHILES

Linked directly. Hydrazine **14** and its monosubstituted derivatives react smoothly with benzoylpyruvates in a highly chemoselective manner to afford 3,5-difunctionalized pyrazoles. In the simple case of hydrazine **14**

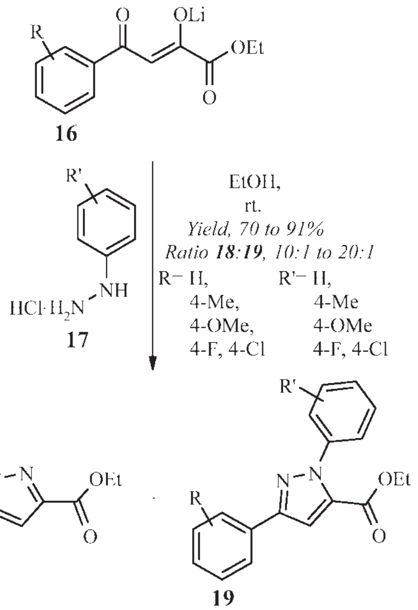
Scheme 3. Expected tautomeric contributions in benzoylpyruvates.



Scheme 4. Possible outcomes of reaction between benzoylpyruvates and dinucleophiles.



Scheme 6. Observed regioselectivity in reactions between benzoylpyruvates and arylhydrazines.



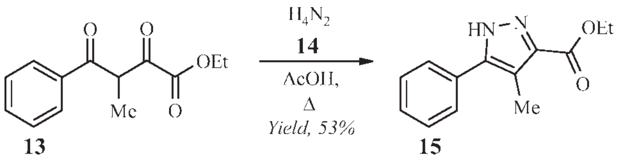
itself the regiochemical feature is void and the reaction proceeds to yield only one product [11–16]. As the starting benzoylpyruvate, exemplified by **13**, provides the carbon framework in its entirety, densely functionalized pyrazoles like **15** can be obtained in this manner (Scheme 5) [11,12,15,16].

On the other hand, attaching a substituent on hydrazine **14** could *a priori* be expected to give rise to regiochemical ambiguity. In practice, there is generally an accentuated preference, favoring formation of the 1-substituted pyrazole **18** over the 2-substituted pyrazole **19**, when arylhydrazines **17** are employed [17–19]. Nonetheless, the regioselectivity is subject to some extent of electronic modulation, both in terms of the substitution pattern on the benzoylpyruvate **16**, as well as on the arylhydrazine **17** (Scheme 6) [10]. Thus, with regard to matching the condensing partners, the regioselectivity is enhanced when an electron rich benzoylpyruvate **16** reacts with an electron poor arylhydrazine **17**.

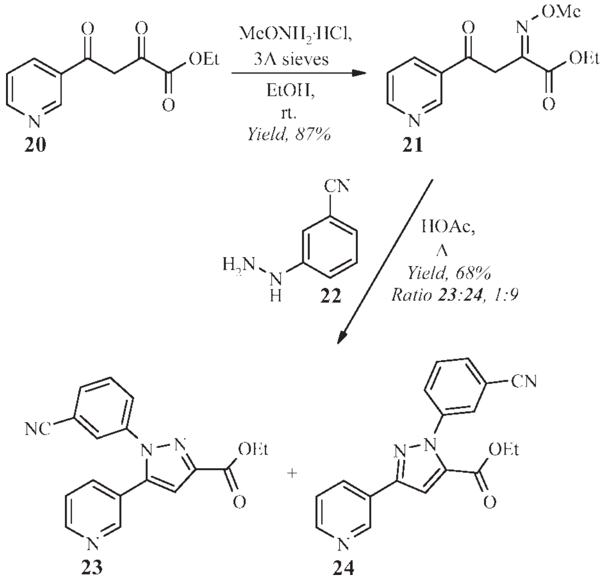
Taking advantage of the observed regiochemical preference, it is possible to invert the outcome of the reaction. Thus, transiently blocking the α-position in **20** as an oxime **21**, prior to performing the cyclodehydration step, allows the selective preparation of 2-substituted pyrazoles **24** (Scheme 7) [20].

Switching from an aryl to an alkyl substituent on hydrazine **14** may influence the regioisomeric distribution, for electronic reasons residing on the dinucleophile. On the other hand, interplay of steric factors can act as a counter to the erosion. Thus, in the case of bulky alkyl substituents, like cyclohexyl, the selectivity matches that which is observed for arylhydrazines **17** (*vide supra*) [21]. However, as expected when steric demand becomes smaller, reacting a benzoylpyruvate with a

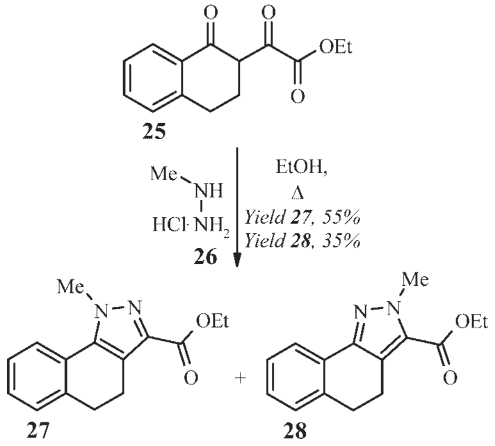
Scheme 5. Example on reaction between benzoylpyruvates and hydrazine.



Scheme 7. Example on path leading to inverted regioselectivity in reactions between benzoylpyruvates and arylhydrazines.



Scheme 8. Example on erosion of regioselectivity in the reaction with sterically nonencumbered alkylhydrazines.



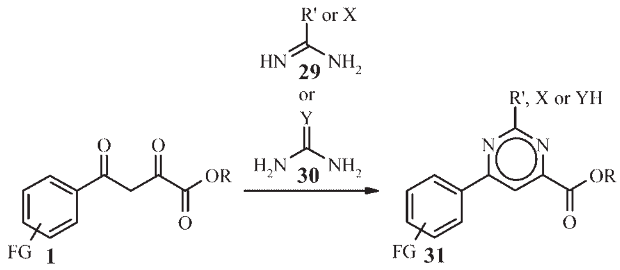
non-bulky alkylhydrazine **26** significantly increases the amount of 2-substituted pyrazole **28** (Scheme 8) [22,23].

Linked by one unit. The category of *N,N′*-dinucleophiles mutually appended to a central atom is generally restricted to compounds carrying a linker consisting of an sp^2-hybridized carbon. Thus, within that scope fall several interesting structural families, like amidines **29a** (R = H, alkyl or aryl), isoureas **29b** (R = O-alkyl or O-aryl), guanidines **29c** (R = NH_2, NH-alkyl, NH-aryl etc.) and ureas **30** (R = O or S). However, the majority of these dinucleophiles have as yet not seen any use in the chemistry of benzoylpyruvates, although having been applied to other β-diketones [24–27]. Resulting in the formation of an aromatic or latent aromatic system, the reaction should accordingly be highly favored, yielding 2,4,6-trifunctionalized pyrimidines **31** or derivatives thereof (Scheme 9).

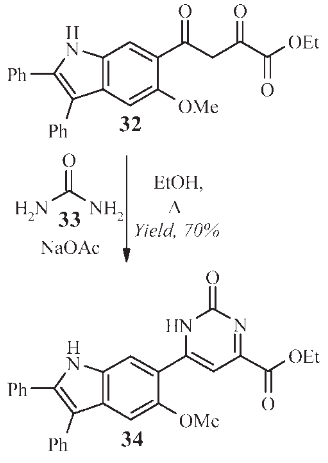
Amongst the examples following the delineated strategy, is the synthesis of pyrimidin-2-ones like **34**. Thus, the presence of base has been used to promote condensation between a benzoylpyruvate **32** and urea **33** (Scheme 10) [28].

In a similar fashion, condensation between a benzoylpyruvate **35** and guanidine **36** gives an entry to the imprinted 2-aminopyrimidine **37** (Scheme 11) [29].

Scheme 9. Strategy leading to 2,4,6-trisubstituted pyrimidines.



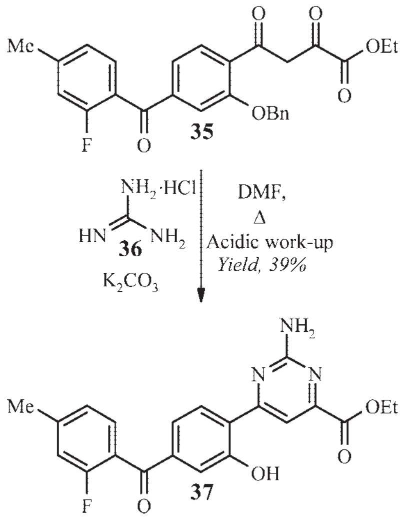
Scheme 10. Example on preparation of pyrimidin-2-ones.



On the other hand, the *N,N′*-dinucleophile may be encased within a cyclic framework. Thus, the amidine and the guanidine make-up can be found as an integral part of heterocyclic amines, like in 2-aminopyrrole **38a** (X = H, Y = H, and Z = H,) and in 2-aminoimidazole **38b** (X = H, Y = H, and Z = N) (Fig. 2).

Reaction between benzoylpyruvates and five-membered aza-heterocyclic amines may offer an entry to a variety of [*a*]-fused pyrimidines, in consonance with the regiochemical supposition. An illustration of this strategy is cyclodehydration involving 3-aminopyrazole **40**, which affords only pyrazolo[1,5-*a*]pyrimidine **41** (Scheme 12) [30].

Scheme 11. Example on preparation of 2-aminopyrimidines.



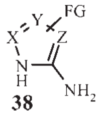


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Figure 2. Five-membered aza-heterocyclic amines as potential *N*,*N*′-dinucleophiles with a one-unit linker.

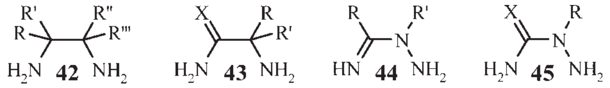
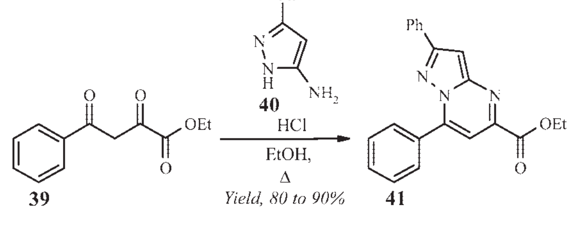


Figure 3. Selection of *N*,*N*′-dinucleophiles with a two-unit linker.

Linked by two units. The selection of potentially applicable *N*,*N*′-dinucleophiles carrying a two-unit linker is wide in terms of a cyclodehydration sequence on benzoylpyruvates. Considering the acyclic case, the linker may contain both carbon and heteroatom in combination, as well as varying in terms of hybridization, *i.e.* *C*-sp^3 versus *C*-sp^2. Accordingly, *N*,*N*′-dinucleophiles such as ethylene diamines **42**, α-amino amides **43** (X = O or S), aminoamidines **44**, semicarbazides **45a** (X = O or S), and aminoguanidines **45b** (X = NH) fall within this category (Fig. 3).

In contrast to the *N*,*N*′-dinucleophiles carrying shorter linkers, the product will not be aromatic when condensation involves the β-diketo moiety of the benzoylpyruvate. This mode of cyclisation will only lead to a labile seven-membered diimine. On the other hand, when condensation takes place across the α-keto ester moiety, the resulting annulet may or may not be aromatic. This mode of cyclisation leads however to a stabile six-membered ring containing a lactam function. As a consequence the observed chemoselectivity is altered relative to the previous examples (*vide supra*). Several of the dinucleophilic types listed in Figure 3 have been reacted with benzoylpyruvates and in all cases annulation involved the α-keto ester moiety [31–34]. Examples on these reactions are rendered in Scheme 13. Reactions involving ethylene diamines **49** or α-amino acrylamides **51** lead to piperazine-2-one derivatives like **50** and **52**. Similarly, reaction with semicarbazides **47** and aminoamidine **53** lead to 1,2,4-triazine-5-one derivatives like **48** and **53**. An important feature is the generation of a γ-related diketonoid motif that may be utilized in a second cyclodehydration step [34].

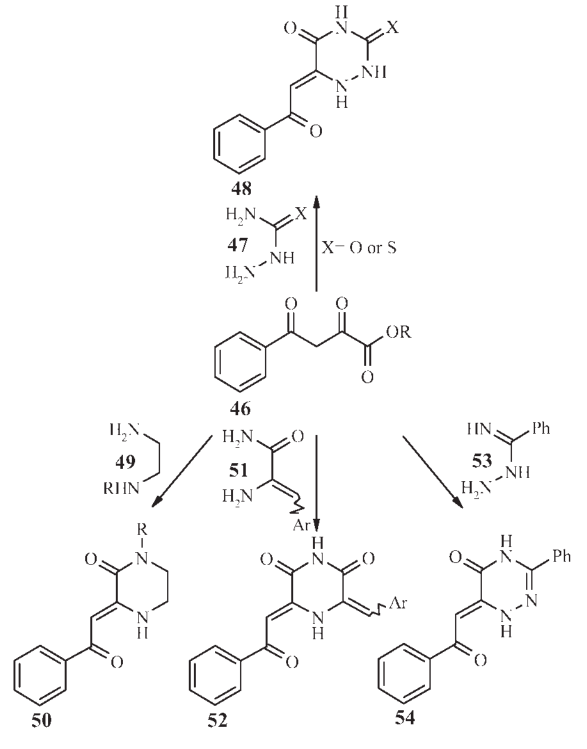
Scheme 12. Example on cyclodehydration involving cyclic *N*,*N*′-dinucleophiles with a one-unit linker.



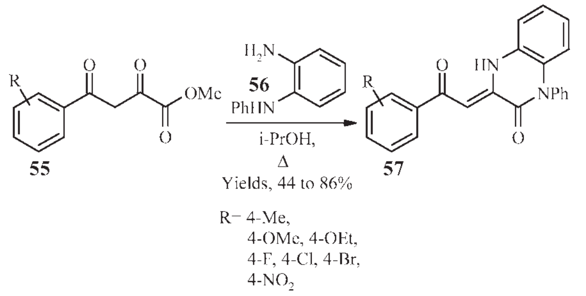
For the cyclic *N*,*N*′-dinucleophiles carrying a two-unit linker, the number of feasible candidates resonate the acyclic counterpart. In addition, the two amino groups may be joined through an ethene bridge, as is the case with aromatic systems containing vicinal amines. Accordingly, 3-functionalized 1H-quinoxaline-2-ones **57** can be made by reacting benzoylpyruvates **55** with a 1,2-aminobenzene **56** (Scheme 14) [35–39].

In some cases, the ethene bridged diamines need not an aromatic framework as support. For instance, benzoylpyruvates react with 5,6-diaminopyrimidine-2,4-dione derivatives **59**, yielding dihydropteridine-2,4,6-trione **60** and **61** (Scheme 15) [40]. It has been demonstrated that, depending on whether the reaction media is basic or acidic, it is possible to influence the

Scheme 13. Summary of examples on cyclodehydration involving acyclic *N*,*N*′-dinucleophiles with a two-unit linker.



Scheme 14. Example on cyclodehydration involving cyclic *N,N′*-dinucleophiles carrying a two-unit linker.

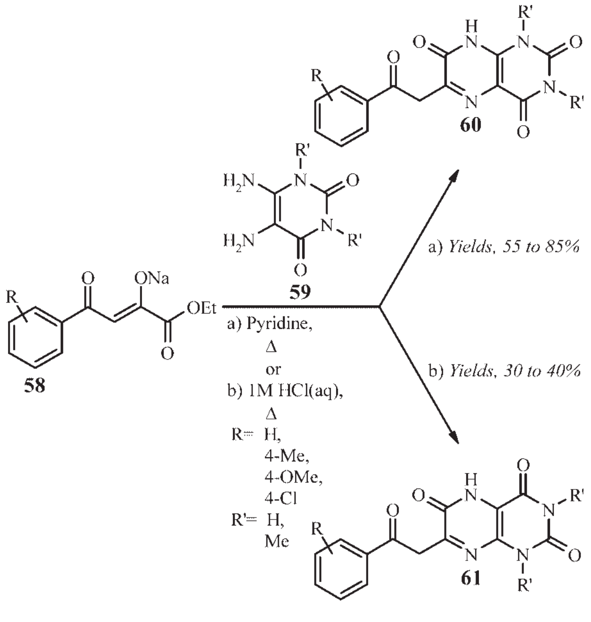


regioselectivity residing on the non-symmetrical nature of the *N,N′*-dinucleophile.

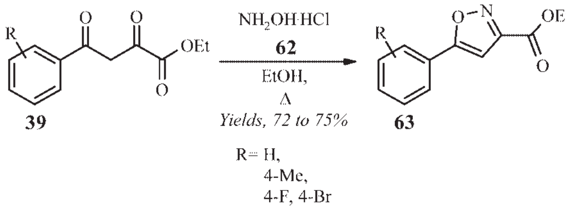
N,O-DINUCLEOPHILES

Linked directly. Because of the monovalent nature of oxygen, the category comprising directly linked *N,O*-dinucleophiles is limited to only one member, namely hydroxylamine **62**. However, the reaction between benzoylpyruvates and hydroxylamine **62** is facile, proceeding with both excellent regio- and chemoselectivity to afford the corresponding 5-arylisoxazole-3-carboxylic esters **63** (Scheme 16) [41–44]. Accordingly, the sequence of attack is therefore in adherence to what is expected of a Michael acceptor, where the softer amino group takes precedence over the hard oxygen.

Scheme 15. Example on regiochemical control involving cyclodehydration with *N,N′*-dinucleophiles carrying a two-unit linker.



Scheme 16. Example on cyclodehydration involving directly linked *N,O*-dinucleophiles.



Linked by one unit. Compounds filling the role as potential *N,O*-dinucleophiles appended with a one-unit linker are difficult to conceive. Thus, by analogy, when a β-diketone **64** is treated with ammonium carbamate **65**, the reaction results in quantitative formation of the corresponding α,β-unsaturated 1,3-aminoketone **66** [45]. Evidently, decomposition of either the prospect *N,O*-dinucleophile or any of the condensed intermediates preclude formation/isolation of a 1,3-oxazin-2-one, yielding instead β-enaminone **66** (Scheme 17).

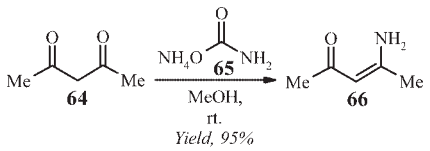
Linked by two units. As in the deliberations for the *N,N′*-dinucleophiles with a two-unit linker (*vide supra*), the same general considerations do apply for the *N,O*-dinucleophiles. In the acyclic case, one would therefore expect species like 2-aminoethanols and glycolamides to react with benzoylpyruvates following the hard/soft argument, affording dihydro-1,4-oxazine-2-ones and 1,4-oxazine-2,5-diones, respectively, via condensation across the α-keto ester moiety. However, apparently the literature does not contain any such examples.

Cyclic *N,O*-dinucleophiles appended by a two-unit linker are restricted to 2-aminophenols. Thus, when a benzoylpyruvate **55** reacts with 2-aminophenol **67** itself, the result is formation of the corresponding 1,4-benzoxazine-2-one **68** (Scheme 18) [46–48].

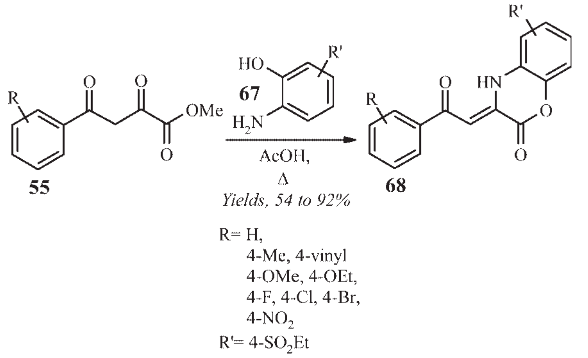
C,N-DINUCLEOPHILES

Linked directly. In the strict sense, directly linked *C,N*-dinucleophiles do not exist. However, some species might serve as surrogates to fulfill this purpose. One example is the radical anions, generated from imines or hydrazones in the presence of Ti(0), that react with β-

Scheme 17. Analogous example on reaction with a prospect *N,O*-dinucleophile.



Scheme 18. Example on cyclodehydration involving cyclic *N,O*-dinucleophiles carrying a two-unit linker.

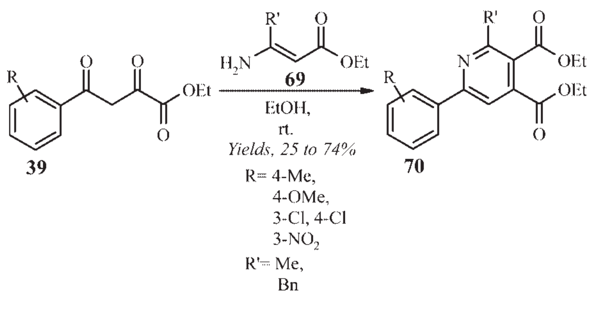


diketones to afford *N*-substituted pyrroles [49]. Another example is prodinucleophiles, such as 2-aminomethylpyridines, which are capable of reacting via an incipient active methylene, condensing with β-diketones to form 2-(2-pyridyl)pyrroles [50]. As yet, their extension to benzoylpyruvates has not been reported.

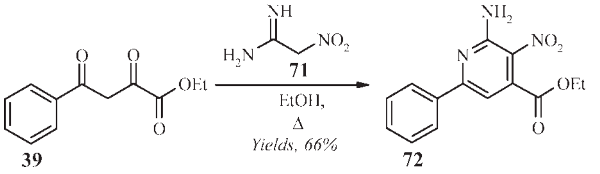
Linked by one unit. The *C,N*-dinucleophiles containing a one-unit linker are in principle diverse and the scope is wide, because it will afford substituted pyridines. In terms of regiochemistry, the directional preference of the cyclodehydration is perceivably unambiguous: The soft *C*-nucleophile is expected to attack at the benzoylpyruvate α-position, followed by annulation via the *N*-nucleophile on the γ-position. Thus, in the acyclic case, examples involving condensation with certain acetamide derivatives and enamines like **69** have appeared, resulting in the formation of pyridines **70** functionalized in the 2-,3-,4-, and 6-position (Scheme 19) [51–53]. This approach provides an expedient entry to densely ornamented pyridines.

Acetamidines carrying an electron withdrawing substituent may participate in a cyclodehydration sequence with β-diketones. This process is commonly referred to as Guareschi-Thorpe condensation [54]. An account of its application to benzoylpyruvates has been reported, involving reaction with nitroacetamidine **71** to afford pyridine **72** (Scheme 20) [55]. Subsequent elaboration via reduction of the nitro group can then be used to furnish fused pyridines.

Scheme 19. Example on cyclodehydration involving acyclic *C,N*-dinucleophiles carrying a one-unit linker.

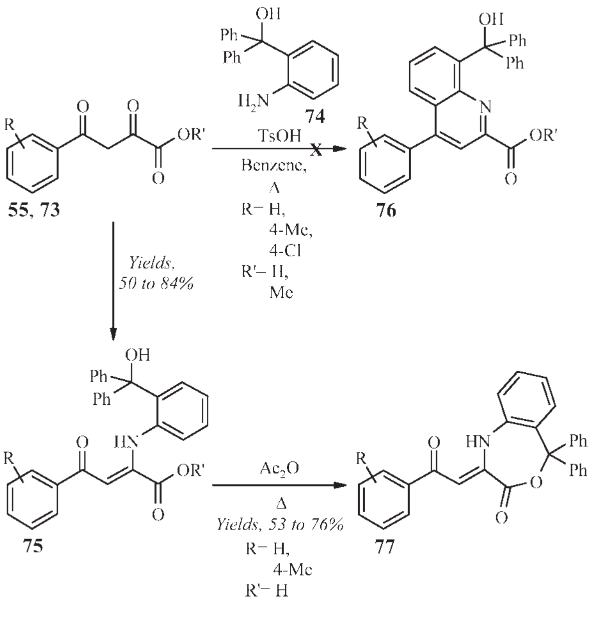


Scheme 20. Example on Guareschi-Thorpe condensation involving benzoylpyruvates.

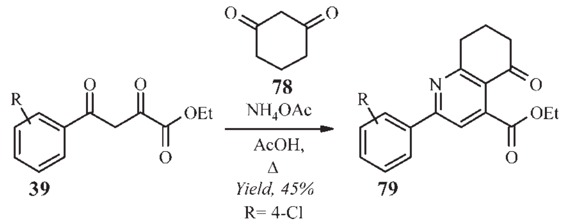


Applied to the cyclic case, in addition to performed enamines, aromatic amines could conceivably also serve as *C,N*-dinucleophiles. However, due to the relatively poor *C*-nucleophilicity, one would expect the amino group to take precedence. Formally, this type of cyclodehydration would be classified as a variation of the Skraup-Doebner-von Miller quinoline synthesis [56]. The major difference is the expected regiochemical outcome, since it is projected to occur with opposite sense of what is generally observed for the classical reaction. A route involving benzoylpyruvates would thus offer a complement in the preparation of substituted quinolines. Unfortunately, only the first step of the sequence leading to intermediate β-enaminone **75** has been demonstrated, emphasising that the critical point is the *C*-nucleophilicity (Scheme 21) [57]. Instead of yielding pyridine **76**, the overall sequence leads to annulation across the α-keto ester moiety, affording **77**. By analogy, the reaction between benzoylacetones and electron rich anilines is facile under acidic conditions [58].

Scheme 21. Reaction with a prospective cyclic *C,N*-dinucleophile carrying a one-unit linker.



Scheme 22. Example on cyclodehydration involving cyclic *C,N*-dinucleophiles carrying a one-unit linker.



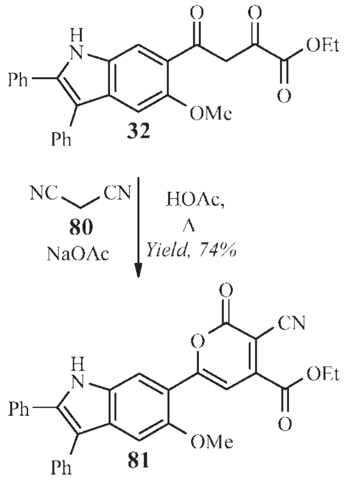
The reaction with performed cyclic enamines is nonetheless a facile process. In this case, the regiochemistry corresponds to that observed with acyclic enamines. Thus, when treating a benzoylpyruvate **39** with cyclohexane-1,3-dione **78** in the presence of an ammonia source, the reaction yields quinoline derivative **79** (Scheme 22) [59].

Linked by two units. Literature does not contain any example on the application of *C,N*-dinucleophiles with a two-unit linker, neither in relation to benzoylpyruvates nor β-diketones.

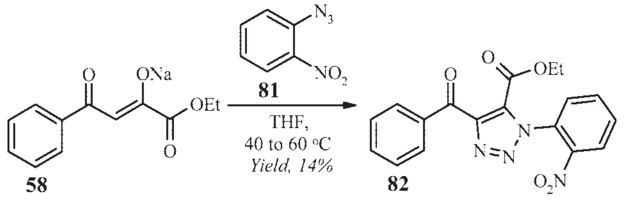
MISCELLANEOUS

The preparation of heterocyclic compounds from benzoylpyruvates needs not be limited to condensation entailing dinucleophilic species. An example is the reaction between malononitrile **80** and benzoylpyruvate **32** (Scheme 23) [28]. The incipient enol ate, formed by initial conjugate addition, attacks in turn one of the electrophilic nitriles to render a 3,4,6-functionalized pyran-2-one **81**. Therefore, within this context, reactants combining both nucleophilic and electrophilic features offer an alternative mode to form highly substituted rings.

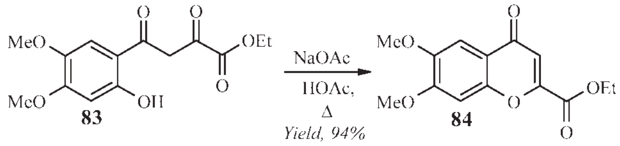
Scheme 23. Example on cyclodehydration via mixed mode.



Scheme 24. Example on 1,3-dipolar cycloaddition on benzoylpyruvates.



Scheme 25. Example on intramolecular cyclodehydration.



Another aspect related to the partially unsaturated nature bestowed on benzolpyruvates by the β-diketo moiety is a certain proclivity to engage with 1,3-dipoles. Thus, when treated with an organic azide, benzoylpyruvates may react to form cycloadducts, like 1,2,3-triazole **82** (Scheme 24) [60].

Benzoylpyruvates may themselves serve as cyclic precursors in the absence of external nucleophiles. With heteroatoms located at the 2-position of the aryl moiety, as in the case of **83**, it is possible to obtain fusion by intramolecular cyclodehydration across the α-keto group. This approach has been used to prepare chromone esters like **84** (Scheme 25) [61].

CONCLUSION

This review has highlighted the value of benzoylpyruvates as a synthetic template in the preparation of functionalized heterocycles. In particular, the value is evident when considering strategies towards biaryls, as an alternative to cross-coupling protocols.

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Synthetic Strategies of Nonpeptidic β-Secretase (BACE1) Inhibitors

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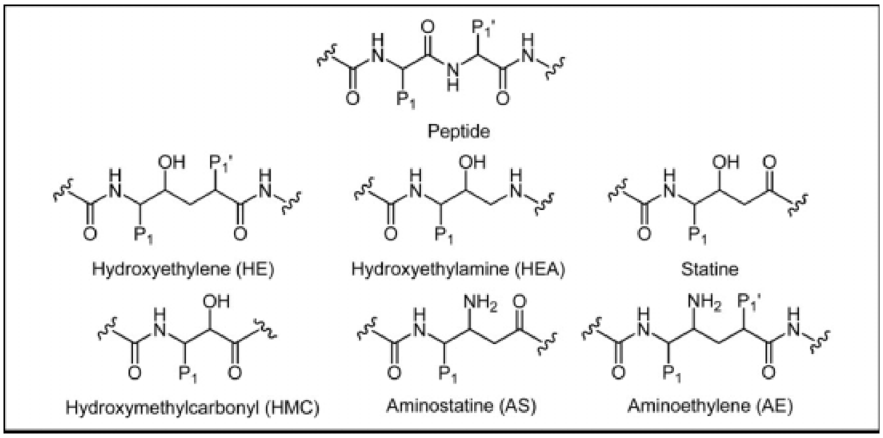

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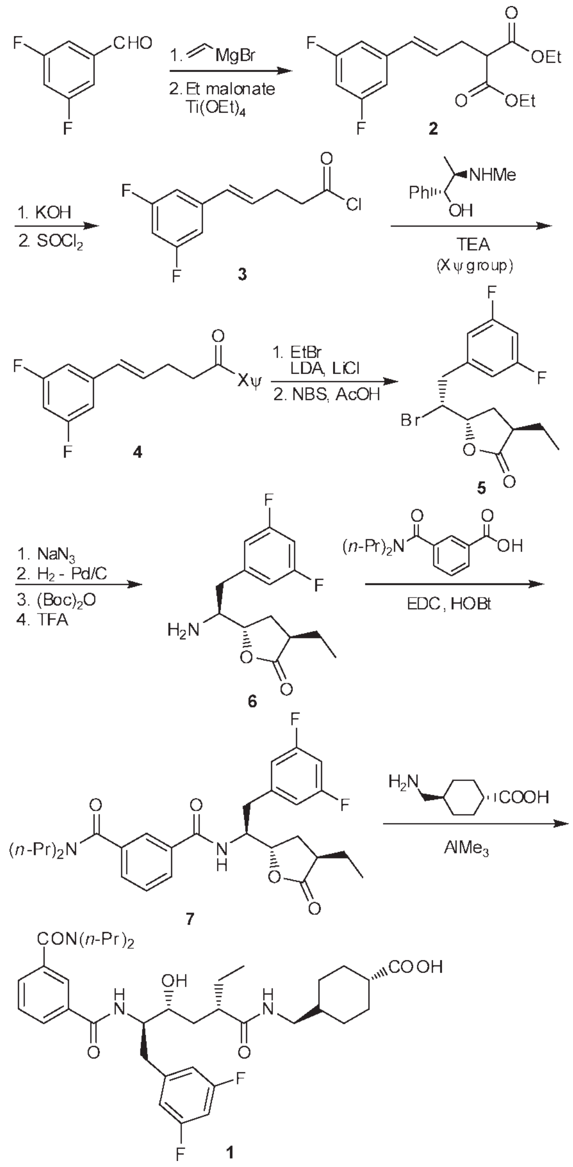
INTRODUCTION

Alzheimer's disease (AD), the neurodegenerative syndrome first described by Alois Alzheimer in 1906, affects more than 37 million people worldwide [1]. β-Amyloid cleaving enzyme-1 (BACE1) is an aspartyl protease isoform which is the principle neuronal protease responsible for the formation of Aβ fragments in the brain [2]. BACE1 is an excellent target for antiamyloid AD therapy and potent inhibitors of this enzyme have already been reported [3]. However, first generation inhibitors based on the peptidomimetic strategy showed problems related to the nature of their structure, such as blood-brain barrier crossing, poor oral bioavailability, and susceptibility to P-glycoprotein transport [4,5]. To overcome these difficulties, new nonpeptidomimetic β-secretase inhibitors were designed. After the discovery of the first nonpeptidomimetic inhibitors by Takeda Chemicals in 2001 [6], intensive efforts in research by both institutional and industrial laboratories resulted in the synthesis of hundreds of new generation inhibitors. We here review the synthesis of the most significant inhibitors, with particular emphasis on those developed by pharmaceutical companies.

ISOPHTHALAMIDE-BASED INHIBITORS

Elan Pharmaceuticals synthesized a variety of hydroxyethylene (HE) BACE1 inhibitors bearing the optimal isophthalamide *N*-terminus of the statin series and different C termini at the P1′ substituent. As an example, compound **1** inhibited BACE1 at 50 n*M* concentration [7]. Reaction of 3,5-difluorobenzaldehyde with vinylmagnesium bromide according to Orito [8] afforded 3-(3,5-difluorophenyl)-1-propen-3-ol which was treated with diethyl malonate in the presence of titanium tetraethoxide to give ethyl 4-(3,5-difluorophenyl)-3-butenoate **2**. Ester **2** underwent alkaline hydrolysis to the acid which was transformed into the corresponding acid chloride **3** with thionyl chloride. Coupling reaction of **3** with (1*R*,2*R*)-(-)-pseudoephedrine in the presence of triethylamine (TEA) and subsequent treatment of **4** with ethyl bromide in the presence of lithium diisopropylamide (LDA) and LiCl afforded a compound, which on treatment with *N*-bromosuccinimide (NBS) and AcOH at reflux underwent intramolecular lactonization to give **5**. The bromide was transformed to the corresponding azide by nucleophilic attack with sodium azide and concomitant inversion of the alpha chiral center. The azide was reduced with hydrogen in the presence of palladium as a catalyst and protected with bis-(*tert*-butoxycarbonyl)anhydride to give a compound, which then was treated with trifluoroacetic acid to afford **6**. *N*-Ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide (EDC)/1-hydroxy-benzotriazole (HOBt) amide coupling to the isophthalamide furnished the lactone **7**. Finally, **7** was ring-opened using trimethylaluminum and the required amine to provide **1** (Scheme 1) [7,9].

Scheme 1



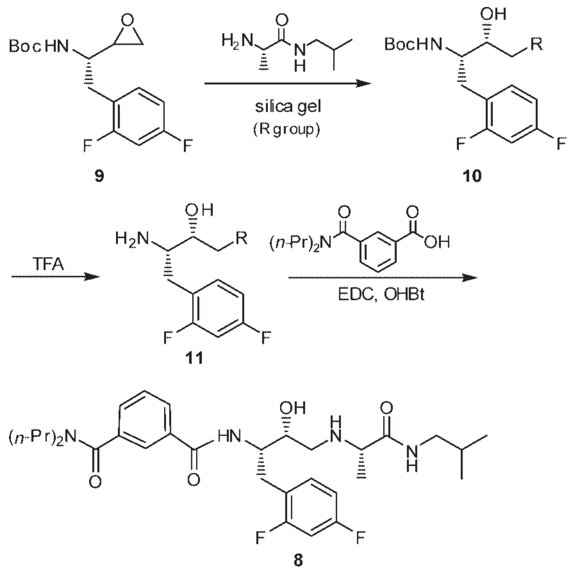
HE transition state-based inhibitor was replaced by an hydroxyethyl secondary amine (HEA) isosteric group in order to improve cell-to-enzyme potency. Compound **8** was a potent cellular inhibitor of Aβ production (more potent than the statin and the HE BACE inhibitors with comparable enzyme potency) [10]. The synthesis of **8** was accomplished starting from the erythro (*R*)-amino epoxide **9**, which was transformed into the Boc-protected amino alcohol **10**. Removal of the protecting group under TFA acidic conditions (**11**) and subsequent coupling reaction provided **8** (Scheme 2) [10].

Merck Research Laboratories synthesized HEA isosteres among potential HE motifs because of its lower molecular weight and one less amide bond. In addition, introduction of a sulfonamide group in a series of isophthalamides led to potent and selective BACE1 inhibitors [11–18].

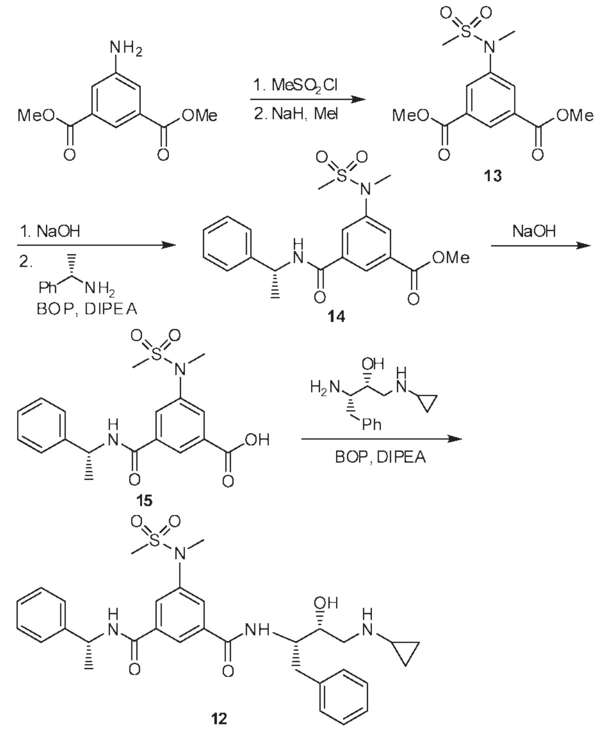
Compound **12** displayed excellent activity in both enzymatic ($IC_{50} = 15$ n*M*) and cell-based assays ($IC_{50} = 29$ n*M*), but showed moderate BACE1/BACE2 selectivity [12]. Isophthalamide **12** was prepared from 5-aminoisophthalic ester which was mesylated and then *N*-alkylated with methyl iodide to give **13**. Alkaline hydrolysis of **13** furnished the mono-ester which was coupled with (*R*)-α-methylbenzylamine in the presence of (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP)/*N*,*N*-diisopropylethylamine (DIPEA) to furnish **14**. Subsequent hydrolysis of the remaining ester, and amide coupling of **15** with 1-benzyl-3-cyclopropylamino-2-hydroxypropylamine gave **12** (Scheme 3) [12].

Analogues of **12** with both lower polar surface area and fewer H-bond donor/acceptor groups showed better pharmacodynamic and/or pharmacokinetic properties. Compound **16** was synthesized as S3-truncated analogue of **12**, and showed excellent binding activity [16]. An optimized synthesis of **16** is depicted in Scheme 4. Methyl 3-nitrobenzoate was treated with *N*-iodosuccinimide (NIS) in triflic acid (TfOH) to produce methyl 5-iodo-3-nitrobenzoate which was reduced to amine **17** with stannous chloride dihydrate. The aniline **17** was mesylated and then methylated with iodomethane in the presence of sodium hydride to give **18**. One-pot hydroindation/Suzuki coupling reaction furnished (*Z*)-methyl 3-(2-cyclopropylvinyl)-5-(*N*-methylmethylsulfonamido)-benzoate exclusively in 93% yield according to Oshima and coworkers [19]. The ester intermediate was then transformed into acid **19** by alkaline hydrolysis.

Scheme 2



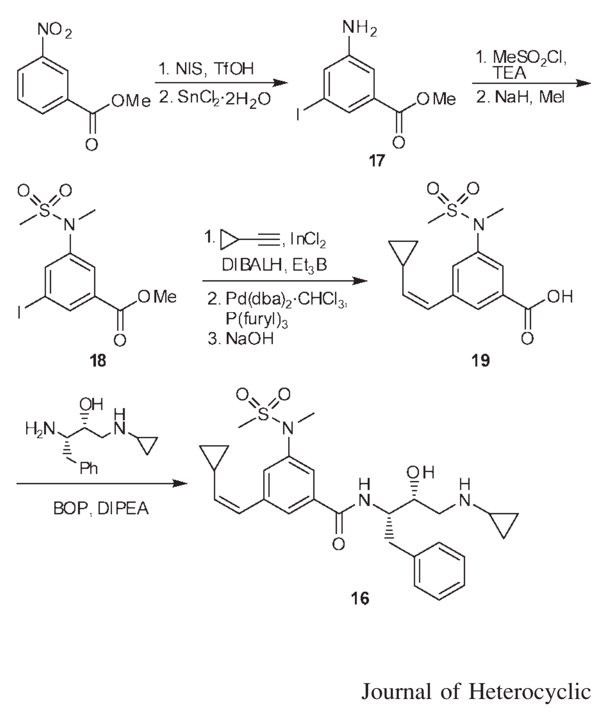
Scheme 3



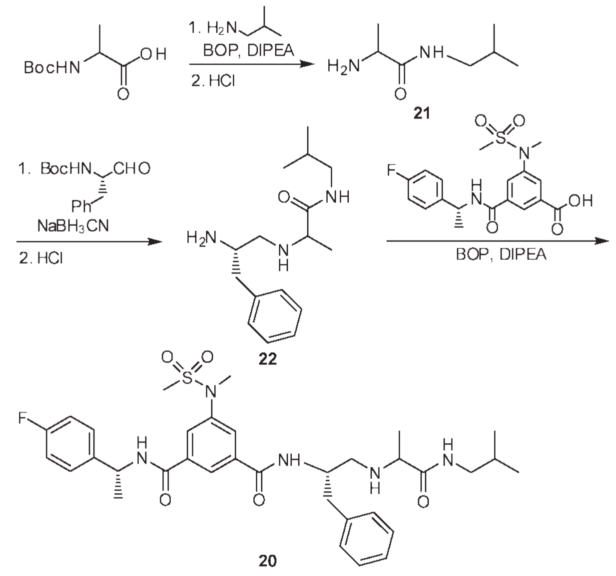
Reaction of **19** with the required amine in the presence of BOP and DIPEA afforded **16** [16].

Either small alkyl groups or longer hydrophilic substituents at the P1′ region produced compounds endowed with high BACE1 inhibitory potencies, and selectivity over BACE2 and human renin. Compound **20** was prepared by reaction of *iso*-butylamine with *N*-Boc-L-alanine and subsequent deprotection with gaseous HCl to afford *N*-*iso*-butylalaninamide (**21**). This compound was treated with *N*-Boc-L-phenylalanylaldheyde in the presence of sodium cyanoborohydride, and then deprotected with HCl to give **22**. Subsequent amide coupling of **22** with the appropriate benzoic acid in the presence of BOP and DIPEA afforded **20** (Scheme 5) [17].

Scheme 4



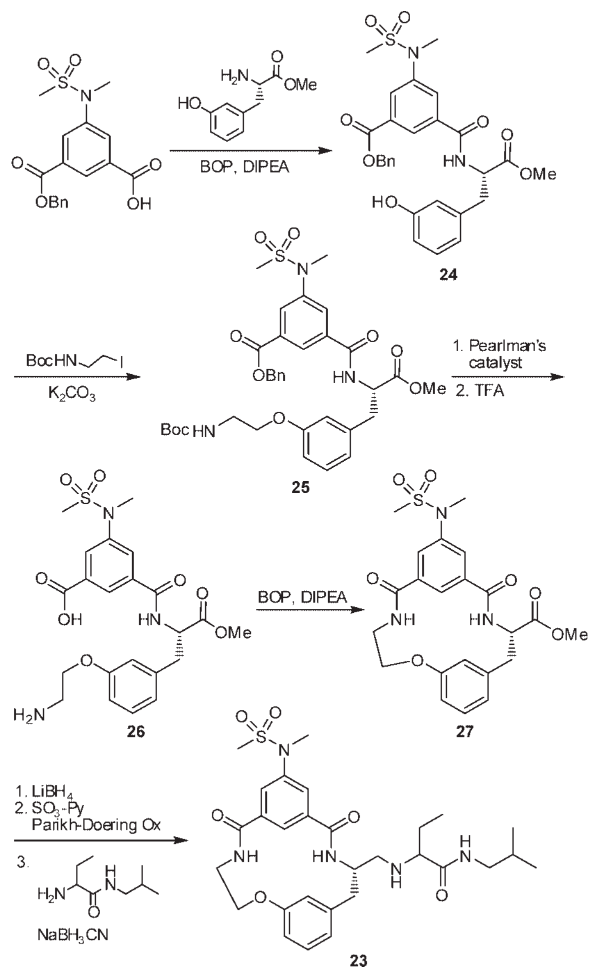
Scheme 5



X-ray crystallographic data of the **12**/BACE1 complex revealed the presence of space in proximity of the P1 and P3 groups. This observation prompted the design of macrocycles that would link these groups in an isophthalamide-based inhibitor. Macrocyclic **23**, which also incorporated a ψ[CH$_2$NH]-reduced amide bioisosteric group, exhibited high inhibitory potency (IC$_{50}$ = 32 n*M*, assayed as 1:1 diastereomeric mixture); however, in the cell-based assay **23** was significantly less potent (IC$_{50}$ = 5.4 μ*M*) [18]. Compound **23** was synthesized by reaction of 3-(*N*-methyl-methansulfonamido)-5-benzyloxycarbonylbenzoic acid with 3-tyrosine methyl ester in the presence of BOP and DIPEA to produce phenol **24** which was alkylated to **25** with *tert*-butyl (2-iodoethyl)carbamate. Deprotection of the benzyl ester using Pearlman's catalyst, followed by removal of the amino Boc protecting group afforded the corresponding *seco*-acid **26**. This acid underwent macrocyclization to **27** in the presence of BOP reagent and DIPEA. Subsequent two-steps transformation of **27** into the corresponding aldehyde and final reductive amination with (*S*)-2-amino-*N*-*iso*-butylbutanamide afforded **23** (Scheme 6) [18].

Efforts to improve potency culminated in the synthesis of macrocycle **28** as a single diastereomer. As BACE1 inhibitor, **28** (IC$_{50}$ = 4 n*M*) was 8-fold more potent than **23**, and showed significantly improved

Scheme 6

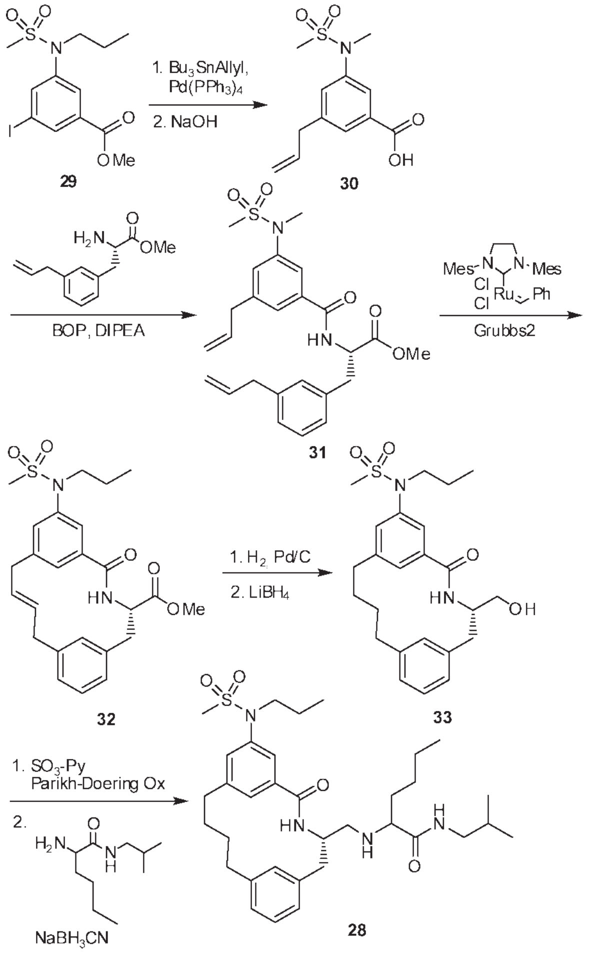


apparent permeability. An elegant synthesis of **28** is depicted in Scheme 7. Allylation of the iodoarene **29** under Stille conditions and subsequent hydrolysis of the methyl ester provided benzoic acid **30**. This acid was coupled with (*S*)-3-allyl phenylalanine to furnish the precursor **31**. Macrocyclization was accomplished through metathesis reaction using second-generation Grubbs catalyst. Hydrogenation of the *E*-olefin **32** and subsequent reduction of the ester using $LiBH_4$ provided alcohol **33**. The latter compound underwent Parikh-Doering oxidation, and finally reductive amination with *N*-isobutyl-L-norleucinamide to afford **28** [18].

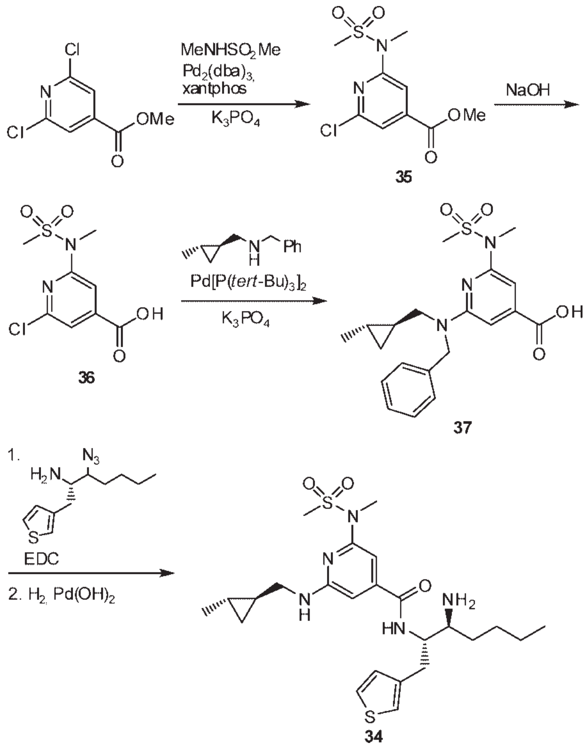
ISONICOTINAMIDES

In an effort to improve CNS penetration and pharmacokinetic stability of BACE1 inhibitors, Merck discovered a series of highly potent and selective isonicotinamides [20–22]. The improvement in potency was due to the incorporation of a *trans*-methyl-cyclopropane P3 that could be responsible for enhanced van der Waals contacts within the context of a 10s-loop down BACE1 conformation. Noncapped compound **34** displayed potent activity in both BACE1 (IC_{50} = 11 n*M*) and sAPP_NF cellular (IC_{50} = 38 n*M*) assays. Compound **34** was synthesized by reaction of methyl 2,6-dichloroisonicotinate with *N*-methyl methylsulfonamide in the presence of tris(dibenzylideneacetone)di-palladium(0) ($Pd_2(dba)_3$) and 9,9-dimethyl-4,5-bis (diphenylphosphino)xanthene (xantphos) to afford the intermediate arylsulfonamide **35**. Amide **35** underwent alkaline hydrolysis to afford the corresponding carboxylic acid **36**. Cross coupling reaction of **36** with *trans*-1-methyl-2-benzylaminomethylcyclopropane in the presence of palladium(0)tributyl-phosphine (Pd/P(*tert*-Bu)$_3$) gave **37**. Aminoacid **37** was coupled with the amino azide in the presence of *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide (EDC), and then hydrogenated with concomitant deprotection to provide **34** (Scheme 8) [20].

Scheme 7



Scheme 8



HETEROCYCLIC DERIVATIVES

Bristol-Myers Squibb synthesized heterocyclic derivatives, *i.e.*, pyrrolidine, pyrrolidinone, and azepinone compounds as β-secretase inhibitors [23–27]. Compound **38** inhibited BACE1 at concentration <0.1 μ*M* [26]. Compound **38** was obtained by treatment of the starting pyrrolidine derivative with rhodium tris(triphenylphosphine) chloride (Wilkinson's catalyst) to afford (2*R*,4*R*)-*tert*-butyl 2-((1*S*,2*S*)-2-benzyloxycarbonyl)-1-(*tert*-butyl dimethylsilyloxy)-3-phenylpropyl)-4-hydroxypyrrolidine -1-carboxylate (**39**). This compound was transformed into the corresponding mesylate by reaction with methanesulfonic acid in the presence of triphenylphosphine and diethyl azodicarboxylate, and then treated with sodium propanethiolate to give the 4-propylthiopyrrolidine derivative **41**. After oxidation of sulfur to sulfone with oxone (**42**), the Cbz protecting group was removed by catalytic reduction with hydrogen (Pd/C) to give **43**. Coupling the amino group of **43** with 3-dipropylaminocarbonyl-5-oxazol-2-yl-benzoic acid in the presence of *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) and DIPEA gave a compound which was deprotected with 4*N* HCl to provide **38** (Scheme 9) [26].

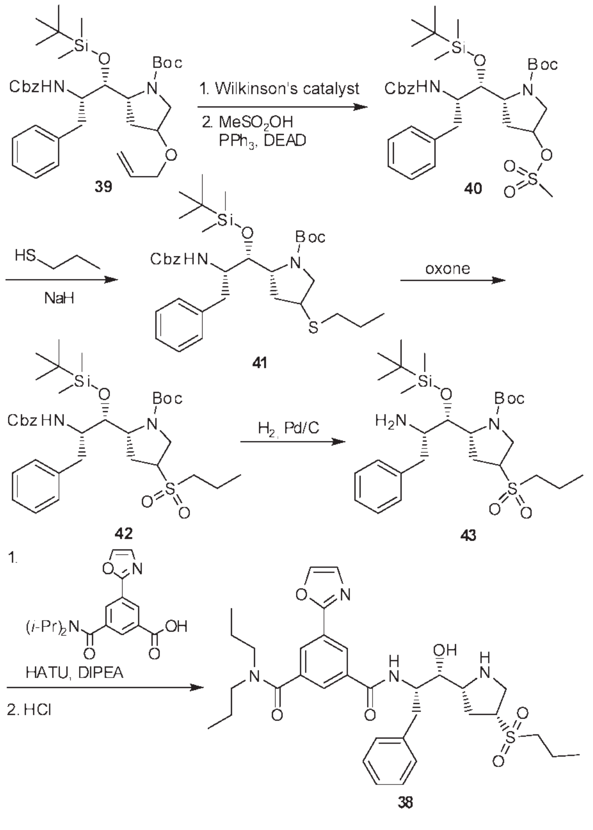
GUANIDINES

Guanidines were also reported as β-secretase inhibitors [28–38]; among these, indoleacetic acid acyl guanidine **44** inhibited BACE at <0.1 μ*M* concentration [38]. Compound **44** was obtained from 3,5-dichloro-4-aminobenzonitrile which was treated with sodium hexamethyldisilazane (NaHMDS) and acetyl chloride to form **45** which was reduced to benzylamine with lithium aluminum hydride. Amine **46** was treated with *N*-Boc-*S*-methylisothiourea in the presence of trifluoroacetic anhydride (TFAA) and DIPEA to give *tert*-butyl *N*-4-acetamido-3,5-dichlorobenzylcarbamidoyl-carbamate (**47**). This compound was coupled with 6-bromoindole-3-acetic acid in the presence of HATU and DIPEA to give **48**, which after deprotection with TFA afforded **44** (Scheme 10) [38].

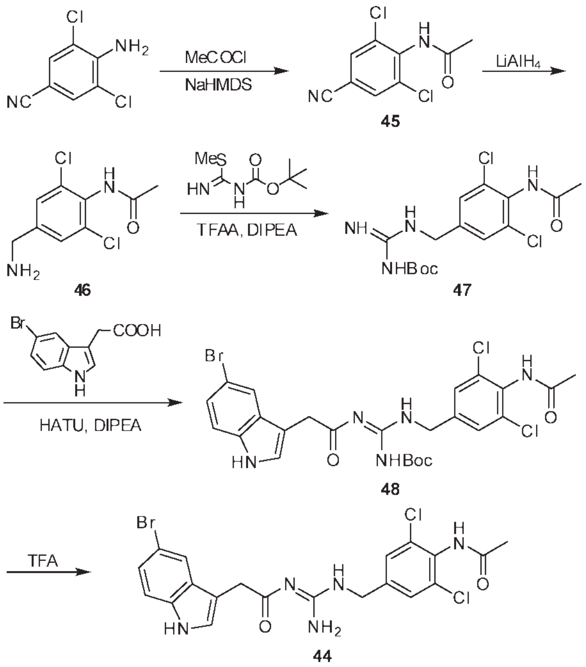
High-throughput screening (HTS) of Wyeth's compound library by means of a FRET assay identified acylguanidines as a new class of BACE1 inhibitors (*i.e.*, **49**: BACE1 IC_{50} = 3.7 μ*M*) [28]. Wyeth synthesized analogues **50–52** which were potent BACE1 inhibitors.

With the exception of **49**, these compounds were generally highly selective for BACE1 over cathepsin and

Scheme 9



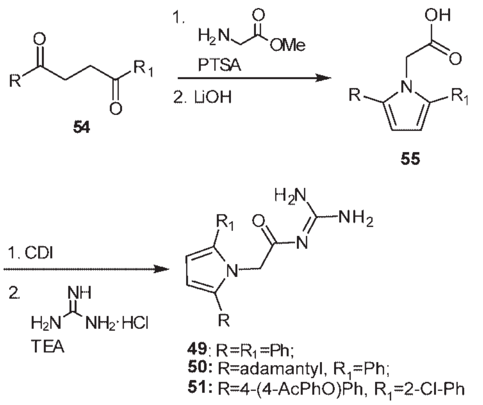
Scheme 10



pepsin ($IC_{50} > 50$ μ*M*). Compounds **49–53** were synthesized from the 1,4-diones **54** which were coupled with glycine methyl ester followed by alkaline hydrolysis to give different 2-(2,5-disubstituted-1*H*-pyrrol-1- yl)-acetic acids **55**. Activation of the acid with 1,1′-carbonyldiimidazole (CDI) and subsequent reaction with guanidine hydrochloride gave **49–51** (Scheme 11). The substituted acylguanidines **52** and **53** were prepared by reaction of the corresponding pyrroleacetic acid **55** with 1*H*-pyrazole-1-carboximidamide in the presence of CDI and subsequent displacement of the pyrazole leaving group of **56** with 3-amino-1-propanol (Scheme 12) [28].

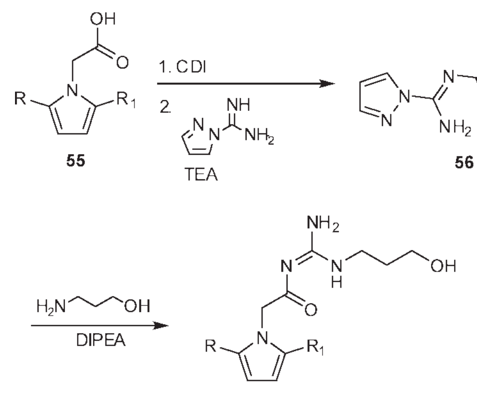
Janssen Pharmaceuticals applied for 2-amino-3,4-dihydropyrido[3,4-*d*]pyrimidines which showed K_i values in the submicromolar range of concentration [37].

Scheme 11



49: R=R₁=Ph;
50: R=adamantyl, R₁=Ph;
51: R=4-(4-AcPhO)Ph, R₁=2-Cl-Ph

Scheme 12



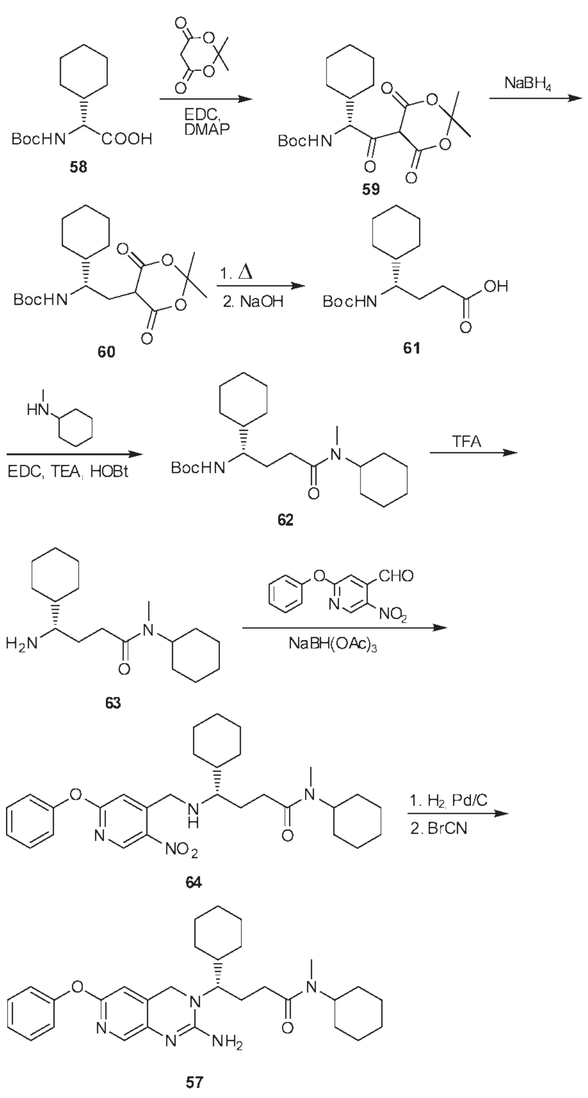
52: R=adamantyl, R₁=Ph;
53: R=4-*n*-PrOPh, R₁=2-Cl-Ph.

Johnson & Johnson Pharmaceuticals also focused SAR development on 2-amino-3,4-dihydroquinazoline [35]. The *S*-enantiomer **57** inhibited BACE1 with $K_i = 11$ n*M* (as racemate $K_i = 30$ n*M*). This compound exhibited excellent potency in a cellular assay, and additionally, lowered β-amyloid$_{1-40}$ in plasma by 40–70% in rats after per oral administration. Compound **57** was prepared from (*R*)-cyclohexylglycine **58** (>97% e.e.) which was treated with Meldrum's acid in the presence of EDC and 4-(dimethylamino)pyridine (DMAP) to afford **59**. $NaBH_4$ reduction of the ketone functionality provided **60** which underwent thermolysis in boiling toluene to give a lactam which was transformed into acid **61** by alkaline hydrolysis. Compound **61** was coupled with cyclohexylmethylamine in the presence of EDC, TEA, and HOBt to give amide **62**. After acidic cleavage of **62**, reaction of amine **63** with 2-phenoxy-5-nitropyridin-4-carboxaldehyde in the presence of sodium triacetoxyborohydride gave the nitroaminoalkyl intermediate **64** which was reduced to amine with hydrogen in the presence of palladium on carbon, and then cyclized to **57** with cyanogen bromide (Scheme 13) [35].

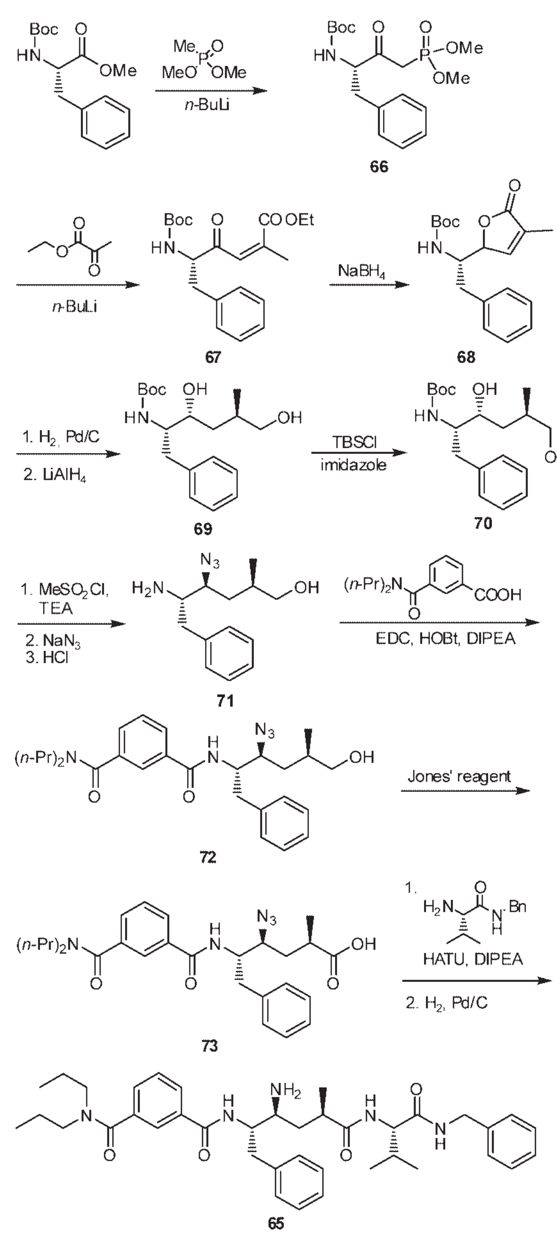
OTHER COMPOUNDS

Sunesis Pharmaceuticals considered the primary amine group as a possible bioisostere of the hydroxyl group present in HE-containing BACE1 inhibitors [39]. Replacement of the HE motif with the aminoethylene bioisostere afforded compounds endowed with slightly reduced enzymatic inhibitory activity but distinctly improved cell potency (the *S*-isomer was preferred for activity). Incorporation of a benzyl P_1 substituent (*i.e.*, **65**) resulted in a net increase in inhibitory potency relative to the isobutyl analogues. Compound **65** was synthesized from *N*-Boc-L-phenylalanine methyl ester which was treated with dimethyl methylphosphonate in the presence of *n*-butyl lithium to provide the corresponding phosphonate **66**. Reaction of crude **66** with ethyl pyruvate and *n*-butyl lithium gave ethyl (5*S*,2*Z*)-2-methyl-[5-(*tert*-butoxycarbonyl)amino]-4-oxo-6-phenyl-hex-2-enonate (**67**). Sodium borohydride reduction of **67** with concomitant intramolecular cyclization gave 2,5-dihydrofuran-2-one **68**. This compound was reduced to tetrahydrofuran-2-one with hydrogen in the presence of palladium over carbon, and then with lithium aluminum hydride to furnish (2*S*,3*R*,5*R*)-2-*tert*-butoxycarbonylamino-1-phenyl-5-methylhexan-3,6-diol (**69**). The diol was subsequently treated with *tert*-butyl-dimethylsilyl chloride (TBSCl) and imidazole (**70**), and then with methanesulfonyl chloride and triethylamine to furnish the corresponding methanesulfonate. Introduction of the azido group by displacing the methanesulfonate with sodium azide, and cleavage of both protecting groups with hydrochloric acid resulted in aminoalcohol **71** which was coupled with *N*,*N*-dipropyl isophthalamic acid in the presence of ECD, HOBt and DIPEA to form **72**. Oxidation of **72** to acid **73** with Jones' reagent (chromium trioxide and sulfuric acid) and further elaboration as above reported provided **65** (Scheme 14) [39].

Scheme 13



Scheme 14



CONCLUSION

Three-dimensional structural information for BACE1 in complex with a variety of inhibitors has led to great strides in the development of new effective agents for the treatment of AD. Both academia and pharmaceutical companies focused their efforts to develop new synthetic strategies for the synthesis of potent BACE1 inhibitors, such as isophthalamides, isonicotinamides, heterocycles and other derivatives, which showed improved drug properties when compared with first generation peptidic inhibitors. These synthetic routes may serve as useful tools for medicinal chemists in discovering new AD therapeutics.

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2*H*-Pyran-2-one-3-carbothioamide Derivatives: Synthesis and Reaction with Hydrazine Hydrate

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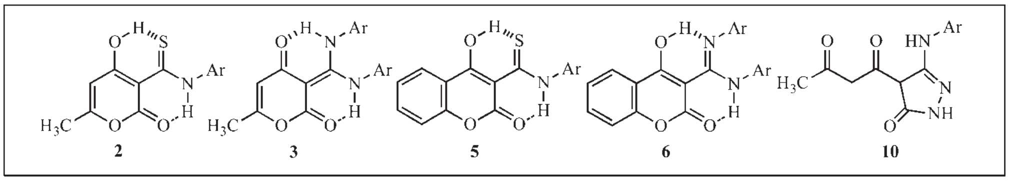

N-Aryl-4-hydroxy-6-methyl-2*H*-pyran-2-one-3-carbothiamides and *N*-aryl-4-hydroxycoumarin-3-carbothiamides were synthesized by the reaction of arylisothiocyanates with 4-hydroxy-6-methylpyran-2-one and 4-hydroxycoumarin, respectively. Novel products 3-[bis(arylamino)methylene]-6-methyl-2*H*,4*H*-pyran-2,4-diones and *N*,*N*′-diaryl-4-hydroxycoumarin-3-carboximidamides have also been obtained in the same reactions. Novel 4-acetoacetyl-3-phenylamino-4,5-dihydro-5*H*-pyrazol-5-ones were synthesized from the reaction of *N*-aryl-4-hydroxy-6-methyl-2*H*-pyran-2-one-3-carbothiamides with an excess of hydrazine. The structure of all compounds was established by NMR and mass spectra.

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INTRODUCTION

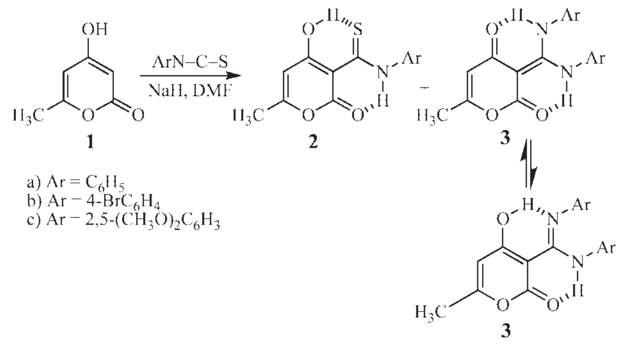
2-Pyrones and coumarins are an important class of heterocyclic compounds presenting important pharmaceutical properties. They have been found in a large number of natural products displaying significant biological activities, and certain synthetic derivatives are biologically active compounds (*e.g.*, potent HIV-1 protease and photosynthetic electron transport inhibitors; presenting sedative, anticonvulsive, anesthetic, and antifungal properties) [1–8]. These important potential applications led to the development of a plethora of synthetic procedures to synthesize pyrone derivatives either by traditional approaches or by transition metal-catalyzed procedures [9–21].

Taking into consideration the referred important biological activities of the 2-pyrones and coumarins and following our studies on the transformations of 4-hydroxy-6-methylpyran-2-one (triacetic acid lactone, TAL) **1** [22] and 4-hydroxycoumarin **4** [23–25], we developed a new synthetic method for *N*-aryl-4-hydroxy-6-methyl-2*H*-pyran-2-one-3-carbothioamides **2** and *N*-aryl-4-hydroxycoumarin-3-carbothioamides **5**. In these transformations, novel products 3-[bis(arylamino)methylene]-6-methyl-2*H*,4*H*-pyran-2,4-diones **3** and *N*,*N*′-diaryl-4-hydroxycoumarin-3-carboximidamides **6** have also been obtained. In this communication, the synthesis of novel 4-acetoacetyl-3-arylamino-4,5-dihydro-5*H*-pyrazol-5-ones **10** were also established, by the reaction of *N*-aryl-4-hydroxy-6-methyl-2*H*-pyran-2-one-3-carbothioamides **2** with hydrazine hydrate.

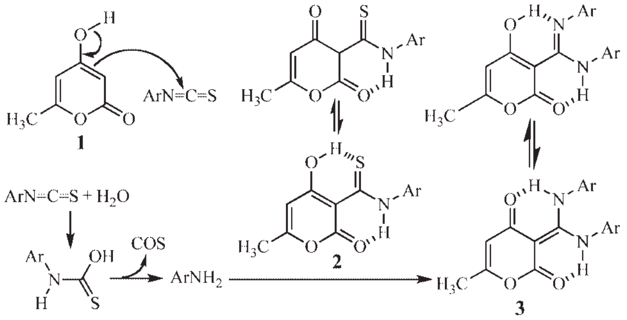
RESULTS AND DISCUSSION

Treatment of 4-hydroxy-6-methylpyran-2-one **1** with arylisothiocyanates in the presence of sodium hydride in DMF for 15 h led to the formation of a solid after the addition of water to the reaction mixture. The aqueous layer was acidified with hydrochloric acid (pH = 4–5), and after vigorous stirring at room temperature for 1.5 h, it led to the formation of a new solid. The elemental analysis and the mass spectra of the first solid indicated the absence of sulfur in the structure and that two molecules of arylisothiocyanates reacted with **1**. In the case of compound **3a**, apart from the molecular ion at *m*/*z* 320 ($C_{19}H_{16}N_2O_3$), its mass spectrum presents peaks corresponding to the loss of Ph—NH$_2$ and Ph—NH and intense peaks at *m*/*z* 85 and 65 corresponding to the characteristic fragments from cleavage of the 2-pyrone ring. These data suggest the formation of 3-(bis-phenylaminomethylene)-6-methyl-2*H*,4*H*-pyran-2,4-dione **3a**. This structure was also supported by its ^{1}H NMR spectrum, which presents four signals as singlets at δ 2.23, 5.73, 12.00, and 14.18 ppm because of the 6-Me, H-5, and two N*H* proton resonances, respectively. The ^{13}C NMR spectrum of **3a** presents two signals for the resonance of each carbon of the pyrandione moiety: C-3 (δ 85.2 and 104.4 ppm), C-5 (δ 105.8 and 108.4 ppm), C-6 (δ 140.3 and 163.4 ppm), C-4 (δ 178.8 ppm assigned to C—OH; δ 186.2 ppm assigned to C=O), and C-1′ [δ 168.9 ppm assigned to =C(NHAr)$_2$; δ 182.5 ppm

Scheme 1



Scheme 2



assigned to —C(NHAr)=NAr and the signals of the aromatic carbon. The appearance of this type of double ^{13}C NMR spectra is due to the presence of two tautomeric forms of compound **3a** (Scheme 1). All the spectroscopic features of **3b** and **3c** are similar to those described for **3a**, except for the resonances of the aromatic moieties and for the corresponding *m*/*z* values; confirming the generality of the reaction for other substituted arylisothiocyanates (Scheme 1).

The elemental analysis and the mass spectrum of the second solid are consistent with the structure of *N*-aryl-4-hydroxy-6-methyl-2*H*-pyran-2-one-3-carbothiamides **2a–c**, bearing sulfur and nitrogen atoms in the structure. The ^{1}H NMR spectra of **2a–c** present four singlets at δ 2.29–2.30, 6.36–6.38, 12.70–12.92, and 14.90–15.89 ppm because of the resonance of 6-Me, H-5, NH, and OH, respectively. The ^{13}C NMR spectra of **2a–c** present signals characteristics of the carbothiamoyl group at δ 187.5–189.6 ppm. The mass spectra of **2a–c** present peaks corresponding to the molecular ion followed by the peaks corresponding to the loss of Ar—NH_2 and Ar—NH and intense peaks at *m*/*z* 85 and 65 corresponding to the characteristic fragments from cleavage of the 2-pyrone ring.

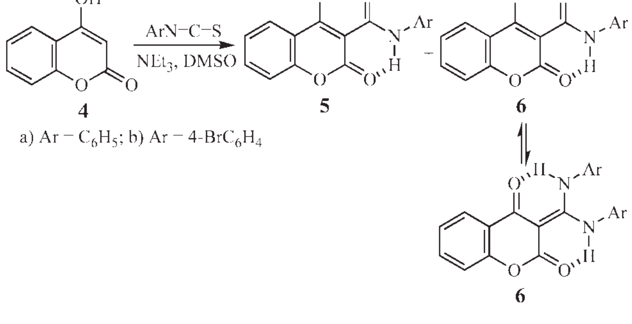
Surprisingly, to the best of our knowledge, 3-[bis(arylamino)methylene]-6-methyl-2*H*,4*H*-pyran-2,4-diones **3a–c** or related compounds have never been described in the literature; however, Bruno et al. have studied an analogous reaction of 5,6-dihydro-4-hydroxy-6-methyl-2*H*-pyran-2-one with arylisothiocyanates under the same experimental conditions and have isolated only 5,6-dihydro derivatives of compounds **2a–c** [26]. The formation of compounds **3a–c** would be explained through the formation of unstable intermediates thiocarbamic acid derivatives from arylisothiocyanates, which yields aniline derivatives after a decarboxylation-type reaction [27] that react with the already formed *N*-aryl-4-hydroxy-6-methyl-2*H*-pyran-2-one-3-carbothioamides **2a–c** affording **3a–c** (Scheme 2). The yield of **3a** was considerably dependent on the amount of phenylisothiocyanate; using one molar equivalent 4-hydroxy-6-methyl-*N*-phenyl-2*H*-pyran-2-one-3-carbothioamide **2a** was the major product (75%), while using two molar equivalent led to the formation of 3-[bis(phenylamino)methylene]-6-methyl-2*H*,4*H*-pyran-2,4-dione **3a** as the major product (90%). This condensation was attempted in DMSO as solvent and in the presence of triethylamine giving rise to the expected products **2a** and **3a** in 45 and 55% yield, respectively.

To confirm the formation mechanism of **3a–c**, we have reacted **2a** with one equivalent of aniline in DMF for 2 h at room temperature and **3a** was obtained in good yield (90%).

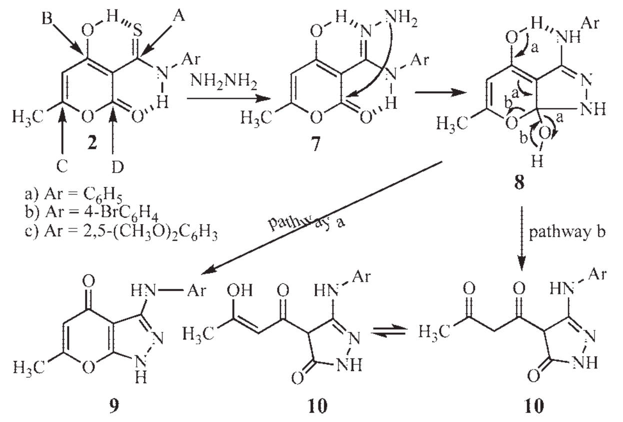
The condensation of 4-hydroxycoumarin **4** with arylisothiocyanates, using DMSO as solvent, gave the corresponding *N*-aryl-4-hydroxycoumarin-3-carbothioamides **5a,b** and also *N*,*N*′-diaryl-4-hydroxycoumarin-3-carboximidamides **6a,b** (Scheme 3). The ^{1}H NMR spectra of **5a,b** show two singlets at δ 13.34–13.35 and 17.45–17.60 ppm because of the resonance of NH and OH groups, whereas the ^{13}C NMR spectra show a characteristic carbothiamoyl signal at δ 188.4–189.1 ppm.

The IR spectrum of **6a** presented strong peaks at 1636–1617 and 3479–3407 cm^{-1}, which were attributed to the carbonyl (C=O) and —OH groups on the coumarin ring, respectively. The mass spectra of compounds **6a,b** indicated that the coumarin ring was conserved, with peaks being observed corresponding to the fragmentation of the coumarin ring at *m*/*z* 134, 143, and 117 [28,29]. From their ^{1}H NMR spectra, it is possible to observe the presence of signals corresponding to the resonances of two

Scheme 3



Scheme 4



exchangeable protons at δ 13.30–13.35 and 17.46–17.54 ppm, then assigned to the NH and OH groups, respectively. The ^{13}C NMR spectra showed that compound **6a,b** exist as a mixture of two tautomers (Scheme 3).

The next step of our work considered the reaction of compounds **2a–c** with hydrazine hydrate. These compounds **2a–c** have four (A, B, C, D) susceptible centers of nucleophilic attack, three of them into the pyrone ring, and a single molecule of hydrazine would therefore be liable to give a wide range of products (Scheme 4). Compounds **2a–c** reacted with hydrazine hydrate under reflux in a (1:1) mixture of ethanol/acetic acid and yielded only a single isolated solid as the reaction product. Elemental analysis and mass spectra showed that only one molecule of hydrazine had reacted, and the mass spectra also indicated the presence of fragments corresponding to an acetoacetyl group, with peaks at *m/z* 85, 56, and 43. This structure was also supported by the ^{1}H NMR spectra of **10a–c**, which present five singlets characteristics of a tautomeric equilibrium of acetoacetyl groups at δ 2.06–2.07, 2.32–2.33, 4.30–4.40, 6.11–6.13, and 16.30–16.70 ppm. These signals are assigned to the proton resonances of CH_3 (keto-enol form), CH_3 (β-diketone), CH_2 (β-diketone), CH, and OH (keto-enol form), respectively. We also observed two other singlets at δ 7.90–8.62 and 13.00–13.15 ppm, which were assigned to the NH-pyrazolone and NH—Ar groups, respectively. This condensation reaction allowed us to synthesize novel aminopyrazole derivatives in good yields (95–98%).

An explanation for the formation of pyrazole derivatives **10a–c** considered the hydrazine attack to the thioamide group (center A) of compounds **2a–c** leading to the carboximidamides **7a–c**. An intramolecular nucleophilic attack of the amine group from the amide moiety to the lactone carbonyl carbon (center D) gave rise to intermediates **8a–c**, which can follow two possible pathways (a and b). However, the isolation of pyrazole-type compounds **10a–c** led us to conclude that **8a–c** underwent the opening of the pyran ring by pathway b.

EXPERIMENTAL

Melting points were determined on a Stuart scientific SPM3 apparatus fitted with a microscope and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solutions on Bruker Avance 300 (300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C) and Nujeol GSX 270 WB (270.00 MHz for ^{1}H and 67.5 MHz for ^{13}C) spectrometers. Chemical shifts are reported in ppm (δ) using TMS as internal reference and coupling constants (*J*) are given in Hz. ^{13}C assignments were made using DEPT-135, HSQC, and HMBC (delays for one bond and long-range *J* C/H couplings were optimized for 145 and 7 Hz, respectively) experiments. Mass spectra are obtained with ESI(+) and GC-MS. Positive-ion ESI mass spectra were acquired using a Q-TOF 2 instrument [diluting 1 μL of the sample chloroform solution ($\sim 10^{-5}$ *M*) in 200 μL of 0.1% trifluoroacetic acid/methanol solution. Nitrogen was used as nebulizer gas and argon as collision gas. The needle voltage was set at 3000 V, with the ion source at 80°C and desolvation temperature at 150°C. Cone voltage was 35 V].

General procedure for the synthesis of *N*-aryl-4-hydroxy-6-methyl-2*H*-pyran-2-one-3-carbothioamides (2a–c) and 3-[bis(arylamino)methylene]-6-methyl-2*H*,4*H*-pyran-2,4-diones (3a–c). A solution of arylisothiocyanates (21 mmol) dissolved in 5 mL of DMF was added to a stirred solution of 2.52 g (20 mmol) of 4-hydroxy-6-methylpyran-2-one **1** and 0.576 g (24 mmol) of NaH 20% in mineral oil in 10 mL of DMF, under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 15 h. After this period, 50 mL of cold water was added to the reaction mixture, and the precipitate thus formed was collected by filtration and washed several times with a (1:1) mixture of diethyl ether:light petroleum. The solid was in each case recrystallized from isopropyl alcohol giving 3-[bis-(arylamino)methylene]-6-methyl-2*H*,4*H*-pyran-2,4-diones **3a–c**: **3a**, 1.92 g (30%); **3b**, 1.92 g (20%); **3c**, 3.08 (35%).

The aqueous layer was acidified with HCl 1*N* (pH = 4–5). After vigorous stirring at room temperature for 1.5 h, the precipitate thus formed was collected by filtration and washed several times with diethyl ether. The solid was in each case recrystallized from methanol giving *N*-aryl-4-hydroxy-6-methyl-2*H*-pyran-2-one-3-carbothioamides **2a–c**: **2a**, 3.13 g (60%); **2b**, 5.10 g (75%); **2c**, 2.57 g (40%).

4-Hydroxy-6-methyl-N-phenyl-2H-pyran-2-one-3-carbothioamide (2a). This compound was obtained as yellow powder, mp 189–190°C; ^{1}H NMR ($CDCl_3$): δ 2.30 (s, 3H, C*H*$_3$), 6.37 (s, 1H, H-5), 7.31 (t, 1H, *J* = 7.5 Hz, ArH), 7.43 (t, 2H, *J* = 7.50 Hz, ArH), 7.53 (d, 2H, *J* = 7.5 Hz, ArH), 12.92 (s, 1H, N*H*), 15.89 (s, 1H, O*H*); ^{13}C NMR ($CDCl_3$): δ 19.1, 97.6, 102.6, 124.8, 127.0, 128.6, 137.1, 162.8, 165.3, 175.7, 187.5; ms (EI): *m/z* 263 (6, ^{34}S), 262 [28, $(M+H)^+$], 261 ($M^{+\cdot}$, 100, ^{32}S), 260 (77), 228 (87), 93 (42), 77 (40), 85 (32), 69 (12). *Anal.* Calcd. for $C_{13}H_{11}NO_3S$ (261.30): C, 59.76; H, 4.24; N, 5.36. Found: C, 60.07; H, 4.60; N, 5.59.

N-(4-Bromophenyl)-4-hydroxy-6-methyl-2H-pyran-2-one-3-carbothioamide (2b). This compound was obtained as yellow powder, mp 190–191°C; ^{1}H NMR (DMSO-d_6): δ 2.29 (s, 3H, C*H*$_3$), 6.38 (s, 1H, H-5), 7.58 (d, 2H, *J* = 8.0 Hz, ArH), 7.63 (d, 2H, *J* = 8.0 Hz, ArH), 12.70 (s, 1H, N*H*), 15.30 (s, 1H, O*H*); ^{13}C NMR (DMSO-d_6): δ 20.0, 99.7, 102.9, 120.0, 128.0, 132.7, 137.4, 163.2, 166.0, 174.8, 188.7; ms (ESI+): *m/z* 364 [7, $(M+Na)^+$, ^{81}Br, ^{32}S), 362 [9, $(M+Na)^+$, ^{79}Br, ^{32}S], 342

[80, (M+H)$^+$, ^{81}Br, ^{32}S], 340 [100, (M+H)$^+$, ^{79}Br, ^{32}S]. *Anal.* Calcd. for $C_{13}H_{10}BrNO_3S$ (340.19): C, 45.90; H, 2.96; N, 4.11. Found: C, 45.95; H, 3.01; N, 4.16.

N-(2,5-Dimethoxyphenyl)-4-hydroxy-6-methyl-2H-pyran-2-one-3-carbothioamide (2c). This compound was obtained as yellow powder, mp 169–170°C; ^{1}H NMR (DMSO-d_6): δ 2.28 (s, 3H C*H*$_3$), 3.80 (s, 3H, OC*H*$_3$), 3.90 (s, 3H, OC*H*$_3$), 6.36 (s, 1H, H-5), 7.60 (d, 1H, *J* = 7.3 Hz, ArH), 7.70 (d, 1H, *J* = 7.3 Hz, ArH), 8.10 (s, 1H, ArH), 12.70 (s, 1H, N*H*), 14.90 (s, 1H, O*H*); ^{13}C NMR (DMSO-d_6): δ 20.3, 58.0, 60.0, 100.9, 102.7, 125.8, 127.0, 129.6, 131.2, 131.5, 131.8, 162.9, 165.9, 174.0, 189.6; ms (EI): *m/z* 321 (M^{+-}, 45), 233 (100), 221 (5), 189 (8), 125 (8), 116 (10), 85 (20), 69 (55). *Anal.* Calcd. for $C_{15}H_{15}NO_5S$ (321.40): C, 56.06; H, 4.70; N, 4.36. Found: C, 55.95; H, 4.57; N, 4.36.

3-[Bis(phenylamino)methylene]-6-methyl-2H,4H-pyran-2,4-dione (3a). This compound was obtained as yellow powder, mp 147–148°C; ^{1}H NMR (CDCl$_3$): δ 2.23 (s, 3H, C*H*$_3$), 5.73 (s, 1H, H-5), 6.70–6.86 (m, 5H, ArH), 7.14–7.28 (m, 5H, ArH), 12.00 (s, 1H, N*H*) 14.18 (s, 1H, O*H*); ^{13}C NMR (CDCl$_3$): δ 19.1, 19.5, 85.2, 104.4, 105.8, 108.4, 117.4, 119.8, 123.4, 126.8, 128.2, 129.3, 140.3, 142.1, 144.8, 161.0, 163.4, 168.9, 178.8, 182.5, 186.2; IR: ν (cm^{-1}) 3478, 3209, 3031, 1636, 1550, 1448, 1342, 927, 759, 696; ms (EI): *m/z* 320 (M^{+-}, 18), 227 (14), 194 (38), 93 (100), 85 (4), 69 (17). *Anal.* Calcd. for $C_{19}H_{16}N_2O_3$ (320.34): C, 71.24; H, 5.03; N, 8.74. Found: C, 71.79; H, 5.13; N, 8.72.

3-[Bis(4-bromophenylamino)methylene]-6-methyl-2H,4H-pyran-2,4-dione (3b). This compound was obtained as yellow powder, mp 159–160°C; ^{1}H NMR (DMSO-d_6): δ 2.27 (s, 3H, C*H*$_3$), 5.93 (s, 1H, H-5), 7.43 (d, *J* = 8.0 Hz, 2H, ArH), 7.49 (d, *J* = 8.1 Hz, 2H, ArH), 7.55 (d, *J* = 8.1 Hz, 2H, ArH), 7.62 (d, J = 8.0 Hz, 2H, ArH), 13.20 (s, 1H, N*H*), 14.3 (s, 1H, O*H*); ^{13}C NMR (DMSO-d_6): δ 19.6, 20.0, 88.9, 103.3, 108.0, 117.1, 119.9, 126.1, 131.8, 132.3, 135.6, 137.6, 158.7, 162.3, 165.7, 166.3, 174.9, 182.9, 188.8; ms (ESI+): *m/z* 503 [5, (M+Na)$^+$, 2 × ^{81}Br], 501 [9, (M+Na)$^+$, ^{81}Br, ^{79}Br), 499 [4, (M+Na)$^+$, 2 × ^{79}Br], 481 [50, (M+H)$^+$, 2 × ^{81}Br], 479 [100, (M+H)$^+$, ^{81}Br, ^{79}Br], 477 [52, (M+H)$^+$, 2 × ^{79}Br]. *Anal.* Calcd. for $C_{19}H_{14}Br_2N_2O_3$ (478.13): C, 47.73; H, 2.95; N, 5.86. Found: C, 47.78; H, 2.96; N, 5.88.

3-[Bis(2,5-dimethoxyphenylamino)methylene]-6-methyl-2H,4H-pyran-2,4-dione (3c). This compound was obtained as white powder, mp 186–187°C; ^{1}H NMR (DMSO-d_6): δ 2.24 (s, 3H, C*H*$_3$), 3.80 (s, 3H, OC*H*$_3$), 3.90 (s, 3H, OC*H*$_3$), 6.25 (s, 1H, H-5), 7.40 (d, *J* = 7.2 Hz, 1H, ArH), 7.58 (d, *J* = 7.2 Hz, 1H, ArH), 7.60 (s, 1H, ArH), 7.67 (d, *J* = 8.2 Hz, 1H, ArH), 7.70 (d, *J* = 8.2 Hz, 1H, ArH), 8.12 (s, 1H, ArH), 13.20 (s, 1H, N*H*), 14.20 (s, 1H, O*H*); ^{13}C NMR (DMSO-d_6): δ 19.6, 19.9, 56.6, 88.9, 100.8, 103.3, 124.3, 125.5, 125.6, 126.5, 126.9, 130.8, 131.1, 131.3, 138.8, 139.8, 140.0, 147.0, 149.0, 162.9, 164.0, 165.0, 174.9, 180.0, 189.9; ms (EI): *m/z* 440 (20), 368 (14), 358 (29), 253 (9), 233 (69), 207 (100), 85 (12), 69 (20). *Anal.* Calcd. for $C_{23}H_{24}N_2O_7$ (440.45): C, 60.52; H, H 5.30; N, 6.14. Found: C, 61.07; H, 5.61; N, 6.39.

General procedure for the synthesis of *N*-aryl-4-hydroxycoumarin-3-carbothioamides (5a,b) and *N,N′*-diaryl-4-hydroxycoumarin-3-carboximidamides (6a,b). Aryliso-thiocyanates (15 mmol) was added to a stirred solution of 0.81 g (5 mmol) of 4-hydroxycoumarin **4** and 0.8 mL (5 mmol) of triethylamine dissolved in 10 mL of DMSO. The reaction mixture was stirred at room temperature for 15 h. After the addition of 50 mL of cold water, the precipitate thus formed was filtered and washed several times with a (1:1) mixture of diethyl ether:light petroleum. The solid was in each case recrystallized from isopropyl alcohol giving *N,N′*-diaryl-4-hydroxycoumarin-3-carboximidamides **6a,b**: **6a**, 979.0 mg (55%); **6b**, 1.15 g (45%).

The aqueous layer was acidified with HCl 1*N* (pH = 4–5). After vigorous stirring at room temperature for 1.5 h, the precipitate thus formed was collected by filtration and washed several times with diethyl ether. The solid was in each case recrystallized from isopropyl alcohol giving *N*-aryl-4-hydroxycoumarin-3-carbothioamides **5a,b**: **5a**, 445.5 mg (30%); **5b**, 659.8 mg (35%).

4-Hydroxy-N-phenylcoumarin-3-carbothioamide (5a). This compound was obtained as yellow powder, mp 145–146°C; ^{1}H NMR (CDCl$_3$): δ 6.88–7.54 (m, 5H, ArH), 7.68–8.17 (m, 4H, ArH), 13.35 (s, 1H, N*H*), 17.60 (s, 1H, O*H*); ^{13}C NMR (CDCl$_3$): δ 98.2, 117.0, 124.1, 125.4, 126.2, 128.1, 128.9, 129.5, 135.7, 137.7, 152.5, 163.6, 175.1 (C—OH), 189.1 (C=S), ms (ESI+): *m/z* 320 [100, (M+Na)$^+$], 298 [45, (M+H)$^+$]. *Anal.* Calcd. for $C_{16}H_{11}NO_3S$ (297.33): C, 64.63; H, 3.73; N, 4.71. Found: C, 64.68; H, 3.71; N, 4.71.

N-(4-Bromophenyl)-4-hydroxycoumarin-3-carbothioamide (5b). This compound was obtained as yellow powder, mp 270–271°C; ^{1}H NMR (CDCl$_3$): δ 6.75 (d, 2H, *J* = 9.8 Hz, ArH), 7.17 (d, 2H, *J* = 9.8 Hz, ArH), 7.31 (t, 1H, *J* = 9.0 Hz, ArH), 7.37 (d, 1H, *J* = 9.0 Hz, ArH), 7.69 (t, 1H, *J* = 9.0 Hz, ArH), 8.12 (d, 1H, *J* = 9.0 Hz, ArH), 13.34 (s, 1H, N*H*), 17.45 (s, 1H, O*H*); ^{13}C NMR (CDCl$_3$): δ 97.3, 116.0, 123.7, 125.3, 126.8, 131.2, 131.7, 134.7, 135.7, 136.0, 151.5, 162.7, 179.4 (C—OH), 188.4 (C=S); ms (ESI+): *m/z* 400 [26, (M+Na)$^+$, ^{81}Br], 398 [29, (M+Na)$^+$, ^{79}Br], 378 [96, (M+H)$^+$, ^{81}Br], 376 [100, (M+H)$^+$, ^{79}Br]. *Anal.* Calcd. for $C_{16}H_{10}BrNO_3S$ (376.23): C, 51.08; H, 2.68; N, 3.72. Found: C, 51.39; H, 3.04; N, 3.95.

4-Hydroxy-N,N′-diphenylcoumarin-3-carboximidamide (6a). This compound was obtained as white powder, mp 179–180°C; ^{1}H NMR (CDCl$_3$): δ 6.82–7.68 (m, 10 H, ArH), 8.05–8.10 (m, 4H, ArH), 13.30 (s, 1H, N*H*), 17.54 (s, 1H, O*H*); ^{13}C NMR (CDCl$_3$): δ 89.3, 97.7, 116.2, 116.5, 120.7, 123.6, 124.0, 124.9, 125.7, 125.8, 127.6, 128.4, 129.0, 135.2, 136.0, 137.2, 152.0, 152.6, 158.7, 163.0, 165.9, 174.6, 179.6, 188.6; IR: ν (cm^{-1}) 3479, 3407, 3235, 1617, 1381, 1048, 754; ms (ESI+): *m/z* 379 [80, (M+Na)$^+$], 357 [100, (M+H)$^+$]. *Anal.* Calcd. for $C_{22}H_{16}N_2O_3$ (356.34): C, 74.15; H, 4.53; N, 7.86. Found: C, 73.60; H, 4.52; N, 7.88.

N,N′-Di(4-bromophenyl)-4-hydroxycoumarin-3-carboximidamide (6b). This compound was obtained as white powder, mp 235–236°C; ^{1}H NMR (CDCl$_3$): δ 6.74 (d, 2H, *J* = 9.6 Hz, ArH), 7.17 (d, 2H, *J* = 8.7 Hz, ArH), 7.28 (d, 1H, *J* = 9.3 Hz, ArH), 7.31 (d, 2H, *J* = 8.7 Hz, ArH), 7.37 (t, 1H, *J* = 9.3 Hz, ArH), 7.55 (d, 2H, *J* = 9.6 Hz, ArH), 7.69 (t, 1H, *J* = 9.3 Hz, ArH), 8.12 (d, 1H, *J* = 9.3 Hz, ArH), 13.35 (s, 1H, N*H*), 17.46 (s, 1H, O*H*); ^{13}C NMR (CDCl$_3$): δ 89.4, 97.4, 116.1, 122.2, 123.8, 124.5, 124.7, 126.9, 131.3, 135.7, 149.2, 151.6, 158.7, 162.7, 166.0, 174.3, 180.2, 189.5; ms (EI): *m/z* 512 (40), 449 (9), 447 (10), 359 (18), 357 (20), 216 (15), 215 (100), 214 (15), 213 (99), 183 (3.9), 181 (4), 158 (2.5), 156 (3), 155 (25), 143 (2), 134 (50), 117 (2), 107 (9), 76 (8). *Anal.*

Calcd. for $C_{22}H_{14}Br_2N_2O_3$ (514.17): C, 51.39; H, 2.74; N, 5.45. Found: C, 51.64; H, 2.80; N, 5.51.

General procedure for the synthesis of 4-acetoacetyl-3-arylamino-4,5-dihydro-5*H*-pyrazol-5-ones (10a–c). Acetic acid (10 mL) and 5 mL ethanol were added to a mixture of *N*-aryl-4-hydroxy-6-methyl-2*H*-pyran-2-one-3-carbothioamides **2a–c** (10 mmol) and 5 mL (0.1 mol) of hydrazine hydrate. The reaction mixture was refluxed for 5 h and poured into crushed ice, and then the solid was collected by filtration, washed with water, and with a (1:1) mixture of water:ethanol. The solid was in each case recrystallized from A (1:1) mixture of ethanol:acetone giving 4-acetoacetyl-3-arylamino-4,5-dihydro-5*H*-pyrazol-5-ones **10a–c** (which are in equilibrium with the corresponding enolic form): **10a**, 2.47 g (95%); **10b**, 3.21 g (95%); **10c**, 3.13 g (98%).

4-Acetoacetyl-3-phenylamino-4,5-dihydro-5H-pyrazol-5-one (10a). This compound was obtained as green powder, mp 179–180°C; ^{1}H NMR ($CDCl_3$): δ 2.06 (s, CH_3-enol), 2.32 (s, CH_3-dione), 3.90 (s, 1H, H-4), 4.40 (s, CH_2-dione), 6.11 (s, C*H*-enol), 7.31–7.53 (m, 5H, ArH), 8.60 (s, 1H, N*H*), 13.15 (s, 1H, N*H*), 16.70 (s, 1H, O*H*); ^{13}C NMR ($CDCl_3$): δ 20.7, 64.0, 97.2, 104.0, 126.0, 127.6, 129.6, 137.3, 164.2, 164.5, 177.9, 188.3; ms (EI): *m/z* 260 [100, $(M+H)^+$], 228 (80), 217 (9), 203 (7), 175 (20), 93 (67), 77 (47), 85 (50), 56 (14), 43 (20). *Anal.* Calcd. for $C_{13}H_{13}N_3O_3$ (259.26): C, 60.23; H, 5.02; N, 16.22. Found: C, 60.73; H, 5.38; N, 16.45.

4-Acetoacetyl-3-(4-bromophenylamino)-4,5-dihydro-5H-pyrazol-5-one (10b). This compound was obtained as green powder, mp 200–202°C; ^{1}H NMR ($CDCl_3$): δ 2.07 (s, CH_3-enol), 2.32 (s, CH_3-dione), 3.91 (s, 1H, H-4), 4.40 (s, CH_2-dione), 6.11 (s, C*H*-enol), 7.40 (d, 2H, $J = 9.1$ Hz, ArH), 7.56 (d, 2H, $J = 9.1$ Hz, ArH), 8.62 (s, 1H, N*H*), 13.15 (s, 1H, N*H*), 16.50 (s, 1H, O*H*); ^{13}C NMR ($CDCl_3$): δ 20.1, 65.0, 97.3, 104.0, 121.0, 127.3, 132.2, 136.3, 164.1, 164.7, 178.0, 188.6; ms (ESI+): *m/z* 362 [96, $(M+Na)^+$, ^{81}Br], 360 [100, $(M+Na)^+$, ^{79}Br], 340 [45, $(M+H)^+$, ^{81}Br], 338 [50, $(M+H)^+$, ^{79}Br]. *Anal.* Calcd. for $C_{13}H_{12}BrN_3O_3$ (338.16): C, 46.29; H, 3.56; N, 12.46. Found: C, 45.74; H, 3.20; N, 12.23.

4-Acetoacetyl-3-(2,5-dimethoxyphenylamino)-4,5-dihydro-5H-pyrazol-5-one (10c). This compound was obtained as green powder, mp 186–187°C; ^{1}H NMR ($CDCl_3$): δ 2.07 (s, CH_3-enol), 2.33 (s, CH_3-dione), 3.86 (s, 1H, H-4), 3.93 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.30 (s, CH_2-dione), 6.13 (s, C*H*-enol), 7.37 (d, 1H, $J = 8.9$ Hz, ArH), 7.49 (d, 1H, $J = 8.9$ Hz, ArH), 7.70 (s, 1H, ArH), 7.90 (s, 1H, N*H*), 13.00 (s, 1H, N*H*), 16.40 (s, 1H, O*H*); ^{13}C NMR ($CDCl_3$): δ 20.1, 54.0, 58.0, 65.0, 104.0, 122.7, 125.2, 127.5, 131.3, 132.9, 136.6, 164.1, 164.9, 178.0, 188.0; ms (ESI+): *m/z* 342 [100, $(M+Na)^+$], 320 [33, $(M+H)^+$]. *Anal.* Calcd. for $C_{15}H_{17}N_3O_5$ (319.31): C, 56.43; H, 5.33; N, 13.16. Found: C, 56.98; H, 5.34; N, 13.70.

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A New Route to Allyl Thiols and Allyl Thiocarbamates from Baylis-Hillman Adducts

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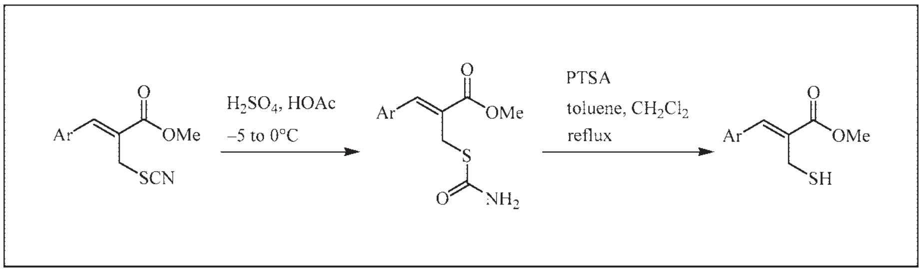

A facile synthesis of trisubstituted allyl thiols and allyl thiocarbamates has been accomplished from Baylis-Hillman adducts through bromination, thiocyanation, and acid-assisted hydrolysis reaction.

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INTRODUCTION

Thiols have attained significant importance as synthetic intermediates for valuable sulfur-containing compounds [1]. A number of reports have appeared on the potential applications of thiol functionality in various scientific disciplines such as pharmaceutical chemistry [2], self-assembled monolayers [3], nanoparticles [4], and conducting polymers [5]. Also, *S*-alkyl thiocarbamates are an important class of compounds that have received considerable attention [6,7] because of their numerous biological effects including anesthetic [8], fungicidal [9], bactericidal [9,10], pesticidal [11,12], and antiviral [13]. Despite the aforementioned reasons, thiocarbamates are most noted for their use as commercial herbicides [14].

Generally, thiols have been synthesized mainly from alkyl halides with thioacetate ion followed by deacetylation with base [15], disulfides *via* reduction [16], alkenes *via* anti-Markovnikov addition of thiolacetic acid, followed by deacetylation with strong base [17], alcohols *via* refluxing with hydrobromic acid and thiourea, followed by hydrolysis with strong base [18], thiocyanates *via* reduction [19], and thiocarbamates *via* hydrolysis [20]. The most widely used method for the preparation of thiocarbamates makes use of gaseous carbonyl sulfides and an amine, followed by subsequent treatment with base and alkyl halide [12,21], condensation of a thiol with an isocyanate [10], nucleophilic substitution of trichloroacetyl chloride with a thiol, followed by treatment of an amine [22], and the hydration of an organic thiocyanate [23,24]. In view of their significance in organic synthesis, it is still necessary to extend the scope of the allyl thiol and thiocarbamate families and develop new and convenient synthetic routes. Here the Baylis-Hillman (BH) chemistry [25] has been applied for the synthesis of these compounds.

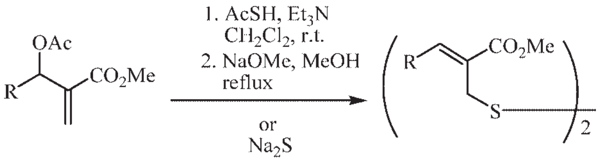
RESULTS AND DISCUSSION

The BH reaction is well known as a powerful carbon–carbon bond forming methods in organic synthesis [26]. Nucleophilic displacement of BH acetates or bromides is an important protocol for the synthesis of trisubstituted alkenes. Although there exist several methods for the nucleophilic displacement of BH acetates or bromides with various reagents [27], displacement with sulfur nucleophiles is limited [28].

Recently, we reported substitution reaction of BH acetates **1** with thiolacetic acid followed by deacetylation with base [29], and with sodium sulfide [30] to give the symmetric diallyl disulfides **2**, respectively, as shown in Scheme 1. No traces of the intended allyl thiols were produced. Although the literature has reported some interesting schemes to obtain allyl thiols, we felt that thiols can be obtained from allyl thiocyanates.

The known allyl thiocyanates **4** were obtained in high yields by displacement of 2-(bromomethyl)alkenoates with sodium thiocyanate [31], derived from BH adducts with *N*-bromosuccinimide-dimethyl sulfide [32]. Treatment of allyl thiocyanates **4** with 95% sulfuric acid–acetic acid (9:1, v/v) at −5 to 0°C produced allyl thiocarbamates **5** in 54–96% yields. On hydrolysis reaction of **5**

Scheme 1



1 2

with one equivalent of *p*-toluenesulfonic acid monohydrate (PTSA) in toluene and dichloromethane (9:1, v/v) reflux temperature, allyl thiols **6** were obtained in 75–94% yields (Scheme 2, Table 1). When using 0.1 equivalent of PTSA, the reaction was sluggish and the yield was low (Entries 1, 2, 7). Direct one-pot transformation of thiocyanate **4** to thiol **6** was unsuccessful with PTSA in refluxing toluene. All the products are unambiguously characterized using infrared spectra, ^{1}H and ^{13}C NMR data. In the ^{1}H NMR spectra, the characteristic chemical shift of the thiol protons of **6** were found at $\delta = 2.05$–2.12 as a triplet ($J = 7.6$–8.3 Hz), the methylene protons were observed at $\delta = 3.33$–3.60 as a doublet ($J = 7.6$–8.3 Hz), and the methine protons resonated at $\delta = 7.63$–7.92 as a singlet. Their infrared spectra showed absorption at 2557–2593 cm^{-1} for the thiol band.

CONCLUSION

In conclusion, a new method for the synthesis of trisubstituted allyl thiols from BH adducts has been developed through bromination, thiocyanation, and acid-assisted hydrolysis reaction.

EXPERIMENTAL

Silica gel 60 (70–230 mesh ASTM) used for column chromatography was supplied by E. Merck. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F$_{254}$ TLC plates. Melting points were measured by an Electrothermal melting point apparatus and were uncorrected. Microanalysis was obtained using a Thermo Electron Corporation Flash EA 1112 element analyzer. Infrared spectra were recorded with a Nicolet Magna 550 FTIR spectrometer. The ^{1}H and ^{13}C NMR spectra were measured on a Gemini 300 spectrometer using deuteriochloroform. All chemical shifts are reported in parts per million relative to tetramethylsilane. The coupling constants (*J*) are expressed in Hertz.

The known methyl 3-aryl-2-(thiocyanatomethyl)propenoates **4** were prepared according to the literature procedure [31].

General procedure for the preparation of methyl (*Z*)-3-aryl-2-(carbamoylthiomethyl)propenoates 5. To an ice-cold mixture of 95% sulfuric acid (9 mL) and acetic acid (1 mL), allyl thiocyanate **4** (2 mmoles) was added in small portions for 15 min under stirring at −5 to 0°C. After dissolution of **4**, the mixture was stirred at room temperature for 0.5–2.5 h and then poured onto crushed ice. The white precipitate was collected by suction filtration, dried, and crystallized from dichloromethane and petroleum ether to give compound **5**.

The physical and spectral data of **5** prepared by this general method are as follows.

Methyl (Z)-2-carbamoylthiomethyl-3-phenylpropenoate (5a). Reaction time: 1 h; white solid; yield: 75%; mp: 99–100°C; ir (potassium bromide): 3419, 3327, 3182, 1707, 1675, 1597 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.85 (s, 3 H, OCH$_3$), 4.11 (s, 2 H, CH$_2$), 5.58 (s, 2 H, NH$_2$), 7.37–7.47 (m, 5 H, aromatic), 7.82 (s, 1 H, CH); ^{13}C NMR (deuteriochloroform): δ 27.8, 52.4, 127.1, 128.7, 129.3, 129.5, 134.4, 142.5, 167.6, 168.4. *Anal.* Calcd. for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.57; S, 12.76. Found: C, 57.20; H, 5.07; N, 5.39; S, 12.53.

Methyl (Z)-2-carbamoylthiomethyl-3-(4-chlorophenyl)propenoate (5b). Reaction time: 1 h; white solid; yield: 84%; mp: 108–109°C; ir (potassium bromide): 3396, 3298, 3202, 1707, 1655, 1619, 1592 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.85 (s, 3 H, OCH$_3$), 4.07 (s, 2 H, CH$_2$), 5.50 (s, 2 H, NH$_2$), 7.40 (s, 4 H, aromatic), 7.75 (s, 1 H, CH); ^{13}C NMR (deuteriochloroform): δ 27.7, 52.4, 127.7, 129.0, 130.9, 132.8, 135.3, 141.0, 167.4, 168.2. *Anal.* Calcd. for $C_{12}H_{12}ClNO_3S$: C, 50.44; H, 4.23; N, 4.90; S, 11.22. Found: C, 50.19; H, 4.08; N, 5.20; S, 10.96.

Scheme 2

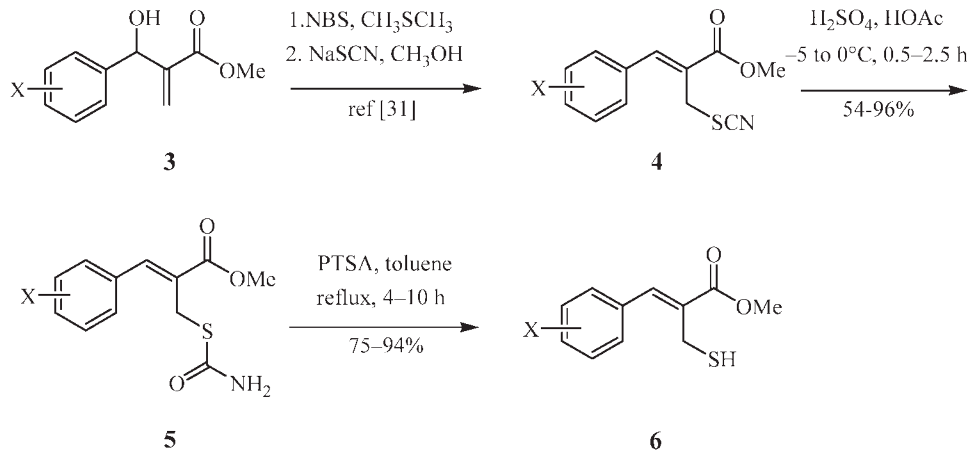


Table 1

Allyl thiocarbamates **5** and allyl thiols **6**.

Entry	X	Reactant	Time (h)	Product	Yield (%)	Time[a] (h)	Product	Yield[a] (%)
1	H	**4a**	1	**5a**	75	7 (32)	**6a**	94 (82)
2	4-Cl	**4b**	1	**5b**	84	4 (56)	**6b**	89 (77)
3	2-Cl	**4c**	2.5	**5c**	85	10	**6c**	83
4	2-Br	**4d**	2	**5d**	86	5	**6d**	77
5	2-F	**4e**	1	**5e**	87	5	**6e**	78
6	4-NO_2	**4f**	1	**5f**	96	6	**6f**	85
7	2-NO_2	**4g**	0.5	**5g**	89	4 (26)	**6g**	94 (68)
8	4-Me	**4h**	1	**5h**	54	7	**6h**	75

[a] Values in parentheses indicate when 0.1 equivalent of PTSA was used.

Methyl (Z)-2-carbamoylthiomethyl-3-(2-chlorophenyl)propenoate (5c). Reaction time: 2.5 h; white solid; yield: 85%; mp: 102–103°C; ir (potassium bromide): 3419, 3326, 3308, 1698, 1662, 1607, 1438 cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.87 (s, 3 H, OCH_3), 3.97 (s, 2 H, CH_2), 5.42 (s, 2 H, NH_2), 7.30–7.46 (m, 4 H, aromatic), 7.89 (s, 1 H, CH); ^{13}C NMR (deuteriochloroform): δ 27.7, 52.5, 126.8, 129.5, 129.6, 130.1, 130.2, 133.2, 134.1, 139.3, 167.0, 168.1. *Anal.* Calcd. for $C_{12}H_{12}ClNO_3S$: C, 50.44; H, 4.23; N, 4.90; S, 11.22. Found: C, 50.22; H, 4.12; N, 4.76; S, 11.03.

Methyl (Z)-3-(2-bromophenyl)-2-(carbamoylthiomethyl)propenoate (5d). Reaction time: 2 h; white solid; yield: 86%; mp: 93–95°C; ir (potassium bromide): 3418, 3334, 1712, 1673, 1465, 1435 cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.87 (s, 3 H, OCH_3), 3.94 (s, 2 H, CH_2), 5.47 (s, 2 H, NH_2), 7.20–7.39 (m, 3 H, aromatic), 7.62–7.64 (m, 1 H, aromatic), 7.82 (s, 1 H, CH); ^{13}C NMR (deuteriochloroform): δ 27.6, 52.5, 124.0, 127.4, 129.3, 130.2, 130.3, 132.8, 135.1, 141.4, 167.0, 168.0. *Anal.* Calcd. for $C_{12}H_{12}BrNO_3S$: C, 43.65; H, 3.66; N, 4.24; S, 9.71. Found: C, 43.42; H, 3.40; N, 4.38; S, 9.52.

Methyl (Z)-2-(carbamoylthiomethyl)-3-(2-fluorophenyl)propenoate (5e). Reaction time: 1 h; white solid; yield: 87%; mp: 102–104°C; ir (potassium bromide): 3421, 3323, 3310, 3193, 1701, 1662, 1610, 1485, 1438 cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.86 (s, 3 H, OCH_3), 4.04 (s, 2 H, CH_2), 5.42 (s, 2 H, NH_2), 7.09–7.49 (m, 4 H, aromatic), 7.85 (s, 1 H, CH); ^{13}C NMR (deuteriochloroform): δ 27.8, 52.4, 115.6 (J = 22.0 Hz), 122.5 (J = 13.4 Hz), 124.2, 129.6, 130.2, 131.0, 134.7, 160.4 (J = 250 Hz), 167.0, 168.3. *Anal.* Calcd. for $C_{12}H_{12}FNO_3S$: C, 53.52; H, 4.49; N, 5.20; S, 11.91. Found: C, 53.70; H, 4.37; N, 5.02; S, 11.76.

Methyl (Z)-2-(carbamoylthiomethyl)-3-(4-nitrophenyl)propenoate (5f). Reaction time: 1 h; white solid; yield: 96%; mp: 144–145°C; ir (potassium bromide): 3401, 3324, 1717, 1633, 1592, 1517, 1345 cm^{-1}; ^1H NMR (dimethyl sulfoxide-d_6): δ 3.78 (s, 3 H, OCH_3), 3.90 (s, 2 H, CH_2), 7.66 (s, 2 H, NH_2), 7.73 (s, 1H, CH), 7.76 (d, 2 H, J = 8.8 Hz, aromatic), 8.27 (d, 2 H, J = 8.8 Hz, aromatic); ^{13}C NMR (dimethyl sulfoxide-d_6): δ 26.2, 52.4, 123.6, 130.6, 131.6, 137.9, 141.1, 147.2, 165.7, 166.6. *Anal.* Calcd. for $C_{12}H_{12}N_2O_5S$: C, 48.64; H, 4.08; N, 9.45; S, 10.82. Found: C, 48.39; H, 4.27; N, 9.28; S, 10.63.

Methyl (Z)-2-(carbamoylthiomethyl)-3-(2-nitrophenyl)propenoate (5g). Reaction time: 0.5 h; white solid; yield: 89%; mp: 113–114°C; ir (potassium bromide): 3436, 3335, 3175, 1712, 1680, 1606, 1522, 1437, 1344 cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.79 (s, 2 H, CH_2), 3.87 (s, 3 H, OCH_3), 5.37 (s, 2 H, NH_2), 7.37–7.73 (m, 3 H, aromatic), 8.06 (s, 1 H, CH), 8.21–8.24 (m, 1 H, aromatic); ^{13}C NMR (deuteriochloroform): δ 27.3, 52.5, 124.9, 129.4, 129.5, 130.9, 131.2, 133.7, 139.2, 147.3, 166.7, 167.8. *Anal.* Calcd. for $C_{12}H_{12}N_2O_5S$: C, 48.64; H, 4.08; N, 9.45; S, 10.82. Found: C, 48.40; H, 3.88; N, 9.20; S, 10.59.

Methyl (Z)-2-(carbamoylthiomethyl)-3-(4-methylphenyl)propenoate (5h). Reaction time: 1 h; white solid; yield: 54%; mp: 119–120°C; ir (potassium bromide): 3376, 3298, 1699, 1678, 1616, 1436 cm^{-1}; ^1H NMR (deuteriochloroform): δ 2.38 (s, 3 H, CH_3), 3.84 (s, 3 H, OCH_3), 4.13 (s, 2 H, CH_2), 5.49 (s, 2 H, NH_2), 7.23 (d, 2 H, J = 7.9 Hz, aromatic), 7.37 (d, 2 H, J = 7.9 Hz, aromatic), 7.80 (s, 1 H, CH); ^{13}C NMR (deuteriochloroform): δ 21.4, 28.0, 52.3, 126.0, 129.5, 129.7, 131.5, 139.6, 142.6, 167.8, 168.6. *Anal.* Calcd. for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28; S, 12.09. Found: C, 58.61; H, 5.43; N, 5.03; S, 12.31.

General procedure for the preparation of methyl (Z)-3-aryl-2-(mercaptomethyl)propenoates 6. A stirred solution of thiocarbamate **5** (1 mmole) and PTSA (0.19 g, 1 mmole) in a mixture of toluene (9 mL) and dichloromethane (1 mL) was heated at reflux temperature for 4–10 h. After cooling to room temperature, the mixture was diluted with saturated aqueous sodium bicarbonate solution (5 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over anhydrous magnesium sulfate and the solvent was evaporated *in vacuo.* The resulting mixture was chromatographed on silica gel eluting with hexane/ethyl acetate (15:1) to produce **6**.

The physical and spectral data of **6** prepared by this general method are as follows.

Methyl (Z)-2-(mercaptomethyl)-3-phenylpropenoate (6a). Reaction time: 7 h; colorless oil; yield: 94%; ir (neat): 2571, 1712, 1628, 1493, 1447, 1434 cm^{-1}; ^1H NMR (deuteriochloroform): δ 2.06 (t, 1 H, J = 7.9 Hz, SH), 3.60 (d, 2 H, J = 7.9 Hz, CH_2), 3.87 (s, 3 H, OCH_3), 7.35–7.45 (m, 5 H, aromatic), 7.70 (s, 1 H, CH); ^{13}C NMR (deuteriochloroform): δ 21.2, 52.2, 128.7, 129.0, 129.3, 131.8, 134.8, 139.7, 167.4. *Anal.* Calcd. for $C_{11}H_{12}O_2S$: C, 63.43; H, 5.81; S, 15.40. Found: C, 63.19; H, 5.75; S, 15.27.

Methyl (Z)-3-(4-chlorophenyl)-2-(mercaptomethyl)propenoate (6b). Reaction time: 4 h; colorless oil; yield: 89%; ir (neat): 2573, 1712, 1630, 1591, 1489, 1435 cm^{-1}; ^1H NMR (deuteriochloroform): δ 2.06 (t, 1 H, $J = 7.6$ Hz, SH), 3.55 (d, 2 H, $J = 7.6$ Hz, CH_2), 3.86 (s, 3 H, OCH_3), 7.36–7.41 (m, 4 H, aromatic), 7.63 (s, 1 H, CH); ^{13}C NMR (deuteriochloroform): δ 21.1, 52.3, 129.0, 130.7, 132.3, 133.2, 135.0, 138.3, 167.1. *Anal*. Calcd. for $C_{11}H_{11}ClO_2S$: C, 54.43; H, 4.57; S, 13.21. Found: C, 54.22; H, 4.29; S, 12.90.

Methyl (Z)-3-(2-chlorophenyl)-2-(mercaptomethyl)propenoate (6c). Reaction time: 10 h; colorless oil; yield: 83%; ir (neat): 2582, 1714, 1633, 1468, 1436 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ2.08 (t, 1 H, $J = 8.3$ Hz, SH), 3.45 (d, 2 H, $J = 8.3$ Hz, CH_2), 3.88 (s, 3 H, OCH_3), 7.31–7.48 (m, 4 H, aromatic), 7.76 (s, 1 H, CH); ^{13}C NMR (deuteriochloroform): δ 21.3, 52.4, 126.9, 129.7, 129.9, 130.0, 133.5, 133.6, 134.1, 136.5, 166.8. *Anal*. Calcd. for $C_{11}H_{11}ClO_2S$: C, 54.43; H, 4.57; S, 13.21. Found: C, 54.31; H, 4.40; S, 13.03.

Methyl (Z)-3-(2-bromophenyl)-2-(mercaptomethyl)propenoate (6d). Reaction time: 5 h; colorless oil; yield: 77%; ir (neat): 2574, 1714, 1633, 1464, 1434 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.07 (t, 1 H, $J = 8.0$ Hz, SH), 3.43 (d, 2 H, $J = 8.0$ Hz, CH_2), 3.89 (s, 3 H, OCH_3), 7.23–7.65 (m, 4 H, aromatic), 7.70 (s, 1 H, CH); ^{13}C NMR (deuteriochloroform): δ 21.2, 52.4, 124.0, 127.5, 130.0, 130.2, 132.9, 133.3, 135.4, 138.7, 166.8. *Anal*. Calcd. for $C_{11}H_{11}BrO_2S$: C, 46.01; H, 3.86; S, 11.17. Found: C, 45.88; H, 3.60; S, 11.31.

Methyl (Z)-3-(2-fluorophenyl)-2-(mercaptomethyl)propenoate (6e). Reaction time: 5 h; white solid; yield: 78%; mp 32–34°C; ir (potassium bromide): 2557, 1708, 1632, 1608, 1482, 1461, 1434 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.08 (t, 1 H, $J = 7.9$ Hz, SH), 3.52 (d, 2 H, $J = 7.9$ Hz, CH_2), 3.87 (s, 3 H, OCH_3), 7.08–7.51 (m, 4 H, aromatic), 7.72 (s, 1 H, CH); ^{13}C NMR (deuteriochloroform): δ 21.4, 52.3, 115.8 ($J =$ 22.0 Hz), 122.8 ($J = 13.4$ Hz), 130.1, 130.8, 130.9, 132.1, 133.8, 160.4 ($J = 250$ Hz), 166.8. *Anal*. Calcd. for $C_{11}H_{11}FO_2S$: C, 58.39; H, 4.90; S, 14.17. Found: C, 58.52; H, 4.72; S, 14.02.

Methyl (Z)-2-(mercaptomethyl)-3-(4-nitrophenyl)propenoate (6f). Reaction time: 6 h; yellowish solid; yield: 85%; mp 78–80°C; ir (potassium bromide): 2593, 1717, 1633, 1592, 1517, 1434, 1345 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.12 (t, 1 H, $J = 7.7$ Hz, SH), 3.53 (d, 2 H, $J = 7.7$ Hz, CH_2), 3.90 (s, 3 H, OCH_3), 7.60 (d, 2 H, $J = 8.3$ Hz, aromatic), 7.70 (s, 1 H, CH), 8.28 (d, 2 H, $J = 8.8$ Hz, aromatic); ^{13}C NMR (deuteriochloroform): δ 21.0, 52.6, 123.9, 130.0, 134.9, 136.8, 141.3, 147.6, 166.5. *Anal*. Calcd. for $C_{11}H_{11}NO_4S$: C, 52.16; H, 4.38; N, 5.53; S, 12.66. Found: C, 51.90; H, 4.02; N, 5.32; S, 12.37.

Methyl (Z)-2-(mercaptomethyl)-3-(2-nitrophenyl)propenoate (6g). Reaction time: 4 h; yellowish solid; yield: 94%; mp 48–49°C; ir (potassium bromide): 2569, 1721, 1635, 1605, 1569, 1513, 1429, 1337 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.08 (t, 1 H, $J = 8.2$ Hz, SH), 3.33 (d, 2 H, $J = 8.2$ Hz, CH_2), 3.89 (s, 3 H, OCH_3), 7.53–7.74 (m, 3 H, aromatic), 7.92 (s, 1 H, CH), 8.18–8.21 (m, 1 H, aromatic); ^{13}C NMR (deuteriochloroform): δ 21.2, 52.4, 125.1, 129.6, 130.8, 131.0, 133.1, 133.8, 136.4, 147.4, 166.4. *Anal*. Calcd. for $C_{11}H_{11}NO_4S$: C, 52.16; H, 4.38; N, 5.53; S, 12.66. Found: C, 52.03; H, 4.11; N, 5.42; S, 12.82.

Methyl (Z)-2-(mercaptomethyl)-3-(4-methylphenyl)-propenoate (6h). Reaction time: 7 h; colorless oil; yield: 75%; ir (neat): 2566, 1710, 1627, 1608, 1511, 1435 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.05 (t, 1 H, $J = 7.6$ Hz, SH), 2.38 (s, 3 H, CH_3), 3.60 (d, 2 H, $J = 7.6$ Hz, CH_2), 3.85 (s, 3H, OCH_3), 7.23 (d, 2 H, $J = 7.9$ Hz, aromatic), 7.35 (d, 2 H, $J =$ 7.9 Hz, aromatic), 7.67 (s, 1 H, CH); ^{13}C NMR (deuteriochloroform): δ 21.3, 21.4, 52.2, 129.4, 129.5, 130.9, 131.9, 139.3, 139.8, 167.5. *Anal*. Calcd. for $C_{12}H_{14}O_2S$: C, 64.83; H, 6.35; S, 14.42. Found: C, 64.61; H, 6.22; S, 14.28.

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Reactivity of 3-Cyano-*N*-ethoxycarbonyl-iminocoumarin with Hydrazides as N-Nucleophiles

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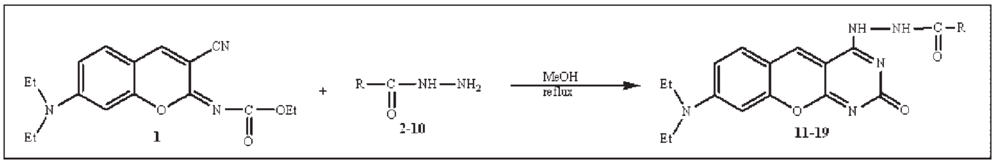

Condensation of 3-cyano-7-diethylamino-*N*-ethoxycarbonyl-iminocoumarin with various hydrazides as N-nucleophiles gave a new series of 2-oxo-2*H*-1-benzopyrano[2,3-*d*]pyrimidines bearing an acylhydrazino fragment in the 4-position. The structures of the products obtained were characterized using IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. The optical properties were reported for three of these compounds.

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INTRODUCTION

Benzopyranopyrimidines have been increasingly investigated because of their important biological properties. They exhibit for example anticancer [1,2], analgesic [3], and antithrombotic [4] activities. In addition, benzopyranopyrimidines could also be of interest because their structure is close to that of rhodols, rhodamines, and fluoresceins [5], which constitute a well-known class of dyes. Different routes have been described in the literature for the synthesis of this class of condensed heterocycles [6–8]. As part of our investigations on the synthesis of benzopyranopyrimidines, we have reported previously [9], a new method based on the transformation of 3-cyano-iminocoumarins under the action of primary aliphatic and aromatic amines, on heating in methanol. We have shown that the reaction proceeded by an original mechanism that involves several consecutive steps including nucleophilic attack of the iminolactone ring, pyran ring opening, E/Z isomerization, and subsequent cyclization. As a continuation of our studies on the reactivity of 3-cyano-iminocoumarins with N-nucleophiles, we wish to report in this article on the condensation of 3-cyano-7-diethylamino-*N*-ethoxycarbonyl-iminocoumarin **1** with different hydrazides. The aim is to obtain a new series of benzopyranopyrimidines incorporating an acylhydrazino fragment in the 4-position, since the presence of this function could improve physiological activities. The optical properties of some benzopyranopyrimidines were also regarded.

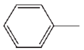
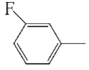
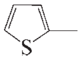
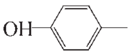
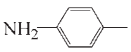
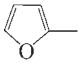
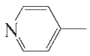
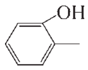
RESULTS AND DISCUSSION

Iminocoumarin **1** was obtained by Knoevenagel condensation followed by *N*-ethoxycarbonylation as previously described in [9]. The condensation of this compound with various hydrazides (**2–11**, see Table 1) was studied, first focusing on a specific system, namely **1** and benzoic hydrazide **2** (Scheme 1), to determine the best conditions for synthesis. The progress of the reaction was followed by TLC analysis and by the changes in FTIR spectra of samples taken at regular intervals from the reaction medium. Thus, the FTIR spectra showed the progressive disappearance of the original peaks at 2214 and 1724 cm^{-1} arising from the C≡N and COOEt functions, respectively, as well as the appearance of characteristic peaks of the pyrimidine moiety at 1632 cm^{-1} (C=N), 1664 cm^{-1} (NH—NH—C=O) and 1644 cm^{-1} (C=0). The best result was obtained by refluxing the mixture of **1** and **2** in methanol during 2 h. 4-(2-Benzoylhydrazino)-8-diethylamino-2-oxo-2*H*-1-benzopyrano[*2,3-d*]pyrimidine (**11**) was thus obtained with a yield of 92% (Scheme 1). This product was isolated by simple filtration with high purity as confirmed by ^{1}H NMR, which showed the absence of resonance at 1.37 and 4.32 ppm arising from the original ethoxy fragment, and the presence of two peaks in the region of 10–11 ppm indicating the presence of the NH—NH—CO function.

When the reaction was carried out in acetic acid at room temperature the condensation of **1** with **2** did not

Table 1

Benzopyranopyrimidines obtained by condensation of iminocoumarin (**1**) with various hydrazides.

Hydrazide (RC(O)NH NH_2)	R	Benzopyranopyrimidine	Time (h)	Yield (%)
2		11	2	92
3		12	3	63
4		13	7	52
5		14	1	87
6		15	2	75
7		16	8	48
8		17	16	70
9	CH_3	18	1	45
10		19	3	85

Reaction time and yield according to the nature of substituent R.

take place and no benzopyranopyrimidine **11** was detected. It was found that **1** reacted intramolecularly in these conditions to produce the oxidized derivative **11a** (Scheme 1). This type of compound was reported by Blythin *et al.* [10] when carrying out the Knoevenagel reaction with salicylaldehydes and *N*-cyanoacety-lurethane.

On sight of these results, compound **1** was then condensed with hydrazides **3–10** at reflux in methanol and the progress of the reaction was monitored by TLC. The reagent specific structure induced changes in reactivity and the reaction time had to be modified (Table 1).

In each case, the reaction afforded the corresponding 4-acylhydrazinobenzopyranopyrimidine **12–19** as shown in Scheme 2 that summarizes the synthesis. The FTIR and NMR data relative to these compounds were in good agreement with their structure. It is interesting to note that the presence of both amine and hydrazide functions in hydrazide **6** could lead to the formation of two isomers (**15** and **15a**) resulting from the interaction of the imidic carbon with the two N-nucleophilic centers in the first step of the mechanism (Scheme 3). However, chromatographic and spectroscopic analyses showed that the iminocoumarin was selectively converted into **15** whereas **15a** was not detected, probably because the amine function is less nucleophilic than the hydrazide function. The structure of **15** was clearly confirmed by the ^1H NMR spectrum, which showed the presence of Ar—NH_2 (s, 2H, 5.71 ppm), NH—NH—CO (s, 1H, 10.16 ppm and s, 1H, 10.60 ppm) and the absence of peak around 4–5 ppm related to the NH_2 group of the hydrazidic fragment.

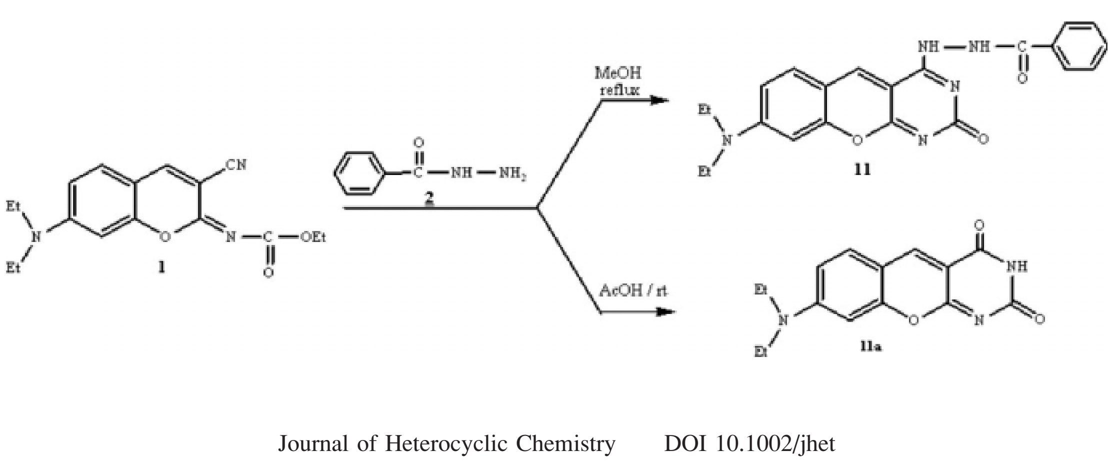
OPTICAL PROPERTIES

The electron conjugated system of benzopyranopyrimidines **11–19** is identical and should be poorly affected by the nature of the R substituent. It can therefore be expected that all these compounds share common spectroscopic behaviour. The optical properties were measured on three of them (namely compounds **12**, **13**, and **15**). The results are gathered in Table 2.

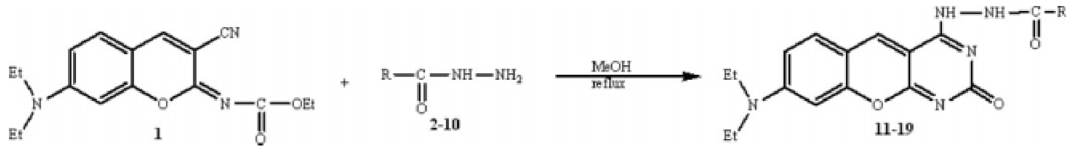
Compounds **12**, **13**, and **15** were poorly soluble in organic solvents. All were studied in dimethylsulfoxide, but only two of them could be dissolved in dichloromethane. The solutions were filtered on paper filter prior to spectroscopic study. However, for most of the samples, the absorption spectrum was particularly wide, with a markedly high baseline. This indicates that in spite of filtration, some particles were present in solution and scattered light.

For each sample, the excitation spectrum was much narrower than the absorption spectrum. For compound **13**, both spectra had almost the same maximum. For **15**

Scheme 1



Scheme 2. General scheme of the synthesis. Substitutent R as described in Table 1.



and **12**, the excitation spectra showed a considerable blue shift reaching 50 nm compared with the absorption spectra. Besides, the excitation spectra did not vary with the emission wavelength, and conversely, the emission spectra were independent of the excitation wavelength. This indicates the presence of only one fluorophore in each solution. The discrepancy between the absorption and excitation spectra could thus be attributed to the presence of nonfluorescent impurities. But, the TLC analyses of the three compounds gave a single spot, so the presence of impurities could be discarded. Consequently, it is most likely that these poorly soluble compounds form nonfluorescent aggregates in solution, these aggregates being particularly visible at long wavelengths on the absorption spectra.

The emission spectra did not show fine resolution. Their maximum was rather close for the three compounds, around 520 nm in DMSO and slightly above 500 nm in dichloromethane. A small solvent effect can thus be noted. The lifetimes were found to be monoexponential, above the nanosecond. The quantum yields were not calculated since the absorption spectra corresponded to two species at least, only one of which is fluorescent. Therefore, the quantum yields measured would have been lower than their actual value.

If comparing the properties of these benzopyranopyrimidines with those of parent compound **1** in the same solvents [11,12], it appears, as could be expected, that cyclization has led to a moderate shift of the absorption and emission wavelengths towards longer wavelengths. In contrast, the fluorescence lifetime is quite similar for the two types of compounds.

CONCLUSION

This article reported the facile synthesis of new 2-oxo-2*H*-1-benzopyrano[*2,3-d*]pyrimidines from the condensation of a 3-cyanoiminocoumarin with various hydrazides. The products were easily purified and obtained with a good yield. Their limited solubility in most of organic solvents could be a drawback for subsequent applications. However, it is possible that these compounds display interesting biological properties, which would deserve further investigations.

EXPERIMENTAL

7-Diethylamino-2-hydroxybenzaldehyde, malonitrile and hydrazides were commercially available from Aldrich. All melting points were determined on an Electrothermal 9100 apparatus. Infrared spectra were registered on a Jasco FT-IR 420 spectrophotometer apparatus using KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WP 200 spectrometer at 300 MHz in DMSO-d$_6$ with TMS as internal standard (chemical shifts in ppm).

Scheme 3

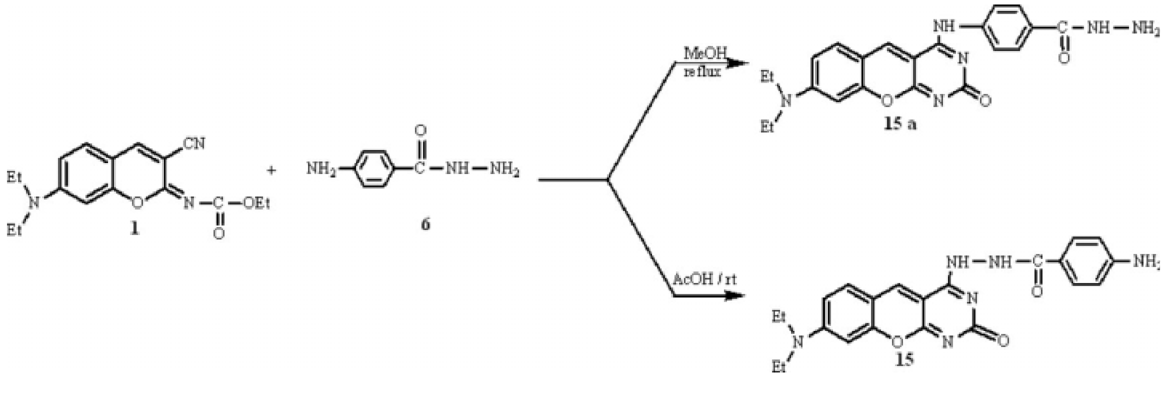


Table 2

Maximum absorption wavelength (λ_{abs}), maximum excitation wavelength (λ_{ex}), maximum emission wavelength (λ_{em}), and fluorescence lifetime (τ) for compounds 12, 13, and 15 in dimethylsulfoxide and dichloromethane.

Compound	λ_{abs} (nm)	λ_{ex} (nm)	λ_{em} (nm)	τ (ns)
12 (DMSO)	504	458	520	2.6 ± 0.3
13 (DMSO)	486	476	518	2.9 ± 0.2
13 (CH_2Cl_2)	484 (508 sh)	480	502	3.2 ± 0.2
15 (DMSO)	508	480	520	1.5 ± 0.2
15 (CH_2Cl_2)	502	451	507	1.9 ± 0.2

UV/vis absorption spectra were recorded on a Hewlett-Packard 8452A diode array spectrophotometer. Steady state fluorescence work was performed on a Photon Technology International (PTI) Quanta Master 1 spectrofluorometer. All excitation and emission spectra were corrected. Fluorescence decay was measured with the stroboscopic technique using a Strobe Master fluorescence lifetime spectrophotometer from PTI. The excitation source was a flash lamp filled with a mixture of nitrogen and helium (30/70). Data were collected over 200 channels with a time-base of 0.1 ns per channel. Analysis of fluorescence decay was performed using the multiexponential method software from PTI. All spectrophotometric measurements were conducted in a thermostated cell at 25°C.

3-Cyano-*N*-ethoxycarbonyl-7-diethylamino iminocoumarin 1. 3-Cyano-*N*-ethoxycarbonyl-7-diethylamino iminocoumarin **1** was prepared as previously described in [9].

General procedure for the synthesis of benzopyranopyrimidines 11–19. A solution of 3-cyano-*N*-ethoxycarbonyl-7-diethylamino iminocoumarin 1 (1.56 g, 5 mmol) and (5 mmol) of hydrazide in 30 mL of absolute methanol was refluxed during the time indicated in Table 1. After complete reaction, the benzopyranopyrimidine obtained was separated by filtration and washed with ethanol. For spectroscopic use, compound 12, 13, and 15 were purified on TLC plates using chloroform as the eluent.

4-(2-Benzoylhydrazino)-8-diethylamino-2-oxo-2H-benzopyrano[2,3-d]pyrimidine (11). Mp: 244°C. IR (cm^{-1}): 1632 (C=N), 1644 (C=O), 1664 (N—CO—N), 3331 (NH). ^1H NMR: $\delta = 1.14$ (t, $J = 6.9$ Hz, 6H, CH_3), 3.51 (q, $J = 6.9$ Hz, 4H, CH_2N), 6.74 (s, 1H, H_9), 6.88 (d, $J = 9.0$, 1H, H_7), 7.45–7.55 (3 H, COR), 7.75 (d, $J = 9.0$ Hz, 1H, H_6), 7.87–7.89 (2 H, COR), 8.47 (s, 1H, H_5), 10.49 (s, 1H, NH), 10.64 (s, 1H, NH). *Anal.* Calcd. for $C_{22}H_{21}N_5O_3$: C, 65.50; H, 5.25; N, 17.36. Found: C, 65.46; H, 5.33; N, 17.35.

4-[2-(3-Fluorobenzoyl)hydrazino]-8-diethylamino-2-oxo-2H-benzopyrano[2,3-d]pyrimidine (12). Mp: 249°C. IR (cm^{-1}): 1634 (C=N, C=O), 1664 (N—CO—N), 3331 and 3335 (NH). ^1H NMR: $\delta = 1.14$ (t, $J = 6.9$ Hz, 6H, CH_3), 3.51 (q, $J = 6.9$ Hz, 4H, CH_2N), 6.75 (s, 1H, H_9), 6.89 (dd, $J = 7.2$, 1.8 Hz, 1H, H_7), 7.39 (m, 1H, COR), 7.53 (m, 1H, COR), 7.76 (m, 2H, COR), 7.74 (d, $J = 7.2$, 1H, H_6), 8.49 (s, 1H, H_5), 10.50 (s,1H, NH), 10.60 (s, 1H, NH). ^{13}C NMR: $\delta =$ 12.71 (CH_3), 44.90 (CH_2—NH), 96.73 (C_9), 104.92, 110.00 (C_{12}, C_{13}), 111.80 (C_7), 114.74, 118.26, 124.35, 130.63 (CH—R), 132.02 (C_6), 136.76 (R), 138.04 (C_5), 140.76 (C_8), 153.31 (C_4), 156.14 (C_{10}), 160.52 (C_{11}), 162.13 (C—F), 163.75 (C=O), 167.95 (NH—C=O). *Anal.* Calcd. for $C_{22}H_{20}FN_5O_3$: C, 62.70; H, 4.78; N, 16.62. Found: C, 63.10; H, 4.80; N, 16.50.

4-[2-(2-Thienylcarbonyl)hydrazino]-8-diethylamino-2-oxo-2H-benzopyrano[2,3-d]pyrimidine (13). Mp: 247°C. IR (cm^{-1}): 1619 (C=N), 1639 (C=O), 1660 (N—CO—N), 3289 (NH). ^1H NMR: $\delta = 1.14$ (t, $J = 7.0$ Hz, 6H, CH_3), 3.51 (q, $J = 7.0$ Hz, 4H, CH_2N), 6.76 (d, $J = 2.1$ Hz, 1H, H_9), 6.61 (s, 1H, COR), 6.89 (dd, $J = 9.0$, 2.1 Hz, 1H, H_7), 7.18 (s, 1H, COR), 7.71 (d, $J = 9.0$ Hz, 1H, H_6), 7.80 (s, 1H, COR) , 8.46 (s, 1H, H_5), 10.46 (s,1H, NH), 10.69 (s, 1H, NH). *Anal.* Calcd. for $C_{20}H_{19}N_5O_3S$: C, 58.67; H, 4.68; N, 17.10. Found: C, 59.01; H, 4.64; N, 17.11.

4-[2-(4-Hydroxybenzoyl)hydrazino]-8-diethylamino-2-oxo-2H-benzopyrano[2,3-d]pyrimidine (14). Mp: 270°C. IR (cm^{-1}): 1608 (C=N), 1636 (C=O), 1664 (N—CO—N), 3326 (NH), 3423 (OH). ^1H NMR: $\delta = 1.13$ (t, $J = 6.9$ Hz, 6H, CH_3), 3.50 (q, $J = 6.9$ Hz, 4H, CH_2N), 6.73 (s, 1H, H_9), 6.82 (d, $J = 8.7$ Hz, 2H, COR), 7.77 (d, $J = 8.7$ Hz, 2H, COR), 6.85 (d, $J = 9.3$ Hz, 1H, H_7), 7.72 (d, $J = 9.3$ Hz, 1H, H_6), 8.42 (s, 1H, H_5), 10.28 (s,1H, OH), 10.46 (s,1H, NH), 10.69 (s, 1H, NH). *Anal.* Calcd. for $C_{22}H_{21}N_5O_4$: C, 63.00; H, 5.05; N, 16.70. Found: C, 62.90; H, 5.23; N, 17.71.

4-[2-(4-Aminobenzoyl)hydrazino]-8-diethylamino-2-oxo-2H-benzopyrano[2,3-d]pyrimidine (15). Mp: 245°C. IR (cm^{-1}): 1605 (C=N), 1637 (C=O), 1663 (N—CO—N), 3210 and 3334 (NH), 3439 (NH_2). ^1H NMR: $\delta = 1.12$ (t, $J = 6.9$ Hz, 6H, CH_3), 3.47 (q, $J = 6.9$ Hz, 4H, CH_2N), 5.71 (s, 2H, NH_2), 6.57 (d, $J = 8.4$ Hz, 2H, COR), 6.65 (d, $J = 8.4$ Hz, 2H, COR), 6.69 (s, 1H, H_9), 6.82 (d, $J = 9.3$ Hz, 1H, H_7), 7.67 (d, $J = 9.3$ Hz, 1H, H_6), 8.36 (s, 1H, H_5), 10.16 (s,1H, NH), 10.60 (s, 1H, NH). ^{13}C NMR: $\delta =$ 12.69 (CH_3), 44.84 (CH_2—NH), 96.68 (C_9), 105.67, 109.90 (C_{12}, C_{13}), 111.58 (C_7), 112.77 (CH—R), 120.49 (C—R) 129.78 (C_6), 131.67 (CH—R),136.96 (C_5), 137.38 (C—R), 152.32 (C_8), 152.93 (C_4), 155.81 (C_{10}), 156.30 (C_{11}) 163.57 (C=O), 168.09 (NH—C=O). *Anal.* Calcd. for $C_{22}H_{22}N_6O_3$: C, 63.15; H, 5.30; N, 20.08. Found: C, 62.90; H, 5.33; N, 20.00.

4-[2-(2-Furoyl)hydrazino]-8-diethylamino-2-oxo-2H-benzopyrano[2,3-d]pyrimidine (16). Mp: 246°C. IR (cm^{-1}): 1607 (C=N), 1636 (C=O), 1663 (N—CO—N), 3290 (NH). ^1H NMR: $\delta = 1.13$ (t, $J = 7.0$ Hz, 6H, CH_3), 3.51 (q, $J = 7.0$ Hz, 4H, CH_2N), 6.66 (m, 1H, COR), 6.76 (d, $J = 2.1$ Hz, 1H, H_9), 6.89 (dd, $J = 9.0$, 2.1 Hz, 1H, H_7), 7.24 (d, 1H, COR), 7.76 (d, $J = 9.0$ Hz, 1H, H_6), 7.89 (m, 1H, COR), 8.46 (s, 1H, H_5), 10.15 (s,1H, NH), 10.55 (s, 1H, NH). *Anal.* Calcd. for $C_{20}H_{19}N_5O_4$: C, 61.06; H, 4.87; N, 17.80. Found: C, 61.20; H, 4.93; N, 17.84.

4-(2-Isonicotinoylhydrazino)-8-diethylamino-2-oxo-2H-benzopyrano[2,3-d]pyrimidine (17). Mp: >270°C. IR (cm^{-1}): 1607 (C=N), 1640 (C=O), 1661 (N—CO—N),3234 (NH). ^1H NMR: $\delta = 1.15$ (t, $J = 6.9$ Hz, 6H, CH_3), 3.52 (q, $J = 6.9$

Hz, 4H, CH_2N), 6.66 (m, 1H, COR), 6.68 (d, J = 2.1 Hz, 1H, H_9), 6.89 (dd, J = 7.0, 1.5 Hz, 1H, H_7), 7.73 (d, 1H, COR), 7.77 (d, J = 7.0 Hz, 1H, H_6), 7.82 (dd, 2H, COR), 8.53 (s, 1H, H_5), 10.67 (s, 2H, 2NH). *Anal*. Calcd. for $C_{21}H_{20}N_6O_3$: C, 62.37; H, 4.98; N, 20.78. Found: C, 61.97; H, 4.80; N, 20.44.

4-(2-Acetylhydrazino)-8-diethylamino-2-oxo-2H-benzopyrano[2,3-d]pyrimidine (18). Mp: >270°C. IR (cm^{-1}): 1609 (C=N), 1636 (C=O), 1662 (N—CO—N),3232 (NH).^{1}H NMR: δ = 1.14 (t, J = 6.9 Hz, 6H, CH_3), 2.17 (s, 3H, CH_3), 3.42 (q, J = 6.9 Hz, 4H, CH_2N), 6.63 (d, J = 2.1 Hz, 1H, H_9), 6.78 (d, J = 7.0, 2.1 Hz, 1H, H_7), 7.50 (d, J = 7.0 Hz, 1H, H_6), 8.12 (s, 1H, H_5), 10.73 (s, 1H, NH), 10.76 (s, 1H, NH). *Anal*. Calcd. for $C_{17}H_{19}N_5O_3$: C, 59.81; H, 5.61; N, 20.52. Found: C, 60.07; H, 5.63; N, 20.80.

4-[2-(2-Hydroxybenzoyl)hydrazino]-8-diethylamino-2-oxo-2H-benzopyrano[2,3-d]pyrimidine (19). Mp: >270°C. IR (cm^{-1}): 1606 (C=N), 1640 (C=O), 1661 (N—CO—N),3234 (NH), 3433 (OH).^{1}H NMR: δ = 1.13 (t, J = 6.9 Hz, 6H, CH_3), 3.51 (q, J = 6.9 Hz, 4H, CH_2N), 6.77 (s, J = 1.5 Hz, 1H, H_9), 6.90 (dd, J = 7.0, 1.5 Hz, 1H, H_7), 7.39 (dd, 2H, COR), 7.75 (d, J = 7.0 Hz, 1H, H_6), 7.90 (d, 2H, COR), 8.53 (s, 1H, H_5), 10.60 (s, 1H, 1NH), 10.75 (s, 1H, OH), 10.90 (s, 1H, NH). *Anal*. Calcd. for $C_{22}H_{21}N_5O_4$: C, 63.00; H, 5.05; N, 16.70. Found: C, 62.61; H, 5.42, N, 16.57.

Synthesis of 8-diethylamino 2*H*-benzopyrano[2,3-*d*]pyrimidine-2,4(3*H*)-dione (11a). A mixture of (1.56 g, 5 mmol) of 1 and (0.68 g, 5 mmol) of benzoic hydrazide 2 were stirred at 20°C in 20 mL of glacial acetic acid for 20 h. The product was isolated by filtration and recrystallized in dimethylsulfoxide. Mp 250°C. Yield: 55%. IR (cm^{-1}): 1641 (C=O), 3246 (NH). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.14 (t, J = 6.9 Hz, 6H, CH_3), 3.53 (q, J = 6.9Hz, 4H, CH_2N), 6.80 (d, J = 1.5 Hz, 1H, H_9), 6.89 (dd, J = 6.9, 1.5 Hz, 1H, H_7), 7.74 (d, J = 6.9 Hz, 1H, H_6), 8.59 (s, 1H, H_5), 11.06 (s,1H, NH). ^{13}C NMR: δ = 12.86 (CH_3), 45.29 (CH_2—NH), 96.97 (C_9), 104.98, 110.31 (C_{12}, C_{13}), 112.49 (C_7), 133.41 (C_6), 144.38 (C_5), 154.89 (C_8), 157.34 (C_4), 157.57 (C_{10}), 162.52 (C=O), 168.57 (C=O). *Anal*. Calcd. for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.96; H, 5.21; N, 14.69.

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Syntheses of New Quinoline-Containing Heterocyclic Scaffolds Using Inter- and Intramolecular Pd-Catalyzed Amination

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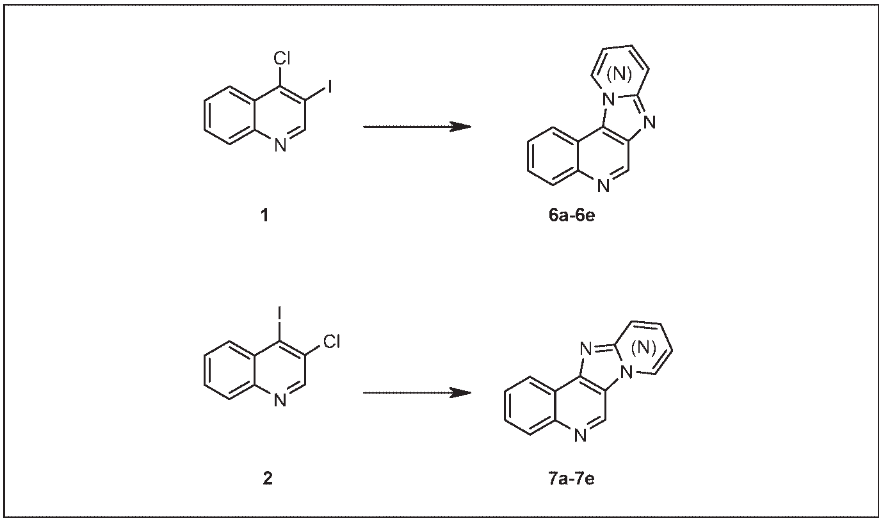

A tandem inter- and intramolecular Pd-catalyzed amination protocol was studied on 4-chloro-3-iodoquinoline and 3-chloro-4-iodoquinoline with different aminohetarenes. Applying this method, ten novel quinoline derivatives and eight new heterocyclic ring systems were synthesized.

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INTRODUCTION

The quinoline-containing polycyclic compounds are expected to have interesting biological activity. Pyrazoloquinoline derivatives are active agents for the treatment of cancer and herpes virus infections [1,2]. Substituted indoloquinolines display biological properties such as antimalarial, antimuscarinic, antibacterial, antiviral, and cytotoxic activities *in vivo*, and significant antitumor properties *in vitro* [3–6].

The aim of this work was to prepare new heterocyclic ring systems, containing the quinoline skeleton. 4-Chloro-3-iodoquinoline (**1**) and 3-chloro-4-iodoquinoline (**2**) were reacted with aminohetarenes **3a-3e** to get hitherto unknown heterocyclic scaffolds.

RESULTS AND DISCUSSION

In 2004, Loones *et al*. described the first auto-tandem inter- and intramolecular Pd-catalyzed amination protocol on 2-chloro-3-iodopyridine with different amino (benzo)(di)azines [7]. A few years later, they extended their amination procedure on the benzo-analogue of 2-chloro-3-iodopyridine; 2-chloro-3-iodoquinoline [8]. To the best of our knowledge, there are no reports on the above-mentioned Pd-catalyzed amination of either 4-chloro-3-iodoquinoline (**1**) or 3-chloro-4-iodoquinoline (**2**).

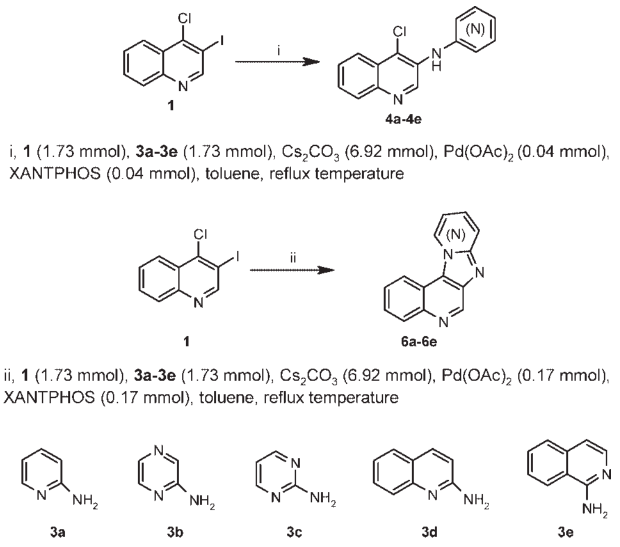
At the beginning of this work, we had some doubt whether this one-pot double amination reaction would work on our substrates **1-2**. To find the optimal conditions for the synthesis of **4-7,** some preliminary experiments were needed. The effects of solvent and ligand on the reaction rate were investigated for compound **1**.

In a first approach, we studied the effect of ligand on the auto-tandem Pd-catalyzed amination. *rac*-BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) [9] and XANTPHOS (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) [10] are commonly used ligands in the Buchwald-Hartwig aminations [11,12]. Concerning the amination of **1** with 2-aminopyridine (**3a**) under the same conditions ($Pd(OAc)_2$, Cs_2CO_3, toluene, reflux), XANTPHOS gave higher conversion for **6a** than *rac*-BINAP after the same reaction time (Scheme 1).

The effects of different solvents like toluene, DMF, and DME were studied keeping the other reaction conditions unchanged. The fastest reaction was observed in toluene.

On the basis of the small-scale experiments, different amino(benzo)(di)azines **3a-3e** were coupled with 4-

Scheme 1. Synthesis of **4a-4e** and **6a-6e**.



i, **1** (1.73 mmol), **3a-3e** (1.73 mmol), Cs_2CO_3 (6.92 mmol), $Pd(OAc)_2$ (0.04 mmol), XANTPHOS (0.04 mmol), toluene, reflux temperature

ii, **1** (1.73 mmol), **3a-3e** (1.73 mmol), Cs_2CO_3 (6.92 mmol), $Pd(OAc)_2$ (0.17 mmol), XANTPHOS (0.17 mmol), toluene, reflux temperature

chloro-3-iodoquinoline (**1**) in toluene in the presence of $Pd(OAc)_2$, XANTPHOS and Cs_2CO_3 at reflux temperature to get the unknown 3-amino-4-chloroquinoline derivatives **4a-4e** and the new polycyclic heterocycles **6a-6e**.

Table 1

Synthesis of **4a-4e.**

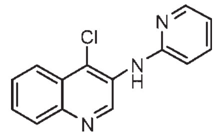
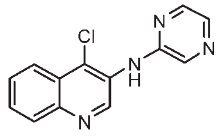
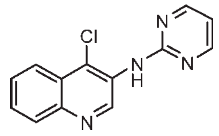
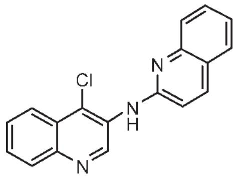
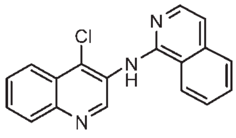
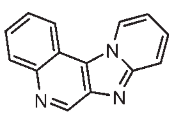
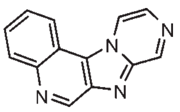
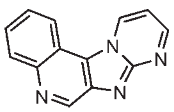
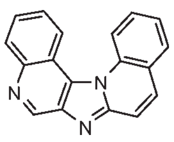
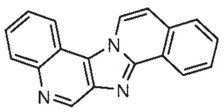
3	Time (h)	Yield (%)	4
3a	6	61	
3b	3	61	
3c	6 20	8 72	
3d	5	78	
3e	4	43	

Table 2

Synthesis of **6a-6e.**

3	Time (h)	Yield (%)	6
3a	21	32	
3b	20	84	
3c	21	Traces	
3d	29	30	
3e	22	51	

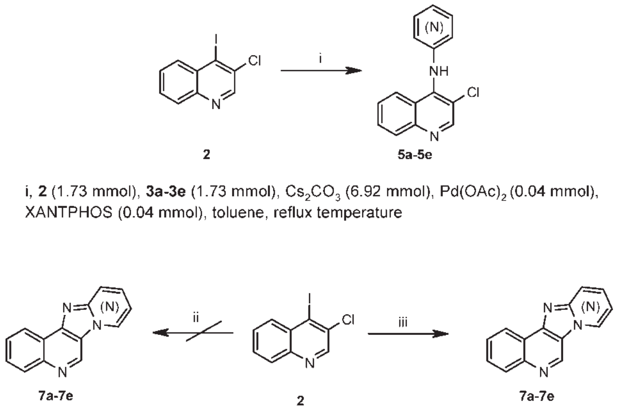
The desired intermediates **4a-4e** were obtained in moderate to good yields, 43–78%. The reaction time was different in every case but was comprised between 3 and 6 h. In the case of 4-chloro-3-(pyrimidin-2-yl)amino-quinoline (**4c**), only traces could be detected after 6 h; so the reaction was left longer (20 h) at reflux temperature resulting in a good yield of 72% being achieved. The results are reported in Table 1 and in the Experimental Section.

The new ring systems **6a, 6b, 6d, 6e** were obtained after 20–29 h, with varying yields (30–83%). 5,7,8,11a-Tetraazabenzo[*c*]fluorene (**6c**) was also formed, but only as a minor compound (Table 2).

We expanded our investigation to 3-chloro-4-iodoquinoline (**2**) as a substrate. The coupling reactions were carried out with the same aminohetarenes **3a-3e**. The monosubstituted intermediates **5a-5e** were prepared in the same way as when using 4-chloro-3-iodoquinoline (**1**) (Scheme 2).

A similar behavior was observed as in the case of **4a-4e**. The Pd-catalyzed intermolecular aminations afforded compounds **5a-5e** in moderate to good yields (50–78%). The reaction time was again the longest with 2-aminopyrimidine (**3c**), which resulted in 3-chloro-4-

Scheme 2. Synthesis of **5a-5e** and **7a-7e**.



i, **2** (1.73 mmol), **3a-3e** (1.73 mmol), Cs_2CO_3 (6.92 mmol), $Pd(OAc)_2$ (0.04 mmol), XANTPHOS (0.04 mmol), toluene, reflux temperature

ii, **2** (1.73 mmol), **3a-3e** (1.73 mmol), Cs_2CO_3 (6.92 mmol), $Pd(OAc)_2$ (0.17 mmol), XANTPHOS (0.17 mmol), toluene, reflux temperature
iii, **2** (1.73 mmol), **3a-3e** (1.73 mmol), Cs_2CO_3 (6.92 mmol), $Pd(OAc)_2$ (0.17 mmol), XANTPHOS (0.17 mmol), CuI (0.35 mmol), DME, reflux temperature

(pyrimidin-2-yl)aminoquinoline (**5c**). The results are reported in Table 3 and in the Experimental Section.

In contrast, the reaction conditions optimized for **6a-6e** did not work for the synthesis of **7a-7e**: in all cases, the reactions stopped at the stage of **5a-5e**. No intramolecular amination was observed, so we had to change our strategy. We wondered if it would be possible to prepare **7a-7e** in one-pot *via* orthogonal tandem catalysis (with simultaneously operating palladium and copper catalysts). Fortunately, by adding CuI (0.2 eq) to the reaction mixture (**2**, **3a-3e**, $Pd(OAc)_2$, XANTPHOS, Cs_2CO_3 and DME as solvent), the desired heterocycles **7a-7e** could be synthesized [8] (Scheme 2).

The formation of **7a-7e** directly from 3-chloro-4-iodoquinoline (**2**) and **3a-3e** gave varying results. Only traces of 5,6b,10,11-tetraazabenzo[*a*]fluorene (**7c**) were formed. Low yields were obtained in the reaction with 2-aminopyridine (**3a**) and 2-aminoquinoline (**3d**). In the coupling with **3b** and **3e,** moderate yields were achieved (Table 4).

In conclusion, the tandem inter- and intramolecular Pd-catalyzed amination protocol was applied on 4-chloro-3-iodoquinoline (**1**) and 3-chloro-4-iodoquinoline (**2**) with five different amidines **3a-3e**, affording novel heterocyclic systems. The reactions that were performed with compound **1** gave higher yields compared to the experiments with the other isomer **2**. Unfortunately in two cases—**1** and **2** with 2-aminopyrimidine (**3c**)—the reactions only gave traces of the desired products **6c**, **7c**.

In summary, we succeeded in preparing ten monosubstituted intermediates **4a-4e** and **5a-5e** and eight new heterocyclic scaffolds **6a**, **6b**, **6d**, **6e**, **7a**, **7b**, **7d**, **7e** whose biological activity warrants further investigation.

EXPERIMENTAL

All melting points were measured on a Büchi-545 apparatus and are uncorrected. Magnetic resonance spectra (^1H NMR) were recorded on a Varian 400 MHz spectrometer. Chemical shift values are reported in δ (ppm) relative to an internal standard (tetramethylsilane). All coupling constants are given in Hertz. Multiplicity is indicated using the following abbreviations: br, broad; d, doublet; t, triplet; m, multiplet; s, singlet. The mass spectra were measured on a FISONS TRIO 1000. Elemental analyses were carried out on an Elementar VARIO EL. Reactions were monitored by TLC on silica gel-protected aluminium sheets (Type 60 F 254, Merck), and the spots were detected by exposure to a UV-Lamp at 254 nm for a few seconds. Column chromatography was performed on silica gel. 4-Chloro-3-iodoquinoline (**1**) and 3-chloro-4-iodoquinoline (**2**) were synthesized using a modification of a known procedure described in literature [13,14]. All reagents were purchased from Aldrich except 2-aminopyrazine and 2-aminoquinoline, which were ordered from Fluka and Apollo, respectively. All the solvents were of the highest analitical grade.

General procedure for the preparation of 4a-4e and 5a-5e. A round-bottomed flask was charged with $Pd(OAc)_2$ (9 mg, 0.04 mmol, 0.02 eq), Xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) (24 mg, 0.04 mmol, 0.02 eq) and toluene (8 mL). The solution thus obtained was flushed with argon for 1 h under magnetic stirring at room temperature. Meanwhile, a three-necked round-bottomed flask was charged with 4-chloro-3-iodoquinoline (**1**) (0.50 g, 1.73 mmol, 1.00 eq) or 3-chloro-4-iodoquinoline (**2**) (0.50 g, 1.73 mmol, 1.00 eq), the corresponding amidine **3a-3e** (1.73 mmol, 1.00 eq), Cs_2CO_3 (2.25 g, 6.92 mmol, 4.00 eq) and toluene (15 mL). To this suspension, the preformed Pd-catalyst was added. The resulting mixture was flushed with argon again and heated for 3–21 h at reflux temperature. After cooling to room temperature, toluene was removed by evaporation, the residue was mixed with silica gel, and it was brought on top of a silica gel column and purified by flash chromatography.

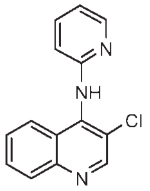
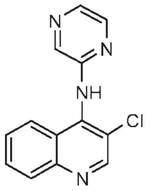
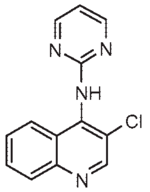
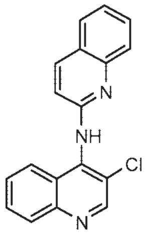
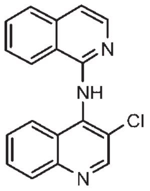
4-Chloro-3-(pyridin-2-yl)aminoquinoline (4a). Purification by flash chromatography using hexane:EtOAc = 7:3 resulted in a white solid. Yield: 0.27 g, 1.05 mmol, 61%; mp. 213.4–213.5°C; ^1H NMR ($CDCl_3$) δ 6.86–6.88 (m, 3H, ArH, NH), 7.57–7.64 (m, 3H, ArH), 8.05–8.11 (m, 2H, ArH), 8.25–8.27 (m, 1H, ArH), 9.62 (s, 1H, ArH); MS: m/z = 255 ($M^{+\cdot}$); *Anal.* Calcd. for $C_{14}H_{10}ClN_3$ (255.71) C, 65.76; H, 3.94; N, 16.43. Found: C, 65.94; H, 3.93; N 16.38.

4-Chloro-3-(pyrazin-2-yl)aminoquinoline (4b). Purification by flash chromatography using toluene:MeOH = 95:5 resulted in a brownish solid, which was recrystallized from toluene to give a beige solid. Yield: 0.27 g, 1.05 mmol, 61%; mp. 176.2–176.3°C; ^1H NMR ($CDCl_3$) δ 6.98 (br, 1H, NH), 7.61–7.68 (2H, m, Ar), 8.08–8.18 (m, 4H, ArH), 8.32 (d, 1H, ArH, *J* = 1.2 Hz), 9.70 (s, 1H, ArH); MS: m/z = 256 ($M^{+\cdot}$); *Anal.* Calcd. for $C_{13}H_9ClN_4$ (256.70) C, 60.83; H, 3.53; N, 21.83. Found: C, 60.62; H, 3.52; N 21.89.

4-Chloro-3-(pyrimidin-2-yl)aminoquinoline (4c). Purification by flash chromatography using hexane:EtOAc = 3:2 resulted in a white solid. Yield: 0.32 g, 1.25 mmol, 72%; mp. 156.5–157.2°C; ^1H NMR ($CDCl_3$) δ 6.81 (t, 1H, ArH, *J* = 4.8 Hz), 7.55–7.64 (m, 2H, ArH), 7.71 (br, 1H, NH), 8.05–8.10 (m, 2H, ArH), 8.44 (d, 2H, ArH, *J* = 4.8 Hz), 9.90 (s, 1H, ArH); MS:

Table 3

Synthesis of **5a-5e.**

3	Time (h)	Yield (%)	**5**
3a	3	57	
3b	3	50	
3c	21	74	
3d	3	66	
3e	6	78	

m/z = 256 (M$^+$); *Anal.* Calcd. for $C_{13}H_9ClN_4$ (256.70) C, 60.83; H, 3.53; N, 21.83. Found: C, 60.93; H, 3.52; N 21.88.

4-Chloro-3-(quinolin-2-yl)aminoquinoline (4d). Purification by flash chromatography using hexane:EtOAc = 7:3, 1:1 resulted in a light yellowish solid. Yield: 0.41 g, 1.34 mmol, 78%; mp. 171.0–172.1°C; ^{1}H NMR ($CDCl_3$) δ 7.00 (d, 1H, ArH, *J* = 8.8 Hz), 7.13 (br, 1H, NH), 7.33–7.37 (m, 1H, ArH), 7.59–7.69 (m, 4H, ArH), 7.83 (d, 1H, ArH, *J* = 8.4 Hz), 8.02 (d, 1H, ArH, *J* = 8.8 Hz), 8.03–8.13 (m, 2H, ArH), 10.23 (s, 1H, ArH); MS: m/z = 305 (M$^+$); *Anal.* Calcd. for $C_{18}H_{12}ClN_3$ (305.77) C, 70.71; H, 3.96; N, 13.74. Found: C, 70.84; H, 3.95; N 13.71.

4-Chloro-3-(isoquinolin-1-yl)aminoquinoline (4e). Purification by flash chromatography using hexane:EtOAc = 7:3 resulted in an orange solid which was recrystallized from EtOH to give a yellowish solid. Yield: 0.23 g, 0.75 mmol, 43%; mp. >250°C; ^{1}H NMR ($CDCl_3$) δ 7.26 (d, 1H, ArH, *J* = 6.0 Hz), 7.61–7.71 (m, 5H, ArH, NH), 7.81 (d, 1H, ArH, *J* = 8.0 Hz), 8.06–8.14 (m, 4H, ArH), 9.98 (s, 1H, ArH); MS: m/z = 305 (M$^{+\cdot}$); *Anal.* Calcd. for $C_{18}H_{12}ClN_3$ (305.77) C, 70.71; H, 3.96; N, 13.74. Found: C, 70.83; H, 3.95; N, 13.71.

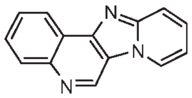
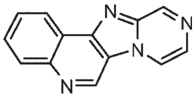
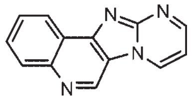
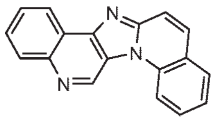
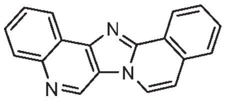
3-Chloro-4-(pyridin-2-yl)aminoquinoline (5a). Purification by flash chromatography using hexane:EtOAc = 3:2 resulted in a beige solid. Yield: 0.25 g, 0.98 mmol, 57%; mp. 177.6–178.5°C; ^{1}H NMR ($CDCl_3$) δ 6.41 (d, 1H, ArH, *J* = 8.0 Hz), 6.85–6.88 (m, 1H, ArH), 7.12 (br, 1H, NH), 7.46–7.50 (m, 2H, ArH), 7.69–7.72 (m, 1H, ArH), 7.81–7.83 (m, 1H, ArH), 8.11 (d, 1H, ArH, *J* = 8.4 Hz), 8.24–8.25 (m, 1H, ArH), 8.88 (s, 1H, ArH); MS: m/z = 255 (M$^{+\cdot}$); *Anal.* Calcd. for $C_{14}H_{10}ClN_3$ (255.71) C, 65.76; H, 3.94; N, 16.43. Found: C, 65.51; H, 3.95; N, 16.47.

3-Chloro-4-(pyrazin-2-yl)aminoquinoline (5b). Purification by flash chromatography using toluene:2-propanol = 9:1 resulted in a beige solid. Yield: 0.22 g, 0.86 mmol, 50%; mp. >250°C; ^{1}H NMR ($CDCl_3$) δ 7.08 (br, 1H, NH), 7.44–7.53 (m, 1H, ArH), 7.70–7.74 (m, 1H, ArH), 7.77–7.80 (m, 1H, ArH), 7.93 (d, 1H, ArH, *J* = 1.2 Hz), 8.10–8.14 (m, 3H, ArH), 8.89 (s, 1H, ArH); MS: m/z = 256 (M$^{+\cdot}$); *Anal.* Calcd. for $C_{13}H_9ClN_4$ (256.70) C, 60.83; H, 3.53; N, 21.83. Found: C, 60.62; H, 3.54; N, 21.87.

3-Chloro-4-(pyrimidin-2-yl)aminoquinoline (5c). Purification by flash chromatography using hexane:EtOAc = 3:2, 2:3, 1:9

Table 4

Synthesis of **7a-7e.**

3	Time (h)	Yield (%)	**7**
3a	19	5	
3b	28	66	
3c	28	Traces	
3d	28	4	
3e	21	43	

resulted in a white solid. Yield: 0.33 g, 1.28 mmol, 74%; mp. 232.8–232.9°C; ^{1}H NMR ($CDCl_3$) δ 6.80 (t, 1H, ArH, *J* = 4.8 Hz), 7.37 (br, 1H, NH), 7.49–7.53 (m, 1H, ArH), 7.68–7.72 (m, 1H, ArH), 7.87 (d, 1H, ArH, *J* = 8.4 Hz), 8.10 (d, 1H, ArH, *J* = 8.4 Hz), 8.37 (d, 2H, ArH, *J* = 4.8 Hz), 8.90 (m, 1H, ArH); MS: m/z = 256 ($M^{+\cdot}$); *Anal*. Calcd. for $C_{13}H_9ClN_4$ (256.70) (C, 60.83; H, 3.53; N, 21.83. Found: C, 60.71; H, 3.54; N 21.79.

3-Chloro-4-(quinolin-2-yl)aminoquinoline (5d). Purification by flash chromatography using hexane:EtOAc = 3:2 resulted in a white solid. Yield: 0.35 g, 1.14 mmol, 66%; mp. 118.3–119.2°C; ^{1}H NMR ($CDCl_3$) δ 6.61 (d, 1H, ArH, *J* = 8.8 Hz), 7.31–7.35 (m, 1H, ArH), 7.41–7.45 (m, 1H, ArH), 7.57–7.61 (m, 1H, ArH), 7.65–7.71 (m, 3H, ArH, NH), 7.85–7.89 (m, 2H, ArH), 8.10 (d, 1H, ArH, *J* = 8.0 Hz), 8.87 (s, 1H, ArH); MS: m/z = 305 ($M^{+\cdot}$); *Anal*. Calcd. for $C_{18}H_{12}ClN_3$ (305.77) C, 70.71; H, 3.96; N, 13.74. Found: C, 70.88; H, 3.95; N, 13.71.

3-Chloro-4-(isoquinolin-1-yl)aminoquinoline (5e). Purification by flash chromatography using hexane:EtOAc = 3:2, 1:1, 2:3 resulted in an orange solid. Yield: 0.41 g, 1.34 mmol, 78%; mp. >250°C; ^{1}H NMR ($CDCl_3$) (the mixture of two tautomers) δ 7.32–9.00 (m, 12 H, ArH, NH); MS: m/z = 305 ($M^{+\cdot}$); *Anal*. Calcd. for $C_{18}H_{12}ClN_3$ (305.77) C, 70.71; H, 3.96; N, 13.74. Found: C, 70.85; H, 3.95; N, 13.70.

General procedure for the preparation of 6a-6e. A round-bottomed flask was charged with $Pd(OAc)_2$ (39 mg, 0.17 mmol, 0.10 eq), Xantphos (4,5-bis(diphenylphosphino)-9,9-dimethyl-xanthene) (0.10 g, 0.17 mmol, 0.10 eq) and toluene (8 mL). The solution thus obtained was flushed with argon for 1 h under magnetic stirring at room temperature. Meanwhile, a three-necked round-bottomed flask was charged with 4-chloro-3-iodoquinoline (1) (0.50 g, 1.73 mmol, 1.00 eq), the corresponding amidine 3a-3e (1.73 mmol, 1.00 eq), Cs_2CO_3 (2.25 g, 6.92 mmol, 4.00 eq) and toluene (15 mL). To this suspension, the preformed Pd-catalyst was added. The resulting mixture was flushed with argon again and heated for 20–29 h at reflux temperature. After cooling to room temperature, toluene was removed by evaporation, the residue was mixed with silica gel and it was brought on top of a silica gel column and purified by flash chromatography.

5,7,11a-Triazabenzo[c]fluorene (6a). Purification by flash chromatography using toluene:2-propanol = 4:1, 3:2, 2:3 resulted in a brownish solid which was recrystallized from toluene to give a beige solid. Yield: 0.12 g, 0.55 mmol, 32%; mp. 192.5-193.3°C; ^{1}H NMR ($CDCl_3$) δ 7.05–7.08 (m, 1H, ArH), 7.47–7.51 (m, 1H, ArH), 7.66–7.71 (m, 2H, ArH), 7.85 (d, 1H, ArH, *J* = 6.4 Hz), 8.32–8.34 (m, 2H, ArH), 8.96 (d, 1H, ArH, *J* = 4.8 Hz), 9.51 (s, 1H, ArH); MS: m/z = 219 ($M^{+\cdot}$); *Anal*. Calcd. for $C_{14}H_9N_3$ (219.25) C, 76.70; H, 4.14. Found: C, 76.96; H, 4.13.

5,7,9,11a-Tetraazabenzo[c]fluorene (6b). Purification by flash chromatography using toluene:2-propanol = 9:1, 4:1, 3:2, 1:1 resulted in a light brownish solid. Yield: 0.32 g, 1.45 mmol, 84%; mp. >250°C; ^{1}H NMR (DMSO-d_6) δ 7.82–7.90 (m, 2H, ArH), 8.23 (d, 1H, ArH, *J* = 4.8 Hz), 8.30–8.32 (m, 1H, ArH), 8.88–8.91 (m, 1H, ArH), 9.52–9.57 (m, 3H, ArH); MS: m/z = 220 ($M^{+\cdot}$); *Anal*. Calcd. for $C_{13}H_8N_4$ (220.24) C, 70.90; H, 3.66. Found: C, 70.75; H, 3.96.

5,7,13b-Triazadibenzo[c,g]fluorene (6d). Purification by flash chromatography using DCM:MeOH = 100:1, 100:2, 95:5 resulted in a yellowish solid. Yield: 0.14 g, 0.52 mmol, 30%; mp. 179.6–181.0°C; ^{1}H NMR ($CDCl_3$) δ 7.55–7.78 (m, 6H, ArH), 7.89 (d, 1H, ArH, *J* = 7.6 Hz), 8.36 (d, 1H, ArH, *J* = 8.0 Hz), 8.62 (d, 1H, ArH, *J* = 8.4 Hz), 9.53 (s, 1H, ArH); MS: m/z = 269 ($M^{+\cdot}$); *Anal*. Calcd. for $C_{18}H_{11}N_3$ (269.31) C, 80.28; H, 4.12. Found: C, 80.55; H, 4.11.

6a,11,13-Triazadibenzo[a,g]fluorene (6e). Purification by flash chromatography using toluene:2-propanol = 4:1, 3:2, 2:3 resulted in a brownish solid which was recrystallized from EtOH to give a dark yellowish solid. Yield: 0.24 g, 0.89 mmol, 51%; mp. 229.7–229.8°C; ^{1}H NMR (DMSO-d_6) δ 7.57 (d, 1H, ArH, *J* = 7.6 Hz), 7.80–7.87 (m, 4H, ArH), 8.05–8.07 (m, 1H, ArH), 8.28–8.31 (m, 1H, ArH), 8.76–8.78 (m, 1H, ArH), 8.91–8.93 (m, 1H, ArH), 9.33 (d, 1H, ArH, *J* = 7.6 Hz), 9.52 (s, 1H, ArH); MS: m/z = 269 ($M^{+\cdot}$); *Anal*. Calcd. for $C_{18}H_{11}N_3$ (269.31) C, 80.28; H, 4.12. Found: C, 80.07; H, 4.13.

General procedure for the preparation of 7a-7e. A round-bottomed flask was charged with $Pd(OAc)_2$ (39 mg, 0.17 mmol, 0.10 eq), Xantphos (4,5-bis(diphenylphosphino)-9,9-dimethyl-xanthene) (0.10 g, 0.17 mmol, 0.10 eq) and 1,2-dimethoxy-ethane (8 mL). The suspension thus obtained was flushed with argon for 1 h under magnetic stirring at room temperature. Meanwhile, a three-necked round-bottomed flask was charged with 3-chloro-4-iodoquinoline (2) (0.50 g, 1.73 mmol, 1.00 eq), the corresponding amidine (1.73 mmol, 1.0 eq), Cs_2CO_3 (2.255 g, 6.92 mmol, 4.0 eq), CuI (66 mg, 0.35 mmol, 0.20 eq) and 1,2-dimethoxyethane (10 mL). To this mixture, the preformed Pd-catalyst was added. The resulting mixture was flushed with argon again and heated for 19–28 h at reflux temperature. After cooling to room temperature, 1,2-dimethoxyethane was removed by evaporation, the residue was mixed with silica gel and it was placed on top of a silica gel column and purified by flash chromatography.

5,6b,11-Triazabenzo[a]fluorene (7a). Purification by flash chromatography using toluene:MeOH = 95:5 resulted in a yellowish solid which was recrystallized from EtOH to give a beige solid. Yield: 0.02 g, 0.09 mmol, 5%; mp. 244.7–244.8°C; ^{1}H NMR ($CDCl_3$) δ 7.08–7.11 (m, 1H, ArH), 7.58–7.62 (m, 1H, ArH), 7.70–7.81 (m, 2H, ArH), 7.91–7.92 (m, 1H, ArH), 8.26–8.28 (m, 1H, ArH), 8.73–8.75 (m, 2H, ArH), 9.50 (s, 1H, ArH); MS: m/z = 219 ($M^{+\cdot}$) *Anal*. Calcd. for $C_{14}H_9N_3$ (219.25) C, 76.70; H, 4.14. Found: C, 76.81; H, 4.13.

5,6b,9,11-Tetraazabenzo[a]fluorene (7b). Purification by flash chromatography using toluene:MeOH = 9:1, 4:1, 1:1 resulted in a brownish solid which was recrystallized from EtOH to give a light brownish solid. Yield: 0.25 g, 1.14 mmol, 66%; mp. >250°C; ^{1}H NMR (DMSO-d_6) δ 7.75–7.85 (m, 2H, ArH), 8.19–8.22 (m, 1H, ArH), 8.27 (d, 1H, ArH, *J* = 4.8 Hz), 8.61–8.63 (m, 1H, ArH), 9.41–9.42 (m, 1H, ArH), 9.49–9.50 (m, 1H, ArH), 9.91 (s, 1H, ArH); MS: m/z = 220 ($M^{+\cdot}$); *Anal*. Calcd. for $C_{13}H_8N_4$ (220.24) C, 70.90; H, 3.66. Found: C, 70.79; H, 3.67.

5,6b,13-Triazadibenzo[a,g]fluorene (7d). Purification by flash chromatography using hexane:EtOAc = 3:2, 1:1, 2:3 resulted in a brownish solid which was recrystallized from EtOH to give a beige solid. Yield: 20 mg, 0.07 mmol, 4%; mp. >250°C; ^{1}H NMR ($CDCl_3$) δ 7.58–7.62 (m, 1H, ArH), 7.71–7.96 (m, 6H, ArH), 8.29 (d, 1H, ArH, *J* = 8 Hz), 8.67 (d, 1H, ArH, *J* = 8.4 Hz), 8.77–7.79 (m, 1H, ArH), 10.07 (s, 1H, ArH); MS: m/z = 269 ($M^{+\cdot}$); *Anal*. Calcd. for $C_{18}H_{11}N_3$ (269.31) C, 80.28; H, 4.12. Found: C, 80.05; H, 4.13.

5,6b,13-Triazadibenzo[a,i]fluorene (7e). Purification by flash chromatography using toluene:MeOH = 95:5, 1:1 resulted in a brownish solid which was recrystallized from EtOH to give a beige solid. Yield: 0.20 g, 0.74 mmol, 43%; mp. >250°C; ^{1}H NMR ($CDCl_3$) δ 7.28 (d, 1H, ArH, $J = 7.2$ Hz), 7.71–7.83 (m, 5H, ArH), 8.26–8.28 (m, 1H, ArH), 8.41 (d, 1H, ArH, $J = 7.2$ Hz), 8.81–8.83 (m, 1H, ArH), 8.95–8.98 (m, 1H, ArH), 9.46 (s, 1H, ArH); MS: m/z = 269 ($M^{+\cdot}$) *Anal.* Calcd. for $C_{18}H_{11}N_3$ (269.31) C, 80.28; H, 4.12. Found: C, 80.43; H, 4.11.

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Synthesis of Substituted 4-(5-Alkyl-thiazol-2-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazines and 5-(2,3-Dihydro-1,4-benzoxazin-4-ylmethyl)-4-methyl-1-phenyl-1*H*-pyrazol-3-ylamine

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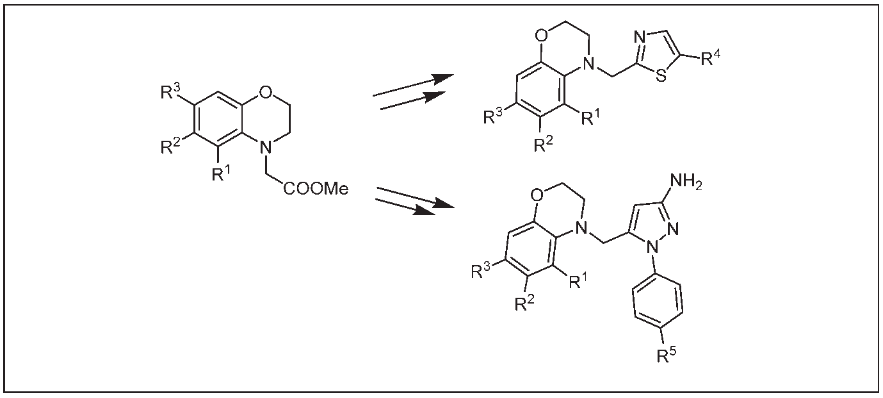

Substituted 4-(5-alkyl-thiazol-2-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazines and 5-(2,3-dihydro-1,4-benzoxazin-4-ylmethyl)-4-methyl-1-phenyl-1*H*-pyrazol-3-ylamines were prepared by the reaction of (2,3-dihydro-1,4-benzoxazin-4-yl)-acetic acid methyl ester and some common reagents to provide the product in satisfactory yields.

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INTRODUCTION

Benzoxazines have been used as intermediates in the synthesis of many heterocyclic structures of biological importance. These derivatives have been shown to be selective serotonin reuptake inhibitors. They have also shown activities toward 5-HT$_{1A}$ receptor while the 1,4-benzoxazine imidazole derivatives have shown *in vivo* activities against a murine experimental model of candidiasis. Some of the benzoxazines were most effective in promoting HUVEC apoptosis and inhibiting A549 cell proliferation [1–4]. Some of the *N*-substituted benzoxazines have been reported to cure thrombi-related diseases, for instance, platelet aggregation, thrombosis, myocardial infarction [5] *etc*. Derivatives of benzomorpholine have been incorporated to show hypotensive/antihypertensive effectiveness [6] as well as potential dopamine D$_3$ receptor ligands and inhibitions of cardiac phosphodiestrase (PDE) fraction *in vitro* and for positive inotropic activity *in vivo* [7]. They also tend to inhibit oxidative stress mediated neuronal degeneration in neuronal cell cultures [8,9].

The pyrazole and thiazole ring systems are common structural motifs in a number of biologically active molecules. Thiazole ring systems originate in nature as a consequence of peptide modification containing cysteine side chain residue and are the product of cyclodehydration and redox reactions. More recently, extensive studies have been focused on aryl pyrazoles for exhibiting cyclooxygenase-2 (COX-2) and non-nucleoside HIV-1 reverse transcriptase inhibitory properties. This structure has found applications in drug development for the treatment of allergies, hypertension, schizophrenia, inflammation, bacterial, and HIV7 infections. Aminothiazoles are known to be ligands of estrogen receptors as well as a novel class of adenosine receptor antagonists, whereas other analogues are used as fungicides, inhibiting *in vivo* growth of *Xanthomonas* and as an ingredient of herbicides or as schistosomicidal and antihelmintic drugs [10–15].

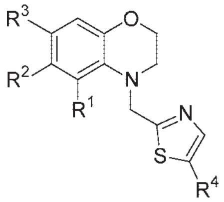
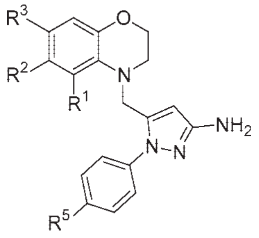
RESULTS AND DISCUSSION

As part of an ongoing program aimed at synthesizing benzoxazine derivatives of biological interest, we wanted to introduce different heterocyclic ring systems on the *N*-atom of the benzoxazines. Our literature survey revealed that benzoxazines-bearing pyrazole and thiazole rings on the *N*-atom have not been reported in spite of the fact that these two heterocyclic systems played an important role in drug development.

Earlier, we have reported [16] the synthesis of 3,4-dihydro-1,4-2*H*-benzoxazine from 2-aminophenols and

Table 1

Preparation of N-substituted 3,4-dihydro-2H-1,4-benzoxazines.

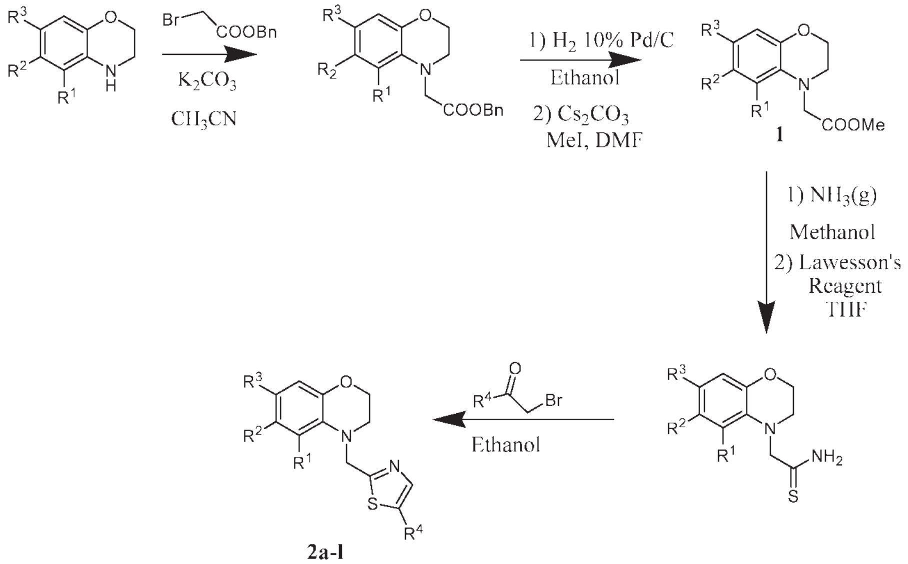
Entry	Product (**2a–j**)  	Yield **2a–j** (%)	Product (**3a–j**)  	Yield **3a–j** (%)
a	R^1 = H, R^2 = H, R^3 = H R^4 = Me	64	R^1 = H, R^2 = H, R^3 = H, R^5 = H	59
b	R^1 = H, R^2 = H, R^3 = H R^4 = CH_2CH_3	61	R^1 = H, R^2 = H, R^3 = H, R^5 = Me	57
c	R^1 = H, R^2 = H, R^3 = Me, R^4 = Me	53	R^1 = Me, R^2 = H, R^3 = H, R^5 = H	59
d	R^1 = H, R^2 = H, R^3 = Me, R^4 = CH_2CH_3	54	R^1 = H, R^2 = Me, R^3 = H, R^5 = H	61
e	R^1 = H,R^2 = Me,R^3 = H, R^4 = CH_2CH_3	61	R^1 = H, R^2 = F, R^3 = H, R^5 = H	62
f	R^1 = Me, R^2 = H, R^3 = H, R^4 = CH_2CH_3	57	R^1 = H, R^2 = CF_3, R^3 = H, R^5 = H	45
g	R^1 = H, R^2 = H, R^3 = H, R^4 = Ph	58	R^1 = H, R^2 = Cl, R^3 = H, R^5 = Me	41
h	R^1 = H, R^2 = H, R^3 = Me R^4 = Ph	59	R^1 = H, R^2 = Me, R^3 = H, R^5 = Me	47
i	R^1 = H, R^2 = Me, R^3 = H R^4 = Ph	62	R^1 = H, R^2 = F, R^3 = H, R^5 = Me	46
j	R^1 = Me, R^2 = H, R^3 = H R^4 = Ph	62	R^1 = H, R^2 = H, R^3 = Me, R^5 = H	61

1,2-dibromoethane using K_2CO_3 in DMF, which was then subjected to N-substitution using alkyl bromide. Subsequent debenzylation and esterification yielded (2,3-dihydro-1,4-benzoxazin-4-yl)-acetic acid methyl ester **1**. Here, we report the synthesis of 4-(5-alkyl-thiazol-2-ylmethyl)-3,4-dihydro-2H-1,4-benzoxazines and 5-(2,3-dihydro-1,4-benzoxazin-4-ylmethyl)-4-methyl-1-phenyl-1H-pyrazol-3-ylamine starting from (2,3-dihydro-1,4-benzoxazin-4-yl)-acetic acid methyl ester.

The compounds **2a–j** (Table 1) were first prepared by converting the methyl ester derivatives to amide derivatives by passing NH_3 (g) through the solution of **3** at 0–5°C and then to the corresponding thioamides using Lawesson's reagent (Scheme 1). Further treatment with 1-bromo-alkan-2-one in ethanol gave the desired products in about 53–64% yields.

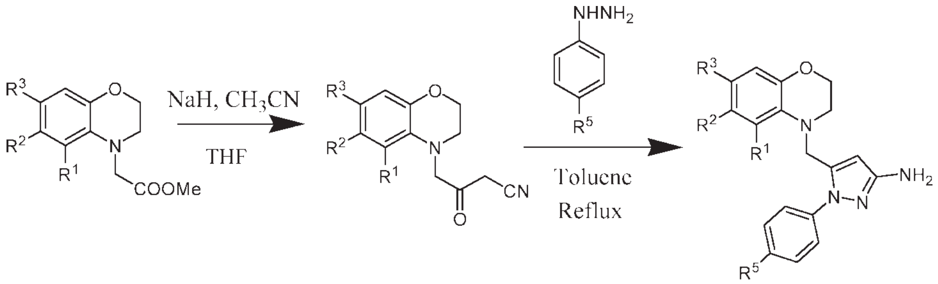
Compounds **3a–j** (Table 1) was prepared by first converting the methyl ester derivatives to the corresponding butyronitrile derivatives using NaH and acetonitrile. Further treatment with phenyl hydrazine yielded the desired products in 41–62% yields (Scheme 2). Catalytic amounts of KF increased the rate of the reaction and hence the yield.

Scheme 1



2a-l

Scheme 2



3a-j

EXPERIMENTAL

Carbon, hydrogen, and nitrogen analysis were performed with a Perkin-Elmer 2400 series II instrument. IR spectra were recorded on a BOMEM DA-8 FTIR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 spectrometer. Positive-ion and negative-ion electrospray ionization (ESI) mass spectra were measured on an ion trap analyzer Esquire 3000 (Bruker Daltonics).

Synthesis of Substituted 4-(5-alkyl-thiazol-2-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazine. The methyl ester derivative (**1**) was first dissolved in methanol, the reaction mixture was cooled in ice, and NH_3 gas was passed through it for 10 min. The reaction mixture was stirred overnight at room temperature, resulting in separation of dirty white solids, which were separated by filtration to yield the amide derivative. The crude product was washed with hexane to yield the pure product. IR (KBr) ν cm^{-1} 3330 (m) and 3050 (m) ($CONH_2$) H^1 NMR (DMSO-d$_6$, 400 MHz) δ ppm 3.3 (t, 2H, *J* = 14.1 Hz), 4.07 (s, 2H,), 4.32 (t, 2H, *J* = 9.1 Hz), 6.24 (b, 2H), 6.46–6.5 (m, 4H). Calc. for $C_{10}H_{12}N_2O_2$ C, 62.49; H, 6.29; N, 14.57%; observed were C, 62.50; H, 6.28; N, 14.56%.

The amide derivative was then dissolved in Dry THF and treated with Lawesson's reagent (0.5 eq) and stirred overnight under N_2 atm. The reaction on completion was evaporated in vacuum and extracted with ethylacetate. The complete organic extract was dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography using ethyl acetate and hexane (1:10) as an eluent to yield the desired product. IR (KBr) ν cm^{-1} 1175. The 2-(2,3-dihydro-1,4-benzoxazin-4-yl)-thioacetamide was then refluxed with 1-bromo butan-2-one in ethanol, the reaction was monitored using TLC. The reaction on completion was evaporated in vacuum and extracted with DCM. The complete organic extract was dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography using ethyl acetate and hexane (1:20) as an eluent to yield the desired product (**2b**). IR (KBr) ν cm^{-1} 1725 (C=N stretching) H^1 NMR ($CDCl_3$, 400 MHz) δ ppm 1.17 (t, 3H, *J* = 14.2 Hz), 3.3–3.31 (q, 2H, *J* = 8.6 Hz), 3.82 (t, 2H, *J* = 14.3 Hz), 4.27 (t, 2H, *J* = 8.9 Hz), 5.72 (s, 2H), 6.46–6.65 (m, 4H), 7.04 (s, 1H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 15.6, 22.8, 57.6, 60.2 (NCH_2), 73.1 (OCH_2), 112.8, 116.8, 117.3, 119.5, 130.2, 133.4, 140.1, 141.3, 166.1, *m*/*z* = 261.26. Calc. for $C_{14}H_{16}N_2OS$ C, 64.58; H, 6.19; N, 10.76%; observed were C, 64.60; H, 6.18; N, 10.75%.

(**2a**). IR (KBr) ν cm^{-1} 1720 (C=N stretching) H^1 NMR ($CDCl_3$, 400 MHz) δ ppm 2.37 (s, 3H), 3.81 (t, 2H, *J* = 14.3 Hz), 4.22 (t, 2H, *J* = 8.9 Hz), 4.72 (s, 2H), 6.46–6.65 (m, 4H, ArH), 7.23 (s, 1H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 14.2, 58.6, 60.2 (NCH_2), 73.1 (OCH_2), 113.8, 115.8, 118.3, 120.5, 130.6, 133.7, 140.1, 143.3, 165.4, *m*/*z* = 247.26. Calc. for $C_{13}H_{14}N_2OS$ C, 63.39; H, 5.73; N, 11.37%; observed were C, 63.41; H, 5.75; N, 11.36%.

(**2c**). IR (KBr) ν cm^{-1} 1722 (C=N stretching) H^1 NMR ($CDCl_3$, 400 MHz) δ ppm 2.32 (s, 3H), 2.47 (s, 3H), 3.84 (t, 2H, *J* = 12.3 Hz), 4.22 (t, 2H, *J* = 9.1 Hz), 4.76 (s, 2H), 6.46–6.65 (m, 3H, ArH), 7.31 (s, 1H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 14.5, 21.7, 58.4, 60.2 (NCH_2), 74.1 (OCH_2), 113.5, 115.9, 121.5, 127.1, 127.8, 133.7, 140.1, 143.3, 165.0, *m*/*z* = 247. Calc. for $C_{14}H_{16}N_2OS$ C, 64.58; H, 6.19; N, 10.76%; observed were C, 64.60; H, 6.20; N, 10.75%.

(**2d**). IR (KBr) ν cm^{-1} 1721 (C—N stretching) H^1 NMR ($CDCl_3$, 400 MHz) δ ppm 1.18 (t, 3H, *J* = 14.1 Hz), 2.31 (s, 3H), 3.29–3.39 (q, 2H, *J* = 8.7 Hz), 3.82 (t, 2H, *J* = 14.3 Hz), 4.27 (t, 2H, *J* = 14.1 Hz), 5.69 (s, 2H), 6.41(s, 1H), 6.38 (d, 1H, *J* = 7.2 Hz), 6.47 (d, 1H, *J* = 7.2 Hz), 7.11 (s, 1H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 15.5, 21.9, 22.7, 57.7, 60.1 (NCH_2), 73.3 (OCH_2), 112.8, 113.3, 119.9, 127.1, 130.4, 133.5, 140.2, 141.4, 166.1, *m*/*z* = 274.26. Calc. for $C_{15}H_{18}N_2OS$ C, 65.66; H, 6.61; N, 10.21%; observed were C, 65.64; H, 6.60; N, 10.22%.

(**2e**). IR (KBr) ν cm^{-1} 1718 (C=N stretching) H^1 NMR ($CDCl_3$, 400 MHz) δ ppm 1.15 (t, 3H, *J* = 14 Hz), 3.29–3.33 (q, 2H, *J* = 8.7 Hz), 3.80 (t, 2H, *J* = 14.2 Hz), 4.26 (t, 2H, *J* = 14 Hz), 5.69 (s, 2H), 6.51–6.60 (m, 4H), 7.15 (s, 1H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 15.7, 22.9, 57.4, 60.2 (NCH_2), 73.4 (OCH_2), 113.1, 114.3, 118.9, 120.5, 130.9, 133.9, 140.6, 141.9, 166.3, *m*/*z* = 261.10. Calc. for $C_{14}H_{16}N_2OS$ C, 64.58; H, 6.19; N, 10.76%; observed were C, 64.60; H, 6.18; N, 10.74%.

(**2f**). IR (KBr) ν cm^{-1} 1719 (C=N stretching) H^1 NMR ($CDCl_3$, 100 MHz) δ ppm 1.15 (t, 3H, *J* = 14.1 Hz), 2.30 (s, 3H), 3.34–3.39 (q, 2H, *J* = 8.9 Hz), 3.84 (t, 2H, *J* = 14.2 Hz), 4.29 (t, 2H, *J* = 14.0 Hz), 5.70 (s, 2H), 6.41–6.47 (m, 3H), 7.16 (s, 1H). C^{13} NMR ($CDCl_3$, 400 MHz) δ ppm 15.5, 16.9, 22.5, 57.5, 60.2 (NCH_2), 73.6 (OCH_2), 112.8, 119.9, 120.7, 127.1, 130.4, 130.9, 133.5, 141.4, 165.8, *m*/*z* = 275.12. Calc. for $C_{15}H_{18}N_2OS$ C, 65.66; H, 6.61; N, 10.21%; observed were C, 65.64; H, 6.62; N, 10.20%.

(**2g**). IR (KBr) ν cm^{-1} 1720 (C=N stretching) H^1 NMR ($CDCl_3$, 400 MHz) δ ppm 3.84 (t, 2H, *J* = 14.0 Hz), 4.20 (t, 2H, *J* = 9.0 Hz), 4.76 (s, 2H), 6.46–6.65 (m, 4H, ArH), 7.23–7.32 (m, 5H, ArH), 8.21 (s, 1H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 14.5, 21.7, 58.4, 60.2 (NCH_2), 74.1 (OCH_2), 113.5, 115.9, 121.5, 127.1, 127.8, 133.7, 140.1, 143.3, 165.0, *m/z* = 247. Calc. for $C_{14}H_{16}N_2OS$ C, 64.58; H, 6.19; N, 10.76%; observed were C, 64.61; H, 6.21; N, 10.75%.

(**2i**). IR (KBr) ν cm^{-1} 31722 (C=N stretching) H^1 NMR ($CDCl_3$, 400 MHz) δ ppm 2.34 (s, 3H), 3.80 (t, 2H, *J* = 14 Hz), 4.32 (t, 2H, *J* = 14.1 Hz), 5.76 (s, 2H), 6.33 (s, 1H), 6.39 (d, 1H, *J* = 7.8 Hz), 6.47 (d, 1H, *J* = 7.8 Hz), 7.39–7.45 (m, 5H), 7.89 (s, 1H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 23.5, 57.9, 60.7 (NCH_2), 73.9 (OCH_2), 112.8, 114.9, 118.7, 126.1, 128.2, 129.1, 130.3, 135.7, 133.5, 141.4, 142.8, 147.3, 166.8, *m/z* = 322.11. Calc. for $C_{19}H_{18}N_2OS$ C, 70.78; H, 5.63; N, 8.69%; observed were C, 70.77; H, 5.61; N, 8.68%.

(**2j**). IR (KBr) ν cm^{-1} 1715 (C=N stretching) H^1 NMR ($CDCl_3$, 400 MHz) δ ppm 2.31 (s, 3H), 3.82 (t, 2H, *J* = 14 Hz), 4.31 (t, 2H, *J* = 14.1 Hz), 5.79 (s, 2H), 6.43–6.49 (m, 3H), 7.36–7.42 (m, 5H), 7.91(s, 1H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 15.5, 57.9, 60.7 (NCH_2), 73.9 (OCH_2), 112.8, 119.9, 120.7, 126.1, 127.1, 128.2, 129.1, 130.9, 135.4, 133.5, 141.4, 147.3, 166.8, *m/z* = 322.12. Calc. for $C_{19}H_{18}N_2OS$ C, 70.78; H, 5.63; N, 8.69%; observed were C, 70.76; H, 5.62; N, 8.70%.

Synthesis of 5-(2,3-dihydro-1,4-benzoxazin-4-ylmethyl)-4-methyl-1-phenyl-1*H*-pyrazol-3-ylamine. It involves the synthesis of butyronitrile derivative from the methyl ester(**1**) using acetonitrile (1.5 eq) and NaH (1.5 eq) in THF under N_2 atmosphere. The NaH was dissolved in THF, and acetonitrile was added drop wise at 0°C. The reaction mixture was allowed to stir at room temperature for ½ h and followed by drop wise addition of (**1**) solution in THF at 0°C. The reaction was then stirred at room temperature for 3 h. On completion of the reaction, the solvent was evaporated and work-up using ethyl acetate, the complete organic extracts were dried over Na_2SO_4 and evaporated to yield the crude product, which was purified by column chromatography using ethyl acetate and hexane (1:20). IR (KBr) ν cm^{-1} 2242 (CN stretching) H^1 NMR ($CDCl_3$, 400 MHz) δ ppm 3.61 (s, 2H), 3.82–3.86 (m, 2H), 4.24–4.26 (m, 2H), 4.56(s, 2H), 6.5–6.84 (m, 4H). Calc. for $C_{12}H_{12}N_2O_2$ C, 66.65; H, 5.59; N, 12.96%; observed were C, 66.64; H, 5.60; N, 12.94%. The butyronitrile derivative was then refluxed with substituted phenyl hydrazine (1.2 eq) for 4–5 h. The reaction on completion was evaporated under vacuum and worked-up using DCM. The complete organic was dried over Na_2SO_4 and evaporated to yield the crude product, which was purified by column chromatography using methanol and DCM (1:50) as an eluent.

(**3a**). IR (KBr) ν cm^{-1} 3420 (NH_2 stretching) H^1 NMR (DMSO-d_6, 400 MHz), δ ppm 3.84–3.86 (t, 2H, *J* = 14 Hz), 4.25–4.27 (t, 2H, *J* = 8.9 Hz), 5.56 (s, 2H), 6.4–6.84 (m, 4H) 7.3–7.5 (m, 5H) 7.9 (s, 1H) 8.2 (b, 2H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 50.1, 60.2 (NCH_2), 73.1 (OCH_2), 94.8, 112.8, 116.8, 117.3, 118.8, 119.5, 126.5, 129.1, 130.2, 135.6, 139.8, 141.1, 164.3. *m/z* = 307. Calc. for $C_{18}H_{18}N_4O$ C, 70.57; H, 5.92; N, 18.29%; observed were C, 70.59; H, 5.91; N, 18.3%.

(**3b**). IR (KBr) ν cm^{-1} 3412 (NH_2 stretching) H^1 NMR (DMSO-d_6, 400 MHz), δ ppm 2.36 (s, 3H), 3.86 (t, 2H, *J* = 14 Hz), 4.27 (t, 2H, *J* = 8.9 Hz), 5.42 (s, 2H), 6.35 (s, 1H), 6.48–6.64 (m, 4H) 7.35–7.51 (m, 4H, ArH), 8.12 (b, 2H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 21.2, 50.2, 59.2 (NCH_2), 74.1 (OCH_2), 94.8, 113.8, 115.8, 117.9, 118.3, 121.5, 129.5, 130.8, 135.2, 136.1, 136.9, 143.1, 164.1. *m/z* = 321. Calc. for $C_{19}H_{20}N_4O$ C, 71.23; H, 6.29; N, 17.49%; observed were C, 71.25; H, 6.31; N, 17.51%.

(**3c**). IR (KBr) ν cm^{-1} 3412 (NH stretching) H^1 NMR (DMSO-d_6, 400 MHz), δ ppm 2.42 (s, 3H), 3.81 (t, 2H, *J* = 9.8 Hz), 4.20 (t, 2H, *J* = 9.0 Hz), 5.22 (s, 2H), 6.31 (s, 1H), 6.40–6.44 (m, 3H) 7.31–7.45 (m, 5H, ArH), 7.02 (b, 2H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 13.2, 50.4, 59.6 (NCH_2), 73.9 (OCH_2), 94.9, 112.8, 118.0, 118.6, 121.8, 126.2, 129.2, 131.1, 136.1, 136.9, 139.9, 143.1, 163.8. *m/z* = 319. Calc. for $C_{19}H_{20}N_4O$ C, 71.23; H, 6.29; N, 17.49%; observed were C, 71.24; H, 6.30; N, 17.48%.

(**3d**). IR (KBr) ν cm^{-1} 3421 (NH stretching) H^1 NMR (DMSO-d_6, 400 MHz), δ ppm 2.47 (s, 3H), 3.85 (t, 2H, *J* = 9.5 Hz), 4.23 (t, 2H, *J* = 9.1 Hz), 5.27 (s, 2H), 6.39 (s, 1H), 6.41 (s, 1H), 6.47 (d, 1H, *J* = 7.2 Hz), 6.52 (d, 1H, *J* = 7.2 Hz), 7.31–7.45 (m, 5H, ArH), 7.06 (b, 2H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 23.2, 32.3, 59.3 (NCH_2), 74.1 (OCH_2), 92.9, 113.8, 114.5, 115.1, 118.6, 126.2, 129.2, 130.1, 136.1, 137.9, 139.9, 143.1, 160.8. *m/z* = 320.16 Calc. for $C_{19}H_{20}N_4O$ C, 71.23; H, 6.29; N, 17.49%; observed were C, 71.22; H, 6.30; N, 17.47%.

(**3e**). IR (KBr) ν cm^{-1} 3420 (NH stretching) H^1 NMR (DMSO-d_6, 400 MHz), δ ppm 2.45 (s, 3H), 3.82 (t, 2H, *J* = 9.5 Hz), 4.21 (t, 2H, *J* = 9.1 Hz), 5.25 (s, 2H), 6.38 (s, 1H), 6.40 (s, 1H), 6.44 (d, 1H, *J* = 7.1 Hz), 6.50 (d, 1H, *J* = 7.1 Hz), 7.33–7.45 (m, 5H, ArH), 7.03 (b, 2H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 32.9, 59.4 (NCH_2), 74.2 (OCH_2), 92.9, 103.7, 105.8, 116.1, 118.6, 126.2, 129.2, 136.1, 137.9, 138.9, 146.1, 154.1, 160.8. *m/z* = 324.16 Calc. for $C_{18}H_{17}FN_4O$ C, 66.65; H, 5.28; N, 17.27%; observed were C, 66.63; H, 5.30; N, 17.26%.

(**3f**). IR (KBr) ν cm^{-1} 3427 (NH stretching) H^1 NMR (DMSO-d_6, 400 MHz), δ ppm 3.86 (t, 2H, *J* = 9.1 Hz), 4.24 (t, 2H, *J* = 9.2 Hz), 5.28 (s, 2H), 6.41 (s, 1H), 6.74 (s, 1H), 6.79 (d, 1H, *J* = 7.0 Hz), 6.85 (d, 1H, *J* = 7.0 Hz), 7.36–7.45 (m, 5H, ArH), 7.23 (b, 2H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 33.1, 59.5 (NCH_2), 74.4 (OCH_2), 93.2, 110.5, 115.1, 116.0, 120.8, 124.1, 125.9, 129.2, 136.1, 137.9, 138.9, 144.1, 146.1, 160.8. *m/z* = 374.26 Calc. for $C_{19}H_{17}F_3N_4O$ C, 60.96; H, 4.58; N, 14.97%; observed were C, 60.97; H, 4.60; N, 14.96%.

(**3g**). IR (KBr) ν cm^{-1} 3439 (NH stretching) H^1 NMR (DMSO-d_6, 400 MHz), δ ppm 2.31 (s, 3H), 3.85 (t, 2H, *J* = 9.0 Hz), 4.21 (t, 2H, *J* = 9.1 Hz), 5.30 (s, 2H), 6.39 (s, 1H), 6.54 (s, 1H), 6.69 (d, 1H, *J* = 7.2 Hz), 6.75 (d, 1H, *J* = 7.2 Hz), 7.45 (d, 2H, *J* = 7.1 Hz), 7.48 (d, 2H, *J* = 7.1 Hz), 7.18 (b, 2H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 24.1, 33.5, 59.8 (NCH_2), 74.1 (OCH_2), 93.7, 115.1, 116.0, 119.2, 120.8, 125.9, 129.2, 136.1, 137.2, 139.9, 144.1, 145.2, 160.8. *m/z* = 354.16 Calc. for $C_{19}H_{19}ClN_4O$ C, 64.31; H, 5.40; N, 15.79%; observed were C, 64.30; H, 5.41; N, 15.80%.

(**3h**). IR (KBr) ν cm^{-1} 3424 (NH stretching) H^1 NMR (DMSO-d_6, 400 MHz), δ ppm 2.31 (s, 3H), 2.35 (s, 3H), 3.80 (t, 2H, *J* = 9.0 Hz), 4.23 (t, 2H, *J* = 9.0 Hz), 5.31 (s, 2H), 6.35 (s, 1H), 6.44 (s, 1H), 6.51 (d, 1H, *J* = 7.1 Hz), 6.59 (d, 1H, *J* = 7.1 Hz), 7.42 (d, 2H, *J* = 7.0 Hz), 7.49 (d, 2H, *J* = 7.0 Hz), 7.21 (b, 2H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 24.1, 33.5, 59.8 (NCH_2), 74.1 (OCH_2), 93.7, 114.5, 115.5, 119.7, 120.8, 129.2, 130.3, 136.1, 137.2, 139.1, 144.1, 145.1, 160.8. *m/z* = 335.16 Calc. for $C_{20}H_{22}N_4O$ C, 71.83; H, 6.63; N, 16.75%; observed were C, 71.82; H, 6.62; N, 16.77%.

(**3i**). IR (KBr) ν cm^{-1} 3429 (NH stretching) H^1 NMR (DMSO-d_6, 400 MHz), δ ppm 2.32 (s, 3H), 3.82 (t, 2H, J = 9.0 Hz), 4.24 (t, 2H, J = 9.0 Hz), 5.32 (s, 2H), 6.41 (s, 1H), 6.56 (s, 1H), 6.70 (d, 1H, J = 7.0 Hz), 6.75 (d, 1H, J = 7.0 Hz), 7.45 (d, 2H, J = 7.1 Hz), 7.48 (d, 2H, J = 7.1 Hz), 7.23 (b, 2H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 24.3, 33.7, 59.9 (NCH_2), 74.5 (OCH_2), 93.4, 115.1, 116.0, 119.2, 120.8, 125.9, 129.2, 136.1, 137.2, 139.9, 145.1, 144.1, 160.8. m/z = 339.16 Calc. for $C_{19}H_{19}FN_4O$ C, 67.44; H, 5.66; F, 5.61; N, 16.56%; observed were C, 67.43; H, 5.60; N, 16.58%.

(**3j**). IR (KBr) ν cm^{-1} 3422 (NH stretching) H^1 NMR (DMSO-d_6, 400 MHz), δ ppm 2.45 (s, 3H), 3.85 (t, 2H, J = 9.0 Hz), 4.28 (t, 2H, J = 9.1 Hz), 5.32 (s, 2H), 6.37 (s, 1H), 6.41 (s, 1H), 6.47 (d, 1H, J = 7.1 Hz), 6.52 (d, 1H, J = 7.1 Hz), 7.36–7.45 (m, 5H, ArH), 7.16 (b, 2H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 23.6, 32.6, 59.5 (NCH_2), 74.3 (OCH_2), 92.5, 113.9, 114.5, 115.1, 118.6, 126.2, 129.2, 130.1, 136.1, 137.9, 139.9, 143.1, 160.8. m/z = 321.21 Calc. for $C_{19}H_{20}N_4O$ C, 71.23; H, 6.29%; N, 17.49; observed were C, 71.22; H, 6.30; N, 17.47%.

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New Imidazole Derivatives of 2(3*H*)-Benzazolones as Potential Antifungal Agents

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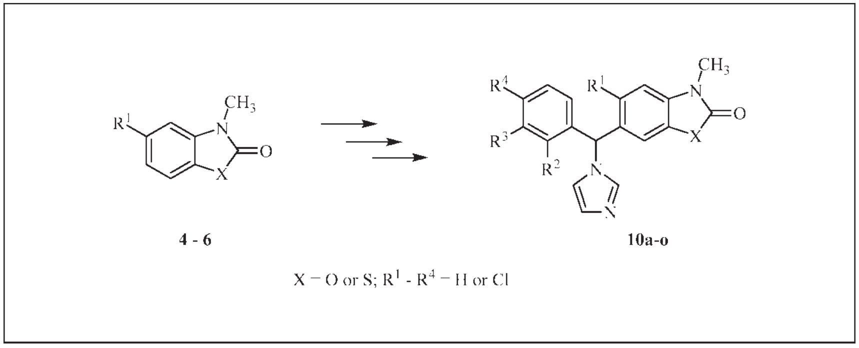

A series of new imidazole derivatives containing 2(3*H*)-benzoxazolone or 2(3*H*)-benzothiazolone ring were synthesized as analogues of the antifungal drug bifonazole. All compounds were tested *in vitro* against *Candida albicans*, *Candida parapsilosis*, and *Candida krusli*.

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INTRODUCTION

As a result of the dramatic increase in fungal infections, in recent years serious attention has been directed toward the discovery and development of new antifungal drugs. Mostly caused by *Candida albicans*, these infections are often spread through the use of broad-spectrum antibiotics, immunosuppressive agents, anticancer, and anti-AIDS drugs [1]. The main problem in the treatment of fungal infections is the increasing prevalence of drug resistance especially in patients chronically subjected to antimycotic therapy such as persons infected with HIV [2].

Azoles (imidazole and triazole) are presented in many effective antifungal drugs widely used for the treatment of topical or inner mycoses, in particular AIDS-related mycotic pathologies [3]. Their main effect is to block fungal ergosterol biosynthesis by preventing the access of natural substrate lanosterol to the active site of the cytochrome P-450-dependent enzyme 14α-lanosterol demethylase [4,5]. Since the identification of clotrimazole in 1972 [6], a number of antifungal imidazole agents have been studied and now are used in clinical practice: miconazole, bifonazole, *etc* [7]. Fluconazole is one of the most important drugs in the triazole family (Fig. 1).

In searching for new compounds with potential antifungal activity, we synthesized a number of imidazole derivatives, containing 2(3*H*)-benzoxazolone or 2(3*H*)-benzothiazolone moiety. These compounds could be examined as heterocyclic analogues of bifonazole, in which the biphenyl moiety could be replaced with benzoxazole or benzothiazole ring. A chlorine atom was introduced at different position on benzene cycle.

In this article, we present the synthesis and the results of the initial biological investigations of series bifonazole-like imidazole derivatives.

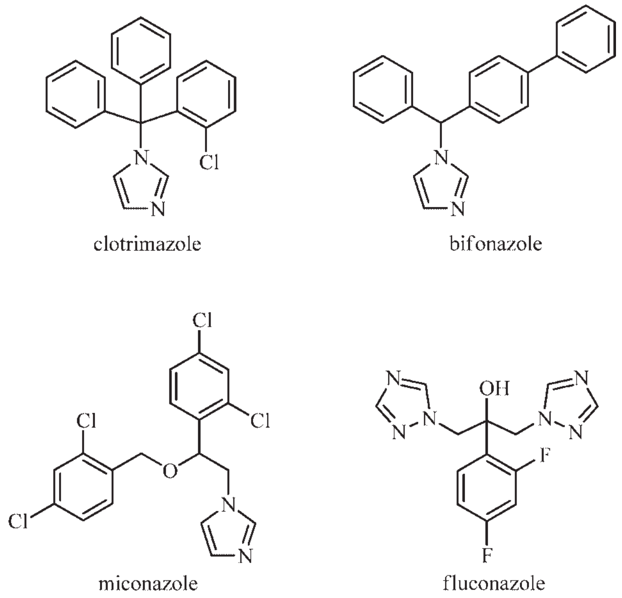


Figure 1. The structures of azole antifungal drugs used in clinical practice.

RESULTS AND DISCUSSION

A series of new imidazole derivatives **10a–o** with 2(3*H*)-benzoxazolone or 2(3*H*)-benzothiazolone moiety were prepared as potential antifungal agents as shown in Scheme 1.

The acylation of 3-methyl-2(3*H*)-benzoxazolone (**4**), 5-chloro-3-methyl-2(3*H*)-benzoxazolone (**5**), and 3-methyl-2(3*H*)-benzothiazolone (**6**) was carried out in polyphosphoric acid (PPA) with unsubstituted and various chloro-substituted benzoic acids and led to the corresponding 6-benzoyl derivatives **7a–o**.

The acylation of 2(3*H*)-benzoxazolone and 2(3*H*)-benzothiazolone was previously studied and was found to proceed with high regioselectivity [8–10]. The precise position of acylation was unequivocally assigned by X-ray single-crystal diffraction in the case of 6-benzoyl-2(3*H*)-benzoxazolone and 6-benzoyl-2(3*H*)-benzothiazolone [11,12].

Compounds **8a–o** were obtained in high yields and purity by a sodium borohydride reduction of the corresponding ketones **7a–o**. The reaction was carried out at room temperature in methanol and afforded the desired hydroxyl derivatives, which were the starting materials for the imidazole series.

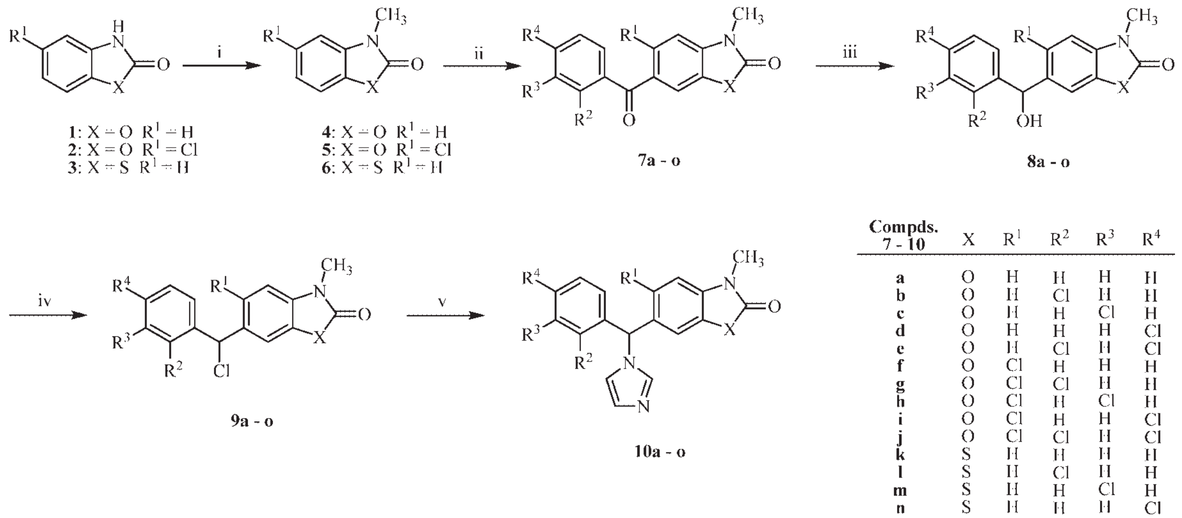
Two general approaches can be used for the synthesis of imidazole derivatives **10a–o**: by reaction of carbinols **8a–o** with *N,N′*-carbonyldiimidazole (CDI) [13] or *N,N′*-sulfinyldiimidazole (SDI) [14] or by conversion of corresponding hydroxyl derivatives **8a–o** *via* their chlorides to the desired heterocycles **10a–o**. Our early experiments showed that the use of the first method of approach (CDI or SDI) brought low yields or in any case did not form the expect imidazole derivative. It may be possible, instead of the desired compounds **10a–o**, imidazole-*N*-carboxylic ester intermediates are formed [13]. Therefore, we followed the second approach: the compounds **8a–o** were converted to the corresponding chlorides **9a–o** by refluxing with thionyl chloride in toluene. This reaction afforded sufficiently pure chlorides **9a–o**, which were used without further purification. The condensation of crude chlorides **9a–o** with two equivalents of 1*H*-imidazole provided target imidazole derivatives **10a–o** and the formation of imidazole hydrochloride as a by-product. Compounds **10a–o** were isolated in good yields (Table 1) and purified by recrystallization.

The imidazole derivatives **10a–o** have one asymmetric carbon atom; however, we did not make any efforts for the separation of individual enantiomers in view of the fact that both enantiomers of bifonazole have been reported to possess the same antimycotic profile and potency [15].

The yields, melting points, and molecular formula of imidazole derivatives **10a–o** are listed in Table 1. All spectral data are in accordance with the assumed structures. In addition to the signals for aromatic protons, ^{1}H NMR spectra of the compounds **10a–o** reveal singlet at 3.39–3.47 ppm for the N-CH_3 protons from 2(3*H*)-benzoxazolone or 2(3*H*)-benzothiazolone ring. Furthermore, the spectra show singlet for methyne proton at the asymmetric carbon atom in range 6.53–6.92 ppm.

IR spectra of compounds **10a–o**, containing 2(3*H*)-benzoxazolone or 2(3*H*)-benzothiazolone ring showed carbonyl bands at 1750–1795 cm^{-1} and 1650–1680 cm^{-1}, respectively.

Scheme 1



Compds. 7 - 10	X	R^1	R^2	R^3	R^4
a	O	H	H	H	H
b	O	H	Cl	H	H
c	O	H	H	Cl	H
d	O	H	H	H	Cl
e	O	H	Cl	H	Cl
f	O	Cl	H	H	H
g	O	Cl	Cl	H	H
h	O	Cl	H	Cl	H
i	O	Cl	H	H	Cl
j	O	Cl	Cl	H	Cl
k	S	H	H	H	H
l	S	H	Cl	H	H
m	S	H	H	Cl	H
n	S	H	H	H	Cl
o	S	H	Cl	H	Cl

Reagents and conditions: (i) $(CH_3)_2SO_4$, NaOH; (ii) benzoic acid or chloro substituted benzoic acid, PPA, 140^{0}C; (iii) $NaBH_4$, CH_3OH; (iv) $SOCl_2$, toluene, reflux; (v) imidazole, toluene, reflux.

Table 1

Yields and physical data of compounds **10a-o**.

Compd	X	R^1	R^2	R^3	R^4	Yield (%)	Mp (°C)	Molecular formula
10a	O	H	H	H	H	80	144-145	$C_{18}H_{15}N_3O_2$
10b	O	H	Cl	H	H	82	143-144	$C_{18}H_{14}ClN_3O_2$
10c	O	H	H	Cl	H	60	124-125	$C_{18}H_{14}ClN_3O_2$
10d	O	H	H	H	Cl	68	108-110	$C_{18}H_{14}ClN_3O_2$
10e	O	H	Cl	H	Cl	50	167-168	$C_{18}H_{13}Cl_2N_3O_2$
10f	O	Cl	H	H	H	69	195-196	$C_{18}H_{14}ClN_3O_2$
10g	O	Cl	Cl	H	H	70	189-190	$C_{18}H_{13}Cl_2N_3O_2$
10h	O	Cl	H	Cl	H	55	232-234	$C_{18}H_{13}Cl_2N_3O_2$
10i	O	Cl	H	H	Cl	52	119-121	$C_{18}H_{13}Cl_2N_3O_2$
10j	O	Cl	Cl	H	Cl	53	208-210	$C_{18}H_{12}Cl_3N_3O_2$
10k	S	H	H	H	H	64	132-133	$C_{18}H_{15}N_3OS$
101	S	H	Cl	H	H	84	182-184	$C_{18}H_{14}ClN_3OS$
10m	S	H	H	Cl	H	78	149-150	$C_{18}H_{14}ClN_3OS$
10n	S	H	H	H	Cl	75	188-189[a]	$C_{18}H_{14}ClN_3OS \times HNO_3$
10o	S	H	Cl	H	Cl	70	196-197	$C_{18}H_{13}Cl_2N_3OS$

[a] Compound was isolated as a nitrate.

The new imidazole derivatives **10a–o** were evaluated *in vitro* against several pathogenic fungi responsible for human diseases using the twofold agar dilution method [16]. The results of this biological investigation did not report any significant activity against yeast. The most active compounds in the series showed weak antimicrobial activity against *Candida albicans*, *Candida parapsilosis*, and *Candida krusli* with MIC values 100–400 μM.

The results of the biological tests revealed that the replacement of the biphenyl portion of the bifonazole with 2(3*H*)-benzoxazolone or 2(3*H*)-benzothiazolone moiety afforded heterocyclic analogues, which are inactive as antimycotic agents toward *Candida* strains.

EXPERIMENTAL

Melting points were determined on a Boetius hot-stage microscope and are uncorrected. IR spectra (nujol) were recorded on a Specord 71 spectrophotometer. ^1H NMR spectra were obtained on a Bruker DRX 300 spectrometer operating at 300 MHz in $CDCl_3$. Chemical shifts were reported in δ units (ppm) relative to $(CH_3)_4Si$ as internal standard. Coupling constants (*J*) were reported in Hz. Elemental analyses (C, H, N, S) for final compounds were performed on a Vario III microanalyzer. Obtained results were within 0.4% of theoretical values. Thin layer chromatography (TLC) was carried out on Silica gel plates (Merck 60 F_{254}) using toluene–chloroform–ethyl acetate (3:1:1) and ethyl acetate–isopropanol (3:1) as eluent.

Ketones **7a–o** and corresponding alcohols **8a–o** were prepared according to the method described previously [17,18].

6-[(1*H*-Imidazol-1-yl)phenylmethyl]-3-methyl-2(3*H*)-benzoxazolone (10a). A solution of hydroxyl derivative **8a** (1.28 g, 5 mmol) in toluene (10 mL) and thionyl chloride (1 mL, 14 mmol) was refluxed for 30 min and then the excess of thionyl chloride was evaporated under reduced pressure. The obtained oil of **9a** was dissolved in toluene (15 mL) and imidazole (0.68 g, 10 mmol) was added. The mixture was refluxed for 6 h, until the chloride **9a** was no longer detectable (TLC). After cooling of the reaction mixture, 5% aqueous NaOH (10 mL) was added. The organic layer was washed with water and extracted with 10% HCl. The aqueous layer was neutralized with 10% NaOH, extracted with dichloromethane, dried ($MgSO_4$), and evaporated under reduced pressure. The obtained crude product **10a** crystallized slowly. Yield 1.22 g (80%), mp 144–145 °C (ethyl acetate); ir (nujol): 1765 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.41 (s, 3H, NCH_3), 6.56 (s, 1H, CH), 6.84–7.11 (m, 7H, ArH and ImH), 7.36–7.42 (m, 4H, ArH and ImH). Anal. Calcd. for $C_{18}H_{15}N_3O_2$: C 70.81; H 4.95; N 13.76. Found: C 70.56; H 4.98; N 13.46.

6-[(2-Chlorophenyl)(1*H*-imidazol-1-yl)methyl]-3-methyl-2(3*H*)-benzoxazolone (10b). This compound was obtained according to the procedure for **10a**, using compound **8b** as a starting material. Yield: 1.36 g (82%), mp 143–144 °C (hexane–ethyl acetate 1:1); ir (nujol): 1780 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.43 (s, 3H, NCH_3), 6.79–6.85 (m, 2H, ArH and ImH), 6.92 (s, 1H, CH), 6.95–6.96 (m, 3H, ArH and ImH), 7.14 (s, 1H, ArH), 7.28 (dt, 1H, ArH, *J* = 1.8 Hz, *J* = 7.8 Hz), 7.35 (dt, 1H, ArH, *J* = 1.8 Hz, *J* = 7.8 Hz), 7.42 (s, 1H, ImH), 7.45 (dd, 1H, ArH, *J* = 1.8 Hz, *J* = 7.8 Hz). Anal. Calcd. for $C_{18}H_{14}ClN_3O_2$: C 63.63; H 4.15; N 12.37. Found: C 63.90; H 4.18; N 12.44.

6-[(3-Chlorophenyl)(1*H*-imidazol-1-yl)methyl]-3-methyl-2(3*H*)-benzoxazolone (10c). This compound was obtained according to the procedure for **10a**, using compound **8c** as a starting material. Yield: 1.02 g (60%), mp 124–125 °C (hexane–ethyl acetate, 1:1); ir (nujol): 1780 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.43 (s, 3H, NCH_3), 6.54 (s, 1H, CH), 6.85 (s, 1H, ImH), 6.96–7.08 (m, 5H, ArH and ImH), 7.14 (s, 1H, ArH), 7.33–7.36 (m, 2H, ArH), 7.44 (s, 1H, ImH). Anal. Calcd. for $C_{18}H_{14}ClN_3O_2$: C 63.63; H 4.15; N 12.37. Found: C 63.86; H 4.18; N 12.45.

6-[(4-Chlorophenyl)(1*H*-imidazol-1-yl)methyl]-3-methyl-2(3*H*)-benzoxazolone (10d). This compound was obtained according to the procedure for **10a**, using compound **8d** as a starting material. Yield: 1.16 g (68%), mp 108–110 °C (cyclohexane–ethyl acetate, 1:1); ir (nujol): 1760 (C=O) cm^{-1}; ^1H

NMR ($CDCl_3$): δ 3.43 (s, 3H, NCH_3), 6.55 (s, 1H, CH), 6.84 (s, 1H, ImH), 6.95–6.96 (m, 3H, ArH and ImH), 7.02 (d, 2H, ArH, *J* = 8.4 Hz), 7.14 (s, 1H, ArH), 7.34 (d, 2H, ArH, *J* = 8.4 Hz), 7.44 (s, 1H, ImH). Anal. Calcd. for $C_{18}H_{14}ClN_3O_2$: C 63.63; H 4.15; N 12.37. Found: C 63.96; H 4.10; N 12.56.

6-[(2,4-Dichlorophenyl)(1*H*-imidazol-1-yl)methyl]-3-methyl-2(3*H*)-benzoxazolone (10e). This compound was obtained according to the procedure for **10a**, using compound **8e** as a starting material. Yield: 0.94 g (50%), mp 167–168 °C (ethyl acetate); ir (nujol): 1750 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.43 (s, 3H, NCH_3), 6.7 (d, 1H, ArH, *J* = 7.4 Hz), 6.81 (s, 1H, ImH), 6.85 (s, 1H, CH), 6.93–6.98 (m, 3H, ArH and ImH), 7.15 (s, 1H, ArH), 7.27 (dd, 1H, ArH, *J* = 2.0 Hz, *J* = 7.4 Hz), 7.39 (s, 1H, ImH), 7.48 (d, 1H, ArH, *J* = 2.0 Hz). Anal. Calcd. for $C_{18}H_{13}Cl_2N_3O_2$: C 57.77; H 3.50; N 11.23. Found: C 57.68; H 3.62; N 11.07.

5-Chloro-6-[(1*H*-imidazol-1-yl)phenylmethyl]-3-methyl-2(3*H*)-benzoxazolone (10f). This compound was obtained according to the procedure for **10a**, using compound **8f** as a starting material. Yield: 1.17 g (69%), mp 195–196°C (ethyl acetate); ir (nujol): 1790 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.41 (s, 3H, NCH_3), 6.70 (s, 1H, CH), 6.81 (s, 1H, ImH), 6.91 (s, 1H, ArH), 7.05–7.07 (m, 3H, ArH and ImH), 7.13 (s, 1H, ArH), 7.34–7.40 (m, 4H, ArH and ImH). Anal. Calcd. for $C_{18}H_{14}ClN_3O_2$: C 63.63; H 4.15; N 12.37. Found: C 63.88; H 4.16; N 12.56.

5-Chloro-6-[(2-chlorophenyl)(1*H*-imidazol-1-yl)methyl]-3-methyl-2(3*H*)-benzoxazolone (10g). This compound was obtained according to the procedure for **10a**, using compound **8g** as a starting material. Yield: 1.31 g (70%), mp 189–190 °C (ethyl acetate); ir (nujol): 1780 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.42 (s, 3H, NCH_3), 6.63 (s, 1H, CH), 6.76 (dd, 1H, ArH, *J* = 1.5 Hz, *J* = 7.5 Hz), 6.81 (s, 1H, ImH), 7.10 (s, 1H, ArH), 7.15 – 7.17 (m, 2H, ArH and ImH), 7.23 (dt, 1H, ArH, *J* = 1.5 Hz, *J* = 7.5 Hz), 7.33–7.39 (m, 2H, ArH and ImH), 7.46 (dd, 1H, ArH, *J* = 1.5 Hz, *J* = 7.5 Hz). Anal. Calcd. for $C_{18}H_{13}Cl_2N_3O_2$: C 57.77; H 3.50; N 11.23. Found: C 57.83; H 3.49; N 10.86.

5-Chloro-6-[(3-chlorophenyl)(1*H*-imidazol-1-yl)methyl]-3-methyl-2(3*H*)-benzoxazolone (10h). This compound was obtained according to the procedure for **10a**, using compound **8h** as a starting material. Yield: 1.03 g (55%), mp 232–234 °C (toluene); ir (nujol): 1790 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.39 (s, 3H, NCH_3), 6.65 (s, 1H, CH), 6.81 (s, 1H, ImH), 6.89 (s, 1H, ArH), 6.93–6.96 (m, 1H, ArH), 7.04–7.15 (m, 3H, ArH and ImH), 7.31–7.41 (m, 3H, ArH and ImH). Anal. Calcd. for $C_{18}H_{13}Cl_2N_3O_2$: C 57.77; H 3.50; N 11.23. Found: C 57.93; H 3.41; N 11.36.

5-Chloro-6-[(4-chlorophenyl)(1*H*-imidazol-1-yl)methyl]-3-methyl-2(3*H*)-benzoxazolone (10i). This compound was obtained according to the procedure for **10a**, using compound **8i** as a starting material. Yield: 0.97 g (52%), mp 119–121 °C (cyclohexane–ethyl acetate, 2:1); ir (nujol): 1795 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.42 (s, 3H, NCH_3), 6.67 (s, 1H, CH), 6.80 (s, 1H, ImH), 6.88 (s, 1H, ArH), 6.99 (d, 2H, ArH, *J* = 7.0 Hz), 7.07 (s, 1H, ArH), 7.14 (s, 1H, ImH), 7.35–7.39 (m, 3H, ArH and ImH). Anal. Calcd. for $C_{18}H_{13}Cl_2N_3O_2$: C 57.77; H 3.50; N 11.23. Found: C 58.09; H 3.72; N 11.27.

5-Chloro-6-[(2,4-dichlorophenyl)(1*H*-imidazol-1-yl)methyl]-3-methyl-2(3*H*)-benzoxazolone (10j). This compound was obtained according to the procedure for **10a**, using compound **8j** as a starting material. Yield: 1.04 g (53%), mp 208–210 °C (toluene); ir (nujol): 1780 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.42 (s, 3H, NCH_3), 6.61 (s, 1H, CH), 6.69 (d, 1H, ArH, *J* = 8.4 Hz), 6.79 (s, 1H, ImH), 7.09–7.15 (m, 3H, ArH and ImH), 7.27 (dd, 1H, ArH, *J* = 2.1 Hz, *J* = 8.4 Hz), 7.37 (s, 1H, ImH), 7.49 (d, 1H, ArH, *J* = 2.1 Hz). Anal. Calcd. for $C_{18}H_{12}Cl_3N_3O_2$: C 52.90; H 2.96; N 10.28. Found: C 52.79; H 3.22; N 10.33.

6-[(1*H*-Imidazol-1-yl)phenylmethyl]-3-methyl-2(3*H*)-benzothiazolone (10k). This compound was obtained according to the procedure for **10a**, using compound **8k** as a starting material. Yield: 1.03 g (64%), mp 132–133 °C (ethyl acetate); ir (nujol): 1680 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.44 (s, 3H, NCH_3), 6.54 (s, 1H, CH), 6.84 (s, 1H, ImH), 6.99–7.13 (m, 6H, ArH and ImH), 7.35–7.43 (m, 4H, ArH and ImH). Anal. Calcd. for $C_{18}H_{15}N_3OS$: C 67.23; H 4.70; N 13.07. Found: C 67.09; H 4.55; N 13.43.

6-[(2-Chlorophenyl)(1*H*-imidazol-1-yl)methyl]-3-methyl-2(3*H*)-benzothiazolone (10l). This compound was obtained according to the procedure for **10a**, using compound **8l** as a starting material. Yield: 1.49 g (84%), mp 182–184 °C (cyclohexane–ethyl acetate, 1:1); ir (nujol): 1670 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.47 (s, 3H, NCH_3), 6.81–6.84 (m, 2H, ArH and ImH), 6.91 (s, 1H, CH), 7.02–7.13 (m, 4H, ArH and ImH), 7.29 (dt, 1H, ArH, *J* = 1.8 Hz, *J* = 7.8 Hz), 7.34 (dt, 1H, ArH, *J* = 1.8 Hz, *J* = 7.8 Hz), 7.39 (s, 1H, ImH), 7.45 (dd, 1H, ArH, *J* = 1.8 Hz, *J* = 7.8 Hz). Anal. Calcd. for $C_{18}H_{14}ClN_3OS$: C 60.76; H 3.97; N 11.81. Found: C 60.87; H 3.99; N 11.62.

6-[(3-Chlorophenyl)(1*H*-imidazol-1-yl)methyl]-3-methyl-2(3*H*)-benzothiazolone (10m). This compound was obtained according to the procedure for **10a**, using compound **8m** as a starting material. Yield: 1.39 g (78%), mp 149–150 °C (ethyl acetate); ir (nujol): 1670 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.47 (s, 3H, NCH_3), 6.53 (s, 1H, CH), 6.85 (s, 1H, ImH), 6.96–7.16 (m, 6H, ArH and ImH), 7.32–7.35 (m, 2H, ArH), 7.43 (s, 1H, ImH). Anal. Calcd. for $C_{18}H_{14}ClN_3OS$: C 60.76; H 3.97; N 11.81. Found: C 60.53; H 4.02; N 11.81.

6-[(4-Chlorophenyl)(1*H*-imidazol-1-yl)methyl]-3-methyl-2(3*H*)-benzothiazolone nitrate (10n). This compound was obtained according to the procedure for **10a**, using compound **8n** as a starting material. The crude product **10n**, obtained as a viscous oily residue was dissolved in isopropanol and conc. HNO_3 was added. The obtained precipitate was collected by filtration and washed with cold isopropanol. Yield: 1.57 g (75%), mp 188–189 °C (isopropanol); ir (nujol): 2770–2250 (NH^+), 1660 (C=O) cm^{-1}. Anal. Calcd. for $C_{18}H_{14}ClN_3OS \times HNO_3$: C 51.62; H 3.61; N 13.38. Found: C 52.00; H 4.01; N 13.10.

6-[(2,4-Dichlorophenyl)(1*H*-imidazol-1-yl)methyl]-3-methyl-2(3*H*)-benzothiazolone (10o). This compound was obtained according to the procedure for **10a**, using compound **8o** as a starting material. Yield: 1.37 g (70%), mp 196–197 °C (ethyl acetate); ir (nujol): 1650 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.47 (s, 3H, NCH_3), 6.75 (d, 1H, ArH, *J* = 8.4 Hz), 6.81 (s, 1H, ImH), 6.85 (s, 1H, CH), 7.02–7.16 (m, 4H, ArH and ImH), 7.27 (dd, 1H, ArH, *J* = 1.8 Hz, *J* = 8.4 Hz), 7.38 (s, 1H, ImH), 7.48 (d, 1H, ArH, *J* = 1.8 Hz). Anal. Calcd. for $C_{18}H_{13}Cl_2N_3OS$: C 55.39; H 3.36; N 10.77. Found: C 55.78; H 3.46; N 10.55.

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Microwave-Assisted, Solvent-Free Synthesis of 3′-(Aryl/Heteroaryl)-1-morpholinomethyl/piperidinomethylspiro[3*H*-indole-3,2′-thiazolidine]-2,4′(1*H*)-diones *via* 3-Isatinimines

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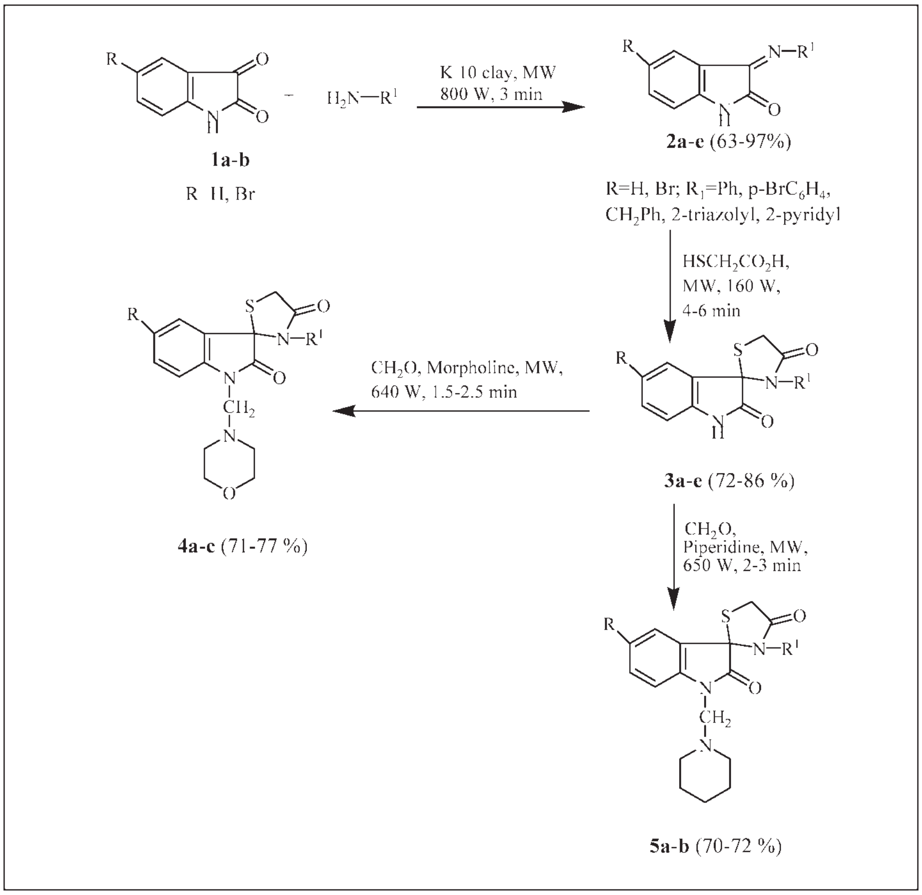

The solvent-free, microwave (MW)-assisted synthesis of a new series of 3′-(aryl/heteroaryl)-1-morpholinomethyl/piperidinomethylspiro[3*H*-indole-3,2′-thiazolidine]-2,4′(1*H*)-diones has been achieved in an open vessel. Isatins **1** undergo an easy condensation with various aryl/heteroaryl amines by MW using montmorillonite K10 clay as a solid support to afford Schiff bases **2**, which subsequently undergo smooth cyclization with TGA under neat MW conditions to afford the spiro thiazolidinones **3**. The spiro-compounds are made to react with morpholine/piperidine and formaldehyde to give the corresponding Mannich bases **4/5** in reasonably good yield.

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INTRODUCTION

Microwave-assisted organic synthesis (MAOS) has been recognized as one of the most fascinating areas of current research [1–3]. Coupling of microwave (MW) irradiation with the use of catalysts or mineral supported reactions, under solvent-free conditions, provides a clean chemical process with an advantageous merit of enhanced reaction rates, higher yields, greater selectivity, and ease of manipulation [4–7]. Isatin Mannich bases are found to have cytotoxicity against a panel of human cancer cells [8]. They also possess antibacterial, antifungal, antiviral, anti-HIV, anti-protozoal, and anthelmintic activities. Indole ring, when joined to the other aryl/heteroaryl systems through a spiro carbon atom at C-3, the resulting spiroindoles exhibit an

Table 1

Physical and analytical data of compounds **2**.

Compound	R	R^1	Time (min)	Mp (°C)	Yield (%)	Molecular formula
2a	H	p-BrC_6H_4	3	242	94	$C_{14}H_9BrN_2O$
2b	H	Ph	3	183	97	$C_{14}H_{10}N_2O$
2c	Br	$CH_2C_6H_5$	3	105	90	$C_{15}H_{11}BrN_2O$
2d	Br	2-thiazolyl	2.5	120	63	$C_{11}H_6BrN_3OS$
2e	Br	2-pyridinyl	2	190	65	$C_{13}H_8BrN_3O$

increased spectrum of biological activities [9–11]. Further, spiro[indole-thiazolidine]-diones show a wide range of pharmacological properties as anticonvulsant, anti-inflammatory, antibacterial, and anti-fungal [12–14]. *N*-Piperidino-(or morpholino-) methylisatin-3-anils possess potential biological activity and have been prepared by the condensation of isatin with arylamines followed by the Mannich reaction with piperidine or morpholine [15]. Some new spiro[indoline-3,2′-thiazolidine]-2,4′-(1*H*)-diones and bis[spiro[indoline-3,2′-thiazolidine]-2,4′(1*H*)-diones] have been obtained thermally and under MW irradiation by the condensation of isatin, aromatic amines, and mercaptoacetate without isolating the imine intermediates [16]. 3′-Substituted phenylspiro[3*H*-indole-3,2′-thiazolidine]-2,4′-(1*H*)-diones are reported to have significant antimicrobial activity [17]. A convenient synthesis of spiro[3*H*-indole-3,2′thiazolidine]-2,4′(1*H*)-diones has also been carried out by the condensation and cyclization of isatin with various aromatic amines [18]. In view of the above and prompted by the solvent-free MAOS, we describe herein a MW-assisted regioselective synthesis of 3′-(aryl/heteroaryl)-1-morpholinomethyl/piperidinomethylspiro[3*H*-indole-3,2′-thiazolidine]-2,4′(1*H*)-diones under solvent-free conditions.

RESULTS AND DISCUSSION

The reaction sequence involves MW-induced preparation of Schiff bases **2a–e** (Table 1) from isatins **1a–b** and amines (R^2-NH_2) using montmorillonite K10 clay as a solid support, followed by the cyclocondensation of Schiff bases **2a–e** and mercaptoacetic acid under neat MW irradiation conditions to achieve the synthesis of spiro[indole-thiazolidine]-diones **3a–e** (Table 2). The resulting compounds **3a–e** are then allowed to react with either morpholine or piperidine and 37% formaldehyde, under solvent-free MW irradiation conditions, to afford the corresponding Mannich bases **4a–c** and **5a**,**b** (Table 3) in reasonably good yields (Scheme 1).

To optimize the yield of products, the effect of various parameters such as MW power, irradiation time, and molar proportions of the reactants were investigated in detail. The preparation of **2a** as reference compound was observed under three different sets of reaction conditions. In the first run, isatin was refluxed with *p*-bromoaniline in absolute ethanol for 2 h, yielding the product **2a** (83%). In the second run, the reactants were refluxed in triply distilled water containing a few drops of glacial acetic acid for 30 min affording **2a** (82%). Finally, the reaction was carried out under MW-assisted (800 W) solvent free conditions using K10 clay as a solid support, to afford **2a** (94%) in just 3 min. Because of the unambiguous merits, MW method was adopted for the preparation of the rest of the compounds (Table 1). It is worthwhile to mention that in the case of compounds **2d** and **2e** (*cf*. Table 1); a 500-mL Borosil beaker containing 200 mL of water was kept as a heat sink to avoid the burning of the compound. For compound **3a**, a higher MW power (420 W and 320 W) resulted in reasonably poor yield of product probably due to the loss of low boiling mercaptoacetic acid.

However, 160 W irradiation using equimolar quantities of **2a** and mercaptoacetic acid gave rise to an enhanced yield (65%) of the product **3a**. The yields of **3a–e** were considerably increased (72–86%) when the molar ratio of the reactants **2a** and mercaptoacetic acid were kept to be 1:2. A trace of acidic compound was also observed in this run. To achieve the optimum yield of Mannich bases **4**/**5**,

Table 2

Physical and analytical data of compounds **3**.

Compound	R	R^1	Time (min)	Mp (°C)	Yield (%)	Molecular formula
3a	H	p-BrC_6H_4	6	90	72	$C_{16}H_{11}BrN_2O_2S$
3b	H	Ph	5	230	76	$C_{16}H_{12}N_2O_2S$
3c	Br	$CH_2C_6H_5$	5	125	75	$C_{17}H_{13}BrN_2O_2S$
3d	Br	2-thiazolyl	4	135	78	$C_{13}H_8BrN_3O_2S_2$
3e	Br	2-pyridinyl	4	120	87	$C_{15}H_{10}BrN_3O_2S$

Table 3

Physical and analytical data of compounds **4**/**5**.

Compound	R	R^1	X	Time (min)	Mp (°C)	Yield (%)	Molecular formula
4a	H	p-BrC_6H_4	O	2	114	71	$C_{21}H_{20}N_3O_3S$
4b	H	Ph	O	1.5	101	77	$C_{21}H_{21}N_3O_3S$
4c	Br	2-pyridinyl	O	2.5	70	74	$C_{20}H_{19}BrN_4O_3S$
5a	Br	$CH_2C_6H_5$	C	2	85	70	$C_{23}H_{24}BrN_3O_2S$
5b	Br	2-thiazolyl	C	3	120	72	$C_{19}H_{19}BrN_4O_2S_2$

the reaction mixture was irradiated intermittently (30 s/cycle) to avoid the loss of low boiling reactants.

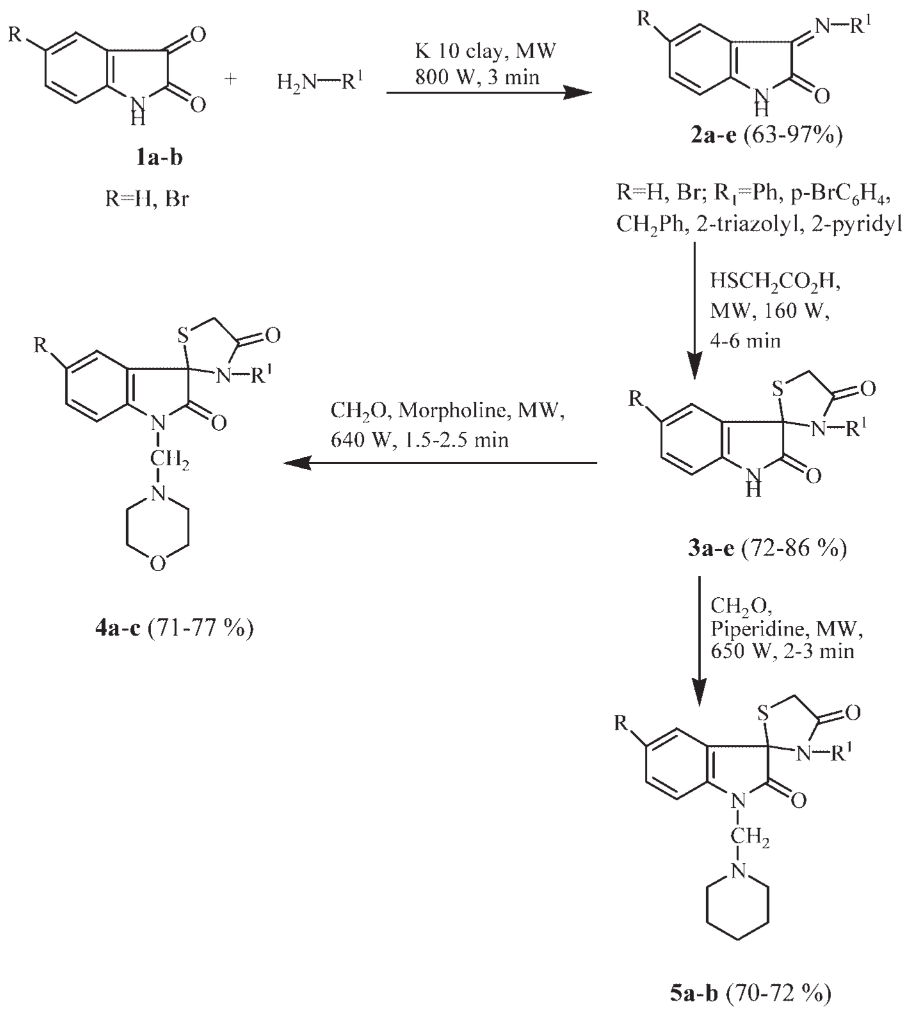
All the reactions were monitored by TLC and then worked up to afford the products, which exhibited physical and spectral data consistent with their structures.

EXPERIMENTAL

IR spectra were recorded on a JASCO FT/IR-5300 spectrophotometer, whereas NMR was run on a JEOL AL300 FTNMR spectrometer. The chemical shifts are given in δ ppm with respect to TMS as internal standard. The TLC spots were detected using iodine chamber. All commercially available chemicals were purchased from Aldrich and Merck.

General procedure for the synthesis of isatin Schiff bases (2). Equimolar quantities (1 mmole) of either isatin or 5-bromoisatin and corresponding amino reagent were blended with Montmorillonite K10 clay (20 mg) and heated for 2–3 min in a MW oven set (LG, Model MS-194W) for 900 W. Upon completion of the reaction, as checked by TLC, the product was extracted with CH_2Cl_2 (3 × 10 mL). After evaporation of

Scheme 1



the solvent under reduced pressure, the product was recrystallized from ethanol.

3-(p-Bromophenylimino)-isatin (2a). From *p*-bromoaniline, yellow crystals (94%), mp 242°C; ir (potassium bromide): NH 3236, C=O 1700, C=N 1619 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.2 (s, 1H, NH), 7.0–7.8 ppm (m, 8H, Ar—H); ^{13}C NMR (DMSO-d_6): 168 (C=O), 160 (C=N), 152 (C—N=C), 120–139 ppm (Ar—C's). Anal. Calcd. For $C_{14}H_9BrN_2O$: C, 55.84; H, 3.01; Br, 26.53; N, 9.30; O, 5.31. Found: C, 55.89; H, 3.06; Br, 26.48; N, 9.33; O, 5.28.

3-(Phenylimino)-isatin (2b). From aniline, yellow solid (97%), mp 183°C; ir (potassium bromide): NH 3260, C=O 1695, C=N 1612 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.3 (s, 1H, N—H,); 6.8–7.6 ppm (m, 9H, Ar—H); ^{13}C NMR (DMSO-d_6): 166 (C=O), 162 (C=N), 155 (C—N=C), 120–138 ppm (Ar—C's); Anal. Calcd. For $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60; O, 7.20. Found: C, 75.63; H, 4.55; N, 12.63; O, 7.18.

5-Bromo-3-(benzylimino)-isatin (2c). From benzyl amine, shiny light brown solid (90%), mp 105°C, ir (potassium bromide): NH 3350, C=O 1690, C=N 1610 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.1 (s, 1H, NH); 7.1–7.7 (m, 8H, Ar—H); 4.8 ppm (m, 2H, N—CH_2—C); ^{13}C NMR (DMSO-d_6): 168 (C=O), 161 (C=N), 152 (C—N=C), 118–137 (Ar—C's), 57 ppm (N—CH_2—C); Anal. Calcd. For $C_{15}H_{11}BrN_2O$: C, 57.16; H, 3.52; Br, 25.35; N, 8.89; O, 5.08. Found: C, 57.21; H, 3.57; Br, 25.27; N, 8.91; O, 4.91.

5-Bromo-3-(2-thiazolylimino)-isatin (2d). From 2-thiazolyl amine, dark brown solid (63%), mp 120°C; ir (potassium bromide): NH 3370, C=O 1692, C=N 1615 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.2 (s, 1H, NH); 7.4–7.8 (m, 3H, Ar—H); 7.3, 8.0 ppm (m, 2H, heteroAr—H); ^{13}C NMR (DMSO-d_6): 166 (C=O), 163 (C=N), 154 (C—N=C), 118–153 ppm (Ar and heteroAr C's); Anal. Calcd. For $C_{11}H_6BrN_3OS$: C, 42.87; H, 1.96; Br, 25.93; N, 13.64; O, 5.19; S, 10.41. Found: C, 42.79; H, 1.91; Br, 25.97; N, 13.60; O, 5.24; S, 10.50.

5-Bromo-3-(2-pyridinylimino)-isatin(2e). From 2-pyridinyl amine, yellow–orange solid (65%), mp 190°C; ir (potassium bromide): NH 3452, C=O 1685, C=N 1618 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.0 (s, 1H, NH); 7.4–7.8 (m, 3H, Ar—H); 7.2, 8.6 ppm (m, 2H, heteroAr—H); ^{13}C NMR (DMSO-d_6): 168 (C=O), 162 (C=N), 152 (C—N=C), 118–175 ppm (Ar and heteroAr C's); Anal. Calcd. For $C_{13}H_8BrN_3O$: C, 51.68; H, 2.67; Br, 26.45; N, 13.91; O, 5.30. Found: C, 51.61; H, 2.72; Br, 26.50; N, 13.85; O, 5.38.

General procedure for the synthesis of 3′-arylspiro[3*H*–indole-3,2′-thiazolidine]-2,4′(1*H*)-2,4-dione (3). A mixture of **2** (1 mmol) and mercaptoacetic acid (2 mmol) was heated for 4–6 min in a MW oven set for 160 W. The completion of the reaction was checked by TLC. The reaction content was then treated with 15 mL, 10% $NaHCO_3$ solution and stirred well. The resulting compound was filtered, washed with water, dried and recrystallized from ethanol to give the pure product.

3-(p-Bromophenyl)spiro[3H-indole-3,2′-thiazolidine]-2,4′(1H)-dione (3a). From **2a**, yellow solid (72%), mp 90°C; ir (potassium bromide): NH 3260, C=O 1720, 1690, C=N 1608 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.5 (s, 1H, NH), 6.8–7.5 ppm (m, 8H, Ar—H); ^{13}C NMR (DMSO-d_6): 77 (spiro C), 170,168 (2 C=O), 35 (S—CH_2—C), 118–141 ppm (Aromatic-C); Anal. Calcd. For $C_{16}H_{11}BrN_2O_2S$: C, 51.21; H, 2.95; Br, 21.29; N, 7.49; O, 8.53; S, 8.55. Found: C, 51.17; H, 3.09; Br, 21.37; N, 7.53; O, 8.44; S, 8.61.

3′-(Phenyl)spiro[3H-indole-3,2′-thiazolidine]-2,4′(1H)-dione (3b). From **2b**, dark brown solid (76%), mp 230°C; ir (potassium bromide): NH 3258, C=O 1730, 1695, C=N 1608 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.1 (s, 1H, NH), 6.8–7.5 (m, 9H, Ar—H), 3.5 ppm (S—CH_2—C); ^{13}C NMR (DMSO-d_6): 77 (spiro C), 170,168 (2 C=O), 35 (S—CH_2—C), 120–141 ppm (Aromatic-C); Anal. Calcd. For $C_{16}H_{12}N_2O_2S$: C, 64.85; H, 4.08; N, 9.45; O, 10.80; S, 10.82. Found: C, 64.91; H, 3.95; N, 9.52; O, 10.87; S, 10.90.

5-Bromo-3′-(benzyl)spiro[3H-indole-3,2′-thiazolidine]-2,4′(1H)-dione (3c). From **2c**, brown solid (75%), mp 125°C; ir (potassium bromide): NH 3345, C=O 1732, 1687 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.3 (s, 1H, NH), 7.1–7.4 (m, 8H, Ar—H), 3.4 (S—CH_2—C), 4.5 ppm (N—CH_2—C); ^{13}C NMR (DMSO-d_6): 74 (spiro C), 170,171 (2 C=O), 35 (S—CH_2—C), 47 (N—CH_2—C) 119–137 ppm (Aromatic-C), Anal. Calcd. For $C_{17}H_{13}BrN_2O_2S$: C, 52.45; H, 3.37; N, 7.20; O, 8.22; S, 8.24. Found: C, 52.39; H, 3.31; N, 7.14; O, 8.30; S, 8.38.

5-Bromo-3′-(2-thiazolyl)spiro[3H-indole-3,2′-thiazolidine]-2,4′(1H)-dione (3d). From **2d**, shiny blackish solid (78%), mp 135°C; ir (potassium bromide): NH 3360, C=O 1730, 1698 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.5 (s, 1H, NH), 7.2–7.4 (m, 3H, Ar—H), 3.5 (S—CH_2—C), 6.6–7.5 ppm (2H, thiazolyl), ^{13}C NMR (DMSO-d_6): 76 (spiro C), 170,168 (2 C=O), 35 (S—CH_2—C), 119–141 ppm (Aromatic-C), 108, 138, 172 (thiazolyl C), Anal. Calcd. For $C_{13}H_8BrN_3O_2S_2$: C, 40.85; H, 2.11; Br, 20.90; N, 10.99; O, 8.37; S, 16.78. Found: C, 40.91; H, 2.04; Br, 20.83; N, 11.03; O, 8.31; S, 16.84.

5-Bromo-3′-(2-piperidinyl)spiro[3H-indole-3,2′-thiazolidine]-2,4′(1H)-dione (3e). From **2e**, brown solid (87%), mp 120°C; ir (potassium bromide): NH 3450, C=O 1732, 1690 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.7 (s, 1H, NH), 7.2–7.4 (m, 3H, Ar—H), 7.1–8.5 (4H, pyridine), 3.5 ppm (S—CH_2—C), ^{13}C NMR (DMSO-d_6): 76 (spiro C), 170,168 (2 C=O), 35 (S—CH_2—C), 119–152 ppm (Aromatic-C and heteroAr-C), Anal. Calcd. for $C_{15}H_{10}BrN_3O_2S$: C, 47.89; H, 2.68; Br, 21.25; N, 11.17; O, 8.51; S, 8.52. Found: C, 47.95; H, 2.73; Br, 21.19; N, 11.11; O, 8.57; S, 8.46.

General procedure for the synthesis of 3′-aryl-1-morpholino/piperidinomethylspiro[3*H*-indole-thiazolidine]-2,4′(1*H*)-dione (4/5). An equimolar quantity of **3** (5 mmol) and morpholine/piperidine (5 mmol) was blended with 37 % formaldehyde (0.5 mL) and then irradiated in a MW oven at 640 W with 30 s/cycle for 2–3 min, as checked by TLC. After cooling, the product mixture was recrystallized from aqueous ethanol to afford product.

3′-(p-Bromophenyl)-1-morpholinomethylspiro[3H-indole-thiazolidine]-2,4′(1H)-dione (4a). From **3a**, yellow solid (71%), mp 114°C; ir (potassium bromide): C=O 1720, 1690 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.9–7.5 (m, 8H, Ar—H), 2.4–3.7 (m, 10H, 5 × CH_2), 4.6 ppm (s, N—CH_2—N); ^{13}C NMR (DMSO-d_6): 74 (spiro C), 170,168 (2 C=O), 35 (—CH_2—), 70 (N—CH_2—N), 54–71 (4 × CH_2), 118–142 ppm (Aromatic-C); Anal. Calcd. for $C_{21}H_{20}BrN_3O_3S$: C, 53.17; H, 4.25; Br, 16.84; N, 8.86; O, 10.12; S, 6.76. Found: C, 53.26; H, 4.18; Br, 16.76; N, 8.80; O, 10.21; S, 6.82

3′-(Phenyl)-1-morpholinomethylspiro[3H-indole-thiazolidine]-2,4′(1H)-dione (4b). From **3b**, yellow solid (77%), mp 101°C; ir. (potassium bromide): C=O 1730, 1695 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.9–7.3 (m, 9H, Ar—H), 2.4–3.4 (m, 10H, 5 × CH_2), 4.6 (s, N—CH_2—N), 3.4 ppm (S—CH_2—C), ^{13}C NMR

(DMSO-d_6): 74 (spiro C), 169,168 (2 C=O), 33 (—CH_2—), 71 (N—CH_2—N), 54–71 (4 × CH_2), 120–140 ppm (Aromatic-C), Anal. Calcd. for $C_{21}H_{21}N_3O_3S$: C, 63.78; H, 5.35; N, 10.63; O, 12.14; S, 8.11. Found: C, 63.85; H, 5.28 N, 10.60; O, 12.08; S, 8.28.

5-Bromo-3′-(2-piperidinyl)-1-morpholinomethylspiro [3H-indole-thiazolidine]-2,4′(1H)-dione (4c). From **3e**, brown solid (74%), mp 70°C; ir (potassium bromide): C=O 1740, 1700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.9–7.3 (m, 3H, Ar—H), 2.3–3.7 (m, 8H, 4 × CH_2), 4.5 (s, N—CH_2—N), 3.3 (S—CH_2—C), 7.2–8.5 ppm (4H, pyridine), ^{13}C NMR (DMSO-d_6): 75 (spiro C), 170,168 (2 C=O), 33 (S—CH_2—C), 70 (N—CH_2—N), 54–71 (4 × CH_2), 119–142 (Aromatic-C), 115–153 ppm (pyridine C), Anal. Calcd. for $C_{20}H_{19}BrN_4O_3S$: C, 50.53; H, 4.03; Br, 16.81; N, 11.79; O, 10.10; S, 6.75. Found: C, 50.59; H, 4.11; Br, 16.77; N, 11.84; O, 10.17; S, 6.81.

5-Bromo-3′-(benzyl)-1-piperidinomethylspiro[3H-indole-thiazolidine]-2,4′(1H)-dione (5a). From **3c**, brown solid (70%), mp 85°C; ir (potassium bromide): C=O 1728, 1695 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.9–7.5 (m, 8H, Ar—H), 1.5–3.3 (m, 12H, 6 × CH_2), 4.6 (s, N—CH_2—N), 4.5 (N—CH_2—C), 3.3 ppm (S—CH_2—C), ^{13}C NMR (DMSO-d_6): 68 (spiro C), 171,168 (2 C=O), 35 (S—CH_2—C), 70 (N—CH_2—N), 54–71 (4 × CH_2), 125–141 ppm (Aromatic-C), Anal. Calcd. for $C_{23}H_{24}BrN_3O_3S$: C, 56.79; H, 4.97; Br, 16.43; N, 8.64; O, 6.58; S, 6.59. Found: C, 56.67; H, 5.08; Br, 16.49; N, 8.70; O, 6.49; S, 6.50.

5-Bromo-3′-(2-thiazolyl)-1-piperidinomethylspiro[3H-indole-thiazolidine]-2,4′(1H)-dione (5b). From **3d**, coffee colored shiny powder (72%), mp 120°C; ir (potassium bromide): C=O 1735, 1692 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.8–7.3 (m, 3H, Ar—H), 1.5–2.4 (m, 10H, 5 × CH_2), 4.5 (s, N—CH_2—N), 6.5,7.5 (2H, thiazole), 3.3 ppm (S—CH_2—C), ^{13}C NMR (DMSO-d_6): 74 (spiro C), 173,172 (2 C=O), 35 (S—CH_2—C), 70 (N—CH_2—N), 54–71 (5 × CH_2), 119–141 (Aromatic-C), 138,168,171 ppm (thiazole), Anal. Calcd. for $C_{19}H_{19}BrN_4O_2S_2$: C, 47.60; H, 3.49; Br, 16.67; N, 11.69; O, 6.67; S, 13.38. Found: C, 47.51; H, 3.56; Br, 16.71; N, 11.75; O, 6.59; S, 13.47

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A Simple Three-Component Condensation: Highly Efficient Microwave-Assisted One-Pot Synthesis of Polyfunctional Pyridine Derivatives

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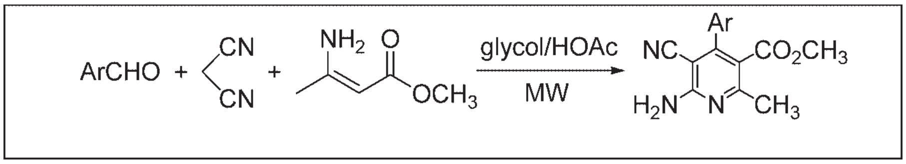

A simple facile one-step microwave-enhanced synthesis of methyl 4-substituted-6-amino-5-cyano-2-methylpyridine-3-carboxylate derivatives *via* a three-component reaction of aromatic aldehydes, malononitrile, and methyl 3-aminobut-2-enoate has been developed. It is an efficient and promising synthetic strategy to build the polyfunctional pyridine skeleton.

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INTRODUCTION

Multicomponent reactions (MCRs), an important class of organic reactions, are one-pot processes with at least three components to form a single product, which incorporates most or even all of the starting materials [1]. The huge interest for such multicomponent reactions during the last years has been oriented toward developing combinatorial chemistry procedures, because of their high efficiency and convenience of these reactions in comparison with multistage procedures. Hence, much scientific effort has been focused on the development of multicomponent procedures to prepare diverse heterocyclic compound libraries [2].

Pyridine and its derivatives have a vast range of biological activities. They have been used as herbicides [3], for enrichment of cereals [4], for regulation of arterial pressure [5], and cholesterol levels in blood [6]. In addition, some pyridines constitute an important class of antitumor compounds, which have been attracting significant attention [7,8]. Some polyfunctional pyridines are used as nonlinear optical materials [9], electrical materials [10], chelating agents in metal-ligand chemistry [11], and as fluorescent liquid crystals [12]. Therefore, development of efficient procedures toward functionalized pyridines is a quite important task in organic synthesis [13].

There is a great variety of methods described in the literature to synthesize similar skeleton [14]. Many precedent methods, however, have inevitable drawbacks: the aromatized polysubstituted pyridines were previously mostly synthesized through two steps: 1,4-DHPs were first prepared, which further proceeded to be oxidized to provide the corresponding aromatized compounds.

As part of an ongoing development of efficient protocols for the preparation of polysubstituted heterocycles from common intermediates [15], we recently discovered a simple and efficient method for the synthesis of polysubstituted pyridines (Scheme 1) *via* aldehydes, malononitrile, and methyl 3-aminobut-2-enoate under microwave (MW) irradiation.

RESULTS AND DISCUSSION

To optimize the reaction conditions, different organic solvents, such as ethanol, glycol, acetic acid, DMF, and mixed glycol-HOAc were tested in the synthesis of **4b** at 100°C. Table 1 show that the reactions in mixed glycol-HOAc (2:1, v/v) gave the best results (entry 6 of Table 1).

Moreover, to further optimize the reaction temperature, reactions using 4-chlorobenzaldehyde (**1b**, 1.0 mmol), malononitrile (**2**, 1.0 mmol), and methyl 3-aminobut-2-enoate (**3**, 1.0 mmol) were carried out in the range of 90–150°C in increments of 10°C each time in mixed glycol-HOAc (2:1, v/v) under microwave irradiation (initial power 100 W, maximum power 200 W). The results are shown in Table 2. When the temperature was increased from 90 to 120°C, the yield of product **4b** was improved. However, no significant increase in the

Scheme 1

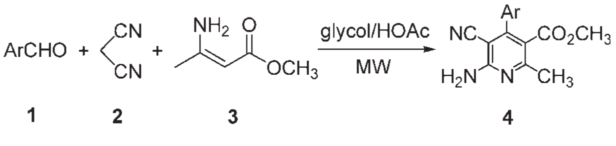


Table 1

Solvent optimization for the synthesis of **4b** under MW.

Entry	Solvent	Time (min)	Yield (%)
1	EtOH	12	37
2	glycol	10	54
3	HOAc	10	55
4	DMF	10	48
5	glycol-HOAc(1:1)[a]	9	60
6	glycol-HOAc(2:1)[a]	9	76
7	glycol-HOAc(3:1)[a]	9	70
8	glycol-HOAc(4:1)[a]	9	64

[a] Volume ratio.

Table 2

Temperature optimization for the synthesis of **4b** under MW.

Entry	*T* (°C)	Time (min)	Yield (%)
1	90	9	70
2	100	9	76
3	110	9	83
4	120	7	88
5	130	7	85
6	140	7	83
7	150	7	80

yield of product **4b** was observed as the reaction temperature was raised from 130 to 150°C. Therefore, the temperature of 120°C was chosen for all further MW-assisted reactions.

The use of these optimal microwave experimental conditions [120°C, glycol-HOAc (2:1)] for the reactions of different aromatic aldehydes afforded good yields of polysubstituted pyridine derivatives. The results (Table 3, entries 1–10) indicated that aromatic aldehydes bearing either electron-donating (such as alkoxyl groups) or electron-withdrawing (such as nitro or halide groups) functional groups were all suitable for the reaction. Moreover, a heterocyclic aldehyde, thiophene-2-carbaldehyde (Table 3, entry 11), still showed high reactivity under these standard conditions.

Although the detailed mechanism of the above reaction remains to be fully clarified, the formation of **4** could be explained by a possible reaction sequence presented in Scheme 2. Compound **4** is expected to proceed *via* initial condensation of aromatic aldehydes with malononitrile to afford alkylidenemalononitrile **5**, which further undergoes *in situ* Michael addition with methyl 3-aminobut-2-enoate **3**, to yield intermediate **7**, which is then cyclized and subsequently dehydrogenated to afford the aromatized product **4**. This type of hydrogen loss was well precedented [16].

To test the mechanism described earlier, the reaction of intermediate product **5c** and methyl 3-aminobut-2-enoate **3** was carried out under microwave irradiation conditions. The target compound **4c** was obtained, in similar yields by the one-pot reaction. The results supported the proposed mechanism (Scheme 3).

In this study, all the products were characterized by IR and ^{1}H NMR spectral data as well as elemental analyses. Furthermore, the structure of **4a** [17] was established by X-ray crystallographic analysis. The molecular structure of **4a** was shown in Figure 1.

In conclusion, the microwave-assisted synthesis of polysubstituted pyridines in this paper is an efficient methodology allowing the facile preparation of these important polycyclic compounds. This procedure offers several advantages including operational simplicity, increased safety for small-scale high-speed synthesis that makes it a useful and attractive process for the synthesis of these compounds.

EXPERIMENTAL

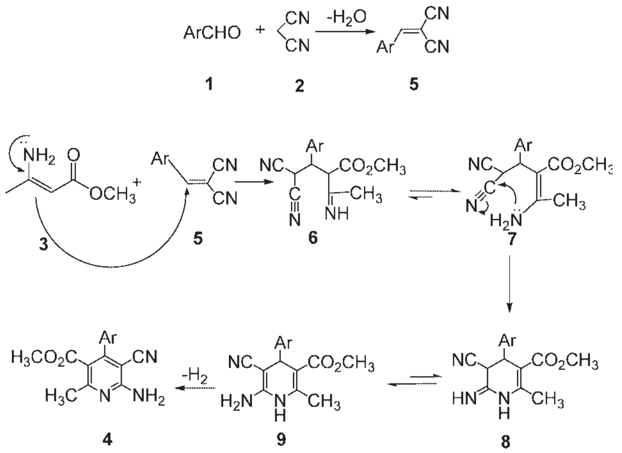
Microwave irradiation was carried out with a microwave oven Emrys^{TM} Creator from Personal Chemistry, Uppsala,

Table 3

Synthesis of products **4** under MW.

Entry	Product	Ar	Time (min)	Yield (%)	Mp (°C)
1	**4a**	4-FC_6H_4	6	89	279–281
2	**4b**	4-ClC_6H_4	7	88	254–256
3	**4c**	4-BrC_6H_4	6	89	248–250
4	**4d**	4-$NO_2C_6H_4$	6	87	280–282
5	**4e**	4-$CH_3C_6H_4$	9	88	295–297
6	**4f**	2-ClC_6H_4	7	85	268–270
7	**4g**	C_6H_5	6	86	256–258
8	**4h**	3,4-$Cl_2C_6H_3$	8	88	252–254
9	**4i**	2,3-$(CH_3O)_2C_6H_3$	10	84	230–232
10	**4j**	3,4-$(OCH_2O)C_6H_3$	9	83	263–265
11	**4k**	thiophen-2-yl	8	82	274–276

Scheme 2



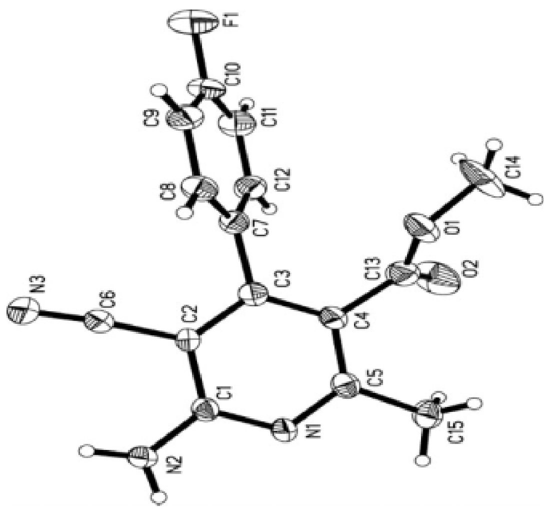


Figure 1. ORTEP diagram of **4a**.

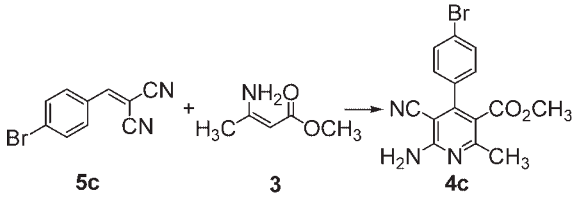
Sweden. Melting points were determined in the open capillaries and were uncorrected. IR spectra were taken on a FTIR-Tensor 27 spectrometer in KBr pellets and reported in cm^{-1}. ^1H NMR spectra were measured on a Bruker DPX 400 MHz spectrometer using TMS as an internal standard and DMSO-d_6 as solvent. Elemental analysis was determined by using a Perkin–Elmer 240c elemental analysis instrument. X-Ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer.

General procedure for the one-pot synthesis of compounds 4 under microwave irradiation conditions. Typically, in a 10-mL Emrys^{TM} reaction vial, aldehyde **1** (1 mmol), malononitrile **2** (1 mmol, 0.066 g), methyl 3-aminobut-2-enoate **3** (1 mmol, 0.115 g), glycol (1.0 mL), and HOAc (0.5 mL) were mixed and then capped. The mixture was irradiated for a given time at 120°C under microwave irradiation (initial power 100 W and maximum power 200 W). Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature and then poured into cold water. The solid product was collected by Büchner filtration and was further purified by recrystallization from EtOH (95%) to give the pure product.

Methyl 6-amino-5-cyano-4-(4-fluorophenyl)-2-methyl-pyridine-3-carboxylate (4a). This compound was obtained according to the above general procedure; ir (potassium bromide): 3390, 3321, 3172, 3076, 2220, 1715, 1652, 1565, 1434, 1376, 1229, 1166, 1077, 958, 882, 665 cm^{-1}; ^1H NMR: 7.39–7.37 (m, 2H, 3′,5′-ArH), 7.36 (s, 2H, NH_2), 7.34–7.31 (m, 2H, 2′,4′-ArH), 3.43 (s, 3H, OCH_3), 2.38 (s, 3H, CH_3). Anal. calcd for $C_{15}H_{12}FN_3O_2$: C, 63.15; H, 4.24; N, 14.73. Found: C, 63.12; H, 4.28; N, 14.75.

Methyl 6-amino-4-(4-chlorophenyl)-5-cyano-2-methyl-pyridine-3-carboxylate (4b). This compound was obtained according to the above general procedure, this compound is known (RN: 176689-71-7) [14d]; ir (potassium bromide): 3383, 3324, 3178, 3086, 2221, 1721, 1653, 1576, 1496, 1378, 1284, 1197, 1094, 960, 863, 661 cm^{-1}; ^1H NMR: 7.57 (d, 2H, J = 8.4 Hz, 2′,4′-ArH), 7.40 (s, 2H, NH_2), 7.34 (d, 2H, J = 8.4 Hz, 3′,5′-ArH), 3.44 (s, 3H, OCH_3), 2.39 (s, 3H, CH_3). Anal. calcd for $C_{15}H_{12}ClN_3O_2$: C, 59.71; H, 4.01; N, 13.93. Found: C, 59.76; H, 4.05; N, 13.90.

Scheme 3



Methyl 6-amino-4-(4-bromophenyl)-5-cyano-2-methyl-pyridine-3-carboxylate (4c). This compound was obtained according to the above general procedure; ir (potassium bromide): 3405, 3313, 3161, 3069, 2217, 1718, 1651, 1557, 1437, 1376, 1283, 1104, 1012, 957, 882, 665 cm^{-1}; ^1H NMR: 7.71 (d, 2H, J = 8.4 Hz, 3′,5′-ArH), 7.40 (s, 2H, NH2), 7.27 (d, 2H, J = 8.4 Hz, 2′,4′-ArH), 3.45 (s, 3H, OCH_3), 2.39 (s, 3H, CH_3). Anal. calcd for $C_{15}H_{12}BrN_3O_2$: C, 52.04; H, 3.49; N, 12.14. Found: C, 52.00; H, 3.45; N, 12.15.

Methyl 6-amino-5-cyano-2-methyl-4-(4-nitrophenyl)-pyridine-3-carboxylate (4d). This compound was obtained according to the above general procedure; ir (potassium bromide): 3383, 3331, 3151, 3061, 2222, 1720, 1661, 1562, 1433, 1382, 1282, 1107, 1017, 955, 888, 665 cm^{-1}; ^1H NMR: 8.35 (d, 2H, J = 8.8 Hz, 3′,5′-ArH), 7.62 (d, 2H, J = 8.4 Hz, 2′,4′-ArH), 7.53 (s, 2H, NH_2), 3.40 (s, 3H, OCH_3), 2.43 (s, 3H, CH_3). Anal. calcd for $C_{15}H_{12}N_4O_4$: C, 57.69; H, 3.87; N, 17.94. Found: C, 57.70; H, 3.85; N, 17.95.

Methyl 6-amino-5-cyano-2-methyl-4-p-tolylpyridine-3-carboxylate (4e). This compound was obtained according to the above general procedure; ir (potassium bromide): 3338, 3321, 3173, 3048, 2219, 1712, 1652, 1560, 1434, 1376, 1286, 1110, 1077, 961, 882, 664 cm^{-1}; ^1H NMR: 7.30 (d, 2H, J = 7.6 Hz, 2′,4′-ArH), 7.19 (d, 2H, J = 8.0 Hz, 3′,5′-ArH), 7.11 (s, 2H, NH_2), 3.43 (s, 3H, OCH_3), 2.37 (s, 6H, CH_3). Anal. calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.35; H, 5.39; N, 14.95.

Methyl 6-amino-4-(2-chlorophenyl)-5-cyano-2-methyl-pyridine-3-carboxylate (4f). This compound was obtained according to the above general procedure; ir (potassium bromide): 3385, 3325, 3177, 3052, 2222, 1717, 1654, 1594, 1431, 1378, 1283, 1168, 1035, 958, 802, 663 cm^{-1}; ^1H NMR: 7.61–7.59 (m, 1H, ArH), 7.49 (s, 2H, NH2), 7.47–7.42 (m, 2H, ArH), 7.29–7.27 (m, 1H, ArH), 3.37 (s, 3H, OCH_3), 2.45 (s, 3H, CH_3). Anal. calcd for $C_{15}H_{12}ClN_3O_2$: C, 59.71; H, 4.01; N, 13.93. Found: C, 59.75; H, 4.04; N, 13.95.

Methyl 6-amino-5-cyano-2-methyl-4-phenylpyridine-3-carboxylate (4g). This compound was obtained according to the above general procedure, this compound is known (RN: 176689-69-3) [14d]; ir (potassium bromide): 3395, 3320, 3169, 3057, 2219, 1714, 1652, 1558, 1436, 1377, 1284, 1168, 1077, 960, 803, 662 cm^{-1}; ^1H NMR: 7.50–7.48 (m, 3H, ArH), 7.35 (s, 2H, NH_2), 7.31–7.29 (m, 2H, ArH), 3.39 (s, 3H, OCH_3), 2.39 (s, 3H, CH_3). Anal. calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72; Found: C, 67.44; H, 4.95; N, 15.70.

Methyl 6-amino-4-(3,4-dichlorophenyl)-5-cyano-2-methylpyridine-3-carboxylate (4h). This compound was obtained according to the above general procedure; ir (potassium bromide): 3395, 3315, 3168, 3066, 2216, 1712, 1650, 1505, 1449, 1377, 1287, 1167, 1038, 926, 820, 775 cm^{-1}; ^1H NMR: 7.78 (d, 1H, $J = 8.4$ Hz, ArH), 7.68–7.67 (m, 1H, ArH), 7.47 (s, 2H, NH_2), 7.32 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 2.4$ Hz, ArH), 3.47 (s, 3H, OCH_3), 2.41 (s, 3H, CH_3). Anal. calcd for $C_{15}H_{11}Cl_2N_3O_2$: C, 53.59; H, 3.30; N, 12.50. Found: C, 53.60; H, 3.33; N, 12.55.

Methyl 6-amino-5-cyano-4-(2,3-dimethoxyphenyl)-2-methylpyridine-3-carboxylate (4i). This compound was obtained according to the above general procedure; ir (potassium bromide): 3384, 3331, 3177, 3050, 2224, 1713, 1657, 1567, 1433, 1335, 1265, 1193, 1091, 818, 743 cm^{-1}; ^1H NMR: 7.31 (s, 2H, NH_2), 7.15–7.09 (m, 2H, ArH), 6.64 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 2.4$ Hz, ArH), 3.86 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3), 3.41 (s, 3H, OCH_3), 2.40 (s, 3H, CH_3). Anal. calcd for $C_{17}H_{17}N_3O_4$: C, 62.38; H, 5.23; N, 12.84. Found: C, 62.36; H, 5.25; N, 12.80.

Methyl 6-amino-4-(benzo[d][1,3]dioxol-6-yl)-5-cyano-2-methylpyridine-3-carboxylate (4j). This compound was obtained according to the above general procedure; ir (potassium bromide): 3380, 3325, 3171, 3052, 2225, 1712, 1658, 1567, 1430, 1338, 1264, 1183, 1090, 810, 750 cm^{-1}; ^1H NMR: 7.27 (s, 2H, NH_2), 7.02 (d, 1H, $J = 8.0$ Hz, ArH), 6.92–6.91 (m, 1H, ArH), 6.75 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 1.6$ Hz, ArH), 6.12 (s, 2H, CH_2), 3.48 (s, 3H, OCH_3), 2.35 (s, 3H, CH_3). Anal. calcd for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21; N, 13.50. Found: C, 61.76; H, 4.25; N, 13.54.

Methyl 6-amino-5-cyano-2-methyl-4-(thiophen-2-yl)pyridine-3-carboxylate (4k). This compound was obtained according to the above general procedure; ir (potassium bromide): 3390, 3320, 3163, 3060, 2219, 1713, 1654, 1560, 1434, 1330, 1261, 1168, 1041, 839, 736 cm^{-1}; ^1H NMR: 7.81 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 1.2$ Hz, ArH), 7.35 (s, 2H, NH_2), 7.29–7.28 (m, 1H, ArH), 7.21–7.19 (m, 1H, ArH), 3.55 (s, 3H, OCH_3), 2.35 (s, 3H, CH_3). Anal. calcd for $C_{13}H_{11}N_3O_2S$: C, 57.13; H, 4.06; N, 15.37; S, 11.73. Found: C, 57.16; H, 4.05; N, 15.34; S, 11.75.

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[17] The single-crystal growth was carried out in ethanol at room temperature. X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Semens P4 diffractometer (graphite monochromator, MoKa radiation $\lambda = 0.71073$ Å). Crystal data for **4a**: Empirical formula $C_{15}H_{12}FN_3O_2$, colorless, crystal dimensions 0.38 × 0.10 × 0.07 mm, triclinic, space group p-1, $a = 6.549(5)$ Å, $b = 7.658(5)$ Å, $c = 14.093(10)$ Å, $\alpha = 81.691(11)°$, $\beta = 86.585(11)°$, $\gamma = 84.035(10)°$, $V = 694.8(8)$ $Å^3$, $M_r = 285.28$, $Z = 2$, $D_c = 1.364$ Mg/m^3 , $\lambda = 0.71073$ Å, μ (MoKα) = 0.102 mm^{-1}, $F(000) = 296$, $S = 0.937$, $R_1 = 0.0655$, $wR_2 = 0.1296$.

Synthesis of New 1-(2-, 3-, Or 4-Methanesulfonylphenyl)-2-[5-(*N*-hydroxypyridin-2(1*H*)-one)]acetylene Regioisomers: A Search for Novel Cyclooxygenase and Lipoxygenase Inhibitors

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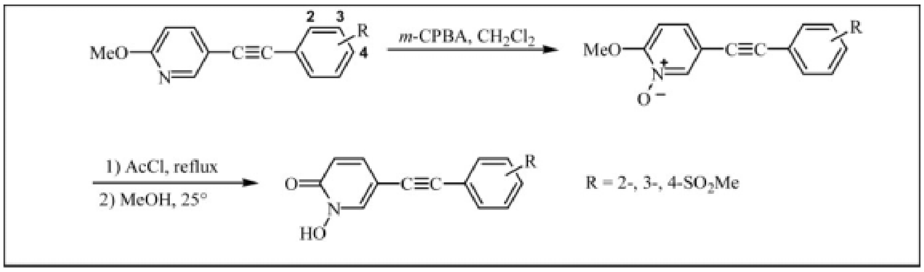

A group of acetylene regioisomers were designed such that a cyclooxygenase-2 (COX-2) SO_2Me pharmacophore was located at the ortho-, meta-, or para-position of the acetylene C-1 phenyl ring, and an iron-chelating 5-lipoxygenase (5-LOX) *N*-hydroxypyridin-2(1*H*)-one moiety was attached *via* its C-5 position to the C-2 position on an acetylene template (scaffold). These target linear acetylene regioisomers were synthesized *via* a palladium-catalyzed Sonogashira cross-coupling reaction. Structure-activity data acquired using *in vitro* cell-based inhibition assays indicated that this novel class of 1-(2-, 3-, or 4-methanesulfonylphenyl)-2-[5-(*N*-hydroxypyridin-2(1*H*)-one)]acetylene regioisomers did not inhibit the COX-2 or (5-LOX) enzymes, and that they are devoid of *in vivo* anti-inflammatory activities.

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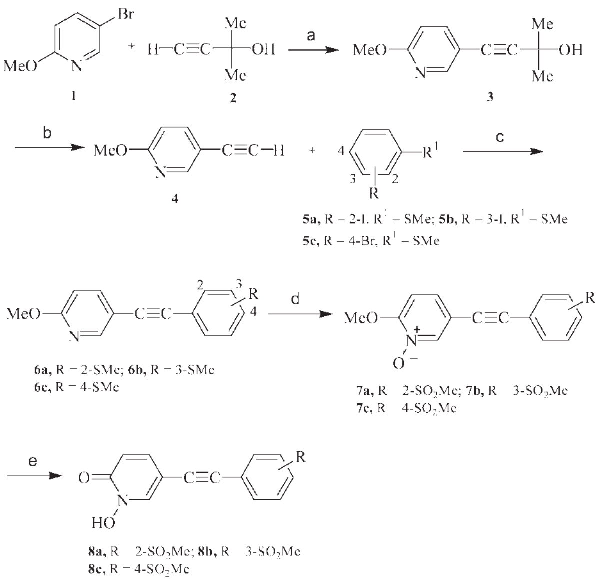
INTRODUCTION

Dual inhibitors of cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) represent an attractive safer alternative to selective COX-2 inhibitors. This view is based on a potentially greater anti-inflammatory efficacy because of their ability to synergistically block both metabolic pathways of the arachidonic acid (AA) cascade [1]. A group of 1-(2-, 3-, and 4-methanesulfonylphenyl)-2-(2-, 3-, and 4-pyridyl)acetylene regioisomers, which are effective COX-1/COX-2 inhibitors that exhibit *in vivo* anti-inflammatory activities, were recently reported [2]. The most successful effort to develop 5-LOX inhibitors has been in the area of hydroxamic acids and related *N*-hydroxyureas that likely chelate iron present in the 5-LOX enzyme [3]. The recently described 1-(methanesulfonlylphenyl)-2-(pyridyl)acetylene regioisomers possess a suitable scaffold (template) to design novel acyclic dual inhibitors of the COX and LOX enzymes [2]. It was anticipated that replacement of the pyridyl ring in these parent acetylenes by a *N*-hydroxypyridin-2(1*H*)one moiety, which has the potential to chelate iron, may provide a hitherto unknown class of dual COX/5-LOX inhibitory anti-inflammatory agents. Accordingly, we now describe the synthesis of a novel group of 1-(2-, 3-, or 4-methanesulfonylphenyl)-2-[5-(*N*-hydroxypyridin-2(1*H*)-one)]acetylene regioisomers (**8a–c**), to determine their potential utility as inhibitors of the COX-2 and 5-LOX enzymes.

RESULTS AND DISCUSSION

1-(Methylthiophenyl)-2-(2-methoxypyrid-5-yl)acetylenes (**6a–c**) were prepared in 28–72% yield using two consecutive palladium-catalyzed Sonogashira cross-coupling reactions [2,4–7]. The subsequent transformation of **6a–c** to the target 1-(2-, 3-, or 4-methanesulfonylphenyl)-2-[5-(*N*-hydroxypyridin-2(1*H*)-one)]acetylene regioisomers (**8a–c**) was carried out using the synthetic methodologies shown in Scheme 1. A modified procedure [8] was used to synthesize 5-ethynyl-2-methoxypyridine (**4**). Thus, Sonogashira coupling of 5-bromo-2-methoxypyridine (**1**) with 2-methylbut-3-yn-2-ol (**2**) in the presence of Et_3N, cuprous iodide (CuI), and dichloro-bis(triphenylphosphine)palladium(0) ([$PdCl_2(PPh_3)_2$]) catalyst afforded 4-(2-methoxypyridin-5-yl)-2-methyl-but-3-yn-2-ol (**3**) in 75% yield. Subsequent removal of the isopropanol moiety using sodium hydride furnished 5-ethynyl-2-methoxypyridine (**4**) in 82% yield.

Scheme 1. Reagents and conditions: (a) Et_3N, $Pd(PPh_3)_2Cl_2$, CuI, 70–75°C, 3 h; (b) benzene, NaH, 105–110°C, 1 h; (c) Et_3N, $Pd(PPh_3)_2Cl_2$, CuI, 90°C, 5 h; (d) *m*-chloroperoxybenzoic acid, CH_2Cl_2, 25°C, overnight; (e) (i) acetyl chloride, reflux, 1 h; (ii) MeOH, 25°C, overnight.



A second Sonogashira cross-coupling reaction of **4** with the halothioanisole (**5a–c**) regioisomers was carried out under an argon atmosphere in Et_3N using $[PdCl_2(PPh_3)_2]$/CuI as catalyst to furnish the respective 1-(methylthiophenyl)-2-(2-methoxypyrid-5-yl)acetylenes **6a–c** in 28–72% yield. Oxidation of **6a–c** with *meta*-chloroperbenzoic acid in dichloromethane [9] afforded the 1-(methanesulfonylphenyl)-2-(1-oxido-2-methoxypyrid-5-yl)acetylenes (**7a–c**) in 44–51% yield. Finally, reaction of the *N*-oxides **7a–c** with acetyl chloride at reflux, and then methanolysis in place of hydrolysis [9] furnished the target *N*-hydroxypyridin-2(1*H*)-ones (**8a–c**) in 69–91% yield.

Replacement of the carboxyl (CO_2H) in traditional arylacetic acid nonsteroidal anti-inflammatory drugs (NSAIDs) by a hydroxamic acid (CONHOH) moiety provided potent orally active 5-LOX inhibitory agents [10]. NSAIDs having a CONHOH or CON(Me)OH (pKa 9–11 range) in place of the CO_2H in traditional NSAIDs (pKa generally in the 4–5 range) are much less acidic, which decreases ulcerogenicity [11].

The rational for the design of the acyclic acetylenes **8a-c** was based on the expectations that (i) the phenyl ring bearing the SO_2Me pharmacophore will confer COX-2 inhibitory activity, and (ii) the *N*-hydroxypyridin-2(1*H*)one moiety will confer 5-LOX inhibitory activity. The CONOH part of the *N*-hydroxypyrid-2(1*H*)-one ring present in **8a–c** can be viewed as a cyclic hydroxamic acid mimetic. These *N*-hydroxypyridin-2(1*H*)-ones, like acyclic hydroxamic acids, are expected to serve as effective iron chelators to exhibit 5-LOX inhibitory activity. However, these cyclic *N*-hydroxypyridin-2(1*H*)-ones, unlike acyclic hydroxamic acids which undergo facile biotransformation to the carboxylic acids, are expected to be metabolically stable with improved oral efficacy.

In vitro cell-based inhibition assays were carried out to determine the biological effect of compounds **8a–c** on eicosanoid synthesis/release by measuring the amounts of cysteinyl leukotrienes (collectively referred to as a group of 5-LOX derived metabolites LTC_4, LTD_4, and LTE_4) and prostaglandin E_2 (PGE_2) secreted into the culture medium of human brain cancer cells. The assay to determine the ability of **8a–c** to inhibit *in vitro* cell-based 5-LOX activity showed that all three regioisomers failed to inhibit the 5-LOX enzyme ($IC_{50} > 50$ μM) relative to the reference drug nordihydroguaiaretic acid (NDGA, $IC_{50} = 35$ μM). Compounds **8a–c** were similarly inactive ($IC_{50} > 100$ μM) inhibitors of the COX-2 isozyme relative to the reference drug celecoxib ($IC_{50} = 2.5$ μM) in a cell-based assay.

The anti-inflammatory activities exhibited by the regioisomers **8a–c** were determined using a carrageenan-induced rat foot paw edema model at a 50 mg/kg oral dose. In this assay, compounds **8a–c** were all inactive anti-inflammatory (AI) agents compared with the reference drug celecoxib (79.9 ± 1.9% inhibition at 50 mg/kg po; $ID_{50} = 10.8$ mg/kg po).

The biological data acquired in this study indicate that the 1-(methanesulfonylphenyl)-2-[5-(*N*-hydroxypyridin-2(1*H*)-one)]acetylene structure is not a suitable template for the design of anti-inflammatory agents that act by inhibition of the 5-LOX and/or COX-2 enzymes.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Unless otherwise noted, infrared (IR) spectra were recorded as films on NaCl plates using a Nicolet 550 Series II Magna FTIR spectrometer. ^1H NMR spectra were measured on a Bruker AM-300 spectrometer in $CDCl_3$ or $CDCl_3$ + DMSO-d_6 with TMS as the internal standard. Microanalyses were performed for C, H, N (Micro-Analytical Service Laboratory, Department of Chemistry, University of Alberta) and were within ±0.4% of theoretical values. Silica gel column chromatography was performed using Merck silica gel 60 ASTM (70-230 mesh). 2-Iodothioanisole (**5a**) [12] and 3-iodothioanisole (**5b**) [13] were synthesized in 91% and 76% yields, respectively, starting from 2-(methylthio)aniline and 3-(methylthio)aniline using the procedure of Ullmann [14]. All other reagents, purchased from the Aldrich Chemical Company (Milwaukee, WI), were used without further purification.

4-(2-Methoxypyridin-5-yl)-2-methylbut-3-yn-2-ol (3). $PdCl_2(PPh_3)_2$ (63 mg, 0.09 mmoles) and CuI (19 mg, 0.10 mmoles) were added to a stirred solution of 5-bromo-2-methoxypyridine

(**1**) (2.75 mL, 21.39 mmoles) and 2-methylbut-3-yn-2-ol (**2**) (2.20 mL, 22.61 mmoles) in Et$_3$N (40 mL) under an argon atmosphere at 25°C, and the reaction was allowed to proceed at 70–75°C for 3 h. The reaction mixture was allowed to cool to 25°C, filtered, and excess Et$_3$N was removed from the filtrate *in vacuo*. The dark brown residue obtained was purified by silica gel column chromatography using hexane-EtOAc (3:1, v/v) as eluent to afford **3** in 75% yield; yellowish oil; IR (film): 3368 (OH), 2235 ($C{\equiv}C$) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.62 (s, 6H, C*Me*$_2$), 2.44 (br s, 1H, O*H*), 3.94 (s, 3H, O*Me*), 6.69 (d, *J* = 8.5 Hz, 1H, pyridyl H-3), 7.59 (dd, *J* = 8.5, 2.1 Hz, 1H, pyridyl H-4), 8.27 (d, *J* = 2.1 Hz, 1H, pyridyl H-6).

5-Ethynyl-2-methoxypyridine (4). Sodium hydride (26 mg, 1.08 mmoles) was added to a solution of 4-(2-methoxypyridin-5-yl)-2-methylbut-3-yn-2-ol (**3**) (1.52 g, 7.96 mmoles) in benzene (7 mL), and the reaction mixture was heated at 105–110°C for 1 h. Removal of the solvent *in vacuo* gave a dark brown oil, which was purified by silica gel column chromatography using hexane-EtOAc (3:1, v/v) as eluent to afford **4** in 82% yield; brown oil; IR (film): 2230 ($C{\equiv}C$) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.12 (s, 1H, $C{\equiv}CH$), 3.96 (s, 3H, O*Me*), 6.72 (d, *J* = 8.5 Hz, 1H, pyridyl H-3), 7.66 (dd, *J* = 8.5, 2.1 Hz, 1H, pyridyl H-4), 8.27 (d, *J* = 2.1 Hz, 1H, pyridyl H-6).

General procedure for the synthesis of 1-(methylthiophenyl)-2-(2-methoxypyrid-5-yl)acetylenes (6a–c). CuI (46 mg, 0.24 mmoles) was added with stirring to a solution containing PdCl$_2$(PPh$_3$)$_2$ (85 mg, 0.12 mmoles), 5-ethynyl-2-methoxypyridine (**4**) (6 mmoles), and a halothioanisole **5a**, **5b**, or **5c** (4 mmoles), in Et$_3$N (10 mL) under an argon atmosphere. The reaction mixture was heated at 90°C for 5 h, cooled to 25°C, and filtered to remove the inorganic salts. The solvent from the filtrate was removed *in vacuo*, and the residue obtained was purified by silica gel column chromatography using hexane-EtOAc (10:1, v/v) as eluent to furnish the respective product **6a–c**. Some physical and spectroscopic data for **6a–c** are listed below.

1-(2-Methylthiophenyl)-2-(2-methoxypyrid-5-yl)acetylene (6a). The product was obtained as a pale yellow oil using the Sonogashira coupling reaction of **4** with 2-iodothioanisole (**5a**) in 72% yield; IR (film): 2213 ($C{\equiv}C$), 1615, 1580, 1488 (Ar) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.52 (s, 3H, S*Me*), 4.00 (s, 3H, O*Me*), 6.77 (d, *J* = 8.5 Hz, 1H, pyridyl H-3), 7.12 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H, phenyl H-5), 7.19 (dd, *J* = 7.6, 1.2 Hz, 1H, phenyl H-3), 7.31 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H, phenyl H-4), 7.48 (d, *J* = 7.6, 1.2 Hz, 1H, phenyl H-6), 7.77 (dd, *J* = 8.5, 2.1 Hz, 1H, pyridyl H-4), 8.41 (d, *J* = 2.1 Hz, 1H, pyridyl H-6).

1-(3-Methylthiophenyl)-2-(2-methoxypyrid-5-yl)acetylene (6b). The product was obtained as a pale yellow oil using the Sonogashira coupling reaction of **4** with 3-iodothioanisole (**5b**) in 44% yield; IR (film): 2229 ($C{\equiv}C$), 1588, 1560, 1495 (Ar) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.51 (s, 3H, S*Me*), 3.99 (s, 3H, O*Me*), 6.77 (d, *J* = 8.9 Hz, 1H, pyridyl H-3), 7.20–7.31 (m, 3H, phenyl H-4, H-5, H-6), 7.39 (s, 1H, phenyl H-2), 7.72 (dd, *J* = 8.9, 2.1 Hz, 1H, pyridyl H-4), 8.36 (d, *J* = 2.1 Hz, 1H, pyridyl H-6).

1-(4-Methylthiophenyl)-2-(2-methoxypyrid-5-yl)acetylene (6c). The product was obtained as a pale yellow solid using the Sonogashira coupling reaction of **4** with 4-bromothioanisole (**5c**) in 28% yield; mp 85–87°C; IR (film): 2230 ($C{\equiv}C$), 1602, 1560, 1495 (Ar) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.51 (s, 3H, S*Me*), 4.00 (s, 3H, O*Me*), 6.77 (d, *J* = 8.5 Hz, 1H, pyridyl H-3), 7.21 (d, *J* = 8.5 Hz, 2H, phenyl H-3, H-5), 7.43 (d, *J* = 8.5 Hz, 2H, phenyl H-2, H-6), 7.72 (dd, *J* = 8.5, 2.1 Hz, 1H, pyridyl H-4), 8.36 (d, *J* = 2.1 Hz, 1H, pyridyl H-6).

General procedure for the synthesis of 1-(methanesulfonylphenyl)-2-(1-oxido-2-methoxypyrid-5-yl)acetylenes (7a-c). *m*-Chloroperoxybenzoic acid (77% max.) (12 mmoles) was added to a stirred solution of a 1-(methylthiophenyl)-2-(2-methoxypyrid-5-yl)acetylene (**6a**, **6b**, or **6c**, 2 mmoles) in dry CH$_2$Cl$_2$ (25 mL), and the reaction was allowed to proceed with stirring at 25°C overnight. The solvent CH$_2$Cl$_2$ was removed *in vacuo* to give a crude product, which was purified by silica gel column chromatography using methanol-EtOAc (2:3, v/v) as eluent to afford the respective product **7a–c**. Some physical and spectroscopic data for **7a–c** are listed below.

1-(2-Methanesulfonylphenyl)-2-(1-oxido-2-methoxypyrid-5-yl)acetylene (7a). Yield, 48%; pale yellow solid; mp 140–142°C; IR (film): 2220 ($C{\equiv}C$), 1669, 1602, 1521 (Ar), 1313, 1145 (SO$_2$) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.25 (s, 3H, SO$_2$*Me*), 4.16 (s, 3H, O*Me*), 6.98 (d, *J* = 8.5 Hz, 1H, pyridyl H-3), 7.52–7.70 (m, 3H, pyridyl H-4, phenyl H-4, H-5), 7.74 (dd, *J* = 7.6, 1.5 Hz, 1H, phenyl H-6), 8.15 (dd, *J* = 7.6, 1.5 Hz, 1H, phenyl H-3), 8.54 (d, *J* = 1.8 Hz, 1H, pyridyl H-6).

1-(3-Methanesulfonylphenyl)-2-(1-oxido-2-methoxypyrid-5-yl)acetylene (7b). Yield, 51%; pale yellow solid; mp 172–174°C; IR (film): 2227 ($C{\equiv}C$), 1609, 1528 (Ar), 1307, 1145 (SO$_2$) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.09 (s, 3H, SO$_2$*Me*), 4.14 (s, 3H, O*Me*), 6.93 (d, *J* = 8.5 Hz, 1H, pyridyl H-3), 7.47 (dd, *J* = 8.5, 1.8 Hz, 1H, pyridyl H-4), 7.61 (dd, *J* = 7.6, 7.6 Hz, 1H, phenyl H-5), 7.77 (ddd, *J* = 7.6, 1.5, 1.2 Hz, 1H, phenyl H-6), 7.95 (ddd, *J* = 7.6, 1.5, 1.2 Hz, 1H, phenyl H-4), 8.10 (dd, *J* = 1.5, 1.2 Hz, 1H, phenyl H-2), 8.45 (d, *J* = 1.8 Hz, 1H, pyridyl H-6).

1-(4-Methanesulfonylphenyl)-2-(1-oxido-2-methoxypyrid-5-yl)acetylene (7c). Yield, 44%; white solid; mp 175–177°C; IR (film): 2227 ($C{\equiv}C$), 1602, 1522 (Ar), 1300, 1146 (SO$_2$) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.08 (s, 3H, SO$_2$*Me*), 4.14 (s, 3H, O*Me*), 6.93 (d, *J* = 8.9 Hz, 1H, pyridyl H-3), 7.48 (d, *J* = 8.9, 1.8 Hz, 1H, pyridyl H-4), 7.71 (d, *J* = 8.5 Hz, 2H phenyl H-2, H-6), 7.95 (d, *J* = 8.5 Hz, 2H, phenyl H-3, H-5), 8.46 (d, *J* = 1.8 Hz, 1H, pyridyl H-6).

General procedure for the synthesis of 1-(methanesulfonylphenyl)-2-[5-(*N*-hydroxypyridin-2(1*H*)-one)]acetylenes (**8a-c**). Acetyl chloride (6 mL) was added to a 1-(methanesulfonylphenyl)-2-(1-oxido-2-methoxypyrid-5-yl)acetylene (7a, 7b or 7c, 2 mmoles) and the reaction was allowed to proceed at reflux for 1 hour. The reaction mixture was cooled to 25°C, and excess acetyl chloride was removed *in vacuo*. The residue was dissolved in methanol prior to stirring at 25°C overnight. Methanol was removed *in vacuo* to give a solid product which was then mixed with Et$_2$O (10 mL) to form a slurry. Finally the product was filtered out and dried under vacuum to give the respective product (**8a-c**). The spectral and microanalytical data for compounds **8a-c** are listed below.

1-(2-Methanesulfonylphenyl)-2-[5-(*N*-hydroxypyridin-2(1*H*)-one)]acetylene (8a). Yield, 71%; brown solid; mp 198–200°C; IR (film): 2210 ($C{\equiv}C$), 1650 (CO), 1300, 1140 (SO$_2$) cm^{-1}; ^{1}H NMR (CDCl$_3$ + DMSO-d_6) δ 3.18 (s, 3H, SO$_2$*Me*), 6.54 (d, *J* = 9.2 Hz, 1H, pyridone H-3), 7.39 (dd, *J* = 9.2, 1.2 Hz, 1H, pyridone H-4), 7.46 (dd, *J* = 7.6, 7.6 Hz, 1H, phenyl H-

5), 7.55 (dd, $J = 7.6, 7.6$ Hz, 1H, phenyl H-4), 7.60 (d, $J = 7.6$ Hz, 1H, phenyl H-6), 7.93 (d, $J = 1.2$ Hz, 1H, pyridone H-6), 7.99 (d, $J = 7.6$ Hz, 1H, phenyl H-3). Anal. Calcd for $C_{14}H_{11}NO_4S{\cdot}1/2H_2O$: C, 56.32; H, 4.02; N, 4.69. Found: C, 56.30; H, 4.10; N, 4.83.

1-(3-Methanesulfonylphenyl)-2-[5-(*N*-hydroxypyridin-2(1*H*)-one)]acetylene (8b). Yield, 69%; brown solid; mp 205–207°C; IR (KBr): 2210 (C≡C), 1650 (CO), 1300, 1145 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 3.01 (s, 3H, SO_2Me), 6.54 (d, $J = 9.4$ Hz, 1H, pyridone H-3), 7.35 (dd, $J = 9.4, 2.4$ Hz, 1H, pyridone H-4), 7.50 (dd, $J = 7.6, 7.6$ Hz, 1H, phenyl H-5), 7.65 (ddd, $J = 7.6, 2.7, 1.5$ Hz, 1H, phenyl H-6), 7.80 (ddd, $J = 7.6, 2.7, 1.5$ Hz, 1H, phenyl H-4), 7.89 (d, $J = 2.4$ Hz, 1H, pyridone H-6), 7.93 (dd, $J = 1.5, 1.5$ Hz, 1H, phenyl H-2). Anal. Calcd for $C_{14}H_{11}NO_4S{\cdot}1/2H_2O$: C, 56.32; H, 4.02; N, 4.69. Found: C, 56.71; H, 3.80; N, 4.83.

1-(4-Methanesulfonylphenyl)-2-[5-(*N*-hydroxypyridin-2(1*H*)-one)]acetylene (8c). Yield, 91%; pale yellow solid; mp 234–236°C; IR (film): 2211 (C≡C), 1651 (CO), 1300, 1144 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.20 (s, 3H, SO_2Me), 6.55 (d, $J = 9.5$ Hz, 1H, pyridone H-3), 7.50 (dd, $J = 9.5, 2.4$ Hz, 1H, pyridone H-4), 7.70 (d, $J = 8.5$ Hz, 2H phenyl H-2, H-6), 7.93 (d, $J = 8.5$ Hz, 2H, phenyl H-3, H-5), 8.33 (d, $J = 2.4$ Hz, 1H, pyridone H-6), 12.1 (br s, 1H, N-O*H*). Anal. Calcd for $C_{14}H_{11}NO_4S$: C, 58.12; H, 3.83; N, 4.84. Found: C, 57.80; H, 3.87; N, 4.95.

***In vitro* cell-based enzyme immunoassays for determination of prostaglandin E_2 (COX-2) and cysteinyl leukotrienes (5-LOX).** The biological effects of the test compounds **8a–c** on eicosanoid synthesis/release were determined by measuring the amounts of prostaglandin E_2 and cysteinyl leukotrienes (collectively referred to as a group of 5-LOX derived metabolites LTC_4, LTD_4, and LTE_4) secreted into the culture medium of human brain cancer cells. Primary culture of ED 273b-BT human glioblastoma cells derived from patient was established and characterized in our laboratory as previously described [15]. Cells were seeded in 12-well plates (2×10^5cells/well) and cultured in Dulbecco's modified Eagle's medium and F-12 nutrition mixture (Invitrogen, Grand Islands, NY) supplemented with 10% heat-inactivated fetal calf serum, 100 units/mL penicillin, and 100 units/mL streptomycin at 37°C in a humidified atmosphere of 5% CO_2. The cells were stimulated with the appropriate concentrations of the test compounds and the positive controls celecoxib (LKT Laboratories, St. Paul, MN) for COX-2 activity and NDGA (Cayman Chemical, Ann Arbor, MI) for 5-LOX activity. After a 24-h incubation, supernatants were harvested, centrifuged for 10 min at 2000 rpm and stored at −80°C until assayed. The concentrations of eicosanoids were determined using prostaglandin E_2 (catalog number 514010) and cysteinyl leukotriene (catalog number 520501) enzyme immunoassay kits (Cayman Chemical, Ann Arbor, MI) according to a previously reported method [16].

***In vivo* anti-inflammatory assay.** The test compounds **8a–c** and the reference drug celecoxib were evaluated using the in vivo carrageenan-induced foot paw edema model reported previously [17].

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Regioselective Unusual Formation of Spirocyclic 4-{3′-Benzo(2′,3′-Dihydro)furo}-9-Methyl-2,3,9-Trihydrothiopyrano [2,3-*b*]indole by Acid-Catalyzed Reaction of Enol Ethers

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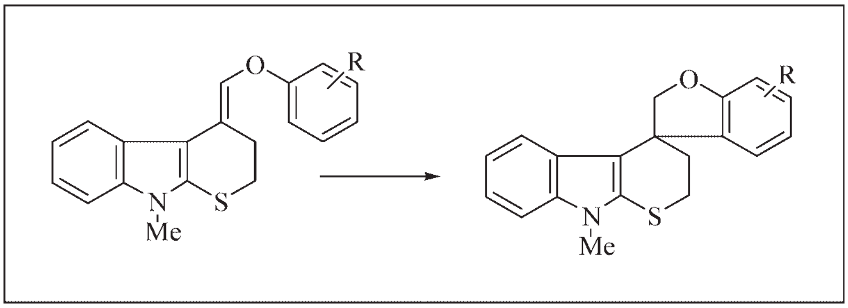

Spirocyclic 4-{3′-benzo(2′,3′-dihydro)furo}-9-methyl-2,3,9-trihydrothiopyrano[2,3-*b*]indoles are regioselectively synthesized by treating suitable enol ethers, 4-aryloxymethylene-9-methyl-2,3,9-trihydrothiopyrano[2,3-*b*]indoles with H_2SO_4 in dichloromethane-methanol-water. The substrates for the aforesaid reaction are in turn synthesized by the *thio*-Claisen rearrangement of 2-(4′-aryloxybut-2′-ynylthio)-1-methylindoles.

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INTRODUCTION

Indoline-2-thiones are important starting materials in the synthesis of thiopyranoindole derivatives and have been applied for the synthesis of biologically active compounds [1]. There are many biologically active indole derivatives in the alkaloid family and indole derivatives are well known as medicinal compounds for their pharmaceutical and physiological activities [2]. Synthesis of oxygen-, nitrogen-, and sulfur-containing heterocyclic compounds [3] have received great attention in the field of synthetic organic chemistry and the synthesis of indole-annulated heterocyclic compounds are important as they are present in the wide range of natural products, many of which exhibit potent bioactivity [2,4]. The familiar bioactivity of various indole derivatives has drawn our interest to this area and we have tried to synthesize oxygen and sulfur containing indole derivatives. In this study after construction of a thiopyran ring fused with indole by means of *thio*-Claisen rearrangement [1,5] of the suitable sulfides we focused our attention to the synthesis of indole-annulated poly-heterocyclic compounds by acid catalyzed reaction of the enol ether [6–8]. Herein, we report the results of our investigation.

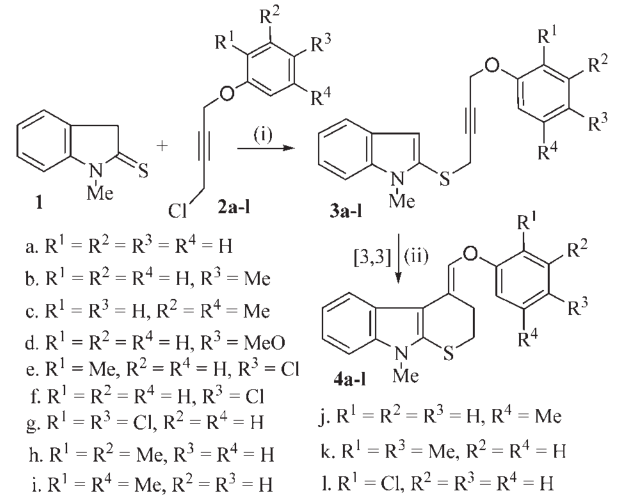
RESULTS AND DISCUSSION

The required precursors for our present study 4-(aryloxymethylene)-9-methyl-2,3,9-trihydrothiopyrano-[2,3-*b*]indoles (**4a-l**) were synthesized in 80–88% yield by the *thio*-Claisen rearrangement [5a] of 2-(4′-aryloxybut-2′-ynylthio)-1-methylindoles (**3a–l**) in refluxing chloro-benzene for 1 h. The compounds **3a–l** in turn were prepared in 90–94% yield by the reaction of 1-methyl-indoline-2-thione (**1**) and 1-aryloxy-4-chlorobut-2-yne (**2a–l**) under phase transfer catalysis (PTC) condition [5a,9] using benzyltriethyl ammonium chloride (BTEAC) as a phase transfer catalyst (Scheme 1).

A close examination of compounds **4** reveals that these are enol ethers and it is well known that enol ethers undergo hydrolysis in the presence of acid leading to the formation of corresponding aldehyde or ketone and alcohol or phenol [6–8]. With a view to hydrolyse the enol ether [8], compound **4a** was refluxed with conc. H_2SO_4 in dichloromethane-methanol-water mixture for 4 h. Three different products were obtained, a spiroheterocycle (**5a**, 11%), exocyclic double bond reduced product (**6a**, 42%) and a ketone (**7**, 8%) (Scheme 2).

The ^1H NMR spectrum of product **5a** showed two sets of one proton multiplets at δ 2.12–2.20 and 2.43–2.48 due to $—SCH_2C\mathbf{H}_2$ and another two sets of one proton multiplet at δ 3.11–3.15 and 3.19–3.23 due to $—SC\mathbf{H}_2$; two sets of one proton doublet at δ 4.40 (J = 9 Hz) and 4.65 (J = 9 Hz) due to $—OC\mathbf{H}_2$ (which are diastereotropic protons). ^{13}C NMR and DEPT-135 spectrum of **5a** indicates the presence of nineteen carbon atoms; among them one is CH_3, three are CH_2, eight are CH, and seven are

Scheme 1. Reagents and conditions: (i) 1% NaOH sol., DCM, BTEAC, stirring, 15 min., rt. (ii) Chlorobenzene, reflux, 1 h.



quaternary carbons. The ^{1}H NMR spectrum of product **6a** exhibited two sets of one proton multiplets at δ 2.09–2.20 and 2.60–2.67 due to —SCH$_2$C**H**$_2$, another two sets of one proton multiplets at δ 2.97–3.04 and 3.23–3.32 due to —SC**H**$_2$; one proton multiplet at δ 3.64–3.73 due to —CH$_2$C**H** at the asymmetric centre; one proton triplet at δ 3.86 ($J = 9.4$ Hz) and another one proton double of a doublet at δ 4.38 ($J = 9.4$, 3.9 Hz) due to —OC**H**$_2$ (diastereotropic protons). IR spectrum of compound **7** revealed a peak at 1719 cm^{-1} due to carbonyl group. ^{1}H NMR spectrum displayed to sets of two proton doublets at δ 6.93 ($J = 8.7$ Hz) and at δ 7.13 ($J = 8.7$ Hz) due to —SCH=C**H** and —SC**H**=CH, respectively.

The products **5a**, **6a**, and **7** were characterized from their elemental analyses and spectral data as 9′-methyl-2′,3′-dihydro-9′*H*-spiro{1-benzofuran-3,4′-thiopyrano[2,3-*b*]in-dole} (**5a**), 9-methyl-4-(phenyloxymethyl)-2,3,4,9-tetra-hydrothiopyrano[2,3-*b*]indole (**6a**) and 9-methyl-2,3,9-tri-hydrothiopyrano[2,3-*b*]indole-4-one (**7**). The product **5a** is the structural isomer of the spiroheterocyclic compound obtained by the aryl radical cyclization [5a] of the corresponding *o*-bromoenol ether.

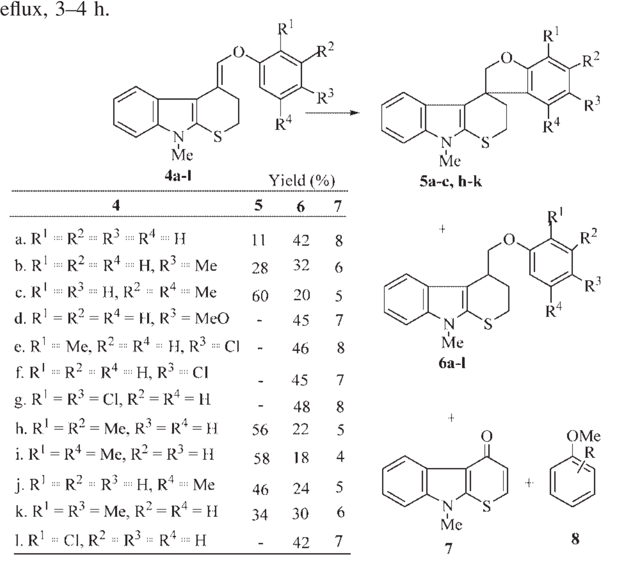
To generalize the reaction all the substrates **4b–l** were similarly treated. The spiroheterocyclic products **5b-c, h–k** were obtained in 28–60% yield, the products **6b–l** were isolated in 18–48% yield along with the product **7** (4–8%) (Scheme 2).

Formation of products **5** to **7** from compounds **4** by acid catalysis may be explained by the initial protonation of the enol ether double bond of **4** to form a latent carbonium ion **9**. The protonation of vinyl ether normally occurs at the remote position relative to the oxygen function [6,7]. But, here the more basic nitrogen function of the diene unit is the controlling site of protonation [8]. The potential carbonium ion **9** may undergo nucleophilic attack by the aromatic double bond (pathway a, Scheme 3) to give a resonance-stabilized carbocation **10**, which may then lose a proton to give spiroheterocyclic compounds **5**.

Intermediate **9** may also undergo nucleophilic attack by water molecule (pathway b, Scheme 3) followed by deprotonation and elimination of anisole **8** to give **13** which may then undergo double group transfer reaction [8,10] with **4** to give compound **6** and compound **7** (Scheme 3). Removal of the anisole (**8**) was demonstrated by the GC analysis of the crude reaction mixture after usual workup of the reaction mixture of compound **4a** (Compared with a standard sample of anisole). RT (min) of the standard sample of anisole was 2.762 whereas; the reaction mixture gave a peak at 2.802.

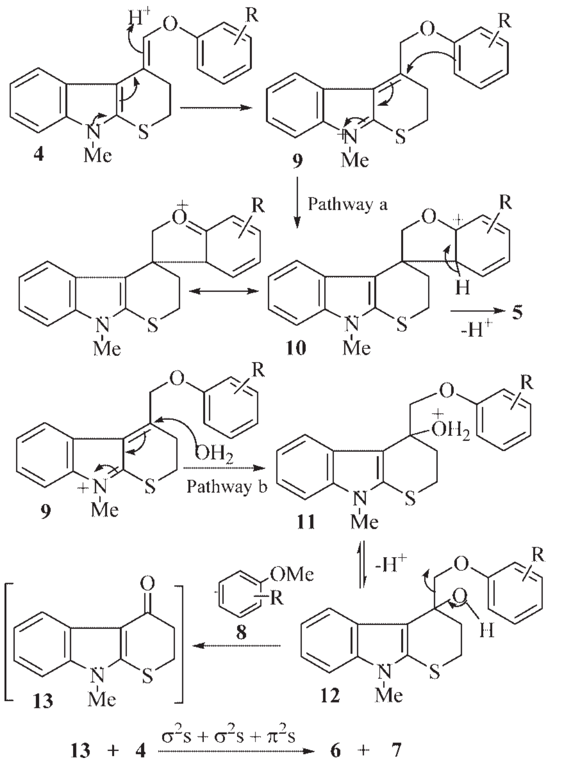
The nucleophilic attack by the aromatic double bond to the latent carbonium ion **9** becomes facile when the phenyl ring becomes electron rich. The unsubstituted phenyl ring participate in nucleophilic attack leads to only 11% spiroheterocyclic product **5a** but the presence of electron donating methyl group in the phenyl ring increases the yield of the product **5**. The dimethyl substituted phenyl ring gives higher yield of the product **5** and the yield markedly increased when the methyl group is present at the *o*-, *p*- position with respect to the participating carbon atom of the phenyl ring, *e.g.* **5c** was obtained in 60% yield. Product **5** was not obtained for *p*-methoxy substituted phenyl ring. The presence of the electron withdrawing chlorine atom at the phenyl ring inhibits the nucleophilic attack by the phenyl ring to the latent carbonium ion **9** and the spiroheterocyclic product for those cases were not obtained. The double group transfer reaction is possible in all cases irrespective of the substitution in the

Scheme 2. Reagents and conditions: DCM, MeOH, H$_2$SO$_4$, H$_2$O, reflux, 3–4 h.



4	Yield (%) 5	6	7
a. R¹ = R² = R³ = R⁴ = H	11	42	8
b. R¹ = R² = R⁴ = H, R³ = Me	28	32	6
c. R¹ = R³ = H, R² = R⁴ = Me	60	20	5
d. R¹ = R² = R⁴ = H, R³ = MeO	-	45	7
e. R¹ = Me, R² = R⁴ = H, R³ = Cl	-	46	8
f. R¹ = R² = R⁴ = H, R³ = Cl	-	45	7
g. R¹ = R³ = Cl, R² = R⁴ = H	-	48	8
h. R¹ = R² = Me, R³ = R⁴ = H	56	22	5
i. R¹ = R⁴ = Me, R² = R³ = H	58	18	4
j. R¹ = R² = R³ = H, R⁴ = Me	46	24	5
k. R¹ = R³ = Me, R² = R⁴ = H	34	30	6
l. R¹ = Cl, R² = R³ = R⁴ = H	-	42	7

Scheme 3



phenyl ring. Therefore, we obtained the products **6** and **7** in all the cases studied so far.

In conclusion the conditions under which the spiroheterocycles are formed is normally the usual ones for enol ether cleavage. From the experimental observation it is clear that the substituents on the phenyl ring seem to have a pronounced effect on the course of this reaction. We have developed an attractive strategy for the successful synthesis of spirocyclic indole annulated oxygen heterocyclic compounds having different connectivity between the furan and thiopyran ring with respect to the spirocyclic product obtained by the aryl radical cyclization [5a]. The methodology described here is synthetically useful and exhibits appreciable regioselectivity.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer L 120-000A spectrometer (λ_{max} in cm^{-1}) on KBr disks. UV absorption spectra were recorded in EtOH on a Shimadzu UV-2401PC spectrophotometer (λ_{max} in nm). ^1H NMR (300 MHz, 500 MHz) and ^{13}C NMR spectra were recorded on a Bruker DPX-300 and Bruker DPX-500 spectrometer in $CDCl_3$ (chemical shift in δ) with TMS as an internal standard. Elemental analyses were recorded on a Leco 932 CHNS analyzer instrument; mass spectra were recorded on JEOL JMS-600 and Q-Tof micro instrument. ^1H NMR and ^{13}C NMR spectra were recorded at the Indian Institute of Chemical Biology, Kolkata and Bose Institute, Kolkata. GC analysis was performed at IICB, Kolkata on a Hewlett-Packard 6890 puls fitted with FID. Silica gel [(60–120 mesh), (230–400 mesh), Spectrochem, India] was used for chromatographic separation. Silica gel G [E-Merck (India)] was used for TLC. Petroleum ether refers to the fraction boiling between 60 and 80°C.

General procedure for the synthesis of compounds 3a–l. To a mixture of 1-methylindoline-2-thione (**1**, 0.49 g, 3 mmol) and 1-aryloxy-4-chlorobut-2-yne (**2a**, 0.58 g, 3 mmol) in dichloromethane (30 mL) was added a solution of benzyl triethyl ammonium chloride (BTEAC, 0.5 g, 1.8 mmol) in 1% aqueous NaOH (30 mL) and the mixture was magnetically stirred at room temperature for 15 minutes. The reaction mixture was then diluted with water (20 mL) and the dichloromethane layer was washed with 2*N* HCl (2 × 20 mL), water (2 × 20 mL), brine (20 mL), and dried (Na_2SO_4). Removal of dichloromethane at room temperature left an oily residue, which was subjected to column chromatography over silica gel (230–400 mesh). Elution of the column with petroleum ether-ethyl acetate (50:1) afforded compound **3a**. Compounds **3b–l** were prepared similarly.

Experimental data of compounds **3a–g** were published earlier [9].

1-Methyl-2-{4-(p-tolyloxy)but-2-ynylthio}-1H-indole (3h). Yield: 91%; Viscous liquid. IR (neat): ν_{max} = 1462, 2923 cm^{-1}. UV (EtOH): λ_{max} = 220, 290 nm. ^1H NMR (300 MHz, $CDCl_3$): δ_H = 2.16 (*s*, 3H, $ArCH_3$), 2.23 (*s*, 3H, $ArCH_3$), 3.44 (*s*, 2H, $-SCH_2$), 3.75 (*s*, 3H, $-NCH_3$), 4.59 (*s*, 2H, $-OCH_2$), 6.65–6.83 (*m*, 3H, ArH), 6.92 (s, 1H, =CH), 7.03–7.56 (*m*, 4H, ArH). MS: *m*/*z* = 335 (M^+). Anal. Calc. for $C_{21}H_{21}NOS$: C, 75.19; H, 6.31; N, 4.18%. Found: C, 75.35; H, 6.36; N, 4.07%.

2-{4-(3,5-Dimethylphenoxy)but-2-ynylthio}-1-methyl-1H-indole (3i). Yield: 94%; Viscous liquid. IR (neat): ν_{max} = 1466, 2931 cm^{-1}. UV (EtOH): λ_{max} = 224, 287 nm. ^1H NMR (300 MHz, $CDCl_3$): δ_H = 2.30 (*s*, 3H, $ArCH_3$), 2.31 (*s*, 3H, $ArCH_3$), 3.43 (*s*, 2H, $-SCH_2$), 3.72 (*s*, 3H, $-NCH_3$), 4.55 (*s*, 2H, $-OCH_2$), 6.51–6.58 (*m*, 3H, ArH), 6.75 (*s*, 1H, =CH), 7.04–7.54 (*m*, 4H, ArH). MS: *m*/*z* = 335 (M^+). Anal. Calc. for $C_{21}H_{21}NOS$: C, 75.19; H, 6.31; N, 4.18%. Found: C, 75.38; H, 6.21; N, 4.05%.

2-{4-(4-Chloro-2-methylphenoxy)but-2-ynylthio}-1-meth-yl-1-indole (3j). Yield: 89%; Viscous liquid. IR (neat): ν_{max} = 1456, 2930 cm^{-1}. UV (EtOH): λ_{max} = 219, 289 nm. ^1H NMR (300 MHz, $CDCl_3$): δ_H = 2.26 (*s*, 3H, $ArCH_3$), 3.46 (*s*, 2H, $-SCH_2$), 3.76 (*s*, 3H, $-NCH_3$), 4.58 (*s*, 2H, $-OCH_2$), 6.65–6.83 (*m*, 3H, ArH), 6.92 (*s*, 1H, =CH), 7.03–7.56 (*m*, 5H, ArH). MS: *m*/*z* = 321 (M^+). Anal. Calc. for $C_{20}H_{19}NOS$: C, 74.73; H, 5.96; N, 4.36%. Found: C, 74.58; H, 6.02; N, 4.25%.

2-{4-(2,4-Dichlorophenoxy)but-2-ynylthio}-1-methyl-1H-indole (3k). Yield: 94%; Viscous liquid. IR (neat): ν_{max} = 1459, 2919 cm^{-1}. UV (EtOH): λ_{max} = 217, 226, 286 nm. ^1H NMR (300 MHz, $CDCl_3$): δ_H = 2.16 (*s*, 3H, $ArCH_3$), 2.23 (*s*, 3H, $ArCH_3$), 3.44 (*s*, 2H, $-SCH_2$), 3.75 (*s*, 3H, $-NCH_3$), 4.59 (*s*, 2H, $-OCH_2$), 6.66–6.85 (*m*, 3H, ArH), 6.92 (*s*, 1H, =CH), 7.06–7.56 (*m*, 4H, ArH). MS: *m*/*z* = 335 (M^+). Anal. Calc. for $C_{21}H_{21}NOS$: C, 75.19; H, 6.31; N, 4.18%. Found: C, 75.39; H, 6.22; N, 4.25%.2-{4-(2,3-dimethylphenoxy)but-2-ynylthio}-1-methyl-1H-indole (3l): Yield: 92%; Viscous liquid. IR (neat): ν_{max} = 1460, 2931 cm^{-1}. UV (EtOH): λ_{max} = 221, 289 nm. ^1H NMR (300 MHz, $CDCl_3$): δ_H = 3.44 (*s*, 2H, $-SCH_2$), 3.76 (*s*, 3H, $-NCH_3$), 4.73 (*s*, 2H, $-OCH_2$), 6.74 (*s*, 1H, =CH), 6.93–7.82 (*m*, 8H, ArH). MS: *m/z* = 341, 343 (M^+). Anal. Calc. for $C_{19}H_{16}ClNOS$: C, 66.75; H, 4.72; N, 4.10%. Found: C, 66.63; H, 4.80; N, 4.04%.

General procedure for the synthesis of compounds 4a–l. Compound **3a** (0.46 g, 1.5 mmol) was refluxed in chlorobenzene (10 mL) for 1 h. Then the crude mass was subjected to column chromatography over silica gel (60–120 mesh). Elution of the column with petroleum ether followed by petroleum ether-ethyl acetate (50:1) gave compound **4a** as white solid. Similarly, compounds **4b–l** were synthesized from **3b–l**.

9-Methyl-4-(phenoxymethylene)-2,3,4,9-tetrahydrothiopyrano[2,3-b]indole (4a). Yield: 83%; White solid; mp 120–122°C. IR (KBr): ν_{max} = 1482, 2921, 3044 cm^{-1}. UV (EtOH): λ_{max} = 216, 230, 247, 257, 277, 308 nm. ^1H NMR (300 MHz, $CDCl_3$): δ_H = 3.06–3.08 (*m*, 2H, —SCH_2CH_2), 3.13–3.17 (*m*, 2H, —SCH_2), 3.64 (*s*, 3H, —NCH_3), 6.98–7.10 (*m*, 2H, ArH), 7.12 (*s*, 1H, =CH), 7.14–7.70 (*m*, 7H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 24.12, 27.81, 29.83, 108.48, 115.98, 116.40, 117.22, 118.82, 120.09, 120.90, 122.30, 124.77, 129.65, 132.99, 133.57, 137.55, 157.85. MS: *m/z* = 307 (M^+). Anal. Calc. for $C_{19}H_{17}NOS$: C, 74.23; H, 5.57; N, 4.56%. Found: C, 74.41; H, 5.49; N, 4.66%.

9-Methyl-4-(p-tolyloxymethylene)-,3,4,9-tetrahydrothiopyrano[2,3-b]indole (4b). Yield: 83%; White solid; mp 122–124°C. IR (KBr): ν_{max} = 1466, 1499, 2916 cm^{-1}. UV (EtOH): λ_{max} = 205, 253, 277, 310 nm. ^1H NMR (300 MHz, $CDCl_3$): δ_H = 2.32 (*s*, 3H, $ArCH_3$), 3.08–3.11 (*m*, 2H, —SCH_2CH_2), 3.14–3.17 (*m*, 2H, —SCH_2), 3.65 (*s*, 3H, —NCH_3), 6.81–7.02 (*m*, 3H, ArH), 7.15 (*s*, 1H, =CH), 7.25–7.65 (*m*, 5H, ArH). MS: *m/z* = 321 (M^+). Anal. Calc. for $C_{20}H_{19}NOS$: C, 74.73; H, 5.96; N, 4.36%. Found: C, 74.88; H, 6.02; N, 4.48%.

4-{(3,5-Dimethylphenoxy)methylene}-9-methyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]indole (4c). Yield: 88%; White solid; mp 100–102°C. IR (KBr): ν_{max} = 1464, 2904, 3047 cm^{-1}. UV (EtOH): λ_{max} = 217, 247, 252, 257, 276, 307 nm. ^1H NMR (300 MHz, $CDCl_3$): δ_H = 2.29 (*s*, 3H, $ArCH_3$), 2.31 (*s*, 3H, $ArCH_3$), 3.03–3.07 (*m*, 2H, —SCH_2CH_2), 3.12–3.16 (*m*, 2H, —SCH_2), 3.64 (*s*, 3H, —NCH_3), 6.57–7.13 (*m*, 4H, ArH), 7.14 (*s*, 1H, =CH), 7.17–7.67 (*m*, 3H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C =21.33, 24.06, 27.81, 29.77, 108.43, 112.47, 113.70, 114.17, 116.87, 118.82, 120.02, 120.86, 123.30, 124.06, 133.80, 137.52, 139.46, 157.86. MS: *m/z* = 335 (M^+). Anal. Calc. for $C_{21}H_{21}NOS$: C, 75.19; H, 6.31; N, 4.18%. Found: C, 75.35; H, 6.42; N, 4.22%.

4-{(4-Methoxyphenoxy)methylene}-9-methyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]indole (4d). Yield: 86%; White solid; mp 72–74°C. IR (KBr): ν_{max} = 1497, 2938 cm^{-1}. UV (EtOH): λ_{max} = 216, 252, 257, 276 nm. ^1H NMR (300 MHz, $CDCl_3$): δ_H = 3.06–3.08 (*m*, 2H, —SCH_2CH_2), 3.13–3.17 (*m*, 2H, —SCH_2), 3.64 (*s*, 3H, —NCH_3), 3.79 (*s*, 3H, —OCH_3), 6.86–7.09 (*m*, 4H, ArH), 7.11 (*s*, 1H, =CH), 7.13–7.64 (*m*, 4H, ArH). MS: *m/z* = 337 (M^+). Anal. Calc. for $C_{20}H_{19}NO_2S$: C, 71.19; H, 5.68; N, 4.15%. Found: C, 71.13; H, 5.72; N, 4.11%.

4{(4-chloro-2-methylphenoxy)methylene}-9-methyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]indole (4e). Yield: 84%; White solid; mp 122–124°C. IR (KBr): ν_{max} = 1477, 2922 cm^{-1}. UV (EtOH): λ_{max} = 212, 230, 256, 279, 311 nm. ^1H NMR (300 MHz, $CDCl_3$): δ_H = 2.31 (*s*, 3H, $ArCH_3$), 3.04–3.08 (*m*, 2H, —SCH_2CH_2), 3.14–3.17 (*m*, 2H, —SCH_2), 3.65 (*s*, 3H, —NCH_3), 6.96–6.99 (*m*, 1H, ArH), 7.10 (*s*, 1H, =CH), 7.12–7.63 (*m*, 6H, ArH). MS: *m/z* = 355, 357 (M^+). Anal. Calc. for $C_{20}H_{18}ClNOS$: C, 67.50; H, 5.10; N, 3.94%. Found: C, 67.38; H, 5.15; N, 3.85%.

4-{(4-Chlorophenoxy)methylene}-9-methyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]indole (4f). Yield: 80%; White solid; mp 108–110°C. IR (KBr): ν_{max} = 1486, 2920 cm^{-1}. UV (EtOH): λ_{max} = 212, 219, 253, 278, 310 nm. ^1H NMR (300 MHz, $CDCl_3$): δ_H = 3.03–3.05 (*m*, 2H, —SCH_2CH_2), 3.14–3.16 (*m*, 2H, —SCH_2), 3.65 (*s*, 3H, —NCH_3), 7.03–7.05 (*m*, 2H, ArH), 7.11 (*s*, 1H, =CH), 7.13–7.63 (*m*, 6H, ArH). MS: *m/z* = 341, 343 (M^+). Anal. Calc. for $C_{19}H_{16}ClNOS$: C, 66.75; H, 4.72; N, 4.10%. Found: C, 66.85; H, 4.67; N, 4.21%.

4-{(2,4-Dichlorophenoxy)methylene}-9-methyl-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (4g). Yield: 85%; White solid; mp 116–118°C. IR (KBr): ν_{max} = 1474, 2928 cm^{-1}. UV (EtOH): λ_{max} = 211, 252, 280, 311 nm. ^1H NMR (300 MHz, $CDCl_3$): δ_H = 3.07–3.10 (*m*, 2H, —SCH_2CH_2), 3.14–3.18 (*m*, 2H, —SCH_2), 3.65 (*s*, 3H, —NCH_3), 6.96–7.07 (*m*, 1H, ArH), 7.10 (*s*, 1H, =CH), 7.14–7.62 (*m*, 6H, ArH). MS: *m/z* = 375, 377, 379 (M^+). Anal. Calc. for $C_{19}H_{15}Cl_2NOS$: C, 60.64; H, 4.02; N, 3.72%. Found: C, 60.48; H, 4.09; N, 3.65%

4-{(2,3-Dimethylphenoxy)methylene}-9-methyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]indole (4h). Yield: 86%; White solid; mp 114–116°C. IR (KBr): ν_{max} = 1466, 2918 cm^{-1}. UV (EtOH): λ_{max} = 206, 254, 276, 306 nm. ^1H NMR (300 MHz, $CDCl_3$): δ_H = 2.26 (*s*, 3H, $ArCH_3$), 2.31 (*s*, 3H, $ArCH_3$), 3.09–3.11 (*m*, 2H, —SCH_2CH_2), 3.14–3.18 (*m*, 2H, —SCH_2), 3.64 (*s*, 3H, —NCH_3), 6.87–7.08 (*m*, 3H, ArH), 7.11 (*s*, 1H, =CH), 7.13–7.65 (*m*, 4H, ArH). MS: *m/z* = 335 (M^+). Anal. Calc. for $C_{21}H_{21}NOS$: C, 75.19; H, 6.31; N, 4.18%. Found: C, 75.39; H, 6.24; N, 4.29%.

4-{(2,5-Dimethylphenoxy)methylene}-9-methyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]indole (4i). Yield: 88%; White solid; mp 112–114°C. IR (KBr): ν_{max} = 1465, 2925 cm^{-1}. UV (EtOH): λ_{max} = 209, 253, 275, 307 nm. ^1H NMR (300 MHz, $CDCl_3$): δ_H = 2.29 (*s*, 3H, $ArCH_3$), 2.31 (*s*, 3H, $ArCH_3$), 3.06-3.10 (*m*, 2H, —SCH_2CH_2), 3.14–3.18 (*m*, 2H, —SCH_2), 3.66 (*s*, 3H, —NCH_3), 6.77–7.07 (*m*, 2H, ArH), 7.09 (*s*, 1H, =CH), 7.12–7.67 (*m*, 5H, ArH). MS: *m/z* = 335 (M^+). Anal. Calc. for $C_{21}H_{21}NOS$: C, 75.19; H, 6.31; N, 4.18%. Found: C, 75.36; H, 6.19; N, 4.13%.

9-Methyl-4-(m-tolyloxymethylene)-2,3,4,9-tetrahydrothiopyrano[2,3-b]indole (4j). Yield: 84%; White solid; mp 118–120°C. IR (KBr): ν_{max} = 1475, 2922 cm^{-1}. UV (EtOH): λ_{max} = 208, 252, 276, 308 nm. ^1H NMR (300 MHz, $CDCl_3$): δ_H = 2.32 (*s*, 3H, $ArCH_3$), 3.08–3.12 (*m*, 2H, —SCH_2CH_2), 3.14–3.18 (*m*, 2H, —SCH_2), 3.65 (*s*, 3H, -NCH_3), 6.81–7.04 (*m*, 3H, ArH), 7.15 (*s*, 1H, =CH), 7.23–7.63 (*m*, 5H, ArH). MS: *m/z* = 321 (M^+). Anal. Calc. for $C_{20}H_{19}NOS$: C, 74.73; H, 5.96; N, 4.36%. Found: C, 74.63; H, 6.03; N, 4.30%.

4-{(2,4-Dimethylphenoxy)methylene}-9-methyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]indole (4k). Yield: 85%; White solid; mp 110–112°C. IR (KBr): ν_{max} = 1488, 2918 cm^{-1}. UV (EtOH): λ_{max} = 206, 254, 275, 305 nm. ^1H NMR (300 MHz, $CDCl_3$): δ_H = 2.29 (*s*, 3H, $ArCH_3$), 2.30 (*s*, 3H, $ArCH_3$), 3.08–3.10 (*m*, 2H, —SCH_2CH_2), 3.13–3.17 (*m*, 2H, —SCH_2), 3.64 (*s*, 3H, —NCH_3), 6.93–7.12 (*m*, 3H, ArH), 7.14 (*s*, 1H, =CH), 7.16–7.64 (*m*, 4H, ArH). MS: *m/z* = 335 (M^+). Anal. Calc. for $C_{21}H_{21}NOS$: C, 75.19; H, 6.31; N, 4.18%. Found: C, 75.32; H, 6.42; N, 4.26%.

4-{(2-Chlorophenoxy)methylene}-9-methyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]indole (4l). Yield: 82%; White solid; mp

98–100°C. IR (KBr): ν_{max} = 1471, 2920 cm^{-1}. UV (EtOH): λ_{max} = 216, 247, 252, 257, 278, 310 nm. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 3.09–3.12 (*m*, 2H, —SCH_2CH_2), 3.14–3.17 (*m*, 2H, —SCH_2), 3.64 (*s*, 3H, —NCH_3), 6.87–6.95 (*m*, 1H, ArH), 7.12 (*s*, 1H, =CH), 7.13–7.64 (*m*, 7H, ArH). MS: *m/z* = 341, 343 (M$^+$). Anal. Calc. for $C_{19}H_{16}ClNOS$: C, 66.75; H, 4.72; N, 4.10%. Found: C, 66.87; H, 4.64; N, 4.05%.

General procedure for the acid catalyzed reaction of compounds 4a-l. To the dichloromethane (8.4 mL) solution of compound **4a** (0.3 g, 1 mmol), water (3 mL), methanol (13.5 mL) and concentrated sulfuric acid (2.3 mL) were added. The reaction mixture was then refluxed on water bath for 4 h, allowed to cool and extracted with dichloromethane (2 × 10 mL). The combined extract was washed with sodium bicarbonate solution (3 × 15 mL), water (3 × 15 mL), brine (15 mL) and dried (Na_2SO_4). After removal of the solvent the crude mass was subjected to column chromatography. Elution of the column with petroleum ether-ethyl acetate (50:1) on silica gel (60–120 mesh) afforded the compounds **5a**, **6a**, and **7**. Compounds **4b–l** were also treated similarly.

9′-Methyl-3′,9′-dihydro-2*H*,2′*H*-spiro[benzofuran-3,4′-thiopyrano[2,3-*b*]indole] (5a). Yield: 11%; White solid; mp 156–158°C. IR (KBr): ν_{max} = 1479, 2898, 2918 cm^{-1}. UV (EtOH): λ_{max} = 233, 289, 297 nm. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 2.12–2.20 (*m*, 1H, —$SCH_2C\mathbf{H}_2$), 2.43–2.48 (*m*, 1H, —$SCH_2C\mathbf{H}_2$), 3.11–3.15 (*m*, 1H, —$SC\mathbf{H}_2$), 3.19–3.23 (*m*, 1H, —$SC\mathbf{H}_2$), 3.64 (*s*, 3H, —NCH_3), 4.40 (d, 1H, *J* = 9 Hz, —OCH_2), 4.65 (d, 1H, *J* = 9 Hz, —OCH_2), 6.70–7.23 (*m*, 8H, Ar**H**). ^{13}C NMR and DEPT-135 (75 MHz, $CDCl_3$): δ_C = 25.49 (CH_2), 30.21 (CH_3), 38.03 (CH_2), 46.65 (C), 82.63 (CH_2), 107.80 (C), 108.60 (CH), 110.32(CH), 118.93 (CH), 119.60 (CH), 120.89 (CH), 121.46 (CH), 124.72 (CH), 126.71 (C), 128.99 (CH), 131.86 (C), 134.54 (C), 137.87 (C), 160.17 (C). MS: *m/z* = 307 (M$^+$). Anal. Calc. for $C_{19}H_{17}NOS$: C, 74.23; H, 5.57; N, 4.56%. Found: C, 74.34; H, 5.66; N, 4.68%.

5,9′-Dimethyl-3′,9′-dihydro-2*H*,2′*H*-spiro[benzofuran-3,4′-thiopyrano[2,3-*b*]indole] (5b). Yield: 28%; White solid; mp 114–116°C. IR (KBr): ν_{max} = 1466, 2920 cm^{-1}. UV (EtOH): λ_{max} = 234, 288, 300 nm. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 2.16 (*s*, 3H, ArC**H**$_3$), 2.38–2.42 (*m*, 1H, —$SCH_2C\mathbf{H}_2$), 2.43–2.46 (*m*, 1H, —$SCH_2C\mathbf{H}_2$), 3.11–3.16 (*m*, 1H, —$SC\mathbf{H}_2$), 3.18–3.23 (*m*, 1H, —$SC\mathbf{H}_2$), 3.65 (*s*, 3H, —NCH_3), 4.38 (d, 1H, *J* = 9 Hz, —OCH_2), 4.65 (d, 1H, *J* = 9 Hz, —OCH_2), 6.71–7.25 (*m*, 7H, Ar**H**). MS: *m/z* = 321 (M$^+$). Anal. Calc. for $C_{20}H_{19}NOS$: C, 74.73; H, 5.96; N, 4.36%. Found: C, 74.92; H, 6.02; N, 4.28%.

4,6,9′-Trimethyl-3′,9′-dihydro-2*H*,2′*H*-spiro[benzofuran-3,4′-thiopyrano[2,3-*b*]indole] (5c). Yield: 60%; White solid; mp 172–174°C. IR (KBr): ν_{max} = 1463, 2914 cm^{-1}. UV (EtOH): λ_{max} = 236, 289, 299 nm. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 1.65 (*s*, 3H, ArC**H**$_3$), 2.14–2.23 (*m*, 1H, —$SCH_2C\mathbf{H}_2$), 2.30 (*s*, 3H, ArC**H**$_3$), 2.33–2.40 (*m*, 1H, —$SCH_2C\mathbf{H}_2$), 3.05–3.11 (*m*, 1H, —$SC\mathbf{H}_2$), 3.17–3.26 (*m*, 1H, —$SC\mathbf{H}_2$), 3.64 (*s*, 3H, —NCH_3), 4.33 (d, 1H, *J* = 9 Hz, —OCH_2), 4.52 (d, 1H, *J* = 9 Hz, —OCH_2), 6.41 (*s*, 1H, Ar**H**), 6.59 (*s*, 1H, Ar**H**), 6.78–7.23 (*m*, 4H, Ar**H**). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 17.27, 21.89, 25.69, 30.26, 34.75, 46.36, 82.26, 107.69, 108.47, 108.72, 118.44, 119.63, 120.89, 124.49, 127.15, 127.98, 131.08, 135.35, 137.75, 139.05, 160.61. MS: *m/z* = 335 (M$^+$). Anal. Calc. for $C_{21}H_{21}NOS$: C, 75.19; H, 6.31; N, 4.18%. Found: C, 75.35; H, 6.20; N, 4.29%.

6,7,9′-Trimethyl-3′,9′-dihydro-2*H*,2′*H*-spiro[benzofuran-3,4′-thiopyrano[2,3-*b*]indole] (5h). Yield: 56%; White solid; mp 154–156°C. IR (KBr): ν_{max} = 1462, 2929 cm^{-1}. UV (EtOH): λ_{max} = 225, 237, 288, 299 nm. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 2.13–2.16 (*m*, 1H, —$SCH_2C\mathbf{H}_2$), 2.23 (*s*, 3H, ArC**H**$_3$), 2.27 (*s*, 3H, ArC**H**$_3$), 2.40–2.42 (*m*, 1H, —$SCH_2C\mathbf{H}_2$), 3.12–3.14 (*m*, 1H, —$SC\mathbf{H}_2$), 3.15–3.18 (*m*, 1H, —$SC\mathbf{H}_2$), 3.64 (*s*, 3H, —NCH_3), 4.39 (d, 1H, *J* = 9 Hz, —OCH_2), 4.63 (d, 1H, *J* = 9 Hz, —OCH_2), 6.62–7.24 (*m*, 6H, Ar**H**). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 12.10, 19.91, 25.47, 30.17, 37.95, 46.94, 82.38, 107.97, 108.49, 118.97, 119.12, 119.45, 120.76, 121.21, 122.79, 126.78, 131.32, 131.71, 137.55, 137.80, 158.64. MS: *m/z* = 335 (M$^+$). Anal. Calc. for $C_{21}H_{21}NOS$: C, 75.19; H, 6.31; N, 4.18%. Found: C, 75.01; H, 6.38; N, 4.31%.

4,7,9′-Trimethyl-3′,9′-dihydro-2H,2′H-spiro[benzofuran-3,4′-thiopyrano[2,3-*b*]indole] (5i). Yield: 58%; White solid; mp 170–172°C. IR (KBr): ν_{max} = 1466, 2920, 2941 cm^{-1}. UV (EtOH): λ_{max} = 224, 235, 288, 299 nm. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 1.65 (*s*, 3H, ArC**H**$_3$), 2.18–2.22 (*m*, 1H, —$SCH_2C\mathbf{H}_2$), 2.27 (*s*, 3H, ArC**H**$_3$), 2.35–2.42 (*m*, 1H, —$SCH_2C\mathbf{H}_2$), 3.05–3.12 (*m*, 1H, —$SC\mathbf{H}_2$), 3.18–3.27 (*m*, 1H, —$SC\mathbf{H}_2$), 3.64 (*s*, 3H, —NCH_3), 4.35 (d, 1H, *J* = 9 Hz, —OCH_2), 4.53 (d, 1H, *J* = 9 Hz, —OCH_2), 6.48–7.23 (*m*, 6H, Ar**H**). MS: *m/z* = 335 (M$^+$). Anal. Calc. for $C_{21}H_{21}NOS$: C, 75.19; H, 6.31; N, 4.18%. Found: C, 75.30; H, 6.37; N, 4.26%.

4,9′-Dimethyl-3′,9′-dihydro-2H,2′H-spiro[benzofuran-3,4′-thiopyrano[2,3-*b*]indole] (5j). Yield: 46%; White solid; mp 104–106°C. IR (KBr): ν_{max} = 1464, 2912 cm^{-1}. UV (EtOH): λ_{max} = 235, 288, 299 nm. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 1.70 (*s*, 3H, ArC**H**$_3$), 2.16–2.25 (*m*, 1H, —$SCH_2C\mathbf{H}_2$), 2.35–2.42 (*m*, 1H, —$SCH_2C\mathbf{H}_2$), 3.15–3.19 (*m*, 1H, —$SC\mathbf{H}_2$), 3.23–3.28 (*m*, 1H, —$SC\mathbf{H}_2$), 3.66 (*s*, 3H, —NCH_3), 4.35 (d, 1H, *J* = 9 Hz, —OCH_2), 4.55 (d, 1H, *J* = 9 Hz, —OCH_2), 6.58–7.25 (*m*, 7H, Ar**H**). MS: *m/z* = 321 (M$^+$). Anal. Calc. for $C_{20}H_{19}NOS$: C, 74.73; H, 5.96; N, 4.36%. Found: C, 74.92; H, 5.90; N, 4.29%.

5,7,9′-Trimethyl-3′,9′-dihydro-2H,2′H-spiro[benzofuran-3,4′-thiopyrano[2,3-*b*]indole] (5k). Yield: 34%; White solid; mp 158–160°C. IR (KBr): ν_{max} = 1466, 2909 cm^{-1}. UV (EtOH): λ_{max} = 225, 235, 290, 297 nm. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 2.13 (*s*, 3H, ArC**H**$_3$), 2.18–2.23 (*m*, 1H, —$SCH_2C\mathbf{H}_2$), 2.28 (*s*, 3H, ArC**H**$_3$), 2.36–2.47 (*m*, 1H, —$SCH_2C\mathbf{H}_2$), 3.06–3.16 (*m*, 1H, —$SC\mathbf{H}_2$), 3.17–3.27 (*m*, 1H, -$SC\mathbf{H}_2$), 3.65 (*s*, 3H, —NCH_3), 4.36 d, 1H, *J* = 9 Hz, —OCH_2), 4.53 (d, 1H, *J* = 9 Hz, —OCH_2), 6.48–7.24 (*m*, 6H, Ar**H**). MS: *m/z* = 335 (M$^+$). Anal. Calc. for $C_{21}H_{21}NOS$: C, 75.19; H, 6.31; N, 4.18%. Found: C, 75.34; H, 6.22; N, 4.30%.

9-Methyl-4-(phenoxymethyl)-2,3,4,9-tetrahydrothiopy-rano [2,3-b]indole (6a). Yield: 42%; White solid; mp 90–92°C. IR (KBr): ν_{max} = 1469, 2912 cm^{-1}. UV (EtOH): λ_{max} = 224, 238, 279, 300 nm. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 2.09–2.20 (*m*, 1H, —$SCH_2C\mathbf{H}_2$), 2.60–2.67 (*m*, 1H, —$SCH_2C\mathbf{H}_2$), 2.97–3.04 (*m*, 1H, —$SC\mathbf{H}_2$), 3.23–3.32 (*m*, 1H, —$SC\mathbf{H}_2$), 3.61 (*s*, 3H, —NCH_3), 3.64–3.73 (*m*, 1H, —$CH_2C\mathbf{H}$), 3.86 (*t*, 1H, *J* = 9.4 Hz, —OCH_2), 4.38 (dd, 1H, *J* = 9.4, 3.9 Hz, —OCH_2), 6.90–7.51 (*m*, 9H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 24.27, 25.59, 30.15, 32.04, 69.92, 105.45, 108.74, 115.01, 115.33, 117.12, 119.75, 120.90, 121.25, 128.14, 130.00, 131.01, 137.57, 159.40. MS: *m/z* 309 (M$^+$). Anal. Calc. for $C_{19}H_{19}NOS$: C, 73.75; H, 6.19; N, 4.53%. Found: C, 73.90; H, 6.24; N, 4.65%.

9-Methyl-4-(p-tolyloxymethyl)-2,3,4,9-tetrahydrothiopy-rano [2,3-b]indole (6b). Yield: 32%; Viscous liquid. IR (neat): ν_{max} = 1466, 2921 cm^{-1}. UV (EtOH): λ_{max} = 226, 238, 286, 300 nm. ^{1}H NMR (300 MHz, CDCl$_3$): δ_H = 2.08–2.17 (*m*, 1H, —SCH$_2$C**H**$_2$), 2.27 (*s*, 3H, ArC**H**$_3$), 2.60–2.66 (*m*, 1H, —SCH$_2$C**H**$_2$), 2.96–3.01 (*m*, 1H, —SC**H**$_2$), 3.22–3.30 (*m*, 1H, —SC**H**$_2$), 3.60 (*s*, 3H, —NC**H**$_3$), 3.65–3.68 (*m*, 1H, —CH$_2$C**H**), 3.83 (*t*, 1H, *J* = 9.4 Hz, —OC**H**$_2$), 4.35 (dd, 1H, *J* = 9.4, 3.8 Hz, —OC**H**$_2$), 6.80–7.50 (*m*, 8H, Ar**H**). MS: *m/z* = 323 (M$^+$). Anal. Calc. for $C_{20}H_{21}NOS$: C, 74.27; H, 6.54; N, 4.33%. Found: C, 74.45; H, 6.59; N, 4.40%.

4-{(3,5-Dimethylphenoxy)methyl}-9-methyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]indole (6c). Yield: 20%; White solid; mp 92–94°C. IR (KBr): ν_{max} = 1464, 2919 cm^{-1}. UV (EtOH): λ_{max} = 224, 235, 255, 300 nm. ^{1}H NMR (300 MHz, CDCl$_3$): δ_H = 2.05–2.19 (*m*, 1H, —SCH$_2$C**H**$_2$), 2.27 (*s*, 6H, ArC**H**$_3$), 2.59–2.67 (*m*, 1H, —SCH$_2$C**H**$_2$), 2.96–3.03 (*m*, 1H, —SC**H**$_2$), 3.23–3.32 (*m*, 1H, —SC**H**$_2$), 3.62 (*s*, 3H, —NC**H**$_3$), 3.65–3.71 (*m*, 1H, —CH$_2$C**H**), 3.83 (*t*, 1H, *J* = 9.4 Hz, —OC**H**$_2$), 4.35 (dd, 1H, *J* = 9.4, 3.8 Hz, —OC**H**$_2$), 6.56–7.51 (*m*, 7H, Ar**H**). ^{13}C NMR (75 MHz, CDCl$_3$): δ_C = 21.83, 24.18, 25.47, 30.09, 31.97, 69.73, 105.47, 108.66, 112.70, 117.03, 119.65, 120.81, 122.93, 128.07, 130.92, 137.51, 139.67, 159.40. MS: *m/z* = 337 (M$^+$). Anal. Calc. for $C_{21}H_{23}NOS$: C, 74.74; H, 6.87; N, 4.15%. Found: C, 74.93; H, 6.94; N, 4.06%.

4-{(4-Methoxyphenoxy)methyl}-9-methyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]indole (6d). Yield: 45%; White solid; mp 62–64°C. IR (KBr): ν_{max} = 1467, 1510, 2924 cm^{-1}. UV (EtOH): λ_{max} = 226, 235, 240, 255, 261, 300 nm. ^{1}H NMR (300 MHz, CDCl$_3$): δ_H = 2.09–2.19 (*m*, 1H, —SCH$_2$C**H**$_2$), 2.60–2.66 (*m*, 1H, —SCH$_2$C**H**$_2$), 2.97–3.04 (*m*, 1H, —SC**H**$_2$), 3.23–3.31 (*m*, 1H, —SC**H**$_2$), 3.61 (*s*, 3H, —NC**H**$_3$), 3.64–3.69 (*m*, 1H, —CH$_2$C**H**), 3.76 (*s*, 3H, —OC**H**$_3$), 3.82 (*t*, 1H, *J* = 9.4 Hz, —OC**H**$_2$), 4.33 (dd, 1H, *J* = 9.4, 3.8 Hz, —OC**H**$_2$), 6.80–7.50 (*m*, 8H, Ar**H**). MS: *m/z* = 339 (M$^+$). Anal. Calc. for $C_{20}H_{21}NO_2S$: C, 70.77; H, 6.24; N, 4.13%. Found: C, 70.65; H, 6.35; N, 4.21%.

4-{(4-Chloro-2-methylphenoxy)methyl}-9-methyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]indole (6e). Yield: 46%; Viscous liquid. IR (neat): ν_{max} = 1467, 1492, 2922 cm^{-1}. UV (EtOH): λ_{max} = 235, 289, 300 nm. ^{1}H NMR (300 MHz, CDCl$_3$): δ_H = 2.02–2.19 (*m*, 1H, —SCH$_2$C**H**$_2$), 2.23 (*s*, 3H, ArC**H**$_3$), 2.58–2.65 (*m*, 1H, —SCH$_2$C**H**$_2$), 2.97–3.04 (*m*, 1H, —SC**H**$_2$), 3.23–3.31 (*m*, 1H, —SC**H**$_2$), 3.60 (*s*, 3H, —NC**H**$_3$), 3.67–3.73 (*m*, 1H, —CH$_2$C**H**), 3.82 (*t*, 1H, *J* = 9.2 Hz, —OC**H**$_2$), 4.35 (dd, 1H, *J* = 9.2, 3.8 Hz, —OC**H**$_2$), 6.66–7.48 (*m*, 7H, Ar**H**). MS: *m/z* = 357, 359 (M$^+$). Anal. Calc. for $C_{20}H_{20}ClNOS$: C, 67.12; H, 5.63; N, 3.91%. Found: C, 67.01; H, 5.50; N, 3.96%.

4-{(4-Chlorophenoxy)methyl}-9-methyl-2,3,4,9-tetrahy-drothiopyrano[2,3-b]indole (6f). Yield: 45%; White solid; mp 106–108°C. IR (KBr): ν_{max} = 1465, 1491, 2917 cm^{-1}. UV (EtOH): λ_{max} = 234, 290, 300 nm. ^{1}H NMR (300 MHz, CDCl$_3$): δ_H = 2.09–2.21 (*m*, 1H, —SCH$_2$C**H**$_2$), 2.55–2.64 (*m*, 1H, —SCH$_2$C**H**$_2$), 2.98–3.05 (*m*, 1H, —SC**H**$_2$), 3.21–3.30 (*m*, 1H, —SC**H**$_2$), 3.61 (*s*, 3H, —NC**H**$_3$), 3.64–3.72 (*m*, 1H, —CH$_2$C**H**), 3.84 (*t*, 1H, *J* = 9.4 Hz, —OC**H**$_2$), 4.33 (dd, 1H, *J* = 9.4, 4 Hz, —OC**H**$_2$), 6.81–7.49 (*m*, 8H, Ar**H**). MS: *m/z* = 343, 345 (M$^+$). Anal. Calc. for $C_{19}H_{18}ClNOS$: C, 66.36; H, 5.28; N, 4.07%. Found: C, 66.52; H, 5.35; N, 3.97%.

4-{(2,4-Dichlorophenoxy)methyl}-9-methyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]indole (6g). Yield: 48%; White solid; mp 94–96°C. IR (KBr): ν_{max} = 1466, 1483, 2927 cm^{-1}. UV (EtOH): λ_{max} = 236, 294 nm. ^{1}H NMR (300 MHz, CDCl$_3$): δ_H = 2.14–2.25 (*m*, 1H, —SCH$_2$C**H**$_2$), 2.65–2.72 (*m*, 1H, —SCH$_2$C**H**$_2$), 3.00–3.07 (*m*, 1H, —SC**H**$_2$), 3.25–3.34 (*m*, 1H, —SC**H**$_2$), 3.62 (*s*, 3H, —NC**H**$_3$), 3.73–3.78 (*m*, 1H, —CH$_2$C**H**), 3.87 (*t*, 1H, *J* = 9.2 Hz, —OC**H**$_2$), 4.42 (dd, 1H, *J* = 9.2, 3.8 Hz, —OC**H**$_2$), 6.79–7.49 (*m*, 7H, Ar**H**). MS: *m/z* = 377, 379, 381 (M$^+$). Anal. Calc. for $C_{19}H_{17}Cl_2NOS$: C, 60.32; H, 4.53; N, 3.70%. Found: C, 60.44; H, 4.45; N, 3.81%.

4-{(2,3-Dimethylphenoxy)methyl}-9-methyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]indole (6h). Yield: 22%; White solid; mp 116–118°C. IR (KBr): ν_{max} = 1466, 2916 cm^{-1}. UV (EtOH): λ_{max} = 235, 239, 300 nm. ^{1}H NMR (300 MHz, CDCl$_3$): δ_H = 2.12–2.14 (*m*, 1H, —SCH$_2$C**H**$_2$), 2.21 (*s*, 3H, ArC**H**$_3$), 2.28 (*s*, 3H, ArC**H**$_3$), 2.65–2.69 (*m*, 1H, —SCH$_2$C**H**$_2$), 2.98–3.03 (*m*, 1H, —SC**H**$_2$), 3.25–3.31 (*m*, 1H, —SC**H**$_2$), 3.62 (*s*, 3H, —NC**H**$_3$), 3.69–3.74 (*m*, 1H, —CH$_2$C**H**), 3.84 (*t*, 1H, *J* = 9.2 Hz, —OC**H**$_2$), 4.40 (dd, 1H, *J* = 9.2, 4 Hz, —OC**H**$_2$), 6.67–7.49 (*m*, 7H, Ar**H**). MS: *m/z* = 337 (M$^+$). Anal. Calc. for $C_{21}H_{23}NOS$: C, 74.74; H, 6.87; N, 4.15%. Found: C, 74.59; H, 6.95; N, 4.22%.

4-{(2,5-Dimethylphenoxy)methyl}-9-methyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]indole (6i). Yield: 18%; White solid; mp 72–74°C. IR (KBr): ν_{max} = 1464, 2924 cm^{-1}. UV (EtOH): λ_{max} = 239, 282, 300 nm. ^{1}H NMR (300 MHz, CDCl$_3$): δ_H = 2.12–2.18 (*m*, 1H, —SCH$_2$C**H**$_2$), 2.23 (*s*, 3H, ArC**H**$_3$), 2.26 (*s*, 3H, ArC**H**$_3$), 2.64–2.70 (*m*, 1H, —SCH$_2$C**H**$_2$), 2.97–3.04 (*m*, 1H, —SC**H**$_2$), 3.25–3.34 (*m*, 1H, —SC**H**$_2$), 3.62 (*s*, 3H, —NC**H**$_3$), 3.69–3.75 (*m*, 1H, —CH$_2$C**H**), 3.83 (*t*, 1H, *J* = 9.3 Hz, —OC**H**$_2$), 4.39 (dd, 1H, *J* = 9.3, 3.6 Hz, —OC**H**$_2$), 6.62–7.51 (*m*, 7H, Ar**H**). MS: *m/z* = 337 (M$^+$). Anal. Calc. for $C_{21}H_{23}NOS$: C, 74.74; H, 6.87; N, 4.15%. Found: C, 74.92; H, 6.77; N, 4.06%.

9-Methyl-4-(m-tolyloxymethyl)-2,3,4,9-tetrahydrothio-pyrano [2,3-b]indole (6j). Yield: 24%; White solid; mp 86–88°C. IR (KBr): ν_{max} = 1464, 2922 cm^{-1}. UV (EtOH): λ_{max} = 235, 288, 299 nm. ^{1}H NMR (300 MHz, CDCl$_3$): δ_H = 2.07–2.15 (*m*, 1H, —SCH$_2$C**H**$_2$), 2.29 (*s*, 3H, ArC**H**$_3$), 2.57–2.63 (*m*, 1H, —SCH$_2$C**H**$_2$), 2.91–2.98 (*m*, 1H, —SC**H**$_2$), 3.19–3.27 (*m*, 1H, —SC**H**$_2$), 3.56 (*s*, 3H, —NC**H**$_3$), 3.64–3.67 (*m*, 1H, —CH$_2$C**H**), 3.83 (*t*, 1H, *J* = 9.3 Hz, —OC**H**$_2$), 4.34 (dd, 1H, *J* = 9.3, 3.7 Hz, —OC**H**$_2$), 6.70–7.49 (*m*, 8H, Ar**H**). MS: *m/z* = 323 (M$^+$). Anal. Calc. for $C_{20}H_{21}NOS$: C, 74.27; H, 6.54; N, 4.33%. Found: C, 74.13; H, 6.62; N, 4.45%.

4-{(2,4-Dimethylphenoxy)methyl}-9-methyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]indole (6k). Yield: 30%; White solid; mp 68–70°C. IR (KBr): ν_{max} = 1466, 2920 cm^{-1}. UV (EtOH): λ_{max} = 232, 286, 298 nm. ^{1}H NMR (300 MHz, CDCl$_3$): δ_H = 2.10–2.19 (*m*, 1H, —SCH$_2$C**H**$_2$), 2.24 (*s*, 6H, ArC**H**$_3$), 2.62–2.68 (*m*, 1H, —SCH$_2$C**H**$_2$), 2.94–3.01 (*m*, 1H, —SC**H**$_2$), 3.22–3.35 (*m*, 1H, —SC**H**$_2$), 3.58 (*s*, 3H, —NC**H**$_3$), 3.64–3.72 (*m*, 1H, —CH$_2$C**H**), 3.80 (*t*, 1H, *J* = 9.2 Hz, —OC**H**$_2$), 4.37 (dd, 1H, *J* = 9.2, 3.6 Hz, —OC**H**$_2$), 6.66–7.49 (*m*, 7H, Ar**H**). MS: *m/z* = 337 (M$^+$). Anal. Calc. for $C_{21}H_{23}NOS$: C, 74.74; H, 6.87; N, 4.15%. Found: C, 74.85; H, 6.97; N, 4.07%.

4-{(2-Chlorophenoxy)methyl}-9-methyl-2,3,4,9-tetrahy-drothiopyrano[2,3-b]indole (6l). Yield: 42%; White solid; mp 102–104°C. IR (KBr): ν_{max} = 1465, 2920 cm^{-1}. UV (EtOH): λ_{max} = 208, 222, 238, 300 nm. ^{1}H NMR (300 MHz, CDCl$_3$): δ_H = 2.14–2.25 (*m*, 1H, —SCH$_2$C**H**$_2$), 2.72–2.79 (*m*, 1H, —SCH$_2$C**H**$_2$), 3.00–3.07 (*m*, 1H, —SC**H**$_2$), 3.27–3.36 (*m*, 1H,

—SC**H**$_2$), 3.62 (*s*, 3H, —NC**H**$_3$), 3.76–3.85 (*m*, 1H, —CH$_2$C**H**), 3.88 (*t*, 1H, *J* = 9.2 Hz, —OC**H**$_2$), 4.48 (dd, 1H, *J* = 9.2, 3.6 Hz, —OC**H**$_2$), 6.80–7.56 (*m*, 8H, Ar**H**). MS: *m/z* = 343, 345 (M$^+$). Anal. Calc. for $C_{19}H_{18}ClNOS$: C, 66.36; H, 5.28; N, 4.07%. Found: C, 66.18; H, 5.35; N, 3.98%.

9-Methylthiopyrano[2,3-*b*]indol-4(9H)-one (7). Yield: 4–8%; Viscous liquid. IR (neat): ν_{max} = 1453, 1719, 2922 cm^{-1}. UV (EtOH): λ_{max} = 201, 229, 289 nm. ^{1}H NMR (300 MHz, CDCl$_3$): δ_H = 3.67 (*s*, 3H, —NC**H**$_3$), 6.93 (d, 1H, *J* = 8.7 Hz. —SCH=C**H**), 7.13 (d, 1H, *J* = 8.7 Hz. —SC**H**=CH), 7.32–7.60 (*m*, 4H, Ar**H**). MS: *m/z* = 215 (M$^+$). Anal. Calc. for $C_{12}H_9NOS$: C, 66.95; H, 4.21; N, 6.51%. Found: C, 67.11; H, 4.30; N, 6.44%.

GC analysis of Compound (8). The crude reaction mixture of compound **4a** after usual work up was injected into the column (oven temperature 40°-5-12C/mim-240-18). RT (min) of the standard sample of anisole was 2.762 whereas; the reaction mixture gave a peak at 2.802.

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DBU-Catalyzed Three-Component One-Pot Synthesis of Highly Functionalized Pyridines in Aqueous Ethanol

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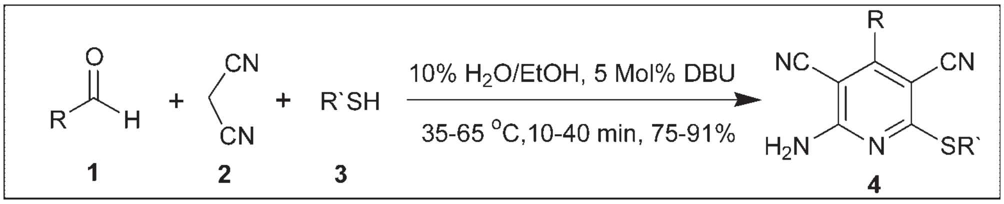

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) efficiently catalyzes three-component one-pot condensations of aldehyde, malononitrile, and thiophenol to produce highly functionalized pyridines in excellent yield in aqueous ethanol.

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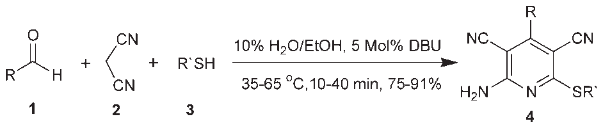
INTRODUCTION

The pyridine scaffold is a key constituent of a wide range of naturally occurring and synthetic bioactive compounds, pharmaceuticals, and functional materials [1–3]. Penta-substituted pyridines are known as medicinally privileged scaffold, inhibit MAPK-activated PK-2 [4] and modulate androgen receptor functions [5]. These compounds are also useful in the treatment of urinary incontinence [6], HBF infections [7], Creutzfeldt-Jacob disease [8], and Parkinson's disease, hypoxia/ischemia, asthma, kidney disease, epilepsy, cancer [9–11] and also exhibit antibacterial, anti-biofilm and anti-infective activities [12]. The importance of this class of compounds can be realized by the number of patents filed in the recent years [4–7,12]. Thus, synthesis of highly functionalized pyridine derivatives, with the aim to develop new drug molecules has been an active area of research [13–15]. Various synthetic protocols have been developed for the synthesis of pyridine-3,5-dicarbonitriles [16–25]. The most interesting synthetic methodology has been three-component condensation of aldehydes, malononitrile, and thiolphenols [17,26,27]. Various bases such as Et_3N, DABCO [17,26,27], and piperidine, morpholine, thiomorpholine, pyrrolidine, N,N-DIPEA, pyridine, 2,4,6-collidine, DMAP, aniline, *N*-methyl-aniline, *N*,*N*-dimethylaniline, and *N*,*N*-diethylaniline [27] have been used. However, the major drawback of these procedures is the formation of various side products [26], thus reducing the yield of the desired product to 20–48% [26,27]. It is important to mention here that Ranu *et al.* [28] have reported a better synthetic protocol for this reaction and immidazolium-based ionic liquid and ethanol have been used as reaction media. Although ionic liquids are considered to be green solvents as the risk of air pollution is significantly reduced due to their nonvolatile nature [29,30] but their toxicity, especially, immidazolium-based ionic liquids and cost has been a matter of concerns [31,32]. So, development of an improved synthetic protocol for the generation of pyridine-3,5-dicarbonitriles for lead optimization is of considerable interest. As a part of our ongoing effort towards the synthesis of biologically active compounds [33–35] and keeping the medicinal values of pyridine-3,5-dicarbonitriles in mind, we considered it necessary to develop an efficient high yielding synthetic protocol for the synthesis of this class of compounds.

RESULTS AND DISCUSSION

Careful literature analyses revealed that a variety of bases with pK_a ranges from 4 to 11 have been used for this multicomponent reaction. We speculated that use of neutral organic base that have high basicity, and can form a stable protonated species, may suppress the formation of enaminonitrile and other side products. 1,8-Diazabicyclo-[5.4.0]undec-7-ene (DBU) fulfills these requirements, and it has been used in many organic transformations in recent years. DBU is commercially available, cheap homogenous catalyst. It is a sterically hindered amidine base and especially useful where side reactions due to the inherent nucleophilicity of a basic nitrogen are a problem [36–40]. DBU is one of the strongest organic neutral base ($pK_a = 12$) and the +M effect of the adjacent nitrogen stabilizes the protonated species. Inspired with the catalytic potential of DBU, we examined the catalytic role of DBU in the synthesis of pyridine-3,5-dicarbonitriles *via* three component reaction of aldehydes, malononitriles, and thiols. The reaction of

Scheme 1

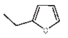
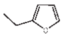
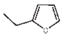
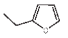
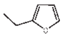
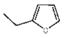
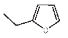


an aldehyde (**1**), malononitrile (**2**), and thiol (**3**) was carried out in the presence of catalytic amount of DBU (Scheme 1). We were pleased to observe that use of 5 mol % DBU as a catalyst in 10% aqueous ethanol significantly increases the rate of reaction and yield of the product at lower temperatures (Table 1). A wide range of substituted aromatic as well as heteroaromatic aldehydes underwent this three-component condensation with malononitrile and thiols to produce pyridine-3,5-dicarbonitriles (**4**) in high yield. The results are summarized in Table 1. All the utilized functionalities were found to be compatible under the reaction conditions.

For example, three-component reaction of benzaldehyde, malononitrile, and thiophenol lead to the formation of **4a** at 35°C in 15 min in 80% yield, while the same reaction takes 1.5 h to complete at reflux temperature in ethanol, and yield of the product was reported to be 35% when other bases were used [26]. Encouraged by this observation, a series of reactions were carried out under identical reaction conditions, and in all of the cases the product was isolated in very good yield (Table 1). However, reaction temperature was increased up to 65°C in some cases. A library of compounds was synthesized using 5 mol % DBU as base. The same reactions were also carried out in ethanol, but it was observed that the addition of 10% water in the reaction lead to increase in the yield to 8–10%. However, when ethanol-water (1:1) and water was used as a reaction media, no or very low yield was observed even at elevated temperature, due to the insolubility of the starting materials. We have also explored the possibility of using polyethylene glycol (PEG) as a reaction media, but no product formation was observed in PEG. This multicomponent reaction works well for unsubstituted (entry **4a**, **4q**, **4w**), electron poor (entry **4g**, **4h**), electron rich (entry **4b–4e**, **4i–4v**), and

Table 1

DBU catalyzed three-component synthesis of substituted pyridine-3,5-dicarbonitriles *via* Scheme 1.

Compd. No.	R	R′	Temp (°C)	Time (min)	Yield (%)	MP (°C)	
						Found	Reported
4a	Ph	Ph	35	15	80	220–221	218 [26]
4b	4-Cl-Ph	Ph	35	15	87	223	222 [26]
4c	4-OMe-Ph	Ph	50	15	90	241–244	240 [27]
4d	4-OH-Ph	Ph	55	15	89	313	315 [17]
4e	3-Pyridinyl	Ph	50	25	85	<300	305–306 [26]
4f	1-Naphthyl	Ph	65	15	87	258–260	–
4g	3-NO_2-Ph	Ph	55	15	85	219–220	–
4h	2-NO_2-Ph	4-Me-Ph	50	20	83	290–291	–
4i	4-Cl-Ph	Ph	50	15	85	230–231	228–230 [28]
4j	2-Naphthyl	Ph	50	10	89	236	–
4k	4-F-Ph	Ph	50	20	88	248–249	250 [10]
4l	2-OH-Ph	Ph	50	15	88	265–266	–
4m	3-Me-Ph	Ph	55	20	89	278–280	280 [10]
4n	4-Br-Ph	Ph	35	20	90	255–257	–
4o	3-Me-Ph	4-Me-Ph	55	20	91	236	–
4p	4-Cl-Ph	4-Me-Ph	55	15	89	245–246	–
4q	Ph	4-Me-Ph	50	15	86	238	–
4r	4-Me-Ph	2-NH_2-Ph	55	30	80	208–210	207–208 [41]
4s	4-OMe-Ph	2-NH_2-Ph	55	35	85	232	235–236 [41]
4t	4-Cl-Ph	2-NH_2-Ph	60	30	80	233	239–240 [26]
4u	4-OH-Ph	2-NH_2-Ph	60	40	75	175	–
4v	1-Naphthyl	2-NH_2-Ph	55	25	88	220–222	–
4w	Ph		60	40	85	189	–
4x	4-Me-Ph		60	35	80	180–181	–
4y	4-Br-Ph		55	30	79	180–182	–
4z	1-Naphthyl		60	25	83	220–222	–
4aa	2-Naphthyl		60	25	85	248	–
4ab	4-OMe-Ph		60	40	85	198	–
4ac	4-Cl-Ph		55	30	85	193–195	–

heteroaromatic aldehydes (entry **4e**). However, aliphatic aldehydes either gave very poor yield or did not react.

According to the proposed mechanisms, the first step of this reaction is the formation of Knoevenagel product by the condensation of an aldehyde with malononitrile [26,27,41,42]. During this base-catalyzed three-component reaction, formation of many side products such as enaminonitrile, higher adducts, reduced products, and malononitrile self addition products have been noticed [26,41]. We believe that low reaction temperature, higher basicity, and stability of DBU-H^+ species generated in this reaction suppress the formation of these side products and, hence, yield of the product increases. It is important to mention here that use of DABCO has been shown to promote the reaction of hindered aldehydes, with marginal increase of yield of the product [26].

To assess the feasibility of the methodology on higher scale under identical reaction conditions, we carried out the reaction on a 50 gm scale (entry **4b**, **4g**) and it was observed that the reaction proceeded smoothly and the desired product was isolated in 87% and 85% yields, respectively. It is important to mention here that the reaction media can be reused for further reactions. For example, after completion of the reaction, the reaction mixture was cooled, and solid product was collected by filtration (entry 4b). To the filtrate, *p*-chlorobenzaldehyde, malononitrile, and thiophenol were added in the same molar ratio without additional load of DBU. The reaction mixture was stirred for specified time, marginal loss of the yield was observed in first three run (87%, 86%, and 83%), while in fourth and fifth run the yield dropped to 75% and 65%, respectively. Structures of all of the compounds were identified by their mp and spectral data.

CONCLUSION

In conclusion, we have developed a novel synthetic methodology for the synthesis of pyridine-3,5-dicarbonitriles using 5 mol % DBU as a catalyst and 10% aqueous ethanol as the reaction media through a three component condensation of aldehydes, malononitrile and thiols. The short reaction times, high yields, use of commercially inexpensive DBU as a catalyst, and reusability of the reaction media are the main advantages of this process.

EXPERIMENTAL

All of the chemicals used in the synthesis were purchased from Sigma-Aldrich and used as received. Thin-layer chromatography was used to monitor reaction progress. Compounds were purified either by crystallization or over silica gel column. Melting points were determined on a melting point apparatus and are uncorrected. IR (KBr) spectra were recorded using Perkin-Elmer FTIR spectrophotometer and the values are expressed as ν_{max} cm^{-1}. Mass spectral data were recorded on a waters micromass LCT Mass Spectrometer/Data system. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Spectrospin spectrometer at 300 MHz and 75.5 MHz, respectively using TMS as an internal standard. The chemical shift values are recorded on δ scale and the coupling constants (*J*) are in Hz. Elemental analysis were performed on a Carlo Erba Model EA-1108 elemental analyzer and data of C, H, and N is within ±0.4% of calculated values.

General procedure for the synthesis of substituted pyridines. To a stirred solution of substituted benzaldehyde (4.71 mmol) in 10% aqueous ethanol (5 mL), DBU (5 mol %) was added followed by dropwise addition of malononitrile (9.43 mmol) at room temperature. To this stirred mixture substituted thiols (4.71 mmol) was added dropwise. The reaction mixture was stirred at 35–65°C as specified in Table 1; reaction progress was monitored by TLC. The crude product was collected by filtration and was purified by crystallization or by SiO_2 column chromatography. Spectral data of all unknown compounds is given later.

2-Amino-4-(1-naphthyl)-6-phenylsulphanylpyridine-3,5-dicarbonitrile (4f). IR: 3437, 3327, 3217, 2219, 1626, 1552, 1462, 1377, 1270, 798, 776, 750, 721 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.53–7.62 (*m*, 5H), 7.66–7.68 (*m*, 5H), 7.91 (brs, 2H), 8.07–8.15 (*m*, 2H); HRMS calc. for $C_{23}H_{14}N_4S$: 378.0939, found: 378.0929; Anal. calc. for $C_{23}H_{14}N_4S$: C, 72.99; H, 3.73; N, 14.80; S, 8.47; found: C, 72.89; H, 3.66; N, 14.88; S, 8.42.

2-Amino-4-(3-nitrophenyl)-6-phenylsulphanylpyridine-3,5-dicarbonitrile (4g). IR: 3400, 3323, 3230, 2213, 1647, 1550, 1526, 1426, 1377, 1260, 1037, 805, 754 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.52–7.61 (*m*, 5H), 7.89–7.94 (*m*, 2H), 8.07 (*d*, *J* = 6 Hz, 1H), 8.45 (*d*, *J* = 6 Hz, 1H), 8.52 (brs, 2H); HRMS calc. for $C_{19}H_{11}N_5O_2S$: 373.0633, found: 373.0631; Anal. calc. for $C_{19}H_{11}N_5O_2S$: C, 61.12; H, 2.97; N, 18.76; S, 8.59; found: C, 61.18; H, 3.01; N, 18.69; S, 8.51.

2-Amino-4-(2-nitrophenyl)-6-(4-tolyl)sulphanylpyridine-3,5-dicarbonitrile (4h). IR: 3395, 3323, 3231, 2211, 1645, 1551, 1523, 1463, 1354, 1258, 1036, 813, 736 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.37 (s, 3H), 7.30 (*d*, *J* = 8 Hz, 2H), 7.50 (*d*, *J* = 8 Hz, 2H), 7.91–7.94 (*m*, 2H), 8.05 (*d*, *J* = 6 Hz, 1H), 8.43 (*d*, *J* = 6Hz, 1H), 8.52 (brs, 2H); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 87.15, 93.22, 114.78, 115.09, 123.36, 123.59, 125.13, 130.18, 130.65, 134.92, 135.21, 135.42, 139.66, 147.66, 156.26, 159.52, 166.64; HRMS calc. for $C_{20}H_{13}N_5O_2S$: 378.0790, found: 378.0799; Anal. calc. for $C_{20}H_{13}N_5O_2S$: C, 62.00; H, 3.38; N, 18.08; S, 8.28; found: C, 61.96; H, 3.42; N, 18.13; S, 8.20.

2-Amino-4-(2-naphthyl)-6-phenylsulphanylpyridine-3,5-dicarbonitrile (4j). IR: 3371, 2209, 1615, 1545, 1458, 1377, 1246, 815, 736 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.50–7.53 (*m*, 5H), 7.63–7.65 (*m*, 5H), 7.89 (brs, 2H), 8.06–8.18 (*m*, 2H); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 87.34, 93.63, 115.06, 115.38, 125.38, 127.03, 127.75, 128.41, 129.46, 129.67, 131.41, 132.25, 133.33, 134.82, 158.66, 159.68, 166.18; HRMS calc. for $C_{23}H_{14}N_4S$: 378.0939, found: 378.0935; Anal. calc. for $C_{23}H_{14}N_4S$: C, 72.99; H, 3.73; N, 14.80; S, 8.47; found: C, 72.93; H, 3.64; N, 14.85; S, 8.42.

2-Amino-4-(2-hydroxyphenyl)-6-phenylsulphanylpyridine-3,5-dicarbonitrile (4l). IR: 3422, 3338, 3208, 2183, 1639, 1614, 1579, 1545, 1460, 1404, 1377, 1263, 1193, 1046, 763, 749 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.95–7.15 (*m*, 6H), 7.33 (brs, 1H), 7.50–7.61 (*m*, 5H); HRMS calc. for $C_{19}H_{12}N_4OS$: 344.0732, found: 344.0738; Anal. calc. for $C_{19}H_{12}N_4OS$: C, 66.26; H, 3.51; N, 16.27; S, 9.31; found: C, 66.30; H, 3.55; N, 16.33; S, 9.40.

2-Amino-4-(4-bromophenyl)-6-phenylsulphanylpyridine-3,5-dicarbonitrile (4n). IR: 3441, 3336, 3220, 2219, 1629, 1555, 1529, 1459, 1378, 1312, 1257, 1022, 784, 758 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.52–7.60 (*m*, 5H), 7.80–7.82 (*m*, 4H), 7.88 (brs, 2H); Anal. calc. for $C_{19}H_{11}BrN_4S$: C, 56.03; H, 2.72; N, 13.76; S, 7.87; HRMS calc. for $C_{19}H_{11}BrN_4S$: 405.9888, found: 405.9885; found: C, 56.09; H, 2.78; N, 13.69; S, 7.81.

2-Amino-4-(3-tolyl)-6-(4-tolyl)sulphanylpyridine-3,5-dicarbonitrile (4o). IR: 3487, 3324, 3219, 2215, 1631, 1548, 1460, 1377, 1264, 1243, 1016, 801, 716 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.40 (*s*, 3H), 2.44 (*s*, 3H), 6.89 (brs, 2H), 7.25–7.30 (m, 4H), 7.33–7.36 (m, 1H), 7.40–7.45 (m, 3H); HRMS calc. for $C_{21}H_{16}N_4S$: 356.1096; found: 356.1099; Anal. calc. for $C_{21}H_{16}N_4S$: C, 70.76; H, 4.52; N, 15.72; S, 9.00; found: C, 70.80; H, 4.48; N, 15.77; S, 9.05.

2-Amino-4-(4-chlorophenyl)-6-(4-tolyl)sulphanylpyridine-3,5-dicarbonitrile (4p). IR: 3477, 3346, 3222, 2214, 1635, 1574, 1495, 1457, 1377, 1258, 1092, 836, 805, 795 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.37 (*s*, 3H), 7.30 (*d*, J = 8Hz, 2H), 7.48 (d, J = 8Hz, 2H), 7.58–7.68 (*m*, 4H), 7.83 (brs, 2H); HRMS calc. for $C_{20}H_{13}ClN_4S$: 376.0549, found: 376.0546; Anal. calc. for $C_{20}H_{13}ClN_4S$: C, 63.74; H, 3.48; N, 14.87; S, 8.51; found: C, 63.77; H, 3.51; N, 14.81; S, 8.4.

2-Amino-4-phenyl-6-(4-tolyl)sulphanylpyridine-3,5-dicarbonitrile (4q). IR: 3451, 3323, 3208, 2215, 1618, 1547, 1523, 1458, 1377, 1266, 1015, 897, 810, 755 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.37 (*s*, 3H), 7.30 (*d*, J = 8Hz, 2H), 7.47 (*d*, J = 8Hz, 2H), 7.54–7.56 (*m*, 5H), 7.80 (brs, 2H); HRMS calc. for $C_{20}H_{14}N_4S$: 342.0939; found: 342.0949; Anal. calc. for $C_{20}H_{14}N_4S$: C, 70.15; H, 4.12; N, 16.36; S, 9.36; found: C, 70.20; H, 4.08; N, 16.30; S, 9.30.

2-Amino-4-(4-hydroxyphenyl)-6-(2-aminophenyl)sulphanylpyridine-3,5-dicarbonitrile (4u). IR: 3317, 2197, 1638, 1610, 1542, 1508, 1456, 1410, 1247, 1170, 1023, 845, 760 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.50 (brs, 2H), 5.88 (brs, 1H), 6.40–6.46 (*m*, 2H), 6.79–6.86 (*m*, 4H), 7.28–7.31 (*m*, 2H), 7.69 (brs, 2H); HRMS calc. for $C_{19}H_{13}N_5OS$: 359.4056; found: 359.4146; Anal. calc. for $C_{19}H_{13}N_5OS$: C, 63.49; H, 3.65; N, 19.49; S, 8.92; found C, 63.51; H, 3.70; N, 19.41; S, 8.96.

2-Amino-4-(1-naphthyl)-6-(2-aminophenyl)sulphanylpy-ridine-3,5-dicarbonitrile (4v). IR: 3429, 3333, 3219, 2217, 1632, 1611, 1548, 1468, 1310, 1271, 1162, 1022, 996, 797 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.50 (brs, 2H), 6.58 (*t*, 1H), 6.81 (*d*, J = 8 Hz, 1H), 7.20 (*t*, 1H), 7.29 (*d*, J = 8 Hz, 1H), 7.55–7.69 (*m*, 4H), 7.77 (brs, 3H), 8.05–8.13 (*m*, 2H); HRMS calc. for $C_{23}H_{15}N_5S$: 393.4649; found: 393.4556; Anal. calc. for $C_{23}H_{15}N_5S$: C, 70.21; H, 3.84; N, 17.80; S, 8.15; found: C, 70.25; H, 3.88; N, 17.88; S, 8.11.

2-((Furan-2-yl)methylthio)-6-amino-4-phenylpyridine-3,5-dicaronitrile (4w). IR: 3470, 3325, 3215, 2210, 1625, 1540, 1419, 1243, 1150, 1010, 930, 780 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.59 (*s*, 2H), 6.40–6.56 (*m*, 2H), 7.54–7.60 (*m*, 6H), 8.16 (brs, 2H); HRMS calc. for $C_{18}H_{12}N_4OS$: 332.3802; found: 332.3781; Anal. calc. for $C_{18}H_{12}N_4OS$: C, 65.04; H, 3.64; N, 16.86; S, 9.65; found: C, 65.09; H, 3.57; N, 16.90; S, 9.69.

2-((Furan-2-yl)methylthio)-6-amino-4-(4-tolyl)pyridine-3,5-dicaronitrile (4x). IR: 3458, 3331, 3225, 2208, 1634, 1543, 1263, 1007, 769, 732 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.38 (*s*, 3H), 4.58 (*s*, 2H), 6.39–6.54 (*m*, 2H), 7.34–7.59 (*m*, 5H), 8.16 (brs, 2H); HRMS calc. for $C_{19}H_{14}N_4OS$: 346.4068; found: 346.4159; Anal. calc. for $C_{19}H_{14}N_4OS$: C, 65.88; H, 4.07; N, 16.17; S, 9.26; found: C, 65.82; H, 4.17; N, 16.21; S, 9.30.

2-((Furan-2-yl)methylthio)-6-amino-4-(4-bromophenyl)pyridine-3,5-dicaronitrile (4y). IR: 3407, 3337, 3245, 2216., 1629, 1573, 1527, 1487, 1373, 1294, 1133, 1090, 1016, 806, 743 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.11 (*s*, 2H), 7.29–7.33 (*m*, 3H), 7.50–7.65 (*m*, 4H), 7.99 (brs, 2H); HRMS calc. for $C_{18}H_{11}BrN_4OS$: 411.2763; found: 411.2753; Anal. calc. for $C_{18}H_{11}BrN_4OS$: C, 52.57; H, 2.70; N, 13.62; S, 7.80; found: C, 52.61; H, 2.71; N, 13.61; S, 7.89.

2-((Furan-2-yl)methylthio)-6-amino-4-(1-naphthyl)pyridine-3,5-dicaronitrile (4z). IR: 3475, 3328, 3220, 3053, 2993, 2214, 1630, 1547, 1503, 1419, 1269, 1245, 1211, 1155, 1040, 1010, 933, 825, 780, 733, 685 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.64 (*s*, 2H), 6.43–6.61 (*m*, 2H), 7.57–7.63 (*m*, 4H), 8.05–8.10 (*m*, 4H), 8.13 (brs, 2H); HRMS calc. for $C_{22}H_{14}N_4OS$: 382.4389; found: 382.4487; Anal. calc. for $C_{22}H_{14}N_4OS$: C, 69.09; H, 3.69; N, 14.65; S, 8.38; found: C, 69.10; H, 3.73; N, 14.61; S, 8.39.

2-((Furan-2-yl)methylthio)-6-amino-4-(2-naphthyl)pyridine-3,5-dicaronitrile (4aa). IR: 3475, 3328, 3220, 2214, 1630, 1547, 1461, 1419, 1269, 1245, 1211, 1155, 1040, 1010, 933, 860, 780, 733 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.60 (*s*, 2H), 6.40–6.56 (*m*, 2H), 7.61–7.63 (*m*, 4H), 8.00–8.09 (*m*, 4H), 8.12 (brs, 2H); Anal. calc. for $C_{22}H_{14}N_4OS$: C, 69.09; H, 3.69; N, 14.65; S, 8.38; found: C, 69.13; H, 3.79; N, 14.66; S, 8.32.

2-((Furan-2-yl)methylthio)-6-amino-4-(4-methoxyphenyl)-pyridine-3,5-dicaronitrile (4ab). IR: 3469, 3326, 3211, 2218, 1616, 1574, 1542, 1455, 1294, 1255, 1177, 1019, 839, 816, 749 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.83 (*s*, 3H), 4.58 (*s*, 2H), 6.40–6.55 (*m*, 2H), 7.09–7.11 (*m*, 2H), 7.48–7.60 (*m*, 3H), 8.12 (brs, 2H); HRMS calc. for $C_{19}H_{14}N_4O_2S$: 362.4062; found: 362.4162; Anal. calc. for $C_{19}H_{14}N_4O_2S$: C, 62.97; H, 3.89; N, 15.46; S, 8.85; found: C, 62.92; H, 3.93; N, 15.40; S, 8.79.

2-((Furan-2-yl)methylthio)-6-amino-4-(4-chlorophenyl)pyridine-3,5-dicaronitrile (4ac). IR: 3455, 3336, 3229, 2211, 1634, 1573, 1544, 1494, 1264, 1092, 929, 805, 742 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.58 (*s*, 2H), 6.39–6.55 (*m*, 2H), 7.56–7.66 (*m*, 5H), 8.20 (brs, 2H); HRMS calc. for $C_{18}H_{11}ClN_4OS$: 366.8250; found: 366.8151; Anal. calc. for $C_{18}H_{11}ClN_4OS$: C, 58.94; H, 3.02; N, 15.27; S, 8.74; found: C, 58.99; H, 3.03; N, 15.29; S, 8.78.

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Solvent-Free Chemoselective Synthesis of Some Novel Substituted 2-Arylbenzimidazoles Using Amino Acid-Based Prolinium Nitrate Ionic Liquid as Catalyst

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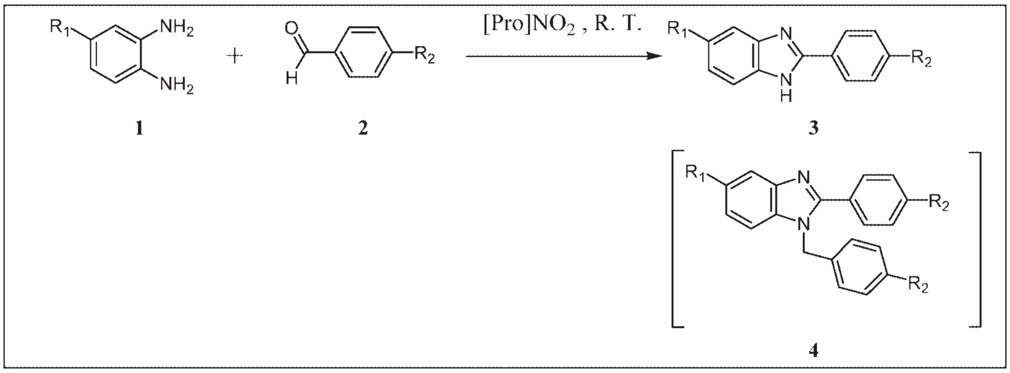

A simple and eco-friendly protocol for the synthesis of substituted 2-arylbenzimidazoles is described. In this process, 2-arylbenzimidazoles were prepared in the presence of a newly introduced ionic liquid prolinium nitrate [Pro]NO$_3$ as catalyst, under solvent-free condition. This process was performed under mild condition without using any oxidant with good to excellent yields and remarkable chemoselectivity in the absence of any byproduct. The ionic liquid can be recovered easily and reused.

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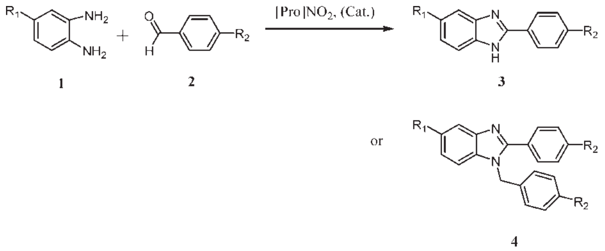
INTRODUCTION

The benzimidazole ring system is an important pharmacophore in medicinal chemistry and modern drug discovery. Benzimidazole derivatives exhibit activities against several viruses such as influenza [1a], human cytomegalovirus [1b], and HIV [1c]. Benzimidazole and its derivatives have also been known to act as topoisomerase inhibitors [2], selective neuropeptide Y Y 1 receptor antagonists [3], potential antitumor [4] and antimicrobial agents [5], and factor Xa inhibitor [6]. The widespread interest in benzimidazole-containing structures has led to extensive studies toward their synthesis. The most important methodology toward synthesis of benzimidazoles is the oxidative cyclo-dehydrogenation of aniline Schiff bases, which are often generated *in situ* from the coupling reaction between *o*-phenylenediamines and aldehydes. Various oxidants have been examined for this two step process which we hereby refer to some of them such as nitrobenzene (high-boiling oxidant/solvent) [7], 1,4-benzoquinone [8] DDQ [9], tetracyanothylene [10], benzofuroxan [11], MnO$_2$ [12], Pb(OAc)$_4$ [13], oxone [14], and NaHSO$_3$ [15]. The availability of a vast number of aldehydes has certainly caused this two-step process to be extensively investigated by chemists. However, most of these procedures produce toxic or environmentally harmful byproducts, which often require laborious work-up to remove them from the reaction mixture, and/or suffer from low yields of isolation product. Molecular oxygen as oxidant has also been used but drawbacks such as prolonged reaction times and high temperature make it less useful [16]. In the case of I$_2$/KI/K$_2$CO$_3$/H$_2$O system, the yields for aldehydes with electron-donating groups were poor [17]. Very recently, iodobenzene diacetate (IBD) as oxidant in dioxane as solvent has led to significant results but the use of dioxane as a toxic solvent is the major limitation for this process from the environmental viewpoint [18]. In another report, application of L-proline in CHCl$_3$ as organocatalyst was presented but this route led to the formation of 1,2-di-substituted benzimidazoles exclusively not the 2-aryl derivatives [19].

The drive to environmentally sustainable, or so-called ‘‘green chemistry,’’ has provided one of the greatest challenges for the chemists of today [20a]. One of the major areas of research in this field is using ionic liquids (ILs) as both solvents and catalysts [20b]. There is only one report regarding formation of these compounds using an imidazolium IL (butylimidazolium tetrafluoroborate, ([Hbim]BF$_4$) as medium. In this process, the yields are good and the reaction times were short, and

Scheme 1



formation of byproducts had a negative effect on the yield [21].

ILs based on amino acids such as proline are one of the most important groups of recently developed ILs referred to as fully green ILs based on natural products. Their importance includes two different aspects. Bio-renewability and economical benefits are the major features of materials of this kind. Moreover, ILs of this type do not show defects such as air- or water-sensitivity of chloroaluminate ILs nor the potential HF releasing of hexafluorophosphate ILs. So, because of these advantages, attempts for the development and introduction of novel ILs based on natural products such as amino acids have been intensively investigated [22]. The main thrust of this work was to provide a new oxidant-free, selective and more sustainable protocol for the synthesis of 2-arylbenzimidazoles.

To the best of our knowledge, benzimidazole derivatives have rarely been synthesized with electron withdrawing substituents such as NO_2 and CO_2H on the fused benzo ring of benzimidazole. So, our other goal was to synthesize such derivatives using 4-nitro-1,2-phenyl-enediamine and 3,4-diaminobenzoic acid as reactant.

RESULTS AND DISCUSSION

During our investigation, at first, we chose *o*-phenylenediamine and 4-chlorobenzaldehyde as model reactants and examined the effect of the amount of prolinium nitrate ([Pro]NO_3) IL as catalyst in the absence of solvent under various temperatures (Scheme 1, Table 1).

Table 1

Prolinium nitrate ([Pro]NO_3) promoted preparation of 2-(4-chlorophenyl)benzimidazole (**3e**) under various conditions.

Entry	Amount of IL (mol %)	Temperature (°C)	Time (min)	Product (%)[a] 3	4
1	20	r.t.	20	89	–
2	20	60	20	89	Trace
4	40	r.t.	25	89	–
5	40	60	25	89	Trace
7	60	r.t.	25	85	Trace
8	60	60	25	70	20
10	100	r.t.	50	85	15
11	100	100	40	80	20

[a] Isolated yield.

To determine the optimum reaction conditions, three moles of phenylenediamines and three moles of 4-chlorobenzaldehyde together with a specified amount of IL were reacted under different temperatures. The results in Table 1 showed some interesting points. First of all, increasing amount of IL did not improve obviously the yield of **3e**. So, the optimum amount of IL was found to be 20% relative to reactants. The second important point which could be elicited evidently from these results is that raising the reaction temperature from r.t. to 60°C did not increase the yield and also did not improve the reaction rates. Moreover, the chemoselectivity decreased and formation of the byproduct **4** was observed in the process. These results indicates that the reaction is better to be carried out at r.t. using 20 mol % amount of IL without solvent to achieve the best results for the preparation of desired product **3** not product **4**.

Then, we continued our study to examine the reusability and recoverability of the catalyst as an additional important factor in the field of ILs. To achieve this, the model reaction of *o*-phenylenediamine (4 mmol) with 4-chlorobenzaldehyde (4 mmol) was carried out in the presence of IL (0.8 mmol). After completion of the reaction, the IL could be recovered as specified in Experimental section. The results of which are given in Table 2. These results showed a good recoverability and reusability for the synthesis of product **3e**. It can clearly be seen that even after four runs, the recovery percentage is high. However, the yield decreased significantly after four runs (Table 2, Run No. 4).

The decrease in the yields of the reaction after each use of IL could possibly be due to the fact that we could not manage to recover the catalyst quantitatively after each run. Consequently, we repeated the reaction with lower amounts of catalyst. To test this idea, we repeated the reaction by adding some fresh catalyst to the IL recovered after the first use and the result was the same as the first run (Table 2, No. 1). Moreover, we observed a slight change in appearance for the recovered IL,

Table 2

Results for reusability of IL [Pro]NO_3 in the process of 2-(4-chlorophenyl)benzimidazole (3e) synthesis.

Run no.	Recovery percent	Reaction time (min)	Yield (%)[a]
1	95	30	89
2	90	40	82
3	90	55	78
4	90	60	70

[a] Isolated yield.

which would be due to trace impurities from the reaction. These changes in appearance were observed more obviously after any recovery.

To evaluate the scope and limitations of this IL under solvent-free condition various benzaldehyde derivatives and different derivatives of *o*-phenylenediamines were examined (Table 3, entries 1–17). Among the various benzaldehydes tested, the best yields were achieved for benzaldehydes with electron-withdrawing substituents (Table 3, entries 4–7). While among *o*-phenylenediamine derivatives the yield of products obtained from 4-nitro-*o*-phenylenediamine were high and the rates of reactions were also remarkable (Table 3, entries 8–12). In all reactions, byproduct **4** was not observed by TLC. Only in the case of 4-methylbenzaldehyde as reactant (Table 3, entry 11), the reaction rate was relatively long and the yield was moderate not high. Repeating the reaction with 3,4-diaminobenzoic acid showed the best yield and reactivity for 4-nitrobenzaldehyde (Table 3, entry 17) and the other derivatives were also synthesized with interesting yield. These results demonstrate a great level of versatility and efficiency for the synthesis of 2-arylbenzimidazole derivatives.

To complete evaluation of chemoselectivity, our attempts were focused on performing the reaction with a new variation. At this stage, we carried out the model reaction of *o*-phenylenediamine derivatives (1 mmol) with 4-chlorobenzaldehyde (2 mmol) under optimal conditions (r.t. and 20% of IL relative to *o*-phenylenediamine derivatives). Surprisingly, even after 3 h, no byproduct **4** (**4e**, **4i**, and/or **4n**) were formed and TLC analysis showed only the presence of products **3** (**3e**, **3i**, and/or **3n**) with the excess amount of benzaldehydes used.

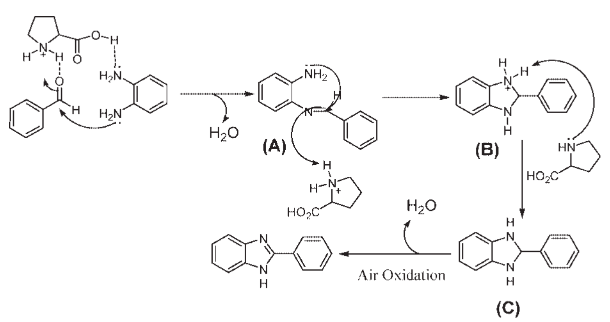
Table 3

Synthesis of 2-phenylbenzimidazole derivatives using amino acid based IL [pro]NO_3.

Entry	R_1	R_2	Time (min)	Product	Yield (%)[a]
1	H	H	50	3a	85
2	H	Me	45	3b	82
3	H	Ome	45	3c	85
4	H	Br	30	3d	93
5	H	Cl	30	3e	89
6	H	F	20	3f	81
7	H	NO_2	25	3g	90
8	NO_2	Br	60	3h	92
9	NO_2	Cl	50	3i	93
10	NO_2	CN	45	3j	95
11	NO_2	Me	80	3k	76
12	NO_2	NO_2	25	3l	85
13	CO_2H	Br	45	3m	86
14	CO_2H	Cl	45	3n	90
15	CO_2H	CN	30	3o	88
16	CO_2H	Me	60	3p	80
17	CO_2H	NO_2	20	3q	92

[a] Isolated yield.

Scheme 2



According to these findings, a proposed reaction pathway for the synthesis of 2-arylbenzimidazoles is shown in Scheme 2. As can be seen, prolinium cation from IL first interacts with both reactants to form the Schiff base intermediate (A) which then undergoes cyclization *via* intramolecular attack by another amino moiety on Schiff base to form protonated benzimidazoline intermediate (B). Then, this intermediate would be deprotonated to 2,3-dihydrobenzimidazoline (C). Finally, the intermediate (C) would be aromatized by air oxidation under reaction vessel conditions.

In summary, we have developed an efficient, eco-friendly as well as solvent and oxidant-free protocol for the synthesis of 2-arylbenzimidazole derivatives starting from phenylenediamine derivatives and diverse benzaldehydes using fully "green" IL L-prolinium nitrate as catalyst. The yields of products are very good to excellent and use of toxic solvents is avoided. Synthesis of some novel 2-arylbenzimidazole derivatives under mild conditions is the most important aspect of this study. Simple work-up and high degree of IL reusability are other interesting points of the developed procedure.

EXPERIMENTAL

Melting points were recorded on a Buchi B-540 apparatus. IR spectra were recorded on an ABB Bomem Model FTLA200-100 instrument. ^1H and ^{13}C NMR spectra were measured with a Bruker DRX-300 Avance spectrometer at 300 and 75 MHz using TMS as an internal standard. Chemical shifts (δ) are reported relative to TMS, and coupling constants (J) are reported in Hertz (Hz). Mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer with 70 eV ionization potential. Elemental analyses of new compounds were performed with a Vario EL III 0 Serial No. 11024054 instrument.

Typical experimental procedure for the preparation of substituted 2-arylbenzimidazoles using [Pro]NO_3 as catalyst. To a mixture of 4-chlorobenzaldehyde (3 mmol) and *o*-phenylenediamine (3 mmol) was added prolinium nitrate (prepared according to literature [22]) (0.6 mmol, 20% relative to reactants). The reaction mixture was stirred at 30°C and monitored by TLC (ethyl acetate:petroleum ether, 1:4). After completion of the reaction, water (10 mL) was added and the mixture was scratched and stirred for at least 30 min. The aqueous layer was filtered and the residues were purified by crystallization from EtOH:Water mixture. The product **3e** was obtained with 89% yield.

Aqueous layer containing IL was concentrated *in vacuo* to recycle and reuse the prolinium nitrate in another reaction.

Spectral and analytical data for substituted 2-arylbenzimidazoles.

2-Phenylbenzimidazole (3a). Light yellow solid; mp 283–285°C (Lit. [19] mp 289–291°C). IR (KBr): 1621 (C=N), 3447 cm^{-1} (NH). ^1H NMR (300 MHz, DMSO-d_6): δ 13.31 (s, 1H), 8.27 (d, 2H, J = 3.0), 7.69 (m, 2H), 7.59 (s, 3H), 7.34 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 114.65, 123.62, 127.13, 127.35, 129.20, 131.23, 136.34, 150.16.

2-(4-Methylphenyl)benzimidazole (3b). Light yellow solid; mp 268–270°C (Lit. [24] mp 277°C). IR (KBr): 1617 (C=N), 3060, 3435 (NH) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 12.87 (s, 1H), 8.10 (d, 2H, J = 8.1 Hz), 7.61 (m, 2H), 7.33 (d, 2H, J = 8.1 Hz), 7.19 (m, 2H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.96, 111.21, 118.72, 121.59, 126.42, 127.50, 129.52, 139.56, 151.45.

2-(4-Methoxyphenyl)benzimidazole (3c). Light yellow solid; mp 217–220°C (Lit. [19] mp 224–226°C). IR (KBr): 1612 (C=N), 3420 cm^{-1} (NH). ^1H NMR (300 MHz, DMSO-d_6): δ 12.73 (s, 1H), 8.11 (d, 2H, J = 9.0 Hz), 7.54 (s, 2H), 7.16 (m, 2H), 7.11 (d, 2H, J = 9.0 Hz), 3.82 (s, 3H).

2-(4-Bromophenyl)benzimidazole (3d). Light yellow solid; mp 294–296°C (Lit. [19] mp 299–300°C). IR (KBr): 1597 (C=N), 3420 cm^{-1} (NH). ^1H NMR (300 MHz, DMSO-d_6): δ 12.99 (s, 1H), 8.12 (d, 2H, J = 9.0 Hz), 7.75 (d, 2H, J = 9.0 Hz), 7.65 (m, 1H), 7.53 (m, 1H), 7.21 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 111.43, 118.98, 121.86, 123.26, 128.35, 129.39, 131.98, 150.22.

2-(4-Chlorophenyl)benzimidazole (3e). Light yellow solid; mp 283–286°C (Lit. [19] mp 292–294°C). IR (KBr): 1597 (C=N), 3420 cm^{-1} (NH). ^1H NMR (300 MHz, DMSO-d_6): δ 12.98 (s, 1H), 8.18 (d, 2H, J = 9.0 Hz), 7.62 (d, 3H, J = 9.0 Hz), 7.52 (d, 1H, J = 6.0 Hz), 7.21 (m, 2H).

2-(4-Fluorophenyl)benzimidazole (3f). Light yellow solid; mp 242–245°C (Lit. [19] mp 250–251°C). IR (KBr): 1602 (C=N), 3405 cm^{-1} (NH). ^1H NMR (300 MHz, DMSO-d_6): δ 12.92 (s, 1H), 8.22 (m, 2H), 7.58 (m, 2H), 7.39 (t, 2H, J = 6.0 Hz), 7.19 (d, 2H, J = 6.0 Hz).

2-(4-Nitrophenyl)benzimidazole (3g). Light red solid; mp 307–309°C (Lit. [19] mp 316°C). IR (KBr): 1606 (C=N), 3409 cm^{-1} (NH). ^1H NMR (300 MHz, DMSO-d_6): δ 13.28 (s, 1H), 8.40 (m, 4H), 7.65 (m, 2H), 7.26 (m, 2H).

2-(4-Bromophenyl)-5-nitrobenzimidazole (Mixture of tautomeric 3h and 4h). Yellow solid; mp 161–164°C. IR (KBr): 1608 (C=N), 3481 cm^{-1} (NH). ^1H NMR (300 MHz, DMSO-d_6): δ 13.64 (s, 1H), 8.11 (d, 1H, J = 8.4 Hz), 8.01 (d, 3H, J = 9 Hz), 7.91 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.4 Hz), 7.78 (d, 1H, J = 8.4 Hz), 7.70 (d, 3H, J = 9 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 108.05, 112.88, 113.13, 115.60, 124.55, 125.20, 128.24, 128.87, 131.00, 131.71, 132.20, 133.47, 133.96, 135.26, 135.90, 142.81, 143.36, 151.18, 158.54. MS (EI): *m*/*e* = 318 (M^+), 272, 162, 116. *Anal.* Calcd. For $C_{13}H_8BrN_3O_2$: C, 49.06; H, 2.52; N, 13.21. Found: C, 48.89; H, 3.0; N, 13.23.

2-(4-Chlorophenyl)-5-nitrobenzimidazole (3i). Yellow solid; mp 277–281°C. IR (KBr): 1601 (C=N), 3281 cm^{-1}(NH). ^1H NMR (300 MHz, DMSO-d_6): δ 13.60 (s, 1H), 8.41 (s, 1H), 8.16 (d, 2H, J = 7.5 Hz), 8.08 (d, 1H, J = 8.4 Hz), 7.71 (d, 1H, J = 8.4 Hz), 7.62 (d, 2H, J = 7.5 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 118.08, 120.60, 122.3, 123.64, 127.85, 128.63, 129.23, 135.66, 136.59, 142.75, 154.62. Ms (EI): *m*/*e* = 273 (M^+), 227, 192, 111. *Anal.* Calcd. for $C_{13}H_8ClN_3O_2$: C, 57.05; H, 2.95; N, 15.35. Found: C, 57.44; H, 2.61; N, 15.62.

2-(4-Cyanophenyl)-5-nitrobenzimidazole (Mixture of tautomeric 3j and 4j). Yellow solid; mp 190–193°C. IR (KBr): 1602 (C=N), 2228 (C≡N), 3363 cm^{-1} (NH). ^1H NMR (300 MHz, DMSO-d_6): δ 13.73 (s, 1H), 8.88 (s, 1H), 8.41–7.73 (m, 12H), 6.88 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 112.88, 113.20, 118.39, 118.66, 124.93, 127.46, 129.60, 132.52, 132.73, 133.00, 135.85, 139.96, 142.98, 151.43, 153.73, 157.75. MS (EI): *m*/*e* = 264 (M^+), 218, 192, 162, 118. *Anal.* Calcd. for $C_{14}H_8N_4O_2$: C, 63.64; H, 3.05; N, 21.20. Found: C, 63.98; H, 2.77; N, 20.88.

2-(4-Methylphenyl)-5-nitrobenzimidazole (3k). Yellow solid; mp 211–214°C. IR (KBr): 1637 (C=N), 3435 cm^{-1}(NH). ^1H NMR (300 MHz, DMSO-d_6): δ 13.53 (s, 1H), 7.39 (d, 2H, J = 9.0 Hz), 6.54 (d, 1H, J = 12.0 Hz), 6.04 (s, 2H), 5.06 (s, 2H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.08, 108.03, 111.44, 115.61, 126.98, 129.78, 133.96, 136.79, 143.36, 153.14. MS (EI): *m*/*e* = 253 (M^+), 153, 107, 80. *Anal.* Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.39; H, 4.38; N, 16.59. Found: C, 66.28; H, 4.09; N, 16.34.

2-(4-Nitrophenyl)-5-nitrophenylbenzimidazole (Mixture of tautomeric 3l and 4l). Red solid; mp 222–224°C. IR (KBr): 1612 (C=N), 3101, 3388, 3486 (NH) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 8.98 (s, 2H), 8.32 (s, 4H), 8.11 (s, 1H), 7.94 (d, 1H, J = 9 Hz), 6.91 (s, 2H), 6.78 (d, 1H, J = 9 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 113.26, 113.39, 122.27, 123.63, 123.77, 125.09, 130.11, 132.72, 135.88, 136.49, 141.69, 148.77, 151.51, 157.41. MS (EI): *m*/*e* = 284 (M^+), 238, 192, 164, 118. *Anal.* Calcd for $C_{13}H_8N_4O_4$: C, 51.41; H, 3.77; N 18.59. Found: C, 51.88; H, 4.13; N, 18.20.

2-(4-Bromophenyl)benzimidazole-5-carboxylic acid (3m). Pale yellow solid; mp 183–185°C. IR (KBr): 1635 (C=N), 1678 (C=O), 3091, 3379 (NH) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 13.49 (s, 1H), 12.74 (s, 1H), 8.14 (m, 3H), 7.80 (m, 3H), 7.65 (m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 123.88, 124.79, 128.64, 128.82, 132.09, 151.95, 167.76. MS (EI): *m*/*e* = 316 (M^+ − 1), 273, 271, 191. *Anal.* Calcd. for $C_{14}H_9BrN_2O_2$: C. 53.02; H, 2.86; N, 8.83. Found: C. 53.11; H, 2.54; N, 8.75.

2-(4-Chlorophenyl)benzimidazole-5-carboxylic acid (3n). Pale yellow solid; mp 168–169°C. IR (KBr): 1622 (C=N), 1683 (C=O), 3101, 3414 (NH) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 13.29 (s, 1H), 12.76 (s, 1H), 8.20 (d, J = 9 Hz, 3H), 7.84 (m, 1H), 7.64 (d, J = 9 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 123.67, 124.55, 128.45, 128.51, 129.20, 135.10, 147.1, 154.32, 156.63, 167.80. MS (EI): *m*/*e* = 272 (M^+), 227, 192. *Anal.* Calcd. for $C_{14}H_8ClN_2O_2$: C, 61.89; H, 2.97; N, 10.31. Found: C, 62.14; H, 2.69; N, 10.12.

2-(4-Cyanophenyl)benzimidazole-5-carboxylic acid (Mixture of tautomeric 3o and 4o). Pale yellow solid; mp 183–185°C. IR (KBr): 1606 (C=N), 2228 (C≡N), 3368 cm^{-1} (NH). ^1H NMR (300 MHz, DMSO-d_6): δ 13.48 (s, 1H), 13.05 (s, 1H), 8.14 (m, 3H), 7.82 (m, 3H), 7.67 (m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 112.43, 112.80, 113.72, 117.28, 118.54, 118.76, 125.23, 127.32, 129.33, 130.21, 132.57, 133.06 (2 × C), 133.72, 140.44, 148.96, 151.68, 155.43, 167.51, 167.71. MS (EI): *m/e* = 263 (M^+), 246, 218, 116. *Anal.* Calcd. for $C_{15}H_9N_3O_2$: C, 64.76; H, 3.64; N, 15.11. Found: C, 64.27; H, 3.94; N, 14.66.

2-(4-Methylphenyl)benzimidazole-5-carboxylic acid (mixture of tautomeric 3p and 4p). Pale yellow solid; mp 200–205°C. IR (KBr): 1628 (C=N), 1689 (C=O), 3369 (NH), 3426 (OH) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 12.70 (s, 1H), 8.16 (s, 1H), 8.08 (d, 2H, J = 6.0 Hz), 7.82 (d, 1H, J = 6.0 Hz), 7.63 (d, 1H, J = 6.0 Hz), 7.36 (d, 2H, J = 6.0 Hz), 2.49 (s, 2H), 2.37 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 18.56, 21.01, 123.47, 124.46, 126.69, 126.86, 129.82, 140.27, 153.70, 167.87. MS (EI): *m/e* = 252 (M^+), 237, 207. *Anal.* Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.35; H, 4.61; N, 10.98.

2-(4-Nitrophenyl)benzimidazole-5-carboxylic acid (mixture of tautomeric 3q and 4q). Pale red solid; mp 270–272°C. IR (KBr): 1602 (C=N), 1671(C=O), 3394 (NH), 3501(OH) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 13.62 (s, 1H), 12.50 (s, 1H), 8.92 (s, 1H), 8.44 (m, 3H), 8.32 (s, 4H), 8.24 (s, 0.5H), 8.14 (m, 0.8H), 7.88 (m, 0.5H), 7.72 (s, 0.7H), 7.61 (d, 1H, J = 6.0 Hz), 6.75 (d, 1H, J = 6.0 Hz).^{13}C NMR (75 MHz, DMSO-d_6): δ 113.80, 117.32, 118.54, 123.80 (2 × C), 124.37, 127.82, 129.75, 130.36, 130.66, 133.01, 142.18, 148.18, 148.54, 149.05, 154.96, 167.49, 167.69. MS (EI): *m/e* = 283 (M^+), 238, 192. *Anal.* Calcd. for $C_{14}H_9N_3O_4$: C, 56.43; H, 3.28; N, 13.79. Found: C, 56.07; H, 3.67; N, 13.41.

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Synthetic Strategy Toward 1,9-Functionalized Pyrido[2,3-*d*:6,5-*d*′]dipyrimidine-2,4,6,8-tetrones

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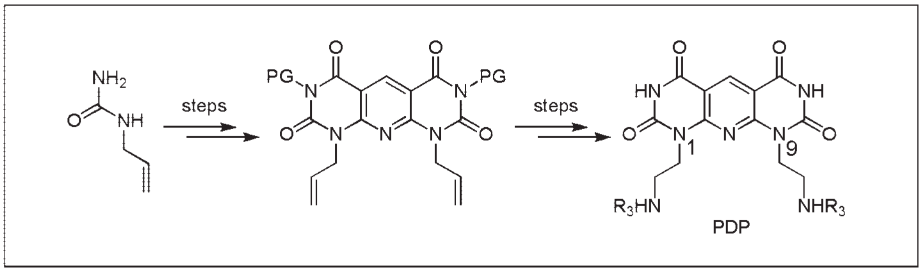

A synthetic approach involving a solubilizing protecting group strategy is described to generate pyrido[2,3-*d*:6,5-*d*′]dipyrimidine-2,4,6,8-tetrones functionalized at positions 1 and 9 with alkylamine substitutents.

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INTRODUCTION

Pyrido[2,3-*d*:6,5-*d*′]dipyrimidine-2,4,6,8-tetrones (PDP) **4** illustrated in Scheme 1 are an interesting class of biannulated pyridine compounds. Derivatives of **4** have been shown to exhibit antibacterial and antiviral properties [1] as well as NAD-type redox catalytic activity [2]. Solid-state ribbons have also been described from the self-assembly of an amine derivative of **4**, which demonstrates the potential of these heterocyclic compounds in supramolecular synthesis applications [3].

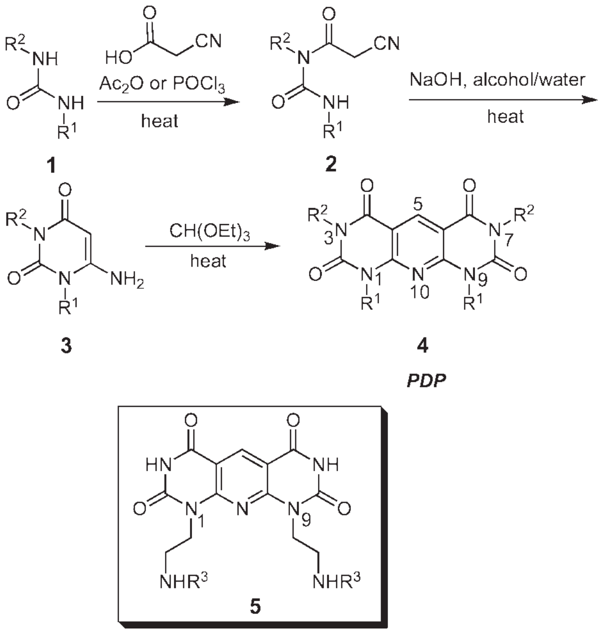
A typical synthetic scheme for these nitrogen-containing tricycles **4** is shown in Scheme 1 and begins with an often low-yielding condensation reaction of functionalized urea **1** with cyanoacetic acid under thermal conditions, followed by a base induced cyclization of **2** to generate 6-amino-uracil **3** [4]. A second condensation reaction between **3** and an electrophile such as triethyl orthoformate [3] (or an aromatic aldehyde [5a], or dimethyl sulfoxide [5b]), generates the target compound **4** (Scheme 1).

As part of our research program on the hierarchical self-assembly of a DNA-based G^C hybrid molecule into rosette nanotubes in aqueous media [6], we required PDP substrates **5** shown in Scheme 1, which were selectively functionalized at positions 1 and 9 with a variety of NHR^3 substituents such as L-Lysine. Given the harsh conditions required to construct the intermediate 6-aminouracil **3** and **4** (Scheme 1), we reasoned that it would be best to introduce these amine substituents (some of which would be incompatible with the acidic/basic conditions) after the PDP core **4** was constructed. A convergent strategy was therefore proposed as shown in Scheme 2, whereby the desired PDPs **5** would be derived from a common intermediate aldehyde **6** *via* a reductive amination reaction with the requisite amines. Aldehyde **6** would originate from an oxidative cleavage of di-alkene **7**, which in turn would be prepared from urea **8** containing a robust allyl group. Herein we describe the synthesis of **5** in detail, which required overcoming some challenging solubility constraints.

RESULTS AND DISCUSSION

The synthesis of **5** commenced according to Scheme 3, by treating commercially available *N*-allyl urea (**8**) with cyanoacetic acid and acetic anhydride at 85°C to provide the condensed adduct **9**. Cyclization of **9** in the presence of 10% sodium hydroxide in a 2:1 mixture of water and ethanol at 85°C generated uracil **10** with a moderate 57% yield [4c]. Finally, treatment of **10** with triethyl orthoformate in acetic acid under refluxing conditions for 2 h provided the desired allyl functionalized PDP adduct **7** in 80% yield [3]. Unfortunately, this adduct was found to be insoluble in many common organic solvents such as dichloromethane, ether, tetrahydrofuran, acetone, and methanol and could only be maintained in solution using dimethyl sulfoxide, refluxing *N*,*N*-dimethylformamide (DMF), or pyridine. This restricted our solvent choices for the subsequent two-step dihydroxylation/sodium periodate oxidative

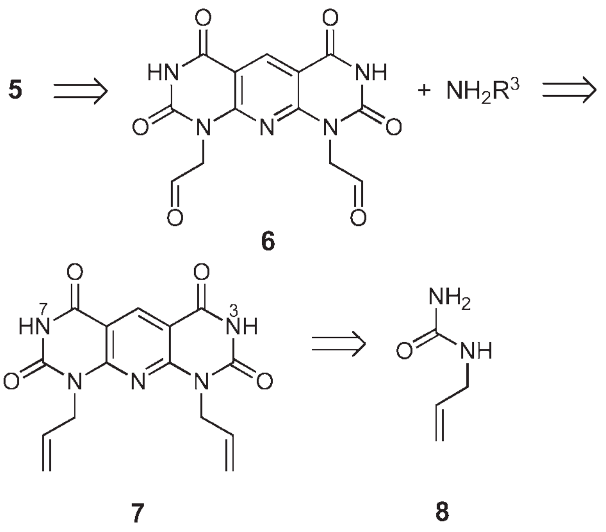
Scheme 1



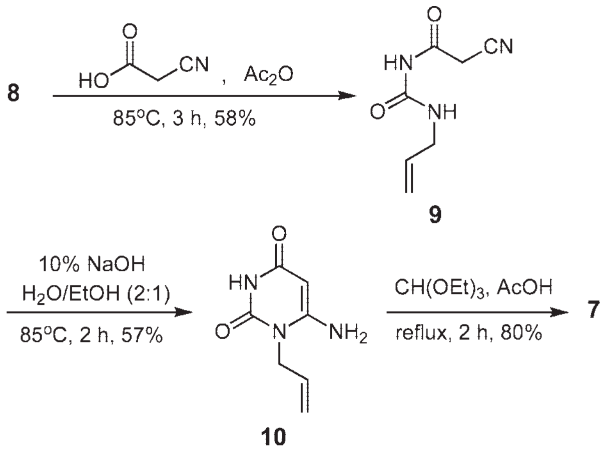
cleavage reaction for the preparation of **6**. Diol formation was therefore attempted using catalytic osmium tetroxide and an excess of 4-methyl-morpholine *N*-oxide (NMO) co-oxidant in a mixture of dimethyl sulfoxide and water, but only starting material was recovered.

To confer the required solubility to the PDP core **7**, various protecting groups (PGs) were installed on the nitrogen atoms at positions 3 and 7. The benzoyl (Bz) group was initially chosen and although it did afford the required solubility to conduct the oxidative cleavage reaction as illustrated in Scheme 4, the following reductive amination step of aldehyde **12** with protected lysine in the presence of sodium triacetoxyborohydride and *N*,*N*-diisopropylethylamine was very low yielding (5%). This was attributed to the removal of the Bz group(s) on **12** under the basic conditions, which caused the resulting material to precipitate out of the solution prior to undergoing the coupling reaction.

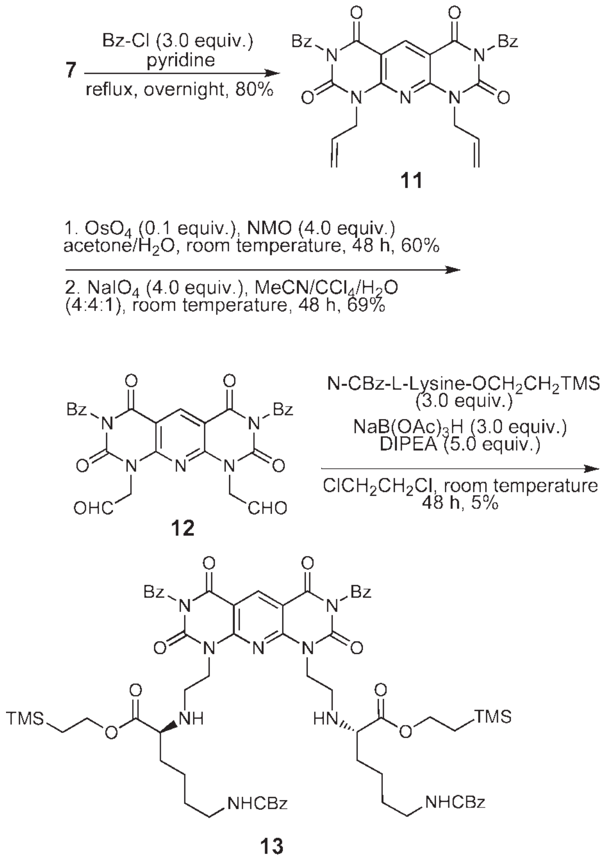
Scheme 2



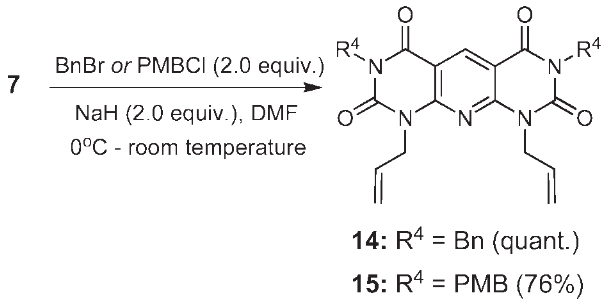
Scheme 3



Scheme 4



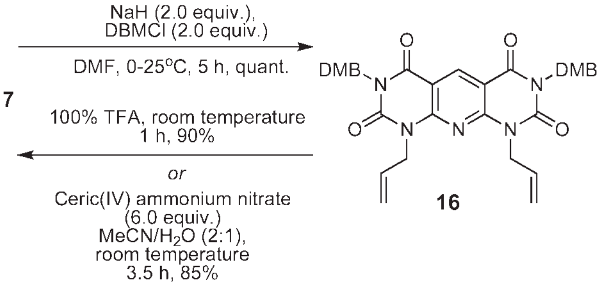
Scheme 5



Base-stable benzyl (Bn) and *p*-methoxy benzyl (PMB) PGs were subsequently installed on the PDP core **7** under standard conditions (Scheme 5). To ensure that these groups could also be easily removed, the deprotection of **14** and **15** was attempted under radical (2,3-dichloro-5,6-dicyano-*p*-benzoquinone, wet dichloromethane, room temperature, 1 day), acidic (98% trifluoroacetic acid (TFA), 2 days) and hydrogenation (H_2/Pd(C), acetic acid, 20 psi) conditions. Surprisingly, only starting material was recovered in all cases, except for the latter, in which the allyl group was reduced. Only in the presence of ceric (IV) ammonium nitrate in a 2:1 mixture of acetonitrile-water at room temperature for 14 h was the desired deprotected product **7** isolated, although in a mere 50% and 68% yield from **14** and **15**, respectively.

As a result of these unsatisfactory deprotection yields and limited conditions in which to remove the PMB/Bn groups, a fourth *N*-PG, DMB (di-(4-methoxyphenyl)-methyl) was also examined. Although it is less common than other *N*-PGs [7], examples of its applications can be found in amino acid [8a], allylic amine [8b], β-lactam [8c], and urethane/uridine [8d] synthesis to name a few. Gratifyingly, installation of DMB on compound **7** proceeded smoothly in the presence of sodium hydride and di-(4-methoxyphenyl)methyl chloride [9] in *N,N*-DMF to afford the bis-protected product **16** in quantitative yield (Scheme 6). Solubility tests also confirmed that **16** was soluble in a range of solvents such as acetone, dichloromethane, dimethylsulfoxide, *N,N*-DMF and ether with heating. Furthermore, the DMB group was easily removed under both acidic (100% TFA, room temperature, 1 h) and oxidative conditions (ceric (IV) ammonium nitrate, acetonitrile:water (2:1), room temperature, 3.5 h) in excellent yields of 90% and 85%, respectively (Scheme 6).

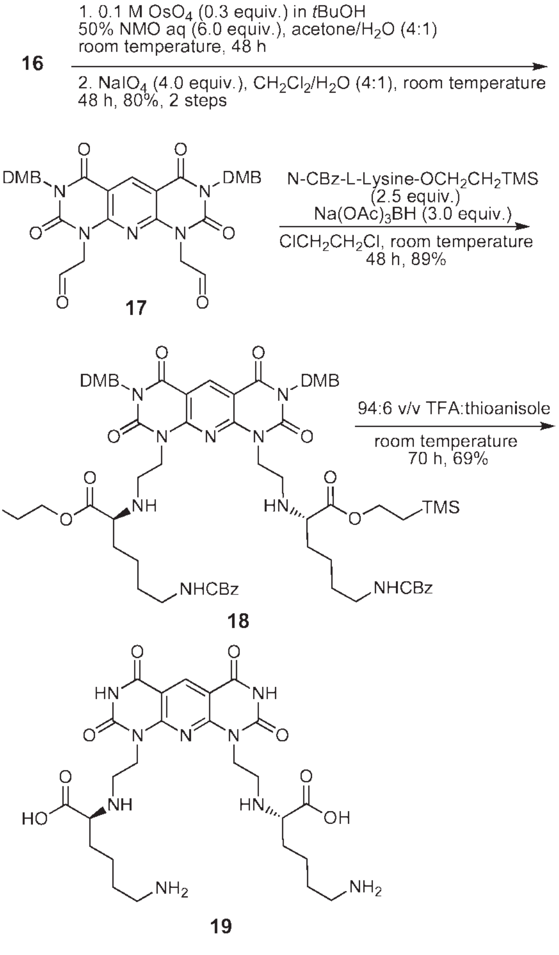
Scheme 6



With this PG strategy in hand, the synthesis was continued from compound **16**. Oxidative cleavage in the presence of catalytic osmium tetroxide and NMO followed by treatment with sodium periodate provided aldehyde **17** in 80% yield for the two steps. Double reductive amination of **17** with L-Lysine furnished the coupled adduct **18** in 89% yield. Finally, treatment of **18** with a 94:6 *v*/*v* TFA:thioanisole solution ensured complete removal of all six PGs (*i.e.*, benzyloxycarbonyl (Cbz), trimethylsilyl (TMS) and DMB) and the desired water-soluble PDP adduct **19** was obtained in 69% yield (~94% yield per PG).

In conclusion, a convergent synthetic strategy has been developed to access PDP substrates functionalized at positions 1 and 9 with amines such as L-lysine (*i.e.*,

Scheme 7



19) from the common intermediate aldehyde **17**. Central to this strategy is the protection of the nitrogen atoms at positions 3 and 7 on compound **7** with the base-stable DMB group. This PG provides the necessary solubility to the parent compound for the alkene cleavage and double reductive amination reactions and yet is sufficiently labile on the PDP core under both oxidative and acidic conditions for its eventual removal (Scheme 7).

EXPERIMENTAL

General. All commercial reagents and solvents were used without further purification except for dichloroethane which was purified on an MBraun solvent purification system. Reactions were monitored by TLC analysis using silica-coated TLC plates (Merck F 60254) and visualized under UV light. Flash chromatography was carried out using Merck 60 (0.040–0.063 mm) or Merck 60 (0.063–0.2 mm) silica. ^{1}H and ^{13}C NMR spectra were recorded on Varian Inova NMR spectrometers (300, 400, 500, or 600 MHz) with the solvent as the internal reference. The NMR data is presented as follows: chemical shift, multiplicity, coupling constant, integration. The mass spectra were performed at the Mass Spectrometry Laboratory at the Department of Chemistry, University of Alberta, or at the Analytical Laboratory of The National Institute for Nanotechnology, University of Alberta.

N-(Allylcarbamoyl)-2-cyanoacetamide (9). A mixture of allylurea (104.8 g, 1.046 mol), cyanoacetic acid (89.03 g, 1.046 mol) and acetic anhydride (197.4 mL, 2.092 mol) was heated for 3 h at 85°C. On cooling to room temperature, ether (530 mL) was added and the mixture was placed in an ice-bath for 2 h. The resulting solid was isolated, washed with ether and dried on the high vacuum to yield **9** as a white powder ($C_7H_9N_3O_2$, 98 g, 58%). $R_f = 0.6$ (SiO_2, 75% ethyl acetate/hexane); mp 140.1–141.9°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 10.56 (brs, 1H), 8.03 (brs, 1H), 5.83 (ddt, J = 17.1, 10.2, 5.1 Hz, 1H), 5.16–5.05 (m, 2H), 3.90 (s, 2H), 3.78 (ddd, J = 5.1, 2.4, 1.5 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 165.0, 152.2, 134.9, 115.2, 115.0, 41.3, 26.7; MS: *m/z* 168.40 (M$^+$ + 1). *Anal.* Calcd. for $C_7H_9N_3O_2$: C, 50.29; H, 5.43; N, 25.14. Found: C, 49.90, H, 5.35, N, 24.83.

1-Allyl-6-aminopyrimidine-2,4(1H,3H)-dione (10). A mixture of **9** (91 g, 0.54 mol) in water (248 mL) and ethanol (124 mL) was warmed to 85°C and slowly treated with 10% aqueous sodium hydroxide until a pH of 10 was obtained and the starting material was fully dissolved. After 10 min, the desired product **10** began to precipitate out of solution. The reaction mixture was stirred for an additional 2 h at 85°C and then treated with 1 *N* hydrochloric acid until the solution was slightly acidic. On cooling to room temperature, the resulting solid was isolated and dried on the high vaccum to furnish **10** as a white powder ($C_7H_9N_3O_2$, 51.5 g, 57%). $R_f = 0.6$ (SiO_2, 20% methanol/dichloromethane); mp 271.2–273.1°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.38 (s, 1H), 6.71 (s, 2H), 5.79 (ddt, J = 17.2, 10.2, 4.5 Hz, 1H), 5.12–5.03 (m, 2H), 4.55 (s, 1H), 4.39–4.38 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 162.5, 155.7, 151.0, 132.4, 115.7, 75.2, 42.5; HRMS: *m/z* 167.0699 (M$^+$). *Anal.* Calcd. for $C_7H_9N_3O_2$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.40, H, 5.39, N, 25.15.

1,9-Diallylpyrido[2,3-d:6,5-d′]dipyrimidine-2,4,6,8 (1H, 3H,-7H,9H)-tetrone (7). A mixture of **10** (51.5 g, 0.308 mol), triethyl orthoformate (118 mL, 0.709 mol) and glacial acetic acid (1.2 L, 21 mol) was heated to reflux for 2 h. After cooling to room temperature, the precipitate was washed with glacial acetic acid, isolated by filtration and dried under high vacuum to provide **7** as a white solid ($C_{15}H_{13}N_5O_4$, 41.2 g, 80%). mp = 351.6–353.2°C (decomposes); ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 11.87 (s, 2H), 8.58 (s, 1H), 5.95–5.87 (m, 2H), 5.19–5.12 (m, 4H), 4.72–4.71 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 160.1, 154.0, 150.1, 137.6, 132.3, 116.9, 106.7, 43.8; HRMS: *m/z* 327.0971 (M$^+$). *Anal.* Calcd. for $C_{15}H_{13}N_5O_4$: C, 55.05; H, 4.00; N, 21.40. Found: C, 55.11, H, 4.03, N, 21.53.

1,9-Diallyl-3,7-(bis(4-methoxyphenyl)methyl)pyrido[2,3-d:6,5-d′] dipyrimidine-2,4,6,8(1H,3H,7H,9H)-tetrone (16). Compound **7** (1.3 g, 3.8 mmol) was slowly added to a mixture of NaH (183 mg, 7.63 mmol) in *N,N*-DMF (26 mL) at 0°C. After stirring for 1 h, di-(4-methoxyphenyl)methyl chloride (2.0 g, 7.6 mmol) was added and the reaction was slowly warmed to room temperature and stirred for 5 h. After re-cooling to 0°C, saturated aqueous ammonium chloride (50 mL) was added and the product was extracted with dichloromethane (3×). The combined organic phases were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to provide **16** as a white foam ($C_{45}H_{41}N_5O_8$, 3.09 g, quantitative yield). $R_f = 0.8$ (50% ethyl acetate/hexane). ^{1}H NMR (600 MHz, CD_2Cl_2) δ (ppm): 9.06 (s, 1H), 7.36 (s, 2H), 7.33–7.30 (m, 8H), 6.87–6.86 (m, 8H), 5.95 (ddt, J = 22, 10.8, 5.4 Hz, 2H), 5.24–5.20 (m, 4H), 4.88 (d, J = 5.5 Hz, 4H), 3.80 (s, 12H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ (ppm): 160.2, 159.3, 153.7, 150.6, 141.9, 132.0, 130.7, 130.3, 118.0, 113.7, 107.3, 59.9, 55.6, 45.7; MS: *m/z* 752.6 ((M$^+$ + 1)-C_2H_3). *Anal.* Calcd. for $C_{45}H_{41}N_5O_8$: C, 69.31; H, 5.30; N, 8.98. Found: C, 69.68, H, 5.53, N, 8.74.

1,9-Diacetaldehyde-3,7-(bis(4-methoxyphenyl)methyl)pyrido [2,3-d:6,5-d′]dipyrimidine-2,4,6,8(1H,3H,7H,9H)-tetrone (17). A solution of **16** (1 g, 1.3 mmol) in acetone/water (4:1, 50 mL) was treated with 50% aqueous *N*-methylmorpholine *N*-oxide (1.9 mL, 7.8 mmol) at room temperature. After stirring for 5 min, OsO_4 (4 mL, 0.1*M* solution in *t*-BuOH, 0.4 mmol) was added over a period of 5 min and the resulting solution was stirred at room temperature for 48 h. Sodium sulfite ($\sim$500 mg) was then added to quench the reaction and stirring was continued for an additional 1 h. The solvent was subsequently removed under reduced pressure, water was added and the product was extracted with dichloromethane (3×). The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to provide 1.1 g of crude tetrol. $R_f = 0.3$ (5% methanol/dichloromethane). A solution of the tetrol (1.1 g, 1.3 mmol) and sodium periodate (1.11 g, 5.2 mmol) in dichloromethane:water (4:1, 200 mL) was stirred at room temperature for 48 h. The organic layer was then separated, washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated. Purification by flash chromatography on silica gel (0–2% methanol in dichloromethane) provided the desired product which was subsequently re-dissolved in dichloromethane and precipitated with hexane, filtered and dried under reduced pressure to provide **17** ($C_{43}H_{37}N_5O_{10}$, 812 mg, 80%) as a white solid. $R_f = 0.2$ (90% ethyl acetate/hexane); mp 172.8–173.9°C; ^{1}H NMR (500 MHz, acetone-d_6) δ (ppm): 9.63 (s, 2H), 8.94 (s, 1H), 7.33–7.30 (m, 10H), 6.87–6.85 (m, 8H), 5.11 (s, 4H), 3.77 (s, 12H); ^{13}C NMR (125 MHz, acetone-d_6) δ (ppm): 196.8, 161.1, 160.5, 154.8, 151.9, 142.3, 131.8, 131.4, 114.8, 108.6, 60.8, 56.1, 53.4; MS: *m*/*z* 784.6 ($M^+ + 1$). *Anal*. Calcd. for $C_{43}H_{37}N_5O_{10}$: C, 65.89; H, 4.76; N, 8.94. Found: C, 65.98, H, 4.93, N, 8.60.

1,9-Di((S)-2-(trimethylsilyl)ethyl-2-amino-6-(benzyloxy-carbonylamino)hexanoate)-3,7-(bis(4-methoxyphenyl)methyl)pyrido[2,3-d:6,5-d′]dipyrimidine-2,4,6,8(1H,3H,7H,9H)-tetrone (18). A solution of **17** (200 mg, 0.26 mmol) in dichloroethane (20 mL) was treated with *N*-Cbz-L-Lysine-OCH_2CH_2TMS (250 mg, 0.65 mmol) at room temperature. After stirring for 15 min, $Na(AcO)_3BH$ (165 mg, 0.78 mmol) was added and stirring was continued for an additional 48 h. The reaction was then quenched with water and the product was extracted with dichloromethane (2×). The combined organic layers were washed successively with 10% aqueous citric acid, water, 5% aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulfate. Concentration under reduced pressure followed by purification by silica gel preparative thin layer chromatography (90% ethyl acetate/hexane) yielded compound **18** as white foam ($C_{81}H_{101}N_9O_{16}Si_2$, 346 mg, 89%). $R_f = 0.8$ (90% ethyl acetate/hexane); ^{1}H NMR (600 MHz, CD_2Cl_2) δ (ppm): 9.02 (s, 1H), 7.34–7.29 (m, 20H), 6.85–6.84 (m, 8H), 5.03 (s, 4H), 4.98 (s, 2H), 4.35 (dt, $J = 13.2$, 6.6 Hz, 4H), 4.16–4.13 (m, 4H), 3.77 (s, 12H), 3.15 (t, $J = 6.6$ Hz, 2H), 3.06 (dt, $J = 13.2$, 6.6 Hz, 4H), 2.97 (dt, $J = 13.0$, 6.0 Hz, 2H), 2.80–2.76 (m, 2H), 2.0 (broad s, 2H), 1.60–1.25 (m, 12H), 0.96–0.93 (m, 4H), 0.02 (s, 18H) ^{13}C NMR (150 MHz, CD_2Cl_2) δ (ppm): 175.8, 160.4, 159.6 , 156.8, 154.2, 151.4, 141.9, 137.7, 131.0, 130.9, 130.5, 128.9, 128.5, 113.9, 107.5, 66.8, 63.4, 61.7, 60.0, 55.8, 46.1, 43.6, 41.4, 33.6, 30.2, 23.6, 17.9, −1.2; MS: *m*/*z* 1512.8 ($M^+ + 1$). *Anal*. Calcd. for $C_{81}H_{101}N_9O_{16}Si_2$: C, 64.31; H, 6.73; N, 8.33. Found: C, 64.05, H, 6.78, N, 7.93.

1,9-Di((S)-2,6-diaminohexanoic acid)pyrido[2,3-d:6,5-d′]dipyrimidine-2,4,6,8 (1H,3H,7H,9H)-tetrone (19). A 94:6 *v*/*v* solution of TFA:thioanisole (10 mL) was added to **18** (70 mg, 0.046 mmol) at room temperature. After stirring for 70 h, ether (50 mL) was added and the resulting precipitate was filtered, washed with ether and dried under vacuum to provide **19** as a white solid (31 mg, 69%). ^{1}H NMR (500 MHz, D_2O) δ (ppm): 8.93 (s, 1H), 4.69–4.65 (m, 4H), 3.82 (t, $J = 6.5$ Hz, 2H), 3.58–3.44 (m, 4H), 3.01 (t, $J = 7.5$ Hz, 4H), 2.02–1.90 (m, 4H), 1.75–1.69 (m, 4H), 1.57–1.45 (m, 4H); ^{13}C NMR (150 MHz, D_2O) δ (ppm): 173.1, 162.1, 154.8, 152.1, 140.2, 108.0, 62.6, 44.5, 39.3, 39.0, 29.6, 26.7, 21.8; HRMS: *m*/*z* 592.2838 (M^+). *Anal*. Calcd. for $C_{25}H_{37}N_9O_8 \cdot 3.2CF_3$-$COOH \cdot 0.5H_2O$: C, 39.06; H, 4.30; N, 13.06. Found: C, 38.66, H, 4.69, N, 13.39.

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Functionalization of Benzo[*c,d*]indole System for the Synthesis of Visible and Near-Infrared Dyes

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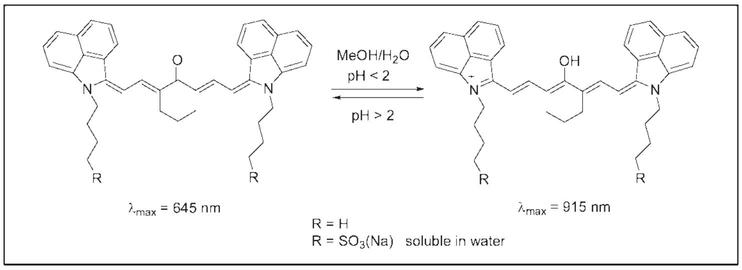

A number of benzo[*c,d*]indolium derivatives have been synthesized.

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INTRODUCTION

Cationic indolium and benzo-fused indolium moieties are common heterocyclic end units in cyanine and other polymethine dyes. As a general rule, the dyes containing benzo[*c,d*]indolium systems are more stable and show a batochromic shift in their electronic spectra in comparison with indolium, benzo[*e*]indolium, and benzo[*g*]indolium counterparts [1,2]. Synthesis of several 1-substituted 2-methylbenzo[*c,d*]indolium salts and examples of their use in the preparation of visible and near-infrared dyes are described in this report. We have concentrated on the chemistry of a hydrophobic *N*-butyl derivative **4** (Schemes 1 and 2) and its water-soluble analog **13** (Scheme 3). The common precursor to these compounds is readily available 1,8-naphtholactam (**1**) [3,4].

RESULTS AND DISCUSSION

One of the synthetic routes to *N*-alkylbenzo[*c,d*]indolium salts starting with **1** involves the intermediary of a derivative **2** [5,6]. Following the well-established chemistry, compound **2** was alkylated with *n*-butyl bromide and the resultant *N*-butyl derivative **3** was transformed to the desired iodide salt **4** by treatment with a mixture of acetic acid, hydrochloric acid, and potassium iodide. We found that it is not necessary to purify the intermediate product **3** as the synthesis of **4** proceeds in high yield with crude substrate **3**. The 2-methyl group in **4** is activated toward a reaction with a base such as pyridine to generate an intermediate anhydrobase or an enamine by proton abstraction (not shown). This intermediate product is nucleophilic and, as such, can undergo a reaction with the electrophilic Vilsmeier reagent derived from *N,N*-dimethylformamide and phosphorus oxychloride (Scheme 1).

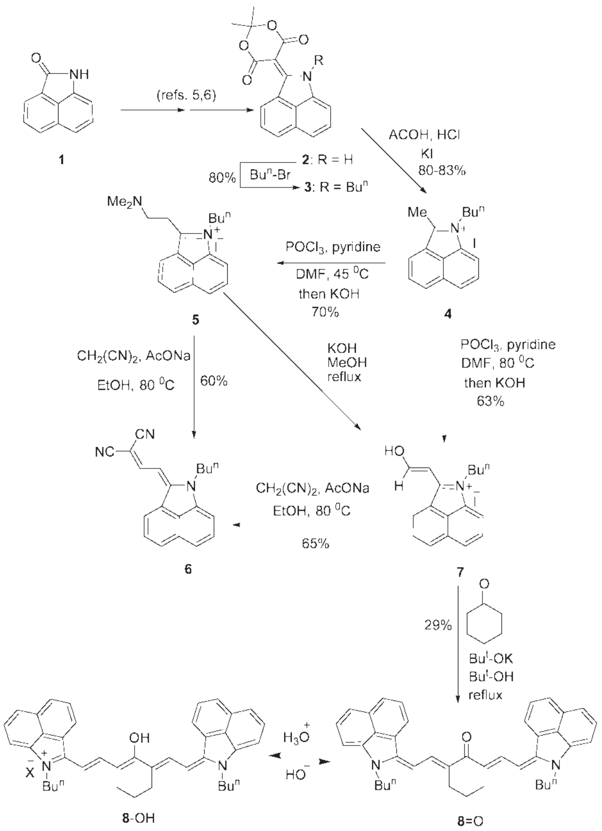
Interestingly, depending on conditions, two different products are formed, namely an enamine **5** or an unsaturated aldehyde **7**. The enamine **5** was independently transformed to the aldehyde **7** by treatment with potassium hydroxide in methanol under reflux conditions. Either compound **5** or **7**, can be efficiently condensed with malononitrile to give a visible dye **6**.

On the other hand, condensation of aldehyde **7** with cyclohexanone under basic conditions furnished a bis(aminodien)one **8=O** in low yield. This ketone is a visible dye (λ_{max} = 645 nm) in methanol under neutral or basic conditions. Under acidic conditions (pH < 2) dye **8=O** undergoes protonation at the carbonyl group with the formation of a hydroxy-substituted cyanine **8—OH** that absorbs in the near-infrared region (λ_{max} = 915 nm). The ketone/cyanine conversions are fully reversible, depending solely on pH conditions. Although the cyanine **8—OH** absorbs mainly in the invisible near-infrared region, it shows a residual absorption of low intensity in the visible region and is pink to the naked eye. The color change from deep dirty-green at basic or neutral pH to beautiful light-pink at low pH is quite dramatic. It should be noted that an attempted condensation of enamine **5** with cyclohexanone under conditions similar to those indicated above failed to produce dye **8=O**.

A different synthetic route to the dye system **8=O/8—OH** is presented in Scheme 2. We have previously used this approach for the synthesis of other pH-sensitive dyes [7].

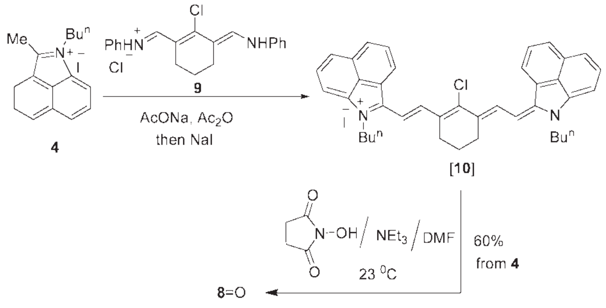
In this two-step preparation the substrate **4** was treated with the Vilsmeier-Haack reagent **9** [8] in acetic anhydride in the presence of sodium acetate as a base

Scheme 1

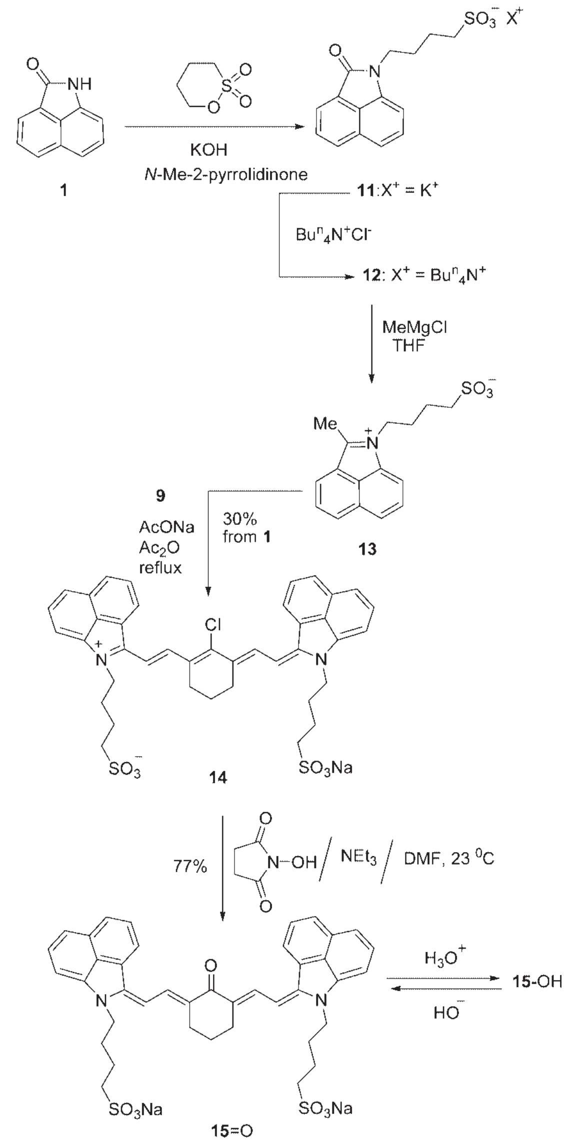


catalyst to furnish a chloro-substituted cyanine **10**, which then was transformed to **8=O** by the reaction with *N*-hydroxysuccinimide. The mechanism of this highly efficient transformation has been discussed previously [7]. This synthesis of **8=O** (Scheme 2) is more efficient and experimentally simpler than that shown in Scheme 1. Because of the high efficiency it was not necessary to purify the intermediate dye **10**. The final product **8=O** was obtained in an analytically pure form by using simple crystallization.

Scheme 2



Scheme 3



The synthesis of a water soluble pH-sensitive system **15=O/15—OH** is given in Scheme 3. The aqueous solubility is provided by the presence of sulfonate groups. As with other preparations discussed above, the starting material is 1,8-naphtholactam (**1**). Compound **1** was alkylated by the reaction with 1,4-butanesultone to give a sulfonatobutyl derivative **11**, the subsequent treatment of which with methylmagnesium chloride furnished the indolium product **13** [9]. The latter Grignard addition reaction gave compound **13** in low yield, which is due to low solubility of the potassium salt **11** in solvents suitable for organometallic reactions. This problem was overcome by transformation of the potassium salt **11** to a highly soluble tetrabutylammonium salt **12**. The reaction of **12** with methylmagnesium chloride in tetrahydrofuran furnished the desired product **13** in 85% yield. The subsequent construction of the dye system **15=O/15—OH** is similar to that of **8=O/8—OH**. The difference is in the use of a sulfonatobutyl derivative **13** (Scheme 3) rather than a butyl derivative **4** (Scheme 2) for the condensation reaction with the Vilsmeier-Haack reagent **9**.

Since compounds **8** and **15** share the same chromophore, they show virtually identical spectral properties that depend on pH conditions. The transition ketone/cyanine for both **8** and **15** is characterized by $pK_a = 2$, as obtained by spectrophotometric titrations.

EXPERIMENTAL

1-Butyl-2-methylbenzo[*c,d*]indolium iodide, 4. Conversion of the commercial substrate **1** to 2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)1*H*-benzo[*c,d*]indole (**2**), alkylation of **2** with *n*-butyl bromide to give **3**, and then the treatment of crude product **3** with a mixture of acetic acid, hydrochloric acid and potassium iodide to give the desired salt **4** were conducted by using general procedures for the preparation of similar derivatives [5,6]. After crystallization from ethanol/water (1:5), compound **4** was obtained in a total yield of 40% starting from **1**, mp > 300°C; ^{1}H NMR (deuteriochloroform): δ 0.95 (t, $J = 7$ Hz, 3H), 1.45 (m, 2H), 1.78 (m, 2H), 3.20 (s, 3H), 4.17 (t, $J = 7$ Hz, 2H), 7.07 (d, $J = 8$ Hz, 1H), 7.47 (t, $J = 8$ Hz, 1H), 7.59 (d, $J = 8$ Hz, 1H), 7.87 (t, $J = 8$ Hz, 1H), 8.02 (d, $J = 8$ Hz, 1H), 9.10 (d, $J = 8$ Hz, 1H). *Anal.* Calcd. for $C_{16}H_{18}IN$: C, 54.71; H, 5.17; N, 3.99. Found: C, 54.80; H, 5.13; N, 4.06.

1-Butyl-2-(2-dimethylaminovinyl)benzo[*c,d*]indolium iodide, 5. *N,N*-Dimethylformamide (1.0 mL) was cooled to 0°C and treated dropwise with phosphorus oxychloride (0.21 mL, 2.3 mmol) and then with a solution of salt **4** (0.35 g, 1.0 mmol) and pyridine (0.2 mL) in *N,N*-dimethylformamide (2.0 mL). The mixture was heated to 65°C for 40 min, then treated with an aqueous solution of potassium hydroxide (60%, 1 mL) and heated to 45°C for an additional 30 min. Extraction with dichloromethane (4 × 10 mL) followed by concentration of the extract and silica gel chromatography of the residue eluting with dichloromethane/methanol (19:1) gave 0.28 g (70%) of **5**; mp 182–183°C; ^{1}H NMR (deuteriochloroform): δ 0.95 (t, $J = 8$ Hz, 3H), 1.45 (m, 2H), 1.78 (m, 2H), 3.47 (s, 3H), 3.86 (s, 3H), 4.17 (t, $J = 8$ Hz, 2H), 5.87 (d, $J = 12$ Hz, 1H), 7.07 (d, $J = 8$ Hz, 1H), 7.47 (t, $J = 8$ Hz, 1H), 7.59 (d, $J = 8$ Hz, 1H), 7.87 (t, $J = 8$ Hz, 1H), 8.02 (d, $J = 8$ Hz, 1H), 8.96 (d, $J = 12$ Hz, 1H), 9.10 (d, $J = 8$ Hz, 1H); ms (esi): *m/z* 279 (M^+). *Anal.* Calcd. for $C_{19}H_{23}IN_2$: C, 56.17; H, 5.71; N, 6.89. Found: C, 56,05; H, 5.72; N, 6.83.

[2-(1-Butyl-1,2-dihydrobenzo[*c,d*]indol-2-ylidene)ethylidene]malononitrile, 6. A solution of salt **5** (63 mg, 0.15 mmol), malononitrile (15 mg, 0.22 mmol) and sodium acetate (16 mg, 0.20 mmol) in anhydrous ethanol (15 mL) was heated under reflux for 1 h. Silica gel chromatography eluting with hexanes/dichloromethane (5:1) gave 27 mg (60%) of **6**; mp 180–181°C; ^{1}H NMR (deuteriochloroform): δ 1.00 (t, $J = 7$ Hz, 3H), 1.46 (m, 2H), 1.80 (m, 2H), 4.01 (t, $J = 7$ Hz, 2H), 6.25 (d, $J = 9$ Hz, 1H), 6.99 (m, 1H), 7.52 (m, 2H), 7.74 (t, $J = 8$ Hz, 1H), 8.00 (d, $J = 8$ Hz, 1H), 8.10 (d, $J = 8$ Hz, 1H), 8.32 (d, $J = 9$ Hz, 1H); ms (maldi) *m/z* 299 (M^+) and 300 ($M^+ + 1$); vis: λ_{max} in methanol, 519 nm and 556 nm. *Anal.* Calcd. For $C_{20}H_{17}N_3$: C, 80.24; H, 5.72; N, 14.04. Found: C, 80.22; H, 5.75; N, 13.91.

(1-Butyl-1,2-dihydrobenzo[*c,d*]indol-2-ylidene)acetaldehyde, 7. *N,N*-Dimethylformamide (1 mL) was stirred at 10°C and treated dropwise with phosphorus oxychloride (0.21 mL, 2.3 mmol) and then with a solution of **4** (1.9 g, 0.54 mmol) and pyridine (0.6 mL) in *N,N*-dimethylformamide (2 mL). The mixture was heated to 80°C for 40 min, then treated with an aqueous solution of potassium hydroxide (60%, 2.5 mL) and heated to 80°C for an additional 90 min. After cooling the mixture was extracted with dichloromethane (4 × 10 mL), the extracts were concentrated, and the residue was purified by silica gel chromatography eluting with dichloromethane/methanol (19:1) to furnish 1.6 g (65%) of **7**; mp 104–105°C; ^{1}H NMR (deuteriochloroform): δ 0.93 (t, $J = 7$ Hz, 3H), 1.39 (m, 2H), 1.66 (m, 2H), 4.00 (t, $J = 7$ Hz, 2H), 5.85 (d, $J = 8$ Hz, 1H), 7.12 (t, $J = 8$ Hz, 1H), 7.52 (m, 2H), 7.74 (t, $J = 8$ Hz, 1H), 8.07 (d, $J = 8$ Hz, 1H), 8.60 (d, $J = 8$ Hz, 1H), 10.33 (d, $J = 8$ Hz, 1H); ms (esi): *m/z* 252 (M^+). *Anal.* Calcd. for $C_{17}H_{18}NO$: C, 80.92; H, 7.19; N, 5.55. Found: C, 81.05; H, 6.88; N, 5.56.

2,6-Bis[(1-ethyl-1,2-dihydrobenzo[*c,d*]indol-2-ylidene)ethylidene]cyclohexanone, 8=O. A solution of potassium *tert*-butoxide (116 mg, 1 mmol) in *tert*-butanol (15 mL) was stirred under a nitrogen atmosphere and treated with the aldehyde **7** (150 mL, 0.67 mmol) and cyclohexanone (0.34 μL, 0.33 mmol). The mixture was heated under reflux for 12 h, then cooled and quenched with water (1.0 mL). The resultant precipitate was collected by filtration, washed with water and cold methanol, and dried under reduced pressure at 23°C; yield 54 mg (29%); mp 188–190°C; ^{1}H NMR (deuteriochloroform): δ 1.00 (m, 6H), 1.48 (m, 4H), 1.80 (m, 4H), 1.99 (m, 2H), 2.79 (m, 4H), 3.88 (m, 4H), 6.06 (d, $J = 13$ Hz, 2H), 6.68 (d, $J = 8$ Hz, 2H), 7.29 (d, $J = 8$ Hz, 2H), 7.40 (t, $J = 8$ Hz, 2H), 7.65 (t, $J = 8$ Hz, 2H), 7.77 (d, $J = 8$ Hz, 2H), 8.42 (d, $J = 8$ Hz, 2H), 8.77 (d, $J = 8$ Hz, 2H); vis: λ_{max} in methanol, 645 nm (ε 50800 M^{-1} cm^{-1}); nir: λ_{max} in methanol with one drop of concentrated hydrochloric acid (pH < 2, **8—OH**), 915 nm (ε 142000 M^{-1} cm^{-1}). *Anal.* Calcd. for $C_{40}H_{40}N_2O$: C, 85.06; H, 7.13; N, 4.96. Found: C, 85.33; H, 7.12; N, 4.95.

Alternative synthesis of 8=O. The Vilsmeier-Haack reagent **9** was obtained as reported previously [8]. Condensation of **9** with **4** was conducted in ethanol in the presence of sodium acetate by using a general procedure [10]. Crude product **10** was collected as a precipitate after treatment of the mixture with ether (nir: λ_{max} in methanol, 1025 nm) and used for the subsequent transformation to **8=O** without purification. Thus, crude dye **10**, obtained from 351 mg (1.0 mmol) of **4**, was dissolved in anhydrous *N,N*-dimethylformamide (15 mL), and this solution was treated with *N*-hydroxysuccinimide (0.33 g, 2.9 mmol) and triethylamine (0.5 mL) under a nitrogen atmosphere. The mixture was stirred at 23°C under nitrogen for 10 h and then diluted with ether (35 mL), which caused precipitation of **8=O**. The product was crystallized by dropwise dilution of a solution in methanol with *tert*-butyl methyl ether; yield 338 mg (60%) from **4**. The spectral characteristics of **8=O** thus obtained were virtually identical with those reported above.

1-(4-Sulfonatobutyl)-1,2-dihydrobenzo[*c,d*]indol-2-one, potassium salt, 11. This compound was obtained by the following modification of the published procedure [9] which did not include any characterization of the product. A mixture of **1** (1.69 g, 10 mmol), powdered potassium hydroxide (1.12 g, 20 mmol), and *N*-methyl-2-pyrrolidone (5 mL) was stirred at 23°C for 15 min and then treated with 1,4-butanesultone (1.49 g, 11 mmol). The mixture was stirred at 80°C for an additional 10 h, then cooled and treated dropwise with acetone (25 mL), which caused crystallization of product **11**; yield 3.26 g (95%); mp 235–240°C; ^{1}H NMR (deuterated dimethyl sulfoxide): δ 1.63 (t, $J = 7$ Hz, 2H), 1.78 (m, 2H), 2.45 (m, 2H), 3.90 (t, $J = 7$ Hz, 2H), 7.24 (d, $J = 7$ Hz, 1H), 7.56 (t, $J = 8$ Hz, 1H), 7.65 (d, $J = 8$ Hz, 1H), 7.82 (t, $J = 8$ Hz, 1H), 8.06 (d, $J = 8$Hz, 1H), 8.20 (d, $J = 8$ Hz, 1H). *High-resolution ms* (esi, negative ion mode): calcd. for $C_{15}H_{14}NO_4S$, *m*/*z* 304.0643 (M^-); found *m*/*z* 304.0655.

1-(4-Sulfonatobutyl)-1,2-dihydrobenzo[*c*,*d*]indol-2-one, tetrabutylammonium salt, 12. This compound was obtained by the following modification of the published procedure [9] which did not include any characterization of the product. A mixture of salt **11** (3.0 g, 10 mmol) and tetrabutylammonium chloride (3.1 g, 11 mmol) in acetic acid (10 mL) was stirred at 90°C, treated dropwise with ethyl acetate, cooled, and filtered from the precipitate of potassium chloride. The filtrate was concentrated on a rotary evaporator and the oily residue was dissolved in dry toluene (50 mL). The azeotropic removal of traces of water by concentration on a rotary evaporator gave salt **12** (5.0 g, 93%) as a viscous oil; ^{1}H NMR (deuterated dimethyl sulfoxide): δ 0.99 (t, $J = 8$ Hz, 12H), 1.43 (m, 8H), 1.65 (m, 8H), 1.95 (m, 4H), 2.90 (m, 2H), 3.27 (t, $J = 8$ Hz, 8H), 3.94 (t, $J = 7$ Hz), 6.98 (d, $J = 7$ Hz, 1H), 7.18 (d, $J = 7$ Hz, 1H), 7.25 (d, $J = 7$ Hz, 1H), 7.50 (m, 2H), 7.69 (t, $J = 7$ Hz, 1H), 8.02 (t, $J = 7$ Hz, 1H). *High-resolution ms* (esi, negative ion mode): calcd. for $C_{15}H_{14}NO_4S$ (M^-) , *m*/*z* 304.0643 ; found 304.0640.

1-(4-Sulfonatobutyl)-2-methylbenzo[*c*,*d*]indolium inner salt, 13. This compound was obtained by the following modification of the published procedure [9] which did not include any characterization of the product. Methylmagnesium chloride (3.0*M* solution in tetrahydrofuran, 15.0 mL, 45 mmol) was added dropwise to a stirred solution of salt **12** (5.46 g, 10 mmol) in anhydrous tetrahydrofuran under a nitrogen atmosphere. The mixture was stirred at 60°C for 1 h, then cooled, neutralized by dropwise addition of 3*M* hydrochloric acid, and consecutively diluted with ethanol (30 mL) and ether (30 mL). Cooling to 0°C for several hours resulted in crystallization of product **13**; yield 2.58 g (85%); mp 143–145°; ^{1}H NMR (deuterium oxide): δ 1.77 (t, $J = 8$ Hz, 2H), 2.03 (m, 2H), 2.84 (m, 2H), 3.01 (s, 3H), 4.50, (t, $J = 8$ Hz, 2H), 7.72 (t, $J = 8$ Hz, 1H), 7.84 (t, $J = 8$ Hz, 1H), 8.08 (m, 2H), 8.42 (d, $J = 8$ Hz, 1H), 8.50 (d, $J = 8$ Hz, 1H). *High-resolution ms* (maldi): calcd. for $C_{16}H_{18}NO_3S$ ($M^+ + 1$), *m*/*z* 304.1007; found *m*/*z* 304.1015.

Cyanine dye 14. A solution of inner salt **13** (303 mg, 1 mmol) Vilsmeier-Haack reagent **9** [8] (180 mg, 0.5 mmol), and sodium acetate (82 mg, 1 mmol) in acetic anhydride (20 mL) was heated under reflux for 8 h, then cooled and treated with ether (30 mL). The resultant precipitate of cyanine **14** was crystallized from methanol/ether; yield 115 mg (30%); mp > 300°C; ^{1}H NMR (deuterated dimethyl sulfoxide): δ 1.82 (m, 14H), 2.83 (t, $J = 7$ Hz, 4H), 4.01 (t, $J = 7$ Hz, 4H), 6.20 (d, $J = 13$ Hz, 2H), 6.88 (d, $J = 7$ Hz, 2H), 7.29 (d, $J = 7$ Hz, 2H), 7.42 (t, $J = 7$ Hz, 2H), 7.73 (t, $J = 7$ Hz, 2H), 7.84 (d, $J = 7$ Hz, 2H), 8.04 (d, $J = 7$ Hz, 2H), 8.37 (d, $J = 13$ Hz, 2H); nir: λ_{max} in methanol, 1013 nm. *High-resolution ms* (esi, negative ion mode): calcd. for $C_{40}H_{38}{}^{35}ClN_2O_6S_2$ (M^-), *m*/*z* 741.1860; found *m*/*z* 741.1871.

2,6-Bis[2-[1-(sodium4-sulfonatobutyl)-1,2-dihydrobenzo-[*c*,*d*]indol-2-ylidene)]ethylidene]cyclohexanone, 15=O. Cyanine **14** was allowed to react with *N*-hydroxy-succinimide in the presence of triethylamine in *N*,*N*-dimethylformamide as described above for a similar transformation of **10** to **8=O**. Product **15=O** was precipitated by addition of ether and crystallized from methanol/ether; yield 115 mg starting with 150 mg of **14** (77%); mp > 300°C; ^{1}H NMR (deuterated dimethyl sulfoxide): δ 1.86 (m, 14H), 2.85 (t, $J = 7$ Hz, 4H), 4.02 (t, $J = 7$ Hz, 4H), 6.20 (d, $J = 13$ Hz, 2H), 6.90 (d, $J = 7$ Hz, 2H), 7.32 (d, $J = 7$ Hz, 2H), 7.45 (t, $J = 7$ Hz, 2H), 7.75 (t, $J = 7$ Hz, 2H), 7.87 (d, $J = 7$ Hz, 2H), 8.06 (d, $J = 7$ Hz, 2H), 8.42 (d, $J = 7$ Hz, 2H); vis: λ_{max} in methanol, 645 nm (ε 50800 M^{-1} cm^{-1}); nir: λ_{max} in methanol with one drop of concentrated hydrochloric acid (pH < 2, **15—OH**), 914 nm (ε 142000 M^{-1} cm^{-1}). *High-resolution ms* (maldi, negative ion mode): calcd. for $C_{40}H_{39}N_2O_7S_2$ ($M^- + 1$), *m*/*z* 723.2199; found *m*/*z* 723.2234.

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New Heterocycles from Tetrazines and Oxadiazoles

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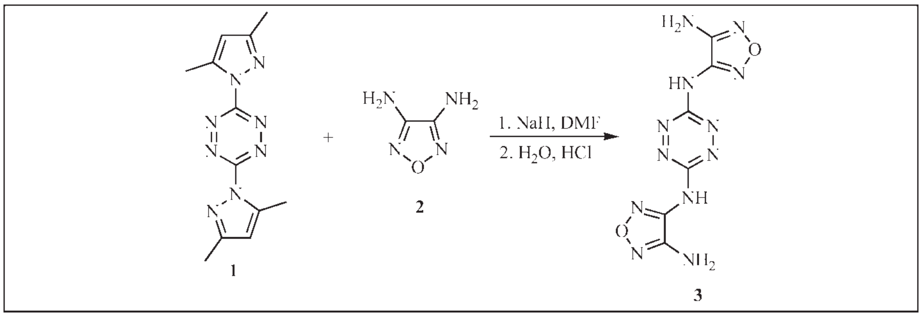

The reactivity of 3,4-diamino-1,2,5-oxadiazole (**2**) toward nucleophilic substitution of 3,6-bis(3,5-dimethylpyrazol-1yl)-1,2,4,5-tetrazine (**1**) was studied. A new class of high nitrogen heterocyclic systems was prepared. It was determined that 3,4-diamino-1,2,5-oxadiazole did not display the required nucleophilicity to be reactive. However, the anion of 3,4-diamino-1,2,5-oxadiazole, prepared by treatment with strong base, was sufficiently reactive to act as a nucleophile.

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INTRODUCTION

High nitrogen heterocyclic systems have seen increasing interest over the past decade due to their potential utility in numerous applications, such as propellants, explosives, and pyrotechnics [1–4]. We have primarily focused on the investigation of tetrazines [5–9] and 1,2,5-oxadiazoles [9] in the past, but had not combined the two heterocycles into a new heterocyclic system. Nucleophilic substitutions of tetrazines, in particular 3,6-bis(3,5-dimethylpyrazol-1yl)-1,2,4,5-tetrazine (**1**), have been studied extensively by us [10] and others [11,12]. Additionally, the nucleophilicity of 3,4-diamino-1,2,5-oxadiazole (**2**) has been studied as well [13], but there exist no literature examples describing the reactivity of **1** with **2** or any other tetrazine. We began our investigations by studying the substitution reaction of **1** with **2**. We wish to report here that we have been successful in identifying conditions that allow us to prepare the desired tetrazine-oxadiazole heterocyclic systems in good yield. We have also confirmed the structure through X-ray crystallography.

RESULTS AND DISCUSSION

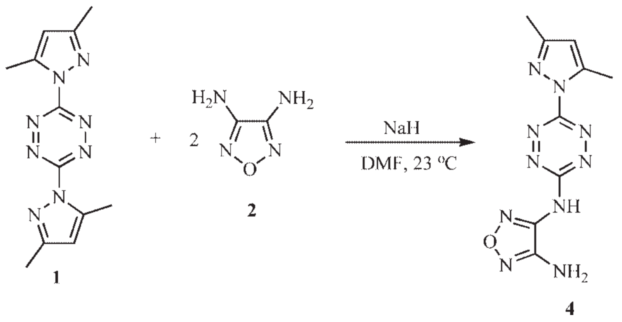
Our initial efforts toward the synthesis of **3** involved the reaction of **1** and **2** in refluxing acetonitrile (Scheme 1). Unfortunately, no reaction was observed even after 2 days. More polar solvents, such as dimethylformamide (DMF) were also investigated, but only trace amounts of product was observed by thin layer chromatography. Because of these setbacks, we focused on an approach we employed recently [5]. In this approach, we reported the synthesis of some new high nitrogen materials by reacting with the anion of nitroguanidine with **1** in methanol. The success of this chemistry led us to investigate whether similar conditions might be applicable with **1** and **2**.

As shown in Scheme 1, our strategy involved the deprotonation of **2** with sodium hydride in DMF. Our ultimate goal was to prepare **3** and as such, we employed two equivalents of **2**. When the reaction was performed at ambient temperature, we observed the complete conversion of **1** to a new product after a few hours as analyzed by thin layer chromatography. Isolation and analysis of the product showed that the material isolated was the mono-substituted product **4**.

It was believed that as the product **4** began to form, an acidic proton was generated, in the form of the oxadiazol-ylamino proton. This acidic proton serves to neutralize the anion of **2**, thus resulting in an unreactive form of **2**. We subsequently reasoned that the addition of more equivalents of the anion of **2** would allow for complete conversion of the intermediate **1** to **3**.

Indeed, when four equivalents of the anion of are generated in DMF by the reaction of sodium hydride and **2**, followed by the addition of **1** at ambient temperature, complete conversion of intermediate **4** to product **3**

Scheme 1



was observed. To isolate the product, the reaction was quenched by pouring into ice water and acidifying to pH = 1 (Scheme 2). Compound **3** was determined to be very thermally stable and doesn't begin to decompose until 280°C. An alternative approach that was equally successful was the use of two equivalents of **2** and four equivalents of sodium hydride.

X-ray quality crystals were grown from DMSO with slow diffusion of water. A crystal structure was determined for bis-substituted product **3** and is shown in Figure 1. The crystals obtained were a DMSO solvate containing two DMSO molecules and one molecule of **3**.

Interestingly, as shown in Scheme 3, a bis-tetrazine substituted 1,2,5 oxadiazole can be prepared by using two equivalents of **1** and only one equivalent of **2**. Although these new heterocycles contain a large percentage of nitrogen, they are not energetic materials. They are insensitive to impact, spark and friction. Each of these new heterocyclic molecules will now be investigated as potential starting materials for new high-nitrogen energetic materials.

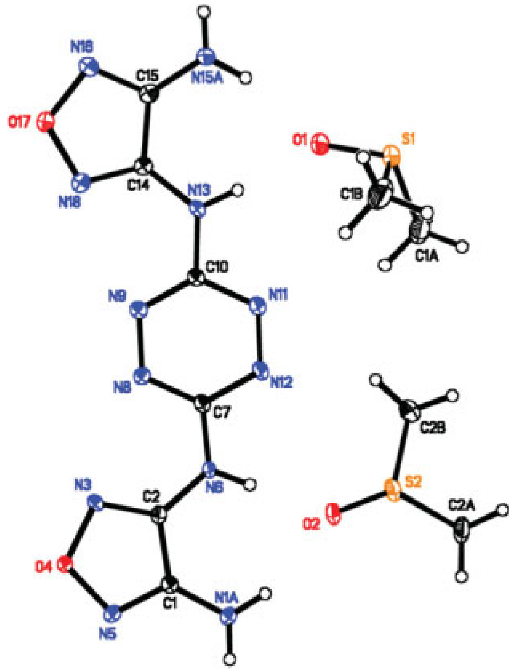
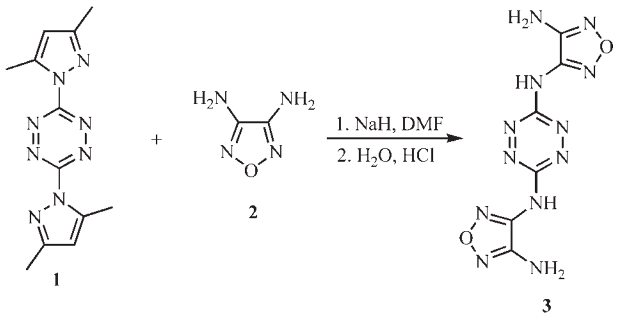


Figure 1. View of **3** showing the labeling of the nonhydrogen atoms. Thermal ellipsoids are shown at the 50% probability level. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

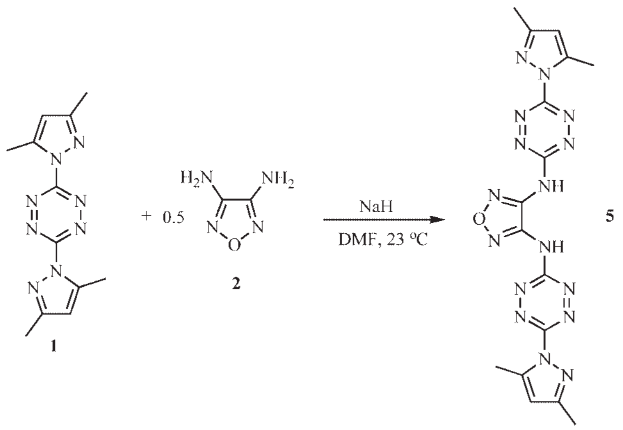
EXPERIMENTAL

3-(3,5-Dimethylpyrazol-1yl), 6-(3-amino-1,2,5-oxadiazol-4-ylamino)-1,2,4,5-tetrazine (4). To dimethylformamde (10 mL) was added 70 mg of NaH (60% dispersion in oil, 1.7 mmol), and 100 mg of 3,4-diamino-1,2,5-oxadiazole (1 mmol). The mixture was stirred at 23°C for 30 min. To the reaction mixture, 135 mg of **1** (0.5 mmol) was added. The reaction was then stirred at 23°C for 30 min. After this time **1** was completely consumed. The reaction mixture was then poured into ice water and acidified to pH = 1. The reaction was allowed to stand at 5°C for 16 h and a red precipitate formed. The material was collected by filtration, washed with water and air dried to provide 200 mg (73%), mp 87–89°C; IR (ν, cm^{-1}) 3477, 3354, 3227, 2925, 2851, 1646, 1609, 1581, 1558, 1527, 1450, 1417, 1323, 1262, 1082, 1049, 1025, 976, 955, 833, 800, 563. ^{1}H NMR (deuteriochloroform, ppm): δ 2.23 (s, 3H), 2.43 (s, 3H), 6.2 (s, 2H), 6.25 (s, 1H), 11.42 (s, 1H); ^{13}C NMR (deuteriodimethyl sulfoxide): δ 12.84, 13.37, 109.58,

Scheme 2



Scheme 3



142.01, 143.37, 151.13, 152.36, 157.88, 159.98. *Anal*. Calcd. for $C_9H_{10}N_{10}O$: C, 39.43; H, 3.68; N, 51.07. Found: C, 39.47; H, 3.65; N, 51.04.

3,4-Bis[6-(3,5-dimethylpyrazol-1yl)-1,2,4,5-tetrazin-6-ylamino]-1,2,5-oxadiazole (5). To a mixture of 540 mg of **1** (2.0 mmol) and 100 mg of 3,4-diamino-1,2,5-oxadiazole (1 mmol) in 5 mL of DMF was added 140 mg of NaH (60% dispersion in oil, 3.4 mmol) at 23°C. The reaction mixture was allowed to stir for 1 h. The reaction mixture was poured into 20 mL of water, acidified to pH = 1, the solid collected by filtration and washed with water to give a orange product 202 mg (45%), mp 196°C (dec); IR (ν, cm^{-1}) 3228, 3056, 2986, 2933, 1577, 1480, 1421, 1274, 1077, 1047, 1027, 971, 951, 801, 568. ^1H NMR (deuterioacetonitrile, ppm): δ 2.27 (s, 6H), 2.52 (s, 6H), 6.20 (s, 2H), 9.63 (bs, 2H). ^{13}C NMR (deuterioacetonitrile): δ 13.72, 13.74, 111.20, 143.97, 147.01, 153.69, 159.81, 161.06. *Anal*. Calcd. for $C_{16}H_{14}N_{16}O$: C, 43.05; H, 3.16; N, 50.20. Found: C, 43.06; H, 3.17; N, 50.19.

3,6-Bis(3-amino-1,2,5-oxadiazol-4-ylamino)-1,2,4,5-tetrazine (3). To a solution of 3.0 g (60% dispersion in oil, 75 mmol) of NaH in 50 mL of DMF was added 2.0 g (20 mmol) of **2**. The mixture was allowed to stir at 25°C for 30 min. A total of 1.35 g (5.0 mmol) of **1** was then added in one portion and the reaction allowed to stir at 25°C for 1 h. The reaction mixture was then poured into 200 mL of water and acidified to pH = 1. A red precipitate formed, the mixture was cooled in an ice bath, the solid collected by filtration and the orange-red solid was washed with water and air-dried to give 1.27 g (91%), mp 280°C (dec); IR (ν, cm^{-1}) 3391, 3329, 3260, 3080, 2953, 2921, 2851, 1642, 1634, 1511, 1446, 1421, 1307, 1262, 1074, 1008, 980, 861, 812. ^1H NMR (deuteriodimethylsulfoxide): δ 6.15 (bs, 4H), 10.8 (s, 2H); ^{13}C NMR (deuteriodimethylsulfoxide): δ 143.71, 151.76, 158.78. *Anal*. Calcd. for $C_6H_6N_{12}O_2$: C, 25.9; H, 2.17; N, 60.42. Found: C, 25.5; H, 2.19; N, 60.44.

Single-crystal X-ray diffraction analysis of 3. $C_{10}H_{18}N_{12}O_4S_2$, FW = 434.48, monoclinic, $P2_1/c$, $a = 10.1881(8)$ Å, $b = 19.4198(15)$ Å, $c = 9.9515(8)$ Å, $\alpha = 90°$, $\beta = 114.649(2)°$, $\gamma = 90°$, $V = 1789.5(2)$ Å^3, $Z = 4$, $\rho_{calc} = 1.613$ mg/m^3, $\mu = 0.186$ mm^{-1}, $F(000) = 904$, $R_1 = 0.0456$ for 3369 observed ($I > 2\sigma I$) reflections and 0.0545 for all 3680 reflections, Goodness-of-fit = 1.095, 253 parameters.

A thin red/orange plate of dimensions 0.56 mm × 0.21 mm × 0.007 mm was mounted on glass fiber using a small amount of Cargille immersion oil. Data were collected at the Advanced Photon Source in Argonne National Laboratory. A Bruker three-circle platform diffractometer equipped with a SMART 6000 CCD detector was used to collect the data. An Oxford Cryojet low temperature device was used to keep the crystals at a constant 103(2) K during data collection.

Data collection was performed and the unit cell was initially refined using *SMART* v5.625 [14]. Data reduction was performed using *SAINT* v6.36A [15] and *XPREP* v6.12 [16]. Corrections were applied for Lorentz, polarization, and absorption effects using *SADABS* v2.03 [17]. The structure was solved and refined with the aid of the programs in the *SHELXTL-plus* v6.10 system of programs [18]. The full-matrix least-squares refinement on F^2 included atomic coordinates and anisotropic thermal parameters for all non-H atoms. The H atoms were included using a riding model.

CCDC 685362 contains the supplementary crystallographic data for this article. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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Water-Promoted Dowex 50W Catalyzed Highly Efficient Green Protocol for 2-Arylbenzothiazole Formation

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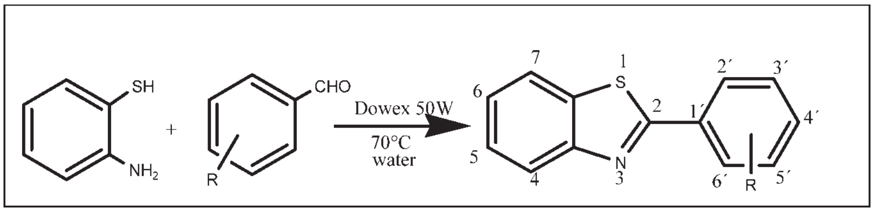

2-Aminothiophenol and a variety of aryl aldehydes were allowed to react in one-pot operation to give 2-aryl-benzothiazoles in excellent yields in the presence of Dowex 50W in water. Very high yields coupled with the ease of work-up procedure, formation of no side products, employment of ''reusable'' catalyst, and ''green'' synthesis in aqueous medium without maintaining anhydrous reaction conditions are the most important aspects of this methodology.

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INTRODUCTION

The 2-substituted benzothiazole moiety is particularly very interesting in the area of medicinal and organic chemistry. The benzothiazolyl system possesses highly selective and potent antitumor activity. An example is that of substituted 2-(4-aminophenyl)-benzothiazoles, which show nanomolar inhibitory *in vitro* activity against a wide range of human breast, ovarian, colon, and renal cell lines [1]. Another such compound that shows potent and selective inhibitory activity against lung, colon, and breast cancer cell lines is 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole [2]. Also, the 2-(4-dimethylaminophenyl)-benzothiazole is an integral component used for the treatment of Alzheimer's disease [3]. The presence of the benzothiazole nucleus is essential in the thermally stable rigid-rod polymers with high tensile strength and modulus [4]. Thus, the synthesis of this benzothiazole moiety is always a great challenge.

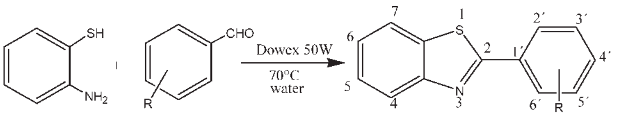
A number of synthetic routes are available for the construction of the benzothiazole nucleus. Among them, the most common ones being the condensation of 2-aminothiophenols with substituted carboxylic acids, acyl chlorides, aldehydes, and nitriles [5]. An alternate method includes potassium ferricyanide cyclization of thiobenzanilides (Jacobson's method [6]). Solvent-free synthesis of benzothiazoles under microwave irradiation in the presence of silica gel is also known [7a]. Very recently, the synthesis of this moiety under microwaves in absence of any catalyst has been reported by us [7b]. Most of these methods employ costly reagents and perfectly dry reaction conditions or the use of microwaves. Thus, a truly efficient diverse green synthetic scheme of such an important organic moiety in aqueous medium still needs to be explored.

RESULTS AND DISCUSSION

It has been recently reported from our laboratory [8] that Dowex 50W has proved to be a very effective and efficient catalyst for the construction of the 4-aryl-dihydropyrimidone nucleus. On the basis of such observation, we chose the sulfonic acid resin Dowex 50W in aqueous medium for the construction of the benzothiazole ring. Thus, a variety of aromatic aldehydes (**1**) were coupled with 2-aminothiophenol (**2**) in the presence of 10 mol % of Dowex 50W in water in a one-pot operation for the first time to synthesize the 2-substituted benzothiazoles (**3**) (Scheme 1, Table 1) in excellent yields. Water proved to be the best medium for this reaction. The yields of the products decreased on performing the reaction in water-methanol, water-ethanol, or water-tetrahydrofuran mixed solvents (all 50:50 by volume).

The advantages of using Dowex 50W are as follows: (a) it can be reused at least three times without

Scheme 1



2 **1** **3**

Table 1

Synthesis of 2-arylbenzothiazoles by Dowex 50W in water under aerial oxygen.

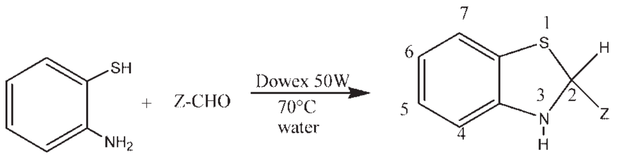
Entry	R (1)	Time (h)	Yield (%) (3)	Observed mp (°C)	Reported mp (°C)	References
1	a: H	12	a: 85	112–114	114–115	[5a,10]
2	b: 4-OMe	10	b: 89	120–121	121–122	[5a,10]
3	c: 2-OMe	08	c: 83	101–103	101–102	[7]
4	d: 3-NO_2	08	d: 88	181–182	183–185	[5b]
5	e: 4-Cl	12	e: 90	115–117	117–118	[5a,11]
6	f: 4-NO_2	06	f: 87	228–230	229–230	[5a,7]
7	g: 4-OH	10	g: 92	225–226	227–228	[7]
8	h: 3-OH	12	h: 86	161–163	160–162	[12]
9	i: 3-OMe- 4-OH	10	i: 90	162–164	161–163	[12]
10	j: 3-Br	08	j: 92	84–86	83–84	[13]
11	k: 4-$N(CH_3)_2$	10	k: 88	160–162	160–161	[3]
12	l: 2-furanyl	09	l: 85	103–104	103–104	[5a,7,11]
13	m: 2-NO_2	05	m: 83	135–136	138–140	[7]
14	n: 2-Cl	10	n: 85	84–85	82	[7]
15	o: 2-cinnamyl	07	o: 82	110–111	112	[5b]
16	p: 4- Br	08	p: 84	132	130	[14]
17	q: 3,4- $(OMe)_2$	07	q: 87	141–143	142–144	[15]
18	r: 2.5-$(OMe)_2$	07	r: 85	147–149	Not reported	[16]

substantial loss of activity (b) dry conditions are not required (c) the reaction takes place very smoothly (d) no side products are obtained (e) the purification of the final product is very simple (f) no hazardous wastes from solvents or chemicals take place (g) the reaction conditions are very mild employing temperature of only 70°C, thus being able to sustain quite a large number of functional groups. Therefore, Dowex 50W is a ''green catalyst'' for the 2-aryl-benzothiazole formation in aqueous medium.

With salicaldehyde (**1s**), the reaction stopped at the benzothiazoline [**4**(**i**)(**s**)] stage (Scheme 2, Table 2, entry 1), and the stability of this intermediate by six-membered hydrogen bond (intramolecular) (Fig. 1) prevents it to react further to produce the benzothiazole. The isolation of this intermediate [**4**(**i**)(**s**)] confirms our earlier proposed mechanism [7b].

The fact that the reaction of salicaldehyde (**1s**) and 2-aminothiophenol (**2**) stops at the benzothiazoline stage is further proved by the work of Charles and Freiser [9]. The intermediate benzothiazoline [**4**(**i**)(**s**)] from salicaldehyde (**1s**) is converted to 2-hydroxyphenyl benzothiazole (**3s**) in good yield but under very drastic conditions (Scheme 3, Table 3, entry 1). The isolation of 2-hydroxyphenyl benzothiazoline [**4**(**i**)(**s**)] surely proves that the reaction passes through this intermediate. Following the same mechanistic pathway cited in our earlier reference [7b], benzothiazoles (**3**) are the final products for all the cases cited in Table 1.

Scheme 2



2 [Z=(R substituted aryl)(**1**) Z=alkyl] **4**(i) Z=R-substituted aryl (ii) Z=alkyl

The reaction therefore proceeds *via* the intermediate formation of benzothiazoline [7b]. This is further proved by the actual isolation of such intermediates from 2-chloro and 4-nitrobenzaldehydes by carrying out the reaction for a shorter time (entries 2 and 3, Table 2), which then proceed to completion (entries 2 and 3, Table 3). When the same reaction with Dowex 50W was carried out under argon atmosphere (in absence of oxygen) (carried out with 2-chloro, 4-nitro- and 2-hydroxy benzaldehydes), the reactions stopped at the benzothiazoline stage, which never proceeded to benzothiazoles. This surely proves that aerial oxygen is not essential for benzothiazoline formation, though it is absolutely essential for the oxidation step leading to the formation of benzothiazoles. The overall yield of the stepwise reaction was more or less the same as that of the one-step reaction, although the total time required for the stepwise reaction was slightly greater. It was not possible to isolate the intermediate benzothiazoline for all the other substrates as the next steps of oxidation and dehydration were very fast leading to the formation of benzothiazoles (the ultimate products in all cases). Stopping the reaction at various stages resulted in the formation of a mixture of benzothiazoline and benzothiazole of varied percentage compositions (done for 4-methoxy

Table 2

Synthesis of 2-aryl and 2-alkyl-benzothiazolines by Dowex 50W in water both under aerobic and anaerobic conditions.

Entry	*Z* (Scheme 2)	Time (h)	Yield (%)(4)	Observed mp (°C)	Literature mp (°C)	References
1	1s: (2-OH)C_6H_4	06	(i) s: 90	141–142	141–144	[9,17]
2	1n: (2-Cl)C_6H_4	02	(i) n: 85	76	Not reported	[18]
3	1f: (4-NO_2)C_6H_4	01	(i) f: 87	115–117	117–118	[19]
4	t: $-(CH_2)_2CH_3$	06	(ii) t: 50			[20]
5	u: $-CH_2CH_3$	07	(ii) u: 55			[20]

benzaldehyde) [benzothiazoline: benzothiazole = 43:57 (obtained by the ^{1}H NMR integration of the methoxy peaks after 2 h and benzothiazoline: benzothiazole = 26:74 after 6 h].

Thus, Dowex 50W catalyses both the steps; the formation of the benzothiazoline ring and the formation of benzothiazole from benzothiazoline. Carrying out the reaction in argon (truly oxygen free) atmosphere, results in the isolation of benzothiazolines (for 2-chloro and 4-nitro benzaldehydes). Thus, the presence of the aerial oxygen is essential for the benzylic oxidation (C—H to C—OH) step, which is the penultimate one for benzothiazole formation. Without Dowex 50W, the reaction just initializes to 20% formation of the benzothiazoline along with unreacted aldehyde, which then never proceeds further. Thus, Dowex 50W has a definitive catalytic role toward benzothiazole formation. The reaction is widely applicable to a variety of substrates; nitro, methoxy, chloro, bromo, and hydroxy groups on the aryl nucleus perform smooth reactions (Table 1). With aliphatic aldehydes, the reaction stops at the benzothiazoline stage (done with *n*-propanal and *n*-butanal, Table 2), probably because of lower stability of the resultant benzothiazole (absence of conjugation with the aromatic ring).

CONCLUSIONS

This procedure of the synthesis of 2-aryl-benzothiazoles by Dowex 50W in aqueous medium in one-pot operation is a green, highly efficient, and cost effective method than the existing procedures. We hope that our method will be highly beneficial to both academic and industrial processes, being a highly general one with varied substituents in the aromatic aldehydes.

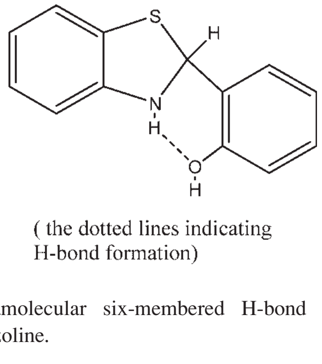


Figure 1. Intramolecular six-membered H-bond formation in 2-phenylbenzothiazoline.

EXPERIMENTAL

A typical experimental procedure is as follows: A mixture of 2-aminothiophenol (5 mmol), aromatic aldehyde (5 mmol), and Dowex 50W (10 mol %) were stirred in water (4 mL) at 70°C for the specified time period (Table 1), till the TLC showed the absence of the starting aldehyde. The reaction mixture was cooled, diluted with ethyl acetate (20 mL), filtered to remove Dowex 50W and extracted the aqueous part with ethyl acetate (2 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude products were purified by crystallization from ethyl acetate and petroleum ether (60–80°C) to afford the 2-aryl-benzothiazoles (or 2-aryl-benzothiazolines) in excellent yields. All the products were characterized by their melting points, IR, ^{1}H NMR, and ^{13}C NMR spectral analyses. The data for a few selected compounds are given below:

2-(2′-Methoxyphenyl)-benzothiazole. (Table 1, entry 3): IR (KBr): 3435, 2932, 2372, 1586, 1458, 1427, 1286, 1246, 1013, and 754 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ: 8.51 (dd, *J* = 7.9 Hz and 1.7 Hz, 1H, C$_4$-H), 8.07 (dt, *J* = 7.8 Hz and 1.0 Hz, 1H, C$_7$-H), 7.89 (dt, *J* = 7.4 Hz and 0.6 Hz, 1H, C$_{6'}$-H), 7.48–7.38 (m, 2H, C$_5$-H and C$_6$-H), 7.33 (dt, *J* = 7.5 Hz and 1.1 Hz, 1H, C$_{4'}$-H), 7.10 (dt, *J* = 7.8 Hz and 1.1 Hz, 1H, C$_{5'}$-H), 7.02 (dd, *J* = 8.0 Hz and 0.7 Hz, 1H, C$_{3'}$-H), 4.00 (s, 3H, OMe); ^{13}C NMR (CDCl$_3$, 75 MHz), δ: 163.1, 157.2, 152.2, 136.1, 131.7, 129.5, 125.8, 124.5, 122.8, 122.3, 121.1, 121.1, 111.7, 55.7.

2-(4′-Hydroxyphenyl)-benzothiazole. (Table 1, entry 7): IR (KBr): 3436, 2366, 1601, 1479, 1308, 1256, 1171, 1025, 832, and 760 cm^{-1}; ^{1}H NMR (DMSO-*d*$_6$, 300 MHz) δ: 10.23 (brs, 1H, OH), 8.07 (brd, *J* = 7.9 Hz, 1H, C$_4$-H), 7.98 (brd, *J* = 8.1

Scheme 3

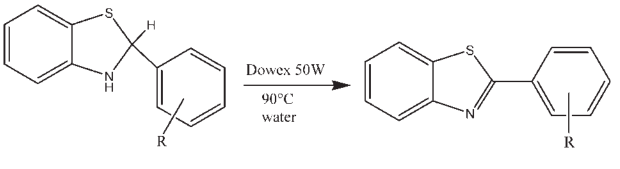


Table 3

Conversion of 2-arylbenzothiazolines to 2-arylbenzothiazoles under aerobic conditions (does not take place without oxygen).

Entry	R [4(i)] (Scheme 3)	Time (h)	Yield (%) (overall) (w.r.t. starting aldehyde) (3)	Observed mp (°C)	Literature [7b] mp (°C)
1	s: 2-OH	25	s: 70	124–126	127–128
2	n: 2-Cl	10	n: 85	84–85	82
3	f: 4-NO_2	05	f: 88	228–230	229–230

Hz, 1H. C_7-H), 7.94 (d, J = 8.6 Hz, 2H, $C_{2'}$-H and $C_{6'}$-H), 7.50 (brt, J = 7.1 Hz, 1H, C_5-H), 7.40 (brt, J = 7.6 Hz, 1H, C_6-H), 6.94 (d, J = 8.6 Hz, 2H, $C_{3'}$-H and $C_{5'}$-H); ^{13}C NMR (DMSO-d_6, 75 MHz), δ: 167.9, 161.0, 154.2, 134.6, 129.5, 126.9, 125.4, 124.5, 122.8, 122.6, 116.6.

2-(2′-Hydroxyphenyl)-benzothiazoline. (Table 2, entry 1): IR(KBr): 3256, 1585, 1484, 1460, 1232, 755 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 9.87 (s, 1H. OH), 7.39 (dd, J = 7.6 Hz and 1.5 Hz, 1H, $C_{6'}$-H), 7.11 (dt, J = 7.6 Hz and 1.2 Hz, 1H, $C_{4'}$-H), 6.94 (brd, J = 7.3 Hz,1H, C_7-H), 6.89–6.76 (m, 3H, C_4-H, C_5-H and C_6-H), 6.67 (dd, J = 7.8 Hz and 0.7 Hz, 1H, $C_{3'}$-H), 6.57 (dt, J = 7.5 Hz and 1.1 Hz, 1H, $C_{5'}$-H), 6.48 (d, J = 1.4 Hz, 1H, C_2-H), [the absence of the NH proton around δ (4–4.5) indicates that it is H-bonded to the more electronegative O-atom]; ^{13}C NMR (DMSO-d_6, 75 MHz), δ: 154.0, 148.3, 130.1, 129.1, 126.4, 125.7, 125.6, 121.7, 119.3, 119.0, 115.4, 109.1, 63.5.

2-(2′-Hydroxyphenyl)-benzothiazole. (Table 3, entry 1): IR (KBr): 3437, 2923, 2372, 1580, 1477, 1210, 742 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 12.52 (brs, 1H, OH), 8.00 (brd, J = 8.1 Hz, 1H, C_4-H), 7.91 (brd, J = 7.7 Hz, 1H, C_7-H), 7.71 (dd, J = 7.9 Hz and 1.5 Hz, 1H, $C_{6'}$-H), 7.51 (dt, J = 7.2 Hz and 1.2 Hz, 1H, C_5-H), 7.40 (dt, J = 7.4 Hz and 1.1 Hz, 2H, C_6-H and $C_{4'}$-H), 7.11 (dd, J = 8.4 Hz and 1.1 Hz, 1H, $C_{3'}$-H), 6.97 (dt, J = 7.5 Hz and 1.0 Hz, 1H, $C_{5'}$-H); ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 169.4, 158.0, 151.9, 132.8, 132.6, 128.4, 126.7, 125.6, 122.2, 121.5, 119.5, 117.9, 116.8.

2-(2′-Chlorophenyl)-benzothiazoline. (Table 2, entry 2): IR(KBr): 3344, 3063, 2371, 1573, 1462, 1240, 1033 and 734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.77–7.71(m, 1H, $C_{3'}$-H), 7.40–7.31(m, 1H, C_4-H), 7.28–7.18 (m, 2H, $C_{4'}$-H and $C_{6'}$-H), 7.04 (dd, J = 7.5 Hz and 0.9 Hz, 1H, C_7-H), 6.95 (dt, J = 9.0 Hz and 1.3 Hz, 1H, C_5-H), 6.79–6.71 (m, 2H, C_6-H and $C_{5'}$-H), 6.66 (s, 1H, C_2-H), 4.43 (brs, 1H, NH) ; ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 146.1, 140.0, 131.6. 129.6, 129.3, 127.4, 127.3, 126.3, 125.5, 122.0, 121.1, 110.4, 65.6.

2-(2′-Chlorophenyl)-benzothiazole. (Table 3, entry 2): IR (KBr): 3435, 2363, 1423, 1266, 1053 and 755 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.21–8.18 (m, 1H, $C_{3'}$-H), 8.12 (dd, J = 9.0 Hz and 0.6 Hz, 1H, C_4-H), 7.94 (dd, J = 7.8 Hz and 0.6 Hz, 1H, C_7-H), 7.54–7.49 (m, 2H, $C_{4'}$-H and $C_{6'}$-H), 7.44–7.38 (m, 3H, C_5-H, C_6-H and $C_{5'}$-H); ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 164.2, 152.5, 136.1, 132.7, 132.3, 131.7, 131.1, 130.8, 127.1, 126.3, 125.4, 123.5 and 121.4.

2-(4′-Nitrophenyl)-benzothiazoline. (Table 2, entry 3): IR (KBr): 3333, 2371, 1595, 1515, 1340, 853 and 756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.22 (dt, J = 8.8 Hz and 1.9 Hz, 2H, $C_{3'}$-H and $C_{5'}$-H), 7.68 (dt, J = 8.5 Hz and 2.3 Hz, 2H, $C_{2'}$-H and $C_{6'}$-H), 7.06 (dd, J = 6.5 Hz and 1.0 Hz, 1H, C_4-H), 7.00 (dt, J = 6.4 Hz, and 1.3 Hz, 1H, C_5-H), 6.81(dt, J = 6.4 Hz and 1.1 Hz, 1H, C_6-H), 6.75 (dd, J = 6.7 Hz and 0.8 Hz, 1H, C_7-H), 6.43 (d, J = 3.7 Hz, 1H, C_2-H), 4.52 (s, 1H, NH) ; ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 149.3, 147.9, 145.8, 127.2, 126.0, 125.9, 124.1, 121.8, 121.5, 110.5, 68.3.

2-(4′-Nitrophenyl)-benzothiazole. (Table 3, entry 3): IR (KBr): 3436, 2372, 1520, 1343, 852 and 764 cm^{-1}; ^{1}H NMR, $CDCl_3$, 300 MHz) δ: 8.43–8.35 (m, 4H, $C_{3'}$-H, $C_{5'}$-H, $C_{2'}$-H and $C_{6'}$-H), 8.24 (dd, J = 7.7 Hz and 1.0 Hz, 1H, C_4-H), 8.16 (dd, J = 7.7 Hz and 0.9 Hz, 1H, C_7-H), 7.63 (dt, J = 6.0 Hz and 1.3 Hz, 1H, C_5-H), 7.55 (dt, J = 6.9 Hz and 1.4 Hz, 1H, C_6-H) ; ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 165.4, 154.0, 149.3, 138.8, 135.6 128.9, 127.6, 126.9, 125.1, 124.0, 123.1.

2-(*n*-Propyl)-benzothiazoline. (Table 2, entry 4): IR (KBr): 3355, 2958, 2930, 2872, 2360, 1583, 1468, 1402, 1119 and 741 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.04 (dd, J = 7.5 Hz and 1.2 Hz, 1H, C_4-H), 6.88 (dt, J = 6.0 Hz and 1.3 Hz, 1H, C_5-H), 6.71 (dt, J = 6.0 Hz and 1.2 Hz, 1H, C_6-H), 6.61 (dd, J = 6.0 Hz and 1.1 Hz, 1H, C_7-H), 5.24 (t, J = 6.6 Hz, 1H, C_2-H), 1.87–1.77 (m, 2H, -CH_2-CH_2-CH_3), 1.49–1.36 (m, 2H, -CH_2-CH_2-CH_3), 0.94 (t, J = 7.3 Hz, 3H, -CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 146.6, 127.5, 125.0, 121.9, 120.7, 110.7, 68.5, 40.6, 19.3, 13.7.

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The Reaction of (Chlorocarbonyl)phenyl Ketene with Enaminones: A Novel Synthesis of Some 5-Acyl-4-hydroxy-2-(1*H*)-pyridinones and 7-Hydroxy-5-oxo-1,4-diazepin Derivative

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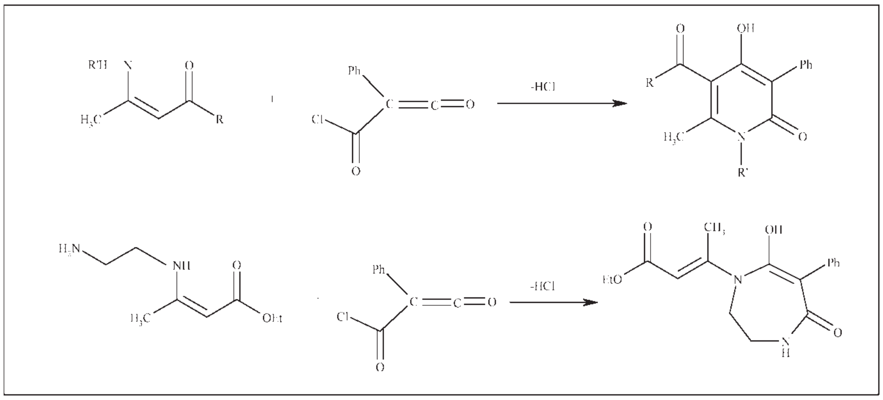

A series of substituted 5-acyl-4-hydroxy-2-(1*H*)-pyridinone derivatives has been prepared in a one-step procedure from condensation of (chlorocarbonyl)phenyl ketene with some enaminones which were prepared from 1,3-diketones, such as 2,4-pentanedione, 1-phenyl-1,3-butanedione, and ethyl acetoacetate in boiling toluene as a solvent. A mechanism is presented to account for the formation of the products. The overall sequence provides a simple and efficient route to prepare 3,4,5,6-tetrasubstituted 2-(1*H*)-pyridinone in good to excellent yields and in a short experimental time.

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INTRODUCTION

Heterocycles having a 2-pyridinone framework are an extensively studied class of compounds, owing partly to their diverse biological activities such as antibacterial [1] and antifungal [2] agents for free radical scavengers [3]. Ring fused 2-pyridinones have also attracted attention as lead compounds for the preparation of selective anticancer drugs [4,5], antiviral agents [6], angiotensin-converting enzyme (ACE) inhibitors [7], as well as inhibitors of A β-peptide aggregation [8], which is believed to play an important role in amyloid formation in Alzheimer's disease. In addition, dihydro and tetrahydro derivatives of 2-pyridinones have been applied as scaffolds for the construction of constrained amino acids [9,10]. With all these diverse properties in mind, medicinal chemists often incorporate these motifs in the design of novel biologically active molecules.

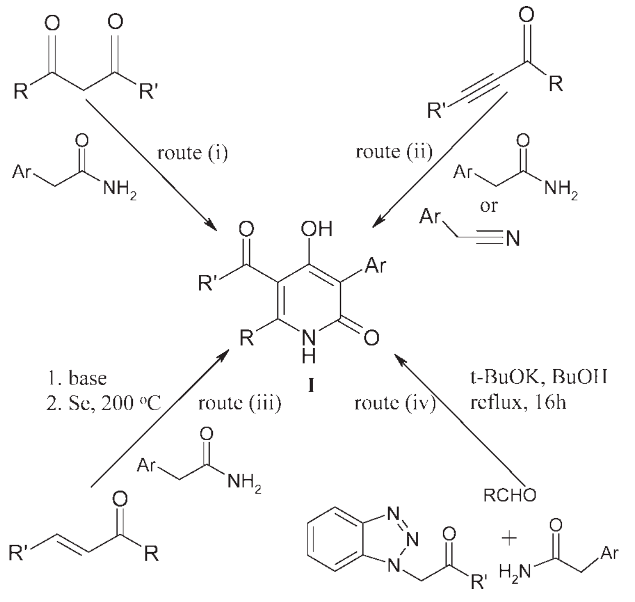
Ever since the first synthesis of 2-pyridinones was reported *via* a ferricyanide-mediated oxidation of pyridinium salts [11], many different methods for constructing these heterocycles in solution have appeared in the literature. Some of these reports include intramolecular Dieckmann like condensations [12], Michael additions [13,14], as well as cycloaddition [15] and cyclization procedures [16].

Fewer general methods exist for the preparation of 2-pyridinones substituted with aryl substituents and electron withdrawing groups such as CN, COR, COOR, and CONR2 at positions C3 and C5. Reported of 5-acyl-3-aryl-2-pyridinones usually include (Scheme 1) (i) reaction of 1,3-diketones with 2-arylacetamides (yields of **I** *ca*. 40%) [17]; (ii) Michael addition of arylacetamides or arylacetonitrile to 1,3-diaryl-2-propyne-1-ones affording products with limited diversity (3,4,6-triaryl substituted pyridinones in yields about 20%) [18]; (iii) Michael addition of 2-arylacetamides to 1,3-diaryl-2-propene-1-ones, is followed by cyclization subsequent oxidative aromatization of the intermediate dihydropyridinones with selenium at the high-temperature to yield 76–94% of the product I [19]; (iv) and finally synthesis *via* one-step [1 + 2 + 3] reactions of an aldehyde, α-benzotriazolyl ketone and arylacetamides [20].

RESULTS AND DISCUSSION

In continuing our interest in the synthesis of heterocyclic compounds by using chlorocarbonyl ketenes and

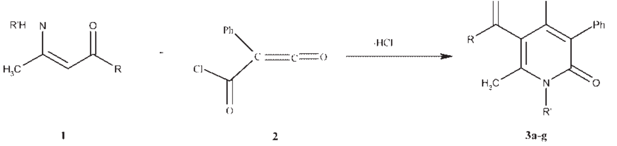
Scheme 1



1,3-binucleophiles such as 1,3-diketones [21], amides [22,23] and thioamides [24]; in this article we wish to report a one-pot synthesis of 5-acyl-4-hydroxy-2-(1*H*)-pyridinone derivatives which were prepared in a one-step procedure from readily available (chlorocarbonyl)-phenyl ketene and enaminones as 1,3-binucleophile. This method provides an easy route to prepare 2(1*H*)-pyridinones in good to excellent yields and short experimental time (Scheme 2).

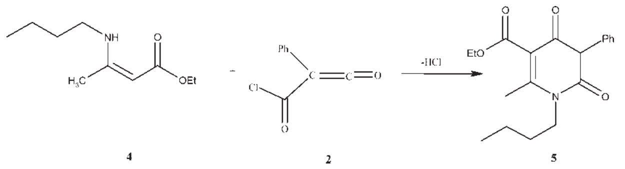
Enaminones are versatile synthetic intermediatates that combine the ambident nucleophilicity of enamines with the ambident electrophilicity of enones [25]. There are many reports in the literature on the functionalization of enaminone by the introduction of different substituents on the nitrogen, the α-carbon and the β-carbonylic carbon atoms. These derivatives have been extensively used for the preparation of a variety of heterocyclic systems including some natural products and analogues [26]. Thomas Kappe *et al.* [27], have reported

Scheme 2



3a: R= CH_3, R'= C_6H_5
3b: R= CH_3, R'= 4-$MeOC_6H_5$
3c: R= CH_3, R'= 4-$(Me)_2NC_6H_5$
3d: R= CH_3, R'= 4-MeC_6H_5
3e: R= C_6H_5 , R'= isoButyl
3f: R= C_6H_5 , R'= n-Butyl
3g: R= CH_3, R'= H

Scheme 3



the synthesis of 5-acyl-4-hydroxy-2-(1*H*)-pyridinone derivatives from the reaction of enaminones with dialkyl malonates under harsh experimental conditions [low yields (42–68%) and also long reaction times].

The chemical importance and diversity of pyridinones have made these compounds important synthetic goals and have stimulated new methods and reagents for the preparation of these heterocyclic compounds. In an effort to extend the scope and generality of the condensation reaction (Scheme 1) (chlorocarbonyl)phenyl ketene **2** was treated with enaminones **1**. The only product formed under these conditions was 5-acyl-4-hydroxy-3-phenyl-2-(1*H*)-pyridinones **3** in excellent yields in a short experimental time.

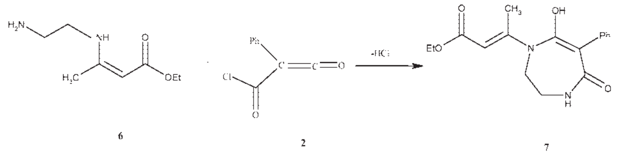
In this case, it was also found that the reaction of ethyl-3-(butylamino)-2-butenoate **4** with (chlorocarchloro-carbonyl)phenyl ketene **2** produce the corresponding pyridinone **5** (Scheme 3). It is pertinent to note that with the same experimental condition as the previous reaction different tautomer was formed.

The cycloaddition reaction of 4-[(2-aminoethyl) amino]-3-penten-2-one **6** with (chlorocarbonyl)phenyl ketene **2** resulted in the formation of ethyl (*E*)-3-(7-hydroxy-5-oxo-6-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-diazepin-1-yl)-2-butanoate **7** as the only product (Scheme 4).

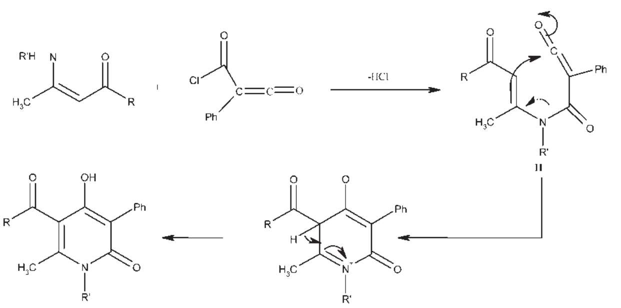
On the basis of this report, (chlorocarbonyl)aryl ketenes undergo a degenerate 1,3-shift of chlorine, as determined by ^{13}C NMR spectroscopy [28]. On the basis of our results, which was aforementioned, a plausible mechanism has been proposed for the reactions of (chlorocarbonyl)phenyl ketene with enaminones to yield 2-(1*H*)-pyridinone derivatives, as shown in Scheme 5. Initially, the NH group of enaminone as a good nucleophile will attack the acyl chloride of ketene, followed by ring closure of intermediate **2** to produce the product.

The structure of **3a-g** and compounds **5** and **7** were determined on the basis of their mass spectra, ^1H and

Scheme 4



Scheme 5



^{13}C NMR and IR spectroscopic data. The ^{1}H NMR and ^{13}C NMR spectra of 4-hydroxy-3,6-disubstituted-2(1*H*)-pyridinone derivatives **3a-d** exhibited only one tautomer.

The ^{1}H NMR spectrum of **3a** showed four kinds of proton signals. One signal quite downfield (δ 10.70 ppm) which is the proton of enol OH and a multiplet (δ = 7.62–7.10) for the aromatic protons (10 H) along with two signals at (δ = 2.33 and 2.17 ppm) which were identified as an acyl group in position 5 and the other methyl group in position 6. The ^{13}C NMR and mass spectra are also in accordance with the proposed structure.

We have shown that the condensation reaction of (chlorocarbonyl)phenyl ketene with enaminones occurs efficiently in boiling toluene as a solvent, providing a convenient and rapid synthesis of 4-hydroxy-3,4,6-tri substituted-2(1*H*)-pyridinone in high yield, by a simple procedure and short experimental time. Furthermore, the products are solid and precipitate out from the reaction mixture and their purifications are simple.

EXPERIMENTAL

(Chlorocarbonyl)phenyl ketene was prepared according to the literature procedure [29]. The enaminones are known and were prepared according to the general procedure reported in the literature [30].

Toluene, hexane, diethyl ether, and THF were dried over sodium and distilled prior to use. Melting points were measured on a calibrated Gallenkamp melting point apparatus. IR spectra were measured with a Mattson 1000 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively. Mass spectra were recorded on a MS-QP2000A Shimadzu mass spectrometer operating at an ionization potential of 70 eV.

General procedure (3a-d). To a stirred solution of corresponding enaminone (2 mmol) in 20 mL dry boiling toluene, a mixture of 0.36 g (chlorocarbonyl)phenyl ketene (2 mmol) in 5 mL dry THF was added dropwise over 2 min. The product was formed immediately as a color precipitate. The reaction mixture was cooled and the solid product was collected and recrystallized from dry ethyl acetate hexane.

5-Acetyl-4-hydroxy-6-methyl-1,3-diphenyl-2(1*H*)-pyridinone (3a). A 0.60 g red crystals, yield 95%, mp 224–226°C (dec.); IR (KBr): 3200–2500 (broad peak, OH), 1716, 1641 (C=O), 1567 (C=C) cm^{-1}; ^{1}H NMR (DMSO): δ 10.7 (1H, broad, OH), 7.62–7.10 (10H, m, arom), 2.33(3H, s, CH$_3$), 2.17(3H, s, CH$_3$); ^{13}C NMR (DMSO): δ 200.36, 163.90, and 163.13, 161.61, 131. 88, 131.15, 130.81, 129.65, 128.05, 128.00, 127.44, 123.28, 115.38, 103.79, 32.20, and 19.26; MS, *m*/*z* (relative intensity %): 319(M$^+$, 4), 291(5), 244(18), 216(32), 198(17), 160(17), 145(8), 127(15), 118(30), 93(38), 77(28), 65(20), 43(100). Anal. Calcd. For $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39%. Found: C, 74.89; H, 5.46; N, 4.16%.

5-Acetyl-4-hydroxy-1-(4-methoxy-phenyl)-6-methyl-3-phenyl-2(1*H*)-pyridinone (3b). A 0.61 g red crystals, yield 88%, mp 230–232°C (dec.); IR (KBr): 3200–2550 (broad peak, OH), 1741, 1666(C=O), 1517 (C=C) cm^{-1}; ^{1}H NMR (DMSO): δ 10.58(1H, broad, OH), 7.38–7.00 (9H, m, arom), 3.74 (3H, s, OCH$_3$), 2.49(3H, s, CH$_3$), 2.32(3H, s, CH$_3$); ^{13}CNMR (DMSO): δ 200.37, 163.89 and 163.15, 161.63, 158.75, 131.10, 130.65, 128.06, 128.51, 127.46, 124.11, 115.41, 114.79, 103.40, 55.45, 32.21, and 19.27; MS, *m*/*z* (relative intensity %): 349 (M$^+$, 2), 244 (25), 216(70), 198(18), 190 (16), 127(20), 123 (100), 118(35), 85(48), 80(35), 63(17), 43(90). Anal. Calcd. For $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01%. Found: C, 71.98; H, 5.50; N; 3.70%.

5-Acetyl-1-(4-dimethylaminophenyl)-4-hydroxy-6-methyl-3-phenyl-2(1*H*)-pyridinone (3c). A 0.62 g yellow crystals, yield 86%, mp 235–238°C (dec.); IR (KBr): 3200–2550 (broad peak, OH), 1741, 1666 (C=O), 1535 (C=C) cm^{-1}; ^{1}H NMR (DMSO): δ 10.37 (1H, broad, OH), 7.78–7.25 (9H, m, arom), 3.03 (6H, s, 2CH$_3$), 2.05 (3H, s, CH$_3$), 1.93 (3H, s, CH$_3$), 2.05 (3H, s, CH$_3$), 1.93 (3H, s, CH$_3$); ^{13}CNMR (DMSO): δ 200.10, 168.74, and 162.25, 159.67, 146.83, 132.81, 130.84, 129.34, 127.78, 121.34, 110.17, 100.17, 42.67, 32.66, 19.38; MS, *m*/*z* (relative intensity %): 362 (M$^+$, 40), 347(5), 334(10), 294(15), 203(65), 187 (42), 178(28), 161(38), 135(95), 121(38), 105(25), 91(100), 77(48), 65(68), 50(27). Anal. Calcd. For $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73%. Found: C, 72.60; H, 6.20; N, 7.53%.

5-Acetyl-4-hydroxy-6-methyl-3-phenyl-1-*p*-tolyl-2(1*H*)-pyridinone (3d). A 0.61 g red crystals, yield 92%, mp 228–232°C (dec.); IR (KBr): 3200–2550 (broad peak, OH), 1716, 1641 (C=O), 1567 (C=C) cm^{-1}; ^{1}H NMR (DMSO): δ 10.63 (1H, broad, OH), 7.49–6.88 (9H, m, arom), 2.32 (3H, s, CH$_3$), 2.28 (3H, s, CH$_3$), 2.14 (3H, s, CH$_3$); ^{13}C NMR (DMSO): δ 200.37, 163.97 and 163.16, 161.60, 137.56, 130.81, 130.01, 129.05, 128.87, 128.18, 128.04, 123.16, 115.36, 103.38, 32.21, 20.52, and 19.30; MS, *m*/*z* (relative intensity %): 333(M$^+$, 5), 244(20), 216(25), 178(20), 149(18), 135(50), 121(26), 105(100), 91(82), 77(43), 58(70), 51(27). Anal. Calcd. For $C_{21}H_{19}NO_3$: C, 75.66; H, 5.74; N, 4.20%. Found: C, 75.30; H, 5.69; N; 3.85%.

5-Benzoyl-4-hydroxy-1-isobutyl-6-methyl-3-phenyl-2(1*H*)-pyridinone (3e). A 0.65 g purple crystals, yield 90%, mp 230–232°C (dec.); IR (KBr): 3200–2550 (broad peak, OH), 1716, 1641 (C=O), 1535 (C=C) cm^{-1}; ^{1}H NMR (DMSO): δ 10.80 (1H, broad, OH), 7.58–7.27 (10H, m, arom), 3.51 (2H, d, ^3J = 7.00 Hz, CH$_2$), 2.25 (3H, s, CH$_3$), 1.88 (1H, m, CH), 0.91 (3H, d, $^3J = 6.00$ Hz, CH_3), 0.76 (3H, d, $^3J = 6.00$ Hz, CH_3); ^{13}CNMR (DMSO): δ 200.28, 163.21, and 162.50, 159.30, 131.54, 131.06, 130.79, 129.03, 128.90, 128.32, 128.10, 127.26, 116.23, 104.57, 45.59, 32.21, 26.30, 19.80, and 19.79; MS, *m*/*z* (relative intensity %): 361 (M^+, 7), 346(4), 306(38), 278 (30), 200(20), 189(15), 129(13), 118(18), 105(100), 89(22), 77(90), 63(14), 51(20). Anal. Calcd. For $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88%. Found: C, 76.08; H, 6.10; N, 3.56%.

5-Benzoyl-1-butyl-4-hydroxy-6-methyl-3-phenyl-2(1*H*)-pyridinone (3f). A 0.65 g purple crystals, yield 91%, mp 220–222°C (dec.); IR (KBr): 3200–2550 (broad peak, OH), 1716, 1641(C=O), 1515(C=C) cm^{-1}; ^{1}H NMR (DMSO): δ 10.50 (1H, broad, OH), 7.54–7.26 (10H, m, arom), 2.71 (2H, t, $^3J =$ 5.10 Hz, CH_2), 2.27 (3H, s, CH_3), 1.52 (2H, m, CH_2), 1.30 (2H, m, CH_2), 0.83 (3H, t, $^3J = 5.00$ Hz, CH_3); ^{13}CNMR (DMSO): δ 200.95, 164.88, and 162.03, 158.07, 132.36, 131.94, 130.84, 130.69, 128.78, 128.16, 127.76, 126.76, 117.83, 103.16, 40.33, 32.27, 28.97, 19.14, and 13.45; MS, *m*/*z* (relative intensity %): 361 (M^+, 4), 346(5), 306(60), 278 (35), 200(18), 189(15), 147(10), 129(10), 118(18), 105(100), 89(20), 77(84), 63(10), 51(20), 43(37), 41(10). Anal. Calcd. For $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88%. Found: C, 76.13; H, 6.30; N, 3.58%.

5-Acetyl-4-hydroxy-6-methyl-3-phenyl-2(1*H*)-pyridinone (3g). A 0.46 g orange crystals, yield 96%, mp 258–260°C (dec.); IR (KBr): 3100–2550 (broad peak, OH), 1741, 1666 (C=O), 1527 (C=C)cm^{-1}; ^{1}H NMR (DMSO): δ 12.90(1H, s, OH), 11.92 (1H, s, NH), 7.40–7.23(5H, m, arom), 2.58 (6H, s, $2CH_3$). ^{13}C NMR (DMSO): δ 203.88, 165.08, and 162.57, 154.73, 133.59, 131.72, 128.28, 127.32, 109.69, 109.48, 33.57, and 21.57; MS, *m*/*z* (relative intensity %): 243 (M^+, 12), 216(19), 148(35), 118(25), 91(100), 77(35), 65(37), 51(23).

Ethyl 1-butyl-2-methyl-4,6-dioxo-5-phenyl-1,4,5,6-tetrahydro-3-pyridinecarboxylate (5). A 0.28 g yellow crystals, yield 75%, mp 72–74°C. IR (KBr): 1740, 1717 and 1650 (C=O) 1530 (C=C) cm^{-1}; ^{1}H NMR (DMSO): δ 7.41–7.07 (5H, m, arom), 4.47 (1H, s, malonyl-H on C_5), 4.14 (2H, t, ^3J $= 7.00$ Hz, OCH_2), 4.06 (2H, t, $^3J = 6.00$ Hz, NCH_2), 2.52 (3H, s, CH_3), 1.68 (2H, m, CH_2), 1.42 (2H, quin, $^3J = 6.50$ Hz, CH_2), 1.21 (3H, t, $^3J = 5.00$ Hz, CH_3), 0.96 (3H, t, $^3J =$ 5.00 Hz, CH_3); ^{13}C NMR (DMSO): δ 170.46 and 164.87, 164.53, 162.59, 147.05, 129.83, 129.18, 128.69, 128.11, 62.04, 57.00, 45.79, 30.21, 22.68, 19.66, 14.04, and 13.66; MS, *m*/*z* (relative intensity %): 330 (M+1, 9), 329 (M^+, 35), 314(82), 283(80), 288(35), 227(92), 213(28), 199(25), 128(23), 91(100), 77(15), 67(24). Anal. Calcd. For $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25%. Found: C, 69.03; H, 7.14; N, 4.07%.

Ethyl (*E*)-3-(7-hydroxy-5-oxo-6-phenyl-2,3,4,5-tetra hydro-1*H*-1,4-diazepin-1-yl)-2-butanoate (7). A 0.27 g Yellow crystals, yield 81%, mp 215–216°C. IR (KBr): 3100–2550 (broad peak, OH), 1721, 1655 (C=O), 1530 (C=C) cm^{-1}; ^{1}H NMR (DMSO): δ 10.45(1H, s, OH), 8.35 (1H, broad, NH), 7.38–7.26 (5H, m, arom), 4.31 (2H, q, $^3J = 7.50$ Hz, OCH_2), 4.19 (1H, s, =CH), 3.65 (4H, m, CH_2), 2.62 (3H, s, CH_3), 1.29 (3H, t, $^3J = 7.50$ Hz, CH_3); ^{13}CNMR (DMSO): δ 170.46 and 164.87, 164.53, 162.59, 147.05, 129.83, 129.18, 128.69, 128.11, 62.04, 57.00, 45.79, 30.21, 22.68, 19.66, 14.04, and 13.66; MS, *m*/*z* (relative intensity%): 330 (M+1, 9), 329(M^+, 35), 314(82), 283(80), 288(35), 227(92), 213(28), 199(25), 128(23), 91(100), 77(15), 67(24). Anal. Calcd. For $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.85%. Found: C, 64.23; H, 6.25; N, 8.55%.

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Polystyrene-Supported Palladium(II) Ethylenediamine Complex: A Highly Active and Recyclable Catalyst for the Synthesis of 2-Benzylimidazo[2,1-*b*]pyridines Through Heteroannulation of Acetylenic Compounds

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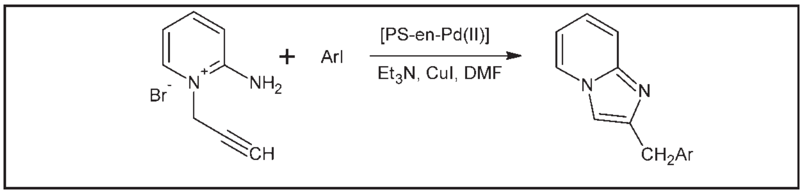

The polymer-supported palladium(II) ethylenediamine [PS-en-Pd(II)] complex is a highly active catalyst for the heterocyclization that takes place during the Sonogashira reaction between an aryl iodide and 2-amino-1-(2-propynyl)pyridinium bromide. This heterogeneous palladium catalyst can readily be recovered from the reaction medium by simple filtration and reused without a significant loss in its activity.

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INTRODUCTION

Sonogashira reaction, the palladium-catalyzed cross-coupling reaction of terminal alkynes with aryl and vinyl halides, is one of the most important, powerful, and versatile tools in organic synthesis, and it has been widely applied to diverse areas such as natural product synthesis and material science [1]. The reaction generally proceeds in the presence of a homogeneous palladium catalyst, which makes the catalyst recovery a tedious operation and might result in unacceptable palladium contamination of the product. From the standpoint of green chemistry, the development of more environmentally benign conditions for the reaction, for example, the use of a heterogeneous palladium catalysts' would be desirable [2].

So far, cross-linked polystyrene or silica-supported palladium catalysts have been used for the Sonogashira reaction [3]. Unfortunately, they often result in lower catalytic activity compared with their soluble counterparts. To overcome this limitation, a novel methodology for creating insoluble and highly active catalysts is needed. Our approach was guided by three imperatives: (1) the support should be easily accessible; (2) starting with readily available and inexpensive reagents; and (3) the ligand anchored on the support should be air stable at room temperature, which should allow its storage in normal bottles with unlimited shelf life. To date, a few palladium complexes on functionalized polystyrene support have been prepared and successfully used in organic reactions [4]. However, to the best of our knowledge, there has been no examples involving arylation of imidazopyridine by [PS-en-Pd(II)] catalyzed (Sonogashira coupling) reactions described to date.

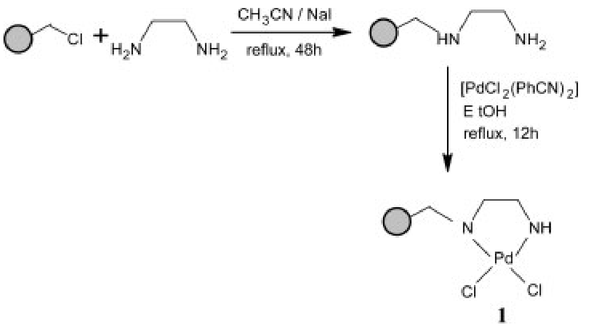
In continuation of our recent studies on the synthesis of fused heterocycles and the Pd-catalyzed reactions of acetylenes leading to heterocyclic compounds of biological significance [5], we became interested in developing a novel synthesis route to 2-substituted imidazo[1,2-*a*]pyridines. In this article, we wish to report the synthesis of the first polystyrene-supported palladium(II) ethylenediamine complex, abbreviated as PS-en-Pd(II), and its catalytic properties in the Sonogashira coupling reaction for the synthesis of imidazo[1,2-*a*]pyridines [6]. The supported catalyst could be reused several times without a significant degradation in its catalytic activity.

RESULTS AND DISCUSSION

We used the well-known chloromethylated polystyrene cross-linked with 2% divinylbenzene as support, because it is flexible enough and allows metallic atoms to be graft on *via* the ligands that are attached to the polymer beads. Reaction of the polystyrene resin with ethylenediamine in acetonitrile under reflux and the subsequent reaction of the aminated polystyrene with a solution of $[PdCl_2(C_6H_5CN)_2]$ in ethanol gave the polymer-supported palladium(II) complex catalyst **1** (Scheme 1).

Successful functionalization of the polymer was confirmed by elemental analysis. The *N* content of the resin was found to be 2.42% (0.82 mmol/g), which indicates

Scheme 1 Polystyrene-supported palladium(II) ethylenediamine complex **1**.



that only 58% of the total chlorines were substituted by amine. The metal loading of the polymer-supported palladium complex, which was determined by neutron activation analysis (NAA), was found to be 4.35% (0.41 mmol/g). In the IR spectrum of the polymer-bound ethylenediamine, the sharp C—Cl peak (due to the —CH_2Cl groups) at 1264 cm^{-1} in the starting polymer was practically omitted or was seen as a weak band after introduction of ethylenediamine and palladium on the polymer. The various IR frequencies for the catalyst were assigned as (Pd—N) $\approx$ 506 cm^{-1}, (C—N) $\approx$ 1100 cm^{-1}, and (N—H) $\approx$ 3400 cm^{-1}.

To evaluate the catalytic activity of the first polymer-supported PS-en-Pd(II) complex, the heterocyclization during Sonogashira coupling of 2-amino-1-(2-propynyl)-pyridinium bromide **3** with the aryl iodides **4a–i** was studied (Scheme 2). The reactions were performed under conditions similar to those used in the corresponding homogenous reactions. The influences of the bases, solvents, amounts of copper(I) iodide, and the catalyst on the catalytic property of the [PS-en-Pd(II)] complex were investigated using the coupling reaction of compound **3** with *o*-iodonitrobenzene. The results are tabulated in Table 1.

Among the bases tested, triethylamine proved to be the most efficient, and among the solvents used, dimethylformamide was the best choice. Increasing the amount of the palladium catalyst could shorten the reaction time, but does not increase the yield (entry 11). Low palladium concentration often prolonged the reaction time and decreased the yield (entries 12 and 13). We also found that with increase in the amount of copper(I) iodide, the reaction yield did not increase (entry 14). No product was obtained under copper-free conditions (entry 15). Copper(I) iodide was found to be an essential cocatalyst.

The reactions had to be carried out under an argon atmosphere, and we had to degas the mixture of DMF and triethylamine prior to use. The experimental results are summarized in Table 2. As it can be seen in this table, reaction of the aryl iodides with compound **3** proceeded smoothly under very mild conditions, giving the corresponding products in excellent yields.

The stability of [PS-en-Pd(II)] was studied in repeated Sonogashira coupling reactions. The coupling reaction of *o*-iodonitrobenzene with compound **3** was chosen as a model substrate to study the catalyst reuse and stability. The catalyst was separated from the reaction mixture after each experiment by filtration, washed with water and acetonitrile, and dried carefully before using it in the subsequent run. The reaction promoted by the fifth recycled catalyst gave **5a** in 75% yield (Table 3, entry 5).

The low yield could be due to the formation of byproducts. For instance, formation of a coupled intermediate without ring formation or ring closure without participation of the aryl group could be responsible for the low yield.

This reusability demonstrates the stability of the heterogeneous catalyst. Although no significant change in the activity of the catalyst was observed, we performed analysis of the catalyst after the fifth run in order to determine any change in the catalyst structure. The nature of the recovered catalyst was traced by IR spectroscopy. The results indicated that the catalyst showed no change in its IR spectrum after reuse for several times.

To determine the absolute amount of the palladium species leached into the solution, the crude reaction mixtures were evaporated to dryness and analyzed by NAA. It was shown that less than 0.5% of the total amount of the original palladium species was lost into the solution during the course of the reaction.

In conclusion, we developed a reusable heterogeneous catalyst [PS-en-Pd(II)] by first reacting the commercially available cross-linked chloromethylated polystyrene with ethylenediamine and the subsequent reaction of the product thus formed with dibenzonitrile palladium chloride. It efficiently catalyzed the heterogeneous Sonogashira coupling followed by cyclization reaction for the syntheses of various 2-substituted imidazopyridines. The

Scheme 2

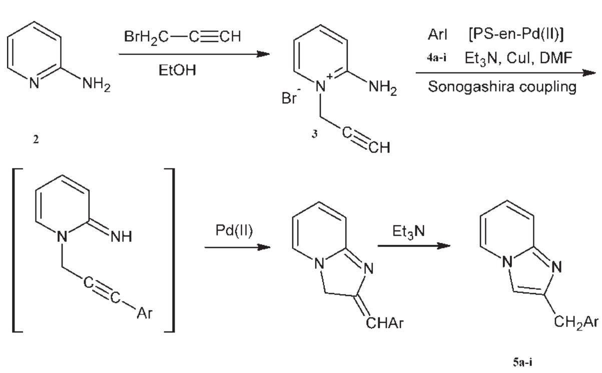


Table 1

Heterocyclization during the Sonogashira coupling of *o*-iodonitrobenzene with compound **3** in the presence of several bases, solvents, and amounts of catalyst.[a]

Entry	Base	Solvent	[PS-en-Pd(II)] (mmol)	CuI (mmol)	Time (hours)	Yield (%)
1	Et_3N	Dioxan	0.03	0.2	14	30
2	Et_3N	CH_3CN	0.03	0.2	16	45
3	Et_3N	DMF	0.03	0.2	12	92
4	Et_3N	Et_3N	0.03	0.2	15	25
5	DIEA	DMF	0.03	0.2	17	60
6	DIEA	DIEA	0.03	0.2	16	50
7	Piperidine	DMF	0.03	0.2	14	35
8	Piperidine	Piperidine	0.03	0.2	16	32
9	Pyrrolidine	DMF	0.03	0.2	14	23
10	Pyrrolidine	Pyrrolidine	0.03	0.2	19	20
11	Et_3N	DMF	0.06	0.4	10	88
12	Et_3N	DMF	0.02	0.12	20	75
13	Et_3N	DMF	0.005	0.03	24	62
14	Et_3N	DMF	0.03	0.3	14	87
15	Et3N	DMF	0.03	0	24	0

[a] All reactions were performed using 1.5 mmol of **3**, 1.0 mmol of *o*-iodonitrobenzene, 0.06 mmol of PPh_3, 3.0 mmol of base, and 5 mL of solvent at room temperature.

catalyst could be reused five times with reasonable catalytic activity on the fifth cycle. The advantages of our heterogeneous catalytic system over others are as follows: (1) the catalyst could be conveniently prepared from commercially available reagents; and (2) excellent performance and reusability of the catalyst.

EXPERIMENTAL

All the reagents used were of commercial reagent grade. Chloromethylated polystyrene (4–5% Cl and 2% cross-linked with divinylbenzene) was a Merck product. Scanning electron micrographs of the catalyst and polymer were taken on a SEM Philips XL 30. The IR spectra were obtained as potassium bromide pellets in the range 400–4000 cm^{-1} on a Shimadzo Model 460. The ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker BRX 500 AVANCE spectrometer. The elemental analyses were obtained on a Thermo Finnigan Flash EA microanalyzer.

Preparation of polymer-bound ethylenediamine. To functionalize the polymer support with ethylenediamine, it was prepared by the following procedure: to a 250-mL round bottom flask equipped with a magnetic stir bar containing 120 mL acetonitrile, chloromethylated polystyrene (2 g, 2.5 mmol/Cl), and ethylenediamine (25 mmol), NaI (0.13 mmol) was added. The reaction mixture was refluxed for 48 h at which time the solid material and was collected by filtration and washed with 5 × 40 mL of CH_3CN, 5 × 40 mL of CH_3OH:K_2CO_3 (1 *M*) (1:1, v/v), 5×40 mL of CH_3OH:H_2O (1:1 v/v), and 3 × 40 mL of diethyl ether, and was subsequently dried in an oven.

Preparation of polystyrene-supported PS-en-Pd(II) complex (1). The functionalized polymer was kept in contact with 100 mL of ethanol for 30 min. An ethanolic solution of 0.25 g of $[PdCl_2(C_6H_5CN)_2]$ was added to it and heated to 50° for 6 h. The bright yellow colored polymer, impregnated with the metal complex, was collected by filtration, washed thoroughly with ethanol, and finally dried in vacuum at 70° for 24 h.

Synthesis of 2-amino-1-(2-propynyl) pyridinium bromide (3). A mixture of 2-amino pyridine (1.9 g, 20 mmol) and propargyl bromide (2 mL, 24 mmol) in ethanol (10 mL) was heated under reflux for 1 h. The precipitate formed was filtered off and recrystallized from ethanol to afford the title compound.

80% yield; m.p. 168–169°; ^1H NMR (DMSO-d_6): δ 3.85 (s, 1H, CH), 5.12 (s, 2H, CH_2), 6.85–8.23 (m, 4H, PyH), 8.72(s, 2H, NH_2); ^{13}C NMR (DMSO-d_6): δ 43.86, 76.04, 80.46, 114.00, 115.84, 139.83, 143.57, 154.52; ir (potassium bromide): 3300, 3200, 2100 cm^{-1}; Anal. Calcd. for $C_8H_9BrN_2$ (213.06): C, 45.09; H, 4.26; N, 13.15. Found: C, 45.50; H, 4.08; N, 13.51.

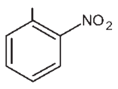
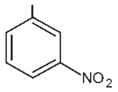
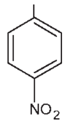
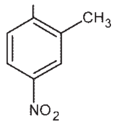
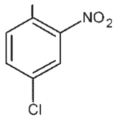
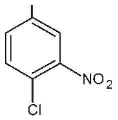
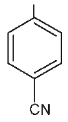
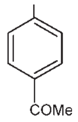
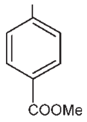
Synthesis of 2-substituted imidazo[2,1-b]pyridines (5a–i). A mixture of the aryl iodides (1.0 mmol), [(PS-en-Pd(II)] (60 mg, 0.03 mmol Pd), CuI (0.2 mmol), and triethylamine (3 mmol) was stirred in DMF (5 mL) at room temperature under an argon atmosphere. 2-Amino-1-(2-propynyl)pyridinium bromide (3) (1.50 mmol) was then added, and the mixture was stirred at room temperature for 12–16 h. After completion of the reaction, the resulting solution was concentrated *in vacuo*, and the crude product was subjected to column chromatography using $CHCl_3$:CH_3OH (95:5, v/v) as eluent to afford the pure product (Table 1).

2-(2-Nitrobenzyl)imidazo[1,2-a]pyridine (5a). This compound was obtained as a white solid. ^1H NMR (DMSO-d_6): δ 4.46(s, 2H, CH_2), 6.98–8.00 (m, 8H, PyH, ArH), 8.66 (s, 1H, imidazole proton); ^{13}C NMR (DMSO-d_6): δ 34.25, 114.60, 116.24, 122.85, 123.15, 129.10, 130.22, 130.95, 132.15, 134.27, 136.23, 139.12, 146.25, 148.33; ir (potassium bromide): 1510, 1340 cm^{-1}; Anal. Calcd. for $C_{14}H_{11}N_3O_2$ (253.25): C, 66.4; H, 4.38; N, 16.59. Found: C, 66.12; H, 4.11; N, 16.65.

2-(3-Nitrobenzyl)imidazo[1,2-a]pyridine (5b). This compound was obtained as a white solid. ^1H NMR (DMSO-d_6): δ

Table 2

Melting points and yields of 2-benzylimidazo [1,2-*a*]pyridines **5a–i**.[a]

Product	Ar	Time (hours)	Mp (°C)	Yield (%)
5a		12	250–251	92
5b		14	294–295	71
5c		14	256–257	87
5d		16	263–264	72
5e		16	231–232	60
5f		14	246–247	83
5g		13	210–211	85
5h		15	236–237	77
5i		16	260–261	89

[a] All reactions were performed using 1.5 mmol of **3**, 1.0 mmol of aryliodides, 0.2 mmol of CuI, 0.03 mmol of [PS-en-Pd(II)], 0.06 mmol of PPh_3, 3.0 mmol of Et_3N, and 5 mL of DMF at room temperature.

4.29 (s, 2H, CH_2), 6.97–8.32 (m, 8H, PyH, ArH), 8.58(s, 1H, imidazole proton); ^{13}C NMR (DMSO-d_6): δ 33.92, 114.35, 116.55, 122.30, 127.95, 128.26, 130.15, 130.90, 133.17, 133.86, 135.86, 138.60, 146.20, 147.31; ir (potassium bromide): 1500, 1335 cm^{-1}; Anal. Calcd. for $C_{14}H_{11}N_3O_2$ (253.25): C, 66.4; H, 4.38; N, 16.59. Found: C, 66.51; H, 4.42; N, 16.37.

2-(4-Nitrobenzyl)imidazo[1,2-a]pyridine (5c). This compound was obtained as a white solid. ^{1}H NMR (DMSO-d_6): δ 4.31(s, 2H, CH_2), 6.96–8.31 (m, 8H, PyH, ArH), 8.65(s, 1H, imidazole proton); ^{13}C NMR (DMSO-d_6): δ 34.21, 114.60, 116.76, 123.25, 128.30, 131.10, 131.87, 132.90, 135.82, 138.86, 145.27, 147.32; ir (potassium bromide): 1510, 1340 cm^{-1}; Anal. Calcd. for $C_{14}H_{11}N_3O_2$ (253.25): C, 66.4; H, 4.38; N, 16.59. Found: C, 66.22; H, 4.26; N, 16.41.

2-(2-Methyl-4-nitrobenzyl)imidazo[1,2-a]pyridine (5d). This compound was obtained as a white solid. ^{1}H NMR (DMSO-d_6): δ 2.35 (s, 3H, CH_3), 4.28 (s, 2H, CH_2), 7.00–8.02 (m, 7H, PyH, ArH), 8.58(s, 1H, imidazole proton); ^{13}C NMR (DMSO-d_6): δ 20.03, 33.95, 114.86, 116.46, 121.65, 121.97, 125.30, 128.06, 130.83, 131.38, 133.05, 136.21, 139.13, 146.35, 147.86; ir (potassium bromide): 1520, 1340 cm^{-1}; Anal.

Table 3

Heterocyclization during Sonogashira coupling of *o*-iodonitrobenzene with compound **3** catalyzed by recycled catalyst.[a]

Entry	Catalyst cycle	Isolated yield (%)
1	1st	92
2	2nd	90
3	3rd	87
4	4th	82
5	5th	75

[a] All reactions were performed using 1.5 mmol of **3**, 1.0 mmol of *o*-iodonitrobenzene, 0.2 mmol of CuI, 0.03 mmol of [PS-en-Pd(II)], 0.06 mmol of PPh_3, 3.0 mmol of Et_3N, and 5 mL of DMF at room temperature.

Calcd. for $C_{15}H_{13}N_3O_2$ (267.28): C, 67.40; H, 4.90; N, 15.72. Found: C, 66.91; H, 4.24; N, 15.91.

2-(4-Chloro-2-nitrobenzyl)imidazo[1,2-a]pyridine (5e). This compound was obtained as a white solid. ^{1}H NMR (DMSO-d_6): δ 4.41 (s, 2H, CH_2), 6.94–8.32 (m, 7H, PyH, ArH), 8.56 (s, 1H, imidazole proton); ^{13}C NMR (DMSO-d_6): δ 33.81, 114.16, 116.32, 123.30, 128.36, 130.04, 130.64, 131.24, 132.43, 134.27, 137.46, 138.87, 144.30, 148.68; ir (potassium bromide): 1510, 1350 cm^{-1}; Anal. Calcd. for $C_{14}H_{10}ClN_3O_2$ (287.70): C, 58.45; H, 3.50; N, 14.61. Found: C, 58.30; H, 3.41; N, 14.50.

2-(4-Chloro-3-nitrobenzyl)imidazo[1,2-a]pyridine (5f). This compound was obtained as a white solid. ^{1}H NMR (DMSO-d_6): δ 4.25 (s, 2H, CH_2), 6.95–8.03 (m, 7H, PyH, ArH), 8.59 (s, 1H, imidazole proton); ^{13}C NMR (DMSO-d_6): δ 33.75, 114.37, 116.86, 123.80, 126.58, 127.72, 128.23, 130.85, 131.47, 132.36, 135.30, 137.65, 141.11, 148.15; ir (potassium bromide): 1510, 1345 cm^{-1}; Anal. Calcd. for $C_{14}H_{10}ClN_3O_2$ (287.70): C, 58.45; H, 3.50; N, 14.61. Found: C, 58.34; H, 3.38; N, 13.95.

2-(4-Cyanobenzyl)imidazo[1,2-a]pyridine (5g). This compound was obtained as a white solid. ^{1}H NMR (DMSO-d_6): δ 4.31 (s, 2H, CH_2), 6.99–8.32 (m, 8H, PyH, ArH), 8.59 (s, 1H, imidazole proton); ^{13}C NMR (DMSO-d_6): δ 34.26, 113.15, 114.86, 116.34, 120.06, 129.10, 130.55, 131.08, 131.67, 137.35, 140.22, 141.37, 148.24; ir (potassium bromide): 2200 cm^{-1}; Anal. Calcd. for $C_{15}H_{11}N_3$ (233.26): C, 77.23; H, 4.75; N, 18.01. Found: C, 77.52; H, 4.63; N, 18.08.

2-(4-Acetylbenzyl)imidazo[1,2-a]pyridine (5h). This compound was obtained as a white solid. ^{1}H NMR (DMSO-d_6): δ 2.51(s, 3H, CH_3), 4.22 (s, 2H, CH_2), 6.96–7.87 (m, 8H, PyH, ArH), 8.60(s, 1H, imidazole proton); ^{13}C NMR (DMSO-d_6): δ 27.49, 34.20, 114.33, 116.12, 127.51, 129.26, 130.09, 130.77, 133.27, 135.98, 137.35, 138.49, 145.30, 198.26; ir (potassium bromide): 1690 cm^{-1}; Anal. Calcd. for $C_{16}H_{14}N_2O$ (250.29): C, 76.78; H, 5.64; N, 11.19. Found: C, 76.60; H, 5.46; N, 11.25.

2-[4-(Methoxycarbonyl)benzyl]imidazo[1,2-a]pyridine (5i). This compound was obtained as a white solid. ^{1}H NMR (DMSO-d_6): δ 3.81 (s, 3H, CH_3), 4.24 (s, 2H, CH_2), 7.01–8.32(m, 8H, PyH, ArH), 8.64(s, 1H, imidazole proton); ^{13}C NMR (DMSO-d_6): δ 33.89, 51.76, 114.54, 116.28, 128.36, 129.15, 130.05, 130.68, 132.84, 136.98, 138.08, 139.31, 148.93, 167.35; ir (potassium bromide): 1710 cm^{-1}; Anal. Calcd. for $C_{16}H_{14}N_2O_2$ (266.29): C, 72.16; H, 5.30; N, 10.52. Found: C, 71.74; H, 5.45; N, 10.30.

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Synthesis of 7,8-Dihydroxy-3-(3,4-dihydroxyphenyl)-2*H*-chromen-2-one Derivatives of Crown Ethers

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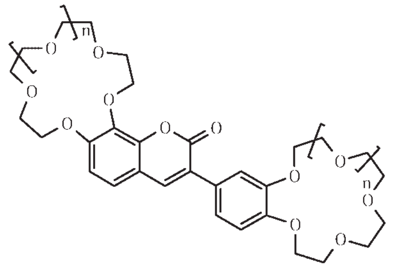

5a - 5c

	n
5a	0
5b	1
5c	2

The novel 1-(3,4-dimethoxyphenyl)-2-(2,3,4-trimethoxyphenyl)acrylonitrile was prepared from the condensation of the mixture of 2,3,4-trimethoxybenzaldehyde and 3,4-dimethoxyphenylacetonitrile in ethanol at 70°C with 20% aqueous sodium hydroxide solution. Cyclization and demethylation of the acrylacetonitrile was performed using pyridine hydrochloride. The obtained 7,8-dihydroxy-3-(3,4-dihydroxyphenyl)-2*H*-chromen-2-one was reacted with the poly(ethylene glycol) ditosylates in CH_3CN/alkali carbonate to afford bis-[12]crown-4, -[15]crown-5, and -[18]crown-6 chromenones. The chromatographically purified novel chromenone crown ethers were identified by IR, ^1H NMR, ^{13}C NMR, and MALDI-TOF mass spectrometry and elemental analysis.

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INTRODUCTION

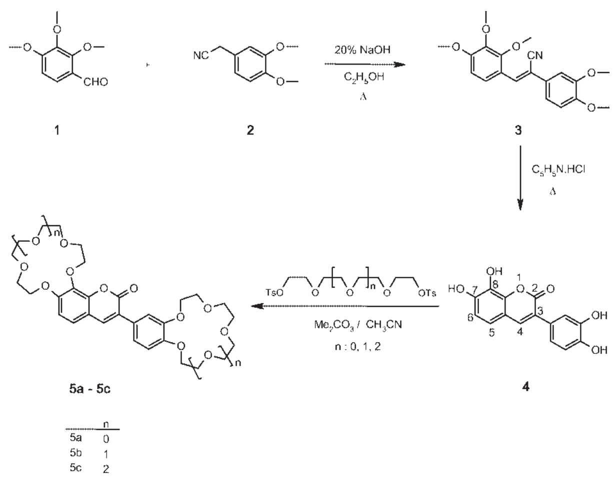
Macrocyclic molecules have attracted much attention because of their potential use in a variety of chemical processes, selective complexing agents for earth and alkaline metal ions, and photoinduced electron transfer [1]. Several macrocyclic ethers possessing oxygen dipoles have been synthesized to investigate their alkali and alkaline-earth cation membrane transport and binding properties by means of potentiometry, optical spectroscopy, as well as NMR spectroscopic methods [2,3]. The ionophores bearing suitable light sensitive moieties may undergo intermolecular changes at the electronic level upon cationic interactions of donor oxygen atoms [2]. Essentially, the fluorescence spectra of fluorogenic macrocycles is a reliable method to study cationic recognitions [2,4,5]. Crown ethers have also been used for chromatographic separations [6,7]. We have recently synthesized fluorogenic coumarin-[12]crown-4, -[15]crown-5, and -[18]crown-6 derivatives and examined cation binding effects using steady state fluorescence spectroscopy and reported their cationic interaction in acetonitrile [5,8–11]. However, the oxygen atom, which is contained in the phenyl moiety in coumarin arms potentially can participate along with the other oxygen atoms in the analog crown ether moiety formed 1:1 complex with a host ion [12–16].

We report here the synthesis of novel bis-[12]crown-4, -[15]crown-5, and -[18]crown-6 derivatives of 7,8-dihydroxy-3-(3,4-dihydroxyphenyl)-2*H*-chromen-2-one.

RESULTS AND DISCUSSION

The synthesis of the precursor compound, 1-(3,4-dimethoxyphenyl)-2-(2,3,4-trimethoxyphenyl)acrylonitrile (**3**) was accomplished using Knoevenagel condensation reaction [17]. Equal molar amounts of 2,3,4-trimethoxybenzaldehyde (**1**) and 3,4-dimethoxyphenylacetonitrile (**2**) in ethanol at 70°C (see Scheme 1) was reacted with 20% aqueous sodium hydroxide solution. The Knoevenagel reaction is stereoselective and resulted in the *E*-product. The precipitated acrylonitrile (**3**) was collected by filtration, washed with distilled water, and dried. The crude product was purified by crystallization from ethanol. Then, the ring closure of (**3**) was

Scheme 1



performed with freshly prepared pyridine hydrochloride at 180 °C. The compound, 7,8-dihydroxy-3-(3,4-dihydroxyphenyl)-2*H*-chromen-2-one, **(4)** was washed with water until neutral, dried, and recrystallized from acetic acid.

Compound **4** was reacted with poly(ethylene glycol) ditosylates in the presence of alkali carbonate in CH_3CN (Scheme 1) to give the 7,8-dihydroxy-3-(3,4-dihydroxyphenyl)-2*H*-chromen-2-one crown ethers (coumarino crown ether) **5a**, **5b**, **5c**, respectively.

The purification of crown ethers were done by column chromatography (silica gel-chloroform) to give pure coumarino crown ethers **(5a–5c)** in 12–23% yields. They were soluble in $CHCl_3$ or CH_2Cl_2. The novel compounds have been characterized by elemental analysis IR, ^1H NMR, ^{13}C NMR, and MALDI-TOF-MS.

The IR spectra of **3** showed absorption bands at 2840 and 2973 cm^{-1} for the C—H stretching. The characteristic band of the nitrile group (CN), benzene ring (C=C), and methoxy group (OCH_3) appeared at 2206, 1583–1403, 1350–1023 cm^{-1}, respectively. The IR spectrum of **4** showed a characteristic band for the hydroxyl group (OH), carbonyl group (C=O), benzene ring (C=C), and (C—O) 3560–3328, 1681, 1618–1535, 1311–1109 cm^{-1}, respectively.

The ^1H NMR spectra of **5a–5c** showed characteristic signals for etheral (—O—CH_2—CH_2—O—) protons at δ 3.85–4.48 ppm, each a triplet. In addition, the chemical shifts of the aromatic protons are observed at δ 6.86–7.81 ppm.

The ^{13}C NMR spectrum of **5a–5c** showed expected signals for aromatic, carbonyl, and etheral carbons at δ 109.83–140.63, 160.46–173.90, 69.06–75.17 ppm, respectively. Also the MALDI-TOF-MS and elemental analysis confirmed the formation of coumarino crown ether derivatives.

The obtained new coumarino crown ether compounds will next be examined for their cation binding properties using fluorescence spectroscopy.

EXPERIMENTAL

The starting chemicals were purchased from Aldrich or Merck unless otherwise cited. Melting points have been obtained on a Gallenkamp apparatus and are uncorrected. IR spectra were obtained from KBr pellets with a Schimadzu FTIR spectrometer, model 8300. Mass spectra have been obtained with a MALDI-TOF instrument, model Bruker Autoflex III. The ^1H NMR spectra have been obtained with a BRUKER spectrometer, model AVANCE-400 Cpx and TMS was used as the internal reference. Combustion analyses have been acquired with a LECO-932 CHN.

Synthesis of 1-(3,4-dimethoxyphenyl)-2-(2,3,4-trimethoxyphenyl)acrylonitrile (3). The typical procedure for synthesis of acrylonitrile **(3)** is performed according to the literature [18]. A mixture of 2,3,4-trimethoxybenzaldehyde **(1)** (4.82 g, 24.59 mmol) and 3,4-dimethoxyphenylacetonitrile **(2)** (4.34 g, 24.59 mmol) in ethanol (100 mL) was heated to 70°C; 20% aqueous sodium hydroxide solution was then added dropwise to the stirred solution until the onset of turbidity. The acrylonitrile **(3)** precipitated when the solution was cooled to room temperature. The precipitate was collected by filtration, washed with water, and dried. The crude product was purified by recrystallization from ethanol. 6.85 g (78%), mp 114–115 °C. ir (KBr): 2973–2840 (C—H), 2206 (CN), 1583–1403 (C=C), 1350–1023 (C—O) cm^{-1}; ^1H NMR (400 MHz/$CDCl_3$): δ 3.89 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.78 (d, J = 9.0 Hz, 1H), 6.91 (d, J = 8.2 Hz, 1H), 7.15 (d, J = 2.3 Hz, 1H,), 7.24 (dd, J = 8.2 Hz and 2.3 Hz, 1H), 7.72 (s, 1H), 7.96 (d, J = 9.0 Hz, 1H); ms: *m/z* 355.14 (M^+), 356.15 $(M+1)^+$, 357.15 $(M+2)^+$.

Synthesis of 7,8-dihydroxy-3-(3,4-dihydroxyphenyl)-2*H*-chromen-2-one (4). A mixture of the acrylonitrile **(3)** (6.85 g, 19.24 mmol) and freshly prepared pyridine hydrochloride (11.11 g, 96.20 mmol) was heated for 2 h at 180°C; the cooled solution was treated with water. The precipitated coumarin was washed with water until neutral, dried, and recrystallized from acetic acid. 4.6 g (83%), mp 295°C (lit: 297 °C [19]); ir (KBr): 3560–3328 (Ar—OH), 1681 (C=O), 1618–1535 (C=C), 1311–1109 (C—O) cm^{-1}; ^1H NMR (400 MHz/DMSO-d_6): δ 6.71 (d, J = 8.5 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 6.95 (dd, J = 8.5 Hz and 2.0 Hz 1H), 7.15 (d, J = 8.5 Hz, 1H), 7.22 (d, J = 2 Hz, 1H), 7.95 (s, 1H), 9.05 (br-s, 1H), 9.12 (br-s, 1H), 9.40 (br-s, 1H), 9.95 (br-s, 1H).

General procedure for the synthesis of 7,8-dihydroxy-3-(3,4-dihydroxyphenyl)-2*H*-chromen-2-one crown ethers (5a–5c). The typical procedure for the cyclization reaction leading to macrocyclic ethers **(5a–5c)** is as follows. A mixture of **4** (5 mmol), poly(ethylene glycol) ditosylate (10 mmol), and metal carbonate (20 mmol) was dissolved in 60 mL CH_3CN in a 100-mL reaction flask. The reaction mixture was heated for 35–40 h at 80–85°C. The solvent was distilled. Diluted HCl was added to the residue and the mixture was extracted with $CHCl_3$ (3 × 50 mL). The combined organic extracts were washed with water, dried over $CaCl_2$, and the

$CHCl_3$ solution evaporated *in vacuo*. Chromatography of the crude products (silica gel 60, Merck) with chloroform gave pure coumarino crown ethers (**5a–5c**).

14-(2,3,5,6,8,9-Hexahydrobenzo[b][1,4,7,10]tetraoxacyclododecin-12-yl)-5,6,8,9-tetrahydro-2H-[1,4,7,10]tetra-oxacyclododeca[2,3-h]chromen-15(3H)-one (5a; $C_{27}H_{30}O_{10}$). Compound **4** (1.5 g, 5.2 mmol), Na_2CO_3 (2.2 g, 21 mmol), tri(ethylene glycol) ditosylate (4.8 g, 10 mmol) in CH_3CN (60 mL) was reacted as described earlier to afford light yellow solid **5a**, 0.6 g (22%), mp 126–128°C; ^{1}H NMR (400 MHz/$CDCl_3$): δ 3.85 (t, J = 4Hz, 4H), 3.95 (t, J = 4Hz, 4H), 3.97 (t, J = 4Hz, 4H), 4.21 (t, J = 4Hz, 4H), 4.23 (t, J = 4Hz, 4H), 4.40 (t, 4Hz, 4H), 6.86 (d, J = 8.7 Hz, 1H, H-5′), 7.01 (d, J = 8.5 Hz, 1H, H-6), 7.19 (d, J = 8.7 Hz, 1H, H-5), 7.31 (dd, J = 8.5 Hz and 1.5 Hz, 1H, H-6′), 7.37 (d, J = 1.5 Hz, 1H, H-2′), 7.69 (s, 1H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ 69.75, 69.87, 70.31, 70.34, 70.51, 70.87, 71.18, 71.32, 71.66, 72.16, 72.23, 75.17, 111.06, 115.02, 117.74, 118.97, 123.17, 124.53, 126.25, 129.14, 136.26, 139.75, 147.72, 150.37, 151.25, 155.12, 160.46; ms: m/z 513.94 (M^+), 536.95 $(M+Na)^+$. Anal. Calc. for $C_{27}H_{30}O_{10}$: C, 63.03; H, 5.88. Found: C, 62.97; H, 5.68.

17-(2,3,5,6,8,9,11,12-Octahydrobenzo[b][1,4,7,10,13]pentaoxacyclopentadecin-15-yl)-5,6,8,9,11,12-hexahydro-2H-[1,4,7,10,13]pentaoxacyclopentadeca[2,3-h]chromen-18(3H)-one (5b; $C_{31}H_{38}O_{12}$). Compound 4 (1.0 g, 3.5 mmol), K_2CO_3 (1.93 g, 14 mmol), tetra(ethylene glycol) ditosylate (3.52 g, 7 mmol) in CH_3CN (60 mL) reacted as described earlier to afford light yellow solid 5b, 0.5 g (23%), mp: 136 °C; ^{1}H NMR (400 MHz/$CDCl_3$): δ 4.04 (t, J = 4Hz, 4H), 4.06 (t, J = 4Hz, 4H), 4.09 (t, J = 4Hz, 4H), 4.11 (t, J = 4Hz, 4H), 4.34 (t, J = 4Hz, 4H), 4.37 (t, 4Hz, 4H), 4.39 (t, 4Hz, 4H), 4.48 (t, 4Hz, 4H), 7.02 (d, J = 8 Hz, 1H, H-5′), 7.07 (d, J = 8 Hz, 1H, H-6), 7.25 (d, J = 8 Hz, 1H, H-5), 7.40 (dd, J = 8 Hz and 2 Hz, 1H, H-6′), 7.43 (d, J = 2 Hz, 1H, H-2′), 7.81 (s, 1H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ 69.08, 69.26, 69.45, 69.47, 69.75, 69.78, 70.42, 70.53, 70.61, 70.72, 70.77, 71.08, 71.16, 71.28, 71.30, 73.79, 109.83, 113.93, 114.92, 121.86, 122.87, 124.81, 128.43, 135.47, 139.30, 139.35, 147.73, 148.96, 149.83, 154.92, 160.58; ms: m/z 602.07 (M^+), 625.04 $(M+Na)^+$, 641.02 $(M+K)^+$. Anal. Calc. for $C_{31}H_{38}O_{12}$: C, 61.78; H, 6.36. Found: C, 61.58; H, 6.05.

20-(2,3,5,6,8,9,11,12,14,15-Decahydrobenzo[b][1,4,7,10,13,16]hexaoxacyclooctadecin-18-yl)-5,6,8,9,11,12,14,15-octahydro-2H-[1,4,7,10,13,16]hexa-oxacyclooctadeca[2,3-h]chromen-21(3H)-one (5c; $C_{35}H_{46}O_{14}$). Compound **4** (1.0 g, 3.5 mmol), K_2CO_3 (1.93 g, 14 mmol), penta(ethylene glycol) ditosylate (3.52 g, 7 mmol) in CH_3CN (60 mL) reacted as described earlier to afford light yellow solid **5c**, 0.28 g (12%), mp: 95 °C; ^{1}H NMR (400 MHz/$CDCl_3$): δ 3.92 (t, J = 4Hz, 4H), 3.95 (t, J = 4Hz, 4H), 3.97 (t, J = 4Hz, 4H), 4.02 (t, J = 4Hz, 4H), 4.21 (t, J = 4Hz, 4H), 4.22 (t, J = 4Hz, 4H), 4.24 (t, J = 4Hz, 4H), 4.25 (t, J = 4Hz, 4H), 4.27 (t, 4Hz, 4H), 4.37 (t, 4Hz, 4H), 6.88 (brd, J = 8.6 Hz, 1H, H-5′), 6.93 (brd, J = 8.6 Hz, 1H, H-6), 6.99 (d, J = 8.6 Hz, 1H, H-5), 7.17 (dd, J = 8.7 Hz and 2 Hz, 1H, H-6′), 7.29 (d, J = 2 Hz, 1H, H-2′), 7.67 (s, 1H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ: 69.06, 69.21, 69.36, 69.44, 69.68, 69.82, 70.55, 70.60, 70.67, 70.78, 70.84, 70.90, 70.94, 70.97, 71.01, 71.12, 71.18, 71.27, 71.39, 73.24, 110.62, 113.61, 114.57, 116.14, 121.78, 122.88, 124.97, 128.18, 136.19, 139.34, 148.63, 152.38, 152.45, 154.75, 173.90 ; ms: m/z 690.2 (M^+), 713.18 $(M+Na)^+$, 629.16 $(M+K)^+$. Anal. Calc. for $C_{35}H_{46}O_{14}$: C, 60.86; H, 6.71. Found: C, 60.36; H, 6.81.

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Efficient and Convenient Method for the Synthesis of Isoxazoles in Ionic Liquid

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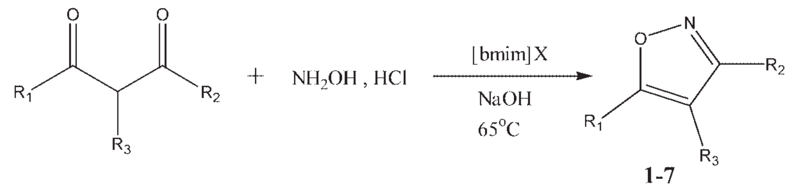

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An efficient one-pot synthesis of 3,5-disubstitueted isoxazoles from β-diketones in room temperature ionic liquids (ILs) is described. Compared with the classical reaction conditions, this new synthetic method is environmentally friendly and has the advantages of recyclability of IL and very good to excellent yields.

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INTRODUCTION

Synthesis of substituted isoxazole derivatives is particularly important because a lot of compounds containing the isoxazole ring system are known to have a variety of biological activities in pharmaceutical and agricultural areas [1]. Their range of uses includes medicinal, herbicidal, fungicidal, pesticidal applications, dyes, insulating oils, and lubricants. Since Claisen's report in 1891 [2], many methods have been developed for the preparation of substituted isoxazoles which can generally be divided into two synthetic routes. The first involves the condensation reaction of a hydroxylamine with a carbonyl compound and provides easy access to 3,5-disubstituted isoxazoles [1]. The second route involves the 1,3-dipolar cycloaddition of a nitrile oxide with an alkyne. In this transformation, nitrile oxides react intermolecularly with monosubstituted alkynes to again give a preponderance of 3,5-disubstituted isoxazoles [3] and furoxan is a significant byproduct.

Room temperature ionic liquids (ILs) have been the subject of considerable interest as new, nonvolatile, and environmentally friendly alternatives to conventional organic solvents. They are salts of organic cations and a variety of anions [4–7]. ILs are compatible with several organic transformations [8–10], they readily immobilize several catalysts in their native form [11,12] or the supported catalysts [13]. They have been found to alter the outcome of chemical reactions in a dramatic fashion [14], thus forming a new paradigm in organic synthesis.

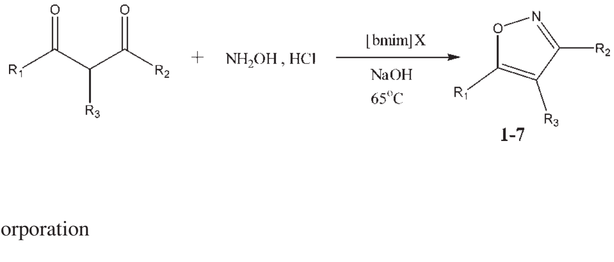
In continuation of our recent interest to use ILs, water or solventless systems as green reaction mediums [15], we report herein the synthesis of isoxazole derivatives in reusable imidazolium-based ILs using NaOH as base Scheme 1.

A typical reaction of dibenzoylmethane with hydroxyl-amine was carried out in the IL, [bmim]Br, at ambient conditions to form 3,5-diphenyl isoxazole. However, at room temperature, reaction does not proceed further to afford the product even in trace amounts. Consequently, the reaction was carried out at higher temperatures and optimum results were obtained at 65°C (75%).

For further optimization, several ILs based on butylmethylimidazolium salts [bmim]X with varying anions were screened for the typical reaction of dibenzoil-methane with hydroxylamine at 65°C for complete conversions as monitored by TLC to afford 3,5-diphenyl isoxazole. The results are recorded in Table 1. Evidently, [bmim]BF_4 was found to be superior in terms of yield (83%) and reaction time (5 h) when compared with other ILs.

Consequently, all further reactions with other β-diketones were conducted by using [bmim]BF_4 as the reaction medium Table 2. Acetylacetone and 2,4-hexanedione were mostly recovered unchanged. All the products were fully characterized by M.P., ^{13}C NMR, ^{1}H

Scheme 1



1-7

Table 1

Synthesis of 3,5-diphenyl isoxazole in [bmim]X at 65°C.

Entry	Ionic liquid	Time (h)	Yield[a] (%)
1	[bmim]Br	5	75
2	[bmim]BF_4	5	83
3	[bmim]Cl	5	72
4	[bmim]ClO_4	5	70
5	[bmim]PF_6	5	72

[a] Isolated yield after column chromatography.

NMR, and the values [16] were in agreement with those reported in literature.

Recycling of the IL was carried out for the reaction of β-diketone and hydroxylamine hydrochloride following an extremely straightforward protocol. After complete reaction and workup the residue containing IL was dissolved in EtOAc, filtered through a filter paper, dried over Na_2SO_4, and the solvent was removed on a rotary evaporator. The IL was further vacuum dried at 0.1 mmHg for 1 h and used for two more runs under identical conditions as for run 1. The results gained are shown in Table 3. It can be seen that a slight reduction in yield was observed in runs carried out using ''old'' IL, and furthermore the products obtained were of the same purity as in the first run.

In conclusion, a novel method for the one-pot synthesis of the biologically active isoxazoles has been developed by the reaction of β-diketone and hydroxylamine hydrochloride in the IL [bmim]Br in excellent isolated yields. The solvent IL was recovered almost entirely and recycled successfully. The moderate reaction conditions, easy workup procedure and recyclability of the nonvolatile IL make this an environment friendly method amenable for scaleup.

EXPERIMENTAL

All of the melting points are uncorrected and were determined with a Stuart scientific apparatus. Infrared spectra were recorded in KBr and were determined on a PerkinElmer FT-IR spectrometer. ^1H NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer in $CDCl_3$ as solvent and TMS as internal standard. All solvents and chemicals were of research grade and were used as obtained from Merck. The imidazolium-based ILs investigated were prepared according to the procedure reported in the previous literature [17].

Table 2

Preparation of 3,5-disubstituted isoxazoles in [bmim]BF_4.

					Melting point (°C)		
Product number	R_1	R_2	R_3	Time (h)	Found	Reported	Yield[a] (%)
1	Ph	Ph	H	5	138–142	140-141 [18]	83
2	Ph	Me	H	6.2	65–68	67 [19]	78
3	Ph	Ph	Me	5.5	121–123	–	78
4	Ph	4-$NO_2C_6H_4$	H	6	223–227	226–228 [20]	78
5	Ph	4-ClC_6H_4	H	6	170–177	172–178 [21]	81
6	4-$MeOC_6H_4$	4-$NO_2C_6H_4$	H	5.5	169–174	172–175 [21]	75
7	4-$MeOC_6H_4$	4-ClC_6H_4	H	5.5	207–211	210 [20]	73

[a] Isolated yield after column chromatography.

Table 3

Ionic liquid recycling for the reaction of β-diketone and hydroxylamine hydrochloride.

	Cycle 1		Cycle 2		Cycle 3	
Ionic liquid	Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)
[bmim]Br	5	80	6	78	7	76
[bmim]BF_4	5	83	6	80	7	79
[bmim]Cl	5	72	6	70	7	69
[bmim]ClO_4	5	70	6	68	7	65
[bmim]PF_6	5	72	6	71	7	67

[a]Isolated yields of 3,5-diphenylisoxazole.

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[16] General procedure for compounds (**1–7**): A mixture of β-diketone (1 mmol), hydroxylamine hydrochloride (1.1 mmol), and NaOH (1 mmol) was heated in 2 mL [bmim]BF_4 at 65°C for appropriate time (Table 1). The completion of reaction was monitored by TLC using (EtOAc/petroleum 1:8) as eluent. After completion of the reaction, the mixture was extracted with Et_2O (15 mL × 3). The Et_2O layers were collected and concentrated in vacuum. Then the crude mixture was purified by column chromatography using (HEX/EtOAc 9:1) on silica gel to afford corresponding isoxazoles. $C_{15}H_{11}NO$ (**1**): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.65$ (d, 4H, Ph), 7.34 (m, 6H, Ph), 6.43 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 156.9$, 147.1, 136.9, 127.9, 127.0, 126.1, 98.3; *Anal.* Calcd. for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33; O, 7.23. Found: C, 81.40; H, 4.98; N, 6.30; O, 7.32. $C_{10}H_9NO$ (**2**): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.63$ (d, 2H, Ph), 7.34 (m, 3H, Ph), 6.46 (s, 1H, CH), 2.25 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 157.9$, 146.1, 136.4, 127.9, 127.7, 126.0, 98.4, 17.3. $C_{16}H_{13}NO$ (**3**): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.66$ (d, 4H, Ph), 7.36 (m, 6H, Ph), 2.35 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 159.9$, 149.1, 138.4, 129.9, 129.0, 128.2, 96.4, 19.3; *Anal.* Calcd. for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95; O, 6.80. Found: C, 81.66; H, 5.54; N, 5.93; O, 6.87. $C_{15}H_{10}N_2O_3$ (**4**): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.85$ (d, 2H, Ph), 7.44–7.49 (m, 5H, Ph), 7.44 (d, 2H, Ph), 6.33 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 159.9$, 158.9, 152.7, 150.1, 146.6, 142.6, 138.4, 129.9, 129.2, 127.2, 99.7. $C_{15}H_{10}ClNO$ (**5**): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.82$ (d, 2H, Ph), 7.38–7.5045 (m, 5H, Ph), 7.44 (d, 2H, Ph), 6.46 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 158.8$, 158.9, 151.7, 149.1, 144.5, 140.9, 137.4, 128.0, 127.0, 125.2, 98.0. $C_{16}H_{12}N_2O_4$ (**6**): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.90$ (d, 2H, Ph), 7.34–7.50 (m, 4H, Ph), 7.25 (d, 2H, Ph), 6.35 (s, 1H, CH), 4.32 (s, 3H, OMe); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 160.8$, 157.9, 151.7, 149.1, 145.5, 140.6, 136.4, 128.9, 128.0, 126.2, 98.4. $C_{16}H_{12}ClNO_2$ (**7**): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.80$ (d, 2H, Ph), 7.30–7.45 (m, 4H, Ph), 7.25 (d, 2H, Ph), 6.32 (s, 1H, CH), 4.35 (s, 3H, OMe); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 161.8$, 158.1, 152.5, 150.1, 146.5, 139.6, 136.0, 126.9, 126.9, 127.2, 100.1; *Anal.* Calcd. for $C_{16}H_{12}ClNO_2$: C, 67.26; H, 4.23; Cl, 12.41; N, 4.90; O, 11.20. Found: C, 67.21; H, 4.20; Cl, 12.37; N, 4.88; O, 11.34.

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Mild Oxidative Cyclization of Sydnone-Benzoylhydrazone with Lead Oxide to 2,5-Disubstituted-1,3,4-Oxadiazole–Sydnone Hybrid Derivatives

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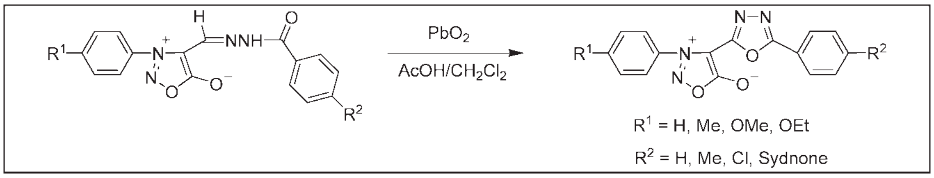

The mild oxidation of sydnone-benzoylhydrazone hybrids with lead oxide in acetic acid/dichloromethane solution inducted their intramolecular cyclization to provide the corresponding 2,5-disubstituted-1,3,4-oxidiazole derivatives. The sydnone moiety has been efficient preserved for the future work in the mild oxidation.

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INTRODUCTION

Sydnones attract attention due to their wildly useful properties, including biological and pharmaceutical usage [1], synthetic application [2], photochromic properties [3], and preparation of electroluminescent materials [4]. Sydones, also considered as the masked hydrazines, can react with HCl for de-masking for the further formation of heterocycles [5].

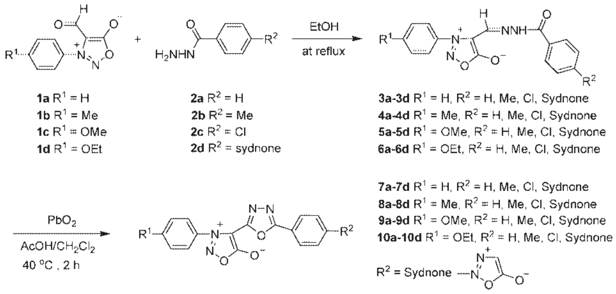
1,3,4-Oxadiazoles have been reported to be biologically versatile compounds displaying a variety of biological effects, which include anti-inflammatory [6], antifungal [7], antiparasitic [8], and antimicrobial activities [9]. In addition, they have been used as bioisosteres on the carboxamide moiety [10]. The most common synthetic approach to 1,3,4-oxidiazoles involves cyclodehydration of 1,2-diacylhydrazines. Typically, the reaction is carried out by using thionyl chloride [11], phosphorous oxychloride [12], phosphorous pentoxide [13], triphenylphosphine [14], or trifluoromethane–sulfonic anhydride as the dehydrating agent [15].

Another alternative route to 1,3,4-oxadiazoles by oxidative cyclization from the corresponding aldehyde *N*-acylhydrazones proceeds with lead tetraacetate [16], lead oxide [17], potassium permanganate [18], electrochemical methods [19], iodobenzene diacetate [20], or chloramine T [21]. The azines were used as oxidative cyclization precursors. Herein, we report the aldehyde *N*-acylhydrazone containing sydnone moiety with lead oxide reagent, at 40°C for 2 h to afford 2,5-disubstituted-1,3,4-oxadiazole–sydnone hybrids in 51–63%. In this mild oxidative cyclization, the sydnone moiety is able to be successful preserved without decomposition.

RESULTS AND DISCUSSION

The synthetic pathway of the 2,5-disubstituted-1,3,4-oxadiazole–sydnone hybrid derivatives (**7**–**10**) was depicted in Scheme 1. Following by the published procedure [2,22], the sydnone compounds were easily converted to the 3-aryl-4-formyl-sydnone derivatives **1a**–**1d** in a solution of $POCl_3$ and DMF by the Schmidt reaction. And benzoyl chloride reacted with hydrazine monohydrate to generate benzoylhydrazones **2a–2d**. Then various 3-aryl-4-formyl-sydnone derivatives **1a**–**1d** (p-R^1 = H, Me, OMe, and OEt) were mixed with benzoylhydrazones **2a–2d** (p-R^2 = H, Me, Cl, and sydnone) and stirred for 2.0–6.0 h in an EtOH solution to achieve the elimination and give the corresponding products **3–6** in good yields (74–86%, see Table 1) [23].

Scheme 1. The synthetical route of 2,5-disubstituted-1,3,4-oxadiazole–sydnone hybrid derivatives.



Aldehyde *N*-acylhydrazones **3–6** were performed the oxidative–cyclization by using fresh $KMnO_4$ in acetic acid/dichloromethane solution. The low isolable oxidative–cyclization products were provided because of the further oxidation formation and the damage of sydnone ring by $KMnO_4$. In the controllable and improvable experiment, the commercially available reagent lead oxide (PbO_2) was selected for the mild oxidative–cyclization agent [17,24]. When the aldehyde *N*-acylhydrazones **3–6** were oxidized with 2.5 equiv of lead oxide (PbO_2), the 2,5-disubstituted-1,3,4-oxadiazole–sydnone hybrid derivatives **7–10** were formed in 50–63% yields. The long range of the substitution effects on R^1 (H, Me, OMe, and OEt) and R^2 (H, Me, Cl, and sydnone) positions are not clearly a function of the isolated yield and the results are shown in Table 1.

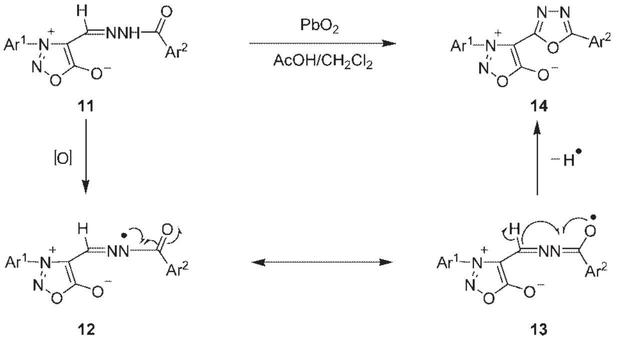
The proposed oxidative–cyclization mechanism is shown in the Scheme 2. The aldehyde *N*-acylhydrazone **11** can be oxidized by lead oxide (PbO_2) to trap the hydrogen and afford the hydrazonyl radical **12** [17]. Because of the electron radical can be stabilized by the strong electronegativity of oxygen atom, the electron radical migrates from nitrogen to oxygen atom to form the radical intermediate **13**. The intermediate **13** undergoes the further oxidative cyclization to yield 2,5-disubstituted-1,3,4-oxadiazole–sydnone hybrid **14** [23].

Table 1

The yields of aldehyde *N*-acylhydrazones **3–6** and 2,5-disubstituted-1,3,4-oxadiazole–sydnone hybrid derivatives **7–10**.

Entry		Compounds	Yield	Compounds	Yield
R^1	R^2	**3–6**	(%)	**7–10**	(%)
H	H	**3a**	80	**7a**	57
	Me	**3b**	86	**7b**	57
	Cl	**3c**	77	**7c**	50
	Sydnone	**3d**	84	**7d**	51
Me	H	**4a**	83	**8a**	59
	Me	**4b**	83	**8b**	58
	Cl	**4c**	75	**8c**	51
	Sydnone	**4d**	87	**8d**	53
OMe	H	**5a**	82	**9a**	61
	Me	**5b**	85	**9b**	60
	Cl	**5c**	75	**9c**	53
	Sydnone	**5d**	89	**9d**	58
OEt	H	**6a**	82	**10a**	63
	Me	**6b**	84	**10b**	62
	Cl	**6c**	74	**10c**	53
	Sydnone	**6d**	89	**10d**	57

Scheme 2. The proposed mechanism of the oxidative cyclization.



In conclusion, we have developed a mild and efficient oxidative–cyclization method for the synthesis of 2,5-disubstituted-1,3,4-oxadiazole–sydnone hybrid derivatives. Using this mild radical cyclization, the sydnone ring was successfully preserved to provide 1,3,4-oxadiazole–sydnone hybrids in the core molecular.

EXPERIMENTAL

General procedure. Analytical thin-layer chromatography was performed on precoated plates (silica gel 60 F-254), purchased from Merck Inc. Purification by gravity column chromatography was carried out by use of Merck Reagents Silica Gel 60 (particle size 0.063–0.200 mm, 70–230 mesh ASTM). Infrared (IR) spectra were measured on a Bomem Michelson Series FT-IR spectrometer. The wave numbers reported are referenced to the polystyrene 1601 cm^{-1} absorption. Absorption intensities are recorded by the following abbreviations: s, strong; m, medium; w, weak. Proton NMR spectra were obtained on a Bruker-300 (400 MHz) spectrometer by use of $CDCl_3$ and d_6-DMSO as solvent. Carbon-13 NMR spectra were obtained on a Varian a Bruker-300 (100 MHz) spectrometer by used of $CDCl_3$ as solvent. Carbon-13 chemical shifts are referenced to the center of the $CDCl_3$ triplet (δ 77.0 ppm). Multiplicities are recorded by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; *J*, coupling constant (hertz). Elemental analyses were carried out on a Heraeus CHN–O RAPID element analyzer. Mass spectra were measured on a VG Platform II GC-MS Instruments. FAB mass and High-resolution mass spectra were obtained by means of a Finnigan/Thermo Quest MAT 95XL mass spectrometer.

Standard procedure for the substitution reaction. To a solution of 3-aryl-4-formyl-sydnone derivatives (**1a–1d**, 0.38 g, 2.00 mmol, 1.0 equiv) and benzoylhydrazones (**2a–2d**, 0.27 g, 2.00 mmol, 1.6 equiv) in EtOH (10 mL) was stirred and added one drop of aqueous H_2SO_4 solution.

The reaction mixture was stirred at room temperature for 2.0 h. After the reaction was completed, the resultant precipitate was filtrated, washed with cold EtOH (20 mL × 2), and dried in vacuum oven. The residue was purified by recrystallization from EtOAc to give pure aldehyde *N*-acylhydrazones **3–6** as white powder in 74–86% yields.

3-Phenyl-4-formylsydnone benzoylhydrazone (3a). Mp (recrystallized from EtOAc) 196–198°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.40–7.82 (m, 10 H), 8.11 (s, 1 H), 11.69 (s, 1 H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 106.1, 125.9, 127.7, 128.7, 130.3, 132.1, 133.2, 133.4, 134.5, 142.1, 162.9, 164.3; IR (KBr) 3370 (s, NH), 1755 (m, C=O), 1695 m cm^{-1}; FABMS *m/z* (relative intensity) 309 (M + 1, 59), 308 (M$^+$, 15).

3-Phenyl-4-formylsydnone p-methylbenzoylhydrazone (3b). Mp (recrystallized from EtOAc) 197–199°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.21 (s, 3H, CH$_3$), 7.12–7.72 (m, 9 H), 8.03 (s, 1 H), 11.56 (s, 1 H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 21.2, 106.2, 125.9, 127.5, 127.7, 129.2, 130.3, 132.8, 133.4, 134.3, 142.2, 162.8, 164.1; IR (KBr) 3338 (s, NH), 1754 (m, C=O), 1692 m cm^{-1}; FABMS *m/z* (relative intensity) 323 (M + 1, 74), 322 (M$^+$, 35).

3-Phenyl-4-formylsydnone p-chlorolbenzoylhydrazone (3c). Mp (recrystallized from EtOAc) 200–202°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.10–7.80 (m, 9 H), 7.86 (s, 1 H), 11.68 (s, 1 H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 106.0, 125.3, 125.8, 127.1, 128.5, 130.2, 132.1, 133.2, 133.5, 142.3, 161.8, 163.9; IR (KBr) 3364 (s, NH), 1755 (m, C=O), 1689 m cm^{-1}.

3-Phenyl-4-formylsydnone 4-(sydnon-3-yl)benzoylhydrazone (3d). Mp (recrystallized from MeOH) 183–185°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.05–8.68 (m, 11 H, ArH + sydnone), 12.35 (s, 1 H, NH); IR (KBr) 3091 (s, NH), 1745 (m, C=O), 1681 m cm^{-1}; FABMS *m/z* (relative intensity) 393 (M + 1, 3), 392 (M$^+$, 24).

3-(p-Methylphenyl)-4-formylsydnone benzoylhydrazone (4a). Mp (recrystallized from EtOAc) 191–193°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.46 (s, 3H, CH$_3$), 7.25–7.75 (m, 9 H), 8.11 (s, 1 H), 11.66 (s, 1 H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 21.1, 106.1, 125.7, 127.3, 127.7, 129.0, 129.3, 130.3, 131.1, 134.5, 143.2, 162.8, 164.7; IR (KBr) 3352 (s, NH), 1758 (m, C=O), 1692 m cm^{-1}.

3-(p-Methylphenyl)-4-formylsydnone p-methylbenzoylhydrazone (4b). Mp (recrystallized from EtOAc) 197–199°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.20 (s, 3H, CH$_3$), 2.46 (s, 3H, CH$_3$), 7.25–7.75 (m, 8 H), 8.16 (s, 1 H), 11.67 (s, 1 H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 21.0, 21.2, 106.3, 126.2, 127.3, 127.9, 129.8, 130.4, 132.6,134.5, 142.6, 162.5, 164.0; IR (KBr) 3345 (s, NH), 1752 (m, C=O), 1695 m cm^{-1}.

3-(p-Methylphenyl)-4-formylsydnone p-chlorolbenzoylhydrazone (4c). Mp (recrystallized from EtOAc) 201–203°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.43 (s, 3H, CH$_3$), 7.28–7.90 (m, 8 H), 7.98 (s, 1 H), 11.63 (s, 1 H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 21.0, 106.0, 125.1, 127.0, 127.4, 128.8, 129.1, 130.2, 130.9, 134.2, 143.1, 162.4, 164.1; IR (KBr) 3359 (s, NH), 1752 (m, C=O), 1695 m cm^{-1}.

3-(p-Methylphenyl)-4-formylsydnone 4-(sydnon-3-yl)benzoylhydrazone (4d). Mp (recrystallized from MeOH) 210–212°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.43 (s, 3H, CH$_3$), 7.39–8.15 (m, 10 H, ArH + sydnone), 11.93 (s, 1 H, NH); IR (KBr) 3095 (s, NH), 1751 (m, C=O), 1679 m cm^{-1}.

3-(p-Methoxyphenyl)-4-formylsydnone benzoyl-hydrazone (5a). Mp (recrystallized from EtOAc) 183–185°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.88 (s, 3H, OCH$_3$), 7.12–7.72 (m, 9 H), 8.03 (s, 1 H), 11.56 (s, 1 H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 56.8, 106.2, 121.2, 121.7, 127.7, 129.3, 130.5, 130.6, 133.7, 134.8, 142.3, 162.8, 164.0; IR (KBr) 3334 (s, NH), 1755 (m, C=O), 1704 m cm^{-1}; FABMS *m/z* (relative intensity) 339 (M + 1, 68), 338 (M$^+$, 6).

3-(p-Methoxyphenyl)-4-formylsydnone p-methylbenzoylhydrazone (5b). Mp (recrystallized from EtOAc) 178–180°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.34 (s, 3H, CH$_3$), 3.88 (s, 3H, OCH$_3$), 7.25–7.79 (m, 8 H), 8.02 (s, 1 H), 11.66 (s, 1 H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 21.1, 56.7, 106.4, 121.3, 121.8, 127.7, 129.1, 130.3, 131.8, 133.8, 134.5, 142.1, 162.7, 164.0; IR (KBr) 3332 (s, NH), 1748 (m, C=O), 1701 m cm^{-1}; FABMS *m/z* (relative intensity) 353 (M + 1, 21), 352 (M$^+$, 2).

3-(p-Methoxyphenyl)-4-formylsydnone p-chlorolbenzoylhydrazone (5c). Mp (recrystallized from EtOAc) 191–193°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.87 (s, 3H, OCH$_3$), 7.03–7.70 (m, 8 H), 7.90 (s, 1 H), 11.52 (s, 1 H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 56.6, 106.1, 121.1, 121.2, 127.4, 129.2, 130.1, 130.5, 132.9, 134.5, 142.0, 161.7, 163.8; IR (KBr) 3361 (s, NH), 1755 (m, C=O), 1699 m cm^{-1}; FABMS *m/z* (relative intensity) 373 (M + 1, 62), 372 (M$^+$, 13).

3-(p-Methoxyphenyl)-4-formylsydnone 4-(sydnon-3-yl)benzoylhydrazone (5d). Mp (recrystallized from MeOH) 204–206°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.87 (s, 3H, OCH$_3$), 7.24–8.15 (m, 10 H, ArH + sydnone), 11.92 (s, 1 H, NH); IR (KBr) 3092 (s, NH), 1746 (m, C=O), 1683 m cm^{-1}; FABMS *m/z* (relative intensity) 423 (M + 1, 6), 422 (M$^+$, 1).

3-(p-Ethoxyphenyl)-4-formylsydnone benzoyl-hydrazone (6a). Mp (recrystallized from EtOAc) 192–194°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.37 (t, 3 H, J = 7.0 Hz, CH$_3$), 4.15 (q, 2 H, J = 7.0 Hz, CH$_2$), 7.20–7.83 (m, 9 H), 8.15 (s, 1 H), 11.70 (s, 1 H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 14.7, 64.2, 106.2, 125.8, 127.5, 127.7, 128.7, 129.1, 132.2, 133.2, 134.9, 142.3, 161.5, 163.0; IR (KBr) 3352 (s, NH), 1749 (m, C=O), 1698 m cm^{-1}; FABMS *m/z* (relative intensity) 353 (M + 1, 21), 352 (M$^+$, 3).

3-(p-Ethoxyphenyl)-4-formylsydnone p-methylbenzoylhydrazone (6b). Mp (recrystallized from EtOAc) 189–191°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.33 (t, 3 H, J = 7.0 Hz, CH$_3$), 2.44 (s, 3H, CH$_3$), 4.13 (q, 2 H, J = 7.0 Hz, CH$_2$), 7.20–7.78 (m, 9 H), 8.15 (s, 1 H), 11.65 (s, 1 H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 14.7, 21.2, 64.2, 106.1, 125.8, 127.4, 127.7, 128.7, 129.2, 130.2, 133.2, 134.6, 142.3, 164.0; IR (KBr) 3358 (s, NH), 1740 (m, C=O), 1695 m cm^{-1}; FABMS *m/z* (relative intensity) 367 (M + 1, 19), 366 (M$^+$, 4).

3-(p-Ethoxyphenyl)-4-formylsydnone p-chlorolbenzoylhydrazone (6c). Mp (recrystallized from EtOAc) 195–197°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.36 (t, 3 H, J = 7.0 Hz, CH$_3$), 4.13 (q, 2 H, J = 7.0 Hz, CH$_2$), 7.13–7.80 (m, 8 H), 7.91 (s, 1 H), 11.66 (s, 1 H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 14.6, 64.1, 105.8, 125.5, 127.2, 127.7, 128.8, 129.4, 132.2, 133.0, 134.6, 142.1, 160.8, 162.9; IR (KBr) 3350 (s, NH), 1745 (m, C=O), 1699 m cm^{-1}; FABMS *m/z* (relative intensity) 387 (M + 1, 51), 386 (M$^+$, 3).

3-(p-Ethoxyphenyl)-4-formylsydnone 4-(sydnon-3-yl)benzoylhydrazone (6d). Mp (recrystallized from MeOH) 178–180°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.37 (t, 3 H, J = 6.9 Hz, CH$_3$), 4.14 (q, 2 H, J = 6.9 Hz, CH$_2$), 7.21–8.16 (m, 10 H, ArH + sydnone), 11.93 (s, 1 H, NH); IR (KBr) 3094 (s, NH), 1749 (m, C=O), 1677 m cm^{-1}; FABMS *m/z* (relative intensity) 437 (M + 1, 6), 436 (M$^+$, 4).

Standard procedure for the oxidative–cyclization. Aldehyde *N*-acylhydrazones **3–6** (0.31 g, 1.00 mmol, 1.0 equiv) was dissolved in glacial acetic acid/dichloromethane (1/1, 15 mL). Lead oxide (PbO_2, 0.60 g, 2.50 mmol, 2.5 equiv) was added to the reaction mixture and stirred at 35–40°C for 1.5–6 h. After the reaction was completed, the reaction mixture was filtrated to remove the lead oxide residue and washed with cold dichloromethane (10 mL × 3). The filtrate was washed and extracted with saturated $NaHCO_3$ aqueous solution (20 mL × 2) to remove the residue glacial acetic acid. The combined organic layer was dried with $MgSO_{4\ (s)}$ and concentrated under reduced pressure. The residue was purified by recrystallization from dichloromethane to give pure 2,5-disubstituted-1,3,4-oxidiazole–sydnone hybrid derivatives **7–10** as a white powder in 50–63% yields.

3-Phenyl-4-(5-phenyl-1,3,4-oxadiazol-2-yl)sydnone (7a). Mp (recrystallized from CH_2Cl_2) 177–179°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.51–7.96 (m, 10 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 97.6, 120.6, 126.0, 126.5, 129.7, 129.9, 132.5, 133.0, 134.5, 154.1, 163.1, 163.9; IR (KBr) 1749 m cm^{-1}; FABMS *m*/*z* (relative intensity) 307 (M + 1, 77), 306 (M$^+$, 9); *Anal.* Calcd for $C_{16}H_{10}N_4O_3$: C, 62.74; H, 3.72; N, 18.30. Found: C, 62.51; H, 3.35; N, 18.04.

3-Phenyl-4-[5-(p-methylphenyl)-1,3,4-oxadiazol-2-yl]-sydnone (7b). Mp (recrystallized from CH_2Cl_2) 205–207°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.42 (s, 3H, CH_3), 7.34–7.94 (m, 9 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 21.2, 106.2, 125.9, 127.5, 127.7, 129.2, 130.3, 132.8, 133.4, 134.3, 142.2, 162.8, 164.1; IR (KBr) 1743 m cm^{-1}; FABMS *m*/*z* (relative intensity) 321 (M + 1, 48), 320 (M$^+$, 14); *Anal.* Calcd for $C_{17}H_{12}N_4O_3$: C, 63.75; H, 3.75; N, 17.50. Found: C, 63.91; H, 3.87; N, 17.81.

3-Phenyl-4-[5-(p-chlorophenyl)-1,3,4-oxadiazol-2-yl]sydnone (7c). Mp (recrystallized from CH_2Cl_2) 187–189°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.43–7.99 (m, 9 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 97.4, 121.3, 126.2,128.4, 129.5, 132.0, 133.1, 136.5, 154.5, 162.9, 164.0; IR (KBr) 1755 m cm^{-1}; *Anal.* Calcd for $C_{16}H_9N_4O_3Cl$: C, 56.38; H, 2.64; N, 16.45. Found: C, 56.63; H, 2.41; N, 16.64.

3-Phenyl-4-[5-(p-chlorophenyl)-1,3,4-oxadiazol-2-yl]-sydnone (7c). Mp (recrystallized from CH_2Cl_2) 187–189°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.43–7.99 (m, 9 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 97.4, 121.3, 126.2,128.4, 129.5, 132.0, 133.1, 136.5, 154.5, 162.9, 164.0; IR (KBr) 1755 m cm^{-1}; *Anal.* Calcd for $C_{16}H_9N_4O_3Cl$: C, 56.38; H, 2.64; N, 16.45. Found: C, 56.62; H, 2.41; N, 16.64.

3-p-Methylphenyl-4-(5-phenyl-1,3,4-oxadiazol-2-yl)sydnone (8a). Mp (recrystallized from CH_2Cl_2) 204–206°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.43 (s, 3H, CH_3), 7.41–7.78 (m, 9 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 21.2, 97.5, 122.6, 125.8, 126.7, 129.3, 129.9, 132.1, 133.5, 134.6, 154.5, 162.8, 163.6; IR (KBr) 1752 m cm^{-1}; FABMS *m*/*z* (relative intensity) 321 (M + 1, 45), 320 (M$^+$, 13); *Anal.* Calcd for $C_{17}H_{12}N_4O_3$: C, 63.75; H, 3.75; N, 17.50. Found: C, 63.68; H, 3.42; N, 17.86.

3-p-Methylphenyl-4-(5-phenyl-1,3,4-oxadiazol-2-yl)sydnone (8a). Mp (recrystallized from CH_2Cl_2) 204–206°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.43 (s, 3H, CH_3), 7.41–7.78 (m, 9 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 21.2, 97.5, 122.6, 125.8, 126.7, 129.3, 129.9, 132.1, 133.5, 134.6, 154.5, 162.8, 163.6; IR (KBr) 1752 m cm^{-1}; FABMS *m*/*z* (relative intensity) 321 (M + 1, 45), 320 (M$^+$, 13); *Anal.* Calcd for $C_{17}H_{12}N_4O_3$: C, 63.75; H, 3.75; N, 17.50. Found: C, 63.68; H, 3.42; N, 17.86.

3-(p-Methylphenyl)-4-[5-(p-chlorophenyl)-1,3,4-oxadiazol-2-yl]sydnone (8c). Mp (recrystallized from CH_2Cl_2) 202–205°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.42 (s, 3H, CH_3), 7.43–7.99 (m, 9 H); IR (KBr) 1749 m cm^{-1}; FABMS *m*/*z* (relative intensity) 357 (M + 1, 51), 356 (M$^+$, 16); *Anal.* Calcd for $C_{17}H_{11}N_4O_3Cl$: C, 57.55; H, 3.10; N, 15.80. Found: C, 57.33; H, 3.07; N, 15.72.

4-[5-(4-Sydnon-3-yl-phenyl)-1,3,4-oxadiazol-2-yl]-3-(4-methylphenyl)sydnone (8d). Mp (recrystallized from CH_2Cl_2) 215–217°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.45 (s, 3H, CH_3), 7.52 (d, 2 H, *J* = 8.2 Hz), 7.79 (d, 2 H, *J* = 8.2 Hz), 7.88 (s, 1 H), 8.01 (d, 2 H, *J* = 8.6 Hz), 8.14 (d, 2 H, *J* = 8.6 Hz); IR (KBr) 1753 m cm^{-1}; FABMS *m*/*z* (relative intensity) 397 (M + 1, 64), 396 (M$^+$, 11); *Anal.* Calcd for $C_{18}H_{10}N_6O_5$: C, 56.43; H, 2.97; N, 20.79. Found: C, 56.18; H, 3.24; N, 20.96.

3-p-Methoxyphenyl-4-(5-phenyl-1,3,4-oxadiazol-2-yl)-sydnone (9a). Mp (recrystallized from CH_2Cl_2) 224–226°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.89 (s, 3H, OCH_3), 7.25–7.78 (m, 9 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 56.6, 97.4, 122.3, 125.9, 126.3, 129.1, 130.2, 132.1, 133.6, 134.7, 154.8, 162.2, 164.0; IR (KBr) 1748 m cm^{-1}; FABMS *m*/*z* (relative intensity) 337 (M + 1, 37), 336 (M$^+$, 4); *Anal.* Calcd for $C_{17}H_{12}N_4O_4$: C, 60.71; H, 3.57; N, 16.67. Found: C, 60.87; H, 3.67; N, 16.54.

3-(p-Methoxyphenyl)-4-[5-(p-methylphenyl)-1,3,4-oxadiazol-2-yl]sydnone (9b). Mp (recrystallized from CH_2Cl_2) 188–190°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.38 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 7.19–7.88 (m, 8 H); IR (KBr) 1755 m cm^{-1}; FABMS *m*/*z* (relative intensity) 350 (M + 1, 28), 349 (M$^+$, 8); *Anal.* Calcd for $C_{18}H_{13}N_4O_4$: C, 61.71; H, 3.71; N, 16.00. Found: C, 61.52; H, 3.54; N, 15.86.

3-(p-Methoxyphenyl)-4-[5-(p-chlorophenyl)-1,3,4-oxadiazol-2-yl]sydnone (9c). Mp (recrystallized from CH_2Cl_2) 203–205°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.88 (s, 3H, OCH_3), 7.25–7.75 (m, 8 H); IR (KBr) 1744 m cm^{-1}; FABMS *m*/*z* (relative intensity) 372 (M + 1, 31), 371 (M$^+$, 9); *Anal.* Calcd for $C_{17}H_{11}N_4O_4Cl$: C, 55.06; H, 2.97; N, 15.11. Found: C, 54.94; H, 2.81; N, 14.89.

4-[5-(4-Sydnon-3-yl-phenyl)-1,3,4-oxadiazol-2-yl]-3-(4-methoxyphenyl)sydnone (9d). Mp (recrystallized from CH_2Cl_2) 225–227°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.86 (s, 3H, OCH_3), 7.35 (d, 2 H, *J* = 8.2 Hz), 7.82 (d, 2 H, *J* = 8.2 Hz), 7.88 (s, 1 H), 8.03 (d, 2 H, *J* = 8.5 Hz), 8.13 (d, 2 H, *J* = 8.5 Hz); IR (KBr) 1749 m cm^{-1}; FABMS *m*/*z* (relative intensity) 421 (M + 1, 3), 420 (M$^+$, 1); *Anal.* Calcd for $C_{19}H_{12}N_6O_6$: C, 53.77; H, 2.83; N, 22.64. Found: C, 53.97; H, 2.96; N, 22.81.

3-p-Ethoxyphenyl-4-(5-phenyl-1,3,4-oxadiazol-2-yl)sydnone (9a). Mp (recrystallized from CH_2Cl_2) 187–189°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.38 (t, 3 H, *J* = 6.9 Hz, CH_3), 4.16 (q, 2 H, *J* = 6.9 Hz, CH_2), 7.18–7.84 (m, 9 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 14.6, 64.2, 97.5, 115.3, 122.7, 126.5, 126.8, 127.5, 129.7, 132.5, 154.2, 161.7, 163.1, 164.0; IR (KBr) 1751 m cm^{-1}; FABMS *m*/*z* (relative intensity) 351 (M + 1, 49), 350 (M$^+$, 4); *Anal.* Calcd for $C_{18}H_{14}N_4O_4$: C, 61.71; H, 4.00; N, 16.00. Found: C, 61.58; H, 4.10; N, 15.89.

3-(p-Ethoxyphenyl)-4-[5-(p-methylphenyl)-1,3,4-oxadiazol-2-yl]sydnone (10b). Mp (recrystallized from CH_2Cl_2) 204–206°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.38 (t, 3 H, *J* = 6.9 Hz, CH_3), 2.43 (s, 3H, CH_3), 4.19 (q, 2 H, *J* = 6.9 Hz, CH_2), 7.22 (d, 2 H, *J* = 9.0 Hz), 7.36 (d, 2 H, *J* = 8.1 Hz), 7.64 (d, 2 H, *J* = 8.1 Hz), 7.82 (d, 2 H, *J* = 9.0 Hz); ^{13}C

NMR (DMSO-d_6, 75 MHz) δ 14.6, 21.3, 64.2, 97.5, 115.2, 120.0, 126.5, 126.8, 127.5, 130.2, 142.8, 153.9, 161.7, 163.2, 164.0; IR (KBr) 1751 m cm^{-1}; FABMS *m*/*z* (relative intensity) 365 (M + 1, 91), 364 (M$^+$, 7); *Anal.* Calcd for $C_{19}H_{16}N_4O_4$: C, 62.64; H, 4.40; N, 15.37. Found: C, 62.19; H, 4.08; N, 15.01.

3-(p-Ethoxyphenyl)-4-[5-(p-chlorophenyl)-1,3,4-oxadiazol-2-yl]sydnone (10c). Mp (recrystallized from CH_2Cl_2) 190–192°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.39 (t, 3 H, J = 7.0 Hz, CH_3), 4.17 (q, 2 H, J = 7.0 Hz, CH_2), 7.21–7.89 (m, 8 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 14.7, 64.3, 97.6, 114.8, 122.9, 125.9, 127.0, 127.8, 130.0, 132.1, 154.4, 161.5, 163.2, 164.1; IR (KBr) 1749 m cm^{-1}; FABMS *m*/*z* (relative intensity) 385 (M + 1, 11), 384 (M$^+$, 3); *Anal.* Calcd for $C_{18}H_{13}N_4O_4Cl$: C, 56.17; H, 3.38; N, 15.43. Found: C, 56.54; H, 3.68; N, 15.94.

4-[5-(4-Sydnon-3-yl-phenyl)-1,3,4-oxadiazol-2-yl]-3-(4-ethoxyphenyl)sydnone (10d). Mp (recrystallized from CH_2Cl_2) 178–181°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.38 (t, 3 H, J = 7.0 Hz, CH_3), 4.16 (q, 2 H, J = 7.0 Hz, CH_2), 7.25 (d, 2 H, J = 8.2 Hz), 7.85 (d, 2 H, J = 8.2 Hz), 7.88 (s, 1 H), 8.03 (d, 2 H, J = 8.5 Hz), 8.16 (d, 2 H, J = 8.5 Hz); IR (KBr) 1746 m cm^{-1}; FABMS *m*/*z* (relative intensity) 437 (M + 1, 28), 436 (M$^+$, 13); *Anal.* Calcd for $C_{20}H_{16}N_6O_6$: C, 55.05; H, 3.67; N, 19.27. Found: C, 55.37; H, 3.84; N, 19.47.

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The Synthesis and Application of 2-acetyl-6-(1-naphthyl)-pyridine Oxime as a New Ligand for Palladium Precatalyst in Suzuki Coupling Reaction

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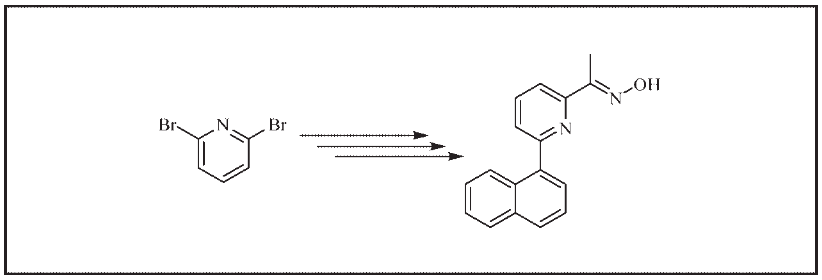

The synthesis of 2-acetyl-6-(1-naphthyl)-pyridine oxime ligand from 2,6-dibromopyridine and 1-bromo-naphthalene is described, and the new palladium(II) complex used as a Pd(0) precatalyst in the Suzuki cross-coupling reaction was studied. The results showed that the novel naphthalene pyridine oxime complex could serve as an efficient precatalyst.

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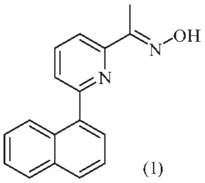
INTRODUCTION

It is widely accepted that palladium-catalyzed cross-coupling reaction are one of the most important processes in synthesis chemistry, of which Suzuki–Miyaura cross-coupling reaction of aryl halides with organoboron reagents has become one of the most efficient and widely utilized methods for the formation of sp^2-sp^2 carbon-carbon bonds [1–4]. Traditional phosphane containing palladium catalysts have many disadvantages such as high cost, air- and thermo-sensitivity, low activity towards deactivated substrates, contamination of the products with the phosphane-based byproducts [5,6]. Therefore, many efforts have been made to find more active and stable palladium catalysts. In our lab, oxime containing molecule [7] was synthesized and its catalyst activity in cross-coupling reaction was examined. Poor enantioselectivity was observed. So, we want to improve the activity by substitution of naphthalene group to pyridine.

Some common conclusions concerning the influence of the electronic and steric properties of the ligands on the efficiency of the catalysts in Suzuki-Miyaura reaction were made based on the structure-activity analysis of these catalysts. Increasing the electronic density on palladium could enhance the catalytic activity particularly by promoting the aryl halide oxidative addition; while the bulkness of the ligand presumably could facilitate the reductive elimination step [6]. We introduced the 1-naphthalene group to the pyridine oxime to obtain more active catalyst, and here, we reported the synthesis and application of a novel naphthalene pyridine oxime ligand on the Suzuki reaction (1).



(1)

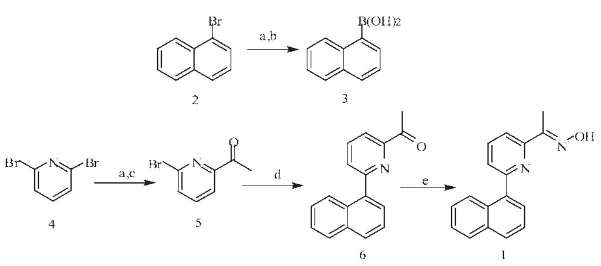
RESULTS AND DISCUSSION

Scheme 1 outlined the synthetic route employed in our lab for preparation of the substrate 1-[6-(1-naphthyl)-2-pyridyl]-1-ethanone oxime 1.

Our strategy for the synthesis of **6** was first based on the selective lithiation of 2,6-dibromopyridine [8–11] and then Suzuki cross coupling reaction [7]. After the synthesis of substrate of oxime, the precatalyst **7** was prepared by Scheme 2.

After the synthesis of (**7**), the application of naphthlene oxime ligand on Suzuki-cross coupling reaction was studied. At first, the optimal reaction time was investigated. The reaction was preceded very quickly at the first 60 min. Higher yield was not observed when the reaction time was longer as shown in Figure 1. So the optimal value for reaction time was 60 min.

Scheme 1



Conditions: a) ^{n}-BuLi, THF, -78 °C ; b) B(OBu)$_3$,-78 °C to r.t.; c) N,N-Dimethylacetamide,-78 °C to r.t.; d) Pd(PPh$_3$)$_2$Cl$_2$, 2M Na$_2$CO$_3$, Toluene, EtOH,reflux; e) NH$_2$OH HCl, EtOH,Pyridine,110 °C

The activity of the ligand was examined as shown in Table 1. The results demonstrated that the yield was influenced by the substitution of the aryl halides. The yield of bromo-benzene was the highest; the yield of *p*-bromo toluene was higher than that of *o*- and *m*-bromo toluene. 1-Methyl-4-nitrobenzene showed the lowest yield among all the reactions. This may be the reason that the substituents had the effect on reactivity of aryl halides. The nitro group was one of electron-withdrawing substituents decreasing the reactivity of the aryl halides, leading to the low yield in reaction. In addition, the effect of substituents on orientation was shown in Table 1. The methyl group was the weak electron-donating substituent. Therefore, the *ortho*/*para* bromo toluene was more active than the *meta* one because of a steric effect of the *ortho* methyl group behind the electron effection, the yield of *para* one was higher than that of *ortho* one. When water was added during the reaction, the yields become lower. When the 1-bromo-4-nitrobenzene was used as aryl halide in toluene with base of $CsCO_3$ for reflux 60 min, the yield was decreased to 33% (Run 8).

When the reaction of 1-(6-bromopyridin-2-yl)ethanone with naphthalen-1-ylboronic acid was carried out in toluene as solvent and Na_2CO_3 as base for refluxing 60 min and the yield was up to 85%, (Run 11), higher than the former reaction (Run 10).

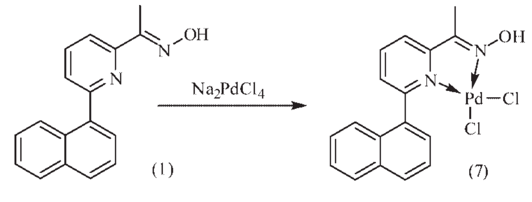
Further research related to higher activity based on the date is also underway.

EXPERIMENTAL

Deuterium NMR and CMR spectra were measured with a JNM-ECS400 NMR spectrometer at 400 MHz. Mass spectra (MS) were recorded on a JOEL JMS-AX505HA. The melting point was determined by MFB-595-030G digital thermometer apparatus.

1-Naphthylboronic acid(3). Dropwise addition of 7.95 mL (13.5 mmol) of a 1.7*M* solution of *t*-BuLi in pentane to a stirred solution of 1-bromonaphthaline (**2**) (2.67 g, 12.9 mmol) in 50 mL of THF at –78°C led to the formation of a white precipitate. After 45 min, 1.40 g (1.5 mL, 13.5 mmol) of $B(OMe)_3$ was added, and the resulting clear solution was maintained at –78°C for 1 h. The reaction mixture was allowed to warm to room temperature and stirring was continued for 3 h. A 10% solution of HCl (25 mL) and ethyl acetate (50 mL) were added. The aqueous layer was extracted with 4 × 20 mL of ethyl acetate. The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The off-white solid residue was suspended

Scheme 2



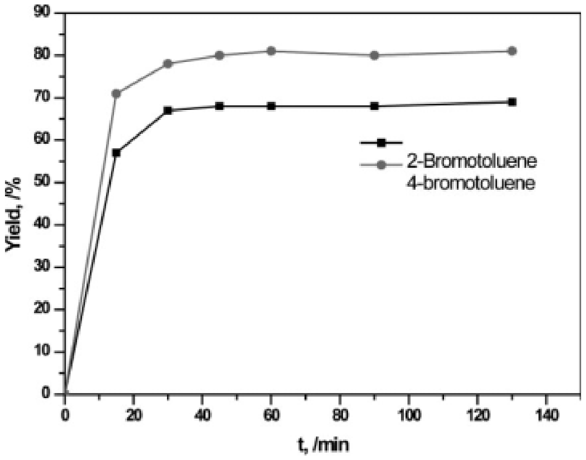
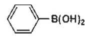
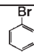
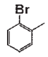
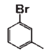
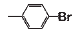
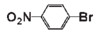
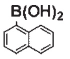
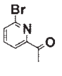


Figure 1. The yield-time relationship.

Table 1

Suzuki cross-coupling reaction.

Run	Ar-boronic acid	Br-Ar	Base	Water/ Toluene	Yield
1			Na_2CO_3	0:20	90
2			Na_2CO_3	0:20	73
3			Na_2CO_3	10:20	60
4			Na_2CO_3	0:20	60
5			Na_2CO_3	0:20	82
6			Na_2CO_3	10:20	55
7			Na_2CO_3	0:20	79
8			Ca_2CO_3	10:20	33
9			Na_2CO_3	0:20	94[a]
10			Na_2CO_3	10:20	80[b]
11			Na_2CO_3	10:20	85

Reagents and conditions: (2 mol%) Pd-catalyst, toluence, base, reflux, 60 min.

[a] Reactions time is 360 min.

[b] Catalyst is $Pd(PPh_3)_4$, reaction time is 12 h.

in 50 mL of petroleum ether and filtered to give **3** (2.13 g, yield 96%).

Mp 202–203°C; MS: *m/z* 172[M$^+$]; ^{1}H NMR (400 MHz, DMSO, δ, ppm); 7.50–8.10(*m*, 6H, Hnaph), 8.38(*s*, 2H, H_{OH}), 8.53(*d*, 1H, Hnaph, $J = 13.5$ Hz); IR(cm^{-1}) 3310 (—OH).

1-(6-Bromopyridin-2-yl)ethanone (5). A solution of 7.08 g (30 mmol) of 2,6-dibromopyridine (**4**) dissolved in 42 mL of dry THF was cooled to −78°C. The 2,6-dibromopyridine was lithiated by slowly adding 12 mL of a 2.6*M* solution of *n*-butyllithium in hexane. After the addition, the resulting dark yellow solution was stirred at −78° for 30 min. Then neat *N*,*N*-dimethylacetamide (4.2 mL, 54.3 mmol) was added over a period of 30 s. The reaction solution was stirred at −78 °C for 15 min, and then the solution was allowed to warm to room temperature. The resulting yellow solution was hydrolyzed with saturated NH_4Cl (40 mL). The mixture was stirred for additional 60 min, and the aqueous layer was separated and extracted with diethyl ether twice (100 mL and 60 mL, respectively). The combined organic layer was washed with brine 60 mL, dried (sodium sulfate) and evaporated to *ca.* 10 mL in volume and cooled to 0°C. After a few hours, a brown solid was isolated by filtration. The crude product was purified by chromatography on silica eluting with hexane/ethyl acetate (95:5) to afford white crystals, 5.1g (85%).

Mp 54–55°C; MS: *m/z* 199[M$^+$]; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 2.69(*s*, 3H, CH_3),7.65–7.71(*m*, 2H, H_{Ar}), 7.97–7.99 (dd, $J = 7.25$, 1.36, 1H, CH_{Ar}); IR(KBr, cm^{-1}) 1696 (C=O); 593 (C—Br).

1-(6-Naphalen-1-yl)pyridin-2-yl]ethanone(6). To a solution of 3 (0.72 g, 3.60 mmol) and $Pd(OAc)_2$ (0.13 g) in 10 mL of deaerated toluene, 4 mL of a 4.4*M* aqueous solution of Na_2CO_3 were added, followed by a solution of 0.79 g (4.58 mmol) of 1-naphthylboronic acid in 10 mL of MeOH. The mixture was heated to 80–85°C under stirring for 30 h. The resulting solution was allowed to cool to room temperature and a solution of 8 mL of concentrated aqueous NH_3 in 20 mL of saturated aqueous Na_2CO_3 was added. The mixture was extracted with 3 × 50 mL of CH_2Cl_2. The combined organic layers were washed with 50 mL of water and 100 mL of brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave 1.15 g of the crude product which was purified by flash chromatography [CC, SiO_2, i) petroleum ether/CH_2Cl_2 (4:1), $R_f = 0.1$, ii) CH_2Cl_2]. The desired product was obtained as an off-white solid in 80% yield (0.71 g).

MS: *m/z* 246[M − 1], 247 [M$^+$], 248[M + 1]; IR(cm^{-1}) 1698(C=O); ^{1}H NMR (400MHz, $CDCl_3$, δ, ppm) 2.76 (*s*, 3H, CH_3), 7.47–7.55 (*m*, 2H, H_{Ar}), 7.56–7.60 (*t*, $J = 7.30$, 7.70, 7.25, 1H, H_{Ar}), 7.64–7.66 (dd, $J = 7.02$, 0.91, 1.36, 1H, H_{Ar}), 7.76–7.78 (dd, $J = 7.70$, 0.91, 1H, H_{Ar}), 7.92–7.98(*m*, 3H, H_{Ar}),8.16-8.18(*d*, $J = 8.15$, 1H, H_{Ar})

1-(6-(Naphtgalene-1-yl)pyridin-2-yl)ethanone oxime (1). To a solution of $NH_2OH{\cdot}HCl$ (0.75 g, 10.8 mmol) in 10 mL of pyridine was added **6** (1.00 g, 5.22 mmol) and the mixture was stirred at 80°C for 4 h. After cooling to room temperature, the reaction mixture was poured into cold water and allowed to stay for 24 h. Precipitate thus formed was then collected by filtration, washed with water and dried in air to give 1.05 g (91%) of 3,5-diacetyl-2,6-dimethyl-pyridine dioxime.

Mp: 150–151°C; MS: *m/z* 262 [M$^+$]; ^{1}H NMR (400 MHz, DMSO, δ,ppm) 2.19(*s*, 3H, CH_3), 7.47–7.55(*m*, 2H, H_{Ar}), 7.57–7.61(*t*, $J = 7.25$, 1H, H_{Ar}), 7.61–7.63(dd, $J = 4.76$, 1.81, 1.36, 1H, H_{Ar}), 7.87–7.92(*t*, $J = 8.83$, 8.15, 9.51, 1H, H_{Ar}), 7.92–7.96(*t*, $J = 7.70$, 7.25, 8.15, 1H, H_{Ar}), 7.98–8.01(dd, $J = 7.16$, 1.36, 2H, H_{Ar}), 8.09–8.11(d, $J = 8.15$, 1H, H_{Ar}), 11.53(*s*, 1H, N-OH); ^{13}C NMR (400 MHz, DMSO, δ, ppm) 10.87, 118.67, 124.97, 125.90, 125.99, 126.53, 127.07, 128.06, 128.88, 129.33, 131.10, 134.06, 137.91, 138.39, 154.57, 157.96, 159.48. IR (KBr, cm^{-1}) 3300 (—OH).

Oxime-derived palladacycle (7) (preparation of precatalyst). To a stirred solution of sodium tetrachloropalladate(II) (147 mg, 0.5 mmol), which was obtained as well-formed crystals by treating $PdCl_2$ solutions with stoichiometric quantities of sodium chlorides and slowly evaporating the solutions in MeOH (2 mL), 2-acetyl-6-(1-naphthyl)-pyridine oxime (131 mg, 0.5 mmol) in MeOH (1 mL) was added dropwise. The precipitate was collected by filtration after stirring for 2 h and washed with MeOH and H_2O, then dried in vacuum over P_2O_5. Precatalyst **7** was obtained as a yellow-brownish powder (400 mg, 80%).

Mp > 300°C; IR(cm^{-1}): 1755, 1730, 1705 (C—O); MS: *m/z* 440[M + 1],880[M + M]; ^{1}H NMR (400 MHz, DMSO, δ, ppm) 2.19(*s*, 3H, CH_3), 7.47–7.64 (*m*, 5H, H_{Ar}), 7.87–8.00 (*m*, 4H, H_{Ar}), 11.53(*s*, 1H, N—OH); ^{13}C NMR (400 MHz, DMSO, δ, ppm) 10.87, 118.67, 124.96, 125.89, 125.98, 126.51, 127.06, 128.05, 128.87, 129.33, 131.09, 134.05, 137.91, 138.39, 154.57, 155.05, 157.96.

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An Efficient Biginelli One-Pot Synthesis of New Benzoxazole-Substituted Dihydropyrimidinones and Thiones Catalysed by Alumina-Supported Trifluoromethane Sulfonic Acid Under Solvent Free Conditions

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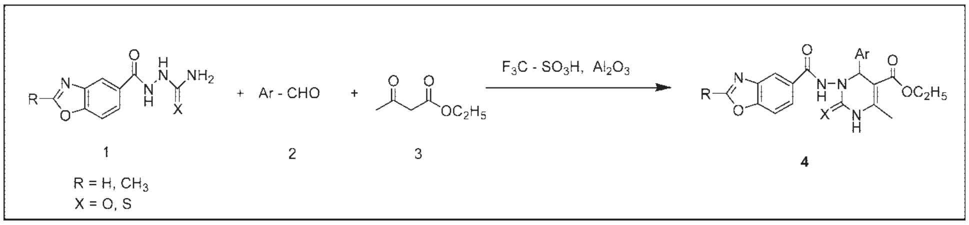

An efficient synthesis of benzoxazole-substituted 3,4-dihydropyrimidinones (DHPMs) using alumina supported trifluoromethane sulfonic acid as the catalyst for the first time from an aldehyde, β-keto ester, and benzoxazole-substituted urea and thiourea under solvent-free conditions is described. When compared with the classical Biginelli reaction conditions, this new method consistently has the advantage of excellent yields (80–93%) and short reaction time (30–120 minutes) at 120°C temperature.

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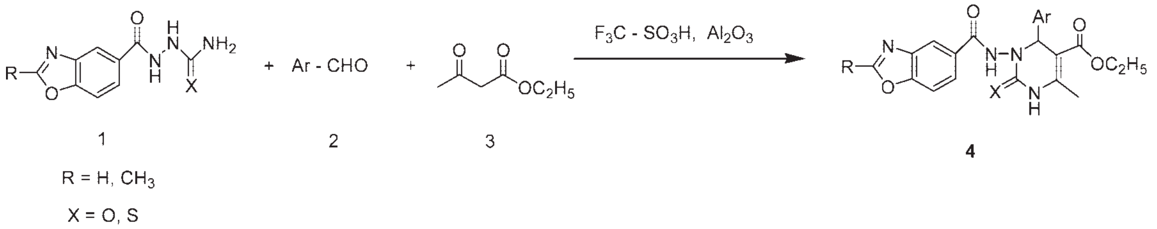
INTRODUCTION

The Biginelli (1893) reaction [1] is a simple one-pot condensation of an aldehyde, keto ester, and urea or thiourea in the presence of catalytic amount of acid to produce 3,4-dihydropyrimidin-2(1*H*)-ones. Dihydropyrimidinones (DHPMs) and their derivatives exhibit wide range of biological activities such as antibacterial, antiviral, antitumour, and anti-inflamatory actions [2]. Biginelli compounds exhibit pharmacological activities as calcium channel blockers, antihypertensive agents, α - 1a–antagonists, and neuro peptide Y(NPY) antagonists [3–6]. Biological activities of some marine alkaloids isolated were also found to contain the dihydropyrimidinone-5-carboxylate core [7]. Most notably among them are batezelladine alkaloids, which have been found to be potent HIV gp-120-CD4 inhibitors [8–10]. Consequently, syntheses of Biginelli compounds have gained importance, which often suffer from low yields practically in case of substituted aromatic and aliphatic aldehydes [11–13]. Even though, high yields could be achieved by following complex multistep procedures [14–17], these methods lack the simplicity of original one-pot Biginelli protocol. Therefore, Biginelli reaction continues to attract the attention of researchers for the discovery of a milder and efficient procedure for the synthesis of dihydropyrimidinones.

Similarly, benzoxazole nucleus can also be frequently recognized in the structure of numerous naturally occurring compounds with interesting biological and pharmacological properties. Benzaxazoles have been found to possess marked biological effects as anti inflammatory [18,19], anticancer [20] and antimicrobial [21,22] agents. In view of this benzoxazole-substituted urea and thiourea are used in the synthesis of 3,4-dihydropyrimidinones to get more biodynamic compounds.

In recent years, several synthetic procedures for preparing of DHPMs have been reported including classical conditions with microwave irradiation [23,24] and by using Lewis acids as well as protic acids as promoters such as [25–30] Conc. HCl, $BF_3.OEt_2$, PPE, KSF clay, $InCl_3$, $LaCl_3$, lanthanide triflate, H_2SO_4, ceric ammonium nitrate (CAN), $Mn(OAc)_3$, ion-exchange resin, 1*n*-butyl-3-methyl imidazolium tetra fluoroborate (BMImBF4), $BiCl_3$, $LiClO_4$, $InBr_3$, $FeCl_3$, $ZrCl_4$, $Cu(OTf)_2$, $Bi(OTf)_3$, LiBr, ytterbium triflates, NH_4Cl, $MgBr_2$, $SiO_2/NaHSO_4$, $CdCl_2$, and other reagents [31] have been found to be effective. Many of these methods involve expensive reagents, stochiometric amounts of catalysts, strongly acidic conditions, long reaction times, unsatisfactory yields, and incompatibility with other functional groups. Therefore, the development of a neutral alternative would extend the scope of the Biginelli reaction.

Scheme 1



Recently, the use of solid supported reagents [32] has received considerable importance in organic synthesis because of their ease of handling, enhanced reaction rates, greater selectivity, simple workup, and recoverability of catalysts. Among the various heterogeneous catalysts, particularly, alumina supported trifluoromethane sulfonic acid has advantages of low cost, ease of preparation, and catalyst recycling. As the reaction is heterogeneous in nature, the catalyst can conveniently be separated by simple filtration. In view of the recent surge in the use of heterogeneous catalysts [33–35], we wish to report a simple, convenient, and efficient method for the preparation of benzoxazole-substituted dihydropyrimidinone derivatives using alumina [36] supported trifluoromethane sulfonic acid, as an inexpensive and eco-friendly catalyst. This catalyst can act as eco-friendly for a variety of organic transformations because it is nonvolatile, recyclable, inexplosive, easy to handle, and thermally robust. In view of the emerging importance of heterogeneous catalysts, we wish to explore the use of alumina supported trifluoromethane sulfonic acid [37] as recyclable catalyst in the synthesis of DHPMs using substituted urea and thiourea.

RESULTS AND DISCUSSION

Initially, we have studied the Bignelli's one-pot condensation reaction of benzaldehyde (1.0 mmol) with benzoxazole-substituted urea (1.2 mmol) and ethyl acetoacetate (1.2 mmol) using 5 mol % of alumina-supported trifluoromethane sulfonic acid as catalyst under solvent free conditions (Scheme 1). The reaction is very fast and 90% conversion was observed in 1 h.

Encouraged by these results, we examined several aromatic and aliphatic aldehydes under optimized conditions (Table 1). Furthermore, the use of just 5 mol % alumina-supported trifluoromethane sulfonic acid as catalyst is sufficient to promote the reaction. There are no improvements in the reaction rates and yields by increasing the amount of the catalyst from 5 to 10 mol %. The best results were achieved when the reactions were carried out at 120°C temperature in an oil bath for 30–120 minutes in the presence of catalytic amount of alumina supported trifluoromethane sulfonic acid catalyst. The results are listed in Table 1. Another important feature of this procedure is the stability of a variety of functional groups such as ether, hydroxy, halides, nitro, *etc*., under these reaction conditions.

Benzoxazole-substituted urea and thiourea has been used with similar success to provide the corresponding dihydropyrimidinones and thiones in high yields, which are also of much interest with regard to biological activity. An acid sensitive aldehyde, worked well without formation of any side product. It is noteworthy which the survival of a variety of functional groups such as ether, hydroxy, halides, nitro, unsaturation, *etc*, under the reaction conditions.

The efficiency of the recovered catalyst was verified with the reaction of benzaldehyde, benzoxazole -substituted urea and ethyl acetoacetate (Entry 1). Using fresh catalyst, the yield of product (4**a**) was 90% while the recovered catalyst in the three subsequent recyclization the yields were 89, 87, and 86.

CONCLUSION

In summary, we have developed a new methodology for the synthesis of substituted DHPMs by using substituted urea and thiourea in the presence of a catalytic amount of alumina supported trifluoromethane sulfonic acid at 120°C temperature. Thus, alumina-supported trifluoromethane sulfonic acid mediated one-pot synthesis of DHPMs is, therefore, a simple, high yielding, time saving, and eco-friendly process. The catalyst can be prepared from available inexpensive reagents and can be easy recycled, which is heterogeneous and nonhazardous.

EXPERIMENTAL

All chemicals were A. R. grade obtained from Qualigens, India. All the solvents were purified by standard techniques. Column chromatographic separations were carried out on Silicagel 100–200 mesh size. I.R Spectra were scanned on a Perkin-Elmer, 1310 Spectrophotometer with sodium chloride optics. NMR spectra were recorded on a varian FT-200 MHz

Table 1

Alumina-supported trifluoromethane sulfonic acid-catalyzed synthesis of dihydropyrimidinones and thio derivatives.

Entry	R	Ar	X	Products	Time (min)	M.P. (°C)	Yield (%)
1	H	C_6H_5	O	**4a**	30	171–173	90
2	CH_3	C_6H_5	O	**4b**	60	164–165	87
3	H	$4\text{-}ClC_6H_4$	O	**4c**	40	193–194	90
4	CH_3	$4\text{-}ClC_6H_4$	O	**4d**	70	201–203	88
5	H	$4\text{-}NO_2C_6H_5$	O	**4e**	40	196–198	91
6	CH_3	$4\text{-}NO_2C_6H_4$	O	**4f**	80	209–210	87
7	H	$4\text{-}(CH_3)_2NC_6H_4$	O	**4g**	60	183–185	88
8	CH_3	$4\text{-}(CH_3)_2NC_6H_4$	O	**4h**	120	188–190	84
9	H	$2\text{-}OHC_6H_4$	O	**4i**	40	151–153	93
10	CH_3	$2\text{-}OHC_6H_4$	O	**4j**	60	167–168	86
11	H	Furyl	O	**4k**	50	217–219	82
12	CH_3	Furyl	O	**4l**	70	213–214	80
13	H	C_6H_5	S	**4m**	40	178–180	88
14	CH_3	C_6H_5	S	**4n**	70	161–163	85
15	H	$4\text{-}ClC_6H_4$	S	**4o**	60	199–200	87
16	CH_3	$4\text{-}ClC_6H_4$	S	**4p**	70	191–192	84
17	H	$4\text{-}NO_2C_6H_4$	S	**4q**	60	204–206	90
18	CH_3	$4\text{-}NO_2C_6H_4$	S	**4r**	80	211–212	88
19	H	$4\text{-}(CH_3)_2NC_6H_4$	S	**4s**	90	181–182	80
20	CH_3	$4\text{-}(CH_3)_2NC_6H_4$	S	**4t**	120	186–187	87
21	H	$2\text{-}OHC_6H_4$	S	**4u**	60	147–149	90
22	CH_3	$2\text{-}OHC_6H_4$	S	**4v**	90	156–158	82
23	H	Furyl	S	**4w**	80	207–208	83
24	CH_3	Furyl	S	**4x**	120	219–221	85

(GEMINI) using tetramethyl silane (TMS) as the internal standard. Mass spectra were obtained on micro Mass VG70-70H spectrometer operating at 70 eV using a direct inlet system.

Preparation of the catalyst. The catalyst was prepared by mixing alumina (5 mmol) with a trifluoromethane sulfonic acid (5 mmol) in distilled water (10 mL). The resulting mixture was stirred for 30 minutes to absorb triflouromethane sulfonic acid on the surface of alumina. After removal of water in a rotary evaporator, the solid powder was dried at 120°C for 2–3 h under reduced pressure. The drying temperature was maintained below the decomposition temperatures of the salts.

General procedure for the synthesis of DHPMs. A solution of an appropriate β-keto ester (1.2 mmol), corresponding aldehyde (1.0 mmol), benzaxazole substituted urea or thiourea (1.2 mmol), and alumina-supported trifluoromethane sulfonic acid (5 mol %) under solvent-free conditions was heated at 120°C (completion of reaction was monitored by TLC). The reaction mixture was washed thoroughly with water, filtered and recrystallized from methanol to afford pure product. The spectral data of the compounds are given below.

Entry 1 (4a). Solid, m.p. 171–173°C, ^1H NMR ($CDCl_3$): δ 1.20 (*t*, 3H, *J* = 7.0 Hz), 2.30 (*s*, 3H), 4.10 (*q*, 2H, *J* = 7.0 Hz), 4.72 (*s*, 1H), 6.72–8.94 (*m*, 9H, Ar—H), 9.64 (bs, 1H, NH), 10.48 (bs, 1H, NH). EMS: *m*/*z*: 420(M^+). IR (KBr): ν = 3427, 1715, 1686, 1608, 1584. Anal. Calc. for $C_{22}H_{20}N_4O_5$ (420.14): C, 62.85; H, 4.79; N, 13.33. Found: C, 62.83; H, 4.76; N, 13.32.

Entry 2 (4b). Solid, m.p. 164–165°C, ^1H NMR ($CDCl_3$): δ 1.22 (*t*, 3H, *J* = 7.0 Hz), 2.34 (*s*, 3H), 2.51(*s*, 3H), 4.16 (*q*, 2H, *J* = 7.0 Hz), 4.76 (*s*, 1H), 6.64–8.73 (*m*, 8H, Ar—H), 9.46 (bs, 1H, NH), 10.24 (bs, 1H, NH). EMS: *m*/*z*: 434(M^+). IR (KBr): ν = 3345, 1721, 1682, 1610, 1589. Anal. Calc. for $C_{23}H_{22}N_4O_5$ (434.16): C, 63.59; H, 5.10; N, 12.90. Found: C, 63.57; H, 5.06; N, 12.80.

Entry 3 (4c). Solid, m.p. 193–194°C, ^1H NMR ($CDCl_3$): δ 1.24 (*t*, 3H, *J* = 7.0 Hz), 2.38 (*s*, 3H), 4.20 (*q*, 2H, J = 7.0 Hz), 4.84 (*s*, 1H), 6.84–8.89 (*m*, 8H, Ar—H), 9.42 (bs, 1H, NH), 10.12 (bs, 1H, NH). EMS: *m*/*z*: 454(M^+). IR (KBr): ν = 3340, 1725, 1695, 1612, 1578. Anal. Calc. for $C_{22}H_{19}ClN_4O_5$ (454.1): C, 58.09; H, 4.21; N, 12.32; Cl, 7.79;. Found: C, 58.03; H, 4.18; N, 12.30; Cl, 7.70.

Entry 4 (4d). Solid, m.p. 201–203°C, ^1H NMR ($CDCl_3$): δ 1.19 (*t*, 3H, *J* = 7.0 Hz), 2.36 (*s*, 3H), 2.56(*s*, 3H), 4.18 (*q*, 2H, *J* = 7.0 Hz), 4.83 (*s*, 1H), 6.78–8.74 (m, 7H, Ar—H), 9.24 (bs, 1H, NH), 10.76 (bs, 1H, NH). EMS: *m*/*z*: 468(M^+). IR (KBr): ν = 3319, 1722, 1895, 1605, 1592. Anal. Calc. for $C_{23}H_{21}ClN_4O_5$ (468.12): C, 58.91; H, 4.51; N, 11.95; Cl, 7.56. Found: C, 58.89; H, 4.48; N, 11.90; Cl, 7.47.

Entry 5 (4e). Solid, m.p. 196–198°C, ^1H NMR ($CDCl_3$): δ 1.22 (*t*, 3H, *J* = 7.0 Hz), 2.34 (*s*, 3H), 4.25 (*q*, 2H, *J* = 7.0 Hz), 4.81 (*s*, 1H), 6.78–8.92 (*m*, 8H, Ar—H), 9.24 (bs, 1H, NH), 10.67 (bs, 1H, NH). EMS: *m*/*z*: 465(M^+). IR (KBr): ν = 3470, 1725, 1682, 1602, 1573. Anal. Calc. for $C_{22}H_{19}N_5O_7$ (465.13): C, 56.77; H, 4.11; N, 15.05. Found: C, 56.75; H, 4.08; N, 15.04.

Entry 6 (4f). Solid, m.p. 209–210°C, ^1H NMR ($CDCl_3$): δ 1.21 (*t*, 3H, J = 7.0 Hz), 2.41 (*s*, 3H), 2.62(*s*, 3H), 4.00 (*q*, 2H, *J* = 7.0 Hz), 4.87 (s, 1H), 6.91 – 8.72 (*m*, 7H, Ar—H), 9.24 (bs, 1H, NH), 10.96 (bs, 1H, NH). EMS: *m*/*z*: 479(M^+). IR (KBr): ν = 3345, 1723, 1695, 1605, 1592. Anal. Calc. for $C_{23}H_{21}N_5O_7$ (479.14): C, 57.62; H, 4.41; N, 14.61. Found: C, 57.60; H, 4.38; N, 14.60.

Entry 7 (4g). Solid, m.p. 183–185°C, ^1H NMR ($CDCl_3$): δ 1.04 (*t*, 3H, *J* = 7.0 Hz), 2.41 (*s*, 3H), 2.65(*s*, 6H, $N(CH_3)_2$), 4.08 (*q*, 2H, *J* = 7.0 Hz), 4.83 (*s*,1H), 6.67–8.76 (*m*, 8H, Ar—H), 9.18 (bs, 1H, NH), 10.86 (bs, 1H, NH). EMS: *m*/*z*: 463(M$^+$). IR (KBr): ν = 3295, 1714, 1677, 1611, 1575. Anal. Calc. for $C_{24}H_{25}N_5O_5$ (463.19): C, 62.19; H, 5.44; N, 15.10. Found: C, 62.17; H, 5.39; N, 15.09.

Entry 8 (4h). Solid, m.p. 188–190°C, ^{1}H NMR ($CDCl_3$): δ 1.19 (*t*, 3H, *J* = 7.0 Hz), 2.35 (*s*, 3H), 2.52(*s*, 3H), 2.67(*s*, 6H, $N(CH_3)_2$), 4.16 (*q*, 2H, *J* = 7.0 Hz), 4.78 (*s*,1H), 6.89–8.72 (*m*, 7H, Ar—H), 9.24 (bs, 1H, NH), 10.98 (bs, 1H, NH). EMS: *m*/*z*: 477(M$^+$). IR (KBr): ν = 3485, 1727, 1682, 1610, 1586. Anal. Calc. for $C_{25}H_{27}N_5O_5$ (477.2): C, 62.88; H, 5.70; N, 14.67. Found: C, 62.86; H, 5.23; N, 14.66.

Entry 9 (4i). Solid, m.p. 151–153°C, ^{1}H NMR ($CDCl_3$): δ 1.15 (*t*, 3H, *J* = 7.0 Hz), 2.36 (*s*, 3H), 4.20 (*q*, 2H, *J* = 7.0 Hz), 4.84 (*s*, 1H), 6.91–8.72 (*m*, 8H, Ar—H), 9.24 (bs, 1H, NH), 10.78 (bs, 1H, NH), 11.12 (bs, 1H, OH). EMS: *m*/*z*: 436(M$^+$). IR (KBr): ν = 3395, 1716, 1680, 1614, 1581. Anal. Calc. for $C_{22}H_{20}N_4O_6$ (436.14): C, 60.55; H, 4.62; N, 12.84. Found: C, 60.53; H, 4.58; N, 12.83.

Entry 10 (4j). Solid, m.p. 167–168°C, ^{1}H NMR ($CDCl_3$): δ 1.08 (*t*, 3H, *J* = 7.0 Hz), 2.36 (*s*, 3H), 2.61(*s*, 3H), 4.12 (*q*, 2H, *J* = 7.0 Hz), 4.89 (s, 1H), 6.84–8.67 (*m*, 7H, Ar—H), 9.14 (bs, 1H, NH), 10.29 (bs, 1H, NH), 11.20 (bs, 1H,OH). EMS: *m*/*z*: 450(M$^+$). IR (KBr): ν = 3410, 1712, 1692, 1607, 1575. Anal. Calc. for $C_{23}H_{22}N_4O_6$ (450.15): C, 61.33; H, 4.92; N, 12.44. Found: C, 61.31; H, 4.88; N, 12.40.

Entry 11 (4k). Solid, m.p. 217–219°C, ^{1}H NMR ($CDCl_3$): δ 1.18 (*t*, 3H, *J* = 7.0 Hz), 2.24 (*s*, 3H), 4.23 (*q*, 2H, *J* = 7.0 Hz), 4.76 (*s*, 1H), 7.12–8.53 (m, 7H, Ar—H), 9.20 (bs, 1H, NH), 10.76 (bs, 1H, NH). EMS: *m*/*z*: 410(M$^+$). IR (KBr): ν = 3317, 1719, 1675, 1610, 1594. Anal. Calc. for $C_{20}H_{18}N_4O_6$ (410.12): C, 58.53; H, 4.42; N, 13.65. Found: C, 58.51; H, 4.38; N, 13.60.

Entry 12 (4l). Solid, m.p. 213–214°C, ^{1}H NMR ($CDCl_3$): δ 1.19 (*t*, 3H, *J* = 7.0 Hz), 2.37 (*s*, 3H), 2.65(*s*, 3H), 4.16 (*q*, 2H, *J* = 7.0 Hz), 4.78 (*s*, 1H), 7.19–8.42 (m, 6H, Ar—H), 9.75 (bs, 1H, NH), 10.95 (bs, 1H, NH). EMS: *m*/*z*: 424 (M$^+$). IR (KBr): ν = 3347, 1716, 1689, 1612, 1589. Anal. Calc. for $C_{21}H_{20}N_4O_6$ (424.14): C, 59.43; H, 4.75; N, 13.20. Found: C, 59.41; H, 4.71; N, 13.18.

Entry 13 (4m). Solid, m.p.178–180°C, ^{1}H NMR ($CDCl_3$): δ 1.24 (*t*, 3H, *J* = 7.0 Hz), 2.32 (*s*, 3H), 4.18 (*q*, 2H, *J* = 7.0 Hz), 4.81 (*s*, 1H), 6.74–8.92 (*m*, 9H, Ar—H), 9.42 (bs, 1H, NH), 10.29 (bs, 1H, NH). EMS: *m*/*z*: 436 (M$^+$). IR (KBr): ν = 3489, 1717, 1689, 1602, 1591, 1242. Anal. Calc. for $C_{22}H_{20}N_4O_4S$ (436.12): C, 60.54; H, 4.62; N, 12.84. Found: C, 60.53; H, 4.58; N, 12.80.

Entry 14 (4n). Solid, m.p. 161–163°C, ^{1}H NMR ($CDCl_3$): δ 1.10 (*t*, 3H, *J* = 7.0 Hz), 2.22 (*s*, 3H), 2.46(*s*, 3H), 4.18 (*q*, 2H, *J* = 7.0 Hz), 4.92 (*s*, 1H), 6.84–8.86 (*m*, 8H, Ar—H), 9.82 (bs, 1H, NH), 10.46 (bs, 1H, NH). EMS: *m*/*z*: 450 (M$^+$). IR (KBr): ν = 3310, 1723, 1685, 1612, 1592, 1256. Anal. Calc. for $C_{23}H_{22}N_4O_4S$ (450.14): C, 61.32; H, 4.92; N, 12.44. Found: C, 61.31; H, 4.88; N, 12.40.

Entry 15 (4o). Solid, m.p. 199–200°C, ^{1}H NMR ($CDCl_3$): δ 1.09 (*t*, 3H, *J* = 7.0 Hz), 2.39 (*s*, 3H), 4.24 (*q*, 2H, *J* = 7.0 Hz), 4.86 (*s*, 1H), 6.89–8.87 (*m*, 8H, Ar—H), 9.24 (bs, 1H, NH), 10.74 (bs, 1H, NH). EMS: *m*/*z*: 470 (M$^+$). IR (KBr): ν = 3320, 1721, 1686, 1608, 1584, 1262. Anal. Calc. for $C_{22}H_{19}ClN_4O_4S$ (470.93): C, 56.11; H, 4.07; N, 11.90; Cl, 7.53. Found: C, 56.05; H, 4.03;; N, 11.89; Cl, 7.43.

Entry 16 (4p). Solid, m.p. 189–191°C, ^{1}H NMR ($CDCl_3$): δ 1.21 (*t*, 3H, *J* = 7.0 Hz), 2.34 (*s*, 3H),2.61(*s*, 3H), 4.26 (*q*, 2H, *J* = 7.0 Hz), 4.87 (*s*, 1H), 6.69–8.78 (*m*, 7H, Ar—H), 9.56 (bs, 1H, NH), 10.84 (bs, 1H, NH). EMS: *m*/*z*: 484 (M$^+$). IR (KBr): ν = 3359, 1716, 1888, 1618, 1589, 1259. Anal. Calc. for $C_{23}H_{21}ClN_4O_4S$ (484.1): C, 56.96; H, 4.36; N, 11.55; Cl, 7.31. Found: C, 56.90; H, 4.33; N, 11.50, Cl, 7.22.

Entry 17 (4q). Solid, m.p. 191–193°C, ^{1}H NMR ($CDCl_3$): δ 1.18 (*t*, 3H, *J* = 7.0 Hz), 2.31 (*s*, 3H), 4.28 (*q*, 2H, J = 7.0 Hz), 4.76 (*s*, 1H), 6.82–8.88 (*m*, 8H, Ar—H), 9.21 (bs, 1H, NH), 10.89 (bs, 1H, NH). EMS: *m*/*z*: 491 (M$^+$). IR (KBr): ν = 3478, 1720, 1679, 1598, 1559, 1242. Anal. Calc. for $C_{22}H_{19}N_5O_6S$(481.11): C, 54.88; H, 3.98; N, 14.55. Found: C, 54.87; H, 3.94; N, 14.54.

Entry 18 (4r). Solid, m.p. 207–208°C, ^{1}H NMR ($CDCl_3$): δ 1.16 (*t*, 3H, *J* = 7.0 Hz), 2.39 (*s*, 3H), 2.58 (*s*, 3H), 4.09 (*q*, 2H, *J* = 7.0 Hz), 4.69 (*s*, 1H), 6.87–8.79 (*m*, 7H, Ar—H), 9.32 (bs, 1H, NH), 10.76 (bs, 1H, NH). EMS: *m*/*z*: 495 (M$^+$). IR (KBr): ν = 3338, 1724, 1689, 1611, 1582, 1256. Anal. Calc. for $C_{23}H_{21}N_5O_6S$ (495.12): C, 55.75; H, 4.27; N, 14.13. Found: C, 55.74; H, 4.24; N, 14.10.

Entry 19 (4s). Solid, m.p. 182–183°C, ^{1}H NMR ($CDCl_3$): δ 1.14 (*t*, 3H, *J* = 7.0 Hz), 2.46 (*s*, 3H), 2.58(*s*, 6H, $N(CH_3)_2$), 4.16 (*q*, 2H, *J* = 7.0 Hz), 4.74 (*s*, 1H), 6.69–8.59 (m, 8H, Ar—H), 9.24 (bs, 1H, NH), 10.89 (bs, 1H, NH). EMS: *m*/*z*: 479 (M$^+$). IR (KBr): ν = 3291, 1718, 1659, 1602, 1561, 1269. Anal. Calc. for $C_{24}H_{25}N_5O_4S$ (479.16): C, 60.11; H, 5.25; N, 14.60. Found: C, 60.10; H, 5.21; N, 14.56.

Entry 20 (4t). Solid, m.p. 185–187°C, ^{1}H NMR ($CDCl_3$): δ 1.21 (*t*, 3H, *J* = 7.0 Hz), 2.24 (*s*, 3H), 2.56 (*s*, 3H), 2.71 (*s*, 6H, $N(CH_3)_2$), 4.12 (q, 2H, *J* = 7.0 Hz), 4.69 (*s*,1H), 6.79 – 8.77 (*m*, 7H, Ar—H), 9.31 (bs, 1H, NH), 11.04 (bs, 1H, NH). EMS: *m*/*z*: 493 (M$^+$). IR (KBr): ν = 3481, 1718, 1675, 1602, 1569, 1262. Anal. Calc. for $C_{25}H_{27}N_5O_4S$ (493.18): C, 60.83; H, 5.51; N, 14.19. Found: C, 60.82; H, 5.47; N, 14.15.

Entry 21 (4u). Solid, m.p. 165–165°C, ^{1}H NMR ($CDCl_3$): δ 1.12 (*t*, 3H, *J* = 7.0 Hz), 2.46 (*s*, 3H), 4.26 (*q*, 2H, J = 7.0 Hz), 4.79 (s, 1H), 6.86–8.82 (*m*, 8H, Ar—H), 9.36 (bs, 1H, NH), 10.89 (bs, 1H, NH), 11.14(bs, 1H, OH). EMS: *m*/*z*: 452 (M$^+$). IR (KBr): ν = 3386, 1712, 1669, 1609, 1579, 1248. Anal. Calc. for $C_{22}H_{20}N_4O_5S$ (452.12): C, 58.40; H, 4.46; N, 12.38. Found: C, 58.39; H, 4.42; N, 12.35.

Entry 22 (4v). Solid, m.p. 171–173°C, ^{1}H NMR ($CDCl_3$): δ 1.10 (*t*, 3H, *J* = 7.0 Hz), 2.31 (*s*, 3H), 2.49(*s*, 3H), 4.08 (*q*, 2H, *J* = 7.0 Hz), 4.74 (*s*, 1H), 6.69–8.66 (*m*, 7H, Ar—H), 9.19 (bs, 1H, NH), 10.21 (bs, 1H, NH), 11.18 (bs, 1H,OH). EMS: *m*/*z*: 466 (M$^+$). IR (KBr): ν = 3402, 1718, 1688, 1598, 1563, 1253. Anal. Calc. for $C_{23}H_{22}N_4O_5S$ (466.13): C, 59.22; H, 4.75; N, 12.01. Found: C, 59.21; H, 4.71; N, 12.00.

Entry 23 (4w). Solid, m.p. 212–214°C, ^{1}H NMR ($CDCl_3$): δ 1.14 (*t*, 3H, *J* = 7.0 Hz), 2.29 (*s*, 3H), 4.21 (*q*, 2H, *J* = 7.0 Hz), 4.58 (*s*, 1H), 7.16–8.59 (*m*, 7H, Ar-H), 9.28 (bs, 1H, NH), 10.81 (bs, 1H, NH). EMS: *m*/*z*: 426 (M$^+$). IR (KBr): ν = 3326, 1723, 1665, 1612, 1598, 1264. Anal. Calc. for $C_{20}H_{18}N_4O_5S$ (426.1): C, 56.33; H, 4.25; N, 13.14. Found: C, 56.32; H, 4.22; N, 13.10.

Entry 24 (4x). Solid, m.p. 206–207°C, ^{1}H NMR ($CDCl_3$): δ 1.23 (*t*, 3H, *J* = 7.0 Hz), 2.41 (*s*, 3H), 2.71 (*s*, 3H), 4.12 (*q*, 2H, *J* = 7.0 Hz), 4.72 (*s*, 1H), 7.12–8.56 (*m*, 6H, Ar—H), 9.89 (bs, 1H, NH), 10.89 (bs, 1H, NH). EMS: *m*/*z*: 440 (M$^+$). IR (KBr): ν = 3352, 1721, 1679, 1603, 1576, 1261. Anal. Calc.

for $C_{21}H_{20}N_4O_5S$ (440.12): C, 57.26; H, 4.58; N, 12.72. Found: C, 57.25; H, 4.54; N, 12.70.

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Efficient Synthesis of 1,2,4-Triazolo[4,3-*a*][1,8]naphthyridines Under Microwave Irradiation

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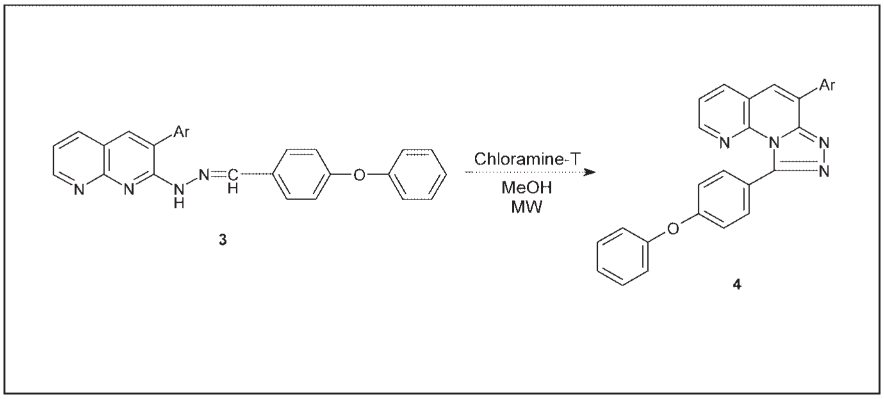

A simple and highly efficient procedure has been described for the synthesis of 6-aryl-9-(4-phenoxphenyl)-1,2,4-triazolo [4,3-a] [1,8] napthyridines **(4)** by the oxidation of 4-phenoxybenzaldehyde 3-aryl-1,8-naphthyridin-2-ylhydrazones **(3)** with chloramines-T in methanol under microwave irradiation. The products were obtained in very good yields and excellent purities.

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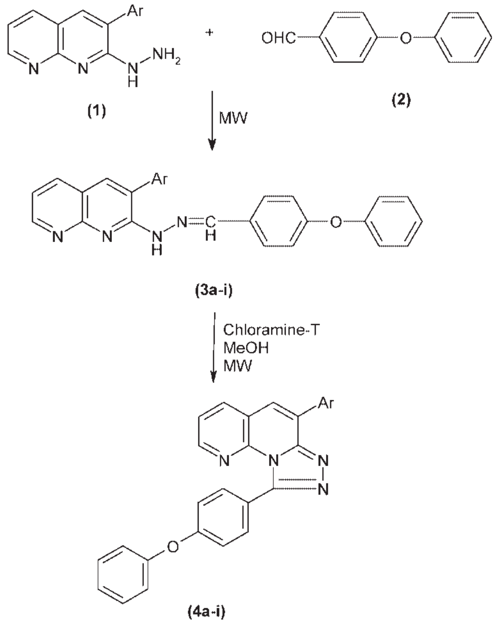
INTRODUCTION

1,8-Naphthyridines constitute an important class of compounds possessing diverse biological activities [1–3]. Various 1,2,4-triazoles have been extensively explored for their applications in the field of biological and pharmacological activities [4–6]. Therefore, it was envisaged that chemical entities with both 1,8-naphthyridine and 1,2,4-triazole might result in compounds with interesting biological activity. Microwave-assisted organic synthesis has attracted considerable attention in recent years [7–10], due to enhanced reaction rates, high yields, improved selectivity, and cleaner products. Several methods have been developed for performing reactions with microwave irradiation in solution and under solvent-free conditions, but a homogeneous mixture is preferred to obtain uniform heating. The solvents with higher dielectric constants are superheated and the reactions take place rapidly. Chloramine-T (CAT) is a very versatile oxidizing agent and is of much importance in its synthetic utility [11,12]. In view of this and in continuation of our interest in microwave-assisted organic transformations on 1,8-napthyridine derivatives [13–17], we report herein, a convenient, practical and efficient method for the synthesis of 1,2,4-triazolo[4,3-*a*][1,8] naphthyridines using CAT in methanol under microwave irradiation.

Scheme 1



Compd 3 and 4	Ar	Compd 3 and 4	Ar
a	C_6H_5	**f**	2-FC_6H_4
b	4-$CH_3OC_6H_4$	**g**	3-FC_6H_4
c	2-ClC_6H_4	**h**	4-FC_6H_4
d	3-ClC_6H_4	**i**	4-$CF_3C_6H_4$
e	4-ClC_6H_4		

RESULTS AND DISCUSSION

Condensation of 3-aryl-2-hydrazino-1,8-napthyridines (**1**) with 4-phenoxybenzaldehyde (**2**) in the presence of catalytic amount of DMF under microwave irradiation afforded the respective 4-phenoxybenzaldehyde 3-aryl-1,8-napthyridin-2-ylhydrazones (**3**) in excellent yields.

Oxidative cyclization of hydrazones **3** with CAT in methanol under microwave irradiation resulted in the formation of 6-aryl-9-(4-phenoxyphenyl)-1,2,4-triazolo-[4,3-*a*][1,8]naphthyridines (**4**). The oxidative transformation is clean and efficient. The experimental procedure is very simple. The high yield transformation did not form any undesirable by-products. Furthermore, the products were obtained with a higher degree of purity by this procedure and in most cases no further purification was needed. Interestingly, this oxidative reaction proceeds only to a minor extent (5–8% in 3.5–4.5 min) when conducted under conventional conditions in an oil-bath preheated to 110°C (temperature measured at the end of exposure during microwave experiment) which confirms the rate augmentation during microwave heating (Scheme 1).

The structural assignments of compounds **3** and **4** were based on their spectroscopic (IR and ^{1}H NMR; Table 1) and analytical data (Table 2).

The significant advantages of this procedure are operational simplicity, short reaction time, pure products, inexpensive, and nontoxicity of the reagent and high yields.

EXPERIMENTAL

Melting points were measured on a Cintex melting point apparatus and are uncorrected. The purity of the compounds was checked using precoated TLC plates (Merk, 60F-254). IR spectra (KBr) (ν_{max}: cm^{-1}) were recorded on a Perkin-Elmer BX series FTIR spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer (Chemical shifts in δ, ppm) using TMS as internal standard. Microanalyses were performed on a Perkin-Elmer 240 CHN elemental analyzer. Microwave irradiation was carried out in a domestic microwave oven (LG MG 556p, 2450 MHz). The starting compounds **1** were prepared according to our reported

Table 1

IR and ^{1}H NMR spectral data of 4-phenoxybenzaldehyde 3-aryl-1,8-naphthyridin-2-ylhydrazones (**3**) and 6-aryl-9-(4-phenoxyphenyl)-1,2,4-triazolo-[4,3-*a*][1,8]naphthyridines (**4**).

Compd	IR cm^{-1} (KBr)	^{1}H NMR (δ, ppm) ($CDCl_3$)
3a	3377 (NH), 1623 (C=N)	7.63 (m, 2H, C_4—H, C_6—H), 7.82 (m, 1H, C_5—H), 8.44 (m, 1H, C_7—H), 8.59 (s, 1H, N=CH), 6.92—7.50 (m, 15H, NH, 14Ar—H)
3b	3330 (NH), 1622 (C=N)	3.90 (s, 3H, OCH_3), 7.92 (m, 2H, C_4—H, C_6—H), 8.15 (m, 1H, C_5—H), 8.52 (m, 1H, C_7—H), 8.85 (s, 1H, N=CH), 6.95–7.72 (m, 14H, NH, 13Ar—H)
3c	3431 (NH), 1627 (C=N)	7.60 (m, 2H, C_4—H, C_6—H), 7.78 (m, 1H, C_5—H), 8.45 (m, 1H, C_7—H), 8.59 (s, 1H, N=CH), 6.90–7.38 (m, 14H, NH, 13Ar—H)
3d	3390 (NH), 1625 (C=N)	7.65 (m, 2H, C_4—H, C_6—H), 7.87 (m, 1H, C_5—H), 8.53 (m, 1H, C_7—H), 8.65 (s, 1H, N=CH), 6.92–7.45 (m, 14H, NH, 13Ar—H)
3e	3425 (NH), 1623 (C=N)	7.62 (m, 2H, C_4—H, C_6—H), 7.89 (m, 1H, C_5—H), 8.43 (m, 1H, C_7—H), 8.62 (s, 1H, N=CH), 6.91–7.40 (m, 14H, NH, 13Ar—H)
3f	3360 (NH), 1628 (C=N)	7.67 (m, 2H, C_4—H, C_6—H), 7.80 (m, 1H, C_5—H), 8.25 (m, 1H, C_7—H), 8.78 (s, 1H, N=CH), 6.90–7.43 (m, 14H, NH, 13Ar—H)
3g	3353 (NH), 1625 (C=N)	7.65 (m, 2H, C_4—H, C_6—H), 7.85 (m, 1H, C_5—H), 8.47 (m, 1H, C_7—H), 8.66 (s, 1H, N=CH), 6.92–7.45 (m, 14H, NH, 13Ar—H)
3h	3345 (NH), 1626 (C=N)	7.60 (m, 2H, C_4—H, C_6—H), 7.88 (m, 1H, C_5—H), 8.14 (m, 1H, C_7—H), 8.63 (s, 1H, N=CH), 6.88–7.42 (m, 14H, NH, 13Ar—H)
3i	3360 (NH), 1626 (C=N)	7.75 (m, 2H, C_4—H, C_6—H), 8.00 (m, 1H, C_5—H), 8.22 (m, 1H, C_7—H), 8.78 (s, 1H, N=CH), 6.91–7.43 (m, 14H, NH, 13Ar—H)
4a	1603 (C=N)	8.12 (m, 3H, C_3—H, C_4—H, C_5—H), 8.45 (m, 1H, C_2—H), 7.02–7.70 (m, 14H, Ar—H)
4b	1608 (C=N)	3.89 (s, 3H, OCH_3), 8.10 (m, 3H, C_3—H, C_4—H, C_5—H), 8.40 (m, 1H, C_2—H), 7.00–7.65 (m, 13H, Ar—H)
4c	1605 (C=N)	7.70 (m, 2H, C_3—H, C_5—H), 8.15 (m, 1H, C_4—H), 8.50 (m, 1H, C_2—H), 7.02–7.52 (m, 13H, Ar—H)
4d	1608 (C=N)	7.82 (m, 2H, C_3—H, C_5—H), 8.20 (m, 1H, C_4—H), 8.48 (m, 1H, C_2—H), 7.00–7.54 (m, 13H, Ar—H)
4e	1604 (C=N)	7.78 (m, 2H, C_3—H, C_5—H), 8.18 (m, 1H, C_4—H), 8.45 (m, 1H, C_2—H), 7.02–7.56 (m, 13H, Ar—H)
4f	1605 (C=N)	7.63 (m, 1H, C_3—H), 8.05 (m, 1H, C_5—H), 8.15 (m, 1H, C_4—H), 8.47 (m, 1H, C_2—H), 7.00–7.53 (m, 13H, Ar—H)
4g	1610 (C=N)	7.80 (m, 2H, C_3—H, C_5—H), 8.16 (m, 1H, C_4—H), 8.45 (m, 1H, C_2—H), 7.02–7.66 (m, 13H, Ar—H)
4h	1606 (C=N)	8.13 (m, 3H, C_3—H, C_4—H, C_5—H), 8.44 (m, 1H, C_2—H), 7.00–7.65 (m, 13H, Ar—H)
4i	1607 (C=N)	8.20 (m, 3H, C_3—H, C_4—H, C_5—H), 8.48 (m, 1H, C_2—H), 7.03—7.82 (m, 13H, Ar—H)

Table 2

Physical and analytical data of 4-phenoxybenzaldehyde 3-aryl-1,8-naphthyridin-2-ylhydrazones (**3**) and 6-aryl-9-(4-phenoxyphenyl)-1,2,4-triazolo-[4,3-*a*][1,8]naphthyridines (**4**).

					Elemental analysis Found/(Calcd)		
Compd	Reaction time (min)	MP (°C)	Yield (%)	Mol. formula	C	H	N
3a	1.0	170–172	95	$C_{27}H_{20}N_4O$	77.75 (77.89)	4.86 (4.81)	13.53 (13.46)
3b	1.5	156–158	94	$C_{28}H_{22}N_4O_2$	75.50 (75.34)	4.97 (4.93)	12.64 (12.56)
3c	1.0	152–153	93	$C_{27}H_{19}ClN_4O$	71.77 (71.92)	4.26 (4.22)	12.50 (12.43)
3d	1.5	145–147	92	$C_{27}H_{19}ClN_4O$	71.78 (71.92)	4.28 (4.22)	12.49 (12.43)
3e	1.0	159–160	96	$C_{27}H_{19}ClN_4O$	71.76 (71.92)	4.27 (4.22)	12.51 (12.43)
3f	1.0	172–174	93	$C_{27}H_{19}FN_4O$	74.81 (74.65)	4.43 (4.38)	12.98 (12.90)
3g	1.5	148–150	94	$C_{27}H_{19}FN_4O$	74.79 (74.65)	4.44 (4.38)	12.97 (12.90)
3h	1.5	162–163	95	$C_{27}H_{19}FN_4O$	74.80 (74.65	4.42 (4.38)	12.96 (12.90)
3i	1.5	140–142	94	$C_{28}H_{19}F_3N_4O$	69.58 (69.42)	3.98 (3.93)	11.66 (11.57)
4a	3.5	208–210	90	$C_{27}H_{18}N_4O$	78.41 (78.26)	4.40 (4.35)	13.61 (13.53)
4b	4.5	200–202	87	$C_{28}H_{20}N_4O_2$	75.83 (75.68)	4.60 (4.50)	12.70 (12.61)
4c	4.0	228–230	86	$C_{27}H_{17}ClN_4O$	72.40 (72.24)	3.84 (3.79)	12.56 (12.49)
4d	4.0	214–216	85	$C_{27}H_{17}ClN_4O$	72.38 (72.24)	3.85 (3.79)	12.58 (12.49)
4e	3.5	230–232	92	$C_{27}H_{17}ClN_4O$	72.39 (72.24)	3.84 (3.79)	12.57 (12.49)
4f	3.5	206–208	87	$C_{27}H_{17}FN_4O$	75.15 (75.00)	3.99 (3.94)	13.05 (12.96)
4g	4.0	210–212	86	$C_{27}H_{17}FN_4O$	75.16 (75.00)	3.98 (3.94)	13.04 (12.96)
4h	3.5	238–240	90	$C_{27}H_{17}FN_4O$	75.14 (75.00)	3.99 (3.94)	13.03 (12.96)
4i	4.5	218–220	89	$C_{28}H_{17}F_3N_4O$	69.86 (69.71)	3.57 (3.53)	11.69 (11.62)

procedures [16–20]. The 4-phenoxylbenzaldehyde (**2**) was purchased from Aldrich Chemical Company.

General procedure for the synthesis of 4-phenoxybenzaldehyde 3-aryl-1,8-naphthyridin-2-ylhydrazones (3). A mixture of 1 (20.0 mmol), 4-phenoxy-benzaldehyde (2, 20.0 mmol) and DMF (5 drops) was subjected to microwave irradiation at 400 watts intermittently at 30 s intervals for the specified time (Table 2). On completion of reaction, as monitored by TLC, the reaction mixture was cooled and treated with cold water. The resulting solid product was collected by filtration, washed with water and re-crystallized from ethanol to give **3** (Table 2).

General procedure for the synthesis of 6-aryl-9-(4-phenoxyphenyl)-1,2,4-triazolo[4,3-*a*][1,8]napthyridines (4). To a solution of appropriate hydrazone **4** (20.0 mmol) in methanol (15 mL), CAT (20.0 mmol) was added. The reaction mixture was exposed to microwaves at 400 watts intermittently at 30 s intervals for specified time (Table 2). After complete conversion as indicated by TLC, the reaction mixture was cooled and digested with cold water. The solid then obtained was collected by filtration, washed with water and re-crystallized from ethanol to afford **4** (Table 2).

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PhI(OAc)$_2$-Al$_2$O$_3$ Mediated Synthesis of 1,8-Naphthyridinyl-1,3,4-Oxadiazoles Under Microwave Irradiation

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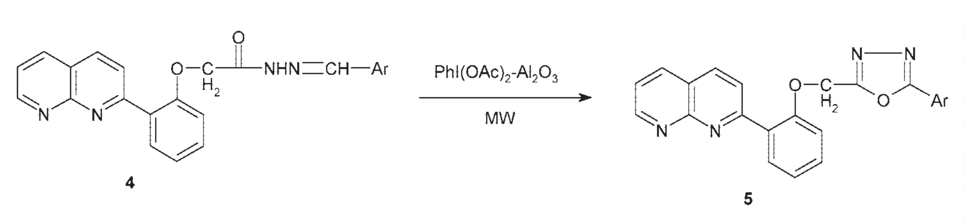

Alumina-supported iodobenzene diacetate [PhI(OAc)$_2$-Al$_2$O$_3$] is a highly efficient reagent for the oxidative cyclization of [*o*-(1,8-naphthyridin-2-yl)phenoxy]acetic acid arylidene hydrazides **4** to 5-aryl-2-[*o*-(1,8-naphthyridin-2-yl)phenoxymethyl]-1,3,4-oxadiazoles **5** in solvent-free conditions under microwave irradiation. The products are obtained in good yields and in a state of high purity.

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INTRODUCTION

1,8-Naphthyridine derivatives acquired a special place in the heterocyclic field because of their diversified activities such as antibacterial [1], antitumor [2], antihypertensive [3], and anti-inflammatory [4]. 1,3,4-Oxadiazoles are biologically active [5,6], synthetically useful and important heterocyclic compounds. For these reasons the chemistry of 1,3,4-oxa-diazoles have been the subject of many investigations [7–10]. However, most of these investigations suffer from serious drawbacks which include the use of hazardous, highly toxic, long reaction times, low yields, drastic reaction conditions, and expensive or commercially unavailable reagents. In view of the rapidly increasing demands for green chemistry, an efficient and convenient method for the synthesis of 1,3,4-oxadiazoles is highly desirable.

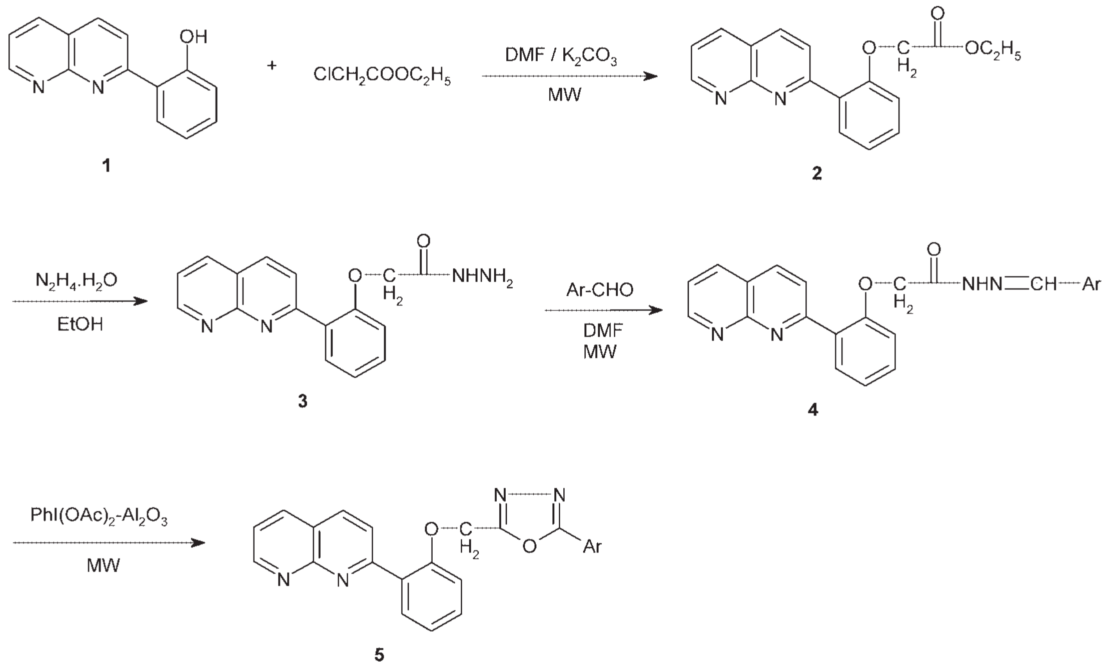
The versatile synthetic utility of organic hypervalent iodine reagents in general and iodobenzene diacetate (IBD) in particular is of current interest [11–13]. Microwave (MW) activation has become a very popular and useful technology in synthetic organic chemistry [14–16]. Recently, more interest has been focused on ''dry media'' synthesis using inorganic solid supports. The coupling of MW heating mode with the use of mineral solid support [17–19] such as alumina, silica, and clays have been used for the synthesis of several organic compounds with higher selectivity, yield and purity compared to traditional methods. In continuation of our interest in the MW assisted organic transformations of 1,8-naphthyrdines [20–23], we report herein, a practical and highly efficient method for the synthesis of 1,8-naphthyridinyl-1,3,4-oxadiazoles using alumina-supported IBD [PhI(OAc)$_2$-Al$_2$O$_3$] in solvent free conditions under MW irradiation.

RESULTS AND DISCUSSION

Alkylation of 2-(*o*-hydroxyphenyl)-1,8-naphthyridine **1** [24] with ethyl chloroacetate in DMF in the presence of anhydrous K$_2$CO$_3$ under MW irradiation resulted in the formation of ethyl [*o*-(1,8-naphthyridin-2-yl)phenoxy] acetate **2**, which on hydrazinolysis with refluxing hydrazine hydrate afforded [*o*-(1,8-naphthyridin-2-yl)phenoxy]acetic acid hydrazide **3**. Treatment of hydrazide **3** with aromatic aldehydes in the presence of catalytic amount of DMF under MW irradiation furnished the corresponding hydrazones, [*o*-(1,8-naphthyridin-2-yl)phenoxy]acetic acid arylidenehydrazides **4** in excellent yields.

The hydrazones **4** on oxidative cyclization with alumina-supported IBD [PhI(OAc)$_2$-Al$_2$O$_3$] [25] in the absence of solvent under MW irradiation resulted in the formation of 5-aryl-2-[*o*-(1,8-naphthyridin-2-yl)phenoxymethyl]-1,3,4-oxadiazoles **5** (Scheme 1). The reaction proceeds efficiently in good yields at ambient pressure within a few minutes. The transformation is very clean and rapid. The reaction conditions and work-up procedures are mild, simple and convenient. Furthermore, it is to be noted that highly pure products were obtained using this simple procedure and in most cases no further purification was needed. The recyclability of the alumina support makes this an environmentally friendly ''green'' protocol. On comparing the rate enhancement effect of MW irradiation on the investigated reaction, the oxidative

Scheme 1



cyclization of hydrazone **4a** was chosen as a model reaction. The reaction gave compound **5a** in 10% yield in 5.0 min, when conducted under conventional conditions in an oil-bath preheated to 120°C (temperature measured at the end of exposure during MW experiment).

The structural assignments to compounds **2–5** were based on their spectral (IR and ^{1}H NMR) and analytical data. To the best of our knowledge this is the first report of the rapid synthesis of 1,3,4-oxadiazoles using PhI(OAc)$_2$-Al$_2$O$_3$ under solvent-free MW irradiation conditions.

In conclusion, the present procedure with PhI(OAc)$_2$-Al$_2$O$_3$ provides a very efficient method for the synthesis of 1,3,4-oxadiazoles under solvent-free conditions using MW irradiation. The notable advantages of this method are: operational simplicity, ready availability of reagents and general applicability, mild reaction conditions, short reaction times, good yields, and environmentally benign procedure.

EXPERIMENTAL

Melting points were measured on a Cintex melting point apparatus and are uncorrected. The purity of the compounds was checked by TLC. IR spectra in KBr were recorded on a Perkin-Elmer BX series FTIR spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer (chemical shifts in δ, ppm) using TMS as internal standard. Elemental analyses (CHN) were performed on a Perkin-Elmer 240 CHN analyzer. Irradiation was carried out in a domestic MW oven (LG MG-556P, 2450 MHz).

Ethyl [*o*-(1,8-naphthyridin-2-yl)phenoxy]-acetate 2. A mixture of 2-(*o*-hydroxyphenyl)-1,8-naphthyridine **1** (0.01 mol), ethyl chloroacetate (0.01 mol), anhydrous K$_2$CO$_3$ (0.01 mol), and DMF (10 mL) was exposed to MWs at 400 watts intermittently at 30 s intervals for 4.5 min. After completion of reaction, as indicated by TLC, the reaction was cooled and poured onto crushed ice. The precipitate thus obtained was collected by filtration, washed with water and re-crystallized from ethanol to give **2**, yield 96%, mp 130°C; IR: 1755, 1610 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.29 (t, J = 7.0 Hz, 3H, CH$_3$), 4.28 (q, J = 7.0 Hz, 2H, CH$_2$), 4.71 (s, 2H, O—CH$_2$), 8.28 (m, 3H, C$_3$—H, C$_4$—H, C$_5$—H), 7.98 (m, 1H, C$_6$—H), 9.13 (m, 1H, C$_7$—H), 6.90–7.59 (m, 4H, Ar—H); *Anal.* Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.13; H, 5.19; N, 9.09. Found : C, 70.29; H, 5.24; N, 9.15%.

[*o*-(1,8-Naphthyridin-2-yl)-phenoxy]acetic acid hydrazide 3. A mixture of **2** (0.01 mol) and hydrazine hydrate (0.015 mol) in ethanol (20 mL) was refluxed on a water-bath for 6 h. The reaction mixture was cooled, the separated solid was collected by filtration and re-crystallized from ethanol to furnish **3**, yield 92%, mp 150°C; IR: 3450, 3275, 3082, 1675, 1605 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.92 (br, 2H, NH$_2$), 4.83 (s, 2H, CH$_2$), 8.22 (m, 3H, C$_3$—H, C$_4$—H, C$_5$—H), 7.95 (m, 1H, C$_6$—H), 9.12 (m, 1H, C$_7$—H), 6.97–7.54 (m, 4H, Ar—H), 9.56 (s, 1H, CONH); *Anal.* Calcd. for $C_{16}H_{14}N_4O_2$: C, 65.31; H, 4.76; N, 19.05. Found: C, 65.49; H, 4.80; N, 19.12%.

General procedure for the synthesis of [*o*-(1,8-naphthyridin-2-yl)phenoxy]acetic acid arylidene hydrazides 4. A mixture of **3** (0.01 mol), aromatic aldehyde (0.01 mol), and DMF (five drops) was subjected to MW irradiation at 400 watts intermittently at 30 s intervals for the specified time (Table 1). On completion of the reaction, as monitored by TLC, the reaction mixture was digested with cold water. The resulting solid

Table 1

Physical and analytical data of [*o*-(1,8-naphthyridin-2-yl)phenoxy]acetic acid arylidenehydrazides **4** and 5-aryl-2-[*o*-(1,8-naphthyridin-2-yl)phenoxymethyl]-1,3,4-oxadiazoles **5**.

Entry	Ar	Reaction period (min)	M.p. (°C)	Yield (%)	Mol. formula	Found % (Calcd)		
						C	H	N
4a	C_6H_5	1.0	184	96	$C_{23}H_{18}N_4O_2$	72.43 (72.25)	4.76 (4.71)	14.74 (14.66)
4b	*p*-$CH_3C_6H_4$	0.5	176	98	$C_{24}H_{20}N_4O_2$	72.91 (72.73)	4.08 (5.05)	14.21 (14.14)
4c	*p*-$CH_3OC_6H_4$	1.5	234	94	$C_{24}H_{20}N_4O_3$	69.72 (69.90)	4.49 (4.85)	13.66 (13.59)
4d	*p*-ClC_6H_4	1.0	180	97	$C_{23}H_{17}ClN_4O_2$	66.45 (66.27)	4.02 (4.08)	13.49 (13.45)
4e	*o*-BrC_6H_4	1.5	200	94	$C_{23}H_{17}BrN_4O_2$	59.71 (59.87)	3.74 (3.69)	12.22 (12.15)
4f	*m*-$NO_2C_6H_4$	0.5	210	92	$C_{23}H_{17}N_5O_4$	64.80 (64.64)	3.94 (3.98)	16.46 (16.39)
4g	2,4-$Cl_2C_6H_3$	1.0	185	93	$C_{23}H_{16}Cl_2N_4O_2$	61.38 (61.20)	3.40 (3.55)	12.47 (12.42)
4h	2,6-$Cl_2C_6H_3$	1.5	223	92	$C_{23}H_{16}Cl_2N_4O_2$	61.36 (61.20)	3.41 (3.55)	12.49 (12.42)
5a	C_6H_5	5.0	>300	90	$C_{23}H_{16}N_4O_2$	72.76 (72.63)	4.26 (4.21)	14.80 (14.74)
5b	*p*-$CH_3C_6H_4$	4.5	>300	95	$C_{24}H_{18}N_4O_2$	73.27 (73.10)	4.61 (4.57)	14.29 (14.21)
5c	*p*-$CH_3OC_6H_4$	5.5	>300	92	$C_{24}H_{18}N_4O_3$	70.42 (70.24)	4.43 (4.39)	13.72 (13.66)
5d	*p*-ClC_6H_4	5.0	>300	93	$C_{23}H_{15}ClN_4O_2$	66.75 (66.59)	3.66 (3.62)	13.58 (13.51)
5e	*o*-BrC_6H_4	6.0	>300	90	$C_{23}H_{15}BrN_4O_2$	60.30 (60.13)	3.32 (3.27)	12.29 (12.20)
5f	*m*-$NO_2C_6H_4$	6.5	>300	88	$C_{23}H_{15}N_5O_4$	64.78 (64.94)	3.58 (3.53)	16.41 (16.47)
5g	2,4-$Cl_2C_6H_3$	5.5	>300	89	$C_{23}H_{14}Cl_2N_4O_2$	61.63 (61.47)	3.16 (3.12)	12.55 (12.47)
5h	2,6-$Cl_2C_6H_3$	6.5	>300	87	$C_{23}H_{14}Cl_2N_4O_2$	61.62 (61.47)	3.17 (3.12)	12.56 (12.47)

product was collected by filtration, washed with water, and re-crystallized from ethanol to afford **4**.

4a. IR: 3432, 1690, 1615 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.90 (s, 2H, CH_2), 8.18 (m, 3H, C_3—H, C_4—H, C_5—H), 7.92 (m, 1H, C_6—H), 9.10 (m, 1H, C_7—H), 6.92–7.55 (m, 10H, N=CH, 9Ar—H), 12.53 (s, 1H, CONH).

4b. IR: 3440, 1685, 1612 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.22 (s, 3H, CH_3), 4.92 (s, 2H, CH_2), 8.27 (m, 3H, C_3—H, C_4—H, C_5—H), 7.94 (m, 1H, C_6—H), 9.12 (m, 1H, C_7—H), 6.90–7.58 (m, 9H, N=CH, 8Ar—H), 12.36 (s, 1H, CONH).

4c. IR: 3448, 1696, 1604 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.82 s, 3H, OCH_3), 4.91 (s, 2H, CH_2), 8.28 (m, 3H, C_3—H, C_4—H, C_5—H), 7.98 (m, 1H, C_6—H), 9.13 (m, 1H, C_7—H), 6.83–7.80 (m, 9H, N=CH, 8Ar—H), 12.42 (s, 1H, CONH).

4d. IR: 3420, 1702, 1609 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.94 (s, 2H, CH_2), 8.25 (m, 3H, C_3—H, C_4—H, C_5—H), 8.00 (m, 1H, C_6—H), 9.13 (m, 1H, C_7—H), 7.03–7.80 (m, 9H, N=CH, 8Ar—H), 12.89 (s, 1H, CONH).

4e. IR: 3450, 1705, 1604 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.92 (s, 2H, CH_2), 8.20 (m, 3H, C_3—H, C_4—H, C_5—H), 7.93 (m, 1H, C_6—H), 9.14 (m, 1H, C_7—H), 7.00–7.73 (m, 9H, N=CH, 8Ar—H), 12.89 (s, 1H, CONH).

4f. IR: 3435, 1697, 1604 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.95 (s, 2H, CH_2), 8.17 (m, 3H, C_3—H, C_4—H, C_5—H), 7.91 (m, 1H, C_6—H), 9.08 (m, 1H, C_7—H), 6.90–7.49 (m, 9H, N=CH, 8Ar—H), 12.42 (s, 1H, CONH).

4g. IR: 3425, 1702, 1607 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.92 (s, 2H, CH_2), 8.24 (m, 3H, C_3—H, C_4—H, C_5—H), 7.95 (m, 1H, C_6—H), 9.10 (m, 1H, C_7—H), 6.98–7.62 (m, 8H, N=CH, 7Ar—H), 12.52 (s, 1H, CONH).

4h. IR: 3422, 1707, 1604 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.90 (s, 2H, CH_2), 8.19 (m, 3H, C_3—H, C_4—H, C_5—H), 7.90 (m, 1H, C_6—H), 9.12 (m, 1H, C_7—H), 6.96–7.58 (m, 8H, N=CH, 7Ar—H), 12.73 (s, 1H, CONH).

General procedure for the synthesis of 5-aryl-2-[*o*-(1,8-naphthyridin-2-yl)-phenoxymethyl]-1,3,4-oxadiazoles 5. Compound **4** (0.01 mol) and $PhI(OAc)_2$ (0.01 mol) doped on neutral alumina (1 g) are mixed thoroughly and exposed to MWs at 800 watts intermittently at 30 s intervals for the specific time (Table 1). After complete conversion as indicated by TLC, the reaction mixture was cooled and treated with methanol (30 mL). The methanol solution was poured into ice-cold water (50 mL), the precipitated solid was collected by filtration and re-crystallized from ethanol to furnish **5** (Table 1).

5a. IR: 1605 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 5.46 (s, 2H, CH_2), 8.20 (m, 3H, C_3—H, C_4—H, C_5—H), 8.00 (m, 1H, C_6—H), 9.15 (m, 1H, C_7—H), 7.04–7.60 (m, 9H, Ar—H).

5b. IR: 1602 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 2.30 (s, 3H, CH_3), 5.42 (s, 2H, CH_2), 8.18 (m, 3H, C_3—H, C_4—H, C_5—H), 7.98 (m, 1H, C_6—H), 9.14 (m, 1H, C_7—H), 7.00–7.56 (m, 8H, Ar—H).

5c. IR: 1604 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 3.87 (s, 3H, OCH_3), 5.41 (s, 2H, CH_2), 8.17 (m, 3H, C_3—H, C_4—H, C_5—H), 7.92 (m, 1H, C_6—H), 9.12 (m, 1H, C_7—H), 6.92–7.60 (m, 8H, Ar—H).

5d. IR: 1605 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 5.43 (s, 2H, CH_2), 8.20 (m, 3H, C_3—H, C_4—H, C_5—H), 7.81 (m, 1H, C_6—H), 9.09 (m, 1H, C_7—H), 7.10–7.32 (m, 8H, Ar—H).

5e. IR: 1602 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 5.46 (s, 2H, CH_2), 8.23 (m, 3H, C_3—H, C_4—H, C_5—H), 7.92 (m, 1H, C_6—H), 9.03 (m, 1H, C_7—H), 7.20–7.74 (m, 8H, Ar—H).

5f. IR: 1603 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 5.42 (s, 2H, CH_2), 8.21 (m, 3H, C_3—H, C_4—H, C_5—H), 7.97 (m, 1H, C_6—H), 9.11 (m, 1H, C_7—H), 7.05–7.52 (m, 8H, Ar—H).

5g. IR: 1600 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 5.45 (s, 2H, CH_2), 8.19 (m, 3H, C_3—H, C_4—H, C_5—H), 7.92 (m, 1H, C_6—H), 9.13 (m, 1H, C_7—H), 6.94–7.56 (m, 7H, Ar—H).

5h. IR: 1601 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 5.43 (s, 2H, CH_2), 8.21 (m, 3H, C_3—H, C_4—H, C_5—H), 7.98 (m, 1H, C_6—H), 9.10 (m, 1H, C_7—H), 7.01–7.52 (m, 7H, Ar—H).

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[25] Iodobenzene diacetate (0.01 mol) per gram of neutral alumina is ground using a pestle and mortar; the recovered alumina after removal of the products is reused without any loss of activity.

One-Pot Microwave-Assisted Solvent Free Synthesis of Simple Alkyl 1,2,3-Triazole-4-carboxylates by Using Trimethylsilyl Azide

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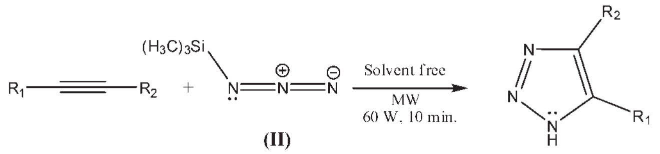

(II)

R_1=H ; R_2= -$COOCH_3$	**1**	**2** (82%)
R_1=H ; R_2= -$COOCH_2CH_3$	**3**	**4** (83%)
R_1=R_2= -$COOCH_3$	**5**	**6** (77%)

A fast one-pot microwave-assisted solvent free synthesis of simple alkyl 1,2,3-triazole-4-carboxylate derivatives by 1,3-dipolar cycloaddition reactions with trimethylsilyl azide (Me_3Si-N_3) on the alkylpropiolates and DMAD in high yields is described.

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INTRODUCTION

The synthesis of important compounds with many applications in chemistry and medicinal area has been observed in the literature. Microwave-assisted synthesis has been utilized as a powerful and effective technique to promote a group of chemical reactions [1–9]. Since the first publications on the use of microwave irradiation in organic chemistry, the accelerated process described have been a lure for chemists to further apply new reactions to this technology [10]. Huisgen's 1,3-dipolar cycloaddition of alkynes and azides yielding triazoles is, undoubtedly, the premier example of click chemistry reactions [11–21]. This type of reaction is an effective and excellent reaction for preparation of 1,2,3-triazoles. 1,2,3-Triazoles are known to be relatively resilient to metabolic degradation and have known utility in several medicinal chemistry campaigns as isosteres for phenyl rings and carboxyl functionalities [19]. The triazoles may display a wide range of biological activity as anti-HIV and antimicrobial agents, as well as selective β_3 adrenergic receptor agonist and antiallergic agents [20–23]. Additionally, 1,2,3-triazoles are found in herbicides, fungicides, and dyes [14,24].

Because of these interesting activities, fast and new methods for the synthesis of these compounds should be significant. In general, 1,2,3-triazole formation requires harsh conditions, that is, high temperature and longer reaction times. In the original description, the explored examples showed that although these were relatively clean processes, they could take from 12 to 48 h at high temperatures (~110°C) [19]. Several examples of Cu(I)-catalyzed alkyne-azide 1,3-dipolar cycloaddition under milder conditions have been described. The mechanistic proposal of the Cu(I)-catalyzed alkyne-azide 1,3-dipolar cycloaddition was reported and found to involve polar transition states, favorable for microwave activation [25]. These Huisgen 1,3-dipolar cycloaddition of azides and alkynes resulting in 1,2,3-triazoles is one of the most powerful click reactions [14,24–26]. An example of microwave-assisted azide-alkyne cycloaddition was reported by Katritzky and Singh [11]. The reactions involved primary azides and acetylenic amide. Recently, the synthesis of simple alkyl 1,2,3-triazole-4-carboxylate derivatives was reported by reaction between N_3^- and alkylpropyolates [27–30]. The total reaction time was 48 h [29,30]. In another report, the reaction time for synthesis of **2**, **4**, and **6** was 90 h [30].

Here, was reported a fast one-pot microwave-assisted (60 W, 10 min) solvent free synthesis of simple alkyl 1,2,3-triazole-4-carboxylate (**2**, **4**, and **6**) derivatives by 1,3-dipolar cycloaddition reactions with trimethylsilyl azide **II** (Me_3Si-N_3) on the alkylpropyolates (**1**,**3**) and DMAD (**5**) in high yields.

RESULTS AND DISCUSSION

The results show that the trimethylsilyl (Me_3Si-) was removed at the final simple alkyl 1,2,3-triazole-4-carboxylate (**2**, **4**, and **6**) products. No details are given about the by-products and only the final products are considered.

The ^{13}C NMR results show 4, 5, and 3 C-atom types for **2**, **4**, and **6**, respectively. See results in the Experimental section. The [M^+] for **2**, **4**, and **6**, were 127, 141, and 185, respectively. The percentages of C, H, and N are explained in the Experimental section. In accordance with the results that were shown in the Experimental section the MS (and CI) spectrums and CHN analysis demonstrated that the trimethylsilyl (Me_3Si-) was removed from the products during the synthesis process.

EXPERIMENTAL

The simple imides that were synthesized (**2**, **4**, and **6**), are known compounds and those physical data, infrared and ^{1}H NMR spectra were essentially identical with those of authentic samples [27–30]. The FTIR spectra was recorded as KBr pellets on a Shimadzu FTIR 8000 spectrometer. ^{1}H NMR spectra was determined on a 300 MHz Brüker spectrometer. The solvent for NMR recording was DMSO. It should be noted that a limited amount of compounds is required for this experiment. Therefore some small quality of vapor is evolved during irradiation. The power generated by the microwave oven was measured before the experiments by the method described in the literature [31].

Caution: For safety reasons all of the experiments should be performed in an efficient hood in order to avoid contact with vapors, as some quantity of substances can be vaporized during irradiation.

Typical experimental procedure for synthesis of methyl-1*H*-1,2,3-triazole-4-carboxylate (2). A mixture of methyl-propiolate 1 (1 g, 1 mL, 0.012 mol) and trimethylsilyl azide (Me_3Si-N_3) II (1.2 g, 1.5 mL, 0.012 mol) was made in a dried heavy wall Pyrex tube. The tube was sealed and then exposed to microwave oven. After 10 min irradiation at 60 W power, the mixture was cooled to room temperature. The residue of compounds was evaporated under air and reduced pressure. An off-white solid was afforded. The product **2** can be re-crystallized from chloroform + acetone and petroleum ether. These stages afforded 0.049 g product (workup yield 82% and GC yield $\approx$100%).

The amounts of ethylpropiolate **3** and trimethylsilyl azide **II** (Me_3Si-N_3) for synthesis ethyl-1*H*-1,2,3-triazole-4-carboxylate (**4**) are: 0.965 g (1 mL, 0.010 mol) and 1.1 g (1.3 mL, 0.01 mol), respectively. The yield of **4** was 0.054 g, 83%. The amounts of DMAD **5** and Me_3Si-N_3 (**II**) for synthesis dimethyl-1*H*-1,2,3-triazole-4,5-carboxylate (**6**): are: 1.157 g (1 mL, 0.0082 mol) and 1 g (1.2 mL, 0.009 mol), respectively. The yield of **4** was 0.072 g, 77%.

Methyl-1*H*-1,2,3-triazole-4-carboxylate (2). White crystals, mp 127–128°C (lit. 126–128°C) [27–30]. FTIR (KBr): 3150 (N—H), 3138, 3005, 2937, 1708 (C=O), 1660, 1538, 1480, 1432, 1352, 1212, 1116, 1023, 843, 779 cm^{-1}. ^{1}H NMR δ_H (DMSO): 8.56 (s, 1H), 3.83 (s, 3H). ^{13}C NMR: 161, 138.8, 130.1, and 51.83. MS: *m/z* (relative intensity), $M_w = 127$; 127 (M^+, 8.8), 95 (70.6), 96 (100), 78 (17.6), and 63 (18.5). $C_4H_5N_3O_2$, CHN-analysis; calculated: C (37.80%), H (3.97%), and N (33.06%), experiment: C (37.73%), H (3.95%), and N (33.01%).

Ethyl-1*H*-1,2,3-triazole-4-carboxylate (4). White crystals, mp 102–104°C (lit. 102–104°C) [27–30]. FTIR (KBr): 3224 (N—H), 3167, 2986, 1723 (C=O), 1661, 1533, 1466, 1375, 1332, 1238, 1202, 1114, 1029, 843, 780 cm^{-1}. ^{1}H NMR δ_H (DMSO): 8.46 (s, 1H), 4.27–4.35 (q, 2H, 7.0 Hz) and 1.27–1.32 (t, 3H, 7.0 Hz). ^{13}C NMR: 160.4, 138.2, 131.4, 60.4, and 14.0. MS: *m/z* (relative intensity); $M_w = 141$; CI = 141 (6.82), 113 (47.73), 95 (100), 71, 68 (78.5), and 44 (34.1). $C_5H_7N_3O_2$, CHN-analysis; calculated: C (42.55%), H (5.00%), and N (29.77%), experiment: C (42.50%), H (5.03%), and N (29.74%).

Dimethyl-1*H*-1,2,3-triazole-4,5-carboxylate (6). White crystals, mp 116–118°C (lit. 117–118°C) [27–30]. FTIR (KBr): 3239 (N—H), 3100, 2996, 2861, 1742 (C=O), 1658, 1519, 1437, 1389, 1304, 1228, 1190, 1084, 990, 833, 767 cm^{-1}. ^{1}H NMR δ_H (DMSO): 3.87 (s). ^{13}C NMR: 160.2, 131.0, and 52.4. MS: *m/z* (relative intensity); $M_w = 185$; 187 ($M2H^+$, 38.2), 154 (67.65), 124 (58.8), 93, 58, and 43 (100). $C_6H_7N_3O_4$, CHN-analysis; calculated: C (38.92%), H (3.81%), and N (22.70%), experiment: C (38.98%), H (3.85%), and N (22.66%).

The simple one-pot microwave assisted solvent free synthesis of useful alkyl 1,2,3-triazole-4-carboxylate derivatives (**2**, **4**, and **6**) by Huisgen 1,3-dipolar cycloaddition reactions with trimethylsilyl azide (Me_3Si-N_3) on the alkylpropyolates **1**,**3** and DMAD (**5**), in high yields is described. Comparison of this procedure with the other methods confirms the facility and rapidity of this method for synthesis of the alkyl 1,2,3-triazole-4-carboxylate derivatives.

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A Simple Method for the Synthesis of 5-Isoxazolyl-4-thioxo-1,3,5-benzoxadiazocines

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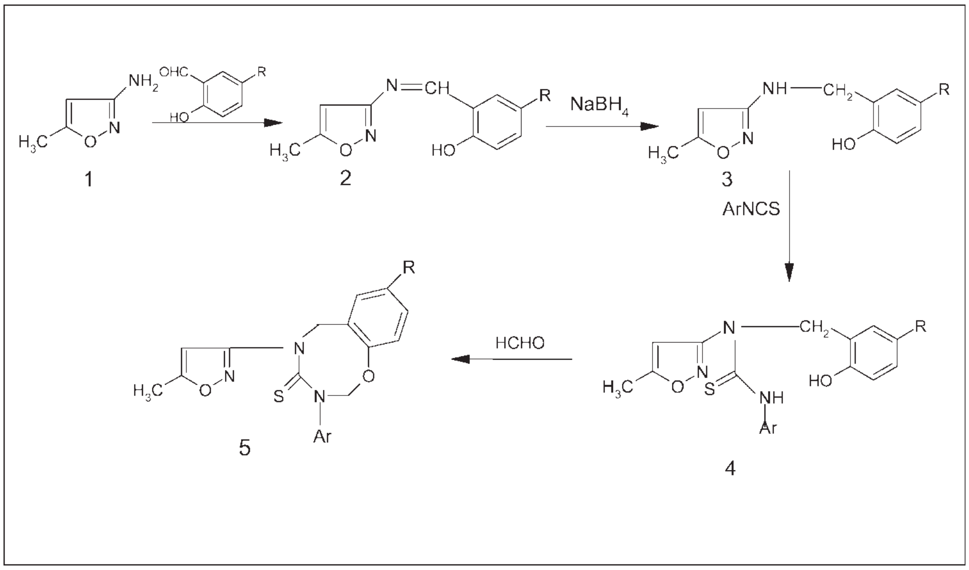

Synthesis of novel isoxazolyl 1,3,5-benzoxadiazocines **5** has been accomplished by condensation of 3-amino-5-methylisoxazole **1** with salicylaldehydes, followed by reduction, treatment with arylisothiocyanates, and subsequent ring closure in the presence of formaldehyde. The methodology used in this synthesis is the first approach of its kind.

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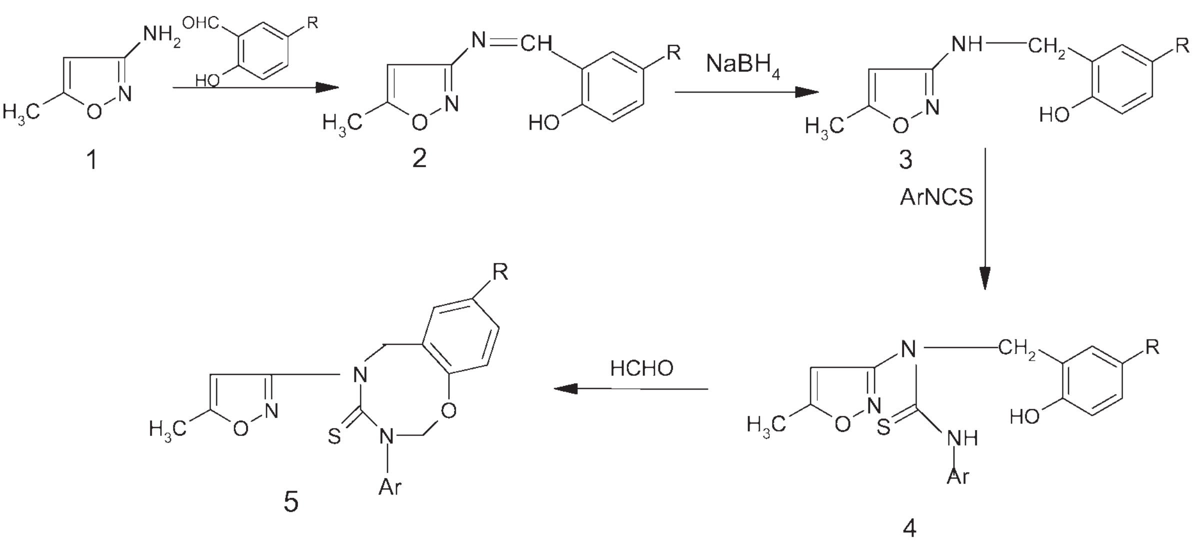
INTRODUCTION

Benzoxadiazocines have been claimed to exhibit sedative, muscle relaxant and anticonvulsant effects [1]. Oxadiazocines are shown to act as bacteriocides, hypnotic agents [2], central nervous system stimulants [3], and are also known to possess pharmacological activity [4]. The biological importance and considerable therapeutic potential of these compounds generated interest in designing the synthesis of a number of derivatives [5], which might become potential drug candidates as inhibitors of HIV-1 reverse transcriptase [6]. Very recently, oxadiazocines are reported to have been used as immuno therapeutics, antimicrobial drugs, and vaccines [7]. Similarly isoxazole nucleus can be found frequently in the structure of numerous naturally occurring and synthetic compounds with interesting biological and pharmacological properties [8]. In spite of such a high potential significance for benzoxadiazocines and oxadiazocines, a survey of literature showed that little attention has been given toward the synthesis of this class of heterocyclic compounds. In view of this, and as a sequel to our work on the synthesis of a variety of heterocycles linked to the isoxazole moiety [9], we undertook the synthesis of isoxazolyl benzoxadiazocines to explore the pharmacological activity of these compounds. Herein, we present our results on the synthesis of isoxazolyl 1,3,5-benzoxadiazocines by adopting simple methodology.

RESULTS AND DISCUSSION

The reaction of 3-amino-5-methylisoxazole **1** with substituted salicylaldehydes in hot alcohol led to the formation of Schiff bases **2** in quantitative yields. The Schiff bases **2** on reduction with sodium borohydride produced 2-[(5-methyl-isoxazol-3-yl-amino)-methyl] phenols **3** in moderate to good yields. The nucleophilic addition of amino methyl phenols **3** with aryl isothiocyanates has been carried out in hot chloroform with stirring for 6 h. The resulting product has been identified as *N*-(5-methyl-isoxazol-3-yl)-*N*-(2-hydroxybenzyl)-*N*′-aryl thioureas **4**. The thioureas **4** on heating with formaldehyde in methanol solution underwent ring closure, involving an internal Mannich reaction, to give novel

Scheme 1



2, 3a = R = H
2, 3b = R = CH_3
2, 3c = R = OCH_3
2, 3d = R = Cl
2, 3e = R = Br

4, 5a = R = H, Ar = C_6H_5
4, 5b = R = H, Ar = C_6H_4-Cl(p)
4, 5c = R = H, Ar = C_6H_4-Br(p)
4, 5d = R = H, Ar = C_6H_4-CH_3(p)
4, 5e = R = CH_3, Ar = C_6H_5
4, 5f = R = OCH_3, Ar = C_6H_5

5-(5-methyl-isoxazol-3-yl)-3-aryl-3,4,5,6-tetrahydro-2*H*-1,3,5-benzoxadiazocine-4-thiones **5** in moderate to good yields (Scheme 1).

It can be concluded that a simple and efficient method to synthesize isoxazolyl benzoxadiazocines in good yields under mild conditions has been achieved. It is possible that these compounds may have applications as drugs; the activity data will be published elsewhere. This happens to be the first report on the synthesis of benzoxadiazocines linked to an isoxazole unit.

EXPERIMENTAL

All the melting points were determined on a Cintex melting point apparatus and are uncorrected. Analytical TLC was performed on Merck precoated 60 F_{254} silica gel plates. Visualization was done by exposing to Iodine vapor IR spectra (KBr pellet) were recorded on Perkin-Elmer BX series FTIR spectrophotometer. ^1H NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer. Chemical shift values are given in ppm (δ) with tetramethylsilane as internal standard. Mass spectral measurements were carried out by EI method on a Jeol JMC-300 spectrometer at 70 eV. Elemental analyses were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer.

General procedure for the preparation of 2-[(5-methyl-3-isoxazolyl)imino]methylphenols (2a–2e). 3-Amino-5-methyl-isoxazole **1** (0.01 mol) and salicylaldehyde (0.01 mol) were refluxed in ethanol (10 mL) for 2 h. The solution was cooled and the separated solid was collected by filtration and re-crystallized from pet ether.

2-[(5-Methyl-3-isoxazolyl)imino]methylphenol (2a). This compound was obtained as yellow crystals, yield 95%; mp 57–59°C, ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.38$ (s, 3H, CH_3), 5.95 (s, 1H, isoxazole-H), 6.82–7.55 (m, 4H, ArH), 8.82 (s, 1H, —N=CH—), 12.02 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m*/*z* 203 ($M + H^+$); IR (KBr): 3400 (O—H), 1607 (C=N), 1577, 1400 (C=C), 1282 cm^{-1} (C—O). *Anal.* Calcd. for $C_{11}H_{10}N_2O_2$ (202): C, 65.34; H, 4.95; N, 13.86. Found: C, 65.38; H, 5.10; N, 13.79.

4-Methyl-2-[(5-methyl-3-isoxazolyl)imino]methylphenol (2b). This compound was obtained as yellow crystals, yield 90%; mp 68–70°C, ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.41$ (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 6.02 (s, 1H, isoxazole-H), 6.80–7.50 (m, 3H, ArH), 8.75 (s, 1H, —N=CH—), 12.85 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m*/*z* 217 ($M + H^+$); IR (KBr): 3390 (O—H), 1615 (C=N), 1580, 1450 (C=C), 1275 cm^{-1} (C—O). *Anal.* Calcd. for $C_{12}H_{12}N_2O_2$ (216): C, 66.66; H, 5.55; N, 12.96. Found: C, 66.60; H, 5.62; N, 12.90.

4-Methoxy-2-[(5-methyl-3-isoxazolyl) imino] methyl phenol (2c). This compound was obtained as yellow crystals, yield 90%; mp 80–82°C, ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.35$ (s, 3H, CH_3), 3.8 (s, 3H, OCH_3), 6.12 (s, 1H, isoxazole-H), 6.80–

7.10 (m, 3H, ArH), 8.80 (s, 1H, —N=CH—), 12.05 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 233 (M + H$^+$); IR (KBr): 3385 (O—H), 1620 (C=N), 1575, 1425 (C=C), 1280 cm^{-1} (C—O). *Anal.* Calcd. for $C_{12}H_{12}N_2O_3$ (232): C, 62.06; H, 5.17; N, 12.06. Found: C, 62.15; H, 5.13; N, 12.14.IR.

4-Chloro-2-[(5-methyl-3-isoxazolyl)imino]methylphenol (2d). This compound was obtained as yellow crystals, yield 88%; mp 93–95°C, ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.41$ (s, 3H, CH_3), 5.90 (s, 1H, isoxazole-H), 7.50–8.02 (m, 3H, ArH), 8.85 (s, 1H, —N=CH—), 12.50 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 237 (M + H$^+$); IR (KBr): 3405 (O—H), 1615 (C=N), 1580, 1400 (C=C), 1275 cm^{-1} (C—O). *Anal.* Calcd. for $C_{11}H_9N_2O_2Cl$ (236): C, 55.93; H, 3.81; N, 11.86. Found: C, 56.05; H, 3.85; N, 11.88.

4-Bromo-2-[(5-methyl-3-isoxazolyl)imino]methylphenol (2e). This compound was obtained as yellow crystals, yield 95%; mp 110–112°C, ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.35$ (s, 3H, CH_3), 6.02 (s, 1H, isoxazole-H), 7.70–8.02 (m, 3H, ArH), 8.90 (s, 1H, —N=CH—), 12.40 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 281 (M + H$^+$); IR (KBr): 3368 (O—H), 1612 (C=N), 1489 (C=C), 1275 cm^{-1} (C—O). *Anal.* Calcd. for $C_{11}H_9N_2O_2Br$ (280): C, 47.14; H, 3.21; N, 10.00. Found: C, 47.20; H, 3.29; N, 9.95.

General procedure for the preparation of 2-[(5-methyl-3-isoxazolyl)amino]methyl phenols (3a–3e). To an ethanolic solution (10 mL) of Schiff base **2** (0.01 mol) sodium borohydride (0.02 mol) was slowly added with stirring. The reaction was conducted at room temperature with stirring for 30 min. The solid that separated on pouring the reaction mixture into ice-cold water was collected filtration and re-crystallized from ethanol.

2-[(5-Methyl-3-isoxazolyl)amino]methylphenol (3a). This compound was obtained as brown crystals, yield 82%; mp 85–87°C, ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.25$ (s, 3H, CH_3), 4.31 (s, 2H, —CH_2—), 5.20 (bs, 1H, NH, D_2O exchangeable), 5.66 (s, 1H, isoxazole-H), 6.80–7.25 (m, 4H, ArH), 9.45 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 205 (M + H$^+$); IR (KBr): 3640 (N—H), 3376 (O—H), 1631 (C=N), 1458 (C=C), 1210 cm^{-1} (C—O). *Anal.* Calcd. for $C_{11}H_{12}N_2O_2$ (204): C, 64.70; H, 5.88; N, 13.72. Found: C, 64.65; H, 5.82; N, 13.66.

4-Methyl-2-[(5-methyl-3-isoxazolyl)amino]methylphenol (3b). This compound was obtained as brown crystals, yield 85%; mp 79–81°C, ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.30$ (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 4.35 (s, 2H, —CH_2—), 5.50 (bs, 1H, NH, D_2O exchangeable), 5.70 (s, 1H, isoxazole-H), 7.00–7.50 (m, 3H, ArH), 10.05 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 219 (M + H$^+$); IR (KBr): 3500 (N—H), 3368 (O—H), 1605 (C=N), 1455 (C=C), 1065 cm^{-1} (C—O). *Anal.* Calcd. for $C_{12}H_{14}N_2O_2$ (218): C, 66.05; H, 6.42; N, 12.84. Found: C, 66.01; H, 5.98; N, 12.81.

4-Methoxy-2-[(5-methyl-3-isoxazolyl)amino]methylphenol (3c). This compound was obtained as brown crystals, yield 85%; mp 92–93°C, ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.35$ (s, 3H, CH_3), 3.7 (s, 3H, CH_3), 4.00 (s, 2H, —CH_2—), 5.50 (bs, 1H, NH, D_2O exchangeable), 5.80 (s, 1H, isoxazole-H), 6.85–7.40 (m, 3H, ArH), 9.85 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 235 (M + H$^+$); IR (KBr): 3490 (N—H), 3350 (O—H), 1620 (C=N), 1460 (C=C), 1150 cm^{-1} (C—O). *Anal.* Calcd. for $C_{12}H_{14}N_2O_3$ (234): C, 61.53; H, 5.98; N, 11.96. Found: C, 61.88; H, 5.88; N, 11.85.

4-Chloro-2-[(5-methyl-3-isoxazolyl)amino]methylphenol (3d). This compound was obtained as brown crystals, yield 80%; mp 105–107°C, ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.35$ (s, 3H, CH_3), 3.70 (s, 2H, —CH_2—), 4.50 (bs, 1H, NH, D_2O exchangeable), 6.02 (s, 1H, isoxazole-H), 7.00–7.50 (m, 3H, ArH), 10.02 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 239 (M + H$^+$); IR (KBr): 3550 (N—H), 3415 (O—H), 1630 (C=N), 1510 (C=C), 1205 cm^{-1} (C—O). *Anal.* Calcd. for $C_{11}H_{11}N_2O_2Cl$ (238): C, 55.46; H, 4.62; N, 11.76. Found: C, 55.50; H, 4.58; N, 11.80.

4-Bromo-2-[(5-methyl-3-isoxazolyl)amino]methylphenol (3e). This compound was obtained as brown crystals, yield 80%; mp 121–123°C, ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.40$ (s, 3H, CH_3), 3.95 (s, 2H, —CH_2—), 5.00 (bs, 1H, NH, D_2O exchangeable), 5.95 (s, 1H, isoxazole-H), 7.20–7.80 (m, 3H, ArH), 9.80 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 283 (M + H$^+$); IR (KBr): 3500 (N—H), 3395 (O—H), 1615 (C=N), 1560 (C=C), 1180 cm^{-1} (C—O). *Anal.* Calcd. for $C_{11}H_{11}N_2O_2Br$ (282): C, 46.80; H, 3.90; N, 9.92. Found: C, 46.95; H, 4.01; N, 9.85.

General procedure for the preparation of *N*-(2-hydroxybenzyl)-*N*-(5-methyl-3-isoxazolyl)-*N*′-phenylthioureas (4a–4f). To chloroform solution (15 mL) of amino methylphenols 3 (0.01 mol) arylisothio cyanate (0.01 mol) was slowly added with stirring. The reaction mixture was stirred at 90°C for 6 h. The solvent was removed by distillation under reduced pressure and the crude product was re-crystallized from ethanol.

N-(2-Hydroxybenzyl)-N-(5-methyl-3-isoxazolyl)-N′-phenylthiourea (4a). This compound was obtained as brown crystals, yield 85%; mp 100–102°C, ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 2.30 (s, 3H, CH_3), 4.60 (s, 2H, CH_2), 6.01 (s, 1H, isoxazole-H), 6.8–7.8 (m, 9H, ArH), 8.52 (bs, 1H, NH, D_2O exchangeable), 9.42 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 340 (M + H$^+$); IR (KBr): 3239 (N—H), 3180 (O—H), 1641 (C=N), 1582, 1515 (C=C), 1225 cm^{-1} (C=S). *Anal.* Calcd. for $C_{18}H_{17}N_3O_2S$ (339): C, 63.71; H, 5.01; N, 12.38.Found: C, 63.59; H, 4.95; N, 12.35.

N′-(4-Chlorophenyl)-N-(2-hydroxybenzyl)-N-(5-methyl-3-isoxazolyl) thiourea (4b). This compound was obtained as brown crystals, yield 88%; mp 124–126°C, ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.35$ (s, 3H, CH_3), 4.94 (s, 2H, CH_2), 5.96 (s, 1H, isoxazole-H), 7.01–7.82 (m, 8H, ArH), 8.80 (bs, 1H, NH, D_2O exchangeable), 9.50 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 374 (M + H$^+$); IR (KBr): 3300 (N—H), 3225 (O—H), 1640 (C=N), 1575 (C=C), 1230 cm^{-1} (C=S). *Anal.* Calcd. for $C_{18}H_{16}N_3O_2SCl$ (373): C, 57.90; H, 4.28; N, 11.26. Found: C, 57.86; H, 4.25; N, 11.29.

N′-(4-Bromophenyl)-N-(2-hydroxybenzyl)-N-(5-methyl-3-isoxazolyl) thiourea (4c). This compound was obtained as brown crystals, yield 80% mp 133–135°C, ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.38$ (s, 3H, CH_3), 4.85 (s, 2H, CH_2), 6.00 (s, 1H, isoxazole-H), 7.23–7.85 (m, 8H, ArH), 9.00 (bs, 1H, NH, D_2O exchangeable), 10.25 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 418 (M + H$^+$); *Anal.* Calcd. for $C_{18}H_{16}N_3O_2SBr$ (417): C, 51.79; H, 3.83; N, 10.07. Found: C, 51.82; H, 3.85; N, 9.98. IR (KBr): 3350 (N—H), 3200 (O—H), 1515 (C=C), 1225 cm^{-1} (C=S).

N-(2-Hydroxybenzyl)-N-(5-methyl-3-isoxazolyl)-N′-(4-methylphenyl) thiourea (4d). This was obtained as compound brown crystals, yield 85%; mp 120–122°C, ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.40$ (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 4.75 (s, 2H, CH_2), 6.12 (s, 1H, isoxazole-H), 7.50–8.20 (m, 8H, ArH), 8.90 (bs, 1H, NH, D_2O exchangeable), 10.08 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 354 (M + H$^+$); IR

(KBr): 3329 (N—H), 3215 (O—H), 1510 (C=C), 1220 cm^{-1} (C=S). *Anal.* Calcd. for $C_{19}H_{19}N_3O_2S$ (353): C, 64.58; H, 5.38; N, 11.89. Found: C, 64.49; H, 5.32; N, 11.92.

N-(2-Hydroxy-5-methylbenzyl)-N-(5-methyl-3-isoxazolyl)-N′-phenylthiourea (4e). This compound was obtained as brown crystals, yield 88%; mp 136–138°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.41 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 4.66 (s, 2H, CH_2), 5.98 (s, 1H, isoxazole-H), 7.20–8.00 (m, 8H, ArH), 9.00 (bs, 1H, NH, D_2O exchangeable), 10.05 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 354 (M + H$^+$); IR (KBr): 3380 (N—H), 3290 (O—H), 1565 (C=C), 1235 cm^{-1} (C=S). *Anal.* Calcd. for $C_{19}H_{19}N_3O_2S$ (353): C, 64.58; H, 5.38; N, 11.89. Found: C, 64.55; H, 5.35; N, 11.95.

N-(2-Hydroxy-5-methoxybenzyl)-N-(5-methyl-3-isoxazolyl)-N′-phenylthiourea (4f). This compound was obtained as brown crystals, yield 80%; mp 127–129°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.38 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.70 (s, 2H, CH_2), 6.20 (s, 1H, isoxazole-H), 7.00–7.85 (m, 8H, ArH), 8.98 (bs, 1H, NH, D_2O exchangeable), 9.80 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 370 (M + H$^+$); IR (KBr): 3375 (N—H), 3185 (O—H), 1560 (C=C), 1215 cm^{-1} (C=S). *Anal.* Calcd. for $C_{19}H_{19}N_3O_2S$ (369): C, 61.78; H, 5.14; N, 11.38. Found: C, 61.82; H, 5.08; N, 11.35.

General procedure for the preparation of 5-(5-methylisoxazol-3-yl)-3-aryl-3,4,5,6-tetrahydro-2*H*-1,3,5-benzoxadiazocine-4-thiones (5a–5f). To an ethanolic solution (15 mL) of thioureas 4 (0.01 mol), Formaldehyde (0.01 mol) was slowly added with stirring. The mixture was refluxed for 6–8 h (Monitored with TLC). The gummy product obtained, after the removal of solvent, was processed with pet ether. The product was purified by re-crystallization from ethanol.

5-(5-Methyl-3-isoxazolyl)-3-phenyl-3,4,5,6-tetrahydro-2H-1,3,5-benzoxadiazocine-4-thione (5a). This compound was obtained as pale brown crystals, yield 90%; mp 128–129°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.30 (s, 3H, CH_3), 4.55 (s, 2H, CH_2), 5.88 (s, 2H, CH_2), 6.02 (s, 1H, isoxazole-H), 7.02–7.65 (m, 9H, ArH). EI-MS: *m/z* 352 (M + H$^+$); IR (KBr): 1610 (C=N), 1220 cm^{-1} (C=S). *Anal.* Calcd. for $C_{19}H_{17}N_3O_2S$ (351): C, 64.95; H, 4.84; N, 11.96. Found: C, 65.01; H, 4.82; N, 11.92.

3-(4-Chlorophenyl)-5-(5-methyl-3-isoxazolyl)-3,4,5,6-tetrahydro-2H-1,3,5-benzoxadiazocine-4-thione (5b). This compound was obtained as pale brown crystals, yield 85%; mp 145–147°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 3H, CH_3), 4.62 (s, 2H, CH_2), 6.00 (s, 2H, CH_2), 6.20 (s, 1H, isoxazole-H), 7.23–7.85 (m, 8H, ArH). EI-MS: *m/z* 386 (M + H$^+$); IR (KBr): 1625 (C=N), 1210 cm^{-1} (C=S). *Anal.* Calcd. for $C_{19}H_{16}N_3O_2SCl$ (385): C, 59.22; H, 4.15; N, 10.90. Found: C, 59.17; H, 4.10; N, 11.00.

3-(4-Bromophenyl)-5-(5-methyl-3-isoxazolyl)-3,4,5,6-tetrahydro-2H-1,3,5-benzoxadiazocine-4-thione (5c). This compound was obtained as pale brown crystals, yield 85%; mp 160–162°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 3H, CH_3), 4.80 (s, 2H, CH_2), 6.05 (s, 2H, CH_2), 6.25 (s, 1H, isoxazole-H), 7.50–7.88 (m, 8H, ArH). EI-MS: *m/z* 430 (M + H$^+$); IR (KBr): 1600 (C=N), 1202 cm^{-1} (C=S). *Anal.* Calcd. for $C_{19}H_{16}N_3O_2SBr$ (429): C, 53.14; H, 3.72; N, 9.79. Found: C, 53.09; H, 3.70; N, 9.75.

5-(5-Methyl-3-isoxazolyl)-3-(4-methylphenyl)-3,4,5,6-tetrahydro-2H-1,3,5-benzoxadiazocine-4-thione (5d). This compound was obtained as pale brown crystals, yield 88%; mp 140–142°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.38 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 4.75 (s, 2H, CH_2), 5.85 (s, 2H, CH_2), 6.05 (s, 1H, isoxazole-H), 7.25–7.98 (m, 8H, ArH). EI-MS: *m/z* 366 (M + H$^+$); IR (KBr): 1618 (C=N), 1215 cm^{-1} (C=S). *Anal.* Calcd. for $C_{20}H_{19}N_3O_2S$ (365): C, 65.75; H, 5.20; N, 11.50. Found: C, 65.81; H, 5.15; N, 11.48.

8-Methyl-5-(5-methyl-3-isoxazolyl)-3-phenyl-3,4,5,6-tetrahydro-2H-1,3,5-benzoxadiazocine-4-thione (5e). This compound was obtained as pale brown crystals, yield 80%; mp 155–157°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.42 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 4.60 (s, 2H, CH_2), 5.80 (s, 2H, CH_2), 6.02 (s, 1H, isoxazole-H), 7.00–7.65 (m, 8H, ArH). EI-MS: *m/z* 366 (M + H$^+$); IR (KBr): 1610 (C=N), 1225 cm^{-1} (C=S). *Anal.* Calcd. for $C_{20}H_{19}N_3O_2S$ (365): C, 65.75; H, 5.20; N, 11.50. Found: C, 65.70; H, 5.22; N, 11.47.

8-Methoxy-5-(5-methyl-3-isoxazolyl)-3-phenyl-3,4,5,6-tetrahydro-2H-1,3,5-benzoxadiazocine-4-thione (5f). This compound was obtained as pale brown crystals, yield 80%; mp 165–167°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.38 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.80 (s, 2H, CH_2), 6.00 (s, 2H, CH_2), 6.15 (s, 1H, isoxazole-H), 7.00–7.50 (m, 8H, ArH). EI-MS: *m/z* 382 (M + H$^+$); IR (KBr): 1625 (C=N), 1235 cm^{-1} (C=S). *Anal.* Calcd. for $C_{20}H_{19}N_3O_3S$ (381): C, 62.99; H, 4.98; N, 11.02. Found: C, 63.05; H, 5.01; N, 11.00.

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The First Example of a Regioselective Biginelli-Like Reaction Based on 3-Alkylthio-5-amino-1,2,4-triazole

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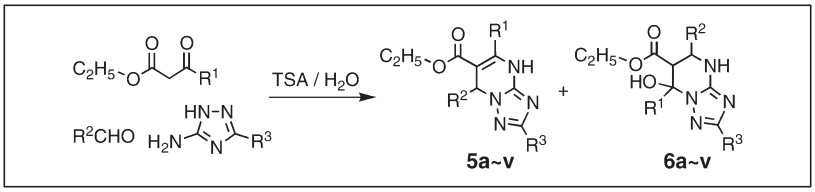

5a~v **6a~v**

The three-component condensation of 3-amino-5-alkylthio-1,2,4-triazoles with aromatic aldehydes and β-ketoester was studied to develop a regioselective Biginelli-like reaction. The results indicated that the reaction solvent and the properties of the β-ketoester component displayed great influence on the regioselectivity. This is the first report about the regioselectivity of the aminotriazole-based Biginelli-like reaction.

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INTRODUCTION

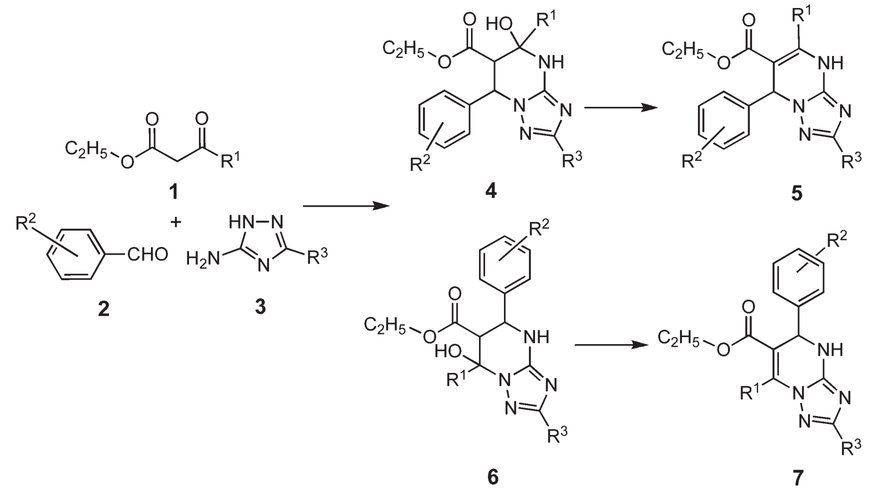
In the last decades, dihydropyrimidinones (DHPMs) and their sulfur analogs have attracted much attention because of their wide range of biological activities. For example, many DHPMs were reported to be calcium or/and potassium channel blockers and openers [1], antihypertensive agents [2], α-adrenergic antagonists [3], neuropeptide Y (NPY) antagonists [4], and HIV gp-120-CD4 inhibitors [5]. The most important and direct method for the synthesis of DHPMs is based on the Biginelli reaction reported first in 1893 [6]. The classical Biginelli reaction of an aldehyde, a β-ketoester, and urea or thiourea requires strongly acidic conditions. Recently, the Biginelli reaction was extended to the synthesis of dihydrotriazolo-pyrimidine by replacing the urea component with 5-amino-1,2,4-triazole [7–12]. Because the β-ketoester and 5-amino-1,2,4-triazole are asymmetric, four possible products (**4**, **5**, **6**, and **7**) could be obtained theoretically (Scheme 1) according to the mechanism of the traditional Biginelli reaction. However, so far no attention has been paid to the regioselectivity of the aminoazole-based Biginelli reaction.

The existing results about the aminoazole-based Biginelli-like reaction indicated that only product **5** was obtained or only product **4** was obtained at first, which then suffered subsequent dehydration to afford product **5** [7–12]. No reports about the formation of products **6** or **7** could be found in the existing literature. As a continuation of our systematic research work on the synthesis and biological activity of triazolopyrimidines [13–16], we report herein the first example of regioselective Biginelli-like reactions based on 3-alkylthio-5-amino-1,2,4-triazole, in which products **5** and **6** could be produced by regioselectivity depending on the reaction conditions.

RESULTS AND DISCUSSION

First, the reaction of ethyl acetoacetate, 4-methoxybenzaldehyde, and 3-methylthio-5-amino-1,2,4-triazole was selected as a model reaction. Some reported catalysts or additives, such as H_3BO_3 [17], *p*-toluene sulfonic acid (TSA) [18], $FeCl_3$ [19], $InCl_3$ [20], and HCl [21], and solvents, such as C_2H_5OH, DMF, H_2O, THF, HOAc, CH_2Cl_2, and $CHCl_3$, were screened. As shown in Table 1, the TSA/H_2O system was found to give almost equivalent amounts of products **5a** and **6a** with a moderate overall yield (**5a** and **6a**, 69%). Then, this system was extended to other substrates, and the results are listed in Table 2. As shown in Table 2, when ethyl acetoacetate and ethyl chloroacetoacetate acted as β-ketoester components, two isomers were isolated in all cases. Interestingly, only one isomer was isolated for the reaction of ethyl trifluoroacetoacetate and 4-substituted benzaldehyde. For example, the reactions of 4-methoxybenzaldehyde (Table 2, entry 15), 4-chlorobenzaldehyde (Table 2, entry 16), 4-chlorobenzaldehyde (Table 2, entry 17), 3,4-dichlorobenzaldehyde (Table 2, entry 18), and 4-nitrobenzaldehyde (Table 2, entry 19) afforded isomers **5o–s** in isolated yields of 40, 48, 49, 51, and 55%, respectively. However, the reactions of benzaldehyde (Table 2, entry 21) and 4-methylbenzaldehyde (Table 2, entry 22) afforded product **6u-v** in isolated yields of 80% and 60%, respectively. However, the reactions of 2-fluorobenzaldehyde (Table 2, entry 20) also

Scheme 1

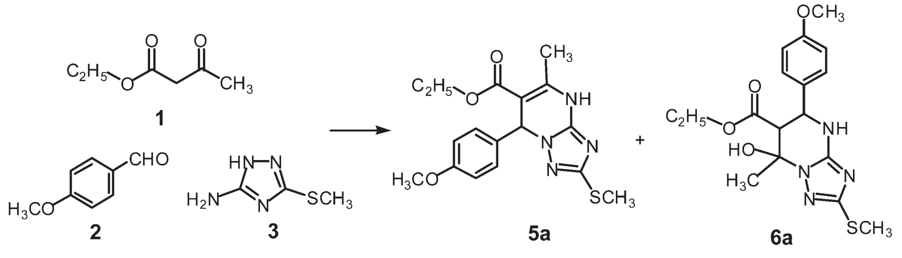


afforded product **6t**. From these results, we can conclude that the electronic property and the position of the R^1 group has the most important effect on the regioselectivity of the aminotriazole-based Biginelli reaction in H_2O solution. Additionally, the effect of R^2 group on the regioselectivity is complex, whereas the R^3 group seems to have no obvious effect on the regioselectivity.

In addition, as shown in Table 1, the reaction under the system of HCl/C_2H_5OH afforded regioselectivity isomer **5a** in a yield of 32%, a little higher than that in DMF solution. Then, we studied the extension of this reaction system to other substrates, and the results are listed in Table 3. Additionally, microwave irradiation has been proven to be a powerful technique for promoting a variety of chemical reactions [22–25]. The main benefits of performing reactions under microwave irradiation conditions are significant rate enhancements and higher yields. Recently, the technique of microwave irradiation was also applied to improve the yields and shorten the reaction time of Biginelli reactions [26–28]. So, the results in C_2H_5OH solution under microwave irradiation were compared with those under conventional heating as listed in Table 3, which indicated that the yields under microwave irradiation were improved as

Table 1

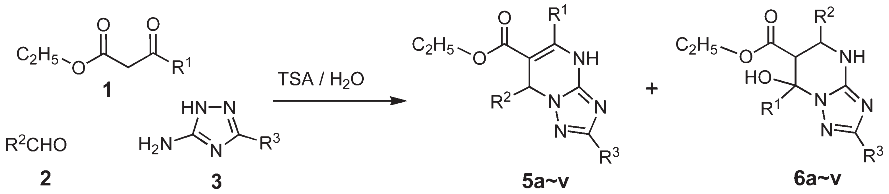
Results of the model reaction under various conditions.



No.	Reaction conditions	Products
1	HBO_3 (cat.), HOAc, reflux	Very complex
2	$FeCl_3$ (10%), THF, reflux	Very complex
3	$AlCl_3$ (cat.), THF, reflux	Very complex
4	$InCl_3$ (20%), THF, reflux	Very complex
5	HCl (cat.), H_2O, reflux	Very complex
6	TSA, CH_2Cl_2, reflux	No reaction
7	TSA, $CHCl_3$, reflux	No reaction
8	TSA, H_2O, reflux	**5a**, 34%; **6a**, 35%
9	HCl (cat.), C_2H_5OH, reflux	**5a**, 32%
10	DMF, reflux	**5a**, 30%

Table 2

Results of the Biginelli-like reaction in H_2O solution using TSA as catalyst.



No.	R^1	R^2	R^3	Isolated yields of products (%)	
1	CH_3	$4\text{-}CH_3OC_6H_4$	SCH_3	**5a** (34)	**6a** (35)
2	CH_3	$4\text{-}CH_3C_6H_4$	SCH_3	**5b** (25)	**6b** (~5)[a]
3	CH_3	$4\text{-}ClC_6H_4$	SCH_3	**5c** (36)	**6c** (~5)[a]
4	CH_3	$2,4\text{-}Cl_2C_6H_3$	SCH_3	**5d** (32)	**6d** (24)
5	CH_3	4-Pyridyl	SCH_3	**5e** (48)	**6e** (~5)[a]
6	CH_3	$4\text{-}CH_3C_6H_4$	SCH_2Ph	**5f** (32)	**6f** (19)
7	CH_3	$4\text{-}CH_3OC_6H_4$	SCH_2Ph	**5g** (41)	**6g** (~5)[a]
8	CH_3	$4\text{-}ClC_6H_4$	SCH_2Ph	**5h** (29)	**6h** (39)
9	$ClCH_2$	$4\text{-}CH_3C_6H_4$	SCH_3	**5i** (36)	**6i** (20)
10	$ClCH_2$	$4\text{-}CH_3OC_6H_4$	SCH_3	**5j** (31)	**6j** (~5)[a]
11	$ClCH_2$	$4\text{-}ClC_6H_4$	SCH_3	**5k** (43)	**6k** (~5)[a]
12	$ClCH_2$	$4\text{-}CH_3C_6H_4$	SCH_2Ph	**5l** (35)	**6l** (~5)[a]
13	$ClCH_2$	$4\text{-}CH_3OC_6H_4$	SCH_2Ph	**5m** (30)	**6m** (25)
14	$ClCH_2$	$4\text{-}ClC_6H_4$	SCH_2Ph	**5n** (28)	**6n** (35)
15	CF_3	$4\text{-}CH_3OC_6H_4$	SCH_3	**5o** (40)	**6o** (0)
16	CF_3	$4\text{-}ClC_6H_4$	SCH_3	**5p** (48)	**6p** (0)
17	CF_3	$4\text{-}ClC_6H_4$	SCH_2Ph	**5q** (49)	**6q** (0)
18	CF_3	$3,4\text{-}Cl_2C_6H_3$	SCH_3	**5r** (51)	**6r** (0)
19	CF_3	$4\text{-}NO_2C_6H_4$	SCH_3	**5s** (55)	**6s** (0)
20	CF_3	$2\text{-}FC_6H_4$	SCH_3	**5t** (0)	**6t** (54)
21	CF_3	C_6H_5	SCH_3	**5u** (0)	**6u** (80)
22	CF_3	$4\text{-}CH_3C_6H_4$	SCH_3	**5v** (0)	**6v** (60)

[a] Detected by HPLC, but unable to be isolated.

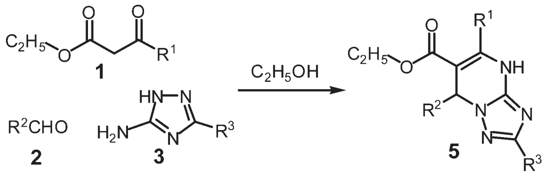
expected by 3–10%, and the reaction time was also shortened from 18 h to 30 min.

The structures of compounds **4–7** correspond to the direction of the interaction established earlier in the reactions between 3-amino-5-alkylthio-1,2,4-triazoles and arylidenacetoacetates (**8**) (Scheme 2). Formation of the pyrimidine ring with the participation of the arylidene derivatives (**8**) occurs *via* interaction of the β-carbon atom of the acetoacetate with the carbonyl group of the aldehydes. For example, in H_2O solution with TSA as catalyst, the reaction proceeded first with the participation of $N_{(2)}$ or $3\text{-}NH_2$ of the 3-amino-5-alkylthio-1,2,4-triazoles to afford regioselectivity ethyl 7-aryl-2-alkylthio-4,7-dihydro-1,2,4-triazolo-[1,5-*a*]pyrimidine-6-carboxylate (**5**) or ethyl-7-hydroxy-7-alkyl-5-aryl-2-alkylthio-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxylate (**6**) depending on the property of the aromatic aldehydes when ethyl trifluoroacetoacetate was used as the β-ketoester component. When ethyl acetoacetate and ethyl chloroacetoacetate acted as β-ketoester components, the reaction always produced two isomers **5** and **6**. However, the reactions in C_2H_5OH solution always proceeded first with the participation of $N_{(2)}$ to produce regioselectivity of the isomer **5**.

Recently, Chebanov *et al.* reported the three-component condensation of 3-amino-5-alkylthio-1,2,4-triazoles with aromatic aldehydes and acetoacetamides in C_2H_5OH solution under microwave irradiation without any catalyst [12]. Prompted by these results, we also examined the microwave-assisted aminoazole-based Biginelli-like reaction in C_2H_5OH solution without any catalyst. The results shown in Table 3 indicated that the yields were improved significantly compared with those in the presence of HCl as catalyst. Further, it should be noted that different from the situation in H_2O solution using TSA as catalyst, only isomer **5** was formed using C_2H_5OH as reaction solvent no matter what β-ketoester component was used. Additionally, the properties of the R^1 and R^2 group displayed great effects on the yields of product **5**. Ethyl trifluoroacetoacetate always gave higher yields than ethyl acetoacetate and ethyl chloroacetoacetate. Benzaldehydes with electron-withdrawing group

Table 3

Results of the Biginelli-like reaction in C_2H_5OH solution.



				Conventional heating			Microwave irradiation	
No.	R^1	R^2	R^3	Isolated yields (%)		Reaction time (h)	Isolated yields (%)	Reaction time (min)
1	CH_3	$4\text{-}CH_3OC_6H_4$	SCH_3	**5a**	30	18	$36^a/52^b$	30
2	CH_3	$4\text{-}CH_3C_6H_4$	SCH_3	**5b**	36	18	$39^a/55^b$	30
3	CH_3	$4\text{-}ClC_6H_4$	SCH_3	**5c**	40	18	$45^a/60^b$	30
4	CH_3	$2,4\text{-}Cl_2C_6H_3$	SCH_3	**5d**	40	18	$48^a/62^b$	30
5	CH_3	4-Pyridyl	SCH_3	**5e**	70	18	$80^a/82^b$	30
6	CH_3	$4\text{-}CH_3C_6H_4$	SCH_2Ph	**5f**	40	18	$46^a/60^b$	30
7	CH_3	$4\text{-}CH_3OC_6H_4$	SCH_2Ph	**5g**	34	18	$40^a/54^b$	30
8	CH_3	$4\text{-}ClC_6H_4$	SCH_2Ph	**5h**	45	18	$49^a/53^b$	30
9	$ClCH_2$	$4\text{-}CH_3C_6H_4$	SCH_3	**5i**	39	18	$34^a/50^b$	30
10	$ClCH_2$	$4\text{-}CH_3OC_6H_4$	SCH_3	**5j**	31	18	$35^a/51^b$	30
11	$ClCH_2$	$4\text{-}ClC_6H_4$	SCH_3	**5k**	43	18	$47^a/61^b$	30
12	$ClCH_2$	$4\text{-}CH_3C_6H_4$	SCH_2Ph	**5l**	42	18	$44^a/60^b$	30
13	$ClCH_2$	$4\text{-}CH_3OC_6H_4$	SCH_2Ph	**5m**	37	18	$41^a/56^b$	30
14	$ClCH_2$	$4\text{-}ClC_6H_4$	SCH_2Ph	**5n**	48	18	$53^a/67^b$	30
15	CF_3	$4\text{-}CH_3OC_6H_4$	SCH_3	**5o**	51	18	$56^a/61^b$	30
16	CF_3	$4\text{-}ClC_6H_4$	SCH_3	**5p**	61	18	$68^a/75^b$	30
17	CF_3	$4\text{-}ClC_6H_4$	SCH_2Ph	**5q**	63	18	$70^a/78^b$	30
18	CF_3	$3,4\text{-}Cl_2C_6H_3$	SCH_3	**5r**	61	18	$66^a/72^b$	30
19	CF_3	$4\text{-}NO_2C_6H_4$	SCH_3	**5s**	60	18	$69^a/73^b$	30
20	CF_3	$2\text{-}FC_6H_4$	SCH_3	**5t**	64	18	$67^a/68^b$	30
21	CF_3	C_6H_5	SCH_3	**5u**	68	18	$72^a/79^b$	30
22	CF_3	$4\text{-}CH_3C_6H_4$	SCH_3	**5v**	59	18	$63^a/68^b$	30

[a] Yields of the reactions without any catalyst under conventional heating.

[b] Yields of the reactions without any catalyst under microwave irradiation.

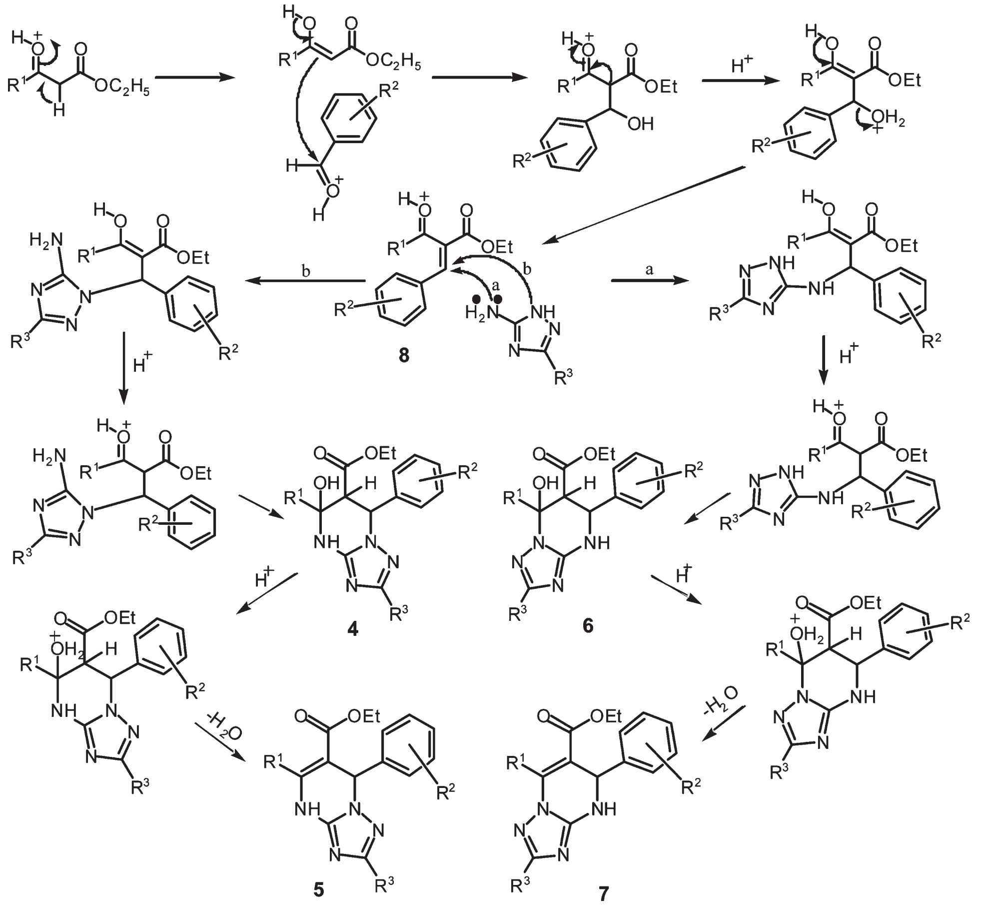
always afforded higher yields of products than benzaldehydes with electron-donating groups. For example, the reaction of 4-pyridylaldehyde (entry 5, Table 3) gave the highest yield (80% in the presence of HCl, 82% without any catalyst) among eight aromatic aldehydes used in this study.

Structure determination. As shown in Scheme 1, four possible products could be obtained theoretically, but only two isomers, compounds **5** and **6**, were identified in this study. The structures of **5** and **6** were assigned by ^1H NMR, ^{13}C NMR, MS, and X-ray diffraction analysis to be ethyl 7-aryl-2-alkylthio-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxylate and ethyl 7-hydroxy-7-alkyl-5-aryl-2-alkylthio-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxylate, respectively. For example, compound **5d** displayed two single peaks at 6.77 and 10.90 ppm for 7-CH and 4-NH, respectively, whereas an obvious AB system at 3.44 and 5.62 ppm for 5-CH and 6-CH was observed in the ^1H NMR spectrum of compound **6d**. The peak for the 4-NH of compound **6d** appeared at 6.88 ppm. Ultimately, the structures of **5d** and **6d** were established on the basis of a X-ray analysis as shown in Figure 1.

CONCLUSIONS

In summary, the three-component condensation of 3-amino-5-alkylthio-1,2,4-triazoles with aromatic aldehydes and β-ketoester was studied. The obtained results showed that the reaction solvent and the properties of the β-ketoester components had a great influence on the regioselect. In H_2O solution with TSA as catalyst, the reaction proceeded first with the participation of $N_{(2)}$ or $3\text{-}NH_2$ of the 3-amino-5-alkylthio-1,2,4-triazoles to afford regioselectivity ethyl 7-aryl-2-alkylthio-4,7-

Scheme 2. The hypothetic mechanism of reaction.



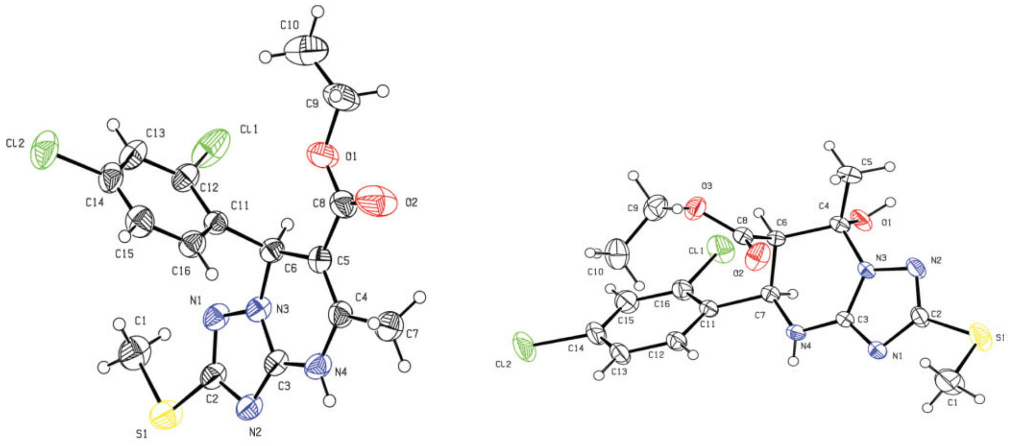
dihydro-1,2,4-triazolo-[1,5-*a*]pyrimidine-6-carboxylate (**5**) or ethyl-7-hydroxy-7-alkyl-5-aryl-2-alkylthio-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxylate (**6**) depending on the property of the aromatic aldehydes when ethyl trifluoroacetoacetate was used as the β-ketoester component. When ethyl acetoacetate and ethyl chloroacetoacetate acted as β-ketoester components, the reaction always produced two isomers **5** and **6**. However, the reactions in C_2H_5OH solution always proceeded first with the participation of $N_{(2)}$ to produce regioselectivity isomer **5**. The yields of the reaction in C_2H_5OH solution in the absence of any catalyst were improved significantly when compared with those in the presence of HCl as catalyst. Additionally, compared with the conventional heating, microwave irradiation improved the yields of the reaction in C_2H_5OH solution and shortened the reaction time to a great extent. To our knowledge, this is the first report about the regioselectivity of aminotriazole-based Biginelli-like reactions.

EXPERIMENTAL

Melting points are uncorrected. Mass spectra were measured on a Finnigan Trace MS spectrometer. NMR spectra were recorded in $CDCl_3$ on a Varian Mercury 400 spectrometer, and resonances are given in ppm (δ) relative to TMS. HPLC analyses were performed on an Agilent 1100 MWD instrument. Microwave irradiation reactions were carried out on a Smith-synthesizer^{TM} instrument.

General procedure for the three-component reaction in H_2O solution. A solution of β-ketoester (1 mmol), aromatic aldehyde (1 mmol), and 3-amino-5-alkylthio-1,2,4-triazoles (1 mmol) in H_2O (3 mL) containing a catalytic amount of TSA was heated under 80°C for 10 h. The resulting mixture was extracted with CH_2Cl_2 (10 mL × 3), and then the extract was dried over sodium sulfate and filtered. The filtrate was condensed under reduced pressure, and the residue was purified by chromatography on SiO_2 ($V_{\text{acetone}}/V_{\text{petroleum ether}} = 1/10$) to afford products **5** and **6**.

General procedure for the three-component reaction in C_2H_5OH solution using HCl as catalyst. A solution of β-ketoester (1 mmol), aromatic aldehyde (1 mmol), and 3-amino-5-alkylthio-1,2,4-triazoles (1 mmol) in EtOH (3 mL)



5d **6d**

Figure 1. Crystal structures of products **5d** and **6d**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

containing 10 μL of concentrated HCl (37%) were refluxed for 18 h. The reaction mixture was cooled to room temperature, and the precipitate was filtered and recrystallized from ethanol to give pure product **5**.

General procedure for the three-component reaction in C_2H_5OH solution using HCl as catalyst under microwave irradiation. A mixture of β-ketoester (1 mmol), aromatic aldehyde (1 mmol), and 3-amino-5-alkylthio-1,2,4-triazoles (1 mmol) in EtOH (3 mL) containing 10 μL of concentrated HCl (37%) was added into a microwave tube. The sealed tube was placed in a Smithsynthesizer^{TM} and irradiated at 150°C for 30 min. The reaction mixture was cooled to room temperature, and the precipitate was filtered and recrystallized from ethanol to give pure product **5**.

General procedure for the reaction in C_2H_5OH solution without any catalyst under microwave irradiation. A mixture of β-ketoester (1 mmol), aromatic aldehyde (1 mmol), and 3-amino-5-alkylthio-1,2,4-triazoles (1 mmol) in EtOH (3 mL) was added into a microwave tube. The sealed tube was placed in a Smithsynthesizer^{TM} and irradiated at 150°C for 30 min. The reaction mixture was cooled to room temperature, and the precipitate was filtered and recrystallized from ethanol to give pure product **5**.

Determination of the X-ray crystal structure of compounds 5d and 6d. Crystals of **5d** and **6d** were grown by slowly evaporating an acetone solution at room temperature. Compound **5d**, $C_{16}H_{16}Cl_2N_4O_2S$ (Mr = 399.29), Monoclinic space group *Pbca*, $Z = 4$, $a = 10.7044(10)$ Å, $b = 22.128(2)$ Å, $c = 8.2341(8)$ Å, $\alpha = 90°$, $\beta = 110.663(2)°$, $\gamma = 90°$, $V = 1824.9(3)$ Å^3, Mo Kα radiation, $1.84° < \theta < 26.99°$, 15129 measured reflections, $T = 292(2)$ K on a Brucker-Nonius kappa CCD. The structure was solved using direct methods (SHELXS 97) and refined with SHELXK 97 final R [$F^2 > 2\sigma(F^2)$] = 0.066 and $wR = [w = 1/[\sigma^2(F_o^2) + (0.0737P)^2 + 1.1468P]$, where $P = (F_o^2 + 2F_c^2)/3$. Compound **6d**, $C_{16}H_{18}Cl_2N_4O_3S$ (Mr = 417.30), Monoclinic space group *Pbca*, $Z = 4$, $a = 11.9765(10)$ Å, $b = 8.7314(8)$ Å, $c = 18.7954(16)$ Å, $\alpha = 90°$, $\beta = 91.3200(10)°$, $\gamma = 90°$, $V = 1824.9(3)$ Å^3, Mo Kα radiation, $2.00° < \theta < 25.99°$, 13069 measured reflections, $T = 292(2)$ K on a Brucker-Nonius kappa CCD. The structure was solved using direct methods (SHELXS 97) and refined with SHELXK 97 final R [$F^2 > 2\sigma(F^2)$] = 0.064 and $wR = [w = 1/[\sigma^2(F_o^2) + (0.0865P)^2 + 1.8162P]$, where $P = (F_o^2 + 2F_c^2)/3$.

CCDC 639763 and 639764 contain the supplementary crystallographic data for compounds **5d** and **6d**, respectively, from this article. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk/data_request/cif.

Data for characterizations of 5 and 6.

Compound 5a. White solid, mp 219–220; ^{1}H NMR (CDCl$_3$, 400 MHz) δ (ppm): 1.15 (t, 3H, J = 6.8 Hz), 2.50 (s, 3H), 2.60 (s, 3H), 3.78 (s, 3H), 4.07 (q, 2H, J = 6.8 Hz), 6.32 (s, 1H), 6.82–7.23 (m, 4H), 10.26 (s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ (ppm): 14.10, 14.41, 19.30, 55.19, 59.45, 60.01, 99.36, 113.68, 128.55, 133.65, 145.74, 148.26, 158.95, 159.32, 165.72; EI-MS (70Ev, *m/z*) (relative intensity %): 362 (20), 360 (M$^+$, 99), 345 (25), 331 (66), 313 (100), 287 (57), 259 (26), 253 (98), 240 (31), 225 (67), 207 (15), 180 (12), 179 (28), 159 (19), 143 (12), 127 (15), 115 (36), 108 (31); Elemental *Anal.* Calcd. for $C_{17}H_{20}N_4O_3S$: C, 56.65; H, 5.59; N, 15.54; Found: C, 56.89; H, 5.32; N, 15.79.

Compound 5b. White solid, mp 227–228; ^{1}H NMR (CDCl$_3$, 400 MHz) δ (ppm): 1.16 (t, 3H, J = 7.2 Hz), 2.31 (s, 3H), 2.49 (s, 3H), 2.62 (s, 3H), 4.07 (q, 2H, J = 7.2 Hz), 6.33 (s, 1H), 7.19–7.22 (m, 4H), 10.76 (s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ (ppm): 14.10, 14.43, 19.32, 21.15, 59.78, 60.03, 99.49, 127.24, 129.10, 137.88, 138.38, 145.75, 148.28, 158.97, 165.67; EI-MS (70Ev, *m/z*) (relative intensity %): 346 (20), 344 (M$^+$, 94), 315 (45), 297 (100), 271 (30), 253 (99), 225 (86), 207 (11), 179 (26), 161 (10), 141 (12), 128 (18), 115 (17); Elemental *Anal.* Calcd. for $C_{17}H_{20}N_4O_2S$: C, 59.28; H, 5.85; N, 16.27; Found: C, 59.55; H, 5.64; N, 16.40.

Compound 5c. White solid, mp 254–255; ^{1}H NMR (CDCl$_3$, 400 MHz) δ (ppm): 1.15 (t, 3H, J = 7.2 Hz), 2.49 (s, 3H), 2.63 (s, 3H), 4.07 (q, 2H, J = 7.2 Hz), 6.33 (s, 1H), 7.25–7.30 (m, 4H), 10.66 (s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ (ppm): 14.10, 14.37, 19.43, 59.49, 60.23, 99.06, 128.68, 128.81, 134.09, 139.60, 145.98, 147.97, 159.13, 165.38; EI-MS (70Ev, *m*/*z*) (relative intensity %): 366 (30), 364.5 (M^+, 94), 349 (10), 337 (22), 335 (48), 318 (100), 289 (23), 275 (11), 253 (71), 244 (11), 225 (46), 207 (8), 179 (17), 154 (4), 127 (13), 111 (5); Elemental *Anal.* Calcd. for $C_{16}H_{17}ClN_4O_2S$: C, 52.67; H, 4.70; N, 15.36; Found: C, 52.78; H, 4.92; N, 15.09.

Compound 5d. White solid, mp 242–243; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.12 (t, 3H, *J* = 7.2 Hz), 2.48 (s, 3H), 2.65 (s, 3H), 4.04 (q, 2H, *J* = 7.2 Hz), 6.77 (s, 1H), 7.18–7.38 (m, 3H), 10.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 14.10, 14.32, 19.39, 56.84, 60.19, 97.94, 127.52, 129.63, 130.71, 134.18, 134.53, 137.27, 146.9, 147.9, 159.2, 165.2; EI-MS (70Ev, *m*/*z*) (relative intensity %): 403 (10), 401 (16), 399 (M^+, 32), 398 (87), 371 (52), 369 (80), 363 (55), 353 (25), 333 (9), 325 (12), 317 (8), 287 (15), 253 (100), 225 (56), 207 (12), 179 (19), 161 (17), 126 (7); Elemental *Anal.* Calcd. for $C_{16}H_{16}Cl_2N_4O_2S$: C, 48.13; H, 4.04; N, 14.03; Found: C, 48.32; H, 3.86; N, 14.29.

Compound 5e. White solid, mp 243–244; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.17 (t, 3H, *J* = 7.2 Hz), 2.49 (s, 3H), 2.66 (s, 3H), 4.10 (q, 2H, *J* = 7.2 Hz), 6.36 (s, 1H), 7.27 (d, 2H, *J* = 6.4 Hz), 8.59 (d, 2H, *J* = 6.0 Hz), 11.15 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 14.10, 14.22, 19.43, 58.87, 60.33, 97.49, 122.34, 147.21, 148.38, 149.50, 149.92, 159.39, 165.23; EI-MS (70Ev, *m*/*z*) (relative intensity %): 333 (10), 331 (M^+, 60), 287 (35), 253 (100), 225 (59), 207 (24), 180 (29), 159 (19), 143 (12), 127 (36), 115 (29); Elemental *Anal.* Calcd. for $C_{15}H_{17}N_5O_2S$: C, 54.36; H, 5.17; N, 21.13; Found: C, 54.59; H, 5.46; N, 21.44.

Compound 5f. White solid, mp 165–166; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.15 (t, 3H, *J* = 7.2 Hz), 2.24 (s, 3H), 2.56 (s, 3H), 4.06 (q, 2H, *J* = 6.8 Hz), 4.14 (d, 1H, *J* = 12.8 Hz), 4.26 (d, 1H, *J* = 12.8 Hz), 6.33 (s, 1H), 7.19–7.22 (m, 9H), 10.76 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 14.09, 19.40, 21.17, 36.49, 59.92, 60.03, 99.26, 127.24, 127.29, 128.37, 128.97, 129.12, 137.35, 137.86, 138.40, 145.82, 148.13, 157.45, 165.67; EI-MS (70Ev, *m*/*z*) (relative intensity %): 422 (18), 420 (M^+, 100), 387 (58), 376 (10), 359 (5), 341 (26), 329 (42), 297 (45), 283 (9), 269 (15), 251 (11), 239 (8), 224 (11), 205 (16), 169 (11), 141 (15), 128 (15), 123 (39), 115 (14); Elemental *Anal.* Calcd. for $C_{23}H_{24}N_4O_2S$: C, 65.69; H, 5.75; N, 13.32; Found: C, 65.37; H, 5.96; N, 13.54.

Compound 5g. White solid, mp 191–192; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.15 (t, 3H, *J* = 6.8 Hz), 2.57 (s, 3H), 3.80 (s, 3H), 4.07 (q, 2H, *J* = 6.8 Hz), 4.14 (d, 1H, *J* = 12.8 Hz), 4.27 (d, 1H, *J* = 12.8 Hz), 6.33 (s, 1H), 7.19–7.22 (m, 9H), 10.76 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 14.11, 19.41, 36.47, 55.26, 59.65, 60.07, 99.48, 113.80, 127.27, 128.39, 128.60, 128.98, 133.56, 137.33, 145.47, 147.89, 157.41, 159.49, 165.65; EI-MS (70Ev, *m*/*z*) (relative intensity %): 438 (31), 436 (M^+, 100), 403 (44), 389 (7), 357 (12), 345 (38), 329 (11), 313 (35), 285 (10), 267 (8), 241 (5), 229 (8), 197 (8), 185 (6), 159 (6), 123 (17); Elemental *Anal.* Calcd. for $C_{23}H_{24}N_4O_3S$: C, 63.28; H, 5.54; N, 12.83; Found: C, 63.04; H, 5.28; N, 13.06.

Compound 5h. White solid, mp 204–205; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.14 (t, 3H, *J* = 7.2 Hz), 2.58 (s, 3H), 4.06 (q, 2H, *J* = 7.2 Hz), 4.12 (d, 1H, *J* = 13.2 Hz), 4.26 (d, 1H, *J* = 13.2 Hz), 6.32 (s, 1H), 7.19–7.30 (m, 9H), 10.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 14.10, 19.47, 36.28, 59.57, 60.19, 98.62, 127.34, 128.37, 128.65, 128.81, 128.91, 134.02, 137.20, 139.75, 146.23, 148.00, 157.71, 165.43; EI-MS (70Ev, *m*/*z*) (relative intensity %): 444 (6), 442 (25), 440 (M^+, 100), 407 (60), 395 (5), 361 (19), 349 (26), 329 (21), 317 (21), 289 (11), 275 (5), 247 (9), 207 (12), 189 (10), 163 (10), 123 (43); Elemental *Anal.* Calcd. for $C_{22}H_{21}ClN_4O_2S$: C, 59.92; H, 4.80; N, 12.71; Found: C, 60.23; H, 4.51; N, 12.84.

Compound 5i. White solid, mp 292–293; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.17 (t, 3H, *J* = 6.8 Hz), 2.32 (s, 3H), 2.51 (s, 3H), 4.11 (q, 2H, *J* = 7.2 Hz), 4.95 (d, 1H, *J* = 12.4 Hz), 5.14 (d, 1H, *J* = 12.4 Hz), 6.36 (s, 1H), 7.11–7.22 (m, 4H), 10.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.94, 14.50, 21.19, 40.21, 59.82, 60.90, 101.76, 127.25, 129.34, 137.22, 138.50, 142.39, 147.19, 159.34, 164.38; EI-MS (70Ev, *m*/*z*) (relative intensity %): 381 (32), 379 (M^+, 99), 342 (100), 331 (19), 313 (51), 297 (20), 287 (69), 267 (37), 255 (36), 223 (29), 194 (9), 177 (11), 153 (8), 141 (14) 126 (13), 115 (21); Elemental *Anal.* Calcd. for $C_{17}H_{19}ClN_4O_2S$: C, 53.89; H, 5.05; N, 14.79; Found: C, 54.13; H, 5.28; N, 14.91.

Compound 5j. White solid, mp 286–287; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.17 (t, 3H, *J* = 7.2 Hz), 2.52 (s, 3H), 3.78 (s, 3H), 4.11 (q, 2H, *J* = 7.2 Hz), 4.95 (d, 1H, *J* = 12.0 Hz), 5.13 (d, 1H, *J* = 12.0 Hz), 6.36 (s, 1H), 6.83–7.27 (m, 4H), 10.78 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.9,7 14.58, 40.19, 55.25, 59.55, 60.850, 101.72, 126.98, 128.62, 132.57, 142.51, 147.38, 159.56, 159.73, 164.46; EI-MS (70Ev, *m*/*z*) (relative intensity %): 397 (13), 395 (M^+, 100), 358 (99), 329 (36),313 (29), 287 (62), 271 (41), 251 (27), 240 (15), 222 (27), 194 (14), 177 (10), 158 (9), 145 (10), 115 (14), 108 (18), 77 (10); Elemental *Anal.* Calcd. for $C_{17}H_{19}ClN_4O_3S$: C, 51.71; H, 4.85; N, 14.19; Found: C, 51.93; H, 5.07; N, 14.43.

Compound 5k. White solid, mp 270–271; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.17 (t, 3H, *J* = 7.2 Hz), 2.51 (s, 3H), 4.12 (q, 2H, *J* = 7.2 Hz), 4.96 (d, 1H, *J* = 12.0 Hz), 5.12 (d, 1H, *J* = 12.0 Hz), 6.37 (s, 1H), 7.26–7.31 (m, 4H), 10.85 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.95, 14.57, 39.80, 59.39, 60.98, 100.81, 128.79, 128.84, 134.45, 138.76, 143.67, 147.60, 159.68, 164.16; EI-MS (70Ev, *m*/*z*) (relative intensity %): 402 (11), 400 (44), 399 (M^+, 21), 398 (81), 362 (80), 353 (10), 333 (36), 317 (17), 287 (100), 275 (45), 259 (23), 251 (10), 223 (22), 208 (5), 194 (5), 177 (9), 162 (7), 149 (10), 140 (6), 127 (9); Elemental *Anal.* Calcd. for $C_{16}H_{16}Cl_2N_4O_2S$: C, 48.13; H, 4.04; N, 14.03; Found: C, 47.87; H, 4.27; N, 13.86.

Compound 5l. White solid, mp 297–298; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.16 (t, 3H, *J* = 6.8 Hz), 2.34 (s, 3H), 4.12 (q, 2H, *J* = 7.2 Hz), 4.16 (d, 1H, *J* = 12.8 Hz), 4.27 (d, 1H, *J* = 12.8 Hz), 4.88 (d, 1H, *J* = 12.0 Hz), 5.09 (d, 1H, *J* = 12.0 Hz), 6.36 (s, 1H), 7.11–7.23 (m, 9H), 10.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.93, 21.18, 36.67, 39.87, 59.86, 60.79, 101.31, 127.25, 127.29, 128.36, 128.97, 129.29, 137.22, 137.49, 138.31, 143.25, 147.64, 157.94, 164.43; EI-MS (70Ev, *m*/*z*) (relative intensity %): 456 (19), 454 (M^+, 59), 418 (59), 385 (20), 363 (10), 357 (13), 339 (12), 327 (11), 297 (6), 267 (8), 227 (6), 212 (6), 168 (4), 141 (8), 123 (12); Elemental *Anal.* Calcd. for $C_{23}H_{23}ClN_4O_2S$: C, 60.72; H, 5.10; N, 12.31; Found: C, 60.54; H, 4.87; N, 12.09.

Compound 5m. White solid, mp 293–294; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.17 (t, 3H, *J* = 6.8 Hz), 3.80 (s, 3H), 4.11 (q, 2H, *J* = 6.8 Hz), 4.16 (d, 1H, *J* = 12.8 Hz), 4.28 (d, 1H, $J = 12.8$ Hz), 4.90 (d, 1H, $J = 12.0$ Hz), 5.07 (d, 1H, $J = 12.0$ Hz), 6.35 (s, 1H), 6.84–7.24 (m, 9H), 10.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.95, 36.67, 39.83, 55.25, 59.56, 60.77, 101.29, 113.91, 127.26, 128.36, 128.64, 128.97, 132.71, 137.22, 143.25, 147.61, 157.84, 159.64, 164.44; EI-MS (70Ev, *m/z*) (relative intensity %): 472 (10), 470 (M^+, 40), 462 (7), 434 (70), 401 (16), 373 (10), 355 (12), 327 (12), 313 (21), 283 (24), 267 (23), 241 (22), 228 (25), 197 (20), 185 (20), 172 (14), 158 (12), 123 (28), 115 (10), 91 (100); Elemental *Anal.* Calcd. for $C_{23}H_{23}ClN_4O_3S$: C, 58.65; H, 4.92; N, 11.90; Found: C, 58.88; H, 5.12; N, 12.05.

Compound 5n. White solid, mp > 300; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.16 (t, 3H, $J = 7.2$ Hz), 4.11 (q, 2H, $J = 7.2$ Hz), 4.15 (d, 1H, $J = 13.6$ Hz), 4.27 (d, 1H, $J = 13.6$ Hz), 4.92 (d, 1H, $J = 12.0$ Hz), 5.07 (d, 1H, $J = 12.0$ Hz), 6.36 (s, 1H), 7.17–7.32 (m, 9H), 10.92 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.95, 36.54, 39.80, 59.52, 60.95, 100.63, 127.34, 128.37, 128.81, 128.86, 128.92, 134.46, 137.12, 138.87, 143.75, 147.59, 158.28, 164.18; EI-MS (70Ev, *m/z*) (relative intensity %): 478 (14), 476 (54), 474 (M^+, 73), 438 (57), 405 (31), 391 (23), 377 (10), 362 (17), 327 (9), 288 (10), 258 (13), 246 (14), 228 (9), 162 (7), 149 (8), 133 (34), 105 (22), 91 (100); Elemental *Anal.* Calcd. for $C_{22}H_{20}Cl_2N_4O_2S$: C, 55.58; H, 4.24; N, 11.79; Found: C, 55.41; H, 4.51; N, 11.63.

Compound 5o. White solid, mp 154–155; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.16 (t, 3H, $J = 7.2$ Hz), 2.46 (s, 3H), 3.79 (s, 3H), 4.12 (m, 2H), 6.38 (s, 1H), 6.86–7.26 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.60, 14.16, 55.21, 60.11, 61.66, 106.45, 114.11, 115.73, 118.48, 121.22, 123.97, 128.78, 130.15, 130.52, 130.87, 147.11, 159.98, 160.76, 163.17; EI-MS (70Ev, *m/z*) (relative intensity %): 416 (5), 414 (M^+, 100), 385 (25), 367 (78), 341 (44), 325 (12), 294 (10), 279 (16), 233 (6), 213 (9), 170 (4), 85 (4); Elemental *Anal.* Calcd. for $C_{17}H_{17}F_3N_4O_3S$: C, 49.27; H, 4.13; N, 13.52; Found: C, 49.42; H, 4.36; N, 13.69.

Compound 5p. White solid, mp 188–189; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.17 (t, 3H, $J = 7.2$ Hz), 2.45 (s, 3H), 4.13 (m, 2H), 6.40 (s, 1H), 7.25–7.35 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.60, 14.12, 60.02, 61.87, 92.29, 105.74, 115.60, 118.36, 121.11, 123.86, 128.87, 129.09, 130.83, 131.20, 131.57, 135.05, 136.76, 147.06, 161.17, 162.92; EI-MS (70Ev, *m/z*) (relative intensity %): 420 (29), 418 (M^+, 100), 389 (32), 371 (62), 349 (32), 307 (21), 279 (17), 263 (3), 233 (8), 217 (5), 182 (3), 111 (5); Elemental *Anal.* Calcd. for $C_{16}H_{14}ClF_3N_4O_2S$: C, 45.88; H, 3.37; N, 13.38; Found: C, 45.62; H, 3.47; N, 13.11.

Compound 5q. White solid, mp 160–161; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.16 (t, 3H, $J = 7.2$ Hz), 4.12 (m, 2H), 4.12 (d, 1H, $J = 13.2$ Hz), 4.24 (d, 1H, $J = 13.2$ Hz), 6.39 (s, 1H), 7.18–7.34 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.59, 35.77, 59.99, 61.84, 105.47, 115.57, 118.32, 121.07, 123.82, 127.22, 128.27, 128.90, 129.07, 129.82, 130.94, 131.31, 131.68, 132.04, 135.01, 136.77, 146.96, 159.64, 162.94; EI-MS (70Ev, *m/z*) (relative intensity %): 496 (32), 494 (M^+, 100), 461 (65), 449 (4), 415 (12), 403 (6), 390 (4), 217 (3), 172 (4), 121 (7), 91 (99); Elemental *Anal.* Calcd. for $C_{22}H_{18}ClF_3N_4O_2S$: C, 53.39; H, 3.67; N, 11.32; Found: C, 53.62; H, 3.84; N, 11.08.

Compound 5r. White solid, mp 188–189; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.20 (t, 3H, $J = 7.2$ Hz), 2.47 (s, 3H), 4.16 (m, 2H), 6.39 (s, 1H), 7.14–7.45 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.60, 14.11, 59.58, 61.92, 104.87, 114.19, 115.54, 118.33, 121.08, 123.79, 126.80, 129.61, 130.93, 131.37, 131.82, 132.22, 132.51, 133.03, 133.42, 138.44, 147.06, 161.54, 162.80; EI-MS (70Ev, *m/z*) (relative intensity %): 454 (100), 452 (M^+, 88), 423 (32), 405 (84), 383 (43), 359 (10), 307 (39), 279 (26), 251 (6), 233 (10), 201 (5), 165 (7), 109 (6); Elemental *Anal.* Calcd. for $C_{16}H_{13}Cl_2F_3N_4O_2S$: C, 42.40; H, 2.89; N, 12.36; Found: C, 42.50; H, 3.05; N, 12.05.

Compound 5s. Yellow solid, mp 209–210; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.19 (t, 3H, $J = 7.2$ Hz), 2.45 (s, 3H), 4.15 (m, 2H), 6.54 (s, 1H), 7.51–8.25 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.60, 14.02, 59.83, 62.14, 104.58, 115.49, 118.30, 120.87, 124.13, 128.61, 131.88, 132.22, 132.60, 132.93, 144.79, 147.20, 148.14, 161.73, 162.68; EI-MS (70Ev, *m/z*) (relative intensity %): 244 (3), 227 (2), 199 (2), 138 (20), 107 (33), 77 (100); Elemental *Anal.* Calcd. for $C_{16}H_{14}F_3N_5O_4S$: C, 44.76; H, 3.29; N, 16.31; Found: C, 45.02; H, 3.38; N, 16.05.

Compound 5t. White solid, mp 155–156; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.15 (t, 3H, $J = 7.2$ Hz), 2.45 (s, 3H), 4.04 (m, 2H), 6.65 (s, 1H), 7.03–7.35 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.54, 14.10, 55.83, 61.68, 104.53, 115.56, 115.89, 116.22, 118.40, 121.13, 123.83, 124.44, 125.46, 125.60, 129.82, 130.87, 131.61, 131.92, 132.27, 132.58; EI-MS (70Ev, *m/z*) (relative intensity %): 402 (M^+, 53), 373 (13), 353 (27), 333 (22), 307 (12), 279 (9), 266 (10), 249 (22), 198 (14), 168 (99), 139 (100), 124 (92), 106 (32); Elemental *Anal.* Calcd. for $C_{16}H_{14}F_4N_4O_2S$: C, 47.76; H, 3.51; N, 13.92; Found: C, 48.02; H, 3.76; N, 14.15.

Compound 5u. White solid, mp 179–180; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.14 (t, 3H, $J = 7.2$ Hz), 2.46 (s, 3H), 4.04 (m, 2H), 6.43 (s, 1H), 7.30–7.38 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.60, 14.11, 60.58, 60.72, 61.74, 106.19, 115.68, 118.48, 121.19, 123.90, 127.43, 128.83, 129.04, 130.51, 130.79, 131.20, 131.57, 138.33, 147.29, 160.81, 163.10; EI-MS (70Ev, *m/z*) (relative intensity %): 385 (19), 384 (M^+, 100), 355 (20), 337 (50), 315 (19), 307 (25), 279 (19), 133 (8); Elemental *Anal.* Calcd. for $C_{16}H_{15}F_3N_4O_2S$: C, 50.00; H, 3.93; N, 14.58; Found: C, 50.08; H, 4.00; N, 14.30.

Compound 5v. White solid, mp 156–157; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.16 (t, 3H, $J = 7.2$ Hz), 2.33 (s, 3H), 2.46 (s, 3H), 4.12 (m, 2H), 6.38 (s, 1H), 7.15 (dd, 2H, $J = 8.4$ Hz), 7.19 (dd, 2H, $J = 8.0$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.60, 14.12, 21.17, 60.39, 61.57, 106.44, 115.73, 118.54, 121.16, 123.92, 127.33, 129.48, 130.41, 130.72, 131.14, 131.50, 135.45, 138.93, 147.23, 160.83, 163.12; EI-MS (70Ev, *m/z*) (relative intensity %): 400 (5), 398 (M^+, 100), 369 (25), 351 (81), 329 (28), 307 (30), 278 (31), 233 (8), 197 (4), 165 (3), 115 (7); Elemental *Anal.* Calcd. for $C_{17}H_{16}F_4N_4O_2S$: C, 49.04; H, 3.87; N, 13.46; Found: C, 49.25; H, 3.67; N, 13.19.

Compound 6a. White solid, mp 154–155; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.96 (t, 3H, $J = 7.2$ Hz), 1.89 (s, 3H), 2.43 (s, 3H), 3.04 (d, 1H, $J = 11.2$ Hz), 3.81 (s, 3H), 3.95 (m, 2H), 4.95 (d, 1H, $J = 11.2$ Hz), 5.93 (s, 1H), 6.87–7.34 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.71, 14.30, 25.69, 53.84, 55.33, 57.10, 61, 50, 81.83, 114.12, 129.08, 129.74, 153.14, 159.09, 160.10, 169.87; EI-MS (70Ev, *m/z*) (relative intensity %): 379 (8), 378 (M$^+$, 32), 360 (12), 335 (7), 313 (9), 289 (8), 247 (100), 233 (41), 200 (38), 174 (24), 161 (64), 146 (61), 129 (64), 115 (23); Elemental *Anal.* Calcd. for $C_{17}H_{22}N_4O_4S$: C, 53.95; H, 5.86; N, 14.80; Found: C, 53.76; H, 6.04; N, 14.92.

Compound 6d. White solid, mp 151–152; ^{1}H NMR (CDCl$_3$, 400 MHz) δ (ppm): 0.97 (t, 3H, *J* = 7.2 Hz), 1.86 (s, 3H), 2.43 (s, 3H), 3.44 (d, 1H, *J* = 11.2 Hz), 4.01 (m, 2H), 5.62 (d, 1H, *J* = 11.2 Hz), 6.88 (s, 1H), 7.25–7.50 (m, 3H); ^{13} C NMR (CDCl$_3$, 100 MHz) δ (ppm): 13.69, 14.30, 24.38, 49.63, 52.14, 61.88, 82.10, 127.61, 129.67, 133.89, 139.11, 153.69, 159.52, 169.83; EI-MS (70Ev, *m/z*) (relative intensity %): 418 (4), 416 (M$^+$, 7), 373 (5), 327 (9), 287 (23), 251 (100), 223 (21),199 (15), 170 (8), 13 0 (28), 114 (8); Elemental *Anal.* Calcd. for $C_{16}H_{18}Cl_2N_4O_3S$: C, 46.05; H, 4.35; N, 13.43; Found: C, 46.33; H, 4.08; N, 13.80.

Compound 6f. White solid, mp 140–141; ^{1}H NMR (CDCl$_3$, 400 MHz) δ (ppm): 0.96 (t, 3H, *J* = 7.2 Hz), 1.80 (s, 3H), 2.31 (s, 3H), 3.05 (d, 1H, *J* = 11.2 Hz), 3.92 (m, 2H), 4.20 (d, 1H, *J* = 13.2 Hz), 4.27 (d, 1H, *J* = 13.2 Hz), 4.94 (d, 1H, *J* = 11.2 Hz), 5.86 (s, 1H), 7.13–7.37 (m, 9H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ (ppm): 13.60, 21.11, 25.69, 36.13, 54.33, 56.74, 61.48, 81.87, 127.21, 127.72, 128.44, 129.13, 129.49, 134.52, 137.47, 138.86, 152.90, 157.88, 170.12; EI-MS (70Ev, *m/z*) (relative intensity %): 438 (M$^+$, 5), 369 (2), 308 (50), 275 (30), 231 (27), 217 (72), 206 (65), 187 (21), 173 (24), 143 (28), 115 (51), 102 (16), 90 (100); Elemental *Anal.* Calcd. for $C_{23}H_{26}N_4O_3S$: C, 62.99; H, 5.98; N, 12.78; Found: C, 62.77; H, 6.17; N, 12.94.

Compound 6h. White solid, mp 152–153; ^{1}H NMR (CDCl$_3$, 400 MHz) δ (ppm): 0.96 (t, 3H, *J* = 7.2 Hz), 1.78 (s, 3H), 3.01 (d, 1H, *J* = 11.2 Hz), 3.92 (m, 2H), 4.12 (d, 1H, *J* = 13.2 Hz), 4.20 (d, 1H, *J* = 13.2 Hz), 4.96 (d, 1H, *J* = 11.6 Hz), 6.63 (s, 1H), 7.23–7.35 (m, 9H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ (ppm): 13.70, 25.61, 35.92, 53.68, 56.84, 61.73, 81.85, 127.20, 128.44, 128.91, 129.04, 129.29, 134.77, 136.32, 137.28, 152.91, 157.83, 169.64; EI-MS (70Ev, *m/z*) (relative intensity %): 458 (M$^+$, 2), 328 (64), 295 (48), 251 (49), 237 (36), 217 (42), 206 (100), 189 (9), 173 (46), 165 (37), 141 (11), 115 (11), 101 (18); Elemental *Anal.* Calcd. for $C_{22}H_{23}ClN_4O_3S$: C, 57.57; H, 5.05; N, 12.21; Found: C, 57.82; H, 5.30; N, 12.09.

Compound 6i. White solid, mp 147–148; ^{1}H NMR (CDCl$_3$, 400 MHz) δ (ppm): 0.93 (t, 3H, *J* = 7.2 Hz), 2.36 (s, 3H), 2.39 (s, 3H), 3.55 (d, 1H, *J* = 11.6 Hz), 3.88 (d, 1H, *J* = 12.0 Hz), 3.94 (m, 2H), 4.36 (d, 1H, *J* = 11.6 Hz), 4.93 (d, 1H, *J* = 11.2 Hz), 5.82 (s, 1H), 7.17–7.34 (m, 4H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ (ppm): 13.52, 14.20, 21.24, 46.08, 51.73, 54.14, 61.88, 83.63, 127.81, 129.50, 134.08, 139.22, 153.91, 159.79, 169.90; EI-MS (70Ev, *m/z*) (relative intensity %): 396 (M$^+$, 6), 360 (2), 273 (3), 266 (6), 251 (6), 231 (100), 217 (53), 185 (5), 164 (4), 145 (13), 130 (36), 115 (47), 103 (9); Elemental *Anal.* Calcd. for $C_{17}H_{21}ClN_4O_3S$: C, 51.45; H, 5.33; N, 14.12; Found: C, 51.57; H, 5.05; N, 14.34.

Compound 6m. White solid, mp 147–148; ^{1}H NMR (CDCl$_3$, 400 MHz) δ (ppm): 0.94 (t, 3H, *J* = 7.2 Hz), 3.52 (d, 1H, *J* = 11.6 Hz), 3.76 (s, 3H), 3.87 (d, 1H, *J* = 12.0 Hz), 3.96 (m, 2H), 4.02 (d, 1H, *J* = 12.8 Hz), 4.16 (d, 1H, *J* = 12.8 Hz), 4.34 (d, 1H, *J* = 11.6 Hz), 4.91 (d, 1H, *J* = 11.6 Hz), 6.33 (s, 1H), 6.85–7.36 (m, 9H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ (ppm): 13.60, 35.82, 46.19, 51.89, 53.04, 55.22, 61.73, 83.61, 113.88, 127.11, 128.26, 128.86, 129.37, 137.24, 154.13, 158.30, 160.04, 169.11; EI-MS (70Ev, *m/z*) (relative intensity %): 324 (16), 291 (8), 282 (17), 233 (89), 206 (38), 189 (9), 173 (24), 161 (22), 137 (19), 115 (50), 91 (100); Elemental *Anal.* Calcd. for $C_{23}H_{25}ClN_4O_4S$: C, 56.49; H, 5.15; N, 11.46; Found: C, 56.78; H, 5.06; N, 11.57.

Compound 6n. White solid, mp 150–151; ^{1}H NMR (CDCl$_3$, 400 MHz) δ (ppm): 0.97 (t, 3H, *J* = 7.2 Hz), 3.51 (d, 1H, *J* = 11.2 Hz), 3.87 (d, 1H, *J* = 11.2 Hz), 3.94 (m, 2H), 4.03 (d, 1H, *J* = 13.2 Hz), 4.15 (d, 1H, *J* = 13.2 Hz), 4.34 (d, 1H, *J* = 11.2 Hz), 4.93 (d, 1H, *J* = 11.2 Hz), 6.78 (s, 1H), 7.23–7.39 (m, 9H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ (ppm): 13.60, 35.91, 45.86, 51.69, 53.40, 61.87, 83.73, 127.32, 128.45, 128.86, 129.02, 129.64, 135.03, 135.87, 137.11, 154.10, 158.50, 169.14; EI-MS (70Ev, *m/z*) (relative intensity %): 493 (M$^+$, 1), 419 (1), 366 (2), 328 (61), 295 (43), 286 (21), 251 (4), 237 (99), 206 (100), 190 (10), 173 (45), 165 (33), 136 (23), 115 (29), 101 (25); Elemental *Anal.* Calcd. for $C_{22}H_{22}Cl_2N_4O_3S$: C, 53.55; H, 4.49; N, 11.36; Found: C, 53.78; H, 4.72; N, 11.70.

Compound 6t. White solid, mp 158–159; ^{1}H NMR (CDCl$_3$, 400 MHz) δ (ppm): 0.88 (t, 3H, *J* = 7.2 Hz), 2.33 (s, 3H), 3.78 (d, 1H, *J* = 4.0 Hz), 3.84 (m, 2H), 5.44 (d, 1H, *J* = 4.0 Hz), 7.12–7.46 (m, 4H); ^{13}C NMR (DMSO, 100 MHz) δ (ppm): 13.54, 47.03, 48.10, 60.43, 60.61, 81.23, 81.46, 115.25, 115.44, 121.42, 123.74, 123.79, 124.23, 124.67, 127.88, 130.50, 153.93, 155.62, 157.67, 158.33, 159.40, 160.77, 164.65, 165.52; EI-MS (70Ev, *m/z*) (relative intensity %): 422 (6), 420 (M$^+$, 100), 401 (20), 373 (7), 353 (12), 277 (14), 235 (72), 217 (83), 184 (5), 149 (25), 134 (27), 115 (22); Elemental *Anal.* Calcd. for $C_{16}H_{16}F_4N_4O_3S$: C, 45.71; H, 3.84; N, 13.33; Found: C, 45.54; H, 4.05; N, 13.56.

Compound 6u. White solid, mp 143–144; ^{1}H NMR (CDCl$_3$, 400 MHz) δ (ppm): 0.88 (t, 3H, *J* = 7.2 Hz), 2.26 (s, 3H), 3.59 (d, 1H, *J* = 4.0 Hz), 3.85 (m, 2H), 5.10 (d, 1H, *J* = 4.4 Hz), 7.32–7.40 (m, 5H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ (ppm): 13.60, 14.22, 49.89, 54,14, 61.12, 81.87, 82.32, 121.24, 124.13, 126.65, 126.91, 136.14, 155.10, 160.83, 165.44; EI-MS (70Ev, *m/z*) (relative intensity %): 402 (M$^+$, 8), 369 (4), 272 (3), 230 (4), 217 (100), 203 (5), 184 (9), 171 (6), 139 (15), 115 (22); Elemental *Anal.* Calcd. for $C_{16}H_{17}F_3N_4O_3S$: C, 47.76; H, 4.26; N, 13.92; Found: C, 48.04; H, 4.02; N, 14.15.

Compound 6v. White solid, mp 153–154; ^{1}H NMR (CDCl$_3$, 400 MHz) δ (ppm): 0.92 (t, 3H, *J* = 7.2 Hz), 2.29 (s, 3H), 2.34 (s, 3H), 3.56 (d, 1H, *J* = 4.0 Hz), 3.87 (q, 2H, *J* = 7.2 Hz), 5.06 (d, 1H, *J* = 4.0 Hz), 7.07–7.24 (m, 4H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ (ppm): 13.22, 13.58, 14.20, 49.87, 53.90, 61.23, 81.91, 82.19, 118.22, 121.14, 123.88, 126.55, 127.64, 129.61, 132.88, 138.83, 139.74, 155.13, 160.89, 165.54; EI-MS (70Ev, *m/z*) (relative intensity %): 416 (M$^+$, 6), 286 (2), 271 (3), 231 (100), 217 (8), 184 (5), 139 (9), 130 (14), 115 (19); Elemental *Anal.* Calcd. for $C_{17}H_{19}F_3N_4O_3S$: C, 49.03; H, 4.60; N, 13.45; Found: C, 49.37; H, 4.63; N, 13.13.

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Microwave-Assisted Reactions: Three Component Process for the Synthesis of 2-Amino-2-chromenes Under Microwave Heating

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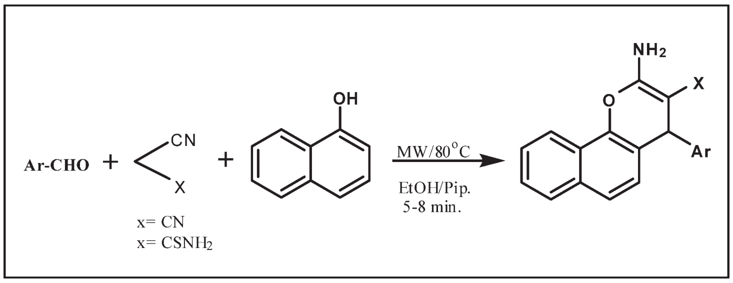

A simple and efficient three component process for the synthesis of 2-amino-2-chromenes utilizing the reaction of aryl aldehydes **1a–1h** with active methylenes **2a,b** and 1-naphthol **3** in refluxing ethanol/piperidine under microwave-heating is described.

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INTRODUCTION

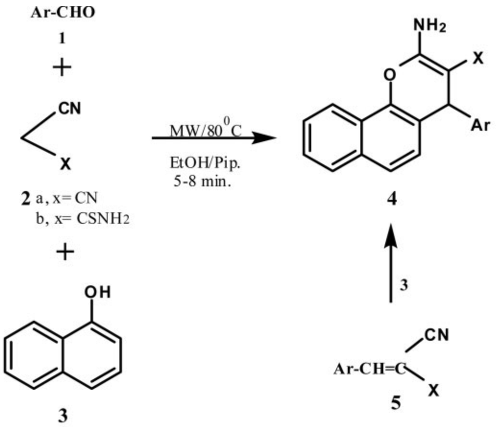
Substituted 2-amino-2-chromenes have received considerable attention due to their importance as pigments, cosmetics, potential agrochemicals, and being the main constituents of many natural products [1–5]. Accordingly, their synthesis has received much attention from organic chemists. These compounds are generally prepared by multicomponent condensation of aromatic aldehyde **1**, active methylene derivatives **2** and activated phenol or naphthol **3** in the presence of piperidine using acetonitrile or ethanol as a solvent under conventional heating for periods ranging from 2–3 h in moderate yields [6–9]. Also, relatively benign reagents such as cetyltrimethylammonium chloride (CTACl) and basic alumina in water have been used [10]. Thus, substituted 2-amino-2-chromenes **4** will be produced in moderate to good yields by heating a mixture of **1**, **2**, and **3** in water in the presence of a catalytic amount of CTACl for 6 h under reflux. It is obvious that, most of these require prolonged reaction time, reagents in stoichiometric amounts and provide moderate yields of the product. Recently [11], a three component condensation in MeOH in the presence of nanosized magnesium oxide as a catalyst at room temperature has been reported. Although, this process is efficient and convenient, the usage of MeOH as a solvent for the reaction and work-up is not recommended due to the toxicity.

In recent years, there has been extensive effort to adapt green technologies in synthetic organic chemistry, so as to minimize waste production, material and energy consumption, and the use of hazardous compounds. Microwave-assisted reactions have received great interest because of their simplicity in operation, enhanced reaction rates, products with high purity, and better yields compared to those conducted by conventional heating [12–14]. Also, a three-component one step reaction is of great interest for cost savings due to raw materials consumption, energy use, and time. We do believe that combining microwave heating technique with a three-component one step reaction will be beneficial and interesting. In continuation to our interest for the synthesis of azoles, azines, and fused rings [15–17], we report herein the synthesis of 2-amino-2-chromenes *via* three-component synthesis by using microwave technique.

RESULTS AND DISCUSSION

The synthesis of 2-amino-2-chromenes under conventional heating technique requires prolonged reaction time and affords moderate yields of products. Conducting a three-component synthesis of these target molecules under microwave irradiation and, to the best of our knowledge, has never been published before. Thus, when a mixture of benzaldehyde **1a**, malononitrile **2a** and α-naphthol **3** in 10 mL of ethanol and in the presence of piperidine as a catalyst was refluxed in a microwave labstation for 5 min at 80°C, the corresponding 2-amino-2-chromene derivative **4a** was obtained in almost quantitative yield (Scheme 1). The structure of the formed product was established by spectral and analytical data and also by comparison with authentic sample synthesized by reaction of benzylidene malononitrile **5** with α-naphthol under conventional heating [18]. Thus,

Scheme 1



1,4, 5	Ar	X	Time (min.)	Yield (%)
a	C_6H_5	CN	5	93
b	4-OCH_3-C_6H_4	CN	5	94
c	4-Cl-C_6H_4	CN	5	88
d	4-NO_2-C_6H_4	CN	10	85
e	3-pyridyl	CN	5	95
f	4-pyridyl	CN	5	89
g	H	CN	5	94
h	2-furyl	$CSNH_2$	5	93

Three component synthesis of 2-amino-2-chromenes.

IR spectrum for compound **4a** revealed both amino and cyano groups at ν_{max} 3400 and 2200 cm^{-1}, respectively. ^{1}H NMR spectrum of this product revealed signals that are in accord with the proposed structure. It reveals signals at $\delta = 4.77$ (s, 1H, 4H-pyran); 6.8 (br, s, 2H, NH_2), 6.93 (d, $J = 8$ Hz, 1H, H-5), 7.08–7.23 (m, 5H, Ar—H); 7.33–7.43 (m, 3H, Ar—H), 7.52 (d, $J = 8$ Hz, 1H, H-7), 8.10 (d, $J = 8$ Hz, 1H, H-10). ^{13}C NMR revealed signals at $\delta = 40.92$, 61.06, 108.50, 116.6, 120.80, 123.20, 124.80, 125.90, 126.80, 126.92, 127.80, 129.10, 129.50, 133.22, 133.40, 142.90, 143.30, 158.60. To examine the aromatic aldehyde substrate effect on the rate and overall yield, various aldehydes **1b–1d** were used under the aforementioned reaction conditions. From the results, we can see that all reactions proceeded smoothly to afford the corresponding 2-amino-2-chromene derivatives **4b–4d** in high yield. Slightly diminished yields were observed when the substituent is an electron withdrawing group.

To examine the scope of such techniques, heteroaryl and aliphatic aldehydes **1e–1h** were also used and the corresponding 2-amino-2-chromene derivatives **4e–4h** were obtained in high yields. The structure assigned for the reaction products were established based on analytical and spectral data (*cf*. Experimental part for details). Cyanothioacetamide (**2b**) was also examined as an active methylene compound and the corresponding 2-amino-2-chromen **4h** was obtained.

In conclusion, in green chemistry it is generally recognized that the best reaction requires no solvent. In our procedure we used a little amount of ethanol compared to the quantities of starting materials. Refluxing under microwave technique in the presence of this little amount of solvent perform a homogenous heating, which prevents charring of neat samples and offers a simple and high yield process for the synthesis of 2-amino-2-chromene derivatives.

EXPERIMENTAL

All melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. The reactions were conducted in milestone START-Labstation for microwave enhanced chemistry provided with a sensor for adjusting the temperature and a refluxing condenser. IR spectra (KBr) were measured with a Schimadzu Model 470 spectrophotometer.

^{1}H NMR (300 MHz) and ^{13}C NMR (100 MHz) spectra were measured on a Varian spectrometer using DMSO-d_6 as solvent and TMS as internal Standard, chemical shifts are expressed as δ ppm. Analytical data were determined on the Microanalytical Data Unit at Cairo University. Compounds **4g,4h** were found identical with authentic samples [18].

General procedure for the synthesis of 2-amino-2-chromenes (4a–4g). A solution of the appropriate aldehyde **1**, α-naphthol (**2**) and active methylene **3** (0.01 mol) in ethanol (10 mL), and catalytic amount of piperidine (2 drops) was heated under reflux in a milestone labstation at 80°C for a period of 5–8 min. Upon standing at room temperature a solid product was formed which was collected by filtration to afford compounds **4a–4g**. An additional amount of products were obtained *via* evaporation of the solvent under reduced pressure.

2-Amino-3-cyano-4-phenyl-4H-benzo[h]chromene (4a). Compound **4a** (93%) was obtained as colorless crystals (ethanol). M.P. 179–180°C. *Anal.* Calcd. for $C_{20}H_{14}N_2O$ (298.35): C, 80.52; H, 4.73; N, 9.40. Found: C, 80.40; H, 4.63; N, 9.50. IR (KBr): 3420 (NH_2); 2200 (CN) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.77 (s, 1H, 4H-pyran); 6.8 (br, s, 2H, NH_2), 6.93 (d, J = 8 Hz, 1H, H-5), 7.08–7.23 (m, 5H, Ar—H); 7.33–7.43 (m, 3H, Ar—H), 7.52 (d, J = 8 Hz, 1H, H-7), 8.10 (d, J = 8 Hz, 1H, H-10).

2-Amino-3-cyano-4-(4-methoxyphenyl)-4H-benzo[h]chromene (4b). Compound **4b** (94%) was obtained as yellow crystals (ethanol). M.P. 188–189°C. *Anal.* Calcd. for $C_{21}H_{16}N_2O_2$ (328.36): C, 76.80; H, 4.91; N, 8.53. Found: C, 76.70; H, 4.80; N, 8.33. IR (KBr): 3430 (NH_2); 2200 (CN) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.90 (s, 3H, OCH_3), 4.54 (s, 1H, 4H-pyran), 6.82 (br, s, 2H, NH_2), 7.0 (d, J = 8 Hz, 1H, H-5), 7.10–7.22 (m, 4H, Ar—H), 7.39–7.40 (m, 3H, Ar—H), 7.53 (d, J = 8 Hz, 1H, H-7), 8.12 (d, J = 8 Hz, 1H, H-10).

2-Amino-3-cyano-4-(4-chlorophenyl)-4H-benzo[h]chromene (4c). Compound **4c** (94%) was obtained as yellow crystals (ethanol). M.P. 232–234°C. *Anal.* Calcd. for $C_{20}H_{13}ClN_2O$ (332.78): C, 72.18; H, 3.94; Cl, 10.65; N, 8.42. Found: C, 72.10; H, 3.70; Cl, 10.50; N, 8.20. IR (KBr): 3450 (NH_2); 2200 (CN) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.55 (s, 1H, 4H-pyran), 6.70 (br, s, 2H, NH_2), 7.1 (d, J = 8 Hz, 1H, H-5), 7.21–7.33 (m, 4H, Ar—H), 7.40–7.45 (m, 3H, Ar—H), 7.56 (d, J = 8 Hz, 1H, H-7), 8.15 (d, J = 8 Hz, 1H, H-10).

2-Amino-3-cyano-4-(4-nitrophenyl)-4H-benzo[h]chromene (4d). Compound **4d** (85%) was obtained as yellow crystals (ethanol). M.P. 240–241°C. *Anal.* Calcd. for $C_{20}H_{13}N_3O_3$ (343.34): C, 69.96; H, 3.82; N, 12.24. Found: C, 69.80; H, 3.92; N, 12.13. IR (KBr): 3440 (NH_2), 2220 (CN) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.58 (s, 1H, 4H-pyran), 6.79 (br, s, 2H, NH_2), 7.18 (d, J = 8 Hz, 1H, H-5), 7.25–7.41 (m, 4H, Ar—H), 7.46–7. 51 (m, 3H, Ar—H), 7.61 (d, J = 8 Hz, 1H, H-7), 8.21 (d, J = 8 Hz, 1H, H-10).

2-Amino-3-cyano-4-(3-pyridyl)-4H-benzo[h]chromene (4e). Compound **4e** (95%) was obtained as yellow crystals (ethanol). M.P. 240–241°C. *Anal.* Calcd. for $C_{19}H_{13}N_3O$ (299.33): C, 76.24; H, 4.38; N, 14.04. Found: C, 76.10; H, 4.50; N, 14.00. IR (KBr): 4310 (NH_2); 2220 (CN) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.90 (s, 1H, 4H-pyran); 7.11 (d, J = 8 Hz, 1H, H-5 or H-6), 7.22 (s, 2H, NH_2); 7.33 (dd, J = 8 Hz and 4.5 Hz, pyridine H-5); 7.50–7.70 (m, 4H, H-6 or H-5, H-7, H-8, and pyridine H-6), 7.89 (d, J = 8 Hz, 1H, H-7 or H-10); 8.24 (d, J = 8 Hz,1H, H-7 or H-10), 8.46 (d, J = 4.5 Hz, 1H, pyridine H-4), 8.55 (s, 1H, pyridine H-2).

2-Amino-3-cyano-4-(4-pyridyl)-4H-benzo[h]chromene (4f). Compound **4f** (93%) was obtained as yellow crystals (ethanol). M.P. 200–202°C. *Anal.* Calcd. for $C_{19}H_{13}N_3O$ (299.33): C, 76.24; H, 4.38; N, 14.04. Found: C, 76.13; H, 4.34; N, 14.24. IR (KBr): 3354 (NH_2); 2220 (CN) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.97 (s, 1H, 4H-pyran), 7.14 (d, J = 8 Hz, 1H, H-5 or H-6), 7.27 (m, 4H, pyridine H-3, pyridine H-5 and NH_2), 7.56–7.73 (m, 2H, H-8 or H-9), 7.66 (d, J = 8 Hz, 1H, H-6 or H-5), 7.80 (d, J = 8 Hz, 1H, H-7 or H-10), 8.22 (d, J = 8 Hz, 1H, H-7, or H-10), 8.52 (d, 2H, J = 5 Hz, pyridine H-2 and H-6).

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An Efficient and Facile Synthesis of Pyrimidine and Quinazoline Derivatives via One-Pot Three-Component Reaction under Solvent-Free Conditions

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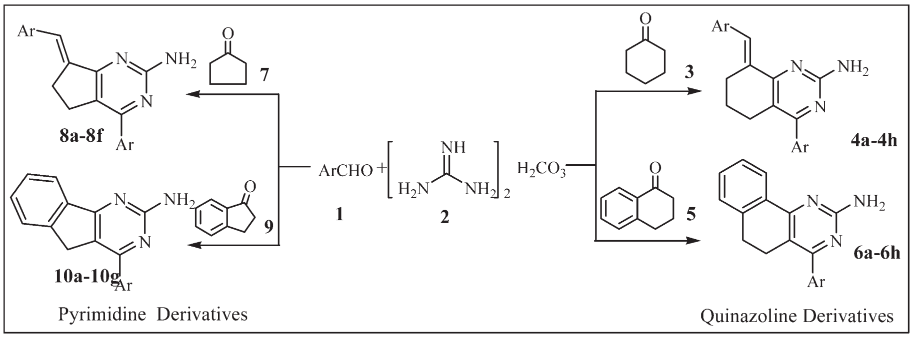

An efficient and convenient method for the preparation of pyrimidine and quinazoline derivatives by the one-pot reaction of aromatic aldehydes, cyclic ketones and guanidine carbonate, in the presence of sodium hydroxide under solvent-free condition was reported. This method has the advantages of excellent yields, mild reaction conditions, easy work-up, and being environmentally friendly over the existing procedures.

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INTRODUCTION

Pyrimidine and its derivatives, as the nitrogen-containing heterocycles, are extremely important compounds with high biological activities [1]. The quinazoline nucleus is also a very attractive and useful scaffold in medicinal chemistry: it can be found as a pharmacophore in a wide variety of biologically active compounds, such as antitumorals [2], antibacterials [3], antivirals [4], and many other therapeutic agents [5].

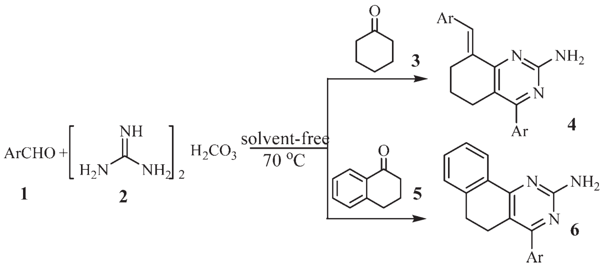
In recent years, because of increasing environmental concerns and the regulatory constraints faced in the chemical and pharmaceutical industries, the development of environmentally friendly organic synthesis has become a crucial and demanding area in modern organic chemical research [6]. In order to avoid using organic solvents, solvent-free organic reactions [7], a ''green'' organic chemistry method, have been of great interest. These have many advantages such as high efficiency and selectivity, easy separation and purification, mild reaction conditions, and reduction in waste produced. Many organic reactions have been carried out just by heating [8].

In continuation to our current studies on the application of solvent-free conditions for the synthesis of organic compounds [9], herein, we would like to report a practical and simple method to prepare pyrimidine and quinazoline derivatives by heating the starting materials under dry conditions.

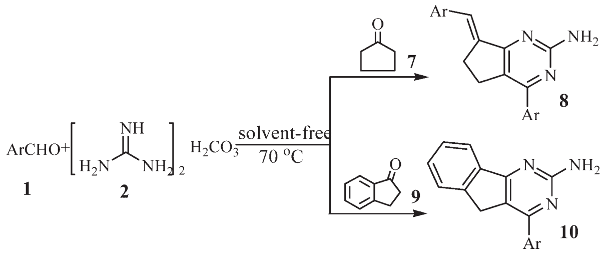
RESULTS AND DISCUSSION

At first, cyclohexanone (2 mmol), aromatic aldehyde (4 mmol), guanidine carbonate (1 mmol) and NaOH (0.2 g) were chosen to react together under solvent-free conditions at 70°C, and the reaction proceeded smoothly in short time (about 15 min) and the corresponding compounds 4-aryl-8-arylidene)-5,6,7,8-tetrahydroquinaz-olin-2-amine (**4a–4h**) could be gained with high yields (Scheme 1). Then, the reagent of 3,4-dihydronaphthalen-1(2*H*)-one (2 mmol) was chosen to replace cyclohexanone to react with aromatic aldehyde (2 mmol), guanidine carbonate (1 mmol) under the same conditions, and the corresponding fused-ring quinazoline derivatives: *viz*. 4-(4-bromophenyl)-5,6-dihydrobenzo[*h*]quinazolin-2-amine (**6a–6h**), were obgained with excellent yields. The results of reactions were listed in Table 1. As shown in Table 1, all the reactions proceeded smoothly with high yields. We also observed that electron-

Scheme 1



Scheme 2



withdrawing substituents (—Cl, —Br), and electron-donating substituents (—CH_3, —OCH_3) had no effect on the reaction.

In order to apply this reaction to a library synthesis, cyclopentanone and indan-1-one were chosen to react with aromatic aldehyde, and guanidine carbonate under same reaction conditions (Scheme 2). To our delight, all reactions could be completed successfully, and (*E*)-7-arylidene)-4-aryl-6,7-dihydro-5*H*-cyclopenta[*d*] pyrimidin-2-amine (**8a–8f**) and 4-aryl-5*H*-indeno[1,2-*d*]pyrimidin-2-amine (**10a–10g**) could be gained with good yields. The reaction results are summarized in Table 2. The structures of **4**, **6**, **8,** and **10** were confirmed by ir, ^{1}H NMR and elemental analysis, furthermore, the reported products were identified by comparison of melting point with those described in the literatures [10].

Although similar compounds have been reported in the literature and the disadvantages of reported methods were obvious, such as long reaction time, lower product yields and harsh conditions, furthermore, the excess of organic solvent was requisite.

In conclusion, an efficient method for the synthesis of pyrimidine and quinazoline derivatives by condensation of cyclic ketone, aromatic aldehydes, and guanidine carbonate was successfully established under solvent-free condition catalyzed by NaOH. The advantages of this procedure are high yields, mild reaction conditions, easy work-up, and environmentally friendly procedure.

EXPERIMENTAL

Melting points were determined on XT-5 microscopic melting-point apparatus and were uncorrected. IR spectra were recorded on a FT Bruker Tensor 27 spectrometer. ^{1}H NMR spectra were obtained from solution in DMSO-d_6 with Me_4Si as internal standard using a Bruker-400 spectrometer. Microanalyses were carried out using a Perkin-Elmer 2400 II analyzer.

General procedure for the synthesis of pyrimidine and quinazoline derivatives. The mixture of ketones **3** and **7**, or **5** and **9** (2 mmol), aromatic aldehydes **2** (4 mmol or 2 mmol), guanidine carbonate **3** (1 mmol) and NaOH (0.2 g) was put in a reaction flask and heated at 70°C for about 15 min. After completing the reaction, the reaction mixture was poured into water, and then washed with water thoroughly. The product was filtered, dried, and recrystallized from 95% ethanol.

(*E*)-8-(4-Methylbenzylidene)-4-*p*-tolyl-5,6,7,8-tetrahydroquinazolin-2-amine (4a). This compound was obtained as yellow crystals, mp 210–212°C, Lit. [10d] 210–212°C; ir (KBr, ν, cm^{-1}): 3502, 3282, 3152, 2929, 1626, 1541, 1456, 1220; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.00 (1H, s, ArCH=),

Table 1

Synthesis of quinazoline derivatives under solvent-free conditions.

Entry	Ar^1	Product	Yields
1	4-$CH_3C_6H_4$	**4a**	90
2	4-$CH_3OC_6H_4$	**4b**	95
3	3,4-$(CH_3)_2C_6H_3$	**4c**	96
4	3,4-$(CH_3O)_2C_6H_3$	**4d**	94
5	4-BrC_6H_4	**4e**	92
6	4-ClC_6H_4	**4f**	97
7	3-ClC_6H_4	**4g**	90
8	3,4-$Cl_2C_6H_3$	**4h**	95
9	4-$CH_3C_6H_4$	**6a**	96
10	4-$CH_3OC_6H_4$	**6b**	97
11	3,4-$(CH_3O)_2C_6H_3$	**6c**	96
12	4-FC_6H_4	**6d**	96
13	4-BrC_6H_4	**6e**	98
14	4-ClC_6H_4	**6f**	97
15	3,4-Cl_2C_6H	**6g**	93
16	C_6H_5	**6h**	95

Table 2

Synthesis of pyrimidine derivatives under solvent-free conditions.

Entry	Ar^1	Product	Yields
1	4-$CH_3C_6H_4$	**8a**	93
2	4-$CH_3OC_6H_4$	**8b**	92
3	4-FC_6H_4	**8c**	90
4	4--ClC_6H_4	**8d**	93
5	3-ClC_6H_4	**8e**	90
6	4-BrC_6H_4	**8f**	95
7	4-$CH_3C_6H_4$	**10a**	93
8	4-$CH_3OC_6H_4$	**10b**	92
9	3,4-$(CH_3O)_2C_6H_3$	**10c**	93
10	4-FC_6H_4	**10d**	90
11	4-ClC_6H_4	**10e**	93
12	4-BrC_6H_4	**10f**	90
13	3,4-$Cl_2C_6H_3$	**10g**	95

7.45 (2H, d, J = 7.2 Hz, ArH), 7.36 (2H, d, J = 8.0 Hz, ArH), 7.26 (4H, t, J = 8.8 Hz, ArH), 6.33 (2H, s, $\mathrm{NH_2}$), 2.78 (2H, t, J = 5.2 Hz, $\mathrm{CH_2}$), 2.60 (2H, t, J = 5.2 Hz, $\mathrm{CH_2}$), 2.37 (3H, s, $\mathrm{CH_3}$), 2.34 (3H, s, $\mathrm{CH_3}$), 1.63 (2H, t, J = 5.2 Hz, $\mathrm{CH_2}$). Anal. Calcd. For $\mathrm{C_{23}H_{23}N_3}$: C 80.90, H 6.79, N 12.31. Found: C 80.72, H 6.73, N 12.25.

(*E*)-8-(4-Methoxybenzylidene)-4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinazolin-2-amine (4b). This compound was obtained as yellow crystals, mp 230–232°C, Lit. [10d] 245–247°C; ir (KBr, ν, $\mathrm{cm^{-1}}$): 3482, 3377, 3202, 2934, 1606, 1579, 1538, 1509, 1447, 1406, 1356, 1333, 1298, 1247; ^{1}H NMR (400MHz, DMSO-d$_6$) (δ, ppm): 7.98 (1H, s, ArCH=), 7.53 (2H, d, J = 8.4 Hz, ArH), 7.42 (2H, d, J = 8.4 Hz, ArH), 7.01 (4H, dd, J = 6.0 Hz, J = 6.0 Hz, ArH), 6.28 (2H, s, $\mathrm{NH_2}$), 3.81 (3H, s, $\mathrm{OCH_3}$), 2.80 (3H, s, $\mathrm{OCH_3}$), 2.79 (2H, t, J = 5.6 Hz, $\mathrm{CH_2}$), 2.64 (2H, t, J = 5.6 Hz, $\mathrm{CH_2}$), 1.62 (2H, t, J = 5.2 Hz, $\mathrm{CH_2}$). Anal. Calcd. For $\mathrm{C_{23}H_{23}N_3O_2}$: C 73.97, H 6.21, N 11.25. Found: C 73.78, H 6.27, N 11.31.

(*E*)-8-(3,4-Dimethylbenzylidene)-4-(3,4-dimethylphenyl)-5,6,7,8-tetrahydroquinazolin-2-amine (4c). This compound was obtained as yellow crystals, mp 191–193°C; ir (KBr, ν, $\mathrm{cm^{-1}}$): 3494, 3284, 3155, 2921, 1625, 1540, 1503, 1459, 1359, 1335, 1221; 1H NMR (400MHz, DMSO-d$_6$) (δ, ppm): 7.98 (1H, s, ArCH=), 7.33 (1H, s, ArH), 7.25 (3H,m, ArH), 7.19 (2H, t, J = 8.8 Hz, ArH), 6.30 (2H, s, $\mathrm{NH_2}$), 2.80 (2H, t, J = 5.2 Hz, $\mathrm{CH_2}$), 2.61 (2H, t, J = 5.2 Hz, $\mathrm{CH_2}$), 2.28 (6H, s, 2$\mathrm{CH_3}$), 2.27 (3H, s, $\mathrm{CH_3}$), 2.25 (3H, s, $\mathrm{CH_3}$),1.61 (2H, t, J = 5.2 Hz, $\mathrm{CH_2}$). Anal. Calcd. For $\mathrm{C_{25}H_{27}N_3}$: C 81.26, H 7.37, N 11.37. Found: C 81.51, H 7.35, N 11.40.

(*E*)-8-(3,4-Dimethoxybenzylidene)-4-(3,4-dimethoxyphenyl)-5,6,7,8-tetrahydroquinazolin-2-amine (4d). This compound was obtained as yellow crystals, mp 249–251°C, Lit. [10d] 231–233°C; ir (KBr, ν, $\mathrm{cm^{-1}}$): 3484, 3280, 3154, 3074, 2936, 1619, 1541, 1459, 1260, 1234; ^{1}H NMR (400MHz, DMSO-d$_6$) (δ, ppm): 7.99 (1H, s, ArCH=), 7.11–7.15 (2H, m, ArH), 7.03 (4H, dd, J = 8.0 Hz, J = 8.0 Hz, ArH), 6.28 (2H, s, $\mathrm{NH_2}$), 3.81 (3H, s, $\mathrm{OCH_3}$), 3.80 (3H, s, $\mathrm{OCH_3}$), 3.79 (3H, s, $\mathrm{OCH_3}$), 3.77 (3H, s, $\mathrm{OCH_3}$), 2.84 (2H, t, J = 5.2 Hz, $\mathrm{CH_2}$), 2.65 (2H, t, J = 5.2 Hz, $\mathrm{CH_2}$), 1.63 (2H, t, J = 5.2 Hz, $\mathrm{CH_2}$). Anal. Calcd. For $\mathrm{C_{25}H_{27}N_3O_4}$: C 69.27, H 6.28, N 9.69. Found: C 69.08, H 6.35, N 9.61.

(*E*)-8-(4-Bromobenzylidene)-4-(4-bromophenyl)-5,6,7,8-tetrahydroquinazolin-2-amine (4e). This compound was obtained as yellow crystals, mp 211–213°C; ir (KBr, ν, $\mathrm{cm^{-1}}$): 3488, 3287, 3157, 2934, 1625, 1591, 1540, 1486, 1456, 1332, 1231; ^{1}H NMR (400MHz, DMSO-d$_6$) (δ, ppm): 7.98 (1H, s, ArCH=), 7.67 (2H, d, J = 8.4 Hz, ArH), 7.62 (2H, d, J = 8.4 Hz, ArH), 7.52 (2H, d, J = 8.4 Hz, ArH), 7.41 (2H, d, J = 8.4 Hz, ArH), 6.45 (2H, s, $\mathrm{NH_2}$), 2.77 (2H, t, J = 5.2 Hz, $\mathrm{CH_2}$), 2.60 (2H, t, J = 6.0 Hz, $\mathrm{CH_2}$), 1.63 (2H, t, J = 5.2 Hz, $\mathrm{CH_2}$). Anal. Calcd. For $\mathrm{C_{21}H_{17}Br_2N_3}$: C 53.53, H 3.64, N 8.92. Found: C 53.33, H 3.62, N 8.96.

(*E*)-8-(4-Chlorobenzylidene)-4-(4-chlorophenyl)-5,6,7,8-tetrahydroquinazolin-2-amine (4f). This compound was obtained as yellow crystals, mp 195–197°C, Lit. [10d] 224–226°C; ir (KBr, ν, $\mathrm{cm^{-1}}$): 3497, 3319, 3202, 2939, 1631, 1606, 1543, 1507, 1464, 1417, 1357, 1333, 1317, 1224; ^{1}H NMR (400MHz, DMSO-d$_6$) (δ, ppm): 8.01 (1H, s, ArCH=), 7.61 (2H, dd, J = 6.0 Hz, J = 6.0 Hz, ArH), 7.51 (2H, dd, J = 6.0 Hz, J = 6.0 Hz, ArH), 7.28 (4H, q, J = 8.8 Hz, J = 6.4 Hz, ArH), 6.41 (2H, s, $\mathrm{NH_2}$), 2.78 (2H, br, $\mathrm{CH_2}$), 2.60 (2H, t, J = 5.2 Hz, J = 5.2 Hz, $\mathrm{CH_2}$), 1.63 (2H, t, J = 5.2 Hz, J = 5.2 Hz, $\mathrm{CH_2}$). Anal. Calcd. For $\mathrm{C_{21}H_{17}Cl_2N_3}$: C 65.98, H 4.48, N 10.99. Found: C 65.72, H 4.55, N 10.68.

(*E*)-8-(3-Chlorobenzylidene)-4-(3-chlorophenyl)-5,6,7,8-tetrahydroquinazolin-2-amine (4g). This compound was obtained as yellow crystals, mp 237–238°C; ir (KBr, ν, $\mathrm{cm^{-1}}$): 3484, 3285, 3157, 3078, 2932, 1624, 1592, 1543, 1461, 1436, 1411, 1351, 1334, 1268, 1219; ^{1}H NMR (400MHz, DMSO-d$_6$) (δ, ppm): 7.98 (1H, s, ArCH=), 7.60 (1H, s, ArH), 7.38-7.54 (7H, m, ArH), 6.48 (2H, s, $\mathrm{NH_2}$), 2.78 (2H, t, J = 5.2 Hz, $\mathrm{CH_2}$), 2.61 (2H, t, J = 6.0 Hz, $\mathrm{CH_2}$), 1.63 (2H, t, J = 5.2 Hz, $\mathrm{CH_2}$). Anal. Calcd. For $\mathrm{C_{21}H_{17}Cl_2N_3}$: C 65.98, H 4.48, N 10.99. Found: C 65.80, H 4.50, N 10.95.

(*E*)-8-(3,4-Dichlorobenzylidene)-4-(3,4-dichlorophenyl)-5,6,7,8-tetrahydroquinazolin-2-amine (4h). This compound was obtained as yellow crystals, mp 200–202°C; ir (KBr, ν, $\mathrm{cm^{-1}}$): 3479, 3296, 3184, 1625, 1541, 1472, 1415, 1389, 1351, 1331, 1215; ^{1}H NMR (400MHz, DMSO-d$_6$) (δ, ppm): 7.95 (1H, s, ArCH=), 7.82 (1H, s, ArH), 7.74 (1H, J = 8.4 Hz, ArH), 7.68 (2H, J = 8.4 Hz, ArH), 7.57 (1H, J = 8.4 Hz, ArH), 7.44 (1H, J = 8.4 Hz, ArH) 6.53 (2H, s, $\mathrm{NH_2}$), 2.77 (2H, t, J = 5.2 Hz, J = 5.2 Hz, $\mathrm{CH_2}$), 2.61 (2H, t, J = 6.0 Hz, J = 6.0 Hz, $\mathrm{CH_2}$), 1.63 (2H, t, J = 5.2 Hz, J = 5.2 Hz, $\mathrm{CH_2}$). Anal. Calcd. For $\mathrm{C_{21}H_{15}Cl_4N_3}$: C 55.90, H 3.35, N 9.31. Found: C 55.78, H 3.34, N 9.34.

4-*p*-Tolyl-5,6-dihydrobenzo[*h*]quinazolin-2-amine (6a). This compound was obtained as yellow crystals, mp 192–194°C, Lit. [10g] 193–194°C; ir (KBr, ν, $\mathrm{cm^{-1}}$): 3472, 3394, 3296, 2940, 1613, 1586, 1545, 1445, 1373, 1322, 1210; ^{1}H NMR (400MHz, DMSO-d6) (δ, ppm): 8.18 (1H, dd, J = 1.2 Hz, J = 1.6 Hz, ArH), 7.48 (2H, d, J = 8.0 Hz, ArH), 7.39 (2H, q, J = 6.8 Hz, J = 7.2 Hz, ArH), 7.29 (3H, d, J = 7.6 Hz, ArH), 6.48 (2H, s, $\mathrm{NH_2}$), 2.77 (4H, s, 2$\mathrm{CH_2}$), 2.38 (3H, s, $\mathrm{CH_3}$). Anal. Calcd. For $\mathrm{C_{19}H_{17}N_3}$: C 79.41, H 5.96, N 14.62. Found: C 79.60, H 5.89, N 14.70.

4-(4-Methoxyphenyl)-5,6-dihydrobenzo[*h*]quinazolin-2-amine (6b). This compound was obtained as yellow crystals, mp 186–187°C, Lit. [10g] 182–183°C; ir (KBr, ν, $\mathrm{cm^{-1}}$): 3467, 3287, 3178, 2940, 2830, 1609, 1578, 1547, 1510, 1453, 1405, 1374, 1322, 1302, 1277, 1251, 1214; ^{1}H NMR (400MHz, DMSO-d$_6$) (δ, ppm): 8.18 (1H, dd, J = 1.2 Hz, J = 1.6 Hz, ArH), 7.56 (2H, d, J = 8.4 Hz, ArH), 7.39 (2H, q, J = 6.0 Hz, J = 7.2 Hz, ArH), 7.32 (1H, d, J = 6.0 Hz, ArH), 7.04 (2H, d, J = 8.4 Hz, ArH), 6.47 (2H, s, $\mathrm{NH_2}$), 3.82 (3H, s, $\mathrm{CH_3O}$), 2.78 (4H, d, J = 3.2 Hz, 2$\mathrm{CH_2}$). Anal. Calcd. For $\mathrm{C_{19}H_{17}N_3O}$: C 75.23, H 5.65, N 13.85. Found: C 75.42, H 5.69, N 13.79.

4-(3,4-Dimethoxyphenyl)-5,6-dihydrobenzo[*h*]quinazolin-2-amine (6c). This compound was obtained as yellow crystals, mp 198–200°C, Lit. [10c] 203–204°C; ir (KBr, ν, $\mathrm{cm^{-1}}$): 3437, 3341, 3221, 2996, 2957, 1625, 1603, 1583, 1543, 1511, 1451, 1420, 1388, 1370, 1329, 1209; ^{1}H NMR (400MHz, DMSO-d$_6$) (δ, ppm): 8.17 (1H, dd, J = 1.2 Hz, J = 1.6 Hz, ArH), 7.39 (2H, q, J = 6.4 Hz, J = 7.2 Hz, ArH), 7.29 (1H, d, J = 6.4 Hz, ArH), 7.18 (1H, s, ArH), 7.14 (1H, d, J = 8.0 Hz, ArH), 7.05 (1H, d, J = 8.0 Hz, ArH), 6.48 (2H, s, $\mathrm{NH_2}$), 3.82 (3H, s, $\mathrm{CH_3O}$), 3.79 (3H, s, $\mathrm{CH_3O}$), 2.82 (2H, t, J = 1.6 Hz, J = 4.0 Hz, $\mathrm{CH_2}$), 2.78 (2H, t, J = 1.6 Hz, J = 4.0 Hz, $\mathrm{CH_2}$). Anal. Calcd. For $\mathrm{C_{20}H_{19}N_3O_2}$: C 72.05, H 5.74, N 12.60. Found: C 72.21, H 5.69, N 12.71.

4-(4-Fluorophenyl)-5,6-dihydrobenzo[*h*]quinazolin-2-amine (6d). This compound was obtained as yellow crystals, mp 194–196°C; ir (KBr, ν, cm^{-1}): 3489, 3302, 3175, 2946, 1627, 1604, 1553, 1499, 1452, 1413, 1398, 1373, 1321, 1297, 1222; ^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 8.18 (1H, dd, *J* = 1.2 Hz, *J* = 1.6 Hz, ArH), 7.64 (2H, dd, *J* = 5.6 Hz, *J* = 5.6 Hz, ArH), 7.40 (2H, q, *J* = 7.2 Hz, *J* = 8.0 Hz, ArH), 7.30 (3H, dd, *J* = 5.6 Hz, *J* = 8.0 Hz, ArH), 6.53 (2H, s, NH_2), 2.77 (4H, s, $2CH_2$). Anal. Calcd. For $C_{18}H_{14}FN_3$: C 74.21, H 4.84, N 14.42. Found: C 74.35, H 4.82, N 14.46.

4-(4-Bromophenyl)-5,6-dihydrobenzo[*h*]quinazolin-2-amine (6e). This compound was obtained as yellow crystals, mp 228–230°C; ir (KBr, ν, cm^{-1}): 3385, 3319, 3216, 2942, 1634, 1589, 1569, 1541, 1487, 1450, 1413, 1390, 1371, 1322, 1211; ^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 8.18 (1H, dd, *J* = 1.2 Hz, *J* = 1.6 Hz, ArH), 7.69 (2H, d, *J* = 8.4 Hz, ArH), 7.55 (2H, d, *J* = 8.4 Hz, ArH), 7.40 (2H, q, *J* = 6.8 Hz, *J* = 8.4 Hz, ArH), 7.30 (1H, d, *J* = 6.8 Hz, ArH), 6.56 (2H, s, NH_2), 2.77 (4H, s, $2CH_2$). Anal. Calcd. For $C_{18}H_{14}BrN_3$: C 61.38, H 4.01, N 11.93. Found: C 61.50, H 4.03, N 11.90.

4-(4-Chlorophenyl)-5,6-dihydrobenzo[*h*]quinazolin-2-amine (6f). This compound was obtained as yellow crystals, mp 216–218°C, Lit. [10g] 222–223°C; ir (KBr, ν, cm^{-1}): 3391, 3327, 3221, 2942, 1638, 1597, 1586, 1572, 1543, 1492, 1458, 1412, 1394, 1372, 1323, 1212; ^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 8.18 (1H, dd, *J* = 1.2 Hz, *J* = 1.6 Hz, ArH), 7.62 (2H, d, *J* = 8.4 Hz, ArH), 7.55 (2H, d, *J* = 8.4 Hz, ArH), 7.40 (2H, q, *J* = 6.0 Hz, *J* = 8.4 Hz, ArH), 7.30 (1H, d, *J* = 6.4 Hz, ArH), 6.56 (2H, s, NH_2), 2.77 (4H, s, $2CH_2$). Anal. Calcd. For $C_{18}H_{14}ClN_3$: C 70.24, H 4.58, N 13.65. Found: C 70.43, H 4.50, N 13.58.

4-(3,4-Dichlorophenyl)-5,6-dihydrobenzo[*h*]quinazolin-2-amine (6g). This compound was obtained as yellow crystals, mp 210–212°C, Lit. [10c] 221–223°C; ir (KBr, ν, cm^{-1}): 3485, 3297, 3183, 2934, 1622, 1564, 1544, 1492, 1470, 1450, 1410, 1386, 1365, 1350, 1317, 1298, 1247, 1212; ^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 8.18 (1H, d, *J* = 7.2 Hz, ArH), 7.84 (1H, d, *J* = 2.0 Hz, ArH), 7.56 (1H, d, *J* = 8.4 Hz, ArH), 7.58 (1H, dd, *J* = 2.0 Hz, *J* = 2.0 Hz, ArH), 7.40 (2H, q, *J* = 7.2 Hz, *J* = 8.0 Hz, ArH), 7.30 (1H, d, *J* = 7.2 Hz, ArH), 6.63 (2H, s, NH_2), 2.78 (4H, s, CH_2). Anal. Calcd. For $C_{18}H_{13}Cl_2N_3$: C 63.17, H 3.83, N 12.28. Found: C 63.40, H 3.76, N 12.21.

4-Phenyl-5,6-dihydrobenzo[*h*]quinazolin-2-amine (6h). This compound was obtained as yellow crystals, mp 164–165°C, Lit. [10h] 174–175°C; ir (KBr, ν, cm^{-1}): 3387, 3321, 3214, 2936, 1634, 1606, 1585, 1544, 1495, 1451, 1440, 1411, 1373, 1384, 1322, 1208; ^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 8.18 (1H, dd, *J* = 1.2 Hz, *J* = 1.6 Hz, ArH), 7.57 (2H, dd, *J* = 1.6 Hz, *J* = 2.0 Hz, ArH), 7.47-7.52 (3H, m, ArH), 7.40 (2H, q, *J* = 5.6 Hz, *J* = 7.6 Hz, ArH), 7.30 (1H, d, *J* = 7.6 Hz, ArH), 6.51 (2H, s, NH_2), 2.77 (4H, s, CH_2). Anal. Calcd. For $C_{18}H_{15}N_3$: C 79.10, H 5.53, N 15.37. Found: C 79.33, H 5.48, N 15.25.

(*E*)-7-(4-Methylbenzylidene)-4-p-tolyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-2-amine (8a). This compound was obtained as yellow crystals, mp 229–230°C; ir (KBr, ν, cm^{-1}): 3474, 3313, 3184, 2916, 1624, 1549, 1510, 1455, 1413, 1361, 1224, 1202; ^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 7.84 (2H, d, *J* = 8.0 Hz, ArH), 7.45 (2H, d, *J* = 8.0 Hz, ArH), 7.41 (1H, s, ArCH=), 7.31 (2H, d, *J* = 8.0 Hz, ArH), 7.24 (2H, *J* = 8.0 Hz, ArH), 6.51 (2H, s, NH_2), 3.12 (2H, d, *J* = 7.2 Hz, CH_2), 3.04 (2H, d, *J* = 4.0 Hz, CH_2), 2.37 (3H, s, CH_3), 2.33 (3H, s, CH_3). Anal. Calcd. For $C_{22}H_{21}N_3$: C 80.70, H 6.46, N 12.83. Found: C 80.86, H 6.48, N 12.80.

(*E*)-7-(4-Methoxybenzylidene)-4-(4-methoxyphenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-2-amine (8b). This compound was obtained as yellow crystals, mp 256–258°C; ir (KBr, ν, cm^{-1}): 3475, 3370, 3217, 2934, 1624, 1606, 1582, 1542, 1510, 1460, 1440, 1399, 1366, 1308, 1248, 1220; ^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 7.94 (2H, d, *J* = 8.8 Hz, ArH), 7.53 (2H, d, *J* = 8.8 Hz, ArH), 7.39 (1H, s, ArCH=), 7.07 (2H, d, *J* = 8.8 Hz, ArH), 7.02 (2H, d, *J* = 8.8 Hz, ArH), 6.42 (2H, s, NH_2), 3.83 (3H, s, CH_3O), 3.80 (3H, s, CH_3O), 3.17 (2H, t, *J* = 6.4 Hz, CH_2), 3.06 (2H, t, *J* = 6.4 Hz, CH_2). Anal. Calcd. For $C_{22}H_{21}N_3O_2$: C 73.52, H 5.89, N 11.69. Found: C 73.38, H 5.91, N 11.73.

(*E*)-7-(4-fluorobenzylidene)-4-(4-fluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-2-amine (8c). This compound was obtained as yellow crystals, mp 187–189°C; ir (KBr, ν, cm^{-1}): 3485, 3337, 3239, 3064, 2934, 1624, 1615, 1582, 1542, 1509, 1459, 1440, 1316, 1248, 1227; ^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 8.01(2H, dd, *J* = 5.6 Hz, *J* = 5.6 Hz, ArH), 7.63 (2H, dd, *J* = 5.6 Hz, *J* = 5.6 Hz, ArH), 7.43 (1H, s, ArCH=), 7.35 (2H, t, *J* = 8.8 Hz, ArH), 7.27 (2H, t, *J* = 8.8 Hz, ArH), 6.57 (2H, s, NH_2), 3.15 (2H, d, *J* = 7.2 Hz, CH_2), 3.08 (2H, t, *J* = 4.4 Hz, *J* = 4.4 Hz, CH_2). Anal. Calcd. For $C_{20}H_{15}F_2N_3$: C 71.63, H 4.51, N 12.53. Found: C 71.47, H 4.53, N 12.48.

(*E*)-7-(4-Chlorobenzylidene)-4-(4-chlorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-2-amine (8d). This compound was obtained as yellow crystals, mp 165–167°C; ir (KBr, ν, cm^{-1}): 3483, 3323, 3192, 2928, 1672, 1623, 1594, 1544, 1492, 1460, 1407, 1361, 1295, 1225; ^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 7.97 (2H, d, *J* = 8.8 Hz, ArH), 7.62 (2H, d, *J* = 8.8 Hz, ArH), 7.58 (1H, s, ArCH=), 7.50 (2H, d, *J* = 8.8 Hz, ArH), 7.42 (2H, t, *J* = 8.8 Hz, ArH), 6.63 (2H, s, NH_2), 3.16 (2H, d, *J* = 6.8 Hz, CH_2), 3.09 (2H, t, *J* = 6.8 Hz, CH_2). Anal. Calcd. For $C_{20}H_{15}Cl_2N_3$: C 65.23, H 4.11, N 11.41. Found: C 65.48, H 4.13, N 11.37.

(*E*)-7-(3-Chlorobenzylidene)-4-(3-chlorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-2-amine (8e). This compound was obtained as yellow crystals, mp 135–137°C; ir (KBr, ν, cm^{-1}): 3469, 3298, 3174, 2913, 1689, 1621, 1590, 1561, 1541, 1476, 1459, 1421, 1351, 1279, 1250, 1228, 1205; ^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 8.01 (2H, d, *J* = 7.6 Hz, ArH), 7.68 (2H, d, *J* = 6.8 Hz, ArH), 7.61 (1H, s, ArCH=), 7.54 (2H, d, *J* = 6.8 Hz, ArH), 7.40 (2H, d, *J* = 7.6 Hz, ArH), 6.67 (2H, s, NH_2), 3.18 (2H, t, *J* = 5.6 Hz, CH_2), 3.03 (2H, t, *J* = 5.6 Hz, CH_2). Anal. Calcd. For $C_{20}H_{15}Cl_2N_3$: C 65.23, H 4.11, N 11.41. Found: C 65.48, H 4.13, N 11.37.

(*E*)-7-(4-Bromobenzylidene)-4-(4-bromophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-2-amine (8f). This compound was obtained as yellow crystals, mp 180–182°C; ir (KBr, ν, cm^{-1}): 3454, 3293, 3170, 2956, 1672, 1620, 1588, 1488, 1459, 1403, 1351, 1176; ^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 7.95 (2H, d, *J* = 8.8 Hz, ArH), 7.70 (2H, d, *J* = 8.8 Hz, ArH), 7.66 (1H, s, ArCH=), 7.59 (2H, d, *J* = 8.8 Hz, ArH), 7.42 (2H, d, *J* = 8.8 Hz, ArH), 6.98 (2H, s, NH_2), 3.09 (2H, t, *J* = 5.6 Hz, CH_2), 2.88 (2H, t, *J* = 5.6 Hz, CH_2). Anal. Calcd. For $C_{20}H_{15}Br_2N_3$: C 52.54, H 3.31, N 9.19. Found: C 52.67, H 3.34, N 9.15.

4-*p*-Tolyl-5*H*-indeno[1,2-*d*]pyrimidin-2-amine (10a). This compound was obtained as yellow crystals, mp 199–200°C; ir (KBr, ν, cm^{-1}): 3480, 3305, 3177, 2898, 1625, 1586, 1561, 1509, 1483, 1465, 1452, 1413, 1398, 1369, 1308, 1251; ^1H NMR (400MHz, DMSO-d_6) (δ, ppm): 8.02 (2H, d, J = 8.0 Hz, ArH), 7.91 (1H, d, J = 7.6 Hz, ArH), 7.68 (1H, d, J = 7.2 Hz, ArH), 7.54 (1H, t, J = 7.2 Hz, ArH), 7.48 (1H, t, J = 7.2 Hz, ArH), 7.36 (2H, J = 8.0 Hz, ArH), 6.64 (2H, s, NH_2), 4.12 (2H, s, CH_2), 2.40 (3H, s, CH_3). Anal. Calcd. For $C_{18}H_{15}N_3$: C 79.10, H 5.53, N 15.37. Found: C 79.35, H 5.51, N 15.31.

4-(4-Methoxyphenyl)-5*H*-indeno[1,2-*d*]pyrimidin-2-amine (10b). This compound was obtained as yellow crystals, mp 206–208°C, Lit. [10f] 240–241°C; ir (KBr, ν, cm^{-1}): 3312, 3178, 2887, 1643, 1608, 1591, 1567, 1533, 1510, 1481, 1466, 1438, 1422, 1395, 1370, 1301, 1255, 1209; ^1H NMR (400MHz, DMSO-d_6) (δ, ppm): 8.11 (2H, d, J = 8.8 Hz, ArH), 7.94 (1H, d, J = 7.6 Hz, ArH), 7.68 (1H, d, J = 7.2 Hz, ArH), 7.54 (1H, t, J = 7.2 Hz, ArH), 7.48 (1H, t, J = 7.2 Hz, ArH), 7.11 (2H, J = 8.0 Hz, ArH), 6.60 (2H, s, NH_2), 4.12 (2H, s, CH_2), 3.85 (3H, s, CH_3O). Anal. Calcd. For $C_{18}H_{15}N_3O$: C 74.72, H 5.23, N 14.52. Found: C 74.58, H 5.30, N 14.61.

4-(3,4-Dimethoxyphenyl)-5*H*-indeno[1,2-*d*]pyrimidin-2-amine (10c). This compound was obtained as yellow crystals, mp 271–273°C; ir (KBr, ν, cm^{-1}): 3405, 3310, 3189, 2962, 2935, 1640, 1604, 1542, 1511, 1484, 1463, 1449, 1423, 1401, 1378, 1326, 1250, 1235, 1211; ^1H NMR (400MHz, DMSO-d_6) (δ, ppm): 7.91 (1H, d, J = 7.6 Hz, ArH), 7.68–7.72 (3H, m, ArH), 7.49–7.54 (2H, m, ArH), 7.12 (1H, d, J = 8.0 Hz, ArH), 6.60 (2H, s, NH_2), 4.15 (2H, s, CH_2), 3.88 (3H, s, CH_3O), 3.85 (3H, s, CH_3O). Anal. Calcd. For $C_{19}H_{17}N_3O_2$: C 71.46, H 5.37, N 13.16. Found: C 71.70, H 5.35, N 13.22.

4-(4-Fluorophenyl)-5*H*-indeno[1,2-*d*]pyrimidin-2-amine (10d). This compound was obtained as yellow crystals, mp 225–227°C; ir (KBr, ν, cm^{-1}): 3482, 3306, 3176, 2890, 1632, 1588, 1566, 1509, 1488, 1463, 1449, 1419, 1394, 1372, 1300, 1279, 1253, 1222; ^1H NMR (400MHz, DMSO-d_6) (δ, ppm): 8.17 (2H, dd, J = 5.6 Hz, J = 5.6 Hz, ArH), 7.92 (1H, d, J = 7.2 Hz, ArH), 7.68 (1H, d, J = 7.2 Hz, ArH), 7.54 (1H, t, J = 7.2 Hz, ArH), 7.49 (1H, t, J = 7.2 Hz, ArH), 7.38 (2H, t, J = 8.8 Hz, ArH), 6.70 (2H, s, NH_2), 4.13 (2H, s, CH_2). Anal. Calcd. For $C_{17}H_{12}FN_3$: C 73.63, H 4.36, N 15.15. Found: C 73.78, H 4.34, N 15.18.

4-(4-Chlorophenyl)-5*H*-indeno[1,2-*d*]pyrimidin-2-amine (10e). This compound was obtained as yellow crystals, mp 237–238°C, Lit. [10f] 245–246°C; ir (KBr, ν, cm^{-1}): 3454, 3302, 3181, 1635, 1592, 1581, 1565, 1545, 1485, 1468, 1453, 1413, 1391, 1369, 1301, 1250, 1212; ^1H NMR (400MHz, DMSO-d_6) (δ, ppm): 8.14 (2H, d, J = 8.8 Hz, ArH), 7.92 (1H, d, J = 7.2 Hz, ArH), 7.69 (1H, d, J = 7.2 Hz, ArH), 7.62 (2H, d, J = 8.4 Hz, ArH), 7.56 (1H, t, J = 7.2 Hz, ArH), 7.49 (1H, t, J = 7.2 Hz, ArH), 6.72 (2H, s, NH_2), 4.13 (2H, s, CH_2). Anal. Calcd. For $C_{17}H_{12}ClN_3$: C 69.51, H 4.12, N 14.30. Found: C 69.69, H 4.20, N 14.21.

4-(4-Bromophenyl)-5*H*-indeno[1,2-*d*]pyrimidin-2-amine (10f). This compound was obtained as yellow crystals, mp 233–234°C, Lit. [10f] 218–219°C; ir (KBr, ν, cm^{-1}): 3455, 3302, 3182, 1634, 1591, 1579, 1562, 1547, 1486, 1468, 1452, 1409, 1388, 1366, 1300, 1251, 1212; ^1H NMR (400MHz, DMSO-d_6) (δ, ppm): 8.07 (2H, d, J = 8.0 Hz, ArH), 7.92 (1H, d, J = 7.6 Hz, ArH), 7.76 (2H, d, J = 8.4 Hz, ArH), 7.69 (1H, d, J = 7.6 Hz, ArH), 7.56 (1H, t, J = 7.2 Hz, J = 7.2 Hz, ArH), 7.50 (1H, t, J = 7.2 Hz, J = 7.2 Hz, ArH), 6.73 (2H, s, NH_2), 4.13 (2H, s, CH_2). Anal. Calcd. For $C_{17}H_{12}BrN_3$: C 60.37, H 3.58, N 12.42. Found: C 60.49, H 3.51, N 12.33.

4-(3,4-Dichlorophenyl)-5*H*-indeno[1,2-*d*]pyrimidin-2-amine (10g). This compound was obtained as yellow crystals, mp 232–233°C; ir (KBr, ν, cm^{-1}): 3481, 3316, 3185, 2903, 1646, 1613, 1592, 1558, 1487, 1469, 1408, 1375, 1361, 1286, 1260, 1245, 1203; ^1H NMR (400MHz, DMSO-d_6) (δ, ppm): 8.33 (1H, d, J = 1.6 Hz, ArH), 8.09 (1H, dd, J = 1.6 Hz, J = 2.0 Hz, ArH), 7.93 (1H, d, J = 7.6 Hz, ArH), 7.81 (1H, d, J = 7.6 Hz, ArH), 7.70 (1H, d, J = 7.6 Hz, ArH), 7.56 (1H, t, J = 7.6 Hz, ArH), 7.52 (1H, t, J = 7.6 Hz, ArH), 6.80 (2H, s, NH_2), 4.16 (2H, s, CH_2). Anal. Calcd. For $C_{17}H_{11}Cl_2N_3$: C 62.21, H 3.38, N 12.80. Found: C 62.35, H 3.36, N 12.77.

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2-Trifluoroacetyl-1-methoxycycloalkenes: A Convenient Precursor for the Synthesis of Geminated Polymethylene Trifluoromethyl Substituted Heterocycles

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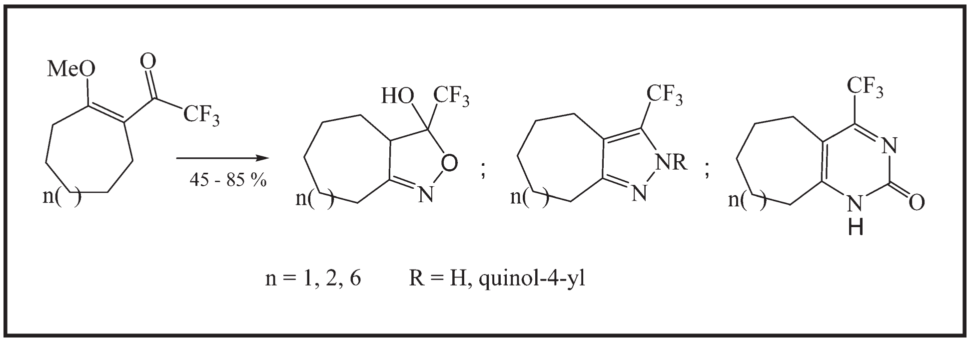

This article describes the methodology that allows the simultaneous introduction of a trifluoromethyl group and a 7-, 8-, and 10-membered cycloalkane ring fused to heterocyclic derivatives. A series of 10 geminated polymethylene trifluoromethyl substituted isoxazolines, pyrazoles, pyrimidinones, and a pyrazolyl-quinoline were obtained in moderate to good yields from the reaction of three 2-trifluoroacetyl-1-methoxycycloalkenes derived from cycloheptanone, cyclooctanone, and cyclododecanone with hydroxylamine hydrochloride, hydrazine hydrochloride, urea, and 7-chloro-4-hydrazinoquinoline.

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INTRODUCTION

Among some classes of compounds that show biological activity, heterocycles [1] such as isoxazolines, pyrazoles, and pyrimidinones have been shown to be of great importance. These compounds present a wide range of biological applications [2–9] both in the pharmaceutical area and the agrochemical industry, including as CNS depressants and analgesics, as well as for their antitumor, antibacterial, and anti-HIV activity, and antifungal, antiviral, antiparasitic, antitubercular, and insecticidal properties.

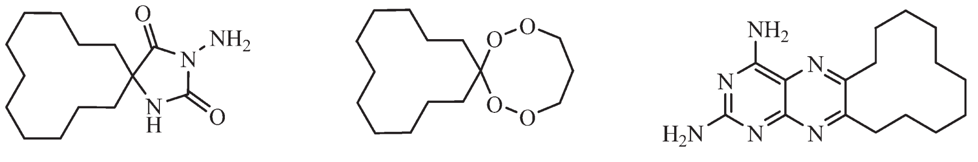
A review of the literature has shown that the synthesis of heterocyclic compounds derived from cycloalkane has been relatively unexplored. In many cases, it has been observed that enlargement of the cycloalkane ring-size influences the biological effect, where cyclododecane derivatives present an advantageous position (Fig. 1) [10–12]. Moreover, some cycloalkanespiro-5-hydantoins have a modest anticonvulsive effect.

However, a study of structure-activity relationships of various 3-aminocycloalkanespiro-hydantoins showed that (**I**) [10] and similar compounds, in contrast to hydantoins, exerted well pronounced atropinsensitive and contractile effects on guinea-pig ileum longitudinal muscle preparations.

In 2001, Kim *et al.* [11] prepared tetraoxacycloalkanes and the subsequent evaluation of antimalarial activity of the cyclic peroxides *in vitro* and *in vivo* revealed cyclododecane (**II**) derivatives to be a promising potent antimalarial drug.

Taylor *et al.* [12] synthesized cycloalka[*g*]pteridines (**III**) and studied their biological activity as dihydrofolate reductase inhibitors against *Lactobacillus casei* and *Trypanosoma cruzi*. Activity was found to depend upon ring size, with the greatest activity exhibited by the cyclododecane derivative, which was ~1000 times more active than the cyclohexane derivative.

In addition, fluorine-containing heterocyclic compounds are of significant interest because of their biological properties [13]. The introduction of a trifluoromethyl and its higher homologue groups into a heterocycle frequently results in more potent activity than that of the parent compound, a fact, which is probably related to the high lipophilicity of perfluoroalkyl substituents [14,15]. As a consequence, in recent years much attention has been devoted to the synthesis of



I II III

Figure 1. Cycloalkane derivatives of biological relevance.

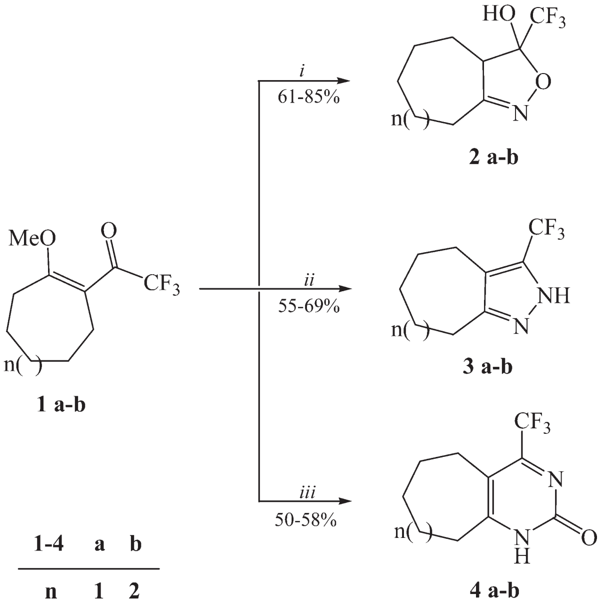
trifluorinated compounds and many have proven to be of important therapeutic value [16,17].

The preparation of trifluoromethylated heterocyclic compounds from cyclocondensation reactions of β-alkoxyvinyl trihalomethyl ketones with 1,2 and 1,3 dinucleophilic compounds has been developed by our research group [18–23]. Recently, the synthesis [24] and ^{17}O NMR spectroscopy of 2-trifluoroacetyl-1-methoxycycloalkenes [25] derived from cyclopentanone, cyclohexanone, cycloheptanone, cyclooctanone, and cyclododecanone [26] were reported. However, there is no publication in the literature with the objective of carrying out a regiospecific and simultaneous introduction of a trifluoromethyl group and a fused 7-, 8-, and 10-membered cycloalkane ring fused to heterocyclic derivatives starting from b-alkoxyvinyl trifluoromethyl ketones and hydroxylamine, hydrazines or urea.

Although many methods for the synthesis of isoxazolines, pyrazoles, and pyrimidinones and functionalized derivatives have been published, attempts at the synthesis of trifluoromethyl substituted and geminated cycloalka-heterocycles have not yet been successful. A search of the literature showed that by a conventional procedure, only 3-trifluoromethyl-1,4,5,6,7,8-hexahydrocyclohepta[*c*]pyrazole has been obtained from a direct reaction of trifluoroacetylcycloheptanone and hydrazine hydrochloride [27].

Considering the biological importance of trifluoromethyl substituted heterocyclic compounds derived from cycloalkanes, we reported our new results on the reaction of 2-trifluoroacetyl-1-methoxycycloalkenes derived from cycloheptanone and cyclooctanone in the synthesis and isolation of novel cycloalka -isoxazolines, -pyrazoles, and -pyrimidinones containing a fused 7-, 8-membered ring (Scheme 1). Because of the fact that heterocycles derived from cyclododecanone have shown greater activity in relation to derivatives of cyclohexanone, we also reported the synthesis and isolation of novel heterocyclic compounds fused to a cyclododecane ring (Scheme 2).

Scheme 1. Reagents and conditions: (i) $NH_2OH.HCl$, Pyridine, H_2O, 45°C, 24 h; (ii) $NH_2NH_2.HCl$, Pyridine, EtOH, reflux, 8 h; (iii) $NH_2CONH_2/BF_3.OEt_2$, *i*-PrOH, reflux, 20 h.

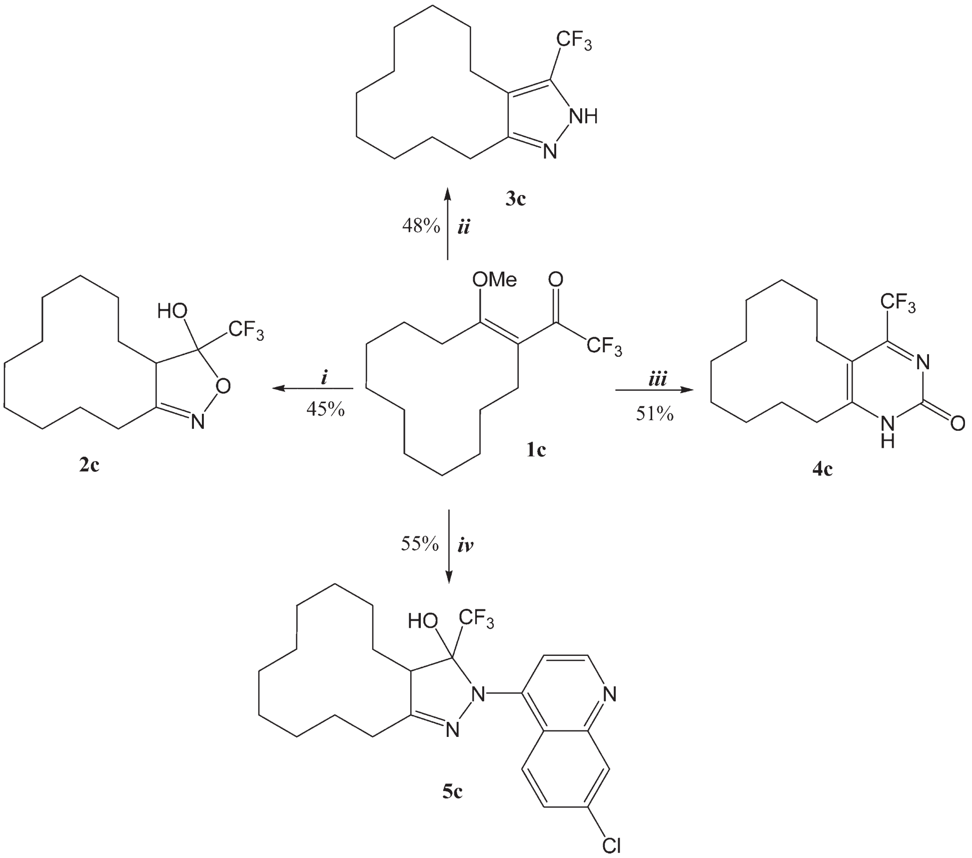


RESULTS AND DISCUSSION

2-Trifluoroacetyl-1-methoxycycloalkenes **1a–c** were obtained by a direct acylation reaction of the 1,1-dimethoxycycloalkanes derived from the respective cycloalkanones with trifluoracetic anhydride in the presence of pyridine, as described in the literature [20,28–30]. Subsequently, we reacted pure 2-trifluoroacetyl-1-methoxycycloalkenes **1a–c** with hydroxylamine, hydrazines, and urea, regiospecifically obtaining, in an one-step reaction, 3-hydroxy-3-trifluoromethyl-3,4-dihydro-cycloalka[*c*]isoxazoles **2a–c** (45–85%), 3-trifluoromethyl-3,4-dihydrocycloalka[*c*]pyrazoles **3a–c** (48–69%), 4-trifluoromethylcycloalka[*d*]-2(1*H*)pyrimidinones **4a–c** (50–58%) and 4-(3-hydroxy-3-trifluoromethyl-cyclododeca[*c*]pyrazol-2-yl)-7-chloroquinoline (**5c**) (55%).

Presumably, the reactions start with the Michael addition of the amino groups of the dinucleophiles at the β-carbon atom of the enones **1a–c** furnishing addition products. The aminoether function is unstable in pyridine/water or in alcohol (reaction solvents) and the methoxy group is eliminated as methanol. Subsequently,

Scheme 2. Reagents and conditions: (i) $NH_2OH.HCl$, Pyridine, H_2O, 45°C, 24 h; (ii) $NH_2NH_2.HCl$, Pyridine, EtOH, reflux, 8 h; (iii) NH_2CONH_2/$BF_3.OEt_2$, *i*-PrOH, reflux, 20 h; (iv) 7-chloro-4-hydrazino-quinoline, MeOH, reflux, 6 h.



the intramolecular cyclization reaction occurs and involves the carbonyl function of the not isolated β-enaminone and the second heteroatom of the dinucleophile reagent. In addition, the elimination of a water molecule is not likely to occur in the isoxazole structures (**2a–c**) because of the electron-withdrawing effect of the oxygen and the basic reaction condition employed (pyridine/water) or because of the electronic effect of cloro-quinoline substituent (**5c**).

The reactions of 2-trifluoroacetyl-1-methoxycycloalkenes **1a–c** with hydroxylamine hydrochloride using pyridine/H_2O as solvent were carried out under mild conditions at 45°C for 24 h. After 24 h, the isoxazolines **2a–c** were isolated by a simple extraction with diethyl ether.

Cycloalka[*c*]pyrazoles **3a–c**, were obtained from the reaction of 2-trifluoroacetyl-1-methoxycycloalkenes **1a–c**, with hydrazine hydrochloride in the presence of pyridine. The reactions to obtain **3a–b, 7** were carried out at a molar ratio of 1:1 in methanol as solvent at 80°C for 8 h.

Cycloalka[*d*]-2(1*H*)pyrimidinones **4a–c**, were prepared from the cyclocondensation reaction of 2-trifluoroacetyl-1-methoxycycloalkenes **1a–c**, with urea, carried out at a 1:1.5 molar ratio in anhydrous propan-2-ol as solvent. The most satisfactory results were obtained when the reactions were performed under mild conditions by stirring the reagents for 20 h at 80–85°C, using a Lewis acid as catalyst ($BF_3.OEt_2$). After 20 h, the reactions were refrigerated and the solids were isolated by filtration.

Subsequently, 2-trifluoroacetyl-1-methoxycyclododecene (**1c**) was used to prepare cyclododeca[*c*]pyrazoles (**5c**) derived from 7-chloro-4-hydrazinoquinoline. The objective of synthesizing compound **5c** was to build a molecule that would serve as the foundation for a family of new antimalarials. The reaction was carried out in methanol for 6 h at 65°C, similar to the methodology systematized by Bonacorso *et al.* [31] to obtain pyrazolylquinolines. Compound **5c** was obtained in satisfactory yield (55%), after recrystallization from methanol.

The unambiguous ^1H and ^{13}C NMR chemical shift assignments of cycloalka -isoxazolines (**2a–c**), -pyrazoles (**3a–c**), -pyrimidinones (**4a–c**), and -pyrazoline (**5c**), were made with the help of homo- and hetero- nuclear COSY, HMQC, and HMBC 2D NMR experiments and by comparison with NMR data of the literature [27] and from other 2-pyrazolines previously synthesized in our laboratory [26,31(a)].

In conclusion, we consider the one-step and regiospecific reaction reported here to be a useful, simple, new, and convenient method, which employs commercially available reagents and mild conventional conditions to obtain novel interesting trifluoromethylated heterocycles fused to a cycloalkane ring.

EXPERIMENTAL

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. All melting points were determined on a Reichert Thermovar apparatus and are uncorrected. Mass spectra were registered in a HP 5973 MSD connected to a HP 6890 GC and interfaced by a Pentium PC. The GC was equipped with a split–splitless injector, auto sampler, cross-linked HP-5 capillary column (30 m, 0.32 mm internal diameter), and helium was used as the carrier gas. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DPX 200 or Bruker DPX 400 spectrometer (^{1}H at 20.13 MHz or 40.13 MHz and ^{13}C at 50.32 MHz or 100.62 MHz, respectively), 5 mm sample tubes, 298 K digital resolution ± 0.01 ppm, in methyl sulfoxide-d_6 using tetramethylsilane as internal reference. The CHN elemental analyses were performed on a Perkin–Elemer 2400 CHN elemental analyzer (São Paulo University, USP/Brazil).

Synthetic procedures. ***General procedure for the preparation of 3-hydroxy-3-trifluoromethyl-3,4-dihydro-cycloalka[c]isoxazoles (2a–c).*** To a stirred solution of 2-trifluoroacetyl-1-methoxycycloalkenes (**1a**–**c**) (5 mmol) in pyridine (0.4 g; 5 mmol), was added a solution of hydroxylamine hydrochloride (0.35 g; 5 mmol) in H_2O (2 mL). The mixture was stirred at 45°C for 24 h. After 24 h, water (50 mL) was added and extracted with diethyl ether (3 × 15 mL), dried with Na_2CO_3 and evaporated. The solids were recrystallized from methanol or diethyl ether.

3-Hydroxy-3-trifluoromethyl-3H-3a,4,5,6,7,8-hexahydro-cyclohepta[c]isoxazole (2a). This compound was obtained as white crystals (85% yield), Mp. 128–130°C.^{1}H NMR (DMSO-d_6): δ 8.02 (s, 1H, OH), 3.52 (m, 1H, CH), 2.63–2.42 (m, 2H, CH_2), 1.74–1.48 (m, 8H, CH_2).^{13}C NMR (DMSO)-d_6): δ 163.7 (C-8a), 122.8 (q, CF_3, ^1J = 285.4), 102.7 (q, C-3, ^2J = 31.8) 54.3 (C-3a), 30.4 (CH_2), 27.5 (CH_2), 26.6 (CH_2), 25.2 (CH_2), 23.8 (CH_2). Anal. Calc. for $C_9H_{12}F_3NO_2$ (223.08): C, 48.43%; H, 5.42%; N, 6.28% Found: C, 48.24%; H, 5.18%; N, 6.09%. MS [*m*/*z*(%)] for $C_9H_{12}F_3NO_2$ (223.08): 223 (M$^+$, 10), 154 (32), 136 (38), 108 (100), 69 (70).

3-Hydroxy-3-trifluoromethyl-3,3a,4,5,6,7,8,9-octahydro-cycloocta[c]isoxazole (2b). This compound was obtained as white crystals (61% yield), Mp. 105–107°C. ^{1}H NMR (DMSO-d_6): δ 8.1 (s, 1H, OH), 3.43–3.36 (m, 1H, CH), 2.6–2.5 (m, 2H, CH_2), 1.82–1.49 (m, 10H, CH_2). ^{13}C NMR (DMSO)-d_6): δ 162.8 (C-9a), 122.8 (q, CF_3, ^1J = 284.7), 103.3 (q, C-3, ^2J = 31.1) 52.3 (C-3a), 26.0 (CH_2), 25.2 (CH_2), 24.9 (CH_2), 24.8 (CH_2), 24.2 (CH_2), 22.3 (CH_2). Anal. Calc. for $C_{10}H_{14}F_3NO_2$ (237.10): C, 50.63%; H, 5.95%; N, 5.90% Found: C, 50.56%; H, 5.73%; N, 5.79%. MS [*m*/*z*(%)] for $C_{10}H_{14}F_3NO_2$ (237.10): 237 (M$^+$, 34), 168 (26), 150 (15), 122 (82), 112 (86), 99(70), 69 (34), 55(100).

3-Hydroxy-3-trifluoromethyl-3,3a,4,5,6,7,8,9,10,11,12,13-dodecahydro-cyclododeca[c]isoxazole (2c). This compound was obtained as white crystals (45% yield), Mp. 129–132°C. ^{1}H NMR (DMSO-d_6): δ 8.3 (s, 1H, OH), 3.3–3.2 (m, 1H, CH), 2.47–2.41 (m, 2H, CH_2), 1.66–1.60 (m, 2H, CH_2), 1.36–1.27 (m, 16H, CH_2). ^{13}C NMR (DMSO)-d_6): δ 162.5 (C-13a), 122.8 (q, CF_3, ^1J = 285.4), 103 (q, C-3, ^2J = 31.8) 50.4 (C-3a), 25.3 (CH_2), 24.2 (CH_2), 23.9 (CH_2), 23.8 (CH_2), 23.6 (CH_2), 23.2 (CH_2), 22.7 (CH_2), 22.5 (CH_2), 21.9 (CH_2). Anal. Calc. for $C_{14}H_{22}F_3NO_2$ (293.16): C, 57.33%; H, 7.56%; N, 4.78% Found: C, 57.38%; H, 7.82%; N, 5.03%. MS [*m*/*z*(%)] for $C_{14}H_{22}F_3NO_2$ (293.16): 293 (M$^+$, 5), 224 (100), 100 (25), 69 (20), 55(43).

General procedure for the preparation of 3-trifluoromethyl-cycloalka[c]1H-pyrazole (3a–c). To a solution of hydrazine hydrochloride (0.35 g; 5 mmol) in the presence of pyridine (0.4 g; 5 mmol), was added 2-trifluoroacetyl-1-methoxycycloalkenes (5 mmol) (**1a**–**c**) in ethanol (10 mL) and the mixture was stirred in ice bath. The mixture was then stirred at room temperature for 30 min and under reflux for another 8 h. After 8 h, the solution was concentrated and cooled (<10°C). The crystalline solids were isolated by filtration and washed with cold ethanol.

3-Trifluoromethyl-1,4,5,6,7,8-hexahydrocyclohepta[c]pyrazole (3a). This compound was obtained as white crystals [27] (69% yield), Mp. 132–134°C. (Lit. [27], Mp. 154.1°C). ^{1}H NMR (DMSO-d_6): δ 13.09 (s, 1H, NH), 2.76–2.74 (m, 2H, CH_2), 2.61–2.58 (m, 2H, CH_2), 1.80–1.61 (m, 6H, CH_2). ^{13}C NMR (DMSO)-d_6): δ 144.63 (C-8a), 138.46 (q, C-3, ^2J = 34.6), 122.51 (q, CF_3, ^1J = 269.15), 117.17 (C-3a), 30.96 (CH_2), 27.93 (CH_2), 26.43 (CH_2), 25.75 (CH_2), 23.19 (CH_2). Anal. Calc. for $C_9H_{11}F_3N_2$ (204.19): C, 52.94%; H, 5.43%; N, 13.72% Found: C, 52.38%; H, 5.71%; N, 13.63%. MS [*m*/*z*(%)] for $C_9H_{11}F_3N_2$ (204.19): 204 (M$^+$, 98), 203 (100), 175 (63), 162 (85), 135(55), 69(9).

3-Trifluoromethyl-4,5,6,7,8,9-hexahydrocycloocta[c]1H-pyrazole (3b). This compound was obtained as white crystals (55% yield), Mp. 119–122°C. ^{1}H NMR (DMSO-d_6): δ 13.09 (s, 1H, NH), 2.77–2.71 (m, 2H, CH_2), 2.642.57 (m, 2H, CH_2), 1.59–1.33 (m, 8H, CH_2). ^{13}C NMR (DMSO)-d_6): δ 142.85 (C-8a), 138.31 (q, C-3, ^2J = 33.91), 122.51 (q, CF_3, ^1J = 269.15), 114.73 (C-3a), 28.84 (CH_2), 4.78 (CH_2), 22.71 (CH_2), 19.9 (CH_2). Anal. Calc. for $C_{10}H_{13}F_3N_2$ (218.22): C, 55.04%; H, 6.00%; N, 12.84% Found: C, 55.38%; H, 5.82%; N, 13.03%. MS [*m*/*z*(%)] for $C_{10}H_{13}F_3N_2$ (218.22): 218 (M$^+$, 83), 189 (72), 162 (100), 149 (53), 69(10).

3-Trifluoromethyl-4,5,6,7,8,9,10,11,12,13-decahydrocyclododeca[c]-1H-pyrazole (3c). This compound was obtained as white crystals (48% yield), Mp. 147–148°C. ^{1}H NMR (DMSO-d_6): δ 2.55–2.59 (m, 2H, CH_2), 2.44–2.48 (m, 2H, CH_2), 1.73 (s, 2H, CH_2), 1.59–1.58 (d, 2H, CH_2), 1.41 (s, 4H, CH_2), 1.22–1.35 (m, 8H, CH_2). ^{13}C NMR (DMSO)-d_6): δ 142.63 (C-13a), 138.1 (q, C-3, ^2J = 35.0), 122.6 (q, CF_3, ^1J = 268.7), 115.3 (C-3a), 28.0 (CH_2), 26.8 (CH_2), 24.5 (CH_2), 24.4 (CH_2), 23.9 (CH_2), 23.7 (CH_2), 22.2 (CH_2), 21.7 (CH_2), 20.0 (CH_2), 19.1 (CH_2). Anal. Calc. for $C_{14}H_{21}F_3N_2$ (274.33): C, 61.30%; H, 7.72%; N, 10.21% Found: C, 61.38%; H, 7.62%; N, 10.19%. MS [*m*/*z*(%)] $C_{14}H_{21}F_3N_2$ (274.33): 274 (M$^+$, 66), 205 (62), 162 (100), 69 (22), 55(47).

General procedure for the preparation of 4-trifluoromethyl-cycloalka[d]-2(1H)pyrimidinone (4a–c). To a stirred solution of urea (0.42 g; 7 mmol) in propan-2-ol (10 mL) kept at room temperature (20–25°C), were added 2-trifluoroacetyl-1-methoxycycloalkenes (1**a–c**) (5 mmol) and boron trifluoride diethyl etherate (sol. 45% in MeOH) (10 drops). The mixture was stirred at 85°C for 20 h. After cooling (<10°C), the crystalline solids were isolated by filtration, washed with cold propan-2-ol, and recrystallized from ethanol.

4-Trifluoromethyl-5H-6,7,8,9-tetrahydrocyclohepta[d]-2(1H)pyrimidinone (4a). This compound was obtained as white crystals (58% yield), Mp. 229–230°C. ^{1}H NMR (DMSO-d_6): δ 12.5 (s, 1H, NH), 2.8 (m, 2H, CH_2), 2.7 (m, 2H, CH_2), 1.7 (m, 2H, CH_2), 1.6 (m, 2H, CH_2), 1.5 (m, 2H, CH_2). ^{13}C NMR (DMSO)-d_6): δ 170.7 (C=O), 156.8 (C-4), 156.3 (C-9a), 120.7 (q, CF_3, ^1J = 278.3), 116.4 (C-4a), 33.7 (CH_2), 30.8 (CH_2), 26.4 (CH_2), 25.2 (CH_2), 24.7 (CH_2). Anal. Calc. for $C_{10}H_{11}F_3N_2O$ (232.20): C, 51.73%; H, 4.77%; N, 12.06%. Found: C, 51.46%; H, 4.74%; N, 11.97%. MS [*m*/*z*(%)] for $C_{10}H_{11}F_3N_2O$ (232.20): 232 (M^+, 100), 163 (21), 69 (7).

4-Trifluoromethyl-5,6,7,8,9,10-hexahydrocycloocta[d]-2(1H) pyrimidinone (4b). This compound was obtained as white crystals (50% yield), Mp. 145–147°C. ^{1}H NMR (DMSO-d_6): δ 2.8 (m, 1H, CH_2), 2.7 (m, 1H, CH_2), 2.65–2.61 (m, 2H, CH_2), 2.4 (m, 1H, CH_2), 1.63–1.61 (m, 3H, CH_2), 1.27 (m, 4H, CH_2). ^{13}C NMR (DMSO)-d_6): δ 164.3 (C=O), 158.1 (q, C-4, ^2J = 28.3), 156.5 (C-10a), 120.6 (CF_3, ^1J = 279), 113.0 (C-4a), 31.2 (CH_2), 30.4 (CH_2), 29.8 (CH_2), 25.2 (CH_2), 25.3 (CH_2), 23.2 (CH_2). Anal. Calc. for $C_{11}H_{13}F_3N_2O$ (246.10): C, 53.66%; H, 5.32%; N, 11.38% Found: C, 54.01%; H, 5.42%; N, 11.74%. MS [*m*/*z*(%)] for $C_{11}H_{13}F_3N_2O$ (246.10): 246 (M^+, 40), 217 (100), 177 (18), 69 (30).

4-Trifluoromethyl-5,6,7,8,9,10,11,12,13,14-decahydro-cyclododeca[d]-2(1H)pyrimidinone (4c). This compound was obtained as white crystals (51% yield), Mp. 221–223°C. ^{1}H NMR (DMSO-d_6): δ 12.5 (s, 1H, NH), 2.69 (m, 2H, CH_2), 2.6 (m, 2H, CH_2), 1.79 (m, 2H, CH_2), 1.50–1.42 (m, 14H, CH_2). ^{13}C NMR (DMSO)-d_6): δ 167.4 (C=O), 158.8 (C-4), 156.5 (C-14a), 120.7 (CF_3, ^1J = 278.3), 114.1 (C-4a), 28.9 (CH_2), 26.9 (CH_2), 26.5 (CH_2), 25.9 (CH_2), 23.2 (CH_2), 22.3 (CH_2), 21.6 (CH_2). Anal. Calc. For $C_{15}H_{23}F_3N_2O$ (304.18): C, 59.59%; H, 7.00%; N, 9.27% Found: C, 59.61%; H, 6.79%; N, 9.17%. MS [*m*/*z*(%)] for $C_{15}H_{23}F_3N_2O$ (304.18): 302 (M^+, 9), 245 (20), 233 (100), 192 (41), 69 (5).

General procedure for the preparation of 4-(3-hydroxy-3-trifluoromethyl-3,3a,4,5,6,7,8,9,10,11,12,13-dodecahydrocyclododeca[c]pyrazol-2-yl)-7-chloroquinoline (5c). To a stirred solution of 2-trifluoroacetyl-1-methoxycyclododeceno (1c) (5 mmol) in methanol (30 mL), was added 7-chloro-4-hydrazinoquinoline (0.96 g; 5 mmol). The mixture was stirred at 65°C for 6 h. Subsequently, the solvent was evaporated and a solution of methanol/H_2O (3:1) was added. The solids were filtered and recrystallized from methanol. This compound was obtained as white crystals (55% yield), Mp. 108–110°C. ^{1}H NMR (DMSO-d_6) δ 8.28 (s,1H, OH), 3.20–3.21 (d, 1H, H-3a);(quinoline) = δ 8.79–8.80 (s,1H, H-2), 8.36–8.39 (d,1H, H-8), 8.01–8.02 (d,1H, H-6), 7.69–7.70 (d, 1H, H-5), 7.54–7.57 (m, 1H, H-8); (cyclododeca) = δ 3.20–3.21 (m, 2H, CH_2), 1.83–1.87 (d, 2H, CH_2), 1.57–1.66 (m, 3H, CH_2), 1.46 (s, 4H, CH_2), 1.38 (s, 9H, CH_2). ^{13}C NMR (DMSO-d_6): δ 156.8 (C-13a), 123.1 (q, CF_3, ^1J = 287.5), 94.7 (q, C-3, ^2J = 29.9), 51.4 (C-3a); (quinolyl): δ151.2 (C-2), 149.8 (C-8a), 147.0 (C-4), 133.6 (C-7), 128.0 (C-8), 127.4 (C-6), 125.5 (C-5), 122.6 (C-4a), 113.4 (C-3); (cyclododeca): δ 25.6 (CH_2), 25.3 (CH_2), 24.2 (2CH_2), 23.8 (CH_2), 23.7 (CH_2), 23.4 (CH_2), 22.8 (CH_2), 22.5 (CH_2), 21.1 (CH_2). Anal. Calc. for $C_{23}H_{27}ClF_3N_3O$ (453.93): C, 60.86%; H, 6.00%; N, 9.26%. Found: C, 61.01%; H, 5.78%; N, 9.54%. MS [*m*/*z*(%)] for $C_{23}H_{27}ClF_3N_3O$ (453.93): 435 (M^+-H_2O, 100), 336 (61), 325 (72), 162 (45), 69(8).

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Mesoionic Carbenes: Reactions of 1,3-Diphenyltetrazol-5-ylidene with Electron-Deficient Alkenes, and Synthesis and Catalytic Activities of the (Tetrazol-5-ylidene)rhodium(I) Complexes

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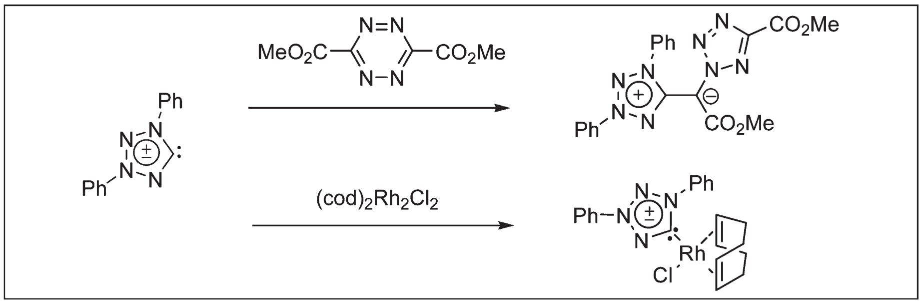

The reactions of 1,3-diphenyltetrazol-5-ylidene, a rare example of mesoionic carbenes, with electron-deficient unsaturated compounds were studied. The carbene reacted with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate to give a 5-tetrazoliomethylide, together with hydrazine derivatives. The reaction with tetracyanoethylene gave another methylide in low yield. On the contrary, the reactions with weaker electrophiles, such as 3,6-diphenyl-1,2,4,5-tetrazine, fumalonitrile, *N*-phenylmaleimide, and dimethyl acetylenedicarboxylate, did not give any coupling products, but gave phenylated products and/or Michael addition products *via* the degradation of the 1,3-diphenyltetrazole ring. Novel mesoionic mono- and bis(carbene)-rhodium(I) complexes were synthesized and the structures were characterized by X-ray crystallography. Their catalytic activities for the decarbonylative addition reaction of benzoyl chloride to ethynylbenzene were investigated.

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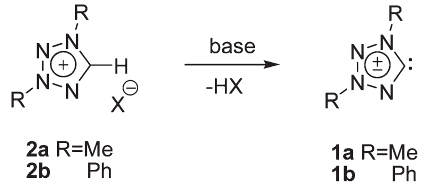
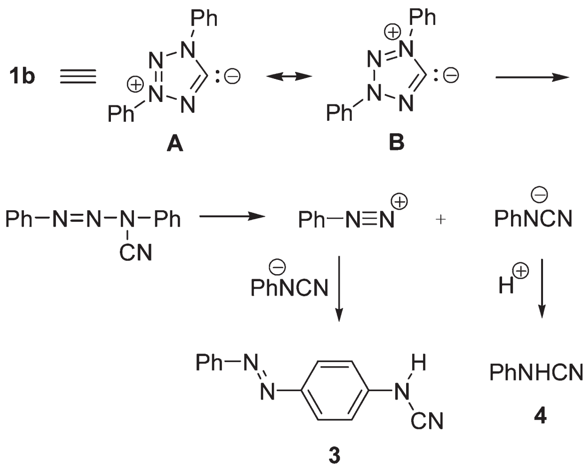
INTRODUCTION

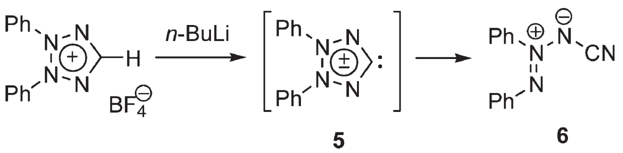
Since the Arduengo's pioneering work on stable heterocyclic carbenes, various heterocyclic carbenes, including *N*-heterocyclic carbenes (NHCs) such as imidazol-2-ylidene and 1,2,4-triazol-3-ylidene, have hitherto been prepared and their physical and chemical properties have intensively been investigated [1]. Mesoionic compounds are the unique family of heterocycles owing to their interesting electronic nature; *i.e.*, they cannot be formulated satisfactorily by a single covalent or polar structure, but expressed as a resonance hybrid of a series of dipolar canonical structures [2]. Mesoionic carbenes, which are derived formally from mesoionic compounds by a removal of the exo-cyclic atom(s), are also resonance hybrids of several canonical structures. Contrary to the extensive study on NHCs, mesoionic carbenes are scarcely studied. 1,3-Dimethyl- (**1a**) and 1,3-diphenyltetrazol-5-ylidene (**1b**) are rare examples of such mesoionic carbenes. These carbenes are easily prepared by deprotonation of the corresponding 1,3-disubstituted tetrazolium salts **2a**,**b** with a base at low temperature [3,4]. Alternatively, **1b** can also be generated by the reaction of 5-azido-1,3-diphenyltetrazolium salt with sodium azide [5]. Carbene **1** is thermally labile; upon warming to room temperature, **1** undergoes a ring-opening to give 3-cyanotriazene. In the case of **1b**, further degradation and recombination reactions occur spontaneously to give 4-(phenylazo)phenylcyanamide (**3**) and phenylcyanamide (**4**) (Scheme 1) [6]. As an isomeric carbene of **1**, 2,3-diphenyltetrazol-5-ylidene (**5**) is also known, which is generated similarly by deprotonation of 2,3-diphenyltetrazolium salts [7]. This mesoionic carbene is also unstable to give cyanoazimine **6** (Scheme 2). Although various stable NHCs have recently been attracting increasing interest, only these two examples **1** and **5** of mesoionic carbenes are thus far synthesized.



Scheme 1



Scheme 2



Our previous work demonstrated that carbene **1b** has a nucleophilic nature and hence is best expressed by the singlet structures **A** and **B**. For example, although the attempted reactions with alkyl halides or carbonyl compounds were unsuccessful, **1b** reacts readily with nitrogen electrophiles such as benzenediazonium and azidotetrazolium salts [4,5]. Here, we report further reactions of **1b** with electron-deficient tetrazine and alkene electrophiles. Furthermore, the synthesis and characterization of stable rhodium(I) complexes of **1b** are disclosed as examples of transition-metal complexes of mesoionic carbenes.

RESULTS AND DISCUSSION

A. Reaction with 1,2,4,5-tetrazines. It is reported that 1,2,4-triazol-3-ylidene reacts with 3,6-diphenyl-1,2,4,5-tetrazine to give a [4+1] cycloaddition product [8]. We attempted the reaction of **1b** with 3,6-diphenyl-1,2,4,5-tetrazine. However, no reaction occurred and only the degradation products **3** and **4** were obtained. Next, dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate **8**, a more electron-poor tetrazine bearing the electron-withdrawing substituents, was employed. The carbene **1b** was generated *in situ* from the tetrazolium salt **2b** and reacted with **8** under different reaction conditions, by changing the solvent and the reaction temperature. These results are summarized in Table 1.

Three products **9**, **10**, and **11** have been isolated from the reaction mixtures in varying yields, together with small amounts of olate **7** and **4** (Scheme 3). Olate **7** is considered to be formed by the reaction of **1b** with atmospheric oxygen [4]. The compound **9** has been revealed to be a 1:1 adduct of **1b** and **8** on the basis of the MS and elemental analyses. A characteristic signal at 78.7 ppm in the ^{13}C NMR spectrum suggests that this compound is a 5-tetrazoliomethylide derivative [9]. The structure was finally comfirmed by X-ray chrystallography (Fig. 1). The exo-cyclic methylide C—C—N plane and the tetrazolium ring share almost the same plane. The phenyl ring at N^3 lies in this plane; on the contrary, the phenyl ring at N^1 as well as the tetrazole ring attached to the methylide carbon tilt considerably. The pivotal carbon—carbon bond length is 1.406(3) Å, indicating a mixed nature of single and double bonds. Compound **10** has a molecular formula $C_{19}H_{16}N_6O_4$, which corresponds to a loss of N_2 from the sum of **1b** and **8**. ^{1}H and ^{13}C NMR data show that **10** has a *p*-substituted benzene ring and two inequivalent CO_2Me groups. The structure was eventually deduced to be 4-(*p*-phenylazo) phenylhydrazone of a pyrazolone derivative. Compound **11** has a structure similar to **10**, bearing an unsubstituted phenylhydrazone moiety. An attempted reaction of **11** with benzene-diazonium salt did not give **10**. This fact suggests that **10** might be formed *via* an intramolecular migration of the phenylazo group. The most plausible mechanism for the formation of compounds **9**, **10**, and **11** is shown in Scheme 4.

A nucleophilic attack of **1b** to the electron-deficient carbon of tetrazine **8** followed by a ring-contraction

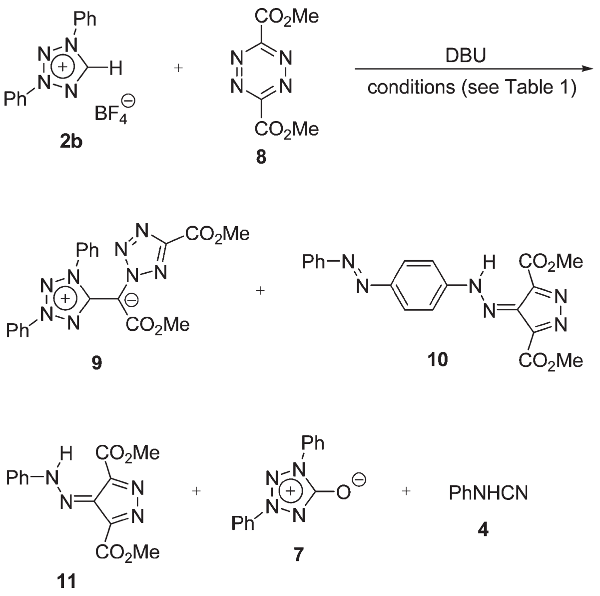
Table 1

The reaction of mesoionic carbene **1b** with **8**.

Entry	Temperature	Solvent	*t* (h)	Yield (%)				
				9	**10**	**11**	**7**	**4**
1	−20°C to r.t.	DMA	3	Trace	6[a]	24[a]	8	18
2	−20°C to r.t.	DMF	3	2[a]	7[a]	37[a]	3	5
3	−60°C to r.t.	DMF	4	15[a]	4[a]	22[a]	2	8

[a] Determined by ^{1}H NMR.

Scheme 3



furnishes **9**. Compounds **10** and **11** are considered to be formed *via* the spiro intermediate **C** which is akin to the product of the reaction of 1,2,4-triazol-3-ylidene and diphenyltetrazine [8]. The cleavage of the tetrazole ring of **C** followed by an intramolecular migration of the phenylazo group (aza para-Claisen rearrangement) gives **10**, whereas a loss of the phenylazo group furnishes **11**. Now it has been found that carbene **1b** reacts readily with the electron-deficient unsaturated compound. Then, the reactions of **1b** with alkenes with electron-withdrawing groups were next undertaken.

B. Reaction with tetracyanoethylene. A mixture of the tetrazolium salt **2b** and tetracyanoethylene was treated with DBU at –60°C, and the mixture was warmed to room temperature. The reaction gave a complex mixture of products, from which only cyanomethylide **12** was isolated as stable yellow crystals in low yield (9%) after column chromatography. The formation of **12** is rationalized by Scheme 5. The initially formed Michael adduct is considered to undergo a cyano group migration to furnish the fully conjugated methylide **12**.

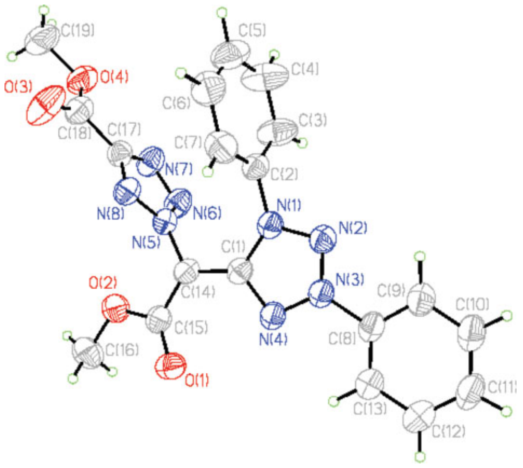
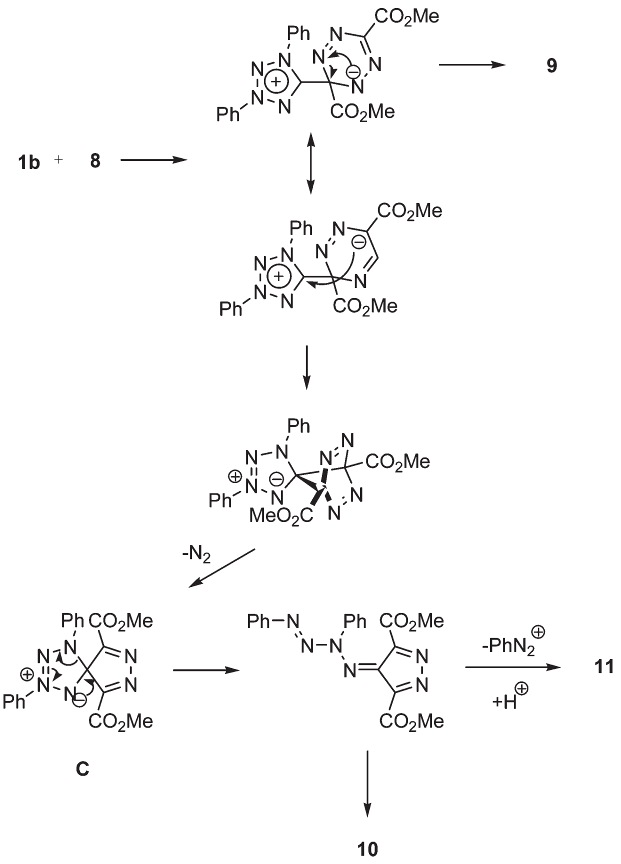


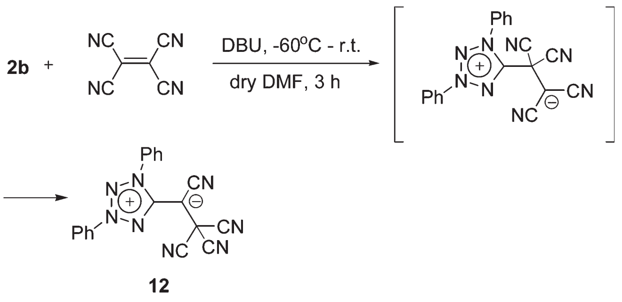
Figure 1. Molecular structure of methylide **9**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Scheme 4

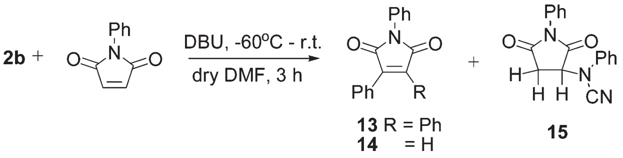


C. Reaction with *N*-phenylmaleimide, fumalonitrile, and dimethyl acetylenedicarboxylate. The reaction of mesoionic carbene **1b** with *N*-phenylmaleimide at –60°C to room temperature gave phenylated maleimides **13** and **14** together with cyanamide **15** (Scheme 6). To determine the origin of the phenyl group of **13** and **14**,

Scheme 5



Scheme 6

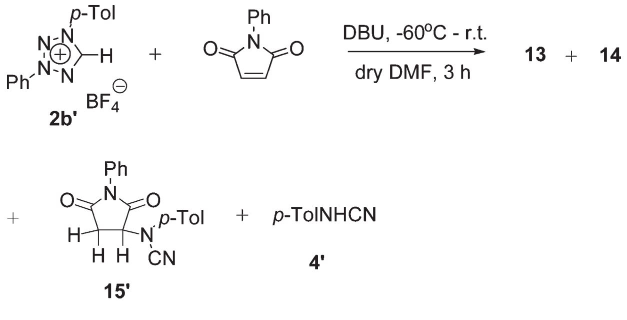


1-(*p*-tolyl)-3-phenyltetrazolium **2b′** was employed in place of **2b**. The reaction gave **13** and **14**, and the *p*-tolylcyanamide adduct **15′**. *p*-Tolylcyanamide **4′** itself was also isolated (Scheme 7). On the basis of these results, a plausible reaction mechanism is illustrated in Scheme 8. Carbene **1b** decomposes thermally to give benzendiazonium cation and phenylcyanamide anion; the former is considered to give phenyl radical [10] which reacts with *N*-phenylmaleimide to furnish the phenylated compounds **13** and **14**. The phenylcyanamide anion gives the adduct **15** *via* the Michael addition to *N*-phenylmaleimide.

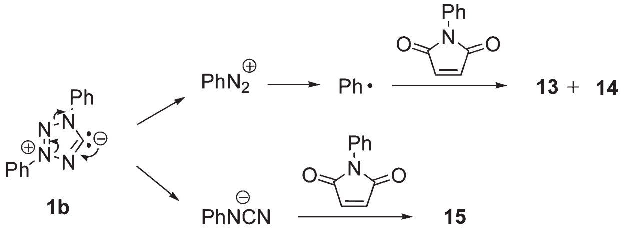
The reaction of **1b** with fumalonitrile also gave the phenylation products **16**, **17**, and **18** in low yields, together with the degradation products **3** and **4**. The reaction with dimethyl acetylenedicarboxylate gave the addition product **19** in 29% yield *via* a similar mechanism to the *N*-phenylmaleimide case (Scheme 9).

D. Preparation and characterization of rhodium(I) complexes of 1,3-diphenyltetrazol-5-ylidene. It is well known that carbenes can be stabilized by complexation with metals. Indeed, a large number of main group metal as well as transition metal complexes of NHCs have hitherto been prepared and characterized. Of such NHCs, imidazol-2-ylidene [11] and 1,2,4-triazol-3-ylidene [12] are most extensively studied, and some imidazol-2-ylidene-metal complexes have been used as effective catalysts in organic syntheses [13]. On the other hand, very few examples of mesoionic carbene-metal complexes, such as mercury(II) and palladium(II) complexes, have been synthesized by us [4]. Here, we describe the preparation and characterization of rhodium(I) complexes of **1b** as a new entry of mesoionic carbene-metal complexes.

Scheme 7



Scheme 8

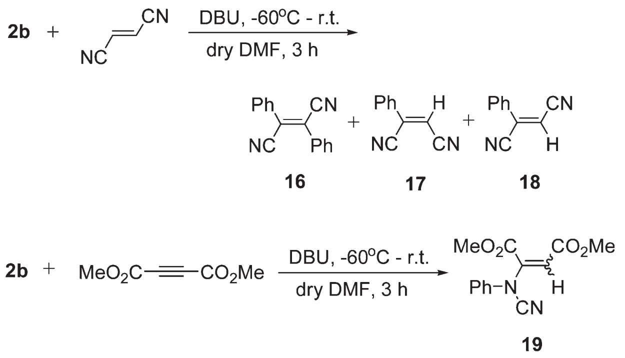


The reactions of tetrazolium salt **2b** with bis(1,5-cyclooctadiene)-μ,μ′-dichlorodirhodium (**20**) in DMF mediated by DBU were performed under various conditions. Two products, namely, mono- **21** and bis(tetrazol-5-ylidene)rhodium(I) complexes **22**, were isolated as stable crystalline solids (Scheme 10, Table 2). When an excess tetrazolium salt **2b** was used **22** was formed exclusively. Obviously, the cationic bis-carbene complex **22** is formed *via* the neutral mono-carbene complex **21**. Indeed, the reaction of **21** with **2b**/DBU gave **22**.

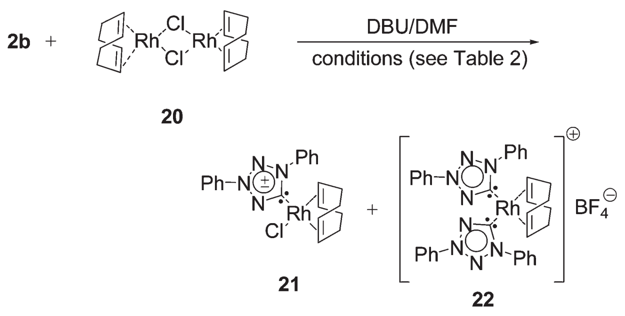
The molecular structures of the rhodium(I) complexes **21** and **22** were analyzed by X-ray crystallography (Figs. 2 and 3). In the square planner complex **21**, the tetrazol-5-ylidene ring is twisted relative to the coordination plane. The bond angle C(carbene)-Rh-Cl is 90.59(8)°. The C(carbene)-Rh length [2.017(3) Å] is almost coincident to that of (imidazol-2-ylidene)rhodium complex [11] [2.023(2) Å] and somewhat longer than that of (1,2,4-triazol-3-ylidene)rhodium complex [12(a)] [2.004 (7) Å]. The cationic bis(tetrazol-5-ylidene) complex **22** is also square planner. The bond angle C(carbene)-Rh-C(carbene) is 90.47(13)°. The C(carbene)-Rh lengths [2.039(3) and 2.031(3) Å] are longer than that of **21**, whereas they are shorter than the averaged length (2.047 Å) of the corresponding (imidazol-2-ylidene)rhodium complex [11].

To evaluate the catalytic activities, the complexes **21** and **22** were subjected to the decarbonylative addition reaction of benzoyl chloride to ethynylbenzene. The reaction is known to give (*Z*)-1-chloro-1,2-diphenylethene (**23**) by the catalysis of the $(cod)_2Rh_2Cl_2$ (**20**)

Scheme 9



Scheme 10



[14]. The mono(tetrazol-5-ylidene)Rh complex **21** (10 mol%) was found to be as effective as **20** to give **23** in 61% yield (Scheme 11). On the contrary, the bis (tetrazol-5-ylidene) complex **22** is less reactive to give lower yield (22%) of **23**, probably owing to the steric crowding around the rhodium atom.

CONCLUSION

The nucleophilic nature of 1,3-diphenyltetrazol-5-ylidene **1b** was demonstrated in the reactions with the electron-deficient tetrazine and alkene to yield the new 5-tetrazoliomethylide compounds **9** and **12**. In the cases of weak electrophiles, the degradation of the tetrazole ring took place and the phenylated products were obtained. Two (tetrazol-5-ylidene)rhodium(I) complexes **21** and **22** were synthesized *via* a nucleophilic displacement of the chlorine atoms of **20** with **1b**. Catalytic activities of **21** and **22** were investigated for the chloroarylation of ethynylbenzene. Further catalytic properties of these new rhodium complexes are now under way.

EXPERIMENTAL

Table 2

The reaction of tetrazolium salt **2b** with **20**.

Entry	**2b** (mmol)	**20** (mmol)	Conditions	Yield (%) **21**	Yield (%) **22**
1	0.50	0.25	−60°C, 3 h	12	31
2	0.25	0.25	0°C, 3 h	30	13
3	0.25	0.25	−60°C, 3 h	31	26
4	0.25	0.25	−60°C, 25 h	53	17
5	0.50	0.13	−60°C, 18 h	Trace	99

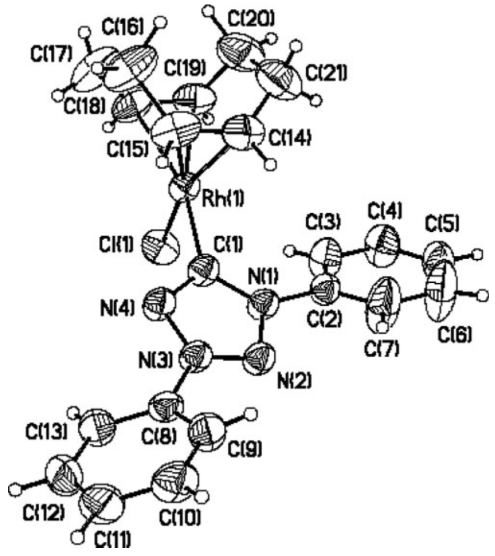


Figure 2. Molecular structure of the (tetrazol-5-ylidene)rhodium complex **21**.

Melting points were measured with a hot-stage apparatus and are uncorrected. Elemental analyses were carried with a Perkin–Elmer 2400 II CHNS/O. IR spectra were taken as KBr discs on a JASCO A-102 spectrometer. Electronic spectra were measured on a U-3500 spectrophotometer. ^1H NMR spectra were obtained using a Varian Gemini 200 (200 MHz) or a Varian Gemini 300 (300 MHz), and ^{13}C NMR spectra were obtained using a Varian Gemini-200 (50 MHz). Chemical shifts are recorded in ppm downfield from tetramethylsilane. *J* values are given in Hz. Mass spectra were taken with a Hitachi M-2000 spectrometer (EI, 70 eV). For TLC, Merck Silica gel 60 F_{254} Plate and Fuji Silysia Chemical Ltd. NH TLC Plate were used. For column chromatography, Merck Silica gel 60 (0.063–0.200 mm) and Fuji Silysia Chemical Ltd. Chromatorex NH Chromatography Silica Gel (100–200 mesh) were used.

Although no problems were hitherto encountered, it should be noted that polyaza compounds may in general be explosive and should be handled with due care.

Reaction with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (8).

Typical procedure. To a solution of **2b** (1.6 g, 5.0 mmol) and **8** (0.99 g, 5.0 mmol) in dry DMF (20 mL), DBU (0.75 mL, 5.0 mmol) was added at −60°C, and the mixture was warmed gradually to room temperature during a period of 4 h (Table 1, entry 3). Water was added and the precipitated

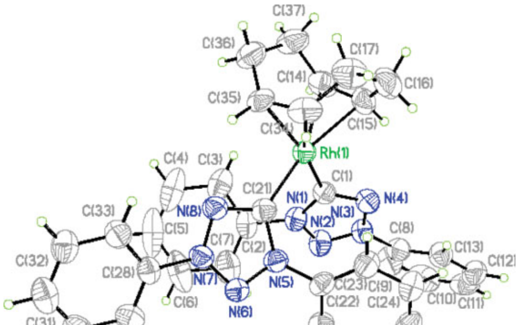
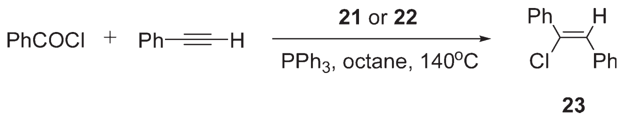


Figure 3. Molecular structure of the bis(tetrazol-5-ylidene)rhodium complex **22**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Scheme 11



solid was filtered off. The products were extracted from the filtrate with dichloro-methane. The extracts were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue (reddish brown solid, 1.0 g) was chromatographed (SiO_2/CH_2Cl_2:EtOAc gradient and MeOH) to give **4** (49 mg, 8%), **7** (26 mg, 2%), and a mixture of **9**, **10**, and **11** (0.72 g). On the basis of the ^1H NMR analysis, the yields were estimated to be **9** (15%), **10** (4%), and **11** (22%). Pure samples of **9**, **10**, and **11** were obtained after repeated column chromatography. The entries 1 and 2 were similarly carried out by changing the solvent and the reaction temperature. The results are summarized in Table 1.

(Ethoxycarbonyl)(5-ethoxycarbonyltetrazol-2-yl)-α-(1,3-diphenyl-5-tetrazolio)methylide (9). Yellow crystals, Mp. 179–184°C (CH_2Cl_2/hexane); ir (KBr): 1744, 1680, 1552, 1490, 1380, 1362, 1346, 1238, 1224, 1186, 1118, 1072, 1040, 1022, 996, 898, 816, 758, 696, 682, 670/cm; ^1H NMR (200 MHz, deuteriochloroform): δ 3.58 (s, 3H, Me), 3.99 (s, 3H, Me), 7.30–7.41 (m, 5H, Ph), 7.61–7.68 (m, 3H, Ph), 8.19 (dd, 2H, $J = 8.1$ Hz, $J = 1.7$ Hz, Ph); ^{13}C NMR (50 MHz, deuteriochloroform): δ 50.6 (Me), 52.8 (Me), 78.7 (C^-), 120.7 (*o*-Ph), 124.8 (*o*-Ph), 129.1 (*m*-Ph), 129.9 (*m*-Ph), 130.6 (*p*-Ph), 132.6 (*p*-Ph), 133.2 (*i*-Ph), 135.1 (*i*-Ph); 156.5, 157.6, 158.0, 163.4 ($CO_2Me \times 2$, $C = N$, C^+); uv/vis (MeCN): λ_{max} (log ε) = 392.0 (3.16), 279.0 nm (4.48). ms (EI, 70 eV): *m/z* 393 (32, M^++1-N_2), 293 (33), 248 (100), 231 (62), 219 (26), 169 (72), 131 (88), 119 (97), 101 (21). *Anal.* Calcd. for $C_{19}H_{16}N_8O_4$ (420.4): C, 54.28; H, 3.84; N, 26.66. Found C, 53.94; H, 3.76; N, 26.39.

Dimethyl 4-(4-phenylazophenylhydrazono)-4H-pyrazole-3,5-dicarboxylate (10). Orange crystals, Mp. 191–192.5°C (MeOH). ir (KBr): 2935, 2855, 1750, 1700, 1614, 1598, 1570, 1530, 1444, 1406, 1364, 1286, 1226, 1202, 1174, 1102, 1080, 1036, 844, 796, 770, 720, 684/cm. ^1H NMR (200 MHz, deuteriochloroform): δ 4.10 (s, 3H, Me), 4.15 (s, 3H, Me), 7.50–7.54 (m, 3H, Ph), 7.91–8.02 (m, 6H, Ph), 10.70 (bs, 1H, NH). ^{13}C NMR (50 MHz, deuteriochloroform): δ 53.7 (Me), 53.9 (Me), 121.8 (*o*-Ph), 122.8, 124.0 (Ph), 129.0 (*m*-Ph), 131.0 (*p*-Ph), 136.0 138.6 (*i*-Ph, C=N), 149.6, 152.0, 152.5, 155.5, 162.6, 165.7 (C—$CO_2Me \times 2$, $CO_2Me \times 2$, C—N=N—C); uv/vis (MeCN): λ_{max} (log ε) = 449.0 (3.36), 353.0 (4.53), 288.0 (4.07), 235.0 nm (4.22); ms (EI, 70 eV): *m/z* 393 (M^++1, 17), 392 (M^+, 69), 288 (19), 287 (100), 143 (10), 77 (56). *Anal.* Calcd. for $C_{19}H_{16}N_6O_4$ 0.5(CH_3OH) (408.4): C, 57.73; H, 4.04; N, 20.58. Found C, 57.36; H, 4.04; N, 20.65.

Dimethyl 4-(phenylhydrazono)-4H-pyrazole-3,5-dicarboxylate (11). Blass crystals; Mp. 159.5–162°C (MeOH); ir (KBr): 3280–2800, 1740, 1698, 1618, 1578, 1528, 1496, 1450, 1366, 1338, 1292, 1230, 1208, 1178, 1076, 1034, 962, 850–820, 772, 740, 730, 698/cm; ^1H NMR (200 MHz, deuteriochloroform): δ 4.07 (s, 3H, Me), 4.13 (s, 3H, Me), 7.20–7.27 (m, 1H, *p*-Ph), 7.40–7.48 (m, 2H, *m*-Ph), 7.77–7.81 (m, 2H *o*-Ph), 10.47 (bs, 1H, NH); ^{13}C NMR (50 MHz, deuteriochloroform): δ 53.5 (Me), 53.8 (Me), 121.6 (*o*-Ph), 125.7 (*p*-Ph), 129.2 (*m*-Ph), 135.8, 136.1 (*i*-Ph, C=N), 152.1, 155.6, 162.7, 165.7 ($CO_2Me \times 2$, C—$CO_2Me \times 2$); uv/vis (MeCN): λ_{max} (log ε) = 362.0 (3.44), 292.0 (4.21), 261 (3.96), 228 nm (3.97); ms (EI, 70 eV): *m/z* 289 (M^++1, 18), 288 (M^+, 100), 229 (41), 170 (77), 144 (82), 117 (72), 77 (73). *Anal.* Calcd. for $C_{13}H_{12}N_4O_4$ (288.3): C, 54.16; H, 4.20; N, 19.44. Found C, 54.00; H, 4.13; N, 19.01.

Reaction with tetracyanoethylene. DBU (0.15 mL, 1.0 mmol) was added to a mixture of **2b** (0.31 g, 1.0 mmol) and tetracyanoethylene (0.13 g, 1.0 mmol) in DMF (3.0 mL) at –60°C. The mixture was gradually warmed to room temperature and allowed to stand at room temperature for 3 h. Water was added and the black solid deposited was collected by filtration (0.33 g). The solid was chromatographed (SiO_2/CH_2Cl_2-MeCN gradient and MeOH) to give 12 (32 mg, 9%), 7 (59 mg, 25%), together with two unknown compounds. ^1H NMR and ^{13}C NMR spectra of the unknown compounds are very similar to those of 2. However, the structures of these products could not be determined.

(Cyano)(tricyanomethyl)-α-(1,3-diphenyl-5-tetrazolio)-methylide (12). Yellow crystals, Mp. 153–157°C (acetone/hexane); ir (KBr): 2940, 2180, 1592, 1560, 1486, 1466, 1456, 1364, 1342, 1292, 1268, 1176, 1072, 998, 842, 760, 720, 710, 688/cm; ^1H NMR (200 MHz, deuteriochloroform): δ 7.64–7.73 (m, 8H, Ph), 8.18 (dd, 2H, $J_1 = 8.0$ Hz, $J_2 = 1.5$ Hz, Ph). ^{13}C NMR (50 MHz, deuteriochloroform): δ 30.5 [—$C(CN)_3$], 38.6 (C^-), 107.4 (CN × 3), 115.9 (CN), 120.6 (*o*-Ph), 126.4 (*o*-Ph), 129.8 (*m*-Ph), 130.4 (*m*-Ph), 131.2 (*i*-Ph), 132.6 (*p*-Ph), 133.2 (*p*-Ph), 134.7 (*i*-Ph), 157.2 (C^+); uv/vis (MeCN): λ_{max} (log ε) = 379.0 (3.68), 276.0 nm (4.31); ms (EI, 70 eV): *m/z* 351 (M^++1, 3), 350 (M^+, 10), 324 (9), 270 (10), 245 (3), 194 (60), 179 (40), 152 (23), 128 (100), 118 (67), 103 (32). *Anal.* Calcd. for $C_{19}H_{10}N_8$ (350.35): C, 65.13; H, 2.88; N, 31.99. Found C, 64.94; H, 2.99; N, 32.18.

Reaction with *N*-phenylmaleimide. To a mixture of 2b (0.31 g, 1.0 mmol) and *N*-phenylmaleimide (0.17 g, 1.0 mmol) in DMF (3.0 mL) was added DBU (0.15 mL, 1.0 mmol) at –60°C, and the mixture was gradually warmed to room temperature in a period of 1.5 h, and then further stirred at room temperature for 1.5 h. Water was added and the products were extracted with dichloromethane. The extracts were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue (0.32 g) was chromatographed (SiO_2/CH_2Cl_2:hexane =1:1 to MeOH) to give 13 (37 mg, 11%), 14 (22 mg, 9%), 15 (57 mg, 20%) and 7 (4 mg, 2%).

1,3,4-Triphenyl-1H-pyrrole-2,5-dione (13). Yellow crystals, Mp. 174–176°C (EtOH) (lit Mp. 175°C) [15].

1,3-Diphenyl-1H-pyrrole-2,5-dione (14). Pale yellow crystals, Mp. 115–120°C (EtOH) (lit Mp. 117°C) [16].

(2,5-Dioxo-1-phenylpyrrolidin-3-yl)phenylcyanamide (15). Colourless crystals; Mp. 138.5–140.5°C (acetone/hexane); ir (KBr): 2220, 1720, 1596, 1498, 1396, 1380, 1370, 1250, 1186, 748, 700, 684/cm; ^1H NMR (200 MHz, deuteriochloroform): δ 3.25 (dd, $J = 18.4$ Hz, $J = 6.3$ Hz, 1H, trans-CH_2), 3.46 (dd, $J = 18.4$ Hz, $J = 9.1$ Hz, 1H, cis-CH_2), 4.92 (dd, J=9.1 Hz, $J = 6.3$ Hz, 1H, CH), 7.21–7.55 (m, 10H, Ph); ^{13}C NMR (50 MHz, deuteriochloroform): δ 35.6 (CH_2), 59.1 (CH), 112.7 (CN), 120.0 (*o*-Ph), 127.4 (*p*-Ph), 127.9 (*o*-Ph), 130.8 (*p*-Ph), 130.9 (*m*-Ph), 131.7 (*m*-Ph), 132.6 (*i*-NPh), 140.9 (*i*-NCNPh), 172.9, 173.2 (C=O); ms (EI, 70 eV): *m/z* 292 (M^++1, 21), 291 (M^+, 100), 173 (63), 144 (90), 129, (17), 118 (56), 104

(70), 91 (65), 77 (81). *Anal.* Calcd. for $C_{17}H_{13}N_3O_2$ (291.304): C, 70.09; H, 4.50; N, 14.43. Found C, 70.12; H, 4.51; N, 14.47.

The reaction of 3-phenyl-1-*p*-tolyltetrazolium salt **2b**′ and *N*-phenylmaleimide was similarly conducted as above to yield **13** (54 mg, 17%), **14** (26 mg, 10%), **15**′ (70 mg, 23%), and **4**′ (29 mg, 22%).

(2,5-Dioxo-1-phenylpyrrolidin-3-yl)-*p*-tolylcyanamide (15′). Colourless crystals, Mp. 140–142°C (acetone/hexane); ir (KBr): 3075, 2935, 2855, 2210, 1716, 1512, 1398, 1370, 1250, 1176, 818, 810, 740, 700/cm; ^{1}H NMR (200 MHz, deuteriochloroform): δ 2.36 (s, 3H, Me), 3.22 (dd, *J* = 18.5 Hz, *J* = 6.4 Hz, 1H, trans-CH_2), 3.43 (dd, *J* = 18.5 Hz, *J* = 9.2 Hz, 1H, cis-CH_2), 4.86 (dd, *J* = 9.2 Hz, *J* = 6.4 Hz, 1H, CH), 7.21–7.35 (m, 6H, Ph), 7.44–7.51 (m, 3H, Ph); ^{13}C NMR (50 MHz, deuteriochloroform): δ 20.7 (Me), 33.8 (CH_2), 57.9 (CH), 111.6 (CN), 118.9 (Ph), 126.2 (Ph), 129.0 (*p*-Ph), 129.2 (Ph), 130.5 (Ph), 130.9 (*i*-NPh), 135.9, 136.6 (*i*-NCNPh, *C*—Me), 171.3, 171.6 (C=O); ms (EI, 70 eV): *m*/*z* 306 (M^++1, 12), 305 (M^+, 55), 173 (100), 158 (42), 132 (9), 131 (90), 91 (78). *Anal.* Calcd. for $C_{18}H_{15}N_3O_2$ (305.33): C, 70.80; H, 4.95; N, 13.77. Found C, 70.46; H, 4.78; N, 13.64.

***p*-Tolylcyanamide (4′).** Oil; ir (KBr): 3175–2900, 2215, 1704, 1614, 1594, 1514, 1398, 1310, 1282, 1248, 804/cm; ^{1}H NMR (200 MHz, deuteriochloroform): δ 2.31 (s, 3H, Me), 6.31 (bs, 1H, NH), 6.91 (d, *J* = 8.5 Hz, 2H, Ph), 7.13 (d, *J* = 8.5 Hz, 2H, Ph) [17].

Reaction with fumaronitrile. To a mixture of **2b** (0.31 g, 1.0 mmol) and fumaronitrile (0.78 g, 1.0 mmol) in DMF (3.0 mL) was added DBU (0.15 mL, 1.0 mmol) at –60°C, and the mixture was gradually warmed to room temperature in a period of 1.5 h, and then further stirred at room temperature for 1.5 h. Water was added and the products were extracted with dichloromethane. The extracts were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue (0.23 g) was chromatographed (SiO_2/CH_2Cl_2: hexane = 2:3→MeOH) to give **16** (21 mg, 9%), **17** (5 mg, 3%), **18** (11 mg, 7%) and **7** (18 mg, 8%). A mixture of **3** and **4** (42 mg, 3:4 = 31:69) was also obtained.

2,3-Diphenylfumalonitrile (16). Colourless crystals, Mp. 157–159°C (hexane) (lit Mp. 160–161°C) [18].

2-Phenylmaleonitrile (17). Colourless crystals, Mp. 37–43°C (lit Mp. 40.5–41°C) [18].

2-Phenylfumalonitrile (18). Colourless crystals, Mp. 86–91°C (hexane) (lit Mp. 87.5–88°C) [18].

Reaction with dimethyl acetylenedicarboxylate. To a mixture of **2b** (0.31 g, 1.0 mmol) and dimethyl acetylene-dicarboxylate (DMAD) (0.25 mL, 2.0 mmol) in DMF (2.0 mL) was added DBU (0.15 mL, 1.0 mmol) at –60°C, and the mixture was gradually warmed to room temperature in a period of 1.5 h, and then further stirred at room temperature for 1.5 h. Water was added and the products were extracted with dichloromethane. The extracts were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue (0.57 g) was chromatographed (SiO_2/CH_2Cl_2-EtOAc gradient and MeOH) to give **19** (75 mg, 29% yield, *E*/*Z* mixture = 3:1) and **7** (18 mg, 8% yield). DMAD was recovered (53 mg, recovery 19%).

Dimethyl 2-(phenylcyanamido)-2-butenedicarboxylate (19). Pale yellow crystals; Mp. 77–85.5°C (CH_2Cl_2/hexane); ir (KBr, *E*/*Z* mixture): 2230, 1736, 1722, 1640, 1594, 1492, 1436, 1270, 1222, 1066, 1014, 894, 774, 760, 692/cm; ^{1}H NMR (200 MHz, deuteriochloroform, *E* isomer): δ 3.77 (s, 3H, Me), 3.81 (s, 3H, Me), 7.00 (s, 1H, =C*H*CO_2Me), 7.06–7.11 (m, 2H, *o*-Ph), 7.16–7.23 (m, 1H, *p*-Ph), 7.34–7.42 (m, 2H, *m*-Ph); ^{13}C NMR (50 MHz, $CDCl_3$, *E* isomer): δ 52.7 (Me), 53.6 (Me), 117.4 (*o*-Ph), 125.5, 126.1 (C=*C*HCO_2Me, *p*-Ph), 129.7 (*m*-Ph), 136.3, 139.0 (*C*=CH, *i*-Ph), 162.2 (*C*O_2Me), 162.5 (*C*O_2Me); uv/vis (MeCN, *E* isomer): λ_{max} (log ε) = 317.0 (3.37), 227 nm (4.23); ms (EI, 70 eV, *E*/*Z* mixture): *m*/*z* (%): 261 (M^++1, 18), 260 (M^+, 100), 245 (25), 229 (37), 201 (61), 200 (33), 169 (27), 157 (52), 142 (28), 115 (30). *Anal.* Calcd. for $C_{13}H_{12}N_2O_4$ (288.27): C, 59.99; H, 4.65; N, 10.77. Found C, 60.30; H, 4.70; N, 10.88.

Reaction of tetrazolium salt 2b with bis(1,5-cyclooctadiene)-μ,μ′-dichlorodirhodium (20). Typical procedure (Table 2, entry 1): A mixture of **2b** (0.16 g, 0.50 mmol) and bis (1,5-cyclooctadiene)-μ,μ′-dichlorodirhodium (**20**) (0.13 g, 0.25 mmol) in dry DMF (10 mL) was cooled to –60°C. DBU (75 μL, 0.5 mmol) was added and the mixture was stirred at −60°C for 3 h. Cold water was added and the precipitated solid (0.13 g) was filtered. The filtrate was extracted with CH_2Cl_2, washed with water, and dried (Na_2SO_4). The solvent was evaporated and the residue (90 mg) was chromatographed (SiO_2/CH_2Cl_2→ MeOH) to give bis(1,5-cyclooctadiene)-μ,μ′-dichlorodirhodium (16 mg, 12% recovery), **21** (29 mg, 12%), and **22** (16 mg). The precipitated solid was purified by column chromatography (SiO_2/CH_2Cl_2→MeOH) to give **22** (43 mg). The total yield of **22** is 59 mg (31%). Other reactions were conducted similarly, and the results are summarized in Table 2.

Complex 21. Yellow crystals, Mp. 165°C (EtOH); ir (KBr): 2940, 2860, 1488, 1362, 1230, 1140, 1014, 762, 680/cm; ^{1}H NMR (200 MHz, deuteriochloroform): δ 1.86–1.95 (m, 4H, cod-CH_2), 2.32–2.37 (m, 4H, cod-CH_2), 3.35 (s, 2H, cod-CH), 5.17 (s, 2H, cod-CH), 7.59–7.67 (m, 6H, Ph), 8.21–8.26 (m, 2H, Ph), 8.74–8.78 (m, 2H, Ph); ^{13}C NMR (50 MHz, deuteriochloroform): δ 29.0, 32.7 (cod-CH_2), 69.7 (d, *J* (^{103}Rh-^{13}C) = 14.3 Hz, cod-CH), 98.7 (d, *J* (^{103}Rh-^{13}C) = 7.2 Hz, cod-CH), 120.6, 123.9 (*o*-Ph), 128.9, 129.7 (*m*-Ph), 130.2, 131.6 (*p*-Ph), 135.0, 135.9 (*i*-Ph), 187.7 (d, *J* (^{103}Rh-^{13}C) = 51.6 Hz, Rh-C); uv/vis (MeCN): λ_{max} (log ε) = 280.5 (3.20), 384.0 nm (2.23). *Anal.* Calcd. for $C_{21}H_{22}ClN_4Rh$ (468.77): C 53.80, H 4.69, N 11.95; found C 53.70, H 4.60, N 11.90.

Complex 22. Yellow crystals, Mp. 152–154°C (EtOH); ir (KBr): 1590, 1492, 1468, 1358, 1310, 1230, 1124, 1096, 1038, 1010, 766, 684/cm; ^{1}H NMR (200 MHz, deuteriochloroform): δ 2.22–2.44 (m, 8H, cod-CH_2), 4.65 (s, 4H, cod-CH), 7.51–7.63 (m, 12H, Ph), 7.96–8.01 (m, 4H, Ph), 8.40–8.45 (m, 4H, Ph). ^{13}C NMR (50 MHz, deuteriochloroform): δ 31.1 (cod-CH_2), 90.7 (d, *J* (^{103}Rh-^{13}C) = 8.0 Hz, cod-CH), 120.6, 123.6 (*o*-Ph), 129.3, 129.9 (*m*-Ph), 130.8, 132.0 (*p*-Ph), 134.7, 135.2 (*i*-Ph), 185.3 (d, *J* (^{103}Rh-^{13}C) = 54.8 Hz, Rh-C); uv/vis (MeCN): λ_{max} (log ε) = 282.0 (3.37), 409.5 nm (2.21). *Anal.* Calcd. for $C_{34}H_{32}BF_4N_8Rh$ (742.01): C, 55.03; H, 4.31; N, 15.09. Found C, 54.86; H, 4.26; N, 14.96.

Reaction of tetrazolium salt 2b with complex 21. A mixture of **2b** (22 mg, 0.070 mmol) and **21** (33 mg, 0.070 mmol) in dry DMF (1 mL) was cooled to –60°C. DBU (11 μL, 0.07 mmol) was added and the mixture was stirred at –60°C for 4 h. Cold water was added and the precipitated solid (0.16 g) was filtered. The product was purified by column chromatography (SiO_2/CH_2Cl_2) to give **22** (23 mg, 44%). A small amount of complex **21** was recovered (11 mg, 33%).

Reaction of ethynylbenzene and benzoyl chloride catalyzed by 21 or 22. A mixture of ethynylbenzene (0.33 mL, 3.0 mmol), benzoyl chloride (0.23 mL, 2.0 mmol), triphenylphosphine (5.2 mg, 0.020 mmol), and **21** (9.4 mg, 0.020 mmol) in octane (5 mL) was heated overnight at 140°C. 2-Methylnaphthalene (20 mg) was added as an internal standard, and the reaction mixture was analyzed by glc. The yield of the product (**23**) was estimated to be 61%. The mixture was chromatographed (SiO_2/hexane) and **23** was isolated (0.18 g, 43%). The reaction with **22** was similarly carried out and the yield of **23** was 22% (glc).

X-ray crystallography. X-ray analysis of **9** was performed on a sample recrystallized from CH_2Cl_2/hexane. Complex **21** was recrystallized from ethanol, and **22** from a mixture of CH_2Cl_2:EtOAc:hexane = 1:9:1.

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1,2,3,9-Tetrahydro-4*H*-carbazol-4-one and 8,9-Dihydropyrido-[1,2-*a*]indol-6(7*H*)-one from 1*H*-Indole-2-butanoic Acid

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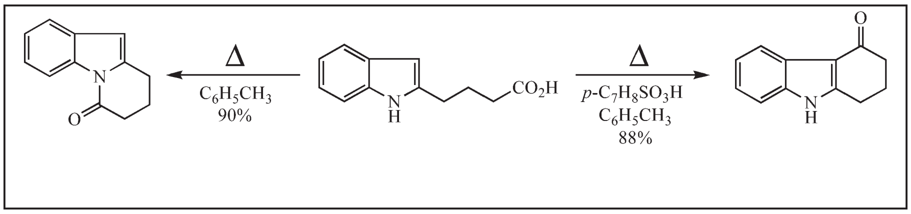

Efficient syntheses of the title ring systems have been developed from 1*H*-indole-2-butanoic acid, which was easily prepared from 2-fluoro-1-nitrobenzene in four steps. Heating 1*H*-indole-2-butanoic acid in toluene containing *p*-toluenesulfonic acid at 110°C furnished 1,2,3,9-tetrahydro-4*H*-carbazol-4-one in 88% yield. Heating this same acid in toluene with no added acid gave 8,9-dihydropyrido[1,2-*a*]-indol-6(7*H*)-one in 90% yield. The tetrahydro-4*H*-carbazol-4-one was also prepared directly in 92% yield from methyl 6-(2-nitrophenyl)-5-oxohexanoate by a tandem reduction—cycloaromatization—acylation reaction with iron in concentrated hydrochloric acid at 110°C. Application of this approach to the closure of five- and seven-membered rings was also successful.

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INTRODUCTION

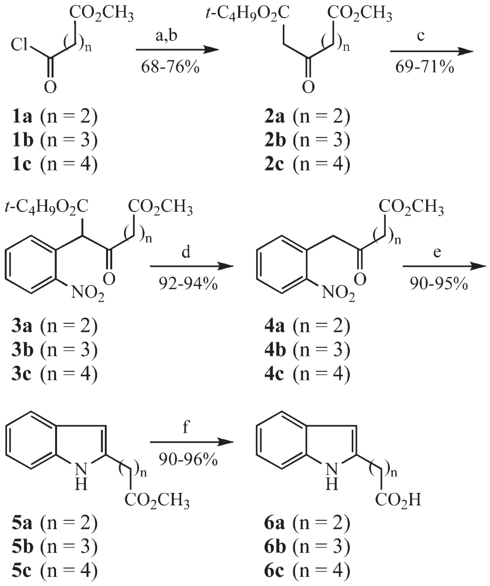
Earlier studies from this laboratory [1] and by others [2] described the synthesis of substituted indoles from 2-nitrobenzyl ketones based on a tandem reduction—cycloaromatization reaction. Our recent work has sought to assemble more complex structures using this strategy. In this study, we have developed a route to synthesize 1,2,3,9-tetrahydro-4*H*-carbazol-4-one and 8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one from 1*H*-indole-2-butanoic acid. In the course of this study, we also discovered that the tetrahydro-4*H*-carbazol-4-one could be prepared from methyl 6-(2-nitrophenyl)-5-oxohexanoate in one step by a tandem reduction—cycloaromatization—acylation sequence. Tetrahydro-4*H*-carbazol-4-one is an important building block for the synthesis of alkaloids [3] as well as the core ring structure in current drugs used for the treatment of cancer [4], HIV [5], congestive heart failure [6], and emesis resulting from chemotherapy [7]; 8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-ones have been studied for the treatment of ischemic disorders [8] and vomiting caused by cancer treatment [9].

Several other approaches have been reported for the tetrahydro-4*H*-carbazol-4-one system. The Fischer indole synthesis between phenylhydrazine and 1,3-cyclohexanedione is the simplest, but only provides a 50% yield [10]. Other routes include C4 oxidation of tetrahydrocarbazole [11]; base-promoted cyclization of 2-(2-trifluoroacetamidophenyl)-2-cyclohexen-1-one [12]; copper(I)-mediated [13] or photochemical [14] arylation of *N*-substituted enaminones; and a number of palladium-catalyzed coupling reactions [15]. Our synthesis requires several steps, but permits the preparation of two pharmacologically valuable compounds without excessively hazardous reagents or expensive catalysts. We have also found that other saturated ring homologues of the title compounds are available using this strategy.

RESULTS AND DISCUSSION

Our cyclization studies required access to a series of 1*H*-indole-2-alkanecarboxylic acids. To this end, a synthesis of these precursors was devised and carried out from Meldrum's acid [16] and commercially available (ω-chlorocarbonyl)alkanoic esters **1a–c** (Scheme 1). Acylation of Meldrum's acid with **1a–c** in the presence of pyridine followed by refluxing in *tert*-butyl alcohol gave the *tert*-butyl methyl 3-oxoalkanedicarboxylic esters **2a-c** in 68–76% yields [17]. Deprotonation of **2a–c** with sodium hydride in anhydrous *N*,*N*-dimethylformamide and reaction with 2-fluoro-1-nitrobenzene at 55–60°C afforded the nucleophilic aromatic substitution products **3a–c** in yields ranging from 69 to 71% [1,2]. Subsequent exposure of **3a–c** to trifluoroacetic acid in the presence of triethylsilane [18] resulted in *tert*-butyl ester cleavage and decarboxylation to provide nitro ketoesters **4a–c** in 92–94% yields. Treatment of **4a-c** with iron powder in acetic acid then initiated a tandem reduction—cycloaromatization reaction to furnish 1*H*-indole-2-alkanecarboxylic esters **5a–c** in 90–95% yields [1]. Finally, basic hydrolysis of **5a–c** provided acids **6a–c** in 90–96% yields.

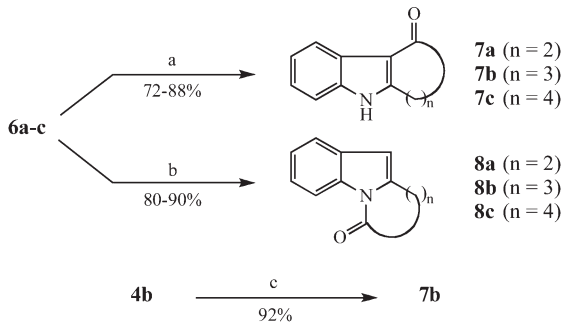
Scheme 1 [a]



[a] Key: (a) Meldrum's acid, pyridine, CH_2Cl_2, 0–22°C; (b) t-C_4H_9OH, reflux; (c) NaH, dimethylformamide; 2-fluoro-1-nitrobenzene, 55–60 °C, 48 h; (d) CF_3CO_2H, $(C_2H_5)_3SiH$, CH_2Cl_2, 22°C, 1 h; (e) Fe (>100 mesh), CH_3CO_2H, 115°C, 30 min; (f) 1*M* aqueous NaOH, dioxane, 22°C, 1 h.

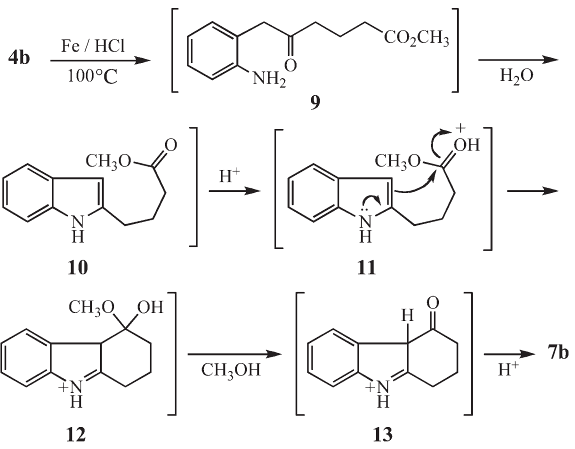
The results of our cyclization studies are summarized in Scheme 2. Treatment of **6a–c** with 2.0–6.0 equivalents of *p*-toluenesulfonic acid in refluxing toluene resulted in a Friedel-Crafts-like ring closure of the acid to C3 of the indole moiety to yield **7a–c** in 72–88% yields. Refluxing **6b** in toluene without the added *p*-toluenesulfonic acid resulted in closure to lactam **8b** (90%); acids **6a** and **6c** did not cyclize under these conditions reflecting stereoelectronic problems in closing the five- and seven-membered rings. Lactamization of **6a** and **6c** was possible in ≥80% yields, however, using *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride [19] in the presence of 1.6 equivalents of 4-(dimethylamino)pyridine [20]. Numerous other ring-closing regimes [21] failed to give the desired lactams. This seems to be the first report describing the use of *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide with 4-(dimethylamino)pyridine for lactam closures. The function of the base in this reaction is two-fold, neutralizing the hydrochloride salt of the carbodiimide and scavenging a proton from the cyclized amide.

Scheme 2 [a]



[a] Key: (a) p-$C_7H_8SO_3H$, $PhCH_3$, 110°C; (b) for **6a** and **6c**, *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride, 4-(dimethylamino)pyridine, CH_2Cl_2, 22°C; for **6b**, $PhCH_3$, 110°C; (c) Fe (>100 mesh), concentrated HCl, 110°C, 20 min.

Scheme 3



Remarkably, it was found that treatment of **4b** with iron in concentrated hydrochloric acid yielded **7b** in 92% yield by a tandem process involving a reduction—cycloaromatization—acylation sequence. Attempts to cyclize **6a** and **6c** under the same conditions afforded significantly lower yields and the product mixtures were more complex. The one-step conversion of **4b** to **7b** represents a new tandem reaction sequence.

Mechanistically, reduction of the aromatic nitro group is followed by cycloaromatization to the indole system as previously observed [1,2]. Under strong acid conditions, however, the methyl ester is cyclized onto the C3 position of indole. This most likely occurs by protonation of the ester carbonyl, addition of the electron-rich indole double bond to the carbonyl carbon, loss of methanol and rearomatization (Scheme 3). The closure of acids **6a** and **6c**–**7a** and **7c** should be analogous to the conversion of **10** to **7b** with loss of water in the penultimate step. Finally, the lactamization reactions proceed *via* the expected cyclocondensation mechanisms, with and without added carbodiimide.

CONCLUSION

We have developed a new approach to the synthesis of the title compounds using 1*H*-indole-2-butanoic acid (**6b**) as a common intermediate. Heating this acid in refluxing toluene containing *p*-toluenesulfonic acid affords 1,2,3,9-tetrahydro-4*H*-carbazol-4-one (**7b**), while heating in toluene with no added acid yields 8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one (**8b**). A high yield of **7b** can also be achieved directly from **4b** *via* a tandem reduction—cycloaromatization—acylation reaction promoted by iron in concentrated hydrochloric acid. Homologues **7a** and **7c** can also be prepared by heating **6a** and **6c** in toluene with *p*-toluenesulfonic acid, but direct conversion from **4a** and **4c** with iron in concentrated hydrochloric acid was unsuccessful. Lactamization of **6a** and **6c** requires treatment with *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride in the presence of excess 4-(dimethylamino)pyridine. The synthesis requires several steps, but provides a number of pharmacologically useful compounds in high yield without excessively hazardous or expensive reagents.

EXPERIMENTAL

The commercial acid chlorides were used as received. *N*,*N*-Dimethylformamide, from a freshly opened bottle, was dried over 4 Å molecular sieves under nitrogen and transferred by syringe into reactions where it was used. The hydrochloric acid (1*M*, 2*M*, and 6*M*), sodium hydroxide (1*M*), ammonium chloride (saturated), sodium bicarbonate (saturated), and sodium chloride (saturated) employed in various procedures refer to aqueous solutions. All reactions were run under N_2 in oven-dried glassware. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech 21521). Preparative separations were performed using flash column chromatography [22] on silica gel (grade 62, 60–200 mesh) mixed with ultraviolet-active phosphor (Sorbent Technologies UV-5) or thin layer chromatography on 20 cm x 20 cm silica gel GF plates (Analtech 02015). Band elution, for both methods, was monitored using a hand-held ultraviolet lamp. Hexanes used in chromatography had a boiling range of 65–70°C. Melting points were uncorrected. Infrared spectra were run as thin films on sodium chloride disks and were referenced to polystyrene. Unless otherwise indicated, ^{1}H and ^{13}C nuclear magnetic resonance spectra were measured in chloroform-d_1 at 300 MHz and 75 MHz, respectively, and were referenced to internal tetramethylsilane; coupling constants (*J*) are reported in Hertz. Low-resolution mass spectra (electron impact/direct probe) were run at 70 electron volts.

Representative procedure for the preparation of *tert*-butyl methyl 3-oxoalkanedicarboxylic esters: *tert*-butyl methyl 3-oxohexanedioate (2a). The procedure of Yonemitsu and coworkers was used [18]. To a stirred solution of 7.00 g (48.6 mmoles) of Meldrum's acid and 7.68 g (97.2 mmoles) of pyridine in 50 mL of dichloromethane at 0°C was added a solution of 7.68 g (51.0 mmoles) of **1a** in 10 mL of dichloromethane. Stirring was continued at 0°C for 30 min and at 22°C for 1 h. The crude reaction mixture was washed with 2*M* hydrochloric acid (three times) to remove the excess pyridine and the solution was dried (magnesium sulfate) and concentrated under vacuum. The resulting oil was dissolved in 50 mL of *tert*-butyl alcohol and refluxed for 3 h. The crude reaction mixture was cooled, concentrated under vacuum and distilled under high vacuum to give 8.20 g (73%) of keto diester **2a** containing some enol as a colorless oil, bp 85–110°C (0.5 mmHg). IR: 1737, 1717 cm^{-1}; ^{1}H NMR: δ 3.68 (s, 3H), 3.41 (s, 2H), 2.87 (t, 2H, *J* = 6.6), 2.62 (t, 2H, *J* = 6.6), 1.47 (s, 9H); ^{13}C NMR: δ 201.4, 172.8, 166.2, 81.9, 51.7, 50.4, 37.2, 27.8 (3C), 27.5.

***tert*-Butyl methyl 3-oxoheptanedioate (2b).** This compound (9.00 g, 76% containing some enol) was isolated as a colorless oil, bp 110–130°C (0.5 mmHg). IR: 1738, 1716 cm^{-1}; ^{1}H NMR: δ 3.67 (s, 3H), 3.35 (s, 2H), 2.62 (t, 2H, *J* = 7.0), 2.36 (t, 2H, *J* = 7.2), 1.92 (quintet, 2H, *J* = 7.1), 1.47 (s, 9H); ^{13}C NMR: δ 202.5, 173.5, 166.4, 82.0, 51.5, 50.5, 41.6, 32.7, 27.9 (3C), 18.5.

***tert*-Butyl methyl 3-oxooctanedioate (2c).** This compound (8.50 g, 68% containing some enol) was isolated as a colorless oil, bp 125–140°C (0.5 mmHg). IR: 1735, 1716 cm^{-1}; ^{1}H NMR: δ 3.67 (s, 3H), 3.35 (s, 2H), 2.56 (distorted t, 2H, *J* = 6.7), 2.33 (distorted t, 2H, *J* = 6.7), 1.63 (m, 4H), 1.47 (s, 9H); ^{13}C NMR: δ 202.8, 173.7, 166.4, 81.9, 51.5, 50.5, 42.3, 33.7, 27.9 (3C), 24.2, 22.7.

Representative procedure for nucleophilic aromatic substitution: *tert*-butyl methyl 2-(2-nitrophenyl)-3-oxohexanedioate (3a). A modification of the procedure described by Bunce *et al.* was used [1]. To a suspension of 1.36 g (56.7 mmoles) of oil-free sodium hydride in 20 mL of dry *N*,*N*-dimethylformamide was added 4.00 g (28.4 mmoles) of 2-fluoro-1-nitrobenzene in 25 mL of dimethylformamide. Stirring was initiated and a solution of 6.35 g (29.7 mmoles) of **2a** in 5 mL of dimethylformamide was added. The reaction mixture was heated to 55–60°C and stirred for 48 h, then cooled, added to 50 mL of saturated ammonium chloride and extracted with ether (three times). The combined organic extracts were washed with saturated sodium chloride (one time), dried (magnesium sulfate) and concentrated under vacuum. The crude product was purified by flash chromatography on a 50 cm × 2 cm silica gel column using 10% ether in hexanes to give 6.65 g (69%) of keto diester **3a** containing some enol as a yellow oil. IR: 1736, 1640, 1613, 1520, 1351 cm^{-1}; ^{1}H NMR: δ 7.98 (dd, 1H, *J* = 8.0, 1.2), 7.58 (td, 1H, *J* = 7.6, 1.4), 7.46 (td, 1H, *J* = 7.9, 1.6), 7.33 (dd, 1H, *J* = 7.6, 1.4), 5.28 (s, 1H), 3.64 (s, 3H), 2.50 (m, 4H), 1.32 (s, 9H); ^{13}C NMR: δ 200.4, 172.7, 170.6, 149.7, 133.7, 132.6, 130.1, 128.3, 124.5, 82.6, 61.3, 51.7, 37.4, 29.8, 27.8 (3C).

***tert*-Butyl methyl 2-(2-nitrophenyl)-3-oxoheptanedioate (3b).** This compound (6.00 g, 69% containing some enol) was isolated as a yellow oil. IR: 1738, 1645, 1526, 1394, 1352 cm^{-1}; ^{1}H NMR: δ 7.98 (dd, 1H, *J* = 8.0, 1.2), 7.57 (td, 1H, *J* = 7.6, 1.4), 7.45 (td, 1H, *J* = 7.9, 1.4), 7.25 (dd, 1H, *J* = 7.6, 1.4), 5.25 (s, 1H), 3.57 (s, 3H), 2.25 (m, 4H), 1.88 (m, 2H), 1.33 (s, 9H); ^{13}C NMR: δ 200.8, 172.7, 170.7, 149.7, 133.7, 132.8, 130.1, 128.4, 124.3, 82.6, 61.3, 51.8, 37.4, 29.9, 28.0, 27.8 (3C).

***tert*-Butyl methyl 2-(2-nitrophenyl)-3-oxooctanedioate (3c).** This compound (4.20 g, 71% containing some enol) was isolated as a yellow oil. IR: 1735, 1643, 1615, 1524, 1352 cm^{-1}; ^{1}H NMR: δ 7.98 (dd, 1H, *J* = 8.0, 1.3), 7.56 (td, 1H, *J* = 7.5, 1.4), 7.45 (td, 1H, *J* = 7.9, 1.6). 7.25 (dd, 1H, *J* = 7.7. 1.4), 5.26 (s, 1H), 3.63 (s, 3H), 2.21 (m, 2H), 2,12 (m, 2H), 1.57 (m, 4H), 1.24 (s, 9H); ^{13}C NMR: δ 201.8, 173.7, 170.7, 149.7, 133.7, 132.5, 130.5, 128.8, 124.3, 82.4, 61.0, 51.5, 33.6, 32.5, 27.8 (3C), 25.7, 24.3.

Representative procedure for *tert*-butyl ester cleavage and decarboxylation: methyl 5-(2-nitrophenyl)-4-oxopentanoate (4a). The procedure of Mehta *et al.* [17] was used. To a solution of 5.20 g (14.8 mmoles) of **3a** in 50 mL of dichloromethane were added 27.6 g (18.0 mL, 242 mmoles) of trifluoroacetic acid and 4.88 g (6.70 mL, 42.0 mmoles) of triethylsilane. The mixture was stirred at 22°C for 1 h and then concentrated under vacuum to give 3.50 g (94%) of **4a** as a light yellow oil, which was used without further purification. IR: 1735, 1722, 1525, 1351 cm^{-1}; ^{1}H NMR: δ 8.11 (dd, 1H, *J* = 8.0, 1.1), 7.60 (td, 1H, *J* = 7.7, 1.3), 7.46 (td, 1H, *J* = 7.9, 1.5), 7.31 (dd, 1H, *J* = 7.7, 1.1), 4.16 (s, 2H), 3.67 (s, 3H), 2.93 (t, 2H, *J* = 6.5), 2.65 (t, 2H, *J* = 6.5); ^{13}C NMR: δ 204.0, 173.1, 148.5, 133.7, 133.6, 130.1, 128.5, 125.2, 51.8, 47.8, 37.1, 27.8; ms: *m/z* 251 (M^{+}). *Anal.* Calcd. for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.18; N, 5.58. Found: C, 57.41; H, 5.21; N, 5.53.

Methyl 6-(2-nitrophenyl)-5-oxohexanoate (4b). This compound (3.46 g, 92%) was isolated as a light yellow oil and used without further purification. IR: 1729, 1525, 1346 cm^{-1}; ^{1}H NMR: δ 8.11 (dd, 1H, *J* = 8.0, 1.1), 7.59 (td, 1H, *J* = 7.7, 1.5), 7.46 (td, 1H, *J* = 7.9, 1.5), 7.28 (dd, 1H, *J* = 7.7, 1.1), 4.09 (s, 2H), 3.68 (s, 3H), 2.70 (t, 2H, *J* = 7.1), 2.38 (t, 2H, *J* = 7.1), 1.96 (quintet, 2H, *J* = 7.1); ^{13}C NMR: δ 204.9, 173.6, 148.6, 133.6 (2C), 130.2, 128.4, 125.2, 51.6, 47.9, 41.4, 32.9, 18.7; ms: *m/z* 265 (M^{+}). *Anal.* Calcd. for $C_{13}H_{15}NO_5$: C, 58.87; H, 5.66; N, 5.28. Found: C, 59.00: H, 5.58; N, 5.23.

Methyl 7-(2-nitrophenyl)-6-oxoheptanoate (4c). This compound (1.45 g, 92%) was isolated as a light yellow oil and used without further purification. IR: 1727, 1528, 1352 cm^{-1}; ^{1}H NMR: δ 8.10 (dd, 1H, *J* = 8.2, 1.3), 7.59 (td, 1H, *J* = 7.5, 1.3), 7.46 (td, 1H, *J* = 8.1, 1.5), 7.27 (dd, 1H, *J* = 7.6, 1.1), 4.10 (s, 2H), 3.67 (s, 3H), 2.62 (distorted t, 2H, *J* = 6.8), 2.34 (distorted t, 2H, *J* = 6.8), 1.67 (m, 4H); ^{13}C NMR: δ 205.2, 173.8, 148.6, 133.5 (2C), 130.3, 128.3, 125.2, 51.5, 47.8, 42.2, 33.7, 24.3, 22.9; ms: *m/z* 279 (M^{+}). *Anal.* Calcd. for $C_{14}H_{17}NO_5$: C, 60.22; H, 6.09; N, 5.02. Found: C, 60.24; H, 6.10; N, 4.98.

Representative procedure for reductive cyclization to the 1*H*-indoles: methyl 1*H*-indole-2-propanoate (5a). The procedure of Bunce *et al*. [1] was used. A mixture of 1.50 g (5.98 mmoles) of **4a**, 25 mL of acetic acid and 2.00 g (35.9 mmoles, 6.0 eq) of iron powder (>100 mesh) was heated with stirring at 115°C (oil bath) until thin layer chromatography indicated complete consumption of starting material (*ca* 30 min). The crude reaction was cooled, transferred to a separatory funnel containing 50 mL of water and extracted with ether (three times). The combined ether layers were washed with water (one time), saturated sodium bicarbonate (three times), saturated sodium chloride (one time), then dried (magnesium sulfate) and concentrated under vacuum to give a brown solid. Recrystallization from hexanes gave 1.10 g (91%) of **5a** as a tan solid, mp 97–98°C (lit [23] mp 97–98°C, hexane). IR: 3357, 1720 cm^{-1}; ^{1}H NMR: δ 8.47 (br s, 1H), 7.52 (dd, 1H, *J* = 7.9, 0.6), 7.31 (dq, 1H, *J* = 8.0, 0.9), 7.12 (td, 1H, *J* = 7.9, 1.3), 7.06 (td, 1H, *J* = 7.9, 1.1), 6.24 (dd, 1H, *J* = 2.0, 0.9), 3.72 (s, 3H), 3.08 (t, 2H, *J* = 6.7), 2.73 (t, 2H, *J* = 6.7); ^{13}C NMR: δ 174.3, 138.1, 136.0, 128.4, 121.3, 119.9, 119.6, 110.5, 99.8, 51.9, 33.9, 23.1; ms: *m/z* 203 (M^{+}). *Anal.* Calcd. for $C_{12}H_{13}NO_2$: C, 70.94; H, 6.40; N, 6.90. Found: C, 70.92; H, 6.39; N, 6.92.

Methyl 1*H*-indole-2-butanoate (5b). This compound (1.15 g, 95%) was isolated as a tan solid, mp 69–71°C. IR: 3392, 1718 cm^{-1}; ^{1}H NMR: 8.06 (br s, 1H), 7.52 (d, 1H, *J* = 7.6 Hz), 7.30 (d, 1H, *J* = 6.0 Hz), 7.08 (m, 2H), 6.25 (s, 1H), 3.66 (s, 3H), 2.81 (t, 2H, *J* = 7.2 Hz), 2.40 (t, 2H, *J* = 7.2 Hz), 2.04 (m, 2H); ^{13}C NMR: δ 173.9, 138.4, 128.8, 121.1, 119.8, 119.6, 110.3, 100.0, 51.6, 33.1, 30.0, 27.3, 24.5; ms: *m/z* 217 (M^{+}). *Anal.* Calcd. for $C_{13}H_{15}NO_2$: C, 71.89; H, 6.91; N, 6.45. Found: C, 71.85; H, 6.92; N, 6.43.

Methyl 1*H*-indole-2-pentanoate (5c). This compound (1.10 g, 90%) was isolated as a tan solid, mp 121–124°C. IR: 3353, 1719 cm^{-1}; ^{1}H NMR: δ 7.98 (br s, 1H), 7.52 (d, 1H, *J* = 6.8 Hz), 7.28 (d, 1H, *J* = 8.0 Hz), 7.08 (m, 2H), 6.24 (s, 1H), 3.67 (s, 3H), 2.76 (t, 2H, *J* = 7.2 Hz), 2.37 (t, 2H, *J* = 3.6 Hz), 1.76 (m, 4H); ^{13}C NMR: δ 174.2, 139.3, 136.0, 128.9, 121.2, 119.6, 119.8, 110.5, 99.8, 51.7, 33.9, 28.7, 28.0, 24.6; ms: *m/z* 231 (M^{+}). *Anal.* Calcd. for $C_{14}H_{17}NO_2$: C, 72.73; H, 7.36; N, 6.06. Found: C, 72.70; H, 7.33; N, 6.10.

Representative procedure for the ester hydrolysis: 1*H*-indole-2-propanoic acid (6a). A mixture of 1.00 g (4.93 mmoles) of **5a** in 20 mL of dioxane and 15 mL of 1*M* sodium hydroxide was stirred at 22°C for 1 h. The solution was concentrated to one-half volume under vacuum, acidified with 3*M* hydrochloric acid and extracted with ether (three times). The combined ether layers were washed with saturated sodium chloride (one time), then dried (magnesium sulfate) and concentrated under vacuum. The crude product was purified by flash chromatography on a 15 cm × 2 cm silica gel column using 50% ether in hexanes to give 0.85 g (91%) of **6a** as a white solid, mp 165–167°C (lit [24] mp 167°C). IR: 3462–2300, 3392, 1701 cm^{-1}; ^{1}H NMR: δ 9.87 (br s, 1H), 8.26 (br s, 1H), 7.52 (dd, 1H, *J* = 7.7, 0.7), 7.30 (dd, 1H, *J* = 8.0, 0.9), 7.13 (td, 1H, *J* = 7.7, 1.3), 7.07 (td, 1H, *J* = 7.9, 1.1), 6.26 (dd, 1H, *J* = 1.9, 0.8), 3.08 (t, 2H, *J* = 6.8), 2.81 (t, 2H, *J* = 6.8); ^{13}C NMR: δ 178.4, 137.6, 135.5, 128.4, 121.4, 119.9, 119.7, 110.5, 99.9, 33.6, 22.9; ms: *m/z* 189 (M^{+}). *Anal.* Calcd. for $C_{11}H_{11}NO_2$: C, 69.84; H, 5.82; N, 7.41. Found: C, 69.88; H, 5.85; N, 7.37.

1*H*-Indole-2-butanoic acid (6b). This compound (0.33 g, 90%) was isolated as a white solid, mp 114–115°C. IR: 3252–2348, 3386, 1700 cm^{-1}; ^{1}H NMR: 10.85 (br s, 1H), 7.95 (br s, 1H), 7.52 (dd, 1H, *J* = 7.7, 0.7), 7.29 (dd, 1H, *J* = 8.0, 0.9), 7.12 (td, 1H, 7.9, 1.3), 7.07 (td, 1H, *J* = 7.7, 1.1), 6.27 (dd, 1H, *J* = 2.0, 0.8), 2.83 (t, 2H, *J* = 7.3), 2.45 (t, 2H, *J* = 7.3), 2.06 (quintet, 2H, *J* = 7.3); ^{13}C NMR: δ 179.2, 138.1, 135.9, 128.7, 121.2, 119.9, 119.7, 110.4, 100.1, 33.0, 27.3, 24.2; ms: *m/z* 203 (M^{+}). *Anal.* Calcd. for $C_{12}H_{13}NO_2$: C, 70.94; H, 6.40; N, 6.90. Found: C, 70.98; H, 6.41; N, 6.85.

1*H*-Indole-2-pentanoic acid (6c).. This compound (0.90 g, 96%) was isolated as a white solid, mp 145–147°C. IR: 3425–2350, 3384, 1700 cm^{-1}; ^{1}H NMR: δ 10.50 (s, 1H), 7.92 (br s, 1H), 7.52 (d, 1H, *J* = 6.8 Hz), 7.30 (d, 1H, *J* = 8.0 Hz), 7.10 (m, 2H), 6.24 (s, 1H), 2.80 (t, 2H, *J* = 6.8 Hz), 2.42 (t, 2H, *J* = 7.2 Hz), 1.76 (m, 4H); ^{13}C NMR: δ 178.4, 138.9, 135.7, 128.7, 121.0, 119.7, 119.6, 110.2, 99.7, 33.4, 28.4, 27.8, 24.1; ms: *m/z* 217 (M^{+}). *Anal.* Calcd. for $C_{13}H_{15}NO_2$: C, 71.89; H, 6.91; N, 6.45. Found: C, 71.88; H, 6.86; N, 6.47.

Representative procedure for indole acylation: 3,4-dihydrocyclopent[*b*]indol-1(2*H*)-one (7a). A solution of 200 mg (1.06 mmoles) of **6a** in 10 mL of toluene was heated to reflux and 200 mg of *p*-toluenesulfonic acid monohydrate was slowly added through the top of the condenser. After 1 h at reflux, a second 200-mg portion of *p*-toluenesulfonic acid (total 400 mg, 2.10 mmoles, 2.0 eq) was added and refluxing was continued for a total of 12 h. The resulting solution was cooled, added to water and extracted with ether. The ether layer was washed with saturated sodium bicarbonate (three times) and saturated sodium chloride (one time), then dried (magnesium sulfate) and concentrated under vacuum. The crude product was purified by flash chromatography on a 20 cm × 2 cm silica gel column using increasing concentrations of ether in hexanes to give 136 mg (75%) of **7a** as an off-white solid, mp 250–252°C (lit [11] mp 252–253°C). IR: 3371, 1648 cm^{-1}; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 12.0 (br s, 1H), 7.67 (d, 1H, *J* = 7.5), 7.45 (d, 1H, *J* = 8.0), 7.22 (td, 1H, *J* = 7.7, 1.3), 7.16 (td, 1H, *J* = 7.7, 1.3), 3.08 (m, 2H), 2.82 (m, 2H); ^{13}C NMR (dimethyl sulfoxide-d_6): δ 194.7, 167.7, 142.2, 129.8, 127.6, 122.9, 121.5, 119.4, 112.6, 40.6, 21.0; ms: *m*/*z* 171 (M$^+$). *Anal.* Calcd. for $C_{11}H_9NO$: C, 77.19; H, 5.26; N, 8.19. Found: C, 76.94; H, 5.20; N, 8.23.

1,2,3,9-Tetrahydro-4H-carbazol-4-one (7b). This compound was prepared from 150 mg (0.74 mmoles) of **6b** using a modified procedure. In this case, 844 mg (4.44 mmoles, 6.0 eq) of *p*-toluenesulfonic acid monohydrate was required and this was added in 2.0-eq portions at 1-h intervals during the first 3 h of the 12-h reflux period. Product **7b** (120 mg, 88%) was isolated as an off-white solid, mp 225–228°C (dec) (lit [11] mp 219–221°C). IR: 3368, 1588, 1566 cm^{-1}; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 11.7 (br s, 1H), 7.99 (d, 1H, *J* = 7.5), 7.46 (dd, 1H, *J* = 7.8, 1.1), 7.25 (td, 1H, *J* = 7.7, 1.2), 7.19 (td, 1H, *J* = 7.7, 1.2), 2.99 (t, 2H, *J* = 6.3), 2.42 (t, 2H, *J* = 6.4), 2.13 (quintet, 2H, *J* = 6.4); ^{13}C NMR (dimethyl sulfoxide-d_6): δ 192.1, 148.4, 134.1, 122.7, 122.2, 120.5, 120.2, 108.8, 106.5, 37.7, 22.9, 20.4; ms: *m*/*z* 185 (M$^+$). *Anal.* Calcd. for $C_{12}H_{11}NO$: C, 77.84; H, 5.95; N, 7.57. Found: C, 77.78; H, 5.94; N, 7.60.

6,7,8,9-Tetrahydrocyclohept[b]indol-10(5H)-one (7c). This compound was prepared as described for **7b** using 203 mg (0.93 mmoles) of **6c** to give 133 mg (72%) of **7c** as a tan solid, mp 217–218 °C (lit [11] mp 220–221°C). IR: 3365, 1718 cm^{-1}; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 11.7 (br s, 1H), 8.14 (dd, 1H, *J* = 7.4, 1.4), 7.34 (dd, 1H, *J* = 7.9, 1.3), 7.12 (m, 2H), 3.10 (t, 2H, *J* = 6.3), 2.64 (m, 2H), 1.93 (quintet, 2H, *J* = 6.4), 1.83 (m, 2H); ^{13}C NMR (dimethyl sulfoxide-d_6): δ 196.4, 149.0, 135.0, 127.3, 122.2, 121.2, 120.9, 113.7, 110.9, 42.7, 27.0, 24.3, 21.8; ms: *m*/*z* 199 (M$^+$). *Anal.* Calcd. for $C_{13}H_{13}NO$: C, 78.39; H, 6.53; N, 7.04. Found: C, 78.19; H, 6.48; N, 7.05.

Direct preparation of 7b from 4b. A 100-mL single-necked round-bottomed flask equipped with a reflux condenser (N_2 inlet) and a magnetic stir bar was charged with 200 mg (0.75 mmoles) of **4b** and 8 mL of concentrated hydrochloric acid. The mixture was heated to 80°C (oil bath) and 126 mg (2.25 mmoles, 3.0 eq) of iron powder (>100 mesh) was added (*Caution!* This addition is sufficiently exothermic to boil the mixture). The reaction is contained by using a large flask and immediately replacing the condenser after adding the iron). The reaction was refluxed at 110°C until thin layer chromatography indicated complete consumption of starting material (*ca* 20 min), then cooled, added to 15 mL of water and extracted with ether (three times). The combined ether layers were washed with saturated sodium chloride (one time), dried (magnesium sulfate) and concentrated under vacuum. The resulting solid was flash chromatographed on a 20 cm × 2 cm silica gel column eluted with increasing concentrations of ether in hexanes to give 128 mg (92%) of **7b**. The physical properties and spectral data matched those reported above.

Representative procedures for lactam formation: 1,2-dihydro-3*H*-pyrrolo[1,2-*a*]indol-3-one (8a). To a suspension of 100 mg (0.53 mmoles) of **6a** in 5 mL of dichloromethane was added 103 mg (0.85 mmoles, 1.6 eq) of 4-(dimethylamino)pyridine. The mixture was stirred for 10 min to give a clear light brown solution. To this solution was added 101 mg (0.53 mmoles) of *N*-(3-dimethylaminopropyl-*N*′-ethylcarbodiimide hydrochloride and the reaction mixture was stirred at 22°C for 24 h. The crude reaction mixture was washed with water, 1*M* hydrochloric acid, saturated sodium bicarbonate and saturated sodium chloride, then dried (magnesium sulfate) and concentrated under vacuum. The resulting oil was purified by preparative thin layer chromatography using 60% ether in hexanes to give 72 mg (80%) of the lactam as a white solid, mp 149–151°C (lit [25] mp 151–153°C). IR: 1731 cm^{-1}; ^{1}H NMR: δ 8.07 (m, 1H), 7.48 (m, 1H), 7.25 (m, 2H), 6.27 (s, 1H), 3.14 (A of ABm, 2H), 3.08 (B of ABm, 2H); ^{13}C NMR: δ 171.6, 143.6, 135.3, 130.4, 124.0, 123.2, 120.5, 113.5, 100.3, 34.9, 19.6; ms: *m*/*z* 171 (M$^+$). *Anal.* Calcd. for $C_{11}H_9NO$: C, 77.19; H, 5.26; N, 8.19. Found: C, 77.14; H, 5.24; N, 8.21.

8,9-Dihydropyrido[1,2-a]indol-6(7H)-one (8b). This compound was prepared by dissolving 100 mg (0.49 mmoles) of **6b** in 15 mL of dry toluene and refluxing for 36 h. The reaction mixture was cooled and the solvent was evaporated to dryness under vacuum. The crude product was purified by preparative thin layer chromatography using 50% ether in hexanes to give 82 mg (90%) of **8b** as a white solid, mp 78–79°C (lit [25] mp 79–81°C). IR: 1690, cm^{-1}; ^{1}H NMR: δ 8.44 (dd, 1H, *J* = 8.1, 0.9), 7.45 (dd, 1H, *J* = 6.8, 1.6), 7.25 (m, 2H), 6.31 (s, 1H), 2.97 (td, 2H, *J* = 6.8, 1.2), 2.78 (t, 2H, *J* = 6.4), 2.07 (quintet, 2H, *J* = 6.4); ^{13}C NMR: δ 169.4, 138.1, 134.8, 129.7, 124.0, 123.9, 119.6, 116.3, 104.8, 34.4, 23.8, 21.4; ms: *m*/*z* 185 (M$^+$). *Anal.* Calcd. for $C_{12}H_{11}NO$: C, 77.84; H, 5.95; N, 7.57. Found: C, 77.76; H, 5.93; N, 7.59.

7,8,9,10-Tetrahydro-6H-azepino[1,2-a]indol-6-one (8c). This compound was prepared as described for **8a** on an 80 mg (0.37 mmole) scale to give 60 mg (81%) of the lactam as a white solid, mp 172–175°C. IR: 1692 cm^{-1}; ^{1}H NMR: δ 8.42 (dm, 1H, *J* = 7.9), 7.46 (dm, 1H, *J* = 7.3), 7.32–7.20 (complex, 2H), 6.36 (s, 1H), 3.06 (t, 2H, *J* = 5.9), 2.94 (distorted t, 2H, *J* = 5.8), 1.94 (m, 4H); ^{13}C NMR: δ 173.8, 139.5, 136.9, 129.6, 124.1, 123.5, 119.5, 116.3, 107.9, 35.9, 25.8, 23.7, 20.8; ms: *m*/*z* 199 (M$^+$). *Anal.* Calcd. for $C_{13}H_{13}NO$: C, 78.39; H, 6.53; N, 7.04. Found: C, 78.35; H, 6.54; N, 7.06.

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A Novel Microwave-Assisted Green Synthesis of Condensed 2-Substituted-pyrimidin-4(3*H*)-ones Under Solvent-Free Conditions

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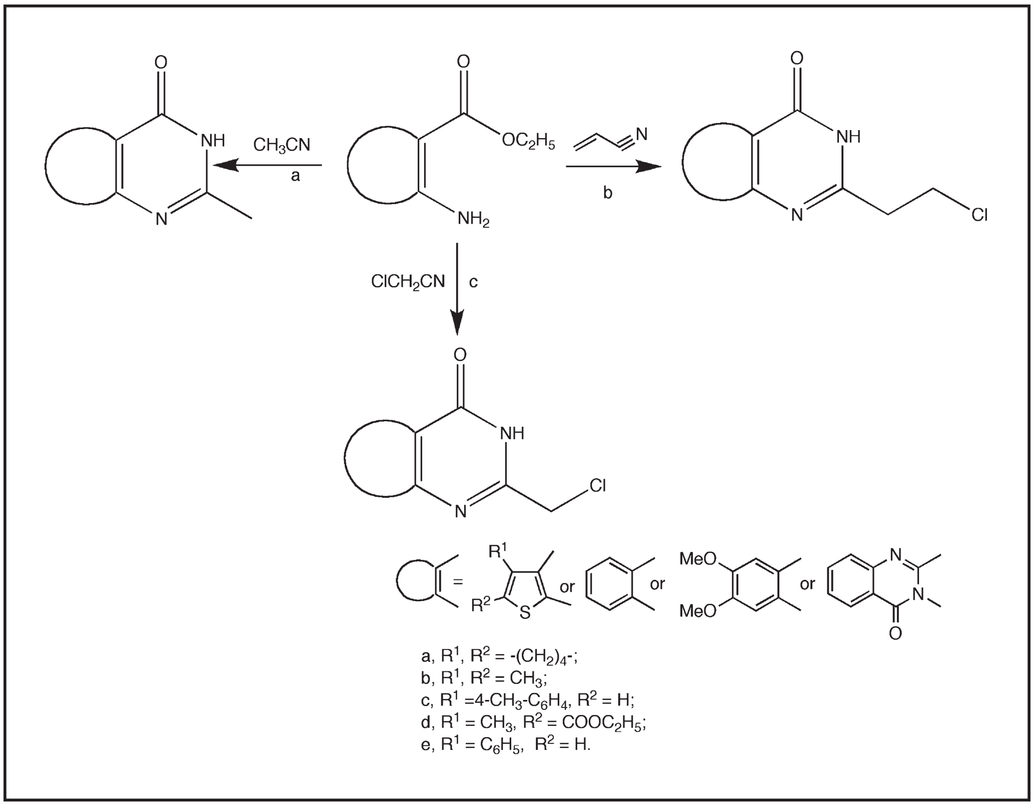

A rapid microwave-assisted green chemical synthesis of condensed 2-substituted-pyrimidin-4(3*H*)-ones **3, 4,** and **5** involving the condensation of a variety of nitriles with *o*-aminoesters of thiophene **2a–e**, benzene **2f**, dimethoxybenzene **2g** and quinazolinone **2h** in the presence of catalytic amount of HCl alone or with the Lewis acid $AlCl_3$ under solvent-free conditions, is described for the first time. This novel and clean one-pot methodology, which is characterized by very short reaction times and easy workup procedures, can be exploited to generate a diverse library of condensed pyrimidine heterocycles.

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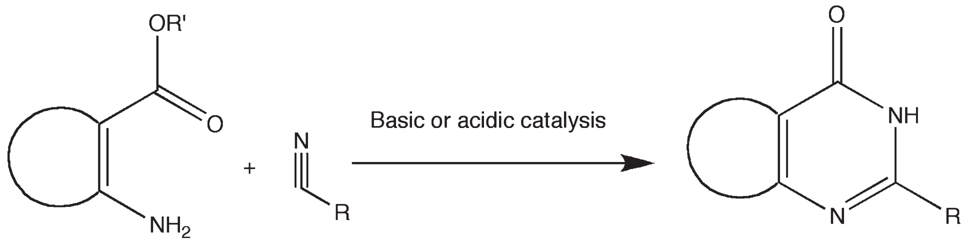
INTRODUCTION

Pyrimidines and condensed pyrimidines have a long and distinguished history of their numerous biological and medicinal applications [1]. The synthesis and biological evaluation [2] of potentially bioactive condensed pyrimidines, appropriately functionalized, especially at the 2- and 4-positions have attracted considerable attention of medicinal chemists worldwide. Therefore, the synthesis of condensed pyrimidines has been a very important process, subject to improvement, from time to time. The regularly employed synthetic methodologies involve annelation of the pyrimidine ring on an appropriately substituted carbocycle or heterocycle [3].

Of these the most popularly used synthetic methodology is the ‘‘Principal Pyrimidine Synthesis’’, which involves mainly the cyclocondensation of *o*-aminocarbonyl substrates with reagents like amidines, ureas, thiourea or imidates [3]. Alternatively use of nitriles as reagents for cyclocondensation with *o*-aminocarbonyl substrates is relatively less exploited and is reported under basic [4,5] as well as

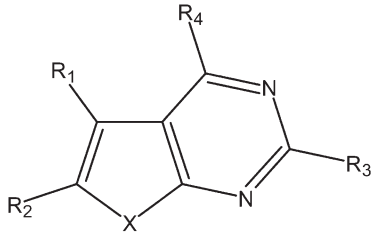
Scheme 1



acidic [6,7] conditions. The direct use of nitriles in these cyclocondensations is attractive as it offers more flexibility and generates a variety of 2-substituents in the resultant condensed pyrimidines. Nitriles often being the precursors for amidines are also more economical than the amidines (Scheme 1).

It would be very interesting to adopt this reaction for high throughput synthesis in order to generate diverse libraries of condensed pyrimidines of type **1** with four diverse points for further functionalization.

The direct use of the electrophilic properties of nitriles in such syntheses, though previously reported [8], has received only scant attention. Shishoo and coworkers [6,7,9–15] have exploited the reactions of a variety of nitriles with a host of *o*-aminocarbonyl substrates, under the influence of dry HCl gas under conventional conditions to obtain a wide range of 2-substituted-4-oxo/4-amino/4-chloro and 4-aryl condensed pyrimidines (Scheme 2). These reactions are known to proceed *via* the imidoyl halide intermediate, whose carbon is highly electrophilic. The cyclocondensation proceeds *via* the transient amidine intermediate. This interesting reaction has been developed as a synthetic method of general applicability to obtain a variety of condensed 2-substituted-4-functionalized pyrimidines. The reaction generally takes 8–12 h for completion and typically involves bubbling of dry HCl gas through the reaction mixture in dioxane (Scheme 2).



1

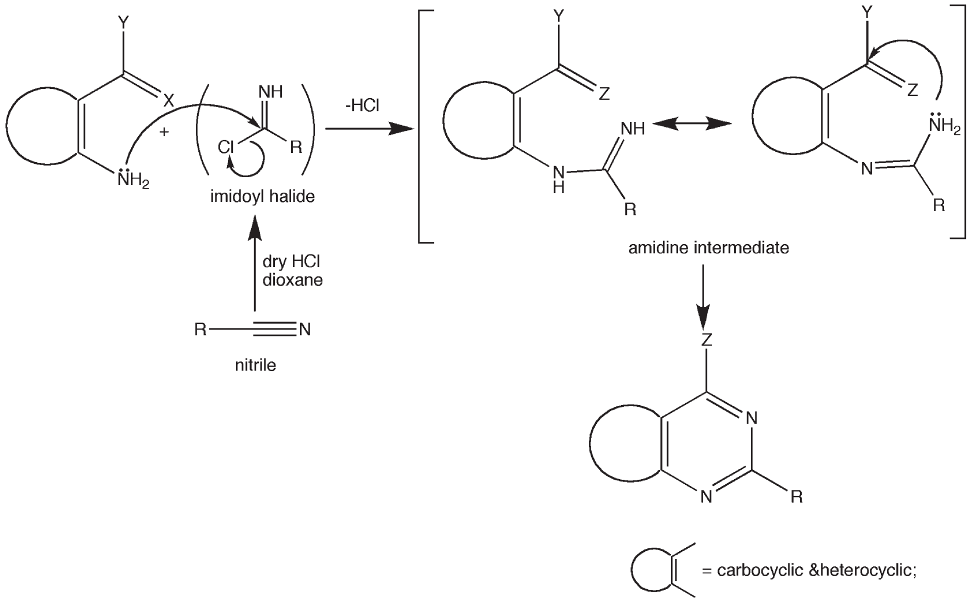
X = S, -CH=CH-, N, O, *etc*

R^1, R^2 = H, alkyl, aryl, cycloalkyl, carboalkoxy, carbocyclic, heterocyclic, *etc*

R^3 = alkyl, aryl, arylalkyl, heteroaryl, substituted amino, heteroalkyl,aryl, *etc*

R^4 = OH, alkyl, aryl, Cl, NH_2

Scheme 2

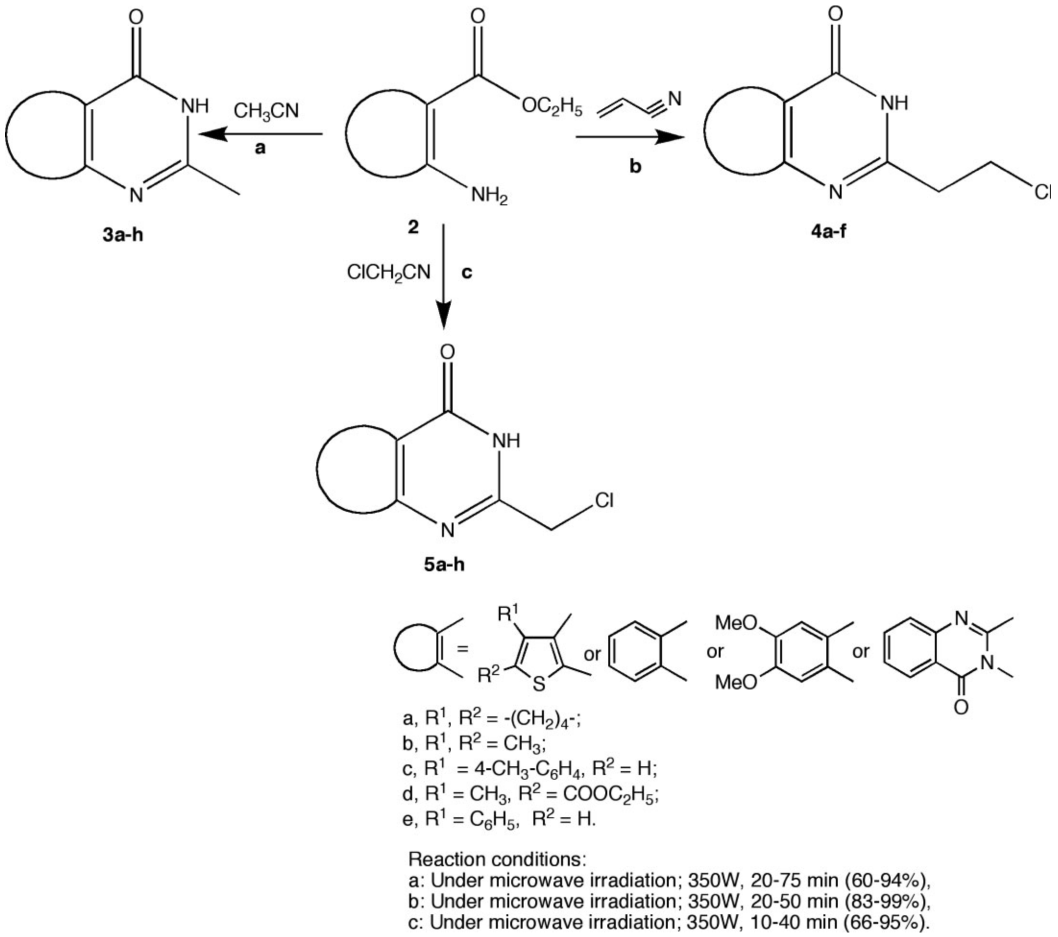


= carbocyclic &heterocyclic;

Z = OH, NH_2, Cl, aryl, alkyl

R = alkyl, aryl, aralkyl, heteroaryl, *etc.*

Scheme 3



a, R^1, R^2 = -$(CH_2)_4$-;
b, R^1, R^2 = CH_3;
c, R^1 = 4-CH_3-C_6H_4, R^2 = H;
d, R^1 = CH_3, R^2 = $COOC_2H_5$;
e, R^1 = C_6H_5, R^2 = H.

Reaction conditions:
a: Under microwave irradiation; 350W, 20-75 min (60-94%),
b: Under microwave irradiation; 350W, 20-50 min (83-99%),
c: Under microwave irradiation; 350W, 10-40 min (66-95%).

Reactions that are adaptable for high speed throughput syntheses have become an important component of the modern medicinal chemist's armory, as a great number of compounds can be produced through such rapid parallel synthetic programs [16]. Synthetic methods that enable the rapid production of an array of heterocycles, useful for the identification of new lead structures are of critical importance from the point of new drug discovery. Moreover, quinazolines, thienopyrimidines and other condensed pyrimidine scaffolds are important heterocyclic building blocks and have been shown to possess significant pharmacological activity against a variety of molecular targets [17].

Our encouraging results in the MWI-based syntheses of thiophene *o*-aminoesters involving Gewald reaction [18], as well as, thienopyrimidine bioisosteres of gefitinib [19] under microwave irradiation conditions, motivated us to assess whether the use of MWI could be extended to the single pot cyclocondensation of the nitriles with various *o*-aminoester substrates under solvent-free conditions for generating compound libraries of condensed pyrimidines of type **1**.

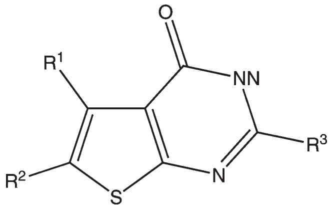
Herein, we report for the first time a rapid microwave-assisted green synthesis of condensed 2-substitutedpyrimidin-4(3*H*)-ones, **3**, **4**, and **5** involving the condensation of a variety of nitriles with *o*-aminoesters of thiophene **2a–e**, benzene **2f**, dimethoxybenzene **2g** and quinazolinone **2h** in the presence of catalytic amount of HCl alone or with the Lewis acid, $AlCl_3$ under solvent-free conditions (Scheme 3).

RESULTS AND DISCUSSION

We started the experiments using different nitriles such as acetonitrile, chloroacetonitrile and acrylonitrile. The conventional methods for the synthesis of the target condensed 2-substitutedpyrimidin-4(3*H*)-ones are through the cyclization of appropriate *o*-amino esters **2** with these nitriles under acidic conditions in the solvent, 1,4-dioxane at 0–5°C. This particular reaction requires

Table 1

Physical data of 2-substituted-thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **3a–e**, **4a–e**, and **5a–e**



				Conventional method			Microwave-assisted method		
	R^1	R^2	R^3	Yield (%)	mp (°C)	Time (h)	Yield (%)	mp (°C)	Time (min)
3a	$-CH_2)_4-$		$-CH_3$	66	300–302[a]	8–10	68	298	75
3b	$-CH_3$	$-CH_3$	$-CH_3$	76	286–288[b]	10–12	89	286	60
3c	4-$CH_3C_6H_4-$	$-H$	$-CH_3$	93	243–245	8–10	94	248	55
3d	$-CH_3$	$-COOC_2H_5$	$-CH_3$	71	260–262[c]	8–10	85	262	40
3e	$-C_6H_5$	$-H$	$-CH_3$	69	262–264[d]	8–10	75	264	65
4a	$-(CH_2)_4-$		$-CH_2CH_2Cl$	84	218–220	8–10	96[e]	218	45
4b	CH_3	$-CH_3$	$-CH_2CH_2Cl$	85	199–200	20–24	99	201	50
4c	4-$CH_3C_6H_4-$	$-H$	$-CH_2CH_2Cl$	91	167–168	10–12	92[e]	169	35
4d	$-CH_3$	$-COOC_2H_5$	$-CH_2CH_2Cl$	85	165–167	8–10	88	167	20
4e	$-C_6H_5$	$-H$	$-CH_2CH_2Cl$	94	267–268	8–10	96	267	45
5a	$-(CH_2)_4-$		$-CH_2Cl$	77	257–259[f]	6–8	90	258	30
5b	$-CH_3$	$-CH_3$	$-CH_2Cl$	83	246–247[g]	8–10	91	256	25
5c	4-$CH_3C_6H_4-$	$-H$	$-CH_2Cl$	88	246–248	6–8	93	249	40
5d	CH_3	$-COOC_2H_5$	$-CH_2Cl$	86	243–245[h]	6–8	95	225	10
5e	$-C_6H_5$	$-H$	$-CH_2Cl$	90	208–210[i]	6–8	91	214	35

[a] Reported m.p. 300–302°C [10].
[b] Reported m.p. 286–288°C [10].
[c] Reported m.p. 260–262°C [6].
[d] Reported m.p. 262–264°C [20].
[e] Catalytic amount of anhydrous. $AlCl_3$ was added to the reaction mixture as per General Procedure B (experimental section).
[f] Reported m.p. 257–259°C [21].
[g] Reported m.p. 246–247°C [9].
[h] Reported m.p. 243–245°C [12].
[i] Reported m.p. 208–210°C [12].

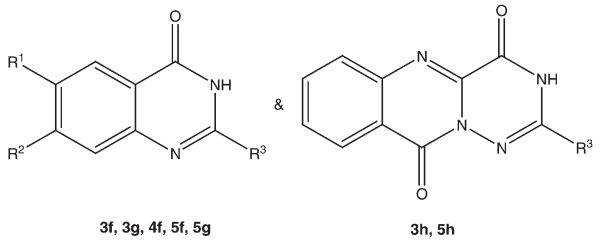
bubbling of dry HCl gas in the reaction mixture for 8–12 h, which is the time taken to complete the reaction depending upon the nature of nitrile used. Interestingly, these same reactions under microwave irradiation at 350 W were accomplished by using catalytic amount of concentrated HCl (33% w/v, 5.0 mL) in very short time periods. The physical data for the 2-substituted-thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **3a–e**, **4a–e**, **5a–e** synthesized under MWI is presented in Table 1 and that for the 2-substitutedquinazolines **3f–h**, **4f,** and **5f–h** is recorded in Table 2. The reaction time varied depending upon the type of nitrile used. The reactions with acetonitrile were completed in 40–75 min to obtain the condensed 2-methylpyrimidin-4(3*H*)-ones **3a–h** with isolated yields ranging from 68–94%. The reactions with acrylonitrile were completed in 20–50 min and afforded the condensed 2-chloroethylpyrimidin-4(3*H*)-ones **4a-f** in 85–96% yields (Scheme 3).

Interestingly, when the reactive nitrile, chloroacetonitrile was used, the reaction went to completion in just 10–40 min and afforded the corresponding 2-chloromethylpyrimidin-4(3*H*)-ones **5a–h** in generally excellent isolated yields (>90%). Thus, in all the aforementioned cases, there is considerable reduction in the reaction times, when conventional heating is replaced by microwave-assisted heating, *i.e*., from 6–12 h to 10–75 min, respectively. Considerable improvement in yields was also observed.

A very important and noteworthy fact is that all the reactions depicted in Scheme 3 failed to proceed in the absence of HCl. This indicates that these reactions under MWI, may also be involving the imidoyl chloride intermediates [22,23]. Further, in a few typical cases, only catalytic amount of HCl failed to bring about the completion of the reaction. This was observed in the reaction of **2a** and **2c** with acrylonitrile to prepare

Table 2

Physical data of other 2-substitutedpyrimidin-4(3*H*)-ones **3f–h**, **4f**, and **5f–h**



				Conventional method			Microwave-assisted method		
	R^1	R^2	R^3	Yield (%)	mp (°C)	Time (h)	Yield (%)	mp (°C)	Time (min)
3f	—H	—H	—CH_3	70	240–242[a]	8–10	80	240	45
3g	—OCH_3	—OCH_3	—CH_3	62	239–241	8–10	70	240	45
3h	–		—CH_3	52	243–245	8–10	71	243	20
4f	—H	—H	—CH_2CH_2Cl	80	200–202	8–10	83	202	30
5f	—H	—H	—CH_2Cl	90	246–248[b]	6–8	94	241	30
5g	—OCH_3	—OCH_3	—CH_2Cl	65	242–244	6–8	70	242	25
5h	–		—CH_2Cl	53	240–242	8–10	66	241	20

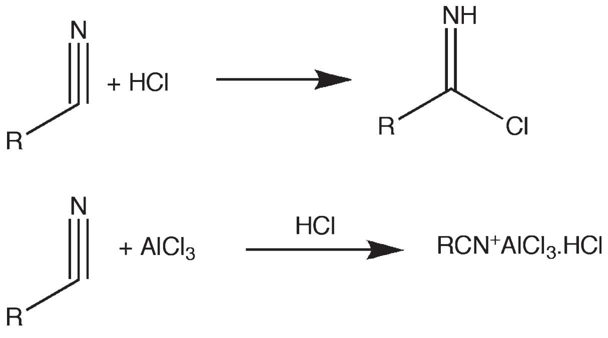
[a] Reported m.p. 240–242°C [10].
[b] Reported m.p. 246–248°C [10].

compounds **4a** and **4c,** respectively. However, addition of catalytic amount of a Lewis acid, anhydrous $AlCl_3$ along with conc. HCl, accomplished the successful completion of the aforementioned reactions to afford the target condensed 2-substitutedpyrimidin-4(3*H*)-ones **4a** and **4c** in excellent isolated yields (Table 1). Thus, the Lewis acid $AlCl_3$, has forwarded the reactions, probably by way of forming the electrophilic nitrile-metal halide, hydrohalide complex as shown below (Scheme 4) [24].

CONCLUSION

A novel microwave-assisted green synthesis of the condensed 2-substitutedpyrimidin-4(3*H*)-ones **3**, **4**, and **5** under solvent-free conditions has been reported for the first time. The unusually rapid synthetic methodology involves the cyclocondensation of a variety of nitriles with *o*-aminoesters of thiophene **2a-e**, benzene **2f**, dimethoxybenzene **2g** and quinazolinone **2h** in the presence of catalytic amount of conc. HCl alone or with the Lewis acid, $AlCl_3$. This novel synthesis involving nitriles as the building blocks, under microwave irradiation for these condensed 2-substitutedpyrimidin-4(3*H*)-ones requires only 10–75 min as compared to the conventional heating protocols requiring 6–12 h, thereby showing a significant acceleration in reaction rates (Tables 1 and 2). The reaction proceeds through the same activated electrophilic nitrile derivatives, the imidoyl halide intermediate and affords the products in yields superior to that by the conventional protocols. Coupled with simple workup procedures and superior yields the methodology is eminently suitable for the generation of diverse libraries of condensed 2-substituted-pyrimidin-4(3*H*)-ones employing parallel synthesis procedures.

Scheme 4



EXPERIMENTAL

Microwave synthesizer (Questron Technologies, Canada; model: Q-Pro M) having monomode open-vessel was used for the synthesis. All the chemicals used in the synthesis were of laboratory grade. The melting points were determined in open capillary on Veego (VMP-D) electronic apparatus and are uncorrected. The IR spectra of synthesized compounds were recorded on Perkin Elmer BX_2 FT-IR Spectrophotometer in KBr and reported in cm^{-1}. ^1H NMR spectra were measured on a Varian Mercury YH-300 FT NMR spectrometer in DMSO-d_6 with chemical shifts (δ) given in ppm relative to TMS as internal standard. Thin layer chromatography was performed on precoated silica plates (Merck Silicagel F_{254}) using hexane-ethyl acetate-glacial acetic acid (4.5 mL:0.5 mL:2drops), chloroform-methanol (4.5 mL:0.5 mL) as the solvent systems and the spots were visualized by exposure to iodine vapors or under ultra violet (UV) light. The HCl used was 33% w/v aqueous and was of LR grade.

General procedure A.

Reaction of 2-amino-3-carbethoxysubstrates 2 with nitriles (in presence of only conc. HCl). A mixture of the appropriate 2-amino-3-carbethoxy substrate **2** (0.02 moles), nitrile (0.022 moles) and catalytic amount of HCl (33% w/v, 5.0 mL) was irradiated at 350 W for 10–75 min in a microwave synthesizer. The progress of reaction was monitored (using TLC) after 5-min intervals. The reaction mixture was allowed to cool to room temperature, and after completion of the reaction poured into ice-water. The resulting precipitated solid was collected by filtration, washed with chilled water and dried. The crude product on recrystallization from methanol-chloroform mixture yielded the appropriate condensed 2-substitutedpyrimidin-4-(3*H*)-ones **3a–h, 4b, 4d–f,** and **5a–h.**

2-Methyl-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one (3a). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1659 cm^{-1}; ^1H NMR: δ 1.77 (s, 4H, 6- and 7-CH_2), 2.30 (s, 3H, 2-CH_3), 2.70 (s, 2H, 5-CH_2), 2.83 (s, 2H, 8-CH_2). Anal. Calcd. for $C_{11}H_{12}N_2OS$: C, 59.90; H, 5.47. Found: C, 59.66; H, 5.38.

2,5,6-Trimethylthieno[2,3-d]pyrimidin-4(3H)-one (3b). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1665 cm^{-1}; ^1H NMR: δ 2.37 (s, 3H, 2-CH_3), 2.46 (s, 3H, 5-CH_3), 2.51 (s, 3H, 6-CH_3), 12.04 (s, br, 1H, 3-NH). Anal. Calcd. for $C_9H_{10}N_2OS$: C, 55.64; H, 5.15. Found: C, 55.81; H, 5.52.

2-Methyl-5-(4-methylphenyl)thieno[2,3-d]pyrimidin-4(3H)-one (3c). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1670 cm^{-1}; ^1H NMR: δ 2.39 (s, 3H, 2-CH_3), 2.47 (s, 3H, Ar—CH_3), 7.04 (s, 1H, 6-H), 7.16–7.48 (m, 4H, phenyl protons), 11.90 (s, 1H, 3-NH). Anal. Calcd. for $C_{14}H_{14}N_2OS$: C, 65.66; H, 4.73. Found: C, 65.76; H, 4.52.

Ethyl 3,4-dihydro-2,5-dimethyl-4-oxothieno[2,3-d]pyrimidin 6-carboxylate (3d). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1718, 1667 cm^{-1}; ^1H NMR: δ 1.40 (t, 3H, 6-$COOCH_2$*CH_3*, *J* = 7.3 Hz), 2.55 (s, 3H, 2-CH_3), 2.94 (s, 3H, 5-CH_3), 4.36(q, 2H, 6-COO*CH_2*CH_3, *J* = 7.1 Hz,); 10.95 (1H, s, 3-NH). Anal. Calcd. for $C_{10}H_{11}N_2O_2S$: C, 52.37; H, 4.74. Found: C, 52.56; H, 4.97.

2-Methyl-5-phenylthieno[2,3-d]pyrimidin-4(3H)-one (3e). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1671 cm^{-1}; ^1H NMR: δ 3.36 (s, 3H, 2-CH_3), 7.31–7.50 (m, 5H, phenyl protons and 6-H), 12.28(s, 1H, 3-NH). Anal. Calcd. for $C_{13}H_{10}N_2OS$: C, 64.46; H, 4.12. Found: C, 64.15; H, 4.46.

2-Methylquinazolin-4(3H)-one (3f). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1666 cm^{-1}; ^1H NMR: δ 2.50 (s, 2H, 2-CH_3), 7.38–7.74 (m, 4H, phenyl protons), 12.13 (s, br, 1H, 3-NH). Anal. Calcd. for $C_9H_8N_2O$: C, 67.44; H, 5.02. Found: C, 67.63; H, 5.42.

6,7-Dimethoxy-2-methylquinazolin-4(3H)-one (3g). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1669 cm^{-1}; ^1H NMR: δ 2.55 (s, 3H, 2-CH_3), 3.99 (s, 6H, 6- and 7-OCH_3), 7.02–7.55 (m, 2H, phenyl protons), 10.87 (s, 1H, 3-NH). Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.90; H, 5.41. Found: C, 58.99; H, 5.72.

2-Methyl-3H-[1,2,4]triazino[6,1-b]quinazolin-4,10-dione (3h). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1680 cm^{-1}; ^1H NMR: δ 2.37 (s, 3H, 2-CH_3), 7.72–8.22 (m, 4H, phenyl protons). Anal. Calcd. for $C_{11}H_8N_4O_2$: C, 57.90; H, 3.51. Found: C, 57.69; H, 3.71.

2-(2-Chloroethyl)-5,6-dimethylthieno[2,3-d]pyrimidin-4(3H)-one (4b). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1669 cm^{-1}; ^1H NMR: δ 2.38 (s, 3H, 5-CH_3), 2.47 (s, 3H, 6-CH_3), 3.19 (t, 2H, 2-CH_2CH_2Cl, *J* = 7.5 Hz), 3.97 (t, 2H, 2-CH_2CH_2Cl , *J* = 7.2 Hz), 12.34 (s, br, 1H, 3-NH). Anal. Calcd. for $C_{10}H_{11}ClN_2OS$: C, 49.40; H, 4.53. Found: C, 49.14; H, 4.35.

Ethyl 2-(2-chloroethyl)-3,4-dihydro-5-methyl-4-oxothieno [2,3-d]pyrimidin 6-carb-oxylate (4d). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1719, 1670 cm^{-1}; ^1H NMR: δ 1.41 (t, 3H, 6-$COOCH_2$*CH_3*, *J* = 7.3 Hz), 2.9 (s, 3H, 5-CH_3), 3.24 (t, 2H, 2-*CH_2*CH_2Cl, *J* = 6.7 Hz), 4.29 (t, 2H, 2-CH_2*CH_2*Cl, *J* = 7.3 Hz CH_2), 4.3 (q, 2H, 6-COO*CH_2*CH_3, *J* = 7.1 Hz), 12.30 (s, 1H, 3-NH). Anal. Calcd. for $C_{11}H_{13}ClN_2O_2S$: C, 47.93; H, 4.35. Found: C, 47.97; H, 4.42.

2-(2-Chloroethyl)-5-phenylthieno[2,3-d]pyrimidin-4(3H)-one (4e). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1685cm^{-1}; ^1H NMR: δ 3.19 (t, 2H, 2-*CH_2*CH_2Cl, *J* = 7.2 Hz), 4.02 (t, 2H, 2-*CH_2*CH_2Cl, *J* = 7.5 Hz), 7.30–7.50 (m, 6H, phenyl protons and 6-H), 12.40 (s, br, 1H, 3-NH). Anal. Calcd. for $C_{14}H_{11}ClN_2OS$: C, 57.83; H, 3.81. Found: C, 57.74; H, 3.89.

2-(2-Chloroethyl)quinazolin-4(3H)-one (4f). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1678 cm^{-1}; ^1H NMR: δ 3.18 (t, 2H, 2-*CH_2*CH_2Cl, *J* = 6.3, 7.2 Hz), 4.06 (t, 2H, 2-*CH_2*CH_2Cl, *J* = 6.3, 7.2 Hz), 7.44–8.07 (m, 4H, phenyl protons), 10.25 (s, 1H, 3-NH). Anal. Calcd. for $C_{10}H_9ClN_2O$: C, 57.55; H, 4.37. Found: C, 57.49; H, 4.80.

2-Chloromethyl-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one (5a). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1663 cm^{-1}; ^1H NMR: δ 1.86 (s, 4H, 6- and 7-CH_2), 2.79 (s, 2H, 5-CH_2), 3.02 (s, 2H, 8-CH_2), 4.55 (s, 2H, 2-*CH_2*Cl), 10.65 (s, br, 1H, 3-NH). Anal. Calcd. for $C_{11}H_{11}ClN_2OS$: C, 51.87; H, 4.30. Found: C, 57.69; H, 4.25.

2-Chloromethyl-5,6-dimethylthieno[2,3-d]pyrimidin-4(3H)-one (5b). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1662 cm^{-1}; ^1H NMR: δ 2.39 (s, 3H, 5-CH_3), 2.47 (s, 3H, 6-CH_3), 4.51 (s, 2H, 2-*CH_2*Cl), 10.03(s, br, 1H, 3-N*H*). Anal. Calcd. for $C_9H_9ClN_2OS$: C, 47.20; H, 3.95. Found: C, 47.30; H, 3.40.

2-Chloromethyl-5-(4-methylphenyl)thieno[2,3-d]pyrimidin-4(3H)-one (5c). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1651 cm^{-1}; ^{1}H NMR: δ 2.39 (s, 3H, Ar-CH_3), 4.53 (s, 2H, 2-*CH*$_2$Cl), 7.13 (s, 1H, 6-H), 7.19–7.46 (m, 4H, phenyl protons), 10.43 (s, 1H, 3-NH). Anal. Calcd. for $C_{14}H_{13}ClN_2OS$: C, 57.89; H, 3.80. Found: C, 57.79; H, 3.87.

Ethyl 2-chloromethyl-3,4-dihydro-5-methyl-4-oxothieno [2,3-d]pyrimidine 6-carboxylate (5d). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1725, 1670 cm^{-1}; ^{1}H NMR: δ 1.41 (t, 3H, 6-COOCH$_2$*CH*$_3$ $J = 7.0$ Hz,), 2.95 (s, 3H, 5-CH_3), 4.38 (q, 2H, 6-COO*CH*$_2$CH$_3$, $J = 7.0$ Hz), 4.57 (s, 2H, 2-*CH*$_2$Cl), 10.62 (s, 1H, 3-NH). Anal. Calcd. for $C_{10}H_{11}ClN_2O_2S$: C, 46.04; H, 3.86. Found: C, 46.10; H, 3.92.

2-Chloromethyl-5-phenylthieno[2,3-d]pyrimidin-4(3H)-one (5e). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1663 cm^{-1}; ^{1}H NMR: δ 4.58 (s, 2H, 2-*CH*$_2$Cl), 7.31–7.52 (m, 5H, aryl protons and 6-H), 12.69 (s, br, 1H, 3-NH). Anal. Calcd. for $C_{13}H_9ClN_2OS$: C, 56.49; H, 3.23. Found: C, 56.62; H, 3.33.

2-Chloromethylquinazolin-4(3H)-one (5f). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1697 cm^{-1}; ^{1}H NMR: δ 4.53 (s, 2H, 2-*CH*$_2$Cl), 7.49–7.82 (m, 4H, aryl protons), 12.56 (s, br, 1H, 3-NH). Anal. Calcd. for $C_9H_7ClN_2O$: C, 55.50; H, 3.64. Found: C, 55.62; H, 3.24.

2-Chloromethyl-6,7-dimethoxyquinazolin-4(3H)-one (5g). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1668 cm^{-1}; ^{1}H NMR: δ 4.0 (s, 6H, 6- and 7-OCH_3), 4.57 (s, 2H, 2-*CH*$_2$Cl), 7.01–7.59 (m, 2H, aryl protons) 9.75 (s, 1H, 3-NH). Anal. Calcd. for $C_{11}H_{11}ClN_2O_3$: C, 51.85; H, 4.36. Found: C, 51.66; H, 4.20.

2-Chloromethyl-3H-[1,2,4]triazino[6,1-b]quinazoline-4,10-dione (5h). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1690 cm^{-1}; ^{1}H NMR: δ 4.59 (s, 2H, 2-*CH*$_2$Cl), 7.53–7.79 (m, 4H, aryl protons), 9.48 (s, br, 1H, 3-NH). Anal. Calcd. for $C_{11}H_7ClN_4O_2$: C, 50.35; H, 2.66. Found: C, 50.29; H, 2.81.

General procedure B.

Reaction of 2-amino-3-carbethoxythiophenes 2a and 2c with acrylonitrile (in presence of conc. HCl and AlCl$_3$). A mixture of appropriate 2-amino-3-carbethoxythiophene **2a** or **2c** (0.02 moles), acrylonitrile (0.022 moles), aq. HCl (33% w/v, 5.0 mL) and anhydrous $AlCl_3$ (0.1–0.25 g) was irradiated at 350 W for 35–45 min in a microwave synthesizer. After completion of reaction, the reaction mixture was allowed to cool to room temperature then was poured into ice-water. The resulting precipitated solid was collected by filtration, washed with chilled water and dried. The crude product on recrystallization from methanol–chloroform mixture yielded the appropriate condensed 2-chloroethylthieno[2,3-*d*]pyrimidin-4-(3*H*)-ones **4a** or **4c**.

2-(2-Chloroethyl)-5,6,7,8-tetrahydro-3H-benzo[b]thieno[2,3-d]pyrimidin-4-one (4a). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1665 cm^{-1}; ^{1}H NMR: δ 1.90 (4H, s, 6- and 7-CH_2), 2.81 (s, 2H, 5-CH_2), 3.02 (s, 2H, 8-CH_2), 3.23 (t, 2H, 2-*CH*$_2$CH$_2$Cl, $J = 7.0$ Hz), 4.02 (t, 2H, 2-*CH*$_2$CH$_2$Cl, $J = 6.2$ Hz), 11.90 (s, 1H, br, 3-NH); Anal. Calcd. for $C_{11}H_7ClN_4O_2$: C, 53.66; H, 4.83. Found: C, 53.44; H, 4.60.

2-(2-Chloroethyl)-5-(4-methylphenyl)thieno[2,3-d]pyrimidin-4(3H)-one (4c). This compound was obtained according to the aforementioned general procedure; IR (potassium bromide): CO 1672 cm^{-1}; ^{1}H NMR: δ 2.40 (3H, s, Ar-CH_3), 3.06 (2H, t, 2-*CH*$_2$CH$_2$Cl, $J = 7.0$ Hz,), 3.87 (t, 2H, 2-CH$_2$*CH*$_2$Cl, $J = 7.0$ Hz, 7.06 (s, 1H, 6-H), 7.15–7.45 (m, 4H, aryl protons), 12.99 (s, 1H, 3-NH). Anal. Calcd. for $C_{15}H_{15}ClN_2OS$: C, 59.10; H, 4.33; Found: C, 59.25; H, 4.20.

General procedure C: Conventional method. A stream of dry hydrogen chloride gas was bubbled through an ice-cold mixture of the appropriate 2-amino-3-carbethoxysubstrate, **2a–h** (0.06 mole) and appropriate nitrile (0.09 mole) in dry dioxane (60 mL) for 8–12 h while maintaining the temperature below 10°C. The reaction mixture was allowed to stand thereafter at room temperature for 12 h. The reaction was then heated on a water bath for 2–3 h, cooled to room temperature and poured onto ice-water mixture (150–200 mL) and neutralized with strong ammonium hydroxide solution (50%v/v). The solid that separated was collected by filtration, washed with water, dried and recrystallized from appropriate solvent.

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New Functionalized *N*-Heterocyclic Carbene Ligands for Arylation of Benzaldehydes

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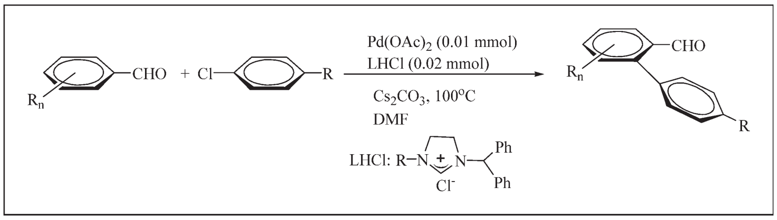

Novel functionalized 1,3-dialkylimidazolinium salts (LHCl) as NHC precursors have been prepared and successfully applied in palladium-catalyzed arylation of benzaldehydes. The ortho position of aromatic aldehydes was directly and selectively arylated with aryl chlorides in the presence of a catalytic system prepared *in situ* from $Pd(OAc)_2$, 1,3-dialkylimidazolinium chlorides (**2a–c**), and Cs_2CO_3.

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INTRODUCTION

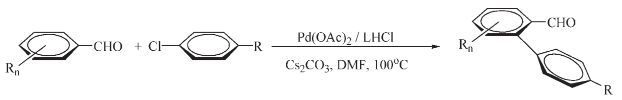
The functionalization of aryl compounds is of major importance in the field of modern arene chemistry because of the ubiquity of aromatic and heteroaromatic units in fine chemical intermediates, pharmaceutical, agrochemicals, polymers, liquid crystals, new materials [1], and ligands for homogeneous transition metal catalysts [1]. Among the different aromatic functionalization reactions, palladium-catalyzed coupling processes such as the Heck [2], Suzuki [3], Kumada [4], Sonogashira [5], Buchwald-Hartwig amination [6], and other C—C and C—O bond forming reactions offer elegant possibilities for the synthesis of substituted arenas. The main advantages of the coupling processes are based on the ready availability of starting materials, the simplicity and generality of the methods, and the broad tolerance of palladium catalysts toward various functional groups. Therefore, the ability to couple an aryl halide directly at the unreactive C—H position of an arene without the need for a sacrificial electrophilic boron or tin fragment would be highly desirable [7]. The selective functionalization of C—H bonds has attracted substantial interest due to potential shortening of synthetic sequences [8]. At present, development of methods for sp^2 C—H bond functionalization in directing-group containing arenas and electron-rich heterocycles has received the most attention. For a number directing group containing substances, the conversion of aromatic *ortho*-C—H bonds to C—C bonds has been demonstrated. Compounds containing amide, pyridine, oxazoline, imine, ketone, and phenol directing groups have been ortho-arylated or alkylated under palladium, ruthenium, or rhodium catalysis [9]. However, aryl chlorides were rarely used, despite the fact that chlorinated arenes are cheaper to manufacture and therefore play a vital role as intermediates in the chemical industry. Presumably, this is due to the fact that the chlorides were generally found to be unreactive under the conditions employed to couple bromides, iodides, and triflates.

Recently, it has been shown that palladium complexes of *N*-heterocyclic carbene [NHC] ligands offer distinct advantages as possible alternatives for Pd/phosphine systems in C—C coupling reactions [10]. Thus, some highly active palladium systems with monodentate carbene ligands have been developed for the activation of aryl chlorides [11].

We have previously reported the use of an *in situ* formed imidazolidin-2-ylidene, tetrahydropyrimidin-2-ylidene and tetrahydrodiazepin-2-ylidene, benzimidazol-2-ylidene palladium(II) systems that exhibit high activity for various coupling reactions of aryl bromides and aryl chlorides [12]. Recently, we report that the *in situ* generation of catalysts, from $[RuCl_2(p\text{-cymene})]_2$ and pyrimidinium or benzimidazolium salt in the presence of Cs_2CO_3, selectively promote the diarylation of 2-pyridylbenzene with aryl bromides [13].

The nature of the NHC ligand has a tremendous influence on the rate of catalyzed reactions. To find more efficient palladium catalysts, we have prepared a series of new bulky or functional 1,3-dialkylimidazolinium (**2a–c**), containing imidazoline ring. Herein, we report a Miaura coupling of aryl chlorides (Scheme 1) using a

Scheme 1



mild practical *in situ* generated catalytic system composed of commercially available and stable reagents, $Pd(OAc)_2$ as the palladium source, 1,3-dialkylimidazolinium chloride (**2a–c**) as a carbene precursor, and Cs_2CO_3 as a base.

RESULTS AND DISCUSSION

1,3-Dialkylimidazolinium chlorides (**2a–c**) are conventional NHC precursors. The functionalized or bulky imidazolinium salts, **2a–c**, were synthesized by consecutive alkylation of 1-benzhydrylimidazoline (**1**) with alkyl halides (Scheme 2).

According to Scheme 2, the salts (**2a–c**) were obtained in almost quantitative yield by quarternization of 1-benzhydrylimidazoline [1] in DMF with alkyl halides [14,15]. The salts are air- and moisture-stable both in the solid state and in solution. The structures of **2a–c** were determined by their characteristic spectroscopic data and elemental analyses. ^{13}C NMR chemical shifts are consistent with the proposed structure; the imino carbon resonance appeared as a typical singlet in the ^1H-decoupled mode at 157.8, 158.6, and 157.7 ppm, respectively, for imidazolinium chlorides **2a–c**. The ^1H NMR spectra of the imidazolinium salts further supported the assigned structures; the resonances for C[2]-H were observed as sharp singlets in the 8.75, 8.58, and 8.31 ppm, respectively, for **2a–c**. The IR data for imidazolinium salts **2a–c** clearly indicate the presence of the —C=N— group with a ν(C=N) vibration at 1636, 1650, and 1645 cm^{-1}, respectively, for **2a–c**. The NMR values are similar to those found for other 1,3-dialkylimidazolinium salts [15].

It is worth noting that *in situ* formation of the NHC complex by deprotonation of the imidazolinium salt led to significantly better results than the use of the preformed complex. The success of these processes as well as the recent reports by Miura and coworkers [16–19] prompted us to examine whether *in situ* generated NHC complexes could be used for the direct arylation of the arene rings of aromatic aldehydes. Formyl groups are synthetically very useful because they can be converted to many other functional groups. Herein, we report a mild, practical, Pd-catalyzed arylation of benzaldehydes using air-stable $Pd(OAc)_2$ as the catalyst, 1,3-dialkylimidazolinium chlorides (LHCl, **2a–c**, Scheme 2) as the NHC ligand precursors, Cs_2CO_3 as the base, and DMF as the solvent. Our initial exploration of the reaction conditions for the palladium-catalyzed arylation of aldehydes focused on the coupling of benzaldehyde and 4-chloroacetophenone [Table 1, entries 1–3]. The best results for mono ortho-arylation of benzaldehydes using 4-chloroacetophenone were obtained at 100°C in DMF using Cs_2CO_3 as base, and a catalyst system generated *in situ* from 1% mmol of $Pd(OAc)_2$ and 2% mmol of LHCl (**2a–c**).

Table 1 summarizes representative results from screening the three imidazolinium salts (LHCl), for a variety of substrates that undergo ortho-arylation. Several trends are readily apparent: The use of NHC ligand precursors **2a–c** allowed lower reaction temperatures (100°C), and shorter reaction times. The procedure is simple and does not require induction periods. All complexes led to good conversions (79 to 95%) at low catalyst concentration (1.0 mmol%). Although not dramatic, consistent differences in yields were observed in the reactions according to the ligand precursors **2a–c**. Presumably, the bulkier ligands derived from **2a–c** are more effective in stabilizing the palladium complex. This new method was compatible with the presence of both electron-withdrawing and electron-donating groups in the para position of the halobenzene. Table 1 also shows that a diverse group of aromatic aldehydes can be coupled. Control experiments showed that in the absence of either $Pd(OAc)_2$ or LHCl, no reaction was observed. It is worth noting that, in contrast to our

Scheme 2. Synthesis of 1,3-dialkylimidazolinium chlorides (LHCl).

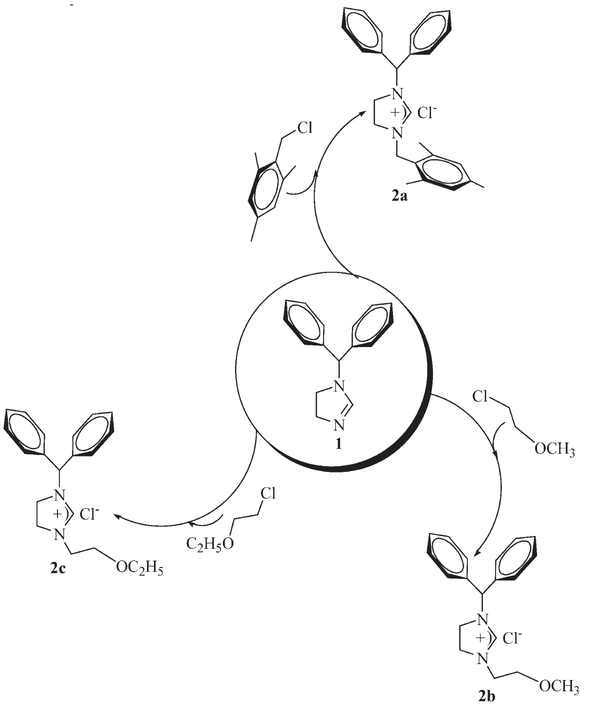
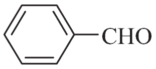
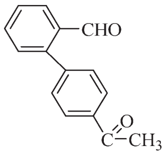
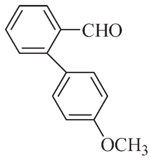
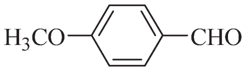
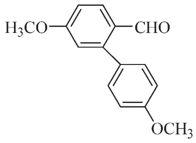
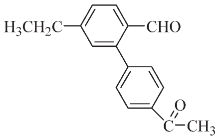
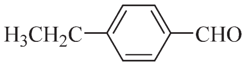
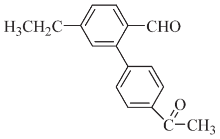
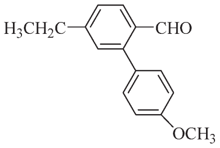
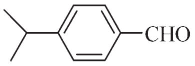
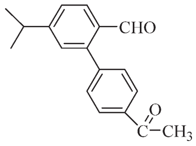
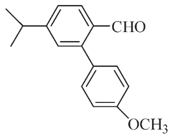


Table 1

Arylation of benzaldehyde derivatives by Pd-NHC complexes.

Entry	LHCl	R	Aromatic aldehyde	Product	Yield[a,b] (%)
1	**2a**	$COCH_3$			84
2	**2b**	$COCH_3$			87
3	**2c**	$COCH_3$			89
4	**2a**	OCH_3			83
5	**2b**	OCH_3			88
6	**2c**	OCH_3			90
7	**2a**	$COCH_3$			89
8	**2b**	$COCH_3$			95
9	**2c**	$COCH_3$			92
10	**2a**	OCH_3			79
11	**2b**	OCH_3			82
12	**2c**	OCH_3			83
13	**2a**	$COCH_3$			92
14	**2b**	$COCH_3$			94
15	**2c**	$COCH_3$			92
16	**2a**	OCH_3			84
17	**2b**	OCH_3			91
18	**2c**	OCH_3			89
19	**2a**	$COCH_3$			82
20	**2b**	$COCH_3$			87
21	**2c**	$COCH_3$			85
22	**2a**	OCH_3			80
23	**2b**	OCH_3			79
24	**2c**	OCH_3			80

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[a] Reactions conditions: 1.0 mmol of R-C_6H_4Cl-*p*, 1.0 mmol of aldehyde, 2 mmol Cs_2CO_3, 1.0 mmol% $Pd(OAc)_2$, 2 mmol% 1,3-dialkylimidazolinium salt, DMF (3 mL), 100°C, 15 h.

[b] Yield determined by NMR and GC, purity of compounds was checked by NMR and yields are based on the aldehyde.

findings, arylation of benzaldehyde with 4-bromoanisole in the presence of $\mathrm{Ni(dppe)Br_2/Zn}$ has been reported to give diaryl carbinols [20].

The palladium-catalyzed arylation of carbonyl compounds or phenols, reported by Miura is considered to proceed *via* coordination between the phenolate or enolate oxygen of the substrates and the arylpalladium intermediate [16]. Consequently, one may expect that oxygen from the aldehyde may function as a phenolate oxygen.

EXPERIMENTAL

All reactions for the preparation of 1,3-dialkylimidazolinium salts [2a–c] were carried out under argon using standard Schlenk-type flasks. All reagents were purchased from Aldrich Chemical (Istanbul). The solvents, $\mathrm{Et_2O}$ over Na, DMF over BaO, EtOH over Mg were distilled before use. All ^{1}H and ^{13}C NMR experiments were performed in $\mathrm{CDCl_3}$. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker AC300P FT spectrometer operating at 300.13 MHz (^{1}H), 75.47 MHz (^{13}C). Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. Melting points were measures in open capillary tubes with an Electrothermal-9200 melting point apparatus and are uncorrected. Elemental analyses were performed by TUBITAK (Ankara, Turkey) Microlab.

Preparation of 1-benzhydryl-3-(2,4,6-trimethylbenzyl)-imidazolinium chloride (2a). To a solution of 1-(benzhydryl) imidazolin (2.0 g, 9.6 mmol) in DMF (3 mL), 2,4,6-tri-methylbenzylchloride (1.78 g, 10.5 mmol) was added; the resulting solution was stirred for 1 h at room temperature and heated for 12 h at 80°C. $\mathrm{Et_2O}$ (10 mL) was added to the reaction mixture. A white solid precipitated during this period. The precipitate was then crystallized from $\mathrm{EtOH/Et_2O}$ (1:2). Yield: 3.12 g (86%), mp 209–210°C; ir: 1636 $\mathrm{cm^{-1}}$ (C=N). ^{1}H NMR (δ, $\mathrm{CDCl_3}$): 2.19 (3H, $\mathrm{CH_2C_6H_2(C}H_3)_3$-4), 2.26 (s, 6H, $\mathrm{CH_2C_6H_2(C}H_3)_3$-2,6), 3.88 (s, 4H, $\mathrm{NC}H_2\mathrm{C}H_2\mathrm{N}$), 5.79 (s, 2H, $\mathrm{C}H_2\mathrm{—(C_6H_2)—(CH_3)_3}$-2,4,6), 6.80 (s, 2H, $\mathrm{CH_2—(C_6}H_2)\mathrm{—(CH_3)_3}$), 6.45 (s, 1H, $\mathrm{C}H\mathrm{(C_6H_5)_2}$), 7.26–7.37 (m, 10H, Ar), 8.75 (s,1H, 2—CH). ^{13}C NMR (δ, $\mathrm{CDCl_3}$): 21.1 ($\mathrm{CH_2C_6H_2(}C\mathrm{H_3)_3}$-4), 20.3 ($\mathrm{CH_2C_6H_2(}C\mathrm{H_3)_3}$-2,6), 47.1 ($C\mathrm{H_2—(C_6H_2)—(CH_3)_3}$-2,4,6), 48.0 and 48.7 ($\mathrm{N}C\mathrm{H_2}C\mathrm{H_2N}$), 65.9 ($C\mathrm{H(C_6H_5)_2}$), 125.5, 128.6, 129.1, 129.5, 139.9, 135.9, 139.0, and 139.3 (Ar), 157.8 (2—CH). Anal. Calcd. for $\mathrm{C_{26}H_{29}N_2Cl}$: C, 72.54; H, 7.23; N, 6.59. Found: C, 72.56; H, 7.28; N, 6.55.

Preparation of 1-benzhydryl-3-(methoxyethyl)-imidazolinium chloride (2b). This compound was prepared from 1-(benzhydryl)imidazolin (2 g, 9.6 mmol) and 2-methoxyethyl chloride (1.0 g, 10.5 mmol) in DMF (3 mL). Yield:2.65 g (91%), mp 144–145°C; ir: 1650 $\mathrm{cm^{-1}}$ (C=N). ^{1}H NMR (δ, $\mathrm{CDCl_3}$): 3.25 (s, 3H, $\mathrm{OC}H_3$), 3.57 (t, 2H, J = 4.4 Hz, $\mathrm{NCH_2C}H_2\mathrm{O}$), 3.78 (t, 2H, J = 4.4 Hz, $\mathrm{NC}H_2\mathrm{CH_2O}$), 3.89 and 4.13 (m, 4H, $\mathrm{NC}H_2\mathrm{C}H_2\mathrm{N}$), 6.37 (s, 1H, $\mathrm{C}H\mathrm{(C_6H_5)_2}$), 7.32 (m, 10H, Ar); 8.58 (s, 1H, 2—CH). ^{13}C NMR (δ, $\mathrm{CDCl_3}$): 48.3 and 48.8 ($\mathrm{N}C\mathrm{H_2}C\mathrm{H_2N}$), 59.3 ($\mathrm{O}C\mathrm{H_3}$), 66.1 ($\mathrm{NCH_2}C\mathrm{H_2O}$), 50.3 ($\mathrm{N}C\mathrm{H_2CH_2O}$), 69.0 ($C\mathrm{H(C_6H_5)_2}$), 128.9, 129.3, 129.7, and 136.1 (Ar), 158.6 (2—CH). Anal. Calcd. for $\mathrm{C_{19}H_{23}N_2OCl}$: C, 68.97; H, 7.01; N, 8.47. Found: C, 68.93; H, 6.98; N, 8.50.

Preparation of 1-benzhydryl-3-(ethoxyethyl)imidazolinium chloride (2c). This compound was prepared from 1-(benzhydryl)imidazolin (2 g, 9.6 mmol) and 2-ethoxyethyl chloride (1.15 g, 10.5 mmol) in DMF (3 mL). Yield: 2.70 g (89%), ir: 1645 $\mathrm{cm^{-1}}$ (C=N). ^{1}H NMR (δ, $\mathrm{CDCl_3}$): 0.89 (t, 3H, J = 5.7 Hz, $\mathrm{OCH_2C}H_3$), 3.31 (q, 2H, J = 5.7 Hz, $\mathrm{OC}H_2\mathrm{CH_3}$), 3.46 (t, 2H, J = 4.2 Hz, $\mathrm{NCH_2C}H_2\mathrm{O}$), 3.58 (t, 2H, J = 3.9 Hz, $\mathrm{C}H_2\mathrm{CH_2O}$), 3.73 and 4.04 (m, 4H, $\mathrm{NC}H_2\mathrm{C}H_2\mathrm{N}$), 6.26 (s, 1H, $\mathrm{C}H\mathrm{(C_6H_5)_2}$), 6.96–7.59 (m, 10H, Ar), 8.31 (s, 1H, 2—CH). ^{13}C NMR (δ, $\mathrm{CDCl_3}$): 14.9 ($\mathrm{OCH_2}C\mathrm{H_3}$), 47.8 ($\mathrm{O}C\mathrm{H_2CH_3}$), 65.5 ($\mathrm{NCH_2}C\mathrm{H_2O}$), 66.2 ($\mathrm{N}C\mathrm{H_2CH_2O}$), 48.3 and 49.9 ($\mathrm{N}C\mathrm{H_2}C\mathrm{H_2N}$); 66.4 ($C\mathrm{H(C_6H_5)_2}$); 128.3, 128.8, 129.2, and 135.7 (Ar), 157.8 (2—CH). Anal. Calcd. for $\mathrm{C_{20}H_{25}N_2OCl}$: C, 69.65; H, 7.31; N, 8.12. Found: C, 69.66; H, 7.29; N, 8.11.

General procedure for arylation of benzaldehyde derivatives. A dried Schlenk flask equipped with a magnetic stirring bar was charged with the aldehyde (1.0 mmol), aryl chloride (1.0 mmol), $\mathrm{Pd(OAc)_2}$ (0.01 mmol), imidazolinium chloride (0.02 mmol), $\mathrm{Cs_2CO_3}$ (2.0 mmol), and DMF (3 mL). After stirring at 100°C for 15 h, the mixture was cooled to room temperature and then quenched by addition of aqueous 1*N* HCl and extracted with diethyl ether. The isolated organic layer was dried over $\mathrm{MgSO_4}$, filtered, concentrated *in vacuo*, and purified by column chromatography on silica gel eluting with ethyl acetate/hexane (1:5). Analysis of the reaction product was carried out by NMR and GC-MS.

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Synthesis of the Hypotensive Agent 8-Amino-7-[2-hydroxy-3-morpholinopropyl]theophylline (P23) and Analogs

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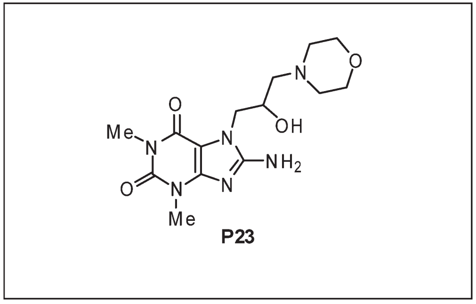

P23

Synthesis of a number of 7,8-disubstituted theophyllines including enantiomers of the hypotensive agent **P23** is described.

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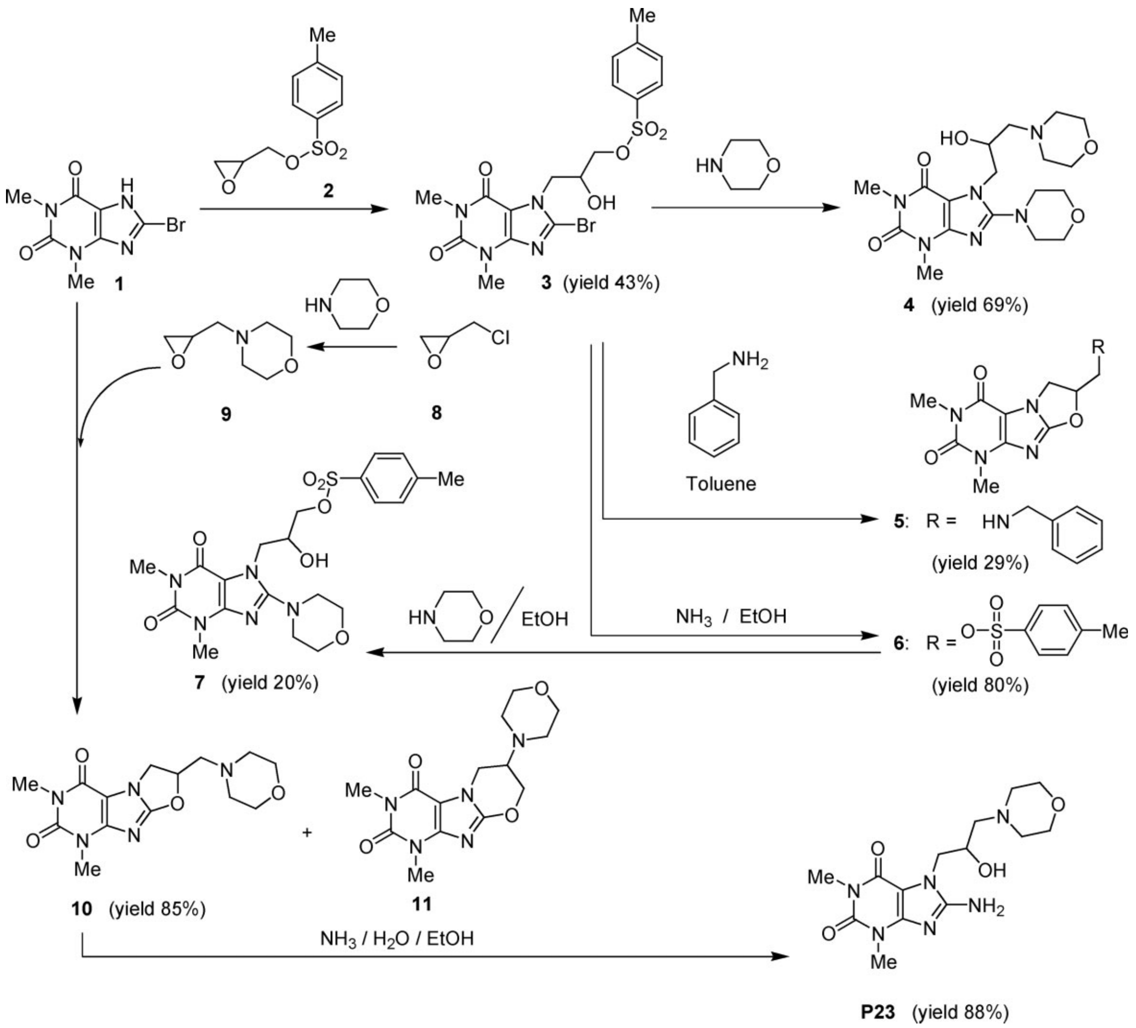
INTRODUCTION

N-Methyl derivatives of xanthine including caffeine, theobromine, and theophylline show diverse biological activities. An additional substitution of these compounds results in modulation of their biological responses. In particular, a 7,8-disubstituted theophylline **P23** (structure in Scheme 1) was synthesized two decades ago and protected by patents as a potent hypotensive agent that acts on the cardiovascular system [1]. The original synthesis of **P23** was based on a reaction of theophylline with racemic epichlorohydrin to give the racemic intermediate and final products. No attempts were made to synthesize enantiomers of **P23**, which is a requirement of the current drug development process. More specifically, two enantiomers of a chiral drug candidate must be biologically assayed. Since the patent protection of the chemistry leading to the racemate of **P23** has recently expired, the patented information is in the public domain. Therefore, it was of interest to review the previously published chemistry in an attempt to synthesize enantiomers of **P23**. Unfortunately, we have found that the use of enantiomerically pure epichlorohydrin instead of a racemic substrate in the reaction with 8-bromotheophylline (**1**) results in an extensive racemization of the intermediate adduct. Additional methodologies are illustrated in Scheme 1.

To test the feasibility of the designed synthetic routes, the first experiments involved the reaction of **1** with racemic reagents, namely 2,3-epoxypropyl 4-toluenesulfonate (**2**) and 2,3-epoxypropylmorpholine (**9**).

Compound **2** [2] and the reagent **9** [3] were synthesized by using the published procedures. Treatment of **1** with **2** gave the expected adduct **3** in 43% yield. It was believed that a selective nucleophilic displacement of the tosylate function in **3** by the reaction with morpholine followed by the addition of ammonia to the C=N—Br moiety of the resultant intermediate product and then elimination of bromide anion would produce the desired product **P23**. Unfortunately, the treatment of **3** with morpholine resulted in the displacement and addition reactions simultaneously to give a dimorpholino derivative **4**. On the other hand, it was thought that the addition reaction of less sterically hindered benzylamine with the C=N—Br moiety of **3** would be a selective process. The benzyl group could be removed later by hydrogenation. To our surprise a tricyclic product **5** was formed instead, showing that the third ring system is formed by the benzylamine-aided ionization of the hydroxyl function in the side chain followed by addition of the alkoxide anion to the C=N—Br moiety and a subsequent elimination of bromide. The treatment of **3** with ammonia also resulted in cyclization, however, without nucleophilic displacement of the tosylsulfonyl group, to give **6** as the final product. Another surprising result was obtained upon an attempted nucleophilic displacement of the tosylsulfonyl group in **6** by treatment with morpholine. Thus, the tosylsulfonyl group was retained in the bicyclic product **7**. The loss of the third ring can be explained in terms of the addition reaction

Scheme 1



of morpholine to the C=N function of **6** followed by elimination of alkoxide anion from the resultant adduct.

The successful preparation of **P23** that is also amendable to the synthesis of individual enantiomers is based on the reaction of 8-bromotheophylline (**1**) with *N*-(2,3-epoxypropyl)morpholine (**9**). Reagent **9** is not a commercial product and was obtained by the reaction of morpholine with epichlorohydrin (**8**) which is available in the form of a racemate or individual enantiomers. It has been suggested previously that the reaction of morpholine with an optically active substrate (*S*)-(+)-**8** is accompanied by extensive racemization of the epoxyamino product (*S*)-(−)-**9** [3-5]. We have shown that the racemization can be minimized by using mild conditions. As can be seen from the experimental part, the absolute values of the optical rotations for the enantiomers of **9** obtained by us are virtually identical. The greater optical purity of our sample of (−)-**9** is indicated by the absolute rotation, $[\alpha]_D = -25.4^\circ$ (c = 10% in toluene), as opposed to the value published previously, $[\alpha]_D = -20.2^\circ$, and measured under similar conditions [3]. The optical rotation of the (+)-**9** enantiomer has not been reported previously.

We have published recently that the treatment of 8-bromotheophylline (**1**) with the reagent **9** yields the oxazoline derivative **10** and, depending on conditions, varying amounts of the rearrangement product **11**. Relatively short reaction time and temperature favour the formation of **10** which can be obtained in an 85% yield. Conversely, heating the mixture at an elevated temperature for a prolonged period of time results in an efficient rearrangement of the initially formed compound **10** to the oxazine derivative **11** [6].

The racemic compound **10** was treated with ammonia in aqueous ethanol to give racemic product **P23**.

After optimization of the conditions a similar treatment of the enantiomers of **10** furnished optically active samples of **P23**. Their enantiomeric excess (defined as the percent excess of the enantiomer over the racemate) was calculated by analysis of the ^{1}H NMR spectra of diastereomeric esters of the samples of **P23** with (*S*)-(+)-α-methoxyphenylacetic acid. The procedure has been published previously [7], and the relative intensity of the singlets for the methine protons MeOC**H**(Ph)COO (δ 4.70-4.80) is the most informative. The obtained values of the enantiomeric excess for the samples containing (+)-**P23** and (−)-**P23** as the major enantiomers were 54% and 58%, respectively. These values correspond to the enantiomerically enriched samples containing 77% and 79% of the major enantiomer, respectively. The partial racemization observed for the synthesis of **P23** may be related to the partial racemization of **9**, as already mentioned [3]. Nevertheless, on the basis of the stereospecific chemistry involved, it can be safely assumed that the absolute configuration of the major enantiomer in the samples, (*R*)-(−)-**P23** and (*S*)-(+)-**P23**, are as shown. More specifically, the chemical transformations **8** → **9** → **10** → **P23** do not involve stereocenters in these compounds and, as a result, the absolute configurations, *R* or *S*, are retained in the intermediate and final products.

EXPERIMENTAL

Melting points (Pyrex capillary) are uncorrected. Electron-impact mass spectra (ei-ms) were recorded at 70 eV. High resolution time-of-flight mass spectra were recorded using electron-spray ionization (*high resolution ms*) with 0.5% ammonia in methanol for the negative ion mode and 0.1% formic acid in methanol for the positive ion mode. ^{1}H NMR spectra were obtained at 300 MHz in deuteriochloroform solution with the solvent used as an internal standard. All commercial reagents were purchased from Aldrich or Fluka and used without purification.

8-Bromo-7-[2-hydroxy-3-(4-tolylsulfonyloxy)propyl]theophylline [(±)-3]. A solution of (±)-2,3-epoxypropyl 4-toluenesulfonate (**2**, 0.27 g, 1.2 mmol), 8-bromotheophylline (**1**, 0.21 g, 0.8 mmol), and a catalytic amount of pyridine (0.02 g, 0.2 mmol) in *n*-propanol (2.5 mL) was heated under reflux for 1 hour. After cooling the mixture was concentrated on a rotary evaporator, and the residue was subjected to silica gel chromatography eluting with dichloromethane/methanol (49:1). Product (±)-**3** was obtained in a 43% yield, mp 78–79°C; ^{1}H NMR: δ 2.46 (s, 3H), 3.38 (s, 3H), 3.56 (s, 3H), 3.80 (br s, 1H), 4.12–4.18 (m, 3H), 4.48 (d, *J* = 1.4 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.85 (d, *J* = 8.5 Hz, 2H). *High resolution ms.* Calcd for $C_{17}H_{20}{}^{79}BrN_4O_6{}^{32}S$ ($M^+ + 1$): m/z 487.0287. Found: m/z 487.0290.

7-(2-Hydroxy-3-morpholinopropyl)-8-morpholinotheophylline [(±)-4]. A solution of (±)-**3** (0.05 g, 0.10 mmol) and morpholine (0.02 g, 0.21 mmol) in toluene (5 mL) was heated under reflux for 1.5 hours. The mixture was concentrated on a rotary evaporator, and the residue was subjected to silica gel chromatography eluting with dichloromethane/methanol (49:1). Compound **4** was obtained in a 69% yield, mp 175–176°C; ^{1}H NMR: δ 2.46 (m, 4H), 2.63 (m, 2H), 3.22 (m, 2H), 3.46 (m, 2H), 3.37 (s, 3H), 3.54 (s, 3H), 3.70 (m, 4H), 3.83 (m, 4H), 4.04 (m, 2H), 4.18 (m, 1H), 4.30 (m, 1H); ei-ms: m/z 408 (M^+, 10), 308 (50), 265 (10), 126 (50), 100 (100). *High resolution ms.* Calcd. for $C_{18}H_{27}N_6O_5$ ($M^- - 1$): m/z 407.2043. Found: m/z 407.2055.

7-[(Benzylamino)methyl]-1,3-dimethyl-6,7-dihydro-oxazolo[2,3-*f*]purine-1*H*,3*H*-2,4-dione [(±)-5]. A solution of **2** (0.05 g, 0.10 mmol) and benzylamine (0.02 g, 0.20 mmol) in toluene (5 mL) was heated under reflux. The reaction was completed after 1.5 hours, as judged by TLC analysis on silica gel eluting with chloroform/methanol (9:1). The resultant precipitate of benzylammonium 4-toluenosulfonate was filtered off and the solution was concentrated on a rotary evaporator. Product **5** was isolated by chromatography on silica gel eluting with chloroform/methanol (9:1), yield 29%, mp 252–253°C; ^{1}H NMR: δ 3.30 (s, 3H), 3.35 (s, 2H), 3.49 (s, 3H), 3.80 (s, 1H), 4.40 (m, 2H), 4.47 (m, 1H), 4.80 (m, 2H), 7.30 (m, 5H); ei-ms: m/z 341 (M^+, 100), 250 (25), 91 (40). *High resolution ms.* Calcd. for $C_{17}H_{20}N_5O_3$ ($M^+ + 1$): m/z 342.1566. Found: m/z 342.1570.

7-[(4-Tolylsulfonyloxy)methyl]-1,3-dimethyl-6,7-dihydro-oxazolo[2,3-*f*]purine-1*H*,3*H*-2,4-dione [(±)-6]. Gaseous ammonia was slowly bubbled at 0° through a solution of **3** (0.27 g, 0.6 mmol) in anhydrous ethanol. After 3 hours the resultant precipitate of **6** was collected by filtration and dried at 25°; yield 80%, mp 215–220°C; ^{1}H NMR: δ 2.50 (s, 3H), 3.42 (s, 3H), 3.55 (s, 3H), 4.40 (m, 4H), 5.68 (m, 1H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.80 (d, *J* = 8.5 Hz, 2H); ei-ms: m/z 406 (M^+, 100), 234 (25), 91 (30). *High resolution ms.* Calcd. for $C_{17}H_{17}N_4O_6{}^{32}S$ ($M^- - 1$): m/z 405.0869. Found: m/z 405.0883.

7-[2-Hydroxy-3-(4-tolylsulfonyloxy)propyl]-8-morpholinotheophylline (±)-7]. A mixture of (±)-**6** (0.03 g, 0.08 mmol), morpholine (0.015 g, 0.16 mmol), and ethanol (2 mL) was stirred at 25°C for 24 h. Concentration of the mixture on a rotary evaporator followed by chromatography of the residue on silica gel eluting with dichloromethane/methanol (49:1) gave product 7 in a 20% yield, mp 163–164°C; ^{1}H NMR: δ 2.50 (s, 3H), 3.31 (m, 4H), 3.40 (s, 3H), 3.57 (s, 3H), 3.88 (m, 4H), 3.94 (m, 1H), 4.25 (m, 4H), 5.52 (br s, 1H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.82 (d, *J* = 8.2 Hz, 2H). *High resolution ms.* Calcd. for $C_{21}H_{28}N_5O_7{}^{32}S$ ($M^+ + 1$): m/z 494.1709. Found: m/z 494.1685.

(±)-*N*-(2,3-Epoxypropyl)morpholine [(±)-9]. A mixture of morpholine (8.5 g, 0.1 mol) and water (0.5 mL) was treated dropwise with (±)epichlorohydrin (**8**, 9.25 g, 0.1 mol) in such a way that the temperature did not exceed 35 °C (exothermic reaction). After the addition was completed (1.5 h), the mixture was treated with an aqueous solution of sodium hydroxide (38%, 12.5 g) and then stirred for an additional 1 hour. The precipitate of sodium chloride was filtered off, and the filter and the flask was washed with ether (3 × 30 mL). The ether solution was dried (anhydrous K_2CO_3), then concentrated on a rotary evaporator, and the oily residue was distilled under reduced pressure (45–48°C/20 mmHg). Racemic product **9** was obtained in a 40% yield and its ^{1}H NMR spectrum was virtually identical with that reported [3] for the compound obtained by using a different synthetic route.

(2*R*)-(+)-*N*-(2,3-Epoxypropyl)morpholine [(2*R*)-(+)-9]. The reaction with (2*R*)-(−)-epichlorohydrin with morpholine and workup were conducted as described above; $[\alpha]_D = +24.1°$ (c = 10% in toluene).

(2*S*)-(-)-*N*-(2,3-Epoxypropyl)morpholine [(2*S*)-(−)-9]. The reaction with (2*S*)-(+)-epichlorohydrin with morpholine and workup were conducted as described above; $[\alpha]_D = -25.4°$ (c = 10% in toluene); reported $[\alpha]_D = -20.2°$ in toluene [3].

1,3-Dimethyl-7-morpholinomethyl-6,7-dihydrooxazolo-[2,3-*f*]-purine-1*H*,3*H*-2,4-dione [(±)-10, (7*S*)-(−)-10 and (7*R*)-(+)-10]. A mixture of 8-bromotheophylline (**1**, 0.39 g, 1.5 mmol), racemic compound **9** (0.31 g, 2 mmol), and pyridine (0.08 g, 1 mmol) in ethanol (5 mL) was stirred at room temperature for up to 10 days until TLC analysis (silica gel, chloroform/triethylamine, 9:1) showed the absence of **1** and/or the presence of a small amount of a byproduct **11**. Then the mixture containing precipitate of **10** was cooled to 0°C for an additional 24 h and filtered. Product (±)-**10** was obtained in an analytically pure form by chromatography on silica gel eluting with chloroform/methanol (9:1): yield 85%, mp 230–231°C. A similar treatment of **1** with (R)-(+)-**9** gave (R)-(+)-**10**, mp 176–178°C, $[\alpha]_D = +55.3°$ (c = 3% in dichloromethane/metanol, 49:1). A similar treatment of **1** with (*S*)-(−)-**9** gave (*S*)-(−)-**10**, mp 180–182°C, $[\alpha]_D = -49.7°$ (c = 3% in dichloromethane/methanol, 49:1). The ^{1}H NMR spectra of these three products were virtually identical with that reported previously for (±)-**10** [6]; ei-ms (identical in all cases): m/z 321 (M^+, 30), 234 (40), 126 (55), 113 (20), 100 (100). Anal. Calcd. for $C_{14}H_{19}N_5O_4$ [(±)-**10**]: C, 52.33; H, 5.95; N, 21.79. Found: C, 52.06; H, 5.93; N, 21.53.

8-Amino-7-(2-hydroxy-3-morpholinopropyl)theophylline [(±)-P23, (*S*)-(+)-P23, and (*R*)-(−)-P23]. A mixture of (±)-**10** (0.32 g, 1.0 mmol), aqueous ammonia (25%, 10 mL), and ethanol (15 mL) was heated in a pressure vessel to 110°C for 6 hours. After cooling the mixture was concentrated on a rotary evaporator and subjected to silica gel chromatography eluting with chloroform/methanol (49:1), yield 88%, mp 221–222°C (reported [1] mp 226–228°C for the racemic product); ^{1}H NMR: δ 2.44 (m, 2H), 2.66 (m, 4H), 3.37 (s, 3H), 3.50 (s, 3H), 3.66 (m, 4H), 4.18 (m, 1H), 4.40 (m, 2H), 4.50 (br s, 1H), 5.74 (br s, 2H); ei-ms: m/z 338 (20), 238 (45), 126 (50), 100 (100). The treatment of (7S)-(−)-**10** with ammonia gave (*S*)-(+)-**P23**, $[\alpha]_D = +5.3°$ (c = 2.2% in dichloromethane/methanol, 49:1). The treatment of (7*R*)-(+)-**10** with ammonia gave (*R*)-(−)-**P23**, $[\alpha]_D = -8.0°$ (c = 2.2% in dichloromethane/methanol, 49:1). The mp, NMR and ms data reported above are identical for all three products. Anal. Calcd. for $C_{14}H_{22}N_6O_4$ [(+)-**P23**]: C, 49.72; H, 6.55; N, 24.84. Found: C, 49.49; H, 6.90; N, 24.51.

Derivatization of P23 for analysis of the enantiomeric excess by ^{1}H NMR. Esterification of the secondary alcohol function of **P23** with (*S*)-(+)-α-methoxyphenylacetic acid was conducted by using a published procedure [7]. The ester was purified by chromatography on silica gel eluting with chloroform/methanol (49:1). The ^{1}H NMR spectra of the diastereomeric derivatives were taken in deuteriochloroform, and the ratio of the signals of the methine protons MeOCH(Ph)COO (δ 4.70–4.80) were analyzed [7].

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Synthesis and Antimicrobial Activity of Novel Analogs of Trifenagrel

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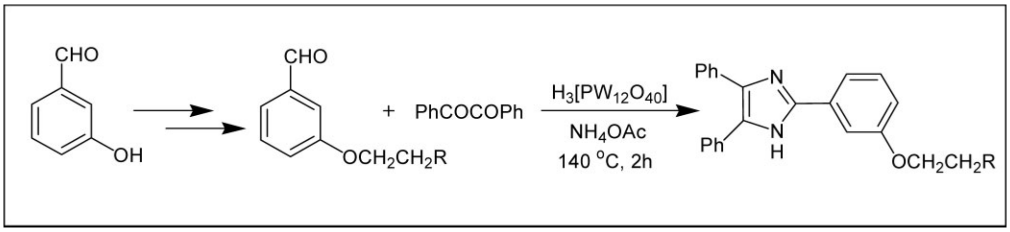

Novel analogs of trifenagrel were synthesized by using inexpensive and reusable phosphotungstic acid, $H_3[PW_{12}O_{40}]$ (3 mol %) catalyst under classical heating. Two of the newly synthesized triaryl imidazoles exhibited moderate antibacterial activity.

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INTRODUCTION

In 1858, Debus [1] reported the reaction between glyoxal and ammonia and this reaction pioneered a novel synthetic route to imidazole. Subsequently imidazoles have received significant attention because of their synthesis, reactions, and biochemical properties [2]. The prevalence of imidazoles in natural products and pharmacologically active compounds has instituted a diverse array of synthetic approaches to these heterocycles. Even today, research in imidazole chemistry continues unabated because compounds containing an imidazole moiety have biological and pharmaceutical importance.

Synthesizing analogs of biologically active molecules is part of the drug discovery process and is a basic application of synthetic organic chemistry. One such pharmacologically potent 2,4,5-triaryl imidazole is trifenagrel (**1**) (Fig. 1) that inhibits both arachidonate and collagen induced aggregation of platelets with equal or greater potency (5–12 fold) than indomethacin and aspirin, without exhibiting the gastric damage associated with these typical cyclogenase inhibitors [3]. The potential of trifenagrel (as an antithrombic compound) rekindled an interest in us to synthesize its analogs for detailed structural activity relationship studies, efficient lead structure identification, and optimization in a drug discovery program.

Trifenagrel was first synthesized by Phillips *et al.* [4], by reaction of 2-(2-dimethylaminoethoxy) benzaldehyde, benzil, and ammonium acetate using glacial acetic acid as solvent under reflux condition. Later Wolkenberg *et al.* [5] reported the same reaction under microwave irradiation. The synthetic methods proposed for trifenagrel have limitations of harsh reaction conditions and use of polar solvent (acetic acid) leading to complex isolation and recovery procedures. Therefore, there is merit in using a nonsophisticated, recoverable, and reusable catalyst for the synthesis of analogs of trifenagrel.

In recent years, heteropoly acids (HPAs) have proved to be good catalysts in one-pot multicomponent construction of heterocyclic compounds. HPAs have a very strong Bronsted acidity and are efficient oxidants, exhibiting fast reversible multielectron redox transformations under mild conditions. HPAs are useful as catalysts because of the following unique characteristics: (a) catalytic performance, (b) chemical and physical properties, (c) molecular and bulk composition, and (d) method of synthesis of the catalyst [6]. One such mild HPA is phosphotungstic acid (PTA), $H_3[PW_{12}O_{40}]$ which has emerged as a powerful catalyst in recent years due to economic and environmental considerations. Recently, Heravi *et al.* [7] reported synthesis of tetrasubstituted imidazoles using HPAs as green and reusable catalysts. Therefore, we decided to investigate its catalytic activity for synthesis of novel triaryl imidazoles. In continuation of our work [8,9] in exploring applications of HPAs in fine organic chemistry, we have developed a method for solvent free synthesis of novel analogs of trifenagrel by using inexpensive and reusable PTA, $H_3[PW_{12}O_{40}]$ (3.0 mol %) catalyst under classical heating in a highly efficient manner.

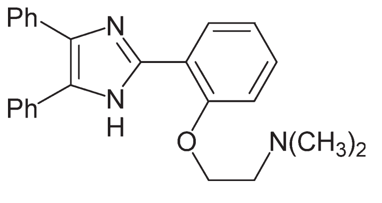

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Figure 1. Trifenagrel.

RESULTS AND DISCUSSION

As a starting point of our study, we have selected 3-hydroxybenzaldehyde (**2**) and allowed it to react with 1,2-dibromoethane in the presence of 6*N* NaOH to give 3-(2-bromoethoxy) benzaldehyde (**3**) with 62% yield (Scheme 1). The formation of compound (**3**) was evident from the ^1H NMR by the appearance of aliphatic protons at δ 3.58 and δ 4.24 as triplets. Compound (**3**) was then treated with dimethylamine in the presence of methanol to afford compound (**4a**) in 90% yield. In the ^1H NMR spectrum of compound (**4a**) characteristic methyl protons appeared as a singlet at δ 2.90.

Similarly two more amine derivatives (**4b, 4c**) were prepared from compound (**3**). 3-(2-Piperidinoethoxy) benzaldehyde (**4a**) was obtained in 66% yield by the reaction of piperidine with compound (**3**). In the ^1H NMR spectrum of compound (**4b**), the aliphatic protons of piperidine appeared at δ 1.45 as multiplet and at δ 3.48 as triplet, respectively. In an identical manner, compound (**4c**) was prepared in 73% yield and ^1H NMR spectrum of this compound showed two triplets at δ 2.45 and δ 3.68.

The three-component condensation of benzil (**5**), aldehydes (**4a–c**), and ammonium acetate in the presence of 3 mol % of PTA gave trisubstituted imidazoles (**6a–c**) (Scheme 1). The compound (**6a**) was characterized from mass spectrum (ESI) by the appearance of $[M + H]^+$ peak at *m/z* 384 and from ^1H NMR by the appearance of increased aromatic protons at δ 7.22–7.60 and the absence of CHO proton at δ 10.01. Similarly the compounds (**6b, 6c**) were synthesized and their spectroscopic features fully supported the assigned structures.

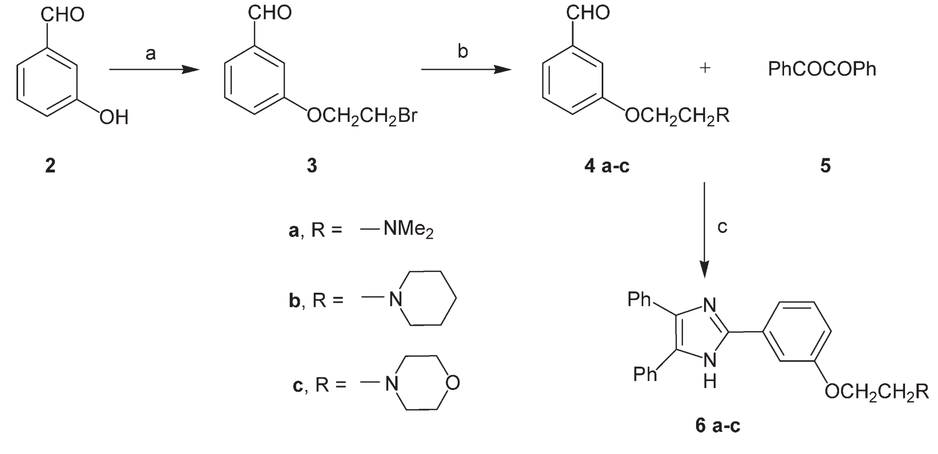
The scope of the reaction was further extended for the preparation of 4-hydroxybenzaldehyde (**7**) and vanillin (**8**) derived analogs of trifenagrel. Thus, compounds (**7** and **8**) on reaction with 1,2-dibromoethane in the presence of 6*N* NaOH provided the compounds (**9** and **10**), respectively. The formation of compounds (**9** and **10**) was evident from the appearance of $[M + H]^+$ peak at *m/z* 230 and 250 in mass spectrum (ESI) respectively, $-C{=}O$ stretching of aldehyde at 1684 and 1680 cm^{-1} respectively in IR and the appearance of methylene protons as triplets at δ 3.66 and δ 4.36 respectively in ^1H NMR of both the compounds (**9** and **10**).

Compounds (**9** and **10**) were then treated with dimethylamine in the presence of methanol to afford compounds (**11a** and **11b**) as liquids in excellent yield (Scheme 2). The formation of the compound (**11a** and **11b**) was evident by the appearance of $[M + H]^+$ peak at *m/z* 193 and 224 respectively in the mass spectrum (ESI), $-C{=}O$ stretching of aldehyde at 1690 and 1682 cm^{-1} in IR and by the appearance of a singlet at δ 2.33 and δ 2.32 respectively in ^1H NMR spectra corresponding to methyl protons of amine.

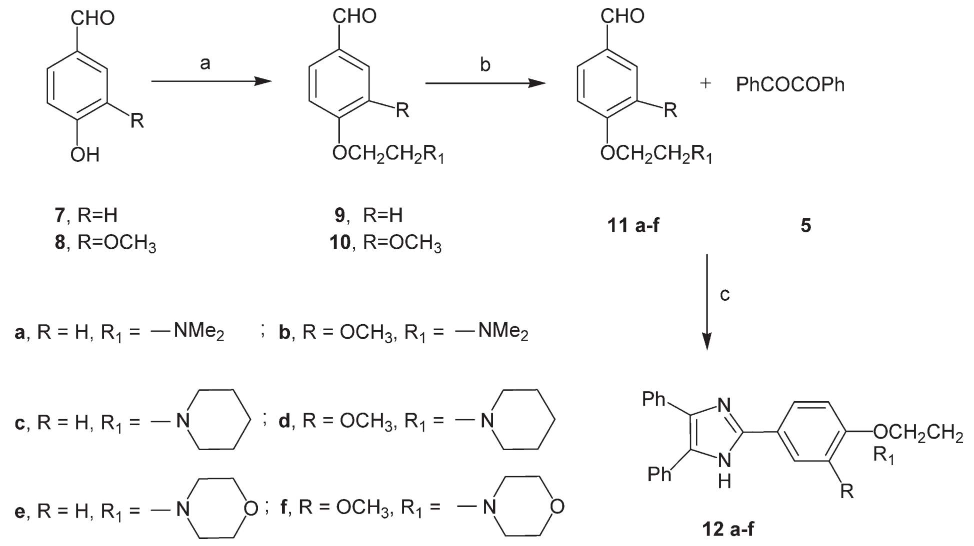
In a similar way two more derivatives for each (**11c, 11d, 11e,** and **11f**) were synthesized and their spectroscopic features fully supported its assigned structure.

The three-component condensation of benzil (**5**), aldehydes (**11a–f**), and ammonium acetate in the presence of 3 mol % of PTA gave trisubstituted imidazoles (**12a–f**) (Scheme 2). The compound (**12a**) was characterized

Scheme 1. Reagents and conditions: (a) $BrCH_2CH_2Br$, 6N NaOH (b) amine, MeOH (c) PTA (3.0 mol %), NH_4OAc, 2h.



Scheme 2. Reagents and conditions: (a) $BrCH_2CH_2Br$, 6N NaOH (b) amine, MeOH (c) PTA (3 mol %), NH_4OAc, 2h.



from mass spectrum (ESI) by the appearance of $[M + H]^+$ peak at *m/z* 384, IR by the appearance of —NH band at 3058 cm^{-1} and from ^1H NMR by the appearance of increased aromatic protons at δ 7.30–7.90 and the absence of CHO proton at δ 9.93. Similarly the compounds **(11b-f)** were synthesized and their spectroscopic data are in agreement with the assigned structures.

All the newly synthesized compounds **6a–c** and **12a–f** were screened for antibacterial and antifungal activities [10]. All the compounds were active against Gram-negative and Gram-positive bacteria. Among the screened compounds, **12a** showed good activity against Gram-negative and Gram-positive bacteria. Compounds **12a** and **12b** exhibited moderate activity against *Bacillus subtilis* (Table 1).

All the compounds were screened for antifungal activity against *Sacchromyces cerevisiae*, *Aspergillus niger*, *Rhizopus oryzae,* and *Candida albicans* by agar cup diffusion method [11] using Amphotericin-B as standard. All the compounds showed mild antifungal activity.

In summary, novel analogs of trifenagrel were synthesized by using inexpensive and reusable PTA, $H_3[PW_{12}O_{40}]$ catalyst under classical heating and screened for antibacterial and antifungal activities. Compounds **12a** and **12b** showed moderate antibacterial activity.

EXPERIMENTAL

Melting points were measured with Fiescher-Johns melting point apparatus. ^1H NMR spectra were recorded with an AVANCE 300 Bruker (at 300 MHz) and Gemini 200 MHz

Table 1

Antibacterial activies as MIC (μg/mL) for **6a–c** and **12a–f**.

	Gram-positive organisms			Gram-negative organisms		
Compound no.	*B. subtilis*	*S. aureus*	*S. epidermidis*	*E. coli*	*P. aeroginosa*	*K. pneumoniae*
6a	150	150	150	150	150	150
6b	75	150	150	75	150	150
6c	150	150	150	150	150	150
12a	18.75	37.5	37.5	150	37.5	37.5
12b	75	75	150	150	150	150
12c	150	150	150	150	150	150
12d	37.5	37.5	75	150	75	75
12e	150	150	150	150	150	150
12f	150	150	150	150	150	150
Streptomycin	6.25	1.562	1.562	2.35	3.125	3.125
Pencillin	1.526	6.25	3.125	7.81	12.5	6.25

spectrometers in $CDCl_3$. Chemical shifts relative to TMS as internal standard are given as δ values in ppm. ^{13}C NMR was recorded in $CDCl_3$ on a Varian (75 Hz) spectrometer. IR spectra were taken with a Perkin-Elmer 1725A FT-IR spectrophotometer. EI-MS mass spectra were measured at 70 eV (EI).

3-(2-Bromoethoxy)-benzaldehyde (3). A mixture of 3-hydroxybenzaldehyde (6.20 g, 50.8 mmol), 1,2-dibromoethane (38.14 g, 203 mmol), and methanol (50 mL) were heated to reflux. Then, 6*N* NaOH (10 mL) was added in 1.0 mL portions with 30 min intervals. After 18 h of stirring at reflux, the methanol was removed on rotary evaporator. Water (25 mL) was added to the residue and the mixture was extracted into ether (2 × 25 mL). The ethereal extracts were combined and washed with 6*N* NaOH (2 × 10 mL). Again ether layer was separated, dried over Na_2SO_4, concentrated to obtain crude product as brown syrup which was chromatographed over silica gel (60–120 mesh) using hexane:ethyl acetate (8:2) as eluent to obtain titled compound (7.21 g, 62%) (**3**) as brown liquid. IR (Neat): ν 3448, 1695, 1258 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$): δ 3.58 (t, 2H, $-CH_2$), 4.24 (t, 2H, $-CH_2$), 7.03–7.15 (m, 1H, Ar-H), 7.26 (m, 1H, Ar-H), 7.32–7.43 (m, 2H, Ar-H), 9.89 (s, 1H, $-CHO$), ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.77, 67.78, 112.81, 121.65, 123.73, 129.97, 137.54, 158.39, 191.61. EI-MS: *m*/*z* 229 $[M]^+$. Anal.Cacld. for: $C_9H_9O_2Br$: C, 47.19; H, 3.95. Found: C, 47.02; H, 3.98.

3-(2-Dimethylaminoethoxy)benzaldehyde (4a). A mixture of 3-(2-bromoethoxy)-benzaldehyde (1.00 g, 4.36 mmol), 40% dimethylamine solution (10 mL, 81.6 mmol), and methanol (20 mL) was stirred at room temperature for 60 h. After completion of the reaction, methanol was removed on rotary evaporator to obtain the titled compound (**4a**) (0.75 g, 90%) as pale yellow solid. mp: 175–177°C, IR (KBr): ν 3423, 2958, 1679 cm^{-1}, ^1H NMR (200 MHz, DMSO-d_6): δ 2.90 (s, 6H, 2 × CH_3), 3.58 (t, 2H, $-CH_2$), 4.44 (t, 2H, $-CH_2$), 7.30–7.40 (m, 1H, Ar-H), 7.48–7.53 (m, 1H, Ar-H), 7.60–7.63 (m, 2H, Ar-H), 10.01 (s, 1H, $-CHO$), ^{13}C NMR (75 MHz, DMSO-d_6): δ 42.68, 55.17, 62.31, 113.61, 121.44, 123.30, 130.39, 137.49, 157.91, 192.76. EI-MS: *m*/*z* 193 $[M]^+$. Anal. Cacld. for: $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82. Found: C, 68.33; H, 7.89.

2-(3-[2-Dimethylaminoethoxy) phenyl]-4,5-diphenylimidazole (6a). A mixture of benzil (0.42 g, 2.0 mmol), 3-(2-dimethylaminoethoxy) benzaldehyde (0.42 g, 2.0 mmol), ammonium acetate (0.54 g, 7.0 mmol), and PTA (0.1 g, 3 mol %) was heated at 140°C for 2 h. After completion of the reaction, the reaction mixture was cooled to room temperature and diluted with acetone (20 mL). Reaction mixture was filtered to remove catalyst and the filtrate was concentrated on rotary evaporator to syrup. Basification (of the syrup) with ammonium hydroxide (4 mL) resulted in separation of solid, which was collected by filtration *in vacuo* to obtain the titled compound (0.66 g, 86%) (**6a**) as white solid. mp: 182–183°C, IR (KBr): ν 3423, 2928, 1594, 1461 cm^{-1}, ^1H NMR (200 MHz, DMSO-d_6): δ 2.38 (s, 6H, 2 × CH_3), 2.80 (t, 2H, $-CH_2$), 4.17 (t, 2H, $-CH_2$), 6.72–6.81 (m, 1H, Ar-H), 7.22–7.40 (m, 7H, Ar-H), 7.55–7.60 (m, 4H, Ar-H), 7.65–7.72 (m, 2H, Ar-H), ^{13}C NMR (75 MHz, DMSO-d_6): δ 45.26, 57.45, 65.57, 110.95, 114.57, 117.71, 125.21, 127.10, 127.65, 128.37, 129.76, 131.61, 135.11, 145.33, 158.69. ESI-MS: *m*/*z* 384 $[M + H]^+$. Anal. Cacld. for: $C_{25}H_{25}N_30$: C, 78.30; H, 6.57. Found: C, 78.36; H, 6.51.

3-(2-Piperidinoethoxy)benzaldehyde (4b). A mixture of 3-(2-bromoethoxy)-benzaldehyde (1.50 g, 6.55 mmol), piperidine (1.55 g, 18.2 mmol), and methanol (15 mL) was refluxed for 3 h. After completion of the reaction, methanol was removed on rotary evaporator and to the resulting residue 4*N* NaOH (10 mL) was added and stirred for 10 min. Then reaction mixture was extracted into ether (3 × 25 mL) and the combined ethereal phases were extracted into 4*N* HCl (2 × 10 mL) and water (2 × 10 mL). The combined HCl and water extracts were basified with 8*N* NaOH (20 mL) and extracted into ether (2 × 25 mL). The ethereal extracts were washed with water (2 × 50 mL). Organic phase was separated, dried over Na_2SO_4, concentrated to obtain the titled compound (**4b**) (1.0 g, 66%) as brown syrup. IR (Neat): ν 3422, 2932, 1697, 1262 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$): δ 1.42–1.63 (m, 6H, 3 × $-CH_2$), 2.48 (t, 4H, 2 × $-CH_2$), 2.74 (t, 2H, $-CH_2$), 4.14 (t, 2H, $-CH_2$), 6.95–6.98 (m, 1H, Ar-H), 7.77–7.81 (m, 3H, Ar-H), 9.85 (s, 1H, $-CHO$). ESI-MS: *m*/*z* 234 $[M + H]^+$. Anal. Cacld. for: $C_{14}H_{19}NO_2$: C, 72.07; H, 8.20. Found: C, 72.02; H, 8.01.

2-(3-[2-(Piperidino)ethoxy)phenyl]-4,5-diphenylimidazole (6b). Prepared following the procedure described for (**6a**) using benzil (0.42 g, 2.0 mmol), 3-(2-piperidinoethoxy) benzaldehyde (0.51 g, 2.1 mmol), ammonium acetate (0.54 g, 7.0 mmol), and PTA (0.1 g, 3 mol %) to obtain the titled compound (**6b**) (0.70 g, 83%) as brown solid. mp: 142–145°C, IR (Neat): ν 3421, 2923, 1026 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 1.47–1.53 (m, 2H, $-CH_2$), 1.66–1.71 (m, 4H, 2 × $-CH_2$), 2.63–2.72 (m, 2H, $-CH_2$), 2.90 (t, 2H, $-CH_2$), 4.27 (t, 2H, $-CH_2$), 6.78 (d, 2H, Ar-H), 7.18–7.30 (m, 5H, Ar-H), 7.53–7.56 (d, J = 6.98 Hz, 4H, Ar-H), 7.64–7.67 (m, 2H, Ar-H), 7.84 (m, 1H, Ar-H), ^{13}C NMR (75 MHz, DMSO-d_6): δ 125.73, 125.95, 126.58, 127.40, 127.68, 127.79, 128.10, 128.25, 128.37, 130.01,135.93, 144.91, 145.43, 159.26. ESI-MS: *m*/*z* 424 $[M + H]^+$. Anal. Cacld. for: $C_{28}H_{29}N_3O$: C, 79.40; H, 6.89. Found: C, 79.48; H, 6.94.

3-(2-Morpholinoethoxy)-benzaldehyde (4c). Prepared following the procedure described for (**4b**) using 3-(2-bromoethoxy)-benzaldehyde (2.50 g, 10.9 mmol), morpholine (2.62 g, 30.1 mmol), and methanol (25 mL) to obtain the titled compound (**4c**) (1.88 g, 73%) as brown syrup. IR (Neat): ν 3446, 1696,1263 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$): δ 2.54 (t, 4H, 2 × $-CH_2$), 2.78 (t, 2H, $-CH_2$), 3.68 (t, 4H, 2 × $-CH_2$), 4.14 (t, 2H, $-CH_2$), 7.12–7.17 (m, 1H, Ar-H), 7.26 (m, 1H, Ar-H), 7.40–7.43 (m, 2H, Ar-H), 9.94 (s, 1H, $-CHO$). ESI-MS: *m*/*z* 236 $[M + H]^+$. Anal. Cacld. for: $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28. Found: C, 66.31; H, 7.30.

2-(3-[2-(Morpholino)ethoxy)phenyl]-4,5-diphenylimidazole (6c). Prepared following the procedure described for (**6a**) using benzil (0.42 g, 2.0 mmol), 3-(2-morpholinoethoxy) benzaldehyde (0.51 g, 2.1 mmol), ammonium acetate (0.54 g, 7.0 mmol), and PTA (0.1 g, 3 mol %) to obtain the titled compound (**6c**) (0.68 g, 81%) as pale brown solid. mp: 218–219°C, IR (Neat): ν 3422, 1654, 1026 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 2.58 (t, 4H, 2 × $-CH_2$), 2.79 (t, 2H, $-CH_2$), 3.68 (t, 4H, 2 × $-CH_2$), 4.18 (t, 2H, $-CH_2$), 6.81–6.86 (m, 1H, Ar-H), 7.15–7.70 (m, 13H, Ar-H), 12.26 (brs, 1H, $-NH$), ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 52.62, 56.16, 65.29, 76.99, 109.80, 113.45, 116.65, 126.94, 128.25, 136.49, 144.56, 157.58. ESI-MS: *m*/*z* 426 $[M + H]^+$.

Anal. Cacld. for: $C_{27}H_{27}N_3O_2$: C, 76.28; H, 6.31. Found: C, 76.28; H, 6.31.

4-(2-Bromoethoxy) benzaldehyde (9). Prepared following the procedure described for (**3**) using 4-hydroxybenzaldehyde (6.20 g, 50.8 mmol), 1,2-dibromoethane (38.14 g, 203 mmol), and methanol (50 mL) to obtain the titled compound (7.55 g, 65%) (**9**) as white solid. mp: 55–58°C, IR (KBr): ν 3349, 2927, 1601 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.64 (t, 2H, —CH_2), 4.36 (t, 2H, —CH_2), 7.00 (d, J = 9.06 Hz, 2H, Ar-H), 7.81 (d, J = 8.30 Hz, 2H, Ar-H), 9.82 (s, 1H, —CHO), ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.59, 29.66, 67.98, 76.72, 77.14, 77.57, 114.90, 130.47, 131.98, 163.00, 190.63. EI-MS: *m/z* 229 [M]$^+$. Anal. Cacld. for: $C_9H_9O_2Br$: C, 47.19; H, 3.95. Found: C, 47.10; H, 4.01.

4-(2-Dimethylaminoethoxy)benzaldehyde (11a). Prepared following the procedure described for (**4a**) using 4-(2-bromoethoxy)-benzaldehyde (1.00 g, 4.36 mmol), 40% dimethylamine solution (10 mL, 81.6 mmol), and methanol (20 mL) to obtain the title compound (0.77 g, 92%) (**11a**) as brown liquid. IR (Neat): υ 3437, 1690, 1600 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 6H, 2 × CH_3), 2.78 (t, 2H, —CH_2), 4.16 (t, 2H, —CH_2), 6.99–6.94 (m, 2H, Ar-H), 7.36–7.39 (m, 2H, Ar-H), 9.80 (s, 1H, —CHO). EI-MS: *m/z* 193 [M]$^+$. Anal. Cacld. for: $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82. Found: C, 68.41; H, 7.80.

2-(4-[2-Dimethylaminoethoxy)phenyl]-4,5-diphenylimidazole (12a). Prepared following the procedure described for (**6a**) using benzil (0.14 g, 0.67 mmol), 4-(2-dimethylaminoethoxy) benzaldehyde (0.15 g, 0.77 mmol), ammonium acetate (0.18 g, 2.30 mmol), catalyst PTA (0.1 g, 3 mol %) to obtain the titled compound (0.22 g, 89%) (**12a**) as brown solid. mp: 120–125°C, IR (Neat): ν 3058, 2928, 1494, 1245 cm^{-1}, ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 2.32 (s, 6H, 2 × CH_3), 2.72 (t, 2H, —CH_2), 4.08 (t, 2H, —CH_2), 6.90 (d, J = 6.86 Hz, 3H, Ar-H), 7.24–7.28 (m, 5H, Ar-H), 7.54 (d, J = 7.55 Hz, 4H, Ar-H), 7.98 (d, J = 10.98 Hz, 2H, Ar-H), ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 21.81, 44.77, 64.77, 122.85, 125.64, 113.93, 126.46, 127.61, 127.37, 127.92, 128.04,129.77, 132.71, 145.73, 158.11. ESI-MS: *m/z* 384 [M + H]$^+$. Anal. Cacld. for: $C_{25}H_{25}N_3O$: C, 78.30; H, 6.57. Found: C, 78.36; H, 6.51.

4-(2-Piperidinoethoxy) benzaldehyde (11c). Prepared following the procedure described for (**4b**) using 4-(2-bromoethoxy)-benzaldehyde (0.85 g, 3.71 mmol), piperidine (0.80 g, 9.41 mmol), and methanol (15 mL) to obtain the titled compound (**11c**) (0.83 g, 95%) as brown syrup. IR (Neat): υ 2934, 1692, 1601 cm^{-1}, ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 1.42–1.64 (m, 6H, 3 × CH_2), 2.47 (t, 4H, 2 × —CH_2), 2.74 (t, 2H, —CH_2), 4.11 (t, 2H, —CH_2), 7.09–7.15 (m, 2H, Ar-H), 7.34–7.45 (m, 2H, Ar-H), 9.93 (s, 1H, —CHO). ESI-MS: *m/z* 234 [M + H]$^+$. Anal. Cacld. for: $C_{14}H_{19}NO_2$: C, 72.07; H, 8.20. Found: C, 72.02; H, 8.01.

2-(4-[2-(Piperidino)ethoxy)phenyl]-4,5-diphenylimidazole (12c). Prepared following the procedure described for (**7a**) using benzil (0.42 g, 2.0 mmol), 4-(2-piperidinoethoxy)-benzaldehyde (0.51 g, 2.1 mmol), ammonium acetate (0.54 g, 7.0 mmol), catalyst PTA (0.1 g, 3 mol %) to obtain the titled compound (0.74 g, 88%) (**12c**) as pale brown solid. mp: 188–190°C, IR (Neat): ν 3419, 1651, 1025 cm^{-1}, ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 1.38 (m, 6H, 3 × CH_2), 2.50 (t, 4H, 2 × —CH_2), 2.74 (t, 2H, —CH_2), 4.11 (t, 2H, —CH_2), 6.90–6.94 (d, J = 8.86 Hz, 2H, Ar-H), 7.21–7.33 (m, 6H, Ar-H), 7.53–7.56 (d, J = 7.55 Hz, 4H, Ar-H), 7.97–8.02 (m, 2H, Ar-H), ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 19.71, 21.69, 66.60, 108.53, 112.11, 113.14, 120.12, 121.91, 125.49, 126.42, 126.79, 127.61, 128.86, 129.68, 132.04, 133.50, 136.23, 150.13, 157.10, 190.60. ESI-MS: *m/z* 424 [M + H]$^+$. Anal. Cacld. for: $C_{28}H_{29}N_3O$: C, 79.40; H, 6.89. Found: C, 79.48; H, 6.94.

4-(2-Morpholino)ethoxy)benzaldehyde (11e). Prepared following the procedure described for **(5b)** using 4-(2-bromoethoxy)-benzaldehyde (1.00 g, 4.3 mmol), morpholine (1.06 g, 12.18 mmol), and methanol (12.5 mL) to obtain the titled compound (**11e**) (0.97 g, 97%) as brown syrup. IR (Neat): ν 2953, 1689, 1600 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.54 (t, 4H, 2 × —CH_2), 2.79 (t, 2H, —CH_2), 3.68 (t, 4H, 2 × —CH_2), 4.15 (t, 2H, —CH_2), 6.95–7.00 (d, J = 9.06 Hz, 2H, Ar-H), 7.79 (d, J = 8.30 Hz, 2H, Ar-H), 9.85 (s, 1H, —CHO). ESI-MS: *m/z* 236 [M + H]$^+$. Anal. Cacld. for: $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28. Found: C, 66.31; H, 7.30.

2-(4-[2-(Morpholino)ethoxy)phenyl]-4,5-diphenylimidazol (12e). Prepared following the procedure described for (**7a**) using benzil (0.42 g, 2.0 mmol), 4-(2-morpholinoethoxy) benzaldehyde (0.51 g, 2.1 mmol), ammoniumacetate (0.54 g, 7.0 mmol), catalyst phosphotungsticacid (0.1 g, 3 mol %) to obtain the titled compound (**11e**) (0.65 g, 70%) as brown semisolid. IR (Neat): ν 3059, 1603, 1247 cm^{-1}, ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 2.55 (t, 4H, 2 × —CH_2), 2.78 (t, 2H, —CH_2), 3.68 (t, 4H, 2 × —CH_2), 4.13 (t, 2H, —CH_2), 6.90 (d, J = 8.86 Hz, 2H, Ar-H), 7.20–7.57 (m, 10H, Ar-H), 8.00 (m, 2H, Ar-H), ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 23.57, 53.42, 56.85, 65.22, 66.07, 100.85, 113.96, 122.97, 125.67, 125.88, 126.40, 127.33, 127.67, 128.31, 129.59,132.01, 129.95, 145.58, 158.23, 163.30. ESI-MS: *m/z* 426 [M + H]$^+$. Anal. Cacld. for: $C_{27}H_{27}N_3O_2$: C, 76.28; H, 6.31. Found: C, 76.28; H, 6.31.

4-(2-Bromoethoxy)-3-methoxybenzaldehyde (10). Prepared following the procedure described for (**3**) using 4-(3-methoxy) hydroxybenzaldehyde (8.00 g, 52.2 mmol), 1,2-dibromoethane (39.19 g, 208.6 mmol), and methanol (50 mL) to obtain the titled compound (**10**) (9.30 g, 68%) as white crystalline solid. mp: 62–65°C, IR (KBr): ν 3342, 1680, 1270 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.66 (t, 2H, —CH_2), 3.92 (s, 3H, —OCH_3), 4.37 (t, 2H, —CH_2), 6.94 (d, J = 8.30 Hz, 2H, Ar-H), 7.36–7.40 (m, 2H, Ar-H), 9.82 (s, 1H, —CHO), ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.09, 56.03, 68.67, 109.77, 112.34, 126.30, 130.75, 149.92, 152.80, 190.75. ESI-MS: *m/z* 261 [M + H]$^+$. Anal. Cacld. for: $C_{10}H_{11}O_3Br$: C, 46.35; H, 4.27. Found: C, 46.30; H, 4.30.

4-(2-Dimethylaminoethoxy)-3-methoxybenzaldehyde (11b). Prepared following the procedure described for (**5a**) using 4-(2-bromoethoxy)-3-methoxybenzaldehyde (1.00 g, 3.84 mmol), 40% dimethylamine solution (10 mL, 81.6 mmol), and methanol (20 mL) to obtain the title compound (**11b**) (0.77 g, 89%) as yellow syrup. IR (Neat): ν 2941,1682, 1270 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 6H, 2 × CH_3), 2.77 (t, 2H, —CH_2), 3.91 (s, 3H, —OCH_3), 4.15 (t, 2H, —CH_2), 6.93 (d, 1H, Ar-H), 7.36 (d, 2H, Ar-H), 9.81 (s, 1H, —CHO), ^{13}C NMR (75 MHz, $CDCl_3$): δ 45.60, 55.76, 57.58, 66.66, 109.06, 111.28, 126.58, 129.96, 149.59, 153.60, 190.74. EI-MS: *m/z* 224 [M]$^+$. Anal. Cacld. for: $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67. Found: C, 64.49; H, 7.73.

2-(4-[2-Dimethylaminoethoxy)-3-methoxyphenyl]-4,5-diphenylimidazole (12b). Prepared following the procedure described for (**7a**) using benzil (0.42 g, 2.0 mmol), 4-(2-

dimethylaminoethoxy)-3-methoxybenzaldehyde (0.49 g, 2.23 mmol), ammonium acetate (0.54 g, 7.0 mmol), catalyst PTA (0.1 g, 3 mol %) to obtain the titled compound (**12b**) (0.70 g, 85%) as gray solid. mp: 188–190°C, IR (KBr): ν 3386, 1506, 1264 cm^{-1}, ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.29 (s, 6H, 2 × CH_3), 2.69 (t, 2H, —CH_2), 3.91 (s, 3H, —OCH_3), 4.09 (t, 2H, —CH_2), 6.98 (d, J = 6.86 Hz, 1H, Ar-H), 7.21–7.39 (m, 5H, Ar-H), 7.52–7.71 (m, 7H, Ar-H), ^{13}C NMR (75 MHz, DMSO-d_6): δ 44.97, 55.60, 57.19, 65.79, 108.95, 113.38, 117.87, 123.57, 128.35, 145.59, 147.90, 148.99. ESI-MS: *m/z* 414 [M + H]$^+$. Anal. Cacld. for: $C_{26}H_{27}N_3O_2$: C, 75.48; H, 6.51. Found: C, 75.40; H, 6.59.

4-(2-Piperidino)ethoxy)-3-methoxybenzaldehyde (11d). Prepared following the procedure described for (**5b**) using 4-(2-bromoethoxy)-3-methoxybenzaldehyde (1.00 g, 3.84 mmol), piperidine (0.81 g, 9.41 mmol), and methanol (15 mL) to obtain the titled compound (**11d**) (0.84 g, 83%) as brown syrup. IR (Neat): ν 2934, 1683, 1269 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41–1.48 (m, 2H, —CH_2), 1.59–1.64 (m, 4H, 2 × —CH_2), 2.49 (t, 4H, 2 × —CH_2), 2.80 (t, 2H, —CH_2), 3.92 (s, 3H, —OCH_3), 4.18 (t, 2H, —CH_2), 6.93 (d, J = 7.55 Hz, 1H, Ar-H), 7.36–7.39 (m, 2H, Ar-H), 9.81 (s, 1H, —CHO), ESI-MS: *m/z* 264 [M + H]$^+$. Anal. cacld. for: $C_{15}H_{21}NO_3$: C, 68.39; H, 8.04. Found: C, 68.43; H, 8.01.

2-(4-[2-(Piperidino)ethoxy)-3-methoxyphenyl]-4,5-diphenylimidazole (12d). Prepared following the procedure described for (**7a**) using benzil (0.42 g, 2.0 mmol), 4-(2-piperidinoethoxy)-3-methoxybenzaldehyde (0.58 g, 2.2 mmol), ammonium acetate (0.64 g, 8.3 mmol), catalyst PTA (0.10 g, 3 mol %) to obtain the titled compound (**12d**) (0.72 g, 80%) as yellow solid. mp: 100–102°C, IR (Neat): ν 3422, 1647, 1025 cm^{-1}, ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 1.45–1.61 (m, 6H, 3 × CH_2), 2.52 (t, 4H, 2 × —CH_2), 2.79 (t, 2H, —CH_2), 3.92 (s, 3H, —OCH_3), 4.14 (t, 2H, —CH_2), 5.05 (brs, 1H, —NH), 6.88 (d, J = 8.86 Hz, 1H, Ar-H), 7.20–7.33 (m, 6H, Ar-H), 7.53–7.67 (m, 6H, Ar-H), ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 21.39, 22.05, 23.27, 24.66, 53.97, 55.55, 56.77, 65.23, 109.04, 112.53, 117.96, 123.54, 126.58, 127.63, 127.88, 132.92, 145.91, 147.76, 148.76, 172.88, 173.86. ESI-MS: *m/z* 454 [M + H]$^+$. Anal. Cacld. for: $C_{29}H_{31}N_3O_2$: C, 76.79; H, 6.88. Found: C, 76.87; H, 6.80.

4-(2-Morpholino)ethoxy)-3-methoxybenzaldehyde (11f). Prepared following the procedure described for (**5b**) using, 4-(2-bromoethoxy)-3-methoxybenzaldehyde (1.00 g, 3.84 mmol), morpholine (0.93 g, 10.7 mmol), and methanol (15 mL) to obtain the titled compound (**11f**) (0.99 g, 97%) as brown syrup. IR (Neat): υ 2924, 1681, 1269 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.57 (t, 4H, 2 × —CH_2), 2.84 (t, 2H, —CH_2), 3.67 (t, 4H, 2 × —CH_2), 3.91 (s, 3H, —OCH_3), 4.18 (t, 2H, —CH_2), 6.92 (d, J = 9.06 Hz, 1H, Ar-H), 7.37 (d, J = 8.30 Hz, 2H, Ar-H), 9.81 (s, 1H, —CHO). ESI-MS: *m/z* 266 [M + H]$^+$. Anal. Cacld. for: $C_{14}H_{19}NO_4$: C, 63.38; H, 7.21. Found: C, 63.32; H, 7.28.

2-(4-[2-(Morpholino)ethoxy)-3-methoxyphenyl]-4,5-di-phenylimidazole (12f). Prepared following the procedure described for (**7a**) using, benzil (0.42 g, 2.0 mmol), 4-(2-morpholinoethoxy)-3-methoxybenzaldehyde (0.58 g, 2.1 mmol), ammonium acetate (0.64 g, 8.3 mmol), catalyst PTA (0.1 g, 3 mol %) to obtain the titled compound (**12f**) (0.78 g, 86%) as pale brown solid. mp: 198–200°C, IR (Neat): ν 3061, 2939, 1500 cm^{-1}, ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.51–2.56 (m, 4H, 2 × —CH_2), 2.76 (t, 2H, —CH_2), 3.61 (t, 4H, 2 × —CH_2), 3.89 (s, 3H, —OCH_3), 4.12 (t, 2H, —CH_2), 6.95–7.65 (m, 13H, Ar-H), 12.34 (brs, 1H, —NH), ^{13}C NMR (75 MHz, DMSO-d_6): δ 53.13, 55.67, 56.48, 65.20, 65.36, 113.71, 117.94, 127.06, 127.69, 128.38, 145.53, 147.87, 149.07. ESI-MS: *m/z* 456 [M + H]$^+$. Anal. Cacld. for: $C_{28}H_{29}N_3O_3$: C, 73.82; H, 6.41. Found: C, 73.74; H, 6.49.

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Synthesis, Characterization, and Reactions of Selected Multichalcone Derivatives

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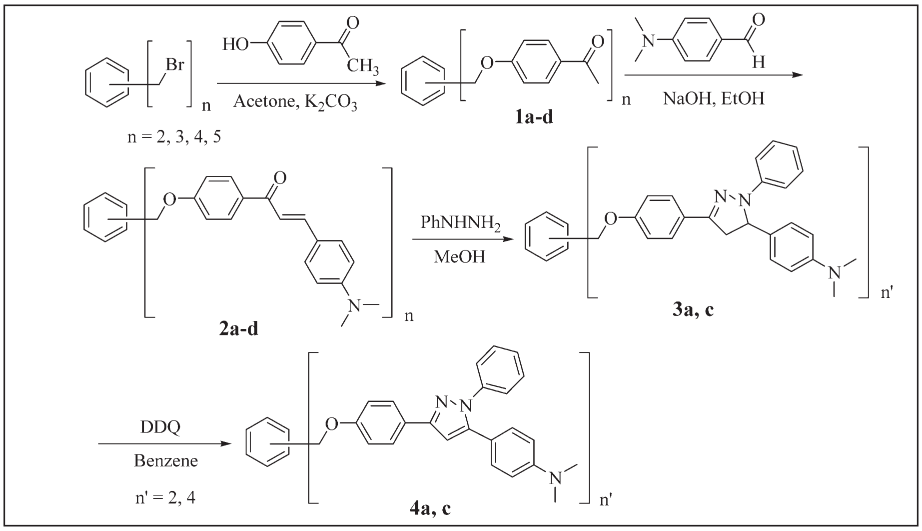

New multiarm aromatic chalcone derivatives **2a-d** were prepared through cross-aldol condensation reaction between multiarm aromatic ketones **1a-d** and 4-(dimethyl amino)benzaldehyde in basic medium. The multiarm aromatic chalcones **2a** and **2c** were able to undergo cyclization reactions when treated with hydrazine or any of it's derivatives to yield the corresponding pyrazolines **3a** and **3c** that were reacted with 2,3-dichloro-5,6-dicyano-1,4-benzoquenone in benzene to yield the aromatic pyrazoles **4a** and **4c**, respectively.

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INTRODUCTION

Heterocyclic chemistry is one of the most interesting and rapidly growing areas of chemical research. Heterocyclic components are found in many natural molecules, such as enzymes, vitamins, hormones, antibiotics and alkaloids, as well as pharmaceuticals, herbicides and dyes [1].

Chemically, chalcones consist of open-chain flavonoids in which the two aromatic rings are joined by a three carbon α,β-unsaturated carbonyl system. Chalcones can undergo many reactions to produce desirable products with desirable applications. They are precursors of flavonoids and isoflavonoids which are abundant in plants [2,3]. Chalcone derivatives have shown good physicochemical and biological activity, including antibacterial, antifungal, and anti-inflammatory [4]. Oxygenated chalcones serve as potential antimalarial agents [5], as antiplasmodial [6], as antiprotozoal, anti-HIV and antimicrobial and they also have an inhibitory effect on the proliferation of human leukemia cells [7]. Chalcones are also a class of anticancer agents, displaying promising therapeutic efficacy for the treatment of human cancers. For example, a chalcone derivative isolated from Chinese licorice root, has been associated with a wide variety of anticancer activity such as Licochalcone-A [8]. Chalcones have also found potential applications as artificial sweeteners, drugs, and agrochemicals [9]. The importance of this class of compounds is not only due to their biological activities but also due to their colors; they give yellow to orange colors in flowers. So, they are attractive to insects in such a way that they contribute to the flower's pollination [10]. Also they are part of some biological macromolecules and microenvironment in micelles [11]. Polymers that have pendent chalcone group become more photoconductive and photosensitive. Such polymers act as negative photo resist material [12]. Recently, the inhibitive action of chalcone derivatives on the corrosion of steel in hydrochloric acid and sulfuric acid solution was studied by Benkaddour and coworkers [13]. In addition, chalcones were widely used for various optical applications including second harmonic generation materials in nonlinear optics [14], liquid crystal display [15], photorefractive polymers, holographic recording materials, and fluorescent probes for sensing of metal ions. As a result, the photophysical properties of chalcones containing alkylamino groups as electron donors have been studied by numerous researchers [16,17].

Various heterocyclic systems can be obtained using chalcone as starting material. These derivatives have different applications. For example, pyrimidine is used as analgesic, antitumor, antifungal and antibacterial agent. Pyrazoles are used as ultraviolet stabilizer, anticancer, muscle relaxant, anti-inflammatory, antipyretic, antiarrhythmic, tranquilizing, anticonvulsant, hypotensive, monoamino oxidase inhibitor, antidiabetic and antibacterial agent [18–23]. Pyrazolines are used to produce photoconductive polymers [24], also used as scintillation solutes [25], as cytotoxic agent [26], they have also broad biological activities; such as psychoanaleptic, anticonvulsant, and antidepressant [27]. Thiazol derivatives have been reported to possess tuberculostatic, antibacterial, and antifungal activities [28].

Therefore, due to the wide application of chalcones and their heterocyclic derivatives, we have synthesized new compounds containing the benzene ring as a nucleus that is substituted with two, three, four or five-arm chalcone moieties. These multiarm chalcones were used for the synthesis of the corresponding heterocyclic compounds containing more than one pyrazoline or pyrazole rings.

RESULTS AND DISCUSSION

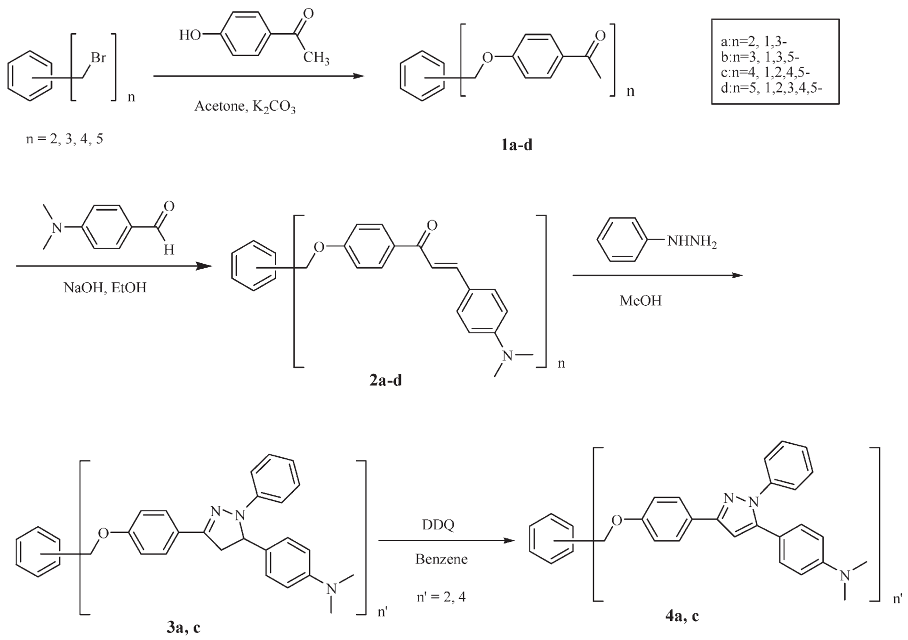
New heterocyclic five-membered ring compounds containing two, four pyrazolines **3a, c** and pyrazoles **4a, c** rings respectively were synthesized and characterized. The synthesis of the compounds **3a, c** and **4a, c** was carried out in a multistep procedure starting from cross-aldol condensation reaction between multiarm aromatic ketones **1a-d** and 4-(dimethylamino)benzaldehyde in basic medium to form the corresponding multiarm aromatic chalcones **2a-d**. We have already described the synthesis of the multiarm aromatic ketones **1b** and **1c** in previous work [29]. The ketones **1a** and **1d** are prepared by a similar procedure through nucleophilic substitution reaction between the corresponding 1,3-bis(bromomethyl)benzene and 1,2,3,4,5-pentakis(bromomethyl)-benzene with 4-hydroxyacetophenone respectively in the presence of potassium carbonate in refluxing dry acetone. The IR spectra of the chalcones **2a-d** showed characteristic bands in the range 1661–1679 for the carbonyl group, 1227–1261 cm^{-1} for the ether linkage and 1595–1599 cm^{-1} for the conjugated double bond. The ^{1}H NMR spectra of the chalcones **2a-d** showed characteristic singlet peak in the range 4.65–5.28 ppm for methylene protons ($-CH_2O-$), another singlet peak at 3.02–3.04 ppm for methyl protons on the nitrogen atom [$-N(CH_3)_2$] and appearance of new peaks at 7.47–7.66 ppm and 7.73–7.96 ppm for the protons of the conjugated double bond ($-CH=CH-$). The coupling constant value ($^3J_{-CH=CH-} = 16$ Hz) of the protons substituted on the double bond, showed that they are in the *trans* orientation relative to each other and thus the multiarm aromatic chalcones have *E*-configuration. The ^{13}C NMR spectra of the chalcones **2a-d** exhibit characteristic peaks at 66.7–69.9 ppm for the methylene carbon ($-CH_2O-$), at 40.0–40.2 ppm for the methyl carbons on the nitrogen atom [$-N(CH_3)_2$] and appearance of new peaks at 121.0–124.2 ppm and 143.0–145.2 ppm for the carbons of the double bond ($-CH=CH-$). The cyclization reaction of the chalcones **2a, c** was carried by treatment with phenylhydrazine in methanol at 0°C to yield the corresponding pyrazolines **3a, c** (**3a**: 63%, **3c**: 55%), which are nonaromatic. Aromatization of the pyrazolines **3a, c** was carried out through reacting them with 2,3-dichloro-5,6-dicyano-1,4-benzoquenone (DDQ) in boiling benzene to yield the aromatic pyrazoles **4a, c** in 75 and 43% yields, respectively.

The IR spectra of the pyrazolines **3a, c** and pyrazoles **4a, c** exhibited absorption bands at 1599–1601 cm^{-1} for the (C=N) bond, at 1340–1382 cm^{-1} for the (C−N) bond in pyrazoline and at 1669–1672 cm^{-1} for the (C=C) double bond in pyrazole. The ^{1}H NMR spectra of the pyrazolines **3a, c** showed characteristic doublet of doublet peaks in the range 4.12–5.04 ppm for the protons ($-CH-N-$) and two doublet of doublets at 3.07–3.76 ppm for the protons of the methylene group ($-CH_2-$) of the pyrazoline. However, a singlet peak at 6.68–7.09 ppm for the pyrazole aromatic proton was observed. The ^{13}C NMR spectra of the pyrazolines **3a, c** showed characteristic signals at 40–42 ppm for the carbon of the ($-CH_2-$) and another signal at 52–53 ppm for the carbon of the ($-CH-N-$) of the pyrazoline. In case of the pyrazole, the characteristic signals were observed at 105–106 ppm for the ($-CH=C-N-$) carbon bearing a proton and at 142–145 ppm for the ($-C-N-$) carbon of the pyrazole ring.

Since compounds **3a, c** and **4a, c** are solid, it was found that the melting point of the compound increases by increasing the number of the carbon atoms present. Also, it was found that the melting point of the pyrazoline derivatives is higher than that for the corresponding aromatic pyrazole derivatives.

The cytotoxicity and the biological activity of the chalcones **2a-d**, their pyrazoline and pyrazole

Scheme 1



derivatives will be studied in the near future (Scheme 1, Table 1).

EXPERIMENTAL

The melting points (mp) of all compounds were determined on an electrothermal digital melting point apparatus. Infrared (IR) spectra of the prepared compounds were recorded using a NICOLET 410 FTIR spectrometer (ν in cm^{-1}). The IR spectra of pure substances were measured as KBr-pellets. The ^1H and ^{13}C NMR spectra were recorded on Bruker AM400 and AC200 ultra shield spectrometers in deuterochloroform or dimethyl sulfoxide-d_6 with tetramethylsilane as an internal standard. The spectral data were reported in delta (δ) units relative to the tetramethylsilane reference line. Mass spectra were acquired using a MAT95 instrument of the Finnigan Company (FD: 5 kV Ionizing energy, field desorption) instruments. The signals were given as *m/z* with the relative intensity between brackets. Elemental analyses were performed in the analytical laboratory of the Institute of Organic Chemistry of the University of Mainz, Mainz, Germany. Analytical thin layer chromatography (TLC) was carried out using TLC-silica plates 60F254 (0.2 mm) of the Merck Company. The detection was followed by UV-lamp or through coloring with iodine. Chromatographic separation was carried out using Merck silica gel (60–230 mesh). The ratios of the solvents and mixed mobile phase were given in volume ratio.

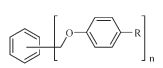
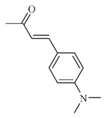
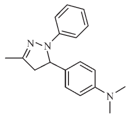
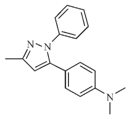
M-xylene, mesitylene, tetra- and penta-methylbenzene were obtained from Aldrich. 4-Hydroxyacetophenone, *N*-bromosuccinimide, 4-(dimethyl amino)benzaldhyde, 2,3-dichloro-5,6-dicyano-1,4-benzo-quenone were obtained from ACROS. These chemicals were used without further purification.

General Procedure for the Preparation of Ketones (1a-d). Ketones **1b**, **c** were prepared from the corresponding bromomethylbenzene derivatives which were prepared from the corresponding methylbenzene derivatives and characterized as described in ref. 29. Whereas the new ketones **1a** and **1d** were prepared following the same procedure but using a mixture of 4-hydroxyacetophenone (1.36 g, 10.0 mmol) and (1.19 g, 4.5 mmol) of 1,3-bis(bromomethyl)benzene or (0.74 g, 1.4 mmol) of 1,2,3,4,5-pentakis(bromomethyl)benzene, respectively, potassium carbonate (1.38 g, 10.0 mmol) and the same equivalent amount of potassium iodide as the bromo compound in dry acetone (100 mL) were refluxed for 48–72 h. The reaction was followed up by TLC (20% chloroform:40% hexane:40% ethyl acetate) until completion. After cooling, the reaction mixture was diluted with water (50 mL) and extracted with dichloromethane (3 × 40 mL). The combined organic layers were dried over magnesium sulphate. The solvent was evaporated under vacuum and the residual solid was washed with diethyl ether. When necessary, a recrystalization from acetone or chloroform was performed.

1,1′-[1,3-Benzenediylbis(methyleneoxy-4,1-phenylene)]bisethanone (1a). This compound was obtained as colorless crystals (1.43 g, 85%)(acetone), mp 139–141°C; IR (potassium bromide): 2936, 1674, 1597, 1242, 1505, 831 cm^{-1}; ^1H NMR (deuteriochloroform): δ 2.55 (s, 6H, CH_3), 5.15 (s, 4H, $2xOCH_2$), 6.98 (d, J = 7.4 Hz, 4H, Ph-H), 7.40 (m, 3H, central-Ph-H), 7.49 (s, 1H, central-Ph-H), 7.91 (d, J = 7.4 Hz, 4H, Ph-H); ^{13}C NMR (deuteriochloroform): δ 26.31 (2C, CH_3), 69.87 (2C, 2 × OCH_2), 114.53 (4C, Ph-C), 126.39 (2C, Ph-C), 127.24 (2C, central-Ph-C), 129.10 (2C, central-Ph-C), 130.13 (1C, central-Ph-C), 130.63 (4C, Ph-C), 136.83 (1C, central-Ph-C), 162.48 (2C, Ph-C), 196.78 (2C, 2 × C=O); ms: (5 kV, fd) *m/z* (%) 374 (100). *Anal.* Calcd. for $C_{24}H_{22}O_4$: C, 76.99; H, 5.92. Found: C, 76.78; H, 5.81.

Table 1

Chemical percentage yield of the compounds (**1a**, **1d**, **2a-d**, **3a**, **3c** and **4a**, **4c**).

 R	Cpd*	Yield (%)	Cpd*	Yield (%)	Cpd*	Yield (%)	Cpd*	Yield (%)
	**1a**	85					**1d**	87
	**2a**	85	**2b**	30	**2c**	75	**2d**	20
	**3a**	63			**3c**	55		
	**4a**	75			**4c**	43		

a:n = 2, 1,3-.
b:n = 3, 1,3,5-.
c:n = 4, 1,2,4,5-.
d:n = 5, 1,2,3,4,5-.
[Cpd*] is compound.

1,1′,1″,1‴,1⁗,1′′′′′-[1,2,3,4,5-Benzenepentaylpentakis(methyleneoxy-4,1-phenylene)]pentakisethanone (1d). This compound was obtained as pale yellow powder (1.13 g, 87%), mp 234–235°C; IR (potassium bromide): 2932, 1674, 1598, 1575, 1505, 1241, 1171, 831 cm^{-1}. ^{1}H NMR (deuteriochloroform): δ 2.50 (s, 15H, CH_3), 5.10 (s, 10H, 5 × OCH_2), 6.99 (d, *J* = 7.4 Hz, 10H, Ph-H), 7.46 (s, 1H, central-Ph-H), 7.93 (d, *J* = 7.4 Hz, 10H, Ph-H); ^{13}C NMR (deuteriochloroform): δ 26.35 (5C, CH_3), 63.57 (5C, 5 × OCH_2), 114.41 (10C, Ph-C), 126.39 (5C, Ph-C), 130.61 (10C, Ph-C), 130.50–131.18 (5C, central-Ph-C), 137.64 (1C, central-Ph-C), 161.83 (5C, Ph-C), 196.54 (5C, 5 × C=O); ms: (5 kV, fd) *m*/*z* (%) 818 (100). *Anal*. Calcd. for $C_{51}H_{46}O_{10}$: C, 74.80; H, 5.66. Found: C, 74.79; H, 5.56.

General procedure for the preparation of multi arm Chalcones (2a-d). A mixture of 4-(dimethylamino)benzaldhyde (1.49 g, 10.0 mmol) and (1.50 g, 4.0 mmol) of ketone **1a**, or (1.41 g, 2.7 mmol) of ketone **1b**, or (1.27 g, 1.9 mmol) of ketone **1c**, or (0.98 g, 1.2 mmol) of ketone **1d**, respectively, was prepared by dissolving the ketone in dry and warm ethanol (25 mL) at 50°C. A second solution of equivalent amount of sodium hydroxide was dissolved in dry ethanol (20 mL) and was added very slowly to the first solution with stirring at 50°C until completion. The mixture was left stirring for 2–5 days. The reaction progress was followed by TLC with different ratio of mobile phase (hexane:ethyl acetate) for each compound until completion. The solvent was evaporated under vacuum and the residual solid was purified by Column chromatography using different ratio of eluants (hexane:ethyl acetate) for each compound.

(2E,2′E)-1,1′-[1,3-Benzenediylbis(methyleneoxy-4,1-phenylene)] bis{3-[4-(dimethylamino)phenyl]-2-propen-1-one} (2a). This compound was obtained as pale-yellow powder (1.46 g, 85%), mp 130°C (decomposition); IR (potassium bromide): 1672, 1598, 1254, 1227, 981, 811 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.02 (s, 12H, CH_3), 5.15 (s, 4H, 2 × OCH_2), 7.02 (d, 4H, Ph-H), 7.46 (m, 3H, central-Ph-H), 7.05 (s, 1H, central-Ph-H), 7.92 (d, 4H, Ph-H), 7.54 (d, 2H, $^3J_{11-12}$ = 16 Hz, Ph-H), 7.94 (d, 2H, Ph-H), 6.99 (d, 4H, Ph-H), 6.86 (d, 4H, Ph-H); ^{13}C NMR (deuteriochloroform): δ 40.18 (4C, CH_3), 69.90 (2C, 2 × OCH_2), 111.29 (4C, Ph-C), 130.26 (2C, Ph-C), 127.14 (2C, central-Ph-C), 128.90 (2C, central-Ph-C), 130.28 (1C, central-Ph-C), 130.30 (4C, Ph-C), 142.03 (1C, central-Ph-C), 163.04 (2C, Ph-C), 121.21 (2C, Ph-C), 145.11 (2C, Ph-C), 121.69 (2C, Ph-C), 114.55 (4C, Ph-C), 127.36 (4C, Ph-C), 142.19 (2C, Ph-C), 188.67 (2C, 2 × C=O); ms: (5 kV, fd) *m*/*z* (%) 637 (100). *Anal*. Calcd. for $C_{42}H_{40}N_2O_4$: C, 79.22; H, 6.33; N, 4.40. Found: C, 79.34; H, 6.49; N, 4.33.

(2E,2′E,2″E)-1,1′,1″-[1,3,5-Benzenetriyltris(methyleneoxy-4,1-phenylene)]tris{3-[4-(dimethylamino)phenyl]-2-propen-1-one} (2b). This compound was obtained as orange solid (0.74 g, 30%), mp 180°C (decomposition); IR (potassium bromide): 1679, 1595, 1261, 1096, 799 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.02 (s, 18H, CH_3), 4.65 (s, 6H, 3 × OCH_2), 6.96 (d, 6H, Ph-H), 7.48 (s, 3H, central-Ph-H), 7.99 (d, 6H, Ph-H), 7.47 (d, 3H, $^3J_{11-12}$ = 16 Hz, Ph-H), 7.96 (d, 3H, Ph-H), 6.99 (d, 6H, Ph-H), 6.86 (d, 6H, Ph-H); ^{13}C NMR (deuteriochloroform): δ 40.20 (6C, CH_3), 69.78 (3C, 3 × OCH_2), 115.51 (6C, Ph-C), 131.29 (3C, Ph-C), 128.94 (3C, central-Ph-C), 130.32

(3C, central-Ph-C), 130.95 (6C, Ph-C), 161.90 (3C, Ph-C), 122.70 (3C, Ph-C), 143.70 (3C, Ph-C), 122.74 (3C, Ph-C), 114.55 (6C, Ph-C), 127.30 (6C, Ph-C), 142.10 (3C, Ph-C), 189.50 (3C, 3 × C=O); ms: (5 kV, fd) *m/z* (%) 916 (100). *Anal*. Calcd. for $C_{60}H_{57}N_3O_6$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.43; H, 6.39; N, 4.45.

(2E,2′E,2″E,2‴E)-1,1′,1″,1‴-[1,2,4,5-Benzenetetrayltetrakis(methyleneoxy-4,1-phenylene)]tetrakis{3-[4-(dimethylamino)phenyl]-2-propen-1-one} (2c). This compound was obtained as pale-yellow powder (1.70 g, 75%), mp 240°C (decomposition); IR (potassium bromide): 1671, 1599, 1575, 1258, 1274, 827 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.03 (s, 24H, CH_3), 5.25 (s, 8H, 4 × OCH_2), 6.99 (d, 8H, Ph-H), 7.42 (s, 2H, central-Ph-H), 7.92 (d, 8H, Ph-H), 7.57 (d, 4H, $^{3}J_{11-12}$ = 16 Hz, Ph-H), 7.94 (d, 4H, Ph-H), 7.00 (d, 8H, Ph-H), 6.71 (d, 8H, Ph-H); ^{13}C NMR (deuteriochloroform): δ 40.00 (8C, CH_3), 67.65 (4C, 4 × OCH_2), 114.39 (8C, Ph-C), 130.90 (4C, Ph-C), 114.12 (2C, central-Ph-C), 129.82 (4C, central-Ph-C), 130.67 (8C, Ph-C), 162.00 (4C, Ph-C), 124.20 (4C, Ph-C), 145.70 (4C, Ph-C), 124.20 (4C, Ph-C), 114.10 (8C, Ph-C), 127.10 (8C, Ph-C), 139.20 (4C, Ph-C), 189.01 (4C, 4 × C=O); ms: (5 kV, fd) *m/z* (%) 1195 (100). *Anal*. Calcd. for $C_{78}H_{74}N_4O_8$: C, 78.37; H, 6.24; N, 4.69. Found: C, 78.23; H, 6.12; N, 4.54.

(2E,2′E,2″E,2‴E,2⁗E)-1,1′,1″,1‴,1⁗-[1,2,3,4,5-Benzenepentaylpentakis(methyleneoxy-4,1-phenylene)]pentakis{3-[4-(dimethylamino)phenyl]-2-propen-1-one} (2d). This compound was obtained as red solid (0.35 g, 20%), mp 205°C (decomposition); IR (potassium bromide): 1661, 1598, 1505, 1371, 1231, 1165, 824 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.04 (s, 30H, CH_3), 5.19 (s, 10H, 5 × OCH_2), 6.87 (d, 10H, Ph-H), 7.40 (s, 1H, central-Ph-H), 7.83 (d, 10H, Ph-H), 7.66 (d, 5H, $^{3}J_{11-12}$ = 16 Hz, Ph-H), 7.72 (d, 5H, Ph-H), 6.82 (d, 10H, Ph-H), 6.67 (d, 10H, Ph-H); ^{13}C NMR (deuteriochloroform): δ 40.00 (10C, CH_3), 66.70 (5C, 5 × OCH_2), 114.41 (10C, Ph-C), 132.00 (5C, Ph-C), 114.19 (1C, central-Ph-C), 122.40–125.14 (5C, central-Ph-C), 130.79 (10C, Ph-C), 161.70 (5C, Ph-C), 122.30 (5C, Ph-C), 143.00 (5C, Ph-C), 121.20 (5C, Ph-C), 114.10 (10C, Ph-C), 128.60 (10C, Ph-C), 143.00 (5C, Ph-C), 190.76 (5C, 5 × C=O); ms: (5 kV, fd) *m/z* (%) 1475 (100). *Anal*. Calcd. for $C_{96}H_{91}N_5O_{10}$: C, 78.18; H, 6.22; N, 4.75. Found: C, 78.06; H, 6.15; N, 4.68.

General procedure for the preparation of Multi arm pyrazolines (3a, c) and pyrazoles (4a, c). Phenylhydrazine (0.43 g, 4 mmol) in methanol (1.0 mL) was added dropwise at 0°C under nitrogen atmosphere to a solution of (0.31 g, 0.50 mmol) enone 2a or (0.30, 0.25 mmol) enone 2c respectively in dry methanol (20 mL). The addition was completed within 5 h after which the mixture was left stirring for about 30 h. The reaction was followed by TLC in (40% toluene:60% ethyl acetate) until completion. The solvent was evaporated under vacuum and the residual solid was purified by column chromatography using (40% toluene:60% ethyl acetate) as eluant to yield the pyrazolines 3a, c which already contains some autoxidation product of pyrazoles 4a, c. The regular oxidation of pyrazolines 3a, c to the corresponding pyrazoles 4a, c was achieved by evaporating methanol and dissolving the residual solid in boiling benzene (3.0 mL) then (0.09 g, 0.4 mmol) 2,3-dichloro-5,6-dicyano-1,4-benzoquenone was added slowly with stirring. After 1–2 h, the products were purified by column chromatography using (50% toluene:50% ethyl acetate) as the eluant for the compounds.

3,3′-[1,3-Benzenediylbis(methyleneoxy-4,1-phenylene)]bis{4,5-dihydro-5-[4-(dimethylamino)phenyl]-1-phenylpyrazol-3-yl} (3a). This compound was obtained as orange solid (0.25 g, 63%), mp 172–174°C; IR (potassium bromide): 1601, 1455, 1382, 1219, 1076, 792 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.10 (s, 12H, CH3), 5.26 (s, 4H, 2 × OCH_2), 7.09 (d, 4H, Ph-H), 7.76 (m, 3H, central-Ph-H), 7.55 (s, 1H, central-Ph-H), 7.76 (d, 4H, Ph-H), 2.07 (dd, 4H, —CH_2—), 4.12 (m, 2H, —CH—), 6.70 (d, 4H, Ph-H), 6.99 (d, 4H, Ph-H), 7.10 (m, 10H, Phen-H); ^{13}C NMR (deuteriochloroform): δ 40.23 (4C, CH_3), 67.78 (2C, 5 × OCH_2), 111.86 (4C, Ph-C), 125.09 (2C, Ph-C), 140.48 (2C, central-Ph-C), 128.90 (2C, central-Ph-C), 130.14 (1C, central-Ph-C), 130.67 (4C, Ph-C), 128.35 (1C, central-Ph-C), 162.09 (2C, Ph-C), 152.02 (2C, Ph-C), 40.23 (2C, —CH_2—), 53.29 (2C, —CH—), 121.06 (2C, Ph-C), 114.40 (4C, Ph-C), 128.35 (4C, Ph-C), 143.52 (2C, Ph-C), 135.12 (2C, Ph-C), 113.57, 130.42, 132.08 (10C, Ph-C); ms: (5 kV, fd) m/z (%) 817 (100). *Anal*. Calcd. For $C_{54}H_{52}N_6O_2$: C, 79.38; H, 6.42; N, 10.29. Found: C, 79.23; H, 6.29; N, 10.21.

3,3′,3″,3‴-[1,2,4,5-Benzenetetrayltetrakis(methyleneoxy-4,1-phenylene)]pentakis{4,5-dihydro-5-[4-(dimethylamino)phenyl]-1-phenylpyrazol-3-yl} (3c). This compound was obtained as brown solid (0.21 g, 55%), mp 106°C (decomposition); IR (potassium bromide): 1648, 1599, 1340, 1255, 1164, 812 cm^{-1}; ^{1}H NMR (deuteriodimethylsulfoxide-d_6): δ 2.89 (s, 24H, CH_3), 5.02 (s, 8H, 4 × OCH_2), 6.84 (d, 8H, Ph-H), 7.34 (s, 2H, central-Ph-H), 7.40 (d, 8H, Ph-H), 3.69 (dd, 8H, —CH_2—), 5.04 (m, 4H, —CH—), 7.01 (d, 8H, Ph-H), 6.71 (d, 8H, Ph-H), 6.92 (m, 20H, Ph-H); ^{13}C NMR (deuteriodimethylsulfoxide-d_6): δ 40.99 (8C, CH_3), 69.10 (4C, 4 × OCH_2), 112.90 (8C, Ph-C), 125.67 (4C, Ph-C), 114.12 (2C, central-Ph-C), 129.09 (4C, central-Ph-C), 130.63 (8C, Ph-C), 164.12 (4C, Ph-C), 152.29 (4C, Ph-C), 42.28 (4C, —CH_2—), 52.29 (4C, —CH—), 124.84 (4C, Ph-C), 114.40 (8C, Ph-C), 128.79 (8C, Ph-C), 139.74 (4C, Ph-C), 136.73 (4C, Ph-C), 113.60, 130.63, 130.84 (20C, Ph-C); ms: (5 kV, fd) *m/z* (%) 1556 (100). *Anal*. Calcd. For $C_{102}H_{98}N_{12}O_4$: C, 78.74; H, 6.35; N, 10.80. Found: C, 78.66; H, 6.28; N, 10.69.

3,3′-[1,3-Benzenediylbis(methyleneoxy-4,1-phenyl-ene)]bis{5-[4-(dimethylamino)phenyl]-1-phenylpyrazol-3-yl} (4a). This compound was obtained as dark brown solid (0.30 g, 75%), mp 135–137°C; IR (potassium bromide): 1669, 1599, 1255, 1213, 811 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.92 (s, 12H, CH_3), 5.11 (s, 4H, 2 × OCH_2), 6.97 (d, 4H, 7-H), 7.40 (m, 3H, central-Ph-H), 7.27 (s, 1H, central-Ph-H), 7.54 (d, 4H, Ph-H), 7.09 (s, 2H, Pyrazol-H), 7.38 (d, 4H, Ph-H), 6.97 (d, 4H, Ph-H), 7.14 (m, 10H, Ph-H); ^{13}C NMR (deuteriochloroform): δ 40.35 (4C, CH_3), 63.14 (2C, 2 × OCH_2), 114.98 (4C, Ph-C), 130.30 (2C, Ph-C), 142.16 (2C, central-Ph-C), 129.58 (2C, central-Ph-C), 130.37 (1C, central-Ph-C), 130.63 (4C, Ph-C), 127.10 (1C, central-Ph-C), 161.90 (2C, Ph-C), 159.40 (2C, Ph-C), 105.35 (2C, Pyrazol-C), 142.16 (2C, Pyrazol-C), 125.34 (2C, Ph-C), 114.56 (4C, Ph-C), 128.82 (4C, Ph-C), 140.90 (2C, Ph-C), 139.83 (2C, Ph-C), 113.30, 127.19, 129.89 (10C, Ph-C); ms: (5kV, fd) *m/z* (%) 813 (100). *Anal*. Calcd. For $C_{54}H_{48}N_6O_2$: C, 79.78; H, 5.95; N, 10.34. Found: C, 79.64; H, 5.88; N, 10.31.

3,3′,3″,3‴-[1,2,4,5-Benzenetetrayltetrakis(methyleneoxy-4,1-phenyl-ene)]pentakis{5-[4-(dimethylamino)phenyl]-1-phenyl-pyrazol-3-yl} (4c). This compound was obtained as dark brown solid (0.17 g, 43%), mp 190°C (decomposition); IR (potassium bromide): 1672, 1597, 1356, 1124, 997 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.97 (s, 24H, CH_3), 5.17 (s, 8H, 4 × OCH_2), 6.90 (d, 8H, Ph-H), 7.44 (s, 2H, central-Ph-H), 7.59 (d, 8H, Ph-H), 7.19 (s, 4H, Pyrazol-H), 7.38 (d, 8H, Ph-H), 6.87 (d, 8H, Ph-H), 7.28 (m, 20H, Ph-H); ^{13}C NMR (deuteriochloroform): δ 40.17 (8C, CH_3), 64.17 (4C, 4 × OCH_2), 116.60 (8C, Ph-C), 130.63 (4C, Ph-C), 114.46 (2C, central-Ph-C), 129.23 (4C, central-Ph-C), 130.70 (8C, Ph-C), 161.62 (4C, Ph-C), 151.97 (4C, Ph-C), 106.60 (4C, Pyrazol-C), 145.34 (4C, Pyrazol-C), 122.81 (4C, Ph-C), 114.61 (8C, Ph-C), 127.23 (8C, Ph-C), 149.94 (4C, Ph-C), 145.34 (4C, Ph-C), 116.60, 130.64, 130.70 (20C, Ph-C); ms: (5kV, fd) *m/z* (%) 1548 (100). *Anal.* Calcd. For $C_{102}H_{90}N_{12}O_4$: C, 79.15; H, 5.86; N, 10.86. Found: C, 79.04; H, 5.78; N, 10.71.

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A New Synthetic Route to 2*H*-Benzo[*g*]chromene-5,10-diones Involving Ring Closing Metathesis

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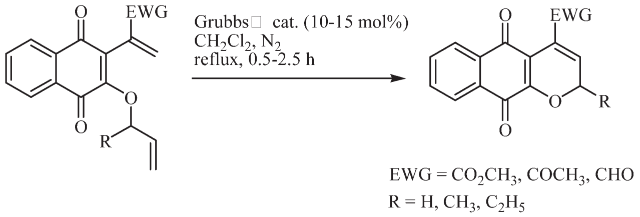

A simple synthesis of several 2*H*-benzo[*g*]chromene-5,10-diones *via* the ring closing metathesis reaction of prerequisite bisolefins, prepared from the α-vinylnaphthoquinones, is described.

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INTRODUCTION

Heterocyclic compounds sharing quinonoid constituents are wide spread in nature and exhibit a broad range of biological activities [1]. Among them, pyranonaphthoquinones with some famous examples such as α-lapachone [2], β-lapachone [3], pentalongin [4], and pyranokunthone A and B [5] have attracted considerable synthetic attention because of their interesting pharmacological actions (Fig. 1) [6]. Specifically, lapachone derivatives and lapachol-type naphthoquinone compounds obtained from the bark of the lapacho tree (*Tabebuia avellanedae*) from Central and South America [2a] are known to display antitumor [7], anti-inflammatory [8], antifungal [9], antimalarial [10], and antibacterial [11] properties. Owing to the remarkable biological activities of lapachones, there has been much interest in the development of easy and simple methodologies to synthesize lapachone derivatives. Pyranonaphthoquinones including lapachone derivatives are most typically produced through the alkylation of 2-hydroxy-1,4-naphthoquinone followed by cyclization [12]. Recently, Lee and coworkers reported one-pot synthesis of pyranonaphthoquinone derivatives starting from 2-hydroxy-1,4-naphthoquinone with a variety of α,β-unsaturated aldehydes by a tandem Knoevenagel-electrocyclic reaction [6b].

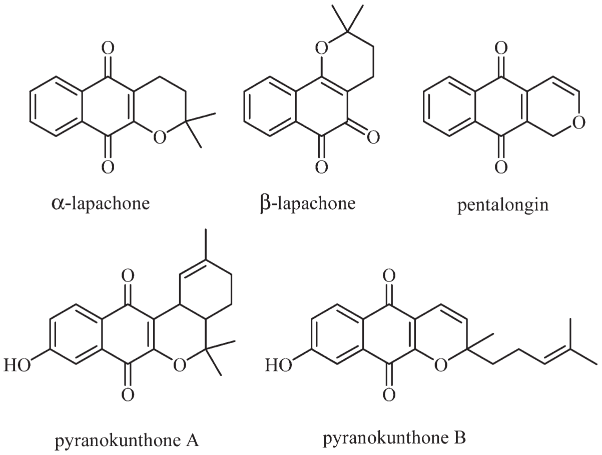
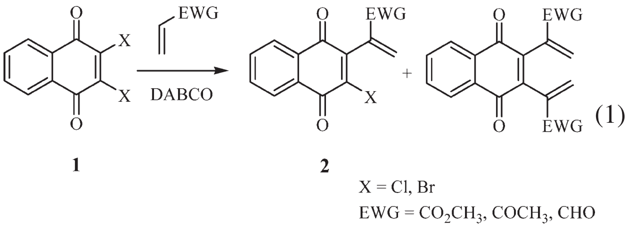


Figure 1. Naturally occuring pyranonaphthoquinones.

The Morita–Baylis–Hillman (MBH) reaction has been one of the most intensively studied carbon–carbon bond-forming reactions in organic synthesis [13]. Many efforts have been focused on the extension of useful electrophiles in the MBH reaction [14] besides aldehydes, which are the traditional source of electrophiles. In our earlier articles [15], we have demonstrated that 1,4-diazabicyclo[2,2,2]octane (DABCO)-assisted enolate anions of several activated olefins were useful in substitution reactions of 2,3-dihalo-1,4-naphthoquinones, leading to the formation of α-vinylnaphthoquinones and divinylnaphthoquinones under MBH reaction conditions [eq. (1)]. We also reported that these α-vinylated products were useful substrates for the synthesis of 4-chloro-5-hydroxy-1*H*-benzo[*g*]indoles in the presence of primary amines *via* the Nenitzescu indole synthetic route [15b].

As a continuation of our interest in the syntheses of heterocyclic compounds with possible biological activities using MBH chemistry [16], we now report a new synthetic pathway to 2*H*-benzo[*g*]chromenes from α-vinylnaphthoquinones using Grubbs second generation catalyst for the ring closing step [4b,17]. Although various 2*H*-benzo[*g*]chromenes were prepared earlier [6], to our knowledge, no synthetic example of 4-acyl-2*H*-benzo[*g*]chromene derivatives has been previously reported.



RESULTS AND DISCUSSION

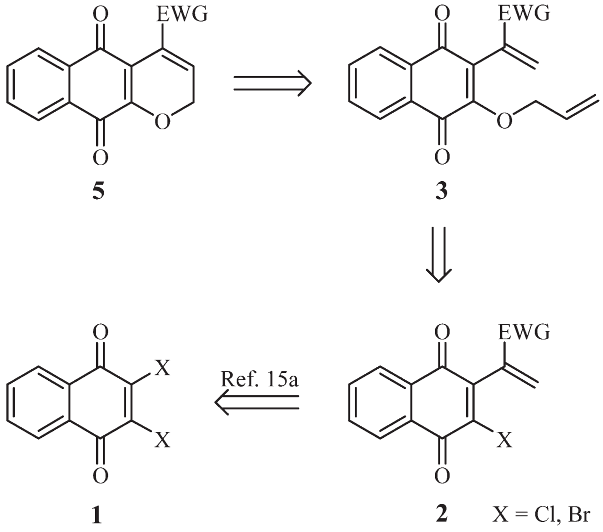
We hypothesized that a pyran ring might be obtained from the ring closing metathesis (RCM) reaction of an appropriate bisolefin precursor **3** as shown in Scheme 1. The bisolefin **3** would result from the nucleophilic substitution reaction of a halogen atom on the known α-vinylnaphthoquinone **2** into allyl alkoxide. Accordingly, the known α-vinylnaphthoquinone **2a** was first synthesized as the stating material under MBH reaction condition [15a]. Treatment of **2a** with a suspension of 1.2 equivalent of allyl alcohol and sodium hydride in *N*,*N*-dimethylformamide at room temperature afforded disubstituted naphthoquinone **3a** in a moderate yield (47%) (Scheme 2). With this precursor **3a** in hand, we undertook the RCM reaction using 1 mol % of Grubbs second generation catalyst in refluxing dichloromethane (0.01*M*) under nitrogen atmosphere. Unfortunately, the reaction did not proceed at all and no trace of ring closed product was detected on thin layer chromatography (TLC). However, to our delight, an increased amount of catalyst (5 mol %) allowed the formation of the desired RCM product **5a** in a moderate yield (56%) after 2 h, without dimerized compounds. Moreover, the yield improved to 74% and the reaction time was shortened to 30 min with increased amount of catalyst (10 mol %).

We then aimed to extend the utility of this RCM reaction; therefore, we investigated further reactions of other types of bisolefins with various allyl alcohols. At first, bisolefins **3b** and **3c**, which have more steric hinderance at the allylic position than **3a**, were prepared in 78 and 54% yields, respectively, and RCM reactions of **3b** and **3c** furnished cyclized products **5b** (63%) and **5c** (80%) in good yields after 2 h with 10 mol % of catalyst. In these cases, we observed that the steric effect of allyl alcohol moiety required greater loading of catalyst and more reaction time to complete the RCM reaction [18].

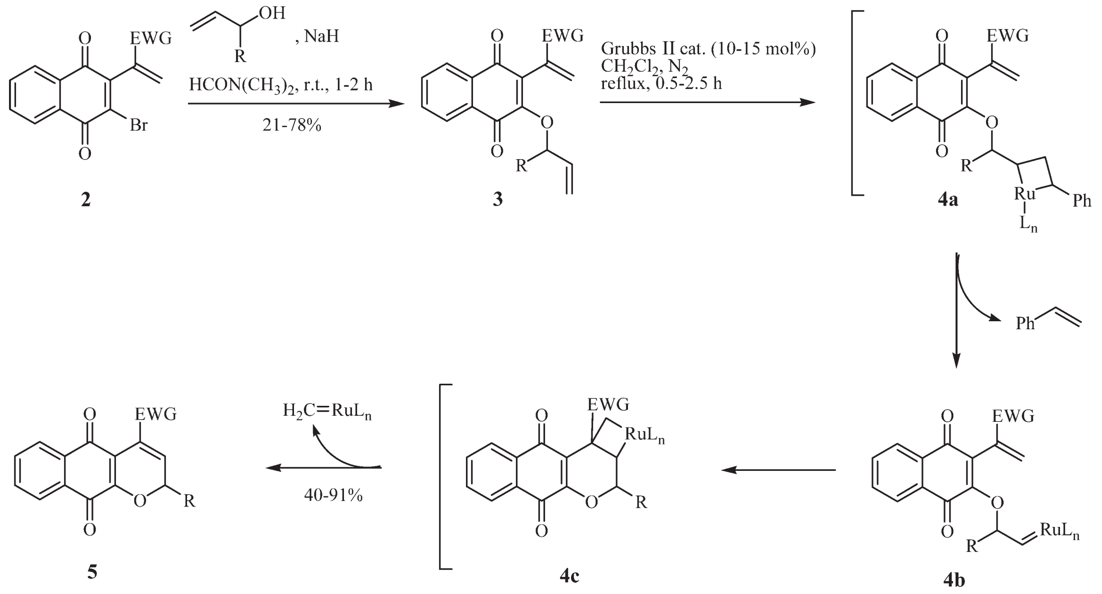
We next examined the reactivity of other electron-deficient olefin systems such as acetyl and formyl groups. The bisolefins **3d-f** were prepared under similar reaction conditions from **2b** [15a] in 56–69% yields. Generally, the RCM reactions of **3d-f** required more catalyst and longer reaction times as shown in Table 1. In the case of **3d**, 5 mol % loading of catalyst was not sufficient to obtain the desired product **5d**. The bisolefin **3d** was transformed into the desired 2*H*-benzo[*g*]chromene **5d** in an excellent yield (91%) using 10 mol % of catalyst in refluxing dichloromethane (0.01*M*) after 40 min. Also, addition of 15 mol % catalyst led to successful formation of **5e** and **5f** in acceptable yields (41 and 66%) from the bisolefin **3e** and **3f**, respectively [19]. Additionally, the reactions of **2c** [15a] with 3-buten-2-ol and 1-penten-3-ol afforded the corresponding bisolefin **3g** and **3h** in low yields (21 and 31%), respectively. These relatively poor yields may arise from the high reactivity of *O*-nucleophiles toward the aldehyde group. On exposure of these bisolefins to RCM reaction conditions (15 mol % of catalyst), the RCM products **5g** [20] and **5h** were obtained in 40 and 42% yields, respectively. Efforts to obtain more steric secondary and tertiary alcohols such as α-vinylbenzyl alcohol, 1,4-pentadien-3-ol, and 2-methyl-3-buten-2-ol from the substitution reaction of **2a** were unsuccessful under various reaction conditions.

The mechanism for the formation of **5** is proposed in Scheme 2. The ruthenium carbene complex adds to one of the olefins as a [2 + 2] cycloaddition to give a four-membered ring **4a** with the metal atom in the ring. In this instance, the same reaction happens in reverse, either to give the starting materials or, by cleavage of the other two bonds, a new carbene complex **4b** and

Scheme 1

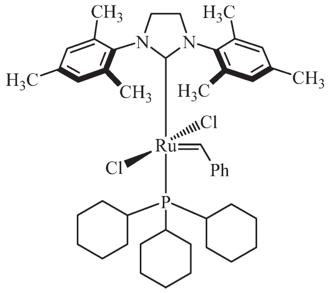


Scheme 2



2	EWG	3, 5	R	EWG
a	CO_2CH_3	**a**	H	CO_2CH_3
		b	CH_3	CO_2CH_3
		c	C_2H_5	CO_2CH_3
b	$COCH_3$	**d**	H	$COCH_3$
		e	CH_3	$COCH_3$
		f	C_2H_5	$COCH_3$
c	CHO	**g**	CH_3	CHO
		h	C_2H_5	CHO

Grubbs II catalyst



styrene. Next, an intramolecular [2 + 2] cycloaddition joins up the six-member ring and produces a second metalla cyclobutane **4c**, which decomposes in the same way as the first one to give a third carbene complex and the product **5**.

The structure of **5** was established on the basis of spectroscopic data. The ^1H NMR spectra of both **5a** and **5d** showed disappearance of terminal alkenic protons. In the ^1H NMR of **5a**, the signal from the two C2 methylene protons appeared at δ 5.03 as a doublet ($J = 4.1$ Hz), and C3 vinylic proton appeared at δ 6.34 as a triplet ($J = 4.1$ Hz). In the case of **5d**, the signal corresponding to the two C2 methylene protons was observed at δ 5.05 as a doublet ($J = 4.0$ Hz), and C3 vinylic proton appeared at δ 6.10 as a triplet ($J = 4.0$ Hz). The ^{13}C NMR spectra of **5a** and **5d** each exhibited fifteen absorption peaks, including a signal at δ 166.3 for the ester carbonyl group of **5a** and a signal at δ 199.2 for the acetyl carbonyl group of **5d**.

CONCLUSION

In summary, we have synthesized several 2*H*-benzo[*g*]chromene derivatives with electron-withdrawing substituents at C4 position *via* RCM reaction from the easily accessible α-vinylnaphthoquinones. However, couplings

Table 1

4-Acyl-2*H*-benzo[*g*]chromene-5,10-diones **5**.

Bisolefin	Catalyst (mol %)	Time[a]	Product	Yield (%)
3a	5/10	2 h/30 min	**5a**	56/74
3b	10	2 h	**5b**	63
3c	10	2 h	**5c**	80
3d	10	40 min	**5d**	91
3e	15	2 h 30 min	**5e**	41
3f	15	2 h 30 min	**5f**	66
3g	15	1 h	**5g**	40
3h	15	1 h 30 min	**5h**	42

[a] Reflux temperature.

between α-vinylnaphthoquinones and some steric allyl alcohols to produce bisolefin precursors remain limited.

EXPERIMENTAL

Silica gel 60 (70-230 mesh ASTM) used for column chromatography was supplied by E. Merck. Analytical TLC was performed on Merck silica gel 60 F_{254} TLC plates. Melting points were measured by an Electrothermal melting point apparatus and were uncorrected. Microanalysis was obtained using a Thermo Electron Corporation Flash EA 1112 element analyzer. Infrared spectra were recorded with a Nicolet Magna 550 FTIR spectrometer. Electron impact (EI) mass and high resolution mass spectra were obtained using a Jeol SX 102 mass spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were measured on a Gemini 300 spectrometer using deuteriochloroform. All chemical shifts are reported in parts per million relative to tetramethylsilane. The coupling constants (*J*) are expressed in Hertz.

Allyl alcohol, 3-buten-2-ol, 1-penten-3-ol, 1,4-pentadien-3-ol, 2-methyl-3-buten-2-ol, α-vinylbenzyl alcohol, and Grubbs second-generation catalyst were obtained from Aldrich and used without further purification. The known α-vinylnaphthoquinones **2a**, **2b**, and **2c** were prepared according to the published procedures [15a].

Methyl 2-[3-(allyloxy)-1,4-dihydro-1,4-dioxonaphthalen-2-yl]acrylate (3a). To a stirred suspension of ally alcohol (0.16 mL, 2.4 mmol) and sodium hydride (58 mg, 2.4 mmol) in *N*,*N*-dimethylformamide (5 mL) was added **2a** (642 mg, 2 mmol) at room temperature. After stirring for 2 h, the reaction mixture was diluted with water (40 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried over anhydrous magnesium sulfate and the solvent was evaporated *in vacuo*. The resulting mixture was chromatographed on silica gel eluting with hexane/ethyl acetate (6:1) to produce **3a** (280 mg, 47%) as an oil; IR (neat): 1727, 1673, 1657, 1595, 1576, 1335 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.77 (s, 3H), 4.91 (d, *J* = 5.5 Hz, 1H), 5.24 (d, *J* = 10.4 Hz, 1H), 5.35 (d, *J* = 17.1 Hz, 1H), 5.88 (s, 1H), 5.97 (ddd, *J* = 17.1, 10.4 and 5.5 Hz, 1H), 6.69 (s, 1H), 7.72–7.75 (m, 2H), 8.08–8.11 (m, 2H). ^{13}C NMR (deuteriochloroform): δ 52.3, 74.3, 118.7, 126.3, 126.5, 129.2, 131.3, 131.5, 131.6, 131.7, 132.9, 133.5, 134.2, 156.6, 166.1, 181.6, 183.7; *Anal*. Calcd. for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73. Found: C, 68.27; H, 4.82.

Methyl 2-[3-(but-3-en-2-yloxy)-1,4-dihydro-1,4-dioxonaphthalen-2-yl]acrylate (3b). A mixture of 3-buten-2-ol (0.21 mL, 2.4 mmol), sodium hydride (58 mg, 2.4 mmol), and **2a** (642 mg, 2 mmol) in *N*,*N*-dimethylformamide (5 mL) was stirred at room temperature for 2 h. The work-up procedure was the same as described earlier to produce **3b** (487 mg, 78%) as an oil; IR (neat): 1728, 1673, 1657, 1596, 1576, 1437 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 1.41 (d, *J* = 6.4 Hz, 3H), 3.76 (s, 3H), 5.10 (d, *J* = 10.1 Hz, 1H), 5.19 (d, *J* = 17.4 Hz, 1H), 5.48 (qd, *J* = 7.0 and 6.4 Hz, 1H), 5.82 (ddd, *J* = 17.4, 10.1, and 7.0 Hz, 1H), 5.87 (s, 1H), 6.67 (s, 1H), 7.71–7.74 (m, 2H), 8.06–8.10 (m, 2H); ^{13}C NMR (deuteriochloroform): δ 21.4, 52.2, 80.8, 117.5, 126.3, 126.5, 128.9, 130.9, 131.5, 131.7, 131.8, 133.4, 134.1, 138.3, 156.3, 166.2, 181.9, 183.8; *Anal*. Calcd. for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 69.44; H, 5.23.

Methyl 2-[1,4-dihydro-1,4-dioxo-3-(pent-1-en-3-yloxy)-naphthalene-2-yl]acrylate (3c). A mixture of 1-penten-3-ol (0.25 mL, 2.4 mmol), sodium hydride (58 mg, 2.4 mmol) and **2a** (642 mg, 2 mmol) in *N*,*N*-dimethylformamide (5 mL) was stirred at room temperature for 2 h. The work-up procedure was the same as described earlier to produce **3c** (352 mg, 54%) as an oil; IR (neat): 1728, 1672, 1656, 1595, 1575, 1436 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 0.94 (t, *J* = 7.6 Hz, 3H), 1.59–1.73 (m, 1H), 1.76–1.87 (m, 1H), 3.76 (s, 3H), 5.15 (d, *J* = 10.1 Hz, 1H), 5.17 (d, *J* = 17.1 Hz, 1H), 5.31 (td, *J* = 7.9 and 7.3 Hz, 1H), 5.72 (ddd, *J* = 17.1, 10.1, and 7.9 Hz, 1H), 5.87 (s, 1H), 6.68 (s, 1H), 7.69–7.76 (m, 2H), 8.05–8.09 (m, 2H); ^{13}C NMR (deuteriochloroform): δ 9.3, 28.4, 52.2, 85.8, 119.0, 126.3, 126.5, 127.8, 130.7, 131.5, 131.7, 131.8, 133.4, 134.0, 136.8, 156.5, 166.2, 181.9, 183.8; *Anal*. Calcd. for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 69.69; H, 5.44.

3-(Allyloxy)-2-(but-3-en-2-one-3-yl)naphthalene-1,4-dione (3d). A mixture of allyl alcohol (0.16 mL, 2.4 mmol), sodium hydride (58 mg, 2.4 mmol), and **2b** (610 mg, 2 mmol) in *N*,*N*-dimethylformamide (5 mL) was stirred at room temperature for 2 h. The work-up procedure was the same as described earlier to produce **3d** (288 mg, 51%) as an oil; IR (neat): 1673, 1654, 1594, 1576, 1364, 1333 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.45 (s, 3H), 4.86 (d, *J* = 5.8 Hz, 1H), 5.23 (d, *J* = 10.4 Hz, 1H), 5.33 (d, *J* = 17.1 Hz, 1H), 5.94 (ddd, *J* = 17.1, 10.4 and 5.8 Hz, 1H), 6.00 (s, 1H), 6.48 (s, 1H), 7.70–7.76 (m, 2H), 8.05–8.09 (m, 2H); ^{13}C NMR (deuteriochloroform): δ 26.1, 74.3, 118.8, 126.3, 126.5, 129.7, 130.3, 131.4, 131.7, 132.9, 133.5, 134.1, 140.5, 156.9, 181.5, 183.8, 197.8; *Anal*. Calcd. for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.48; H, 5.23.

3-(But-3-en-2-yloxy)-2-(but-3-en-2-one-3-yl)naphthalene-1,4-dione (3e). A mixture of 3-buten-2-ol (0.21 mL, 2.4 mmol), sodium hydride (58 mg, 2.4 mmol) and **2b** (610 mg, 2 mmol) in *N*,*N*-dimethylformamide (5 mL) was stirred at room temperature for 2 h. The work-up procedure was the same as described earlier to produce **3e** (397 mg, 67%) as an oil; IR (neat): 1673, 1652, 1595, 1334, 1254 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 1.39 (d, *J* = 6.4 Hz, 3H), 2.44 (s, 1H), 5.11 (d, *J* = 10.4 Hz, 1H), 5.18 (d, *J* = 17.4 Hz, 1H), 5.45 (qd, *J* = 7.0 and 6.4 Hz, 1H), 5.80 (ddd, *J* = 17.4, 10.4, and 7.0 Hz, 1H), 5.97 (s, 1H), 6.45 (s, 1H), 7.69–7.75 (m, 2H), 8.04–8.08 (m, 2H); ^{13}C NMR (deuteriochloroform): δ 21.3, 26.3, 80.8, 117.6, 126.3, 126.5, 129.5, 131.4, 131.7, 132.1, 133.4, 134.0, 138.3, 140.6, 156.5, 181.8, 183.9, 197.9; *Anal*. Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.72; H, 5.28.

2-(But-3-en-2-one-3-yl)-3-(pent-1-en-3-yloxy)naphthalene-1,4-dione (3f). A mixture of 1-penten-3-ol (0.25 mL, 2.4 mmol), sodium hydride (58 mg, 2.4 mmol), and **2b** (610 mg, 2 mmol) in *N*,*N*-dimethylformamide (5 mL) was stirred at room temperature for 2 h. The work-up procedure was the same as described earlier to produce **3f** (428 mg, 69%) as an oil; IR (neat): 1673, 1656, 1595, 1573, 1334, 1293 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 0.93 (t, *J* = 7.3 Hz, 3H), 1.40–1.71 (m, 1H), 1.73–1.85 (m, 1H), 2.43 (s, 3H), 5.15 (d, *J* = 10.4 Hz, 1H), 5.17 (d, *J* = 17.1 Hz, 1H), 5.31 (td, *J* = 7.9 and 7.0 Hz, 1H), 5.7 (ddd, *J* = 17.1, 10.4, and 7.9 Hz, 1H), 5.96 (s, 1H), 6.45 (s, 1H), 7.68–7.74 (m, 2H), 8.03–8.07 (m, 2H); ^{13}C NMR (deuteriochloroform): δ 9.3, 26.3, 28.4, 85.8, 119.1, 126.3, 126.4, 129.4, 131.5, 131.7, 131.8, 133.4, 134.0, 136.8, 140.7, 156.7, 181.8, 183.9, 197.9; *Anal*. Calcd. for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.40; H, 5.66.

2-[3-(But-3-en-2-yloxy)-1,4-dihydro-1,4-dioxonaphthalen-2-yl]acrylaldehyde (3g). A mixture of 3-buten-2-ol (0.21 mL, 2.4 mmol), sodium hydride (58 mg, 2.4 mmol), and **2c** (582 mg, 2 mmol) in *N*,*N*-dimethylformamide (5 mL) was stirred at room temperature for 1 h. The work-up procedure was the same as described earlier to produce **3g** (119 mg, 21%) as an oil; IR (neat): 1697, 1673, 1654, 1595, 1575, 1331 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 1.38 (d, J = 6.1 Hz, 3H), 5.11 (d, J = 10.4 Hz, 1H), 5.17 (d, J = 17.4 Hz, 1H), 5.53 (qd, J = 7.3 and 6.1 Hz, 1H), 5.80 (ddd, J = 17.4, 10.4, and 7.3 Hz, 1H), 6.48 (s, 1H), 6.58 (s, 1H), 7.69–7.77 (m, 2H), 8.05–8.09 (m, 2H), 9.64 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 21.4, 80.8, 117.7, 126.4, 126.5, 128.7, 131.4, 131.7, 133.5, 134.1, 138.1, 138.2, 140.9, 157.0, 181.6, 183.3, 191.1; *Anal.* Calcd. for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.08; H, 5.29.

2-[1,4-Dihydro-1,4-dioxo-3-(pent-1-en-3-yloxy)-naphthalene-2-yl]acrylaldehyde (3h). A mixture of 1-penten-3-ol (0.25 mL, 2.4 mmol), sodium hydride (58 mg, 2.4 mmol), and **2c** (582 mg, 2 mmol) in *N*,*N*-dimethylformamide (5 mL) was stirred at room temperature for 1 h. The work-up procedure was the same as described earlier to produce **3h** (184 mg, 31%) as an oil; IR (neat): 1697, 1674, 1655, 1595, 1575, 1331 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 0.92 (t, J = 7.3 Hz, 3H), 1.56–1.70 (m, 1H), 1.72–1.86 (m, 1H), 5.15 (d, J = 9.8 Hz, 1H), 5.18 (d, J = 17.7 Hz, 1H), 5.35 (td, J = 7.9 and 7.0 Hz, 1H), 5.70 (ddd, J = 17.7, 9.8, and 7.9 Hz, 1H), 6.48 (s, 1H), 6.60 (s, 1H), 7.67–7.75 (m, 2H), 8.04–8.08 (m, 2H), 9.64 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 9.3, 28.4, 85.9, 119.3, 126.4, 126.5, 127.9, 131.5, 131.7, 133.5, 134.1, 136.7, 138.1, 140.9, 157.3, 181.7, 183.3, 191.1; *Anal.* Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.63; H, 5.28.

Preparation of 2*H*-benzo[*g*]chromenes 5a-h: General Procedure. Bisolefin **3a-h** (0.5 mmol) was dissolved in 50 mL (0.01*M*) of dichloromethane. Then Grubbs II catalyst was added (10–15 mol %) and the solution was refluxed for 0.5–2.5 h under nitrogen atmosphere. The mixture was concentrated *in vacuo*. Purification on silica gel (hexane/ethyl acetate, 2:1) afforded **5a-h** as a solid.

The physical and spectral data of **5a**-**h** prepared by this general method are listed in the following paragraphs.

Methyl 5,10-dihydro-5,10-dioxo-2H-benzo[g]chromene-4-carboxylate (5a). Yellow solid; yield 74%; mp 182–183°C; IR (potassium bromide): 1724, 1676, 1650, 1631, 1591, 1571, 1455 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.86 (s, 3H), 5.03 (d, J = 4.1 Hz, 2H), 6.34 (t, J = 4.1 Hz, 1H), 7.70–7.79 (m, 2H), 8.08–8.13 (m, 2H); ^{13}C NMR (deuteriochloroform): δ 52.6, 66.3, 119.8, 126.0, 126.4, 126.6, 127.2, 130.8, 131.5, 133.5, 134.5, 154.9, 166.3, 178.8, 180.3; ms: m/z (%) = 270 (28) [M$^+$], 238 (15), 210 (16), 183 (42), 127 (64), 115 (26), 104 (100); hrms (EI): m/z Calcd. for $C_{15}H_{10}O_5$: 270.0528; Found: 270.0518; *Anal.* Calcd. for $C_{15}H_{10}O_5$: C, 66.67; H, 3.73. Found: C, 66.52; H, 3.59.

Methyl 5,10-dihydro-2-methyl-5,10-dioxo-2H-beno[g]chromene-4-carboxylate (5b). Yellow solid; yield 63%; mp 148–149°C; IR (potassium bromide): 1732, 1677, 1651, 1632, 1591, 1571, 1438 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 1.61 (d, J = 6.7 Hz, 3H), 3.86 (s, 3H), 5.24 (qd, J = 6.7 and 3.7 Hz, 1H), 6.21 (d, J = 3.7 Hz, 1H), 7.69–7.77 (m, 2H), 8.08–8.13 (m, 2H); ^{13}C NMR (deuteriochloroform): δ 19.9, 52.6, 73.7, 118.9, 126.3, 126.4, 126.6, 130.2, 131.0, 131.6, 133.4, 134.4, 154.1, 166.6, 179.0, 180.4; ms: m/z (%) = 284 (73) [M$^+$], 269 (100), 252 (99), 241 (66), 224 (64), 197 (80), 196 (72), 163 (30), 139 (34), 115 (39), 104 (37). hrms (EI): m/z Calcd. for $C_{16}H_{12}O_5$: 284.0685; Found: 284.0683; *Anal.* Calcd. for $C_{16}H_{12}O_5$: C, 67.60; H, 4.25. Found: C, 61.45; H, 4.43.

Methyl 2-ethyl-5,10-dihydro-5,10-dioxo-2H-benzo[g]-chromene-4-carboxylate (5c). Yellow solid; yield 80%; mp 94–95°C; IR (potassium bromide): 1729, 1676, 1652, 1634, 1590, 1570, 1456, 1435 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 1.09 (t, J = 7.4 Hz, 3H), 1.86–2.03 (m, 2H), 3.86 (s, 1H), 5.05 (td, J = 6.3 and 3.9 Hz, 1H), 6.23 (d, J = 3.9 Hz, 1H), 7.68–7.78 (m, 2H), 8.07–8.13 (m, 2H); ^{13}C NMR (deuteriochloroform): δ 8.8, 27.0, 52.5, 78.4, 119.0, 126.3, 126.5, 126.7, 129.2, 131.0, 131.6, 133.4, 134.3, 154.3, 166.7, 178.9, 180.4; ms: m/z (%) = 298 (31) [M$^+$], 270 (96), 269 (100), 241 (100), 239 (47), 210 (31), 181 (29), 153 (30), 104 (52); hrms (EI): m/z Calcd. for $C_{17}H_{14}O_5$: 298.0841; Found: 298.0839; *Anal.* Calcd. for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73. Found: C, 68.20; H, 4.55.

4-Acetyl-2H-benzo[g]chromene-5,10-dione (5d). Red solid; yield 91%; mp 173–174°C; IR (potassium bromide): 1702, 1678, 1650, 1591, 1571, 1404 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.37 (s, 3H), 5.05 (d, J = 4.0 Hz, 2H), 6.10 (t, J = 4.0 Hz, 1H), 7.71–7.79 (m, 2H), 8.07–8.13 (m, 2H); ^{13}C NMR (deuteriochloroform): δ 29.0, 66.4, 120.3, 122.8, 126.4, 126.6, 130.8, 131.3, 133.7, 134.5, 135.6, 155.2, 178.8, 180.9, 199.2; ms: m/z (%) = 254 (45) [M$^+$], 212 (19), 183 (77), 155 (28), 139 (12), 128 (100), 127 (100), 104 (66); hrms (EI): m/z Calcd. for $C_{15}H_{10}O_4$: 254.0579; Found: 254.0580; *Anal.* Calcd. for $C_{15}H_{10}O_4$: C, 70.86; H, 3.96. Found: C, 70.59; H, 4.21.

4-Acetyl-2-methyl-2H-benzo[g]chromene-5,10-dione (5e). Red solid; yield 41%; mp 137–138°C; IR (potassium bromide): 1695, 1675, 1646, 1592, 1569, 1394 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 1.61 (d, J = 6.7 Hz, 3H), 2.36 (s, 3H), 5.25 (qd, J = 6.7 and 3.7 Hz, 1H), 5.95 (d, J = 3.7 Hz, 1H), 7.71–7.78 (m, 2H), 8.07–8.13 (m, 2H); ^{13}C NMR (deuteriochloroform): δ 20.2, 29.2, 73.8, 119.4, 126.4, 126.6, 127.0, 131.0, 131.3, 133.6, 134.4, 134.7, 154.4, 179.1, 181.0, 199.6; ms: m/z (%) = 268 (100) [M$^+$], 253 (27), 225 (47), 197 (56), 183 (30), 141 (22), 115 (28), 105 (18); hrms (EI): m/z Calcd. for $C_{16}H_{12}O_4$: 268.0736; Found: 268.0733; *Anal.* Calcd. for $C_{16}H_{12}O_4$: C, 71.64; H, 4.51. Found: C, 71.51; H, 4.42.

4-Acetyl-2-ethyl-2H-benzo[g]chromene-5,10-dione (5f). Yellow solid; yield 66%; mp 85–86°C; IR (potassium bromide): 1700, 1676, 1652, 1593, 1569, 1394 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 1.09 (t, J = 7.3 Hz, 3H), 1.86–2.05 (m, 2H), 2.36 (s, 3H), 5.07 (td, J = 6.1 and 3.7 Hz, 1H), 5.97 (d, J = 3.7 Hz, 1H), 7.70–7.78 (m, 2H), 8.06–8.13 (m, 2H); ^{13}C NMR (deuteriochloroform): δ 8.8, 27.4, 29.2, 78.6, 119.4, 125.9, 126.4, 126.6, 131.0, 131.4, 133.6, 134.4, 135.1, 154.6, 179.0, 181.0, 199.8; ms: m/z (%) = 282 (57) [M$^+$], 253 (100), 239 (28), 225 (100), 211 (29), 197 (39), 183 (33), 165 (31), 105 (33); hrms (EI): m/z Calcd. for $C_{17}H_{14}O_4$: 282.0892; Found: 282.0892; *Anal.* Calcd. for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.11; H, 4.85.

5,10-Dihydro-2-methyl-5,10-dioxo-2H-benzo[g]chromene-4-carbaldehyde (5g). Orange solid; yield 40% [20]; ^{1}H NMR (deuteriochloroform): δ 1.62 (d, J = 7.0 Hz, 3H), 5.35 (qd, J = 4.0 and 7.0 Hz, 1H), 6.49 (d, J = 4.0 Hz, 1H), 7.74–7.81 (m, 2H), 8.12–8.14 (m, 2H), 10.16 (s, 1H).

2-Ethyl-5,10-dihydro-5,10-dioxo-2H-benzo[g]chromene-4-carbaldehyde (5h). Orange solid; yield 42%; mp 109–110°C; IR (potassium bromide): 1719, 1676, 1647, 1612, 1592, 1561, 1458, 1346 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 1.10 (t, J = 7.4 Hz, 3H), 1.93–1.99 (m, 2H), 5.17 (td, J = 6.1 and 4.1 Hz, 1H), 6.52 (d, J = 4.1 Hz, 1H), 7.72–7.80 (m, 2H), 8.11–8.13 (m, 2H), 10.16 (s, 1H); ^{13}C NMR (deuteriochloroform): δ

8.7, 27.4, 78.8, 118.0, 126.4, 126.6, 131.0, 131.4, 131.6, 131.7, 133.7, 134.5, 154.7, 178.9, 182.0, 189.0; ms: *m/z* (%) = 268 (69) [M^+], 240 (100), 222 (56), 197 (37), 165 (36), 135 (21), 105 (14); *Anal*. Calcd. for $C_{16}H_{12}O_4$: C, 71.64; H, 4.51. Found: C, 71.90; H, 4.38.

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[18] No RCM product was observed using 5 mol % of Grubbs second-generation catalyst during expanded reaction time.

[19] 10 mol % loading of catalyst was ineffective in these cases.

[20] The RCM product 5 g decomposed during vacuum drying. This unstableness resulted in only ^{1}H NMR spectroscopic data.

Synthesis and Spectroscopic Properties of Some Di- and Trideuterated Methylpyridines

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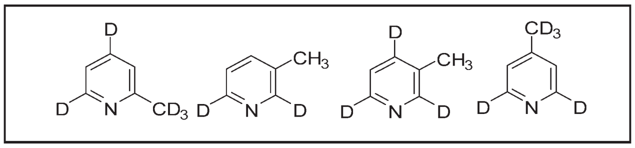

2-Trideuteriopyridine-4,6-d_2 (**1-4,6-d_2**), 3-methylpyridine-2,6-d_2 (**2-2,6-d_2**), 3-methylpyridine-2,4,6-d_3 (**2-2,4,6-d_3**), and 4-trideuteriopyridine-2,6-d_2 (**3-2,6-d_2**) were synthesized from the appropriate 2-, 3-, or 4-methylpyridine N-oxides. These deuterated products were characterized by their ^{1}H NMR and ^{13}C NMR spectra.

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INTRODUCTION

Work in our laboratory has shown that irradiation of pyridine [1,2], cyanopyridines [3], and methylpyridines [3] in the vapor phase results in deep-seated rearrangements in which the ring atoms, along with the attached substituents, change their relative positions. To map the transpositions of these atoms within the heteroaromatic ring, the photo-rearrangements of a variety of deuterated pyridine derivatives were studied. The deuterium atoms served as positional labels and allowed determination of where a particular ring atom in the photoproduct originated in the reactant.

The synthesis and characterization of the six isomeric dideuteriopyridines and the three isomeric trideuteriopyridines [4] and three isomeric dideuteriocyanopyridines [5] have already been reported. To complete our work in this area, we now report the synthesis and characterization of the three dideuterio and one trideuteriomethylpyridines shown in Scheme 1.

RESULTS AND DISCUSSION

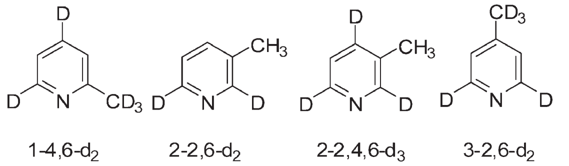
In the case of 3- and 4-methylpyridines, both open positions α to the ring nitrogen were deuterated by two successive base catalyzed H/D exchanges [6] in the commercially available 3- and 4-methylpyridine N-oxides, **4-a,b**, followed by reduction using phosphorous trichloride in dichloromethane [7] as shown in Scheme 2.

The structures of **2-2,6-d_2** and **3-2,6-d_2** were confirmed by the spectroscopic data shown in Tables 1 and 2. Deuteration at ring positions 2 and 6 of each compound was confirmed by ^{1}H NMR and ^{13}C NMR spectra. In particular, in the case of **2-2,6-d_2**, the ^{1}H NMR spectrum exhibited a pair of doublets ($J = 7.6$ Hz) at δ 7.18 and 7.40 where H4 and H5 are known to absorb, but only very low intensity signals at δ 8.37 and 8.38 due to residual protons at ring positions 2 and 6. Similarly, the complete proton decoupled ^{13}C NMR spectrum exhibited singlets at δ 123.4, 133.3, and 136.8 due to C5, C3, and C4 respectively and triplets at δ 146.9 ($J =$ 28.3 Hz) and 150.2 ($J = 28.4$ Hz) due to C6 and C2 confirming that these ring carbon atoms are bonded to deuterium.

As expected, the ^{1}H NMR spectrum of the more symmetrical **3-2,6-d_2** exhibited an intense singlet at δ 7.06, where H3 and H5 are known to absorb, but only a very small signal at δ 8.40, where H2 and H6 are known to absorb. In addition, the ^{13}C NMR spectrum exhibited singlets at 124.9 and 147.3 due to C3,5 and C4 respectively, and a triplet ($J = 28.4$ Hz) confirming that the equivalent C2,6 carbon atoms are both bonded to deuterium. These results confirm that in both compounds, deuteration has taken place exclusively at ring positions 2 and 6.

As shown in Scheme 3, **4a-2,6-d_2** is also a suitable precursor for the trideuterated methylpyridine **2-2,4,6-d_3**. As shown, the conversion involved electrophilic nitration at C4 [7], replacement of the nitro group with chloro [7], reduction of the N-oxide [6], and finally, replacement of the C4 chloro with deuterium using palladium on charcoal in a deuterium atmosphere [8]. The spectral data in Tables 1 and 2 confirm that the three-deuterium atoms are exclusively at ring positions 2, 4, and 6. In particular, the ^{1}H NMR spectrum exhibits an

Scheme 1



intense singlet at δ 7.10 indicating that the ring contains a single proton at the C5 position. Furthermore, the ^{13}C NMR spectrum shows triplets at δ 136.7 (J = 24.3 Hz), 146.9 (J = 27.3 Hz), and 150.3 Hz (J = 26.7 Hz) for C4, C6, and C2, respectively, whereas the signals at δ 123.5 and 136.7 due to C5 and C3 appeared as sharp singlets.

In the case of the 2-methylpyridine isomer, which has only one open position α to the ring nitrogen, the synthetic approach outlined in Scheme 4 was followed. Thus, commercially available 2-methylpyridine N-oxide (**8**) was first monodeuterated at ring position 6, α to the ring nitrogen, using two successive base catalyzed H/D exchanges [6]. Introduction of deuterium into ring position 4 was then accomplished by nitration [7], replacement of nitro with chloro [7], reduction of the N-oxide [6], and finally replacement of chlorine for deuterium using D$_2$ and Pd/C [8].

The spectral data in Tables 1 and 2 confirm that the two deuterium atoms are exclusively at ring positions 4 and 6. Accordingly, the ^{1}H NMR spectrum exhibited singlets at δ 7.06 and 7.13 where protons at ring positions 5 and 3 are known to absorb but signals of very low intensity at δ 7.55 and 8.40 indicating only residual protons at ring positions 4 and 6. In addition, the ^{13}C NMR spectrum exhibited a singlet for a quaternary carbon at δ 159.4 due to the C2 ring carbon and sharp singlets at δ 124.0 and 121.6 where the C3 and C5 ring carbons are known to absorb. In contrast, the signals due to the C6 and C4 carbon atoms appeared as triplets at δ 149.9 (J = 27.6 Hz) and 136.9 (J = 28.3 Hz) due to coupling of these carbon atoms with deuterium.

CONCLUSION

The synthetic procedures described allow the synthesis of the four deuterated-methylpyridines shown in Scheme 1. The positions of the deuterium atoms in the pyridine ring were unambiguously confirmed by the ^{1}H NMR and ^{13}C NMR data shown in Tables 1 and 2.

EXPERIMENTAL

Melting points were determined using a MEL-TEMP apparatus and are uncorrected. ^{1}H NMR and ^{13}C spectra were recorded at 400.1 and 100.6 MHz in acetone-d$_6$ on a Brucker FT-NMR system. ^{1}H NMR and ^{13}C chemical shifts were measured relative to internal tetramethylsilane and chloroform, respectively. All ^{13}C NMR spectra are proton-decoupled. Mass spectra were recorded with an HP 5970B mass selective detector interfaced to an HP 588 capillary gas chromatograph.

2-Trideuteriomethylpyridine N-oxide-6-d, (8-6-d$_1$), 3-methylpyridine N-oxide-2,6-d$_2$ (4a-2,6-d$_2$), and 4-trideuteromethylpyridine-2,6-d$_2$ (4b-2,6-d$_2$). The open positions α to nitrogen were deuterated by dissolving 3-methylpyridine N-oxide (4a) (1.0g, 9.0 mmol), 4-methylpyridine N-oxide (4b) (1.0g, 9.0 mmol), or 2-methylpyridine N-oxide (8) (3.4g, 36.5 mmol) in a solution of sodium carbonate (2.0 g) in deuterium oxide (20 mL). The mixture was heated in an oil bath at 110°C for 12 h. The resulting solution was allowed to cool and extracted with dichloromethane (5 × 30 mL). The combined dichloromethane extracts were dried (sodium sulfate) and concentrated to give partially deuterated product which was subjected to a second hydrogen-deuterium exchange as mentioned earlier to provide the final products, which were purified by Kugelrohr distillation (water aspirator).

Compound **4a-2,6-d$_2$** was obtained as a colorless liquid in a yield of 0.8 g (7.2 mmol, 80%); ^{1}H NMR (deuterium oxide) δ 2.3 (s, 3H), 7.26 (d, 1H, J = 8.1 Hz) 7.42 (d, 1H, J = 8.1 Hz); ^{13}C NMR (deuterium oxide) δ 18.4, 125.4, 127.8, 136.3 (t, J = 27.6 Hz), 136.6, 139.3 (t, J = 26.8 Hz).

Compound **4b-2,6-d$_2$** was obtained as a colorless liquid in a yield of 0.7 g (6.0 mmol, 79%); ^{1}H NMR (deuterium oxide) δ 2.1 (residual methyl protons), 7.28 (s, 2H); ^{13}C NMR (deuterium oxide) δ 19.8 (m), 128.4, 138.5 (t, J = 29.1 Hz), 146.2.

Compound **8-6-d$_1$**, was obtained as a colorless liquid in a yield of 3.0 g (27.3 mmol, 84.5%); ^{1}H NMR (deuterium oxide) δ 2.6 (residual methyl protons), 7.06–7.22 (m, 3H); ^{13}C NMR (deuterium oxide) δ 17.5 (m), 123.9, 126.3, 139.2 (t, J = 28.4 Hz), 149.4.

3-Methylpyridine-2,6-d$_2$ (2-2,6-d$_2$) and 4-trideuteriomethylpyridine-2,6-d$_2$ (3-2,6-d$_2$). 3-Methylpyridine N-oxide-2-6-d$_2$ (4a-2,6-d$_2$) (0.80 g, 7.2 mmol) or 4-trideuteriomethylpyridine N-oxide-2,6-d$_2$ (4b-2,6-d$_2$) (0.70 g, 6.0 mmol) dissolved in dichloromethane (40 mL) was added dropwise to phosphorous trichloride (2.4 mL) at 0°. The resulting mixture was heated at reflux for 1 h, cooled to room temperature and poured onto ice (15 g). The resulting mixture was made basic with aqueous sodium hydroxide (10%) and extracted with

Scheme 2

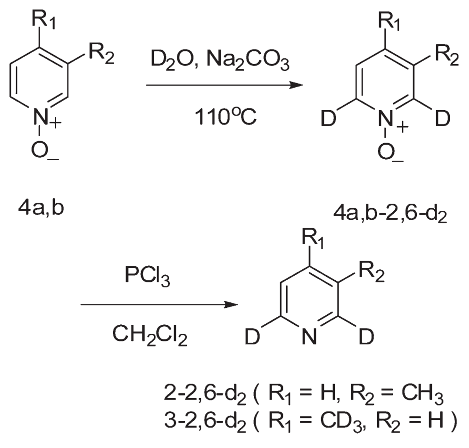


Table 1

^{1}H NMR chemical shifts (δ ppm) of deuterated methylpyridines.

	Ring position				
Compound	2	3	4	5	6
1-4,6-d$_2$	7.13	–	7.06, s	2.5^a	–
2-2,6-d$_2$	2.20 (CH$_3$)	7.40,d	7.18,d J = 7.6 Hz, J = 7.6 Hz	–	–
2-2,4,6-d$_3$	2.40 (CH$_3$)	–	7.10	–	–
3-2,6-d$_2$	–	7.06	2.20^a	7.06	–

^{a} These signals are due to residual protons in the methyl group.

dichloromethane (5 × 5 mL). The combined extract was dried (sodium sulfate) and concentrated.

3-Methylpyridine-2,6-d$_2$ (**2-2,6-d$_2$**) was obtained as a colorless oil (0.50 g, 5.3 mmol, 73%); MS *m/z* (%) 95 (100), 68 (36), 67 (39). The NMR data are given in Tables 1 and 2.

4-Trideuteriomethylpyridine-2,6-d$_2$ (**3-2,6-d$_2$**) was obtained as a colorless oil (0.45 g, 4.5 mmol, 75%); MS *m/z* (%) 98 (100), 80 (5), 70 (43). The NMR data are given in Tables 1 and 2.

2-Trideuteriomethylpyridine-4,6-d$_2$(1-4,6-d$_2$)

4-Nitro-2-trideuteriomethylpyridine N-oxide-6d (9-6-d$_1$). 2-Trideuteriomethylpyridine N-oxide-6d$_1$(**8-6-d$_1$**) (2.5 g, 22.1 mmol) was added dropwise to a cold mixture of concentrated sulfuric acid (5.0 mL) and concentrated nitric acid (5.0 mL) while keeping the temperature below 50°C. The resulting clear solution was allowed to stir at room temperature for 10 min and then heated at 110°C for 5 h. The resulting solution was allowed to cool to room temperature and neutralized with saturated aqueous sodium bicarbonate. The neutralized solution was extracted with dichloromethane (3 × 50 mL). The extract was dried (sodium sulfate) and concentrated to give crude 4-nitro-2-trideuteriomethylpyridine N-oxide-6d$_1$ (**9-6-d$_1$**) as a yellow solid (1.7 g). Recrystallization from acetone gave **9-6-d$_1$** as yellow crystals; mp 153–155°C; ^{1}H NMR (deuteriochloroform) δ 2.3 (residual methyl protons), 7.90 (s, 1H), 8.10 (s, 1H); ^{13}C NMR (deuteriochloroform) δ 1.71 (m), 117.5, 120.2, 139.3 (t, J = 28.4 Hz), 141.2, 150.1.

4-Chloro-2-trideuteriomethylpyridine N-oxide-6d$_1$ (10-6-d$_1$). 4-Nitro-2-trideuterio-methylpyridine N-oxide-6d$_1$ (**9-6-d$_1$**) (1.5 g, 9.5 mmol) was dissolved in concentrated hydrochloric acid (20 mL) and heated in an oil bath at 135°C for 18 h. The reaction mixture was allowed to cool to room temperature and extracted with chloroform (5 × 20 mL). The combined chloroform extracts were dried (sodium sulfate) and concentrated to give a yellow solid (1.0g) which was subjected to column chromatography (silica gel). Elution with ethyl acetate provided unreacted starting material. Elution with methanol provided 4-chloro-2-trideuteriopyridine N-oxide-6d$_1$ (**10-6-d$_1$**) as a yellow viscous liquid (0.60 g, 4.1 mmol, 43%); ^{1}H NMR (deuteriochloroform) δ 2.3 (residual methyl protons), 7.0 (s, 1H) 7.2 (s, 1H); ^{13}C NMR (deuteriochloroform) δ 17.7 (m), 124.2, 126.8, 131.7, 140.1 (t, J = 29.1 Hz), 150.5; MS *m/z* (%), 149 (22), 147 (70), 146 (45), 129 (100), 128 (45), 92 (40).

4-Chloro-2-trideuteriomethylpyridine-6d$_1$ (11-6-d$_1$). 4-Chloro-2-trideuteriomethyl-pyridine N-oxide-6d$_1$ (**10-6-d$_1$**) (0.80 g, 5.4 mmol) dissolved in dichloromethane (40 mL) was added to phosphorous trichloride (3.0 mL) at 0°C. The resulting mixture was heated at reflux for 1 h, cooled to room temperature, and poured onto ice (20 g). The resulting mixture was made basic with aqueous sodium hydroxide (10%) and extracted with dichloromethane (5 × 30 mL). The combined extract was dried (sodium sulfate) and concentrated to give **11-6-d$_1$** as a brown viscous liquid (0.50 g, 3.7 mmol, 69%); ^{1}H NMR (deuteriochloroform) δ 2.3 (residual methyl protons), 6.9 (s, 1H), 7.0 (s, 1H); ^{13}C NMR (deuteriochloroform) δ 23.9 (m), 121.1, 123.5, 144.1, 149.7 (t, J = 27.6 Hz), 159.9; MS *m/z* (%) 133 (30), 131 (100), 130 (62), 95 (33), 94 (13).

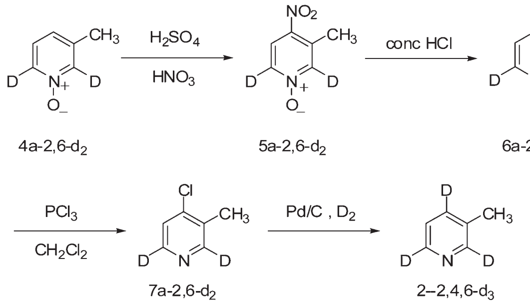
2-Trideuteriomethylpyridine-4,6-d$_2$ (1-4,6-d$_2$). 4-Chloro-2-trideuteriomethylpyridine-6-d$_1$) (**11-6-d$_1$**) (0.50 g, 3.8 mmol) dissolved in diethyl ether (20 mL) was placed in a Büchner

Table 2

Decoupled ^{13}C NMR chemical shifts (δ ppm) of deuterated methylpyridines.

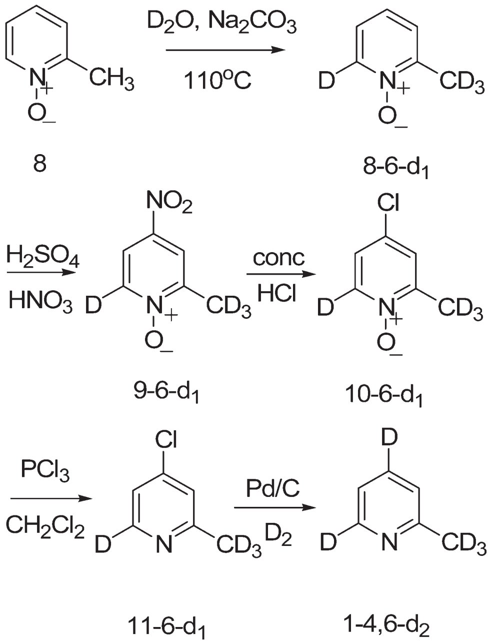
	Ring position					
Compound	2	3	4	5	6	CH$_3$(CD$_3$)
1-4,6-d$_2$	159.4,s	124.0,s	136.9,t J = 28.3 Hz	121.6,s	149.4,t J = 27.6 Hz	(24.1)
2-2,6-d$_2$	150.2,t J = 28.4 Hz	133.3,s	136.8,s	123.4,s	146.9,t J = 28.3 Hz	17.5
2-2,4,6-d$_3$	150.3,t J = 26.7 Hz	136.7,s	136.7,t J = 24.3 Hz)	123.5,s	146.9,t J = 27.3 Hz	18.7
3-2,6-d$_2$	149.5,t (J = 28.4 Hz)	124.9,s	149.5,s	124.9s	149.5,t	(20.5,m) (J = 28.4 Hz)

Scheme 3



flask containing potassium carbonate (1.5 g), Pd-C (10%, 0.030g), and a magnetic stirring bar. The flask was sealed with a septum and equipped with a balloon at the side arm. A side-arm test tube containing sodium metal (1.2 g) was sealed with a septum and the side-arm was connected to the Büchner flask. The entire system was purged with nitrogen for 10 min. Deuterium oxide (3.0 mL) was then added through the septum to the sodium in the side-arm test tube. The deuterium gas generated filled the system and caused the balloon to expand. The reaction mixture in the Büchner flask was stirred in the deuterium atmosphere for 4 h. The Pd-C was removed by filtration and washed with dichloromethane. The combined ether and dichloromethane was concentrated by distillation through a Vigreux column to give a brown liquid residue (0.30 g) which was purified by Kugelrohr distillation (atm. pressure, oven temperature 130°C). **1-4,6-d$_2$** was collected as a clear liquid (0.13 g, 1.3 mmol, 34%); MS *m/z* (%), 98 (100), 70 (42), 69 (12). See Tables 1 and 2 for NMR data.

Scheme 4



3-Methylpyridine-2,4,6-d$_3$ (2-2,4,6-d$_3$)

3-Methyl-4-nitropyridine N-oxide-2,6-d$_2$ (5a-2,6-d$_2$). 3-Methylpyridine N-oxide-2,6-d$_2$ (4a-2,6-d$_2$) (1.9 g, 17.2 mol) was treated as for the nitration of 8-6-d$_1$ presented earlier to give 5a-2,6-d$_2$ as yellow crystals (1.3 g, 8.3 mmol, 48%, mp 154–157°C); ^{1}H NMR (deuteriochloroform), δ 2.60 (s, 3H), 8.00 (s, 1H); ^{13}C NMR (deuteriochloroform) δ 18.5, 122.5, 133.2, 137.9 (t, J = 28.4 Hz); 141.8 (t, J = 26.8 Hz), 143.4; MS *m/z* (%) 156 (100), 140 (7), 139 (13), 84 (30).

4-Chloro-3-methylpyridine N-oxide-2,6-d$_2$ (6a-2,6-d$_2$). 3-Methyl-4-nitropyridine N-oxide-2,6-d$_2$ (**5a-2,6-d$_2$**) (1.3 g, 8.3 mmol) was treated as for the conversion of **9-6-d$_1$** to **10-6-d$_1$** presented earlier to give **6a-2,6-d$_2$** as a yellow viscous liquid (0.5 g, 3.5 mmol, 42%); ^{1}H NMR (deuteriochloroform) δ 2.2 (s, 3H), 7.2 (s, 1H); ^{13}C NMR (deuteriochloroform) δ 16.8, 124.3, 132.3, 144.4, 148.2 (t, J = 28.4 Hz), 151.5 (t, J = 28.4 Hz); MS *m/z* (%) 145 (100), 129 (63), 94 (42), 54 (47).

4-Chloro-3-methylpyridine-2,6-d$_2$ (7-2,6-d$_2$). **6a-2,6-d$_2$** (0.5 g, 3.5 mmol) was treated as for the conversion of **10-6-d$_1$** to **11-6-d$_1$**, presented earlier to give **7a-2,6-d$_2$** as a brown viscous liquid (0.3 g, 2.3 mmol, 66%); ^{1}H NMR (deuteriochloroform) δ 2.3 (s, 3H), 6.9 (s, 1H), 7.2 (s, 1H); ^{13}C NMR (deuteriochloroform) δ 16.8, 124.2, 132.5, 148.2 (t, J = 28.4 Hz), 151.6 (t, J = 28.4 Hz); MS *m/z* (%) 131 (35), 129 (100), 94 (87), 66 (74).

3-Methylpyridine-2,4-6-d$_3$ (2-2,4,6-d$_3$). **7a-2,6-d$_2$** (0.25 g, 1.9 mmol) in methanol (10 mL) was treated as for the conversion of **11-6-d$_1$** to **1-4,6-d$_2$**. Kugelrohr distillation of the crude product (atmospheric pressure, oven temperature 130° C) gave **2-2,4,6-d$_3$** as a clear liquid (0.1 g, 1.0 mmol, 53%): MS *m/z* (%) 96 (100), 29 (37), 68 (46), 67 (31). See Tables 1 and 2 for NMR data.

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Synthesis and Bioactivity Evaluation of 3-Hydroxy-3-(phenylethynyl)indol-2-one Analogues

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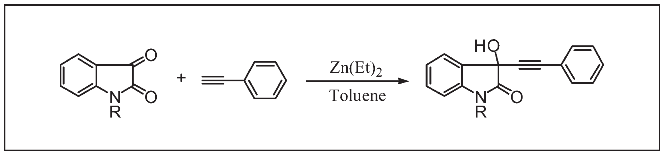

A series of propargylic alcohol was synthesized by the addition of phenylacetylene to isatin and its N-substituted derivatives for the first time. This reaction involves activation of zinc reagent *via* coordination with carbonyl substrates that behave ''ligand like.'' The bioactivities on protective effect on the apoptosis of PC12 cells induced by H_2O_2 and cytotoxicity against lung cancer A549 and P388 cell line of these compounds were investigated, and several compounds showed potent activities.

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INTRODUCTION

The reactions, which lead to carbon–carbon bond formation by addition of nucleophiles to carbonyl group electrophiles, are of great importance in the continuing development of efficient processes for synthesis. Addition of acetylides to carbonyl substrates has attracted the attention of organic chemists and is still a very active field of organic reactions. The reaction gives access to preparation of propargylic alcohols, which are well known as versatile building blocks in the synthesis of complex natural products [1,2] and can be transformed into other functional groups, such as chalcones [3], and oxasilacyclopentene [4,5]. The addition of alkynes to ketones is also a very useful practical strategy to create tertiary alcohols with a new stereogenic center [6–8].

Some natural products with the structure of propargylic alcohol showed potent bioactivities, such as panaxyno1 (PNN), which performs potent activities on neuro-protection [9] and antitumor [10]. Isatin has been found in many natural products, with the function of modulating biochemical processes [11–13]. The advances in the use of isatin for organic synthesis and a survey of its biological activities are continuously reported [14–16]. In 1963, Ried reported the synthesis of 3-hydroxy-3-(phenyl-ethynyl)indol-2-one for the first time, with a low yield of 28% [17]. But in the following years, there was no further attention paid to the synthesis and its bioactivity.

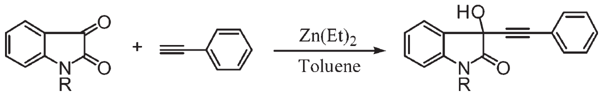
In this article, we describe the addition of phenyl-acetylene to isatin and (*N*-substituted) isatins promoted by Et_2Zn without employing specific ligands to form 3-hydroxy-3-(phenylethynyl)indol-2-one analogues (Scheme 1). Furthermore, the bioactivity on neuroprotection and antitumor of these isatin derivatives was evaluated for the first time.

RESULTS AND DISCUSSION

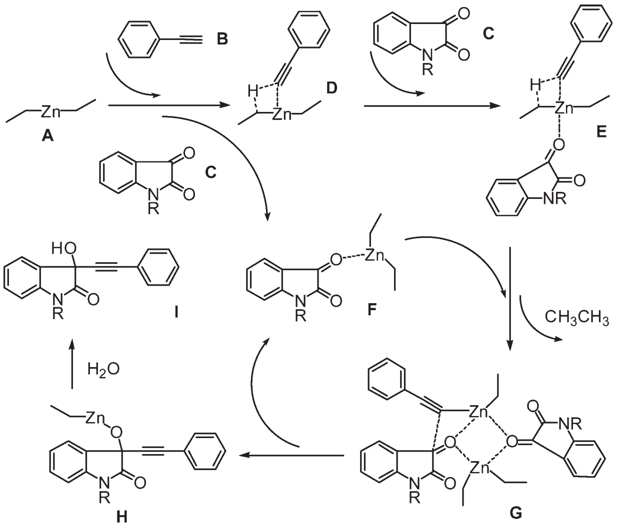
Chemistry. The *in situ* generated $ZnMe_2$-acetylides from Me_2Zn and acetylides have been used in a direct addition process with aldehydes and ketones without the employment of specific ligands [18]. In our preliminary studies, the reaction was carried out at room temperature. Unfortunately, the outcome was found very complex (by TLC), and the desired product was in a low yield after purification by flash chromatography. Higher yields were obtained at lower temperatures. Also, a variety of substrates were examined at 0°C, and the results are summarized in Table 1.

It can be found from Table 1 that the temperature deeply effects the reaction of the addition of phenyl-acetylene to (*N*-methyl) isatin. The reaction at relatively higher temperature (rt) gave poor yield, and the yields increased as the temperature is decreased, and the yield

Scheme 1



Scheme 2



was highest at 0°C. Significantly, lower temperatures such as −10°C did not improve the yield.

In consideration of the accepted mechanism for ligand-assisted addition of Et_2Zn to aldehydes, Pier *et al.* [18] investigated the possibility that a zinc-ketone complex acts as a bifunctional catalyst, bringing together an additional 1 equiv of ketone and zinc reagent in a bicyclic transition state (TS). On the basis of the proposed mechanism, we assumed that this reaction involves activation of the zinc reagent *via* coordination with isatins. The activated TS are shown in Scheme 2. In the TS (G), two molecules of (*N*-substituted) isatin behaved in a ''ligand like'' fashion to activate a phenylacetylene by two oxygen atoms coordinating with two Zn as bridged-atoms. The addition of activated phenylacetylene to a neighbor carbonyl formed H, and F was released into another cycle. The desired product (I) is provided through hydrolysis in the final step of the reaction.

Because the substrates have more than one coordinative and reactive point, the TS might be more complex, which lead to several side reactions, the addition of ethyl to isatins can be considered as an example. We could find the yields were very low in entries 7 and 11 because of the more reactive substrates. (*N*-Acyl) isatins (entries 12 and 13) were also introduced into this reaction, but the product was too complex to determine whether there was a desired product.

Biological activity. Compounds 2–9 were screened for their biological activities on protective effect on the apoptosis of PC12 cells induced by H_2O_2 and cytotoxicity against A549 and P388 cell line at various concentrations by the reported methods [19,20]. The neuroprotection and cytotoxicity in *vitro* screening results are shown in Table 2.

From the table, we find that compounds **4**, **5**, and **6** showed potent activity, which were more effective than VE ((±) α-Tocophreol), with the percentage of 46.62, 65.93, and 35.89% at 2 μg/mL respectively, as compound **5** was not cytotoxic against PC12 cell under the concentration of 2–200 μg/mL, whereas compounds **4** and **6** showed some cytotoxicity. Other compounds were either inactive or cytotoxic against PC12 cell. The results of in *vitro* cytotoxicity of compounds 2–9 against A549 and P388 cell line were given in Table 3.

From the results, it was found that almost all compounds could inhibit both cancer cells effectively at the concentration of 100 μ*M*. Compounds **6** and **8** showed

Table 1

Alkynylation of (*N*-substituted)isatins with phenylacetylene using Et_2Zn as promoter.

Entry	R	Time (h)	Temp. (°C)	Yield (%)	Compound
1	H	12	0	38.7	1
2	CH_3	12	25	8.1	2
3	CH_3	12	10	31.3	2
4	CH_3	12	0	58.1	2
5	CH_3	24	−10	51.6	2
6	C_2H_5	12	0	66.7	3
7	$(CH_2)_2CH_3$	12	0	60	4
8	$(CH_2)_3CH_3$	12	0	70.2	5
9	$(CH_2)_5CH_3$	12	0	71.3	6
10	CH_2CHCH_2	12	0	40.5	7
11	Bn	12	0	67.9	8
12	$CH_2CO_2C_2H_5$	12	0	35.8	9
13	$COCH_3$	12	0	/	/
14	$COCH_3CH_3$	12	0	/	/

Table 2

Protective effect on the apoptosis of PC12 cells induced by H_2O_2.

	Inhibition of PC12 cell (%)			Inhibition of apoptosis of PC12 cells induced by H_2O_2 (%)		
Compound	200 μ*M*	20 μ*M*	2 μ*M*	200 μ*M*	20 μ*M*	2 μ*M*
2	55.56	18.43	26.61	–	–	–
3	54.36	3.59	15.02	–	0	0
4	18.77	0	3.53	–	43.70	46.62
5	0.00	0	0	44.20	62.88	65.93
6	90.06	14.67	5.63	–	0	35.89
7	89.33	5.66	2.99	–	0	0
8	89.51	7.41	2.36	–	0	0
9	29.56	14	9.07	–	0	0
VE						22.46

Table 3

In vitro cytotoxicity against A549 and P388 cell line.

	P388 (%)		A459 (%)	
Compound	100 μ*M*	10 μ*M*	100 μ*M*	10 μ*M*
2	48.7	9.4	75.6	12.2
3	54.6	4.5	58.5	0
4	54.0	10.1	50.7	0
5	17.8	8.1	55.8	0
6	97.2	0	95.3	3.7
7	61.4	2.5	76.5	9.8
8	68.7	5.6	76.0	14.2
9	97.9	14.4	85.9	3.2

potent activity, with the inhibition percentage of 97.2, 95.3 and 97.9, 85.9, only compound **5** was inactive against P388.

EXPERIMENTAL

In an oven-dried flask connected to a nitrogen/vacuum line was placed phenylacetylene (1.6 mmol) followed by the slow addition of Et_2Zn 1*M* solution in toluene (1.5 mmol, 1.5 mL) (2.5 mmol Et_2Zn for isatin). The resulting solution was stirred at room temperature for 1 h and then cooled to 0°C with an ice-water bath. The (*N*-substituted) isatin (1 mmol) was added to the reaction mixture. The resulting solution was stirred at 0°C for 12 h, and then warmed to room temperature. The reaction was quenched with water (10 mL). The mixture was stirred for 10 min and then filtered over Celite. The mixture evaporated under reduced pressure and was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 10: 1–4: 1).

3-Hydroxy-3-(phenylethynyl)indolin-2-one (1). ^1H NMR (CD_3OD, 400 MHz), δ: 7.50 (1H, d, *J* = 7.2 Hz), 7.43 (2H, m), 7.30–7.33 (4H, m), 7.10 (1H, m), 6.91 (1H, d, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz), δ: 177.6, 142.4, 132.8, 132.2, 131.3, 130.0, 129.5, 125.6, 124.2, 123.3, 111.5, 87.3, 86.3; MS (ESI): *m*/*z* 272 (M + Na^+). HR-ESI-MS: *m*/*z* 272.0684 (calcd. for $C_{16}H_{11}NNaO_2^+$ 272.0687); Anal. Calcd for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62. Found: C, 77.33; H, 4.14, N, 5.52.

1-Methyl-3-hydroxy-3-(phenylethynyl)indolin-2-one (2). ^1H NMR ($CDCl_3$, 400 MHz), δ: 7.62 (1H, d, *J* = 6.8 Hz), 7.43 (2H, d, *J* = 6.8 Hz), 7.38 (1H, t, *J* = 7.6 Hz), 7.24–7.30 (3H, m), 7.16 (1H, t, *J* = 7.6 Hz), 6.85 (1H, d, *J* = 8.0 Hz), 4.05 (1H, s), 3.23 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz), δ: 173.9, 142.9, 132.0, 130.5, 128.9, 128.8, 128.2, 124.7, 123.7, 121.5, 108.8, 86.3, 85.4, 69.5, 26.6; MS (ESI): *m*/*z* 286 (M + Na^+). HR-ESI-MS: *m*/*z* 286.08849 (calcd. for $C_{17}H_{13}NNaO_2^+$ 286.0844); Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.43; H, 4.77, N, 5.23.

1-Ethyl-3-hydroxy-3-(phenylethynyl)indolin-2-one (3). ^1H NMR ($CDCl_3$, 400 MHz), δ: 7.62 (1H, d, *J* = 7.6 Hz), 7.27–7.45 (6H, m), 7.16 (1H, t, *J* = 7.6 Hz), 6.89 (1H, d, *J* = 7.6 Hz), 3.78 (2H, m), 3.75 (1H, s), 1.31 (3H, t, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz), δ: 173.5, 142.2, 132.0, 130.4, 129.2, 128.9, 128.1, 124.9, 123.5, 121.7, 108.9, 86.2, 85.6, 35.2, 12.4; MS (ESI): *m*/*z* 300 (M + Na^+). HR-ESI-MS: *m*/*z* 300.1006 (calcd. for $C_{18}H_{15}NNaO_2^+$ 300.1000); Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.78; H, 5.41, N, 5.11.

1-Propyl-3-hydroxy-3-(phenylethynyl)indolin-2-one (4). ^1H NMR ($CDCl_3$, 400 MHz), δ: 7.62 (1H, d, *J* = 7.6 Hz), 7.27–7.45 (6H, m), 7.16 (1H, t, *J* = 7.6 Hz), 6.89 (1H, d, *J* = 7.6 Hz), 3.78 (2H, m), 3.75 (1H, s), 1.31 (3H, t, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz), δ: 173.5, 142.2, 132.0, 130.4, 129.2, 128.9, 128.1, 124.9, 123.5, 121.7, 108.9, 86.2, 85.6, 35.2, 12.4; MS (ESI): *m*/*z* 314 (M + Na^+). HR-ESI-MS: *m*/*z* 314.1158 (calcd. for $C_{19}H_{17}NNaO_2^+$ 314.1157); Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.30; H, 5.76, N, 4.45.

1-Butyl-3-hydroxy-3-(phenylethynyl)indolin-2-one (5). ^1H NMR ($CDCl_3$, 400 MHz), δ: 7.62 (1H, d, *J* = 7.2 Hz), 7.25–7.44 (6H, m), 7.14 (1H, t, *J* = 7.6 Hz), 6.87 (1H, d, *J* = 8.0 Hz), 3.83 (1H, s), 3.68 (2H, m), 7.74 (2H, m), 0.98 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz), δ: 173.7, 142.3, 132.1, 130.3, 129.2, 128.9, 128.1, 124.9, 123.5, 121.7, 108.9, 86.2, 85.7, 33.2, 25.7, 12.8; MS (ESI) *m*/*z*: 328 (M + Na^+). HR-ESI-MS: *m*/*z* 328.1318 (calcd. for $C_{20}H_{19}NNaO_2^+$ 328.1313); Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.67; H, 6.33, N, 4.42.

1-Hexyl-3-hydroxy-3-(phenylethynyl)indolin-2-one (6). ^1H NMR ($CDCl_3$, 400 MHz), δ: 7.61 (1H, d, *J* = 7.6 Hz), 7.43 (2H, m), 7.37 (1H, t, *J* = 8.0 Hz), 7.30 (2H, m), 7.15 (1H, t, *J* = 7.6 Hz), 6.88 (2H, d, *J* = 8.0 Hz), 3.71 (2H, t, *J* = 6.8 Hz), 3.64 (1H, s), 1.70 (3H, m), 1.25–1.38 (5H, m), 0.87 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz), δ: 173.9, 142.4, 132.1, 130.1, 129.0, 128.9, 128.2, 124.9, 123.5, 121.8, 109.1, 86.1, 85.6, 69.5, 48.6, 40.0, 31.1, 28.9, 26.8, 22.3; MS (ESI): *m*/*z* 356 (M + Na^+). HR-ESI-MS: *m*/*z* 356.1625 (calcd. for $C_{22}H_{23}NNaO_2^+$ 356.1626); Anal. Calcd for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20. Found: C, 79.31; H, 6.78, N, 4.41.

1-Allyl-3-hydroxy-3-(phenylethynyl)indolin-2-one (7). ^1H NMR ($CDCl_3$, 400 MHz), δ: 7.62 (1H, d, *J* = 7.6 Hz), 7.44 (2H, d, *J* = 7.6 Hz), 7.26–7.36 (4H, m), 7.15 (1H, t, *J* = 7.6 Hz), 6.86 (1H, d, *J* = 7.6 Hz), 5.85 (1H, m), 5.26 (2H, m), 4.36 (2H, m), 3.80 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz), δ: 173.8, 143.0, 130.6, 133.1, 131.3, 129.2, 128.4, 128.2, 124.9, 123.6, 121.4, 118.8, 109.4, 86.2, 85.5, 69.5, 43.3; MS (ESI): *m*/*z* 312 (M + Na^+). HR-ESI-MS: *m*/*z* 312.9997 (calcd. for $C_{19}H_{15}NNaO_2^+$ 312.1000); Anal. Calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 78.66; H, 5.15, N, 4.77.

1-Benzyl-3-hydroxy-3-(phenylethynyl)indolin-2-one (8). ^1H NMR ($CDCl_3$, 400 MHz), δ: 7.62 (1H, d, *J* = 7.2 Hz), 7.45 (2H, d, *J* = 7.6 Hz), 7.23–7.33 (4H, m), 7.12 (1H, t, *J* = 7.6 Hz), 6.72 (1H, d, *J* = 7.6 Hz), 4.94 (2H, s), 3.80 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz), δ: 174.1, 142.2, 135.0, 132.0, 130.3, 128.9, 128.8, 128.2, 127.7, 127.1, 124.8, 123.7, 121.6, 108.9, 86.5, 85.5, 69.6, 44.1. MS (ESI): *m*/*z* 362 (M + Na^+). HR-ESI-MS: *m*/*z* 362.1157 (calcd. for $C_{23}H_{17}NNaO_2^+$ 362.1157); Anal. Calcd for $C_{23}H_{17}NO_2$: C, 81.40; H, 5.05; N, 4.13. Found: C, 81.51; H, 5.13, N, 4.22.

Ethyl-2-(3-hydroxy-2-oxo-3-(phenylethynyl)indolin-1-yl)-acetate (9). ^1H NMR ($CDCl_3$, 400 MHz), δ: 7.64 (1H, d, *J* = 7.6 Hz), 7.43 (2H, d, *J* = 7.2 Hz), 7.25–7.37 (4H, m), 7.17 (1H, t, *J* = 7.6 Hz), 7.66 (1H, d, *J* = 8.0 Hz), 4.48 (2H, s), 4.21 (2H, q, *J* = 7.2 Hz), 3.76 (1H, s), 1.25 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz), δ: 173.8, 167.1, 141.2, 132.1, 130.5, 129.0, 128.7, 128.2, 124.9, 124.1, 121.5, 108.9, 86.7, 85.1, 69.4, 61.9, 41.7, 14.1; MS (ESI): *m/z* 358 (M + Na^+). HR-ESI-MS: *m/z* 358.1054 (calcd. for $C_{20}H_{17}NNaO_4^+$ 358.1055); Anal. Calcd for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18; O, 19.08. Found: C, 71.58; H, 5.20, N, 4.23.

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Synthesis and Application of Novel Styryl Dyes Derived from 1,4-Diethyl-1,2,3,4-tetrahydro-6-methoxyquinoxaline

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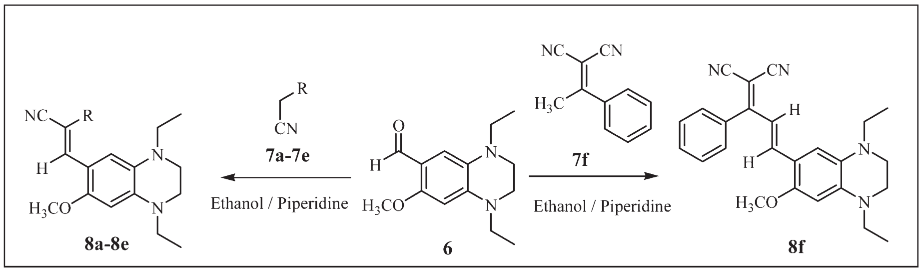

The novel 1,4-diethyl-1,2,3,4-tetrahydro-7-methoxyquinoxalin-6-carboxaldehyde was synthesized, characterized, and condensed with suitably substituted active methylene compounds by classical Knoevenagel condensation reaction to obtain novel monostyryl dyes **8a-8e** and a bis-styryl dye **8f**. These novel styryl dyes have hue varying from orange to violet. The dyes were applied to polyester fibers. The spectral and thermal characteristics of the dyes and fastness properties of the dyed polyester fabric were investigated.

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INTRODUCTION

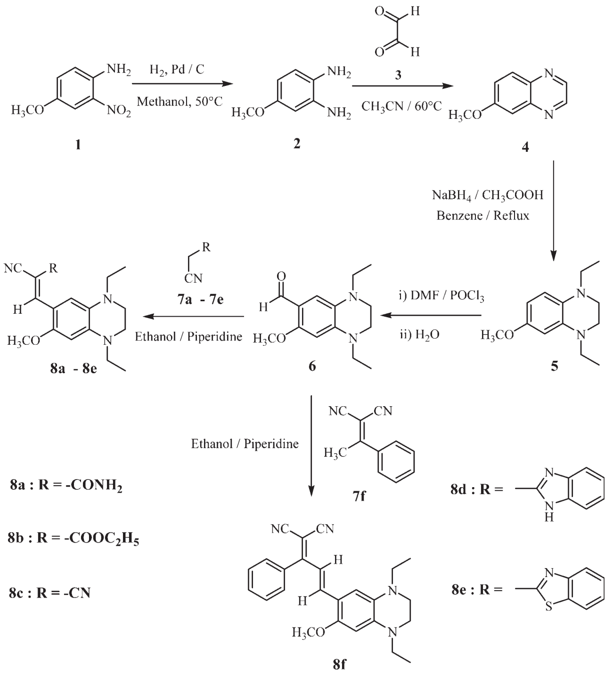
Heterocyclic compounds are of interest as functional materials in the emitters of electroluminescence devices and in molecular probes used for biochemical research, as well as in the traditional textile and polymer fields [1–3]. Heterocyclic chromophores are useful materials in the search for new biologically active compounds and diagnostic methods [4]. They are generally known to have planar and rigid π-conjugation system, and many of them are based on rigid ring systems such as coumarin, naphthalimide, perylene, pyrromethene, and rhodamine. Our research group has been interested in the chemistry of nitrogen containing heterocyclic molecules for many years. Various heterocyclic chromophores based on quinoxaline nucleus have been studied in our laboratory. Fluorescent compounds based on 2-methylthiazolo[4,5-*b*]quinoxaline [5,6], 2-methyl-(1,3)-dithiolium[4,5-*b*]quinoxaline [7] have been reported. In this contribution, we want to report synthesis and application of some new 1,4-diethyl-1,2,3,4-tetrahydroquinoxaline derivatives with different electron donating abilities.

Quinoxalines are, in general, comparatively easy to prepare and numerous derivatives thereof have been designed and synthesized for potential use as biologically active molecules. The classical synthesis of quinoxalines involves condensation of aromatic 1,2-diamines with 1,2-dicarbonyl compounds. The reaction is facile and is the most widely used synthetic method for both quinoxaline itself and its derivatives. They can be easily reduced to 1,2,3,4-tetrahydroquinoxalines by reducing agents such as lithium aluminum hydride [8] and sodium borohydride [9] in excellent yields. Sequential reduction and alkylation of N-heterocycles such as indole to N-alkylated indoline and quinoline to N-alkylated-1,2,3,4-tetrahydroquinoline by sodium borohydride and trifluoroacetic acid is well known [10–13]. Quinoxalines can also be sequentially reduced and dialkylated using sodium borohydride and carboxylic acids. 6-Nitroquinoxaline has been subjected to reductive alkylation using sodium borohydride and glacial acetic acid to obtain 1,4-diethyl-1,2,3,4-tetrahydro-6-nitroquinoxaline [14]. These results led us to explore the utility of substituted tetrahydroquinoxalines to prepare novel styryl dyes.

In this study, 6-methoxyquinoxaline was subjected to alkylative reduction to afford 1,4-diethyl-1,2,3,4-tetrahydro-6-methoxyquinoxaline. This key intermediate was then used to prepare novel red to violet styryl dyes by convenient method of synthesis. We have varied the electron accepting groups to study the influence of the nature of substituents on spectral characteristics of the dyes. To increase the bathochromicity further and study the effect of incorporation of another styryl group, 1,4-diethyl-7-methoxy-1,2,3,4-tetrahydroquinoxalin-6-carboxaldehyde was condensed with

Scheme 1

Synthetic pathway of the dyes **8a-8f**



1,1-dicyano-2-methyl-2-phenylethene. The extended styryl dye thus obtained showed violet hue and displayed absorption maxima at 585 nm. The spectral properties of these novel heterocycles in various solvents differing considerably in polarity and their application as disperse dyes for polyester fabric are reported latter. The thermogravimetric analysis was also carried out to study thermal stability of the dyes.

RESULTS AND DISCUSSION

Synthesis of styryl dyes. The novel styryl dyes were prepared by classical Knoevenagel condensation of 1,4-diethyl-7-methoxy-1,2,3,4-tetrahydroquinoxalin-6-carboxaldehyde **6** and various active methylene compounds **7a-7f** as shown in Scheme 1. In the first stage, 4-methoxy-2-nitroaniline **1** was hydrogenated over palladium charcoal catalyst in methanol to obtain 4-methoxy-1,2-phenylenediamine **2**, which was subsequently condensed with glyoxal **3** in acetonitrile to afford 6-methoxyquinoxaline **4** in excellent yield. Reductive alkylation of 6-methoxyquinoxaline with sodium borohydride and glacial acetic acid in dry benzene yielded 1,4-diethyl-6-methoxy-1,2,3,4-tetrahydroquinoxaline **5**. The electron rich 1,2,3,4-tetrahydroquinoxaline derivative **5** was subjected to Vilsmeier–Haack reaction to yield 1,4-diethyl-7-methoxy-1,2,3,4-tetrahydroquinoxalin-6-carboxaldehyde **6**. To obtain styryl dyes **8a-8f**, a mixture of this aldehyde **6** and the corresponding active methylene compound was refluxed in absolute ethanol and catalytic amount of piperidine. The structures of the dyes were confirmed by IR, ^{1}H NMR, and elemental analysis. The results are summarized in experimental section.

Spectral characteristics of the dyes. Basic absorption characteristics of the compounds such as the absorption maxima (λ_{max}), extinction coefficient (ε) were measured in different solvents and are presented in Table 1. The electronic absorption spectra of the dyes **8a-8f** in methanol displayed absorption maxima in the visible region from 480 to 585 nm, which underwent bathochromic shift depending on the extent of conjugation as well as electron withdrawing nature of the acceptor group. The values of molar extinction coefficients were in the range from 12,477 L/mol cm to 31,899 L/mol cm. In the case of monostyryl dyes, introduction of heterocyclic ring as electron acceptor caused a strong bathochromic shift. Especially, dye containing benzothiazole ring showed remarkable shift towards longer wavelength with ε_{max} value of 25,514. This is due to high electronegativity of sulphur atom in the ring and increase in π-delocalization conjugation in the dye. The bis-styryl dye **8f** showed well pronounced maxima at 585 nm, longest among the reported dyes in this communication. This further increase in bathochromicity was attributed to incorporation of another styryl group which produced dye based on 1,1-dicyano-2,4-

Table 1

Spectral properties of the dyes **8a-8f** in different solvents.

	Acetone		Methanol		Acetonitrile		DMF	
Dye No.	λ_{max} (nm)	ε (L/mol cm)	λ_{max} (nm)	ε (L/mol cm)	λ_{max} (nm)	ε (L/mol cm)	λ_{max} (nm)	ε (L/mol cm)
8a	475	24,554	480	18,499	484	21,859	478	18,918
8b	490	26,511	489	31,899	493	29,347	499	31,041
8c	499	15,801	498	12,477	502	19,980	508	20,794
8d	496	29,939	501	29,218	502	23,916	502	30,702
8e	529	35,498	528	25,514	529	28,235	538	33,065
8f	583	39,123	585	24,306	586	42,354	598	46,035

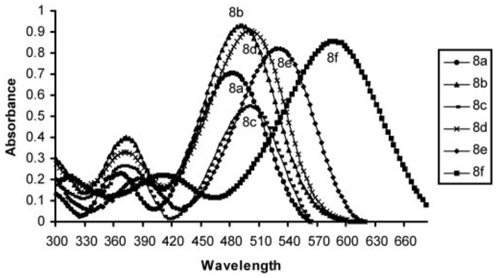


Figure 1. Absorption maxima of the dyes **8a-8f** in methanol.

diarylbutadiene system. The ε_{max} value of the dye was 24,306. The dye exhibited intense violet hue, which is usually difficult to obtain with small styryl structures.

To investigate the influence of solvents on the absorption maxima of the dyes, their absorption spectra were measured in different solvents such as dimethyl formamide, acetonitrile, methanol, and acetone. The solvents differ considerably in polarity and ability to form H-bonding. The electronic absorption spectra of the styryl dyes showed absorption maxima in the visible region at 475–583 nm in acetone, 484–586 nm in acetonitrile, and 478–598 nm in dimethyl formamide (DMF). From the presented values in Table 1, it is evident that practically no solvent effect was observed. Only in case of DMF slight bathochromicity was noticed. The dyes reported in this study exhibit no fluorescence in solvents; however, very weak fluorescence was observed when dissolved in DMF. Figure 1 displays absorption maxima of the dyes **8a-8f** in methanol.

Thermal properties of the dyes. The dyes were subjected to the thermogravimetric analysis to investigate their thermal stability. The change in weight of the dye was measured as a function of temperature. Figures 2 and 3 display thermograph of the representative dyes **8b** and **8f**, respectively. The thermogravimetric curve for the monostyryl dye **8b** (Fig. 2) shows a clear plateau followed by a sharp decomposition curve. The loss in weight of the dye is rapid when heated above 266°C. These results indicate that the dye is stable up to 266°C after which it decomposes rapidly and decomposition completes above 466°C. Almost similar pattern of thermogravimetric curve was obtained for the bis-styryl dye **8f** (Fig. 3) which is stable up to 274°C then starts decomposing slowly and completely decomposes above 502°C. It is clear from the presented data that both monostyryl and bis-styryl dyes have good thermal stability.

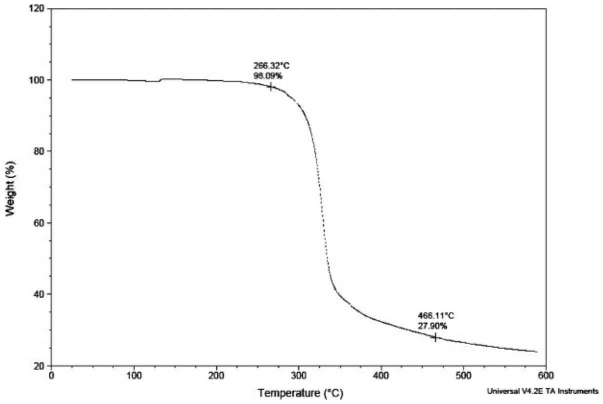


Figure 2. Thermogravimetric curve for the monostyryl dye **8b**.

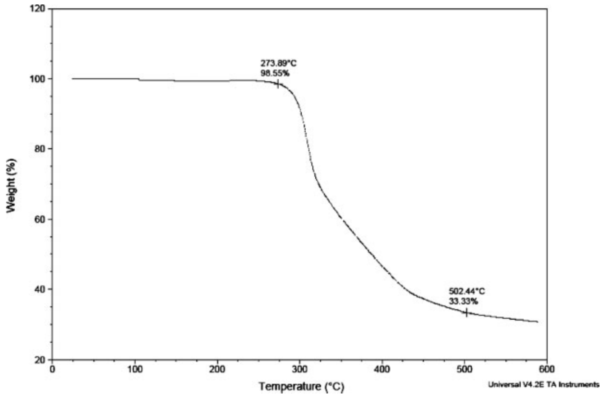


Figure 3. Thermogravimetric curve for the bis-styryl dye **8f**.

Fastness properties of the dyes. Fastness properties of the dyes under study were determined from the standpoint of their application as disperse dyes for polyester fabrics. The dyes **8a-8f** were applied to polyester fiber at 2% shade by high temperature-pressure technique and generally gave bright intense hue ranging from orange to violet. The fastness properties of the dyed fabric such as wash fastness, light fastness, and sublimation fastness were evaluated and assessed on 1 (poor) to 7 (outstanding) rating. The light fastness, wash fastness, and sublimation fastness properties were evaluated as per AATCC standard test methods [15–17]. Table 2 presents values of the fastness properties of dyed polyester fabric. For sublimation fastness determinations, the dyed

Table 2

Fastness properties of the dyes **8a–8f** on polyester fabric.

Dye No.	Light fastness (1–7)	Wash fastness (1–5)	Sublimation fastness (1–5)
8a	4	4	3
8b	3	5	2
8c	3	3	4
8d	5	4	4
8e	6	5	3
8f	4	5	3

1, Poor; 2, Fair; 3, Fairly good; 4, Good; 5, Very good; 6, Excellent; 7, Outstanding.

polyester fabrics were stitched between two pieces of undyed polyester fabrics (stain cloths) and treated at 200°C for 1 min. Any staining on the undyed piece, change in tone, or loss in depth was assessed on a 1 (poor) to 5 (very good) rating.

All the dyes built up well on polyester to give strong, bright colors. The light fastness of the dyes was of generally good order and varied from 3 to 6, dye **8e** exhibited excellent light fastness. The sublimation fastness of the dyes was in the range of 2–4, thus showed good sublimation fastness properties on polyester fabric. The dyes showed good wash fastness, as it is usual with disperse dyes.

EXPERIMENTAL

All melting points were uncorrected and in degree Celsius (°C). IR spectra were recorded on a Bomem Hartmann and Braun MB-Series FIIR spectrometer (KBr). ^{1}H NMR spectra were recorded on Varian 300 MHz mercury plus spectrometer, and chemical shifts are expressed in δ ppm using TMS as an internal standard. Microanalysis for C, H, and N were performed on Thermofignnin Elemental analyzer. Electronic spectra were recorded on Spectronic spectrophotometer from dye solutions in DMF, methanol, acetone, and acetonitrile. Thermogravimetric analysis was carried out on SDT Q600 v8.2 Build 100 model of TA instruments.

Synthesis of 6-methoxyquinoxaline (4). 4-Methoxy-2-nitroaniline (16.8 g, 0.1 mol) was dissolved in methanol (200 mL) and hydrogenated in Parr hydrogenator using 10% Pd/C catalyst at 60°C for 6 h (reaction monitored on TLC). After cooling, the reaction mass was filtered to separate catalyst and concentrated in roto-evaporator. Residue obtained was dissolved in dry acetonitrile (350 mL) and to this solution was added glyoxal (40%, 32.0 mL, 2.6 mol). Reaction mixture was then stirred at 60°C for 6 h and cooled. Solvent was removed in roto-evaporator and the dark brown sticky solid obtained was passed over silica gel column to remove base impurities (Eluent: 70% ethyl acetate in hexane). 6-Methoxyquinoxaline was obtained as white solid in excellent yield, 13.6 g (85%), mp 58–60°C (Lit mp 60°C [18]).

Synthesis of 1,4-diethyl-6-methoxy-1,2,3,4-tetrahydroquinoxaline (5). 6-Methoxyquinoxaline (5.5 g, 0.034 mol) was dissolved in dry benzene (350 mL) and cooled to 5°C. To this cold solution was added sodium borohydride (13.2 g, 0.35 mol) over a period of 15 min. Pale yellow slurry thus obtained was stirred for 10 min. Glacial acetic acid (57.3 mL, 60 g, 1.0 mol) was added to it drop wise over a period of 1 h maintaining the temperature 5–10°C. The brownish slurry that formed was stirred for another 1 h at 10°C and allowed to attain room temperature. It was then heated to gentle reflux for 5 h (reaction monitored on TLC). On cooling, thick red resinous mass was obtained to which water (250 mL) was added. The benzene layer formed was separated and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). Combined extracts and benzene layer were washed repeatedly with dilute sodium carbonate solution and water, dried over anhydrous sodium sulfate, filtered and vacuum evaporated. The dark brown oil obtained was purified by vacuum distillation to afford golden yellow oil, 6.35 g (84%), bp 142–144°C at 2 mm.

Synthesis of 1,4-diethyl-7-methoxy-1,2,3,4-tetrahydro-6-quinoxalinecarboxaldehyde (6). Phosphorous oxychloride (8.0 mL, 0.09 mol) was added to dimethyl formamide (10.1 mL, 0.13 mol) at 5°C under stirring. After 15 min, 1,4-diethyl-6-methoxy-1,2,3,4-tetrahydroquinoxaline (11.0 g, 0.05 mol) was added to the cooled reagent under stirring. The mixture was then heated at 70–80°C for 4 h and poured on ice water. The clear solution was neutralized by adding cold sodium hydroxide solution (15%) maintaining the temperature at 10–15°C. The sticky mass obtained was extracted in ethyl acetate (4 × 100 mL). Ethyl acetate extracts were combined, dried over anhydrous sodium sulfate, and vacuum evaporated. Brown sticky solid showing dark yellow spot on TLC was purified by column chromatography using neutral activated aluminum oxide (Eluent: 40% ethyl acetate in hexane), 8.43 g (68%), bp 146–148°C, IR: CO 1712 cm^{-1}, ^{1}H NMR: δ 1.16 (t, 6.9Hz, 3H, CH_3), δ 1.23 (t, 6.9Hz, 3H, CH_3), δ 3.13–3.18 (m, 2H), δ 3.31 (q, 6.9Hz, 2H, CH_2), δ 3.41 (q, 6.9Hz, 2H, CH_2), δ 3.49–3.54 (m, 2H), δ 3.93 (s, 3H, OCH_3), δ 6.0 (s, 1H, phenyl proton), δ 7.0 (s, 1H, phenyl proton), δ 10.20 (s, 1H, aldehydic proton), *Anal.* Calcd for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.81; H, 8.14; N, 11.34.

Synthesis of styryl dyes (8a–8f).

Synthesis of 2-cyano-3-(1,4-diethyl-7-methoxy-1,2,3,4-tetrahydroquinoxalin-6-yl)-2-propenoic acid ethylester (8b). 1,4-Diethyl-7-methoxy-1,2,3,4-tetrahydro-6-quinoxalinecarboxaldehyde (2.48 g, 0.01 mol) and ethyl cyanoacetate 1.13 g (0.01 mol) were dissolved in dry ethanol. Piperidine (0.1 mL) was added to it and reaction mixture was refluxed for 2 h. Ethanol was removed by distillation and reddish crystals were washed with water and dried. Dye **(8b)** thus obtained was further purified by column chromatography using neutral activated aluminum oxide (Eluent: 30% ethyl acetate in hexane), 2.7 g, 78%, mp 128–132°C, IR: CO 1755, CN 2210 cm^{-1}, ^{1}H NMR: δ 1.21 (t, 6.9Hz, 3H, CH_3), δ 1.26 (t, 6.9Hz, 3H, CH_3), δ 1.36 (t, 6.9Hz, 3H, CH_3), δ 3.16–3.22 (m, 2H), δ 3.34 (q, 6.9Hz, 2H, CH_2), δ 3.44 (q, 6.9Hz, 2H, CH_2), δ 3.53–3.59 (m, 2H), δ 3.92 (s, 3H, OCH_3), δ 4.44 (q, 6.9Hz, 2H, CH_2), δ 6.0 (s, 1H, phenyl proton), δ 7.7 (s, 1H, phenyl proton), δ 8.6 (s, 1H, olefinic proton), *Anal.* Calcd for $C_{19}H_{25}N_3O_3$: C, 66.45; H, 7.34; N, 12.24. Found: C, 66.56; H, 7.35; N, 12.31.

Synthesis of 2-cyano-3-(1,4-diethyl-7-methoxy-1,2,3,4-tetrahydroquinoxalin-6-yl)-2-propenamide (8a). 2.54 g (81%), mp 172–175°C, IR: CO 1685, CN 2218 cm^{-1}, ^{1}H NMR: δ 1.20 (t, 7.1Hz, 3H, CH_3), δ 1.25 (t, 7.1Hz, 3H, CH_3), δ 3.18–3.23 (m, 2H), δ 3.35 (q, 6.9Hz, 2H, CH_2), δ 3.44 (q, 6.9Hz, 2H, CH_2), δ 3.54–3.59 (m, 2H), δ 3.90 (s, 3H, OCH_3), δ 5.3 (s, 2H, $CONH_2$ proton), δ 6.0 (s, 1H, phenyl proton), δ 7.6 (s, 1H, phenyl proton), δ 8.5 (s, 1H, olefinic proton), *Anal.* Calcd for $C_{17}H_{22}N_4O_2$: C, 64.95; H, 7.05; N, 17.82. Found: C, 64.83; H, 7.07; N, 17.99.

Synthesis of [(1,4-diethyl-7-methoxy-1,2,3,4-tetrahydroquinoxalin-6-yl)methylene]propanedinitrile (8c). 2.22 g (75%), mp 226–228°C, IR: CN 2223 cm^{-1}, ^{1}H NMR: δ 1.22 (t, 7.0Hz, 3H, CH_3), δ 1.28 (t, 7.0Hz, 3H, CH_3), δ 3.16–3.21 (m, 2H), δ 3.33 (q, 7.0Hz, 2H, CH_2), δ 3.42 (q, 7.0Hz, 2H, CH_2), δ 3.52–3.57 (m, 2H), δ 3.93 (s, 3H, OCH_3), δ 6.1 (s, 1H, phenyl proton), δ 7.7 (s, 1H, phenyl proton), δ 8.9 (s, 1H, olefinic proton), *Anal.* Calcd for C17H20N4O: C, 68.89; H, 6.80; N, 18.90. Found: C, 68.99; H, 6.83; N, 18.97.

Synthesis of α-[(1,4-diethyl-7-methoxy-1,2,3,4-tetrahydroquinoxalin-6-yl)methylene]-1-H-benzimidazoleacetonitrile (8d). 2.82 g (73%), mp 258–260°C, IR: CN 2220 cm^{-1}, ^{1}H NMR: δ 1.20 (t, 7.0Hz, 3H, CH_3), δ 1.26 (t, 7.0Hz, 3H, CH_3), δ 3.19–3.25 (m, 2H), δ 3.36 (q, 7.0Hz, 2H, CH_2), δ 3.46 (q, 7.0Hz, 2H, CH_2), δ 3.55–3.61 (m, 2H), δ 3.90 (s, 3H, OCH_3), δ 6.0 (s, 1H, phenyl proton), δ 7.5 (s, 1H, phenyl proton), δ 8.3 (s, 1H, olefinic proton), δ 7.5 (d, 2H, phenyl proton), δ 7.2 (d, 2H, phenyl proton), δ 10.2 (s, 1H, NH proton), *Anal.* Calcd for $C_{23}H_{25}N_5O$: C, 71.29; H, 6.50; N, 18.07. Found: C, 71.41; H, 6.54; N, 18.08.

Synthesis of α-[(1,4-diethyl-7-methoxy-1,2,3,4-tetrahydroquinoxalin-6-yl)methylene]benzthiazoleacetonitrile (8e). 3.03 g (75%), mp 170–172°C, IR: CN 2225 cm^{-1}, ^{1}H NMR: δ 1.20 (t, 7.1Hz, 3H, CH_3), δ 1.26 (t, 7.1Hz, 3H, CH_3), δ 3.19–3.25 (m, 2H), δ 3.33 (q, 7.1Hz, 2H, CH_2), δ 3.43 (q, 7.1Hz, 2H, CH_2), δ 3.55–3.61 (m, 2H), δ 3.93 (s, 3H, OCH_3), δ 6.1 (s, 1H, phenyl proton), δ 7.6 (s, 1H, phenyl proton), δ 8.4 (s, 1H, olefinic proton), δ 7.7 (d, 2H, phenyl proton), δ 7.2 (d, 2H, phenyl proton), *Anal.* Calcd for $C_{23}H_{24}N_4OS$: C, 68.29; H, 5.98; N, 13.85; S, 7.93. Found: C, 68.28; H, 5.96; N, 13.90; S, 7.87.

Synthesis of [3-(1,4-diethyl-7-methoxy-1,2,3,4-tetrahydroquinoxalin-6-yl)-1-phenyl-2-propenylidene]propanedinitrile (8f). 3.2 g (81%), mp 218–220°C, IR: CN 2210 cm^{-1}, ^{1}H NMR: δ 1.18 (t, 6.9Hz, 3H, CH_3), δ 1.24 (t, 6.9Hz, 3H, CH_3), δ 3.15–3.20 (m, 2H), δ 3.30 (q, 6.9Hz, 2H, CH_2), δ 3.42 (q, 6.9Hz, 2H, CH_2), δ 3.48–3.55 (m, 2H), δ 3.73 (s, 3H, OCH_3), δ 5.99 (s, 1H, aromatic proton), δ 6.63 (s, 1H, aromatic proton), δ 7.28 (m, 1H, phenyl proton), δ 7.33–7.34 (m, 2H, phenyl proton), δ 7.53–7.56 (m, 2H, phenyl proton), δ 7.12–7.17 (d, 15.03Hz, 1H, olefinic proton), δ 7.40–7.45 (d, 15.03Hz, 1H, olefinic proton), *Anal.* Calcd for $C^{25}H^{26}N^{4}O$: C, 75.35.; H, 6.58; N, 14.06. Found: C, 74.96; H, 6.33; N, 14.28.

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Investigation on the Reactions of *o*-Hydroxybenzyl Alcohols with Vinyl Ethers Under Acidic and/or Thermal Conditions

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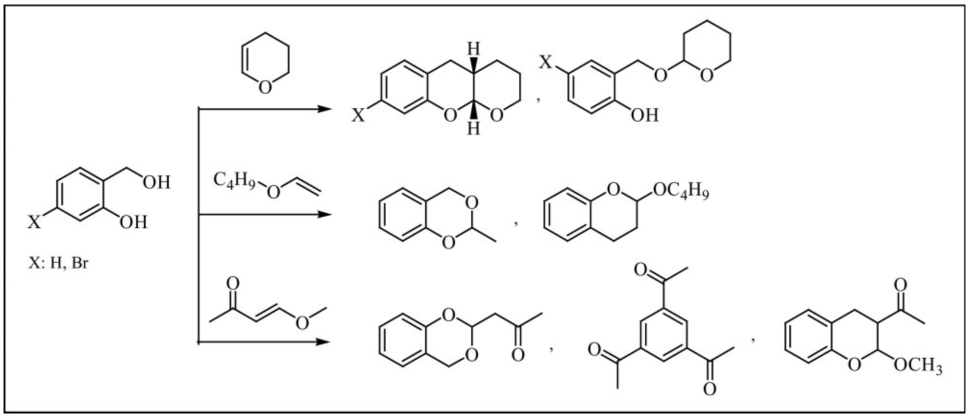

The reaction of vinyl ethers with *o*-hydroxybenzyl alcohols under different reaction conditions was investigated. The aim of this attempt was to find out whether the protection reactions or the hetero Diels–Alder reaction of quinone methide *in situ* generated from *o*-hydroxybenzyl alcohol is more likely to occur. *o*-hydroxybenzyl alcohols can give hetero Diels–Alder reactions with dihydro-2*H*-pyran at high temperatures but only when used with acid catalysts. At room temperature, even in the presence of acid catalyst, reactions yielded regular protection products. However, butyl vinyl ether and 4-methoxy-3-butenone could not give intermolecular cycloaddition reactions under the acidic conditions, because both decomposed to the new products with acids. Hetero-Diels–Alder products obtained only under thermal conditions but in low yields.

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INTRODUCTION

Protective groups play important roles in modern multistep synthetic organic chemistry and numerous publications on the selection of more suitable protecting groups for hydroxyl functions have appeared in recent years.

In our previous study, we reported selective *o*-benzylation of primary hydroxyl groups of di-and tri-hydroxyl compounds by using bis(acetylacetonato) copper as a catalyst [1].

Another well-known method for the protection of hydroxy groups is forming tetrahydropyranyl ether by reaction with 3,4-dihydro-2*H*-pyran (DHP). By using this method, diols, in which two hydroxyl groups are far away from each other can be protected in good yields. Hence, the main products are monotetrahydropyranyl ethers [2]. In these reactions, the reason for the low yield of the diprotection products is not well understood.

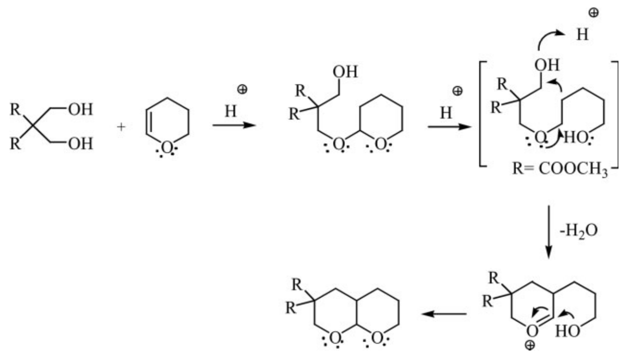
However, we have recently demonstrated that bicyclic acetals can readily be obtained with high diastereoselectivity from the reaction of 1,2- and 1,3-diols and DHP [3] (Scheme 1). In reactions carried out at 25°C using pyridine-*p*-toluene sulfonic acid (PPTS) as the catalyst, the first step is acetal formation by the addition of one of the hydroxyl groups of the diol to DHP in the usual way, the second step is ring opening of the DHP moiety and the generation of an enol ether, and the third step is water elimination and recyclization to the oxonium ion.

In particular, fused pyranobenzoxepine (**I**) was obtained from the *o*-hydroxymethylbenzyl alcohol (Fig. 1).

Formation of bicyclic acetals under catalytic conditions from aliphatic dihydroxy compounds leads us to investigate the reactions of aromatic dihydroxy compounds with DHP. We have chosen *o*-hydroxybenzyl alcohol as the diol because it has either two types of OH groups for protection reactions or it is the precursor of the quinone methide intermediate [4–6].

The aim of this study is to compare whether the protection reactions are more likely, or the hetero

Scheme 1



Diels–Alder reaction of quinone methide *in situ* generated from *o*-hydroxybenzyl alcohol is more likely to occur.

RESULTS AND DISCUSSION

Quinone methides are generally produced under thermal, photolytic, or catalytic conditions. In past years, *o*-hydroxybenzaldehydes have been preferred for generation of quinone methides under catalytic conditions [7–9]. Treatment of salicylaldehydes with 3,4-DHP in the presence of metal triflates resulted in pyrano[2,3-*b*]benzopyrans. For the reactions carried out under thermal conditions different precursors were used; while Ohwada and coworkers [10] used 4*H*-1,2-benzoxazines as precursor, Baldwin and coworkers [11] proposed a new method for *o*-quinone methide generation from *o*-methyleneacetoxy-phenols. They investigated the reactions of *o*-acetyloxymethyl phenol (2-hydroxybenzyl acetate) with dienophiles (including DHP) under thermal conditions (Scheme 2). Bray reported the generation and hetero-Diels–Alder reaction of an *o*-quinone methide using ^{i}PrMgCl under mild, anionic conditions [11]. Reactions of another precursor *o*-hydroxybenzyl alcohol and open-chain enol ethers under thermal conditions was investigated by Pochini and coworkers [12].

Under photolytic conditions *o*-hydroxybenzyl alcohol and DHP also produced benzopyranopyran derivatives [13] (Scheme 2).

However, there are no reports on the reaction of *o*-hydroxybenzyl alcohol with DHP under both catalytic and thermal conditions. Therefore, in this study, we have investigated the reaction products of DHP and *o*-hydroxybenzyl alcohol, both with acid catalysts and under thermal conditions.

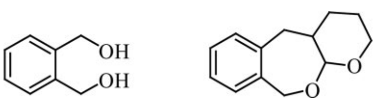
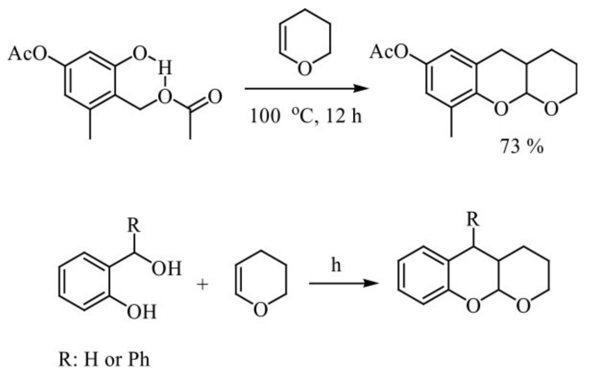


Figure 1. Reaction product of DHP and *o*-hydroxymethylbenzyl alcohol.

Scheme 2

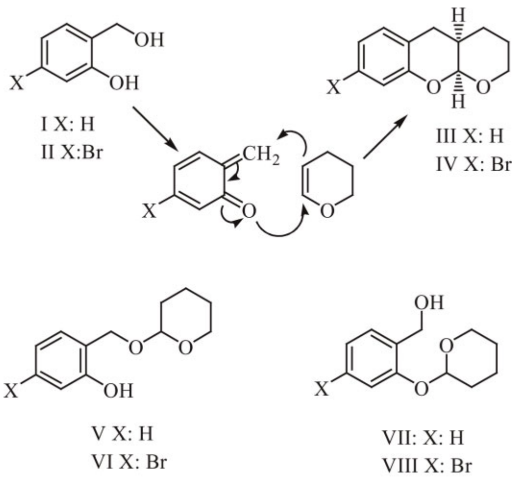


On the basis of the concept mentioned earlier, we reacted *o*-hydroxybenzyl alcohol with DHP in the presence of PPTS at the reflux temperature of toluene. The reaction produced *cis*-fused pyrano[2,3-*b*]benzopyran (**III**) and self-reaction products of DHP (**IX**) (Scheme 3). However, the yield was lower than that of Baldwin's method. The regular mono protection product (**V**) was also obtained in low yield. Diprotection products were not detected.

The structure and the stereochemistry of compound (**III**) was elucidated by spectroscopic and chromatographic data and the results were compared with former results [7–9]. Spectroscopic data showed that the reaction was highly diastereoselective, and the coupling constant, $J = 2.6$ Hz for the bridgehead protons proved the formation of the *cis*-fused bicyclic structure.

However, when the reaction was performed in toluene without catalyst, a desired pyranobenzopyran formed in very low yield, in contrast to Baldwin's result. Mono protection product **V** was observed as main product and

Scheme 3



Self -reaction products of DHP
IX

Table 1

Reaction conditions and products with yields.

Subs	Catalyst	Solvent	Temp. (°C)	Products and yields (%)[a]
I	PPTS	CH_2Cl_2	25	**V** (75) **VII** (7)[b]
I	Amb. 15	CH_2Cl_2	25	**V** (62) **VII** (10)[b]
I	PPTS	Toluene	110	**III** (35) **IX** (50) **V** (6)
I	Amb. 15	Toluene	110	**III** (15) **IX** (75)
I	–	Toluene	110	**V** (30) **III** (10)
II	PPTS	CH_2Cl_2	25	**VI** (80) **VIII** (5)[b]
II	Amb. 15	CH_2Cl_2	25	**VI** (70) **VIII** (9)[b]
II	PPTS	CH_3Cl	62	**VI** (60) **VIII** (6)[b] **IX** (10)
II	PPTS	Toluene	110	**IV** (36) **IX** (52)
II	PPTS	Toluene	110[c]	**IV** (40) **IX** (50) **VI** (4)
II	Amb. 15	Toluene	110	**IV** (15) **IX** (75)

[a] Not isolated.

[b] Reaction was performed with Dean–Stark apparatus.

[c] Yields are from GC analysis.

the rest of the reaction mixture was mainly unreacted *o*-hydroxybenzyl alcohol.

Furthermore, the reaction of 3-bromo-2-hydroxymethyl phenol with DHP under similar reaction conditions resulted in the corresponding pyranobenzopyran (**IV**).

To investigate the effect of reaction conditions on product types and their distribution, reactions were repeated at different temperatures, using different solvents and catalysts. Results of these studies are tabulated in Table 1.

The catalysts are PPTS and the strong acidic ion exchange resin Amberlyst-15. The reason for choosing Amberlyst-15 was to investigate the influence of acid structure on diastereoselectivity, but no change on stereoselectivity was observed. Increasing the reaction time did not effect the reaction yield or type of products. At room temperature, the expected protection products were obtained. As the reaction temperature was increased to 62°C self-reaction products of DHP began to form.

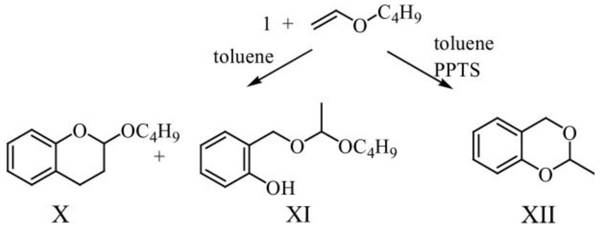
After determination of the appropriate reaction conditions for the formation of quinone methides, we worked on similar reactions of open-chain enol ethers. In this attempt, the aim was to compare the type of products with the products produced before. Butyl vinyl ether was chosen as open-chain enol ether. The reaction of butyl vinyl ether with *o*-hydroxybenzyl alcohol in toluene without catalyst resulted, mainly in two products; a corresponding 2-butoxychroman **X** (10%) and a usual addition compound **XI** (50%) (Scheme 4). The ratio of two products was determined by GC analysis of the crude product. 2-Butoxychroman has been recently produced by Ohwada and coworkers [10] under thermal conditions from 4*H*-1,2-benzoxazines, and also by Bray [11] from *o*-hydroxybenzyl acetate.

When this reaction was carried out with catalyst, none of the corresponding acetalic structures were found in the reaction mixture, instead the sole product (90%) was compound **XII** which resulted from the reaction of *o*-hydroxybenzyl alcohol and acetaldehyde produced from the decomposition of butyl vinyl ether in acidic medium. Compound **XII** was synthesized [14] before, from *o*-hydroxybenzyl alcohol and acetaldehyde dimethylacetal with 42% yield. There are several studies on the decomposition of vinyl ethers yielding acetaldehyde [15,16]. As seen in Scheme 4, similar to DHP, vinyl butyl ether afforded the desired acetalic structure with yield lower than that of the regular protection product.

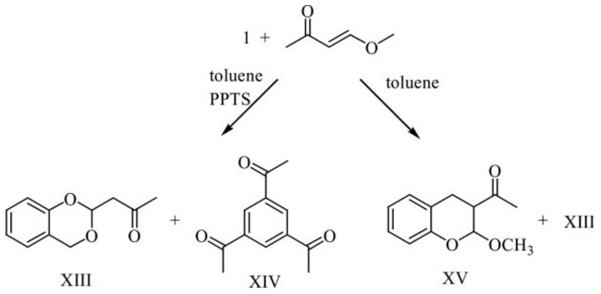
The reaction of 4-methoxy-3-butenone with *o*-hydroxybenzyl alcohol was also performed with and without catalyst. In the presence of catalyst mainly two products were obtained; compounds **XIII** (80%) and **XIV** (10%). Compound **XIII** resulted from *o*-hydroxybenzyl alcohol and 3-oxo-butanal formed *in situ* from the transformation of 4-methoxy-3-butenone [17] (Scheme 5).

Formation of compound **XIV** can be explained with the cyclization reaction of 4-methoxy-3-butenone in acidic medium as described previously [18]. When the reaction was performed without catalyst, the main product was again compound **XIII** (50%). However,

Scheme 4



Scheme 5



compound **XV** was also detected from GC-MS and ^{1}H NMR analysis with a yield of 20%. This compound is formed through the [4 + 2] cycloaddition reaction of quinone methide to 4-methoxy-3-butenone. Desktop molecular modeling calculations indicated that substituents existing in diaxial positions are more favorable structures for compound **XV**. NMR studies also supports the MM$_2$ calculations, because the coupling constant for acetalic and methine protons is $J = 2.8$.

These results indicated that *o*-hydroxybenzyl alcohols can give hetero Diels–Alder reactions with DHP at high temperatures but only when used with acid catalysts. At room temperature, even in the presence of acid catalyst, reactions yielded regular protection products. However, butyl vinyl ether and 4-methoxy-3-butenone could not give intermolecular cycloaddition reactions under the acidic conditions, because both decomposed to the new products with acids. Hetero-Diels–Alder products were obtained only under thermal conditions but in low yields.

EXPERIMENTAL

All general chemicals and starting materials purchased from commercial sources, except PPTS. IR spectra were recorded on a Jasco FTIR 5300 spectrometer using neat compounds as films between NaCl cells. ^{1}H and ^{13}C NMR spectra were run with Bruker 250 MHz spectrometer and reported as ppm relative to TMS. GC-MS spectra were obtained on Thermo Finnigan Trace DSQ instrument using ZB-5MS capillary column. The products were purified by column chromatography on neutral silicagel 60 (0.040–0.063 mm) from Merck, Darmstadt. Purity of compounds was proved by GC analysis (column: HP-1, 30m, 5′ 100°C, 20°C/min to 290°C, 5′ 290°C).

Preparation of PPTS. 0.15 mol of pyridine was added to 0.003 mol of *p*-toluenesulfonic acid and the mixture was stirred at room temperature for 20 min. After evaporation of pyridine, the product was crystallized from acetone.

General procedure A (with catalyst). Vinyl ether compound (2 mmol) was added dropwise to a stirred solution of I or III (1 mmol) and PPTS (0.1 mmol) in toluene (30 mL). The mixture was stirred at reflux temperature for 24 h in a Dean Stark apparatus. Then the solution was washed with half-saturated brine to remove the catalyst. After the evaporation of solvent, the crude products were purified by column chromatography using ethyl acetate/hexane as the eluent.

General procedure B (without catalyst). Vinyl ether compound (2 mmol) was added dropwise to the solution of I (1 mmol) in toluene (30 mL) and the solution was stirred for 24 h under reflux conditions. Then the solvent was evaporated and the crude product was purified by column chromatography using ethyl acetate/hexane as the eluent.

Crude products	(EtOAc/hexane)
III, IX	5/95
IV, IX	5/95
V, VII	15/85
X, XI	10/90
XII	30/70
XIII, XIV	30/70
XIII + XV	20/70/10 (ether/hexane/methanol)

3,4,4a-10a-Tetrahydro-2H,5H-pyrano[2,3-b]chromene (III). Colorless oil. ^{1}H NMR (DMSO-d_6) δ: 7.09 (d, J = 8.4, 1H, Ar-H$_6$), 7.04 (t, J = 7.6, 1H, Ar-H$_8$), 6.86 (t, J = 7.4, 1H, Ar-H$_7$), 6.78 (d, J = 8.2, 1H, Ar-H$_9$), 5.28 (d, J = 2.4, 1H, H$_{10a}$), 3.85 (td, J = 11.9, J = 8.1, 1H, H$_{2ax}$), 3.61 (dt, J = 11.4, J = 8.2, 1H, H$_{2eq}$), 2.86 (dd, J = 16.6, J = 6.8, 1H, H$_{5ax}$), 2.64 (dd, J = 16.6, J = 5.6, 1H, H$_{5eq}$), 2.08 (m, 1H, H$_{4a}$), 1.8–1.53 (m, 4H, 1H, H$_{3,4}$); ^{13}C NMR (DMSO-d_6) δ: 152.7, 129.5, 127.3, 120.7, 120.4, 115.9, 96.2, 62.4, 31.1, 27.8, 24.0, 22.8; ms: *m*/*z*: 190 (M$^+$), 131(58), 84 (55), 83 (100), 55 (30).

7-Bromo-3,4,4a-10a-tetrahydro-2H,5H-pyrano[2,3-b]chromene (IV). Yellowish oil. IR: 3054, 2949, 1607, 1484, 1421, 1265, 1078, 909, 756, 739, 705 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 7.18 (d, J = 8.6, 1H, Ar-H$_8$), 7.14 (s,1H, Ar-H$_6$), 6.74 (d, J = 8.6, 1H, Ar-H$_9$), 5.31 (d, J = 2.6, 1H, H$_{10a}$), 3.98 (td, J = 12.2, J = 6.1, 1H, H$_{2ax}$), 3.71 (dt, J = 11.8, J = 4.8, 1H, H$_{2eq}$), 2.90 (dd, J = 16.7, J = 5.9, 1H, H$_{5ax}$), 2.60 (dd, J = 16.7, J = 4.9, 1H, H$_{5eq}$), 2.16 (m, 1H, 1H, H$_{4a}$), 1.81–1.61 (m, 4H, H$_{3,4}$); ^{13}C NMR (CDCl$_3$): δ 152.1, 131.8, 130.3, 122.1, 118.2, 112.7, 96.7, 62.6, 31.4, 28.7, 24.0, 23.4; ms: *m*/*z*: 270 (M + 2), 268 (M$^+$), 209 (15), 84 (100), 83 (85), 55 (40).

2-[(Tetrahydro-2H-pyran-2-yloxy)methyl]phenol (V). Yellowish oil. ^{1}H NMR (CDCl$_3$): δ 8.6 (broad s, 1H, OH), 7.20 (d, J = 7.8, 1H, Ar), 7.01–6.84 (m, 2H, Ar), 6.82 (d, J = 8.1, 1H, Ar), 4.90 (d, J = 12.1, 1H, benzylic H), 4.71 (t, J = 2.7, 1H, acetalic H), 4.64 (d, J = 12.2, 1H, benzylic H), 3.99–3.90 (m, 1H, OCH$_2$), 3.63–3.56 (m, 1H, OCH$_2$), 1.82–1.25 (m, 6H, pyran ring H); ^{13}C NMR (CDCl$_3$): δ 204.1, 152.6 128.0, 124.9, 121.3, 120.6, 116.72, 96.4, 66.5, 48.3, 31.17; ms: *m*/*z*: 208 (M$^+$), 124 (83), 108 (90), 85 (100), 77 (60).

2-Butoxychroman (X). Colorless oil. IR: 3054, 2949, 1607, 1484, 1421, 1265, 1078, 909, 756, 739, 705 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 7.01–6.79 (m, 4H, Ar), 5.23 (d, J = 2.8, 1H, acetalic H), 3.84 (dt, J = 9.6, J = 7.1, J = 3.6, 1H, benzylic H$_{a(e)}$), 3.56 (dt, J = 10.2, J = 6.7, J = 3.1, 1H, benzylic H$_{e(a)}$), 2.95 (td, J = 11.2, J = 6.2, J = 4.7, 1H, OCH$_2$), 2.60 (dt, J = 16.3, J = 3. 7, 1H, OCH$_2$), 2.16–1.87 (m, 2H,1H, ring CH$_2$), 1.59–1.47 (m, 2H, CH$_2$), 1.36–1.22 (m, 2H, CH$_2$), 0.86 (t, J = 3.6, 3H,CH$_3$); ^{13}C NMR (CDCl$_3$): δ 152.3, 129.2, 127.2, 122.7, 120.5,116.9, 112.7, 97.1, 67.9, 31.7, 26.6, 20.6, 19.22, 13.7; ms: *m/z*: 206.28 (M^+), 132 (72), 131 (100), 107 (38), 77 (32).

2-Methyl-4H-benzo[d][1,3]dioxine (XII). Orange liquid, IR: 3047, 2959, 2872, 1588, 1480, 1406, 1271, 1230, 1112 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.01–684 (m, 4H, Ar), 5.19 (t, $J = 5.2$, 1H, acetalic H), 5.01(d, $J = 14.6$, 1H, CH_2), 4.82 (d, $J = 14.6$, 1H, CH_2), 1.58 (d, $J = 4.9$, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 152.8, 127.6, 125.0, 120.9, 120.6, 116.7, 98.0, 66.3, 20.5; ms: *m/z*: 150.0 (M^+),105 (65), 78 (100).

1-(4H-Benzo[d][1,3]dioxin-2-yl)propan-2-one (XIII). Yellowish oil, IR: 3047, 2916, 2865, 1718, 1588, 1489, 1271, 1231, 1124, 910 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.17–6.81 (m, 4H, Ar), 5.43 (t, $J = 5.1$, 1H, acetalic H), 5.01 (d, $J = 4.6$, 1H, benzylic $H_{a(e)}$), 4.81(d, $J = 4.5$, 1H, benzylic $H_{e(a)}$), 2.97 (d, $J = 5.1$, 2H, CH_2), 2.25 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 204.1, 152.61 128.02, 124.91, 121.34, 120.64, 116.72, 96.42, 66.50, 48.34, 31.17; ms: *m/z*: 192 (M^+), 174 (42), 106 (99), 78 (100).

1,3,5,-Triacetylbenzene (XIV). White crystals (mp = 163°C). ^1H NMR ($CDCl_3$): δ 8.69 (s, 3H, Ar), 2.7 (s, 9H, CH_3); EI-MS: *m/z*: 204 (M^+), 189 (100), 161 (32), 43 (53).

trans-2-Methoxy-3-acetylchroman (XV). Yellowish oil, IR: 3050, 2880, 1715, 1489, 1217, 1183, 1018, 755 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.15–6.83 (m, 4H, Ar), 5.20 (d, $J = 2.9$, 1H, acetalic H), 3.54 (s, 3H, *O*-methyl), 3.09–2.91 (m, 3H, benzylic and methine H), 2.25 (s, 3H, CH_3); ^{13}C NMR (250 MHz, $CDCl_3$): δ 205.6, 152.6, 128.91, 127.60, 124.90, 121.20, 116.90, 99.64, 58.2, 49.78, 30.75, 24.78; ms: *m/z*: 206 (M^+), 174 (24), 132 (26), 130 (100), 43 (24). *Anal.* Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.62, H, 6.95.

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Preparation of 2*H*-spiro[Benzo[*d*]isothiazole-3,3′-pyrazole]-1, 1-dioxide-2′(4′*H*)-carboxylates from Dilithiated *C*(α), *N*-Carboalkoxyhydrazones and Methyl 2-(Aminosulfonyl)benzoate

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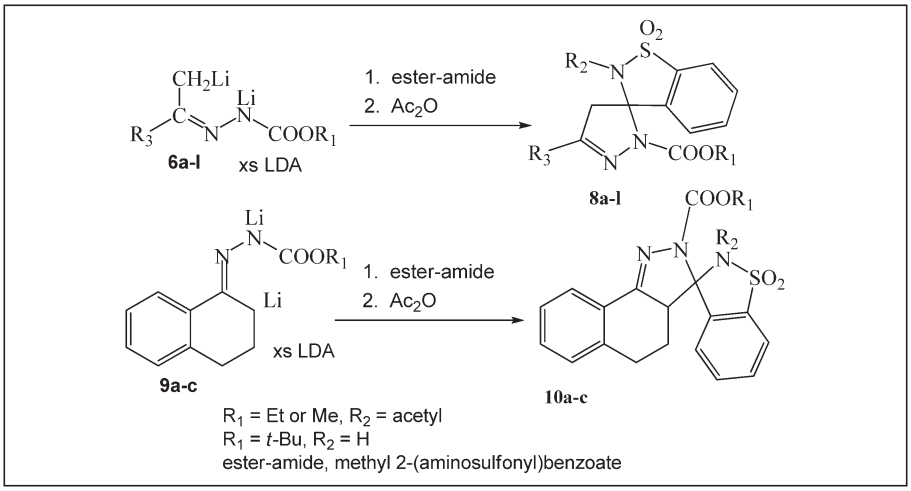


A variety of substituted spiro(benzoisothiazole-pyrazoles) have been prepared by the condensation of dilithiated *C*(α),*N*-carboalkoxyhydrazones with lithiated methyl 2-(aminosulfonyl)benzoate followed by the cyclization of intermediates with acetic anhydride, which also resulted in spiro *N*-acetylated products when carbomethoxyhydrazones or carboethoxyhydrazones were used, and spiro *NH* products when carbo-*tert*-butoxyhydrazones were used.

J. Heterocyclic Chem., **46**, 231 (2009).

INTRODUCTION

Pyrazoles [1] and benzoisothiazole dioxides [2] have been prepared and studied because of their biological potential, serving as intermediate compounds in other syntheses, spectral studies, theoretical studies, and other uses. Various spiro pyrazoles have been investigated [3], and spiro benzoisothiazoles dioxides (BIDs) have received limited study [4]. There are no reports concerning the preparation of spiro(benzoisothiazole-pyrazole) dioxides.

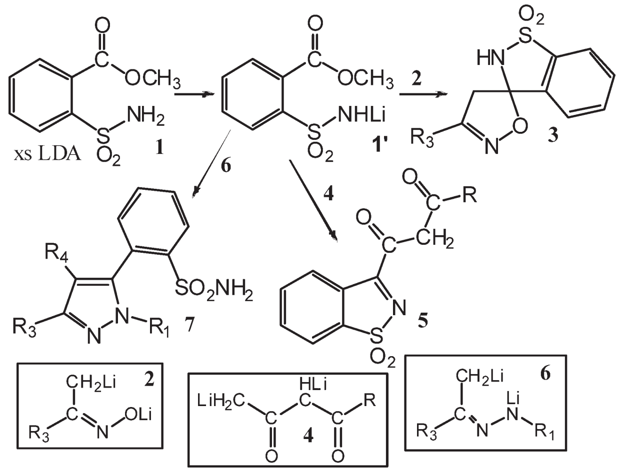
In this laboratory, BIDs and pyrazoles have been synthesized by the condensation-cyclization of polylithiated intermediates, prepared in excess lithium diisopropylamide (LDA), with methyl 2-(aminosulfonyl)benzoate **1**, Scheme 1. Specifically, anionic electrophile **1′** has been condensed-cyclized with dilithiated oximes **2** to afford spiro(BID-isoxazoles) **3** [5]; with dilithiated β-ketoesters **4** (R = OMe or OEt) to afford BID-β-ketoesters **5** (R = OMe or OEt); with dilithiated β-diketones **4** (R = Ar) to afford BID-β-diketones **5** (R = Ar); or with trilithiated β-ketoamides **4** (R = $NLiC_6H_5$) resulting in BID β-ketoamides **5** (R = NHC_6H_5) [6].

N-Phenyl-, or *NH*- pyrazolebenzenesulfonamides **7** resulted [7,8] when dilithiated phenylhydrazones (R_1 = Ph) or dilithiated carbo-*tert*-butoxyhydrazones (R_1 = *t*-Bu) were condensed-cyclized (also hydrolysis-decarboxylation for **7**, *NH*-) with **1′** (from **1**).

RESULTS AND DISCUSSION

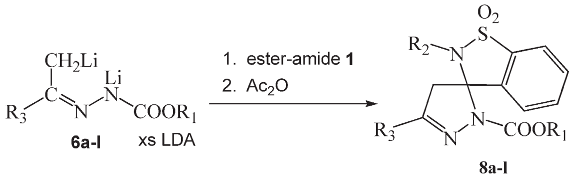
During the current investigation dilithiated carboalkoxyhydrazones **6a–l** (**6f**, trilithiated) or **9a–c** were

Scheme 1. Condensation-cyclization syntheses with methyl 2-(aminosulfonyl)benzoate.

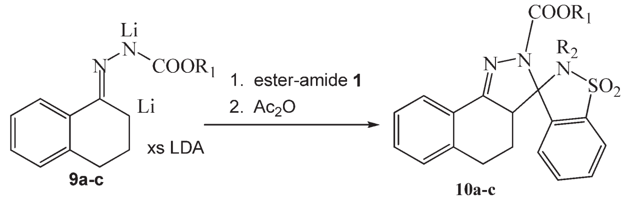


condensed-cyclized with lithiated methyl 2-(aminosulfonyl)benzoate **1′** (from **1**) to afford spiro(BID-pyrazoles) **8a–l** or **10a–c** and not pyrazole-benzenesulfon-amides **7** Scheme 2.

Scheme 2. Reactants/products.



6a, 8a. R_1 = Et; R_2 = Ac; R_3 = Ph
6b., 8b. R_1 = Me; R_2 = Ac; R_3 = 4-ClPh
6c., 8c. R_1 = Me; R_2 = Ac; R_3 = 2-furanyl
6d., 8d. R_1 = Et; R_2 = Ac; R_3 = 2-furanyl
6e., 8e. R_1 = Me; R_2 = Ac; R_3 = 4-MePh
6f., 8f. R_1 = Me; R_2 = Ac; R_3 = 2-acetoxyPh
6g., 8g. R_1 = *t*-Bu; R_2 = H; R_3 = 4-MeOPh
6h., 8h. R_1 = *t*-Bu; R_2 = H; R_3 = 3,4-diMeOPh
6i., 8i.. R_1 = *t*-Bu; R_2 = H; R_3 = Ph
6j., 8j. R_1 = *t*-Bu, R_2 = H; R_3 = 4-MePh
6k., 8k. R_1 = *t*-Bu; R_2 = H; R_3 = 4-ClPh
6l., 8l. R_1 = *t*-Bu; R_2 = H; R_3 = 3,4-diMePh



9a.,10a. R_1 = Et; R_2 = Ac
9b.,10b. R_1 = Me; R_2 = Ac
9c., 10c. R_1 = *t*-Bu; R_2 = H

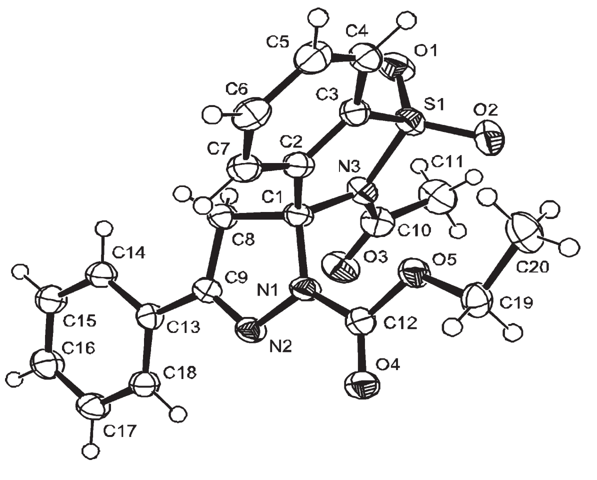


Figure 1. ORTEP diagram (50% ellipsoids for non-hydrogen atoms), $C_{20}H_{19}N_3O_5S$ **8a** [9].

Specifically, **6a–l** or **9a–c** underwent an anion-anion condensation with **1′** to form intermediate compounds that were isolated but not characterized followed by cyclization and *N*-acetylation with acetic anhydride to afford *N*-acetyl spiro(BID-pyrazoles) **8a–f, 10a,** and **10b**. Trilithiated 2′-hydroxyacetophenone carbomethoxyhydrazone **6f** (R_3 = 2-LiOC_6H_4) was condensed with **1′**, and intermediates were cyclized to afford *O*-acetylation and *N*-acetylation spiro product **8f**. The *N*-acetylation process did not occur when dilithiated carbo-*tert*-butoxyhydrazone intermediates were used instead, and only *NH* spiro(BID-pyrazoles) **8g–l** and **10c** were isolated.

N-Acetylated spiro(BID-pyrazoles) **8a–f** were not originally anticipated, and an X-ray single crystal analysis was determined for spiro product **8a** resulting from the condensation-cyclization of **6a** (R_1 = Et, R_3 = C_6H_5) with **1′**.

The molecular structure of **8a** is shown in Figure 1 (atoms assigned numbers), and selected bond distances and angles are listed in Table 1. The bond lengths agree with the assignment of the double bond shown between C9 and N2. Because the unit cell of each compound is centrosymmetric, both enantiomorphic structures about the C1 chiral center are present.

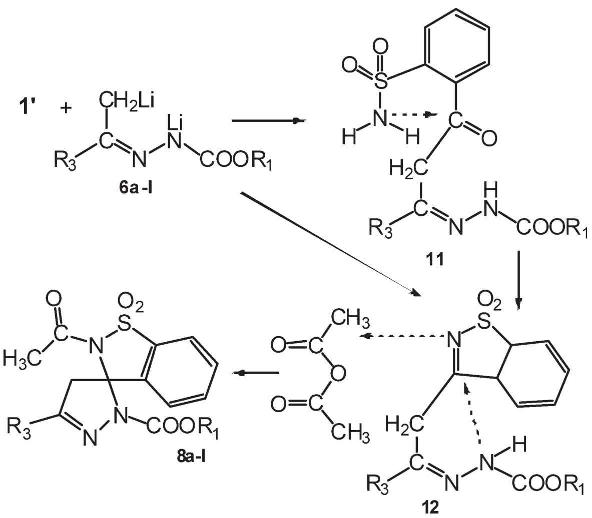
The least squares best planes representing the fused rings are nearly coplanar with angles of 1.52° between

Table 1

Selected bond distances (Å) and angles (°), $C_{20}H_{19}N_3O_5S$ **8a**.

C1-C2	1.524(3)	C1-C2-C3	115.4(2)
C2-C3	1.376(3)	C2-C3-S1	112.0(2)
C3-S1	1.742(2)	C3-S1-N3	92.8(1)
S1-N3	1.690(2)	S1-N3-C1	115.6(1)
N3-C1	1.491(3)	N3-C1-C2	104.1(2)
C1-N1	1.475(2)	C1-C8-C9	103.1(2)
N1-N2	1.399(2)	C8-C9-N2	114.0(2)
N2-C9	1.288(3)	C9-N2-N1	107.8(2)
C9-C8	1.500(3)	N2-N1-C1	113.7(2)
C8-C1	1.550(3)	N1-C1-C8	100.5(2)
C9-C13	1.472(3)	C14-C13-C9-N2	172.8(2)
N1-C12	1.371(3)	C13-C9-N2-N1	176.8(2)
C12-O4	1.206(3)	N2-N1-C12-O4	−4.1(3)
C12-O5	1.342(3)		

Scheme 3. Mechanistic Details.



them. The two five-member rings in each molecule are nearly perpendicular with an angle of 89.54°. The rings connected by C9 and C13 are nearly coplanar with angles of 9.19°, which allows for extended pi bonding between these rings and possibly with the atoms in the C12 carboxylate group.

In addition to single crystal X-ray analysis leading to results illustrated in the ORTEP diagram, Figure 1, other representative characterization parameters supported the spiro structure, such as DEPT clearly identifying CH_2 or CH in appropriate products. The ^{1}H-NMR CH_2 absorption for **8a–l** were noted as a pair of doublets δ 3.54–3.66 and δ 3.97–4.04 ppm, $J = 18.0$–18.7 Hz; *N*-acetyl singlet proton absorptions were displayed at δ 2.52–2.64, usually 2.63 or 2.64 ppm in products **8a–f**, **10a** and **10b** and absent in products **8g–l** and **10c**. The ^{13}C NMR for all products displayed the spiro carbon absorption from δ 80.4–84.0 ppm. Combustion analysis indicated incorporation of water (methanol in **8k**) [10] in the analytical crystalline products **8a, 8c, 8d, 8j,** and **8l**. LCMS for most of the products contained the expected $(M + H)^+$; for **8i** and **8j** it was not detected. Base ions for each of these products may be explained by loss of a carbo-*tert*-butoxy fragment.

Mechanistic details, Scheme 3, to explain the formation of products may involve dilithiated carboalkoxyhydrazone and monolithiated ester-sulfonamide **1′**, leading to intermediates **11** and/or **12** (*e.g.,* from acetophenones), with each having potential for difficulty in cyclodehydration. Attempts to isolate saccharin from treatment of **1** (to **1′**) with LDA under the same reaction conditions were unsuccessful.

Products **8g–l** and **10c** were only formed from cyclization and not accompanied by *N*-acetylation, which may be attributed to the larger size of the *tert*-butoxy group hindering further reaction at the BIDs nitrogen with acetic anhydride, and its success was dependant on the strong cyclization ability of acetic anhydride/pyridine.

EXPERIMENTAL

Melting points were obtained with a Mel-Temp II melting point apparatus in open capillary tubes and are uncorrected. Entry compounds, *C*(α),*N*-carboalkoxy-hydrazones were prepared from *C*(α),*O*-ketones in a 1:1 condensation with methyl, ethyl, or *tert*-butyl carbazate [11]. The tetrahydrofuran (THF) was distilled from sodium (benzophenone ketyl as an indicator of dryness) prior to use, and organic chemicals were obtained from Aldrich Chemical Co. Infrared spectra were obtained with a Nicolet Impact 410 FT-IR. Proton and ^{13}C NMR spectra were obtained with a Varian Associates Mercury Oxford 300 MHz nuclear magnetic resonance spectrometer, and chemical shifts were recorded in δ ppm downfield from an internal tetramethylsilane standard. Combustion analyses were performed by Quantitative Technologies, Inc., P.O. Box 470, Whitehouse, NJ 08888. LCMS analyses were measured on a Thermo-Finnigan LCQ Advantage system with the Surveyor autosampler, Surveyor pump, and LCQ Advantage Max mass spectral detector using electrospray ionization; 2 mg samples were prepared in 2 mL/L of acetonitrile; 10 μL injections were pumped at 1.00 mL/min isocratically with 70% acetonitrile and 30% water, each buffered with 0.1% formic acid by volume; 15 min runs were reproduced in both the positive and negative (when needed) MS modes. Data were collected at full scan from 100 to 650 amu.

2*H*-spiro[Benzo[*d*]isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-carboxylates (8a–l) and (10a–c). LDA (0.0788 mol or 0.0945 mol for **8f**) was prepared by the addition of 49 mL (or 59 mL for **8f**) of 1.6*M* *n*-butyllithium in hexanes to a three-neck round-bottomed flask (*e.g.*, 500 mL), equipped with a nitrogen inlet tube, a side-arm addition funnel (*e.g.*, 125 mL), and a magnetic stir bar. The flask was cooled in an ice water bath and 8.02 g or 9.54 g for **8f** (0.0788 mol or 0.0945 mol for **8f**) of diisopropylamine, dissolved in 25–30 mL of dry THF, was added from the addition funnel at a fast dropwise rate during a 5 min period (0°C, nitrogen). The solution was stirred for an additional 15–20 min, and then 0.0150 mol of the carboalkoxyhydrazone dissolved in 50 mL of THF was added at a fast dropwise rate during 5–10 min. After 1 hr (2 h for **8f**), 3.39 g (0.0158 mol) of methyl 2-(aminosulfonyl)benzoate **1**, dissolved in 25-35 mL of THF was added, during 5 min, to the polylithiated intermediate, and the solution was stirred and condensed for 1 h. Finally, 100 mL of 3*M* hydrochloric acid was added quickly followed by 100 mL of solvent grade ether, then stirring the two-phase mixture for 5 min, followed by careful neutralization with solid sodium bicarbonate, and the two liquid phases or solid materials separated. If a solid appeared at this point, the biphasic mixture could be filtered. The aqueous layer was extracted with ether or THF (2 × 75 mL), and the organic fractions were combined, filtered, evaporated, and the solid organic materials were air-dried.

The twofold cyclization and acetylation required 6 mL of acetic anhydride and 4 mL of pyridine for each 1 g of dry intermediate(s) compound(s) [12]. Each gram of solid intermediate(s) was dissolved in pyridine followed by the dropwise addition of acetic anhydride. The solution was stirred at room temperature for 1 h. The addition of *ca.* 80 g of ice usually resulted in a precipitate, which was collected by filtration, washed with water and recrystallized from methanol or ethanol.

Ethyl2-acetyl-5′-phenyl-2*H*-spiro[benzo-[*d*]isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-carboxylate (8a). Compound **8a** was obtained in 69% yield, mp 179–182°C (methanol), from the two-step procedure for the condensation-cyclization of dilithiated acetophenone carboethoxyhydrazone and **1′**. IR: 1709 and 1727 cm^{-1}. ^{1}H NMR (deuteriochloroform): δ 1.67 (m, 3H), 2.64 (s, 3H, CH_3), 3.68–4.06 (m, 4H) [13], and 7.41–7.68, 7.71–7.91 (m, 9H, ArH). ^{13}C NMR (deuteriochloroform): δ 14.8, 23.7, 49.5 (DEPT CH_2), 53.6, 81.2, 121.2, 122.9, 127.6, 128.9, 129.2, 131.3, 132.5, 133.5, 135.3, 137.1, 147.7, 151.0 and 166.9. LCMS, exact mass, 413.10: $(M + H)^+$, 414.04. *Anal.* Calcd for $C_{20}H_{19}N_3O_5S \cdot 1/4\ H_2O$: C, 57.47; H, 4.70; N, 10.05. Found: C, 57.47; H, 4.63; N, 10.08.

Single crystal X-ray structure determination. Yellow crystals of $C_{20}H_{19}N_3O_5S$ **8a** were recrystallized from ethanol in order to give satisfactory crystals for X-ray determination. Crystal data for X-ray studies were collected at −120°C on a Mercury CCD area detector coupled with a Rigaku AFC8 diffractometer with graphite monochromated Mo-K radiation. Data were collected in 0.50° oscillations in ω with 20 s exposures. A sweep of data was done using ω oscillations from −40.0° to 90.0° at $\chi = 45.0°$ and $\varphi = 0.0°$; a second sweep was performed using ω oscillations from −30.0° to 80.0° at $\chi = 45.0°$ and $\varphi = 90.0°$. The crystal-to-detector distances were 27.7147 mm. Details of the data collection is reported in Table 2. Data were collected, processed, and corrected for Lorentz polarization and for absorption using CrystalClear (Rigaku) [15].

Table 2

Crystallographic data, $C_{20}H_{19}N_3O_5S$ **8a**.

CCDC deposit number [17]	689213
Color/shape	Yellow/Parallelopiped
Crystal dimensions (mm)	0.36 × 0.36 × 0.31
Formula	$C_{20}H_{19}N_3O_5S$
Formula mass	413.44
T (°C)	−120(2)
Crystal system	Monoclinic
Space Group	$P2_1/c$
a (Å)	12.372(3)
b (Å)	17.490(4)
c (Å)	9.655(2)
β (°)	107.12(3)
V (Å^3)	1996.6(7)
Z	4
d_{calc} (g cm^{-3})	1.375
λ (Å)	0.71073
μ (mm^{-1})	0.199
F(000)	864
θ range (°)	3.45–25.15
Reflections collected	3952
Miller indices	$-14 \leq h \leq 14$, $0 \leq k \leq 20$, $0 \leq l \leq 11$
Unique reflections	3,544
Unique reflections $I > 2\sigma(I)$	3,121
Max and min transmission	0.9408, 0.9317
Data, restraints, parameters	3544, 0, 264
Final *R* indices $I > 2\sigma(I)$	$R_1 = 0.0515$ $wR_2 = 0.1243$
R indices all data	$R_1 = 0.0585$ $wR_2 = 0.1305$
Goodness of fit on F^2	1.098
Largest diff peak and hole (e Å^{-3})	0.245, −0.373

The non-hydrogen atoms were refined anisotropically. Ideal hydrogen atom coordinates were calculated and the hydrogen atoms were allowed to ride on their respective carbon atoms. The temperature factors of all hydrogen atoms were varied isotropically. Structure solution, refinement, and the calculation of derived results were performed using the *SHELX-97* [16] package of computer programs. Neutral atom scattering factors were those of Cromer and Waber [16], and the real and imaginary anomalous dispersion corrections were those of Cromer [17].

Methyl 2-acetyl-5′-(4-chlorophenyl)-2*H*-spiro-[benzo[*d*] isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-carboxylate (8b). Compound **8b** was obtained in 74% yield, mp 181°C dec (benzene/hexanes), from the two-step procedure for the condensation-cyclization of dilithiated 4′-chloroacetophenone carbomethoxyhydrazone and **1′**. IR: 1705 cm^{-1}. ^{1}H NMR (deuteriochloroform): δ 2.64 (s, 3H, CH_3), 3.67(d, 1H, *J* = 18.7 Hz), 3.74 (s, 3H, CH_3O), and 3.99 (d, 1H) and 7.39–7.50, 7.68–7.82 (m, 7H, ArH) and 7.90 (d, 1H, *J* = 7.5 Hz). ^{13}C NMR (deuteriochloroform): δ 24.0, 49.0 (DEPT CH_2), 53.9, 81.6, 121.5, 123.1, 128.2, 129.3, 131.6, 132.7, 135.6, 136.9, 151.1. LCMS, exact mass, 433.05: $(M + H)^+$, 433.99; $(M - H)^-$, 432.10. *Anal.* Calcd for $C_{19}H_{16}\ Cl\ N_3O_5S$: C, 52.60; H, 3.72; N, 9.69. Found: C, 52.75; H, 3.64; N, 9.70.

Methyl 2-acetyl-5′-(2-furanyl)-2*H*-spiro-[benzo[*d*]isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-carboxylate (8c). Compound **8c** was obtained in 44% yield, mp 177–178°C (benzene/hexanes), from the two-step procedure for the condensation-cyclization of dilithiated 2-acetylfuran carbomethoxyhydrazone and **1′**. IR: 1709 and 1728 cm^{-1}. ^{1}H NMR (deuteriochloroform): δ 2.64 (s, 3H, CH_3), 3.66 (d, 1H, *J* = 18.6 Hz), 3.74 (s, 3H, CH_3O), 3.97 (d, 1H, *J* = 18.6 Hz), 6.51–6.53 (m, 1H), 6.87 (s br, 1H), 7.47–7.54 (m, 1H), 7.69–7.83 (m, 3H, ArH) and 7.89 (d, 1H, *J* = 7.5 Hz). ^{13} C NMR (deuteriochloroform): δ 23.9, 48.6 (DEPT CH_2), 53.7, 80.9, 112.2, 112.7, 121.4, 123.0, 131.5, 132.6, 135.5, 137.2, 144.0, 144.9, 145.8, 151.2, and 167.0. LCMS exact mass, 389.07: $(M + H)^+$, 389.94. *Anal.* Calcd for $C_{17}H_{15}N_3O_6S \cdot 1/2\ H_2O$: C, 51.25; H, 4.05; N, 10.55. Found: C, 51.30; H, 3.91; N, 10.33.

Ethyl 2-acetyl-5′-(2-furanyl)-2*H*-spiro-[benzo[*d*]-isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-carboxylate (8d). Compound **8d** was obtained in 40% yield, mp 145–147 °C (ethanol), from the two-step procedure for the condensation-cyclization of dilithiated 2-acetylfuran carboethoxyhydrazone and **1′**. IR: 1712 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.06 (t, 3H), 2.50 (s, 3H), 3.43–3.46 (m, 1H), 3.88–3.96 (m, 3H), 6.67–6.69 (m, 1H), 6.94 (d, 1H, *J* = 3.6 Hz), 7.76–7.92 (m, 5H), and 8.14 (d, 1H, *J* = 7.8 Hz). ^{13}C NMR (DMSO-d_6): δ 23.4, 48.1, 61.7, 80.8, 112.2, 113.6, 121.0, 123.9, 131.6, 135.8, 143.9, 145.6, and 166.1. LCMS, exact mass, 403.08: $(M + H)^+$, 403.95; $(M - H)^-$, 402.11. *Anal.* Calcd for $C_{18}H_{17}N_3O_6S \cdot 7/8\ H_2O$: C, 51.58; H, 4.51; N, 10.02. Found: C, 51.48; H, 3.38; N, 9.95.

Methyl 2-acetyl-5′-(4-methylphenyl)-2*H*-spiro-[benzo[*d*]-isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-carboxylate (8e). Compound **8e** was obtained in 40% yield, mp 166–168°C (methanol), from the two-step procedure for the condensation-cyclization of dilithiated 4′-methylacetophenone carbomethoxyhydrazone and **1′**. IR: 1709 and 1728 cm^{-1}. ^{1}H NMR (deuteriochloroform): δ 2.39 (s, 3H), 2.63 (s, 3H), 3.65–4.03 (m, 5H) [13], 7.21–7.28, 7.46–7.48, and 7.63–7.90 (m, 8H). ^{13}C NMR (DMSO-d$_6$): δ 21.7, 24.1, 48.9 (DEPT CH$_2$), 53.4, 82.0, 121.4, 124.5, 127.4, 128.5, 130.0, 132.2, 136.4, 137.5, 140.1, 151.2, 153.1, and 166.7. LCMS, exact mass, 413.10: (M + H)$^+$, 414.08. *Anal.* Calcd for $C_{20}H_{19}N_3O_5S$: C, 58.10; H, 4.63; N, 10.16. Found: C, 58.06; H, 4.70; N, 9.97.

Methyl 2-acetyl-5′-(2-acetoxyphenyl)-2*H*-spiro-[benzo[*d*]-isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-carboxylate (8f). Compound **8f** was obtained in 58% yield, mp 218–220°C (benzene/hexanes) from the two-step procedure for the condensation-cyclization of trilithiated 2′-hydroxyacetophenone carbomethoxyhydrazone and **1′**. IR: 1703 and 1728 cm^{-1}. ^{1}H NMR (deuteriochloroform): δ 2.39 (s, 3H), 2.63(s, 3H), 3.65–3.71 (m, 4H), 4.02 (d, 1H, *J* = 18.3 Hz), 7.18 (d, 1H, *J* = 7.8 Hz), 7.26–7.31 (m, 1H), 7.42–7.49 (m, 2H), 7.69–7.80 (m, 3H), and 7.87 (d, 1H, *J* = 7.8 Hz). ^{13}C NMR (deuteriochloroform): δ 22.3, 23.8, 50.2, 53.4 (DEPT CH$_2$), 80.6, 121.2, 123.0, 123.3, 124.9, 126.3, 129.5, 131.4, 132.5, 135.5, 137.2, 148.8, 149.0, 151.1, 166.9, and 170.1. LCMS, exact mass, 457.09: (M + H)$^+$, 457.93. *Anal.* Calcd for $C_{21}H_{19}N_3O_7S$: C, 58.10; H, 4.63; N, 10.16. Found: C, 58.06; H, 4.70; N, 9.97.

1,1-Dimethylethyl 5′-(4-methoxyphenyl)-2*H*-spiro-[benzo-[*d*]isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-carboxylate (8g). Compound **8g** was obtained in 92% yield, mp 190–191°C (methanol), from the two-step procedure for the condensation-cyclization of dilithiated 4′-methoxyacetophenone carbo-*t*-butoxyhydrazone and **1′**. IR: 1696 and 3128 cm^{-1}. ^{1}H NMR (DMSO-d$_6$): δ 1.03 (s, 9H, CH$_3$), 3.68–3.91 (m, 2H, CH$_2$), 3.82 (s, 3H, OCH$_3$), 7.04 (d, 2H, *J* = 9.0 Hz), 7.63–7.88 (m, 6H), and 9.18 (s, NH). ^{13}C NMR (DMSO-d$_6$): δ 27.2, 49.3 (DEPT CH$_2$), 55.4, 80.6, 80.9, 114.2, 120.6, 123.5, 123.9, 128.2, 130.3, 133.6, 135.5, 139.8, 149.9, 151.3, and 160.8. LCMS, exact mass, 429.14: (M + H)$^+$, 429.67. *Anal.* Calcd for $C_{21}H_{23}N_3O_5S$: C, 58.73; H, 5.40; N, 9.78. Found: C, 58.41; H, 5.49; N, 9.65.

1,1-Dimethylethyl 5′-(3,4-dimethoxyphenyl)-2*H*-spiro-[benzo[*d*]isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-carboxylate (8h). Compound **8h** was obtained in 38% yield, mp 200–203°C (ethanol), from the two-step procedure for the condensation-cyclization of dilithiated 3′,4′-dimethoxyacetophenone carbo-*t*-butoxyhydrazone and **1′**. IR: 1727 and 3231 cm^{-1}. ^{1}H NMR (deuteriochloroform): δ 1.17 (s, 9H, CH$_3$), 3.65 (d, 1H, *J* = 15.0 Hz), 3.90 (s, 3H, OCH$_3$), 3.91 (s, 3H, OCH$_3$), 3.95 (d, 1H, *J* = 18.3 Hz), 6.81 (d, 1H, *J* = 8.4 Hz), 7.01 (dd, 1H, *J* = 8.1 Hz), 7.39 (d, 1H, *J* = 2.1 Hz), 7.51 (d, 1H, *J* = 7.8 Hz), 7.61–7.74 (m, 2H), and (7.81 and 7.83 singlets broad, 1H). ^{13}C NMR (deuteriochloroform): δ 27.8, 50.5 (DEPT CH$_2$), 81.3, 83.4, 108.6, 110.6, 120.7, 121.3, 123.9, 123.3, 130.5, 133.9, 136.1, 141.3, 149.1, 150.3, 151.3, and 151.6. LCMS, exact mass, 459.15: (M + H)$^+$, 459.64. *Anal.* Calcd for $C_{22}H_{25}N_3O_6S$: C, 57.50; H, 5.48; N, 9.14. Found: C, 57.26; H, 5.55; N, 9.03.

1,1-Dimethylethyl 5′-phenyl-2*H*-spiro-[benzo[*d*]-isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-carboxylate (8i). Compound **8i** was obtained in 59% yield, mp 193–197°C (methanol), from the two-step procedure for the condensation-cyclization of dilithiated acetophenone carbo-*t*-butoxyhydrazone and **1′**. IR: 1701, 1728, and 3195 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 1.25 (s, 9H, CH$_3$), 3.66 (d, 1H, *J* =18.3 Hz), 4.04 (d, 1Hz, *J* = 18.3 Hz), 5.78 (s, 1H), and 7.39–7.41, 7.61–7.82 (m, 9H). ^{13}C NMR (deuteriochloroform): δ 27.7, 50.5 (DEPT CH$_2$), 81.4, 83.6, 121.1, 122.8, 126.8, 128.3, 128.8, 130.2, 130.4, 130.7, 133.8, 136.2, and 151.9. LCMS, exact mass, 399.13: LCMS, (M + H)$^+$ not detected, base peak 299.07. *Anal.* Calcd for $C_{20}H_{21}N_3O_4S$: C, 60.13; H, 5.30; N, 10.52. Found: C, 59.98; H, 5.37; N, 10.50.

1,1-Dimethylethyl 5′-(4-methylphenyl)-2*H*-spiro-[benzo-[*d*]isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-carboxylate (8j). Compound **8j** was obtained in 33% yield, mp 181.5–182°C (methanol), from the two-step procedure for the condensation-cyclization of dilithiated 4′-methylacetophenone carbo-*t*-butoxyhydrazone and **1′**. IR: 1697 and ~3100 broad cm^{-1}. ^{1}H NMR (deuteriochloroform): δ 1.17 (s, 9H, CH$_3$), 2.37 (s, 3H, CH$_3$), 3.62 (d, 1H, *J* = 18.0 Hz), 3.99 (d, 1H, CH$_3$, *J* = 18.0 Hz), 5.84 (s), 7.20 (d, 1H, *J* = 8.0 Hz), 7.47 (d, 1H, *J* = 7.8 Hz), 7.59–7.72 (m, 5H), and 7.81 (d, 1H, *J* = 7.8 Hz). ^{13}C NMR (deuteriochloroform): δ 21.7, 27.8, 50.7, 81.5, 83.6, 121.3, 123.0, 127.0, 127.4, 127.6, 129.7, 130.5, 133.8, 136.3, 141.4, 141.7, 150.3, and 152.1. LCMS, exact mass, 413.14: (M + H)$^+$ not detected, base peak 314.00. *Anal.* Calcd for $C_{21}H_{23}N_3O_5S\cdot \frac{1}{4} H_2O$: C, 60.34; H, 5.67; N, 10.05. Found: C, 60.28; H, 5.70; N, 10.05.

1,1-Dimethylethyl 5′-(4-chlorophenyl)-2*H*-spiro-[benzo-[*d*]isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-carboxylate (8k). Compound **8k** was obtained in 35% yield, mp 152–155°C (methanol), from the two-step procedure for the condensation-cyclization of dilithiated 4′-chloroacetophenone carbo-*t*-butoxyhydrazone and **1′**. IR: 1693 and 3438 broad cm^{-1}. ^{1}H NMR (deuteriochloroform): δ 1.15 (s, 9H), 3.54 (d, 1H, *J* = 18.0 Hz), 4.00 (d, 1H, *J* = 18.3 Hz), 7.38 (d, 2H, *J* = 8.7 Hz), 7.49 (d, 1H, *J* = 7.5 Hz), 7.63–7.70 (m, 4H), and 7.79 (d, 1H, *J* = 6.9 Hz). ^{13}C NMR (deuteriochloroform): δ 27.9, 50.6, 51.0, 81.7, 83.9, 121.5, 123.1, 128.3, 129.1, 129.4, 130.7, 134.1, 136.3, 137.0, 141.3, 150.4, and 151.1. LCMS, exact mass, 433.09: (M + H)$^+$, 433.75. *Anal.* Calcd for $C_{20}H_{20}\,Cl\,N_3O_4S\cdot 5/4\,CH_3OH$ [10]: C, 53.74; H, 5.52; N, 8.85. Found: C, 53.88; H, 5.19; N, 8.94.

1,1-Dimethylethyl 5′-(3,4-dimethylphenyl)-2*H*-spiro-[benzo[*d*]isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-car-boxylate (8l). Compound **8l** was obtained in 31% yield, mp 197–201°C (methanol), from the two-step procedure for the condensation-cyclization of dilithiated 3′,4′-dimethylacetophenone carbo-*t*-butoxyhydrazone and **1′**. IR: 1712 and 3415 cm^{-1}. ^{1}H NMR (deuteriochloroform): δ 1.18 (s, 9H, CH$_3$), 2.28 (s, 3H, CH$_3$), 2.30 (s, 3H, CH$_3$), 3.64 (d, 1H, *J* = 18.3 Hz), 4.01(d, 1H, CH$_3$, *J* = 18.0 Hz), 5.7 (s), 7.17 (d, 1H, *J* = 8.1 Hz), 7.42–7.59 (m, 2H), 7.60–7.73 (m, 4H), and 7.81 (d, 2H, *J* = 7.8 Hz). ^{13}C NMR (deuteriochloroform): δ 19.7, 19.9, 27.7, 50.7 (DEPT CH$_2$), 81.3, 83.4, 107.4, 121.1, 122.8, 124.4, 127.7, 127.9, 130.0, 130.3, 133.8, 136.2, 137.2, 140.0, and 152.2. LCMS, exact mass, 427.16: (M + H)$^+$, 427.70. *Anal.* Calcd for $C_{22}H_{25}N_3O_4S\cdot 1H_2O$: C, 59.31; H, 6.11; N, 9.43. Found: C, 59.69: H, 6.26; N, 9.07.

Ethyl 2-acetyl-3′-(4,5-dihydrobenz[*g*]indazinyl)-2*H*-spiro-[benzo[*d*]isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-carboxylate (10a). Compound **10a** was obtained in 60% yield, mp 257–259°C dec (methanol), from the two-step procedure for the condensation-cyclization of dilithiated 1-tetralone carboethoxyhydrazone and **1′**. IR: 1703 and 1739 cm^{-1}. ^{1}H NMR (deuteriochloroform): δ 0.91 (m, 1H), 1.27 (m, 3H), 1.80–1.84 (m, 1H), 2.03–2.05 (m, 1H), 2.52 (s, 3H, CH$_3$), 3.70–3.91 (m, 3H, OCH$_3$), 7.16–7.18 (m, 1H), 7.29–7.37 (m, 3H), 7.61–7.90 (m, 4H), and 8.22–8.24 (m, 1H). ^{13}C NMR (deuteriochloroform): δ 14.3, 22.1 (DEPT CH$_2$), 24.1 (CH$_3$ DEPT), 29.5 (CH$_2$ DEPT), 59.1 (DEPT CH), 62.9, 84.0, 121.4, 123.4, 125.9, 126.4, 127.2, 129.2, 131.0, 131.3, 132.6, 135.3, 138.9, 152.9, and 167.6. LCMS, exact mass, 439.12: (M + H)$^+$, 439.99. *Anal*. Calcd for C$_{22}$H$_{21}$N$_3$O$_5$S: C, 60.12; H, 4.82; N, 9.56. Found: C, 59.82; H, 4.54; N, 9.95.

Methyl 2-acetyl-3′-(4,5-dihydrobenz[*g*]indazinyl)-2*H*-spiro[benzo[*d*]isothiazole-3,3′-pyrazole]-1,1-di-oxide-2′(4′*H*)-carboxylate (10b). Compound **10b** was obtained in 71% yield, mp 209°C dec (ethanol), from the two-step procedure for the condensation-cyclization of dilithiated 1-tetralone carbomethoxyhydrazone and **1′**. IR: 1701 cm^{-1}. ^{1}H NMR (deuteriochloroform): δ 1.80–1.85 (m, 1H), 2.03–2.06 (m, 1H), 2.63 (s, 3H, CH$_3$), 2.75–2.98 (m, 2H), 3.60–3.82 (m, 4H, CH and OCH$_3$), 7.16–7.39, 7.57–7.90 (m, 7H), and 8.21 (d, 1H, J = 6.6 Hz). ^{13}C NMR (deuteriochloroform): δ 22.1, 24.1, 29.5, 53.9 (DEPT CH$_2$), 59.2, 84.0, 121.5, 123.3, 125.8, 127.3, 129.2, 131.1, 131.4, 131.7, 132.7, 135.4, 139.1, 152.0, 153.2, and 167.8. LCMS, exact mass, 425.10: (M + H)$^+$, 426.05. *Anal*. Calcd for C$_{21}$H$_{19}$N$_3$O$_5$S: C, 59.28; H, 4.50; N, 9.88. Found: C, 58.94; H, 4.63; N, 9.60.

1,1-Dimethylethyl 3′-(4,5-dihydrobenz[*g*]indazinyl)-2*H*-spiro[benzo[*d*]isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-carboxylate (10c). Compound **10c** was obtained in 39 % yield, mp 187–188°C (methanol), from the two-step procedure for the condensation-cyclization of dilithiated 1-tetralone carbo-*t*-butoxyhydrazone and **1′**. IR: 1689 and 3183 broad cm^{-1}. ^{1}H NMR (DMSO-d$_6$): δ 1.05 (s, 9H, CH$_3$), 1.70–1.74 (m, 1H of CH$_2$), 1.91–1.99 (m, 1H of CH$_2$), 2.69–3.00 (m, 2H, CH$_2$), 3.85 (dd, 1H, CH, J = 4.4, 13.2 Hz), 7.29–7.42 (m, 3H), and 7.67–7.92 (m, 4H), 7.93 (d, 1H, J = 7.2 Hz), and 9.27 (s, NH). ^{13} C NMR (DMSO-d$_6$): δ 21.9, 27.8, 28.9, 56.3 (DEPT CH), 81.3, 83.9, 121.2, 124.5, 124.7, 127.47, 127.52, 129.9, 139.9, 131.1, 133.9, 136.3, 139.9, 140.2, 150.9, and 153.0. LCMS, exact mass, 425.14: (M + H)$^+$, 425.74. *Anal*. Calcd for C$_{22}$H$_{23}$N$_3$O$_4$S: C, 62.10; H, 5.45; N, 9.88. Found: C, 62.14; H, 5.52; N, 9.78.

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An Efficient Synthesis of Pyrimido[4,5-*b*]quinoline Derivatives *via* Three-Component Reaction in Aqueous Media

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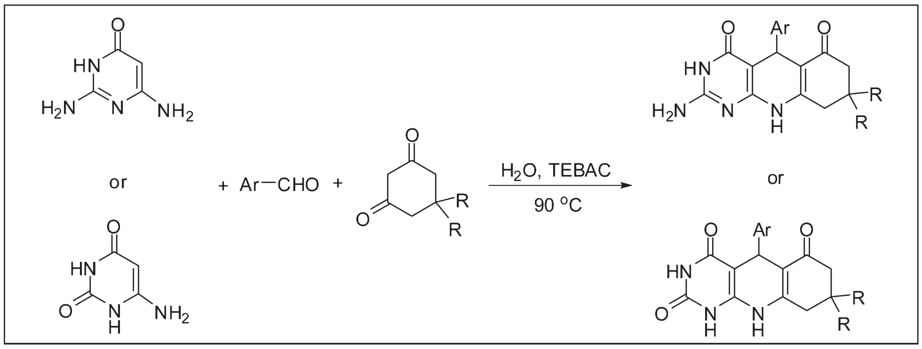


A series of pyrimido[4,5-*b*]quinoline derivatives was synthesized by three-component reaction of 6-aminopyrimidine, aromatic aldehydes and 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione in aqueous media in the presence of triethylbenzylammonium chloride. This protocol has the advantages of higher yields, lower lost, easy work-up, and environmentally friendly procedure.

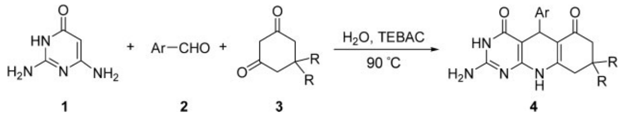
J. Heterocyclic Chem., **46**, 237 (2009).

INTRODUCTION

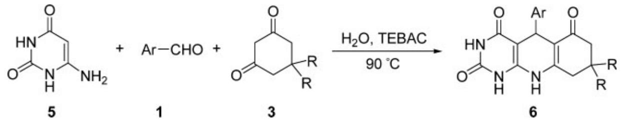
The importance of uracil and its annelated derivatives is well recognized by synthetic [1] as well as biological [2] chemists. With the development of clinically useful anticancer and antiviral drugs [3], there has recently been remarkable interest in the synthetic manipulations of uracils [4]. Uracil derivatives have been reported in the literature to be versatile building blocks for the synthesis of a wide range of heterocyclic motifs, including pyridopyrimidines [5] and pyrazolopyrimidines [6]. Pyrido[2,3-*d*]pyrimidines have received considerable attention over the past years because of their wide range of biological activities, such as antitumor [7], antibacterial [8], anti-inflammatory [9], antifungal [10], antileishmaniasis [11], and also act as cyclin-dependent kinase 4 inhibitors [12]. Recently, Tu *et al.* [13] reported the synthesis of pyrimido[4,5-*b*]quinoline-4,6-dione through one-pot condensation of 2,6-diaminopyrimidine-4-one, aldehyde and cyclic a 1,3-dicarbonyl compound in glycol under microwave irradiation without catalyst. However, they were reacted in organic solvent and needed a special reaction instrument.

Multicomponent reactions (MCRs), in which multiple reactions are combined into one synthetic operation, have been used extensively to form carbon–carbon and carbon-heteroatom bonds in synthetic chemistry [14]. Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step, thus avoid complicated purification operations and allow savings of both solvents and reagents. The need to reduce the amount of toxic waste and by-product arising from chemical process requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods. One of the most promising approaches is using water as reaction media. Breslow *et al.* [15], who showed that hydrophobic effects could strongly enhance the rate of several organic reactions, rediscovered the use of water as a solvent in organic chemistry in the 1980s. There has been growing recognition that water is an attractive medium for many organic reactions [16]. Many MCRs in aqueous medium have been reported [17]. As part of our current studies on the development of new routes to heterocyclic systems [18], we now report an efficient and clean synthetic route to pyrimido[4,5-*b*]quinoline derivatives in aqueous media.

Scheme 1



Scheme 2



RESULTS AND DISCUSSION

When the three-component reaction of 2,6-diaminopyrimidine-4-one **1**, aromatic aldehyde **2**, and 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione **3** was performed in water in the presence of TEBAC at 90°C, 2-amino-5-aryl-8,9-dihydropyrimidino[4,5-*b*]quinoline-4,6 (1*H*,3*H*,5*H*,10*H*)-dione **4** were obtained in high yields (Scheme 1). The results are summarized in Table 1.

As expected, when the 2,6-diaminopyrimidine-4-one **1** was replaced by 6-aminopyrimdine-1,3-dione **5**, another series of 5-aryl-8,9-dihydropyrimido[4,5-*b*]quinoline-2,4,6(1*H*,3*H*,5*H*,10*H*)-trione **6** were obtained under the same reaction conditions (Scheme 2). The results are summarized in Table 2.

As shown in Tables 1 and 2, this protocol can be applied not only to aromatic aldehydes with either electron-withdrawing groups (such as nitro- or halide-groups) or electron-donating groups (such as alkoxy or alkyl groups), but also to heterocyclic aldehydes with excellent yields under same conditions. Therefore, we concluded that the electronic nature of the substituents has no significant effect on these reactions.

In this study, all the products were characterized by mp, IR, and ^{1}H NMR spectral data as well as elemental analyses.

A reasonable mechanism for the formation of the product **4** is outlined in Scheme 3. The reaction occurs *via* an initial formation of α,β-unsaturated ketone, from the Knoevenagel condensation of aldehyde and 1,3-dicarbonyl compounds, which suffers nucleophilic attack to give the Michael adduct **7**. The intermediate product **7** then cyclizes and subsequently dehydrates to afford the product **4**.

Table 1

The synthesis of pyrimido[4,5-*b*]quinoline derivatives **4** in aqueous media.

Entry	R	Ar	Reaction time (h)	Isolated yield (%)
4a	H	4-FC_6H_4	12	95
4b	H	4-HOC_6H_4	16	93
4c	H	3-$NO_2C_6H_4$	18	94
4d	H	4-$NO_2C_6H_4$	16	90
4e	H	4-ClC_6H_4	20	92
4f	H	4-BrC_6H_4	20	86
4g	CH_3	4-ClC_6H_4	18	95
4h	CH_3	4-HOC_6H_4	20	86
4i	CH_3	4-$NO_2C_6H_4$	16	86
4j	CH_3	3,4-$(CH_3O)_2C_6H_3$	17	92
4k	CH_3	3,4-$Cl_2C_6H_3$	20	96
4l	CH_3	3-$NO_2C_6H_4$	13	94
4m	CH_3	4-BrC_6H_4	12	94
4n	CH_3	3,4-$OCH_2OC_6H_3$	21	92
4o	CH_3	Pyridine-3-yl	14	88

In summary, a series of pyrimido[4,5-*b*]quinoline derivatives were synthesized *via* three-component reaction of aldehydes, 6-amminopyrimidine and 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione in water in the presence of TEBAC. Compared with other methods, this new method has the advantages of high yields, mild reaction conditions, easy work-up, inexpensive reagents, and environmentally friendly procedure.

EXPERIMENTAL

Melting points were determined with a TX-5 microscopic melting-point apparatus and were uncorrected. IR spectra were recorded on a Tensor 27 spectrometer in KBr. ^{1}H NMR spectra were measured on a Bruker DPX-400 MHz spectrometer using TMS standard and DMSO-d_6 as solvent. Elemental analyses were performed on Perkin-Elmer 2400II elemental analyzer.

General Procedure for the Synthesis of Pyrimido[4,5-*b*]quinoline Derivatives. A suspension of a mixture of 6-aminopyrimidine **1** or **5** (2 mmol), aldehyde **2** (2 mmol), 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione **3** (2 mmol) and TEBAC (0.15 g, 0.66 mmol) was stirred in water (10 mL) at 90°C for several hours. After completion monitored by TLC, the reaction mixture was allowed to cool to room temperature. The crystalline powder formed recrystallized from DMF to give pure **4** or **6**.

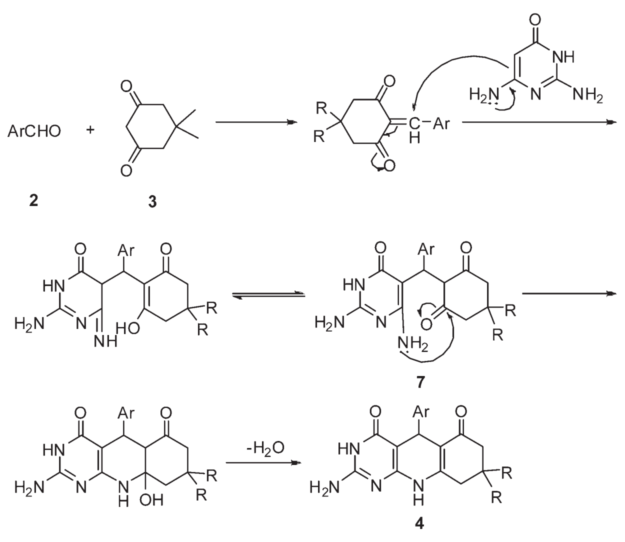
2-Amino-5-(4-fluorophenyl)-8,9-dihydropyrimido[4,5-b]-quinoline-4,6(3H,5H,7H,10H)-dione (4a). This compound was obtained as white needles with mp > 300°C; IR (potassium

Table 2

The synthesis of pyrimido[4,5-*b*]quinoline derivatives **6** in aqueous media.

Entry	R	Ar	Reaction time (h)	Isolated yield (%)
6a	H	3,4- $Cl_2C_6H_3$	8	76
6b	H	3-$NO_2C_6H_4$	20	98
6c	H	2,4-$Cl_2C_6H_3$	16	75
6d	H	2-$NO_2C_6H_4$	12	93
6e	H	4-$NO_2C_6H_4$	13	86
6f	CH_3	3,4-$(CH_3O)_2C_6H_3$	20	91
6g	CH_3	4-HOC_6H_4	22	98

Scheme 3



bromide): 3328, 3148, 2947, 1676, 1644, 1514, 1447, 1362, 1287, 1229, 1149, 1089, 1050, 1014, 994, 897, 839, 816, 770, 750, 735, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6): 1.70–1.95 (m, 2H, CH$_2$), 2.13–2.25 (m, 2H, CH$_2$), 2.45–2.73 (m, 2H, CH$_2$), 4.85 (s, 1H, CH), 6.34 (br. s, 2H, NH$_2$), 6.97 (dd, J_1 = 6.0 Hz, J_2 = 8.8 Hz, 2H, ArH), 7.19 (dd, J_1 = 6.0 Hz, J_2 = 8.8 Hz,, 2H, ArH), 9.38 (br. s, 1H, NH), 10.44 (br. s, 1H, NH). *Anal.* Calcd. for $C_{17}H_{15}FN_4O_2$: C, 62.57; H, 4.63; N, 17.17. Found: C, 62.82; H, 4.48; N, 17.36.

2-Amino-5-(4-hydroxyphenyl)-8,9-dihydropyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (4b). This compound was obtained as pale yellow prisms with mp > 300°C; IR (potassium bromide): 3556, 3335, 3151, 2955, 1679, 1651, 1519, 1455, 1372, 1267, 1187, 1049, 994, 896, 839, 818, 772, 734, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6): 1.72–1.95 (m, 2H, CH$_2$), 2.15–2.24 (m, 2H, CH$_2$), 2.42–2.60 (m, 2H, CH$_2$), 4.76 (s, 1H, CH), 6.27 (br. s, 2H, NH$_2$), 6.54 (d, J = 8.4 Hz, 2H, ArH), 6.96 (d, J = 8.4 Hz, 2H, ArH), 8.98 (s, 1H, OH), 9.28 (br. s, 1H, NH), 10.33 (br. s, 1H, NH). *Anal.* Calcd. for $C_{17}H_{16}N_4O_3$: C, 62.95; H, 4.97; N, 17.27. Found: C, 63.05; H, 5.08; N, 17.13.

2-Amino-5-(3-nitrophenyl)-8,9-dihydropyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (4c). This compound was obtained as pale yellow prisms with mp > 300°C (Lit. [13] > 300°C); IR (potassium bromide): 3462, 3249, 2934, 1679, 1647, 1517, 1426, 1345, 1287, 1227, 1191, 1134, 1095, 1050, 994, 913, 824, 802, 772, 759, 705 cm^{-1}; ^{1}H NMR (DMSO-d_6): 1.73–1.96 (m, 2H, CH$_2$), 2.12–2.30 (m, 2H, CH$_2$), 2.50–2.65 (m, 2H, CH$_2$), 4.96 (s, 1H, CH), 6.40 (br. s, 2H, NH$_2$), 7.49 (t, J = 8.0 Hz, 1H, ArH), 7.36 (d, J = 8.0 Hz, 1H, ArH), 7.94–7.96 (m, 1H, ArH), 8.02 (s, 1H, ArH), 9.52 (br. s, 1H, NH),10.44 (br. s, 1H, NH). *Anal.* Calcd. for $C_{17}H_{15}N_5O_4$: C, 57.79; H, 4.28; N, 19.82. Found: C, 57.98; H, 4.15; N, 20.05.

2-Amino-5-(4-nitrophenyl)-8,9-dihydropyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (4d). This compound was obtained as pale yellow prisms with mp > 300°C (Lit. [13] > 300°C); IR (potassium bromide): 3328, 3149, 3028, 2957, 1681, 1639, 1618, 1522, 1458, 1426, 1367, 1349, 1289, 1268, 1231, 1205, 1183, 1138, 995, 823, 704 cm^{-1}; ^{1}H NMR (DMSO-d_6): 1.73–1.95 (m, 2H, CH$_2$), 2.12–2.28 (m, 2H, CH$_2$), 2.51–2.63 (m, 2H, CH$_2$), 4.95 (s, 1H, CH), 6.39 (br. s, 2H, NH$_2$), 7.44 (d, J = 8.8 Hz, 2H, ArH), 8.06 (d, J = 8.8 Hz, 2H, ArH), 9.51 (br. s, 1H, NH), 10.45 (br. s, 1H, NH). *Anal*. Calcd. for $C_{17}H_{15}N_5O_4$: C, 57.79; H, 4.28; N, 19.82. Found: C, 58.01; H, 4.16; N, 19.69.

2-Amino-5-(4-chlorophenyl)-8,9-dihydropyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (4e). This compound was obtained as pale yellow prisms with mp > 300°C (Lit. [13] > 300°C); IR (potassium bromide): 3358, 3151, 2955, 1683, 1647, 1617, 1519, 1488, 1457, 1426, 1370, 1290, 1267, 1230, 1204, 1188, 1137, 1089, 1014, 994, 832, 813 cm^{-1}; ^{1}H NMR (DMSO-d_6): 1.72–1.95 (m, 2H, CH$_2$), 2.13–2.27 (m, 2H, CH$_2$), 2.45–2.59 (m, 2H, CH$_2$), 4.83 (s, 1H, CH), 6.34 (br. s, 2H, NH$_2$), 7.17–7.24 (m, 4H, ArH), 9.40 (br. s, 1H, NH), 10.44 (br. s, 1H, NH). *Anal.* Calcd. for $C_{17}H_{15}ClN_4O_2$: C, 59.57; H, 4.41; N, 16.34. Found: C, 59.83; H, 4.26; N, 16.56.

2-Amino-5-(4-bromophenyl)-8,9-dihydropyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (4f). This compound was obtained as pale yellow prisms with mp > 300°C (Lit. [13] > 300°C); IR (potassium bromide): 3343, 3152, 2954, 1676, 1652, 1520, 1485, 1457, 1426, 1397, 1369, 1290, 1257, 1230, 1203, 1183, 1137, 1071, 1051, 1010, 994, 898, 831, 811, 777, 733, 706 cm^{-1}; ^{1}H NMR (DMSO-d_6): 1.71–1.95 (m, 2H, CH$_2$), 2.11–2.27 (m, 2H, CH$_2$), 2.45–2.60 (m, 2H, CH$_2$), 4.82 (s, 1H, CH), 6.33 (br. s, 2H, NH$_2$), 7.13 (d, J = 8.4 Hz, 2H, ArH), 7.35 (d, J = 8.4 Hz, 2H, ArH), 9.40 (br. s, 1H, NH), 10.40 (br. s, 1H, NH). *Anal.* Calcd. for $C_{17}H_{15}BrN_4O_2$: C, 52.73; H, 3.90; N, 14.47. Found: C, 52.94; H, 3.86; N, 14.63.

2-Amino-5-(4-chlorophenyl)-8,8-dimethyl-8,9-dihydropyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (4g). This compound was obtained as yellow needles with mp > 300°C (Lit. [13] > 300°C); IR (potassium bromide): 3397, 3169, 2965, 1679, 1647, 1621, 1515, 1478, 1446, 1363, 1303, 1279, 1246, 1217, 1198, 1155, 1140, 1090, 1014, 860, 805, 778, 690 cm^{-1}; ^{1}H NMR (DMSO-d_6): 0.89 (s, 3H, CH$_3$), 1.00 (s, 3H, CH$_3$), 1.98 (d, J = 16.0 Hz, 1H, CH), 2.17 (d, J = 16.0 Hz, 1H, CH), 2.38 (d, J = 17.2 Hz, 1H, CH), 2.45 (d, J = 17.2 Hz, 1H, CH), 4.79 (s, 1H, CH), 6.34 (br. s, 2H, NH$_2$), 7.17 (d, J = 8.4 Hz, 2H, ArH), 7.21 (d, J = 8.4 Hz, 2H, ArH), 9.35 (br. s, 1H, NH), 10.41 (br. s, 1H, NH). *Anal.* Calcd. for $C_{19}H_{19}ClN_4O_2$: C, 61.54; H, 5.16; N, 15.11. Found: C, 61.76; H, 5.09; N, 15.28.

2-Amino-5-(4-hydroxyphenyl)-8,8-dimethyl-8,9-dihydropyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (4h). This compound was obtained as pale yellow prisms with mp > 300°C; IR (potassium bromide): 3440, 3330, 2955, 1675, 1647, 1615, 1514, 1455, 1372, 1284, 1250, 1226, 1202, 1173, 1168, 1139, 1105, 1057, 1028, 975, 854, 808, 769 cm^{-1}; ^{1}H NMR (DMSO-d_6): 0.90 (s, 3H, CH$_3$), 1.00 (s, 3H, CH$_3$), 1.98 (d, J = 16.0 Hz, 1H, CH), 2.15 (d, J = 16.0 Hz, 1H, CH), 2.36 (d, J = 17.2 Hz, 1H, CH), 2.43 (d, J = 17.2 Hz, 1H, CH), 4.71 (s, 1H, CH), 6.25 (br. s, 2H, NH$_2$), 6.53 (d, J = 8.0 Hz, 2H, ArH), 6.95 (d, J = 8.0 Hz, 2H, ArH), 8.95 (br. s, 1H, OH), 9.23 (br. s, 1H, NH), 10.31 (br. s, 1H, NH). *Anal.* Calcd. for $C_{19}H_{20}N_4O_3$: C, 64.76; H, 5.72; N, 15.90. Found: C, 64.83; H, 5.84; N, 15.78.

2-Amino-5-(4-nitrophenyl)-8,8-dimethyl-8,9-dihydropyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (4i). This compound was obtained as yellow needles with mp > 300°C (Lit. [13] > 300°C); IR (potassium bromide): 3470, 3335, 3256, 3179, 3069, 2958, 1661, 1618, 1594, 1516, 1453, 1419, 1366, 1352, 1285, 1245, 1227, 1204, 1188, 1157, 881, 830, 805, 785, 739, 684 cm^{-1}; ^1H NMR (DMSO-d_6): 0.89 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.98 (d, $J = 16.0$ Hz, 1H, CH), 2.18 (d, $J = 16.0$ Hz, 1H, CH), 2.41 (d, $J = 17.2$ Hz, 1H, CH), 2.48 (d, $J = 17.2$ Hz, 1H, CH), 4.91 (s, 1H, CH), 6.38 (br. s, 2H, NH_2), 7.43 (dd, $J_1 = 6.8$ Hz, $J_2 = 6.0$ Hz, 2H, ArH), 8.08 (dd, $J_1 = 6.8$ Hz, $J_2 = 6.0$ Hz 2H, ArH), 9.46 (br. s, 1H, NH), 10.43 (br. s, 1H, NH). *Anal.* Calcd. for $C_{19}H_{19}N_5O_4$: C, 59.84; H, 5.02; N, 18.36. Found: C, 60.05; H, 4.97; N, 18.54.

2-Amino-5-(3,4-dimethoxyphenyl)-8,8-dimethyl-8,9-dihydropyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (4j). This compound was obtained as yellow prisms with mp > 300°C (Lit. [13] > 300°C); IR (potassium bromide): 3432, 3263, 3184, 2956, 1669, 1625, 1588, 1513, 1451, 1369, 1283, 1266, 1246, 1224, 1199, 1139, 1025, 803, 766 cm^{-1}; ^1H NMR (DMSO-d_6): 0.94 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.00 (d, $J = 15.6$ Hz, 1H, CH), 2.18 (d, $J = 15.6$ Hz, 1H, CH), 2.38 (d, $J = 17.2$ Hz, 1H, CH), 2.45 (d, $J = 17.2$ Hz, 1H, CH), 3.65 (s, 3H, CH_3O), 3.67 (s, 3H, CH_3O), 4.77 (s, 1H, CH), 6.28 (br. s, 2H, NH_2), 6.64 (d, $J = 8.0$ Hz, 1H, ArH), 6.74 (d, $J = 8.0$ Hz, 1H, ArH), 6.83 (s, 1H, ArH), 9.24 (br. s, 1H, NH), 10.33 (br. s, 1H, NH). *Anal.* Calcd. for $C_{21}H_{24}N_4O_4$: C, 63.62; H, 6.10; N, 14.13. Found: C, 63.74; H, 6.02; N, 14.26.

2-Amino-5-(3,4-dichlorophenyl)-8,8-dimethyl-8,9-dihydropyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (4k). This compound was obtained as white needles with mp > 300°C; IR (potassium bromide): 3462, 3252, 3059, 2957, 1677, 1603, 1519, 1461, 1372, 1307, 1284, 1228, 1191, 1173, 1140, 1097, 1028, 878, 842, 818, 791, 748, 703 cm^{-1}; ^1H NMR (DMSO-d_6): 0.90 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 2.00 (d, $J = 16.0$ Hz, 1H, CH), 2.18 (d, $J = 16.0$ Hz, 1H, CH), 2.40 (d, $J = 17.2$ Hz, 1H, CH), 2.46 (d, $J = 17.2$ Hz, 1H, CH), 4.78 (s, 1H, CH), 6.39 (br. s, 2H, NH_2), 7.12 (dd, $J_1 = 2.0$ Hz, $J_2 = 8.0$ Hz, 1H, ArH), 7.33 (d, $J = 2.0$ Hz, 1H, ArH), 7.44 (d, $J = 8.0$ Hz, 1H, ArH), 9.42 (br. s, 1H, NH), 10.44 (br. s, 1H, NH). *Anal.* Calcd. for $C_{19}H_{18}Cl_2N_4O_2$: C, 56.31; H, 4.48; N, 13.82. Found: C, 56.48; H, 4.33; N, 13.97.

2-Amino-5-(3-nitrophenyl)-8,8-dimethyl-8,9-dihydropyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (4l). This compound was obtained as yellow needles with mp > 300°C (Lit. [13] > 300°C); IR (potassium bromide): 3470, 3350, 3257, 3194, 2958, 1664, 1649, 1509, 1443, 1417, 1364, 1308, 1285, 1242, 1226, 1202, 1188, 1157, 1098, 1025, 881, 830, 806, 785, 738 cm^{-1}; ^1H NMR (DMSO-d_6): 0.90 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.99 (d, $J = 16.0$ Hz, 1H, CH), 2.19 (d, $J = 16.0$ Hz, 1H, CH), 2.42 (d, $J = 17.6$ Hz, 1H, CH), 2.49 (d, $J = 17.6$ Hz, 1H, CH), 4.92 (s, 1H, CH), 6.39 (br. s, 2H, NH_2), 7.50 (t, $J = 8.0$ Hz, 1H, 1H, ArH), 7.64 (d, $J = 7.6$ Hz, 1H, ArH), 7.95 (d, $J = 7.6$ Hz, 1H, ArH), 7.99 (s, 1H, ArH), 9.45 (br. s, 1H, NH), 10.42 (br. s, 1H, NH). *Anal.* Calcd. for $C_{19}H_{19}N_5O_4$: C, 59.84; H, 5.02; N, 18.36. Found: C, 59.98; H, 5.14; N, 18.19.

2-Amino-5-(4-bromophenyl)-8,8-dimethyl-8,9-dihydropyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (4m). This compound was obtained as yellow needles with mp > 300°C; IR (potassium bromide): 3471, 3323, 3250, 3186, 1659, 1621, 1515, 1486, 1451, 1370, 1284, 1238, 1227, 1204, 1155, 1070, 1011, 842, 809, 782 cm^{-1}; ^1H NMR (DMSO-d_6): 0.89 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.98 (d, $J = 16.0$ Hz, 1H, CH), 2.17 (d, $J = 16.0$ Hz, 1H, CH), 2.38 (d, $J = 17.2$ Hz, 1H, CH), 2.45 (d, $J = 17.2$ Hz, 1H, CH), 4.77 (s, 1H, CH), 6.32 (br. s, 2H, NH_2), 7.12 (d, $J = 8.4$ Hz, 2H, ArH), 7.35 (d, $J =8.4$ Hz, 2H, ArH), 9.34 (br. s, 1H, NH), 10.38 (br. s, 1H, NH). *Anal.* Calcd. for $C_{19}H_{19}BrN_4O_2$: C, 54.95; H, 4.61; N, 13.49. Found: C, 55.06; H, 4.53; N, 13.41.

2-Amino-5-(3,4-dimethylenedioxyphenyl)-8,8-dimethyl-8,9-dihydropyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (4n). This compound was obtained as yellow needles with mp > 300°C (Lit. [13] > 300°C); IR (potassium bromide): 3216, 3188, 2958, 2902, 1622, 1558, 1540, 1508, 1488, 1455, 1372, 1283, 1232, 1200, 1041, 1029, 931, 882, 784 cm^{-1}; ^1H NMR (DMSO-d_6): 0.91 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 2.00 (d, $J = 16.0$ Hz, 1H, CH), 2.16 (d, $J = 16.0$ Hz, 1H, CH), 2.38 (d, $J = 17.2$ Hz, 1H, CH), 2.44 (d, $J = 17.2$ Hz, 1H, CH), 4.73 (s, 1H, CH), 5.89 (s, 2H, OCH_2O), 6.35 (br. s, 2H, NH_2), 6.60 (d, $J = 8.0$ Hz, 1H, ArH), 6.66–6.72 (m, 2H, ArH), 9.32 (br. s, 1H, NH), 10.46 (br. s, 1H, NH). *Anal.* Calcd. for $C_{20}H_{20}N_4O_4$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.07; H, 5.42; N, 14.86.

2-Amino-5-(pyridin-3-yl)-8,8-dimethyl-8,9-dihydropyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (4o). This compound was obtained as yellow needles with mp > 300°C; IR (potassium bromide): 3417, 3373, 3263, 3194, 2960, 1660, 1625, 1544, 1513, 1470, 1453, 1400, 1370, 1277, 1242, 1227, 1197, 1154, 1140, 1044, 843, 804, 783, 752, 711 cm^{-1}; ^1H NMR (DMSO-d_6): 0.89 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.99 (d, $J = 16.0$ Hz, 1H, CH), 2.18 (d, $J = 16.0$ Hz, 1H, CH), 2.41 (d, $J = 16.8$ Hz, 1H, CH), 2.47 (d, $J = 16.8$ Hz, 1H, CH), 4.79 (s, 1H, CH), 6.36 (br. s, 2H, NH_2), 7.20 (dd, $J_1 = 4.8$ Hz, $J_2 = 8.0$ Hz, 1H, ArH), 7.49 (dd, $J_1 = 2.0$ Hz, $J_2 = 4.8$ Hz, 1H, ArH), 8.25 (dd, $J_1 = 2.0$ Hz, $J_2 = 4.8$ Hz, 1H, ArH), 8.39 (d, $J = 2.0$ Hz, 1H, ArH), 9.41 (br. s, 1H, NH), 10.42 (br. s, 1H, NH). *Anal.* Calcd. for $C_{18}H_{19}N_5O_2$: C, 64.08; H, 5.68; N, 20.76. Found: C, 64.32; H, 5.54; N, 20.92.

5-(3,4-Dichlorophenyl)-8,9-dihydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,5H,7H,10H)-trione (6a). This compound was obtained as white prisms with mp > 300°C; IR (potassium bromide): 3247, 3207, 3078, 2949, 1714, 1682, 1629, 1609, 1522, 1476, 1439, 1378, 1330, 1303, 1252, 1228, 1182, 1143, 1112, 1029, 994, 955, 901, 820, 778 cm^{-1}; ^1H NMR (DMSO-d_6): 1.71–1.96 (m, 2H, CH_2), 2.10–2.30 (m, 2H, CH_2), 2.54–2.66 (m, 2H, CH_2), 4.76 (s, 1H, CH), 7.16 (dd, $J_1 = 2.0$ Hz, $J_2 = 8.4$ Hz, 1H, ArH), 7.38 (d, $J = 2.0$ Hz, 1H, ArH), 7.47 (d, $J = 8.4$ Hz, 1H, ArH), 9.00 (br. s, 1H, NH), 10.29 (br. s, 1H, NH), 10.80 (br. s, 1H, NH). *Anal.* Calcd. for $C_{17}H_{13}Cl_2N_3O_3$: C, 53.99; H, 3.46; N, 11.11. Found: C, 54.08; H, 3.56; N, 11.04.

5-(3-Nitrophenyl)-8,9-dihydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,5H,7H,10H)-trione (6b). This compound was obtained as pale yellow prisms with mp > 300°C; IR (potassium bromide): 3279, 3221, 3074, 2970, 1720, 1684, 1632, 1597, 1528, 1470, 1447, 1382, 1358, 1258, 1207, 1186, 1147, 1128, 1089, 994, 914, 845, 822, 772, 740 cm^{-1}; ^1H NMR (DMSO-d_6): 1.75–1.99 (m, 2H, CH_2), 2.18–2.30 (m, 2H, CH_2), 2.53–2.69 (m, 2H, CH_2), 4.91 (s, 1H, CH), 7.52 (t, $J = 8.0$ Hz, 1H, ArH), 7.66 (d, $J = 6.0$ Hz, 1H, ArH), 7.98 (t, $J = 8.0$ Hz, 1H, ArH), 8.03 (s, 1H, ArH), 9.05 (br. s, 1H, NH), 10.32 (br. s, 1H, NH), 10.81 (br. s, 1H, NH). *Anal.* Calcd. for $C_{17}H_{14}N_4O_5$: C, 57.63; H, 3.98; N, 15.81. Found: C, 57.81; H, 4.02; N, 15.69.

5-(2,4-Dichlorophenyl)-8,9-dihydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,5H,10H)-trione (6c). This compound was obtained as white prisms with mp > 300°C; IR (potassium bromide): 3248, 3207, 3079, 2952, 1723, 1670, 1629, 1603, 1537, 1483, 1426, 1418, 1382, 1341, 1267, 1187, 1149, 1110, 1036, 994, 904, 862, 815, 760, 705 cm^{-1}; ^{1}H NMR (DMSO-d_6): 1.70–1.95 (m, 2H, CH_2), 2.10–2.27 (m, 2H, CH_2), 2.51–2.60 (m, 2H, CH_2), 5.03 (s, 1H, CH), 7.26 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H, ArH), 7.31 (d, J = 8.4 Hz, 1H, ArH), 7.34 (d, J = 2.0 Hz, 1H, ArH), 8.97 (br. s, 1H, NH), 10.21 (br. s, 1H, NH), 10.67 (br. s, 1H, NH). *Anal.* Calcd. for $C_{17}H_{13}Cl_2N_3O_3$: C, 53.99; H, 3.46; N, 11.11. Found: C, 54.07; H, 3.28; N, 11.25.

5-(2-Nitrophenyl)-8,9-dihydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,5H,7H,10H)-trione (6d). This compound was obtained as red prisms with mp > 300°C; IR (potassium bromide): 3298, 3246, 3010, 2962, 2829, 1734, 1664, 1644, 1531, 1485, 1429, 1378, 1359, 1304, 1261, 1227, 1188, 1143, 1000, 893, 867, 755, 706, 689 cm^{-1}; ^{1}H NMR (DMSO-d_6): 1.74–1.96 (m, 2H, CH_2), 2.10–2.28 (m, 2H, CH_2), 2.51–2.62 (m, 2H, CH_2), 5.61 (s, 1H, CH), 7.29–7.34 (m, 1H, ArH), 7.41 (dd, J_1 = 1.2 Hz, J_2 = 7.6 Hz, 1H, ArH), 7.51–7.57 (m, 1H, ArH), 7.71 (dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 1H, ArH), 8.92 (br. s, 1H, NH), 10.18 (br. s, 1H, NH), 10.68 (br. s, 1H, NH). *Anal.* Calcd. for $C_{17}H_{14}N_4O_5$: C, 57.63; H, 3.98; N, 15.81. Found: C, 57.82; H, 4.06; N, 15.96.

5-(4-Nitrophenyl)-8,9-dihydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,5H,7H,10H)-trione (6e). This compound was obtained as yellow needles with mp > 300°C; IR (potassium bromide): 3360, 3272, 3194, 3052, 2947, 1713, 1669, 1522, 1483, 1438, 1411, 1380, 1348, 1265, 1207, 1188, 1148, 1109, 998, 869, 824, 765, 697 cm^{-1}; ^{1}H NMR (DMSO-d_6): 1.73–1.98 (m, 2H, CH_2), 2.15–2.30 (m, 2H, CH_2), 2.55–2.70 (m, 2H, CH_2), 4.90 (s, 1H, CH), 7.48 (d, J = 8.8 Hz, 2H, ArH), 8.08 (d, J = 8.8 Hz, 2H, ArH), 9.04 (br. s, 1H, NH), 10.30 (br. s, 1H, NH), 10.80 (br. s, 1H, NH). *Anal.* Calcd. for $C_{17}H_{14}N_4O_5$: C, 57.63; H, 3.98; N, 15.81. Found: C, 57.88; H, 4.09; N, 15.74.

5-(3,4-Dimethoxyphenyl)-8,9-dihydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,5H,7H,10H)-trione (6f). This compound was obtained as pale yellow needles with mp > 300°C; IR (potassium bromide): 3598, 3179, 2954, 1723, 1653, 1595, 1536, 1470, 1417, 1377, 1335, 1266, 1231, 1202, 1169, 1141, 1087, 1025, 974, 930, 864, 797, 762 cm^{-1}; ^{1}H NMR (DMSO-d_6): 0.89 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.04 (d, J = 16.0 Hz, 1H, CH), 2.22 (d, J = 16.0 Hz, 1H, CH), 2.42 (d, J = 17.2 Hz, 1H, CH), 2.49 (d, J = 17.6 Hz, 1H, CH), 3.67 (s, 6H, 2 × CH_3O), 4.71 (s, 1H, CH), 6.66 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H, ArH), 6.77 (d, J = 8.0 Hz, 1H, ArH), 6.81 (d, J = 1.6 Hz, 1H, ArH), 8.73 (br. s, 1H, NH), 10.21 (br. s, 1H, NH), 10.71 (br. s, 1H, NH). *Anal.* Calcd. for $C_{21}H_{23}N_3O_5$: C, 63.46; H, 5.83; N, 10.57. Found: C, 63.72; H, 5.69; N, 10.75.

5-(4-Hydroxyphenyl)-8,9-dihydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,5H,7H,10H)-trione (6g). This compound was obtained as pale yellow needles with mp > 300°C; IR (potassium bromide): 3328, 3201, 3021, 2954, 2933, 2874, 1707, 1679, 1614, 1542, 1512, 1480, 1416, 1376, 1329, 1296, 1252, 1227, 1206, 1177, 1164, 1146, 1050, 1003, 861, 851, 830, 797, 786, 764 cm^{-1}; ^{1}H NMR (DMSO-d_6): 0.89 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.01 (d, J = 16.0 Hz, 1H, CH), 2.19 (d, J = 16.0 Hz, 1H, CH), 2.40 (d, J = 16.8 Hz, 1H, CH), 2.47 (d, J = 16.8 Hz, 1H, CH), 4.64 (s, 1H, CH), 6.56 (d, J = 8.0 Hz, 2H, ArH), 6.96 (d, J = 8.0 Hz, 2H, ArH), 8.70 (br. s, 1H, OH), 9.09 (br. s, 1H, NH), 10.18 (br. s, 1H, NH), 10.72 (br. s, 1H, NH). *Anal.* Calcd. F or $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89. Found: C, 64.63; H, 5.36; N, 11.97.

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Symmetrical Diamides Based on 2,6-Bis(methoxycarbonyl)pyridine: Syntheses and Metal Ion Binding Studies

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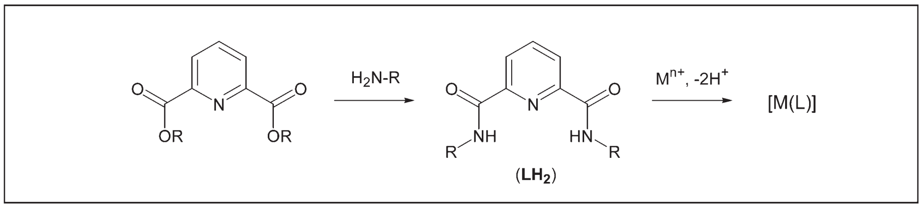

Symmetrically-armed molecules based on a 2,6-diamidopyridine core, 2,6-bis[*N*-(1′-piperidinylethyl)-carbamyl]pyridine (**1**), 2,6-bis[*N*-(1′-piperazinylethyl)carbamyl]pyridine (**2**), 2,6-bis[*N*-2′-(5″-nitropyridine)-1′-azapropyl)carbamyl]pyridine (**3**), 2,6-bis[*N*-(3′-hydroxypropyl)carbamyl]pyridine (**4**), 2,6-bis[*N*-(5′-hydroxy-3′-azapentyl)carbamyl]pyridine (**5**), 2,6-bis[*N*-2′-oxo-2′,3′-dihydropyrimidin-4′-yl)carbamyl]-pyridine (**6**) as well as the thioamide analogue 2,6-bis[(S-2′-pyridinyl)carbothiyl]pyridine (**7**) have been prepared and characterized. An X-ray crystal structure of **1** confirms its formation. These molecules are potentially multidentate ligands for metal ions, and complexation has been probed through spectroscopic characterization, particularly by electrospray ionization mass spectrometry, and isolation of some first-row transition metal complexes. The ligands, with potentially coordinating arms extending from each amide, dominantly form simple 1:1 M:L complexes. They show no tendency toward polynuclear helicate formation.

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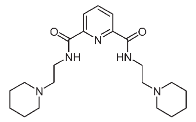
INTRODUCTION

Development of molecules that contain pyridine-2-carboxamido functionality within larger frameworks have been vigorously pursued in recent years [1–7]. Molecules with a —HN—OC—pyridine—CO—NH— core have found wide application, ranging from use in electroluminescent devices to oxidation catalysts. Recently, systems based on a 2,6-diamidopyridine core that support helicate metal complex formation have been developed [3,6,8], and represent a novel extension of this chemistry. This type of structure appears to arise in systems with aromatic nitrogen heterocycles terminating the two pendant arms, where favorable π-π stacking interactions support oligomer self-assembly. It is therefore of interest to develop and examine examples of symmetrical molecules with different potentially chelating arms, here 2,6-bis[*N*-(1′-piperidinylethyl)carbamyl]-pyridine (**1**), 2,6-bis[*N*-(1′-piperazinylethyl)carbamyl]-pyridine (**2**), 2,6-bis[*N*-(2′-(5″-nitropyridine)-1′-azapropyl)carbamyl]pyridine (**3**), 2,6-bi[*N*-(3′-hydroxypropyl) carbamyl]pyridine (**4**), and 2,6-bis[*N*-(5′-hydroxy-3′-azapentyl)carbamyl]pyridine (**5**). To extend the examination further, we have prepared two examples without methylene linkages in the arms, 2,6-bis[*N*-(2′-oxo-2′,3′-dihydropyrimidin-4′-yl)carbamyl]pyridine (**6**) and the thioamide analogue 2,6-bis[*S*-(2′-pyridyl)carbothiyl]pyridine (**7**).



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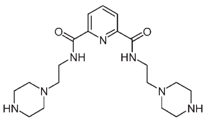

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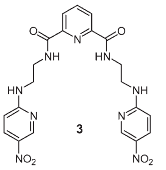

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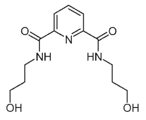

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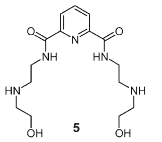

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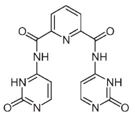

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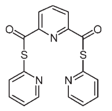

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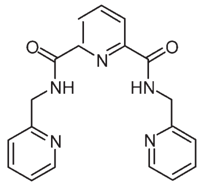
While 2,6-bis[*N*-(2′-pyridylmethyl)carbamyl]pyridine (**8**) has a strong tendency to form helical species on metal ion complexation [8], the longer-chain analogue **9** shows no tendency toward helicate formation [9], suggesting that forces that control helicate formation are subtle. Further, although **8** displays no chirality as a free ligand [10], adopting the *syn*, *syn* conformation resulting from intramolecular hydrogen bonding, a bisoxazoline analogue adopts a helical superstructure in the crystal even when a metal is absent [11]. Combining strands containing heteroatoms with a core subunit containing a heteroatom such as **10** or **11** can lead in a very simple way to structures where a helical conformation is stabilized by a network of intramolecular hydrogen bonds [12]. Whether this capacity for helicate formation, either as free or complexed species, also extends to systems with aliphatic side chains reported here was one factor driving this study. Complexation of the new molecules reported here is explored in part with a view to probing stoichometry and to explore the thesis that terminating saturated amine and alcohol groups, although capable of strong hydrogen bonding interactions, do not tend to support the formation of helicates because they have no π-π stacking ability.



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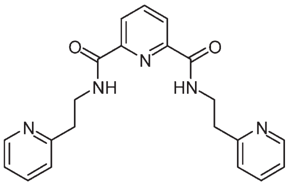

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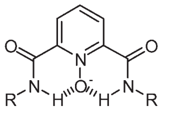

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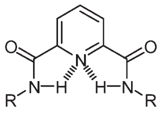

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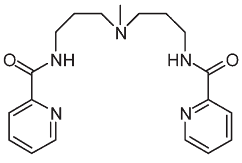

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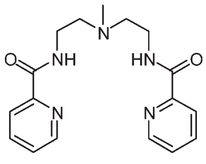

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RESULTS AND DISCUSSION

Synthesis of diamides. The new symmetrically armed compounds have been prepared using as the core reagent 2,6-bis(methoxy-carbonyl)pyridine, reacting with an amine. Conventional reflux in an organic solvent was not always successful, and a microwave reactor was used in some cases to drive the reaction to completion. For example, the synthesis of **2** was not achieved by refluxing in toluene, even for extended periods; the product obtained after 3 days reflux was assigned as a mixture of the diester precursor and the one-armed monoamide, from spectroscopy. However, solvent-free reaction conducted in a microwave proved successful. Possibly, reaction with an acid chloride rather than an ester may have been more successful conventionally, but the microwave technology supplied the answer to low reactivity without the need to change the key reagent; yields of up to 90% were achieved. Only with the synthesis of the thioamide 7, where a thiol rather than an amine is involved in the reaction, was the acid chloride approach necessarily adopted.

Compounds isolated were all microanalytically pure and readily characterized spectroscopically. For example, with diamide **1**, the NMR spectra are fully consistent with the structure assigned. The proton-decoupled ^{13}C spectrum displays nine peaks (five methylene, three aromatic and one amide carbon resonances), as expected for the symmetric diamide. The methylenes on the piperidine ring can be assigned unambiguously, with large signals at δ 54.1 and 25.0 ppm associated with the equivalent pairs of —***C***H$_2$—N— and adjacent —C—***C***H$_2$—C, respectively, and the remaining single central methylene found at 23.5 ppm. The two remaining methylenes of the aminoethyl chain are at 35.5 (—***C***H$_2$—N$_{sec}$) and 58.4 (—***C***H$_2$—NHCO—) ppm. By analogy to the spectra of the known diamide **8** and the diester precursor, the aromatic resonances can be assigned to the single ***C***H opposite the N group (138.0), the adjacent equivalent pair of ***C***H groups (124.0) and the equivalent pair of tertiary ***C*** (148.3), with the amide resonance at 163.4 ppm. Assignment in the ^{1}H NMR spectrum is facile from comparison with known analogues. Three resonances in the aromatic region display a ratio of 2:2:1, with the —NH—CO— resonance (a broadened triplet) at δ 9.17 ppm. Other resonances at 7.98 and 8.30 ppm are assigned to the protons of the single CH opposite the N group and the adjacent equivalent pair of CH groups, respectively. A set of resonances between δ 1.5 and 4.2 ppm arise from the 14 methylene protons, all of which are coupled, yielding a complex pattern that is not fully resolved. The set of methylenes in **1** give rise to strong resonances in the IR spectrum between 2760 and 2930 cm^{-1}. A strong —CO— resonance also occurs at 1658 cm^{-1}, with other —NHCO— bands at 1538 and 1444 cm^{-1}. The most characteristic pyridine resonances are those at 753 and 644 cm^{-1}. In the electrospray ionization mass spectrometry (ESI-MS), the species $\mathbf{1}\cdot H^{+}$ is observed at *m*/*z* 388 (calc. 388), with a minor peak due to the dihydrate at *m*/*z* 424. Details for other compounds prepared appear in summary form in the Experimental section.

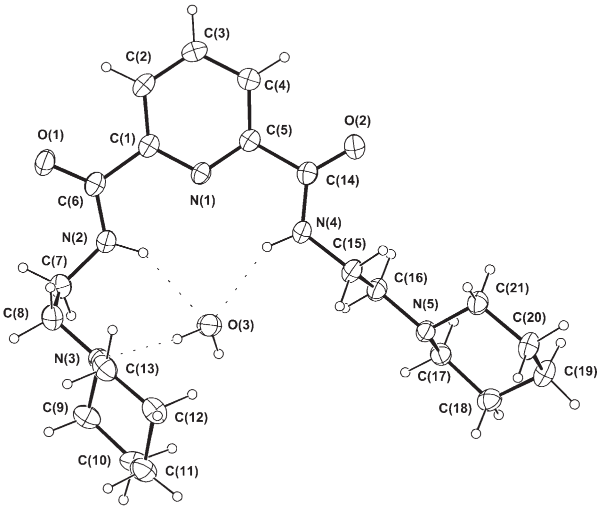

Figure 1. An ORTEP view of **1**, with 50% displacement ellipsoids.

An X-ray crystal structure analysis of **1** confirms the proposed connectivity in this molecule (Fig. 1), with distances and angle that are typical of these types of systems. The C—N distances to pyridine N (av. 1.339 Å), amide N (av. 1.335 Å to CO, av. 1.451 Å to CH_2), and tertiary amine (av. 1.469 Å) are consistent with the character of these groups. The pyridine ring is essentially planar, with the piperidine rings in chair conformations. The water molecule (O(3)) is structurally important, being strongly hydrogen-bonded to amide protons (HN(2) and HN(4)) and to the piperidine nitrogen (N(3)) of one of the two pendant arms. The N(2)H…O(3) and N(4)H…(O(3) distances are 1.331 and 1.450 Å, with the O(3)H….N(3) distance 1.473 Å. This water molecule is not only intramolecularly bonded to **1** but is also connected intermolecularly to an adjacent molecule, building a chain parallel to the *c*-axis. The arm that is not hydrogen-bonded (which includes N(5)) is displaced well away from the water molecule, with C—N_{tert} distances slightly longer (~10 pm) for the hydrogen-bonded compared with the nonbonded arm. Helicity seen in some aromatic-rich examples is not evident here.

The product **2** is anticipated to be spectroscopically somewhat similar to **1**, because the sole difference is the replacement of the methylene opposite the tertiary amine in the six-membered ring by an —NH— group, reducing the number of inequivalent carbons from nine to eight. Aromatic resonances occur at δ 124.4 (124.0 in **1**), 139.3 (138.0 in **1**), and 147.4 (C_{tert}, 148.3 in **1**), with the amide C at 164.9 ppm (163.4 in **1**). Methylenes in the aliphatic ring are unambiguously defined by their intensity, and occur at 43.3 and 51.5 ppm. Notably, the equivalent methylenes occur at 25.0 and 54.1 ppm in **1**, with the significant shift of one methylene here arising from transition for one equivalent pair from a —C—***C***H_2—C— to a —C—***C***H_2—N— environment, as required in the structure. Other methylenes in the chain linking to the amide have resonances at 35.5 and 56.1 ppm. Notable in the ^1H NMR is the absence of any resonance above 2.2 ppm, fully consistent with there being no —C—CH_2—C— entities. A complex pattern of peaks occur from 2.3 to 3.6 ppm for the methylene groups, with the two types of pyridine protons found at 7.95 and 8.08 ppm. In the ESI-MS, the species **2**·H^+ is dominant at *m*/*z* 390.

The synthesis of **3** is of interest because it has pyridine groups terminating the chains and thus provides an extension of the series from a compound with a one atom chain, **8**, and a two atom chain, **9**, to now a three atom chain, joining each terminal pyridine group to the amide. Other differences resulting from the commercial precursor used here are the 5-nitro group on the pyridine ring, characterized clearly by IR resonances at 1540 and 1334 cm^{-1}, and an aza group in the propyl chain. Strong amine bands occur at 3280, 3230, and 1590 cm^{-1} in the IR spectrum. The amide group is defined by resonances in the NMR spectra at 161.4 ppm (^{13}C), and 8.84 ppm (^1H), analogous to positions in other molecules synthesized. The presence of two magnetically distinctly types of pyridine ring is clear in the ^{13}C NMR, with a complex set of resonances, some overlapping, between 146.6 and 108.4 ppm. Methylene resonances occur at 43.0 and 48.5 ppm. The ^1H NMR spectrum displays aliphatic resonances between 2.5 and 3.1 ppm, and aromatic resonances between 6.5 and 8.2 ppm, with protons adjacent to the nitro group being shifted to higher field. In the ESI-MS, the dominant species is **3**·H^+ (*m*/*z* 496).

The aminoalcohol-based ligands **4** and **5** were prepared in good yield by conventional methods. Their spectroscopy has characteristics consistent with their formation. For **4**, the ^{13}C resonances of the aliphatic chains shows the three expected signals at 30.5 (central C—CH_2—C), 36.2 (—CH_2—N—) and 59.0 (—CH_2—OH) ppm, with three resonances from the single pyridine (124.3, 139.3, 147.6 (pyC_{tert}) ppm) and a single carbonyl resonance (165.3 ppm) as required for a symmetrically armed ligand. The alcohol has a characteristic strong IR resonance at 3425 cm^{-1}, apart from the compound showing typical amide bands. The analogue **5** is also spectroscopically consistent with the structure assigned.

The ligand **6**, based on cytosine, forms readily under microwave conditions despite there being possibly greater steric demands as a result of the reacting amine being attached directly to an aromatic ring. Two carbonyl resonances are found in the ^{13}C NMR near 160 ppm, due to the amide and pendant ring carbonyl groups, as well as a set of six aromatic resonances due to the carbons in the cytosine and pyridine rings.

The final example, **7** is a thioamide; as such, it was appropriate to prepare it by reaction of an acid chloride rather than a diester, due to the different reactivity of the thiol group. This is a very rapid and clean reaction, with the product isolated in high yield. The —CO—S— functionality leads to a shift in the carbonyl resonance in the ^{13}C NMR to near 190 ppm; the presence of aromatic resonances, five from the pendant pyridine and three from the core pyridine, is consistent with the presence of two equivalent chains.

Transition metal complexes. Complexation behavior was probed spectroscopically (particularly by ESI-MS), with only selected examples prepared and isolated as solids. The type of complexes formed by the 2,6-diamidopyridines is influenced by the type of pendant chains present, and the donor groups therein. With Cu(II), all of **1–6** apparently form only simple 1:1 complexes in solution from ESI-MS, with several examples isolated as blue-purple solids. For **1–5**, the relatively long chains from the amide to the terminal donors suggest sufficient flexibility that would allow the donor groups terminating these arms to bind in addition to the planar —$^{-}$N—OC—pyridine—CO—N^{-}— unit; the two pendant arms donors may thus promote the favored five-coordination. Others symmetric N_5-diamide compounds such as **12** and **13** have been described [13], prepared by a different route. The copper(II) complex of **12** reportedly binds copper(II) ion as a 1:1 M:L species to form a pentadentate mononuclear copper(II) ion. This complex is one of a number of mononuclear copper(II) complexes that contain dicarboxamido ligation in CuN_5 chromophores [9,14], and support the assignment of similar geometries for the present complexes. Unfortunately, crystals suitable for X-ray structure have not been obtained. However, ESI-MS clearly supports simple ML structures and not higher order polymetallic systems. For example, **2** in the presence of $Cu(OAc)_2$ exhibits no peaks that can be assigned to polymetallic species, but a signal at *m*/*z* 479, 481 arises from $[Cu(\mathbf{2})(OAc)]^+$. The ligands **1** and **2** not only have flexible two-carbon chains linking the amide groups to the terminal group, but the terminal group in each case is an aliphatic amine in a nonaromatic ring, unable to stabilize polynuclear assemblies through π-stacking of terminal groups, and are not expected to form helicates.

The way the pendant chains can influence coordination outcomes has been illustrated with **8** and **9**; whereas **8** shows a strong tendency toward helicate formation on complexation, the analogue with a longer methylene chain, **9**, is not known to form helicates [8]. It is not surprising, therefore, that the even longer chain analogue **3** studied here also does not form helicates, from spectroscopic and ESI-MS evidence. For **4** and **5**, with pendant chains terminated by alcohol groups, we also observe no evidence of helicates despite the potential for alcohol groups to be involved in strong hydrogen bonding interactions that could stabilize more complex assemblies. The general observation of only simple 1:1 complexes forming with aliphatic amines or alcohols as arms indirectly supports a key role for π-stacking in helicate assembly.

For **6** and **7**, where no methylene spacer groups separate the amide groups from the pendant rings, there is again no evidence for oligomeric complexes forming. For the copper(II) complex of **6**, binding of at least the central pyridine N and the two amido N is expected, but this has not been explored in any detail at this stage. For **7**, there is limited evidence that complexation was achieved, consistent with the thioamide being a poor donor, disrupting binding by other groups. However, an apparent Zn(II) complex precipitated readily, suggesting that complexation is possible. Although the nature of this species is uncertain, the limited studies show no real evidence for other than simple 1:1 speciation, and hence further examination was not pursued.

Complexation of diamides with nickel(II) usually yield species that are light brown and thus presumably low-spin square-planar d^8 species, also assigned as simple 1:1 monomers from ESI-MS. There is no clear evidence of helicate formation with these ligands and this metal; in solution, ESI-MS shows no peaks assignable to polynuclear species. For example, spectra of mixtures of **1** or **2** with nickel(II) acetate are dominated by peaks due to $Ni(L\text{-}H)^+$ (*m*/*z* 445 and 447 for **1** and **2**, respectively). With **4**, where alone an N_3O_2 donor set is offered, an orange diamagnetic solid was isolated, its magnetic and spectroscopic properties confirming it as a monomeric square-planar species, presumably with one pendant arm unbound. Cobalt(III) complexes of **1** and **3** were prepared to probe the mode of binding of these systems to an inert metal ion strongly favoring octahedral coordination. Simple 1:1 complexes with ligand bound symmetrically to the metal ion are supported, from spectroscopic characterization and comparison with analogues [15], with either *mer*-CoN_3X_3 geometry with pendant amines or as a CoN_5X complex involving binding of all five nitrogen donors found. Complexation of inert octahedral Co(III) by these ligand systems is fully consistent with expected behavior, and the chemistry does not warrant further extension.

CONCLUSION

Synthesis of symmetrically armed diamides based on the 2,6-diamidopyridine core with a range of new pendants has been established, with microwave synthesis promoting formation of desired products. Consistent with earlier studies, 2,6-diamidopyridines with pendant chains including at least two methylene groups do not undergo helicate formation irrespective of the type of donor group terminating the chains. For aliphatic-terminated molecules like **1** and **2**, loss of the ability of the pendants to participate in π-stacking, found to stabilize helicates with **8**, further restricts the likelihood of helicate formation. It is notable that all known polynuclear helicates of this class of ligand have high levels of aromaticity, and the failure of saturated ligand systems examined here to helicate indirectly supports a role for aromatic groups as structure makers. A more extensive examination of the coordination of these new ligand systems is not warranted, as complexation has been defined adequately here as dominated by simple 1:1 M:L species. Because none of the variety of diamide ligand systems prepared here, irrespective of the type of pendant groups involved, showed a propensity toward helicate formation, the view that stabilization of helicates is not routinely promoted simply because of the presence of the —NHCO—py—CONH— core is supported; this means that the character of the pendant groups is particularly important, as otherwise conventional coordination chemistry results.

EXPERIMENTAL

NMR spectra were recorded on solutions of ligand and complexes, usually in $CDCl_3$ or D_2O, using a Bruker DPX300 spectrometer, whereas FTIR spectra were recorded on a Bio-Rad Win-IR spectrometer with compounds dispersed in KBr disks. UV–Vis spectra were recorded using a Hitachi 150-20 UV–Vis spectrophotometer. ESI-MS were recorded for aqueous or methanolic 10^{-4} *M* solutions, using a Micromass VG Platform II single quadrupole mass spectrometer; experimental peak values are identified by the *m/z* ratio of the most abundant peak. Microanalysis was performed by the Microanalytical Unit, A.N.U., Canberra. 2,6-Bis(methoxycarbonyl)pyridine was made as reported in [8].

Diamide syntheses. ***2,6-Bis[N-(1′-piperidinylethyl)carbamyl]pyridine (1).*** 2,6-Bis(methoxycarbonyl)pyridine (5 g, 25.5 mmol) was suspended in toluene (300 mL) and a solution of the 1-(2′-aminoethyl)-piperidine (7.5 g, 58.5 mmol) was added slowly to the stirring solution. The solution was stirred and heated (~100°C) for 30 min, then refluxed for 24 h. The heat source was removed, the condenser replaced by a $CaCl_2$ drying tube, and stirring continued for another 2 days. Evaporation of solvent yielded a brown oily product. This was twice taken up with diethyl ether and re-evaporated, resulting in a brown sticky solid, which was washed well with water three times and crystallized on standing (1.8 g, 20%). ^{13}C NMR ($CDCl_3$): δ 23.5, 25.1 (—C—CH$_2$—C), 35.7, 54.0, 58.0 (—CH$_2$—N), 123.9, 137.9 (pyCH), 148.4 (pyC$_{tert}$), 163.3 (CO) ppm; ^{1}H NMR ($CDCl_3$): δ 1.5–4.2 (m, 28H, —CH$_2$—), 7.98 (t, 1H, pyH), 8.30 (d, 2H, pyH), 9.17 (t, 2H, —NHCO—); IR: 3470 (OH_2), 3317, 1657, 1538, 1444 (NHCO), 1119, 753, 682 (py) cm^{-1}; ESI-MS (H_2O): *m/z* 388 (**1**) H$^+$). *Anal.* Calcd for $C_{21}H_{33}N_5O_2{\cdot}H_2O$: C, 62.2; H, 8.7; N, 17.5. Found: C, 62.1; H, 8.7; N, 17.2.

2,6-Bis[N-(1′-piperazinylethyl)carbamyl]pyridine (2). Reaction as for **1** was unsuccessful, but using a microwave reactor (Panasonic Dimension 4, Genius NN-C 2000W) proved successful. The diester (1 g, 5.1 mmol) and 1-(2′-aminoethyl)-piperazine (1.44 g, 11.1 mmol) were mixed in a small flask fitted with a microcondenser. The mixture was placed in the microwave for 180 s on high power, and a brown oily product resulted. After standing at room temperature overnight, diethyl ether (20 mL) was added. Further standing for ~24 h resulted in an oily solid, which was washed with water (50 mL) three times, yielding a light brown solid on drying (1.04 g, 80%). ^{13}C NMR ($CDCl_3$): δ 35.5, 43.3, 51.4, 56.1 (—CH$_2$—N), 124.4, 139.3 (pyCH), 147.4 (pyC$_{tert}$), 164.9 (—NHCO—) ppm; ^{1}H NMR ($CDCl_3$): δ 2.3–3.6 (m, 24H, —CH$_2$—), 4.6 (br m, 2H, —NH—), 7.95 (t, 1H, pyH), 8.08 (d, 2H, pyH), 9.12 (br t, 2H, —NHCO—) ppm; IR: 3475 (OH_2), 3290, 1627 (—NH—), 1608, 1540, 1444 (NHCO), 1080, 763, 690 (py) cm^{-1}; ESI-MS (H_2O): *m/z* 390 (**2**·H$^+$). *Anal.* Calcd for $C_{20}H_{34}N_7O_2 \cdot 1.25H_2O$: C, 56.2; H, 8.8, N, 22.9. Found: C, 55.9; H, 8.8; N, 22.9.

2,6-Bis[N-2′-(5″-nitropyridine)-1′-azapropyl)carbamyl]pyridine (3). 2-(3′-Amino-1′-azapropyl)-5-nitropyridine (2.04 g, 16 mmol) and 2,6-bis(methoxycarbonyl)pyridine (2.0 g, 8 mmol) were mixed in a small flask fitted with a condenser and microwaved for 25 min at medium power. The resulted brown oil was left at room temperature overnight after diethyl ether (30 mL) was added, and the pale yellow solid that formed was washed with water (3 × 50 mL), collected, washed with small amounts of ethanol then diethyl ether in turn, and dried in a desiccator (3.7 g, 74%). ^{13}C NMR ($CDCl_3$): δ 43.0, 48.5 (—CH$_2$—), 108.4, 124.2, 131.8, 134.2, 134.4 (pyC), 139.4, 146.6, (pyC$_{tert}$), 161.3 (CO) ppm; ^{1}H NMR ($CDCl_3$): δ 2.5–3.1 (m, 8H, —CH$_2$), 6.5–8.1 (m, 9H, overlapping pyH), 8.83 (br t, 2H, —NHCO—) ppm; IR: 3470 (OH_2), 1608, 1458 (—NHCO), 1545, 1333 (—NO$_2$), 1108, 1037, 823, 763, 688 (py) cm^{-1}; ESI-MS (H_2O): *m/z* 496 (**3**·H$^+$). *Anal.* Calcd for $C_{21}H_{21}N_9O_6{\cdot}2H_2O$: C, 47.5; H, 4.8; N, 23.7. Found: C, 47.5; H, 5.1; N, 23.5.

2,6-Bis[N-(3′-hydroxypropyl)carbamyl]pyridine (4). A solution of 2,6-bis(methoxycarbonyl)pyridine (0.975 g, 5 mmol) in toluene (30 mL) was stirred and heated (60°C), and a solution of 3-amino-1-propanol (0.976 g, 13 mmol) in toluene (11 mL) was added slowly. The mixture was heated to ~100°C using an oil bath and stirred for 1 h, then refluxed for 22 h; some white solid commenced forming after refluxing ~6 h. Heating was discontinued and slow cooling allowed as the mixture was stirred for a further 24 h at room temperature. During this time, white solid continued to form; this was collected, washed in turn with diethyl ether (3 × 5 mL) and a little chloroform, and air dried (1.36 g, 98%). ^{13}C NMR (D_2O): δ 30.5 (—C—CH$_2$—C), 36.2 (—CH$_2$—N), 59.0 (—CH$_2$—O), 124.3, 139.3 (pyCH), 147.7 (pyC$_{tert}$), 165.3 (CO) ppm; ^{1}H NMR (D_2O): δ 1.89 (m, 4H, —C—CH$_2$—C), 3.50 (t, 4H, —CH$_2$—O), 3.69 (t, 4H, —CH$_2$—N), 8.12 (m, 3H, overlapped pyH); IR: 3425 (OH), 3286, 1659, 1543 (NHCO), 1110, 1072, 1034, 941, 848, 748, 679 (py) cm^{-1}. *Anal.* Calcd for $C_{13}H_{19}N_3O_4{\cdot}{}^1/_4H_2O$: C, 54.6; H, 6.7; N, 14.7. Found: C, 54.6; H, 6.2; N, 14.7.

2,6-Bis[N-(5′-hydroxy-3′-azapentyl)carbamyl]pyridine (5). A solution of 2,6-bis(methoxycarbonyl)pyridine (1.953 g, 10 mmol) in toluene (15 mL) was stirred and heated (85°C), and a solution of 2-(2′-aminoethylamino)ethan-1-ol (2.185 g, 21 mmol) in toluene (5 mL) was added slowly. The mixture was heated to ~100°C and stirred for 0.5 h, then refluxed for 24 h; a yellow oily product commenced forming after ~1 h. The heat was turned off and slow cooling allowed as the mixture was stirred for a further 24 h at room temperature. During this time more product formed; this was collected, washed with a little diethyl ether, redissolved in chloroform (20 mL) and extracted with water (3 ×15 mL). The aqueous phase was collected, and the water was removed by rotary evaporation, resulting in a light yellow oily product (2.4 g, 71 %). ^{13}C NMR (D_2O): δ 39.2, 47.7, 50.2 (—CH_2—N), 60.6 (—CH_2—O), 125.1, 139.9 (pyCH), 148.0 (pyC$_{tert}$), 165.8 (CO) ppm; ^{1}H NMR (D_2O): δ 2.88 (t, 4H, —CH_2—N), 2.94 (t, 4H, —CH_2—N), 3.61 (t, 4H, —CH_2—N), 3.78 (t, 4H, —CH_2—O), 8.10 (m, 3H, overlapped pyH) ppm; IR: 3480 (OH_2), 3325 (OH), 1651, 1543 (NHCO), 1126, 1057, 918, 849, 748, 671 (py) cm^{-1}. *Anal.* Calcd for $C_{15}H_{25}N_5O_4\cdot 2H_2O$: C, 47.9; H, 7.8; N, 18.7. Found: C, 47.5; H, 7.8; N, 19.1.

2,6-Bis[N-(2′-oxo-2′,3′-dihydropyrimidin-4′-yl)carbamyl]-pyridine (6). Cytosine (1.14 g, 8 mmol) and 2,6-bis(methoxycarbonyl)pyridine (1.0 g, 4 mmol) were mixed in a small flask fitted with a condenser and microwaved for 20 min at low power. On cooling to room temperature, a glistening white precipitate formed and was collected. Spectroscopy identified this as a mixture of the desired product and some unreacted cytosine. Selective dissolution of the product in hot acetone (~100 mL) and filtration effected separation. The solution was taken to dryness, the product collected, washed with small amounts of diethyl ether, and dried in a desiccator (0.9 g, 65%). ^{13}C NMR (D_2O): δ 93.6, 128.7, 142.6, 144.9 (pyC, pyrimC), 146.0, 148.4 (pyC$_{tert}$, pyrimC$_{tert}$), 159.7, 164.6 (CO) ppm; ^{1}H NMR (D_2O): δ 6.20 (m, 4H, pyrimH), 7.76 (m, 3H, overlapped pyH), 8.50 (br m, 2H, —NHCO—) ppm; IR: 1670 (C=N), 1653, 1455 (NHCO), 1110, 1037, 825, 765 (py) cm^{-1}; ESI-MS (MeOH): *m/z* 363 (**6**·H$^+$). *Anal.* Calcd for $C_{15}H_{11}N_7O_4$: C, 51.0; H, 3.2; N, 27.7. Found: C, 50.8; H, 3.3; N, 27.5.

2,6-Bis[S-(2′-pyridyl)carbothiyl]pyridine (7). A mixture of pyridine-2-thiol (2.18 g, 19.6 mmol) and triethylamine (1.98 g, 19.6 mmol) dissolved in dichloromethane (50 mL) was added dropwise over ~10 min to a solution of 2,6-bis(chlorocarbonyl)-pyridine (2.0 g, 9.8 mmol) in dichloromethane (50 mL) stirring in an icebath. The reaction was rapid and was halted after 20 min, when the insoluble white hydrochloride salt of triethylamine was removed *via* gravity filtration. The resultant filtrate was taken to dryness under reduced pressure to yield a crude orange solid. This was mixed with ethyl acetate (40 mL) and the suspended product collected by vacuum filtration. Washing the solid with several fractions of diethyl ether gave a pale orange solid on drying (3.0 g, 86%). ^{13}C NMR ($CDCl_3$): δ 123.7, 124.6, 130.6, 137.2, 139.2, 146.4 (pyC), 150.6, 152.1 (pyC$_{tert}$), 190.9 (CO) ppm; ^{1}H NMR ($CDCl_3$): δ 7.3–8.1 (m, 9H, overlapped pyH), 8.65 (m, 2H, NpyH) ppm; IR: 3490 (OH_2), 1607, 1459 (CO), 1109, 1041, 822, 765 (py) cm^{-1}; ESI-MS (MeOH): *m/z* 353 (**7**·H$^+$) *Anal.* Calcd for $C_{17}H_{11}N_3O_2S_2\cdot\frac{1}{3}H_2O$: C, 56.8; H, 3.3; N, 11.7. Found: C, 56.9; H, 3.6; N, 11.4.

Metal complex syntheses. ***Aqua(hydrogen 2,6-bis[N-(1′-piperidinylethyl)carbamido]pyridine)dichlorocobalt(III), [Co((1)-H)Cl₂(OH₂)].*** To a solution of **1** (1.63 g, 4 mmol) in methanol (50 mL) was added a solution of $CoCl_2\cdot 6H_2O$ (0.95 g, 4.2 mmol) in water (50 mL). The resulted dark brown solution was stirred and heated (60°C) for 4 h. After stirring at room temperature overnight, HCl (10*M*, 1 mL) was added to the solution, and stirring was continued for ~24 h. The solution was diluted to 1 L with water and sorbed onto a column of Dowex 50W × 2 cation exchange resin. The column was washed with 1*M* HCl to remove any unreacted Co(II)$_{aq}$. The major product was removed by elution with 5*M* HCl, and was rotary evaporated to a small volume then set aside for crystallization. After a few weeks standing, anation yielded a neutral green powder (brown-yellow in aqueous solution) that was collected, washed with ethanol, ether, and dried in a desiccator (1.1 g, 56%). ^{13}C NMR (D_2O): δ 20.4, 22.1 (C—CH_2—C), 33.7, 53.1, 55.2 (—CH_2—N), 124.8, 139.5, 147.1 (pyC), 166.0 (NCO) ppm; ^{1}H NMR (D_2O): δ 1.7–3.8 (m, 28H, —CH_2—), 7.9 (br t, 1H, pyH), 8.18 (br d, 2H, pyH) ppm; IR: 3450 (OH_2), 1675, 1648 (CO), 1541, 1455, 1418 (NCO), 1120, 755, 676 (py) cm^{-1}; UV–Vis (OH_2): λ_{max} (ε_{max}) 518 nm (61 M^{-1} cm^{-1}), 332 (807). *Anal.* Calcd for $C_{21}H_{34}N_5O_3Cl_2Co$: C, 47.1; H, 6.6; N, 13.1%. Found: C, 47.0; H, 7.1; N, 13.0.

Aqua(2,6-bis[N-(2′-(5″-nitropyridine)-1′-azapropyl)carbamido]pyridine)cobalt(III) chloride, [Co((3)-2H)(OH₂)]Cl. A solution of **3** (0.5 g, 4 mmol) in methanol (100 mL) was mixed with $CoCl_2\cdot 6H_2O$ (0.95 g, 4 mmol) in water (100 mL) and pH adjusted to ~7. The brown solution was stirred overnight, and then 10*M* hydrochloric acid (1 mL) was added to the solution, which was stirred at room temperature for ~24 h, then diluted to 1 L with water and sorbed onto a column of Dowex 50W × 2 cation exchange resin. The column was washed with water, then eluted with 1*M* HCl to remove any unreacted Co(II)$_{aq}$. The product was removed with 3*M* HCl and concentrated on a rotary evaporator to a small volume, then set aside for crystallization. After a few weeks, red-brown microcrystals were collected, washed with a small amount of absolute ethanol then diethyl ether in turn, and dried in a desiccator (1.7 g, 71%). IR: 1604 (NH), 1475, 1420, 1365 (NCO), 1505, 1373 (—NO_2), 1154, 1077, 822, 766 (py) cm^{-1}; UV–Vis (OH_2): λ_{max} (ε_{max}) 584 nm (48 M^{-1} cm^{-1}); (1*M* HCl) 508 nm (ε 28), 348 (118); ESI-MS: *m/z* 588 ([ML(OH_2)]$^+$·OH_2). *Anal.* Calcd for $C_{21}H_{19}N_9ClCoO_7\cdot 1\frac{3}{4}H_2O$: C, 39.8; H, 3.6; N, 19.8. Found: C, 40.0; H, 3.7; N, 19.7.

(2,6-Bis[N-(2′-(5′-nitropyridine)-1′-azapropyl)carbamido]-pyridine)copper(II), [Cu((3)-2H)]. Solutions of **3** (0.05 g, 0.09 mmol) in methanol (50 mL) and copper chloride (0.01 g, 0.09 mmol) in water (5 mL) were mixed in a flask, pH adjusted (~7) and then warmed (60°C) for 2 h with stirring, giving a clear blue solution. This was rotary evaporated dry, redissolved in methanol (25 mL), filtered, and stood in a flask (lightly stoppered with cotton wool) in a fume cupboard. After a week some blue crystals were collected by filtration, washed with a small amount of ethanol then diethyl ether in turn, and air dried (0.025 g, 41%). IR: 1590, 1417 (NCO), 1546, 1375 (NO_2), 1151, 1033, 820, 767 (py) cm^{-1}; UV–Vis (OH_2): λ_{max} (ε_{max}) 687 nm (131 M^{-1} cm^{-1}). *Anal.* Calcd for $C_{21}H_{19}CuN_9O_6\cdot 2\frac{1}{2}H_2O$: C, 41.9, H, 4.1, N, 20.9. Found: C, 41.9, H, 4.3, N, 20.8.

(2,6-Bis[N-(3′-hydroxypropyl)carbamido]pyridine)copper(II), [Cu((4)-2H)]. To a stirring solution of **4** (0.143 g, 0.5 mmol) and NaOH (0.052 g, 1.3 mmol) in methanol (10 mL) was slowly added a solution of $Cu(ClO_4)_2\cdot 6H_2O$ (0.185 g, 0.5 mmol) in methanol (2 mL). The immediately formed purple solution was stirred at room temperature for 30 min, and then stood in a sealed jar in a diethyl ether atmosphere. Purple microcrystals formed after several days, and were collected and air dried; these were a sesqui(hydrate hydrogen perchlorate) salt (0.153 g, 59%). IR: 3379 (OH), 1651 (CO), 1574 (NCO), 1142, 1088, 987, 841, 756, 687 (py), 1119, 632 (ClO_4^-) cm^{-1}; UV–Vis (OH_2): λ_{max} (ε_{max}) 576 nm (142 M^{-1} cm^{-1}). *Anal.* Calcd for $C_{13}H_{17}CuN_3O_4 \cdot 1\frac{1}{2}H_2O \cdot 1\frac{1}{2}HClO_4$: C, 30.0; H, 4.2; N, 8.0. Found: C, 29.9; H, 4.5; N, 7.8.

(2,6-Bis[N-(3′-hydroxypropyl)carbamido]pyridine)nickel(II), [Ni(4-2H)]. To a stirring solution of **4** (0.428 g, 1.5 mmol) and NaOH (0.120 g, 3 mmol) in methanol (25 mL) was slowly added a solution of $Ni(ClO_4)_2 \cdot 6H_2O$ (0.549 g, 1.5 mmol) in methanol (5 mL), and the pH was raised to ∼10 with methanolic NaOH solution. The resulting orange-red solution was heated for 2 h at 60°C, and then allowed to cool and filtered to remove some green solid. The orange-red filtrate was rotary evaporated to dryness, washed with diethyl ether (2 × 20 mL), then was redissolved in a small volume of methanol (∼10 mL) and crystals grown in a diethyl ether atmosphere. Some orange crystals formed after several days, and were collected, washed with a little diethyl ether and air dried; they crystallized as a diamagnetic monohydrogen perchlorate salt (0.34 g, 68%). ^{1}H NMR (D_2O): δ 1.92 (m, 4H, CH_2), 3.53 (t, 4H, CH_2), 3.73 (t, 4H, CH_2), 8.14 (m, 3H, pyH); ^{13}C NMR (D_2O): δ 30.5 (CH_2), 36.2 ($-CH_2-N$), 59.0 ($-CH_2-O$), 124.2, 139.2 (pyCH), 147.4 (pyC$_{tert}$), 165.0 (CO) ppm; IR: 3333 (OH), 1651, 1543 (NCO), 1149, 1088, 995, 849, 748, 687 (py) 1119, 630 (ClO_4^-) cm^{-1}; UV–Vis (OH_2): λ_{max} (ε_{max}) 365 nm (72 M^{-1} cm^{-1}). *Anal.* Calcd for $C_{13}H_{17}NiN_3O_4 \cdot HClO_4$: C, 35.6; H, 4.2; N, 9.6. Found: C, 35.9; H, 4.6; N, 9.2.

(2,6-Bis[N-(5′-hydroxy-3′-azapentyl)carbamido]pyridine)-copper(II), [Cu((5)-2H)]. To a stirring solution of **5** (0.190 g, 0.5 mmol) and NaOH (0.050 g, 1.25 mmol) in methanol (10 mL) was slowly added a solution of $Cu(ClO_4)_2 \cdot 6H_2O$ (0.185 g, 0.5 mmol) in methanol (2 mL). The immediately formed blue solution was stirred at room temperature for 30 min, and then stood in a sealed jar in a diethyl ether bath. Blue solid formed after several days, and was collected and air dried; it crystallized as a sesqui(hydrate hydrogen perchlorate) salt (0.155 g, 52%). IR: 3425 (OH), 1651, 1574 (NCO), 1142, 1119, 1088, 841, 764, 687 (py), 1068, 633 (ClO_4^-) cm^{-1}; UV–Vis (OH_2): λ_{max} (ε_{max}) 598 nm (113 M^{-1} cm^{-1}). *Anal.* Calcd for $C_{15}H_{23}CuN_5O_4 \cdot 1\frac{1}{2}H_2O\ 1\frac{1}{2}HClO_4$: C, 31.2; H, 4.8; N, 12.1. Found: C, 31.3; H, 4.5; N, 11.8.

(2,6-Bis[N-(2′-oxo-2′,3′-dihydropyrimidin-4′-yl)carbamido]-pyridine)copper(II), [Cu((6)-2H)]. A solution of **6** (0.35 g, 1 mmol) in water was stirred at room temperature. A solution of $Cu(ClO_4)_2 \cdot 6H_2O$ (0.37 g, 1 mmol) was added. The resulting blue solution was allowed to evaporate slowly over the course of several weeks, yielding light blue crystals that were collected *via* filtration and air dried; it crystallized as a hydrogen perchlorate trihydrate salt (0.28 g, 55%). IR: 1670 (C=N), 1610, 1540, 1445 (NCO), 1110, 825, 765, 690 (py), 1070, 630 (ClO_4^-) cm^{-1}; UV–Vis (OH_2): λ_{max} (ε_{max}) 570 nm (120 M^{-1} cm^{-1}). *Anal.* Calcd for $C_{15}H_9N_7O_4Cu \cdot 3H_2O \cdot HClO_4$: C, 31.5; H, 3.0; N, 17.1. Found: C, 31.7; H, 2.85; N, 16.8.

(2,6-Bis[S-(2′-pyridyl)carbothiyl]pyridine)zinc(II) acetate monohydrate, [Zn(7)](CH$_3$COO)$_2$·H$_2$O. To a stirred ethanolic solution of **7** (0.2 g, 0.57 mmol) was added dropwise an aqueous solution containing zinc acetate monohydrate (0.11 g, 0.57 mmol). During the addition, a thick white precipitate formed, and this was collected by vacuum filtration, washed in turn with water and ethanol portions, and air dried (0.20 g, 83%). ^{13}C NMR (d_6-DMSO): δ 34.4 (CH_3), 115.3, 119.1, 128.0 131.3, 137.3, 138.8 (pyC), 144.3, 147.9 (pyC$_{tert}$), 169.2 (COO), 188.0 (CO) ppm; ^{1}H NMR (d_6-DMSO): δ 2.35 (s, 3H, CH_3), 6.83 (t, 2H, pyH), 7.07 (t, 2H, pyH), 7.24 (d, 2H, pyH), 7.42 (t, 1H, pyH), 7.62 (br s, 2H, pyH), 7.85 (m, 2H, pyH); IR: 1612, 1540, 1451 (CO), 1595 (COO^-), 1060, 820, 765, 680 (py) cm^{-1}. *Anal.* Calcd for $C_{21}H_{17}N_3O_6S_2Zn \cdot H_2O$: C, 56.3; H, 3.4; N, 11.6. Found: C, 56.9; H, 3.6; N, 11.4.

X-ray crystallography. A pale yellow prismatic crystal of **1**, crystallized by diethyl ether diffusion into a methanol solution in a sealed vessel, was mounted and quenched in a cold nitrogen gas stream from an Oxford Cryosystems Cryostream. A Bruker SMART 1000 CCD diffractometer using graphite monochromated MoKα radiation was used for data collection. Cell constants were obtained from a least squares refinement against 1014 reflections located between 5 and 56° 2θ. Data were collected at 150(2) Kelvin with ω scans to 57° 2θ. The data integration and reduction were undertaken with SAINT and XPREP [16], and subsequent computations were carried out with the teXsan [17], WinGX [18], and XTAL [19] graphical user interfaces. The intensities of 161 standard reflections recollected at the end of the experiment did not change significantly during the data collection. A Gaussian absorption correction [16,20] was applied to the data.

The structure was solved in the space group *C*2/c(#15) by direct methods with SIR97 [21], and extended and refined with SHELXL-97 [22]. The nonhydrogen atoms were modeled with anisotropic displacement parameters and a general riding atom model was used for H atoms. Amine and water sites were located and modeled with isotropic displacement parameters. The crystallographic data (excluding structure factors) for the structure are available from the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC671132. Copies may be obtained from CCDC, Union Road, Cambridge CB2 1EZ, UK (deposit@ccdc.cam.ac.uk).

Crystal data. Formula $C_{21}H_{35}N_5O_3$, MW 405.54, monoclinic, space group *C*2/c(#15), *a* 31.825(5) Å, *b* 10.7930(16) Å, *c* 13.972(2) Å, β 114.147(4)°, *V* 4379.3(11) Å^3, D_c 1.230 g cm^{-3}, *Z* 8. Crystal size 0.382 × 0.261 × 0.184 mm^3, color yellow, crystal habit prisms. Temperature 150(2) K, λ(MoKα) 0.71073 Å, μ(MoKα) 0.084 mm^{-1}, T(Gaussian)$_{min,max}$ 0.975, 0.989; $2\theta_{max}$ 56.64°, *hkl* range −41 41, −14 13, −18 18. *N* 21092, N_{ind} 5237 (R_{merge} 0.0372), N_{obs} 3821 ($I > 2\sigma(I)$), N_{var} 278. Residual* $R1(F)$, $wR2(F^2)$ 0.0354, 0.0836. GoF(all) 1.264. Residual extrema −0.203, 0.209 e$^-$Å^{-3} [$^*R1 = \Sigma||F_o|-|F_c||/\Sigma|F_o|$ for $F_o > 2\sigma(F_o)$; $wR2 = (\Sigma w(F_o^2-F_c^2)^2/\Sigma(wF_c^2)^2)^{1/2}$, all reflections, $w = 1/[\sigma^2(F_o^2) + (0.03P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$].

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Microwave-Assisted Synthesis, Metallation, and Duff Formylation of Porphyrins

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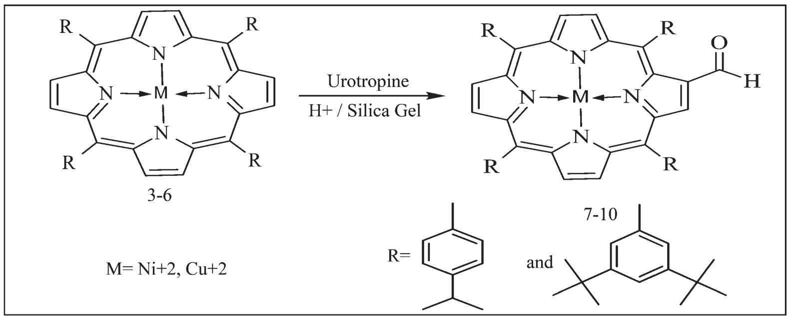

Microwave assisted synthesis, metallation, and β-formylation of porphyrins is described. All synthetic reactions were carried out on inorganic polymer solid support using microwave energy. It is the first documented application of the Duff reaction in the field of porphyrins and metalloporphyrins. The overall process is simple, easy, and environment friendly. FTIR, UV–visible, elemental analysis, ^{1}H NMR, and mass spectrometry were used to characterize the compounds.

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INTRODUCTION

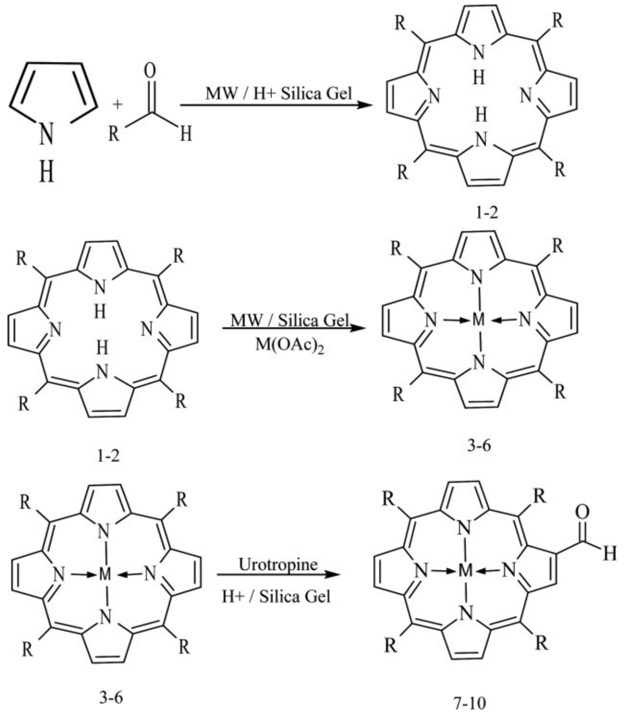
The solid-state synthetic methods have attracted much attention and are widely used for the synthesis of a variety of compounds [1–3]. Microwave assisted organic synthesis has became an increasingly popular technique in academic and industrial laboratories because of certain advantages particularly shorter reaction times, minimum solvent requirement, and ease of purification [4–6]. Application of microwave power in synthesis, metallation, and substitution reactions of porphyrins is not a new concept [7–9]. In the past few years, porphyrin chemistry under microwave heating has been under intense study with significant benefits. Microwave assisted reactions are believed to facilitate the polarization of the substrate thereby increasing the rate of the reactions [10–12]. Herein, we wish to report the use of inorganic polymer solid support for synthesis, metallation, and formylation of porphyrins.

Porphyrins are tetrapyrrolic molecules, the electronic properties of which can be tailored by the variation of peripheral substitution or by central atom [13]. A single porphyrin molecule offers twelve peripheral substitution positions; four meso and eight β-positions. As a result peripheral substitution reactions of porphyrin with different functional groups are highly important reactions. Known functionalization reactions of porphyrins include sulfonation, nitration, halogenation, and Vilsmeier formylation [14,15]. One functional group that allows asymmetric modification and is widely used in porphyrin chemistry is the formyl group [16,17]. Formyl porphyrins are not only prepared synthetically but also occur naturally [18]. Formyl porphyrins are important precursors for the synthesis of multiporphyrin systems [19]. Many methods are available in the literature to formylate the porphyrins at meso and β-positions [20–22]. Both synthetic and natural porphyrins have been formylated by different methods but the most popular is the Vilsmeier reaction [23]. According to the best of our knowledge, there has not been a single example to formylate the porphyrins by Duff reaction over inorganic solid support under microwave radiations.

RESULTS AND DISCUSSION

The classical porphyrin synthesis popularized by Alder, Longo, and Lindsey makes use of toxic and corrosive solvents [24–26]. However, with the advent of microwave radiation as source of energy for chemical reactions, it has been possible to synthesize the porphyrins and metalloporphyrins under solventless conditions

Scheme 1



[27]. The first report of solid-state synthesis of porphyrins under microwave radiations used silica gel, alumina, clay, and montmonillonite. According to that report, the yields were poor and not more than 10% [28].

The experimental technique applied for the organic synthesis described below is based on microwave power. The aim of this work was to investigate the solid phase synthesis, metallation, and formylation of porphyrins. The overall process for the synthesis of formyl porphyrins is rapid, efficient, and eco-friendly (Scheme 1).

Two reaction techniques were used namely (i) Solventless heating with controlled temperature, and (ii) Dry media procedure with controlled temperature. Initially, we used microwave radiation under solventless conditions for the synthesis of Porphyrin **1** and **2** without using any solid support (Table 1). In another experiment, the mixtures of aldehyde and pyrrole were supported on dry neutral silica gel and irradiated with microwave radiation to get Porphyrin **1** and **2** but the yields were not greater than 10%. Alternatively, silica gel was first acidified with propanoic acid, dried in an oven at 50°C for 12 h. This silica gel was used to support the mixtures of reacting aldehyde and pyrrole. Upon microwave irradiation, Porphyrin **1** and **2** were obtained in good yields (Table 2).

Table 1

Solventless synthesis of porphyrins.

Mixture	Porphyrin	% Age yield
Pyrrole and Cuminaldehyde	Porphyrin [1]	22
Pyrrole and 3,5-di-*tert*-butyl benzaldehyde	Porphyrin [2]	20

W = 200 Watts; Time = 6 min; Temperature = 100°C.

Table 2

Solid phase supported porphyrin synthesis.

Mixture over H^+/silica gel	Porphyrin	% Age yield
Pyrrole and Cuminaldehyde	Porphyrin [1]	37
Pyrrole and 3,5-di-*tert*-butyl benzaldehyde	Porphyrin [2]	32

W = 200 Watts; Time = 10 min; Temperature = 100°C.

Metallation of Porphyrin **1** and **2** was achieved when mixture of Porphyrin **1** and **2** and metal acetate adsorbed on neutral silica gel were irradiated under microwave radiation (Table 3). In another experiment, propanoic acid/silica gel containing synthesized crude Porphyrin **1** and **2** were washed thoroughly with the saturated solution of metal acetate in methanol. After drying, silica gel was irradiated with microwave radiation to get Metallo-porphyrin **3**, **4**, **5**, and **6** (Table 3). Hence, after the synthesis of Porphyrin **1** and **2** on acidic silica gel one may use the same silica gel for the synthesis of Metalloporphyrin **3**, **4**, **5**, and **6** without any purification step. One pot synthesis of Metalloporphyrin **3**, **4**, **5**, and **6** was also investigated when mixture of reacting aldehyde, pyrrole, and metal acetate were simultaneously heated under microwave radiations over neutral silica gel. The results were not more than 6% probably because of poor synthesis of Porphyrin **1** and **2** over neutral silica gel. On the other hand, when acidic silica gel was used for one pot synthesis of Metalloporphyrin **3**, **4**, **5**, and **6**, under microwave radiations, metallation failed because of the acidic environment.

Table 3

Metalloporphyrins.

Mixture over silica gel	Metalloporphyrin	% Age yield
$Ni(OAc)_2$ and Porphyrin [1]	Metalloporphyrin [3]	90
$Ni(OAc)_2$ and Porphyrin [2]	Metalloporphyrin [4]	92
$Cu(OAc)_2$ and Porphyrin [1]	Metalloporphyrin [5]	94
$Cu(OAc)_2$ and Porphyrin [2]	Metalloporphyrin [6]	93

W = 250 Watts; Time = 15 min; Temperature = 111°C.

Table 4

Formylporphyrins.

Mixture on H^+/ silica gel	Product	% Age yield
Urotropine and porphyrin [3]	Formyl porphyrin [7]	54
Urotropine and porphyrin [4]	Formyl porphyrin [8]	50
Urotropine and porphyrin [5]	Formyl porphyrin [9]	54
Urotropine and porphyrin [6]	Formyl porphyrin [10]	51

W = 200 Watts; Time = 18 min; Temperature = 111°C.

After successful synthesis (Table 2) and metallation of Porphyrin **1** and **2** (Table 3), we applied the standard Vilsmeier method for the introduction of formyl group onto Metalloporphyrin **3**, **4**, **5**, or **6**. Dry neutral silica gel containing Metalloporphyrin **3**, **4**, **5**, or **6** was mixed with the Vilsmeier salt adsorbed on silica gel. On microwave irradiation, demetallattion was exclusively observed. When all attempts to formylate the Metalloporphyrin **3**, **4**, **5**, and **6** over silica gel solid support under microwave radiations were failed, we applied Duff reaction. Duff reaction require strongly acidic conditions whereas under such conditions metalloporphyrins demetallate [29]. To overcome this problem, we used acidified silica gel instead of acid itself under solventless conditions to get formyl porphyrin **7**, **8**, **9**, and **10** (Table 4).

UV–visible spectra of Porphyrin **1** and **2** showed characteristic Soret and Q bands. On metallation, two visible bands appeared along with a Soret band. ^{1}H NMR spectra of free-base Porphyrin **1** and **2** showed a singlet in the high field region for imino-protons that disappeared on metallation. Formyl porphyrin **7**, **8**, **9**, and **10** showed two clear singlets at downfield region; one for formyl proton and second for β-pyrrolic proton immediately next to formyl group. FTIR of formyl porphyrin **7**, **8**, **9**, and **10** showed clear sharp peak around 1660 cm^{-1} for C=O group.

EXPERIMENTAL

Melting points were determined on a Kofler micromelting point apparatus without correction. IR spectra were recorded on a Nicolet Impact-410 FTIR spectrophotometer in KBr. ^{1}H NMR spectra were measured in $CDCl_3$ using TMS as internal standard with a Bruker 500 MHz spectrometer. MS spectra were taken on a KRATOS-AEI-MS50 spectrometer. Elemental analyses were performed on a PE-2400 CHN elemental analyzer. UV/Vis measurements were performed with a Shimadzu Multispec-1501. All the reactions were performed in the commercial microwave oven having maximum output power 500 Watts. Reagents from Merck and Aldrich Chemical were used. Anhydrous Silica gel 60–100 (0.063–0.2 mm) was used as solid support after dehydration under microwave irradiation for 4 min.

General procedures

(i) Solventless heating with controlled temperature. The reagents were mixed together in a low boiling point solvent at room temperature. Solvent was removed under vacuum. The reaction mixture was heated under microwave radiation in a quartz flask having an outer solvent circulating jacket for the control of temperature. The sample was cooled in an ice bath. TLC was used to monitor the reaction progress. The reaction product was extracted with solvent; the extract was filtered, dried over anhydrous sodium sulfate, and then the solvent was removed. The product was purified by column chromatography.

(ii) Dry media procedure with controlled temperature. The reagents were dissolved in a low boiling point solvent at room temperature; anhydrous microwave transparent inorganic solid support (silica gel) was added and the solvent was removed under vacuum. The adsorbed reaction mixture was introduced in an open quartz flask having an outer solvent circulating jacket for the control of temperature. It was subjected to microwave irradiation. The reaction mixture was cooled in an ice bath. TLC was used to monitor the reaction progress. The reaction product was purified by column chromatography. For column chromatography, the reaction mixture was applied as such onto silica column and eluted with mixture of solvents. Solvents were removed under vacuum to get product.

Preparation of propanoic acid/silica. Silica gel (15 g, Merck, 60–100 mesh size) was mixed well with 5 g of propanoic acid in a mortar. The resultant mixture was dried in an oven at 60°C for 12 h. Acidic silica gel was obtained as white powder.

Preparation of H_2SO_4/silica gel. H_2SO_4 (5 g, 95%) and silica gel (15 g, Merck, 60–100 mesh size) were mixed in a mortar. The resultant mixture was dried in an oven at 90°C for 12 h. Acidic silica gel was obtained as white powder.

Porphyrin [1] (1A). A mixture of pyrrole (0.04 mole, 2.68 g) and cuminaldehyde (0.04 mole, 5.93 g) was subjected to microwave irradiation according to solventless heating with controlled temperature method (i) (Table 1). After cooling, the reaction mixture was applied onto silica column and eluted with chloroform: *n*-hexane (1:2). The fast moving band was collected and the solvent was evaporated to get Porphyrin [1] (22%). mp > 350°C; Anal. Calcd. for $C_{56}H_{54}N_4$: C, 85.89; H, 6.96; N, 7.16. Found: C, 85.79; H, 6.93; N, 7.18. IR(KBr): ν_{max} 3315 (N—H), 2956, 1470, 1348, 1186, 1053, 966, 802, 735 cm^{-1}; UV($CHCl_3$) λ_{max} 420, 450, 515, 555, 670 nm; ^{1}H NMR ($CDCl_3$): δ −2.74 (bs, 2NH), 1.53 (d, J = 6.9 Hz, 8CH$_3$), 3.25 (sep, J = 6.9 Hz, 4CH), 7.58 (d, J = 7.8 Hz, 4m-Ph2H), 8.12 (d, J = 7.8, 4o-Ph2H), 8.84 (s, β-pyrrolic H 2, 3, 7, 8, 12, 13, 17, 18). MS (*m*/*z*, %): 782.3 (M$^+$, 100%), 780.4 (2.14%), 391.3 (7.74%).

Porphyrin [1] (1B). A mixture of pyrrole (0.04 mole, 2.68 g) and cuminaldehyde (0.04 mole, 5.93 g) was supported on propanoic acid/silica gel (5 g) and subjected to microwave irradiation according to dry media procedure (ii) (Table 2). After cooling, the reaction mixture was applied as such onto silica column and eluted with chloroform: *n*-hexane (1:2). The fast moving band was collected and the solvent was evaporated to get Porphyrin [1] (37%).

Porphyrin [2] (2A). A mixture of pyrrole (0.04 mole, 2.68 g) and 3,5-di-*tert*-butylbenzaldehyde (0.04 mole, 8.73 g) was subjected to microwave irradiation according to solventless heating with controlled temperature method (i) (Table 1). After cooling, the reaction mixture was applied onto silica column and eluted with chloroform: *n*-hexane (1:2). The fast moving band was collected and the solvent was evaporated to get Porphyrin [2] (20%). mp > 350°C; Anal. Calcd. for $C_{76}H_{94}N_4$: C, 85.82; H, 8.90; N, 5.20. Found: C, 85.66; H, 8.87; N, 5.23. IR(KBr):ν_{max} 3320 (N—H), 3060, 2960, 2900, 2860, 1600, 1470, 1420 cm^{-1}; UV($CHCl_3$) λ_{max} 420, 520, 555, 590, 645 nm; ^1H NMR ($CDCl_3$): δ −2.67 (bs, 2NH), 1.51 (s, 8t-Bu), 7.74 (t, *J* = 1.7 Hz, 4p-PhH), 8.07 (d, *J* = 1.7 Hz, 8o-PhH), 8.87 (s, β-pyrrolic H 2, 3, 7, 8, 12, 13, 17, 18). MS (*m*/*z*, %): 1063 (M^+, 100%), 189 (5%).

Porphyrin [2] (2B). A mixture of pyrrole (0.04 mole, 2.68 g) and 3,5-di-*tert*-butylbenzaldehyde (0.04 mole, 8.73 g) was supported on propanoic acid/silica gel (5 g) and subjected to microwave irradiation according to dry media procedure (ii) (Table 2). After cooling, the reaction mixture was applied as such onto silica column and eluted with chloroform: *n*-hexane (1:2). The fast moving band was collected and the solvent was evaporated to get Porphyrin [2] (32%).

Metalloporphyrin [3] (3A). A mixture of Porphyrin [1] (0.04 mmole, 31.32 mg) and nickel acetate (1 mmole, 176.78 mg) was supported on propanoic acid/silica gel (5 g) and subjected to microwave irradiation according to dry media procedure (ii) (Table 3). After cooling, the reaction mixture was applied as such onto silica column and eluted with chloroform: petroleum ether; b.p 60–90°C (1:3). The fast moving band was collected, and the solvent was evaporated to get Metalloporphyrin [3] (90%). mp > 350°C; Anal. Calcd. for $C_{56}H_{52}N_4Ni$: C, 80.10; H, 6.25; N, 6.67. Found: C, 80.05; H, 6.28; N, 6.68. IR(KBr):ν_{max} 2956, 1654, 1660, 1351, 1261, 1055, 1004, 812 cm^{-1}; UV($CHCl_3$) λ_{max} 420, 445, 530 nm. ^1H NMR ($CDCl_3$): δ 1.48 (d, *J* = 6.9 Hz, $8CH_3$), 3.18 (sep, *J* = 6.9 Hz, 4CH), 7.50 (d, *J* = 7.9 Hz, 4m-Ph2H), 7.90 (d, *J* = 7.9 Hz, 4o-Ph2H), 8.74 (s, β-pyrrolic H 2, 3, 7, 8, 12, 13, 17, 18). MS (*m*/*z*, %): 839 (M^+, 75%) 837.7 (100%), 55.1 (16.79%).

Metalloporphyrin [3] (3B). Silica gel obtained directly from Experiment-1B having adsorbed crude Porphyrin [1] was thoroughly washed with 50 mL of a saturated solution of nickel acetate in methanol. Silica gel was dried and heated under microwave according dry media procedure (ii) (Table 3). After cooling, the reaction mixture was applied as such onto silica column and eluted with chloroform: petroleum ether; b.p 60–90°C (1:3). The fast moving band was collected, and the solvent was evaporated to get Metalloporphyrin [3] (90%).

Metalloporphyrin [4] (3C). A mixture of Porphyrin [2] (0.04 mmole, 42.54 mg) and nickel acetate (1 mmole, 176.78 mg) was supported on propanoic acid/silica gel (5 g) and subjected to microwave irradiation according to dry media procedure (ii) (Table 3). After cooling, the reaction mixture was applied as such onto silica column and eluted with chloroform: petroleum ether; b.p 60–90°C (1:3). The fast moving band was collected, and the solvent was evaporated to get Metalloporphyrin [4] (92%). mp >350°C; Anal. Calcd. for $C_{76}H_{92}N_4Ni$: C, 81.48; H, 8.28; N, 5.00. Found: C, 81.52; H, 8.30; N, 5.01. IR(KBr):ν_{max} 3060, 2960, 2900, 2860, 1600, 1480, 1440, 1400 cm^{-1}; UV($CHCl_3$) λ_{max} 415, 530 nm. ^1H NMR ($CDCl_3$): δ 1.46 (s, 8t-Bu), 7.70 (t, *J* = 2.0 Hz, 4p-PhH), 7.86 (d, *J* = 2.0 Hz, 8o-PhH), 8.79 (s, β-pyrrolic H 2, 3, 7, 8, 12, 13, 17, 18). MS (*m*/*z*, %) 1118 (M^+, 100%), 57 (84%).

Metalloporphyrin [4] (3D). Silica gel obtained directly from Experiment-2B having adsorbed crude Porphyrin [2] was thoroughly washed with 50 mL of saturated solution of nickel acetate in methanol. Silica gel was dried and heated under microwave according dry media procedure (ii) (Table 3). After cooling, the reaction mixture was applied as such onto silica column and eluted with chloroform: petroleum ether; b.p 60–90°C (1:3). The fast moving band was collected, and the solvent was evaporated to get Metalloporphyrin [4] (92%).

Metalloporphyrin [5] (3E). Experiment-3A procedure was repeated with copper acetate (1 mmole, 181.63 mg) to get Metalloporphyrin [5] (Table 3) (94%). mp > 350°C; Anal. Calcd. for $C_{56}H_{52}CuN_4$: C, 79.62; H, 6.21; N, 6.63. Found: C, 79.50; H, 6.23; N, 6.65. IR(KBr):ν_{max} 2922, 1670, 1460, 1342, 1000, 802, 722 cm^{-1}; UV($CHCl_3$) λ_{max} 415, 540 nm. MS (*m*/*z*, %): 844.6 (M^+, 15.85%), 842.6 (72%), 837.6 (100%).

Metalloporphyrin [5] (3F). Silica gel obtained directly from experiment 1-B having crude synthesized Porphyrin 1 was washed thoroughly with 50 mL of a saturated solution of copper acetate in methanol. After drying, silica gel was irradiated with microwave (Table 3). Pure Metalloporphyrin [5] was obtained by column chromatography using chloroform: petroleum ether; b.p 60–90°C (1:3) as mobile phase. The fast moving band was collected and the solvent was evaporated to get pure Metalloporphyrin [5] (94%).

Metalloporphyrin [6] (3G). Experiment-3C procedure was repeated with copper acetate (1 mmole, 181.63 mg) to get Metalloporphyrin [6] (Table 3) (93%). mp > 350°C; Anal. Calcd. for $C_{76}H_{92}CuN_4$: C, 81.13; H, 8.24; N, 4.98. Found: C, 81.20; H, 8.22; N, 5.0. IR.(KBr)ν_{max} 3060, 2980, 2940, 2860, 1600, 1520, 1480, 1440, 1400 cm^{-1}; UV($CHCl_3$) λ_{max} 420, 540 nm. MS (*m*/*z*, %) 1123 (M^+, 23%), 57 (34%).

Metalloporphyrin [6] (3H). Silica gel obtained directly from the experiment 2-B having crude synthesized Porphyrin 2 was washed thoroughly with 50 mL of a saturated solution of copper acetate in methanol. After drying, silica gel was irradiated with microwave (Table 3). Purification was done by column chromatography using chloroform: petroleum ether; b.p 60–90°C (1:3) as mobile phase. The fast moving band was collected, and the solvent was evaporated to get pure Metalloporphyrin [6] (93%).

Formyl porphyrin [7] (4A). Urotropine (1 mmole, 140.19 mg) and Metalloporphyrin [3] (0.04 mmole, 33.59 mg) were powder together in an agate mortar. These were doped on H_2SO_4/silica gel (15 g) and heated under microwave according to dry media procedure (ii) (Table 4). After cooling, 50 mL of water was added and reaction mixture was stirred at room temperature for 30 min. Water was removed by filtration and residue was dried in vacuum desiccator. It was applied onto silica column and eluted with chloroform: petroleum ether; b.p 60–90°C (2:1). The fast moving band was collected and the solvent was evaporated to get 2-formyl-5,10,15,20-tetrakis(4′-isopropylphenyl)porphyrinatonickel(II) [7] (54%). mp > 350°C; Anal.Calcd. for $C_{57}H_{52}N_4NiO$: C, 78.90; H, 6.04; N, 6.46. Found: C, 78.80; H, 6.03; N, 6.50. IR(KBr)ν_{max} 2956, 2923, 1669 (C=O), 1545, 1507, 1459, 1351, 1056, 1001, 937, 813, 797, 719 cm^{-1}; UV($CHCl_3$)λ_{max} 435, 545, 585 nm. ^1H NMR($CDCl_3$): δ 1.48 (d, *J* = 6.7 Hz, $8CH_3$), 3.18 (sep, *J* = 6.7 Hz, 4CH), 7.52 (d, *J* = 6.9 Hz, 4m-Ph2H), 7.89 (d, *J* = 6.9 Hz, 4o-Ph2H), 8.72 (m, β-pyrrolic H 7, 8, 12, 13, 17, 18), 9.20 (s, CH 3), 9.34 (s, CHO). MS (*m*/*z*, %), 867 (M^+, 1%), 413 (100%), 277 (24%).

Formyl porphyrin [8] (4B). Urotropine (1 mmole, 140.19 mg) and Metalloporphyrin [4] (0.04 mmole, 44.81 mg) were treated according to the procedure describe in experiment (4A) to get 2-formyl-5,10,15,20-tetrakis(3′,5′-di-*tert*-butylphenyl)porphyrinatonickel(II) [8] (50%). mp > 350°C; Anal.Calcd. for $C_{77}H_{92}N_4NiO$: C, 80.54; H, 8.08; N, 4.88. Found: C, 80.45; H, 8.09; N, 4.89. IR(KBr)ν_{max} 3080, 2970, 2920, 2880, 1680 (C=O), 1600, 1480, 1440, 1400, 1370, 1360 cm^{-1}; UV ($CHCl_3$)λ_{max} 435, 545, 585 nm. ^1H NMR($CDCl_3$): δ 1.45 (m, 8t-Bu), 7.71 (m, C_5 p-PhH, C_{10} p-PhH, C_{15} p-PhH); 7.74 (t, J = 1.8 Hz, C_{20} p-PhH), 7.79 (d, J = 1.8 Hz, C_5 o-Ph2H, 6H), 7.82 (d, J = 1.8 Hz, C_{10} o-Ph2H), 7.82 (d, J = 1.8 Hz, C_{15} o-Ph2H), 7.88 (d, J = 1.8 Hz, C_{20} o-Ph2H), 8.77 (m, β-pyrrolic H 7, 8, 12, 13, 17, 18), 9.03 (s, CH 3), 9.34 (s, CHO). MS (*m*/*z*, %) 1147 (M^+, 1%), 235 (23%), 193 (18%), 189 (25%), 57 (100%).

Formyl porphyrin [9] (4C). Experiment (4A) procedure was repeated by using Metalloporphyrin [5] (0.04 mmole) to get 2-formyl-5, 10, 15, 20-tetrakis(4′-isopropylphenyl)porphyrinatocopper(II) [9] (54%) (Table 4). mp > 350°C; Anal.-Calcd. for $C_{57}H_{52}CuN_4O$: C, 78.46; H, 6.01; N, 6.42. Found: C, 78.51; H, 6.03; N, 6.44. IR (KBr) ν_{max} 2957, 2923, 1670 (C=O), 1559, 1540, 1507, 1458, 1342, 1055, 1000, 798, 721 cm^{-1};UV($CHCl_3$)λ_{max} 430, 550, 595 nm. MS (*m*/*z*, %) 872 (M^+, 3%), 349 (100%), 236 (71%).

Formyl porphyrin [10] (4D). Experiment (4B) procedure was repeated by using Metalloporphyrin [6] to get 2-formyl-5,10,15,20-tetrakis(3′,5′-di-*tert*-butylphenyl)porphyrinatocopper (II) [10] (51%) (Table 4). mp > 350°C; Anal.Calcd. for $C_{77}H_{92}CuN_4O$: C, 80.20; H, 8.04; N, 4.86. Found: C, 80.18; H, 8.04; N, 4.85. IR(KBr)ν_{max} 2961, 1671 (C=O), 1591, 1560, 1540, 1362, 1345, 1288 cm^{-1}. UV($CHCl_3$) λ_{max} 430, 550, 595 nm. MS (*m*/*z*, %) 1154 (M^+, 3%), 349 (100%), 236 (71%), 189 (24%).

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Regioselective Synthesis and Bioactivity of New 5-Amino-6-arylamino-pyrazolo[3,4-*d*]-pyrimidin-4(5*H*)-one Derivatives

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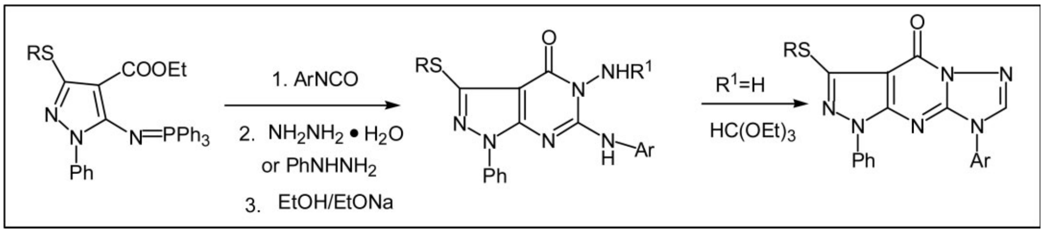

A novel approach to regioselective synthesis of new 5-amino-6-arylamino-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one **5** derivatives *via* a tandem aza-wittig and annulation reaction of iminophosphorance **2**, aromatic isocyanates and hydrazine in 69.6–94.7% isolated yields is reported. The compound **5** reacted with triethyl orthoformate to give compound **6** in good yield (65.8–82.8%). Their structure was clearly confirmed by spectroscopy data (IR, ^{1}H NMR, MS, elemental analysis) and the results of preliminary bioassay indicated that compounds **5** and **6** possess high antifungal activity against *Botrytis cinerea Pers* and *Sclerotinia sclerotiorum*, and compound **5h** showed 100, 96.4, and 90.2% inhibitory rate to *Botrytis cinerea Pers*, *Pyricularia oryzae,* and *Sclerotinia sclerotiorum* at the concentration of 50 mg/L. The antifungal activities of compound **6** were generally higher than those of compound **5**.

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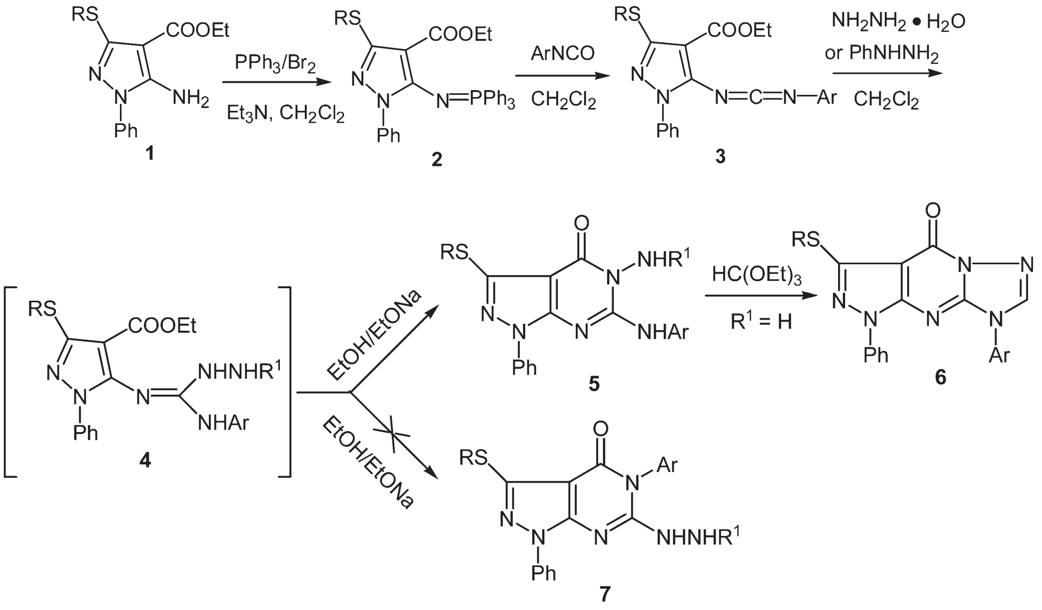
INTRODUCTION

Pyrazolopyrimidines and related fused heterocycles have been the focus of great interest over many years due to the fact that many compounds containing a fused pyrimidinone ring have remarkable biological and chemotherapeutic properties [1]. Pyrazolo[3,4-*d*]-pyrimidines are often employed as mGluR1 antagonists [2], antimicrobial and antifungal or antitumor agents [3], various animal enzyme inhibitors [4], and agrochemicals [5]. Moreover, triazole and its fused heterocycles form part of an extensive investigation of biologically active compounds, such as substituted triazole derivatives [6], triazolo[1,5-*a*]pyrimidine derivatives [7], and their derivatives [8]. In our previous research [5a–d], we reported a reaction of ethyl 3-alkylthio-1-phenyl-5-triphenylphosphoranoimino-1*H*-pyrazole-4-carboxylate (abbreviation iminophosphorane) **2** with isocycanates and alkylamine to give 6-alkylamino-5-aryl-pyrazolo[3,4-*d*]pyrimidin-4-one derivatives, the nitrogen atom of which were from isocyanates. Those compounds showed satisfactory antifungicidal activities. Inspired by the manifold biological activities of pyrazolo[3,4-*d*]pyrimidines and pyrazolotriazolopyrimidine derivatives, we set out to utilize hydrazine to produce new compounds of potential biochemical interest. However, we obtained 5-amino-6-arylamino-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-ones **5** instead of 6-hydrazino-5-aryl-pyrazolo[3,4-*d*]pyrimidin-4-one **7** derivatives. Here, we report a novel facile regioselective synthesis of a new series of 5-amino-6-arylamino-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-ones **5**, having nitrogen atoms from hydrazine, and 2*H*-pyrazolo[3,4-*d*][1,2,4]triazolo[1,5-*a*] pyrimidin-4-one derivatives **6** and their results of preliminary bioassay against *Botrytis cinerea Pers*, *Pyricularia oryzae*, *Gibberella zeae*, and *Sclerotinia sclerotiorum.*

RESULTS AND DISCUSSION

Iminophosphoranes **2** [5a–c] reacted with isocyanates to give the key intermediates carbodiimide **3**. Treatment of **3** with hydrazines at room temperature gave the intermediate guanidines **4** [5a], which, in the presence of NaOEt, reacted to give the crude target compound **5**. After evaporation of part of the solvent, the crude products were collected by filtration. After recrystallization from DMF/petroleum ether or column chromatography on a silica gel, white crystals were obtained in 69.6–94.7% yields (Scheme 1, Table 1). The spectra data

Scheme 1



identified the white crystal as 3-alkylthio-5-amino-6-arylamino-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-ones **5** instead of the isomer 3-alkylthio-6-hydrazine-5-aryl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-ones **7**. In this reaction, a variety of substituents can be tolerated in Ar group, such as electron-donating group (*e.g*., Me), or electron-withdrawing group (*e.g*., F, Cl). R^1 also could be C_6H_5 or H. In the absence of sodium ethoxide, the compound **5** would be obtained with very low yields if the quantity of hydrazine was equal to iminophosphoranes **2**. In contrast, in the presence of a large excess of hydrazine the reaction took place smoothly and the compound **5** was obtained in satisfactory yields even in the absence of NaOEt. On refluxing Compound **5** with triethyl orthoformate, compound **6** was obtained in 65.8–82.8% yields in the present *p*-TsOH.

The structures of compounds **5** and **6** were deduced from their spectra data (^{1}H NMR, IR, EI-MS, and elementary analysis). ^{1}H NMR spectra of compound **5** showed the signal of NH_2 at δ 5.55–5.74 as singlet and compound **6** showed the signal of triazole at δ 9.23–9.34 as singlet [8b]. A combination of chemical shift and couplings allowed the complete and unambiguous assignment of all signals and demonstrated that the major products correspond to structure. The IR spectra of **5** exhibited N—H, C=O, and C=N absorptions. The EI-MS spectra of **5** and **6** showed the molecular ion peak. All the fragmentation ions were consistent with their structures and could be clearly assigned. In addition, the structures of compound **6** further verified the proposed structure of compound **5**. The results of the elementary analysis are within the acceptable range.

Table 1

Yields of compounds **5** and **6**.

Compounds	R	R_1	Ar	Yield of **5** (%)	Yield of **6** (%)
5a, 6a	Me	H	C_6H_5	75.8	71.6
5b, 6b	Me	H	*p*-MeC_6H_4	84.6	73.2
5c, 6c	Me	H	*o*-ClC_6H_4	69.6	82.8
5d, 6d	Me	H	*o*-FC_6H_4	92.5	77.6
5e, 6e	$PhCH_2$	H	C_6H_5	72.3	69.0
5f, 6f	$PhCH_2$	H	*p*-MeC_6H_4	94.7	65.8
5g, 6g	$PhCH_2$	H	*o*-ClC_6H_4	73.8	76.3
5h	Me	H	*p*-ClC_6H_4	77.0	
5i	Me	C_6H_5	*p*-MeC_6H_4	83.0	
5j	Me	C_6H_5	*m*-ClC_6H_4	86.2	
5k	$PhCH_2$	C_6H_5	*p*-MeC_6H_4	74.2	

Isolated yields based on iminophosphoranes **2**.

Table 2

Antifungal activity of compounds **5**, **6**, and thiabendazole (50 mg/L, inhibitory rate %).

	Relative inhibition (%)			
Compounds	*Botrytis*	*Pyricularia*	*Gibberella*	*Sclerotinia*
5a/6a	13.2/98.6	35.7/80.0	14.3/65.8	80.2/100.0
5b/6b	94.7/82.2	57.1/28.6	40.0/51.4	86.5/96.4
5c/6c	73.3/62.9	0.0/50.0	40.0/23.7	82.1/81.0
5d/6d	93.0/60.0	62.5/5.2	51.2/25.7	97.1/50.0
5e/6e	60.5/73.3	50.0/28.6	28.6/60.0	83.5/92.9
5f/6f	89.5/91.8	85.7/14.3	37.1/48.6	78.5/89.3
5g/6g	42.2/77.8	0.0/28.6	37.1/68.7	60.7/92.9
5h	100.0	96.4	85.7	90.2
5i	26.3	21.4	22.9	81.9
5j	7.9	50.0	5.7	79.3
5k	21.0	28.6	5.7	76.2
Thiabendazole	100	87	100	100

Biological activities. The fungi were obtained from the College of Plant Protect, Central China Agriculture University, China. The antifungal activities of all compounds **5**, **6**, and 2-(4′-thiazoly)-benzimidazole (commercial name: thiabendazole), a commercially available fungicide, were evaluated *in vitro* according to the reported method [9], as shown in Table 2 by contrasting to distilled water. The results showed that all compounds **5** and **6** possessed good inhibition effects against *Sclerotinia sclerotiorum* (inhibition rates 60.7–97.1% and 81.0–100%). Comparing compounds **5** with **6**, it showed that the antifungal activities of compound **6** were generally higher than those of compound **5**. Some of the compounds **5** and **6** exhibited good inhibitory rates against *Botrytis cinerea Pers* and *Pyricularia oryzae*. For example, the inhibitory rates of compounds **6a**, **5b**, **6b**, **5d**, **5f**, and **6f** were 91.8, 94.7, 82.2, 93.0, 89.5, and 91.8% to *Botrytis cinerea Pers* and that of **5f** was 85.7% to *Pyricularia oryzae* at 50 mg/L. It was also interesting to note that compound **5h** showed high antifungal activities to all of *Botrytis cinerea Pers*, *Pyricularia oryzae*, *Gibberella zeae*, and *Sclerotinia sclerotiorum.*

EXPERIMENTAL

Melting points were determined using a WRS-1B Digital melting point apparatus. MS was measured on a Finnigan Trace Mass 2000 Spectrometer at 70 eV. IR was recorded on an Avatar 360 Spectrometer as KBr pellets with absorption given in cm^{-1}. ^{1}H NMR spectra were obtained using a Varian Mercury 400 (or 300) Spectrometer with TMS as the internal reference and DMSO-d_6 or $CDCl_3$ as the solvent. Elementary analysis was taken on a Vario EL III elementary analysis instrument. All of the solvents and materials were of reagent grade and purified as required. Ethyl 5-amino-3-alkylthio-1-phenyl-1*H*-pyrazole-4-carboxylate **1** [10], iminophosphoranes **2** [5a–c] were prepared according to literature.

General procedure for the preparation of 3-alkylthio-5-amino-6-arylamino-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-ones (5). To a solution of iminophosphorane **2** (2 mmol) in dry methylene dichloride (20 mL) aryl isocyanate (2 mmol) was added under nitrogen atmosphere at room temperature. After the reaction mixture was stirred for 1.5 h, 0.118 g (2.0 mmol, 85%) of hydrazine hydrate or 0.227 g (2.0 mmol) phenylhydrazine was added, and the resulting mixture was stirred for an additional 30 min. Then the solvent was removed under reduced pressure, and 25 mL anhydrous ethanol and 1.5 mL of sodium ethoxide (3 mol/L) in ethanol were added to the mixture. After 3 h of stirring at room temperature, the solution was concentrated under reduced pressure and successively cooled. The crude product was collected by filtration. After recrystallization from DMF/petroleum ether or column chromatography on silica gel, white crystal was obtained.

5-Amino-3-methylthio-1-phenyl-6-phenylamino-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (5a). White crystals, mp 236.2–238.1°C; IR (KBr) ν (cm^{-1}): 3336, 3267, 1692, 1596, 1554, 909, 770, 743, 688; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.60 (s, 3H, SCH_3), 5.57 (br s, 2H, NH_2), 7.11 (t, 1H, $J = 7.2$ Hz, Ph), 7.25 (t, 1H, $J = 7.2$ Hz, Ph), 7.36 (t, 2H, $J = 7.6$ Hz, Ph), 7.46 (d, 2H, $J = 7.6$ Hz, Ph), 7.73 (d, 2H, $J = 7.5$ Hz, Ph), 8.03 (d, 2H, $J = 7.8$ Hz, Ph), 9.67 (s, 1H, *NH*Ph); EI-MS (70 eV, *m*/*z*, rel. int.) 365 (M + 1, 49), 364 (M^+, 81); *Anal.* Calcd. for $C_{18}H_{16}N_6OS$: C, 59.32; H, 4.43; N, 23.06; Found: C, 59.1; H, 4.37; N, 22.96.

5-Amino-3-methylthio-1-phenyl-6-tolylamino-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (5b). White crystals, mp 235.3–238.6°C; IR (KBr) ν (cm^{-1}): 3333, 3261, 1691, 1597, 1555, 751, 690; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.30 (s, 3H, *p*-$CH_3C_6H_4$), 2.60 (s, 3H, SCH_3), 5.55 (s, 2H, NH_2), 6.85–7.68 (m, 7H, Ar), 8.03 (d, 2H, $J = 7.5$ Hz, Ar), 9.57 (s, 1H, NH); EI-MS (70 eV, *m*/*z*, rel. int.) 379 (M + 1, 31), 378 (M^+,100); *Anal.* Calcd. for $C_{19}H_{18}N_6OS$: C, 60.30; H, 4.79; N, 22.21; Found: C, 59.99; H, 4.61; N, 22.45.

5-Amino-3-methylthio-1-phenyl-6-(o-chlorophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (5c). White crystals, mp 248.1–248.8°C; IR (KBr) ν (cm^{-1}): 3328, 3189, 1688, 1598, 1582, 1562, 1543, 1398, 752, 682; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.61 (s, 3H, SCH_3), 5.74 (s, 2H, NH_2), 7.20 (t, 1H, *J* = 7.6 Hz, Ar), 7.30 (t, 1H, *J* = 7.6 Hz, Ar), 7.43–7.50 (m, 3H, Ar), 7.58 (d, 1H, *J* = 8.0 Hz, Ar), 8.00 (d, 2H, *J* = 7.6 Hz, Ar), 8.30 (d, 1H, *J* = 8.0 Hz, Ar), 9.85 (br s, 1H, NH); EI-MS (70 eV, *m*/*z*, rel. int.) 399 (M + 1, 41), 398 (M^+, 66); *Anal.* Calcd. for $C_{18}H_{15}ClN_6OS$: C, 54.20; H, 3.79; N, 21.07; Found: C, 54.32; H, 3.76; N, 21.22.

5-Amino-3-methylthio-1-phenyl-6-(o-fluorophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (5d). White crystal, mp 238–239°C; IR (KBr) ν (cm^{-1}): 3352, 3314, 3266, 1721, 1621, 1600, 1542 (Ar), 1455, 922, 768; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.61(s, 3H, SCH_3), 5.65 (s, 2H, NH_2), 7.25–7.46 (m, 6H, Ar), 7.98 (d, 3H, *J* = 8.4 Hz, Ar), 9.61(s, 1H, *o*-FC_6H_4*NH*); EI-MS (70 eV, *m*/*z*, rel. int.): 384 (M + 2, 13), 383 (M + 1, 49), 382 (M^+, 89); *Anal.* Calcd. for $C_{18}H_{15}FN_6OS$: C, 56.53; H, 3.95; N, 21.98; Found: C, 56.39; H, 3.92; N, 22.03.

5-Amino-3-benzylthio-1-phenyl-6-phenylamino-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (5e). White crystals, mp 226.0–227.8°C, IR (KBr) ν (cm^{-1}): 3319, 1684, 1596, 1554, 927, 759, 689,501; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.47 (s, 2H, *CH_2*Ph), 5.58 (s, 2H, NH_2), 7.12 (t, 1H, *J* = 7.2 Hz, Ph), 7.20–7.50 (m, 10H, Ph), 7.73 (d, 2H, *J* = 8.1 Hz), 8.04 (d, 2H, *J* = 8.4 Hz), 9.69 (s, 1H, Ph*NH*); EI-MS (70 eV, *m*/*z*, rel. int.): 442 (M + 2, 2), 441 (M^+, 7); *Anal.* Calcd. for $C_{24}H_{20}N_6OS$: C, 65.44; H, 4.58; N, 19.08; Found: C, 65.52; H, 4.43; N, 19.07.

5-Amino-3-benzylthio-1-phenyl-6-(p-tolylamino)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (5f). White crystals, mp 250.0–250.6°C; IR (KBr) ν (cm^{-1}): 3314, 3255, 1689, 1596, 1556, 770, 692; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.29 (s, 3H, CH_3), 4.46 (s, 2H, $PhCH_2$), 5.56 (s, 2H, NH_2), 6.83–6.91 (m, 1H, Ar), 7.16 (d, 2H, *J* = 7.5 Hz, Ar) 7.14–7.49 (m, 7H, Ar), 7.59 (d, 2H, *J* = 7.8 Hz, Ar), 8.04 (d, 2H, *J* = 8.1 Hz, Ar), 9.54 (br s, 1H, NH); EI-MS (70 eV, *m*/*z*, rel. int.) 454 (M^+, 26); *Anal.* Calcd. for $C_{25}H_{22}N_6OS$: C, 66.06; H, 4.88; N, 18.49; Found: C, 66.25; H, 4.89; N, 18.36.

5-Amino-3-benzylthio-1-phenyl-6-(o-chlorophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (5g). White crystals, mp 219.6–220.3°C; IR (KBr) ν (cm^{-1}): 3333, 3257, 3192, 1677, 1598, 1585, 1545, 1215, 754, 687; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.48 (s, 2H, Ph*CH_2*), 5.74 (br s, 2H, NH_2), 7.22–7.52 (m, 10H, Ar), 7.59 (d, 1H, *J* = 7.6 Hz, Ar), 7.99 (d, 2H, *J* = 7.6 Hz, Ar), 8.30 (d, 1H, *J* = 8.0 Hz, Ar), 9.83 (br s, 1H, NH); EI-MS (70 eV, *m*/*z*, rel. int.) 474 (M^+, 13); *Anal.* Calcd. for $C_{24}H_{19}ClN_6OS$: C, 60.69; H, 4.03; N, 17.69; Found: C, 60.58; H, 4.09; N, 17.82.

5-Amino-3-methylthio-1-phenyl-6-(p-chlorophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (5h). White crystals, mp 245.2–247.5°C; IR (KBr) ν (cm^{-1}): 3380, 3311, 3125, 1718, 1601, 1562, 1543, 925, 768; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.60 (s, 3H, SCH_3), 5.57 (s, 2H, NH_2), 7.28 (t, 1H, *J* = 7.2 Hz, Ar), 7.40 (d, 2H, *J* = 8.7 Hz, Ar), 7.49 (t, 2H, *J* = 7.9 Hz, Ar), 7.78 (d, 2H, *J* = 8.7 Hz, Ar), 8.00 (d, 2H, *J* = 7.8 Hz, Ar), 9.81 (s, 1H, NH); EI-MS (70 eV, *m*/*z*, rel. int.) 399 (M + 1, 41), 398 (M^+, 78); *Anal.* Calcd. for $C_{18}H_{15}ClN_6OS$: C, 54.20; H, 3.79; N, 21.07; Found: C, 54.07; H, 3.71; N, 21.30.

3-Methylthio-1-phenyl-5-phenylamino-6-(p-tolylamino)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (5i). White crystals, mp 222.4–222.8°C; IR (KBr) ν (cm^{-1}): 3369, 3252, 1690, 1598, 1546, 949, 761, 689; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.34 (s, 3H, C_6H_4*CH_3*), 2.58 (s, 3H, SCH_3), 6.86 (d, 2H, *J* = 7.5 Hz, Ar), 6.91 (t, 1H, *J* = 7.2 Hz, Ar), 7.06 (br s, 1H, Ph*NH*N), 7.13 (d, 2H, *J* = 8.1 Hz, Ar), 7.24–7.27 (m, 3H, Ar), 7.41 (t, 2H, *J* = 8.0 Hz, Ar), 7.50 (d, 2H, *J* = 8.1 Hz, Ar), 8.06 (d, 2H, *J* = 8.1 Hz, Ar), 8.35 (s, 1H, NH); EI-MS (70 eV, *m*/*z*, rel. int.) 455 (M + 1, 46), 454 (M^+, 81); *Anal.* Calcd. for $C_{25}H_{22}N_6OS$: C, 66.06; H, 4.88; N, 18.49; Found: C, 65.80; H, 4.85; N, 18.57.

3-Methylthio-1-phenyl-5-phenylamino-6-(m-chlorophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (5j). White crystals, mp 208.5–210.5°C; IR (KBr) ν (cm^{-1}): 3342, 3261, 1695, 1599, 1545, 951, 759, 683; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.54 (s, 3H, SCH_3), 6.84 (d, 2H, *J* = 7.5 Hz, Ar), 7.01 (t, 2H, *J* = 7.2 Hz), 7.08–7.29 (m, 5H, Ar and Ph*NH*N), 7.45 (t, 2H, *J* = 7.8 Hz, Ar), 8.01 (d, 2H, *J* = 7.8 Hz, Ar), 8.14 (s, 1H, *m*-ClC_6H_4), 8.51 (s, 1H, Ar*NH*); EI-MS (70 eV, *m*/*z*, rel. int.) 475 (M + 1, 35), 474 (M^+, 69); *Anal.* Calcd. for $C_{24}H_{19}ClN_6OS$: C, 60.69; H, 4.03; N, 17.69; Found: C, 60.39; H, 4.00; N, 17.72.

3-Benzylthio-1-phenyl-5-phenylamino-6-(p-tolylamino)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (5k). White crystals, mp 198.6–198.8°C; IR (KBr) ν (cm^{-1}): 3317, 3271, 1701, 1592, 1547, 772, 688; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.34 (s, 3H, C_6H_4*CH_3*), 4.42 (s, 2H, Ph*CH_2*), 6.86 (d, 2H, *J* = 7.5 Hz, Ar), 7.01 (t, 2H, *J* = 6.9 Hz, Ar), 7.12–7.28 (m, 8H, Ar and Ph*NH*N), 7.39–7.43 (m, 4H, Ar), 7.48 (t, 2H, *J* = 6.4 Hz, Ar), 8.07 (d, 2H, *J* = 7.8 Hz, Ar), 8.33 (s, 1H, NH); EI-MS (70 eV, *m*/*z*, rel. int.) 531 (M + 1, 26), 530 (M^+, 50); *Anal.* Calcd. for $C_{31}H_{26}N_6OS$: C, 70.17; H, 4.94; N, 15.84; Found: C, 69.89; H, 5.00; N, 15.63.

General Procedure for the preparation of 3-alkylthio-8-aryl-phenyl-1,8-dihydropyrazolo[3,4-*d*][1,2,4]triazolo[1,5-*a*] pyrimidin-4-one (6). To a suspension of the appropriate 5-amino-3-alkylthio-6-arylamino-1-phenyl-1*H*- pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one **5** (1.5 mmol) in 25 mL of triethyl orthoformate *p*-toluenesulfonic acid (*p*-TsOH) (0.4 g, 2.25 mmol) was added. The reaction mixture was refluxed for 15 h under stirring. After cooling to room temperature, a yellowish substance precipitated. The crude product was collected by filtration and washed with water. After recrystallization from dimethylformamide, the products were obtained as colorless crystal.

3-Methylthio-1,8-diphenyl-1,8-2H-pyrazolo[3,4-d][1,2,4]triazolo[1,5-a]pyrimidin-4-one (6a). White crystals, mp 253–255°C, IR (KBr) ν (cm^{-1}): 3144, 3081, 2925, 1718, 1605, 1578, 1560, 1527, 1388, 1265, 1165, 902, 768; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.65 (s, 3H, SCH_3), 7.31 (t, 1H, *J* = 6.8 Hz, Ph), 7.49–7.57 (m, 3H, Ph), 7.67 (t, 2H, *J* = 8.2 Hz, Ph), 7.93 (d, 2H, *J* = 8.0 Hz, Ph), 8.08 (d, 2H, *J* = 8.4 Hz, Ph), 9.34 (s, 1H, triazole-H); EI-MS (70 eV, *m*/*z*, rel. int.) 375 (M + 1, 13), 374 (M^+, 36); *Anal.* Calcd. for $C_{19}H_{14}N_6OS$: C, 60.95; H, 3.77; N, 22.45; Found: C, 61.02; H, 3.75; N, 22.53.

3-Methylthio-1-phenyl-8-(p-methylphenyl)-1,8-2H-pyrazolo[3,4-d][1,2,4]triazolo[1,5-a]pyrimidin-4-one (6b). White crystals, mp 253–256°C, IR(KBr) ν (cm^{-1}): 3133, 3076, 2919, 1721, 1596, 1574, 1398, 1169, 900, 767, 673; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.41 (s, 3H, *p*-*CH_3*Ph), 2.67 (s, 3H, SCH_3), 7.31 (t, 1H, *J* = 7.6 Hz, Ar), 7.45–7.53 (m, 4H, Ar), 7.80 (d, 2H, *J* = 8.0 Hz, Ar), 8.07 (d, 2H, *J* = 8.0 Hz, Ar), 9.29 (s, 1H, triazole-H); EI-MS (70 eV, *m/z*, rel. int.) 389 (M + 1, 22), 388 (M^+, 62); *Anal.* Calcd. for $C_{20}H_{16}N_6OS$: C, 61.84; H, 4.15; N, 21.63; Found: C, 61.90; H, 4.13; N, 21.65.

3-Methylthio-1-phenyl-8-(o-chlorophenyl)-1,8-dihydropyrazolo[3,4-d][1,2,4]triazolo[1,5-a]pyrimidin-4-one (6c). White crystals, mp 216–218°C, IR (KBr) ν (cm^{-1}): 3139, 3069, 1722, 1609, 1585, 1525, 1398, 1229, 1124, 902, 766, 687; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.64 (s, 3H, SCH_3), 7.27 (t, 1H, $J = 7.6$ Hz, Ar), 7.44 (t, 2H, $J = 7.8$ Hz, Ar), 7.66–7.70 (m, 2H, Ar), 7.83–7.90 (m, 2H, Ar), 7.94 (d, 2H, $J = 8.0$ Hz, Ph), 9.23 (s, 1H, triazole-H); EI-MS (70 eV, *m/z*, rel. int.): 409 (M + 1, 32), 408 (M^+, 57); *Anal.* Calcd. for $C_{19}H_{13}ClN_6OS$: C, 55.81; H, 3.20; N, 20.55; Found: C, 55.85; H, 3.22; N, 20.51.

3-Methylthio-1-phenyl-8-(o-fluorophenyl)-1,8-dihydropyrazolo[3,4-d][1,2,4]triazolo[1,5-a]pyrimidin-4-one (6d). White crystal, mp 224–225°C; IR (KBr) ν (cm^{-1}): 3146, 1712, 1607, 1585, 1525, 1509, 1398, 1234, 904, 769, 752; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.65 (s, 3H, SCH_3), 7.29 (t, 1H, $J = 7.4$ Hz, Ar), 7.44–7.69 (m, 5H, Ar), 7.92 (t, 1H, $J = 7.6$ Hz, Ar), 8.00 (d, 2H, $J = 8.0$ Hz, Ar), 9.23 (s, 1H, triazole-H); EI-MS (70 eV, *m/z*, rel. int.): 393 (M + 1, 31), 392 (M^+, 63); *Anal.* Calcd. for $C_{19}H_{13}FN_6OS$: C, 58.15; H, 3.34; N, 21.42; Found: C, 58.13; H, 3.32; N, 21.48.

3-Benzylthio-1,8-diphenyl-1,8-dihydropyrazolo[3,4-d][1,2,4]triazolo[1,5-a]pyrimidin-4-one (6e). White crystals, mp 224–226°C; IR (KBr) ν (cm^{-1}): 3118, 3064, 1718, 1608, 1580, 1528, 1389, 1163, 757, 685; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.51 (s, 2H, PhCH_2), 7.26 (t, 1H, $J = 7.2$ Hz, Ph), 7.34 (t, 3H, $J = 7.4$ Hz, Ph), 7.50–7.67 (m, 7H, Ph), 7.92 (d, 2H, $J = 7.6$ Hz, Ph), 8.08 (d, 2H, $J = 7.6$ Hz, Ph), 9.34 (s, 1H, triazole-H); EI-MS (70 eV, *m/z*, rel. int.) 450 (M^+, 8); *Anal.* Calcd. for $C_{25}H_{18}N_6OS$: C, 66.65; H, 4.03; N, 18.65; Found: C, 66.70; H, 4.02; N, 18.70.

3-Benzylthio-8-(p-tolyl)-1-phenyl-1,8-dihydropyrazolo[3,4-d][1,2,4]triazolo[1,5-a]pyrimidin-4-one (6f). White crystals, mp 257–259°C; IR (KBr) ν (cm^{-1}): 3137, 2923, 1718, 1601, 1580, 1527, 1390, 1165, 978, 769, 702; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.41 (s, 3H, *p*-CH_3Ph), 4.52 (s, 2H, PhCH_2), 7.32–7.53 (m, 10H, Ar), 7.79 (d, 2H, $J = 8.0$ Hz, Ar), 8.08 (d, 2H, $J = 8.0$ Hz, Ar), 9.29 (s, 1H, triazole-H); EI-MS (70 eV, *m/z*, rel. int.): 464 (M^+, 6); *Anal.* Calcd. for $C_{26}H_{20}N_6OS$: C, 67.22; H, 4.34; N, 18.09; Found: C, 67.26; H, 4.37; N, 18.12.

3-Benzylthio-8-(o-chlorophenyl)-1-phenyl-1,8-dihydropyrazolo[3,4-d][1,2,4]triazolo[1,5-a]pyrimidin-4-one (6g). White crystals, mp 221–223°C; IR (KBr) ν (cm^{-1}): 3144, 1718, 1704, 1605, 1561, 1399, 1122, 1065, 905, 770, 687; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.52 (s, 2H, PhCH_2), 7.26–7.89 (m, 12H, Ar), 7.94 (d, 2H, $J = 8.4$ Hz, Ar), 9.23 (s, 1H, triazole-H); EI-MS (70 eV, *m/z*, rel. int.): 393 (M + 1, 9), 392 (M^+, 6); *Anal.* Calcd. for $C_{15}H_{17}ClN_6OS$: C, 61.92; H, 3.53; N, 17.33; Found: C, 62.00; H, 3.58; N, 17.32.

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Synthesis and *in Vitro* Study of Novel Bis-[3-(2-arylmethylidenimino-1,3-thiazol-4-yl)-4-hydroxy-*2H*-chromen-2-one-6-yl]methane and Bis-[3-(2-arylidenhydrazo-1,3-thiazol-4-yl)-4-hydroxy-*2H*-chromen-2-one-6-yl]methane as Potential Antimicrobial Agents

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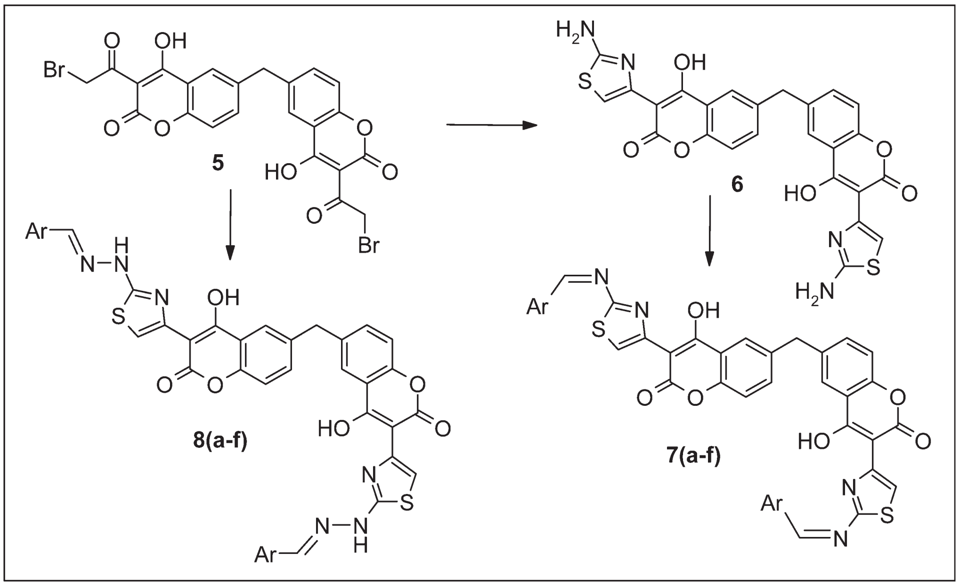

A series of novel bis-[3-(2-arylmethylidenimino-1,3-thiazol-4-yl)-4-hydroxy-*2H*-chromen-2-one-6-yl]methane **7a-f** and bis-[3-(2-arylidenhydrazo-1,3-thiazol-4-yl)-4-hydroxy-*2H*-chromen-2-one-6-yl]-methane **8a-f** were synthesized in good yields from bis-[3-(2-bromoacetyl-4-hydroxy-*2H*-chromen-2-one-6-yl]methane **5**. The chemical structures of the newly synthesized compounds were elucidated by their IR, ^{1}H NMR, MS, and elemental analyses. Further, all the compounds were screened for their antimicrobial activity against Gram-positive, Gram-negative bacteria, and fungi. Among the synthesized compounds, **7c**, **7e,** and **8c** were found to be the most active against almost all the test bacteria. The compound **8c** displayed notable antibacterial activity against *Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC6538p), *Micrococcus luteus* (IFC 12708), *Proteus vulgaris* (ATCC 3851) and *Salmonella typhimurium* (ATCC 14028), equal to that of ampicillin. Similarly these compounds also showed potent antifungal effect against *Candida albicans* (ATCC 10231), *Aspergillus fumigatus* (HIC 6094), *Trichophyton rubrum* (IFO 9185), and *Trichophyton mentagrophytes* (IFO 40996).

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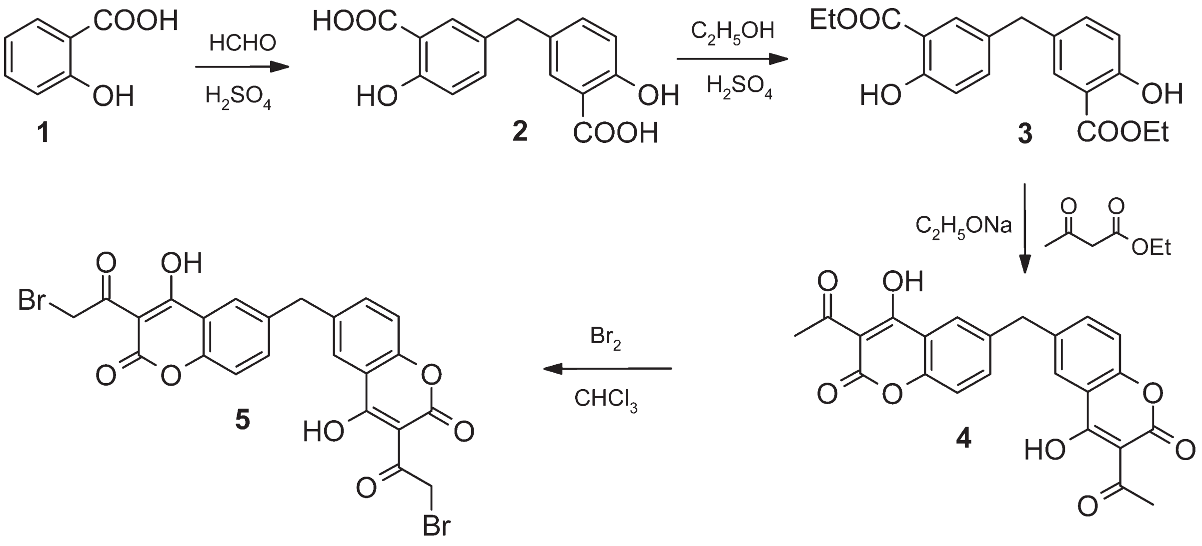
INTRODUCTION

The treatment of infectious diseases still remains an important and challenging problem because of a combination of factors including emerging infectious diseases and the increasing number of multidrug resistant microbial pathogens. Despite a large number of antibiotics and chemotherapeutics available for medical use, at the same time the emergence of old and new antibiotic resistance created in the last decades revealed a substantial medical need for new classes of antimicrobial agents. There is a real perceived need for the discovery of new compounds endowed with antimicrobial activity, possibly acting through mechanism of action, which are distinct from those of well-known classes of antibacterial agents to which many clinically relevant pathogens are now resistant. Similarly in the recent decades, an increased incidence of fungal infections has been observed as a consequence of the growing number of immunocompromised patients and the frequent use of antibacterial and cytotoxic drugs. For many fungal

Scheme 1



infections, polyenes, such as amphotericin B, represent the standard therapy. Polyenes bind to membrane sterols, leading to membrane permeability, leakage, and cell death. However, the clinical use of amphotericin B is limited by a high frequency of renal toxicity, and several adverse effects [1]. Although the various molecules were designed and synthesized for the above aim and to reduce the adverse effects, it was demonstrated that azoles and thiazoles, such as fluconazole, which act on ergosterol biosynthesis, offer several advantages in terms of decreased toxicity after oral or intravenous [2] administration and are often employed in the treatment of fungal infections, therefore the thiazoles, azoles, and their derivatives could be considered as possible antimicrobial agents [3].

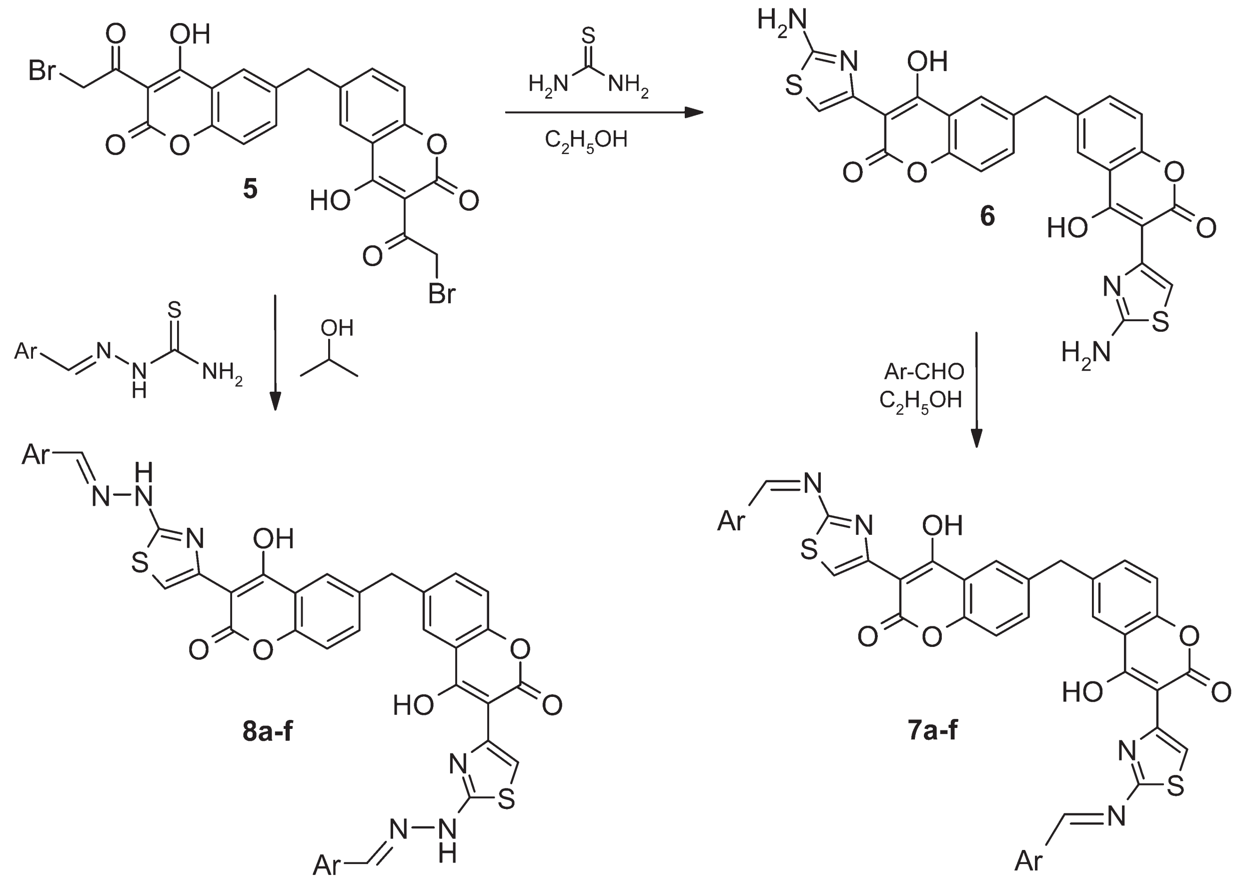
The thiazole nucleus also appears frequently in the structure of various natural products and biologically active compounds, notably thiamine (vitamin-B), antibiotics such as penicillin, micrococcin [4], troglitazone [5], and many metabolic products of fungi and primitive marine animals, including 2-(aminoalkyl)thiazole-4-carboxylic acids [6]. Similarly coumarins are a class of compounds with biological activity [7], such as analgesics [8], anticoagulant [9], specific inhibitors of α-chymotripsin [10], human leukocyte elastase [11], diuretics [12], platelet aggregation [13], anticancer [14], inhibitor of HIV-1 protease [15], and antibacterial agents [16]. Following the successful introduction of antimicrobial agents, inspired by the biological profile of thiazole and coumarin and their increasing importance in pharmaceutical and biological fields, and in continuation of our research on biologically active heterocycles [17] considering the scope to introduce thiazolyl moiety into the coumarin ring, it was thought worthwhile to undertake the synthesis of the title compounds with the view to obtain certain new chemical entities with both active pharmacophores in a single molecular frame work for the potential intensified biological activities.

In this article, we wish to report the synthesis of novel bis-[3-(2-arylmethylidenimino-1,3-thiazol-4-yl)-4-hydroxy-2*H*-chromen-2-one-6-yl]methane **7** in good yields, from bis-[3-(2-amino-1,3-thiazol-4-yl)-4-hydroxy-2*H*-chromen-2-one-6-yl]methane **6**, which in tern is synthesized by the reaction of bis-[3-(2-bromoacetyl-4-hydroxy-2*H*-chromen-2-one-6-yl]methane **5** with thiourea, and also the synthesis of novel bis-[3-(2-arylidenhydrazo-1,3-thiazol-4-yl)-4-hydroxy-2*H*-chromen-2-one-6-yl]methane **8** in good yields, from compound **5** and arylthiosemicarbazone (Schemes 1 and 2). The antibacterial and antifungal activities of the compounds **7a-f** and **8a-f** have also been evaluated.

RESULTS AND DISCUSSION

The key intermediate **5**, required for the synthesis of the title compounds was prepared according to the procedure outlined in the Scheme 1. Condensation of the salicylic acid **1** and formaldehyde in the presence of sulfuric acid gave bis-(4-hydroxy-3-carboxyphenyl)methane **2** in good yield [18]. Compound **2** was then reacted with ethyl alcohol in presence of catalytic amount of sulfuric acid to afford bis-(4-hydroxy-3-carbethoxyphenyl)methane **3** in good yield [17b], subsequently cyclocondensation of compound **3** with ethylacetoacetate in presence of sodium ethoxide gave bis-(3-acetyl-4-hydroxy-2*H*-chromen-2-one-6-yl)methane **4** [17b]. α-Bromination of compound **4** with bromine in chloroform

Scheme 2



7/8: Ar = **a**) C_6H_5; **b**) 4-NO_2-C_6H_4; **c**) 4-Br-C_6H_4; **d**) 4-MeO-C_6H_4; **e**) 3,4-(O-CH_2-O)C_6H_3; **f**) 2-furyl

at low temperature afforded bis-[3-(2-bromoacetyl-4-hydroxy-2*H*-chromen-2-one-6-yl] methane **5** in 85% yield. The cyclocondensation of compound **5** with thiourea in refluxing ethanol gave bis-[3-(2-amino-1,3-thiazol-4-yl)-4-hydroxy-2*H*-chromen-2-one-6-yl]methane **6** in 78% yield. Subsequently condensation of compound **6** with various aromatic aldehydes in refluxing ethanol gave the title compound bis-[3-(2-arylmethylidenimino-1,3-thiazol-4-yl)-4-hydroxy-2*H*-chromen-2-one-6-yl]methane **7a-f** in good to excellent yields (Scheme 2).

Further, the intermediate **5** was treated with the various arylthiosemicarbazone (prepared by the reaction of aromatic aldehydes with thiosemicarbazide in presence of sodium acetate in acetic acid) in refluxing isopropyl alcohol to give the other title compound bis-[3-(2-arylidenhydrazo-1,3-thiazol-4-yl)-4-hydroxy-*2H*-chromen-2-one-6-yl]methane **8a-f** in good yields (Scheme 2). The structures of all the synthesized compounds were confirmed by their IR, ^{1}H NMR, MS, and elemental analyses and further screened for their antibacterial and antifungal activities.

Antibacterial activity. The *in vitro* antibacterial activity of the newly prepared compounds was screened against three representative gram-positive bacteria *viz. Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 6538p), and *Micrococcus luteus* (IFC 12708), three Gram-negative bacteria *viz. Proteus vulgaris* (ATCC 3851), *Salmonella typhimurium* (ATCC 14028), and *Escherichia coli* (ATCC 25922) by the broth dilution method, recommended by National Committee for Clinical Laboratory Standards (NCCLS) [19]. Bacteria were grown over night in Luria Bertani (LB) broth at 37°C, harvested by centrifugation, and then washed twice with sterile distilled water. Stock solutions of the series of compounds were prepared in DMSO. Each stock solution was diluted with standard method broth (Difco) to prepare serial two-fold dilutions in the range of 50–0.8 μg/mL. Ten microtiters of the broth containing about 10^5 colony forming units (cfu)/mL of test bacteria was added to each well of 96-well microtiter plate. Culture plates were incubated for 24 h at 37°C, and the growth was monitored visually and

Table 1

Antibacterial activity of compounds **7a-f** and **8a-f**.

	Minimum inhibitory concentration (MIC, μg/mL)					
Compound	*B. subtilis*	*S. aureus*	*M. luteus*	*P. vulgaris*	*S. typhimurium*	*E. coli*
7a	25.0	25.0	—	—	25.0	—
7b	12.5	12.5	12.5	12.5	12.5	25.0
7c	3.12	6.25	1.56	1.56	3.12	6.25
7d	12.5	12.5	6.25	—	12.5	25.0
7e	6.25	6.25	3.12	12.5	12.5	12.5
7f	25.0	12.5	3.12	12.5	6.25	25.0
8a	25.0	25.0	50.0	—	50.0	—
8b	6.25	12.5	12.5	25.0	12.5	25.0
8c	1.56	1.56	1.56	1.56	1.56	12.5
8d	12.5	12.5	12.5	12.5	12.5	—
8e	3.12	3.12	3.12	6.25	3.12	6.25
8f	12.5	12.5	6.25	6.25	12.5	12.5
Ampicillin	1.56	1.56	1.56	3.12	3.12	12.5

—Indicates bacteria are resistant to the compound >50 μg/mL concentration. Standard deviation 0.05.

spectrophotometrically. Amphicillin was used as a standard drug, the lowest concentration (highest dilution) required to arrest the growth of bacteria was regarded as minimum inhibitory concentration (MIC, μg/mL), was determined for all the compounds and compared with the control. The MIC values of the compounds screened are given in Table 1.

The investigation of antibacterial screening data revealed that all the tested compounds exhibited interesting biological activity however, with a degree of variation. Compound **8c** is highly active against all the microorganisms employed, except *E. coli*, at 1.56 μg/mL concentration, it is almost equal to the standard. Compound **7c** is also highly active but only against *M.luteus* and *P. vulgaris* at the same concentration as **8c**. The compound **8e** also showed good antibacterial activity against *B.subtilis*, *S. aureus*, *M. Luteus*, and *S. typhimurium*.

Compound **7a** is almost inactive towards *M. luteus*, *P. vulgaris*, and *E. coli*. The remaining compounds showed moderate to good activity.

Antifungal activity. The newly prepared compounds were screened for their antifungal activity against four fungal organism *viz*. *Candida albicans* (ATCC 10231), *Aspergillus fumigatus* (HIC 6094), *Trichophyton rubrum* (IFO 9185), and *Trichophyton mentagrophytes* (IFO 40996). *C. albicans* was grown for 48 h at 28°C in YPD broth (1% yeast extract, 2% peptone, and 2% dextrose), harvested by centrifugation and then washed twice with sterile distilled water. *A. fumigatus*, *T. rubrum*, and *T. mentagrophytes* were plated in potato dextrose agar (PDA) (Difco) and incubated at 28°C for two weeks. Spores were washed three times with sterile distilled water and resuspended in distilled water to obtain an initial inoculum size of 10^5 spores/mL. Each test compound was dissolved in DMSO and diluted with potato dextrose broth (Difco) to prepare serial two-fold dilutions in the range of 100 to 0.8 μg/mL. Ten microtiters of the broth containing about 10^3 (for yeast) and 10^4 (for filamentous fungi) cells/mL of test fungi was added to each well of a 96-well microtiter plate. Culture plates were incubated for 48 ~ 72 h at 28°C. The fungal activity of each compound was compared with standard drug Amphotericin B. Minimum inhibitory concentration (MIC, μg/mL) were measured and compared with controls; the MIC values of the compounds screened are given in Table 2.

The antifungal screening data showed only moderate activity of the test compounds. Among the screened compounds, compound **7c** is highly active against *T. rubrum*, *T. mentagrophytes*, compound **7e** is also active against only *C. albicans* and compound **8c** is highly active against *C. albicans*, *T. mentagrophytes*, the activity of these compounds are almost equal to the standard, it is interesting to note that compounds **7e** and **8c** showed good antifungal activity toward *C. albicans* at the concentration of 3.12 μg/mL, it is less than the concentration of standard.

In conclusion, a series of novel bis-[3-(2-arylmethyllidenimino-1,3-thiazol-4-yl)-4-hydroxy-*2H*-chromen-2-one-6-yl]methane **7** and novel bis-[3-(2-arylidenhydrazo-1,3-thiazol-4-yl)-4-hydroxy-*2H*-chromen-2-one-6-yl]methane **8** has been designed and synthesized. The antimicrobial activity of these compounds was evaluated against various Gram-positive, Gram-negative bacteria and fungi. Among the synthesized compounds, **7c**, **7e,** and **8c** showed good activity against bacteria and fungi

Table 2

Antifungal activity of compounds **7a-f** and **8a-f**.

Compound	Minimum inhibitory concentration (MIC, μg/mL)			
	C. albicans	*A. fumigatus*	*T. rubrum*	*T. mentagropytes*
7a	—	—	—	25.0
7b	25.0	25.0	25.0	25.0
7c	12.5	6.25	3.12	3.12
7d	25.0	12.5	6.25	12.5
7e	3.12	12.5	12.5	25.0
7f	50.0	25.0	12.5	12.5
8a	25.0	25.0	12.5	25.0
8b	6.25	12.5	25.0	12.5
8c	3.12	6.25	6.25	3.12
8d	50.0	50.0	50.0	25.0
8e	12.5	25.0	6.25	25.0
8f	25.0	6.25	6.25	12.5
Amphotericin B	6.25	3.12	3.12	3.12

—Indicates fungi are resistant to the compound >50 μg/mL concentration. Standard deviation 0.05.

and emerged as potential molecules for further development.

EXPERIMENTAL

Research chemicals were purchased from either Aldrich Company or Fluka and used without further purification, or were prepared according to the procedure described in the literature. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F_{254}; Merck) visualizing with ultraviolet light or iodine vapors. The yields of the products reported here are unoptimized. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR 5000 spectrometer, using KBr pellets. ^{1}H NMR spectra were recorded on a Varian Gemini spectrometer, operating at 300 MHz. Chemical shifts (δ) are reported in parts per million down field from tetramethylsilane. Mass spectra were obtained on a VG micro mass 7070H spectrometer operating at 70 eV. Elemental analyses were performed on a Perkin-Elmer 240 CHN elemental analyzer.

Synthesis of bis-[3-(2-bromoacetyl-4-hydroxy-2*H*-chromen- 2-one-6-yl] methane (5). To a stirred solution of **4** (1 mmol) in chloroform (20 mL), was added drop wise a solution of bromine (3 mmol) dissolved in chloroform (20 mL) at 0–5°C. The mixture was further stirred for 4 h. After completion of the reaction, monitored by TLC, the mixture was then poured into ice cold water. Crude product was collected by filtration, washed with water, dried, and recrystallized from ethanol to give pure compound **5** in 85% of yield as red solid, mp 208–210°C; IR (KBr): ν 3480, 1728, 1680, 1587, 1180, 586 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 15.07 (2H, s, OH), 7.50 (2H, s, ArH), 7.18 (2H, d, J = 8.62 Hz, ArH), 7.14 (2H, d, J = 8.62 Hz, ArH), 4.21 (4H, s, CH_2Br), 3.98 (2H, s, CH_2); MS: m/z 578 (M^+). Anal. calcd for $C_{23}H_{14}Br_2O_8$: C, 47.78; H, 2.44. Found: C, 47.72; H, 2.46.

Synthesis of bis-[3-(2-amino-1,3-thiazol-4-yl)-4-hydroxy-2*H*-chromen-2-one-6-yl]methane (6). To a stirred solution of thiourea (3 mmol) in 1-propanol (20 mL), was added drop wise a solution of **5** (1 mmol) in 1-propanol (20 mL) over a period of 30 min. The mixture was refluxed for 3 h, and then pyridine (5 mL) was added and continued reflux for 5 h. After completion of the reaction, monitored by TLC, the solvent was removed *in vacuo*. The crude product was dried and crystallized from ethanol to give compound **6** in 78% of yield as brown solid, mp 224-26°C; IR (KBr): ν 3480-3275, 1720, 1614, 1582, 758, 638 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.78 (2H, s, ArH), 7.63 (2H, s, ArH), 7.40 (4H, bs, NH_2), 7.32 (2H, s, OH), 7.23 (2H, d, J = 8.72 Hz, ArH), 7.14 (2H, d, J = 8.72 Hz, ArH), 3.98 (2H, s, CH_2); MS: m/z 532 (M^+). Anal. calcd for $C_{25}H_{16}N_4O_6S_2$: C, 56.39; H, 3.03; N, 1052. Found: C, 55.82; H, 3.09; N, 10.44.

Synthesis of bis-[3-(2-arylmethylidenimino-1,3-thiazol-4-yl)-4-hydroxy-2*H*-chromen-2-one-6-yl]methane (7a-f). A mixture of aromatic aldehyde (2 mmol) and compound **6** (1 mmol) in ethanol (20 mL) was refluxed for 1 h. After completion of the reaction (monitored by TLC), the mixture was cooled and the solvent evaporated. The formed crude product was washed with cold aq. ethanol and then the product was purified by recrystallization from ethanol to afford pure compound **7**.

Bis-[3-(2-phenylmethylidenimino-1,3-thiazol-4-yl)-4-hydroxy-2*H*-chromen-2-one-6-yl]methane (7a). This compound was obtained as yellow solid; Yield 81%; Mp 254-56°C; IR (KBr): ν 3410, 3062, 1720, 1615, 1580, 1471, 1180, 638 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 11.07 (2H, s, OH), 8.47 (2H, s, ArH), 8.26 (2H, s, CH), 7.62 (2H, s, ArH), 7.38 (4H, d J = 7.2 Hz, ArH), 7.30 (4H, d, J = 7.2 Hz, ArH), 7.19 (2H, d, J = 8.72 Hz, ArH), 7.17 (4H, s, ArH), 3.99 (2H, s CH_2); MS: m/z 532 (M^+). Anal. calcd. for $C_{39}H_{24}N_4O_6S_2$: C, 66.09; H, 3.41; N, 7.90. Found: C, 66.00; H, 3.36; N, 7.92.

Bis-[3-(2-(4-nitrophenyl)methylidenimino-1,3-thiazol-4-yl)-4-hydroxy-2*H*-chromen-2-one-6-yl]methane (7b). This compound was obtained as brown solid; Yield 76%; Mp 247-49°C;

IR (KBr): ν 3410, 3065, 1728, 1612, 1580, 1472, 1345, 1180, 638 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 11.72 (2H, s, OH), 8.46 (2H, s, ArH), 8.28 (2H, s, CH), 8.24 (4H, d, J = 8.5 Hz, ArH), 7.72 (4H, d, J = 8.5 Hz, ArH), 7.62 (2H, s, ArH), 7.20 (2H, d, J = 8.72 Hz, ArH), 7.17 (2H, d, J = 8.7 Hz, ArH), 4.00 (2H, s CH$_2$); MS: m/z 799 (M$^+$ +1). Anal. calcd. for $C_{39}H_{22}N_6O_{10}S_2$: C, 58.65; H, 2.78; N, 10.52. Found: C, 58.60; H, 2.80; N, 10.46.

Bis-[3-(2-(4-bromophenyl)methylidenimino-1,3-thiazol-4-yl)-4-hydroxy-2*H*-chromen-2-one-6-yl]methane (7c). This compound was obtained as yellow solid; Yield 75%; Mp 223-25°C; IR (KBr): ν 3410, 3065, 1720, 1616, 1582, 1474, 1180, 638, 586 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 11.72 (2H, s, OH), 8.46 (2H, s, ArH), 8.28 (2H, s, CH), 7.62 (2H, s, ArH), 7.49 (4H, d, J = 8.5 Hz, ArH), 7.38 (4H, d, J = 8.3 Hz, ArH), 7.20 (2H, d, J = 8.72 Hz, ArH), 7.17 (2H, d, J = 8.7 Hz, ArH), 4.00 (2H, s CH$_2$); MS: m/z 866 (M$^+$). Anal. calcd. for $C_{39}H_{22}Br_2N_4O_6S_2$: C, 54.06; H, 2.56; N, 6.47. Found: C, 54.00; H, 2.51; N, 6.50.

Bis-[3-(2-(4-methoxyphenylmethylidenimino-1,3-thiazol-4-yl)-4-hydroxy-2*H*-chromen-2-one-6-yl]methane (7d). This compound was obtained as red solid; Yield 74%; Mp 252-54°C; IR (KBr): ν 3410, 3065, 1728, 1615, 1584, 1472, 1250, 1180, 638 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 11.42 (2H, s, OH), 8.49 (2H, s, ArH), 8.34 (2H, s, CH), 7.62 (2H, s, ArH), 7.21 (2H, d, J = 8.52 Hz, ArH), 7.14 (2H, d, J = 8.52 Hz, ArH), 7.09 (4H, d, J = 8.51 Hz, ArH), 6.72 (4H, d, J = 8.51 Hz, ArH), 4.00 (2H, s CH$_2$), 3.79 (6H, s, OCH$_3$); MS: m/z 768 (M$^+$). Anal. calcd. for $C_{41}H_{28}N_4O_8S_2$: C, 64.05; H, 3.67; N, 7.29. Found: C, 64.09; H, 3.64; N, 7.22.

Bis-[3-(2-(3,4-methylendioxyphenyl)methylidenimino-1,3-thiazol-4-yl)-4-hydroxy-2*H*-chromen-2-one-6-yl]methane (7e). This compound was obtained as black solid; Yield 76%; Mp 262-64°C; IR (KBr): ν 3415, 3062, 1728, 1615, 1584, 638 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 11.59 (2H, s, OH), 8.52 (2H, s, ArH), 8.30 (2H, s, CH), 7.62 (2H, s, ArH), 7.20-7.18 (2H, m, ArH), 7.12 (2H, d, J = 8.52 Hz, ArH), 6.87 (2H, d, J = 7.56 Hz, ArH), 6.80 (2H, d, J = 7.56 Hz, ArH), 5.81 (4H, s, CH$_2$), 4.00 (2H, s, CH$_2$); MS: m/z 796 (M$^+$). Anal. calcd. for $C_{41}H_{24}N_4O_{10}S_2$: C, 61.81; H, 3.04; N, 7.03. Found: C, 61.76; H, 2.99; N, 7.08.

Bis-[3-(2-(2-furyl)methylidenimino-1,3-thiazol-4-yl)-4-hydroxy-2*H*-chromen-2-one-6-yl]methane (7f). This compound was obtained as black solid; Yield 82%; Mp 271-73 °C; IR (KBr): ν 3400, 3065, 1728, 1615, 1584, 1130, 1070, 638 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 11.78 (2H, s, OH), 8.52 (2H, s, ArH), 8.12 (2H, s, CH), 7.62 (2H, s, ArH), 7.52 (2H, d, J = 3.2 Hz, ArH), 7.19 (2H, d, J = 7.52 Hz, ArH), 7.17 (2H, d, J = 7.52 Hz, ArH), 6.76 (2H, d, J = 1.56 Hz, ArH), 6.47 (2H, m, ArH), 4.00 (2H, s, CH$_2$); MS: m/z 688 (M$^+$). Anal. calcd. for $C_{35}H_{20}N_4O_8S_2$: C, 61.04; H, 2.93; N, 8.14. Found: C, 61.00; H, 3.05; N, 8.11.

Bis-[3-(2-arylidenhydrazo-1,3-thiazol-4-yl)-4-hydroxy-2*H*-chromen-2-one-6-yl]methane (8a-f). A mixture of arylthiosemicarbazone (2 mmol) and compound **5** (1 m mol) in isopropylalcohol (20 mL) was refluxed for 1.5 h. When the foaming product was formed, the mixture was allowed to cool and the solid filtered, purified by recrystallization from aq. ethanol afforded pure compound **8**.

Bis-[3-(2-phenylidenhydrazo-1,3-thiazol-4-yl)-4-hydroxy-2*H*-chromen-2-one-6-yl]methane (8a). This compound was obtained as yellow solid; Yield 76%; Mp 222-24°C; IR (KBr): ν 3400-3300, 3065, 1720, 1614, 1580, 1471, 1180, 638 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 11.20 (2H, s, OH), 9.52 (2H, s, NH), 8.19 (2H, s, CH), 7.67 (2H, s, ArH), 7.56 (2H, s, ArH), 7.35-7.25 (10H, m, ArH), 7.23 (2H, d, J = 8.7 Hz, ArH), 7.10 (2H, d, J = 8.7 Hz, ArH), 4.00 (2H, s, CH$_2$); MS: m/z 738 (M$^+$). Anal. calcd. for $C_{39}H_{26}N_6O_6S_2$: C, 63.41; H, 3.55; N, 11.38. Found: C, 63.45; H, 3.49; N, 11.29.

Bis-[3-(2-(4-nitrophenyliden)hydrazo-1,3-thiazol-4-yl)-4-hydroxy-2*H*-chromen-2-one-6-yl]methane (8b). This compound was obtained as red solid; Yield 72%; Mp 272-74°C; IR (KBr): ν 3400-3300, 3065, 1720, 1614, 1580, 1471, 1365, 1180, 638 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 11.20 (2H, s, OH), 9.52 (2H, s, NH), 8.30 (2H, d, J = 8.4 Hz, ArH), 8.21 (2H, s, CH), 7.81 (2H, d, J = 8.4 Hz, ArH), 7.67 (2H, s, ArH), 7.52 (2H, s, ArH), 7.23 (2H, d, J = 8.7 Hz, ArH), 7.12 (2H, d, J = 8.7 Hz, ArH), 4.00 (2H, s, CH$_2$); MS: m/z 828 (M$^+$). Anal. calcd. for $C_{39}H_{24}N_8O_{10}S_2$: C, 56.52; H, 2.92; N, 13.52. Found: C, 56.46; H, 2.98; N, 13.46.

Bis-[3-(2-(4-bromophenyliden)hydrazo-1,3-thiazol-4-yl)-4-hydroxy-2*H*-chromen-2-one-6-yl]methane (8c). This compound was obtained as brown solid; Yield 70%; Mp 239-41°C; IR (KBr): ν 3400-3300, 3062, 1720, 1615, 1580, 1471, 1180, 638, 586 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 11.20 (2H, s, OH), 9.52 (2H, s, NH), 8.21 (2H, s, CH), 7.67 (2H, s, ArH), 7.52 (2H, s, ArH), 7.42 (4H, d, J = 8.3 Hz, ArH), 7.38 (4H, d, J = 8.3 Hz, ArH), 7.23 (2H, d, J = 8.7 Hz, ArH), 7.12 (2H, d, J = 8.7 Hz, ArH), 4.00 (2H, s, CH$_2$); MS: m/z 896 (M$^+$). Anal. calcd. for $C_{39}H_{24}Br_2N_6O_6S_2$: C, 52.25; H, 2.70; N, 9.37. Found: C, 52.20; H, 2.72; N, 9.31.

Bis-[3-(2-(4-methoxyphenyliden)hydrazo-1,3-thiazol-4-yl)-4-hydroxy-2*H*-chromen-2-one-6-yl]methane (8d). This compound was obtained as brown solid; Yield 79%; Mp 238-40°C; IR (KBr): ν 3400-3300, 3062, 1728, 1619, 1580, 1471, 1270, 1180, 640 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 11.20 (2H, s, OH), 9.52 (2H, s, NH), 8.21 (2H, s, CH), 7.67 (2H, s, ArH), 7.52 (2H, s, ArH), 7.23 (6H, m, ArH), 7.12 (2H, d, J = 8.7 Hz, ArH), 6.67 (4H, d, J = 8.5 Hz, ArH), 4.00 (2H, s, CH$_2$), 3.76 (6H, s, OCH$_3$); MS: m/z 798 (M$^+$). Anal. calcd. for $C_{41}H_{30}N_6O_8S_2$: C, 61.65; H, 3.79; N, 10.52. Found: C, 61.70; H, 3.71; N, 10.46.

Bis-[3-(2-(3,4-methylendioxyphenyliden)hydrazo-1,3-thiazol-4-yl)-4-hydroxy-2*H*-chromen-2-one-6-yl]methane (8e). This compound was obtained as black solid; Yield 70%; Mp 248-50 °C; IR (KBr): ν 3400-3300, 3065, 1720, 1620, 1580, 1471, 1365, 1180, 637 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 11.20 (2H, s, OH), 9.52 (2H, s, NH), 8.19 (2H, s, CH), 7.67 (2H, s, ArH), 7.52 (2H, s, ArH), 7.24 (2H, s, ArH), 7.17 (2H, d, J = 8.5 Hz, ArH), 7.12 (2H, d, J = 8.5 Hz, ArH), 7.09-6.98 (4H, m, ArH), 5.84 (4H, s, CH$_2$), 4.00 (2H, s, CH$_2$); MS: m/z 826 (M$^+$). *Anal.* calcd. for $C_{41}H_{26}N_6O_{10}S_2$: C, 59.56; H, 3.17; N, 10.16. Found: C, 59.46; H, 3.14; N, 10.20.

Bis-[3-(2-(2-furyliden)hydrazo-1,3-thiazol-4-yl)-4-hydroxy-2*H*-chromen-2-one-6-yl]methane (8f). This compound was obtained as black solid; Yield 79%; Mp 286-88°C; IR (KBr): ν 3400, 3065, 1720, 1620, 1180, 1030, 637 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 11.20 (2H, s, OH), 9.52 (2H, s, NH), 7.72 (2H, s, CH), 7.67 (4H, m, ArH), 7.52 (2H, s, ArH), 7.17 (2H, d, J = 8.5 Hz, ArH), 7.12 (2H, d, J = 8.5 Hz, ArH), 6.78-6.60 (4H, m, ArH), 4.00 (2H, s, CH$_2$); MS: m/z 718 (M$^+$). Anal. calcd. for $C_{35}H_{22}N_6O_8S_2$: C, 58.49; H, 3.09; N, 11.69. Found: C, 58.41; H, 3.10; N, 11.61.

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Synthesis of Pyrone Carbaldehydes, Pyrone Sulfonium Ylides and Related Epoxides

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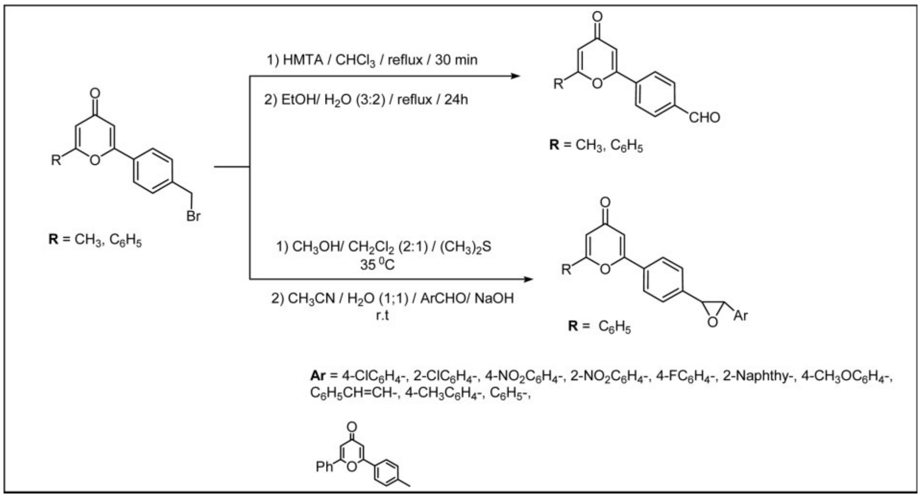

Hexaminium salts of 4-pyrones **3a, b** were synthesized by treatment of 2-(4-bromomethylphenyl)-6-methyl-4*H*-pyran-4-one **2a** and 2-(4-bromomethylphenyl)-6-phenyl-4*H*-pyran-4-one **2b** with hexamethylenetetramine in chloroform in 71 and 84% yields respectively. Hydrolysis of **3a** and **3b** in EtOH:H_2O produced the corresponding aldehydes **4a** and **4b** in 43 and 58% yields respectively. The reaction of bromopyrones **2b** and **2c** with dimethylsulfide in MeOH: CH_2Cl_2 afforded the corresponding sulfonium salts **5b** and **5c** in 66 and 65% yields respectively. Treatment of **5b** and **5c** with arene carbaldehydes such as (Ar = *p*-ClC_6H_4, *o*-ClC_6H_4, *p*-$NO_2C_6H_4$, *o*-$NO_2C_6H_4$, *p*-FC_6H_4, 2-naphthyl, *p*-$MeOC_6H_4$, C_6H_5CH=CH, *p*-MeC_6H_4, C_6H_5 and 4-(4-oxo-6-phenyl-4*H*-pyran-2-yl)-benzaldehyde **4b**) in the presence of sodium hydroxide in CH_3CN:H_2O afforded eleven *trans*-epoxides in 61–93% yields.

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INTRODUCTION

For many years, 4-pyrones have been extensively studied due to a wide range of applications. They are biologically active and synthetically useful compounds [1–9]. Among their various biological properties anti-HIV [10,11] and anti-cancer effects have aroused considerable attention [12,13]. Furthermore epoxides are useful and important synthetic precursors and have found divers applications in organic synthesis [14,15]. There are many reports on the synthesis of epoxides possessing various heterocyclic moieties [16–18]. However synthesis and reactions of pyrone sulfonium salts and corresponding ylides with arene carbaldehydes have not been reported as yet. Thus, we became interested in the synthesis, characterization and evaluation of this category of compounds.

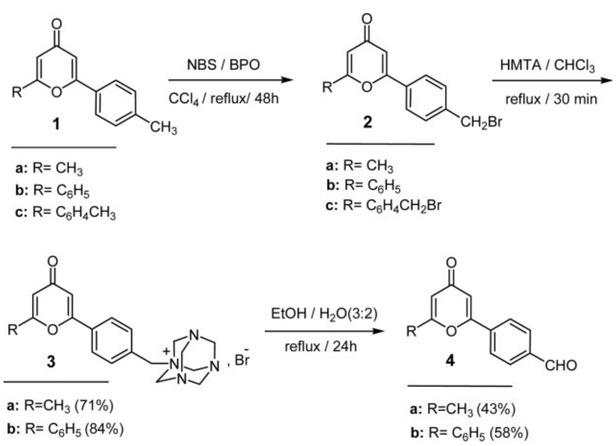
RESULTS AND DISCUSSION

We are interested in synthesis and developing the chemistry of pyrone derivatives [19–21]. In continuation of our investigations we have synthesized pyrone sulfonium ylides, arene carbaldehydes **4a**, **b** and corresponding *trans*-epoxides.Arylpyrones **1a** and **1b** were prepared according to the literature in two steps [22]. Bromination of pyrones **1(a–c)** with *N*-bromosuccinimide (NBS) produced the corresponding bromopyrones **2(a–c)** in 55–70% yields respectively [23]. The hexaminium salts **3a, b** were synthesized by reaction of bromopyrones **2a, b** with hexamethylenetetramine (HMTA) in dry chloroform in 71 and 84% yields respectively. Treatment of **3a** and **3b** with EtOH:H_2O under reflux afforded the corresponding aldehydes **4a** and **4b** in 43 and 58% yields respectively (Scheme 1).

The structures of all new compounds **3a, b** and **4a, b** were established on the basis of the FT-IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analysis.

The sulfonium salts **5b** and **5c** were synthesized by reaction of bromopyrones **2b** and **2c** with dimethylsulfide in MeOH:CH_2Cl_2 in 66 and 65% yields respectively

Scheme 1



(Scheme 2). It can be seen from the experimental section that all spectroscopic data (FT-IR, ^{1}H NMR, ^{13}C NMR) and elemental analysis are in full agreement with proposed structures.

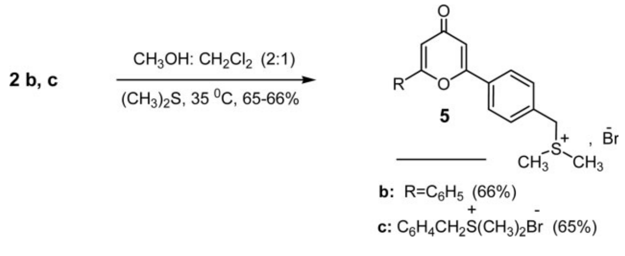
Synthesis of epoxides was the final step of this investigation. Thus treatment of 2,6-bis-sulfonium salt **5c** with eight arene carbaldehydes produced the bis-epoxides in 30–73% yields. Solubility of bis-epoxides in various solvents was very low; consequently purification and evaluation of these compounds was very difficult, time consuming and materials intensive. For these reasons we focused our attention on the synthesis of mono-epoxides. Thus treatment of mono-sulfonium salt of pyrone **5b** with various arene carbaldehydes resulted in the formation of mono-epoxides **6(b$_1$-b$_{10}$)** and **7** in 61–93% yields (Scheme 3).

The structures of the epoxides were established on the basis of FT-IR, ^{1}H NMR, ^{13}C NMR [24], mass spectral data and elemental analysis and by comparison with literature ^{1}H NMR data for epoxide protons [25,26]. In a similar manner the reaction of sulfonium salt **5b** with aldehyde **4b** resulted in the formation of epoxide **7** in 61% yield (Scheme 4).

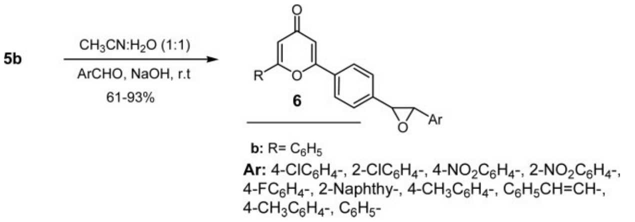
CONCLUSION

In this study, hexaminium salts of 4-pyrones have been synthesized by reaction of bromomethylpyrones with hexamethylenetetramine. Aldehyes **4a, b** were synthesized by hydrolysis of hexaminium salts. Mono-epoxide derivatives of 4-pyrone have been synthesized by reaction of arene carbaldehydes with 4-pyrone sulfonium ylide. Ring opening reactions of epoxides are under investigation.

Scheme 2



Scheme 3

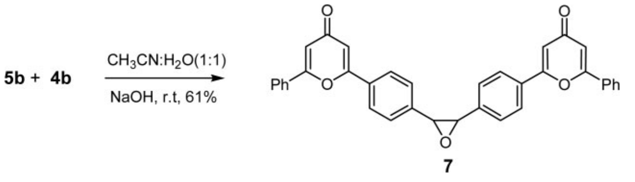


EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded with a FT-NMR-Bruker spectrometer at 400 and 100 MHz respectively. FT-IR spectra were obtained using KBr pellets on tensor 27-Bruker. Mass spectra were recorded on Finnigan-Mat 8400, 70ev mass spectrometer. Elemental analyses were carried out on a Heareus CHN-Rapid, and were found to agree favorably with the calculated values. Thin layer chromatography was performed using silica gel 60 HF$_{254}$. Melting points were recorded on Mel-TEMP 1202D apparatus and are uncorrected.

2-(4-Bromomethylphenyl)-6-methyl-4*H*-pyran-4-one (2a). A mixture of 2-methyl-6-(4-methylphenyl)-4*H*-pyran-4-one 1a (1g, 5 mmol), NBS (0.91g, 5.12 mmol) and catalytic amount of benzoyl peroxide in CCl$_4$ (20 mL) was heated at reflux for 48 h. The reaction mixture was cooled to room temperature and the precipitate was collected by filtration. The solid was dissolved in CH$_2$Cl$_2$ (40 mL), washed with saturated aqueous NaHCO$_3$ solution (3 × 10 mL) and water (2 × 10 mL) then dried over MgSO$_4$. The crude product was purified by preparative layer chromatography (PLC) on silica gel using *n*-hexane:acetone (2:1) as eluent to produce the title compound. White solid, 0.77g (55%), mp 170–172°C; FT-IR(KBr): 3041, 2973, 1660 (pyrone C=O), 1596, 1507, 1389, 1233, 917, 841cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 2.36 (s, 3H, CH$_3$), 4.50 (s, 2H, CH$_2$), 6.17 (d, 1H, J = 1.1 Hz, vinyl-H), 6.68 (d, 1H, J = 2 Hz, vinyl-H), 7.49 (d, 2H, J = 8 Hz, Ar-H), 7.72 (d, 2H, J = 8 Hz, Ar-H) ppm; ^{13}C NMR (CDCl$_3$): δ 18.81, 31.14, 109.97, 113.40, 125.13, 128.59, 130.20, 139.94, 161.72, 164.35, 178.98 ppm; ms: m/z (%): 280 and 278 (M^{+}, 6 and 6), 199 (40), 171 (100), 115 (56). Anal. Calcd. for C$_{13}$H$_{11}$BrO$_2$: C, 55.95; H, 3.94. Found: C, 55.59; H, 3.90.

Scheme 4



General procedure for synthesis of hexaminium salts (3a and 3b). 2-(4-Bromomethylphenyl)-6-methyl-4*H*-pyran-4-one 2a and 2-(4-bromomethylphenyl)-6-phenyl-4*H*-pyran-4-one 2b (5.86 mmol) were dissolved in dry $CHCl_3$ (20 mL). Then a solution of hexamethylenetetramine (5.86 mmol) in $CHCl_3$ (20 mL) was added dropwise to the flask. The mixture was refluxed for 30 min to complete precipitation. The precipitate collected by was filtered, and washed with chloroform and dried *in vacuo* to give hexaminium salts.

Hexaminium salt (3a). White solid, 2.12 g (71%), FT-IR (KBr): 3046, 2967, 2899, 1656 (pyrone C=O), 1600, 1511, 1390, 1036, 931, 821 cm^{-1}; ^1H NMR (D_2O): δ 2.37 (s, 3H, CH_3), 4.18 (s, 2H, CH_2), 4.59 and 4.62 (AB system, J_{AB} = 12 Hz, 3 × CH_2), 5.15 (s, 6H, 3 × CH_2), 6.19 (d, 1H, *J* = 1.5 Hz, vinyl-H), 6.69 (d, 1H, *J* = 2 Hz, vinyl-H), 7.58 (d, 2H, *J* = 8 Hz, Ar-H), 7.91 (d, 2H, *J* = 8 Hz, Ar-H) ppm; ^{13}C NMR (D_2O): δ 18.02, 59.08, 68.87, 77.12, 108.77, 111.94, 125.71, 126.69, 131.26, 131.97, 162.78, 168.32, 181.59 ppm. Anal. Calcd. for $C_{19}H_{23}O_2N_4Br$: C, 54.45; H, 5.40; N, 13.36. Found: C, 54.16; H, 5.50; N, 13.30.

Hexaminium salt (3b). White solid, 2.30g (84%), FT-IR (KBr): 3056, 2949, 2893, 1646 (pyrone C=O), 1601, 1500, 1457, 1437, 1005, 775 cm^{-1}; ^1H NMR (D_2O): δ 4.04 (s, 2H, CH_2), 4.60 and 4.62 (AB system, J_{AB} = 16 Hz, 3 × CH_2), 5.11 (s, 6H, 3 × CH_2), 6.32 (d, 1H, *J* = 2 Hz, vinyl-H), 6.42 (d, 1H, *J* = 2 Hz, vinyl-H), 7.26 (d, 2H, *J* = 8 Hz, Ar-H), 7.38-7.44 (m, 5H, Ar-H), 7.63 (d, 2H, *J* = 8 Hz, Ar-H) ppm; ^{13}C NMR (DMSO-d_6): δ 58.38, 69.77, 77.73, 110.98, 111.59, 126.01, 126.57, 128.92, 129.21, 130.77, 131.58, 132.47, 133.25, 161.50, 162.41, 178.87 ppm. Anal. Calcd. for $C_{24}H_{25}O_2N_4Br$: C, 59.91; H, 5.14; N, 11.63. Found: C, 59.60; H, 5.20; N, 11.25.

4-(6-Methyl-4-oxo-4*H*-pyran-2-yl)benzaldehyde (4a). A solution of hexaminium salt 3a (0.1g, 0.24 mmol) in 10 mL of EtOH:H_2O (3:2) was refluxed for 24 h. The reaction mixture was cooled and solvent was removed under reduced pressure and then water was added (5 mL). The reaction mixture was extracted by ethyl acetate (3 × 10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and crude product was purified by PLC on silica gel using *n*-hexane:acetone (2:1) as eluent. White solid, 0.022 g (43%), mp 183–85°C. FT-IR (KBr): 3055, 2960, 2857, 2769, 1698 (aldehyde C=O), 1662 (pyrone C=O), 1607, 1391, 1171, 956, 825 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.41 (s, 3H, CH_3), 6.23 (s, 1H, vinyl-H), 6.80 (d, 1H, *J* = 2 Hz, vinyl-H), 7.93 (d, 2H, *J* = 8.4 Hz, Ar-H), 8.0 (d, 2H, *J* = 8.4 Hz, Ar-H), 10.09 (s, 1H, aldehyde-H) ppm; ^{13}C NMR ($CDCl_3$): δ 20.31, 112.86, 115.14, 126.76, 130.53, 136.99, 138.30, 162.25, 166.13, 180.13, 191.64 ppm; ms: m/z (%); 214 (M^+, 28), 186 (94), 129 (100), 77 (38). Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.92; H, 4.67. Found: C, 72.80; H, 4.80.

4-(4-Oxo-6-phenyl-4*H*-pyran-2-yl)-benzaldehyde (4b). A solution of hexaminium salt 3b (2g, 14.16 mmol) in 50 mL of EtOH: H_2O (3:2) was refluxed for 24 h. The mixture was cooled and diluted with water. The precipitate was collected by filtration, washed with water and dried *in vacuo*. The crude product was purified by column chromatography on silica gel using *n*-hexane:acetone (2:1) as eluent to give the title compound. White solid, 0.66 g (58%), mp 185–187°C. FT-IR (KBr): 3062, 2830, 2738, 1697 (aldehyde C=O), 1646 (pyrone C=O), 1384, 890 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.85 (d, 1H, *J* = 2 Hz, vinyl-H), 6.90 (d, 1H, *J* = 2 Hz, vinyl-H), 7.55-7.56 (m, 3H, Ar-H), 7.85-7.87 (m, 2H, Ar-H), 8.04 (s, 4H, Ar-H), 10.11 (s, 1H, aldehyde-H) ppm; ^{13}C NMR ($CDCl_3$): δ 110.76, 112.08, 124.98, 125.52, 128.25, 129.26, 130.19, 130.68, 135.74, 136.99, 160.70, 162.69, 178.77, 190.14 ppm; ms: m/z (%): 276 (M^+, 85), 247 (100), 220 (48), 189 (44), 165 (35), 129 (23), 105 (17), 102 (29), 77 (25). Anal. Calcd. for $C_{18}H_{12}O_3$: C, 78.31; H, 4.34. Found: C, 77.95; H, 4.50.

General procedure for the synthesis of sulfonium salts (5b and 5c). To a stirred solution of 2-(4-bromomethylphenyl)-6-phenyl-4*H*-pyran-4-one 2b (2 g, 5.865 mmol) in dry MeOH:CH_2Cl_2 (2:1) was added dimethylsulfide (1.7 mL, 23.46 mmol) in one portion at 35°C under argon and the mixture was stirred for 72 h. The crude product was purified by concentration, precipitation in cold acetone (0°C), filtration followed by vacuum drying to give 5b.

In a similar manner, sulfonium salt 5c was prepared by reaction of 2,6-bis (4-bromomethylphenyl)-4*H*-pyran-4-one 2c (1g, 30 mmol) and dimethylsulfide (1.4 mL, 18.43 mmol).

Dimethyl[4-(4-oxo-6-phenyl-4*H*-pyran-2-yl)benzyl] sulfoniumbromide (5b). White powder, 1.56 g (66%), FT-IR (KBr): 3096, 2988, 2923, 2823, 1644 (pyrone C=O), 1428, 1388, 1016, 850 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.87 (s, 6H, 2 × CH_3), 4.82 (s, 2H, CH_2), 7.04 (d, 1H, *J* = 2 Hz, Vinyl-H), 7.08 (d, 1H, *J* = 2 Hz, Vinyl-H), 7.56-7.61 (m, 3H, Ph-H), 7.68 (d, 2H, *J* = 8 Hz, Ar-H), 8.17 (d, 2H, *J* = 8 Hz, Ar-H) ppm; ^{13}C NMR (DMSO-d_6): δ 23.88, 44.95, 110.98, 111.49, 126.07, 126.86, 129.23, 130.81, 131.49, 131.60, 131.77, 131.97, 161.55, 162.45, 178.92 ppm. Anal. Calcd. for $C_{20}H_{19}$ BrO_2S: C, 59.59; H, 4.71; S, 7.93. Found: C, 59.30; H, 4.70; S, 7.71.

2,6-Bis[dimethyl(4-methyphenyl)sulfoniumbromide]-4*H*-pyran-4-one (5c). Yellow solid, 0.83 g (65%), FT-IR (KBr): 3046, 2996, 2907, 2826, 1643 (pyrone C=O), 1599, 1505, 1420, 1383, 847cm^{-1}; ^1H NMR (D_2O): δ 2.85 (s, 12H, 4 × CH_3), 4.62 (s, 4H, 2 × CH_2), 6.52 (s, 2H, vinyl-H), 7.48 (d, 4H, *J* = 8 Hz, Ar-H), 7.69 (d, 4H, *J* = 8 Hz, Ar-H) ppm; ^{13}C NMR (D_2O): δ 24.35, 46.38, 110.65, 127.25, 131.30, 131.41, 131.87, 163.46, 182.15 ppm. Anal. Calcd. for $C_{23}H_{26}Br_2O_2S_2$: C, 49.49; H, 4.65; S, 11.48. Found: C, 49.47; H, 4.69; S, 11.49.

General procedure for the synthesis of epoxides 6(b_1-b_{10}) and 7. To a solution of sulfonium salt 5b (0.248 mmol) and aromatic aldehyde or pyronecarbaldehyde 4b (0.248 mmol) in acetonitrile:water (1:1) was added NaOH powder (0.248 mmol) at r.t and was stirred for 1 h to complete reaction. The resulting precipitates were filtered off and washed with water to remove remaining sulfonium salt, then dried in vacuum to give the epoxide.

2-{4-[3-(4-Chlorophenyl)oxiranyl]phenyl}-6-phenyl-4*H*-pyran-4-one ($6b_1$). White solid, 0.08g (81%), mp 208–210°C, FT-IR (KBr): 3059, 2990, 1645 (pyrone C=O), 1601, 1394, 1085, 832 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.86 (d, 1H, *J* = 1.6 Hz, epoxide-H), 3.90 (d, 1H, *J* = 1.6 Hz, epoxide-H), 6.83 (s, 2H, vinyl-H), 7.26-7.31 (m, 2H, Ar-H), 7.36-7.39 (m, 2H, Ar-H), 7.49-7.56 (m, 5H, Ar-H), 7.85-7.89 (m, 4H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$): δ 61.21, 61.42, 110.50, 110.55, 124.94, 125.22, 125.23, 125.84, 127.87, 128.17, 130.42, 130.47, 130.55, 133.42, 134.07, 139.37, 161.79, 162.39, 179.08 ppm; ms: m/z (%): 402 and 400 (M^+, 13 and 40), 371 (46), 365 (30), 275 (15), 191 (13), 147 (23), 133 (36), 105 (59), 102 (92), 89 (100), 77 (30), 69 (14). Anal. Calcd. for $C_{25}H_{17}ClO_3$: C, 74.95; H, 4.24. Found: C, 74.62; H, 4.30.

2-{4-[3-(2-Chlorophenyl)oxiranyl]phenyl}-6-phenyl-4*H*-pyran-4-one (6b$_2$). White solid, 0.039 g (78%), mp 195–196°C, FT-IR (KBr): 3039, 2987, 1646 (pyrone C=O), 1604, 1391, 1032, 764 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 3.83 (d, 1H, $J = 1.2$ Hz, epoxide-H), 4.23 (d, 1H, $J = 1.2$ Hz, epoxide-H), 6.85 (s, 2H, vinyl-H), 7.26-7.40 (m, 4H, Ar-H), 7.54-7.56 (m, 5H, Ar-H), 7.86-7.91 (m, 4H, Ar-H) ppm; ^{13}C NMR (CDCl$_3$): δ 59.35, 60.52, 110.43, 110.48, 124.78, 124.97, 125.27, 125.39, 126.16, 128.19, 128.30, 130.38, 130.51, 132.20, 133.61, 139.43, 161.99, 162.49, 179.15 ppm; ms: m/z (%): 402 and 400 (M$^+$, 5 and 14), 371 (7), 105 (73), 102 (100), 89 (97), 77 (39). Anal. Calcd. for $C_{25}H_{17}ClO_3$: C, 74.95; H, 4.24. Found: C, 74.70; H, 4.30.

2-{4-[3-(4-Nitrophenyl)oxiranyl]phenyl}-6-phenyl-4*H*-pyran-4-one (6b$_3$). White solid, 0.09 g (89%), mp 228–230°C, FT-IR (KBr): 3060, 2985, 1645 (pyrone C=O), 1597, 1514 (N=O), 1442, 1393, 1339 (N=O), 846 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 3.94 (d, 1H, $J = 1.2$ Hz, epoxide-H), 4.00 (d, 1H, $J = 1.2$ Hz, epoxide-H), 6.82 (s, 2H, vinyl-H), 7.50-7.55 (m, 7H, Ar-H), 7.85-7.91 (m, 4H, Ar-H), 8.26 (d, 2H, $J = 8$ Hz, Ar-H) ppm; ^{13}C NMR (CDCl$_3$): 60.87, 61.62, 110.49, 110.63, 122.96, 124.95, 125.31, 128.20, 130.34, 130.55, 130.86, 138.65, 142.75, 147.02, 161.69, 162.49, 179.03 ppm. Anal. Calcd. for $C_{25}H_{17}NO_5$: C, 73.05; H, 4.16; N, 3.40. Found: C, 72.80; H, 4.00; N, 3.40.

2-{4-[3-(2-Nitrophenyl)oxiranyl]phenyl}-6-phenyl-4*H*-pyran-4-one (6b$_4$). White solid, 0.094 g (93%), mp 240–241°C, FT-IR (KBr): 3068, 2855, 1643 (pyrone C=O), 1591, 1520 (N=O), 1399, 1340 (N=O), 852 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 3.87 (d, 1H, $J = 2$ Hz, epoxide-H), 4.49 (d, 1H, $J = 2$ Hz, epoxide-H), 6.81-6.82 (m, 2H, vinyl-H), 7.51-7.57 (m, 6H, Ar-H), 7.73-7.74 (m, 2H, Ar-H), 7.84-7.90 (m, 4H, Ar-H), 8.19 (d, 1H, $J = 8$ Hz, Ar-H) ppm; ^{13}C NMR (CDCl$_3$): δ 59.40, 60.37, 110.44, 110.55, 123.77, 124.92, 125.25, 125.53, 126.04, 127.92, 128.14, 130.38, 130.43, 130.66, 132.42, 133.44, 138.87, 146.47, 161.86, 162.35, 179.10 ppm. Anal. Calcd. for $C_{25}H_{17}NO_5$: C, 73.05; H, 4.13; N, 3.40. Found: C, 72.65; H, 4.00; N 3.40.

2-{4-[3-(4-Fluorophenyl)oxiranyl]-phenyl}-6-phenyl-4*H*-pyran-4-one(6b$_5$). White solid, 0.083g (88%), mp 186–187°C, FT-IR (KBr): 3058, 2984, 1645 (pyrone C=O), 1601, 1507, 1447, 1392, 1230, 831 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 3.87 (d, 1H, $J = 1.6$ Hz, epoxide-H), 3.91 (d, 1H, $J = 1.6$ Hz, epoxide-H), 6.83 (s, 2H, vinyl-H), 7.07-7.11 (m, 2H, Ar-H), 7.32-7.35 (m, 2H, Ar-H), 7.49-7.55 (m, 5H, Ph-H), 7.85-7.89 (m, 4H, Ar-H) ppm; ^{13}C NMR (CDCl$_3$): δ 61.18, 61.53, 110.54, 114.59, 114.80, 124.96, 125.23, 126.19, 126.27, 128.19, 130.43, 130.50, 131.28, 131.31, 139.52, 160.69, 161.84, 162.40, 163.15, 179.13 ppm; ms: m/z (%): 384 (M$^+$, 16), 355 (17), 147 (13), 108 (85), 105 (67), 102 (100), 77 (36), 69 (18). Anal. Calcd. for $C_{25}H_{17}FO_3$: C, 78.16; H, 4.42. Found: C, 77.77; H, 4.40.

2-[4-(3-Naphthalen-2-yl-oxiranyl)-phenyl]-6-phenyl-4*H*-4-one (6b$_6$). White solid, 0.086g (84%), mp 187–189°C, FT-IR (KBr): 3051, 2976, 1642 (pyrone C=O), 1600, 1503, 1390, 824 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 4.05 (d, 1H, $J = 1.6$, epoxide-H), 4.06 (d, 1H, $J = 1.6$, epoxide-H), 6.83 (s, 2H, vinyl-H), 7.42-7.57 (m, 8H, Ar-H), 7.48-7.57 (m, 7H, Ar-H), 7.84-7.90 (m, 8H, Ar-H) ppm; ^{13}C NMR (CDCl$_3$): δ 61.21, 62.30, 110.41, 110.42, 121.56, 124.15, 124.86, 125.12, 125.20, 125.26, 125.48, 126.75, 126.77, 127.51, 128.10, 130.35, 130.39, 132.07, 132.38, 132.91, 139.70, 161.74, 162.24, 178.99 ppm; ms: m/z (%): 416 (M$^+$, 3), 387 (8), 155 (21), 40 (68), 139 (100), 105 (55), 102 (38), 91 (79), 77 (52), 69 (8). Anal. Calcd. for $C_{29}H_{20}O_3$: C, 83.69; H, 4.80. Found: C, 83.30; H, 4.90.

2-{4-[3-(4-Methoxyphenyl)oxiranyl]phenyl-6-phenyl-4*H*-pyran-4-one (6b$_7$). White solid, 0.06g (62%), mp 170–171°C, FT-IR (KBr): 3055, 2955, 1644 (pyrone C=O), 1605, 1511, 1388, 1249, 829 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 3.82 (s, 3H, OCH$_3$), 3.83 (d, 1H, $J = 1.6$ Hz, epoxide-H), 3.92 (d, 1H, $J = 1.6$ Hz, epoxide-H), 6.81 (s, 2H, vinyl-H), 6.92 (d, 2H, $J = 8$ Hz, Ar-H), 7.26-7.29 (m, 2H, Ar-H), 7.48-7.55 (m, 5H, Ar-H), 7.84-7.87 (m, 4H, Ar-H) ppm; ^{13}C NMR (CDCl$_3$): δ 54.30, 60.99, 62.02, 110.40, 110.42, 113.07, 124.89, 125.11, 125.15, 125.80, 127.47, 128.13, 130.22, 130.37, 130.42, 139.93, 158.93, 161.85, 162.29, 179.07 ppm; ms: m/z (%): 396 (M$^+$, 31), 368 (52), 367 (100), 275 (21), 121 (68), 120 (58), 105 (66), 102 (38), 91 (79), 77 (52), 69 (8). Anal. Calcd. for $C_{26}H_{20}O_4$: C, 78.84; H, 5.04. Found: C, 78.45; H, 5.20.

2-Phenyl-6-[4-(3-styryloxiranyl)phenyl]-4*H*-pyran-4-one (6b$_8$). Yellow solid, 0.069g (71%), mp 97–99°C, FT-IR (KBr): 3057, 2858, 1650 (pyrone C=O), 1600, 1497, 1447, 1395, 884 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 3.54 (dd, 1H, $J = 1.6$, 8 Hz, epoxide-H), 3.96 (d, 1H, $J = 1.6$ Hz, epoxide-H), 6.08 (dd, 1H, $J = 8$, 16 Hz, vinyl-H), 6.82 (s, 2H, C$_3$- and C$_5$-H), 6.85 (d, 1H, $J = 16$ Hz, vinyl-H), 7.28-7.56 (m, 10H, Ar-H), 7.85-7.88 (m, 4H, Ar-H) ppm; ^{13}C NMR (CDCl$_3$): δ 59.12, 62.44, 110.43, 110.46, 124.52, 124.93, 125.14, 125.20, 125.52, 127.32, 127.70, 128.16, 130.28, 130.40, 130.46, 134.00, 134.79, 139.82, 161.89, 162.37, 179.15 ppm; ms: m/z (%): 392 (M$^+$, 4), 364 (6), 363 (100), 276 (12), 275 (33), 248 (23), 147 (30), 133 (34), 130 (33), 116 (53), 115 (100), 105 (57), 102 (39), 77 (30), 69 (21). Anal. Calcd. for $C_{27}H_{20}O_3$: C, 82.67; H, 5.09. Found: C, 82.43; H, 4.14.

2-Phenyl-6-[4-(3-*p*-tolyloxiranyl)phenyl]-4*H*-pyran-4-one (6b$_9$). White solid, 0.075g (80%), mp 203–205°C, FT-IR (KBr): 3058, 2992, 1641 (pyrone C=O), 1614, 1391, 1021, 813 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 2.37 (s, 3H, CH$_3$), 3.85 (d, 1H, $J = 1.6$ Hz, epoxide-H), 3.93 (d, 1H, $J = 1.6$ Hz, epoxide-H), 6.82 (s, 2H, vinyl-H), 7.19-7.26 (m, 4H, Ar-H), 7.49-7.55 (m, 5H, Ar-H), 7.85-7.88 (m, 4H, Ar-H) ppm; ^{13}C NMR (CDCl$_3$): δ 20.22, 61.11, 62.16, 110.47, 110.48, 124.46, 124.93, 125.16, 125.20, 128.16, 128.33, 130.31, 130.43, 130.45, 132.52, 137.50, 139.94, 161.89, 162.35, 179.1 ppm; ms: m/z (%): 380 (M$^+$, 46), 351 (59), 275 (33), 133 (25), 114 (53), 105 (100), 102 (88), 89 (27), 77 (55). Anal. Calcd. for $C_{26}H_{20}O_3$: C, 82.14; H, 5.26. Found: C, 82.00; H, 5.58.

2-Phenyl-6-[4-(3-phenyloxiranyl)phenyl]-4*H*-pyran-4-one (6b$_{10}$). White solid, 0.075g (83%), mp 197–199°C, FT-IR (KBr): 3059, 2986, 1645 (pyrone C=O), 1603, 1393, 879cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 3.88 (d, 1H, $J = 1.6$ Hz, epoxide-H), 3.93 (d, 1H, $J = 1.6$ Hz, epoxide-H), 6.81 (s, 2H, vinyl-H), 7.35-7.39 (m, 5H, Ar-H), 7.49-7.54 (m, 5H, Ar-H), 7.84-7.87 (m, 4H, Ar-H) ppm; ^{13}C NMR (CDCl$_3$): δ 61.12, 62.05, 110.65, 110.79, 124.45, 124.87, 125.11, 125.18, 127.53, 127.59, 128.11, 130.31, 130.35, 130.41, 135.47, 139.73, 161.80, 162.29, 179.14 ppm; ms: m/z (%): 366 (M$^+$, 75), 337 (5), 195 (16), 191 (32), 133 (22), 130 (31) 105 (100), 102 (100), 89 (81), 77 (56), 69 (15). Anal. Calcd. for $C_{25}H_{18}O_3$: C, 82.01; H, 4.91. Found: C, 81.66; H, 5.00.

2,3-Bis[4-(4-oxo-6-phenyl-4*H*-pyran-2-yl)phenyl]oxirane (7). Yellow powder, 0.081g (61%), mp 282–284°C, FT-IR (KBr): 3058, 2963, 1648 (pyrone C=O), 1603, 1501, 1386, 942, 839cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 3.97 (s, 2H, epoxide-H), 6.83 (s, 4H, vinyl-H), 7.52-7.59 (m, 10H, Ar-H), 7.84-7.91 (m, 8H, Ar-H) ppm; ^{13}C NMR (CDCl$_3$): δ 61.46, 110.59, 110.66, 124.94, 125.27, 125.28, 128.19, 130.40, 130.50, 130.69, 139.16, 161.72, 162.40, 179.03 ppm; ms: m/z (%): 536 (M$^+$, 17), 508 (40), 264 (73), 248 (73), 234 (73), 191 (73), 189 (73), 105 (70), 102 (53), 77 (63). Anal. Calcd. for $C_{36}H_{24}O_5$: C, 80.61; H, 4.47. Found: C, 80.68; H, 4.51.

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Synthesis of 2,6-Bis(1*H*-indole-6-yl)-4*H*-pyran-4-ones *via* Leimgruber–Batcho Indole Synthesis

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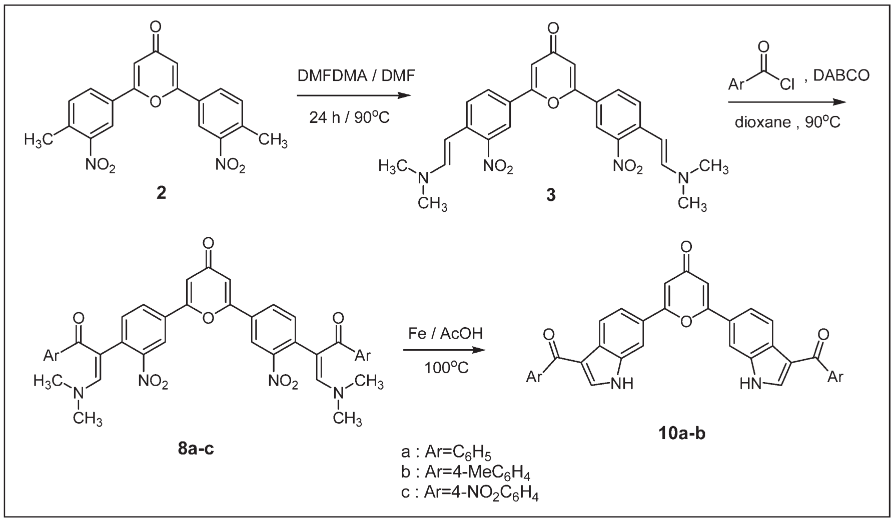

2,6-Bis(1*H*-indole-6-yl)-4*H*-pyran-4-one **4** was synthesized *via* Leimgruber–Batcho methodology starting from 2,6-bis(4-methyl-3-nitrophenyl)-4*H*-pyran-4-one **2**. Enamine intermediate in this reaction, **3**, reacts with aroyl chlorides in the presence of 1,4-diazabicyclo[2.2.2]octane in dioxane to give the substituted enamines **8(a-c)**. Enamines **8a,b** undergo reductive cyclization with Fe/AcOH to the corresponding 3-aroylindoles **10a,b**.

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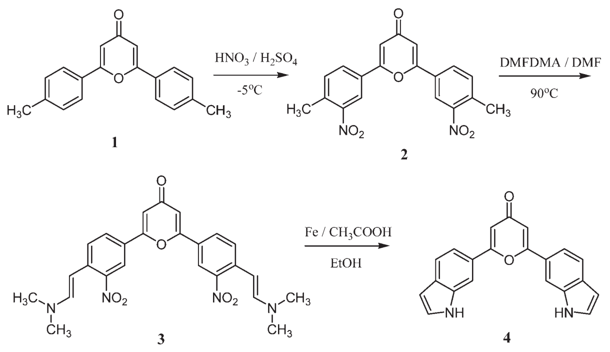
INTRODUCTION

The indole ring system is one of the most ubiquitous heterocycles in nature and an important structural component in many pharmaceutical agents [1]. Therefore synthesis and functionalization of indoles has been a major area of focus for synthetic organic chemists, and numerous methods for the preparation of indoles have been developed [2]. One powerful procedure is the Leimgruber–Batcho indole synthesis [3]. The classical sequence of this reaction that has been used for the preparation of 2,3-unsubstituted indoles, involves the condensation of methyl group positioned adjacent to an aromatic nitro group (as 2, Scheme 1) with *N*,*N*-dimethyl formamide-dimethyl acetal (DMFDMA) to give the enamine intermediate such as **3**. Subsequent reduction of the nitro group leads to spontaneous cyclization and formation of the corresponding indole derivative (as **4**). Modifications of Leimgruber–Batcho procedure to accelerate products formation [4] or to the production of *N*-substituted indoles [5] have also been described.

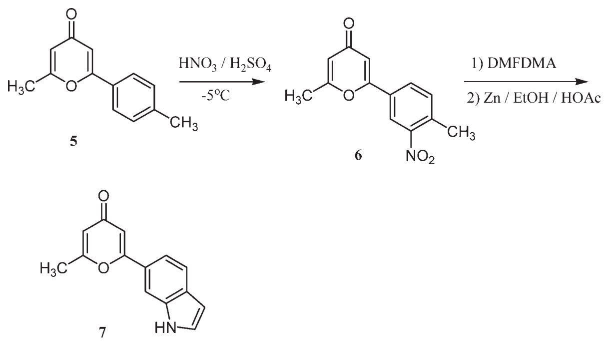
Synthesis of 3-substituted indoles has also received continued attention. 3-Acylindoles are precursors to a variety of biologically important alkaloids [6]. 3-Aroylindoles represent significant biological activities, for example, some of these have potential as promising anticancer agents [7]. For the synthesis of 3-aroylindoles, electrophilic substitution at C-3 position of indole ring through reaction of indoles with aroyl chlorides in the presence of Grignard reagents as base and/or metal chlorides as Lewis acid is well known [7]. Another appropriate method for synthesis of 3-substituted indoles, which include functionalization of enamine intermediates in Leimgruber–Batcho procedure, has rarely been reported [8]. This modification, in which reaction of the enamine intermediate with aroyl chlorides carried out in the presence of a tertiary amine, can be considerable for its potential regiochemical control in the synthesis of 3-substituted indoles.

Polycyclic aryl and heteroaryl substituted 4-pyrones have also been found in a variety of natural and synthetic biologically active compounds [9]. They have been shown to be anticoagulant [10a], anti-HIV [10b], and antitumor [10c] agents. Through our attempts to prepare various azaaryl substituted 4-pyrones, we turned

Scheme 1



Scheme 2



our attention to the 4-pyrone derivatives that would allow for the construction of the indole moiety. Herein, we report synthesis of two (1*H*-indole-6-yl)-4-pyrones *via* the Leimgruber–Batcho methodology and then reaction of enamine intermediate **3** with aroylchlorides in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) as tertiary amine and the results of reductive cyclization of obtained enaminones for synthesis of 3-aroyl substituted indole derivatives.

RESULTS AND DISCUSSION

Scheme 1 shows the synthetic sequences for preparation of product **4**. The starting compound **1** was synthesized through cyclization of related 1,3,5-triketone derivative under acidic conditions, which is an important method for the synthesis of a variety of 4-pyrone structures [11]. Nitration of **1** with HNO_3/H_2SO_4 at −5°C for 0.5 h afforded the dinitro **2** in quantitative yield. These nitration conditions were different from those reported for nitration of diphenyl-4-pyrones [12]. Treatment of **2** with 8 equiv. of DMFDMA at 90°C for 24 h gave stable dienamine **3** in 86% yield. Reductive cyclization of **3** was carried out using Fe or Zn in EtOH/HOAc at 80°C, that provided the 2,6-bis(1*H*-indole-6-yl)-4*H*-pyran-4-one **4** after 5 and 24 h, respectively. Therefore the conditions using Fe/EtOH/AcOH were optimal resulting in a faster and also a cleaner reaction.

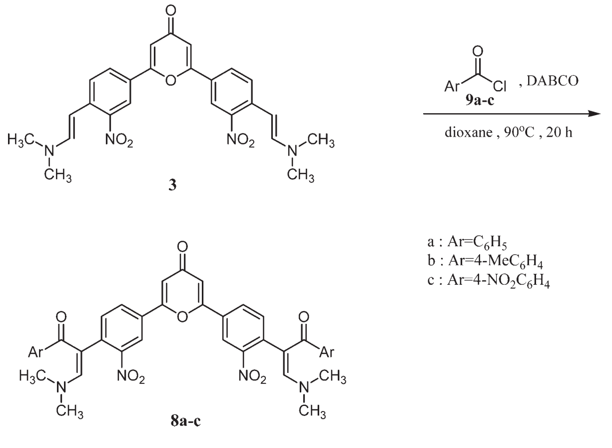
We also used 2-(4-methylphenyl)-6-methyl-4*H*-pyran-4-one **5** in the same synthetic sequence. This compound was synthesized according to reported procedure [13]. Nitration of **5** gave the *ortho*-nitrotolyl derivative **6**. Treatment of **6** with DMFDMA at 80°C and subsequent reduction of nitro group resulted the indole **7** in 33% yield. The enamine intermediate in this reaction that was not isolated was readily converted to indole **7**, by stirring with the Zn/EtOH/AcOH mixture at room temperature for 4 h. This result indicated that oxidation of the methyl ortho- to nitro-group in compound **6** has predominantly been achieved (Scheme 2).

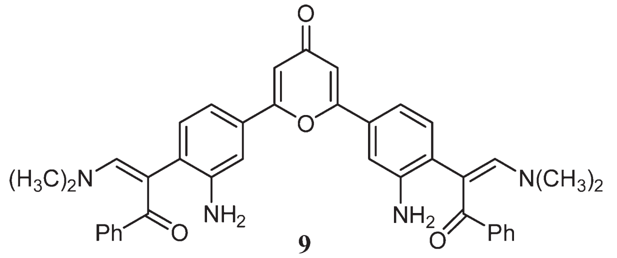
We then examined the incorporation of aroyl substituents onto the enamine intermediate **3**. The reactivity of enamine **3** toward aroyl chlorides such as benzoylchloride, 4-methylbenzoylchloride, and 4-nitrobenzoylchloride was explored initially using triethylamine in dry dioxane at 90°C. Under these conditions no reactivity was observed. Then, we used 2 equiv. of DABCO instead of triethylamine, and the substitution was successfully achieved as shown in Scheme 3. The structures of products **8a-c** were characterized by spectroscopic data and elemental analysis.

In the final step, a few reagents and conditions were evaluated to optimize the reductive cyclization of enaminones **8a-c** to form the 3-aroyl substituted indole derivatives. When the compound **8a** was treated with Zn or Fe in 1:1 mixture of EtOH–AcOH at 90–100°C for 24 h, the major product that was formed and separated, showed a singlet at 3.0 ppm for 12 protons in ^1H NMR spectrum (in DMSO-d_6), which indicated the presence of $-N(CH_3)_2$ groups in molecule and established that the cyclization has not been accomplished. Spectroscopic data confirmed the symmetrical structure of **9**, which was obtained in 32% yield under these conditions (Fig. 1).

Treatment of enaminones **8a** and **8b** with Fe/AcOH at 100°C for 24 h, gave the desired bis(indole) derivatives

Scheme 3





9

Figure 1. Structure of compound **9** obtained from reduction of the enaminone **8a** with Zn in EtOH–AcOH (1:1).

10a and **10b** as major products, respectively (Scheme 4). These compounds were separated and characterized by spectroscopic methods. The Fe/AcOH system has been described previously for reduction-cyclization of nitro group for construction of a variety of indole structures [14].

We also found that using Fe in 1*M* aqueous HCl solution/MeOH with heating resulted in a complex mixture with unidentified residues.

In conclusion, we have reported the synthesis of two (1*H*-indole-6-yl)-4-pyrones *via* Leimgruber–Batcho indole synthesis, starting from the corresponding *ortho*-methylnitrophenyl derivatives. Aroyl substituents at C-3 of the bis(indole) derivative were installed *via* reaction of the enamine intermediate with aroylchlorides before the final reductive cyclization. Among the different conditions and reagents that were examined for reductive cyclization of enaminoketones, the Fe/AcOH at 100°C was the appropriate method for this purpose. This modified Leimgruber–Batcho procedure is attractive because of the regioselectivity of substitution, which may be observed less in the direct C-3 aroylation of indole nucleus.

EXPERIMENTAL

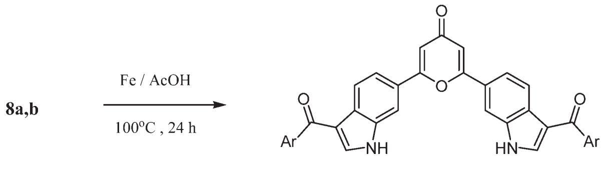
Melting points were determined on a 1202D model Electrothermal MEL-TEMP apparatus and are uncorrected. FTIR spectra were obtained with a Bruker Tensor 27 spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded with a Bruker Spectrospin Avance 400 spectrometer operating at 400 and 100 MHz, respectively; chemical shifts are given in parts per million (ppm, δ) relative to solvent peaks as internal standards (δ: $CDCl_3$: 7.26 ppm (^1H), 76 ppm (^{13}C); DMSO-d_6: 2.50 ppm (^1H), 39.5 ppm (^{13}C)). Mass spectra (MS) were measured by a Shimadzo (70 ev) spectrometer and elemental analyses were measured by Vario EL III apparatus (Elementar Co.). Column chromatography was done using silica gel (Merk Kieselgel 60, no. 9385, 230-400 mesh ASTM). Thin-layer chromatography was done with prepared glass-backed plates (20 × 20 cm^2, 500 μ) using silica gel (Merk Kieselgel 60 HF_{254}, no. 7739).

2,6-Bis(4-methyl-3-nitrophenyl)-4*H*-pyran-4-one (2). A stirred solution of 3.66 g (0.013 mol) of 2,6-bis(4-methylphenyl)-4*H*-pyran-4-one (**1**) in 11.5 mL of concentrated sulfuric acid (95–98%) cooled to −5°C using ice-salt bath. To this solution, 7 mL of fuming nitric acid was added dropwise over 15 min. The reaction mixture was stirred at −5°C for a further 0.5 h and then poured to 100 g ice. The produced precipitate was collected by filtration and washed with water and dried *in vacuo* to give **2** (4.7 g, 98% yield) as a white solid, mp 254°C; FTIR (KBr): ν 3065, 2977, 1663 (pyrone C=O), 1614, 1528, 1444, 1355 cm^{-1}; ^1H NMR($CDCl_3$): δ 2.703 (s, 6H, CH_3), 6.861 (s, 2H, pyrone H-3), 7.564 (d, 2H, J = 8.1 Hz, phenyl H-5), 7.948 (dd, 2H, J = 8.0, 1.9 Hz, phenyl H-6), 8.438 (d, 2H, J = 1.9 Hz, phenyl H-2) ppm; ^{13}C NMR ($CDCl_3$): δ 19.5 (CH_3), 111.4, 121.1, 128.6, 129.3, 133.0, 136.1, 148.7, 160.0, 178.0 (pyrone CO) ppm. MS (*m/z*, %): 366 (M^+, 30), 338 (100). *Anal.* Calcd. for $C_{19}H_{14}N_2O_6$: C, 62.32; H, 3.82; N, 7.65. Found: C, 61.94; H, 3.89; N, 7.39.

2,6-Bis{4-[*trans*-2-(*N,N*-dimethylamino)ethenyl]-3-nitrophenyl}-4*H*-pyran-4-one (3). A mixture of (**2**) (4.70 g, 0.013 mol) and DMFDMA(12.4 g, 0.104 mol) in 100 mL DMF was heated at 90°C under Ar for 24 h. After cooling, the precipitated product was filtered, washed several times with H_2O, and dried *in vacuo* to provide 5.3 g (86.5 %) of **3** as a deep red solid, mp 250°C; FTIR(KBr): ν 3075, 2900, 2802, 1640 (pyrone C=O), 1591, 1516, 1375, 1209, 1098 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.975 (s, 12H, $-N(CH_3)_2$), 5.713 (d, 2H, J = 13.2 Hz, PhCH=), 6.961 (s, 2H, pyrone H-3), 7.777 (d, 2H, J = 13.2 Hz, $=CH-N(Me)_2$), 7.859 (d, 2H, J = 8.9 Hz, phenyl H-5), 7.935 (dd, 2H, J = 8.8, 1.9 Hz, phenyl H-6), 8.364 (d, 2H, J = 2.0 Hz, phenyl H-2) ppm; ^{13}C NMR ($CDCl_3$): δ 39.9 (CH_3-N), 89.5, 109.2, 122.4, 123.0, 123.2, 127.6, 137.8, 143.2, 145.7, 160.4, 178.6 (pyrone CO) ppm; MS (*m/z*, %): 476 (M^+, 65), 459 (40), 386 (50), 42 (100); *Anal.* Calcd. for $C_{25}H_{24}N_4O_6$: C, 63.02; H, 5.04; N, 11.76. Found: C, 62.86; H, 5.27; N, 11.90.

2,6-Bis(1*H*-indole-6-yl)-4*H*-pyran-4-one (4). A suspension of (**3**) (0.476 g, 1 mmol), AcOH (6 mL), EtOH (6 mL), and Fe (2.24 g, 40 mmol) was heated with stirring at 80°C. After 5 h, the dark color of the reaction mixture disappeared and a brown suspension was obtained, indicating the completion of reaction. The reaction mixture was cooled, concentrated by rotary evaporator to remove EtOH, neutralized by saturated $NaHCO_3$ solution, and then extracted by EtOAc. The extract was dried over anhydrous Na_2SO_4, concentrated and purified by thin-layer chromatography (silica gel, 1:1 acetone:*n*-hexane) to give 0.114 g (35% yield) of **4**, mp 280°C (decomp.); FTIR (KBr): ν 3367 (NH), 3161, 2918, 1637 (pyrone C=O), 1575, 1554, 1456, 1395, 1181 cm^{-1}; ^1H NMR (DMSO-d_6): δ 6.557 (t, br., 2H, J = 1.8 Hz, indole H-3), 6.891 (s, 2H, pyrone H-3), 7.568 (t, 2H, J = 2.7 Hz, indole H-2), 7.674 (dd, 2H, J = 8.4, 1.5 Hz, indole H-5), 7.739 (d, 2H, J = 8.4 Hz, indole H-4), 8.091 (s, 2H, indole H-7), 11.506 (s, 2H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 101.6, 109.4,

Scheme 4



10a : Ar=C_6H_5
10b : Ar=4-MeC_6H_4

109.6, 116.6, 120.6, 123.7, 128.6, 130.1, 135.7, 163.9, 178.8 (pyrone CO) ppm; MS (*m/z*, %): 326 (M^+, 80), 298 (100), 269 (20), 141 (45); *Anal*. Calcd. for $C_{21}H_{14}N_2O_2$: C, 77.30; H, 4.29; N, 8.59. Found: C, 77.0; H, 4.55; N, 8.53.

2-(4-Methyl-3-nitrophenyl)-6-methyl-4*H*-pyran-4-one (6). A stirred solution of 0.4 g (2 mmol) of 2-(4-methylphenyl)-6-methyl-4*H*-pyran-4-one (**5**) in 1 mL of concentrated sulfuric acid (95–98 %) cooled to −5°C using ice-salt bath. To this solution, 0.6 mL of fuming nitric acid was added dropwise over 15 min. The reaction mixture was stirred at −5°C for a further 0.5 h and then poured to 100 g ice. The precipitate was collected by filtration, washed with water, and dried *in vacuo* to give **6** (0.45 g, 92% yield) as a white solid, mp 160°C; FTIR (KBr): ν 3066, 2970, 1660 (pyrone C=O), 1612, 1531, 1402, 1350, 1168, 920, 796 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.378 (s, 3H, CH_3), 2.627 (s, 3H, CH_3), 6.172 (d, 1H, J = 1.1 Hz, pyrone H-5), 6.695 (d, 1H, J = 1.9 Hz, pyrone H-3), 7.457 (d, 1H, J = 8.1 Hz, phenyl H-5), 7.828 (dd, 1H, J = 8.4, 1.7 Hz, phenyl H-6), 8.324 (d, 1H, J = 1.6 Hz, phenyl H-2) ppm; ^{13}C NMR ($CDCl_3$): δ 18.8, 19.3, 110.3, 113.5, 120.7, 128.3, 129.4, 132.6, 135.4, 148.4, 159.7, 164.5, 178.4 (pyrone CO) ppm; MS (*m/z*, %): 245 (M^+, 89), 228 (42), 217 (32), 172 (100), 89 (46); *Anal*. Calcd. for $C_{13}H_{11}NO_4$; C, 63.67; H, 4.49; N, 5.71. Found: C, 63.30; H, 4.52; N, 5.47.

2-(1*H*-indole-6-yl)-6-methyl-4*H*-pyran-4-one (7). A mixture of (**6**) (0.4 g, 1.63 mmol) and DMFDMA (0.78 g, 6.53 mmol) in 1 mL DMF was heated at 80°C under Ar for 24 h. After cooling, 30 mL H_2O was added to the reaction mixture and the precipitated product was filtered, washed with H_2O, and dried *in vacuo*. The red solid was mixed with Zn (2.12 g, 32.6 mmol), EtOH (4 mL), and AcOH (4 mL). The mixture was stirred at r.t. for 4 h and then concentrated by rotary evaporator. The residue was neutralized by saturated $NaHCO_3$ solution and the precipitate was filtered. This solid was purified by thin-layer chromatography (silica gel, 1:1 acetone:*n*-hexane) to give **7** (0.12 g, 33% yield). mp 228°C; FTIR (KBr): ν 3331(NH), 3002, 2976, 1650 (pyrone C=O), 1590, 1406, 1324, 1159, 916, 676 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.393 (s, 3H, CH_3), 6.185 (d, 1H, J = 1.0 Hz, pyrone H-5), 6.608 (s, 1H, pyrone H-3), 6.768 (d, 1H, J = 2.2 Hz, indole H-3), 7.380 (t, 1H, J = 2.8 Hz, indole H-2), 7.516 (dd, 1H, J = 8.4, 1.5 Hz, indole H-5), 7.710 (d, 1H, J = 8.4 Hz, indole H-4), 7.869 (s, 1H, indole H-7), 8.896 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$): δ 18.9 (CH_3), 102.0, 108.1, 108.7, 113.1, 116.4, 120.1, 123.8, 126.2, 129.4, 134.6, 164.1, 164.2, 179.5 (pyrone CO) ppm; MS (*m/z*, %): 225 (M^+, 28); *Anal*. Calcd. for $C_{14}H_{11}NO_2$: C, 74.67; H, 4.89; N, 6.22. Found: C, 74.29; H, 5.00; N, 6.51.

General procedure for the synthesis of enaminoketones (8a-c). A mixture of enamine (**3**) (0.952 g, 2 mmol), DABCO (0.448 g, 4 mmol), and aroylchlorides (**9a-c**) (12 mmol) in 20 mL dioxane (dry) was heated at 90°C for 20 h. The resulting suspension was cooled to r.t. and water (120 mL) was added. The resulting mixture was stirred for 5 min and then extracted with chloroform (4 × 50 mL). The combined chloroform extract was washed with 150 mL of H_2O, dried over Na_2SO_4, and concentrated to dryness. The residue was purified by column chromatography (silica gel, 6:4 acetone:*n*-hexane) to give the products **9a-c**.

2,6-Bis{4-[(Z)-1-benzoyl-2-(N,N-dimethylamino) ethenyl]-3-nitrophenyl}-4H-pyran-4-one (8a). This compound was obtained as a red solid in 67% yield, mp 160–162°C; FTIR (KBr): ν 3062, 2921, 1702 (benzoyl C=O), 1649 (pyrone C=O), 1579, 1534, 1382, 1312 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.832 (s, 12H, —$N(CH_3)_2$), 6.887 (s, 2H, pyrone H-3), 7.262 (d, 2H, J = 1.9 Hz, =CH—$N(Me)_2$), 7.470–7.362 (m, 10H, benzoyl-H), 7.519 (d, 2H, J = 6.9 Hz, phenyl H-5), 8.006 (d, 2H, J = 6.5 Hz, phenyl H-6), 8.392 (s, 2H, phenyl H-2) ppm; ^{13}C NMR ($CDCl_3$): δ 42.8 (CH_3-N), 106.5, 111.4, 120.5, 127.0, 127.4, 127.6, 129.0, 129.5, 134.2, 134.7, 139.6, 149.8, 154.3, 160.1, 178.2 (pyrone CO), 192.3 (benzoyl CO) ppm; *Anal*. Calcd. for $C_{39}H_{32}N_4O_8$: C, 68.35; H, 4.67; N, 8.18. Found: C, 68.63; H, 5.00; N, 8.05.

2,6-Bis{4-[(Z)-2-(N,N-dimethylamino)-1-(4-methylbenzoyl) ethenyl]-3-nitrophenyl}-4H-pyran-4-one (8b). This compound was obtained as a red solid in 65% yield, mp 165–168°C; FTIR (KBr): ν 3021, 2918, 1702 (aroyl C=O), 1649 (pyrone C=O), 1579, 1531, 1382, 1308, 1096 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.383 (s, 6H, *p*-CH_3-benzoyl), 2.844 (s, 12H, $N(CH_3)_2$), 6.911 (s, 2H, pyrone H-3), 7.187 (d, 4H, J = 7.8 Hz, aroyl H-3), 7.298 (s, 2H, =CH—$N(Me)_2$), 7.439 (d, 4H, J = 7.9 Hz, aroyl H-2), 7.476 (s, 2H, phenyl H-5), 8.005 (s, br, 2H, phenyl H-6), 8.391 (s, 2H, phenyl H-2) ppm; ^{13}C NMR ($CDCl_3$): 28.2 (*p*-CH_3-benzoyl), 42.9 (CH_3-N), 106.5, 111.5, 120.6, 127.0, 127.5, 127.6, 129.0, 129.6, 134.2, 134.7, 139.6, 149.8, 154.2, 160.1, 178.1 (pyrone CO), 192.3 (aroyl CO) ppm; *Anal*. Calcd. for $C_{41}H_{36}N_4O_8$: C, 69.03; H, 5.05; N, 7.85. Found: C, 68.98; H, 5.09; N, 7.78.

2,6-Bis{4-[(Z)-2-(N,N-dimethylamino)-1-(4-nitrobenzoyl)-ethenyl]-3–nitrophenyl}-4H-pyran-4-one (8c). This compound was obtained as an orange solid in 54% yield, mp 172–174°C; FTIR (KBr): ν 3070, 2921, 1711 (aroyl C=O), 1648 (pyrone C=O), 1571, 1524, 1389, 1347, 1313, 1097 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.881 (s, 12H, $N(CH_3)_2$), 6.920 (s, 2H, pyrone H-3), 7.184 (s, 2H, =CH—$N(Me)_2$), 7.490 (d, 2H, J = 8.0 Hz, phenyl H-5), 7.666 (d, 4H, J = 8.5 Hz, aroyl H-3), 8.028 (d, 2H, J = 7.8 Hz, phenyl H-6), 8.252 (d, 4H, J = 8.5 Hz, aroyl H-2), 8.429 (d, 2H, J = 1.4 Hz, phenyl H-2) ppm; ^{13}C NMR ($CDCl_3$): δ 45.9 (CH_3-N), 111.7, 120.8, 122.4, 122.5, 127.7, 128.1, 130.1, 133.7, 134.2, 145.6, 147.4, 149.8, 154.3, 178.1 (pyrone CO), 189.9 (aroyl CO) ppm; *Anal*. Calcd. for $C_{39}H_{30}N_6O_{12}$: C, 60.41; H, 3.87; N, 10.84. Found: C, 60.09; H, 4.13, N, 10.71.

2,6-Bis{3-amino-4-[(*Z*)-1-benzoyl-2-(*N*,*N*-dimethylamino)ethenyl]phenyl}-4*H*-pyran-4-one (9). A suspension of **8a** (0.342 g, 0.5 mmol), AcOH (3 mL), EtOH (3 mL), and Zn (1.30 g, 20 mmol) was heated with stirring at 90°C for 24 h. The hot reaction mixture was then filtered and washed with an appropriate amount of warm methanol. The combined filtrate was then concentrated by rotary evaporator to remove the alcohols (EtOH, MeOH), neutralized by saturated $NaHCO_3$ solution and extracted by EtOAc. The extract was dried over anhydrous Na_2SO_4, concentrated, and purified by thin-layer chromatography (silica gel, 1:1 acetone:chloroform) to give 0.099 g (32% yield) of **9** as brown solid, mp 300°C (decomp.), FTIR (KBr): ν 3383, 3217 (NH_2), 3067, 2920, 1737 (benzoyl C=O), 1635 (pyrone C=O), 1562, 1460, 1406 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.024 (s, 12H, —$N(CH_3)_2$), 6.713 (s, 2H, pyrone H-3), 6.777 (d, 2H, J = 8.5 Hz, phenyl H-5), 7.419 (dd, 2H, J = 8.5, 1.5 Hz, phenyl H-6), 7.493–7.530 (m, 6H: 2H, =CH—$N(Me)_2$, 4H, benzoyl H-3), 7.586 (t, 2H, J = 7.3 Hz, benzoyl H-4), 7.670 (d, 4H, J = 7.6 Hz, benzoyl H-2), 7.957 (d, 2H, J = 1.2 Hz, phenyl H-2), 11.686 (br., NH_2) ppm; ^{13}C

NMR (DMSO-d_6): δ 41.7 (CH_3-N), 97.3, 107.3, 108.0, 117.5, 118.3, 121.6, 128.4, 128.5, 131.2, 131.9, 133.1, 141.9, 155.5, 163.0, 178.9 (pyrone CO), 188.2 (benzoyl CO) ppm; *Anal.* Calcd. for $C_{39}H_{36}N_4O_4$: C, 75.00; H, 5.77; N, 8.97. Found C, 74.88; H, 5.59; N, 9.16.

General procedure for the synthesis of 3-aroylindoles (10a-b). A mixture of the enaminone **8a** or **8b** (0.3 mmol), iron powder (0.5 g), and glacial HOAc (4 mL) was refluxed at 100°C. After 24 h, the dark color of the reaction mixture disappeared and a brown suspension was obtained. The reaction mixture was cooled, neutralized by saturated $NaHCO_3$ solution, and then extracted by EtOAc. The extract was dried over anhydrous Na_2SO_4, concentrated and purified by thin-layer chromatography (silica gel, EtOAc) to give the products **10a** or **10b** in 25 and 22% yield, respectively.

2,6-Bis(3-benzoyl-1H-indole-6-yl)-4H-pyran-4-one (10a). This compound was obtained as a pale-yellow solid in 25% yield, mp 270°C (decomp.); FTIR (KBr): ν 3416 (NH), 3122, 2923, 1736 (benzoyl C=O), 1637 (pyrone C=O), 1576, 1502, 1451 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.011 (s, 2H, pyrone H-3), 7.550–7.586 (m, 4H, benzoyl H-3), 7.639 (t, 2H, $J = 7.0$ Hz, benzoyl H-4), 7.828 (d, 4H, $J = 7.1$ Hz, benzoyl H-2), 7.954 (d, 2H, $J = 8.0$ Hz, indole H-4), 8.140 (s, 2H, indole H-7), 8.234 (s, 2H, indole H-2), 8.404 (d, 2H, $J = 8.5$ Hz, indole H-5), 8.879 (s, 2H, NH, deuterium oxide-exchangeable) ppm; ^{13}C NMR (DMSO-d_6): δ 110.3, 110.6, 115.2, 119.8, 122.1, 125.9, 128.5, 128.6, 128.7, 131.5, 136.8, 138.2, 140.1, 163.4, 179.1 (pyrone CO), 190.0 (benzoyl CO) ppm; *Anal.* Calcd. for $C_{35}H_{22}N_2O_4$: C, 78.65; H, 4.12; N, 5.24. Found: C, 78.60; H, 4.23; N, 5.01.

2,6-Bis[1H-indole-3-(4-methylbenzoyl)-6-yl]-4H-pyran-4-one (10b). This compound was obtained as a pale-yellow solid, mp 240°C (decomp.); FTIR (KBr): ν 3398 (NH), 3100, 2925, 1737 (aroyl C=O), 1641 (pyrone C=O), 1600, 1517, 1452, 1423, 1383 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.422 (s, 6H, CH_3), 7.011 (s, 2H, pyrone H-3), 7.376 (d, 4H, $J = 7.9$ Hz, aroyl H-3), 7.751 (d, 4H, $J = 7.9$ Hz, aroyl H-2), 7.946 (d, 2H, $J = 8.6$ Hz, indole H-4), 8.147 (s, 2H, indole H-7), 8.225 (s, 2H, indole H-2), 8.302 (s, 2H, NH, deuterium oxide-exchangeable) 8.389 (d, 2H, $J = 8.5$ Hz, indole H-5) ppm; ^{13}C NMR (DMSO-d_6): δ 28.4, 109.6, 110.8, 115.3, 119.3, 121.9, 125.3, 128.7, 128.9, 129.1, 131.2, 137.6, 138.2, 141.4, 162.9, 179.0 (pyrone CO), 189.6 (aroyl CO) ppm; *Anal.* Calcd. for $C_{37}H_{26}N_2O_4$: C, 79.00; H, 4.62; N, 4.98. Found: C, 78.77; H, 4.45; N, 4.77.

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Microwave-Assisted, Solvent-Free, Parallel Syntheses and Elucidation of Reaction Mechanism for the Formation of Some Novel Tetraaryl Imidazoles of Biological Interest

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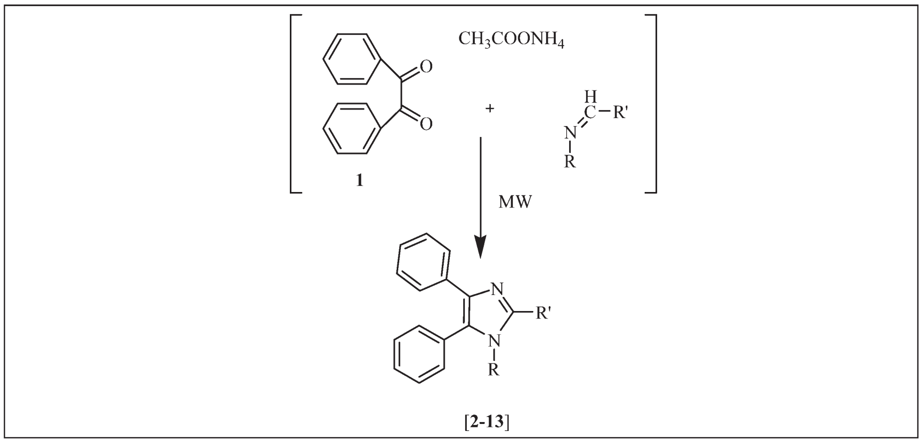

The microwave assisted, solvent free, parallel syntheses of title compounds is described in this protocol. Twelve new tetraaryl imidazoles, which are incorporated with the chemotherapeutic pharmacophores, have been synthesized by adopting one pot multicomponent reaction. Attempt has been made to investigate the mechanism behind the formation of tetraaryl imidazoles by product identification method. The synthesized compounds were analyzed by physical and analytical data. The synthesized compounds were evaluated for their antibacterial, antitubercular, and short-term anticancer activity. Compound **13** was found to be the candidate compound to investigate further for its potential anticancer activity.

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INTRODUCTION

Syntheses of heterocyclic compounds from readily available reagents by simple and efficient methods are the major requirements of heterocyclic chemistry. A survey of the pertinent literature reveals that, tetraaryl imidazoles possess diverse biological activities apart from their synthetic interests [1–3]. They are reported to exhibit pharmacological activities such as antirheumatoid arthritis [4], antituberculosis [5], antiHIV [6], antiepileptic [7], and anticancer activity [8,9]. Some of the best-selling therapies today contain this versatile heterocycle in their core structures. Therefore, it would be difficult to underestimate the importance of imidazoles in the pharmaceutical industry. Structurally, imidazole shows all the typical properties of an aromatic ring system.

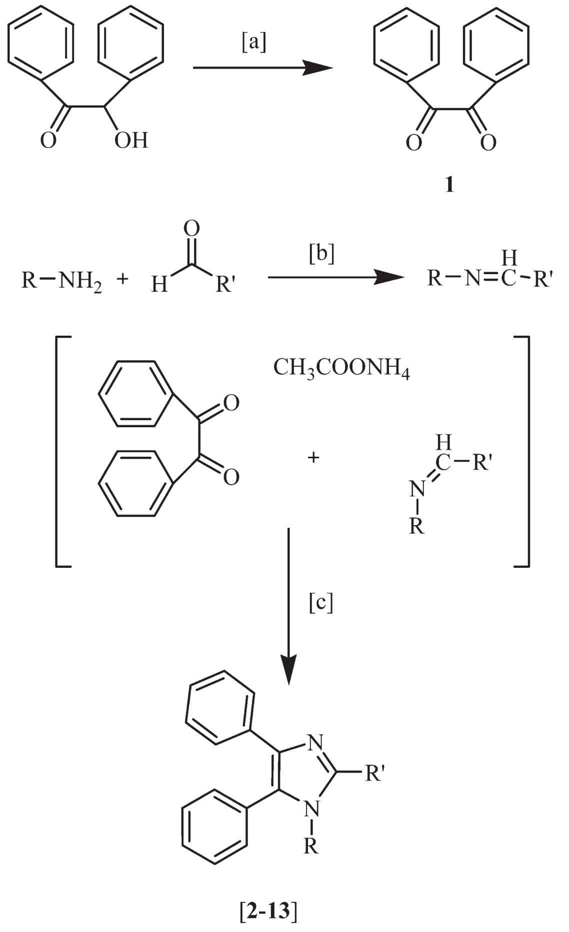
In 1858, Debus reported the reaction between glyoxal and ammonia, ever since this reaction became a novel route to the syntheses of imidazoles [10]. Later, a number of articles have described the syntheses of various imidazoles [11–19].

On the basis of the above observations, we have sought to synthesize novel tetraaryl imidazoles which are incorporated with the chemotherapeutic pharmacophores such as sulphanilamide, its bioisoster PABA (*p*-aminobenzoic acid) and INH (isoniazid) as possible antibacterial, antitubercular, or anticancer agents.

RESULTS AND DISCUSSION

Benzoin on oxidation gave Benzil **1** (Scheme 1). In an attempt to search for oxidizing agent to oxidize a mono ketone to diketone, we tried using oxidizing agents such as aluminium nitrate, cerric ammonium sulphate, ferric ammonium sulphate, potassium nitrate, and sodium nitrite. Among these oxidizing agents, only sodium nitrite was able to oxidize mono ketone to

Scheme 1. Preparation of tetraaryl imidazoles. (a) $NaNO_2$, AcOH, reflux for 50 min. (b) Conv; AcOH, Reflux 5-6 h. MW; Activated silica gel, 1000 W, 8 min. (c) Conv; Ammonium acetate, Reflux 12-15 h. MW; Ammonium acetate, 1000 W, 14–23 min.



diketone efficiently in the presence of glacial acetic acid as a solvent. In the literature [20], nitric acid and lead nitrate were used to oxidize benzoin to benzil taking 1.5 h for completing reaction, involving a nasty brown nitrogenous gas evolution. The same reaction using sodium nitrite just takes 50 min for completion. The yield of benzil was better when compared with the existing oxidizing agents and the brown nitrogenous gas evolution was also been reduced.

The primary aromatic or heteroarylamine was condensed with aryl or heteroaryl aldehydes to afford the corresponding Schiff's base. Schiff's base was further treated with ammonium acetate and benzil in the presence of glacial acetic acid as a solvent, gave the corresponding tetraaryl imidazoles (**2-13**) according to Scheme 1. The microwave assisted parallel syntheses were performed under solvent-free conditions using activated silica gel at the full power of 1000 W. Schiff's base formation was completed after 8 min of microwave irradiation, whereas tetraaryl imidazoles formed after 14–23 min of microwave irradiation.

We have an opinion that, the acidic nature of silica gel would have enhanced this reaction particularly during dehydration steps. All the synthesized compounds were analyzed by TLC, mp, IR, ^1H NMR, MASS, and elemental analysis. The ^1H NMR showed a characteristic peak for NH between 8.77 and 8.86 δ ppm for compounds containing INH (**2-4**). A characteristic peak for NH_2 was observed between 6.57 and 6.82 δ ppm for compounds containing sulphanilamide (**5-9**). A characteristic peak for COOH was observed between 12.94 and 13.04 δ ppm for compounds containing PABA (**10-13**).

Initially, we tried to synthesize the tetraaryl imidazoles by adopting a one-pot single-step multicomponent reaction by both conventional and microwave method [21–23], involving primary aromatic amine, aldehyde, benzyl, and ammonium acetate as shown in Scheme 2.

However, the above reaction gave triaryl imidazole in addition to the tetraaryl imidazole with incorporated aryl amine in a yield ratio of 3:1, respectively. This result indicated that, the formation of triaryl imidazole is relatively easy when compared with tetraaryl imidazole. To improve the yield of tetraaryl imidazoles and to synthesize them selectively, we have modified the procedure according to the Scheme 1. Hence, for this reason we prepared the Schiff's bases first and then taken further to the cyclization step involving equivalent amount of diketone and excess of ammonium acetate. The list of synthesized compounds and the comparative yield statement between microwave and conventional method is as shown in Table 1.

Scheme 2. (a) Multicomponent reaction, Conv; Glacial acetic acid, reflux 12–15 h, MW; 1000 W, 14–23 min.

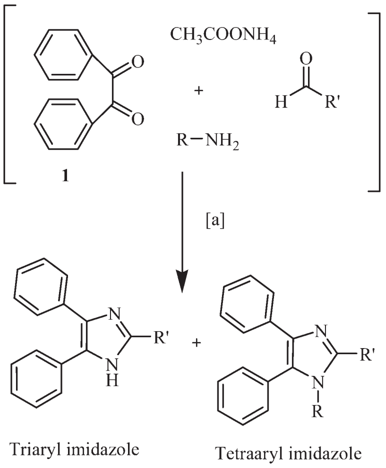
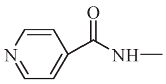
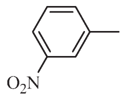
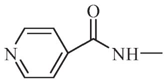
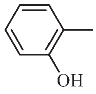
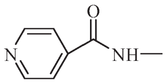
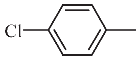
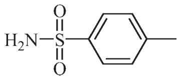
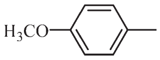
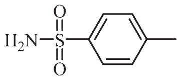
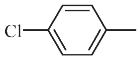
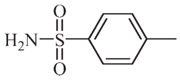
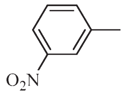
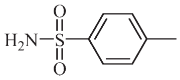
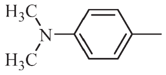
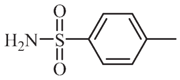
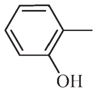
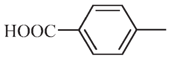
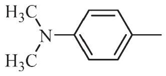
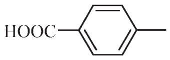
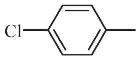
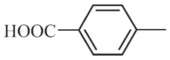
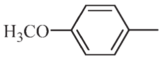
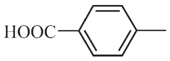
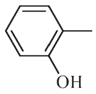


Table 1

Physical and analytical data of compounds **2-13**

Compound	R	R′	Reaction time		Yield (%)[a]		CTC$_{50}$[c] (μg/mL)
			MW[b] (min)	Conven (h)	MW	Conven	
2			14	13	89	61	190.26
3			16	13	83	58	>500
4			15	14	86	67	500
5			20	15	90	62	>500
6			22	15	91	63	>500
7			21	15	88	61	>500
8			19	15	93	72	>500
9			17	14	81	77	438.50
10			22	15	92	90	>500
11			21	15	86	86	>500
12			20	13	97	88	>500
13			23	15	84	71	94.63

[a] Isolated yield.

[b] Microwave irradiation (Whirlpool™ domestic microwave oven).

[c] The cytotoxic concentration (which inhibited 50% growth of total cells).

To understand the reaction mechanism, we performed a couple of experiments to find out the possible intermediates formed during the formation of tetraaryl imidazoles [24]. The experiments were designed to identify the intermediates under similar reaction conditions as follows,

1. Benzil with ammonium acetate
2. Benzil with PABA
3. PABA with anisaldehyde
4. Ammonium acetate with anisaldehyde
5. Product of experiment 3 with benzil and excess of ammonium acetate.

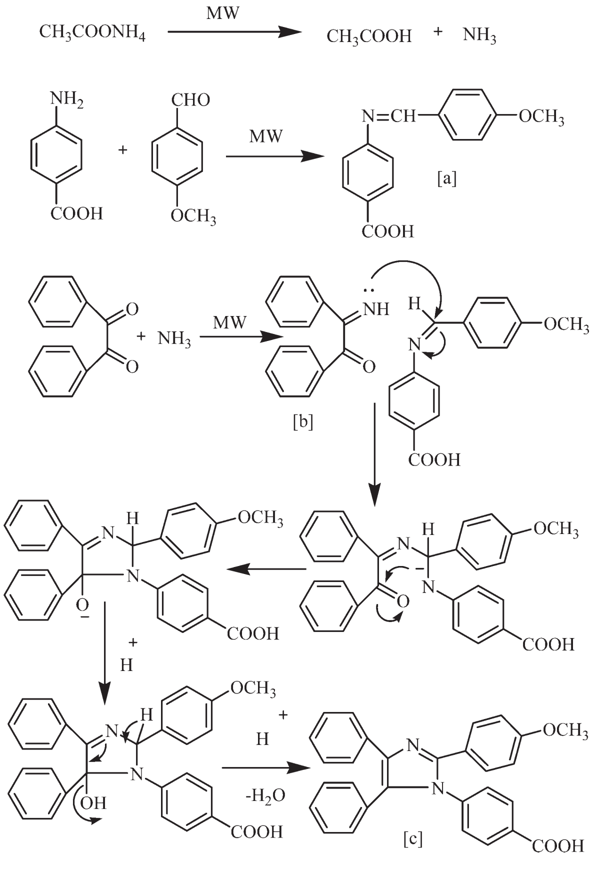
The reaction mixtures were irradiated with microwaves for 8 min and directly fed to the mass spectrometry to find out the intermediates formed under APCI (atmospheric pressure chemical ionization) technique. The reaction mixture of experiment 1 showed a molecular ion peak at 209.0 confirming the formation of mono imine and another molecular ion peak at 208.0 for a di imine. TLC also showed one spot each for mono imine and di imine. Further, isolated yield ratio was found to be 7:1 for the mono imine and di imine, respectively. This experiment indicated that, mono imine formation is favored over the di imine. The reaction mixture of experiment 2 showed the molecular ion peak at 329.1. However, the isolated yield was found to be just 4%. This result indicates that the formation of Schiffs base from diketone is quite difficult in this reaction. Probably, the steric crowding around the diketone (benzil) and less reactivity of aromatic amine may not have favored the formation of Schiff's base. The reaction mixture of experiment 3 showed a molecular ion peak at 255.0 confirming the formation of Schiff's base between aldehyde and aromatic amine, the TLC showed a clear single spot. The isolated yield was found to be about 98%. The reaction mixture of experiment 4 showed a molecular ion peak at 135.0 indicating formation of imine. But, we could not isolate the product, which may be because of its instability or its being formed in very low quantities. The reaction mixture of experiment 5 showed a molecular ion peak at 444.95 confirming the formation of tetraaryl imidazole and no peak was observed for triaryl imidazole. The TLC showed single spot for the formation of tetraaryl imidazole and isolated yield was found to be 99%. The experiment 5 clearly indicates that the Schiffs base formation between aldehyde and aromatic amine is more likely during the formation of tetraaryl imidazole. In contrast to this, the experiment 2 results reveal that possibility of Schiffs bases formation between aryl amine and diketone is less likely under this set of reactants and provided reaction conditions. All the above experiments were conducted by both conventional and microwave method. Acetic acid was used as a solvent in conventional method, whereas activated silica gel was used in the microwave method. By the conventional method all the above reaction mixtures were refluxed for 10 h. The observations were found to be same under both the methods.

In addition to the above experiments, we stopped the reaction between benzil, anisaldehyde, PABA, and ammonium acetate at the half way stage under both microwave and conventional methods. The reaction mixtures were directly fed to the mass spectromet. Presence of triaryl imidazole, tetraaryl imidazole, and product of experiment 1 and 3 was observed.

All the above experimental results revealed the possible intermediates formed during the formation of title compounds. The possible motive or driving force for this reaction would be the formation of relatively more stable imidazole ring system. On the basis of these facts the possible mechanism may be postulated as shown in the Scheme 3.

Even though, protocol and postulated mechanism for the formation of triaryl imidazoles is reported by

Scheme 3. (a) Schiff's base, (b) Imine, (c) Tetraaryl imidazole.



Siddiqui [25] recently in the year 2005. The present protocol and postulated mechanism for the formation of tetraaryl imidazoles attempts to give the better insight based on the experimental facts. We differ from their postulated mechanism by saying; imine formation will be favored between diketone and ammonia, rather between aldehyde and ammonia. The reason for this as already explained in the results of experiment 4. However, further studies are required to come to any hard core conclusion.

All the synthesized tetraaryl imidazoles incorporated with chemotherapeutic pharmacophores were evaluated for their *in vitro* antibacterial activity against two-gram positive bacteriae such as *B. subtilis* and *S. aureus* and two gram negative bacteriae *E. coli* and *K. pneumoniae*. Only compound no **13** exhibited a moderate activity with minimum inhibitory concentration (MIC) of 250 μg against *S. aureus*. Surprisingly, no other compound exhibited an antibacterial activity.

All the synthesized compounds were evaluated for their possible antimycobacterial activity toward a strain of *M. tuberculosis* $H_{37}Rv$ sensitive to isoniazid. Middlebrook (MB) 7H10 agar medium was used for testing antitubercular activity. The MIC determination was performed from 1 to 50 μg/mL concentrations. But, no compound exhibited MIC below 50 μg/mL concentration including the tetraaryl imidazoles containing isoniazid moiety (**2**, **3**, and **4**).

Anticancer activity of the synthesized compounds was evaluated by determining the percentage growth inhibition of DLA (Dalton's lymphoma ascites) cells by tryphan blue dye exclusion technique. Compounds **2**, **9**, and **13** showed good anticancer activity with CTC_{50} (cytotoxic concentration) at 190.26, 438.50, and 94.63 μg/mL, respectively. The synthesized tetraaryl imidazoles and their CTC_{50} values are as shown in Table 1.

In conclusion, we have developed a microwave assisted, convenient, efficient, and environmentally benign protocol for the syntheses of biologically active tetraaryl imidazoles. The present microwave method was found to be better than conventional method in terms of reaction time, yield, and relatively simple method to perform parallel syntheses. Thus, this methodology becomes an efficient strategy for the rapid syntheses of tetraaryl imidazoles, selectively. From the point of biological interest, compound **13** was found to be the candidate compound to investigate further for its anticancer activity.

EXPERIMENTAL

The laboratory grade chemicals and reagents were used to synthesize all the reported compounds. The melting points were determined in open capillaries. Temperatures are expressed in °C and are uncorrected. The IR spectra of compounds were recorded on Perkin-Elmer infrared–283 FTIR spectrometer by KBr pellet technique and are expressed in cm^{-1}. ^1H NMR spectra were recorded on Bruker DRX-300 (300 MHZ, FT-NMR) spectrophotometer using TMS as an internal standard, $CDCl_3$, or DMSO-d_6 as a solvent. The chemical shifts are expressed in δ ppm and following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartlet; and m, multiplet. Mass spectrum was obtained using LC-MS (Schimadzu-2010AT) under atmospheric pressure chemical ionization technique (APCI) and elemental analysis was performed using Elemental Vario EL III, Carlo-Erba 1108. TLC was performed to monitor the reactions and to determine the purity of the products on precoated aluminum plates using 10% methanol in chloroform or 20% ethyl acetate in pet ether as a mobile phase.

Procedure for the preparation of benzil (1). Crude benzoin (10 g, 0.048 mole) and 15 g of sodium nitrite were transferred to a 250-mL round bottom flask containing 40 mL of glacial acetic acid. The reaction mixture was refluxed using an air condenser for about 50 min (till the evolution of white gaseous vapors ceases). Then the reaction mixture was cooled and poured into a beaker containing 100 mL of ice-cold water. The mixture was stirred well until the oil separates completely as a yellow solid. The crude benzil was collected by filtration, washed thoroughly with water, and recrystallized from ethanol. The reaction was monitored through TLC. Yellow crystals (97%); mp 95°C, IR (cm^{-1}, KBr): 3047 (Ar C—H), 1707 (C=O), 1601 (C=C).

General procedure for the preparation of Schiff's bases

Conventional method. Equimolar amounts (0.01 mole) of aromatic amine and aromatic aldehyde were transferred to a 250-mL flat bottom flask containing 15 mL of glacial acetic acid to serve as a solvent, then refluxed with stirring for about 6 h. After completion of the reaction, the reaction mixture was allowed to cool to give a corresponding product. The reactions were monitored through TLC. The completed reactions were taken directly for the preparation tetraaryl imidazoles.

Microwave method. This reaction was carried out in a parallel synthetic way as shown in Scheme 1. Equimolar amounts (0.01 mole) of aromatic amine and aromatic aldehyde were transferred to a clean and dry mortar containing 2 g of activated silica gel, triturate to become a uniform mixture. The reaction mixture was then transferred to a 100 mL beaker. Like this all other beakers containing different reaction mixtures were kept inside the microwave oven in a circle and then microwave irradiation was carried out at 1000 W power for about 8 min. Intermittent cooling was done after every 60 s of microwave irradiation. During intermittent cooling, the reaction mixtures were thoroughly mixed using a glass rod. The reactions were monitored through TLC. The completed reactions were taken directly for the preparation of tetraaryl imidazoles without any work up.

General procedures for the preparation of tetraaryl imidazoles (2-13)

Conventional method. Benzil (0.01 mole) was transferred along with excess of ammonium acetate (0.1 mole) into a flask containing the Schiff's base (0.01 mole) obtained in the previous conventional procedure. The reaction mixture was stirred and refluxed on heating plate with magnetic stirrer for about 12–15 h. The reaction was monitored through TLC. When complete, the reaction mixture was poured into 250 mL of water to remove ammonium acetate and acetic acid and the product was collected by filtration dried in a hot air oven. The crude product was washed with 2 × 10 mL of toluene to remove traces of any unreacted benzil; further purification by was by recrystallized using ethyl acetate.

Microwave method. This reaction was carried out in a parallel synthetic way as shown in Scheme 1. Benzil (0.01 mole) was transferred along with excess of ammonium acetate (0.1 mole) into a dry mortar containing the Schiff's base (0.01 mole) obtained in the previous microwave procedure. Triturate to become a uniform mixture. The reaction mixture was then transferred to 100 mL beaker. Likewise, all other beakers containing different reaction mixtures were kept inside the microwave oven in a circle and then microwave irradiation was carried out at 1000 W power for about 14–23 min. Intermittent cooling was done after every 60 s of microwave irradiation. During intermittent cooling, the reaction mixtures were thoroughly mixed. The reactions were monitored through TLC. The reaction mixtures were withdrawn from microwave oven soon after the reactions were completed. The completed and cooled reaction mixture was poured in to 250 mL of water to remove ammonium acetate and acetic acid, filtered, and dried it in hot air oven. The crude product along with silica gel was washed with 2 × 10 mL of toluene to remove traces of any unreacted benzil, further extracted with ethyl acetate. The ethyl acetate was heated, filtered in hot condition, and allowed to cool. The solid crystals formed were collected by filtration and dried under vacuum.

The physical, analytical, and spectral data of final compounds are given in the following text.

N*-[2-(3-Nitrophenyl)-4,5-diphenylimidazol-1-yl]-pyridamide (2).* Pale yellow crystals; mp 45°C; IR (cm^{-1}, KBr): 3250 (NH), 3032 (Ar C-H), 1654 (C=O), 1621 (C=C), 1595 (C=N), 1528 (NO), 1368 (NO), 1275 (C—N); ^{1}H NMR (δ ppm): 7.25-7.82 (m, 17H, ArH), 8.5 (s, 1H, ArH), 8.82 (bs, 1H, NH); MS (m/z): found 461.80, calcd 462 (M+H)$^+$. 311.05, 326.9, 342.0, 385.10. Anal. Calcd for $C_{27}H_{19}N_2O_3$: C, 70.27; H, 4.14; N, 15.18. Found: C, 70.20; H, 4.20; N, 15.30.

N*-[2-(2-Hydroxyphenyl)-4,5-diphenylimidazol-1-yl]-pyridamide (3).* Yellow crystals; mp 48°C; IR (cm^{-1}, KBr): 3401 (OH), 3260 (NH), 3052 (Ar C—H), 1669 (C=O), 1623 (C=C), 1595 (C=N), 1255 (C=O), 1132 (C=N); ^{1}H NMR (δ ppm): 6.81-8.49 (m, 18H, ArH), 8.80 (bs, 1H, NH), 8.91 (bs, 1H, OH); MS (m/z): found 432.95, calcd 433 (M+H)$^+$. 266.0, 312.95, 352.10. Anal. Calcd for $C_{27}H_{20}N_4O_2$: C, 74.99; H, 4.66; N, 12.95. Found: C, 74.91; H, 4.52; N, 12.81.

N*-[2-(4-Chlorophenyl)-4,5-diphenylimidazol-1-yl]-pyridamide (4).* Pale yellow crystals; mp 190°C; IR (cm^{-1}, KBr): 3245 (NH), 3057 (Ar C—H), 1601 (C=O), 1618 (C=C), 1501 (C=N), 1132 (C—N), 694 (C—Cl); ^{1}H NMR (δ ppm): 7.25-7.94 (m, 18H, ArH), 8.77 (bs, 1H, NH); MS (m/z): found 449.15, calcd 449 (M-H)$^-$. 110.95, 329.30. Anal. Calcd for $C_{27}H_{19}N_4OCl$: C, 71.92; H, 4.25; N, 12.42. Found: C, 72.27; H, 4.23; N, 12.36.

4-[2-(4-Methoxyphenyl)-4,5-diphenylimidazole-1-yl]-benzenesulphonamide (5). White amorphous solid; mp 222°C; IR (cm^{-1}, KBr): 3357 (NH), 3003 (Ar C—H), 1620 (C—C), 1612 (SO), 1578 (C—N), 1327 (SO, asym. Stre), 1291 (C—O), 1251 (C—N), 1143 (SO, sym. Stre), 1071 (C—S); ^{1}H NMR (δ ppm): 3.80 (s, 3H, CH_3), 6.71 (d, 2H, NH_2), 7.28-7.88 (m, 18H, ArH); MS (m/z): found 481.95, calcd, 482 (M+H)$^+$. 327.0, 329.10. Anal. Calcd for $C_{28}H_{23}N_3O_3S$: C, 69.84; H, 4.81; N, 8.73. Found: C, 69.49; H, 4.70; N, 8.54.

4-[2-(4-Chlorophenyl)-4,5-diphenylimidazole-1-yl]-benzenesulphonamide (6). Cream colored crystals; mp 280°C; IR (cm^{-1}, KBr): 3358 (NH), 3026 (Ar C—H), 1654 (C=C), 1560 (C=C), 1485 (C=N), 1324 (SO, asym. stre), 1203 (C—N), 1139 (SO, sym. stre), 1014 (C—S), 697 (C—Cl); ^{1}H NMR (δ ppm): 6.78 (s, 2H, NH_2), 7.29-7.85 (m, 18H, ArH); MS (m/z): found 485.85, calcd, 486 (M+H)$^+$. 327.0, 297.1, 330.0, 333.0, 373.0, 469.95. Anal. Calcd for $C_{28}H_{23}N_3O_3S$: C, 66.73; H, 4.15; N, 8.65. Found: C, 66.57; H, 4.37; N, 8.77.

4-[2-(3-Nitrophenyl)-4,5-diphenylimidazole-1-yl]-benzenesulphonamide (7). Yellow amorphous solid; mp 305°C; IR (cm^{-1}, KBr): 3400 (NH), 3056 (Ar C—H), 1598 (C=C), 1522 (NO, asym. stre), 1479 (C=N), 1348 (NO, sym. stre), 1328 (SO, asym. Stre), 1252 (C—N), 1132 (SO, sym. Stre), 1025 (C—S); ^{1}H NMR (δ ppm): 6.82 (s, 2H, NH_2), 7.25-7.81 (m, 18H, ArH); MS (m/z): found 496.90, calcd 497 (M+H)$^+$. 297.05, 342.05, 344.0, 465.0. Anal. Calcd for $C_{27}H_{20}N_4O_4S$: C, 65.31; H, 4.06; N, 11.28. Found: C, 65.1; H, 4.14; N, 11.42.

4-[2-(4-Dimethylaminophenyl)-4,5-diphenylimidazole-1-yl]-benzenesulphonamide (8). Bright yellow amorphous solid; mp 200°C; IR (cm^{-1}, KBr): 3326 (NH), 3050 (Ar C—H), 2928 (Ali C—H), 1634 (C=C), 1576 (C=N), 1328(SO, asym. Stre), 1229 (C—N), 1128 (SO, sym. Stre), 1063 (C—S); ^{1}H NMR (δ ppm): 1.56 (s, 6H, CH_3), 6.68 (s, 2H, NH_2), 6.9-7.75 (m, 18H, ArH); MS (m/z): found 494.95, calcd 495 (M+H)$^+$. 149.9, 340.05. Anal. Calcd for $C_{29}H_{26}N_4O_2S$: C, 70.42; H, 5.30; N, 11.33. Found: C, 70.35; H, 5.25; N, 11.12.

4-[2-(2-Hydroxyphenyl)-4,5-diphenylimidazole-1-yl]-benzenesulphonamide (9). White crystals; mp 203°C; IR (cm^{-1}, KBr): 3218 (OH), 3064 (Ar C—H), 1666 (C=C), 1540 (C=N), 1325 (asym. stre), 1262 (C—N), 1133 (SO, sym. Stre), 1025 (C—S); ^{1}H NMR (δ ppm): 6.57 (bs, 2H, NH_2), 6.89-7.66 (m, 18H, ArH), 7.92 (bd, 1H, OH); MS (m/z): found 467.85, calcd 468 (M+H)$^+$. 313.05. Anal. Calcd for $C_{27}H_{21}N_3O_3S$: C, 69.36; H, 4.53; N, 8.99. Found: C, 69.42; H, 4.39; N, 8.78.

4-[2-(*p*-Dimethylaminophenyl)-4,5-diphenylimidazole-1-yl]-benzoic acid (10). Yellow amorphous solid; mp 250°C; IR (cm^{-1}, KBr): 3410 (OH), 3058 (Ar C—H), 2879 (Ali C—H), 1717 (C=O), 1360 (C=N), 1228 (C=O), 1198 (C=N); ^{1}H NMR (δ ppm): 3.06 [s, 6H, $(CH_3)_2$], 6.72-7.8 (m, 18H, ArH); 12.94(bs, 1H, COOH) MS (m/z): found 460.0 calcd, 460 (M+H)$^+$. 340.05, 444.95, 427.90. Anal. Calcd for $C_{30}H_{25}N_3O_2$: C, 78.41; H, 5.48; N, 9.14. Found: C, 78.55; H, 5.37; N, 9.30.

4-[2-(4-Chlorophenyl)-4,5-diphenylimidazole-1-yl]-benzoic acid (11). White crystals; mp 272°C; IR (cm^{-1}, KBr): 3390 (OH), 3058 (Ar C—H), 2852 (Ali C—H), 1709 (C=O), 1654 (C=C), 1485 (C=N), 1292 (C—O), 1248 (C—N); ^{1}H NMR (δ ppm): 7.32-7.87 (m, 18H, ArH); 13.01(bs, 1H, COOH) MS (m/z): found 450.90, calcd 451(M+H)$^+$. 313.0. Anal. Calcd for $C_{28}H_{19}N_2O_2Cl$: C, 74.58; H, 4.25; N, 6.21 Found: C, 74.51; H, 4.10; N, 6.02.

4-[2-(4-Methoxyphenyl)-4,5-diphenylimidazole-1-yl]-benzoic acid (12). White crystals; mp 255°C; IR (cm^{-1}, KBr): 3398 (OH), 3042 (Ar C—H), 2958 (Ali C—H), 1710 (C=O), 1667 (C=C), 1493 (C=N), 1292 (C—O), 1248 (C—N); ^{1}H NMR (δ ppm): 3.78 (s, 3H, OCH_3), 6.80-7.84 (m, 18H, ArH), 12.98 (bs, 1H, COOH) MS (m/z): found 446.8, calcd 447 $(M+H)^+$. 313.0. Anal. Calcd for $C_{29}H_{22}N_2O_3$: C, 78.01; H, 4.97; N, 6.27 Found: C, 78.06; H, 4.79; N, 6.24.

4-[2-(2-Hydroxyphenyl)-4,5-diphenylimidazole-1-yl]-benzoic acid (13). White crystals; mp 235°C; IR (cm^{-1}, KBr): 3374 (OH), 3060 (Ar C—H), 1716 (C=O), 1653 (C=C), 1262 (C—O), 1202 (C—N); ^1H NMR (δ ppm): 6.8-8.1 (m, 18H, ArH), 13.04 (bs, 1H, COOH); MS (m/z): found 432.95, calcd 433 $(M+H)^+$. 313.0. Anal. Calcd for $C_{28}H_{20}N_2O_3$: C, 77.76; H, 4.66; N, 6.48 Found: C, 77.45; H, 4.36; N, 6.16.

Antibacterial activity screening procedure. All the synthesized compounds were screened for their antibacterial activity against two-gram positive bacteria such as *B. subtilis* and *S. aureus* and two gram negative bacteria *E. coli* and *K. pneumoniae* according to the standard procedure [26,27]. The primary screen was carried out using the agar disc-diffusion method using Muller-Hinton agar medium. Sterile filter paper discs (8 mm diameter) were moistened with test compound solution in DMSO of specific concentration 500 μg/disc were carefully placed on agar culture plates that had been previously inoculated separately with bacteria. The plates were incubated at 37°C and inhibition of growth was measured after 24 h. The minimal inhibitory concentration (MIC) for the compound 13 against *S. aureus* was carried out using the microdilution susceptibility method in Muller-Hinton Broth by two-fold dilution method and it was found to be 250 μg/mL. Streptomycin was used as a standard drug (MIC $<$ 18 μg against all the bacteria).

Antimycobacterial activity screening procedure. Middlebrook (MB) 7H10 agar medium was used for testing of antitubercular activity of the compounds. Culture of *M. tuberculosis* $H_{37}Rv$ grown on Lowenstein-Jensen (L-J) was harvested in saline containing 0.05% Tween-80 and used according to the standard procedure [28]. The minimum concentration of the drug or compounds that completely inhibited the growth of different mycobacterium was recorded as minimum inhibitory concentration (MIC) with respect to the used inoculum. The MIC for test compounds was performed up to 50 μg/mL concentrations. Isoniazid (INH) was used as a standard drug (MIC, 21 μg/mL).

Anticancer activity screening procedure. Anticancer activities [29–33] of the synthesized compounds were assessed by determining the percentage inhibition of DLA (Dalton's lymphoma ascite) cells by tryphan blue dye exclusion technique according to the standard procedure [33]. We checked anticancer activity of all the synthesized compounds at the concentration of 500, 250, 125, 62.5, 31.25 μg/mL. The percentage growth inhibition was calculated by using the following formula: % Growth inhibition = [(Total cells – Live cells) × 100]/Total cells.

The CTC_{50} values were calculated by plotting the graph between concentration versus percentage growth inhibition and by bisecting concentration at the 50% growth inhibition. The synthesized tetraaryl imidazoles and their CTC_{50} values are as shown in Table 1. Cyclophospamide was used as standard drug (CTC_{50}, 12 μg/mL).

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New Dihydro-1,2,4-Triazolo[1,5-*a*]pyrimidines Based on Arylidene Derivatives of 5-Acetylbarbituric and Dehydroacetic Acids

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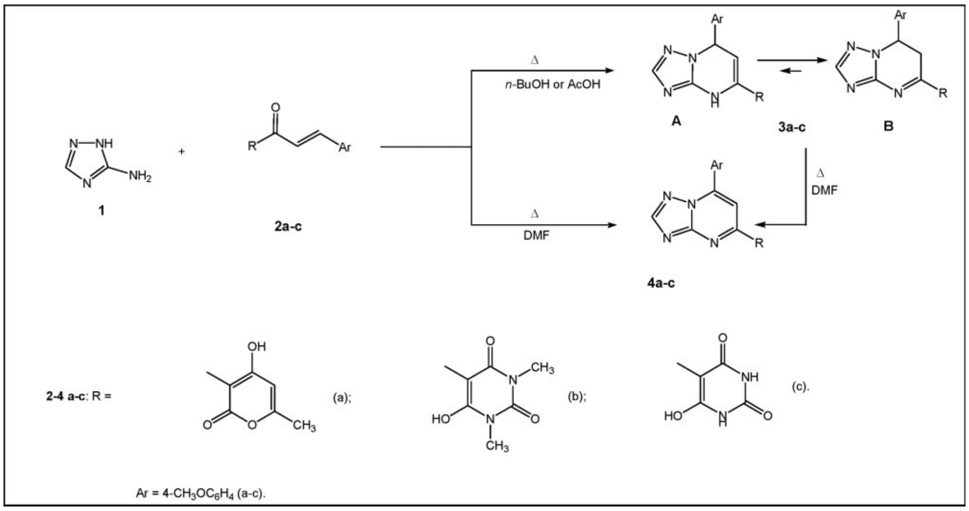

The reaction of 3-amino-1,2,4-triazole (**1**) with arylidene-5-acetyl barbituric acid (**2b,c**) or dehydroacetic acid (**2a**) by refluxing in butanol leads to the formation of dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines **3a–c**.

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INTRODUCTION

Azolopyrimidines are analogs of many naturally occurring compounds, such as purines, and therefore they have been excellent objects for the search of new physiologically active compounds for quite a long time [1–3]. The entrance of a pharmacofore into the molecule of azolopyrimidine can lead to compounds with interesting biological properties.

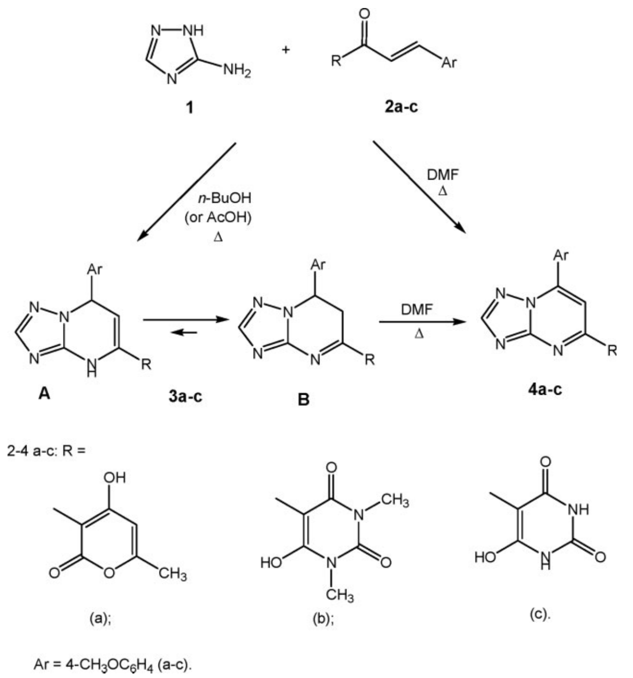
From the other side, it was shown [4] that partially hydrogenated azoloazines with a nodal nitrogen are useful for studying a wide set of theoretical problems, for example, imine-enamine tautomerization. Therefore, the important aim of this work was a continuation of our previous research about tautomerization processes in dihydroazolopyrimidines [5,6], especially synthesis of dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines with a proton-acceptor substituent which could lead to the intramolecular hydrogen bond between a substituent and the NH group of pyrimidine ring, and investigation of the tautomeric equilibrium in such compounds. In our opinion, one of the possible solutions for both problems would be synthesis of dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines that contained 6-hydroxypyrimidine-2,4-dion-5-yl or 4-hydroxy-6-methylpyran-2-on-3-yl substituents.

It is known [4] that the most convenient preparative method for synthesis of dihydroazolopyrimidines with nodal nitrogen atom is the reaction of aromatic α,β-unsaturated ketones or their synthetic precursors with aminoazoles which contain an amidine fragment. This synthetic way allowed obtaining a large number of dihydroazolopyrimidine derivatives that have different electronic properties of azole ring and contain various alkyl or aryl substituents in pyrimidine ring causing a wide set of electronic and solvation properties.

RESULTS AND DISCUSSION

We established that 3-amino-1,2,4-triazole (**1**) can react with arylidene derivatives of dehydroacetic acid (3-acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one**, 2a**), 5-acetyl-1,3-dimethylbarbituric (**2b**) and 5-acetylbarbituric (**2a**) acids by heating their equimolar amounts in

Scheme 1



n-buthanol or acetic acid, which leads to 6,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines (**3a–c**) that contain a 4-hydroxy-6-methyl-2*H*-pyrane-2-one-3-yl (**3a**), 6-hydroxy-1,3-dimethylpyrimidine-2,4-dione-5-yl (**3b**), and 6-hydroxy-1*H*-pyrimidine-2,4-dione-5-yl (**3c**), respectively, on the C-5 of triazolopyrimidine system.

Performing the reaction between amine **1** and compounds **2a–c** by heating in dimethylformamide led to the formation of heteroaromatic azolopyrimidines (**4a–c**). The same compounds were obtained by heating **3a–c** in DMF.

The structure of **3a–c** was established by their NMR data. ^{1}H NMR spectra of **3a–c** (in DMSO-d_6) contained signals corresponding to an AMX system, multiplet of aromatic ring, singlet of triazole proton, and signals of heterocyclic substituent. Thus, the NMR data showed the existence of **3a–c** in the tautomeric 6,7-dihydro form exclusively (*i.e.*, ‘‘**B**’’ form on the Scheme 1). Additionally, ^{13}C NMR spectra of **3a** and **3c** confirmed their structure. The mass spectra of **3a–c** showed molecular ion peaks.

Concerning the tautomerism of considered dihydroazolopyrimidines, it is necessary to mention that, according to our previous research, 4,7-diphenyldihydro-1,2,4-triazolo-[1,5-*a*]pyrimidine (**5**) exists exclusively in the 1,4-dihydro form (*i.e.*, ‘‘**A**’’ form on the Scheme 2) in the solid state and in solutions [6], whereas 2-hydroxyaryl derivative (**6**) is a mixture of two tautomeric forms ‘‘**A**’’ and ‘‘**B**’’ in DMSO-d_6 with relative ratio of ‘‘**A**’’ form 75–85% [5].

Further, it was shown [7] that the ‘‘**B**’’ form can be partially stabilized by entrance of electron-donating aryl, *e.g., p*-dimethylaminophenyl, on C-5 of the corresponding dihydroazolopyrimidine (according to [7] azolopyrimidine **7** leads to mixture of imine and enamine forms in ratio ~55:45).

The relative stabilization of the ‘‘**B**’’ form in **3a–c** should be explained, in our opinion, by the influence of two effects, especially electron-donating properties of substituent on C-5 on the one hand and hydrogen bond formation on the other hand.

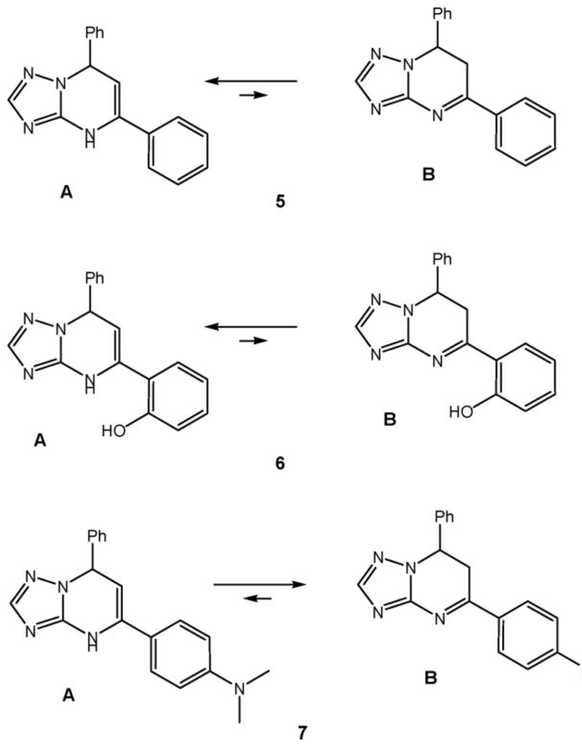
The ^{1}H NMR spectra of **4a–c** contained multiplets of 4-methoxyphenyl substituent in the aromatic area, singlets of pyrimidine and triazole ring in the low-field area, signals corresponding to the substituents at C-5 of triazolopyrimidine, and a broad singlet corresponding to the hydroxy group at 16–18 ppm, which is totally consistent with proposed structure of **4a–c**.

EXPERIMENTAL

Starting 3-amino-1,2,4-triazole, dehydroacetic acid, 5-acetylbarbituric, and 5-acetyl-1,3-dimethylbarbituric acid are commercially available. The compounds **2a,c** were prepared according to [8] (**2a**), [9] (**2c**). Compound **2b** was prepared similar to **2c** [9].

Each reaction was monitored by TLC on Silufol UV-254 plates with ethyl acetate/chloroform (1:1). Melting points were

Scheme 2



determined with a Kofler apparatus. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 at 200 MHz (50 MHz for ^{13}C) on a Varian Mercury VX-200 spectrometer and analyzed with ADVASP$^{\mathrm{TM}}$ Analyzer program (Umatek International Inc.). Chemical shifts are reported in ppm (δ−scale), coupling constants (*J*) in Hz, internal standard was $Si(CH_3)_4$. The EI mass spectra were obtained on Varian 1200L with electron energy 70 eV.

6-Hydroxy-5-[3-(4-methoxyphenyl)-propenon-1-yl]-1,3-dimethyl-pyrimidine-2,4-dione (2b). The mixture of 3.96 g (0.02 mol) 5-acetyl-1,3-dimethylbarbituric acid, 2.72 g (0.02 mol) of 4-methoxybenzaldehyde and 0.8 g (0.02 mol) of sodium hydroxide in 20 mL of methanol was refluxed for 12 h. The reaction mixture was cooled to room temperature and neutralized with concentrated HCl. The precipitate formed was filtered off. Yield 4.0 g (63%), mp 190–191°C (from methanol); ^{1}H NMR: δ 3.19 (s, 6H, 2*CH_3); 3.81 (s, 3H, CH_3O); 7.03 (m, 2H, *m*-ArH); 7.68 (m, 2H, *o*-ArH); 7.94 (d, 1H, J = 15.8 Hz (α-H)); 8.34 (d, 1H, (β-H)); 17.0 (br. s, 1H, (OH)). Anal. Calcd. for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.86. Found C, 60.45; H, 4.95; N, 8.77.

5-(4-Hydroxy-6-methylpyran-2-on-3-yl)-7-(4-methoxy-phenyl)-6,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (3a). ***Method A.*** The mixture of 3-(4-hydroxy-6-methyl-2-oxo-2*H*-3-pyranyl)-1-(4-methoxyphenyl)-2-propen-1-one (**2a** [8], 2.86 g, 0.01 mol) and 3-amino-1,2,4-triazole (**1,** 0.92 g, 0.011 mol) in 15 mL of *n*-buthanol was refluxed for 1 h. The reaction mixture was cooled to room temperature, the precipitate that formed was filtered off. The yield was 2.53 g (72%), mp 181–183°C (from ethanol).

Method B. The 2.86 g (0.01 mol) of **2a** and 0.92 g (0.011 mol) of **1** in 5 mL glacial acetic acid were refluxed for 2 h. The mixture was cooled and diluted with 10 mL of acetone. The precipitate that formed was filtered off. Yield was 1.96 g (56%), mp 181–183°C (from ethanol).

^{1}H NMR ($CDCl_3$): δ 2.16 (s, 3H, CH_3); 3.76 (s, 3H, CH_3O); 3.98 (dd, 1H, ^3J = 7.1, ^2J = 18.7 H_a-6); 4.41 (dd, 1H, ^3J = 5.6, H_b-6); 5.58 (dd, 1H, H-7); 5.82 (s, 1H, H-5'); 6.85 (m, 2H, *m*-ArH); 7.02 (m, 2H, *o*-ArH); 7.82 (s, 1H, H-2); 16.4 (br. s, 1H, OH); ^{13}C NMR: δ 19.9 (CH_3); 34.7 (C-6); 55.4 (CH_3O); 55.6 (C-7); 97.4 (C-5'); 114.8 (*m*-C_{Ar}), 128.5 (*o*-C_{Ar}), 130.2 (*i*-C_{Ar}), 159.9 (*p*-C_{Ar}); 151.0 (C-2); 106.8, 146.5, 161.9, 166.2, 169.8, 185.4 (C-3*a* + C-4*a* + C_{HetAr}); MS (EI, *m/z* (rel. %)): 352 (96) [M^+], 325 (46), 309 (12), 267 (22), 245 (100), 227 (12), 161 (14). Anal. Calcd. for $C_{18}H_{16}N_4O_4$: C, 61.36; H, 4.58; N, 15.90. Found C, 61.28; H, 4.57; N, 15.88.

5-[6-Hydroxy-1,3-dimethylpyrimidine-2,4-dion-5-yl]-7-(4-methoxyphenyl)-6,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (3b). Compound **3b** was prepared similar to **3a** from 0.01 mol of **1** and 5-acetyl-1,3-dimethylbarbituric acid **2b**. Yield 2.48 g (65%); mp 192–194°C (from ethanol). ^{1}H NMR: 3.12 (s, 3H, CH_3); 3.20 (s, 3H, CH_3); 3.71 (s, 3H, CH_3O); 4.17 (dd, 1H, ^3J = 6.8, ^2J = 18.2, H_a-6); 4.51 (dd, 1H, ^3J = 5.6 H_b-6); 5.76 (dd, 1H, H-7), 6.90 (m, 2H, *m*-ArH); 7.09 (m, 2H, *o*-ArH); 7.93 (s, 1H, H-2); 14.3 (s, 1H, OH); ^{13}C NMR: δ 28.3, 28.4 (CH_3); 33.8 (C-6); 55.2 (CH_3O); 55.7 (C-7); 130.4 (*i*-C_{Ar}); 114.8 (*m*-C_{Ar}), 128.2 (*o*-C_{Ar}), 159.8 (*p*-C_{Ar}); 150.8 (C-2), 93.4 (C-5'), 146.5, 150.6, 162.1, 165.6, 166.4 (C-3*a* + C-4*a* + C_{HetAr}); MS (EI, *m/z* (rel. %)): 382 (100) [M^+], 355 (14), 275 (83), 266 (16). Anal. Calcd. for $C_{18}H_{18}N_6O_4$: C, 56.54; H, 4.74; N, 21.98. Found C, 56.50; H, 4.75; N, 21.93.

5-[6-Hydroxy-1H-pyrimidine-2,4-dion-5-yl]-7-(4-methoxy-phenyl)-6,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (3c). Compound **3c** was prepared similar to **3a** from **1** and 5-acetylbarbituric acid **2c**. Yield 2.3 g (65%); mp > 300°C (from ethanol). ^{1}H NMR: δ 3.71 (s, 3H, CH_3O); 4.17 (dd, 1H, ^3J = 6.6, J = 17.9, H_a-6); 4.41 (dd, 1H, ^3J = 6.0, H_b-6); 5.71 (dd, 1H, H-7), 6.91 (m, 2H, *m*-ArH); 7.11 (m, 2H, *o*-ArH); 7.90 (s, 1H, H-2); 11.0 (br.s. 1H, NH); 11.4 (br.s. 1H, NH); 14.2 (s, 1H, OH); ^{13}C NMR: δ 33.3 (C-6); 55.2 (CH_3O); 55.6 (C-7); 150.6 (C-2); 114.8 (*m*-C_{Ar}), 128.3 (*o*-C_{Ar}), 130.3 (*i*-C_{Ar}), 159.8 (*p*-C_{Ar}); 93.0 (C-5'), 146.5, 149.6, 163.9, 165.4, 168.6 (C-3*a* + C-4*a* + C_{HetAr}); MS (EI, *m/z* (rel. %)): 354 (100) [M^+], 336 (14), 325 (24), 286 (18), 266 (14), 256 (14), 247 (19), 225 (17), 121 (34), 115 (19). Anal. Calcd. for $C_{16}H_{14}N_6O_4$: C, 54.24; H, 3.98; N, 23.72. Found C, 54.30; H, 3.99; N, 23.75.

5-(4-Hydroxy-6-methyl-pyran-2-on-3-yl)-7-(4-methoxy-phenyl)-1,2,4-triazolo-[1,5-*a*]pyrimidine (4a). The mixture of 3-(4-hydroxy-6-methyl-2-oxo-2a-3-pyranyl)-1-(4-methoxy-phenyl)-2-propene-1-one (**2a**, 0.286 g, 0.001 mol) and **1** (0.092 g 0.0011 mol) in dimethylformamide (0.5 mL) was refluxed for 30 min and after cooling to room temperature diluted with benzene (10 mL). The precipitate formed was filtered off and dried. Yield 0.15 g (44%), mp 252–254°C (from ethanol). ^{1}H NMR: δ 2.28 (s, 3H, CH_3), 3.88 (s, 3H, CH_3O), 6.33 (s, 1H, H-5'), 7.20 (m, 2H, *m*-ArH); 8.14 (m, 2H, *o*-ArH); 8.63 (s, 1H, C_2-H), 8.67 (s, 1H, C_6-H), 17.5 (br. s, 1H, OH). MS (EI, *m/z* (rel. %)): 350 (100) [M^+], 335 (17), 307 (21), 265 (62), 251 (15). Anal. Calcd for $C_{18}H_{14}N_4O_4$: C, 61.71; H, 4.03; N, 15.99. Found C, 61.75; H, 4.05; N, 15.95.

5-(6-Hydroxy-1,3-dimethylpyrimidine-2,4-dion-5-yl)-7-(4-methoxyphenyl)-1,2,4-triazole[1,5-*a*]pyrimidine (4b). Compound **4b** was prepared similar to **4a** from 1 and 5-acetyl-1,3-dimethylbarbituric acid **2b**. Yield 0.18 g (47%), mp > 270°C (from ethanol). ^{1}H NMR: δ 3.23 (s, 6H, 2*CH_3), 3.88 (s, 3H, CH_3O), 7.21 (m, 2H, *m*-ArH); 8.10 (m, 2H, *o*-ArH); 8.53 (s, 1H, C_2-H), 8.87 (br. s, 1H, C_6-H), 16.6 (br. s, 1H, OH). MS (EI, *m/z* (rel. %)): 380 (100) [M^+], 353 (15), 275 (73). Anal. Calcd. for $C_{18}H_{16}N_6O_4$: C, 56.84; H, 4.24; N, 22.10. Found C, 56.90; H, 4.22; N, 22.07.

5-(6-Hydroxy-1*H*-pyrimidine-2,4-dion-5-yl)-7-(4-methoxy-phenyl)-1,2,4-triazole[1,5-*a*]pyrimidine (4c). Compound **4c** was prepared similar to **4a** from **1** and 5-acetylbarbituric acid **2c** and **1**. Yield 0.17 g (48%), mp > 300°C (from ethanol). ^{1}H NMR: δ 3.87 (s, 3H, CH_3O), 7.19 (m, 2H, *m*-ArH); 8.07 (m, 2H, *o*-ArH); 8.51 (s, 1H, C_2-H), 8.78 (br. s, 1H, C_6-H), 16.5 (br. s, 1H, OH). MS (EI, *m/z* (rel. %)): 352 (100) [M^+], 321 (29), 245 (82), 225 (15). Anal. Calcd for $C_{16}H_{12}N_6O_4$: C, 54.55; H, 3.43; N, 23.85. Found C, 54.45; H, 3.44; N, 23.81.

Transformation of 6,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines 3a–c into 1,2,4-triazolo[1,5-*a*]pyrimidines (4a-c). The 0.001 mol (0.35 g) of **3a** in 1 mL DMF was heated for 30 min and diluted with 20 mL benzene after cooling. 0.28 g (79%) of **4a** was isolated.

In analogous way, **4b** and **4c** were isolated with yields 75 and 84%, correspondingly.

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Sulfamic Acid Catalyzed One-Pot Synthesis of 2,5-Diaryl-1,3,4-oxadiazoles Under Microwave Irradiation and Conventional Heating

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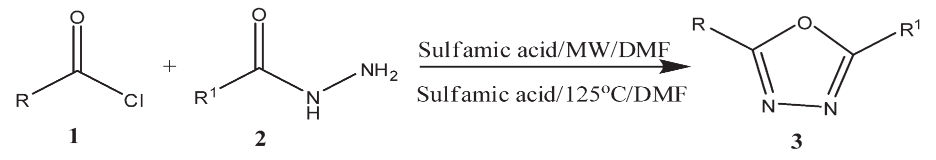

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Sulfamic acid has been found to be an efficient catalyst for the one-pot synthesis of novel 2,5-diaryl-1,3,4-oxadiazoles by condensation of different coumarinoyl hydrazides with various coumarinoyl or quinolinoyl chlorides under microwave irradiation and conventional heating. Some of the advantages of this method are low reaction times, operational simplicity, and high yields.

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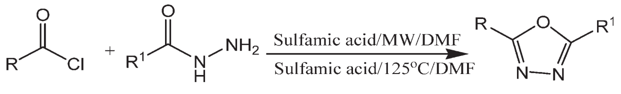
INTRODUCTION

1,3,4-Oxadiazoles and their derivatives have a wide range of biological and therapeutic properties such as antimicrobial [1], antifungal [2], and anti-inflammatory action [3]. Also, vinblastine-like [4] oxadiazole molecules that incorporate a coumarin moiety have been reported as potent antitumor and antibacterial agents [5,6]. Because of these important findings, the synthesis of these kinds of molecules has attracted significant interest. The general synthesis of oxadiazoles can be classified into four main synthetic strategies as follows: (i) cyclization of diacylhydrazines [7–11], (ii) oxidation of acyl hydrazones [12,13], (iii) acid-catalyzed condensation of acyl hydrazides with orthoesters [14–18], and (iv) solid-state synthesis and other methods [19–27]. However, these methods suffer from harsh reaction conditions and long reaction times. Therefore, it was deemed necessary to develop efficient and simple procedures for the synthesis of these biologically important oxadiazole derivatives.

RESULTS AND DISCUSSION

Sulfamic acid (SA) has emerged as an excellent solid acid catalyst for acid-catalyzed reactions such as functional group protection and deprotection [28], and is used in some important organic transformations such as the synthesis of xanthenes [29], Beckmann rearrangement reactions [30], Pechmann [31] and Biginelli [32] condensations. SA is a recyclable and very stable crystalline solid [33], because of its immiscible nature with common organic solvents and its ease in handling. Microwave irradiation accelerated synthesis is emerging as a powerful tool in organic synthesis [34], since this technique affords short reaction times, increased yields, and high purities of reaction products, as well as ease in manipulation. These observations prompted us to investigate an efficient SA-catalyzed one-pot synthesis of novel 2,5-diaryl-1,3,4-oxadiazoles from aryl acid chlorides and aryl hydrazides in dimethylformamide (DMF) utilizing both microwave irradiation and conventional heating (Scheme 1). In the microwave irradiation procedure for the synthesis of 2,5-diaryl-1,3,4-oxadiazoles, the reaction mass containing the aryl acid chloride and the aryl hydrazide was irradiated in a domestic microwave oven at a 300 watt power level over 30 s intervals in an open vessel for 4–5 min. The oxadiazoles were also conventionally prepared at 125°C over 4–5 h. The structures of all newly synthesized 2,5-diaryl-1,3,4-

Scheme 1. Sulfamic acid catalyzed synthesis of 2,5-diaryl-1,3,4-oxadiazoles.



1 2 3

oxadiazoles were confirmed by IR, ^{1}H NMR and mass spectral data.

To study the efficiency of a number of acidic catalysts compared with SA in the synthesis of the 2,5-diaryl-1,3,4-oxadiazoles, we conducted a model reaction between 3-coumarinoyl chloride and 3-coumarinoyl hydrazide in the presence of either SA, silica sulfuric acid, *p*-toluenesulfonic acid, or sulfuric acid (all at 4 mol %) under both microwave irradiation (Method A) and conventional heating (Method B) conditions (Table 1). In this study it was found that, compared with the other acid catalysts utilized, SA was a more effective catalyst with respect to reaction time and yield of the resulting 1,3,4-oxadiazole (Table 1).

A variety of symmetrical and unsymmetrical 2,5-diaryl-1,3,4-oxadiazoles were also synthesized *via* the above microwave procedure, all of which were obtained in good yields (Table 2), illustrating the versatility of the method.

CONCLUSION

In conclusion, an efficient, facile and flexible one-pot synthesis of 2,5-diaryl-1,3,4-oxadiazoles *via* SA-catalyzed microwave irradiation has been developed. We consider this methodology to be superior to existing methodologies for the synthesis of 2,5-disubstituted-1,3,4-oxadiazoles.

EXPERIMENTAL

All the melting points were determined in open capillary in liquid paraffin bath and are uncorrected. The purity of the compounds was checked by TLC. IR spectra (KBr) were recorded on Shimadzu FTIR model 8010 spectrometer and the ^{1}H NMR spectra on Varian Gemini 200 MHz Spectrometer using TMS as an internal standard. The C, H, and N analysis of the compounds was done on a Carlo Erba model EA1108. Mass spectra were obtained on a Jeol JMS D-300 Spectrometer. For the microwave irradiation experiments (BPL 800T) domestic microwave oven was used.

General procedure for the synthesis of 2,5-diaryl-1,3,4-oxadiazoles (3a-m) *via* methods A and B.

Method A. The coumarinoyl or quinolinoyl chloride (1.1 mmol), coumarinoyl hydrazide (1.5 mmol), and SA (0.04 mmol) were added to DMF (2 mL). The reaction mass was irradiated in a microwave oven (BPL, 800 model) at a power level of 300 W over 30 s intervals in an open vessel for 4–5 min (Table 2). Completion of the reaction was determined by TLC monitoring. The reaction mass was cooled to room temperature, poured over crushed ice, and stirred for 15 min at 0–5°C. The precipitated product was collected by filtration, washed with cold water and air-dried. Pure product was obtained by recrystallization from ethanol.

Method B. The coumarinoyl or quinolinoyl chloride (1.1 mmol), coumarinoyl hydrazide (1.5 mmol), and SA (0.04 mmol) were added to DMF (3 mL). The reaction mixture was stirred at 125°C for 4–5 h (Table 2). The progress of the reaction was monitored by TLC. After completion of the reaction, the contents were cooled to room temperature, poured over crushed ice and stirred for 15 min at 0–5°C. The precipitated product was collected by filtration, washed with cold water and air-dried. Pure product was obtained by recrystallization from ethanol.

Spectral data and combustion analyses for 2,5-diaryl-1,3,4-oxadiazoles.

3-(5-(2-Oxo-2H-chromen-3-yl)-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one (3a). IR (KBr, cm^{-1}): 1745 (—C=O), 1610 (—C=N), 1567 (—C=C—), 1122 (—C—O—C—); ^{1}H NMR (300MHz, DMSO-d$_6$): δ = 7.30–7.90 (m, 8H), 8.78 (s, 2H); EIMS, 70 E.V, *m/z*: 358 (M$^+$); Anal. Calcd. for $C_{20}H_{10}N_2O_5$: C, 67.04; H, 2.81; N, 7.82; Found: C, 67.08; H, 2.84; N, 7.79.

6-Bromo-3-(5-(6-bromo-2-oxo-2H-chromen-3-yl)-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one (3b). IR (KBr, cm^{-1}): 1719 (—C=O), 1610 (—C=N), 1568 (—C=C—), 1120 (—C—O—C—); ^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 7.54 (t, 2H), 7.65–7.80 (m, 4H), 8.76 (s, 2H); EIMS, 70 E.V, *m/z*: 516 (M$^+$); Anal. Calcd. for $C_{20}H_8Br_2N_2O_5$: C, 46.54; H, 1.56; N, 5.43; Found: C, 46.57; H, 1.52; N, 5.40.

6,8-Dibromo-3-(5-(6,8-dibromo-2-oxo-2H-chromen-3-yl)-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one (3c). IR (KBr, cm^{-1}): 1745 (—C=O), 1620 (—C=N), 1575 (—C=C—), 1135 (—C—O—C—); ^{1}H NMR (300 MHz, DMSO-d$_6$): δ =7.55 (d, 2H), 7.70 (d, 2H), 8.78 (s, 2H); EIMS, 70 E.V, *m/z*: 673 (M$^+$); Anal. Calcd. for $C_{20}H_6Br_4N_2O_5$: C, 35.65; H, 0.90; N, 4.16; Found: C, 35.63; H, 0.92; N, 4.19.

6-Nitro-3-(5-(6-nitro-2-oxo-2H-chromen-3-yl)-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one (3d). IR (KBr, cm^{-1}): 1730 (—C=O), 1618 (—C=N), 1570 (—C=C—), 1130 (—C—O—C); ^{1}H NMR (300 MHz, DMSO-d$_6$): δ =7.60 (m, 4H), 7.70 (d, 2H), 8.75 (s, 2H); EIMS, 70 E.V, *m/z*: 448 (M$^+$); Anal. Calcd. for $C_{20}H_8N_4O_9$: C, 53.58; H, 1.80; N, 12.50; Found: C, 53.57; H, 1.82; N, 12.53.

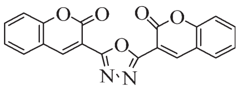
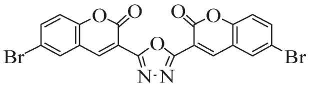
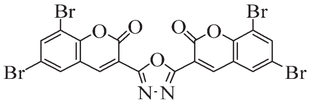
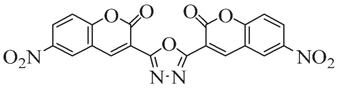
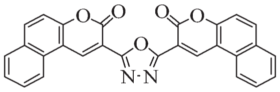
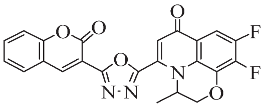
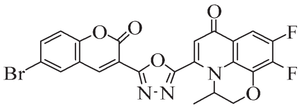
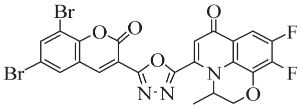
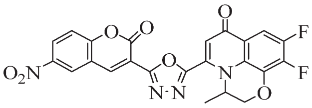
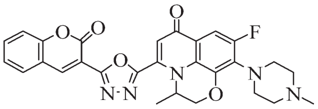
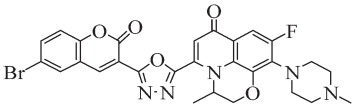
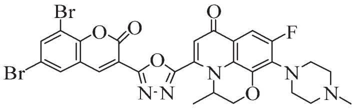
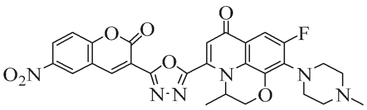
2-(5-(3-Oxo-3H-benzo[f]chromen-2-yl)-1,3,4-oxadiazol-2-yl)-3H-benzo[f]chromen-3-one (3e). IR (KBr, cm^{-1}): 1720 (—C=O), 1600 (—C=N), 1565 (—C=C—), 1120 (—C—O—C—); ^{1}H NMR (300 MHz, DMSO-d$_6$): δ =7.45–8.30 (m, 12H), 8.70 (s, 2H); EIMS, 70 E.V, *m/z*: 458 (M$^+$); Anal. Calcd. for $C_{28}H_{14}N_2O_5$: C, 73.36; H, 3.08; N, 6.11; Found: C, 73.38; H, 3.04; N, 6.13.

9,10-Difluoro-2,3-dihydro-3-methyl-5-(5-(2-oxo-2H-chromen-3-yl)-1,3,4-oxadiazol-2-yl)-[1,4]oxazino[2,3,4-ij]quinolin-7-one (3f). IR (KBr, cm^{-1}): 1718 (lactone C=O), 1683 (—C=O), 1615 (C=N), 1565 (—C=C—), 1131 (—C—O—C—); ^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 1.59 (d, 3H), 4.35 (d, 1H), 4.50 (d, 1H), 4.76 (d, 1H), 6.90 (d, 2H), 7.51 (d, 2H), 7.81 (t, 1H), 8.72 (s, 1H), 8.90 (s, 1H): EIMS, 70 E.V, *m/z*: 449 (M$^+$); Anal. Calcd. for $C_{23}H_{13}F_2N_3O_5$: C, 61.48; H, 2.92; N, .35; Found: C, 61.46; H, 2.96; N, .37.

5-(5-(6-Bromo-2-oxo-2H-chromen-3-yl)-1,3,4-oxadiazol-2-yl)-9,10-difluoro-2,3-dihydro-3-methyl-[1,4]oxazino[2,3,4-ij]quinolin-7-one (3g). IR (KBr, cm^{-1}): 1719 (lactone C=O), 1681 (—C=O),1621(C=N), 1567 (—C=C—), 1135 (—C—O—C—); ^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 1.60 (d, 3H), 4.41 (d, 1H), 4.52 (d, 1H), 4.82 (d, 1H), 6.91 (d, 1H), 7.53 (d, 2H), 7.82 (t, 1H), 8.75 (s, 1H), 8.95 (s,1H): EIMS, 70 E.V, *m/z*: 528 (M$^+$); Anal. Calcd. for $C_{23}H_{12}BrF_2N_3O_5$: C, 52.29; H, 2.29; N, 7.95; Found: C, 52.32; H, 2.27; N, 7.97.

Table 1

2,5-Diaryl-1,3,4-oxadiazoles (3a–m) synthesized by using sulfamic acid as catalyst.

		Method A		Method B		
Entry	Product	Time (min)	Yield (%)[a]	Time (h)	Yield (%)[a]	mp (°C)
1		5.0	96	4.0	93	180
2		5.0	95	4.5	91	179
3		4.5	96	4.5	91	250
4		5.0	95	5.0	90	140
5		5.0	87	5.0	90	165
6		4.0	96	5.0	93	280
7		4.0	97	5.0	94	255
8		4.5	98	5.0	93	250
9		5.0	96	5.0	94	260
10		4.5	97	5.0	95	220
11		4.0	97	4.0	93	210
12		5.0	98	5.0	95	259
13		5.0	96	5.0	93	190

[a] Yields refer to isolated pure products and were characterized by NMR, IR, and mass spectral data.

Table 2

Effect of five acid-catalysts on the reaction of 3-coumarinoyl chloride with 3-coumarinyl hydrazide under conventional and microwave heating.

	Method A		Method B	
Catalyst	Time (min)	Yield (%)	Time (h)	Yield (%)
Sulfamic acid	5	96	4	93
Silicaulfuric acid	5	88	4	82
p-TsOH	5	63	4	56
H_2SO_4	5	32	4	28

5-(5-(6,8-Dibromo-2-oxo-2H-chromen-3-yl)-1,3,4-oxadiazol-2-yl)-9,10-difluoro-2,3-dihydro-3-methyl-[1,4]oxazino[2,3,4-ij]quinolin-7-one (3h). IR (KBr, cm^{-1}): 1717(lactone C=O), 1683 (C=O),1623(C=N), 1565 (—C=C—), 1181 (—C—O—C—); ^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 1.61 (d, 3H), 4.44 (d, 1H), 4.56 (d, 1H), 4.86 (d, 1H), 6.91 (d, 1H), 7.55 (d, 1H), 7.82 (t, 1H), 8.76 (s, 1H), 8.95 (s, 1H): EIMS,70 E.V, *m/z*: 607 (M$^+$); Anal. Calcd. for $C_{23}H_{11}Br_2F_2N_3O_5$: C, 45.50; H, 1.83; N, 6.92; Found: C, 45.48; H, 1.86; N, 6.94.

9,10-Difluoro-2,3-dihydro-3-methyl-5-(5-(6-nitro-2-oxo-2H-chromen-3-yl)-1,3,4-oxadiazol-2-yl)-[1,4]oxazino[2,3,4-ij]quinolin-7-one (3i). IR (KBr, cm^{-1}): 1718 (lactone—C=O), 1683 (—C=O), 1632 (—C=N), 1572 (—C=C—), 1115 (—C—O—C—); ^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 1.49 (d, 3H), 4.47 (d, 1H), 4.67 (d, 1H), 5.01 (d, 1H), 7.10 (t, 1H), 7.77–7.87 (m, 2H), 7.95 (t, 1H), 8.52 (s,1H), 8.70 (s, 1H); EIMS, 70 E.V, *m/z*: 494 (M$^+$); Anal. Calcd. for $C_{23}H_{12}F_2N_4O_7$: C, 55.88; H, 2.45; N, 11.33; Found: C, 55.84; H, 2.47; N, 11.35.

9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl piperazin-1-yl)-5-(5-(2-oxo-2H-chromen-3-yl)-1,3,4-oxadiazol-2-yl)-[1,4]oxazino[2,3,4-ij]quinolin-7-one (3j). IR (KBr, cm^{-1}): 1745 (lactone C=O), 1683 (—C=O), 1610 (C=N), 1567 (—C=C—), 1122 (—C—O—C—); ^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 1.30 (d, 3H), 2.81 (s, 3H), 3.24 (s, 4H), 3.54 (s, 4H), 4.41 (d, 1H), 4.55 (d, 1H), 4.85 (d, 1H), 7.43 (d, 2H), 7.56 (d, 2H), 7.74 (t, 1H), 8.73 (s, 1H), 8.87 (s, 1H): EIMS, 70 E.V, *m/z*: 529(M$^+$); Anal. Calcd. for $C_{28}H_{24}FN_5O_5$: C, 63.51; H, 4.57; N, 13.23; Found: C, 63.54; H, 4.54; N, 13.27.

5-(5-(6-Bromo-2-oxo-2H-chromen-3-yl)-1,3,4-oxadiazol-2-yl)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methylpiperazin-1-yl)-[1,4]oxazino[2,3,4-ij]quinolin-7-one (3k). IR (KBr, cm^{-1}): 1745 (lactone C=O), 1687 (—C=O), 1615 (C=N), 1580 (—C=C), 1135 (—C—O—C—); ^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 1.32 (d, 3H), 2.72 (s, 3H), 3.35 (s, 4H), 3.58 (s, 4H), 4.43 (d, 1H), 4.58 (d, 1H), 4.90 (d, 1H), 7.54 (d, 2H), 7.56 (d, 1H), 7.77 (t, 1H), 8.70 (s, 1H), 8.87 (s, 1H): EIMS, 70 E.V, *m/z*: 608 (M$^+$); Anal. Calcd. for $C_{28}H_{23}BrFN_5O_5$: C, 55.27; H, 3.81; N, 11.51 Found: C, 55.29; H, 3.84; N, 11.47.

5-(5-(6,8-Dibromo-2-oxo-2H-chromen-3-yl)-1,3,4-oxadiazol-2-yl)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methylpiperazin-1-yl)-[1,4]oxazino[2,3,4-ij]quinolin-7-one (3l). IR (KBr, cm^{-1}): 1745 (lactone C=O), 1685 (—C=O),1620 (C=N), 1580 (—C=C—), 1130 (—C—O—C—); ^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 1.35 (d, 3H), 2.65 (s, 3H), 3.36 (s, 4H), 3.55 (s, 4H), 4.58 (d, 1H), 4.65 (d, 1H), 4.90 (d, 1H), 7.56 (d, 1H), 7.59 (d, 1H), 7.77 (t, 1H), 8.75 (s, 1H), 8.90 (s, 1H): EIMS, 70 E.V, *m/z*: 687 (M$^+$); Anal. Calcd. for $C_{28}H_{22}Br_2FN_5O_5$: C, 48.93; H, 3.23; N, 10.19; Found: C, 48.91; H, 3.25; N, 10.20.

9-Fluoro-2,3-dihydro-3-methyl-10-(4-methylpiperazin-1-yl)-5-(5-(6-nitro-2-oxo-2H-chromen-3-yl)-1,3,4-oxadiazol-2-yl)-[1,4]oxazino[2,3,4-ij]quinolin-7-one (3m). IR 1740 (lactone C=O), 1680 (—C=O), 1618 (C=N), 1585 (—C=C—), 1130 (—C—O—C—); ^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 1.30 (d, 3H), 2.70 (s, 3H), 3.30 (s, 4H), 3.55 (s, 4H), 4.35 (d, 1H), 4.50 (d, 1H), 4.80 (d, 1H), 7.57 (d, 2H), 7.65 (d, 1H), 7.80 (m, 1H), 8.67 (s, 1H), 8.80 (s, 1H): EIMS, 70 E.V, *m/z*: 574 (M$^+$); Anal. Calcd. for $C_{28}H_{23}FN_6O_7$: C, 58.54; H, 4.04; N, 14.63; Found: C, 58.58; H, 4.07; N, 14.59.

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Synthesis and Laser Activity of Halo-Acridinedione Derivatives

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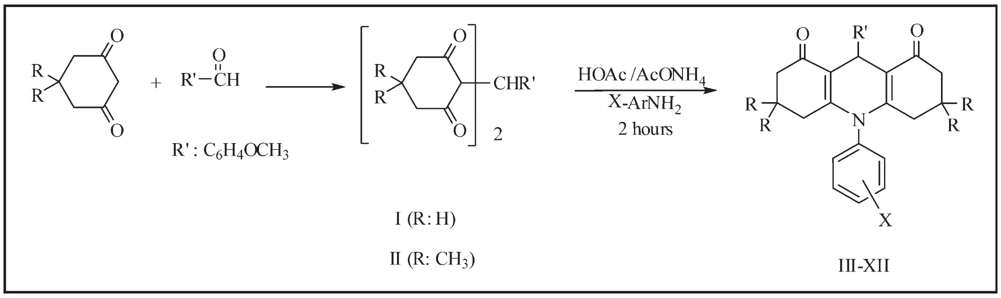

Synthesis of 10-(halophenyl)-9-(4-methoxyphenyl)-3,4,6,7,9,10-hexahydroacridine-1,8-(2H,5H)-dione derivates have been prepared and their absorption, emission, and laser properties have been evaluated. The structures of all the synthesized compounds were characterized by spectroscopic methods IR, ^{1}H NMR, ^{13}C-APT, MS, and elemental analysis.

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INTRODUCTION

Many organic compounds demonstrated laser activity in the 310–1100 nm region [1]. These laser dyes have been classified as xanthene dyes, cyanine or polymethine dyes, linear and condensed polybenzoid compounds, and heterocyclic compounds. In the heterocyclic series, rhodamine, coumarin, and acridinedione have been known as efficient laser dyes. So far, the acridinedione ring system reported possesses laser activity in the 475–500 nm region [2–5]. The effectiveness of lasing can be controlled by substituents at the 9- and 10-positions of the acridine chromophore [6]. Therefore, acridinediones with substituents at 9- or 10-positions have already been synthesized by using different methods [7–13]. Photochemical properties of some acridinedione dyes were reported in literature [14–16]. In this study, we reported the synthesis of novel halogen substitute acridinediones. In addition to UV, fluorescence spectra and laser activity of the acridinedione dyes were examined (Table 1).

RESULTS AND DISCUSSION

The tetraketones were formed by the condensation of cyclohexane-1,3-dione or 5,5-dimethyl-1,3-cyclohexanedione with 4-methoxybenzaldehyde furnishing compounds **I** and **II**. Then, tetraketones were refluxed together various halo-anilines with acetic acid-ammonium acetate system in toluene for the syntheses of acridinediones (Scheme 1). Acridinediones were obtained with high yield (from 75 to 92%) and short reaction time 2 h data for all compounds. Physical and analytical data of compounds were given in Table 1.

The purity of the compounds was checked by using TLC. All of the products were characterized by IR, ^{1}H NMR, ^{13}C-APT, mass spectrometry, and elemental analyses.

All spectral data are in accordance with assigned structures. In IR spectra, aromatic C—H, aliphatic C—H, and C=O stretching bands were observed at expected values. In the ^{1}H NMR spectra, methyl protons were seen at ~0.85–1.10 ppm as two singlet peaks. Aromatic, methylene, methane, and OCH$_3$ protons were seen at expected values. The ^{13}C-APT spectra of the compounds displayed the number of resonance that fit exactly with the number of expected carbon resonances. Mass spectra of the compounds were taken using the chemical ionization (CI) technique. In general molecular ion peaks were seen in spectra and the base peaks were found by cleavage of the aryl ring from the parent molecule. The structure of compounds IX was further confirmed by an X-ray crystallographic analysis [17]. In summary, all compounds show good florescence and laser activity in chloroform ($1 \times 10^{-4}M$). Table 1 gives the absorption, emission, and laser activity of the dyes that have high

Table 1

Yields, melting points, UV, fluorescence, laser, and elemental analyses data for **III–XIV**.

Compound	X	R	Yield (%)	mp (°C) (Ref.)	λ_{UV} (nm)	λ_{Flu} (nm)	λ_{laser} (nm)	Molecular formula	Elemental analyses (%) Calc./Found C	H	N
III	4-F	H	79	265–266	272, 356	424	554	$C_{26}H_{24}FNO_3$	74.80 74.51	5.79 5.77	3.36 3.34
IV	4-Cl	H	90	283, 285 [18]	238, 360	431	546	$C_{26}H_{24}ClNO_3$	71.97 71.70	5.57 5.55	3.23 3.19
V	2-Cl	H	77	248	242, 361	443	548	$C_{26}H_{24}ClNO_3$	71.97 71.89	5.57 5.49	3.23 3.22
VI	4-Br	H	92	217–219	243, 357	423	558	$C_{26}H_{24}BrNO_3$	65.28 65.20	5.06 5.04	2.93 2.89
VII	4-I	H	85	242–243	247, 361	422	534	$C_{26}H_{24}INO_3$	59.44 59.37	4.60 4.58	2.67 2.66
VIII	4-F	CH_3	77	230 (dec)	240, 358	423	540	$C_{30}H_{32}FNO_3$	76.08 75.85	6.81 6.79	2.96 2.93
IX	2-F	CH_3	75	209	244, 364	433	535	$C_{30}H_{32}FNO_3$	76.08 76.01	6.81 6.77	2.96 2.95
X	4-Cl	CH_3	80	220–221	248, 367	434	550	$C_{30}H_{32}ClNO_3$	73.53 73.36	6.58 6.56	2.86 2.81
XI	2-Cl	CH_3	90	245	247, 366	421	530	$C_{30}H_{32}ClNO_3$	73.53 73.45	6.58 6.56	2.86 2.82
XII	4-Br	CH_3	81	245, 247–248 [19]	250, 369	425	542	$C_{30}H_{32}BrNO_3$	67.41 67.20	6.03 6.01	2.62 2.60
XIII	2-Br	CH_3	86	268	249, 369	427	530	$C_{30}H_{32}BrNO_3$	67.41 67.28	6.03 5.97	2.62 2.61
XIV	4-I	CH_3	75	263, 259–263 [20]	240, 363	422	536	$C_{30}H_{32}INO_3$	61.97 61.78	5.55 5.53	2.41 2.39

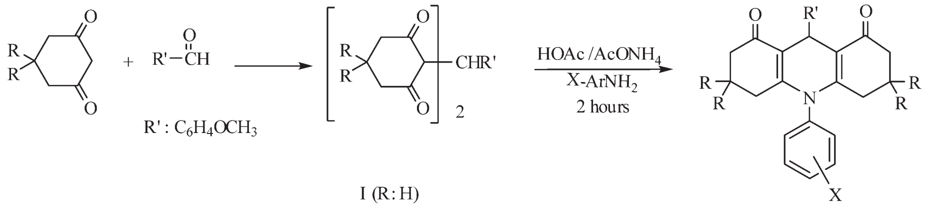
lasing efficiencies using chloroform as solvent. The tuning range for the dyes lies between 530 and 558 nm (Fig. 1).

EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus. Absorption spectra were performed on an ATI Unicam UV-100 spectrophotometer. Infrared absorption spectra were recorded from a Mattson 1000-FTIR spectrometer, using KBr pellets. ^1H NMR (300 MHz) and ^{13}C-APT (75 MHz) spectra were obtained with a Bruker DPX-300 FT-NMR instrument with $CDCl_3$ as solvent. Mass spectra with CI were recorded on a AGILENT 1100 MSD instrument. The elemental analyses (C, H, N) were conducted using the Elemental Analyser LECO CHNS-932. Fluorescence spectra were obtained with Varian CARY Eclipse Fluorescence Spectrophotometer. The dye solutions (in a 2 cm × 2 cm quartz cell) were excited by using Ar ion laser; its wavelength was 488 nm and the pulse duration 6 ns and were detected by a diode. All measurements were performed in the presence of air at room temperature.

General procedure. The syntheses of compounds **I** and **II** were achieved according to the procedure described in the literature [20]. For that purpose, 4-methoxybenzaldehyde (3.40 g, 25 mmol) was added to the solution of cyclohexane-l,3-dione (5.60 g, 50 mmol) in aq. methanol (20 mL) and warmed until the solution became cloudy. The tetraketone started to separate out. Then, the reaction mixture was diluted with water to 250 mL and allowed to stand overnight; the tetraketone was collected by filtration and dried and recrystallized from methanol (**I:** yield 92%, mp 196°C; lit. mp for **I:** 196°C [20] and **II:** yield 90%, mp 142–143°C; lit. mp for **II:** 142–143°C [21], 125.5–126.5°C [21]).

Scheme 1



I (R: H)

II (R: CH3)

III-XII

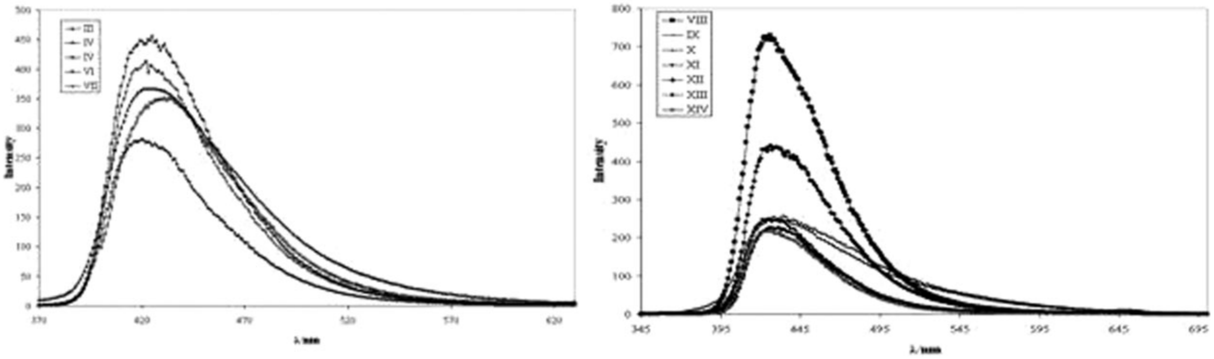


Figure 1. Fluorescence spectra of the dyes **III–XIV**.

10-(4-Fluorophenyl)-9-(4-methoxyphenyl)-3,4,6,7-hexadroacridine-1,8-(2*H*,5*H*-dione (III). The solution of 2,2'-((4-methoxyphenyl)methylene) dicyclohexane-1,3-dione **(I)** (1.03 g, 3 mmol), 4-fluorobenzenamine (0.34 g, 3.0 mmol), and excess amount of ammonium acetate were prepared with 20 mL toluene-acetic acid mixture (1:1). The formed solution was refluxed for 2 h by using a Dean-Stark apparatus. Then, the reaction mixture was poured into 100 mL water. Afterwards, last mixture was taken to a separation flask and 25 mL $CHCl_3$ was added. The organic phase was separated and evaporated. Halo-acridinedione **(III)** was separated from residue by thin layer chromatography and dried and then recrystallized from $CHCl_3$–MeOH (9:1). This compound was obtained as yellow solid, mp 265–266°C; IR: 3063 (Ar-H), 2954 (C—H), 1631 (C=O), 1585 (C=C) cm^{-1}. ^1H NMR: δ 1.73–1.97 (m, 4H, 2 × CH_2), 2.03–2.47 (m, 8H, 4 × CH_2), 3.77 (s, 3H, OCH_3), 5.32 (s, 1H, CH), 6.82 (d, 2H, J = 8.5 Hz, ArH), 7.18–7.36 (m, 6H, ArH). ^{13}C-APT: δ 21.10 (CH_2), 28.33 (CH_2), 31.18 (CH), 36.65 (CH_2), 55.18 (OCH_3), 113.63 (CH), 116.04 (C), 116.98 (CH), 129.33 (CH), 131.67 (CH), 135.07 (C), 138.79 (C), 151.30 (C), 160.90 (C), 164.23 (C), 196.14 (C). MS: *m*/*z* 417 (M^+), 291 (M^+-$C_6H_4FOCH_3$).

10-(4-Chlorophenyl)-9-(4-methoxyphenyl)-3,4,6,7,9,10-hexahydroacridine-1,8-(2*H*,5*H*)-dione (IV). This compound was obtained as yellow solid (chloroform–methanol), mp 283°C Ref. [17] 285°C. IR: 3034 (Ar-H), 2947 (C—H), 1640 (C=O), 1573 (C=C) cm^{-1}. ^1H NMR: δ 1.76–2.00 (m, 4H, 2 × CH_2), 2.05–2.47 (m, 8H, 4 × CH_2), 3.78 (s, 3H, OCH_3), 5.34 (s, 1H, CH), 6.78 (d, 2H, J = 8.7 Hz, ArH), 7.20 (d, 2H, J = 8.5 Hz, ArH), 7.33 (d, 2H, J = 8.7 Hz, ArH), 7.54 (d, 2H, J = 8.5 Hz, ArH). ^{13}C-APT: δ 21.10 (CH_2), 28.33 (CH_2), 31.18 (CH), 36.67 (CH_2), 55.18 (OCH_3), 113.50 (CH), 116.07 (C), 128.66 (CH), 129.32 (CH), 130.80 (CH), 135.49 (C), 137.59 (C), 138.75 (C), 151.00 (C), 157.86 (C), 196.10 (C). MS: *m*/*z* 433 (M^+), 326 (M^+-$C_6H_4OCH_3$).

10-(2-Chlorophenyl)-9-(4-methoxyphenyl)-3,4,6,7,9,10-hexahydroacridine-1,8-(2*H*,5*H*)-dione (V). This compound was obtained as yellow solid (chloroform–methanol), mp 248°C. IR: 3030 (Ar-H), 2940 (C—H), 1635 (C=O), 1575 (C=C) cm^{-1}. ^1H NMR: δ 1.66–1.94 (m, 4H, 2 × CH_2), 2.25–2.59 (m, 8H, 4 × CH_2), 3.68 (s, 3H, OCH_3), 4.56 (s, 1H, CH), 6.81 (d, 2H, J = 8.5 Hz, ArH), 7.28–7.38 (m, 6H, ArH). ^{13}C-APT: δ 21.18 (CH_2), 26.54 (CH_2), 31.45 (CH), 36.79 (CH_2), 55.12 (OCH_3), 113.57 (CH), 113.28 (CH), 116.04 (C), 128.01 (CH), 129.59 (CH), 130.83 (CH), 130.97 (CH), 134.87 (C), 137.14 (C), 139.15 (C), 150.89 (C), 157.78 (C), 196.10 (C). MS: *m*/*z* 433 (M^+), 326 (M^+-$C_6H_4OCH_3$), 215 (M^+-$C_{12}H_8ClOCH_3$).

10-(4-Bromophenyl)-9-(4-methoxyphenyl)-3,4,6,7,9,10-hexadroacridine-1,8-(2*H*,5*H*)-dione (VI). This compound was obtained as yellow solid (chloroform–methanol), mp 217–219°C. IR: 3031 (Ar-H), 2940 (C—H), 1638 (C=O), 1573 (C=C) cm^{-1}. ^1H NMR: δ 1.75–1.98 (m, 4H, 2 × CH_2), 2.20–2.47 (m, 8H, 4 × CH_2), 3.90 (s, 3H, OCH_3), 5.32 (s, 1H, CH), 6.80 (d, 2H, J = 8.7 Hz, ArH), 7.17 (d, 2H, J = 8.4 Hz, ArH), 7.32 (d, 2H, J = 8.7 Hz, ArH), 7.7 (d, 2H, J = 8.4 Hz, ArH). ^{13}C-APT: δ 21.10 (CH_2), 28.33 (CH_2), 31.18 (CH), 36.67 (CH_2), 55.18 (OCH_3), 113.52 (CH), 116.47 (C), 124.66 (C), 128.02 (CH), 131.20 (CH), 133.47 (CH), 137.59 (C), 138.75 (C), 151.00 (C), 157.86 (C), 196.10 (C). MS: *m*/*z* 477 (M^+), 370 (M^+-$C_6H_4OCH_3$), 215 (M^+-$C_{12}H_8BrOCH_3$).

10-(4-Iodophenyl)-9-(4-methoxyphenyl)-3,4,6,7,9,10-hexaoacridine-1,8-(2*H*,5*H*)-dione (VII). This compound was obtained as yellow solid (chloroform–methanol), mp 242–243°C. IR: 3050 (Ar-H), 2940 (C—H), 1645 (C=O), 1580 (C=C) cm^{-1}. ^1H NMR: δ 1.72–1.96 (m, 4H, 2 × CH_2), 2.18–2.47 (m, 8H, 4 × CH_2), 3.78 (s, 3H, OCH_3), 5.29 (s, 1H, CH), 6.80 (d, 2H, J = 8.7 Hz, ArH), 7.04 (d, 2H, J = 8.4 Hz, ArH), 7.32 (d, 2H, J = 8.7 Hz, ArH), 7.88 (d, 2H, J = 8.4 Hz, ArH): ^{13}C-APT: δ 21.04 (CH_2), 28.36 (CH_2), 31.19 (CH), 36.41 (CH_2), 55.19 (OCH_3), 95.13 (C), 113.67 (CH), 116.12 (C), 128.67 (CH), 131.35 (CH), 138.49 (C), 138.71 (C), 139.24 (CH), 151.44 (C), 157.92 (C), 196.23 (C). MS: *m*/*z* 525 (M^+), 418 (M^+-$C_6H_4OCH_3$).

10-(4-Fluorophenyl)-9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8-(2*H*,5*H*)-dione (VIII). This compound was obtained as yellow solid (chloroform–methanol), dec. 230°C. IR: 3028 (Ar-H), 2944 (C—H), 1637 (C=O), 1580 (C=C) cm^{-1}. ^1H NMR: δ 0.86 (s, 6H, 2 × CH_3), 1.02 (s, 6H, 2 × CH_3), 1.80–2.06 (d, 4H, 2 × CH_2), 2.25–2.40 (d, 4H, 2 × CH_2), 3.83 (s, 3H, OCH_3), 4.71 (s, 1H, CH), 6.76 (d, 2H, J = 8.5 Hz, ArH), 7.20–7.37 (m, 6H, ArH). ^{13}C-APT: δ 26.92 (CH_3), 27.33 (CH_3), 29.30 (CH), 32.21 (C), 41.85 (CH_2), 50.10 (CH_2), 55.14 (OCH_3), 113.50 (CH), 115.07 (C), 123.47 (C), 128.77 (CH), 131.27 (CH), 133.40 (CH), 138.15 (C), 138.44 (C), 149.05 (C), 157.71 (C), 195.87 (C). MS: *m*/*z* 473 (M^+), 378 (M^+-C_6H_4F), 271 (M^+-$C_{12}H_8FOCH_3$).

10-(2-Fluorophenyl)-9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8-(2*H*,5*H*)-dione (IX). This compound was obtained as yellow solid (ethanol), mp. 209°C. IR: 3032 (Ar-H), 2944 (C—H), 1645 (C=O), 1575 (C=C) cm^{-1}. ^1H NMR: δ 0.85 (s, 6H, 2 × CH_3), 0.91 (s, 6H, 2 × CH_3), 1.64 (s, 2H, CH_2), 2.09–2.24 (m, 6H, 3 × CH_2), 3.75 (s, 3H, OCH_3), 5.21 (s, 1H, CH), 6.79 (d, 2H, J = 8.4 Hz, ArH), 7.27 (d, 1H, ArH), 7.49–7.52 (m, 4H, ArH), 7.68 (d, 1H, ArH). ^{13}C-APT: δ 26.80 (CH_3), 29.30 (CH_3), 30.96 (CH), 32.48 (C), 40.63 (CH_2), 50.76 (CH_2), 55.14 (OCH_3), 113.46 (CH), 115.07 (C), 116.75 (CH), 117.02 (CH), 128.78 (CH), 129.31 (CH), 131.37 (CH), 138.46 (C), 140.48 (C), 140.60 (C), 40.87 (C), 157.73 (C), 195.88 (C). MS: *m*/*z* 472 (M^+-H), 366 (M^+-$C_6H_4OCH_3$), 347 (M^+-$C_6H_4OCH_3F$).

10-(4-Chlorophenyl)-9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8-(2*H*,5*H*)-dione (X). This compound was obtained as yellow solid (chloroform–methanol), mp 220–221°C. IR: 3030 (Ar-H), 2940 (C—H), 1638 (C=O), 1580 (C=C) cm^{-1}. ^1H NMR: δ 0.9 (s, 6H, 2 × CH_3), 1.1 (s, 6H, 2 × CH_3), 2.09–2.36 (m, 8H, 4 × CH_2), 3.73 (s, 3H, OCH_3), 4.71 (s, 1H, CH), 6.77 (d, 2H, J = 8.5 Hz, ArH), 7.16 (d, 2H, J = 8.5 Hz, ArH), 7.25 (d, 2H, J = 8.6 Hz, ArH), 7.46 (d, 2H, J = 8.6 Hz, ArH). ^{13}C-APT: δ 27.33 (CH_3), 29.27 (CH_3), 30.97 (CH), 32.20 (C), 40.86 (CH_2), 50.77 (CH_2), 55.11 (OCH_3), 113.48 (CH), 115.79 (C), 121.03 (C), 123.04 (CH), 129.00 (CH), 129.30 (CH), 136.45 (C), 158.20 (C), 162.11 (C), 168.00 (C), 196.58 (C). MS: *m*/*z* 489 (M^+), 271 (M^+-$C_{12}H_8ClOCH_3$), 256 (M^+-$C_{12}H_8ClOCH_3CH_3$).

10-(2-Chlorophenyl)-9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8-(2*H*,5*H*)-dione (XI). This compound was obtained as yellow solid (ethanol), mp. 245°C. IR: 3042 (Ar-H), 2955 (C—H), 1640 (C=O), 1585 (C=C) cm^{-1}. ^1H NMR: δ 0.84 (s, 6H, 2 × CH_3), 0.92 (s, 6H, 2 × CH_3), 1.63 (s, 2H, CH_2), 2.05–2.20 (d, 6H, 3 × CH_2), 3.74 (s, 3H, OCH_3), 5.17 (s, 1H, CH), 6.77 (d, 2H, J = 8.7 Hz, ArH), 7.32 (d, 1H, ArH), 7.45–7.52 (m, 4H, ArH), 7.63 (d, 1H, ArH). ^{13}C-APT: δ 26.28 (CH_3), 30.11 (CH_3), 32.46 (C), 32.84 (CH), 41.77 (CH_2), 50.01 (CH_2), 55.09 (OCH_3), 113.21 (CH), 115.04 (C), 128.79 (CH), 129.67 (CH), 130.80 (CH), 130.91 (CH), 131.17 (CH), 134.70 (C), 136.57 (C), 138.72 (C), 148.31 (C), 157.65 (C), 195.81 (C). MS: *m*/*z* 489 (M^+), 474 (M^+-CH_3), 367 (M^+-$CH_3C_6H_4OCH_3$).

10-(2-Bromophenyl)-9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8-(2*H*,5*H*)-dione (XIII). This compound was obtained as yellow solid (ethanol), mp. 268°C. IR: 3049 (Ar-H), 2955 (C—H), 1660 (C=O), 1595 (C=C) cm^{-1}. ^1H NMR: δ 0.87 (s, 6H, 2 × CH_3), 0.94 (s, 6H, 2 × CH_3), 1.77 (s, 2H, CH_2), 1.92–2.07 (d, 2H, CH_2), 2.35–2.47 (d, 4H, 2 × CH_2), 3.70 (s, 3H, OCH_3), 5.20 (s, 1H, CH), 6.77 (d, 2H, J = 8.5 Hz, ArH), 7.31 (d, 1H, ArH), 7.42–7.60 (m, 4H, ArH), 7.85 (d, 1H, ArH). ^{13}C-APT: δ 26.79 (CH_3), 27.30 (CH_3), 29.75 (CH), 31.82 (C), 41.84 (CH_2), 50.76 (CH_2), 55.15 (OCH_3), 113.60 (CH), 115.02 (C), 126.43 (C), 129.14 (CH), 130.70 (CH), 132.18 (CH), 132.45 (CH), 134.51 (CH), 138.21 (C), 138.47 (C), 147.82 (C), 157.49 (C), 195.82 (C). MS: *m*/*z* 533 (M^+), 426 (M^+-$C_6H_4OCH_3$), 347 (M^+-$C_6H_4OCH_3Br$).

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Synthesis of New 1,3-Thiazepine Derivatives

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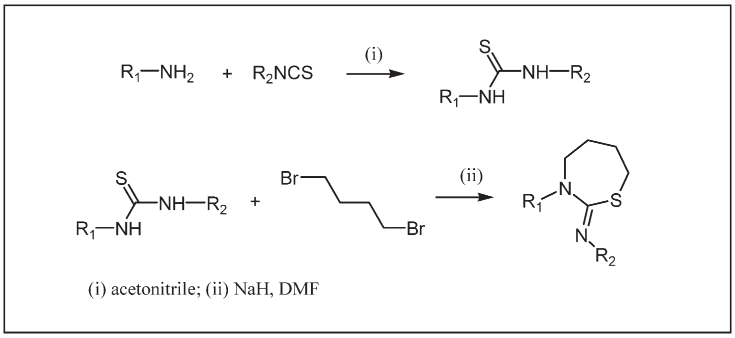

Condensation of thiourea derivatives with 1,4-dibromobutane gave 1,3-thiazepine derivatives (**1a**, **b**, **c** – **3a**, **b**, **c**). Elementary analysis, MS and ^{1}H NMR spectra confirmed the identity of the products. The molecular structure of **2b** was determined by an X-ray analysis.

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INTRODUCTION

Derivatives of 1,3-thiazepine rings are important because of their biological activity [1–4]. The 1,3-thiazepine rings is present in Omipatrilat, which is currently in the phase IV of clinical trials. By inhibiting the activity of the angiotensin converting enzyme (ACE), that causes blood vessels to constrict, Omapatrilat lowers blood pressure. Another advantage of this drug is inhibition of the enzyme known as neutral endopeptidase (NEP), which causes blood vessels to relax [5,6].

The noncondensed 1,3-thiazepine rings can be prepared by using various methods. They can be divided into two main groups.

The first synthetic route is based on the cyclocondensation of thiourea derivatives resulting in 1,3-thiazepine ring systems. Following this way, diethyl allylmalonate reacted with thiourea in an unique manner giving an excellent yield of ethyl 2-amino-7-methyl-4-oxo-4,5,6,7-tetrahydro-1,3-thiazepine-5-carboxylate [7,8]. By this method, 2-amino derivatives of 7-methyl-4-oxo-4,5,6,7-tetrahydro-1,3-thiazepine-5-carboxylic acid ester in reaction of 1-alkyl-3-pent-4-enoyl-thiourea with Br_2 were obtained [9,10]. Furthermore, 4-bromo-butyryl chloride was also used as a cyclizing agent of *N*,*N*'-diphenylthiourea [11]. Condensation reaction of 4-amino-butan-1-ol with isothiocyanate leads to thiourea derivatives. Cyclization reaction of these thiourea derivatives in acidic solution resulted in 4-substituted (methyl, benzyl and propyl) imino-4,5,6,7-tetrahydro-1,3-thiazepine [12–15].

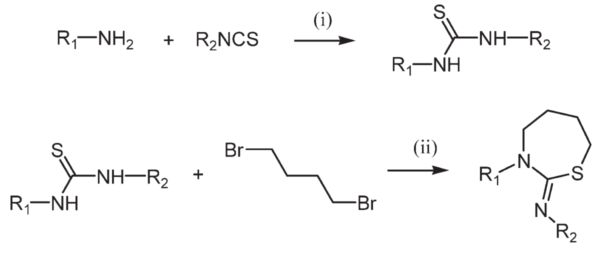
The second method for preparation of noncondensed 1,3-thiazepine ring systems is cyclization of compounds possessing N and S atoms in their chains. In this case, amines, aldehydes and halogen derivatives are utilized as highly effective cyclization reagents. Following this way, the reaction of 4-bromobutyl isothiocyanate with aromatic amines served as general preparative method for homologous 2-arylimino-1,3-thiazepines [16]. Further-more, hexahydro-1,3-thiazepin-4-ones were obtained *via* cyclocondensation of 4-mercapto-butyric acid alkyl ester with alkyl or aryl-aldehydes [17]. Moreover, 2*H*-hexa-hydro-1,3-thiazepine derivatives substituted by a nitro-methylene group in the second position were obtained in reaction of 1-methylo-thiolo-propylamine with 2,2,2-tri-halo-1-nitroethane [18]. 1,3-Thiazepine ring system was also synthesized by the alkilation of *N*-[1-mercapto-1-alkylamino-methylidene]-benzenesulfonamide sodium salt with dihaloalkanes [19].

In the present paper the 1,3-thiazepine system was obtained by the condensation reaction of thiourea derivatives with 1,4-dibromobutane.

RESULTS AND DISCUSSION

The preparation of nine new 1,3-thiazepine derivatives of 10-isopropyl-8-methyl-4-azatricyclo [5.2.2.0^{2,6}] undec-8-ene-3,5-dione, 1-isopropyl-7-methyl-4-azatricyclo-[5.2.2.0^{2,6}]undec-8-ene-3,5-dione and 1,7,8,9,10-

Scheme 1



(i) acetonitrile; (ii) NaH, DMF

1a, b, c - 3a, b, c

penta-methyl-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione (Scheme 1) is described.

Anhydrides and imides obtained in Diels-Alder reaction were used as starting materials. Anhydride or imide **1** was obtained in the reaction of enantiomeric (*R*)-(-)-α-phellandrene with furan-2,5-dione or pyrrole-2,5-dione [20,21]. The reaction of α-terpinene with furan-2,5-dione or pyrrole-2,5-dione gave compound **2** [21–23] while compound **3** was obtained in reaction of 1,2,3,4,5-penta-methylcyclopentadiene with furan-2,5-dione or pyrrole-2,5-dione [24,25].

Obtained tricyclic anhydrides or imides were subjected to the reaction of hydrazine (80 % aqueous solution) as described previously [26,27].

In order to obtain the corresponding thiourea derivatives of above compounds they were subjected to the reaction with phenyl-, 4-methoxyphenyl-, cyclohexyl-isothiocyanate [27].

Products were transformed into 1,3-thiazepine derivatives by condensation with 1,4-dibromobutane. This method of synthesis of 1,3-thiazepine noncondensed rings has not been described in literature so far. The general synthetic pathway is given in Scheme 1. Formula of the investigated compounds is given in Table 1.

Obtained compounds were purified by flash chromatography. Elementary analysis, MS and ^{1}H NMR spectra confirmed the identity of the products. The molecular structure of **2b** was determined by an X-ray analysis.

Compounds investigated using EI MS show distinct signals of molecular ions at the expected m/z values, *i.e.* for **1a**, **2a**, and **3a** the value 437 was noted, and for **2b** the corresponding value was 467.

In the spectrum of **3a** an intense (100%) signal due to the ion $[M\text{-}135]^{+\bullet}$ has been observed, apparently due to the elimination of phenylisothiocyanate (PhNCS). Analogous splitting was noted for **2a** and **1a**, whereas in case of **2b**, consequently, 4-methoxyphenylisothiocyanate (CH_3O-PhNCS) was severed. However, the intensities of these signals for **2a**, **1a,** and **2b** were only 6, 20 and 2 %, respectively.

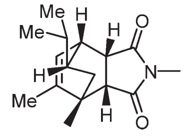
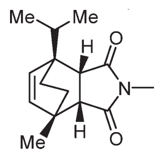
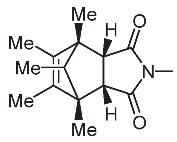
Furthermore, in the fragmentation patterns of **1a**, **2a,** and **2b** the most intense (100%) signal appeared at m/z 70. This value matches with the composition C_5H_{10} for which the isopentene cation-radical structure $[(CH_3)_2CHCH = CH_2]^{+\bullet}$ could be proposed, resulting from the sequential cleavage of the parent molecule. It might be assumed that above fragmentation path corresponds to the presence of the isopropyl substituent in the parent compounds **1a**, **2a**, and **2b**, which is absent in **3a**. Formation of the isopentene moiety from **2a** and **2b** requires a rearrangement of isopropyl substituent, whereas in **1a** the isopentane moiety already occurs as a part of condensed rings, serving as precursor for isopentene. The weak signal in the spectrum of **3a** at m/z 70 (13) occurs in close sequence of other signals showing similar intensity and was not referred to above fragmentation. Proposed fragmentation paths are shown in the Figure 1.

Above results concerning the m/z values of molecular ions and also the fragmentation patterns confirm the expected composition of investigated compounds.

The structure of 1,3-thiazepine and the exocyclic imino form of thiourea fragment were confirmed by the X-ray crystallography of **2b**. In its crystal structure two conformations of thiazepine ring are stabilized. The disorder of S1 and C4 atoms results in twist chair (TC) and deformed boat (B) conformers which are energetically nearly equivalent [28]. The major component (TC)

Table 1

Structure of the investigated compounds **1a**,**b**,**c**–**3a**,**b**,**c**.

R_2	R_1		
	C_6H_5—	$(4-OCH_3)C_6H_5$—	C_6H_{11}
	**1a**	**1b**	**1c**
	**2a**	**2b**	**2c**
	**3a**	**3b**	**3c**

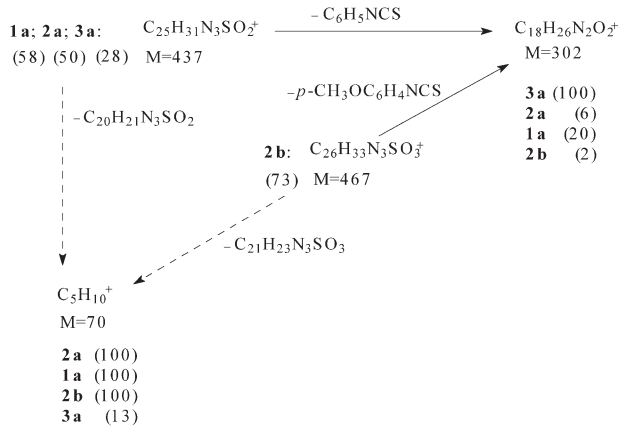


Figure 1. Selected proposed fragmentation patterns for investigated compounds. The relative intensities of the signals are given for each fragment in parentheses. The dashed arrows indicate multistep fragmentation.

with the population of about 88 % is presented on Figure 2.

EXPERIMENTAL

Melting points were determined in a Kofler's apparatus and are uncorrected. The ^1H NMR spectra were recorded on a Bruker AVANCE DMX400 spectrometer, operating at 400 MHz. The chemical shift values are expressed in ppm relative to TMS as an internal standard. Elemental analyses were recorded with a CHN 2400 Perkin-Elmer model. Mass spectra of **1a**, **2a**, **3a,** and **2b** were recorded on an AMD-604 double focusing spectrometer with BE geometry (AMD Intectra, Germany). EI low resolution spectra were obtained with electron energy 70 eV, acceleration voltage 8 kV and ion source temperature 220°C. Samples were introduced using a direct insertion probe heated, when required, in the range 30–120°C. Mass spectral ESI measurements for **1b**, **3b**, **1c**, **2c**, **3c** were carried out on Waters ZQ Micromass instruments with quadrupol mass analyzer. The spectra were performed in the positive ion mode at a declustering potential of 40–60 V. The sample was previously separated on a UPLC column (C18) using UPLC ACQUITY^{TM} system by Waters connected with DPA detector.

Diffraction data for **2b** were measured at 292 K on a KM4 diffractometer using variable scan speed in the $\omega/2\theta$ scan mode and graphite monochromated Cu K_α radiation (λ = 1.54178 Å). A single crystal of dimensions 0.46 × 0.43 × 0.43 mm^3 was used for the data collection.

Flash chromatography was performed on Merck silica gel 60 (200-400 mesh) using chloroform as eluant. Analytical TLC was carried out on silica gel F_{254} (Merck) plates (0.25 mm thickness).

1,3-THIAZEPINE DERIVATIVES (1a,b,c–3a,b,c)

General procedure. Sodium hydride dispersion (60%) in mineral oil (0.44 g, ~10 mmol) was added in a single portion to a stirred solution of thiourea derivative (10 mmol) in anhydrous *N,N*-dimethylformamide at room temperature. After hydrogen evolution ceased, 1,4-dibromobutane (15 mmol) was added to the reaction mixture, after 5 and 15 min. respectively. The mixture was stirred for 6 h. Evaporation in vacuum gave a residue which was then purified by column chromatography (chloroform was used as eluant). The compound was crystallized from ethanol.

10-Isopropyl-8-methyl-4-{2-[(Z)-phenylimino]-1,3-thiazepan-3-yl}-4-aza-tricyclo[5.2.2.$0^{2,6}$]undec-8-ene-3,5-dione (1a). Yield 30 %; mp 174-175°C; ^1H NMR ($CDCl_3$):d 0.83 (d, J = 6.6 Hz, 3H, CH_3); 0.91 (d, J = 6.6 Hz, 3H, CH_3); 1.01-1.17 (m, 2H, CH_2); 1.27-1.42 (m, 2H, CH_2); 1.52-1.63 (m, 1H, CH); 1.77 (s, 3H, CH_3), 1.81-1.85 (m, 3H, CH, CH_2); 2.0-2.09 (m, 2H, CH); 2.67-2.85 (m, 2H, CH_2-N); 3.2-3.24 (m, 2H, CH—C=O); 3.87-3.95 (m, 2H, CH_2—S); 5.74 (d, J = 6.3 Hz, 1H, CH=); 6.82-7.04 (m, 5H, phenyl). Anal. Calcd for $C_{25}H_{31}N_3O_2S$: C, 68.62; H, 7.14; N, 9.6. Found: C, 68.46; H, 6.98; N, 9.60. ei ms: m/z = 437 (58%).

10-Isopropyl-4-{2-[(Z)-4-methoxy-phenylimino]-1,3-thiazepan-3-yl}-8-methyl-4-aza-tricyclo[5.2.2.$0^{2,6}$]undec-8-ene-3,5-dione (1b). Yield 40%; mp 178-179°C; ^1H NMR ($CDCl_3$): d 0.82 (d, J = 6.6 Hz, 3H, CH_3); 0.91 (d, J = 6.6 Hz, 3H, CH_3); 1.01-1.18 (m, 2H, CH_2); 1.27-1.46 (m, 2H, CH_2); 1.52-1.63 (m, 1H, CH); 1.76 (s, 3H, CH_3), 1.81-1.85 (m, 3H, CH, CH_2); 2.0-2.09 (m, 2H, CH); 2.67-2.85 (m, 2H, CH_2—N); 3.2-3.24 (m, 2H, CH—C=O); 3.79 (s, 3H, OCH_3); 3.87-3.95 (m, 2H, CH_2—S); 5.74 (d, J = 6.3 Hz, 1H, CH=); 6.82-7.04 (m, 4H, CH phenyl). Anal. Calcd for $C_{26}H_{33}N_3O_3S$: C, 66.78; H, 7.11; N, 8.99. Found: C, 66.70; H, 7.09; N, 9.03. esi ms: m/z = 468.2 $[M + H]^+$ (100%).

4-{2-[(Z)-Cyclohexylimino]-1,3-thiazepan-3-yl}-10-isopropyl-8-methyl-4-aza-tricyclo[5.2.2.$0^{2,6}$]undec-8-ene-3,5-dione (1c). Yield 40%; mp 173-174°C; ^1H NMR ($CDCl_3$): d 0.82 (d, J = 8.4 Hz, 3H, CH_3); 0.91 (d, J = 8.4 Hz, 3H,

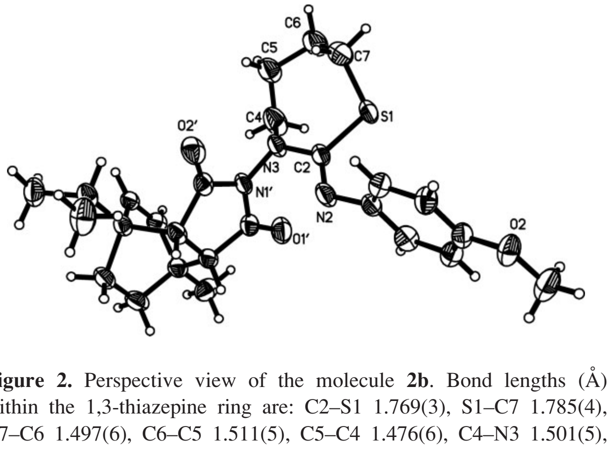


Figure 2. Perspective view of the molecule **2b**. Bond lengths (Å) within the 1,3-thiazepine ring are: C2–S1 1.769(3), S1–C7 1.785(4), C7–C6 1.497(6), C6–C5 1.511(5), C5–C4 1.476(6), C4–N3 1.501(5), N3–C2 1.390(4). The endocyclic torsion angle values (°) for TC conformer are: S1–C2–N3–C4 31.0(4), C2–N3–C4–C5 -91.7(4), N3–C4–C5–C6 79.9(5), C4–C5–C6–C7 -59.8(6), C5–C6–C7–S1 71.0(5) C6–C7–S1–C2 –79.0(4), C7–S1–C2–N3 38.4(4).

CH_3); 0.98-1.23 (m, 2H, CH_2); 1.4-1.74 (m, 14H, CH_2, CH); 1.77 (s, 3H, CH_3), 1.83-1.91 (m, 2H, CH_2); 2.10-2.12 (m, 2H, CH); 2.95-2.99 (m, 1H, CH—C=O); 3.2-3.26 (m, 3H, CH—C=O, CH_2—N); 3.55-3.57 (m, 2H, CH_2—S); 4.03 (d, J = 8.8 Hz, 1H, CH—N=); 5.96 (d, 1H, CH—). *Anal.* Calcd for $C_{25}H_{37}N_3O_2S$: C, 67.68; H, 8.41; N, 9.47. Found: C, 68.04; H, 8.52; N, 9.51. esi ms: m/z = 444.1 $[M + H]^+$ (100%).

1-Isopropyl-7-methyl-4-{2-[(Z)-phenylimino]-1,3-thiazepan-3-yl}-4-aza-tricyclo[5.2.2.0^{2,6}]undec-8-ene-3,5-dione (2a). Yield 45%; mp 147-148°C; ^{1}H NMR ($CDCl_3$): d 0.99 (d, J = 6.8 Hz, 3H, CH_3); 1.11 (d, J = 6.4 Hz, 3H, CH_3); 1.22-1.35 (m, 2H, CH_2); 1.4-1.47 (m, 3H, CH, CH_2); 1.51 (s, 3H. CH_3); 1.71-1.77 (m, 2H, CH_2); 1.9-1.97 (m, 2H, CH_2); 2.63 (dd, J = 8 Hz, 2H, CH—C=O), 2.98-3.06 (m, 2H, CH_2—N); 3.77-3.84 (m, 2H, CH_2—S); 6.04 (dd, J = 8.4 Hz, 2H, CH=); 6.68 (d, J = 7.6 Hz, 2H, CH phenyl); 6.98-7.03 (m, 1H, CH phenyl); 7.2-7.24 (m, 2H, CH phenyl). *Anal.* Calcd for $C_{25}H_{31}N_3O_2S$: C, 68.62; H, 7.14; N, 9.60. Found: C, 68.76; H, 7.10; N, 9.51. ei ms: m/z = 437 (50%).

1-Isopropyl-4-{2-[(Z)-4-methoxy-phenylimino]-1,3-thiaz-epan-3-yl}-7-methyl-4-aza-tricyclo[5.2.2.0^{2,6}]undec-8-ene-3,5-dione (2b). Yield 49%; mp 185-186°C; ^{1}H NMR ($CDCl_3$): d 0.99 (d, J = 6.8 Hz, 3H, CH_3); 1.12 (d, J = 6 Hz, 3H, CH_3); 1.26-1.37 (m, 2H, CH_2); 1.4-1.46 (m, 3H, CH, CH_2); 1.5 (s, 3H. CH_3); 1.71-1.73 (m, 2H, CH_2); 1.96-1.98 (m, 2H, CH_2); 2.62 (dd, J = 8 Hz, 2H, CH—C=O), 2.99-3.07 (m, 2H, CH_2—N); 3.75-3.78 (m, 2H, CH_2—S); 3.75 (s, 3H, O—CH_3); 6.04 (dd, J = 8.4 Hz, 2H, CH=); 6.6-6.66 (m, 2H, CH phenyl); 6.76-6.81 (m, 2H, CH phenyl). *Anal.* Calcd for $C_{26}H_{33}N_3O_3S$: C, 66.78; H, 7.11; N, 8.99. Found: C, 66.49; H, 7.11; N, 8.99. ei ms: m/z = 467 (73%).

Crystal data for **2b**: monoclinic, space group $P2_1/c$, a = 14.407(3), b = 11.586(2), c = 14.851(3) Å, β = 92.92(3)°, V = 2475.7(8) Å^3, Z = 4, d_{calc} = 1.255 g/cm^3, μ(Cu K_α) = 1.415 mm^{-1}. In the θ range 3.07–73.51°, 4971 reflections were collected of which 4793 were unique (R_{int} = 0.0264). The structure was solved by direct methods using SHELXS-97 program [29] and refined by full-matrix least-squares on F^2 using SHELXL-97 program [29]. The non-H atoms were refined with anisotropic displacement parameters, except of S1A and C4A atoms. The two atoms of thiazepine ring are disordered over two positions with sof's of 0.877(4) and 0.123(4) for S1, C4, and S1A, C4A, respectively. H-atom positions were calculated from the geometry. H-atoms were given isotropic factors of 1.2 or 1.5 Ueq of the bonded C-atoms; the C–H bond 'riding' model was used in the refinement.

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as CCDC No. 684835. Copies of the data can be obtained on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

4-{2-[(Z)-Cyclohexylimino]-1,3-thiazepan-3-yl}-1-isoprop-yl-7-methyl-4-aza-tricyclo[5.2.2.0^{2,6}]undec-8-ene-3,5-dione (2c). Yield 21%, mp 151-152°C; ^{1}H NMR ($CDCl_3$): d 0.85-0.88 (m, 6H, CH_2); 0.99 (d, J = 7.2 Hz, 3H, CH_3); 1.12 (d, J = 6.8 Hz, 3H, CH_3); 1.25-1.32 (m, 7H, CH, CH_2); 1.5 (s, 3H, CH_3); 1.74-1.91 (m, 4H, CH_2); 2.33-2.37 (m, 2H, CH_2); 2.54-2.64 (m, 2H, CH—C=O); 3.37-3.43 (m, 2H, CH_2—N); 3.52-3.56 (m, 2H, CH_2—S); 4.36-4.42 (m, 1H, CH—N=); 5.87 (dd, J = 8.8 Hz, 2H, CH=). *Anal.* Calcd for $C_{25}H_{37}N_3O_2S$: C, 67.68; H, 8.41; N, 9.47. Found: C, 67.25; H, 8.82; N, 9.32. esi ms: m/z = 444.1 $[M + H]^+$ (100%).

1,7,8,9,10-Pentamethyl-4-{2-[(Z)-phenylimino]-1,3-thiazepan-3-yl}-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (3a). Yield 41%; mp 107-108°C; ^{1}H NMR ($CDCl_3$): d 0.61 (d, J = 6.4 Hz, 3H, CH_3); 1.22-1.32 (m, 2H, CH_2); 1.36 (s, 6H, CH_3); 1.62 (s, 6H, CH_3); 1.6-1.64 (m, 1H, CH); 1.96-1.99 (m, 2H, CH_2); 2.91-3.18 (m, 4H, CH—C=O, CH_2—N); 3.75-3.78 (m, 2H, CH_2—S); 6.77-7.07 (m, 5H, CH phenyl). *Anal.* Calcd for $C_{25}H_{31}N_3O_2S$: C, 68.62; H, 7.14; N, 9.59. Found: C, 68.28; H, 6.92; N, 9.16. ei ms: m/z = 437 (28%).

1,7,8,9,10-Pentamethyl-4-{2-[(Z)-4-methoxy-phenylimino]-1,3-thiazepan-3-yl}-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-di-one (3b). Yield 19%; mp 126-127°C; ^{1}H NMR ($CDCl_3$): d 0.61 (d, J = 6.4 Hz, 3H, CH_3); 1.22-1.32 (m, 2H, CH_2); 1.36 (s, 6H, CH_3); 1.62 (s, 6H, CH_3); 1.6-1.64 (m, 1H, CH); 1.96-1.99 (m, 2H, CH_2); 2.91-3.18 (m, 4H, CH—C=O, CH_2—N); 3.75-3.78 (m, 2H, CH_2—S); 3.77 (s, 3H, O—CH_3); 6.57-6.63 (m, 2H, CH phenyl); 6.78 (d, 2H, CH phenyl). *Anal.* Calcd for $C_{26}H_{33}N_3O_3S$: C, 66.78; H, 7.11; N, 8.99. Found: C, 66.56; H, 7.2; N, 8.99. esi ms: m/z = 468.2 $[M + H]^+$ (100%).

4-{2-[(Z)-Cyclohexylimino]-1,3-thiazepan-3-yl}-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (3c). Yield 23%; mp 112-113°C; ^{1}H NMR ($CDCl_3$): d 0.61 (d, J = 5.6 Hz, 3H, CH_3); 1.05-1.26 (m, 6H, CH_2); 1.32 (s, 6H, CH_3); 1.38-1.95 (m, 9H, CH, CH_2); 1.53 (s, 6H, CH_3); 2.7-2.73 (m, 2H, CH_2—N); 2.8-2.84 (m, 2H, CH—C=O); 3.3-3.36 (m, 2H, CH_2—S); 3.94-4.0 (m, 1H, CH—N=). *Anal.* Calcd for $C_{25}H_{37}N_3O_2S$: C, 67.68; H, 8.41; N, 9.47. Found: C, 67.60; H, 8.52; N, 9.40. esi ms: m/z = 444.1 $[M + H]^+$ (100%).

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Ultrasound-Accelerated Synthesis of Some Bis-Compounds and Their Biological Evaluation

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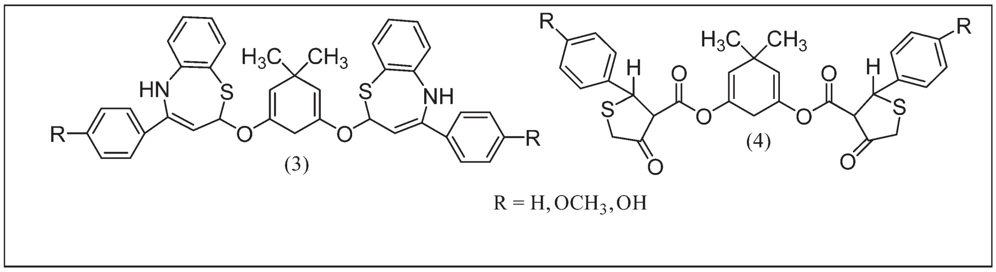

A new series of bis-1,5-[2′*H*,3′*H*-dihydro-4′(substituted phenyl)-1′,5′-benzothiazipin-2′-oxy]-3,3-dimethyl-1,4-cyclohexadiene 3 and bis-1,5-[-2′,3′,4′,5′-teterahydro-2′-(substitutedphenyl)-4′-oxo-thiophen-3′-carboxylate]-3,3-dimethyl-1,4-cyclohexadiene 4 have been synthesized by reacting 1,3-bis-[substituted cinnamate]-3,3-dimethyl-1,4-cyclohexadiene 2 with 2-aminothiophenol and thiogylcolic acid, respectively, through an environmentally benign procedure. The title compounds have been evaluated for their antimicrobial activities. Reaction under ultrasound irradiation resulted in enhancement of yields and reaction rates. Structures of the synthesized compounds have been elucidated on the basis of the elemental analysis and spectral data.

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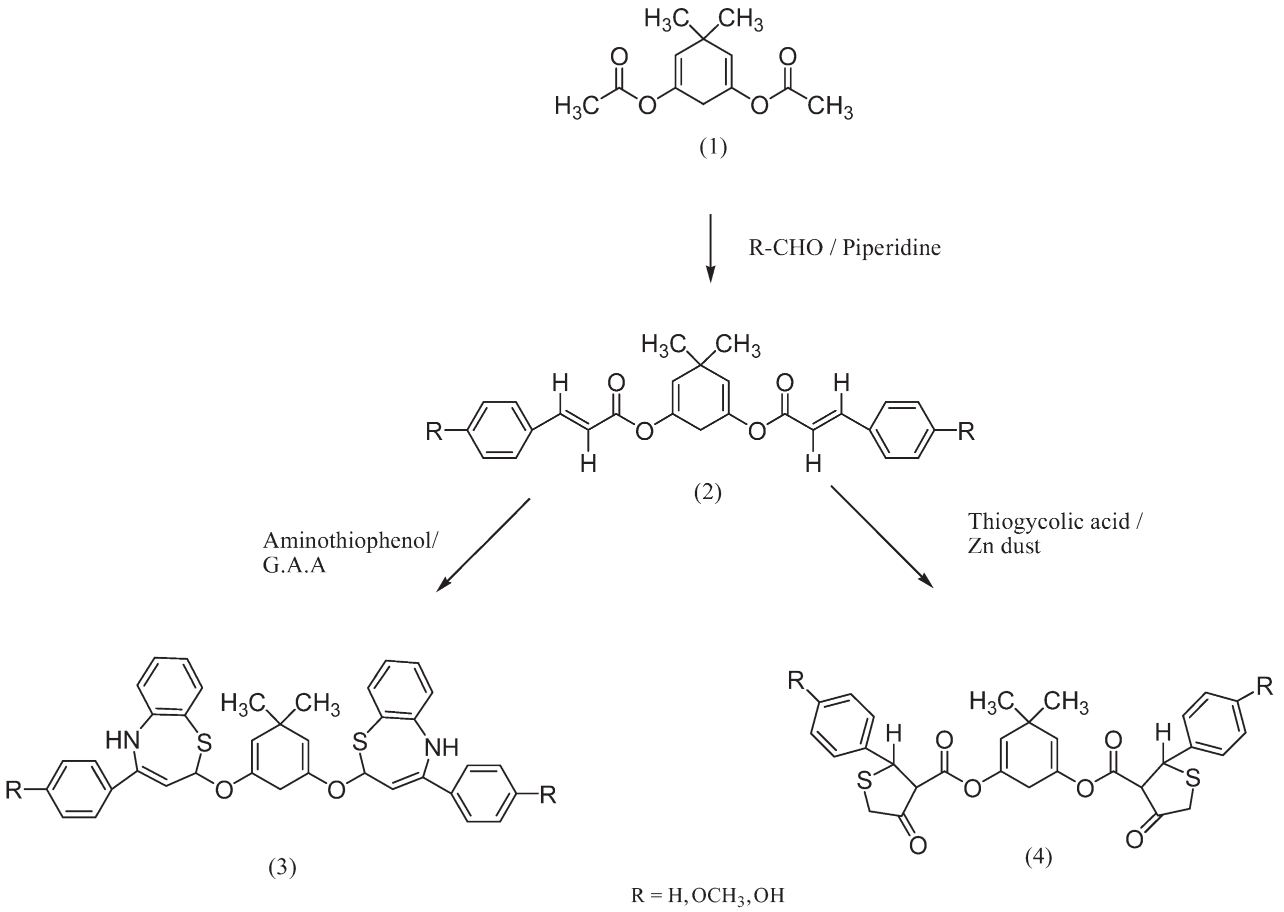
INTRODUCTION

The use of ultrasound irradiation for activating various reactions is well documented in the literature such as synthesis of azoles and diazenes [1], Reformatsky reaction [2], oxidation of substrates like hydroquinones [3], conversion of nitro compounds to carbamates [4], pinacol coupling [5], Ullmann condensation [6] *etc*.

The advantages of ultrasound-assisted chemical reactions include higher yields, shorter reaction times, and milder reaction conditions when compared with classical methods [7–11]. The effect of ultrasound has mostly been shown by increasing the yields of reactions and in some cases, changing the ratio of products formed. The most important effects of ultrasound arise from acoustic cavitation; formation, growth, and implosive collapse of bubbles in the liquid by passing ultrasonic waves through this medium [12,13]. The implosive collapse of the bubble generates localized hot spots through adiabatic compression or shock wave formation within the gas phase of the collapsing bubble. These bubbles create pressures of hundreds of atmospheres and temperature of thousands of degrees within the cavities during their collapse [14,15]. In all of these reactions, it was found that ultrasound accelerates the reactions [16–22].

Benzothiazepine derivatives possess potential anti-ulcer [23], analgesic [24], vaso-depressant [25], anti hypertensive [26], antidementia [27], antibacterial, and anti-fungal activities [28–30]. The biodynamic nature of benzothiazepines derivatives led to the current synthesis of 1,5-benzothiazepines having various substituents, which may prove to be of medical significance. Similarly, thiophenes derivatives are also well known for diverse biological activities and play a key role as anti-inflammatory [31,32], anti-protozoa [33], antitumor agents [34], and alternate substrate inhibitors of cholesterol eastrase [35]. In recent years, attention has been increasingly paid to the synthesis of bis-heterocyclic compounds, which exhibit various biological activities [36–45]. The wide range of therapeutic value of the above ring system prompted us to synthesize several new bis-1,5-[substituted cinnamate]-3,3-dimethyl-1,4-cyclohexadiene **2** and its utility as a building block in the synthesis of several new bis-1,5-[2′H,3′H-dihydro-4′(substituted phenyl)-1′,5′-benzothiazepin-2′-oxy]-3,3-dimethyl-1,4-cyclohexadiene **3** and bis-1,5-[-2′,3′,4′,5′-teterahydro-2′-(substitutedphenyl)-4′-oxothiophen-3′-carboxylate]-3,3-dimethyl-1,4-cyclohexadiene **4** compounds (Scheme 1). The structures of the products were confirmed by elemental analysis, IR, ^{1}H, ^{13}C NMR, and MS spectral analysis. The antimicrobial activities of the newly synthesized compounds were also investigated.

Scheme 1



RESULTS AND DISCUSSION

The reaction sequences leading to the different bis-heterocyclic ring is outlined in Scheme 1. The reaction of 3,3-dimethyl-1,5-dihydroxy-1,4-cyclohexadiene with acetic anhydride yielded bis-1,5-[acetoxy]-3,3-dimethyl-1,4-cyclohexadiene which was converted into bis-1,5-[substituted cinnamate]-3,3-dimethyl-1,4-cyclohexadiene **2**, on treatment with substituted aromatic aldehydes. Formation of compound **2** was evidenced by the appearance of a signal at 7.8 ppm (α,β unsaturated carbonyl) in the ^{1}H NMR spectra and in IR spectra band because of carbonyl at 1634 cm^{-1}. In the ^{13}C NMR spectra, the signal 188.24 ppm was observed due to O=C< in compound **2**. The reaction of 2-aminothiophenol with compounds having α,β unsaturated in conjugation with carbonyl system in acidic media afforded bis-1,5-[2′*H*,3′*H*-dihydro-4′(substitutedphenyl)-1′,5′-benzothiazipin-2′-oxy]-3,3-dimethyl-1,4-cyclohexadiene **3**. In ^{1}H NMR spectra of compound **3**, the signal at 3.74 was observed due to —NH—, 6.0 due to C—H and at 7.35 due to C—H and in the IR spectra of bis-benzothiazepine **3**, the band at 3070 (—N—H—) and 1432 cm^{-1} (—C—S—) also confirmed. In ^{13}C NMR spectra, the signal at 65 ppm was observed because of >CH—S— and 70 (>C—S—benzothiazepine ring).

Similarly, the bis-1,5-[substituted cinnamate]-3,3-dimethyl-1,4-cyclohexadiene **2** on treatment with thioglycolic acid underwent cyclization to the bis-1,5-[2′,3′,4′,5′-teterahydro-2′-(substitutedphenyl)-4′-oxothiophen-3′-carboxylate]-3,3-dimethyl-1,4-cyclohexadiene **4** (Scheme 1). The spectral data are in agreement with the proposed structures. The IR spectrum of **4** showed C—S stretching bands at 1340–1350 cm^{-1} and its ^{1}H NMR spectrum the chemical shifts due to CH_2 of ring was observed at 3.42 ppm. Appearance of two C=O at 196.66 and 199.23 ppm in ^{13}C NMR confirmed the formation of **4**. Keeping in view the advantages of ultrasound irradiation technique, the reaction was also carried out under sonication condition. The formation of compounds **2, 3,** and **4** was completed in 15 to 25 min under sonication condition when compared with conventional method, which took 4 to 5 h. The compounds obtained by both the routes were found identical as they showed same melting point and similar spectral data.

Table 1

Physical and analytical data of compounds **2**, **3**, and **4**.

Compound	*R*	m.p (°C)	Yield (%)	Yield (%) Conv	Molecular formula	Analysis % Calcd./Found C	H	N	S
2a	H	200–202	82	58	$C_{26}H_{24}O_4$	78.21	6.01	–	–
						77.87	5.91	–	–
2b	OCH_3	215–217	87	59	$C_{28}H_{28}O_6$	73.04	6.08	–	–
						72.84	5.85	–	–
2c	OH	198–199	81	59	$C_{26}H_{24}O_6$	72.22	5.55	–	–
						72.14	5.24	–	–
3a	H	70–72	72	58	$C_{38}H_{34}N_2O_2S_2$	73.22	5.76	4.74	10.84
						73.08	5.47	4.59	10.68
3b	OCH_3	73–76	79	67	$C_{40}H_{38}N_2O_4S_2$	70.15	5.84	4.30	9.84
						69.41	5.68	4.12	9.73
3c	OH	95–97	75	65	$C_{38}H_{34}N_2O_4S_2$	69.45	5.46	4.50	10.28
						69.32	5.34	4.38	10.11
4a	H	165–167	77	60	$C_{30}H_{28}O_6S_2$	69.49	5.40	–	12.35
						69.21	5.23	–	12.21
4b	OCH_3	148–149	70	58	$C_{32}H_{32}O_8S_2$	63.15	5.26	–	10.58
						62.94	5.11	–	10.32
4c	OH	158–160	76	55	$C_{30}H_{28}O_8S_2$	65.45	5.09	–	11.63
						65.23	4.96	–	11.32

The comparative data of the compounds have been listed in Table 1.

Antibacterial activity. All the newly synthesized compounds were initially screened for their *in vitro* antibacterial activities against the gram-positive *S aureus, C diphtheriae*, and *S cerevisiae,* the gram-negative *E coli* and *P aeruginosa* by disc diffusion method [46].The compounds were tested at a concentration of 100 μg/mL. The zone of inhibition was measured in mm and was compared with the reference standard antibiotics namely ampicillin trihydrates drugs 50 μg/mL. Compounds displayed good activity toward the gram-positive bacteria S *aureus, C diphtheriae*, and *S cerevisiae*, but the compounds showed less activity toward gram-negative bacteria *E coli* and *P aeruginosa*. The results of antibacterial screening studies are reported in Table 2.

CONCLUSIONS

In conclusion, the ultrasound irradiation for synthesis of the title compound offers significant reduction in the reaction time, operation simplicity, cleaner reaction, easy work-up, and improved yields. The procedure clearly highlights the advantages of ultrasound. The synthesized compounds also displayed noteworthy convincing antibacterial activity against gram-positive bacteria *S aureus, C diphtheriae*, *and S cerevisiae*.

Table 2

Antibacterial activity of compounds **2**, **3**, and **4**.

		Zone of inhibition (mm)[a]				
		Gram positive			Gram negative	
Compound	Concentration (μg/mL)	*S. aureus*	*S. cervesiae*	*C.diphtheria*	*E. coli*	*P. aerugnosa*
2a	100	16	18	17	08	09
2b	100	17	19	18	09	08
2c	100	18	19	17	09	10
3a	100	19	18	18	08	09
3b	100	21	21	19	09	11
3c	100	22	20	17	09	10
4a	100	21	19	18	11	10
4b	100	20	17	21	09	11
4c	100	19	19	22	11	10
Ampicilin trihydrate	50	26	23	28	24	21
DMSO	–	00	00	00	00	00

[a] Diameter of the hole was 6 mm.

EXPERIMENTAL

Melting points of all synthesized compounds were determined in open capillary tubes on an electrothermal apparatus and are uncorrected. The purity of the compounds was monitored by TLC on silica gel coated aluminium plates (Merck) as adsorbent and UV light as visualizing agent; IR spectra (potassium bromide in cm^{-1}) were recorded on a Perkin-Elmer spectrophotometer in the range of 4000–400 cm^{-1}. ^{1}H NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer using deuteriochloroform as solvent and trimethylsilane as an internal standard (chemical shifts in δ ppm) and MS spectra were taken on a Jeol sx-102/PA-6000 (EI) spectrometer. C, H, N estimation was recorded on Carlo Erba 1108 (CHN) Elemental Analyzer. Experiment under ultrasound irradiation is carried out in probe sonicator manufactured by Dakshin.

General preparation of bis-1,5-[substituted cinnamate]-3,3-dimethyl-1,4-cyclohexadiene (2a-c)

Method A (ultrasound method). A mixture of (0.02 mol) substituted aromatic aldehyde, (0.01 mol) 1, 2 mL (0.02 mol) of piperidine in 15 mL of ethanol were exposed to ultrasound irradiation for 15 min. On completion of the reaction (monitoring on TLC), the mixture was poured on crushed ice. The product that precipitated out was collected by filtration, washed with water, and recrystallized from ethanol.

Method B (conventional method). A solution of (0.02 mol) substitute aromatic aldehydes, (0.01 mol) 1, 2 mL (0.02 mol) piperidine in 15 mL of ethanol were refluxed on water bath for 4 h. The reaction was monitored by TLC, and after completion of the reaction, the contents were poured on crushed ice. The solid obtained was collected by filtration, washed with water, and recrystallized from ethanol to obtain compound 2(a-c).

Bis-1,5-[cinnamate]-3,3-dimethyl-1,4-cyclohexadiene (2a). This compound was obtained as white crystal, mp 200–202°C; IR (potassium bromide): CO 1645, C=C 1625 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 0.96 (s, 6-H, 2xCH_3), 2.44 (s, 2-H, CH_2), 4.69 (s, 2-H, CH), 7.82 (s, 4H, α, β unsaturated carbonyl), 6.98–8.02 (m, 10-H, aromatic protons). ^{13}C NMR: 27.28 $(CH_3)_2$, 37.33 (CH_2), 73.08 (tetrahedral carbon) and 108.21–115.32 (4xC=C), 125.69–131.56 (Ar—C), 188.42 (C=O), MS: *m/z* 402 (m^{+2}). *Anal.* Calcd. for $C_{26}H_{24}O_4$: C, 78.21; H, 6.01. Found: C, 77.87; H, 5.91.

Bis-1,5-[4″-methoxycinnamate]-3,3-dimethyl-1,4-cyclohexadiene (2b). This compound was obtained as light green crystal, mp 215–217°C; IR (potassium bromide): CO 1652, C=C 1620 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 1.07 (s, 6-H, 2xCH_3), 2.25 (s, 2-H, CH_2), 3.73 (s, 6-H, OCH_3), 4.75 (s, 2-H, CH), 7.89 (s, 4-H, α, β unsaturated carbonyl), 6.88–7.89 (m, 8-H, aromatic proton). ^{13}C NMR: 26.32 $(CH_3)_2$, 37.89 (CH_2), 41.21 (OCH_3), 73.87 (tetrahedral carbon) and 111.32–114.45 (4xC=C), 126.34–132.43 (Ar—C), 189.09 (C=O), MS: *m/z* 462 (m^{+2}). *Anal.* Calcd. for $C_{28}H_{28}O_6$: C, 73.04; H, 6.08. Found: C, 72.84; H, 5.85.

Bis-1,5-[4″-hydroxycinnamate]-3,3-dimethyl-1,4-cyclohexadiene (2c). This compound was obtained as yellow crystal, mp 198–199°C; IR (potassium bromide): OH 3421, CO 1631, C=C 1610 cm^{-1}, ^{1}H NMR (deuteriochloroform): δ 0.98 (s, 6-H, 2xCH_3), 2.34 (s, 2-H, CH_2), 4.56 (s, H, OH), 4.67 (s, 2-H, CH), 7.76 (s, 4-H, α, β unsaturated carbonyl), 6.95–7.79 (m, 8-H, aromatic proton). ^{13}C NMR: 26.86 $(CH_3)_2$, 37.64 (CH_2), 40.76 (OCH_3), 72.89 (tetrahedral carbon) and 113–115.35 (4xC=C), 125.89–131.83 (Ar—C), 189.98 (C=O), MS: *m/z* 432 (m^{+2}). *Anal.* Calcd. for $C_{26}H_{24}O_6$: C, 72.22; H, 5.67. Found: C, 72.14; H, 5.63.

General preparation of bis-1,5-[2′H,3′H-dihydro-4′(substitutedphenyl)-1′,5′-benzothiazipin-2′-oxy]-3,3-dimethyl-1,4-cyclohexadiene (3a-c)

Method A (ultrasound method). A mixture of (0.01 mol) 2, 2.14 mL (0.02 mol) 2-aminothiophenol and 1 mL acetic acid in 10 mL of ethanol was subjected to ultrasound irradiation for 24 min. The reaction mixture was poured on crushed ice. The solid separated, filtered, washed with water, and recrystallized from ethanol.

Method B (conventional method). A solution of (0.01 mol) 2, 2.14 mL (0.02 mol) 2-aminothiophenol and 1 mL acetic acid in 10 mL of ethanol was reflux on water bath for 3 h then poured on to ice, the product was isolated in a similar manner as described in the above method.

Bis-1,5-[2′H,3′H-dihydro-4′phenyl-1′,5′-benzothiazipin-2′-oxy]-3,3-dimethyl-1,4-cyclohexadiene (3a). This compound was obtained as light yellow crystal, mp 70–72°C; IR (potassium bromide): C=C 1632, C—S—C 1456 cm^{-1}, ^{1}H NMR (deuterio-chloroform): δ 0.96 (s, 6-H, 2xCH_3), 2.44 (s, 2-H, CH_2), 3.62 (s, 2-H, NH), 4.25 (s, 2-H, CH), 6.56 (d, 2-H, C_2—H), 7.24 (d, 2-H, C_3—H), 6.56–8.06 (m, 18-H, Aromatic protons). ^{13}C NMR: 27.24 (2xCH_3), 32.45 (CH_2), 65.45 (C_2—H), 72.21 (C_3—H), 73.54 (tetrahedral carbon) and 108.15–136.748 (C=C and Ar—C), MS: *m/z* 616 (m^{+2}). *Anal.* Calcd. for $C_{38}H_{34}N_2O_2S_2$: C, 73.22; H, 5.76; N,4.74; S, 10.84 Found: C, 73.08;H, 5.47; N, 4.59; S, 10.68.

Bis-1,5-[2′H,3′H-dihydro-4′(4″-methoxyphenyl)-1′,5′-benzothiazipin-2′-oxy]-3,3-dimethyl-1,4-cyclohexadiene (3b). This compound was obtained as greenish yellow crystal, mp 73–76°C; IR (potassium bromide): C=C 1625, C—S—C 1443 cm^{-1}, ^{1}H NMR (deuteriochloroform): δ 0.99 (s, 6-H, 2xCH_3), 2.44 (s, 2-H, CH_2), 3.55 (s, 2-H, NH), 3.85 (s, 6-H, OCH_3), 4.32 (s, 2-H, CH), 6.43 (d, 2-H, C_2—H), 7.37 (d, 2-H, C_3—H), 6.96–8.03 (m, 16-H, Aromatic protrons). ^{13}C NMR: 26.31 (2xCH_3), 32.89 (CH_2), 39.32 (OCH_3), 65.52 (C_2—H), 72.63 (C_3—H), 73.76 (tetrahedral carbon), 108–136.31 (C=C and Ar—C), MS: *m/z* 676 (m^{+2}). *Anal.* Calcd. for $C_{40}H_{38}N_2O_4S_2$: C, 70.15; H, 5.84; N,4.30; S, 9.84. Found: C, 69.41; H, 5.68; N, 4.12; S, 9.73.

Bis-1,5-[2′H,3′H-dihydro-4′(4″-hydroxyphenyl)-1′,5′-benzothiazipin-2′-oxy]-3,3-dimethyl-1,4-cyclohexadiene (3c). This compound was obtained as colorless crystal, mp 95–97°C; IR (potassium bromide): OH 3448, C=C 1636, C—S—C 1421 cm^{-1}, ^{1}H NMR (deuteriochloroform): δ 1.02 (s, 6-H, 2xCH_3), 2.34 (s, 2-H, CH_2), 3.57 (s, 2-H, NH), 4.32 (s, 2-H, CH), 4.73 (s, 1-H, OH), 6.38 (d, 2-H, C_2—H), 7.63 (d, 2-H, C_3—H), 6.73–7.83 (m, 16-H, Aromatic proton). ^{13}C NMR: 27.45 (2xCH_3), 31.67 (CH_2), 65.68 (C_2—H), 73.54 (C_3—H), 73.76 (tetrahedral carbon), 105.45–137.76 (C=C and Ar—C), MS: m/z 648 (m^{+2}). *Anal.* Calcd. for $C_{38}H_{34}N_2O_4S_2$: C, 69.45; H, 5.49; N,4.50; S, 10.28. Found: C, 69.32; H, 5.34; N, 4.38; S, 10.11.

General preparation of bis-1,5-[-2′,3′,4′,5′-teterahydro-2′-(substitutedphenyl)-4′-oxo-thiophen-3′-carboxylate]-3,3-dimethyl-1,4-cyclohexadiene (4a-c).

Method A (ultrasound method). A mixture of (0.01 mol) 2, 1.38 mL (0.02 mol) thiogylcolic acid, 1 g zinc dust in 10 mL of dioxane were subjected to ultrasound irradiation for 20 min.

After completion of the reaction, as monitored by TLC, the mixture was poured into ice-cold water. The solid obtained was collected by filtration and recrystallized from alcohol. The characteristic data of the compound are given in Table 2.

Method B (conventional method). A mixture of (0.01 mol) 2, 1.38 mL (0.02 mol) thiogylcolic acid and 1 g zinc dust in 10 mL of ethanol were heated under mild condition for 4.5 h. The product was isolated in a similar manner as described above.

Bis-1,5-[-2′,3′,4′,5′-teterahydro-2′-(phenyl)-4′-oxo-thiophen-3′-carboxylate]-3,3-dimethyl-1,4-cyclohexadiene (4a). This compound was obtained as light cream crystal, mp 165–167°C; IR (potassium bromide): CO 1628, C—S—C 1408 cm^{-1}. ^1H NMR (deuteriochloroform): δ 0.97 (s, 6-H, $2xCH_3$), 2.44 (s, 2-H, CH_2), 3.21 (s, 2-H, C'_2—H), 3.46 (s, 4-H,$2XCH_2$), 3.90 (s, 2-H, C'_3—H), 4.69 (s, 2-H, CH), 7.19–8.02 (m, 10-H, Aromatic proton). ^{13}C NMR: 27.29 ($2xCH_3$), 29.28 (C'_2), 32.18 (CH_2), 42.21 (C'_3), 50.71(CH_2—C'_5), 73.21 (tetrahedral carbon), 109.10–115.5 (2xC=C), 128.21–131.56 (Ar—C), 196.44 (C=O), 210.21 (C=O). MS: *m/z* 520 (m^{+2}). *Anal*. Calcd. for $C_{30}H_{28}O_6S_2$: C, 69.49; H, 5.40; S, 12.35. Found: C, 69.21; H, 5.23; S, 12.21.

Bis-1,5-[-2′,3′,4′,5′-teterahydro-2′-(4″-methoxyphenyl)-4′-oxothiophen-3′-carboxylate]-3,3-dimethyl-1,4-cyclohexadiene (4b). This compound was obtained as dark green crystal, mp 148–149°C; IR (potassium bromide): CO 1610, C—S—C 1443 cm^{-1}. ^1H NMR (deuteriochloroform): δ 0.96 (s, 6-H, $2xCH_3$), 2.36 (s, 2-H, CH_2), 3.21 (s, 2-H, C'_2—H), 3.46 (s, 4-H, $2xCH_2$), 3.83 (s, 2-H, C'_3—H), 3.94 (s, 6-H, OCH_3), 4.43 (s, 2-H, CH), 6.81–7.83 (m, 8-H, Aromatic proton). ^{13}C NMR: 27.32 ($2xCH_3$), 29.43 (C'_2), 31.67 (CH_2), 39.34 (OCH_3), 41.54 (C'_3), 52.56 (CH_2—C'_5), 73.02 (tetrahedral carbon), 110.98–116.12 (2xC=C), 116.32–133.34 (Ar—C), 198.07 (C=O), 209.87 (C=O). MS: *m/z* 610 (m^{+2}). *Anal*. Calcd. for $C_{32}H_{32}O_6S_2$: C, 63.15; H, 5.26; S, 10.58. Found: C, 62.94; H, 5.11; S, 10.32.

Bis-1,5-[-2′,3′,4′,5′-teterahydro-2′-(4″-hydroxyphenyl)-4′-oxo-thiophen-3′-carboxylate]-3,3-dimethyl-1,4-cyclohexadiene (4c). This compound was obtained as colorless crystal, mp 158–160°C; IR (potassium bromide): CO 1615, C—S—C 1448 cm^{-1}. ^1H NMR (deuteriochloroform): δ 9.86 (s, 6-H, $2xCH_3$), 2.21 (s, 2-H, CH_2), 3.28 (s, 2-H, C'_2—H), 3.38 (s, 4-H, $2xCH_2$), 3.97 (s, 2-H, C'_3—H), 4.51 (s, 2-H, CH), 4.75 (s, 2-H, OH), 7.08–8.16 (m, 8-H, Aromatic proton). ^{13}C NMR: 27.12 ($2xCH_3$), 29.87 (C'_2), 32.54 (CH_2), 41.84 (C'_3), 52.93 (CH_2—C'_5), 73.12 (tetrahedral carbon), 109.12–116.23 (2xC=C), 116.34–136.65 (Ar—C), 196.78 (C=O), 204.45 (C=O). MS: *m/z* 552 (m^{+2}). *Anal*. Calcd. for $C_{30}H_{28}O_8S_2$: C, 65.45; H, 5.09; S, 11.63. Found: C, 65.23; H, 4.96; S, 11.32.

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Synthesis of Substituted *N*-[4(5-Methyl/phenyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2*H*)-yl]benzamide/benzene Sulfonamides as Anti-Inflammatory and Anti-Cancer Agents

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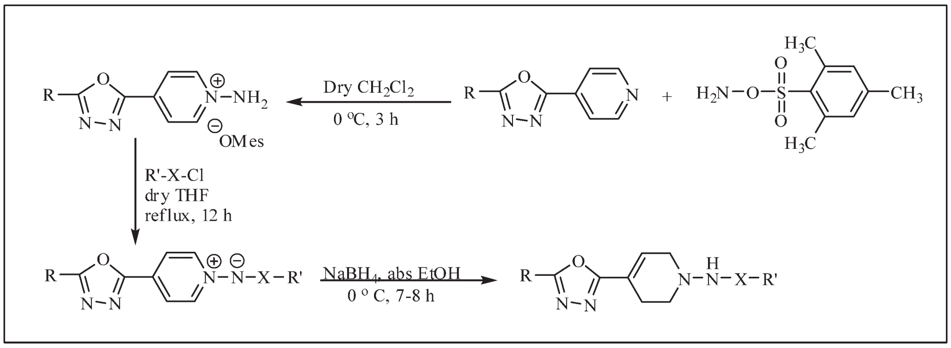

Fourteen novel substituted *N*-[4(5-methyl/phenyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2*H*)-yl] benzamide/benzene sulfonamides (**11a–n**) were synthesized in fair to good yields *via* sodium borohydride reduction of the corresponding substituted *N*-(benzoylimino)-4-(5-methyl/5-phenyl-1,3,4-oxadiazol-2yl) pyridinium ylide **(10a–n)** in absolute ethanol.

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INTRODUCTION

Non steroidal anti-inflammatory drugs (NSAIDs) are of huge therapeutic benefit in the treatment of rheumatoid arthritis and anti-inflammatory, analgesic, and antipyretic activities and are widely used to treat acute and chronic inflammatory disorders [1,2]. NSAIDs are not only useful in the treatment of inflammatory diseases but they can also reduce the risk of Alzheimer's disease [3,4]. Although NSAIDs are the most widely used drugs, their long-term clinical employment is associated with significant side effects and the steady use determines the onset of gastrointestinal lesions, bleeding, and nephrotoxicity [5,6]. Therefore, the discovery of new safer anti-inflammatory drugs represents a challenging goal for such a research area. Functionalized tetrahydropyridine (THP) ring systems are widely found in biologically active natural products and pharmaceuticals [7–12]. The anti-inflammatory activities of compounds consisting of reduced pyridine systems have been investigated [13–18]. The chemistry of substituted 1,3,4-oxadiazoles and their derivatives received considerable attention during the last decade as potential antimicrobial, antifungal, anti-inflammatory, analgesic, CNS-stimulating, anticonvulsive, anti-cancer, diuretic, and antihypertensive agents [19–30]. The electrophilic cyclization of iminium ions (Mannich cyclization) to generate unsaturated azacyclic systems [31] and the synthesis of tetrahydropyridine derivatives by partial reduction of *N*-ylides constitute some of the most important methods for preparing tetrahydropyridines. From our previous research, Redda and coworkers reported the synthesis and anti-inflammatory activity profiles of a few 1,2,3,6-terahydropyrines [32]. The results showed the pharmacological activites of the derivatives of THP depended on the nature of the substituents on the THP ring system (Fig. 1). This investigation is a continuation of synthesis of 1,2,3,6-tetrahydropyridine designed to modify the tetrahydropyridine ring and phenyl moieties by introducing groups with various electronic properties. Incorporation of the 1,3,4-oxadiazole moiety might enhance biological activity of the tetrahydropyridine derivatives. Hence, it was thought worthwhile to synthesize 1,3,4-oxadizol-2-yl tetrahydropyridines and study their anti-inflammatory and anti-cancer activities.

In the current investigation, we have synthesized many analogs maintaining the 1,3,4-oxadiazole-2-yl-1,2,3,6-tetrahydropyridine ring and having modifications on the oxadiazole, phenyl ring, and interchanging the sulfonyl/carbonyl groups at position X to compare their biological activities. We expect that these structural modifications would affect the compounds electron density, lipophilicity, and the compounds steric configurations.

Chemistry. The starting compound was 4-(5-methyl/phenyl-1,3,4-oxadiazol-2-yl)pyridine (**3**) obtained by the

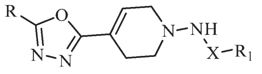


Figure 1. General structure of the target compounds. R = —CH_3, C_6H_5; R_1 = C_6H_5, 4-OCH_3—C_6H_4, 4-F—C_6H_4, 4-Br—C_6H_4, 4-*tert*-butyl-C_6H_4, X = CO, SO_2.

reaction of isonicotinic acid hydrazide and triethyl orthoacetate/triethylorthobenzoate, which was heated under reflux for 24 h [33] as outlined in Scheme 1. Substituted *N*-[4(5-methyl/phenyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2*H*)-yl]benzamide/benzenesulfonamides (**11a–n**) were prepared *via* partial reduction of *N*-ylides with a mild reducing agent, as outlined in Scheme 2. The ylides were prepared by coupling *N*-aminopyridinum salt (**8**) with appropriate acyl chlorides or sulfonyl chlorides. *O*-mesitylene sulfonyl hydroxylamine (MSH) (**7**) was used to prepare the *N*-amino salt as an aminating agent [34]. Reaction of *N*-aminopyridinium derivatives with substituted acylating agents like acyl chlorides and sulfonyl chlorides, followed by treatment with a base afforded *N*-ylides (**10**) as stable crystalline solids. Sodium borohyride reduction of (**10a–n**) in absolute ethanol furnished the target compounds substituted *N*-[4(5-methyl/phenyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2*H*)-yl] benzamide/benzene sulfonamides (**11a–n**).

RESULTS AND DISCUSSION

The results of synthesis of the pyridinium ylides (**10a–n**) and corresponding tetrahydropyridines (**11a–n**) are summarized in Table 1 and Table 2. The tetrahydropyridines are thermally stable and soluble in chloroform, dichloromethane, and other polar solvents. Analytical data of these compounds **10a–n** and **11a–n** are presented in Tables 3 and 4. The pharmacological evaluations of the compounds for anti-inflammatory and anti cancer activities are underway.

EXPERIMENTAL

The structures of the products described were confirmed by IR, ^{1}H NMR, and elemental analysis data. ^{1}H NMR spectra were determined on a Varian Gemini HX 300 MHz spectrometer using $CDCl_3$ as solvent unless otherwise specified. Chemical shifts (δ) are reported in parts per million (ppm) downfield from TMS as an internal standard. Infrared spectra were run with KBr pellets on a Perkin–Elmer 1430 FT spectrometer. Elemental analyses were performed by Galbraith Laboratories (Knoxville, TN). Melting points were determined on a Mel-Temp 3.0 melting point apparatus and were uncorrected. Chemicals and solvents were purchased from Sigma-Aldrich Chemical Company (Milwaukee, WI), Fisher Scientific Company (Suwannee, GA). Separations on column chromatography were performed on silica gel (200–425 mesh). All reactions and purification procedures were monitored by TLC on Whatman AL SIL g/UV, 250 μm layer flexible plates, with visualization under UV light.

General procedure-1

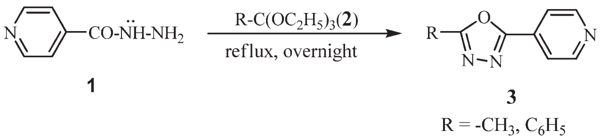
Synthesis of 4-(5-methyl-1,3,4-oxadiazol-2-yl)pyridine (3). To a solution of isonicotinic acid hydrazide 25 g (182.3 mmol) in triethyl orthoacetate (135 mL) was added and refluxed for 24 h. The excess triethyl orthoacetate was distilled under reduced pressure, and the residue was washed with cold ethanol. The residue was recrystallized from ethanol and obtained as brown crystals, yield 24 g (81.7%); Mp 148–150°C; ^{1}H NMR ($CDCl_3$): δ 2.66 (s, 3H, —CH_3); 7.88 (dd, *J* = 1.8, 1.5 Hz, 2H, C_3, C_5—H); 8.81 (dd, *J* = 1.8, 1.5 Hz; 2 H, C_2, C_6—H).

Synthesis of 4-(5-phenyl-1,3,4-oxadiazol-2-yl)pyridine (3). To a solution of isonicotinic acid hydrazide 20 g (145.6 mmol) in triethyl orthobenzoate (135 mL) was added and refluxed for 24 h. The excess triethyl orthobenzoate was distilled under reduced pressure, and the residue was washed with cold ethanol. The residue was recrystallized from ethanol and obtained as light yellow color solid, yield 29.17 g (89.8%); Mp 160–161°C. ^{1}H NMR ($CDCl_3$): δ 7.51–7.61 (m. 3H, $C_{3'}$, $C_{4'}C_{5'}$—H); 7.98 (d, *J* = 5.1 Hz, 2H, $C_{2'}$, $C_{6'}$—H); 8.12 (dd, *J* = 1.8, 1.5 Hz; 2 H, C_3, C_5—H), 8.84 (d, *J* = 6.9 Hz, 2H, C_2, C_6—H).

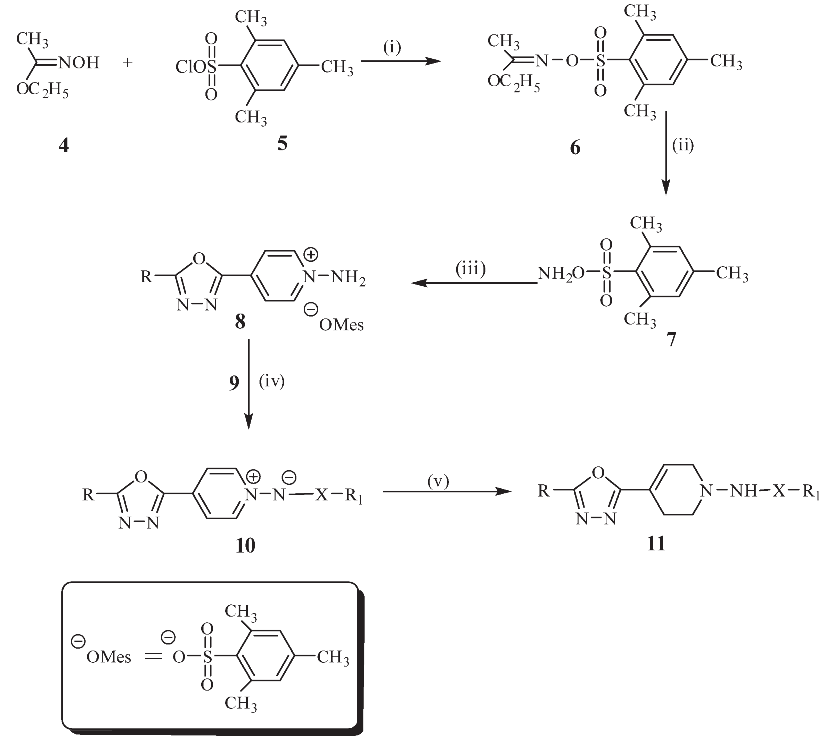
General procedure-2

Synthesis of 1-(benzoylimino)-4-(5-methyl-1,3,4-oxadiazol-2yl) pyridinium ylide (10a). To an ice cooled solution of 4-(5-methyl-1,3,4-oxadiazol-2yl)pyridine (4.35 g, 26.99 mmol) in 15 mL of dry methylene chloride was added dropwise *O*-mesitylenesulfonylhydroxylamine (5.81 g, 26.99 mmol) in 10 mL of dry methylene chloride over 5 min with stirring. The reaction stirred at 0°C for 3 h at which time 60 mL of ether was added and the suspension filtered. The precipitate was recrystallized from ethyl acetate-methanol (5:1 v/v) to give 1-amino-4-(5-methyl-1,3,4,-oxadiazol-2-yl)pyridinium mesitylene sulfonate (**7**) in 57.5% yield. The *N*-aminopyridinium salt (2.0 g, 5.096 mmol) in 30 mL of anhydrous tetrahydrofuran (THF) containing triethylamine at 70°C was stirred for 5 min before benzoyl chloride (1.43 g, 10.19 mmol) was added. The mixture was allowed to proceed for 12 h at which time 70 mL of saturated sodium bicarbonate ($NaHCO_3$) was used to arrest the reaction. The product 1-[(benzoylimino)-4-(5-methyl-1,3,4-oxadiazol-2yl)]pyridinium ylide (**10a**) was extracted with (2 × 100 mL) of chloroform and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to give crude product, which was purified by column chromatography (2.5 × 22 cm) on silica gel (200–425 mesh) using ethyl acetate: methanol (9:1 v/v) as eluent. The resultant product (**10a**) was off-white solid obtained in 34.4% yield, Mp 273–275°C; IR (KBr): ν 1593 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 2.71 (s, 3H, —CH_3 of oxadiazol ring), 7.43 (m, 3H, $C_{3'}$, $C_{4'}$ and $C_{5'}$—H), 8.18 (m,

Scheme 1



Scheme 2. Reaction conditions: (i) DMF, Et_3N, 0°C, 45 min; (ii) 70% $HC1O_4$, *p*-dioxane, 0°C, 45 min; (iii) 4-substituted pyridine, CH_2C1_2, 0°C, 3 h; (iv) 4-substituted acyl/sulfonyl chloride, dry THF, 70°C; (v) $NaBH_4$, abs. EtOH, 7 h, X = CO, SO_2. R_1 = C_6H_5, 4-OCH_3—C_6H_4, 4-F—C_6H_4, 4-Br—C_6H_4, 4-tert-C_4H_9—C_6H_4.



4H, C_3, C_5 and $C_{2'}$, $C_{6'}$—H), 9.18 (d, *J* = 7.2 Hz, 2H, C_2, C_6—H).

Synthesis of 1-[(4-methoxy benzoyl)imino]-4-(5-methyl-1,3,4-oxadiazol-2-yl) pyridinium ylide (10b). The compound **10b** was obtained following general procedure 2 as yellow crystalline solid obtained in 50.6% yield, Mp 253–254°C; IR (KBr) ν 1605 (C=O)/cm ; ^{1}H NMR ($CDCl_3$): δ 2.70 (s, 3H, —CH_3 of oxadiazol ring), 3.86 (s, 3H, —OCH_3 group), 6.94 (d, *J* = 9.0 Hz, 2H, $C_{3'}$,$C_{5'}$—H), 8.16 (dd, *J* = 7.2, 8.7 Hz, 4H, C_3,C_5, and $C_{2'}$,$C_{6'}$—H), 9.18 (d, *J* = 7.5 Hz, 2H, C_2, C_6—H).

Synthesis of 1-[(4-fluorobenzoyl)imino]-4-(5-methyl-1,3,4-oxadiazol-2-yl) pyridinium ylide (10c). The compound **10c** was obtained following general procedure 2 as white solid obtained in 51.3% yield, Mp 283–284°C; IR (KBr): ν 1604 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 2.71 (s, 3H, —CH_3 of oxadiazol ring), 7.09 (t, 2H, *J* = 9.0 Hz, $C_{3'}$, $C_{5'}$—H), 8.16 (d, 2H, *J* = 6.0 Hz, $C_{2'}$, $C_{6'}$—H), 8.21 (d, 2H, *J* = 7.2 Hz, C_3, C_5—H), 9.16 (d, 2H, *J* = 6.6 Hz, C_2, C_6—H).

Synthesis of 1-[(4-bromobenzoyl)imino]-4-(5-methyl-1,3,4-oxadiazol-2-yl) pyridinium ylide (10d). The compound **10d** was obtained following general procedure 2 as yellow color solid obtained in 61.9% yield, Mp 290–291°C; IR (KBr): ν 1601 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 2.69 (s, 3H, —CH_3 of oxadiazol ring), 7.53 (d, 2H *J* = 8.4 Hz, $C_{3'}$, $C_{5'}$—H), 8.03 (d, 2H, *J* = 8.4 Hz, $C_{2'}$, $C_{6'}$—H), 8.20 (d, 2H, *J* = 7.2 Hz, C_3, C_5—H), 9.15 (d, 2H, *J* = 7.2 Hz, C_2, C_6—H).

Synthesis of 1-[(4-tert-butylbenzoyl)imino]-4-(5-methyl-1,3,4-oxadiazol-2-yl) pyridinium ylide (10e). The compound **10e** was obtained following general procedure 2 as yellow crystalline solid obtained in 24.6% yield, Mp 246–248°C; IR (KBr): ν 1604 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 1.35 (s 9H, *tert*-butyl group), 2.70 (s, 3H, —CH_3 of oxadiazol ring), 7.44 (d, 2H, *J* = 8.4 Hz, $C_{3'}$, $C_{5'}$—H), 8.09 (d, 2H, *J* = 8.1 Hz, $C_{2'}$, $C_{6'}$—H), 8.18 (d, 2H, *J* = 6.9 Hz, C_3, C_5—H), 9.18 (d, 2H, *J* = 7.2 Hz, C_2, C_6—H).

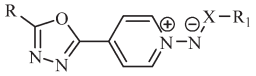
Synthesis of 4-(5-methyl-1,3,4-oxadiazol-2-yl)-1-[(phenylsulfonyl)amino]pyridinium ylide (10f). The compound **10f** was obtained following general procedure 2 as brown crystalline solid obtained in 47.8% yield, Mp 268–269°C; IR (KBr): ν 1332, 1205 (SO_2)/cm; ^{1}H NMR ($CDCl_3$): δ 2.69 (s, 3H, —CH_3 of oxadiazol ring), 7.37–7.45 (m, 3H, $C_{3'}$, $C_{4'}$ and $C_{5'}$—H), 8.16 (ddd, 4H, *J* = 7.2, 1.7, and 2.3 Hz, C_3, C_5 and $C_{2'}$, $C_{6'}$—H), 9.16 (d, 2H, *J* = 7.2 Hz, C_2, C_6—H).

Synthesis of 1-{[(4-methoxyphenyl)sulfonyl]imino}-4-(5-methyl-1,3,4-oxadiazol-2-yl) pyridinium ylide (10g). The compound **10g** was obtained following general procedure 2 as brown crystalline solid obtained in 56.2% yield, Mp 218–220°C; IR (KBr): ν 1280, 1137 (SO_2)/cm; ^{1}H NMR ($CDCl_3$): δ 2.66 (s, 3H, —CH_3 of oxadiazol ring), 3.81 (s, 3H, —OCH_3 group), 6.87 (d, 2H, *J* = 8.8 Hz, $C_{3'}$, $C_{5'}$—H), 7.74(dd, 2H, *J* = 1.9, 5.0 Hz, $C_{2'}$, $C_{6'}$—H), 8.06 (d, 2H, *J* = 7.1 Hz, C_3, C_5—H), 8.63 (d, 2H, *J* = 7.1 Hz, C_2, C_6—H).

Synthesis of 1-(benzoylimino)-4-(5-phenyl-1,3,4-oxadiazol-2yl) pyridinium ylide (10h). The compound **10h** was obtained following general procedure 2 as white crystalline solid obtained in 39.6% yield, Mp 262–263°C; IR (KBr): ν 1548 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 7.38–7.62 (complex multiplet, 6H, phenyl protons), 8.16 (ddd, 4H, *J* = 4.2, 1.5, 1.5 Hz,

Table 1

Pyridinium ylides synthetic data (**10a–n**).



Compound	R	R_1	X	M.W.	Mp (°C)	Yield (%)
10a	CH_3	C_6H_5	CO	280.28	273–275	34.4
10b	CH_3	4-OCH_3—C_6H_4	CO	319.32	253–254	50.6
10c	CH_3	4-F—C_6H_4	CO	307.28	283–284	51.3
10d	CH_3	4-Br—C_6H_4	CO	375.4	290–291	61.9
10e	CH_3	4-*tert*-C_4H_9—C_6H_4	CO	340.9	246–248	24.6
10f	CH_3	C_6H_5	SO_2	316.34	268–269	47.8
10g	CH_3	4-OCH_3—C_6H_4	SO_2	346.36	218–220	56.2
10h	C_6H_5	C_6H_5	CO	342.35	262–263	39.6
10i	C_6H_5	4-OCH_3—C_6H_4	CO	372.38	277–278	48.5
10j	C_6H_5	4-F—C_6H_4	CO	360.34	296–297	50.5
10k	C_6H_5	4-*tert*-C_4H_9—C_6H_4	CO	398.46	271–272	82.5
10l	C_6H_5	C_6H_5	SO_2	378.4	211–213	43.6
10m	C_6H_5	4-OCH_3—C_6H_4	SO_2	408.43	259–261	37.5
10n	C_6H_5	4-*tert*-C_4H_9—C_6H_4	SO_2	434.51	242–244	74.2

$C_{2'}$, $C_{6'}$ and $C_{2''}$, $C_{6''}$—H), 8.29 (d, 2H, J = 7.2 Hz, C_3, C_5—H), 9.21 (d, 2H, J = 7.2 Hz, C_2, C_6—H).

Synthesis of 1-[(4-methoxybenzoylimino)]-4-(5-phenyl-1,3,4-oxadiazol-2yl) pyridinium ylide (10i). The compound **10i** was obtained following general procedure 2 as yellow solid obtained in 48.5% yield, Mp 277–278°C; IR (KBr): ν 1593 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 3.84 (s, 3H, OCH_3), 6.92 (d, 2H, J = 8.7 Hz $C_{3''}$, $C_{5''}$—H), 7.54–7.65 (m, 3H, $C_{3'}$, $C_{4'}$, $C_{5'}$—H), 8.15(dd, 4H, J = 1.2, 8.7 Hz, $C_{2'}$, $C_{6'}$ and $C_{2''}$, $C_{6''}$—H), 8.28 (d, 2H, J = 7.2 Hz, C_3, C_5—H), 9.21 (d, 2H, J = 7.2 Hz, C_2, C_6—H).

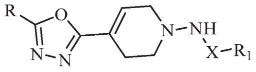
Synthesis of 1-[(4-fluorobenzoylimino)]-4-(5-phenyl-1,3,4-oxadiazol-2yl) pyridinium ylide (10j). The compound **10j** was obtained following general procedure 2 as yellow solid obtained in 50.5% yield, Mp 296–297°C; IR (KBr): ν 1557 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 7.38 (d, 2H, J = 8.7 Hz $C_{3''}$, $C_{5''}$—H), 7.55–7.63 (m, 3H, $C_{3'}$, $C_{4'}$, $C_{5'}$—H), 8.19 (ddd, 4H, J = 5.4, 3.3, 2.4 Hz, $C_{2'}$, $C_{6'}$ and $C_{2''}$, $C_{6''}$—H), 8.34 (d, 2H, J = 6.6 Hz, C_3, C_5—H), 9.21 (d, 2H, J = 6.9 Hz, C_2, C_6—H).

Synthesis of 1-[(4-tert-butylbenzoyl)imino]-4-(5-phenyl-1,3,4-oxadiazol-2-yl) pyridinium ylide (10k). The compound **10k** was obtained following general procedure 2 as yellow shiny crystals obtained in 82.5% yield, Mp 271–272°C; IR (KBr): ν 1585 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 9H, *t*-butyl group), 7.43 (d, 2H, J = 8.4 Hz, $C_{3''}$, $C_{5''}$—H), 7.53–7.64 (m, 3H, $C_{3'}$, $C_{4'}$, $C_{5'}$—H), 8.09 (d, 2H, J = 8.4 Hz, $C_{2'}$, $C_{6'}$—H), 8.15 (dd, 2H, J = 1.2, 6.6 Hz, $C_{2''}$, $C_{6''}$—H), 8.28 (d, 2H, J = 7.2 Hz, C_3, C_5—H), 9.20 (d, 2H, J = 7.2 Hz, C_2, C_6—H).

Synthesis of 4-(5-Phenyl-1,3,4-oxadiazol-2-yl)-1-[(phenyl)-sulfonyl]imino] pyridinium Ylide (10l). The compound **10l** was obtained following general procedure 2 as yellow crystals

Table 2

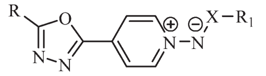
Tetrahydropyridines synthetic data (**11a–n**).



Compound	R	R_1	X	M.W.	Mp (°C)	Yield (%)
11a	CH_3	C_6H_5	CO	284.31	208–210	61.0
11b	CH_3	4-OCH_3—C_6H_4	CO	314.34	238–240	54.3
11c	CH_3	4-F—C_6H_4	CO	302.30	215–217	68.7
11d	CH_3	4-Br—C_6H_4	CO	363.21	215–217	33.8
11e	CH_3	4-*tert*-C_4H_9—C_6H_4	CO	340.42	211–213	65.4
11f	CH_3	C_6H_5	SO_2	320.37	208–210	48.2
11g	CH_3	4-OCH_3—C_6H_4	SO_2	350.39	150–152	54.4
11h	C_6H_5	C_6H_5	CO	366.21	203–204	30.4
11i	C_6H_5	4-OCH_3—C_6H_4	CO	376.41	217–218	44.8
11j	C_6H_5	4-F—C_6H_4	CO	364.37	213–215	51.4
11k	C_6H_5	4-*tert*-C_4H_9—C_6H_4	CO	402.49	209–211	32.5
11l	C_6H_5	C_6H_5	SO_2	382.44	162–163	33.6
11m	C_6H_5	4-OCH_3—C_6H_4	SO_2	412.46	135–136	42.5
11n	C_6H_5	4-*tert*-C_4H_9—C_6H_4	SO_2	438.54	163–164	48.5

Table 3

Elemental analysis of pyridinium ylides (**10a–z**).



Compound	R	R_1	X	Molecular formula	M.W.	Analysis % Cacld/Found C	H	N
10a	CH_3	C_6H_5	CO	$C_{15}H_{12}N_4O_2$	280.28	64.28 64.11	4.32 4.30	19.99 19.83
10b	CH_3	4-OCH_3—C_6H_4	CO	$C_{16}H_{14}N_4O_3$ 0.5 H_2O	319.32	60.18 60.43	4.73 4.57	17.55 17.40
10c	CH_3	4-F—C_6H_4	CO	$C_{15}H_{11}FN_4O_2$ 0.9 H_2O	307.28	58.63 58.69	3.77 3.79	18.23 18.04
10d	CH_3	4-Br—C_6H_4	CO	$C_{15}H_{11}BrN_4O_2$ 0.9 H_2O	375.4	47.99 48.27	3.44 3.11	14.92 14.61
10e	CH_3	4-*tert*-C_4H_9—C_6H_4	CO	$C_{19}H_{20}N_4O_2$ 0.25 H_2O	340.9	66.07 66.03	5.98 6.06	16.22 15.99
10f	CH_3	C_6H_5	SO_2	$C_{14}H_{12}N_4O_3S$	316.34	54.16 53.97	3.82 3.76	17.71 17.56
10g	CH_3	4-OCH_3—C_6H_4	SO_2	$C_{15}H_{14}N_4O_4S$	346.36	52.02 51.53	4.07 4.27	16.18 16.30
10h	C_6H_5	C_6H_5	CO	$C_{20}H_{14}N_4O_2$	342.35	67.02 67.31	3.94 4.19	15.63 15.78
10i	C_6H_5	4-OCH_3—C_6H_4	CO	$C_{21}H_{16}N_4O_3$	372.38	67.73 67.57	4.33 4.61	15.05 14.66
10j	C_6H_5	4-F—C_6H_4	CO	$C_{20}H_{13}FN_4O_2$	360.34	66.66 67.04	3.64 3.47	15.55 15.60
10k	C_6H_5	4-*tert*-C_4H_9—C_6H_4	CO	$C_{24}H_{22}N_4O_2$	398.46	72.34 72.39	5.57 5.38	14.06 13.82
10l	C_6H_5	C_6H_5	SO_2	$C_{19}H_{14}N_4O_3S$	378.4	60.31 60.71	3.73 3.53	14.81 14.44
10m	C_6H_5	4-OCH_3—C_6H_4	SO_2	$C_{20}H_{16}N_4O_4S$	408.43	62.06 61.93	3.47 3.25	16.08 16.01
10n	C_6H_5	4-*tert*-C_4H_9—C_6H_4	SO_2	$C_{23}H_{22}N_4O_3S$	434.51	63.58 63.32	5.10 5.14	12.89 12.42

obtained in 43.6% yield, Mp 211–213°C; IR (KBr): ν 1282, 1150 (SO_2)/cm; ^{1}H NMR ($CDCl_3$): δ 7.37–7.64 (complex multiplet, 6H, phenyl protons), 7.80 (d, 2H, J = 6.9 Hz, $C_{2'}$, $C_{6'}$—H), 8.12 (d, 2H, J = 6.9 Hz, $C_{2''}$, $C_{6''}$—H), 8.20 (d, 2H, J = 6.3 Hz, C_3, C_5—H), 8.67 (d, 2H, J = 6.6 Hz, C_2, C_6—H).

Synthesis of 1-{[(4-methoxyphenyl)sulfonyl]imino}-4-(5-phenyl-1,3,4-oxadiazol-2-yl)-pyridinium Ylide (10m). The compound **10m** was obtained following general procedure 2 as yellow solid obtained in 37.5% yield, Mp 259–261°C; IR (KBr): ν 1280, 1134 (SO_2)/cm; ^{1}H NMR ($CDCl_3$): δ 3.81 (s, —OCH_3), 6.88 (d, 2H, J = 8.7 Hz, $C_{3''}$, $C_{5''}$—H), 7.54–7.65 (m, 3H, $C_{3'}$, $C_{4'}$, $C_{5'}$—H), 7.76 (d, 2H, J = 8.7 Hz, $C_{2'}$, $C_{6'}$—H), 8.12 (d, 2H, J = 6.9 Hz, $C_{2''}$, $C_{6''}$—H), 8.19 (d, 2H, J = 6.6 Hz, C_3, C_5—H), 8.70 (d, 2H, J = 6.3 Hz, C_2, C_6—H).

Synthesis of 1-{[(4-tert-butylphenyl)sulfonyl]imino}-4-(5-phenyl-1,3,4-oxadiazol-2-yl) pyridinium ylide (10n). The compound **10n** was obtained following general procedure 2 as yellow solid obtained in 74.2% yield, Mp 242–244°C; IR (KBr): ν 1296, 1136 (SO_2)/cm; ^{1}H NMR ($CDCl_3$): δ 1.28 (s, 9H, *t*-butyl group), 7.41 (d, 2H, J = 8.4 Hz, $C_{3''}$, $C_{5''}$—H), 7.52–7.64 (m, 3H, $C_{3'}$, $C_{4'}$, $C_{5'}$—H), 7.74 (d, 2H, J = 8.4 Hz, $C_{2'}$, $C_{6'}$—H), 8.11 (dd, 2H, J = 1.5, 6.9 Hz, $C_{2''}$, $C_{6''}$—H), 8.19 (d, 2H, J = 6.6 Hz, C_3, C_5—H), 8.70 (d, 2H, J = 6.3 Hz, C_2, C_6—H).

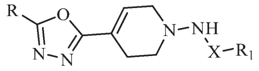
General procedure-3

N-[4[(5-Methyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2H)-yl] benzamide (11a). A solution of 1-(Benzoylimino)-4-(5-methyl-1,3,4-oxadiazol-2yl) pyridinium ylide **10a** (0.25 g, 0.79 mmol) in dichloromethane: ethanol (1:1 v/v, 40 mL) was added dropwise to a stirred suspension of sodium borohydride (0.12 g, 3.16 mmol) in 10 mL of absolute ethanol over a period or 30 min. The resulting solution was stirred for 4 h at 0°C and then overnight for a total of 24 h. The excess sodium borohyride was treated with 50 mL distilled water. It was then extracted with dichloromethane (200 mL) and dried over anhydrous sodium sulfate. The dichloromethane filtrate was evaporated *in vacuo* and the product chromatographed on a column of silica gel using ethyl acetate: methanol (9:1 v/v) as an eluent. The solid obtained was further crystallized from dichlormethane: ethylacetate (3:2 v/v) and furnished **11a** as a white flakes (61.0% yield), Mp 208–210°C; IR (KBr): ν 3213 (NH), 1638 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 2.54 (s, 3H, —CH_3 of oxadiazol ring), 2.86 (m, 2H, C_3—H), 3.34 (t, J = 5.7 Hz, 2H, C_2—H), 3.84 (m, 2H, C_6—H), 6.65 (m, 1H, C_5—H olefinic proton), 7.17 (brs, 1H, —NH D_2O exchange), 7.48 (m, 3H, $C_{3'}$,$C_{4'}$ and $C_{5'}$—H), 7.74 (d, J = 7.5 Hz, 2H, $C_{2'}$,$C_{6'}$—H).

4-Methoxy-N-[4-(5-methyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2H)-yl]-benzamide (11b). The compound **11b** was

Table 4

Elemental analysis of tetrahydropyridines (**11a–z**).



						Analysis % Cacld/Found		
Compound	R	R$_1$	X	Molecular formula	M.W.	C	H	N
11a	CH_3	C_6H_5	CO	$C_{15}H_{16}N_4O_2$	284.31	63.37	5.67	19.71
						63.34	5.73	19.62
11b	CH_3	4-OCH_3—C_6H_4	CO	$C_{16}H_{18}N_4O_3$	314.34	61.13	5.77	17.82
						61.11	5.83	17.65
11c	CH_3	4-F—C_6H_4	CO	$C_{15}H_{15}FN_4O_2$	302.30	59.60	5.00	18.53
						59.45	5.05	18.37
11d	CH_3	4-Br—C_6H_4	CO	$C_{15}H_{15}BrN_4O_2$	363.21	49.60	4.16	15.43
						49.51	4.38	15.15
11e	CH_3	4-*tert*-C_4H_9—C_6H_4	CO	$C_{19}H_{24}N_4O_2$	340.42	67.04	7.11	16.46
						67.4	7.15	16.26
11f	CH_3	C_6H_5	SO_2	$C_{14}H_{16}N_4O_3S$	320.37	52.49	5.03	17.49
						52.74	5.11	17.65
11g	CH_3	4-OCH_3—C_6H_4	SO_2	$C_{15}H_{18}N_4O_4S$	350.39	51.42	5.18	15.99
						51.70	5.30	15.79
11h	C_6H_5	C_6H_5	CO	$C_{20}H_{18}N_4O_21.1H_2O$	342.35	65.60	4.95	15.30
						65.58	5.04	15.01
11i	C_6H_5	4-OCH_3—C_6H_4	CO	$C_{21}H_{20}N_4O_3$	376.41	67.01	5.59	15.55
						66.81	5.40	14.59
11j	C_6H_5	4-F—C_6H_4	CO	$C_{20}H_{17}FN_4O_2$	364.37	65.93	4.70	15.38
						65.92	4.75	15.18
11k	C_6H_5	4-*tert*-C_4H_9—C_6H_4	CO	$C_{24}H_{26}N_4O_2$	402.49	71.62	6.51	13.92
						71.78	6.56	13.79
11l	C_6H_5	C_6H_5	SO_2	$C_{19}H_{18}N_4O_3S$	382.44	59.67	4.74	14.65
						59.38	4.78	14.34
11m	C_6H_5	4-OCH_3—C_6H_4	SO_2	$C_{20}H_{20}N_4O_4S$	412.46	58.24	4.89	13.58
						58.26	4.96	13.47
11n	C_6H_5	4-*tert*-C_4H_9—C_6H_4	SO_2	$C_{23}H_{26}N_4O_3S$	438.54	62.99	5.98	12.78
						62.89	5.91	12.45

obtained following general procedure 3 as off-white solid 54.3% yield, Mp 238–240°C; IR (KBr): ν 3183 (NH), 1625 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 2.54 (s, 3H, CH_3), 2.85 (m, 2H, C_3—H), 3.32 (t, 2H, J = 6.0 Hz, C_2—H), 3.82 (brs, 2H, C_6—H), 3.84 (s, —OCH_3 group), 6.64 (m, C_5—H, olefinic), 6.92 (d, 2H, J = 8.7 Hz, $C_{3'}$,$C_{5'}$—H), 7.14 (brs, —NH, D_2O exchange), 7.72 (d, 2H, J = 8.4 Hz, $C_{2'}$, $C_{6'}$—H).

4-Fluoro-**N*****-[4-(5-methyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2H)-yl]-benzamide (11c).*** The compound **11c** was obtained following general procedure 3 as white granules 68.7% yield, Mp 215–217°C; IR (KBr): ν 3190 (NH), 1636 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 2.52 (s, 3H, CH_3 of oxadiazol ring), 2.84 (m, 2H, C_3—H), 3.30 (t, 2H, J = 6.2 Hz, C_2—H), 3.81 (brs, 2H, C_6—H), 6.62 (m, 1H, C_5—H, olefinic proton), 7.71 (t, 2H, J = 8.6 Hz, $C_{3'}$, $C_{5'}$—H), 7.15 (brs, 1H, NH proton, D_2O exchange), 7.75 (d, 2H, J = 8.4 Hz, $C_{2'}$, $C_{6'}$—H).

4-Bromo-**N*****-[4-(5-methyl-1,3,4-oxadiazol-2-yl)-3,6-dihydro pyridin-1(2H)-yl]-benzamide (11d).*** The compound **11d** was obtained following general procedure 3 as yellow solid 33.8% yield, Mp 216–217°C; IR (KBr): ν 3185 (NH), 1635 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 2.53 (s, 3H, CH_3 of oxadiazol ring), 2.85 (m, 2H, C_3—H), 3.31 (t, 2H, J = 6.2 Hz, C_2—H), 3.81 (brs, 2H, C_6—H), 6.64 (m, 1H, C_5—H, olefinic proton), 7.72 (t, 2H, J = 8.6 Hz, $C_{3'}$, $C_{5'}$—H), 7.13 (brs, NH proton, D_2O exchange), 7.75 (d, 2H, J = 8.4 Hz, $C_{2'}$, $C_{6'}$—H).

4-tert-Butyl--**N*****-[4-(5-methyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2H)-yl]-benzamide (11e).*** The compound **11e** was obtained following general procedure 3 as off-white solid 65.4% yield, Mp 211–213°C; IR (KBr): ν 3274 (NH), 1643 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 1.31 (s 9H, *tert*-butyl group), 2.52 (s, 3H, —CH_3 of oxadiazol ring), 2.84 (m, 2H, C_3—H), 3.30 (t, 2H, J = 5.4 Hz, C_2—H), 3.81 (brs, 2H, C_6—H), 6.62 (m, 1H, C_5—H, olefinic proton), 7.14 (brs, 1H, —NH proton, D_2O exchange), 7.43 (d, 2H, J = 8.3 Hz, $C_{3'}$, $C_{5'}$,—H), 7.66 (d, 2H, J = 8.1 Hz, $C_{2'}$, $C_{6'}$—H).

N***-[4-(5-Methyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2H)-yl]-benzene sulfonamide (11f).*** The compound **11f** was obtained following general procedure 3 as white solid 48.2% yield, Mp 208–210°C; IR (KBr): ν 3069 (NH), and 1332, 1164 (SO_2)/cm; ^{1}H NMR ($CDCl_3$): δ 2.53 (s, 3H, —CH_3 of oxadiazol ring), 2.85 (m, 2H, C_3—H), 3.31 (t, 2H, J = 5.8 Hz, C_2—H), 3.82 (brs, 2H, C_6—H), 6.63 (m, 1H, C_5—H, olefinic proton), 7.16 (brs, —NH, D_2O exchange), 7.40–7.54 (m 3H, $C_{3'}$, $C_{4'}$, $C_{5'}$—H), 7.73 (d, 2H, J = 7.3 Hz, $C_{2'}$, $C_{6'}$—H).

4-Methoxy-**N*****-[4-(5-methyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2H)-yl]-benzene sulfonamide (11g).*** The compound **11g** was obtained following general procedure 3 as white granules 54.4% yield, Mp 150–152°C; IR (KBr): ν 3078 (NH), and 1331, 1163 (SO$_2$)/cm; ^{1}H NMR (CDCl$_3$): δ 2.50 (s, 3H, —CH$_3$ of oxadiazol ring), 2.49 (m, 2H, C$_3$—H), 2.77 (t, 2H, J = 5.4 Hz, C$_2$—H), 3.45 (d, 2H, J = 3 Hz, C$_6$—H), 3.86 (s, 3H, —OCH$_3$), 5.47 (s, 1H, —NH, D$_2$O exchange), 6.46 (m, 1H, C$_5$—H olefinic proton), 6.96 (d, 2H, J = 9.0 Hz, C$_{3'}$, C$_{5'}$—H), 7.86 (dd, 2H, J = 3.0, 6.9 Hz, C$_{2'}$,C$_{6'}$—H).

N***-[4-(5-Phenyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2H)-yl]benzamide (11h).*** The compound **11h** was obtained following general procedure 3 as white granules 30.4% yield, Mp 203–204°C; IR (KBr): ν 3189 (NH), 1635 (C=O)/cm; ^{1}H NMR (CDCl$_3$): δ 2.93 (m, 2H, C$_3$—H), 3.36 (t, 2H, J = Hz, C$_2$—H), 3.88 (brs, 2H, C$_6$—H), 6.79 (m, 1H, C$_5$—H, olefinic proton), 7.21 (brs, 1H, —NH, D$_2$O exchange), 7.40–7.53 (complex m, 6H, C$_{3'}$, C$_{4'}$, C$_{5'}$ and C$_{3''}$, C$_{4''}$, C$_{5''}$—H), 7.74 (d, 2H, J = 7.2 Hz, C$_{2'}$, C$_{6'}$—H), 8.05 (dd, 2H, J = 1.2, 6.0 Hz C$_{2''}$, C$_{6''}$—H,).

4-Methoxy-**N*****-[4-(5-phenyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2H)-yl]-benzamide (11i).*** The compound **11i** was obtained following general procedure 3 as white solid 44.8% yield, Mp 217–218°C; IR (KBr): ν 3221 (NH), 1638 (C=O)/cm; ^{1}H NMR (CDCl$_3$): δ 2.91 (m, 2H, C$_3$—H), 3.34 (t, 2H, J = 5.7 Hz, C$_2$—H), 3.83 (s, 3H, —OCH$_3$), 3.86 (brs, 2H, C$_6$—H), 6.78 (m, 1H, C$_5$—H, olefinic proton), 6.90 (d, 2H, J = 8.7 Hz, C$_{3''}$, C$_{5''}$—H), 7.15 (brs, 1H, —NH, D$_2$O exchange), 7.45–7.54 (m, 3H, C$_{3'}$, C$_{4'}$, C$_{5'}$—H), 7.71 (d, 2H, J = 7.8 Hz, C$_{2''}$, C$_{6''}$—H), 8.05 (dd, 2H, J = 1.5, 6.0 Hz, C$_{2'}$, C$_{6'}$—H).

4-Fluoro-**N*****-[4-(5-phenyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2H)-yl]-benzamide (11j).*** The compound **11j** was obtained following general procedure 3 as white solid 51.4% yield, Mp 213–215°C; IR (KBr): ν 3185 (NH), 1637 (C=O)/cm; ^{1}H NMR (CDCl$_3$): δ 2.92 (m, 2H, C$_3$—H), 3.34 (t, 2H, J = 5.8 Hz, C$_2$—H), 3.86 (brs, 2H, C$_6$—H), 6.78 (m, 1H, C$_5$—H, olefinic proton), 7.10 (t, 2H, J = 8.7 Hz, C$_{3''}$, C$_{5''}$—H), 7.25 (brs, 1H, —NH, D$_2$O exchange), 7.45–7.55 (m, 3H, C$_{3'}$, C$_{4'}$, C$_{5'}$—H), 7.71 (d, 2H, J = 7.8 Hz, C$_{2'}$, C$_{6'}$—H), 8.05 (dd, 2H, J = 0.9, 6.3 Hz, C$_{2''}$, C$_{6''}$—H).

4-tert-Butyl-**N*****-[4-(5-methyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2H)-yl]benzamide (11k).*** The compound **11k** was obtained following general procedure 3 as white solid 32.5% yield, Mp 209–211°C; IR (KBr): ν 3211 (NH), 1638 (C=O)/cm; ^{1}H NMR (CDCl$_3$): δ 1.31 (s, 9H, *t*-butyl group), 2.94 (m, 2H, C$_3$—H), 3.40 (t, 2H, J = 5.7 Hz, C$_2$—H), 3.92 (d, 2H, J = 2.4 Hz, C$_6$—H), 6.78 (m, 1H, C$_5$—H, olefinic proton), 7.39 (brs, 1H, —NH, D$_2$O exchange), 7.43–7.53 (m, 5H, phenyl protons), 7.69 (d, 2H, J = 8.1 Hz, C$_{3''}$, C$_{5''}$—H), 8.05 (d, 2H, J = 8.1 Hz, C$_{2''}$, C$_{6''}$—H).

N***-[4-(5-Phenyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2H)-yl]-benzene sulfonamide (11l).*** The compound **11l** was obtained following general procedure 3 as white granules 33.6% yield, Mp 162–163°C; IR (KBr): ν 3106 (NH), 13323, 1168 (SO$_2$)/cm; ^{1}H NMR (CDCl$_3$): δ 2.65 (m, 2H, C$_3$—H), 2.81 (t, 2H, J = 5.7 Hz, C$_2$—H), 3.03 (brs, 2H, C$_6$—H), 5.72 (brs, 1H, —NH, D$_2$O exchange), 6.62 (m, 1H, C$_5$—H, olefinic proton), 7.44—7.64 (complex m, 6H, C$_{3'}$, C$_{4'}$, C$_{5'}$ and C$_{3''}$, C$_{4''}$, C$_{5''}$—H), 7.96 (dd, 2H, J = 1.2 and 7.2 Hz, C$_{2'}$, C$_{6'}$—H), 8.01 (dd, 2H, J = 1.5, 6.0 Hz, C$_{2''}$, C$_{6''}$ —H).

4-Methoxy-**N*****-[4-(5-phenyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2H)-yl]-benzene-sulfonamide (11m).*** The compound **11m** was obtained following general procedure 3 as white solid 42.5% yield, Mp 135–136°C; IR (KBr): ν 3089 (NH), 1330, 1154 (SO$_2$)/cm; ^{1}H NMR (CDCl$_3$): δ 2.67 (m, 2H, C$_3$—H), 2.81 (t, 2H, J = 5.4 Hz, C$_2$—H), 3.51 (d, 2H, J = 3.0 Hz, C$_6$—H), 3.87 (s, 3H, —OCH$_3$), 5.45 (s, 1H, —NH, D$_2$O exchange), 6.63 (m, 1H, C$_5$—H, olefinic proton), 6.98 (d, 2H, J = 9.0 Hz, C$_{3''}$, C$_{5''}$—H), 7.45–7.54 (m, 3H, C3′, C4′, C$_{5'}$—H), 7.88 (d, 2H, J = 9.0 Hz, C$_{2'}$, C$_{6'}$—H), 8.02 (dd, 2H, J = 1.2, 6.6 Hz, C$_{2''}$, C$_{6''}$—H).

4-tert-butyl-**N*****-[4-(5-phenyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2H)-yl]benzene sulfonamide (11n).*** The compound **11n** was obtained following general procedure 3 as white solid 48.5% yield, Mp 163–134°C; IR (KBr): ν 3088 (NH), 1335, 1152 (SO$_2$)/cm; ^{1}H NMR (CDCl$_3$): δ 1.33 (s, 9H, t-butyl group), 2.67 (m, 2H, C$_3$—H), 2.81 (t, 2H, J = 5.4 Hz, C$_2$—H), 3.52 (d, 2H, J = 2.4 Hz, C$_6$—H), 5.55 (brs, 1H, —NH, D$_2$O exchange), 6.64 (m, 1H, C$_5$—H, olefinic proton), 6.98 (d, 2H, J = 9.0 Hz, C$_{3''}$, C$_{5''}$—H), 7.45–7.54 (m, 3H, C$_{3'}$, C$_{4'}$, C$_{5'}$—H), 7.88 (d, 2H, J = 9.0 Hz, C$_{2'}$, C$_{6'}$—H), 8.02 (dd, 2H, J = 1.2, 6.6 Hz, C$_{2''}$, C$_{6''}$—H).

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Synthesis of 2,3-Dichloroquinoxalines *via* Vilsmeier Reagent Chlorination

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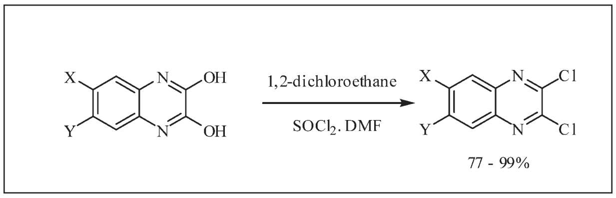

A convenient and high-yielding synthesis of 2,3-dichloroquinoxalines from the corresponding 2,3-dihydroxyquinoxalines has been developed. Treatment of a slurry of the 2,3-dihydroxyquinoxaline **1a–j** with *N*,*N*-dimethylformamide in the presence of excess thionylchloride in 1,2-dichloroethane results in the rapid and high-yielding formation of the 2,3-dichloroquinoxaline derivatives **2a–j**. Simplified workup and purification procedures for these compounds are also described.

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INTRODUCTION

The chemistry of 2,3-dichloroquinoxalines has received considerable attention in the past [1]. This class of compounds has previously been shown to exhibit a broad range of biological activity. For example, various derivatives of 2,3-dichloroquinoxalines have been shown to exhibit fungicidal and bactericidal activity [2]. They have also shown utility in industrial applications such as use as reactive dyes for fibers [3].

These dichloroquinoxaline compounds have traditionally been prepared by chlorination of the corresponding quinoxaline 2,3-diones (2,3-dihydroxyquinoxalines) with phosphorous-based chlorinating reagents. Phosphorus oxychloride ($POCl_3$) is the most common agent used, usually in the presence of an initiator such as *N*,*N*-dimethylaniline [4], or phosphorus pentachloride (PCl_5). However, the hazards of handling phosphorus oxychloride or phosphorus pentachloride are not to be taken lightly. Moreover, phosphorus containing waste streams is becoming increasingly difficult to dispose of in industrial settings.

Recently, Zimcik and coworkers [5] reported the synthesis of 2,3-dichloro-6,7-dicyanoquinoxaline from 2,3-dihy-droxy-6,7-dicyanoquinoxaline, using thionyl chloride in the presence of small amounts of *N*,*N*-dimethylformamide (DMF). Similarly, Tanaka and coworkers [6] has reported the synthesis of 2,3-dichloro-6-trifluoromethylquinoxaline from 2,3-dihydroxy-6-trifluoromethylquinoxaline with an excess of thionyl chloride ($SOCl_2$) in *N*,*N*-DMF as the solvent. In both of these cases, the actual chlorinating reagent is undoubtedly the Vilsmeier reagent, generated *in situ* from the reaction of *N*,*N*-DMF with thionyl chloride.

We have recently synthesized a series of 2,3-dichloroquinoxalines using a similar approach of generating the Vilsmeier reagent *in situ* by the addition of catalytic amounts of *N*,*N*-DMF to a slurry of 2,3-dihydroxyquinoxalines and thionyl chloride in 1,2-dichloroethane. Inspired by these earlier reports, we herein report the general utility of this reaction protocol and give experimental details for simplified workup and purification procedures for the synthesis of 2,3-dichloroquinoxalines *via* chlorination of 2,3-dihydroxyquinoxalines with the Vilsmeier reagent.

RESULTS AND DISCUSSION

2,3-Dichloroquinoxalines, **2** (Scheme 1), can be readily prepared by chlorination of 2,3-dihydroxyquinoxalines, **1**, which in turn can be prepared by the

Scheme 1

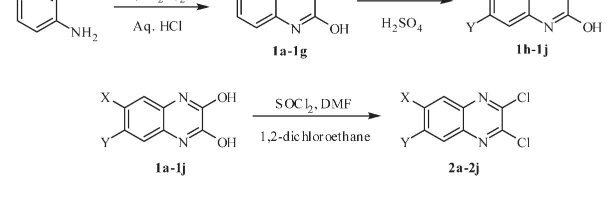

Table 1

Physical and analytical data of compounds **2a–j**.

Compound	X	Y	Time (h)	Mp (°C)	Yield (%)
2a	H	H	2	100–102[a]	95
2b	NO_2	H	4	152–153[a]	99
2c	Cl	H	4	144[a]	99
2d	CH_3	H	2	113–114[a]	93
2e	F	H	2	143–145[b]	98
2f	CN	H	2	239–240[b]	77
2g	CF_3	H	2	91–93[b]	81
2h	CH_3	NO_2	2	134–136[b]	95
2i	Cl	NO_2	0.5	135–137[b]	93
2j	NO_2	NO_2	0.5	210–212[b]	92

[a] Recrystallized from CH_3CN/H_2O.

[b] Filtered through SiO_2 with CH_2Cl_2.

condensation of commercially available 1,2-phenylenediamines with oxalic acid in aqueous hydrochloric acid (HCl) [1]. Mono and dinitroquinoxalines **1b** and **1h–1j** were prepared by nitration of the parent dihydroxyquinoxaline with one or two equivalents of potassium nitrate (KNO_3) in sulfuric acid (H_2SO_4) [7].

We have found that 2,3-dichloroquinoxalines **2a–2j** are readily formed by the drop wise addition of catalytic amounts of *N*,*N*-DMF (10 mol %) to slurry of the corresponding 2,3-dihydroxyquinoxalines **1a–1j** in 1,2-dichloroethene and an excess (2.5–3.0 molar equivalents) of thionyl chloride (Table 1).

In all cases, the desired 2,3-dichloroquinoxaline was rapidly formed by bringing the reaction mixture to reflux. After complete conversion, the reaction mixture was cooled to ambient temperature, followed by concentration to dryness. Purification of the desired product can then be readily accomplished by recrystallization of the crude product from acetonitrile/water, giving the desired 2,3-dichloroquinoxaline in high yield and purity. Alternatively, and particularly convenient for larger scale reactions, the residual material obtained after evaporation of the excess thionyl chloride and 1,2-dichloroethane can be purified by slurrying the initially isolated residue in water, followed by filtration and re-dissolving the crude product into methylene chloride (CH_2Cl_2) and filtering through a plug of silica gel.

There are several advantages to this method over those previously reported. First is that $SOCl_2$/DMF is considerably less expensive and less hazardous than using $POCl_3$/*N*,*N*-dimethylaniline. Also, in general, the reaction requires much shorter reaction times. For example, in our experiments, chlorination of **1c** with $POCl_3$/*N*,*N*-dimethylaniline required refluxing for 6 days for complete conversion and **2c** was obtained in 76% yield. In contrast, chlorination of **1c** with $SOCl_2$/DMF in 1,2-dichloroethane led to complete reaction within 4 h, giving a near quantitative yield of **2c**.

EXPERIMENTAL

General experimental procedures. All solvents and reagents were reagent grade and were used without further purification. ^1H and ^{13}C NMR spectra were obtained on a Varian XM-300 NMR. All yields reported are those of isolated material judged homogeneous by ^1H NMR.

General procedure for the synthesis of 2,3-dihydroxyquinoxalines 1a–j. ***2,3-Dihydroxyquinoxline (1a).*** A solution of oxalic acid (27.1 g, 0.215 mol) in 4*N* aqueous HCl (50 mL) was added to a solution of 1,2-diaminobenzene (20.9 g, 0.193 mol) in 4*N* HCl (150 mL), and the resulting solution was heated to reflux for 2 h. The reaction mixture was cooled to ambient temperature, and the resulting precipitate was isolated by filtration, washed with water, and dried, giving 30.5 g (98%) of **1a** as an off white powder, mp >300°C: ^1H NMR (DMSO-d_6): δ 11.90 (s, 2H), 7.13–7.04 (m, 4H); ^{13}C NMR (DMSO-d_6): δ 155.12, 125.52, 122.91, 115.06.

General procedure for the nitration of 2,3-dihydroxyquinoxalines 1h–j. ***2,3-Dihydroxy-6-nitro-7-methylquinoxaline (1h).*** To a solution of 2,3-dihydroxy-6-methylquinoxaline (10.0 g, 0.0574 mol) in H_2SO_4 (124 mL) at 0°C was added, in several portions, KNO_3 (6.39 g, 0.0632 mol), and the resulting solution was allowed to warm to ambient temperature and stirred overnight. The reaction mixture was carefully poured into 500 mL of ice/water, stirred 30 min, filtered, washed with water and dried, giving 12.2 g (96%) of **1h** as a pale yellow solid, mp >300°C. ^1H NMR (DMSO-d_6): δ 12.20 (s, 1H), 12.02 (s, 1H), 7.72 (s, 1H), 6.95 (s, 1H), 2.47 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 155.10, 154.47, 142.21, 130.10, 128.69, 124.05, 117.70, 111.60, 20.31.

General procedure for the chlorination of dihydroxyquinoxalines. ***2,3-Dichloroquinoxaline (2a).*** *N*,*N*-Dimethylformamide (0.045 g, 0.00062 mol, 0.1 eq) was added dropwise to a slurry of 2,3-dihydroxyquinoxaline (2.0 g, 0.012 mol) and thionyl chloride (3.7 g, 0.031 mol) in 1,2-dichloroethane (20 mL). The resulting reaction mixture was heated to reflux for 2 h then concentrated to dryness. The residue was dissolved in 1,2-dichloroethane (25 mL) and concentrated to dryness. The resulting solid was recrystallized from CH_3CN/H_2O, giving 2.3 g (95%) of **2a** as fine, off white needles, mp 100–102°C; ^1H NMR ($CDCl_3$): δ 8.10–8.06 (m, 2H), 7.98–7.93 (m, 2H); ^{13}C NMR ($CDCl_3$) 144.50, 139.92, 131.67, 127.81. *Anal.* Calcd. for $C_8H_4Cl_2N_2$: C, 48.28; H, 2.03; N, 14.07. Found: C, 47.87; H, 2.1; N, 14.00.

2,3-Dichloro-6-nitroquinoxaline (2b). This compound was prepared from *N*,*N*-DMF (0.11 g, 0.0014 mol), 2,3-dihydroxy-6-nitroquinoxaline (3.0 g, 0.0145 mol) and thionylchloride (4.31 g, 0.035 mol) in 1,2-dichloroethane (30 mL) as previously described, to give 3.52 g (99%) of **2b** after recrystallization (CH_3CN/H_2O) as a tan powder, mp 152–153°C; ^1H NMR (DMSO-d_6) (d, J = 2.4 Hz, 1H), 8.57 (dd, J = 9.2, 2,5 Hz, 1H), 8.28 (d, J = 9.2 Hz, 1H); ^{13}C NMR (DMSO-d_6) 148.18, 148.07, 147.28, 142.3, 138.83, 129.68, 124.74, 123.67. *Anal.* Calcd. for $C_8H_3Cl_2N_3O_2$: C, 39.37; H, 1.24; N, 17.22. Found: C, 39.11; H, 1.03; N, 16.99.

2,3,6-Trichloroquinoxaline (2c). This compound was prepared from *N*,*N*-DMF (0.074 g, 0.001 mol), 6-chloro-2,3-dihydroxyquinoxaline (2.0 g, 0.0102 mol), and thionylchloride (3.02 g, 0.025 mol) in 1,2-dichloroethane (10 mL) after 4 h reflux to give 3.52 g (99%) of **2c** after recrystallization from

CH_3CN/H_2O as yellow needles, mp 144°C; ^1H NMR (DMSO-d_6) 8.23 (d, $J = 2.2$ Hz, 1H), 8.12 (d, $J = 8.9$ Hz, 1H), 7.98 (dd, $J = 9.0$, 2.3 Hz, 1H); ^{13}C NMR (DMSO-d_6) 145.87, 145.05, 140.28, 138.67, 135.91, 132.10, 129.57, 126.72, 126.72. *Anal.* Calcd. for $C_8H_3Cl_3N_2$: C, 41.15; H, 1.30; N, 12.00. Found: C, 40.83; H, 1.22; N, 12.20.

2,3-Dichloro-6-methylquinoxaline (2d). This compound was prepared from *N,N*-DMF (0.083 g, 0.0011 mol), 2,3-dihydroxy-6-methylquinoxaline (2.0 g, 0.012 mol) and thionylchloride (3.38 g, 0.028 mol) in 1,2-dichloroethane (20 mL) after 2 h at reflux. Recrystallized from CH_3CN/H_2O to give 2.25 g (93%) of **2d** as fine, light tan colored needles, mp 113–114°C; ^1H NMR (DMSO-d_6): δ 7.94 (d, $J = 8.3$ Hz, 1H), 7.82 (s, 1H), 7.77 (d, $J = 8.4$ Hz, 1H), 3.38 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 144.27, 143.39, 142.33, 139.97, 138.34, 133.72, 127.30, 126.54, 21.30. *Anal.* Calcd. for $C_9H_6Cl_2N_2$: C, 50.73; H, 2.84; N, 13.15. Found: C, 50.37; H, 2.88; N, 13.22.

2,3-Dichloro-6-fluoroquinoxaline (2e). This compound was prepared from *N,N*-DMF (0.41 g, 0.0056 mol), 6-fluoro-3-dihydroxyquinoxaline (10.0 g, 0.0555 mol) and thionyl chloride (16.5 g, 0.139 mol) in 1,2-dichloroethane (50 mL), and the resulting reaction mixture was heated at reflux for 2 h. The resulting solution was cooled to room temperature and concentrated to dryness. The resulting solid was slurried in water (150 mL) for 30 min, then filtered and dried. The residue was taken up in a minimum of CH_2Cl_2 and filtered through a short column of silica gel, eluting with CH_2Cl_2. Concentration then gave 11.75 g (98%) of **2e** as a pale yellow solid, mp 143–145°C; ^1H NMR (DMSO-d_6): δ 8.18 (dd, $J = 9.2$, 5.6 Hz, 1H), 7.95 (dd, $J = 9.2$, 2.7 Hz, 1H), 7.88 (dd, $J = 8.4$, 2.7 Hz, 1H). *Anal.* Calcd. for $C_8H_3Cl_2FN_2$: C, 44.27; H, 1.39; N, 12.91. Found: C, 44.03; H, 1.33; N, 12.88.

2,3-Dichloro-6-cyanoquinoxaline (2f). *N,N*-dimethylformamide (0.039 g, 0.0005 mol) was added dropwise to a slurry of 6-cyano-2,3-dihydroxyquinoxaline (1.0 g, 0.0054 mol) and thionyl chloride (1.6 g, 0.013 mol) in 1,2-dichloroethane (5 mL), and the resulting solution was heated at reflux for 2 h. The solution was cooled and concentrated. The residue was slurried in water (50 mL) for 30 min, then filtered and dried. The residue was taken up in a minimum of CH_2Cl_2 and filtered through a short column of silica gel, eluting with CH_2Cl_2. Concentration gave 0.92 g (77%) of **2f** as a light gray powder, mp 239–240°C; ^1H NMR ($CDCl_3$): δ 8.40 (d, $J = 1.8$ Hz, 1H), 8.15 (d, $J = 8.7$ Hz, 1H); 7.97 (dd, $J = 8.7$, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 147.58, 146.71, 141.42, 139.03, 133.74, 132.49, 129.35, 117.47, 113.51. *Anal.* Calcd. for $C_9H_3Cl_2N_3$: C, 48.25; H, 1.35; N, 18.76. Found: C, 48.22; H, 1.15; N, 18.57.

2,3-Dichloro-6-trifluoromethylquinoxaline (2g). This compound was prepared from *N,N*-DMF (0.19 g, 0.0026 mol), 2,3-dihydroxy-6-trifluoromethylquinoxaline (6.0 g, 0.026 mol) and thionyl chloride (7.8 g, 0.065 mol) in 1,2-dichloroethane (50 mL) after 2 h reflux to give 5.62 g (81%) of **2g** after filtration through a short column of silica gel, eluting with CH_2Cl_2, mp 91–93°C; ^1H NMR (DMSO-d_6): δ 8.50 (bs, 1H), 8.30 (d, $J = 8.8$ Hz, 1H), 8.20 (dd, $J = 8.8$, 2.0 Hz, 1H). *Anal.* Calcd. for $C_9H_3Cl_2F_3N_2$: C, 40.48; H, 1.13; N, 10.49. Found: C, 40.20; H, 1.15; N, 10.50.

2,3-Dichloro-7-methyl-6-nitroquinoxaline (2h). This compound was prepared from *N,N*-DMF (0.072 g, 0.00090 mol), 2,3-dihydroxy-6-nitro-7-methylquinoxaline (2.0 g, 0.00090 mol) and thionyl chloride (2.69 g, 0.023 mol) in 1,2-dichloroethane (5 mL) after 2 h at reflux to give 5.62 g (81%) of **2h** after filtration through a short column of silica gel, eluting with CH_2Cl_2, mp 134–136°C; ^1H NMR (DMSO-d_6): δ 8.66 (s, 1H), 8.18 (s, 1H), 2.67 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 150.56, 147.81, 146.48, 140.94, 137.57, 134.57, 130.88, 123.65, 19.00. *Anal.* Calcd. for $C_9H_5Cl_2N_3O_2$: C, 41.89; H, 1.95; N, 16.28. Found: C, 41.93; H, 1.22; N, 16.50.

2,3,6-Trichloro-7-nitroquinoxaline (2i). This compound was prepared from *N,N*-DMF (0.364 g, 0.0050 mol), 2,3-dihydroxy-6-chloro-7-nitroquinoxaline (12.0 g, 0.0498 mol) and thionyl chloride (14.8 g, 0.124 mol) in 1,2-dichloroethane (50 mL) after 30 min at reflux to give 12.8 g (93%) of **2i** as a golden yellow powder after filtration through short column of silica gel, eluting with CH_2Cl_2, mp 135–137°C; ^1H NMR (DMSO-d_6): δ 8.89 (s, 1H), 8.58 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 148.72, 148.58, 147.62, 140.88, 138.01, 130.35, 126.02, 124.72. *Anal.* Calcd. for $C_8H_2Cl_3N_3O_2$: C, 34.50; H, 0.72; N, 15.09. Found: C, 34.52; H, 0.81; N, 15.11.

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Synthesis and Bioactivity of Novel Benzisothiazolone Derivatives as Potential Microbiocides

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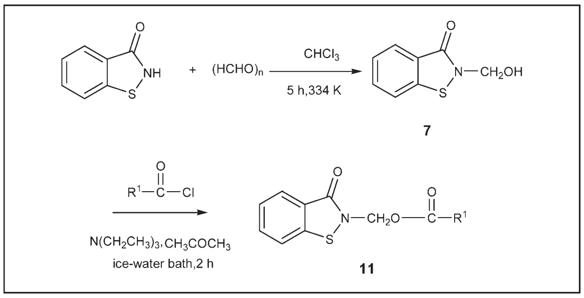

Novel microbiocides 2-(hydroxymethyl)benzo[*d*]isothiazol-3(2*H*)-one (**7**) and (3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)methyl benzencarboxylates (**11a-c**) were synthesized in good yields, and their structures were characterized by means of ^{1}H NMR, MS, and elemental analysis. The new compounds were tested preliminarily in laboratory assays against the aquicolous bacteria including *Escherichia coli, Staphyloccus aurueus, Vibrio alginolyticus, Aeromonas hydrophila*, and *Bacillus subtilis*. The results show all the synthesized compounds have good antimicrobial activity. The antimicrobial activity of all the tested compounds against all test bacteria is >96.6% at the concentration of 10^{-2} mg mL^{-1}. These compounds can be further developed for effective microbiocides in the future.

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INTRODUCTION

Marine biological fouling, usually termed marine biofouling, can be defined as the undesirable accumulation of microorganisms, plants, and animals on artificial surfaces immersed in sea water. The first phase of the fouling is the attachment of microorganisms. So it is important to inhibit the microorganism for antifouling. After the definitive ban on tin-based antifouling substances, the most important issue for paint manufacturers is to develop an alternative antifouling paint that achieves the same performance as the organic tin-based antifouling paints without significant cost increase.

As a class of antimicrobial agents against bacteria and fungi isothiazole derivatives have many advantages such as highly efficient, low poisonous; they are environmentally friendly [1]. Isothiazole-3(2*H*)-ones and heterocyclic bioisomeric derivatives such as **1-10** shown in Figure 1 are potent industrial and medicinal microbiocides with antifungal and antibacterial activities [2–4]. Okachi *et al*. synthesized 2-(hydroxymethyl)benzo[*d*]isothiazol-3(2*H*)-one **7** and its derivatives (**8** and **9**) and tested for their *in vitro* antibacterial activity against *Mycobacterium tuberculosis* H37Rv including resistant strains against streptomycin, kanamycin, or isonicotinic acid hydrazide. All the compounds showed good antibacterial activity and no crossresistance between the current antitubercular agents [5]. Vicini *et al*. described a series of 2-aminobenzo[*d*]isothiazol-3(2*H*)-one derivatives **10**, which were synthesized and screened *in vitro* for inhibition of platelet aggregation and for their spasmolytic activity, with the awareness that the development of antiplatelet agents with additional vasodilation activity could be beneficial in the treatment of various vaso-occlusive disorders. The tested compounds show a powerful antiplatelet activity and various modifications resulted in molecules possessing antiaggregating effects as well as spasmolytic actions [6].

According to the earlier-mentioned facts and the principle of combination of bioactive substructure, we herein designed and synthesized benzisothiazolone derivatives 2-(hydroxymethyl)benzo[*d*]isothiazol-3(2*H*)-one (**7**) and (3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)methyl benzencarboxylates (**11a-c**) in good yields, and their structures as shown in Scheme 1. The structures of **11** were confirmed by means of ^{1}H NMR, MS, and

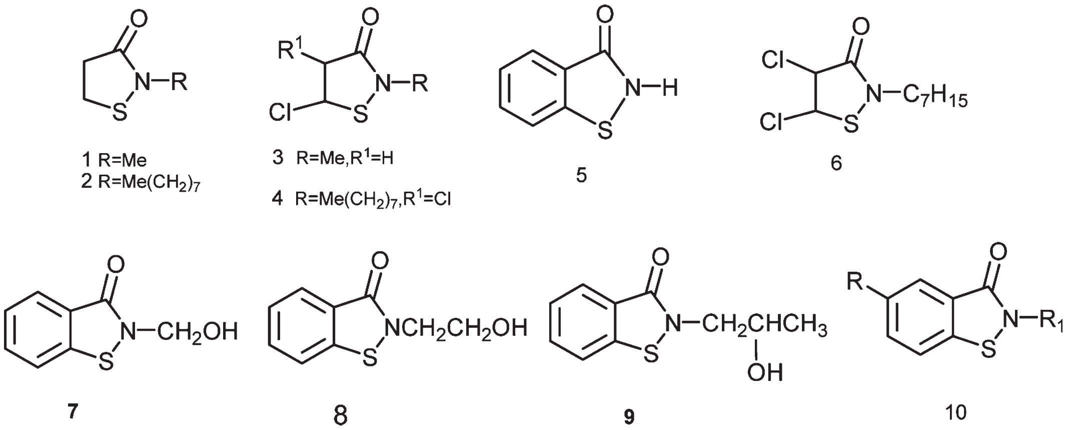


Figure 1. Previously reported bioactive compounds **1-10**.

elemental analysis. Their bioactivities were also tested preliminarily.

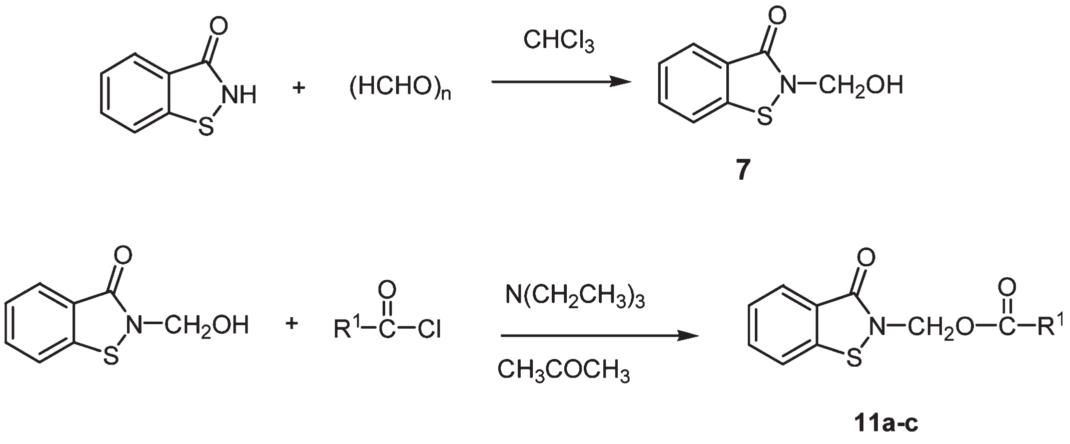
RESULTS AND DISCUSSION

We synthesized novel compounds (3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)methyl benzencarboxylates (**11a-c**) by the reaction of 2-(hydroxymethyl)benzo[*d*]isothiazol-3(2*H*)-one (**7**) and benzoyl chloride derivatives (see Scheme 1) in good yield (66–72%). Their structures were characterized by means of ^{1}H NMR, MS, and elemental analysis.

The compounds **7** and **11a-c** were preliminarily tested in laboratory *in vitro* to evaluate their antimicrobial effect. The five bacterium used here include *Escherichia coli, Staphyloccus aurueus, Vibrio alginolyticus, Aeromonas hydrophila*, and *Bacillus subtilis*. We tested the antimicrobial activity using the viable cells plate count method as described in the literature [7,8].

Plate cultures were prepared as follows (g L^{-1}): 3 g beef, 5 g peptone, 5 g sodium chloride, 1 g yeast extract, and 18 g agar. The medium was dissolved completely and the pH value of the culture medium was adjusted to 7.2 with NaOH. And then the medium was autoclaved at 121°C and 20 psi for 15 min. The compounds synthesized in this article were dissolved in DMSO concentration in different concentration and then absolutely mixed with cultures (same as plate cultures except agar) containing bacteria. The mixture was homogenized in a laboratory homogenizer (IKA, MS2, minishaker, China) and serial dilutions were prepared, then 0.1 mL of each dilution was spread with a bent sterile glass rod on duplicate prepoured plates. After

Scheme 1. Synthesis route to the title compounds **7** and **11**.



11a, R^1=C_6H_5, **11b**, R^1= 4-FC_6H_4, **11c**, R^1= 3,5-$Me_2C_6H_3$

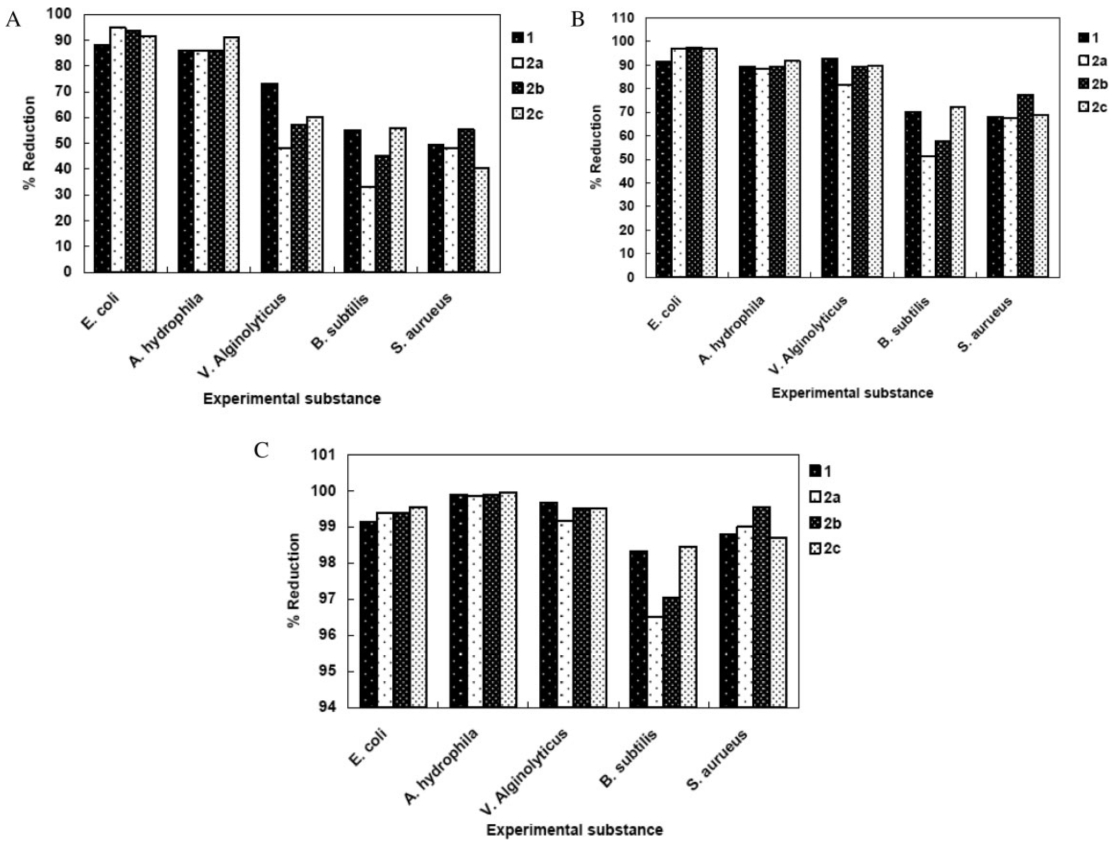


Figure 2. Microbial activity data of compounds **7** and **11a-c** in different concentration: 10^{-4} mg mL^{-1} (A), 10^{-3} mg mL^{-1} (B), 10^{-2} mg mL^{-1} (C), expressed as percent viable counting reduction.

24 h incubation at 28°C, colonies were counted. Pure DMSO (17 μL, 8.5% *v*/*v*) was used as negative control. The antimicrobial activity of the tested compounds (**11a-c**) was compared with compound **7** under similar culture conditions and has proved to be a good antimicrobial compound. Percent viable counting reduction was calculated using the following formula [9]:

$$100\% - \frac{\text{Experimental viable count}}{\text{DMSO viable count}} \times 100\% \qquad (1)$$

The antimicrobial activity of the synthesized compounds is shown in Figure 2. All the synthesized compounds showed certain antimicrobial activities against the tested bacterium. It is shown in Figure 2 that the microbial activity increased obviously with the increasing of the concentration of the compounds. When the concentration of the compounds is 10^{-4} mg mL^{-1} [Fig. 2(A)], the compounds showed good microbial activity against *Escherichia coli* and *Aeromonas hydrophila* with the viable cell reduction about 90%. When the compounds concentration reached 10^{-2} mg mL^{-1} [Fig. 2(C)], all the tested compounds showed excellent microbial activity against all the tested bacterium with the viable cell reduction >96.6%. Compared with compound **7** under similar culture conditions, the tested compounds (**11a-c**) showed equivalent or better antimicrobial activity. So the novel synthesized compounds should be potential microbial inhibitors.

CONCLUSION

In conclusion, we have achieved a short total synthesis of (3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)methyl benzencarboxylates (**11a-c**) in good yield and their microbial activities were evaluated against the aquicolous bacteria *Escherichia coli, Staphyloccus aurueus, Vibrio alginolyticus, Aeromonas hydrophila*, and *Bacillus subtilis*. The synthesized **11a-c** exhibited high-antimicrobial activity. These results will allow us to investigate the structure-activity relationships in more detail by using more various derivatives of 2-(hydroxymethyl)benzo[*d*]isothiazol-3(2*H*)-one (**7**) in the future.

EXPERIMENTAL

Melting points were determined with an Electrothermal-XT4-100 digital melting point apparatus. The ^{1}H NMR spectra were recorded on a Bruker AV-400 FT NMR spectrometer using

TMS as internal standard and DMSO-d_6 as solvent. The elemental analyses were performed with a Bruker DALTONICS analyzer. The MS spectra were taken on a HP-5988A spectrometer.

Procedure for preparation of 7. A mixture of benzoisothiazolone (3.02 g, 0.02 mol commercial from National Medicine Corporation, Shanghai of China), polyoxymethylene (5.28 g, 0.022 mol) in 10 mL of chloroform was refluxed for 5 h at 60°C under stirring. Compound **7** (3.13 g, 87%) was obtained by the usual work-up of the reaction mixture. The physical and spectral data of compound **7** were in accordance with the data reported by Morley *et al.* [4].

General procedure for the synthesis of (3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)methyl benzencarboxylates 11a-c. To the stirred and cooled solution of compound **7** (1.81 g, 10 mmol), triethylamine (1.22 g, 11 mmol) in 20 mL of acetone (dried before used) with ice-water bath, benzoyl chloride (1.41 g, 10 mmol) was added dropwise. The colorless precipitates were obtained as soon as by addition of benzoyl chloride. When benzoyl chloride was added completely, the ice-water bath was removed and the resulting mixture was continuously refluxed for 2 h with stirring. After the reaction quenched, the reaction mixture was concentrated under reduced pressure, and purified by column chromatography on silica gel (petroleum ether:ethyl acetate = 3:1) to gave pure crystals of **11a**, mp 114–116°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 6.15 (s, 2H, CH_2), 7.27~7.87 (m, 9H, Ar-H); GC-MS (ESI) *m*/*z*: 285 (M^+), 256, 164, 136, 105, 77; *Anal.* Calcd. for $C_{15}H_{11}NO_3S$: C, 63.14; H, 3.89; N, 4.91; Found: C, 62.87; H, 3.46; N 4.88.

(3-Oxobenzo[d]isothiazol-2(3H)-yl)methyl 4-fluorobenzencarboxylate (11b). This compound (2.18 g, 72%) was obtained as crystals, mp 95–96°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 6.14 (s, 2H, CH_2), 7.07~7.85 (m, 9H, Ar-H); MS (ESI) *m*/*z*: 303.3(M^+); *Anal.* Calcd. for $C_{15}H_{10}FNO_3S$: C, 59.40; H, 3.32; N, 4.62; Found: C, 59.10; H, 3.39; N, 4.57.

(3-Oxobenzo[d]isothiazol-2(3H)-yl)methyl 3,5-dimethylbenzencarboxylate (11c). This compound (2.16 g, 69%) was obtained as crystals, mp 109–111°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.27 (m, 6H, $2CH_3$), 6.10 (s, 2H, CH_2), 7.07~7.79 (m, 7H, Ar-H); MS (ESI) *m*/*z*: 313.4 (M^+); *Anal.* Calcd. for $C_{17}H_{15}NO_3S$: C, 65.16; H, 4.82; N, 4.47; Found: C, 64.96; H, 4.45; N 4.41.

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A Palladium Catalyzed New Synthesis of *N,N*-Dimethyl[1,8]-naphthyridine-2-amines: Facile Incorporation of *N,N*-Dimethylamino Group From DMF in Aqueous Medium

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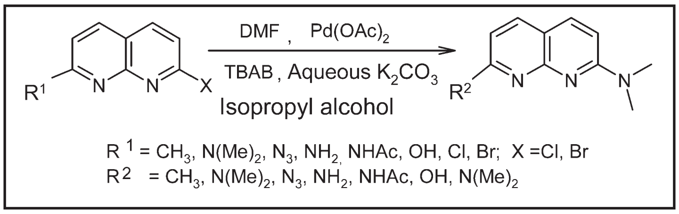

Here we report Pd catalyzed synthesis of *N,N*-dimethyl[1,8]naphthyridine-2-amines by facile incorporation of N(Me)$_2$ group from DMF in moderate to good yield.

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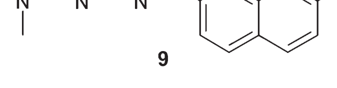
INTRODUCTION

Naphthyridine system is of great importance because of their broad applications in medicine. 1,8-Naphthyridine or naphthyridone systems are potentially useful as antihypertensives, antitumor agents, immunostimulants, and herbicide safeners. Also, *N,N*-dimethyl amino substituted 1,8-naphthyridines act as diuretic agents [1]. *N,N*-Dimethylamino group is present in methylene blue, crystal violet, 4-*N,N*-dimethylaminopyridine *etc*. (which are both biologically and chemically important compounds) [2]. In addition to palladium catalyzed C—C homo and hetero coupling reactions of aryl halides [3], it has been emerging as a powerful approach for the C—N coupling reactions [4,5]. Hawes *et al*. [1d] were able to incorporate the *N,N*-dimethylamino group in 1,8-napthyridines by treatment with gaseous dimethylamine. Palladium catalyzed aminocarbonylation using formamides as the amine source is also reported [5c]. With this information, we became interested to explore the reactions capable of introducing *N,N*-dimethylamino group in halo[1,8]naphthyridine systems.

RESULTS AND DISCUSSION

In our attempt to synthesize *N,N*-dimethylamino substituted 1,8-naphthyridines, we have carried out the reaction at room temperature with *N,N*-dimethylamine for direct replacement of halides but it does not work. Even under refluxing condition, the reaction does not proceed. The reaction is then carried out in the presence of Pd(OAc)$_2$ at room temperature and then it is also refluxed but the reaction fails. We then intended to change to *N,N*-dimethylformamide to see whether it may be a possible source of *N,N*-dimethylamino group by use of palladium catalysis. By several attempts, the reaction of one mmol of halo-napthyridine using DMF (0.95 mL), aqueous K$_2$CO$_3$ (1 mmol in 0.35 mL of water), TBAB (0.5 mmol), and Pd(OAc)$_2$ (0.05 mmol) at room temperature does not proceed but under reflux at 115°C, the reaction is successful with moderate to high yield (Table 1). The reaction rate and the yields are increased by the addition of isopropyl alcohol due to acceleration in the generation of Pd (0) [3g]. Although this method is similar to carbon-carbon homo-coupling reaction as reported by Lamaire, [3g] we are able to isolate only in one case the carbon-carbon homo-coupled yellow crystalline product *N,N,N′,N′*-tetramethyl-3,3′-bi-[1,8]-naphthyridin-7,7′-diamine **9** from (7-chloro-[1,8]-napthyridin-2-yl)-dimethylamine **2**.

Although various types of palladium catalyzed amination reactions are known [4], the incorporation of *N,N*-dimethylamino group is not hitherto reported from DMF in the [1,8]-naphthyridine system. So we report for the first time the incorporation of *N,N*-dimethylamino group from DMF under this reaction condition in the variously substituted [1,8]-napthyridines (Table 1). In the other aryl halides including pyridine halides homocoupled products result as reported in the literature [3g].



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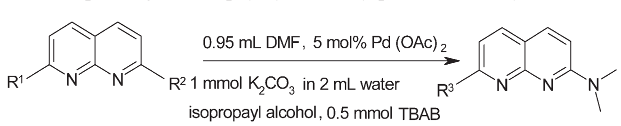
Scheme 1. Synthesis of *N*,*N*-dimethyl-1,8-naphthyridin-2-amines from the corresponding halo-naphythyridines by palladium catalysis.



In Table 1, entry 8, 7-bromo-1*H*-[1,8]naphthyridine-2-one **8** is represented as the enol-form for convenience but it is actually present in the lactam form.

The yield of the products increases as the number of chlorine atoms decreases from **5** to **7** which may be due to the C—Cl bond strength. In case of 2,7-dichloro-1,8-naphthyridine **5**, after 4 h reflux, mono- and disubstituted products **2** and **2a** are, respectively, formed with the same ratio but after 8 h no mono substituted product **2** is found. For mixed bromo chloro napthyridine **7**, the same result is observed where bromo group is always substituted but not chloro, which may be due to the lower bond strength of C—Br bond than C—Cl bond. The starting chloro and bromo derivatives are made according to the literature procedure [6,7].

EXPERIMENTAL

Representative experimental procedure for *N*-(7-dimethyl amino[1,8]naphthyridin-2-yl)acetamide 4a. In a round-bottomed flask, a mixture of *N*-(7-chloro-[1,8]naphthyridin-2-yl)-acetamide **4** (170 mg, 0.813 mmol), $Pd(OAc)_2$ (11.3 mg, 0.05 mmol), K_2CO_3 (112 mg, 0.813 mmol), TBAB (130.1 mg, 0.4065 mmol), water (0.8 mL), DMF (1.5 mL), and 2 mL of isopropyl alcohol is taken and refluxed for 7.5 h under nitrogen atmosphere. The whole solution is then passed through a celite bed (2 cm), washed well with isopropyl alcohol, the filtrate is then evaporated under reduced pressure and washed well with brine followed by water. The organic layer is then dried with Na_2SO_4 (anhydrous) and evaporated under reduced pressure followed by column chromatography using 2% methanol in CH_2Cl_2 offering the corresponding *N*,*N*-dimethylamino derivative, *N*-(7-dimethylamino-[1,8]naphthyridin-2-yl)-acetamide **4a** as yellow crystals. mp. 214–216°C; IR (KBr): 3219, 3062, 1692, 1609, 1326, 1151, 834, 796.45 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.349 (bs, 1H), 8.094 (d, 1H, J = 8.5 Hz), 7.914(d, 1H, J = 8.5 Hz), 7.786 (d, 1H, J = 9.0Hz), 6.827 (d, 1H, J = 9.0Hz), 3.266 (s, 6H), 2.215 (s, 3H); ms (ESI) *m*/*z* 244.97 (M^++H+Na, 100), 497.97 (2M+H+Na, 80). Anal. Calcd. for $C_{12}H_{14}N_4O$: C, 62.59; H, 6.13; N, 24.33. Found: C, 62.56; H, 6.16; N, 24.37.

Methyl(7-methyl[1,8]napthyridin-2-yl)amine 1a. mp. 140–142°C; IR (KBr): 1665, 1348, 1153, 842, 782 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.99 (d, 1H, J = 9.04 Hz), 7.98 (d, 1H, J = 7.96 Hz), 7.07 (d, 2H, J = 8.48 Hz), 3.17 (s, 6H), 2.55 (s, 3H). ms (ESI): *m*/*z* 188.3 (M^++ 1, 100), (M^++ 2, 10). Anal. Calcd. for $C_{11}H_{13}N_3$: C 70.56; H, 7.00; N, 22.44. Found: C 70.58; H, 7.03; N, 22.40.

***N*,*N*,*N*′,*N*′-Tetramethyl[1,8]naphthyridine-2,7-diamine 2a.** mp. 155–157°C; IR (KBr): 2928, 1540, 1379, 1148, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.61 (d, 2H, J = 8.9 Hz), 6.54 (d, 2H, J = 8.9 Hz), 3.23 (s, 12H). ms (ESI): *m*/*z* 217.3 (M^++ 1, 100), 218.1 (M^++ 2, 15). Anal. Calcd. for $C_{10}H_{10}N_6$: C, 66.64; H, 7.46; N, 25.90. Found: C, 66.66; H, 7.43; N, 25.94.

(7-Azido[1,8]naphthyrin-2-yl)dimethylamine 3a. mp. 135–137°C; IR (KBr): 2927, 2122, 1531, 1354, 1148, 900, 739 cm^{-1}; ^1H NMR (d_6-DMSO, 400 MHz): δ 8.15 (d, 1H, J = 8.2 Hz), 8.08 (d, 1H, J = 9.2 Hz), 7.21 (d, 1H, J = 8.3 Hz), 7.18 (d, 1H, J = 9.1 Hz), 3.29 (s, 6H). Anal. Calcd. for $C_{10}H_{10}N_6$: C, 56.07; H, 4.71; N, 39.23. Found: C, 56.05; H, 4.68; N, 39.26.

7-Dimethylamino-1*H*-[1,8]naphthyridin-2-one 5a. mp. 118–120°C; IR (KBr): 2931, 1659, 1612, 1370, 1150, 830 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.92 (bs, 1H), 7.56 (d, 1H, J = 9 Hz), 7.51 (d, 1H, J = 9 Hz), 6.46 (d, 1H, J = 8.7 Hz), 6.32 (d, 1H, J = 9.0 Hz), 3.16 (s, 6H), ms (ESI): *m*/*z* 212.1 (M^++Na, 67), 401.1 ($2M^+$+Na, 100). Anal. Calcd. for $C_{10}H_{11}N_3O$: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.44; H, 5.91; N, 22.18.

***N*,*N*,*N*′,*N*′-Tetramethyl-3,3′-bi[1,8]naphthyridin-7,7′-diamine 9.** mp > 300°C, IR (KBr): 1615, 1529, 1378, 1121, 844 cm^{-1}; ^1H NMR (CDCl3, 400 MHz): δ 8.65 (d, 1H, J = 8.2 Hz), 8,05 (d, 1H, J = 8.2 Hz), 7.88 (d, 1H, J = 9.0 Hz), 6.95 (d, 1H, J = 9.0 Hz). ms (ESI): *m*/*z* 345.4 (M^++H, 65), 376.5 (M^++HCl, 100). 376.5 (M^++H+HCl, 70). Anal. Calcd.

Table 1

Synthesis of *N*,*N*-dimethyl-1,8-naphthyridines from the corresponding halo-naphthyridines by palladium catalysis.

Entry	Reactant	Product	Time (h)	Yield (%)
1	R^1 = CH_3, R^2 = Br (**1**)	R^3 = CH_3 (**1a**)	5	75
2[a,b]	R^1 = $N(Me)_2$, R^2 = Cl (**2**)	R^3 = $N(Me)_2$ (**2a**)	6	30
3	R^1 = N_3, R^2 = Cl (**3**)	R^3 = N_3 (**3a**)	5.5	70
4	R^1 = NHAc, R^2 = Cl (**4**)	R^3 = NHAc (**4a**)	7.5	55
5	R^1 = Cl, R^2 = Cl (**5**)	R^3 = $N(Me)_2$ (**2a**)	8	58
6	R^1 = Cl, R^2 = Br (**6**)	R^3 = $N(Me)_2$ (**2a**)	6.5	65
7	R^1 = Br, R^2 = Br (**7**)	R^3 = $N(Me)_2$ (**2a**)	6	70
8	R^1 = OH, R^2 = Br (**8**)	R^3 = $N(Me)_2$ (**5a**)	12	72

[a] In this case dehydro halogenated product is obtained in 20% yield. All reactions are carried out at 115°C, $Pd(OAc)_2$ (0.05 mmol), K_2CO_3 (1 mmol in 0.35 mL of water), TBAB (0.5 mmol), and 2 mL of isopropyl alcohol with respect to 1 mmol of the naphthyridine halide.

[b] Also C—C coupled product *N*,*N*,*N*′,*N*′-tetramethyl-3,3′-bi-[1,8]-naphthyridine-7,7′-diamine **9** is isolated in 15% yield.

for $C_{20}H_{20}N_6$: C, 69.75; H, 5.85; N, 24.40. Found: C, 69.78; H, 5.80; N, 24.44.

Preparation of 2-bromo-7-methyl[1,8]naphthyridine 1. In a round-bottomed flask, hydrobromic acid (0.624 mL 48%, 5.65 mmol) is taken. The flask is cooled to 0°C by ice-salt bath and then 7-methyl-[1,8]-napthyridin-2-yl-amine (200 mg, 1.257 mmol) is added to it over a period of 10 min. Then bromine [0.194 mL (0.464 mg), 3.77 mmol] is added dropwise carefully maintaining the temperature at 0°C. After addition of bromine, $NaNO_2$ (216.66 mg, 3.14 mmol) in water (0.31 mL) is added for a period of 1.5 h. Here, the temperature of the reaction should be maintained at 0°C to −5°C. After addition is complete, it is stirred for 30 min. The precipitate obtained is filtered and finally washed well with water to make it acid-free and the mother liquor is collected and neutralized with NaOH adding crushed ice and then it is extracted with CH_2Cl_2 (4 × 25 mL) and is dried with anhydrous Na_2SO_4. The solvent is removed by evaporation under reduced pressure. This crude product is pure enough to be crystallized to afford white microcrystals of the title compound **1**, 215 mg (77%). mp. 202–205°C, IR (KBr): 2931, 1277, 1150, 545 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.07 (d, 1H, $J = 9.33$ Hz), 7.97 (d, 1H, $J = 8.4$ Hz), 7.58 (d, 1H, $J = 8.1$ Hz), 7.41 (d, 1H, $J = 8.1$ Hz), 2.80 (s, 3H), ms (ESI): m/z 244.96 (M^++Na, 100), 246.97 (M^++Na+2, 98). Anal. Calcd. for $C_{20}H_{20}N_6$: C, 48.46; H, 3.16; N, 12.56. Found: C, 48.51; H, 3.12; N, 12.58.

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Vilsmeier–Haack Formylation of Acetonitrile Revisited: Synthesis of Novel Pyrazolo[1,5-*a*]pyrimidines and Triazolo[1,5-*a*]pyrimidine

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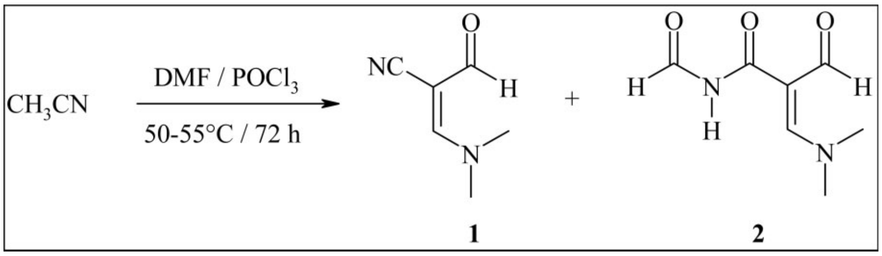

Vilsmeier–Haack formylation of acetonitrile using dimethylformamide and phosphorus oxychloride leading to a novel intermediate, *N*-((*E*)-3-(dimethylamino)-2-formylacryloyl)formamidine **2** and its utility in the synthesis of pyrimidine-fused heterocycles such as pyrazolo[1,5-*a*]pyrimidines and triazolo[1,5-*a*]pyrimidine is reported.

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INTRODUCTION

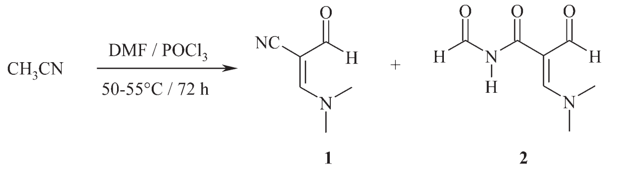
The synthesis of pyrazolo[1,5-*a*]pyrimidines is a promising avenue of research owing to various bioactivities displayed by this class of compounds. They have been established as selective inhibitors of adenosine cyclic mono phosphate (cAMP) phosphodiesterase *in vitro* [1,2]. In addition to this some of these compounds showed antischistosomal activity [3]. Another class of compounds, [1,2,4]triazolo[1,5-*a*]pyrimidine derivatives are promising inhibitors against trypanosomatid parasites [4], displaying inhibition percentages far higher than those reached with traditional drugs used against *T. cruzi* and *L. donovani*, such as ketoconazole [5], pentavalent antimonials [6], nitroimidazole, and itraconazole [7].

Vilsmeier–Haack formylation has emerged as a powerful tool for the formylation of various organic compounds. In 1970, Reichardt and Kermer [8] demonstrated the synthesis of 3-dimethylamino-2-formyl acrylonitrile **1** *via* the Vilsmeier–Haack formylation of acetonitrile. However, after intensive investigation of the same reaction we have achieved two products, *i.e.*, 3-dimethylamino-2-formyl acrylonitrile **1** and an unusual product *N*-((*E*)-3-(dimethylamino)-2-formylacryloyl)formamidine **2** (Scheme 1). From literature, it was noted that the related synthons have been used for the synthesis of pyrimidines and condensed pyrimidines [9–12]. Previously, we have used compound **1** for the synthesis of different annulated heterocycles [13,14]. Considering the synthetic utility of Compound **1** [15–17] and our interest in this area [18–20] prompted us to perform various condensation reactions of **2** with 5(3)amino heterocycles. We herein report the synthesis of an unexpected compound, *N*-((*E*)-3-(dimethylamino)-2-formylacryloyl) formamidine **2** and its utility in the synthesis of pyrimidine-fused heterocycles such as pyrazolo[1,5-*a*]pyrimidines and triazolo[1,5-*a*]pyrimidine.

RESULTS AND DISCUSSION

The Vilsmeier–Haack formylation of acetonitrile was carried out by Reichardt and Kermer by refluxing the reaction mixture of acetonitrile, DMF, and phosphorus oxychloride (1:0.6:0.6 mol) to furnish 3-dimethylamino-2-formyl acrylonitrile **1** in 10–12% yield. The same reaction carried out by us resulted in the formation of two products **1** and **2**. Encouraged by these results, we optimized the reaction conditions using different molar ratios of DMF and phosphorus oxychloride with respect to acetonitrile (Table 1). The ratio of molar equivalents played an important role in the formation of compounds **1** and **2**. Thus, the best results were obtained when a mixture of acetonitrile, DMF, and phosphorus oxychloride (1:3:3 mol) was heated to 50–55°C for 72 h. The reaction mixture was then poured into ice and neutralized with sodium hydrogencarbonate. The resultant

Scheme 1. Vilsmeier–Haack formylation of acetonitrile leading to a novel intermediate **2**.



suspension was extracted with dichloromethane. The organic layer was dried and concentrated under vacuum to give crude product, which was then recrystallized from ethanol to afford a pale yellow solid, *i.e.*, compound **2** in 25% yield. The aqueous layer was concentrated under vacuum to a semisolid, which on recrystallization with ethanol furnished compound **1** in 20% yield. Compound **1** gave satisfactory spectral and physical data and was identical with that of reported earlier [8].

The structure of compound **2** was deduced from its ^{1}H and ^{13}C NMR spectra. The mass spectrum of **2** displayed the molecular ion (M^{+}) peak at 170 *m*/*z,* which is consistent with the molecular weight of **2**. The ^{1}H NMR spectrum of **2** showed singlet at δ 8.03 representing olefinic proton, doublet at δ 9.10 corresponding to aldehyde proton neighboring to —NH of amide. The singlet at δ 9.31 represented another aldehyde proton. The other signals appeared at δ 3.20 (s, 3H, NCH_3) and 3.40 (s, 3H, NCH_3). The —NH proton appeared at δ 11.43 as abroad singlet.

We observed that Vilsmeier–Haack formylation of acetonitrile with the optimized reaction conditions furnished two compounds with different yields. The structure of compound **2** was also supported by further nucleophilic substitution reaction with 5(3)-amino heterocycles. Thus condensation of compound **2** with 5(3)-amino pyrazoles **3a-c** furnished pyrazolo[1,5-*a*]pyrimidines **4a-c** in (Scheme 2, Table 2) 75–80% yield. During condensation of **2** with **3a-c** it was observed that the *N*-formyl group in **2** undergoes hydrolysis to amido function in **4a-c**. The condensation of **2** with pyrimidine-2-carboxamidine **5** furnished 2-(pyrimidine-2-yl)pyrimidine-5-carboxamide **6** (Scheme 3) in 80% yield. Similarly, 1,2,4 triazolo[1,5-*a*]pyrimidine-6-carboxamide **8** (Scheme 4) was synthesized in 82% yield from the reaction of 5(3)-amino[1,2,4]triazole **7** with **2**. The structure of the compounds **4**, **6**, and **8** were determined from spectroscopic data. Several attempts to cyclize **2** with 2-amino heterocycles **9a-e** did not lead to the desired product (**11a-e**). However, compound **2** on condensation with 2-aminopyridines or 2-aminopyrimidine in ethanol at reflux temperature furnished open chain compounds **10a-e** in 75–80% yield (Scheme 5, Table 3). It was interesting to observe that, the condensation of **2** with *o*-phenylenediamine **12** under similar reaction conditions furnished open chain compound **13** with the *N*-formyl group remaining intact (Scheme 6). Attempts to cyclize compound **12–14** were unsuccessful.

To conclude the Vilsmeier–Haack formylation of acetonitrile with optimized reaction conditions leads to a highly stable synthone *N*-((*E*)-3-(dimethylamino)-2-formyl acryloyl)formamide **2** which can further be used for the synthesis of various new heterocycles. Herein, we have reported the synthesis of some pyrazolopyrimidines and triazolopyrimidines. These heterocycles can exhibit a number of bioactivities specifically inhibitory action against cAMP phosphodiesterase. Biological investigations are in progress in our laboratory and shall be reported in a due course.

EXPERIMENTAL

Melting points were determined on a Buchi melting point apparatus, Mod. B-545 and are uncorrected. The ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian XL-300 spectrometer. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane, and multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplate). The solvent for NMR spectra was DMSO-d_6 unless otherwise stated. Infrared spectra were taken on Thermo Electron Corporation NICOLET 380 FTIR

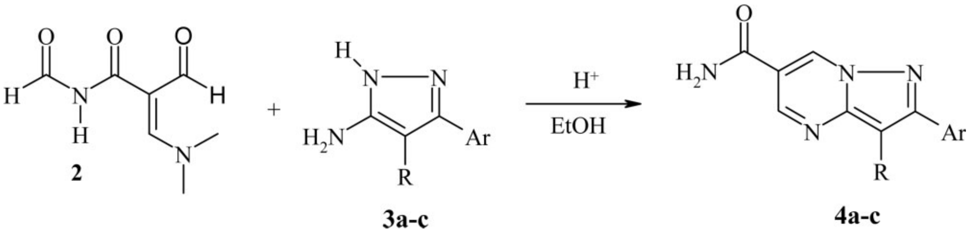
Table 1

Vilsmeier–Haack formylation of acetonitrile,[a] comparison of the product yield with the molar proportion.

Entry	CH_3CN (molar equiv.)	DMF (molar equiv.)	$POCl_3$ (molar equiv.)	Compound 1 Yield (%)[b]	Compound 2 Yield (%)[b]
1	1 mol	0.6 mol	0.6 mol	12.00%	02.50%
2	1 mol	1 mol	1 mol	11.50%	04.70%
3	1 mol	2 mol	2 mol	10.70%	11.90%
4	1 mol	1 mol	2 mol	04.00%	05.20%
5	1 mol	2 mol	1 mol	–	–
6	1 mol	3 mol	3 mol	20.00%	25.00%

[a] Carried out at 50–55°C for 72 h.

[b] Isolated yields.



Scheme 2. Synthesis of compound **4a-c**.

instrument in potassium bromide pellets unless otherwise stated. Mass spectrum was recorded on Shimadzu GC-MS QP 2010A mass spectrometer with an ionization potential of 70 eV. Elemental analysis was performed on a Hosli CH-Analyzer and was within ±0.4 of the theoretical percentage. All reactions were monitored by thin layer chromatography, carried out on 0.2-mm silica gel 60 F-254 (Merck) plates using UV light (254 and 366 nm) for detection. Common reagent grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures.

***N*-((E)-3-(Dimethylamino)-2-formylacryloyl) formamidine (2).** To a stirred solution of acetonitrile (41.05 g, 1000 mmol) and DMF (219.30 g, 3000 mmol) at 0–5°C was added dropwise over 1.5 h phosphorus oxychloride (459.99 g, 3000 mmol). The mixture was stirred at 50–55°C for 72 h. It was then quenched in ice, neutralized with sodium hydrogencarbonate. The resultant suspension was extracted with dichloromethane (9 × 500 mL). The combined organic extractions were washed with saturated aqueous NaCl and dried. The solvent was evaporated under reduced pressure, and the solid residue was recrystallized from ethanol affording compound 2 as a pale yellow solid, 42.5 g (25%) (Table 1, Entry 6); m.p 145–147°C, IR (KBr): 3049, 2920, 1700, 1653, 1578, 1273, 1176, 840 cm^{-1}. ^{1}H NMR (300 MHz, DMSO): δ 11.43 (d, J = 6.9 Hz,1H, NH), 9.31 (s, 1H, CHO), 9.10 (d, J = 9.9 Hz,1H, NH—CHO), 8.03 (s, 1H, CH), 3.41 (s, 3H, N—CH$_3$), 3.21 (s, 3H, N—CH$_3$). ^{13}C NMR (75 MHz, DMSO): δ 186.8, 164.3, 163.5, 162.7, 101.7, 48.6, 43.3. *Anal*. Calcd. for $C_7H_{10}N_2O_3$ Calcd. C: 49.41; H: 5.92; N: 16.46. Found. C: 49.39; H: 5.90; N: 16.47.

General procedure for the synthesis of compound 4a-c, 6, 8, 10a-e and 13

2-(4-Bromo-phenyl)-pyrazolo[1,5-a]pyrimidine-6-carboxalic acid amide (4a). A mixture of 2 (0.5 g, 2.9 mmol), 3a (0.88 g, 3.7 mmol) in ethanol (2.5 mL) and catalytic amount of acetic acid was refluxed until the starting material had been consumed in the reaction (4–5 h, TLC monitoring). Reaction mass was then cooled to room temperature. The precipitated solid was collected by filtration and washed with cold ethanol to obtain the crude product which was then recrystallized from ethanol to give compound 4a as brown solid, 0.745 g (80%); mp 318–320°C. IR (KBr): 3371, 3179, 3033, 1651, 1614, 1452, 1396, 77 cm^{-1}. ^{1}H NMR (300 MHz, DMSO): δ 9.53 (d, J = 3.0 Hz, 1H, Ar-H), 8.91 (d, J = 3.0 Hz, 1H, Ar-H), 8.18 (bs, 1H, NH), 8.03 (d, J = 8.4 Hz, 2H, Ar-H), 7.74 (bs, 1H, NH), 7.70 (d, J = 8.70 Hz, 2H, Ar-H), 7.38 (s, 1H, Ar-H). ^{13}C NMR (75 MHz, DMSO): δ 163.7, 157.9, 148.6, 146.7, 134.9, 132.6, 132.1, 128.9, 127.3, 126.6, 124.2, 121.9, 85.5. *Anal*. Calcd. for $C_{13}H_9BrN_4O$ Calcd. C: 49.23; H: 2.86; N: 17.67. Found. C: 49.25; H: 2.80; N: 17.50.

Table 2

Synthesis of compounds **4a-c**[a].

Entry	3, 4	R	Ar	Time (h)	Yield (%)[a]
1	a	H	p-Br-C_6H_4	4	80
2	b	H	p-Cl-C_6H_4	5	75
3	c	CN	H	5	78

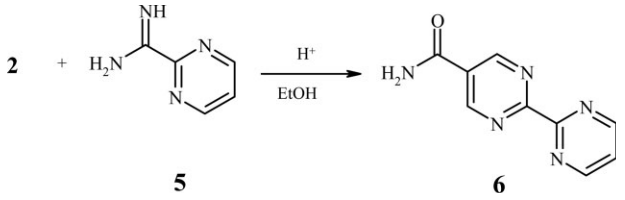
[a] Yield refer to those of pure isolated products characterized by spectroscopic data.

(4-Chloro-phenyl)-pyrazolo[1,5-a]pyrimidine-6-carboxalic acid amide (4b). Brown solid; Yield: 75%; mp 308–310°C. IR (KBr): 3373, 3178, 3035, 1651, 1614, 1453, 1396, 1614, 1097 cm^{-1}. ^{1}H NMR (300 MHz, DMSO): δ 9.52 (d, J = 1.5 Hz, 1H, Ar-H), 8.90 (d, J = 1.8 Hz, 1H, Ar-H), 8.18 (bs, 1H, NH), 8.08 (d, J = 8.7 Hz, 2H, Ar-H), 7.73 (bs, 1H, NH), 7.57 (d, J = 8.4 Hz, 2H, Ar-H), 7.36 (s, 1H, Ar-H). ^{13}C NMR (75 MHz, DMSO): δ 163.1, 157.6, 148.4, 146.0, 135.4, 132.4, 131.6, 128.6, 126.7, 126.1, 124.7, 122.1, 84.5. *Anal*. Calcd. for $C_{13}H_9ClN_4O$ Calcd. C: 57.26; H: 3.33; N: 20.55. Found. C: 57.20; H: 3.25; N: 20.50.

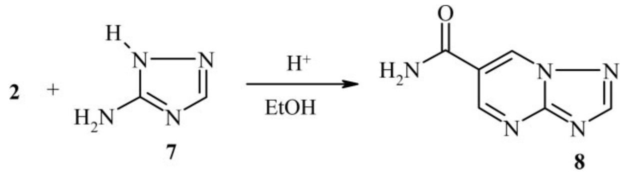
3-Cyano-pyrazolo[1,5-a]pyrimidine-6-carboxalic acid amide (4c). Yellow solid; Yield: 78%; mp 310–312°C. IR (KBr): 3395, 3328, 3058, 3121, 2235, 1674, 1624, 1421 cm^{-1}. ^{1}H NMR (300 MHz, DMSO): δ 9.74 (d, J = 2.1 Hz, 1H, Ar-H), 9.20 (d, J = 2.1 Hz, 1H, Ar-H), 8.94 (s, 1H, Ar-H), 8.33 (bs, 1H, NH), 7.93 (bs, 1H, NH). ^{13}C NMR (75 MHz, DMSO): δ 162.9, 152.8, 149.7, 149.0, 137.5, 117.9, 112.6, 81.5. *Anal*. Calcd. for $C_8H_5N_5O$ Calcd. C: 51.34; H: 2.69; N: 37.42. Found. C: 51.20; H: 2.55; N: 37.40.

2-(Pyrimidine-2-yl)pyrimidine-5-carboxamide (6). White solid; Yield: 80%; mp 315–317°C. IR (KBr): 3353, 3156, 3057,

Scheme 3. Synthesis of compound **6**.



Scheme 4. Synthesis of compound **8**.



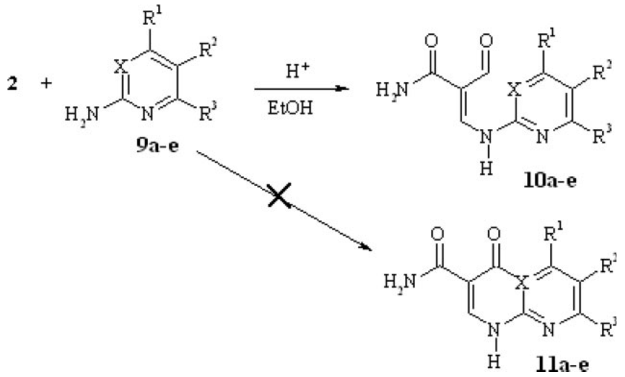
1713, 1626, 1403, cm^{-1}. ^{1}H NMR (300 MHz, DMSO): δ 9.34 (s, 2H, Ar-H), 9.04 (d, J = 4.8 Hz, 2H, Ar-H), 8.43 (bs, 1H, NH), 7.91 (bs, 1H, NH), 7.69 (t, J = 4.5Hz, 1H, Ar-H). ^{13}C NMR (75 MHz, DMSO): δ 169.2, 165.4, 164.1, 158.5, 157.9, 156.3, 155.4, 127.2, 115.6. *Anal*. Calcd. for $C_9H_7N_5O$ Calcd. C: 53.73; H: 3.51; N: 34.81. Found. C: 53.50; H: 3.62; N: 34.75.

[1,2,4]Triazolo[1,5-a]pyrimidine-6-carboxalic acid amide (8). Yellow solid; Yield: 82%; mp 235–237°C. IR (KBr): 3337, 3130, 3054, 1674, 1625, 1506, 1417 cm^{-1}. ^{1}H NMR (300 MHz, DMSO): δ 9.80 (d, J = 2.4 Hz, 1H, Ar-H), 9.25 (d, J = 2.1 Hz, 1H, Ar-H), 8.79 (s, 1H, Ar-H), 8.30 (bs, 1H, NH), 7.90 (bs, 1H, NH). ^{13}C NMR (75 MHz, DMSO): δ 163.2, 157.1, 154.9, 154.6, 137.2, 117.7. *Anal*. Calcd. for $C_6H_5N_5O$ Calcd. C: 44.17; H: 3.09; N: 42.93. Found. C: 44.20; H: 3.00; N: 42.80.

2-Formyl-3-(pyridine-2-ylamino)-acrylamide (10a). Pale yellow solid; Yield: 75%; mp 187–189°C. IR (KBr): 3371, 3057, 2873, 1666, 1628, 1594, 1408, 1152, 814, cm^{-1}. ^{1}H NMR (300 MHz, DMSO): δ 12.30 (d, J = 12.3 Hz, 1H, NH), 9.26 (s, 1H, CHO), 8.76 (d, J = 12.3 Hz 1H, CH), 8.39–8.30 (m, 1H, Ar-H), 8.29 (bs, 1H, NH), 7.88–7.82 (m, 1H, Ar-H), 7.57 (bs, 1H, NH), 7.45–7.41 (m, 1H, Ar-H), 7.23–7.18 (m, 1H, Ar-H). ^{13}C NMR (75 MHz, DMSO): δ 190.5, 168.1, 156.6, 149.9, 148.2, 139.1, 120.3, 112.3, 106.7. *Anal*. Calcd. for $C_9H_9N_3O_2$ Calcd. C: 56.54; H: 4.74; N: 21.98. Found. C: 56.44; H: 4.50; N: 21.70.

2-Formyl-3-(4-methyl-pyridine-2-ylamino)-acrylamide (10b). Yellow solid; Yield: 78%; mp 205–207°C. IR (KBr): 3342, 3166, 2756, 1676, 1611, 1587, 1556, 1413, 1151, 838 cm^{-1}. ^{1}H NMR (300 MHz, DMSO): δ 12.24 (d, J = 12.3 Hz, 1H, NH), 9.24 (s, 1H, CHO), 8.73 (d, J = 12.3 Hz 1H, CH), 8.30 (bs, 1H, NH), 8.23 (d, J = 5.1 Hz, 1H, Ar-H), 7.55 (bs, 1H, NH), 7.25 (s, 1H, Ar-H), 7.05 (dd, J = 0.9 and 4.2 Hz, 1H Ar-H), 2.33 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO): δ 190.5, 168.1, 156.6, 147.7, 121.4, 112.4, 106.5, 20.5. *Anal*. Calcd. for $C_{10}H_{11}N_3O_2$ Calcd. C: 58.53; H: 5.40; N: 20.48. Found. C: 58.65; H: 5.50; N: 20.35.

Scheme 5. Synthesis of compounds **10a-e**.



2-Formyl-3-(5-methyl-pyridine-2-ylamino)-acrylamide (10c). Yellow solid; Yield: 78%; mp 194–196°C. IR (KBr): 3371, 3190, 1644, 1601, 1491, 1394, 1209, 797 cm^{-1}. ^{1}H NMR (300 MHz, DMSO): δ 12.31 (d, J = 12.3 Hz, 1H, NH), 9.23 (s, 1H, CHO), 8.71 (d, J = 12.6 Hz 1H, CH), 8.32 (bs, 1H, NH), 8.21 (d, J = 0.9 Hz, 1H, Ar-H), 7.69–7.66 (m, 1H, Ar-H), 7.54 (bs, 1H, NH), 7.35 (d, J = 8.4 Hz, 1H Ar-H), 2.27 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO): δ 190.3, 168.2, 156.6, 147.9, 147.9, 139.5, 129.6, 111.8, 106.3, 17.3. *Anal*. Calcd. for $C_{10}H_{11}N_3O_2$ Calcd. C: 58.53; H: 5.40; N: 20.48. Found. C: 58.40; H: 5.45; N: 20.55.

2-Formyl-3-(6-methyl-pyridine-2-ylamino)-acrylamide (10d). Yellow solid; Yield: 80%; mp 192–194°C. IR (KBr): 3344, 3171, 2748, 1681, 1561, 1217, 809 cm^{-1}. ^{1}H NMR (300 MHz, DMSO): δ 12.26 (s, 1H, NH), 9.26 (s, 1H, CHO), 8.76 (bs, 1H, NH), 8.74 (d, J = 12.3 Hz 1H, CH), 7.58 (t, J = 7.8 Hz, 1H, Ar-H), 6.94 (d, J = 7.8 Hz, 1H, Ar-H), 6.73 (d, J = 8.4 Hz 1H, Ar-H), 5.55 (bs, 1H, NH), 2.52 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO): δ 189.9, 169.3, 158.2, 156.5, 148.9, 139.0, 120.1, 109.8, 106.4, 24.5. *Anal*. Calcd. for $C_{10}H_{11}N_3O_2$ Calcd. C: 58.53; H: 5.40; N: 20.48. Found. C: 58.45; H: 5.35; N: 20.45.

2-Formyl-3-(pyrimidine-2-ylamino)-acrylamide (10e). Off-white solid; Yield: 76%; mp 206–208°C. IR (KBr): 3360, 3177, 2764, 1677, 1654, 1576, 1560, 1205, 792 cm^{-1}. ^{1}H NMR (300 MHz, DMSO): δ 12.50 (d, J = 12.3 Hz, 1H, NH), 9.34 (s, 1H, CHO), 8.76–8.72 (m, 3H, CH, and Ar-H), 8.29 (bs, 1H, NH_2), 7.74 (bs, 1H, NH_2), 7.33 (t, J = 4.8 Hz, 1H, Ar-H). ^{13}C NMR (75

Table 3

Synthesis of compounds **10a-e**[a].

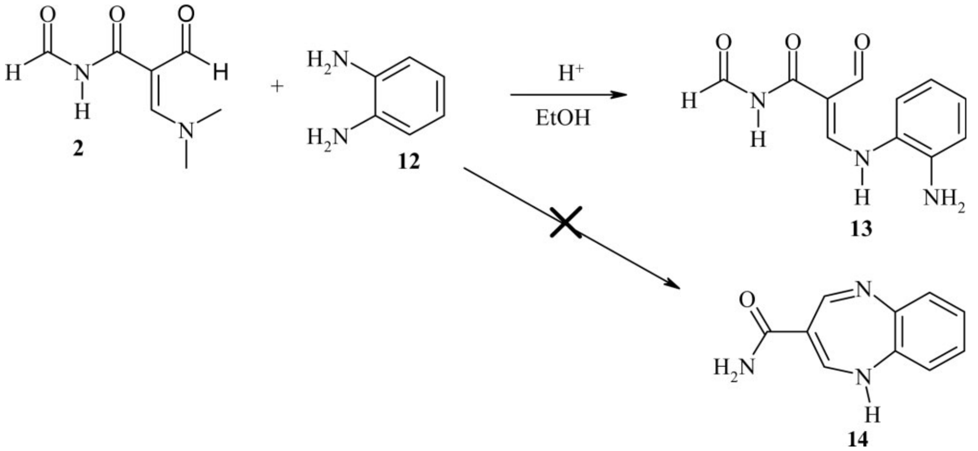
Entry	9, 10	R^1	R^2	R^3	X	Yield (%)[b]	Mp (°C)[c]
1	a	H	H	H	C	75	187–189
2	b	CH_3	H	H	C	78	205–207
3	c	H	CH_3	H	C	78	194–196
4	d	H	H	CH_3	C	80	192–194
5	e	H	H	H	N	76	206–208

[a] All spectroscopic data are compatible with the proposed structures.

[b] Isolated yields.

[c] Melting points are uncorrected.

Scheme 6. Synthesis of compound **13**.



MHz, DMSO): δ 191.1, 167.9, 158.9, 156.7, 155.5, 117.6, 107.9. *Anal*. Calcd. for $C_8H_8N_4O_2$ Calcd. C: 50.00; H: 4.20; N: 29.15. Found. C: 50.21; H: 4.00; N: 29.35.

(E)-3-(2-Aminophenylamino)-N, 2-diformylacrylamide (13). Yellow solid; Yield: 75%; mp 179–181°C. IR (KBr): 3366, 3200, 2855, 1700, 1631, 1489, 1471, 1195, 745 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 11.53 (d, J = 13.5 Hz, 1H, NH), 11.35 (d, J = 10.5 HZ, 1H, NH), 9.24 (s, 1H, CHO), 9.22 (d, J = 7.2 Hz, 1H, CHO), 8.54 (d, J = 13.8 Hz, 1H, CH), 7.35 (d, J = 6.9 Hz, 1H, Ar-H), 7.06 (t, J = 6.9 Hz, 1H, Ar-H), 6.87 (d, J = 6.6 Hz, 1H, Ar-H), 6.76 (t, J = 8.1 Hz, 1H, ArH), 5.16 (s, 2H, NH_2). ^{13}C NMR (75 MHz, DMSO): δ 190.3, 166.5, 162.2, 161.8, 140.3, 127.5, 126.2, 119.6, 118.2. *Anal*. Calcd. for $C_{11}H_{11}N_3O_3$ Calcd. C: 56.65; H: 4.75; N: 18.02. Found. C: 56.50; H: 4.80; N: 18.25.

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Reaction of 2-[(2-Oxo-2-arylethyl)anilino]-1-aryl-1-ethanones with *o*-Phenylenediamine: Formation of Quinoxalines

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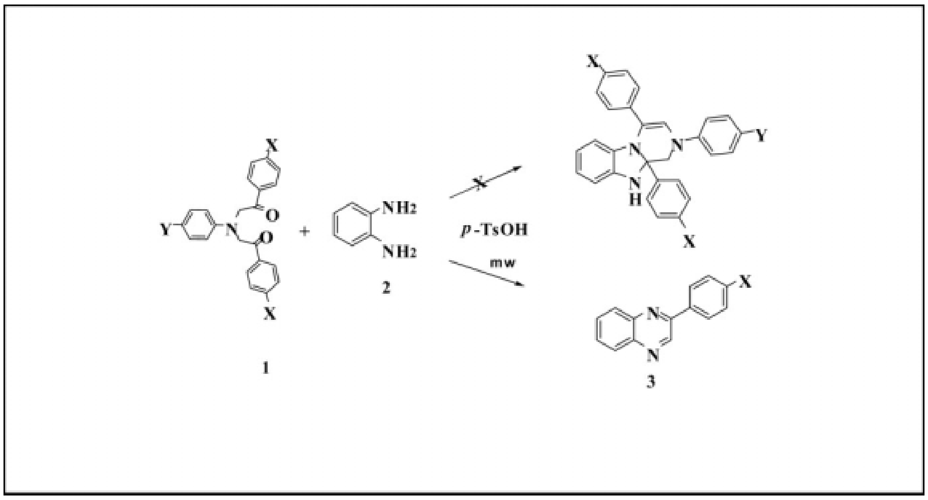

Unexpected quinoxalines (**3**) have been obtained from a one-pot reaction of 2-[(2-oxo-2-arylethyl)anilino]-1-aryl-1-ethanones (**1**) with *o*-phenylenediamine (**2**) in the presence of a catalytic amount of *p*-toluene sulfonic acid. The reaction presumably involves a tandem carbonyl addition—eliminative cyclization—air oxidation sequence.

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INTRODUCTION

Solvent-free approach using microwave irradiation opens numerous possibilities for conducting rapid heterocyclic synthesis *via* cyclocondensation reactions using a variety of supported reagents [1]. Generally, cyclocondensation reactions, where light polar molecules as water and alcohol are eliminated, constitute good candidates for microwaves. Furthermore, there are advantages of these solvent-free protocols with reduced reaction time and generally improved yields.

Nitrogen-containing heterocyclic compounds are indispensable structural units for both the chemist and the biochemist. In continuation of our work [2] on the chemistry of bis(aroylmethyl)anilines, which is relatively unexplored [3], herein, we report the condensation reaction of bis(aroylmethyl)anilines with 1,2-diaminobenzene. The reaction of diphenacyl aniline with 2-aminophenol and 2-aminothiophenol has led to diazine-fused benzheteroazole derivatives [4] (Fig. 1). In the same angle, the reaction of diphenacyl aniline with *o*-phenylenediamine is expected to give a related product. But unexpected quinoxaline is obtained as the major product in this reaction and the details are presented in this article.

RESULTS AND DISCUSSION

Hinsberg [5] reported that 2-bromoacetophenone gave directly 2-arylquinoxalines when reacted with *o*-phenylenediamine or *m*-tolylenediamine in boiling alcohol. He suggested that dihydroquinoxaline was an intermediate product which was readily oxidized by air to the corresponding quinoxaline. Buu-Hoi and Khoi [6] reported quantitative yields of 2-arylquinoxalines directly from the reaction of 2-bromo-3′-nitroacetophenone and 2-bromo-4′-nitroacetophenone with *o*-phenylenediamine in the presence of sodium acetate.

Quinoxalines constitute the basis of many insecticides, fungicides, herbicides, and anthelmintics, as well as being important in human health and as receptor antagonists [7]. There are numerous methods of preparing quinoxalines, but the double condensation of a 1,2-dicarbonyl compound and a 1,2-diaminoaromatic is commonly used [8]. This article describes the first report

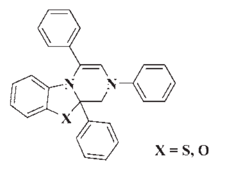
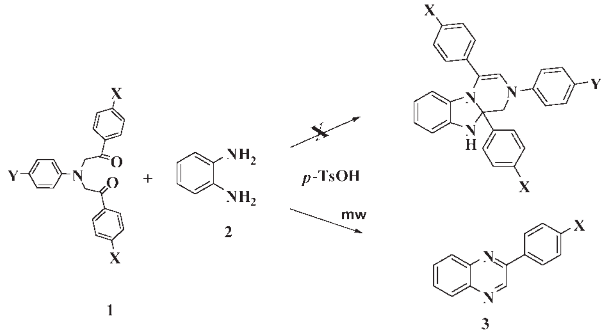


Figure 1. Benzheteroazoles.

of the formation of quinoxalines from 3-aza-1,5-diketones.

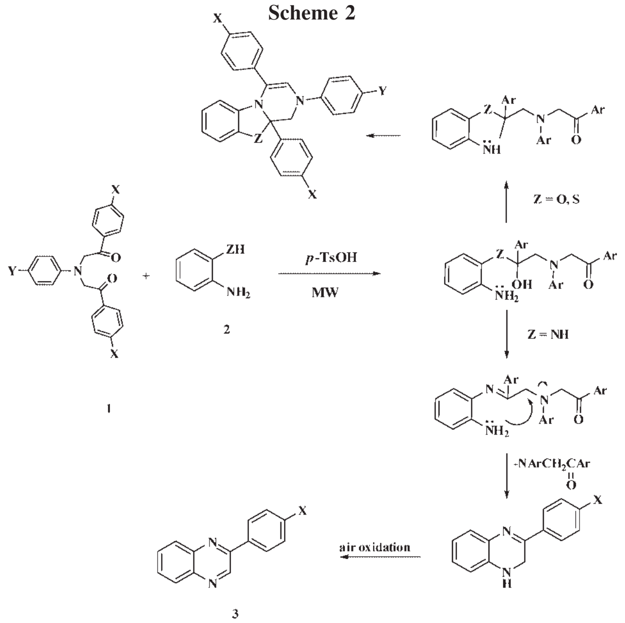
A mixture of *o*-phenylenediamine **2** with appropriately substituted diphenacyl aniline **1** was taken in a 1:1 molar ratio along with a catalytic amount of *p*-toluene sulfonic acid and ground well to ensure thorough mixing with no solvent. This mixture was placed in an open glass tube over a silica bath in a domestic microwave oven and irradiated for 10 min at 540 W. The major product **3** (Scheme 1) was isolated from the remaining mass of the reaction mixture by column chromatography and the product eluted first. Compound **3** was obtained in considerable yield and all the compounds were characterized by their NMR spectral data. The ^{1}H NMR spectrum of a representative compound, 2-(4-methylphenyl)quinoxaline (3, X = Me) showed the presence of one singlet at 2.38 ppm accounting for three hydrogen atoms. A two proton doublet is visible at 7.30 ppm (J = 8.4 Hz) and a six proton multiplet appears in the region 7.65–8.18 ppm. There is a singlet appearing downfield, 9.24 ppm. The ^{13}C NMR spectrum of this compound has signals at 20.4, 126.4, 128.0, 128.2, 128.5, 128.8, 129.2, 133.0, 139.5, 140.4, 141.3, 142.3, and 150.8 ppm. The data are very much consistence with 2-arylquinoxaline. Thus the major compound **3** formed in the reaction is unexpected 2-arylquinoxalines, which has been confirmed by comparing with an authentic sample of 2-phenylquinoxaline.

Scheme 1



Starting compound	X	Y	Percentage Yield of **3**
1a	H	H	68
1b	Cl	H	73
1c	Me	H	65
1d	Cl	Me	70
1e	Me	Me	75
1f	Me	OMe	70

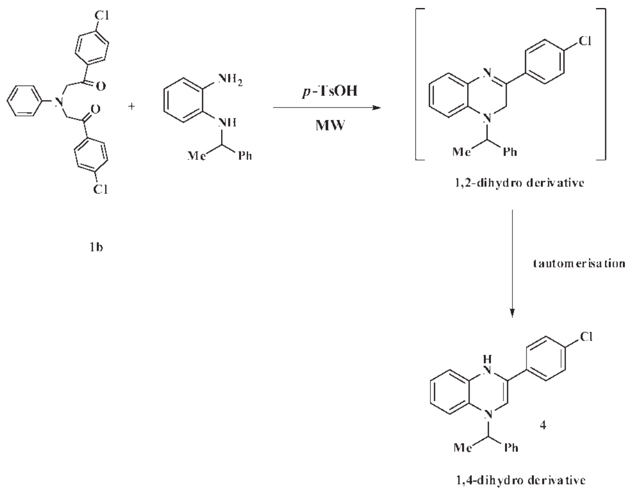
Scheme 2



The quinoxalines **3** presumably arise from a tandem sequence of reactions and the mechanism (Scheme 2) envisages an acid catalyzed imine formation followed by the attack of amino group on the methylene carbon—not on the imino carbon—displacing $NPhCH_2COPh$ group. This is contrary to the case of the reaction **1** with 2-aminophenol and 2-aminothiophenol. There the initial attack by the nucleophilic center SH or OH on the electrophilic carbonyl gives a tertiary alcohol and the nitrogen of the amino group attacks this carbon center, displacing hydroxyl group (probably *via* the initially formed carbocation with the help of *p*-toluene sulphonic acid). But in the present case, the initially formed tertiary alcohol undergoes 1,2-elimination forming an imine. Now the second nitrogen of the amino group does not attack this imino carbon rather attacks the methylene carbon displacing $NPhCH_2COPh$ group (again aided by *p*-toluene sulphonic acid through protonation of the leaving group, thus increasing its leaving group ability).

With the successful optimization results in hand, we investigated the scope of this process to another substituted diamine, *N*-(1-phenylethyl)-1,2-diaminobenzene.

Scheme 3



When the reaction is carried out with substituted 1,2-diaminobenzene, *N*-(1-phenylethyl)-1,2-diaminobenzene, prepared from 2-chloronitrobenzene and dl-phenylethylamine, the final oxidation step shown in Scheme 2 is not possible and the 1,2-dihydroquonoxaline can be expected. Hence, the proposed reaction of **1b** with *N*-(1-phenylethyl)-1,2-diaminobenzene was carried out under identical condition as depicted in Scheme 2. The reaction proceeds smoothly giving a product **4** (Scheme 3). The ^{1}H NMR spectrum has a three hydrogen doublet and one hydrogen multiplet at 1.85 ppm and 4.63 ppm, respectively. In the aromatic/olefinic region, there are 14 hydrogen resonances. In the ^{13}C NMR spectrum, there are signals at 22.2 and 43.9 ppm apart from 16 signals in the olefinic/aromatic region. There is no methylenic carbon or hydrogen. Thus the ^{1}H NMR and ^{13}C NMR spectra of the compound **4** clearly suggest the structure to be a 1,4-dihydroquinoxazine and not a 1,2-dihydroquinoxazine. It is surprising that the 1,2-dihydro system obtained has rearranged to a 1,4-dihydro system.

Even in the case of **3**, it is probable that if the air oxidation is prevented, then the 1,2-dihydro system would have not been isolated and the 1,4-dihydro system would have been obtained.

EXPERIMENTAL

All chemicals were of reagent grade quality and used without further purification. All melting points were recorded in open capillaries and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 300 MHz spectrometer at 300 and 75 MHz respectively in CDCl$_3$ using TMS as internal standard. The related 2D NMR spectra also recorded on the same instrument. Chemical shifts are given in parts per million (δ-scale) and coupling constants are given in hertz.

General procedure for the preparation of 2-arylquinoxaline (3). A mixture of 2-[(2-oxo-2-arylethyl)anilino]-1-aryl-1-ethanone **1** (0.0015 mol), 1,2-benzenediamine (0.2 g, 0.0015 mol) and catalytic amount of *p*-toluenesulfonic acid was irradiated in an open glass tube over a silica bath in a domestic microwave oven and irradiated for 10 min at power level 5 (540 W). The reaction mixture was treated with water and then extracted with dichloromethane. The organic layer was washed with water repeatedly and dried over anhydrous calcium chloride and evaporated to give the crude product. Purification of the product was performed by column chromatography on silica gel using petroleum ether-ethyl acetate [97:3 (*v*/*v*)] mixture as eluent. The signal due to NH hydrogen is so broad that it is not visible in these compounds. However, when exchanged with D$_2$O, the HOD peak appears confirming the presence of NH signal.

2-Phenylquinoxaline (3, X = H). This compound was obtained as colorless solid, mp, 79°C (Lit. m.p. 76–77°C [9]); ^{1}H NMR (300 MHz, CDCl$_3$): 7.51–7.56 (m, 3H), 7.73–7.82 (m, 2H), 8.11–8.22 (m, 4H), 9.3 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): 127.5 (d), 129.0 (d), 129.1 (d), 129.5 (d), 129.6 (d), 130.1 (d), 130.3 (d), 136.7 (s), 141.5 (s), 142.2 (s), 143.3 (d), 151.8 (s).

2-(4-Chlorophenyl)quinoxaline (3, X = Cl). This compound was obtained as colorless solid, mp, 128°C (Lit. m.p. 137°C [10]); ^{1}H NMR (300 MHz, CDCl$_3$): 7.53–7.56 (m, 2H), 7.78–7.83 (m, 2H), 8.15–8.18 (m, 4H), 9.3 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): 129.2 (d), 129.5 (d), 129.8 (d), 129.9 (d), 130.2 (d), 130.8 (d), 135.5 (s), 137.0 (s), 142.0 (s), 142.6 (s), 143.3 (d), 151.0 (s).

2-(4-Methylphenyl)quinoxaline (3, X = Me). This compound was obtained as colorless solid, mp, 92°C (Lit. m.p. 94°C [10]); ^{1}H NMR (300 MHz, CDCl$_3$): 2.38 (s, 3H); 7.30(d, 2H, J = 8.4 Hz); 7.65–7.73 (m, 2H); 8.02–8.08 (m, 4H); 9.24 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): 20.4 (q), 126.4 (d), 128.0 (d), 128.2 (d), 128.5 (d), 128.8 (d), 129.2 (d), 133.0 (s), 139.5 (s), 140.4 (s), 141.3 (s), 142.3 (d), 150.8 (d).

3-(4-Chlorophenyl)-1-(1-phenylethyl)-1,4-dihydroquinoxaline (4). This compound was obtained as yellow solid, yield 68%, mp, 146°C; ^{1}H NMR (300 MHz, CDCl$_3$): 1.85 (d, J = 6.9 Hz, 3H); 4.63 (q, J = 6.9 Hz, 1H); 7.14–8.31 (m, 14H); ^{13}C NMR (75 MHz, CDCl$_3$): 22.2 (q), 43.9 (d), 126.4 (d), 127.8 (d), 128.4 (d), 128.5 (d), 129.0 (d), 129.1 (d), 129.6 (d), 129.8 (d), 130.3 (d), 135.0 (d), 137.4 (s), 140.4 (s), 141.5 (s), 144.2 (s), 154.2 (s), 157.3 (s); *Anal.* Calcd. for $C_{22}H_{19}ClN_2$: C, 76.18; H, 5.52; N, 8.08%. Found: C, 76.25, H, 5. 54; N, 8.03%.

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Facile, Microwave-Assisted Parallel Syntheses of *N*-Substituted 1,4-Dihydropyridines of Biological Interest

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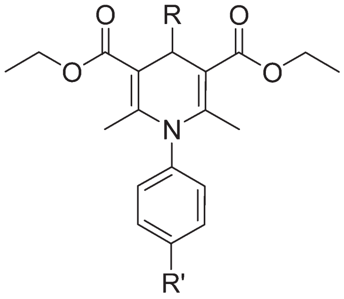

6 Compounds

A solventless parallel synthesis of some novel, *N*-substituted dihydropyridines by the application of microwaves is reported. The synthetic methodology adopted to synthesize the titled compounds and their antioxidant activity is described.

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INTRODUCTION

Heterocyclic synthesis plays an important role in medicinal chemistry by virtue of its application in the production of large number of medicinal compounds. Among many utility of heterocyclic syntheses one such important use is in the production of drugs, either currently on the market or those yet to be released.

Dihydropyridine (DHP) chemistry began in 1882, when Hantzsch for the first time published the syntheses of DHPs by multicomponent reaction, which now bears his name [1–3]. 1,4-DHPs such as nifedipine and nitrendipine are used even today as antihypertensive agents [4–6].

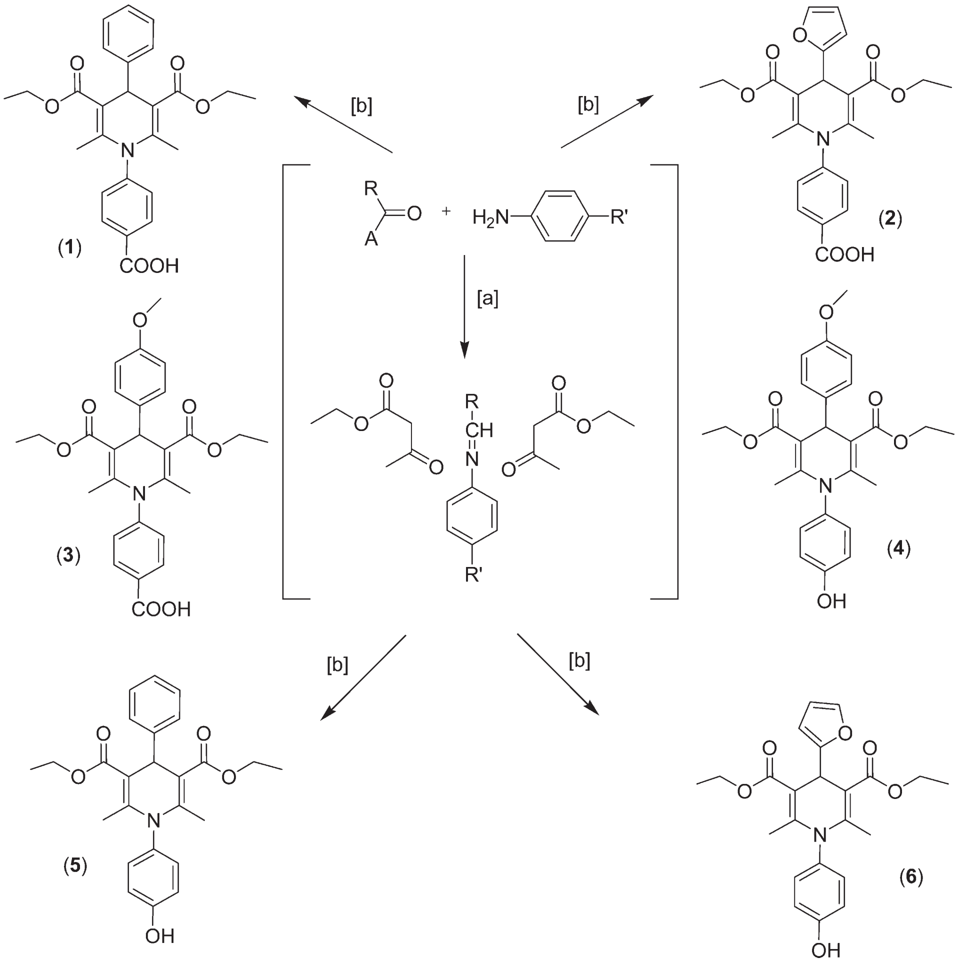
1,4-DHPs are known to possess various biological activities such as multidrug reversal (MDR) in tumor cells [7], potential immunomodulating [8], as well as antitubercular activities [9]. The 3D QSAR results show the minimum structure requirement for DHPs to exhibit antitubercular activity [10]. A further study of *N*-substitution at the labile hydrogen of DHPs skeleton proved to be important for MDR reversal in tumor cells apart from analytical and synthetic interest [11]. These observations provoked us to work on *N*-substituted DHPs for their possible antioxidant activity by incorporating phenolic and carboxyl groups [12].

Industrial chemistry in this millennium is widely adopting the concept of green chemistry to meet the fundamental scientific challenges of protecting the human health and environment while maintaining commercial viability. The emerging area of green chemistry envisages minimum hazard as the performance criteria while designing new chemical process. One of the thirst areas for achieving this target is to explore alternative reaction conditions and reaction media to accomplish the desired chemical transformations with minimized by-products or waste as well as eliminating the use of conventional organic solvents, if possible. Microwaves (MWs) as an alternative energy source has become an attractive tool in organic synthesis [13,14], resulting in a significant decrease in reaction times, especially for endothermic reactions.

RESULTS AND DISCUSSION

Because of biological interest, we have synthesized *N*-substituted 1,4-DHPs by parallel syntheses using *p*-toluenesulphonic acid (PTSA) as a catalyst under MW irradiation conditions as per Scheme 1. The PTSA was found to be a better catalyst than $AlCl_3$ and HCl in

Scheme 1. Microwave-assisted parallel syntheses of *N*-substituted-1,4-dihydropyridines; (a) Silica gel, MW, 700 W, 8 min; (b) PTSA, MW, 700 W, 12–15 min.

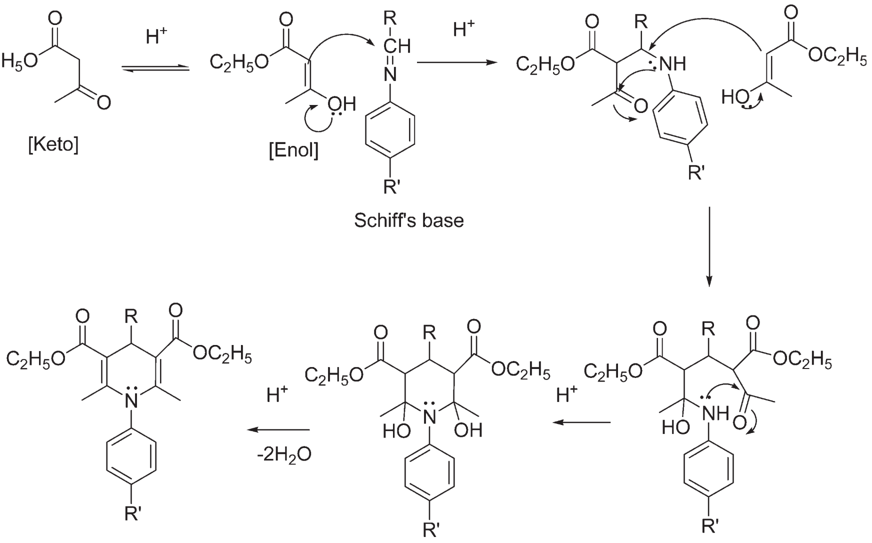


terms of yields. Also, it was convenient to perform the parallel synthesis under solvent free conditions using PTSA as a cyclizing agent and silica gel as adsorbent.

Initially, we made an attempt to synthesize *N*-aryl-1,4-DHPs through conventional and MW methods. In both the methods there was a formation of Schiff's base, but by the conventional method, we could not prepare *N*-substituted 1,4-DHPs, successfully. We repeated the experiment several times under conventional heating. In each case, the thin layer chromatography (TLC) was unclear and showed multiple spots. PTSA was developed as an efficient catalyst for the formation of final products under MWs when compared with the other reported catalysts such as HCl, $AlCl_3$, *etc.* [2].

We had also made an attempt to prepare the titled compounds by adopting one pot, one step, multicomponent reaction involving equivalent amounts of aryl amine, aryl aldehyde with two equivalent amount of ethyl acetoacetate under similar MW irradiation conditions. However, only 10–20% yields of the final compounds were obtained. In addition, the products were found to be impure with many by-products. One of the major reason why the single step syntheses was not successful was found to be the formation of acetoacetanilide because of a reaction between arylamine and ethyl acetoacetate. This was conformed by subjecting the crude reaction mixture to high-resolution mass spectrometry (HRMS). The syntheses of the titled compounds through the Schiff's base preparation escaped from the formation of acetoacetanilide. Another reason for the success of the reaction was due to the possibility of the correct steric alignment of the Schiff's base with a β-keto ester to react during its reaction mechanism as shown in Scheme 2.

Scheme 2. The possible reaction mechanism for the formation of *N*-substituted1,4-dihydropyridines.



Final compounds were first analyzed by TLC and melting point determination. Then, the synthesized compounds were subjected to spectral analysis such as IR, NMR, and MASS spectrometry to confirm the structures. All the analytical details showed satisfactory results. For all compounds, a characteristic singlet peak for symmetric CH was observed between 5.0 and 5.5 ppm in the ^{1}H NMR spectrum.

The synthesized compounds were tested for *in vitro* antioxidant activity using standard nitric oxide assay method [15]. Among all the synthesized compounds, compounds **4** and **6** exhibited potential antioxidant activity with IC_{50} value at 11 and 28 μg concentrations, respectively. The *in vitro* antioxidant results reveal that there is need for further investigation. Hence, the work in this direction is in progress and it will be reported in our next publication.

In conclusion, a simple protocol for the syntheses of *N*-aryl-1,4-DHPs was developed under environmentally benign, MW irradiation conditions using PTSA as a catalyst. It was found that the MW method is selective and efficient when compared with the conventional method.

EXPERIMENTAL

The IR was recorded on Perkin Elmer Infrared-283 FTIR by KBr pellet technique. NMR was taken on Bruker ACF-300 MHz spectrometer apparatus using TMS as internal standard and $CDCl_3$ or DMSO-d_6 as a solvent. The chemical shifts are expressed in δ ppm and following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. HRMS analysis was done on Perkin-Elmer Sciex API-150-EX by ESI ionization technique. Elemental analysis was carried out for carbon, hydrogen, and nitrogen using an Elementar Vario (EL III Carlo Erba11080). MW irradiation was done using, Whirl Pool domestic MW oven as well as MW Synthesizer (2450 MHz, Catalyst Systems, India). All the reactions were monitored using thin layer chromatogram. TLC was performed using 4% methanol in chloroform as mobile phase on aluminum plates that are precoated with silica gel GF.

General procedure for the preparation of Schiff's bases. Equimolar amounts (0.01*M*) of aromatic amine and aromatic aldehyde were transferred to a clean and dry mortar, triturate to become a uniform mixture. The reaction mixture was then transferred to a 100 mL beaker containing 2 g of activated silica gel. Similarly, all other beakers containing different reaction mixtures were kept inside the MW oven in a circle and then MW irradiation was carried out at 700 W power for about 8 min. Intermittent cooling was done after every 60 s of MW irradiation. During intermittent cooling, the reaction mixtures were thoroughly mixed. The reactions were monitored through TLC. The completed reactions were taken directly for the preparation *N*-substituted DHPs without any work up, immediately.

General procedure for the preparation of *N*-substituted-1,4-DHPs (1-6). This reaction was carried out in a parallel synthetic way as shown in Scheme 1. Ethyl acetoacetate (0.02*M*) was transferred in to a dry mortar containing the Schiff's base (~0.01*M*) obtained in the previous MW procedure. Add a catalytic amount or pinch of PTSA and triturate to become a uniform mixture. The reaction mixture was then transferred to 100 mL beaker. Similarly, all other beakers containing different reaction mixtures were kept inside the MW oven in a circle and then MW irradiation was carried out at 700 W power for about 12–15 min. Intermittent cooling was done after every 60 s of MW irradiation. During intermittent cooling, the reaction mixtures were thoroughly mixed. The reactions were monitored through TLC. The reaction mixtures were withdrawn from MW oven soon after the reaction is completed based on TLC data at regular intervals. The reaction mixtures were poured in to the beaker containing water and extracted with ethyl acetate. The ethyl acetate layer was dried over sodium sulfate and evaporated under vacuum to get crude products. The obtained crude products were further purified by recrystallization using ethyl acetate-hexane mixture (1:1) or by column chromatography using 5% EtOAc in pet ether as a mobile phase over silica gel.

4-(3,5-Di(ethoxycarbonyl)-2,6-dimethyl-4-phenylpyridin-1(4H)-yl)benzoic acid (1). Pale yellow colored solid, Yield 61%, mp 135–137°C; IR (KBr, cm^{-1}): 3471 (O—H), 3081 (Ar C—H), 2919 (Ali C—H), 1721 (C=O), 1713 (C=O), 1626 (C=C). ^1H NMR (δ ppm, $CDCl_3$): 1.19 (t, 6H, $2CH_3$), 2.10 (s, 6H, $2CH_3$), 4.04 (q, 4H, $2CH_2$), 5.31 (s, 1H, CH), 6.94–7.59 (m, 9H, ArH), 12.98 (s, 1H, OH). MS (*m/z*): calcd. 449, found 449.21 (M^+). MS: 434, 398, 311, 243, 121. *Anal.* Calcd. for $C_{26}H_{27}NO_6$: C, 69.47; H, 6.05; N, 3.12. Found: C, 69.63; H, 5.94; N, 3.08.

4-(3,5-Di(ethoxycarbonyl)-4-(furan-2-yl)-2,6-dimethylpyridin-1(4H)-yl)benzoic acid (2). Pink-colored solid, Yield 77 %, mp 93–95°C; IR (KBr, cm^{-1}): 3428 (O—H), 3037 (Ar C—H), 2989 (Ali C—H), 1724 (C=O), 1716 (C=O). ^1H NMR (δ ppm, $CDCl_3$): 1.22 (t, 6H, $2CH_3$), 1.85 (s, 6H, $2CH_3$), 4.24 (q, 4H, $2CH_2$), 5.34 (s, 1H, CH), 6.01 (d, 1H, CH Fur), 6.23 (t, 1H, CH Fur), 6.88 (d, 2H, ArH), 7.02 (d, 2H, ArH), 7.21 (d, 1H, CH Fur), 12.70 (s, 1H, OH). MS (*m/z*): calcd.439, found 439.13 (M^+). MS: 401, 329, 277, 211, 121. *Anal.* Calcd. for $C_{24}H_{25}NO_7$: C, 65.59; H, 5.73; N, 3.19. Found: C, 65.44; H, 5.87; N, 3.57.

4-(3,5-Di(ethoxycarbonyl)-4-(4-methoxyphenyl)-2,6-dimethylpyridin-1(4H)-yl)benzoic acid (3). Pale yellow solid, Yield 75 %, mp 99–101°C; IR (KBr, cm^{-1}): 3446 (O—H), 3053 (Ar C—H), 2939 (Ali C—H), 1717 (C=O), 1709 (C=O), 1623 (C=C). ^1H NMR (δ ppm, $CDCl_3$): 1.21 (t, 6H, $2CH_3$), 2.19 (s, 6H, $2CH_3$), 3.71 (s, 3H, OCH_3), 4.07 (q, 4H, $2CH_2$), 5.07 (s, 1H, CH), 6.91–7.53 (m, 8H, ArH), 12.48 (s, 1H, OH). MS (*m/z*): calcd. 479, found 479.11 (M^+). MS 464, 387, 301, 142. *Anal.* Calcd. for $C_{27} H_{29}NO_7$: C, 67.63; H, 6.10; N, 2.92. Found: C, 67.78; H, 5.89; N, 2.77.

Diethyl-1,4-dihydro-1-(4-hydroxyphenyl)-4-(4-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (4). Yellowish brown solid, Yield 81 %, mp 88–90°C; IR (KBr, cm^{-1}): 3436 (O—H), 3048 (Ar C—H), 2927 (Ali C—H), 1719 (C=O), 1638 (C=C). ^1H NMR (δ ppm, $CDCl_3$): 1.26 (t, 6H, $2CH_3$), 2.22 (s, 6H, $2CH_3$), 3.81 (s, 3H, OCH_3), 4.02 (q, 4H, $2CH_2$), 5.19 (s, 1H, CH), 6.90–7.40 (m, 8H, ArH), 9.41 (s, 1H, OH). MS (*m/z*): calcd. 451, found 451.48 (M^+). MS: 436, 398, 312, 151. *Anal.* Calcd. for $C_{26} H_{29}NO_6$: C, 69.16; H, 6.47; N, 3.10. Found: C, 69.35; H, 6.39; N, 2.89.

Diethyl-1,4-dihydro-1-(4-hydroxyphenyl)-2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate(5). Yellow crystals, Yield 78 %, mp 89–91°C; IR (KBr, cm^{-1}): 3448 (O—H), 3078 (Ar C—H), 2912 (Ali C—H), 1719 (C=O), 1712 (C=O), 1611 (C=C). ^1H NMR (δ ppm, $CDCl_3$): 1.23 (t, 6H, $2CH_3$), 2.21 (s, 6H, $2CH_3$), 4.10 (q, 4H, $2CH_2$), 5.23 (s, 1H, CH), 6.84–7.47 (m, 9H, ArH), 9.90 (s, 1H, OH). MS (*m/z*): calcd. 421, found 421.17 (M^+). MS: 406, 353, 331, 262, 121. *Anal.* Calcd. for $C_{25} H_{27}NO_5$: C, 71.24; H, 6.46; N, 3.32. Found: C, 70.87; H, 6.33; N, 3.41.

Diethyl-4-(furan-2-yl)-1,4-dihydro-1-(4-hydroxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (6). Light brown colored solid, Yield 72%, mp 67–69°C; IR (KBr, cm^{-1}): 3410 (O—H), 3054 (Ar C—H), 2967 (Ali C—H), 1715 (C=O). ^1H NMR (δ ppm, $CDCl_3$): 1.20 (t, 6H, $2CH_3$), 1.91 (s, 6H, $2CH_3$), 4.1 (q, 4H, $2CH_2$), 5.25 (s, 1H, CH), 5.9 (d, 1H, CH Fur), 6.1 (t, 1H, CH Fur), 6.8 (d, 2H, ArH), 6.9 (d, 2H, ArH), 7.2 (d, 1H, CH Fur), 9.83 (s, 1H, OH). MS (*m/z*): calcd. 411, found 411.32 (M^+). MS: 397, 346, 251, 220, 121. *Anal.* Calcd. for $C_{23}H_{25}NO_6$: C, 67.14; H, 6.12; N, 3.40. Found: C, 67.49; H, 5.85; N, 3.32.

Antioxidant activity screening by nitric oxide radical inhibition assay. The reaction mixture (6 mL) containing sodium nitroprusside (10 m*M*, 4 mL), phosphate buffer saline (1 mL), and compound (1–64 μg/mL) was incubated at 25°C for 150 min. After incubation, 0.5 mL of the reaction mixture was removed, 1 mL of sulfanilic acid reagent (0.33% in 20% glacial acetic acid) was mixed and allowed to stand for 5 min for completion of diazotization reaction, and 1 mL of naphthyl ethylene diamine dihydrochloride was added, mixed, and allowed to stand for 30 min in diffused light. The absorbance was measured at 540 nm against the blank in a 96-well microtitre plate using an ELISA reader.

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Bis(enaminones): Key Intermediates for Novel α,ω-Bis(pyrazolylphenoxy), Bis(pyranylphenoxy), and Bis(benzo[*b*]furanylphenoxy) Alkanes

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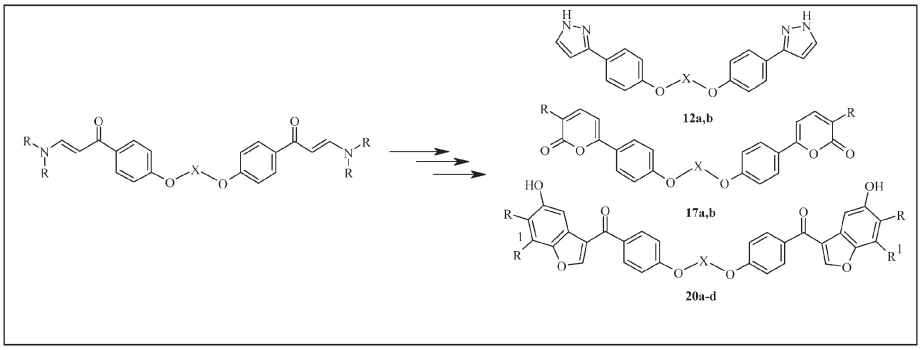

New bis(enaminone) derivatives, **5a,b** and **9a,b**, were prepared in good yields. Their synthetic utilities as key intermediates for the synthesis of novel bis(pyrazole) **12a,b**, bis(pyrane) **17a,b**, and bis(benzo[*b*]-furan) **20a–d** derivatives were also investigated.

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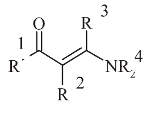
INTRODUCTION

There has been continuous interest in the synthesis of new heterocyclic systems containing pyrazole, pyrane, and benzofuran moieties because of their wide applications in different areas. Various series of pyrazole and their annelated derivatives are reported to have diverse biological activities as antifungal [2], antitumor [3], anti-inflammatory [4], and antinociceptive activities [4,5]. In addition, some pyrazole derivatives have been reported to be useful as inhibitor for cyclooxygenase-2, lipoxygenase [6], elastase [7], and factor Xa (fXa) [8]. Moreover, some of bis(pyrazole) palladium complexes are used as phenylacetylene polymerization catalyst [9]. On the other hand, pyrane and its related fused heterocycles are of interest as potential bioactive molecules. They are known to be used as anticancer [10], antibacterial [11], and anti-inflammatory agents [12] and to inhibit the amidolytic activity of human thrombin [13]. In addition, benzofuran derivatives constitute a structural unit of a number of natural products and biologically active compounds [14–17]. Furthermore, bis(compounds) have received great attention as being model compounds for main chain polymers [18–22]. It is also reported that many biologically active natural and synthetic products have molecular symmetry [23].

Keeping the above facts in mind and in continuation of our interest in the synthesis of bis(hetrocycles) [24–27], we describe herein a simple and efficient route for the synthesis of novel bis(enaminones) and studied their synthetic utilities as key intermediates for the synthesis of novel bis(pyrazolylphenoxy), bis(pyranylphenoxy), and bis(benzo[*b*]furanylphenoxy)alkanes.

RESULTS AND DISCUSSION

Recently, enaminones **1** were prepared by different synthetic approaches and their use as key intermediates for the synthesis of a wide variety of heterocycles have been investigated [28].



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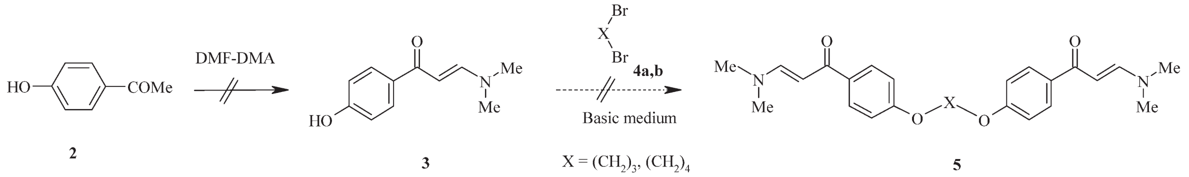
In continuation of these studies, we report here on the synthesis of the novel α,ω-bis(enaminones) and investigated its synthetic utility as building blocks for new symmetrical bis(heterocycles). Two strategies were studied for the synthesis of the target enaminones **5**. In the

Scheme 1



first one, we planed to prepare compound **5** starting from 4-hydroxyacetophenone (**2**) by reaction with dimethylformamide-dimethylacetal (DMF-DMA) to give the corresponding enaminone **3** followed by bis-alkylation with the appropriate dibromoalkanes **4a,b** as shown in Scheme 1.

Unfortunately, reaction of **2** with DMF-DMA afforded oily residue that cannot be handled and could not be characterized.

In the second strategy, we investigated the synthesis of **5** using α,ω-bis(4-acetylphenoxy)alkanes **7a,b** as starting materials. Compounds **7a,b** could be obtained by the reaction of the potassium salt **6** (obtained upon treatment of 4-hydroxyacetophenone (**2**) with ethanolic potassium hydroxide) with the appropriate dibromoalkanes **4a,b** in boiling DMF. Solventless heating of compounds **7a,b** with DMF-DMA furnished the corresponding bis(enaminone) derivatives **5a,b** in moderate yields. The ^{1}H NMR spectra of the isolated products revealed, in each case, one singlet near δ 3.0 due to the *N*,*N*-dimethylamino protons and two doublets near δ 5.7 and 7.8 characteristic for the olefinic–C*H*=C*H*—N protons with the same coupling constant value $J = 12$ Hz (typical for trans-configuration) [29], in addition to the other signals characteristic for the alkane and the aromatic moieties. The mass spectra of **5a,b** showed their correct molecular ion peaks at *m*/*z* 422 and 436, respectively.

Treatment of the bis(enaminone) derivatives **5a,b** with piperidine in refluxing ethanol afforded the new bis(enaminones) **9a,b** in 65 and 64% yields, respectively. Furthermore, treatment of the bis(enaminone) **5a,b** with morpholine under similar reaction conditions gave the bis(enaminones) **9c,d** in 60% yields, respectively. The formation of the bis(enaminones) **9a–d** from **5a,b** is suggested to proceed through the formation of the intermediate **8a–d** followed by elimination of two molecules of dimethylamine as outlined in Scheme 2.

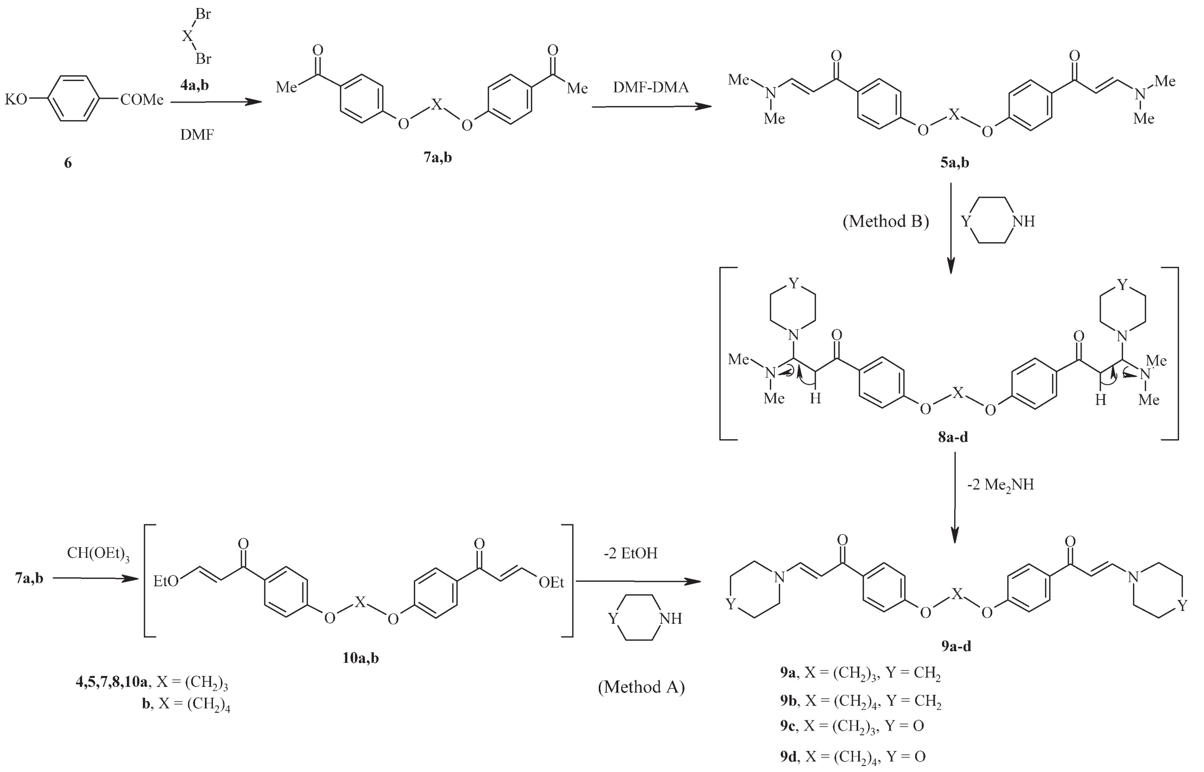
In view of the low yield of the above synthetic methodology, compounds **9a–d** could be obtained by alternative procedures through heating a mixture of the α,ω-bis(acetyl) derivatives **7a,b**, and triethylorthoformate with piperidine or morpholine to afford the corresponding bis(enaminone) derivatives **9a–d** in 71–82% yields. It is proposed that triethylorthoformate reacts with the bis(acetyl) **7a,b** to give the nonisolable bis(vinyl) ethers **10a,b**. Reaction of **10a,b** with piperidine or morpholine *via* Michael-type addition followed by ethanol elimination to give compounds **9a–d**. Elemental analyses and spectral data (IR, MS, ^{1}H NMR, and ^{13}C NMR) of the reaction products confirmed the assigned structures **9a–d**. The ^{1}H NMR spectrum of **9a**, for example, showed two multiplets at δ 1.57 and 3.38 integrated for 12 and 8 protons, respectively, for the piperidyl-CH_2's, a quintet at δ 2.19 and a triplet at δ 4.19 ($J = 5.7$ Hz) due to the propane-2-CH_2 and 1,3-CH_2O-, respectively, in addition to two doublet at δ 5.96 and 7.60 corresponding to the olefinic–C*H*=C*H*—N protons ($J = 12.3$ Hz, typical for trans-configuration) and two doublets at δ 6.96 and 7.87 due to the 1,4-disubstituted phenyl protons ($J = 7.2$ Hz). Its mass spectrum also showed the correct molecular ion peak at *m*/*z* 502.

Having now available the new bis(enaminones) **5a,b** and **9a,b** prompted us to study their synthetic utilities as key intermediates for novel bis(5- and 6-membered) heterocycles. Thus, heating the 1,3-bis(enaminone) **5a**, as a representative example, with hydrazine hydrate in glacial acetic acid resulted in the formation of the 1,3-bis(1*H*-3-pyrazolylphenoxy)propane (**12a**) in 66% yield as depicted in Scheme 3. The structure of compound **12a** was substantiated from its elemental and spectral analyses. Its IR spectrum showed the absence of an absorption band characteristic for C=O as well as the presence of pyrazole-NH absorption at 3199 cm^{-1}. The ^{1}H NMR spectrum of **12a** showed three singlet signals at δ 3.47, 6.56, and 7.62 due to the pyrazole 1-NH, 4-CH, and 5-CH protons, respectively. Similarly, treatment of bis(enaminone) **5b** with hydrazine in acetic acid gave the corresponding 1,4–bis(1*H*-3-pyrazolylphenoxy) butane **12b** in 70% yield (Scheme 3).

It is noteworthy to mention that the bis(pyrazolylphenoxy)alkanes **12a,b** could also be prepared from the appropriate bis(enaminones) **9a,b** in 48 and 55% yields, respectively, using the above synthetic methodology (Scheme 3).

The formation of the bis(pyrazoles) **12a,b** from **5a,b** or **9a,b** is supposed to proceed through the formation of the nonisolable intermediates **11a,b** followed by the elimination of two molecules of the appropriate secondary amines as depicted in Scheme 3.

Scheme 2

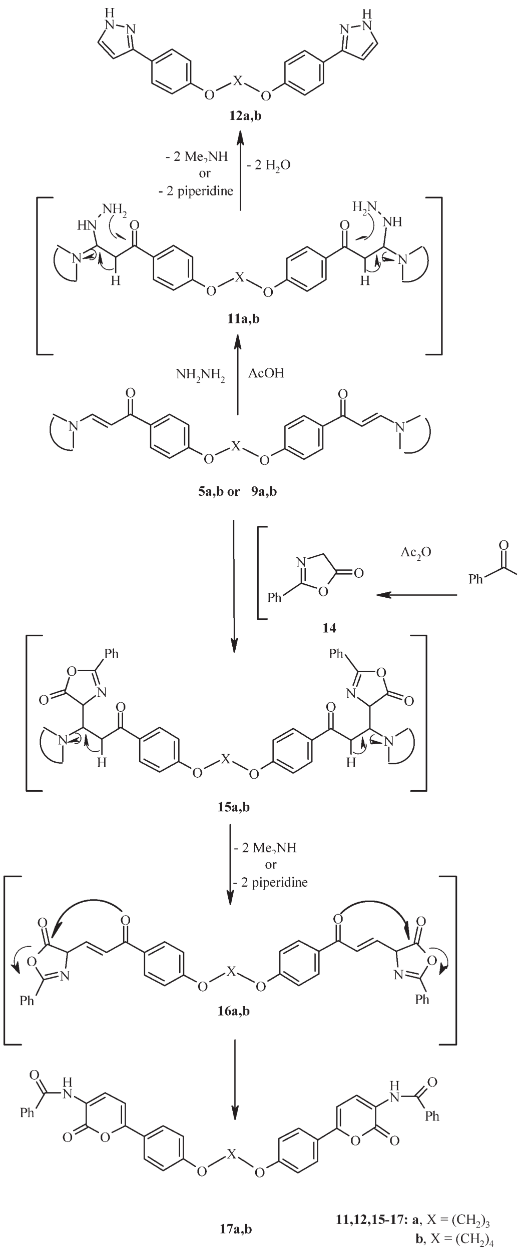


Our study is now extended to include the synthesis of new bis(pyran) derivatives **17a**,**b**. Thus, the bis(enaminone) **5a** was allowed to react with *N*-benzoylglycine **13** in refluxing acetic anhydride to give a single product as examined by TLC. Elemental analyses and mass spectrum of the isolated product were completely in agreement with the molecular formula $C_{39}H_{30}N_2O_8$. The structure of the product is assumed to be **17a** according to the rationale outlined in Scheme 3, which is also similar to analogous reported results [30,31]. Firstly, the nonisolable oxazolone **14** was supposed to be formed from *N*-benzoylglycine **13** upon reaction with acetic anhydride. The latter compound reacts with the enaminone **5a** to form the intermediates **15a**, which eliminate two molecules of dimethylamine or piperidine to give **16a**. The latter then undergoes intramolecular cyclization accompanied with ring opening to give compound **17a** in 74% yield. The ^{1}H NMR of compound **17a** was free of any aliphatic protons except that of the 1,3-dioxypropane moiety and exhibited two characteristic doublets at δ 7.03 and 8.16 each integrated for 2H with J = 7.2 Hz (for 5-H and 4-H protons of the pyranone moiety). In addition, two doublets at δ 7.8 and 7.94 each one integrated for four protons with J = 7.8 Hz (for the two 1,4-disubstituted phenyl moieties) besides the aromatic multiplet for two phenyl groups. Furthermore, the appearance of NH absorption at 3405 cm^{-1} in the IR spectrum as well as its appearance as a broad singlet at δ 9.50 in the ^{1}H NMR spectrum strongly supported this assignment. Similarly, reaction of compound **5b** or **9a,b** with *N*-benzoylglycine **13** under the same reaction conditions gave the corresponding bis(pyranylphenoxy) alkane derivatives **17b** in 77% or **17a,b** in 45 and 52% yields, respectively, as depicted in Scheme 3.

Next, we have also described the synthesis of the new bis(benzofuran) derivatives **20a–d** in 61–79% by the reaction of the appropriate bis(enaminone) derivatives **5a,b** or **9a,b** with the corresponding quinones **18a,b**. Thus, reaction of **5a,b** or **9a,b** with 4-benzoquinone (**18a**) in refluxing acetic acid afforded the corresponding 1,3-bis(benzofuran) derivatives **20a,b** in 43–79% yields. Similarly, reaction of **5a,b** or **9a,b** with 1,4-naphthoquinone (**18b**) under the same reaction conditions gave the target bis(naphthofuran) **20c,d** in 31–74% yields as outlined in Scheme 4. It is assumed that quinines **18a,b** are initially added to the enaminones **5a,b** or **9a,b** to give the nonisolable intermediate **19a–d**. Subsequent intermolecular cyclization *via* dimethylamine or piperidine elimination gave the target compounds **20a–d**. The structures of compounds **20a–d** were inferred from different spectroscopic and analytical data.

It is noteworthy to mention here that the bis(heterocycles) **12a,b**, **17a,b**, and **20a–d** were also prepared from the corresponding enaminones **9c,d** but in very

Scheme 3



low yields compared with those obtained from **5a,b** and **9a,b**.

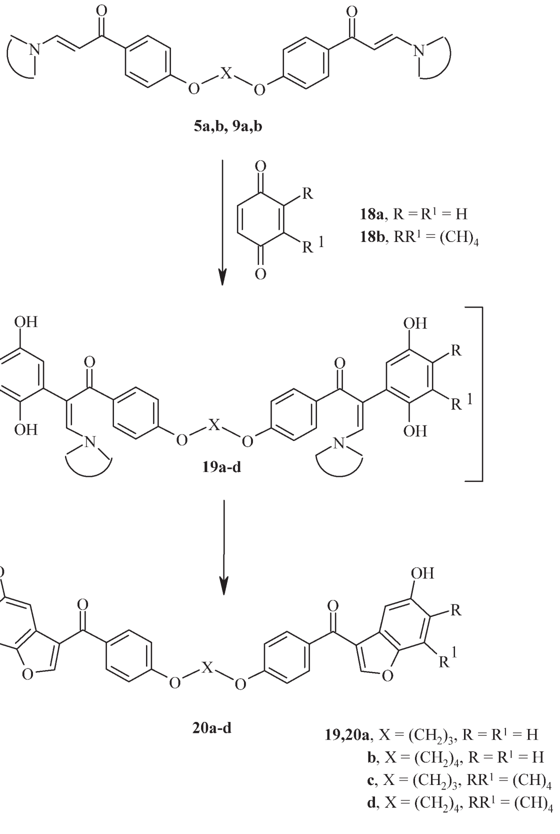
In conclusion, the present investigation describes an efficient method for access toward bis(enaminones) as well as novel bis(heterocycles) containing two biologically active moieties. We believe that these new series of symmetrical bis(hetrocycles) may exhibit potentially diverse useful applications in the field of medicinal chemistry. Also, development of the above synthetic methodology should lead to synthesis of a large number of symmetrical bis(hetrocycles) with a wide variety of substituents as well as different bridges. Moreover, our synthetic methodology offers the advantage of their easy use on a large scale in a simple procedure from inexpensive starting materials.

EXPERIMENTAL

Melting points were measured with a Gallenkamp apparatus. IR spectra were recorded on Shimadzu FT-IR 8101 PC infrared spectrophotometer. The ^{1}H NMR spectra were determined in CDCl$_3$ or DMSO-d_6 at 300 MHz on a Varian Mercury VX 300 NMR spectrometer using TMS as an internal standard. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical center of Cairo University. 1,3-Dibromopropane, 1,4-dibromobutane, 1,4-benzoquinone (**18a**), and 1,4-naphthoquinone (**18b**) were used as purchased from Aldrich.

Synthesis of α,ω-bis(4-acetylphenoxy)alkanes 7a,b. 4-Hydroxyacetophenone (**2**) (20 mmol) was dissolved in hot ethanolic KOH solution [prepared by dissolving 1.12 g (20 mmol) of KOH in 20 mL of absolute ethanol], and the solvent was then removed *in vacuo*. The remaining material was dissolved in DMF (15 mL) and the appropriate dibromides **4a,b** (10 mmol) was added. The reaction mixture was refluxed for 5 min during which KCl was separated. The solvent was then removed *in vacuo* and the remaining material was poured over crushed ice. The solid obtained was recrystallized from ethanol to give colorless crystals of compound **7a**, mp 125–127°C (ref. [32] mp 126°C) and compound **7b** mp 146–148°C (ref. [33] mp 149°C).

Scheme 4



Synthesis of bis(enaminones) 5a,b. A mixture of bis(acetyl) derivatives 7**a,b** (10 mmol) and dimethylformamide-dimethylacetal (DMF-DMA) (5.4 g, 45 mmol) was refluxed for 10 h. The reaction mixture was left to cool to room temperature and the resulting yellow solid products were collected by filtration, washed with ethanol, dried, and finally recrystallized from ethanol to afford the corresponding bis(enaminone) derivatives **5a,b**, as pale yellow crystals respectively.

1,3-Bis{4-[(*E*)-3-(*N,N*-dimethylamino)prop-2-enoyl]phenoxy}propane (5a). Yield 2.62 g (62%); mp 170–172°C; IR (KBr) ν_{max}/cm^{-1} 1642 (C=O), 1599 (C=C); ^{1}H NMR (CDCl$_3$) δ 2.29 (quintet, *J* = 6 Hz, 2H, OCH$_2$*CH*$_2$CH$_2$O), 3.01 (brs, 12H, 4 NCH$_3$), 4.21 (t, *J* = 6 Hz, 4H, O*CH*$_2$CH$_2$*CH*$_2$O), 5.69 (d, *J* = 12 Hz, 2H, 2 N—CH=*CH*—CO), 6.91 (d, *J* = 9 Hz, 4H, ArH), 7.77 (d, *J* = 12 Hz, 2H, 2 N—*CH*=CH—CO), 7.88 (d, *J* = 9 Hz, 4H, ArH); MS: *m/z* (%) 422 (M$^+$, 5), 403 (15.4), 307 (6.8), 213 (5.4), 160 (12.1), 121 (25.8), 107 (19.3), 98 (100), 70 (75.5). Anal. for $C_{25}H_{30}N_2O_4$ Calcd: C, 71.07; H, 7.16; N, 6.63. Found: C, 70.84; H, 7.22; N, 6.48%.

1,4-Bis{4-[(*E*)-3-(*N,N*-dimethylamino)prop-2-enoyl]phenoxy}butane (5b). Yield 2.49 g (57%); mp 200–202°C; IR (KBr) ν_{max}/cm^{-1} 1640 (C=O), 1600 (C=C); ^{1}H NMR (CDCl$_3$) δ 2.0 (brs, 4H, OCH$_2$*CH*$_2$*CH*$_2$CH$_2$O), 3.02 (brs, 12H, 4 NCH$_3$), 4.1 (brs, 4H, O*CH*$_2$CH$_2$CH$_2$*CH*$_2$O), 5.71 (d, *J* = 12 Hz, 2H, 2 N—CH=*CH*—CO), 6.90 (d, *J* = 9 Hz, 4H, ArH), 7.78 (d, *J* = 12 Hz, 2H, 2 N—*CH*=CH—CO), 7.89 (d, *J* = 9 Hz, 4H, ArH); MS: *m/z* (%) 436 (M$^+$,7.6), 418 (18.7), 363 (7.0), 245 (14.7), 227 (12.6), 161 (15.1), 120 (36.8), 97 (100), 70 (90.2). Anal. for $C_{26}H_{32}N_2O_4$ Calcd: C, 71.53; H, 7.39; N, 6.42. Found: C, 71.80; H, 7.22; N, 6.18%.

Synthesis of bis(piperidyl) and bis(morpholinyl) enaminones 9a–d ***Method A: General procedure.*** A mixture of the bis(acetyl) derivatives **7a,b** (5 mmol), triethylorthoformate (4.5 g, 15 mmol), and the appropriate cyclic amine (piperidine or morpholine) (20 mmol) was heated at refluxing temperature for 6 h. The reaction mixture was then allowed to cool and the resulting precipitate was collected by filtration, washed with ethanol, and dried. Recrystallization from EtOH/DMF afforded the corresponding bis(cyclic) amine derivatives 9**a–d** in 70–82% yield.

Method B: General procedure. A mixture of the bis(enaminone) derivative **5a,b** (5 mmol) and the appropriate cyclic amine (piperidine or morpholine) (20 mmol) in ethanol (30 mL) was refluxed for 8 h. After cooling, the precipitated product was collected by filtration, washed with ethanol, and dried. Recrystallization from the EtOH/DMF afforded compounds identical in all respects with 9**a–d** obtained above but in slightly lower yields 60–65%.

1,3-Bis{4-[(*E*)-3-(*N*-piperidyl)prop-2-enoyl]phenoxy}propane (9a). Yield: method A/method B (80/65%); yellow powder; mp 160–162°C (EtOH); IR (KBr) ν_{max}/cm^{-1} 1638 (C=O), 1600 (C=C); ^{1}H NMR (DMSO-*d*$_6$) δ 1.57 (brs, 12H, 6 piperidyl-*CH*$_2$), 2.20 (quintet, *J* = 5.7 Hz, 2H, OCH$_2$*CH*$_2$CH$_2$O), 3.38 (brs, 8H, 4 piperidyl-N*CH*$_2$), 4.19 (t, *J* = 5.7 Hz, 4H, O*CH*$_2$CH$_2$*CH*$_2$O), 5.96 (d, *J* = 12.3 Hz, 2H, 2 N—CH=*CH*—CO), 6.96 (d, *J* = 7.2 Hz, 4H, ArH), 7.60 (d, *J* = 12.3 Hz, 2H, 2 N—*CH*=CH—CO) 7.87 (d, *J* = 7.2 Hz, 4H, ArH); MS: *m/z* (%) 502 (M$^+$, 2), 485 (5.7), 420 (10.2), 347 (6.4), 160 (6.8), 137 (8.7), 120 (24.5), 109 (100), 83 (29.3), 54 (39.3). Anal. for $C_{31}H_{38}N_2O_4$ Calcd: C, 74.07; H, 7.62; N, 5.57. Found: C, 74.15; H, 7.41; N, 5.69%.

1,4-Bis{4-[(*E*)-3-(*N*-piperidyl)prop-2-enoyl]phenoxy}butane (9b). Yield: method A/method B (71/64%); yellow powder; mp 250–252°C (EtOH/DMF); IR (KBr) ν_{max}/cm^{-1} 1674 (C=O); ^{1}H NMR (DMSO-*d*$_6$) δ 1.58 (brs, 12H, 6 piperidyl-*CH*$_2$), 1.89 (brs, 4H, OCH$_2$*CH*$_2$*CH*$_2$CH$_2$O), 3.39 (brs, 8H, 4 piperidyl-N*CH*$_2$), 4.10 (brs, 4H, O*CH*$_2$CH$_2$CH$_2$*CH*$_2$O), 5.97 (d, *J* = 12 Hz, 2H, 2 N—CH=*CH*—CO), 6.95 (d, *J* = 9 Hz, 4H, ArH), 7.60 (d, *J* = 12 Hz, 2H, 2 N—*CH*=CH—CO) 7.87 (d, *J* = 9 Hz, 4H, ArH); MS: *m/z* (%) 517 (M+1, 15.4), 498 (40.1), 434 (36.8), 110 (100), 95 (24.4). Anal. for $C_{32}H_{40}N_2O_4$ Calcd: C, 74.39; H, 7.80; N, 5.42. Found: C, 74.52; H, 7.98; N, 5.50%.

1,3-Bis{4-[(*E*)-3-(*N*-morpholinyl)prop-2-enoyl]phenoxy}propane (9c). Yield: method A/method B (82/60%); yellow crystals; mp 205–207°C (EtOH); IR (KBr) ν_{max}/cm^{-1} 1664 (C=O); ^{1}H NMR (CDCl$_3$) δ 2.30 (quintet, *J* = 6 Hz, 2H, OCH$_2$*CH*$_2$CH$_2$O), 3.38 (t, *J* = 5.1 Hz, 8H, 4 N*CH*$_2$CH$_2$O), 3.76 (t, *J* = 5.1 Hz, 8H, 4 O*CH*$_2$CH$_2$N), 4.22 (t, *J* = 6 Hz, 4H, O*CH*$_2$CH$_2$*CH*$_2$O), 5.87 (d, *J* = 12.6 Hz, 2H, 2 N—CH=*CH*—CO), 6.93 (d, *J* = 7.2 Hz, 4H, ArH), 7.70 (d, *J* = 12.6 Hz, 2H, 2 N—*CH*=CH—CO) 7.88 (d, *J* = 7.2 Hz, 4H, ArH); MS: *m/z* (%) 506 (M$^+$, 43.3), 423 (100), 310 (38.5), 256 (26.9), 218 (34.6), 186 (34.6), 149 (25.0), 133 (49.0), 121 (53.8), 91 (23.1), 81 (60.6), 68 (36.5). Anal. for $C_{29}H_{34}N_2O_6$ Calcd: C, 68.76; H, 6.76; N, 5.53. Found: C, 69.01; H, 6.58; N, 5.32%.

1,4-Bis{4-[(*E*)-3-(*N*-morpholinyl)prop-2-enoyl]phenoxy}butane (9c). Yield: method A/method B (74/60%); yellow crystals; mp 211–213°C (EtOH/DMF); IR (KBr) ν_{max}/cm^{-1} 1671 (C=O); ^{1}H NMR (DMSO-*d*$_6$) δ 1.86 (brs, 4H, OCH$_2$*CH*$_2$*CH*$_2$CH$_2$O), 3.46 (m, 8H, 4 N*CH*$_2$CH$_2$O), 3.62 (brs, 8H, 4 O*CH*$_2$CH$_2$N), 4.06 (brs, 4H, O*CH*$_2$CH$_2$CH$_2$*CH*$_2$O), 6.04 (d, *J* = 12.6 Hz, 2H, 2 N—CH=*CH*—CO), 6.95 (d, *J* = 8.4 Hz, 4H, ArH), 7.63 (d, *J* = 12.6 Hz, 2H, 2 N—*CH*=CH—CO) 7.89 (d, *J* = 8.4 Hz, 4H, ArH); ^{13}C NMR (DMSO-*d*$_6$) δ 25.2, 46.0, 65.6, 67.2, 113.7, 129.1, 130.3, 132.4, 152.1, 160.9, 185.3; MS: *m/z* (%) 520 (M$^+$, 17.3), 437 (31.3), 407 (92.7), 272 (22.9), 191 (64.1), 149 (65.1), 112 (72.4), 82 (95.8), 55 (100). Anal. for $C_{30}H_{36}N_2O_6$ Calcd: C, 69.21; H, 6.97; N, 5.38. Found: C, 69.58; H, 7.11; N, 5.45%.

Synthesis of the bis(pyrazole) Derivatives 12a,b. ***Method A: General procedure.*** A mixture of the bis(enaminone) derivatives **5a,b** (2 mmol) and hydrazine hydrate (1 mL, 99%) in glacial acetic acid (20 mL) was left to stir at room temperature overnight. The precipitated product was collected by filtration, washed with ethanol, and dried. Recrystallization from ethanol furnished the corresponding pyrazole derivatives **12a** and **12b** in 66 and 70% yields, respectively.

Method B: General procedure. The reactions were carried out under the same conditions in method A by replacing the enaminones **5a,b** with piperidyl ones **9a,b**. The yields of this method were lower than that of method A (**12a**: 48% and **12b**: 55%).

1,3-Bis[4-(1*H*-pyrazol-3-yl)phenoxy]propane (12a). Colorless powder, mp 182–184°C; IR (KBr) ν_{max}/cm^{-1} 3199 (NH), 1602 (C=N); ^{1}H NMR (DMSO-*d*$_6$) δ 2.25 (m, 2H, OCH$_2$*CH*$_2$CH$_2$O), 3.47 (brs, 2H, 2 NH, D$_2$O-exchangeable), 4.18 (m, 4H, O*CH*$_2$CH$_2$*CH*$_2$O), 6.56 (s, 2H, 2 pyrazole-4-CH), 7.62 (s, 2H, 2 pyrazole-5-CH), 7.69 (d, *J* = 8.1 Hz, 4H, ArH), 7.84 (d, *J* = 8.1 Hz, 4H, ArH); MS *m/z* (%) 360 (M$^+$, 57.8), 201 (100), 159 (68.8), 131 (72.5), 116 (48.6), 89 (41.3). Anal. for

$C_{21}H_{20}N_4O_2$ Calcd: C, 69.98; H, 5.59; N, 15.54. Found: C, 69.62; H, 5.74; N, 15.30%.

1,4-Bis[4-(1*H*-pyrazol-3-yl)phenoxy]butane (12b). Colorless powder, mp 227–229°C; IR (KBr) ν_{max}/cm^{-1} 3186 (NH), 1612 (C=N); ^{1}H NMR (DMSO-*d*$_6$) δ 1.91 (s, 4H, OCH$_2$*CH$_2$CH$_2$*CH$_2$O), 3.3 (brs, 2H, 2 NH, D$_2$O-exchangeable), 4.07 (s, 4H, O*CH$_2$*CH$_2$CH$_2$*CH$_2$*O), 6.59 (d, J = 2.1 Hz, 2H, 2 pyrazole-4-CH), 6.98 (d, J = 8.4 Hz, 4H, ArH), 7.64 (d, J = 1.8 Hz, 2H, 2 pyrazole-5-CH), 7.70 (d, J = 8.4 Hz, 4H, ArH); MS: *m*/*z* (%) 374 (M$^+$, 17.7), 215 (100), 173 (55.5), 160 (31.2), 131 (27.1), 77 (22.2), 55 (28.3). Anal. for $C_{22}H_{22}N_4O_2$ Calcd: C, 70.57; H, 5.92; N, 14.96. Found: C, 70.94; H, 5.78; N, 14.86%.

Synthesis of the bis(pyran-2-one) derivatives 17a,b ***Method A: General procedure.*** A solution of the bis(enaminones) **5a,b** (1 mmol) and *N*-benzoylglycine (**13**) (0.36 g, 2 mmol) in acetic anhydride (20 mL) was heated under reflux for 1 h then left to cool to room temperature. The solid product that formed upon cooling was collected by filtration and recrystallized from DMF/water to give the bis(pyran-2-one) derivatives **17a,b**, in 74 and 77% yields, respectively.

Method B: General procedure. The reactions were carried out under the same experimental conditions mentioned in method A earlier using the piperidyl derivatives **9a,b** instead of the enaminones **5a,b** to afford the bis(pyran-2-one) derivatives **17a,b** in 45 and 52% yields, respectively.

1,3-Bis[4-(3-benzoylamino-2-oxo-2*H*-pyran-6-yl)phenoxy]-propane (17a). Orange-colored powder, mp 250–252°C; IR (KBr) ν_{max}/cm^{-1} 3405 (NH), 1705, 1671 (C=O); ^{1}H NMR (DMSO-*d*$_6$) δ 2.24 (m, 2H, OCH$_2$*CH$_2$*CH$_2$O), 4.25 (m, 4H, O*CH$_2$*CH$_2$*CH$_2$*O), 7.03 (d, J = 7.2 Hz, 2H, 2 pyranone-5-CH), 7.1–7.96 (m, 18H, ArH), 8.16 (d, J = 7.2 Hz, 2H, 2 pyranone-4-CH), 9.50 (brs, 2H, 2 NH, D$_2$O-exchangeable); MS: *m*/*z* (%) 654 (M$^+$, 48.5), 105 (100), 77 (23.1), 50 (16.4). Anal. for $C_{39}H_{30}N_2O_8$ Calcd: C, 71.55; H, 4.62; N, 4.28. Found: C, 71.86; H, 4.43; N, 4.21%.

1,4-Bis[4-(3-benzoylamino-2-oxo-2H-pyran-6-yl)phenoxy]-butane (17b). Orange-colored powder, mp > 300°C; IR (KBr) ν_{max}/cm^{-1} 3403 (NH), 1698, 1637 (C=O); ^{1}H NMR (DMSO-*d*$_6$) δ 1.91 (m, 4H, OCH$_2$*CH$_2$CH$_2$*CH$_2$O), 4.14 (m, 4H, O*CH$_2$*CH$_2$CH$_2$*CH$_2$*O), 7.03–7.13 (m, 20H, ArH, 2 pyranone-5-CH), 8.16 (d, J = 7.5 Hz, 2H, 2 pyranone-4-CH), 9.56 (brs, 2H, 2 NH, D$_2$O-exchangeable); Anal. for $C_{40}H_{32}N_2O_8$ Calcd: C, 71.85; H, 4.82; N, 4.19. Found: C, 72.11; H, 4.65; N, 4.38%.

Synthesis of the bis(benzofurans) 20a,b and bis(naphthofurans) 20c,d ***Method A: General procedure.*** To a stirred solution of the bis(enaminones) **5a,b** (2 mmol) in acetic acid (20 mL), *p*-benzoquinone (**18a**) or 1,4-naphthoquinone (**18b**) (4 mmol) was added and the reaction mixture was stirred overnight at room temperature. The solid product formed was collected by filtration, washed with water and ethanol, dried, and finally recrystallized from EtOH/DMF to give the corresponding bis(benzofurans) **20a,b** and bis(naphthofurans) **20c,d**, respectively.

Method B: General procedure. This method is similar to method A except that the enaminone derivatives **9a,b** were used instead of **5a,b** to afford the corresponding bis(benzofurans) **20a,b** and bis(naphthofuran) derivatives **20c,d** but in lower yields compared to that obtained in method A.

1,3-Bis[4-(5-hydroxybenzo[*b*]furan-3-ylcarbonyl)phenoxy]propane (20a). Yield: method A/method B (66/43%); pale yellow powder, mp 190–192°C; IR (KBr) ν_{max}/cm^{-1} 3258 (OH), 1658 (C=O); ^{1}H NMR (DMSO-*d*$_6$) δ 2.25 (m, 2H, OCH$_2$*CH$_2$*CH$_2$O), 4.28 (m, 4H, O*CH$_2$*CH$_2$*CH$_2$*O), 6.83–6.88 (m, 2H, ArH), 7.05–7.15 (m, 5H, ArH), 7.45–7.52 (m, 2H, ArH), 7.87–7.94 (m, 5H, ArH), 8.54 (s, 2H, 2 furan-2-CH), 9.44 (brs, 2H, 2 OH, D$_2$O-exchangeable); ^{13}C NMR (DMSO-*d*$_6$): δ 28.4, 64.6, 106.5, 111.9, 114.3, 114.5, 119.9, 125.9, 130.4, 131.02, 148.9, 153.4, 154.6, 162.03, 187.9; MS: *m*/*z* (%) 548 (M$^+$, 50), 161 (100), 121 (26.8), 105 (36.2), 93 (26.1), 76 (25.4), 51 (24.6). Anal. for $C_{33}H_{24}O_8$ Calcd: C, 72.26; H, 4.41. Found: C, 72.63; H, 4.27%.

1,4-Bis[4-(5-hydroxybenzo[*b*]furan-3-ylcarbonyl)phenoxy]butane (20b). Yield: method A/method B (79/47%); pale yellow powder, mp 283–285°C; IR (KBr) ν_{max}/cm^{-1} 3277 (OH), 1662 (C=O); ^{1}H NMR (DMSO-*d*$_6$) δ 1.94 (m, 4H, OCH$_2$*CH$_2$CH$_2$*CH$_2$O), 4.15 (m, 4H, O*CH$_2$*CH$_2$CH$_2$*CH$_2$*O), 6.84–7.09 (m, 6H, ArH), 7.45–7.52 (m, 4H, ArH), 7.85–7.92 (m, 4H, ArH), 8.53 (s, 2H, 2 furan-2-CH), 9.38 (brs, 2H, 2 OH, D$_2$O-exchangeable); MS: *m*/*z* (%) 562 (M$^+$, 35.2), 428 (60.2), 309 (25), 254 (25.8), 161 (100), 121 (64.8), 76 (32), 55 (65.6). Anal. for $C_{34}H_{26}O_8$ Calcd: C, 72.59; H, 4.66. Found: C, 72.44; H, 4.84%.

1,3-Bis[4-(5-hydroxynaphtho[1,2-*b*]furan-3-ylcarbonyl)-phenoxy]propane (20c). Yield: method A/method B (61/31%); pale yellow powder, mp 258–260°C; IR (KBr) ν_{max}/cm^{-1} 3224 (OH), 1672 (C=O); ^{1}H NMR (DMSO-*d*$_6$) δ 2.24 (m, 2H, OCH$_2$*CH$_2$*CH$_2$O), 4.26 (m, 4H, O*CH$_2$*CH$_2$*CH$_2$*O), 7.04–7.16 (m, 6H, ArH), 7.55–7.95 (m, 10H, ArH), 8.18–8.28 (m, 2H, ArH), 8.62 (s, 2H, 2 furan-2-CH), 10.17 (s, 2H, 2 OH, D$_2$O-exchangeable); ^{13}C NMR (DMSO-*d*$_6$): δ 28.4, 64.6, 114.3, 114.5, 119.3, 120.8, 121.1, 121.5, 123.3, 123.5, 124.9, 127.4, 130.5, 131.2, 144.5, 150.8, 151.7, 162.3, 188.2. Anal. for $C_{41}H_{28}O_8$ Calcd: C, 75.92; H, 4.35. Found: C, 76.22; H, 4.29%.

1,4-Bis[4-(5-hydroxynaphtho[1,2-*b*]furan-3-ylcarbonyl)-phenoxy]butane (20d). Yield: method A/method B (74/40%); pale yellow powder, mp > 300°C; IR (KBr) ν_{max}/cm^{-1} 3213 (OH), 1706 (C=O); ^{1}H NMR (DMSO-*d*$_6$) δ 1.93 (m, 4H, OCH$_2$*CH$_2$CH$_2$*CH$_2$O), 4.12 (m, 4H, O*CH$_2$*CH$_2$CH$_2$*CH$_2$*O—), 7.09–7.13 (m, 6H, ArH), 7.54–7.96 (m, 10H, ArH), 8.18–8.28 (m, 2H, ArH), 8.64 (s, 2H, 2 furan-2-CH), 10.25 (brs, 2H, 2 OH, D$_2$O-exchangeable); ^{13}C NMR (DMSO-*d*$_6$): δ 25.3, 67.6, 114.0, 114.3, 119.3, 120.7, 121, 121.4, 123.3, 123.5, 124.9, 127.3, 129.1, 131.1, 144.5, 150.7, 151.5, 162.3, 188.2. Anal. for $C_{42}H_{30}O_8$ Calcd: C, 76.12; H, 4.56. Found: C, 76.00; H, 4.44%.

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A Simple and Novel Eco-Friendly Process for the Synthesis of Cyclic Dithiocarbonates from Epoxides and Carbon Disulfide in Water

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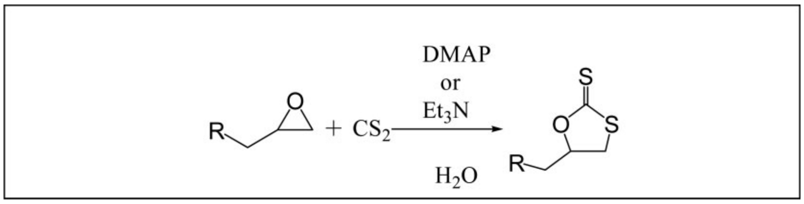

The reaction of oxiranes with carbon disulfide for preparation of cyclic dithiocarbonates was carried out in water under catalytic amount of an organic base such as dimethylaminopyridine or triethylamine. The reaction conditions are simple and give high yields of desired products.

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INTRODUCTION

Because it was reported that Diels–Alder reactions could be greatly accelerated by using water as a solvent instead of organic solvents [1], considerable attention has been directed toward the development of organic reactions in water. Besides Diels–Alder reaction, water was used in almost all of the useful organic reactions, even reactions involving water sensitive materials [2]. It is obvious that water is the most inexpensive and environmentally benign solvent. Thus, development of novel reactivity as well as selectivity that cannot be attained in conventional organic solvents is one of the challenging goals of aqueous chemistry [1].

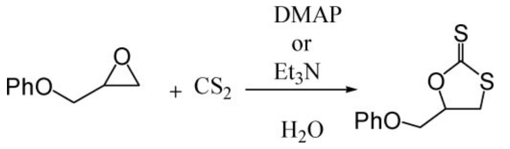
Tertiary amines- and pyridine-based organo catalysts were introduced to synthetic chemistry as a powerful nucleophilic group-transfer catalyst since more than 3 decades ago [3], because of their ability to catalyze important reactions such as acylation [4], esterification [5], macrolactonization [6], Baylis-Hillman [7], and silylation reactions [8]. Also, because of high potential of these compounds for developing of chiral acylating catalyst [9], several research groups are interested in this field of chemistry. 4-(Dimethylamino) pyridine (DMAP) is one of the standard catalysts for nucleophilic group-transfer reactions.

There are many reports on the reaction of epoxide with carbon disulfide [10]. Usually, high pressure and elevated temperature as well as long reaction times have been used for the synthesis of cyclic dithiocarbonates. Harsh reaction conditions have been reported for the synthesis and purification of five-membered cyclic dithiocarbonates, its regioisomers, and trithiocarbonates depending on the catalyst, temperature, and pressure. Shi and his coworkers studied the reaction between epoxy propane and carbon disulfide in the presence of DMAP and *p*-methoxyphenol as a catalyst at high temperature to afford the cyclic dithiocarbonate in 45% yield [11]. Recently, Maggi *et. al* reported a very interesting method for the synthesis of cyclic dithiocarbonates in the presence of hydrotalcite catalyst with good yields [12]. But there is no report for the preparation of cyclic dithiocarbonates in water therefore availability of a facile and green procedure to cover these drawbacks is interesting.

RESULTS AND DISCUSSION

Encouraged by our good experience to open the epoxide ring by nucleophiles such as amines [13] and dithiocarbamate anion [14] in water and in continuation of our previous work for the synthesis of dithiocarbamates in water and solvent-free conditions [15], we were interested to investigate the reaction of epoxides with CS_2 in the presence of Lewis bases in aqueous medium (Scheme 1). For this purpose, different Lewis bases such as Et_3N, DMAP, DABCO, and DBU were examined, and we have found that DMAP and Et_3N (10 mol %) gave the best results for the preparation of cyclic

Scheme 1. Synthesis of cyclic dithiocarbonate in water.



dithiocarbonates. We also tried the halide salts such as LiCl in water as catalyst, but we did not obtain good results (Table 1, entry 12). Also solvent effect was examined for the reaction of 2,3-epoxypropyl phenyl ether and CS_2 by using different organic solvents, but we did not obtain any desired products, except for ethanol, which gave only 10% yield (*ca.* Table 1).

After optimizing the reaction conditions, we tried to expand our results to other epoxides and the results are reported in Table 2. As shown in Table 2, 1,2-epoxides gave moderate to good yields but for cyclic epoxides such as cyclohexane epoxide, we obtained the product in low yield. For epichlorohydrin, 91% isolated yield was obtained. Only for styrene epoxide two regioisomers were obtained in 2:1 ratio and total yields of 52%. The ratio was determined by ^{1}H NMR with using the area of the peak of benzylic hydrogen in the two regioisomers (Entry 7, Table 2).

A plausible mechanism for this reaction is shown in Scheme 2. It is possible that the ability of water to give hydrogen bond with epoxides makes this transformation very efficient. We supposed that DMAP activates the CS_2 to dithiocarbamate anion **1**, which attacks to the water-activated epoxide to give compound **2**. In the next step, the epoxide's oxygen attacks the thiocarbonyl to remove DMAP and to form the cyclic dithiocarbonate 3.

CONCLUSIONS

In conclusion, we showed a very mild, facile, economical, and friendly method for the synthesis of cyclic dithiocarbonates in the presence of catalytic amount of DMAP. Also in large scale synthesis, extraction of products does not need to any organic solvent and only separation of organic phase from aqueous phase gives the crude products. Trying to do this reaction under asymmetrical conditions with chiral Lewis bases is undertaken in our laboratory.

EXPERIMENTAL

General. All chemicals were purchased and used without any further purification. NMR spectra were recorded at 500 MHz for proton and at 125 MHz for carbon nuclei in $CDCl_3$. The products were purified by column chromatography carried out on silica gel using ethyl acetate/petroleum ether mixtures. All compounds were characterized by their spectroscopic data (IR, ^{1}H NMR, and ^{13}C NMR) by comparison with those reported in the literature. Reactions were carried out at room temperature. Carbon disulfide, DMAP, and all epoxides are commercially available and used without further purification.

General procedure for the synthesis of the cyclic dithiocarbonates in water. In a round-bottomed flask equipped with magnet stirrer, epoxide (5 mmol), carbon disulfide (10 mmol) and water (20 mL) were added. To this mixture, DMAD or Et_3N (0.5 mmol) was added and stirred for 20 h. The progress of the reaction was checked by TLC. After completion of the reaction, the product was extracted with ethyl acetate and washed with water to remove the catalyst. The crude products were purified with column chromatography using silica gel as stationary phase and mixture of hexane and ethyl acetate (7:3) as an eluent to give the pure products with the yields shown in Table 2. Unreacted epoxides were recovered with column chromatography. Selected spectroscopic data for compounds are given in Table 2.

Compound (3a). Yellow crystal; mp 55–57°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.78–3.85 (m, 2H, CH_2), 4.35 (m, 2H, CH_2), 5.48 (m, 1H, CH), 6.96 (d, $J = 7.9$ Hz, 2H, $2CH_{ar}$), 7.06 (t, $J = 7.4$, 1H, CH_{ar}), 7.36 (m, 2H, $2CH_{ar}$) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 36.8, 66.7, 88.2, 114.9, 122.4, 130.2, 158.1, 211.9 ppm; IR (KBr): 1595, 1498, 1199, 1059 cm^{-1}.

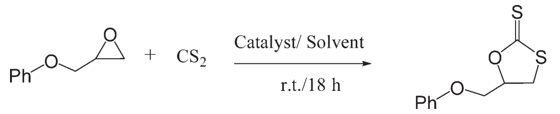
Compound (3b). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.15 (d, $J = 7.5$ Hz, 6H, $2CH_3$), 3.60–3.65 (m, 3H, CH_2 and CH), 3.70 (m, 2H, CH_2), 5.16 (m, 1H, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 22.4, 36.6, 67.1, 73.2, 89.7, 211.8 (C=S) ppm. IR (KBr): 1703, 1452, 1417, 1372, 1332 cm^{-1}.

Compound (3c). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.73–3.78(m, 2H, CH_2), 3.9 (m, 2H, CH_2), 5.3 (m, 1H, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 31.2, 37.3, 42.9, 88.4, 209.9 (C=S) ppm. IR (KBr): 1706, 1430, 1425, 1377, 1141, 1072 cm^{-1}.

Compound (3d). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.60–3.70 (m, 2H, CH_2), 3.73–3.83 (m, 2H, CH_2), 4.07 (d, $J = 5.7$ Hz, 2H, CH_2), 5.2–5.3 (m, 3H, CH and CH_2), 5.88 (m, 1H, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 36.5, 68.9, 72.9, 89.5, 118.3, 134.2, 211.2 (C=S) ppm. IR (KBr): 1702, 1638, 1423, 1419, 1354 cm^{-1}.

Table 1

Solvent and catalyst effects on the syntheis of cyclic dithiocarbonates.

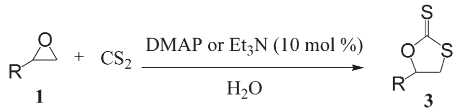


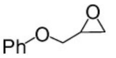
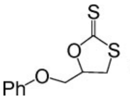
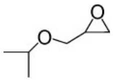
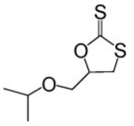
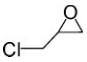
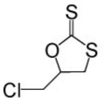
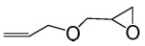
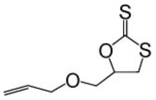
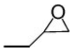
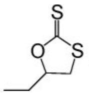
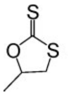
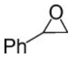
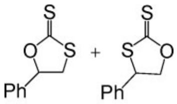
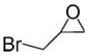
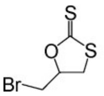
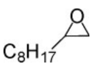
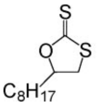
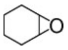
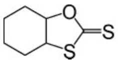
Entry	Solvent	Catalyst (mol %)	Yield (%)
1	H_2O	DMAP (50%)	84
2	H_2O	DMAP (10%)	76
3	H_2O	Et_3N (10%)	72
4	C_2H_5OH	DMAP (10%)	10
5	CH_2Cl_2	DMAP (10%)	0
6	$ClCH_2CH_2Cl$	DMAP (10%)	0
7	CH_3CN	DMAP (10%)	0
8	THF	DMAP (10%)	0
9	Toluene	DMAP (10%)	0
10	Acetone	DMAP (10%)	0
11	Solvent free	DMAP (10%)	50
12	H_2O	LiCl (10%)	0

Compound (3e). Yellow oil ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08 (t, J = 7.5 Hz, 3H, CH_3), 1.85 (m, 1H, one proton of CH_2), 2.00 (m, 1H, one proton of CH_2), 3.39 (dd, J = 11.7, 7.2 Hz, 1H, one proton of CH_2), 3.61 (dd, J = 11.7, 5.4 Hz, 1H, one proton of CH_2), 5.05 (m, 1H, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 10.2, 27.2, 39.4, 93.2, 212.1 (C=S) ppm. IR (KBr): 1714, 1619, 1511, 1426, 1332, 1268 cm^{-1}.

Table 2

Synthesis of cyclic dithiocarbonates by reaction of epoxide and carbon sisulfide in water.

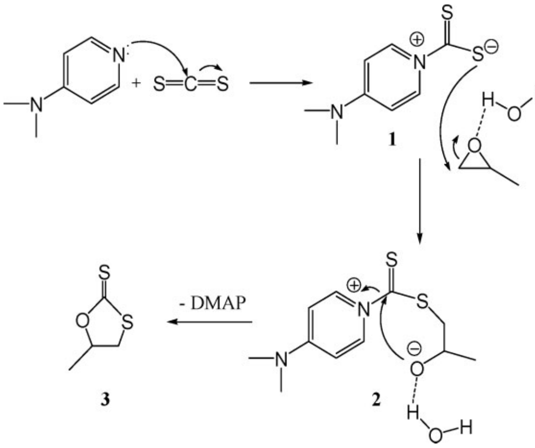


Entry	Epoxide	Product	Yield (%)[a]
1		 3a	76[16]
2		 3b	79 [16]
3		 3c	91
4		 3d	77(56)[b] [16]
5		 3e	50 [16]
6		 3f	30(45)[b] [16]
7		 3g 66:33 3h	52 [10j]
8		 3i	26
9		 3j	24
10		 3k	18 [16]

[a] Isolated yield.

[b] Triethyl amine as catalyst.

Scheme 2. Proposed mechanism for the synthesis of cyclic dithiocarbonate.



Compound (3f). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.66 (d, J = 6.3 Hz, 3H, CH_3), 3.39 (dd, J = 11.7, 7.2 Hz, 1H, one proton of CH_2), 3.66 (dd, J = 11.7, 4.5 Hz, 1H, one proton of CH_2), 5.27 (m, 1H, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 19.8, 41.2, 88.0, 211.6 (C=S) ppm. IR (KBr): 1703, 1439, 1417, 1370, 1141, 1079 cm^{-1}.

Compound (3g). Yellow crystal; mp 115–117°C. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 4.03 (1 H, dd, J = 12.0 Hz, J = 5.7 Hz, CH), 4.17 (1 H, dd, J = 12.0 Hz, J = 11.8 Hz, CH), 5.65 (1 H, dd, J = 10.3 Hz, J = 5.7 Hz, CH), 7.37–7.50 ($5H_{Ar}$). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 49.8 (CH2), 64.2 (CH), 127.5 (2 CH), 129.2 (2 CH), 129.3 (CH), 135.3 (C), 227.2 (C=S). IR (KBr): 1568, 1470, 1438, 1413, 1357, 1048 cm^{-1}.

Compound (3h). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 3.70–3.88 (2 H, CH_2), 5.35 (1 H, dd, J = 10.3 Hz, J = 5.7 Hz, CH), 7.37–7.44 7.50 (5 H_{Ar}). IR (KBr): 1560, 1461, 1445, 1410, 1351, 1049 cm^{-1}.

Compound (3i). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.63–3.73(m, 2H, CH_2), 3.8 (m, 2H, CH_2), 5.25 (m, 1H, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 30.3, 36.3, 41.9, 87.4, 206.9 (C=S) ppm. IR (KBr): 1700, 1425, 1370, 1143, 1071 cm^{-1}.

Compound (3j). Yellow oil; ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 0.79–1.68 (15 H), 1.80 (1 H, m, CH_2), 1.98 (1H, m, CH_2), 3.44–3.79 (2H, CH2), 5.12 (1H, CH). IR (KBr): 1701, 1455, 1417, 1374, 1338 cm^{-1}.

Compound (3k). Yellow crystal; mp 176–178°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.6–2.4 (m, 8H, $4CH_2$), 3.47–4.70 (m, 2H, 2CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 23.6, 24.9, 28.1, 29.7, 56.3, 94.6, 212.4(C=S) ppm; IR (KBr): 1628, 1431, 1326, 1272, 1094 cm^{-1}.

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A Novel Method for the Synthesis of 1(2*H*)-Phthalazinones Using Silica-Supported Perchloric Acid

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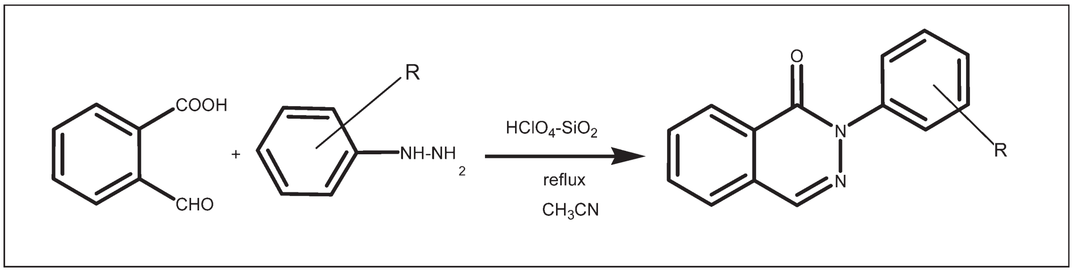

A simple and efficient synthesis of 1(2*H*)-phthalazinone derivatives was achieved *via* reaction of phthalaldehydic acid and various phenyl hydrazines in acetonitrile using $HClO_4$-SiO_2 as a catalyst in very good yields.

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INTRODUCTION

Heterocyclic compounds occur very widely in nature and are essential to life. Nitrogen-containing heterocyclic molecules constitute the largest portion of chemical entities, which are part of many natural products, fine chemicals, and biologically active pharmaceuticals vital for enhancing the quality of life [1]. Phthalazine scaffold have shown its potential as a privileged structure for the generation of drug-like libraries in drug-discovery process [2]. 2*H*-Phthalazin-1-ones are of considerable interest due to their antidiabatic [3] and antiallergic activities [4], and its bioactivity has been researched extensively [5–8]. They are also useful intermediates for the synthesis of inhibitors of the VEGF (vascular endothelial growth factor) receptor tyrosine kinases for the treatment of cancer [9]. However, phthalazinone derivatives have attracted considerable attention in the development of novel antiasthmatic agents with dual activities of thromboxane A_2 (TXA_2) synthetase inhibition and bronchodialation [10]. Consequently, there is a need to develop new methods to synthesis of these compounds.

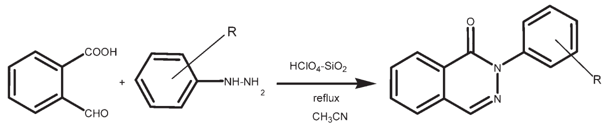
Solid-supported reagents are unique catalysts that have become popular over the last 2 decades [11]. The high catalytic activity, low toxicity, moisture, and air tolerance, their recyclability and particularly low price make the use of solid supported reagents attractive alternatives to conventional Lewis acids and triflates [12]. Although the catalytic applications of solid supported reagents for organic synthesis have been well established, relatively few examples are reported on the use of $HClO_4$-SiO_2 [13]. We have recently used $HClO_4$–SiO_2 for the synthesis of 14-aryl or alkyl-14-H-dibenzoxanthenes [14]. As part of our program aimed at developing new selective and environmental friendly methodologies for the preparation of fine chemicals [15–18], herein we report an efficient and convenient procedure for the synthesis of 1(2*H*)-phthalazinones using $HClO_4$-SiO_2 as a reusable and heterogeneous catalyst in good yields (Scheme 1).

RESULTS AND DISCUSSION

1(2*H*)-Phthalazinone were obtained by phthalaldehydic acid and various phenyl hydrazines in CH_3CN using $HClO_4$-SiO_2 as a reusable catalyst (Scheme 1) in good yields (Table 1). It has been proven recently that $HClO_4$-SiO_2 is a mild, worthwhile heterogeneous catalyst, which efficiently and selectively catalyzes various organic transformations and synthesis. The effect of temperature was studied by carrying out the reactions at different temperature (25°C), 50°C and under refluxing temperature (82°C). As it shown in Table 1, the yields of reactions increased as the reaction temperature was raised. These results showed that refluxing temperature would be the temperature of choice for all reactions. The reaction proceeded very cleanly under reflux condition and were free of side products.

Influences of solvents are the important parameter for the determination of yield of the products. The reaction was conducted in various solvents on the synthesis of 3a using $HClO_4$-SiO_2 as a reusable catalyst.

Scheme 1

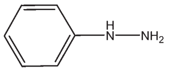
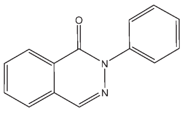
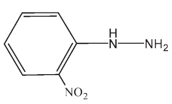
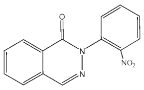
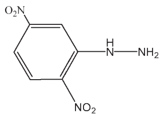
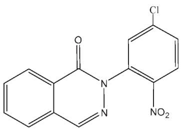
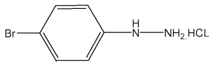
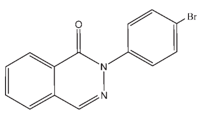
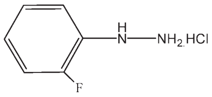
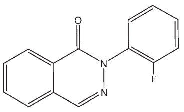
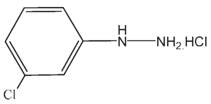
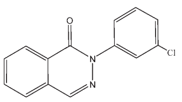
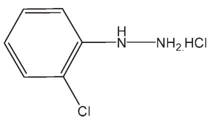
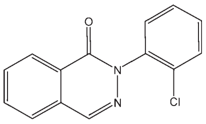


As shown in Table 2, the performance of various solvents are in the following order: acetonitrile > ethyl acetate > THF > toluene > dichloromethane.

Acetonitrile shows better yields, when compared with other solvents. In addition, the time required for

Table 1

Synthesis of 2,4,5-triaryl-imidazoles using various heteropolyacids under refluxing condition.

Entry	Substrate	Product	Time (h)	*M*p (°C)		Yield (%)[a]		
				Observed	Reported	25°C	50°C	82°C
1		 3a	1	104	104–105 [19]	50	85	95
2		 3b	1.5	206	204–206 [20]	43	76	92
3		 3c	2	176	175–177 [21]	40	63	80
4		 3d	2	170	168–169 [22]	45	70	81
5		 3e	1.5	121	120.5–121.5 [19]	50	79	90
6		 3f	1.5	136	135 [23]	50	75	90
7		 3g	2	127	126–127 [24]	43	70	80

[a] Yields were analyzed by GC.

Table 2

Synthesis of 3a with $HClO_4$-SiO_2 in the presence of different solvents.

Entry	Solvent	Temperature	Time (min)	Yield (%)[a]
1	Acetonitrile	reflux	1	95
2	Ethyl acetate	reflux	1	92
3	THF	reflux	1.20	90
4	Toluene	reflux	2	90
5	Dichloromethane	reflux	2	89

[a] Yields were analyzed by GC.

completion of the reaction was found to be less in acetonitrile. This is due to higher solvent polarity of acetonitrile when compared with that of other solvents. We expect that the solvent removes products from the active surface of the catalyst. Therefore, more polar solvents may remove the product better and thus regenerate the catalyst active sites allowing continuation of the catalytic reaction.

The reactions proceeded efficiently at mild conditions and are completed within 1–2 h, in contrast to conventional methods that require long reaction times. This method not only affords the products in good yields but also avoids the problems associated with catalyst cost, handling, safety, and pollution. This catalyst is eco-friendly for a variety of organic transformations. It is nonvolatile, nonexplosive, easy to handle, and thermally robust. The time required for completion of the reaction was found to be less for phenyl hydrazine when compared with substrates bearing electron withdrawing groups (Table 1, entries 2–7). Moreover, the steric hindrance seems to have significant effects on reaction times and yields (Table 2, entries 3, 4, 7).

In conclusion, we are reporting an efficient process for the synthesis of biologically interesting functionalized 1(2*H*)-phthalazinone derivatives starting from readily available and inexpensive reagents. It can be concluded that $HClO_4$-SiO_2 is an efficient and excellent catalyst for the synthesis of these compounds in high yields and mild conditions in short reaction times. This method offers some advantages in terms of simplicity of performance. The low cost of the catalyst, low toxicity of the catalyst, fast reaction times, recyclability of the catalyst, and high yields of the products are the other advantages for this synthesis. We believe our procedure will find important applications in the synthesis of 1(2*H*)-phthalazinones. The method is also relatively environmentally benign.

EXPERIMENTAL

All products are known compounds and were characterized by mp, IR, ^1H NMR, and GC/MS. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. ^1H NMR spectra were recorded on a Bruker AQS AVANCE-300 MHz spectrometer using TMS as an internal standard ($CDCl_3$ solution). IR spectra were recorded from KBr disk on the FTIR Bruker Tensor 27. GC/MS spectra were recorded on an Agilent Technologies 6890 network GC system and an Agilent 5973 network Mass selective detector. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254 was used to monitor the progress of reactions. All products were characterized by spectra and physical data.

Preparation of 2-phenyl-2*H*-phthalazin-1-one (3a): A typical procedure. To a mixture of phthalaldehydic acid (1 mmol, 15 g) and phenylhydrazine (1 mmole, 1 mL) in acetonitrile (5 mL), a catalytic amount of $HClO_4$–SiO_2 (0.01 mmol) was added and refluxing was continued for 1 h. The reaction progress was monitored by TLC. After completion of the reaction, the mixture was then filtrated (in order to separation of catalyst from the mixture). The filtrate was then diluted with 5% $NaHCO_3$ (5 mL) and the product was extracted with diethyl ether (2 × 5 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was obtained. The resulting solid product was recrystallized from ethanol to give the pure product.

3a: mp. 104°C; IR: 1620 (C=N), 1670 (C=O) cm^{-1}; ^1H NMR:δ 7.59–8.27 (m, 9H, Ar—H), 8.8 (s, 1H); ms: *m*/*z* 222 (M^+).

3c: mp. 176°C; IR: 1633 (C=N), 1674 (C=O) cm^{-1}; ^1H NMR:δ 7.61–8.43 (m, 7H, Ar—H); ms: *m*/*z* 301 (M^+).

Preparation of the $HClO_4$–SiO_2 catalyst [13]. $HClO_4$ (1.8 g, 12.5 mmol, as a 70% aq. solution) was added to a suspension of SiO_2 (230–400 mesh, 23.7 g) in Et_2O (70.0 mL). The mixture was concentrated and the residue was heated at 100°C for 72 h under vacuum to furnish $HClO_4$–SiO_2 (0.5 mmol/g) as a free flowing powder (50 mg = 0.025 mmol of $HClO_4$).

Caution. Although no explosions were reported under these conditions, extreme care has to be taken for large scale reactions. The preparation of the catalyst should be performed with special care and in a safe environment.

Reusability of catalyst. Next, we investigated the reusability of $HClO_4$–SiO_2. When the reaction was completed, the catalyst was separated by simple filtration and recovered with $CHCl_3$ (2 × 5 mL) and subsequently dried at 80°C in order to be. $HClO_4$–SiO_2 can be reused in subsequent reactions without significant decrease in activity even after five runs (Table 3).

Table 3

Reuse of the $HClO_4$-SiO_2 for synthesis of 2-phenyl-2*H*-phthalazin-l-one (3a).

Entry	Time (h)	Yield (%)[a]
1	1	95
2	1	93
3	1.20	92
4	2	90
5	2.20	90

[a] Yields were analyzed by GC.

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Synthesis and Properties of Diaza-, Triaza-, and Tetraazaphenothiazines

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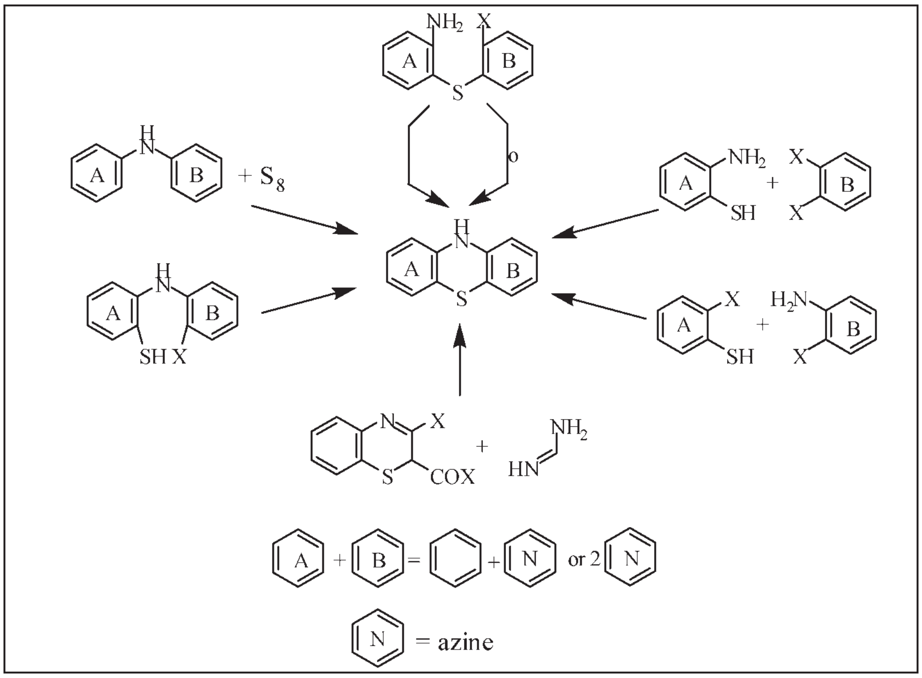

The review surveys the chemistry of diaza-, triaza-, and tetraazaphenothiazines and their benzo and dibenzo derivatives consisting of over 30 different heterocyclic systems.

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INTRODUCTION

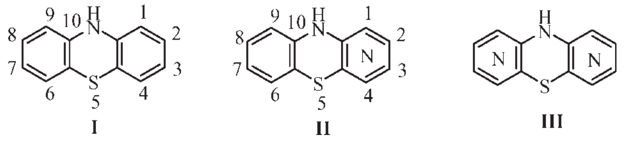
Phenothiazine (10*H*-dibenzo-1,4-thiazine, **I**) was obtained for the first time by Bernthsen in 1883 in the thionation of diphenylamine [1]. Since this moment over 5000 phenothiazine derivatives have been obtained and this class of organic compounds became very important because of their varied biological and chemical properties. Phenothiazines (mainly substituted at positions 2 and 10) exhibit valuable activities such as neuroleptic, antiemetic, antihistaminic, antipuritic, analgesic, and antihelmintic. At least 100 phenothiazines were used in therapy. Recent reports deal with anticancer, antiplasmid, and antibacterial activities, reversal of multidrug resistance and potential treatment in Alzheimer's and Creutzfeldt-Jakob diseases [2–6].

Modifications of the parent phenothiazine structure have been carried out by:

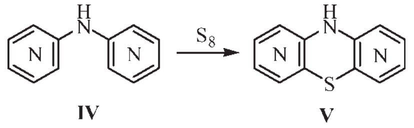
1. an introduction of a substituent at the thiazine nitrogen atom (at position 10),
2. an introduction of a substituent at the benzene ring (at positions 1–4 and 6–9, most often at position 2),
3. an oxidation of the sulfide function into sulfoxide and sulfone ones,
4. a substitution of one or two benzene rings with homoaromatic and heteroaromatic rings (most often azine rings).

Substitution with one or two azine rings led to new type of fused heterocyclic compounds being azinobenzo-1,4-thiazines II and diazino-1,4-thiazines III. Depending on the structure of an azine ring (pyridine, pyridazine, pyrimidine, pyrazine, quinoline, quinoxaline, and 1,2,4-triazine) they can form tri-, tetra-, and pentacyclic heterocycles. There has been known over 30 types of such heterocyclic systems. Okafor, Castle, and Wise synthesized a significant portion of these systems. As the azine rings contain one or more nitrogen atoms, these compounds are named as azaphenothiazines (monoaza-, di-, tri-, and tetraazaphenothiazines) (Scheme 1).

Scheme 1



Scheme 2



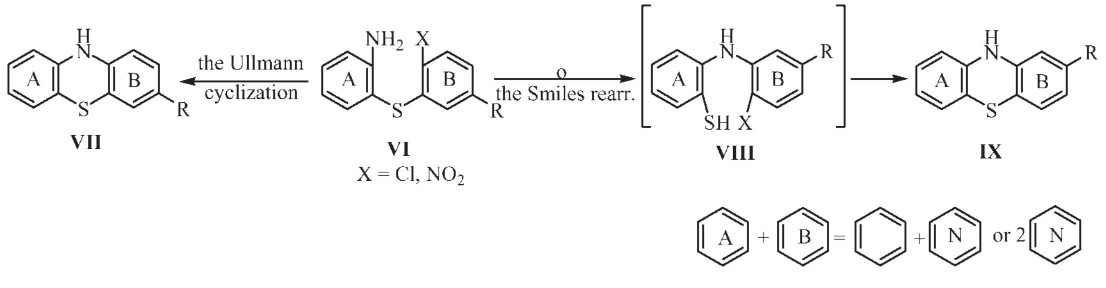
Synthesis of azaphenothiazines has been achieved by the following methods (generally outlined in Schemes 2–6):

1. thionation of diazinyl amines with elemental sulfur as a hydrogen atom substitution.
2. cyclization of phenyl azinyl sulfides or diazinyl sulfides proceeding directly as the Ullmann cyclization or with the Smiles rearrangement (the S→N type, phenyl or azinyl part migrates from sulfur atom to the nitrogen atom giving amine, not isolated) depending on the reaction conditions. The amino group might be attached to the phenyl ring and a leaving group X to an azinyl ring or inversely. Sometimes, it is impossible to state if a reaction goes with or without the rearrangement because the Ullmann's and Smiles's products are the same. The rearrangement proceeds under basic (most often) but also under acidic and neutral conditions.
3. cyclization of phenyl azinyl amines or diazinyl amines possessing a mercapto and good leaving groups (chlorine, nitro).
4. reactions of pairs of *ortho*-aminobenzenethiols or *ortho*-aminoazinethiols (or tautomers) with *ortho*-disubstituted azines, proceeding through formation of sulfides or amines which were not isolated during synthesis.
5. building of an azine ring to the benzo-1,4-thiazine moiety.

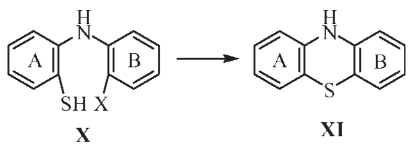
Phenothiazines were reviewed in the 50s and 70s [7–10] and exhaustively in a monograph edited by Gupta in the 80s [11]. Recently, a retrosynthetic approach to the synthesis of phenothiazines was described [12]. Syntheses and properties of monoazaphenothiazines were reviewed in 1990 in Polish based on 78 references [13]. Monoaza-, diaza-, triaza-, and tetraazaphenothiazines have already been reviewed by Okafor in the 70s in two articles [14,15], but those reviews were incomplete. Synthesis of azaphenothiazines from diazinyl sulfides was also a part in a chapter of the monograph [16]. Reading the chemical literature on the azaphenothiazines, we found misunderstanding chemical names and ring numbering, not to mention some incorrect names. As in the 60s and 70s, there were three nomenclature systems of azaphenothiazines, two based on the azaphenothiazine name (x-azaphenothiazine, x,y-diazaphenothiazine, x,y,z-triazaphenothiazine, and x,y,z,w-tetraazaphenothiazine) but with different numbering of the tricyclic ring system (British and American system **A**, German system **B**) and one based on heterocylic ring system **C** (Scheme 7) as the azino[...]benzo [1,4]thiazine, diazino[...][1,4]thiazine, or azino[...]azino[...][1,4]thiazine names (in the last two examples, the two azine rings are the same or different) but with another numbering system. The last system was not always used properly with determination of a place of the ring fusion in square brackets. All those systems were used in Chemical Abstracts after original articles. All of it led to confusion: 1,2-diazaphenothiazines in German articles and patents were in fact 3,4-diazaphenothiazines in American and British articles and patents, 1,3-diazaphenothiazines in fact 2,4-diazaphenothiazines, 2,7-diazaphenothiazines in fact 3,7-diazaphenothiazines. The wrong system numbering causes some misunderstandings, for example: 2,3,6,9-tetraazaphenothiazine should be named as 1,4,7,8-tetraazaphenothiazine. Unfortunately, we found that this confusion is still valid.

It is worth noting that not all azaphenothiazines structures were unequivocally determined, some structures were deduced from chemical properties or spectroscopic

Scheme 3



Scheme 4



data and only a few structures were based on X-ray analysis.

We think that the chemistry of diaza-, triaza-, and tetraazaphenothiazines which consists of over 30 different heterocyclic systems and is published in over 100 articles and patents requires to be reviewed.

The aim of this review is:

1. to arrange and to clarify the chemistry (synthesis and properties) of diazaphenothiazines, triazaphenothiazines, and tetraazaphenothiazines,
2. to discuss the articles and patents of this field up to 2008 and
3. to correct some azaphenothiazine names.

This material has been divided into tricyclic, tetracyclic, and pentacyclic azaphenothiazines with increasing numbers of nitrogen atoms in the systems:

1. diazaphenothiazines (1,2-, 1,3-, 1,4-, 1,6-, 1,9-, 2,3-, 2,4-, 2,7-, 3,4-, 3,6-, and 3,7-),
2. triazaphenothiazines (1,3,4-, 1,3,6-, 1,3,9-, 1,4,6-, 1,4,9-, and 2,3,6-),
3. tetraazaphenothiazines (1,2,6,7-, 1,2,7,8-, 1,3,6,8-, 1,3,6,9-, 1,4,7,8-, 2,3,6,7-, 2,3,6,8-, 2,3,7,8-, 2,4,6,8-, and 3,4,6,7-) and
4. their benzo, dibenzo, and naphtho derivatives.

For this review, to compare the structures of all azaphenothiazines and to clarify discussion, the structures were drawn as the phenothiazine derivatives (the structure **A** in Scheme 7).

Tricyclic diazaphenothiazines. ***1,2-Diazaphenothiazines (pyridazino[4,3-b][1,4]benzothiazines).*** 1,2-Diazaphenothiazines accompanied by 2,3- and 3,4-diazaphenothiazines were achieved in synthesis of the pyridazine derivatives. The first synthesis was carried out by Druey using *o*-aminophenyl 3,6-dichloro-4-pyridazinyl sulfide **1** (obtained from *o*-aminobenzenethiol and 3,4,6-trichloropyridazine) which in acidic medium led to 3-chloro-1,2-diazaphenothiazine **2** (no experimental data included). The same result was obtained when acetylated sulfide **3** was used [17]. Later this first synthesis was repeated giving in concentrated hydrochloric acid expected 3-chloro-1,2-diazaphenothiazine **2** (through postulated its hydrochloride **4**, not isolated) but in diluted hydrochloric acid or acetic acid giving isomeric compound, 2-chloro-3,4-diazaphenothiazine **6** (no yields given), as a product of the Smiles rearrangement to amine **5**. The same product **6** was obtained even from sulfide **7** (Scheme 8) [18,19].

Similar mixtures of isomeric products, 4-chloro-1,2-diazaphenothiazine **10** and 1-chloro-2,3-diazaphenothiazine **11**, were obtained in 51 and 17% yields directly from *o*-aminobenzenethiol **8** and 3,4,5-trichloropyridazine **9** in ethanol in the presence of potassium hydroxide at room temperature. When this reaction of trichloropyridazine **9** was carried out at 30–60°C or with two equivalents of *o*-aminobenzenethiol **8**, the only product was 4-(*o*-aminophenylthio)-1,2-diazaphenothiazine **13**. As 4-chloro-1,2-diazaphenothiazine **10** did not react with aminobenzenethiol **8** in ethanolic potassium hydroxide, the authors postulated the formation of bis-sulfide **12** as an intermediate product (Scheme 9) [20].

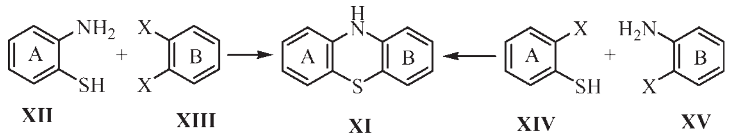
Reaction of 3,4,5-trichloropyridazine **9** with *N*-methylated *o*-aminobenzenethiol **14** (obtained by hydrolysis of 3-methyl-2(3*H*)-benzothiazolinone) in ethanolic potassium hydroxide at 0°C led unexpectedly to 4-chloro-10-methyl-2,3-diazaphenothiazine **15** as the sole product. The same reaction in methanolic potassium hydroxide at room temperature led to expected 4-(*o*-methylaminophenylthio)-1,2-diazaphenothiazine **16** (Scheme 10) [20].

The *N*-methyl analogous of sulfide **1**, sulfide **17**, heated in ethanol (with diluted hydrochloric acid) gave the rearrangement product, 10-methyl-2-chloro-3,4-diazaphenothiazine **18**, but in concentrated hydrochloric acid 10-methyl-3-chloro-1,2-diazaphenothiazine **19** (Scheme 11) [19].

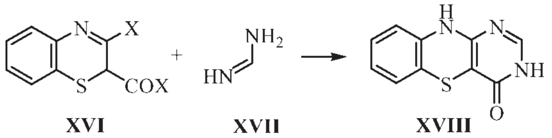
3-Chloro- and 4-chloro-1,2-diazaphenothiazines **10** and **2** were dechlorinated over palladium charcoal to unsubstituted 1,2-diazaphenothiazine **20** what proved the chloro compound structures (Scheme 12) [19,20].

10*H*-3-Chloro-1,2-diazaphenothiazine **2** was alkylated with methyl iodide and diethylaminoethyl chloride in liquid ammonia (with sodium amide) to 10-substituted 1,2-diazaphenothiazines **21** and **22**. The chlorine atom in 3-chloro-1,2-diazaphenothiazines **2** and **21** was

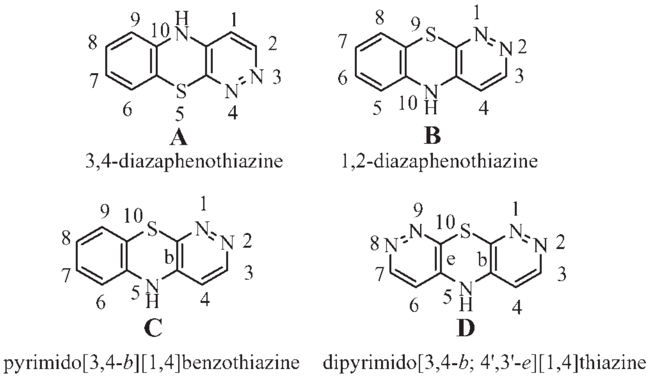
Scheme 5



Scheme 6



Scheme 7



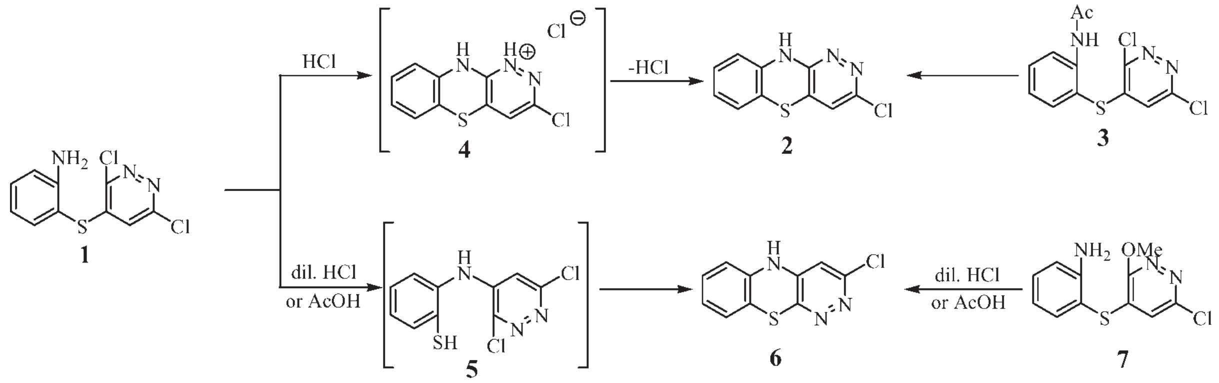
substituted in the reactions of with sodium methoxide and diethylaminoethylamine to give 3-substituted diazaphenothiazines **22** and **23**. Diazaphenothiazine **2** was oxidized with hydrogen peroxide to compound **24**, possessing *S,S*-dioxide and *N*-oxide functions (Scheme 13) [17,18].

Similarly, the chlorine atom in 10*H*-4-chloro-1,2-diazaphenothiazine **10** was substituted with the alkoxy group in the reactions with methanol and ethanol in the presence of sodium, and with dimethylamine in a sealed tube at 160°C to give 4-substituted 1,2-diazaphenothiazines **25** (Scheme 14) [20].

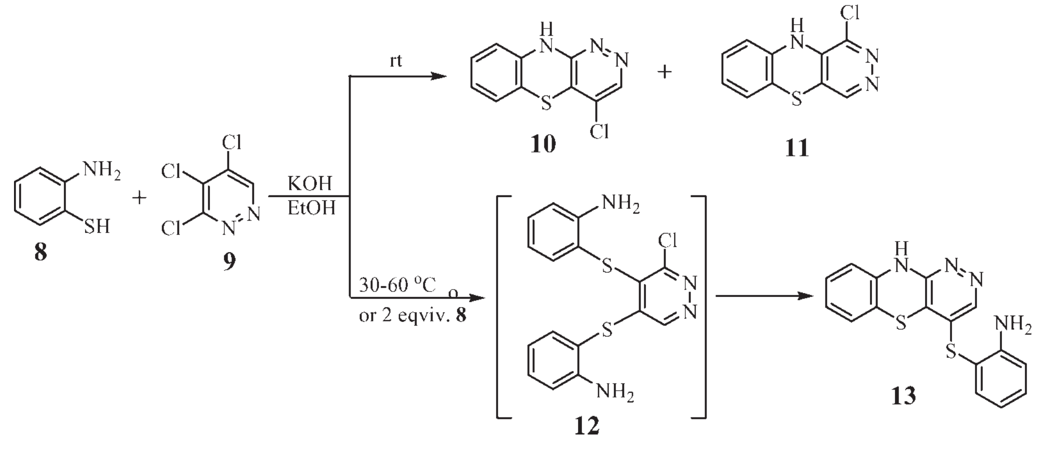
The reactions discussed earlier were later patented [21–24]. Diazaphenothiazine **22** (R_1 = OMe, R = $CH_2CH_2NEt_2$) showed antihistaminic activity [17].

1,3-Diazaphenothiazines (pyrimido[5,4-b][1,4]benzothiazines). 1,3-Diazaphenothiazines were obtained with the use of pyrimidine compounds in reactions which also produced 2,4-diazaphenothiazines. The first synthesis of this azaphenothiazine was carried out by Westermann and coworkers in 1958 who underwent a cyclization of *o*-aminophenyl 4-pyrimidinyl sulfide **25** in DMF (with potassium carbonate) under nitrogen atmosphere

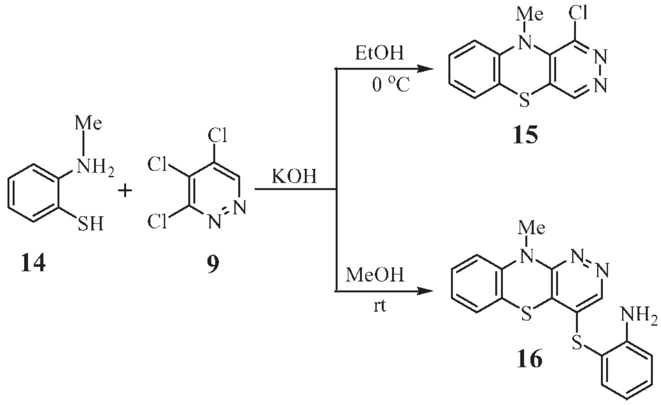
Scheme 8



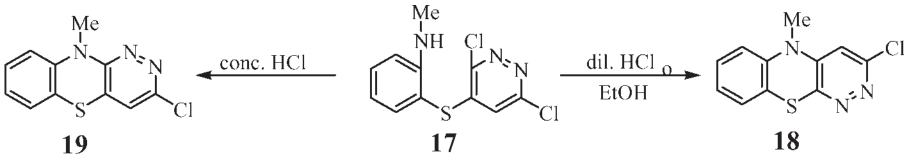
Scheme 9



Scheme 10



Scheme 11

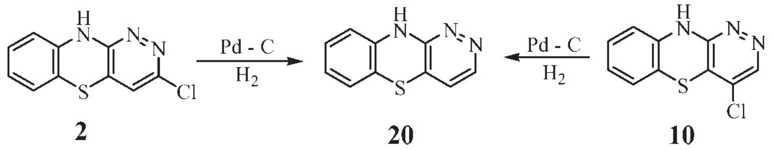


to isomeric 1,3-diazaphenothiazine **26** and 2,4-diazaphenothiazine **27** in very low yield. The discrimination of the isomers was arbitrary. One of the products, diazaphenothiazine **26**, was a result of the Smiles rearrangement occurring during the reaction course (Scheme 15) [25].

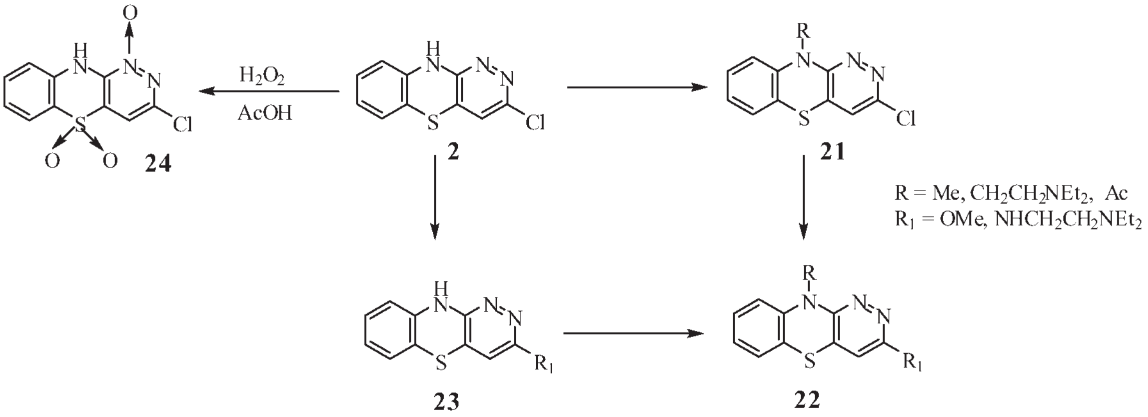
Further cyclizations of substituted sulfides **28** in DMF (with potassium carbonate and copper powder) led to only one product, namely substituted 1,3-diazaphenothiazines **29** in 15–71% yields, through the Smiles rearrangement to the appropriate amines, which, however, were not isolated. Such *o*-mercaptophenyl pyrimidinyl amines **30** (obtained separately) under the same reaction conditions gave 1,3-diazaphenothiazines **29** in moderate yields (42–58%) (Scheme 16) [25].

Later Roth and Phillips with coworkers independently developed a synthesis of 1,3-diazaphenothiazines. Reaction of 4-bromo-5-chloropyrimidine **31** with aminobenzenethiol **8** under basic conditions (ethanol,

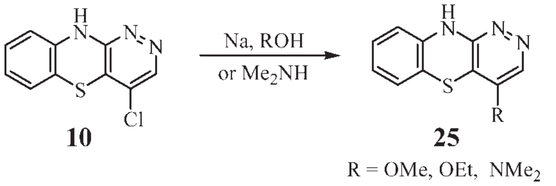
Scheme 12



Scheme 13



Scheme 14

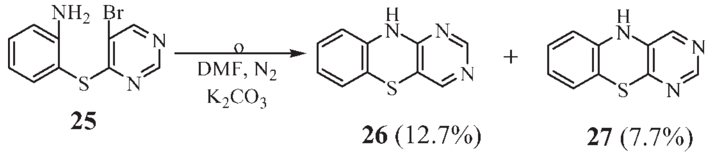


triethylamine) led to aminophenyl 4-pyrimidinyl sulfide **32** which in ethanol and ethanolic hydrogen chloride underwent rearrangement to amine **33** (not isolated) and subsequent acid catalyzed cyclization to 2,4-diamino-1,3-diazaphenothiazine **34** in high yield (95%). The same product was obtained (in 90% yield) directly from compounds **8** and **31** in diluted hydrochloric acid through postulated amine **33** (Scheme 17) [26–28].

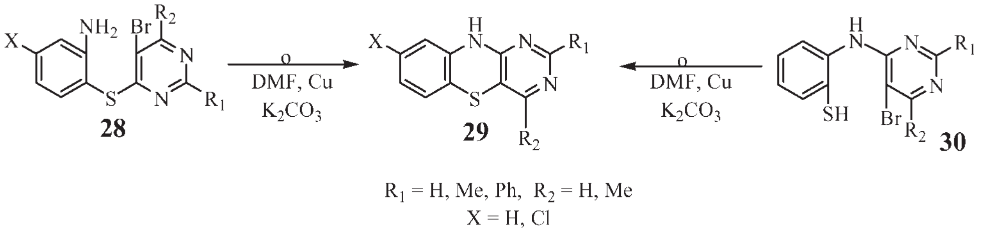
Substituted *o*-aminophenyl 4-hydroxy-5-pyrimidinyl sulfides **35** (obtained from substituted 5-bromoisocytosine or 5-bromouracil and substituted aminobenzenethiols) reacted in a different manner under similar acidic conditions (hydrochloric acid or sulfuric acid in 85% ethanol) to produce various substituted 1,3-diazaphenothiazines **37** without the Smiles rearrangement [29]. Later the authors (Roth and Bunnett) [30] proposed another structure of starting materials, the keto tautomers, *o*-aminophenyl 4-oxo-3,4-dihydro-5-pyrimidinyl sulfides **36** which explains well the attack of the amino group at the carbonyl carbon (at position 4, instead of position 5) and the resulting formation of the thiazine ring. Cyclization of various sulfides **36** led to substituted 1,3-diazaphenothiazines **37**, possessing substituents in positions 2 (mainly), 4, 7, and 8 (Scheme 18). 2-Hydroxy-1,3-diazaphenothiazines **37** (R_1 = OH) were transformed into the chloro derivatives **37** (R_1 = Cl) in the reaction with phosphoryl chloride and further *via* dichloro substitution to other derivatives **37** (R_1 = OMe, OCH_2CH_2OMe, SH, $NHNH_2$, $NHCH_2CH_2NMe_2$, $NHCH_2CH_2CH_2NMe_2$, *etc*). 2-Hydrazino-1,3-diazaphenothiazine **37** (R_1 = NH_2NH_2, R_2 and X = H) was transformed to parent 1,3-diazaphenothiazine **26** in the action of hydrochloric acid and copper sulfate [29].

Many various multisubstituted 1,3-diazaphenothiazines were obtained using these methods and were patented [30–35]. When alkylamino compounds **38** were

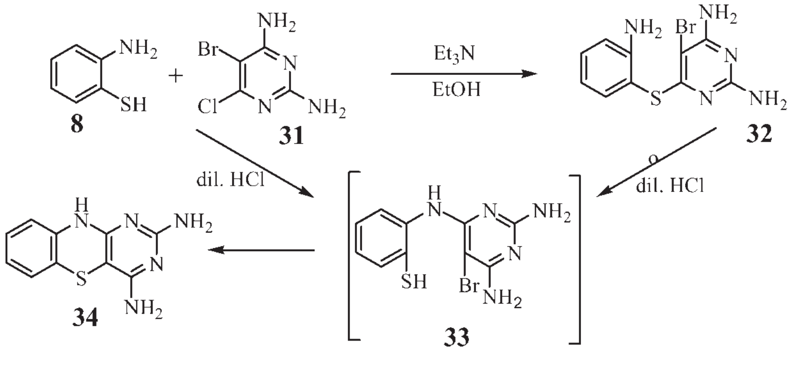
Scheme 15



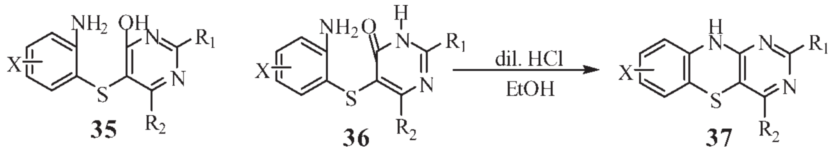
Scheme 16



Scheme 17



Scheme 18

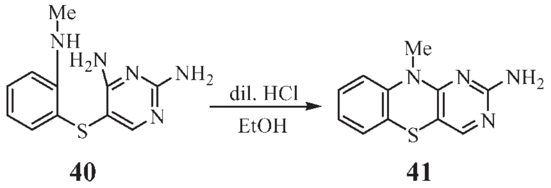


R_1 = OH, NH_2, NMe_2, morpholinyl, piperidynyl, $NHCH_2CH_2CH_2NMe_2$
R_2 = H, Me, Cl
X = 7,8-Me_2, 8-Cl

Scheme 19

R = Me, Bu

Scheme 20



used in ethylene glycol (with potassium carbonate) under nitrogen, the reaction led to 10-alkyl-1,3-diazaphenothiazines **39** (Scheme 19) [36].

The very interesting sulfide **40** possessing three amino groups, reacted by intramolecular substitution of the amino group with the methylamino group in ethanol containing hydrochloric acid, giving 10-methyl-1,3-diazaphenothiazine **41** (Scheme 20) [36].

Reactions of *N*-substituted phenyl uracilyl sulfides **42** (obtained from substituted aminobenzenethiols and bromochlorouracils) in ethanol or DMF underwent the Smiles rearrangement and cyclization to 10-substituted 1,3-diazaphenothiazine-2,4(1*H*,3*H*)-diones **43** in excellent yield (75–93%) [37]. On the contrary, phenyl uracilyl sulfide **44** in acetic acid or in alcohol with hydrochloric acid underwent cyclization without the rearrangement (Scheme 21) [38,39].

Reactions of substituted aminobenzenethiols **45** with 5-bromo- and 5-bromo-5-nitrobarbituric acids **46** and **47** led to 10*H*- and 10*H*-4a-nitro-1,3-diazaphenothiazine derivatives **48** and **49** (Scheme 22) [40].

Reaction of aminobenzenethiol **8** with *N*-substituted chloronitrouracil **50** in benzene (with triethylamine) proceeded *via* the Smiles rearrangement to give 10*H*-1,3-diazaphenothiazine-2,4(1*H*,3*H*)-dione **51** (Scheme 23) [41].

Very interesting transformations were described in Pfizer's patents [42,43]. Substituted anilinouracils **52** underwent cyclization with thionyl chloride in chloroform under nitrogen atmosphere to 4a-chloro derivatives of 1,3-diazaphenothiazine **53**. The chloro derivatives **53** with reducing agents (hydrazines, zinc, or reducing cations and anions) in methylene chloride gave stable radicals **54** or (with excess of agents) 1,3-diazaphenothiazine-2,4(1*H*,-3*H*)-diones **55**. The chloro derivatives **53** were transformed into 4a-substituted derivatives **56** by substitution of the reactive chlorine atom (Scheme 24).

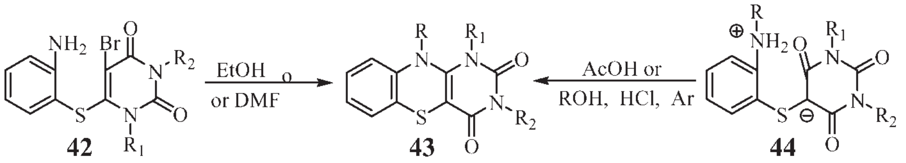
Reaction of *N*-tetraacetylribityl derivative of anilinouracil **57** with sulfur chloride in chloroform led to 10-tetraacetylribityl-1,3-diazaphenothiazinedione **58** which was deacetylated with ammonia in moderate yield (Scheme 25) [44].

Pyrimidobenzothiazepines **60** in the reaction with iodine in morpholine underwent a ring contraction to give 10*H*-1,3-diazaphenothiazinedione **51** but with iodine or *N*-halogenosuccinimide in other solvents gave 4a-substituted derivatives **61** (Scheme 26) [45].

An unusual synthesis was described by Granik and Luszkov who built the 1,3-diazine ring in benzothiazine **62** in reactions with substituted amidines **63** giving 1,3-diazaphenothiazines **64** or **65** (Scheme 27) [46].

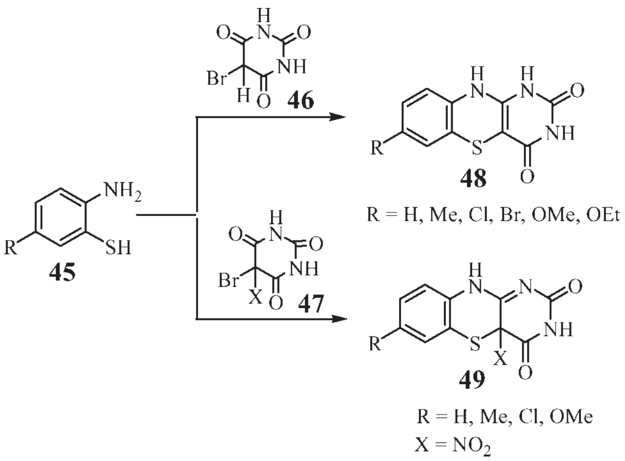
10*H*-1,3-Diazaphenothiazines **37** were transformed into 10-substituted 1,3-diazaphenothiazines **66** in the

Scheme 21



R = H, Me, $CH_2CH_2CH_2NMe_2$
R_1, R_2 = H, Me

Scheme 22



reaction with alkyl and aminoalkyl chlorides in DMF or xylene (with sodium amide or sodium hydride) (Scheme 28) [36,47].

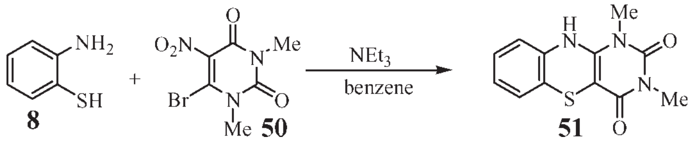
Much more complicated was the alkylation of 1,3-diazaphenothiazine-2,4(1*H*,3*H*)-diones which led to *N*-, *O*-, *C*-, and *N*-alkylated products. The alkylation of 1,3-dialkyl compound **67** with alkyl halides or sulfates in DMF (with sodium hydride) led unexpectedly to the *S*-alkyl ylide **68** alone or with 4a-alkyl derivatives **69** [42,48]. When only allyl iodide was used, 4a-allyl derivative **69** was obtained (Scheme 29) [48]. In contrast to the alkylation of 10*H*-1,3-diazaphenothiazine, the alkylation of 10*H*-1,3-diazaphenothiazinediones **67** (R = H) did not proceed at the nitrogen atom in position 10.

Alkylation of 1,3-unsubstituted 1,3-diazaphenothiazines **70** in DMF (with potassium carbonate) yielded the *N*-, *O*-, and *C*-alkylated products **71-73** (Scheme 30) [39].

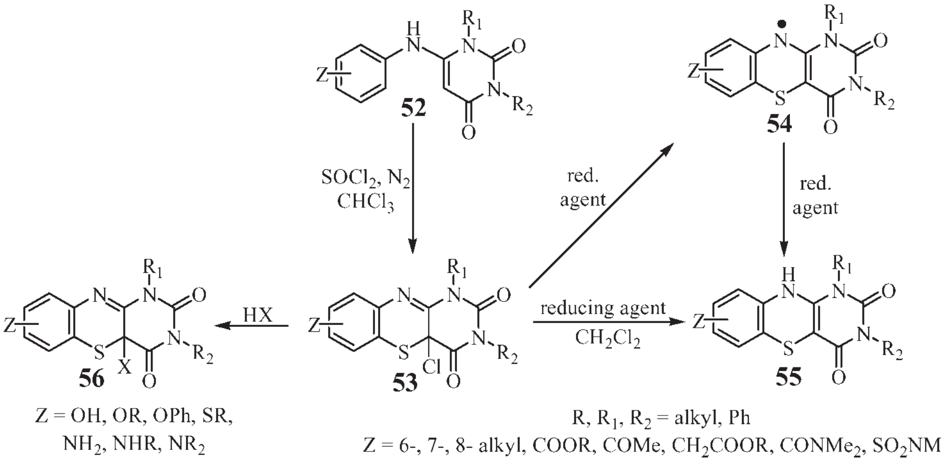
When 3,10-dimethyl-1,3-diazaphenothiazinedione **74** was alkylated in chloroform in the presence of diisopropylethylamine, the *S*-alkyl ylide of another type **75** was obtained in 100% yield (Scheme 31). Alkylation in DMF gave different products depending on the alkyl halide nature [39].

An X-ray analysis of selected sulfonium ylide (provided by Pfizer Co.) confirmed the structure as the *S*-alkyl compound and the major canonical structure was proposed as **76** (Scheme 32) [49].

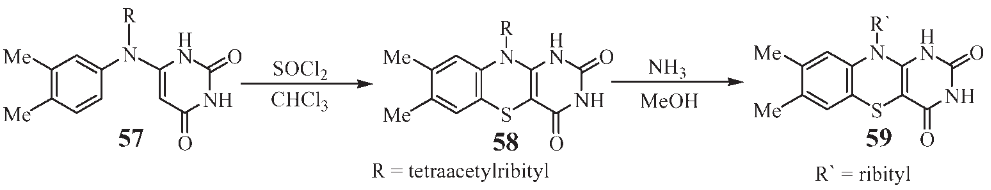
Scheme 23



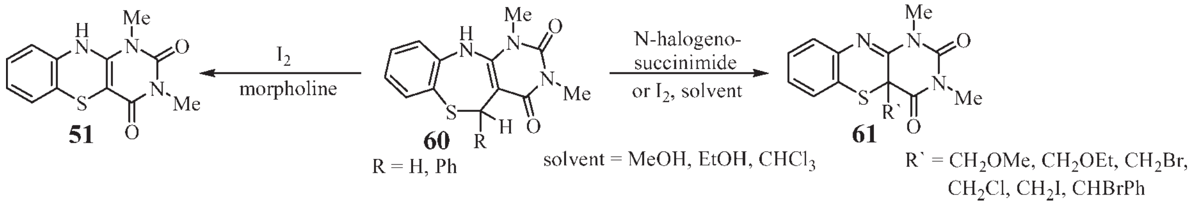
Scheme 24



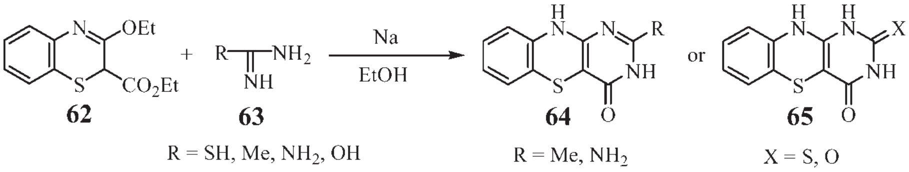
Scheme 25



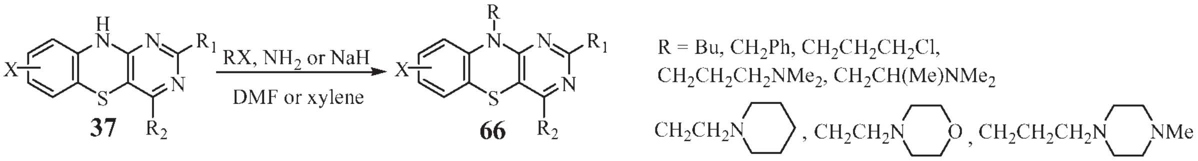
Scheme 26



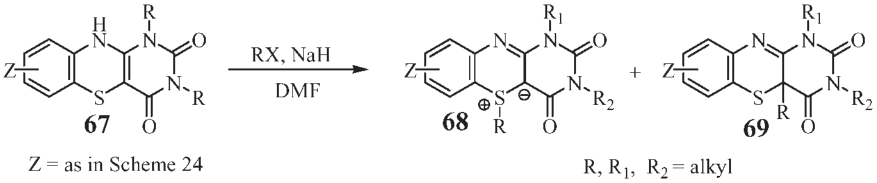
Scheme 27



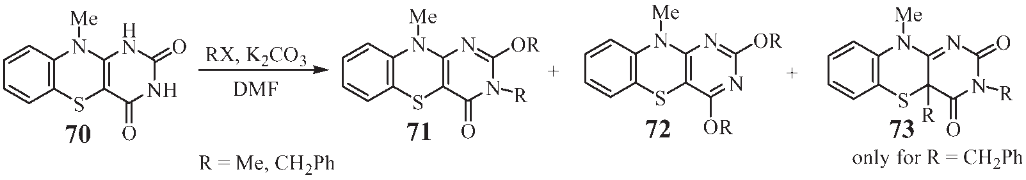
Scheme 28



Scheme 29

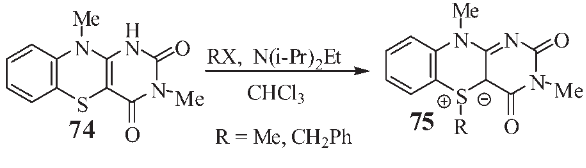


Scheme 30

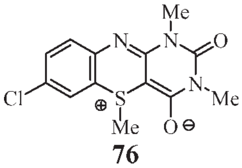


Although alkylation of 10*H*-1,3-dialkyl-1,3-diazaphenothiazinediones **77** proceeded mainly to *S*-ylides, heating those compounds induced thermal rearrangement (the S→N type) to 10-alkyl derivatives **78**. Ultraviolet irradiation induced a ring expansion to pyrimidobenzothiazepines **79** (Scheme 33) [48].

Scheme 31

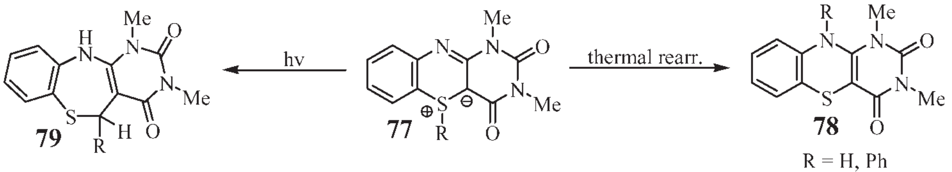


Scheme 32



76

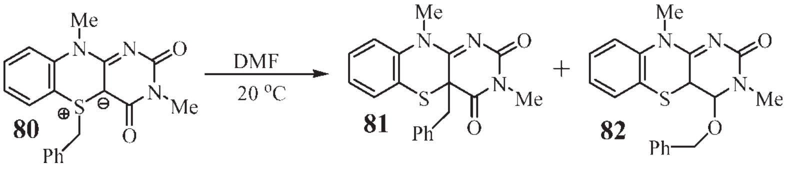
Scheme 33



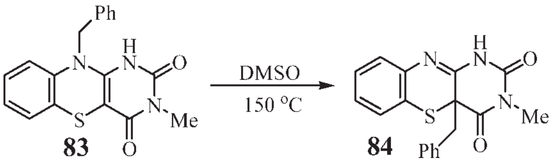
R = Me, Et

R = H, Ph

Scheme 34



Scheme 35



On the other hand, *S*-ylide **80** in DMF underwent the S→C and S→O benzyl group migration to give 4a-benzyl and *O*-benzyl derivatives **81** and **82** (Scheme 34) [49].

The benzyl group in compound **83** during heating in DMSO underwent the N→C migration to give derivative **84** (Scheme 35) [49].

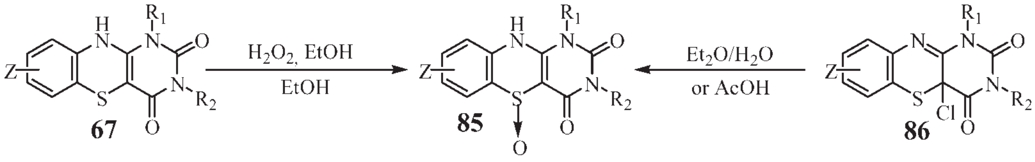
10*H*-1,3-Diazaphenothiazinediones **67** were oxidized with hydrogen peroxide in ethanol giving *S*-oxide derivatives **85**. The same compounds were obtained from 4a-chloro compound **86** in ether/water or acetic acid (Scheme 36) [42].

Both 4a-chloro derivatives **53** and *S*-oxide **85** heated in aqueous acetone or glacial acetic acid on a steam bath underwent degradation to imidazolylbenzothiazole derivatives **87** (Scheme 37) [43].

1,3-Diazaphenothiazine-2,4-diones with sulfuric acid and diacetyl gave a radical cation and a radical, respectively [50]. Several alkyl, amino, and aminoalkyl 1,3-diazaphenothiazines exhibited antibacterial activity against *Streptococcus fecalis, Escherichia coli, Staphylococcus aureus, Proteus vulgaris*, and *Pseudomonas aeruginosa* [31–36], and analgesic and anti-inflammatory activity [37].

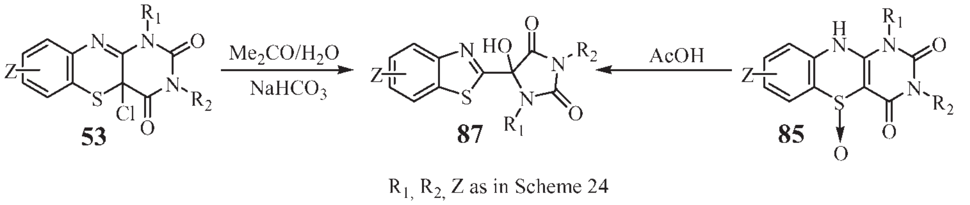
1,4-Diazaphenothiazines (pyrazino[2,3-b][1,4]benzothiazines). The first synthesis of 1,4-diazaphenothiazine was described by Gulbenk and coworkers in their patents in 1972–1974 [51–53]. Reaction of

Scheme 36



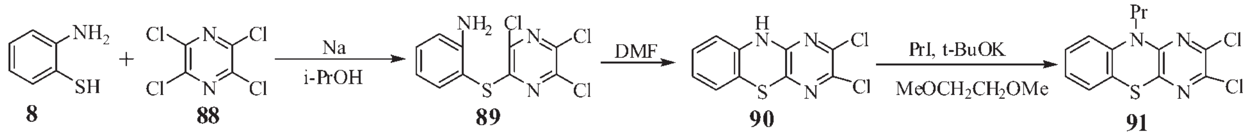
R_1, R_2, Z as in Scheme 24

Scheme 37

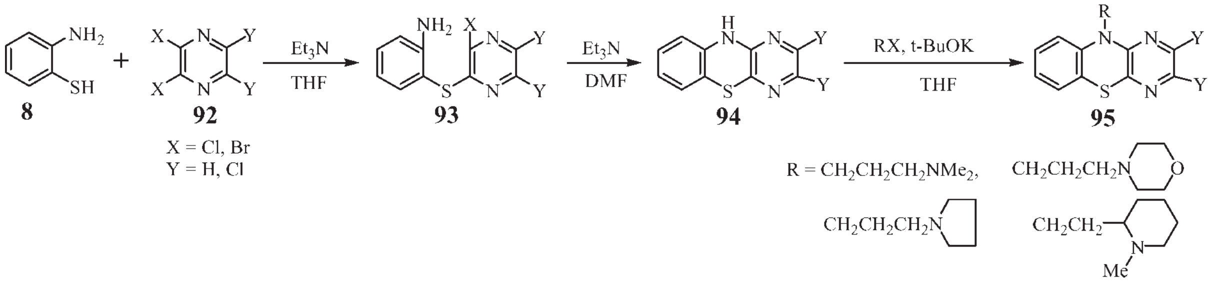


R_1, R_2, Z as in Scheme 24

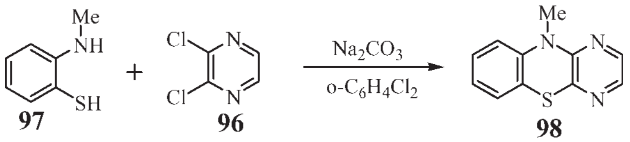
Scheme 38



Scheme 39



Scheme 40



tetrachloropyrazine **88** with aminobenzenethiol **8** in isopropyl alcohol (in the presence of sodium) led to aminophenyl pyrazinyl sulfide **89** which further in DMF cyclized to 2,3-dichloro-1,4-diazaphenothiazine **90**. *N*-Alkylation of compound **90** with propyl iodide in dimethoxyethane (with potassium *t*-butoxide) gave 10-propyl derivative **91** (Scheme 38).

During the same time period, Tong in his patent [54] described reactions of aminobenzenethiol **8** not only with tetrachloropyrazine **88** but also with dichloro- and dibromopyrazine **92** in THF in the presence of triethylamine. The obtained aminophenyl pyrazinyl sulfides **93** underwent cyclization in DMF to yield 1,4-diazaphenothiazines **94** (in 70% yield for unsubstituted product). The last compounds were transformed into the 10-aminoalkyl derivatives **95** in the aminoalkylation with aminoalkyl chlorides in THF (with potassium *t*-butoxide, Scheme 39).

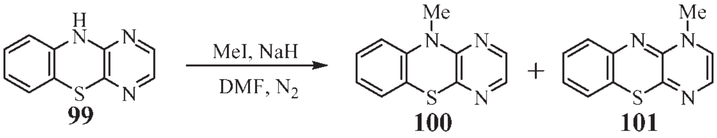
Later other authors [55,56], unaware of those patents, carried out the reaction of 2,3-dichloropyrazine **96** with aminobenzenethiol **8** in *o*-dichlorobenzene (with sodium carbonate) to give 10*H*-1,4-diazaphenothiazine **94** (Y = H) in 62% yield. Excellent yield (94%) of diazaphenothiazine **94** was achieved when this reaction was carried out in DMF (with sodium hydroxide) [57]. When *o*-methylaminobenzenethiol **97** was used instead of compound **8**, 10-methyl-1,4-diazaphenothiazine **98** was obtained in 63% yield (Scheme 40) [55].

Methylation of 10*H*-1,4-diazaphenothiazine **99** with methyl iodide in DMF (in the presence of sodium hydride) under nitrogen atmosphere gave the expected 10-methyl derivative **100** in 75% yield and the unexpected side product **101** (1-methyl derivative) in 1.2% yield (Scheme 41) [55].

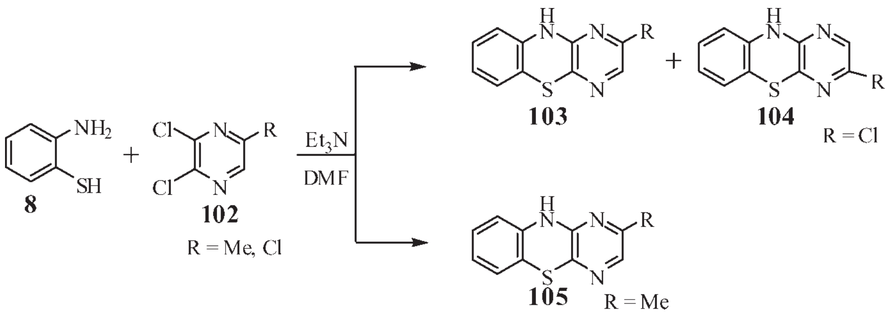
When unsymmetrical pyrazine derivatives, 2,3,5-trichloropyrazine and 2,3-dichloro-5-methylpyrazine **102** were used, one or two diazaphenothiazines were formed because of possibility of accompanying Smiles rearrangement. Reaction of compound **102** (R = Cl) with aminobenzenethiol **8** in DMF led to 2-chloro- and 3-chloro-10*H*-diazaphenothiazines **103** and **104** in 26 and 15% yields. The isomers were discriminated on the basis of NMR long range ^{13}C-^{1}H couplings and confirmed by X-ray analysis of isomer **103**. Reaction with compound **102** (R = Me) led only to one product, 2-methyl derivative **105**, in 66% yield (Scheme 42) [58].

In the reaction of dichloropyrazine **96** with 4-chloro-2-aminobenzenethiol **106** the sulfide **107** was isolated in 57% yield which further heated without solvent at 220°C underwent cyclization to 8-chloro-1,4-diazaphenothiazine **108** in 47% yield (Scheme 43) [58].

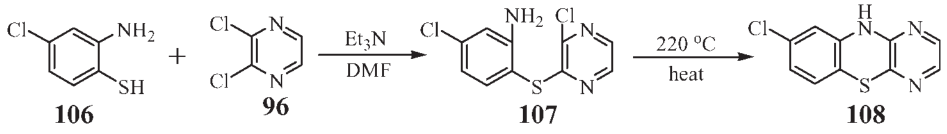
Scheme 41



Scheme 42



Scheme 43

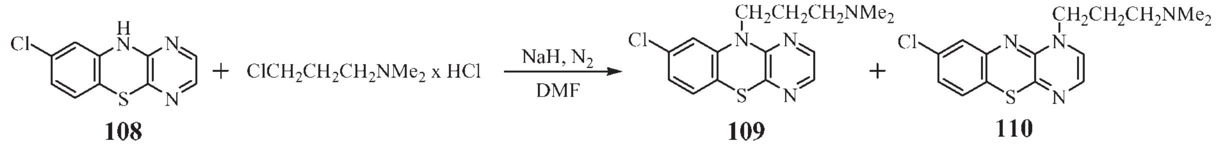


Alkylation of substituted 10*H*-1,4-diazaphenothiazines with aminoalkyl chlorides or their hydrochlorides in DMF (with sodium hydride) in nitrogen atmosphere gave 10-aminoalkyl derivatives which were transformed further into hydrochlorides. Only when 8-chloro-1,4-diazaphenothiazine **108** was alkylated with dimethylaminopropyl chloride hydrochloride two products, 10- and 1-dimethylaminopropyl-1,4-diazaphenothiazine **109** and **110**, were isolated as hydrochlorides in 47 and 17% yields (Scheme 44) [58].

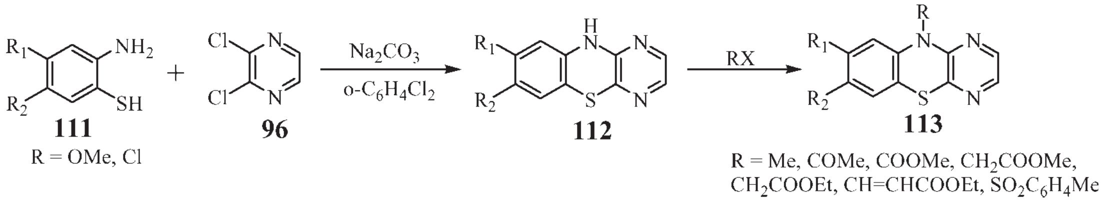
10*H*-1,4-Diazaphenothiazine **99** was once more obtained from sulfide **93** (X = Cl, Y = H) but this time with DBU in pyridine. Using substituted *o*-aminobenzenethiols **111** and 2,3-dichloropyrazine **96** in *o*-dichlorobenzene (with sodium carbonate), 1,4-diazaphenothiazines **112** were obtained, which were further *N*-alkylated, acylated, and sulfonylated to give various derivatives **113** (Scheme 45) [59].

Very recently Kaneko et al. [60–62] synthesized 8-methoxycarbonyl-10*H*-1,4-diazaphenothiazine **115** from 2-amino-4-methoxycarbonylbenzenethiol **114** and 2,3-dichloropyrazine **96** in DMF. The obtained 8-methoxycarbonyl compound was reduced with lithium aluminum hydride to 8-hydroxymethyl derivative **116**. Because of low stability of aminobenzenethiol **114**, a second route was elaborated from phenyl pyrazinyl sulfide **117** (obtained from 3-nitro-4-mercaptobenzyl alcohol and 2,3-dichlo-ropyrazine **96** followed by reduction of the nitro group). Sulfide **117** cyclized in methanol containing hydrochloric acid to give 8-hydroxymethyl derivative **116** in high yield of 99%. This compound was transformed into the chloromethyl derivative **118** by chlorination with methanesulfonyl chloride in DMF/pyridine under nitrogen atmosphere. Reactions of chloromethyl compound **118** with secondary monocyclic and bicyclic amines gave about 60 of 2-aminomethyl

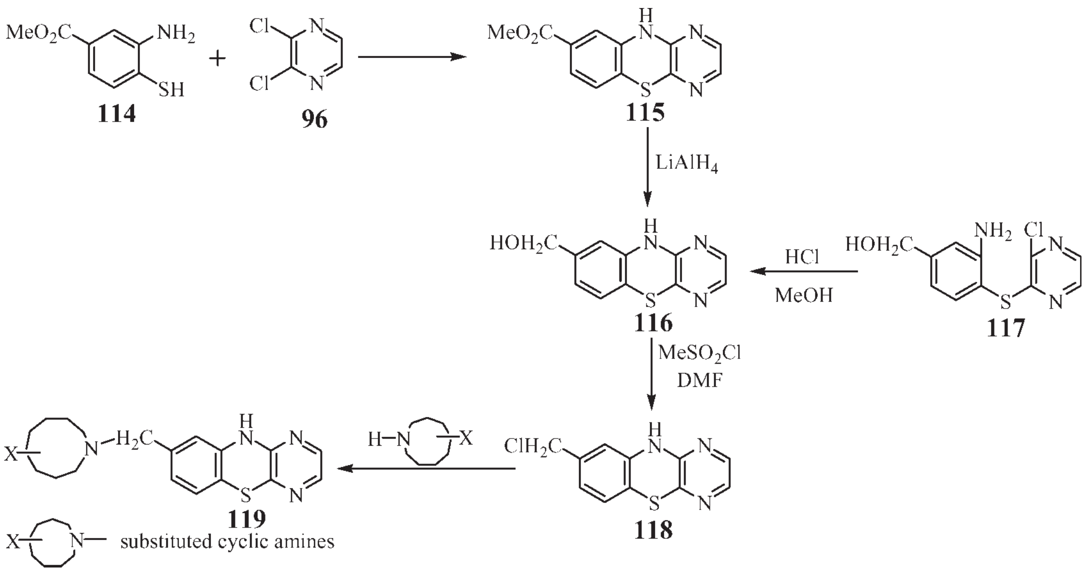
Scheme 44



Scheme 45



Scheme 46



derivatives **119** of biological activity (Scheme 46) [60–62].

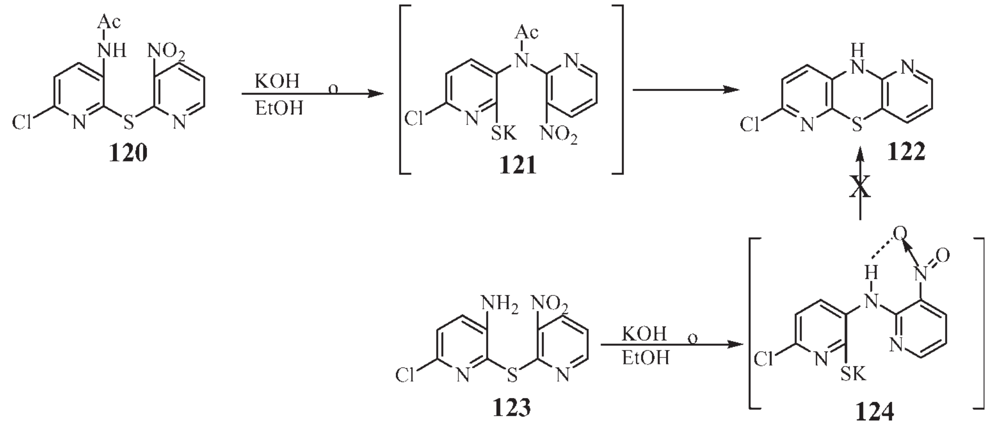
1,4-Diazaphenothiazines were transformed into other derivatives: by oxidation with hydrogen peroxide or potassium permanganate to *S*-oxides and *S,S*-dioxides [55,56,59,63], by nitration to the nitro compounds [55,56] or by reaction with iodobenzene to benzothiazole compound [55]. Most of 1,4-diazaphenothiazines exhibited very interesting biological activities: bactericidal, fungicidal, herbicidal [51–54,63], insecticidal [51–54], helminthicidal, pesticidal [51–53], neuroleptic [58], and are inhibitors of the 5-lipoxygenase enzyme system [59] and promising candidates for the treatment of autoimmune inflammatory diseases [61,62].

1,6-Diazaphenothiazines (dipyrido[2,3-b;2′,3′-e][1,4] thiazines). The first synthesis of 1,6-diazaphenothiazines was described by Maki [64]. Reaction of 3-acetylamino-6-chloro-3′-nitro-2,2′-dipyridinyl sulfide **120** (obtained from 3-amino-6-chloro-2(1*H*)-pyridinethione and 2-chloro-3-nitropyridine followed by acetylation) in ethanol (with sodium hydroxide) underwent cyclization to 7-chloro-10*H*-1,6-diazaphenothiazine **122** in 68% yield through the Smiles rearrangement to dipyridinyl amine **121**. During cyclization the acetyl group was hydrolyzed. It is interesting that the nonacetylated sulfide **123** did not undergo cyclization due to a conformation **124** produced by the hydrogen bondings between the amino and nitro groups (Scheme 47).

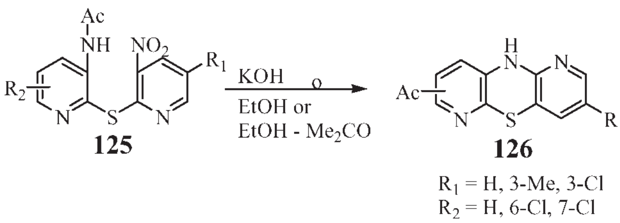
Similar procedures were used to obtain unsubstituted, 3-methyl-, 3,6-dichloro-, and 3,7-dichloro-1,6-diazapheno-thiazines **126** from appropriate dipyridinyl sulfides **125** with acetylamino groups (Scheme 48) [65–67].

Nonacetylated amines **127** (obtained directly from appropriate aminopyridinethiones and chloronitropyridines or from 3-amino-3′-nitro-2,2′-dipyridinyl sulfides *via* the Smiles rearrangement in basic or acidic media)

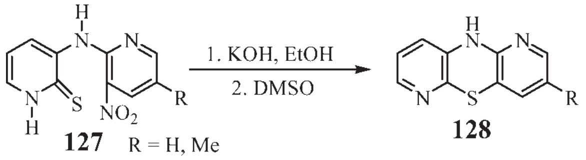
Scheme 47



Scheme 48



Scheme 49



[67,68] were able to undergo cyclization to 1,6-diazaphenothiazines **128** in DMSO (potassium hydroxide and ethanol were used to obtain potassium pyridinethiolate) (Scheme 49) [67].

Very interesting was the reaction of dipyridinyl amine **129** with 2-chloro-3-nitropyridine **130** to give compound **131**, possessing three pyridine units, which cyclized in DMSO through the Smiles rearrangement to 10-(3′-nitro-2′-pyridinyl)-1,6-diazaphenothiazine **132** (in 78% yield, Scheme 50) [67].

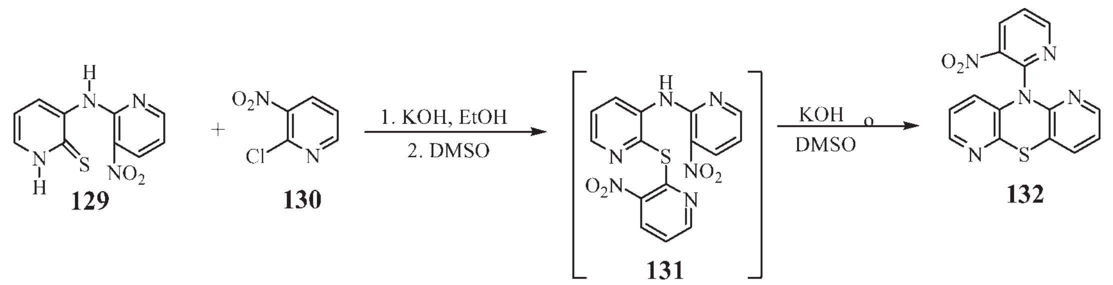
10-Substituted 1,6-diazaphenothiazines **133** and **134** were obtained from unsubstituted compound **126** in the reaction with acrylonitrile and dimethylaminopropyl chlorides (Scheme 51) [65,67].

3-Dimethylaminopropyl derivatives turned out to be more toxic than chlorpromazine and produced CNS depression) [65,67].

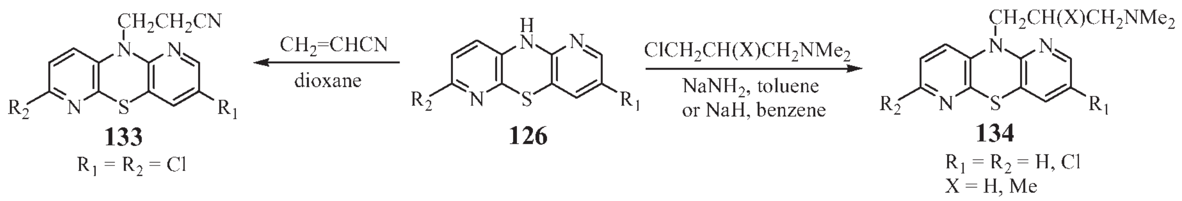
1,9-Diazaphenothiazines (dipyrido[3,2-b;2′,3′-e][1,4] thiazines). 10*H*-1,9-Diazaphenothiazine **136** was obtained by Rath in the sulfurization of 2,2′-dipyridinyl amine **135** with elemental sulfur at higher temperature (no details) and was converted into dimethylaminopropyl derivative **137** using dimethylaminopropyl chloride in xylene (with sodium amide) (Scheme 52) [69].

2,3-Diazaphenothiazines (pyridazino[4,5-b][1,4] benzothiazines). 1-Chloro-2,3-diazaphenothiazine **11** was obtained beside 4-chloro-1,2-diazaphenothiazine **10** in the reaction of aminobenzenethiol **8** with trichloropyridazine **9** as was already mentioned (Scheme 9) [20]. The first synthesis of 2,3-diazaphenothiazine was carried out in 1962 by heating aminophenyl pyridazinyl sulfide **138** in acetic anhydride to give 10-acetyl-2,3-diazaphenothiazin-1(2*H*)-one **139** which was deacetylated to 10*H*-derivative **140** in methanolic potassium hydroxide (Scheme 53) [70].

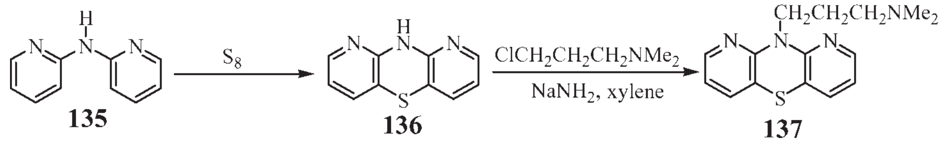
Scheme 50



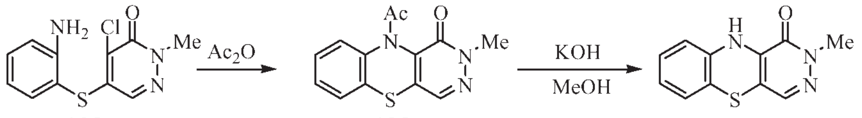
Scheme 51



Scheme 52

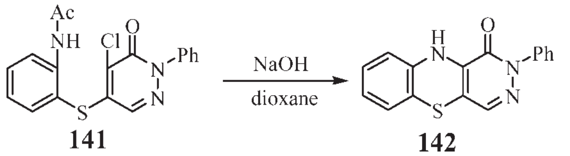


Scheme 53



138 **139** **140**

Scheme 54



141 **142**

Similarly, *N*-acetylaminophenyl pyridazinyl sulfide **141** heated in dioxane (with sodium hydroxide) gave at once 10*H*-2,3-diazaphenothiazinone **142** (Scheme 54) [70].

Later, Yoneda, Nitta, and Ohtaka published and patented reactions of aminophenyl pyrazinyl sulfides **143** which underwent cyclization with or without the Smiles rearrangement to isomeric 10*H*-2,3-diazaphenothiazinones **144** or **145** depending on the reaction conditions (basic or acidic, Scheme 55) [20,71–74].

In the same time Scapini, Duro, and Pappalardo carried out cyclization of sulfide **146** under basic conditions (acetone, potassium hydroxide) to obtain 10*H*-2,3-diazaphenothiazinon-4(3*H*)-ones **147** *via* the Smiles rearrangement (Scheme 56) [75].

Later, two teams (Pappalardo, Duro, and Maki with coworkers) independently carried out a similar cyclization of sulfide **141** under basic conditions to give phenyl derivatives of 10*H*-2,3-diazaphenothiazinon-4(3*H*)-one **148** *via* the Smiles rearrangement [76,77]. Sulfide **141** in acidic medium gave isomeric 10*H*-2,3-diazaphenothiazinon-1(2*H*)-one **142** (Scheme 57) [76].

The same product **142** was obtained in the cyclization of sulfide **149** under acidic conditions. The structure of the product was supported by unequivocal synthesis using amine **150** (Scheme 58) [76].

The 2,3-diazaphenothiazine chemistry was later widely explored mainly by Duro and Pappalardo with coworkers. They used various substituted aminophenyl pyridazinyl sulfides **151** which under basic conditions cyclized *via* the Smiles rearrangement, but under acidic conditions without the rearrangement, to give isomeric substituted 2,3-diazaphenothiazinones **152** and **153**, respectively. Whereas the acetyl group was deacetylated in the acidic medium during the synthesis (to form 10*H*-2,3-diazaphenothiazinones **153**, R = H), in basic medium was most often stable (Scheme 59) [78–84].

A very unusual synthesis was carried out using bis-sulfide **154** which underwent cyclization under basic conditions to 10*H*-2,3-diazaphenothiazin-4-one **155**. The *N*-acetylaminobenzenethiolate group turned out to be a quite good leaving group (Scheme 60) [75].

Similarly, bis-sulfide **156** gave 10*H*- and 10-acetyl-2,3-diazaphenothiazine-1,4-diones **157** (Scheme 61) [85].

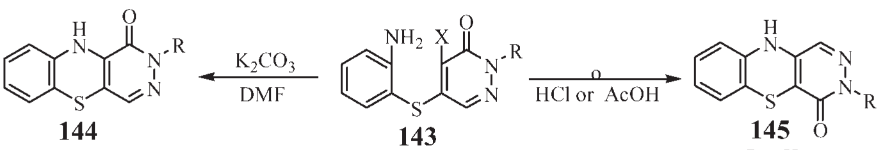
When *N*-methylaminophenyl pyridazinyl sulfide **158** was used in acidic medium, the product was identified as 3,10-dimethylphenothiazinium perchlorate **159** (Scheme 62) [79].

The direct synthesis of 2,3-diazaphenothiazinones with the use of aminobenzenethiols and pyridazine derivatives was less explored. Reactions of *N,S*-diacetyl derivatives of aminobenzenethiol **160** with dibromopyridazinones **161** under basic conditions led to 10*H*-2,3-diazaphenothiazinon-4(3*H*)-ones **147** (Scheme 63) [75].

On the other hand, aminobenzenethiol and its acetyl derivatives **162** reacted with dihalogenopyridazinones **163** in the presence of equimolar amount of sodium hydroxide (in methanol) to form 10*H*-2,3-diazaphenothiazin-1(2*H*)-one **164**. The same product **164** was obtained when potassium carbonate in DMF was used. When two equivalents of sodium hydroxide or equimolar amount of potassium hydroxide were used, isomeric 10*H*-2,3-diazaphenothiazinon-4(3*H*)-ones **165** were formed (Scheme 64) [72,86].

Similarly, reaction of *N*-methylaminobenzenethiol **97** with dibromopyridazinedione **166** led to two 2,3-diazaphenothiazine-1,4-diones **167** and **168** depending on the amount of sodium hydroxide (Scheme 65) [82].

Scheme 55

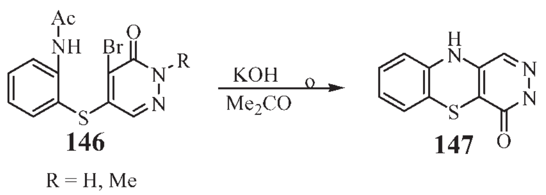


144
R = H, Me

143
X = Cl, Br

145
R = H

Scheme 56



When potassium hydroxide was used in the reaction of *N*-acetylaminobenzenethiol **14** with dibromopyridazinedione **169** only one 2,3-diazaphenothiazine-1,4-dione **170** was obtained (Scheme 66) [83].

Reaction of *N,S*-diacetyl derivative of aminobenzenethiol **160** with dibromopyridazinediones **171** under basic conditions led to 10*H*- or 10-acetyl-2,3-diazaphenothiazine-1,4-diones **172** (Scheme 67) [85,87].

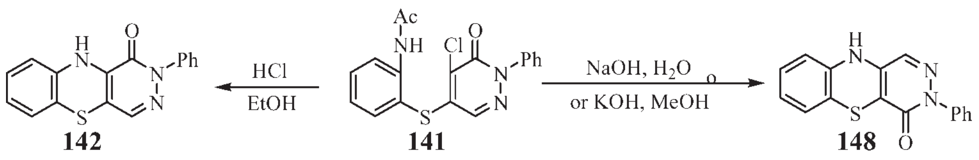
A very rare method of synthesis of an azine ring in the multiazaphenothiazine chemistry was applied by Pappalardo and coworkers. 2,3-Di(ethoxycarbonyl)-1,4-benzothiazine **173** in the annulation reaction with hydrazines led to 10*H*-2,3-diazaphenothiazine-1,4-diones **174** by building of the pyridazinedione ring (Scheme 68) [85,87].

The chemistry of 2,3-diazaphenothiazines involves alkylation, the transformation of the oxo functions, substitution of the chlorine atoms, building an azole ring, nitration and oxidation. Alkylation of 10*H*-2,3-diazaphenothiazine **175** with methyl iodide or sulfate in methanol (with addition of perchloric acid) proceeded smoothly in the pyridazine ring to give a mixture of 2- and 3-methyl-10*H*-2,3-diazaphenothiazinium perchlorates **159** and **176** (Scheme 69) [79].

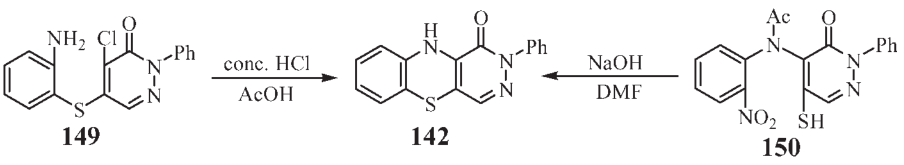
Chloro-2,3-diazaphenothiazines **177** gave only one methylation product with the methyl group farther from the chlorine atom (Scheme 70) [79].

The alkylation of 10*H*-2,3-diazaphenothiazinones **180** and **181** with methyl iodide or aminoalkyl chlorides

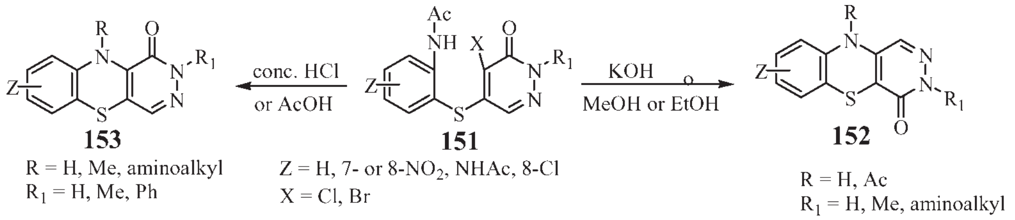
Scheme 57



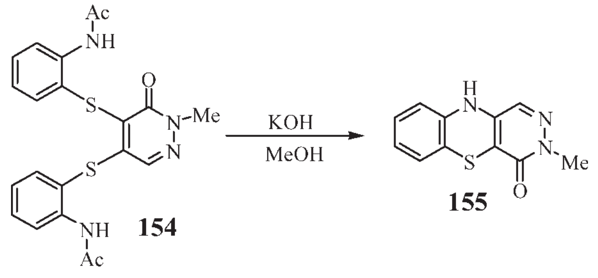
Scheme 58



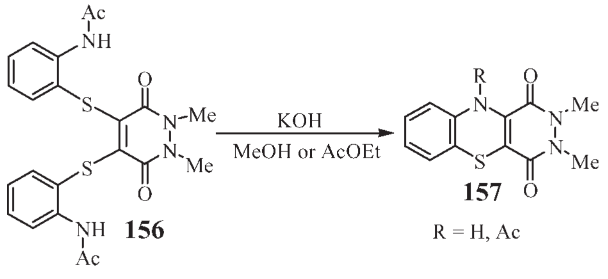
Scheme 59



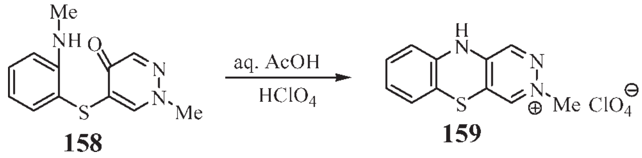
Scheme 60



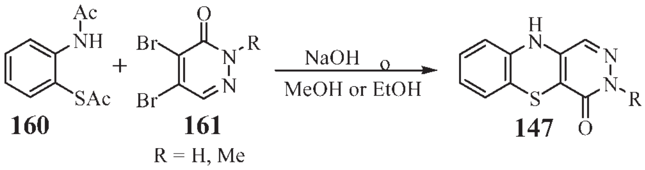
Scheme 61



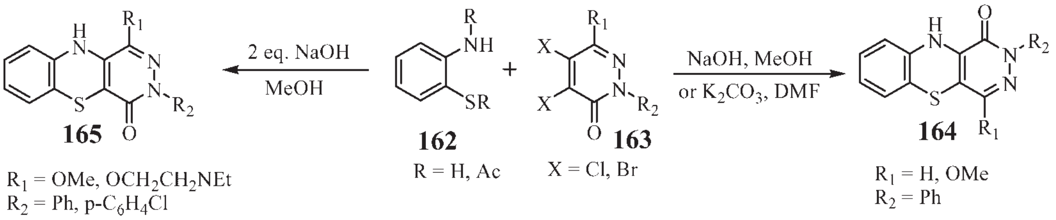
Scheme 62



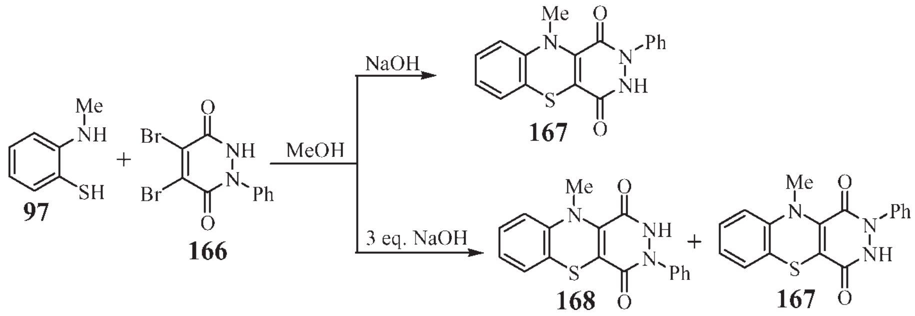
Scheme 63



Scheme 64



Scheme 65

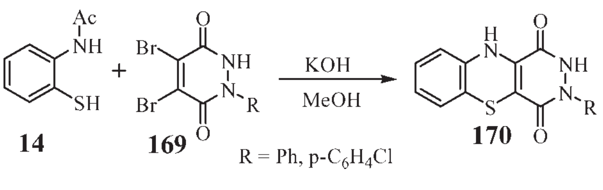


under basic conditions proceeded in the pyridazinone ring to give appropriate 2- and 3-alkyl derivatives **182** and **183** (Scheme 71) [20,71,73,83,84,88,89]. Much more complicated was the alkylation of 10*H*- and 10-methyl-2,3-diazaphenothiazine-1,4-diones giving not only expected *N*-methyl but also *O*-methyl derivatives [77,86].

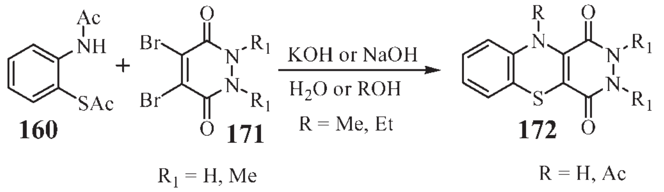
A very interesting distinction of isomeric phenyl derivatives of 10*H*-2,3-phenothiazinones **142** and **148** was carried out by action of sodium ethoxide. Whereas isomer **142** gave the product of a ring contraction **184**, isomer **148** gave sodium salt of diazaphenothiazine **185** which was further methylated to form 10-methyl derivative **186** and dimer **187** (Scheme 72) [76].

Isomeric diazaphenothiazinones **188** and **189** were converted to chloro compounds **11** and **190** which were further transformed to the hydrazine and amine derivatives **191** and **192**. The hydrazine compounds were oxidized with cupric ions to the same parent 10*H*-2,3-diazaphenothiazine **175**. On the other hand, the hydrazine

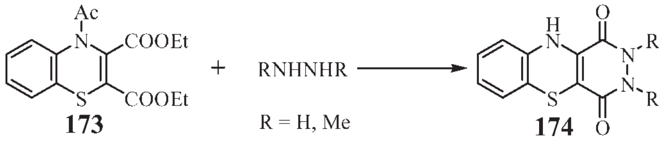
Scheme 66



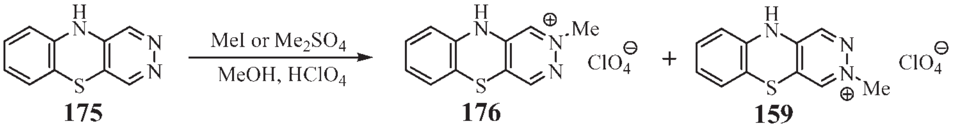
Scheme 67



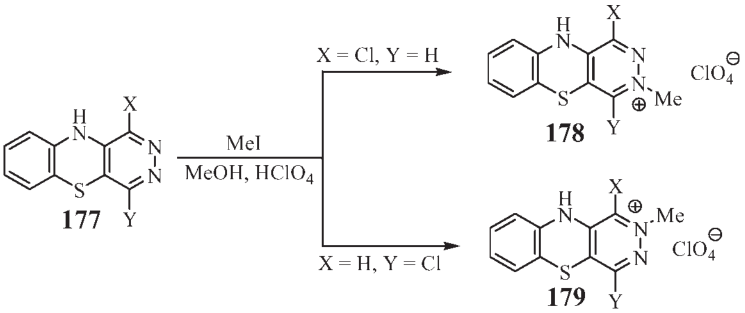
Scheme 68



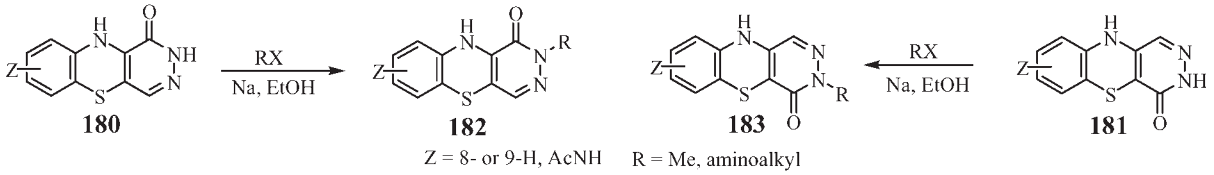
Scheme 69



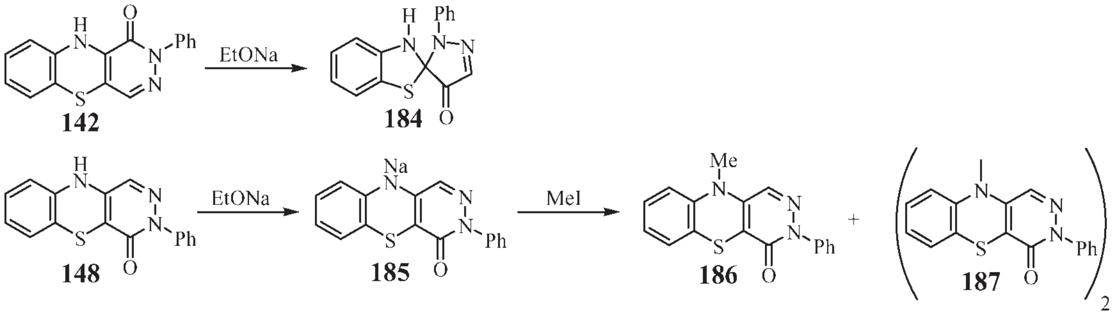
Scheme 70



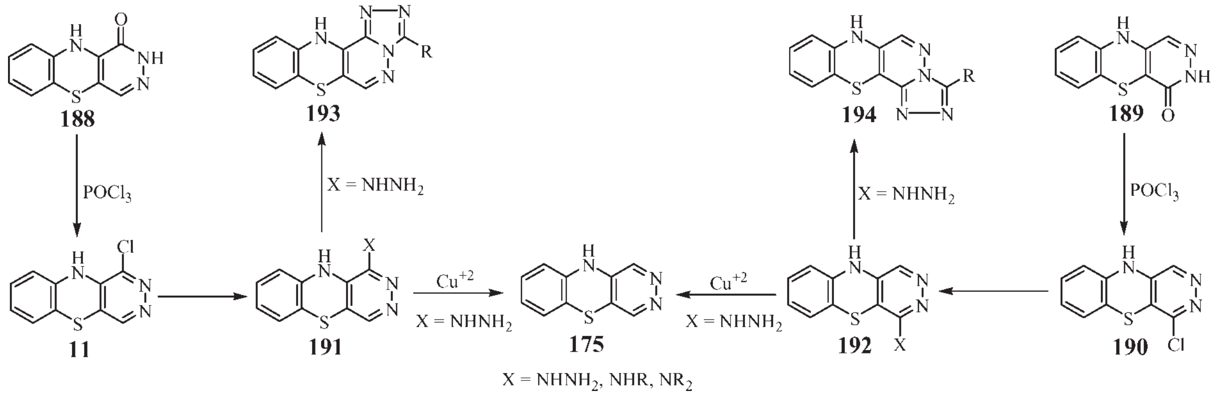
Scheme 71



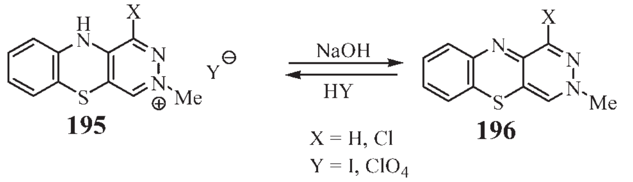
Scheme 72



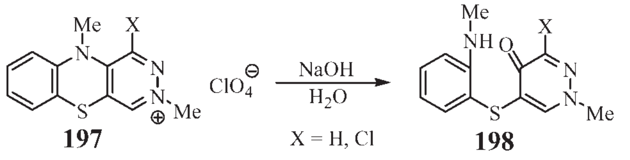
Scheme 73



Scheme 74



Scheme 75



compounds with acetic acid gave tetracyclic triazolodiazaphenothiazines **193** and **194** (R = Me, Scheme 73) [90]. Similar triazolo compounds (R = alkyl, *S*-alkyl, *S*-aminoalkyl) were obtained from the same or other hydrazine substrates [78,80,91].

2,3-Diazaphenothiazinium salts exhibited different properties under basic conditions. Whereas the 10*H*-2-alkyl salt was unreactive, the 10*H*-3-alkyl salt **195** gave 3-methyl-2,3-diazaphenothiazine **196**. This product can be converted back to the thiazinium salt **195** by action of acid (perchloric or hydroiodic, Scheme 74) [79,90].

When position 10 was methylated as in 3,10-dimethyl-2,3-diazaphenothiazinium perchlorate **197**, action of alkali led unexpectedly to opening of the 1,4-thiazine ring to give sulfide **198** (Scheme 75) [79].

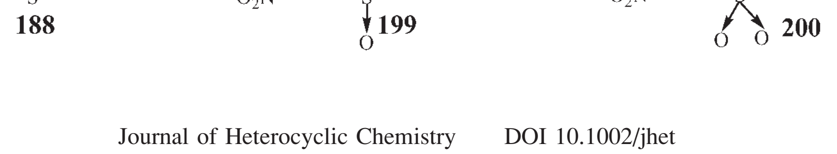
Nitration of 10*H*-diazaphenothiazin-1-one **188** with fuming nitric acid led to 7-nitro-2,3-diazaphenothiazin-1-one *S*-oxide **199**, which can be further converted to *S,S*-dioxide **200** by action of hydrogen peroxide in acetic acid (Scheme 76) [81]. Other transformations of 2,3-diazaphenothiazines were connected with the chlorine atom substitution, reduction of the nitro group and acetylation of the 10*H* position [75–78,82–85,90].

The postulated structures of 2,3-diazaphenothiazines and their salts were based on chemical transformations to known compounds (*e.g.*, 2,3-diazaphenothiazin-1(2*H*)-ones and 2,3-diazaphenothiazin-4(3*H*)-ones to chloro-2,3-diazaphenothiazines), on the ^{1}H NMR spectra (a shift of the H-1 proton [92], shielding of the H-1 and H-4 protons in salts [79], long range coupling between the H-4 and H-10 protons [80,90]) and UV spectra (distinction of 1,2-, 2,3-, and 3,4-diazaphenothiazines [20], distinction of 3- and 10-substituted 2,3-diazaphenothiazines [80]). Unquestionable structure evidences came from X-ray analysis of the selected compounds: 10-methyl-2,3-azaphenothiazine, 1-chloro-10-methyl-2,3-azaphenothiazine, 10*H*-2,3-azaphenothiazin-1(2*H*)-one, and 10*H*-2,3-azaphenothiazin-4(3*H*)-one [93–95].

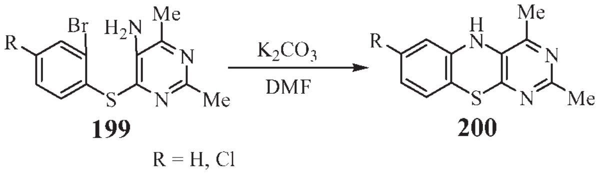
Some 2,3-diazaphenothiazines exhibited wide spectrum of biological activities: anti-inflammatory [88,89,91], analgesic [88,89,91,96], sedative [73,74,89], antiallergic [80], antiparasitic [96], antihistaminic [74,96], and antiarrhythmic [80].

2,4-Diazaphenothiazines (pyrimidino[4,5-b][1,4] benzothiazines). As was shown in Scheme 15, 10*H*-2,4-diazaphenothiazine **27** was the minor product of cyclization of amino-phenyl 4-pyrimidinyl sulfide **25** in DMF

Scheme 76



Scheme 77



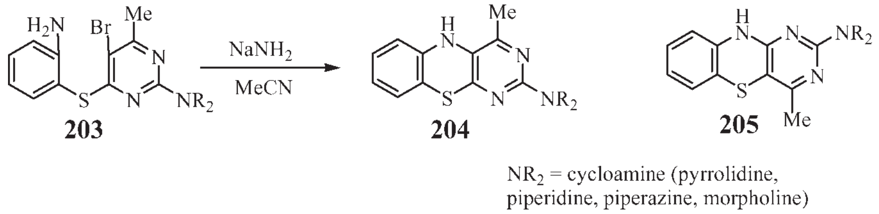
(with potassium carbonate) [25]. Reactions of *o*-bromophenyl 4-pyrimidinyl sulfides **201** in DMF (with potassium carbonate and copper powder), according to the authors, proceeded without the Smiles rearrangement to substituted 10*H*-2,4-diazaphenothiazines **202** (Scheme 77) [25,47].

Very recently an interesting cyclization of substituted *o*-aminophenyl 4-pyrimidinyl sulfides **203** in acetonitrile (with sodium amide) was published. According to the authors, the products were identified on the spectral (^{1}H NMR, IR, and MS) and microanalytical data as 3-substituted 2,4-diazaphenothiazines **204**. As the reaction conditions seem to favor the Smiles rearrangement, the obtained products are rather 1,3-diazaphenothiazines **205** (Scheme 78) [97].

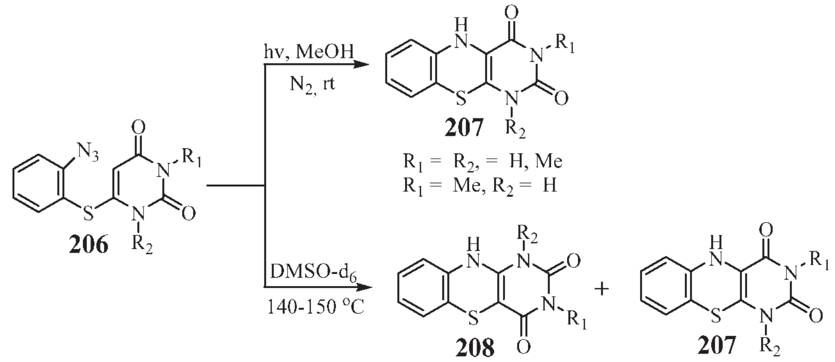
Although an irradiation of 6-(2-azidophenylthio)uracil **206** in methanol with a mercury lamp under nitrogen atmosphere resulted in exclusive formation of 2,4-diazaphenothiazine-1,3-diones **207**, thermolysis in DMSO-*d*$_6$ led to 1,3-diazaphenothiazine-2,4-diones **208** and 2,4-diazaphenothiazine-1,3-diones **207** in ratio of 2:1 (Scheme 79) [98].

Japanese groups [99–101] carried out reactions of the uracil compounds **209** with *N*-bromosuccinimide in ethanol followed by reaction with aminobenzenethiol **8** to obtain 2,4-diazaphenothiazinones **210**. It was found that those reactions proceeded through formation of 6-bromouracils which further formed with ethanol the diethoxy derivatives. The isolated diethoxy compound **211** reacted with aminobenzenethiol **8** to give 2,4-diazaphenothiazinedione **210** (R$_1$, R$_2$ = H, X = O, Scheme 80) [99].

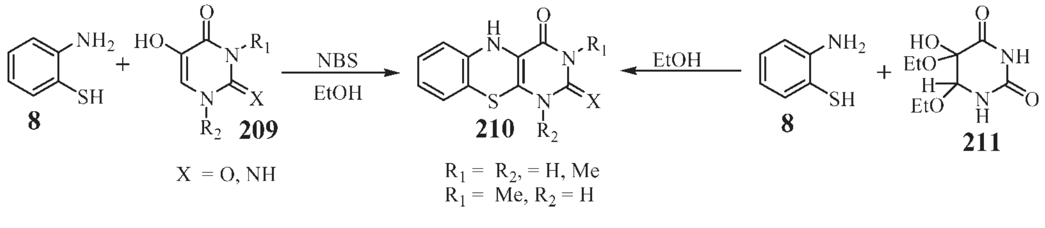
Scheme 78



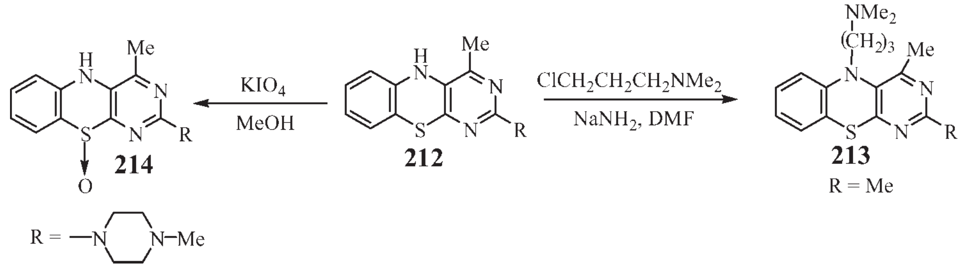
Scheme 79



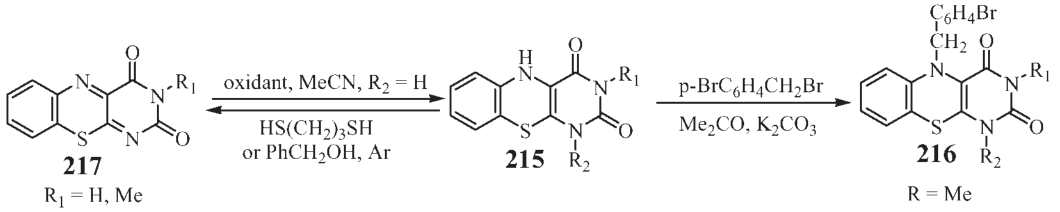
Scheme 80



Scheme 81



Scheme 82



1,3-Disubstituted 10*H*-2,4-diazaphenothiazine **212** was alkylated with dimethylaminopropyl chloride to give 10-aminoalkyl derivative **213** [25] and oxidized with potassium metaperiodate to give the 2,4-diazaphenothiazine *S*-oxide **214** (Scheme 81) [97].

Similarly, 1,3-disubstituted 10*H*-2,4-diazaphenothiazine-1,3-dione **215** was alkylated in acetone with *p*-bromobenzyl bromide to form 10-bromobenzyl derivative **216** [101]. Reaction with an oxidant (*e.g.*, 1,4-benzoquinone) in acetonitrile led to 2,4-diazaphenothiazine-1,3(2*H*)-diones **217** (called also as 10-thiaisoalloxazines). Reduction with propanedithiol or benzyl alcohol gave substrate **215** back (Scheme 82) [98,101]. Compound **217** underwent a smooth ring contraction on reaction with amines [102].

Some 2,4-diazaphenothiazines showed anti-inflammatory, antibacterial, antifungal, and analgesic activities [25–47] and some 2,4-diazaphenothiazine-1,3-diones inhibiting activity to lipoxygenases [97,100].

2,7-Diazaphenothiazines (dipyrido[3,4-b;3′,4′-e][1,4] thiazines). Reactions of 4-chloro-3-nitropyridine **218** with sodium sulfide in DMF led unexpectedly to 10*H*- and 10-(3′-nitro-4′-pyridinyl)-2,7-diazaphenothiazines **219** and **220** as major products (in modest yields) and to isomeric 2,7- and 2,8-diazathianthrenes **221** and **222** as minor products (Scheme 83, the last compounds were only products in DMSO) [103].

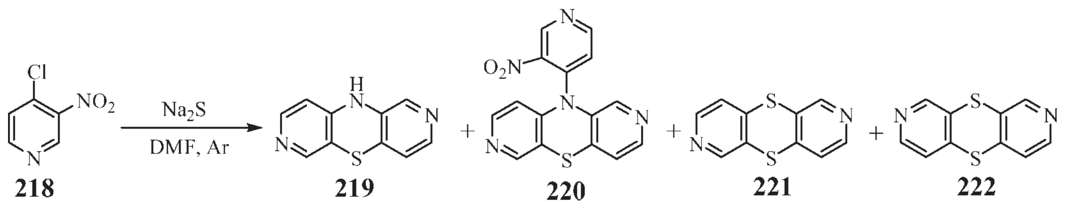
It is worth noting that the unexpected products **219** and **220** were results of single and double Smiles rearrangements of sulfides **224** and **226** and reductive properties of DMF (Scheme 84).

Later the synthesis was improved using sodium 3-nitro-4-pyridinethiolate **223**, or pairs of disubstituted pyridines **218** and **227–229**, or dipyridinyl sulfide **224**. 2,7-Diazaphenothiazine **219** was further transformed into 10-substituted derivatives **230** in reactions with appropriate halogenocompounds in DMF (with sodium hydride) or dioxane (with sodium hydroxide, Scheme 85) [104].

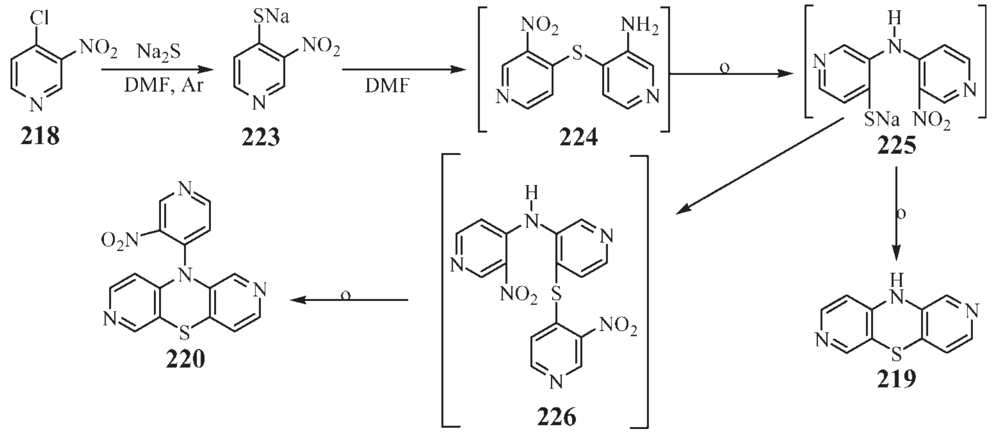
The structures of 2,7-diazaphenothiazines **219**, **220**, and **230** were determined on the basis of spectroscopic analyses (^{1}H NMR, ^{1}H-^{1}H COSY, and NOE) and confirmed by X-ray analysis of compound **220** [103,104]. For selected compounds lipophilic character and promising anti-cancer activities against lung, colon, renal cancers, and leukemia were determined [105,106].

3,4-Diazaphenothiazines (pyridazino[3,4-b][1,4] benzothiazines). The first synthesis of 3,4-diazaphenothiazine was achieved when *o*-aminophenyl 4-pyridazinyl sulfides **1** and **7** were heated in diluted

Scheme 83



Scheme 84



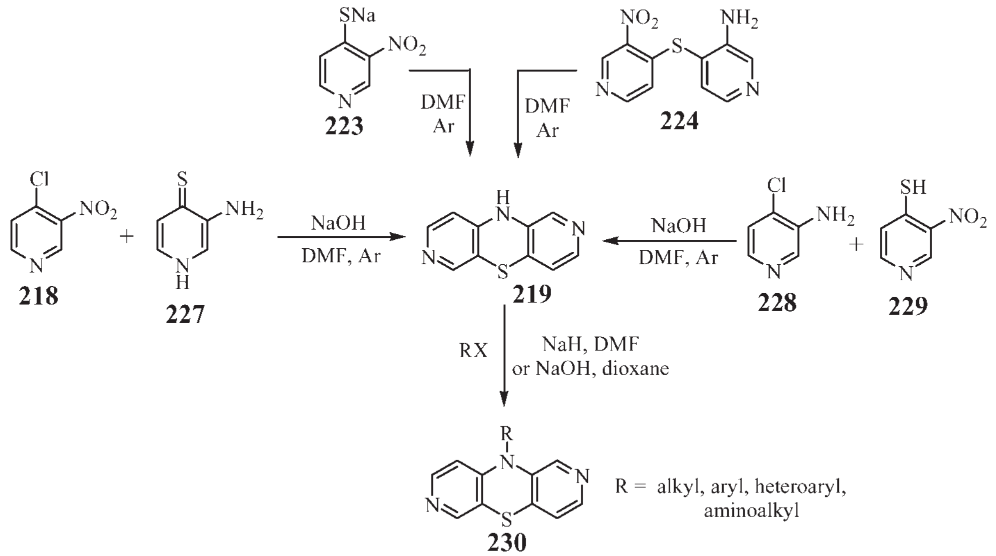
hydrochloric acid or acetic acid to give 2-chloro-3,4-diazaphenothiazine **6** through the Smiles rearrangement as is shown in Scheme 8. It worth noting that sulfide **1** in methanolic potassium hydroxide did not lead to 3,4-diazaphenothiazine **6** but to sulfide **7** which under acidic conditions underwent rearrangement and cyclization. The 10-methyl derivative **18** was obtained under the same conditions when the *N*-methylated sulfide **17** was used as depicted in Scheme 11 [18,19].

Attempts to obtain the parent 10*H*-3,4-diazaphenothiazine **232** from chloro compound **6** with catalytic hydrogenation over palladium charcoal was unsuccessful [19]. Only when aminophenyl 4-cyano-3-pyridazinyl sulfide **231** was stirred in DMSO (with sodium hydride) at room temperature 3,4-diazaphenothiazine **232** was obtained (in 85% yield). Reaction proceeded without the rearrangement (Scheme 86) [107].

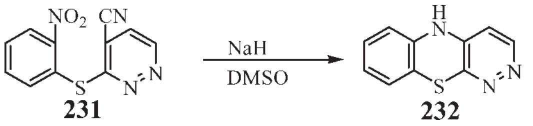
10-Substituted 3,4-diazaphenothiazines **237** were obtained when N-substituted *o*-aminobenzenethiols **233** (obtained from 3-substituted benzothiazolinone by alkaline decomposition) reacted with 3,4,6-trichloropyridazine **234** in ethanol (with potassium hydroxide) to give aminophenyl 4-pyridazinyl sulfide **235** (not always isolated) whose treatment in ethanol (with diluted hydrochloride acid) yielded 10-substituted 3,4-diazaphenothiazine **237** through rearrangement to amine **236** (Scheme 87) [108].

In a German patent [109], 10-substituted 3,4-diazaphenothiazines were described as the products of the reactions of 10*H*-3,4-diazaphenothiazine with dialkylaminoalkyl chlorides but lack of appropriate structures questioned the used 3,4-diazaphenothiazine (rather 1,2-diazaphenothiazine). 2-Chloro-3,4-diazaphenothiazines **6** underwent acetylation with acetic anhydride to

Scheme 85



Scheme 86



derivative **238**, the chlorine atom substitution with methoxy and dimethylamino groups to derivatives **239** and oxidation to *S,S*-dioxide *N*-oxide derivative **240** (Scheme 88) [18,19,108]. 2-Methoxy derivatives were also obtained for 10-substituted diazaphenothiazines (**237**, R = benzyl, dimethylaminoethyl) [19,108].

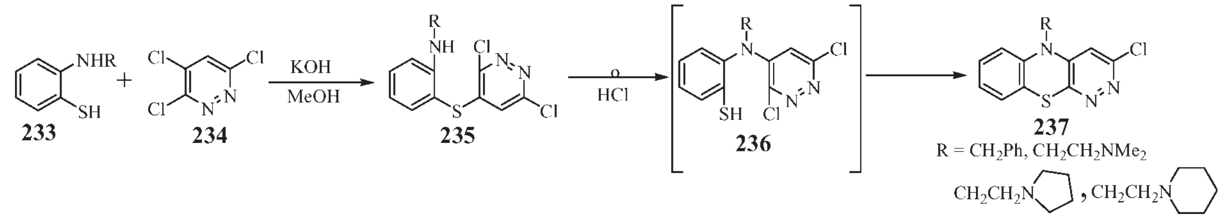
10-Pyrrolidinylethyl and dimethylaminoethyl derivatives **237** exhibited antihistaminic activity [107].

3,6-Diazaphenothiazines (dipyrido[2,3-b;4′,3′-e][1,4] thiazines). The first synthesis was described by Okafor [110] who carried out reactions of 3-amino-2(1*H*)-pyridinethione **241** with 3,5-dinitro-4-chloropyridine **242** in methanolic potassium hydroxide. The reaction proceeds through a formation of dipyridinyl sulfide **243** which undergoes rearrangement to dipyridinyl amine **244** to give 3,6-diazaphenothiazine **245**. The product structure was determined on the basis of strong hydrogen bonding between the NH and NO_2 groups (Scheme 89) [110].

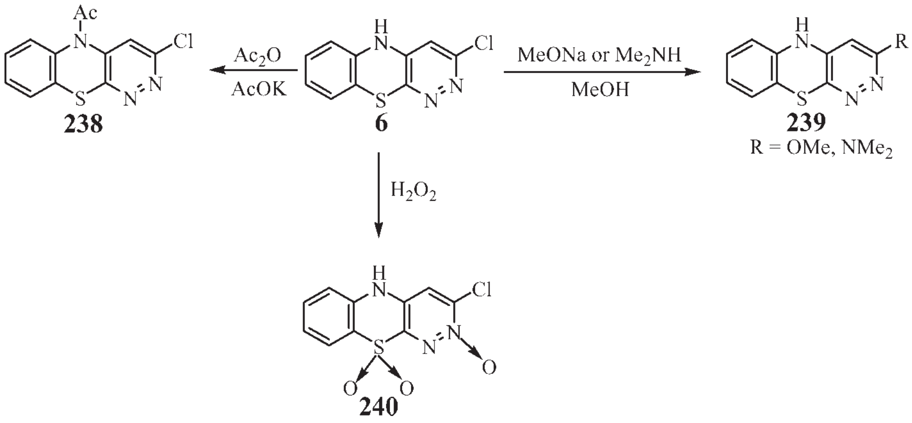
3,6-Diazaphenothiazines **245** were oxidized by sulfuric and nitric acids to *S*-oxide derivatives [111].

3,7-Diazaphenothiazines (dipyrido[3,4-b;4′,3′-e][1,4] thiazines). 10*H*-3,7-Diazaphenothiazine **247** was obtained in very low yield (9 and 6%, respectively) from sulfurization of 4,4′-dipyridinyl amine **246** with elemental sulfur at very high temperature (280–290°C) in the presence of iodine or with disodium tetrasulfide (at 260°C) [112,113]. When the cylization was carried out in *o*-dichlorobenzene with sulfur dichloride or when 3,7-diazaphenothiazine **247** was heated under those conditions, X,X′-dichloro-10*H*-3,7-diazaphenothiazine was formed (where X, X′ are most likely 4 and 4′) [114]. *N*-Alkylation with diethylaminoethyl and

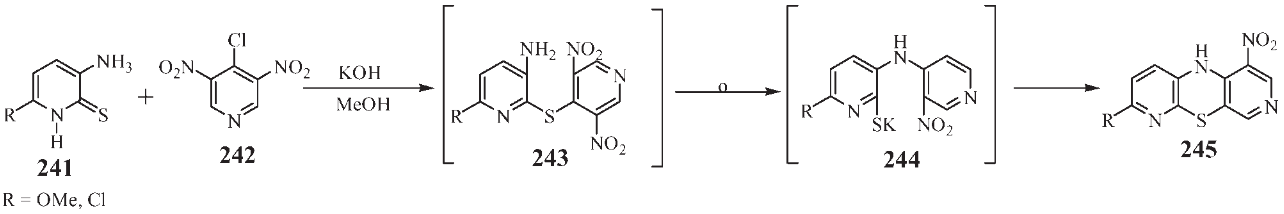
Scheme 87



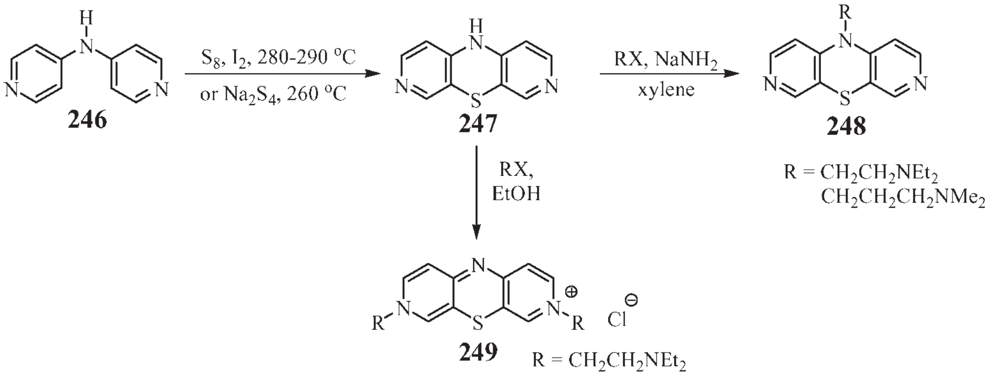
Scheme 88



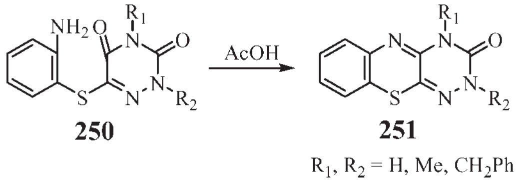
Scheme 89



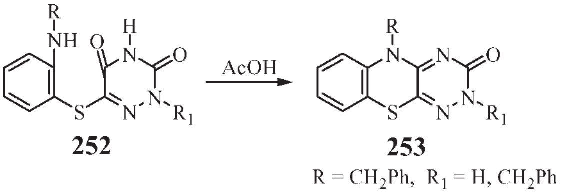
Scheme 90



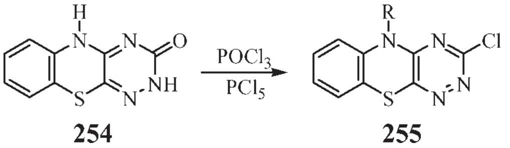
Scheme 91



Scheme 92



Scheme 93



dimethylaminopropyl chlorides proceeded at the thiazine or pyridine nitrogen atoms depending on the reaction conditions (xylene with sodium amide or only ethanol) to give 10-dialkylaminoalkyl derivatives **248** or the ammonium compound **249** (Scheme 90) [115].

3,7-Diazaphenothiazines **248** exhibited antihistaminic activity [115].

Tricyclic triazaphenothiazines. ***1,3,4-Triazaphenothiazines (benzo[1,2,4]triazino-[5,6-e][1,4]thiazines).*** Kaji et al. heated aminophenyl 1,2,4-triazinyl sulfides **250** in acetic acid to give 1*H*-1,3,4-triazaphenothiazin-2(1*H*)-one **251** without the rearrangement (Scheme 91) [116].

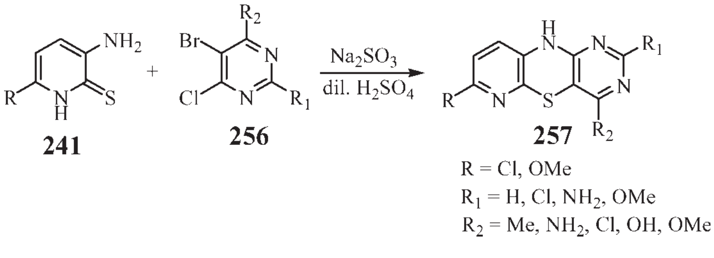
When *N*-benzyl derivative of aminophenyl triazinyl sulfide (with 4*H* function) **252** was used, appropriate 10-benzyl-1,3,4-triazaphenothiazin-2(1*H*)one **253** was obtained in low yield (20%, Scheme 92) [117].

The oxo group was substituted by the chlorine atom in 10*H*-1,3,4-triazaphenothiazinone **254** in the reaction with phosphoryl chloride giving 2-chloro derivative **255** (Scheme 93) [118].

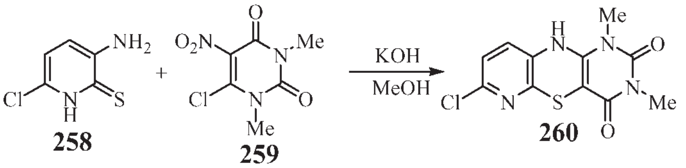
1,3,6-Triazaphenothiazine (pyrido[2,3-b]pyrimido-[4,5-e][1,4]thiazines). Reactions of substituted 3-aminopyridine-2(1*H*)-thiones **241** with chlorobromopyrimidines **256** in highly diluted sulfuric acid (100:1) (with sodium sulfite) led without rearrangement directly to 1,3,6-triazaphenothiazines **257** in low to excellent yields (11–95%, Scheme 94). The structure of the product as 1,3,6-triaza compounds (but not the 2,4,6-triaza isomers) was based on the lack of formation of the 1,10-diazole ring during diazotization of the amino derivative [119,120].

A similar reaction of aminopyridinethione **258** with 1,3-dimethyl-5-nitro-6-chlorouracil **259** in methanol (in the presence of base) led to 1,3,6-triazaphenothiazine-2,4-(1*H*,3*H*)-dione **260** in 66% yield (Scheme 95) [121,122].

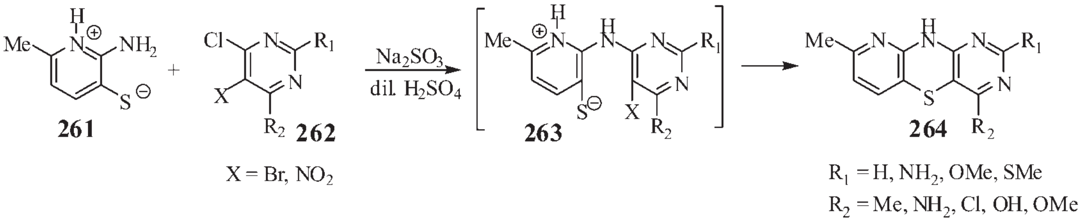
Scheme 94



Scheme 95



Scheme 96



1,3,6-Triazaphenothiazines **257** exhibited appreciable CNS-depressant activities [120].

1,3,9-Triazaphenothiazine (pyrido[3,2-b]pyrimido-[4,5-e][1,4]thiazines). The reaction of the betaine **261** with chlorobromopyrimidines or chloronitropyrimidines **262** in diluted sulfuric acid (with sodium sulfite) led directly to 1,3,9-triazaphenothiazines **264** (Scheme 96) [120,123–125]. The same reaction under basic conditions gave no products. The authors postulated that the reaction proceeded *via* formation of diazinyl amine **263**, which underwent cyclization smoothly, as they isolated compound **263** ($X = H$, $R_1 = R_2 =$ OMe) from the reaction of compound **261** with 4-chloropyrimidine **262** (without the 5-bromo function, $X = H$). The structure of the resulting product **264** was reported as the 1,3,9-triaza compound (but not the 2,4,9-triaza isomer) based on the lack of formation of the 1,10-diazole ring during diazotization of the amino derivative [124].

1,3,9-Triazaphenothiazines **264** exhibited appreciable CNS-depressant activities [120].

1,4,6-Triazaphenothiazine (pyrido[2,3-b]pyrimido[2′,3′-e][1,4]thiazines). Reaction of substituted 3-aminopyridine-2(1*H*)-thiones **241** with 2,3-dichloropyrazine **96** in aqueous propylene glycol (with sodium hydroxide) led to 7-substituted 1,4,6-triazaphenothiazines **265** in 67–89% yield (Scheme 97).

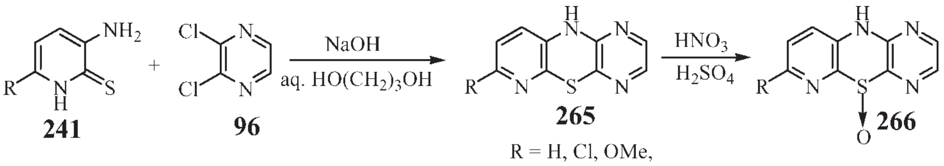
Triazaphenothiazines **265** were converted to their *S*-oxide derivatives **266** by the action of mixed concentrated nitric and sulfuric acids [125].

1,4,9-Triazaphenothiazines (pyrido[3,2-b]pyrazino[2′,3′-e][1,4]thiazines). The reaction of the betaine **261** with trichloropyrazine **267** in DMA (with sodium hydroxide) aimed at obtaining triazaphenothiazines **268** or **269** gave unexpectedly the bis-sulfide **270** in 82% yield. The formation of the second sulfide function proceeded more smoothly than the thiazine ring closure (Scheme 98) [126].

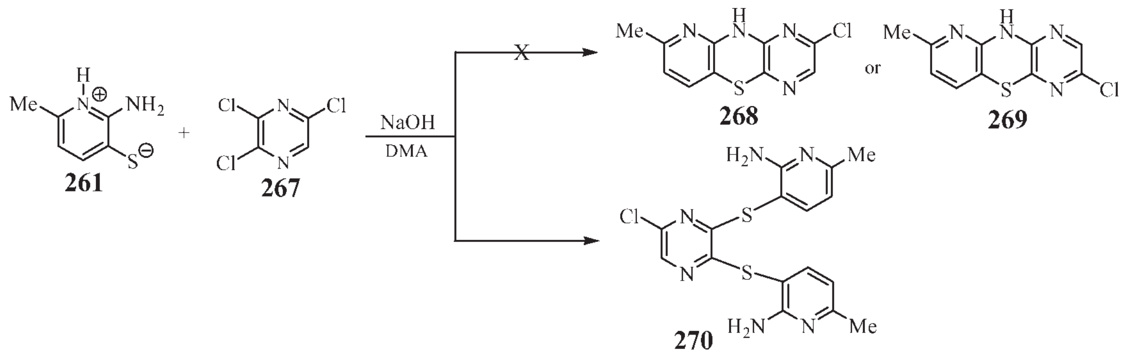
2,3,6-Triazaphenothiazine (pyrido[2,3-b]pyridazino-[4′,5′-e][1,4]thiazines). Reaction of 6-methoxy-3-aminopyridine-2(1*H*)-thione **271** with 4,5-dichloropyridazin-3(2*H*)-one **272** in aqueous DMSO (with sodium hydroxide) gave the pyridinyl pyridazinyl sulfide **273** which further in concentrated hydrochloric acid underwent cyclization to 2,3,6-triazaphenothiazin-1(2*H*)-one **274** in 82% yield. Direct reaction of compounds **271** and **272** in aqueous DMSO (for prolonged periods of time) gave the same triazaphenothiazinone **274** in 41% yield and the sulfide **275** (in 26% yield). Sulfide **273**, when heated in acetic acid, underwent the Smiles rearrangement and cyclization to isomeric 2,3,6-triazaphenothiazin-4(3*H*)-one **276** in 89% yield (Scheme 99). The structure of isomeric triazaphenothiazinones was established on the basis of a very broad signal for 10-H proton of isomer **274** (1-one) because of strong NHO hydrogen bonding [127].

Reaction of 3-aminopyridine-2(1*H*)-thione **277** with 4,5-dichloropyridazine **278** in ethanol (with potassium hydroxide) under nitrogen atmosphere led to 2,3,6-triazaphenothiazine **279** in 63% yield (Scheme 100) [126].

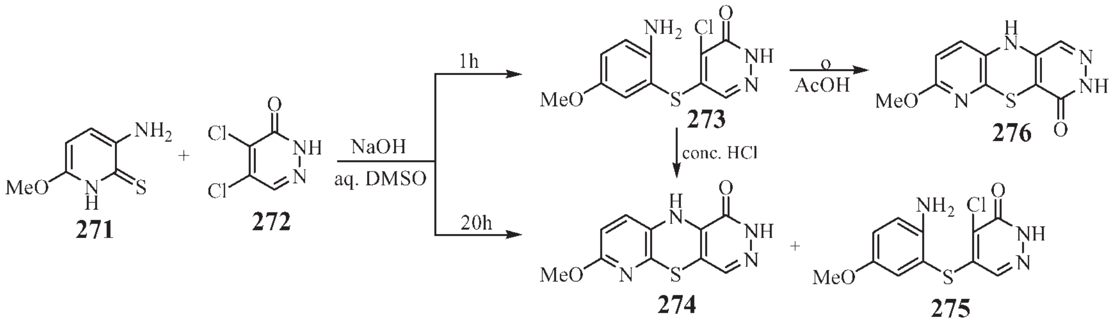
Scheme 97



Scheme 98



Scheme 99

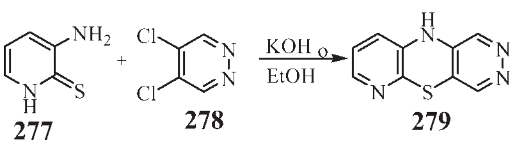


Later, Baltrop and Owen repeated this reaction and questioned the previous result. The obtained product was also identified as 2,3,6-triazaphenothiazine **279** [128] but possessed a different melting point, ^{1}H NMR, UV spectra, and elemental analysis only was similar.

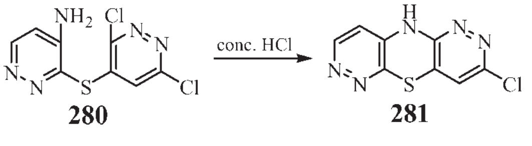
Tricyclic tetraazaphenothiazines. ***1,2,6,7-Tetraazaphenothiazine (dipyridazino[3,4-b;3′,4′-e][1,4]thiazines).*** Heating dipyridazinyl sulfide **280** in concentrated hydrochloric acid led to 1,2,6,7-tetraazaphenothiazine **281** in 61% yield (Scheme 101) [129].

1,2,7,8-Tetraazaphenothiazine (dipyridazino[4,3-b;4′,5′-e][1,4]thiazines). Cyclization of dipyridazinyl sulfide **282** in concentrated hydrochloric acid gave 1,2,7,8-tetraazaphenothiazine **283** in 63% yield (Scheme 102) [129].

Scheme 100



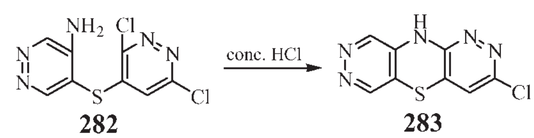
Scheme 101



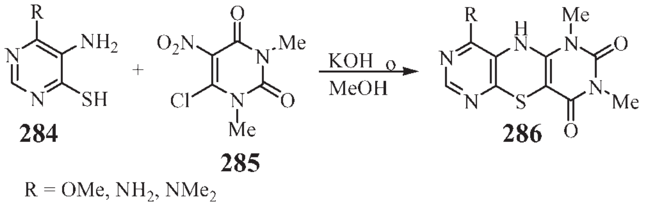
1,3,6,8-Tetraazaphenothiazine (dipyrimido[4,5-b;4′,5′-e][1,4]thiazines). Reactions of substituted 5-aminopyrimidine-4-thiols **284** with 1,3-dimethyl-5-nitro-6-chlorouracil **285** in ethanol (with potassium hydroxide) led to 1,3,6,8-tetraazaphenothiazine-2,4(1*H*,3*H*)-diones **286** in 54–78% yield *via* the Smiles rearrangement (Scheme 103).

When 1,3-dimethyl-5-amino-6-mercaptouracil **287** was used in the reaction, 1,3,6,8-tetraazaphenothiazine-2,4,7,-9(1*H*,3*H*,6*H*,8*H*)-tetraone **288** was obtained in 58% yield (Scheme 104) [121,122].

Scheme 102

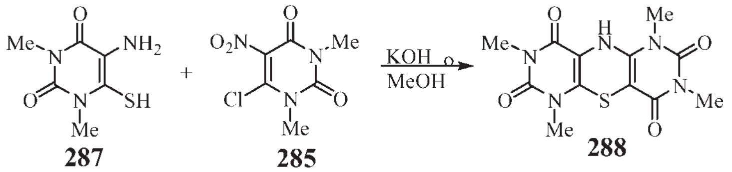


Scheme 103

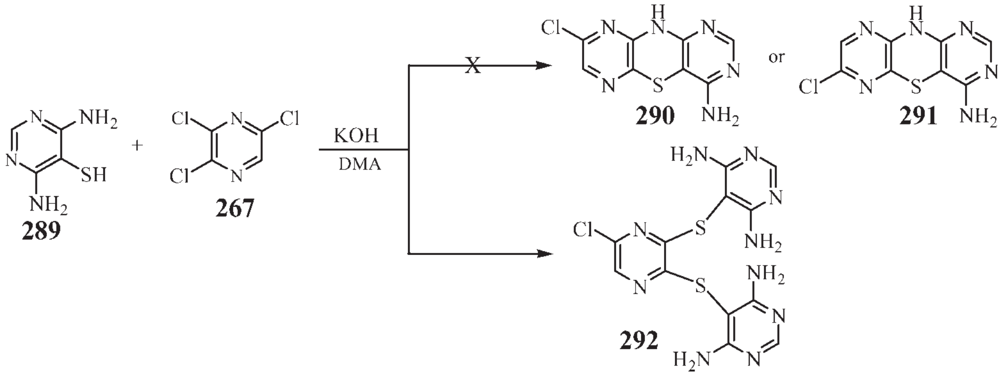


R = OMe, NH_2, NMe_2

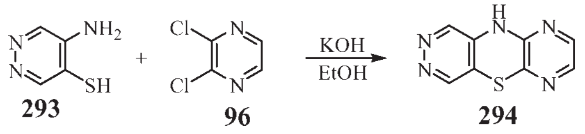
Scheme 104



Scheme 105



Scheme 106



1,3,6,9-Tetraazaphenothiazine (pyrazino[2,3-b]pyrimido[4′,5′-e][1,4]thiazines). Reaction of 4,6-diaminopyrimidine-5-thiol **289** with trichloropyrazine **267** in DMA did not lead to tetraazaphenothiazine **290** or **291** but unexpectedly to the bis-sulfide **292** in high yield (93%, Scheme 105) [126].

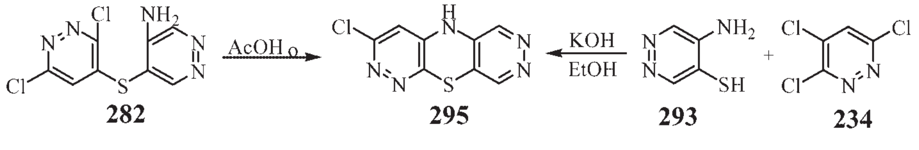
1,4,7,8-Tetraazaphenothiazine (pyrazino[2,3-b]pyridazino[4′,5′-e][1,4]thiazines). Reaction of 4-aminopyridazine-5-thiol **293** with dichloropyrazine **96** (with potassium hydroxide) led to 1,4,7,8-tetraazaphenothiazine **294** in low yield (30%, Scheme 106) [126].

2,3,6,7-Tetraazaphenothiazine (dipyridazino[3,4-b;4′,5′-e][1,4]thiazines). Dipyridazinyl sulfide **282** in acetic acid underwent the Smiles rearrangement and cyclization to give 8-chloro-2,3,6,7-tetraazaphenothiazine **295** in 82% yield. The same product was obtained in the reaction of aminopyridazinethiol **293** with trichloropyridazine **234** in ethanol (with potassium hydroxide) in 88% yield (Scheme 107).

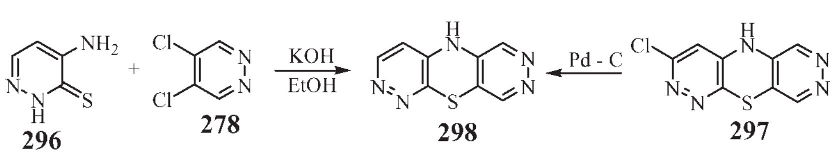
The parent 2,3,6,7-tetraazaphenothiazine **298** was obtained in the reaction of 4-aminopyridazine-3-thione **296** with dichloropyrazine **278** in ethanol (with a base) in 57% yield or by dechlorination of chlorotetraazaphenothiazine **297** in 55% yield with a use of palladium charcoal (Scheme 108).

Alkylation of tetraazaphenothiazine **297** with aminoalkyl chlorides in liquid ammonia (with sodium amide) yielded aminoalkyl derivatives **298** in 43–55% yield (Scheme 109) [129].

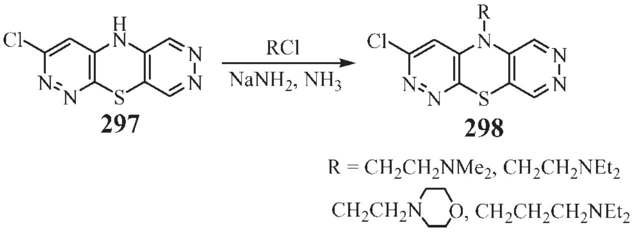
Scheme 107



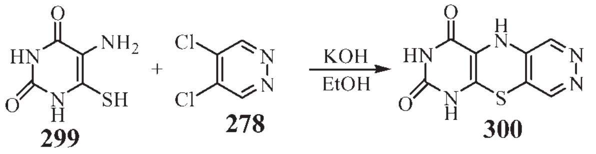
Scheme 108



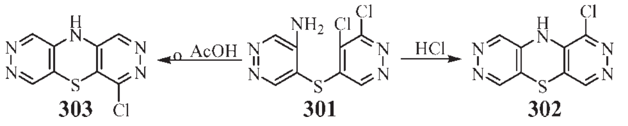
Scheme 109



Scheme 110



Scheme 111



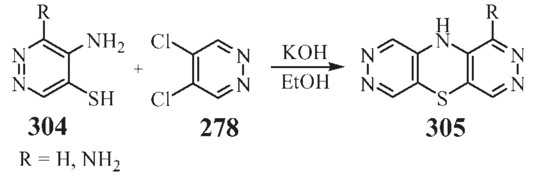
2,3,6,8-Tetraazaphenothiazine (pyridazino[4,5-b]pyrimido[5′,4′-e][1,4]thiazines). Reaction of 5-aminouracil-6-thiol **299** with dichloropyridazine **278** in ethanol (with potassium hydroxide) led to 2,3,6,8-tetraazaphenothiazine-7,9(6*H*,8*H*)-dione **300** in 50% yield (Scheme 110) [126].

2,3,7,8-Tetraazaphenothiazine (dipyridazino[4,5-b;4′,5′-e][1,4]thiazines). Whereas dipyridazinyl sulfide **301** in hydrochloric acid underwent cyclization to 1-chloro-2,3,7,8-tetraazapheno-thiazine **302** in 58% yield, in acetic acid it underwent the Smiles rearrangement and cyclization to isomeric 4-chloro-2,3,7,8-tetraazaphenothiazine **303** in 57% yield (Scheme 111).

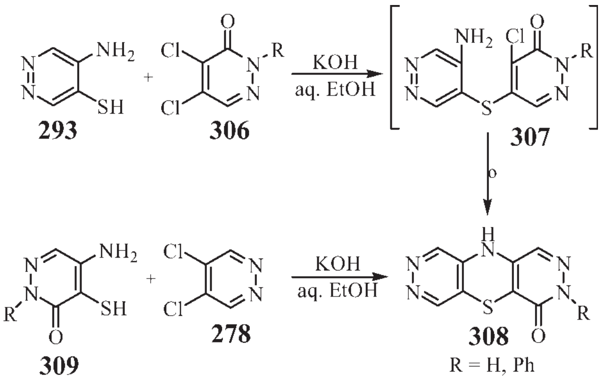
The parent tetraazaphenothiazine and the amino derivative **305** were obtained in the reaction of 4-amino-3-pyridazinethiols **304** with dichloropyridazine **278** in ethanol (with potassium hydroxide) in 66 and 72% yield (Scheme 112).

With dichloropyridazinones **306** in aqueous ethanol (in the presence of a base) the aminopyridazinethiol **293** underwent the Smiles rearrangement and cyclization to 2,3,7,8-tetraazaphenothiazin-4-ones **308**. Crude dipyridazinyl sulfide **307** (R = H) underwent the rearrangement and cyclization during crystallization from ethanol. The structures of the products **308** were established by independent synthesis using 5-amino-4-mercaptopyridazin-3(2*H*)-one **309** and dichloropyridazine **278** under the same conditions (Scheme 113).

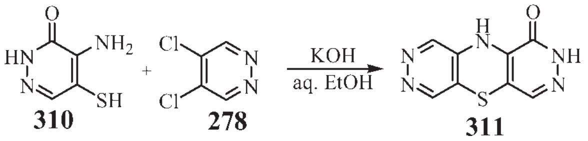
Scheme 112



Scheme 113



Scheme 114

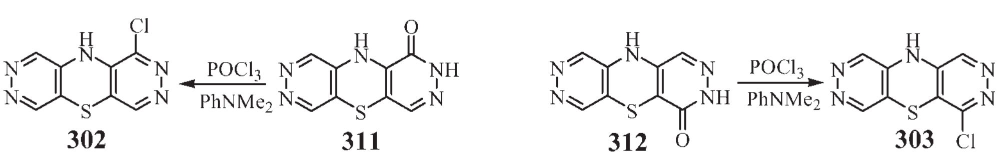


When 5-amino-4-mercaptopyridazin-6(1*H*)-one **310** was used in the reaction with dichloropyridazine **278**, isomeric 2,3,7,8-tetraazaphenothiazin-1-one **311** was obtained in 75% yield (Scheme 114).

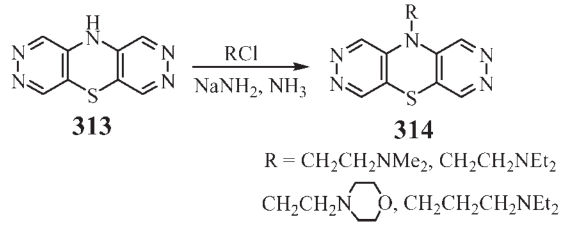
Both tetraazaphenothiazinones **311** and **312** were converted into the chloro derivatives **302** and **303** in low yield (27 and 40%) by the action of phosphoryl chloride with *N*,*N*-dimethylaniline (Scheme 115).

The parent 10*H*-tetraazaphenothiazine **313** was transformed into aminoalkyl derivatives **314** in 39–51% yield by *N*-alkylation with aminoalkyl chlorides in liquid ammonia (in the presence of sodium amide, Scheme 116) [129].

Scheme 115



Scheme 116



2,4,6,8-Tetraazaphenothiazine (dipyrimido[4,5-b;5′,4′-e][1,4]thiazines). Reaction of 5,6-diamino-1,3-dimethyluracil **315** with liquid hydrogen sulfide in pyridine in a sealed tube led unexpectedly to 2,4,6,8-tetraazaphenothiazine-1,3,7,9(2*H*,4*H*,6*H*,8*H*)-tetraone **316** in 55% yield. To establish the correct structure of the product, an independent synthesis (in 58% yield) was carried out using aminomercaptouracil **287** and 5-hydroxy-1,3-dimethyluracil **317** in the presence of N-bromosuccinimide in ethanol (Scheme 117).

N-Alkylation of tetraazaphenothiazine **316** with benzyl and *p*-bromobenzyl bromides in DMF or acetone (with bases) led not only to the expected benzyl derivatives **317** (in 29 and 14% yield) but also to the unexpected benzyl derivatives of the ring contraction product, dipyrimidopyrroles **318** (in 7 and 46% yield, respectively, Scheme 118) [101].

3,4,6,7-Tetraazaphenothiazine (dipyridazino[3,4-b;4′,3′-e][1,4]thiazines). Whereas dipyridazinyl sulfide **280** gave in concentrated hydrochloric acid 1,2,6,7-tetraazaphenothiazine **281** (Scheme 101), in acetic acid gave 2-chloro-3,4,6,7-tetraazaphenothiazine **319** (in 47% yield) as a result of the Smiles rearrangement (Scheme 119).

Reaction of aminopyridazinethione **296** with dichloropyridazine **320** in ethanol (in the presence of potassium hydroxide) led to parent 3,4,6,7-tetraazaphenothiazine **321** in 60% yield (Scheme 120) [129].

Tetracyclic phenothiazines (benzo derivatives of phenothiazines).

Benzo derivatives of 1,4-diazaphenothiazines (quinoxalino[2,3-b]benzo[1,4]thiazines). The first synthesis was carried out by Walter and co-workers as early as 1933 using aminobenzenethiol **8** and 2,3-dichloroquinoxaline **322** (no details). The product structure was postulated as 12*H*-benzo-1,4-diazaphenothiazine **323** (Scheme 121) [130].

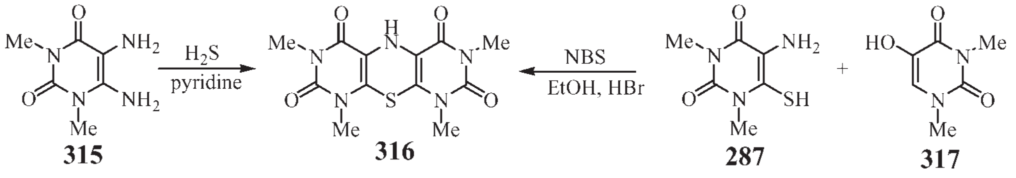
Almost 30 years later Schindler and Peterili (1961) repeated this synthesis using 5-chloro-2-aminobenzenethiol **324** and substituted 2,3-dichloroquinoxalines **325** to obtain substituted 12*H*-8-chlorobenzo-1,4-diazaphenothiazines **326** (Scheme 122) [131].

In the same time Riedel and Deuschel [132] and later Carter with Cheeseman [55] and Okafor [57] carried out the same reaction of aminobenzenethiol **8** with 2,3-dichloroquinoxalines **325** in *o*-dichlorobenzene or DMF (with bases) to obtain postulated 11*H*-benzo-1,4-diazaphenothiazines **327** (Scheme 123). When R ≠ H, the product was assigned as the 2-chloro compound **327** (X = Cl [57]) or was not determined at all (X = Me, Cl, OMe [132]).

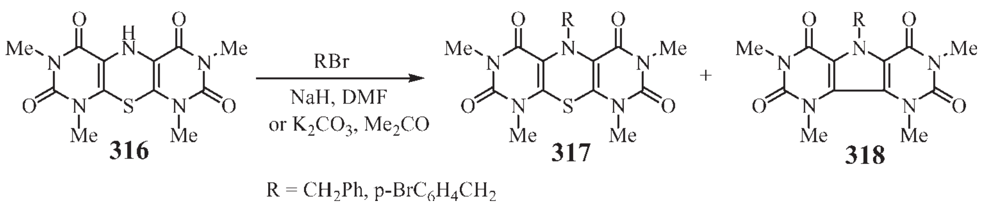
When *N*-substituted aminobenzenethiols **328** and substituted 2,3-dichloroquinoxalines **325** or quinoxaline-2,3-(1*H*,4*H*)-diones **329** were used, the obtained products were assigned as 11-substituted benzo-1,4-diazaphenothiazines **330** (Scheme 124) [55,132].

Whereas 11*H*- or 12*H*-benzo-1,4-diazaphenothiazines **323** or **331** (according to the authors), when methylated with methyl iodide in DMF (with sodium hydride), gave two compounds: the expected 11-methyl derivative as the main product **332** (in 45% yield) and the 12-methyl derivative **333** as the minor product (in 25% yield) [55], alkylated with aminoalkyl chlorides gave only one product: 11- or 12-substituted compound (**334** or **335**, not

Scheme 117

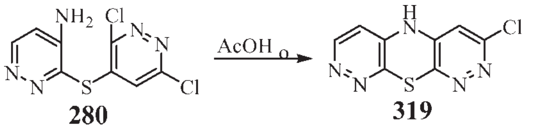


Scheme 118

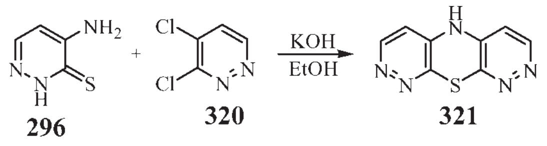


R = CH_2Ph, p-$BrC_6H_4CH_2$

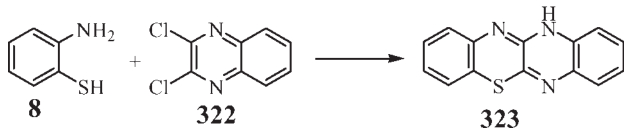
Scheme 119



Scheme 120



Scheme 121



determined) [131]. Acetylation with acetic anhydride gave only one product assigned as the 11-acetyl derivative **336** (Scheme 125) [55].

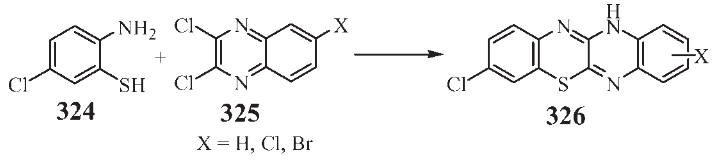
Oxidation of the 11-methyl derivative **332** with iodobenzene dichloride led to *S*-oxide derivative **337**, but with potassium permanganate to *S*,*S*-dioxide **338** (Scheme 126) [55].

Nitration of benzo-1,4-diazaphenothiazines **339** gave products depending on the nitrating agents. Nitration with sodium nitrate led to the mononitro derivative **340** but with mixed nitric and sulfuric acid to the nitration and oxidation product, the dinitro and *S*-oxide derivative **341** (Scheme 127) [55,57]. The last nitration was carried out to determine the correct structure of chlorobenzo-1,4-diazaphenothiazine (the position of the chlorine atom) **339** (X = Cl) by analysis of the directive influence of the functional groups [57].

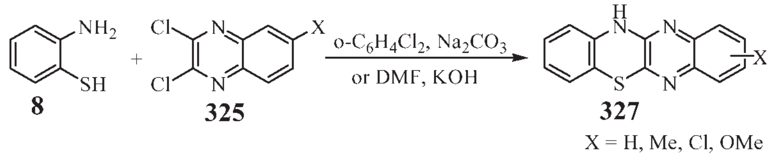
Some benzo-1,4-diazaphenothiazines exhibited antiallergic, anticonvulsive, sedative, adrenolytic, and serotonin-antagonistic activities [131] and yellow pigment dye properties [132].

Benzo derivatives of 3,6-diazaphenothiazines (pyrido[2,3-b]quino[4′,3′-e][1,4]-thiazines). Reactions of 5,12-dialkylthioquinanthrenediinium dichlorides **342** with 3-aminopyridine in pyridine proceeded *via* the 1,4-dithiin ring opening to give 1-alkyl-4-(3-pyridinylamino)-quinolinium-3-thiolate **343** in 63–70% yield or 5-alkyl-12*H*-benzodiazaphenothiazinium chlorides **344** in 60–66% yield, depending on the presence of atmospheric oxygen in the reaction mixture. Quinolinium thiolate **343** in the presence of aniline hydrochloride and air was converted

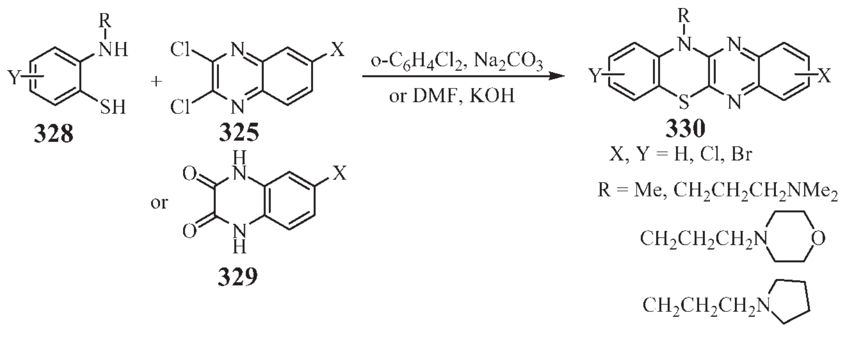
Scheme 122



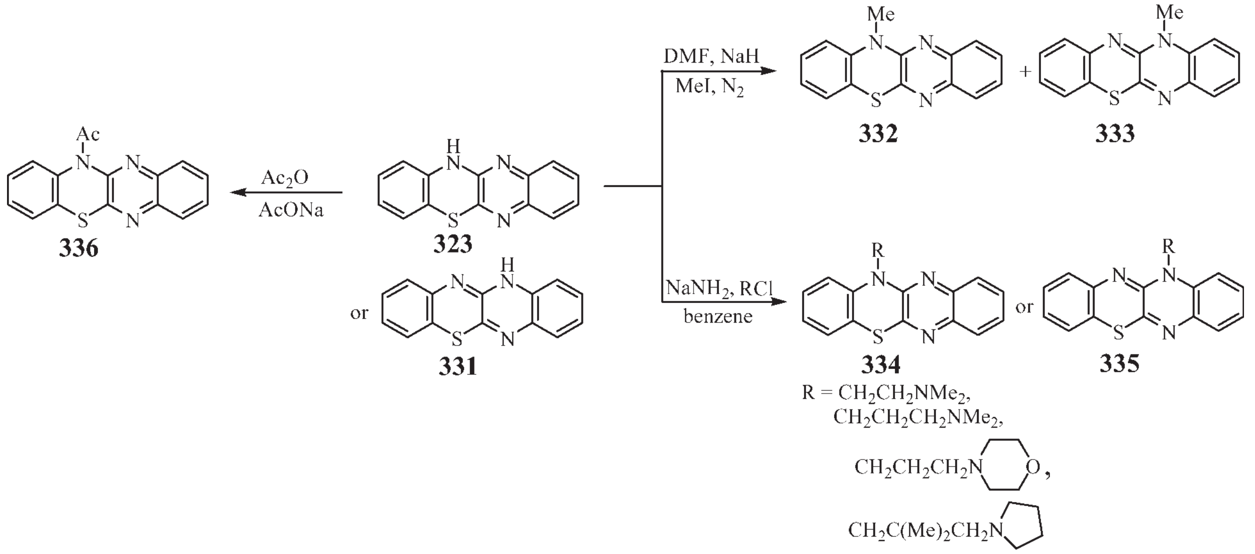
Scheme 123



Scheme 124



Scheme 125



336 **323** **331** **332** **333** **334** **335**

to benzodiazaphenothiazinium salt **344** in 67–69% yield which was further transformed into 5-alkylbenzodiazaphenothiazines **345** in quantitative yield (Scheme 128).

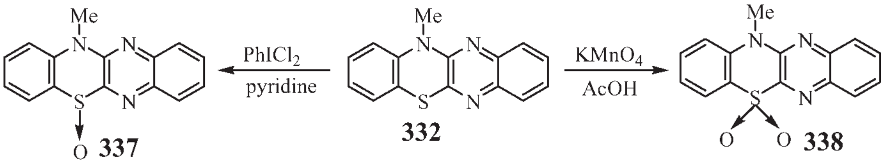
The structure of phenothiazinium salts was determined based on coupling constants analysis and was confirmed by X-ray analysis of the ethyl derivative **344** (R = Et) [133].

Benzo derivatives of 1,4,9-triazaphenothiazines (pyrido[3,2-b]quinoxalino[2′,3′-e][1,4]thiazines). Reaction of 2-amino-6-methylpyridine-3-thiol **261** with dichloro- and trichloroquinoxalines **325** in DMF (with sodium hydroxide) did not lead to tetracyclic azaphenothiazines **346** or **347** but unexpectedly to the bis-sulfide **348** in 77 and 71% yield, respectively (Scheme 129) [127].

Benzo derivative of 1,3,6,9-tetraazaphenothiazines (pyrimido[5,4-b]quinoxalino[2′,3′,-e][1,4]thiazines. Reactions of substituted 4-aminopyridazine-5-thiols **349** with 2,3-dichloroquinoxalines **325** in aqueous propylene glycol (with potassium hydroxide) led to benzo derivatives of 1,3,6,9-tetraazaphenothiazines **350** in 84–95% yield *via* the Smiles rearrangement. The structures of the products were established on the basis of further nitration under mild conditions and the discussion of the directive influence of the NH group. The products were identified as substituted 8-nitrotetraazabenzophenothiazine-*S*-oxides **351** (Scheme 130) [134].

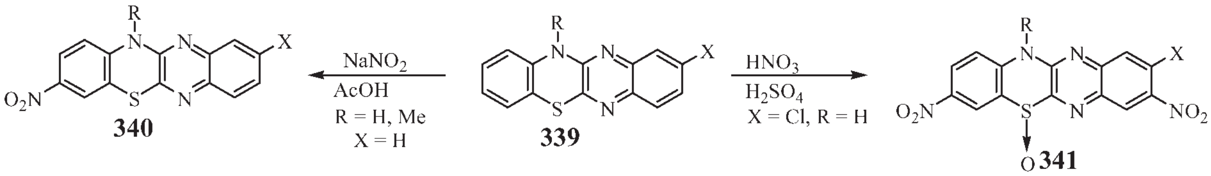
Benzo derivatives of 1,4,6,8-tetraazaphenothiazines (pyrimido[4,5-b]quinoxalino[2′,3′-e][1,4]thiazines). Reactions of 4,5-diaminopyrimidine-6(1*H*)-thione **352** with 2,3-dichloroquinoxalines **325** in aqueous DMF (with sodium hydroxide) proceeded *via* the Smiles rearrangement to give benzo derivatives of 1,4,6,8-tetraazaphenothiazines **353** in high yield (92 and 85% yield, respectively). The structure of the chloro product was based on further nitration under mild conditions and the discussion of the directive influence of the functional groups. The product

Scheme 126



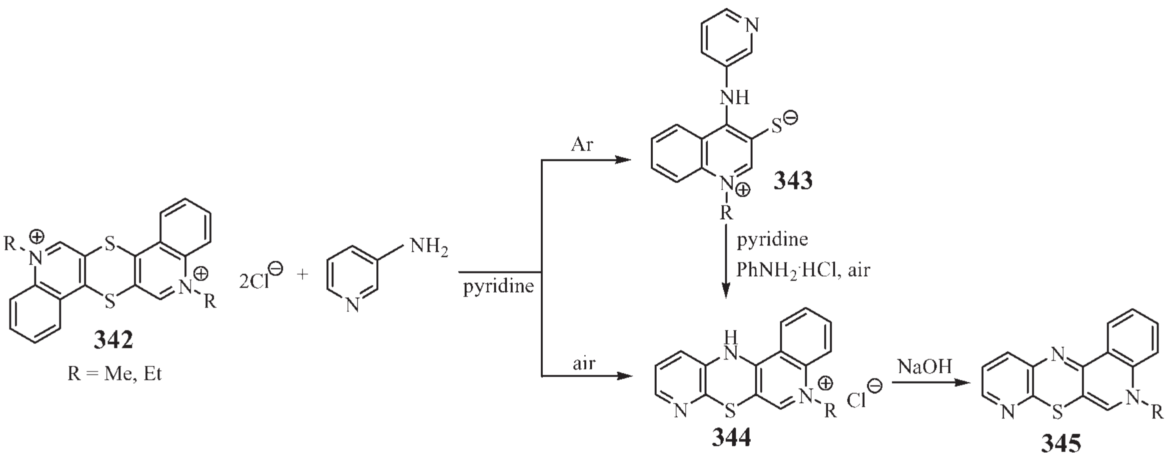
337 **332** **338**

Scheme 127



340 **339** **341**

Scheme 128



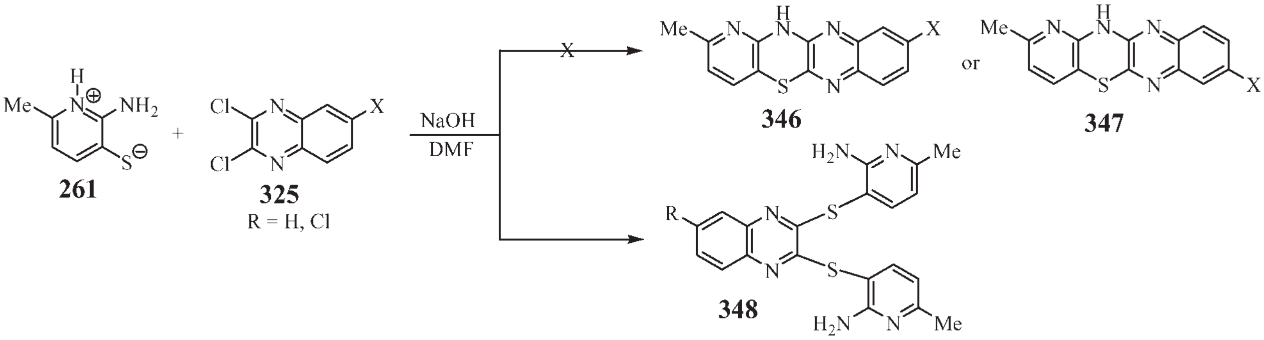
was identified as 10-amino-2-chloro-3-nitrotetraazabenzo[*b*]phenothiazine *S*-oxide **354** (Scheme 131).

To confirm the presence of the proton at the thiazine nitrogen atom compound **353** (R = H) was diazotized and heated to give triazolobenzotetraazaphenothiazine **355** in 81% yield (Scheme 132) [135].

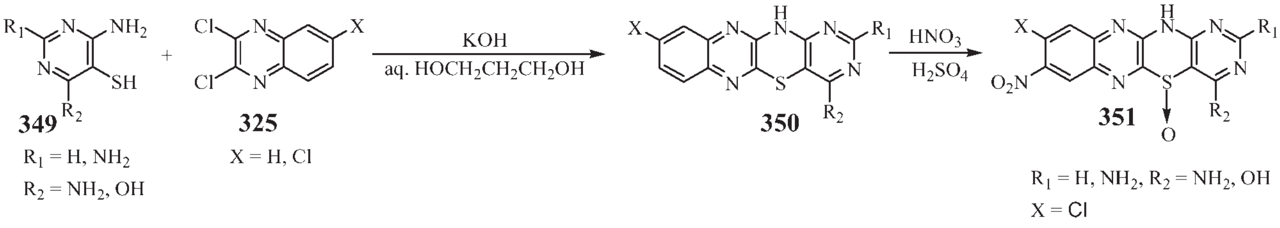
Pentacyclic phenothiazines (dibenzo derivatives of phenothiazines).

Dibenzo derivatives of 1,9-diazaphenothiazines (diquino[3,2-b;2′,3′-e]thiazines). Reaction of dihydroquinolin-2(1*H*)-one **356** with thionyl chloride in DMF led unexpectedly to the diquinothiazine **357** (in 21%

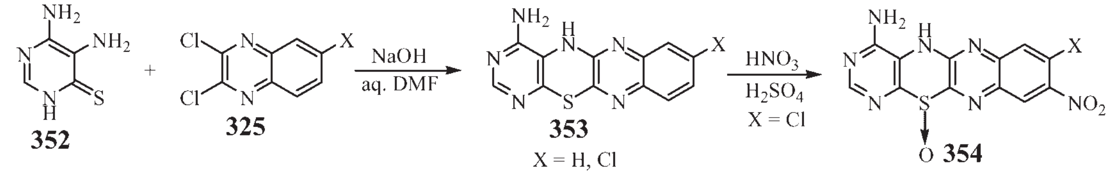
Scheme 129



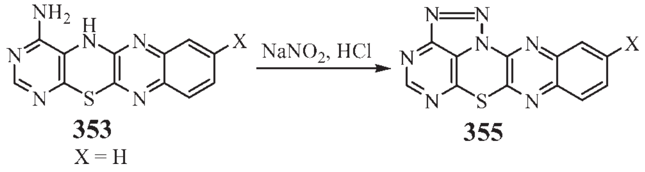
Scheme 130



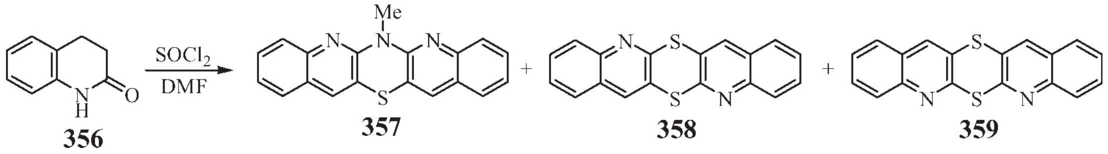
Scheme 131



Scheme 132



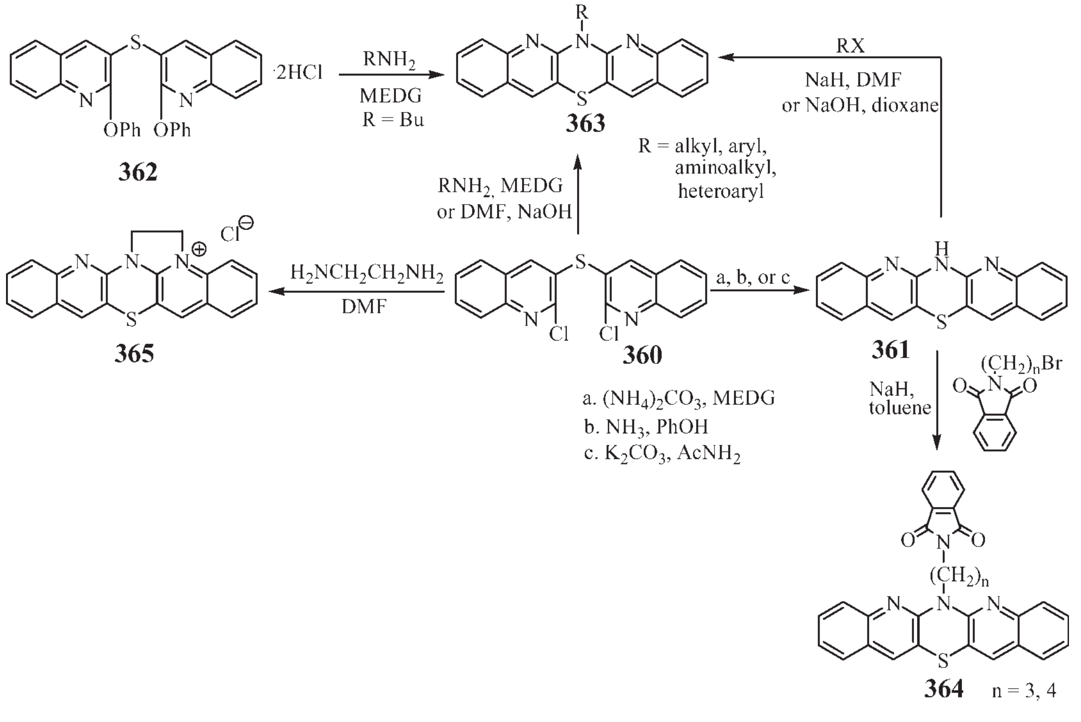
Scheme 133



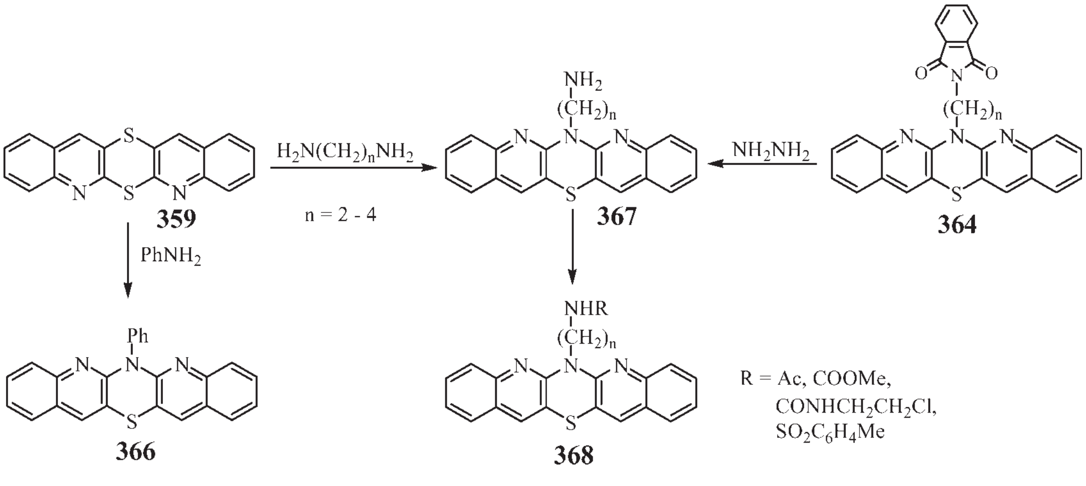
yield) and the isomeric diquinodithiins **358** and **359** (Scheme 133) [136].

Annulation reactions of 2,2′-dichloro-3,3′-diquinolinyl sulfide **360** with ammonium carbonate in MEDG (mono-methyl ether of diethylene glycol) or with gaseous ammonia in phenol or with acetamide (in the presence of potassium carbonate) led to 6*H*-diquinothiazine **361** (the dibenzo derivative of 1,9-diazaphenothiazine) in 10%, 13 and 57% yield, respectively. Further annulation reactions of sulfide **360** with primary aliphatic, aromatic, and heteroaromatic amines in MEDG or with DMF (in the presence of sodium hydroxide) and dihydrochloride of 2,2′-diphenoxy-3,3′-diquinolinyl sulfide **362** (the main product in the reaction of sulfide **360** with ammonia in phenol) with butylamine in MEDG gave various alkyl-, aminoalkyl-, aryl-, and heteroaryldiquinothiazines **363** in low to good yields. The alkyl derivatives were also obtained by alkylation of 6*H*-diquinothiazine **361** with alkyl and aminoalkyl halides in DMF (with sodium hydride) or in dioxane (with sodium hydroxide). Alkylation with phthalimidoalkyl bromides in toluene (with sodium hydride) gave phthalimidoalkyl derivatives **364** in good yields. When 2-chloroethylamine was used, the reaction proceeded through the formation of 2-chloroethyldiquinothiazine which underwent very smoothly intramolecular alkylation to give hexacyclic compound,

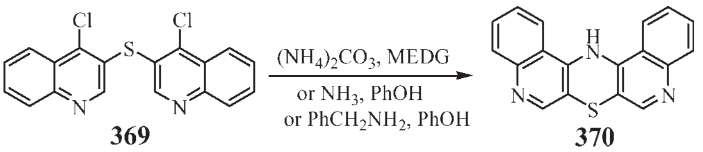
Scheme 134



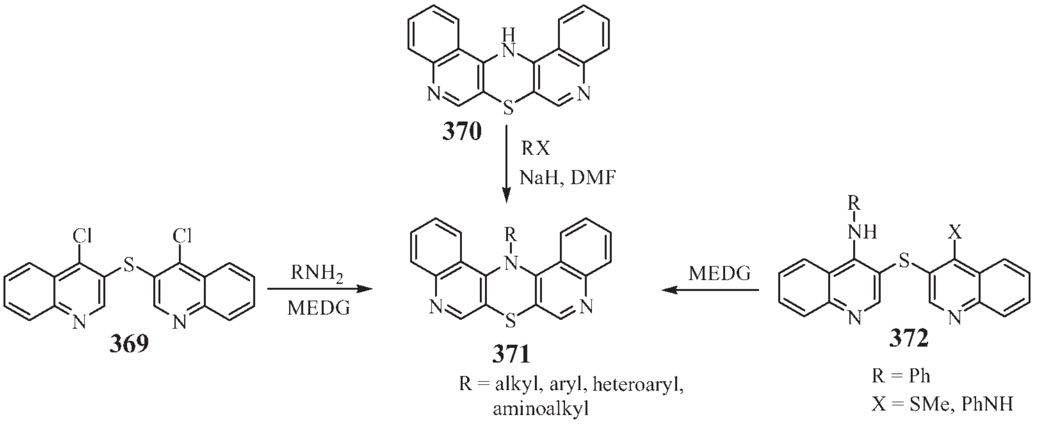
Scheme 135



Scheme 136



Scheme 137



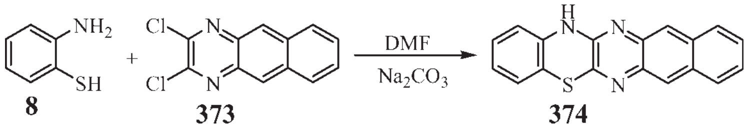
5,6-ethylenediquinothiazinium chloride **365** in 53% yield (Scheme 134) [136–138].

Diquinodithiin **359** turned out to be good substrate in the reaction with aniline and diaminoalkanes to give phenyl and aminoalkyl derivatives **366** and **367** in good yields. The last compounds were also obtained from phthalimidoalkyl derivatives **364** by action of hydrazine. The aminoalkyldiquinothiazines **367** were converted into acyl, sulfonyl, and half-mustard derivatives **368** in 68–90% yield (Scheme 135) [138].

The structures of diquinothiazines were established on the basis of ^{1}H NMR (^{1}H-^{1}H COSY and NOE) spectra and were confirmed by X-ray analysis of the phenyl and 4-nitrophenyl derivatives [137,139]. The diquinothiazine system turned out to be very lipophilic [140,141]. Some selected diquinothiazines exhibited significant anticancer activities against lung, colon, breast, renal and CNS cancers, melanoma and leukemia [138].

Dibenzo derivatives of 3,7-diazaphenothiazines (diquino [3,4-b;4′,3′-e]thiazines). Annulation reactions of 4,4′-dichloro-3,3′-diquinolinyl sulfide **369** with ammonium carbonate in MEDG or with gaseous ammonia in phenol led to 14*H*-diquinothiazine **370** (the dibenzo derivative of 3,7-diazaphenothiazine) in 27 and 65% yield. The same product was formed in 86% yield when benzylamine was used (Scheme 136).

Scheme 138



Further annulation reactions with primary aliphatic, aromatic and heteroaromatic amines in MEDG led to various 14-substituted dibenzodiazaphenothiazines **371**. 14-Alkyl derivatives were also obtained by *N*-alkylation of unsubstituted diquinothiazine **370** with alkyl halides in DMF (with sodium hydride). The phenyl derivative was also formed in cyclization of diquinolinyl sulfides **372** in MEDG (Scheme 137) [142–144].

The structure of dibenzodiazaphenothiazines **371** was based on ^{1}H NMR (^{1}H-^{1}H COSY, NOE) spectra and was confirmed by X-ray analyses of the methyl and phenyl derivatives [145,146].

Naphtho derivative of 1,4-diazaphenothiazine (benzo-[g]quinoxalinobenzo[1,4]thiazine). Reaction of aminobenzenethiol **8** with 2,3-dichlorobenzoquinoxaline **373** led to the pentacyclic naphtho-1,4-diazaphenothiazine **374**, an orange pigment dye (Scheme 138) [132].

CONCLUDING REMARKS

Modification of the phenothiazine structures by substitution of the benzene ring with an azine ring brought over 30 different azaphenothiazine systems. The authors hope that this review will provide the arranged knowledge of the diaza-, triaza-, and tetraazaphenothiazine chemistry and will clarify their nomenclature. The reader should take into account that not all the cited authors were aware of the Smiles rearrangement step and not all the azaphenothiazines were identified unequivocally. Re-emergence of classical phenothiazines in the treatment of various diseases perhaps will pay attention to the synthesis and structure of monoaza-, diaza-, triaza-, and tetraazaphenothiazines as potential biological phenothiazine derivatives.

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Facile Synthesis of 4-Alkoxycarbonylisoquinoline-1,3-diones and 5-Alkoxycarbonyl-2-benzazepine-1,3-diones *via* a Mild Alkaline Cyclization

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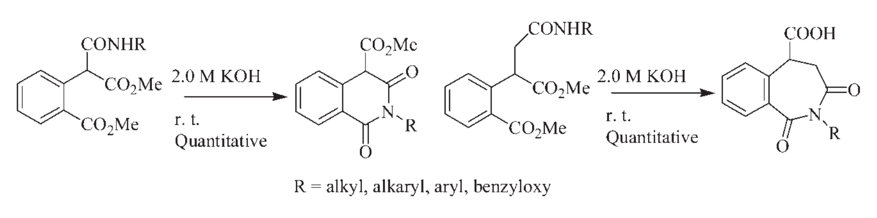

A series of 4-methoxycarbonylisoquinoline-1,3-diones was obtained from homophthalic acid in four steps. The key step was the quantitative and rapid alkaline cyclization of 2-methoxycarbonyl-2-(2-methoxycarbonylphenyl) acetamides. Homologation easily afforded in the same conditions 5-carboxy-2-benzazepine-1,3-dione.

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INTRODUCTION

4-Substituted isoquinoline-1,3-dione framework may serve as the backbone for the production of several series of biologically active compounds, mainly in the field of diabetes (aldose reductase inhibitors) [1], inflammation [2] (cycloxygenase [3] and lipoxygenase [4] inhibitors), herbicides, and plant growth regulators [5]. Our current research program is devoted to the evaluation of 2-hydroxyisoquinoline-1,3-diones as potential HIV-1 integrase and/or ribonuclease H inhibitors. For that purpose, we needed to develop a facile and efficient route to 4-alkoxycarbonyl-2-benzyloxyquinoline-1,3-diones as precursor of the lead compounds.

Two routes were possible (Scheme 1). The first one consists in synthesizing the 4-unsubstituted isoquinoline-1,3-dione by reaction of a primary amine with homophthalic anhydride, acid or diester (Scheme 1; route a) [1,3,5]. Then functionalization at position 4 is usually performed by reacting the isoquinoline-1,3-dione with a cyanoformate [1], a chloroformate [5], an acylchloride [3], or a sulfonylchloride [3] in presence of a base (pyridine, $LiN(SiMe_3)_2$, NaH or DBU) [1,3,5]. In our hands, the reaction of 2-benzyloxyisoquinoline-1,3-dione with methyl chloroformate in presence of a base (LDA or NaH) allowed us to isolate the desired product only in poor yields, because of a low reactivity and a degradation of the quinoline ring. Alternatively, ortho-halogenated benzoic acids can be converted to a dimethylmalonate derivative by the Hurtley reaction and the treatment with the appropriate amine gives 4-alkoxycarbonyl-isoquinoline-1,3-diones after activation with thionyl chloride (Scheme 1; route b) [1,6,7].

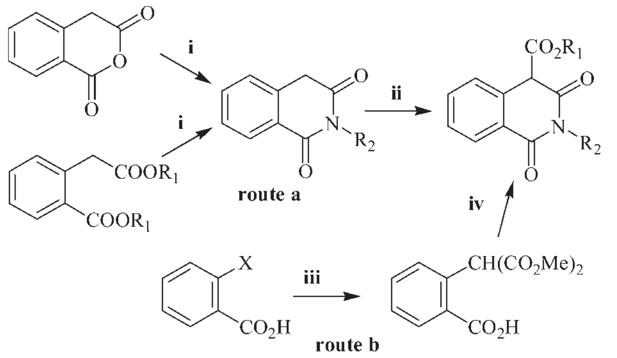
Once again, we could not obtain satisfactorily the cyclized product by this method. We also noticed a third possibility, which consists in treating quinone monoacetals with diethylmalonate in presence of KOtBu. However, to date, only one example using this method has been reported [8].

These failures led us to modify route b by activating a carboxylic acid function of the malonate derivative instead of activating the benzoic acid function. We report herein synthetic studies on this novel four step procedure (Scheme 2). A series of 4-methoxycarbonylisoquinoline-1,3-diones variously substituted at the nitrogen atom was obtained (Table 1).

RESULTS AND DISCUSSION

Homophthalic acid **1** was quantitatively esterified with methylic alcohol. The anion of the homophthalic diester **2** obtained by treatment with LDA reacted with carbon dioxide according to Lazer *et al.* [9] to yield the methyl 2-(2-methoxycarbonylphenyl) malonate monoester **3** in 62% yield. Using activation with the BOP reagent [10], the corresponding amides **4a-h** were synthesized with

Scheme 1. Reagents and conditions: (i) R_2NH_2, DMF, or xylenes; (ii) $ClCOOR_1$, pyridine, or $CNCOOR_1$, $LiN(SiMe_3)_2$, THF; (iii) NaH, CuBr, $CH_2(COOMe)_2$; (iv) $SOCl_2$ then R_2NH_2, THF.



several alkyl, alkylaryl, aryl, benzyloxy amines, and glycine in satisfactory yields (52–85%). The cyclization was easily achieved using 2.5*M* potassium hydroxide in aqueous methanol at room temperature for 5 min. This reaction was quantitative and the 2-substituted-4-methoxycarbonylisoquinoline-1,3-diones **5a-h** were isolated as variable mixtures of keto (0–50%) and enol (50–100%) forms. When the nitrogen atom was substituted by an ethoxycarbonylmethyl group (**4f**, Table 1), hydrolysis of this ethyl ester function occurred during the cyclization process whereas the residual methyl ester of the malonate derivative was conserved. Thus compound **5f** is substituted at position 2 by a carboxymethyl group, which could be variously functionalized (by a peptidic structure for example). Conversely, the carbon-chlorine bond in compound **4g** (Table 1) was found to be resistant to the basic conditions of cyclization.

This easy alkaline cyclization process led us to investigate the possible synthesis of homologous derivatives. For this purpose, homophthalic dimethyl ester **2** was first alkylated with allyl bromide in the presence of LDA (Scheme 3) to give **6**. The allylic oxidation with potassium periodate and potassium permanganate afforded methyl 2-(carboxymethyl)-2-(2-methoxycarbonylphenyl) ethanoate **7** in 63% yield. Using benzyloxyamine as a model, we synthesized the corresponding amide **8** in 42% yield. Cyclization of **8** was of particular interest since it may give either a five-membered ring (1-benzyloxy-3-arylsuccinimide **9**) or a seven-membered ring (a 2-benzazepine-1,3-dione **11**) depending on the reactivity of the two methyl ester functions (Fig. 1). With a 5 min reaction time, a mixture of **10** (80%) and **11** (20%) was obtained. Prolonging the reaction time (15 min) gave only quantitatively the 1,3-dioxo-2-benzazepine-5-carboxylic acid **10**.

To determine the structure of **10**, it was quantitatively converted into **11** using classical esterification

Scheme 2

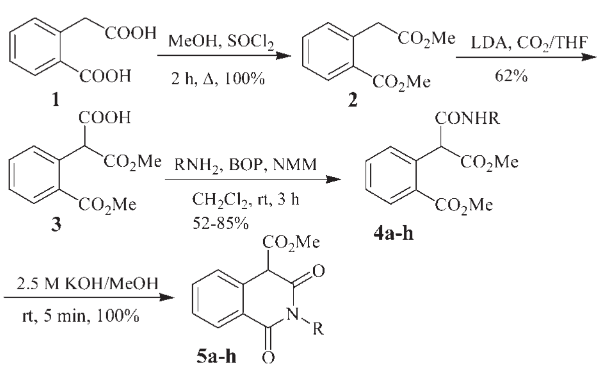


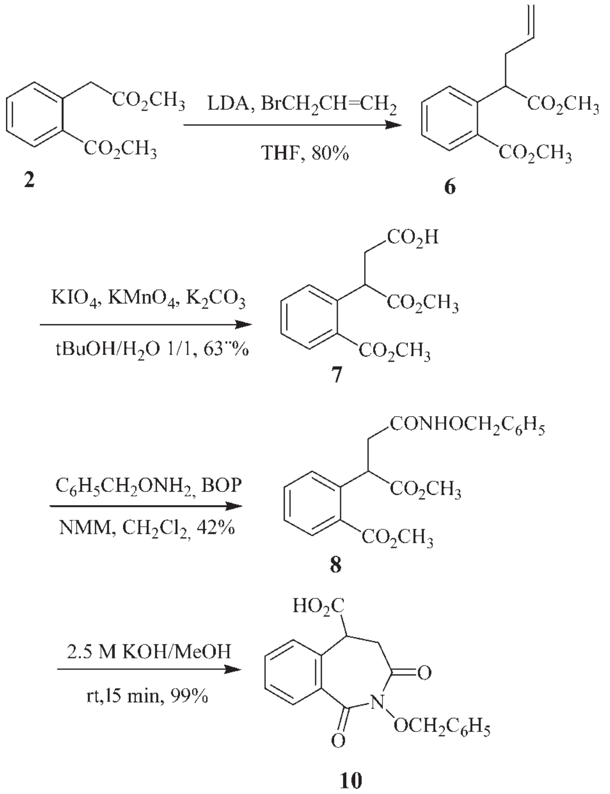
Table 1

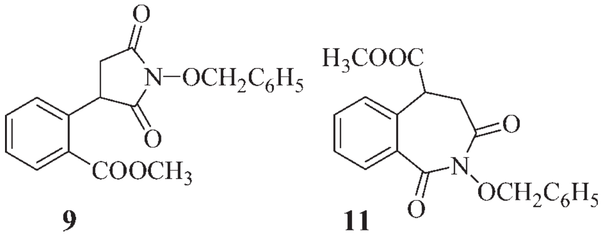
Structures of the synthesized 2-substituted-4-methoxycarbonylisoquinoline-1,3-diones **5a-h**.

Entry	R	Yield (%)[a]
5a	$CH_2C_6H_4$-pF	52
5b	$CH_2C_6H_3$-o,p(OCH_3)$_2$	67
5c	$(CH_2)_2C_6H_3$-m,p(OCH_3)$_2$	63
5d	C_6H_{13}	57
5e	C_6H_4-mCl	85
5f	$CH_2COOC_2H_5$	73
5g	$CH_2CH_2CH_2Cl$	69
5h	$OCH_2C_6H_5$	69

[a] Yields for the conversion of **3** into **4a-h**.

Scheme 3





9 **11**

Figure 1. Possible products from the cyclization of **8**.

conditions. The benzazepine structure of **11** was established on the basis of ^{1}H-^{13}C correlation experiments. Briefly, the CO signal of the ester function (170.6 ppm) can be easily identified *via* the methyl group (3.57 ppm). This CO signal correlated with H-5 (4.23 ppm) which also gave a correlation with carbon 3 (168.5 ppm). On the other side, carbon 1 (161.1 ppm) gave correlations with H-9 and H-8 (8.27 and 7.30 ppm, respectively). The isolation of **10** as a single cyclized product clearly shows that the benzoic ester function of **8** was more reactive than the aliphatic one.

In conclusion, eight 2-substituted-4-methoxycarbonylisoquinoline-1,3-diones (substituents: alkyl, alkylaryl, aryl, benzyloxy, carboxymethylene) have been synthesized in a four-step procedure in overall yields ranging between 29 and 53%. Other alkoxycarbonyl groups may be introduced at position 4 (data not shown). This novel synthetic scheme employs four steps. In terms of yield, the introduction of the carboxylic acid function and the subsequent coupling with an amine are the two limiting steps whereas the two remaining ones are quantitative. In terms of cumulative reaction time, this novel route is undoubtedly more advantageous than route a (Scheme 1) starting from homophtalic acid derivatives, which requires much longer reaction times (4–72 h for the amine condensation and 3–24 h for the subsequent substitution) [1,3,5].

We compared our synthetic scheme to route b. Malamas *et al.* [1] reported the synthesis of **5** (R = CH$_2$-C$_6$H$_4$-oF-pBr) in 78% overall yield. Other analogues were also briefly described without any experimental information about the final cyclization step using variously substituted benzylamines and alkylamines. We compared the two routes for the synthesis of **5a**, **5d**, **5e**, and **5h**. Compounds **5a** and **5d** were synthesized by both methods with similar overall yields around 40%. In contrast our method was better than route b for the synthesis of **5e** and **5h**, which were obtained with 54 and 44% overall yields, respectively while route b failed to give these compounds. Crude residues contained mixtures of byproducts without any trace of the desired cyclized compound. So the two methods are comparable when the R substituent at position 2 is an alkyl or a benzyl group. When this substituent is an aryl or a benzyloxy group, our method is largely superior to route b. But the main advantage of our route over routes a and b lies in the clean, efficient and rapid last cyclization step, which is quantitatively performed within only 5 min reaction time. The homologation showed the better reactivity of the benzoate ester versus the malonate one and led also efficiently to the formation of a 5-carboxy-2-benzazepine-1,3-dione derivative. This route could also be employed and modified to synthesize variously substituted 2-benzazepine-1,3-diones since the elaboration of such compounds have been scarcely investigated. To the best of our knowledge, only diphenimides [11] and a few examples of 2- and 4-substituted derivatives have been so far reported [12,13].

EXPERIMENTAL

Silica gel, 200–400 mesh (Merck) was used for column chromatography. Melting points were obtained on a Reichert Thermopan melting point apparatus, equipped with a microscope. NMR spectra were obtained on an AC 300 Bruker spectrometer in the appropriate solvent with TMS as internal reference. J values are given in Hz. Elemental analyses were performed by CNRS laboratories (Vernaison) and were within 0.4% of the theoretical values.

Methyl 2-(2-methoxy-2-oxoethyl)benzoate (2). Homophtalic acid **1** (5 g, 28.0 mmol) was dissolved in MeOH (100 mL) and thionyl chloride (5.5 mL, 62.0 mmol) was added dropwise. The solution was heated under reflux for 2 h and concentrated *in vacuo*. The residue was dissolved in AcOEt and washed several times with 10% NaHCO$_3$. After drying over Na$_2$SO$_4$, the solvent was evaporated *in vacuo* to yield **2** as a yellow oil (99%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.60 (s, 3H, OCH$_3$), 3.78 (s, 3H, OCH$_3$), 4.00 (s, 2H, CH$_2$), 7.36 (m, 3H, H$_{Ar}$), 7.92 (dd, ^3J = 8.2 Hz, ^4J = 2.0 Hz, 1H, H$_{Ar}$); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 36.7 (CH$_2$), 51.4 (OCH$_3$), 51.8 (OCH$_3$), 127.4 (CH), 129.5 (C), 130.3 (CH), 132.4 (CH), 132.6 (CH), 135.9 (C), 166.9 (CO), 172.4 (CO).

3-Methoxy-2-[2-(methoxycarbonyl)phenyl]-3-oxopropanoic acid (3). A solution of freshly distilled diisopropylamine (0.75 mL, 5.35 mmol) in 10.0 mL of dry THF under an argon atmosphere was cooled to –78°C and 3.34 mL of 1.6*M* *n*-butyllithium (5.35 mmol) was added. After 30 min reaction at –78°C, a solution of **2** (0.79 g, 3.8 mmol) in 10.0 mL of THF was added dropwise. After stirring the solution for 30 min, the temperature had risen to –5°C and the argon inlet was removed. CO$_2$ formed from addition of sulfuric acid on anhydrous barium carbonate was bubbled through the reaction mixture for 20 min. The mixture was acidified with 2.0*M* HCl and then extracted with CHCl$_3$. The combined organic extracts were extracted with 10% Na$_2$CO$_3$. The basic extracts were made acidic by the careful addition of 2.0*M* HCl and the product was extracted into CHCl$_3$ (3 × 100 mL). The combined CHCl$_3$ extracts were dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure to give an oily residue, which crystallized on cooling. Orange solid (0.49 g; 62%); mp 100°C; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 3.75 (s, 3H, OCH$_3$), 3.87 (s, 3H, OCH_3), 5.16 (s, 1H, CH), 7.38 (dd, $^{3}J = 7.7$ Hz, $^{4}J = 1.2$ Hz, 1H, H_{Ar}), 7.44 (td, $^{3}J = 7.7$ Hz, $^{4}J = 1.2$ Hz, 1H, H_{Ar}), 7.57 (td, $^{3}J = 7.7$ Hz, $^{4}J = 1.2$ Hz, 1H, H_{Ar}), 8.07 (dd, $^{3}J = 7.7$ Hz, $^{4}J = 1.2$ Hz, 1H, H_{Ar}), 11.22 (br s, 1H, COOH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 52.5$ (OCH_3), 53.3 (OCH_3), 55.5 (CH), 128.5 (CH), 128.6 (C), 131.3 (CH), 132.3 (CH), 132.9 (CH), 134.4 (C), 167.7 (CO), 170.6 (CO), 170.8 (CO).

Methyl 2-{1-[(4-fluorobenzyl)amino]-3-methoxy-1,3-dioxopropan-2-yl}benzoate (4a). BOP (1.69 g, 4.0 mmol) was added to an ice-cooled solution of **3** (1.00 g, 4.0 mmol), 4-fluorobenzylamine (0.50 g, 4.0 mmol) and 4-methylmorpholine (2.2 mL, 20.0 mmol) in a minimum of CH_2Cl_2. After 30 min stirring at 0°C and 3 h at room temperature, the mixture was washed with 1.0*M* HCl, 1.0*M* $NaHCO_3$ solutions and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. After column chromatography of the residue (eluent: petroleum ether/AcOEt, 70/30 then 50/50), the product was obtained as beige crystals (52%); mp 127°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.59$ (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 4.25 (dd, $^{2}J = 14.9$ Hz, $^{3}J = 6.0$ Hz, 1H, CH_2), 4.32 (dd, $^{2}J = 14.9$ Hz, $^{3}J = 6.0$ Hz, 1H, CH_2), 5.20 (s, 1H, CH), 6.85 (t, $^{3}J = 8.4$ Hz, 2H, H_{Ar}), 7.08 (dd, $^{3}J = 8.8$ Hz, $^{4}J = 5.4$ Hz, 2H, H_{Ar}), 7.29 (td, $^{3}J = 7.5$ Hz, $^{4}J = 2.0$ Hz, 1H, H_{Ar}), 7.40–7.50 (m, 2H, H_{Ar}), 7.64 (t, $^{3}J = 5.3$ Hz, 1H, NH), 7.87 (dd, $^{3}J = 7.6$ Hz, $^{4}J = 1.2$ Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 42.7$ (CH_2), 52.2 (OCH_3), 52.5 (OCH_3), 55.1 (CH), 115.1 (d, $^{2}J = 21.4$ Hz, 2CH), 127.8 (CH), 128.8 (C), 129.0 (d, $^{3}J = 8.3$ Hz, 2CH), 130.6 (CH), 131.6 (CH), 132.5 (CH), 133.9 (d, $^{4}J = 3.3$ Hz, C), 135.5 (C), 161.8 (d, $^{1}J = 243.3$ Hz, C), 167.3 (CO), 168.0 (CO), 170.1 (CO); *Anal.* Calc for $C_{19}H_{18}FNO_5$: C, 63.50; H, 5.05; O, 22.26. Found: C, 63.61; H, 5.09; O, 22.11.

Methyl 2-{1-[(2,4-dimethoxybenzyl)amino]-3-methoxy-1,3-dioxopropan-2-yl}benzoate (4b). After column chromatography (eluent: petroleum ether/AcOEt, 50/50), the product was obtained as a yellow oil (67%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.62$ (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 4.30 (d, $^{3}J = 5.7$ Hz, 2H, CH_2), 5.30 (s, 1H, CH), 6.31 (dd, $^{3}J = 8.1$ Hz, $^{4}J = 2.2$ Hz, 1H, H_{Ar}), 6.34 (d, $^{4}J = 2.2$ Hz, 1H, H_{Ar}), 7.05 (d, $^{3}J = 8.1$ Hz, 1H, H_{Ar}), 7.30 (td, $^{3}J = 7.5$ Hz, $^{4}J = 1.5$ Hz, 1H, H_{Ar}), 7.41–7.54 (m, 3H, NH, 2 H_{Ar}), 7.89 (dd, $^{3}J = 7.9$ Hz, $^{4}J = 1.2$ Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 38.9$ (CH_2), 52.0 (OCH_3), 52.2 (OCH_3), 54.9 (OCH_3), 55.0 (OCH_3), 55.1 (CH), 98.1 (CH), 103.5 (CH), 118.4 (C), 127.5 (CH), 129.0 (C), 129.8 (CH), 130.4 (CH), 131.2 (CH), 132.2 (CH), 135.3 (C), 158.2 (*C*—OCH_3), 160.1 (*C*—OCH_3), 166.8 (CO), 167.6 (CO), 169.9 (CO); *Anal.* Calc for $C_{21}H_{23}NO_7$: C, 62.83; H, 5.78; O, 27.90. Found: C, 62.72; H, 5.68; O, 28.08.

Methyl 2-(1-{[2-(2,4-dimethoxyphenyl)ethyl]amino}-3-methoxy-1,3-dioxopropan-2-yl)benzoate (4c). Yellow oil (63%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.70$ (t, $^{3}J = 7.0$ Hz, 2H, CH_2), 3.42 (dd, $^{3}J = 7.0$ Hz, $^{3}J = 5.2$ Hz, 2H, CH_2), 3.66 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 5.28 (s, 1H, CH), 6.57 (dd, $^{3}J = 8.0$ Hz, $^{4}J = 1.5$ Hz, 1H, H_{Ar}), 6.66 (d, $^{4}J = 1.5$ Hz, 1H, H_{Ar}), 6.69 (d, $^{3}J = 8.0$ Hz, 1H, H_{Ar}), 7.24 (t, $^{3}J = 5.3$ Hz, 1H, NH), 7.35 (td, $^{3}J = 7.6$ Hz, $^{4}J = 1.5$ Hz, 1H, H_{Ar}), 7.46–7.56 (m, 2H, 2 H_{Ar}), 7.91 (dd, $^{3}J = 7.6$ Hz, $^{4}J = 1.5$ Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 38.9$ (CH_2), 40.9 (CH_2), 52.1 (OCH_3), 52.3 (OCH_3), 54.7 (CH), 55.5 (OCH_3), 55.6 (OCH_3), 110.9 (CH), 111.6 (CH), 120.4 (CH), 127.6 (CH), 128.7 (C), 130.4 (CH), 131.1 (C), 131.2 (CH), 132.3 (CH), 135.3 (C), 147.2 (*C*—OCH_3), 148.5 (*C*—OCH_3), 167.3 (CO), 167.8 (CO), 169.5 (CO); *Anal.* Calc for $C_{22}H_{25}NO_7$: C, 63.60; H, 6.07; O, 26.96. Found: C, 63.51; H, 5.98; O, 27.12.

Methyl 2-[1-(hexylamino)-3-methoxy-1,3-dioxopropan-2-yl] benzoate (4d). After column chromatography (eluent: petroleum ether/AcOEt, 50/50), the product was obtained as a transparent oil (57%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.85$ (t, $^{3}J = 6.5$ Hz, 3H, CH_3), 1.20–1.26 (m, 6 H, CH_2), 1.47 (m, 2H, CH_2), 3.22 (q, $^{3}J = 6.5$ Hz, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 5.30 (s, 1H, CH), 7.19 (t, $^{3}J = 6.5$ Hz, 1H, NH), 7.38 (td, $^{3}J = 7.5$ Hz, $^{4}J = 1.5$ Hz, 1H, H_{Ar}), 7.52 (td, $^{3}J = 7.5$ Hz, $^{4}J = 1.5$ Hz, 1H, H_{Ar}), 7.62 (dd, $^{3}J = 7.5$ Hz, $^{4}J = 1.5$ Hz, 1H, H_{Ar}), 7.93 (dd, $^{3}J = 7.5$ Hz, $^{4}J = 1.5$ Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.1$ (CH_3), 22.5 (CH_2), 26.4 (CH_2), 29.2 (CH_2), 31.3 (CH_2), 39.7 (CH_2), 52.4 (OCH_3), 52.5 (OCH_3), 54.9 (CH), 127.7 (CH), 128.5 (C), 130.6 (CH), 131.6 (CH), 132.5 (CH), 135.6 (C), 167.3 (CO), 168.2 (CO), 170.2 (CO); *Anal.* Calc for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; O, 23.85. Found: C, 64.72; H, 7.36; O, 23.62.

Methyl 2-{1-[(3-chlorophenyl)amino]-3-methoxy-1,3-dioxopropan-2-yl}benzoate (4e). After column chromatography (eluent: petroleum ether/AcOEt, 50/50), the product was obtained as a transparent oil (85%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.75$ (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 5.32 (s, 1H, CH), 7.05 (dd, $^{3}J = 7.5$ Hz, $^{4}J = 1.5$ Hz, 1H, H_{Ar}), 7.29 (td, $^{3}J = 7.5$ Hz, $^{4}J = 1.2$ Hz, 1H, H_{Ar}), 7.38 (dd, $^{3}J = 7.6$ Hz, $^{4}J = 2.0$ Hz, 1H, H_{Ar}), 7.42 (td, $^{3}J = 7.5$ Hz, $^{4}J = 1.5$ Hz, 1H, H_{Ar}), 7.57 (td, $^{3}J = 7.5$ Hz, $^{4}J = 1.5$ Hz, 1H, H_{Ar}), 7.64 (dd, $^{3}J = 7.5$ Hz, $^{4}J = 1.5$ Hz, 1H, H_{Ar}), 7.69 (d, $^{4}J = 1.3$ Hz, 1H, H_{Ar}), 7.98 (dd, $^{3}J = 7.6$ Hz, $^{4}J = 1.2$ Hz, 1H, H_{Ar}), 9.76 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 52.7$ (OCH_3), 52.9 (OCH_3), 56.1 (CH), 117.7 (CH), 119.8 (CH), 124.2 (CH), 128.2 (CH), 128.9 (C), 129.8 (CH), 130.8 (CH), 132.1 (CH), 132.8 (CH), 134.5 (C), 134.9 (C), 139.1 (C), 165.7 (CO), 168.7 (CO), 170.0 (CO); *Anal.* Calc for $C_{18}H_{16}ClNO_5$: C, 59.76; H, 4.46; O, 22.11. Found: C, 60.02; H, 4.70; O, 21.94.

Methyl 2-{1-[(2-ethoxy-2-oxoethyl)amino]-3-methoxy-1,3-dioxopropan-2-yl}benzoate (4f). After column chromatography (eluent: petroleum ether/AcOEt, 50/50), the product was obtained as a white crystals (73%); mp 75°C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.13$ (t, $^{3}J = 7.0$ Hz, 3H, CH_3), 3.60 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.90 (t, $^{3}J = 5.3$ Hz, 2H, CH_2), 4.06 (q, $^{3}J = 7.0$ Hz, 2H, CH_2), 5.33 (s, 1H, CH), 7.28 (td, $^{3}J = 7.5$ Hz, $^{4}J = 1.4$ Hz, 1H, H_{Ar}), 7.44–7.50 (m, 2H, H_{Ar}), 7.69 (br t, $^{3}J = 5.3$ Hz, 1H, NH), 7.87 (dd, $^{3}J = 7.5$ Hz, $^{4}J = 1.4$ Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.0$ (CH_3), 41.6 (CH_2), 52.4 (OCH_3), 52.6 (OCH_3), 54.9 (CH), 61.3 (CH_2), 127.9 (CH), 129.1 (C), 130.7 (CH), 131.5 (CH), 132.5 (CH), 135.1 (C), 167.7 (CO), 168.0 (CO), 169.4 (CO), 169.9 (CO); *Anal.* Calc for $C_{16}H_{19}NO_7$: C, 56.97; H, 5.68; O, 33.20. Found: C, 56.73; H, 5.41; O, 33.39.

Methyl 2-{1-[(3-chloropropyl)amino]-3-methoxy-1,3-dioxopropan-2-yl}benzoate (4g). Pale yellow crystals (69%); mp 84–85°C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.94$ (quin, $^{3}J = 6.5$ Hz, 2H, CH_2), 3.37 (quin, $^{3}J = 6.7$ Hz, 2H, CH_2), 3.50 (sext, $^{3}J = 5.4$ Hz, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.86 (s, 3H,

OCH_3), 5.21 (s, 1H, CH), 7.37 (m, 1H, H_{Ar}), 7.48 (t, ^3J = 6.6 Hz, 1H, NH), 7.45 (m, 2H, H_{Ar}), 7.97 (dd, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.8 (CH_2), 36.9 (CH_2), 42.2 (CH_2), 52.3 (OCH_3), 52.5 (OCH_3), 55.2 (CH), 127.8 (CH), 128.8 (C), 130.6 (CH), 131.6 (CH), 132.5 (CH), 135.4 (C), 167.6 (CO), 168.0 (CO), 170.3 (CO); *Anal.* Calc for $C_{15}H_{18}ClNO_5$: C, 54.97; H, 5.54; O, 24.41. Found: C, 54.78; H, 5.39; O, 24.66.

Methyl 2-{1-[(benzyloxy)amino]-3-methoxy-1,3-dioxopropan-2-yl}benzoate (4h). After column chromatography (eluent: petroleum ether /AcOEt, 70/30), the product was obtained as a pale yellow oil (69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.63 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 4.79 (s, 2H, CH_2), 5.20 (s, 1H, CH), 7.18–7.28 (m, 5H, H_{Ar}), 7.33 (td, ^3J = 7.5 Hz, ^4J = 1.2 Hz, 1H, H_{Ar}), 7.48 (td, ^3J = 7.5 Hz, ^4J = 1.2 Hz, 1H, H_{Ar}), 7.57 (dd, ^3J = 7.5 Hz, ^4J = 1.2 Hz, 1H, H_{Ar}), 7.87 (dd, ^3J = 7.5 Hz, ^4J = 1.2 Hz, 1H, H_{Ar}), 9.64 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.5 (OCH_3), 52.7 (OCH_3), 52.8 (CH), 78.0 (OCH_2), 116.7 (C), 128.1 (CH), 128.5 (2CH), 128.6 (CH), 128.8 (C), 129.3 (2CH), 130.8 (CH), 131.9 (CH), 132.8 (CH), 134.5 (C), 165.4 (CO), 168.3 (CO), 169.3 (CO); *Anal.* Calc for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.36; O, 26.86. Found: C, 63.99; H, 5.62; O, 26.77.

Methyl 2-(4-fluorobenzyl)-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (5a). Compound **4a** (0.359 g, 1.0 mmol) was dissolved in a solution of methanol (10.0 mL) and 2.0*M* KOH (10.0 mL). After 5 min stirring, the solution was acidified with 2.0*M* HCl and extracted three times with ether (20.0 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to afford **5a** as off-white crystals (0.324 g, 99%); mp 167°C; 100% enol form. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.98 (s, 3H, OCH_3), 5.30 (s, 2H, CH_2), 6.90 (t, ^3J = 8.4 Hz, 2H, H_{Ar}), 7.24 (td, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 1H, H_{Ar}), 7.41 (dd, ^3J = 8.8 Hz, ^4J = 5.4 Hz, 2H, H_{Ar}), 7.08 (dd, ^3J = 8.8 Hz, ^4J = 5.4 Hz, 2H, H_{Ar}), 7.54 (td, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 1H, H_{Ar}), 8.29 (dd, ^3J = 7.6 Hz, ^4J = 1.6 Hz, 1H, H_{Ar}), 8.32 (dd, ^3J = 7.6 Hz, ^4J = 1.6 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 43.8 (CH_2), 52.7 (OCH_3), 84.8 (C), 115.1 (d, ^2J = 21.4 Hz, 2CH), 123.9 (CH), 124.3 (CH), 127.0 (C), 128.5 (CH), 130.6 (d, ^3J = 8.3 Hz, 2CH), 130.6 (CH), 132.2 (d, ^4J = 3.3 Hz, C), 135.5 (C), 162.0 (CO), 132.1 (d, ^1J = 241.3 Hz, C), 166.9 (CO), 173.8 (CO); *Anal.* Calc for $C_{18}H_{14}FNO_4$: C, 66.05; H, 4.31; O, 19.55. Found: C, 66.17; H, 4.15; O, 19.22.

Methyl 2-(2,4-dimethoxybenzyl)-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (5b). Off-white crystals (99%); mp 121°C; 85% enol form, 15% keto form. Enol form: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.76 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 5.40 (s, 2H, CH_2), 6.37 (dd, ^3J = 8.5 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 6.49 (d, ^4J = 1.5 Hz, 1H, H_{Ar}), 6.83 (d, ^3J = 8.3 Hz, 1H, H_{Ar}), 7.33 (td, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.64 (td, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 8.40–8.46 (dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 2H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.8 (CH_2), 52.8 (COO*C*H_3), 55.3 (OCH_3), 55.5 (OCH_3), 84.6 (C), 98.5 (CH), 104.2 (CH), 116.8 (C), 121.0 (C), 124.1 (CH), 124.3 (CH), 127.3 (CH), 128.7 (CH), 133.5 (CH), 133.8 (C), 157.9 (*C*—OCH_3), 160.1 (*C*—OCH_3), 162.0 (CO), 164.4 (CO), 173.9 (CO); Keto form: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.74 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 4.97 (s, 1H, CH), 5.15 (d, ^2J = 15.1 Hz, 1H, CH_2), 5.26 (d, ^2J = 15.1 Hz, 1H, CH_2), 6.38–6.50 (m, 2H, H_{Ar}), 7.07 (d, ^3J = 8.3 Hz, 1H, H_{Ar}), 7.33 (td, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.45 (dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.52 (td, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 8.26 (dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.9 (CH_2), 53.5 (OCH_3), 53.7 (OCH_3), 55.3 (OCH_3), 55.5 (CH), 98.4 (CH), 103.9 (CH), 116.8 (C), 125.2 (C), 126.9 (CH), 128.3 (CH), 128.9 (CH), 129.6 (CH), 132.1 (C), 134.0 (CH), 158.1 (*C*—OCH_3), 160.1 (*C*—OCH_3), 164.0 (CO), 166.7 (CO), 167.5 (CO); *Anal.* Calc for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; O, 25.99. Found: C, 65.34; H, 5.09; O, 25.72.

Methyl 2-[2-(3,4-dimethoxyphenyl)ethyl]-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (5c). Beige crystals (99%); mp 101°C; 90% enol form, 10% keto form. Enol form: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.93 (t, ^3J = 8.0 Hz, 2H, CH_2), 3.84 (s, 6H, 2 × OCH_3), 4.03 (s, 3H, OCH_3), 4.35 (t, ^3J = 8.0 Hz, 2H, CH_2), 6.75–6.88 (m, 3H, H_{Ar}), 7.28 (td, ^3J = 7.6 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.58 (td, ^3J = 7.6 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 8.33 (dd, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 1H, H_{Ar}), 8.35 (dd, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.6 (CH_2), 43.0 (CH_2), 52.6 (OCH_3), 55.6 (OCH_3), 55.7 (OCH_3), 84.3 (C), 111.0 (CH), 111.8 (CH), 120.6 (C), 120.7 (CH), 123.8 (CH), 124.1 (CH), 128.2 (CH), 130.6 (C), 133.2 (CH), 133.4 (C), 147.5 (C—OH), 148.7 (C—OH), 161.5 (CO), 163.8 (CO), 173.7 (CO); Keto form: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.87 (t, ^3J = 7.7 Hz, 2H, CH_2), 3.72 (s, 3H, OCH_3), 3.84 (s, 6H, 2 × OCH_3), 4.20 (t, ^3J = 7.7 Hz, 2H, CH_2), 4.88 (s, 1H, CH), 6.75–6.88 (m, 3H, H_{Ar}), 7.40 (dd, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 1H, H_{Ar}), 7.49 (td, ^3J = 7.6 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.58 (td, ^3J = 7.6 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 8.21 (dd, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.4 (CH_2), 41.8 (CH_2), 53.4 (OCH_3), 53.5 (OCH_3), 55.8 (OCH_3), 55.9 (CH), 111.2 (CH), 111.8 (CH), 120.6 (CH), 125.0 (C), 126.9 (CH), 128.9 (CH), 129.3 (CH), 130.9 (C), 133.2 (C), 134.0 (CH), 147.6 (C—OH), 148.8 (C—OH), 163.8 (CO), 166.8 (CO), 167.4 (CO); *Anal.* Calc for $C_{21}H_{21}NO_6$: C, 65.79; H, 5.52; O, 25.04. Found: C, 65.65; H, 5.23; O, 24.91.

Methyl 2-hexyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (5d). Purple crystals (99%); mp 88°C; 90% enol form, 10% keto form. Enol form: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, ^3J = 7.1 Hz, 3H, CH_3), 1.30–1.43 (m, 6H, 3 × CH_2), 1.71 (m, 2H, CH_2), 4.04 (s, 3H, OCH_3), 4.16 (t, ^3J = 7.6 Hz, 2H, CH_2), 7.29 (td, ^3J = 8.0 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.59 (td, ^3J = 7.5 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 8.33–8.38 (2dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 2H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.8 (CH_3), 23.2 (CH_2), 26.6 (CH_2), 28.0 (CH_2), 31.5 (CH_2), 41.8 (CH_2), 52.7 (OCH_3), 84.4 (C), 120.9 (C), 124.0 (CH), 124.2 (CH), 128.4 (CH), 133.3 (C), 133.7 (C), 161.9 (CO), 164.2 (CO), 174.0 (CO); Keto form: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, ^3J = 7.1 Hz, 3H, CH_3), 1.30–1.43 (m, 6H, 3 × CH_2), 1.71 (m, 2H, CH_2), 3.21 (t, ^3J = 7.0 Hz, 2H, CH_2), 3.73 (s, 3H, OCH_3), 5.91 (s, 1H, CH), 7.29 (td, ^3J = 8.0 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.42 (dd, ^3J = 8.0 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.50 (td, ^3J = 8.0 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 8.23 (dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.8 (CH_3), 23.2 (CH_2), 26.6 (CH_2), 27.7 (CH_2), 29.6 (CH_2), 40.7 (CH_2), 52.7 (OCH_3), 53.5 (CH), 125.1 (C), 126.9 (CH), 128.9 (CH), 129.4 (CH), 132.0 (C), 133.9 (C), 162.1 (CO), 166.9 (CO), 167.5 (CO); *Anal.* Calc for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; O, 21.10. Found: C, 67.05; H, 7.15; O, 21.27.

Methyl 2-(3-chlorophenyl)-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (5e). White crystals (99%); mp 128°C; 100% enol. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 4.09$ (s, 3H, OCH$_3$), 7.23 (td, $^3J = 7.5$ Hz, $^4J = 1.5$ Hz, 1H, H$_{Ar}$), 7.35–7.38 (m, 2H, H$_{Ar}$), 7.48–7.51 (m, 2H, H$_{Ar}$), 7.68 (td, $^3J = 7.7$ Hz, $^4J = 1.4$ Hz, 1H, H$_{Ar}$), 8.38 (dd, $^3J = 8.0$ Hz, $^4J = 1.3$ Hz, 1H, H$_{Ar}$), 8.48 (dd, $^3J = 8.3$ Hz, $^4J = 1.5$ Hz, 1H, H$_{Ar}$); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 53.1$ (OCH$_3$), 84.8 (C), 121.2 (C), 124.4 (CH), 124.8 (CH), 126.9 (CH), 128.8 (CH), 128.9 (CH), 129.4 (CH), 130.4 (CH), 133.9 (C), 134.1 (CH), 134.9 (CH), 135.9 (C), 161.9 (CO), 163.7 (CO), 173.9 (CO); *Anal.* Calc for $C_{17}H_{12}ClNO_4$: C, 61.92; H, 3.67; O, 19.41. Found: C, 61.63; H, 3.55; O, 19.36.

[4-(methoxycarbonyl)-1,3-dioxo-3,4-dihydroisoquinolin-2(1*H*)-yl]acetic acid (5f). Off-white crystals (99%); mp 175°C; 50% enol form, 50% keto form. We give the NMR data of the keto/enol mixture since the contributions of the two forms exhibited strong overlaps. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 3.70$ (s, 3H, OCH$_3$), 4.03 (s, 3H, OCH$_3$), 4.54 (d, $^2J = 15.0$ Hz, 1H, CH$_2$), 4.59 (d, $^2J = 15.0$ Hz, 1H, CH$_2$), 4.80 (s, 2H, CH$_2$), 5.50 (s, 1H, CH), 7.40 (td, $^3J = 7.5$ Hz, $^4J = 1.5$ Hz, 1H, H$_{Ar}$), 7.46 (dd, $^3J = 7.6$ Hz, $^4J = 1.5$ Hz, 1H, H$_{Ar}$), 7.61 (td, $^3J = 7.5$ Hz, $^4J = 1.3$ Hz, 1H, H$_{Ar}$), 7.72–7.80 (2td, $^3J = 7.6$ Hz, $^4J = 1.5$ Hz, 2H, H$_{Ar}$), 8.13 (dd, $^3J = 7.7$ Hz, $^4J = 1.5$ Hz, 1H, H$_{Ar}$), 8.20 (dd, $^3J = 7.7$ Hz, $^4J = 1.5$ Hz, 1H, H$_{Ar}$), 8.41 (dd, $^3J = 7.8$ Hz, $^4J = 1.4$ Hz, 1H, H$_{Ar}$); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 41.7$ (CH$_2$), 42.7 (CH$_2$), 53.2 (CH), 53.8 (OCH$_3$), 53.9 (OCH$_3$), 84.4 (C), 121.2 (C), 124.4 (C), 124.5 (CH), 125.1 (CH), 127.8 (CH), 128.4 (CH), 129.0 (CH), 129.4 (CH), 133.3 (C), 133.8 (C), 134.5 (CH), 135.1 (CH), 161.1 (CO), 163.2 (CO), 163.8 (CO), 167.0 (CO), 167.8 (CO), 169.2 (CO), 169.4 (CO), 173.5 (CO); *Anal.* Calc for $C_{13}H_{11}NO_6$: C, 56.32; H, 4.00; O, 34.63. Found: C, 56.05; H, 4.29; O, 34.74.

Methyl 2-(3-chloropropyl)-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (5g). Pale yellow crystals (99%); mp 98°C; 95% enol, 5% keto form. We give the NMR data of the keto/enol mixture since the contributions of the two forms exhibited strong overlaps. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 2.23$ (quin, $^3J = 7.0$ Hz, 2H, CH$_2$), 3.64 (t, $^3J = 6.6$ Hz, 2H, CH$_2$), 4.07 (s, 3H, OCH$_3$), 4.35 (t, $^3J = 7.2$ Hz, 2H, CH$_2$), 4.92 (s, 1H, CH), 7.32 (td, $^3J = 7.6$ Hz, $^4J = 1.5$ Hz, 1H, H$_{Ar}$), 7.45 (dd, $^3J = 7.7$ Hz, $^4J = 1.6$ Hz, 1H, H$_{Ar}$), 7.53 (td, $^3J = 7.6$ Hz, $^4J = 1.5$ Hz, 1H, H$_{Ar}$), 7.62 (td, $^3J = 7.6$ Hz, $^4J = 1.5$ Hz, 1H, H$_{Ar}$), 8.25 (dd, $^3J = 7.8$ Hz, $^4J = 1.6$ Hz, 1H, H$_{Ar}$), 8.34 (dd, $^3J = 7.8$ Hz, $^4J = 1.5$ Hz, 1H, H$_{Ar}$), 8.39 (dd, $^3J = 7.8$ Hz, $^4J = 1.6$ Hz, 1H, H$_{Ar}$); ^{13}C NMR (75 MHz, CDCl$_3$):$\delta = 31.1$ (CH$_2$), 39.6 (CH$_2$), 42.4 (CH$_2$), 52.9 (OCH$_3$), 84.6 (C), 120.7 (C), 124.1 (CH), 124.4 (CH), 128.5 (CH), 133.6 (CH), 133.6 (C), 161.9 (CO), 164.0 (CO), 174.0 (CO); *Anal.* Calc for $C_{14}H_{14}ClNO_4$: C, 56.86; H, 4.77; O, 21.64. Found: C, 56.65; H, 4.63; O, 21.80.

Methyl 2-(benzyloxy)-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (5h). Purple crystals (99%); mp 126°C; 82% enol, 18% keto form. We give the ^{1}H NMR data of the keto/enol mixture since the contributions of the two forms exhibited strong overlaps. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 3.77$ (s, 3H, OCH$_3$), 4.11 (s, 3H, OCH$_3$), 5.03 (s, 1H, CH), 5.29 (s, 2H, CH$_2$), 6.37 (dd, $^3J = 8.5$ Hz, $^4J = 1.5$ Hz, 1H, H$_{Ar}$), 7.25 (dd, $^3J = 7.7$ Hz, $^4J = 1.5$ Hz, 1H, H$_{Ar}$), 7.29–7.65 (m, 7H, H$_{Ar}$), 8.45 (m, 2H, H$_{Ar}$); Enol form: ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 53.1$ (CH$_3$), 79.0 (CH$_2$), 84.3 (C), 121.2 (C), 124.3 (CH), 124.6 (CH), 128.3 (CH), 128.6 (2CH), 129.4 (CH), 130.1 (2CH), 132.9 (C), 133.5 (C), 133.8 (CH), 158.8 (CO), 163.0 (CO), 173.5 (CO); Keto form: ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 53.8$ (CH$_3$), 54.8 (CH), 78.5 (CH$_2$), 119.3 (C), 123.5 (C), 127.3 (CH), 128.5 (2CH), 129.2 (CH), 129.3 (CH), 129.5 (CH), 130.0 (2CH), 131.4 (C), 133.5 (C), 134.4 (CH), 160.7 (CO), 162.9 (CO), 171.6 (CO); *Anal.* Calc for $C_{18}H_{15}NO_5$: C, 66.46; H, 4.65; O, 24.59. Found: C, 66.52; H, 4.94; O, 24.51.

Methyl 2-(1-methoxy-1-oxopent-4-en-2-yl)benzoate (6). A solution of freshly distilled diisopropylamine (0.75 mL, 5.35 mmol) in 10.0 mL of dry THF under an argon atmosphere was cooled to –78°C and 3.34 mL of 1.6*M* *n*-butyllithium (5.35 mmol) in THF was added. After 20 min reaction at –78°C, a solution of **2** (0.79 g, 3.8 mmol) in 10.0 mL of THF was added dropwise. After stirring the solution for 30 min at –78°C, allyl bromide (0.66 mL, 7.6 mmol) was added dropwise. Stirring was pursued 1 h at –78°C and then 1 h at room temperature. The reaction was quenched with NH$_4$Cl and the solution was extracted several times with ether. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (eluent: petroleum ether/AcOEt, 80/20) to give **6** as an orange oil (80%); ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 2.39$ (m, 1H, CH$_2$), 2.71 (m, 1H, CH$_2$), 3.45 (s, 3H, OCH$_3$), 3.70 (s, 3H, OCH$_3$), 4.60 (t, $^3J = 7.6$ Hz, 1H, CH), 4.81 (dd, $^3J = 10.8$ Hz, $^2J = 2.0$ Hz, 1H, CH), 4.88 (dd, $^3J = 17.5$ Hz, $^2J = 2.0$ Hz, 1H, CH), 5.54–5.74 (m, 1H, CH), 7.12 (td, $^3J = 7.8$ Hz, $^4J = 1.5$ Hz, 1H, H$_{Ar}$), 7.28 (m, 2H, H$_{Ar}$), 7.75 (dd, $^3J = 7.7$ Hz, $^4J = 1.2$ Hz, 1H, H$_{Ar}$); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 37.2$ (CH$_2$), 46.5 (CH), 51.4 (OCH$_3$), 51.6 (OCH$_3$), 116.4 (=*C*H$_2$), 126.6 (CH), 128.4 (CH), 129.3 (C), 130.3 (CH), 131.8 (CH), 135.1 (C), 139.6 (C), 167.2 (CO), 173.3 (CO); *Anal.* Calc for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50; O, 25.78. Found: C, 67.95; H, 6.28; O, 25.59.

4-Methoxy-3-[2-(methoxycarbonyl)phenyl]-4-oxobutanoic acid (7). To **6** (1.6 g, 6.0 mmol) in *t*-BuOH (10.0 mL) was added a solution of K$_2$CO$_3$ (2.49 g, 18.0 mmol) in H$_2$O (20 mL). To the resulting mixture were added KIO$_4$ (4.14 g, 18.0 mmol) and KMnO$_4$ (0.66 g, 4.2 mmol). After stirring for 1 h at room temperature, the mixture was extracted with AcOEt and this organic layer was discarded. The aqueous layer was acidified with concentrated HCl solution and again exhaustively extracted with AcOEt. The combined organic layers were dried over Na$_2$SO$_4$ and evaporation of the solvent *in vacuo* gave an oil which crystallized on standing. The obtained beige crystals were carefully rinsed with ether (63%); mp 144°C; ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 2.80$ (dd, $^2J = 17.4$ Hz, $^3J = 5.0$ Hz, 1H, CH$_2$), 3.25 (dd, $^2J = 17.3$ Hz, $^3J = 9.2$ Hz, 1H, CH$_2$), 3.69 (s, 3H, OCH$_3$), 3.91 (s, 3H, OCH$_3$), 4.99 (dd, $^3J = 9.2$ Hz, $^3J = 5.0$ Hz, 1H, CH), 7.28–7.39 (m, 2H, H$_{Ar}$), 7.50 (td, $^3J = 7.5$ Hz, $^4J = 1.3$ Hz, 1H, H$_{Ar}$), 7.97 (dd, $^3J = 7.9$ Hz, $^4J = 1.5$ Hz, 1H, H$_{Ar}$), 9.58 (br s, 1H, OH); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 37.6$ (CH$_2$), 44.1 (CH), 52.3 (OCH$_3$), 52.4 (OCH$_3$), 127.6 (CH), 129.1 (CH), 129.2 (C), 131.2 (CH), 132.7 (CH), 139.0 (C), 167.6 (CO), 173.4 (CO), 177.7 (CO); *Anal.* Calc for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30; O, 36.06. Found: C, 58.87; H, 5.18; O, 36.25.

Methyl 2-{4-[(benzyloxy)amino]-1-methoxy-1,4-dioxobutan-2-yl}benzoate (8). Same method as for the preparation of **4a**. Yellow oil (42%). ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 2.48$

(dd, ^2J = 15.1 Hz, ^3J = 5.9 Hz, 1H, CH_2), 2.94 (dd, ^2J = 15.1 Hz, ^3J = 7.8 Hz, 1H, CH_2), 3.53 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 4.69 (d, ^2J = 11.1 Hz, 1H, OCH_2), 4.76 (d, ^2J = 11.1 Hz, 1H, OCH_2), 4.99 (t, ^3J = 6.9 Hz, 1H, CH), 7.20–7.30 (m, 7H, H_{Ar}), 7.39 (td, ^3J = 7.5 Hz, ^4J = 1.3 Hz, 1H, H_{Ar}), 7.86 (dd, ^3J = 7.9 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 9.47 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.9 (CH_2), 44.5 (CH), 51.7 (OCH_3), 51.8 (OCH_3), 77.5 (OCH_2), 127.0 (CH), 127.9 (2CH), 128.0 (CH), 128.8 (2CH), 128.8 (C), 129.7 (CH), 130.7 (CH), 132.1 (CH), 135.1 (C), 138.9 (C), 167.3 (CO), 168.3 (CO), 173.0 (CO); *Anal.* Calc for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; O, 25.85. Found: C, 64.77; H, 5.91; O, 25.64.

2-(Benzyloxy)-1,3-dioxo-2,3,4,5-tetrahydro-1*H*-2-benzazepine-5-carboxylic acid (10). Compound **8** was reacted for 15 min with a 2.5*M* KOH solution in aqueous methanol and, after the usual work-up (see preparation of **5a**), an oil was obtained, which crystallized on standing. The white crystals were washed with ether (80 %); mp 94–95°C. ^1H NMR (300 MHz, CD_3COCD_3): δ = 3.43 (dd, ^2J = 11.8 Hz, ^3J = 4.2 Hz, 1H, CH_2), 3.57 (dd, ^2J = 12.0 Hz, ^3J = 4.3 Hz, 1H, CH_2), 4.45 (t, ^3J = 4.3 Hz, 1H, CH), 5.11 (s, 2H, OCH_2), 7.37–7.48 (m, 3H, H_{Ar}), 7.54 (td, ^3J = 7.6 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.60–7.69 (m, 3H, H_{Ar}), 7.73 (td, ^3J = 7.5 Hz, ^4J = 1.3 Hz, 1H, H_{Ar}), 8.19 (dd, ^3J = 7.8 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 11.0 (s, 1H, OH); ^{13}C NMR (75 MHz, CD_3COCD_3): δ = 37.5 (CH_2), 43.3 (CH), 77.7 (OCH_2), 126.8 (C), 127.2 (CH), 128.2 (CH), 128.7 (CH), 128.9 (2CH), 129.3 (CH), 130.1 (2CH), 134.4 (CH), 135.7 (C), 138.7 (C), 164.2 (CO), 169.2 (CO), 172.0 (CO); *Anal.* Calc for $C_{18}H_{15}NO_5$: C, 66.46; H, 4.65; O, 24.59. Found: C, 66.59; H, 4.74; O, 24.35.

Methyl 2-(benzyloxy)-1,3-dioxo-2,3,4,5-tetrahydro-1*H*-2-benzazepine-5-carboxylate (11). Compound **11** was reacted for 5 min with a 2.5*M* KOH solution in aqueous methanol to give a yellow oil (20%). Esterification of **10** with methanolic thionyl chloride (1 h reflux) also yielded quantitatively **11**. ^1H NMR (300 MHz, CD_3COCD_3): δ = 3.12 (dd, ^2J = 17.2 Hz, ^3J = 4.5 Hz, 1H, CH_2), 3.51 (dd, ^2J = 17.2 Hz, ^3J = 4.5 Hz, 1H, CH_2), 3.57 (s, 3H, OCH_3), 4.23 (t, ^3J = 4.5 Hz, 1H, CH), 5.14 (d, ^2J = 8.9 Hz, 1H, OCH_2), 5.18 (d, ^2J = 8.9 Hz, 1H, OCH_2), 7.30 (td, ^3J = 7.6 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.35–7.43 (m, 3H, H_{Ar}), 7.49 (td, ^3J = 7.6 Hz, ^4J = 1.3 Hz, 1H, H_{Ar}), 7.60–7.65 (m, 3H, H_{Ar}), 8.27 (dd, ^3J = 7.8 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, CD_3COCD_3): δ = 37.8 (CH_2), 42.9 (CH), 52.2 (OCH_3), 78.1 (OCH_2), 125.7 (C), 126.1 (CH), 128.2 (CH), 128.5 (2CH), 129.0 (CH), 129.2 (CH), 129.9 (2CH), 134.1 (CH), 134.1 (C), 136.6 (C), 161.1 (CO), 168.5 (CO), 170.6 (CO); *Anal.* Calc for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.05; O, 23.57. Found: C, 67.02; H, 5.09; O, 23.45.

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Synthesis and Reactivity of Spiro[1,3,4-thiadiazoline-2,4′-thioflavans] and Analogues

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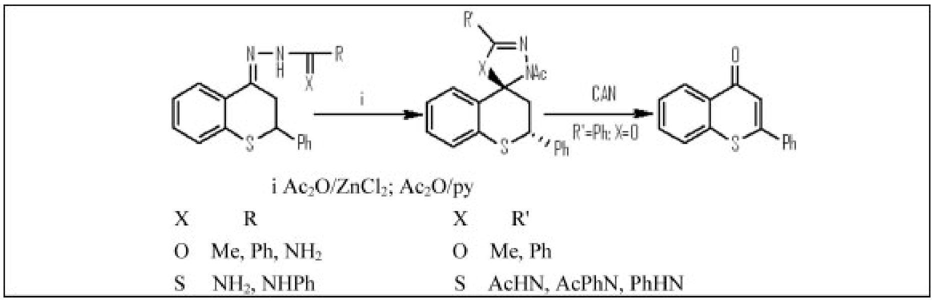

Racemic thioflavanone (thio)acylhydrazones undergo transformation into *racemic* 3-acetylspiro[1,3,4-oxa(thia)-diazoline-2,4′-thioflavans] with *trans* O(1) or S(1) and Ph(2′eq) under acetylating conditions. Conjugation between the ethylenic bond and sp^2 C(4) in thioflavones encumber both the formation of (thio)acylhydrazones and their subsequent spirocyclization. On the other hand, subsequent dehydrogenation of the thiopyran moiety of spiro compounds results in formation of sp^2 C(4) and simultaneous degradation of the spirodiazoline ring.

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INTRODUCTION

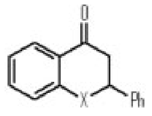
A great variety of natural benzopyrans, *e.g.*, chrom(an)ones, flav(an)ones, exhibit biological activity and have beneficial effects as free radical scavengers, antioxidants, CNS active agents, aldose reductase inhibitors [1], aromatase inhibitors [2], *etc*. Some synthetic (halogenated, nitro) derivatives have significant anxiolytic properties [3]. Carbonyl condensation products, *e.g.*, oximes [4], imines [5], acyl hydrazones, thiosemicarbazones [6] have been reported to display antimicrobial and estrogen receptor activities, respectively. Also flavone-related, naturally occurring 2-arylquinolines [7] and antimitotic 2-phenylquinolones [8] are known.

Recently, also the chemistry and the biological properties of the bioisosteric thioflavonoid compounds [9], including (spiro)heterocyclic derivatives [10], excite increasing interest. Thiochrom(an)ones and thioflav(an)ones as well as their 1-oxides and 1,1-dioxides have been reported to have antimicrobial [11], antiviral [12], and antitumor [8,9c,13] properties. The synthesis and herbicidal properties of benzothiopyran-4-one hydrazones [14a] and related cyclic *O*-*O*-acetals spiro[benzothiopyran-4,2′-dioxolanes] [14b] have been described, as well.

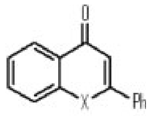
Formerly, we have observed that under physiological conditions the potentially biological active cyclic *N*,*O*- and *N*,*S*-acetals 3-acetyl-1,3,4-oxa(thia)diazolines undergo deacetylation and transform into (thio)acylhydrazones [15]. Therefore, in consideration of the aforementioned literature findings, as an extension of our examinations for the synthesis of 2-phenyltetrahydroquinoline (**5j**) [16] and flavanone-spiro-oxa(thia)diazolines (**5k**, **l**) [17a], respectively, we aimed at the synthesis of their bioisosteric spiro-thioflavonoid analogs [17b].

RESULTS AND DISCUSSION

As potential substrates for cyclization into oxa(thia)-diazolines **5a–i** under acetylating conditions, hydrazone derivatives **3** and **4** of thioflav(an)ones **1** and **2** were prepared from the corresponding carbonyl parent compounds **1** and **2**, respectively, by known methods (see Table 3 and Experimental section).

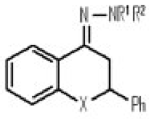


	X
1a	S
b	SO
c	SO$_2$
d	O



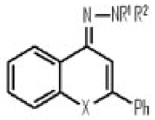
	X
2a	S
b	SO
c	SO$_2$
d	O

In comparison with aryl aralkyl ketones due to electronic (*e.g.*, conjugative) effects aryl vinyl ketones exhibit a diminished reactivity toward carbonyl condensation agents. This is markedly valid for the cyclic analogs (thio)flavones [18], capable of resonance between contributing (thio)benzopyrylium dipole structures. Moreover also the oxidation state of sulfur in these unsaturated compounds (*e.g.*, **2a–c**) affects reactivity [19]. Nevertheless, analogously to the synthesis of flavone (acyl)hydrazones [18a,b] thioflavone hydrazone (**4a**) has been successfully produced [19b,c] by condensing hydrazine with thioflaven-4-thione [20] or its derivative 4-methylthioflavylium iodide [19b], instead of thioflavone (**2a**).

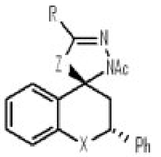


	X	R^1	R^2
3a	S	H	H
b	S	H	Ac
c	S	Ac	Ac
d	S	H	CO-NH_2
e	S	H	CS-NH_2
f	S	H	CS-NHPh
g	SO_2	H	CS-NH_2
h	SO_2	H	CO-NH_2
i	SO_2	H	CO-NHAc
j	S	H	CO-Ph

As to the conjugation between the sp^2 C(4) and the C═C bond of the thioflaven ring, similarly to that previously found [17a] for the flavone analogs, this encumbered not only the formation of (thio)acylhydrazones but also their subsequent cyclization into spiro(thia)oxadiazolines. On the other hand, devoid of a chance for conjugation, dehydrogenation of the thiopyran ring of the spiroheterocycles **5** became difficult in comparison with that of the thioflavanone parent compound (**1a**) [21], nevertheless when eventually performed, it led to the cleavage of the diazoline rings with transformation of the spiro-C into the sp^2 hybrid state (C(4)═O,N). Therefore, the mutual action of the hybrid electron orbital states of C(4) and C(2), C(3) carbons was studied experimentally in detail with the (trans)formation of spirocompounds **5** and their precursors (acyl)hydrazones **3**, **4**, and related compounds as well.



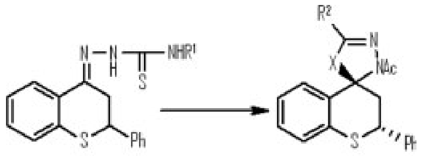
	X	R^1	R^2
4a	S	H	H
b	S	H	Ac
c	S	Ac	Ac
d	S	H	CS-NH_2
e	SO_2	H	CS-NH_2
f	SO_2	H	Ac
g	S	H	CO-Ph



	X	Z	R
5a	S	O	Me
b	S	O	Ph
c	S	S	AcHN
d	S	S	PhHN
e	S	S	AcPhN
f	SO	O	Me
g	SO	O	Ph
h	SO_2	O	Me
i	SO_2	O	Ph
j	NAc	S	AcHN
k	O	O	Me
l	O	S	AcHN

Spirocyclization of *racemic* thioflavanone (thio)acylhydrazones **3** into spiro(thia)oxadiazolines **5a–e** was accomplished (see Table 4) in good yields by using acetylating agents Ac_2O/py or $Ac_2O/ZnCl_2$ previously successfully applied [16,17,21] for (spiro)cyclization of various ketone (thio)acylhydrazones. As a result of the heterocyclization, C(4) of the thiopyran ring became sp^3 hybridized and asymmetric, thus theoretically enabling the formation of *racemic* 2,4-diastereomers. Newly spirothiadiazolines **5c**,**d**,**e** with trans S(1) and Ph($2'_{eq}$) structures were stated to form HPLC separable isomers in solution due to a hindered rotation of the endocyclic N(3)Ac group [17b] (Scheme 1). Recently, the stereostructure of 3-acetylspiro[1,3,4-oxadiazoline-2,4′-thioflavan] (**5a**) and 3-acetylspiro[1,3,4-thiadiazoline-2,4′-thioflavans] (**5c**,**d**,**e**), prepared likewise under acetylating conditions, has been stated by ^{1}H- and ^{13}C NMR, as well as X-ray analytical methods and MOPAC QM calculations to have *trans* O(1) or S(1) and Ph($2'_{eq}$) [17b]. The "anomalous" ^{1}H NMR spectra (remarkable downfield shift of signals H($3'_{ax}$), attributed to the anisotropy

Scheme 1



			X	R^2
3e	R^1=H	**5a**	O	Me
f	R^1=Ph	**c**	S	AcHN
		d	S	PhHN
		e	S	PhAcN

Table 1

200 MHz ^1H NMR($CDCl_3$) data of thioflavans **3a-c**.[a]

	δ (ppm)			*J* (Hz)			
Compound	$H(2_{ax})$	$H(3_{ax})$	$H(3_{eq})$	$2_{ax},3_{ax}$	$2_{ax},3_{eq}$	$3_{ax},3_{eq}$	δ other
3a	4.35	2.88	3.27	12.4	3.5	16.8	5.39 (2H,NH_2)
3b	4.40	3.02	3.31	12.5	3.5	17.0	9.08 (NH), 2.38 (Ac)
3c	4.47	2.92	3.08	11.5	3.5	15.5	2.34 (2Ac)

[a] For data of **1a-c** see ref. [22a].

effect of the near *N*(3)Ac C=O group) are observed also in the present work (Tables 1 and 2) confirming the analogous stereostructure of spiro products **5a**,**b**,**f–i**. Treatment of semicarbazone **3d** with $Ac_2O/ZnCl_2$ at room temperature for **3d** afforded oxadiazoline **5a** (Scheme 2) but with Ac_2O/py at 100°C for 3 h **5a** and diacetylhydrazone **3c**. Similarly, on treatment with Ac_2O/py at 145°C (bath) for 45 min phenylthiosemicarbazone **3f** underwent transformation to give thiadiazoline **5e** (mp 192–194°C, from EtOAc) and oxadiazoline **5a** (mp 210.5–212°C, from $CHCl_3$/EtOAc), after purification by column chromatography, in 60 and 6% yields, respectively [17b]. The degradation of semicarbazones [23] and thiosemicarbazones [17a,23a,c] under acylating conditions is well documented. By treatment with Ac_2O/$ZnCl_2$ at room temperature, thioflavanone acetylhydrazone (**3b**) was transformed into spiro-oxadiazoline **5a** (see Scheme 2 and Table 4). Under similar conditions, however, semicarbazone 1,1-dioxide **3h** resisted cyclization and also degradation to the corresponding acetylhydrazone, instead acetylsemicarbazone **3i** was formed (Scheme 3), 200 MHz ^1H NMR(DMSO-d_6, δ, ppm): 11.53 and 10.75, 2 brs, 2H, 2NH; 2.14, s, 3H, Ac. Attempted syntheses of **5h** and **5j** by treating **3h** and **3g**, respectively, with Ac_2O/pyridine at 100°C for 3 h resulted in the formation of multicomponent mixtures.

Thus, the tendency for spiro-cyclization seems to be diminished or even ceased by the presence of strong electron-withdrawing components at position 1. Therefore, the synthesis of spiro-oxadiazoline 1′-oxides and 1′,1′-dioxides was attempted by oxidation of the corresponding spirothioflavans. Hot $NaIO_4$/aq. 2-PrOH (substrate/oxidant ratio, 1:4) has been reported [24] to transform thioflavanone (**1a**) into thioflavone 1,1-dioxide (**2c**). Presumably due to the absence of a sp^2 hybridization at position 4, under similar conditions (mole ratio 1:8) spiro-oxadiazoline **5a** was transformed, without dehydrogenation, into a mixture of the corresponding 1′-oxide **5f** and 1′,1′-dioxide **5h**. The selective syntheses of sulfoxides **5a**→**5f** and **5b**→**5g** were accomplished by treatment with $NaIO_4$/aq. 2-PrOH or with dimethyldioxirane generated *in situ* by potassium peroxymonosulfate ($2\ KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) in aq. Me_2CO. Potassium permanganate oxidation of spiro-oxadiazoline **5a**,**b** afforded the corresponding sulfones **5h**,**i** in very good yields (see Scheme 4 and Experimental section).

The effect of a C(2)=C(3) unsaturation and also that of the oxidation state of sulfur in the benzo heterocycle

Table 2

200 MHz ^1H NMR($CDCl_3$) data of 5-substituted 3-acetylspiro[1,3,4-oxadiazoline-2,4′-thioflavans] as well as 1′- and 1′,1′-oxides **5a,b,f–i**.

	δ (ppm)[a]			*J* (Hz)			
Compound	$H(2'_{ax})$	$H(3'_{ax})$	$H(3'_{eq})$	$2'_{ax},3'_{ax}$	$2'_{ax},3'_{eq}$	$3'_{ax},3'_{eq}$	δ CH_3
5a	4.70	3.59	2.50	13.3	2.1	13.8	[b]
5b	4.83	3.65	2.62	13.5	2.0	14.0	[c]
5f	4.40	3.66	2.57	7.4	0.8	8.5	[d]
5g	4.55	3.74	2.70	13.5	1.5	15.5	[e]
5h	4.90	4.33	2.63	13.5	1.3	14.7	[f]
5i	5.03	4.40	2.75	13.6	1.7	14.7	[g]

[a] The $H(3'_{ax})$ signals of spiro compounds are downfield shifted in comparison with those of hydrazones **3** (cf. Table 1). This can be attributed to the carbonyl neighbouring anisotropy effect of Ac(3) [17b].

[b] 2.28, Ac(3); 2.07, Me(5).

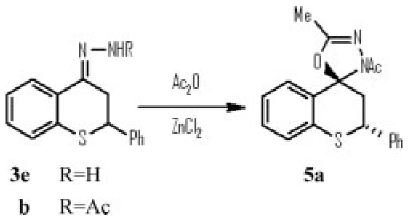
[c] 2.40, Ac(3); 2.08, Me(5).

[e] 2.39, Ac(3).

[f] 2.31, Ac(3); 2.07, Me(5).

[g] 2.44, Ac(3).

Scheme 2



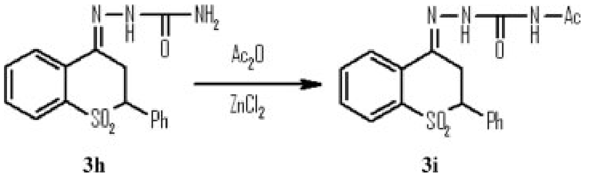
could be well demonstrated. Thus, though treatment with Ac_2O/py at 100°C has been reported [17a] to transform flavone thiosemicarbazone into the corresponding diacetylhydrazone, a similar treatment of thioflavone thiosemicarbazone (**4d**) afforded (see Experimental section) spirothiadiazoline **6** and diacetylhydrazone **4c** in 56 and 18% yields, respectively. However, on treatment with Ac_2O/py even under milder conditions (see Experimental section), thioflavone 1,1-dioxide thiosemicarbazone (**4e**) was degraded to acetylhydrazone **4f** in 69% yield and no 3-acetyl-5-acetylaminospiro[1,3,4-thiadiazoline-2,4′-thioflaven] 1′,1′-dioxide could be isolated (Scheme 5).

As an alternative rout for preparing spiro[oxa(thia)-diazoline-2,4′-thioflavens] the dehydrogenation of the corresponding thioflavan analogs **5** was investigated. The powerful one-electron acceptor oxidant CAN is known [24,25] to dehydrogenate thioflavanone (**1a**) to thioflavone (**2a**) readily at room temperature. However, for transforming spirothioflavans **5** into the corresponding thioflaven analogs, CAN turned out to be unsuitable as this agent transformed **5b** into thioflavone (**2a**) with simultaneous degradation of the spiro-oxadiazoline moiety (see Scheme 6 and Experimental section). This early experience prompted us to investigate the dehydrogenation of thiopyran [21,24,22] and that of the *N*,*S*-acetal 1,3,4-thiadiazoline [26] or *N*,*O*-acetal 1,3,4-oxadiazoline [27] systems separately, by using various types of oxidants and dehydrogenating agents of diverse mechanisms of action. Also the attempts for dehydrogenating the thiopyran ring of spirocompound **5** by iodobenzene 1,1-diacetate (IBDA, (diacetoxyiodo)-benzene) or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) produced unsatisfactory results. After treating spiro-oxadiazoline **5a** with IBDA for preserving the diazoline moiety at room temperature in AcOH for 7 d or in MeOH for 14 d the substrate could be recovered in *ca.* 60% yield. Moreover, reaction of spiro-oxadiazoline **5b** with hot DDQ/dioxane/TsOH led to the formation of a mixture comprising substrate **5b** and degradation product thioflavone **2a**.

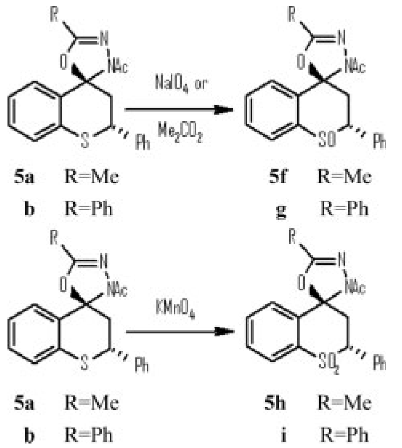
For dehydrogenation of the benzoheterocycle, in comparison with flavanones, as an additional reaction rout is known the transformation of thiochromanone 1-oxides (*e.g.* **1b**) into thiochromones (*e.g.* **2a**) in alkaline solution [28,19b] or under Pummerer-type reaction conditions [29,19b,25b]. Thus, treatments with Ac_2O/TsOH or Ac_2O/dimethylaminopyridine (DMAP) have been reported [22b] to transform **1b** into **2a**, but with the Ac_2O/Et_3N couple *via* cleavage of the thiopyran ring, into disulfide **7** (Scheme 6).

On the basis of these findings, the dehydrogenation of spirocompounds **5** (X = S) to the corresponding spirothioflavens *via* transformation of the spirothioflavan 1-oxides (X = SO) under acetylating conditions in the presence of acid or base (nucleophilic) catalysts, hence under circumstances successfully applied just for the

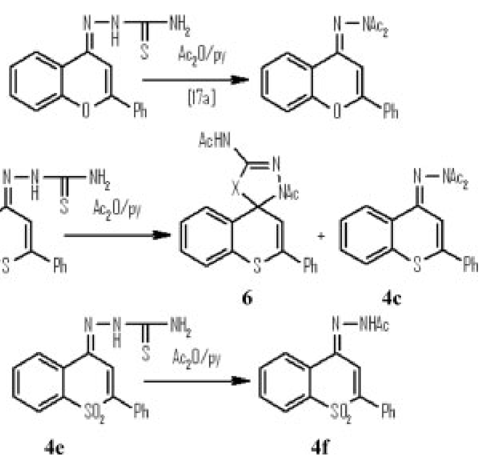
Scheme 3



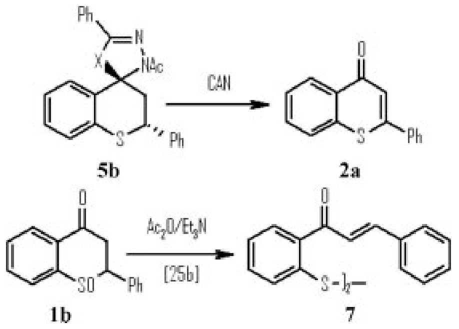
Scheme 4



Scheme 5



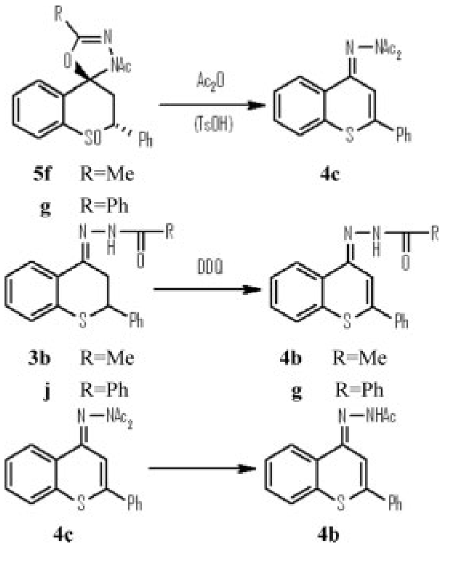
Scheme 6



spirocyclization, seemed to be feasible. However, presumably due to the lack of a sp^2 C(4) moiety similar treatments of sulfoxide **5f** with Ac_2O/Et_3N at room temperature for 48 h and that of **5g** with the Ac_2O/DMAP couple at room temperature for 72 h or with Ac_2O/py at 100°C for 22 h were found to be ineffective and the unchanged substrates could be recovered in 78, 90, and 67% yields, respectively. Treatment with Ac_2O/(TsOH) transformed spirothioflavan 1′-oxides, both **5f** and **5g**, into thioflavone diacetylhydrazone (**4c**) with cleavage of the oxadiazoline ring and a subsequent transacetylation, respectively (see Experimental section); thus, 2,3-dehydrogenation of the benzothiopyran ring was accompanied by a sp^3→sp^2 change at C(4) (Scheme 7).

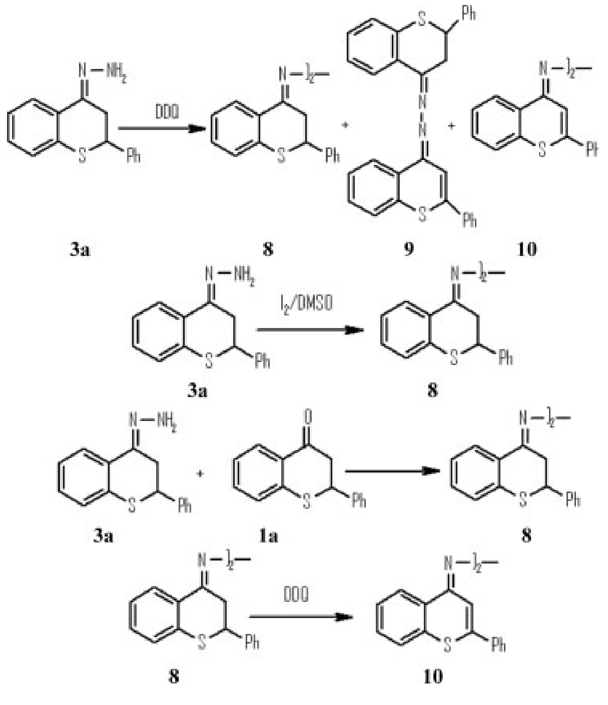
Owing to the unsatisfactory results with the dehydrogenation of spirocompounds **5**, also similar transformation of their nitrogen-containing precursors thioflavanone (acyl)hydrazones (**3**) with sp^2 C(4) was investigated. Treatment with DDQ dehydrogenated acylhydrazones **3b**,**j** to acetylhydrazone **4b** (prepared also by partial deacetylation of diacetylhydrazone **4c**, see Experimental section) and benzoylhydrazone **4g**, respectively, in very good yields, but it converted thiosemicarbazone **3e** in dioxane solution to give a multicomponent mixture. Reaction with DDQ transformed hydrazone **3a** into the corresponding azine **8** as well as its partially and fully dehydrogenated derivatives **9** and **10**, respectively. Azine **8** was obtained also by treating hydrazone **3a** with I_2/DMSO or by condensing hydrazone **3a** with thioflavanone (**1a**). DDQ dehydrogenation of azine **8** afforded azine **10** in 80% yield (see Scheme 8 and Experimental section). Attempts for dehydrogenating azine **8–10** by treatment with hot $NaIO_4$/aq. dioxane or hot IBDA/MeOH (or dioxane) were unsuccessful as in these cases very complex mixtures of products were formed. Hypervalent iodine oxidation of hydrazine [30] to the reductive, instable diimide and that of aromatic hydrazones to azines [31] have been reported already.

Scheme 7

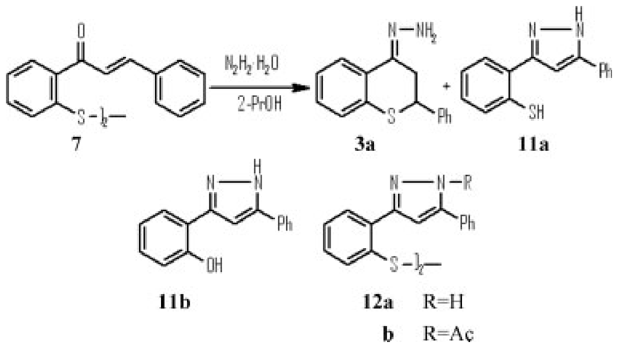


The synthesis of thioflavanone hydrazones [19b] (*e.g.*, by boiling thioflavanone **1a** with $N_2H_4 \cdot H_2O$/EtOH to give the corresponding hydrazone **3a**) is a clear-cut reaction. Because of a reversible flavanone (**1d**) ⇌ 2′-hydroxychalcone (2-cinnamoyl-phenol, 2-hydroxyphenyl styryl ketone) transformation, on treatment with hydrazine flavanone undergoes reaction, depending on the reaction conditions, to give the corresponding hydrazone and 3-(2-hydroxyphenyl)-5-phenyl-4,5-dihydropyrazole, respectively [32a,b,18e]. An analogous treatment of flavone (**2d**) with hydrazine or the thermal rearrangement of flavone hydrazone has been reported to afford the

Scheme 8



Scheme 9



corresponding pyrazole derivative **11b** [32b,18e]. As a result of the special electron shell structure the more pronounced nucleophilicity and the conjugative interaction of sulfur [19] within the heterocycle may appear in some characteristic properties of the molecule, thus extending our synthetic works with (thio)flavonoids [16,17a,21,24,22a] we (re)examined the reaction between thioflavone and hydrazine. Recently we have found [33] that the treatment of thioflavone (**2a**) with $N_2H_4 \cdot H_2O$ in hot 2-PrOH leads to the formation of 3-(2-mercaptophenyl)-5-phenylpyrazole (**11a**) which by a subsequent spontaneous oxidation in a $CHCl_3$ solution affords disulfide **12a**. (It is well known that the oxidation of alkyl- and arylthiols by molecular oxygen to disulfides may be catalyzed by aliphatic amines or alkali hydroxides [34].) As due to the possibility for a prototropic change, the structure of pyrazoles [35] with aromatic substituents cannot be unequivocally elucidated by IR and NMR spectrometry, this has been carried out [33] eventually by a MALDI-TOF mass spectrometric study of the acetyl derivative **12b**.

In connection with our previous findings [22b] that heterolysis of disulfide **7** leads to the formation of thioflavanone (**1a**) and 2-benzylidenebenzo[*b*]thiophen-3(2*H*)-one (thioaurone) we attempted the transformation of disulfide **7** with $N_2H_4 \cdot H_2O$/2-PrOH to obtain the 4,5-dihydro analogs of **11a** or **12a**. However, this reaction afforded thioflavanone hydrazone (**3a**) and pyrazole **11a** which was isolated as disulfide **12a** (see Scheme 9 and Experimental section).

CONCLUSION

Thioflavanone (thio)acylhydrazones transform into 3-acetylspiro[1,3,4-(thia)oxadiazoline-2,4′-thioflavans] with trans S(l) or O(l) and Ph($2'_{eq}$) under acetylating conditions. The presence of 2,3-unsaturation or oxidation of sulfur of thioflav(an)one render more difficult both the synthesis of (thio)acylhydrazones and the subsequent spirocyclization. Additional 2′,3′-dehydrogenation of the spirocompounds with various dehydrogenating agents had no result or was accompanied by degradation of the spirodiazoline ring with a simultaneous $sp^3 \rightarrow sp^2$ change at C(4).

EXPERIMENTAL

Melting points (uncorrected): Kofler block. Solutions were concentrated under reduced pressure in a rotary evaporator (<50°C, bath), TLC: Kieselgel 60 F_{254} (Merck, Alurolle). IR (KBr disks): Perkin-Elmer 16 PC-FT spectrometer. 200 MHz ^{1}H- and 50 MHz ^{13}C NMR: Bruker WP 200 SY, 360 MHz ^{1}H- and 90 MHz ^{13}C NMR: Bruker AM 360 spectrometer; for recording the ^{13}C spectra, *J*-echo techniques were used.

General operations of processing the reaction mixtures (see Tables 3 and 4). (**A**) The product was collected by filtration in the cold. (**B**) The cold mixture was poured into ice-water. (**C**) A solution of the product in $CHCl_3$ was treated with fuller's earth and charcoal and then concentrated. (**D**) For decomposing the excess of BzCl, drop-by-drop water (1.25 mL) was added with cooling and stirring and the mixture was kept at room temperature for 1 h. (**E**) The mixture was concentrated. (**F**) The residue was triturated with MeOH in the cold. (**G**) The residue was triturated with water in the cold.

Dehydrogenation of thioflavanone (1a) by $PhI(OAc)_2$ to 2a. A solution of **1a** (0.120 g, 0.5 mmol) and $PhI(OAc)_2$ (0.247 g, 0.75 mmol) in MeOH (5 mL) was kept at room temperature for 12 d and then concentrated (finally at *ca.* 1 Torr). A solution of the residue in MeOH (0.5 mL) deposited on seeding TLC homogeneous and with an authentic compound identical thioflavone (**2a**, 0.082 g, 68.6%; when reacted at boiling for 2 d, in a sixfold scale, a 86.2% yield has been observed [21]), mp 125.5°C.

Thioflavone acetylhydrazone (4b). (**a**) A mixture of thioflavanone acetylhydrazone (**3b**, 0.371 g, 1.25 mmol), DDQ (0.307 g, 1.32 mmol, 98%), anhydrous dioxane (12 mL), and a catalytic amount of *p*-toluenesulphonic acid (TsOH) was boiled with stirring for 24 h, then cooled to give a solid (0.597 g, a mixture of **4b** and $DDQH_2$), which when stirred with aq. $NaHCO_3$ in excess, in the presence of some 2-PrOH as a humidifier, afforded undissolved title acetyl-hydrazone **4b** (0.250 g, 68%), mp 256–257°C.

(**b**) A mixture of diacetylhydrazone **4c** (0.168 g, 0.5 mmol), MeOH (10 mL) and pyridine (2 drops) was boiled with stirring for 6 h to give, on cooling, acetylhydrazone **4b** (0.131 g, 89%), mp 257.5°C. A similar partial deacetylation was observed during purification of **4c** by CC [Kieselge1 60, Merck; $CHCl_3$/EtOAc (95:5)], when **4b**, mp 258°C was isolated. IR(KBr, ν, cm^{-1}): 1666 (s, Amide-I). ^{1}H NMR(200 MHz, DMSO-d_6, δ, ppm): 11.17 (s, 0.7 H, NH) and 10.79 (s, 0.3 H, NH) presumably due to an *E*/*Z* isomerism, 8.33–8.25 (m, 1 H, H(5)), 7.90–7.78 (m, 2 H, H—Ar), 7.61 (s, 1 H, H(3)), 7.58–7.43 (m, 6 H, H—Ar), 2,29 (s, 2.1 H, 0.7 Ac) and 2.07 (s, 0.9 H, 0.3 Ac). *Anal.* Calcd. for $C_{17}H_{14}N_2OS$ C, 69,4; H, 4.8; N, 9.5; S, 10.9. Found: C, 69.3; H, 4.8; N, 9.6; S, 11.0.

Thioflavone thiosemicarbazone (4d). A mixture of thioflavone (**2a**, 10.008 g, 42 mmol), powdered thiosemicarbazide (6.000 g, 65.8 mmol), MeOH (100 mL), and conc. HCl (1 mL, 11.7 mmol) was boiled with stirring for 65 h and then cooled.

Table 3

Preparation and properties of thioflavanone hydrazones **3** (see also ref. [17b]).

Product	Reaction components (mmol)		Solvent (mL)	Reaction temp. (°C)[b] (time (h))	Workup[c]	% Yield crude[d] (pure)	Mp (°C) (solvent)	Formula[a] (mol. mass)
3b	**3a**	Ac_2O[e]	py[f]	15	B	100[g,h]	243	$C_{17}H_{16}N_2OS$
	(10)	(40)	(10)	(3.5)			($CHCL_3$/hexane)	(296.4)
3c	**3a**	Ac_2O(530)		23	B		137	$C_{19}H_{18}N_2O_2S$
	(20)	$ZnCl_2$(37)[f]		(20)[i]	C[j]	(6.7)	(PhH/hexane)	(338.4)
3i	**3h**[k]	Ac_2O(185)		23	B	99.5	241	$C_{18}H_{17}N_3O_4S$
	(5)	$ZnCl_2$(13)[f]		(62)		(69)	(EtOH)	(371.4)
3j	**3a**	BzCl	py[f]	<10 (0.2)[l]	D	99[m]	237–238	$C_{22}H_{18}N_2OS$
	(10)	(11)	(15)	23 (7)	B	(85)[n]	($CHCl_3$/2-PrOH)	(358.4)

[a] The C, H, N, and S analyses date for the products are agreeing with the theoretical values within ± 0.3–0.4% limit.

[b] Bath if not bp.

[c] For general operations of processing the reaction mixtures see Experimental.

[d] Without workup of the mother liquors if not stated otherwise.

[e] To a solution of **3a** in pyridine was added Ac_2O dropwise with cooling and stirring during 10 min.

[f] Anhydrous.

[g] TLC homogeneous.

[h] Mp 242°C.

[i] The mixture was stirred at least until the dissolution was complete.

[j] To give spiro compound isomer **5a** see also Table 4. The $CHCl_3$ mother liquor was concentrated and the residue stirred with PhH at room temperature to extract **3c**, IR (KBr, v, cm^{-1}); 1725 (s), 1689 (s), 1652 (m), 1610 (s).

[k] TLC ($CHCl_3$/MeOH(9:1)) homogeneous; mp 253–254°C, ref. [19b] 245–247°C (EtOH); the sample was a generous gift of J Bálint Ph.D and prepared [19b] by boiling a mixture of thioflavanone 1,1-dioxide (**1c**), semicarbazide hydrochloride (in 10% excess), and EtOH containing a catalytic amount of concd. HCl for ca. 4 h.

[l] Dropwise addition of BzCl to a solution of **3a** in anhydrous pyridine with ice cooling and stirring.

[m] TLC almost homogeneous, 234–236°C.

[n] IR (KBr, v, cm^{-1}): 1642 (s).

The solid was collected by filtration and washed several times with water and then with hexane to give crude product **4d** (10.877 g, 83%), mp 208–210°C (ref. [19b] 204–207°C (from EtOH)). The mother liquor was concentrated and the residue triturated with water to give a second crop (1.624 g, 12%) of **4d**. $C_{16}H_{13}N_3S_2$.

Thioflavone thiosemicarbazone 1,1-dioxide(4e). A mixture of powdered sulfone **2c** (0.270 g, 1 mmol), powdered

Table 4

Preparation and properties of 3-acetylspiro[1,3,4-thiadiazoline-2,4′-thioflavans] **5a,b**.[a]

Product	Reaction components (mmol)		Reaction temp. (°C)[b] (time (h))	Workup[c]	% Yield crude (pure)[d]	Mp(°C) (solvent)	Formula[e] (mol.mass)
5a	**3b**	Ac_2O(64)	25	B[h]	99[i,j]	210–211	$C_{19}H_{18}N_2O_2S$
	(2)	$ZnCl_2$(4.4)[f]	(20)[g]	C	(95)	($CHCl_3$/EtOAc)	(338.4)
	3a	Ac_2O(53)	23	B[h]	95	210–211	
	(2)	$ZnCl_2$(3.7)[f]	(20)[g]	C	(85)[k]	($CHCl_3$/EtOAc)	
	3a	Ac_2O(159)	135	B[h]	99.5	210	
	(10)	py(124)[l]	(2)	C	(60)	($CHCl_3$/EtOAc)	
5b	**3j**	Ac_2O(106)	100	E,F	99	206	$C_{24}H_{20}N_2O_2S$
	(4)	py(74)[l]	(4)	C	(88)	(EtOAc)	(400.5)

[a] For preparation of analogous spiro 1,3,4-thiadiazolines (**5c,d,e**) see ref. [17b].

[b] Bath, if not bp.

[c] For general operations of processing the reaction mixtures see Experimental.

[d] Without workup of mother liquors if not stated otherwise.

[e] The C,H,N, and S analyses data for the products are agreeing with the theoretical values within ± 0.3-0.4% limit.

[f] To a solution of anhydrous $ZnCl_2$ in Ac_2O was added the substrate.

[g] The reaction mixture was stirred at least until the dissolution was complete.

[h] To give a crude product.

[i] TLC homogeneous product.

[j] Mp 206-208 °C.

[k] From the mother liquor TLC homogeneous diacetythydrazone **3c**,(6.7%), mp 137°C (from PhH/hexane) could be isolated, cf. Table 3.

[l] Pyridine, anhydrous.

thiosemicarbazide (0.100 g, 1.1 mmol), MeOH (4.7 mL), and MeOH/HCl (0.3 mL *ca*. 0.35 mmol HCl; prepared by mixing 4.5 mL MeOH and 0.5 mL conc. HCl) was boiled with stirring for 9 h to give crude thiosemicarbazone **4e** (0.318 g, 92.5), mp 234–236°C, identical with an authentic [19b] compound (found mp 233–236°C, reported [19b] 192°C (from EtOH)). $C_{16}H_{13}N_3O_2S_2$. The crude product was pure enough for subsequent transformations.

Degradation of thioflavone thiosemicarbazone 1,1-dioxide (4e) to acetylhydrazone 4f. A mixture of thiosemicarbazone **4e** (1.030 g, 3 mmol), Ac_2O (4.5 mL, 48 mmol) and anhydrous pyridine (3 mL, 37 mmol) was stirred at 51°C bath for 5 h and kept at room temperature for 16 h. The crystalline solid was collected by filtration, washed with Ac_2O and hexane, dried over KOH and silica gel in vacuum desiccator to give TLC [$CHCl_3$/EtOAc (8:2), $CHCl_3/Et_2O$ (8:2), or $CHCl_3$/MeOH (95:5)] homogeneous crude product (0.678 g, 69.2%), mp 275–276°C (the hot melt resolidified and melted finally at 281–282°C) or when recrystallized from $CHCl_3$/EtOH, mp 275°C. The Ac_2O/py mother liquor was concentrated, the solid residue was triturated with anhydrous EtOH (1 mL) in the cold to give a second crop of **4f** (0.079 g, 8.1%), mp 278°C and then 284°C. IR(KBr, ν, cm^{-1}): 1678 (s), 1638 (m), 1562 (m). ^1H NMR(200 MHz, DMSO-d_6, δ, ppm); 8.36–8.31 and 8.08–8.03 (both m and 1 H, 2 H-Ar), 7.97 (s, 1 H, H(3)) 7.90–7.86 and 7.84–7.72 (both m and 2 H, 4 H—Ar), 7.63–7.58 (m, 3 H, H—Ar), 2.34 (s, 3 H, Ac). *Anal*. Calcd. for $C_{17}H_{14}N_2O_3S$ C, 62.6; H, 4.3; N, 8.6; S 9.8. Found C, 63.0; H, 4.4; N, 8.4; S, 10.0.

Thioflavone benzoylhydrazone (4g). A mixture of thioflavanone benzoylhydrazone (**3j**, 0.166 g, 0.462 mmol), DDQ (0.112 g, 0.485 mmol, 98%), anhydrous dioxane (4 mL), and a catalytic amount of TsOH was boiled with stirring tor 14 h, then cooled and concentrated. For the removal of $DDQH_2$, the residue was stirred with aq. $NaHCO_3$ in the presence of some drops of 2-PrOH as a humidifier to leave undissolved crude product **4g** (0.152 g, 92%). A solution of the crude product in $CHCl_3$ was treated with charcoal and concentrated. Crystallization of the residue from 2-PrOH (7 mL) afforded pure **4g** (0.121 g, 73%), mp 240°C. ^1H NMR(360 MHz, DMSO-d_6,δ, ppm): 11.28 (bs, 1 H, NH), 8.47 (bs shaped m, 1 H, H(5)), 7.90–7.83 (m, 4 H, H(6,7,8) and H(3)), 7.61–7.51 (m, 10 H, 2 Ph). *Anal*. Calcd. for $C_{22}H_{16}N_2OS$ C, 74.1; H, 4.5; N, 7.9. Found C, 74.3; H, 4.6; N, 7.9.

Attempted dehydrogenation of spirothioflavan 5a by $PhI(OAc)_2$. A mixture of finely powdered **5a** (0.169 g, 0.5 mmol), $PhI(OAc)_2$ (0.247 g, 0.75 mmol) and MeOH (5 mL) was stirred at room temperature for 14 d. The solid was collected by filtration to give TLC homogeneous starting **5a** (0.104 g, 62%), mp 215–216°C.

For a transformation of thioflavanone (**1a**) to **2a**, under similar conditions, see Experimental section.

CAN degradation of spiro-oxadiazoline 5b to thioflavone (2a). According to the literature method [25] for the CAN dehydrogenation of thioflavanone (**1a**), to a solution of finely powdered spirocompound **5b** (0.401 g, 1 mmol) in MeCN (30 mL), placed in a separatory funnel, was added a solution of CAN (3.838 g, 7 mmol) in water (10 mL). The mixture was shaken carefully and when the effervescence ceased, diluted with water (50 mL) and extracted with Et_2O (6 × 12 mL). The Et_2O solution was washed with aq. $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated. Separation of the multicomponent residue by CC (Silica Woelm 100–200 μm, $CHCl_3/Et_2O$ (95:5)] afforded thioflavone (**2a**, 0.096 g, 40%), mp 124°C [ref. [25] 124.5–125.5°C (from anhydrous EtOH), ref. [36] 122–123°C (from MeOH)]. ^1H NMR(200 MHz, $CDCl_3$, δ, ppm): 8.58–8.53 (m, 1 H, H(5)), 7.73–7.50 (m, 8 H, H—Ar), 7.25 [s, 1 H, H(3) (for $CHCl_3$ was δ 7.26); ref. [37] 7.27 (s, 1 H, H(3) ($CDCl_3$); Bruker 300 spectrometer), ref. [36] 7.35 ($CDCl_3$; Varian T-60 and/or EM-390 instruments)]. The product was identical in all respects [inclusive also TLC and IR(KBr)] with an authentic compound.

Attempted dehydrogenation of spirothioflavan 5b by DDQ. A mixture of **5b** (0.200 g, 0.5 mmol), DDQ (0.243 g, 0.525 mmol, 98%), anhydrous dioxane (6 mL), and anhydrous 4-toluenesulfonic acid (a catalytic amount) was stirred at room temperature for 5 h and at 93°C (bath) for 17 h, then concentrated. For the removal of TsOH and $DDQH_2$, the doughy residue was partitioned between aq. $NaHCO_3$ and $CHCl_3$. The organic layer washed with water and dried ($MgSO_4$) contained [TLC, $CHCl_3$/EtOAc (95:5)] *ca*. equal amounts of unchanged **5b** and thioflavone (**2a**) as the major components besides traces of four minor ones.

3-Acetyl-5-methylspiro[1,3,4-oxadiazoline-2,4′-thioflavan] 1′-oxide (5f). (**a**) To a solution of $NaIO_4$ (0.428 g, 2 mmol) in water (10 mL) were added **5a** (0.169 g, 0.5 mmol) and 2-PrOH (10 mL). The mixture was boiled with stirring for 5 h, cooled and then concentrated. The residue was diluted with water up to *ca*. 30 mL to give **5f** (0.103 g, 85%), mp 209–212°C.

(**b**) To a suspension of powdered **5a** (3.384 g, 10 mmol) in Me_2CO (300 mL) were added, both in small portions, powdered OXONE (2 $KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, 3.60 g, 5.85 mmol) and water (35 mL) with stirring at 4–8°C (bath temperature) during 6 h. The mixture was stirred with cooling for 4 h and at room temperature for 14 h, and then filtered. The filtrate was concentrated and the residue crystallized from EtOAc to give crude **5f** (3.395 g, 96%), mp 200–202°C, contaminated (TLC) with a small amount of **5a**. Purification of the crude product by CC [silica gel 60; $CHCl_3$/EtOAc (9:1)] and subsequent crystallization from EtOAc afforded TLC homogeneous **5f** (2.381 g, 67%), mp 208–209°C. IR(KBr, ν, cm^{-1}): 1046 (s, S=O); ^{13}C NMR(50 MHz, $CDCl_3$, δ, ppm): 166.19 (*C*=O), 153.89 (C(5)), 143.39, 134.50 and 132.88 (3 quat. aromatic C), 131.18, 130.92, 129.07, 128.99 (2 C), 128.48 (2 C), 127.22, and 126.29 (9 aromatic =CH), 97.65 (spiro C(2,4′)), 62.99 (C(2′)), 34.08 (C(3′)), 22.02 (*C*H_3—CO), 11.36 (CH_3(5)). *Anal*. Calcd. for $C_{19}H_{18}N_2O_3S$ C, 64.4; H, 5.1; N 7.9; S, 9.05. Found: C, 64.1; H, 5.1; N, 7.8; S, 9.1.

3-Acetyl-5-phenylspiro[1,3,4-oxadiazoline-2,4′-thioflavan] 1′-oxide (5g). (**a**) To a solution of **5b** (3.604 g, 9 mmol) in hot 2-PrOH (290 mL) was added a solution of $NaIO_4$ (3.850 g, 18 mmol) in warm water (100 mL). The mixture was boiled for 2 h and then diluted with water up to *ca*. 600 mL to give crude **5g** (2.917 g, 78%) contaminated with a small amount of sulfone **5i**. Purification by CC [Silica Woelm 100–200 μm, $CHCl_3$/EtOAc (95:5)] afforded TLC homogeneous product **5g** (1.929 g, 51.5%) mp 216–218°C (from $CHCl_3$/EtOAc). IR(KBr, ν, cm^{-1}): 1044 (s, S=O). *Anal*. Calcd. for $C_{24}H_{20}N_2O_3S$ C, 69.2; H, 4.8; N 6.7; S 7.7. Found: C 69.4; H 4.9; N, 6.6; S, 7.6.

(**b**) To a suspension of powdered **5b** (4.005 g, 10 mmol) in Me_2CO (300 mL) were added, both in small portions, powdered OXONE (potassium peroxymonosulfate, 3.70 g, 6 mmol) and water (35 mL) with stirring at 4–8°C (bath temperature) during 4 h. The mixture was stirred on with cooling for 7 h and at room temperature for 12 h and then filtered; the solid was washed with water to leave undissolved crude **5g** (2.071 g, 50%). The aq. Me_2CO mother liquor was concentrated, the residue triturated with water to give a second crop of **5g** (1.967 g 47%). A solution of the crude products in $CHCl_3$ was treated with charcoal and concentrated. The residue was crystallized from EtOAc to give pure title compound **5g** (3.666 g 88%), mp 208–210°C, TLC identical with the product described in (**a**).

Transformation of spiro[oxadiazoline-2,4′-thioflavan] 1′-oxides 5f and 5g into thioflavone diacetylhydrazone (4c). (**a**) A mixture of 5-methyl spirocompound **5f** (3.544 g, 10 mmol), Ac_2O (50 mL, 530 mmol) and TsOH (like a pea) was heated at 98°C (bath) with stirring for 16 h, then cooled and concentrated. The cold residue was triturated with ice/water for 1 h, and then extracted with $CHCl_3$. The $CHCl_3$ solution was washed with aq. $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated. Recrystallization of the residue two times from EtOAc afforded pale yellow crystals of **4c** (1,534 g, 46%), mp 175°C. IR(KBr, ν, cm^{-1}): 1720(s), 1706(s), 1690(s), 1682(s), 1648(w), 1592(s). ^1H NMR(360 MHz, $CDCl_3$, δ, ppm): 8.77–8.75 (m, 1 H, H(5)), 7,58–7.43 (m, 8 H, H—Ar), 6.80 (s, 1 H, H(3), 2.47 (s, 6 H, 2 Ac). ^{13}C NMR(90 MHz, $CDCl_3$, δ, ppm): 170.28 (2 C, 2 *C*=O), 162.56, 148.81, 136.98, and 134.45 (quat. aromatic C), 130.62 (2 C), 129.15 (2 C), 127.82, 127.02 (3 C), and 126.34 (aromatic CH), 111.99 (C(3)), 25.90 (2 C, *C*H_3—C=O). *Anal.* Calcd. for $C_{19}H_{16}N_2O_2S$ C, 67.8; H, 4.8; N, 8.3; S, 9.5. Found: C, 67.8; H, 4.8; N, 8.4; S, 9.6.

(**b**) A mixture of 5-pheny1 spirocompound **5g** (0.833 g, 2 mmol), Ac_2O (10 mL, 106 mmol) and TsOH (like a pepper) was heated at 100°C (bath) with stirring for 18 h, then cooled and concentrated. The cold residue was triturated with MeOH (2 mL) for 2.5 h and then water (*ca.* 7 mL) was added in portions to give a solid (0.707 g). A solution of the product in $CHCl_3$ was treated with charcoal and concentrated. The residue was crystallized from EtOAc to give **4c** (0.292 g, 43%), mp 174.5–175°C, identical (TLC, IR) with the product obtained from the 5-methyl spirocompound **5f** aforementioned in (**a**).

3-Acetyl-5-methylspiro[1,3,4-oxadiazoline-2,4′-thioflavan] 1′,1′-dioxide (5h). To a suspension of powdered spirothioflavan **5a** (1.692 g, 5 mmol) in 96% AcOH (50 mL) were added, both in small portions, powdered $KMnO_4$ (1.613 g, 10.2 mmol) and water (10 mL) at room temperature with cooling and stirring during 45 min. The mixture was stirred further for 1.5 h and then under cooling 30% H_2O_2 (*ca.* 1.2 mL) was added drop-by-drop until discoloration. The mixture was diluted with water up to *ca.* 200 mL, kept at 4°C for 1.5 h to give crystalline crude 1′,1′-dioxide **5h** (1.449 g, 78%), mp 224–225°C. Recrystallization from PhMe afforded pure **5h** (1.313 g 71%), mp 227°C. IR(KBr, ν, cm^{-1}): 1314 (s), 1154 (s), 1138 (s) (SO_2). *Anal.* Calcd. for $C_{19}H_{18}N_2O_4S$ C, 61.6; H, 4.9; N, 7.6; S, 8.7. Found: C, 61.8; H, 4.9; N, 7.5; S, 8.6.

3-Acetyl-5-phenylspiro[1,3,4-oxadiazoline-2,4′-thioflavan] 1′,1′-dioxide (5i). To a solution of spirothioflavan **5b** (0.401 g, 1 mmol) in 96% AcOH (16 mL) was added powdered $KMnO_4$ (0.395 g, 2.5 mmol) in small portions with stirring at room temperature during 20 min. The mixture was stirred further for 2 h, and then for dissolving the oxidant, water (12 mL) was added in portions during 1.5 h. After an additional stirring for 1 h the precipitated solid was collected by filtration, washed with water to give TLC homogeneous crude **5i** (0.389 g, 90%), mp 227–228°C. A solution of the crude product in $CHCl_3$ was treated with charcoal and concentrated. The residue was boiled in 2-PrOH (3 mL) to give analytically pure **5i** (0.378 g, 87%), mp 228°C. IR(KBr, ν, cm^{-1}): 1312 (s), 1156 (s) and 1136 (s) (SO_2). *Anal.* Calcd. for $C_{24}H_{20}N_2O_4S$ C, 66.6; H, 4.7; N, 6.5; S, 7.4. Found: C, 66.5; H, 4.7; N, 6.4; S, 7.4.

5-Acetamido-3-acetylspiro[1,3,4-thiadiazoline-2,4′-thioflaven] (6). A mixture of thíosemicarbazone **4d** (1.869 g, 6 mmol), Ac_2O (15 mL, 159 mmol) and pyridine (3 mL, 37 mmol) was kept at 100°C for 3 h and then at 4°C for 18 h to give yellow crystals of crude diacetylhydrazone **4c** (0.367 g, 18%), mp 170–171°C, TLC [$CHCl_3$/MeOH (9:1)] identical with an authentic compound. The mother liquor was concentrated and the residue triturated with anhydrous EtOH under cooling, and for increasing the separation of crystals, gradually hexane (16 mL) was added then kept at room temperature for *ca.* 16 h to give a crystalline second crop of product (1.090 g). The mother liquor of the second crop was concentrated and the residue triturated with water to give a solid (0.874 g). The second and third crops of crude products contained the same compound as the major component [TLC, $CHCl_3$/MeOH (9:1)]. Purification of the third crop by CC [silica gel 60; $CHCl_3/Et_2O$ (8:2)] and when combined with the second crop, subsequent crystallization from Et_2O with addition of hexane afforded pure **6** (1.328 g, 56%), mp 248–249°C. IR(KBr, ν, cm^{-1}): 1674 (s), 1646 (s), 1614 (s). ^1H NMR(200 MHz,$CDCl_3$, δ, ppm): 9.20 (s, 1 H, N*H*Ac), 7.59–7.54 (m, 2 H, H—Ar), 7.39–7.22 (m, 7 H, H—Ar), 6.50 (s, 1 H, H(3′)), 2.43 (s, 3 H, Ac), 1.91(s, 3 H, Ac). ^{13}C NMR(50 MHz, $CDCl_3$, δ, ppm): 169.74 and 169.47 (2 C=O), 145.02 (C(5)), 136.74, 133.42, 132.96, and 129.70 (3 quat. aromatic C, and C(2′)), 129.27, 128.72 (2 C), 128.01, 127.48, 126.75 (2 C), 126.33, and 125.16 (9 aromatic =CH), 120.08 (C(3′)), 79.92 (spiro C(2,4′)), 23.69 and 22.30 (2 *C*H_3—C=O). *Anal.* Calcd. for $C_{20}H_{17}N_3O_2S_2$ C, 60.7; H, 4.3; N, 10.6; S, 16.2. Found C, 60.8; H, 4.4; N, 10.6; S, 16.3.

Thioflavanone azine (8). (**a**) To a solution of hydrazone **3a** (0.509 g, 2 mmol) in DMSO (3 mL) at *ca.* 60°C was added 0.1*M* I_2/DMSO (3 mL, 0.3 mmol). The mixture was kept at 100°C for 45 min and then gradually water (*ca.* 25 mL) was added to give crude **8** (0.471 g, 99%, mp 267°C) containing some unchanged **3a**. Heating the crude product in MeOH (5 mL) left undissolved pure **8** (0.358 g, 75%), mp 270–271°C (ref. [19b] 270°C (PhH), prepared by condensing thioflavanone **1a** with hydrazine hydrate).

(**b**) A mixture of thioflavanone (**1a**, 1.502 g, 6.25 mmol), hydrazone **3a** (1.272 g, 5 mmol), 2-PrOH (25 mL), and a catalytic amount of TsOH was boiled with stirring for 10 h to give crude (1.697 g, 71%; mp 269–270°C) or recrystallized **8** (1.495 g, 63%), mp 270°C (from Diglyme or PhH), TLC identical with the product described in (**a**). $C_{30}H_{24}N_2S_2$.

Dehydrogenation of thioflavanone azine (8) to azine 10. A mixture of azine **8** (0.119 g, 0.25 mmol), DDQ (0.122 g, 0.525 mmol, 98%), anhydrous dioxane (10 mL), and a catalytic amount of TsOH was boiled with stirring for 18 h then concentrated. The residue was washed with $CHCl_3$ and the solid stirred with aq. $NaHCO_3$ in the presence of some drops of 2-PrOH as a humidifier to give **10** (0.095 g, 80%), purplish crystals of a metallic lustre, mp 283–286°C (ref. [19b] 280–285°C (from EtOH), prepared by treatment of 4-methylthio-thioflavylium iodide or thioflaven-4-thione with $N_2H_4{\cdot}H_2O$). $C_{30}H_{20}N_2S_2$.

Reaction of thioflavanone hydrazone (3a) with DDQ, formation of azines 8 and 9. A mixture of hydrazone **3a** (1.017 g 4 mmol), DDQ (0.973 g, 4.2 mmol, 98%) and anhydrous dioxane (20 mL) was stirred at room temperature for some minutes, whilst the deep green color of the solution, produced by a transiently formed charge-transfer complex, became brownish-red and under significant effervescence the mixture thickened. Hereupon, the mixture was boiled for 4 h with stirring, and then concentrated. For removing $DDQH_2$ the residue was stirred with aq. $NaHCO_3$ at room temperature to leave undissolved a brownish solid (0.967 g, mp 213–220°C) consisting of two major components (TLC, $CHCl_3$). Purification by CC (silica gel 60, $CHCl_3$) afforded azine **8** (0.387 g, 41%, mp 270°C (from PhMe) and orange-red crystals of **9** (0.104 g, 11%), mp 255–256°C (from $CHCl_3$/EtOAc). ^1H NMR(200 MHz, $CDCl_3$, δ, ppm): 8.59–8.56 (m, 1 H, H(5)), 8.48–8.45 (m, 1 H H(5)), 7.81 (s, 1 H, =CH(3)), 7.71–7.66 (m, 2 H, H—Ar), 7.50–7.16 (m, 14 H, H—Ar), 4.48 (dd, 1 H, $J_{2,3e} = 3$ Hz, $J_{2,3a} = 13$ Hz, H(2)), 4.19 (q, 1 H, $J_{2,3e} = 3$ Hz, $J_{3e3a} = 17.5$ Hz, $H_e(3)$), 3.13 (q, 1 H, $J_{2,3a} = 13$ Hz, $J_{3e,3a} = 17.5$ Hz, $H_a(3)$). *Anal.* Calcd. for $C_{30}H_{22}N_2S_2$ C, 75.9; H, 4.7; N, 5.9. Found: C, 75.8; H, 4,6; N, 5,9.

Transformation of 2-cinnamoylphenyl disulfide (7) into thioflavanone hydrazone (3a) and pyrazole 11a. A mixture of 98% $N_2H_4{\cdot}H_2O$ (9 mL, ~180 mmol), 2-PrOH (25 mL) and **7** [22b] (4.307 g, 9 mmol, 18 mmol of chalcone moiety) was stirred at room temperature for 5 h and then the clear solution formed was kept at 100°C for 16 h. The solution was cooled and deep freezed at *ca.* −20°C for 2.5 d to give crude (2.093 g, 91.4%, yield calculated for 9 mmol, mp 116–117°C) or recrystallized **3a**, mp 120–121°C (from MeOH), identical [mp, TLC: $CHCl_3$/EtOAc (95:5), IR] with an authentic compound prepared from **1a** (see ref. [17b]). The mother liquor of the crude product was concentrated, the residue dissolved in Me_2CO (3 mL) and for transforming **11a** into the more easily isolable disulfide **12a**, kept at 4°C for 4 d. The deposited crystals were collected by filtration and washed with Me_2CO/hexane (1:1) to give crude (0.190 g, 4.2%, mp 226–227°C) or recrystallized **12a**, mp 230°C (from 2-methoxyethyl ether with addition of water). The product is identical [mp, TLC: $CHCl_3$/MeOH (9:1), IR] with that obtained by treating thioflavone with hydrazine hydrate [33]. *Anal.* Calcd. for $C_{30}H_{22}N_4S_2$ C, 71.7; H, 4.4; N, 11.1. Found: C, 71.8; H, 4.5; N, 11.1.

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Reaction of 4,5-Dichloro-2-chloromethylpyridazin-3(2*H*)-one with phenols

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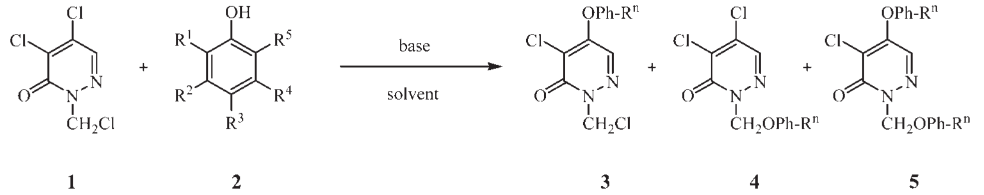

R^1 - R^5 = H, Cl, F, Me, MeO, EtO, CHO, or NO_2
R^n = R^1 - R^5

The regiochemistry was investigated for the reaction of 2-chloromethyl-4,5-dichloropyridazin-3(2*H*)-one (**1**) with some phenols **2** in the presence of a base in organic solvents. Seven diphenoxy derivatives **5** were synthesized selectively from **1** and phenols **2** under two optimized conditions. The product distributions of these reactions are dependent on the base, the solvent, and/or the substitutes of phenols.

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INTRODUCTION

Chloromethyl-4,5-dichloropyridazin-3(2*H*)-one (**1**) is a key intermediate for the synthesis of their derivatives, fluorescence molecules containing pyridazinone ring [1,2], and also biologically active compounds [3–7]. Because of involving four electrophilic carbons such as $ClCH_2N$-, C-3, C-4, and C-5, however, the reaction of compound **1** with a nucleophile such as phenol affords two or three products [8,9]. Also, the retro-ene reaction of compound **1** under basic condition was reported [9]. Based upon the atomic charges of compound **1** [10], the reactivity of the C-5 position about the nucleophile is more active than the α-C and C-4 positions (Fig. 1). Therefore, the selective synthesis of 5-phenoxy-2-phenoxymethyl-, 5-phenoxy-, or 2-phenoxymethyl derivative under basic condition is difficult.

In connection with the SAR study and the evaluation of biological activity such as cardiovascular activity or immunosuppressive activity, we need some 2-(phenoxymethyl)-5-phenoxylpyridazin-3(2*H*)-ones. Thus, we attempted to study on the regiochemistry in the reaction of compound **1** with phenols under basic condition (Scheme 1). In this article, we report the results for the title reactions.

RESULTS AND DISCUSSION

First, we examined the effect of the bases in the reaction of **1** with *o*-vaniline (**2a**) in acetonitrile. Reaction of compound **1** with two equivalents *o*-vaniline (**2a**) in the presence of base in refluxing acetonitrile gave products **3a**, **4a**, and **5a**. The distribution of the products for these reactions is shown in Table 1.

When K_2CO_3, Cs_2CO_3, and Na_2CO_3 as the base were used, compound **5a** was the main product. However, the reaction did not progress using NaH, Et_3N, and *N*,*N*-dimethylaminopyridine as base in refluxing acetonitrile. We selected potassium carbonate as the suitable base for this reaction.

On the other hand, we examined the effect of the solvents for the same reaction under different conditions such as at reflux temperature or under microwave irradiation.

Although two products were detected, the reaction of **1** with **2a** in acetonitrile, ethyl acetate, tetrahydrofuran, or acetone under the same conditions gave **5a** as the main product (entries 1, 2, 5, 6, 7, 8, 9, and 10, in Table 2). Compound **1** was reacted with **2a** in the presence of potassium carbonate in refluxing methanol or under microwave irradiation to afford selectively **5a** in

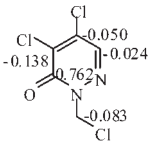
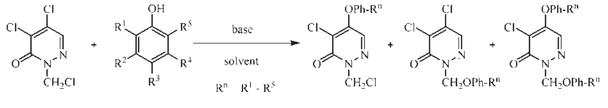


Figure 1. Atomic charge of carbons at the MP2/6-311+G** for compound **1**.

excellent yield, respectively (entries 3 and 4 in Table 2). Compound **4a** was the main product when refluxing toluene was used, whereas the reaction did not occur in toluene under microwave irradiation. Even though the conversion ratio of **1** was low, **4a** was the main product in the reaction in methylene chloride and diethyl ether under microwave irradiation (entries 14 and 16 in Table 2). We did not find significant differences for the distribution of the products between the classical heating system and microwave irradiation system. According to TLC analysis, the product **5a** yielded *via* the 2-phenoxymethyl compound **4a** in the reaction of **1** with **2a**, whereas the 5-phenoxy derivative **3a** did not convert to **5a** under the same condition. Based upon the selectivity and the practical reaction conditions, therefore, we selected the optimized conditions, that is, (i) refluxing acetonitrile/potassium carbonate system and (ii) refluxing methanol/potassium carbonate system. Using the two optimized system, we investigated the effect of the substitutes of phenols. Most interestingly, reaction of **1** with 2**b** (2 equiv.) or **2e** (2 equiv.) under two optimized conditions gave selectively the corresponding 5-phenoxy derivatives **3b** or **3e** in excellent yields (entries 1, 2, 7, and 8 in Table 3). Treatment of **1** with **2j** under our two conditions also afforded selectively α-phenoxy derivative **4j** in excellent yield (entries 17 and 18 in Table 3).

Scheme 1



1 **2** **3** **4** **5**

2-5	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**
R^1	MeO	H	Cl	H	Cl	H	H	H	H	H
R^2	H	H	H	Cl	H	H	H	H	H	H
R^3	H	H	H	H	NO_2	H	F	NO_2	NO_2	NO_2
R^4	H	H	H	H	H	EtO	F	Me	H	H
R^5	CHO	H	Cl	Cl	Cl	CHO	H	H	H	NO_2

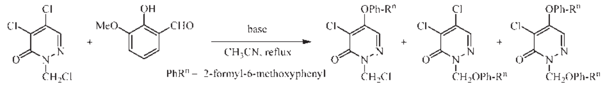
Although compound **1** was reacted with **2c** in refluxing acetonitrile to afford **4c** (48%) and **5c** (46%), the same reaction was carried out in refluxing methanol to give selectively **5c** in 94% yield (entries 3 and 4 in Table 3). On the other hand, compound **1** was reacted with **2d** or **2f–2i** under the same conditions to afford selectively α-diphenoxy derivatives **5d** or **5f–5i** in good to excellent yields, respectively (entries 5–6 and 9–16 in Table 3). The chemical structures of the all products were characterized by IR spectroscopy, NMR spectroscopy, and the elemental analysis.

CONCLUSIONS

In conclusion, the regiochemistry was investigated for the reaction of compound **1** with some phenols **2** in the presence of a base in organic solvents. Although diphenoxy derivatives **5** were synthesized selectively under two optimized conditions, we did not find any regularity. Although significant differences for the distribution of the products did not show under the classical heating system and microwave irradiation, the regiochemistry in

Table 1

Screening of bases for the reactions of one equivalent of **1** with two equivalents of **2a** in acetonitrile.[a]



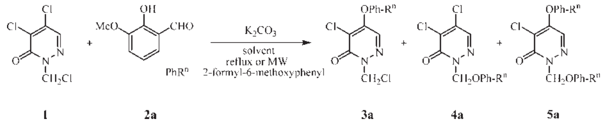
1 **2a** **3a** **4a** **5a**

Entry	Base	Reaction time (hours)	Conversion ratio[b]	Product (%)[b] **3a**	**4a**	**5a**
1	K_2CO_3	1.5	100	–	7	93
2	Cs_2CO_3	1	100	1	33	66
3	Na_2CO_3	13	100	12	40	48
4	NaH	48	0	–	–	–
5	Et_3N	48	0	–	–	–
6	DMAP[c]	48	0	–	–	–

[a] Mole ratio of reactants:**2**/**3a** = 1:2 equivalents.
[b] Determination by using proton NMR.
[c] *N*,*N*-Dimethylaminopyridine.

Table 2

The products distribution for the reactions of **1** with **2a** in the presence of K_2CO_3 in organic solvents.[a]

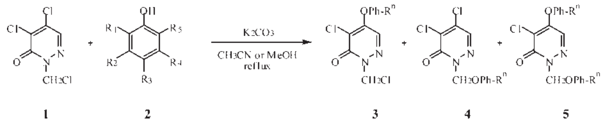


Entry	Solvent	Reaction conditions[b]	Conversion ratio[c]	Product (%)[c]		
				3a	**4a**	**5a**
1	CH_3CN	Reflux,1.5 h	100	–	7	93
2		MW, 1.5 h	100	–	8	92
3	MeOH	Reflux, 1h	100	–	–	100
4		MW, 0.5 h	100	–	–	100
5	EtOAc	Reflux, 14 h	100	2	48	50
6		MW, 5 h	73	8	44	48
7	THF	Reflux, 48 h	100	45	23	32
8		MW, 5 h	90	15	42	43
9	Acetone	Reflux, 24 h	100	10	36	54
10		MW,2 h	100	8	42	50
11	Toluene	Reflux, 32 h	100	4	64	32
12		MW, 5 h	0	–	–	–
13	CH_2Cl_2	Reflux, 48 h	0	–	–	–
14		MW, 5 h	78	4	80	16
15	Ether	Reflux, 48 h	0	–	–	–
16[d]		MW, 1 h	59	25	63	12
17	*n*-Hexane	Reflux, 48 h	0	–	–	–
18		MW, 5 h	0	–	–	–

[a] Mole ratio of reactants:**2**/**3a** = 1:2 equivalents.
[b] MW = Microwave irradiation.
[c] Determination by using proton NMR.
[d] After 30 minutes, the solvent was refilled.

Table 3

The products distribution for the reactions of **1** with **2** in the presence of potassium carbonate in acetonitrile or methanol.[a]



Entry	2	Reaction conditions	Product (%)[b]		
			3	**4**	**5**
1	**2b**	CH_3CN, 13 h	**3b**(93)	–	–
2		MeOH, 1 h	**3b**(94)	–	–
3	**2c**	CH_3CN, 8 h	–	**4c**(48)	**5c**(46)
4		MeOH, 5 h	–	–	**5c**(94)
5	**2d**	CH_3CN, 9 h	–	–	**5d**(93)
6		MeOH, 12 h	–	–	**5d**(94)
7	**2e**	CH_3CN, 34 h	**3e**(90)	–	–
8		MeOH, 20 h	**3e**(95)	–	
9	**2f**	CH_3CN, 4 h	–	–	**5f**(90)
10		MeOH, 2 h	–	–	**5f**(92)
11	**2g**	CH_3CN, 0.2 h	–	–	**5g**(94)
12		MeOH, 10 min	–	–	**5g**(95)
13	**2h**	CH_3CN, 1 h	–	–	**5h**(84)
14		MeOH, 20 min	–	–	**5h**(90)
15	**2i**	CH_3CN, 3 h	–	–	**5i**(89)
16		MeOH, 2h	–	–	**5i**(91)
17	**2j**	CH_3CN, 60 h	–	**4j**(85)	–
18		MeOH, 48 h	–	**4j**(90)	–

[a] Mole ratio of reactants:**2**/**3a** = 1:2 equivalents.
[b] Isolated yields.

the reaction is effected by the base, the solvent, and/or the substitutes of phenols. Further work including the theoretical study on the regiochemistry and the biological activity are under way in our laboratory.

EXPERIMENTAL

Melting points were determined with a capillary apparatus and uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz spectrophotometer with chemical shift values reported in δ units (ppm) relative to an internal standard (TMS). IR spectra were obtained on an IR spectrophotometer. Elemental analyses were performed with a CHNS-932 (Leco). 2-Chloromethyl-4,5-dichloropyridazin-3(*2H*)-one was synthesized by the literature method [2]. Microwave reaction was carried out by using a CEM, Discover microwave apparatus.

General procedure for the reaction of 2-chloromethyl-4,5-dichloropyridazin-3(2*H*)-one (1) with phenols (2).

Method 1. A solution of 2-hydroxy-3-methoxybenzaldehyde (2.8 g, 2 equiv.) and base (2 equiv.), 2-chloromethyl-4,5-dichloro-pyridazin-3(*2H*)-one (**2**) (2 g, 1 equiv.), and solvent (30 mL) was refluxed until **2** disappeared by TLC monitoring. After cooling the mixture to room temperature, the mixture was filtered and concentrated. The distribution of products was analyzed by ^{1}H NMR quantitative analysis. The products 3, 4, and 5 were also isolated by column chromatography on silica gel (2.5 × 8 cm) with *n*-hexane/EtOAc (2:1, v/v).

Method 2. 2-Chloromethyl-4,5-dichloropyridazin-3(2*H*)-one (**2**) (0.1 g, 1 equiv.) was dissolved in solvent (7 mL) in a 10 mL microwave vessel. 2-Hydroxy-3-methoxybenzaldehyde (0.14 g, 2 equiv.) and base (2 equiv.) were added. The vessel was closed and placed into a microwave apparatus. The mixture was irradiated per 10 min at 120°C with a set power of 300 W. After cooling, the mixture was filtered on a glass filter under vacuum. The distribution of products was analyzed by ^{1}H NMR quantitative analysis.

2-(5-Chloro-l-chloromethyl-6-oxo-l,6-dihydropyridazin-4-yloxy)-3-methoxybenzaldehyde (3a). Prepared by the Method 1 and 2. mp; 145°C. IR (KBr) 3081, 3045, 2935, 2878, 1663, 1581, 1479, 1452, 1387, 1254, 1213 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 3.87 (s, 3H), 5.86 (s, 2H, N-CH$_2$), 7.35 (d, 1H, J = 6 Hz), 7.42 (s, 1H), 7.46 (t, 1H, J = 6 Hz), 7.58 (d, 1H, J = 6 Hz), 10.30 ppm (s, CHO 1H); ^{13}C NMR (CDCl$_3$): δ 56.55, 58.29, 118.31, 121.12, 127.71, 129.26, 130.17, 142.79, 151.25, 153.83, 157.77, 187.75 ppm; Elemental analysis calcd. for $C_{13}H_{10}Cl_2N_2O_4$: C,47.44; H,3.06; N, 8.51; Found: C, 47.50; H, 3.10; N, 8.57.

4-Chloro-2-(chloromethyl)-5-phenoxypyridazin-3-(*2H*)-one (3b). Prepared by the Method 1. mp 78°C. IR (KBr) 3067, 3011, 1660, 1609, 1585, 1487, 1393, 1311, 1278, 1216, 1155 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 5.85 (s, 2H), 7.11 (d, 2H, J = 7.64 Hz), 7.32 (m, 1H), 7.48 (m, 2H), 7.53 ppm (s, 1H); ^{13}C NMR (CDCl$_3$): δ 58.29, 115.99, 119.79, 126.42, 130.55, 130.62, 131.23, 153.31, 153.72 ppm; Elemental analysis calcd. for $C_{11}H_8Cl_2N_2O_2$: C, 48.73; H, 2.97; N, 10.33. Found: C, 48.80; H, 3.00; N, 10.37.

4-Chloro-2-chloromethyl-5-[(2,6-dichloro-4-nitrophenoxy) methyl]pyridazin-3(*2H*)-one (3e). Prepared by the Method 1. mp 152°C. IR(KBr) 3086, 3054, 1678, 1588, 1523, 1506, 1349, 1293, 1249, 1215, 973, 956 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 6.11 (s, 2H), 7.77 (s, 1H), 8.21 ppm (s. 2H); ^{13}C NMR (CDCl$_3$): δ 81.58, 124.51, 129.94, 134.90, 136.66, 137.53, 144.20, 155.33, 156.82 ppm; Elemental analysis calcd. for $C_{12}H_7Cl_4N_3O_4$: C, 36.12; H, 1.77; N, 10.53. Found: C, 36.17; H, 1.79; N, 10.57.

2-[(4,5-Dichloro-6-oxopyridazin-l(*6H*)-yl)methoxy]-3-methoxybenzaldehyde (4a). Prepared by the Method 1 and 2. mp 143°C. IR (KBr) 3077, 3011, 2993, 2885, 2846, 1695, 1666, 1615, 1581, 1481, 1460, 1392, 1278, 1250,1217 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 3.91 (s, 3H), 6.09 (s, 2H, N-CH$_2$), 7.16 (d, 2H, J = 3 Hz), 7.34 (t, 1H, J = 5.1 Hz), 7.72 (s, 1H), 10.16 ppm (s, 1H); ^{13}C NMR (CDCl$_3$): δ 56.21, 81.44, 117.99, 119.41, 125.34, 129.93, 134.87, 136.33, 137.20, 148.32, 152.35, 156.58, 189.73 ppm; Elemental analysis calcd. for $C_{13}H_{10}Cl_2N_2O_4$: C,47.44; H,3.06; N, 8.51; Found: C, 47.49; H, 3.11; N, 8.58.

4,5-Dichloro-2-[(2,6-dichlorophenoxy)methyl]pyridazin-3(*2H*)-one (4c). Prepared by the Method 1. mp 142°C. IR (KBr) 3093, 3053, 1676, 1663, 1584, 1456, 1440, 1402, 1297, 1242, 1224, 1003, 990, 962 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 6.03 (s, 2H), 7.05 (t, 1H, J = 8.15 Hz), 7.29 (m, 2H), 7.72 ppm (s, 1H); ^{13}C NMR (CDCl$_3$): δ 81.46, 126.17, 129.07, 129.14, 134.84, 136.12, 137.17, 149.68, 156.80 ppm; Elemental analysis calcd. for $C_{11}H_6Cl_4N_2O_2$: C, 38.86; H, 1.78; N, 8.24. Found: C, 38.90; H, 1.82; N, 8.27.

4,5-Dichloro-2-((2,4-dinitrophenoxy)methyl)pyridazin-3(*2H*)-one (4j). Prepared by the Method 1. mp 147–149°C. IR (KBr) 3095, 3062, 1681, 1607, 1586, 1525, 1349, 1273, 1249, 987, 964 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 6.24 (s, 2H), 7.75 (d, 1H, J = 9.24 Hz), 7.90 (s, 1H), 8.47 (dd, 1H, J = 2.77, 6.45 Hz), 8.70 ppm (d, 1H, J = 2.74 Hz); ^{13}C NMR (CDCl$_3$): δ 79.10, 117.90, 121.72, 128.99, 135.14, 137.46, 137.85, 140.17, 141.90, 154.30, 156.62 ppm; Elemental analysis calcd. for $C_{11}H_6Cl_2N_4O_6$: C, 36.59; H, 1.67; N, 15.52. Found: C, 36.63; H, 1.70; N, 15.58.

2-(5-Chloro-l-((2-formyl-6-methoxyphenoxy)methyl)-6-oxo-l,6-dihydropyridazin-4-yloxy)-3-methoxybenzaldehyde (5a). Prepared by the Method 1 and 2. mp 165°C. IR (KBr): 3085, 3021, 2988, 2946, 2843, 1694, 1663, 1617, 1584, 1482, 1461, 1394, 1377, 1312, 1271, 1248, 990 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 3.86 (s, 3H), 3.96 (s, 3H), 6.15 (s, 2H), 7.19 (d, 2H, J = 6 Hz), 7.28 (t, 1H, J = 4.5 Hz), 7.33 (s, 1H), 7.38 (t, 1H, J = 3.8 Hz), 7.43 (s, 1H, J = 8.1 Hz), 7.56 (dd, 1H, J = 1.2, 7.7 Hz), 10.19 (s, 1H, CHO), 10.31 ppm (s, 1H, CHO); ^{13}C NMR (CDCl$_3$): δ 56.20, 56.44, 80.85, 117.91, 118.21, 119.00, 120.74, 125.27, 127.52, 129.15, 129.41, 142.98, 151.15, 152.49, 153.71, 187.80, 189.82 ppm; Elemental analysis calcd. for $C_{21}H_{17}ClN_2O_7$: C, 56.70; H, 3.85; N, 6.30; Found: C, 56.75; H, 3.87; N, 6.34.

4-Chloro-5-(2,6-dichlorophenoxy)-2-[(2,6-dichloro-phenoxy)-methyl]pyridazin-3(*2H*)-one (5c). Prepared by the Method 1. mp 145–147°C. IR (KBr): 3074, 3054, 2923, 1674, 1445, 1270 1237 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 6.04 (s, 2H), 7.05 (m, 1H), 7.29 (m, 3H), 7.44 (d, 2H, J = 8.11 Hz), 7.72 ppm (s, 1H); ^{13}C NMR (CDCl$_3$): δ 81.15, 126.04, 126.17, 128.11, 128.16, 128.98, 129.07, 129.25, 129.47, 136.12, 145.21, 152.46, 158.90 ppm; Elemental analysis calcd. for $C_{17}H_9Cl_5N_2O_3$: C, 43.77; H, 1.94; N, 6.00. Found: C, 43.79; H, 2.00; N, 6.07.

4-Chloro-5-(2,5-dichlorophenoxy)-2-[(2,5-dichlorophenoxy)-methyl]pyridazin-3(*2H*)-one (5d). Prepared by the Method 1. mp 143°C. IR (KBr): 3073, 3057, 3018, 1659, 1612, 1578, 1474, 1434, 1393, 1379, 1273, 1255, 1220, 1161, 1137 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 6.05 (s, 2H), 7.02 (dd, 1H, J = 2.26, 6.27 Hz), 7.22 (d, 1H, J = 2.30 Hz), 7.30 (m, 3H), 7.47 ppm (t, 2H, J = 8.59 Hz); ^{13}C NMR (CDCl$_3$): δ 79.41, 118.54, 120.22, 122.31, 123.35, 124.22, 124.72, 127.88, 129.64, 131.06, 131.96, 133.12, 134.05, 149.26, 152.68, 153.00, 158.49 ppm; Elemental analysis calcd. for $C_{17}H_9Cl_5N_2O_3$: C, 43.77; H, 1.94; N, 6.00. Found: C, 43.80; H, 2.02; N, 6.09.

2-(5-Chloro-l-[(3-ethoxy-2-formylphenoxy)methyl]-6-oxo-l,6-dihydropyridazin-4-yloxy)-6-ethoxybenzaldehyde (5f). Prepared by the Method 1. mp 188°C. IR (KBr): 2987, 2975, 2930, 2893, 2861, 1693, 1666, 1616, 1583, 1483, 1469, 1394, 1378, 1319, 1269, 1246, 1214, 1181, 1159, 1049, 987 cm^{-1}; ^{1}H NMR (CDCl$_3$):δ 1.26 (t, 3H, J = 6.87 Hz), 1.52 (t, 3H, J = 6.89 Hz), 4.16 (m, 4H), 6.17 (s, 2H), 7.35 (m, 7H), 10.19 (s, 1H), 10.32 ppm (s, 1H); ^{13}C NMR (CDCl$_3$): δ 14.42, 14.87, 64.84, 65.25, 80.88, 118.95, 119.01, 119.21, 120.54, 125.09, 127.37, 129.17, 129.77, 12996, 143.46, 148.79, 150.43, 153.88, 158.77, 187.87, 189.88 ppm; Elemental analysis calcd. for $C_{23}H_{22}Cl\ N_2O_7$: C, 58.29; H, 4.68; N, 5.91. Found: C, 58.32; H, 4.71; N, 5.97.

4-Chloro-5-(3,4-difluorophenoxy)-2-((3,4-difluorophenoxy) methyl)pyridazin-3(2*H*)-one (5g). Prepared by the Method 1. liquid. IR (KBr) 3083, 1681, 1668, 1513, 1270, 1252, 1206, 1160, 1132, 1031 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 5.98 (s, 2H), 7.26 (m, 6H), 7.56 ppm (s, 1H); ^{13}C NMR (CDCl$_3$): δ 78.45, 106.16, 106.43, 109.70, 109.97, 111.76, 115.60, 117.31, 117.55, 118.40, 118.67, 120.97, 130.29, 148.77, 151.88, 153.13, 158.54 ppm; Elemental analysis calcd. for $C_{17}H_9ClF_4N_2O_3$: C, 50.95; H, 2.26; N, 6.99.Found: C, 51.01; H, 2.30; N, 7.02.

4-Chloro-5-(3-methyl-4-nitrophenoxy)-2-[(3-methyl-4-nitrophenoxy)methyl]-pyridazin-3-(2*H*)-one (5h). Prepared by the Method 1. mp 128–129°C. IR (KBr): 3072, 3032, 1672, 1580, 1515, 1483, 1343, 1236, 1081, 1051 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 2.63 (d, 6H, J = 10.26 Hz), 6.12 (s, 1H), 7.09 (m, 4H), 7.68 (s, 1H), 8.12 ppm (m, 2H); ^{13}C NMR (CDCl$_3$): δ 21.02, 21.46, 53.49, 113.34, 116.58, 119.36, 122.12, 123.16, 127.46, 127.72, 131.60, 137.06, 137.62, 143.51, 146.02, 152.15, 156.46, 158.39, 159.68 ppm; Elemental analysis calcd. for $C_{19}H_{15}ClN_4O_7$: C, 51.08; H, 3.38; N, 12.54. Found: C, 51.11, H, 3.40; N, 12.57.

4-Chloro-5-(4-nitrophenoxy)-2-[(4-nitrophenoxy) methyl]-pyridazin-3(2*H*)-one (5i). Prepared by the Method 1. mp 177–178°. IR (KBr): 3073, 3057, 1659, 1612, 1578, 1474, 1393, 1379, 1273, 1220, 1095 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 6.15 (s, 2H), 7.26 (m, 4H), 7.69 (s, 1H), 8.33 ppm (m, 4H); ^{13}C NMR (CDCl$_3$): δ 83.90, 115.83, 118.75, 123.80, 125.99, 126.45, 131.81, 142.81, 144.98, 151.96, 158.23, 158.37, 161.27 ppm; Elemental analysis calcd. for $C_{17}H_{11}ClN_4O_7$: C, 48.76; H, 2.65; N, 13.38. Found: C, 48.79; H, 2.70; N, 13.41.

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Syntheses and Fluorescent Properties of 2-Amino Substituted 6,7-Dimethoxy-4-(trifluoromethyl)quinolines

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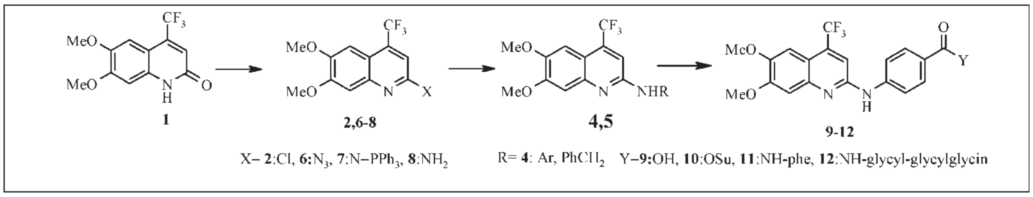

2-Amino-substituted 6,7-dimethoxy-4-trifluoromethyl-quinolines were synthesized from the 2-oxo compound **1** *via* 2-chloroquinoline **2** and aminated with anilines or benzylamine to give highly fluorescent molecules **4**, 5. 2-Aminoquinoline **8** was obtained *via* azidation of **2**–**6**, reaction to the phosphazene **7**, and hydrolysis. 4-Ethoxycarbonyl derivative **4b** is suitable for linking appropriate biomolecules. The construction of a linking group was achieved by conversion of **4b** *via* carboxylic acid **9** to the reactive *O*-succinimide ester **10**, which reacts easily with amino acids or peptides to amides **11** and **12**. The fluorescent properties were investigated and are comparable with derivatives of **1**.

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INTRODUCTION

Coumarins and carbostyrils with push-pull systems are studied extensively as fluorescent dyes [1]. However, many carbostyrils (2-quinolones) show disadvantages in luminescence properties compared with coumarins because of shorter absorption and emission wavelengths [2]. Recently, we reported a series of studies about the fluorescence properties of differently substituted carbostyrils [3] with suitable structure elements which shifted the wavelengths up to 440 nm absorption and 540 nm emission maxima. These structure elements were electron donating substituents such as amino or methoxy groups in both positions 6 and 7 and an electron deficient substituent in position 4. Such properties make this compound class also interesting for the use in sensor and electroluminescence devices [4,5]. The advantage of 3,4-dimethoxycarbostyril derivatives was shown recently in their use as fluorescence resonance energy transfer systems [6], in the study of luminescence resonance transfer techniques [7a] and incorporated in a time resolved pH sensor as covalently attached europium complex [7b].

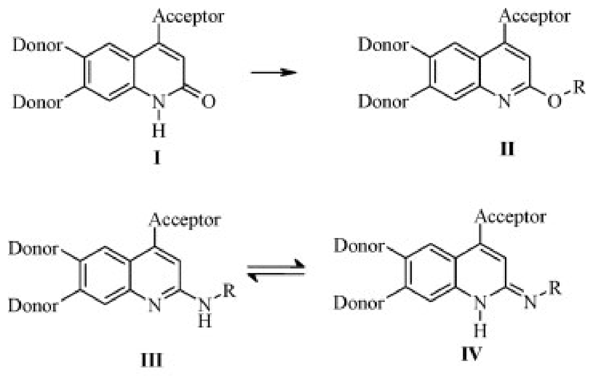
In our earlier articles [3a–f], we described the synthesis of highly fluorescent push-pull substituted carbostyrils (type **I**) with donor substituents at positions 6 and 7 and acceptor substituents at position 4 having widely pH independent properties, large Stokes shifts and medium to high-quantum yields. The functionalization to *O*-succinimidyl (OSu) esters at N-1 and 6-O and labelling of biopolymers such as peptides and carbohydrates was carried out without any blue-shift, resulting in absorbing close to the visible range and emitting in aqueous solution at 430–450 nm, suitable for biochemistry and medicine.

After the variation of substituents at positions 4, 6, and 7, we report in this article about the investigation on the synthesis and properties of 2-aminoquinolines **III**[3g]. In contrast to type **II** structures [3b], 2-aminoquinolines **III** have a possible tautomeric 2-imino structure **IV** as potential fluorescent compounds (Scheme 1).

RESULTS AND DISCUSSION

For our study, we selected 6,7-dimethoxy-4-trifluoromethyl-2-quinolone **1** as the starting compound, with methoxy groups as the donor and a trifluoromethyl group as the acceptor substituents. The synthesis of the carbostyril ring system was achieved by cyclocondensation of 3,4-dimethoxyaniline with trifluoro-methyl-acetoacetate as described recently [3b,c]. The conversion of the 2-oxo group to the reactive 2-chloro moiety in compound **2** was achieved with phosphoryl chloride. Conventional heating required a reaction time of 12 h and produced many by-products. The application of

Scheme 1



Acceptor substituents: e.g. CF_3, CN
Donor substituents: e.g. MeO, RNH

microwave heating allowed the isolation of chloroquinoline **2** after 30 min with similar yields but better purity (Scheme 2).

The conversion of the 2-chloro group in **2** to a free 2-amino group was achieved in a three step reaction by exchange of the 2-chloro substituent against the 2-azido group in dimethylformamide at 80°C using Kryptofix-5 as catalyst, to give 2-azidoquinoline **6**. According to IR spectra the azide **6A** exists predominantly in its tautomeric tetrazolo structure **6T** similar as shown in many investigations [8]. The Staudinger reaction with triphenylphosphane gave the corresponding phosphazene **7**, which is hydrolyzed by acid catalysis with hydrochloric acid in water/methanol to give the free 2-aminoquinoline **8** in an overall yield of about 67%. The aminoquinoline **8**, however, did not show sufficient fluorescent properties for further applications, probably caused by the predominant tautomeric amino-structure of type **III**, so this way was not continued.

On the other hand, 2-arylamino and 2-benzyl-aminoquinolines **4a-c** and **5**, which were obtained from the 2-chloro derivative with the appropriate anilines **3a-c** or benzylamine in a one step reaction in 62–66% yield, showed good fluorescence properties (possibly deriving from the formation of a tautomeric imino structure in the state of fluorescence excitation); see Table 1. Surprisingly, the benzylamino derivative **5** showed similar fluorescence properties as the arylamino derivatives **4**, which means, that the influence of the aryl group attached to the 2-amino group (forming an azomethine-type structure as imino tautomer) has no remarkable influence on luminescence properties. However, products with substituted benzylamines were not stable enough for further investigation (Scheme 3).

Spectral assignment of **4** and **5** to an amino- or imino-structure was not possible, because differences caused by solvent influences are strong and the ^{1}H NMR signals of NH ranged between 5.2 and 10.9 ppm with chloroform as the solvent.

Using suitable substituted derivatives such as 4-(2-quinolinylamino)benzoate **4b** (R^2 = COOEt) allowed the introduction of linker groups attached at the phenyl ring at the amino/imino-position 2. For the construction of linker groups to aminogroups of natural products, a reactive *O*-succinimide ester (OSu-ester) was planned because OSu-esters attached to heterocycles are known to be easily available, stable, and useful to link to biological samples. The synthesis was achieved by saponification of the ethyl ester group of **4b** to the free carboxylic acid **9** in ethanolic sodium hydroxide solution, and re-esterification with *N*-hydroxysuccinimide in the presence of carbodiimide, which gave the active OSu ester **10** in good yields.

The OSu ester **10** reacted smoothly under biological conditions in buffered aqueous DMSO solution below 50°C with biomolecules such as aminoacids and peptides. We synthesized two fluorescence marked

Scheme 2

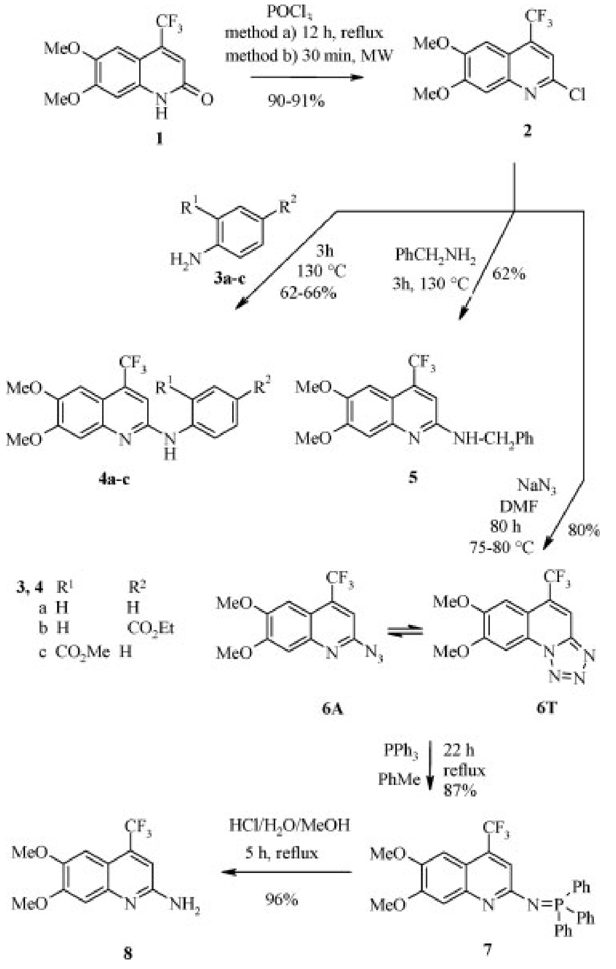


Table 1

Photophysical data for UV spectra, the electronic excitation (exc), and fluorescence (flu) of carbostyrils **4–12**.

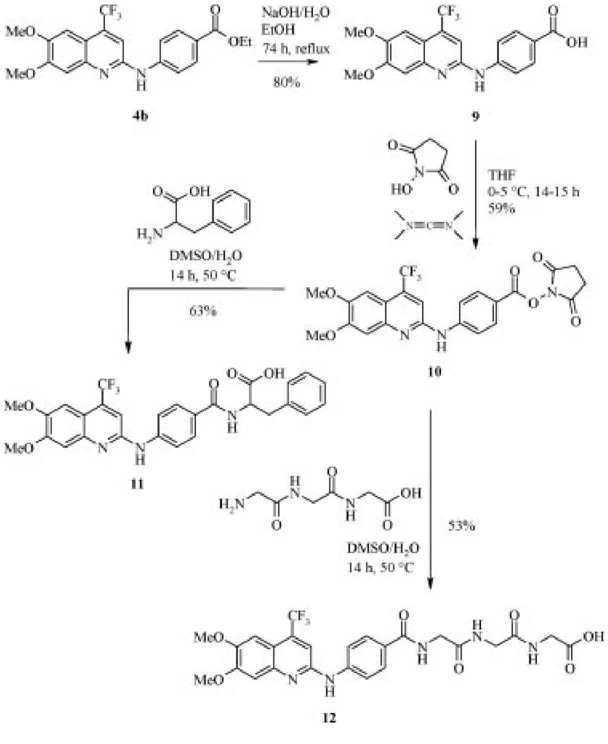
No.	UV (λ_{max})	ε	λ_{exc}[a]	λ_{flu}	Stokes shift	Φ_F
4a	384	9500	380	450	70	0.152
4b	392	13400	380	433	53	0.100
4c	398	18000	394	440	46	0.182
5	375	8600	380	440	60	0.297
9	391	10200	380	433	53	0.072
10	393	9900	380	417	37	0.100
11	393	9900	380	432	52	0.060
12	392	9000	378	433	53	0.033

Solvent: DMSO, Solvent temperatures: 25 °C; λ in nm.
[a] Wavelength of excitation.

examples, the phenylalanine derivative **11** and the glycyl-glycyl-glycin **12** linked at the amino group of the amino acid with the linker molecule.

Electronic spectra. Absorption spectra of recently synthesized 4-(trifluoromethyl)carbostyrils [3b,c] were rather similar with $\lambda_{max} \sim$ 350–380 nm in DMSO or water; there was also no great difference between NH- and N-alkyl derivatives, which means, that in all cases the tautomeric amide group (N1-C2) of structure **I** is predominant. In the 2-amino/imino series (structures **III**/**IV**) comparable absorption wavelengths were obtained (Table 1): The UV wavelengths are slightly higher (375–398 nm), the Stokes' shifts are in the region 50–70 nm. However, the fluorescence quantum yields, which were high for any N1-alkylated analyte of type **I** [3b,c], decreased from $\Phi_F = 0.1$ in the ester **4b** to $\Phi_F = 0.03$–0.06 in linked 2-amino analogues **11**,**12**. Ester **4c** shows a higher ε value because of the asymmetric structure, which causes changes in dipole properties.

Scheme 3



CONCLUSION

We could show that the conversion of the carbostyril **1** to its 2-aza analogues **4** and **5** can be achieved in good yields to obtain subsequently OSu ester **10** with comparable fluorescence spectral properties, however, with too low-quantum yield values for the use in analytical tasks. From the 6,7-dimethoxy-4-(trifluoro-methyl)-carbostyril series until now investigated, only N1-alkylated carbostyrils of structure type **I** [3c] gave quantum yields high enough for this purpose.

EXPERIMENTAL

Melting points were determined using a Stuart SMP3 Melting Point Apparatus in open capillary tubes. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX 360 instrument (360 or 90 MHz) or on a Bruker Avance DRX 500 instrument (500 or 125 MHz). Chemical shifts are given in ppm (δ) from the internal TMS standard. IR spectra were recorded using a Mattson Galaxy Series FTIR 7020 instrument with potassium bromide discs. Elemental analyses were performed at the Microanalytical Laboratory of the University of Vienna, Austria. Mass spectra were obtained from a HP 1100 LC/MSD mass spectral instrument (positive or negative APCI ion source, 50–200 V, nitrogen). UV/Vis spectra were recorded on a Shimadzu UV/Vis scanning spectrophotometer UV-2101 PC; concentration: 0.01 mg/mL. Excitation and emission spectra were recorded using a Shimadzu RF-5001 PC spectrofluorometer, concentration: 0.001 mg/mL. Determination of quantum yields: emission signals were set in relation to the known signal of quinine sulfate at pH 1. Analytical HPLC was performed on a Shimadzu LC 20 system equipped with a diode array detector (215 and 254 nm) on a Pathfinder AS reversed phase (4.6150 mm, 5 μm) column, running an acetonitrile/water gradient (30–100% acetonitrile).

Microwave-assisted syntheses were carried out in an Emrys Synthesizer at 2450 MHz (Biotage AB, Uppsala). All reactions were monitored by thin layer chromatography (TLC) on 0.2-mm silica gel F-254 (Merck) plates using UV light (254 and 366 nm) for detection. Common reagent-grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures. All optical measurements were performed using analytical grade solvents.

2-Chloro-6,7-dimethoxy-4-(trifluoromethyl)quinoline (2)

Method A. A mixture of 6,7-dimethoxy-4-(trifluoromethyl)-quinolone (**1**) [3c] (2.73 g, 10 mmol) and phosphoryl chloride (7.60 g, 50 mmol) was heated under reflux for 12 h. The reaction mixture was cooled to room temperature and poured onto crushed ice (250 g) and kept for 30 min. The solid obtained was filtered by suction, washed with excess of water to afford 2.65 g (91% yield) of colorless needles.

Method B. A mixture of 6,7-dimethoxy-4-(trifluoromethyl)-quinolone (**1**) (0.273 g, 1 mmol) and phosphoryl chloride (3.0 g, 20 mmol) was heated at 120°C for 30 min by microwave irradiation in a sealed tube. After cooling to room temperature, the reaction mixture was worked up as described in method A. The yield was 0.260 g (90%), colorless needles, m.p. 134–136°C (ethanol); IR: 3468 m, 2978 w, 1619 m, 1593 m cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 4.05 (2 s, 6H, 2 OMe), 7.29 (s, 1H, 3-H), 7.43 and 7.56 (2 s, 2H, ArH); *Anal.* Calcd. for $C_{12}H_9ClF_3NO_2$ (291.66): C, 49.42; H, 3.11; N, 4.80; Found C, 49.21; H, 2.90; N, 4.58.

6,7-Dimethoxy-*N*-phenyl-4-(trifluoromethyl)quinolin-2-amine (4a). A mixture of 2-chloroquinoline **2** (0.291 g, 1 mmol) and aniline (**4a**) (0.186 g, 2 mmol) was heated for 3 h to 130°C. The reaction mixture was cooled to room temperature, the formed solid filtered and digested with diethylether (100 mL). The ether solution was taken to dryness under reduced pressure and the oily residue purified by dry flash column chromatography [9] using toluene as the eluent. The yield was 0.230 g (66%), pale yellow needles, m.p. 147–148°C (ethanol); IR: 3438 m, 3385 s, 1630 m, 1618 m, 1599 m cm^{-1}, ^{1}H NMR (CDCl$_3$): δ 4.00 and 4.03 (2 s, 6H, 2 OMe), 6.92 (s, b, 1H, 2-NH), 7.11–7.17 (m, 2H, ArH), 7.21–7.27 (m, 2H, ArH), 7.38 (t, *J* = 7.5 Hz, 2H, ArH), 7.54 and 7.57 (2 s, 2H, ArH);*Anal.* Calcd. for $C_{18}H_{15}F_3N_2O_2$ (348.33): C, 62.07; H, 4.34; N, 8.07; Found C, 62.02; H, 4.16; N, 7.95.

Ethyl 4-{[6,7-dimethoxy-4-(trifluoromethyl)quinolin-2-yl]amino}benzoate (4b). A mixture of 2-chloroquinoline **2** (2.91 g, 10 mmol) and ethyl 4-aminobenzoate (**3b**) (3.30 g, 20 mmol) was heated for 3 h to 130°C. The reaction mixture was cooled to room temperature, the formed solid filtered by suction, washed with ethanol (100 mL), and dried. The yield was 2.85 g (65%), yellow needles, m.p. 210–211°C (ethanol); IR: 3357 s, 3215 m, 2926 m, 1682 s, 1619 m, 1602 s cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.39 (t, *J* = 7.5 Hz, 3H, Me), 4.02 and 4.07 (2 s, 6H, 2 OMe), 4.35 (q, *J* = 7.1 Hz, 2H, CH$_2$), 6.96 (s, 1H, NH), 7.16 (s, 1H, ArH), 7.24 (s, 1H, ArH), 7.29 (s, 1H, ArH), 7.73 (d, *J* = 7.5 Hz, 2H, ArH), 8.07 (d, *J* = 7.5 Hz, 2H, ArH); MS: *m*/*z* (%) = 421 (21, M + 1), 420 (100, M$^+$);*Anal.* Calcd. for $C_{21}H_{19}F_3N_2O_4$ (420.39): C, 60.00; H, 4.56; N, 6.66; Found C, 59.92; H, 4.28; N, 6.65.

Methyl 2-{[6,7-dimethoxy-4-(trifluoromethyl)quinolin-2-yl]amino}benzoate (4c). A mixture of 2-chloroquinoline **2** (0.291 g, 1 mmol) and methyl anthranilate (0.302 g, 2 mmol) was heated for 3 h to 130°C. The mixture was cooled, the formed solid filtered by suction, washed with ethanol (100 mL), and dried. The yield was 0.252 g (62%), yellow needles, m.p. 188–189°C (ethanol); IR: 3266 m, 1684 s, 1601 m, 1570 w, 1536 m cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 3.97, 4.02, and 4.07 (3 s, 9H, 3 OMe), 6.98 (t, *J* = 8.3 Hz, 1H, ArH), 7.17 (s, 1H, ArH), 7.24 (s, 1H, ArH), 7.33 (s, 1H, ArH), 7.60 (t, *J* = 8.1 Hz, 1H, ArH), 8.07 (d, *J* = 8.3 Hz, 1H, ArH), 9.19 (d, *J* = 8.6 Hz, 1H, ArH), 10.96 (s, 1H, NH); MS: *m*/*z* (%) = 407 (20, M + 1), 406 (100, M), 375 (15), 374 (33); *Anal.* Calcd. for $C_{20}H_{17}F_3N_2O_4$ (406.36): C, 59.12; H, 4.22; N, 6.89; Found C, 58.83; H, 4.56; N, 6.54.

***N*-Benzyl-6,7-dimethoxy-4-(trifluoromethyl)quinolin-2-amine (5).** A mixture of 2-chloroquinoline **2** (0.291g, 1 mmol) and benzylamine (0.214 g, 2 mmol) was heated for 3 h to 130°C. The reaction mixture was cooled to room temperature, the formed solid filtered, dissolved in water (100 mL), and brought to pH 13 with conc. aq. sodium hydroxide solution. The aqueous solution was extracted with diethylether (3 × 30 mL), the ether solution taken to dryness under reduced pressure and the oily product purified by dry flash column chromatography [9] using toluene as eluent. The yield was 0.224 g (62%), pale yellow needles, m.p. 98–99°C (ethanol); IR: 3435 s, 3253 m, 1632 s, 1514 m cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 3.98 and 4.02 (2 s, 6H, 2 OMe), 4.71 (d, *J* = 5.8 Hz, 2H, CH$_2$), 5.04 (s, 1H, NH), 6.84 (s, 1H, ArH), 7.18 (s, 2H, ArH), 7.31–7.43 (m, 5H, PhH); MS: *m*/*z* (%) = 363 (25, M + 1), 362 (100, M), 361 (12, M − 1), 272 (8); *Anal.* Calcd. for $C_{19}H_{17}F_3N_2O_2$ (362.35): C, 62.98; H, 4.73; N, 7.73; Found C, 62.79; H, 4.57; N, 7.72.

7,8-Dimethoxy-5-(trifluoromethyl)tetrazolo[1,5-a]quinoline (6). A suspension of 2-chloroquinoline **2** (0.291 g, 1 mmol), sodium azide (0.260 g, 4 mmol), and Kryptofix-5 (0.01 g) in dimethylformamide (7 mL) was heated under TLC monitoring for about 80 h to 75–80°C. Then the mixture was cooled to room temperature and poured into ice/water (100 mL), the formed solid filtered by suction and washed with cold water (100 mL). The yield was 0.240 g (80%), brownish needles, m.p. 237–239°C (ethanol); IR: 1617 w, 1528 m, 1505 w cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 4.08 and 4.18 (2 s, 6H, OMe), 7.51 (s, 1H, ArH), 8.18 (s, 1H, ArH), 8.23 (s, 1H, ArH); MS: *m*/*z* (%) = 299 (14, M + 1), 298 (100, M), 272 (13); *Anal.* Calcd. for $C_{12}H_9F_3N_4O_2$ (298.23): C, 48.33; H, 3.04; N, 18.79; Found: C, 48.08; H, 3.01; N, 18.48.

6,7-Dimethoxy-4-(trifluoromethyl)-*N*-(triphenylphosphoranylidene)quinolin-2-amine (7). A mixture of tetrazolo[1,5-a]quinoline **6** (0.298 g, 1 mmol), and triphenylphosphane (0.524 g, 2 mmol) in toluene (8 mL) was heated under TLC monitoring for about 22 h under reflux. The solvent was removed under reduced pressure and the oily residue triturated with cyclohexane. The formed solid was filtered by suction, and washed with cyclohexane until the excess of triphenylphosphane was removed. The yield was 0.260 g (87%), brownish prisms, m.p. 183–184°C (methanol); IR: 1606 m, 1509 m cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 3.88 and 3.93 (2 s, 6H, 2 OMe), 6.67 (s, 1H, ArH), 7.14 (s, 1H, ArH), 7.37 (s, 1H, ArH), 7.44–7.48 (m, 6H, ArH), 7.52–7.56 (m, 3H, ArH), 7.86–7.92 (m, 6H, ArH); *Anal.* Calcd. for $C_{30}H_{24}F_3N_2O_2P$ (532.51): C, 67.67; H, 4.54; N, 5.26; Found: C, 67.94; H, 4.65; N, 5.06.

6,7-Dimethoxy-4-(trifluoromethyl)quinolin-2-amine (8). A mixture of *N*-(triphenylphosphoranylidene)quinolin-2-amine **7**

(0.532 g, 1 mmol) and conc. hydrochloric acid (7 mL) in methanol (8 mL) was heated under TLC monitoring for 5 h under reflux. The reaction mixture was cooled to room temperature, the formed solid filtered by suction and washed with excess of water until pH of 7 was reached. The yield was 0.262 g (96%), yellowish green crystals, m.p. 283–284°C (ethanol); IR: 3345 s, 3090 s, 1680 s, 1647 m, 1618 w, 1520 m cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.87 and 3.94 (2 s, 6H, OMe), 7.09 (s, 1H, ArH), 7.32 (s, 1H, ArH), 7.38 (s, 1H, ArH), 8.62 (s, b, 2H, NH$_2$); *Anal.* Calcd. for $C_{12}H_{11}F_3N_2O_2$ (272.23): C, 52.95; H, 4.07; N, 10.29; Found: C, 52.65; H, 3.78; N, 10.02.

4-{[6,7-Dimethoxy-4-(trifluoromethyl)quinolin-2-yl]amino}benzoic acid (9). A mixture of 4-(quinolin-2-yl)aminobenzoate **4b** (0.420 g, 1 mmol) and 1*M* aq. sodium hydroxide solution (2 mL) in ethanol (20 mL) was heated for 7 h under reflux, then the solvent was removed under reduced pressure and the residue dissolved in water (10 mL) under cooling. The mixture was acidified with conc. hydrochloric acid to pH = 1–2, the resulting precipitate filtered by suction and washed with excess of water. The yield was 0.310 g (80%), yellow prisms, m.p. 275–276° C (ethyl acetate); IR: 3457 s, 2940 w, 1677 s, 1624 w, 1600 s, 1526 s cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.87 and 3.96 (2 s, 6H, 2 OMe), 7.10 (s, 1H, ArH), 7.36 (s, 1H, ArH), 7.38 (s, 1H, ArH), 7.91 (d, *J* = 8.6 Hz, 2H, ArH), 8.04 (d, *J* = 8.6 Hz, 2H, ArH), 9.95 (s, 1H, NH), 12.54 (s, 1H, OH); MS: *m*/*z* (%) = 393 (18, M + 1), 392 (100, M), 377 (12); *Anal.* Calcd. for $C_{19}H_{15}F_3N_2O_4$ (392.34): C, 58.17; H, 3.85; N, 7.14; Found: C, 57.82; H, 3.76; N, 7.00.

1[(4-{[6,7-Dimethoxy-4-(trifluoromethyl)quinolin-2-yl]amino}benzoyl)oxy]pyrrolidine-2,5-dione (OSu-ester) (10). *N*-Hydroxysuccinimide (0.115 g, 1 mmol) was added slowly with stirring at 0°C to a solution of 4-(quinolin-2-yl)amino-benzoic acid **9** (0.392 g, 1 mmol) in dry tetrahydrofuran (20 mL). Then *N*,*N*-diisopropylcarbodiimide (0.125 g, 1 mmol) was added dropwise with stirring at 0–5°C which formed a yellowish-white precipitate. This mixture was stirred further at 0–5°C for 14–15 h. The solvent was removed under reduced pressure and the solid residue obtained was digested in dry tetrahydrofuran (10 mL), filtered and washed well with dry tetrahydrofuran. Then the solid was stirred in dry ethanol (50 mL) at room temperature for 30 min to remove *N*,*N*-diisopropylurea formed during the reaction. Suction filtration afforded 0.288 g (59%) of OSu-ester, pale yellow prisms, m.p. 268–269°C (ethanol); IR: 3435 s, 3340 s, 3212 m, 1765 s, 1723 s, 1618 w, 1598 s, 1578 w cm^{-1};^{1}H NMR (CDCl$_3$): δ 2.93 (s, 4H, 2 CH$_2$), 4.03 and 4.09 (2 s, 6H, 2 OMe), 7.22 (s, 1H, ArH), 7.25 (s, 1H, ArH), 7.33 (s, 1H, ArH), 7.77 (d, *J* = 8.4, 2H, ArH), 8.16 (d, *J* = 8.6, 2H, ArH); MS: *m*/*z* (%) = 490 (25, M + 1), 489 (100, M), 392 (10); *Anal.* Calcd. for $C_{23}H_{18}F_3N_3O_6$ (489.41): C, 56.45; H, 3.71; N, 8.59; Found: C, 56.44; H, 3.89; N, 8.30.

***N*-(4-{[6,7-Dimethoxy-4-(trifluoromethyl)quinolin-2-yl]amino}benzoyl)phenylalanine (11).** To a solution of (D,L)phenylalanine (38 mg, 0.2 mmol) in dimethyl-sulfoxide/water (9:1, 2.5 mL), a solution of OSu-ester **10** (98 mg, 0.2 mmol) in dimethylsulfoxide/water (9:1, 2.5 mL) was added dropwise at room temperature. Then aq. pH 7 buffer (0.75 mL) was added, the mixture stirred for 14 h at 50°C, poured into water (25 mL) and then acidified with conc. hydrochloric acid to pH = 1–2. A solid separated, which was filtered by suction and washed with excess of water to afford 85 mg (63%) of yellow prisms, m.p. 272–273°C (acetone); IR: 3366 w, 2933 m, 1647 w, 1625 w, 1603 s, 1575 w cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 3.33 and 3.41 (2 dd, *J* = 5.7 and 13.9 Hz, 2H, CH$_2$), 3.99 and 4.05 (2 s, 6H, 2 OMe), 5.09 (dd, 5.8 and 6.7 Hz, 1H, CH), 6.87 (d, *J* = 5.9 Hz, 1H, amide-NH), 7.18–7.24 (m, 6H, ArH), 7.30 and 7.33, (2 s, 2H, ArH), 7.37 (d, *J* = 8.2 Hz, 2H, ArH), 7.75 (d, *J* = 8.3 Hz, 2H, ArH), 10.20 (s, 1H, 2-NH); MS: *m*/*z* (%) = 541 (11, M + 2), 540 (47, M + 1), 539 (100, M), 538 (35, M − 1), 391 (14); *Anal.* Calcd. for $C_{28}H_{24}F_3N_3O_5$ (539.52): C, 62.34; H, 4.48; N, 7.79; Found C, 61.91; H, 4.37; N, 7.63.

***N*-(4-{[6,7-Dimethoxy-4-(trifluoromethyl)quinolin-2-yl]amino}benzoyl)glycylglycylglycine (12).** To a solution of glycylglycyl-glycine (38 mg, 0.2 mmol) in dimethyl-sulfoxide/water (9:1, 2.5 mL), a solution of OSu-ester **10** (98 mg, 0.2 mmol) in dimethylsulfoxide/water (9:1, 2.5 mL) was added dropwise at room temperature. Then aq. pH 7 buffer (0.75 mL) was added, the mixture stirred for 14 h at 50°C, poured into water (25 mL), and then acidified with conc. hydrochloric acid to pH = 1–2. A solid separated, which was filtered by suction and washed with excess of water to afford 75 mg (53%) of yellow prisms, m.p. 238–239°C (acetone); IR: 3338 s, 3306 s, 3117 m, 3088 m, 2961 w, 2925 m, 1721 s, 1662 s, 1625 w, 1605 s, 1568 w, 1531 s cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.76–3.78 (m, 4H, 2 CH$_2$), 3.87 (s, 3H, OMe), 3.90 (d, *J* = 5.4 Hz, 2H, CH$_2$), 3.97 (s, 3H, OMe), 7.11 (s, 1H, ArH), 7.35 and 7.39 (2 s, 2H, ArH), 7.88 (d, *J* = 8.6 Hz, 2H, ArH), 8.01 (d, *J* = 8.3 Hz, 2H, ArH), 8.17–8.24 (m, 2H, amide-NH), 8.64 (t, *J* = 5.3 Hz, 1H, amide-NH), 9.91 (s, 1H, 2-NH); MS: *m*/*z* (%) = 564 (14, M + 1), 563 (42, M), 507 (17), 450 (25), 449 (100), 392(85); *Anal.* Calcd. for $C_{25}H_{24}F_3N_5O_7$ (563.49): Calcd. C, 53.29; H, 4.29; N, 12.43; Found C, 53.63; H, 4.29; N, 12.56.

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From DMF to Isatine: A Novel and General One-Pot Synthesis of Isatine and Its N-Unsubstituted Derivatives *via* Nucleophilic Substitution Reactions on 1,2-Bis(dimethylamino)-1,2-dichloroethene

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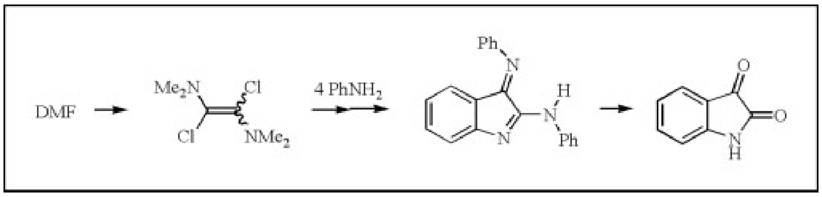

3-Imino-2-amino-isatines were obtained by a one-pot reaction of an excess of aniline (or its derivatives) with 1,2-bis(dimethylamino)-1,2-dichloro-ethene (prepared *in situ* from DMF). Subsequent hydrolysis yielded the corresponding isatine derivatives in reasonable to high yields. DFT calculations with regard to the mechanisms of this reaction sequence are presented.

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INTRODUCTION

Isatine **4** and its derivatives play an important role in the pharmaceutical and dye industry. Drugs containing isatine units cure diseases such as epilepsy [1], tuberculosis [2], and bulimia [3]. Isatin derivatives are furthermore employed as antibacterial [4] or antifugal [5] compounds or to treat inflammations [6].

Because of its importance, various synthetic routes to isatine and its derivatives have been developed. Although the large-scale synthesis of unsubstituted isatine is accomplished by oxidation of indigo [7], several methods are known for the preparation of isatine derivatives on the laboratory or pharmaceutical scale. Among these are the classical methods by Sandmeyer [8] and Gassman and von Bergen [9] as well as a more recent methodology developed by Meth-Cohn and Goon [10], the latter of which is restricted, however, to *N*-methyl isatines. Yet, most of these methods involve harsh conditions, expensive chemicals, and require multiple steps, including the isolation of several intermediates.

In the course of our investigations of nucleophilic substitution reactions on 1,2-bis(dimethylamino)-1,2-bisonio-ethenes [11], we have developed a new versatile one-pot synthesis of N-unsubstituted isatine derivatives, starting from the common solvent DMF and involving mostly customary chemicals, as described in more detail below.

RESULTS AND DISCUSSION

In the early 1980s, Boehme and Sutoyo [12] reported on the dimerization of deprotonated chlorochlorides deriving from DMF (and other formamides), yielding 1,2-bis(dimethylamino)-1,2-dichloro-ethene **1** (Scheme 1).

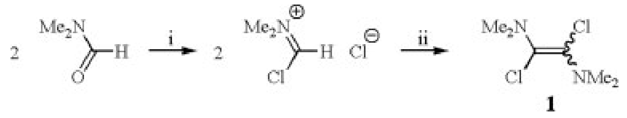
We found that treatment of a solution of **1** in THF with an excess of aniline did not result in the formation of the anticipated tetraaminoethene **2** (Scheme 2). Instead the known [13] isatine derivative **3** was isolated after stirring the reaction mixture for 24 h at room temperature and subsequent exposure to aerial oxygen. Apart from spectroscopic data, the structure of **3** was further confirmed by single-crystal X-ray crystallography, which was in perfect agreement with the already published structural analysis of **3** [14].

Indole derivative **3** could be isolated in 65% yield over all steps (*i.e*., based on the amount of DMF used) by simple recrystallization from ethanol. Hydrolysis of **3** to isatine **4** could be achieved by treating **3** with conc. HCl in glacial acetic acid (yield: 71 %) [15]. Thus, a novel synthetic route to isatine **4** from DMF could be developed, which requires only the isolation of intermediate **3** *via* recrystallization (as ethene **1** can be prepared from DMF in a one-pot reaction and can be treated *in situ* with aniline to give the isatine precursor **3**).

To examine the range of application of our method, we reacted several aromatic amines of different electronic nature with ethene **1**. Results are shown in Table 1.

In all cases, the corresponding N-unsubstituted isatines **4a–g** could be obtained by recrystallization from ethanol. Although reaction conditions were not specifically optimized for the different aniline derivatives, reasonable overall yields (based on the amount of DMF) could be achieved in most cases. Still higher yields

Scheme 1. Synthesis of **1** by deprotonation of a chlorochloride derived from DMF; (i) $C_2O_2Cl_2$, 0 °C and (ii) Hünig's base ($NEt\mathit{i}Pr_2$).

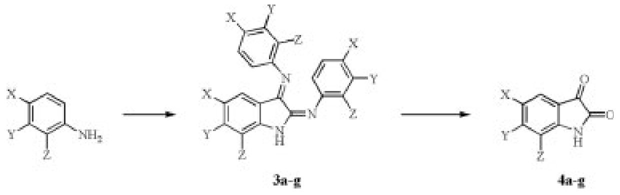


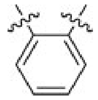
should be within reach by further optimization of the reaction procedure. Based on these (few) orientating experiments, no definitive statement can be made concerning the influence of the various substituents X, Y, and Z on the overall yield. It seems, though, that the presence of electron-withdrawing groups leads to a lower yield of the corresponding intermediate of type **3**. This would be in accordance with the reaction mechanism proposed below. Yet, in our experiments we also observed that addition of the bromo- and fluoro-substituted aniline derivatives to a solution of ethene **1** resulted in a stronger increase of temperature and a faster optical change of the solution (compared with the other derivatives).

In contrast, when adding *N*-methyl aniline to a solution of **1**, no indications of such a cyclization reaction could be observed. Instead, the corresponding bis(dimethylamino)-bis(methyl-phenylamino)-ethene was detected by mass spectrometry (as well as its bis-oxidized form). Obviously, both chloro-substituents had been substituted by *N*-methyl aniline. Thus, only primary anilines are applicable for the synthesis of isatine derivatives according to our new method. A possible reason for this limitation is given below. In the case of secondary aniline derivatives, it should in principle be possible to isolate the corresponding tetraamino-ethenes (*cf.* Scheme 2).

Table 1

Synthesis of isatine derivatives **3a–g** and isatines **4a–g**.



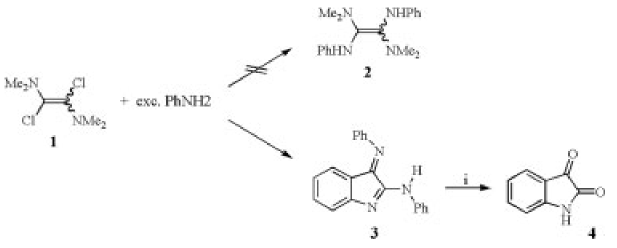
	X	Y	Z	**3** (%)[a]	**4** (%)[b]
a	H	H	H	65	71
b	CH_3	H	H	25	68
c	OCH_3	H	H	65	66
d	H	Br	H	18	93
e	F	H	H	28	85
f	$COOCH_3$	H	H	–	10
g	H			–	31

[a] Yields for **3a–g** are based on the amount of DMF.

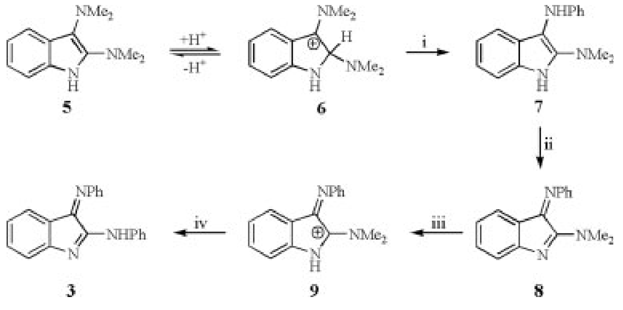
[b] Yields for **4a–e** are based on the amount of **3a–e** and for **4f,g** on the amount of DMF, as intermediates **3f,g** were not isolated.

During the course of our investigations, some intermediates could be detected, which shed some light on the mechanism of the formation of **3** from ethene **1**. It was observed that a clear, red solution of **3** in THF was only obtained after exposure of the reaction mixture to aerial oxygen. Under inert gas conditions, addition of aniline to ethene **1** resulted in an orange suspension. Although the solid compound could be isolated, it proved to be very sensitive to oxygen and could not be characterized by NMR spectroscopy. Its mass spectrum, however, showed a peak at $m/z = 252$, in accord with structure **7** (Scheme 3). When the colorless solid was dissolved in CH_2Cl_2 and stirred on air, the solution turned red rapidly. Apparently, oxidation to **8** had taken place, as evidenced by a mass peak at $m/z = 250$ (substitution at position C2 of the heterocycle can be ruled out due to the fact that its oxidation would produce an anti-aromatic intermediate). Compound **8** could be isolated and characterized by NMR spectroscopy. As expected, its methyl groups show a coalescence phenomenon at about −10°C. Incidentally, analogous compounds could also be detected during the preparation of

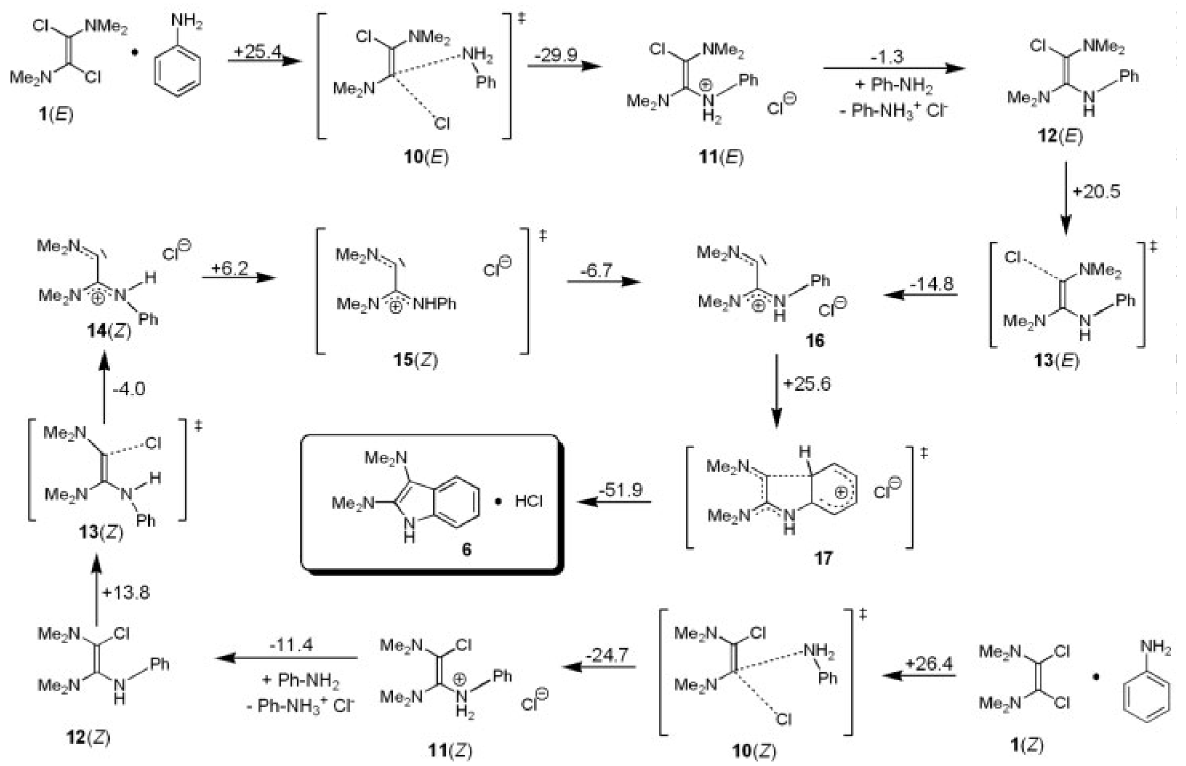
Scheme 2. Reaction of **1** with an excess of aniline; (i) conc. HCl in glacial CH_3COOH.



Scheme 3. Proposed mechanism of the formation of 3 (starting after cyclization to 5) according to experimental hints; (i) + $PhNH_2$, -$HNMe_2$, (ii) oxidation by air, (iii) + H^+, and (iv) + $PhNH_2$, -$HNMe_2$.



Scheme 4



compounds **3d–f**. In the case of compound **3d**, a heterocyclic intermediate containing two dimethylamino groups (analogous to **5** in Scheme 3) could also be detected in the reaction mixture *via* mass spectrometry.

Thus, it seems plausible that the primary product of the ring closure reaction leading to **3**(**a**) is intermediate **5**. After subsequent substitution of the dimethylamino group at C2 by aniline, oxidation by aerial oxygen leads to the (experimentally isolated) compound **8**. Further substitution of the second NMe$_2$ group by aniline finally yields isatine derivate **3**. This mechanism is shown in Scheme 3.

When *N*-methyl aniline instead of aniline is used in the reaction with ethene **1**, the corresponding *N*-methylated intermediate **7** cannot be oxidized *via* formal H$_2$ abstraction, and thus only primary amines are applicable as reactants.

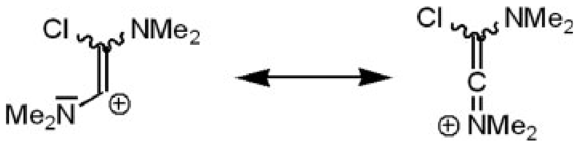
No experimental data could be obtained regarding the mechanisms of the ring closure, ultimately leading to compound **5**. Therefore, DFT calculations were carried out to gain some insight into the first steps of the formation of the isatine derivative from ethene **1**.

Computational section. The reaction sequence starting from ethylene derivative **1** and aniline to yield the isatine derivative **5** includes several mechanistic key steps. To analyze and characterize those steps, DFT-computations were performed using the Gaussian 98W suite of programs (for further details see Supporting Information). Scheme 4 shows the complete reaction path.

The first key step of the reaction sequence is the substitution of chloride in **1** by aniline. In principle such substitutions at vinyl-like carbon centres can proceed in two different ways: (a) *via* an addition/elimination mechanism under formation of an intermediate in analogy to the S$_N$Ar mechanism (subsequently called **A**) or (b) *via* an elimination/addition mechanism in analogy to the S$_N$1 mechanism (subsequently called **B**) [16,17]. Reactions according to **A** were found for ethylene derivatives carrying strong electron withdrawing substituents. In contrast, ethylene derivatives with electron donating substituents show reactions according to **B**. Ethylene derivative **1** has two –I-acceptor substituents (chlorine) and two donor substituents (NMe$_2$). Hence, in principle both alternative mechanisms are to be considered. Because **1** is synthesized *in situ*, a mixture of the *E*- and *Z*-isomer enters the reaction sequence (this problem will be addressed later). Both forms need to be analyzed computationally.

Because of the gas phase conditions in the computations, the formation of ions (as in **B**) will not be favored. Hence, the corresponding reaction barriers should be overestimated in comparison to the real

Scheme 5. Partial formation of ketene-iminium structure in the transition state.



substitution conditions in polar solvents. Even with this handicap, the reaction barrier in **B** was found to be 26.4 kcal/mol for the *Z*-form and 25.4 kcal/mol for the *E*-isomer. A reaction according to **A**, or alternatively *via* a S_N2-in-plane mechanism, could not be determined computationally, but the corresponding reaction barrier was found to be at least 50 kcal/mol for both isomers. NBO analyses of the corresponding transition structures clearly explain this result. The cation in **10**, formed by elimination of chloride from **1**, is stabilized by partial formation of a ketene-iminium structure (*cf.* Scheme 5). The electron distribution of the N—C—π-bond [18] indicates the partial bond formation, whereas the C—C—π-bond is not influenced at all. N—C—C angles are 176° (*Z*-form) and 156° (*E*-form).

The bond lengths between the formally cationic carbon centre and both the chloride ion (351 and 315 pm) and the aniline (355 and 261 pm) indicate the formation of a nearly uncoordinated ketene-iminium-system.

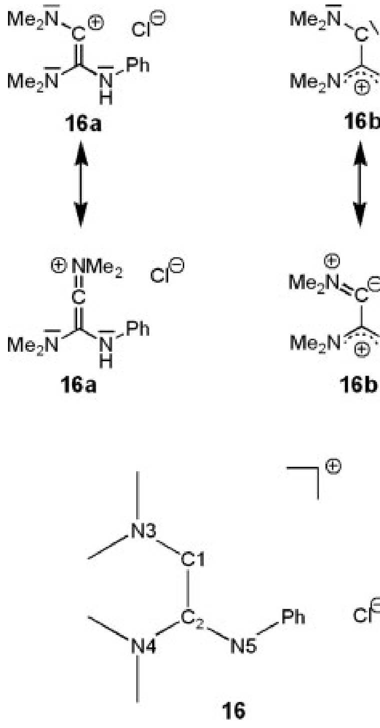
The second key step of the reaction sequence is the substitution of the second chlorine substituent in **12** under formation of the five-ring system **5**. Since **12** carries three donor substituents and only one chlorine substituent, the exchange reaction should proceed *via* the same mechanism as for derivative **1**, or even *via* formation of a ketene-iminium species as an intermediate, and not as a transition structure. Both isomers of **12** can be transformed into the same salt-like structure **16** (*via* transition state **13** (*E*-form) or two transition states **13** and **15**, with one connecting, energetically not favored intermediate **14** (*Z*-form)). This result simplifies the problem of the *E*- and *Z*-isomers because the question of *E* or *Z* does not occur in **16**. The (highest) reaction barrier for this transformation is 21 kcal/mol and the salt **16** is energetically not favored in comparison to **12** (6 kcal/mol for the *E*-isomer, 9 kcal/mol for the *Z*-isomer, respectively). But it should always be taken into account that these energies will be much lower for the experimental reaction due to solvent effects. Those will make structures **12** and **16** energetically at least comparable or even favor the salt **16**. The chloride ion in **16** is stabilized *via* several hydrogen bonds in the gas phase.

Nevertheless, this result brings up another interesting question: What is the electronic nature of **16**? Is this intermediate a cation stabilized *via* a ketene-iminium contribution (**16a**) or must it be seen as a donor–acceptor substituted carbene **16b** (*cf.* Scheme 6) Analysis of bond lengths, bond angles, and tetrahedral angles in context with NBO analysis answers this question (Scheme 6).

The representative bond lengths clearly show that **16** is not a ketene-iminium species. Additionally, NBO analysis identifies a lone pair located at C1 with a hybridization of $sp^{1.65}$ and partial formation of a double bond between C1 and N3 with a density distribution of 26% (C1) and 74% (N3). Hence, the best representation of the nature of **16** is that of a donor–acceptor substituted carbene **16b**, which is stabilized by partial formation of an iminium structure as is shown in Scheme 6.

Because of this electronic nature the subsequent ring formation could occur *via* nucleophilic attack of the carbenes lone pair toward the aniline's π* system or alternatively *via* nucleophilic attack of the aniline's π systems toward to unoccupied orbital of the carbene. The calculated barrier for the ring closure is 25.6 kcal/mol (B3LYP/6-311+G**). NBO analysis of the corresponding transition state **17** shows that the unoccupied orbital at the carbene centre is nucleophilically attacked by the aniline's π system. In the transition state **17**, the new C—C—σ bond starts to form (density distribution: 33% on C1 and 67% on the aromatic centre) and the

Scheme 6. Electronic nature of 16 and geometry at B3LYP/6-311+G**. Selected bond lengths [pm] and angles [°]: C1-C2=146; C1-N3=129; C2-N4=134; C2-N5=135; C2-C1-N3=118; C1-C2-N4=119; C1-C2-N5=122; N4-C2-N5=119; C1-C2-N4-N5=176; N3-C1-C2-N4=107; N3-C1-C2-N5=78.



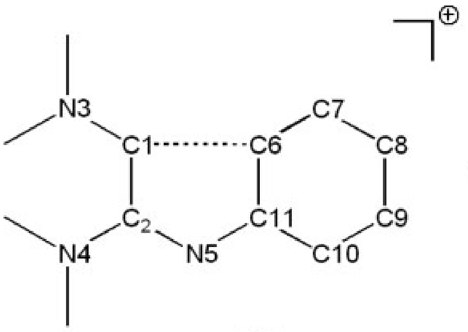
ethylene's C—C—π bond is ''rebuilt'' (density distribution: 46% on C1 and 54% on C2). The C1-N3 double bond, responsible for the partial ''iminium character'' of **16**, is reduced to a distribution of 18% on C1 and 82% on N3. Figure 1 gives representative geometry parameters for **17**.

Retrosynthetical analysis.. Examined from a retrosynthetical point of view, formation of isatine **4** is achieved by the reaction of aniline with C_2O_2 (in combination with an oxidation reaction), which is unstable under normal reaction conditions [19] (Scheme 7). Thus, ethene **1** acts as a synthetic equivalent of C_2O_2.

By substitution of both chloro-substituents of ethene **1**, followed by subsequent oxidation and hydrolysis, the synthesis of further, structurally different diketones appears to be feasible.

CONCLUSIONS

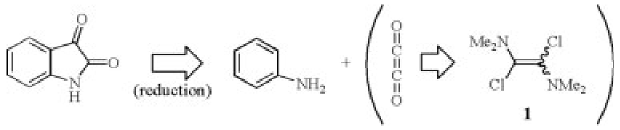
A new synthetic route to *N*-unsubstituted isatines has been presented, which is based on the reaction of ethene **1** with aniline derivatives. The isatine precursors **3a–g** are obtained under mild reaction conditions in a one-pot reaction starting from DMF. Apart from the respective substituted aniline, only standard chemicals such as oxalyl chloride or Hünig's base are employed as reactants, and isolation of the isatine precursors is accomplished by simple recrystallization. In general, reasonable overall yields could be achieved (especially for anilines with electron-donating substituents). Taking all that into account, the method presented in this article shares most of its advantages with the introduced method by Meth-Cohn and Goon [10] but in addition offers the possibility to synthesize N-unsubstituted isatine derivatives. Our method thus seems to have all prerequisites to evolve as a versatile isatine synthesis, especially for small or medium scale amounts.



17

Figure 1. Geometry parameters for **17** (lengths in pm, angles in °): C1-C2=141; C1-N3=132; C1-C6=197; C2-N4=136; C2-N5=137; N5-C11=137; C6-C7=142; C6-C11=142; C7-C8=138; C8-C9=141; C9-C10=139; C10-C11=140; C2-C1-N3=130; C2-C1-C6=95; C1-C2-N4=128; C1-C2-N5=112; N3-C1-N6=118; C1-C2-N4-N5=163; N3-C1-C2-N4=40; N3-C1-C2-N5=157; C2-C1-N3-C6=125; N4-C2-C1-C6=173; N5-C2-C1-C6=24.

Scheme 7. Retrosynthetical analysis.



EXPERIMENTAL

General. All operations in THF were carried out under a dry inert nitrogen atmosphere using standard Schlenk techniques. THF was distilled under nitrogen from sodium-benzophenone. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a Bruker Avance spectrometer. The IR-spectra were taken on Bruker spectrophotometer in KBr pellets. Mass spectra were determined using a Micromass ZabSpec spectrometer. The elemental analyses were obtained on a EA 1110 CHNS analyzer.

General procedure for the preparation of 3a–e. A solution of 0.92 mL (12 mmol) DMF in 25 mL THF was cooled to 0°C, and under inert gas conditions, 1.03 mL (12 mmol) oxalyl chloride was added. After stirring for 2 h at room temperature, the suspension was again cooled to 0°C and a solution of 2.1 mL (12 mmol) Hünig's base (NEt*i*Pr$_2$) was added dropwise. After stirring for 1 h at 0°C and 2 h at room temperature, the precipitate was filtered off, and then 25 mmol of the corresponding aniline was added to the filtrate. After stirring for 16 h at room temperature, aerial oxygen was passed through the solution for several hours. The solvent was evaporated, the residue dissolved in 150 mL CH_2Cl_2 and washed twice with 50 mL H_2O. The organic phase was evaporated to dryness and the residue recrystallized from boiling ethanol.

2-Phenylamino-3-phenylimino-3H-indole 3a. Red solid; ^{1}H NMR ($CDCl_3$): δ = 6.64 (m, 2H, Phen), 7.05 (dd, J = 7.70 Hz, 1.1, 2H, Phen), 7.09 (t, J = 7.70 Hz, 1H, Phen), 7.23 (m, 3H, Phen), 7.42 (m, 4H, Phen), 7.85 (d, J = 7.70 Hz, 2H, Phen), 7.91 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ = 118.9 (CH Phen), 119.3 (CH Phen), 119.6 (C q), 122.8 (CH, Phen), 123.6 (CH, Phen), 125.8 (CH, Phen), 129.4 (CH, Phen), 129.6 (CH, Phen), 134.7 (CH, Phen), 138.5 (C q), 149.0 (C q), 158.3 (C q), 160.4 (C q), 162.9 (C q); IR (KBr): 3337, 164, 1629, 1597, 1574, 1545, 1481, 1440, 1320, 1300, 1244, 1226, 1192, 1146, 902, 785, 755, 715, 690, 582, 532, 509, 494 cm^{-1}; MS (FAB$^+$): *m/z*: 298[M$^+$+1]; elemental analysis calcd for $C_{20}H_{15}N_3$: C 80.78, H 5.08, N 14.13; found C 79.12, H 5.38, N 14.05.

3-(p-Tolylimino)-5-methyl-N-p-tolyl-3H-indole-2-amine 3b. Deep Red solid; ^{1}H NMR ($CDCl_3$): δ = 2.06 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 6.61 (s, 1H, Phen), 6.97 (d, J = 8.17 Hz, 2H, Phen), 7.05 (q, J = 7.81 Hz, 2H, Phen), 7.17 (d, J = 8.17 Hz, 2H, Phen), 7.23 (d, J = 8.05 Hz, 2H, Phen), 7.71 (d, J = 8.42 Hz, 2H, Phen), 7.83 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ = 20.6 (CH_3), 20.8 (CH_3), 118.7 (CH, Phen), 119.1 (CH, Phen), 119.2 (CH, Phen), 119.8 (C q, Phen), 126.2 (CH, Phen), 129.8 (CH, Phen), 130.0 (CH, Phen), 132.0 (C q, Phen), 132.9 (C q, Phen), 134.9 (CH, Phen), 135.6 (C q, Phen),136.2 (C q, Phen), 146.3 (C q, Phen), 158.0 (C q), 160.7 (C q); IR (KBr): 3202, 3025, 2918, 1657, 1602, 1569, 1542, 1511, 1500, 1469, 1449, 1333, 1305, 1248, 1197, 1172, 1101, 1035, 939, 860, 840, 820, 735, 718, 578, 510cm^{-1}; MS (FAB$^+$): m/z: 340[M$^+$+1]; elemental analysis calcd for $C_{23}H_{21}N_3$: C 81.38, H 6.24, N 12.38; found C 80.86, H 6.24, N 12.33.

3-(4-Methoxyphenylimino)-5-methoxy-N-(4-methoxyphenyl)-3H-indol-2-amine 3c. Violet solid; ^{1}H NMR ($CDCl_3$): δ = 3.57 (s, 3H, CH_3), 3.79 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 6.54 (d, J = 2.45 Hz, 1H, Phen), 6.76 (dd, J = 8.43, 2.54 Hz, 1H, Phen), 6.94 (m, 4H, Phen), 7.06 (d, J = 8.95 Hz, 3H, Phen), 7.74 (m, 3H, Phen, NH); ^{13}C NMR ($CDCl_3$): δ = 55.5 (CH_3), 55.6 (CH_3), 112.4 (CH, Phen), 114.4 (CH, Phen), 114.5 (CH, Phen), 118.1 (CH, Phen), 118.8 (CH, Phen), 120.2 (C q, Phen), 120.3 (CH, Phen), 121.0 (CH, Phen), 132.0 (C q, Phen), 141.3 (C q, Phen), 155.2 (C q, Phen), 155.6 (C q, Phen), 156.1 (C q, Phen), 157.5 (C q, Phen), 158.0 (C q), 159.6 (C q); IR (KBr): 3338, 3000, 2946, 2829, 1632, 1608, 1579, 1542, 1506, 1468, 1435, 1299, 1285, 1238, 1212, 1184, 1172, 1132, 1106, 1038, 1024, 879, 852, 823, 801, 771, 739, 636, 589, 503 cm^{-1}; MS (FAB$^+$): m/z: 388[M$^+$+1]; elemental analysis calcd for $C_{23}H_{21}N_3O_3$: C 71.30, H 5.46, N 10.85; found C 70.68, H 5.45, N 10.57.

3-(3-Bromophenylimino)-6-bromo-N-(3-bromophenyl)-3H-indol-2-amine 3d. Red solid; ^{1}H NMR ($CDCl_3$): δ = 6.51 (d, J = 8.24 Hz, 1H, Phen), 6.83 (dd, J = 8.24, 1.65 Hz, 1H, Phen), 6.96 (m, 1H, Phen), 7.22 (m, 4H, Phen), 7.41 (m, 1H, Phen), 7.68 (m, 1H, Phen), 8.06 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ = 117.4 (CH, Phen), 117.7 (C q, Phen), 117.9 (CH, Phen), 121.8 (CH, Phen), 122.2 (CH, Phen), 122.7 (CH, Phen), 122.9 (C q, Phen), 123.1 (C q, Phen), 126.0 (CH, Phen), 126.3 (CH, Phen), 126.9 (CH, Phen), 128.8 (CH, Phen), 129.6 (C q, Phen), 130.5 (CH, Phen), 130.5 (C q, Phen), 130.8 (CH, Phen), 139.3 (C q, Phen), 149.5 (C q, Phen), 157.9 (C q), 159.3 (C q); IR (KBr): 3316, 1672, 1625, 1594, 1564, 1543, 1478, 1466, 1439, 1409, 1308, 1262, 1229, 1187, 1088, 1051, 1022, 994, 921, 872, 853, 808, 767, 738, 677, 657, 596, 424 cm^{-1}; MS (FAB$^+$): m/z: 532[M$^+$-2], 534[M$^+$], 536[M$^+$+2]; elemental analysis calcd for $C_{23}H_{21}Br_3N_3$: C 44.98, H 2.26, N 7.87; found C 44.30, H 2.77, N 7.48.

3-(4-Fluorophenylimino)-5-fluoro-N-(4-fluorophenyl)-3H-indol-2-amine 3e. Red solid; ^{1}H NMR ($CDCl_3$): δ = 6.44 (m, 1H, Phen), 6.83 (m, 2H, Phen), 7.01 (m, 5H, Phen), 7.15 (m, 2H, Phen), 7.78 (m, 2H, Phen); ^{13}C NMR ($CDCl_3$): δ = 112.6, 112.9 (CH, Phen), 115.5, 115.7 (C q, Phen), 115.8, 116.0 (CH, Phen), 116.2, 116.2 (C q, Phen), 116.3, 116.6 (CH, Phen), 119.4 (C q, Phen), 119.6, 119.7 (C q, Phen), 120.5 (CH, Phen), 120.6 (CH, Phen), 120.6 (CH, Phen), 120.7 (CH, Phen), 143.9 (C q), 157.3, 157.7 (C q, Phen), 159.7, 160.1 (C q, Phen), 162.1 (C q); IR (KBr): 3199, 1656, 1629, 1578, 1544, 1500, 1460, 1302, 1270, 1232, 1206, 1184, 1153, 1124, 890, 847, 826, 741, 581, 516, 498, 464 cm^{-1}; MS (FAB$^+$): m/z: 352[M$^+$+1]; elemental analysis calcd for $C_{23}H_{21}F_3N_3$x0.5 H_2O: C 66.66, H 3.64, N 11.66; found C 65.58, H 3.59, N 11.53.

General procedure for the preparation of 4a–e. A solution of 2.3 mmol of the isatin derivatives **3a–e**, 30 mL glacial acetic acid, 4 mL conc. HCl and 4 mL H_2O was refluxed for 20 min. After cooling to RT the solvent was evaporated to dryness *in vacuo*. The orange residue was then taken up in water, filtrated, washed with water and dried under vacuum.

Isatine 4a. Orange solid; ^{1}H NMR (Aceton-d_6): δ = 7.02 (d, J = 7.92 Hz, 1H, H4), 7.11 (t, J = 7.5 Hz, 1H, H5), 7.52 (d, J = 7.23 Hz, 1H, H7), 7.62 (t, J = 7.71 Hz, 1H, H6), 10.00 (s, 1H, NH); ^{13}C NMR (Aceton-d_6): δ = 113.3 (C7), 119.3 (C3a), 124.2 (C5), 125.7 (C4), 139.6 (C6), 151.8 (C7a), 160.2 (C2), 185.3 (C3); IR (KBr): 3192, 1730, 1618, 1461, 1332, 1202, 1144, 1096, 947, 771, 661, 638, 480, 456 cm^{-1}; MS (FAB$^+$): m/z: 148 [M$^+$+1]; elemental analysis calcd for $C_8H_5NO_2 \times 0.25\ H_2O$: C 63.37, H 3.66, N 9.24; found C 63.54, H 3.63, N 8.92.

5-Methylisatine 4b. Orange/red solid; ^{1}H NMR (Aceton-d_6): δ = 2.29 (s, 3H, CH_3), 6.89 (d, J = 7.98 Hz, 1H, H7), 7.31 (s, 1H, H4), 7.41 (d, J = 8.01 Hz, 1H, H6), 9.87 (s, 1H, NH); ^{13}C NMR (Aceton-d_6): δ = 20.4 (CH_3), 113.2 (C7), 119.3 (C3a), 125.8 (C4), 133.9 (C5), 140.0 (C6), 149.7 (C7a), 160.4 (C2), 185.5 (C3); IR (KBr): 3286, 1743, 1626, 1491, 1438, 1399, 1304, 1195, 1127, 825, 738, 659, 552, 456 cm^{-1}; MS (FAB$^+$): m/z 161[M$^+$]; elemental analysis calcd for $C_9H_7NO_2$: C 67.08, H 4.38, N 8.69; found C 67.00, H 4.22, N 8.77.

5-Methoxyisatine 4c. Orange solid; ^{1}H NMR (DMSO-d_6): δ = 3.73 (s, 3H, OCH_3), 6.83 (d, J = 8.52 Hz, 1H, H7), 7.05 (d, J = 2.63 Hz, 1H, H4), 7.17 (dd, J = 8.52, 2.72 Hz, 1H, H6), 10.83 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ = 55.7 (OCH_3), 108.7 (C4), 113.3 (C6), 118.0 (C3a), 124.8 (C7), 144.6 (C7a), 155.3 (C5), 159.5 (C2), 184.6 (C3); IR (KBr): 3156, 3101, 1748, 1732, 1637, 1607, 1492, 1446, 1408, 1309, 1284, 1265, 1242, 1201, 1154, 1035, 982, 903, 825, 773, 740, 703, 657, 603, 459 cm^{-1}; MS (FAB$^+$): m/z 178 [M$^+$+H]; elemental analysis calcd for $C_9H_7NO_3$: C 61.02, H 3.98, N 7.90; found C 60.38, H 4.06, N 7.80.

6-Bromoisatine 4d. Yellow/orange solid; ^{1}H NMR (DMSO-d_6): δ = 7.07 (d, J = 1.47 Hz, 1H, H7), 7.25 (dd, J = 7.99, 1.57 Hz, 1H, H5), 7.43 (d, J = 7.97 Hz, 1H, H4), 11.16 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ = 114.9 (C7), 117.0 (C3a), 125.6 (C5), 126.2 (C3), 131.6 (C6), 151.5 (C7a), 159.3 (C2), 183.2 (C3); IR (KBr): 3172, 1744, 1716, 1609, 1443, 1327, 1262, 1246, 1206, 1100, 1053, 953, 907, 892, 789, 742, 663, 589, 511, 471 cm^{-1}; MS-EI: m/z 224 [M$^+$, ^{79}Br], 226 [M$^+$, ^{81}Br]; elemental analysis calcd for $C_8H_4NO_2Br$: C 42.51, H 1.78, N 6.20; found C 41.80, H 2.15, N 5.78.

5-Fluoroisatine 4e. Orange/red solid; ^{1}H NMR (DMSO-d_6): δ = 6.89 (dd, J = 8.8, 3.85, 1H, H7), 7.35 (dd, J = 7.14, 2.74 Hz, 1H, H4), 7.42 (m, 1H, H6), 11.03 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ = 111.30, 111.53 (C4), 113.46, 113.53 (C7), 118.47, 118.54 (C3a), 124.47, 124.71 (C6), 146.8 (C7a), 156.9 (C2), 159.35, 159.53 (C5), 183.9 (C3); ^{19}F NMR (DMSO-d_6): δ = 121.0 (m, C5F); IR (KBr): 3213, 1738, 1619, 1489, 1389, 1290, 1262, 1141, 1105, 912, 890, 847, 792, 739, 655, 604, 459 cm^{-1}; MS (FAB$^+$): m/z 166 [M$^+$+1]; elemental analysis calcd for $C_8H_4NO_2F \times 0.5\ H_2O$: C 55.18, H 2.89, N 8.04; found C 54.29, H 3.09, N 7.29.

General procedure for the preparation of 4f,g. A solution of 0.92 mL (12 mmol) DMF in 25 mL THF was cooled to 0°C and under inert gas conditions 1.03 mL (12 mmol) oxalyl chloride were added. After stirring for 2 h at room temperature, the suspension was again cooled to 0°C and a solution of 2.1 mL (12 mmol) Hünig's base (NEt*i*Pr_2) was added dropwise. After stirring for 1 h at 0°C and 2 h at room temperature, the precipitate was filtered off, and then to the filtrate, 25 mmol of the corresponding aniline was added. After stirring for 16 h at room temperature, aerial oxygen was passed through the solution for several hours. The solvent was evaporated the residue was taken up in 36 mL glacial acetic acid, 5 mL conc. HCl and 5 mL H_2O. This solution was refluxed for 20 minutes. After cooling to RT the solvent was evaporated to dryness *in vacuo*. The orange residue was then taken up in water, filtrated, washed with water and dried under vacuum.

5-Methyl-carboxylate-isatine 4f. Yellow/orange solid; ^{1}H NMR (DMSO-d_6): $\delta = 3.82$ (s, 3H, $COOCH_3$), 7.62 (d, $J =$ 8.67 Hz, 1H, H7), 7.91 (s, 1H, H4), 8.14 (dd, $J = 8.25, 1.68$, 1H, H6), 11.41 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): $\delta = 52.3$ (CH_3), 112.2 (C7), 118.0 (C3a), 123.8 (C5), 124.9 (C4), 138.9 (C6), 154.1 (C7a), 159.7 (COOMe), 165.2 (C2), 183.3 (C3); IR (KBr): 3255, 1763, 1731, 1703, 1618, 1493, 1431, 1393, 1250, 1199, 1133, 1086, 998, 948, 867, 818, 773, 747, 723, 679, 534, 465 cm^{-1}; MS (FAB$^+$): *m/z* 206 [M$^+$+1]; elemental analysis calcd for $C_{10}H_7NO_4 \times 0.5\ H_2O$: C 56.08, H 3.76, N 6.54; found C 56.63, H 3.62, N 6.87.

6,7-Benzoisatine 4g. Red/brown solid; ^{1}H NMR (Aceton-d_6): $\delta = 7.46$ (d, $J = 8.4$ Hz, 1H, H5), 7.54 (d, $J = 8.4$ Hz, 1H, H4), 7.61 (dt, $J = 7.03, 1.03$ Hz, 1H, H7/8), 7.72 (dt, $J =$ 6.93, 1.14 Hz, 1H, H7/8), 7.94 (d, $J = 8.18$ Hz, 1H, H 6/9), 8.23 (d, $J = 8.16$ Hz, 1H, H6/9), 10.65 (s, 1H, NH); ^{13}C NMR (Aceton-d_6): $\delta = 113.2$ (C3a), 119.8 (C5), 120.7 (C9a), 123.4 (C4/9), 123.7 (C4/9), 127.9 (C8), 129.9 (C6/7), 131.7 (C6/7), 139.7 (C5a), 153.1 (C9b), 160.9 (C2), 183.5 (C3); IR (KBr): 3197, 1741, 1628, 1580, 1531, 1464, 1419, 1387, 1305, 1177, 1077, 971, 895, 876, 829, 797, 774, 738, 715, 658, 558, 418 cm^{-1}; MS (FAB$^+$): *m/z* 198 [M$^+$+1]; elemental analysis calcd for $C_{12}H_7NO_2$: C 73.09, H 3.58, N 7.10; found C 73.46, H 4.37, N 7.71.

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[18] The electron distribution is 31% on the carbon centre and 69% on the nitrogen centre for the Z-isomer (28% and 72% for the E-isomer).

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The Synthesis of 4-(3,3-Dimethyl-3*H*-pyrrolo[2,3-*f*]quinolin-2-yl)pyrazoles and 4-(3,3-Dimethyl-3*H*-pyrrolo[3,2-*h*]quinolin-2-yl)pyrazoles

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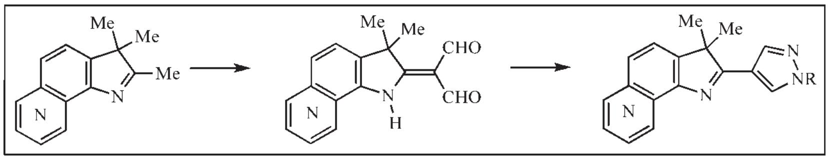

5-Hydrazinoquinoline and 8-hydrazinoquinoline were converted *via* Fischer syntheses with 3-methylbutan-2-one into pyrido-indolenines 2,3,3-trimethyl-3*H*-pyrrolo[2,3-*f*]quinoline **7** and 2,3,3-trimethyl-3*H*-pyrrolo[3,2-*h*]quinoline **11**, respectively. Exposure of the indolenines to the Vilsmeier reagent produced aminomethylene-malondialdehydes **8** and **12**, which reacted with hydrazine or arylhydrazines to give 4-(3*H*-pyrrolo[2,3-*f*]quinolin-2-yl)- and 4-(3*H*-pyrrolo[3,2-*h*]quinolin-2-yl)-pyrazoles, **9** and **13**.

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INTRODUCTION

We recently described the reaction of 2,3,3-trimethylindolenines (3*H*-indoles) **1** with the Vilsmeier reagent formed from dimethylformamide and phosphorus oxychloride to produce aminomethylene malondi-aldehydes **2** [1,2]. Additionally, we showed that these intriguing polyfunctional compounds reacted well with hydrazine or arylhydrazines to produce 4-(3,3-dimethyl-3*H*-indol-2-yl)-substituted pyrazoles, **3**, with migration of the double bond into the dihydropyrrole ring thus restoring the indolenine structure from which the sequence started [2] (Scheme 1). We have now been able to show that the principles embodied in these transformations can be incorporated into more complex heterocyclic systems and thus have prepared several 4-(3,3-dimethyl-3*H*-pyrrolo[2,3-*f*]quinolin-2-yl)pyrazoles and 4-(3,3-dimethyl-3*H*-pyrrolo[3,3-*h*]quinolin-2-yl)pyrazoles.

For the mechanism of formation of the aminomethylene malondialdehydes, we suggested that a small equilibrium concentration of an enamine tautomer **4** is successively *C*-substituted and thus, before hydrolysis during work-up, species **5** is present (Scheme 2). We suggest that a comparable mechanism operates in the work described herein.

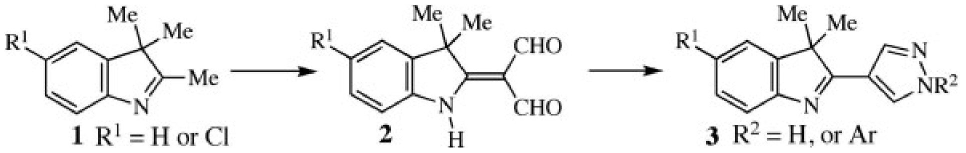
RESULTS AND DISCUSSION

Reduction of 5-nitroquinoline [3] with hydrazine and iron(III) chloride gave 5-aminoquinoline, diazotization of which, then reduction of the diazonium salt with tin(II) chloride, produced the corresponding 5-hydrazino-quinoline **6** [4] dihydrochloride. Reaction of compound **6** with isopropyl methyl ketone in a Fischer reaction [5] produced the pyrido-indolenine (2,3,3-trimethyl-3*H*-pyrrolo[2,3-*f*]quinoline) **7** in acceptable yield (Scheme 3). Similarly, 8-hydrazinoquinoline, prepared by prolonged heating of 8-hydroxyquinoline with hydrazine hydrate [6], reacted with isopropyl methyl ketone in hot acetic acid to give the isomeric pyrido-indolenine (2,3,3-trimethyl-3*H*-pyrrolo[3,2-*h*]quinoline [7]) **11** in 60% yield (Scheme 4). The structures of the two key pyrido-indolenines were evident from their molecular formulae, the six-hydrogen singlets for the geminal methyl groups, at δ 1.35 and 1.37 ppm for **7** and **11**, and singlet signals for the imine-methyl groups, resonating at δ 2.38 and 2.41 ppm, respectively. Each compound had an AB system for the *ortho*-related benzene ring protons, in addition to the three pyridine ring signals in normal positions. Each of the pyrido-indolenines was now reacted with the Vilsmeier reagent and, in yields of 94% and 81%, respectively, aminomethylene malondialdehydes **8** and **12** were obtained (Schemes 3 and 4).

The structures of the aminomethylene malon-dialdehydes rests on the observation of two one-hydrogen singlets at δ 9.83 and δ 9.86 for **8** and δ 9.82 and δ 9.90 for **12** corresponding to aldehyde protons. Absorptions at 3164 cm^{-1} and 3160 cm^{-1} for **8** and **12**, respectively, were evidence for the presence of N—H bonds, further confirmed by ^1H NMR one-hydrogen signals for the *N*-hydrogens appearing at δ 14.03 (**8**) and δ 14.45 (**12**), respectively.

As in our previous work [2], the aminomethylene malondialdehydes reacted smoothly with hydrazine and various arylhydrazines to give pyrazoles, with migration

Scheme 1



of the double bond to reform the imine unit (Schemes 3 and 4). For pyrazoles **9a–g**, the newly formed five-membered heterocyclic ring protons resonated in the range δ 8.30–9.70 and for the isomers, **13a–e**, in the range δ 8.30–9.10.

EXPERIMENTAL

Melting points were recorded on a Philip Harris C4954718 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance AQS 300 MHz spectrometer, at 300 MHz and 75 MHz, respectively. Chemical shifts δ are in parts per million (ppm) measured in $CDCl_3$ as solvent and relative to TMS as the internal standard. Infrared spectra were recorded on a Thermonicolet-Nexus 670 FTIR instrument and elemental analyses were carried out on an Exeter analytical model CE440 C, H and N elemental analyzer. High resolution mass spectra were recorded on an Agilent Technology (HP), MS Model: 5973 Network Mass, selective detector ion source: electron impact (EI) 70 eV, ion source temperature: 230 °C, Analyzer: quadrupole, analyzer temperature: 150 °C, and relative abundances of fragments are quoted in parentheses after the *m*/*z* values.

5-Aminoquinoline. A mixture of 5-nitroquinoline (2.65 g, 15.2 mmol), activated carbon (600 mg), ferric chloride hexahydrate (250 mg), and methanol (50 mL) was refluxed for 10 min with stirring. Hydrazine hydrate (3.75 g, 80%) was added over 30 min to the boiling solution. The mixture was stirred under reflux for an additional 12 h, cooled, and evaporated. The resulting slurry was dissolved in dichloromethane (50 mL), washed with water (2 × 20 mL), and dried ($MgSO_4$). Evaporation of the solvent yielded a yellow solid, which was identified as 5-aminoquinoline. Yield 85%; mp: 108–110 °C (lit. 110 °C); IR: 3196, 1585, 1365, 792 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.22 (bs, 2H), 6.77 (dd, 1H, J = 8.4, 1.2 Hz), 7.26 (dd, 1H, J = 8.4, 4.2 Hz), 7.47 (t, 1H, J = 8.4 Hz), 7.56 (d, 1H, J = 8.4 Hz), 8.14 (dd, 1H, J = 8.4, 1.8 Hz), 8.84 (dd, 1H, J = 4.2, 1.8 Hz); ^{13}C NMR ($CDCl_3$): δ 109.95, 118.69, 119.55, 119.97, 129.60, 130.05, 142.42, 149.10, 150.21.

General procedure for the synthesis of (7) and (11). A mixture of quinolinylhydrazine dihydrochloride (5 g, 21 mmol) and isopropyl methyl ketone (1.85 g, 21 mmol) was refluxed in acetic acid (100 mL) for 3–5 h and then cooled, diluted with water (100 mL), and neutralized with NaOH 2 *M*, then extracted with ethyl acetate (4 × 100 mL). The organic layer was dried over Na_2SO_4. The solvent was evaporated and the resulting viscous oil recrystallized from EtOH to give the quinolinyl-indolenines identified as (**7**) or (**11**).

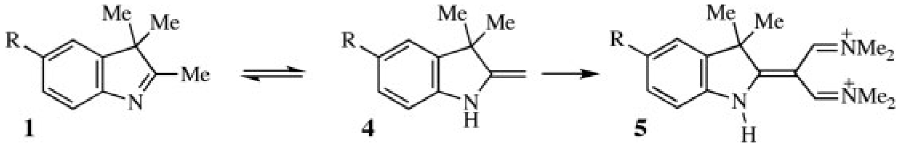
2,3,3-Trimethyl-3H-pyrrolo[2,3-f]quinoline (7). 65% Yield; mp 115–118 °C; IR: 2964, 2928, 1561, 1366 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.35 (s, 6H), 2.38 (s, 3H), 7.44 (dd, 1H, J = 8.4, 4.2 Hz), 7.64 (d, 1H, J = 8.4 Hz), 7.98 (d, 1H, J = 8.4 Hz), 8.84 (dd, 1H, J = 8.4, 1.8 Hz), 8.90 (dd, 1H, J = 4.2, 1.8 Hz); ^{13}C NMR ($CDCl_3$): δ 15.57, 22.50, 54.77, 121.11, 121.87, 122.54, 126.47, 131.80, 142.28, 148.21, 148.67, 149.90, 189.72; *m*/*z*: 210 $[M]^+$, 195 (100), 181, 169, 154, 129, 84. Found: M^+ 210.1158, $C_{14}H_{14}N_2$ requires M^+ 210.1157.

2,3,3-Trimethyl-3H-pyrrolo[3,2-h]quinoline (11). 80% Yield; mp 114–116 °C; IR: 2966, 1686, 1515, 1359 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.37 (s, 6H), 2.41 (s, 3H), 7.38 (dd, 1H, J = 8.4, 4.2 Hz), 7.50 (d, 1H, J = 8.1 Hz), 7.70 (d, 1H, J = 8.1 Hz), 8.17 (dd, 1H, J = 8.4, 1.8 Hz), 9.00 (dd, 1H, J = 4.2, 1.8 Hz); ^{13}C NMR ($CDCl_3$): δ 15.58, 22.43, 55.45, 120.37, 120.97, 125.37, 128.36, 136.59, 140.40, 146.03, 148.64, 150.58, 189.87; *m*/*z*: 210 M^+, 195 (100), 181, 169, 154, 129, 84. Found: M^+ 210.1157, $C_{14}H_{14}N_2$ requires M^+ 210.1157.

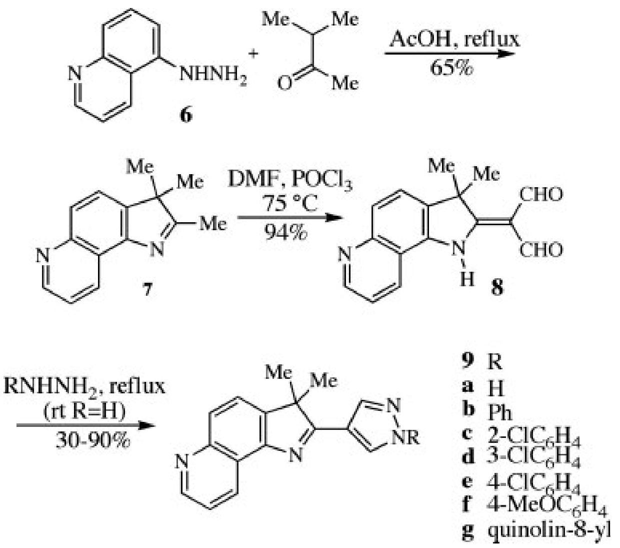
General procedure for the synthesis of (8) and (12). To *N*,*N*-dimethylformamide (10 mL) cooled in an ice bath was added dropwise phosphorus oxychloride (7 mL, 75 mmol) with stirring at below 10 °C. After this addition, a solution of (**7**) or (**11**) (25 mmol, 5.25 g) in DMF (10 mL) was added dropwise. The cooling bath was removed and the reaction mixture was stirred at 75 °C for 4–6 h. The resulting solution was added to ice-cooled water and made alkaline with NaOH(aq.) solution. The resulting precipitate was collected by filtration, dried in air, recrystallized from ethanol, and identified as (**8**) or (**12**).

(3,3-Dimethyl-3H-pyrrolo[2,3-f]quinolin-2-ylidene)malondialdehyde (8). 94% Yield; mp 180–183 °C; IR: NH 3164, 2965, 2763, 1679, 1601, 1518, 1363, 1166, 814, 771 cm^{-1}; ^{1}H NMR

Scheme 2



Scheme 3



($CDCl_3$): δ 1.86 (s, 6H), 7.55 (dd, 1H, *J* = 8.4, 4.2 Hz), 7.72 (d, 1H, *J* = 8.70 Hz), 8.06 (d, 1H, *J* = 8.70 Hz), 8.34 (dd, 1H, *J* = 8.4, 1.8 Hz), 9.02 (dd, 1H, *J* = 4.2, 1.8 Hz), 9.83 (s, 1H), 9.86 (s, 1H,), 14.03 (bs, 1H); ^{13}C NMR ($CDCl_3$): δ 22.84, 52.43, 110.17, 115.82, 121.79, 122.74, 127.55, 129.20, 134.34, 137.27, 148.08, 150.98, 180.33, 187.62, 192.68. Found: % C 72.02; H 5.38; N 10.63. $C_{16}H_{14}N_2O_2$ requires % C 72.16; H 5.30; N 10.52.

(3,3-Dimethyl-3H-pyrrolo[3,2-h]quinolin-2-ylidene)malondialdehyde (12). 81% Yield; mp 166–168 °C; IR: NH 3160, 2966, 2763,1673, 1602, 1504, 1325, 1161, 816, 768 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.87 (s, 6H), 7.50 (dd, 1H, *J* = 8.4, 4.2 Hz), 7.54 (d, 1H, *J* = 8.1 Hz), 7.73 (d, 1H, *J* = 8.1 Hz), 8.23 (dd, 1H, *J* = 8.4, 1.5 Hz), 8.97 (dd, 1H, *J* = 4.2, 1.5 Hz), 9.82 (s, 1H), 9.90 (s, 1H), 14.45 (bs, 1H); ^{13}C NMR ($CDCl_3$): δ 22.75, 53.05, 110.03, 120.02, 121.87, 125.34, 128.26, 135.85, 136.08, 139.95, 150.94, 150.95, 179.05, 187.99, 192.21. Found: % C 71.98; H; 5.31; N 10.44. $C_{16}H_{14}N_2O_2$ requires % C 72.16; H 5.30; N 10.52.

General procedure for the synthesis of (9a) and (13a). A mixture of the malondialdehyde (**8**) or (**12**) (0.5 mmol) and hydrazine monohydrate (0.05 g, 1 mmol) in absolute ethanol (1 mL) was stirred at room temperature for 24 h (R = H). After concentrating the solution, the resulting crystals were collected by filtration and recrystallized from EtOH to give the (**9a**) and (**13a**).

4-(3,3-Dimethyl-3H-pyrrolo[2,3-f]quinolin-2-yl)pyrazole (9a). 60% Yield; mp 130–132 °C; IR: 3137, 2969, 2926, 1570, 1486, 1330, 1062, 924, 832, 822 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.60 (s, 6H), 3.50 (bs, 1H, NH), 7.51 (dd, 1H, *J* = 8.4, 4.3 Hz), 7.74 (d, 1H, *J* = 8.4 Hz), 8.04 (d, 1H, *J* = 8.4 Hz), 8.35 (s, 2H), 8.95–9.01 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 24.28, 54.34, 116.24, 119.55, 121.07, 122.15, 122.28, 126.47, 132.12, 134.22, 142.77, 148.45, 150.12, 179.96. Found: % C 73.07; H 5.32; N 21.49. $C_{16}H_{14}N_4$ requires % C 73.26; H 5.38; N 21.36.

4-(3,3-Dimethyl-3H-pyrrolo[3,3-h]quinolin-2-yl)pyrazole (13a). 65% Yield; mp 135–139 °C; IR: 3163, 2965, 2927, 1566, 1512, 1466, 1326, 1068, 940, 832, 727 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.62 (s, 6H), 4.10 (bs, 1H, NH), 7.49 (dd, 1H, *J* = 8.4, 3.75 Hz), 7.60 (d, 1H, *J* = 8.1 Hz), 7.74 (d, 1H, *J* = 8.1 Hz), 8.28 (d, 1H, *J* = 8.4 Hz), 8.73 (s, 2H), 9.18 (d, 1H, *J* = 3.9 Hz); ^{13}C NMR ($CDCl_3$): δ 24.26, 54.34, 116.25, 121.07, 122.16, 122.30, 126.44, 132.16, 134.21, 142.80, 148.42, 149.28, 150.08, 179.99. Found: % C 73.29; H 5.41; N 21.19. $C_{16}H_{14}N_4$ requires % C 73.26; H 5.38; N 21.36.

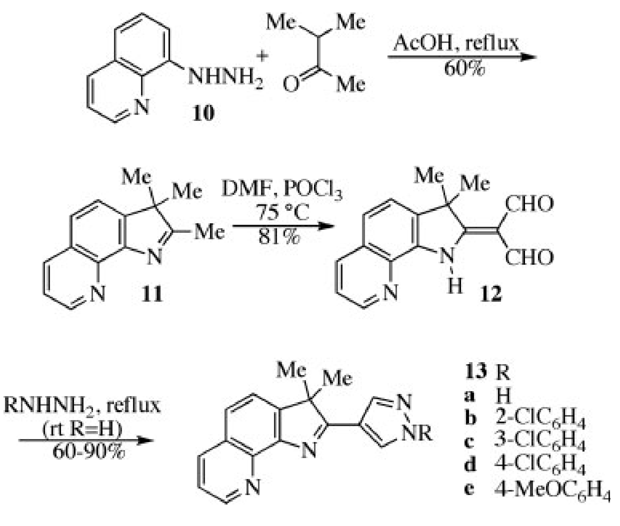
General procedure for the synthesis of (9b–g) and (13b–g). A mixture of the malondialdehyde (**8**) or (**12**) (0.5 mmol) and the arylhydrazine (0.55 mmol) in absolute ethanol (15 mL) was heated with stirring at reflux for 2–3 h. After cooling and concentrating the solution, the resulting crystals were collected by filtration and recrystallized from EtOH to give the corresponding pyrazoles.

1-Phenyl-4-(3,3-dimethyl-3H-pyrrolo[2,3-f]quinolin-2-yl)-pyrazole (9b). 70% Yield; mp 168–170 °C; IR: 3059, 2968, 2928, 2576, 1572, 1561, 1497, 1377, 950 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.61 (s, 6H), 7.34 (dd, 1H, *J* = 8.4, 4.5 Hz), 7.43–7.51 (m, 3H), 7.70 (d, 1H, *J* = 8.4 Hz), 7.77 (m, 2H), 8.07 (d, 1H, *J* = 8.4 Hz), 8.38 (s, 1H), 8.68 (s, 1H), 8.94 (dd, 1H, *J* = 4.5, 1.8 Hz), 9.00 (dt, 1H, *J* = 8.4, 0.9 Hz); ^{13}C NMR ($CDCl_3$): δ 24.18, 54.36, 118.06, 119.52, 121.15, 122.18, 122.74, 125.56, 127.22, 127.43, 129.48, 129.61, 133.06, 139.42, 140.75, 143.14, 147.25, 149.35, 179.77. Found: % C 78.29; H 5.26; N 16.41. $C_{22}H_{18}N_4$ requires % C 78.08; H 5.36; N 16.56.

1-(2-Chlorophenyl)-4-(3,3-dimethyl-3H-pyrrolo[2,3-f]quinolin-2-yl)pyrazole (9c). 90% Yield; mp 100–103 °C; IR: 2958, 2927, 1580, 1559, 1491, 1451, 1365, 940, 816, 755 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.58 (s, 6H), 7.36–7.41 (m, 2H), 7.53–7.58 (m, 2H), 7.65 (dd, 1H, *J* = 7.5, 1.8 Hz), 7.76 (d, 1H, *J* = 8.4 Hz), 8.14 (d, 1H, *J* = 8.4 Hz), 8.45 (s, 1H), 8.59 (s, 1H), 8.95 (dd, 1H, *J* = 4.2, 1.5 Hz), 9.10 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$): δ 24.21, 54.48, 117.25, 121.04,122.27, 123.28, 124.90, 127.66, 127.92, 128.24, 129.78, 130.81, 131.81, 134.12, 137.43, 140.77, 143.47, 146.27, 148.67, 149.26, 179.90. Found: % C 70.71; H 4.68; Cl 9.41; N 15.16. $C_{22}H_{17}ClN_4$ requires % C 70.87; H 4.60; Cl 9.51; N 15.03.

1-(3-Chlorophenyl)-4-(3,3-dimethyl-3H-pyrrolo[2,3-f]quinolin-2-yl)pyrazole (9d). 90% Yield; mp 151–153 °C; IR: 2961, 2928, 1578, 1563, 1488, 1415, 1365, 1033, 959, 839, 772 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.58 (s, 6H), 7.30 (dt, 1H, *J* =

Scheme 4



8.1, 0.9 Hz), 7.40 (t, 1H, J = 8.1 Hz), 7.47 (dd, 1H, J = 8.4, 4.2 Hz), 7.66 (t, 1H, J = 0.9 Hz), 7.70 (d, 1H, J = 8.4 Hz), 7.83–7.84 (m, 1H), 8.03 (d, 1H, J = 8.4 Hz), 8.39 (s, 1H), 8.63 (s, 1H), 8.95 (d, 2H, J = 8.1 Hz); ^{13}C NMR (CDCl$_3$): δ 24.17, 54.31, 117.29, 118.73, 119.73, 119.74, 121.15, 122.19, 126.83, 126.86, 127.28, 130.65, 131.95, 135.43, 140.39, 141.07, 142.84, 148.49, 149.18, 150.20, 179.02. Found: % C 70.93; H 4.61; Cl 9.43; N 14.91. $C_{22}H_{17}ClN_4$ requires % C 70.87; H 4.60; Cl 9.51; N 15.03.

1-(4-Chlorophenyl)-4-(3,3-dimethyl-3H-pyrrolo[2,3-f]quinolin-2-yl)pyrazole (9e). 90% Yield; mp 176–177 °C; IR: 2967, 2927, 1577, 1562, 1492, 1421, 1067, 948, 824, 812 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.62 (s, 6H), 7.48–7.52 (m, 3H), 7.75 (t, 3H, J = 8.4), 8.05 (d, 1H, J = 8.40 Hz), 8.40 (s, 1H), 8.64 (s, 1H), 8.95–8.96 (m, 2H); ^{13}C NMR (CDCl$_3$): δ 24.18, 54.30, 118.65, 120.60, 121.12, 122.17, 126.80, 126.85, 129.70, 131.92, 132.89, 138.05, 140.88, 142.81, 148.52, 149.21, 150.19, 179.11. Found: % C 70.81; H 4.50; Cl 9.56; N 15.10. $C_{22}H_{17}ClN_4$ requires % C 70.87; H 4.60; Cl 9.51;N 15.03.

1-(4-Methoxyphenyl)-4-(3,3-dimethyl-3H-pyrrolo[2,3-f]-quinolin-2-yl)pyrazole (9f). 75% Yield; mp 139–141 °C; IR: 2964, 2931, 1575, 1560, 1518, 1502, 1259, 1250, 1038, 958, 817 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.55 (s, 6H), 3.80 (s, 3H), 6.93–6.97 (m, 2H), 7.44 (dd, 1H, J = 8.4, 4.2 Hz), 7.64–7.69 (m, 3H), 8.00 (d, 1H, J = 8.4 Hz), 8.33 (s, 1H), 8.56 (s, 1H), 8.9 (dd, 1H, J = 4.1, 1.8 Hz), 8.94 (d, 1H, J = 9 Hz); ^{13}C NMR (CDCl$_3$): δ 24.25, 54.25, 55.55, 114.62, 117.92, 121.05, 121.12, 122.11, 122.23, 126.52, 127.04, 132.04, 133.15, 140.28, 142.78, 148.42, 149.28, 150.09, 158.82, 179.55. Found: % C 74.71; H 5.39; N 15.29. $C_{23}H_{20}N_4O$ requires % C 74.98; H 5.47; N 15.21.

4-(3,3-Dimethyl-3H-pyrrolo[2,3-f]quinolin-2-yl)-1-(quinolin-8-yl)pyrazole (9g). 30% Yield; mp 186–188 °C; IR: 3055, 2969, 2926, 1580, 1561, 1471, 1409, 1050, 942, 825, 786 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.62 (s, 6H), 7.55–7.59 (m, 2H), 7.71 (t, 1H, J = 7.8 Hz), 7.80 (d, 1H, J = 8.4 Hz), 7.87–7.90 (m, 1H), 8.13 (d, 1H, J = 8.4 Hz), 8.29–8.38 (m, 2H), 8.57 (s, 1H), 8.97–8.99 (m, 1H), 9.07–9.09 (m, 1H), 9.13 (d, 1H, J = 8.4 Hz), 9.67 (s, 1H); ^{13}C NMR (CDCl$_3$): δ 24.46, 54.45, 117.18, 120.88, 121.76, 122.25, 122.94, 123.79, 125.39, 126.53, 127.43, 129.27, 133.54, 134.25, 136.23, 136.61, 140.46, 140.67, 143.27, 147.18, 149.16, 149.55, 150.60, 180.26. Found: % C 76.92; H 4.81; N 17.93. $C_{25}H_{19}N_5$ requires % C 77.10; H 4.92; N 17.98.

1-(2-Chlorophenyl)-4-(3,3-dimethyl-3H-pyrrolo[3,3-h]-quinolin-2-yl)pyrazole (13b). 75% Yield; mp 97–100 °C; IR: 2965, 2926, 1571, 1488, 1444, 1073, 940, 834, 759 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.63 (s, 6H), 7.36–7.46 (m, 3H), 7.56–7.60 (m, 2H), 7.68 (dd, 1H, J = 8.1, 1.8 Hz), 7.75 (d, 1H, J = 8.1 Hz), 8.23 (d, 1H, J = 8.4 Hz), 8.57 (s, 1H), 8.73 (s, 1H), 9.08 (dd, 1H, J = 4.5, 1.5 Hz); ^{13}C NMR (CDCl$_3$): δ 24.28, 54.60, 117.63, 119.82, 120.88, 125.52, 127.62, 127.86, 128.11, 128.64, 129.54, 130.84, 132.04, 136.30, 137.62, 141.03, 141.33, 146.75, 149.66, 150.85, 179.05. Found: % C 70.69; H 4.53; Cl 9.61; N 15.12. $C_{22}H_{17}ClN_4$ requires % C 70.87;H 4.60; Cl 9.51; N 15.03.

1-(3-Chlorophenyl)-4-(3,3-dimethyl-3H-pyrrolo[3,3-h]-quinolin-2-yl)pyrazole (13c). 80% Yield; mp 110–113 °C; IR: 2962, 2926, 1594, 1570, 1488, 1458, 1074, 940, 833, 772 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.60 (s, 6H), 7.30–7.41 (m, 3H), 7.57–7.80 (m, 4H), 8.21–8.24 (m, 1H), 8.40 (s, 1H), 8.87 (s, 1H), 9.06–9.08 (m, 1H); ^{13}C NMR (CDCl$_3$): δ 24.11, 54.62, 117.11, 118.72, 119.75, 119.95, 120.94, 125.67, 127.21, 127.88, 128.88, 130.67, 135.47, 136.72, 140.43, 140.83, 141, 146.89, 149.22, 150.68, 178.98. Found: % C 70.78; H 4.66; Cl 9.67; N 14.94. $C_{22}H_{17}ClN_4$ requires % C 70.87; H 4.60; Cl 9.51 N 15.03.

1-(4-Chlorophenyl)-4-(3,3-dimethyl-3H-pyrrolo[3,3-h]-quinolin-2-yl)pyrazole (13d). 85% Yield; mp 128–131 °C; IR: 2967, 2930, 1573, 1496, 1378, 1267, 1076, 950, 817 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.65 (s, 6H), 7.48 (d, 1H, J = 8.7 Hz), 7.56 (dd, 1H, J = 8.1, 4.2 Hz), 7.67 (d, 1H, J = 8.1 Hz), 7.77–7.83 (m, 4H), 8.36–8.38 (m, 1H), 8.39 (s, 1H), 9.07 (s, 1H), 9.17 (d, 1H, J = 4.2, Hz); ^{13}C NMR (CDCl$_3$): δ 24.00, 54.76, 118.13, 120.51, 120.67, 120.99, 125.72, 127.75, 128.27, 128.66, 129.58, 132.69, 137.85, 138.35, 138.78, 140.82, 147.77, 149.42, 179.55. Found: % C 70.83; H 4.61; Cl 9.50; N 15.08. $C_{22}H_{17}ClN_4$ requires % C 70.87; H 4.60; Cl 9.51; N 15.03.

1-(4-Methoxyphenyl)-4-(3,3-dimethyl-3H-pyrrolo[3,3-h]-quinolin-2-yl)pyrazole (13e). 75% Yield; mp 187–189 °C; IR: 2964, 2929, 1572, 1519, 1495, 1257, 1032, 953, 831 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.64 (s, 6H), 3.88 (s, 3H), 7.03 (d, 2H, J = 9.0 Hz), 7.45 (dd, 1H, J = 8.4, 4.2 Hz), 7.60 (d, 1H, J = 8.1 Hz), 7.69–7.76 (m, 3H), 8.23 (dd, 1H, J = 8.4, 1.2 Hz), 8.39 (s, 1H), 8.83 (s, 1H), 9.09 (dd, 1H, J = 4.2, 1.2 Hz); ^{13}C NMR (CDCl$_3$): δ 24.27, 54.55, 55.61, 114.71, 118.01, 119.86, 120.88, 120.98, 125.40, 128.01, 128.67, 133.29, 136.39, 140.26, 141.16, 146.70, 149.53, 150.78, 158.81, 179.40. Found: % C 75.06; H 5.40; N 15.25. $C_{23}H_{20}N_4O$ requires % C 74.98; H 5.47; N 15.21.

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The Alkylation of Isatin-Derived Oximes: Spectroscopic and X-Ray Crystallographic Structural Characterization of Oxime and Nitrone Products

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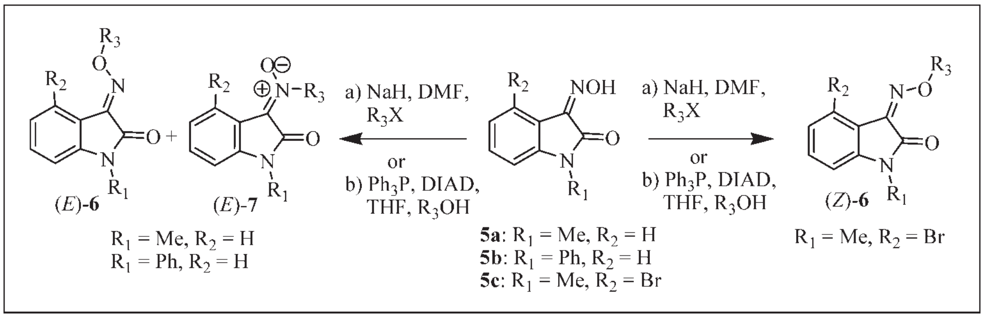

A series of isatin oximes was alkylated with alkyl halides and under Mitsunobu conditions to generate *O*-alkylated oxime ether and *N*-alkylated nitrone products. Alkylation of the sodium salts of oximes **5a** and **5b** with alkyl iodides produced predominantly the *N*-alkylated nitrones (*E*)-**7** while alkylation of **5a** and **5b** with the harder electrophiles alkyl bromides and alkyl chlorides, gave mostly the *O*-alkylated products, oxime ethers (*E*)-**6**. Interestingly, alkylation of oxime **5b** under Mitsunobu conditions with isopropyl alcohol produced the *N*-alkylated nitrone (*E*)-**7bd** as the major product. However, alkylation of oxime **5c**, which incorporates a sterically bulky bromine substituent at the C-4 position of the isatin heterocycle, with 2-bromo- and 2-iodo-propane or with isopropyl alcohol under Mitsunobu conditions gave exclusively the *O*-alkylated product, oxime ether (*Z*)-**6cd**. The oxime ether and nitrone products **6** and **7**, respectively, were characterized by LC/MS, ^{1}H NMR, and ^{13}C NMR. In addition, the structures of oxime ether (*E*)-**6bd** and nitrone (*E*)-**7ad** were determined by X-ray crystallography.

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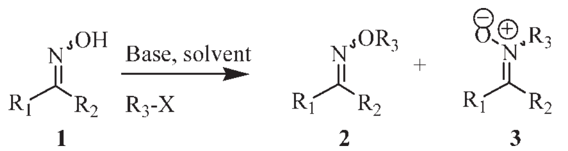
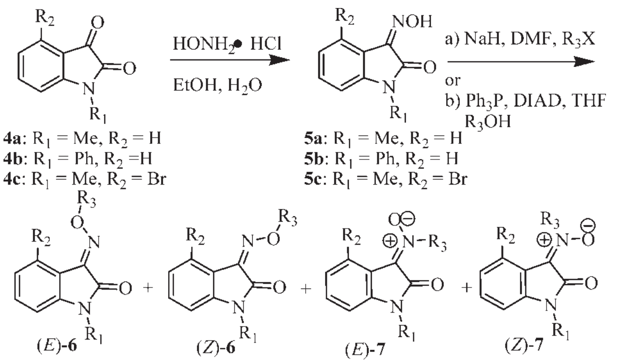
INTRODUCTION

Oximes (**1**) are important synthetic intermediates in organic synthesis that have also found application in a medicinal chemistry setting. As a synthetically useful functionality, oximes can be used to protect carbonyl groups, reduced to an amine or, in the case of oximes derived from aldehydes, undergo dehydration to a nitrile [1]. During the course of our survey of small molecule inhibitors of respiratory syncytial virus (RSV) fusion, we were interested in probing the potential of isatin-derived oximes as bioisosteres of the benzimidazol-2-one template that has provided a series of potent antiviral agents [2]. Isatin derivatives have found wide application as scaffolds in medicinal chemistry, including a series of Schiff bases and hydrazones evaluated as potential anticonvulsants [3] and cyclin-dependent kinase-2 inhibitors [4]. In addition, a number of isatin and oxindole derivatives demonstrate antiviral properties, exemplified by inhibitors of poxvirus [5], ectromelia [6], rhinovirus [7], HIV-1 [8], and the coronavirus responsible for severe acute respiratory syndrome (SARS) [9]. Oximes have been examined as useful pharmacophores in a range of therapeutic agents that encompass multiple disease areas. For example, oxime derivatives have been evaluated as dual agonists of peroxisome proliferator-activated receptors (PPARs) α and γ for the treatment of type II diabetes [10], vascular endothelial growth factor (VEGF)-2 kinase inhibitors as antiproliferative agents [11], *N*-methyl-D-aspartate (NMDA) [12] and AMPA/kainite [13] receptor antagonists, and γ-aminobutyric acid (GABA) uptake inhibitors as potential anticonvulsants [14]. A particularly prominent oxime ether derivative

Scheme 1. Alkylation of oximes of general structure **1**.



Scheme 2. Alkylation of isatin oximes.



that has been evaluated in clinical trials as an antiviral agent for the treatment of HIV infection is SCH 351125, an orally bioavailable CCR5 receptor antagonist [15].

To establish the potential of isatin-derived oxime ethers as RSV fusion inhibitors, a parallel synthesis approach was envisioned as a means of rapidly generating a series of isatin oxime ethers **6** from oximes **5** by a simple alkylation procedure. However, it is well established that the alkylation of oximes of general structure **1** can produce *O*-alkyloxime-ethers **2** and *N*-alkylated nitrones **3**, as shown in Scheme 1, depending upon the site at which alkylation occurs [16,17]. The ratio of *O*- to *N*-alkylated products can be influenced by several factors, including the geometry of the oxime salts derived from **1**. For example, alkylation of an *(E)*-aldoxime sodium salt with alkyl halides produced mainly the *O*-alkylated oximes but alkylation of the (*Z*)-aldoxime sodium salt with the same series of electrophiles produced similar amounts of the *N*- and *O*-alkylated products [17]. Whilst there are many reports in the literature of oxime alkylation procedures, there has not been a systematic study of the alkylation of isatin oximes **5** and structural characterization of the possible products, the oxime ethers **6** and nitrones **7**. The alkylation of oxime **5** is potentially a complex process since four products can be formed: *(E)*- and (*Z*)-oximes **6** and *(E)*- and (*Z*)-nitrones **7**, and it was anticipated that product distribution would show some dependence on the reagents, the reaction conditions, and the substitution patterns of the aryl ring. In this article, we report the results of studies of the alkylation of a series of isatin oximes **5** and characterization of the products by LC/MS, ^1H NMR, ^{13}C NMR and, for select examples, X-ray crystallography.

RESULTS AND DISCUSSION

The procedures for the preparation and alkylation of isatin oximes **5** are summarized in Scheme 2. Isatin oximes **5a-c** were readily obtained from isatins **4a–c** by treatment with $NH_2OH{\cdot}HCl$ in aqueous EtOH. Isatins **4a** and **4b** were available from commercial sources and *N*-methyl-4-bromo isatin (**4c**) was obtained by alkylation of commercially available 4-bromoisatin with methyl iodide in the presence of K_2CO_3 as the base. Alkylation of **5a** and **5b** by deprotonation with NaH in DMF and exposure to alkyl halides gave mixtures of isatin *O*-alkyloxime ethers *(E)*-**6** and nitrones *(E)*-**7**, with the distribution of the products for each reaction summarized in Tables 1 and 2. DMF was chosen as the solvent to

Table 1

Alkylation of isatin oxime **5a** with alkyl halides to give *O*-alkylated oxime ethers and *N*-alkylated nitones.

No.	Oxime	Nitrone	Electrophile	R_1	R_2	R_3	Ratio of oxime: nitrone (%)[b]	Total yield (%)	Rxn time (h)
1	(*E*)-**6aa**[a]	(*E*)-**7aa**[a]	MeI	Me	H	Me	36:64	64[c]	15
2	(*E*)-**6ab**	(*E*)-**7ab**	EtI	Me	H	Et	40:60	90	15
3	(*E*)-**6ac**	(*E*)-**7ac**	nPrI	Me	H	nPr	37:63	91	15
4	(*E*)-**6ad**	(*E*)-**7ad**	iPrI	Me	H	iPr	40:60	89	15
5	(*E*)-**6ae**	(*E*)-**7ae**	$(CH_3CH_2)_2CH$ Br	Me	H	$(CH_3CH_2)_2CH$	57:43	97	15
6	(*E*)-**6af**	(*E*)-**7af**	cPentyl Iodide	Me	H	cPen	58:42	97	15
7	(*E*)-**6ag**	(*E*)-**7ag**	cHexyl Iodide	Me	H	cHex	50:50	94[c]	15
8	(*E*)-**6ah**	(*E*)-**7ah**	4-OMeC_6H_4 CH_2Cl	Me	H	CH_2-Ph-4′-OMe	58:42	64	15
9	(*E*)-**6ai**	(*E*)-**7ai**	$BrCH_2CO_2tBu$	Me	H	CH_2CO_2tBu	90:10	91	15

[a] Letter designations: the first letter represents the substitution pattern on the isatin ring system, whereas the second letter discriminates the different substitutions on the oxime oxygen and nitrone nitrogen.

[b] Ratios between isomers were determined by weights after flash column chromatography, except, entry 1 where the ratio was determined by HPLC since the two products were not separable.

[c] Yields based on 10 and 34% recovered starting material for entries 1 and 7, respectively.

Table 2

Alkylation of **5b** with isopropyl halides under basic conditions and with isopropyl alcohol under Mitsunobu conditions to give *O*-alkylated oxime ether *(E)*-**6bd** and *N*-alkylated nitone *(E)*-**7bd**.

No.	Reagent used[a]	Oxime (*E*)-**6bd**[b] (%)	Nitrone (*E*)-**7bd**[b] (%)	Total yield (%)	Rxn time (h)
1	iPrI	43 (48)	57 (52)	83	15
2	iPrBr	54 (62)	46 (38)	86	15
3	iPrCl	65 (70)	35 (30)	61[c]	76
4	iPrOH	12 (16)	88 (84)	84	18

[a] Alkylation of oxime **5b** with alkyl halides in the presence of NaH and under Mitsunobu reaction conditions with isopropyl alcohol for entries 1–3 and entry 4, respectively.

[b] Isomeric product ratios were determined by weight after purification by flash column chromatography. Ratios in parentheses were determined by integration of HPLC peaks.

[c] Yield based on 6% recovered starting material.

ensure high solubility of the isatin oximes **5a** and **5b** and their sodium salts during the course of the reaction, since heterogeneous reaction conditions caused by the precipitation of oxime salts from solvents such as acetone or toluene have been reported to influence the ratio of products formed [16]. The effect of the counter ion on product distribution was also examined, with lithium, potassium, and tetramethylammonium salts evaluated in addition to sodium [16]. Furthermore, the application of the Mitsunobu reaction to this process was also studied. Several *O*-alkylated isatin oxime ethers were also obtained by combining isatins **4a–c** with *O*-alkylated hydroxylamine hydrochloride salts in aqueous EtOH for the purpose of comparison with the products obtained from the alkylation reactions.

The results of these studies, compiled in Table 1, reveal that the reaction yields are generally excellent, ranging from 64 to 97% and that product distribution between the *O*- and *N*-alkylated products is dependent on the nature of the electrophile. When soft electrophiles such as alkyl iodides were employed, the *N*-alkylated products, isatin nitrones *(E)*-**7**, were favored slightly over the *O*-alkylated oxime ethers **6**, with the ratio ranging from just over 1:1 to 2:1 (Table 1, Entries 1–4 and 7). 2-Iodocyclopentane provided an exception, producing a 58:42 ratio of oxime to nitrone, respectively (Table 1, Entry 6). However, with harder electrophiles, such as alkyl bromides (Table 1, Entries 5 and 9) and alkyl chlorides (Table 1, Entry 8), this trend was largely reversed with the *O*-alkylated products predominating, in the range of 3:2 to 9:1.

The effect of the nature of the alkyl halide on the ratio of *O*- and *N*-alkylated products formed in base-catalyzed processes was observed earlier with both benzophenone oxime [16] and aldoxime [17] systems. In those studies, the *O*-alkylated products predominated by three to ninefold, with alkyl chlorides providing the highest preference for *O*-alkylation. However, the studies were not conducted in a systematic fashion and correlation of the effect of hard and soft electrophiles on product distribution could not be fully appreciated. In addition, the study of aldoxime alkylation was complicated by the geometry of the aldoxime sodium salt which exerted a profound effect on the product ratio [17]. The *(E)*-aldoxime sodium salt was found to give the oxime ether by a preference of three to ninefold over the nitrone products, whereas the (*Z*)-aldoxime sodium salt showed little preference for *O*- *versus N*-alkylation, presumably a consequence of the reduced steric encumbrance around the nitrogen atom in this conformation.

To more closely evaluate the effect of the leaving group on the ratio of *O*- and *N*-alkylated product formation in the isatin oxime system, additional alkylation experiments were conducted with **5b** using 2-iodo-, 2-bromo-, and 2-chloro-propane, which afforded a mixture of *O*-alkyloxime ether *(E)*-**6bd** and the nitrone *(E)*-**7bd**. In addition, since the pKa of many oximes is similar to that of a phenol [18], alkylation of **5b** with isopropyl alcohol under the mild conditions associated with the Mitsunobu reaction was examined [19]. The results of this survey are compiled in Table 2 where the yields of products were generally high, 83–86%, except in the case of 2-chloropropane (Entry 3, 61% yield). The alkylation of **5b** with 2-chloropropane was a sluggish process, and the reaction was worked up after an extended, 76 h time interval. The data in Table 2 reveal a slight preference toward the *N*-alkylated nitrone *(E)*-**7bd** when the soft electrophile 2-iodopropane was employed. However, the *O*-alkylated product, ether *(E)*-**6bd**, predominated slightly when 2-bromopropane was used as the electrophile, and the ratio further amplified in the reaction of **5b** with 2-chloropropane. Interestingly, under Mitsunobu conditions, the oxime **5b** reacted with isopropyl alcohol to afford predominantly the *N*-alkylated nitrone *(E)*-**7bd** in a ratio of 88:12 over the *O*-alkylated oxime ether *(E)*-**6bd** (Table 2, Entry 4). To the best of our knowledge, this experiment represents the first example of oxime alkylation under Mitsunobu conditions affording a nitrone product.

Table 3

Key spectroscopic data for isatin oximes **6** and nitrones **7**.

	Oxime **6**/Nitrone **7**	^{1}H NMR of oxime and nitrone in CDCl$_3$		Chemical shift differences between oximes and nitrones	
Entry No.	Compound No.	C4 Ar-H (ppm)	Oxime CH*n*/Nitrone CH*n* (ppm)	ΔC4 Ar-H (ppm)	ΔOxime CH*n*/ Nitrone CH*n* (ppm)
1	(*E*)-**6ab**	7.96	4.52–4.56	−0.38	−0.27
	(*E*)-**7ab**	8.34	4.79–4.83		
2	(*E*)-**6ac**	7.95	4.44–4.47	−0.40	−0.31
	(*E*)-**7ac**	8.35	4.75–4.78		
3	(*E*)-**6ad**	7.93	4.69–4.80	−0.44	−1.58
	(*E*)-**7ad**	8.37	6.28–6.37		
4	(*E*)-**6ae**	7.94	4.44–4.46	−0.48	−1.69
	(*E*)-**7ae**	8.42	6.13–6.15		
5	(*E*)-**6af**	7.88	5.11–5.14	−0.47	−1.41
	(*E*)-**7af**	8.35	6.52–6.55		
6	(*E*)-**6ag**	7.96	4.50–4.54	−0.40	−1.46
	(*E*)-**7ag**	8.36	5.95–6.01		
7	(*E*)-**6ah**	7.88	5.44	−0.42	−0.44
	(*E*)-**7ah**	8.30	5.88		
8	(*E*)-**6ai**	8.06	4.93	−0.28	−0.52
	(*E*)-**7ai**	8.34	5.45		
9	(*E*)-**6bd**	8.05	4.78–4.87	−0.42	−1.52
	(*E*)-**7bd**	8.47	6.30–6.39		

The structures of the alkylated isatin oximes were determined by a combination of spectroscopic methods. The oxime ethers **6** could readily be distinguished from the nitrones **7** by examination of the infra red spectra. An earlier report identified unique N-O absorbances for the nitrone and oxime between 1170–1280 and 920–1005 cm^{-1}, respectively [16]. The IR spectrum of the oxime ether *(E)*-**6ad** exhibits the characteristic N-O band at 971 cm^{-1}, which is absent in the IR spectrum of the isomeric nitrone *(E)*-**7ad** (Table 1, Entry 4). Conversely, a unique nitrone N-O band appeared at 1241 cm^{-1} in the IR spectrum of nitrone *(E)*-**7ad** that is not exhibited by the oxime ether *(E)*-**6ad**.

The ^{1}H NMR spectra of oxime ethers **6** and nitrones **7** are generally quite similar with the exception of the chemical shifts for the C-4 aryl hydrogen atom and the protons on the carbon atoms attached to the oxime oxygen or nitrone nitrogen atoms. The ^{1}H NMR chemical shifts for the isatin C-4 aryl hydrogen, and the protons on the carbon atom attached to the oxime oxygen and nitrone nitrogen atoms are presented in Table 3. In the ^{1}H NMR, the C-4 aryl hydrogen of isatin nitrones **7** consistently resonates between 0.28 and 0.48 ppm downfield of the chemical shift of the same proton in the corresponding isatin oxime ethers **6**, attributed to a deshielding effect induced by the nitrone moiety. Similarly, the ^{1}H NMR chemical shifts for the protons on the carbon atom attached to the nitrone nitrogen atom in **7** resonate downfield of the protons on the carbon atom bound to the oxygen atom in the oxime ethers **6**. For the series of nitrones **7ab**, **7ac**, **7ah**, and **7ai** and their corresponding oxime ether isomers **6ab**, **6ac**, **6ah**, and **6ai**, compounds all prepared from primary alkyl halides, the ^{1}H NMR chemical shifts of the methylene protons differ by 0.27 to 0.52 ppm (Table 3, Entries 1, 2, 7, and 8). For nitrones **7ad**, **7ae**, **7af**, **7ag**, and **7bd** and oxime ethers **6ad**, **6ae**, **6af**, **6ag**, and **6bd**, derived from secondary alkyl halides, the differences in ^{1}H NMR chemical shifts of the methine protons are more pronounced, with a difference of 1.41 to 1.69 ppm (Table 3, Entries 3–6 and 9).

To provide further support for the structural assignments, a single crystal X-ray structure was obtained for the nitrone *(E)*-**7ad**, which indicates that this compound possesses an *(E)*-geometric configuration, as depicted in Figure 1. Attempts to recrystallize the corresponding oxime ether *(E)*-**6ad** for X-ray crystallographic structure determination to allow a direct comparison with *(E)*-**7ad** were unsuccessful. However, the solid state structure was determined for the close analogue, oxime ether *(E)*-**6bd** in which the isatin *N* substituent is phenyl rather than methyl and, as depicted in Figure 2, this compound also possesses the *(E)*-geometric configuration. In the *(E)*-configuration, the oxygen atoms of the oxime *(E)*-**6bd** and nitrone *(E)*-**7ad** project away from the carbonyl oxygen of the isatin amide moiety, presumably to optimize dipole interactions and minimize the lone pair-lone pair repulsion that would exist in the (*Z*)-oxime and lone pair-negative charge repulsions that would occur in the isomeric (*Z*)-nitrone (*vide infra*). In addition, the

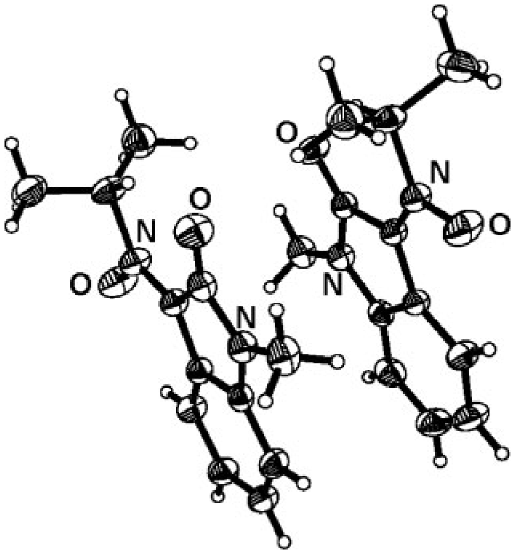


Figure 1. X-ray crystallographic structure of nitrone *(E)*-**7ad**.

crystallographic structures indicate that the oxygen atom of both the oxime ether *(E)*-**6bd** and nitrone *(E)*-**7ad** are situated within hydrogen bonding distance of the C-4-aryl hydrogen, measured at 2.527 Å for *(E)*-**6bd** and 2.446 Å for *(E)*-**7ad**, respectively.

The X-ray crystallographic data for oxime ether *(E)*-**6bd** and nitrone *(E)*-**7ad** indicate without ambiguity that both are *(E)*-isomers. On the basis of the additional studies and *ab initio* calculations described below, we conclude that all of the oxime ethers and nitrones presented in Tables 1 and 2 most likely possess the *(E)*-geometric configuration.

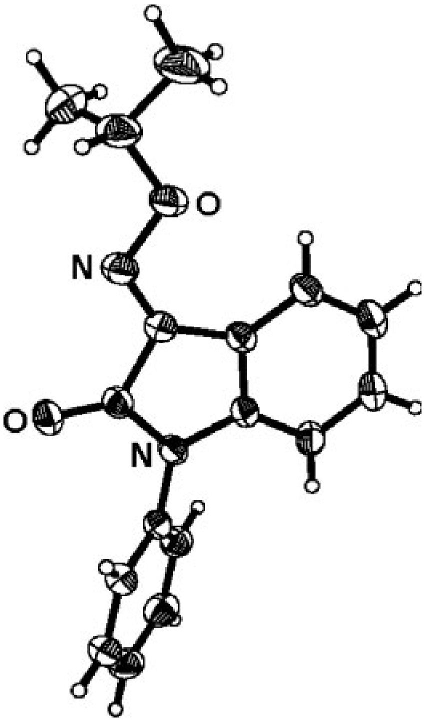


Figure 2. X-ray crystallographic structure of oxime ether*(E)*-**6bd**.

The (*Z*)-isomers of either an oxime ether or nitrone analog were not isolated from any of the alkylation procedures, consistent with an earlier report that indicated that the nitrone (*Z*)-**7aa** could only be produced briefly when nitrone *(E)*-**7aa** was irradiated at a temperature maintained between 6 and 10°C [20,21]. However, warming to room temperature resulted in isomerization of (*Z*)-**7aa** to *(E)*-**7aa**. HPLC analysis of the products produced in the alkylation reaction that afforded oxime *(E)*-**6bd** and nitrone *(E)*-**7bd** indicated a trace of an additional peak with a retention time close to oxime *(E)*-**6bd** that may be the isomeric oxime, (*Z*)-**6bd**; however, this compound could not be isolated. In an attempt to increase the production of the (*Z*)-oxime isomer, direct oxime ether formation from isatin **4b** was examined. Condensation of **4b** with 1.2 equivalents of *O*-isopropylhydroxylamine hydrochloride in EtOH/H_2O gave a 96% yield of oxime product that was an 89:11 mixture of *(E)*-**6bd** and (*Z*)-**6bd** as determined by HPLC (Table 4, Entry 1). Oxime ethers *(E)*-**6bd** and *(Z)*-**6bd** were prepared in 95% yield under the same conditions but with an equimolar quantity of pyridine included to neutralize the HCl present in the reaction mixture in an attempt to reduce interconversion between the (*Z*) to *(E)* isomers (Table 4, Entry 2). Under these conditions, the

Table 4

Condensation of **4b** and **4c** with *O*-isopropyl hydroxylamine to give *(E)*- and (*Z*)-oxime ether **6**.

No.	(*E*)-Oxime	(*Z*)-Oxime	R_1	R_2	Ratio of isomer E:Z-oxime[a] (%)	Total yield (%)[d]
1	(*E*)-**6bd**	(*Z*)-**6bd**	Ph	H	89:11[b]	96
2	(*E*)-**6bd**	(*Z*)-**6bd**	Ph	H	93:7[b]	95
3	(*E*)-**6cd**	(*Z*)-**6cd**	Me	Br	43:57[c]	91

[a] R_3 = iPr for all entries.
[b] Ratio was determined by HPLC peak integration.
[c] Ratio was determined after isolation of the products by flash column chromatography.
[d] Total yield as a mixture.

Table 5

Ab initio calculations for nitrone and oxime ether geometric isomers.

Calculation Method	Nitrone:Δ[(*E*)-**7ad**—(*Z*)-**7ad**] (kcal/mol)	Oxime: Δ[(*E*)-**6ad**—(*Z*)-**6ad**] (kcal/mol)	Oxime:Δ[(*E*)-**6cd**—(*Z*)-**6cd**] (kcal/mol)
B3LYP/6-31G* (solvent: H_2O)	−6.9	−3.2	2.1
B3LYP-31G*// B3LYP-6-31+G* (solvent: H_2O)	−6.1	−3.5	2.3
B3LYP-31G*// B3LYP-aug-cc- pvdz (solvent: H_2O)	−5.6	−3.4	2.3

ratio of oxime ether *(E)*-**6bd** and (*Z*)-**6bd** was 93:7 by analytical HPLC, indicating that (*Z*) to *(E)* product isomerization was not a significant issue when the reaction was conducted under slightly acidic conditions. To further favor the formation of a (*Z*)-oxime isomer, a sterically bulky bromine substituent was introduced at the C-4 position of the isatin heterocycle. Condensation of *N*-methyl-4-bromoisatin (**4c**) with *O*-isopropylhydroxylamine hydrochloride in EtOH/H_2O produced two oxime ether products **6cd**, which were separable by silica gel column chromatography to give products in a ratio of 57:43. The ^{1}H NMR, ^{13}C NMR and LC/MS spectra of the two products were very similar but could be differentiated by close inspection of the data. In the ^{1}H NMR, the methine proton on the carbon atom attached to the oxygen atom of the oxime ether appears as a septet. For the minor oxime ether isomer, this methine proton resonance is centered at 4.77 ppm, which is slightly downfield of the methine proton for the major oxime ether isomer, centered at 4.74 ppm. The isatin *N*-Me protons resonate as singlets at 3.22 ppm for the minor isomer and 3.20 ppm for the major isomer, whereas the signal for the two methyl protons of the isopropyl group appear as doublets at 1.45 ppm for the minor isomer and 1.47 ppm for the major isomer. The minor product completely isomerized to the major oxime ether within an hour as a solution in $CDCl_3$ in an NMR tube. Although the minor isomer was readily recrystallized from a mixture of ether and hexanes at 4°C, the small rod crystals that resulted failed to diffract satisfactorily to allow a structure determination. An attempt to prepare oxime ether *(E)*-**6ad** from the bromo isatin oxime **6cd** by subjecting each one separately to a lithium-halogen exchange reaction followed by protonation to allow correlation with *(E)*-**6ad** was unsuccessful.

In an effort to illuminate further the issue of *(E)* and (*Z*) ratios, *ab initio* studies were conducted. Comparative analysis of *(E)*- and (*Z*)-oximes **6ad** and **6cd** and *(E)*- and (*Z*)-nitrones **7ad** were performed through geometry optimization and relative energy evaluation. The geometries were optimized using DFT at the B3LYP/6-31G* level of theory and basis set. The derived geometries were then used to perform corrections using B3LYP/6-31+G* and Dunning's aug-cc-PVDZ basis sets [22]. Both geometry optimizations and single point energy evaluations were performed in the presence of solvent (water) using the PCM method available in G03 [23]. The relative energies for nitrones *(E)*- and (*Z*)-**7ad**, and oximes *(E)*- and (*Z*)-**6ad**, and *(E)*- and (*Z*)-**6cd** are presented in Table 5. The conformational analysis calculation results presented in Table 5 reveal that the nitrone **7ad** with the *(E)*-geometric configuration is stabilized by 5.9–6.9 kcal/mole when compared to its (*Z*)-isomer due to an unfavorable dipole–dipole interaction between the negatively charged oxygen of the nitrone and the lone pair of electrons on the isatin carbonyl moiety in the (*Z*)-isomer. The experimentally measured dipole moments of a structurally similar pair of nitrone isomers that incorporate an α-carbonyl moiety are reported to differ by four units [21]. For example, the dipole moments for *(E)-N*-(2,2,5,5-tetramethyl-4-oxodihydrofuran-3(2H)-ylidene)methanamine oxide and its (*Z*)-isomer were determined in dioxane to be 1.09 ± 0.13 and 5.31 ± 0.11, respectively [21]. The significant energy difference between the *(E)*- and (*Z*)-nitrones **7ad** is consistent with earlier studies of the isomerization of nitrone *(E)*-**7aa** to (*Z*)-**7aa** upon irradiation and explains the difficulties encountered in isolating the nitrone (*Z*)-**7ad** due to its facile isomerization to *(E)*-**7ad** at room temperature [21]. For the oxime derivatives, repulsion between the lone pairs of electrons on the oxime oxygen atom and the isatin carbonyl moiety leads to *(E)*-**6ad** being the more stable isomer by 3.2–3.5 kcal/mole based on the three molecular calculation methods when compared with (*Z*)-**6ad**. However, in oxime (*Z*)-**6cd** where R_2 = Br, steric hindrance overrides the stereo electronic effects that dominate the geometry of oxime ether (*Z*)-**6ad**. Thus, the oxime ether (*Z*)-**6cd** is more stable by 2.1–2.3 kcal/mole over the *(E)*-isomer. The results of these calculations led us to assign the major product as oxime ether (*Z*)-**6cd** and the minor product as the *trans*-isomer, *(E)*-**6cd** (Table 4, Entry 3).

The insights associated with the effect of a Br substituent at C-4 of the heterocycle on oxime geometry prompted an examination of the effect of this substitution pattern on the outcome of oxime alkylation. Thus,

Table 6

Alkylation of isatin oxime **5c** with *iso*-propyl halides under basic conditions and isopropyl alcohol under Mitsunobu conditions to give *O*-alkylated (*Z*)-oxime ethers.

Entry No.	Reagent used	Oxime (*Z*)-**6cd** (%)	Total yield (%)[a]	Reaction time (h)
1	iPrI	100	90	18
2	iPrBr	100	91	18
3	iPrOH	100	85	18

[a] Isolated yield after silica gel chromatography purification.

N-methyl-4-bromoisatin oxime **5c** was alkylated with *iso*-propyl bromide and *iso*-propyl iodide under basic conditions and also reacted with isopropyl alcohol under Mitsunobu conditions with the result that the *O*-alkylated product (*Z*)-**6cd** was formed exclusively in high yield in all cases. These data are presented in Table 6 and the oxime ether (*Z*)-**6cd** prepared in these reactions was spectroscopically and chromatographically identical to the major oxime ether product (*Z*)-**6cd** prepared by condensing *N*-methyl-4-bromoisatin with *O*-isopropylhydroxylamine hydrochloride (Table 4, Entry 3). This result presumably reflects the development of unfavorable steric interactions between the nitrone *N* substituents and the C-4 bromine atom in the transition state and dominates the previously observed propensity for softer electrophiles to react at the oxime *N* atom.

In summary, alkylation of the sodium salts of a series of isatin oximes **5a** and **5b** with soft electrophiles such as iodoalkanes leads to a slight preference for the *N*-alkylated nitrone products, while harder electrophiles, such as bromo- and chloro-alkanes, preferentially produce *O*-alkylated oxime ether products. Under Mitsunobu conditions, isatin oximes **5b** underwent alkylation preferentially on nitrogen leading to a predominance of the nitrone products. The installation of a bromine atom at C-4 of the heteroaryl ring of oxime **5c** led to the exclusive formation of the (*Z*)-oxime ether, the steric interactions provided by the bromine atom overriding the inherent stereo electronic control exerted by the interaction between the oxime oxygen atom and the α-carbonyl moiety.

EXPERIMENTAL

General directions. ^{1}H- and ^{13}C NMR spectra were obtained at 500 MHz and 126 MHz NMR, respectively. The chemical shifts (δ) are recorded in parts per million (ppm) downfield from TMS. Unless otherwise noted, all NMR samples were prepared in $CDCl_3$. IR spectra were recorded on Perkin Elmer System 2000 FT-IR. Drying of the organic layer during work-up was carried out over anhydrous $MgSO_4$, followed by filtration. Column chromatography was carried out on silica gel (SiO_2) according to Still's flash chromatography technique [24]. Melting points are uncorrected.

Preparative procedures. ***3-(Hydroxyimino)-1-methylindolin-2-one (5a).*** To a slurry of 1-methylisatin (**4a**) (5.28 g, 31.77 mmol) in EtOH (50 mL) was added a solution of $NH_2OH{\cdot}HCl$ (3.31 g, 47.66 mmol) in H_2O (6 mL) and the resulting brown reaction mixture stirred at rt. After 3 h, the solvent was removed *in vacuo* to afford a greenish-yellow paste that was triturated with H_2O (50 mL), filtered, and washed with H_2O (50 mL). The greenish-yellow solid product was dried in a vacuum oven overnight to give **5a** (5.49 g, 98% yield), which was used without further purification, m.p. 193.0–195.5°C (lit. m.p. 193–197°C) [25]; ^{1}H NMR δ 3.25 (s, 3 H), 6.83 (d, J = 7.63 Hz, 1H), 7.08 (t, J = 7.48 Hz, 1H), 7.40 (t, J = 7.78 Hz, 1H), 8.06 (d, J = 7.32 Hz, 1H), 9.57 (s, 1 H); ^{13}C NMR δ 26.2, 108.5, 115.6, 117.6, 123.3, 128.4, 132.7, 144.6, 163.8; LC-MS, MS m/z 177 (M+H).

General alkylation procedure. To a solution of isatin oxime **5** in DMF (0.25*M*) was added 1.2 equivalents of NaH (60% dispersion in oil) followed after 10 min by 1.2 equivalents of an alkyl halide. The progress of the reaction was followed by TLC and LC/MS. When the reaction was complete, the mixture was diluted with EtOAc and washed with dilute aqueous HCl. The reaction of oximes **5** with 2-iodopropane and 2-bromopropane as electrophiles were typically complete after 0.5 and 2.5 h, respectively, as indicated by TLC and LC/MS. The color of the reaction mixture changed during the course of the reaction from an initial dark red, presumably due to the isatin oxime alkoxy anion, to a brown reaction mixture after the oxime alkoxy anion was consumed. However, both reaction mixtures were allowed to stir at room temperature for 15 h before work up. HPLC determination of the ratio of products of the reaction using 2-iodopropane after 0.5 and 15 h showed no change in the product ratio; thus, there was no interconversion of products under the reaction conditions up to 15 h.

(E)-N-(1-methyl-2-oxoindolin-3-ylidene)ethanamine oxide ((E)-7ab). This compound was obtained as orange solid, m.p. 103.0–104.5°C; ^{1}H NMR δ 1.52 (t, J = 7.32 Hz, 3 H), 3.27 (s, 3 H), 4.81 (q, J = 7.32 Hz, 2 H), 6.82 (d, J = 7.63 Hz, 1 H), 7.09 (t, J = 7.63 Hz, 1 H), 7.36 (t, J = 7.63 Hz, 1 H), 8.33 (d, J = 7.63 Hz, 1 H); ^{13}C NMR δ 13.4, 26.2, 42.5, 58.2, 107.8, 118.3, 123.2, 124.9, 131.4, 133.5, 141.1, 160.5; LC-MS, MS m/z 205 (M+H); *Anal.* Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.71. Found: C, 64.75; H, 5.83; N, 13.60.

(E)-3-(ethoxyimino)-1-methylindolin-2-one ((E)-6ab). This compound was obtained as yellow solid, m.p. 76.0–77.0°C; ^{1}H NMR δ 1.44 (t, J = 7.17 Hz, 3 H), 3.23 (s, 3 H), 4.54 (q, J = 7.12 Hz, 2 H), 6.81 (d, J = 7.63 Hz, 1 H), 7.05 (t, J = 7.63 Hz, 1 H), 7.37 (dt, J = 7.78, 0.92 Hz, 1 H), 7.95 (d, J = 7.32 Hz, 1 H); ^{13}C NMR δ 14.8, 26.1, 73.0, 108.3, 116.0, 123.0, 127.8, 132.3, 143.6, 144.5, 163.8; LC-MS, MS m/z 205 (M+H); *Anal.* Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.71. Found: C, 64.55; H, 5.67; N, 13.66.

(E)-N-(1-methyl-2-oxoindolin-3-ylidene)propan-1-amine oxide ((E)-7ac). This compound was obtained as orange solid, m.p. 76.5–78.0°C; ^{1}H NMR δ 1.01 (t, J = 7.48 Hz, 3 H), 1.95–2.03 (m, 2 H), 3.27 (s, 3 H), 4.76 (t, J = 7.32 Hz, 2 H), 6.82 (d, J = 7.63 Hz, 1 H), 7.09 (t, J = 7.63 Hz, 1 H), 7.37 (dt, J = 7.78, 1.22 Hz, 1 H), 8.35 (d, J = 7.63 Hz, 1 H); ^{13}C NMR δ 11.0, 22.0, 26.2, 64.3, 107.7, 118.2, 123.1, 124.9, 131.4, 134.1, 141.0, 160.6; LC-MS, MS m/z 219 (M+H); *Anal.* Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.46; N, 12.83. Found: C, 66.03; H, 6.24; N, 12.79.

(E)-1-methyl-3-(propoxyimino)indolin-2-one ((E)-6ac). This compound was obtained as yellow solid, m.p. 53.0–54.5°C; ^{1}H NMR δ 1.01 (t, J = 7.32 Hz, 3 H), 1.81–1.89 (m, 2 H) 3.23 (s, 3 H), 4.45 (t, J = 6.56 Hz, 2 H), 6.81 (d, J = 7.93 Hz, 1 H), 7.06 (t, J = 7.48 Hz, 1 H), 7.38 (t, J = 7.78 Hz, 1 H), 7.95 (d, J = 7.63 Hz, 1 H); ^{13}C NMR δ 10.3, 22.6, 26.1, 79.0, 108.4, 116.0, 123.0, 127.7, 132.3, 143.6, 144.5, 163.8; LC-MS, MS m/z 219 (M+H); *Anal.* Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.46; N, 12.83. Found: C, 65.97; H, 6.46; N, 12.74.

(E)-3-(Isopropoxyimino)-1-methylindolin-2-one ((E)-6ad) and (E)-N-(1-methyl-2-oxoindolin-3-ylidene)propan-2-amine oxide ((E)-7ad). To a solution of isatin oxime 5a (1.01 g, 5.73 mmol) in DMF (23 mL, 0.25*M*) was added NaH (60% 0.275 g of a dispersion in oil, 6.88 mmol) followed after 10 min by 2-iodopropane (1.18 g, 6.88 mmol). After stirring the brown reaction mixture at rt for 15 h, the DMF was removed *in vacuo*, the residue dissolved in EtOAc (150 mL), and then washed with 1*N* HCl (2 × 50 mL). The aqueous layer was extracted with EtOAc (50 mL), and the combined organic layers washed with brine, dried, and concentrated to afford viscous brown oil. Chromatography on a column of silica gel using a 3:1 mixture of hexane and EtOAc as eluant gave nitrone *(E)*-**7ad** (0.675 g, 54% yield) as an orange solid followed by oxime ether *(E)*-**6ad** (0.441 g, 45% yield) as a viscous yellow oil which solidified upon standing at rt.

***(E)*-7ad**: m.p. 113.0–114.5°C; IR (neat) νmax 3055, 2982, 1701, 1610, 1551, 1466, 1241, 737 cm^{-1}; ^{1}H NMR δ 1.45 (dd, J = 6.56, 1.37 Hz, 6H), 3.27 (d, J = 1.22 Hz, 3 H), 6.28–6.37 (m, 1H), 6.82 (d, J = 7.93 Hz, 1H), 7.07–7.12 (m, 1H), 8.37 (d, J = 7.63 Hz, 2H); ^{13}C NMR δ 20.5, 26.2, 61.9, 107.7, 118.5, 123.2, 124.8, 131.2, 133.1, 140.9, 160.6. LC-MS, MS m/z 219 (M+H); *Anal.* Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.46; N, 12.83; found: C, 66.17; H, 6.24; N, 12.69.

***(E)*-6ad**: m.p. 68.5–72.0°C; IR (neat) νmax 3057, 2976, 1727, 1608, 1468, 1330, 971, 748 cm^{-1}; ^{1}H NMR δ 1.41 (dd, J = 6.41, 1.53 Hz, 6H), 3.21 (d, J = 1.53 Hz, 3H), 4.69–4.80 (m, 1H), 6.79 (d, J = 7.93 Hz, 1H), 7.03 (t, J = 7.48 Hz, 1H), 7.32–7.38 (m, 1H), 7.93 (d, J = 7.32 Hz, 1H); ^{13}C NMR δ 21.8, 26.1, 79.6, 108.3, 116.0, 122.9, 127.7, 132.2, 143.3, 144.4, 163.8; LC-MS, MS m/z 219 (M+H); *Anal.* Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.46; N, 12.83; found: C, 66.03; H, 6.24; N, 12.80.

(E)-N-(1-methyl-2-oxoindolin-3-ylidene)pentan-3-amine oxide ((E)-7ae). This compound was obtained as orange solid, m.p. 82.5–84.0°C; ^{1}H NMR δ 0.89 (t, J = 7.48 Hz, 6 H), 1.64–1.77 (m, 2 H), 1.92–2.05 (m, 2 H), 3.28 (s, 3 H), 6.06–6.14 (m, 1 H), 6.83 (d, J = 7.93 Hz, 1 H), 7.10 (dt, J = 7.63, 0.92 Hz, 1 H), 7.37 (dt, J = 7.78, 1.22 Hz, 1 H), 8.42 (d, J = 6.71 Hz, 1 H); ^{13}C NMR δ 10.4, 26.2, 26.6, 73.0, 107.7, 118.2, 123.2, 124.9, 131.4, 135.4, 140.8, 160.8; LC-MS, MS m/z 247 (M+H); *Anal.* Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.36; N, 11.37. Found: C, 68.18; H, 7.13; N, 11.38.

(E)-1-methyl-3-(pentan-3-yloxyimino)indolin-2-one ((E)-6ae). This compound was obtained as yellow viscous oil, ^{1}H NMR δ 0.96 (t, J = 7.32 Hz, 6 H), 1.69–1.85 (m, 4 H), 3.23 (s, 3 H), 4.38–4.45 (m, 1 H), 6.81 (d, J = 7.93 Hz, 1 H), 7.05 (dt, J = 7.48, 0.92 Hz, 1 H), 7.36 (dt, J = 7.78, 1.22 Hz, 1 H), 7.94 (d, J = 7.63 Hz, 1 H); ^{13}C NMR δ 9.6, 26.2, 89.8, 108.3, 116.1, 123.0, 127.6, 132.1, 143.4, 144.3, 163.9; LC-MS, MS m/z 247 (M+H).

(E)-N-(1-methyl-2-oxoindolin-3-ylidene)cyclopentanamine oxide ((E)-7af). This compound was obtained as orange solid, m.p. 98.0–100.0°C; ^{1}H NMR δ 1.64–1.73 (m, 2 H) 1.88–1.98 (m, 2 H), 2.02–2.09 (m, 2 H), 2.10–2.19 (m, 2 H), 3.27 (s, 3 H), 6.45–6.53 (m, 1 H), 6.81 (d, J = 7.93 Hz, 1 H), 7.08 (dt, J = 7.63, 0.92 Hz, 1 H), 7.35 (dt, J = 7.78, 1.22 Hz, 1 H), 8.35 (d, J = 7.63 Hz, 1 H); ^{13}C NMR δ 26.1, 26.1, 31.8, 70.7, 107.7, 118.5, 123.2, 124.8, 131.2, 133.8, 140.8, 160.7; LC-MS, MS m/z 245 (M+H); *Anal.* Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.46. Found: C, 68.95; H, 6.56; N, 11.44.

(E)-3-(cyclopentyloxyimino)-1-methylindolin-2-one ((E)-6af). This compound was obtained as yellow solid, m.p. 54.0–55.5°C; ^{1}H NMR δ 1.59–1.68 (m, 2 H), 1.70–1.81 (m, 2 H), 1.87–1.96 (m, 2 H), 1.97–2.05 (m, 2 H), 3.21 (s, 3 H), 5.06–5.12 (m, 1 H), 6.79 (d, J = 7.93 Hz, 1 H), 7.03 (dt, J = 7.55, 0.76 Hz, 1 H), 7.35 (dt, J = 7.78, 1.22 Hz, 1 H), 7.88 (d, J = 7.32 Hz, 1 H); ^{13}C NMR δ 23.9, 25.9, 32.6, 89.2, 108.4, 116.0, 123.0, 127.5, 132.3, 143.6, 144.4, 163.8; LC-MS, MS m/z 245 (M+H); *Anal.* Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.46. Found: C, 69.01; H, 6.52; N, 11.47.

(E)-N-(1-methyl-2-oxoindolin-3-ylidene)cyclohexanamine oxide ((E)-7ag). This compound was obtained as orange solid, m.p. 109.5–110.5°C; ^{1}H NMR δ 1.19–1.30 (m, 1 H), 1.40–1.54 (m, 2 H), 1.68–1.75 (m, 1 H), 1.86–1.98 (m, 6 H), 3.27 (s, 3 H), 5.94–6.02 (m, 1 H), 6.81 (d, J = 7.63 Hz, 1 H), 7.08 (dt, J = 7.63, 0.92 Hz, 1 H), 7.35 (dt, J = 7.71, 1.37 Hz, 1 H), 8.36 (d, J = 7.63 Hz, 1 H); ^{13}C NMR δ 25.1, 25.2, 26.1, 30.8, 69.6, 107.7, 118.5, 123.2, 124.8, 131.2, 133.2, 140.8, 160.6; LC-MS, MS m/z 249 (M+H); *Anal.* Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.77; H, 7.00; N, 10.82.

(E)-3-(cyclohexyloxyimino)-1-methylindolin-2-one ((E)-6ag). This compound was obtained as yellow solid, m.p. 57.0–60.0°C; ^{1}H NMR δ 1.30–1.46 (m, 3 H), 1.53–1.59 (m, 1 H), 1.61–1.70 (m, 2 H), 1.72–1.82 (m, 2 H), 2.03–2.11 (m, 2 H), 3.23 (s, 3 H), 4.48–4.57 (m, 1 H), 6.80 (d, J = 7.63 Hz, 1 H), 7.03–7.07 (m, 1 H), 7.36 (dt, J = 7.78, 1.22 Hz, 1 H), 7.95 (d, J = 7.32 Hz, 1 H); ^{13}C NMR δ 23.6, 25.6, 26.2, 31.7, 84.4, 108.3, 116.1, 123.0, 127.7, 132.2, 143.5, 144.4, 163.9; LC-MS, MS m/z 249 (M+H); *Anal.* Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.75; H, 6.96; N, 10.79.

(E)-1-(4-methoxyphenyl)-N-(1-methyl-2-oxoindolin-3-ylidene)methanamine oxide ((E)-7ah). This compound was obtained as orange solid, m.p. 126.0–133.0°C; ^{1}H NMR δ 3.29 (s, 3 H), 3.78 (s, 3 H), 5.88 (s, 2 H), 6.80 (d, J = 7.63 Hz, 1 H), 6.87 (d, J = 8.85 Hz, 2 H), 7.06 (t, J = 7.78 Hz, 1 H), 7.35 (dt, J = 7.71, 1.07 Hz, 1 H), 7.55 (d, J = 8.55 Hz, 2 H), 8.30 (d, J = 7.63 Hz, 1 H); ^{13}C NMR δ 26.3, 55.4, 65.3, 107.8, 114.2, 118.3, 123.2, 125.0, 126.3, 131.2, 131.5, 133.4, 141.1, 160.2, 160.8; LC-MS, MS m/z 297 (M+H); *Anal.* Calcd for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.69; H, 5.42; N, 9.24.

(E)-3-(4-methoxybenzyloxyimino)-1-methylindolin-2-one ((E)-6ah). This compound was obtained as orange solid, m.p. 96.5–101.0°C; ^{1}H NMR δ 3.23 (s, 3 H), 3.81 (s, 3 H), 5.44 (s, 2 H), 6.80 (d, J = 7.94 Hz, 1 H), 6.91 (d, J = 8.55 Hz, 2 H), 7.00 (t, J = 7.63 Hz, 1 H), 7.35 (dt, J = 7.86, 1.07 Hz, 1 H), 7.39 (d, J = 8.54 Hz, 2 H), 7.88 (d, J = 7.32 Hz, 1 H); ^{13}C NMR δ 26.2, 55.4, 79.2, 108.3, 114.1, 116.0, 123.0, 128.0, 128.5, 130.3, 132.5, 144.0, 144.6, 160.0, 163.7; LC-MS, MS m/z 297 (M+H)); *Anal*. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.63; H, 5.31; N, 9.18.

(E)-2-tert-butoxy-N-(1-methyl-2-oxoindolin-3-ylidene)-2-oxoethanamine oxide ((E)-7ai). This compound was obtained as orange solid, m.p. 132.0–142.0°C; ^{1}H NMR δ 1.50 (s, 9 H), 3.25 (s, 3 H), 5.45 (s, 2 H), 6.83 (d, *J* = 7.93 Hz, 1 H), 7.10 (t, *J* = 7.63 Hz, 1 H), 7.39 (dt, *J* = 7.78, 1.22 Hz, 1 H), 8.34 (d, *J* = 7.63 Hz, 1 H); ^{13}C NMR δ 26.2, 28.1, 65.4, 83.7, 107.9, 117.8, 123.3, 125.3, 132.0, 134.9, 141.6, 160.7, 164.3; LC-MS, MS m/z 313 (M+Na); *Anal*. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.24; N, 9.65. Found: C, 61.72; H, 6.50; N, 9.28.

(E)-tert-butyl-2-(1-methyl-2-oxoindolin-3-ylideneaminooxy) acetate ((E)-6ai). This compound was obtained as yellow solid, m.p. 120.5–122.0°C; ^{1}H NMR δ 1.48 (s, 9 H), 3.22 (s, 3 H), 4.90 (s, 2 H), 6.81 (d, *J* = 7.63 Hz, 1 H), 7.06 (dt, *J* = 7.63, 0.92 Hz, 1 H), 7.39 (dt, *J* = 7.78, 1.22 Hz, 1 H), 8.05 (d, *J* = 7.63 Hz, 1 H); ^{13}C NMR δ 26.2, 28.3, 73.3, 82.5, 108.5, 115.7, 123.3, 128.7, 133.0, 144.8, 145.1, 163.5, 167.7; LC-MS, MS m/z 313 (M+Na); *Anal*. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.24; N, 9.65. Found: C, 61.87; H, 6.525; N, 9.56.

(E)-3-(Isopropoxyimino)-1-methylindolin-2-one ((E)-6ad). To a slurry of **4a** (5.02 g, 6.14 mmol) in EtOH (12 mL) was added a brown cloudy solution of 2-(ammoniooxy)propane chloride (0.822 g, 7.37 mmol) in H_2O (4 mL). The resulting brown reaction mixture was stirred at rt for 3 h, the solvent was removed *in vacuo* to leave a greenish-yellow oil which was redissolved in EtOAc (50 mL), and washed with 1*N* aqueous HCl (2 × 10 mL). The aqueous layers were extracted with EtOAc (50 mL), and the organic layers combined and washed with 10% aqueous Na_2CO_3 (10 mL) and brine before being dried and concentrated to afford a viscous yellow oil. ^{1}H NMR δ 1.42 (d, *J* = 6.10 Hz, 6H), 3.23 (s, 3H), 4.73–4.81 (m, 1H), 6.81 (d, *J* = 7.93 Hz, 1H), 7.05 (t, *J* = 7.63 Hz, 1H), 7.37 (t, *J* = 7.32 Hz, 1H), 7.95 (d, *J* = 7.63 Hz, 1H); ^{13}C NMR δ 21.8, 26.1, 79.6, 108.3, 116.1, 122.9, 127.7, 131.7, 143.3, 144.4, 163.9; LC-MS, MS m/z 219 (M+H).

3-(Hydroxyimino)-1-phenylindolin-2-one (5b). 3-(Hy-droxyimino)-1-phenylindolin-2-one (**5b**) was prepared in quantitative yield from 1-phenylisatin (**4b**) according to the procedure described for the preparation of **5a**. This compound was obtained as orange solid, m.p. 219.0–221.0°C (lit. m.p. 221°C) [26]; ^{1}H NMR δ 6.79 (d, *J* = 7.9 Hz, 1 H), 7.14 (dt, *J* = 7.6, 0.6 Hz, 1 H), 7.35 (dt, *J* = 7.8, 1.2 Hz, 1 H), 7.41–7.44 (m, 2 H), 7.46 (t, *J* = 7.6 Hz, 1 H), 7.57 (t, *J* = 7.6 Hz, 2 H), 8.15 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR δ 109.8, 116.2, 123.7, 127.0, 127.8, 128.7, 129.8, 132.1, 134.2, 144.0, 144.3, 164.5; *Anal*. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.75; found: C, 70.45; H, 4.14; N, 11.49.

(E)-3-(Isopropoxyimino)-1-phenylindolin-2-one ((E)-6bd) and (E)-N-(2-oxo-1-phenylindolin-3-ylidene)propan-2-amine oxide ((E)-7bd). Compounds ***(E)*-6bd** and ***(E)*-7bd** were prepared from **5b** in 36% and 47% yield, respectively, following the alkylation procedure used for the preparation of *(E)*-**6ad** and *(E)*-**7ad**.

(*E*)-7bd: This compound was obtained as orange solid, m.p. 83.0–89.0°C; ^{1}H NMR δ 1.47 (d, *J* = 6.4 Hz, 6 H), 6.30–6.39 (m, 1 H), 6.79 (d, *J* = 7.9 Hz, 1 H), 7.11 (t, *J* = 7.5 Hz, 1 H), 7.27 (t, *J* = 7.8 Hz, 1 H), 7.42 (d, *J* = 7.0 Hz, 3 H), 7.52 (t, *J* = 7.5 Hz, 2 H), 8.47 (d, *J* = 7.3 Hz, 1 H); ^{13}C NMR δ 20.5, 62.2, 109.1, 118.7, 123.6, 124.9, 127.0, 128.4, 129.7, 131.2, 132.8, 134.1, 140.8, 160.0; LC-MS, MS m/z 281 (M+H); *Anal*. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.83; H, 5.75; N, 9.99. Found: C, 72.72; H, 5.65; N, 9.92.

(*E*)-6bd: This compound was obtained as yellow solid, m.p. 125.5–127.0°C; ^{1}H NMR δ 1.47 (d, *J* = 6.1 Hz, 6 H), 4.78–4.87 (m, 1 H), 6.81 (d, *J* = 7.9 Hz, 1 H), 7.10 (t, *J* = 7.5 Hz, 1 H), 7.30 (dt, *J* = 7.9, 1.2 Hz, 1 H), 7.41 (d, *J* = 7.0 Hz, 3 H), 7.52 (t, *J* = 7.5 Hz, 2 H), 8.05 (d, *J* = 6.4 Hz, 1 H); ^{13}C NMR δ 21.9, 79.9, 109.7, 116.2, 123.4, 126.8, 127.9, 128.3, 129.8, 132.1, 134.0, 143.1, 144.4, 163.0; LC-MS, MS m/z 281 (M+H); *Anal*. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.83; H, 5.75; N, 9.99. Found: C, 72.77; H, 5.72; N, 9.93.

(E)-3-(Isopropoxyimino)-1-phenylindolin-2-one ((E)-6bd) and (E)-N-(2-oxo-1-phenylindolin-3-ylidene)propan-2-amine oxide ((E)-7bd). To a solution of **5b** (104 mg, 0.437 mmol), 2-propanol (67.4 μL, 0.875 mmol) and triphenylphosphine (229 mg, 0.875 mmol) in THF (1.8 mL) maintained at 0°C was added diisopropyl azodicarboxylate (172 μL, 0.875 mmol). The resulting greenish-yellow solution was stirred at rt for 18 h, diluted with EtOAc (25 mL) and washed with aqueous 10% Na_2CO_3. The aqueous layer was extracted with EtOAc (25 mL), and the combined organic layers washed with 0.1*N* HCl (5 mL) and brine, dried and concentrated to afford a light orange viscous oil. Chromatography on a column of silica gel using a 4:1 mixture of hexane and EtOAc as eluant gave nitrone ***(E)*-7bd** (91 mg, 74% yield) as an orange solid followed by oxime ether ***(E)*-6bd** (12.3 mg, 10% yield) as a yellow viscous oil which solidified upon standing at rt.

(*E*)-7bd: ^{1}H NMR δ 1.48 (d, *J* = 6.4 Hz, 6 H), 6.30–6.39 (m, 1 H), 6.80 (d, *J* = 7.9 Hz, 1 H), 7.13 (t, *J* = 7.6 Hz, 1 H), 7.29 (dt, *J* = 7.8, 0.9 Hz, 1 H), 7.41–7.46 (m, 3 H), 7.54 (t, *J* = 7.5 Hz, 2 H), 8.48 (d, *J* = 7.3 Hz, 1 H).

(*E*)-6bd: ^{1}H NMR δ 1.46 (d, *J* = 6.4 Hz, 6 H), 4.78–4.87 (m, 1 H), 6.81 (d, *J* = 7.9 Hz, 1 H), 7.10 (t, *J* = 7.6 Hz, 1 H), 7.30 (t, *J* = 7.8 Hz, 1 H), 7.39–7.43 (m, 3 H), 7.52 (t, *J* = 7.5 Hz, 2 H), 8.05 (d, *J* = 7.6 Hz, 1 H).

4-Bromo-1-methylindoline-2,3-dione (4c). K_2CO_3 (4.95 g, 35.84 mmol) and CH_3I (10.17 g, 71.67 mmol) were added to a solution of 4-bromoisatin (5.4 g, 23.89 mmol) in DMF (50 mL) and the mixture heated at 80°C for 30 min. After cooling to rt, the mixture was diluted with H_2O (50 mL) and the precipitated red solid collected by filtration and washed with H_2O (2 × 25 mL). The product was dried in a vacuum oven to give **4c** (5.20 g) as a red solid that was used further without purification, m.p.199.5–200.5°C; ^{1}H NMR δ 3.25 (s, 3 H), 6.84 (d, *J* = 7.9 Hz, 1 H), 7.26 (d, *J* = 3.4 Hz, 1 H), 7.41 (t, *J* = 8.1 Hz, 1 H); ^{13}C NMR δ 26.4, 108.7, 116.4, 121.7, 128.6, 138.4, 153.1, 157.4, 180.7; *Anal*. Calcd for $C_9H_6BrNO_2$: C, 45.03; H, 2.51; N, 5.83; Br, 33.28. Found: C, 44.84; H, 2.48; N, 5.83; Br, 33.02.

4-Bromo-3-(hydroxyimino)-1-methylindolin-2-one (5c). Compound **5c** was prepared from **4c** using the procedure described for the preparation of **5a** with the exception that the reaction was heated at 55°C overnight. This compound was obtained as orange solid, m.p. 186.0–188.5°C; ^{1}H NMR δ 3.25 (s, 3 H), 6.84 (d, *J* = 7.9 Hz, 1 H), 7.25 (d, *J* = 7.2 Hz, 1 H), 7.41 (t, *J* = 7.9 Hz, 1 H); ^{13}C NMR δ 26.4, 108.7, 116.4, 121.7, 128.6, 138.4, 153.1, 157.4, 180.7; *Anal*. Calcd for $C_9H_7BrN_2O_2$: C, 42.38; H, 2.76; N, 10.98; Br, 31.32. Found: C, 42.14; H, 2.73; N, 10.74; Br, 30.95.

(Z)-4-Bromo-3-(isopropoxyimino)-1-methylindolin-2-one ((Z)-6cd) and (E)-4-bromo-3-(isopropoxyimino)-1-methylindolin-2-one ((E)-6cd). To a slurry of **4c** (1.03 g, 4.29 mmol) in EtOH (12 mL) was added a brown cloudy solution of 2-(ammoniooxy)propane chloride (0.527 g, 4.72 mmol) in H_2O (4 mL). The brown mixture was stirred at 52°C for 3.5 h, the solvent removed in *vacuo* and the residue dissolved in EtOAc (50 mL) and washed with H_2O (50 mL). The aqueous layer was extracted with EtOAc (50 mL), and the combined organic layers were washed with brine, dried, and concentrated to leave a light orange viscous oil. Chromatography on a column of silica gel using a mixture of hexane and EtOAc (3:1 then 2:1) as eluant afforded oxime ether (*Z*)-**6cd** (0.706 g, 56% yield) followed by oxime ether *(E)*-**6cd** (0.448 g, 35% yield) both isolated as yellow solids.

(Z)-6cd: m.p. 67.0–68.5°C; ^{1}H NMR δ 1.46 (d, J = 6.41 Hz, 6H), 3.20 (s, 3H), 4.70–4.78 (m, 1H), 6.74 (d, J = 7.93 Hz, 1H), 7.15 (t, J = 7.93 Hz, 1H), 7.22 (d, J = 8.24 Hz, 1H); ^{13}C NMR δ 21.4, 25.8, 80.1, 107.0, 116.7, 118.5, 127.6, 131.0, 141.1, 144.9, 156.6; LC-MS, MS m/z 297 (M+H); *Anal*. Calcd for $C_{12}H_{13}BrN_2O_2$: C, 48.50; H, 4.41; N, 9.42; Br, 26.89. Found: C, 48.74; H, 4.28; N, 9.32; Br, 27.00.

***(E)*-6cd**: m.p. 78.0–79.5°C; ^{1}H NMR δ 1.44 (d, J = 6.10 Hz, 6H), 3.22 (s, 3H), 4.76–4.85 (m, 1H), 6.74 (d, J = 7.93 Hz, 1H), 7.16 (t, J = 8.09 Hz, 1H), 7.28 (dd, J = 8.24, 0.92 Hz, 1H); ^{13}C NMR δ 21.8, 26.4, 81.0, 107.4, 117.6, 119.8, 129.3, 132.6, 139.7, 147.1, 163.5; LC-MS, MS m/z 297 (M+H).

(*Z*)-**6cd** was also prepared exclusively by alkylation of **5c** with 2-iodopropane or 2-bromopropane under the same conditions used to prepare *(E)*-**6ad**, m.p. 66.5–68.0°C; ^{1}H NMR δ 1.46 (d, J = 6.4 Hz, 6H), 3.20 (s, 3H), 4.69–4.78 (m, 1H), 6.74 (dd, J = 7.6, 0.6 Hz, 1H), 7.16 (t, J = 7.9 Hz, 1H), 7.23 (dd, J = 8.2, 0.6 Hz, 1H); LC-MS, MS m/z 297 (M+H).

(*Z*)-**6cd** was also prepared exclusively in 85% yield from **5c** and isopropyl alcohol under the Mitsunobu conditions described for the preparation of *(E)*-**6bd** and *(E)*-**7bd** above. This compound was obtained as yellow solid, m.p. 66.0–67.5°C; ^{1}H NMR δ 1.47 (d, J = 6.4 Hz, 6H), 3.21 (s, 3H), 4.70–4.79 (m, 1H), 6.75 (d, J = 7.6 Hz, 1H), 7.16 (t, J = 7.9 Hz, 1H), 7.24 (d, J = 8.2 Hz, 1H); LC-MS, MS m/z 297 (M+H).

X-ray crystallographic data for compounds *(E)*-**6bd** and *(E)*-**7ad** have also been deposited with the Cambridge Crystallographic Data Center as CCDC 661142 and CCDC 661143, respectively.

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A Facile Electrochemical Method for the Synthesis of 5-Phenyl-1,3,4-oxadiazol-2-ylthio-benzene-1,2-diol Derivatives

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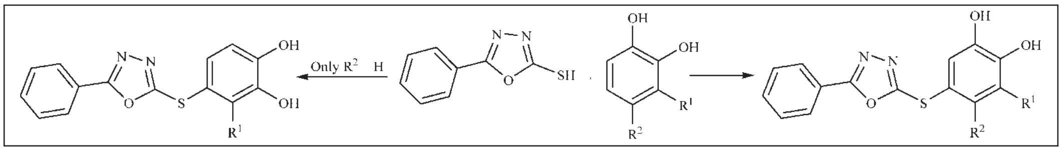

Electrochemical oxidation of catechols to corresponding *o*-quinones was successfully performed in aqueous solution by electrolysis at the controlled potentials. Quinones derived from catechols, participate in Michael addition reactions with 5-phenyl-1,3,4-oxadiazole-2-thiol and *via* EC mechanism, converted to corresponding 5-phenyl-1,3,4-oxadiazol-2-ylthio-benzene-1,2-diol derivatives (**4** and **4′**). The products have been characterized using IR, ^{1}H NMR, ^{13}C NMR, X-ray, and mass spectral data.

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INTRODUCTION

Derivatives of 1,3,4-oxadiazole constitute an important family of heterocyclic compounds. Some material applications of 1,3,4-oxadiazole derivatives lie in the field of liquid crystals [1]. 1,3,4-Oxadiazole derivatives are also among the most widely used electron-conducting and hole-blocking materials in organic light-emitting diodes [2]. Substituted 1,3,4-oxadiazoles are associated with many types of biological properties [3–5]. The 2-aryl-5-(substituted)-1,3,4-oxadiazoles have been reported to show antibacterial [6,7], antifungal [8], anti-inflammatory [9,10], and hypoglycemic [7] activity. Catechols can be oxidized electrochemically to *o*-quinones. *O*-quinones derived from catechols are quite reactive and can be attacked by nucleophiles [11–15]. Regarding the importance of 1,3,4-oxadiazole derivatives in biological systems and following our previous works [16–19], we have reported the simple electrochemical method for the synthesis of some novel 1,3,4-oxadiazole derivatives from catechols and 5-phenyl-1,3,4-oxadiazole-2-thiol in this work.

RESULTS AND DISCUSSION

The electrochemical oxidation of catechols (**1a–d**) in the presence of 5-phenyl-1,3,4-oxadiazole-2-thiol (**3**) undergoes a smooth 1:1 addition reaction in water medium at an ambient temperature to produce 5-phenyl-1,3,4-oxadiazol-2-ylthio-benzene-1,2-diol (**4** and **4′**). Cyclic voltammetry (CV) of 1 m*M* 4-methylcatechol (**1a**) in water/acetonitrile (95/5) solution containing 0.15*M* phosphate buffer (pH 7.2) shows one anodic (A_1) and corresponding cathodic peak (C_1), which is related to the transformation of 4-methylcatechol (**1a**) to *o*-benzoquinone (**2a**) and *vice versa* through a quasi-reversible two-electron process (Fig. 1, curve I).

A peak current ratio (I_P^{C1}/I_P^{A1}) of nearly one, particularly during the repetitive recycling of potential, can be considered as a criterion for the stability of *o*-benzoquinone produced at the surface of electrode under the experimental conditions. In other words, any hydroxylation [20] or dimerization [21] reactions are too slow to be observed on the time scale of the CV. Then, the electrochemical oxidation of catechols (**1**) was studied in the presence of 5-phenyl-1,3,4-oxadiazole-2-thiol (**3**) as a nucleophile. Figure 1 (curve II) shows the cyclic voltammogram obtained for a 1 m*M* 4-methylcatechol (**1a**) in the presence of 1 m*M* 5-phenyl-1,3,4-oxadiazole-2-thiol (**3**). The cyclic voltammogram of 1 m*M* 5-phenyl-1,3,4-oxadiazole-2-thiol (**3**) is shown in Figure 1, curve III, for comparison.

The multicyclic voltammograms of **1a** in the presence of **3** are shown in Figure 2. The voltammograms exhibit a relatively intense decrease in anodic peak (A_1) together with some potential shift in a positive direction. The positive shift of the A_1 peak in the presence of **3** is due to the formation of thin film of product at the surface of the electrode in the experimental condition [22].

Characteristics of the products are shown in Table 1. It can be observed that when methyl and methoxy groups are presented in C-3 position, two products are formed. This could be due to nucleophilic attack at either the C-4 or C-5 position. Further investigations

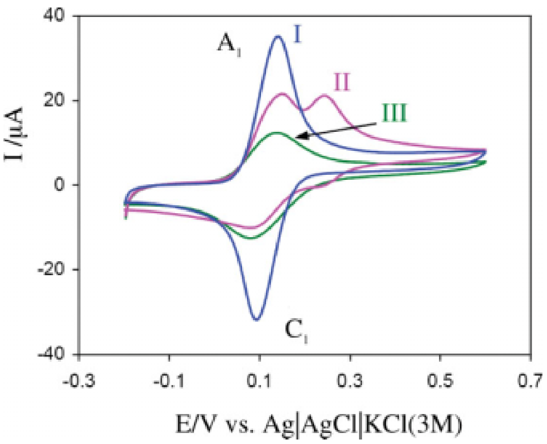


Figure 1. Cyclic voltammograms of 1 m*M* 4-methylcatechol (**1a**) in the absence (I) and in the presence (II) of 1 m*M* 5-phenyl-1,3,4-oxadiazole-2-thiol (**3**) and 1 m*M* 5-phenyl-1,3,4-oxadiazole-2-thiol (**3**) in the absence of 4-methylcatechol (III) at a glassy carbon electrode (1.8 mm diameter), in phosphate buffer (pH 7.2, $C = 0.15M$); scan rate: 100 mV s^{-1}; room temperature. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

confirmed the suggestion using ^1H NMR results and single crystal X-ray diffraction analysis (Fig. 3).

The percentage of each isomer was calculated from the ^1H NMR spectrum according to the intensity of peaks that are observed in both aliphatic and aromatic regions.

These voltammetry and spectral results allowed us to propose an EC mechanism [23] for the electrooxidation of catechols in the presence of 5-phenyl-1,3,4-oxadiazole-2-thiol (Scheme 1).

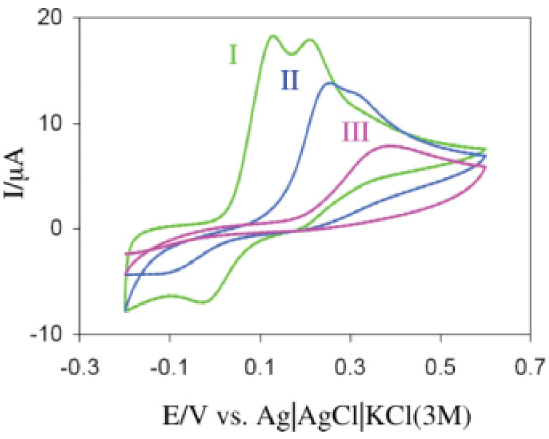
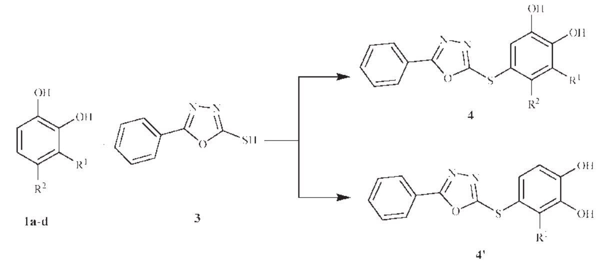


Figure 2. Multicycle voltammograms of 1 m*M* 4-methylcatechol (**1a**) in the presence of 5-phenyl-1,3,4-oxadiazole-2-thiol (**3**), at glassy carbon electrode (1.8 mm diameter) in water/acetonitrile (95/5) containing of phosphates (KH_2PO_4/K_2HPO_4) as the buffer and supporting electrolyte (pH 7.2, $C = 0.15M$), scan rate: 100 mV s^{-1}; room temperature. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Table 1

The electrochemical synthesis of products (**4** and **4′**).



Entry	R^1	R^2	%Product yield[a](**4**:**4′**)
a	H	Me	94
b	H	H	82
c	OCH_3	H	91 (75:25)
d	CH_3	H	93 (32:68)

[a] Isolated yield.

EXPERIMENTAL

Apparatus and reagents. Cyclic voltammetry was performed using µAutolab potentiostat/galvanostat type III. Preparative analysis was carried out using an EG&G PAR A Model 174 A potentiostat/galvanostat. The working electrode (WE) used in the voltammetry experiment was a glassy carbon disc (1.8 mm diameter), and the platinum wire was used as the counter electrode (CE). The WE used in macroscale electrolysis was an assembly of three carbon rods (8 mm diameter and 4 cm length) and a large platinum gauze (3 × 3 cm^2) constituted the CE. The WE potentials were measured *versus* the Ag|AgCl|KCl (3*M*) as a reference electrode (all electrodes were obtained from Azar electrode, Urmia, I. R. Iran). NMR spectra were recorded on a Bruker DRx-300 Avance Instruments. IR spectra were recorded on a Bruker IFS-66 FTIR Spectrophotometer. Mass spectra were obtained using a QP-1100EX Shimadzu GC-MS (EI at 70 eV). Melting points of the products were obtained using an electrothermal melting point model 9200.

Chemicals (catechol, 3-methoxycatechol, 4-methylcatechol, and 5-phenyl-1,3,4-oxadiazole-2-thiol) were reagent-grade, and phosphate salts were of pro-analysis grade from E. Merck and

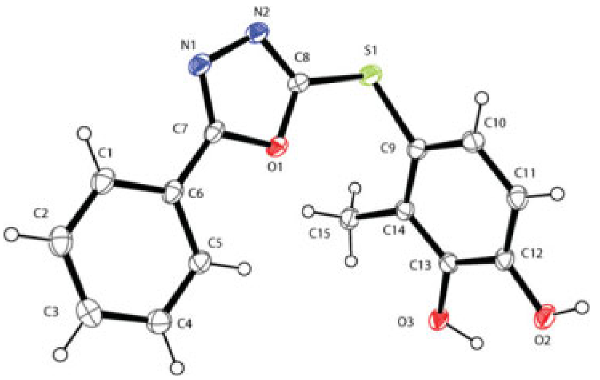
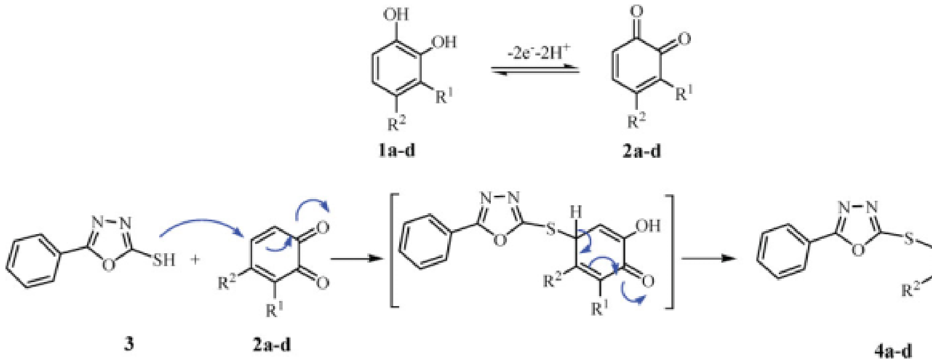


Figure 3. ORTEP structure of **4′d**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Scheme 1. Proposed mechanism for the electrooxidation of catechols in the presence of 5-phenyl-1,3,4-oxadiazole-2-thiol (**3**). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]



3-methylcatechol was reagent-grade from Acros. These chemicals were used without further purification. All experiments were carried out at room temperature.

Electroorganic synthesis of products. In a typical procedure, 100 mL mixture of water/acetonitrile (95/5) containing phosphates (KH_2PO_4/K_2HPO_4) as the buffer and supporting electrolyte (pH 7.2, $C = 0.15M$) was preelectrolyzed at the potential mentioned in Table 2 in an undivided cell. Subsequently, 2 mmol of catechols (**1a**–**d**) and 2 mmol of nucleophile (**3**) were added to the cell. Finally, the electrolysis was performed at the same potential.

The electrolysis was terminated when the decay of the current became more than 95%. The process was interrupted several times during the electrolysis and the carbon anode was washed in acetone to reactivate it. At the end of electrolysis, the cell was placed in a refrigerator overnight. The precipitated solid was collected by filtration and then was washed several times with distilled water. After purification, products were characterized using IR, ^{1}H NMR, ^{13}C NMR, X-ray, and Mass spectral data.

Characteristics of the products. ***4-(5-Phenyl-1,3,4-oxadiazol-2-ylthio)-5-methylbenzene-1,2-diol (4a).*** m.p. 205–207°C. IR (KBr) ν (cm^{-1}): 3443, 2924, 1709, 1608, 1583, 1555, 1472, 1420, 1364, 1292, 1224, 1197. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.29 (s, 3H, CH_3), 6.81 (s, 1H, CH), 7.07 (s, 1H, CH), 7.58 (m, 3H, CH), 7.87 (m, 2H, CH), 9.42 (broad, 2H, OH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 20.08, 113.00, 118.55, 123.08, 123.43, 126.76, 129.90, 132.50, 133.80, 144.55, 148.63, 163.71, 165.76. MS (70 eV) *m/z* (relative intensity): 301 (5), 178 (30), 145 (30), 124 (63), 77 (100), 39 (60).

4-(5-Phenyl-1,3,4-oxadiazol-2-ylthio)benzene-1,2-diol (4b). m.p. 164–166°C. IR (KBr) ν (cm^{-1}): 3447, 2924, 1603, 1550, 1477, 1434, 1358, 1277, 1253, 1187, 1150. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 6.84 (d, $^3J_{HH} = 8.22$ Hz, 1H, CH), 7.01 (d, $^3J_{HH} = 8.22$ Hz, 1H, CH), 7.07 (s, 1H, CH), 7.57 (m, 3H, CH), 7.88 (m, 2H, CH), 9.62 (broad, 2H, OH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 114.21, 117.10, 121.64, 123.40, 126.51, 126.81, 129.91, 132.57, 146.76, 148.34, 163.83, 165.88. MS (70 eV) *m/z* (relative intensity): 287 (10), 178 (55), 145 (30), 110 (70), 77 (100), 51 (55).

Mixture of 5-(5-phenyl-1,3,4-oxadiazol-2-ylthio)-3-methoxybenzene-1,2-diol (4c) 4-(5-phenyl-1,3,4-oxadiazol-2-ylthio)-3-methoxybenzene-1,2-diol (4′c). m.p. 175–178°C. IR (KBr) ν (cm^{-1}): 3367, 2937, 1600, 1551, 1503, 1472, 1341, 1293, 1196, 1088. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.74 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 6.68 (d, $^3J_{HH} = 8.40$ Hz, 1H, CH), 6.80 (s, 1H, CH), 6.83 (s, 1H, CH), 6.98 (d, $^3J_{HH} = 8.40$ Hz, 1H, CH), 7.56 (m, 6H, CH), 7.87 (m, 4H, CH), 9.34 (broad, 4H, OH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 56.59, 61.00, 108.67, 110.03, 112.28, 113.76, 115.55, 123.42, 125.69, 126.72, 126.80, 129.91, 132.56, 137.03, 139.92, 146.91, 149.27, 150.32, 163.66, 165.62, 165.91. MS (70 eV) *m/z* (relative intensity): 317 (20), 178 (40), 140 (100), 97 (50), 77 (75), 43 (60).

5-(5-Phenyl-1,3,4-oxadiazol-2-ylthio)-3-methylbenzene-1,2-diol (4d). m.p. 180–181°C. IR (KBr) ν (cm^{-1}): 3062, 2924, 1591, 1550, 1514, 1471, 1414, 1349, 1266, 1189. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.12 (s, 3H, CH_3), 6.94 (br s, 2H, CH), 7.59 (m, 3H, CH), 7.88 (m, 2H, CH), 8.91 (broad, 1H, OH), 9.77 (broad, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm):16.26, 113.40, 118.94, 123.42, 126.50, 126.84, 127.77, 129.94, 132.59, 146.08, 146.28, 163.88, 165.90. MS (70 eV) *m/z* (relative intensity): 300 (30), 178 (32), 145 (75), 124 (36), 77 (100), 51 (48).

4-(5-Phenyl-1,3,4-oxadiazol-2-ylthio)-3-methylbenzene-1,2-diol (4′d). m.p.178–180°C. IR (KBr) ν (cm^{-1}): 3077, 2660, 1608, 1552, 1479, 1353, 1290, 1213, 1178. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.28 (s, 3H, CH_3), 6.75 (d, $^3J_{HH} =$ 8.29 Hz, 1H, CH), 7.07 (d, $^3J_{HH} = 8.29$ Hz, 1H, CH), 7.56 (m, 3H, CH), 7.87 (m, 2H, CH), 8.74 (broad, 1H, OH), 9.98 (brod, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 14.52, 113.83, 114.46, 126.82, 127.83, 129.62, 132.47, 132.56, 144.95, 148.22, 165.67, 165.89. MS (70 eV) *m/z* (relative intensity): 300 (22), 178 (38), 124 (42), 77 (100), 39 (43).

Crystal data for (4′d) $C_{15}H_{12}N_2O_3S_1$, $M_w = 300.34$: space group monoclinic, $P2_1/a$, $a = 8.3924(6)$ Å, $b = 18.4381(15)$ Å, $c = 9.7245(6)$ Å, $\beta = 111.713(5)°$, $V = 1398.00(17)$ Å^{-3}:

Table 2

Applied potentials for the synthesis of products.

Conversion	Applied potential (*V*) *vs.* Ag|AgCl|KCl (3*M*)
1a → **4a**	0.15
1b → **4b**	0.2
1c → (**4c**:**4′c**)	0.10
1d → (**4d**:**4′d**)	0.15

$Z = 4$, $D_c = 1.427$ mg/m^3: $F(000) = 624$, crystal size = 0.20 mm × 0.16 mm × 0.12 mm, radiation Mo Kα ($\lambda = 0.71073$ Å), theta range for data collection 2.21°–29.28°. Intensity data were collected at 298 K with a STOE IDPS II two-circle diffractometer and using ω-scanning technique, in the range of $-11 \leq h \leq 10$, $-25 \leq k \leq 24$, $-13 \leq l \leq 13$. The structure was solved by direct methods [24] and refined an F^2 by full-matrix least squares using the X-STEP32 program package [25] giving a final $R_1 = 0.0684$, $wR_2 = 0.1520$ for $I > 2\sigma(I)$ reflections.

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Suzuki–Miyaura Arylations of Tetramic Acid Sulfonates: Evaluation of Lactam Protection, Sulfonate Esters, and Sterics

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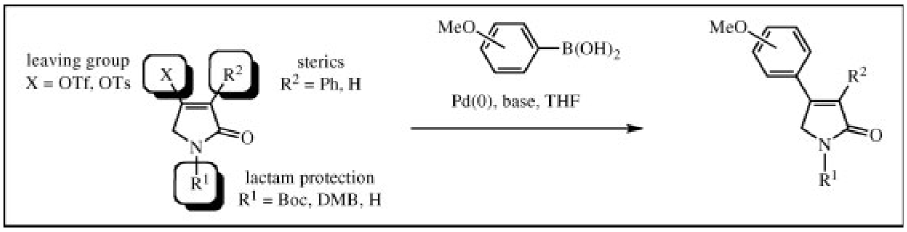

The synthesis of 3,4-diaryl-3-pyrrolin-2-ones and 4-aryl-3-pyrrolin-2-ones using Suzuki–Miyaura cross-coupling reactions of tetramic acid sulfonates with arylboronic acids has been studied. The effect that sulfonate ester, sterics, and lactam protection has on the cross-coupling reaction was evaluated. As expected, triflates were better cross-coupling partners than the corresponding tosylates. The yields were only partially affected by the incorporation of aryl groups at the 3-position. Importantly, tetramic acid triflates (and to a lesser extent tosylates) lacking a lactam protecting group were still competent substrates.

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INTRODUCTION

3,4-Diaryl-3-pyrrolin-2-ones **1a** and 4-aryl-3-pyrrolin-2-ones **1b** are important synthetic targets given their range of biological activity and utility as precursors to other compounds. 3,4-Diaryl-3-pyrrolin-2-ones have been investigated as inhibitors of cyclooxygenase-II (COX-II) [1], vascular endothelial growth factor receptor (VEGF-R) [2], and protein kinase C (PKC) [3]. 3,4-Diaryl-3-pyrrolin-2-ones have been used as building blocks for the preparation of the PKC inhibitor staurosporinone [4] and *N*-protected staurosporinones [5], whereas 4-aryl-3-pyrrolin-2-ones have been used as intermediates in the synthesis of 4-arylpyrrolidinones [6] (*e.g.*, antidepressant rolipram) [7], γ-aminobutyric acids [8] (*e.g.*, antispastic agent baclofen) [9], and β-arylpyrroles [10]. Before our involvement in this field [11,12], nearly all of the known methods to aryl-substituted 3-pyrrolin-2-ones **1** involved linear sequences that culminated in aldol-like cyclocondensations of α-amidoketones **2** [1,2,4,5,10a,13] (Fig. 1). An alternate method that has been explored to prepare 3,4-diaryl-3-pyrrolin-2-ones **1a** involves reducing the corresponding maleimides with borane [3a], but these reactions have proven to be nonselective [14]. Alternate methods used to synthesize 4-aryl-3-pyrrolin-2-ones **1b** include treatment of 4-bromo-2-butenoates with amines [6,8,15] and ring expansion of cyclobutanones [10b]. These literature methods all incorporate the C-4 aryl groups early in the sequence making them less applicable to the synthesis of C-4 aryl analogs [16]. A four component Ugi reaction provided access to 3,4-diaryl-3-pyrrolin-2-ones and 4-aryl-3-pyrrolin-2-ones, but this route was not amenable to the preparation of 5-unsubstituted derivatives [17,18].

Given their importance as drug candidates and building blocks, we initiated a program aimed at developing novel synthetic approaches to aryl-substituted 3-pyrrolin-2-ones that were amenable to the synthesis of new substitution patterns that allowed for the preparation of analogs. We recently reported our progress toward developing methodologies to **1** using Suzuki–Miyaura cross-coupling reactions of tetramic sulfonates **3a** [11a] and **4b** [11b] (Fig. 1). These methods have the potential to be useful in the synthesis of analogs given the late-stage introduction of C-4 aryl groups. The utility of our synthetic methodology was demonstrated by preparing the *N*-unsubstituted lactam analog of Vioxx® from **3a** and the 4-arylpyrrolidinone precursor to baclofen from **4b**.

We were initially inspired to investigate Suzuki–Miyaura cross-coupling reactions for the installation of C-4 aryl groups onto tetramic acid sulfonates by the analogous cross-coupling reactions of tetronic acid sulfonates **5** [19,20] and **6** [21] (Fig. 2). Interestingly, the cross-coupling of **6a** was reported to proceed in very low yield; this was attributed to a steric effect caused by the neighboring phenyl group [21a]. On the other hand, we observed excellent yields in the cross-coupling reactions of triflate **3a** which also contains a vicinal phenyl

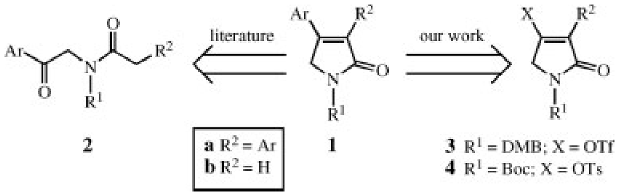


Figure 1. Synthetic approaches to 3,4-diaryl-3-pyrrolin-2-ones and 4-aryl-3-pyrrolin-2-ones.

group [11a]. To better understand the limitations of our methodology, we decided to systematically study the effect that sterics (R^3 = Ph *vs.* R^3 = H), sulfonate ester [trifluoromethanesulfonyl (OTf) *vs.* tosylsulfonyl (OTs)], and lactam protecting group [*tert*-butoxycarbonyl (Boc) *vs.* 3,4-dimethoxybenzyl (DMB)] have on the yield of the cross-coupling reaction. We thus set out to prepare new tetramic acid sulfonates **7** and **8** and compare their competence as cross-coupling substrates to our known tetramic acid sulfonates **3** and **4**. Our progress to date is reported herein.

RESULTS AND DISCUSSION

Tetramic acid sulfonate ester substrates (*e.g.*, **3a**) [11a] were prepared from the corresponding 3-phenyltetramic acids. The latter can be obtained *via* Dieckmann-like cyclocondensations of the corresponding *N*-phenylacetylglycinates [22]. Toward this end, treatment of glycine ethyl ester (**9**) with phenacetyl chloride gave known amide **10** [23] (Scheme 1). Conversion of **10** to **11** was achieved with Boc_2O and 4-(*N*,*N*′-dimethylamino)pyridine (DMAP) [24]. 3-Phenyltetramic acid **12** was then prepared by a Dieckmann cyclocondensation of **11** mediated by sodium *tert*-butoxide. Treatment of **12** with either triflic anhydride or tosyl chloride in the presence of triethylamine gave **7a** and **4a**, respectively.

In some cases, the synthesis of **7a** was accompanied by the formation of small amounts of lactam **13a** *via* a seemingly facile Boc deprotection (this was not observed with **4a**). We therefore decided to investigate cross-coupling reactions of substrates that did not contain protecting groups. Thus, we treated **7a** and **4a** with trifluoroacetic acid (TFA), and obtained lactams **13a** and **14a**, respectively.

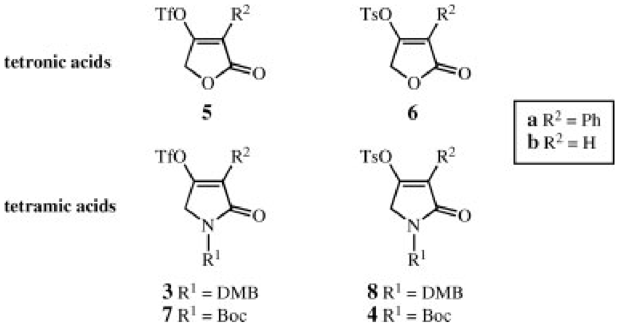
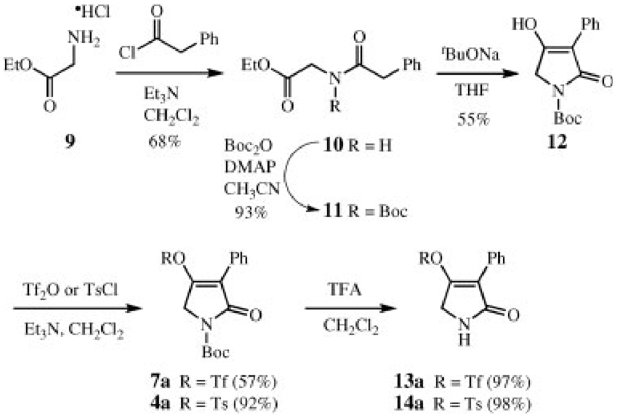


Figure 2. Tetramic acid sulfonates and tetronic acid sulfonates.

Scheme 1

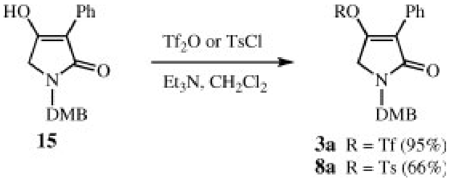


We reported a similar procedure for the synthesis of DMB-protected tetramic acid **15** [11a]. Treatment of **15** with either triflic anhydride or tosyl chloride in the presence of triethylamine gave **3a** [11a] and new compound **8a**, respectively (Scheme 2).

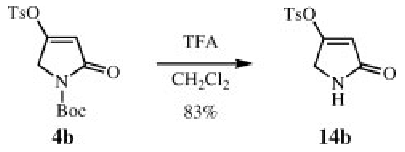
The next substrate that was prepared was *N*-unsubstituted tetramic acid tosylate **14b**. Known compound **4b** was available from our previous studies by the cyclocondensation of Boc-glycine with Meldrum's acid [11b,25]. Treatment of **4b** with TFA led to lactam **14b** (Scheme 3). We were not able to access 4-trifloxy-3-pyrrolin-2-one *via* this route as the requisite starting material, compound **7b**, turned out to be unstable and underwent a facile dimerization [11b].

With the tetramic acid sulfonate substrates in hand, we evaluated the effect that lactam protecting group, sulfonate leaving group, and sterics have on the yield of Suzuki–Miyaura cross-coupling reactions. We used our previously optimized conditions for cross-coupling reactions with tetramic acid triflates [Method A: $Pd(PPh_3)_4$ and Na_2CO_3] [11a] and tetramic acid tosylates [Method B: $Pd(1,1\text{-bis(diphenylphosphino)ferrocen})Cl_2(Pd(dppf)Cl_2)$, Cs_2CO_3] [11b]. To simplify our study and the analysis of the products, we used 4-methoxyphenylboronic acid. Our results are detailed later in Tables 1–3.

Scheme 2



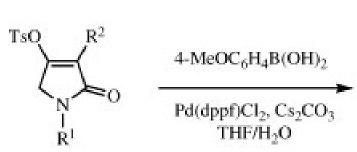
Scheme 3



We first examined the cross-coupling reactions of 3-phenyltetramic acid sulfonates (Table 1). The results shown in Table 1 describe the effect that lactam protecting group (R^1 = Boc *vs.* R^1 = DMB *vs.* R^1 = H) have on the cross-coupling reaction. These results also show the relative capabilities of the sulfonate leaving groups (X = OTf *vs.* X = OTs). In the triflate series, the Boc and DMB protecting groups were equivalent (97% *vs.* 95%); on the other hand in the tosylate series, the Boc protecting group proved to be superior (40% *vs.* Trace). We were pleasantly surprised to see that *N*-unsubstituted triflate **13a** proved to be a viable substrate providing known 3,4-diaryl-3-pyrrolin-2-one **18a** in 62% yield. This result indicates a potential for step savings that could be realized with this methodology during the preparation of analogs. Unlike triflate **13a**, cross-coupling with the corresponding *N*-unsubstituted tosylate **14a** failed to give product **18a**. As expected, triflate leaving groups proved to be superior to tosylate leaving groups; in some cases, triflate leaving groups appear to be required in the cross-coupling of unprotected lactams.

Next, we examined the cross-coupling reactions of tetramic acid tosylates **4** and **14** with 4-methoxyphenylboronic acid using Method B (Table 2). We used tosylates in this study as 3-unsubstituted triflates (R^2 = H) were not available. The results shown in Table 2 describe the effects of sterics (R^2 = Ph *vs.* R^2 = H) on the cross-coupling reactions. With Boc-protected tetramic acid tosylates **4**, the addition of a vicinal phenyl group lowered the yield (74% *vs.* 40%) although it did not shut down the reaction as was observed with the 3-phenyltetronic acid tosylate [21a]. Somewhat unexpectedly with *N*-unsubstituted tetramic acid tosylates **14**, the neighboring phenyl group precluded the reaction (55% *vs.* 0%). When further analyzing the importance of lactam protection, the yield was only partially diminished going from *N*-Boc tosylate **4b** to *N*-unsubstituted tosylate **14b** (74% *vs.* 55%).

Table 2

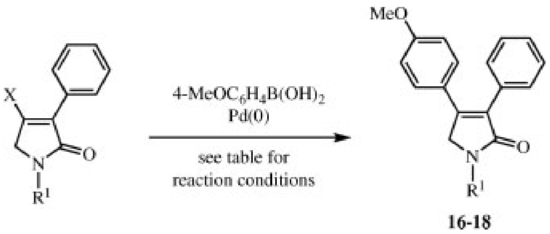


Substrate	R^1	R^2	Product	Yield (%)[a]
4b	Boc	H	**16b**	74
4a	Boc	Ph	**16a**	40
14b	H	H	**18b**	55
14a	H	Ph	**18a**	0

[a] Yields reported are for isolated, chromatographed materials.

Finally, we investigated the reactions of tetramic acid sulfonates with 4-methoxyphenylboronic acid and 2-methoxyphenylboronic acid (Table 3). The results shown in Table 3 describe the effects of sterics of the arylboronic acids on the cross-coupling reactions. With 3-phenyltetramic acid sulfonates **4a** and **7a**, the

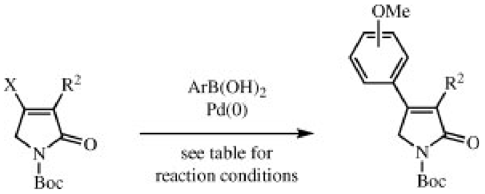
Table 1



Substrate	X	R^1	Methods[a]	Product	Yield (%)[b]
7a	OTf	Boc	A	**16a**	97
3a	OTf	DMB	A	**17a**	95
13a	OTf	H	A	**18a**	62
4a	OTs	Boc	B	**16a**	40
8a	OTs	DMB	B	**17a**	trace
14a	OTs	H	B	**18a**	0

[a] Methods A = $Pd(PPh_3)_4$, Na_2CO_3, THF/H_2O; B = $Pd(dppf)Cl_2$, Cs_2CO_3, THF/H_2O.
[b] Yields reported are for isolated, chromatographed materials.

Table 3



Substrate	X	R^2	Ar	Product	Yield (%)[a]
7a[b]	OTf	Ph	4-$MeOC_6H_4$	**16a**	97
7a[b]	OTf	Ph	2-$MeOC_6H_4$	**19a**	61
4a[c]	OTs	Ph	4-$MeOC_6H_4$	**16a**	40
4a[c]	OTs	Ph	2-$MeOC_6H_4$	**19a**	33
4b[c]	OTs	H	4-$MeOC_6H_4$	**16b**	74
4b[c]	OTs	H	2-$MeOC_6H_4$	**19b**	74

[a] Yields reported are for isolated, chromatographed materials.
[b] Method A.
[c] Method B.

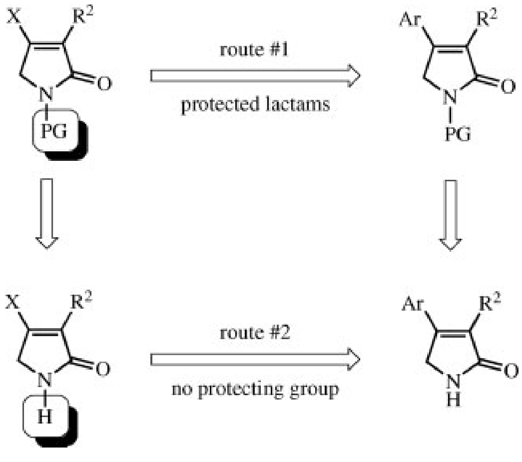
reactions with 4-methoxyphenylboronic acid were higher yielding than the reactions with 2-methoxyphenylboronic acid, although the effect was muted with tosylate **4a**. With the 3-unsubstituted tetramic acid tosylate **4b**, no difference in yield was observed; consequently, the steric effect appears to arise from the vicinal phenyl group (R^2 = Ph) and not from the steric differences of the arylboronic acids.

In conclusion, the Suzuki–Miyaura cross-coupling of tetramic acid sulfonates has proven to be a versatile methodology for the preparation of 3,4-diaryl-3-pyrrolin-2-ones and 4-aryl-3-pyrrolin-2-ones. This synthetic methodology provides facile access to C-4 analogs. The effect that sulfonate ester, sterics, and lactam protection has on the cross-coupling reaction was studied systematically. In all cases, triflates were better cross-coupling partners than the corresponding tosylates. The reactions still proceeded with vicinal phenyl groups, although the yield was partially diminished. We were pleased to find that tetramic acid triflates (and to a lesser extent tetramic acid tosylates) lacking a lactam protecting group proved to be competent substrates [26]. The latter result has the potential to improve the step economy [27] associated with preparing analogs *via* Suzuki–Miyaura cross-coupling reactions of lactams. Each analog can be prepared in one step using *N*-unsubstituted lactam (route #2), while two steps per analog are required with the corresponding *N*-substituted lactam (route #1) (Scheme 4).

EXPERIMENTAL

General remarks. All reactions were performed under a positive argon atmosphere with magnetic stirring unless otherwise noted. Tetrahydrofuran (THF) and CH_2Cl_2 were purified by passage through a column of alumina using a PureSolv 400 solvent purification system. Et_3N was distilled fresh from calcium hydride immediately before use. Unless otherwise indicated, all other reagents and solvents were purchased from commercial sources and were used without further purification. Petroleum ether (PE) refers to the fraction with boiling point 35–60°C. 4-Methoxyphenylboronic acid and 2-methoxyphenylboronic acid were purchased from Aldrich® and used as provided. ^1H NMR and ^{13}C NMR chemical shifts are reported in parts per million (δ) using the solvents residual proton or carbon signal ($CDCl_3$: δH 7.24 ppm, δC 77.3 ppm; d_6-DMSO: δH 2.50 ppm, δC 39.5 ppm) as an internal reference. Flash chromatography was performed with silica gel (230–400 mesh), and thin-layer chromatography (TLC) was performed with glass-backed silica gel plates and visualized with UV (254 nm). IR spectra were measured using a Perkin–Elmer Spectrum 100 with ATR sampler (attenuated total reflectance). Known tetramic acid derivatives **3a** [11a], **4b** [11b], and **15**

Scheme 4



[11a] were prepared using our previously published procedures.

Ethyl 2-(2′-phenylacetamido)acetate (10) [23]. A modification of a known procedure to the corresponding methyl ester was followed [28]. To a 0°C stirred solution of glycine ethyl ester hydrochloride (**9**) (10.0 g, 104 mmol) in CH_2Cl_2 (155 mL) was added ice-cooled, neat Et_3N (21.0 g, 28.9 mL, 208 mmol) followed by a solution of phenylacetyl chloride (16.1 g, 13.8 mL, 104 mmol) in CH_2Cl_2 (45 mL) dropwise *via* addition funnel. The cloudy yellow reaction mixture was stirred at 0°C for 2 h and then at rt for 2 h. The organic layer was then washed with H_2O (250 mL), brine (250 mL), and dried over sodium sulfate. Removal of the solvent *in vacuo* gave a crude yellow oil that solidified on standing. Trituration (ether) gave the known titled compound **10** as a yellow amorphous solid (15.6 g, 70.5 mmol, 68% yield): mp 77–79°C (lit. [23b] mp 79–82°C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24–7.38 (m, 5H), 5.91 (br s, 1H), 4.15 (q, 3H, $J = 7.1$ Hz), 3.97 (d, 2H, $J = 5.1$ Hz), 3.61 (s, 2H), 1.22 (t, 4H, $J = 3.6$ Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.4, 170.0, 134.7, 129.7, 129.3, 127.7, 61.8, 43.7, 41.7, 14.4 ppm.

Ethyl 2-(*N*-(*tert*-butoxycarbonyl)-2′-phenylacetamido)-acetate (11). To a rt stirred solution of **10** (15.6 g, 70.6 mmol) in CH_3CN (170 mL) was added DMAP (0.862 g, 7.06 mmol) followed by a solution of Boc_2O (16.9 g, 79.0 mmol) in CH_3CN (80 mL). The brown reaction mixture was stirred at rt for 3 h. The solvent was then concentrated *in vacuo* to give a brown oil that was taken up in ether (50 mL) and washed with an aqueous solution of HCl (1*M*, 40 mL), brine (40 mL), and dried over sodium sulfate. Removal of the solvent *in vacuo* gave the title compound **11** as a brown oil, which was used directly without further purification (21.0 g, 65.3 mmol, 93% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.19–7.29 (m, 5H), 4.43 (s, 2H), 4.28 (s, 2H), 4.16 (q, 2H, $J = 7.2$ Hz), 1.46 (s, 9H), 1.24 (t, 3H, $J = 7.2$ Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.1, 169.2, 152.4, 135.1, 129.9, 128.6, 127.1, 84.3, 61.5, 45.9, 44.4, 28.1, 14.5 ppm.

***tert*-Butyl 2,5-dihydro-4-hydroxy-2-oxo-3-phenyl-1*H*-pyrrole-1-carboxylate (12).** To a 0°C stirred solution of **11** (15.1 g, 47.1 mmol) in THF (200 mL) was added sodium *tert*-butoxide (5.43 g, 47.1 mmol). The cloudy rust-colored reaction mixture was stirred at 0°C for 2 h and then at rt overnight. An aqueous solution of $KHSO_4$ (12.8 g, 94.0 mmol in 200 mL H_2O) was added to the reaction mixture and allowed to stir for 20 min. The THF was then removed *in vacuo*, and the remaining aqueous layer was extracted with ethyl acetate (EtOAc) (3 × 80 mL). The combined organic layers were then washed with brine (200 mL) and dried over sodium sulfate. Removal of the solvent *in vacuo* gave a crude yellow solid. Trituration (EtOAc) gave the titled compound **12** as white crystals (7.04 g, 25.6 mmol, 55% yield): mp 134–135°C; IR (ATR, neat) 3141, 1745, 1718, 1663, 1639, 1408, 1350, 1313, 1257, 1155, 1103, 1073, 980, 898, 851, 780, 754, 742, 721, 694, 665 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.39 (br s, 1H), 7.84 (d, 2H, $J = 7.2$ Hz), 7.35 (t, 2H, $J = 7.5$ Hz), 7.20 (t, 1H, $J =$ 7.5), 4.27 (s, 2H), 1.48 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.4, 168.0, 149.0, 131.1, 127.9, 127.0, 126.2, 103.5, 81.1, 47.9, 27.8 ppm; *Anal.* calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.23; H, 6.22; N, 5.00.

***tert*-Butyl 2,5-dihydro-2-oxo-3-phenyl-4-(trifluoromethylsulfonoxy)-1*H*-pyrrole-1-carboxylate (7a).** To a −15°C stirred solution of **12** (1.21 g, 4.65 mmol) in CH_2Cl_2 (30 mL) was added neat Et_3N (0.626 g, 0.860 mL, 6.18 mmol) followed by neat trifluoromethanesulfonic anhydride (Tf_2O; 1.44 g, 0.860 mL, 5.11 mmol) dropwise *via* syringe. The reaction mixture was stirred at −15°C for 2.5 h at which point TLC showed complete conversion of the starting material **12**. The reaction mixture first turned green on the addition of Tf_2O, and then turned into a clear yellow solution after 5 min. The reaction mixture was poured onto an aqueous solution of $KHSO_4$ (1.27 g, 9.33 mmol in 75 mL H_2O) and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with an aqueous solution of sodium bicarbonate (1% *w*/*v*, 100 mL), brine (100 mL), and dried over sodium sulfate. Removal of the solvent *in vacuo* gave a crude yellow solid (1.36 g). Purification by flash column chromatography (gradient: 1:15 to 1:11 EtOAc/PE) gave the titled compound **7a** as an analytically pure yellow solid (1.07 g, 2.63 mmol, 57% yield): mp 94–96°C; $R_f = 0.34$ (1:8 EtOAc/PE); IR (ATR, neat) 2980, 1772, 1693, 1449, 1424, 1371, 1328, 1311, 1293, 1247, 1223, 1211, 1151, 1133, 1096, 969, 922, 902, 847, 820, 783, 764, 735, 696, 670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.62–7.65 (m, 2H), 7.41–7.44 (m, 3H), 4.59 (s, 2H), 1.57 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.6, 154.9, 149.2, 130.2, 129.1, 129.0, 126.2, 124.6, 118.5 (q, $J = 320$ Hz), 84.6, 47.8, 28.3 ppm; *Anal.* calcd for $C_{16}H_{16}F_3NO_6S$: C, 47.17; H, 3.96; N, 3.44. Found: C, 47.13; H, 3.89; N, 3.39.

***tert*-Butyl 2,5-dihydro-2-oxo-3-phenyl-4-(tosyloxy)-1*H*-pyrrole-1-carboxylate (4a).** To a rt stirred solution of **12** (1.00 g, 3.65 mmol) in CH_2Cl_2 (40 mL) was added TsCl (0.730 g, 3.83 mmol) followed by neat Et_3N (0.443 g, 0.608 mL, 4.38 mmol) dropwise *via* syringe. The reaction mixture was stirred at rt for 1 h at which point TLC showed complete conversion of the starting material **12**. The reaction mixture was poured onto an aqueous solution of $KHSO_4$ (0.992 g, 7.30 mmol in 50 mL H_2O) and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with an aqueous solution of sodium bicarbonate (1% *w*/*v*, 150 mL), brine (150 mL), and dried over sodium sulfate. Removal of the solvent *in vacuo* gave the titled compound **4a** as a yellow amorphous solid (1.44 g, 3.35 mmol, 92% yield). Recrystallization (CH_2Cl_2) gave the analytical sample as yellow crystals: mp 137–140°C; $R_f = 0.76$ (1:2 EtOAc/PE); IR (ATR, neat) 1770, 1450, 1377, 1335, 1314, 1287, 1192, 1159, 1091, 977, 898, 781, 761, 697, 664 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60 (d, 2H, $J = 8.4$ Hz), 7.35–7.39 (m, 2H), 7.21–7.25 (m, 3H), 7.11 (d, 2H, $J = 9.0$ Hz), 4.58 (s, 1H), 2.35 (s, 3H), 1.57 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.7, 156.6, 149.0, 147.5, 131.1, 129.9, 128.7, 128.6, 128.2, 128.0, 127.0, 122.5, 83.7, 48.2, 28.1, 21.7 ppm; *Anal.* calcd for $C_{22}H_{23}NO_6S$: C, 61.52; H, 5.40; N, 3.26. Found: C, 61.13; H, 5.46; N, 3.31.

2,5-Dihydro-2-oxo-3-phenyl-4-(trifluoromethylsulfonoxy)-1*H*-pyrrole (13a). To a rt stirred solution of **7a** (1.50 g, 3.68 mmol) in CH_2Cl_2 (10 mL) was added TFA (10 mL). The reaction mixture was stirred at rt for 5 min at which point TLC showed complete conversion of the starting material **7a**. Removal of the solvent *in vacuo* gave a crude brown oil that was taken up in $CHCl_3$ (20 mL) and washed with a saturated aqueous solution of sodium bicarbonate (20 mL). The aqueous layer was extracted with $CHCl_3$ (3 × 20 mL) and the combined organic layers were then washed with brine (50 mL) and dried over sodium sulfate. Removal of the solvent *in vacuo* gave the titled compound **13a** as a yellow amorphous solid (1.10 g, 3.58 mmol, 97% yield). Recrystallization (EtOH) gave the analytical sample as yellow crystals: mp 117–119°C; R_f = 0.33 (1:2 EtOAc/PE); IR (ATR, neat) 3072, 1699, 1420, 1333, 1211, 1170, 1134, 1025, 958, 919, 825, 781, 766, 735, 694, 681 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.78 (s, 1H), 7.61–7.64 (m, 2H), 7.46–7.49 (m, 3H), 4.36 (d, 2H, J = 1.2 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.1, 155.6, 129.3, 128.5, 128.4, 127.2, 123.3, 117.7 (q, J = 320 Hz), 44.5 ppm; *Anal.* calcd for $C_{11}H_8F_3NO_4S$: C, 43.00; H, 2.62; N, 4.56. Found: C, 42.91; H, 2.59; N, 4.58.

2,5-Dihydro-2-oxo-3-phenyl-4-(tosyloxy)-1*H*-pyrrole (14a). To a rt stirred solution of **4a** (1.00 g, 2.33 mmol) in CH_2Cl_2 (20 mL) was added TFA (20 mL). The reaction mixture was stirred at rt for 5 min at which point TLC showed complete conversion of the starting material **4a**. Removal of the solvent *in vacuo* gave a crude brown oil that was taken up in $CHCl_3$ (20 mL) and washed with a saturated aqueous solution of sodium bicarbonate (20 mL). The aqueous layer was extracted with $CHCl_3$ (3 × 25 mL) and the combined organic layers were then washed with a saturated aqueous solution of sodium bicarbonate (200 mL), brine (200 mL), and dried over sodium sulfate. Removal of the solvent *in vacuo* gave titled compound **14a** as a yellow amorphous solid (0.750 g, 2.28 mmol, 98% yield). Recrystallization (CH_2Cl_2) gave the analytical sample as light yellow crystals: mp 159–161°C; R_f = 0.21 (1:1 EtOAc/PE); IR (ATR, neat) 3071, 1686, 1593, 1497, 1451, 1360, 1306, 1236, 1204, 1182, 1172, 1088, 1039, 960, 813, 786, 735, 703, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.47 (s, 1H), 7.73–7.76 (m, 2H), 7.28–7.37 (m, 7H), 4.20 (d, 2H, J = 0.9 Hz), 2.35 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.3, 156.6, 146.6, 130.5, 130.2, 128.2, 128.1, 128.0, 127.9, 121.5, 44.9, 21.2 ppm; *Anal.* calcd for $C_{17}H_{15}NO_4S$: C, 61.99; H, 4.59; N, 4.25. Found: C, 62.00; H, 4.64; N, 4.29.

2,5-Dihydro-1-(3′,4′-dimethoxybenzyl)-2-oxo-3-phenyl-4-(tosyloxy)-1*H*-pyrrole (8a). To a rt stirred solution of known tetramic acid **15** [2] (2.00 g, 6.18 mmol) in CH_2Cl_2 (60 mL) was added TsCl (1.23 g, 6.46 mmol) followed by neat Et_3N (0.748 g, 1.028 mL, 7.39 mmol) dropwise *via* syringe. The reaction mixture was stirred at rt for 2 h at which point TLC showed complete conversion of the starting material **15**. The reaction mixture was poured onto an aqueous solution of $KHSO_4$ (1.99 g, 14.6 mmol in 75 mL H_2O) and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with an aqueous solution of sodium bicarbonate (1% *w*/*v*, 150 mL), brine (150 mL), and dried over sodium sulfate. Removal of the solvent *in vacuo* gave a crude clear oil (2.79 g) that was purified by flash column chromatography (gradient: 1:5 to 1:1 EtOAc/PE). Removal of the solvent *in vacuo* gave the titled compound **8a** as a clear oil. Trituration (MeOH) gave the analytical sample as a white solid (1.94 g, 4.05 mmol, 66% yield): mp 110–112°C; R_f = 0.17 (1:2 EtOAc/PE); IR (ATR, neat) 1688, 1593, 1517, 1447, 1405, 1356, 1338, 1296, 1280, 1263, 1356, 1338, 1296, 1280, 1263, 1236, 1205, 1160, 1136, 1090, 1022, 973, 956, 900, 814, 787, 766, 741, 706, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.52 (d, 2H, J = 8.1 Hz), 7.43–7.46 (m, 2H), 7.20–7.22 (m, 3H), 7.05 (d, 2H, J = 8.7 Hz), 6.79 (d, 3H, J = 12 Hz), 4.59 (s, 2H), 4.12 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 2.31 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.3, 154.8, 149.6, 149.0, 146.5, 131.4, 130.0, 129.4, 128.8, 128.6, 128.4, 128.2, 122.5, 120.9, 111.5, 111.4, 56.2, 49.4, 46.1, 21.9 ppm; *Anal.* calcd for $C_{26}H_{25}NO_6S$: C, 65.12; H, 5.25; N, 2.92. Found: C, 65.05; H, 5.37; N, 2.92.

2,5-Dihydro-2-oxo-4-(tosyloxy)-1*H*-pyrrole (14b). To a 0°C stirred solution of known tosylate **4b** [11b] (0.600 g, 1.70 mmol) in CH_2Cl_2 (8.6 mL) was added TFA (8.6 mL) dropwise *via* syringe. The reaction mixture was stirred for 0.5 h. Removal of the solvent *in vacuo* gave a crude product that was taken up in $CHCl_3$ (25 mL) and washed with an aqueous solution of sodium bicarbonate (5% *w*/*v*, 2 × 25 mL), brine (25 mL), and dried over sodium sulfate. Removal of the solvent *in vacuo* gave the titled compound **14b** as a white amorphous solid (0.355 g, 1.40 mmol, 83% yield): mp 151–153°C; IR (ATR, neat) 3102, 1693, 1631, 1596, 1386, 1360, 1325, 1216, 1196, 1184, 1161, 1092, 980, 921, 877, 818, 803, 782, 704, 667 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.03 (s, 1H), 7.96 (d, 2H, J = 8.4 Hz), 7.54 (d, 2H, J = 8.1 Hz), 5.62 (d, 1H, J = 1.5 Hz), 3.93 (t, 2H, J = 1.2 Hz), 2.45 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.8, 163.3, 146.9, 130.6, 130.4, 128.5, 107.4, 46.2, 21.2 ppm; *Anal.* calcd for $C_{11}H_{11}NO_4S$: C, 52.16; H, 4.38; N, 5.53; S, 12.66. Found: C, 52.10; H, 4.30; N, 5.47; S, 12.71.

General procedures for Suzuki–Miyaura reactions

Method A (tetramic acid triflates). To a rt stirred solution of tetramic acid triflate (1.00 mmol) in THF (10 mL) was added an arylboronic acid (1.50 mmol) and was allowed to dissolve completely. To this solution was added $Pd(PPh_3)_4$ (0.050 mmol) followed by an aqueous solution of sodium carbonate (2.2 mmol in 1 mL H_2O). The reaction mixture was stirred at rt for 40 min and then heated to reflux until TLC showed complete conversion of the starting triflate (typically 1–3 h). The reaction mixture was then filtered through a short plug of celite with the aid of EtOAc. Removal of the solvent *in vacuo* gave a crude solid that was purified by flash column chromatography (gradient: 1:4 to 1:1 EtOAc/PE).

Method B (tetramic acid tosylates). To a rt stirred solution of tetramic acid tosylate (1.00 mmol) in THF (10 mL) was added an arylboronic acid (1.50 mmol) and was allowed to dissolve completely. To this solution was added $Pd(dppf)Cl_2$ (0.050 mmol) followed by a solution of an aqueous solution of cesium carbonate (3.00 mmol, 1 mL H_2O). The reaction mixture was stirred at rt for 40 min and heated to reflux until TLC showed complete conversion of the starting material (typically 12–20 h). The reaction mixture was then filtered through a short plug of celite with the aid of EtOAc. The organic layer was washed with a saturated aqueous solution of sodium bicarbonate (50 mL), brine (50 mL), and dried over sodium sulfate. Removal of the solvent *in vacuo* gave a crude oil that was purified by flash column chromatography (gradient: CH_2Cl_2 to 8:92 EtOAc/CH_2Cl_2).

***tert*-Butyl 2,5-dihydro-4-(4′-methoxyphenyl)-2-oxo-3-phenyl-1*H*-pyrrole-1-carboxylate (16a).** Using triflate **7a**, Method **A** was followed and gave the titled compound **16a** as a light yellow amorphous solid (97% yield). Recrystallization (EtOAc) gave the analytical sample as white crystals: mp 177–179°C; R_f = 0.60 (1:2 EtOAc/PE); IR (ATR, neat) 1763, 1686, 1604, 1516, 1450, 1366, 1348, 1313, 1298, 1257, 1160, 1123, 1097, 1027, 926, 912, 851, 835, 787, 743, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33–7.34 (m, 5H), 7.26 (d, 2H,

J = 7.5 Hz), 6.79 (d, 2H, J = 9.0 Hz), 4.64 (s, 2H), 3.79 (s, 3H), 1.58 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.9, 161.2, 150.5, 149.3, 131.8, 130.7, 129.9, 129.7, 128.8, 128.6, 124.7, 114.4, 83.3, 55.6, 50.9, 28.4 ppm; *Anal.* calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.10; H, 6.38; N, 3.87.

Using tosylate **4a**, Method **B** was followed and gave the titled compound **16a** as a light yellow amorphous solid (40% yield) which gave spectral data consistent with the material prepared from triflate **7a**.

2,5-Dihydro-1-(3′,4′-dimethoxybenzyl)-4-(4″-methoxyphenyl)-2-oxo-3-phenyl-1*H*-pyrrole (17a). Using triflate **3a** [11a], Method **A** was followed and gave the titled compound **17a** as a yellow amorphous solid as reported previously [11a] (95% yield).

Using tosylate **8a**, Method **B** was followed in an attempt to obtain the titled compound **17a**; however, only a trace amount of product was formed as seen by TLC. Flash column chromatography gave only starting material **3a**.

2,5-Dihydro-4-(4′-methoxyphenyl)-2-oxo-3-phenyl-1*H*-pyrrole (18a). Using triflate **13a**, Method **A** was followed and gave the titled compound **18a** as a white amorphous solid (62% yield): mp 169–174°C (lit. [11a] mp 193–196°C); R_f = 0.28 (1:1 EtOAc/PE); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.42 (s, 1H), 7.29–7.37 (m, 3H) 7.24–7.28 (m, 4H) 6.87 (d, 2H, J = 8.7 Hz), 4.33 (s, 2H), 3.74 (s, 3H) ppm. The physical properties and spectral data for 18a were consistent to that reported previously [11a].

Using tosylate **14a**, Method **B** was followed in an attempt to obtain **18a**; however, spectroscopic and TLC assessment of the crude material obtained on work-up failed to reveal even reveal a trace of **18a**.

***tert*-Butyl 2,5-dihydro-4-(4′-methoxyphenyl)-2-oxo-1*H*-pyrrole-1-carboxylate (16b).** Using tosylate **4b** [11b], Method **B** was followed and gave the titled compound **16b** as a tan amorphous solid (74% yield): mp 151–154°C (lit. [11b] mp 158–160°C); R_f = 0.31 (1:2 EtOAc/PE); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.59 (d, 2H, J = 9 Hz), 6.92 (d, 2H, J = 8.7 Hz), 6.24 (t, 1H, J = 1.2 Hz), 4.62 (d, 2H, J = 1.5 Hz), 3.82 (s, 3H), 1.55 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.8, 162.2, 156.0, 150.0, 128.1, 123.7, 117.6, 114.8, 83.1, 55.7, 51.2, 28.4 ppm. The physical properties and spectral data for **16b** were consistent to that reported previously [11b].

2,5-Dihydro-4-(4′-methoxyphenyl)-2-oxo-1H-pyrrole (18b). Using tosylate **14b**, Method **B** was followed and gave the titled compound **18b** as a tan amorphous solid (55% yield): mp 185–188°C (lit. [11b] mp 198–199°C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.05 (s, 1H), 7.61 (q, 2H, J = 4.5 Hz), 6.99 (d, 2H, J = 8.7 Hz), 6.38 (d, 1H, J = 1.2 Hz), 6.33 (d, 2H, J = 0.9 Hz), 3.80 (s, 3H) ppm. The physical properties and spectral data for **18b** were consistent to that reported previously [11b].

***tert*-Butyl 2,5-dihydro-4-(2′-methoxyphenyl)-2-oxo-3-phenyl-1*H*-pyrrole-1-carboxylate (19a).** Using triflate **7a**, Method **A** was followed and gave the titled compound **19a** as a yellow oil which partially solidified (61% yield). Crystallization (EtOH) gave the analytical sample as yellow crystals: mp 122–126°C; R_f = 0.44 (1:4 EtOAc/PE); IR (ATR, neat) 2967, 1759, 1680, 1596, 1470, 1350, 1292, 1257, 1152, 1100, 1014, 912, 786, 756, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28–7.31 (m, 3H), 7.21–7.23 (m, 2H), 7.00–7.03 (m, 1H), 6.82–6.90 (m, 2H), 4.65 (s, 2H), 3.65 (s, 3H), 1.57 (s 9H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.5, 157.2, 150.4, 149.8, 133.2, 131.6, 131.1, 130.5, 129.4, 128.3, 128.2, 122.1, 122.0, 111.6, 83.1, 55.5, 52.1, 28.5 ppm; *Anal.* calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.03; H, 6.46; N, 3.81.

Using tosylate **4a**, Method **B** was followed and gave the titled compound **19a** as a yellow oil (33% yield) that gave spectral data consistent with the material prepared from **7a**.

2,5-Dihydro-4-(2′-methoxyphenyl)-2-oxo-1*H*-pyrrole-1-carboxylate (19b). Using tosylate **4b** [11b], Method **B** was followed and gave the titled compound **19b** as a brown amorphous solid (74% yield). Trituration (EtOH) gave the analytical sample as white crystals: mp 127–128°C; R_f = 0.33 (5:95 EtOAc/CH_2Cl_2); IR (ATR, neat) 1756, 1678, 1606, 1577, 1501, 1455, 1362, 1333, 1293, 1251, 1156, 1077, 1015, 876, 852, 789, 759, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38–7.41 (m, 2H), 6.95–6.99 (m, 2H), 6.65 (s, 1H), 4.71 (d, 2H, J = 1.5 Hz), 3.89 (s, 3H), 1.56 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.3, 158.9, 153.1, 150.0, 132.5, 128.4, 123.0, 121.0, 120.1, 111.8, 83.0, 55.7, 52.8 ppm; *Anal.* calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.33; H, 6.67; N, 4.92.

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Synthesis and Antimicrobial Studies of Novel Bis(diamino)thiazoles

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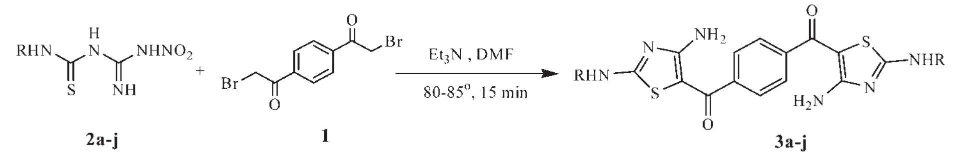

R = *n*-Propyl, *n*-butyl, *t*-butyl, allyl, benzyl, phenyl, *p*-chlorophenyl, *m*-methylphenyl, *p*-ethoxyphenyl, *p*-methylphenyl

The synthesis of novel bis(diamino)thiazoles has been achieved by reacting bis(bromoacetyl)benzene and 1-alkyl(or aryl)-3-(*N*-nitroamidino)thioureas in presence of triethylamine. These new compounds were characterized by spectral analysis and screened for antimicrobial activities.

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INTRODUCTION

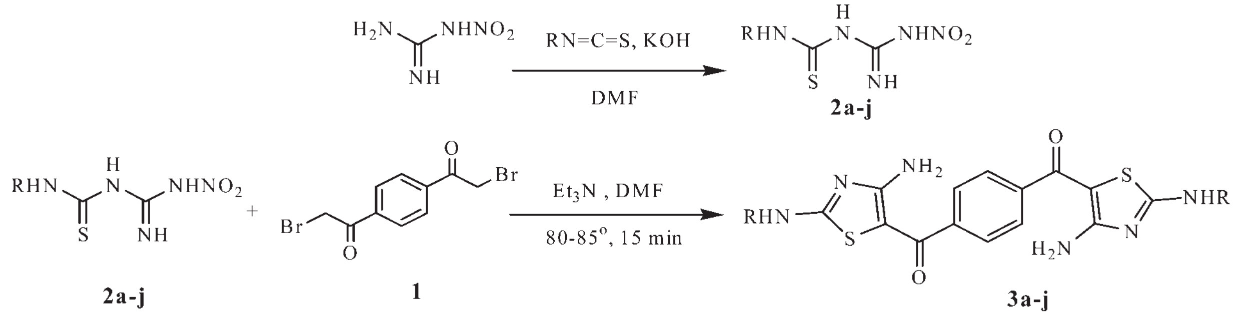
Compounds that incorporate two thiazole rings either directly connected as in bithiazoles or through a linker unit as in bisthiazolyl compounds, show significant biological activity. Bleomycin, isolated from *Streptomyces verticilus* containing a bithiazole moiety, which has been shown to bind to DNA thereby inhibiting DNA synthesis of the tumor cells, is the prime example for such compounds [1]. A number of other bi- or bisthiazoles [2–4] exhibit antibacterial, antiviral and cytotoxic activities. In addition to these compounds, quite a few of the highly active secondary metabolites from marine tunicates also contain bisthiazole units [5]. It also appears that the thiazole units need not always be directly linked for the manifestation of bioactivity; for example, ritonavir, a bisthiazole in which the two thiazole units are separated by a small peptidomimetic chain, is a potent bisthiazole HIV-protease inhibitor [6].

As far back as in 1997, we have observed that 2,4-diamino-5-ketothiazoles show excellent cytotoxic activity [7] based on screening programs at National Cancer Institute, an observation later substantiated further by us [8]. As part of our work in the synthesis of 2,4-diamino-5-ketothiazoles, we have developed a variety of thiourea based synthons, such as amidinothioureas, nitroamidinothioureas, and thiocarbamoylamidinopyrazoles that [9] serve as precursors for 2,4-diaminothiazoles by providing the [C^4—N^3—C^2—S^1] ring atoms for the thiazole ring construction, the remaining C^5 carbon of the thiazole being sourced from a reactive halomethyl compound of the type X—CH_2—EWG where the electron withdrawing group EWG can be O_2N—C_6H_4—, NC—, R—CO—, RO—CO—, Ar—CH=CH—CO— or similar ones, including α-haloketones. This [4 + 1] ring assembly, in a tandem bromination-cyclization strategy has been now applied for the synthesis of novel [4-(4-amino-2-(*N*-substituted amino)thiazole-5-carbonyl)-phenyl]-(4-amino-2-(*N*-substituted amino)thiazol-5-yl)-methanones. The above [(C^4—N^3—C^2—S^1) + C^5] ring assembly of 2,4-diaminothiazole using functionalized thiourea derivatives is distinctly different from the classic Hantzsch synthesis, which is the synthesis of 2-aminothiazoles from halo carbonyl compounds and thioureas is well reviewed [10,11] in literature. The latter is a [3 + 2] ring construction strategy starting from simple thioureas, that give the [N^3—C^2—S^1] ring atoms, and α-haloketones, which provide the remaining [C^4—C^5] atoms, giving 2-aminothiazoles as products.

RESULTS AND DISCUSSION

In a typical case, the reaction of 1-(*N*-nitroamidino)-3-*n*-propylthiourea with 1,4-bis(bromoacetyl)benzene

Scheme 1



R = *n*-Propyl, *n*-butyl, *t*-butyl, allyl, benzyl, phenyl, *p*-chlorophenyl, *m*-methylphenyl, *p*-ethoxyphenyl, *p*-methylphenyl

was done in DMF in the presence of triethylamine at 80–85°C for 15 min to obtain a compound which had a molecular composition $C_{20}H_{24}N_6O_2S_2$ gave a product the FAB mass spectrum of the which showed a MH^+ peak at *m/z* 445 indicating that the molecular mass of the compound is 444. It's ^{1}H NMR spectrum showed the presence of an *n*-propylamino group, a phenylene group and NH hydrogen. The ^{13}C NMR spectrum showed three peaks in the alkyl region at 13.51, 20.12, and 31.50 ppm indicating the presence of the *n*-propyl group. The signals at 143.8, 156.7, and 167 ppm were assignable to thiazole ring carbons, that at 181 ppm to carbonyl carbon and those at 126.4, 127.6, 128, and 129 ppm, to a *p*-phenylene group carbons. Accordingly, the compound was formulated as [4-(4-amino-2-*n*-propylaminothiazole-5-carbonyl)phenyl]-(4-amino-2-*n*-propylaminothiazol-5-yl)methanone **3a**. The reaction was next extended to 1-aryl-3-(*N*-nitroamidino)thioureas. As a typical example, 1-(4-methylphenyl-3-(*N*-nitroamidino)thiourea reacted with 1,4-bis(bromoacetyl)benzene to give a compound with molecular composition $C_{28}H_{24}N_6O_2S_2$. The ^{1}H NMR spectrum of the compound showed a doublet due to four hydrogens at δ 7.02–7.25, assignable to aryl hydrogen *ortho*- to a NH group. Another doublet of four hydrogens at δ 7.35–7.55 was ascribed to the aryl hydrogen *meta*- to a NH group. A singlet of four hydrogens at δ 7.74 was attributable to the aryl hydrogen of a *p*-phenylene group. A broad peak at δ 8.0–8.52 was due to NH hydrogen. A singlet due to two hydrogens at δ 10.72 was also assignable to two NH groups. The ^{13}C NMR spectrum showed fourteen peaks among which the peak at δ 26.98 showed the presence of a methyl group. Based on these data and the fragmentations observed in its EI mass spectrum, the compound was assigned the structure [4-(4-amino-4-phenylaminothiazole-5-carbonyl)phenyl]-(4-amino-4-phenylaminothiazol-5-yl)methanone **3j** (Scheme 1).

The general reaction scheme is depicted above. These new [4-(4-amino-2-(*N*-substituted amino)thiazole-5-carbonyl)phenyl]-(4-amino-2-(*N*-substituted amino)thiazol-5-yl)methanones (**3a–j**) were screened for their antibacterial and antifungal activities. The data from these studies are compiled in Table 1.

In conclusion, we have described an efficient synthetic route to obtain bis(diamino)thiazoles (**3a–j**), several of which show good antibacterial and antifungal activities.

EXPERIMENTAL

Melting points were determined by open capillary method and were uncorrected. The IR spectra were recorded in potassium bromide pellets with an AVATAR 330 FTIR spectrometer and the ^{1}H, ^{13}C NMR experiments were done on AMX-400/DRX-500 NMR spectrometers. The molecular masses of compounds were confirmed by taking EI and the fast atom bombardment mass spectra (FAB-MS). The compounds were purified by column chromatography using silica gel (60–120 mesh, E. Merck). The required alkyl and aryl isothiocyanates and nitroamidinothioureas were synthesized by reported methods [9(c),12] The bromination of 2,4-diacetylbenzene was done in DMF at 80–85°C and the 1,4-bis(bromoacetyl)benzene **1** was isolated and characterized. The antibacterial and antifungal activities were studied by the disc diffusion method against *Staphylococcus aureus*, *Klebsiella pneumonia*, *Candida albicans*, and *Aspergillus niger*. In the case of *C. albicans* and *A. niger* the standard used is ketoconazole and in the case of *S. aureus* and *K. pneumonia* the data has been compared with ciplofloxacin.

Bis(bromoacetyl)benzene (1). To a solution of 1,4-diacetylbenzene (0.21 g, 1.3 mmol) in glacial acetic acid, bromine (2.6 mmol, 90 mL) in glacial acetic acid (2 mL) was added slowly and warmed. The reaction mixture was then heated at 95°C for 1 h, and then poured into ice water and the product was filtered, dried and recrystallized from glacial acetic, to obtain colorless shinning crystals of 1,4-bis(bromoacetyl)benzene (**1**) in 65% yield, mp 165–167°C; IR (KBr): 2998, 2945, 1699, 1402, 1263, 1202, 1121, 987, 811, 683, 565, 499 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ: 4.45 (s, 4H, CH_2), 8.04–8.10 (m, 4H, Ar—H); FAB ms: *m/z* (MH^+) 320.

1-*t*-Butyl-3-(*N*-nitroamidino)thiourea (2c). Finely powdered potassium hydroxide (1.08 g, 1.92 mmol) was added to

Table 1

Antimicrobial activity studies of compounds (**3a-j**) by disc diffusion method.

	Zone of inhibition (mm)							
	Bacterial strain				Fungal strain			
	S. aureus		*K. pneumonia*		*C. albicans*		*A. niger*	
Compound	Std	Sample	Std	Sample	Std	Sample	Std	Sample
3a	29	17	28	19	29	19	26	13
3b	27	22	33	19	33	22	24	19
3c	28	18	31	22	32	18	23	19
3d	22	21	30	20	31	19	19	16
3e	26	18	32	20	33	21	23	19
3f	28	23	33	17	31	20	21	13
3g	27	20	32	23	32	19	20	17
3h	29	20	32	27	33	22	24	19
3i	27	24	32	22	32	19	22	17
3j	29	19	32	26	33	21	23	18

Concentration: 100 μg/mL.

a solution of nitroguanidine (1 g, 9.6 mmol) in *N,N*-dimethylformamide (10 mL) and this mixture was stirred for 15 min. To this, *t*-butyl isothiocyanate (9.6 mmol) in *N,N*-dimethylformamide (5 mL) was added in 15 min and the stirring was continued for another 60 min. The reaction mixture was then poured onto crushed ice and the mixture was acidified with dilute hydrochloric acid (0.1*N*). The precipitated compound was filtered, dried and crystallized from ethanol to obtain 1-*t*-butyl-3-(*N*-nitroamidino)thiourea (**2c**) in 71% yield, mp 146–148°C; IR (KBr) 3353, 3284, 2983, 2934, 2545, 1715, 1647, 1608, 1545, 1365, 1259,1191,1076, 957, 786, 705, 632 cm^{-1},^1H NMR (400 MHz, DMSO-d_6): δ 1.4 (s, 9H, CH_3), 9.10–9.45 (br s, 1H, NH), 9.66 (s, 1H, NH), 9.96 (s, 1H, NH); FAB ms: *m*/*z* (MH^+) 220. *Anal*. Calcd. for $C_6H_{13}N_5O_2S$: C, 32.86; H, 5.98; N, 31.94%. Found: C, 33.00; H, 6.09; N, 31.81%.

General procedure for the synthesis of bis(diamino)thiazoles (3a–j). To a solution of 1,4-bis(bromoacetyl)benzene in DMF (2 mL) kept at 50–60°C containing triethylamine (2 mmol), 1-alkyl/aryl-3-(*N*-nitroamidino)thioureas (1 mmol), in *N,N*-dimethylformamide (2 mL) was added dropwise. After warming for 15 min, the reaction mixture was poured into water. The product obtained, after adjusting the pH to 7, was collected and purified using column chromatography using silica gel by elution using chloroform-ethyl acetate (1:5) to obtain the bisthiazoles in 65–80% yield.

[4-(4-Amino-2-n-propylaminothiazole-5-carbonyl)phenyl]-(4-amino-2-n-propylaminothiazol-5-yl)-methanone (3a). This compound was obtained as yellow-colored microcrystals (65%), mp > 250°C; IR (KBr): 3416, 2963, 2928, 1603, 1567, 1444, 1384, 1279, 1225, 1091, 747 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 0.85 (t, 6H, CH_3, $J = 7$ Hz), 1.53 (sextet, 4H, CH_2, $J = 7$ Hz), 3.68 (t, 4H, CH_2, $J = 5.1$ Hz), 7.60–8.10 (m, 4H, Ar—H), 8.69 (s, NH); ^{13}C NMR (100 MHz, DMSO-d_6)δ: 13.51, 20.12, 31.50, 126.4, 127.6, 128, 129, 143.8, 156.7, 167, 181 ppm; FAB ms: *m*/*z* (MH^+) 445. *Anal*. Calcd. for $C_{20}H_{24}N_6O_2S_2$: C, 54.03; H, 5.44; N, 18.91%. Found: C, 54.00; H, 5.40; N, 18.81%.

[4-(4-Amino-2-n-butylaminothiazole-5-carbonyl)phenyl]-(4-amino-2-n-butylaminothiazol-5-yl)methanone (3b). This compound was obtained as yellow-colored microcrystals (60%), mp > 250°C; IR (KBr): 3347, 2958, 2926, 2857, 1703, 1592, 1518, 1463, 1407, 1261, 1229, 1097, 801, 732, 567 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 0.72 (t, 6H, CH_3),1.32 (m, 4H, CH_2, $J = 7$ Hz), 1.40–1.60 (q, 4H, CH_2), 3.72 (t, 4H, CH_2), 7.40–8.30 (m, 4H, Ar—H), 8.6 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.11, 13.53, 19.46, 30.52, 126.64, 126.92, 128.55, 129.30, 143.8, 156.66, 168, 179, 180ppm; FAB ms: *m*/*z* (MH^+) 473. *Anal*. Calcd. for $C_{22}H_{28}N_6O_2S_2$: C, 55.91; H, 5.97; N, 17.78%. Found: C, 55.85; H, 5.92; N, 17.69%.

[4-(4-Amino-2-t-butylaminothiazole-5-carbonyl)phenyl]-(4-amino-2-t-butylaminothiazol-5-yl)methanone (3c). This compound was obtained as yellow-colored microcrystals (55%), mp > 250°C; IR (KBr): 3281, 2970, 2929, 1685, 1603, 1557, 1437, 1367, 1275, 1200, 1096, 905, 851, 749 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.35 (s, 18H, CH_3), 7.6–8.5 (m, 4H, Ar—H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.34, 28.17, 29.05, 52.39, 126.40, 126.60, 128.04, 129.31, 143.28, 156.31, 166.32, 169.27, 179.74, 180.41 ppm; FAB ms: *m*/*z* (MH^+) 473. *Anal*. Calcd. for: Found: C, 55.89; H, 5.91; N, 17.82%; Calculated for $C_{22}H_{28}N_6O_2S_2$: C, 55.91; H, 5.97; N, 17.78%.

[4-(2-Allylamino-4-aminothiazole-5-carbonyl)phenyl]-(2-allylamino-4-aminothiazol-5-yl)methanone (3d). This compound was obtained as yellow-colored microcrystals (48%), mp > 250°C; IR (KBr): 3440, 2925, 1608, 1566, 1446, 1384, 1309, 1226, 1091, 929, 581 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.70–4.10 (m, 4H, CH_2), 4.9–5.4 (m, 4H, CH_2), 5.70–6.00 (m, 2H, CH), 7.6–8.2 (m, 4H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.81, 46.8, 54.8, 72.15, 92.6, 116.2, 118.37, 166.6, 180.1, 193.6 ppm; FAB ms: *m*/*z* (MH^+) 441. *Anal*. Calcd. for $C_{20}H_{20}N_6O_2S_2$: C, 54.52; H, 4.58; N, 19.08%. Found: C, 54.43; H, 4.44; N, 19.18%

[4-(4-amino-2-n-benzylaminothiazole-5-carbonyl)phenyl]-(4-amino-2-n-benzylaminothiazol-5-yl)methanone (3e). This compound was obtained as yellow-colored microcrystals (51%), mp > 250°C; IR (KBr): 3409, 2958, 2927, 1703, 1581, 1518, 1464, 1407, 1230, 1103 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 4.5 (s, 2H, CH_2), 7.1–8.1 (m, Ar—H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 47, 48, 126, 127, 128, 129, 137.7; FAB ms: *m*/*z* (MH^+) 541. *Anal*. Calcd. for $C_{28}H_{24}N_6O_2S_2$: C, 62.20; H, 4.47; N, 15.55%. Found: C, 62.28; H, 4.54; N, 15.32%.

[4-(4-Amino-2-phenylaminothiazole-5-carbonyl)phenyl]-(4-amino-2-phenylaminothiazol-5-yl)methanone (3f). This compound was obtained as yellow-colored microcrystals (42%), mp > 250°C; IR (KBr): 3435, 2360, 1659, 1598, 1549, 1440, 890, 853, 780, 743, 698 cm^{-1};^1H NMR (400 MHz, DMSO-d_6): δ 7.05 (t, 2H, 2Ar—H), 7.31(t, 4H, 4Ar—H), 7.58 (d, 4H, 4Ar—H), 7.67–7.81(m, 8H, 4Ar—H, $2NH_2$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 93.14, 119.51, 123.66, 127.18, 129.27, 139.93, 143.74, 166.38, 167.92, 182.16 ppm; FAB ms: *m*/*z* (MH^+) 513; *Anal.* Calcd. for $C_{26}H_{20}N_6O_2S_2$: C, 60.92; H, 3.93; N, 16.40%. Found: C, 60.75; H, 3.81; N, 16.30%.

{4-[4-Amino-2-(4-chlorophenylamino)thiazole-5-carbonyl]-phenyl}-[4-amino-2-(4-chlorophenylamino)thiazol-5-yl]methanone (3g). This compound was obtained as yellow-colored microcrystals (42%), mp > 250°C; IR (KBr): 3430, 2360, 1598, 1530, 1492, 1426, 1091, 825, 668 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6):δ 6.75–8.1 (m, 16H), 10.15 (s, 2H, NH); EI ms: *m*/*z* (%) 453 (2), 411 (2), 224 (11),184 (4), 169 (26), 153 (11), 152 (20), 127 (100), 111 (48). *Anal.* Calcd. for $C_{26}H_{18}Cl_2N_6O_2S_2$: C, 53.70; H, 3.12; N, 14.45%. Found: C, 53.55; H, 3.09; N, 14.32%.

{4-[4-Amino-2-(3-methylphenylamino)thiazole-5-carbonyl]-phenyl}-[4-amino-2-(3-methylphenylamino)thiazol-5-yl]methanone (3h). This compound was obtained as yellow-colored microcrystals (58%), mp > 250°C; IR (KBr): 3440, 3220, 2361, 1552, 1422, 1167, 1088, 898, 850, 781, 745, 693 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6): δ 2.65 (s, 6H, CH_3), 6.98–7.2 (d, 4H, $J = 6.38$ Hz), 7.29–7.45 (d, 4H, $J = 6.43$ Hz), 7.75 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 26.82, 94.47, 117.34, 120.97, 125.49, 127.44, 128.34, 129.16, 138.07, 138.90, 139.34, 145.83, 165.87, 169.64, 182.80 ppm; FAB ms: *m*/*z* (MH^+) 541. *Anal.* Calcd. for $C_{28}H_{24}N_6O_2S_2$: C, 62.22; H, 4.47; N, 15.55%. Found: C, 62.17; H, 4.52; N, 15.29%.

{4-[4-Amino-2-(4-ethoxyphenylamino)thiazole-5-carbonyl]-phenyl}-[4-amino-2-(4-ethoxyphenylamino)thiazol-5-yl]methanone (3i). This compound was obtained as yellow-colored microcrystals (35%), mp > 250°C; IR (KBr): 3483, 3311, 3306, 3275, 2996, 1591, 1510, 1428, 1235, 1180, 1092, 1035, 822, 746 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.39 (t, 6H, CH_3), 4.02 (q, 4H, CH_2), 6.86 (d, Ar—H), 7.30–7.50 (m, Ar—H), 7.73 (s, Ar—H), 7.94 (s, Ar—H), 10.40 (s, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.30, 62.83, 114.24, 121.16, 126.34 ppm; FAB ms: *m*/*z* (MH^+) 601. *Anal.* Calcd. for $C_{30}H_{28}N_6O_4S_2$: C, 59.98; H, 4.70; N, 13.99%. Found: C, 59.78; H, 4.61; N, 13.73%.

{4-[4-Amino-2-(4-methylphenylamino)thiazole-5-carbonyl]-phenyl}-[4-amino-2-(4-methylphenylamino)thiazol-5-yl]methanone (3j). This compound was obtained as yellow-colored microcrystals (52%), mp > 250°C; IR (KBr): 3445, 3221, 2358, 1551, 1423, 1167, 1076, 892, 850, 770, 741, 690 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 2.60 (s, 6H, CH_3), 7.02–7.25 (d, 4H, $J = 6.49$ Hz), 7.35–7.55 (d, 4H, $J = 6.52$ Hz), 7.74 (s, 4H), 8.0–8.52 (br, 4H, NH_2), 10.72 (s, 2H), ^{13}C NMR (100 MHz, DMSO-d_6): δ 26.98, 93.76, 117.98, 119.76, 123.91, 127.35, 128.41, 129.21, 138.01, 139.59, 146.05, 166.50, 168.65, 182.03 ppm; El ms: *m*/*z* (%) 149 (34), 147 (8), 133 (10), 107 (64), 106 (38), 91 (100). *Anal.* Calcd. for $C_{28}H_{24}N_6O_2S_2$: C, 62.22; H, 4.47; N, 15.55%. Found: C, 62.14; H, 4.39; N, 15.29%.

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Unexpected C—O Bond Formation in Suzuki Coupling of 4-Chlorothieno[2,3-*d*]pyrimidines

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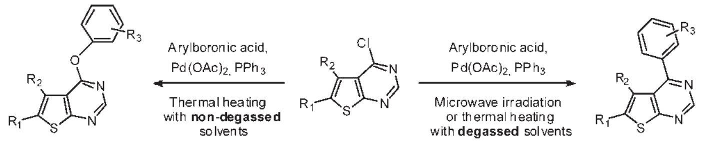

Palladium-catalyzed Suzuki reactions were performed on 4-chlorothieno[2,3-*d*]pyrimidines under classical heating conditions and under microwave irradiation. Some unexpected results were obtained during this study as two kinds of compounds were isolated depending on the conditions used. A careful investigation of experimental details has shown that the expected C—C bond formation occurred when degassed solvents were used (both in classical and microwave heating) whereas an unexpected C—O bond formation happened when solvents were not degassed with argon-bubbling before use.

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INTRODUCTION

Kinase insert domain (KDR)-containing receptor is one of the human tyrosine kinases that has a high affinity for vascular endothelial growth factor (VEGF) and is believed to be a primary mediator of tumor-induced angiogenesis [1]. Compounds which influence the KDR kinase have attracted much attention and are of great interest as potential therapeutic agents. Several compounds with a quinazoline moiety have shown effective antitumor activity and have found clinical applications such as gefitinib (Iressa® from AstraZeneca) or erlotinib (Tarceva® from Genentech) [2].

For many years, thieno[3,2-*d*]pyrimidines and thieno[2,3-*d*]pyrimidines are known to be pharmacophoric elements in numerous active compounds such as analgesic [3], anticancer [4], mGluR1 antagonists [5], or molecules having antimicrobial and anti-inflammatory activities [6] (Fig. 1). Munchhof et al. [7] reported the design and structure activity relationship (SAR) of thieno[3,2-*d*]-pyrimidines and -pyridines as selective VEGFR-2 kinase inhibitors. Since then, many patents were filed and consequently, thienopyrimidines have become a well-sought privileged class of compounds in drug discovery programs and practical strategies for the construction of libraries have been developed [8].

RESULTS AND DISCUSSION

The interest in this heterocyclic core prompted us to set up a short and efficient route toward this nucleus. In 2007, we have reinvestigated the synthesis of thieno[2,3-*d*]pyrimidinone **1a** and 4-chlorothieno[2,3-*d*]pyrimidine **2a** using microwave-assisted procedure [9]. We now extended this procedure to compound **2b** (Scheme 1).

Aiming to extend thienopyrimidine libraries, we then wanted to functionalize those compounds on position 4. Usually, functionalities are introduced at C-4 via nucleophilic substitution reaction of the chlorothienopyrimidine with amines [10]. In this study, we have decided to focus our attention on the introduction of aromatics and heterocycles at this position. Indeed, we thought that easy modulation at C-4 could be done by palladium-catalyzed cross-coupling of 4-chlorothieno[2,3-*d*]pyrimidines **2a**,**b** with different arylboronic acids.

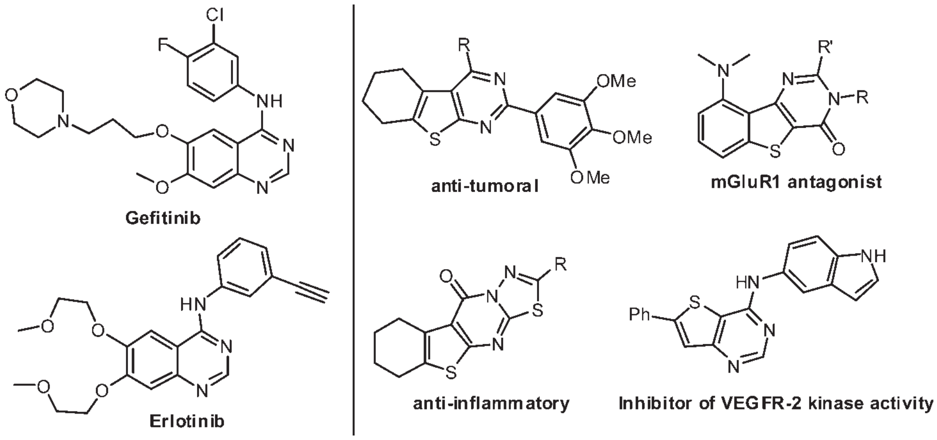


Figure 1. Structures of quinazolines and thienopyrimidines with biological activities.

The electron-deficient nature of the pyrimidine ring makes this system far more reactive in Suzuki coupling compared with the analogous benzenoid halides. 2,4,6-Trichloropyrimidines, 2,4- and 4,6-dihalo pyrimidines have been successfully arylated under classical Suzuki conditions ($Pd(OAc)_2$, PPh_3, Na_2CO_3, benzene/ethanol/water or $Pd(PPh_3)_4$, toluene, Na_2CO_3 2*M*) [11,12]. A sequential Suzuki coupling/amination reaction was recently described on 4,6-dichloropyrimidines under microwave irradiation [13]. Some studies were also done on condensed halopyrimidines as for example on 2,4-dichloropyridopyrimidines [14] or on 4-chloro-2-trichloromethylquinazoline [15]. To the best of our knowledge, there is only one publication with one example on Suzuki coupling on 4-chlorothieno[2,3-*d*]pyrimidine [4a].

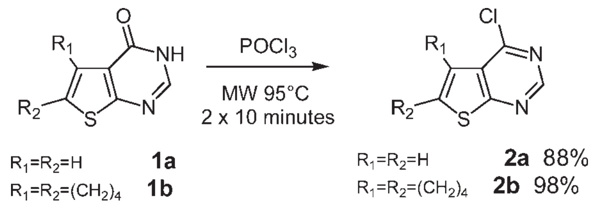
First, we investigated the reactivity of 4-chlorothieno[2,3-*d*]pyrimidine **2a** with 4-methoxyphenylboronic acid under classical Suzuki conditions. The reaction was performed in DME with $Pd(OAc)_2/PPh_3$ catalysis in the presence of Na_2CO_3 2*M* as base at 75–85°C. The reaction was stopped when the starting material had completely disappeared (TLC control) and the product was isolated by column chromatography (Scheme 2).

We then carried out the same Suzuki coupling under microwave irradiation hoping to enhance the yields and decrease reaction times. $Pd(OAc)_2/PPh_3$ was used as catalytic system, with Cs_2CO_3 as base and DME/EtOH/H_2O as solvent. We worked under temperature/time control with 150°C/30 min as parameters. At the end of the time, the TLC control indicated that all starting material was consumed. However, after purification, the ^1H NMR spectrum was not consistent with the one obtained under classical conditions (Fig. 2). Two different products were obtained. First of all, to control these results, we applied under microwave irradiation exactly the same conditions as for classical heating (DME/H_2O was used as solvent and Na_2CO_3 as base). The same product as before was obtained, different from the one resulting from classical heating.

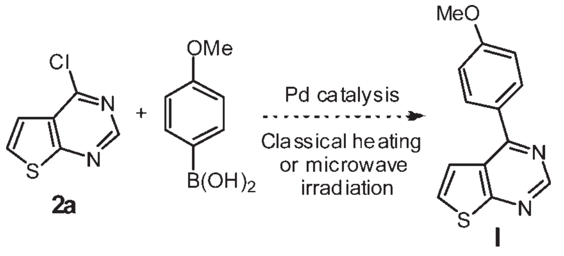
As shown in Figure 2, in both ^1H NMR spectra, the same signals were present although their δ values were slightly different. The thiophene ring seemed to remain unchanged in both compounds (two doublets at 7.63 and 7.94 ppm in compound **A**; two doublets at 7.75 and 8.01 ppm in compound **B**). The presence of an AB signal let us suppose that the *p*-disubstituted phenyl ring was still present in both structures too (two doublets at 7.01 and 7.22 ppm in compound **A**, two doublets at 7.15 and 8.01 ppm in compound **B**). Moreover, NOESY experiment and HMBC sequence showed that the pyrimidine proton was isolated and placed between the two nitrogen atoms in both structures.

The same coupling with 4-methoxyphenylboronic acid was realized on chlorothienopyrimidine **2b** in classical

Scheme 1



Scheme 2



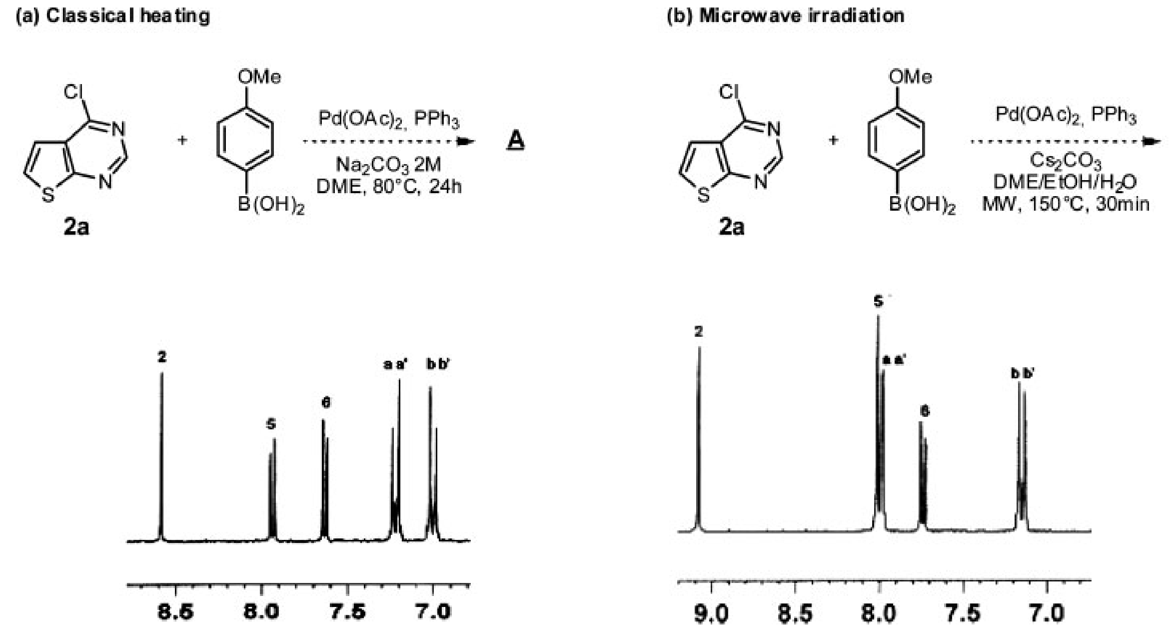


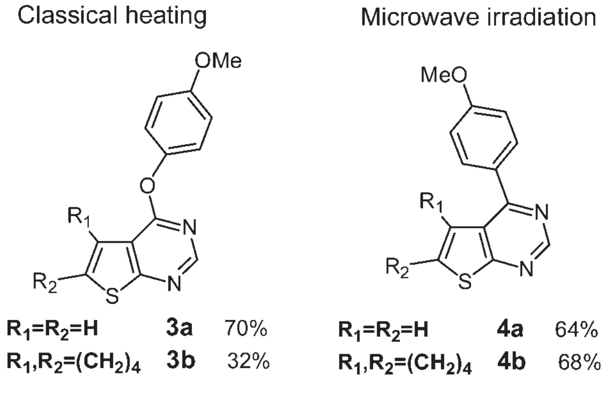
Figure 2. ^{1}H NMR spectra (aromatic part) of compound obtained by classical heating and under microwave irradiation: (a) classical heating and (b) microwave irradiation.

conditions and under microwave irradiation. Two different compounds were obtained and after several attempts, we succeeded in isolating crystals. Those crystallographic data showed that the expected product was obtained under microwave irradiation (with formation of the C—C bond between chlorothienopyrimidine and boronic acid), whereas the classical heating led to the formation of a C—O bond. The compounds obtained are shown in Scheme 3.

Once the structures were elucidated, we tried to explain the formation of compounds **3**. During those first experiments, we have noticed that *p*-methoxyphenol was detected as trace in the crude material. So, we postulated that the boronic acid must have been transformed into *p*-methoxyphenol and after, the phenol would have reacted with the chloropyrimidine under SNAr process giving compounds **3**. As a verification, compound **3b** was synthesized directly by the action of *p*-methoxyphenate on 4-chloropyrimidine **2b** in 55% yield (Scheme 4).

Regarding the yield obtained for compound **3a** (70%), it would mean that the boronic acid was converted into phenol near completely. It is well known that oxygen should be avoided when working with boronic acids since they could be oxidized to the corresponding phenols [16,17]. That is why our reactions were performed under an argon atmosphere both under classical heating and under microwave irradiation. However, there was a very small difference of manipulation when doing those reactions. Under classical heating, the reactions were performed in a Schlenk tube flushed with argon whereas in microwave irradiation, a one-necked round-bottom

Scheme 3



Scheme 4

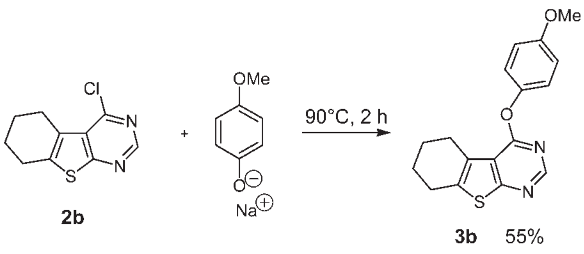
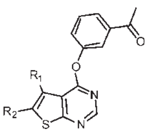
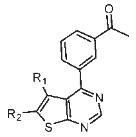
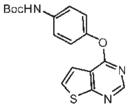
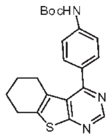
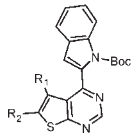


Table 1

Suzuki coupling of 4-chlorothienopyrimidines under classical heating and microwave irradiation.

Entry	Method	Product	Yield		
1	A		$R_1 = R_2 = H$ $R_1,R_2 = (CH_2)_4$	**5a** **5b**	77% 25%[a]
2	B for **6a** C for **6b**		$R_1 = R_2 = H$ $R_1,R_2 = (CH_2)_4$	**6a** **6b**	44% 75%
3	A			**7**	67%
4	C			**8**	61%
5	C		$R_1 = R_2 = H$ $R_1,R_2 = (CH_2)_4$	**9a** **9b**	36% 51%

Method A: Classical heating, nondegassed solvents (75°C, 24 h); Method B: Microwave irradiation (150°C, 30 min); Method C: Classical heating, DME, and H_2O degassed (75°C, 24 h).

[a] Reaction was performed at room temperature.

flask was used and argon was bubbled directly in the solution while loading the reagents. So, we performed the Suzuki cross-coupling under classical heating conditions but this time, solvents (DME and water) were degassed with argon bubbling before being introduced in the reaction mixture. In this case, we only observed C—C bond formation. Compounds **6**, **8–9** were synthesized in good yields under classical heating with degassed solvents whereas the formation of C—O bond occurred when nondegassed solvents were used for compounds **5** and **7** (Table 1).

CONCLUSIONS

In summary, we have demonstrated that 4-chlorothieno[2,3-*d*]pyrimidines undergo Suzuki coupling under both classical heating and microwave irradiation in moderate to good yields. Moreover, because of unexpected results obtained under classical heating, we have shown the importance to use degassed solvents in those reactions and not working only under an argon stream. Further investigation of the mechanism of C—O bond formation in cross-coupling with boronic acid as well as its application to other substrates are ongoing in our laboratory.

EXPERIMENTAL

General methods. Melting points were determined on a Stuart SMP3 apparatus and are uncorrected. ^1H NMR spectra were measured at 250 MHz, and ^{13}C NMR spectra were measured at 62.9 MHz on a Bruker AC 250 spectrometer at 25°C in DMSO-d_6. IR spectra were recorded for neat samples on KBr plates on a Perkin Elmer Spectrum Bx FTIR spectrophotometer. Standard mass spectrometry data were acquired by using GC-MS system in EI mode with a maximum *m*/*z* range of 400 on a GC Varian CP 3800 spectrometer and triple quadrupole 1200 Varian detector. HMRS were collected on a Bruker MICROTOF-Q ESI/QqTOF spectrometer. Elemental analyses were determined with a Thermofinnigan FlashEA 1112 elemental analyzer. Microwave monomode synthesizer, (CEM Corporation) Discover model was used in open-vessel mode for the microwave-assisted synthesis; the temperature was monitored by an infrared sensor located in the microwave cavity floor. When required, all solvents and reagents were purified by standard techniques. All Suzuki cross-coupling reactions were conducted under a positive pressure of argon. Chromatographic separations were carried out with silica gel 60 Å (70–200 μm) or alumina. Yields reported are for chromatographically pure isolated product.

Details of synthesis, purification, and characterization of starting materials **1a**,**b** and **2a**,**b** can be found in literature [9].

CCDC 716544 and CCDC 716545 contain the supplementary crystallographic data for this article (compounds **4b** and **3b**, respectively). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General procedure for Suzuki cross-coupling. ***Method A.*** To a solution of 4-chlorothienopyrimidine (**2a**: 171 mg, **2b**: 225 mg, 1 mmol), boronic acid (1.2 mmol) and PPh_3 (39 mg, 0.15 mmol) in DME (12 mL) were added 2*M* Na_2CO_3 (10 mL) and $Pd(OAc)_2$ (10 mg, 0.04 mmol).The reaction mixture was stirred at 75–80°C for 24 h under argon. After filtration, the aqueous layer was extracted with AcOEt (3 × 30 mL). The combined organic layers were washed with 10% NaOHaq and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to give products **3a**, **3b**, **5a**, **5b**, and **7**.

Method B. A 50-mL round-bottomed flask was charged with 4-chlorothienopyrimidine (**2a**: 171 mg, **2b**: 225 mg, 1 mmol), boronic acid (1.5 mmol), Cs_2CO_3 (1.01 g, 3.1 mmol), PPh_3 (66 mg, 0.25 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), and DME/EtOH/H_20 (30 mL, ratio: 1/1/1) flushed with argon. The reaction mixture was placed in a microwave synthesizer. The microwave vial was purged three times with argon and then heated under microwave irradiation (150°C) for 30 min. After this time, the reaction mixture was allowed to cool to room temperature and was quenched with AcOEt/H_20 (20 mL, ratio: 1/1). The water layer was extracted with AcOEt (3 × 30 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to give products **4a**, **4b**, and **6a**.

Method C. Same procedure as Method A but with DME and water degassed with argon bubbling.

4-(4-Methoxyphenoxy)thieno[2,3-d]pyrimidine (3a). Compound **3a** was obtained according to Method A from **2a** (171 mg, 1 mmol) and 4-methoxyphenylboronic acid (182 mg, 1.2 mmol) and isolated by column chromatography (Silica, CH_2Cl_2 as eluent); the yield was 155 mg (64%), beige solid, mp 111–112°C; IR: 1572, 1534, 1503 cm^{-1}; ^{1}H NMR: δ 3.78 (s, 3H), 7.01 (d, *J* = 9.1 Hz, 2H), 7.22 (d, *J* = 9.1 Hz, 2H), 7.63 (d, *J* = 6 Hz, 1H), 7.94 (d, *J* = 6 Hz, 1H), 8.59 (s, 1H); ^{13}C NMR: δ 55.3, 114.2, 118.4, 118.5, 122.8, 127.1, 145.3, 152.9, 156.9, 163.4, 168.8; GC MS (t_R 9.19 min) *m*/*z* (%) = 257 (100, M^+), 244 (19), 134 (94); HRMS calcd for $[M + H^+]$ $C_{13}H_{11}N_2O_2S$ 259.0536, found 259.0534. *Anal.* Calcd. for $C_{13}H_{10}N_2O_2S$: C, 60.45; H, 3.90; N, 10.85. Found: C, 60.59; H, 3.88; N, 10.89.

4-(4-Methoxyphenoxy)-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine (3b). Compound **3b** was obtained according to Method A from **2b** (225 mg, 1 mmol) and 4-methoxyphenylboronic acid (182 mg, 1.2 mmol) and isolated by column chromatography (Silica, CH_2Cl_2 as eluent); the yield was 101 mg (34%), brown solid, mp 83–84°C, IR: 1570, 1560, 1498 cm^{-1}; ^{1}H NMR: δ 1.85 (m, 4H), 2.85 (m, 2H), 3.00 (m, 2H), 6.99 (d, *J* = 7.5 Hz, 2H), 7.19 (d, *J* = 7.5 Hz, 2H), 8.45 (s, 1H); ^{13}C NMR: δ 21.8, 22.3, 24.9, 25.4, 55.4, 114.5, 118.3, 122.8, 126.9, 135.5, 145.4, 152.0, 156.7, 163.1, 167.4; GC MS (t_R 11.62 min) *m*/*z* (%) = 313 (100, M^+), 298 (40), 205 (44). *Anal.* Calcd. for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97. Found: C, 65.60; H, 5.21; N, 9.06.

4-(4-Methoxyphenyl)thieno[2,3-d]pyrimidine (4a). Compound **4a** was obtained according to the general procedure B from **2a** (171 mg, 1 mmol) and 4-methoxyphenylboronic acid (228 mg, 1.5 mmol) and isolated after purification by chromatography on silica gel (CH_2Cl_2 as eluent), the yield was 155 mg (64%), beige solid, mp 136–137°C, IR: 1609, 1540, 1514 cm^{-1}; ^{1}H NMR: δ 3.85 (s, 3H), 7.15 (d, *J* = 8.6 Hz, 2H), 7.75 (d, *J* = 6 Hz, 1H), 7.98–8.02 (m, 3H), 9.08 (s, 1H); ^{13}C NMR: δ 55.4, 114.4, 121.1, 126.7, 128.3, 129.3, 130.8, 152.9, 159.3, 161.2, 169.1; GC MS (t_R 9.34 min) *m*/*z* (%) = 242 (100, M^+), 211 (66), 134 (5); HRMS calcd for $[M + H^+]$ $C_{13}H_{11}N_2OS$ 243.0587, found 243.0601. *Anal.* Calcd. for $C_{13}H_{10}N_2OS$: C, 64.44; H, 4.16; N, 11.56. Found: C, 64.62; H, 4.17; N, 11.49.

4-(4-Methoxyphenyl)-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine (4b). Compound **4b** was obtained according to the general procedure B from **2b** (225 mg, 1 mmol) and 4-methoxyphenylboronic acid (228 mg, 1.5 mmol) and isolated after purification by column chromatography on silica gel (CH_2Cl_2 as eluent), the yield was 201 mg (68%), white solid, mp 101–102°C, IR: 1608, 1508 cm^{-1}; ^{1}H NMR: δ 1.56–1.60 (m, 2H), 1.79–1.83 (m, 2H), 2.13–2.18 (m, 2H), 2.85–2.90 (m, 2H), 3.83 (s, 3H), 7.06 (d, *J* = 8.6 Hz, 2H), 7.49 (d, *J* = 8.6 Hz, 2H), 8.95 (s, 1H); ^{13}C NMR: δ 21.9, 22.1, 25.4, 26.8, 55.2, 113.2, 127.2, 128.0, 130.5, 130.6, 130.7, 137.6, 151.5, 160.1, 168.0; GC MS (t_R 11.32 min) *m*/*z* (%) = 296 (100, M^+), 265 (12), 211 (9). *Anal.* Calcd. for $C_{17}H_{16}N_2OS$: C, 68.89; H, 5.44; N, 9.45. Found: C, 69.10; H, 5.36; N, 9.53.

1-[3-(Thieno[2,3-d]pyrimidin-4-yloxy)phenyl]ethanone (5a). Compound **5a** was prepared according to Method A from **2a** (171 mg, 1 mmol) and 3-acetylphenylboronic acid (197 mg, 1.2 mmol) and purified by column chromatography (Silica, CH_2Cl_2 as eluent), the yield was 208 mg (77%), white solid, mp 140–141°C; IR: 1694, 1571, 1526 cm^{-1}; ^{1}H NMR: δ 2.59 (s, 3H), 7.64 (m, 2H), 7.69 (d, *J* = 6 Hz, 1H), 7.90 (m, 2H), 7.99 (d, *J* = 6 Hz, 1H), 8.61 (s, 1H); ^{13}C NMR: δ 26.8, 118.4, 118.6, 121.6, 125.7, 127.0, 127.5, 130.2, 138.5, 152.2, 152.8, 163.0, 169.1, 197.2; GC MS (t_R 9.82 min) *m*/*z* (%) = 270 (100, M^+), 255 (99), 242 (29), 227 (98), 135 (97); HRMS calcd for $[M + H^+]$ $C_{14}H_{11}N_2O_2S$ 271.0536, found 271.0516. *Anal.* Calcd. for $C_{14}H_{10}N_2O_2S$: C, 62.21; H, 3.73; N, 10.36. Found: C, 62.48; H, 3.75; N, 10.55.

1-[3-(5,6,7,8-Tetrahydrobenzothieno[2,3-d]pyrimidin-4-yl-oxy)-phenyl]ethanone (5b). Compound **5b** was prepared from **2b** (225 mg, 1 mmol) and 3-acetylphenylboronic acid (197 mg, 1.2 mmol) according to Method A working at room temperature and purified by column chromatography (Silica, Cyclohexane/AcOEt 98:2 as eluent), the yield was 80 mg (25%), white solid, mp 148–149°C, IR: 1683, 1571, 1558 cm^{-1}; ^{1}H NMR: δ 1.85 (m, 4H), 2.58 (s, 3H), 2.86 (m, 2H), 3.02 (m, 2H), 7.55–7.65 (m, 2H), 7.83–7.90 (m, 2H), 8.47 (s, 1H); ^{13}C NMR: δ 21.7, 22.3, 25.0, 25.4, 26.8, 118.4, 121.5, 125.5, 126.9, 127.0, 130.0, 135.9, 138.4, 151.9, 152.3, 162.6, 167.7, 197.2; HRMS calcd for $[M + H^+]$ $C_{18}H_{17}N_2O_2S$ 325.1005, found 325.0985. *Anal.* Calcd. for $C_{18}H_{16}N_2O_2S$: C, 66.64; H, 4.97; N, 8.64. Found: C, 66.87; H, 4.90; N, 8.64.

1-(3-Thieno[2,3-d]pyrimidin-4-ylphenyl)ethanone (6a). Compound **6a** was prepared from **2a** (171 mg, 1 mmol) and 3-acetylphenylboronic acid (246 mg, 1.5 mmol) according to Method B. The pure product was obtained by column chromatography (Silica, CH_2Cl_2 as eluent), the yield was 111 mg (44%), white solid, mp 129–130°C, IR: 1683, 1603, 1545 cm^{-1}; ^{1}H NMR: δ 2.74 (s, 3H), 7.83 (m, 2H), 8.13–8.32 (m, 3H), 8.56 (s, 1H), 9.25 (s, 1H); ^{13}C NMR: δ 26.9, 120.7, 127.3, 128.7, 129.3, 129.4, 130.0, 133.5, 137.3, 137.4, 153.0, 158.9, 169.4, 197.5; GC MS (t_R 9.76 min) *m*/*z* (%) = 254 (100, M^+), 239 (64), 211 (68); HRMS calcd for $[M + H^+]$ $C_{14}H_{11}N_2OS$ 255.0587, found 255.0572. *Anal.* Calcd. for $C_{14}H_{10}N_2OS$: C, 66.12; H, 3.96; N, 11.02. Found: C, 66.26; H, 3.88; N, 10.99.

1-[3-(5,6,7,8-Tetrahydrobenzothieno[2,3-d]pyrimidin-4-yl)phenyl]ethanone (6b). Compound **6b** was prepared from **2b** (225 mg, 1 mmol) and 3-acetylphenylboronic acid (197 mg, 1.2 mmol) according to Method C. The pure product was obtained by column chromatography (Silica, CH_2Cl_2 as eluent), the yield was 231 mg (75%), pale brown solid, mp 121–122°C, IR: 1684, 1579, 1560, 1523 cm^{-1}; ^{1}H NMR: δ 1.53–1.58 (m, 2H), 1.77–1.82 (m, 2H), 2.02–2.07 (m, 2H), 2.63 (s, 3H), 2.86–2.91 (m, 2H), 7.68 (m, 1H), 7.80 (m, 1H), 8.10 (m, 1H), 8.30 (s, 1H), 9.02 (s, 1H); ^{13}C NMR: δ 21.2, 22.0, 25.4, 26.6, 26.8, 126.8, 128.1, 128.4, 128.6, 128.9, 133.6, 136.3, 138.4, 138.5, 151.6, 159.3, 168.1, 197.6; GC MS (t_R 11.78 min) *m*/*z* (%) = 307 (100, M^+), 293 (56), 280 (93), 266 (16); HRMS calcd for $[M + H^+]$ $C_{18}H_{17}N_2OS$ 309.1056, found 309.1030. *Anal.* Calcd. for $C_{18}H_{16}N_2OS$: C, 70.10; H, 5.23; N, 9.08. Found: C, 70.17; H, 5.35; N, 9.12.

tert-Butyl 4-(thieno[2,3-d]pyrimidin-4-yloxy)phenylcarbamate (7). Compound **7** was prepared from **2a** (171 mg, 1 mmol) and 4-[(*tert*-butoxycarbonyl)amino]phenylboronic acid (285 mg, 1.2 mmol) according to Method A. The pure product was obtained by column chromatography (Silica, CH_2Cl_2 as eluent), the yield was 230 mg (67%), pale yellow solid, mp 141–142°C, IR: 1702, 1573, 1535 cm^{-1}; ^1H NMR: δ 1.46 (s, 9H), 7.17 (d, J = 9 Hz, 2H), 7.49 (d, $J = 9$ Hz, 2H), 7.61 (d, $J = 6$ Hz, 1H), 7.91 (d, $J = 6$ Hz, 1H), 8.56 (s, 1H), 9.41 (s, 1H); ^{13}C NMR: δ 28.0, 79.2, 115.0, 118.4, 118.5, 119.2, 122.0, 127.2, 137.1, 146.5, 152.9, 163.3, 168.8; GC MS (t_R 9.74 min) m/z (%) = 243 (100, M^+); HRMS calcd for $[M + H^+]$ $C_{17}H_{18}N_3O_3S$ 344.1063, found 344.1042. *Anal*. Calcd. for $C_{17}H_{17}N_3O_3S$: C, 59.46; H, 4.99; N, 12.24. Found: C, 59.62; H, 4.88; N, 12.29.

tert-Butyl 4-(5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidin-4-yl)phenylcarbamate (8). Compound **8** was prepared from **2b** (225 mg, 1 mmol) and 4-[(*tert*-butoxycarbonyl)amino]phenylboronic acid (285 mg, 1.2 mmol) according to Method C. The pure product was obtained by column chromatography (Alumina, cyclohexane/AcOEt 98:2 as eluent), the yield was 231 mg (61%), white solid, mp 173–174°C, IR: 1702, 1612, 1513 cm^{-1}, ^1H NMR: δ 1.46 (s, 9H), 1.61 (m, 2H), 1.79 (m, 2H), 2.15 (m, 2H), 2.87 (m, 2H), 7.44 (m, 2H), 7.60 (m, 2H), 8.95 (s, 1H), 9.62 (s, 1H); ^{13}C NMR: δ 22.0, 25.4, 26.2, 26.8, 28.1, 79.3, 116.9, 127.2, 128.3, 129.9, 131.7, 137.6, 140.7, 151.5, 152.7, 160.1, 168.0; GC MS (t_R 12.23 min) m/z (%) = 280 (100, M^+); HRMS calcd for $[M + H^+]$ $C_{21}H_{24}N_3O_2S$ 382.1584, found 382.1545. *Anal*. Calcd. for $C_{21}H_{23}N_3O_2S$: C, 66.12; H, 6.08; N, 11.01. Found: C, 66.35; H, 6.10; N, 10.95.

tert-Butyl 2-thieno[2,3-d]pyrimidin-4-yl-1H-indole-1-carboxylate (9a). Compound **9a** was prepared from **2a** (171 mg, 1 mmol) and 1-(*tert*-butoxycarbonyl)-1*H*-indol-2-ylboronic acid (313 mg, 1.2 mmol) according to Method C. The pure product was obtained by column chromatography (Alumina, cyclohexane/AcOEt 98:2 as eluent), the yield was 127 mg (36%), pale brown oil, IR: 1727, 1565, 1539, 1515 cm^{-1}; ^1H NMR: δ 1.11 (s, 9H), 7.29 (s, 1H), 7.34 (m, 1H), 7.47 (m, 1H), 7.57 (d, J = 6 Hz, 1H), 7.74 (d, J = 7.7 Hz, 1H), 8.05 (d, J = 6 Hz, 1H), 8.13 (d, J = 8.3 Hz, 1H), 9.17 (s, 1H); ^{13}C NMR: δ 26.7, 83.9, 113.6, 114.4, 120.5, 121.9, 123.4, 126.1, 128.2, 128.3, 129.2, 134.7, 137.1, 148.9, 152.6, 154.2, 168.3; GC MS (t_R 10.97 min) m/z (%) = 251 (100, M^+); HRMS calcd for $[M + H^+]$ $C_{19}H_{18}N_3O_2S$ 352.1114, found 352.1099. *Anal*. Calcd. for $C_{19}H_{17}N_3O_2S$: C, 64.94; H, 4.88; N, 11.96. Found: C, 65.21; H, 4.88; N, 11.89.

tert-Butyl 2-(5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidin-4-yl)-1H-indole-1-carboxylate (9b). Compound **9b** was prepared from **2b** (225 mg, 1 mmol) 1-(*tert*-butoxycarbonyl)-1*H*-indol-2-ylboronic acid (313 mg, 1.2 mmol) according to Method C. The pure product was obtained by column chromatography (Alumina, cyclohexane/AcOEt 98:2 as eluent), the yield was 207 mg (51%), yellow oil, IR: 1735, 1574, 1512 cm^{-1}; ^1H NMR: δ 0.99 (s, 9H), 1.56 (m, 2H), 1.76 (m, 2H), 2.09 (m, 2H), 2.87 (m, 2H), 6.94 (s, 1H), 7.32 (m, 1H), 7.42 (m, 1H), 7.69 (d, J = 7.2 Hz, 1H), 8.21 (d, J = 7.9 Hz, 1H), 9.04 (s, 1H); ^{13}C NMR: δ 21.6, 22.2, 24.2, 25.3, 26.6, 83.8, 111.6, 115.0, 121.5, 123.5, 125.4, 126.8, 128.3, 129.4, 134.4, 135.6, 138.8, 148.6, 151.5, 153.4, 167.2; GC MS (t_R 13.97 min) m/z (%) = 305 (100, M^+); HRMS calcd for $[M + H^+]$ $C_{23}H_{24}N_3O_2S$ 406.1584, found 406.1560. *Anal*. Calcd. for $C_{23}H_{23}N_3O_2S$: C, 68.12; H, 5.72; N, 10.36. Found: C, 68.13; H, 5.71; N, 10.40.

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An Efficient Synthesis of Indeno[1,2-*b*]pyridine and Benzo[*h*]quinoline Derivatives Under Solvent-Free Conditions

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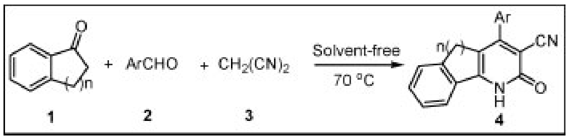

An efficient and convenient multicomponent reaction for the preparation of 4-aryl-2-oxo-2,5-dihydro-1*H*-indeno[1,2-*b*]pyridine-3-carbonitrile and 4-aryl-2-oxo-1,2,5,6-tetrahydrobenzo[*h*]quinoline-3-carbonitrile derivatives by the 2,3-dihydroinden-1-one or 3,4-dihydronaphthalen-1(2*H*)-one, aromatic aldehydes, and malononitrile in the presence of sodium hydroxide under solvent-free condition is reported. The short reaction time coupled with the simplicity of the reaction procedure makes this method one of the most efficient methods for the synthesis of these classes of compounds.

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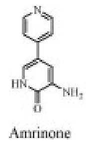
INTRODUCTION

At the new century begins, organic synthetic chemists are placing a greater importance on protecting the environment. A shift in emphasis in chemistry is apparent with the desire to develop more environmentally friendly routes to a myriad of materials. This shift is most apparent in the growth of green chemistry [1–3]. Green chemistry approaches not only hold out significant potential for reduction of by-products, a reduction in the waste produced and lowering of energy costs, but also in the development of new methodologies toward previously unobtainable materials, using existing technologies [4]. Solvent-free organic synthesis [5], as one of efficient synthesis strategies of green chemistry, has caused great interest by chemists in recent years. For they have the many advantages, such as high efficiency and selectivity, easy separation and purification, and mild reaction conditions. Furthermore, the organic solvent could be avoided in this process, and it was very important of protecting the environment.

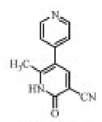
Substituted six-membered lactams have attracted the attention of synthetic organic chemists for many years because these structural features are found in a wide variety of naturally occurring alkaloids [6]. For the compounds with these scaffolds have been shown significant pharmacological properties, medicinal chemists often incorporate these motifs in the design of novel biologically active drugs. For example, arnrinone and milrinone are these type drugs [7] and that have been found to display effective activities on therapy of myocardial infarction. Because of importance of these kinds of compounds, development of a general and efficient synthetic strategy to synthesize those compounds is still desired. Although several synthetic methodologies directed toward the preparation of six-membered lactams have been reported [8], they had many disadvantages, such as long reaction times, low yields, and forces reaction conditions. Especially, in reported reactions, the organic solvents were necessary. In continuation of our research to prepare organic compounds under solvent-free conditions [9], herein, we reported a simple and efficient process to synthesize six-membered lactams, indeno[1,2-*b*]pyridine and benzo[*h*]quinoline derivatives under solvent-free conditions.

RESULTS AND DISCUSSION

The operation of preparation these derivatives could be carried out as follows: 2,3-dihydroinden-1-one, aromatic aldehydes, and malononitrile were put into a round flask, in the presence of a small amount NaOH under solvent-free conditions at 70°C, and corresponding products, 4-aryl-2-oxo-2,5-dihydro-1*H*-indeno[1,2-*b*]pyridine-3-arbo-nitrile could be gained with high yields (Scheme 1 and Table 1). In our investigation, we found that the reaction could be finished within 10–15 min, Furthermore, the aromatic aldehydes, either bearing electron-withdrawing groups (such as halide) or electron-donating groups (such alkoxyl group), could be reacted smoothly in these process.



Amrinone



Milrinone

To examine the efficiency and the applicability of this process, then 3,4-dihydronaphthalen-1(2*H*)-one was chosen to react with aromatic aldehydes and malononitrile under same conditions. To our delight, the six-membered lactams, 4-aryl-2-oxo-1,2,5,6-tetrahydrobenzo[*h*]quinoline-3-carbonitrile was easily obtained with excellent yields, and these reactions could also be completed in a few minutes (about 10 min). Similarly, the aromatic aldehydes, bearing different groups, did not affect the reaction.

The structures of the products were confirmed on the basis of IR, ^{1}H NMR spectroscopic data, elemental analysis, and that of **4c** [10] and **4j** [11] was additionally confirmed by X-ray diffraction analysis (Figs. 1 and 2).

In conclusion, we have developed a rapid and highly efficient method for the synthesis of a variety of 4-aryl-2-oxo-2,5-dihydro-1*H*-indeno[1,2-*b*]pyridine-3-carbonitrile and 4-aryl-2-oxo-1,2,5,6-tetrahydrobenzo[*h*]quinoline-3-carbonitrile derivatives *via* the reaction of different aromatic aldehydes, 2,3-dihydroinden-1-one or 3,4-dihydronaphthalen-1(2*H*)-one, and malononitrile under solvent-free conditions. The advantages of the present method in terms of avoiding to using toxic organic solvent, ease of manipulation, fast reaction rates, and lower cost should make this protocol as a valuable alternative to the existing methods.

EXPERIMENTAL

Melting points were determined on XT-5 microscopic melting-point apparatus and were uncorrected. IR spectra were recorded on a FT Bruker Tensor 27 spectrometer. ^{1}H NMR spectra were obtained from solution in DMSO-d_6 with Me_4Si as internal standard using a Bruker-400 spectrometer. Microanalyses were carried out using a Perkin–Elmer 2400 II analyzer. X-ray diffraction was measured on a Siemens P4 diffractometer.

The mixture of 2,3-dihydroinden-1-one or 3,4-dihydronaphthalen-1(2*H*)-one **1** (2 mmol), aromatic aldehydes **2** (2 mmol), malononitrile **3** (3 mmol), and NaOH (2 mmol) was put in a reaction flask and let them under 70°C about 10–15 min. After completing the reaction, the reaction mixture was poured into water, and then washed with water thoroughly. The product was filtered, dried, and recrystallized from 95% ethanol.

Scheme 1

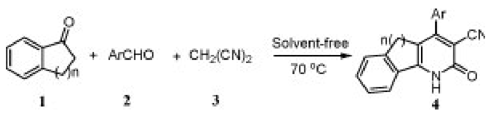


Table 1

Synthesis of product 4 under solvent-free conditions.

Entry	Ar^1	Time (min)	*n*	Product	Yields
1	4-FC_6H_4	10	1	**4a**	88
2	4-BrC_6H_4	10	1	**4b**	89
3	4-ClC_6H_4	10	1	**4c**	95
4	2-ClC_6H_4	10	1	**4d**	90
5	2,4-$Cl_2C_6H_3$	10	1	**4e**	86
6	3,4-$Cl_2C_6H_3$	10	1	**4f**	88
7	4-$CH_3OC_6H_4$	15	1	**4g**	89
8	4-FC_6H_4	10	2	**4h**	91
9	4-BrC_6H_4	10	2	**4i**	93
10	4-ClC_6H_4	10	2	**4j**	92
11	2-ClC_6H_4	10	2	**4k**	89
12	3,4-$Cl_2C_6H_3$	10	2	**4l**	81
13	4-$CH_3C_6H_4$	15	2	**4m**	85
14	4-$CH_3OC_6H_4$	15	2	**4n**	89
15	3,4-$(CH_3)_2C_6H_3$	15	2	**4o**	86

4-(4-Fluorophenyl)-2-oxo-2,5-dihydro-1*H*-indeno[1,2-*b*]pyridine-3-carbonitrile (4a). This compound was obtained as yellow crystals, mp >300°C; IR (KBr, ν, cm^{-1}): 3287, 3045, 2739, 2219, 1635, 1595, 1559, 1486, 1459, 1396, 1356, 1316, 1298, 1264, 1233, 1203, 1159, 1134, 1086, 1014, 955, 899, 835, 772, 734, 684, 634; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 3.67 (2H, s, CH_2), 7.52 (2H, t, J = 3.6 Hz, ArH), 7.62 (1H, d, J = 6.0 Hz, ArH), 7.68 (4H, q, J = 8.4 Hz, ArH), 7.16 (1H, d, J = 6.0 Hz, ArH), 13.65 (1H, s, NH). *Anal.* Calcd. For $C_{19}H_{11}FN_2O$: C 75.49, H 3.67, N 9.27. Found C 75.60, H 3.65, N 9.31.

4-(4-Bromophenyl)-2-oxo-2,5-dihydro-1*H*-indeno[1,2-*b*]pyridine-3-carbonitrile (4b). This compound was obtained as yellow crystals, mp >300°C; IR (KBr, ν, cm^{-1}): 3241, 3016, 2790, 2222, 1636, 1592, 1564, 1486, 1460, 1387, 1354, 1316, 1297, 1271, 1227, 1202, 1161, 1130, 1067, 1010, 945, 898, 824, 768, 733, 674, 628; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 3.66 (2H, s, CH_2), 7.50–7.53 (2H, m, ArH), 7.63 (3H, t, J = 7.8 Hz, ArH), 7.70 (2H, d, J = 7.8 Hz, 8.4 Hz, ArH), 8.17 (1H, d, J = 2.0 Hz, ArH), 13.65 (1H, s, NH). *Anal.* Calcd. For $C_{19}H_{11}BrN_2O$: C 62.83, H 3.05, N 7.71. Found C 62.61, H 3.07, N 7.74.

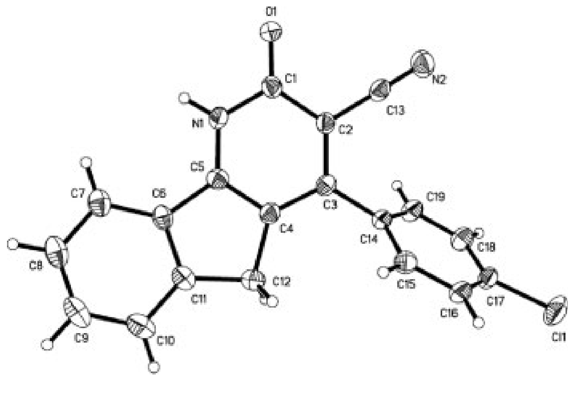


Figure 1. The structure of compound 4c.

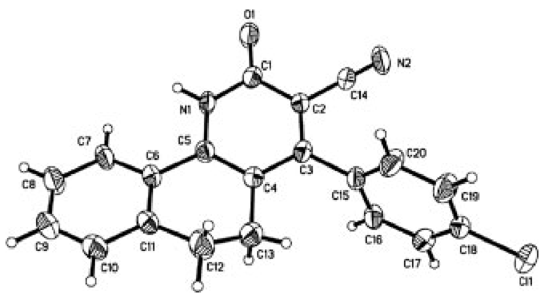


Figure 2. The structure of compound 4j.

4-(4-Chlorophenyl)-2-oxo-2,5-dihydro-1*H*-indeno[1,2-*b*] pyridine-3-carbonitrile (4c). This compound was obtained as yellow crystals, mp >300°C; IR (KBr, ν, cm^{-1}): 3296, 3045, 2696, 2219, 1637, 1596, 1560, 1487, 1459, 1396, 1356, 1298, 1265, 1233, 1203, 1159, 1134, 1086, 1014, 955, 899, 835, 772, 734, 684, 634; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 3.68 (2H, s, CH_2), 7.53 (2H, t, J = 5.6 Hz, ArH), 7.64 (1H, d, J = 5.6 Hz, ArH), 7.70 (4H, dd, J = 8.4 Hz, 8.4 Hz, ArH), 8.19 (1H, d, J = 5.6 Hz, ArH), 13.68 (1H, s, NH). *Anal.* Calcd. For $C_{19}H_{11}ClN_2O$: C 71.59, H 3.48, N 8.79. Found C 71.41, H 3.50, N 8.84.

4-(2-Chlorophenyl)-2-oxo-2,5-dihydro-1*H*-indeno[1,2-*b*] pyridine-3-carbonitrile (4d). This compound was obtained as yellow crystals, mp >300°C; IR (KBr, ν, cm^{-1}): 3337, 3066, 2222, 1698,1612, 1474, 1465, 1442, 1396, 1316, 1281, 1244, 1210, 1179, 1156, 1099, 1034, 1011, 918, 780, 758, 702, 667, 628; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 3.50 (2H, dd, J = 22.4 Hz, J = 22.4 Hz, CH_2), 7.54 (2H, t, J = 3.6 Hz, ArH), 7.58 (2H, br, ArH), 7.62 (2H, t, J = 4.0 Hz, ArH), 7.72 (1H, d, J = 7.2 Hz, ArH), 8.20 (1H, d, J = 4.0 Hz, ArH), 13.68 (1H, s, NH). *Anal.* Calcd. For $C_{19}H_{11}ClN_2O$: C 71.59, H 3.48, N 8.79. Found C 71.40, H 3.45, N 8.82.

4-(2,4-Dichlorophenyl)-2-oxo-2,5-dihydro-1*H*-indeno[1,2-*b*] pyridine-3-carbonitrile (4e). This compound was obtained as yellow crystals, mp >300°C; IR (KBr, ν, cm^{-1}): 3291, 3067, 2781, 2223, 1635, 1594, 1561, 1482, 1458, 1419, 1399, 1375, 1351, 1315, 1298, 1272, 1255, 1202, 1190, 1155, 1135, 1010, 1056, 940, 900, 859, 838, 771, 735, 678, 652, 637; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 4.13 (2H, s, CH_2), 7.50–7.54 (1H, m, ArH), 7.52 (2H, t, J = 6.4 Hz, ArH), 7.84 (2H, t, J = 6.4 Hz, ArH), 7.89 (1H, d J = 6.8 Hz, ArH), 8.00 (1H, s, ArH), 13.85 (1H, s, NH). *Anal.* Calcd. For $C_{19}H_{10}Cl_2N_2O$: C 64.61, H 2.85, N 7.93. Found C 64.88, H 2.84, N 7.89.

4-(3,4-Dichlorophenyl)-2-oxo-2,5-dihydro-1*H*-indeno[1,2-*b*] pyridine-3-carbonitrile (4f). This compound was obtained as yellow crystals, mp >300°C; IR (KBr, ν, cm^{-1}): 3339, 3072, 2744, 2219, 1658, 1616, 1558, 1507, 1488, 1481, 1458, 1419, 1398, 1375, 1355, 1299, 1268, 1229, 1203, 1191, 1139, 1122, 1032, 865, 824, 767, 728, 680, 669; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 3.71 (2H, s, CH_2), 7.54 (2H, q, J = 60 Hz, J = 7.2 Hz, ArH), 7.66 (1H, d, J = 7.2 Hz, ArH), 7.69 (1H, d, J = 8.4 Hz, ArH), 7.89 (1H, d J = 8.0 Hz, ArH), 8.04 (1H, d, J = 7.6 Hz, ArH), 8.19–8.21 (1H, br, ArH), 13.76 (1H, s, NH). *Anal.* Calcd. For $C_{19}H_{10}Cl_2N_2O$: C 64.61, H 2.85, N 7.93. Found C 64.50, H 2.87, N 7.90.

4-(4-Methoxyphenyl)-2-oxo-2,5-dihydro-1*H*-indeno[1,2-*b*] pyridine-3-carbonitrile (4g). This compound was obtained as yellow crystals, mp >300°C; IR (KBr, ν, cm^{-1}): 3292, 3059, 2836, 2219, 1637, 1616, 1560, 1517, 1485, 1458, 1418, 1356, 1294, 1258, 1234, 1179, 1159, 1031, 835, 767, 731, 648; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 3.72 (2H, s, CH_2), 3.87 (3H, s, OCH_3), 7.14 (2H, t, J = 8.8 Hz, ArH), 7.52 (2H, t, J = 3.6 Hz, ArH), 7.66 (1H, m, ArH), 7.89 (2H, d, J = 8.8 Hz, ArH), 8.17 (1H, br, ArH), 13.59 (1H, s, NH). *Anal.* Calcd. For $C_{20}H_{14}N_2O_2$: C 76.42, H 4.49, N 8.91. Found C 76.60, H 4.47, N 8.87.

4-(4-Fluorophenyl)-2-oxo-1,2,5,6-tetrahydrobenzo[*h*]quinoline-3-carbonitrile (4h). This compound was obtained as yellow crystals, mp >300°C; IR (KBr, ν, cm^{-1}): 3131, 3069, 2931, 2220, 1634, 1606, 1555, 1533, 1510, 1499, 1458, 1403, 1345, 1298, 1250, 1218, 1160, 1141, 1098, 894, 843, 824, 794, 772, 736; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 2.33 (2H, br, CH_2), 2.74 (2H, t, J = 7.2 Hz, CH_2), 7.35 (1H, d, J = 6.4 Hz, ArH), 7.39–7.46 (4H, m, ArH), 7.52 (2H, dd, J = 5.2 Hz, J = 5.6 Hz, ArH), 8.07 (1H, br, ArH), 12.77 (1H, s, NH). *Anal.* Calcd. For $C_{20}H_{13}FN_2O$: C 75.94, H 4.14, N 6.01. Found C 75.81, H 4.12, N 6.04.

4-(4-Bromophenyl)-2-oxo-1,2,5,6-tetrahydrobenzo[*h*]quinoline-3-carbonitrile (4i). This compound was obtained as yellow crystals, mp >300°C; IR (KBr, ν, cm^{-1}): 3124, 3032, 2939, 2221, 1638, 1606, 1552, 1497, 1458, 1389, 1344, 1298, 1250, 1215, 1160, 1103, 1071, 1010, 908, 833, 811, 773, 738, 666; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 2.36 (2H, t, J = 6.0 Hz, CH_2), 2.76 (2H, t, J = 6.8 Hz, CH_2), 7.35 (1H, d, J = 6.8 Hz, ArH), 7.43 (4H, dd, J = 8.4 Hz, J = 8.4 Hz, ArH), 7.78 (2H, d, J = 8.8 Hz, ArH), 8.07 (1H, d, J = 7.6 Hz, ArH), 12.62 (1H, s, NH). *Anal.* Calcd. For $C_{20}H_{13}BrN_2O$: C 63.68, H 3.47, N 7.43. Found C 63.50, H 3.49, N 7.46.

4-(4-Chlorophenyl)-2-oxo-1,2,5,6-tetrahydrobenzo[*h*]quinoline-3-carbonitrile (4j). This compound was obtained as yellow crystals, mp >300°C; IR (KBr, ν, cm^{-1}): 3130, 3031, 2931, 2223, 1637, 1553, 1535, 1498, 1460, 1425, 1340, 1346, 1297, 1251, 1217, 1198, 1176, 1142, 1086, 1014, 909, 836, 813, 774, 739, 707, 658; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 2.37 (2H, br, CH_2), 2.76 (2H, t, J = 6.8 Hz, CH_2), 7.35 (1H, d, J = 7.2 Hz, ArH), 7.43 (2H, dd, J = 7.2 Hz, J = 7.2 Hz, ArH), 7.49 (2H, d, J = 8.0 Hz, ArH), 7.64 (2H, d, J = 8.4 Hz, ArH), 8.07 (1H, d, J = 7.6 Hz, ArH), 12.62 (1H, s, NH). *Anal.* Calcd. For $C_{20}H_{13}ClN_2O$: C 72.18, H 3.94, N 8.42. Found C 72.38, H 3.91, N 8.46.

4-(2-Chlorophenyl)-2-oxo-1,2,5,6-tetrahydrobenzo[*h*]quinoline-3-carbonitrile (4k). This compound was obtained as yellow crystals, mp >300°C; IR (KBr, ν, cm^{-1}): 3130, 3031, 2931, 2223, 1637, 1553, 1535, 1498, 1460, 1425, 1340, 1346, 1297, 1251, 1217, 1198, 1176, 1142, 1086, 1014, 909, 836, 813, 774, 739, 707, 658; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 2.37 (2H, br, CH_2), 2.76 (2H, t, J = 6.8 Hz, CH_2), 7.35 (1H, d, J = 7.2 Hz, ArH), 7.44 (4H, dd, J = 8.0 Hz, J = 8.0 Hz, ArH), 7.78 (2H, d, J = 8.4 Hz, ArH), 8.07 (1H, d, J = 7.6 Hz, ArH), 12.66 (1H, s, NH). *Anal.* Calcd. For $C_{20}H_{13}ClN_2O$: C 72.18, H 3.94, N 8.42. Found C 72.32, H 3.91, N 8.46.

4-(3,4-Dichlorophenyl)-2-oxo-1,2,5,6-tetrahydrobenzo[*h*]-quinoline-3-carbonitrile (4l). This compound was obtained as yellow crystals, mp 287–289°C; IR (KBr, ν, cm^{-1}): 3123, 3023, 2940, 2218, 1635, 1557, 1497, 1474, 1455, 1397, 1374, 1341, 1297, 1247, 1212, 1194, 1129, 1031, 952, 896, 821, 773, 737, 664; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 2.28 (1H, t, J = 7.2 Hz, CH_2), 2.38 (1H, t, J = 6.8 Hz, CH_2), 2.75 (2H, q, J = 6.8 Hz, J = 8.0 Hz, CH_2), 7.23–7.30 (1H, m, ArH), 7.35–7.48 (3H, m, ArH), 7.69–7.85 (2H, m, ArH), 8.03–

8.09 (1H, m, ArH), 12.54 (1H, s, NH). *Anal.* Calcd. For $C_{20}H_{12}Cl_2N_2O$: C 65.41, H 3.29, N 7.63. Found C 65.60, H 3.28, N 7.59.

2-Oxo-4-p-tolyl-1,2,5,6-tetrahydrobenzo[*h*]quinoline-3-carbonitrile e (4m). This compound was obtained as yellow crystals, mp >300°C; IR (KBr, ν, cm^{-1}): 3128, 3030, 2930, 2221, 1634, 1555, 1536, 1497, 1457, 1402, 1344, 1322, 1296, 1282, 1250, 1210, 1184, 1171, 1141, 1115, 1041, 1020, 975, 954, 905, 808, 774, 759, 737, 666; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 2.37 (2H, br, CH_2), 2.40 (3H, s, CH_3), 2.76 (2H, t, $J = 7.2$ Hz, CH_2), 7.31 (2H, d, $J = 8.4$ Hz, ArH), 7.36 (3H, d $J = 8.4$ Hz, ArH), 7.43 (2H, q, $J = 6.4$ Hz, $J = 7.2$ Hz, ArH), 8.07 (1H, d, $J = 8.4$ Hz, ArH), 12.65 (1H, s, NH). *Anal.* Calcd. For $C_{21}H_{16}N_2O$: C 80.75, H 5.16, N 8.97. Found C 80.55, H 5.19, N 8.92.

4-(4-Methoxyphenyl)-2-oxo-1,2,5,6-tetrahydrobenzo[*h*]quinoline-3-carbonitrile e (4n). This compound was obtained as yellow crystals, mp >300°C; IR (KBr, ν, cm^{-1}): 3120, 3032, 2936, 2219, 1636, 1556, 1515, 1497, 1457, 1398, 1341, 1295, 1255, 1212, 1180, 1142, 1025, 1020, 975, 838, 819, 772, 761, 736, 667; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 2.41 (2H, t, $J = 6.0$ Hz, CH_2), 2.75 (2H, t, $J = 7.2$ Hz, CH_2), 3.84 (3H, s, CH_3O), 7.11 (2H, d, $J = 8.8$ Hz, ArH), 7.34 (1H, d, $J = 6.8$ Hz, ArH), 7.38 (3H, d, $J = 8.8$ Hz, ArH), 7.43 (1H, t, $J = 7.2$ Hz, ArH), 8.06 (1H, d, $J = 7.2$ Hz, ArH), 12.58 (1H, s, NH). *Anal.* Calcd. For $C_{21}H_{16}N_2O_2$: C 76.81, H 4.91, N 8.53. Found C 76.62, H 4.88, N 8.56.

4-(3,4-Dimethylphenyl)-2-oxo-1,2,5,6-tetrahydrobenzo[*h*]quinoline-3-carbonitrile (4o). This compound was obtained as yellow crystals, mp >300°C; IR (KBr, ν, cm^{-1}): 3123, 3023, 2940, 2218, 1635, 1557, 1497, 1474, 1455, 1397, 1374, 1341, 1297, 1247, 1212, 1194, 1129, 1031, 952, 896, 821, 773, 737, 664; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 2.29 (3H, s, CH_3), 2.30 (3H, s, CH_3), 2.37 (2H, t, $J = 7.2$ Hz, CH_2), 2.73 (2H, t, $J = 7.2$ Hz, CH_2), 7.13 (1H, d, $J = 7.6$ Hz, ArH), 7.08 (1H, s, ArH), 7.32 (2H, t $J = 7.6$ Hz, ArH), 7.39 (1H, t, $J = 7.6$ Hz, ArH), 7.45 (1H, t, $J = 7.6$ Hz, ArH), 8.06 (1H, d, $J = 7.6$ Hz, ArH), 12.72 (1H, s, NH). *Anal.* Calcd. For $C_{22}H_{18}N_2O$: C 80.96, H 5.56, N 8.58. Found C 80.72, H 5.52, N 8.61.

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[10] X-ray crystallography for 4c: Empirical formula $C_{19}H_{11}ClN_2O$, $F_w = 318.75$, $T = 298(2)$ K, triclinic, space group p −1, $a = 7.163$ (4) Å, $b = 9.498(5)$ Å, $c = 11.500(6)$ Å, $\alpha = 87.769(6)°$, $\beta = 79.052(7)°$, $\gamma = 80.758(7)°$, $V = 758.2(7)$ $Å^3$, $Z = 2$, Dcalcd. = 1.396 mg/m^3, λ(MoKα) = 0.71073 Å, $\mu = 0.257$ mm^{-1}, $F(000) = 328$. $1.80° < \theta < 25.00°$, $R = 0.0503$, $wR = 0.1008$. $s = 1.004$. Largest diff. peak and hole: 0.234 and −0.330 e $Å^{-3}$.

[11] X-ray crystallography for 4j: Empirical formula $C_{20}H_{14}ClN_2O$, $F_w = 333.78$, $T = 298(2)$ K, monoclinic, space group C2/c, $a = 22.727$ (11) Å, $b = 8.399(4)$ Å, $c = 18.035(9)$ Å, $\alpha = 90°$, $\beta = 107.651(7)°$, $\gamma = 90°$, $V = 3281(3)$ $Å^3$, $Z = 8$, Dcalcd. = 1.352 mg/m^3, λ(MoKα) = 0.71073 Å, $\mu = 0.241$ mm^{-1}, $F(000) = 1384$. $1.88° < \theta < 25.00°$, $R = 0.0758$, $wR = 0.1783$. $s = 1.043$. Largest diff. peak and hole: 0.280 and −0.433 e $Å^{-3}$.

A Facile Synthesis of Furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5(7*H*)-one Derivatives via Three-Component Reaction in Ionic Liquid without Any Catalyst

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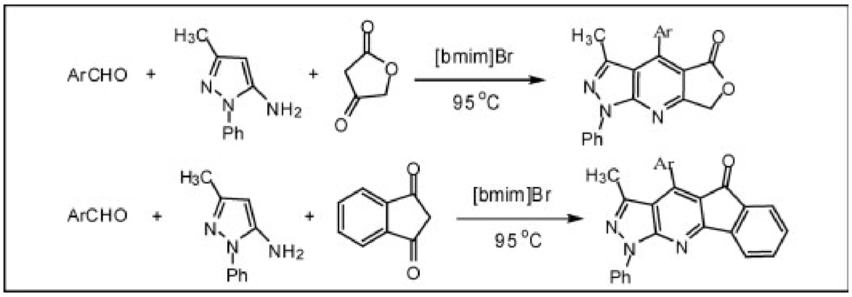

A series of furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5(7*H*)-one and indeno[2,1-*e*]pyrazolo[3,4-*b*]pyridine-5(1*H*)-one derivatives were synthesized via the three-component reaction of an aldehyde, 5-aminopyrazole and either tetronic acid or 1,3-indanedione in ionic liquid without any catalyst. The structures of the products have been established by spectroscopic data and further confirmed by X-ray diffraction analysis. This method has the advantages of easier work-up, mild reaction conditions, high yields and an environmentally benign procedure.

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INTRODUCTION

Multicomponent reactions (MCRs) are of increasing importance in organic and medical chemistry. The first MCR was described by Strecker in 1850 for the synthesis of amino acids [1]. However, in the past decade there have tremendous developments in three- and four-component reactions and great efforts continue to be made to develop new MCRs [2]. Recently, there has been considerable interest in the use of ionic liquids as an environmentally benign reaction media because of its unique properties such as a wide liquid range, good solvating ability, tunable polarity, high-thermal stability, negligible vapor pressure, and ease of recyclablity [3]. Numerous chemical reactions, such as polymerization [4], hydrogenation [5], regioselective alkylation [6], Friedel–Crafts reactions [7], dimerization of alkenes [8], Diels–Alder reactions [9], Michael reactions [10], cross-coupling reactions [11], and some enzymic reactions [12] can be carried out in ionic liquids. Recently, some MCRs in ionic liquids have been reported [13].

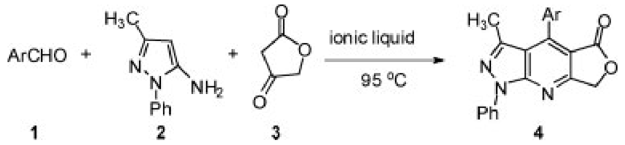
Furopyridines is one of the ''privileged medicinal scaffolds'' which are used for the development of pharmaceutical agents of various applications. Compounds with this motif show a wide range of pharmacological activities such as antipsychotic [14], antiproliferative [15], anticonvulsant [16], antianaphylactic [17], and anthelmintic [18] activities and can be used as calcium influx promoters [19], HIV-1 non-nucleoside reverse transcriptase inhibitors [20], and acetylcholinesterase inhibitors [21]. Pyrazole derivatives have been reported in the literature to be versatile building blocks for the synthesis of a wide range of the heterocyclic motifs, such as pyrazolopyridines [22], pyrazoloquinolines [23], and pyrzolopyrazoles [24]. The pyrazolo[3,4-*b*]pyridine system has interesting biological and pharmacological properties [25], such as adrenocorticotropic hormone (ACTH)-releasing factor antagonist activity [26].

Furopyridines and pyrazolo[3,4-*b*]pyridines have been reported widely in the literature. However, the synthesis of the compounds with both pyrazolo[3,4-*b*]pyridine and furo[3,4-*b*]pyridine motifs was neglected. We herein described a facile three-component reaction consisting of aldehyde **1**, 5-amino-3-methyl-1-phenylpyrazole **2**, and tetronic acid **3** in ionic liquid to synthesize the furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5(7*H*)-one derivatives **4** (Scheme 1).

RESULTS AND DISCUSSION

Choosing an appropriate solvent is of crucial importance for the successful organic synthesis. To search for

Scheme 1



the optimal solvent, the three-component reaction of 4-bromobenzaldehyde **1a**, 5-amino-3-methyl-1-phenylpyrazole **2**, and tetronic acid **3** was examined using ionic liquid such as [bmim]Br, [bmim]BF_4, [pmim]Br, water, glacial acetic acid, acetone, and ethanol as solvent, respectively, at different temperature for the synthesis of **4a**.

It can be seen from Table 1 that the reactions using ionic liquids as the solvent resulted in higher yields and shorter reaction times than those using organic solvents. Using water can also give the higher yields, but the reaction time is very long. On the basis of the obtained results, [bmim]Br was found to be superior in terms of cheap and yield. Under these optimized reaction conditions, a series of furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5(7*H*)-one derivatives **4** were synthesized. The results are summarized in Table 2. The products were different from those in ethanol in the presences of L-proline [27]. The structures of the products may be affected by catalyst and solvents.

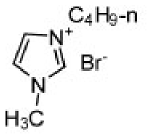
To expand the scope of the present method, the replacement of tetronic acid **3** with 1,3-indanedione **5** was examined. This is particularly attractive because compounds with indenopyridine motifs show a wide range of biological activities such as calcium antagonistic [28], antioxidant [29], antihistamine and antidepressant [30], and also act as phosphodiesterase inhibitors [31], NK-1, and dopamine receptor ligands [32]. To our delight, under the earlier-optimized conditions, the reactions proceeded smoothly. A series of indeno[2,1-*e*]pyrazolo[3,4-*b*] pyridine-5(1*H*)-one derivatives **6** were obtained (Scheme 2) in excellent yields. The products were agreed with those in ethanol [27] or DMF [33]. The results are summarized in Table 3.

Table 1

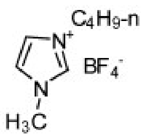
Solvent optimization for the synthesis of **4a**.[a]

Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	[bmim]Br	95	2	98
2	[bmim]BF_4	95	2	94
3	[pmim]Br	95	2	93
4	H_2O/TEBAC	95	20	97
5	AcOH	95	4	92
6	CH_3COCH_3	Reflux	7	75
7	EtOH	Reflux	4	80

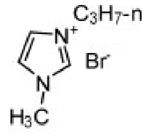
[a] 4-Bromobenzaldehyde (2 mmol), 5-amino-3-methyl-1-phenylpyrazole (2 mmol), tetronic acid (2 mmol), and 2 mL solvent.



[bmim]Br



[bmim]BF_4



[pmim]Br

Table 2

The synthesis of **4** in [bmim]Br.

Entry	Ar	Time (h)	Yield (%)
4a	4-BrC_6H_4	2	98
4b	4-$CH_3OC_6H_4$	2	92
4c	4-FC_6H_4	2	88
4d	4-ClC_6H_4	2	96
4e	4-$NO_2C_6H_4$	3	87
4f	4-HOC_6H_4	3	92
4g	4-$(CH_3)_2NC_6H_4$	3	75
4h	3-$NO_2C_6H_4$	4	86
4i	2,4-$Cl_2C_6H_3$	3	95
4j	3,4-$(CH_3)_2C_6H_3$	2	91
4k	3,4-$(CH_3O)_2C_6H_3$	2	91
4l	2-NO_2-5-ClC_6H_3	3	95
4m	3,4-$OCH_2OC_6H_3$	3	85
4n	Thiophen-2-yl	5	80
4o	Pyridin-3-yl	5	62
4p	Pyridin-4-yl	5	72

As shown in Tables 2 and 3, this method can be applied not only to the aromatic aldehydes with either electron-withdrawing groups (such as nitro and halide groups) or electron-donating groups (such as hydroxyl and alkoxyl groups), but also to heterocyclic aldehydes with excellent yields under same conditions. Therefore, we concluded that the electronic nature of the substituents has no significant effect on this reaction.

Apart from the mild conditions of the process and its excellent results, the simplicity of product isolation and the possibility to recycle the [bmim]Br offer a significant advantage. Because [bmim]Br is miscible with water and the desired products are insoluble in water, the products can be directly separated by adding water into the synthetic system after the reaction is complete. The remaining [bmim]Br can then be recycled after removal of water under vacuum. Studies using **1a**, **2**, and **3** as model substrates showed that the recovered ionic liquid could be successively recycled in subsequent reactions without almost any decrease in its efficiency (Table 4). An overall process for the one-pot synthesis

Scheme 2

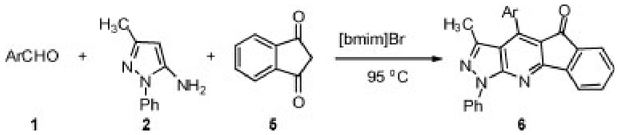


Table 3

The synthesis of **6** in [bmim]Br.

Entry	Ar	Time (°C)	Yield (%)
6a	4-$CH_3C_6H_4$	4	91
6b	4-$CH_3OC_6H_4$	2	90
6c	4-FC_6H_4	2	94
6d	4-ClC_6H_4	2	95
6e	4-BrC_6H_4	2	96
6f	4-$NO_2C_6H_4$	2	91
6g	4-HOC_6H_4	3	90
6h	3-$NO_2C_6H_4$	3	89
6i	3-ClC_6H_4	3	88
6j	4-$(CH_3)_2NC_6H_4$	4	92
6k	2,4-$Cl_2C_6H_3$	3	85
6l	3,4-$(CH_3)_2C_6H_3$	3	92
6m	3,4-$(CH_3O)_2C_6H_3$	3	90
6n	3,4-$OCH_2OC_6H_3$	3	93
6o	3,4-$Cl_2C_6H_3$	3	87
6p	Thiophen-2-yl	4	80
6q	Pyridin-4-yl	5	79

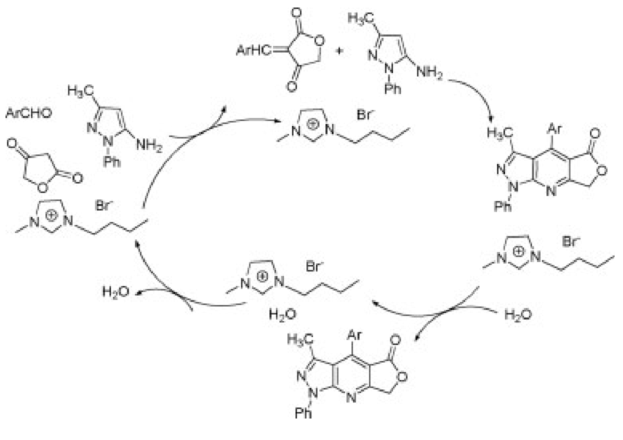


Figure 1. Reaction-isolation-recycle process for the one-pot synthesis of 4 in [bmim]Br.

of furo[3,4-*e*]pyrazolo [3,4-*b*]pyridine-5(7*H*)-one derivatives can be envisaged as shown in Figure 1.

All the products **4** and **6** were characterized by mp, IR, and ^{1}H NMR spectra as well as HRMS. The structure of **4l** was further confirmed by X-ray diffraction analysis [34]. The molecular structure **4l** is shown in Figure 2.

Although the detailed mechanism of the above reaction remains to be fully clarified the formation of furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5(7*H*)-one derivatives **4** could be explained by a reaction sequence presented in Scheme 3. We proposed that the reaction proceeded via a reaction sequence of condensation, addition, cyclization, dehydration, and aromatization. First, the condensation of aldehyde **1** and tetronic acid **3** gave the intermediate product **7**. The addition of **7** to 5-amino-3-methyl-1-phenylpyrazole **2** then furnished the intermediate product **9**, which on intermolecular cyclization and dehydration gave rise to **11**. In the last step, the intermediate product **11** aromatized to product **4**.

Evidence supporting this proposed mechanism came from the observation that when **7a** and **2** were treated under same conditions, the expected product **4a** was obtained in a yield similar to that obtained in the one-pot reaction (Scheme 4).

In conclusion, we have developed a simple three-component reaction of an aldehyde, 5-amino-3-methyl-1-phenylpyrazole and either tetronic acid or 1,3-indanedione for the synthesis of furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5(7*H*)-one and indeno[2,1-*e*]pyrazolo[3,4-*b*]pyridine-5(1*H*)-one derivatives in ionic liquid without any catalyst. This method has the advantages of good yields, convenient procedure, and environmentally friendly reaction conditions.

Table 4

Studies on the reuse of [bmim]Br in the preparation of **4a**.

Round	1	2	3	4	5	6
Yield (%)	97	98	97	97	96	97

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded on a Tensor 27 spectrometer in KBr with absorption in cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were recorded on a

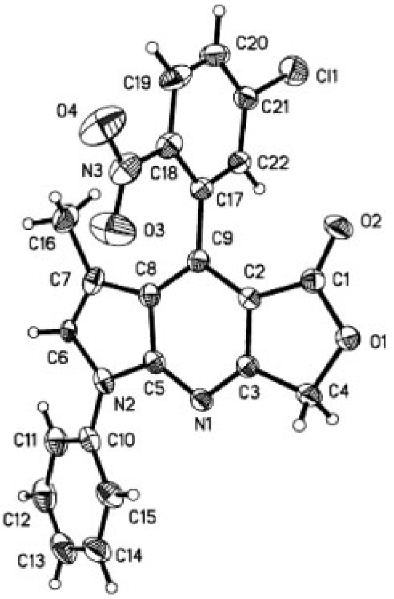
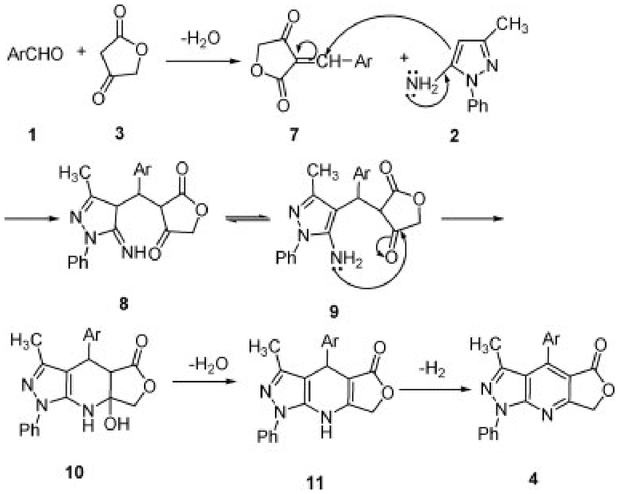


Figure 2. The structure of 4l showing 40% probability displacement ellipsoids.

Scheme 3



Bruker DPX 400-MHz or Inova 300-MHz spectrometer as DMSO-d_6 solution. *J* values are in hertz (Hz). Chemical shifts are expressed in δ downfield from internal tetramethylsilane. HRMS were obtained using TOF-MS instrument. X-ray crystallographic analysis was performed with a Smart-1000 CCD diffractometer.

General procedure for the synthesis of furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5(7*H*)-one derivatives 4 and indeno[2,1-*e*]pyrazolo[3,4-*b*]pyridine-5(1*H*)-one derivatives 6 in ionic liquid. Aldehyde 1 (2 mmol), 5-amino-3-methyl-1-phenylpyrazole 2 (2 mmol), tetronic acid 3 or 1,3-indanedione 5 (2 mmol) were added to a 10 mL round bottom flask containing 2 mL [bmim]Br. The mixture was then stirred at 95°C for given times. After completion of the reaction, the reaction mixture was added with 5 mL water. The precipitate was collected by suction and purified by recrystallization from EtOH to give products 4 or 6. The filtrate was concentrated under reduced pressure and dried at 100°C to recover the ionic liquid for subsequent use.

4-(4-Bromophenyl)-3-methyl-1-phenyl-1H-furo[3,4-e]-pyrazolo[3,4-b]pyridine-5(7H)-one (4a). This compound was obtained as solid with mp 226–227°C; IR (potassium bromide): 3058, 2965, 2929, 1764, 1578, 1557, 1505, 1439, 1386, 1356, 1313, 1210, 1140, 1070, 1048, 1027, 1011, 847, 821, 798, 759, 720 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.13 (s, 3H, CH_3), 5.51 (s, 2H, CH_2), 7.42 (t, *J* = 7.2 Hz, 1H, ArH), 7.55 (d, *J* = 8.4 Hz, 2H, ArH), 7.62 (t, *J* = 7.6 Hz, 2H, ArH), 7.79 (d, *J* = 8.0 Hz, 2H, ArH), 8.19 (d, *J* = 8.8 Hz, 2H, ArH). HRMS [Found: *m/z* 421.0236 (M$^+$); Calcd for $C_{21}H_{14}{}^{79}BrN_3O_2$: M 421.0249].

3-Methyl-4-(4-methoxyphenyl)-1-phenyl-1H-furo[3,4-e] pyrazolo[3,4-b]pyridine-5(7H)-one (4b). This compound was obtained as solid with mp 190–192°C; IR (potassium bromide): 3046, 2971, 2924, 1765, 1608, 1579, 1561, 1509, 1458, 1445, 1426, 1384, 1358, 1309, 1294, 1259, 1208, 1176, 1140, 1071, 1048, 1036, 1019, 824, 797, 758, 692 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.16 (s, 3H, CH_3), 3.88 (s, 3H, CH_3O), 5.47 (s, 2H, CH_2), 7.13 (d, *J* = 8.4 Hz, 2H, ArH), 7.40 (t, *J* = 7.2 Hz, 1H, ArH), 7.53 (d, *J* = 8.4 Hz, 2H, ArH), 7.61 (t, *J* = 8.0 Hz, 2H, ArH), 8.20 (d, *J* = 8.0 Hz, 2H, ArH). HRMS [Found: *m/z* 371.1255 (M$^+$); Calcd for $C_{22}H_{17}N_3O_3$: M 371.1270].

4-(4-Fluorophenyl)-3-methyl-1-phenyl-1H-furo[3,4-e]pyrazolo[3,4-b]pyridine-5(7H)-one (4c). This compound was obtained as solid with mp 235–237°C; IR (potassium bromide): 3070, 2929, 1756, 1597, 1578, 1513, 1490, 1449, 1437, 1422, 1392, 1360, 1315, 1221, 1167, 1137, 1068, 1042, 1028, 830, 798, 757 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.12 (s, 3H, CH_3), 5.49 (s, 2H, CH_2), 7.39–7.45 (m, 3H, ArH), 7.59–7.67 (m, 4H, ArH), 8.19 (d, *J* = 8.0 Hz, 2H, ArH). HRMS [Found: *m/z* 359.1055 (M$^+$); Calcd for $C_{21}H_{14}FN_3O_2$: M 359.1070].

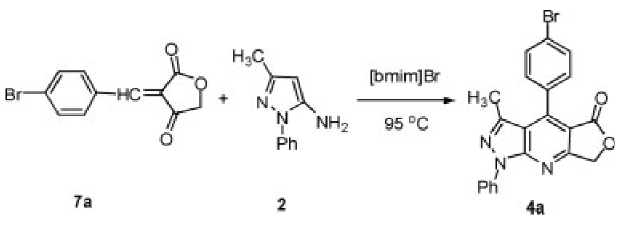
4-(4-Chlorophenyl)-3-methyl-1-phenyl-1H-furo[3,4-e]pyrazolo[3,4-b]pyridine-5(7H)-one (4d). This compound was obtained as solid with mp 223–225°C; IR (potassium bromide): 3062, 2934, 1763, 1598, 1580, 1562, 1505, 1488, 1459, 1442, 1421, 1386, 1358, 1313, 1269, 1211, 1144, 1124, 1089, 1071, 1048, 1027, 1015, 915, 848, 825, 799, 760, 723 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.12 (s, 3H, CH_3), 5.50 (s, 2H, CH_2), 7.39–7.43 (m, 1H, ArH), 7.59–7.67 (m, 6H, ArH), 8.19 (d, *J* = 8.0 Hz, 2H, ArH); ^{13}C NMR (DMSO-d_6): δ 15.62, 69.66, 111.48, 116.50, 121.74, 127.26, 128.64, 129.98, 130.74, 131.92, 135.14, 138.84, 145.41, 146.51, 153.11, 168.02, 168.33. HRMS [Found: *m/z* 375.0768 (M$^+$); Calcd for $C_{21}H_{14}{}^{35}Cl\ N_3O_2$: M 375.0775].

3-Methyl-4-(4-nitrophenyl)-1-phenyl-1H-furo[3,4-e]pyrazolo[3,4-b]pyridine-5(7H)-one (4e). This compound was obtained as solid with mp 288–289°C; IR (potassium bromide): 3068, 2929, 1763, 1580, 1517, 1439, 1388, 1350, 1314, 1293, 1213, 1142, 1108, 1073, 1050, 1022, 838, 802, 754, 709, 692 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.11 (s, 3H, CH_3), 5.54 (s, 2H, CH_2), 7.43 (t, *J* = 7.6 Hz, 1H, ArH), 7.63 (t, *J* = 7.6 Hz, 2H, ArH), 7.90 (d, *J* = 8.4 Hz, 2H, ArH), 8.20 (d, *J* = 8.0 Hz, 2H, ArH), 8.44 (d, *J* = 8.4 Hz, 2H, ArH). HRMS [Found: *m/z* 386.1012 (M$^+$); Calcd for $C_{21}H_{14}N_4O_4$: M 386.1015].

4-(4-Hydroxyphenyl)-3-methyl-1-phenyl-1H-furo[3,4-e] pyrazolo[3,4-b]pyridine-5(7H)-one (4f). This compound was obtained as solid with mp >300°C; IR (potassium bromide): 3312, 1744, 1614, 1591, 1573, 1511, 1490, 1438, 1388, 1360, 1317, 1276, 1214, 1173, 1146, 1082, 1051, 1026, 854, 826, 802, 758 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.17 (s, 3H, CH_3), 5.45 (s, 2H, CH_2), 6.93 (d, *J* = 8.0 Hz, 2H, ArH), 7.40 (d, *J* = 8.0 Hz, 3H, ArH), 7.60 (t, *J* = 7.6 Hz, 2H, ArH), 8.19 (d, *J* = 7.6 Hz, 2H, ArH), 9.97 (s, 1H, OH); ^{13}C NMR (DMSO-d_6): δ 15.88, 69.34, 111.13, 115.27, 116.72, 121.66, 121.96, 127.08, 129.90, 132.04, 138.96, 145.61, 148.82, 153.18, 159.48, 168.14, 168.45. HRMS [Found: *m/z* 357.1092 (M$^+$); Calcd for $C_{21}H_{15}N_3O_3$: M 357.1113].

4-(4-Dimethylaminophenyl)-3-methyl-1-phenyl-1H-furo [3,4-e] pyrazolo[3,4-b]pyridine-5(7H)-one(4g). This compound was obtained as solid with mp 246–248°C; IR (potassium bromide): 2926, 1760, 1615, 1593, 1571, 1531, 1515, 1457, 1441, 1390, 1362, 1311, 1294, 1272, 1213, 1191, 1139, 1070, 1044, 1029,

Scheme 4



943, 850, 813, 796, 759 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.23 (s, 3H, CH$_3$), 3.04 (s, 6H, (CH$_3$)$_2$N), 5.43 (s, 2H, CH$_2$), 6.86 (d, J = 8.4 Hz, 2H, ArH), 7.37–7.45 (m, 3H, ArH), 7.60 (t, J = 7.6 Hz, 2H, ArH), 8.20 (d, J = 8.0 Hz, 2H, ArH); ^{13}C NMR (DMSO-d_6): δ 16.31, 69.25, 110.81, 111.29, 116.57, 118.08, 121.78, 121.82, 127.12, 129.94, 132.13, 132.18, 139.05, 145.72, 149.45, 151.78, 153.34, 168.39, 168.65. HRMS [Found: *m/z* 384.1585 (M$^+$); Calcd for $C_{23}H_{20}N_4O_2$: M 384.15 86].

3-Methyl-4-(3-nitrophenyl)-1-phenyl-1H-furo[3,4-e]pyrazolo[3,4-b]pyridine-5(7H)-one (4h). This compound was obtained as solid with mp 259–261°C; IR (potassium bromide): 3069, 2934, 1773, 1589, 1535, 1516, 1491, 1460, 1439, 1387, 1345, 1315, 1212, 1156, 1125, 1073, 1048, 1029, 875, 800, 755, 738, 713, 702, 692 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.12 (s, 3H, CH$_3$), 5.53 (s, 2H, CH$_2$), 7.42 (t, J = 7.6 Hz, 1H, ArH), 7.62 (t, J = 7.6 Hz, 2H, ArH), 7.90 (t, J = 8.0 Hz, 1H, ArH), 8.10 (d, J = 7.6 Hz, 1H, ArH), 8.20 (d, J = 8.0 Hz, 2H, ArH), 8.47 (d, J = 8.8 Hz, 1H, ArH), 8.51 (s, 1H, ArH); ^{13}C NMR (DMSO-d_6): δ 14.34, 68.57, 108.77, 110.48, 115.22, 120.58, 123.76, 126.07, 128.73, 132.23, 135.37, 135.39, 137.58, 143.49, 143.99, 146.68, 151.99, 166.68, 167.10. HRMS [Found: *m/z* 386.1031 (M$^+$); Calcd for $C_{21}H_{14}N_4O_4$: M 386.1015].

4-(2,4-Dichlorophenyl)-3-methyl-1-phenyl-1H-furo[3,4-e]pyrazolo [3,4-b]pyridine-5(7H)-one (4i). This compound was obtained as solid with mp 206–208°C; IR (potassium bromide): 3064, 2930, 1762, 1585, 1506, 1490, 1475, 1441, 1470, 1389, 1376, 1361, 1316, 1274, 1210, 1180, 1150, 1127, 1100, 1078, 1050, 1024, 893, 853, 821, 801, 757, 689 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.10 (s, 3H, CH$_3$), 5.54 (d, J = 16.0 Hz, 1H, CH), 5.61 (d, J = 16.0 Hz, 1H, CH), 7.43 (t, J = 7.6 Hz, 1H, ArH), 7.60–7.65 (m, 3H, ArH), 7.68 (d, J = 8.4 Hz, 1H, ArH), 7.95 (s, 1H, ArH), 8.19 (d, J = 8.4 Hz, 2H, ArH). HRMS [Found: *m/z* 409.0385 (M$^+$); Calcd for $C_{21}H_{13}{}^{35}Cl_2N_3O_2$: M 409.0385].

4-(3,4-Dimethylphenyl)-3-methyl-1-phenyl-1H-furo[3,4-e]pyrazolo[3,4-b]pyridine-5(7H)-one (4j). This compound was obtained as solid with mp 231–233°C; IR (potassium bromide): 2926, 2861, 1768, 1577, 1513, 1458, 1434, 1386, 1355, 1268, 1228, 1210, 1182, 1128, 1070, 1042, 1027, 852, 818, 808, 798, 758, 719 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.11 (s, 3H, CH$_3$), 2.33 (s, 3H, CH$_3$), 2.36 (s, 3H, CH$_3$), 5.48 (s, 2H, CH$_2$), 7.28 (d, J = 8.0 Hz, 1H, ArH), 7.32–7.35 (m, 2H, ArH), 7.41 (t, J = 7.6 Hz, 1H, ArH), 7.61 (t, J = 7.6 Hz, 2H, ArH), 8.20 (d, J = 8.0 Hz, 2H, ArH); ^{13}C NMR (DMSO-d_6): δ 15.62, 19.98, 69.47, 111.34, 116.68, 121.82, 127.18, 127.47, 129.31, 129.56, 129.95, 130.93, 136.33, 138.43, 138.97, 145.61, 148.48, 153.17, 168.11, 168.31. HRMS [Found: *m/z* 369.1480 (M$^+$); Calcd for $C_{23}H_{19}N_3\ O_2$: M 369.1477].

3-Methyl-4-(3,4-dimethoxyphenyl)-1-phenyl-1H-furo[3,4-e]pyrazolo[3,4-b]pyridine-5(7H)-one (4k). This compound was obtained as solid with mp 203–205°C; IR (potassium bromide): 3059, 3018, 2930, 1768, 1589, 1570, 1512, 1460, 1438, 1412, 1355, 1325, 1309, 1259, 1234, 1203, 1174, 1130, 1070, 1045, 1027, 843, 795, 761, 701 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.19 (s, 3H, CH$_3$), 3.79 (s, 3H, CH$_3$O), 3.88 (s, 3H, CH$_3$O), 5.47 (s, 2H, CH$_2$), 7.10–7.17 (m, 2H, ArH), 7.20 (s, 1H, ArH), 7.41 (t, J = 7.6 Hz, 1H, ArH), 7.61 (t, J = 7.6 Hz, 2H, ArH), 8.19 (d, J = 8.0 Hz, 2H, ArH); ^{13}C NMR (DMSO-d_6): δ 20.44, 60.97, 74.11, 116.36, 119.99, 121.51, 126.54, 127.86, 128.63, 131.88, 134.65, 134.73, 143.71, 150.39, 153.01, 153.34, 155.29, 157.96, 172.81, 173.03. HRMS [Found: *m/z* 401.1386 (M$^+$); Calcd for $C_{23}H_{19}N_3O_4$: M 401.1376].

4-(2-Chloro-5-nitrophenyl)-3-methyl-1-phenyl-1H-furo[3,4-e]pyrazolo[3,4-b]pyridine-5(7H)-one (4l). This compound was obtained as solid with mp 253–255°C; IR (potassium bromide): 3081, 1771, 1587, 1568, 1527, 1507, 1459, 1437, 1422, 1370, 1338, 1325, 1214, 1152, 1124, 1108, 1082, 1054, 1025, 947, 867, 853, 820, 757, 709 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.13 (s, 3H, CH$_3$), 5.54 (d, J = 16.0 Hz, 1H, CH), 5.64 (d, J = 16.0 Hz, 1H, CH), 7.44 (t, J = 7.6 Hz, 1H, ArH), 7.64 (t, J = 7.6 Hz, 2H, ArH), 7.96 (s, 1H, ArH), 8.01 (d, J = 8.8 Hz, 1H, ArH), 8.21 (d, J = 8.0 Hz, 2H, ArH), 8.45 (d, J = 8.8 Hz, 1H, ArH). HRMS [Found: *m/z* 420.0621 (M$^+$); Calcd for $C_{21}H_{13}{}^{35}ClN_4O_4$: M 420.0625].

3-Methyl-4-(3,4-methylinenedioxophenyl)-1-phenyl-1H-furo[3,4-e]pyrazolo[3,4-b]pyridine-5(7H)-one (4m). This compound was obtained as solid with mp 248–249°C; IR (potassium bromide): 3070, 2903, 1764, 1577, 1508, 1490, 1445, 1387, 1364, 1341, 1313, 1240, 1207, 1166, 1119, 1071, 1051, 1031, 924, 796, 758 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.19 (s, 3H, CH$_3$), 5.47 (s, 2H, CH$_2$), 6.18 (s, 2H, OCH$_2$O), 7.04 (d, J = 8.0 Hz, 1H, ArH), 7.12 (d, J = 8.0 Hz, 1H, ArH), 7.18 (s, 1H, ArH), 7.40 (t, J = 7.6 Hz, 1H, ArH), 7.61 (t, J = 7.6 Hz, 2H, ArH), 8.19 (d, J = 8.0 Hz, 2H, ArH); ^{13}C NMR (DMSO-d_6): δ 15.67, 69.45, 102.22, 108.51, 110.70, 111.51, 116.80, 121.71, 124.38, 125.22, 127.15, 129.92, 138.93, 145.56, 147.48, 147.82, 149.03, 153.19, 168.02, 168.27. HRMS [Found: *m/z* 385.1065 (M$^+$); Calcd for $C_{22}H_{15}N_3O_4$: M 385.1063].

3-Methyl-4-(thiophen-2-yl)-1-phenyl-1H-furo[3,4-e]pyrazolo[3,4-b]pyridine-5(7H)-one (4n). This compound was obtained as solid with mp 248–250°C; IR (potassium bromide): 3098, 1761, 1579, 1541, 1515, 1490, 1438, 1384, 1360, 1340, 1311, 1266, 1225, 1201, 1181, 1131, 1116, 1076, 1050, 1028, 852, 817, 794, 762, 732, 716, 720 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.25 (s, 3H, CH$_3$), 5.48 (s, 2H, CH$_2$), 7.32 (t, J = 8.0 Hz, 1H, ArH), 7.40–7.46 (m, 2H, ArH), 7.61 (t, J = 8.0 Hz, 2H, ArH), 7.97 (d, J = 5.2 Hz, 1H, ArH), 8.18 (d, J = 8.0 Hz, 2H, ArH); ^{13}C NMR (DMSO-d_6): δ 19.95, 74.20, 117.01, 122.03, 126.62, 132.01, 132.56, 134.64, 135.02, 135.44, 136.22, 143.56, 145.58, 150.10, 157.81, 172.63, 172.70. HRMS [Found: *m/z* 347.0745 (M$^+$); Calcd for $C_{19}H_{13}N_3O_2S$: M 347.0728].

3-Methyl-4-(pyridin-3-yl)-1-phenyl-1H-furo[3,4-e]pyrazolo[3,4-b]pyridine-5(7H)-one (4o). This compound was obtained as solid with mp 223–225°C; IR (potassium bromide): 3032, 2971, 2947, 1753, 1593, 1579, 1510, 1487, 1440, 1421, 1389, 1357, 1336, 1312, 1293, 1269, 1213, 1194, 1146, 1125, 1071, 1050, 1026, 908, 848, 813, 795, 760, 717, 701 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.14 (s, 3H, CH$_3$), 5.53 (s, 2H, CH$_2$), 7.42 (t, J = 7.6 Hz, 1H, ArH), 7.60–7.65 (m, 3H, ArH), 8.08 (dd, J_1 = 1.5 Hz, J_2 = 7.6 Hz, 1H, ArH), 8.20 (d, J = 8.0 Hz, 2H, ArH), 8.79 (d, J = 2.0 Hz, 2H, ArH); ^{13}C NMR (DMSO-d_6): δ 20.39, 74.46, 116.48, 121.39, 126.52, 128.22, 132.00, 132.72, 134.66, 142.47, 155.85, 157.87, 172.67, 173.11. HRMS [Found: *m/z* 342.1136 (M$^+$); Calcd for $C_{20}H_{14}N_4O_2$: M 342.1117].

3-Methyl-4-(pyridin-4-yl)-1-phenyl-1H-furo[3,4-e]pyrazolo[3,4-b]pyridine-5(7H)-one (4p). This compound was obtained as solid with mp 223–225°C; IR (potassium bromide): 3032, 2976, 2939, 1769, 1583, 1543, 1510, 1491, 1438, 1419, 1388, 1361, 1340, 1314, 1273, 1212, 1178, 1148, 1126, 1072, 1051, 1029, 989, 812, 797, 759 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.11 (s, 3H, CH_3), 5.53 (s, 2H, CH_2), 7.42 (t, J = 7.6 Hz, 1H, ArH), 7.60–7.70 (m, 4H, ArH), 8.18 (d, J = 8.0 Hz, 2H, ArH), 8.80 (d, J = 5.2 Hz, 2H, ArH). HRMS [Found: m/z 342.1099 (M$^+$); Calcd for $C_{20}H_{14}N_4O_2$: M 342.1117].

3-Methyl-1-phenyl-4-p-tolylindeno[2,1-e]pyrazolo[3,4-b]pyridine-5(1H)-one (6a). This compound was obtained as solid with mp 219–221°C (Lit. [32] 217–218°C); IR (potassium bromide): 3028, 2916, 1712, 1592, 1572, 1555, 1498, 1461, 1437, 1383, 1326, 1310, 1278, 1246, 1198, 1178, 1159, 1119, 1083, 1022, 995, 869, 767, 726, 698 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.02 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 7.36 (d, J = 7.2 Hz, 2H, ArH), 7.41–7.47 (m, 3H, ArH), 7.60–7.67 (m, 4H, ArH), 7.77 (t, J = 7.2 Hz, 1H, ArH), 8.01 (d, J = 7.6 Hz, 1H, ArH), 8.29 (d, J = 7.6 Hz, 2H, ArH). HRMS [Found: m/z 401.1533 (M$^+$); Calcd for $C_{27}H_{19}N_3O$: M 401.1528].

4-(4-Methoxyphenyl)-3-methyl-1-phenylindeno[2,1-e]pyrazolo[3,4-b]pyridine-5(1H)-one (6b). This compound was obtained as solid with mp 222–224°C (Lit. [32] 224–225°C); IR (potassium bromide): 2995, 2932, 2834, 1710, 1608, 1560, 1511, 1463, 1439, 1384, 1327, 1311, 1292, 1246, 1201, 1178, 1152, 1122, 1035, 996, 952, 834, 787, 770, 757, 727, 690 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.01 (s, 3H, CH_3), 3.88 (s, 3H, CH_3O), 7.12 (d, J = 7.6 Hz, 2H, ArH), 7.42 (t, J = 7.6 Hz, 1H, ArH), 7.51 (d, J = 7.6 Hz, 2H, ArH), 7.57–7.65 (m, 4H, ArH), 7.74 (t, J = 7.6 Hz, 1H, ArH), 7.96 (d, J = 7.2 Hz, 1H, ArH), 8.30 (d, J = 8.4 Hz, 2H, ArH). HRMS [Found: m/z 417.1474 (M$^+$); Calcd for $C_{27}H_{19}N_3O_2$: M 417.1477].

4-(4-Fluorophenyl)-3-methyl-1-phenylindeno[2,1-e]pyrazolo[3,4-b]pyridine-5(1H)-one (6c). This compound was obtained as solid with mp 256–258°C (Lit. [32] 255–257°C); IR (potassium bromide): 3068, 3019, 1715, 1605, 1596, 1561, 1509, 1462, 1437, 1383, 1324, 1209, 1248, 1226, 1201, 1160, 1121, 1096, 1085, 1015, 995, 911, 872, 839, 803, 763, 730, 697 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.99 (s, 3H, CH_3), 7.37–7.44 (m, 3H, ArH), 7.57–7.64 (m, 6H, ArH), 7.74 (t, J = 7.6 Hz, 1H, ArH), 7.98 (d, J = 7.6 Hz, 1H, ArH), 8.28 (d, J = 8.0 Hz, 2H, ArH). HRMS [Found: m/z 405.1276 (M$^+$); Calcd for $C_{26}H_{16}FN_3O$: M 405.1277].

4-(4-Chlorophenyl)-3-methyl-1-phenylindeno[2,1-e]pyrazolo[3,4-b]pyridine-5(1H)-one (6d). This compound was obtained as solid with mp 265–267°C (Lit. [32] 269–270°C); IR (potassium bromide): 3054, 2924, 1710, 1597, 1572, 1558, 1503, 1461, 1438, 1383, 1325, 1311, 1294, 1270, 1246, 1179, 1153, 1120, 1084, 1015, 996, 953, 867, 835, 767, 728 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.01 (s, 3H, CH_3), 7.42 (t, J = 7.2 Hz, 1H, ArH), 7.56–7.65 (m, 8H, ArH), 7.75 (t, J = 7.2 Hz, 1H, ArH), 7.98 (d, J = 7.2 Hz, 1H, ArH), 8.28 (d, J = 8.0 Hz, 2H, ArH). HRMS [Found: m/z 421.0976 (M$^+$); Calcd for $C_{26}H_{16}{}^{35}ClN_3O$: M 421.0982].

4-(4-Bromophenyl)-3-methyl-1-phenylindeno[2,1-e]pyrazolo[3,4-b]pyridine-5(1H)-one (6e). This compound was obtained as solid with mp 272–274°C (Lit. [32] 274–276°C); IR (potassium bromide): 1712, 1595, 1570, 1503, 1460, 1438, 1383, 1326, 1311, 1293, 1270, 1246, 1201, 1180, 1153, 1120, 1083, 1012, 767, 728 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.99 (s, 3H, CH_3), 7.42 (t, J = 7.6 Hz, 1H, ArH), 7.53 (d, J = 8.0 Hz, 2H, ArH), 7.56–7.64 (m, 4H, ArH), 7.73–7.77 (m, 3H, ArH), 7.98 (d, J = 7.6 Hz, 1H, ArH), 8.27 (d, J = 8.0 Hz, 2H, ArH). HRMS [Found: m/z 465.0479 (M$^+$); Calcd for $C_{26}H_{16}{}^{79}BrN_3O$: M 465.0477].

3-Methyl-4-(4-nitrophenyl)-1-phenylindeno[2,1-e]pyrazolo[3,4-b]pyridine-5(1H)-one (6f). This compound was obtained as solid with mp >300°C (Lit. [26] 318–319°C); IR (potassium bromide): 3065, 1709, 1592, 1566, 1510, 1503, 1462, 1439, 1384, 1347, 1325, 1311, 1290, 1246, 1201, 1180, 1154, 1121, 1084, 1016, 997, 949, 865, 838, 768, 752, 729, 719, 703, 691 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.99 (s, 3H, CH_3), 7.44 (t, J = 7.2 Hz, 1H, ArH), 7.61–7.66 (m, 4H, ArH), 7.78 (t, J = 7.6 Hz, 1H, ArH), 7.90 (d, J = 8.4 Hz, 2H, ArH), 8.03 (d, J = 7.2 Hz, 1H, ArH), 8.28 (d, J = 8.0 Hz, 2H, ArH), 8.42 (d, J = 8.4 Hz, 2H, ArH). HRMS [Found: m/z 432.1220 (M$^+$); Calcd for $C_{26}H_{16}N_4O_3$: M 432.1222].

4-(4-Hydroxyphenyl)-3-methyl-1-phenylindeno[2,1-e]pyrazolo[3,4-b]pyridine-5(1H)-one (6g). This compound was obtained as solid with mp >300°C (Lit. [26] 316–318°C); IR (potassium bromide): 3233, 3067, 3031, 1695, 1614, 1593, 1557, 1510, 1489, 1456, 1436, 1418, 1383, 1332, 1323, 1309, 1293, 1275, 1247, 1232, 1201, 1176, 1157, 1121, 1083, 768, 756, 730 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.04 (s, 3H, CH_3), 6.91 (d, J = 8.4 Hz, 2H, ArH), 7.35–7.41 (m, 3H, ArH), 7.53–7.62 (m, 4H, ArH), 7.72 (t, J = 7.6 Hz, 1H, ArH), 7.94 (d, J = 8.0 Hz, 1H, ArH), 8.27 (d, J = 8.0 Hz, 2H, ArH), 9.90 (s, 1H, OH). HRMS [Found: m/z 403.1317 (M$^+$); Calcd for $C_{26}H_{17}N_3O_2$: M 403.1321].

3-Methyl-4-(3-nitrophenyl)-1-phenylindeno[2,1-e]pyrazolo[3,4-b]pyridine-5(1H)-one (6h). This compound was obtained as solid with mp 269–271°C; IR (potassium bromide): 3086, 1710, 1605, 1593, 1564, 1525, 1503, 1437, 1417, 1384, 1349, 1326, 1311, 1285, 1247, 1204, 1188, 1156, 1123, 1083, 909, 770, 760, 741, 728, 706, 690 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.99 (s, 3H, CH_3), 7.43 (t, J = 7.2 Hz, 1H, ArH), 7.60–7.65 (m, 4H, ArH), 7.77 (t, J = 7.2 Hz, 1H, ArH), 7.88 (t, J = 8.0 Hz, 1H, ArH), 8.02 (d, J = 7.2 Hz, 1H, ArH), 8.08 (d, J = 7.6 Hz, 1H, ArH), 8.29 (d, J = 8.0 Hz, 2H, ArH), 8.46 (d, J = 8.4 Hz, 1H, ArH), 8.51 (s, 1H, ArH). HRMS [Found: m/z 432.1237 (M$^+$); Calcd for $C_{26}H_{16}N_4O_3$: M 432.1222].

4-(3-Chlorophenyl)-3-methyl-1-phenylindeno[2,1-e]pyrazolo[3,4-b]pyridine-5(1H)-one (6i). This compound was obtained as solid with mp 243–245°C; IR (potassium bromide): 3065, 1715, 1593, 1561, 1503, 1474, 1461, 1436, 1382, 1325, 1309, 1293, 1276, 1245, 1203, 1180, 1153, 1119, 1024, 998, 955, 907, 889, 766, 754, 726, 702 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.01 (s, 3H, CH_3), 7.43 (t, J = 7.6 Hz, 1H, ArH), 7.52–7.67 (m, 7H, ArH), 7.70 (s, 1H, ArH), 7.77 (t, J = 7.6 Hz, 1H, ArH), 8.01 (d, J = 7.6 Hz, 1H, ArH), 8.28 (d, J = 7.6 Hz, 2H, ArH). HRMS [Found: m/z 421.0963 (M$^+$); Calcd for $C_{26}H_{16}{}^{35}ClN_3O$: M 421.0982].

4-(4-Dimethylaminophenyl)2-3-methyl-1-phenylindeno[2,1-e]pyrazolo[3,4-b]pyridine-5(1H)-one (6j). This compound was obtained as solid with mp 242–244°C (Lit. [26] 241–242°C); IR (potassium bromide): 2892, 1706, 1617, 1561, 1531, 1504, 1481, 1462, 1441, 1384, 1370, 1325, 1310, 1292, 1244, 1233, 1206, 1194, 1182, 1168, 1156, 1125, 1085, 1059, 1020, 992, 945, 815, 768, 729, 690 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.14 (s, 3H, CH_3), 3.05 (s, 6H, $(CH_3)_2N$), 6.80 (d, J = 8.4 Hz, 2H, ArH), 7.40–7.43 (m, 3H, ArH), 7.56–7.64 (m, 4H, ArH), 7.74 (t, J = 7.2 Hz, 1H, ArH), 7.97 (d, J = 7.6 Hz, 1H, ArH), 8.29 (d, J = 8.0 Hz, 2H, ArH). HRMS [Found: m/z 430.1783 (M$^+$); Calcd for $C_{28}H_{22}N_4O$: M 430.1794].

4-(2,4-Dichlorophenyl)-3-methyl-1-phenylindeno[2,1-e]pyrazolo[3,4-b]pyridine-5(1H)-one (6k). This compound was obtained as solid with mp 179–181°C (Lit. [26] 182–184°C); IR (potassium bromide): 3076, 2990, 1716, 1593, 1561, 1504, 1473, 1464, 1435, 1383, 1321, 1306, 1261, 1246, 1197, 1158, 1124, 1102, 1084, 1055, 995, 946, 872, 829, 791, 772, 760, 728 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.99 (s, 3H, CH_3), 7.43 (t, *J* = 7.6 Hz, 1H, ArH), 7.60–7.68 (m, 6H, ArH), 7.78 (t, *J* = 7.6 Hz, 1H, ArH), 7.93 (s, 1H, ArH), 8.03 (d, *J* = 7.6 Hz, 1H, ArH), 8.27 (d, *J* = 8.0 Hz, 2H, ArH). HRMS [Found: *m/z* 455.0585 (M^+); Calcd for $C_{26}H_{15}{}^{35}Cl_2N_3O$: M 455.0592].

4-(3,4-Dimethylphenyl)-3-methyl-1-phenylindeno[2,1-e]pyrazolo[3,4-b]pyridine-5(1H)-one (6l). This compound was obtained as solid with mp 200–202°C; IR (potassium bromide): 3046, 2969, 2921, 1709, 1591, 1558, 1506, 1456, 1437, 1378, 1326, 1311, 1291, 1280, 1245, 1207, 1187, 1154, 1123, 1084, 1023, 807, 769, 758, 726, 691 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.00 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 7.26 (d, *J* = 7.6 Hz, 1H, ArH), 7.30–7.32 (m, 2H, ArH), 7.42 (t, *J* = 7.6 Hz, 1H, ArH), 7.56–7.64 (m, 4H, ArH), 7.74 (t, *J* = 7.2 Hz, 1H, ArH), 7.98 (d, *J* = 7.6 Hz, 1H, ArH), 8.28 (d, *J* = 8.0 Hz, 2H, ArH). HRMS [Found: *m/z* 415.1686 (M^+); Calcd for $C_{28}H_{21}N_3O$: M 415.1685].

4-(3,4-Dimethoxyphenyl)-3-methyl-1-phenylindeno[2,1-e]pyrazolo[3,4-b]pyridine-5(1H)-one (6m). This compound was obtained as solid with mp 224–226°C (Lit. [26] 230–231°C); IR (potassium bromide): 3054, 2959, 2938, 1703, 1606, 1550, 1510, 1488, 1463, 1444, 1381, 1355, 1328, 1309, 1287, 1275, 1262, 1247, 1232, 1195, 1168, 1158, 1138, 1123, 1086, 1022, 801, 763, 729 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.09 (s, 3H, CH_3), 3.79 (s, 3H, CH_3O), 3.88 (s, 3H, CH_3O), 7.12 (s, 1H, ArH), 7.21 (s, 1H, ArH), 7.42 (t, *J* = 7.2 Hz, 1H, ArH), 7.58–7.65 (m, 4H, ArH), 7.76 (t, *J* = 7.6 Hz, 1H, ArH), 8.00 (d, *J* = 7.2 Hz, 1H, ArH), 8.29 (d, *J* = 8.4 Hz, 2H, ArH). HRMS [Found: *m/z* 447.1599 (M^+); Calcd for $C_{28}H_{21}N_3O_3$: M 447.1583].

4-(3,4-Methylienedioxyphenyl)-3-methyl-1-phenylindeno[2,1-e]pyrazolo[3,4-b]pyridine-5(1H)-one (6n). This compound was obtained as solid with mp 220–222°C (Lit. [32] 223–224°C); IR (potassium bromide): 3075, 3016, 2880, 1714, 1594, 1561, 1503, 1483, 1462, 1440, 1383, 1354, 1324, 1308, 1282, 1239, 1196, 1160, 1138, 1118, 1106, 1081, 1044, 1029, 996, 942, 918, 805, 768, 730, 701 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.04 (s, 3H, CH_3), 6.17 (s, 2H, OCH_2O), 7.01 (d, *J* = 8.0 Hz, 1H, ArH), 7.08 (d, *J* = 8.0 Hz, 1H, ArH), 7.15 (s, 1H, ArH), 7.41 (t, *J* = 7.2 Hz, 1H, ArH), 7.55–7.62 (m, 4H, ArH), 7.72 (t, *J* = 7.2 Hz, 1H, ArH), 7.93 (d, *J* = 7.6 Hz, 1H, ArH), 8.26 (d, *J* = 8.0 Hz, 2H, ArH). HRMS [Found: *m/z* 431.1264 (M^+); Calcd for $C_{27}H_{17}N_3O_3$: M 431.1270].

4-(3,4-Dichlorophenyl)-3-methyl-1-phenylindeno[2,1-e]pyrazolo[3,4-b]pyridine-5(1H)-one (6o). This compound was obtained as solid with mp 194–196°C (Lit. [26] 192–194°C); IR (potassium bromide): 3065, 2985, 2927, 1713, 1596, 1566, 1546, 1503, 1471, 1436, 1416, 1376, 1323, 1307, 1244, 1202, 1180, 1154, 1135, 1118, 1034, 998, 953, 895, 831, 775, 766, 751, 726 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.06 (s, 3H, CH_3), 7.43 (t, *J* = 7.2 Hz, 1H, ArH), 7.60–7.66 (m, 5H, ArH), 7.77 (t, *J* = 7.2 Hz, 1H, ArH), 7.85 (d, *J* = 8.4 Hz, 1H, ArH), 7.95 (s, 1H, ArH), 8.01 (d, *J* = 7.2 Hz, 1H, ArH), 8.28 (d, *J* = 8.0 Hz, 2H, ArH). HRMS [Found: *m/z* 455.0586 (M^+); Calcd for $C_{26}H_{15}{}^{35}Cl_2N_3O$: M 455.0592].

3-Methyl-4-(thiophen-2-yl)-1-phenylindeno[2,1-e]pyrazolo[3,4-b]pyridine-5(1H)-one (6p). This compound was obtained as solid with mp 231–233°C (Lit. [26] 232–233°C); IR (potassium bromide): 3076, 2993, 1705, 1593, 1562, 1510, 1499, 1460, 1434, 1381, 1336, 1320, 1306, 1291, 1247, 1220, 1192, 1170, 1155, 1117, 1082, 1030, 991, 860, 806, 770, 752, 720 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.12 (s, 3H, CH_3), 7.30 (t, *J* = 8.0 Hz, 1H, ArH), 7.41–7.45 (m, 2H, ArH), 7.60–7.67 (m, 4H, ArH), 7.76 (t, *J* = 7.6 Hz, 1H, ArH), 7.92 (d, *J* = 5.2 Hz, 1H, ArH), 8.00 (d, *J* = 7.2 Hz, 1H, ArH), 8.27 (d, *J* = 8.0 Hz, 2H, ArH). HRMS [Found: *m/z* 393.0917 (M^+); Calcd for $C_{24}H_{15}N_3OS$: M 393.09 36].

3-Methyl-4-(pyridin-4-yl)-1-phenylindeno[2,1-e]pyrazolo-[3,4-b]pyridine-5(1H)-one (6q). This compound was obtained as solid with mp >300°C; IR (potassium bromide): 3021, 2986, 1707, 1590, 1568, 1541, 1504, 1462, 1437, 1412, 1385, 1327, 1312, 1249, 1203, 1181, 1157, 1123, 1085, 1068, 996, 950, 831, 772, 763, 732, 691 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.02 (s, 3H, CH_3), 7.44 (t, *J* = 7.2 Hz, 1H, ArH), 7.61–7.67 (m, 6H, ArH), 7.79 (t, *J* = 7.2 Hz, 1H, ArH), 8.04 (d, *J* = 8.0 Hz, 1H, ArH), 8.28 (d, *J* = 8.0 Hz, 2H, ArH), 8.79 (d, *J* = 8.8 Hz, 2H, ArH). HRMS [Found: *m/z* 388.1326 (M^+); Calcd for $C_{25}H_{16}N_4O$: M 388.1324].

The preparation of 4a from 7a. 3-(4-Bromobenzylidene)-furan-2,4(3*H*,5*H*)-dione **7a** (2 mmol) and 5-amino-3-methyl-1-phenylpyrazole **2** (2 mmol) were added to a 10 mL round flask containing 2 mL [bmim]Br. The mixture was then stirred at 95°C for 2 h. After completion of the reaction, the reaction mixture was added with 5 mL water. The precipitate was collected by suction and purified by recrystallization from ethanol to give **4a** in 96% yield.

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[34] The single-crystal growth was carried out in EtOH solutions at r.t. X-ray crystallographic analysis was performed with a Smart-1000 CCD diffractometer (graphite monochromator, MoKα radiation, $\lambda = 0.71073$ Å). Crystal data for 4l: Empirical formula $C_{21}H_{13}ClN_4O_4$, yellow, crystal dimension $0.57 \times 0.52 \times 0.34$ mm^3, monoclinic, space group $P2_1/c$, $a = 9.923(4)$ Å, $b = 22.070(8)$ Å, $c = 9.319(3)$ Å, $\alpha = 90°$, $\beta = 112.894(3)°$, $\gamma = 90°$. $V = 1880.1(12)$ Å^3, $M_r = 419.81$, $Z = 4$, $D_c = 1.483$ Mg/m^3, μ(MoKα) $= 0.240$ mm^{-1}, $F(000) = 864$, $S = 1.054$, $R_1 = 0.0605$, $wR_2 = 0.1478$.

Synthesis, Structure, and Some Chemical Properties of Diferrocenyl-1,2,3-triazines

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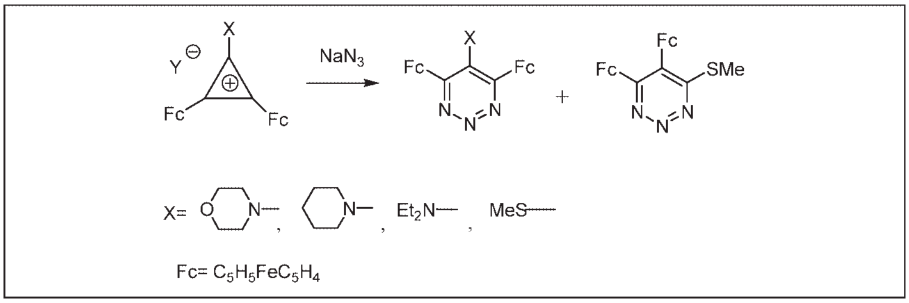

The reactions of 1-amino-2,3-diferrocenylcyclopropenylium tetrafluoroborate (**5a–c**) or 2,3-diferrocenyl-1-methylthiocyclopropenylium iodide with sodium azide afford 5-amino-4,6-diferrocenyl-1,2,3-triazines (**7a–c**) or 5-methylthio-4,6-diferrocenyl- and 4-methylthio-5,6-diferrocenyl-1,2,3-triazines (**8a** and **8b**), respectively. Their structures were established using spectroscopic methods and that of compound **8a** was confirmed using X-ray diffraction analysis. Triazines **5a–c** react with alkyl iodides to yield N(2)- and N-alkyl-C(5)-derivatives. Their alkaline hydrolysis results in 2-methyl-4,6-diferrocenyl-2,5-dihydro-1,2,3-triazin-5-one (**16**) and 4,6-diferrocenyl-5-hydroxy-1,2,3-triazine (**17**). J.

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INTRODUCTION

The study of 1,2,3-triazines has been on-going at least since the early 1970s [1–6]. It is significant that the chemistry of this heterocyclic system is relatively underdeveloped. 1,2,3-Triazines are of particular interest as potential azete precursors [3,7–10]. The first thermodynamically stable trisubstituted azetes **1a** and **1b** with electron-withdrawing groups have been prepared by pyrolysis and photolysis of the corresponding 4,5,6-trisubstituted 1,2,3-triazines [3,9–11] (Scheme 1).

The ability of electron-density-deficient 1,2,3-triazine systems to interact with nucleophilic reagents, such as the Grignard reagents, electron-rich alkenes, and dienes, is also of interest [12–15]. Thus, 4,6-disubstituted 1,2,3-triazine **2a** undergoes nucleophilic attack at the $N_{(2)}$ and $C_{(5)}$ atoms of the heterocycle to yield 2,5-dihydro-1,2,3-triazines **3a** and **4a**, whereas 4,5,6-trisubstituted 1,2,3-triazine **2b** affords adducts **3b,c** exclusively upon nucleophilic attack at $N_{(2)}$ (Scheme 2).

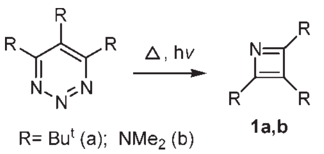
In addition to these reactions of 1,2,3-triazines, pyrolysis and photolysis resulting in substituted alkynes and carbonitriles of mononitrogenous heterocycles are documented [2,4,9]. As bases, they form quaternary salts upon alkylation with alkyl halides at $N_{(2)}$ [16].

On the whole, compounds of the 1,2,3-triazine series are little studied in both the synthetic and practical aspects.

Ferrocenyl-substituted 1,2,3-triazines have not hitherto been described. The interest in these compounds may stem from the peculiarities of their chemical behavior due to the mutual effects of the ferrocene system and the heterocyclic fragment [17]. These effects may result in the emergence of diverse valuable properties, such as biological activity, dyeing ability, possible use as propellant additives or light-sensitive materials, and redox switching receptors in supramolecular chemistry, which has previously been observed for a number of heterylferrocenes [17].

In continuation of our studies in the field of diferrocenyl-substituted cyclopropenylium cations, we describe here the use of the latter for the synthesis of 5-amino- and 5-methylthio-4,6-diferrocenyl-1,2,3-

Scheme 1



triazines **7a–c, 8a,b**, and present first data on their reactivity.

RESULTS AND DISCUSSION

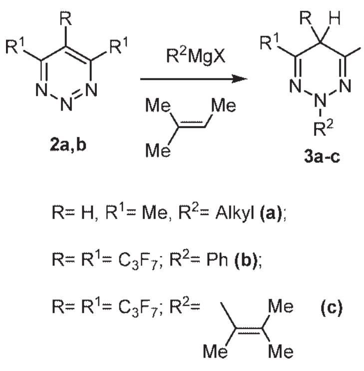
1-Dialkylamino-2,3-diferrocenylcyclopropenylium tetrafluoroborates **5a–c** and 2,3-diferrocenyl-1-methylthiocyclopropenylium iodide **6** obtained as depicted in Scheme 3 [18–20] served as the starting compounds.

Tetrafluoroborates **5a–c** react with sodium azide in dichloromethane, chloroform, acetone, or acetonitrile at ambient temperature (~30 h) or on heating under reflux to give 5-dialkylamino-4,6-diferrocenyl-1,2,3-triazines **7a–c** in ~70–85% yields (Scheme 4). They were obtained as yellow crystalline substances stable on storage in a dry state under ordinary conditions. The structures of compounds **7a–c** were established based on the data from IR spectroscopy, ^{1}H and ^{13}C NMR spectroscopy (which suggest symmetrical structures), and mass spectrometry.

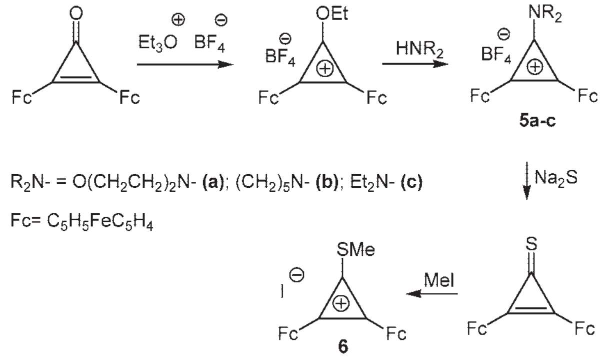
In contrast to tetrafluoroborates **5a–c**, 2,3-diferrocenyl-1-methylthiocyclopropenylium iodide **6** reacted with sodium azide under similar conditions to afford a mixture of isomeric diferrocenyl(methylthio)-1,2,3-triazines **8a** and **8b**. The ratio of the isomers was determined by ^{1}H NMR spectroscopy, this varied depending on the reaction solvent and temperature (Scheme 5, Table 1).

Separation of the isomers was carried out by chromatography on alumina and characterized by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. The data from ^{1}H and ^{13}C NMR spectroscopy suggest symmetrical structure for compound **8a** and nonsymmetrical structure for **8b**.

Scheme 2



Scheme 3



The structure of one of the reaction products, *viz.*, 4,6-diferrocenyl-5-methylthio-1,2,3-triazine **8a** was confirmed by X-ray diffraction analysis of a single crystal prepared by crystallization from chloroform. The general view of the molecule **8a** and its principal characteristics are given in Figures 1 and 2; the main geometrical parameters are given in Table 2.

In the molecule of compound **8a**, the substituted cyclopentadienyl rings of the ferrocene fragments are coplanar with, and the ferrocene sandwiches are oriented in opposite directions with respect to, the central planar six-membered ring. The C=N, N=N, Fe—C, and carbon–carbon bonds of the cyclopentadienyl rings as well as the geometrical parameters of the ferrocene sandwiches are close to the standard values [21].

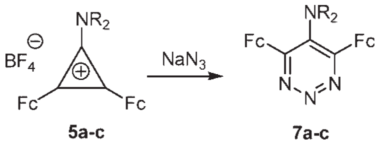
The formation of diferrocenyl-1,2,3-triazines **7a–c** and **8a,b** proceeds apparently with intermediacy of diferrocenylcyclopropenylium azides **9** as ion pairs [1,2,5,9], which undergo reversible transformation to 3-azido(diferrocenyl)cyclopropenes **10a, 10b,**or **11a,b,** representing allyl azides (Scheme 6).

It is known that allyl azides can undergo [3,3]-sigmatropic rearrangements [22] (Scheme 7).

To all appearance, cyclopropenyl azides **10a**, **10b,** and **11b** transform into 1,2,3-triazine systems according to the mechanism of the [3,3]-sigmatropic rearrangement of allyl azides *via* intermediates **12a**, **12b,** and **13b** (Scheme 8).

None of the presumable intermediates **9**, **10a**, **10b** could be detected even when the reactions were conducted at low temperatures (up to −20°C) in methanol or aqueous methanol. Triazines **7a–c** and **8a,b** were the only reaction products in all cases.

Scheme 4



Scheme 5

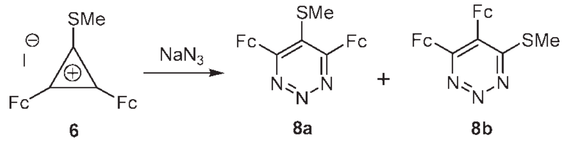


Table 1

Yields of compounds **8a** and **8b**.

			Yield (%)	
Solvent	Temp. (°C)	Time (h)	**8a**	**8b**
CH_2Cl_2	20	36	22	56
CH_2Cl_2	35	20	16	68
$CHCl_3$	20	30	18	59
$CHCl_3$	60	18	15	70
CH_3COCH_3	20	24	19	56
CH_3COCH_3	50	14	17	61
CH_3CN	20	25	18	58
CH_3CN	60	15	17	58

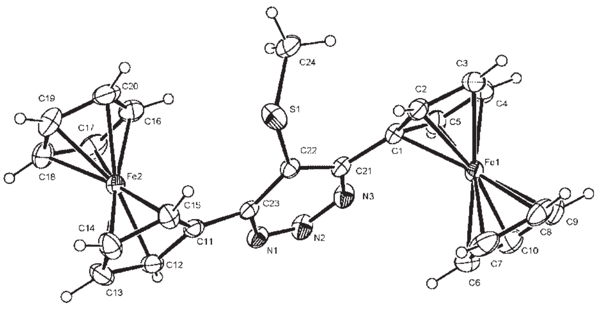


Figure 1. Crystal structure of **8a**.

Different regioselectivity of reactions of 1-amino- and 1-methylthiocyclopro-penylium salts with sodium azide is noteworthy. Compounds **5a–c** afforded symmetrical 1,2,3-triazines stereospecifically, whereas compound **6** gave a mixture of 5-methylthio- and 4-methylthio-substituted 1,2,3-triazines **8a** and **8b** in a ratio of ~1:3 or 1:4 with the nonsymmetrical isomer predominating.

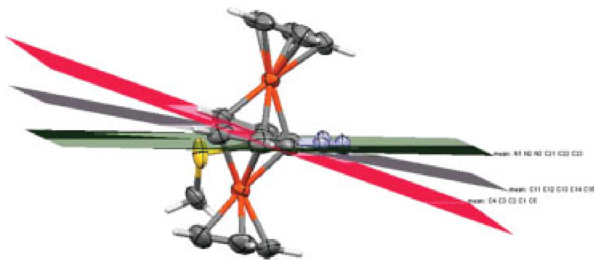


Figure 2. Relative positions of three rings. For plane: C21 C22 C23 N1 N2 N3, maximum deviation from meanplane = −0.136 Å, with respect plane: C11 C12 C13 C14 C15 and maximum deviation from meanplane = 0.218 Å, with respect plane: C1 C2 C3 C4 C5. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Table 2

Selected bond lengths and bond angles for **8a**.

Bond lengths, *r* (Å)		Bond angles, ω (°)	
N(1)-N(2)	1.319(4)	C(23)-N(1)-N(2)	121.1(2)
N(2)-N(3)	1.325(4)	N(1)-N(2)-N(3)	121.2 (2)
N(1)-C(23)	1.355(3)	N(2)-N(3)-C(21)	120.5(2)
C(23)-C(22)	1.405(4)	N(3)-C(21)-C(22)	120.3(3)
C(22)-C(21)	1.399(4)	C(21)-C(22)-C(23)	116.1(2)
C(21)-N(3)	1.349(3)	C(22)-C(23)-N(1)	119.4(3)
C(22)-S(1)	1.773(3)	C(21)-C(22)-S(1)	123.2(2)
C(24)-S(1)	1.799(4)	C(23)-C(22)-S(1)	120.7(2)
C(1)-C(21)	1.479(4)	C(22)-S(1)-C(24)	101.43(14)
C(11)-C(23)	1.470(4)	C(1)-C(21)-N(3)	112.8(2)

Reactions of triazines **7a–c** with methyl iodide resulted in mixtures of salts **14a–c** and **15a–c** in a ~5:1 ratio (^{1}H NMR data) (Scheme 9).

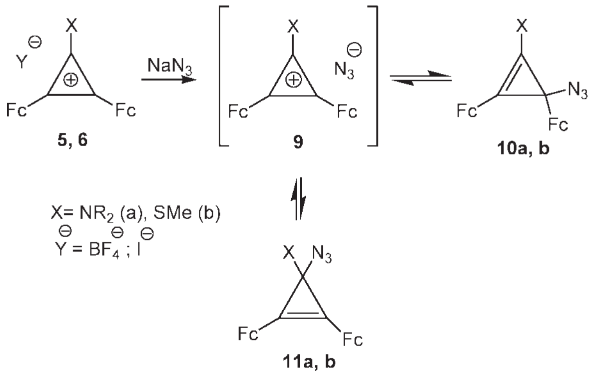
Their structures followed from the spectroscopic data (^{1}H and ^{13}C NMR) and confirmed by chemical transformations. Thus, hydrolysis of salts **14a–c** + **15a–c** with an aqueous-ethanolic alkali afforded 4,6-diferrocenyl-2-methyl-2,5-dihydro-1,2,3-triazin-5-one **16** and 4,6-diferrocenyl-5-hydroxy-1,2,3-triazine **17** separated by column chromatography on alumina (Scheme 10).

Analogously, triazine **7a** reacts with 1,3-diiodopropane to give salts **18** and **19** (Scheme 11) in a ratio of ~5:1.

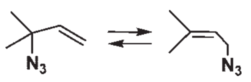
Alkaline hydrolysis converted the compound **18** to N(2)-alkylated ketones as about 2:1 mixture of two isomers (*trans*-**20a**and *cis*-**20b**), which could not be separated by chromatography (Scheme 12). However, their identification based on spectroscopic data of ^{1}H NMR spectra did not present any problems (Table 3). Hydrolysis of the compound **19** affords diketone **21** (Scheme 13).

The structures of compounds **18**, **19**, and **21** were confirmed by the data from ^{1}H and ^{13}C NMR

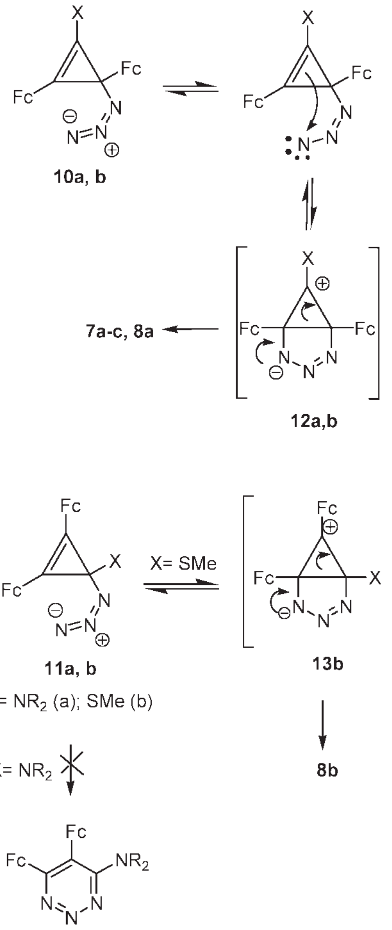
Scheme 6



Scheme 7



Scheme 8

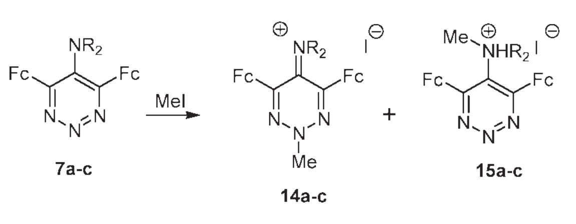


spectroscopy, mass spectrometry, and elemental analysis (Tables 3–5).

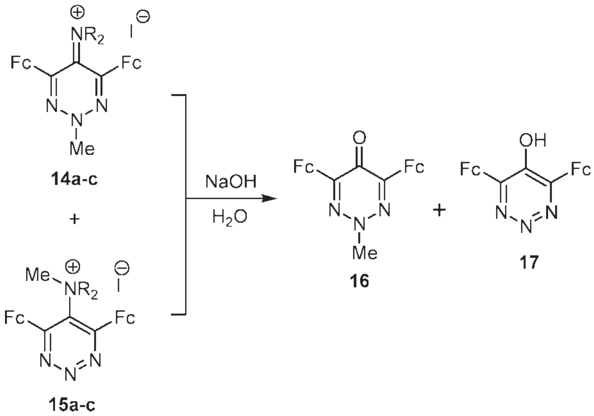
EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Unity Inova Varian spectrometer (300 and 75 MHz) for solutions in $CDCl_3$ with Me_4Si as the internal standard. Chemical shifts are given in ppm and *J* values in Hz. The NMR spectroscopic data are listed in Tables 3 and 4.

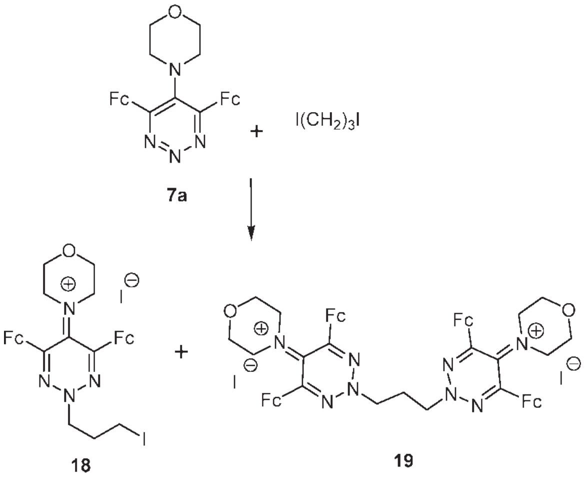
Scheme 9



Scheme 10



Scheme 11



The mass spectra were obtained on a Varian MAT CH-6 instrument (EI MS, 70 eV). An Elemental Analysis system LECO 1 CHNS-900 was used for determination of elemental analyses (Table 5).

IR spectra of compounds **7a, 8a, 8b, 14a, 16,** and **20a,b** were obtained for samples as KBr pellets on a Specord IR-75 instrument; UV spectra of compounds **8a, 8b,** and **16** were recorded on a Specord UV–vis spectrophotometer (Table 6).

Column chromatography was carried out on alumina (Brockmann activity III).

The following reagents were purchased from Aldrich: ferrocene, 98%; aluminum chloride, 99.99%; tetrachlorocyclopropene, 98%; triethyloxonium tetrafluoroborate, 1.0*M* solution in

Scheme 12

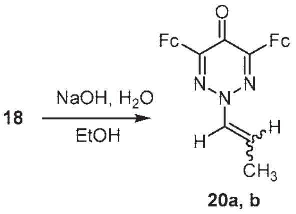


Table 3

^{1}H NMR spectral data of compounds **7a–c, 8a,b, 14a–c, 15a–c,16–19, 20a,b, 21** (δ/ppm, *J*/Hz).

No.	C_5H_5 (s)	C_5H_4 (m)	CH_2(m), CH=, OH (bs)	CH_3S (s), CH_3
7a	4.22 (10H)	4.47 (4H), 4.94 (4H)	2.83 (4H), 3.64 (4H)	–
7b	4.19 (10H)	4.43 (4H), 4.94 (4H)	1.47 (2H), 2.74 (4H), 3.29 (4H)	–
7c	4.13 (10H)	4.48 (4H), 5.06 (4H)	3.00 (q, 4H, *J* = 7.2)	0.99 (t, 6H,*J* = 7.2)
8a	4.14 (10H)	4.61 (4H), 5.41 (4H)	–	2.12 (3H)
8b	4.00(5H), 4.15 (5H)	4.33 (2H), 4.40 (2H), 4.48 (2H), 4.51 (2H)	–	2.86 (3H)
14a	4.16 (10H)	4.58 (4H), 4.99 (4H)	3.66 (4H), 3.75 (4H)	4.67 (3H)
14b	4.04 (10H)	4.48 (4H), 4.89 (4H)	1.51 (6H), 3.62 (4H)	4.48 (3H)
14c	4.07 (10H)	4.64 (4H), 5.11 (4H)	3.27 (q, 4H, *J* = 6.9)	1.12 (t, 6H, *J* = 6.9), 4.53 (3H)
15a	4.23 (10H)	4.82 (4H), 5.29 (4H)	3.71 (4H), 3.89 (4H)	4.95 (3H)
15b	4.12 (10H)	4.78 (4H), 4.87 (4H)	1.98 (2H), 2.34 (4H), 3.93 (4H)	4.67 (3H)
15c	4.17 (10H)	4.67 (4H), 5.19 (4H)	3.63 (q, 4H, *J* = 6.6)	1.47 (t, 6H, *J* = 6.6), 4.68 (3H)
16	4.11 (10H)	4.46 (4H), 5.32 (4H)	–	4.17 (3H)
17	4.09 (10H)	4.49 (4H), 5.27 (4H)	4.52 (1H)	–
18	4.19 (10H)	4.63 (4H), 5.07 (4H)	1.87 (2H), 2.87 (2H), 3.24 (2H), 3.72 (4H), 3.84 (4H)	–
19	4.29 (20H)	4.72 (8H), 5.24 (8H)	3. 16 (2H), 3.52 (4H), 3.81 (8H), 3.98 (8H)	–
20a	4.12 (5H),4.33 (5H)	4.49 (4H), 5.35 (4H)	6.45 (m, 1H, *J* = 6.9, 14.1), 6.90 (dd, 1H, *J* = 1.5, 14.1)	1.91 (dd, 3H,*J* = 1.5, 6.9)
20b	4.10 (5H), 4.13 (5H)	4.39 (4H), 4.65 (4H)	5.50 (m, 1H, *J* = 7.5, 9.3), 6.81 (dd, 1H, *J* = 1.8, 9.3)	2.21 (dd, 3H,*J* = 1.8, 7.5)
21	4.18 (20H)	4.42 (8H), 4.77 (8H)	3.02 (2H), 3.46 (4H)	–

dichloromethane; morpholine, 99+%; sodium hydrosulfide hydrate NaHS·xH_2O; diethylamine, 99.5%; piperidine, 99%; 1,3-diiodopropane, 99%; and sodium azide, 99%.

2,3-Diferrocenylcyclopropenone was obtained from the ferrocene and tetrachlorocyclopropene in the presence of $AlCl_3$ according to the standard procedure [18]. Ethoxy(diferrocenyl)-cyclopropenylium tetrafluoroborate was obtained from the 2,3-diferrocenylcyclopropenone in the presence of triethyloxonium tetrafluoroborate (1.0*M* solution in dichloromethane) [19]. Amino(differocenyl)cyclopropenylium tetrafluoroborates **5a–c** were obtained from ethoxy(diferrocenyl)cyclopropenylium tetrafluoroborate and morpholine, piperidine, or diethylamine in dichloromethane [19,20]. 2,3-Diferrocenylcyclopropenethione was obtained by treating ethanolic differocenyl(morpholino)cyclopropenylium tetrafluoroborate with an aqueous solution of NaSH [20], yield 91%, m.p. 208–209°C. 2,3-Diferrocenyl(methylthio)-cyclopropenylium iodide **6** was obtained from the 2,3-diferrocenylcyclopropenethione and iodomethane [20]. Freshly prepared and thoroughly dried tetrafluoroborates **5a–c** and iodide **6** were used in the synthesis of 1,2,3-triazines **7a–c** and **8a,b**. Reactions were carried out in freshly distilled dry solvents.

5-Amino-4,6-diferrocenyl-1,2,3-triazines (7a–c). Sodium azide (1.3 g, 20 mmol) was added to a solution of 1-amino-2,3-diferrocenylpropenylium tetrafluoroborate (**5a–c**) (10 mmol) in dichloromethane (chloroform, acetone, or acetonitrile) (100 mL), and the mixture was stirred in a dry inert atmosphere at ∼20°C (∼24–36 h) or under reflux (14–20 h). The solvents were removed *in vacuo*, and the residues were chromatographed on alumina (hexane–dichloromethane, 4:1) to give 65–78% of triazines **7a–c**.

Reaction of 1-methylthio-2,3-diferrocenylcyclopropenylium iodide 6 with sodium azide. A solution of compound **6** (2.9 g, 5.0 mmol) in a solvent mentioned in Table 1 (100 mL) was stirred with sodium azide (0.65 g, 10 mmol) at ∼20°C or with heating for 14–36 h. Subsequent work-up of the reaction mixtures as described earlier gave compounds **8a** and **8b** (see Table 1).

Reactions of triazines 7a–c with methyl iodide. A solution of 5-amino-4,6-diferrocenyl-1,2,3-triazine (**7a–c**) (1.5 mmol) and methyl iodide (3 mL) in dichloromethane (50 mL) was kept at ∼20°C for 3 days. The solvent was removed *in vacuo*, and dry benzene (40 mL) was added to the residue. The solids were filtered off and dried to obtain ∼75–85% of mixtures of quaternary salts **14a–c** and **15a–c** (∼5:1).

Reaction of triazine 7a with 1,3-diiodopropane. The title reaction was carried analogously from 4,6-diferrocenyl-5-morpholino-1,2,3-triazine **7a** (1.6 g, 3 mmol) and 1,3-diiodopropane (0.6 g, 2 mmol) in dichloromethane (50 mL). The violet precipitate that formed was filtered off, washed with dry ether, and dried *in vacuo*. The yield of the diiodide **19** was 0.51 g (25%). The solvent from filtrate was removed *in vacuo*, and

Scheme 13

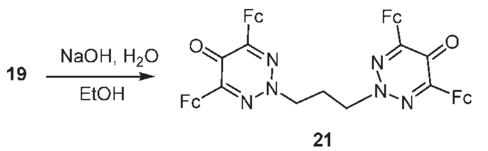


Table 4

^{13}C NMR spectral data of compounds **7a–c, 8a,b, 14a,b, 15a, 16–19, 21**(δ, ppm).

No.	2 C_5H_5	2 C_5H_4	2 C_{ipso}Fc	CH_3	CH_2, CH=	C
7a	70.52	69.81, 71.34	81.79	–	49.87 (2), 66.54 (2)	138.64, 156.17 (2)
7b	70.34	69.20, 70.94	81.93	–	23.43, 25.20 (2), 50.87 (2)	139.53, 155.82 (2)
7c	70.29	69.85, 70.77	79.96	13.77 (2)	46.51 (2)	134.80, 159.15 (2)
8a	70.44	71.29, 71.70	78.83	19.0	–	126.11, 161.19(2)
8b	70.21, 70.24	68.97, 69.79, 71.15, 71.52	80.47, 80.52	14.20	–	124.85, 156.48, 162.19
14a	70.73	69.88, 70.86	80.11	51.47	53.15 (2), 65.07 (2)	141.17 (2), 144.10
14b	70.27	68.88, 70.52	79.90	50.22	22.10, 24.92 (2), 53.87 (2)	139.12 (2), 143.61
14c	70.31	68.94, 70.43	80.01	14.67 (2), 51.24	50.28 (2)	140.85 (2), 143.57
15a	70.34	71.14, 72.24	78.57	51.52	53.31 (2), 65.21 (2)	145.20 (2), 147.50
15b	70.21	70.86, 71.56	78.48	50.33	22.34, 25.72 (2), 54.13 (2)	142.31 (2), 146.19
15c	70.27	70.89, 71.83	78.69	14.22 (2), 50.74	49.94(2)	139.97 (2), 142.88
16	69.75	68.97, 69.10, 70.41, 70.51	86.15	50.70	–	152.78 (2), 199.98 (C=O)
17	69.47	68.79, 69.63	80.14	–	–	146.18(2), 153.65
18	70.89	70.97, 71.28	80.43	–	32.41, 36.62, 46.31, 54.22 (2), 65.19 (2)	140.69 (2), 144.34
19	71.03 (2), 71.07 (2)	71.23, 71.31, 71.48, 71.81	80.56, 80.72	–	37.69, 46.82 (2), 55.14 (4), 66.01 (4)	141.53 (2), 143.73 (2), 148.03 (2)
21	70.09 (4)	69.81 (2), 70.64 (2)	87.44 (4)	–	41.53, 49.34 (2)	154.11 (4), 200.04 (2C=O)

Table 5

Yields, mp., elemental analysis, and MS data for the synthesized compounds.

No	Yield (%) (20°C)	Mp. (°C)	Found (%), calculated (%)e				Molecular formula	MS,*m*/*z*(M^+)
			C	H	F	N		
7a	78	244–245	60.85	5.01	20.99	10.39	$C_{27}H_{26}Fe_2N_4O$	534
			60–70	4.91	20.91	10.48		
7b	74	238–239	63.29	5.18	21.12	10.41	$C_{28}H_{28}Fe_2N_4$	532
			63.19	5.30	21.00	10.52		
7c	81	224–225	62.45	5.39	21.59	10.65	$C_{27}H_{28}Fe_2N_4$	520
			62.34	5.42	21.47	10.77		
8a	18–22	253–254	58.31	4.19	22.69	8.32	$C_{24}H_{21}Fe_2N_3S$	495
			58.22	4.28	22.56	8.48		
8b	56–59	217–218	58.10	4.37	22.43	8.42	$C_{24}H_{21}Fe_2N_3S$	495
			58.22	4.28	22.56	8.48		
14a/15a	65/13	272 dec	49.84	4.40	16.61	8.32	$C_{28}H_{29}Fe_2IN_4O$	676
			49.73	4.32	16.52	8.28		
14b/15b	60/12	235–236	51.79	4.53	16.69	8.21	$C_{29}H_{31}Fe_2IN_4$	674
			51.66	4.64	16.57	8.30		
14c/15c	70/14	224–225	50.65	4.81	16.93	8.31	$C_{28}H_{31}Fe_2IN_4$	662
			50.78	4.72	16.87	8.45		
16	50–62	210–211	60.25	4.50	23.17	8.69	$C_{24}H_{21}Fe_2N_3O$	479
			60.16	4.42	23.31	8.77		
17	8–11	202–203	59.27	4.06	23.89	9.11	$C_{23}H_{19}Fe_2N_3O$	465
			59.40	4.12	24.00	9.03		
18	60	270 dec	43.52	3.92	13.56	6.68	$C_{30}H_{32}Fe_2I_2N_4O$	830
			43.40	3.87	13.45	6.75		
19	25	304 dec	50.29	4.19	16.58	8.12	$C_{57}H_{58}Fe_4I_2N_8O_2$	–
			50.17	4.28	16.37	8.21		
20a,b	71	164–165	61.77	4.48	22.23	8.25	$C_{26}H_{23}Fe_2N_3O$	505
			61.82	4.59	22.11	8.32		
21	69	321–322	60.75	4.29	23.17	8.58	$C_{49}H_{42}Fe_4N_6O_2$	970
			60.66	4.36	23.03	8.66		

Table 6

IR and UV spectral data of compounds **7a**, **8a**, **8b**, **14a**, **16,** and **20a,b**.

No.	ν_{max} (KBr)/cm^{-1}	λ_{max}(CHCl$_3$, 20°)/nm
7a	435, 488, 544, 594, 736, 821, 887, 910, 943, 1001, 1021, 1039, 1067, 1108, 1186, 1261, 1384, 1443, 1509, 1636, 2851, 2897, 2959, 3090, 3440	–
8a	416,482, 503, 548, 674, 750, 786, 824, 890, 1000, 1015, 1064, 1106, 1178, 1237, 1289, 1304,1388, 1408, 1434, 1487, 1503, 1636, 2921, 2994, 3090, 3439	242, 288.15, 492.50
8b	415, 482, 502, 548, 733, 749, 785, 829, 999, 1024, 1068, 1105, 1119, 1177, 1234, 1289, 1306, 1389, 1410, 1438, 1499, 1639, 1670, 2921, 3089, 3428	210, 245, 290
14a/15a	498, 524, 617, 708, 736, 822, 916, 1001, 1028, 1061, 1107, 1240, 1268, 1306, 1356, 1400, 1434, 1483, 1549, 1627, 1703, 2859, 2956, 3048, 3420	–
14b/15b	493, 518, 613, 701, 740, 818, 922, 1003, 1021, 1060, 1106, 1243, 1274, 1332, 1420, 1439, 1482, 1551, 1628, 1708, 2861, 2934, 3042, 3417	–
14c/15c	496, 521, 619, 711, 735, 819, 913, 1002, 1026, 1068, 1103, 1241, 1272, 1337, 1421, 1432, 1478, 1557, 1631, 1704, 2861, 2929, 3046, 3423	–
16	495, 543, 590, 662, 724, 816, 916, 1001, 1023, 1066, 1205, 1292, 1324, 1379,1408, 1438, 1470, 1494, 1595, 1609, 1640, 1692, 2866, 2948, 3089, 3429	210.38, 278.50, 307.50, 346.40
20a,b	427, 465, 479, 553, 724, 818, 843, 912, 1003, 1029, 1050, 1107, 1155, 1230, 1325, 1378, 1411, 1440, 1470, 1494, 1597, 1612, 1643, 1666, 2864, 2971, 3093, 3452	–

dry ether (100 mL) was added to the residue. The solid was filtered off, dried to obtain 1.46 g (60%) of iodide **18**.

Alkaline hydrolysis of salts (14a–c + 15a–c), 18, and 19. A mixture of quaternary salts (**14a** + **15a**), (**14b** + **15b**), (**14c** + **15c**), (**18**), or (**19**) (1 mmol) in 10% aqueous NaOH (5 mL) and ethanol (50 mL) was stirred under reflux for 4 h. On cooling, water (100 mL) and chloroform (50 mL) were added, the reaction mixtures were stirred for additional 10 min, the organic layer was separated and concentrated *in vacuo*. The residues were chromatographed on alumina (hexane–dichloromethane, 5:1) to yield 2,5-dihydro-1,2,3-triazine-5-on and 5-ol **16** and **17**, compounds **20** and **21**.

Determination of the crystal structure. The unit cell parameters and the X-ray diffraction intensities were recorded on a Siemens P4 diffractometer. The structure of compound **8a** was solved by the direct method (SHELXS -97 [23]) and refined using full-matrix least-squares on F^2.

Crystal data for $C_{24}H_{21}Fe_2N_3S$ (**8a**): $M = 495.20$ g mol^{-1}, monoclinic P2$_1$/c, $a = 7.8403(12)$, $b = 16.025(3)$, $c = 16.655(3)$ Å, $\alpha = 90$, $\beta = 99.300(11)$, $\gamma = 90°$, $V = 2065.1(6)$ Å^3, $T = 293(2)$ K, $Z = 4$, $\rho = 1.593$ Mg/m^3, λ (Mo–Kα) = 0.71073 Å, $F(000) = 1016$, absorption coefficient 1.522 mm^{-1}, index ranges $-1 \leq h \leq 9$, $-1 \leq k \leq 19$, $-20 \leq l \leq 20$, scan range $2.48 \leq \theta \leq 25.98°$, 4046 independent reflections, $R_{int} = 0.0395$, 5339 total reflections, 272 refinable parameters, final R indices $[I > 2\sigma(I)]$ $R_1 = 0.0346$, $wR_2 = 0.0759$, R indices (all data) $R_1 = 0.0513$, $wR_2 = 0.0837$, largest difference peak and hole 0.330/−0.359 e·Å^{-3}.

CCDC-676457 (for **8a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/const/retrieving.html.

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Insertion and Fragmentation of 2-Ferrocenylmethylidene-1,3-diketones upon Their Reactions with *N*-Methylhydrazine

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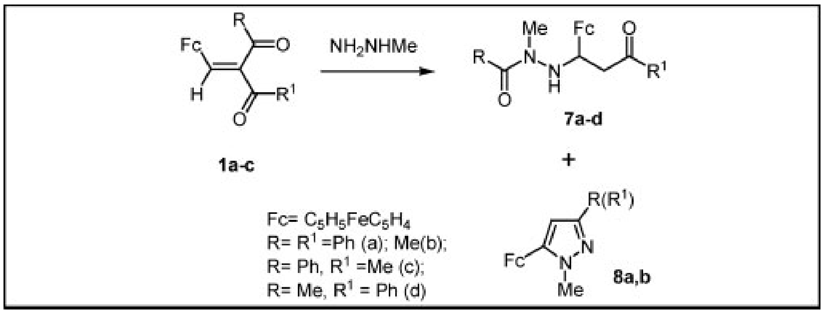

Reactions of 2-ferrocenylmethylidene-1,3-diketones (**1a–c**) with methylhydrazine afford mainly insertion products (~40–58%), *viz*., 1-(*N*′-acyl-*N*′-methylhydrazino)-1-ferrocenyl-2-acylethanes (**7a–d**), together with lesser amounts of pyrazoles (**8a,b**) and dihydropyrazoles (**9a,b**).

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INTRODUCTION

Syntheses of pyrazoles are mainly based on reactions of 1,3-diketones or 2,3-ynones with hydrazines or on the oxidation of 2-pyrazolines [1–3]. Both these methods are virtually inapplicable as approaches to ferrocenylpyrazoles, because 1,3-diketones with ferrocenyl substituents are usually accessible with difficulty, while oxidative methods may result in destruction of the metallocene substituent. Earlier [4,5], we have proposed a method for the preparation of ferrocenylpyrazole derivatives by condensation of 3- and 5-ferrocenyl-4,5-dihydropyrazoles with aromatic aldehydes (Scheme 1).

Biological assays of the thus obtained compounds have shown that the majority of them possessed high antiviral and anti-inflammatory activities [6–11]. The low solubility of the ferrocenylpyrazoles in water, alcohols, and in acidic solutions is their substantial drawback precluding their manifestation in full pharmacological potential.

In view of the aforesaid, the quest for the approaches to introduce new functional groups to increase the solubility of ferrocenyl-containing pyrazoles is topical. One of such approaches might be based on the use of easily accessible ferrocenylmethylidene-1,3-diketones as precursors of ferrocenylpyrazoles with retention of one of the functional groups in the reaction products.

Data on the features of reactions of these compounds with hydrazines are absent in the chemical literature. Here, we describe the results of investigations of the reactions of methylhydrazine with 2-ferrocenylmethylidene-1,3-dicarbonyl compounds.

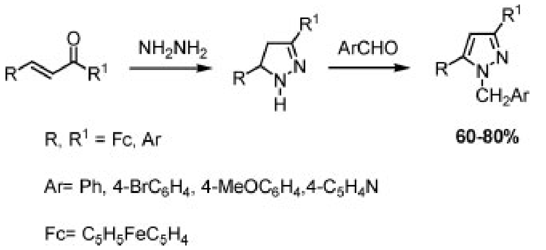
RESULTS AND DISCUSSION

The starting 2-ferrocenylmethylidene-1,3-diketones **1a–c** were obtained by the Knoevenagel condensation of β-dicarbonyl compounds **2a–c** with ferrocenecarbaldehyde in the presence of piperidinium y pyridinium acetates [12–14] (Scheme 2).

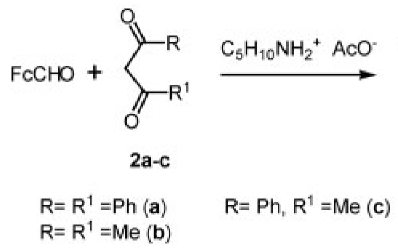
The structure of **1c** was elucidated based on the data from mass spectrometry, elemental analysis, and ^{1}H NMR spectroscopy (see Experimental section). According to the NMR data, compound **1c** is formed as single geometric isomers. The ^{1}H NMR spectrum of compound **1c** contains characteristic signals for one ferrocenyl, one phenyl, and one methyl entities, as well as one signal for the olefinic proton.

The spatial structure of compound **1c** as (*Z*)-2-ferrocenylmethylidene-1-phenylbutane-1,3-dione was determined by X-ray analysis of a single crystal obtained by crystallization from chloroform. The general view of the molecule of **1c** and its principal characteristics are given

Scheme 1



Scheme 2



in Figure 1(a), and the crystal packing is shown in Figure 1(b).

It was anticipated that compounds **1a–c** would react with methylhydrazine to form 4-acyl-5-ferrocenyl-4,5-dihydropyrazoles **3a**,**b** and **4a,b** or 4-acyl-3-ferrocenyl-2,3-dihydropyrazoles **5a**,**b** and **6a,b** [15], respectively (Scheme 3).

However, the results of these reactions turned out to be unexpected. In neither case did the coupling of *N*-methylhydrazine with compounds **1a–c** yield 4-acyl-4,5-dihydropyrazoles **3a,b**, **4a,b**, **5a,b**, and **6a,b**.

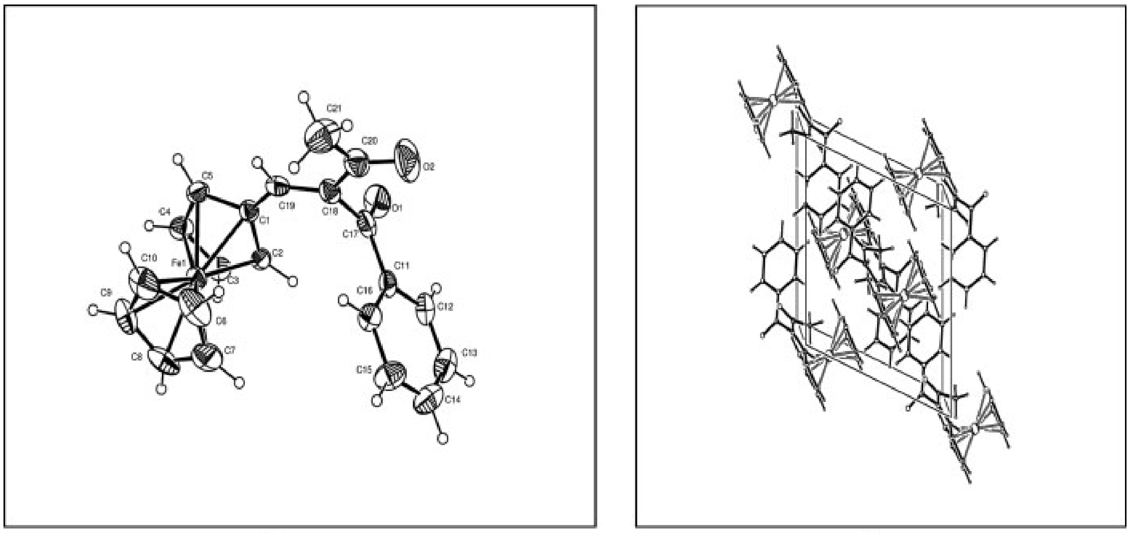
We have found that 1,3-diketones **1a** and **1b** react with *N*-methylhydrazine at 20°C to give mainly (~50%) the insertion products, *viz*., 1-benzoyl-2-(*N*′-benzoyl-*N*′-methylhydrazino)-2-ferrocenylethane **7a** and 4-(*N*′-acetyl-*N*′-methylhydrazino)-4-ferrocenylbutan-2-one **7b** (Scheme 4).

In addition, the fragmentation products, *viz*., 5-ferrocenyl-1-methylpyrazoles **8a,b**, 4,5-dihydropyrazoles **9a,b**, hydrazones **10a**,**b**, and hydrazides **11a**,**b** were isolated in lesser amounts.

Compounds **7a** and **7b** are yellow crystalline substances that precipitated from the reaction mixtures. They are storage-stable in the crystalline state, whereas in solution they gradually decompose. Pyrazole derivatives **8a,b** and **9a,b** were isolated by chromatography from the mother liquors following separation of the insertion products **7a** and **7b**.

The structures of compounds **7a** and **7b** were established based on data from ^{1}H and ^{13}C NMR spectroscopy. Their ^{1}H NMR spectra contain characteristic signals for the protons of the ABM system of the —CH$_2$—CH— fragments, singlets for protons of the CH$_3$— and NH groups, and the signals for the protons of the ferrocenyl and phenyl (for **7a**) substituents (Table 1).

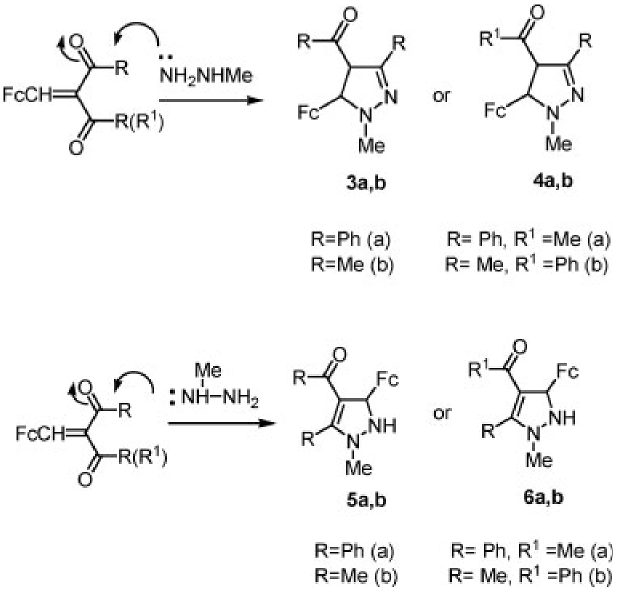
The ^{13}C NMR spectra of compounds **7a** and **7b** contain signals for the carbon atoms of two carbonyl



(a) (b)

Figure 1. (a) Crystal structure of **1c**. Selected bond lengths (Å): C(11)-C(17) = 1.478(7); C(17)-O(1) = 1.223(7); C(17)-C(18) = 1.510(7); C(18)-C(19) = 1.338(7); C(19)-C(1) = 1.439(7); C(18)-C(20) = 1.459(8); C(20)-C(21) = 1.503(9); C(20)-O(2) = 1.215(7). Selected bond angles (°): O(1)-C(17)-C(11) = 121.5(5); C(18)-C(17)-O(1) = 119.8(5); C(17)-C(18)-C(19) = 122.6(5); C(19)-C(18)-C(20) = 122.7(5); C17)-C(18)-C(20) = 114.6(5). (b) Crystal packing of **1c**.

Scheme 3



groups, of one ferrocenyl fragment with one signal for C_{ipso}Fc, and the appropriate number of signals for Me, Ph with two signals for C_{ipso} (**7a**), CH_2, and CH groups (Table 2).

X-ray diffraction analysis of a single crystal of the insertion product **7a** obtained upon crystallization from a 10:1 ethanol–methylhydrazine mixture proves unambiguously its structure. The general view of the molecule **7a** and its main geometric parameters are presented in Figure 2; these require no special comments.

The structures of pyrazole derivatives **8a**,**b** and **9a**,**b**, compounds **10a**,**b** and **11a**,b were unambiguously established based on the data from elemental analysis (Table 3), ^{1}H and ^{13}C NMR spectroscopy (Tables 1 and 2), and mass spectrometry (Table 3). Data from ^{1}H and ^{13}C NMR spectra of compounds **8a**,**b** and **9a**,**b** corroborate their structures. The number of signals for the CH=, C_5H_5, C_5H_4, Ph, Me **8a**,**b** and CH_2, CH, Fc, Ph, and Me **9a**,**b** groups and their chemical shifts correspond completely to the structures **8** and **9**.

The reaction of benzoyl(ferrocenylmethylidene)acetone **1c** with *N*-methylhydrazine affords mainly the insertion products, *viz*., 4-(N'-benzoyl-N'-methylhydrazino)-4-ferrocenylbutan-2-one **7c** and 3-(N'-acetyl-N'-methylhydrazino)-3-ferrocenyl-1-phenylpropan-1-one **7d** ($\sim$1:1) and lesser amounts of pyrazole derivatives **8a**,**b**, **9a**,**b**, hydrazones **10a**,**b,** and hydrazides **11a**,**b** (Scheme 5).

Data from elemental analysis, mass spectrometry, and ^{1}H and ^{13}C NMR spectroscopy including 1D NOE experiments, which have demonstrated the CH_3CO fragment either to be, or not to be, adjacent to the CH_2 group, prove the structure of compounds **7c** and **7d**.

Thus, the results obtained in this study demonstrate that the following processes take place in the reactions of *N*-methylhydrazine with 2-ferrocenylmethylidene-1,3-dicarbonyl compounds: (i) insertion of *N*-methylhydrazine into the molecules of the starting compounds **1a–c**; (ii) fragmentation of 1,3-diones **1a–c** under the action of *N*-methylhydrazine with, apparently, intramolecular redox process with formation of pyrazoles **8a,b**; and (iii) fragmentation of the same 1,3-diones **1a–c** under the action of *N*-methylhydrazine with formation of 4,5-dihydropyrazoles **9a,b** from α,β-unsaturated ketones.

The following putative reaction schemes seem to rationalize the formation of compounds **7a–d**, **8a**,**b**, **9a**,**b**, **10a**,**b,** and **11a**,**b**:

1. The addition of the NH_2 group of *N*-methylhydrazine to the activated double bond of the fragment FcCH=C of β-dicarbonyl compounds **1a–c** (the Michael addition) results in intermediates **12a–d** [Scheme 6(a)]. Subsequent nucleophilic attack by the CH_3NH fragment on the carbon atom of the carbonyl group with higher positive charge ($\delta+$) is accompanied by migration of the carbon–carbon σ bond to the adjacent position with formation of the enol forms of the insertion products (**13a–d**), which are transformed into final compounds **7a–d**.
2. The initial nucleophilic addition of the $-NHCH_3$ group of *N*-methylhydrazine to the carbon atom of a carbonyl group of the starting compounds **1a–c** [Scheme 6(b)] resulting in intermediates **12e–h**, **13e–h**, which are transformed into final compounds **7a–d**.
3. 5-Ferrocenylpyrazoles **8a,b** are formed apparently upon initial nucleophilic attack by the NH_2 group of *N*-methylhydrazine on the carbon atom of a carbonyl

Scheme 4

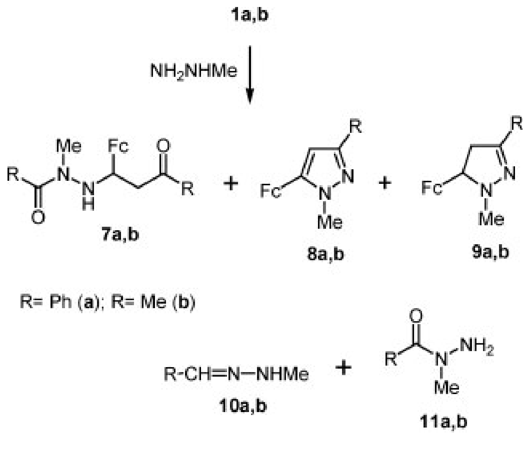


Table 1

^{1}H NMR spectral data of compounds **1c, 7a–d, 8a,b, 9a,b, 10a,b, and 11a,b** (δ, *J*/Hz).

Compound	C_5H_5 (s)	C_5H_4 (m)	CH_3, CH=	CH_AH_B (dd), CH_X (dd)	Ph, NH, NH_2
Z-**1c**	4.13 (5H)	4.24 (2H), 4.35 (2H)	2.31 s (3H), 7.64 s (1H)	–	7.46 m (2H), 7.58 m (1H), 7.94 m (2H)
7a	4.18 (5H)	3.94 (2H), 4.16 (2H)	2.93 s (3H)	3.17 (1H, *J* = 6.9, 16.5 Hz), 3.23 (1H, *J* = 4.5, 16.5 Hz), 3.59 (1H, *J* = 4.5, 6.9 Hz)	7.20–8.00 m (10H), 6.63 bs (1H)
7b	4.10 (5H)	3.89 (1H), 4.06 (1H), 4.17 (1H), 4.21 (1H)	1,79 s (3H), 2.94 s (3H), 3.12 s (3H)	2.60 (1H, *J* = 6.6, 16.8 Hz), 2.85 (1H, *J* = 3.9, 16.8 Hz), 3.41 (1H, *J* = 3.9, 6.6 Hz)	6.39 bs (1H)
7c	4.10 (5H)	4.14 (2H), 4.37 (1H), 4.44 (1H)	2.91 s (3H), 3.16 s (3H)	3.09 (1H, *J* = 6.3, 16.8 Hz), 3.31 (1H, *J* = 9.0, 16.8 Hz), 3.68 (1H, *J* = 6.3, 9.0 Hz)	7.37–7.56 m (3H), 7.95 m (2H), 5.92 bs (1H)
7d	4.19 (5H)	4.13 (1H), 4.15 (2H), 4.50 (1H)	2.18 s (3H), 2.96 s (3H)	3.03 (1H, *J* = 6.7, 16.3 Hz), 3.25 (1H, *J* = 4.8, 16.3 Hz), 3.75 (1H, *J* = 4.8, 6.7 Hz)	7.20–7.40 m (5H), 6.06 bs (1H)
8a	4.14 (5H)	4.33 (2H), 4.64 (2H)	3.78 s (3H), 5.86 s (1H)	–	7.34–7.68 m (5H)
8b	4.08 (5H)	4.24 (2H), 4.63 (2H)	2.27 s (3H), 3.75 s (3H), 6.04 s (1H)	–	–
9a	4.18 (5H)	4.21 (3H), 4.28 (1H)	2.83 s (3H)	3.26 (1H, *J* =13.5, 15.6 Hz), 3.47 (1H, *J* =9.6, 15.6 Hz), 3.97 (1H, *J* = 9.6, 13.5, Hz)	7.32–7.42 m (3H), 7.68–7.71 m (2H)
9b	4.14 (5H)	4.20 (1H), 4.26 (1H), 4.32 (1H), 4.47 (1H)	2.01 s (3H), 2.68 s (3H)	2.92 (1H, *J* = 13.2, 16.2 Hz), 2.97 (1H, *J* = 9.0, 16.2 Hz), 3.75 (1H, *J* = 9.0, 13.2 Hz)	–
10a	–	–	2.98 s (3H), 7,43 s (1H)	–	7.40 m (3H), 7.60 m (2H), 8.72 bs (1H)
10b	–	–	1.92 d (3H, *J* = 7.5 Hz), 3.14 s (3H), 6.87 q (1H, *J* = 7.5 Hz)	–	6.48 bs (1H)
11a	–	–	2.95 s (3H)	–	5.02 bs (2H), 7.50 m (3H), 7.89 m (2H)
11b	–	–	2.19 s (3H), 3.22 s (3H)	–	4.67 bs (2H)

group (preferably, of the C=O group linked with the Ph substituent) of the starting compounds **1a–c** (Scheme 7) resulting in hydrazones **14a–c**.

The subsequent nucleophilic attack by the CH_3NH fragment of hydrazones **14a–c** on the carbon atom of the second carbonyl group is accompanied, in our opinion, by an intramolecular redox process (see Scheme 7) resulting in intermediates **15a–c**, which are transformed into pyrazoles **8a,b** and hydrazones **10a**,**b**.

4. The formation of 4,5-dihydropyrazoles **9a,b** and hydrazides **11a**,**b** from 2-ferrocenylmethylidene-1,3-diones **1a–c** and *N*-methylhydrazine can be explained by the fragmentation of the starting dicarbonyl compounds to yield hydrazones **17a**,**b** according to a tentative Scheme 8.

The insertion products of *N*-methylhydrazine to 2-ferrocenylmethylidene-1,3-diketones have been isolated for the first time. This novel reaction may be regarded as a version of the Michael reaction, which allows preparation of (i) β-ferrocenyl-β-hydrazinoketones and (ii) 1-hydrazinoalkyl-substituted ferrocene derivatives. The synthetic potential of this type of reactions deserves undoubtedly more detailed studies.

Table 2

^{13}C NMR spectral data of compounds **7a–d**, **8a,b**, **9a,b**, **10a,** and **11a** (δ, ppm).

Compound	C_5H_5	C_5H_4	$C_{ipso}Fc$	CH_3	CH, CH=	Ph	CH_2	C, C=O
7a	68.91	67.30, 67.74, 68.09, 68.23	85.84	38.03	53.04	128.42, 128.51, 128.78, 129.78, 132.99	43.77	137.63, 137.77, 187. 01, 197.90
7b	68.15	66.42, 67.29, 67.64, 68.33	86.63	20.49 23.11, 31.58	52.89	–	41.29	170.23,176.15
7c	68.27	66.38, 67.41, 67.73, 67.82	87.47	20.60, 32.93	51.39	127.45, 127.78, 128.34	41.97	132.98, 174.19, 198.50
7d	68.33	66.19, 67.58, 67.64, 67.87	87.80	13.96, 39.46	60.43	127.30, 127.97, 129.88	40.65, 53.35	134.95, 170.91, 171.78
8a	69.49	68.19, 68.86	78.68	37.76	102.68	125.43, 127.48, 128.48	–	134.28, 142.83, 148.03
8b	69.38	66.30, 68.18	78.97	15.21, 35.88	103.03	–	–	139.02, 148.94
9a	69.04	67.87, 69.02	79.86	41.13	55.01	126.84, 128.66, 129.98	42.81	132.17, 134.13
9b	68.48	65.62, 68.14, 68.35, 70.19	79.17	16.57, 42.07	54.44	–	43.31	130.72
10a	–	–	–	34.37	138.21	125.64, 129.63, 136.38	–	130.50
11a	–	–	–	33.80	–	125.91, 130.59, 132. 51	–	134.89, 172.85

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Unity Inova Varian spectrometer (300 and 75 MHz) for solutions in $CDCl_3$with Me_4Si as the internal standard. The NMR spectroscopic data are listed in Tables 1 and 2. The mass spectra were obtained on a Varian MAT CH-6 instrument (EI MS, 70 eV).

Elemental analyses were performed by Galbraith Laboratories, Knoxville. The mass spectrometric data, data from

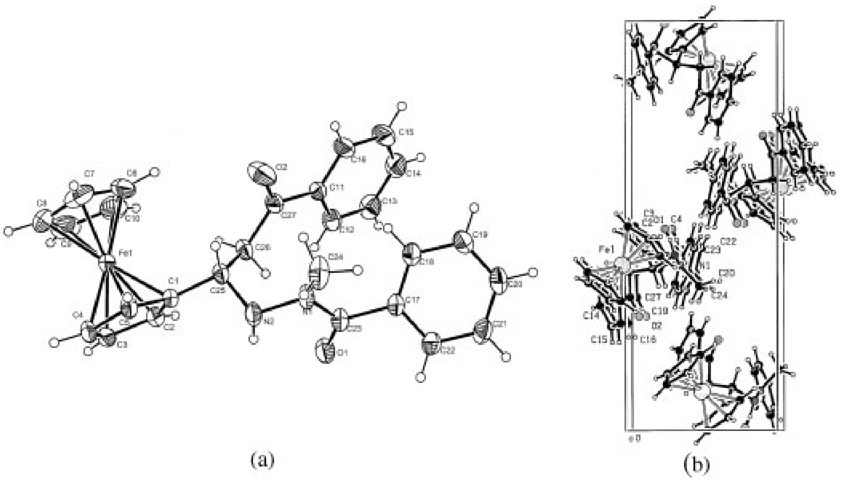


Figure 2. (a) Crystal structure of **7a**. Selected bond lengths (Å): N(1)-N(2)= 1.435(3); C(23)-O(1) = 1.233(3); N(1)-C(24) = 1.462(4); N(1)-C(23) = 1.350(3); N(2)-C(25) = 1.483(3); C(25)-C(26) = 1.535(3); C(26)-C(27) = 1.510(3); C(27)-O(2) = 1.211(3). Selected bond angles (°): O(1)-C(23)-N(1) = 121.0(2); C(23)-N(1)-N(2) = 116.5(2); N(1)-N(2)-C(25) = 111.4(2); C(25)-C(26)-C(27) = 112.1(2); C(26)-C(27)-O(2) = 120.2(2). (b) Crystal packing of **7a**.

Table 3

Elemental analysis data for the compounds **1c**, **7a–d, 8a,b, and 9a,b**.

Compound	Yield (%)	M.p. (°C)	Found (%), calculated (%) C	H	Fe	N	MS, *m*/*z* (M^+)	Molecular formula
1c	76	168–169	70.27 70.41	5.13 5.06	15.46 15.60	–	358	$C_{21}H_{18}FeO_2$
7a	51	208–210	69.39 69.54	5.54 5.62	12.07 11.98	6.05 6.00	466	$C_{27}H_{26}FeN_2O_2$
7b	50	170–171	59.51 59.66	6.53 6.48	16.43 16.32	8.11 8.19	342	$C_{17}H_{22}$ FeN_2O_2
7c	25	Oil	65.45 65.36	6.02 5.98	13.74 13.82	6.77 6.92	404	$C_{22}H_{24}FeN_2O_2$
7d	27	Oil	65.22 65.36	5.82 5.98	13.91 13.82	6.99 6.92	404	$C_{22}H_{24}FeN_2O_2$
8a	15	168–169	70.31 70.20	5.22 5.30	16.40 16.32	8.06 8.18	342	$C_{20}H_{18}FeN_2$
8b	16	137–138	64.19 64.31	5.83 5.76	20.02 19.93	9.86 10.00	280	$C_{15}H_{16}FeN_2$
9a	16	145–146	69.63 69.78	5.91 5.86	16.42 16.23	8.02 8.13	344	$C_{20}H_{20}FeN_2$
9b	14	124–125	63.94 63.85	6.26 6.43	19.71 19.80	9.79 9.92	282	$C_{15}H_{18}FeN_2$

elemental analyses, yields, and melting points of the compounds obtained are given in Table 3. Column chromatography was carried out on alumina (Brockmann activity III).

The following reagents were purchased from Aldrich: ferrocenecarbaldehyde, 99%; dibenzoylmethane, 98%; 2,4-pentanedione, 99+%; 1-benzoylacetone, 99%; methylhydrazine, 98%.

3-Ferrocenylmethylidene-1,3-diphenylpropane-1,3-dione 1a, 3-ferrocenylmethylidenepentane-2,4-dione 1b. These compounds were prepared by condensation of ferrocenecarbaldehyde with dibenzoylmethane, pentane-2,4-dione, respectively, in benzene in the presence of piperidinium acetate [16,17]. The physical and ^{1}H NMR spectroscopic characteristics of compounds 1a,b were in accord with the literature data [18,19].

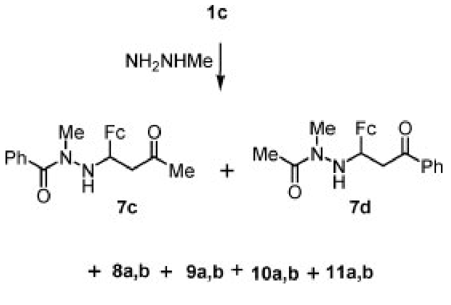
Condensation of ferrocenecarboxaldehyde with 1-benzoylacetone. A mixture of FcCHO (4.3 g, 20 mmol), 1-benzoylacetone (4.86 g, 30 mmol), piperidine (1 mL), pyridine (1 mL), and AcOH (2 mL) in dry benzene (100 mL) was refluxed for 12 h. The reaction mixture was washed with 5% HCl to remove the amines, and the organic layer was concentrated to dryness. Diethyl ether (100 mL) was added to the residue, the precipitate was filtered off, and dried on a filter to give (*Z*)-2-ferrocenylmethylidene-1-phenylbutane-1,3-dione **1c**, yield 5.8 g (81%), violet powder, mp 162–164°C. Subsequent chromatography on Al_2O_3 (hexane/dichloromethane, 4:1) gave 5.44 g (76%) compound **1c**, red crystals, mp 168–169 (lit. [19] 173)°C.

Reactions of 3-ferrocenylmethylidene-1,3-diphenylpropane-1,3-dione 1a or 3-ferrocenylme-thylidenepentane-2,4-dione 1b with *N*-methylhydrazine. A mixture of 1,3-diketone **1a** (2.10 g, 5 mmol) or **1b** (1.48 g, 5 mmol) and *N*-methylhydrazine (1.0 mL) in ethanol (15 mL) was stirred for 18 h at ambient temperature in an inert atmosphere. Yellow crystals of compounds **7a** or **7b** that sedimented were filtered off, washed with ethanol (2 × 5 mL), and dried in air. The yield of compound **7a** was 1.19 g (51%) and **7b** (0.86 g, 50.3%). The filtrates were concentrated *in vacuo* and the residues were chromatographed on alumina (hexane–ether, 3:1) to yield: (1) from **1a—**benzaldehyde *N*-methylhydrazone (**10a**) (0.07 g, 14%, colorless oil [20,21]), *N*′-methylbenzohydrazide **11a** (0.05 g, 12%, yellow oil [22,23]), and pyrazoles **8a** (yellow powder, 0.26 g, 15%) and **9a** (yellow powder, 0.27 g, 16%); (2) from **1b—**compounds **10b** (0.02 g, 10%, colorless oil [20,21]), **11b** (0.022 g, 9%, colorless oil [22,23]), **8b** (0.22 g, 16%), **9b** (0.20 g, 14%).

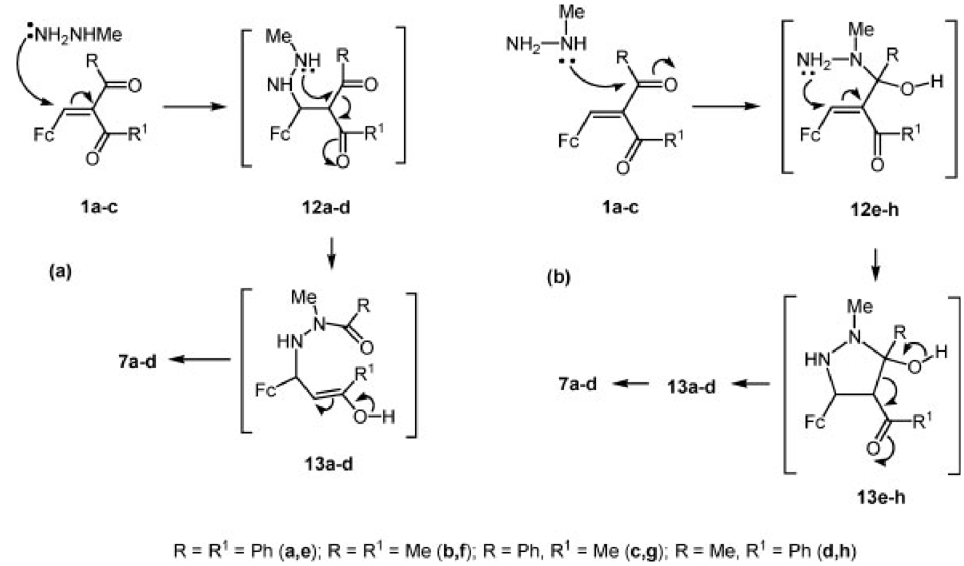
Reaction of *(Z)*-2-ferrocenylmethylidene-1-phenylbutane-1,3-dione 1c with *N*-methylhydrazine. The reaction of compound **1c** (1.79 g, 5 mmol) with *N*-methylhydrazine (1.0 mL) was carried out similarly. Work-up of the reaction mixture as described earlier and column chromatography afforded compounds **10a** + **10b** (0.06 g, 10%, ~1:1), **11a** + **11b** (0.078 g, 13%, ~1:1), **8a** (0.24 g, 14%), **9a** (0.28 g, 16%), and **7c**,**d** (1.17 g, 58%, ~1:1). Compounds **7c,d** were separated by preparative TLC on silica gel (hexane–diethyl ether, 5:1). The yield of compound **7c** was 0.50 g (25%) and that of **7d**, 0.54 g (27%).

Determining the crystal structure. The unit cell parameters and the X-ray diffraction intensities were recorded on a

Scheme 5



Scheme 6



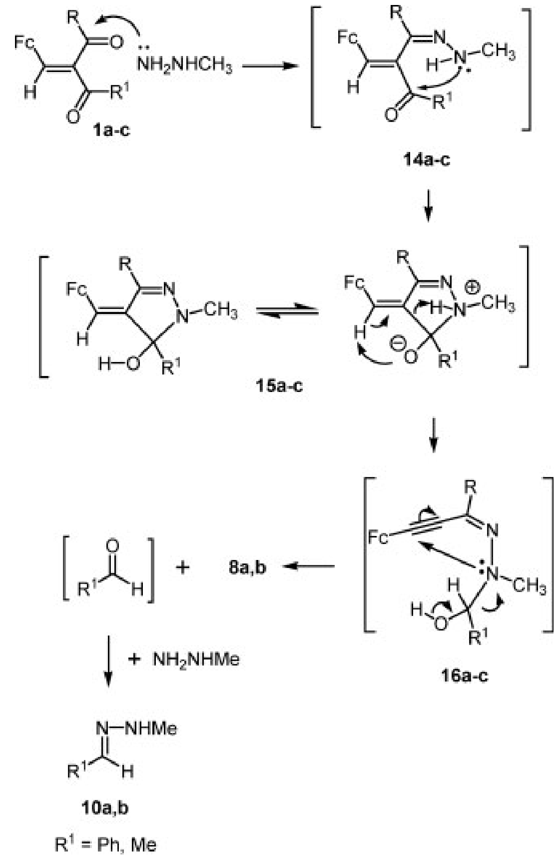
Siemens P4 diffractometer. The structures of compounds **1c** and **7a** were solved by direct methods (SHELXS-97 [24]) and refined using full-matrix least squares on F^2.

Crystal data for $C_{21}H_{18}FeO_2$ (**1c**): $M = 358.20$ g mol^{-1}, monoclinic P21/n, $a = 10.044(2)$, $b = 17.091(4)$, $c = 10.6900(17)$ Å, $\alpha = 90$, $\beta = 109.360(14)$, $\gamma = 90°$, $V = 1731.3(6)$ Å^3, $T = 298(2)$ K, $Z = 4$, $\rho = 1.374$ Mg/m^3, λ (Mo–Kα) = 0.71073 Å, $F(000) = 744$, absorption coefficient 0.880 mm^{-1}, index ranges $-1 \leq h \leq 13$, $-1 \leq k \leq 23$, $-14 \leq l \leq 14$, scan range $2.34 \leq \theta \leq 28.99°$, 4200 independent reflections, $R_{\text{int}} = 0.1571$, 5533 total reflections, 218 refinable parameters, final R indices $[I > 2\sigma(I)]$ $R_1 = 0.0727$, $wR_2 = 0.1340$, R indices (all data) $R_1 = 0.1725$, $wR_2 = 0.1781$, largest difference peak and hole 0.503/−0.399 e Å^{-3}.

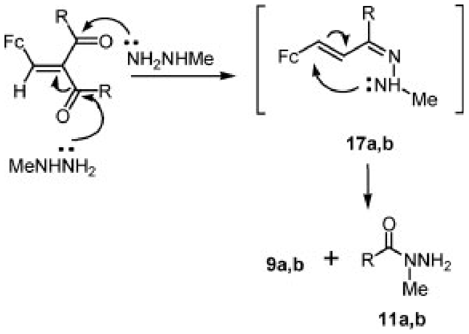
Crystal data for $C_{27}H_{26}FeN_2O_2$ (**7a**): $M = 466.35$ g mol^{-1}, monoclinic P2(1)/n, $a = 7.8840(8)$, $b = 21.2430(19)$, $c = 13.4820(14)$ Å, $\alpha = 90$, $\beta = 91.506(9)$, $\gamma = 90°$, $V = 2257.2(4)$ Å^3, $T = 293(2)$ K, $Z = 4$, $\rho = 1.372$ Mg/m^3, λ (Mo–Kα) = 0.71073 Å, $F(000) = 976$, absorption coefficient 0.695 mm^{-1}, index ranges $-1 \leq h \leq 10$, $-1 \leq k \leq 27$, $-17 \leq l \leq 17$, scan range $1.79 \leq \theta \leq 27.00°$, 4912 independent reflections, $R_{\text{int}} = 0.0415$, 6307 total reflections, 247 refinable parameters, final R indices $[I > 2\sigma(I)]$ $R_1 = 0.0473$, $wR_2 = 0.1169$, R indices (all data) $R_1 = 0.0746$, $wR_2 = 0.1321$, largest difference peak and hole 0.280/−0.271 e·Å^{-3}.

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC no. 689870 for compound **1c** and no. 687244 for

Scheme 7



Scheme 8



compound **7a**. These data can be obtained free of charge at http://www.ccdc.cam.ac.uk/const/retrieving.html.

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Regioselective Synthesis of Bioactive Spiro Heterocyclic Compounds Containing Both Indoline and Quinolone Moieties by Aryl Radical Cyclization

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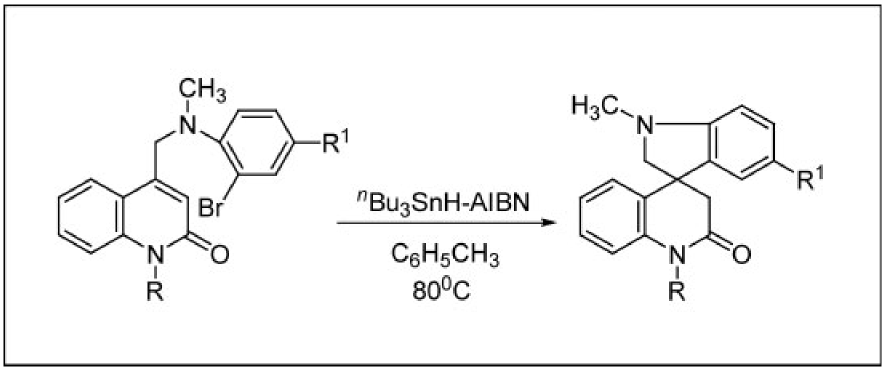

The tin hydride-mediated aryl radical cyclization of a number of 4-(2′-bromo-*N*-methylanilino)-methyl-1-alkylquinolin-2(1*H*)-ones under mild neutral condition afforded 1-alkyl-3,4-dihydroquinolin-2(1*H*)-one-4-spiro-3′-(1-methylindolines) in excellent yield. The starting materials, amines were derived from 4-bromomethyl-*N*-methyl quinolin-2(1*H*)-ones and 2-bromo-*N*-methyl anilines by refluxing in acetone in the presence of anhydrous potassium carbonate and sodium iodide (Finkelstein condition).

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INTRODUCTION

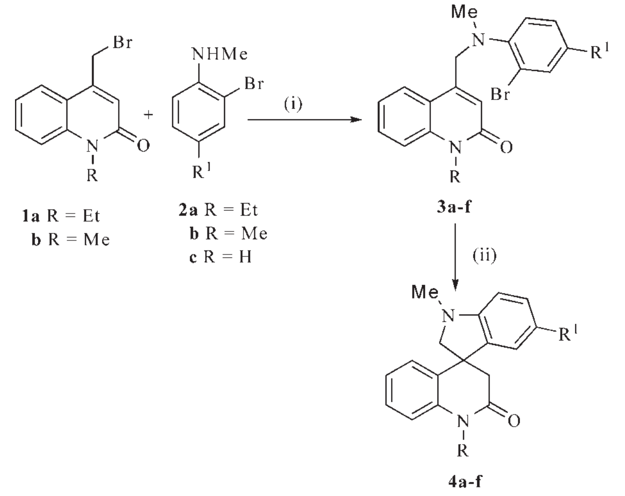
Nitrogen-containing heterocycles as recognized pharmacophores have received great attention in drug discovery and lead optimization [1–3]. In addition to traditional cycloadditions, cyclizations of nitrogen radicals or nitrogen-containing carbon radicals are the new approaches to *N*-heterocyclics [4–11]. Between these two radical reactions, the latter one is more general because carbon radicals are easy to generate and carbon–carbon bond formation by radical cyclization is a well-established process [12–16]. In our continuous effort on the development of free-radical reactions, we recently reported the 5-exo cyclization [17–20] and 6-endo cyclization [21,22] of oxygen heterocycles. We also recently reported the cyclization of 4-(2′-bromo-thioarylmethyl)-1-methylquinolin-2(1*H*)-one by $^{n}Bu_3SnH$ and AIBN, where a 6-endo ring closure took place to generate a six-membered sulfur heterocycle [23]. Several methodologies based on free-radical cyclization for the construction of five- [24–26] and six-membered [27–31] nitrogen heterocycles are available. In contrast, formation of spiro nitrogen heterocycles is almost rarely reported in literature [32–34].

Zhang and Pugh [35] demonstrated that intramolecular free-radical Michael-type addition facilitates the spiro cyclization process when an aryl radical is attached at the β-carbon of an α,β-unsaturated lactone system. Stabilization of the intermediate radical by the carbonyl group controls this regioselectivity [35]. It is also well documented that a 5-hexenyl radical cyclizes preferentially to the cyclopentylmethyl radical *via* 5-exo cyclization and not to the more stable cyclohexyl radical *via* 6-endo cyclization [36,37]. In this context, we undertook a study on the radical cyclizations of 4-(2′-bromo-*N*-methylanilinomethyl)-1-alkylquinolin-2(1*H*)-ones where these very criteria are present. Also quinolones fused with other heterocycles are known to have interesting biological activities and medicinal properties. Quinolone derivatives are biologically significant [38–42] because of their antibacterial activity, DNA-gyrase inhibition and marked cytotoxicity against animal and plant tumors. Keeping these biological activities in mind a number of attempts have been made over the last few decades to synthesize various biologically active quinolone derivatives many of which are abundant in nature [43]. Herein, we report the regioselective formation of spiro quinolone heterocycles by $^{n}Bu_3SnH$ mediated radical cyclization.

RESULTS AND DISCUSSION

The amines **3a–f** required for the present study were readily prepared in 89–95% yield from *o*-bromoanilines

Scheme 1. Reagents and conditions: (i) Acetone, K_2CO_3, NaI, reflux, 8h; (ii) ^{n}Bu$_3$SnH, toluene, 80°C N_2 atm, 1h.



3, 4	R	R^1	Yield (%) (Compound 3)	Yield (%) (Compound 4)
a	Et	H	95	90
b	Et	Mc	90	95
c	Et	Et	89	92
d	Me	H	95	95
e	Me	Me	92	92
f	Me	Et	92	90

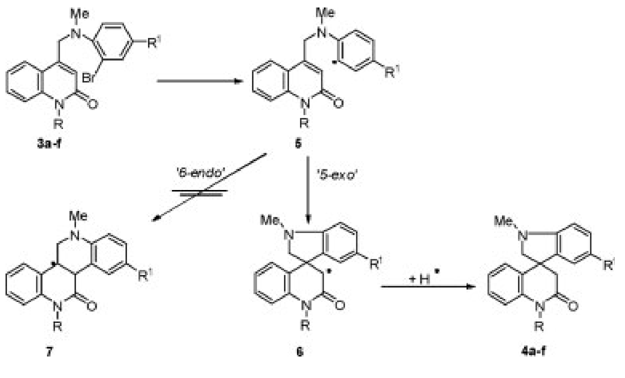
2a–c and 4-bromomethyl-1-alkylquinolin-2(1*H*)-ones **1a,b** in refluxing acetone for 8 h in the presence of anhydrous potassium carbonate and sodium iodide. The amines were subjected to ^{n}Bu$_3$SnH-AIBN induced radical cyclization. Compound **3a** when heated at 80°C in dry degassed toluene under nitrogen with ^{n}Bu$_3$SnH in the presence of catalytic amount of AIBN for 1 h afforded the cyclic product **4a** in 90% yield (Scheme 1). The structure of the compound **4a** was readily confirmed by ^{1}H NMR spectroscopy which exhibited one proton doublet at δ 2.83 (J = 16 Hz), another one proton doublet at δ 2.90 (J = 16 Hz) due to $\text{—COC}H_2$, $\text{—N(CH}_3\text{)C}H_2$ protons appear as two one proton doublet each at δ 3.21 and 3.39 (J = 8.8 Hz). Further confirmation of the structure **4a** came from its COSY, HETCOR and ^{13}C NMR spectrum. COSY spectrum of compound **4a** showed that $\text{—COC}H_2$ protons at δ 2.83 and 2.90 correlate with each other and $\text{—N(CH}_3\text{)C}H_2$ protons at δ 3.21 and 3.39 correlate with each other. The ^{13}C NMR spectrum of **4a** also strongly supported its structure. The ^{13}C chemical shifts of the compound **4a** are assigned by DEPT experiment. DEPT showed thirteen protonated carbons, two —CH_3, three $>\text{CH}_2$ and eight $>\text{CH—}$ moieties. Protonated carbon resonances are established by direct correlation with proton resonance by HETCOR experiment (normal one bond C—H coupling). Methylene protons resonance at δ 2.83 and 2.90 ($\text{C}H_2\text{CO}$) are related with carbon resonance at δ 42.34 and the methylene protons at δ 3.21 and 3.39 ($\text{—N(CH}_3\text{)C}H_2$) are related with carbon resonance at δ 67.42 respectively. Mass spectrum of the compound **4a** showed a molecular ion peak at m/z = 293 ($M^+ + 1$). These clearly indicated the formation of a spiro heterocyclic compound.

The other substrates **3b–f** were also treated similarly to afford exclusively compounds **4b–f** in 90–95% yield.

FMO theory can rationalize the regioselective formation of the spiro heterocyclic ring. Aryl radicals are high energy species and hence are nucleophilic in character. The highly electron withdrawing carbonyl group confers considerable electrophilic character to the C-4 position of the quinolone moiety. Thus in the case of nucleophilic radical **5**, FMO theory suggests that the mode of ring closure is largely determined by the interaction between the radical SOMO (≡HOMO) and the alkene LUMO of the acceptor (electron deficient centre) and accordingly more favorable bond formation occurs between the radical centre (nucleophilic) and C-4 of the quinolone ring for 5-exo product **4a–f** (Scheme 2) containing both the quinolone and indoline moieties which are known to be present in biologically active compounds.

In conclusion, we can say that the exclusive formation of 5-membered spiro heterocyclic pyrrole ring in excellent yield occurs because of two driving forces: first, the stabilization of the radical intermediate and second, stereoelectronically favored 5-exo pathway. This gives a simple and straightforward synthesis for spiro heterocyclic compounds. The methodology described here is mild and attractive because of its simplicity.

Scheme 2



EXPERIMENTAL

Melting points were determined in an open capillary and are uncorrected. IR spectra were recorded on a Perkin–Elmer L

120-000A spectrometer (ν_{max} in cm^{-1}) using samples as neat liquids and solid samples were recorded on KBr disks. UV absorption spectra were recorded in EtOH on a Shimadzu UV-2401PC spectrophotometer (λ_{max} in nm). ^{1}H NMR (400 MHz, 500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Bruker DPX-400 and Bruker DPX-500 spectrometer in $CDCl_3$ (chemical shift in δ) with TMS as internal standard. Elemental analyses and mass spectra were recorded on a Leco 932 CHNS analyzer and on a JEOL JMS-600 instrument respectively. Silica gel [60–120 mesh, Spectrochem, India] was used for chromatographic separation. Silica gel G [E-Merck, India] was used for TLC. Petroleum ether refers to the fraction boiling between 60 and 80°C.

General procedure for the preparation of 4-(2′-bromo-*N*-methylanilino)methyl-1-alkylquinolin-2(1*H*)-ones 3a–f. A mixture of 4-bromomethyl-*N*-alkylquinolone (**1a,b,**5 mmol), 2-bromoaniline (**2a–f**, 5 mmol), anhydrous potassium carbonate (5 g) and sodium iodide (20 mg) was heated under reflux in dry acetone (125 mL) for 8 h. The reaction mixture was cooled, filtered and concentrated. The residual mass was extracted with CH_2Cl_2(3 × 50 mL), washed with 10% Na_2CO_3 solution (2 × 25 mL), brine (3 × 50 mL) and dried (Na_2SO_4). The residual mass after the removal of solvent was subjected to column chromatography on silica gel using petroleum ether EtOAc (4:1) as eluant to give compounds **3a–f** which were recrystallized from $CHCl_3$-petroleum ether.

Compound (3a). Yield 95%, Viscous liquid; IR (Neat) υ_{max}: 2922 (Aromatic CH stretching), 1652 (CO δ lactum), 1590 (C=C) cm^{-1}; UV (EtOH) λ_{max}(log ε): 213 (4.44), 232 (4.49), 329 (3.76) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.35 (t, *J* = 7.1 Hz, 3H, NCH_2CH_3), 2.75 (s, 3H, NCH_3), 4.35 (s, 2H, CH_2NCH_3), 4.36 (q, *J* = 7.1 Hz, 2H, NCH_2CH_3), 6.91–6.96 (m, 1H, Ar*H*), 7.04 (s, 1H, =C*H*), 7.17–7.85 (m, 7H, Ar*H*); MS (*m/z*): 395 (M^+ + 23, 20%), 393 (M^+ + 23, 20%), 373 (M^+ + 1, 91%), 371 (M^+ + 1, 100%), 291 (15%). *Anal.* Calcd for $C_{19}H_{19}BrN_2O$: C, 61.46; H, 5.15; N, 7.54%. Found: C, 61.75; H, 4.95; N, 7.42%.

Compound (3b). Yield 90%, Viscous liquid; IR (Neat) υ_{max}: 2920 (Aromatic CH stretching), 1652 (CO δ lactum), 1591 (C=C) cm^{-1}; UV (EtOH) λ_{max}(log ε): 214 (4.36), 330 (3.51) nm; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.36 (t, *J* = 7.1 Hz, 3H, NCH_2CH_3), 2.29 (s, 3H, $ArCH_3$), 2.73 (s, 3H, CH_2NCH_3), 4.32 (s, 2H, CH_2NCH_3), 4.36 (q, *J* = 7.1 Hz, 2H, NCH_2CH_3), 7.02 (s, 1H, =C*H*), 7.08–7.91 (m, 7H, Ar*H*); MS (*m/z*): 409 (M^+ + 23, 22%), 407 (M^+ + 23, 21%), 387 (M^+ + 1, 100%), 385 (M^+ + 1, 92%), 305 (15%). *Anal.* Calcd for $C_{20}H_{21}BrN_2O$: C, 62.34; H, 5.49; N, 7.27%. Found: C, 62.12; H, 5.68; N, 7.15%.

Compound (3c). Yield 89%, Viscous liquid; IR (Neat) υ_{max}: 2922 (Aromatic CH stretching), 1652 (CO δ lactum), 1592 (C=C) cm^{-1}; UV (EtOH) λ_{max}(log ε): 215 (3.62), 231 (3.67), 330 (2.83) nm; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.19 (t, *J* = 7.5 Hz, 3H, $ArCH_2CH_3$), 1.35 (t, *J* = 7.1 Hz, 3H, NCH_2CH_3), 2.55 (q, *J* = 7.5 Hz, 2H, $ArCH_2CH_3$), 2.72 (s, 3H, NCH_3), 4.31 (s, 2H, CH_2NCH_3), 4.34 (q, *J* = 7.1 Hz, 2H, NCH_2CH_3), 7.01 (s, 1H, =C*H*), 7.09–7.89 (m, 7H, Ar*H*); MS (*m/z*): 401 (M^+ + 1, 100%), 399 (M^+ + 1, 86%), 319 (7%), 317 (17%), 309 (57%), 293 (25%). *Anal.* Calcd for $C_{21}H_{23}BrN_2O$: C, 63.16; H, 5.80; N, 7.01%. Found: C, 63.28; H, 6.03; N, 7.20%.

Compound (3d). Yield 95%, Viscous liquid;. IR (Neat) υ_{max}: 2924 (Aromatic CH stretching), 1656 (CO δ lactum), 1590 (C=C) cm^{-1}; UV (EtOH) λ_{max}(log ε): 215 (4.73), 229 (4.77), 330 (3.96) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.75 (s, 3H, CH_2NCH_3), 3.74 (s, 3H, $CONCH_3$), 4.35 (s, 2H, NCH_2), 6.91–6.95 (m, 1H, Ar*H*), 7.03 (s, 1H, =C*H*), 7.19–7.85 (m, 7H, Ar*H*); MS (*m/z*): 381 (M^+ + 23, 21%), 379 (M^+ + 23, 26%), 359 (M^+ + 1, 96%), 357 (M^+ + 1, 89%), 309 (100%), 277 (31%). *Anal.* Calcd for $C_{18}H_{17}BrN_2O$: C, 60.51; H, 4.79; N, 7.84%. Found: C, 60.76; H, 4.68; N, 7.65%.

Compound (3e). Yield 92%, White solid, mp 100–102°C; IR (KBr) υ_{max}: 2922 (Aromatic CH stretching), 1654 (CO δ lactum), 1588 (C=C) cm^{-1}; UV (EtOH) λ_{max}(log ε): 218 (4.63), 230 (4.66), 330 (3.85) nm; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 2.29 (s, 3H, $ArCH_3$), 2.73 (s, 3H, CH_2NCH_3), 3.73 (s, 3H, $CONCH_3$), 4.32 (s, 2H, NCH_2), 7.00 (s, 1H, =C*H*), 7.07–7.89 (m, 7H, Ar*H*); MS (*m/z*): 395 (M^+ + 23, 21%), 393 (M^+ + 23, 21%), 373 (M^+ + 1, 89%), 371 (M^+ + 1, 100%), 291 (17%). *Anal.* Calcd for $C_{19}H_{19}BrN_2O$: C, 61.46; H, 5.15; N, 7.54%. Found: C, 61.68; H, 5.30; N, 7.31%.

Compound (3f). Yield 92%, White solid, mp 101–102°C; IR (KBr) υ_{max}: 2922 (Aromatic CH stretching), 1651 (CO δ lactum), 1591 (C[dond]C) cm^{-1}; UV (EtOH) λ_{max} (log ε): 215 (4.45), 232 (4.48), 330 (3.87) nm; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.19 (t, *J* = 7.5 Hz, 3H, $ArCH_2CH_3$), 2.55 (q, *J* = 7.5 Hz, 2H, $ArCH_2CH_3$), 2.72 (s, 3H, CH_2NCH_3), 3.72 (s, 3H, $CONCH_3$), 4.31 (s, 2H, NCH_2), 7.01 (s, 1H, =C*H*), 7.09–7.88 (m, 7H, Ar*H*); MS (*m/z*): 409 (M^+ + 23, 14%), 407 (M^+ + 23, 14%), 387 (M^+ + 1, 100%), 385 (M^+ + 1, 85%), 305 (11%); *Anal.* Calcd for $C_{20}H_{21}BrN_2O$: C, 62.34; H, 5.49; N, 7.27%. Found: C, 62.08; H, 5.71; N, 7.11%.

General procedure for the preparation of 1-alkyl-3,4-dihydroquinolin-2(1*H*)-one-4-spiro-3′-(1-methylindoline) 4a–f. Tributyltin hydride (1.1 mmol) was added to a stirred solution of (**3a–f**, 1 mmol) and azobisisobutyronitrile (0.5 mmol) in dry degassed toluene (5 mL) under nitrogen. The mixture was heated at 80°C for 1 h and concentrated. The residue was dissolved in ether (10 mL) and stirred with a 10% aq. potassium fluoride solution (10 mL) for 45 min. The white precipitate was filtered and the aqueous phase was extracted with ether (10 mL). The combined ether extract was washed with brine and dried (Na_2SO_4). The residual mass after the removal of solvent was subjected to column chromatography using petroleum ether-ethyl acetate (4:1) as eluant to give cyclized product **4a–f**.

Compound (4a). Yield 90%, Viscous liquid; IR (Neat) υ_{max}: 2974 (Aromatic CH stretching), 1673 (CO δ lactum) cm^{-1}; UV (EtOH) λ_{max} (log ε): 212 (4.47), 253 (4.19), 305 (3.42) nm; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.28 (t, *J* = 7.1 Hz, 3H, NCH_2CH_3), 2.75 (s, 3H, NCH_3), 2.83 (d, *J* = 16 Hz, 1H, COC*H*), 2.90 (d, *J* = 16 Hz, 1H, COC*H*), 3.21 (d, *J* = 8.8 Hz, 1H, NC*H*), 3.39 (d, *J* = 8.8 Hz, 1H, NC*H*), 4.03 (q, *J* = 7.1 Hz, 2H, NCH_2CH_3), 6.59–7.25 (m, 8H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 12.70 (NCH_2CH_3), 35.52 (NCH_3), 37.16 (NCH_2CH_3), 42.34 ($COCH_2$), 46.55 (CH_2C), 67.42 (CH_2NCH_3), 107.85 (ArCH), 115.02 (ArCH), 118.41 (ArCH), 123.09 (ArCH), 123.52 (ArCH), 127.00 (ArCH), 128.02 (ArCH), 128.82 (ArCH), 131.93 (ArC), 132.55 (ArC), 138.65 (ArC), 153.04 (ArC), 168.05 (CO); MS (*m/z*): 315 (M^+ + 23, 25%), 293 (M^+ + 1, 100%), 289 (20%), 251 (50%). *Anal.* Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.54%. Found: C, 77.90; H, 6.63; N, 9.80%.

Compound (4b). Yield 95%, White solid, mp 124–126°C; IR (KBr) υ_{max}: 2921 (Aromatic CH stretching), 1674 (CO δ lactum) cm^{-1}; UV (EtOH) λ_{max} (log ε): 211 (4.51), 253 (4.18), 313 (3.34) nm; ^{1}H NMR (500 MHz, CDCl$_3$,): δ_H 1.28 (t, J = 7.1 Hz, 3H, NCH$_2$C*H*$_3$), 2.26 (s, 3H, ArC*H*$_3$), 2.71 (s, 3H, NC*H*$_3$), 2.82 (d, J = 16 Hz, 1H, COC*H*), 2.90 (d, J = 16 Hz, 1H, COC*H*), 3.18 (d, J = 8.8 Hz, 1H, NC*H*), 3.33 (d, J = 8.8 Hz, 1H, NC*H*), 4.01 (q, J = 7.1 Hz, 2H, NC*H*$_2$CH$_3$), 6.51–7.29 (m, 7H, Ar*H*); MS (*m/z*): 329 (M$^+$ + 23, 50%), 307 (M$^+$ + 1, 100%), 303 (11%), 265 (39%). *Anal.* Calcd for $C_{20}H_{22}N_2O$: C, 78.39; H, 7.23; N, 9.14%. Found: C, 78.60; H, 7.04; N, 9.02%.

Compound (4c). Yield 92%, Viscous liquid; IR (Neat) υ_{max}: 2926 (Aromatic CH stretching), 1676 (CO δ lactum) cm^{-1}; UV (EtOH) λ_{max} (log ε): 211 (3.85), 253 (3.57), 312 (3.37) nm; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 1.15 (t, J = 7.5 Hz, 3H, ArCH$_2$C*H*$_3$), 1.27 (t, J = 7.1 Hz, 3H, NCH$_2$C*H*$_3$), 2.52 (q, J = 7.5 Hz, 2H, ArC*H*$_2$CH$_3$), 2.71 (s, 3H, NC*H*$_3$), 2.82 (d, J = 16 Hz, 1H, COC*H*), 2.90 (d, J = 16 Hz, 1H, COC*H*), 3.17 (d, J = 8.8 Hz, 1H, NC*H*), 3.33 (d, J = 8.8 Hz, 1H, NC*H*), 3.99 (q, J = 7.1 Hz, 2H, NC*H*$_2$CH$_3$), 6.52–7.29 (m, 7H, Ar*H*); MS (*m/z*): 343 (M$^+$ + 23, 14%), 321 (M$^+$ + 1, 84%), 317 (100%), 289 (38%), 279 (27%). *Anal.* Calcd for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.54; N, 8.74%. Found: C, 78.48; H, 7.69; N, 8.90%.

Compound (4d). Yield 95%, White solid, mp 120–122°C; IR (KBr) υ_{max}: 2952 (Aromatic CH stretching), 1676 (CO δ lactum) cm^{-1}; UV (EtOH) λ_{max} (log ε): 211 (4.72), 251 (4.19), 305 (3.40) nm; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 2.74 (s, 3H, CH$_2$NC*H*$_3$), 2.85 (d, J = 16 Hz, 1H, COC*H*), 2.90 (d, J = 16 Hz, 1H, COC*H*), 3.21 (d, J = 8.8 Hz, 1H, NC*H*), 3.40 (d, J = 8.8 Hz, 1H, NC*H*), 3.42 (s, 3H, CONC*H*$_3$), 6.58–7.30 (m, 8H, Ar*H*); MS (*m/z*): 301 (M$^+$ + 23, 20%), 279 (M$^+$ + 1, 100%), 375 (25%), 237 (17%). *Anal.* Calcd for $C_{18}H_{18}N_2O$: C, 77.66; H, 6.51; N, 10.06%. Found: C, 77.90; H, 6.35; N, 9.86%.

Compound (4e). Yield 92%, White solid, mp 99–101°C; IR (KBr) υ_{max}: 2988 (Aromatic CH stretching), 1676 (CO δ lactum) cm^{-1}; UV (EtOH) λ_{max} (log ε): 211 (4.51), 253 (4.14), 313 (3.36) nm; ^{1}H NMR (500 MHz, CDCl$_3$): δ_H 2.26 (s, 3H, ArC*H*$_3$), 2.72 (s, 3H, CH$_2$NC*H*$_3$), 2.86 (d, J = 16 Hz, 1H, COC*H*), 2.90 (d, J = 16 Hz, 1H, COC*H*), 3.20 (d, J = 8.8 Hz, 1H, NC*H*), 3.35 (d, J = 8.8 Hz, 1H, NC*H*), 3.44 (s, 3H, CONC*H*$_3$), 6.52–7.28 (m, 7H, Ar*H*); MS (*m/z*): 315 (M$^+$ + 23, 14%), 293 (M$^+$ + 1, 100%), 289 (21%), 251 (50%). *Anal.* Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58%. Found: C, 77.78; H, 7.08; N, 9.43%.

Compound (4f). Yield 90%, Viscous liquid, IR (Neat) υ_{max}: 2917 (Aromatic CH stretching), 1674 (CO δ lactum) cm^{-1}; UV (EtOH) λ_{max} (log ε): 214 (4.32), 254 (4.11), 311 (3.40) nm; ^{1}H NMR (500 MHz, CDCl$_3$): δ_H 1.15 (t, J = 7.5 Hz, 3H, ArCH$_2$C*H*$_3$), 2.52 (q, J = 7.5 Hz, 2H, ArC*H*$_2$CH$_3$), 2.71 (s, 3H, C*H*$_2$NCH$_3$), 2.85 (d, J = 16 Hz, 1H, COC*H*), 2.90 (d, J = 16 Hz, 1H, COC*H*), 3.18 (d, J = 8.8 Hz, 1H, NC*H*), 3.35 (d, J = 8.8 Hz, 1H, NC*H*), 3.42 (s, 3H, CONC*H*$_3$), 6.53–7.30 (m, 7H, Ar*H*); ^{13}C NMR (125 MHz, CDCl$_3$): δ_C 15.41 (ArCH$_2$C*H*$_3$), 27.75 (Ar*C*H$_2$CH$_3$), 28.92 (CH$_2$N*C*H$_3$), 35.49 (CON*C*H$_3$), 41.54 (CO*C*H$_2$), 46.00 (CH$_2$*C*), 67.44 (*C*H$_2$NCH$_3$), 107.41 (Ar*C*H), 114.46 (Ar*C*H), 122.47 (Ar*C*H), 122.67 (Ar*C*H), 126.24 (Ar*C*H), 127.42 (Ar*C*H), 127.51 (Ar*C*H), 131.04 (Ar*C*), 132.14 (Ar*C*), 134.13 (Ar*C*), 139.27 (Ar*C*), 150.72 (Ar*C*), 168.21 (*C*O); MS (*m/z*): 329 (M$^+$ + 23, 18%), 307 (M$^+$ + 1, 100%), 303 (50%), 265 (50%). *Anal.* Calcd for $C_{20}H_{22}N_2O$: C, 78.39; H, 7.23; N, 9.14%. Found: C, 78.21; H, 7.45; N, 8.96%.

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Synthesis and *In Vitro* Study of a New Class of Methylene-bis-4,6-diarylbenzo[*d*]isoxazoles as Potential Antifungal Agents

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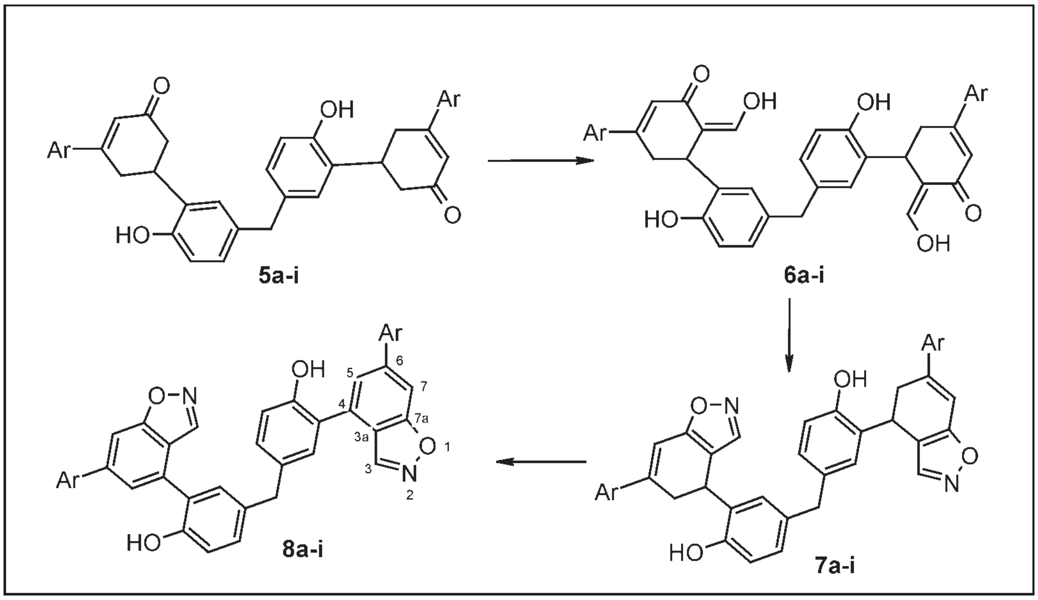

A new class of methylene-bis-4,6-diarylbenzo[*d*]isoxazoles **8a–i** was synthesized by the reaction of methylene-bis-aryl-6-hydroxymethylene-2-cyclohexenone **6** with hydroxylamine hydrochloride, followed by aromatization with DDQ. Chemical structures of the newly synthesized compounds were elucidated by their IR, ^{1}H NMR, ^{13}C NMR, MS, and elemental analyses. Furthermore, all the compounds were screened for their antifungal activity against various fungi and compared with their monomeric compounds. Among the synthesized compounds, **8b**, **8g**, and **8i** were found to be the most active against *Candida albicans* (ATCC 10231), *Aspergillus fumigatus* (HIC 6094), *Trichophyton rubrum* (IFO 9185), and *Trichophyton mentagrophytes* (IFO 40996). It is interesting to note that the compounds **8a**, **8g**, and **8i** showed fungicidal activity toward *C. albicans* at the concentration of 3.12 μg/mL, which is less than the concentration of standard Amphotericin B.

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INTRODUCTION

The treatment of infectious diseases still remains an important and challenging problem because of a combination of factors including emerging infectious diseases and the increasing number of multidrug resistant microbial pathogens. In spite of a large number of antibiotics and chemotherapeutics available for medical use, the emergence of old and new antibiotic resistance created in the last decades revealed a substantial medical need for new classes of antimicrobial agents. There is a real perceived need for the discovery of new compounds endowed with antimicrobial activity, which are distinct from those of well known classes of antibacterial agents to which many clinically relevant pathogens are now resistant. Similarly in recent decades, an increased incidence of fungal infections has been observed as a consequence of the growing number of immunocompromised patients and the frequent use of antibacterial and cytotoxic drugs. For many fungal infections, polyenes, such as Amphotericin B, represent the standard therapy. Polyenes bind to membrane sterols, leading to membrane permeability, leakage, and cell death. However, the clinical use of Amphotericin B is limited by a high frequency of renal toxicity and several adverse effects [1]. Although the various molecules designed and synthesized for the above aim and to reduce the adverse effects, it was demonstrated that isoxazole derivatives could be considered as possible antifungal agents [2]. The other activities include, inhibition of Aβ precursor protein (APP) [3], inhibition of protein tyrosine phosphatase 1B [4], antiviral [5], anthelmintics [6], anti-inflammatory [7], anticonvulsant [8], insecticidal [9], antitubercular [10], immunomodulatory [11], and hypolipemics [12]. Valdecoxib, an isoxazole derivative, is now widely used in the market as an anti-inflammatory drug [13]. The most general and widely employed synthetic route to isoxazoles involves reaction of chalcones with hydroxylamine hydrochloride [14] or 1,3-dipolar cycloaddition of nitrile oxides to alkynes [15] or condensation of open chain α-hydroxymethylene ketones with hydroxylamine [16] or from 3,5-diarylcyclohexenone and hydroxylamine [17].

Following the successful introduction of antimicrobial agents, inspired by the biological profile of isoxazoles and their increasing importance in pharmaceutical and biological fields, and in continuation of our research on biologically active heterocycles [18], and to enhance the biological activity of isoxazole derivatives, it was considered worth while to synthesize certain new chemical entities incorporating two active pharmacophores in a single molecular framework. In this article, we wish to report the synthesis of a new class of methylene-bis-4,6-diarylbenzo[*d*]isoxazoles **8** in good yields from methylene-bis-aryl-6-hydroxy-methylene-2-cyclohexenone **6** (Scheme 1) and *in vitro* antifungal activity.

RESULTS AND DISCUSSION

The key intermediate, **6** required for the synthesis of the title compounds was prepared according to the procedure outlined in the Scheme 1. Condensation of the salicylaldehyde **1** and trioxane in the presence of a mixture of conc. sulfuric acid and acetic acid gave methylene-bis-salicylaldehyde **2** in good yield [19]. Compound **2** on reaction with the aromatic/heteroaromatic methyl ketones in the presence of alc. KOH at room temperature gave methylene-bis-chalcones **3** (yield over 90%) [18(g)], the reaction time as well as the product yield varies depending on the corresponding reagents. The crude product, contaminated by some starting materials, was purified by extracting with ether. Knoevenagel condensation of compound **3** with ethyl acetoacetate gave methylene-bis-aryl-6-carbethoxycyclohexenones **4** (yield over 80%). Decarboxylation of compound **4**, in the presence of HCl/AcOH at reflux temperature, resulted in methylene-bis-arylcyclohexenone **5** (yield over 80%), which on Claisen-like condensation with ethylformate in the presence of sodium methoxide at room temperature afforded methylene-bis-aryl-6-hydroxymethylene-2-cyclo-hexenone **6** in good yields. Compound **6** on

Scheme 1. Reagents and conditions: (i) trioxane, H_2SO_4/AcOH, reflux, 81%; (ii) $ArCOCH_3$, KOH/EtOH, rt, 82–95%; (iii) EAA, NaOEt/EtOH, reflux, 78–86%; (iv) HCl/AcOH, reflux, 74–82%; (v) HCOOEt, NaOMe/C_6H_6, rt, 79–88%; (vi) $H_2NOH{\cdot}HCl$, AcOH, reflux, 77–86%; and (vii) DDQ/dry C_6H_6, N_2–atm, 76–83%.

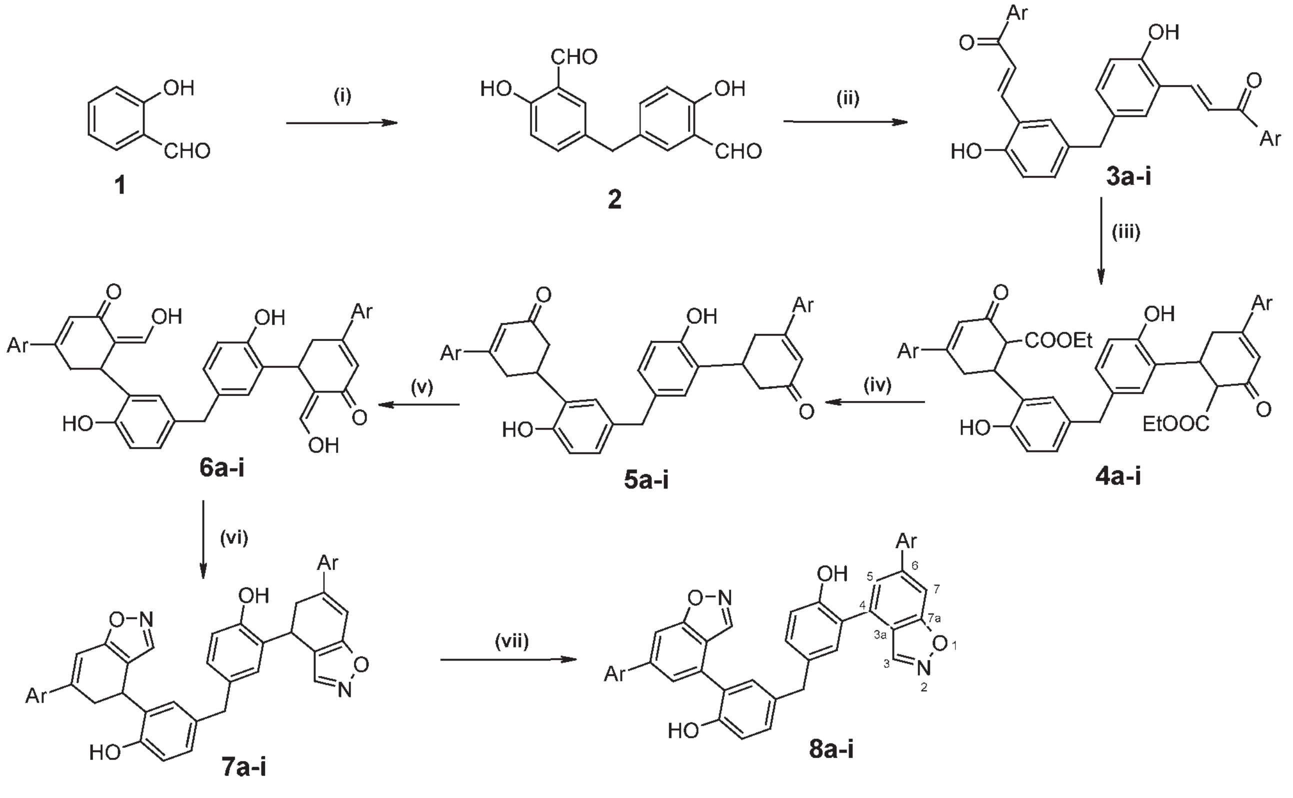
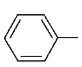
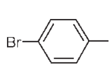
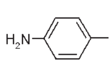
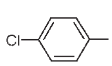
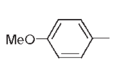
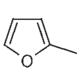
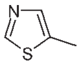
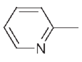
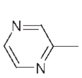


Table 1

Synthesis of compounds **8a–i**.

Product[a]	Ar	Mol. formula	Yield (%)[b]	M.p.°C
8a		$C_{39}H_{26}N_2O_4$	78	158–60
8b		$C_{39}H_{24}Br_2N_2O_4$	84	171–72
8c		$C_{39}H_{28}N_4O_4$	79	158–60
8d		$C_{39}H_{24}Cl_2N_2O_4$	86	144–46
8e		$C_{41}H_{30}N_2O_6$	77	135–37
8f		$C_{35}H_{22}N_2O_6$	80	162–63
8g		$C_{33}H_{20}N_4O_4S_2$	82	149–50
8h		$C_{37}H_{24}N_4O_4$	77	151–53
8i		$C_{35}H_{22}N_6O_4$	81	162–64

[a] All the products were characterized by IR, NMR, MS, and elemental analyses.

[b] Isolated yields after purification.

cyclocondensation with hydroxylamine hydrochloride in refluxing acetic acid gave dihydroisoxazole derivative **7**, in good to excellent yields (yields over 80%). Subsequent aromatization of **7** with dichlorodicyanoparabenzoquinone (DDQ), under N_2-atomsphere at reflux temperature, gave methylene-bis-4,6-diarylbenzo[*d*]isoxazoles **8** in good yields (Table 1). In the ^{1}H NMR spectra of **8**, the absence of signals corresponding to methine and methylene protons of cyclohexadiene ring indicates that aromatization has indeed taken place. The structure of all the synthesized compounds was confirmed by their IR, ^{1}H NMR, ^{13}C NMR, MS, and elemental analyses. Furthermore, the compounds was subjected to antifungal testing and compared with their monomeric compounds prepared from the literature method [17].

In this work, a series of nine new benzo-[*d*]isoxazole derivatives were synthesized and the Scheme 1 illustrates the strategy used for the synthesis of target compounds. Salicylaldehyde and trioxane was used as starting materials to prepare isoxazole derivatives. In the IR spectra of compounds **8a–i**, the C=N and N—O bands of the isoxazole moiety was observed at about 1600 and 1470 cm^{-1}, respectively. In the ^{1}H NMR spectra of compounds **8a–i** recorded in DMSO-d_6, the signal due to methylene bridge protons appeared at 3.98–4.06 ppm as a singlet and the N=CH proton appeared at 8.20–8.28 ppm as a singlet, proved that these compounds have isoxazole nucleus. All the other aromatic and aliphatic protons of **8a–i** were observed at the expected regions. In the ^{13}C NMR spectra of compounds **8a–i** that are taken in DMSO-d_6, the prominent signal corresponding to C-3, C-3a, and C-7a observed at 150.3, 128.0–120.5, 173.0–170.0 ppm, respectively, have proved for further evidence for their structures. Mass spectra of all the synthesized compounds showed M$^+$/M$^+$+1 peaks are in agreement with their molecular formulae.

Antifungal activity. The newly prepared compounds were screened for their antifungal activity against four fungal organisms viz. *Candida albicans* (ATCC 10231), *Aspergillus fumigatus* (HIC 6094), *Trichophyton rubrum* (IFO 9185), and *Trichophyton mentagrophytes* (IFO 40996) by the broth dilution method, recommended by National Committee for Clinical Laboratory Standards (NCCLs) [20]. The *C. albicans* was grown for 48 h at 28°C in YPD broth (1% yeast extract, 2% peptone, and 2% dextrose), harvested by centrifugation, and then washed twice with sterile distilled water. *A. fumigatus*, *T. rubrum*, and *T. mentagrophytes* were plated in potato dextrose agar (PDA) (Difco) and incubated at 28°C for 2 weeks. Spores were washed three times with sterile distilled water and resuspended in distilled water to obtain an initial inoculum size of 10^5 spores/mL. Each test compound was dissolved in DMSO and diluted with potato dextrose broth (Difco) to prepare serial twofold dilutions in the range 100 to 0.8 μg/mL. Ten microliters of the broth containing about 10^3 (for yeast) and 10^4 (for filamentous fungi) cells/mL of test fungi was added to each well of a 96-well microtiter plate. Culture plates were incubated for ~48–72 h at 28°C. The antifungal activity of each compound was compared with the standard drug Amphotericin B. Minimum inhibitory concentration (MIC, μg/mL) was measured and compared with controls; the MIC values of the compounds screened are presented in Table 2.

The antifungal screening data showed only moderate activity of the tested compounds. Among the screened compounds, **8b**, **8g**, and **8i** in which isoxazole moiety bearing 4-bromophenyl, 5-thiazole, and 2-pyrazine nucleus, respectively, were showed high activity against all the microorganisms employed. The activities of these three compounds are almost equal to the standard. It is

Table 2

Antifungal activity of compounds **8a–i**.

	Minimum inhibitory concentration (MIC, μg/mL)			
Compd.	*Candida albicans*	*Aspergillus fumigatus*	*Trichophton rubrum*	*Trichophyton mentagrophytes*
8a	25.0[a] (50.0)[b]	50.0[a] (—)[b]	25.0[a] (—)[b]	50.0[a] (—)[b]
8b	3.12 (12.5)	3.12 (12.5)	3.12 (12.5)	3.12 (12.5)
8c	12.5 (12.5)	25.0 (25.0)	25.0 (50.0)	6.25 (12.5)
8d	6.25 (25.0)	25.0 (50.0)	— (—)	12.5 (50.0)
8e	12.5 (25.0)	12.5 (25.0)	6.25 (—)	6.25 (25.0)
8f	25.0 (50.0)	12.5 (25.0)	6.25 (25.0)	6.25 (25.0)
8g	3.12 (25.0)	3.12 (12.5)	3.12 (6.25)	3.12 (12.5)
8h	12.5 (50.0)	3.12 (6.25)	3.12 (25.0)	3.12 (6.25)
8i	3.12 (25.0)	3.12 (12.5)	3.12 (12.5)	3.12 (12.5)
Amphotericin B	6.25	3.12	3.12	3.12

— Indicates fungi are resistant to the compound >50 μg/mL conc.

[a] Activity of dimeric compounds.

[b] Activity of their monomeric compounds.

also interesting to note that the compounds **8b**, **8g**, and **8i** showed activity toward *C. albicans* at the concentration of 3.12 μg/mL, which is less than the concentration of the standard Amphotericin B. Similarly, compound **8h** in which isoxazole ring bearing 2-pyridine nucleus, also showed good antifungal activity equal to the activity of the standard but only toward *A. fumigatus* and *T. rubrum*. The remaining compounds showed moderate to good antifungal activity. Furthermore, the activity of dimeric compounds was compared with that of their monomeric compounds prepared from the reported method [17]. The results reveal that almost all the dimeric compounds showed enhanced activity than their monomeric compounds (Table 2).

In conclusion, a new class of methylene-bis-4,6-diarylbenzo[*d*]isoxazoles **8a–i** has been designed and synthesized. The antifungal activity of these compounds was evaluated against various fungi. Among the synthesized compounds, **8b**, **8g**, and **8i** showed good activity against test fungi and emerged as potential molecules for further development. With this set of analogues, we are now in a position to investigate the multiple biological activities for these compounds.

EXPERIMENTAL

All the chemicals and solvents were of analytical grade and used as purchased. A proper safety measure was taken while carring out the reactions. Evaporations were performed at reduced pressure below 40°C. The reactions and purifications were monitored by TLC on aluminium sheets coated with silica gel 60 F_{254} (Merck), column chromatography on silica gel 60 (Merck). Melting points were taken using a Fisher-Johns melting point instrument and are uncorrected. IR spectra were obtained on a Perkin-Elmer FTIR 5000 spectrometer, using KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were obtained with Varian Gemini (^{1}H: 300 MHz, ^{13}C: 75 MHz) spectrometer, and the chemical shifts were reported as parts per million (δ ppm) down field from internal tetramethylsilane and coupling constants (*J*) in Hz. Mass spectra were obtained on a VG Micromass 7070H spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 CHN elemental analyzer.

Ethyl-6-(5-{3-[6-(ethoxycarbonyl)-5-oxo-3-phenyl-3-cyclohexenyl]-4-hydroxybenzyl}-2-hydroxyphenyl)-2-oxo-4-phenyl-3-cyclohexene-1-carboxylate (4a). To a solution of sodium metal (2 g) in ethanol (30 mL), a mixture of freshly distilled ethylacetoacetate (3.9 mL, 0.03 mol) and compound **3a** (4.6 g, 0.01 mol) dissolved in ethanol (20 mL) was added. The resulting solution was refluxed on a water bath for 4 h. Allowing the reaction mixture to cool and crystallization of the formed precipitate from ethanol gave **4a** (82% yield) as brown solid; mp 150–152°C; ^{1}H NMR (DMSO-d_6): δ 1.10 (6H, t, CH_3), 2.87 (4H, d, CH_2), 3.72 (2H, s, CH_2), 3.81 (2H, d, CH), 3.87 (2H, q, CH), 4.06 (4H, q, CH_2), 5.20 (2H, s, OH), 6.10 (2H, s, CH), 6.62 (2H, d, $J = 9.2$ Hz, ArH), 6.79 (2H, d, $J = 9.2$ Hz, ArH), 6.80 (2H, s, ArH), 7.10–7.14 (10H, m, ArH); ^{13}C NMR (DMSO-d_6): δ 17.0, 30.7, 37.0, 42.1, 60.6, 61.2, 117.4, 121.9, 123.8, 125.5, 127.9, 128.2, 128.7, 130.0, 133.4, 142.3, 149.5, 154.6, 176.7, 190.1; IR (KBr): υ 3452, 3065, 1702, 1695, 1597, 1245 cm^{-1}; MS: *m/z* 685 (M^+ +1). The other compounds **4b–i** were also prepared by the similar procedure.

5-{2-Hydroxy-5-[4-hydroxy-3-(5-oxo-3-phenyl-3-cyclohexenyl)benzyl]phenyl-3-phenyl}-2-cyclohexen-1-one (5a). To a mixture of glacial AcOH (100 mL) and conc. HCl (50 mL) was added compound **4a** (6.5 g, 0.01 mol) in portions. The mixture was heated to reflux for 10 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The residue was taken up with ethyl acetate and washed with water and brine, dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give oil, which soon solidified. It was purified by recrystallization from ethanol to give compound **5a** (79% yield) as brown solid; mp 132–134°C; ^{1}H NMR (DMSO-d_6): δ 2.67 (4H, d, CH_2), 2.70 (4H, d, CH_2), 3.72 (2H, s, CH_2), 3.83 (2H, m, CH), 5.20 (2H, s, OH), 6.10 (2H, s, CH), 6.62 (2H, d, $J = 9.2$ Hz, ArH), 6.82 (2H, s, ArH), 7.00 (2H, d, *J* = 9.2 Hz, ArH), 7.10–7.14 (10H, m, ArH); ^{13}C NMR (DMSO-d_6): δ 31.0, 38.9, 42.0, 47.5, 116.1, 122.6, 124.5, 126.2, 127.4, 127.8, 128.5, 131.2, 132.3, 140.5, 150.1, 155.2, 198.0; IR (KBr): υ 3357, 3025, 2932, 1687, 1596 cm^{-1}; MS: *m*/*z* 541 (M$^+$ +1). The other compounds **5b–i** were also prepared by the similar procedure.

5-[2-Hydroxy-5-(4-hydroxy-3-{6-[(*Z*)-1-hydroxymethylidene]-5-oxo-3-phenyl-3-cyclohexenyl}benzyl)phenyl]-6-[(*Z*)-1-hydroxymethylidene]-3-phenyl-2-cyclohexen-1-one (6a). In a solution of 10% sodium methoxide (10 mL) in benzene (25 mL), ethylformate (2.24 mL, 0.03 mol) was added and then compound **5a** (5.4 g, 0.01 mol), dissolved in benzene (10 mL), was added over 30 min. The resulting solution was stirred for 10 h at room temperature and allowed to stand overnight, then evaporated to dryness. The suspension obtained was mixed with cold water, acidified with dil HCl (20 mL), and extracted three times with ether (40 mL). The organic layer was dried over $MgSO_4$, evaporated *in vacuo* to give solid, and purified by crystallization in ethanol to afford pure 6a (81% yield) as yellow solid; mp 143–145°C; ^{1}H NMR (DMSO-d_6): δ 3.22 (4H, d, CH_2), 3.72 (2H, s, CH_2), 4.12 (2H, t, CH), 5.67 (2H, s, CH), 6.40–6.49 (4H, m, ArH), 6.80 (2H, s, ArH), 7.10–7.14 (10H, m, ArH), 7.92 (2H, s, CH), 8.97 (2H, s, OH); ^{13}C NMR (DMSO-d_6):δ 37.8, 42.0, 44.1, 115.5, 116.7, 126.2, 127.6, 127.9, 128.0, 128.9, 130.2, 130.6, 131.1, 142.0, 149.7, 156.1, 167.6, 191.3; IR (KBr): υ 3320, 3028, 2952, 1662, 1620, 1597 cm^{-1}; MS: *m*/*z* 596 (M$^+$). The other compounds **6b–i** were also prepared by the similar procedure.

4-[4-Hydroxy-3-(6-phenyl-4,5-dihydrobenzo[*d*]isoxazol-4-yl)benzyl]-2-(6-phenyl-4,5-dihydrobenzo[*d*]isoxazol-4-yl)phenol (7a). To a solution of 6a (5.9 g, 0.01 mol) in glacial acetic acid (50 mL), hydroxylamine hydrochloride (2.0 g, 0.03 mol) was added. After stirring at 80°C for 10 h, the mixture was concentrated *in vacuo*. To the residue was added water and twice extracted with ether. The organic layer was washed with saturated $NaHCO_3$ solution, subsequently with water and birne, dried over $MgSO_4$ and evaporated to dryness. The residue was recrystallized from ethanol to afford 7a (79% yield) as brown solid; mp 123–125°C; ^{1}H NMR (DMSO-d_6): δ 2.82 (4H, d, CH_2), 3.72 (2H, s, CH_2), 4.22 (2H, t, CH), 4.62 (2H, s, OH), 6.70 (2H, s, ArH), 6.73 (2H, d, *J* = 9.0 Hz, ArH), 6.84 (2H, d, *J* = 9.1 Hz, ArH), 6.99 (4H, m, ArH), 7.00 (2H, s, ArH), 7.21 (2H, s, ArH), 7.32 (4H, d, *J* = 9.2 Hz, ArH); ^{13}C NMR (DMSO-d_6): δ 38.1, 39.3, 42.1, 110.5, 117.2, 118.7, 125.4, 126.5, 127.8, 128.0, 128.9, 130.0, 132.0, 132.8, 140.3, 143.4, 156.2, 161.7; IR (KBr): 3390, 3037, 2972, 1609, 1470, 1030 cm^{-1}; MS: *m*/*z* 590 (M$^+$). The other compounds **7b–i** were also prepared by the similar procedure.

4-[4-Hydroxy-3-(6-phenylbenzo[*d*]isoxazol-4-yl)benzyl]-2-(6-phenylbenzo[*d*]isoxazol-4-yl)phenol (8a). To a solution of **7a** (5.9 g, 0.01 mol) in dry benzene (20 mL), DDQ (6.81 g, 0.03 mol), dissolved in dry benzene (20 mL), was added in portions. The mixture was heated to reflux and stirred for 5 h under nitrogen atmosphere. The precipitated DDQ-H_2 was filtered off and the filtrate was subjected to column chromatography on silica gel (60–120 mesh) to afford pure **8a** (78% yield) as orange solid; mp 158–160°C; ^{1}H NMR (DMSO-d_6): δ 3.99 (2H, s, CH_2), 4.65 (2H, s, OH), 6.90 (2H, s, ArH), 6.99 (2H, d, *J* = 8.9 Hz, ArH), 7.29 (2H, d, *J* = 8.9 Hz, ArH), 7.44–7.50 (10H, m, ArH), 7.90 (2H, s, ArH), 8.20 (2H, s, ArH), 8.60 (2H, s, ArH); ^{13}C NMR (DMSO-d_6): δ 40.7, 115.1, 117.0, 125.4, 127.0, 127.9, 128.3, 130.0, 133.2, 134.7, 137.4, 144.9, 145.2, 150.4, 151.2, 153.6, 159.3, 171.4; IR (KBr): υ 3344, 3062, 2972, 1609, 1470, 1030 cm^{-1}; MS: *m*/*z* 586 (M$^+$). Anal. calcd. for $C_{39}H_{26}N_2O_4$: C, 79.85; H, 4.47; N, 4.78. Found: C, 79.90; H, 4.39; N, 4.71. The other compounds **8b–i** were also prepared by the similar procedure.

2-[6-(4-Bromophenyl)benzo[*d*]isoxazol-4-yl]-4-3-[6-(4-bromophenyl)benzo[*d*]isoxazol-4-yl]-4-hydroxybenzylphenol (8b). This compound was obtained as brown solid; yield 84%; mp 171–172°C; ^{1}H NMR (DMSO-d_6): δ 4.00 (2H, s, CH_2), 4.65 (2H, s, OH), 6.90 (2H, s, ArH), 7.00 (2H, d, *J* = 8.9 Hz, ArH), 7.29 (2H, d, *J* = 8.9 Hz, ArH), 7.40–7.45 (8H, m, ArH), 7.90 (2H, s, ArH), 8.20 (2H, s, ArH), 8.60 (2H, s, ArH); ^{13}C NMR (DMSO-d_6): δ 40.7, 115.0, 117.1, 122.1, 125.4, 130.0, 130.6, 132.3, 133.1, 134.6, 137.3, 141.3, 144.9, 147.1, 151.3, 153.6, 159.4, 171.4; IR (KBr): υ 3390, 3065, 2995, 1609, 1470, 1030, 586 cm^{-1}; MS: *m*/*z* 742/744/746 (M$^+$). Anal. calcd. for $C_{39}H_{24}Br_2N_2O_4$: C, 62.92; H, 3.25; N, 3.76. Found: C, 62.85; H, 3.30; N, 3.70.

2-[6-(4-Aminophenyl)benzo[*d*]isoxazol-4-yl]-4-3-[6-(4-aminophenyl)benzo[*d*]isoxazol-4-yl]-4-hydroxybenzylphenol (8c). This compound was obtained as brown solid; yield 79%; mp 158–160°C; ^{1}H NMR (DMSO-d_6): δ 4.06 (2H, s, CH_2), 4.65 (2H, s, OH), 6.68 (4H, d, *J* = 8.5 Hz, ArH), 6.90 (2H, s, ArH), 7.00 (2H, d, *J* = 8.9 Hz, ArH), 7.31 (2H, d, *J* = 8.9 Hz, ArH), 7.52 (4H, d, *J* = 8.5 Hz, ArH), 7.90 (2H, s, ArH), 8.20 (2H, s, ArH), 8.60 (2H, s, ArH); ^{13}C NMR (DMSO-d_6): δ 40.7, 115.9, 116.7, 125.3, 127.3, 128.5, 130.1, 133.0, 134.1, 134.7, 137.5, 139.6, 144.5, 146.3, 151.2, 153.4, 159.2, 171.3; IR (KBr): υ 3390, 3065, 2972, 1612, 1469, 1028 cm^{-1}; MS: *m*/*z* 616 (M$^+$). Anal. calcd. for $C_{39}H_{28}N_4O_4$: C, 75.96; H, 4.58; N, 9.09. Found: C, 75.85; H, 4.60; N, 9.03.

2-[6-(4-Chlorophenyl)benzo[*d*]isoxazol-4-yl]-4-3-[6-(4-chlorophenyl)benzo[*d*]isoxazol-4-yl]-4-hydroxybenzylphenol (8d). This compound was obtained as yellow solid; yield 86%; mp 144–146°C; ^{1}H NMR (DMSO-d_6): δ 4.02 (2H, s, CH_2), 4.68 (2H, s, OH), 6.90 (2H, s, ArH), 7.00 (2H, d, *J* = 8.9 Hz, ArH), 7.31 (2H, d, *J* = 8.9 Hz, ArH), 7.39 (4H, d, *J* = 8.1 Hz, ArH), 7.83 (4H, d, *J* = 8.1 Hz, ArH), 7.90 (2H, s, ArH), 8.22 (2H, s, ArH), 8.51 (2H, s, ArH); ^{13}C NMR (DMSO-d_6): δ 40.7, 115.7, 117.2, 125.4, 127.3, 128.5, 130.1, 133.0, 134.1, 134.7, 137.5, 139.6, 144.5, 146.3, 151.2, 153.4, 159.2, 171.3; IR (KBr): υ 3384, 3062, 2968, 1605, 1470, 1028, 782 cm^{-1}; MS: *m*/*z* 654/656/658 (M$^+$). Anal. calcd. for $C_{39}H_{24}Cl_2N_2O_4$: C, 71.46; H, 3.69; N, 4.27. Found: C, 71.42; H, 3.61; N, 4.31.

4-4-Hydroxy-3-[6-(4-methoxyphenyl)benzo[*d*]isoxazol-4-yl]benzyl-2-[6-(4-methoxyphenyl)benzo[*d*]isoxazol-4-yl]phenol (8e). This compound was obtained as yellow solid; yield 77%; mp 135–137°C; ^{1}H NMR (DMSO-d_6): δ 3.81 (6H, s, OMe), 4.02 (2H, s, CH_2), 4.70 (2H, s, OH), 6.90 (2H, s, ArH), 6.96 (4H, d, *J* = 8.4 Hz, ArH), 7.00 (2H, d, *J* = 8.9 Hz, ArH), 7.32 (2H, d, *J* = 8.9 Hz, ArH), 7.34 (4H, d, *J* = 8.4 Hz, ArH), 7.90 (2H, s, ArH), 8.22 (2H, s, ArH), 8.51 (2H, s, ArH); ^{13}C NMR (DMSO-d_6): δ 40.5, 54.7, 115.0, 112.1, 117.0, 125.0, 129.5, 130.1, 133.1, 134.1, 137.3, 139.5, 144.3, 147.2, 151.1, 153.5, 159.1, 160.7, 172.1; IR (KBr): υ 3384, 3062, 2968, 1605, 1470, 1240 cm^{-1}; MS: *m*/*z* 646 (M$^+$). Anal. calcd. for $C_{41}H_{30}N_2O_6$: C, 76.15; H, 4.68; N, 4.33. Found: C, 76.21; H, 4.61; N, 4.35.

2-[6-(2-Furyl)benzo[*d*]isoxazol-4-yl]-4-3-[6-(2-furyl)benzo-[*d*]isoxazol-4-yl]-4-hydroxybenzylphenol (8f). This compound was obtained as black solid; yield 80%; mp 162–163°C; ^{1}H

NMR (DMSO-d_6): δ 4.02 (2H, s, CH_2), 4.70 (2H, s, OH), 6.34 (2H, m, ArH), 6.82 (2H, s, ArH), 6.70 (2H, m, ArH), 6.96 (2H, d, J = 8.9 Hz, ArH), 7.32 (2H, d, J = 8.9 Hz, ArH), 7.39 (2H, m, ArH), 7.90 (4H, m, ArH), 8.00 (2H, s, ArH), 8.22 (2H, s, ArH); ^{13}C NMR (DMSO-d_6): δ 40.8, 106.2, 106.5, 114.4, 115.1, 121.7, 126.9, 134.1, 138.7, 139.6, 141.9, 143.1, 151.1, 159.1, 159.8, 176.4; IR (KBr): υ 3390, 3071, 2965, 1609, 1470, 1030 cm^{-1}; MS: m/z 566 (M^+). Anal. calcd. for $C_{35}H_{22}N_2O_6$: C, 74.20; H, 3.91; N, 4.94. Found: C, 74.12; H, 3.90; N, 4.83.

4-4-Hydroxy-3-[6-(1,3-thiazol-5-yl)benzo[*d*]isoxazol-4-yl]-benzyl-2-[6-(1,3-thiazol-5-yl)benzo[*d*]isoxazol-4-yl]phenol (8g). This compound was obtained as brown solid; yield 82%; mp 149–150°C; ^{1}H NMR (DMSO-d_6): δ 4.02 (2H, s, CH_2), 4.70 (2H, s, OH), 6.74 (2H, s, ArH), 6.96 (2H, d, J = 8.9 Hz, ArH), 7.32 (2H, d, J = 8.9 Hz, ArH), 7.90–7.95 (4H, m, ArH), 8.10 (2H, s, ArH), 8.22 (2H, s, ArH), 8.62 (2H, s, ArH); ^{13}C NMR (DMSO-d_6): δ 40.6, 105.9, 115.1, 120.1, 120.9, 126.3, 134.0, 137.4, 138.3, 138.9, 140.5, 142.7, 150.9, 151.7, 158.4, 160.3, 173.1; IR (KBr): υ 3390, 3071, 2965, 1609, 1580, 1470, 638 cm^{-1}; MS: m/z 600 (M^+). Anal. calcd. for $C_{33}H_{20}N_4O_4S_2$: C, 65.99; H, 3.36; N, 9.33. Found: C, 65.89; H, 3.40; N, 9.24.

4-4-Hydroxy-3-[6-(2-pyridyl)benzo[*d*]isoxazol-4-yl]benzyl-2-[6-(2-pyridyl)benzo[*d*]isoxazol-4-yl]phenol (8h). This compound was obtained as brown solid; yield 77%; mp 151–153°C; ^{1}H NMR (DMSO-d_6): δ 4.02 (2H, s, CH_2), 4.68 (2H, s, OH), 6.51 (2H, s, ArH), 7.00 (4H, m, ArH), 7.31 (2H, d, J = 8.9 Hz, ArH), 7.59 (2H, m, ArH), 7.72 (2H, m, ArH), 7.92 (2H, s, ArH), 8.22 (2H, s, ArH), 8.62 (2H, d, J = 4.7 Hz, ArH), 8.92 (2H, s, ArH); ^{13}C NMR (DMSO-d_6): δ 40.8, 115.0, 117.0, 121.7, 124.7, 125.3, 130.1, 133.0, 134.0, 135.3, 137.1, 144.1, 144.8, 146.3, 151.1, 153.4, 157.9, 160.3, 169.4; IR (KBr): υ 3390, 3072, 2969, 1605, 1470 cm^{-1}; MS: m/z 588 (M^+). Anal. calcd. for $C_{37}H_{24}N_4O_4$: C, 75.50; H, 4.11; N, 9.52. Found: C, 75.41; H, 4.15; N, 9.47.

4-4-Hydroxy-3-[6-(2-pyrazinyl)benzo[*d*]isoxazol-4-yl]benzyl-2-[6-(2-pyrazinyl)benzo[*d*]isoxazol-4-yl]phenol (8i). This compound was obtained as black solid; yield 81%; mp 162–164°C; ^{1}H NMR (DMSO-d_6): δ 4.02 (2H, s, CH_2), 4.68 (2H, s, OH), 6.72 (2H, s, ArH), 7.00 (2H, d, J = 8.9 Hz, ArH), 7.31 (2H, d, J = 8.9 Hz, ArH), 7.90 (2H, s, ArH), 8.22 (2H, s, ArH), 8.41 (2H, d, J = 2.7 Hz, ArH), 8.64 (2H, d, J = 2.7 Hz, ArH), 8.80 (2H, s, ArH), 8.92 (2H, s, ArH); ^{13}C NMR (DMSO-d_6): δ 40.7, 110.7, 115.1, 127.1, 130.4, 134.0, 137.1, 138.0, 142.1, 143.4, 143.9, 144.1, 144.9, 146.3, 151.2, 156.7, 158.4, 169.4; IR (KBr): υ 3384, 3062, 2968, 1609, 1470, 1028, cm^{-1}; MS: m/z 590 (M^+). Anal. calcd. for $C_{35}H_{22}N_6O_4$: C, 71.18; H, 3.75; N, 14.23. Found: C, 71.11; H, 3.74; N, 14.17.

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In Situ Vinylpyrrole Synthesis. Diels-Alder Reactions with Maleimides to Give Tetrahydroindoles

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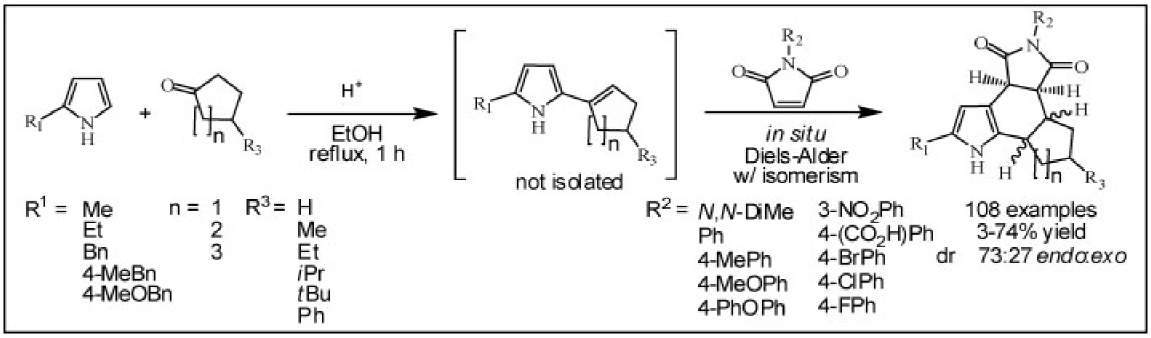

A series of 108 tetrahydroindoles has been prepared by a one-pot synthesis from 2-alkylpyrroles, cyclic ketones, maleimides, and an acid catalyst. A 5-vinylpyrrole is formed by an acid-catalyzed condensation of a 2-alkyl-substituted pyrrole with a ketone, which is subsequently trapped *in situ* by a maleimide in a predominantly *endo*-addition Diels-Alder reaction. Isomerization of the double bond into the pyrrole ring gives a tetrahydroindole with predominant *cis*-fusion of the cycloalkane ring.

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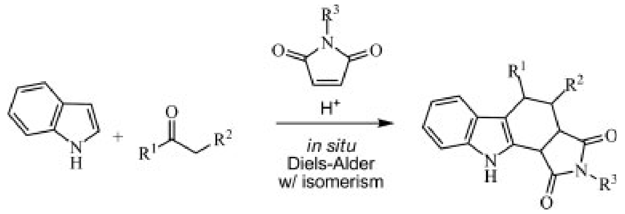
INTRODUCTION

The common occurrence of indole in biologically active compounds [1] highlights the importance of studies on the synthesis of indoles as well as the value of biological testing of indole-containing molecules. Previously, our group has reported the synthesis of 3-vinylindoles, which are trapped *in situ* by a Diels-Alder reaction with various maleimides, a technique which was used to prepare a large variety of tetrahydrocarbazoles [2]. We now wish to report analogous work with cycloadditions of 2-alkyl-substituted vinylpyrroles.

Pyrrole preferentially undergoes electrophilic attack at its 2-position since the most stable resonance structure of the reactive species has its greatest electron density α to the iminium nitrogen. For indole, dearomatization of the fused benzene ring inhibits a similar adjacent placement of charge. Instead, the highest electron-density occurs at the 3-position; thus, indole has favored electrophilic substitution at the 3-position in spite of greater charge separation. Correspondingly, our previous work involved the trapping of 3-vinylindoles produced from condensation of indole with ketones (Scheme 1), whereas in this work, the trapped intermediates are 2-vinylpyrroles. This has bearing on the topology; the products of this work are *e*-side maleimide-fused tetrahydroindoles, whereas the tetrahydroindole component of the products of the vinylindole work is maleimide-fused at the *g*-side.

There are several known examples of 2-vinylpyrroles participating in Diels-Alder reactions [3], including employing as the dienophiles carboxyl-substituted acetylenes [4,5], several acyclic electron-deficient alkenes [5,6], maleic anhydride and/or *N*-phenylmaleimide with *N*-benzenesulfonyl-2-vinylpyrrole [6,7] and methyl 3-nitroacrylate with *N*-*p*-toluenesulfonyl-2-vinylpyrroles [8], tetrachloro- or tetrabromocyclopropene with *N*-*p*-toluenesulfonyl-2-vinylpyrrole [9], *N*-phenylmaleimide with *N*-methyl- and *N*-propanoyloxy-2-vinylpyrrole [6], *N*-H-maleimide with 3-(*N*-alkyl-2-pyrrolyl)acrylates [10] and *N*-alkyl-2-styrylpyrroles [10,11], and one example using various maleimides with both *N*-H and *N*-alkyl-2-vinylpyrroles [12]. Several of these studies report biological activity from this class of compounds, particularly anticancer activity [10–12]. To our knowledge, no prior demonstration of 2-vinylpyrrole formation accompanied by *in situ* trapping with a dienophile exists, a route which avoids the multiple steps involved in synthesizing the vinylpyrrole before the Diels-Alder reaction, affording considerable efficiency over the alternative procedures available for tetrahydroindole formation.

Scheme 1. *In situ* synthesis of tetrahydrocarbazoles from ketones.



RESULTS AND DISCUSSION

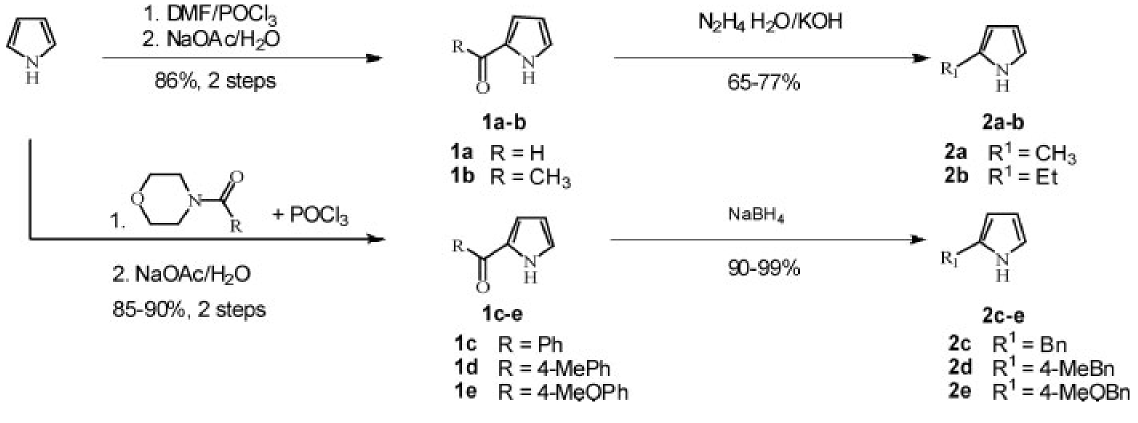
General. Pyrrole is a reactive electron-rich heterocycle which, upon condensation with cyclic ketones, followed by proton-transfer, is believed to form a tertiary alcohol. In the presence of an acid catalyst, the alcohol should readily dehydrate, forming a resonance-stabilized 2-vinylpyrrole. The highly reactive 2-vinylpyrrole is then captured *in situ* by the dienophile. Under acidic conditions, pyrroles are known to form polymers [13]. Tetrameric calix [4] pyrroles are known to form when pyrroles and ketones react in the presence of an acid catalyst [14,15]. When producing vinylpyrroles for *in situ* trapping, we have found that blocking the other 2-position by use of 2-alkyl-substituted pyrroles is useful in preventing formation of complex polymeric mixtures, which generally appeared as dark sticky tars or black powders. Studies using removable blocking groups at the 2-position of pyrroles in the formation of vinylpyrroles for *in situ* trapping and other uses are currently ongoing in our laboratory.

2-Substituted-5-vinylpyrroles were synthesized as outlined in Scheme 2. Pyrrole-2-carboxaldehyde (**1a**) was synthesized *via* Vilsmeier-Haack formylation [16], followed by Wolff-Kishner reduction [17], to give 2-methylpyrrole (**2a**). Wolff-Kishner reduction of commercially available 2-acetylpyrrole (**1b**) produced 2-ethylpyrrole (**2b**) [17]. Vilsmeier-Haack aroylation [18] of pyrrole gave the 2-phenyl (**1c**), 2-(4-methylphenyl) (**1d**), and 2-(4-methoxyphenyl) (**1e**) ketones, which, after sodium borohydride reduction [19], gave the corresponding 2-benzylpyrroles (**2c**–**e**).

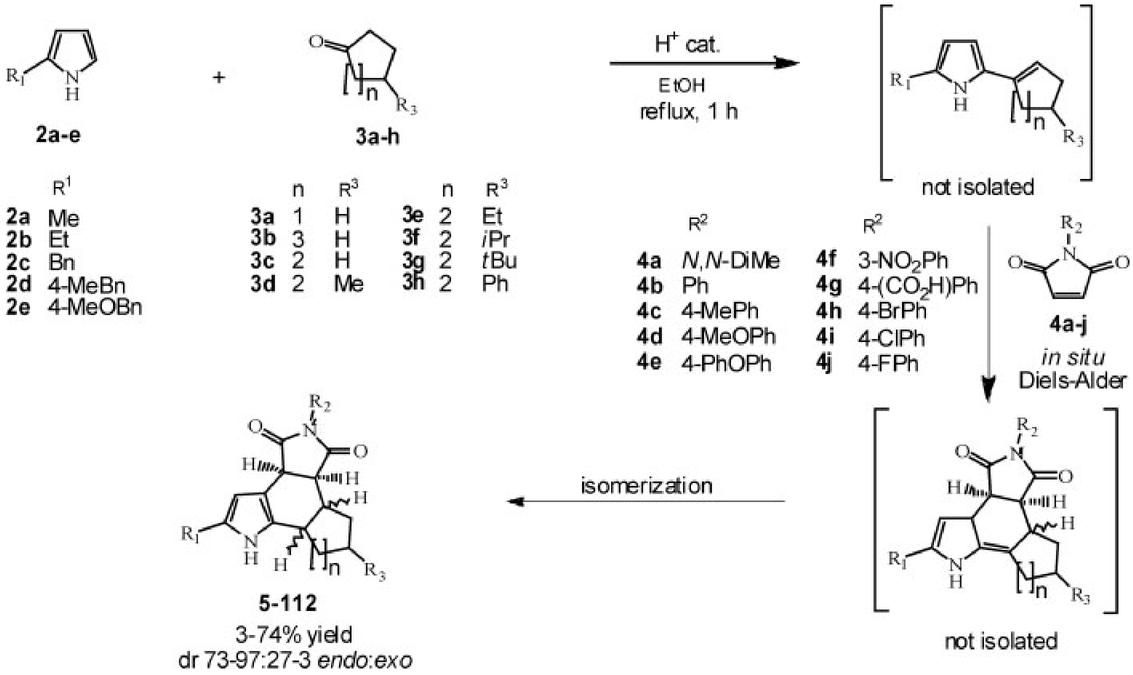
Condensation of **2a**–**e** with cyclopentanone (**3a**), variously 4-substituted-cyclohexanones (**3c**–**h**), or cycloheptanone (**3b**), gave the corresponding vinylpyrroles. These acted as electron-rich dienes for normal electron-demand Diels-Alder reactions, which occurred *in situ* with various substituted maleimides (**4a**–**j**, Scheme 3). The unrearranged form of the Diels-Alder adduct was not isolated. Instead, spontaneous isomerization of the double bond into the five-membered ring gave aromatized tetrahydroindoles (**5-112**, Table 1). *cis*-Fusion of the cycloalkyl ring involves less strain, but, since isomerism to the pyrrole is likely irreversible, thermodynamic equilibration may not determine the type of ring-fusion. Orbital symmetry considerations forbid suprafacial 1,3-hydride shifts and antarafacial 1,3-hydride shifts are geometrically difficult [20]; therefore, the isomerism probably takes place through acid catalysis. A proton should approach preferentially from the less sterically hindered face, the face opposite to the maleimide fusion and the same face from which protons 3b-H and 6a-H protrude (in the Experimental, this face is always designated "α"). This face of hydrogen delivery gives *cis*-fusion of the cycloalkyl ring with a *syn* relationship between all four of the protons on the cyclohexene ring.

The ^{1}H NMR data of **5-112** show mixtures of isomers, which were usually isolated by precipitation from the crude ethanolic reaction mixture, possibly influencing the reported distribution of isomers because of solubility differences. Both *endo*- and *exo*-Diels-Alder additions are possible, and *cis*- or *trans*-fusion gives the possibility of four isomers, *endo*-addition with *cis*-fusion (**En-c**), *endo*-addition with *trans*-fusion (**En-t**), *exo*-addition with *cis*-fusion (**Ex-c**), and *exo*-addition with *trans*-fusion (**Ex-t**, Fig. 1). Between one and four isomers are recognizable in each spectrum, corresponding to these stereoisomeric products. Smaller minor isomer peaks are

Scheme 2. Synthesis of 2-substituted pyrroles.



Scheme 3. *In situ* synthesis of tetrahydrocarbazoles fromcyclic ketones.



visible next to or overlapping the peaks belonging to the major isomer, particularly for protons 1-H, 3b-H, 6a-H, 6b-H, and the proton α to the point of cycloalkane ring-fusion to the pyrrole ring, labeled 9a-H, 10a-H, or 11a-H, the numbers depending on which sized cyclic ketone, **3a**, **3b**, or **3c–h**, was used.

In some products derived from the 4-substituted-cyclohexanones **3d–h**, additional isomerism is observed due to the stereogenic center at position 8 (see Fig. 1 for numbering). This is supported by the observation that the ratio of the integrated areas of proton peaks belonging to the alkyl substituents at position 8 is generally not equal to the ratio of *endo*/*exo*-addition *cis*/*trans*-fusion isomers present in the mixture determined from the integrated areas of protons 1-H, 3b-H, and 6a-H. Since our major concern in analyzing the ^{1}H NMR data is the diastereoselectivity of the Diels-Alder reaction and subsequent isomerization, it is the distribution of the four isomers **En-c**, **En-t**, **Ex-c**, and **Ex-t** that is reported in Table 1 and in the Experimental section, and it is these four isomers to which the text refers in subsequent discussion.

^{1}H NMR, nuclear Overhauser effect (NOE), and computational analyses. For all products, two isomers are present in greater quantity than the other two, corresponding to the expected *endo*-addition Diels-Alder products. At a minimum, in the isolated products, *endo*-addition is preferred over *exo*-addition in a 73:27 diastereomeric ratio, and at a maximum in a 97:3 diastereomeric ratio (in which no **Ex-c** and **Ex-t** isomers are visible by ^{1}H NMR). The *endo*-addition preference in Diels-Alder reactions is commonly explained by a favorable secondary orbital interaction that occurs in the transition state when the molecular orbitals of the carbonyls of the imide dienophile overlap with the developing molecular orbital from the diene, an interaction not present with an *exo*-approach. Although both stepwise and concerted mechanisms are theoretically possible to give tetrahydroindoles **5-112** [21], the stereochemical relationships found below in the major isomers are consistent with that expected for an *endo*-addition; therefore, a concerted reaction pathway is likely. To verify the *endo*-addition preference, and to confirm that *cis*-fusion is predominant, NOE experiments were performed on nine representative tetrahydroindoles, compounds **13**, **20**, **26**, **47**, **55**, **61**, **89**, **84**, and **103**.

Consistent NOE interactions were observed between the 3b-H and 6b-H protons of the two major isomers of each of these products, giving evidence that they arise from *endo*-addition. To determine whether *cis*- or *trans*-fusion occurred in a particular *endo*-addition isomer, NOE experiments must compare interactions of the protons at the points of the cycloalkane ring-fusion. In *trans*-fused products, the distance between the protons should be greater, giving a weaker NOE interaction. For careful comparison of the relative strength of these interactions, a reference NOE interaction of consistent strength should be present in each experiment. Because the distance between the proton α to the point of cycloalkane ring-fusion to the pyrrole ring and the 6a-H

Table 1

Summary of *in situ* cycloaddition results; see structures in Fig. 1.

No.	R^1	R^2	*n*	R^3	Yield %	Ratio of isomers			
						En-c:	En-t:	Ex-c[a]:	Ex-t
5	Me	Ph	1	H	62	3.4	1.0	0.1	
6	Me	4-MePh	1	H	42	3.9	1.0		
7	Me	4-*i*PrPh	1	H	50	7.0	1.0		
8	Me	4-MeOPh	1	H	46	5.4	1.0		
9	Me	4-PhOPh	1	H	52	7.6	1.0		
10	Me	3-NO_2Ph	1	H	35	9.0	1.0		
11	Me	4-(CO_2H)Ph	1	H	20	8.9	1.0	0.7	
12	Me	4-BrPh	1	H	63	4.2	1.0		
13	Me	4-ClPh	1	H	65	2.5	1.0		
14	Me	4-FPh	1	H	59	11.1	1.0		
15	Me	*N*,*N*-DiMe	2	H	45	19.2	1.0		
16	Me	*N*,*N*-DiMe	2	Et	49	8.4	1.0	0.2	
17	Me	*N*,*N*-DiMe	2	*i*Pr	42	1.0			
18	Me	*N*,*N*-DiMe	2	*t*Bu	52	2.4	1.0	0.1	
19	Me	*N*,*N*-DiMe	2	Ph	48	1.0			
20	Me	Ph	2	H	60	12.5	1.0		
21	Me	Ph	2	Me	48	1.8	1.0	0.3	
22	Me	Ph	2	Et	37	5.6	1.0	0.1	
23	Me	Ph	2	*i*Pr	39	5.0	1.0		
24	Me	Ph	2	*t*Bu	38	8.3	1.0	0.2	
25	Me	Ph	2	Ph	43	3.8	1.0		
26	Me	4-MePh	2	H	42	1.0	1.6		
27	Me	4-MePh	2	Me	37	1.1	1.0	0.1	
28	Me	4-MePh	2	Et	38	2.1	1.0		
29	Me	4-MePh	2	*i*Pr	41	3.2	1.0		
30	Me	4-MePh	2	*t*Bu	27	1.0	12.4	0.6	
31	Me	4-MePh	2	Ph	41	11.9	1.0		
32	Me	4-MeOPh	2	H	34	3.5	1.0		
33	Me	4-MeOPh	2	Me	61	2.3	1.0	0.3	
34	Me	4-MeOPh	2	Et	36	4.3	1.0	0.1	
35	Me	4-MeOPh	2	*i*Pr	74	2.9	1.0	0.3	0.3
36	Me	4-MeOPh	2	*t*Bu	35	4.4	1.0	0.3	
37	Me	4-MeOPh	2	Ph	57	4.7	1.0	0.8	
38	Me	4-PhOPh	2	H	44	5.0	1.0		
39	Me	4-PhOPh	2	Me	52	1.2	1.0	0.1	
40	Me	4-PhOPh	2	Et	46	1.7	1.0	0.3	
41	Me	4-PhOPh	2	*i*Pr	42	2.1	1.0	0.3	
42	Me	4-PhOPh	2	*t*Bu	30	4.8	1.0	0.9	
43	Me	4-PhOPh	2	Ph	48	5.4	1.0	1.0	0.7
44	Me	3-NO_2Ph	2	H	40	2.8	1.0		
45	Me	3-NO_2Ph	2	Me	44	3.7	1.0		
46	Me	3-NO_2Ph	2	Et	41	1.0	3.3		
47	Me	3-NO_2Ph	2	*i*Pr	30	2.8	1.0	0.2	
48	Me	3-NO_2Ph	2	*t*Bu	31	2.1	1.0		
49	Me	3-NO_2Ph	2	Ph	40	4.2	1.0	0.6	
50	Me	4-(CO_2H)Ph	2	H	31	1.5	1.0		
51	Me	4-(CO_2H)Ph	2	Me	31	1.6	1.0		
52	Me	4-(CO_2H)Ph	2	Et	31	3.7	1.0	0.1	
53	Me	4-(CO_2H)Ph	2	*i*Pr	30	5.3	1.0	0.2	
54	Me	4-(CO_2H)Ph	2	Ph	46	4.3	1.0		
55	Me	4-BrPh	2	H	41	1.8	1.0		
56	Me	4-BrPh	2	Me	49	3.6	1.0	0.2	
57	Me	4-BrPh	2	Et	47	3.0	1.0	0.3	0.3
58	Me	4-BrPh	2	*i*Pr	41	1.8	1.0	0.3	
59	Me	4-BrPh	2	*t*Bu	31	3.3	1.0	0.5	
60	Me	4-BrPh	2	Ph	43	2.2	1.0	0.6	0.1
61	Me	4-FPh	2	H	45	1.0	1.8		
62	Me	4-FPh	2	Me	38	1.6	1.0	0.2	

(*Continued*)

Table 1. (*Continued*)

No.	R^1	R^2	*n*	R^3	Yield %	Ratio of isomers En-c:	En-t:	Ex-c[a]:	Ex-t
63	Me	4-FPh	2	Et	44	1.0	2.3	0.6	
64	Me	4-FPh	2	*i*Pr	41	1.9	1.0	0.2	
65	Me	4-FPh	2	*t*Bu	34	1.6	1.0	0.3	0.2
66	Me	4-FPh	2	Ph	49	8.0	1.0	0.5	0.4
67	Me	Ph	3	H	21	3.4	1.0	0.9	
68	Me	4-*i*PrPh	3	H	3	3.0	1.0		
69	Me	4-MeOPh	3	H	11	1.9	1.0		
70	Me	3-NO_2Ph	3	H	24	4.1	1.0	0.7	
71	Me	4-ClPh	3	H	17	2.8	1.0		
72	Et	*N*,*N*-DiMe	2	H	28	8.5	1.0		
73	Et	*N*,*N*-DiMe	2	Et	31	4.1	1.0		
74	Et	*N*,*N*-DiMe	2	*t*Bu	23	14.0	1.0		
75	Et	Ph	2	H	48	1.4	1.0		
76	Et	Ph	2	Et	35	1.0	1.2	0.2	0.1
77	Et	Ph	2	*t*Bu	27	4.4	1.0	0.3	
78	Et	4-MeOPh	2	H	41	1.0	5.6		
79	Et	4-MeOPh	2	Et	36	6.5	1.0	0.3	
80	Et	4-MeOPh	2	*t*Bu	28	2.1	1.0	0.1	
81	Bn	*N*,*N*-DiMe	2	H	35	3.2	1.0		
82	Bn	*N*,*N*-DiMe	2	Et	29	5.3	1.0	0.3	
83	Bn	*N*,*N*-DiMe	2	*t*Bu	25	1.0			
84	Bn	Ph	2	H	56	3.6	1.0		
85	Bn	Ph	2	Et	36	1.0	1.7	0.6	0.4
86	Bn	Ph	2	*i*Pr	61	1.0	4.1	0.7	
87	Bn	Ph	2	*t*Bu	39	3.0	1.0	0.5	0.3
88	Bn	Ph	2	Ph	63	1.0	2.8		
89	Bn	4-MeOPh	2	H	59	3.0	1.0	0.3	
90	Bn	4-MeOPh	2	Et	36	2.5	1.0	0.3	0.2
91	Bn	4-MeOPh	2	*i*Pr	63	1.0	3.8	0.8	
92	Bn	4-MeOPh	2	*t*Bu	24	24.0	1.0	0.3	0.2
93	Bn	4-MeOPh	2	Ph	57	1.0	3.2	0.5	
94	4-MeBn	Ph	2	H	64	1.0	1.6		
95	4-MeBn	Ph	2	*i*Pr	61	1.0	2.7	0.8	
96	4-MeBn	Ph	2	Ph	64	1.0	5.0		
97	4-MeBn	4-MeOPh	2	H	65	1.0	1.9		
98	4-MeBn	4-MeOPh	2	*i*Pr	57	1.0	3.4	0.9	
99	4-MeBn	4-MeOPh	2	Ph	62	1.0	3.0		
100	4-MeOBn	*N*,*N*-DiMe	2	H	24	3.8	1.0		
101	4-MeOBn	*N*,*N*-DiMe	2	Et	22	4.0	1.0	0.2	
102	4-MeOBn	*N*,*N*-DiMe	2	*t*Bu	21	1.0			
103	4-MeOBn	Ph	2	H	60	1.0	1.8		
104	4-MeOBn	Ph	2	Et	32	1.1	1.0	0.3	0.3
105	4-MeOBn	Ph	2	*i*Pr	51	1.0	4.5	0.9	
106	4-MeOBn	Ph	2	*t*Bu	29	5.2	1.0	0.6	
107	4-MeOBn	Ph	2	Ph	61	1.0	5.2		
108	4-MeOBn	4-MeOPh	2	H	42	1.2	1.0		
109	4-MeOBn	4-MeOPh	2	Et	29	1.9	1.0	0.2	
110	4-MeOBn	4-MeOPh	2	*i*Pr	53	1.0	3.8	0.6	
111	4-MeOBn	4-MeOPh	2	*t*Bu	22	2.7	1.0	0.7	0.3
112	4-MeOBn	4-MeOPh	2	Ph	59	1.0	8.1		

[a] Ex-c is assumed to be the major *exo*-addition product.

proton should be relatively constant for the *cis*- and *trans*-fused products, NOE interactions between these two protons were used as the reference.

In the cyclohexanone-derived products, the ratio of the strength of the NOE interaction for the **En-c** isomer between the 10a-H and 6b-H protons (**a** in Fig. 2) to the 10a-H and 6a-H protons (**b**) should appear as markedly less than the ratio for the **En-t** isomer between the 10a-H and 6b-H protons (**a′**) to the 10a-H and 6a-H protons (**b′**). Restating using the labels of Figure 2, **a** is less than **a′**, and **b** is approximately equal to **b′**; therefore, **a**:**b** is less than **a′**:**b′**. For the two predominant isomers

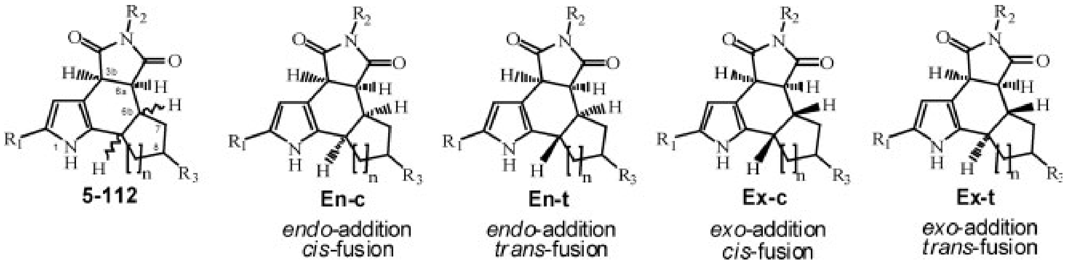


Figure 1. Stereochemistry of the tetrahydroindoles.

in the cyclohexanone-derived products, it was always observed that for one isomer the interaction between the 10a-H and 6b-H protons relative to that between the 10a-H and 6a-H protons was roughly one-third stronger (**En-c**) than for the other (**En-t**). This relationship was also observed for the cyclopentanone-derived product **13**. Thus, NOE evidence supports the assertion that the two most prevalent isomers are **En-c** and **En-t**. Unfortunately, in no ^{1}H NMR spectrum of the cycloheptanone-derived products were protons at position 11a sufficiently free from overlap to allow accurate observation and comparison of the NOE interactions.

To support the bond-length relationships used to analyze the results of the NOE experiments, a general simplified structure was used to perform computational analysis at the RHF/STO-6G level for the *endo*-addition cyclopentane, cyclohexane, and cycloheptane *cis*- and *trans*-fused products. In these simplified structures, the tetrahydroindole had a phenyl group at the 5-position and was unsubstituted at the 2-position. Calculations indicate that in the **En-c** isomer, the ratio of the distance between the proton at the point of the cycloalkane ring fusion α to the pyrrole and the 6b-H proton should differ significantly from the ratio of the distance between these protons in the **En-t** isomer. The computational models indicate that this ratio in the **En-t** isomer is 72.4, 69.2, and 69.5% of the ratio for the **En-c** isomer for the cyclopentane-, cyclohexane-, and cycloheptane-fused products, respectively.

In all nine of the representative NOE experiments performed, the ^{1}H NMR peak of the 1-H proton of the **En-c** isomer always appeared upfield from the peak corresponding to the 1-H proton of the **En-t** isomer. This consistent relationship made identifying the number of products having **En-t** as the major isomer a relatively simple process of inspecting the two predominant 1-H peaks in each spectrum; products with **En-t** as the major isomer display the unique signature of having their major 1-H peak farthest downfield. As expected, **En-c** is usually the major isomer. Out of 108 products, only 23 (21%) had **En-t** as the major isomer.

Based on the observation that there are a maximum of four isomers present, and the common general observations of minor *exo*-addition Diels-Alder products in the literature [22], it seems reasonable to assume that the minor peaks appearing in the ^{1}H NMR spectra indicate *exo*-addition products. Sufficient steric bulk of substituents on the ketone or maleimide may cancel out favorable secondary orbital interactions and allow some *exo*-approach Diels-Alder products. The two minor isomers were not present in sufficient concentration in any sample, nor were the 6b-H protons sufficiently resolved to perform NOE studies to confirm these assertions, or to check whether *cis*- or *trans*-fusion is predominant among the *exo*-addition isomers. Separation of *endo*- and *exo*-addition isomers was not achieved by chromatography nor by crystallization, which prevented analysis of individual isomers.

Diastereotopism of the protons on the methylene unit of a benzyl group is sometimes observed as second-order doublets. The 3bα-H proton appears as a doublet of doublets; COSY experiments indicate that the 3bα-H proton is coupled not only to the 6a-H proton but also to the proton at the point of cycloalkane ring-fusion α to the pyrrole ring (which would be the 10a-H proton in the cyclohexanone case), with a coupling constant of ~2.0 Hz [8,23]. In the 2-methyl compounds **5-71**, the 2-methyl group often appears as a doublet of doublets; COSY experiments indicate that this is due in part to ~0.9 Hz coupling with the 3-H proton [24]. COSY experiments suggest that the 2-methyl group is also sometimes coupled with the 1-H proton at ~0.9 Hz, though to the best of our knowledge, this type of coupling has no literature precedent.

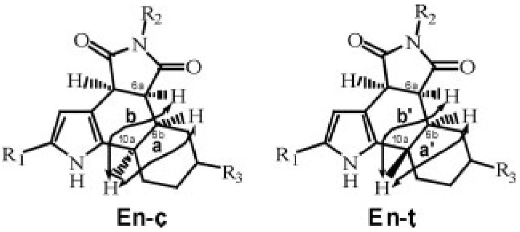


Figure 2. NOE interactions.

Biological activity. By participating in the Developmental Therapeutics Program at the National Cancer Institute (NCI), we submitted 32 representative compounds to the NCI for a one-dose three-human tumor cell line prescreen: compounds **20**, **22**, **24**, **32**, **34**, **72**, **73**, **74**, **75**, **76**, **77**, **78**, **79**, **80**, **81**, **82**, **83**, **84**, **85**, **87**, **89**, **90**, **92**, **100**, **101**, **102**, **103**, **104**, **106**, **108**, **109**, and **111**. Of these, seven compounds, **79**, **101**, **103**, **104**, **106**, **108**, and **109**, were judged by the NCI to have activity sufficient to justify screening with 60 human-tumor cell lines at five concentrations with 10-fold dilutions, from 1×10^{-4}M to 1×10^{-8}M. Of these seven compounds, compounds **103**, **106**, **108**, and **109**, were found to have high levels of activity against many of the 60 different cell lines tested. Compound **103** was most active against non-small cell lung cancer EKVX, with an IC_{50} of 113.2 μg/mL. Compound **109** was most active against colon cancer KM12, with an IC_{50} of 80.9 μg/mL. Compounds **106** and **108** were found to be active against several different cell-lines and were the best performing of the 32 compounds. Compound **106** had its highest activities against melanoma SK-MEL-5, colon cancer KM12, and breast cancer MDA-MB-435, with IC_{50} values of 62.5, 73.5, and 113.8 μg/mL, respectively. Compound **108** was most active against colon cancer HCT-15, with an IC_{50} value of 18.3 μg/mL.

CONCLUSIONS

In summary, a series of 108 novel tetrahydroindoles has been prepared *via* a Diels-Alder reaction of maleimides with 5-alkyl-2-vinylpyrroles formed *in situ* from an acid-catalyzed condensation between 2-alkylpyrroles and cyclic ketones. This one-pot method of tetrahydroindole synthesis is convenient and offers a fair-yielding and highly convergent synthetic route toward substituted indoles with good diastereoselectivity for the **En-c** isomer. Further extensions of this general methodology are currently underway in our laboratory.

EXPERIMENTAL

General. Solvents and reagents were purchased and used as received. Flash chromatography was performed using 230–450 mesh silica gel. TLC analyses were performed on plastic-backed plates precoated with 0.2 mm silica with F_{254} indicator. Infrared spectra were recorded on a 4000 FT-IR spectrometer; only the most intense and/or diagnostic peaks are reported. High-resolution mass spectra were recorded with a time-of-flight instrument using electrospray ionization with PEG as an internal calibrant. For NMR spectra, chemical shifts (δ) were referenced to the solvent. The abbreviations for splitting include: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C NMR spectra were proton decoupled. Melting points are uncallibrated. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

^{1}H NMR analyses. All the Diels-Alder products are identified such that both *endo*- and *exo*-addition products have their protons 3b-H and 6a-H in the α-orientation, as shown in Figure 1. Major and minor isomers are identified when possible with the abbreviations maj and min. The ratio of products is given such that the most prevalent minor isomer is 1.0 for easy readability of the *cis*:*trans* or *trans*:*cis* ratio of the *endo*-addition isomers. When the orientation of a proton is unclear, the orientation is omitted from the identification. Insufficient resolution or peak overlap sometimes leads to the labeling of a splitting pattern as ‘‘apparent’’ (app.), which is used when there are discrepancies between the splitting of the same proton of several isomers in a single ^{1}H NMR spectrum, or when it is certain that coupling from a particular proton occurs but is not visible.

Most of the protons of the fused cycloalkane rings appear upfield as multiplets. For compounds with more than one isomer present, it would be confusing and nonintuitive to label the integration of these multiplets with multiplicity that varies depending on the number of isomers present in the mixture. Therefore, when the peaks of all the isomers overlap into a single peak, the integration is designated as 1H. When it is clear that the protons of several but not all isomers overlap in a particular peak, this multiplicity is indicated with an integration larger than 1H. When it is not clear whether multiple peaks overlap, the integration reflects the number of protons which are thought to be definitely in the peak. Thus, sometimes, fewer isomers are identified for a particular proton than there are isomers present in the mixture, because it is not clear where the peak(s) from one isomer occurs.

With some protons, the peaks belonging to the various isomers overlap. In these cases, sometimes the peak is identified as it would be if there was a single isomer present, omitting the designation maj and min, and also omitting the designation α or β if the orientation is unknown or mixed. These designations are only omitted when it is clear, which isomers overlap into a single identified peak, and when it is clear, the protons are of mixed or unknown orientation. Overlap of signals from a proton with multiple orientations occurs most frequently with protons at the 6b-position in compounds with more than one minor isomer present. In the case of a compound with three isomers present, with the peak from 6bαmaj-H distinct but the peaks from the 6bαmin-H and 6bβmin-H protons overlapping into one, the overlapped peak is labeled 6b-H and is assigned an integration of two. This situation also occurs with peaks belonging to protons α to the point of cycloalkane ring fusion to the pyrrole ring in compounds with more than one isomer present.

General reaction conditions. Method A: A solution of the pyrrole (3.00 mmol), the cyclohexanone (4.00 mmol), and the maleimide (4.00 mmol) was heated to reflux in ethanol (5.0 mL). Hydrochloric acid (0.20 mL, 37% aqueous solution) was added to the hot solution, causing it to turn red-brown in color. The solution was refluxed for 1 h. In most cases, slow precipitation of the *in situ* product was observed throughout this time. After the mixture had cooled to rt, the precipitate was vacuum-filtered, washed with ethanol (5.0 mL), and reprecipitated from ethanol (5.0 mL). In cases where no precipitate was observed during reflux, which occurred particularly when 4-*tert*-butylcyclohexanone and/or 4-methoxyphenylmaleimide were used, the desired product was isolated by flash chromatography on silica gel using ethyl acetate:hexane as the eluent.

Method B: Hydrochloric acid (0.10 mL, 37% aqueous solution) was added to a solution of the pyrrole (5.00 mmol), the cyclic ketone (6.50–9.82 mmol), and the maleimide (4.80 mmol) in ethanol (15.0 mL), and the resulting solution was refluxed with stirring for 1–6 h, as determined by TLC. As the solution was allowed to cool to rt, a precipitate developed, which was vacuum-filtered. Purification to give the desired product was accomplished in one of several ways: (1) washing with diethyl ether (5–20 mL) and/or ethanol (5–20 mL), (2) reprecipitation from ethanol (15–20 mL) and/or diethyl ether (15–20 mL) and then, if necessary, washing with diethyl ether (5–20 mL), (3) purified using flash chromatography on silica gel, or (4) a combination of the above techniques, as noted.

Compounds 5 through 112. *2-Methyl-5-phenyl-3b,6a,6b,7,8,9,9a-heptahydro-1H,5H-cyclopenta[g]pyrrolo[3,4-e]indole-4,6-dione (5).* Method B with **3a** (800 mg, 9.50 mmol), 2-h reflux, ethanol wash (10 mL), and then a diethyl ether wash (10 mL) gave **5** (950 mg, 62%) as a colorless solid, a mixture of three isomers (maj:min:min = 3.4:1.0:0.1): mp 260–262°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.55 (bs, 1H, 1min-H), 8.22 (bs, 1H, 1min-H), 7.64 (bs, 1H, 1maj-H), 7.36–7.52 (m, 3H, Ph), 7.26–7.31 (m, 2H, Ph), 6.11 (dd, J = 2.6, 1.1 Hz, 1H, 3maj-H), 6.03–6.05 (m, 1H, 3min-H), 5.76 (app. d, J = 3.0 Hz, 1H, 3min-H), 4.02 (dd, J = 8.3, 1.7 Hz, 1H, 3bαmin-H), 4.01 (dd, J = 8.4, 1.8 Hz, 1H, 3bαmaj-H), 3.63 (dd, J = 8.9, 6.2 Hz, 1H, 6aαmin-H), 3.55 (dd, J = 8.4, 6.0 Hz, 1H, 6aαmaj-H), 3.20–3.27 (m, 1H, 9aαmaj-H), 3.10–3.16 (m, 1H, 9aβmin-H), 2.75–2.88 (m, 1H, 6b-H), 2.29 (s, 3H, 2-CH$_3$), 1.88–2.08 (m, 2H, cyclopent.), 1.57–1.75 (m, 3H, cyclopent.), 1.38–1.49 (m, 1H, cyclopent.); ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.48 (bs, 1H, 1min-H), 10.29 (bs, 1H, 1maj-H), 7.38–7.54 (m, 3H, Ph), 7.19–7.25 (m, 2H, Ph), 5.76 (dd, J = 2.3, 1.1 Hz, 1H, 3maj-H), 5.57 (dd, J = 2.3, 1.1 Hz, 1H, 3min-H), 4.18 (app. d, J = 8.7 Hz, 1H, 3bαmin-H), 4.05 (dd, J = 8.3, 2.0 Hz, 1H, 3bαmaj-H), 3.53 (dd, J = 8.3, 5.9 Hz, 1H, 6aαmin-H), 3.48 (dd, J = 8.3, 5.9 Hz, 1H, 6aαmaj-H), 3.07–3.14 (m, 1H, 9aαmaj-H), 2.99–3.04 (m, 1H, 9aβmin-H), 2.56–2.66 (m, 1H, 6b-H), 2.04–2.18 (m, 1H, cyclopent.), 2.15 (s, 3H, 2-CH$_3$), 1.77–1.94 (m, 1H, cyclopent.), 1.36–1.61 (m, 3H, cyclopent.), 1.15–1.30 (m, 1H, cyclopent.); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 178.4, 177.0, 132.2, 131.0, 129.3, 129.2, 128.5, 128.1, 127.8, 126.6, 115.5, 109.3, 108.7, 105.6, 104.1, 41.9, 41.7, 38.5, 37.2, 36.5, 31.1, 30.5, 24.9, 22.4, 21.9, 13.3; IR (thin film, cm^{-1}) 3397(bs), 3059(m), 2934(m), 2857(m), 1775(s), 1695(s), 1498, 1391(m), 1189(m), 1170(m); HRMS m/z (M + Na^{+}) calcd 343.1418, found 343.1417. Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 75.20; H, 6.16; N, 8.90.

2-Methyl-5-(4-methylphenyl)-3b,6a,6b,7,8,9,9a-heptahydro-1H,5H-cyclopenta[g]pyrrolo[3,4-e]indole-4,6-dione (6). Method B with **3a** (800 mg, 9.50 mmol), 3.5-h reflux, reprecipitation from ethanol (15 mL), and then a diethyl ether wash (10 mL) gave **6** (670 mg, 42%) as a colorless solid, a mixture of two isomers (maj:min = 3.9:1.0): mp 214–216°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.23 (bs, 1H, 1min-H), 7.65 (bs, 1H, 1maj-H), 7.27 (d, J = 7.8 Hz, 2H, Ph), 7.16 (d, J = 7.8 Hz, 2H, Ph), 6.11 (dd, J = 2.6, 1.1 Hz, 1H, 3maj-H), 5.75 (dd, J = 2.6, 0.75 Hz, 1H, 3min-H), 3.99 (dd, J = 8.6, 2.0 Hz, 1H, 3bα-H), 3.62 (dd, J = 8.9, 6.2 Hz, 1H, 6aαmin-H), 3.53 (dd, J = 8.3, 6.2 Hz, 1H, 6aαmaj-H), 3.19–3.26 (m, 1H, 9aαmaj-H), 3.10–3.16 (m, 1H, 9aβmaj-H), 2.73–2.88 (m, 1H, 6bα-H), 2.40 (s, 3H, 4′-CH$_3$ min), 2.39 (s, 3H, 4′-CH$_3$ maj), 2.28 (s, 3H, 2-CH$_3$), 1.88–2.07 (m, 2H, cyclopent.), 1.50–1.75 (m, 3H, cyclopent.), 1.25–1.49 (m, 1H, cyclopent.); ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.47 (d, J = 2.1 Hz, 1H, 1min-H), 10.28 (d, J = 1.8 Hz, 1H, 1maj-H), 7.28 (d, J = 7.8 Hz, 2H, Ph), 7.08 (d, J = 8.4 Hz, 2H, Ph), 5.75 (dd, J = 2.3, 1.1 Hz, 1H, 3maj-H), 5.57 (dd, J = 2.4, 0.6 Hz, 1H, 3min-H), 4.15 (dd, J = 7.2, 1.2 Hz, 1H, 3bαmin-H), 4.02 (dd, J = 8.4, 1.8 Hz, 1H, 3bαmaj-H), 3.51 (dd, J = 8.3, 5.9 Hz, 1H, 6aαmin-H), 3.46 (dd, J = 8.4, 6.0 Hz, 1H, 6aαmaj-H), 3.07–3.13 (m, 1H, 9aαmaj-H), 2.98–3.04 (m, 1H, 9aβmin-H), 2.52–2.65 (m, 1H, 6bα-H), 2.35 (s, 3H, 4′-CH$_3$ maj), 2.34 (s, 3H, 4′-CH$_3$ min), 2.02–2.18 (m, 1H, cyclopent.), 2.15 (s, 3H, 2-CH$_3$), 1.77–1.89 (m, 1H, cyclopent.), 1.34–1.60 (m, 3H, cyclopent.), 1.14–1.29 (m, 1H, cyclopent.); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 178.6, 177.1, 138.6, 130.0, 129.9, 129.5, 128.0, 127.8, 126.4, 108.7, 105.6, 104.1, 41.9, 41.8, 41.2, 38.5, 37.2, 36.5, 31.4, 30.5, 24.9, 24.5, 22.4, 21.9, 21.3, 13.3; IR (thin film, cm^{-1}) 3381(bs), 2948(m), 2871(m), 2366(w), 1775(w), 1706(s), 1514(m), 1383(m), 1194(m), 1179(m), 1162(m); HRMS m/z (M + Na^{+}) calcd 357.1574, found 357.1572. Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.38; H, 6.58; N, 8.55.

5-(4-Isopropylphenyl)-2-methyl-3b,6a,6b,7,8,9,9a-heptahydro-1H,5H-cyclopenta[g]pyrrolo[3,4-e]indole-4,6-dione (7). Method B with **3a** (800 mg, 9.50 mmol), 4-h reflux, and then a diethyl ether wash (20 mL) gave **7** (760 mg, 50%) as a colorless solid, a mixture of two isomers (maj:min = 7.0:1.0): mp 199–201°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.30 (bs, 1H, 1min-H), 7.69 (bs, 1H, 1maj-H), 7.32 (d, J = 8.4 Hz, 2H, Ph), 7.19 (d, J = 8.4 Hz, 2H, Ph), 6.11 (d, J = 1.8 Hz, 1H, 3maj-H), 5.75 (d, J = 2.1 Hz, 1H, 3min-H), 4.01 (dd, J = 8.3, 1.7 Hz, 1H, 3bαmin-H), 3.99 (dd, J = 8.4, 1.8 Hz, 1H, 3bαmaj-H), 3.62 (dd, J = 8.9, 6.2 Hz, 1H, 6aαmin-H), 3.53 (dd, J = 8.4, 5.7 Hz, 1H, 6aαmaj-H), 3.19–3.25 (m, 1H, 9aαmaj-H), 3.10–3.16 (m, 1H, 9aβmin-H), 2.96 (septet, J = 6.9 Hz, 1H, C*H*(CH$_3$)$_2$ min), 2.95 (septet, J = 6.9 Hz, 1H, C*H*(CH$_3$)$_2$ maj), 2.75–2.88 (m, 1H, 6bα-H), 2.28 (s, 3H, 2-CH$_3$), 1.88–2.09 (m, 2H, cyclopent.), 1.33–1.74 (m, 4H, cyclopent.), 1.271 (d, J = 6.9 Hz, 1H, CH(C*H*$_3$)$_2$ min), 1.269 (d, J = 6.6 Hz, 6H, CH(C*H*$_3$)$_2$ maj); ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.48 (d, J = 2.1 Hz, 1H, 1min-H), 10.28 (bs, J = 1.8 Hz, 1H, 1maj-H), 7.35 (d, J = 8.4 Hz, 2H, Ph), 7.12 (d, J = 8.4 Hz, 2H, Ph), 5.76 (d, J = 1.2 Hz, 1H, 3maj-H), 5.57 (d, J = 1.5 Hz, 1H, 3min-H), 4.16 (app. d, J = 8.4 Hz, 1H, 3bαmin-H), 4.03 (dd, J = 8.4, 1.8 Hz, 1H, 3bαmaj-H), 3.52 (dd, J = 8.3, 5.9 Hz, 1H, 6aαmin-H), 3.46 (dd, J = 8.4, 6.0 Hz, 1H, 6aαmaj-H), 3.03–3.14 (m, 1H, 9aαmaj-H), 2.97–3.04 (m, 1H, 9aβmin-H), 2.94 (septet, J = 6.9 Hz, 1H, C*H*(CH$_3$)$_2$ min), 2.93 (septet, J = 6.9 Hz, 1H, C*H*(CH$_3$)$_2$ maj), 2.53–2.65 (m, 1H, 6bα-H), 2.03–2.19 (m, 1H, cyclopent.), 2.15 (s, 3H, 2-CH$_3$), 1.77–1.91 (m, 1H, cyclopent.), 1.35–1.61 (m, 4H, cyclopent.), 1.23 (d, J = 6.9 Hz, 6H, CH(C*H*$_3$)$_2$ min), 1.22 (d, J = 6.9 Hz, 6H, CH(C*H*$_3$)$_2$ maj); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 178.6, 177.2, 149.3, 129.7, 128.0, 127.9, 127.3, 126.3, 108.7, 105.6, 41.9, 41.7, 38.5, 36.5, 34.0, 30.5, 24.9, 24.0, 22.4, 13.3; IR (thin film, cm^{-1}) 3378(bs), 2961(m), 2872(m), 1774(w), 1701(s), 1515(m), 1384(m), 1182(m), 1162(m); HRMS m/z (M + Na^{+}) calcd 385.1887, found 385.1886. Anal. Calcd for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.18; H, 7.41; N, 7.51.

5-(4-Methoxyphenyl)-2-methyl-3b,6a,6b,7,8,9,9a-heptahydro-1H,5H-cyclopenta[g]pyrrolo[3,4-e]indole-4,6-dione (8). Method B with **3a** (800 mg, 9.50 mmol), 1.5-h reflux, and then reprecipitation from ethanol (15 mL) gave **8** (850 mg, 46%) as a colorless solid, a mixture of two isomers (maj:min = 5.4:1.0): mp 213–215°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.25 (bs, 1H, 1min-H), 7.69 (bs, 1H, 1maj-H), 7.15–7.23 (m, 2H, Ph), 6.95–7.02 (m, 2H, Ph), 6.11 (d, J = 1.5 Hz, 1H, 3maj-H), 5.75 (d, J = 2.1 Hz, 1H, 3min-H), 3.99 (dd, J = 8.4, 1.8 Hz, 1H, 3bα-H), 3.84 (s, 3H, OCH_3 min), 3.83 (s, 3H, OCH_3 maj), 3.61 (dd, J = 8.7, 6.3 Hz, 1H, 6aαmin-H), 3.53 (dd, J = 8.6, 5.9 Hz, 1H, 6aαmaj-H), 3.18–3.25 (m, 1H, 9aαmaj-H), 3.09–3.16 (m, 1H, 9aβmin-H), 2.74–2.87 (m, 1H, 6b-H), 2.28 (s, 3H, 2-CH_3), 1.88–2.07 (m, 2H, cyclopent.), 1.26–1.70 (m, 4H, cyclopent.); ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.46 (bs, 1H, 1min-H), 10.27 (bs, 1H, 1maj-H), 7.12 (d, J = 9.0 Hz, 2H, Ph), 7.02 (d, J = 9.0 Hz, 2H, Ph), 5.74–5.77 (m, 1H, 3maj-H), 5.55–5.58 (m, 1H, 3min-H), 4.12–4.16 (m, 1H, 3bαmin-H), 4.01 (dd, J = 8.4, 1.8 Hz, 1H, 3bαmaj-H), 3.78 (s, 3H, OCH_3), 3.45–3.52 (m, overlapped, 1H, 6aαmin-H), 3.45 (dd, J = 8.3, 5.9 Hz, 1H, 6aαmaj-H), 3.06–3.13 (m, 1H, 9aαmaj-H), 2.98–3.04 (m, 1H, 9aβmin-H), 2.52–2.65 (m, 1H, 6bα-H), 1.99–2.18 (m, 1H, cyclopent.), 2.15 (s, 3H, 2-CH_3), 1.78–1.96 (m, 1H, cyclopent.), 1.32–1.62 (m, 3H, cyclopent.), 1.12–1.28 (m, 1H, cyclopent.); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 178.7, 177.3, 159.5, 128.0, 127.8, 124.8, 114.7, 114.6, 108.7, 105.6, 55.6, 41.9, 41.7, 38.5, 37.2, 36.5, 30.5, 31.5, 24.9, 22.3, 22.0, 13.3; IR (KBr, cm^{-1}) 3384(bs), 2869(m), 1773(w), 1704(s), 1697(bs), 1515(s), 1391(m), 1252(m), 1176(m); HRMS m/z (M + Na^+) calcd 373.1523, found 373.1528. Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 72.12; H, 6.51; N, 7.82.

2-Methyl-5-(4-phenoxyphenyl)-3b,6a,6b,7,8,9,9a-heptahydro-1H,5H-cyclopenta[g]pyrrolo[3,4-e]indole-4,6-dione (9). Method B with **3a** (800 mg, 9.50 mmol), 3-h reflux, reprecipitation from ethanol (15 mL), and then a diethyl ether wash (15 mL) gave **9** (1130 mg, 52%) as a colorless solid, a mixture of two isomers (maj:min = 7.6:1.0): mp 227–228°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.22 (bs, 1H, 1min-H), 7.65 (bs, 1H, 1maj-H), 7.34–7.41 (m, 2H, Ph), 7.13–7.28 (m, 3H, Ph), 7.04–7.10 (m, 4H, Ph), 6.11 (dd, J = 2.4, 0.9 Hz, 1H, 3maj-H), 5.76 (app. d, J = 2.4 Hz, 1H, 3min-H), 4.00 (dd, J = 8.4, 1.8 Hz, 1H, 3bα-H), 3.84 (dd, J = 8.4, 6.0 Hz, 1H, 6aαmaj-H), 3.63 (dd, J = 8.6, 6.2 Hz, 1H, 6aαmin-H), 3.20–3.27 (m, 1H, 9aαmaj-H), 3.13–3.17 (m, 1H, 9aβmin-H), 2.75–2.88 (m, 1H, 6bα-H), 2.29 (s, 3H, 2-CH_3), 1.88–2.08 (m, 2H, cyclopent.), 1.53–1.73 (m, 3H, cyclopent.), 1.30–1.48 (m, 1H, cyclopent.); ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.48 (d, J = 2.4 Hz, 1H, 1min-H), 10.28 (d, J = 2.1 Hz, 1H, 1maj-H), 7.40–7.47 (m, 2H, Ph), 7.16–7.26 (m, 3H, Ph), 7.07–7.11 (m, 4H, Ph), 5.76 (dd, J = 2.1, 0.9 Hz, 1H, 3maj-H), 5.57 (dd, J = 2.4, 0.9 Hz, 1H, 3min-H), 4.17 (app. d, J = 8.4 Hz, 1H, 3bαmin-H), 4.03 (dd, J = 8.4, 1.8 Hz, 1H, 3bαmaj-H), 3.52 (dd, J = 8.3, 5.9 Hz, 1H, 6aαmin-H), 3.47 (dd, J = 8.3, 5.9 Hz, 1H, 6aαmaj-H), 3.07–3.13 (m, 1H, 9aαmaj-H), 2.98–3.04 (m, 1H, 9aβmin-H), 2.54–2.65 (m, 1H, 6bα-H), 2.15 (s, 3H, 2-CH_3), 2.02–2.15 (m, 1H, cyclopent.), 1.76–1.90 (m, 1H, cyclopent.), 1.35–1.61 (m, 3H, cyclopent.), 1.13–1.29 (m, 1H, cyclopent.); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 178.5, 177.1, 157.5, 156.5, 130.0, 128.1, 128.0, 127.8, 126.9, 124.0, 119.6, 118.9, 108.6, 105.6, 41.9, 41.7, 38.5, 37.2, 36.5, 30.5, 24.9, 22.4, 13.3; IR (thin film, cm^{-1}) 3381(bs), 2950(m), 2872(m), 2365(w), 2343(w), 1775(w), 1706(s), 1590(w), 1507(m), 1489(m), 1385(m), 1240(m), 1163(m); HRMS m/z (M + Na^+) calcd 435.1680, found 435.1682. Anal. Calcd for $C_{26}H_{24}N_2O_3$: C, 75.71; H, 5.86; N, 6.79. Found: C, 75.86; H, 5.73; N, 6.76.

4-(2-Methyl-4,6-dioxo-3b,6a,6b,7,8,9,9a-heptahydro-1H,5H-cyclopenta[g]pyrrolo[3,4-e]-5-indolyl) benzoic acid (10) Method B with **3a** (800 mg, 9.50 mmol), 1.5-h reflux, reprecipitation from ethanol (15 mL), and then a diethyl ether wash (10 mL) gave **10** (600 mg, 35%) as a colorless solid, a mixture of two isomers (maj:min = 9.0:1.0): mp 262–264°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 13.10 (bs, 1H, CO_2H), 10.49 (d, J = 3.0 Hz, 1H, 1min-H), 10.29 (d, J = 3.0 Hz, 1H, 1maj-H), 8.05 (d, J = 8.4 Hz, 2H, Ph), 7.39 (d, J = 8.7 Hz, 2H, Ph), 5.76 (d, J = 1.5 Hz, 1H, 3maj-H), 5.58 (d, J = 1.8 Hz, 1H, 3min-H), 4.21 (app. d, J = 8.7 Hz, 1H, 3aαmin-H), 4.04 (dd, J = 8.3, 1.7 Hz, 1H, 3aαmaj-H), 3.56 (dd, J = 8.1, 5.4 Hz, 1H, 6aαmin-H), 3.51 (dd, J = 8.3, 5.9 Hz, 1H, 6aαmaj-H), 3.08–3.15 (m, 1H, 9aαmaj-H), 3.00–3.05 (m, 1H, 9aβmin-H), 2.56–2.67 (m, 1H, 6bα-H), 2.15 (s, 3H, 2-CH_3), 2.02–2.15 (m, 1H, cyclopent.), 1.77–1.90 (m, 1H, cyclopent.), 1.33–1.64 (m, 3H, cyclopent.), 1.15–1.27 (m, 1H, cyclopent.); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 178.4, 177.3, 167.9, 157.2, 136.8, 130.9, 130.6, 127.6, 127.4, 127.1, 108.0, 105.2, 42.1, 41.7, 38.5, 36.8, 31.2, 30.4, 25.1, 22.4, 13.4; IR (thin film, cm^{-1}) 3394(bs), 2910(m), 1773(w),1696(s), 1515(w), 1391(m), 1289(m), 1172(m); HRMS m/z (M + Na^+) calcd for $C_{21}H_{20}N_2O_4$: 387.1316, found 387.1302.

2-Methyl-5-(3-nitrophenyl)-3b,6a,6b,7,8,9,9a-heptahydro-1H,5H-cyclopenta[g]pyrrolo[3,4-e]indole-4,6-dione (11). Method B with **3a** (800 mg, 9.50 mmol), 4-h reflux and then purification with column chromatography (CH_2Cl_2) gave **11** (350 mg, 20%) as a yellow solid, a mixture of three isomers (maj:min:min = 8.9:1.0:0.7): mp 212–216°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.24–8.28 (m, 3H, Ph, Ph, 1min-H), 7.63–7.74 (m, 3H, Ph, 1maj-H), 6.10 (dd, J = 2.6, 1.1 Hz, 1H, 3maj-H), 6.03 (dd, J = 2.9, 1.1 Hz, 1H, 3min-H), 5.77 (dd, J = 2.6, 1.1 Hz, 1H, 3min-H), 4.20 (dd, J = 8.1, 1.8 Hz, 1H, 3bαmin-H), 4.05 (dd, J = 8.4, 2.1 Hz, 1H, 3bαmaj-H), 3.68 (dd, J = 8.6, 6.2 Hz, 1H, 6aαmin-H), 3.63 (dd, J = 8.1, 4.2 Hz, 1H, 6aαmin-H), 3.60 (dd, J = 8.6, 5.9 Hz, 1H, 6aαmaj-H), 3.21–3.29 (m, 1H, 9aαmaj-H), 3.10–3.19 (m, 1H, 9amin-H), 2.79–2.89 (m, 1H, 6b-H), 2.30 (dd, J = 0.8 Hz, 3H, 2-CH_3), 1.90–2.05 (m, 2H, cyclopent.), 1.58–1.74 (m, 3H, cyclopent.), 1.34–1.49 (m, 1H, cyclopent.); ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.52 (d, J = 1.2 Hz, 1H, 1min-H), 10.46 (d, J = 1.8 Hz, 1H, 1min-H), 10.32 (d, J = 1.8 Hz, 1H, 1maj-H), 8.25–8.32 (m, 1H, Ph), 8.15–8.17 (m, 1H, Ph), 7.73–7.86 (m, 2H, Ph), 5.78 (d, J = 1.5 Hz, 1H, 3maj-H), 5.72 (d, J = 1.8 Hz, 1H, 3min-H), 5.58 (d, J = 1.8 Hz, 1H, 3min-H), 4.22 (app. d, J = 8.1 Hz, 1H, 3bαmin-H), 4.09 (dd, J = 8.4, 2.1 Hz, 1H, 3bαmaj-H), 4.03 (dd, J = 8.3, 1.7 Hz, 1H, 3bαmin-H), 3.72 (dd, J = 4.7, 8.0 Hz, 1H, 6aαmin-H), 3.60 (dd, J = 8.3, 5.6 Hz, 1H, 6aαmin-H), 3.54 (dd, J = 8.1, 6.0 Hz, 1H, 6aαmaj-H), 3.09–3.15 (m, 1H, 9aαmaj-H), 2.99–3.06 (m, 1H, 9amin-H), 2.58–2.67 (m, 1H, 6b-H), 2.03–2.17 (m, 1H, cyclopent.), 2.15 (s, 3H, 2-CH_3), 1.74–1.91 (m, 1H, cyclopent.), 1.37–1.64 (m, 3H, cyclopent.), 1.15–1.33 (m, 1H, cyclopent.); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 177.6, 176.3, 133.2, 132.3, 130.0, 128.3, 127.8, 123.1, 121.7, 108.1, 105.5, 42.0, 41.6, 38.6, 36.5, 30.5, 25.0, 22.4, 13.3; IR (thin film, cm^{-1}) 3388(bs), 2953(m), 2926(m), 1779(w),1712(s), 1532(s), 1376(m), 1349(m), 1159(m); HRMS m/z (M + Na^+) calcd for $C_{20}H_{19}N_3O_4$: 388.1269, found 388.1258.

5-(4-Bromophenyl)-2-methyl-3b,6a,6b,7,8,9,9a-heptahydro-1H,5H-cyclopenta[g]pyrrolo[3,4-e]indole-4,6-dione (12). Method B with **3a** (800 mg, 9.50 mmol), 1.5-h reflux, and then reprecipitation from ethanol (15 mL) gave **12** (1250 mg, 63%) as a colorless solid, a mixture of two isomers (maj:min = 4.2:1.0): mp 266–268°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.20 (bs, 1H, 1min-H), 7.63 (bs, overlapped, 1H, 1maj-H), 7.60 (d, J = 8.7 Hz, 2H, Ph), 7.20 (d, J = 8.7 Hz, 2H, Ph), 6.10 (dd, J = 2.6, 1.1 Hz, 1H, 3maj-H), 5.75 (dd, J = 2.9, 0.8 Hz, 1H, 3min-H), 4.00 (dd, J = 8.6, 1.5 Hz, 1H, 3bα-H), 3.63 (dd, J = 8.6, 6.2 Hz, 1H, 6aαmin-H), 3.54 (dd, J = 8.4, 6.0 Hz, 1H, 6aαmaj-H), 3.20–3.27 (m, 1H, 9aαmaj-H), 3.10–3.16 (m, 1H, 9aβmin-H), 2.74–2.88 (m, 1H, 6bα-H), 2.29 (s, 3H, 2-CH$_3$), 1.87–2.08 (m, 2H, cyclopent.), 1.52–1.72 (m, 3H, cyclopent.), 1.23–1.48 (m, 1H, cyclopent.); ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.49 (d, J = 2.4 Hz, 1H, 1min-H), 10.29 (d, J = 1.8 Hz, 1H, 1maj-H), 7.70 (d, J = 8.4 Hz, 2H, Ph), 7.20 (d, J = 8.7 Hz, 2H, Ph), 5.75 (d, J = 2.3, 0.75 Hz, 1H, 3maj-H), 5.57 (d, J = 2.4, 0.6 Hz, 1H, 3min-H), 4.17 (app. d, J = 8.4 Hz, 1H, 3bαmin-H), 4.04 (dd, J = 8.1, 1.8 Hz, 1H, 3bαmaj-H), 3.54 (dd, J = 8.4, 5.7 Hz, 1H, 6aαmin-H), 3.48 (dd, J = 8.3, 5.9 Hz, 1H, 6aαmaj-H), 3.07–3.13 (m, 1H, 9aαmaj-H), 2.98–3.04 (m, 1H, 9aβmin-H), 2.53–2.65 (m, 1H, 6b-H), 2.02–2.18 (m, 1H, cyclopent.), 2.15 (s, 3H, 2-CH$_3$), 1.77–1.89 (m, 1H, cyclopent.), 1.33–1.61 (m, 3H, cyclopent.), 1.13–1.25 (m, 1H, cyclopent.); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 178.5, 132.5, 132.4, 128.0, 127.8, 105.6, 41.9, 41.6, 38.5, 36.5, 24.9, 22.4, 13.3; IR (thin film, cm^{-1}) 3396(bs), 2872(m), 2364(m), 1774(w), 1697(s), 1490(m), 1387(m), 1177(m), 1167(m); HRMS m/z (M + Na$^+$) calcd 421.0523, found 421.0519. Anal. Calcd for $C_{20}H_{19}BrN_2O_2$: C, 60.16; H, 4.80; N, 7.02. Found: C, 60.25; H, 4.98; N, 7.14.

5-(4-Chlorophenyl)-2-methyl-3b,6a,6b,7,8,9,9a-heptahydro-1H,5H-cyclopenta[g]pyrrolo[3,4-e]indole-4,6-dione (13). Method B with **3a** (800 mg, 9.50 mmol), 2-h reflux, reprecipitation from ethanol (10 mL), and then a diethyl ether wash (10 mL) gave **13** (1100 mg, 65%) as a colorless solid, a mixture of two isomers (maj:min = 2.5:1.0): mp 257–260°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.22 (bs, 1H, 1min-H), 7.67 (bs, 1H, 1maj-H), 7.44 (d, J = 8.7 Hz, 2H, Ph), 7.26 (d, J = 9.0 Hz, 2H, Ph), 6.10 (dd, J = 2.6, 1.1 Hz, 1H, 3maj-H), 5.76 (dd, J = 2.7, 0.9 Hz, 1H, 3min-H), 4.01 (dd, J = 8.7, 2.1 Hz, 1H, 3bαmin-H), 4.00 (dd, J = 8.4, 1.8 Hz, 1H, 3bαmaj-H), 3.62 (dd, J = 8.9, 6.2 Hz, 1H, 6aαmin-H), 3.54 (dd, J = 8.4, 5.7 Hz, 1H, 6aαmaj-H), 3.20–3.26 (m, 1H, 9aαmaj-H), 3.10–3.16 (m, 1H, 9aβmin-H), 2.72–2.87 (m, 1H, 6bα-H), 2.29 (s, 3H, 2-CH$_3$), 1.87–2.07 (m, 2H, cyclopent.), 1.52–1.75 (m, 3H, cyclopent.), 1.22–1.49 (m, 1H, cyclopent.); ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.49 (d, J = 1.8 Hz, 1H, 1min-H), 10.29 (d, J = 2.7 Hz, 1H, 1maj-H), 7.57 (d, J = 8.7 Hz, 2H, Ph), 7.27 (d, J = 8.7 Hz, 2H, Ph), 5.76 (d, J = 2.1 Hz, 1H, 3maj-H), 5.57 (d, J = 1.8 Hz, 1H, 3min-H), 4.17 (app. d, J = 8.1 Hz, 1H, 3bαmin-H), 4.04 (dd, J = 8.4, 1.8 Hz, 1H, 3bαmaj-H), 3.54 (dd, J = 8.3, 5.9 Hz, 1H, 6aαmin-H), 3.49 (dd, J = 8.3, 5.9 Hz, 1H, 6aαmaj-H), 3.07–3.14 (m, 1H, 9aαmaj-H), 2.98–3.04 (m, 1H, 9aβmin-H), 2.53–2.65 (m, 1H, 6bα-H), 2.02–2.17 (m, 1H, cyclopent.), 2.15 (s, 3H, 2-CH$_3$), 1.76–1.93 (m, 1H, cyclopent.), 1.35–1.62 (m, 3H, cyclopent.), 1.12–1.28 (m, 1H, cyclopent.); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 178.1, 176.7, 134.3, 130.6, 129.6, 129.4, 128.1, 127.8, 121.2, 115.8, 108.4, 105.6, 104.1, 41.6, 41.1, 38.5, 37.2, 36.5, 31.4, 31.1, 30.5, 24.9, 24.5, 22.4, 21.9, 13.3; IR (thin film, cm^{-1}) 3398(bs), 2929(m), 1774(w), 1696(s), 1494(m), 1391(m), 1177(m), 1168(m); HRMS m/z (M + Na$^+$) calcd 377.1028, found 377.1023. Anal. Calcd for $C_{20}H_{19}ClN_2O_2$: C, 67.70; H, 5.40; N, 7.89. Found: C, 67.81; H, 5.35; N, 8.07.

5-(4-Fluorophenyl)-2-methyl-3b,6a,6b,7,8,9,9a-heptahydro-1H,5H-cyclopenta[g]pyrrolo[3,4-e]indole-4,6-dione (14). Method B with **3a** (800 mg, 9.50 mmol), 2-h reflux, reprecipitation from ethanol (20 mL), and then a diethyl ether wash (10 mL) gave **14** (950 mg, 59%) as a colorless solid, a mixture of two isomers (maj:min = 11.1:1.0): mp 230–232°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.24 (bs, 1H, 1min-H), 7.69 (bs, 1H, 1maj-H), 7.24–7.31 (m, 2H, Ph), 7.11–7.20 (m, 2H, Ph), 6.10 (dd, J = 2.7, 1.2 Hz, 1H, 3maj-H), 5.75 (d, J = 3.3 Hz, 1H, 3min-H), 4.00 (dd, J = 8.4, 2.1 Hz, 1H, 3bα-H), 3.62 (dd, J = 8.6, 6.2 Hz, 1H, 6aαmin-H), 3.54 (dd, J = 8.4, 6.0 Hz, 1H, 6aαmaj-H), 3.19–3.26 (m, 1H, 9aαmaj-H), 3.10–3.16 (m, 1H, 9aβmin-H), 2.76–2.87 (m, 1H, 6bα-H), 2.28 (s, 3H, 2-CH$_3$), 1.88–2.07 (m, 2H, cyclopent.), 1.53–1.72 (m, 3H, cyclopent.), 1.33–1.48 (m, 1H, cyclopent.); ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.49 (bs, 1H, 1min-H), 10.29 (bs, 1H, 1maj-H), 7.24–7.39 (m, 4H, Ph), 5.76 (dd, J = 2.1, 0.6 Hz, 1H, 3maj-H), 5.57 (app. d, J = 1.8 Hz, 1H, 3min-H), 4.17 (app. d, J = 9.3 Hz, 1H, 3bαmin-H), 4.04 (dd, J = 8.1, 1.8 Hz, 1H, 3bαmaj-H), 3.48 (dd, J = 8.4, 5.7 Hz, 1H, 6aαmaj-H), 3.44 (dd, J = 7.1, 5.0 Hz, 1H, 6aαmin-H), 3.07–3.14 (m, 1H, 9aαmaj-H), 2.98–3.04 (m, 1H, 9aβmin-H), 2.53–2.65 (m, 1H, 6bα-H), 2.02–2.18 (m, 1H, cyclopent.), 2.15 (s, 3H, 2-CH$_3$), 1.76–1.89 (m, 1H, cyclopent.), 1.34–1.61 (m, 3H, cyclopent.), 1.13–1.29 (m, 1H, cyclopent.); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 178.3, 176.9, 163.9, 160.1, 128.4, 128.3, 128.1, 127.8, 116.5, 116.4, 116.1, 108.5, 105.6, 41.9, 41.6, 38.5, 36.5, 31.0, 30.5, 24.9, 22.3, 13.3; IR (thin film, cm^{-1}) 3387(bs), 2876(m), 1775(w), 1706(s), 1510(s), 1510(m), 1387(m), 1229(m), 1189(m), 1159(m); HRMS m/z (M + Na$^+$) calcd 361.1324, found 361.1323. Anal. Calcd for $C_{20}H_{19}FN_2O_2$: C, 70.99; H, 5.66; N, 8.28. Found: C, 71.03; H, 5.71; N, 8.21.

5-Dimethylamino-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (15). Method A gave **15** (407 mg, 45%) as a light-orange solid, a mixture of two isomers (maj:min = 19.2:1.0): mp 234–236°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.25 (bs, 1H, 1min-H), 7.65 (bs, 1H, 1maj-H), 6.15 (dd, J = 2.4, 1.2 Hz, 1H, 3maj-H), 5.74 (dd, J = 2.6, 0.7 Hz, 1H, 3min-H), 3.68 (dd, J = 2.0 Hz, 1H, 3bα-H), 3.23 (dd, J = 8.9, 5.6 Hz, 1H, 6aαmin-H), 3.17 (dd, J = 8.6, 5.6 Hz, 1H, 6aαmaj-H), 3.04–3.09 (m, 1H, 10aαmaj-H), 2.92 (s, 6H, N(CH$_3$)$_2$), 2.30 (dd, J = 1.1, 1.1 Hz, 3H, 2-CH$_3$), 2.43–2.53 (m, 1H, 6b-H), 2.08–2.16 (m, 1H, cyclohex.), 1.45–1.79 (m, 3H, cyclohex.), 1.05–1.32 (m, 4H, cyclohex.); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 177.5, 176.6, 127.4, 127.0, 108.9, 105.6, 44.2, 44.1, 38.2, 37.0, 32.7, 27.9, 25.5, 22.8, 21.0, 13.3; IR (thin film, cm^{-1}) 3426(bs), 2930(m), 2859(m), 2124(bw), 1770(bw), 1705(s), 1648(bs), 1446(m), 1362(m), 1193(m), 1146(m); HRMS m/z (M + Na$^+$) calcd 324.1683, found 324.1707. Anal. Calcd for $C_{17}H_{23}N_3O_2$: C, 67.75; H, 7.69; N, 13.94. Found: C, 67.92; H, 7.69; N, 13.76.

5-Dimethylamino-8-ethyl-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (16). Method A gave **16** (484 mg, 49%) as a light-orange solid, a mixture of three isomers (maj:min:min = 8.4:1.0:0.2): mp 230–231°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.24 (bs, 1H, 1min-H), 7.65 (bs, 1H, 1maj-H), 6.15 (dd, J = 2.4 Hz, 0.9 Hz, 1H, 3maj-H), 5.75 (dd, J = 2.4, 0.9 Hz, 1H, 3min-H), 5.71 (dd, J = 2.4, 0.9 Hz, 1H, 3min-H), 3.68 (dd, J = 8.4, 1.8 Hz, 1H, 3bα-H), 3.22 (dd, J = 9.0 Hz, 5.4 Hz, 1H, 6aαmin-H), 3.21 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.17 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmaj-H), 2.99–3.04 (m, 1H, 10aαmaj-H), 2.93 (s, 6H, $N(CH_3)_2$), 2.59–2.70 (m, 1H, 6bαmaj-H), 2.48–2.56 (m, 1H, 6bmin-H), 2.30 (dd, J = 0.9, 0.9 Hz, 1H, 2-CH_3), 1.70–1.99 (m, 2H, cyclohex.), 1.00–1.60 (m, 7H, cyclohex., CH_2CH_3), 0.86 (t, J = 7.2 Hz, 3H, CH_2CH_3 maj), 0.76 (t, J = 7.2 Hz, 3H, CH_2CH_3 min); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 177.5, 177.4, 176.6, 127.5, 127.4, 127.0, 126.8, 109.1, 105.6, 103.7, 44.1, 43.9, 39.0, 38.3, 37.0, 36.0, 34.4, 34.0, 32.8, 32.7, 32.6, 29.6, 29.3, 27.8, 27.5, 26.1, 24.3, 23.6, 22.6, 13.3, 12.2, 11.4; IR (thin film, cm^{-1}) 3455(bs), 2957(m), 1704(m), 2125(bw), 1770(w), 1704(s), 1651(bs), 1558(m), 1446(m), 1194(m), 1142(m); HRMS *m/z* (M + Na$^+$) calcd 352.1996, found 352.2002. Anal. Calcd for $C_{19}H_{27}N_3O_2$: C, 69.27; H, 8.26; N, 12.76. Found: C, 69.50; H, 8.09; N, 12.67.

5-Dimethylamino-8-isopropyl-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (17). Method B with **3f** (982 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL) and then a diethyl ether wash (10 mL) gave **17** (690 mg, 42%) as light-orange crystals, a single isomer: mp 237–238°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.65 (bs, 1H, 1-H), 6.15 (dd, J = 2.4, 0.9 Hz, 1H, 3-H), 3.69 (dd, J = 8.4, 1.8 Hz, 1H, 3bα-H), 3.16 (dd, J = 8.4, 5.4 Hz, 1H, 6aα-H), 3.00–3.05 (m, 1H, 10aα-H), 2.93 (s, 6H, $N(CH_3)_2$), 2.57–2.72 (m, 1H, 6bα-H), 2.31 (s, 3H, 2-CH_3), 1.77–1.96 (m, 3H, cyclohex.), 1.52–1.63 (m, 1H, cyclohex.), 1.10–1.44(m, 4H, $CH(CH_3)_2$, cyclohex.), 0.88 (d, J = 6.6 Hz, 6H, $CH(CH_3)_2$), 0.87 (d, J = 6.6 Hz, 6H, $CH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 177.5, 176.6, 127.4, 127.1, 109.2, 105.6, 44.0, 43.8, 39.7, 37.0, 33.0, 32.7, 25.6, 25.0, 23.0, 21.3, 20.8, 13.3; IR (thin film, cm^{-1}) 3369 (bs), 2952(s), 2868(s), 2363(w), 1769(m), 1706(s), 1602(w), 1522(w), 1449(m), 1365(m), 1312(w), 1244(w), 1192(m), 1144(m), 1046(m); HRMS *m/z* (M + Na$^+$) calcd 366.2153, found 366.2160. Anal. Calcd for $C_{20}H_{29}N_3O_2$: C, 69.94; H, 8.51; N, 12.23. Found: C, 69.87; H, 8.41; N, 12.08.

8-tert-Butyl-5-dimethylamino-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (18). Method A gave **18** (558 mg, 52%) as an orange solid, a mixture of three isomers (maj:min:min = 2.4:1.0:0.1): mp 175–176°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.65 (bs, 1H, 1min-H), 7.61 (bs, 1H, 1maj-H), 6.12 (dd, J = 2.7, 1.2 Hz, 1H, 3min-H), 5.99 (dd, J = 2.6, 1.1 Hz, 1H, 3maj-H), 5.75 (dd, J = 2.7, 1.2 Hz, 1H, 3min-H), 3.77 (dd, J = 7.8, 1.5 Hz, 1H, 3bαmaj-H), 3.68 (dd, J = 8.3, 2.0 Hz, 1H, 3bαmin-H), 3.21 (dd, J = 8.6, 5.6 Hz, 1H, 6aαmin-H), 3.09 (dd, J = 7.8, 6.0 Hz, 1H, 6aαmaj-H), 3.00–3.05 (m, 1H, 10aβmin-H), 2.94 (s, 6H, $N(CH_3)_2$ min), 2.86 (s, 6H, $N(CH_3)_2$ maj), 2.45–2.75 (m, 2H, 6b-H, 10aαmaj-H), 2.29 (dd, J = 0.9, 0.9 Hz, 3H, 2-CH_3 min), 2.24 (d, J = 0.9 Hz, 3H, 2-CH_3 maj), 0.98–2.20 (m, 7H, cyclohex.), 0.90 (s, 9H, *t*-Bu), 0.70 (s, 9H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 177.6, 177.2, 176.65, 176.61, 130.0, 127.6, 127.4, 126.9, 109.1, 108.7, 105.5, 104.6, 58.3, 47.8, 44.2, 44.1, 43.8, 43.3, 40.8, 39.3, 38.9, 37.1, 34.2, 34.0, 32.9, 32.42, 32.40, 30.2, 28.3, 27.6, 27.5, 25.0, 24.2, 22.2, 18.4, 13.3, 13.2; IR (thin film, cm^{-1}) 3411(bs), 2953(m), 2866(m), 2114(bw), 1774(w), 1711(s), 1646(bm), 1365(m), 1200(m), 1148(m); HRMS *m/z* (M + Na$^+$) calcd 380.2309, found 380.2335. Anal. Calcd for $C_{21}H_{31}N_3O_2$: C, 70.55; H, 8.74; N, 11.75. Found: C, 69.84; H, 8.82; N, 11.09.

5-Dimethylamino-2-methyl-8-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (19). Method B with **3h** (1220 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **19** (870 mg, 48%) as light-orange crystals, a single isomer: mp 220–222°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.67 (bs, 1H, 1-H), 7.18–7.34 (m, 5H, Ph), 6.14–6.16 (m, 1H, 3-H), 3.75 (dd, J = 8.4, 1.8 Hz, 1H, 3bα-H), 3.19 (dd, J = 8.3, 5.6 Hz, 1H, 6aα-H), 2.96–3.00 (m, 1H, 10aα-H), 2.96 (s, 6H, $N(CH_3)_2$), 2.72–2.80 (m, 1H, 6bα-H), 2.32 (s, 3H, 2-CH_3), 1.70–2.05 (m, 7H, cyclohex.); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 177.4, 176.5, 128.6, 127.6, 127.3, 127.1, 125.8, 109.4, 105.5, 44.1, 43.7, 32.9–33.5 (overlapped peaks), 13.3; IR (thin film, cm^{-1}) 3380(bs), 3085(w), 3058(w), 3026(w), 2933(s), 2867(m), 2800(w), 1772(w), 1709(s), 1601(w), 1495(w), 1448(m), 1361(m), 1243(w), 1195(m), 1150(w), 1106(w), 1028(m); HRMS *m/z* (M + Na$^+$) calcd for $C_{23}H_{27}N_3O_2$: 400.1996, found 400.2008.

2-Methyl-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (20). Method A gave **20** (602 mg, 60%) as a white solid, a mixture of two isomers (maj:min = 12.5:1.0): mp 268–269°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.30 (bs, 1H, 1min-H), 7.68 (bs, 1H, 1maj-H), 7.43–7.52 (m, 3H, Ph), 7.27–7.33 (m, 2H, Ph), 6.19 (dd, J = 2.6, 1.1 Hz, 1H, 3maj-H), 5.78 (dd, J = 3.0, 0.9 Hz, 1H, 3min-H), 3.96 (dd, J = 8.6, 2.0 Hz, 1H, 3bα-H), 3.47 (dd, J = 8.7, 5.7 Hz, 1H, 6aαmin-H), 3.40 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmaj-H), 3.12–3.18 (m, 1H, 10aαmaj-H), 3.01–3.07 (m, 1H, 10aβmin-H), 2.51–2.60 (m, 1H, 6bα-H), 2.32 (dd, 3H, J = 0.9, 0.9 Hz, 2-CH_3), 2.11–2.20 (m, 1H, cyclohex.), 1.18–1.83 (m, 7H, cyclohex.); ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.52 (bs, 1H, 1maj-H), 10.26 (bs, 1H, 1min-H), 7.35–7.54 (m, 3H, Ph), 7.19–7.26 (m, 2H, Ph), 5.84 (dd, J = 2.1 Hz, 0.6 Hz, 1H, 3maj-H), 5.60 (app. d, J = 2.4 Hz, 1H, 3min-H), 4.16 (app. d, J = 7.5 Hz, 1H, 3bαmin-H), 4.02 (dd, J = 8.7, 1.8 Hz, 1H, 3bαmaj-H), 3.39 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.34 (dd, J = 8.6, 5.3 Hz, 1H, 6aαmaj-H), 2.99–3.06 (m, 1H, 10aαmaj-H), 2.90–2.96 (m, 1H, 10aβ-H), 2.04–2.40 (m, 1H, 6bα-H), 2.18 (s, 3H, 2-CH_3), 1.50–1.64 (m, 2H, cyclohex.), 1.32–1.46 (m, 1H, cyclohex.), 0.98–1.28 (m, 5H, cyclohex.); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 178.1, 176.8, 154.8, 132.1, 129.3, 129.2, 128.8, 128.5, 127.4, 127.1, 126.5, 109.4, 105.9, 103.7, 46.0, 38.9, 38.7, 38.4, 37.8, 33.1, 32.9, 29.1, 28.1, 26.1, 25.6, 23.1, 22.7, 21.1, 20.6, 13.3; IR (thin film, cm^{-1}) 3392(bs), 2943(m), 2855(m), 2181 (bw), 1775 (w), 1697(s), 1645(bs), 1387(m), 1186 (m), 1162(m); HRMS *m/z* (M + Na$^+$) calcd 357.1574, found 357.1584. Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.53; H, 6.80; N, 8.38.

2,8-Dimethyl-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (21). Method B with **3d** (785 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **21** (800 mg, 48%) as a colorless solid, a mixture of three isomers (maj:min:min = 1.8:1.0:0.3): mp 270–272°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.52 (bs, 1H, 1min-H), 10.27 (bs, 1H, 1maj-H), 7.38–7.55 (m, 3H, Ph), 7.20–7.25 (m, 2H, Ph), 5.83 (d, J = 1.2 Hz, 1H, 3maj-H), 5.61 (d, J = 2.1 Hz, 1H, 3min-H), 5.59 (d, J = 2.4 Hz, 1H, 3min-H), 4.16 (app. d, J = 8.4 Hz, 1H, 3bαmin-H), 4.02 (dd, J = 8.6, 1.7 Hz, 1H, 3bαmin-H), 4.01 (dd, J = 9.9, 1.5 Hz, 1H, 3bαmaj-H), 3.40

(dd, J = 8.1, 4.8 Hz, 1H, 6aαmin-H), 3.36 (dd, J = 8.1, 5.4 Hz, 1H, 6aαmaj-H), 2.93–3.02 (m, 1H, 10aα-H), 2.85–2.92 (m, 1H, 10aβ-H), 2.48–2.58 (m, 1H, 6bαmaj-H), 2.30–2.42 (m, 1H, 6bmin-H), 2.18 (s, 3H, 2-CH_3), 1.74–2.16 (m, 2H, cyclohex.), 0.89–1.65 (m, 5H, cyclohex.), 0.95 (d, J = 7.2 Hz, 3H, 8-CH_3 maj), 0.73 (d, J = 6.3 Hz, 3H, 8-CH_3 min); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 178.0, 176.8, 132.1, 129.3, 129.2, 128.7, 128.5, 127.4, 126.5, 117.0, 109.5, 105.8, 103.8, 45.7, 38.9, 37.8, 33.1, 33.0, 32.7, 32.6, 27.1, 26.7, 22.5, 22.4, 17.7, 13.3; IR (thin film, cm^{-1}) 3384(bs), 3063(m), 2950(s), 2866(s), 2361(m), 1778(m), 1712(s), 1598(m), 1501(m), 1457(m), 1384(m), 1182(m); HRMS m/z (M + Na^+) calcd 371.1731, found 371.1737. Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 75.70; H, 7.08; N, 7.88.

8-Ethyl-2-methyl-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (22). Method A gave **22** (402 mg, 37%) as a cream-colored solid, a mixture of three isomers (maj:min:min = 5.6:1.0:0.1): mp 257–258°C; ^1H NMR (300 MHz, $CDCl_3$, δ) 8.30 (bs, 1H, 1min-H), 7.69 (bs, 1H, 1maj-H), 7.36–7.51 (m, Ph, 3H), 7.27–7.32 (m, Ph, 2H), 6.19 (dd, J = 2.4, 1.2 Hz, 1H, 3maj-H), 5.79 (dd, J = 2.9, 1.1, 1H, 3min-H), 5.76 (dd, J = 2.7, 1.2 Hz, 1H, 3min-H), 3.96 (dd, J = 8.4, 1.8 Hz, 1H, 3bα-H), 3.46 (dd, J = 8.7, 5.7 Hz, 1H, 6aαmin-H), 3.43 (dd, J = 8.4, 5.1 Hz, 1H, 6aαmin-H), 3.39 (dd, J = 8.4, 5.7 Hz, 1H, 6aαmaj-H), 3.06–3.12 (m, 1H, 10aαmaj-H), 2.96–2.02 (m, 1H, 10aβmin-H), 2.65–2.75 (m, 1H, 6bαmaj-H), 2.52–2.63 (m, 1H, 6bαmin-H), 2.32 (dd, J = 0.9, 0.9 Hz, 3H, 2-CH_3), 1.72–2.02 (m, 2H, cyclohex.), 1.26–1.64 (m, 5H, cyclohex.), 1.42 (app. q, J = 7.5 Hz, 2H, CH_2CH_3), 0.86 (t, J = 7.2 Hz, 3H, CH_2CH_3); ^1H NMR (300 MHz, DMSO-d_6, δ) 10.52 (bs, 1H, 1min-H), 10.28 (bs, 1H, 1maj-H), 10.27 (bs, 1H, 1min-H), 7.39–7.54 (m, 3H, Ph), 7.20–7.25 (m, 2H, Ph), 5.83 (d, J = 1.5 Hz, 1H, 3maj-H), 5.61 (d, J = 2.4 Hz, 1H, 3min-H), 5.59 (d, J = 2.4 Hz, 1H, 3min-H), 4.15 (app. d, J = 8.4 Hz, 1H, 3bαmin-H), 4.02 (dd, J = 8.4, 2.1 Hz, 1H, 3bαmin-H), 4.01 (dd, J = 8.4, 1.8 Hz, 1H, 3bαmaj-H), 3.42 (dd, J = 8.3, 5.3 Hz, 1H, 6aαmin-H), 3.39 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.35 (dd, J = 8.3, 5.3 Hz, 1H, 6aαmaj-H), 2.94–3.00 (m, 1H, 10aαmaj-H), 2.85–2.91 (m, 1H, 10aβmin-H), 2.41–2.52 (m, 1H, 6bαmaj-H), 2.27–2.39 (m, 1H, 6bmin-H), 2.18 (s, 3H, 2-CH_3), 1.70–2.18 (m, 2H, cyclohex.), 0.98–1.84 (m, 5H, cyclohex.), 1.38 (app. q, J = 7.5 Hz, 2H, CH_2CH_3), 0.80 (t, J = 7.2 Hz, 3H, CH_2CH_3 maj), 0.79 (t, J = 7.2 Hz, 3H, CH_2CH_3 min); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.4, 178.2, 177.4, 176.3, 133.0, 132.9, 129.6, 129.5, 128.8, 128.7, 128.2, 127.4, 127.3, 126.5, 117.0, 114.8, 108.9, 105.4, 103.0, 46.5, 45.7, 45.5, 38.1, 34.2, 34.0, 32.6–33.2 (overlapped peaks), 23.9, 23.8, 23.7, 13.5, 13.4, 12.6; IR (thin film, cm^{-1}) 3420(bs), 2955(m), 2930(m), 2866(m), 2100 (bw), 1771 (w), 1695(s), 1644(bs), 1389(m), 1193(m), 1178(m), 1164(m); HRMS m/z (M + Na^+) calcd 385.1887, found 385.1881. Anal. Calcd for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.40; H, 7.38; N, 7.84.

8-Isopropyl-2-methyl-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (23). Method B with **3f** (982 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **23** (700 mg, 39%) as a colorless solid, a mixture of two isomers (maj:min = 5.0:1.0): mp 278–281°C; ^1H NMR (300 MHz, DMSO-d_6, δ) 10.53 (bs, 1H, 1min-H), 10.28 (bs, 1H, 1maj-H), 7.38–7.55 (m, 3H, Ph), 7.17–7.24 (m, 2H, Ph), 7.82 (app. d, J = 1.5 Hz, 1H, 3maj-H), 5.62 (dd, J = 2.4, 0.6 Hz, 1H, 3min-H), 4.15 (app. d, J = 7.2 Hz, 1H, 3bαmin-H), 4.01 (dd, J = 8.4, 1.5 Hz, 1H, 3bαmaj-H), 3.39 (dd, J = 8.7, 5.4 Hz, 1H, 6aαmin-H), 3.35 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmaj-H), 2.94–3.01 (m, 1H, 10aαmaj-H), 2.86–2.92 (m, 1H, 10aβmin-H), 2.41–2.50 (m, 1H, 6bα-H), 2.18 (s, 3H, 2-CH_3), 1.64–2.12 (m, 2H, cyclohex.), 1.08–1.58 (m, 6H, cyclohex, $CH(CH_3)_2$), 0.86 (d, J = 6.3 Hz, 6H, $CH(CH_3)_2$ maj), 0.79 (d, J = 6.6 Hz, 6H, $CH(CH_3)_2$ min); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.5, 177.4, 144.7, 133.0, 129.6, 128.7, 127.3, 126.5, 108.9, 105.4, 45.5, 32.9–33.2 (overlapped peaks), 21.7, 21.0, 13.5; IR (thin film, cm^{-1}) 3467(m), 3393(bs), 3061(w), 2951(m), 2868(m), 1773(w), 1705(s), 1599(w), 1502(m), 1454(m), 1384(s), 1193(m), 1177(m), 1161(m); HRMS m/z (M + Na^+) calcd 399.2044, found 399.2047. Anal. Calcd for $C_{24}H_{28}N_2O_2$: C, 76.56; H, 7.50; N, 7.44. Found: C, 76.72; H, 7.63; N, 7.33.

8-tert-Butyl-2-methyl-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (24). Method A gave **24** (445 mg, 38%) as a light-orange solid, a mixture of three isomers (maj:min:min = 8.3:1.0:0.2): mp 221–222°C; ^1H NMR (300 MHz, $CDCl_3$, δ) 8.08 (bs, 1H, 1min-H), 7.65 (bs, 1H, 1min-H), 7.61 (bs, 1H, 1maj-H), 7.21–7.56 (m, 5H, Ph), 6.17 (dd, J = 2.7, 1.2 Hz, 1H, 3min-H), 6.03 (dd, J = 2.6, 1.1 Hz, 1H, 3maj-H), 5.74 (dd, J = 2.7, 1.1 Hz, 1H, 3min-H), 4.04 (dd, J = 7.8, 1.5 Hz, 1H, 3bαmaj-H), 3.96 (dd, J = 8.4, 1.8 Hz, 1H, 3bαmin-H), 3.43 (dd, J = 8.6, 5.6 Hz, 1H, 6aαmin-H), 3.34 (dd, J = 7.7, 5.6 Hz, 1H, 6aαmaj-H), 3.10–3.15 (m, 1H, 10aβmin-H), 2.69–2.78 (m, 1H, 6bαmaj-H), 2.61–2.68 (m, 1H, 10aαmaj-H), 2.53–2.62 (m, 1H 6bmin-H), 2.26 (d, J = 0.9 Hz, 3H, 2-CH_3), 1.77–2.07 (m, 3H, cyclohex.), 1.62 (ddd, J = 13.9, 10.1, 7.1 Hz, 1H, cyclohex.), 0.83–1.43 (m, 3H, cyclohex.), 0.91 (s, 9H, *t*-Bu), 0.74 (s, 9H, *t*-Bu); ^1H NMR (300 MHz, DMSO-d_6, δ) 10.37 (bs, 1H, 1min-H), 10.34 (bs, 1H, 1maj-H), 10.29 (bs, 1H, 1min-H), 7.36–7.50 (m, 3H, Ph), 7.10–7.13 (m, 2H, Ph), 5.67 (dd, J = 2.3, 0.8 Hz, 1H, 3maj-H), 5.55 (dd, J = 2.1, 0.6 Hz, 1H, 3min-H), 4.12 (app. d, J = 8.7 Hz, 1H, 3bαmin-H), 4.03 (dd, J = 8.4, 1.5 Hz, 1H, 3bαmin-H), 3.90 (dd, J = 7.7, 1.4 Hz, 1H, 3bαmaj-H), 3.50 (dd, J = 8.4, 6.6 Hz, 1H, 6aαmin-H), 3.47 (dd, J = 7.7, 5.6 Hz, 1H, 6aαmaj-H), 3.38 (dd, J = 8.3, 5.3 Hz, 1H, 6aαmin-H), 2.98–3.03 (m, 1H, 10aβmin-H), 2.56–2.65 (m, 1H, 10aαmaj-H), 2.42–2.53 (m, 1H, 6b-H), 0.90–2.20 (m, 7H, cyclohex.), 2.12 (s, 3H, 2-CH_3), 0.86 (s, 9H, *t*-Bu maj), 0.68 (s, 9H, *t*-Bu min); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 177.9, 177.1, 176.3, 173.8, 146.2, 134.3, 132.3, 130.4, 129.7, 129.4, 129.3, 129.29, 129.26, 129.20, 129.1, 128.6, 128.5, 127.0, 126.8, 126.5, 126.4, 126.2, 119.7, 114.0, 109.7, 104.7, 53.1, 47.8, 46.2, 45.7, 43.9, 43.7, 41.7, 41.2, 40.7, 39.2, 39.0, 38.3, 34.3, 34.2, 32.9, 32.6, 32.5, 32.4, 31.4, 30.5, 28.7, 28.5, 27.7, 27.5, 27.4, 25.5, 24.8, 24.3, 22.2, 13.2; IR (thin film, cm^{-1}) 3390(bs), 2951(m), 2866(w), 2357 (w), 2088(bw), 1772(w), 1708(s), 1647(bs), 1500(m), 1386(m), 1372(m), 1199(m), 1176(m); HRMS m/z (M + Na^+) calcd 413.2200, found 413.2181. Anal. Calcd for $C_{25}H_{30}N_2O_2$: C, 76.89; H, 7.74; N, 7.17. Found: C, 76.65; H, 7.43; N, 7.39.

2-Methyl-5,8-diphenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (25). Method B with **3h** (1220 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **25** (850 mg, 43%) as a colorless solid, a mixture of two isomers (maj:min = 3.8:1.0): mp 282–285°C; ^1H NMR (300 MHz, DMSO-d_6, δ) 10.56 (bs, 1H, 1min-H), 10.38 (bs, 1H, 1maj-H), 7.15–7.56 (m, 10H, Ph), 5.78–5.87 (m, 1H, 3maj-H), 5.68–5.67 (m, 1H, 3min-H), 4.19 (d, J = 8.1 Hz, 1H, 3bαmin-H), 4.02 (d, J = 7.5 Hz, 1H, 3bαmaj-H), 3.36–3.54 (m, 1H, 6aα-H), 2.82–2.98 (m, 1H, 10a-H), 2.48–2.60 (m, 1H, 6bα-H), 2.19 (s, 3H, 2-CH$_3$), 1.34–2.10 (m, 7H, cyclohex.); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 178.0, 176.8, 129.3, 128.6, 127.7, 127.3, 126.6, 125.8, 109.8, 105.6, 105.5, 105.4, 45.6, 33.2–33.6 (overlapped peaks), 13.3; IR (thin film, cm^{-1}) 3462(m), 3431(m), 3394(bs), 3060(w), 3024(w), 2934(s), 2868(m), 1776(w), 1706(s), 1599(w), 1499(m), 1383(m), 1189(m), 1168(m); HRMS m/z (M + Na$^+$) calcd 433.1887, found 433.1908. Anal. Calcd for C$_{27}$H$_{26}$N$_2$O$_2$: C, 79.00; H, 6.38; N, 6.82. Found: C, 78.88; H, 6.58; N, 6.68.

2-Methyl-5-(4-methylphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (26). Method B with **3c** (687 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **26** (700 mg, 42%) as a colorless solid, a mixture of two isomers (maj:min = 1.6:1.0): mp 276–278°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.51 (bs, 1H, 1maj-H), 10.25 (bs, 1H, 1min-H), 7.30 (d, J = 8.1 Hz, 2H, Ph maj), 7.28 (d, J = 7.8 Hz, 2H, Ph min), 7.12 (d, J = 8.1 Hz, 2H, Ph maj), 7.09 (d, J = 8.4 Hz, 2H, Ph min), 5.83 (dd, J = 2.4, 1.2 Hz, 1H, 3min-H), 5.59 (dd, J = 2.4, 0.6 Hz, 1H, 3maj-H), 4.14 (app. d, J = 7.8 Hz, 1H, 3bαmaj-H), 3.99 (dd, J = 8.4, 1.8 Hz, 1H, 3bαmin-H), 3.37 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmaj-H), 3.32 (dd, J = 8.6, 5.3 Hz, 1H, 6aαmin-H), 2.99–3.04 (m, 1H, 10aαmin-H), 2.92 (m, 1H, 10aβmaj-H), 2.06–2.40 (m, 2H, cyclohex., 6bα-H), 2.35 (s, 3H, 4′-CH$_3$ maj), 2.34 (s, 3H, 4′-CH$_3$ min), 2.18 (s, 3H, 2-CH$_3$), 0.98–1.64 (m, 7H, cyclohex.); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.5, 178.3, 177.6, 176.4, 138.4, 138.3, 130.4, 130.2, 130.1, 130.0, 128.2, 127.2, 126.9, 126.5, 119.0, 116.9, 108.8, 105.5, 102.8, 46.2, 45.9, 38.7, 38.5, 38.4, 38.2, 33.1, 33.0, 29.3, 27.6, 26.1, 25.7, 23.2, 22.9, 21.4, 21.3, 20.8, 13.52, 13.45; IR (thin film, cm^{-1}) 3400(bs), 2927(m), 2857(m), 1776(w), 1702(s), 1516(m), 1387(m), 1182(m), 1161(m); HRMS m/z (M + Na$^+$) calcd 371.1731, found 371.1743. Anal. Calcd for C$_{22}$H$_{24}$N$_2$O$_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 75.98; H, 6.92; N, 7.90.

2,8-Dimethyl-2-(4-methylphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (27). Method B with **3d** (785 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **27** (650 mg, 37%) as a colorless solid, a mixture of three isomers (maj:min:min = 1.1:1.0:0.1): mp 255–257°C; ^{1}H NMR (200 MHz, DMSO-d_6, δ) 10.50 (bs, 1H, 1min-H), 10.25 (bs, 1H, 1maj-H), 7.29 (d, J = 8.4 Hz, 2H, Ph min), 7.27 (d, J = 8.2 Hz, 2H, Ph maj), 7.09 (d, J = 8.2 Hz, 1H, Ph min), 7.07 (d, J = 8.2 Hz, 1H, Ph maj), 5.80 (app. d, J = 1.8 Hz, 1H, 3maj-H), 5.58 (dd, J = 2.2, 0.8 Hz, 1H, 3min-H), 5.56–5.58 (m, overlapped, 1H, 3min-H), 4.12 (app. d, J = 7.8 Hz, 1H, 3bαmin-H), 3.97 (dd, J = 8.3, 1.7 Hz, 1H, 3bαmaj-H), 3.38 (dd, J = 7.8, 5.0 Hz, 1H, 6aαmin-H), 3.37 (dd, J = 8.6, 5.4 Hz, 1H, 6aαmin-H), 3.32 (dd, J = 8.6, 5.4 Hz, 1H, 6aαmaj-H), 2.91–2.98 (m, 1H, 10amaj-H), 2.83–2.89 (m, 1H, 10amin-H), 1.64–2.60 (m, 3H, cyclohex., 6bα-H), 2.32 (s, 3H, 4′-CH$_3$), 2.16 (s, 3H, 2-CH$_3$), 0.98 (m, 5H, cyclohex.), 0.94 (d, J = 7.0 Hz, 3H, 8-CH$_3$ maj), 0.70 (d, J = 6.2 Hz, 3H, 8-CH$_3$ min); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.4, 178.2, 177.5, 176.4, 138.2, 130.4, 130.1, 130.0, 127.2, 126.5, 109.0, 105.4, 45.6, 38.8, 38.0, 33.1, 32.3–32.7 (overlapped peaks), 26.8, 26.7, 21.3, 13.4; IR (thin film, cm^{-1}) 3460(m), 3396(bs), 3075(w), 3040(w), 2927(s), 2892(m), 2867(m), 2362(w), 2336(w), 1776(m), 1708(s), 1516(s), 1387(s), 1180(s); HRMS m/z (M + Na$^+$) calcd 385.1887, found 385.1900. Anal. Calcd for C$_{23}$H$_{26}$N$_2$O$_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.01; H, 7.03; N, 7.58.

8-Ethyl-2-methyl-5-(4-methylphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (28). Method B with **3e** (883 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **28** (680 mg, 38%) as a colorless solid, a mixture of two isomers (maj:min = 2.1:1.0): mp 269–271°C; ^{1}H NMR (200 MHz, DMSO-d_6, δ) 10.50 (bs, 1H, 1min-H), 10.25 (bs, 1H, 1maj-H), 7.29 (d, J = 8.0 Hz, 2H, Ph min), 7.27 (d, J = 8.2 Hz, 2H, Ph maj), 7.08 (d, J = 8.2 Hz, 2H, Ph min), 7.06 (d, J = 8.4 Hz, 2H, Ph maj), 5.80 (dd, J = 2.0, 0.8 Hz, 1H, 3maj-H), 5.59 (app. d, J = 2.2 Hz, 1H, 3min-H), 4.11 (app. d, J = 8.2 Hz, 1H, 3bαmin-H), 3.96 (dd, J = 8.6, 1.4 Hz, 1H, 3bαmaj-H), 3.35 (dd, J = 8.7, 5.3 Hz, 1H, 6aαmin-H), 3.31 (dd, J = 8.5, 5.3 Hz, 1H, 6aαmaj-H), 2.92–2.99 (m, 1H, 10aαmaj-H), 2.83–2.88 (m,1H, 10aβmin-H), 1.64–2.50 (m, 2H, cyclohex., 6bα-H), 2.38 (s, 3H, 4′CH$_3$), 2.16 (s, 3H, 2-CH$_3$), 1.00–1.88 (m, 6H, cyclohex.), 1.35 (app. q, J = 7.4 Hz, 2H, CH_2CH$_3$), 0.78 (t, J = 7.2 Hz, 3H, CH$_2$CH_3 maj), 0.77 (t, J = 7.2 Hz, 1H, CH$_2$CH_3 min); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.4, 178.3, 177.5, 176.4, 138.4, 138.2, 130.4, 130.4, 130.1, 130.0, 128.2, 127.2, 126.8, 126.5, 117.0, 108.9, 105.4, 104.5, 103.0, 45.6, 33.8–34.2 (overlapped peaks), 33.1, 32.6–32.8 (overlapped peaks), 23.8, 23.7, 21.3, 13.5, 12.6; IR (thin film, cm^{-1}) 3468(m), 3394(bs), 3038(w), 2958(m), 2932(s), 2867(m), 1776(m), 1706(s), 1516(s), 1386(s), 1181(m), 1165(m); HRMS m/z (M + Na$^+$) calcd 399.2044, found 399.2051. Anal. Calcd for C$_{24}$H$_{28}$N$_2$O$_2$: C, 76.56; H, 7.50; N, 7.44. Found: C, 76.70; H, 7.49; N, 7.43.

8-Isopropyl-2-methyl-5-(4-methylphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (29). Method B with **3f** (982 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **29** (760 mg, 41%) as a colorless solid, a mixture of two isomers (maj:min = 3.2:1.0): mp 296–298°C; ^{1}H NMR (200 MHz, DMSO-d_6, δ) 10.50 (bs, 1H, 1min-H), 10.26 (bs, 1H, 1maj-H), 7.30 (d, J = 8.2 Hz, 2H, Ph min), 7.28 (d, J = 8.0 Hz, 2H, Ph maj), 7.07 (d, J = 8.2 Hz, 2H, Ph min), 7.05 (d, J = 8.2 Hz, 2H, Ph maj), 5.80 (app. d, J = 1.2 Hz, 1H, 3maj-H), 5.59 (dd, J = 2.8, 0.6 Hz, 1H, 3min-H), 4.11 (app. d, J = 9.0 Hz, 1H, 3bαmin-H), 3.96 (dd, J = 8.3, 1.7 Hz, 1H, 3bαmaj-H), 3.35 (dd, J = 8.0, 5.2 Hz, 1H, 6aαmin-H), 3.31 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmaj-H), 2.91–2.99 (m, 1H, 10aαmaj-H), 2.84–2.89 (m, 1H, 10aβmin-H), 2.29–2.49 (m, 1H, 6bα-H), 2.32 (s, 3H, 4′-CH$_3$), 0.73–2.20 (m, 8H, cyclohex., CH(CH$_3$)$_2$), 2.16 (s, 3H, 2-CH$_3$), 0.84 (d, J = 6.6 Hz, 6H, CH(CH_3)$_2$), 0.77 (d, J = 6.4 Hz, 6H, CH(CH_3)$_2$); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.6, 177.5, 138.2, 130.5, 130.0, 128.4, 127.1, 126.5, 108.9, 105.4, 45.5, 32.7–33.2 (overlapped peaks), 21.7, 21.3, 21.0, 13.5; IR (thin film, cm^{-1}) 3393(bs), 2948(m), 2925(m), 2867(m), 1773(w), 1696(s), 1516(m), 1387(m), 1192(m), 1180(m), 1162(m); HRMS m/z (M + Na$^+$) calcd 413.2200, found 413.2201. Anal. Calcd for C$_{25}$H$_{30}$N$_2$O$_2$: C, 76.89; H, 7.74; N, 7.17. Found: C, 76.58; H, 7.82; N, 6.93.

8-tert-Butyl-2-methyl-5-(4-methylphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (30). Method B with **3g** (1079 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **30** (530 mg, 27%) as a pink solid, a mixture of three isomers (maj:min:min = 12.4:1.0:0.6): mp 220–222°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.32 (bs, 1H, 1maj-H), 10.28 (bs, 1H, 1min-H), 10.22 (bs, 1H, 1min-H), 7.25 (d, J = 7.8 Hz, 2H, Ph), 6.99 (d, J = 7.8 Hz, 2H, Ph), 5.79–5.82 (m, 1H, 3min-H), 5.75–5.77 (m, 1H, 3min-H), 5.65–5.68 (m, 1H, 3maj-H), 4.06 (d, J = 6.9 Hz, 1H, 3bαmin-H), 3.89 (d, J = 7.5 Hz, 1H, 3bαmaj-H), 3.44 (dd, J = 7.4, 5.9 Hz, 1H, 6aαmaj-H), 1.46–2.68 (m, 7H, cyclohex., 10a-H, 6b-H), 2.32 (s, 3H, 4′-CH$_3$), 2.12 (s, 3H, 2-CH$_3$), 0.90–1.20 (m, 2H, cyclohex.), 0.85 (s, 9H, *t*-Bu maj), 0.68 (s, 9H, *t*-Bu min); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 178.0, 177.6, 141.5, 137.7, 133.3, 133.1, 131.3, 129.8, 129.7, 126.9, 126.5, 114.2, 109.9, 104.9, 51.9, 47.0, 45.6, 44.2, 41.6, 40.6, 34.2, 32.8, 32.5, 31.9, 27.7, 27.5, 26.8, 24.7, 23.9, 23.8, 23.5, 23.4, 21.3, 18.6, 13.2; IR (thin film, cm^{-1}) 3390(bs), 3038(w), 2953(s), 2869(m), 2360(w), 2340(w), 1767(m), 1708(s), 1516(m), 1384(s), 1367(m), 1175(m), 1169(m); HRMS *m/z* (M + Na$^+$) calcd for $C_{26}H_{32}N_2O_2$: 427.2357, found 427.2356.

2-Methyl-5-(4-methylphenyl)-8-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (31). Method B with **3h** (1220 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **31** (830 mg, 41%) as a colorless solid, a mixture of two isomers (maj:min = 11.9:1.0): mp 298–300°C; ^{1}H NMR (200 MHz, DMSO-d_6, δ) 10.53 (bs, 1H, 1min-H), 10.35 (bs, 1H, 1maj-H), 6.96–7.30 (m, 9H, Ph), 5.78–5.83 (m, 1H, 3maj-H), 5.63 (dd, J = 2.1, 1.5 Hz, 1H, 3min-H), 4.15 (d, J = 9.2 Hz, 1H, 3bαmin-H), 3.98 (d, J = 7.4 Hz, 1H, 3bαmaj-H), 3.36–3.45 (m, 1H, 6aα-H), 2.80–2.96 (m, 1H, 10a-H), 1.70–2.60 (m, 8H, cyclohex., 6bα-H), 2.33 (s, 3H, 4′-CH$_3$), 2.17 (s, 3H, 2-CH$_3$); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.7, 177.5, 138.3, 130.5, 130.0, 128.9, 127.6, 127.3, 126.8, 126.1, 109.2, 45.4, 33.1–33.7 (overlapped peaks), 21.3, 13.5; IR (thin film, cm^{-1}) 3431(bs), 3025(w), 2941(m), 2872(m), 1772(m), 1688(m), 1516(m), 1452(m), 1379(m), 1192(m); HRMS *m/z* (M + Na$^+$) calcd 447.2044, found 447.2065. Anal. Calcd for $C_{28}H_{28}N_2O_2$: C, 79.22; H, 6.65; N, 6.60. Found: C, 78.98; H, 6.70; N, 6.49.

5-(4-Methoxyphenyl)-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (32). Method A gave **32** (372 mg, 34%) as a cream-colored solid, a mixture of two isomers (maj:min = 3.5:1.0): mp 239–240°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.31 (bs, 1H, 1min-H), 7.70 (bs, 1H, 1maj-H), 7.21 (d, J = 9.0 Hz, 2H, Ph), 6.98 (d, J = 9.0 Hz, 2H, Ph), 6.19 (dd, J = 2.4, 0.9 Hz, 1H, 3maj-H), 5.77 (dd, J = 3.3, 1.2 Hz, 1H, 3min-H), 3.94 (dd, J = 8.6, 2.0 Hz, 1H, 3bα-H), 3.83 (s, 3H, OCH$_3$), 3.45 (dd, J = 8.6, 5.6 Hz, 1H, 6aαmin-H), 3.38 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmaj-H), 3.11–3.17 (m, 1H, 10aαmaj-H), 3.00–3.07 (m, 1H, 10aβmin-H), 2.50–2.58 (m, 1H, 6b-H), 2.31–2.32 (dd, J = 0.9, 0.9 Hz, 3H, 2-CH$_3$), 2.10–2.19 (m, 1H, cyclohex.) 1.17–1.80 (m, 7H, cyclohex.); ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.50 (d, J = 1.5 Hz, 1H, 1min-H), 10.24 (app. bs, 1H, 1maj-H), 7.13 (d, J = 9.0 Hz, 2H, Ph), 7.02 (d, J = 9.0 Hz, 2H, Ph), 5.83 (d, J = 0.9 Hz, 1H, 3maj-H), 5.59 (d, J = 1.5 Hz, 1H, 3min-H), 4.12 (d, J = 8.1 Hz, 1H, 3bαmin-H), 3.98 (dd, J = 8.4, 1.5 Hz, 1H, 3bαmaj-H), 3.78 (s, 3H, OCH$_3$), 3.36 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.31 (dd, J = 8.4, 5.1 Hz, 1H, 6aαmaj-H), 2.98–3.05 (m, 1H, 10aαmaj-H), 2.89–2.95 (m, 1H, 10aβmin-H), 2.04–2.40 (m, 2H, cyclohex., 6bα-H), 2.18 (s, 3H, 2-CH$_3$), 0.99–1.64 (m, 7H, cyclohex.); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 178.4, 178.3, 177.1, 176.5, 159.4, 127.7, 127.4, 127.1, 114.6, 114.5, 109.4, 103.7, 55.6, 46.0, 38.8, 38.6, 38.4, 37.8, 33.0, 32.9, 29.1, 28.1, 26.1, 25.6, 23.0, 22.7, 21.1, 20.6, 13.3; IR (thin film, cm^{-1}) 3447(bs), 2935(m), 2858(m), 2150(bw), 1772(w), 1697(s), 1651(bs), 1518(m), 1392(m), 1252(m), 1183(m), 1162(m); HRMS *m/z* (M + Na$^+$) calcd 387.1680, found 387.1701. Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.50; H, 6.64; N, 7.69. Found: C, 72.61; H, 6.84; N, 7.64.

5-(4-Methoxyphenyl)-2,8-dimethyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (33). Method B with **3d** (785 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **33** (1100 mg, 61%) as a colorless solid, a mixture of three isomers (maj:min:min = 2.3:1.0:0.3): mp 265–268°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.50 (bs, 1H, 1min-H), 10.25 (bs, 1H, 1maj-H), 10.23 (bs, 1H, 1min-H), 7.14 (d, J = 9.0 Hz, 2H, Ph min), 7.12 (d, J = 9.0 Hz, 2H, Ph maj), 7.04 (d, J = 8.4 Hz, 2H, Ph min), 7.02 (d, J = 8.7 Hz, 2H, Ph maj), 5.81 (dd, J = 1.5, 0.6 Hz, 1H, 3maj-H), 5.60 (app. d, J = 2.4 Hz, 1H, 3min-H), 5.58 (app. d, J = 2.4 Hz, 1H, 3min-H), 4.12 (app. d, J = 8.4 Hz, 1H, 3bαmin-H), 3.98 (dd, J = 8.4, 1.5 Hz, 1H, 3bαmin-H), 3.97 (dd, J = 8.4, 1.8 Hz, 1H, 3bαmaj-H), 3.79 (s, 3H, OCH$_3$ min), 3.78 (s, 3H, OCH$_3$ maj), 3.37 (dd, J = 8.3, 5.0 Hz, 1H, 6aαmin-H), 3.34 (dd, J = 8.3, 5.6 Hz, 1H, 6aαmin-H), 3.33 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmaj-H), 2.93–3.00 (m, 1H, 10aαmaj-H), 2.85–2.90 (m, 1H, 10aβmin-H), 1.74–2.56 (m, 4H, cyclohex., 6b-H), 2.17 (s, 3H, 2-CH$_3$), 0.90–1.66 (m, 4H, cyclohex.), 0.95 (d, J = 6.9 Hz, 3H, 8-CH$_3$ maj), 0.72 (d, J = 6.6 Hz, 3H, 8-CH$_3$ min); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.5, 178.0, 159.3, 128.6, 126.5, 125.7, 114.7, 109.0, 108.9, 105.0, 104.9, 55.9, 45.5, 33.1, 32.2–32.7 (overlapped peaks), 13.4; IR (thin film, cm^{-1}) 3462(m), 3390(bs), 3068(w), 3012(w), 2957(m), 2924(m), 2863(m), 1776(m), 1705(s), 1516(s), 1391(m), 1303(m), 1253(m), 1177(s); HRMS *m/z* (M + Na$^+$) calcd 401.1836, found 401.1841. Anal. Calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 72.74; H, 6.66; N, 7.38.

8-Ethyl-5-(4-methoxyphenyl)-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (34). Method A gave **34** (424 mg, 36%) as a white solid, a mixture of three isomers (maj:min:min = 4.3:1.0:0.1): mp 249–251°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.30 (bs, 1H, 1min-H), 7.71 (bs, 1H, 1maj-H), 7.16–7.24 (m, 2H, Ph), 6.96–7.02 (m, 2H, Ph), 6.18 (dd, J = 2.4, 0.9 Hz, 1H, 3maj-H), 5.79 (d, J = 2.4 Hz, 1H, 3min-H), 5.75 (d, J = 3.3 Hz, 1H, 3min-H), 3.94 (dd, J = 8.4, 1.8 Hz, 1H, 3bα-H), 3.83 (s, 3H, OCH$_3$), 3.44 (dd, J = 8.7, 5.7 Hz, 1H, 6aαmin-H), 3.41 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.37 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmaj-H), 3.05–3.11 (m, 1H, 10aαmaj-H), 2.95–3.01 (m, 1H, 10aβmin-H), 2.64–2.74 (m, 1H, 6bαmaj-H), 2.53–2.62 (m, 1H, 6bβmin-H), 2.30–2.32 (m, 3H, 2-CH$_3$), 1.81–1.97 (m, 2H, cyclohex.), 1.10–1.60 (m, 7H, cyclohex., $\mathrm{C}\mathit{H}_2\mathrm{CH}_3$), 0.86 (t, J = 7.4 Hz, 3H, $\mathrm{CH_2C}\mathit{H}_3$); ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.51 (bs, 1H, 1min-H), 10.26 (bs, 1H, 1maj-H), 10.23 (bs, 1H, 1min-H), 7.02–7.16 (m, 4H, Ph), 5.82 (dd, J = 2.4, 1.5 Hz, 1H, 3maj-H), 5.60 (dd, J = 2.4, 0.9 Hz, 1H, 3min-H), 5.58 (dd, $J = 2.7$, 1.2 Hz, 1H, 3min-H), 4.11 (app. d, $J = 8.7$ Hz, 1H, 3bαmin-H), 3.98 (dd, $J = 8.4$, 1.8 Hz, 1H, 3bαmin-H), 3.97 (dd, $J = 8.4$, 1.5 Hz, 1H, 3bαmaj-H), 3.791 (s, 3H, OCH$_3$ min), 3.787 (s, 3H, OCH$_3$ min), 3.78 (s, 3H, OCH$_3$ maj), 3.36 (dd, $J = 8.9$, 5.6 Hz, 1H, 6aαmin-H), 3.34 (dd, $J = 8.1$, 5.4 Hz, 1H, 6aαmin-H), 3.32 (dd, $J = 8.4$, 5.4 Hz, 1H, 6aαmaj-H), 2.98–3.02 (m, 1H, 10amin-H), 2.93–2.99 (m, 1H, 10aαmaj-H), 2.85–2.90 (m, 1H, 10aβmin-H), 2.37–2.50 (m, 1H, 6bαmaj-H), 2.26–2.38 (m, 1H, 6bmin-H), 2.17 (s, 3H, 2-CH3), 1.74–2.17 (m, 1H, cyclohex.), 1.68–1.84 (m, 1H, cyclohex.), 0.98–1.66 (m, 5H, cyclohex.), 1.40 (app. q, $J = 7.5$ Hz, 2H, C*H*$_2$CH$_3$), 0.80 (t, $J = 7.2$ Hz, 3H, CH$_2$C*H*$_3$ maj), 0.78 (t, $J = 7.8$ Hz, 3H, CH$_2$C*H*$_3$ min); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 178.3, 178.2, 177.1, 159.4, 127.7, 127.4, 126.8, 124.8, 114.6, 114.5, 109.6, 105.8, 103.8, 55.5, 45.8, 45.6, 39.1, 38.8, 38.4, 34.5, 34.0, 32.7–33.0 (overlapped peaks), 29.7, 27.9, 27.3, 26.5, 24.4, 23.7, 22.9, 13.3, 12.3; IR (thin film, cm^{-1}) 3393(bs), 2916(m), 2862(m), 2400(w), 2150(bw), 1774(w), 1694(s), 1644(bs), 1518(m), 1388(m), 1256(m), 1178(m), 1160(m); HRMS *m*/*z* (M + Na$^+$) calcd 415.1993, found 415.1986. Anal. Calcd for C$_{24}$H$_{28}$N$_2$O$_3$: C, 73.44; H, 7.19; N, 7.14. Found: C, 73.31; H, 7.06; N, 7.03.

8-Isopropyl-5-(4-methoxyphenyl)-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (35). Method B with **3f** (981 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **35** (1450 mg, 74%) as a colorless solid, a mixture of four isomers (maj:min:min:min = 2.9:1.0:0.3:0.3): mp 300–303°C; ^{1}H NMR (300 MHz, DMSO-*d*$_6$, δ) 10.51 (d, $J = 2.1$ Hz, 1H, 1min-H), 10.47–10.50 (m, overlapped, 1H, 1min-H), 10.27 (d, $J = 2.1$ Hz, 1H, 1maj-H), 10.22 (d, $J = 2.7$ Hz, 1H, 1min-H), 7.10 (d, $J = 9.0$ Hz, 2H, Ph), 7.04 (d, $J = 9.3$ Hz, 2H, Ph), 5.82 (dd, $J = 2.4$, 0.6 Hz, 1H, 3maj-H), 5.79–5.81 (m, overlapped, 1H, 3min-H), 5.61 (dd, $J = 2.1$, 0.6 Hz, 1H, 3min-H), 5.58 (dd, $J = 2.7$, 1.5 Hz, 1H, 3min-H), 4.13 (app. d, $J = 8.4$ Hz, 1H, 3bαmin-H), 4.11 (dd, $J = 9.6$, 1.2 Hz, 1H, 3bαmin-H), 3.99 (dd, $J = 8.4$, 1.8 Hz, 1H, 3bαmin-H), 3.96 (dd, $J = 9.6$, 1.8 Hz, 1H, 3bαmaj-H), 3.78 (s, 3H, OCH$_3$), 3.40 (dd, $J = 8.7$, 5.3 Hz, 1H, 6aαmin-H), 3.36 (dd, $J = 8.7$, 5.4 Hz, 1H, 6aαmin-H), 3.35 (dd, $J = 8.4$, 5.1 Hz, 1H, 6aαmin-H), 3.32 (dd, $J = 8.4$, 5.4 Hz, 1H, 6aαmaj-H), 2.93–2.99 (m, 1H, 10aαmaj-H), 2.86–2.91 (m, 1H, 10aβmin-H), 2.25–2.50 (m, 1H, 6b-H), 2.17 (s, 3H, 2-CH$_3$), 0.94–2.17 (m, 8H, cyclohex., C*H*(CH$_3$)$_2$), 0.854 (d, $J = 6.3$ Hz, 6H, CH(C*H*$_3$)$_2$ maj), 0.845 (d, $J = 6.6$ Hz, 6H, CH(C*H*$_3$)$_2$ min), 0.79 (d, $J = 6.3$ Hz, 6H, CH(C*H*$_3$)$_2$ min), 0.75 (d, $J = 6.6$ Hz, 6H, CH(C*H*$_3$)$_2$ min), 0.70 (d, $J = 6.6$ Hz, 6H, CH(C*H*$_3$)$_2$ min); ^{13}C NMR (75 MHz, DMSO-*d*$_6$, δ) 178.8, 177.6, 159.4, 128.9, 128.7, 127.6, 126.8, 126.7, 126.0, 125.6, 114.9, 114.8, 109.2, 104.5, 45.4, 33.1–33.9 (overlapped peaks), 13.5; IR (thin film, cm^{-1}) 3397(bs), 3063(w), 2948(s), 2867(s), 1774(m), 1706(s), 1516(s), 1454(m), 1389(s), 1304(m), 1252(s), 1175(s); HRMS *m*/*z* (M + Na$^+$) calcd 429.2149, found 429.2138. Anal. Calcd for C$_{25}$H$_{30}$N$_2$O$_3$: C, 73.86; H, 7.44; N, 6.89. Found: C, 74.01; H, 7.61; N, 6.98.

8-tert-Butyl-5-(4-methoxyphenyl)-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (36). Method A gave **36** (442 mg, 35%) as a light-orange solid, a mixture of three isomers (maj:min:min = 4.4:1.0:0.3): mp 239–240°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.07 (bs, 1H, 1min-H), 7.62 (bs, 1H, 1min-H), 7.58 (bs, 1H, 1maj-H), 7.12–7.24 (m, 2H, Ph), 6.92–7.02 (m, 2H, Ph), 6.03 (dd, $J = 2.6$, 1.1 Hz, 1H, 3maj-H), 5.75 (dd, $J = 2.6$, 1.1 Hz, 1H, 3min-H), 5.73 (dd, $J = 1.2$, 2.7 Hz, 1H, 3min-H), 4.02 (dd, $J = 7.8$, 1.5 Hz, 1H, 3bαmaj-H), 3.94 (dd, $J = 7.8$, 1.5 Hz, 1H, 3bαmin-H), 3.84 (s, 3H, OCH$_3$ min), 3.81 (s, 3H, OCH$_3$ maj), 3.41 (dd, $J = 8.4$, 5.4 Hz, 1H, 6aαmin-H), 3.40 (dd, $J = 7.8$, 5.4 Hz, 1H, 6aαmin-H), 3.32 (dd, $J = 7.7$, 5.6 Hz, 1H, 6aαmaj-H), 3.08–3.12 (m, 1H, 10aβmin-H), 2.70–2.77 (m, 1H, 6bαmaj-H), 2.59–2.67 (m, 1H, 10aαmaj-H), 2.53–2.60 (m, 1H, 6bαmin-H), 2.26 (d, $J = 0.9$ Hz, 3H, 2-CH$_3$), 1.77–2.06 (m, 3H, cyclohex.), 1.55–1.66 (m, 1H, cyclohex.), 0.83–1.42 (m, 3H, cyclohex.), 0.90 (s, 9H, *t*-Bu maj), 0.74 (s, 9H, *t*-Bu min); ^{1}H NMR (300 MHz, DMSO-*d*$_6$, δ) 10.36 (d, $J = 2.1$ Hz, 1H, 1min-H), 10.32 (d, $J = 2.4$ Hz, 1H, 1maj-H), 10.21 (d, $J = 1.8$ Hz, 1H, 1min-H), 6.97–7.10 (m, 4H, Ph), 5.67 (dd, $J = 2.4$, 0.9 Hz, 1H, 3maj-H), 5.58 (app. d, $J = 2.1$ Hz, 1H, 3min-H), 5.54 (dd, $J = 2.4$, 0.9 Hz, 1H, 3min-H), 4.08 (app. d, $J = 8.4$ Hz, 1H, 3bαmin-H), 3.99 (dd, $J = 7.8$, 2.1 Hz, 1H, 3bαmin-H), 3.88 (dd, $J = 7.7$, 1.4 Hz, 1H, 3bαmaj-H), 3.79 (s, 3H, OCH$_3$ min), 3.78 (s, 3H, OCH$_3$ min), 3.77 (s, 3H, OCH$_3$ maj), 3.46 (dd, $J = 8.3$, 6.5 Hz, 1H, 6aαmin-H), 3.43 (dd, $J = 7.5$, 5.7 Hz, 1H, 6aαmaj-H), 3.38 (dd, $J = 7.5$, 5.1 Hz, 1H, 6aαmaj-H), 2.88–2.91 (m, 1H, 10amin-H), 2.30–2.65 (m, 3H, 6b-H, 10aαmaj-H, 10amin-H), 0.78–2.20 (m, 7H, cyclohex.), 2.18 (s, 3H, 2-CH$_3$ min), 2.13 (s, 3H, 2-CH$_3$ min), 2.12 (s, 3H, 2-CH$_3$ maj), 0.85 (s, 9H, *t*-Bu maj), 0.84 (s, 9H, *t*-Bu min), 0.68 (s, 9H, *t*-Bu min); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 178.8, 178.5, 178.2, 177.3, 159.4, 130.3, 128.0, 127.68, 127.67, 127.2, 127.0, 125.0, 124.9, 114.6, 114.5, 109.7, 109.3, 105.9, 104.7, 55.6, 47.9, 46.1, 45.6, 45.3, 41.6, 40.7, 39.1, 38.9, 34.6, 34.3, 34.2, 32.9, 32.6, 32.5, 30.5, 28.6, 28.4, 27.6, 25.5, 24.3, 22.2, 13.2; ^{13}C NMR (75 MHz, DMSO-*d*$_6$, δ) 178.7, 177.5, 176.3, 159.4, 159.3, 130.2, 128.7, 128.4, 126.9, 125.7, 125.6, 117.0, 114.8, 114.6, 109.4, 104.0, 55.9, 45.2, 44.8, 41.6, 34.2–34.6 (overlapped peaks), 33.9, 33.2, 33.0, 30.7, 28.2, 28.0, 25.7, 13.4; IR (thin film, cm^{-1}) 3386(bs), 2952(m), 2865(m), 2050(bw), 1774(w), 1702(s), 1654(bs), 1513(s), 1390(m), 1251(s), 1168(m); HRMS *m*/*z* (M + Na$^+$) calcd 443.2306, found 443.2292. Anal. Calcd for C$_{26}$H$_{32}$N$_2$O$_3$: C, 74.26; H, 7.67; N, 6.66. Found: C, 74.39; H, 7.82; N, 6.49.

5-(4-Methoxyphenyl)-2-methyl-8-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (37). Method B with **3h** (1220 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **37** (1200 mg, 57%) as a colorless solid, a mixture of three isomers (maj:min:min = 4.7:1.0:0.8): mp 306–309°C; ^{1}H NMR (300 MHz, DMSO-*d*$_6$, δ) 10.54 (app. bs, 1H, 1min-H), 10.36 (d, $J = 0.9$ Hz, 1H, 1maj-H), 10.33 (app. bs, 1H, 1min-H), 6.98–7.37 (m, 9H, Ph), 5.84–5.87 (m, 1H, 3min-H), 5.77–5.85 (m, 1H, 3maj-H), 5.63–5.66 (m, 1H, 3min-H), 4.15 (d, $J = 8.1$ Hz, 1H, 3bαmin-H), 4.03 (dd, $J = 8.1$, 2.4 Hz, 1H, 3bαmin-H), 3.98 (d, $J = 8.1$ Hz, 1H, 3bαmaj-H), 3.79 (s, 3H, OCH$_3$ maj), 3.74 (s, 3H, OCH$_3$ min), 3.48 (dd, $J = 8.1$, 5.4 Hz, 1H, 6aαmin-H), 3.43 (dd, $J = 8.4$, 5.4 Hz, 1H, 6aαmaj-H), 3.07–3.13 (m, 1H, 10amin-H), 2.88–2.96 (m, 1H, 10amaj-H), 2.82–2.88 (m, 1H, 10amin-H), 1.55–2.60 (m, 8H, cyclohex., 6b-H), 2.18(s, 3H, 2-CH$_3$); IR (thin film, cm^{-1}) 3446(m), 3393(bs), 3056(w), 3023(w), 2935(m), 2868(m), 1773(w), 1705(s), 1514(s), 1389(m), 1302(m), 1252(m), 1189(m), 1172(m); HRMS *m*/*z* (M + Na$^+$) calcd 463.1993, found 463.2013. Anal. Calcd for C$_{28}$H$_{28}$N$_2$O$_3$: C, 76.34; H, 6.41; N, 6.36. Found: C, 76.11; H, 6.41; N, 6.16.

2-Methyl-5-(4-phenoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (38). Method B with **3c** (687 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **38** (910 mg, 44%) as a colorless solid, a mixture of two isomers (maj:min = 5.0:1.0): mp 282–284°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.52 (bs, 1H, 1maj-H), 10.25 (bs, 1H, 1min-H), 7.41–7.47 (m, 2H, Ph), 7.17–7.31 (m, 3H, Ph), 7.07–7.11 (m, 4H, Ph), 5.84 (d, J = 1.8 Hz, 1H, 3min-H), 5.60 (d, J = 1.8 Hz, 1H, 3maj-H), 4.15 (app. d, J = 7.8 Hz, 1H, 3bαmaj-H), 4.01 (dd, J = 8.4, 1.5 Hz, 1H, 3bαmin-H), 3.38 (dd, J = 8.3, 5.3 Hz, 1H, 6aαmaj-H), 3.34 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.00–3.05 (m, 1H, 10aβmin-H), 2.90–2.95 (m, 1H, 10aαmaj-H), 2.04–2.40 (m, 2H, cyclohex., 6bα-H), 2.18 (s, 3H, 2-CH_3), 1.02–1.64 (m, 7H, cyclohex.); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 178.1, 176.3, 157.7, 130.0, 128.9, 127.9, 124.1, 123.9, 120.4, 119.7, 119.6, 118.9, 103.7, 46.0, 38.8, 38.7, 38.4, 37.8, 33.0, 32.9, 29.1, 28.1, 26.1, 23.0, 22.7, 21.1, 20.6, 13.4; IR (thin film, cm^{-1}) 3390(bs), 2925(m), 2855(m), 1777(w), 1701(s), 1590(m), 1508(s), 1489(s), 1392(m), 1244(s), 1180(m), 1165(m); HRMS m/z (M + Na$^+$) calcd for $C_{27}H_{26}N_2O_3$: 449.1836, found 449.1837.

2,8-Dimethyl-5-(4-phenoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (39). Method B with **3d** (785 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **39** (1100 mg, 52%) as a colorless solid, a mixture of three isomers (maj:min:min = 1.2:1.0:0.1): mp 278–280°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.67 (bs, 1H, 1min-H), 10.52 (bs, 1H, 1min-H), 10.27 (bs, 1H, 1maj-H), 7.38–7.46 (m, 2H, Ph), 7.15–7.26 (m, 3H, Ph), 7.06–7.14 (m, 4H, Ph), 5.82–5.84 (m, 1H, 3maj-H), 5.60 (d, J = 1.8 Hz, 1H, 3min-H), 5.58 (d, J = 2.1 Hz, 1H, 3min-H), 4.14 (app. d, J = 8.1 Hz, 1H, 3bαmin-H), 4.01 (dd, J = 8.3, 2.3 Hz, 1H, 3bαmin-H), 3.99 (dd, J = 8.4, 1.5 Hz, 1H, 3bαmaj-H), 3.41 (dd, J = 8.4, 6.0 Hz, 1H, 6aαmin-H), 3.40 (dd, J = 8.0, 5.6 Hz, 1H, 6aαmin-H), 3.35 (dd, J = 8.4, 5.7 Hz, 1H, 6aαmaj-H), 2.93–3.00 (m, 1H, 10amaj-H), 2.85–2.92 (m, 1H, 10amin-H), 2.70–2.74 (m, 1H, 10amin-H), 2.44–2.54 (m, 1H, 6bmaj-H), 2.30–2.40 (m, 1H, 6bmin-H), 2.18 (s, 3H, 2-CH_3), 0.98–2.16 (m, 7H, cyclohex.), 0.95 (d, J = 6.9 Hz, 3H, 8-CH_3 maj), 0.71 (d, J = 6.0 Hz, 3H, 8-CH_3 min); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.4, 177.5, 157.0, 156.6, 130.7, 129.3, 129.1, 127.9, 126.6, 124.5, 119.7, 119.0, 108.9, 105.0, 45.6, 33.0–33.3 (overlapped peaks), 32.2–32.6 (overlapped peaks), 26.7, 13.5; IR (thin film, cm^{-1}) 3461(m), 3394(bs), 3077(w), 2954(m), 2923(m), 2864(m), 1777(w), 1711(s), 1591(m), 1508(s), 1489(s), 1391(m), 1245(s), 1192(m), 1165(m); HRMS m/z (M + Na$^+$) calcd 463.1993, found 463.1993. Anal. Calcd for $C_{28}H_{28}N_2O_3$: C, 76.34; H, 6.41; N, 6.36. Found: C, 76.19; H, 6.21; N, 6.23.

8-Ethyl-2-methyl-5-(4-phenoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (40). Method B with **3e** (883 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **40** (1000 mg, 46%) as a colorless solid, a mixture of three isomers (maj:min:min = 1.7:1.0:0.3): mp 272–274°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.52 (bs, 1H, 1min-H), 10.27 (bs, 1H, 1maj-H), 10.24 (bs, 1H, 1min-H), 7.40–7.47 (m, 2H, Ph), 7.17–7.25 (m, 3H, Ph), 7.06–7.13 (m, 4H, Ph), 5.83 (dd, J = 2.1, 0.6 Hz, 1H, 3maj-H), 5.61 (dd, J = 2.4, 0.6 Hz, 1H, 3min-H), 5.58 (dd, J = 2.7, 0.9 Hz, 1H, 3min-H), 4.15 (app. d, J = 8.7 Hz, 1H, 3bαmin-H), 4.14 (app. d, J = 8.1 Hz, 1H, 3bαmin-H), 3.99 (dd, J = 8.4, 1.8 Hz, 1H, 3bαmaj-H), 3.41 (dd. J = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.38 (dd, J = 8.3, 5.3 Hz, 1H, 6aαmin-H), 3.34 (dd, J = 8.3, 5.3 Hz, 1H, 6aαmaj-H), 2.99–3.04 (m, 1H, 10amin-H), 2.93–2.99 (m, 1H, 10aαmaj-H), 2.85–2.91 (m, 1H, 10aβmin-H), 2.24–2.50 (m, 1H, 6b-H), 2.27 (s, 3H, 2-CH_3), 0.84–2.16 (m, 7H, cyclohex.), 1.37 (app. q, J = 7.8 Hz, 2H, CH_2CH_3), 0.80 (t, J = 7.2 Hz, 3H, CH_2CH_3 maj), 0.78 (t, J = 7.2 Hz, 3H, CH_2CH_3 min); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 178.1, 178.0, 176.9, 159.8, 157.9, 130.0, 127.9, 127.4, 127.0, 126.8, 123.9, 119.7, 118.9, 109.5, 105.8, 45.7, 38.9, 34.5, 34.0, 32.8–33.1 (overlapped peaks), 13.3, 12.3; IR (thin film, cm^{-1}) 3462(m), 3393(bs), 3073(w), 2958(m), 2922(s), 2868(m), 1776(w), 1702(s), 1590(m), 1508(s), 1489(s), 1390(m), 1243(s), 1190(m), 1164(m); HRMS m/z (M + Na$^+$) calcd for $C_{29}H_{30}N_2O_3$: 477.2149, found 477.2153.

8-Isopropyl-2-methyl-5-(4-phenoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (41). Method B with **3f** (981 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **41** (950 mg, 42%) as a colorless solid, a mixture of three isomers (maj:min:min = 2.1:1.0:0.3): mp 158–160°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.52 (bs, 1H, 1min-H), 10.28 (bs, 1H, 1maj-H), 10.24 (bs, 1H, 1min-H), 7.40–7.48 (m, 2H, Ph), 7.16–7.26 (m, 3H, Ph), 7.04–7.16 (m, 4H, Ph), 5.80–5.84 (m, 1H, 3maj-H), 5.60–5.63 (m, 1H, 3min-H), 5.57–5.59 (m, 1H, 3min-H), 4.15 (app. d, J = 8.4 Hz, 1H, 3bαmin-H), 4.14 (d, J = 8.1 Hz, 1H, 3bαmin-H), 3.99 (dd, J = 8.7, 1.5 Hz, 1H, 3bαmaj-H), 3.42 (dd, J = 8.1, 4.5 Hz, 1H, 6aαmin-H), 3.38 (dd, J = 8.7, 5.4 Hz, 1H, 6aαmin-H), 3.34 (dd, J = 8.3, 5.3 Hz, 1H, 6aαmaj-H), 2.93–3.10 (m, 1H, 10aαmaj-H), 2.86–2.92 (m, 1H, 10aβmin-H), 2.22–2.50 (m, 1H, 6b-H), 2.18 (s, 3H, 2-CH_3), 0.90–2.12 (m, 8H, cyclohex., $CH(CH_3)_2$), 0.74–0.88 (m, 6H, $CH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 178.3, 176.9, 157.5, 156.5, 130.1, 130.0, 127.9, 127.4, 126.8, 124.1, 124.0, 119.8, 119.7, 118.8, 109.6, 109.5, 105.8, 105.0, 103.8, 45.6, 39.7, 38.9, 33.1, 33.07, 32.8–33.2 (overlapped peaks), 23.3, 21.4, 21.3, 29.1, 25.6, 23.1–23.7 (overlapped peaks), 21.3, 20.9, 20.1, 13.3; IR (thin film, cm^{-1}) 3394(bs), 3064(w), 2930(m), 2866(m), 1776(w), 1705(s), 1591(m), 1508(s), 1490(s), 1389(m), 1243(s), 1189(m), 1165(m); HRMS m/z (M + Na$^+$) calcd 491.2306, found 491.2325. Anal. Calcd for $C_{30}H_{32}N_2O_3$: C, 76.90; H, 6.88; N, 5.98. Found: C, 76.76; H, 6.79; N, 5.78.

8-tert-Butyl-2-methyl-5-(4-phenoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (42). Method B with **3g** (1080 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **42** (700 mg, 30%) as a colorless solid, a mixture of three isomers (maj:min:min = 4.8:1.0:0.9): mp 243–245°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.50 (d, J = 1.8 Hz, 1H, 1min-H), 10.36 (d, J = 1.5 Hz, 1H, 1maj-H), 10.33 (d, J = 2.1 Hz, 1H, 1min-H), 7.38–7.48 (m, 2H, Ph), 7.04–7.27 (m, 7H, Ph), 5.67 (dd, J = 2.7, 1.5 Hz, 1H, 3min-H), 5.58 (dd, J = 2.4, 0.6 Hz, 1H, 3min-H), 5.54 (dd, J = 2.4, 0.9 Hz, 1H, 3maj-H), 4.16 (app. d, J = 7.5 Hz, 1H, 3bαmin-H), 4.10 (app. d, J = 8.4 Hz, 1H, 3bαmin-H), 3.85 (dd, J = 7.5, 1.2 Hz, 1H, 3bαmaj-H), 3.49 (dd, J = 8.4, 6.3 Hz, 1H, 6aαmin-H), 3.46 (dd, J = 7.2, 8.7 Hz, 1H, 6aαmin-H), 3.42 (dd, J = 8.1, 5.1 Hz, 1H, 6aαmaj-H), 2.86–2.92 (m, 1H, 10amin-H), 2.50–

2.66 (m, 1H, 10aαmaj-H), 2.24–2.50 (m, 1H, 6b-H), 2.17 (s, 3H, 2-CH$_3$ min), 2.13 (s, 3H, 2-CH$_3$ maj), 2.12 (s, 3H, 2-CH$_3$ min), 1.38–2.00 (m, 4H, cyclohex.), 0.95–1.24 (m, 3H, cyclohex.), 0.84 (s, 9H, *t*-Bu maj), 0.67 (s, 9H, *t*-Bu min); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.7, 176.1, 157.2, 156.5, 130.8, 129.2, 128.8, 128.5, 127.9, 124.6, 120.1, 119.8, 119.6, 119.0, 116.9, 104.2, 102.7, 44.9, 34.3–34.6 (overlapped peaks), 33.2, 32.6, 28.2, 28.0, 27.8, 13.4; IR (thin film, cm^{-1}) 3388(bs), 3070(w), 2952(s), 2866(m), 1777(w), 1705(s), 1591(m), 1507(s), 1489(s), 1392(m), 1244(s), 1180(m), 1165(m); HRMS *m*/*z* (M + Na$^+$) calcd 505.2462, found 505.2467. Anal. Calcd for $C_{31}H_{34}N_2O_3$: C, 77.15; H, 7.10; N, 5.80. Found: C, 76.92; H, 6.98; N, 5.66.

2-Methyl-5-(4-phenoxyphenyl)-8-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (43). Method B with **3h** (1220 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **43** (1150 mg, 48%) as a colorless solid, a mixture of four isomers (maj:min:min = 5.4:1.0:1.0:0.7): mp 297–299°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.57 (bs, 1H, 1min-H), 10.55 (bs, 1H, 1min-H), 10.38 (bs, 1H, 1maj-H), 10.34 (bs, 1H, 1min-H), 7.37–7.46 (m, 2H, Ph), 6.97–7.35 (m, 12H, Ph), 5.86–5.88 (m, 1H, 3min-H), 5.78–5.86 (m, 1H, 3maj-H), 5.63–5.66 (m, 1H, 3min-H), 4.17 (app. d, *J* = 8.4 Hz, 1H, 3bαmin-H), 4.06 (dd, *J* = 8.6, 1.7 Hz, 1H, 3bαmin-H), 4.01 (d, *J* = 7.8 Hz, 1H, 3bαmaj-H), 3.50 (dd, *J* = 8.4, 5.1 Hz, 1H, 6aαmin-H), 3.45 (dd, *J* = 8.1, 5.1 Hz, 1H, 6aαmaj-H), 3.07–3.13 (m, 1H, 10amin-H), 2.96–3.04 (m, 1H, 10amin-H), 2.86–2.97 (m, 1H, 10aαmaj-H), 2.80–2.89 (m, 1H, 10amin-H), 2.46–2.58 (m, 1H, 6b-H), 1.20–2.30 (m, 7H, cyclohex.), 2.19 (s, 3H, 2-CH$_3$); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.5, 178.3, 177.0, 176.3, 156.5, 130.7, 129.2, 128.9, 127.6, 124.6, 124.5, 119.9, 119.7, 119.1, 45.4, 33.2–33.5 (overlapping peaks), 13.5; IR (thin film, cm^{-1}) 3390(bs), 3060(w), 2932(m), 2866(m), 1774(w), 1702(s), 1590(m), 1507(s), 1490(s), 1391(m), 1243(s), 1191(m), 1165(m); HRMS *m*/*z* (M + Na$^+$) calcd for $C_{33}H_{30}N_2O_3$: 525.2149, found 525.2140.

2-Methyl-5-(3-nitrophenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (44). Method B with **3c** (600 mg, 6.12 mmol), 1-h reflux, reprecipitation from diethyl ether (20 mL), and then a diethyl ether wash (10 mL) gave **44** (700 mg, 40%) as a yellow solid, a mixture of two isomers (maj:min = 2.8:1.0): mp 223–225°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.24–8.31 (m, 3H, Ph, Ph, 1min-H), 7.62–7.77 (m, 3H, Ph, 1maj-H), 6.19 (dd, *J* = 2.4, 1.2 Hz, 1H, 3maj-H), 5.79 (dd, *J* = 2.4, 0.6 Hz, 1H, 3min-H), 4.04 (app. d, *J* = 8.7 Hz, 1H, 3bαmin-H), 4.01 (dd, *J* = 8.6, 2.0 Hz, 1H, 3bαmaj-H), 3.52 (dd, *J* = 8.9, 5.6 Hz, 1H, 6aαmin-H), 3.45 (dd, *J* = 8.4, 5.4 Hz, 1H, 6aαmaj-H), 3.14–3.20 (m, 1H, 10aαmaj-H), 3.03–3.08 (m, 1H, 10aβmin-H), 2.53–2.61 (m, 1H, 6bα-H), 2.33 (s, 3H, 2-CH$_3$), 2.12–2.28 (m, 1H, cyclohex.), 1.43–1.85 (m, 3H, cyclohex.), 1.17–1.38 (m, 4H, cyclohex.); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 177.4, 176.1, 148.5, 133.5, 133.1, 132.3, 130.1, 130.0, 127.7, 127.1, 123.3, 123.1, 121.6, 120.6, 108.8, 105.8, 103.8, 46.0, 38.9, 38.7, 38.4, 37.9, 33.0, 32.8, 29.1, 28.0, 26.0, 25.6, 23.1, 22.7, 21.0, 20.5, 13.3; IR (thin film, cm^{-1}) 3414(bs), 3081(m), 2928(m), 2858(m), 1779(w), 1707(s), 1532(s), 1384(w), 1350(m), 1164(m); HRMS *m*/*z* (M + Na$^+$) calcd for $C_{21}H_{21}N_3O_4$: 402.1425, found 402.1434.

2,8-Dimethyl-5-(3-nitrophenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (45). Method B with **3d** (750 mg, 6.70 mmol), 1-h reflux, reprecipitation from diethyl ether (20 mL), and then a diethyl ether wash (10 mL) gave **45** (820 mg, 44%) as a colorless solid, a mixture of two isomers (maj:min = 3.7:1.0): mp 236–238°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.24–8.30 (m, 3H, Ph, Ph, 1min-H), 7.64–7.76 (m, 3H, Ph, 1maj-H), 6.18 (dd, *J* = 2.6, 1.1 Hz, 1H, 3maj-H), 5.80 (dd, *J* = 2.6, 1.1 Hz, 1H, 3min-H), 4.04 (app. d, *J* = 8.4 Hz, 1H, 3bαmin-H), 4.01 (dd, *J* = 8.4, 1.8 Hz, 1H, 3bαmaj-H), 3.53 (dd, *J* = 8.7, 5.7 Hz, 1H, 6aαmin-H), 3.46 (dd, *J* = 8.6, 5.3 Hz, 1H, 6aαmaj-H), 3.08–3.14 (m, 1H, 10aαmaj-H), 2.98–3.04 (m, 1H, 10aβmin-H), 2.72–2.82 (m, 1H, 6bαmaj-H), 2.55–2.67 (m, 1H, 6bαmin-H), 2.32 (s, 3H, 2-CH$_3$), 1.81–2.12 (m, 3H, cyclohex.), 1.45–1.68 (m, 2H, cyclohex.), 1.18–1.34 (m, 1H, cyclohex.), 0.95–1.14 (m, 1H, cyclohex.), 1.03 (s, 3H, 8-CH$_3$ maj), 1.01 (s, 3H, 8-CH$_3$ min); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 177.3, 176.1, 148.5, 132.2, 129.9, 127.7, 123.1, 121.7, 109.0, 105.7, 45.7, 39.0, 32.9, 32.6, 26.7, 13.3; IR (thin film, cm^{-1}) 3430(bs), 2924(m), 2850(m), 1773(w), 1705(s), 1534(m), 1385(m), 1350(m), 1168(m); HRMS *m*/*z* (M + Na$^+$) calcd 416.1582, found 416.1567. Anal. Calcd for $C_{22}H_{23}N_3O_4$: C, 67.16; H, 5.89; N, 10.68. Found: C, 67.12; H, 5.64; N, 10.53.

8-Ethyl-2-methyl-5-(3-nitrophenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (46). Method B with **3e** (820 mg, 6.50 mmol), 1-h reflux, reprecipitation from diethyl ether (20 mL), and then a diethyl ether wash (10 mL) gave **46** (800 mg, 41%) as a yellow solid, a mixture of two isomers (maj:min = 3.3:1.0): mp 213–215°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.24–8.31 (m, 3H, Ph, Ph, 1min-H), 7.64–7.75 (m, 3H, Ph, 1maj-H), 6.18 (dd, *J* = 2.1, 0.9 Hz, 1H, 3maj-H), 5.81 (app. d, *J* = 2.7 Hz, 1H, 3min-H), 4.01 (dd, *J* = 8.4 Hz, 1H, 3bα-H), 3.52 (dd, *J* = 8.7, 5.7 Hz, 1H, 6aαmin-H), 3.45 (dd, *J* = 8.6, 5.3 Hz, 1H, 6aαmaj-H), 3.08–3.14 (m, 1H, 10aαmaj-H), 2.97–3.04 (m, 1H, 10aβmin-H), 2.67–2.76 (m, 1H, 6bα-H), 2.33 (s, 3H, 2-CH$_3$), 1.80–2.04 (m, 2H, cyclohex.), 1.18–1.66 (m, 6H, cyclohex., 8-C*H*$_2$CH$_3$), 1.10–1.26 (m, 1H, cyclohex.), 0.86 (t, *J* = 7.2 Hz, 3H, 8-CH$_2$C*H*$_3$), 0.85 (t, *J* = 7.2 Hz, 3H, 8-CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 177.3, 176.2, 148.5, 133.1, 132.2, 130.7, 130.0, 127.7, 123.7, 123.1, 121.6, 109.0, 105.7, 45.7, 39.0, 33.9, 32.9, 23.8, 13.3, 12.3; IR (thin film, cm^{-1}) 3401(bs), 2928(m), 2868(m), 1778(w), 1714(s), 1532(s), 1353(m), 1160(m); HRMS *m*/*z* (M + Na$^+$) calcd 430.1738, found 430.1732. Anal. Calcd for $C_{23}H_{25}N_3O_4$: C, 67.80; H, 6.18; N, 10.31. Found: C, 68.29; H, 6.20; N, 10.51.

8-Isopropyl-2-methyl-5-(3-nitrophenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (47). Method B with **3f** (910 mg, 6.50 mmol), 1-h reflux, reprecipitation from diethyl ether (20 mL), and then a diethyl ether wash (10 mL) gave **47** (600 mg, 30%) as a yellow solid, a mixture of three isomers (maj:min:min = 2.8:1.0:0.2): mp 205–207°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.24–8.31 (m, 3H, Ph, Ph, 1min-H), 7.63–7.74 (m, 3H, Ph, 1maj-H), 6.18 (dd, *J* = 2.7, 1.5 Hz, 1H, 3maj-H), 5.81 (dd, *J* = 2.7, 0.6 Hz, 1H, 3min-H), 5.77 (dd, *J* = 2.3, 1.1 Hz, 1H, 3min-H), 4.01 (dd, *J* = 8.4, 1.8 Hz, 1H, 3bα-H), 3.55 (dd, *J* = 8.4, 5.7 Hz, 1H, 6aαmin-H), 3.51 (dd, *J* = 8.9, 5.9 Hz, 1H, 6aαmin-H), 3.44 (dd, *J* = 8.4, 5.4 Hz, 1H, 6aαmaj-H), 3.07–3.15 (m, 1H, 10aαmaj-H), 2.98–3.04 (m, 1H, 10aβmin-H), 2.66–2.75 (m, 1H, 6bαmaj-H), 2.53–2.62 (m, 1H, 6bmin-H), 2.33 (s, 3H, 2-CH$_3$), 1.78–2.02 (m, 3H, cyclohex.), 1.20–1.65 (m, 5H, cyclohex., C*H*(CH$_3$)$_2$), 0.90 (d, J = 6.3 Hz, 6H, CH(C*H*$_3$)$_2$), 0.86 (d, J = 6.6 Hz, 6H, CH(C*H*$_3$)$_2$); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 177.4, 176.1, 148.5, 133.1, 132.2, 130.0, 127.7, 123.1, 121.6, 108.9, 105.7, 45.7, 40.1, 39.6, 39.0, 33.1, 32.9, 26.1, 23.3, 21.3, 20.8, 13.3; IR (thin film, cm^{-1}) 3408(bs), 2937(m), 2850(m), 1778(w), 1708(s), 1531(m), 1381(m), 1353(m), 1195(m), 1164(m); HRMS *m*/*z* (M + Na$^+$) calcd 444.1895, found 444.1889. Anal. Calcd for $C_{24}H_{27}N_3O_4$: C, 68.39; H, 6.46; N, 9.97. Found: C, 68.38; H, 6.26; N, 9.75.

8-tert-Butyl-2-methyl-5-(3-nitrophenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (48). Method B with **3g** (1000 mg, 6.490 mmol), 3-h reflux, removal of solvent under vacuum, elution through a 5-cm silica gel plug with CH$_2$Cl$_2$, and then reprecipitation twice from diethyl ether/hexanes (2:1, 20 mL) gave **48** (650 mg, 31%) as a yellow solid, a mixture of two isomers (maj:min = 2.1:1.0): mp 203–205°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.18–8.26 (m, 3H, Ph, 1maj-H), 7.57–7.71 (m, 3H, Ph, Ph, 1min-H), 7.01 (dd, J = 2.9, 1.1 Hz, 1H, 3maj-H), 7.00 (m, overlapped, 1H, 3min-H), 4.14 (dd, J = 7.5, 2.1 Hz, 1H, 3bαmin-H), 4.09 (dd, J = 7.5, 1.5 Hz, 1H, 3bαmaj-H), 3.39 (dd, J = 7.4, 5.4 Hz, 1H, 6aαmaj-H), 3.35 (dd, J = 7.5, 3.9 Hz, 1H, 6aαmin-H), 2.70–2.78 (m, 1H, 6b-H), 2.62–2.70 (m, 1H, 10aβmaj-H), 2.44–2.54 (m, 1H, 10aαmin-H), 1.75–2.32 (m, 3H, cyclohex.), 2.27 (d, J = 0.6 Hz, 3H, 2-CH$_3$), 1.63 (ddd, J = 13.9, 11.5, 7.1 Hz, 1H, cyclohex.), 1.07–1.40 (m, 3H, cyclohex.), 0.94 (s, 9H, *t*-Bu min), 0.92 (s, 9H, *t*-Bu maj); ^{1}H NMR (300 MHz, DMSO-*d*$_6$, δ) 10.38 (d, J = 1.8 Hz, 1H, 1maj-H), 10.32 (d, J = 2.1 Hz, 1H, 1min-H), 8.21–8.28 (m, 1H, Ph), 8.06–8.08 (m, 1H, Ph), 7.62–7.80 (m, 2H, Ph), 5.67–5.70 (m, 1H, 3-H), 3.98 (dd, J = 7.2, 1.8 Hz, 1H, 3bαmin-H), 3.96 (dd, J = 7.2, 1.2 Hz, 1H, 3bαmaj-H), 3.50–3.55 (m, overlapped, 1H, 6aαmin-H), 3.53 (dd, J = 7.5, 5.7 Hz, 1H, 6aαmaj-H), 2.55–2.70 (m, 1H, 10aβmaj-H), 2.50 (s, 3H, 2-CH$_3$), 1.49–2.33 (m, 5H, cyclohex., 6bα-H), 1.00–1.40 (m, 3H, cyclohex.), 0.89 (s, 9H, *t*-Bu min), 0.86 (s, 9H, *t*-Bu maj); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 177.2, 176.1, 148.5, 133.4, 132.7, 132.3, 130.4, 129.9, 129.7, 128.0, 127.7, 123.0, 122.8, 122.0, 121.7, 109.3, 105.0, 104.1, 49.0, 46.0, 45.9, 42.2, 41.8, 41.1, 40.8, 34.3, 34.2, 34.1, 32.8, 32.7, 30.5, 28.9, 27.7, 27.6, 26.3, 25.6, 13.2; IR (thin film, cm^{-1}) 3393(bs), 3097(m), 2958(s), 2868(s), 2361(m), 2255(m), 1778(m), 1716 (s), 1532(s), 1478(m), 1356(s), 1171(m); HRMS *m*/*z* (M + Na$^+$) calcd for $C_{25}H_{29}N_3O_4$: 458.2051, found 458.2036.

2-Methyl-5-(3-nitrophenyl)-8-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (49). Method B with **3h** (1140 mg, 6.555 mmol), 1-h reflux, reprecipitation twice from ethanol/diethyl ether (4:1, 20 mL), and then a diethyl ether wash (10 mL) gave **49** (900 mg, 40%) as a yellow solid, a mixture of three isomers (maj:min:min = 4.2:1.0:0.6): mp 236–238°C; ^{1}H NMR (300 MHz, DMSO-*d*$_6$, δ) 10.59 (bs, 1H, 1min-H), 10.41 (bs, 1H, 1maj-H), 8.28–8.33 (m, 2H, 5-Ph), 7.74–7.86 (m, 2H, 5-Ph), 7.27–7.35 (m, 4H, 8-Ph), 7.15–7.21 (m, 1H, 8-Ph), 5.86–5.89 (m, 1H, 3min-H), 5.80–5.86 (m, 1H, 3maj-H), 5.65–5.67 (m, 1H, 3min-H), 4.22 (d, J = 9.0 Hz, 1H, 3bαmin-H), 4.13 (d, J = 9.0 Hz, 1H, 3bαmin-H), 4.06 (d, J = 8.1 Hz, 1H, 3bαmaj-H), 3.28–3.58 (m, obscured by H$_2$O, 1H, 6aα-H), 3.08–3.17 (m, 1H, 10amin-H), 2.83–3.00 (m, 1H, 10aαmaj-H), 2.51–2.62 (m, 1H, 6b-H), 2.19 (s, 3H, 2-CH$_3$), 1.34–2.09 (m, 7H, cyclohex.); ^{13}C NMR (75 MHz, DMSO-*d*$_6$, δ) 178.3, 148.4, 134.0, 131.0, 128.8, 127.6, 126.1, 123.6, 122.2, 45.5, 40.9, 39.2, 33.4, 13.5; IR (thin film, cm^{-1}) 3417(bs), 3071(m), 2928(m), 2865(m), 1776(w), 1707(s), 1533(m), 1382(m), 1350(m), 1160(m); HRMS *m*/*z* (M + Na$^+$) calcd for $C_{27}H_{25}N_3O_4$: 478.1738, found 478.1757.

4-(2-Methyl-4,6-dioxo-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-cyclopenta[g]pyrrolo[3,4-e]indol-5-yl)benzoic acid (50). Method B with **3c** (600 mg, 6.12 mmol), 1.5-h reflux, reprecipitation from diethyl ether (10 mL), and then a diethyl ether wash (5 mL) gave **50** (550 mg, 31%) as a colorless solid, a mixture of two isomers (maj:min = 1.5:1.0): mp 257–259°C; ^{1}H NMR (300 MHz, DMSO-*d*$_6$, δ) 13.16 (s, 1H, CO$_2$H), 10.55 (d, J = 2.4 Hz, 1H, 1min-H), 10.27 (d, J = 2.1 Hz, 1H, 1maj-H), 8.07 (d, J = 8.7 Hz, 2H, Ph min), 8.05 (d, J = 8.4 Hz, 2H, Ph maj), 7.41 (d, J = 8.7 Hz, 2H, Ph min), 7.40 (d, J = 8.7 Hz, 2H, Ph maj), 5.84 (dd, J = 2.1, 0.6 Hz, 1H, 3maj-H), 5.60 (dd, J = 2.1, 0.6 Hz, 1H, 3min-H), 4.19 (app. d, J = 8.4 Hz, 1H, 3bαmin-H), 4.05 (dd, J = 8.4, 1.8 Hz, 1H, 3bαmaj-H), 3.37–3.44 (m, 1H, 6aα-H), 3.00–3.06 (m, 1H, 10aαmaj-H), 2.90–2.96 (m, 1H, 10aβmin-H), 2.27–2.41 (m, 1H, 6bα-H), 2.18 (s, 3H, 2-CH$_3$), 0.95–1.62 (m, 8H, cyclohex.); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 178.1, 177.9, 177.2, 167.2, 136.7, 130.9, 130.5, 127.4, 126.9, 126.6, 119.0, 108.6, 105.4, 105.0, 65.5, 46.3, 46.5, 46.0, 38.4, 33.0, 25.7, 21.4, 13.5; IR (thin film, cm^{-1}) 3472(bs), 3409(bs), 2950(m), 2847(m), 2294(w), 1770(w), 1686(s), 1514(w), 1422(m), 1378(m), 1279(m), 1170(m); HRMS *m*/*z* (M + Na$^+$) calcd 401.1473, found 401.1490. Anal. Calcd for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.59; H, 6.20; N, 7.45.

4-(2,8-Dimethyl-4,6-dioxo-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-cyclopenta[g]pyrrolo[3,4-e]indol-5-yl)benzoic acid (51). Method B with **3d** (750 mg, 6.70 mmol), 1.5-h reflux, reprecipitation from ethanol/diethyl ether (1:3, 20 mL), and then a diethyl ether wash (5 mL) gave **51** (550 mg, 31%) as a colorless solid, a mixture of two isomers (maj:min = 1.6:1.0): mp 258–260°C; ^{1}H NMR (300 MHz, DMSO-*d*$_6$, δ) 13.15 (s, 1H, CO$_2$H), 10.54 (d, J = 2.2 Hz, 1H, 1min-H), 10.28 (d, J = 1.6 Hz, 1H, 1maj-H), 8.07 (d, J = 8.4 Hz, 2H, Ph min), 8.05 (d, J = 8.7 Hz, 2H, Ph maj), 7.41 (d, J = 8.4 Hz, 2H, Ph min), 7.39 (d, J = 8.4 Hz, 2H, Ph maj), 5.82 (d, J = 1.2 Hz, 1H, 3maj-H), 5.61 (d, J = 2.1 Hz, 1H, 3min-H), 4.19 (app. d, J = 8.7 Hz, 1H, 3bαmin-H), 4.04 (dd, J = 8.4, 1.8 Hz, 1H, 3bαmaj-H), 3.43 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.39 (dd, J = 8.3, 5.3 Hz, 1H, 6aαmaj-H), 2.94–3.00 (m, 1H, 10aαmaj-H), 2.86–2.92 (m, 1H, 10aβmin-H), 2.35–2.60 (m, overlapped by DMSO, 1H, 6bα-H), 2.17 (s, 3H, 2-CH$_3$), 1.74–1.94 (m, 2H, cyclohex.), 1.30–1.46 (m, 2H, cyclohex.), 1.08–1.22 (m, 1H, cyclohex.), 0.88–1.04 (m, 2H, cyclohex.), 0.96 (d, J = 7.2 Hz, 3H, 8-CH$_3$); ^{13}C NMR (75 MHz, DMSO-*d*$_6$, δ) 178.0, 177.2, 167.2, 136.7, 130.8, 130.5, 127.4, 126.6, 108.8, 105.3, 45.7, 38.3, 34.7, 33.1, 32.6, 27.0, 26.7, 13.5; IR (thin film, cm^{-1}) 3458(bs), 3381(bs), 2919(m), 2285(w), 1780(w), 1700(s), 1515(w), 1425(m), 1382(m), 1285(m), 1161(m); HRMS *m*/*z* (M + Na$^+$) calcd for $C_{23}H_{24}N_2O_4$: 415.1629, found 415.1628.

4-(8-Ethyl-2-methyl-4,6-dioxo-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-cyclopenta[g]pyrrolo[3,4-e]-5-indolyl)benzoic acid (52). Method B with **3e** (820 mg, 6.50 mmol), 1-h reflux, reprecipitation from diethyl ether (20 mL), and then a diethyl ether wash (10 mL) gave **52** (600 mg, 31%) as a colorless solid, a mixture of three isomers (maj:min:min = 3.7:1.0:0.1): mp 233–235°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 13.14 (s, 1H, CO_2H), 10.54 (d, J = 2.4 Hz, 1H, 1min-H), 10.29 (d, J = 2.1 Hz, 1H, 1maj-H), 10.24–10.28 (app. bs, 1H, 1min-H), 8.06 (d, J = 8.7 Hz, 2H, Ph), 7.38 (d, J = 8.4 Hz, 2H, Ph), 5.83 (app. s, 1H 3maj-H), 5.62 (d, J = 1.8 Hz, 1H, 3min-H), 5.59 (app. s, 1H, 3min-H), 4.18 (d, J = 8.1 Hz, 1H, 3bαmin-H), 4.04 (dd, J = 8.6, 1.7, 1H, 3bαmaj-H), 3.42 (dd, J = 8.4, 5.7 Hz, 1H, 6aαmin-H), 3.38 (dd, J = 8.7, 5.1 Hz, 1H, 6aαmaj-H), 2.93–3.00 (m, 1H, 10aαmaj-H), 2.86–2.92 (m, 1H, 10aβ-H), 2.40–2.54 (m, 1H, 6b-H), 1.86–2.40 (m, 2H, cyclohex.), 2.18 (s, 3H, 2-CH_3), 0.92–1.84 (m, 7H, cyclohex., CH_2CH_3), 0.87 (t, J = 7.5 Hz, 3H, CH_2CH_3 min), 0.80 (t, J = 7.2 Hz, 3H, CH_2CH_3 maj); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.1, 177.2, 167.2, 136.7, 130.8, 130.6, 127.3, 126.6, 108.7, 105.3, 45.6, 39.2, 35.0, 33.9, 33.3, 33.1, 32.8, 13.5, 12.6; IR (thin film, cm^{-1}) 3396(bs), 2922(m), 2860(m), 2293(w), 1693(s), 1513(w), 1426(m), 1387(m), 1284(m), 1166(m); HRMS m/z (M + Na$^+$) calcd 429.1786, found 429.1797. Anal. Calcd for $C_{24}H_{26}N_2O_4$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.92; H, 6.37; N, 6.75.

4-(8-Isopropyl-2-methyl-4,6-dioxo-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-cyclopenta[g]pyrrolo[3,4-e]-5-indolyl)benzoic acid (53). Method B with **3f** (910 mg, 6.50 mmol), 1-h reflux, reprecipitation from diethyl ether (20 mL), and then a diethyl ether wash (10 mL) gave **53** (600 mg, 30%) as a colorless solid, a mixture of three isomers (maj:min:min = 5.3:1.0:0.2): mp 260–262°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 13.16 (s, 1H, CO_2H), 10.55 (d, J = 1.8 Hz, 1H, 1min-H), 10.30 (d, J = 2.1 Hz, 1H, 1maj-H), 10.24–10.27 (app. bs, 1H, 1min-H), 8.07 (d, J = 8.4 Hz, 2H, Ph), 7.37 (d, J = 8.7 Hz, 2H, Ph), 5.83 (app. s, 1H, 3maj-H), 5.62 (d, J = 1.2 Hz, 1H, 3min-H), 5.59 (app. s, 1H, 3min-H), 4.18 (app. d, 1H, 3bαmin-H), 4.03 (dd, J = 8.4, 1.5 Hz, 1H, 3bαmaj-H), 3.34–3.48 (m, 1H, 6aα-H), 2.93–3.03 (m, 1H, 10aαmaj-H), 2.86–2.92 (m, 1H, 10aβmin-H), 2.39–2.50 (m, 1H, 6b-H), 2.18 (s, 3H, 2-CH_{-3}), 1.70–2.12 (m, 2H, cyclohex.), 1.10–1.55 (m, 6H, cyclohex., $CH(CH_3)_2$), 0.85 (d, J = 6.6 Hz, 6H, $CH(CH_3)_2$ maj), 0.79 (d, J = 6.6 Hz, $CH(CH_3)_2$ min); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.2, 177.1, 167.2, 136.8, 130.9, 130.6, 127.2, 126.6, 108.7, 105.3, 65.5, 45.6, 39.4, 33.0, 21.7, 21.0, 15.7, 13.5; IR (thin film, cm^{-1}) 3398(bs), 2950(m), 2865(m), 1770(w), 1696(s), 1514(w), 1430(m), 1388(m), 1285(m), 1184(m); HRMS m/z (M + Na$^+$) calcd 443.1942, found 443.1938. Anal. Calcd for $C_{25}H_{28}N_2O_4$: C, 71.41; H, 6.71; N, 6.66. Found: C, 71.16; H, 6.46; N, 6.49.

4-(2-Methyl-4,6-dioxo-8-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-cyclopenta[g]pyrrolo[3,4-e]-5-indolyl)benzoic acid (54). Method B with **3h** (1140 mg, 6.550 mmol), 1-h reflux, reprecipitation from ethanol/diethyl ether (1:2, 20 mL), and then a diethyl ether wash (10 mL) gave **54** (1000 mg, 46%) as a colorless solid, a mixture of two isomers (maj:min = 4.3:1.0): mp 255–257°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 13.16 (s, 1H, CO_2H), 10.57 (bs, 1H, 1min-H), 10.39 (bs, 1H, 1maj-H), 8.06 (d, J = 8.4 Hz, 2H, 5-Ph), 7.41 (d, J = 8.7 Hz, 2H, 5-Ph), 7.27–7.35 (m, 4H, 8-Ph), 7.15–7.23 (m, 1H, 8-Ph), 5.78–5.86 (m, 1H, 3maj-H), 5.64–5.67 (m, 1H, 3min-H), 4.22 (d, J = 8.7 Hz, 1H, 3bαmin-H), 4.04 (d, J = 7.5 Hz, 1H, 3bαmaj-H), 3.25–3.58 (m, obscured by H_2O, 1H, 6aα-H), 2.80–3.00 (m, 1H, 10aαmaj-H), 2.40–60 (m, overlapped by DMSO, 1H, 6bα-H), 2.18 (s, 3H, 2-CH_3), 1.45–2.10 (m, 7H, 1H, cyclohex.); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.2, 177.1, 167.2, 136.8, 130.7, 130.6, 128.8, 127.2, 127.1, 126.6, 108.7, 99.7, 65.5, 45.6, 42.5, 42.1, 39.2, 33.0, 21.8, 15.7, 13.5; IR (thin film, cm^{-1}) 3475(bs), 3399(bs), 2933(m), 2861(m), 1770(w), 1703(s), 1510(w), 1427(m), 1386(m), 1286(m), 1188(m); HRMS m/z (M + Na$^+$) calcd 477.1786, found 477.1804. Anal. Calcd for $C_{28}H_{26}N_2O_4$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.66; H, 5.42; N, 6.00.

5-(4-Bromophenyl)-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (55). Method B with **3c** (687 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **55** (820 mg, 41%) as a colorless solid, a mixture of two isomers (maj:min = 1.8:1.0): mp 284–286°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.53 (bs, 1H, 1min-H), 10.26 (bs, 1H, 1maj-H), 7.72 (d, J = 8.4 Hz, 2H, Ph min), 7.70 (d, J = 8.7 Hz, 2H, Ph maj), 7.23 (d, J = 8.7 Hz, 2H, Ph min), 7.22 (d, J = 8.7 Hz, 2H, Ph maj), 5.83 (dd, J = 1.2, 0.6 Hz, 1H, 3maj-H), 5.59 (dd, J = 2.1, 0.6 Hz, 1H, 3min-H), 4.16 (dd, J = 8.4, 0.9 Hz, 1H, 3bαmin-H), 4.02 (dd, J = 8.6, 1.7 Hz, 1H, 3bαmaj-H), 3.40 (dd, J = 8.1, 5.1 Hz, 1H, 6aαmin-H), 3.35 (dd, J = 8.6, 5.3 Hz, 1H, 6aαmaj-H), 2.99–3.05 (m, 1H, 10aα-H), 2.90–2.95 (m, 1H, 10aβ-H), 2.26–2.40 (m, 2H, cyclohex., 6b-H), 2.25–2.40 (m, 2H, cyclohex.), 2.18 (s, 3H, 2-CH_3), 1.32–1.44 (m, 1H, cyclohex.), 0.96–1.24 (m, 4H, cyclohex.); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.1, 178.0, 177.2, 176.1, 132.6, 132.55, 132.2, 132.0, 129.5, 128.3, 126.9, 126.6, 121.9, 121.7, 119.0, 116.7, 114.0, 108.6, 105.4, 102.9, 94.5, 46.3, 46.0, 38.8, 38.5, 38.4, 38.2, 33.0, 29.3, 27.6, 26.1, 25.7, 23.2, 22.9, 21.4, 20.8, 13.5, 13.4; IR (thin film, cm^{-1}) 3400(bs), 2923(m), 2855(m), 1776(w), 1701(s), 1492(m), 1386(m), 1179(m), 1159(m); HRMS m/z (M + Na$^+$) calcd 435.0679, found 435.0696. Anal. Calcd for $C_{21}H_{21}BrN_2O_2$: C, 61.03; H, 5.12; N, 6.78. Found: C, 61.11; H, 5.03; N, 6.67.

5-(4-Bromophenyl)-2,8-dimethyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (56). Method B with **3d** (785 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **56** (1000 mg, 49%) as a colorless solid, a mixture of three isomers (maj:min:min = 3.6:1.0:0.2): mp 274–276°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.53 (bs, 1H, 1min-H), 10.27 (bs, 1H, 1maj-H), 10.26 (bs, 1H, 1min-H), 7.72 (d, J = 9.0 Hz, 2H, Ph min), 7.71 (d, J = 9.6 Hz, 2H, Ph min), 7.70 (d, J = 8.7 Hz, 2H, Ph maj), 7.23 (d, J = 8.4 Hz, 2H, Ph min), 7.21 (d, J = 8.7 Hz, 2H, Ph min), 7.20 (d, J = 8.7 Hz, 2H, Ph maj), 5.82 (dd, J = 2.1, 0.6 Hz, 1H, 3maj-H), 5.60 (dd, J = 2.1, 0.6 Hz, 1H, 3min-H), 5.59 (d, J = 2.1, 0.6 Hz, 1H, 3min-H), 4.15 (app. d, J = 8.4 Hz, 1H, 3bαmin-H), 4.02 (dd, J = 8.6, 1.7 Hz, 1H, 3bαmin-H), 4.01 (dd, J = 8.4, 1.8 Hz, 1H, 3bαmaj-H), 3.41 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.36 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmaj-H), 2.93–3.02 (m, 1H, 10aαmaj-H), 2.85–2.92 (m, 1H, 10aβmin-H), 2.30–2.52 (m, 1H, 6b-H), 2.17 (s, 3H, 2-CH_3), 1.74–2.16 (m, 2H, cyclohex.), 0.86–1.68 (m, 5H, cyclohex.), 0.95 (d, J = 7.2 Hz, 3H, 8-CH_3 maj), 0.72 (d, J = 6.6 Hz, 3H, 8-CH_3 min); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.1, 177.2, 176.0, 132.6, 132.5, 132.2, 132.1, 129.5, 129.4, 128.4, 128.3, 126.6, 121.8, 121.7, 118.5, 116.8, 108.8, 108.6, 105.3, 105.0, 45.6, 39.0, 38.9, 39.8, 33.1, 32.3–32.9 (overlapped peaks), 26.7, 13.4; IR (thin film, cm^{-1}) 3460(m), 3393(bs), 3095(w), 3066(w), 2959(m), 2922(s), 2889(m), 2866(m), 2854(m), 1777(w), 1705(s), 1492(s), 1383(s), 1188(m), 1177(m), 1159(m); HRMS *m/z* (M + Na$^+$) calcd 449.0836, found 449.0840. Anal. Calcd for $C_{22}H_{23}BrN_2O_2$: C, 61.83; H, 5.42; N, 6.56. Found: C, 62.02; H, 5.21; N, 6.59.

5-(4-Bromophenyl)-8-ethyl-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (57). Method B with **3e** (883 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **57** (1000 mg, 47%) as a colorless solid, a mixture of four isomers (maj:min:min:min = 3.0:1.0:0.3:0.3): mp 277–279°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.53 (bs, 1H, 1min-H), 10.28 (bs, 1H, 1maj-H), 10.25 (bs, 1H, 1min-H), 7.73 (d, *J* = 8.7 Hz, 2H, Ph min), 7.71 (d, *J* = 9.0 Hz, 2H, Ph maj), 7.22 (d, *J* = 8.4 Hz, 2H, Ph min), 7.20 (d, *J* = 8.7 Hz, 2H, Ph maj), 5.81–5.83 (m, 1H, 3maj-H), 5.80–5.82 (m, 1H, 3min-H), 5.61 (d, *J* = 2.4 Hz, 1H, 3min-H), 5.58 (app. d, *J* = 2.1 Hz, 1H, 3min-H), 4.16 (app. d, *J* = 8.1 Hz, 1H, 3bαmin-H), 4.15 (d, *J* = 8.4 Hz, 1H, 3bαmin-H), 4.02 (dd, *J* = 8.4, 1.8 Hz, 1H, 3bαmin-H), 4.00 (dd, *J* = 8.6, 2.0 Hz, 1H, 3bαmaj-H), 3.43 (dd, *J* = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.39 (dd, *J* = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.38 (dd, *J* = 7.5, 5.4 Hz, 1H, 6aαmin-H), 3.35 (dd, *J* = 8.4, 5.4 Hz, 1H, 6aαmaj-H), 2.99–3.04 (m, 1H, 10amin-H), 2.93–2.99 (m, 1H, 10aαmaj-H), 2.86–2.90 (m, 1H, 10amin-H), 2.10–2.50 (m, 1H, 6b-H), 2.17 (s, 3H, 2-CH_3), 0.96–2.17 (m, 9H, cyclohex., CH_2CH$_3$), 0.79 (t, *J* = 7.5 Hz, 3H, CH$_2$CH_3 maj), 0.77 (t, *J* = 7.2 Hz, 3H, CH$_2$CH_3 min); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.1, 177.9, 177.2, 176.0, 132.7, 132.6, 132.2, 129.4, 129.3, 128.3, 126.9, 126.6, 121.7, 116.8, 108.7, 105.3, 103.0, 45.6, 33.9, 33.0, 32.6–32.9 (overlapped peaks), 13.5, 12.6, 11.8; IR (thin film, cm^{-1}) 3468(m), 3388(bs), 3093(w), 3065(w), 2957(m), 2927(m), 2869(m), 1777(w), 1705(s), 1492(s), 1383(m), 1188(m), 1176(m), 1157(m), ; HRMS *m/z* (M + Na$^+$) calcd 463.0992, found 463.0980. Anal. Calcd for $C_{23}H_{25}BrN_2O_2$: C, 62.59; H, 5.71; N, 6.35. Found: C, 62.62; H, 5.63; N, 6.55.

5-(4-Bromophenyl)-8-isopropyl-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (58). Method B with **3f** (982 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **58** (900 mg, 41%) as a colorless solid, a mixture of three isomers (maj:min:min = 1.8:1.0:0.3): mp 291–293°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.53 (bs, 1H, 1min-H), 10.28 (bs, 1H, 1maj-H), 10.24 (bs, 1H, 1min-H), 7.74 (d, *J* = 8.4 Hz, 2H, Ph min), 7.71 (d, *J* = 8.1 Hz, 2H, Ph maj), 7.20 (d, *J* = 8.4 Hz, 2H, Ph min), 7.18 (d, *J* = 8.7 Hz, 2H, Ph maj), 5.79–5.84 (m, 1H, 3maj-H), 5.60–5.63 (m, 1H, 3min-H), 5.58–5.60 (m, 1H, 3min-H), 4.12–4.18 (m, overlapped, 3bαmin-H), 4.14 (d, *J* = 7.8 Hz, 1H, 3bαmin-H), 4.00 (d, *J* = 8.4 Hz, 1H, 3bαmaj-H), 3.31–3.46 (m, 1H, 6a-H), 2.93–3.02 (m, 1H, 10aαmaj-H), 2.86–2.92 (m, 1H, 10aβmin-H), 2.26–2.50 (m, 1H, 6b-H), 2.17 (s, 3H, 2-CH_3), 0.90–2.08 (m, 8H, cyclohex., CH(CH$_3$)$_2$), 0.67–0.86 (m, 6H, CH(CH_3)$_2$); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.1, 176.0, 165.3, 132.7, 132.6, 129.3, 128.2, 126.6, 121.9, 119.0, 116.7, 105.2, 103.0, 45.9, 35.0, 32.7–33.2 (overlapped peaks), 28.9, 25.5, 21.1, 21.0, 20.9, 13.5; IR (thin film, cm^{-1}) 3467(m), 3398(s), 3094(w), 3067(w), 2946(m), 2888(m), 2867(m), 1777(w), 1705(s), 1492(s), 1386(m), 1176(m), 1162(m); HRMS *m/z* (M + Na$^+$) calcd 477.1149, found 477.1152. Anal. Calcd for $C_{24}H_{27}BrN_2O_2$: C, 63.30; H, 5.98; N, 6.15. Found: C, 63.07; H, 5.67; N, 6.16.

5-(4-Bromophenyl)-8-tert-butyl-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (59). Method B with **3g** (1080 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **59** (700 mg, 31%) as a colorless solid, a mixture of three isomers (maj:min:min = 3.3:1.0:0.5): mp 263–265°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.51 (d, *J* = 1.8 Hz, 1H, 1min-H), 10.38 (d, *J* = 1.5 Hz, 1H, 1maj-H), 10.34 (d, *J* = 1.8 Hz, 1H, 1min-H), 7.77 (d, *J* = 8.7 Hz, 2H, Ph min), 7.71 (d, *J* = 9.0 Hz, 2H, Ph maj), 7.66 (d, *J* = 9.0 Hz, 2H, Ph min), 7.17 (d, *J* = 9.0 Hz, 2H, Ph min), 7.15 (d, *J* = 8.7 Hz, 2H, Ph maj), 7.11 (d, *J* = 8.7 Hz, 2H, Ph min), 5.66 (dd, *J* = 2.4, 0.9 Hz, 1H, 3min-H), 5.59 (dd, *J* = 2.4, 0.6 Hz, 1H, 3min-H), 5.54 (dd, *J* = 2.4, 0.9 Hz, 1H, 3maj-H), 4.16 (app. d, *J* = 8.4 Hz, 1H, 3bαmin-H), 4.11 (app. d, *J* = 8.1 Hz, 1H, 3bαmaj-H), 3.90 (dd, *J* = 7.5, 1.2 Hz, 1H, 3bαmin-H), 3.50 (dd, *J* = 8.1, 6.3 Hz, 1H, 6aαmaj-H), 3.47 (dd, *J* = 7.5, 5.4 Hz, 1H, 6aαmin-H), 3.44 (dd, *J* = 8.4, 5.1 Hz, 1H, 6aαmin-H), 2.22–2.68 (m, 2H, 6b-H, 10a-H), 2.18 (s, 3H, 2-CH_3 min), 2.12 (s, 3H, 2-CH_3 maj), 2.11 (s, 3H, 2-CH_3 min), 0.92–2.04 (m, 7H, cyclohex.), 0.85 (s, 9H, *t*-Bu min), 0.84 (s, 9H, *t*-Bu maj), 0.67 (s, 9H, *t*-Bu min); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.3, 178.2, 177.0, 175.8, 175.7, 175.1, 132.6, 132.4, 132.3, 129.5, 129.4, 128.6, 121.8, 116.8, 104.5, 104.2, 44.9, 34.3–34.5 (overlapped peaks), 33.2, 28.2, 28.0, 27.9, 13.4; IR (thin film, cm^{-1}) 3403(bs), 2923(m), 2353(w), 1770(w), 1713(s), 1492(m), 1390(m), 1163(m); HRMS *m/z* (M + Na$^+$) calcd 491.1305, found 491.1328. Anal. Calcd for $C_{25}H_{29}BrN_2O_2$: C, 63.97; H, 6.23; N, 5.97. Found: C, 63.94; H, 6.00; N, 5.73.

5-(4-Bromophenyl)-2-methyl-8-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (60). Method B with **3h** (1220 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **60** (1000 mg, 43%) as a colorless solid, a mixture of four isomers (maj:min:min:min = 2.2:1.0:0.6:0.1): mp 294–296°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.59 (bs, 1H, 1min-H), 10.57 (bs, 1H, 1min-H), 10.38 (bs, 1H, 1maj-H), 10.35 (bs, 1H, 1min-H), 7.64–7.75 (m, 2H, Ph), 7.08–7.35 (m, 7H, Ph), 5.82–5.92 (m, 1H, 3min-H), 5.76–5.88 (m, 1H, 3maj-H), 5.63–5.70 (m, 1H, 3min-H), 5.50–5.55 (d, *J* = 7.2 Hz, 1H, 3min-H), 4.30 (d, *J* = 7.2 Hz, 1H, 3bαmin-H), 4.18 (d, *J* = 8.1 Hz, 1H, 3bαmin-H), 4.01 (d, *J* = 8.1 Hz, 1H, 3bαmaj-H), 3.38–3.54 (m, 1H, 6aα-H), 2.78–2.96 (m, 1H, 10a-H), 2.46–2.58 (m, 1H, 6b-H), 2.18 (s, 3H, 2-CH_3), 1.48–1.98 (m, 7H, cyclohex.); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.4, 177.1, 132.7, 132.6, 132.34, 132.3, 132.3, 132.2, 129.6, 128.9, 127.6, 126.8, 126.7, 126.0, 121.7, 116.9, 105.0, 45.5, 33.1–33.6 (overlapped peaks), 13.5; IR (thin film, cm^{-1}) 3464(m), 3397(s), 3087(m), 3061(m), 3025(m), 2939(s), 2871(m), 1777(m), 1712(s), 1601(m), 1491(s), 1454(m), 1387(s), 1333(m), 1162(s), 1072(m); HRMS *m/z* (M + Na$^+$) calcd 511.0992, found 511.1012. Anal. Calcd for $C_{27}H_{25}BrN_2O_2$: C, 66.26; H, 5.15; N, 5.72. Found: C, 66.25; H, 5.17; N, 5.63.

5-(4-Fluorophenyl)-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (61). Method B with **3c** (687 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **61** (760 mg, 45%) as a light-brown solid, a mixture of two isomers (maj:min = 1.8:1.0): mp 266–268°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.53 (d, *J* = 1.8 Hz, 1H, 1maj-H), 10.26 (d, *J* = 1.2 Hz, 1H, 1min-H), 7.25–7.42 (m, 4H, Ph), 5.83 (dd, *J* = 2.1, 0.6 Hz, 1H, 3min-H), 5.60 (dd, *J* = 2.4, 0.6 Hz, 1H, 3maj-H), 4.15 (dd, *J* = 8.1, 0.9 Hz, 1H, 3bαmaj-H), 4.01 (dd, *J* = 8.4 Hz, 1H, 3bαmin-H), 3.40 (dd, *J* = 8.4, 5.1 Hz, 1H, 6aαmaj-H), 3.35 (dd, *J* = 8.4, 5.4 Hz, 1H, 6aαmin-H), 2.99–3.05 (m, 1H, 10aαmin-H), 2.90–2.95 (m, 1H, 10aβmaj-H), 2.06–2.40 (m, 2H, cyclohex., 6b-H), 2.18 (s, 3H, 2-CH_3), 0.98–1.64 (m, 7H, cyclohex.); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.4, 178.2, 177.4, 176.3, 163.8, 160.0, 129.7, 129.5, 129.3, 129.0, 128.3, 126.9, 126.6, 119.0, 116.8, 116.7, 116.6, 116.4, 116.3, 108.6, 105.4, 102.8, 46.2, 45.9, 38.7, 38.5, 38.4, 38.2, 33.0, 29.3, 27.6, 26.1, 25.7, 23.2, 22.9, 21.4, 20.8, 13.5, 13.4; IR (thin film, cm^{-1}) 3460(m), 3390(s), 3072(w), 2928(m), 2856(m), 1777(w), 1701(s), 1604(w), 1512(s), 1391(m), 1230(m), 1180(m), 1161(m); HRMS *m*/*z* (M + Na^{+}) calcd 375.1480, found 375.1488. Anal. Calcd for $C_{21}H_{21}FN_2O_2$: C, 71.57; H, 6.01; N, 7.95. Found: C, 71.66; H, 6.28; N, 7.73.

5-(4-Fluorophenyl)-2,8-dimethyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (62). Method B with **3d** (785 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **62** (670 mg, 38%) as a colorless solid, a mixture of three isomers (maj:min:min = 1.6:1.0:0.2): mp 265–267°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.52 (d, *J* = 1.5 Hz, 1H, 1min-H), 10.27 (d, *J* = 2.1 Hz, 1H, 1maj-H), 10.24–10.27 (app. bs, 1H, 1min-H), 7.24–7.40 (m, 4H, Ph), 5.82 (dd, *J* = 2.1, 0.9 Hz, 1H, 3maj-H), 5.60 (dd, *J* = 2.4, 0.9 Hz, 1H, 3min-H), 5.59 (dd, *J* = 2.4, 0.9 Hz, 1H, 3min-H), 4.15 (dd, *J* = 8.1, 1.8 Hz, 1H, 3bαmin-H), 4.01 (dd, *J* = 8.4, 1.8 Hz, 1H, 3bαmaj-H), 4.00 (dd, *J* = 8.4, 1.8 Hz, 1H, 3bαmin-H), 3.41 (dd, *J* = 8.3, 5.3 Hz, 1H, 6aαmin-H), 3.37 (dd, *J* = 8.7 Hz, 1H, 6aαmin-H), 3.36 (dd, *J* = 8.1, 5.1 Hz, 1H, 6aαmaj-H), 2.93–3.00 (m, 1H, 10aαmaj-H), 2.87–2.92 (m, 1H, 10aβmin-H), 2.30–2.58 (m, 1H, 6b-H), 2.17 (s, 3H, 2-CH_3), 0.85–2.10 (m, 7H, cyclohex.), 0.951 (d, *J* = 7.2 Hz, 3H, 8-CH_3 maj), 0.949 (d, *J* = 7.2 Hz, 3H, 8-CH_3 min), 0.72 (d, *J* = 6.6 Hz, 1H, 8-CH_3 min); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.3, 178.1, 177.3, 176.2, 163.5, 160.3, 129.7, 129.5, 129.4, 129.2, 129.1, 129.0, 128.2, 126.6, 116.9, 116.7, 116.6, 116.4, 116.3, 108.8, 105.3, 103.0, 45.9, 45.6, 38.5, 38.1, 33.1, 32.6, 32.5, 27.0, 26.7, 18.2, 13.5, 13.4; IR (thin film, cm^{-1}) 3462(m), 3390(bs), 3071(w), 2956(m), 2920(m), 2889(m), 2856(m), 1777(w), 1701(s), 1604(m), 1512(s), 1391(m), 1231(m), 1189(m), 1174(m), 1161(m); HRMS *m*/*z* (M + Na^{+}) calcd 389.1637, found 389.1651. Anal. Calcd for $C_{22}H_{23}FN_2O_2$: C, 72.11; H, 6.33; N, 7.64. Found: C, 72.11; H, 6.28; N, 7.48.

8-Ethyl-5-(4-fluorophenyl)-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (63). Method B with **3e** (883 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **63** (800 mg, 44%) as a colorless solid, a mixture of three isomers (maj:min:min = 2.3:1.0:0.6): mp 283–285°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.53 (d, *J* = 2.1 Hz, 1H, 1maj-H), 10.28 (d, *J* = 1.5 Hz, 1H, 1min-H), 7.23–7.41 (m, 4H, Ph), 5.82 (dd, *J* = 1.8, 0.9 Hz, 1H, 3min-H), 5.61 (dd, *J* = 2.4, 1.2 Hz, 1H, 3maj-H), 5.58 (dd, *J* = 2.1, 0.9 Hz, 1H, 3min-H), 4.15 (dd, *J* = 7.8, 1.2 Hz, 1H, 3bαmaj-H), 4.14 (dd, *J* = 8.1, 0.6 Hz, 1H, 3bαmin-H), 4.00 (dd, *J* = 8.6, 1.7 Hz, 1H, 3bαmin-H), 3.43 (dd, *J* = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.39 (dd, *J* = 8.3, 5.3 Hz, 1H, 6aαmaj-H), 3.35 (dd, *J* = 8.1, 5.41 Hz, 1H, 6aαmin-H), 2.94–2.99 (m, 1H, 10aαmin-H), 2.90–2.93 (m, 1H, 10amin-H), 2.85–2.91 (m, 1H, 10aβmaj-H), 2.40–2.50 (m, 1H, 6bαmaj-H), 2.25–2.40 (m, 1H, 6bmin-H), 2.18 (s, 3H, 2-CH_3), 0.82–2.18 (m, 9H, cyclohex., CH_2CH_3), 0.80 (t, 3H, CH_2CH_3 min), 0.78 (t, 3H, CH_2CH_3 maj); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.2, 177.4, 176.2, 129.6, 129.5, 129.4, 129.0, 128.2, 126.6, 119.0, 118.7, 116.9, 116.8, 116.7, 116.5, 116.3, 108.8, 103.0, 45.9, 38.2, 38.1, 34.3, 33.9, 33.0, 32.9, 32.8, 32.7, 30.0, 23.6–24.0 (overlapped peaks); IR (thin film, cm^{-1}) 3461(m), 3393(bs), 3071(w), 2959(m), 2925(s), 2866(m), 1779(w), 1702(s), 1512(s), 1391(m), 1231(m), 1186(m), 1161(m); HRMS *m*/*z* (M + Na^{+}) calcd for $C_{23}H_{25}FN_2O_2$: 403.1793, found 403.1809.

5-(4-Fluorophenyl)-8-isopropyl-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (64). Method B with **3f** (982 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **64** (770 mg, 41%) as a colorless solid, a mixture of three isomers (maj:min:min = 1.9:1.0:0.2): mp 286–288°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.53 (d, *J* = 2.4 Hz, 1H, 1min-H), 10.28 (d, *J* = 2.4 Hz, 1H, 1maj-H), 10.24 (d, *J* = 2.4 Hz, 1H, 1min-H), 7.21–7.43 (m, 4H, Ph), 5.82 (dd, *J* = 1.8, 0.6 Hz, 1H, 3maj-H), 5.61 (dd, *J* = 2.4, 0.6 Hz, 1H, 3min-H), 5.58 (dd, *J* = 1.8, 0.9 Hz, 1H, 3min-H), 4.16 (dd, *J* = 9.3, 1.2 Hz, 1H, 3bαmin-H), 4.14 (dd, *J* = 7.8, 0.9 Hz, 1H, 3bαmin-H), 3.99 (dd, *J* = 8.4, 1.8 Hz, 1H, 3bαmaj-H), 3.43 (dd, *J* = 8.3, 5.3 Hz, 1H, 6aαmin-H), 3.39 (dd, *J* = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.35 (dd, *J* = 8.4, 5.7 Hz, 1H, 6aαmaj-H), 2.93–3.01 (m, 1H, 10aαmaj-H), 2.86–2.92 (m, 1H, 10aβmin-H), 2.20–2.50 (m, 1H, 6b-H), 2.18 (s, 3H, 2-CH_3), 0.95–2.16 (m, 8H, cyclohex., $CH(CH_3)_2$), 0.85 (d, *J* = 6.3 Hz, 6H, $CH(CH_3)_2$ maj), 0.84 (d, *J* = 6.3 Hz, 6H, $CH(CH_3)_2$ min), 0.79 (d, *J* = 6.3 Hz, 6H, $CH(CH_3)_2$ min); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.5, 177.4, 176.2, 129.5, 129.4, 129.2, 129.1, 129.02, 129.0, 128.5, 128.2, 126.5, 118.9, 116.8, 116.7, 116.5, 116.4, 108.8, 105.3, 105.0, 104.5, 102.9, 45.5, 32.7–33.1, 21.8, 21.7, 21.0, 13.6, 13.5; IR (thin film, cm^{-1}) 3402(bs), 2922(m), 1770(w), 1730(s), 1453(m), 1231(m), 1157(m), 1110(m); HRMS *m*/*z* (M + Na^{+}) calcd 417.1950, found 417.1964. Anal. Calcd for $C_{24}H_{27}FN_2O_2$: C, 73.07; H, 6.90; N, 7.10. Found: C, 72.91; H, 6.76; N, 6.90.

8-tert-Butyl-5-(4-fluorophenyl)-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (65). Method B with **3g** (1080 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **65** (670 mg, 34%) as a light-yellow solid, a mixture of four isomers (maj:min:min:min = 1.6:1.0:0.3:0.2): mp 223–225°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.51 (d, *J* = 1.8 Hz, 1H, 1min-H), 10.37 (d, *J* = 2.4 Hz, 1H, 1min-H), 10.34 (d, *J* = 2.4 Hz, 1H, 1maj-H), 10.23 (d, *J* = 2.7 Hz, 1H, 1min-H), 7.13–7.46 (m, 4H, Ph), 5.81 (dd, *J* = 2.1, 0.6 Hz, 1H, 3min-H), 5.67 (dd, *J* = 2.4, 0.9 Hz, 1H, 3maj-H), 5.59 (dd, *J* = 2.4, 0.9 Hz, 1H, 3min-H), 5.54 (dd, *J* = 2.4, 0.9 Hz, 1H, 3min-H), 4.16 (dd, *J* = 1.8 Hz, 9.6 Hz, 1H, 3bαmin-H), 4.11 (app. d, *J* = 8.7 Hz, 1H, 3bαmin-H), 4.02 (dd, *J* = 8.4. 1.8 Hz, 1H, 3bαmin-H), 3.90 (dd, *J* = 7.7, 1.4 Hz, 1H, 3bαmaj-H), 3.50 (dd, *J* = 8.3, 6.2 Hz, 1H, 6aαmin-H), 3.46 (dd, *J* = 7.8, 5.7 Hz, 1H, 6aαmaj-H), 3.44 (dd, *J* = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.38 (dd, *J* = 8.4, 5.4 Hz, 1H, 6aαmin-H), 2.96–3.02 (m, 1H, 10amin-H), 2.86–2.92 (m, 1H, 10amin-H), 2.24–2.64 (m, 2H, 6b-H, 10aαmaj-H), 0.94–2.22 (m, 7H, cyclohex.), 2.18 (s, 3H, 2-CH_3 min), 2.13 (2, 3H, 2-CH_3 min), 2.11 (s, 3H, 2-CH_3 maj), 0.86 (s, 9H, *t*-Bu maj), 0.84 (s, 9H, *t*-Bu min), 0.68 (s, 9H, *t*-Bu min); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.6, 178.5, 177.2, 176.0, 130.3, 129.7, 129.6, 129.3, 129.25, 129.2, 129.1, 128.5, 126.9, 126.8, 126.6, 122.3, 119.0, 116.8, 116.7, 116.5, 116.4, 116.2, 109.3, 104.2, 104.0, 46.26, 45.3, 44.9, 41.8, 34.4, 33.9, 33.2, 33.0, 32.6, 30.6–30.9 (overlapped peaks), 28.9–29.3 (overlapped peaks), 28.2, 28.0, 27.8, 27.7, 25.9, 13.4 ; IR (thin film, cm^{-1}) 3388(bs), 2921(m), 2864(m), 1774(w), 1713(s), 1512(s), 1391(m), 1231(m), 1160(m); HRMS *m/z* (M + Na$^+$) calcd for $C_{25}H_{29}FN_2O_2$: 431.2106, found 431.2109.

5-(4-Fluorophenyl)-2-methyl-8-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (66). Method B with **3h** (1220 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **66** (1000 mg, 49%) as a colorless solid, a mixture of four isomers (maj:min:min:min = 8.0:1.0:0.5:0.4): mp 310–312°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.58 (app. bs, 1H, 1min-H), 10.56 (app. bs, 1H, 1min-H), 10.38 (d, J = 1.2 Hz, 1H, 1maj-H), 10.35 (app. bs, 1H, 1min-H), 7.15–7.39 (m, 9H, Ph), 5.87 (dd, J = 2.7, 0.6 Hz, 1H, 3min-H), 5.77–5.85 (app. m, 1H, 3maj-H), 5.65 (dd, J = 1.5, 0.6 Hz, 1H, 3min-H), 5.50–5.52 (app. m, 1H, 3min-H), 4.29 (dd, J = 6.9, 0.9 Hz, 1H, 3bαmin-H), 4.18 (dd, J = 8.7, 0.6 Hz, 1H, 3bαmin-H), 4.06 (dd, J = 8.6, 1.7 Hz, 1H, 3bαmin-H), 4.01 (app. d, J = 8.1 Hz, 1H, 3bαmaj-H), 3.34–3.52 (m, 1H, 6aα-H), 3.06–3.12 (m, 1H, 10amin-H), 2.86–2.96 (m, 1H, 10aαmaj-H), 2.80–2.90 (m, 1H, 10aβmin-H), 2.46–2.58 (m, 1H, 6b-H), 2.18 (s, 3H, 2-CH_3), 1.40–2.18 (m, 7H, cyclohex.); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.6, 177.4, 163.5, 160.5, 129.8, 129.7, 129.3, 129.2, 128.9, 127.6, 126.8, 126.1, 116.6, 116.4, 116.3, 75.0, 45.4, 33.1–33.8 (overlapped peaks), 13.5; IR (thin film, cm^{-1}) 3461(m), 3391(bs), 2935(m), 2871(m), 1775(w), 1701(s), 1603(w), 1512(s), 1391(m), 1228(m), 1191(m), 1165(m); HRMS *m/z* (M + Na$^+$) calcd 451.1793, found 451.1797. Anal. Calcd for $C_{27}H_{25}FN_2O_2$: C, 75.68; H, 5.88; N, 6.54. Found: C, 75.53; H, 5.76; N, 6.40.

2-Methyl-5-phenyl-3b,6a,6b,7,8,9,10,11,11a-nonahydro-1H,5H-cyclohepta[g]pyrrolo[3,4-e]indole-4,6-dione (67). Method B with **3b** (1100 mg, 9.820 mmol), 4-h reflux, and then a diethyl ether wash (10 mL) gave **67** (350 mg, 21%) as a colorless solid, a mixture of two isomers (maj:min = 16.7:1.0): mp 232–233°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.20 (bs, 1H, 1min-H), 7.64 (bs, 1H, 1maj-H), 7.31–7.52 (m, 4H, Ph), 7.24–7.31 (m, 1H, Ph), 6.05 (d, J = 1.5 Hz, 1H, 3maj-H), 5.77 (d, J = 2.1 Hz, 1H, 3min-H), 3.97 (dd, J = 7.8, 1.8 Hz, 1H, 3bα-H), 3.45 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.34 (dd, J = 8.0, 5.0 Hz, 1H, 6aαmaj-H), 2.98–3.10 (m, 1H, 11a-H), 2.52–2.63 (m, 1H, 6bα-H), 2.05–2.30 (m, 1H, cyclohept.), 2.27 (s, 3H, 2-CH_3), 1.30–1.92 (m, 9H, cyclohept.); ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.44 (d, J = 1.8 Hz, 1H, 1min-H), 10.34 (d, J = 2.4 Hz, 1H, 1maj-H), 7.35–7.51 (m, 4H, Ph), 7.11–7.16 (m, 1H, Ph), 5.67 (dd, J = 2.1, 0.9 Hz, 1H, 3maj-H), 5.57 (dd, J = 2.4, 0.9 Hz, 1H, 3min-H), 4.09 (dd, J = 9.0, 1.8 Hz, 3bαmin-H), 3.87 (dd, J = 7.7, 1.7 Hz, 1H, 3bαmaj-H), 3.44 (dd, J = 5.1, 4.2 Hz, 1H, 6aαmin-H), 3.42 (dd, J = 7.5, 4.8 Hz, 1H, 6aαmaj-H), 2.88–2.96 (m, 1H, 11a-H), 2.34–2.43 (m, 1H, 6bα-H), 2.10–2.23 (m, 1H, cyclohept.), 2.13 (s, 3H, 2-CH_3), 1.17–1.91 (m, 9H, cyclohept.); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 178.4, 176.7, 132.1, 130.2, 129.1, 128.3, 127.9, 126.5, 109.9, 104.7, 45.3, 40.7, 39.5, 36.8, 31.0, 30.4, 28.0, 26.6, 13.3; IR (thin film, cm^{-1}) 3393(bs), 3059(m), 2937(m), 2907(m), 2854(m), 1775(w), 1704(s), 1505(m), 1498(m), 1455(m), 1383(m), 1190(m), 1166(m), 1112(m); HRMS *m/z* (M + Na$^+$) calcd 371.1731, found 371.1734. Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 75.66; H, 6.93; N, 7.78.

5-(4-Isopropylphenyl)-2-methyl-3b,6a,6b,7,8,9,10,11,11a-nonahydro-1H,5H-cyclohepta[g]pyrrolo[3,4-e]indole-4,6-dione (68). Method B with **3b** (1100 mg, 9.820 mmol), 2-h reflux, and then reprecipitation from diethyl ether (5 mL) gave **68** (50 mg, 3%) as a colorless solid, a mixture of three isomers (maj:min:min = 1.2:1.0:0.05): mp 188–192°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.82 (bs, 1H, 1min-H), 8.20 (bs, 1H, 1min-H), 7.62 (bs, 1H, 1min-H), 7.32 (d, J = 8.4 Hz, 2H, Ph min), 7.29 (d, J = 8.7 Hz, 2H, Ph maj), 7.18 (d, J = 8.4 Hz, 2H, Ph min), 7.17 (d, J = 8.7 Hz, 1H, Ph maj), 6.05 (dd, J = 2.1, 0.6 Hz, 1H, 3maj-H), 5.92 (dd, J = 2.4, 1.2 Hz, 1H, 3min-H), 5.77 (dd, J = 2.7, 0.9 Hz, 1H, 3min-H), 4.07 (app. d, J = 8.1 Hz, 1H, 3bαmin-H), 4.00 (d, J = 8.4 Hz, 1H, 3bαmin-H), 3.96 (dd, J = 7.8, 1.8 Hz, 1H, 3bαmaj-H), 3.45 (dd, J = 8.6, 5.6 Hz, 1H, 6aαmin-H), 3.33 (dd, J = 7.8, 5.1 Hz, 1H, 6aαmaj-H), 2.97–3.09 (m, 1H, 11a-H), 2.93 (septet, J = 6.8 Hz, 1H, C*H*$(CH_3)_2$), 2.52–2.63 (m, 1H, 6b-H), 2.35 (s, 3H, 2-CH_3 min), 2.29 (s, 3H, 2-CH_3 min), 2.27 (s, 3H, 2-CH_3 maj), 2.10–2.26 (m, 1H, cyclohept.), 1.65–1.90 (m, 6H, cyclohept.), 1.32–1.63 (m, 3H, cyclohept.), 1.27 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$ min), 1.25 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$ maj); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 178.4, 149.1, 127.3, 127.2, 126.2, 104.8, 45.3, 40.6, 36.8, 34.0, 31.0, 30.4, 26.7, 24.0, 13.3; IR (thin film, cm^{-1}) 3395(bs), 3047(m), 2957(m), 2919(m), 2858(m), 2361(w), 1774(w), 1698(s), 1516(m), 1389(m), 1181(m), 1171(m); HRMS *m/z* (M + Na$^+$) calcd for $C_{25}H_{30}N_2O_2$: 413.2200, found 413.2203.

5-(4-Methoxyphenyl)-2-methyl-3b,6a,6b,7,8,9,10,11,11a-nonahydro-1H,5H-cyclohepta[g]pyrrolo[3,4-e]indole-4,6-dione (69). Method B with **3b** (1100 mg, 9.820 mmol), 4-h reflux, removal of solvent under reduced pressure, column chromatography eluting with CH_2Cl_2, and then reprecipitation from diethyl ether (20 mL) gave **69** (400 mg, 11%) as a colorless solid, a mixture of three isomers (maj:min:min = 5.8:1.0:0.3): mp 191–193°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.16 (bs, 1H, 1min-H), 7.61 (bs, 1H, 1maj-H), 7.17 (d, J = 9.0 Hz, 2H, Ph), 6.95 (d, J = 9.0 Hz, 2H, Ph), 6.05 (d, J = 2.4 Hz, 1H, 3maj-H), 5.99 (d, J = 2.4 Hz, 1H, 3min-H), 5.77 (d, J = 2.1 Hz, 1H, 3min-H), 4.06 (dd, J = 7.4, 2.0 Hz, 1H, 3bαmin-H), 3.93 (dd, J = 7.8, 1.8 Hz, 1H, 3bαmaj-H), 3.84 (s, 3H, OCH_3 min), 3.82 (s, 3H, OCH_3 maj), 3.81 (s, 3H, OCH_3 min), 3.44 (dd, J = 8.7, 5.7, 1H, 6aαmin-H), 3.35 (dd, J = 7.7, 3.5 Hz, 1H, 6aαmin-H), 3.33 (dd, J = 7.8, 4.8 Hz, 1H, 6aαmaj-H), 3.01–3.09 (m, 1H, 11a-H), 2.53–2.62 (m, 1H, 6b-H), 2.10–2.30 (m, 1H, cyclohept.), 2.29 (s, 3H, 2-CH_3 min), 2.27 (s, 3H, 2-CH_3 maj), 2.24 (s, 3H, 2-CH_3 min), 1.70–1.98 (m, 6H, cyclohept.), 1.32–1.55 (m, 3H, cyclohept.); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 178.5, 177.0, 159.3, 130.2, 127.8, 127.7, 124.8, 114.4, 114.2, 109.9, 105.2, 104.7, 55.6, 48.2, 45.3, 43.2, 42.5, 40.6, 39.6, 37.6, 36.8, 31.9, 31.8, 31.0, 30.9, 30.4, 27.9, 27.5, 26.6, 26.4, 24.8, 13.3; IR (thin film, cm^{-1}) 3379(bs), 2925(m), 2858(m), 1773(w), 1705(s), 1513(s), 1387(m), 1252(m), 1169(m); HRMS *m/z* (M + Na$^+$) calcd 401.1836, found 401.1837. Anal. Calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 72.80; H, 6.92; N, 7.41.

2-Methyl-5-(3-nitrophenyl)-3b,6a,6b,7,8,9,10,11,11a-nonahydro-1H,5H-cyclohepta[g]pyrrolo[3,4-e]indole-4,6-dione (70). Method B with **3b** (1100 mg, 9.820 mmol), 1.5 h-reflux, removal of solvent under reduced pressure, column chromatography eluting with CH_2Cl_2, and then reprecipitation from diethyl ether (20 mL) gave **70** (450 mg, 24%) as a colorless solid, a mixture of two isomers (maj:min = 9.0:1.0): mp 169–170°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.21–8.29 (m, 2H, Ph), 8.13 (bs, 1H, 1min-H), 7.60–7.72 (m, 3H, Ph, Ph, 1maj-H), 6.02 (dd, *J* = 2.4, 0.9 Hz, 1H, 3maj-H), 5.78 (dd, *J* = 3.0, 0.9 Hz, 1H, 3min-H), 4.07 (app. d, *J* = 8.4 Hz, 1H, 3bαmin-H), 4.02 (dd, *J* = 7.8, 1.8 Hz, 1H, 3bαmaj-H), 3.49 (dd, *J* = 8.6, 5.7 Hz, 1H, 6aαmin-H), 3.38 (dd, *J* = 7.7, 5.0 Hz, 1H, 6aαmaj-H), 3.02–3.10 (m, 1H, 11a-H), 2.54–2.63 (m, 1H, 6bα-H), 2.20–2.38 (m, 1H, cyclohex.), 2.28 (s, 3H, 2-CH_3), 1.57–1.95 (m, 6H, cyclohept.), 1.35–1.58 (m, 3H, cyclohept.); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 177.5, 176.0, 148.4, 133.2, 132.3, 130.4, 129.8, 128.3, 122.9, 121.6, 109.5, 104.5, 45.3, 41.0, 39.2, 36.8, 36.7, 31.1, 31.0, 30.6, 28.5, 28.3, 26.3, 13.3; IR (thin film, cm^{-1}) 3394(bs), 2926(m), 2859(m), 1777(w), 1713(s), 1533(s), 1351(m), 1195(w), 1165(m); HRMS *m/z* (M + Na^{+}) calcd 416.1582, found 416.1589. Anal. Calcd for $C_{22}H_{23}N_3O_4$: C, 67.16; H, 5.89; N, 10.68. Found: C, 67.33; H, 5.86; N, 10.80.

5-(4-Chlorophenyl)-2-methyl-3b,6a,6b,7,8,9,10,11,11a-nonahydro-1H,5H-cyclohepta[g]pyrrolo[3,4-e]indole-4,6-dione (71). Method B with **3b** (1100 mg, 9.820 mmol), 4-h reflux, removal of solvent under reduced pressure, column chromatography eluting with CH_2Cl_2, and then reprecipitation from diethyl ether (20 mL) gave **71** (300 mg, 17%) as a colorless solid, a mixture of two isomers (maj:min = 28.0:1.0): mp 219–220°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.15 (bs, 1H, 1min-H), 7.63 (bs, 1H, 1maj-H), 7.41 (d, *J* = 8.7 Hz, 2H, Ph), 7.23 (d, *J* = 9.0 Hz, 2H, Ph), 6.03 (dd, *J* = 2.4, 0.9 Hz, 1H, 3maj-H), 5.77 (dd, *J* = 2.7, 0.9 Hz, 1H, 3min-H), 4.08 (dd, *J* = 7.2, 2.1, 1H, 3bαmin-H), 3.96 (dd, *J* = 7.8, 2.1 Hz, 1H, 3bαmaj-H), 3.45 (dd, *J* = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.33 (*J* = 7.7, 5.0 Hz, 1H, 6aαmaj-H), 3.00–3.08 (m, 1H, 11a-H), 2.52–2.61 (m, 1H, 6bα-H), 2.15–2.25 (m, 1H, cyclohept.), 2.27 (s, 3H, 2-CH_3), 1.68–1.92 (m, 6H, cyclohept.), 1.32–1.55 (m, 3H, cyclohept.); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 178.0, 176.4, 134.0, 130.6, 130.2, 129.2, 128.0, 127.7, 109.7, 104.6, 45.3, 40.7, 39.4, 36.8, 31.0, 30.4, 28.1, 27.8, 26.5, 13.3; IR (thin film, cm^{-1}) 3394(bs), 2925(m), 2858(m), 1775(w), 1709(s), 1494(m), 1381(m), 1195(w), 1166(w), 1092(w); HRMS *m/z* (M + Na^{+}) calcd 405.1341, found 405.1340. Anal. Calcd for $C_{22}H_{23}ClN_2O_3$: C, 69.01; H, 6.05; N, 7.32. Found: C, 69.21; H, 6.33; N, 7.40.

5-Dimethylamino-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (72). Method A gave **72** (265 mg, 28%) as a light-brown solid, a mixture of two isomers (maj:min = 8.5:1.0): mp 218–219°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.29 (bs, 1H, 1min-H), 7.68 (bs, 1H, 1maj-H), 6.18 (d, *J* = 2.7 Hz, 1H, 3maj-H), 5.76 (d, *J* = 2.4 Hz, 1H, 3min-H), 3.70 (dd, *J* = 8.6, 1.6 Hz, 1H, 3bα-H), 3.23 (dd, *J* = 8.7, 5.7 Hz, 1H, 6aαmin-H), 3.17 (dd, *J* = 8.4, 5.4 Hz, 1H, 6aαmaj-H), 3.04–3.10 (m, 1H, 10aαmaj-H), 2.80–2.92 (m, 1H, 10aβmin-H), 2.92 (s, 6H, N$(CH_3)_2$), 2.43–2.71 (m, 3H, 6bα-H, CH_2CH_3), 0.87–2.23 (m, 11H, cyclohex., CH_2CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 177.6, 176.7, 133.4, 126.8, 108.4, 103.6, 44.0, 43.8, 38.2, 36.8, 32.9, 27.6, 25.7, 23.0, 21.4, 21.0, 14.7; IR (thin film, cm^{-1}) 3371(bs), 2932(m), 2857(m), 2380(w), 1770(w), 1704(s), 1445(m), 1369(m), 1194(m); HRMS *m/z* (M + Na^{+}) calcd 338.1840, found 338.1844. Anal. Calcd for $C_{18}H_{25}N_3O_2$: C, 68.54; H, 7.99; N, 13.32. Found: C, 68.36; H, 8.06; N, 13.12.

5-Dimethylamino-2,8-diethyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (73). Method A gave **73** (319 mg, 31%) as a white solid, a mixture of two isomers (maj:min = 4.7:1.0): mp 221–222°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.29 (bs, 1H, 1min-H), 7.68 (bs, 1H, 1maj-H), 6.18 (d, *J* = 2.4 Hz, 1H, 3maj-H), 5.78 (d, *J* = 3.0 Hz, 1H, 3min-H), 3.73 (dd, *J* = 8.6, 2.0 Hz, 1H, 3bαmin-H), 3.70 (dd, *J* = 8.4, 1.8 Hz, 1H, 3bαmaj-H), 3.22 (dd, *J* = 8.7, 5.7 Hz, 1H, 6aαmin-H), 3.17 (d, *J* = 8.4, 5.4 Hz, 1H, 6aαmaj-H), 3.01–3.06 (m, 1H, 10aαmaj-H), 2.92–2.96 (m, 1H, 10aβmin-H), 2.93 (s, 6H, N$(CH_3)_2$), 2.56–2.75 (m, 3H, 6bα-H, 2-CH_2CH_3), 1.80–1.99 (m, 2H, cyclohex.), 1.07–1.52 (m, 10H, cyclohex., 2-CH_2CH_3, 8-CH_2CH_3), 0.85 (t, *J* = 7.4 Hz, 3H, 8-CH_2CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 177.6, 177.4, 176.7, 175.6, 135.0, 133.3, 126.7, 116.9, 112.5, 108.5, 105.0, 103.6, 101.2, 43.8, 43.7, 36.8, 33.9, 33.0, 32.6, 21.1, 14.7, 12.5; IR (thin film, cm^{-1}) 3378(bs), 2931(m), 2857(m), 2342(m), 1770(w), 1703(s), 1447(m), 1362(m), 1194(m); HRMS *m/z* (M + Na^{+}) calcd 366.2153, found 366.2161. Anal. Calcd for $C_{20}H_{29}N_3O_2$: C, 69.94; H, 8.51; N, 12.23. Found: C, 69.78; H, 8.35; N, 12.08.

8-tert-Butyl-5-dimethylamino-2-ethyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (74). Method A gave **74** (256 mg, 23%) as a light-orange solid, a mixture of two isomers (maj:min = 14.0:1.0): mp 190–191°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.61 (bs, 1H, 1maj-H), 6.13 (d, *J* = 2.7 Hz, 1H, 3min-H), 6.02 (d, *J* = 2.4 Hz, 1H, 3maj-H), 3.79 (dd, *J* = 7.8, 1.5 Hz, 1H, 3bα-H), 3.19 (dd, *J* = 12.3, 8.1 Hz, 1H, 6aαmin-H), 3.10 (dd, *J* = 5.9, 8.0 Hz, 1H, 6aαmaj-H), 2.87 (s, 6H, N$(CH_3)_2$), 2.52–2.75 (m, 4H, 6bα-H, 10a-H, CH_2CH_3), 1.72–2.04 (m, 4H, cyclohex.), 1.51 (ddd, *J* = 13.5, 10.2, 6.6 Hz, 1H, cyclohex.), 1.11–1.33 (m, 2H, cyclohex.), 1.25 (t, *J* = 7.5 Hz, 3H, CH_2CH_3), 0.90 (s, 9H, *t*-Bu); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 177.7, 176.4, 133.4, 129.9, 108.8, 102.4, 43.5, 43.1, 34.3, 34.0, 33.0, 30.6, 28.4, 28.0, 25.6, 21.0, 14.3; IR (thin film, cm^{-1}) 3386(bs), 2961(m), 2359(w), 1774(w), 1712(s), 1448(m), 1365(m), 1203(m), 1148(m); HRMS *m/z* (M + Na^{+}) calcd 394.2466, found 394.2473. Anal. Calcd for $C_{22}H_{33}N_3O_2$: C, 71.12; H, 8.95; N, 11.31. Found: C, 71.32; H, 8.75; N, 11.31.

2-Ethyl-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (75). Method A gave **75** (502 mg, 48%) as a white solid, a mixture of two isomers (maj:min = 1.4:1.0): mp 219–220°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.20 (bs, 1H, 1min-H), 7.83 (bs, 1H, 1maj-H), 7.44–7.54 (m, 3H, Ph), 7.27–7.31 (m, 2H, Ph), 6.14 (d, *J* = 2.7 Hz, 1H, 3maj-H), 5.82 (d, *J* = 2.4 Hz, 1H, 3min-H), 4.02 (dd, *J* = 8.9, 2.0 Hz, 1H, 3bαmin-H), 3.97 (dd, *J* = 8.6, 2.0 Hz, 1H, 3bαmaj-H), 3.78 (dd, *J* = 8.6, 5.6 Hz, 1H, 6aαmin-H), 3.40 (dd, *J* = 8.4, 5.4 Hz, 1H, 6aαmaj-H), 3.13–3.19 (m, 1H, 10aαmaj-H), 3.03–3.13 (m, 1H, 10aβmin-H), 2.67 (q, *J* = 7.5 Hz, 2H, 2-CH_2CH_3), 2.47–2.57 (m, 1H, 6b-H), 2.17–2.30 (m, 1H, cyclohex.), 1.10–1.83 (m, 10H, cyclohex., 2-CH_2CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.4, 178.2, 177.5, 176.3, 135.2, 133.5, 133.0, 132.8, 129.6, 129.5, 128.9, 128.8, 127.5, 127.4, 126.9, 118.7, 116.8, 108.5, 103.8, 101.1, 46.3, 46.0, 33.1, 33.07, 29.3, 27.6, 26.1, 25.7, 23.3, 22.9, 21.5, 21.0, 20.9, 14.8, 14.7; IR (thin film, cm^{-1}) 3394(bs), 2938(m), 2857(m), 2310(w), 1774(w), 1698(s), 1499(m), 1387(m), 1190(m), 1160(m); HRMS m/z (M + Na$^+$) calcd 371.1731, found 371.1738. Anal. Calcd for C$_{22}$H$_{24}$N$_2$O$_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 75.92; H, 7.03; N, 8.11.

2,8-Diethyl-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (76). Method A gave **76** (395 mg, 35%) as a cream-colored solid, a mixture of four isomers (maj:min:min:min = 1.2:1.0:0.2:0.1): mp 243–244°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.38 (bs, 1H, 1maj-H), 7.82 (bs, 1H, 1min-H), 7.42–7.55 (m, 3H, Ph), 7.27–7.30 (m, 2H, Ph), 6.13 (d, J = 2.4 Hz, 1H, 3min-H), 5.82 (d, J = 2.7 Hz, 1H, 3maj-H), 5.79 (d, J = 2.7 Hz, 1H, 3min-H), 4.02 (dd, J = 8.7 Hz, 2.1 Hz, 1H, 3bαmaj-H), 3.97 (dd, J = 8.4, 1.8 Hz, 1H, 3bαmin-H), 3.51 (dd, J = 5.6 Hz, 8.6 Hz, 1H, 6aαmin-H), 3.47 (dd, J = 8.7, 5.7 Hz, 1H 6aαmaj-H), 3.43 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.39 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.09–3.16 (m, 1H, 10aαmin-H), 2.98–3.06 (m, 1H, 10aβmaj-H), 2.50–2.72 (m, 1H, 6b-H), 2.67 (q, J = 7.5 Hz, 2H, 2-CH_2CH$_3$), 1.89–2.30 (m, 2H, cyclohex.), 1.19–1.57 (m, 10H, cyclohex., 2-CH$_2$CH_3, 8-CH_2CH$_3$), 0.87 (t, J = 7.2 Hz, 3H, 8-CH$_2$CH_3 min), 0.86 (t, J = 7.5 Hz, 1H, 8-CH$_2$CH$_3$ maj); IR (thin film, cm^{-1}) 3384(bs), 2953(m), 2923(m), 1773(w), 1694(s), 1497(w), 1456(w), 1447(w), 1389(m), 1192(m); HRMS m/z (M + Na$^+$) calcd 399.2044, found 399.2059. Anal. Calcd for C$_{24}$H$_{28}$N$_2$O$_2$: C, 76.56; H, 7.50; N, 7.44. Found: C, 76.41; H, 7.73; N, 7.24.

8-tert-Butyl-2-ethyl-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (77). Method A gave **77** (328 mg, 27%) as a cream-colored solid, a mixture of three isomers (maj:min:min = 4.4:1.0:0.3): mp 209–210°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.20 (bs, 1H, 1min-H), 7.76 (bs, 2H, 1maj-H, 1min-H), 7.37–7.56 (m, 3H, Ph), 7.19–7.29 (m, 2H, Ph), 6.12 (d, J = 2.4 Hz, 1H, 3min-H), 5.98 (d, J = 2.7 Hz, 1H, 3maj-H), 5.76 (d, J = 2.4 Hz, 1H, 3min-H), 4.03 (dd, J = 7.8, 1.5 Hz, 1H, 3bαmaj-H), 3.98 (dd, J = 8.6, 2.0 Hz, 1H, 3bαmin-H), 3.442 (dd, J = 8.3, 5.9 Hz, 1H, 6aαmin-H), 3.437 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.36 (dd, J = 7.8, 5.7 Hz, 1H, 6aαmaj-H), 3.10–3.13 (m, 1H, 10aβmin-H), 2.74–2.81 (m, 1H, 6bαmaj-H), 2.52–2.71 (m, 3H, 10aαmaj-H, CH_2CH$_3$), 1.76–2.28 (m, 3H, cyclohex.), 1.62 (ddd, J = 13.7, 11.0, 6.9 Hz, 1H, cyclohex.), 0.84–1.46 (m, 6H, cyclohex., CH$_2$CH_3), 0.92 (s, 9H, t-Bu), 0.75 (s, 9H, t-Bu); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.5, 178.46, 177.5, 177.3, 133.7, 133.5, 133.1, 133.0, 130.3, 129.6, 129.4, 128.8, 128.6, 127.5, 127.2, 126.9, 115.5, 109.1, 108.4, 103.8, 102.3, 47.5, 46.0, 45.9, 45.3, 41.8, 34.5, 33.9, 33.0, 32.7, 32.6, 30.6–31.0 (multiple peaks), 28.8–29.3 (multiple peaks), 27.6–28.3 (multiple peaks), 25.8–26.0 (multiple peaks), 22.4, 21.1, 21.0, 14.8, 14.3; IR (thin film, cm^{-1}) 3386(bs), 2961(m), 2923(m), 1771(w), 1708(s), 1496(m), 1372(m), 1314(m), 1176(m), 1163(m); HRMS m/z (M + Na$^+$) calcd 427.2357, found 427.2340. Anal. Calcd for C$_{26}$H$_{32}$N$_2$O$_2$: C, 77.19; H, 7.97; N, 6.92. Found: C, 77.34; H, 8.23; N, 7.07.

2-Ethyl-5-(4-methoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (78). Method A gave **78** (466 mg, 41%) as a cream-colored solid, a mixture of two isomers (maj:min = 5.6:1.0): mp 242–243°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.37 (bs, 1H, 1maj-H), 7.70 (bs, 1H, 1min-H), 7.16–7.28 (m, 2H, Ph), 6.95–7.02 (m, 2H, Ph), 6.24 (d, J = 2.7 Hz, 1H, 3min-H), 5.80 (d, J = 3.0 Hz, 1H, 3maj-H), 3.97 (dd, J = 8.9, 2.0 Hz, 1H, 3bαmaj-H), 3.96 (dd, J = 8.6, 2.0 Hz, 1H, 3bαmin-H), 3.843 (s, 3H, OCH$_3$ maj), 3.841 (s, 3H, OCH$_3$ min), 3.46 (dd, J = 8.7, 5.7 Hz, 1H, 6aαmaj-H), 3.39 (dd, J = 8.6, 5.3 Hz, 1H, 6aαmin-H), 3.12–3.17 (m, 1H, 10aαmin-H), 3.02–3.07 (m, 1H, 10aβmaj-H), 2.66 (q, J = 7.8 Hz, 2H, CH_2CH$_3$), 2.49–2.59 (m, 1H, 6bα-H), 2.14–2.27 (m, 1H, cyclohex.), 1.20–1.77 (m, 10H, cyclohex., CH$_2$CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.4, 176.5, 159.4, 135.1, 133.5, 128.6, 125.4, 118.7, 116.9, 114.8, 114.7, 108.5, 101.1, 55.9, 46.2, 46.0, 33.1, 29.3, 26.1, 22.9, 21.1, 20.9, 14.7; IR (thin film, cm^{-1}) 3399(bs), 2935(m), 1774(w), 1697(s), 1518(m), 1456(m), 1395(m), 1304(m), 1256(m), 1182(m); HRMS m/z (M + Na$^+$) calcd 401.1836, found 401.1851. Anal. Calcd for C$_{23}$H$_{26}$N$_2$O$_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 72.78; H, 6.88; N, 7.32.

2,8-Diethyl-5-(4-methoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (79). Method A gave **79** (439 mg, 36%) as a cream-colored solid, a mixture of three isomers (maj:min:min = 6.5:1.0:0.3): mp 252–253°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.35 (bs, 1H, 1min-H), 7.73 (bs, 1H, 1maj-H), 7.16–7.23 (m, 2H, Ph), 6.97–7.01 (m, 2H, Ph), 6.21 (d, J = 2.7 Hz, 1H, 3maj-H), 5.81 (d, J = 2.4 Hz, 1H, 3min-H), 5.78 (d, J = 2.4 Hz, 1H, 3min-H), 3.97 (dd, J = 8.4, 1.8 Hz, 1H, 3bαmin-H), 3.94 (dd, J = 8.4, 1.8 Hz, 1H, 3bαmaj-H), 3.84 (s, 3H, OCH$_3$), 3.45 (dd, J = 8.7, 6.0 Hz, 1H, 6aαmin-H), 3.41 (dd, J = 8.6, 5.3 Hz, 1H, 6aαmin-H), 3.38 (dd, J = 8.6, 5.6 Hz, 1H, 6aαmaj-H), 3.05–3.16 (m, 1H, 10aαmaj-H), 2.98–3.05 (m, 1H, 10aβmin-H), 2.59–2.74 (m, 3H, 6b-H, 2-CH_2CH$_3$), 1.03–2.20 (m, 9H, cyclohex., 8-CH_2CH$_3$), 1.29 (t, J = 7.5 Hz, 3H, 2-CH$_2$CH_3), 0.86 (t, J = 7.5 Hz, 3H, 8-CH$_2$CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.6, 177.7, 159.3, 133.4, 128.6, 125.6, 114.9, 114.8, 108.7, 103.8, 103.7, 55.9, 45.5, 34.0, 33.9, 33.1, 32.9, 32.8, 32.75, 32.7, 21.0, 14.7, 12.6; IR (thin film, cm^{-1}) 3383(bs), 2932(m), 2356(w), 1772(w), 1695(s), 1518(m), 1392(m), 1258(m), 1195(m), 1176(m); HRMS m/z (M + Na$^+$) calcd 429.2149, found 429.2167. Anal. Calcd for C$_{25}$H$_{30}$N$_2$O$_3$: C, 73.86; H, 7.44; N, 6.89. Found: C, 70.74; H, 6.94; N, 6.62.

8-tert-Butyl-2-ethyl-5-(4-methoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (80). Method A gave **80** (365 mg, 28%) as a cream-colored solid, a mixture of three isomers (maj:min:min = 2.1:1.0:0.1): mp 207–208°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.10 (bs, 1H, 1min-H), 7.64 (bs, 1H, 1min-H), 7.61 (bs, 1H, 1maj-H), 7.19 (d, J = 8.7 Hz, 2H, Ph min), 7.14 (d, J = 8.7 Hz, 2H, Ph maj), 7.00 (d, J = 9.3 Hz, 2H, Ph min), 6.95 (d, J = 8.7 Hz, 2H, Ph maj), 6.20 (d, J = 2.4 Hz, 1H, 3min-H), 6.06 (d, J = 2.7 Hz, 1H, 3maj-H), 5.77 (d, J = 2.4 Hz, 1H, 3min-H), 4.04 (dd, J = 7.5, 1.2 Hz, 1H, 3bmaj-H), 3.96 (dd, J = 8.6, 2.0 Hz, 1H, 3bmin-H), 3.84 (s, 3H, OCH$_3$ min), 3.82 (s, 3H, OCH$_3$ maj), 3.42 (dd, J = 8.6, 5.3 Hz, 1H, 6aαmin-H), 3.33 (dd, J = 7.8, 5.4 Hz, 1H, 6aαmaj-H), 3.05–3.14 (m, 1H, 10aβmin-H), 2.55–2.76 (m, 4H, 6b-H, 10aαmaj-H, CH_2CH$_3$), 0.91–2.25 (m, 7H, cyclohex.), 1.27 (t, J = 7.8 Hz, 3H, CH$_{-2}$CH_3), 0.91 (s, 9H, t-Bu maj), 0.73 (s, 9H, t-Bu min); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.7, 178.7, 177.7, 177.5, 176.2, 159.4, 159.3, 135.2, 133.6, 133.5, 130.0, 128.7, 128.6, 128.3, 128.2, 126.9, 125.7, 126.6, 126.55, 114.9, 114.8, 114.6, 109.1, 108.4, 103.8, 102.4, 55.9, 47.5, 46.0, 45.1, 44.7, 34.5, 33.9, 33.3, 33.0, 32.7, 32.6, 28.2, 28.0, 27.8, 21.1, 21.0, 14.8, 14.5, 14.3; IR (thin film, cm^{-1}) 3390(bs), 2963(m), 2935m), 2357(w), 1513, 1770(w), 1705(s), 1640(bm), 1514(s), 1389(m), 1252(m), 1168(m); HRMS *m/z* (M + Na$^+$) calcd 457.2462, found 457.2471. Anal. Calcd for $C_{27}H_{34}N_2O_3$: C, 74.62; H, 7.89; N, 6.45. Found: C, 74.73; H, 7.83; N, 6.36.

2-Benzyl-5-(dimethylamino)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (81). Method A gave **81** (396 mg, 35%) as a light-brown solid, a mixture of two isomers (maj:min = 3.2:1.0): mp 238–239°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.22 (bs, 1H, 1min-H), 7.57 (bs, 1H, 1maj-H), 7.29–7.36 (m, 2H, Ph), 7.21–7.28 (m, 3H, Ph), 6.25 (d, *J* = 2.7 Hz, 1H, 3maj-H), 5.79 (d, *J* = 2.7 Hz, 1H, 3min-H), 4.04 (AA′d, *J* = 16.2 Hz, 1H, Bn maj), 4.02 (AA′d, *J* = 15.9 Hz, 1H, Bn min), 3.95 (AA′d, *J* = 16.2 Hz, 1H, Bn maj), 3.94 (AA′d, *J* = 16.2 Hz, 1H, Bn min), 3.69 (dd, *J* = 8.4, 1.8 Hz, 1H, 3bα-H), 3.21 (dd, *J* = 8.6, 5.4 Hz, 1H, 6aαmin-H), 3.16 (dd, *J* = 8.6, 5.3 Hz, 1H, 6aαmaj-H), 3.01–3.05 (m, 1H, 10a-H), 2.93 (s, 6H, $N(CH_3)_2$), 2.42–2.52 (m, 1H, 6b-H), 1.99–2.22 (m, 1H, cyclohex.), 0.99–1.74 (m, 7H, cyclohex.); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 177.6, 177.4, 176.7, 175.6, 141.53, 141.47, 132.3, 130.4, 129.1, 128.7, 127.4, 126.3, 119.0, 117.4, 108.9, 105.7, 102.9, 44.3, 44.0, 43.8, 38.2, 36.7, 36.3, 34.0, 33.0, 29.2, 27.6, 26.0, 25.7, 23.1, 22.7, 21.4, 20.8; IR (thin film, cm^{-1}) 3450(bs), 2923(m), 2100(bw), 1770(w), 1703(s), 1648(bs), 1442(m), 1366(m), 1194(m), 1148(m); HRMS *m/z* (M + Na$^+$) calcd for $C_{23}H_{27}N_3O_2$: 400.1996, found 400.1992.

2-Benzyl-5-dimethylamino-8-ethyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (82). Method A gave **82** (353 mg, 29%) as a cream-colored solid, a mixture of three isomers (maj:min:min = 5.3:1.0:0.3): mp 239–240°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.54 (bs, 1H, 1min-H), 7.35 (bs, 2H, 1maj-H, 1min-H), 7.23–7.36 (m, 5H, Ph), 6.25 (d, *J* = 2.7 Hz, 1H, 3maj-H), 5.81 (d, *J* = 2.7 Hz, 1H, 3min-H), 5.77 (d, *J* = 2.7 Hz, 1H, 3min-H), 4.04 (AA′d, *J* = 16.2 Hz, 1H, Bn maj), 4.03 (AA′d, *J* = 15.9 Hz, 1H, Bn min), 3.95 (AA′d, *J* = 15.9 Hz, 1H, Bn maj), 3.94 (AA′d, *J* = 15.9 Hz, 1H, Bn min), 3.69 (dd, *J* = 8.4, 2.1 Hz, 1H, 3bα-H), 3.24 (dd, *J* = 6.0 Hz, 1H, 6aαmin-H), 3.20 (dd, *J* = 5.9 Hz, 1H, 6aαmin-H), 3.20 (dd, *J* = 5.4 Hz, 1H, 6aαmin-H), 3.16 (dd, *J* = 5.3 Hz, 1H, 6aαmaj-H), 2.86–3.01 (m, 7H, 10a-H, $N(CH_3)_2$), 2.58–2.67 (m, 1H, 6bαmaj-H), 2.46–2.55 (m, 1H, 6bmin-H), 0.98–2.08 (m, 9H, cyclohex., CH_2CH_3), 0.85 (t, *J* = 7.2 Hz, 3H, CH_2CH_3 maj), 0.77 (t, *J* = 7.2 Hz, 3H, CH_2CH_3 min); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 177.4, 177.3, 176.6, 139.6, 130.4, 128.8, 128.7, 128.7, 127.8, 127.6, 126.5, 120.0, 117.6, 117.5, 109.2, 44.1, 43.9, 39.3, 38.9, 38.5, 38.2, 37.0, 36.0, 34.5, 34.45, 34.37, 33.9, 32.9, 32.8, 32.7, 29.7, 29.6, 29.2, 29.0, 27.7, 27.4, 27.0, 26.1, 24.3, 23.6, 12.2, 11.4; IR (thin film, cm^{-1}) 3452(bs), 2923(m), 2122(bw), 1770(w), 1703(s), 1645(bs), 1446(m), 1367(m), 1190(m), 1151(m); HRMS *m/z* (M + Na$^+$) calcd for $C_{25}H_{31}N_3O_2$: 428.2309, found 428.2327.

2-Benzyl-8-tert-butyl-5-(dimethylamino)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,3bH-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (83). Method A gave **83** (325 mg, 25%) as cream-colored crystals, a single isomer: mp 195–196°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.46 (bs, 1H, 1-H), 7.20–7.35 (m, 5H, Ph), 6.11 (d, *J* = 2.7 Hz, 1H, 3-H), 3.98 (AA′d, *J* = 16.2 Hz, 1H, Bn), 3.90 (AA′d, *J* = 16.2 Hz, 1H, Bn), 3.78 (dd, *J* = 8.1, 1.5 Hz, 1H, 3bα-H), 3.08 (dd, *J* = 6.0, 8.1 Hz, 1H, 6aα-H), 2.87 (s, 6H, $N(CH_3)_2$), 2.63–2.70 (m, 1H, 10aα-H), 2.51–2.58 (m, 1H, 6bα-H), 1.66–2.08 (m, 4H, cyclohex.), 1.50 (ddd, *J* = 13.7, 10.4, 6.8 Hz, 1H, cyclohex.), 1.04–1.30 (m, 2H, cyclohex.), 0.89 (s, 9H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 177.1, 176.5, 139.5, 130.7, 130.6, 128.8, 128.7, 126.5, 109.3, 105.5, 43.8, 43.3, 40.8, 39.3, 34.3, 34.1, 33.9, 32.9, 30.1, 27.7, 24.8; IR (thin film, cm^{-1}) 3388(bs), 2957(m), 2108(bw), 1774(w), 1709(s), 1604(bs), 1448(m), 1364(m), 1202(m), 1146(m); HRMS *m/z* (M + Na$^+$) calcd for $C_{27}H_{35}N_3O_2$: 456.2622, found 456.2631.

2-Benzyl-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (84). Method A gave **84** (690 mg, 56%) as a cream-colored solid, a mixture of two isomers (maj:min = 3.6:1.0): mp 252–253°C; ^{1}H NMR (300 MHz, DMSO-*d6*, δ) 10.70 (bs, 1H, 1min-H), 10.41 (bs, 1H, 1maj-H), 7.38–7.53 (m, 4H, Ph), 7.15–7.32 (m, 6H, Ph), 5.85 (d, *J* = 2.4 Hz, 1H, 3maj-H), 5.60 (d, *J* = 2.4 Hz, 1H, 3min-H), 4.19 (dd, *J* = 8.4, 1.8 Hz, 1H, 3bαmin-H), 4.03 (dd, *J* = 8.6, 1.7 Hz, 1H, 3bαmaj-H), 3.90 (AA′d, *J* = 15.9 Hz, 1H, Bn), 3.85 (AA′d, *J* = 16.5 Hz, 1H, Bn), 3.40 (dd, *J* = 8.1, 4.8 Hz, 1H, 6aαmin-H), 3.35 (dd, *J* = 8.6, 5.3 Hz, 1H, 6aαmaj-H), 3.02–3.08 (m, 1H, 10aαmaj-H), 2.91–2.96 (m, 1H, 10aβmin-H), 2.07–2.42 (m, 2H, 6b-H, cyclohex.), 1.04–1.62 (m, 7H, cyclohex.); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.4, 178.2, 177.4, 176.3, 141.5, 133.0, 132.8, 132.4, 130.5, 129.6, 129.5, 129.1, 128.9, 128.7, 127.5, 127.48, 127.4, 126.3, 119.2, 117.4, 108.9, 105.8, 103.0, 46.2, 45.9, 38.7, 38.5, 38.3, 38.2, 34.1, 34.0, 33.1, 29.3, 27.6, 26.1, 25.7, 23.3, 22.9, 21.4, 20.9; IR (thin film, cm^{-1}) 3390(bs), 2924(m), 2853(m), 2110(bw), 1772(w), 1697(s), 1651(bs), 1496(w), 1455(w), 1444(w), 1382(m), 1187(m), 1157(m), 1004(m); HRMS *m/z* (M + Na$^+$) calcd 433.1887, found 433.1901. Anal. Calcd for $C_{27}H_{26}N_2O_2$: C, 79.00; H, 6.38; N, 6.82. Found: C, 79.03; H, 6.30; N, 6.87.

2-Benzyl-8-ethyl-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (85). Method A gave **85** (474 mg, 36%) as a light-orange solid, a mixture of four isomers (maj:min:min:min = 1.7:1.0:0.6:0.4): mp 225–226°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.60 (bs, 1H, 1maj-H), 7.61 (bs, 1H, 1min-H), 7.59 (bs, 1H, 1min-H), 7.23–7.52 (m, 10H, Ph), 6.30 (d, *J* = 2.4 Hz, 1H, 3min-H), 5.85 (d, *J* = 3.0 Hz, 1H, 3maj-H), 5.82 (d, *J* = 2.7 Hz, 1H, 3min-H), 4.05 (AA′d, *J* = 15.9 Hz, 1H, Bn min), 4.03 (AA′d, *J* = 15.9 Hz, 1H, Bn maj), 3.97 (dd, *J* = 10.5, 1.8 Hz, 1H, 3bα-H), 3.95 (AA′d, *J* = 16.2 Hz, 2H, Bn min, Bn maj), 3.48 (dd, *J* = 9.3, 5.7 Hz, 1H, 6aαmin-H), 3.45 (dd, *J* = 8.7, 5.7 Hz, 1H, 6aαmaj-H), 3.42 (dd, *J* = 8.6, 5.3 Hz, 1H, 6aαmin-H), 3.39 (dd, *J* = 8.6, 5.3 Hz, 1H, 6aαmin-H), 3.08–3.13 (m, 1H, 10amin-H), 3.02–3.07 (m, 1H, 10aαmin-H), 2.98–3.03 (m, 1H, 10aβmaj-H), 2.66–2.75 (m, 1H, 6bαmaj-H), 2.53–2.62 (m, 1H, 6bmin-H), 1.00–2.30 (m, 7H, cyclohex.), 1.44 (app. q, *J* = 7.5 Hz, 2H, CH_2CH_3), 0.86 (t, *J* = 7.5 Hz, CH_2CH_3 maj), 0.80 (t, *J* = 7.5 Hz, 3H, CH_2CH_3 min); ^{13}C NMR (75 MHz, $CDCl_3$, δ); IR (thin film, cm^{-1}) 3422(bs), 2929(m), 2863(m), 2100(bw), 1777(w), 1694(s), 1651(bs), 1500(m), 1454(m), 1388(m), 1188(m), 1166(m); HRMS *m/z* (M + Na$^+$) calcd 461.2200, found 461.2205. Anal. Calcd for $C_{29}H_{30}N_2O_2$: C, 79.42; H, 6.89; N, 6.39. Found: C, 79.19; H, 7.02; N, 6.40.

2-Benzyl-8-isopropyl-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (86). Method B with **3f** (982 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **86** (1325 mg, 61%) as a light-pink solid, a mixture of three isomers (maj:min:min = 4.1:1.0:0.7): mp 246–247°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.72 (d, J = 2.4 Hz, 1H, 1maj-H), 10.70 (d, J = 2.4 Hz, 1H, 1min-H), 10.45 (d, J = 1.2 Hz, 1H, 1min-H), 7.40–7.57 (m, 3H, Ph), 7.14–7.33 (m, 7H, Ph), 5.83 (d, J = 2.7 Hz, 1H, 3min-H), 5.62 (d, J = 2.4 Hz, 1H, 3maj-H), 5.60 (d, J = 2.4 Hz, 1H, 3min-H), 4.20 (dd, J = 7.8, 1.2 Hz, 1H, 3bαmin-H), 4.18 (dd, J = 8.4, 1.8 Hz, 1H, 3bαmaj-H), 4.02 (dd, J = 8.7, 1.2 Hz, 1H, 3bαmin-H), 3.90 (AA′d, J = 15.9 Hz, 1H, Bn), 3.85 (AA′d. J = 15.9 Hz, 1H, Bn), 3.44 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.39 (dd, J = 8.1, 5.4 Hz, 1H, 6aαmaj-H), 3.35 (dd, J = 8.7, 5.7 Hz, 1H, 6aαmin-H), 2.96–3.02 (m, 1H, 10aαmin-H), 2.86–2.93 (m, 1H, 10aβmaj-H), 2.40–2.50 (m, 1H, 6bαmaj-H), 2.28–2.38 (m, 1H, 6bmin-H), 0.94–2.18 (m, 8H, cyclohex., CH(CH$_3$)$_2$), 0.84 (d, J = 6.3 Hz, 6H, CH(CH_3)$_2$ maj), 0.77 (d, J = 6.3 Hz, 6H, CH(CH_3)$_2$ min), 0.70 (d, J = 6.6 Hz, 6H, CH(CH_3)$_2$ min); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 178.0, 176.1, 139.6, 132.1, 131.9, 129.4, 129.3, 129.2, 128.8, 128.7, 128.5, 126.5, 126.44, 126.41, 117.7, 117.6, 106.7, 104.3, 104.2, 46.0, 45.6, 43.9, 40.3, 38.9, 37.9, 34.6, 34.5, 34.4, 33.3, 33.2, 33.0, 32.94, 32.88, 32.8, 29.0, 26.3, 24.0, 21.4, 21.0, 20.0, 19.9; IR (KBr, cm^{-1}) 3462(w), 3381(bs), 3061(w), 3029(w), 2928(w), 2864(m), 2359(w), 1777(w), 1699(s), 1598(w), 1498(m), 1453(m), 1387(m), 1173(m); HRMS m/z (M + Na$^+$) calcd 475.2357, found 475.2372. Anal. Calcd for C$_{30}$H$_{32}$N$_2$O$_2$: C, 79.61; H, 7.13; N, 6.19. Found: C, 79.80; H, 7.24; N, 6.33.

2-Benzyl-8-tert-butyl-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (87). Method A gave **87** (546 mg, 39%) as a cream-colored solid, a mixture of four isomers (maj:min:min:min = 3.0:1.0:0.5:0.3): mp 184–185°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.26 (bs, 1H, 1min-H), 8.04 (bs, 1H, 1min-H), 7.55 (bs, 1H, 1maj-H), 7.22–7.51 (m, 10H, Ph), 6.28 (d, J = 2.4 Hz, 1H, 3maj-H), 6.06 (d, J = 2.4 Hz, 1H, 3min-H), 5.85 (d, J = 2.4 Hz, 1H, 3min-H), 1.59 (d, J = 2.7 Hz, 1H, 3min-H), 4.05 (dd, J = 7.8, 1.2 Hz, 1H, 3bα-H), 3.99 (AA′d, J = 15.9 Hz, 1H, Bn maj), 3.91 (AA′d, J = 15.9 Hz, 1H, Bn maj), 3.41 (dd, J = 8.1, 5.7 Hz, 1H, 6aαmin-H), 3.34 (dd, J = 7.4, 5.3 Hz, 1H, 6aαmaj-H), 2.60–2.73 (m, 2H, 6b-H, 10a-H), 2.15–2.22 (m, 1H, cyclohex.), 2.01–2.07 (m, 1H, cyclohex.), 1.73–1.88 (m, 2H, cyclohex.), 1.59 (ddd, J = 13.8, 11.3, 6.9 Hz, 1H, cyclohex.), 1.29–1.40 (m, 1H, cyclohex.), 1.06–1.19 (m, 1H, cyclohex.), 0.91 (s, 9H, t-Bu); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.5, 177.3, 141.1, 133.2, 131.0, 130.9, 129.4, 129.1, 128.8, 128.6, 127.5, 126.4, 109.4, 104.4, 45.3, 41.7, 34.4, 34.2, 33.9, 33.0, 30.4–30.8 (multiple peaks), 28.8–29.1 (multiple peaks), 28.0, 25.6–26.0 (multiple peaks); IR (thin film, cm^{-1}) 3386(bs), 2951(m), 2866(m), 2126(bw), 1774(w), 1708(s), 1648(bs), 1500(m), 1400(m), 1371(m), 1200(m), 1176(m); HRMS m/z (M + Na$^+$) calcd 489.2513, found 489.2517. Anal. Calcd for C$_{31}$H$_{34}$N$_2$O$_2$: C, 79.79; H, 7.34; N, 6.00. Found: C, 79.69; H, 7.20; N, 6.01.

2-Benzyl-5,8-diphenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (88). Method B with **3h** (1220 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **88** (1471 mg, 63%) as a dark-red solid, a mixture of two isomers (maj:min = 2.8:1.0): mp 222–224°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.73–10.77 (app. m, 1H, 1maj-H), 10.54 (d, J = 1.5 Hz, 1H, 1min-H), 7.10–7.56 (m, 15H, Ph), 5.81–5.85 (app. m, 1H, 3min-H), 5.65 (d, J = 2.1 Hz, 1H, 3maj-H), 4.22 (dd, J = 8.4, 1.2 Hz, 1H, 3bαmaj-H), 4.03 (app. d, J = 7.5 Hz, 1H, 3bαmin-H), 3.90 (s, 2H, Bn), 3.40–3.58 (m, 1H, 6aα-H), 2.80–3.20 (m, 2H, 6bα-H, 10a-H), 1.40–2.60 (m, 7H, cyclohex.); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.4, 176.2, 176.1, 141.4, 132.9, 132.6, 129.7, 129.5, 129.3, 129.0, 128.9, 128.8, 128.76, 128.7, 127.6, 127.4, 127.24, 127.20, 126.3, 126.0, 34.1, 33.3–33.6 (overlapped peaks); IR (KBr, cm^{-1}) 3379(bs), 3058(w), 3026(w), 2928(s), 2858(m), 2359(w), 2334(w), 1776(w), 1709(s), 1598(w), 1496(m), 1452(w), 1383(m), 1185(m), 1155(m); HRMS m/z (M + Na$^+$) calcd 509.2200, found 509.2210. Anal. Calcd for C$_{33}$H$_{30}$N$_2$O$_2$: C, 81.45; H, 6.21; N, 5.76. Found: C, 81.23; H, 5.99; N, 5.47.

2-Benzyl-5-(4-methoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (89). Method A gave **89** (780 mg, 59%) as a white solid, a mixture of three isomers (maj:min:min = 3.0:1.0:0.3): mp 247–248°C; ^{1}H NMR (300 MHz, DMSO-$d6$, δ) 10.67 (bs, 1H, 1min-H), 10.40 (bs, 1H, 1maj-H), 10.30 (bs, 1H, 1min-H), 7.10–7.31 (m, 7H, Ph), 6.96–7.05 (m, 2H, Ph), 5.84 (d, J = 2.4 Hz, 1H, 3maj-H), 5.67 (d, J = 2.1 Hz, 1H, 3min-H), 5.60 (d, J = 2.4 Hz, 1H, 3min-H), 4.15 (app. d, J = 7.5 Hz, 1H, 3bαmin-H), 3.99 (d, J = 8.4, 1.5 Hz, 1H, 3bαmaj-H), 3.87 (s, 2H, Bn), 3.78 (s, 3H, OCH$_3$), 3.42 (dd, J = 7.4, 4.1 Hz, 1H, 6aαmin-H), 3.37 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.32 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmaj-H), 3.02–3.08 (m, 1H, 10aαmaj-H), 2.93–2.98 (m, 1H, 10aβmin-H), 2.20–2.42 (m, 2H, cyclohex., 6b-H), 1.02–1.85 (m, 7H, cyclohex.); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.6, 178.4, 177.6, 176.5, 132.4, 130.5, 129.1, 128.9, 128.7, 128.66, 128.64, 127.5, 126.3, 125.6, 125.4, 119.1, 117.5, 114.8, 114.7, 109.0, 105.8, 103.0, 55.9, 46.2, 45.8, 34.1, 34.0, 33.1, 29.3, 27.6, 26.1, 25.7, 23.3, 22.9, 21.5, 20.9; IR (thin film, cm^{-1}) 3446(bs), 2928(m), 2861(w), 2113(bw), 1770(w), 1697(s), 1646(bs), 1515(m), 1391(m), 1256(m), 1193(m), 1170(m), 1160(m); HRMS m/z (M + Na$^+$) calcd 463.1993, found 463.2008. Anal. Calcd for C$_{28}$H$_{28}$N$_2$O$_3$: C, 76.34; H, 6.41; N, 6.36. Found: C, 76.26; H, 6.59; N, 6.35.

2-Benzyl-8-ethyl-5-(4-methoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (90). Method A gave **90** (506 mg, 36%) as a light-pink solid, a mixture of four isomers (maj:min:min:min = 2.5:1.0:0.3:0.2): mp 231–232°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.25 (bs, 1H, 1min-H), 7.59 (bs, 1H, 1maj-H), 7.14–7.36 (m, 7H, Ph), 6.96–7.01 (m, 2H, Ph), 6.29 (d, J = 2.7 Hz, 1H, 3maj-H), 5.85 (d, J = 2.4 Hz, 1H, 3min-H), 5.81 (d, J = 2.4 Hz, 1H, 3min-H), 4.05 (AA′d, J = 16.2 Hz, 1H, Bn maj), 4.03 (AA′d, J = 16.2 Hz, 1H, Bn min), 3.96 (AA′d, J = 15.9 Hz, 1H, Bn maj), 3.954 (AA′d, J = 15.6 Hz, 1H, Bn min), 3.951 (dd, J = 8.4, 1.8 Hz, 1H, 3bα-H), 3.84 (s, 3H, OCH$_3$), 3.46 (dd, J = 8.7, 5.7 Hz, 1H, 6aαmin-H), 3.43 (dd, J = 8.6, 5.9 Hz, 1H, 6aαmin-H), 3.41 (dd, J = 8.6, 5.6 Hz, 1H, 6aαmin-H), 3.37 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmaj-H), 3.07–3.12 (m, 1H, 10amin-H), 3.02–3.08 (m, 1H, 10aαmaj-H), 2.96–3.02 (m, 1H, 10aβmin-H), 2.64–2.73 (m, 1H, 6bαmaj-H), 2.52–2.61 (m, 1H, 6bmin-H), 1.04–2.28 (m, 9H, cyclohex., CH_2CH$_3$), 0.85 (t, J = 7.4 Hz, 3H, CH$_2$CH_3 maj), 0.79 (t, J = 7.2 Hz, 3H, CH$_2$CH_3 min); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 179.0, 178.6, 178.4, 177.64, 177.6, 176.5, 159.5, 159.4, 159.3, 141.5, 132.3, 130.5, 129.1, 128.9, 128.8, 128.7, 128.6, 127.5, 127.4, 126.3, 125.6, 115.0, 114.9, 114.8, 109.2, 105.9, 105.7, 55.9, 45.5, 34.3, 34.0, 33.9, 33.3, 33.2, 33.1, 33.0, 32.9, 32.8, 32.7, 32.6, 32.0, 28.0, 27.4, 27.36, 23.6, 12.6; IR (thin film, cm^{-1}) 3444(bs), 2930(m), 2100(bw), 1694(s), 1648(bm), 1515(m), 1389(m), 1252(m), 1172(m); HRMS *m/z* (M + Na^{+}) calcd 491.2306, found 491.2299. Anal. Calcd for $C_{30}H_{32}N_2O_3$: C, 76.90; H, 6.88; N, 5.98. Found: C, 77.09; H, 6.76; N, 5.79.

2-Benzyl-8-isopropyl-5-(4-methoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (91). Method B with **3f** (982 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **91** (1459 mg, 63%) as a light-pink solid, a mixture of three isomers (maj:min:min = 3.8:1.0:0.8): mp 254–256°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.84 (d, *J* = 2.4 Hz, 1H, 1maj-H), 10.68 (d, *J* = 3.0 Hz, 1H, 1min-H), 10.44 (d, *J* = 3.0 Hz, 1H, 1min-H), 7.02–7.31 (m, 9H, Ph), 5.82 (d, *J* = 2.1 Hz, 1H, 3min-H), 5.61 (d, *J* = 2.4 Hz, 1H, 3maj-H), 5.60 (d, *J* = 2.4 Hz, 1H, 3min-H), 4.16 (dd, *J* = 8.7, 1.5 Hz, 1H, 3bαmin-H), 4.14 (dd, *J* = 8.6, 1.7 Hz, 1H, 3bαmaj-H), 3.98 (dd, *J* = 8.7, 1.8 Hz, 1H, 3bαmin-H), 3.87 (s, 2H, Bn), 3.79 (s, 3H, OCH$_3$ maj), 3.78 (s, 3H, OCH$_3$ min), 3.41 (dd, *J* = 9.0, 6.0 Hz, 1H, 6aαmin-H), 3.36 (dd, *J* = 8.1, 5.1 Hz, 1H, 6aαmaj-H), 3.32 (dd, *J* = 8.4, 5.4 Hz, 1H, 6aαmin-H), 2.96–3.02 (m, 1H, 10aαmin-H), 2.86–2.92 (m, 1H, 10aβmaj-H), 2.38–2.49 (m, 1H, 6bαmaj-H), 2.26–2.36 (m, 1H, 6bmin-H), 1.00–2.18 (m, 8H, cyclohex., C*H*(CH$_3$)$_2$), 0.84 (d, *J* = 6.6 Hz, 6H, CH(C*H*$_3$)$_2$ maj), 0.77 (d, *J* = 6.6 Hz, 1H, CH(C*H*$_3$)$_2$ min), 0.70 (d, *J* = 6.9 Hz, 1H, CH(C*H*$_3$)$_2$ min); IR (KBr, cm^{-1}) 3459(w), 3372(bs), 3060(w), 3029(w), 2932(s), 2864(m), 2361(w), 1776(w), 1698(s), 1611(w), 1593(w), 1514(s), 1453(m), 1390(m), 1305(m), 1256(m), 1169(s), 1107(w), 1032(w); HRMS *m/z* (M + Na^{+}) calcd for $C_{31}H_{34}N_2O_3$: 505.2462, found 505.2476.

2-Benzyl-8-tert-butyl-5-(4-methoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (92). Method A gave **92** (358 mg, 24%) as a light-orange solid, a mixture of four isomers (maj:min:min:min = 24.0:1.0:0.3:0.2): mp 179–180°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.25 (bs, 1H, 1min-H), 8.05 (bs, 1H, 1min-H), 7.55 (bs, 1H, 1min-H), 7.49 (bs, 1H, 1maj-H), 7.10–7.36 (m, 7H, Ph), 6.91–7.02 (m, 2H, Ph), 6.13 (d, *J* = 2.7 Hz, 1H, 3maj-H), 6.10 (d, *J* = 2.7 Hz, 1H, 3min-H), 5.83 (d, *J* = 2.7 Hz, 1H, 3min-H), 4.03 (dd, *J* = 8.0, 1.7 Hz, 1H, 3bα-H), 3.99 (AA′d, *J* = 16.2 Hz, 1H, Bn), 3.90 (AA′d, *J* = 16.2 Hz, 1H, Bn), 3.82 (s, 3H, OCH$_3$), 3.39 (dd, *J* = 8.1, 5.7 Hz, 1H, 6aαmin-H), 3.32 (dd, *J* = 7.8, 5.4 Hz, 1H, 6aαmaj-H), 3.03–3.07 (m, 1H, 10amin-H), 2.98–3.02 (m, 1H, 10amin-H), 2.59–2.72 (m, 3H, 6b-H, 10aαmaj-H, 10aβmin-H), 1.00–2.22 (m, 7H, cyclohex.), 0.89 (s, 9H, *t*-Bu maj), 0.74 (s, 9H, *t*-Bu min); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.7, 177.5, 159.3, 141.0, 130.9, 129.1, 128.8, 128.7, 126.4, 125.7, 114.6, 109.4, 105.0, 104.3, 55.9, 45.1, 34.2, 33.9, 33.0, 28.0, 28.0; IR (thin film, cm^{-1}) 3387(bs), 2958(m), 2100(bw), 1776(w), 1705(s), 1645(bm), 1513(s), 1391(m), 1301(m), 1252(m), 1168(m); HRMS *m/z* (M + Na^{+}) calcd 519.2619, found 519.2620. Anal. Calcd for $C_{32}H_{36}N_2O_3$: C, 77.39; H, 7.31; N, 5.64. Found: C, 77.56; H, 7.46; N, 5.57.

2-Benzyl-5-(4-methoxyphenyl)-8-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (93). Method B with **3h** (1220 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **93** (1413 mg, 57%) as a pink solid, a mixture of three isomers (maj:min:min = 3.2:1.0:0.5): mp 235–237°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.74 (app. bs, 1H, 1maj-H), 10.53 (d, *J* = 2.1 Hz, 1H, 1min-H), 6.97–7.34 (m, 14 H, Ph), 5.81–5.85 (app. m, 1H, 3min-H), 5.67 (d, *J* = 2.7 Hz, 1H, 3min-H), 5.64 (d, *J* = 1.8 Hz, 1H, 3min-H), 4.21 (dd, *J* = 8.7, 1.5 Hz, 1H, 3bαmin-H), 4.19 (dd, *J* = 8.4, 1.2 Hz, 1H, 3bαmaj-H), 4.00 (app. d, *J* = 8.1 Hz, 1H, 3bαmin-H), 3.90 (s, 2H, Bn), 3.80 (s, 3H, OCH$_3$ maj), 3.79 (s, 3H, OCH$_3$ min), 3.75 (s, 3H, OCH$_3$ min), 3.48 (dd, *J* = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.37–3.46 (m, 2H, 6aαmaj-H, 6aαmin-H), 2.80–3.10 (m, 2H, 6b-H, 10a-H), 1.40–2.00 (m, 7H, cyclohex.); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.8, 178.6, 176.4, 159.5, 159.3, 141.4, 132.5, 129.1, 129.0, 128.8, 128.7, 127.6, 126.7, 126.3, 125.9, 125.4, 117.7, 114.9, 114.8, 55.9, 34.1, 33.2–33.6 (overlapped peaks); IR (KBr, cm^{-1}) 3452(w), 3380(bs), 3083(w), 3059(w), 3026(w), 2930(s), 2859(m), 2263(w), 1775(w), 1701(s), 1601(w), 1514(s), 1451(m), 1389(m), 1302(w), 1254(m), 1170(m), 1106(w), 1301(w); HRMS *m/z* (M + Na^{+}) calcd 539.2306, found 539.2310. Anal. Calcd for $C_{34}H_{32}N_2O_3$: C, 79.04; H, 6.24; N, 5.42. Found: C, 79.20; H, 6.10; N, 5.27.

2-(4-Methylbenzyl)-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (94). Method B with **3c** (687 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **94** (1304 mg, 64%) as a pink solid, a mixture of two isomers (maj:min = 1.6:1.0): mp 223–225°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.67 (d, *J* = 1.8 Hz, 1H, 1maj-H), 10.39 (d, *J* = 1.8 Hz, 1H, 1min-H), 7.38–7.54 (m, 3H, Ph), 7.19–7.27 (m, 2H, Ph), 7.07–7.16 (m, 4H, Ph), 5.81 (d, *J* = 2.1 Hz, 1H, 3min-H), 5.56 (d, *J* = 2.4 Hz, 1H, 3maj-H), 4.19 (dd, *J* = 8.3, 1.7 Hz, 1H, 3bαmaj-H), 4.02 (dd, *J* = 8.4, 1.8 Hz, 1H, 3bαmin-H), 3.87 (s, 2H, Bn), 3.39 (dd, *J* = 8.4, 5.1 Hz, 1H, 6aαmaj-H), 3.35 (dd, *J* = 8.4, 5.1 Hz, 1H, 6aαmin-H), 3.02–3.07 (m, 1H, 10aαmin-H), 2.90–2.95 (m, 1H, 10aβmaj-H), 2.51 (s, 3H, PhC*H*$_3$), 2.03–2.44 (m, 2H, cyclohex., 6b-H), 1.00–1.64 (m, 7H, cyclohex.); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.4, 178.2, 177.4, 176.3, 138.4, 138.3, 135.2, 133.0, 132.8, 132.7, 130.8, 129.6, 129.5, 129.3, 129.0, 128.9, 128.8, 128.7, 127.5, 127.4, 119.1, 117.3, 108.9, 105.7, 102.8, 46.2, 45.9, 38.7, 38.5, 38.4, 38.2, 33.7, 33.6, 33.1, 29.3, 28.0, 27.6, 26.1, 25.7, 23.3, 22.9, 21.5, 21.2, 20.9; IR (KBr, cm^{-1}) 3457(w), 3374(bs), 3052(w), 2924(s), 2856(m), 1777(m), 1701(s), 1597(w), 1500(m), 1444(w), 1388(s), 1310(w), 1185(s), 1160(S); HRMS *m/z* (M + Na^{+}) calcd 447.2044, found 447.2040. Anal. Calcd for $C_{28}H_{28}N_2O_2$: C, 79.22; H, 6.65; N, 6.60. Found: C, 79.02; H, 6.74; N, 6.37.

8-Isopropyl-2-(4-methylbenzyl)-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (95). Method B with **3f** (982 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **95** (1366 mg, 61%) as a pink solid, a mixture of three isomers (maj:min:min = 2.7:1.0:0.8): mp 252–254°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.67 (d, *J* = 2.4 Hz, 1H, 1maj-H), 10.65 (d, *J* = 2.1 Hz, 1H, 1min-H), 10.42 (d, *J* = 2.4 Hz, 1H, 1min-H), 7.40–7.56 (m, 3H, Ph), 7.05–7.24 (m, 6H, Ph), 5.79 (d, *J* = 2.1 Hz, 1H, 3min-H), 5.58 (d, *J* = 2.4 Hz, 1H, 3maj-H), 5.57 (d, *J* = 2.7 Hz, 1H, 3min-H), 4.19 (dd, *J* = 8.3, 1.4 Hz, 1H, 3bαmin-H), 4.18 (dd, *J* = 8.4, 1.5 Hz, 1H, 3bαmaj-H), 4.01 (dd, *J* = 8.4, 1.8 Hz, 1H, 3bαmin-H), 3.82 (s, 2H, Bn), 3.43 (dd, *J* = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.39 (dd, *J* = 8.3, 5.3 Hz, 1H, 6aαmaj-H), 3.35 (dd, *J* = 8.1, 5.4 Hz, 1H, 6aαmin-H), 2.96–3.02 (m, 1H, 10aαmin-H), 2.86–2.92 (m, 1H, 10aβmaj-H), 2.39–2.49 (m, 1H, 6bαmaj-H), 2.28–2.38 (m, 1H, 6bmin-H), 2.26 (s, 3H, PhCH_3), 1.00–1.90 (m, 8H, cyclohex., CH(CH$_3$)$_2$), 0.84 (d, J = 6.6 Hz, 6H, CH(CH_3)$_2$ maj), 0.77 (d, J = 6.3 Hz, 6H, CH(CH_3)$_2$ min), 0.70 (d, J = 6.6 Hz, 6H, CH(CH_3)$_2$ min); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 178.0, 176.2, 160.2, 136.6, 132.4, 129.4, 129.2, 128.8, 128.7, 128.6, 126.5, 126.4, 117.6, 106.4, 105.0, 104.1, 104.0, 46.0, 45.7, 43.9, 40.2, 39.0, 38.9, 37.9, 34.1, 34.05, 34.0, 33.2, 33.0, 32.95, 32.9, 29.0, 24.0, 21.2, 21.1, 21.0; IR (KBr, cm^{-1}) 3458(w), 3380(bs), 3054(w), 3027(w), 2926(m), 2863(s), 1776(m), 1703(s), 1595(w), 1500(m), 1452(m), 1387(s), 1315(w), 1187(s), 1172(s), 1150(s); HRMS m/z (M + Na$^+$) calcd 489.2513, found 489.2527. Anal. Calcd for C$_{31}$H$_{34}$N$_2$O$_2$: C, 79.79; H, 7.34; N, 6.00. Found: C, 79.61; H, 7.15; N, 5.83.

2-(4-Methylbenzyl)-5,8-diphenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (96). Method B with **3h** (1220 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **96** (1538 mg, 64%) as a dark-red solid, a mixture of two isomers (maj:min = 5.0:1.0): mp 215–217°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.71 (app. bs, 1H, 1maj-H), 10.51 (d, J = 1.8 Hz, 1H, 1min-H), 6.98–7.56 (m, 14H, Ph), 5.65 (d, J = 2.4 Hz, 1H, 3min-H), 5.61 (d, J = 2.4 Hz, 1H, 3maj-H), 4.22 (dd, J = 8.7, 1.8 Hz, 1H, 3bαmaj-H), 4.02 (dd, J = 8.4, 1.2 Hz, 1H, 3bαmin-H), 3.84 (s, 2H, Bn), 3.51 (dd, J = 9.0, 5.7 Hz, 1H, 6aαmin-H), 3.40–3.50 (m, 2H, 6aαmaj-H, 6aαmin-H), 2.80–3.10 (m, 2H, 6b-H, 10a-H), 2.26 (s, 3H, PhCH_3), 1.10–2.26 (m, 7H, cyclohex.); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 177.9, 177.8, 176.8, 176.1, 136.4, 136.1, 134.3, 132.7, 131.8, 131.0, 130.2, 129.4, 129.3, 128.8, 128.7, 128.6, 127.4, 127.3, 126.9, 126.7, 126.6, 126.5, 126.1, 125.8, 125.6, 117.6, 104.2, 45.6, 34.1, 34.0, 33.2–33.6 (overlapped peaks), 21.1; IR (KBr, cm^{-1}) 3454(w), 3378(s), 3055(w), 3025(m), 2926(s), 2860(m), 1776(m), 1703(s), 1598(m), 1499(m), 1450(m), 1387(s), 1331(w), 1186(s), 1155(s); HRMS m/z (M + Na$^+$) calcd for C$_{34}$H$_{32}$N$_2$O$_2$: 523.2357, found 523.2382.

2-(4-Methylbenzyl)-5-(4-methoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (97). Method B with **3c** (687 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **97** (1368 mg, 65%) as a light-pink solid, a mixture of two isomers (maj:min = 1.9:1.0): mp 218–220°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.65 (d, J = 2.1 Hz, 1H, 1maj-H), 10.38 (d, J = 2.4 Hz, 1H, 1min-H), 7.00–7.17 (m, 8H, Ph), 5.80 (d, J = 2.4 Hz, 1H, 3min-H), 5.56 (d, J = 2.4 Hz, 1H, 3maj-H), 4.15 (dd, J = 8.4, 1.5 Hz, 1H, 3bαmaj-H), 3.99 (dd, J = 8.6, 1.7 Hz, 1H, 3bαmin-H), 3.82 (s, 2H, Bn), 3.79 (s, 3H, OCH$_3$ maj), 3.78 (s, 3H, OCH$_3$ min), 3.37 (dd, J = 8.1, 5.3 Hz, 1H, 6aαmaj-H), 3.32 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.01–3.06 (m, 1H, 10aαmin-H), 2.89–2.94 (m, 1H, 10aβmaj-H), 2.03–2.42 (m, 2H, cyclohex., 6bα-H), 2.26 (s, 3H, PhCH_3), 1.02–1.62 (m, 7H, cyclohex.); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.6, 178.4, 177.6, 159.4, 138.4, 138.3, 135.2, 130.8, 129.3, 129.0, 128.8, 128.6127.4, 125.5, 125.3, 119.1, 117.4, 114.7, 113.8, 108.9, 105.7, 105.0, 55.9, 45.8, 38.6, 38.4, 38.1, 33.6, 33.1, 27.6, 26.1, 25.7, 23.3, 23.0, 21.5, 21.1; IR (KBr, cm^{-1}) 3457(w), 3380(s), 3050(w), 3004(w), 2926(s), 2856(m), 1776(m), 1714(s), 1610(m), 1593(m), 1514(s), 1459(m), 1443(m), 1390(s), 1302(m), 1255(s), 1189(s), 1166(s), 1108(m), 1031(m); HRMS m/z (M + Na$^+$) calcd 477.2149, found 477.2169. Anal. Calcd for C$_{29}$H$_{30}$N$_2$O$_3$: C, 76.63; H, 6.65; N, 6.16. Found: C, 76.40; H, 6.61; N, 5.96.

8-Isopropyl-2-(4-methylbenzyl)-5-(4-methoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (98). Method B with **3f** (982 mg, 7.00 mmol), 3.5 h-reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **98** (1315 mg, 57%) as a light-pink solid, a mixture of three isomers (maj:min:min = 3.4:1.0:0.9): mp 244–246°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.66 (d, J = 2.4 Hz, 1H, 1maj-H), 10.64 (d, J = 1.8 Hz, 1H, 1min-H), 10.41 (d, J = 1.5 Hz, 1H, 1min-H), 7.02–7.16 (m, 8H, Ph), 5.79 (d, J = 1.8 Hz, 1H, 3min-H), 5.57 (d, J = 2.1 Hz, 1H, 3maj-H), 5.56 (d, J = 2.0 Hz, 1H, 3min-H), 4.15 (dd, J = 8.7, 1.8 Hz, 1H, 3bαmin-H), 4.14 (dd, J = 8.4, 1.5 Hz, 1H, 3bαmaj-H), 3.97 (dd, J = 8.4, 1.5 Hz, 1H, 3bαmin-H), 3.82 (s, 2H, Bn), 3.79 (s, 3H, OCH$_3$ maj), 3.78 (s, 3H, OCH$_3$ min), 3.40 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.36 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmaj-H), 3.32 (dd, J = 8.1, 5.4 Hz, 1H, 6aαmin-H), 2.94–3.02 (m, 1H, 10aαmin-H), 2.85–2.91 (m, 1H, 10aβmaj-H), 2.38–2.49 (m, 1H, 6bαmaj-H), 2.30–2.36 (m, 1H, 6bmin-H), 2.26 (s, 3H, PhCH_3), 0.95–2.26 (m, 8H, cyclohex., CH(CH$_3$)$_2$), 0.84 (d, J = 6.6 Hz, 6H, CH(CH_3)$_2$ maj), 0.77 (d, J = 6.3 Hz, 6H, CH(CH_3)$_2$ min), 0.70 (d, J = 6.6 Hz, 6H, CH(CH_3)$_2$ min); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 178.3, 177.0, 176.4, 159.6, 155.1, 136.5, 136.1, 132.4, 129.4, 128.7, 128.6, 127.6, 124.4, 120.5, 120.1, 117.9, 117.5, 114.7, 14.6, 109.5, 106.5, 104.1, 103.8, 55.6, 45.9, 45.6, 45.5, 43.9, 40.3, 38.9, 38.8, 37.8, 37.7, 34.1, 34.0, 34.9, 33.2, 33.0, 32.9, 32.8, 29.0, 26.3, 24.0, 21.4, 21.1, 21.0, 20.9, 20.0, 19.9; IR (KBr, cm^{-1}) 3463(w), 3380(bs), 3087(w), 3052(w), 3005(w), 2945(bs), 2864(s), 1776(m), 1699(s), 1612(m), 1589(w), 1514(s), 1452(m), 1391(s), 1304(m), 1256(s), 1171(s), 1109(m), 1032(m); HRMS m/z (M + Na$^+$) calcd for C$_{32}$H$_{36}$N$_2$O$_3$: 519.2619, found 519.2637.

2-(4-Methylbenzyl)-5-(4-methoxyphenyl)-8-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (99). Method B with **3h** (1220 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **99** (1532 mg, 62%) as a light-brown solid, a mixture of two isomers (maj:min = 3.0:1.0): mp 227–228°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.67–10.71 (app. bs, 1H, 1maj-H), 10.49 (d, J = 3.0 Hz, 1H, 1min-H), 6.97–7.34 (m, 13H, Ph), 5.76–5.82 (app. m, 1H, 3min-H), 5.60 (d, J = 2.4 Hz, 1H, 3maj-H), 4.18 (dd, J = 8.4, 1.5 Hz, 1H, 3bαmaj-H), 3.99 (app. d, J = 8.4 Hz, 1H, 3bαmin-H), 3.84 (s, 2H, Bn), 3.80 (d, 3H, OCH$_3$ maj), 3.79 (d, 3H, OCH$_3$ min), 3.36–3.51 (m, 1H, 6aα-H), 2.80–3.10 (m, 2H, 10a-H, 6bα-H), 1.50–2.60 (m, 7H, cyclohex.), 2.26 (s, 3H, PhCH_3); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 178.3, 178.2, 177.0, 176.4, 159.7, 159.5, 136.1, 132.7, 129.4, 128.7, 128.6, 128.5, 128.4, 127.8, 127.7, 127.6, 127.4, 127.3, 126.7, 125.8, 125.6, 124.4, 117.6, 114.7, 114.6, 55.6, 45.5, 34.2, 34.1, 33.1–33.7 (overlapped peaks), 21.1; IR (KBr, cm^{-1}) 3458(w), 3389(s), 3085(w), 3057(w), 3023(w), 2933(s), 2860(m), 2368(w), 1775(w), 1698(s), 1607(w), 1514(s), 1448(m), 1390(m), 1301(m), 1253(s), 1170(s), 1108(w), 1032(m); HRMS m/z (M + Na$^+$) calcd 553.2462, found 553.2488. Anal. Calcd for C$_{35}$H$_{34}$N$_2$O$_3$: C, 79.22; H, 6.46; N, 5.28. Found: C, 78.91; H, 6.32; N, 5.19.

5-Dimethylamino-2-(4-methoxybenzyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (100). Method A gave **100** (293 mg, 24%) as a cream-colored solid, a mixture of two isomers (maj:min = 3.8:1.0): mp 228–229°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.20 (bs, 1H, 1min-H), 7.51 (bs, 1H, 1maj-H), 7.16 (d, J = 8.7 Hz, 2H, Ph), 6.87 (d, J =

8.4 Hz, 2H, Ph), 6.23 (d, *J* = 2.4 Hz, 1H, 3maj-H), 5.77 (d, *J* = 2.7 Hz, 1H, 3min-H), 3.97 (AA′d, *J* = 15.9 Hz, 1H, Bn maj), 3.96 (AA′d, *J* = 16.2 Hz, 1H, Bn min), 3.90 (AA′d, *J* = 16.2 Hz, 1H, Bn maj), 3.89 (AA′d, *J* = 15.9 Hz, 1H, Bn maj), 3.81 (s, 3H, OCH_3), 3.69 (dd, 1H, 3bα-H), 3.21 (dd, *J* = 8.4, 5.7 Hz, 1H, 6aαmin-H), 3.16 (dd, *J* = 8.7, 5.7 Hz, 1H, 6aαmaj-H), 3.00–3.06 (m, 1H, 10aαmaj-H), 2.93 (s, 6H, $N(CH_3)_2$), 2.91–2.92 (m, 1H, 10aβmin-H), 2.44–2.52 (m, 1H, 6bα-H), 1.05–2.22 (m, 8H, cyclohex.); ^{13}C NMR (75 MHz, DMSO-*d*$_6$, δ) 177.6, 177.5, 176.7, 159.1, 158.0, 133.4, 131.0, 130.0, 129.9, 127.3, 114.1, 108.8, 105.4, 55.5, 44.3, 44.0, 43.8, 38.2, 36.7, 33.2, 33.1, 32.9, 27.6, 25.6, 23.0, 21.4; IR (thin film, cm^{-1}) 3371(bs), 2924(m), 2852(m), 1770(w), 1703(s), 1515(m), 1444(m), 1360(w), 1252(m), 1193(m); HRMS *m/z* (M + Na$^+$) calcd for $C_{24}H_{29}N_3O_3$: 430.2102, found 430.2087.

5-Dimethylamino-8-ethyl-2-(4-methoxybenzyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (101). Method A gave **101** (287 mg, 22%) as a cream-colored solid, a mixture of three isomers (maj:min = 4.0:1.0:0.2): mp 179–180°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.22 (bs 1H, 1min-H), 7.55 (bs, 1H, 1maj-H), 7.16 (d, *J* = 8.7 Hz, 2H, Ph), 6.86 (d, *J* = 8.7 Hz, 2H, Ph), 6.22 (d, *J* = 2.4 Hz, 1H, 3maj-H), 5.78 (d, *J* = 2.7 Hz, 1H, 3min-H), 5.74 (d, *J* = 2.1 Hz, 1H, 3min-H), 3.97 (AA′d, *J* = 16.2 Hz, 1H, Bn maj), 3.96 (AA′d, *J* = 16.2 Hz, 1H, Bn min), 3.89 (AA′d, *J* = 16.2 Hz, 1H, Bn maj), 3.88 (AA′d, *J* = 16.2 Hz, 1H, Bn min), 3.81 (s, 3H, OCH_3), 3.69 (dd, *J* = 8.4, 1.8 Hz, 1H, 3bα-H), 3.24 (dd, *J* = 5.4, 9.6 Hz, 1H, 6aαmin-H), 3.20 (dd, *J* = 8.7, 5.7 Hz, 1H, 6aαmin-H), 3.19 (dd, *J* = 8.7, 5.6 Hz, 1H, 6aαmin-H), 3.16 (dd, *J* = 8.6, 5.6 Hz, 1H, 6aαmaj-H), 2.91–2.94 (m, 7H, 10a-H, $N(CH_3)_2$), 2.58–2.67 (m, 1H, 6bαmaj-H), 2.46–2.55 (m, 1H, 6bmin-H), 1.00–2.07 (m, 9H, cyclohex., CH_2CH_3), 0.84 (t, *J* = 7.4 Hz, 3H, CH_2CH_3 maj), 0.76 (t, *J* = 7.2 Hz, 3H, CH_2CH_3 maj); ^{13}C NMR (75 MHz, DMSO-*d*$_6$, δ) 177.6, 177.4, 176.7, 176.6, 158.0, 133.3, 131.0, 130.0, 129.9, 129.8, 127.2, 127.15, 127.1, 117.3, 114.1, 114.0, 108.9, 108.8, 105.4, 105.0, 102.8, 55.5, 43.9, 43.8, 43.6, 36.7, 33.9, 33.0–33.2 (multiple peaks), 32.6, 29.9; IR (thin film, cm^{-1}) 3378(bs), 2928(m), 2358(w), 1773(w), 1709(s), 1510(m), 1246(m); HRMS *m/z* (M + Na$^+$) calcd for $C_{26}H_{33}N_3O_3$: 458.2415, found 458.2422.

8-tert-Butyl-5-(dimethylamino)-2-(4-methoxybenzyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (102). Method A gave **102** (292 mg, 21%) as orange crystals, a single isomer: mp 95–96°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.43 (bs, 1H, 1-H), 7.13 (d, *J* = 8.4 Hz, 2H, Ph), 6.85 (d, *J* = 8.7 Hz, 2H, Ph), 6.08 (d, *J* = 2.7 Hz, 1H, 3-H), 3.92 (AA′d, *J* = 17.1 Hz, 1H, Bn), 3.83 (AA′d, *J* = 17.1 Hz, 1H, Bn), 3.81 (s, 3H, OCH_3), 3.78 (dd, *J* = 7.8 Hz, 1.7 Hz, 1H, 3bα-H), 3.09 (dd, *J* = 8.0, 5.9 Hz, 1H, 6aα-H), 2.87 (s, 6H, $N(CH_3)_2$), 2.61–2.70 (m, 1H, 6bα), 2.50–2.57 (m, 1H, 10aα-H), 1.65–2.06 (m, 4H, cyclohex.), 1.49 (ddd, *J* = 13.8, 10.4, 6.8 Hz, 1H, cyclohex.), 1.07–1.30 (m, 2H, cyclohex.), 0.89 (s, 9H, *t*-Bu); ^{13}C NMR (75 MHz, DMSO-*d*$_6$, δ) 177.7, 176.4, 158.0, 133.0, 131.3, 130.5, 130.0, 129.9, 114.1, 109.1, 104.2, 55.5, 43.6, 43.55, 43.1, 33.9, 33.3, 33.0, 32.8, 30.4, 28.0, 27.9; IR (thin film, cm^{-1}) 3364(bs), 2955(m), 1774(w), 1712(s), 1511(s), 1364(m), 1246(m); HRMS *m/z* (M + Na$^+$) calcd for $C_{28}H_{37}N_3O_3$: 486.2728, found 486.2720.

2-(4-Methoxybenzyl)-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (103). Method B with **3c** (687 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **103** (1270 mg, 60%) as a cream-colored solid, a mixture of two isomers (maj:min = 1.8:1.0): mp 234–235°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.27 (bs, 1H, 1maj-H), 7.58 (bs, 1H, 1min-H), 7.37–7.51 (m, 3H, Ph), 7.24–7.32 (m, 2H, Ph), 7.16–7.21 (m, 2H, Ph), 6.85–6.90 (m, 2H, Ph), 6.27 (d, *J* = 2.4 Hz, 1H, 3min-H), 5.81 (*J* = 2.4 Hz, 1H, 3maj-H), 3.99 (AA′d, *J* = 17.1 Hz, 1H, Bn maj), 3.971 (dd, *J* = 8.6, 2.0 Hz, 1H, 3bα-H), 3.968 (AA′d, *J* = 15.9 Hz, 1H, Bn min), 3.91 (AA′d, *J* = 15.9 Hz, 1H, Bn maj), 3.81 (s, 3H, OCH_3), 3.46 (dd, *J* = 8.7, 5.7 Hz, 1H, 6aαmaj-H), 3.39 (dd, *J* = 8.6, 5.3 Hz, 1H, 6aαmin-H), 3.08–3.14 (m, 1H, 10aαmin-H), 3.02–3.07 (m, 1H, 10aβmaj-H), 2.50–2.58 (m, 1H, 6bα-H), 2.04–2.25 (m, 1H, cyclohex.), 1.18–1.76 (m, 7H, cyclohex.); ^{1}H NMR (300 MHz, DMSO-*d*$_6$, δ) 10.65 (d, *J* = 2.1 Hz, 1H, 1maj-H), 10.38 (d, *J* = 1.8 Hz, 1H, 1min-H), 7.38–7.54 (m, 3H, Ph), 7.12–7.26 (m, 4H, Ph), 6.81–6.87 (m, 2H, Ph), 5.80 (d, *J* = 2.4 Hz, 1H, 3min-H), 5.56 (d, *J* = 2.4 Hz, 1H, 3maj-H), 4.18 (dd, *J* = 8.4, 1.8 Hz, 1H, 3bαmaj-H), 4.02 (dd, *J* = 8.4, 1.8 Hz, 1H, 3bαmin-H), 3.80 (s, 2H, Bn), 3.71 (s, 3H, OCH_3), 3.37 (dd, *J* = 8.4, 5.1 Hz, 1H, 6aαmaj-H), 3.34 (dd, *J* = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.01–3.07 (m, 1H, 10aαmin-H), 2.90–2.95 (m, 1H, 10aβmaj-H), 2.03–2.42 (m, 2H, cyclohex., 6b-H), 1.03–1.64 (m, 7H, cyclohex.); ^{13}C NMR (75 MHz, DMSO-*d*$_6$, δ) 178.4, 178.2, 177.4, 176.3, 158.0, 133.4, 138.3, 133.0, 131.1, 130.0, 129.9, 129.6, 129.5, 128.9, 128.8, 127.4, 119.1, 117.3, 114.1, 108.9, 105.6, 102.7, 55.5, 46.2, 45.9, 38.7, 38.5, 38.4, 38.2, 33.2, 33.1, 29.3, 27.6, 26.1, 25.7, 23.5, 22.9, 21.5, 20.9; IR (thin film, cm^{-1}) 3372, 2920, 1697, 1515; HRMS *m/z* (M + Na$^+$) calcd 463.1993, found 463.2009. Anal. Calcd for $C_{28}H_{28}N_2O_3$: C, 76.34; H, 6.41; N, 6.36. Found: C, 76.26; H, 6.59; N, 6.35.

8-Ethyl-2-(4-methoxybenzyl)-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (104). Method A gave **104** (450 mg, 32%) as a cream-colored solid, a mixture of four isomers (maj:min:min:min = 1.1:1.0:0.3:0.3): mp 214–215°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.25 (bs, 1H, 1maj-H), 7.58 (bs, 1H, 1min-H), 7.56 (bs, 1H, 1min-H), 7.37–7.51 (m, 3H, Ph), 7.28–7.32 (m, 2H, Ph), 7.15–7.20 (m, 2H, Ph), 6.85–6.90 (m, 2H, Ph), 6.26 (d, *J* = 2.7 Hz, 1H, 3maj-H), 5.82 (d, *J* = 2.4 Hz, 1H, 3min-H), 5.79 (d, *J* = 3.0 Hz, 1H, 3min-H), 3.98 (AA′d, *J* = 15.9 Hz, 1H, Bn min), 3.97 (AA′d, *J* = 16.2 Hz, 1H, Bn maj), 3.96 (dd, *J* = 8.6, 2.0 Hz, 1H, 3bα-H), 3.91 (AA′d, *J* = 16.2 Hz, 1H, Bn min), 3.90 (AA′d, *J* = 16.2 Hz, 1H, Bn maj), 3.82 (s, 3H, OCH_3), 3.48 (dd, *J* = 9.02, 5.3 Hz, 1H, 6aαmin-H), 3.45 (dd, *J* = 8.1, 5.7 Hz, 1H, 6aαmin-H), 3.42 (dd, *J* = 7.8, 5.4 Hz, 1H, 6aαmin-H), 3.39 (dd, *J* = 8.4, 5.4 Hz, 1H, 6aαmaj-H), 2.97–3.08 (m, 1H, 10a-H), 2.65–2.74 (m, 2H, 6bαmaj-H, 6bαmin-H), 2.53–2.62 (m, 2H, 6bβmin-H), 1.07–2.30 (m, 7H, cyclohex.), 1.43 (app. q, *J* = 7.5 Hz, 2H, CH_2CH_3), 0.85 (t, *J* = 7.2 Hz, 3H, CH_2CH_3 maj), 0.79 (t, *J* = 7.2 Hz, 3H, CH_2CH_3 min); ^{13}C NMR (75 MHz, DMSO-*d*$_6$, δ) 178.4, 178.2, 177.4, 176.3, 158.0, 133.4, 133.35, 133.3, 133.0, 132.9, 132.8, 131.1, 131.0, 130.0, 129.9, 129.8, 129.7, 129.6, 129.5, 128.9, 128.7, 127.4, 127.35, 127.3, 119.0, 118.8, 117.4, 114.1, 109.0, 105.5, 105.0, 102.8, 55.5, 45.9, 45.5, 38.9, 38.7, 38.4, 38.2, 38.1, 34.3, 33.9, 32.7–33.3 (multiple peaks), 30.0, 27.4, 23.7, 23.6, 12.6, 11.8; IR (thin film, cm^{-1}) 3389(bs), 2931(m), 1777(w), 1706(s), 1509(m), 1383(m), 1246(m), 1176(m); HRMS *m/z* (M + Na$^+$) calcd 491.2306, found 491.2323. Anal. Calcd for

$C_{30}H_{32}N_2O_3$: C, 76.90; H, 6.88; N, 5.98. Found: C, 76.98; H, 7.19; N, 5.19.

8-Isopropyl-2-(4-methoxybenzyl)-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (105). Method B with **3f** (982 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **105** (1181 mg, 51%) as a light-pink solid, a mixture of three isomers (maj:min:min = 4.5:1.0:0.9): mp 235–237°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.65 (d, J = 2.4 Hz, 1H, 1maj-H), 10.64 (d, J = 1.8 Hz, 1H, 1min-H), 10.40 (d, J = 1.8 Hz, 1H, 1min-H), 7.41–7.56 (m, 3H, Ph), 7.13–7.24 (m, 4H, Ph), 6.80–6.86 (m, 2H, Ph), 5.78 (d, J = 2.4 Hz, 1H, 3min-H), 5.57 (d, J = 2.4 Hz, 1H, 3maj-H), 5.55 (d, J = 2.1 Hz, 1H, 3min-H), 4.19 (dd, J = 8.4, 1.5 Hz, 1H, 3bαmin-H), 4.17 (dd, J = 7.8, 0.9 Hz, 1H, 3bαmaj-H), 4.00 (dd, J = 8.4, 2.1 Hz, 1H, 3bαmin-H), 3.80 (s, 2H, Bn), 3.713 (s, 3H, OCH$_3$ maj), 3.709 (s, 3H, OCH$_3$ min), 3.70 (s, 3H, OCH$_3$ min), 3.43 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.38 (dd, J = 8.4, 5.1 Hz, 1H, 6aαmaj-H), 3.35 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmin-H), 2.95–3.01 (m, 1H, 10aαmin-H), 2.85–2.91 (m, 1H, 10aβmaj-H), 2.38–2.50 (m, 1H, 6bαmaj-H), 2.20–2.36 (m, 1H, 6bmin-H), 1.20–2.02 (m, 8H, cyclohex, C*H*(CH$_3$)$_2$), 0.84 (d, J = 6.3 Hz, 6H, CH(CH$_3$)$_2$ maj), 0.77 (d, J = 6.3 Hz, 6H, CH(CH$_3$)$_2$ min), 0.69 (d, J = 6.6 Hz, 6H, CH(CH$_3$)$_2$ min); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 178.0, 176.2, 132.6, 131.9, 131.6, 129.8, 129.75, 129.7, 129.4, 129.3, 129.2, 128.8, 128.7, 128.4, 126.5, 126.4, 126.2, 117.6, 114.1, 106.4, 105.0, 104.0, 103.9, 55.4, 45.7, 45.7, 43.9, 40.3, 38.9, 37.8, 32.8–33.7 (overlapped peaks), 26.3, 24.0, 22.5, 21.4, 21.0, 19.9; IR (KBr, cm^{-1}) 3463(w), 3384(bs), 3064(w), 2999(w), 2929(s), 2864(s), 2836(m), 2361(w), 2329(w), 1777(m), 1698(s), 1613(m), 1595(m), 1512(s), 1454(m), 1387(s), 1248(m), 1175(s); HRMS m/z (M + Na$^+$) calcd for $C_{31}H_{34}N_2O_3$: 505.2462, found 505.2483.

8-tert-Butyl-2-(4-methoxybenzyl)-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (106). Method A gave **106** (432 mg, 29%) as a cream-colored solid, a mixture of three isomers (maj:min:min = 5.2:1.0:0.6): mp 219–220°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.26 (bs, 1H, 1min-H), 8.06 (bs, 1H, 1maj-H), 7.36–7.53 (m, 3H, Ph), 7.12–7.28 (m, 4H, Ph), 6.84–6.89 (m, 2H, Ph), 6.10 (d, J = 2.7 Hz, 1H, 3min-H), 5.81 (d, J = 2.7 Hz, 1H, 3min-H), 5.76 (d, J = 2.7 Hz, 1H, 3maj-H), 4.06 (dd, J = 8.1, 1.8 Hz, 1H, 3bα-H), 3.90–3.97 (m, overlapped, 2H, 2XBn min), 3.92 (AA′d, J = 14.4 Hz, 1H, Bn maj), 3.84 (AA′d, J = 14.4 Hz, 1H, Bn maj), 3.81 (s, 3H, OCH$_3$), 3.49 (dd, J = 8.6, 5.6 Hz, 1H, 6aαmin-H), 3.41 (dd, J = 8.1, 5.7 Hz, 1H, 6aαmaj-H), 3.34 (dd, J = 7.8. 5.4 Hz, 1H, 6aαmin-H), 2.53–2.75 (m, 2H, 6bα-H, 10a-H), 1.02–2.32 (m, 7H, cyclohex.), 0.90 (s, 9H, *t*-Bu), 0.74 (s, 9H, *t*-Bu); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.5, 176.0, 158.0, 158.75, 133.2, 133.16, 130.1, 129.8, 129.7, 129.6, 129.4, 128.8, 128.6, 127.5, 127.1, 117.3, 117.26, 114.1, 104.0, 55.5, 44.9, 34.3–34.5 (multiple peaks), 34.0, 33.8, 33.3, 33.2, 33.1, 33.0, 32.7, 28.2, 27.7; IR (thin film, cm^{-1}) 3455(bs), 2950(m), 2360(w), 1770(w), 1702(s), 1648(bm), 1511(m), 1388(m), 1247(m), 1176(m); HRMS m/z (M + Na$^+$) calcd 519.2619, found 519.2627. Anal. Calcd for $C_{32}H_{36}N_2O_3$: C, 77.39; H, 7.31; N, 5.64. Found: C, 77.44; H, 7.68; N, 5.67.

2-(4-Methoxybenzyl)-5,8-diphenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (107). Method B with **3h** (1220 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **107** (1513 mg, 61%) as a brown solid, a mixture of two isomers (maj:min = 5.2:1.0): mp 223–225°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.69 (bs, 1H, 1maj-H), 10.50 (bs, 1H, 1min-H), 7.15–7.56 (m, 12H, Ph), 6.83–6.88 (m, 2H, Ph), 5.79 (d, J = 2.1 Hz, 1H, 3min-H), 5.61 (d, J = 2.7 Hz, 1H, 3maj-H), 4.21 (dd, J = 8.7, 0.9 Hz, 1H, 3bαmaj-H), 4.02 (dd, J = 6.6, 2.7 Hz, 1H, 3bαmin-H), 3.82 (s, 2H, Bn), 3.72 (s, 3H, OCH$_3$), 3.41–3.55 (m, 1H, 6aα-H), 2.70–3.10 (m, 2H, 6b-H, 10a-H), 1.40–2.10 (m, 7H, cyclohex.); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 178.0, 176.0, 158.4, 136.1, 132.9, 131.8, 131.4, 129.8, 129.4, 129.3, 129.2, 128.8, 128.6, 128.5, 128.4, 127.4, 127.3, 126.5, 126.4, 125.6, 114.1, 55.4, 45.6, 33.4–33.8 (overlapped peaks); IR (KBr, cm^{-1}) 3458(w), 3381(bs), 3061(w), 3026(w), 3003(w), 2930(s), 2861(m), 2836(m), 2360(w), 2335(w), 1777(m), 1703(s), 1599(m), 1510(s), 1452(m), 1387(s), 1249(m), 1176(s); HRMS m/z (M + Na$^+$) calcd for $C_{34}H_{32}N_2O_3$: 539.2306, found 539.2308.

2-(4-Methoxybenzyl)-5-(4-methoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (108). Method A gave **108** (593 mg, 42%) as a cream-colored solid, a mixture of two isomers (maj:min = 1.2:1.0): mp 234–235°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.26 (bs, 1H, 1min-H), 7.56 (bs, 1H, 1maj-H), 7.15–7.24 (m, 4H, Ph), 6.96–7.01 (m, 2H, Ph), 6.85–6.87 (m, 2H, Ph), 6.27 (d, J = 2.7 Hz, 1H, 3maj-H), 5.81 (d, J = 2.7 Hz, 1H, 3min-H), 3.99 (AA′d, J = 15.9 Hz, 1H, Bn maj), 3.97 (AA′d, J = 16.2 H, 1H, Bn min), 3.90–3.97 (m, overlapped, 1H, 3bα-H), 3.90 (AA′d, J = 16.5 Hz, 1H, Bn maj), 3.89 (AA′d, J = 15.6 Hz, 1H, Bn min), 3.84 (s, 3H, OCH$_3$), 3.82 (s, 3H, OCH$_3$), 3.44 (dd, J = 8.9, 5.6 Hz, 1H, 6aαmin-H), 3.38 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmaj-H), 3.08–3.12 (m, 1H, 10aαmaj-H), 3.02–3.06 (m, 1H, 10aβmin-H), 2.49–2.57 (m, 1H, 6bα-H), 2.04–2.24 (m, 1H, cyclohex.), 1.08–1.76 (m, 7H, cyclohex.); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.4, 176.5, 159.5, 158.0, 133.3, 132.9, 130.0, 129.9, 128.6, 125.3, 119.0, 117.4, 114.8, 114.7, 114.1, 105.6, 102.7, 74.9, 58.9, 55.9, 55.5, 46.2, 38.4, 38.1, 33.2, 33.12, 33.07, 33.04, 29.3, 26.1, 22.9, 20.9; IR (thin film, cm^{-1}) 3386(bs), 2920(m), 2360(w), 1769(w), 1697(s), 1516(m), 1392(m), 1257(m), 1178(m); HRMS m/z (M + Na$^+$) calcd for $C_{29}H_{30}N_2O_4$: 493.2099, found 493.2116.

8-Ethyl-2-(4-methoxybenzyl)-5-(4-methoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (109). Method A gave **109** (434 mg, 29%) as a cream-colored solid, a mixture of three isomers (maj:min:min = 1.9:1.0:0.2): mp 228–229°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.25 (bs, 1H, 1min-H), 7.57 (bs, 1H, 1maj-H), 7.14–7.23 (m, 4H, Ph), 6.96–7.02 (m, 2H, Ph), 6.85–6.90 (m, 2H, Ph), 6.26 (d, J = 2.4 Hz, 1H, 3maj-H), 5.82 (d, J = 2.7 Hz, 1H, 3min-H), 5.78 (d, J = 2.7 Hz, 1H, 3min-H), 4.99 (AA′d, J = 16.2 Hz, 1H, Bn maj), 4.97 (AA′d, J = 16.8 Hz, 1H, Bn min), 3.91–3.96 (m, overlapped, 1H, 3bα-H), 3.90 (AA′d, J = 16.2 Hz, 1H, Bn maj), 3.89 (AA′d, J = 16.5 Hz, 1H, Bn min), 3.84 (s, 3H, OCH$_3$), 3.82 (s, 3H, OCH$_3$), 3.43 (dd, J = 8.7, 5.7 Hz, 1H, 6aαmin-H), 3.37 (dd, J = 8.4, 5.4 Hz, 1H, 6aαmaj-H), 3.02–3.07 (m, 1H, 10aαmaj-H), 2.96–3.01 (m, 1H, 10aβmin-H), 2.64–2.73 (m, 1H, 6bαmaj-H), 2.53–2.60 (m, 1H, 6bmin-H), 1.07–1.92 (m, 9H, cyclohex., C*H*$_2$CH$_3$), 0.85 (t, J = 7.2 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.5, 178.45, 178.4, 177.6, 176.5, 159.5, 159.4, 159.2, 158.0, 133.3, 132.9, 132.8, 131.0, 131.95, 130.1, 129.9, 129.8, 128.6, 128.5, 127.2, 125.6, 125.4, 118.7, 117.4, 114.9, 114.8, 114.1, 109.1, 105.5, 102.8, 55.9, 55.5, 45.8, 45.5, 34.3, 34.0, 33.0–33.3 (multiple peaks), 33.9, 32.6–32.8 (multiple peaks), 23.6, 23.5, 12.6; IR (thin film, cm^{-1}) 3441(bs), 2934(m), 2100(bw), 1777(w), 1694(s), 1651(bm), 1515(s), 1388(m), 1252(m), 1174(m); HRMS *m*/*z* (M + Na$^+$) calcd 521.2412, found 521.2416. Anal. Calcd for $C_{31}H_{34}N_2O_4$: C, 74.67; H, 6.87; N, 5.62. Found: C, 72.72; H, 6.59; N, 5.45.

8-Isopropyl-2-(4-methoxybenzyl)-5-(4-methoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (110). Method B with **3f** (982 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **110** (1304 mg, 53%) as a colorless solid, a mixture of three isomers (maj:min:min = 3.8:1.0:0.6): mp 252–254°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.64 (d, *J* = 2.4 Hz, 1H, 1maj-H), 10.63 (d, *J* = 2.7 Hz, 1H, 1min-H), 10.39 (d, *J* = 2.4, 1H, 1min-H), 7.01–7.21 (m, 6H, Ph), 6.80–6.86 (m, 2H, Ph), 5.78 (d, *J* = 2.4 Hz, 1H, 3min-H), 5.57 (d, *J* = 2.4 Hz, 1H, 3maj-H), 5.55 (d, *J* = 2.1 Hz, 1H, 3min-H), 4.15 (dd, *J* = 8.4, 1.8 Hz, 1H, 3bαmin-H), 4.13 (dd, *J* = 8.4, 1.5 Hz, 1H, 3bαmaj-H), 3.97 (dd, *J* = 8.7, 2.1 Hz, 1H, 3bαmin-H), 3.80 (s, 2H, Bn), 3.79 (s, 3H, PhOCH_3 min), 3.79 (s, 3H, PhOCH_3 maj), 3.78 (s, 3H, PhOCH_3 min), 3.712 (s, 3H, BnOCH_3 min), 3.710 (s, 3H, BnOCH_3 maj), 3.70 (s, 3H, BnOCH_3 min), 3.40 (dd, *J* = 8.7, 5.4 Hz, 1H, 6aαmin-H), 3.35 (dd, *J* = 8.4, 5.4 Hz, 1H, 6aαmaj-H), 3.31 (dd, *J* = 8.4, 5.4 Hz, 1H, 6aαmin-H), 2.94–3.01 (m, 1H, 10aαmin-H), 2.84–2.91 (m, 1H, 10aβmaj-H), 2.37–2.48 (m, 1H, 6bαmaj-H), 2.26–2.36 (m, 1H, 6bmin-H), 0.88–2.18 (m, 8H, cyclohex., C*H*$(CH_3)_2$), 0.84 (d, *J* = 6.0 Hz, 6H, CH(CH_3)$_2$ maj), 0.76 (d, *J* = 6.6 Hz, 6H, CH(CH_3)$_2$ min), 0.69 (d, *J* = 6.9 Hz, 1H, CH(CH_3)$_2$ min); IR (KBr, cm^{-1}) 3462(w), 3377(bs), 3064(w), 2996(w), 2931(bs), 2864(m), 2837(m), 1776(m), 1695(s), 1612(m), 1589(m), 1514(s), 1452(m), 1391(m), 1303(m), 1250(s), 1169(s), 1106(m), 1033(m); HRMS *m*/*z* (M + Na$^+$) calcd 535.2568, found 535.2589. Anal. Calcd for $C_{32}H_{36}N_2O_4$: C, 74.97; H, 7.08; N, 5.46. Found: C, 74.77; H, 6.82; N, 5.28.

8-tert-Butyl-2-(4-methoxybenzyl)-5-(4-methoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (111). Method A gave **111** (348 mg, 22%) as a cream-colored solid, a mixture of four isomers (maj:min:min:min = 2.7:1.0:0.7:0.3): mp 224–225°C; ^{1}H NMR (300 MHz, CDCl3, δ) 8.25 (bs, 1H, 1min-H), 8.05 (bs, 1H, 1maj-H), 7.50 (bs, 1H, 1min-H), 7.47 (bs, 1H, 1min-H), 7.09–7.18 (m, 4H, Ph), 6.94–7.03 (m, 2H, Ph), 6.83–6.89 (m, 2H, Ph), 6.29 (d, *J* = 2.4 Hz, 1H, 3min-H), 6.10 (d, *J* = 2.4 Hz, 1H, 3min-H), 5.80 (d, *J* = 2.7 Hz, 1H, 3min-H), 5.75 (d, *J* = 2.7 Hz, 1H, 3maj-H), 4.04 (d, *J* = 8.1 Hz, 1H, 3bα-H), 3.80–3.95 (m, 2H, Bn), 3.81 (s, 6H, 2XOCH_3), 3.47 (dd, *J* = 8.7, 5.4 Hz, 1H, 6aαmin-H), 3.42 (dd, *J* = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.38 (dd, *J* = 8.1, 5.7 Hz, 1H, 6aαmaj-H), 3.32 (dd, *J* = 7.5, 5.4 Hz, 1H, 6aαmin-H), 3.03–3.07 (m, 1H, 10amin-H), 2.98–3.02 (m, 1H, 10amin-H), 2.54–2.70 (m, 3H, 6b-H, 10aαmaj-H, 10amin-H), 1.05–2.27 (m, 7H, cyclohex.), 0.89 (s, 9H, *t*-Bu maj), 0.74 (s, 9H, *t*-Bu min); IR (thin film, cm^{-1}) 3440(bs), 2952(m), 2358(m), 1770(w), 1698(s), 1514(s), 1393(m), 1303(m), 1250(m), 1174(m); HRMS *m*/*z* (M + Na$^+$) calcd for $C_{32}H_{38}N_2O_4$: 549.2725, found 549.2694.

2-(4-Methoxybenzyl)-5-(4-methoxyphenyl)-8-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (112). Method B with **3h** (1220 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **112** (1548 mg, 59%) as a light-brown solid, a mixture of two isomers (maj:min = 8.1:1.0): mp 226–227°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.67 (app. bs, 1H, 1maj-H), 10.48 (d, *J* = 2.4 Hz, 1H, 1min-H), 6.97–7.39 (m, 11H, Ph), 6.82–6.90 (m, 2H, Ph), 5.62 (d, *J* = 2.7 Hz, 1H, 3min-H), 5.60 (d, *J* = 2.4 Hz, 1H, 3maj-H), 4.20 (dd, *J* = 8.7, 1.8 Hz, 1H, 3bαmin-H), 4.18 (dd, *J* = 8.4, 1.5 Hz, 1H, 3bαmaj-H), 3.82 (s, 2H, Bn), 3.79 (s, 3H, PhCH_3 maj), 3.78 (s, 3H, PhCH_3 min), 3.73 (s, 3H, BnCH_3 min), 3.72 (s, 3H, BnCH_3 maj), 3.36–3.48 (m, 1H, 6aα-H), 2.80–3.20 (m, 2H, 6b-H, 10a-H), 1.20–2.30 (m, 7H, cyclohex.); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 178.2, 176.4, 159.7, 158.3, 132.9, 131.5, 130.4, 129.8, 128.5, 127.8, 127.4, 127.3, 126.8, 125.6, 124.4, 117.6, 114.7, 114.3, 114.1, 104.1, 57.4, 55.6, 55.4, 45.5, 33.6, 33.2–33.6 (overlapped peaks), 32.3; IR (KBr, cm^{-1}) 3479(w), 3458(w), 3388(bs), 3059(w), 3025(w), 3002(w), 2933(s), 2860(m), 2837(m), 2360(w), 2340(w), 1776(m), 1699(s), 1610(m), 1513(s), 1451(m), 1390(m), 1302(m), 1251(s), 1174(s), 1031(s); HRMS *m*/*z* (M + Na$^+$) calcd 569.2412, found 569.2406. Anal. Calcd for $C_{35}H_{34}N_2O_4$: C, 76.90; H, 6.27; N, 5.12. Found: C, 76.84; H, 6.27; N, 4.89.

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A New Catalytic Method for Ecofriendly Synthesis of Bis- and Trisindolylmethanes by Zirconyldodecylsulfate Under Mild Conditions

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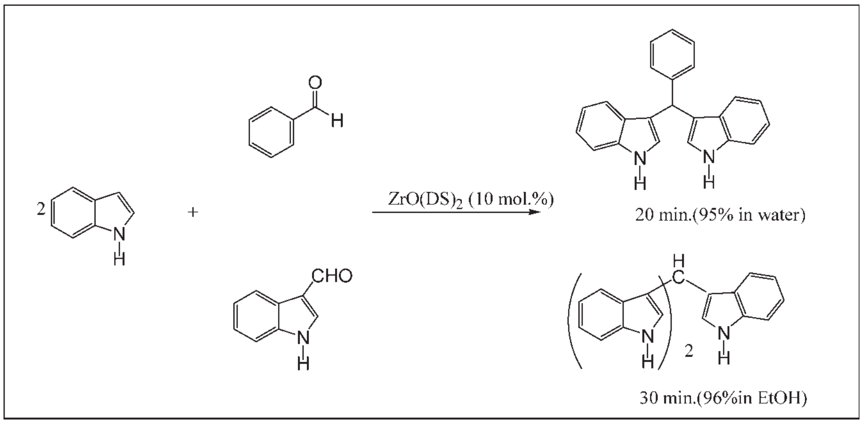

Zirconyldodecylsulfate (ZrO(DS)$_2$) as a versatile Lewis acid-surfactant-combined (LASC) catalyzed ecofriendly synthesis of bis- and tris(indolyl)methanes *via* electrophilic substitution of indoles with carbonyl compounds in high yields at mild conditions.

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INTRODUCTION

Replacing current chemical processes with more environmentally benign alternatives is an increasingly attractive subject [1]. The rapid and extensive growth of synthetic procedures using materials with detrimental effects to the environment has turned the attention of chemists to the development of environmentally benign methods in order to avoid or minimize these harmful effects.

Bis(indolyl)methanes (BIM) are the most active cruciferous substances for promoting beneficial estrogen metabolism in woman and men [2]. BIM increases the body's natural metabolism of hormones and promotes good estrogen (2-hydroxyestrogen). This indole antioxidant is patented for alleviating symptoms of fibromyalgia. BIM is effective in the prevention of cancer because of its ability to modulate certain cancer causing estrogen metabolites [3]. Scientists have demonstrated that BIM induces apoptosis in human cancer cells and may also normalize abnormal cell growth associated with cervical dysplasia.

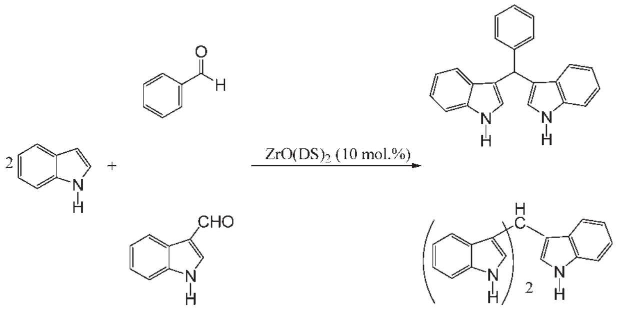
Also 1,1,1-tris(3,3′,3″-indolyl)ethane was found in bacterial metabolites [4], and the triarylmethanes (TIMs) could be converted into important cage molecules [5]. It is reported that the cationic form of TIMs could be used as acceptors of hydride ions.

Thus, indole and its derivatives have been a topic of research interest [6]. Because of their intriguing physiological activities, many synthetic procedures have been reported so far [7–12], where development of environmentally benign methods are currently of interest in process chemistry by using green catalysts.

Green catalysts require high catalytic activity and atom efficiency, as well as low toxicity, low cost, and ease of handling. Fortunately, Zr(IV) compounds generally have low toxicity and are not considered particularly poisonous. Reports on the safety of Zr(IV) salts show that their LD_{50} is high [LD_{50} [$ZrOCl_2.8H_2O$, oral rat] = 3500 mg/Kg] [13]. Although $ZrOCl_2.8H_2O$ has a rather high LD_{50}, it should not be very harmful to mammalians. Also, this material is commercially available and is an inexpensive compound.

In continuation of our ongoing interest on development of new applications of zirconium salts [8,14–18] in synthetic methods, we herein report the use of ZrO(DS)$_2$ as LASC in the electrophilic substitutions of

Scheme 1



indoles with a variety of aldehydes and ketones in H_2O and EtOH, both of which are green solvents, affording excellent yields of bis- and tris(indolyl)methanes under mild condition (Scheme 1).

RESULTS AND DISCUSSION

Optimized reaction conditions were investigated using a reaction of benzaldehyde and indole (1:2.2), with respect to temperature, time, and the molar ratio of $ZrO(DS)_2$ to the substrate in water. We found that 10 mol % of $ZrO(DS)_2$ was sufficient to obtain the desired bisindolylmethane in 96% yield within 20 min at 60°C.

Based on the optimized reaction conditions, the present protocol was applied to a variety of carbonyl compounds (Table 1). As shown in Table 1 aryl aldehydes with both electron-donating and electron-withdrawing characteristics afforded bis(indolyl)methane in excellent yields. Not only aryl aldehydes but also aliphatic aldehydes provided the desired bis(indolyl)methane (Table 1, entry 9).

We have found that the reaction of both activated and deactivated aromatic aldehydes with 2-methyl indole is faster than indole (Table 1, entries 10,11).

When 3-formylindole was used as a carbonyl compound, the corresponding trisindolylmethanes are formed. The reaction proceeded at room temperature in EtOH and the time required for the conversion was short (Table 1, entreis 12,13).

The reaction of acetophenone with indole is slower than with aldehydes, and unreacted ketone and indole remains (Table 1, entry 14).

To show the merit of $ZrO(DS)_2$ in comparison with other catalysts used for the similar reactions in green solvents, we have tabulated some of the results in Table 2.

CONCLUSION

We have developed a highly convenient, efficient, and green catalytic system for the preparation of biologically important bis- and trisindolylmethanes in high yields through the electrophilic substitution reaction of indoles with carbonyl compounds using $ZrO(DS)_2$ as new LASC. This protocol will contribute to reducing the use of harmful organic solvents.

EXPERIMENTAL

General. $ZrOCl_2.8H_2O$, SDS, carbonyl compounds, and indoles were purchased from Merck or Fluka Chemical Companies. Progress of the reactions was monitored by TLC using silica-gel SIL G/UV 254 plates. NMR spectra were recorded on a Brucker Avance DPX 300 MHz and 500 MHz instruments. Mass spectra were recorded on a Shimadzu GC-MS-QP 5050A.

Preparation of $ZrO(DS)_2$ from $ZrOCl_2.8H_2O$ and sodium dodecyl sulfate (SDS). A solution of $ZrOCl_2.8H_2O$ (5 mmol, 1.61 g in 50 mL of water) was added to a solution of sodium dodecyl sulfate (SDS) (10 mmol, 2.88 g in 50 mL of distilled water) while stirring at room temperature. A white precipitate was appeared immediately and the mixture was stirred for another 30 min. The white solid was collected by filtration and washed with water (2 × 100 mL). The isolated solid was dried under reduced pressure and $ZrO(DS)_2$ was obtained as a white powder in 90% yield (2.87 g). M.p: 125°C; ^1H NMR (DMSO, 500 MHz): δ 0.82 (t, 6H, J = 6.8 Hz), 1.1–1.35 (m, 36H), 1.45 (m, 4H), 3.69 (t, 4H, J = 6.6 Hz) ppm; ^{13}C NMR (DMSO, 125.77 MHz): 13.90, 22.14, 25.58, 28.78, 28.90, 29.04, 29.11, 29.13, 31.37, 32.63, 60.83, 65.99 ppm.

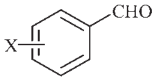
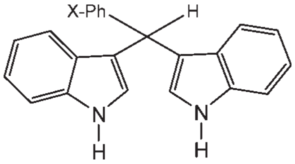
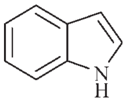
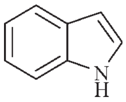
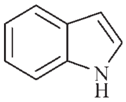
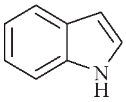
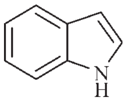
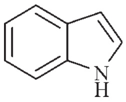
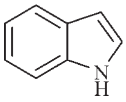
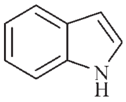
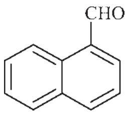
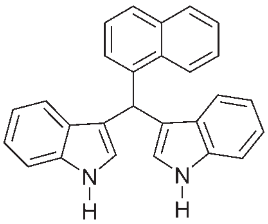
General procedure for condensation of indoles with carbonyl compounds catalyzed by $ZrO(DS)_2$. Indole (2.2 mmol) and carbonyl compound (1 mmol) was added to a suspension of $ZrO(DS)_2$ (10 mol %, 0.0638 g in 2 mL of water or EtOH) (see Table 1). The reaction mixture was stirred at 60°C for appropriate time which was monitored by TLC (Table 1). After completion of the reaction, EtOAc (5 mL) was added to the reaction mixture; organic phase was separated and dried over $CaCl_2$ followed by filtration and evaporation of the solvent. The desired product was secured in high purity (Table 1). Further purification was performed by plate chromatography eluted with *n*-hexan/EtOAc (3/1). Structural assignments of the products are based on their ^1H NMR, ^{13}C NMR, MS spectra and elemental analysis.

Selected spectral data. Table 1, entry 2: Solid; mp: 97–98°C; ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 2.37 (s, 3H), 5.83 (s, 1H), 6.70(d, 2H, J = 2.45 Hz), 7.02(t, 2H, J = 8.2 Hz), 7.12(d, 2H, J = 8.2 Hz), 7.21–7.3(m, 6H), 7.45(d, 2H, J = 8.2 Hz), 7.9(br, s, 2H) ppm; ^{13}C NMR ($CDCl_3$, TMS, 62.9 MHz): 21, 40.25, 110.9, 112, 119.5, 120.2, 121.6, 122.6, 129.5, 131.5, 134.3, 136.8 ppm; MS (70 ev), m/e: 336 [M^+]. Anal. Calcd for ($C_{24}H_{20}N_2$): C, 85.68; H, 5.99; N, 8.33. Found: C, 85.70; H, 5.96; N, 8.35.

Table 1, entry 12: Solid; mp: 161°C(dec.); ^1H NMR (DMSO, 300 MHz): δ 6.08 (s, 1H), 6.89 (s, 3H), 6.87(t, 3H, J = 7.45 Hz), 7.02 (t, 3H, J = 7.25 Hz), 7.44 (d, 3H, J = 7.83 Hz), 7.56 (d, 3H, J = 7.83 Hz), 10.72 (s, 3H) ppm; ^{13}C NMR (DMSO, 62.9 MHz): 30.8 ,111.4, 117.5, 118, 119,120.6, 124, 126.8, 136.5 ppm; MS (70 eV), m/e: 361 [M^+]. Anal. Calcd. for ($C_{25}H_{19}N_3$): C, 83.08; H, 5.30; N, 11.63. Found: C, 83.10; H, 5.32; N, 11.65.

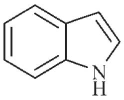
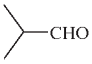
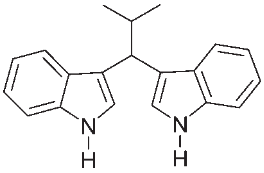
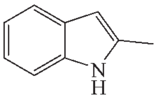
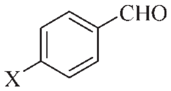
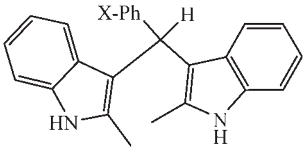
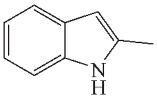
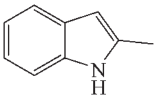
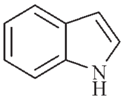
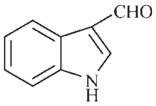
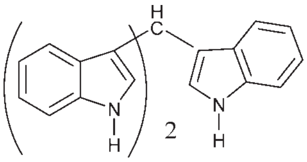
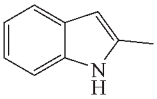
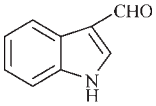
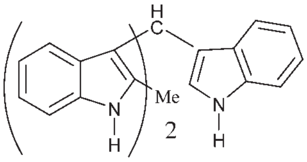
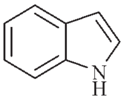
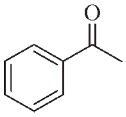
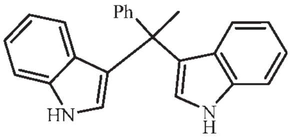
Table 1

Condensation of indoles with carbonyl compounds catalyzed by $ZrO(DS)_2$.

Entry	Indole	Substrate	Product	Time (min)	Isolated Yield%
					
1[a]		X = H	X = H	20	95
2[a]		X = 4-Me	X = 4-Me	30	95
3[a]		X = 4-OMe	X = 4-OMe	45	96
4[a]		X = 4-OH	X = 4-OH	25	94
5[a]		X = 2-Me	X = 2-Me	45	96
6[a]		X = 4-Br	X = 4-Br	15	95
7[a]		X = 4-NO_2	X = 4-NO_2	15	97
8[b]				20	96

(continued)

Table 1
(Continued)

Entry	Indole	Substrate	Product	Time (min)	Isolated Yield%
9[a]				60	94
					
10[b]		X = 4-OMe	X = 4-OMe	15	97
11[a]		X = 4-NO_2	X = 4-NO_2	5	96
12[b]				30	96
13[b]				20	97
14[b]				75	50

[a] Reactions were carried out in water at 60°C.
[b] Reactions were carried out in EtOH at room temperature.
All products were identified by their spectroscopic data and their comparison with known samples [7–12].

Table 2

Reaction of indole with benzaldehyde in the presence of different catalysts.

Entry	Catalyst/solvent	Catalyst (mol %)	Time (h)	Yield (%)	Reference
1	$ZrO(DS)_2/H_2O$	10	20 min	97	
2	$Dy(OTf)_3$/ $EtOH.H_2O$	10	12	95	[19]
3	HMTAB[a]/H_2O	0.1 g	2.5	86	[20]
4	$FeCl_3.6H_2O$/[omim]PF6	5	1.5	98	[21]

[a] Hexamethylenetetraamine-bromine.

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A Simple Preparation of Ethyl 2,5-Dimethylfuran-3-Carboxylate and 2,5-Dimethylfuran-3,4-Dicarboxylic Acid from Diethyl 2,3-Diacetylsuccinate

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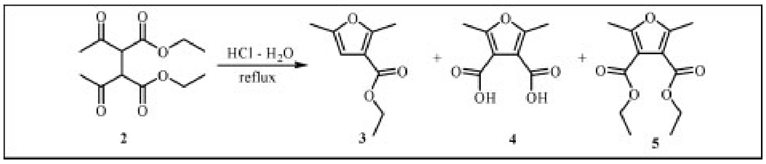

A simple preparation of ethyl 2,5-dimethylfuran-3-carboxylate (**3**), 2,5-dimethylfuran-3,4-dicarboxylic acid (**4**), and diethyl 2,5-dimethylfuran-3,4-dicarboxylate (**5**) by treatment of diethyl 2,3-diacetylsuccinate (**2**) with aqueous HCl is reported. The reaction is performed under organic solvent free conditions from a readily available cheap starting material.

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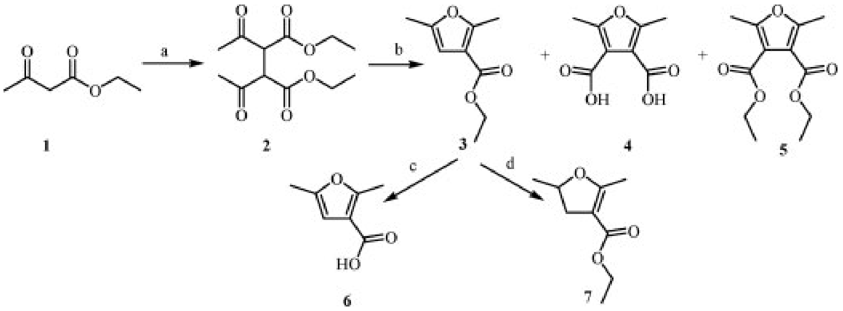
INTRODUCTION

Highly substituted furans play an important role as structural elements of many pharmaceutical and natural substances [1]. Moreover, they are useful building blocks in synthetic organic chemistry [2]. Especially, ethyl 2,5-dimethylfuran-3-carboxylate (**3**) (Scheme 1) is an important trisubstituted furan. Its derivatives have been used as wood preservatives [3], microbicides, insecticides [4], and fungicides [5]. 2,5-Dimethylfuran-3,4-dicarboxylic acid (**4**) and diethyl 2,5-dimethylfuran-3,4-dicarboxylate (**5**) are also useful intermediates in medicinal chemistry and organic synthesis [6–8]. Among the different approaches to multiply substituted furans [9–15], there are some methods for the preparation of **3**, such as gold(I) catalyzed cascade reaction of propargyl Claisen rearrangement and heterocyclization of propargyl vinyl ethers [1], polymer-supported selenium-induced electrophilic cyclization [16], I_2-induced cyclization of 2-alkenyl substituted 1,3-dicarbonyl compounds [17], treatment of α,β-unsaturated ketones with *N*-bromosuccinimide followed by cyclization [18], and treatment of ethyl 2-acetyl-4-oxopentanoate with montmorillonite clay in toluene at reflux with water removal [5]. Some methods require expensive reagents and some use unreadily accessed starting materials or hazardous organic solvents. Thus, the development of convenient strategies is still of considerable interest. We now wish to report a simple preparation of trisubstituted furan (**3**) starting from diethyl 2,3-diacetylsuccinate (**2**) by decarboxylation and subsequent Paal–Knorr cyclization [19–21] in aqueous HCl. Using this procedure, trisubstituted furan (**3**) and tetrasubstituted furan (**4**) or (**5**) can be easily prepared at will by adjusting the concentrations of aqueous HCl. The reaction is simple to perform, and the starting material is cheap and readily available.

RESULTS AND DISCUSSION

Diethyl 2,3-diacetylsuccinate (**2**) (Scheme 1) was prepared according to literature from ethyl acetoacetate (**1**) using sodium in diethyl ether followed by treatment with iodine at room temperature [22]. In our initial exploration, treatment of **2** with 0.4*N* aqueous HCl at reflux for 14–15 h in oil bath afforded trisubstituted furan monoester (**3**) and tetrasubstituted furan diacid (**4**), in 30–50% and 40–60% yields, respectively. Different aqueous HCl concentrations were further compared for the reaction under both oil bath heating and microwave irradiation (Table 1). When **2** was treated with 6*N* aqueous HCl or 3*N* aqueous HCl, tetrasubstituted furan diacid (**4**) was obtained as the only product in excellent to quantitative yields. Whereas using dilute aqueous HCl, trisubstituted furan monoester (**3**) was obtained. The highest yield of **3** was observed in 57% under oil bath heating in 0.3*N* aqueous HCl, and 50% under microwave irradiation in 0.2*N* aqueous HCl. Interestingly, tetrasubstituted furan ester (**5**) was obtained only under microwave irradiation possibly because of the shorter reaction time.

Scheme 1. Reaction conditions: (a) (i) Na, Et_2O, r.t., 12 h, (ii) I_2, Et_2O, r.t., 4 h, 66%; (b) HCl-H_2O, reflux under oil bath heating or under microwave irradiation; (c) 5% NaOH, reflux, 5 h, 96%; (d) H_2, 5% Pd/C, EtOH-H_2O, 4d, 90%.



A previous report by Fales *et al*. described the formation of diethyl 2,5-dimethylfuran-3,4-dicarboxylate (**5**) from diethyl 2,3-diacetylsuccinate (**2**) by using concentrated H_2SO_4 in CCl_4 [23]. In our procedure, tetra- or trisubstituted furans can be easily prepared by using different aqueous HCl concentrations. The product selectivity appears to be controlled by acid concentrations. More dilute aqueous HCl can provide trisubstituted furan monoester (**3**) probably through decarboxylation and subsequent Paal–Knorr dehydrative cyclization. Meanwhile, higher concentrations of aqueous HCl gave tetrasubstituted furan diacid (**4**) as main or even only product possibly through Paal–Knorr cyclization and subsequent hydrolysis. It is notable that no decarboxylation was observed under more acidic conditions. We think that it is possibly because the higher concentrations of aqueous HCl can accelerate dehydrative cyclization step to form furan ring before decarboxylation, and the resulting conjugated system between the furan ring and dicarbonyl groups is strong enough to prevent it from decarboxylation under employed reaction conditions. Actually, no decarboxylation of **4** was observed in our investigation. Therefore, compound **4** would be the major product if cyclization is faster than decarboxylation, otherwise **3** would be the major one.

To confirm the structure of **3**, the hydrolysis of **3** with 5% aqueous NaOH was performed to afford 2,5-dimethylfuran-3-carboxylic acid (**6**) as crystals (Scheme 1). The X-ray crystallographic analysis of **6** was shown in Figure 1 [24].

Moreover, we investigated the selective hydrogenation of **3**. Treatment of **3** with 5% Pd/C in EtOH-H_2O at H_2 atmosphere for 4 days yielded dihydrofuran **7** as the only product in excellent yield (Scheme 1). This selective hydrogenation is a useful approach for dihydrofurans which are also important structural elements of many pharmaceutical and natural products [16,25–27].

The procedure described earlier is a practical method for the preparation of trisubstituted furan **3**. Although **3** was obtained in medium yield, it is still a valuable approach because the starting material is a readily accessed symmetrically substituted 1,4-dicarbonyl compound. Moreover, using this procedure trisubstituted furan (**3**) and tetrasubstituted furan (**4** or **5**) can be easily prepared at will by adjusting the concentrations of

Table 1

Comparison of different HCl concentrations as reagents for diethyl 2,3-diacetylsuccinate (**2**) cyclization.

Entry	Concentration of HCl (*N*)	Reaction condition	Reaction time (h)	Yield (%)[a]		
				3	**4**	**5**
1	6	Oil bath	14		89	
2	3	Oil bath	14		91	
3	1	Oil bath	14	3	82	
4	0.5	Oil bath	14	8	86	
5	0.4	Oil bath	15	50	40	
6	0.3	Oil bath	15	57	38	
7	0.2	Oil bath	15	41	58	
8	0.1	Oil bath	15	44	52	
9	H_2O	Oil bath	15			
10	3	Microwave	1		100	
11	1	Microwave	1	20	24	52
12	0.4	Microwave	2	21		61
13	0.3	Microwave	2	39		52
14	0.2	Microwave	2.5	50		46
15	0.1	Microwave	2.5	38		56
16	H_2O	Microwave	3			

[a] Refers to yield of isolated product.

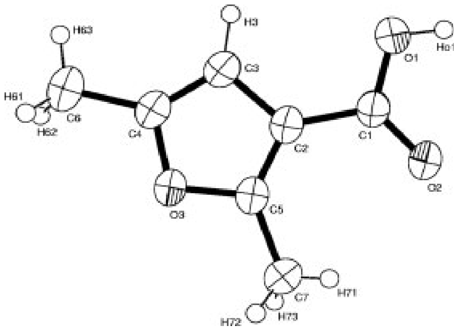


Figure 1. X-ray crystallographic analysis of **6**.

aqueous HCl under organic solvent free conditions. Both conventional and microwave heating were investigated for this method.

EXPERIMENTAL

General methods. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker AV-300 spectrometer with TMS as an internal standard. The chemical shifts (δ) are given in ppm, and the coupling constants (*J*) in hertz (Hz). X-ray diffraction analysis was performed on a Bruker P4 X-ray diffraction meter. Melting points were determined on an X-4 digital display micro melting point apparatus and were uncorrected. Unless otherwise noted, all reagents were obtained from commercial suppliers and were used without further purification. Organic solvents used were dried by standard methods when necessary. All reactions were monitored by TLC with Haiyang GF254 silica gel plates. Flash column chromatography was carried out using 200–300 mesh silica gel at increased pressure.

Ethyl 2,5-dimethylfuran-3-carboxylate (3) and 2,5-dimethylfuran-3,4-dicarboxylic acid (4). A solution of diethyl 2,3-diacetylsuccinate (**2**) (145 mg, 0.56 mmol) in aqueous HCl (0.4*N*, 1.8 mL) was refluxed for 15 h in oil bath. After cooling to r.t., the reaction mixture was extracted with diethyl ether thoroughly. The combined extracts were washed with water, brine, dried (Na_2SO_4), and filtered. The solvents were removed and the residue was purified by flash chromatography (petroleum ether/diethyl ether 5:1, then pure diethyl ether) to give compound **3** (47 mg, 50%) as colorless oil, and compound **4** (41 mg, 40%) as white crystals.

Compound 3. ^{1}H NMR ($CDCl_3$) δ 1.33 (t, 3H, *J* = 7.1 Hz), 2.36 (s, 3H), 2.52 (s, 3H), 4.26 (q, 2H, *J* = 7.1 Hz), 6.21 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.2, 13.7, 14.5, 60.0, 106.3, 114.2, 150.0, 157.6, 164.4. Identical to that previously reported [28].

Compound 4. Mp 214–216°; ^{1}H NMR (CD_3COCD_3) δ 2.60 (s, 2 × 3H); ^{13}C NMR (CD_3COCD_3) δ 14.5, 112.4, 161.5, 166.6. Spectroscopic data were in accordance with commercially available material.

Diethyl 2,5-dimethylfuran-3,4-dicarboxylate (5). A solution of **2** (243 mg, 0.94 mmol) in aqueous HCl (0.4*N*, 3.3 mL) was refluxed under atmospheric pressure for 2 h within a synthetic microwave reactor (Sineo microwave MAS-II), which was equipped with a condenser and set at 100°. After cooling to r.t., the reaction mixture was extracted with diethyl ether thoroughly. The combined extracts were washed with water, brine, dried (Na_2SO_4), and filtered. The solvents were removed and the residue was purified by flash chromatography (petroleum ether/diethyl ether 5:1) to give compound **5** (138 mg, 61%) as colorless oil, and compound **3** (51 mg, 21%) as colorless oil.

Compound 5. ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 2 × 3H, *J* = 7.1 Hz), 2.43 (s, 2 × 3H), 4.29 (q, 2 × 2H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 13.0, 13.8, 60.5, 113.6, 155.5, 163.5. Identical to that previously reported [14].

2,5-Dimethylfuran-3-carboxylic acid (6). A solution of **3** (76 mg, 0.41 mmol) in aqueous NaOH (5%, 3 mL) was refluxed for 5 h. After cooling to r.t., the solution was treated with aqueous HCl to make pH = 3. The reaction mixture was extracted with diethyl ether thoroughly. The combined extracts were washed with water, brine, dried (Na_2SO_4), and filtered. The solvents were removed to obtain compound **6** (61 mg, 96%) as white crystals, mp 131–132°; ^{1}H NMR ($CDCl_3$) δ 2.26 (s, 3H), 2.55 (s, 3H), 6.25 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.3, 14.0, 106.4, 113.5, 150.4, 159.5, 169.9. Identical to that previously reported [29].

Ethyl 2,5-dimethyl-4,5-dihydrofuran-3-carboxylate (7). A mixture of **3** (230 mg, 1.25 mmol) and 5% Pd/C (146 mg) in EtOH-H_2O (6:1, 3 mL) was vigorously stirred at r.t. at H_2 atmosphere under ordinary pressure for 4 days. The reaction mixture was extracted with diethyl ether. The combined extracts were washed with water, brine, dried (Na_2SO_4), and filtered. The solvents were removed and the residue was purified by flash chromatography (petroleum ether/diethyl ether 20:1) to get compound **7** (206 mg, 90%) as colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3H, *J* = 7.1 Hz), 1.34 (d, 3H, *J* = 6.2 Hz), 2.16 (s, 3H), 2.47 (1H, dd, *J* = 7.6, 14.0 Hz), 2.98 (dd, 1H, *J* = 11.0, 14.0 Hz), 4.14 (q, 2H, *J* = 7.1 Hz), 4.76 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.6, 22.0, 37.0, 59.5, 78.8, 101.6, 166.5, 167.7. Identical to that previously reported [30].

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Synthesis and Herbicidal Activity of 3-Aryl-1-[2-(aryloxy)propanoyl]imidazolidine-2,4-diones

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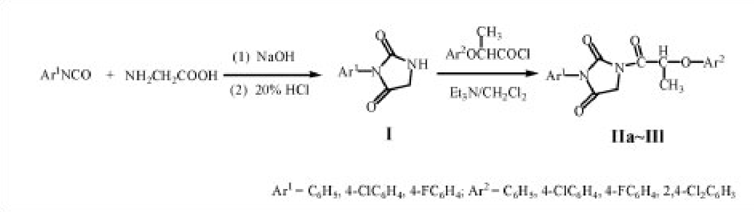

A series of novel 3-aryl-1-[2-(aryloxy)propanoyl]imidazolidine-2,4-diones were synthesized by the condensation of 3-aryl-imidazolidine-2,4-diones with 2-(aryloxy)propanoyl chlorides under mild conditions. Their structures were confirmed by IR, ^{1}H NMR, mass spectroscopy, and elemental analyses. The preliminary bioassay indicated that the target compounds **II** displayed excellent herbicidal activity against monocotyledonous (barnyard grass) and dicotyledonous (oil rape) plants.

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INTRODUCTION

Recently, imidazolidine-2,4-dione derivatives have attracted the interest of chemists because some of them exhibit wide range of pharmaceutical activity such as anti-HIV [1], microbicidal activity [2], or nonpeptide inhibitors of human heart chymase [3] as well as agrochemical activity such as herbicidal [4] and fungicidal activity [5]. In the area of modern crop protection, amide derivatives are widely used as bactericides [6] and fungicides [7]. Especially, some of the amide derivatives are found to be an inhibitor of photosystem II electron transport and used as a very important class of herbicides in the world agrochemical market, there are about 57 amide herbicides; acetochlor, metolachlor, and butachlor are the best selling amide herbicides in the world [8,9]. As a continuation of our ongoing project aimed at investigating novel biologically nitrogen-containing heterocyclic compounds [10,11], we designed and synthesized a series of novel 3-aryl-1-[2-(aryloxy)propanoyl] imidazolidine-2,4-diones, which have both imidazoline-2,4-dione and 2-(aryloxy)propanoyl moieties. Herein, we would like to report the synthesis and biological activity of the title compounds **II** (Scheme 1).

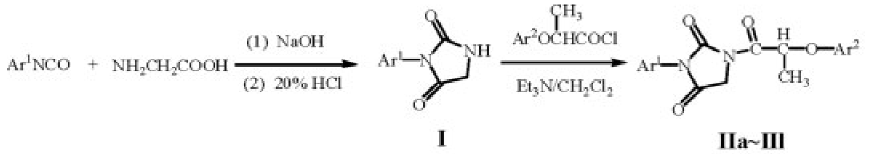
RESULTS AND DISCUSSION

3-Aryl-imidazolidine-2,4-diones (**I**) were prepared from the reaction of aromatic isocyanates with α-amino acids in a basic medium according to the reported method. Compound **I** reacted with various 2-(aryloxy)propanoyl chlorides under mild conditions to give the target compounds **II** in good yields (73–90%).

Their structures of the products were confirmed by IR, ^{1}H NMR, mass spectroscopy, and elemental analyses. The structures of compounds **II** were deduced from their spectroscopic data. In the ^{1}H NMR spectra of compounds **II**, the two methylene protons display two doublets because of their different magnetic environments with the coupling constant of 18 Hz, whereas the two methylene protons in compounds **I** appear as a singlet at δ 4.1. The IR spectra of compounds **II** showed normal stretching absorption bands indicating the existence of the C=O, Ar group, and C—O—C moiety. The EI mass spectra of compounds **II** revealed the existence of their molecular ion peaks and main fragmentation peaks, which were in accordance with the given structures of products **II**.

Herbicidal activity. The herbicidal activity values of the title compounds **II** against *Brassica campestris* (oil rape) and *Echinochloa crus-galli* (barnyard grass) has been investigated at the dosages of 100 mg/L and 10 mg/L compared with distilled water and the commercially available herbicide, 2,4-dichlorophenoxyacetic acid (2,4-D) according to the method described in the Experimental section. The preliminary results of bioassay showed that compounds **II** possessed excellent herbicidal activity. The activity data were listed in Table 1. For example, compounds **IIh** and **IIj** exhibited as good herbicidal activity as the commercially available herbicide 2,4-D. Further structure-activity relationships are under investigation.

Scheme 1. Synthetic route to compounds **II**.



$Ar^1 = C_6H_5$, 4-ClC_6H_4, 4-FC_6H_4; $Ar^2 = C_6H_5$, 4-ClC_6H_4, 4-FC_6H_4, 2,4-$Cl_2C_6H_3$

In conclusion, a series of novel 3-aryl-1-[2-(aryloxy)-propanoyl]imidazolidine-2,4-diones were synthesized by the condensation of 3-arylimidazolidine-2,4-diones with 2-[aryloxy]propanoyl chlorides under mild conditions. The preliminary bioassay indicated that the target compounds II displayed excellent herbicidal activity against monocotyledonous (barnyard grass) and dicotyledonous (oil rape) plants.

EXPERIMENTAL

Melting points were determined with a WRS-1B digital melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded with a Varian Mercury PLUS400 (400 MHz) spectrometer with TMS as the internal reference and $CDCl_3$ as the solvent, whereas mass spectra were obtained with a Finnigan TRACEMS2000 spectrometer using the EI method. IR spectra were measured by a Nicolet NEXUS470 spectrometer. Elemental analyses were performed with an Elementar Vario ELIII CHNSO elemental analyzer. All of the solvents and materials were reagent grade and purified as required. 2-(Aryloxy)propanoyl chlorides and 3-aryl-imidazolidine-2,4-diones were prepared according to the methods described in references [12] and [13–16], respectively.

Table 1

The herbicidal activity of compounds II (inhibitory rate %)

	Relative inhibition (root %/stalk %)			
	Oil rape		Barnyard grass	
Compd.	100 mg/L	10 mg/L	100 mg/L	10 mg/L
IIa	99.0/93.0	94.3/74.4	97.5/33.3	75.0/23.0
IIb	98.1/93.0	97.1/83.7	97.5/23.8	90.0/4.8
IIc	99.0/93.0	97.1/86.0	100/88.0	95.0/73.8
IId	100/95.3	99.0/86.0	97.5/83.3	95.0/78.6
IIe	99.0/95.3	98.1/86.0	97.5/64.3	97.5/31.0
IIf	99.3/95.5	97.1/86.0	97.5/65.3	92.5/38.0
IIg	99.0/93.0	98.1/88.4	100/52.4	97.5/52.4
IIh	100/97.7	99.0/81.4	97.5/78.6	97.5/64.3
IIi	100/97.7	98.1/86.0	97.5/59.5	95.0/52.4
IIj	100/95.3	98.1/83.7	100/90.5	97.5/33.3
IIk	99.0/95.3	98.1/83.7	97.5/54.8	97.5/50.0
IIl	99.0/95.3	98.1/86.0	100/95.0	97.5/61.9
2,4-D	99.0/91.5	98.2/91.2	97.5/33.5	97.5/31.2

General procedure for the preparation of 3-aryl-1-[2-(aryloxy)propanoyl]imidazolidine-2,4-diones II. To the solution of 3-aryl-imidazolidine-2,4-dione (3 mmol) and triethyl amine (6 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise the solution of 2-(aryloxy)propanoyl chloride (3 mmol) in dry CH_2Cl_2 (10 mL) while cooling in an ice-bath, after the addition, the mixture was stirred at room temperature for 3–4 h (monitored by TLC). The workup involved stripping the solvent followed by an addition of water and extraction of the product mixture into CH_2Cl_2. After phase separation, washing by aqueous sodium hydrogen carbonate, drying over anhydrous sodium sulfate, filtration and evaporation, the crude product was purified by flash column chromatography on silica gel using petroleum ether and ethyl acetate (3:1---1:1, *v*/*v*) as the eluent to give white crystals (**IIa~IIl**).

1-(2-Phenoxypropanoyl)-3-phenylimidazolidine-2,4-dione (IIa). Yield: 75%, mp 56.2–57.8°C; ^{1}H NMR ($CDCl_3$): δ 1.70 (d, J = 6.8 Hz, 3H, CH_3), 4.57 (dd, J = 18.4 Hz, 2H, CH_2N), 5.95 (q, J = 6.4 Hz, 1H, CH), 6.90–7.00 (m, 3H, Ar—H), 7.28–7.30 (m, 2H, Ar—H), 7.40–7.55 (m, 5H, Ar—H); IR: C=O 1786, 1738, 1725, Ar 1592, 1484, 1445, Ar—O—C 1040, C—Cl 756 cm^{-1}; ms: *m*/*z* 324 (M$^+$, 16), 247 (23.9), 231 (100), 122 (35.2), 121 (90.2), 105 (15.9), 93 (35.5), 77 (85.6). *Anal.* Calcd. for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.42; H, 5.13; N, 8.79.

3-(4-Fluorophenyl)-1-(2-phenoxypropanoyl)imidazolidine-2,4-dione (IIb). Yield: 73%, mp 56.8–58.2°C; ^{1}H NMR ($CDCl_3$): δ 1.71 (d, J = 6.8 Hz, 3H, CH_3), 4.47 (dd, J = 18.8 Hz, 2H, CH_2N), 5.92 (q, J = 6.8 Hz, 1H, CH); 6.90 (d, 2H, J = 7.6 Hz, Ar—H), 6.97 (q, 1H, J = 7.6 Hz, Ar—H), 7.25–7.30 (m, 2H, Ar—H), 7.37–7.42 (m, 2H, Ar—H), 7.48–7.51 (m, 2H, Ar—H); IR: C=O 1784, 1739, 1727, Ar 1587, 1489, 1425, Ar—O—C 1078, C—Cl 760 cm^{-1}; ms: *m*/*z* 344 (10.1), 342 (M$^+$, 32), 267 (40.6), 265 (100), 223 (15.5), 153 (27.2), 122 (78.1), 121 (78.1), 105 (15.9), 93 (24.9), 77 (70.2). *Anal.* Calcd. for $C_{18}H_{15}FN_2O_4$: C, 63.15; H, 4.42; N, 8.18. Found: C, 63.37; H, 4.60; N, 8.05.

3-(4-Chlorophenyl)-1-(2-phenoxypropanoyl)imidazolidine-2,4-dione (IIc). Yield: 78%, mp 66.8–68.4°C; ^{1}H NMR ($CDCl_3$): δ 1.69 (d, J = 7.2 Hz, 3H, CH_3), 4.45 (dd, J = 18.8 Hz, 2H, CH_2N), 5.93 (q, J = 6.4 Hz, 1H, CH); 6.90 (d, 2H, J = 7.6 Hz, Ar—H), 6.97 (q, 1H, J = 7.6 Hz, Ar—H), 7.17–7.29 (m, 4H, Ar—H), 7.37–7.41 (m, 2H, Ar—H); IR: C=O 1756, 1725, Ar 1578, 1494, 1482, Ar—O—C 1050, C—Cl 759 cm^{-1}; ms: *m*/*z* 360 (7.5), 358 (M$^+$, 22.5), 281 (27.7), 238 (100), 122 (65.0), 121 (88.1), 105 (12.8), 93 (38.7), 77 (65.3). *Anal.* Calcd. for $C_{18}H_{15}ClN_2O_4$: C, 60.26; H, 4.21; N, 7.81. Found: C, 60.33; H, 4.49; N, 7.92.

1-[2-(2,4-Dichlorophenoxy)propanoyl]-3-phenylimidazolidine-2,4-dione (IId). Yield: 81%, mp 52.6–54.2°C; ^{1}H NMR

($CDCl_3$): δ 1.59 (d, J = 6.8 Hz, 3H, CH_3), 4.63 (dd, J = 18.8 Hz, 2H, CH_2N), 5.86 (q, J = 6.8 Hz, 1H, CH); 6.88–7.33 (m, 8H, Ar—H); IR: C=O 1800, 1746, 1725, Ar 1585, 1488, 1440, Ar—O—C 1022, C—Cl 760 cm^{-1}; ms: m/z 394 (16.2), 393 (5.1), 392 (M^+, 25.0), 315 (100), 122 (45.4), 121 (62.6), 105 (19.5), 93 (53.8), 77 (25.2). *Anal.* Calcd. for $C_{18}H_{14}Cl_2N_2O_4$: C, 54.98; H, 3.59; N, 7.12. Found: C, 54.83; H, 3.47; N, 6.95.

1-[2-(2,4-Dichlorophenoxy)propanoyl]-3-(4-fluorophenyl)-imidazolidine-2,4-dione (IIe). Yield: 76%, mp 54.2–55.4°C; ^{1}H NMR ($CDCl_3$): δ 1.74 (d, J = 6.8 Hz, 3H, CH_3), 4.50 (dd, J =18.4 Hz, 2H, CH_2N), 5.86 (q, J = 6.8 Hz, 1H, CH); 6.85 (d, 1H, J = 8.8 Hz, Ar—H), 7.14 (d, 1H, J = 8.4 Hz, Ar—H), 7.33–7.40 (m, 3H, Ar—H), 7.48 (d, 2H, J = 8.4 Hz, Ar—H). IR: C=O 1787, 1740, 1724, Ar 1596, 1487, 1436, Ar—O—C 1076, C—Cl 748 cm^{-1}; ms: m/z 412 (5.2), 410 (M^+, 26.5), 317 (23.8), 300 (100), 111 (58.2), 95 (62.0). *Anal.* Calcd. for $C_{18}H_{13}Cl_2FN_2O_4$: C, 52.57; H, 3.19; N, 6.81. Found: C, 52.69; H, 3.33; N, 6.57.

3-(4-Chlorophenyl)-1-[2-(2,4-dichlorophenoxy)propanoyl] imidazolidine-2,4-dione (IIf). Yield: 87%, mp 54.2–55.4°C; ^{1}H NMR ($CDCl_3$): δ 1.74 (d, J = 6.8 Hz, 3H, CH_3), 4.92 (dd, J = 18.4 Hz, 2H, CH_2N), 5.84 (q, J = 6.4 Hz, 1H, CH); 6.84 (d, 1H, J = 8.0 Hz, Ar—H), 7.13 (q, 1H, J = 7.6 Hz, Ar—H), 7.19 (d, 2H, J = 8.0 Hz, Ar—H), 7.38 (d, 1H, J = 7.6 Hz, Ar—H), 7.40 (d, 2H, J = 8.0 Hz, Ar—H); IR: C=O 1803, 1740, 1728, Ar 1594, 1496, 1485, Ar—O—C 1020, C—Cl 746 cm^{-1}; ms: m/z 430 (2.9), 428 (11.2), 426 (M^+, 13.3), 268 (29.3), 267 (14.6), 265 (100), 237 (3.2), 223 (8.4), 211 (10.7), 189 (6.2), 161 (4.7), 153 (8.6), 125 (6.5), 109 (2.3), 56 (4.1). *Anal.* Calcd. for $C_{18}H_{13}Cl_3N_2O_4$: C, 50.55; H, 3.06; N, 6.55. Found: C, 50.41; H, 2.94; N, 6.34.

1-[2-(4-Chlorophenoxy)propanoyl]-3-phenylimidazolidine-2, 4-dione (IIg). Yield: 86%, mp 74.7–75.5°C; ^{1}H NMR ($CDCl_3$): δ 1.69 (d, J = 6.8 Hz, 3H, CH_3), 4.50 (dd, J = 18.4 Hz, 2H, CH_2N), 5.92 (q, J = 6.8 Hz, 1H, CH); 6.84 (d, 2H, J = 7.6 Hz, Ar—H), 7.23 (d, 2H, J = 7.6 Hz, Ar—H), 7.41–7.54 (m, 5H, Ar—H); IR: C=O 1741, 1726, Ar 1597, 1490, CH_3 1403, Ar—O—C 1046, C—Cl 762 cm^{-1}; ms: m/z 360 (4.2), 358 (M^+, 12.1), 267 (12.4), 265 (100), 237 (36.8), 209 (52.3), 105 (9.3), 93 (52.5), 77 (36.0). *Anal.* Calcd. for $C_{18}H_{15}ClN_2O_4$: C, 60.26; H, 4.21; N, 7.81. Found: C, 60.05; H, 4.14; N, 7.60.

1-[2-(4-Chlorophenoxy)propanoyl]-3-(4-fluorophenyl)imidazolidine-2,4-dione (IIh). Yield: 90%, mp 147.8–149.0°C; ^{1}H NMR ($CDCl_3$): δ 1.69 (d, J = 6.8 Hz, 3H, CH_3), 4.47 (dd, J = 18.4 Hz, 2H, CH_2N), 5.86 (q, J = 6.8 Hz, 1H, CH); 6.84 (d, 2H, J = 8.0 Hz, Ar—H), 7.20–7.24 (m, 2H, Ar—H), 7.35–7.38 (m, 2H, Ar—H), 7.47–7.50 (m, 2H, Ar—H); IR: C=O 1741, 1713, Ar 1500, 1488, CH_3 1386, C—F 1267, Ar—O—C 1090, C—Cl 821 cm^{-1}; ms: m/z 378 (2.5), 376 (M^+, 16.3), 237 (82.3), 210 (100), 139 (24.6), 112 (68.2), 96 (70.2). *Anal.* Calcd. for $C_{18}H_{14}ClFN_2O_4$: C, 57.38; H, 3.75; N, 7.44. Found: C, 57.47; H, 3.70; N, 7.61.

1-[2-(4-Chlorophenoxy)propanoyl]-3-(4-chlorophenyl)imida zolidine-2,4-dione (IIi). Yield: 83%, mp 74.7–75.5°C; ^{1}H NMR ($CDCl_3$): δ 1.69 (d, J = 6.8 Hz, 3H, CH_3), 4.46 (dd, J = 18.4 Hz, 2H, CH_2N), 5.87 (q, J = 6.8 Hz, 1H, CH); 6.82–6.86 (m, 2H, Ar—H), 7.19–7.25 (m, 4H, Ar—H), 7.37–7.41 (m, 2H, Ar—H); IR: C=O 1801, 1737, 1730, Ar 1585, 1494, 1481, Ar—O—C 1022, C—Cl 760 cm^{-1}; ms: m/z 394 (4.8), 392 (M^+, 24.1), 267 (25.1), 265 (100), 237 (65.4), 209 (38.6), 183 (4.9), 127 (58.6), 111 (24.2). *Anal.* Calcd. for $C_{18}H_{14}Cl_2N_2O_4$: C, 54.98; H, 3.59; N, 7.12. Found: C, 54.83; H, 3.71; N, 7.21.

1-[2-(4-Fluorophenoxy)propanoyl]-3-phenylimidazolidine-2, 4-dione (IIj). Yield: 85%, mp 64.2–65.5°C; ^{1}H NMR ($CDCl_3$): δ 1.67 (d, J = 6.8 Hz, 3H, CH_3), 4.47 (dd, J = 18.8 Hz, 2H, CH_2N), 5.85 (q, J = 6.4 Hz, 1H, CH); 6.85–6.98 (m, 4H, Ar—H), 7.38–7.54 (m, 5H, Ar—H); IR: C=O 1738, 1716, Ar 1599, 1504, 1436, CH_3 1402, C—F 1262, 1201, Ar—O—C 1095; ms: m/z 358 (M^+, 3.1), 267 (21.8), 265 (100), 238 (10.5), 210 (45.0), 122 (30.2), 121 (56.9), 105 (9.0), 93 (41.0), 77 (25.2). *Anal.* Calcd. for $C_{18}H_{15}FN_2O_4$: C, 63.15; H, 4.42; N, 8.18. Found: C, 63.30; H, 4.67; N, 7.95.

1-[2-(4-Fluorophenoxy)propanoyl]-3-(4-fluorophenyl)imidazolidine-2,4-dione (IIk). Yield: 82%, mp 162.2–163.8°C; ^{1}H NMR ($CDCl_3$): δ 1.68 (d, J = 6.8 Hz, 3H, CH_3), 4.50 (dd, J = 18.8 Hz, 2H, CH_2N), 5.84 (q, J = 6.8 Hz, 1H, CH); 6.86–6.89 (m, 2H, Ar—H), 6.95–6.99 (m, 2H, Ar—H), 7.38 (d, 2H, J = 8.8 Hz, Ar—H), 7.50 (d, 2H, J = 8.8 Hz, Ar—H); IR: C=O 1787, 1739, 1720, Ar 1576, 1514, 1462, Ar—O—C 1060, C—Cl 765 cm^{-1}; ms: m/z 362 (2.0), 360 (M^+, 4.3), 267 (41.7), 265 (100), 223 (10.2, 211 (13.6), 153 (8.8), 139 (21.4), 125 (4.9), 111 (9.8), 95 (10.2). *Anal.* Calcd. for $C_{18}H_{14}F_2N_2O_4$: C, 60.00; H, 3.92; N, 7.77. Found: C, 59.81; H, 3.75; N, 7.64.

3-(4-chlorophenyl)-1-[2-(4-fluorophenoxy)propanoyl]imidazolidine-2,4-dione (IIl). Yield: 82%, mp 66.8–68.4°C; ^{1}H NMR ($CDCl_3$): δ 1.67 (d, J = 6.8 Hz, 3H, CH_3), 4.48 (dd, J = 18.4 Hz, 2H, CH_2N), 5.85 (q, J = 6.8 Hz, 1H, CH); 6.86–6.99 (m, 4H, Ar—H), 7.29–7.51 (m, 4H, Ar—H); IR: C=O 1785, 1740, 1722, Ar 1586, 1494, 1463, Ar—O—C 1074, C—Cl 758 cm^{-1}; ms: m/z 379 (5.9), 378 (5.8), 376 (M^+, 28.1), 269 (4.4), 267 (40.9), 266 (62.7), 265 (100), 237 (8.2), 223 (13.6), 211 (19.4), 153 (30.4), 140 (44.7), 139 (66.5), 125 (15.7), 111 (37.3), 95 (46.9), 83 (24.3), 56 (53.2). *Anal.* Calcd. for $C_{18}H_{14}ClFN_2O_4$: C, 57.38; H, 3.75; N, 7.44. Found: C, 57.14; H, 3.83; N, 7.60.

Bioassay method. ***Herbicidal activity testing.*** Herbicidal testing of the newly synthesized compounds II was carried out in a greenhouse, with temperature 23 ± 1°C, relative humidity (RH) 60 ± 5%, light intensity 10 Klux, photoperiod 8 h/day. Twenty seeds of each weed species including oil rape and barnyard grass were chosen for testing. Seedlings were grown in the test plate of 9-cm diameter containing two pieces of filter paper and 9 mL solution of the tested compound (100 mg/L and 10 mg/L, respectively). Distilled water and 2,4-D were used as the comparison compounds. The herbicidal activity was assessed as the inhibitory rate in comparison with the distilled water. The herbicidal rating score was based on visual observation. Range from 0 to 100%, 0% means no effect and 100% means complete killing. The test was run three times, and the results were averaged and given as activity in Table 1.

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Synthesis and Antitumor Activity of Novel Pyrazolylenaminone and Bis(Pyrazolyl)ketones *via* Hydrazonoyl Halides

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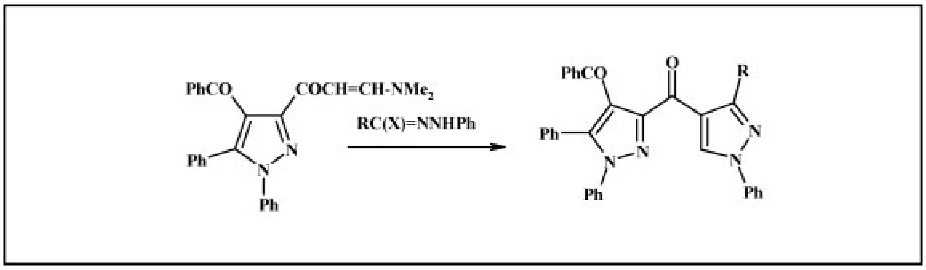

3-Acetyl-4-benzoyl-1,5-diphenylpyrazole reacts with DMF-DMA to give the novel enaminone **2**. The reaction of the latter with various hydrazonoyl halides afforded regioselectively the respective substituted (3-pyrazolyl)(4-pyrazolyl)ketones **4** in good over all yield. The preliminary screening for the antitumor activity of the synthesized compounds **2** and **4a-g** against human breast cancer cell line (MCF-7) revealed that both compounds **2** and **4b** have high-antitumor activity. SAR is discussed.

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INTRODUCTION

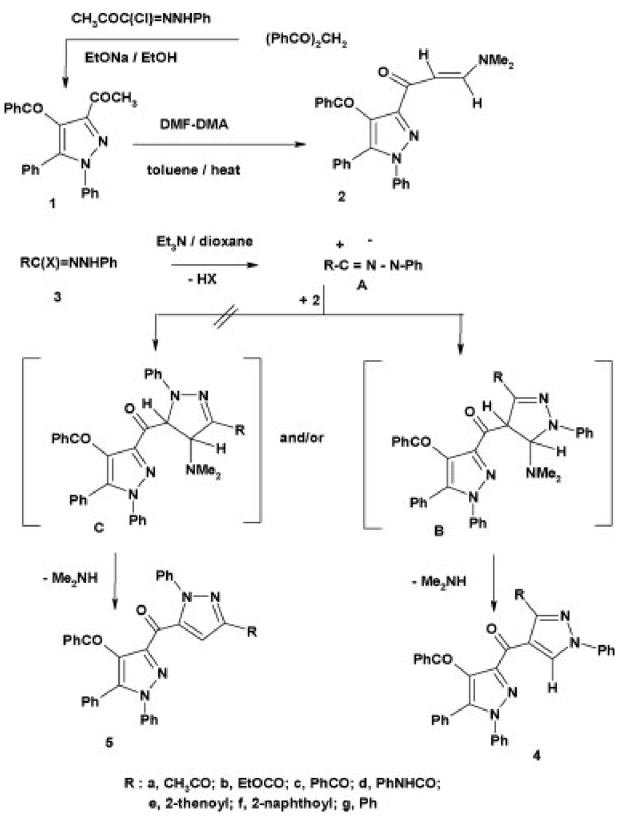
Within the past 10 years, we have been engaged on the utility of hydrazonoyl halides for synthesis of various heterocyclic systems [1–10]. Furthermore, literature cites many reports on valuable biological activity of various pyrazole derivatives [11–21]. On the basis of these facts, it was thought interesting to explore the utility of hydrazonoyl halides for synthesis of the hitherto unreported (3-pyrazolyl)(4-pyrazolyl) ketones and evaluate their antitumor activity against human breast cell line MCF-7. For this purpose, we investigated the reactions of a series of hydrazonoyl halides **3** with the hitherto unreported 3-pyrazolyl-enaminone **2** (Scheme 1). We carried out such reactions to explore also their regiochemistry as they can lead to (3-pyrazolyl)(4-pyrazolyl) ketones **4** and/or their isomers (3-pyrazolyl)(5-pyrazolyl) ketones **5** (Scheme 1).

RESULTS AND DISCUSSION

The hitherto unreported 3-acetyl-4-benzoyl-1,5-diphenylpyrazole 1 was prepared *via* reaction of *N*-phenyl 2-oxopropanehydrazonoyl chloride 3a with dibenzoylmethane in ethanol in the presence of sodium ethoxide. Its structure was confirmed by its spectra (IR, MS, ^{1}H NMR and ^{13}C NMR) and its elemental analysis (see Experimental section). For example, its IR spectrum showed two bands at υ 1692 and 1659 cm^{-1} assignable to two C=O groups. Its ^{1}H NMR (DMSO-d_6) displayed signals at δ 3.34 (s, 3H, CH_3), 7.15–7.80 (m, 15H, ArH). Reaction of compound 1 with dimethylformamide-dimethylacetal (DMF-DMA) in refluxing toluene furnished the required new enaminone 2. The IR spectrum of the latter showed two carbonyl absorption bands at 1678 and 1649 cm^{-1}. Its ^{1}H NMR spectrum revealed, in addition to the aromatic protons multiplet, two doublet signals at δ 5.84 and 7.62 with $J = 19$ Hz assignable to the two olefinic protons and two methyl protons singlet signals at δ 2.86 and 3.09. This finding indicates that this enaminone 2 exists in the indicated trans-configuration (Scheme 1).

Reaction of **2** with each of the hydrazonoyl halides **3a-g** in dioxane in the presence of triethylamine gave, in each case, one isolable product as evidenced by TLC analysis. Both mass spectra and elemental analysis data of the isolated products were consistent with either one of the two isomeric structures **4** or **5** (Scheme 1). On the basis of their ^{1}H NMR spectra, the isolated products were assigned structure **4** and the isomeric structure **5** was discarded. This is because their ^{1}H NMR spectra revealed, in each case, a singlet signal for the pyrazole ring proton in the region δ 9.20–9.33 assignable to pyrazole-5H. Literature reports [22,23] indicate that the ^{1}H NMR spectra of 5- and 4-unsubstituted pyrazoles exhibit the characteristic singlet signals of 5-CH and 4-CH

Scheme 1



protons at δ 8.35 and 7.30, respectively. Furthermore, spectral simulation by ACD/H NMR Predictor (v.6.12) for 5- and 4-unsubstituted pyrazoles showed the 5-H and 4-H signals at d 8.30 and 7.63, respectively. On the basis of such data, it is not unreasonable to conclude that the studied reactions are completely regioselective and the structure of the isolated products is **4** and not **5**. This conclusion is consistent with literature reports that indicate that reactions of hydrazonoyl halides with various enaminones are regioselective and lead to the formation of the respective 5-unsubtituted pyrazole derivatives [8].

To account for the formation of products **4**, it is suggested that the reaction starts with a regioselective 1,3-dipolar cycloaddition of the nitrilimine intermediate **A**, generated *in situ* by base-catalyzed dehydrohalogenation of the hydrazonoyl halide **3**, to the carbon–carbon double bond of the enaminone **2** to afford the nonisolable cycloadduct intrermediate **B**. The latter then undergoes *in situ* elimination of dimethylamine to yield the corresponding pyrazole derivative **4** as end product (Scheme 1).

Antitumor screening. The cytotoxic effects of the new enaminone **2** and bis(pyrazolyl) ketones **4a-g** against human breast cell line MCF-7 were evaluated at the National Institute of Cancer, Cairo, Egypt. Doxorubicin was used as a reference to evaluate the potency of the tested compounds. Five different concentrations of each compound and the reference were used in such screening tests and determination of IC_{50} values. The results are given in Table 1. As shown in Table 1, compound **2** has unpredictable antitumor activity against MCF-7 cell line as its IC_{50} value is 0.87 μg/mL which is close to that of the reference doxotrubicin (IC_{50} = 0.70). Compounds **4a-g** showed, however, less activity than that of compound **2**. This finding indicates that substitution of *N*,*N*-dimethylaminovinyl group in **2** by the 1,3-disubstituted pyrazol-4-yl moiety in **4** decreased the activity. Such a decrease might be due to the fact that the pyrazolyl group is more complex than *N*,*N*-dimethylaminovinyl group. This complexity limits penetration of compounds **4** into the cell or interferes with their metabolism or both and as a result, the antitumor activity decreases. Furthermore, a comparison of the IC_{50} values of compounds **4a-g** indicates further that their activity depends on the nature of the R group. The order of activity is: EtOCO > C_6H_5 > CH_3CO > C_6H_5NHCO > C_6H_5CO = 2-thenoyl > 2-naphthoyl.

In conclusion, a facile synthesis of each of both the novel enaminone **2** and bis(pyrazolyl)ketones **4a-g** is demonstrated. Evaluation of the antitumor activity of these new compounds revealed that compounds **2** (IC_{50} = 0.87 μg/mL) and **4b** (IC_{50} = 1.81 μg/mL) showed good inhibitory activity of human breast cancer cell (MCF-7).

Table I

In vitro cytotoxic activity of the new compounds **2** and **4a-g**.

	Surviving fraction × 10^3, conc. (μg/mL)							Surviving fraction × 10^3, conc. (μg/mL)					
No.	0.0	1.0	2.5	5.0	10.0	IC_{50}	No.	0.0	1.0	2.5	5.0	10.0	IC_{50}
2	1000	444	168	760	700	0.87	**4e**	1000	836	554	240	245	2.68
4a	1000	904	418	234	233	2.21	**4f**	1000	900	671	232	255	2.89
4b	1000	674	471	197	223	1.81	**4g**	1000	716	523	240	232	2.08
4c	1000	828	566	292	222	2.68	Dox[a]	1000	417	260	261	267	0.70
4d	1000	832	501	218	294	2.42							

[a] Doxotrobicin, an antitumor reference.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded in KBr using Pye Unicam SP-1000 Spectrophotometer. ^{1}H NMR spectra were recorded in $DCCl_3$ and DMSO-d_6 using a Varian Em-200 MHz Spectrometer, and TMS as internal reference. Mass spectra were recorded on AEI MS 30 mass spectrometer operating at 70 eV. Elemental analyses were carried out at the Microanalytical Centre of Cairo University. The hydrazonoyl halides **3** were prepared following literature procedures [24].

3-Acetyl-4-benzoyl-1,5-diphenyl-1*H*-pyrazole (1). To an ethanolic sodium ethoxide solution, prepared by dissolving sodium metal (0.12 g, 0.005 g-atom) and absolute ethanol (20 mL), was added dibenzoylmethane (1.12 g, 5 mmol). To the resulting solution *N*-phenyl 2-oxopropanehydrazonoyl chloride **3a** (5 mmol) was added to the solution portionwise while stirring the reaction mixture at room temperature. After complete addition, the reaction mixture was stirred for further 3 h during which the hydrazonoyl chloride dissolved and a new solid precipitated. The latter was filtered off, washed and crystallized from ethanol to give 3-acetyl-4-benzoyl-1,5-diphenyl-1*H*-pyrazole (**1**) as yellow crystals (yield 80%), mp 170–171°C. IR (KBr) ν 1692, 1659 (2C=O); ^{1}H NMR (DMSO-d_6): δ 3.34 (s, 3H, CH_3), 7.15–7.80 (m, 15H, ArH); ^{13}C NMR (DMSO-d_6): δ 26.3, 120.8, 125.8, 127.5, 128.4, 128.6, 128.9, 129.1, 129.3, 129.5, 133.3, 137.3, 138.5, 143.2, 148.5, 177.8, 190.9, 192.2; ms: *m*/*z* (%): 367 ($M^+ + 1$, 25), 366 (M^+, 54), 323 (20), 289 (100), 247 (20), 180 (13), 77 (64). *Anal.* Calcd. for $C_{24}H_{18}N_2O_2$ (366.42): C, 78.67; H, 4.95; N, 7.65%. Found: C, 78.37; H, 5.06; N, 7.66%.

3-[3-(*N*,*N*-Dimethylamino)acryloyl]-4-benzoyl-1,5-diphenyl-1*H*-pyrazole (2). A mixture of 3-acetyl-4-benzoyl-1,5-diphenyl-1*H*-pyrazole (**1**) (3.66 g, 10 mmol) and dimethylformamide-dimethylacetal (DMF-DMA) (2.4 g, 20 mmol) was refluxed for 5 h then left to cool. To the cold mixture was added ether. The resulting yellow solid was filtered, washed with ether, dried and finally crystallized from ethanol to afford the enaminone **2**. This compound was obtained as yellow crystals (yield 70 %), mp 190–192°C; IR (KBr) ν 1678, 1649 (2C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.86 (s, 3H, CH_3), 3.09 (s, 3H, CH_3), 5.84 (d, 1H, *J* = 19 Hz, —CO—CH=), 7.15–7.55 (m, 15H Ar—H), 7.62 (d, 1H, *J* = 19 Hz, =CH—N—); ms: *m*/*z* (%): 422 ($M^+ + 1$, 11), 421 (M^+, 12), 404 (50), 316 (80), 180 (23), 98 (78), 77 (100). *Anal.* Calcd. for $C_{27}H_{23}N_3O_2$ (421.49): C, 76.94; H, 5.50; N, 9.97%. Found: C, 76.70; H, 5.32; N, 10.14%.

(4-Benzoyl-1,5-diphenyl-pyrazol-3-yl)-(1-phenyl-3-substituted-pyrazol-4-yl)ketones (4a-g): General procedure. To a stirred solution of the appropriate hydrazonoyl halide **3** (1 mmol) and the enaminone **2** (0.42 g, 1 mmol) in dry dioxane (50 mL), was added triethylamine (0.5 mL) and the mixture was refluxed for 12 h. The precipitated triethylamine hydrochloride was filtered off, and the filtrate was evaporated under reduced pressure. The residue was triturated with ethanol. The solid product so formed was filtrated, washed with water, and dried. Crystallization from ethanol afforded the corresponding pyrazole derivatives **4**. The physical constants of the products 4a-g are listed in the subsequent sections.

(4-Benzoyl-1,5-diphenyl-pyrazol-3-yl)-(1-phenyl-3-acetyl-pyrazol-4-yl)ketone (4a). This compound was obtained as pale yellow crystals (yield 75%), mp 150–152°C; IR (KBr) ν 1693, 1655, 1620 (3C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.57 (s, 3H, CH_3), 7.24–7.93 (m, 20H, Ar—H), 9.15 (s, 1H, pyrazole); ms: *m*/*z* (%) 537 ($M^+ + 1$, 25), 536 (M^+, 38), 493 (23), 417 (29), 180 (17), 105 (100). *Anal.* Calcd. for $C_{34}H_{24}N_4O_3$ (536.58): C, 76.11; H, 4.51; N, 10.44%. Found: C, 76.41; H, 4.85; N, 10.77%.

(4-Benzoyl-1,5-diphenyl-pyrazol-3-yl)-(1-phenyl-3-ethoxycarbonyl-pyrazol-4-yl)ketone (4b). This compound was obtained as pale orange crystals (yield 68%), mp 105–107°C; IR (KBr) ν 1725, 1663, 1615 (3C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.18 (t, 3H, *J* = 7.5 Hz, CH_3), 4.14 (q, 2H, *J* = 7.5 Hz, CH_2), 7.21–7.90 (m, 20H, Ar—H), 9.2 (s, 1H, pyrazole); ms: *m*/*z* (%) 567 ($M^+ + 1$, 32), 566 (M^+, 74), 493 (82), 417 (74), 316 (42), 260 (42), 215 (22), 180 (25), 77 (100). *Anal.* Calcd. for $C_{35}H_{26}N_4O_4$ (566.61): C, 74.19; H, 4.63; N, 9.89%. Found: C, 73.98; H, 4.78; N, 10.11%.

(4-Benzoyl-1,5-diphenyl-pyrazol-3-yl)-(1-phenyl-3-benzoyl-pyrazol-4-yl)ketone (4c). This compound was obtained as pale brown crystals (yield 70%), mp 110–112°C; IR (KBr) ν 1690, 1663, 1620 (3C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.1–7.97 (m, 25H, Ar—H), 9.33 (s, 1H, pyrazole); ms: *m*/*z* (%) 599 ($M^+ + 1$, 21), 598 (M^+, 34), 493 (62), 404 (74), 351 (24), 316 (72), 105 (100). *Anal.* Calcd. for $C_{39}H_{26}N_4O_3$ (598.65): C, 78.25; H, 4.38; N, 9.36%. Found: C, 78.46; H, 4.20; N, 9.55%.

(4-Benzoyl-1,5-diphenyl-pyrazol-3-yl)-(1-phenyl-3-phenylaminocarbonyl-pyrazol-4-yl)ketone (4d). This compound was obtained as yellow crystals (yield 66%), mp 120–122°C; IR (KBr) ν 3236 (NH), 1699, 1664, 1618 (3C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.19–8.00 (m, 25H, Ar—H), 9.25 (s, 1H, pyrazole), 10.8 (s, 1H, NH, D_2O-exchangeable); ms: *m*/*z* (%) 614 ($M^+ + 1$, 10), 613 (M^+, 37), 521 (46), 260 (8), 222 (9), 180 (10), 105 (100). *Anal.* Calcd. for $C_{39}H_{27}N_5O_3$ (613.66): C, 76.33; H, 4.43; N, 11.41%. Found: C, 76.16; H, 4.58; N, 11.27%.

(4-Benzoyl-1,5-diphenyl-pyrazol-3-yl)-(1-phenyl-3-thenoyl-pyrazol-4-yl)ketone (4e). This compound was obtained as white buff solid (yield 65%), mp 118–120°C; IR (KBr) ν 1694, 1658, 1615 (3C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ, 7.15–8.14 (m, 23H, Ar—H, Het-H), 9.29 (s, 1H, pyrazole); ms: *m*/*z* (%) 605 ($M^+ + 1$, 15), 604 (M^+, 32), 499 (54), 281 (13), 111 (100), 77 (12.5). *Anal.* Calcd. for $C_{37}H_{24}N_4O_3S$ (604.68): C, 73.49; H, 4.00; N, 9.27; S, 5.30%. Found: C, 73.67; H, 3.86; N, 9.10; S, 5.18%.

(4-Benzoyl-1,5-diphenyl-pyrazol-3-yl)-(1-phenyl-3-(2-naphthoyl)-pyrazol-4-yl)ketone (4f). This compound was obtained as white buff crystals (yield 68%), mp 100–102°C; IR (KBr) ν 1688, 1662, 1616 (3C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.01–8.18 (m, 27H, Ar—H), 9.30 (s, 1H, pyrazole); ms: *m*/*z* (%) 649 ($M^+ + 1$, 71), 648 (M^+, 81), 544 (71), 494 (31), 127 (100). *Anal.* Calcd. for $C_{43}H_{28}N_4O_3$ (648.71): C, 79.61; H, 4.35; N, 8.64%. Found: C, 79.47; H, 4.50; N, 8.40%.

(4-Benzoyl-1,5-diphenyl-pyrazol-3-yl)-(1,3-diphenyl-py-razol-4-yl)ketone (4g). This compound was obtained as pale yellow crystals (yield 72%), mp 130–132°C; IR (KBr) ν 1668, 1647 (2C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.16–7.74 (m, 25H, Ar—H), 9.23 (s, 1H, pyrazole); ms: *m*/*z* (%) 571 ($M^+ + 1$, 49), 570 (M^+, 100), 405 (93), 317 (51), 247 (42), 84 (38). *Anal.* Calcd. for $C_{38}H_{26}N_4O_2$ (570.64): C, 79.98; H, 4.59; N, 9.82%. Found: C, 80.14; H, 4.79; N, 9.68%.

Pharmacology. ***Cytotoxic activity against human breast cancer (MCF-7) in vitro.*** The method applied is similar to that reported by Skehan and Storeng [25] using Sulfo-Rhodamine-B stain (SRB). Cells were plated in 96-multiwill plate (10^4 cells/well) for 24 h before treatment with the test compound to allow attachment of cell to the wall of the plate, different concentration of the compound under test (0, 1.0, 2.5, 5, and 10 μg/mL) were added to the cell monolayer in triplicate wells individual dose, monolayer cells were incubated with the compounds for 48 h at 37°C and in atmosphere of 5% CO_2. After 48 h, cells were fixed, washed and stained with SRB stain, excess stain was washed with acetic acid and attached stain was recovered with tris-EDTA buffer, color intensity was measured in an ELISA reader, the relation between surviving fraction and drug concentration is plotted to get the survival curve of tumor cell line and the IC_{50} was calculated. The results are summarized in Table 1.

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Ring-Expansion of 5-Methylene-thiazolidine-2-thione with Hydrazine

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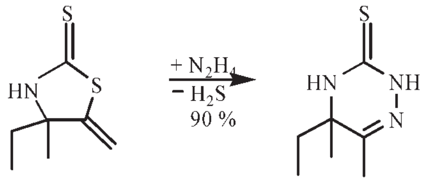

The treatment of 5-methylene-thiazolidine-2-thione with hydrazine hydrate in boiling dioxane leads in a novel type of ring-expansion reaction to 6-methyl-1,2,4-triazine-3-thione.

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INTRODUCTION

Heterocycles represent the class of compounds that contains the majority of biologically or pharmacologically active substances. A vast number of 1,2,4-triazines [1,2] with antifungal, herbicidal, antibacterial, and tubercolo-static activities have been described. Even on 4,5-dihydro-2*H*-1,2,4-triazine-3-thiones, the Crossfire data bank registers presently more than 900 hits. We present here a new synthetic approach to this ring system.

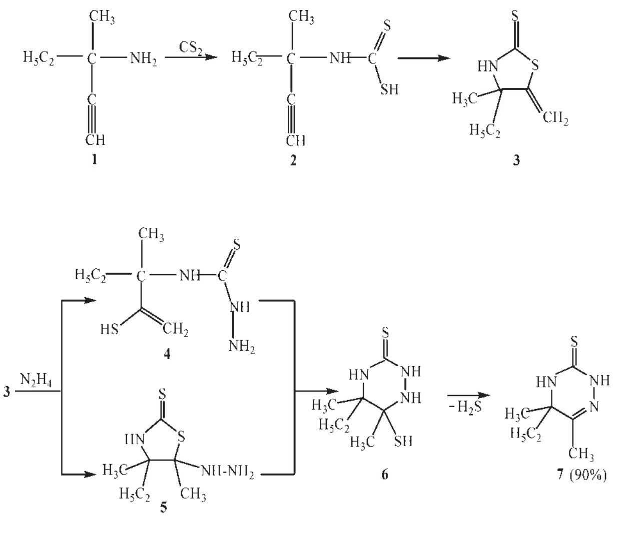
RESULTS AND DISCUSSION

Hennion and Teach [3] published an elegant synthesis of 5-methylene-thiazolidine-2-thiones **3** by the reaction of propargylamines and CS_2 (Scheme 1). The process can be applied to many amines **1** with different substituents [3–8]. We found now that **3** reacts with hydrazine hydrate in ethanol under elimination of H_2S.

Among the variety of conceivable products, we verified the 4,5-dihydro-2*H*-1,2,4-triazine-3-thione structure **7** by one- and two-dimensional NMR studies [HMQC, HMBC]. The (^{1}H,^{15}N) HMBC technique, shown in Figure 1, was the most important tool for the structure determination. Figure 1 depicts the crosspeaks of all expected $^nJ(^1H,^{15}N)$ couplings for $n = 1, 2, 3$. Direct, geminal, and vicinal couplings were observed for 2-H to N-2, N-1, and N-4, respectively. Both diastereotopic methylene protons of the ethyl group on C-5 and the protons of the methyl group on C-5 give vicinal couplings to N-4. The proton on N-4 shows the direct coupling (^1J) to N-4 and a vicinal coupling (^3J) to N-2. Finally, the methyl protons of 6-CH_3 give a ^3J coupling to the sp^2 nitrogen atom N-1. The correlation of the ^{1}H, ^{13}C, and ^{15}N chemical shifts to certain nuclei is presented in Figure 2.

Two possible mechanistic routes for the ring-expansion **3**→**7** are illustrated in Scheme 1. Compound **3** contains C-2 and C-5 as electrophilic centers for the attack of N_2H_4 as nucleophile. The concomitant ring opening to **4**, which represents the hydrazine adduct of an

Scheme 1



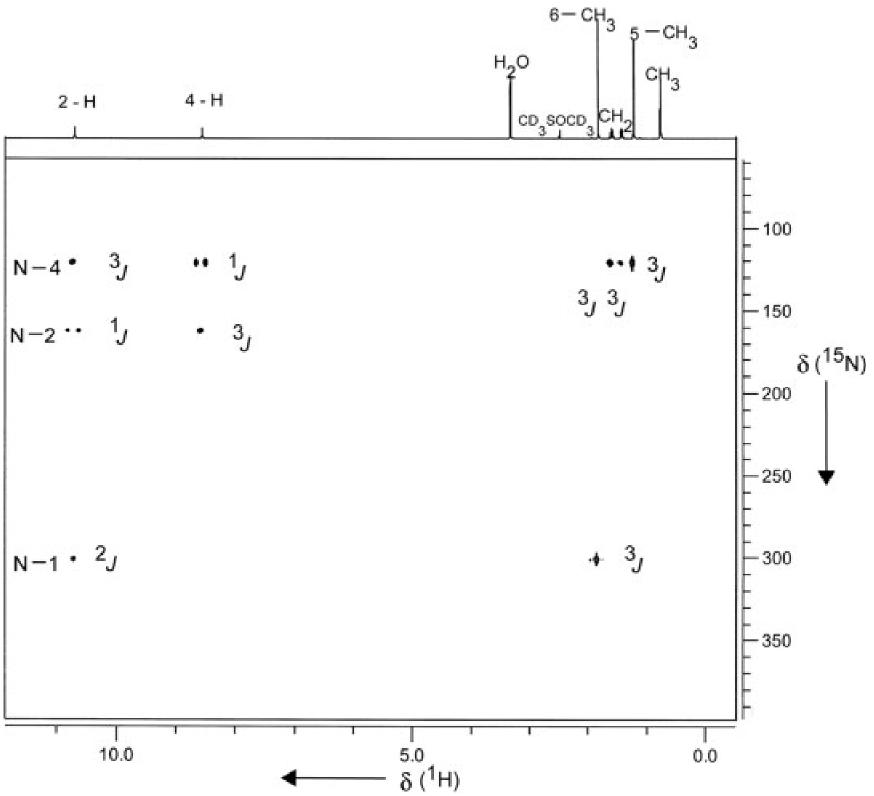


Figure 1. (^1H, ^{15}N) HMBC Spectrum of **7** in CD_3SOCD_3.

isothiocyanate, can be followed by a cyclization to the 1,2,4-triazine derivative **6**. The thiosemicarbazid moiety adds thereby to the polar CC double bond of the ene-thiol function. However, a comparably polar CC double bond is already present in **3**, so that **3**→**5** can be the initial step as well. Ring expansion to **6** and elimination of H_2S (**6**→**7**) can terminate the almost quantitative process **3**→**7**.

We are attempting to apply this ring enlargement reaction in order to generate novel mono- and bicyclic 1,2,4-triazine systems with biological or pharmacological activity [9].

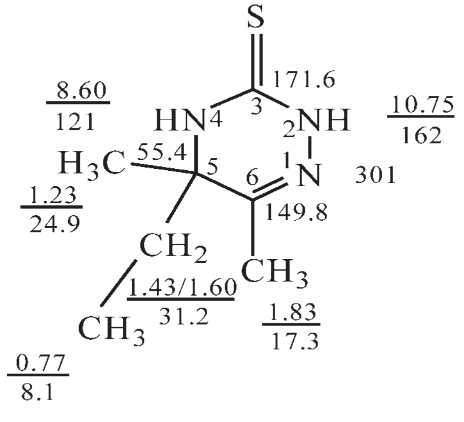


Figure 2. ^1H, ^{13}C, and ^{15}N chemical shifts of **7** in CD_3SOCD_3 [δ (^1H) and δ (^{13}C) values related to TMS as internal standard, δ (^{15}N) values related to NH_3, H_3CNO_2 as external standard]. Because of the chiral center C-5, the CH_2—CH_3 group gives rise to a ABM_3 spin pattern with multiplets at 1.43 and 1.60 ppm for the CH_2 protons and a triplet at 0.77 ppm for the CH_3 protons.

EXPERIMENTAL

Melting points were measured with a Büchi melting point apparatus. NMR spectra were obtained on Bruker AMX 400 and Avance 600 spectrometers. Mass spectra were recorded on a Finnigan MS 95 (field desorption technique) and a Micromass Q-TOF-ULTIMA API (electrospray technique) spectrometer.

5-Ethyl-5,6-dimethyl-4,5-dihydro-2*H*-[1,2,4]triazine-3-thione (7). To 1.73 g (10.0 mmol) 4-ethyl-4-methyl-5-methylene-thiazolidine-2-thione (**3**) [3] in 10 mL dioxane, 20 mL (2.0 g, 40.0 mmol) hydrazine hydrate (65%) were slowly added within 30 min. The vigorously stirred solution was refluxed for 6 h, cooled to 0°C and diluted with 20 mL crushed ice. The formed precipitate was collected by filtration, washed with water, dried, and recrystallized from ethanol. Yield: 1.54 g (90%), mp: 182°C. FD MS: m/z (%) = 171 (100) [M^+]; ESI HRMS m/z: 172.0910 [$M+H^+$], calcd. 172.0908. Anal. Calcd. for $C_7H_{13}N_3S$ (171.3): C, 49.09; H, 7.65; N, 24.54. Found: C, 48.88; H, 7.94; N, 24.39.

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[9] First results showed that the ring-expansion can be realized with 5-methylene-thiazolidine-2-thiones with various substituents in 3- and 4-positon.

Stereoselective Synthesis and Biological Activities of Diethyl (*E*)-{[4-Cyano-5-[[(disubstitutedamino)methylene]amino]-3-(methylthio)-1*H*-pyrazol-1-yl]substituited phenylmethyl}phosphonates

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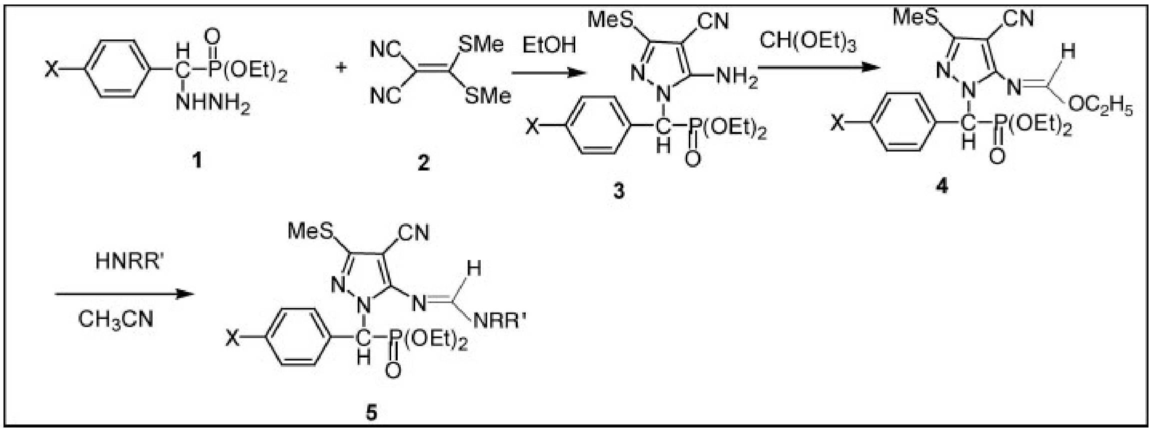

Diethyl {[5-amino-4-cyano-3-(methylthio)-1*H*-pyrazol-1-yl]substitutedphenylmethyl}phosphonates **3** were efficiently synthesized *via* the condensation of [(1-hydrazino)substitutedphenylmethyl]phosphonates **1** with 2-[bis(methylthio)methylene]malononitrile **2**. **3** reacted with triethyl orthoformate to afford diethyl (*E*)-{[4-cyano-5-[(ethoxymethylene)amino]-3-(methylthio)-1*H*-pyrazol-1-yl]substitutedphenylmethyl}phosphonates **4**, which reacted with various secondary amines at room temperature to provide the target compounds **5** in good yields. Their structures were confirmed by ir, ^{1}H and ^{31}P NMR, mass spectroscopy, and elemental analyses. The results of preliminary bioassay indicated that compounds **5** possess potent herbicidal activity against the roots of dicotyledonous (oil rape) plants at the dosage of 100 mg/L, and compounds **5c** and **5g** exhibit 80.8% and 76.7% inhibitory activity against *Colletotrichum gossypi* at the concentration of 50 mg/L, respectively. Abstract end data:

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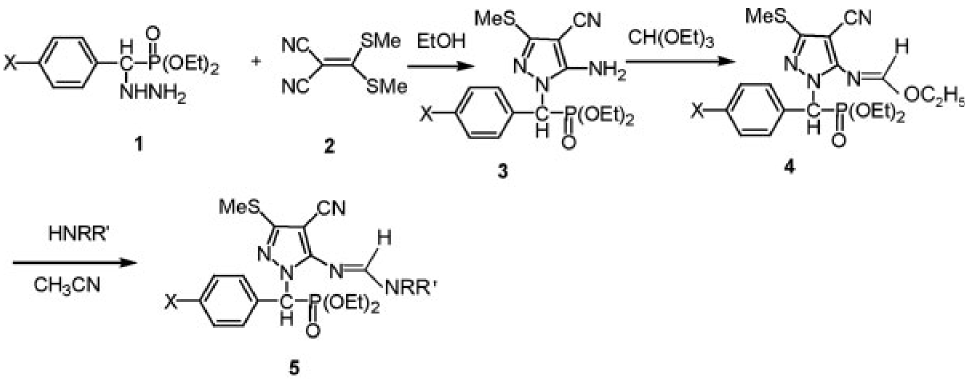
INTRODUCTION

In recent years, 1-aminoalkyl phosphonate analogs, as the phosphorus analogs of natural amino acids are of increasing interest in medicinal chemistry and pesticide science [1,2] because of their wide biological activities such as enzyme inhibitors [3], antibiotics [4], and haptens of catalytic antibodies [5], antifungal agents, herbicides, plant growth regulators, and plant virucides [6]. Recently, pyrazole compounds play an important role in pesticide science, and some pyrazole derivatives have been developed as herbicides [7,8], insecticides (such as Regent and MK-239) [9,10], and fungicides (Furametpyr, Pyraclostrobin) [11]; to the best of our knowledge, some pyrazole derivatives containing phosphorus have shown good biological activities, for example, pyraclofos and flupyrazofos have been developed as good insecticides [12,13]. As a continuation of our search for new biologically active organic phosphorus heterocyclic compounds, we designed and synthesized a series of novel title compounds.

RESULTS AND DISCUSSION

The versatile intermediates, [(1-hydrazino)substitutedphenylmethyl]phosphonates **1** have been reported by several methods [14]. We synthesized it by a modified procedure of Yuan's report [14a]. For converting substituted benzaldehydes to [(1-hydroxy)substitutedphenylmethyl]-phosphonates, an excess of solid catalyst (potassium fluoride, four times) caused difficulty in stirring and incomplete reactivity. Instead, we used one molecular catalyst triethylamine in methylene chloride to avoid these shortcomings and obtained [(1-hydroxy)substitutedphenylmethyl]phosphonates in better yields. Compounds **1** can be obtained in moderate yields by the reaction of diethyl [(1-hydroxy)substitutedphenylmethyl]phosphonates with mesyl

Scheme 1. Synthetic route to compounds **5**.



1a, **3a**, **4a**: X = H; **1b**, **3b**, **4b**: X = F; **5a**: X = H, NRR' = diethylamino; **5b**: X = H, NRR' = piperidin-1-yl; **5c**: X = F, NRR' = diethylamino; **5d**: X = F, NRR' = dipropylamino; **5e**: X = F, NRR' = dibutylamino; **5f**: X = F, NRR' = piperidin-1-yl; **5g**: X = F, NRR' = morpholin-3-yl

chloride, followed by the nucleophilic substitution with hydrazine in a one-pot reaction. Cyclization of compounds **1** with 2-[bis(methylthio)methylene]malononitrile **2** in a mild condition gave diethyl {[5-amino-4-cyano-3-(methylthio) -1*H*-pyrazol-1-yl]substitutedphenylmethyl}phosphonates **3**, which could easily convert to the corresponding imidates **4** in excess triethyl orthoformate. Compounds **4** reacted with various secondary amines such as diethylamine, piperidine, diisopropylamine, dibutylamine, and morpholine to yield the corresponding target compounds **5a**–**5g** conveniently at room temperature (Scheme 1).

The structures of compounds **5a**–**5g** were deduced from their spectral data (ir, ^{1}H and ^{31}P NMR), ms, and elemental analyses. In the ^{1}H NMR spectra of compounds **5**, the methylthio protons display as a singlet at δ 2.6; the CH proton linking with the phosphonyl group appears as a doublet due to coupling with P atom with the coupling constant of 23 Hz, whereas the N=CH proton in compounds **5** appears as a singlet at δ 8.3. The ir spectra of compounds **5** showed normal stretching absorption bands indicating the existence of the CN, Ar group, P=O, and P—O—C moieties. The EI mass spectra of compounds **5** revealed the existence of their molecular ion peaks and main fragmentation peaks. Because of the existence of a C=N bond, it probably existed in *E* and *Z* isomers in compound **4a**–**4b** and target molecules **5a**–**5g**. In ^{1}H NMR spectra, the N=CH proton in compounds **4** and **5** appears as a singlet at δ 8.4 and 8.3, respectively. Due to probably intramolecular hydrogen bonding between the hydrogen of N=CH— moiety with the nitrogen of the CN group and thermodynamic stable isomer, we deduced the stereoconfigurations in compounds **4** and **5** are all in E-configuration, which was also consisted with the configuration of substituted formamides [15] and that of its C=N analog, which was confirmed by single crystal X-ray diffraction [16].

Herbicidal activity. The herbicidal activity of title compounds **5** against *Brassica campestris* L (oil rape) and *Echinochloa crusgalli* (barnyard grass) has been investigated at the dosages of 100 mg/L and 10 mg/L compared with distilled water and the commercially available herbicide, 2,4-dichlorophenoxy acetic acid (**2,4-D**) according to the method described in the experimental section. The preliminary results of bioassay showed that some of compounds **5** possess potent and selective herbicidal activities against dicotyledonous weeds such as oil rape at the dosage of 100 mg/L. For example, compounds **5b**, **5f**, and **5g** exhibit 84.4%, 91.4%, and 96.0% inhibitory activity against the root of rape, respectively. It is also found that compounds **5** exhibit a stronger inhibitory effect against the root of rape than the stem (Table 1). Moreover, the herbicidal activity decreases with the decrease of the dosage of compounds **5**. The QSAR studies of **5** are under investigation.

Fungicidal activities. The preliminary fungicidal activity of the target compounds **5** were evaluated by the classic plate method at a concentration of 50 mg/L. The six fungi used as follows, *Fusarium oxysporium*, *Rhizoctonia solani*, *Botrytis cinereapers*, *Gibberella zeae*, *Dothiorella gregaria*, and *Colletotrichum gossypi*, belong to the group of field fungi and were isolated from corresponding crops. The activity data were also listed in Table 1. The results indicated that most of compounds **5** exhibit moderate to weak inhibitory activities against the above six fungi. For example, compounds **5c** and **5g** exhibit 80.8% and 76.7% inhibitory activity against *Colletotrichum gossypi*, respectively.

In conclusion, we developed an efficient synthesis of diethyl (*E*)-{[4-cyano-5-[[(disubstitutedamino)methylene]amino]-3-(methylthio)-1*H*-pyrazol-1-yl] substituitedphenylmethyl}phosphonates *via* a multistep reaction.

The preliminary bioassays showed that these compounds possess potent herbicidal activity against the roots of dicotyledonous (oil rape) plants at the dosage of 100 mg/L, and some of them displayed moderate fungicidal activity at the concentration of 50 mg/L.

EXPERIMENTAL

Melting points were determined with a WRS-1B digital melting point apparatus and were uncorrected. ^{1}H and ^{31}P NMR spectra were recorded on a Varian MERCURY-PLUS400 (400 MHz) spectrometer with deuteriochloroform as the solvent and TMS and 85% phosphoric acid as the internal and external references, respectively. Mass spectra were obtained with a Finnigan TRACEMS2000 spectrometer using the EI method; IR spectra were measured by a Nicolet NEXUS470 spectrometer; Elemental analyses were performed with an Elementar Vario ELIII CHNSO elementary analyzer. All of the solvents and materials were reagent grade and purified as required. [(1-Hydrazino)substitutedphenylmethyl]-phosphonates **1** [14a], 2-[bis(methylthio)methylene]malononitrile **2** [17] were prepared according to the literature procedures.

General procedure for the preparation of compounds 1. A mixture of substituted benzaldehyde (0.1 moles), diethyl phosphite (13.8 g, 0.1 moles), and triethylamine (5.1 g, 0.05 moles) was heated at 75°C for 0.5 h until the reaction completed (monitored by tlc). After cooling, mesyl chloride (12.5 g, 0.11 moles) in anhydrous methylene chloride (100 mL) was added dropwise at 0°C. After the addition completed, the mixture was stirred at room temperature for 2 h. The solid was removed by filtration, the filtrate was washed by distilled water (30 mL × 3), dried over anhydrous sodium sulphate, and then concentrated *in vacuo* to give [(1-mesyl oxy)-substitutedphenylmethyl]phosphonate as a light yellow liquid, yield: 87–91%, which can be used without further purification.

To the mixture of [(1-mesyl oxy)substitutedphenylmethyl]-phosphonate (0.1 moles) in ethanol (40 mL) was added drop wise 85% hydrazine (26.4 g, 0.4 moles) at 0°C, after the addition finished, the mixture was stirred for 6–8 h at 45–50°C. The workup involved stripping of the solvent followed by an addition of water (100 mL) and extraction of the product into anhydrous ethyl ether (50 mL × 3), after phase separation, drying over anhydrous sodium sulphate, filtration and evaporation, a crude product 1 was yielded as a yellow liquid, yield 40–45%, which can be used without further purification.

General procedure for the preparation of compounds 3. A mixture of 1 (24.3 mmoles), 2 (3.89 g, 22.9 mmoles), and anhydous ethanol (30 mL) was refluxed for 5 h [18]. After cooling, the reaction mixture was concentrated *in vacuo* and recrystallized from ethyl acetate and petroleum ether (1;1, *v*/*v*) to give white crystals.

3a: yield: 64%, mp 161–163°C; ^{1}H NMR: δ 1.19–1.27 (m, 6H, 2CH$_3$), 2.53 (s, 3H, SCH$_3$), 4.01–4.16 (m, 4H, 2CH$_2$), 5.54 (s, 2H, NH$_2$), 5.75 (d, *J* = 24 Hz, 1H, PCH), 7.27–7.52 ppm (m, 5H, Ar—H); ir: NH$_2$ 3358, Ar—H 2995, CN 2215, P=O 1265, P—O—C 1048, P—C 978 cm^{-1}; ms: *m*/*z* 380 (M$^+$, 65), 333 (16), 227 (48), 153 (100); Anal. Calcd for $C_{16}H_{21}N_4O_3PS$: C, 50.52; H, 5.56; N, 14.73. Found: C, 50.69; H, 5.48; N, 14.89.

3b: yield: 71%, mp158–159°C. ^{1}H NMR: δ 1.19–1.27 (m, 6H, 2CH$_3$), 2.53 (s, 3H, SCH$_3$), 4.01–4.16 (m, 4H, 2CH$_2$), 5.56 (s, 2H, NH$_2$), 5.72 (d, *J* = 24 Hz, 1H, PCH), 7.28–7.50 ppm (m, 4H, Ar—H); ir: NH$_2$ 3342, Ar—H 2992, CN 2210, P=O 1256, P—O—C 1045, P—C 975 cm^{-1}; ms: *m*/*z* 398 (M$^+$, 81), 261 (50), 109 (100); Anal. Calcd for $C_{16}H_{20}FN_4O_3PS$: C, 48.24; H, 5.06; N, 14.06. Found: C, 48.39; H, 4.81; N, 14.14.

General procedure for the preparation of compounds 4. 3 (6 mmoles) was dissolved in triethyl orthoformate (4 mL), and the mixture was refluxed for 2 h. After cooling, the solvent was removed under a reduced pressure, and the residue was purified on silica gel (ethyl acetate-light petroleum ether, 1:5, *v*/*v*) to afford 4 as a white solid.

4a. yield: 95%, mp 64–66°C. ^{1}H NMR: δ 1.18–1.27 (m, 6H, 2CH$_3$), 1.40 (t, *J* = 7 Hz, 3H, CH$_3$), 2.62 (s, 3H, SCH$_3$), 4.01–4.20 (m, 4H, 2CH$_2$), 4.39 (t, *J* = 6.6 Hz, 2H, CH$_2$), 5.90 (d, *J* = 22.8 Hz, 1H, PCH), 7.33–7.55 (m, 5H, Ar—H), 8.39 ppm (s, 1H, N=CH); ir: Ar—H 2976, CN 2222, C=N— 1608, P=O 1266, P—O—C 1058, P—C 969 cm^{-1}; ms: *m*/*z* 436 (M$^+$, 65), 391 (79), 389 (52), 109 (100); Anal. Calcd for $C_{19}H_{25}N_4O_4PS$: C, 52.28; H, 5.77; N, 12.84. Found: C, 52.41; H, 5.54; N, 12.72.

4b. yield: 89%, mp 77–78°C. ^{1}H NMR: δ 1.19–1.31 (m, 6H, 2CH$_3$), 1.42 (t, *J* = 7.2 Hz, 3H, CH$_3$), 2.61 (s, 3H, SCH$_3$), 4.02–4.05 (m, 2H, CH$_2$), 4.14–4.18 (m, 2H, CH$_2$), 4.38–4.41 (m, 2H, CH$_2$), 5.87 (d, *J* = 22.4 Hz, 1H, PCH), 7.04 (dd, *J* = 8.4 Hz, *J* = 8.4 Hz, 2H, Ar—H), 7.54 (dd, *J* = 5.2 Hz, *J* = 8.4 Hz, 2H, Ar—H), 8.41 ppm (s, 1H, N=CH); ir: Ar—H 2972, CN 2210, C=N— 1616, P=O 1248, P—O—C 1042, P—C 970 cm^{-1}; ms: *m*/*z* 456 (16), 454 (M$^+$, 45), 411 (36), 409 (57), 109 (100); Anal. Calcd for $C_{19}H_{24}FN_4O_4PS$: C 50.21, H 5.32, N 12.33; found C 50.03, H 5.15, N 12.18.

General procedure for the preparation of compounds 5. A solution of 4 (1 mmole) and secondary amine (1.5 mmoles) in anhydrous acetonitrile (15 mL) was stirred at room temperature for 0.5–1 h (monitorede by tlc). After the reaction was complete, the solvent was removed under reduced pressure, and the residue was purified on silica gel (petroleum ether and acetone, 4:1, *v*/*v*) to yield the corresponding target compounds 5a–5g.

5a. Colorless oil, yield: 75%; ^{1}H NMR: δ 1.18–1.29 (m, 12H, 4CH$_3$), 2.62 (s, 3H, SCH$_3$), 3.32 (q, *J* = 6.8 Hz, 2H, NCH$_2$), 3.34–3.48 (m, 1H, NCH$_2$), 3.56–3.61 (m, 1H, NCH$_2$), 3.99–4.06 (m, 2H, OCH$_2$), 4.16–4.21 (m, 2H, OCH$_2$), 6.06 (d, *J* = 23 Hz, 1H, PCH), 7.27–7.32 (m, 3H, Ar—H), 7.54 (d, 2H, *J* = 6.4 Hz, Ar—H), 8.26 ppm (s, 1H, N=CH); ^{31}P NMR (162 MHz): δ 16.79 ppm; ir: Ar—H 2974, CN 2214, C=N— 1617, P=O 1260, P—O—C 1026, P—C 976 cm^{-1}; ms: *m*/*z* 463 (M$^+$, 35), 326 (100), 279 (18); Anal. Calcd for $C_{21}H_{30}N_5O_3PS$: C, 54.41; H, 6.52; N, 15.11. Found: C, 55.14; H, 6.67; N, 14.98.

5b. Colorless crystals, yield: 95%; mp 87.9–89.6°C; ^{1}H NMR: δ 1.17–1.26 (m, 6H, 2CH$_3$), 1.62–1.71 (m, 6H, CH$_2$CH$_2$CH$_2$), 2.62 (s, 3H, SCH$_3$), 3.37 (t, *J* = 5.2 Hz, 2H, NCH$_2$), 3.64 (t, *J* = 5.2 Hz, 2H, NCH$_2$), 3.98–4.04 (m, 2H, OCH$_2$), 4.14–4.21 (m, 2H, OCH$_2$), 6.07 (d, *J* = 23.2 Hz, 1H, PCH), 7.29–7.35 (m, 3H, Ar—H), 7.56 (d, *J* = 7.6 Hz, 2H, Ar—H), 8.23 ppm (s, 1H, N=CH); ^{31}P NMR (162 MHz): δ 16.98 ppm; ir: Ar—H 2985, CN 2212, C=N— 1618, P=O

Table 1

The herbicidal and fungicidal activities of compounds **5** (inhibitory rate %).

	Herbicidal activity				Fungicidal activity (50 mg/L)					
	Oil rape (root/stem)		Barnyard (root/stem)							
Compd.	100 (mg/L)	10 (mg/L)	100 (mg/L)	10 (mg/L)	*Fusarium oxysporium*	*Rhizoctonia solani*	*Botrytis cinereapers*	*Gibberella zeae*	*Dothiorella gregaria*	*Colletotrichum gossypii*
5a	67.0/60.0	40.7/44.4	56.8/65.6	32.4/15.6	42.9	60.0	33.3	42.9	41.4	50.0
5b	84.4/60.0	33.7/38.9	59.5/37.5	45.9/28.1	42.9	33.3	37.0	63.6	44.8	68.3
5c	74.0/71.1	37.2/50.0	73.0/46.9	48.6/43.7	67.1	63.3	37.0	70.7	65.2	80.8
5d	78.6/60.0	27.9/38.9	27.0/12.5	21.6/3.1	43.3	48.3	25.9	46.4	44.8	60.0
5e	76.3/65.5	16.3/22.2	43.2/25.0	37.8/18.7	19.1	31.7	0.0	17.9	31.0	41.7
5f	91.4/54.4	43.0/33.3	81.1/50.0	43.2/28.1	33.8	36.7	14.8	60.0	44.8	76.7
5g	96.0/65.6	41.9/33.3	75.7/62.5	37.8/21.9	23.8	0.0	18.5	7.1	10.3	33.3
2,4-D	99.0/91.5	98.2/91.2	97.5/33.5	97.5/31.2						

1261, P—O—C 1046, P—C 976 cm^{-1}; ms: *m*/*z* 475 (M$^+$, 26), 428 (10.8), 338 (74), 248 (100); Anal. Calcd for $C_{22}H_{30}N_5O_3PS$: C, 55.56; H, 6.36; N, 14.73. Found: C, 55.30; H, 6.15; N, 14.69.

5c. Colorless crystals, yield: 84%; mp 62.9–64.1°C. ^{1}H NMR: δ 1.18–1.27 (m, 12H, 4CH$_3$), 2.62 (s, 3H, SCH$_3$), 3.34 (q, *J* = 6.8 Hz, 2H, NCH$_2$), 3.46–3.50 (m, 1H, NCH$_2$), 3.57–3.60 (m, 1H, NCH$_2$), 4.00–4.06 (m, 2H, OCH$_2$), 4.15–4.19 (m, 2H, OCH$_2$), 6.04 (d, *J* = 22.8 Hz, 1H, PCH), 6.99 (dd, *J* = 8.8 Hz, *J* = 8.4 Hz, 2H, Ar—H), 7.55 (dd, *J* = 5.2 Hz, *J* = 8.4 Hz, 2H, Ar—H), 8.27 ppm (s, 1H, N=CH); ^{31}P NMR (162 MHz): δ 17.17 ppm; ir: Ar—H 2980, CN 2212, C=N— 1620, P=O 1260, P—O—C 1047, P—C 973 cm^{-1}; ms: *m*/*z* 483 (4.3), 481 (M$^+$, 28), 344 (100), 297 (8), 236 (8), 175 (20), 109 (16); Anal. Calcd for $C_{21}H_{29}FN_5O_3PS$: C, 52.38; H, 6.07; N, 14.54. Found: C, 52.43; H, 6.36; N, 14.73.

5d. Colorless crystals, yield: 85%; mp 56.1–56.9°C; ^{1}H NMR: δ 0.89–0.98 (m, 6H, 2CH$_3$), 1.18–1.27 (m, 6H, 2CH$_3$), 1.60–1.68 (m, 4H, 2CH$_2$), 2.61 (s, 3H, SCH$_3$), 3.23 (t, *J* = 7.2 Hz, 2H, NCH$_2$), 3.32–3.37 (m, 1H, NCH$_2$), 3.45–3.50 (m, 1H, NCH$_2$), 4.00–4.06 (m, 2H, OCH$_2$), 4.14–4.21 (m, 2H, OCH$_2$), 6.01 (d, *J* = 22.8 Hz, 1H, PCH), 7.01 (dd, *J* = 8.8 Hz, *J* = 8.8 Hz, 2H, Ar—H), 7.52 (dd, *J* = 5.6 Hz, *J* = 8.8 Hz, 2H, Ar—H), 8.27 ppm (s, 1H, N=CH); ^{31}P NMR (162 MHz): δ 17.08 ppm; ir: Ar—H 2970, CN 2210, C=N— 1620, P=O 1255, P—O—C 1045, P—C 977 cm^{-1}; ms: *m*/*z* 511 (11.9), 509 (M$^+$, 44), 372 (100), 330 (11), 264 (14), 108 (6), 43 (8); Anal. Calcd for $C_{23}H_{33}FN_5O_3PS$: C, 54.21; H, 6.53; N, 13.74. Found: C, 54.36; H, 6.22; N, 13.57.

5e. Colorless oil, yield: 88%; ^{1}H NMR: δ 0.92–0.99 (m, 6H, 2CH$_3$), 1.18–1.30 (m, 6H, 2CH$_3$), 1.32–1.40 (m, 4H, 2CH$_2$), 1.54–1.63 (m, 4H, 2CH$_2$), 2.61 (s, 3H, SCH$_3$), 3.26 (t, *J* = 7.6 Hz, 2H, NCH$_2$), 3.36–3.41 (m, 1H, NCH$_2$), 3.48–3.54 (m, 1H, NCH$_2$), 3.99–4.06 (m, 2H, OCH$_2$), 4.17–4.19 (m, 2H, OCH$_2$), 6.02 (d, *J* = 22.8 Hz, 1H, PCH), 7.00 (dd, *J* = 8.4 Hz, *J* = 8.8 Hz, 2H, Ar—H), 7.54 (dd, *J* = 5.2 Hz, *J* = 8.8 Hz, 2H, Ar—H), 8.26 ppm (s, 1H, N=CH); ^{31}P NMR (162 MHz): δ 17.06 ppm; ir: Ar—H 2960, CN 2212, C=N— 1619, P=O 1260, P—O—C 1025, P—C 973 cm^{-1}; ms: *m*/*z* 539 (23.8), 537 (M$^+$, 42), 400 (100), 292 (26), 231 (20), 140 (42), 109 (52); Anal. Calcd for $C_{25}H_{37}FN_5O_3PS$: C, 55.85; H, 6.94; N, 13.03. Found: C, 55.74; H, 7.13; N, 12.89.

5f. Colorless crystals, yield: 83%; mp 115.0–116.4°C; ^{1}H NMR: δ 1.18–1.26 (m, 6H, 2CH$_3$), 1.63–1.73 (m, 6H, CH$_2$CH$_2$CH$_2$), 2.59 (s, 3H, SCH$_3$), 3.38 (t, *J* = 5.6 Hz, 2H, NCH$_2$), 3.66 (t, *J* = 5.6 Hz, 2H, NCH$_2$), 4.00–4.05 (m, 2H, OCH$_2$), 4.13–4.19 (m, 2H, OCH$_2$), 6.04 (d, *J* = 23.2 Hz, 1H, PCH), 7.01 (dd, *J* = 8.8 Hz, *J* = 8.8 Hz, 2H, Ar—H), 7.56 (dd, *J* = 8.4 Hz, *J* = 5.2 Hz, 2H, Ar—H), 8.24 ppm (s, 1H, N=CH); ^{31}P NMR (162 MHz): δ 17.25 ppm; ir: Ar—H 2945, CN 2210, C=N— 1622, P=O 1254, P—O—C 1023, P—C 956 cm^{-1}; ms: *m*/*z* 495 (13.0), 493 (M$^+$, 50), 446 (11), 356 (100), 309 (23), 248 (19), 108 (9); Anal. Calcd for $C_{22}H_{29}FN_5O_3PS$: C, 53.54; H, 5.92; N, 14.19. Found: C, 53.31; H, 5.83; N, 14.10.

5g. Colorless crystals, yield: 94%; mp 127.6–129.3°C; ^{1}H NMR: δ 1.18–1.27 (m, 6H, 2CH$_3$), 2.61 (s, 3H, SCH$_3$), 3.45–3.48 (m, 2H, NCH$_2$), 3.70–3.78 (m, 6H, NCH$_2$ + 2OCH$_2$), 3.99–4.05 (m, 2H, CH$_2$O), 4.13–4.21 (m, 2H, CH$_2$O), 6.00 (d, *J* = 23.2 Hz, 1H, PCH), 7.02 (dd, *J* = 8.8 Hz, *J* = 8.4 Hz, 2H, Ar—H), 7.53 (dd, *J* = 5.6 Hz, *J* = 8.4 Hz, 2H, Ar—H), 8.28 ppm (s, 1H, N=CH); ^{31}P NMR (162 MHz): δ 16.60 ppm; ir: Ar—H 2976, CN 2215, C=N— 1621, P=O 1263, P—O—C 1024, P—C 974 cm^{-1}; ms: *m/z* 497 (17.8), 495 (M$^+$, 79), 448 (9), 358 (100), 108 (10), 81 (5); Anal. Calcd for $C_{21}H_{27}FN_5O_4PS$: C, 50.90; H, 5.49; N, 14.13. Found: C, 50.71; H, 5.65; N, 14.32.

Bioassay method

Herbicidal activities testing. Herbicidal testing of the newly synthesized compounds **5** was carried out in a greenhouse, with temperature 23 ± 1°C, relative humidity (RH) 60 ± 5%, light intensity 10 Klux, photoperiod 8 h/day. Twenty seeds of each weed species including oil rape and barnyard grass were chosen for testing. Seedlings were grown in the test plate of 9 cm diameter containing two pieces of filter paper and 9 mL solution of the tested compound (100 mg/L and 10 mg/L, respectively). Distilled water and **2,4-D** were used as the comparison compounds. The herbicidal activity was assessed as the inhibitory rate in comparison with the distilled water. The herbicidal rating score based on visual observation. Range from 0 to 100%, 0% means no effect, 100% means complete killing. The test was run three times, and the results were averaged and given as activity in Table 1.

Fungicidal activity testing. The fungicidal activity measurement method was adapted from the one described by Molina-Torres *et al* [19]. The synthesized target compounds were dissolved in 0.5–1.0 mL of *N,N*-dimethylformamide to the concentration of 500 mg/L. The solutions (1 mL) were mixed rapidly with thawed potato glucose agar culture medium (9 mL) under 50°C. The mixtures were poured into petridishes. After the dished were cooled, the solidified plates were incubated with 4 mm mycelium disk, inverted, and incubated at 28°C for 48 h. Distilled water was used as the blank control. Three replicates of each test were carried out. The mycelial elongation radius (mm) of fungi settlements was measured after 48 h of culture. The growth inhibitory rates were calculated with the following equation: $I = [(C - T)/C] * 100\%$. Here, I is the growth inhibitory rate (%), C and T are the mycelial elongation radius (mm) of fungus settlements and that of treatment group, respectively. The results are also given in Table 1.

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Improved Preparation of 3-(1,1-Dimethylallyl)decursinol

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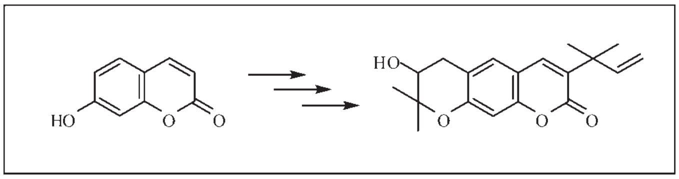

An improved preparation method of 3-(1,1-dimethylallyl)decursinol from inexpensive commercially available start material was described. In the cyclization of **13**, silica gel was used as catalyst to give **1** with high purity and satisfying yield.

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INTRODUCTION

3-(1,1-dimethylallyl)decursinol (**1**) was previously isolated from *Helietta longifoliata* Britt, a plant growing in South America, which has been used in Brazilian folk medicine for the treatment of various disease [1,2]. Compound **1** and it analogues (Fig. 1), such as (+)-decursinol (**2**), decursin (**3**), and decursinol angelate (**4**), constitute a class of dihydropyranocoumarin natural product, which has received considerable attention because of their diverse range of biological activities [2]. Both **3** and**4** have protein kinase C-related cytotoxic activity against various human cancer cells [3,4]. Compound **2** and **3** exhibited *in vitro* activities toward acetylcholinesterase, as well as the two compounds could excellently improve scopolamine-induced amnesia *in vivo*. Additionally, these dihydropyranocoumarin was found to exhibit anti-*Helicobacter pylori* activity and strong analgestic activity [5].

As the resource of **1** is restricted to the species of *Helietta longifoliata*, the detailed biological investigation has not been successful so far. To explore the potential biological activities of **1** and its derivatives, a reliable preparing procedure in large scale was needed. Rosario has semisynthesized the compound of **1** in milligram scale; nevertheless, the resource of start material was also limited [6].

Herein, an improved preparing procedure, staring with inexpensive, commercially available 7-hydroxy-2*H*-chromen-2-one (**5**), was reported (Scheme 1). In the process, compound **9**was deprotected in the presence of active Ni with almost quantitative yield. The cyclization of compound **13** could be promoted by silica gel to obtain compound **1**, and the later was purified by simple crystallization rather than chromatograph.

RESULTS AND DISCUSSION

The hydroxyl in compound **5** was protected by benzyl in the presence of potassium carbonate to give **6**. The latter was treated with sodium methoxide in refluxing methanol, and then reacted with 1-bromo-3-methylbut-2-ene to obtain compound **8**. On heating in refluxing diethylaniline, **8** smoothly rearranged, resulting in prenyl substitution at the free C-3 position with concomitant relactonisation to produce **9** [7].

In the ref. [7], the benzyl group was removed in the presence of trichloroborane; nevertheless, our attempt to scale up the reaction in several hundred grams was failed. The reason was trichloroborane, a strong Lewis-acid, could induce some side-reaction. Hydrogenation of **9** to remove the benzyl, using Raney Ni as catalyst afforded the compound **10**in quantitative yield, although trace of by-product was formed.

The free hydroxyl of **10** was prenylated to furnish the key intermediate **11**, sigmatropic rearrangement of which in refluxing diethylaniline gave the compound **12**. Epoxidation of **12** in dichloromethane gave the unstable intermediate**13**, which could be conversed to compound **1** in the presence of silica gel *in situ*, and the product can be purified conveniently by crystallization in ethyl acetate.

EXPERIMENTAL

All solvents and reagents were purchased from the suppliers and used without further purification. ^{1}H NMR spectra were recorded in deuteriochloroform or DMSO-d_6 at room temperature on a Bruker AMX-400/600 at 400 MHz using TMS as an internal standard. The mass spectrum was recorded on a

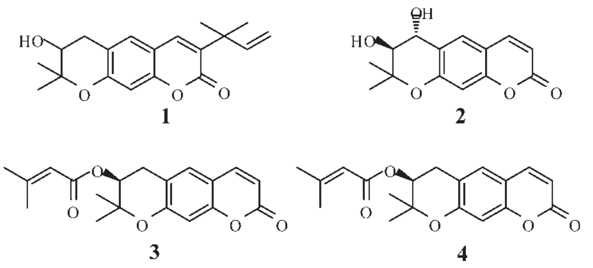


Figure 1. Structures of **1** and its analogues.

Finnigan MAT-95/711 spectrometer. Melting points were measured on a Buchi-510 melting point apparatus, which are uncorrected. TLC analyses were performed on Merck silica gel 60 F_{254} plate.

7-(Benzyloxy)-2*H*-chromen-2-one (6). 1.0 kg (6.18 mol) compound **5** was added to the mixture of 2.0 kg (14.47 mol) K_2CO_3, 0.1 kg KI (0.6 mol), and 12 L acetone and then, 0.86 kg (6.78 mol) benzyl chloride was added. The resulted mixture was heated to reflux for 4 h, cooled to room temperature, filtrated, and the filtration was concentrated under decreased pressure. The residue was dissolved in 20 L CH_2Cl_2, washed with saturated NH_4Cl solution and H_2O, dried over Na_2SO_4, concentrated, and filtrated to obtain 1.5 kg white solid **6**, yield 96.4%, mp 151–154°, ref. [8] 153–155°. The spectroscopic data correspond to those reported in the ref. [8].

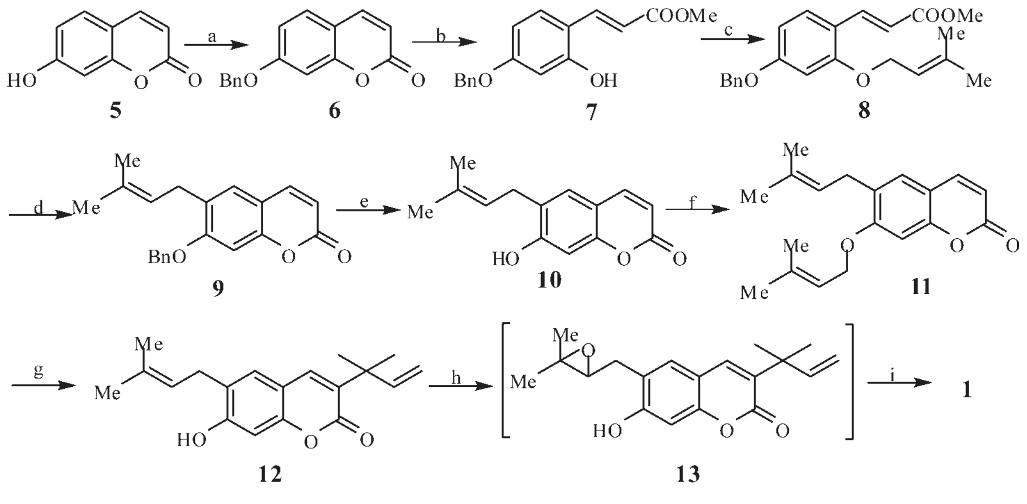
Methyl 3-(4-(benzyloxy)-2-hydroxyphenyl)acrylate (7). 1.5 kg (6 mol) **6** was dissolved in the mixture of 16 L methanol and 2.0 kg (37 mol) sodium methylate. The resulted mixture was heated to reflux for 6 h, cooled to room temperature, added to 40 L of 2.6*M* hydrochloric acid with stirring at 0°, filtrated to obtain white solid. The solid was washed with H_2O, dried at 60° to obtain 1.27 kg **7** as white solid, yield 75%, mp 182–183°, ref. [7] 184.5–186°; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.66 (s, 3H), 5.06 (s, 2H), 6.45 (d, $J = 16$ Hz, 1H), 6.50 (s, 1H), 6.52 (d, $J = 7.2$ Hz, 1H), 7.32–7.43 (m, 5H), 7.52 (d, $J = 7.2$ Hz, 1H), 7.77 (d, $J = 16$ Hz, 1H).

Methyl 3-(4-(benzyloxy)-2-(3-methylbut-2-enyloxy) phenyl) acrylate (8). 1.27 kg (4.45 mol) compound **7** was added to the suspension of 1.24 kg (9.27 mol) K_2CO_3 and 120 g (0.73 mol) KI in 15 L acetone, then the 620 mL (5.34 mol) 1-bromo-3-methylbut-2-ene was added dropwise. The resulted mixture was stirred at room temperature for 3 h, filtrated, and the filtration was concentrated. The obtained residue was dissolved in 8 L CH_2Cl_2, and the organic layer was washed by H_2O and saturated brine, dried over Na_2SO_4, filtrated, and concentrated to oil. The oil was stirred in 3 L petroleum ether for 2 h, filtrated to obtain 1.2 kg **8** as white solid, yield 77%, mp 62–63°, ref. [7] 59–61°; ^{1}H NMR (300 MHz, deuteriochloroform): δ 1.76 (s, 3H), 1.82 (s, 3H), 3.79 (s, 3H), 4.55 (d, $J = 7.2$ Hz, 2H), 5.06 (s, 2H), 5.48 (m, 1H), 6.42 (d, $J = 16$ Hz, 1H), 6.55 (m, 2H), 7.37 (m, 6H), 7.63 (d, $J = 9$ Hz, 1H).

7-(Benzyloxy)-6-(3-methylbut-2-enyl)-2*H*-chromen-2-one (9). 400 g (1.1 mol) **8** was dissolved in 2 L *N*,*N*-diethyl-benzenamine in 5 L reactor equipped with water segregator. The solvent was heated to reflux under N_2. During the removing of methanol, the temperature of reaction mixture developed from 202° to 226°, reflux for another 3 h, cooled to room temperature. The mixture was added into 10 L of 2*M* hydrochloric acid, extracted with ethyl acetate three times. The combined organic layer was washed by saturated brine, dried over Na_2SO_4, concentrated to obtain slurry, filtrated to obtain 713 g **9** as white solid, yield 65%, mp 102–103°, ref. [7] 104–104.5°; ^{1}H NMR (300 MHz, deuteriochloroform): δ 1.66 (s, 3H), 1.76 (s, 3H), 3.37 (d, $J = 7.2$ Hz, 2H), 5.06 (s, 2H), 5.30 (m, 1H), 6.25 (d, $J = 9$ Hz, 1H), 6.83 (s, 1H), 7.21 (s, 1H), 7.42 (m, 5H,), 7.63 (d, $J = 9$ Hz, 1H).

7-Hydroxy-6-(3-methylbut-2-enyl)-2*H*-chromen-2-one (10). 355 g (1.1 mol) compound **9** was dissolved in the mixture of 3.5 L ethanol, 500 mL H_2O, and 10 g Raney Ni, the resulted suspension was stirred under H_2 at room temperature for 24 h, filtrated, the filtration was concentrated to obtain white solid 250 g **10**, yield 98%, mp 133–135°, ref. [7] 133–135°; ^{1}H NMR (300 MHz, deuteriochloroform): δ 1.75 (s, 3H), 1.79 (s, 3H), 3.38 (d, $J = 7.5$ Hz, 2H), 5.34 (m, 1H),

Scheme 1. Conditions: (a) benzyl chloride, K_2CO_3, KI, acetone, reflux, 96%; (b) sodium methoxide, methanol, 75%; (c) 1-bromo-3-methybut-2-ene, K_2CO_3, KI, acetone, r.t., 77%; (d) *N*,*N*-diethylbenzenamine, reflux, 65%; (e) H_2, Riney-Ni, ethanol, H_2O; (f) 1-bromo-3-methylbut-2-ene, K_2CO_3, KI, acetone, r.t., 70%; (g) *N*,*N*-diethylbenzenamine, reflux, 32%; (h) m-CPBA, CH_2Cl_2, 0°C; (i) silica gel, 0°C, 75%.



6.23 (d, $J = 9$ Hz, 1H), 7.00 (s, 1H), 7.11 (s, 1H), 7.42 (m, 5H), 7.66 (d, $J = 9$ Hz, 1H).

6-(3-Methylbut-2-enyl)-7-(3-methylbut-2-enyloxy)-2*H*-chromen-2-one (11). 77 g (4.45 mol) compound **10** was added to the suspension of 120 g (0.95 mol) K_2CO_3 and 5 g (30 mmol) KI in 1 L acetone, then the 60 mL (0.5 mol) 1-bromo-3-methylbut-2-ene was added dropwise. The resulted mixture was stirred at room temperature for 3 h, filtrated, and the filtration was concentrated. The obtained residue was dissolved in 0.5 L CH_2Cl_2, and the organic layer was washed by H_2O and saturated brine, dried over Na_2SO_4, filtrated, and concentrated to oil. The oil was stirred in 300 mL petroleum ether for 2 h, filtrated to obtain 70 g **11** as white solid, yield 70%, mp 76–78°, ref. [7] 78–79°; ^{1}H NMR (300 MHz, deuteriochloroform): δ 1.71 (s, 3H), 1.77 (s, 6H), 1.78 (s, 3H), 3.38 (d, $J = 7.5$ Hz, 2H), 4.63 (d, $J = 7.5$ Hz, 2H), 5.30 (m, 1H), 5.46 (m, 1H), 6.76 (s, 1H), 7.17 (s, 1H), 7.61 (d, $J = 9$ Hz, 1H).

7-Hydroxy-6-(3-methylbut-2-enyl)-3-(2-methylbut-3-en-2-yl)-2*H*-chromen-2-one (12). 82 g (1.1 mol) compound **11** was dissolved in 0.5 L *N*,*N*-diethylbenzenamine in 5 L reactor equipped with water segregator. The solvent was heated to reflux under N_2. During the removing of methanol, the temperature of reaction mixture developed from 202° to 226°, reflux for another 3 h, cooled to room temperature. The mixture was added into 500 mL of 2*M* hydrochloric acid, extracted with ethyl acetate three times. The combined organic layer was washed by saturated brine, dried over Na_2SO_4, concentrated to obtain residue, which was purified on silica gel column (petroleum ether:ethyl acetate = 20:1) filtrated to obtain 27.5 g **12** as white solid, yield 32%, mp 163–165°, ref. [7] 181–183°; ^{1}H NMR (300 MHz, deuteriochloroform): δ 1.47 (s, 6H), 1.77 (s, 3H), 1.79 (s, 3H), 3.38 (d, $J = 7.5$ Hz, 2H), 5.04 (dd, 1H), 5.30 (m, 1H), 6.08–6.21 (m, 2H), 6.84 (s, 1H), 7.17 (s, 1H), 7.50 (s, 1H).

(±)-3-(1,1-Dimethylallyl)decursinol (1). 5 g (16.7 mmol) compound **12** was dissolved in 80 mL ethyl ether, to which 4.3 g (21.2 mmol) m-CPBA was added in portions at 0°C, the mixture was stirred for 6 h at room temperature. The reaction was monitored by TLC. When compound **12** was consumed up, 10 g silica gel was added to the resulted mixture at 0°, stirred for another 1 h. The mixture was filtrated, and the filtration was washed by saturated $NaHCO_3$ and H_2O, dried over Na_2SO_4, concentrated to obtain crude product, which was crystallized in ethyl acetate to give 3.7 g **1** as white solid, yield 70%, mp 182–183°, ref. [6] 181–183°; ms: m/z 337 (M^++Na); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.38 (s, 3H), 1.47 (s, 6H), 2.82 (dd, $J = 14$, 6 Hz, 1H), 3.10 (dd, $J = 14$, 6 Hz, 1H), 3.85 (m, 1H), 1.79 (s, 3H), 3.38 (d, $J = 7.5$ Hz, 2H), 5.06 (m, 2H), 6.17 (dd, $J = 17$, 12 Hz, 1H), 6.74 (s, 1H), 7.15 (s, 1H), 7.47 (s, 1H).

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A Facile and Efficient Synthesis of Novel Pyrimido[5,4-*b*][4,7]phenanthroline-9,11(7*H*,8*H*,10*H*,12*H*)-dione derivatives *via* Microwave-assisted Multicomponent Reactions

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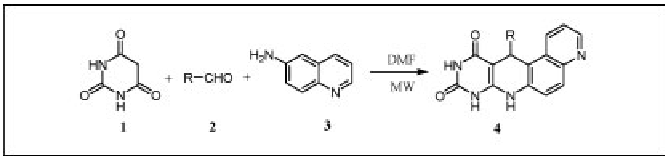

A series of novel pyrimido[5,4-*b*][4,7]phenanthroline-9,11(7*H*,8*H*,10*H*,12*H*)-dione derivatives were synthesized *via* microwave-assisted three-component reactions of barbituric acid, aldehyde, and quinolin-6-amine in DMF without catalyst. This facile synthesis not only offers an economical and efficient synthetic strategy to this class of significant compounds but also enriches the investigations on microwave-assisted multicomponent reactions. Moreover, this protocol has the prominent advantages of short reaction time, good yields, low cost, easy operation, as well as environmental-friendliness.

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INTRODUCTION

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry, because the strategies of MCR offer significant advantages over conventional linear-type syntheses. MCRs leading to interesting heterocyclic scaffolds are particularly useful for the creation of diverse chemical libraries of ''drug-like'' molecules for biological screening, since the combination of three or more small-molecular weight building blocks in a single operation leads to a high-combinatorial efficacy [1]. On the other hand, microwave-assisted organic synthesis has been a topic of continued studies as it could lead to higher yields of pure products, easier operation, and shorter reaction time when compared with the traditional heating method [2].

Thus, it goes without saying that the use of atom-economical MCRs, together with the employment of energy-efficient microwave irradiation (MW), must be considered to be facile and effective synthetic strategy of heterocyclic compounds with important bioactivities in the sense that the combination in itself offers greater potential than the two parts in isolation.

Pyrimido[5,4-*b*][4,7]phenanthroline-9,11(7*H*,8*H*,10*H*,12*H*)-diones (**4**, Fig. 1), a novel class of fused heterocyclic compounds, are incorporated by pyrimido-[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione and [4,7]-phenantroline motifs, both of which possess various important bioactivities. For example, not only are pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione derivatives antitumor [3], anticancer [4], antihypertensive [5], and antibacterial [6], they are also inhibitors of Kaposi's sarcoma-associated herpesvirus (KSHV) [7] and topoisomerase, useful for the treatment of topoisomerase-associated diseases and disorders [8]. At the same time, [4,7]phenantroline derivatives exhibit antitumor [9], anticancer [10], antiviral [11], antimalarial [12], antiinfective [13], cytotoxic [14] activities, as well as being triple-helix DNA stabilizing agents [15]. Hence, it is promising that the fused scaffolds of pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione with [4,7]phenanthroline, *i.e.*, pyrimido[5,4-*b*][4,7]phenanthroline-9,11-(7*H*,8*H*,10*H*,12*H*)-diones, may display novel or enhanced significant bioactivities.

However, survey of the literature revealed that the synthesis of this important fused heterocyclic skeleton was neglected. Therefore, the investigation on the synthesis of pyrimido[5,4-*b*][4,7]phenanthroline-9,11-(7*H*,8*H*,10*H*,12*H*)-diones is of great necessity.

In view of the prominent merits of microwave-assisted multicomponent reactions and the potential

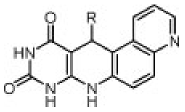

Figure 1. Structure of **4**.

bioactivities of fused heterocyclic compounds, lots of investigations on this topic have been carried out in our laboratory [16]. Herein, we would like to report a facile and efficient synthesis of pyrimido[5,4-*b*][4,7]phenanthroline-9,11-(7*H*,8*H*,10*H*,12*H*)-diones **4** *via* microwave-assisted three-component reactions of barbituric acid **1**, aldehyde **2**, and quinolin-6-amine **3** in DMF without catalyst (Scheme 1).

RESULTS AND DISCUSSION

Initially, the three-component reaction of barbituric acid **1**, 4-bromobenaldehyde **2c** and quinolin-6-amine **3** was employed to optimize the reaction conditions. As illustrated in Table 1, DMF was preferred as the optimal solvent and 110°C was chosen as the most suitable reaction temperature.Moreover, we found that the yield of this reaction was affected by the volume of solvent. The synthesis of **4c** was tested in different volumes of DMF at 110°C. The results show that 1.5 mL of DMF were optimal as solvent since it generated the highest yield of **4c**.

Under these optimized reaction conditions (1.5 mL of DMF, 110°C), a series of pyrimido[5,4-*b*][4,7]phenanthroline-9,11(7*H*,8*H*,10*H*,12*H*)-dione derivatives **4** were synthesized under MW, and the results were summarized in Table 2. It is obvious this protocol could be applied to various aromatic aldehydes with electron-withdrawing groups or electron-donating groups. Besides, the results suggest that the substrates bearing electron-withdrawing groups have higher reactivity (higher yields and shorter reaction time) than those bearing electron-donating groups. So, it is concluded that the electronic nature of the substituents on aldehydes has some effect on this reaction. It seems that the electron-withdrawing groups in aldehydes enhanced the electropositive property of β-C in the intermediates yielded from the Knoevenagel condensation of aldehydes **2** with barbituric acid **1**, which facilitated the nucleophilic attack thereafter.

Scheme 1

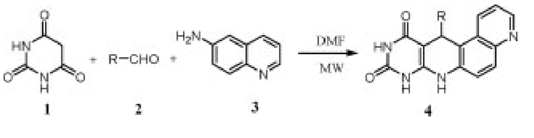

Table 1

Reaction conditions optimization for the synthesis of **4c**.

Entry	Solvent	*T* (°C)	Time (min)	Yield (%)
1	EtOH	90	15	52
2	HOAc	90	15	63
3	Water	90	15	37
4	Glycol	90	12	79
5	DMF	90	10	86
6	DMF	70	15	78
7	DMF	80	12	82
8	DMF	100	8	90
9	DMF	110	6	92
10	DMF	120	6	92

To demonstrate the superiority of MW over standard heating conditions (SC), we also performed the syntheses of **4c** under SC in DMF at 110°C. Under this condition, the reaction time was prolonged from 6 min (under MW) to 4 h and the yield was decreased from 92% (under MW) to 76%. Therefore, MW exhibited several distinct advantages over SC by not only significantly reducing the reaction time and dramatically improving the reaction yield, but also being environmental-friendly.

The structures of all the synthesized compounds were established on the basis of their spectroscopic data and elemental analyses.

In conclusion, we have developed a facile and efficient method on the synthesis of novel pyrimido [5,4-*b*][4,7]phenanthroline-9,11(7*H*,8*H*,10*H*,12*H*)-dione derivatives *via* microwave-assisted three-component reactions in DMF without catalyst. This protocol has the prominent advantages of short reaction time, good yields, low cost, easy operation, as well as environmental-friendliness. At the same time, this synthesis can not only offer an efficient strategy to highly fused heterocyclic compounds with biological significance but also enrich the investigations on microwave-assisted multicomponent reactions. Moreover, this series of novel pyrimido[5,4-*b*][4,7]phenanthroline-9,11(7*H*,8*H*,10*H*,-12*H*)-diones may provide new class of biologically active compounds for biomedical screening.

EXPERIMENTAL

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

Table 2

Synthesis of **4** under microwave irradiation.

Entry	4	R	Time (min)	Yield (%)	M.P. (°C)
1	**4a**	4-FC_6H_4	6	89	>300
2	**4b**	4-ClC_6H_4	8	90	>300
3	**4c**	4-BrC_6H_4	6	92	>300
4	**4d**	3,4-$(CH_3O)_2C_6H_3$	14	78	>300
5	**4e**	3-$NO_2C_6H_4$	6	86	>300
6	**4f**	4-$CH_3C_6H_4$	12	81	>300
7	**4g**	C_6H_5	10	83	>300
8	**4h**	4-OH-3-$NO_2C_6H_3$	13	81	>300
9	**4i**	3,4-$OCH_2OC_6H_3$	15	72	>300

General procedure for the syntheses of compounds 4 with microwave irradiation. Typically, in a 10 mL Emrys^{TM} reaction vial, barbituric acid **1** (1 mmol), aldehyde **2** (1 mmol), quinolin-6-amine **3** (1 mmol), and and DMF (1.5 mL) were mixed and then capped. The mixture was irradiated at 150 W and at 110°C for a given time. The reaction mixture was cooled to room temperature and poured into water (50 mL), filtered to give the crude product, which was further purified by recrystallization from EtOH.

12-(4-Fluorophenyl)pyrimido[5,4-b][4,7]phenanthroline-9,11 (7H,8H,10H,12H)-dione (4a). This compound was obtained according to above general procedure; ir (KBr): ν 3207, 3066, 1714, 1655, 1633, 1543, 1471, 1381, 1265, 1093, 976, 862 cm^{-1}; ^{1}H NMR: δ 10.73 (s, 1H, NH), 10.54(s, 1H, NH), 9.32(s, 1H, NH), 8.70 (d, 1H, J = 4.0 Hz, ArH), 8.35 (d, 1H, J = 8.4 Hz, ArH),7.91–7.96 (m, 1H, ArH), 7.65 (d, 1H, J = 8.8 Hz, ArH),7.42 (dd, 1H, J = 8.4, 4.0 Hz, ArH), 7.29 (dd, 2H, J = 7.6, 6.0 Hz, ArH), 7.00 (t, 2H, J = 8.4 Hz, ArH),5.76 (s, 1H, CH). Anal. calcd for $C_{20}H_{13}FN_4O_2$: C, 66.66; H, 3.64; N, 15.55; Found C, 66.70; H, 3.68; N, 15.52.

12-(4-Chlorophenyl)pyrimido[5,4-b][4,7]phenanthroline-9,11 (7H,8H,10H,12H)-dione (4b). This compound was obtained according to above general procedure; ir (KBr): ν 3203, 3065, 1714, 1683, 1634, 1543, 1487, 1381, 1266, 1089, 976, 830 cm^{-1}; ^{1}H NMR: δ 10.74 (s, 1H, NH), 10.55 (s, 1H, NH), 9.34 (s, 1H, NH), 8.70 (d, 1H, J = 4.0 Hz, ArH), 8.34 (d, 1H, J = 8.4 Hz, ArH), 7.94 (t, 1H, J = 8.4 Hz, ArH), 7.65 (d, 1H, J = 8.4 Hz, ArH), 7.42 (dd, 1H, J = 8.4, 4.0 Hz, ArH), 7.29 (d, 2H, J = 8.4 Hz, ArH), 7.23 (d, 2H, J = 8.4 Hz, ArH), 5.76 (s, 1H, CH). Anal. calcd for $C_{20}H_{13}ClN_4O_2$: C, 63.75; H, 3.48; N, 14.87; Found C, 63.68; H, 3.50; N, 14.90.

12-(4-Bromophenyl)pyrimido[5,4-b][4,7]phenanthroline-9,11 (7H,8H,10H,12H)-dione (4c). This compound was obtained according to above general procedure; ir (KBr): ν 3201, 3065, 1714, 1656, 1633, 1545, 1484, 1381, 1266, 1099, 976, 829 cm^{-1}; ^{1}H NMR: δ 10.74 (s, 1H, NH), 10.57 (s, 1H, NH), 9.39 (s, 1H, NH), 8.70–8.71 (m, 1H, J = 4.0 Hz, ArH), 8.34 (d, 1H, J = 8.8 Hz, ArH), 7.93 (d, 1H, J = 8.8 Hz, ArH), 7.64 (d, 1H, J = 8.8 Hz, ArH),7.42 (dd, 1H, J = 8.4, 4.0 Hz, ArH), 7.36 (d, 2H, J = 8.4 Hz, ArH), 7.23 (d, 2H, J = 8.4 Hz, ArH), 5.74 (s, 1H, CH). Anal. calcd for $C_{20}H_{13}BrN_4O_2$: C, 57.02; H, 3.11; N, 13.30; Found C, 57.07; H, 3.10; N, 13.32.

12-(3,4-Dimethoxyphenyl)pyrimido[5,4-b][4,7]phenanthroline-9,11(7H,8H,10H,12H)-dione (4d). This compound was obtained according to above general procedure; ir (KBr): ν 3262, 3068, 1706, 1653, 1554, 1513, 1418, 1382, 1263, 1138, 973, 820 cm^{-1}; ^{1}H NMR: δ 10.66 (s, 1H, NH), 10.45 (s, 1H, NH), 9.22 (s, 1H, NH), 8.69–8.70 (m, 1H, ArH), 8.38 (d, 1H, J = 8.4 Hz, ArH), 7.91 (d, 1H, J = 8.8 Hz, ArH), 7.63 (d, 1H, J = 8.8 Hz, ArH),7.41 (dd, 1H, J = 8.4, 4.0 Hz, ArH), 7.07 (d, 1H, J = 2.0 Hz, ArH), 6.70 (d, 1H, J = 8.4 Hz, ArH), 6.55 (dd, 1H, J = 8.4, 2.0 Hz, ArH), 5.70 (s, 1H, CH), 3.66 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3). Anal. calcd for $C_{22}H_{18}N_4O_4$: C, 65.66; H, 4.51; N, 13.92; Found C, 65.60; H, 4.50; N, 13.95.

12-(3-Nitrophenyl)pyrimido[5,4-b][4,7]phenanthroline-9,11 (7H,8H,10H,12H)-dione (4e). This compound was obtained according to above general procedure; ir (KBr): ν3252, 3067, 1714, 1660, 1580, 1551, 1451, 1383, 1263, 1098, 975, 829 cm^{-1}; ^{1}H NMR: δ 10.75 (s, 1H, NH), 10.63 (s, 1H, NH), 9.44 (s, 1H, NH), 8.70 (d, 1H, J = 4.0 Hz, ArH), 8.38 (d, 1H, J = 8.4 Hz, ArH), 8.16 (s, 1H, ArH), 7.40–7.98 (m, 2H, ArH), 7.71 (d, 2H, J = 8.8 Hz, ArH), 7.49 (t, 1H, J = 8.0 Hz, ArH), 7.42 (dd, 1H, J = 8.4, 4.0 Hz, ArH), 5.96 (s, 1H, CH). Anal. calcd for $C_{22}H_{17}N_3O_4$: $C_{20}H_{13}N_5O_4$: C, 62.01; H, 3.38; N, 18.08; Found C, 62.05; H, 3.40; N, 18.05.

12-p-Tolylpyrimido[5,4-b][4,7]phenanthroline-9,11(7H,-8H, 10H,12H)-dione (4f). This compound was obtained according to above general procedure; ir (KBr): ν 3193, 3064, 1713, 1658, 1542, 1470, 1451, 1382, 1266, 1037, 976, 832 cm^{-1}; ^{1}H NMR: δ 10.65 (s, 1H, NH), 10.43 (s, 1H, NH), 9.22 (s, 1H, NH), 8.68 (d, 1H, J = 4.0 Hz, ArH), 8.34 (d, 1H, J = 8.4 Hz, ArH), 7.90 (d, 1H, J = 8.8 Hz, ArH), 7.63 (d, 1H, J = 8.8 Hz, ArH), 7.41 (dd, 1H, J = 8.4, 4.0 Hz, ArH), 7.15 (d, 2H, J = 8.0 Hz, ArH), 6.96 (d, 2H, J = 8.0 Hz, ArH), 5.96 (s, 1H, CH), 2.15 (s, 3H, CH_3). Anal. calcd for $C_{21}H_{16}N_4O_2$: C, 70.77; H, 4.53; N, 15.72; Found C, 70.82; H, 4.52; N, 15.74.

12-Phenylpyrimido[5,4-b][4,7]phenanthroline-9,11(7H,-8H, 10H,12H)-dione (4g). This compound was obtained according to above general procedure; ir (KBr): ν 3196, 3067, 1713, 1647, 1599, 1518, 1452, 1382, 1264, 1078, 976, 829 cm^{-1}; ^{1}H NMR: δ 10.69 (s, 1H, NH), 10.49 (s, 1H, NH), 9.27 (s, 1H, NH), 8.69–8.70 (m, 1H, ArH), 8.36 (d, 1H, J = 8.4 Hz, ArH), 7.92 (d, 1H, J = 8.8 Hz, ArH), 7.65 (d, 1H, J = 8.8 Hz, ArH), 7.42 (dd, 1H, J = 8.4, 4.0 Hz, ArH), 7.28 (d, 2H, J = 8.8 Hz, ArH), 7.18 (t, 2H, J = 7.6 Hz, ArH), 7.06 (t, 1H, J = 7.6 Hz, ArH),5.74 (s, 1H, CH). Anal. calcd for $C_{20}H_{14}N_4O_2$: C, 70.17; H, 4.12; N, 16.37; Found C, 70.23; H, 4.10; N, 16.40.

12-(4-Hydroxy-3-nitrophenyl)pyrimido[5,4-b][4,7]phenanthroline-9,11(7H,8H,10H,12H)-dione (4h). This compound was obtained according to above general procedure; ir (KBr):

ν 3350, 3209, 3056, 1715, 1641, 1610, 1529, 1477, 1373, 1274, 1081, 941, 828 cm^{-1}; ^{1}H NMR: δ 11.50 (s, 1H, OH), 10.73 (s, 1H, NH), 10.53 (s, 1H, NH), 9.33 (s, 1H, NH), 8.70 (d, 1H, J = 3.6 Hz, ArH), 8.36 (d, 1H, J = 8.4 Hz, ArH), 7.94 (d, 1H, J = 9.2 Hz, ArH), 7.80 (d, 1H, J = 1.6 Hz, ArH),7.65 (d, 1H, J = 8.8 Hz, ArH),7.38–7.44 (m, 2H, ArH), 6.94 (d, 1H, J = 8.4 Hz, ArH), 5.77 (s, 1H, CH). Anal. calcd for $C_{20}H_{13}N_5O_5$: C, 59.56; H, 3.25; N, 17.36; Found C, 59.52; H, 3.26; N, 17.35.

12-(Benzo[d][1,3]dioxol-5-yl)pyrimido[5,4-b][4,7]phenanthroline-9,11(7H,8H,10H,12H)-dione (4i). This compound was obtained according to above general procedure; ir (KBr): ν 3445, 32119, 3094, 1728, 1687, 1669, 1546, 1453, 1405, 1275, 1254, 1030, 914, 894, 824 cm^{-1}; ^{1}H NMR: δ 10.68 (s, 1H, NH), 10.45 (s, 1H, NH), 9.24 (s, 1H, NH), 8.69–8.70 (m, 1H, ArH), 8.37 (d, 1H, J = 8.4 Hz, ArH), 7.91 (d, 1H, J = 8.8 Hz, ArH), 7.63 (d, 1H, J = 8.8 Hz, ArH), 7.74 (dd, 1H, J = 8.4, 1.2 Hz, ArH), 7.41 (dd, 1H, J = 8.4, 4.4 Hz, ArH), 7.08 (d, 1H, J = 8.4 Hz, ArH), 6.86 (d, 1H, J = 1.2 Hz, ArH), 5.88 (d, 2H, J = 9.6 Hz, CH_2), 5.68 (s, 1H, CH). Anal. calcd for $C_{21}H_{14}N_4O_4$: C, 65.28; H, 3.65; N, 14.50; Found C, 65.32; H, 3.66; N, 14.47.

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Synthesis and Spectral Characterization of a Novel Series of Methylcinnamate Derivatives of 15-Crown-5

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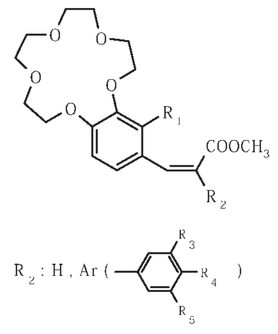

	R1	R2	R3	R4	R5
a	OH	H	-	-	-
b	OMe	H	-	-	-
c	OMe	Ar	H	H	H
d	OMe	Ar	H	OMe	H
e	OMe	Ar	OMe	OMe	H
f	OMe	Ar	OMe	H	OMe
g	OMe	Ar	OMe	OMe	OMe

A series of novel methylcinnamate derivatives of 15-crown-5 have been synthesized. The derivatives of methylcinnamate have been prepared by a synthesis from the corresponding chromenone-crown ether with MeONa/MeOH or KOH, CH_3I, and DMSO as solvent. Novel compounds were characterized by elemental analysis, IR, ^1H NMR, and MALDI-TOF.

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INTRODUCTION

Cinnamic (3-phenylpropenoic) acid analogues are a fundamental part of plant chemistry. The hydroxylated cinnamic acids possess antifungal, antibacterial, and parasite fighting abilities [1]. In the cinnamic acid molecule, the carboxylic acid group is separated from the aromatic ring by a double bond. Conjugation between the —C=C— bond gives very interesting electronic structure to cinnamic acid derivatives.

The flavonoid class compound coumarin (2*H*-chromenone) derivatives exist in many plants as free or glucosides. Because of biological activities, which gain importance in recent years, many coumarin derivatives have been synthesized and took place in literature. Most important coumarins are the ones that have substituted in third position. Some coumarins show a perfect fluorescens characteristic in addition to their anticoagulant, anti-inflammatory, anti-oxidative, anti-aging, and anticancer effects [2,3]. Methyl and acetyl substituents destroy the activities of coumarins. The beneficial effects of phenolic antioxidants on health have been attributed to their antioxidant capacity, particularly their ability to protect low-density lipoproteins from oxidative attack [4]. As a result of this, hydroxy coumarin derivatives gain more importance. Particularly, *o*-dihydroxy-3-phenylcoumarin shows antioxidant property and the 18-crown-6, 15-crown-5, 12-crown-4 derivatives form complexes with alkali metal cations [5–8]. δ-Lacton ring of alkyloxy coumarin compounds can be opened using sodium alkoxide in dry respective alcohol yielding cinnamate derivatives. Then, the phenolic hydroxyl group can be alkylated [9,10].

Because the cinnamic acid analogues show biological activity, we might expect that the crown ether derivatives of methylcinnamate could also have biological activity.

This work introduces the preparation and characterization of some novel crown ether derivatives of methylcinnamate compounds obtained from respective chromenone-crown ethers.

RESULTS AND DISCUSSION

Recent work from our laboratory described general method for the synthesis of chromenone-crown ethers [5–8]. 7,8-Dihydroxy-2*H*-chromenone crown ether derivatives **4a–f** were synthesized from the polyethylene glycol ditosylate or dichloride with corresponding 7,8-dihydroxy-2*H*-chromenone derivatives **3a–f**, which were prepared from pyrogallol and D,L-malic acid **2a** in the presence of H_2SO_4 or 2,3,4-trihydroxybenzaldehyde and corresponding methoxyphenylacetic acid in NaOAc/Ac_2O mixture **3b–f** [5–8]. All these compounds were purified using column chromatography (silica gel) with chloroform. The structures of all synthesized compounds were identified by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry [6–8].

We report herein a general method for the synthesis of methylcinnamate derivatives of 15-crown-5 from the respective chromenone-crown ethers. The phenylacrylic acids have been prepared by a synthesis from the corresponding chromenone-crown ethers with MeONa solution in MeOH refluxed for 4 h to afford **5a** [11–13] or KOH and DMSO as solvent at 60°C for 3–6 h. The phenolic hydroxyl group was methylated with CH_3I to give desired compounds **5b–g** in quantitative yield [14,15]. The structures of all synthesized compounds were identified by elemental analysis, IR, ^{1}H NMR, and mass spectrometry. All spectral data confirm the proposed structures of all of the new compounds **5a–g**.

The IR spectra of novel methylcinnamate derivatives of 15-crown-5 **5a–g** showed C—H stretching bands at about 2940 and 2858 cm^{-1}, an α,β-unsaturated ester carbonyl and double bond in the region 1680–1700, 1600 cm^{-1}, respectively. The bending peaks around 1040–1260 cm^{-1} showed the structure of C—O—C ether chain for all new methylcinnamate derivatives.

The cinnamate skeleton was also elucidated by ^{1}H NMR spectra. The ^{1}H NMR spectrum of compound **5a–g**, which showed triplets for the methylene protons [—OCH_2CH_2O—] at δ 3.66–4.39, a pair of doublet with ortho-coupling constants at δ 6.54–7.40 ppm (d, J = 8.50 Hz, H-6) and δ 7.10–7.90 ppm (d, J = 8.50 Hz, H-5) implied the presence of methylcinnamate derivatives of 15-crown-5. When the ^{1}H NMR spectra of compounds 7,8-dihydroxy-2*H*-chromenone derivatives of 15-crown-5 **4a–f** and methylcinnamate derivatives of 15-crown-5 **5a–g** were compared, one marked difference lay in the aromatic proton region with a singlet (s, H-3) was observed in the spectrum of **5a–g** at lower field than **4a–f**. And, also peaks at 3.68–3.92 ppm indicated the presence of —OCH_3 groups.

The IR spectrum of compound **5a**, the absorption band at 3400 cm^{-1} corresponding to hydroxyl stretching vibration disappears after its conversion into compound **5b**. The rest of spectral data of compound **5a** are very similar to **5b**. The IR spectrum of compound **5a** and **5b** including the stretching bands around 2947–2858 cm^{-1} of the C—H stretching frequency, 1701–1681 cm^{-1}of the carbonyl group, 1623–1604 cm^{-1} of the benzene ring, and 1261–1041 cm^{-1} of the ether chain, respectively. The structural assignments are based on the ^{1}H NMR coupling constants of the olefinic protons, and stereochemistry of the **5a** and **5b** was assigned as *trans*-on the basis of the coupling constant value ($J_{H—H}$ = 15.99 Hz) with reference to previous data [11].

The structures of newly synthesized compounds **5a–g** were checked using MS spectrometry. Also MALDI-TOF mass spectra confirmed the formation of novel methylcinnamate derivatives of 15-crown-5 **5a–g** (Scheme 1).

EXPERIMENTAL

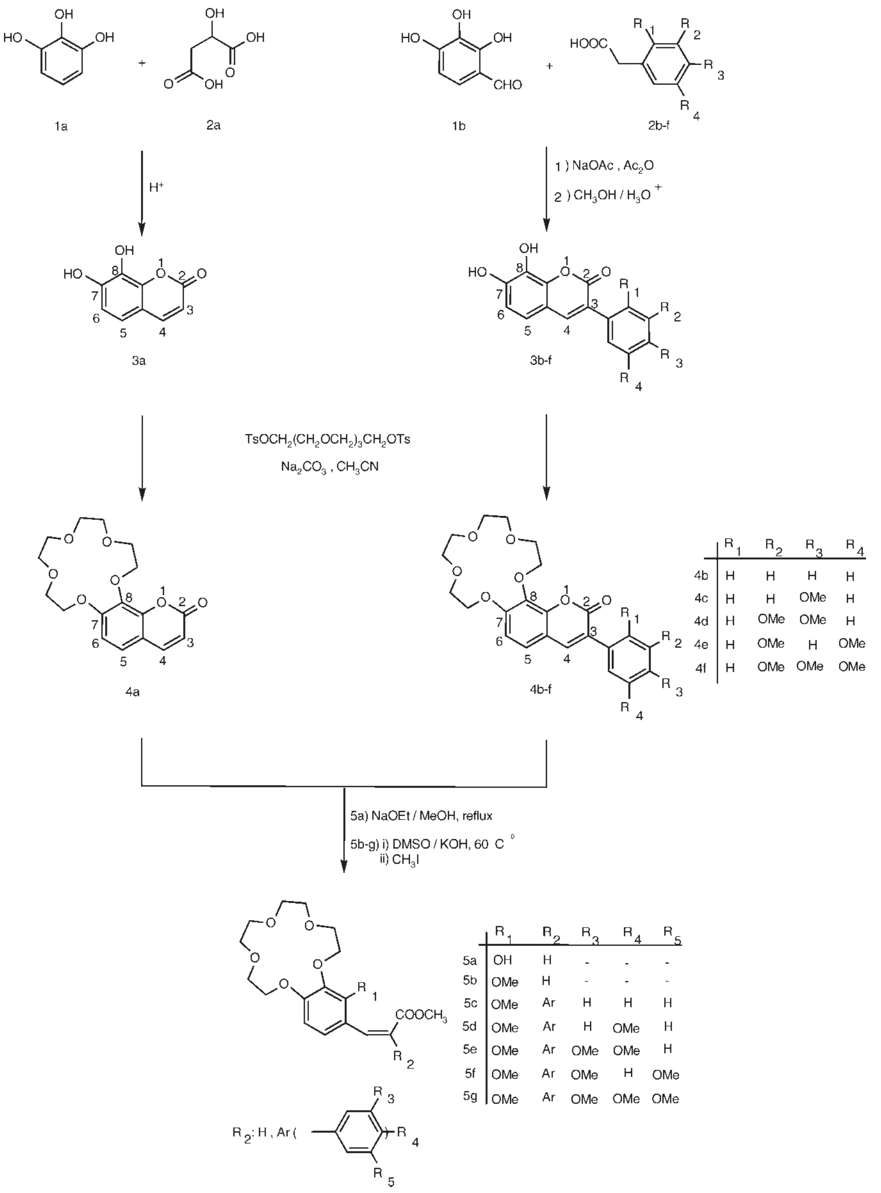
The starting chemicals used were of reagent grade. Melting points were obtained on a Gallenkamp apparatus. Elemental analysis was performed on a LECO CHNS 92 instrument. ^{1}H NMR spectra were determined with a Brucker DPX-400, 400 MHz High Performance Digital FT-NMR spectrometer. IR spectra were recorded as KBr disks in the range of 400–4000 cm^{-1} on a Schimadzu FTIR-8300 spectrometer. Mass spectra have been obtained with MALDI-TOF Instruments, model Bruker Autoflex III.

General procedure for the synthesis of methylcinnamate derivatives of 15-crown-5 5a–g. The crown ethers **4a–f** were prepared according to the known procedure [5–8]. The typical procedure for the reaction leading to a series of novel substituted methylcinnamate 15-crown-5 **5a–g** is as follows: A solution of sodium methoxide (28% in MeOH) (4 mmol) was added to a solution of the crown ether **4a** (2 mmol) in dry MeOH, and the mixture refluxed for 4 h and then the reaction mixture concentrated and extracted with AcOEt. The organic layer washed with brine and dried over $MgSO_4$ and evaporated to give product **5a** [11–13]. The crown ethers **4b–f** and methylcinnamate 15-crown-5 **5a** (1 mmol) were dissolved in DMSO, and then the KOH (2 mmol) was added to the reaction mixture and stirred at 60°C for 3–6 h. The reaction could also be monitored by thin-layer chromatography. CH_3I (2.5 mmol) was then added to the cooled reaction mixture. The reaction mixture was stirred at ambient room temperature for 2–6 h. The reaction was followed by thin-layer chromatography. The resulting mixture was poured into 30–50 mL icy water. The precipitate was collected by filtration, washed with water, and dried to give product **5b–g** [14,15].

(E)-Methyl-3-(14-hydroxy-2,3,5,6,8,9,11,12-octahydrobenzo[*b*][1,4,7,10,13] pentaoxacyclopentadecin-15-yl)acrylate (5a: $C_{18}H_{24}O_8$). A solution of sodium methoxide (28% MeOH) (0.77 mL, 4 mmol) was added to compound **4a** (0.672 g, 2 mmol) in MeOH (10 mL), which was reacted as described earlier to afford **5a**. Yield: 0.42 g (57%), mp 188–189°C; IR (KBr): 3402, 2939, 2873, 2858, 1681, 1604, 1504, 1458, 1261, 1041 cm^{-1}; ^{1}H NMR (400 MHz/$CDCl_3$): δ 3.66 (t, 4H, J = 4.29 Hz), 3.68 (s, 3H, OCH_3), 3.70 (t, 2H, J = 4.29 Hz), 3.79 (t, 2H, J = 4.29 Hz), 3.88 (t, 2H, J = 4.29 Hz), 4.00 (t, 2H, J = 5.46 Hz), 4.20 (t, 2H, J = 4.29 Hz), 4.30 (t, 2H, J = 5.46 Hz), 6.48 (d, 1H, J = 8.97 Hz), 6.55 (d, 1H, J = 15.99 Hz), 7.15 (d, 1H, J = 8.58 Hz), 7.90 (d, 1H, J = 15.99 Hz). *Anal.* Calcd. for $C_{18}H_{24}O_8$: C, 58.69; H, 6.57. Found: C, 58.45; H, 6.78.

(E)-Methyl-3-(14-methoxy-2,3,5,6,8,9,11,12-octahydrobenzo[*b*][1,4,7,10,13] pentaoxacyclopentadecin-15-yl)acrylate (5b: $C_{19}H_{26}O_8$). A mixture of compound **5a** (0.40 g, 1.09 mmol) and CH_3I (0.138 mL, 2.7 mmol) in DMSO was treated as described earlier to give **5b**. Yield: 0.18 g (43%) mp 84–85°C; IR (KBr): 2947, 2904, 2858, 1701, 1623, 1593, 1496, 1461, 1296, 1261, 1041 cm^{-1}; ^{1}H NMR (400 MHz/$CDCl_3$): δ 3.74 (t, 8H, J = 5.46 Hz), 3.79 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.93 (t, 4H, J = 4.68 Hz), 4.16 (t, 2H, J = 4.29 Hz), 4.18 (t, 2H, J = 5.07 Hz), 6.41 (d, 1H, J = 16.38 Hz), 6.64 (d, 1H, J = 8.58 Hz), 7.23 (d, 1H, J = 8.58 Hz), 7.87 (d, 1H, J = 15.99

Scheme 1



	R_1	R_2	R_3	R_4
4b	H	H	H	H
4c	H	H	OMe	H
4d	H	OMe	OMe	H
4e	H	OMe	H	OMe
4f	H	OMe	OMe	OMe

	R_1	R_2	R_3	R_4	R_5
5a	OH	H	-	-	-
5b	OMe	H	-	-	-
5c	OMe	Ar	H	H	H
5d	OMe	Ar	H	OMe	H
5e	OMe	Ar	OMe	OMe	H
5f	OMe	Ar	OMe	H	OMe
5g	OMe	Ar	OMe	OMe	OMe

Hz); ms: *m/z* 382 (M^+), 405 ($M^+ + Na^+$), 421 ($M^+ + K^+$). *Anal.* Calcd. for $C_{19}H_{26}O_8$: C, 59.68; H, 6.85. Found: C, 59.45; H, 6.78.

Methyl-3-(14-methoxy-2,3,5,6,8,9,11,12-octahydrobenzo[*b*][1,4,7,10,13]pentaoxacyclopentadecin-15-yl)-2-phenylacrylate (5c: $C_{25}H_{30}O_8$). A mixture of compound **4c** (0.206 g, 0.5 mmol) and KOH (0.056 g, 1 mmol) in DMSO (5 mL) was heated, then treated with CH_3I (0.068 mL 1.25 mmol), reacted, and then worked up as described earlier to afford **5c**. Yield: 0.044 g (19%) mp 82°C; IR (KBr): 2947, 2904, 2858, 1701, 1623, 1593, 1461, 1261, 1041 cm^{-1}; ^1H NMR (400 MHz/$CDCl_3$) :δ 3.78 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.98 (t, 8H, J = 4.68 Hz), 4.08 (t, 4H, J = 4.60 Hz), 4.18 (t, 4H, J = 4.60 Hz), 6.90 (dd, 2H, J = 8.97 and 2.34 Hz), 6.97 (dd, 1H, J = 8.97 and 2.34 Hz), 7.10 (d, 1H, J = 8.58 Hz), 7.40 (dd, 2H, J = 8.58), 7.90 (d, 1H, J = 8.58 Hz), 7.98 (s, 1H); ms: *m/z* 458 (M^+), 481 ($M^+ + Na^+$), 497 ($M^+ + K^+$). *Anal.* Calcd. for $C_{25}H_{30}O_8$: C, 65.49; H, 6.60. Found: C, 64.85; H, 6.75.

Methyl-3-(14-methoxy-2,3,5,6,8,9,11,12-octahydrobenzo[b][1,4,7,10,13]pentaoxacyclopentadecin-15-yl)-2-(4-methoxyphenyl)acrylate (5d: $C_{26}H_{32}O_9$). Compound **4d** (0.221 g, 0.5 mmol), KOH (0.056 g, 1 mmol), and CH_3I (0.068 mL 1.25 mmol) in DMSO (5 mL) were reacted as described earlier to give **5d**. Yield: 0.058 g (24%) mp 76–77°C; IR (KBr): 2923, 2858, 1728, 1600, 1454, 1292, 1110, 1033 cm^{-1}; ^1H NMR (400 MHz/$CDCl_3$): δ 3.72 (t, 8H, J = 5.04 Hz), 3.73 (s, 3H, OCH_3), 3.85 (s, 6H, OCH_3), 3.90 (t, 4H, J = 5.50 Hz), 4.21 (t, 4H, J = 5.07 Hz), 6.59 (d, 1H, J = 8.58 Hz), 7.00 (d, 1H, J = 8.58 Hz), 7.20 (d, 2H, J = 7.80 Hz), 7.36 (d, 2H, J = 7.80 Hz), 8.05 (s, 1H); ms: *m/z* 488 (M^+), 511 ($M^+ + Na^+$), 527 ($M^+ + K^+$). *Anal.* Calcd. for $C_{26}H_{32}O_9$: C, 63.92; H, 6.60. Found: C, 62.78; H, 6.45.

Methyl-2-(3,4-dimethoxyphenyl)-3-(14-methoxy-2,3,5,6,8,9,11,12-octahydrobenzo[*b*][1,4,7,10,13]pentaoxa-cyclopentadecin-15-yl)acrylate (5e: $C_{27}H_{34}O_{10}$). Compound **4e** (0.236 g, 0.5 mmol), KOH (0.056 g, 1 mmol), and CH_3I (0.068 mL 1.25 mmol) in DMSO (5 mL) were treated as described earlier to give **5e**. Yield: 0.044 g (17%) mp 91–92°C; IR (KBr): 2923, 2858, 1728, 1600, 1454, 1292, 1110, 1033 cm^{-1}; ^{1}H NMR (400 MHz/$CDCl_3$): δ 3.83 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.94 (t, 4H, *J* = 4.29 Hz), 3.98 (t, 4H, *J* = 4.29 Hz), 4.14 (t, 2H, *J* =4.29 Hz), 4.20 (t, 2H, *J* = 5.46 Hz), 4.23 (t, 2H, *J* = 4.29 Hz), 4.38 (t, 2H, *J* = 4.68 Hz), 6.59 (d, 1H, *J* = 8.97 Hz), 6.85 (dd, 1H, *J* = 8.77 and 2.73 Hz), 6.92 (br d, 1H, *J* = 8.19 Hz), 7.19 (d, 1H, *J* = 8.58 Hz), 7.28 (d, 1H, *J* = 1.95 Hz), 7.69 (s, 1H); ms: *m*/*z* 518 (M^+), 541 (M^+ + Na^+), 557 (M^+ + K^+). *Anal*. Calcd. for $C_{27}H_{34}O_{10}$: C, 62.54; H, 6.61. Found: C, 61.45; H, 6.88.

Methyl-2-(3,5-dimethoxyphenyl)-3-(14-methoxy-2,3,5,6,8,9,11,12-octahydrobenzo[*b*][1,4,7,10,13] pentaoxacyclopentadecin-15-yl)acrylate (5f: $C_{27}H_{34}O_{10}$). Compound **4f** (0.236 g, 0.5 mmol), KOH (0.056 g, 1 mmol), and CH_3I (0.068 mL 1.25 mmol) in DMSO (5 mL) were treated as described earlier to give **5f**. Yield: 0.040 g (15%) mp 97–98°C; IR (KBr): 2939, 2873, 2858, 1681, 1604, 1458, 1261, 1041 cm^{-1}; ^{1}H NMR (400 MHz/$CDCl_3$): δ 3.76 (s, 3H, OCH_3), 3.83 (s, 9H, OCH_3), 3.95 (t, 4H, *J* = 4.40 Hz), 3.98 (t, 4H, *J* = 4.40 Hz), 4.24 (t, 4H, *J* = 4.40 Hz), 4.39 (t, 4H, *J* = 4.90 Hz), 6.49 (t, 1H, *J* = 2.40 Hz), 6.83 (d, 2H, *J* = 2.40 Hz), 6.86 (d, 1H, *J* = 9.20 Hz), 7.19 (d, 1H, *J* = 8.40 Hz), 7.73 (s, 1H); ms: *m*/*z* 518 (M^+). *Anal*. Calcd. for $C_{27}H_{34}O_{10}$: C, 62.54; H, 6.61. Found: C, 62.95; H, 6.42.

Methyl-3-(14-methoxy-2,3,5,6,8,9,11,12-octahydrobenzo-[*b*][1,4,7,10,13]pentaoxacyclopentadecin-15-yl)-2-(3,4,5-trimethoxyphenyl)acrylate (5g: $C_{28}H_{36}O_{11}$). Compound **4g** (0.251 g, 0.5 mmol), KOH (0.056 g, 1 mmol), and CH_3I (0.068 mL 1.25 mmol) in DMSO (5 mL) were treated as described earlier to give **5g**. Yield: 0.048 g (18%) mp 89°C; IR (KBr): 2978, 2825 (C—H), 1676 (C=O), 1247, 1040 (C—O) cm^{-1}; ^{1}H NMR (400 MHz/$CDCl_3$): δ 3.75 (t, 8H, *J* = 4.29 Hz), 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.90 (s, 6H, OCH_3), 3.96 (t, 4H, *J* = 4.29 Hz), 4.23 (t, 2H, *J* = 4.29 Hz), 4.398 (t, 2H, *J* = 4.68 Hz), 6.85 (d, 1H, *J* = 8.97 Hz), 6.90 (br s, 2H), 7.19 (d, 1H, *J* = 8.58 Hz), 7.70 (s, 1H); ms: *m*/*z* 573 (M^+ + Na^+). *Anal*. Calcd. for $C_{28}H_{36}O_{11}$: C, 61.30; H, 6.61. Found: C, 61.01; H, 6.75.

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Solvent-Free Microwave-Assisted Synthesis of 1*H*-Indole-2, 3-dione Derivatives

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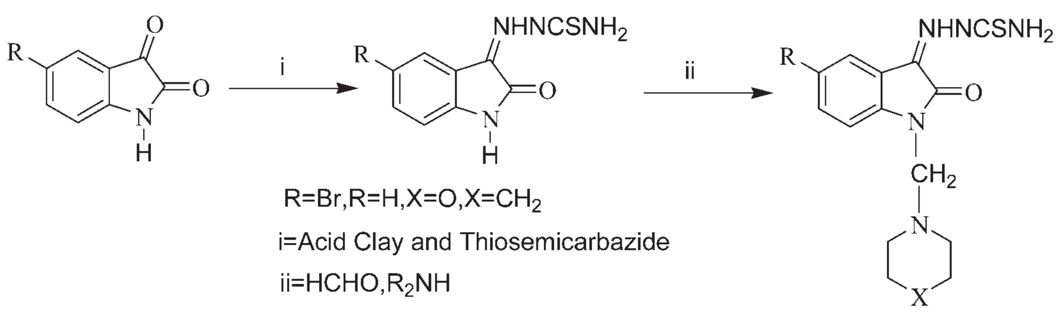

Microwave-assisted synthesis has been found to increase both reaction rates and yields *via* more efficient heating compared with standard thermal conduction. Dry reaction of isatins with thiosemicarbazide and their thiosemicarbazone with secondary amine on acid—washed K10 in microwave oven afforded isatin-3-thiosemicarbazones and N-Mannich bases in reasonably good yield. The chemical structures were confirmed by means of ^{1}H NMR, IR spectral data, and elemental analysis.

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INTRODUCTION

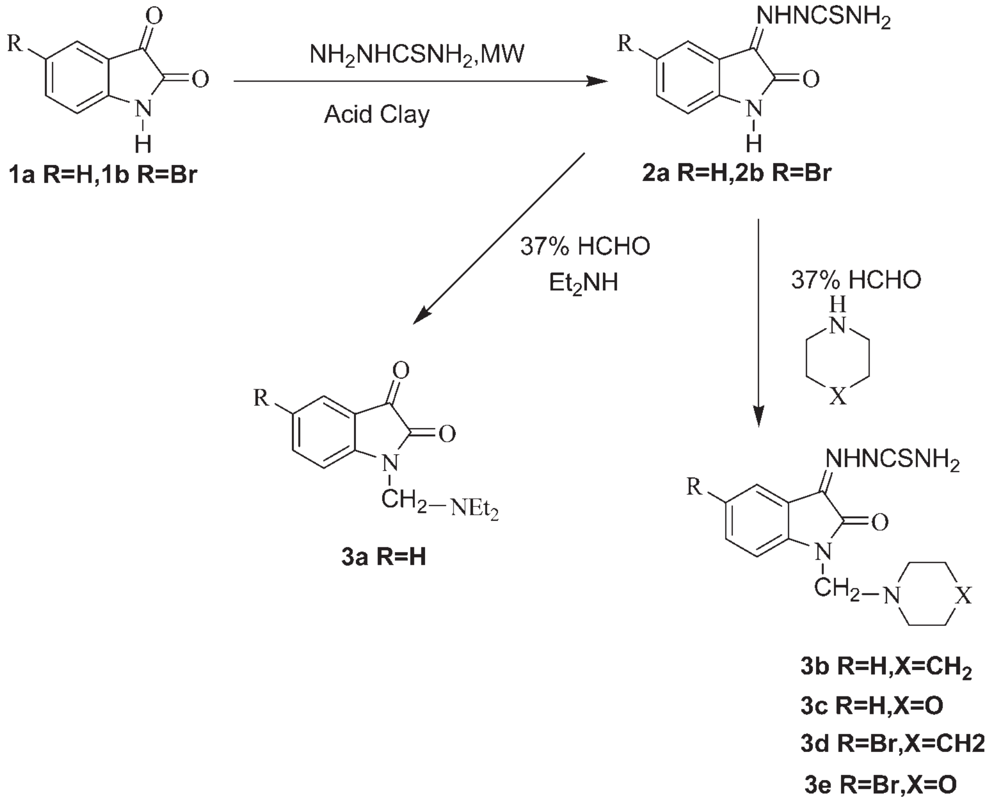
Microwave-assisted organic synthesis is a fascinating and quickly growing area in synthetic organic chemistry [1a–e]. This new synthetic technique is based on the observation that some reactions proceed much faster and with higher yields under microwave irradiation compared with conventional heating. In many cases reactions that normally require many hours at reflux temperature under classical conditions can be completed within a few minutes or even seconds in a microwave oven. The microwave-assisted chemical transformations have become important because of several advantages over the conventional thermal reactions.

Solvent-free chemical synthesis has received much attention recently [2a–e]. Solvent-free processes are not only environmentally benign but also economical [3]. Because a solvent is not required, toxic wastes can be minimized or eliminated, and so the cost of solvent and waste treatment is reduced. Furthermore, operational simplicity is an attractive feature. Recent advances in this area include, for example, aldol and related reactions [4a–f].

In view of the growing need for green chemistry for a cleaner environment and the ever increasing contribution of acidic solid surfaces, especially Montmorillonite clay, we have now developed a general, solvent-free synthesis of Schiff and Mannich bases of isatin.

Montmorillonite clay with its large surface area and high Bronsted and Lewis acidity has emerged as an environmentally benign solid acid catalyst, replacing many hazardous acid catalysts in organic synthesis and reactions, both in laboratory and industry.

Scheme 1



Isatin (1*H*-indole-2,3-dione) derivatives [5a–d] are reported to manifest a variety of biological activities like antibacterial, antifungal, antiplasmodial, and anti-HIV [6–8]. In recent years, Schiff and Mannich bases of 1*H*-indole-2,3-dione are found to exhibit broad-spectrum chemotherapeutic properties such as antiviral [9], anti-TB [10–12], antifungal, anticancer [13,14], antiprotozoal [15], muscle relaxant [16], and antibacterial [17–20]. An insight into the structure activity relationships of isatin reveals that N-Mannich bases and 3-thiosemicarbazones of 5-bromo-isatin are reported to have a profound increase in their biological activities [21–29]. In view of the above, it was thought worthwhile to exploit the use of MW irradiation for the synthesis of some potent bioactive Mannich and Schiff base of isatin.

RESUTS AND DISCUSSION

In the present study, 1*H*-indole-2,3-dione and its 5-bromo derivative (**1a**,**1b**) were allowed to react with thiosemicarbazide in the presence of a catalytic amount of acid clay under microwave irradiation at 160 W to give thiosemicarbazone derivatives (2a/2b) in reasonably good yield. The resulting products 2a/2b was subsequently made to undergo Mannich reaction using formaldehyde solution and morpholine/piperidine/secondary amine to furnish the desired product **3a–e** in excellent yields (Scheme 1). All the products displayed IR and ^{1}H NMR spectra consistent with their assigned structures. The physical data and yield of the products are given in Table 1. For the synthesis of thiosemicarbazone, we initially attempted the dry reaction of isatin with thiosemicarbazide on montmorrillonite K^{10} clay (Bronsted acidity: Hamett acidity function, $H_0 = -5.5$ to -5.9) at room temperature and also under microwave irradiation; however, the reaction was extremely sluggish. To overcome this difficulty, we utilized the fact that washing of this clay with mineral acids increases its acidity sharply ($H_0 = -6$ to -8) [30]. Indeed acid-treated clay has been previously used for a few reactions [31]. Therefore, we washed montmorrillonite K_{10} clay with concentrated HCl, which, after usual work-up, furnish what we designate ‘‘acid clay.’’ It was found to be devoid of any free acid and chloride ions. We next used this acid-clay in the targeted reactions and achieved success.

Table 1

Yield and physical data of the products.

Product	R	Formula	Time		Yield[a] (%)		Mp (°C)
			MW[b] (min)	Conventional (h)	MW	Conventional	
2a	H	$C_9H_8N_4SO$	4	5	88	75	244–245
2b	Br	$C_9H_7N_4SOBr$	4	5	92	80	271–272
3a	H	$C_{14}H_{19}N_5OS$	4	4	93	84	132–134
3b	H	$C_{15}H_{19}N_5OS$	5	4	92	83	178–179
3c	H	$C_{14}H_{17}N_5O_2S$	5	4	94	88	212–213
3d	Br	$C_{15}H_{18}N_5OSBr$	4	4	92	82	216–217
3e	Br	$C_{14}H_{16}N_5O_2SBr$	5	4	94	80	230–231

[a] Isolated yield.
[b] Irradiation at 160 W.

CONCLUSION

The use of MWI provides an efficient, clean, and quick methodology for the synthesis of various 1*H*-indole-2,3-dione derivatives with greater yields than the previously reported conventional methods.

EXPERIMENTAL

Melting points were measured in open capillaries and are uncorrected. IR spectra were recorded on a Jasco FT/IR-5300 spectrophotometer. ^{1}H NMR spectra were run on a Jeol AL 300 FTNMR spectrometer and the chemical shifts are expressed as δ ppm using TMS as internal reference. Elemental analyses were performed on Exeter Analytical Inc. ‘‘Model CE-440 CHN analyzer. All commercially available chemicals were purchased from E. Merck and Aldrich.

General procedure for the preparation for 2a/2b

Microwave-assisted Method. A mixture of isatin/5-bromoisatin (1a/1b, 0.01 mol), thiosemicarbazide (0.011 mol), and catalytic amount of acid clay contained in an Erlenmeyer flask was introduced in to a Le Chef domestic microwave oven and was irradiated for 4 min at 160 W. After completion of the reaction (as monitored by TLC), the mixture was extracted with dichloromethane (3 × 20 mL), the solvent was evaporated and the solid obtained was recrystallized with ethanol and dried to afford the product 2a/2b.

Conventional Method. A solution of thiosemicarbazide (0.011 mol) in ethanol (10 mL) was added to a solution of isatin/5-bromoisatin (1a/1b) (0.01 mol) in ethanol (20 mL). After addition of a drop of acetic acid, the mixture was refluxed on a water bath for 5 h. The product formed after cooling was collected by filtration and washed with ethanol or recrystallized from ethanol.

General procedure for the preparation of 3a–e

Microwave-assisted Method. The mixture of 2a/2b (2 mmol), formaldehyde solution (37%, 0.5 mL), and morpholine/piperidine/*N*,*N*-diethyl amine (2 mmol) was introduced into the microwave oven and was irradiated for 4–5 min at 160 W, while monitoring the course of reaction by TLC. The resulting mixture was extracted with dichloromethane (3 × 20 mL) and washed with petroleum ether. After evaporation of dichloromethane, pure solid 3a–e was obtained.

Conventional Method. To a suspension of 2a/2b (0.002 mol) in absolute ethanol (20 mL), 37% formaldehyde solution (0.5 mL) and morpholine/piperidine/*N*,*N*-diethyl amine (2 mmol) were added dropwise with vigorous stirring. After combining all reagents, the reaction mixture was stirred with gentle refluxing for 4 h. The solid product was collected by filtration and washed with petroleum ether to obtain pure product 3a–3e.

1H-Indole-2,3-dione-3-thiosemicarbazone(2a). (69%) Mp 240–241°C (lit. [23] 239–241°C); IR (KBr): 3425 (N-Hstr of indole), 3238 (N-Hstr of thiosemicarbazone moiety), 1682 (C=Ostr), 1130 (C=Sstr), ^{1}H NMR (DMSO-d_6):δ 12.45 (s, NH of thiosemicarbazone moiety), 11.18 (s,1H-NH proton of indole nucleus), 9.02 (s, 2H NH_2 of thiosemicarbazone moiety), 7.65 (d, 1H-C_7-H of indole nucleus), 7.35 (dd 1H C_6-H proton), 7.08 (dd, 1HC_5-H proton), 6.91 (d, 1HC_4-H proton). Anal Calcd. for $C_9H_8N_4OS$ (220.27) C, 49.03; H, 3.61; N, 25.42. Found: C, 48.97; H, 3.60; N, 25.28.

5-Bromo-1H-indole-2,3-dione-3-thiosemicarbazone (2b). Yield (73%); Mp 271–272°C; IR (KBr): 3430 (N-Hstr of indole nucleus), 3230 (N-Hstr of thiosemicarbazone moiety), 1690 (C=Ostr), 1133 (C=Sstr); ^{1}H NMR (DMSO-d_6): δ 12.47 (s, 1H-NH of thiosemicarbazone moiety), 11.17 (s, 1H NH proton of indole nucleus), 9.02 (s, 1H NH_2 of thiosemicarbazone moiety), 7.74 (d, 1HC_4-H proton), 7.41 (dd, 1H C_6-H proton), 7.12 (d, 1H C_7-H of indole nucleus). Anal Calcd. for $C_9H_7BrN_4OS$ (299.14) C, 36.10; H, 2.34; N,18.72. Found: C, 36.08; H, 2.30; N, 18.74.

N^1-Diethylaminomethyl-indole-2,3-dione-3-thiosemicarbazone (3a). Yield (75%); Mp 132–134°C (Lit. 135°C) [24]; IR (KBr): 3436 (N-Hstr of indole), 3240 (N-Hstr of thiosemicarbazone moiety), 1670 (C=Ostr), 1140 (C=Sstr); ^{1}H NMR (DMSO-d_6) δ 12.11 (s, 1H NH of thiosemicarbazone moiety), 9.06 (s, 2H NH_2 of thiosemicarbazone moiety), 7.73 (d, 1H C_7-H proton), 7.45 (dd, 1H C_6-H proton), 7.17 (dd, 1H C_5-H proton), 7.20 (d, 1H C_4-H proton), 4.52 (s, 2H N-CH_2-N proton), 2.65 (q, 4H), 1.08 (t, 6H). Anal Calcd. for $C_{14}H_{19}N_5OS$ (305.63) C, 55.08; H, 6.23; N, 22.95. Found: C, 54.76; H, 6.17; N, 22.88.

N^1-Piperidin-1-ylmethyl-indole-2,3-dione-3-thiosemicarbazone (3b). Yield (77%); Mp 178–179°C (lit. 177–178°C) [24];

IR (KBr): 3427 (N-Hstr of indole), 2925 (N-Hstr of thiosemicarbazone moiety), 1700 (C=Ostr), 1162 (C=Sstr); ^{1}H NMR (DMSO-d_6): δ 12.36 (s, 1H NH of thiosemicarbazone moiety), 9.06 (s, 1H NH_2 of thiosemicarbazone moiety), 7.71 (d 1H C_7-H proton), 7.41 (dd, 1H C_6-H proton), 7.26 (d, 1H C_4-H proton), 7.17 (dd, 1H C_5-H proton), 4.47 (s, 2H N-CH_2-N proton), 2.54 (t, 4H), 1.46 (m, 4H), 1.33 (m, 2H). Anal Calcd. for (319.14) $C_{14}H_{17}N_5OS$ C, 52.64; H, 5.33; N, 21.93. Found: C, 52.43; H, 5.37; N, 20.96.

N^1-Morpholin-4-ylmethyl-indole-2,3-dione-3-thiosemicarbazone (3c). Yield (68%); Mp 212–213°C: (lit. 215 216°C) [24] IR (KBr): 3447 (N-Hstr of indole), 3206 (N-Hstr of thiosemicarbazone moiety), 1692 (C=Ostr), 1149 (C=Sstr); ^{1}H NMR (DMSO-d_6): δ 12.38 (s, 1H NH of thiosemicarbazone moiety), 9.05 (s, 1H NH_2 of thiosemicarbazone moiety), 7.73 (d, 1H C_7-H proton), 7.42 (dd, 1H C_6-H proton), 7.27 (d, 1H C_4-H proton), 7.15 (dd, 1H C_5-H proton), 4.49 (s, 2H N-CH_2-N proton), 3.54 (br s, 4H), 2.58 (br s, 4H). Anal Calcd. for $C_{15}H_{19}N_5OS$ (317.26) C, 56.76; H, 5.99; N, 22.07. Found C, 56.74; H, 6.03; N, 22.11.

5-Bromo-N^1-piperidin-1-ylmethyl-indole-2,3-dione-3-thiosemicarbazone(3d). Yield (64%); Mp 216–217°C IR (KBr): 3447 (N-Hstr of indole), 2933 (N-Hstr of thiosemicarbazone moiety), 1695 (C=Ostr), 1112 (C=Sstr), ^{1}H NMR (DMSO-d_6): δ 12.37 (s, 1H NH of thiosemicarbazone moiety), 9.06 (s, 1H NH_2 of thiosemicarbazone moiety), 7.78 (dd, 1H C_4-H proton), 7.45 (dd, 1H C_6-H proton), 7.28 (d, 1H C_7-H proton), 4.48 (s, 2H N-CH_2-N proton), 2.52 (t, 4H), 1.46 (m, 4H), 1.34 (m, 2H). Anal Calcd. for $C_{14}H_{16}BrN_5O_2S$ (397.25) C, 42.30; H, 4.05; N, 17.63. Found C, 42.62; H, 4.05; N,17.60.

5-Bromo-N^1-morpholin-4-ylmethyl-indole-2,3-dione-3-thiosemicarbazone(3e). Yield (71%); Mp 230–231°C IR (KBr): 3440 (N-Hstr of indole), 2925 (N-Hstr of thiosemicarbazone moiety), 1691 (C=Ostr), 1145 (C=Sstr), ^{1}H NMR (DMSO-d_6): δ 12.39 (s, 1H NH of thiosemicarbazone moiety), 9.05 (s, 1H NH_2 of thiosemicarbazone moiety), 7.80 (dd, 1H C_4-H proton), 7.47 (dd, 1H C_6-H proton), 7.30 (d, 1H C_7-H proton), 4.50 (s, 2H N-CH_2-N proton), 3.54 (br s, 4H), 2.56 (br s, 4H). Anal Calcd. for $C_{15}H_{18}BrN_5OS$ (395.31) C, 45.55; H, 4.56; N, 17.72. Found C, 45.88; H, 4.63; N, 17.63.

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Synthesis and Biological Evaluation of Novel Conjugated Coumarin-Thiazole Systems

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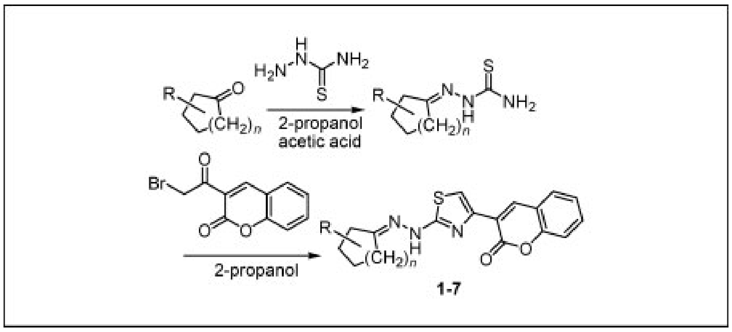

Seven new 2,4-disubstituted thiazoles have been synthesized by Hantzsch condensation and assayed for several biological activities for a preliminary screening. They have been fully characterized by elemental analysis, UV–Vis spectroscopy, TG-DTA, IR, and ^{1}H NMR as well. These structures display different pharmacological (antimicrobic activity, citotoxicity, and hMAO inhibition) and industrial properties (complete transparency in the region between 465–800 nm and high thermal stability) varying on their substituents and could be considered as good lead compounds for further developments.

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INTRODUCTION

In the last few years, researchers have renewed interest in 3-(thiazol-4-yl)coumarins [1–6] for their industrial applications as fluorescent probes and laser dyes [7], for their biological activity as pharmaceutical agents [8–10] and because they could be useful for the construction of the diazepinone ring [11]. In addition, π-conjugated systems are known to show interesting electronic, optical, and electric properties [12]. On the basis of our experience in the synthesis of thiazole and coumarin [13,14] derivatives, we were pursued, therefore, to synthesize a series of novel heterocyclic systems characterized by the association of a coumarin nucleus with a thiazole ring linked to a cycloaliphatic group, whose presence and influence on this kind of molecules have not been described so far (Table 1).

RESULTS AND DISCUSSION

The coumarin-thiazole derivatives (**1–7**) were prepared by Hantzsch condensation between the appropriate thiosemicarbazone and 3-α-bromo-acetyl coumarin in 2-propanol at room temperature according to a protocol used in our laboratory [15]. In these conditions, the isolation of pure products in 86–99% yield was made simply by filtration under vacuum. All the structures were fully supported by elemental analysis and spectral data as reported in the experimental section and in Table 2. In particular, we obtained compound **3** and **4** as racemates, because of the presence of a chiral center in the structure. Knowing that the stereochemistry could affect deeply different biological activities and being commercially available the pure (*R*)-(+) enantiomer of 3-methylcyclohexanone, we planned a stereocontrolled synthesis in order to obtain derivative **5** with correlated (*R*)-(+) absolute configuration. The stereochemistry has been preserved by the stereoconservative synthetic pattern which did not interest the methyl on the cycloaliphatic moiety. The enantiomeric excess has been determined by HPLC on the Chiralpak AS-H chiral stationary phase (CSP) using the mixture *n*-hexane-2-propanol 70:30 (v/v) as a mobile phase: ee > 99%; $[\alpha]_D^{20} = -20$ (0.1, EtOH).

The compounds, correctly analyzed for their molecular formula, showed in the IR spectrum strong bands at 1710 and 1600 cm^{-1} due to the presence of a δ-lactone C=O and C=N group, respectively.

The UV–visible spectral analysis was carried out in methanol as solvent and the data are collected in Table

Table 1

Structure and CLogP (ChemDraw Ultra 8.0) of compounds **1–7**.

Compound	*n*	R	CLogP
1	1	H	3.28
2	2	H	3.84
3	2	2-CH_3	4.36
4	2	3-CH_3	4.36
5	2	(*R*)-(+)-3-CH_3	4.36
6	2	4-CH_3	4.36
7	3	H	4.40

Table 3

MIC values (μg/mL) of some derivatives against eight strains of *Candida spp* and **C** = Clotrimazole.

Compound	*C. albicans* (2 strains)	*C. sakè* (strain)	*C. parapsilopis* (strains)	*C. krusei* (strains)
1	4	32	>128	>128
2	8	16	16	8–16
7	8–16	16	8	8–>128
C	8	8	8	8

2. The absorption spectra of all derivatives are generally characterized by sharp absorption bands in the region of 230–250 nm and 290–300 nm with the λ_{max} independent upon the substituent and size of the cycloaliphatic moiety. Accordingly, the coumarin local π-π excitation appears to be the main type of electronic transition and complete transparency was observed in the region between 465–800 nm.

Further we have also studied the thermal stability of **1–7** using TG-DTA method (heat rate: 10°C/min, Ar flow: 100 cc/min). All the compounds exhibited a decomposition temperature (T_d) in the range 290–315°C, a feature which could be significant for NLO applications because it is superior to that reported (T_d = 290°C) for the benchmark 4-dimethylamino-4′-nitrostilbene (DANS) [16].

From a biological point of view, evaluating the influence of the bioactive coumarin nucleus on the C4 position of the thiazole as a modulator of the biological activity and correlating the results with those obtained in our previous papers [15,17,18], some of the synthesized compounds (which all show calculated log P values < 5) have been widely assayed for a preliminary antimicrobic screening against eight strains of pathogenic fungi (Table 3), several types of routine clinical Gram-positive and negative isolates (MIC values > 128 μg/mL, data not shown), and 20 clinical strains of *Helycobacter pylori* (Table 4). Clotrimazole and Metronidazole were used as standard antifungal and antibacterial drug, respectively.

The results showed that all compounds possess an antibacterial activity targeting selectively towards Metronidazole resistant strains of *Helicobacter pylori* and some *Candida albicans* strain isolates.

In addition, we evaluated the low citotoxic effect of the most representative compound (**7**) against EAhy, a human cell line obtained from a hybridoma between HUVEC and epithelial cells from a lung carcinoma. The viability of cells exposed to test compounds was estimated by the Trypan Blue dye exclusion assay after 24 h of incubation at 37°C. Cells incubated with culture medium alone represented the control and the cell viability was always greater than 97%. Data represent the arithmetic mean ± SD of at least three independent experiments (Table 5).

In the end, all the newly synthesized compounds were investigated for their ability to inhibit both human MAO isoforms by measuring their effects on the production of H_2O_2 from *p*-tyramine, using the Amplex Red MAO assay kit. Microsomial MAO isoforms prepared from insect cells (BTI-TN-5B1-4) infected with recombinant baculovirus containing cDNA inserts for hMAO-A and hMAO–B. Data were calculated as pIC_{50} for both isoforms and pSI referred to log selectivity index = $pIC_{50\ (MAO\text{-}A)} - pIC_{50\ (MAO\text{-}B)}$. The data represent mean values of at least five separate experiments and Clorgyline and *R*-(−)-deprenyl were used as standard drugs (Table 6).

Despite their inhibitory activity in the micromolar range, in examining the influence of the structural variation, some of them (in particular those which did not present substituents on the cycloaliphatic moiety) possessed a moderate A-selectivity. From a qualitative point

Table 2

UV–visible absorption of derivatives **1–7** (MeOH).

Compound	λ_{ab} (nm)	$\varepsilon \times 10^4$
1	293.74	1.60
2	293.57	1.85
3	291.61	1.29
4	292.03	0.88
5	295.37	0.66
6	298.52	1.23
7	292.30	1.24

Table 4

MIC values (μg/mL) of some derivatives and **M** = Metronidazole against 20 *H. pylori* strains.

Compound	Metronidazole sensitive strains (15 strains)	Metronidazole resistant strains (strains)
1	16–32	16–32
2	8–32	8–32
7	8–32	8–32
M	0.5–2	64–>128

Table 5

Citotoxicity of derivative **7** expressed as cell survival fraction ± SD (%).

	Concentration (μg/mL)			
Compound	50	5	0.5	0.05
7	52.94 ± 3.8	81.82 ± 5.6	93.75 ± 4.7	97.50 ± 1.8

of view, it must be highlighted the different selective hMAO inhibition of compound **5** (pure (*R*)-(+) enantiomer) in relation to **4** (racemate) bearing the same substituent in the same position.

CONCLUSION

We reported the synthesis, the spectral characterization, and a preliminary biological evaluation of seven novel heterocyclic systems. According to the biological results, these compounds exhibited a promising antimicrobic activity expecially oriented towards Metronidazole resistant strains of *Helycobacter pylori* and an interesting anti-*Candida* spectrum comparable to that of Clotrimazole. It has been also found a low cytotoxic effect against EAhy, a human immortalized cell line, which could justify a safe and therapeutic use of these derivatives. They further displayed a moderate selective hMAO-A inhibition which is probably affected by the steric hindrance of bulky coumarin nucleus inside the active site. All these results could be useful to evaluate new substitutions on the coumarin nucleus in order to enhance biological activities.

EXPERIMENTAL

The chemicals, solvents for synthesis, and spectral grade solvents were purchased from Aldrich (Italy) without further purification. Melting points (uncorrected) were determined automatically on a FP62 apparatus (Mettler-Toledo). ^{1}H NMR spectra were recorded at 400 MHz on a Bruker spectrometer. Chemical shifts are expressed as δ units (parts per millions) relative to the solvent peak. Coupling constants *J* are valued in Hertz (Hz). IR spectra were registered on a Perkin-Elmer FTIR Spectrometer Spectrum 1000 in potassium bromide. Elemental analysis for C, H, and N were recorded on a Perkin-Elmer 240 B microanalyzer and the analytical results were within ±0.4% of the theoretical values for all compounds. All reactions were monitored by TLC on 0.2 mm thick silica gel plates (60 F254 Merck). UV–vis spectra were recorded on a Perkin-Elmer UV–vis Spectrometer Lambda 10. Thermal analysis was performed under an inert gas flux using TGA/DTA (Pyris Diamond Perkin-Elmer, Waltham, MA).

Typical procedure for the thiosemicarbazones synthesis. The appropriate cycloaliphatic ketone (50 mmol) was dissolved in 100 mL of 2-propanol and stirred at room temperature with an equimolar amounts of thiosemicarbazide for 24 h with acetic acid as catalyst. The desired thiosemicarbazone precipitated from reaction mixture was filtered and crystallized from suitable solvent and dried.

Typical procedure for the Hantzsch protocol for the preparation of derivatives 1–7. Equimolar amounts of the prepared thiosemicarbazones (50 mmol) and 3-α-bromo-acetyl coumarin [19] (50 mmol), both dissolved in 2-propanol, were reacted at room temperature under magnetic stirring for 2 h. The precipitate was filtered, washed with petroleum ether and diethyl ether, and dried to give compounds **1–7** in 86–99% yields. All the yields are on isolated basis. The characterization data are given in Tables 1 and 2.

3-(2-(2-Cyclopentylidenehydrazynyl)thiazol-4-yl)-2*H*-chromen-2-one (1). Yellow crystals, 98% yield, mp 207–209°C; ^{1}H NMR (CDCl$_3$): δ 1.87–1.89 (m, 2H, cyclopentyl), 1.95–1.97 (m, 2H, cyclopentyl), 2.55 (s, 2H, cyclopentyl), 2.64 (s, 2H, cyclopentyl), 7.37–7.39 (m, 1H, C$_5$H-thiaz.), 7.49–7.69 (m, 2H, Ar), 7.81–7.83 (m, 2H, Ar), 8.59 (s, 1H, CH=), 12.20 (br s, 1H, NH, D$_2$O exch.); Anal. Calcd. for $C_{17}H_{15}N_3O_2S$: C, 62.75; H, 4.65; N, 12.91. Found: C, 62.77; H, 4.67; N, 12.92.

3-(2-(2-Cyclohexylidenehydrazynyl)thiazol-4-yl)-2*H*-chromen-2-one (2). Dark yellow crystals, 98% yield, mp 180–182°C; ^{1}H NMR (CDCl$_3$): δ 1.64–1.71 (m, 4H, cyclohexyl), 1.86 (s, 2H, cyclohexyl), 2.58 (s, 2H, cyclohexyl), 2.69 (s, 2H, cyclohexyl), 7.36 (s, 1H, C$_5$H-thiaz.), 7.61–7.63 (m, 2H, Ar), 7.80–7.85 (m, 2H, Ar), 8.62 (s, 1H, CH=), 12.39 (s, 1H, NH, D$_2$O exch.); Anal. Calcd. for $C_{18}H_{17}N_3O_2S$: C, 63.70; H, 5.05; N, 12.38. Found: C, 63.68; H, 5.04; N, 12.39.

3-(2-(2-(2-Methylcyclohexylidenehydrazynyl)thiazol-4-yl)-2*H*-chromen-2-one (3). Off white crystals, 86% yield, mp 171–173°C; ^{1}H NMR (CDCl$_3$): δ 1.16–1.18 (d, *J* = 6.3 Hz, 3H, CH$_3$), 1.21–1.23 (m, 2H, cyclohexyl), 1.27–2.04 (m, 5H, cyclohexyl), 2.50 (s, 1H, cyclohexyl), 3.01 (s, 1H, cyclohexyl), 7.38 (s, 1H, C$_5$H-thiaz.), 7.62–7.64 (m, 2H, Ar), 7.82–7.84 (m, 2H, Ar), 8.60 (s, 1H, CH=), 12.17 (br s, 1H, NH, D$_2$O exch.); Anal. Calcd. for $C_{19}H_{19}N_3O_2S$: C, 64.57; H, 5.42; N, 11.89. Found: C, 64.59; H, 5.40; N, 11.88.

3-(2-(2-(3-Methylcyclohexylidenehydrazynyl)thiazol-4-yl)-2*H*-chromen-2-one (4). Yellow crystals, 99% yield, mp 188–190°C; ^{1}H NMR (CDCl$_3$): δ 1.03–1.05 (d, *J* = 6.3 Hz, 3H, CH$_3$), 1.21–1.23 (m, 2H, cyclohexyl), 1.26–2.08 (m, 5H, cyclohexyl), 2.50 (s, 1H, cyclohexyl), 3.01 (s, 1H, cyclohexyl), 7.38 (s, 1H, C$_5$H-thiaz.), 7.80 (s, 2H, Ar), 7.91 (s, 2H, Ar), 12.20 (br s, 1H, NH, D$_2$O exch.); Anal. Calcd. for $C_{19}H_{19}N_3O_2S$: C, 64.57; H, 5.42; N, 11.89. Found: C, 64.56; H, 5.43; N, 11.90.

Table 6

hMAO inhibition and hMAO-A selectivity of derivatives **1–7**.

Compound	pIC$_{50}$ hMAO-A	pIC$_{50}$ hMAO-B	pSI
1	4.39	<4.00	>0.39
2	5.28	<4.00	>1.28
3	5.04	5.12	−0.08
4	4.96	4.97	−0.01
5	5.11	5.02	0.09
6	5.15	4.87	0.28
7	5.19	<4.00	>1.19
Clorgyline	8.29	4.20	−4.09
R-(−)-deprenyl	4.17	7.77	3.60

(*R*)-(+)-3-(2-(2-(Methylcyclohexylidenehydrazynyl)thiazol-4-yl)-2*H*-chromen-2-one (5). Yellow crystals, 99% yield, mp 200–201°C; ^{1}H NMR ($CDCl_3$): δ 1.02–1.04 (d, *J* = 6.3 Hz, 3H, CH_3), 1.26–1.27 (m, 2H, cyclohexyl), 1.79–1.96 (m, 5H, cyclohexyl), 2.95–2.99 (m, 2H, cyclohexyl), 7.38 (s, 1H, C_5H-thiaz.), 7.62–7.66 (m, 2H, Ar), 7.80–7.84 (m, 2H, Ar), 8.62 (s, 1H, CH=), 12.18 (br s, 1H, NH, D_2O exch.); Anal. Calcd. for $C_{19}H_{19}N_3O_2S$: C, 64.57; H, 5.42; N, 11.89. Found: C, 64.59; H, 5.44; N, 11.90.

3-(2-(2-(4-Methylcyclohexylidenehydrazynyl)thiazol-4-yl)-2*H*-chromen-2-one (6). Dark orange crystals, 86% yield, mp 175–177°C; ^{1}H NMR ($CDCl_3$): δ 0.99 (s, 3H, CH_3), 1.75 (s, 1H, cyclohexyl), 1.99–2.09 (m, 3H, cyclohexyl), 2.19–2.31 (m, 2H, cyclohexyl), 2.55–2.56 (m, 1H, cyclohexyl), 3.06 (s, 1H, cyclohexyl), 7.32 (s, 1H, C_5H-thiaz.), 7.64 (s, 2H, Ar), 7.84 (s, 2H, Ar), 8.59 (s, 1H, CH=), 12.17 (s, 1H, NH, D_2O exch.); Anal. Calcd. for $C_{19}H_{19}N_3O_2S$: C, 64.57; H, 5.42; N, 11.89. Found: C, 64.59; H, 5.42; N, 11.90.

3-(2-(2-(Cycloheptylidenehydrazynyl)thiazol-4-yl)-2*H*-chromen-2-one (7). Yellow crystals, 98% yield, mp 184–186°C; ^{1}H NMR ($CDCl_3$): δ 1.64–1.68 (m, 6H, cycloheptyl), 1.86–1.88 (m, 2H, cycloheptyl), 2.57–2.59 (m, 2H, cycloheptyl), 2.68–2.71 (m, 2H, cycloheptyl), 7.27 (s, 1H, C_5H-thiaz.), 7.38–7.40 (m, 2H, Ar), 7.62–7.64 (t, 1H, Ar), 7.81–7.82 (t, 1H, Ar), 8.62 (s, 1H, CH=), 11.95 (s, 1H, NH, D_2O exch.); Anal. Calcd. for $C_{19}H_{19}N_3O_2S$: C, 64.57; H, 5.42; N, 11.89. Found: C, 64.58; H, 5.41; N, 11.89.

HPLC enantioseparation. HPLC enantioseparation was performed using stainless-steel Chiralpak AS-H (250 mm × 4.6 mm I.D.) columns (Chiral Technologies Europe, Illkirch, France). HPLC-grade solvents were supplied by Carlo Erba (Milan, Italy). The HPLC apparatus consisted of a Perkin-Elmer (Norwalk, CT) 200 LC pump equipped with a Rheodyne (Cotati, CA) injector, a 50-μL sample loop, a HPLC Dionex TCC-100 oven (Sunnyvale, CA), and a Perkin-Elmer UV detector model 290.

Specific rotations of enantiomers of compound **4**, dissolved in ethanol, were measured at 589 nm by a Perkin-Elmer polarimeter model 241 equipped with a Na lamp. The volume of the cell was 1 mL and the optical path 10 cm. The system was set at a temperature of 20°C using a Neslab RTE 740 cryostat.

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Synthesis and Biological Activity of 4-Methylene-pyrido[4,3-d]pyrimidines

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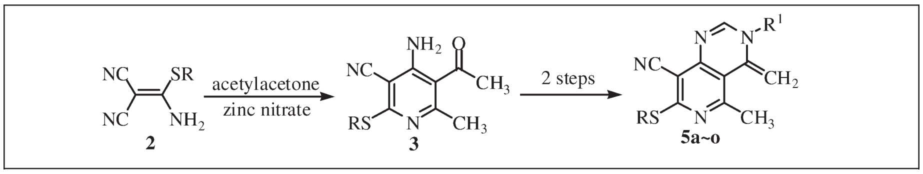

Fifteen novel 3-substituted-5-methyl-4-methylene-7-alkylsulfanyl-3,4-dihydro-pyrido[4,3-d]pyrimidine-8-carbonitriles **5a–o**, were synthesized *via* a facile annulation process in which formation of the pyrimidine ring proceeded smoothly by the regioselective attack of a formamidate group on a neighboring carbonyl group instead of a cyano group. Bioassay results indicated that these compounds showed significant herbicidal activity at a dose of 100 μg/mL on the roots of oil rape and barnyard grass. In addition, some of these compounds displayed fungicidal activity.

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INTRODUCTION

Reports in the literature on the biological activity of pyrido[4,3-d]pyrimidines relate mainly to their pharmaceutical activity as EGFR-TK and DHFR inhibitors [1]. Very little has been reported about their biological activities relating to agriculture [2].

Generally, pyrido[d]pyrimidines have been prepared by routes in which the pyrimidine ring is formed by cyclization of suitable substituents on a pyridine [3]. For example, it has been reported that formamidate reacts with a cyano group in the neighboring position to afford a pyrimidine ring [4]. However, there are no reports about formamidate regioselectively attacking a neighboring carbonyl group instead of a cyano group.

In our previous work, we have synthesized various pyrido[4,3–d]pyrimidine derivatives possessing fungicidal and herbicidal activity [5]. As a progression to this research, we herein describe a highly efficient regioselective cyclization reaction leading to the synthesis of pyrido[4,3–d]pyrimidines under mild conditions and in short reaction times. A preliminary *in vitro* bioassay indicated that these 4-methylene-pyrido[4,3–d]pyrimidines have strong herbicidal activity and that some have fungicidal activity as well.

RESULTS AND DISCUSSION

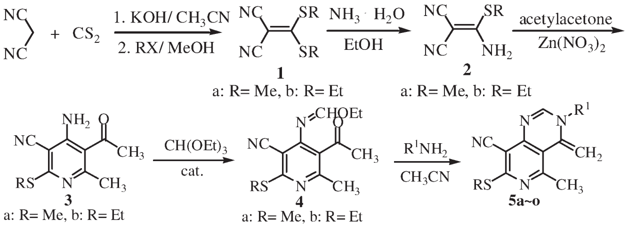
The conventional synthetic route to pyrido[4,3–d]pyrimidines involves formation of the pyrimidine ring by closure of suitable substituents on a pyridine. It was noted that the synthesis of the substituted pyridines, or the pyrimidine ring closure, always suffered from certain drawbacks, such as low yield, long reaction time, or difficulty in isolating or purifying the products [3,4]. In the protocol described here, formation of the pyrimidine ring proceeded regioselectively and with high efficiency (see Scheme 1).

The intermediates **1** and **2** can be prepared according to a published method [6]. It was reported that 4-amino nicotinonitrile 3 was prepared in moderate yield (48%) by using anhydrous stannic chloride as catalyst [7]. We improved the conditions by using zinc nitrate as catalyst to achieve much higher yield than the reported method (over 83%) [8]. By optimizing the reaction conditions, formamidate **4a** was obtained with the yield of 87% yield in the presence of *p*-toluene sulfonic acid. By comparison, only 32% yield was obtained when no catalyst was used, and formamidate **4b** was obtained with 82% yield in the presence of acetic anhydride as the catalyst.

The formamidate **4** reacted with primary amines smoothly and regioselectively in acetonitrile at 40~50°C to give the title compounds **5a–o** in moderate to excellent yields. The products were easily isolated by filtration. The structures of compounds **5a–o** were fully elucidated by a comprehensive analysis of their IR, MS, and ^{1}H NMR spectra and by elemental analysis.

The compounds **5a–o** were screened for activity against six fungi, namely *Fusarium oxysporium, Rhizoctonia solani, Botrytis cinerea, Gibberella zeae, Dothiorella gregaria*, and *Colletotrichum gossypii*, at a

Scheme 1



5a~e: R= Me 5f~o: R= Et

5a: R^1= 2-chloropyridin-4-yl methyl
5b: R^1= α-phenyl ethyl
5c: R^1= 2-Cl-C$_6$H$_4$-CH$_2$$^-$
5d: R^1= 2-CH$_3$-C$_6$H$_4$-CH$_2$$^-$
5e: R^1= 3-CH$_3$-C$_6$H$_4$-CH$_2$$^-$

5f: R^1= Et
5g: R^1= propyl
5h: R^1= butyl
5i: R^1= amyl
5j: R^1= hexyl

5k: R^1= 2-Cl-C$_6$H$_4$-CH$_2$$^-$
5l: R^1= 2-CH$_3$-C$_6$H$_4$-CH$_2$$^-$
5m: R^1= 3-CH$_3$-C$_6$H$_4$-CH$_2$$^-$
5n: R^1= 4-CH$_3$-C$_6$H$_4$-CH$_2$$^-$
5o: R^1= 4-OCH$_3$-C$_6$H$_4$-CH$_2$$^-$

concentration of 50 μg/mL according to a reported method [5]. As the results in Table 1 show, most of the compounds have weak fungicidal activity. Among these compounds, only compound **5a,** in which R^1 is (2-chloropyridin-4-yl)methyl group, exhibited moderate inhibitory activity against each of the six fungi. This might imply that the introduction of pyridine ring to the position 3 of pyrimidines was important for its fungicidal activity. All the remaining compounds, in which the substituent R^1 is alkyl or substituted benzyl, showed only weak antifungal activity.

The herbicidal activity of compounds **5a–o** was also evaluated, against two representative targets, oil rape and barnyard grass, at concentrations of 100 and 10 μg/mL, according to a literature method [9]. The results are listed in Table 2 and show that these compounds have moderate to good herbicidal activity against the roots of these two species at the rate of 100 μg/mL, especially against the root of barnyard grass. Compound **5a** with (2-chloropyridin-4-yl)methyl moiety in position 3 of the pyrimidine ring showed much better activity than the rest of the series with over 85% inhibition even at the lower concentration of 10 μg/mL. Switching the substituent R from methyl to ethyl has no obvious effect on the inhibition rates. In terms of R^1, the substituents with electron-donating groups on the phenyl rings seem to have somewhat higher herbicidal activity. For example, compounds **5d** and **5e** showed better activity than compound **5c**, and compounds **5l–o** were better than compound **5k.**

EXPERIMENTAL

All chemicals were of reagent grade and were commercially available. Solvents were either used directly or were purified as required. *Fusarium oxysporium, Rhizoctonia solani, Botrytis cinerea, Gibberella zeae, Dothiorella gregaria, Colletotrichum gossypii*, and seeds of oil rape and barnyard grass were provided through the courtesy of the Bioassay Center, Central China Normal University.

Melting points were measured on a WRS-1B Digital melting point apparatus. ^{1}H NMR spectra were recorded at 400 MHz in CDCl$_3$ solution on a Varian VNMR-400 Spectrometer, whereas IR spectra were recorded on a Nicolet AVATAR-360 Infrared Spectrometer. The MS spectra were determined using a Finnigan Trace MS Spectrometer, and the signals were given in *m*/*z*. Elementary analysis was carried out on a Vario EL III CHNSO elemental analyzer.

Intermediates **1** and **2** were prepared according to the literature [6].

5-Acetyl-4-amino-6-methyl-2-alkylsulfanyl-nicotinonitrile (3). Acetylacetone (1.0 g, 10 mmol) and **2** (10 mmol) were added to a stirred solution of zinc nitrate in 30 mL alcohol. The mixture was stirred and refluxed for 12 h. The precipitate

Table 1

Antifungal activity of compounds **5a–o** (% inhiblition).

			50 μg/mL					
Compounds	R	R^1	*F. oxysporium*	*R. solani*	*B. cinerea*	*G. zeae*	*D. gregaria*	*C. gossypii*
5a	Me	2-Chloropyridin-4-yl-methyl	36	52	81	43	60	54
5b	Me	α-Phenyl ethyl	42	33	48	56	14	26
5c	Me	2—Cl—C$_6$H$_4$—CH$_2$—	12	3	12	9	20	14
5d	Me	2—CH$_3$—C$_6$H$_4$—CH$_2$—	8	0	19	3	26	14
5e	Me	3—CH$_3$—C$_6$H$_4$—CH$_2$—	0	0	19	11	26	11
5f	Et	Ethyl	50	32	17	6	21	31
5g	Et	Propyl	35	9	14	19	21	27
5h	Et	Butyl	15	7	9	19	10	23
5i	Et	Amyl	19	0	23	16	7	27
5j	Et	Hexyl	15	4	20	9	10	15
5k	Et	2—Cl—C$_6$H$_4$—CH$_2$—	4	7	11	6	0	19
5l	Et	2—CH$_3$—C$_6$H$_4$—CH$_2$—	4	2	23	9	0	15
5m	Et	3—CH$_3$—C$_6$H$_4$—CH$_2$—	4	0	17	3	3	4
5n	Et	4—CH$_3$—C$_6$H$_4$—CH$_2$—	15	0	0	9	0	19
5o	Et	4—OCH$_3$—C$_6$H$_4$—CH$_2$—	19	4	0	3	0	19

Table 2

Herbicidal activity of compounds **5a-o** (% inhibition).

			Oil rape (root/stalk)		Barnyard grass (root/stalk)	
Compds	R	R^1	100 µg/mL	10 µg/mL	100 µg/mL	10 µg/mL
5a	Me	2-Chloropyridin-4-yl-methyl	96/63	91/37	97/81	87/69
5b	Me	α-Phenylethyl	68/26	37/21	72/56	67/50
5c	Me	2—Cl—C_6H_4—CH_2—	62/5	13/0	77/67	62/56
5d	Me	2—CH_3—C_6H_4—CH_2	68/16	18/11	89/77	64/56
5e	Me	3—CH_3—C_6H_4—CH_2	82/21	26/16	87/50	64/60
5f	Et	Ethyl	45/35	54/18	69/59	8/0
5g	Et	Propyl	46/41	17/6	42/41	28/41
5h	Et	Butyl	63/29	25/18	53/48	0/0
5i	Et	Amyl	43/35	32/24	92/76	19/17
5j	Et	Hexyl	71/29	45/24	89/72	39/35
5k	Et	2—Cl—C_6H_4—CH_2—	51/35	17/24	77/59	58/52
5l	Et	2—CH_3—C_6H_4—CH_2—	64/35	32/29	78/62	67/59
5m	Et	3—CH_3—C_6H_4—CH_2—	81/47	26/29	94/72	64/55
5n	Et	4—CH_3—C_6H_4—CH_2—	61/35	39/18	92/76	68/57
5o	Et	4—OCH_3—C_6H_4—CH_2—	86/41	36/35	88/66	64/48

was filtered off, washed with water (10 mL × 3), and recrystalized from alcohol to give **3**.

5-acetyl-4-amino-6-methyl-2-methylsulfanyl-nicotinonitrile (3a). White solid, m.p. 163.5–164.5°C, yield 83%. ^{1}H NMR ($CDCl_3$): δ 2.58 (s, 3H, CH_3), 2.61 (s, 3H, SCH_3), 2.68 (s, 3H, $COCH_3$), 6.60 ppm (br, 2H, NH_2).

5-acetyl-4-amino-6-methyl-2-ethylsulfanyl-nicotinonitrile (3b). Yellowish solid, m.p. 139.0–140.0°C, yield 89%. ^{1}H NMR ($CDCl_3$): δ 1.38 (t, 3H, SCH_2CH_3, J = 7.4 Hz), 2.59 (s, 3H, CH_3), 2.70 (s, 3H, $COCH_3$), 3.15 (q, 2H, SCH_2CH_3, J = 7.4 Hz), 6.68 ppm (br, 2H, NH_2).

***N*-(3-Acetyl-5-cyano-2-methyl-6-alkylsulfanyl-pyridin-4-yl)-formimidic acid ethyl ester (4).** To a solution of **4**-aminopyridine **3** (10 mmol) in triethyl orthoformate (5.92 g, 40 mmol) was added acetic anhydride or *p*-toluene sulfonic acid as catalyst. The mixture was heated and monitored by TLC. The triethyl orthoformate was removed at reduced pressure, and the residue was purified by silica gel chromatography (ether:petroleum ether=1:10) to afford formamidate **4**.

N-(3-acetyl-5-cyano-2-methyl-6-methylsulfanyl-pyridin-4-yl)-formimidic acid ethyl ester (4a). White solid, m.p. 78.5–79.9°C, yield 95%. ^{1}H NMR: δ 1.40 (t, 3H, CH_2CH_3, J = 8.0 Hz), 2.46 (s, 3 H, CH_3), 2.56 (s, 3H, SCH_3), 2.62 (s, 3H, $COCH_3$), 4.39 (q, 2H, CH_2CH_3, J = 8.0 Hz), 8.06 ppm (s, 1H, =CH). ms (70 Ev): *m/z* 277 (M^+, 63).

N-(3-acetyl-5-cyano-2-methyl-6-ethylsulfanyl-pyridin-4-yl)-formimidic acid ethyl ester (4b). Yellowish liquid, yield 82%. ^{1}H NMR: δ 1.38 (t, 3H, SCH_2CH_3, J = 3.8 Hz), 1.40 (t, 3H, CH_2CH_3, J = 3.8 Hz), 2.45 (s, 3H, CH_3), 2.46 (s, 3H, $COCH_3$), 3.27 (q, 2H, SCH_2CH_3, J = 3.6 Hz), 4.27 (q, 2H, CH_2CH_3, J = 3.6 Hz), 7.65 ppm (s, 1H, N=CH).

General procedure for the preparation of compounds (5a–m). To a solution of formamidate **4** (10 mmol) in anhydrous acetonitrile (10 mL) was added the appropriate amine (15 mmol), and the mixture was stirred and heated at 40–50°C for 30 min. The precipitate was isolated by filtration, then recrystalized from acetone/petroleum ether to give pure products **5**.

3-[(2-Chloropyridin-4-yl)methyl]-5-methyl-4-methylene-7-methylsulfanyl-3,4-dihydropyrido[4,3–d]pyrimidine-8-carbonitrile (5a). This compound was obtained as a pale yellow solid, m.p. 167.9–168.2°C, yield 59%. IR (KBr): ν 3036, 2931, 2218, 1610, 1550, 1523, 1390, 1278 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.61 (s, 3H, CH_3), 2.64 (s, 3H, SCH_3), 4.67 (d, 2H, =CH_2), 4.83 (s, 2H, CH_2), 7.20-7.64 (m, 3H, pyridine-H), 7.86 ppm (s, 1H, pyrimidine-H); ms: *m/z* 357 (M^++1 20). *Anal.* Calcd. for $C_{17}H_{14}ClN_5S$ (356): C, 57.38; H, 3.97; N, 19.68. Found C, 57.82; H, 3.44; N, 19.71.

3-(α-Phenylethyl)-5-methyl-4-methylene-7-methylsulfanyl-3,4-dihydropyrido[4,3–d]pyrimidine-8-carbonitrile (5b). This compound was obtained as a white solid, m.p. 147.4–148.5°C, yield 62%. IR (KBr): ν 3170, 2978, 2925, 2211, 1621, 1563, 1514, 1399, 1294 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.63 (d, 3H, Ph—CH_3, J = 4.0 Hz), 2.45 (s, 3H, CH_3), 2.60 (s, 3H, SCH_3), 4.65 (d, 2H, =CH_2), 6.41 (d, 1H, Ph—CH, J = 4.0 Hz), 6.27-7.43 (m, 5H, ArH), 7.75 ppm (s, 1H, pyrimidine-H); ms: *m/z* 334 (M^+ 8). *Anal.* Calcd. for $C_{19}H_{18}N_4S$ (334): C, 68.23; H, 5.42; N, 16.75. Found C, 68.29; H, 5.44;, N, 16.51.

3-(2-Chlorophenyl)-5-methyl-4-methylene-7-methyl sulfanyl-3,4-dihydropyrido[4,3–d]pyrimidine-8-carbonitrile (5c). This compound was obtained as a white solid, m.p. 143.2–144.5°C, yield 63%. IR (KBr): ν 3148, 2927, 2215, 1601, 1548, 1524, 1396, 1280 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.61 (s, 3H, CH_3), 2.66 (s, 3H, SCH_3), 4.46 (d, 1H, =CH^a, J = 2.0 Hz), 4.64 (d, 1H, =CH^b, J = 2.0 Hz), 4.86 (s, 2H, CH_2), 7.21-7.47 (m, 4H, ArH), 7.55 ppm (s, 1H, pyrimidine-H); ms: *m/z* 357 (M^++2 7), 355(M^+ 24). *Anal.* Calcd. for $C_{18}H_{15}ClN_4S$ (355): C, 60.92; H, 4.26; N, 15.79. Found C, 60.72; H, 4.44; N, 15.71.

3-(2-Methylphenyl)-5-methyl-4-methylene-7-methyl sulfanyl-3,4-dihydro-pyrido[4,3–d]pyrimidine-8-carbonitrile (5d). This compound was obtained as a white solid, m.p. 184.2–184.8°C, yield 75%. IR (KBr): ν 3001, 2926, 2218, 1604, 1553, 1521, 1399, 1278 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.32 (s, 3H, Ph—CH_3), 2.62 (s, 3H, CH_3), 2.69 (s, 3H, SCH_3), 4.50 (d, 1H, =CH^a, J = 2.0 Hz), 4.65 (d, 1H, =CH^b, J = 2.0 Hz), 4.69 (s, 2H, —CH_2—), 7.16-7.28 (m, 4H, ArH), 7.44 ppm (s, 1H, pyrimidine-H); ms: *m/z* 335(M$^+$+1 9), 334(M$^+$ 20). *Anal.* Calcd. for $C_{19}H_{18}N_4S$ (334): C, 68.23; H, 5.42; N, 16.75. Found C, 68.72; H, 5.44; N, 16.71.

3-(3-Methylphenyl)-5-methyl-4-methylene-7-methyl sulfanyl-3,4-dihydro-pyrido[4,3–d]pyrimidine-8-carbonitrile (5e). This compound was obtained as a white solid, m.p. 162.1–163.6°C, yield 90%. IR (KBr): ν 3074, 2926, 2219, 1607, 1555, 1522, 1401, 1262 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H, Ph—CH_3), 2.62 (s, 3H, CH_3), 2.64 (s, H, SCH_3), 4.54 (d, 1H, =CH^a, *J* = 2.0 Hz), 4.62 (d, 1H, =CH^b, *J* = 2.0 Hz), 4.74(s,2H, —CH_2—), 7.06–7.28 (m, 4H, ArH), 7.58 ppm (s, 1H, pyrimidine-H); ms: *m/z* 334(M$^+$ 43). *Anal.* Calcd. for $C_{19}H_{18}N_4S$ (334): C, 68.23; H, 5.42; N, 16.75. Found C, 68.39; H, 5.44; N, 16.73.

3-Ethyl-5-methyl-4-methylene-7-ethylsulfanyl-3,4-dihydro-pyrido[4,3–d]pyrimidine-8-carbonitrile (5f). This compound was obtained as a white solid, m.p. 144.1–145.0°C, yield 63%. IR (KBr): ν 3170, 2975, 2931, 2221, 1615, 1547, 1523, 1399 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.36–1.41 (m, 6H, CH_3 in —CH_2CH_3 and —SCH_2CH_3), 2.69 (s, 3H, —CH_3), 3.24 (q, 2H, —SCH_2CH_3, *J* = 7.3 Hz), 3.69 (q, 2H, —CH_2CH_3, *J* = 7.2 Hz), 4.64 (d, 1H, =CH^a, *J* = 3.2 Hz), 4.65 (d, 1H, =CH^b, *J* = 3.2 Hz), 7.52 ppm (s, 1H, pyrimidine-H); ms: *m/z* 273(M$^+$+1 3), 272(M$^+$ 3). *Anal.* Calcd. for $C_{14}H_{16}N_4S$ (272) : C, 61.74; H, 5.92; N, 20.57. Found C, 61.72; H, 5.72; N, 20.30.

3-Propyl-5-methyl-4-methylene-7-ethylsulfanyl-3,4-dihydro-pyrido[4,3–d]pyrimidine-8-carbonitrile (5g). This compound was obtained as a white solid, m.p. 148.8–150.4°C, yield 61%. IR (KBr): ν 3180, 2966, 2875, 2221, 1613, 1548, 1521, 1388 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.99 (t, 3H, —$CH_2CH_2CH_3$, *J* = 7.4 Hz), 1.38 (t, 3H, —SCH_2CH_3, *J* = 8.0 Hz), 1.75^{-1}.81 (m, 2H, —$CH_2CH_2CH_3$), 2.69 (s, 3H, —CH_3), 3.25 (q, 2H, —SCH_2CH_3, *J* = 7.3 Hz), 3.58 (t, 2H, —$CH_2CH_2CH_3$, *J* = 7.2 Hz), 4.63 (d, 1H, =CH^a, *J* = 3.2 Hz), 4.65 (d, 1H, =CH^b, *J* = 3.2 Hz), 7.47 ppm (s, 1H, pyrimidine-H); ms: *m/z* 286(M$^+$ 64). *Anal.* Calcd. for $C_{15}H_{18}N_4S$ (286) : C, 62.91; H, 6.33; N, 19.56. Found C, 62.88; H, 6.40; N, 19.61.

3-Butyl-5-methyl-4-methylene-7-ethylsulfanyl-3,4-dihydro pyrido[4,3–d]pyrimidine-8-carbonitrile (5h). This compound was obtained as a white solid, m.p. 144.6–145.1°C, yield 59%. IR (KBr): ν 3047, 2959, 2871, 2218, 1597, 1550, 1517, 1388 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.96^{-1}.00 (t, 3H, —$CH_2CH_2CH_2CH_3$, *J* = 7.2 Hz), 1.36–1.44 (m, 5H, —$CH_2CH_2CH_2CH_3$ and —SCH_2CH_3), 1.69–1.76 (m, 2H, —$CH_2CH_2CH_2CH_3$), 2.69 (s, 3H, —CH_3), 3.25 (q, 2H, —SCH_2CH_3, *J* = 4.9 Hz), 3.62 (t, 2H, —$CH_2CH_2CH_2CH_3$, *J* = 7.0 Hz), 4.62 (d, 1H, =CH^a, *J* = 3.2 Hz), 4.64 (d, 1H, =CH^b, *J* = 3.2 Hz), 7.47 ppm (s, 1H, pyrimidine-H); ms: *m/z* 301(M$^+$+H 31), 300(M$^+$ 67). *Anal.* Calcd. for $C_{16}H_{20}N_4S$ (300): C, 63.97; H, 6.71; N, 18.65. Found C, 64.02; H, 6.84; N, 18.43.

3-Amyl-5-methyl-4-methylene-7-ethylsulfanyl-3,4-dihydro pyrido[4,3–d]pyrimidine-8-carbonitrile (5i). This compound was obtained as a white solid, m.p. 134.8–135.4°C, yield 56%. IR (KBr): ν 3163, 2957, 2868, 2211, 1613, 1548, 1522, 1395cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.93 (t, 3H, —$CH_2CH_2CH_2CH_2CH_3$, *J* = 6.8 Hz), 1.33–1.40 (m, 7H, —$CH_2CH_2CH_2CH_2CH_3$ and —SCH_2CH_3), 1.73–1.78 (m, 2H, —$CH_2CH_2CH_2CH_2CH_3$), 2.694 (s, 3H, —CH_3), 3.25 (q, 2H, —SCH_2CH_3, *J* = 7.4 Hz), 3.61 (t, 2H, —$CH_2CH_2CH_2CH_2CH_3$, *J* = 7.0 Hz), 4.62 (d, 1H, =CH^a, *J* = 3.2 Hz), 4.65 (d, 1H, =CH^b, *J* = 3.2 Hz), 7.47 ppm (s, 1H, pyrimidine-H); ms: *m/z* 315(M$^+$+1 13), 314(M$^+$ 47), 313(M$^+$−H 14). *Anal.* Calcd. for $C_{17}H_{22}N_4S$ (314): C, 64.93; H, 7.05; N, 17.82. Found C, 64.59; H, 7.28; N, 17.66.

3-Hexyl-5-methyl-4-methylene-7-ethylsulfanyl-3,4-dihydro pyrido[4,3–d]pyrimidine-8-carbonitrile (5j). This compound was obtained as a white solid, m.p. 131.5–132.4°C, yield 79%. IR (KBr): ν 3174, 2950, 2865, 2222, 1615, 1547, 1523, 1397cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.88–0.91 (t, 3H, —$CH_2CH_2CH_2CH_2CH_2CH_3$, *J* = 6.8 Hz), 1.33–1.40 (m, 9H, —$CH_2CH_2CH_2CH_2CH_2CH_3$ and —SCH_2CH_3), 1.72−1.77 (m, 2H, —$CH_2CH_2CH_2CH_2CH_2CH_3$), 2.69 (s, 3H, —CH_3), 3.25 (q, 2H, —SCH_2CH_3, *J* = 7.3 Hz), 3.61 (t, 2H, —$CH_2CH_2CH_2CH_2CH_3$, *J* = 7.2 Hz), 4.63 (d, 1H, =CH^a, *J* = 3.2 Hz), 4.65 (d, 1H, =CH^b, *J* = 3.2 Hz), 7.47 ppm (s, 1H, pyrimidine-H); ms: *m/z* 328(M$^+$ 41). *Anal.* Calcd. for $C_{18}H_{24}N_4S$ (328): C, 65.82; H, 7.36; N, 17.06. Found C, 65.53; H, 7.41; N, 16.99.

3-(2-Chlorobenzyl)-5-methyl-4-methylene-7-ethylsulfanyl-3,4-dihydropyrido[4,3–d]pyrimidine-8-carbonitrile (5k). This compound was obtained as a white solid, m.p. 148.5–149.5°C, yield 61%. IR (KBr): ν 3066, 2928, 2216, 1599, 1548, 1525, 1393 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.37–1.41 (t, 3H, —SCH_2CH_3, *J* = 7.4 Hz), 2.66 (s, 3H, —CH_3), 3.25 (q, 2H, —SCH_2CH_3, *J* = 7.3 Hz), 4.45 (d, 1H, =CH^a, *J* = 3.6 Hz), 4.63 (d, 1H, =CH^b, *J* = 3.2 Hz), 4.86 (s, 2H, —CH_2—), 7.21–7.47 (m, 4H, ArH), 7.55 ppm (s, 1H, pyrimidine-H); ms: *m/z* 370(M$^+$+2 7), 368(M$^+$ 23). *Anal.* Calcd. for $C_{19}H_{17}ClN_4S$ (368): C, 61.86; H, 4.65; N, 15.19. Found C, 61.62; H, 4.74; N, 14.93.

3-(2-Methylbenzyl)-5-methyl-4-methylene-7-ethylsulfanyl-3,4-dihydro-pyrido[4,3–d]pyrimidine-8-carbonitrile (5l). This compound was obtained as a white solid, m.p. 153.9–154.9°C, yield 68%. IR (KBr): ν 3066, 2966, 2218, 1607, 1554, 1523, 1400 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.39 (t, 3H, —SCH_2CH_3, *J* = 7.6 Hz), 2.33 (s, 3H, Ph—CH_3), 2.68 (s, 3H, —CH_3), 3.24 (q, 2H, —SCH_2CH_3, *J* = 7.3 Hz), 4.49 (d, 1H, =CH^a, *J* = 3.6 Hz), 4.65 (d, 1H, =CH^b, *J* = 3.6 Hz), 4.69 (s, 2H, —CH_2—), 7.16–7.27 (m, 4H, ArH), 7.43 ppm (s, 1H, pyrimidine-H); ms: *m/z* 348(M$^+$ 32). *Anal.* Calcd. for $C_{20}H_{20}N_4S$ (348): C, 68.93; H, 5.79; N, 16.08. Found C, 69.06; H, 5.88; N, 15.94.

3-(3-Methylbenzyl)-5-methyl-4-methylene-7-ethylsulfanyl-3,4-dihydro-pyrido[4,3–d]pyrimidine-8-carbonitrile (5m). This compound was obtained as a white solid, m.p. 145.2–146.0°C, yield 80%. IR (KBr): ν 3001, 2967, 2926, 2217, 1606, 1550, 1524, 1401 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.38 (t, 3H, —SCH_2CH_3, *J* = 7.4 Hz), 2.35 (s, 3H, Ph—CH_3), 2.64 (s, 3H, —CH_3), 3.25 (q, 2H, —SCH_2CH_3, *J* = 7.3 Hz), 4.52 (d, 1H, =CH^a, *J* = 3.6 Hz), 4.62 (d, 1H, =CH^b, *J* = 3.6 Hz), 4.74 (s, 2H, —CH_2Ph), 7.06–7.27 (m, 4H, ArH), 7.57 ppm (s, 1H, pyrimidine-H); ms: *m/z* 348(M$^+$ 16). *Anal.* Calcd. for $C_{20}H_{20}N_4S$ (348): C, 68.93; H, 5.79; N, 16.08. Found C, 68.81; H, 5.86; N, 15.91.

3-(4-Methylbenzyl)-5-methyl-4-methylene-7-ethylsulfanyl-3,4-dihydro-pyrido[4,3–d]pyrimidine-8-carbonitrile (5n). This compound was obtained as a white solid, m.p. 163.5–164.5°C, yield 63%. IR (KBr): ν 3030, 2974, 2927, 2218, 1606, 1554, 1521, 1399 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.36–1.40 (t, 3H, —SCH_2CH_3, *J* = 7.2 Hz), 2.36 (s, 3H, Ph—CH_3), 2.63 (s, 3H, —CH_3), 3.25 (q, 2H, —SCH_2CH_3, *J* = 7.3 Hz), 4.53 (d, 1H, =CH^a, *J* = 3.6 Hz), 4.60 (d, 1H, =CH^b, *J* = 3.2 Hz), 4.74 (s, 2H, —CH_2Ph), 7.14-7.20 (m, 4H, ArH), 7.57 ppm (s, 1H, pyrimidine-H); ms: *m/z* 348(M$^+$ 5). *Anal.* Calcd. for $C_{20}H_{20}N_4S$

(348): C, 68.93; H, 5.79; N, 16.08. Found C, 68.84; H, 5.63; N, 15.90.

3-(4-Methoxybenzyl)-5-methyl-4-methylene-7-ethyl sulfanyl-3,4-dihydro-pyrido[4,3–d]pyrimidine-8-carbonitrile (5o). This compound was obtained as a white solid, m.p. 156.1–156.9°C, yield 82%. IR (KBr): ν 2934, 2220, 1612, 1547, 1515, 1404 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.38 (t, 3H, $-SCH_2\mathit{CH_3}$, $J = 7.2$ Hz), 2.63 (s, 3H, $-CH_3$), 3.24 (q, 2H, $-SCH_2CH_3$, $J = 7.5$ Hz), 3.81 (s, 3H, $-OCH_3$), 4.57 (d, 1H, $=CH^a$, $J = 3.2$ Hz), 4.61 (d, 1H, $=CH^b$, $J = 3.2$ Hz), 4.71 (s, 2H, $-CH_2Ph$), 6.90–7.20 (m, 4H, ArH) 7.54 ppm (s, 1H, pyrimidine-H); ms: *m/z* 364(M^+ 12). *Anal.* Calcd. for $C_{20}H_{20}N_4OS$ (364): C, 65.91; H, 5.53; N, 15.37. Found C, 65.84; H, 5.63; N, 15.21.

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A New Method for the Synthesis and Herbicidal Activity of 3-Phenoxy-6-(*1H*-(substituted)pyrazol-1-yl) Pyridazines

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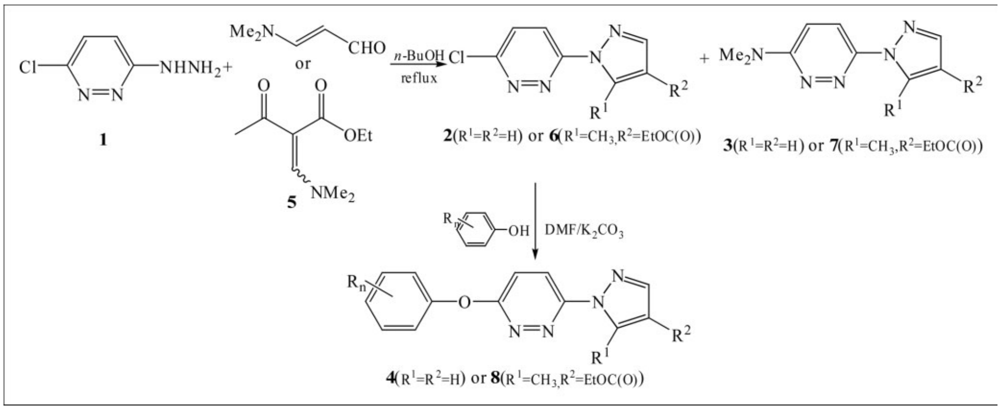

A series of 3-substituted phenoxy-6-((substituted)*1H*-pyrazol-1-yl) pyridazines were synthesized from the condensation of various phenols and 3-chloro-6-(*1H*-pyrazol-1-yl) pyridazine **2** or 3-chloro-6-(5′-methyl-4-ethoxycarbonyl-*1H*-pyrazol-1-yl) pyridazine **6** in N,N-dimethylformamide (DMF) at 120°C with K_2CO_3 as an acid receptor. The intermediates **2** or **6** were obtained from the cyclization of 3-chloro-6-hydrazinyl pyridazine **1** with 3-dimethylamino-acrylaldehyde or ethyl 2-((dimethylamino) methylene)-3-oxobutanoate in *n*-butanol under reflux, respectively, and side products **3** or **7** were also generated. All of the title compounds were confirmed by ^{1}H NMR, infrared spectometry (IR) and elemental analyses. Preliminary bioassay indicated that some of the title compounds showed high inhibitory activity against *Brassica campestris L. (B. campestris)* and moderate inhibitory activity against *Echinochloa crusgalli*. For example, the inhibition percentages of compound **4b** and **4c** against *B. campestris* were both 94% at 10 μg/mL.

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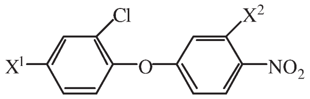
INTRODUCTION

Protoporphyrinogen IX oxidase (Protox, EC 1.3.3.4) is the key enzyme in chlorophyll biosynthesis pathways in plants, which catalyzes the oxidative O_2-dependent aromatization of the colorless protoporphyrinogen IX to the highly conjugated protoporphyrin IX. The phytotoxicity of Protox inhibitors is light dependent and involves intracellular peroxidation caused by protoporphyrin IX, chlorophyll precursor, leading to accumulation of protoporphyrin IX in plant mitochondria and plant chloroplasts. Abnormal accumulated protoporphyrin IX in plant tissue is assumed to cause light-induced formation of active oxygen, which induces disruption of membranes, chlorophyll degradation, and desiccation of plants in the light [1].

So far, several structurally distinct classes of compounds, cyclic imides, phenyltriazolinones, diphenyl ethers (DPEs), etc, targeted at Protox, have been used as herbicides for several decades [2]. DPEs are one of the important Protox inhibitors, and numerous diphenylether compounds have been developed as commercial herbicides (Fig. 1), for example, nitrofen, chlomethoxynil, bifenox, oxyfluorfen, acifluorfen, fluoroglycofen-ethyl, fomesafen, and lactofen.

According to the commercialized Protox inhibitors, DPEs, a pharmacophore of Protox, and its inhibitors were established in our group [3], which indicated that two phenyl rings in DPEs, connected by an oxygen atom as a hydrogen-bonding acceptor, play important roles in their herbicidal activity. In addition, it is deduced from the Protox pharmacophore that a molecule bearing three aromatic rings connected directly or by oxygen atoms or nitrogen atoms maybe also shows good inhibition against Protox.

Heterocyclic rings are the classic phenyl-ring equivalents according to the bioisosterism [4], especially nitrogen-containing heterocyclic rings. So, it is reasonable to



nitrofen(X^1=Cl, X^2=H),
chlomethanoxynil (X^1=Cl, X^2=OMe),
bifenox(X^1=Cl, X^2=CO_2Me),
oxyfluorfen(X^1=CF_3, X^2=OEt),
acifluorfen (X^1= CF_3, X^2=COONa),
fluoroglyfen-ethyl(X^1=CF_3, X^2=$CO_2CH_2CO_2Et$),
fomesafen (X^1= CF_3, X^2=$CONHSO_2Me$),
lactofen (X^1= CF_3, X^2=CH(Me)CO_2Et).

Figure 1. Commercialized herbicides of diphenyl ethers.

use a heterocyclic ring to replace one of the phenyl rings in DPEs. Pyridazine ring is an important moiety in some pharmaceuticals and agrochemicals [5–7]. In our previous work, we synthesized numerous 3-phenoxy-6-dimethylamino pyridazines, and some of them showed inhibitory activity against *Brassica campestris L. (B. campestris)* and *Echinochloacrus-galli (E. crus-galli)* (Fig. 2, X^3 = H, Cl, CF_3, etc) [8]. However, after treatment of above weeds using the synthesized phenoxy pyridazines, *B. campestris* and *E. crus-galli* were desiccated but not killed completely. Ten days later after ''desiccation,'' these two weeds can grow again, which may be attributed to the loss of dimethylamino moiety of phenoxy-pyridazines in above weeds in the light [9]. To get new phenoxy pyridazines, which can be tolerated in above two weeds, we synthesized 3-aryloxy-6-fluoro pyridaiznes and found that they can inhibit the growth of *B. campestris* and *E. crus-galli* to some extent (Fig. 3, X^4 = Cl, OMe, NO_2, etc.) [10]. It was excited that they can be well tolerated in these two weeds. Currently, pyrazole ring is an important moiety in the pesticide researches [11–13]. We introduced pyrazole ring into phenoxy pyridazines because pyrazol-yl moiety has electron-withdrawing characteristic in pyrazolyl pyridazines as nitro group in DPEs (Fig. 4). In addition, the structures in Figure 4 almost meet the requirement of the deducation from Protox pharmacophore. So, we synthesized 3-aryloxy-6-(3′,5′-dimethyl-*1H*-pyrazol-1-yl) pyridazines (Fig. 4, X^5 = Cl, Br, Me, etc.), which showed inhibitory activity against *B. campestris* and *E. crus-galli* to some extent [14].

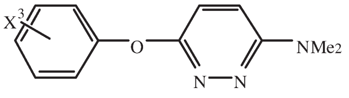


Figure 2. 3-Aryloxy-6-substituted pyridazines.

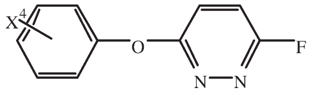


Figure 3. 3-Aryloxy-6-fluoro pyridazines.

In continuation on our research program for the synthesis of novel pyrazolyl-pyridazine derivatives and study on the relationship of structure and herbicidal activity, we design 3-substituted phenoxy-6-(*1H*-pyrazol-1-yl)pyridazines **4** and 3-substituted phenoxy-6-(5′-methyl-4′-ethoxycarbonyl-*1H*-pyrazol-1-yl) pyridazines **8**, which were synthesized from the condensation of various phenols and 3-chloro-6-(1*H*-pyrazol-1-yl) pyridazine or 3-chloro-6-(5′-methyl-4′-ethoxycarbonyl-1*H*-pyrazol-1-yl) pyridazine in DMF at 120°C using K_2CO_3 as an acid acceptor(Scheme 1). All novel compounds were characterized by ^1H NMR, IR, and elemental analyses. Preliminary bioassay indicated that some of the title compounds showed high inhibitory activity against *B. campestris* and moderate inhibitory activity against *E. crus-galli*. Moreover, the title compounds are well tolerated in above weeds during the bioassay procedure.

RESULTS AND DISCUSSION

Synthesis. The synthetic procedure of the title compounds is shown in Scheme 1. The intermediate **2** was achieved from the cyclization of starting materials **1** and 3-(dimethylamino)-acrylaldehyde. When this reaction was carried out in anhydrous ethanol under reflux, side product **3**, rather than the desired compound **2**, was obtained in high yield. However, compound **1** was treated with 3-(dimethylamino)acrylaldehyde in *iso*-propanol or *n*-butanol under reflux to afford compound **2** in 20% and 80% yield, respectively. Steiner *et al.*, [15] Steel and Constable, [16] and Blake *et al.* [17] have previously obtained **2** in 53–74% yield by treatment of pyrazole and 3,6-dichloropyridazine in DMF with NaH as a base. However, side product, 3,6-bis(*1H*-pyrazol-1-yl) pyridazine, was not avoidable.

As such, treatment of starting materials **1** and ethyl 2-((dimethylamino)methylene)-3-oxobutanoate **5** under reflux in *n*-butanol furnished the desired intermediate **6**

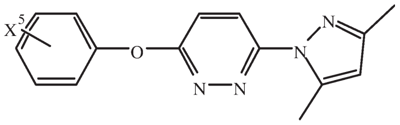
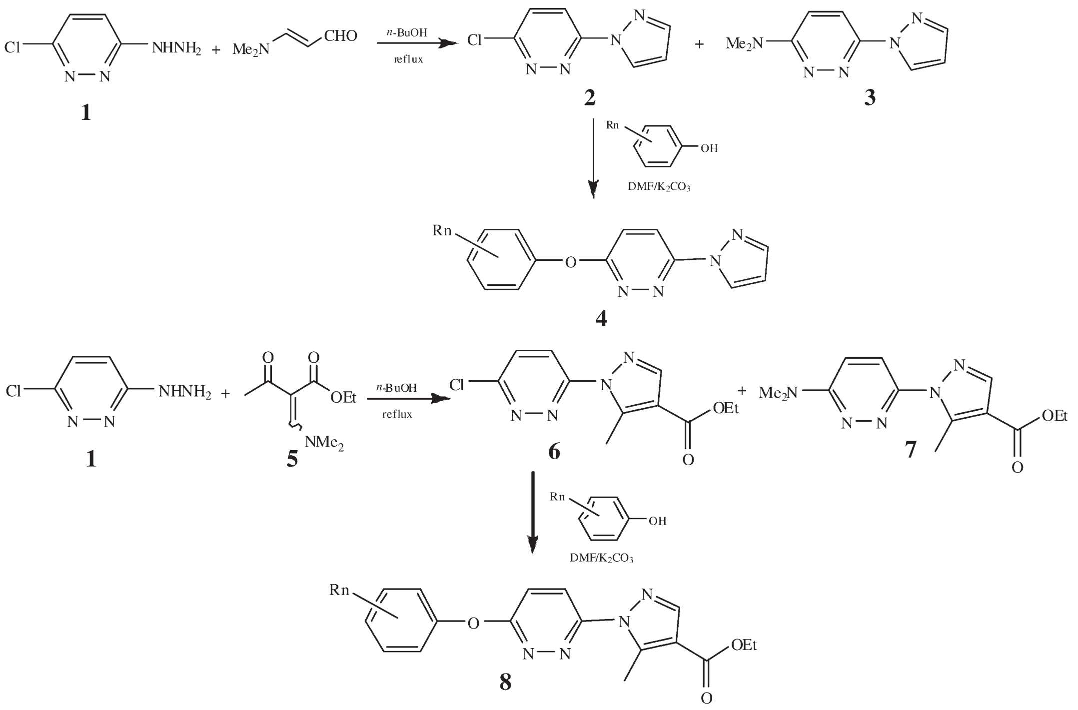


Figure 4. Structure of 3-aryloxy-6-(3′,5′-dimethyl-*1H*-pyrazol-1-yl) pyridazines.

Scheme 1. General procedure for the synthesis of the title compounds.



4a(R_n=3-Cl), **4b**(R_n=4-Cl), **4c**(R_n=4-CH_3), **4d**(R_n=3,4-Cl_2), **4e**(R_n=3-CF_3), **4f**(R_n 4-$CH_3OC(O)$).

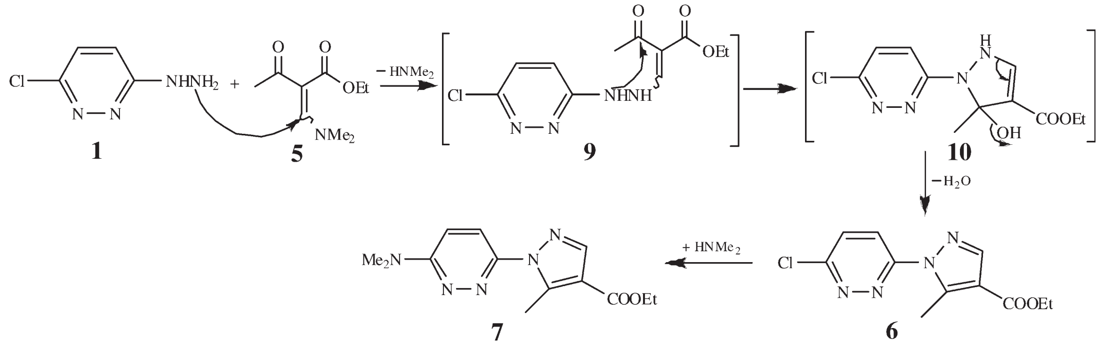
8a(R_n=4-CH_3), **8b**(R_n=3,5-$(CH_3)_2$), **8c**(R_n=2-$CH_3OC(O)$), **8d**(R_n=4-Cl), **8e**(R_n=3-Cl), **8f**(R_n=3,4-Cl_2), **8g**(R_n=4-$CH_3OC(O)$), **8h**(R_n=3-CF_3).

and side product **7** in the yields of 60% and 10%, respectively. Compound **6** was first synthesized by Bagrov [18] from the reaction of ethyl 2-(ethoxymethylene)-3-oxobutanoate with **1**.

A proposed mechanism of the generation of **6** and **7** is shown in Scheme 2. First, the hydrazinyl group in compound **1** attacks the carbon nucleus, which is linked to the dimethylamino moiety, to generate intermediate **9** with elimination of dimethylamine. **9** proceeds the intramolecular cyclization to furnish intermediate **10**, which is dehydrated to give **6**. **7** is obtained through the condensation of **6** and dimethylamine, which is produced from the cyclization of starting materials **1** and **5**. **7** is conformed by X-ray diffraction (Fig. 5) [19], indicating that methyl group is at 5th position and ethoxycarbonyl moiety is at 4th position in the pyrazole ring.

The title compounds **4** or **8** were obtained from the treatment of intermediates **2** or **6** and substituted phenols in DMF at 120°C for several hours until **2** or **6** was consumed completely as indicated by thin layer chromatography. After the reactions were over, the resulting mixtures were poured into cold water, and crude solids were filtrated, which were recrystallized with ethanol and cyclohexane to give pure products. All of the title

Scheme 2. Proposed mechanisms for the generation of **6** and **7**.



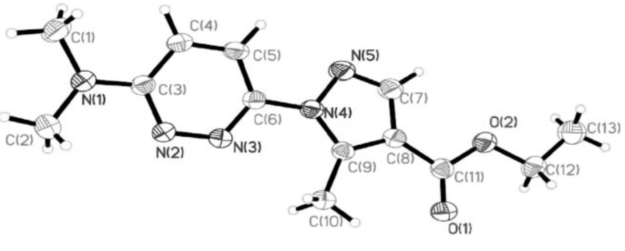


Figure 5. Crystal structure of compound **7**.

compounds were confirmed by ^{1}H NMR, IR, and elemental analyses.

Herbicidal activities. The title compounds were screened for herbicidal activity against *B. campestris* and *E. crus-galli* using a previously reported procedure [20,21], and the data of herbicidal activity were listed in Table 1. It was found that the title compounds are well tolerated in two weeds during the bioassay procedure. Most of compounds **8**, containing a methyl group at 5th position and an ethylcarbony moiety at 4th position in pyrazole ring, have no or slight herbicidal activity against *B. Campestris* and *E. crus-galli*. Compounds **4a–d**, which only have H-atoms at 4th and 5th positions in pyrazole ring, showed high inhibitory activity against *B. Campestris* and moderate inhibitory activity against *E. crus-galli*. at the concentration of 100 and 10 μg/mL, respectively. Compounds **4b** (R_n = 4-Cl) and **4c** (R_n = 4-Me) both showed high inhibitory activity against *B. Campestris*, which indicates that electron-donating groups or weak electron-withdrawing groups at 4th position in phenyl rings are favorable to the increase of herbicidal activity. However, compounds **4e** (R_n = 3-CF_3) and **4f** (R_n = 4-$CH_3OC(O)$) have no herbicidal activity against *B. Campestris*, indicating that strong electron-withdrawing groups at 3rd or 4th positions in phenyl rings are unfavorable to the enhancement of herbicidal activity. When R_n = 3,4-Cl_2, inhibitory activity of compound **4d** against *B. Campestris* decreased slightly compared with that of **4b**, suggesting that introduction of chlorine at 3rd position in phenyl ring be unfavorable to the increase of herbicidal activity. Compound **4a** with chlorine atom at 3rd position in phenyl ring has lower herbicidal activity against *B. Campestris* and *E. crus-galli* than compound **4b** with chlorine atom at 4th position in phenyl ring.

CONCLUSION

In conclusion, a series of 3-substituted phenoxy 6-(substituted pyrazol-yl)pyridazines were obtained from the condensation of various phenols and 3-chloro-6-(*1H*-pyrazol-1-yl) pyridazine or 3-chloro-6-(5′-methyl-4-ethoxycarbonyl-*1H*-pyrazol-1-yl) pyridazine in DMF at 120°C with K_2CO_3 as an acid receptor. The title compounds were screened for herbicidal activity against *B. Campestris* and *E. crus-galli*. Preliminary bioassay indicated that some of title compounds show high inhibitory activity against *B. Campestris* and moderate inhibitory activity against *E. crus-galli* at 10 and 100 μg/mL, respectively. Further study of structure-activity relationship of modified 3-phenoxy 6-substituted pyrazolyl pyridazines is now under investigation.

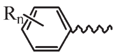
EXPERIMENTAL

General methods. ^{1}H NMR spectra were recorded on a Varian Mercury Plus 400 MHz spectrometer using $CDCl_3$ or DMSO-d_6 as a solvent and chemical shift values (δ) were given in parts per million downfield of internal tetramethylsilane. ^{13}C NMR spectra were recorded on a Varian Mercury Plus 400 MHz spectrometer (100 MHz) using $CDCl_3$ as a solvent, and chemical shift values (δ) were reported in parts per million relative to the residual chloroform (77.00 ppm) and was obtained with ^{1}H decoupling. IR spectra were recorded on a MAGNA-560 FTIR (Nicolet Company) spectrometer using KBr plates (thin film). The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and were not corrected. Elemental analyses were performed on a Yanaca CHN Corder MT-3 elemental analyzer. All anhydrous solvents were dried and purified by standard techniques just before use. 3-Chloro-6-hydrazinylpyridazine **1** was prepared according to the literature procedure [22], and 3-(dimethylamino)acrylaldehyde and 3-((dimethylamino) methylene)-1-ethoxy-pentane-2,4-dione **5** were both available commercially.

Synthesis of 3-chloro-6(1H-pyrazol-1-yl) pyridazine 2 and 3-dimethylamino-6(1H-pyrazol-1-yl) pyridazine 3. A mixture of 3-(dimethylamino)acrylaldehyde (1.09 g, 11.00 mmol) and 3-chloro-6-hydrazinyl pyridazine **1** (1.45 g, 10.00 mmol) in *n*-butanol(20mL) was refluxed for half an hour. When the

Table 1

Herbicidal activity against *B. campestris* and *E. crus-galli* of the title compounds (inhibition percentage, %).

Compounds		*B. campestris* 100 μg/mL	*B. campestris* 10 μg/mL	*E. crusgalli* 100 μg/mL	*E. crusgalli* 10 μg/mL
4a	3-ClC_6H_4	62	54	0	0
4b	4-ClC_6H_4	97	94	65	42
4c	4-$CH_3C_6H_4$	97	94	84	40
4d	3,4-$Cl_2C_6H_3$	83	79	26	19
4e	3-$CF_3C_6H_4$	0	0	0	0
4f	4-$CH_3OC(O)$ C_6H_4	0	0	0	0
8a	4-$CH_3C_6H_4$	54	38	0	0
8b	3,5-$(CH_3)_2C_6H_3$	0	0	14	0
8c	2-$CH_3OC(O)C_6H_4$	0	0	16	0
8d	4-ClC_6H_4	0	0	0	0
8e	3-ClC_6H_4	34	0	9	0
8f	3,4-$Cl_2C_6H_3$	0	0	0	0
8g	4-$CH_3OC(O)$ C_6H_4	0	0	0	0

starting materials were consumed completely as indicated by thin layer chromatography, the reaction mixture was allowed to cool to room temperature. After removal of the solution under pressure, the resulting residue was subjected to flash column chromatography on silica gel to give compound **2** (1.50 g) as a white crystal (eluent: petroleum ether: ethyl acetate=4:1 (*V*/*V*) in 80% yield, mp.143–144°C (ref.: mp. 124–126°C[15]). ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 6.54–6.56 (m, 1H, pyrazole-H), 7.63 (d, J = 9.2 Hz, 1H, pyridazine-H), 7.81 (d, J = 2.0 Hz, 1H, pyrazole-H), 8.22 (d, J = 9.2 Hz, 1H, pyridazine-H), 8.73 (d, J = 2.8 Hz, 1H, pyrazole-H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ: 109.18, 119.92, 127.40, 130.43, 143.28, 153.62, 154.23; IR (KBr) ν (cm^{-1}): 3129, 1635, 1575, 1523, 1448, 1402, 1143, 1016, 860, 765.

Side product 3-dimethylamino-6(1*H*-pyrazol-1-yl) pyridazine **3** was also obtained in 15% yield, mp. 147–149°C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 3.21 (s, 6H, NMe_2), 6.47 (m, 1H, pyrazole-H), 7.00 (d, J=9.6 Hz, 1H, pyridazine-H), 7.73 (d, J=2.0 Hz, 1H, pyrazole-H), 7.97 (d, J=9.6 Hz, 1H, pyridazine-H), 8.62 (d, J=2.4 Hz, 1H, pyrazole-H). GC-MS(EI, m/z(%)): 189.09 (M+, 40), 160.10(100). ^{13}C NMR($CDCl_3$, 100 MHz), δ: 38.38, 107.86, 119.40, 126.26, 141.48, 147.77, 159.08. Anal. calcd. for $C_9H_{11}N_5$: C, 57.13; H, 5.86; N, 37.01; found: C, 57.18; H, 5.72; N, 36.89.

General Procedure for the Synthesis of 3-aryloxy-6-(1H-pyrazol-1-yl) pyridazine 4. A 25-mL three-necked round bottom flask equipped with a thermometer, magnetic stir bar, and a dropping addition funnel was charged sequentially with new distilled DMF (7 mL), compounds **2** (2.00 mmol), substituted phenols (2.00 mmol), anhydrous potassium carbonate 0.29 g (2.10 mmol). The resulting mixture was heated at 120°C. After stirring for 12 h, the reaction mixture was allowed to cool to room temperature, poured into 30 mL of ice water, and filtrated to give the crude product. The resulting precipitate was washed with water (5 mL). The collected solid was dried overnight under vacuum to give a white powder, which was recrystallized from ethanol/cyclohexane (1/3: (*V*/*V*) to generate pure compounds **4**.

3-(3-chlorophenoxy)-6-(1H-pyrazol-1-yl)pyridazine(4a). White solid, yield 86%, mp.130–131°C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 6.51–6.52 (m, 1H, pyrazole-H), 7.15 (dd, J_1=8.8Hz, J_2=2.0Hz, 1H, ArH), 7.22–7.29 (m, 2H, ArH), 7.35 (s, 1H, ArH), 7.37 (d, J = 9.2 Hz, 1H, pyridazine-H), 7.77 (d, J=2.0Hz, 1H, pyrazole-H), 8.30 (d, J = 9.2 Hz, 1H, pyridazine-H), 8.40 (d, J=2.4Hz, 1H, pyrazole-H). IR (KBr) ν (cm^{-1}): 3136, 3093, 3021, 1578, 1523, 1469, 1418, 1290, 1197, 1126, 1085, 1046, 1018, 909, 858, 768. Anal. calcd for $C_{13}H_9ClN_4O$: C, 57.26; H, 3.33; N, 20.55; found: C, 57.36; H, 3.21; N, 20.31.

3-(4-chlorophenoxy)-6-(1H-pyrazol-1-yl)pyridazine(4b). White solid, yield 85%, m.p. 151–152°C.^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.51–6.52 (m, 1H, pyrazole-H), 7.19 (d, J = 8.8 Hz, 2H, ArH), 7.35 (d, J = 9.2 Hz, 1H, pyridazine-H), 7.40 (d, J = 8.8 Hz, 2H, ArH), 7.77 (d, J = 2.0Hz, 1H, pyrazole-H), 8.28 (d, J = 9.2 Hz, 1H, pyridazine-H), 8.63 (d, J = 2.4 Hz, 1H, pyrazole-H); IR (KBr) ν (cm^{-1}): 3150, 3006, 1571, 1530, 1498, 1459, 1408, 1299, 1254, 1200, 1171, 1136, 1043, 1008, 934, 838, 762; Anal. calcd for $C_{13}H_9ClN_4O$: C, 57.26; H, 3.33; N, 20.55; found: C, 57.01; H, 3.48; N, 20.58.

3-(4-methylphenoxy)-6-(1H-pyrazol-1-yl)pyridazine(4c). White solid, yield 70%, mp. 131–132°C.^{1}H NMR ($CDCl_3$, 400 MHz) δ:2.37 (s, 3H, $ArCH_3$), 6.50–6.51 (m, 1H, pyrazole-H), 7.11 (d, J = 8.4 Hz, 2H, ArH), 7.23 (d, J = 8.0 Hz, 2H, ArH), 7.31 (d, J = 9.6 Hz, 1H, pyridazine-H), 7.76 (d, J = 2.0Hz, 1H, pyrazole-H), 8.23 (d, J = 9.2 Hz, 1H, pyridazine-H) 8.63 (d, J = 2.0 Hz, 1H, pyrazole-H); IR (KBr) ν (cm^{-1}): 3136, 3093, 3042, 1581, 1514, 1459, 1411, 1296, 1258, 1203, 1133, 1104, 1032, 1014, 931, 861, 762; Anal. calcd for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21; found: C, 66.78; H, 4.89; N, 22.45.

3-(3,4-dichlorophenoxy)-6-(1H-pyrazol-1-yl)pyridazine (4d). White solid, yield 87%, mp.158–159°C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 6.52–6.56 (m, 1H, pyrazole-H), 7.14 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H, ArH), 7.37 (d, J = 9.6 Hz, 1H, pyridazine-H), 7.40 (d, J = 2.8 Hz, 1H, ArH), 7.50 (d, J = 8.8 Hz, 1H, ArH), 7.77 (d, J=2.0Hz, 1H, pyrazole-H), 8.30 (d, J = 9.6 Hz, 1H, pyridazine-H), 8.63 (d, J = 2.4 Hz, 1H, pyrazole-H); IR (KBr) ν (cm^{-1}): 3143, 3084, 3056, 3028, 1568, 1530, 1469, 1418, 1398, 1299, 1261, 1206, 1120, 1043, 1018, 918, 864, 810, 755; Anal. calcd. for $C_{13}H_8Cl_2N_4O$: C, 50.84; H, 2.63; N, 18.24; found: C, 50.62; H, 2.83; N, 18.34.

3-(3-trifluorophenoxy)-6-(1H-pyrazol-1-yl)pyridazine (4e). White solid, yield 80%, mp. 160–161°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.51–6.53 (m, 1H, pyrazole-H), 7.40 (d, J = 9.6 Hz, 1H, pyridazine-H), 7.46 (d, J = 7.6 Hz, 1H, ArH), 7.51–7.59 (m, 3H, ArH), 7.77(d, J=2.0Hz, 1H, pyrazole-H), 7.82 (d, J = 9.6 Hz, 1H, pyridazine-H), 8.63 (d, J = 2.0 Hz, 1H, pyrazole-H); IR (KBr) ν (cm^{-1}): 3136, 3086, 3035, 1574, 1523, 1459, 1408, 1325, 1286, 1206, 1162, 1136, 1068, 1018, 909, 864 762; Anal. calcd. for $C_{14}H_9F_3N_4O$: C, 54.91; H, 2.96; N, 18.29; found: C, 54.98; H, 2.94; N, 18.29.

3-(4-methoxycarbonylphenoxy)-6-(1H-pyrazol-1-yl) pyridazine (4f). White solid, yield 80%; mp. 187–188°C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 3.93 (s, 3H, $COOCH_3$), 6.51–6.52 (m, 1H, pyrazole-H), 7.31 (d, J = 8.0 Hz, 2H, ArH), 7.39 (d, J = 9.6 Hz, 1H, pyridazine-H), 7.77 (d, J = 2.0 Hz, 1H, pyrazole-H), 8.13 (d, J = 8.0 Hz, 2H, ArH), 8.31 (d, J = 9.6 Hz, 1H, pyridazine-H), 8.64 (d, J = 2.0 Hz, 1H, pyrazole-H); IR (KBr) ν (cm^{-1}): 3136, 3093, 3028, 2958, 1725, 1597, 1517, 1456, 1408, 1283, 1197, 1158, 1110, 1046, 1014, 931, 861, 774; Anal. calcd. for $C_{15}H_{12}N_4O_3$: C, 60.78; H, 4.08; N, 18.91; found: C, 60.78; H, 4.02; N, 18.92.

Synthesis of 3-chloro-6-(4-ethoxycarbonyl-5-methyl-1H-pyrazol-1-yl)pyridazine 6 and 3-dimethylamin-6-(4-ethoxycarbonyl-5-methyl-1H-pyrazol-1-yl)pyridazine 7. A mixture of ethyl 2-((dimethylamino)methylene)-3-oxobutanoate **5** (1.50 g, 8.10 mmol) and 3-chloro-6- hydrazinyl pyridazine **1**(1.16 g, 8.00 mmol) in *n*-butanol (20mL) was refluxed. When the starting materials were consumed completely as indicated by thin layer chromatography, the workup of reaction mixture was the same as that of compound **2** to give compound **6** (1.52 g) as a white crystal in 60% yield, mp. 140–141°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.39 (t, J = 7.2 Hz, 3H, $CH_2\mathbf{CH_3}$), 3.05 (s, 3H, pyrazole-CH_3), 4.35 (q, J = 7.2 Hz, 2H, $\mathbf{CH_2}CH_3$), 7.69 (d, J = 9.2 Hz, 1H, pyridazine-H), 8.10 (s, 1H, pyrazole-H), 8.14 (d, J = 9.2 Hz, 1H, pyridazine-H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ: 13.73, 14.55, 60.53, 115.59, 124.14, 130.73, 143.91, 146.59, 155.38, 156.06, 163.31; LC-MS: 267 (M^+, 100), 269 (33); IR (KBr) ν (cm^{-1}): 3131, 1633, 1448, 1402, 1089, 1018, 860, 765. Anal. calcd. for $C_{11}H_{11}ClN_4O_2$: C, 49.54; H, 4.16; N, 21.01; found: C, 49.28; H, 4.26; N, 20.98.

Side product 3-dimethylamin-6-(4-ethoxycarbonyl-5-methyl-1*H*-pyrazol-1-yl) pyridazine **7** was also obtained in 10% yield.

mp. 102–104°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.38 (t, *J* = 7.2 Hz, 3H, $CH_2\mathbf{CH_3}$), 2.92 (s, 3H, pyrazole-CH_3), 3.24(s, 6H, $N(CH_3)_2$), 4.33 (q, *J* = 7.2 Hz, 2H, $\mathbf{CH_2}CH_3$), 6.98((d, *J* = 10.0 Hz, 1H, pyridazine-H), 7.34 (d, *J* = 9.6 Hz, 1H, pyridazine-H), 8.04 (s, 1H, pyrazole-H). Anal. calcd. for $C_{13}H_{17}N_5O_2$: C, 56.71; H, 6.22; N, 25.44; found: C, 56.77; H, 6.27; N, 25.41. Compound **7** was further confimred by X-ray diffraction (Fig. 5).

3-(4-methylphenoxy)-6-(4-ethoxycarbonyl-5-methyl-1H-pyrazol-1-yl)pyridazine(8a). White solid, yield 41%, mp. 110–111°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.38 (t, *J* = 7.2 Hz, 3H, $CH_2\mathbf{CH_3}$), 2.38 (s, 3H, Ar—CH_3), 2.95 (s, 3H, pyrazole-CH_3), 4.33 (q, *J* = 7.2 Hz, 2H, $\mathbf{CH_2}CH_3$), 7.12 (d, *J* = 8.4 Hz, 2H, ArH), 7.25 (d, *J* = 8.4 Hz, 2H, ArH), 7.34 (d, *J* = 9.2 Hz, 1H, pyridazine-H), 8.06 (s, 1H, pyrazole-H), 8.11 (d, *J* = 9.2 Hz, 1H, pyridazine-H); IR (KBr) ν (cm^{-1}): 3114, 3035, 1710, 1545, 1446, 1402, 1302, 1251, 1184, 1085, 1018, 934, 880, 842, 771; Anal. calcd. for $C_{18}H_{18}N_4O_3$: C, 63.89; H, 5.36; N, 16.56; found: C, 63.92; H, 5.41; N 16.49.

3-(3,5-dimethylphenoxy)-6-(4-ethoxycarbonyl-5-methyl-1H-pyrazol-1-yl) pyridazine(8b). White solid, yield 80%, mp. 119–120°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.38 (t, *J* = 7.2 Hz, 3H, $CH_2\mathbf{CH_3}$), 2.34 (s, 6H, Ar—$(CH_3)_2$), 2.95 (s, 3H, pyrazole-CH_3), 4.34 (q, *J* = 7.2 Hz, 2H, $\mathbf{CH_2}CH_3$), 6.83 (s, 2H, ArH), 6.90 (s, 1H, ArH), 7.33 (d, *J* = 9.6 Hz, 1H, pyridazine-H), 8.06 (s, 1H, pyrazole-H), 8.10 (d, *J* = 9.6 Hz, 1H, pyridazine-H); IR (KBr) ν (cm^{-1}):3114, 3035, 2985, 2934,1718,1619, 1555, 1443, 1402, 1296, 1251, 1184, 1133, 1094, 1034, 934, 835, 784; Anal. calcd. for $C_{19}H_{20}N_4O_3$: C, 64.76; H, 5.72; N, 15.90; found: C, 64.56; H, 6.00; N, 15.97.

3-(2-methoxycarbonylphenoxy)-6-(4-ethoxycarbonyl-5-methyl-1H-pyrazol-1-yl) pyridazine(8c). White solid, yield 75%, mp. 130–131°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.38 (t, *J* = 7.2 Hz, 3H, $CH_2\mathbf{CH_3}$), 2.93 (s, 3H, pyrazole-CH_3), 3.74 (s, 3H, $COOCH_3$), 4.33 (q, *J* = 7.2 Hz, 2H, $\mathbf{CH_2}CH_3$), 7.32 (d, *J* = 8.0 Hz, 1H, ArH), 7.37 (t, *J* = 7.6 Hz, 1H, ArH), 7.45 (d, *J* = 9.6 Hz, 1H, pyridazine-H), 7.65 (t, *J* = 7.6 Hz, 1H, ArH), 8.06 (s, 1H, pyrazole-H), 8.09 (d, *J* = 7.6 Hz, 1H, ArH), 8.17 (d, *J* = 9.6 Hz, 1H, pyridazine-H); IR (KBr) ν (cm^{-1}): 3122, 2992, 1710, 1602, 1552, 1478, 1446, 1402, 1299, 1258, 1184, 1133, 1091, 1034, 931, 880, 835, 774; Anal. calcd. for $C_{19}H_{18}N_4O_5$: C, 59.68; H, 4.74; N, 14.65; found: C, 59.70; H, 4.61; N, 14.69.

3-(4-chlorophenoxy)-6-(4-ethoxycarbonyl-5-methyl-1H-pyrazol-1-yl) pyridazine(8d). White solid, yield 80%, mp. 175–176°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.38 (t, *J* = 7.2 Hz, 3H, $CH_2\mathbf{CH_3}$), 2.95 (s, 3H, pyrazole-CH_3), 4.33 (q, *J* = 7.2 Hz, 2H, $\mathbf{CH_2}CH_3$), 7.19 (d, *J* = 8.8 Hz, 2H, ArH), 7.38 (d, *J* = 9.6 Hz, 1H, pyridazine-H), 7.41 (d, *J* = 8.8Hz, 2H, ArH), 8.06(s, 1H, pyrazole-H), 8.16 (d, *J* = 9.6 Hz, 1H, pyridazine-H); IR (KBr) ν (cm^{-1}): 3134, 3012, 1716, 1578, 1552, 1443, 1402, 1285, 1254, 1168, 1041, 1087, 848, 772; Anal. calcd. for $C_{17}H_{15}ClN_4O_3$: C, 56.91; H, 4.21; N, 15.62; found: C, 56.73; H, 4.34; N, 15.90.

3-(3-chlorophenoxy)-6-(4-ethoxycarbonyl-5-methyl-1H-pyrazol-1-yl) pyridazine(8e). White solid, yield 72%, mp. 130–131°C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.38 (t, *J* =7.2 Hz, 3H, $CH_2\mathbf{CH_3}$), 2.97 (s, 3H, pyrazole-CH_3), 4.34 (q, *J* = 7.2 Hz, 2H, $\mathbf{CH_2}CH_3$), 7.16(dd, *J*=1.6Hz, 6.8Hz, 1H, ArH), 7.27–7.30(m, 2H, ArH), 7.38–7.42 (m, 2H, pyridazine-H + ArH), 8.07 (s, 1H, pyrazole-H), 8.18 (d, *J* = 9.2 Hz, 1H, pyridazine-H); IR (KBr) ν (cm^{-1}): 3136, 3035, 1718, 1584, 1562, 1442, 1402, 1290, 1248, 1187, 1040, 1094, 854, 778; Anal. calcd. for $C_{17}H_{15}ClN_4O_3$: C, 56.91; H, 4.21; N, 15.62; found: C, 57.32; H, 4.05; N, 15. 44.

3-(3,4-dichlorophenoxy)-6-(4-ethoxycarbonyl-5-methyl-1H-pyrazol-1-yl) pyridazine(8f). White solid, yield 58%, mp. 145–146°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.38 (t, *J* = 7.2 Hz, 3H, $CH_2\mathbf{CH_3}$), 2.97 (s, 3H, pyrazole-CH_3), 4.34 (q, *J* = 7.2 Hz, 2H, $\mathbf{CH_2}CH_3$), 7.14 (dd, J_1 = 8.8Hz, J_2 = 2.8Hz, 1H, ArH), 7.36–7.42 (m, 2H, ArH+ pyridazine-H), 7.52 (d, *J* = 8.8 Hz, 1H, ArH), 8.07 (s, 1H, pyrazole-H), 8.20 (d, *J* = 9.2 Hz, 1H, pyridazine-H); IR (KBr) ν (cm^{-1}): 3114, 3021, 1718, 1552, 1443, 1402, 1296, 1246, 1187, 1094, 1037, 922, 890, 838, 771; Anal. calcd. for $C_{17}H_{14}Cl_2N_4O_3$: C, 51.93; H, 3.59; N, 14.25; found: C, 52.11; H, 4.05; N, 14.03.

3-(4-methoxycarbonylphenoxy)-6-(4-ethoxycarbonyl-5-methyl-1H-pyrazol-1-yl) pyridazine(8g). White solid, yield 52%, mp. 129–130°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.38 (t, *J* = 7.2 Hz, 3H, $CH_2\mathbf{CH_3}$), 2.96 (s, 3H, pyrazole-CH_3), 3.94(s, 3H, $COOCH_3$), 4.33 (q, *J* = 7.2 Hz, 2H, $\mathbf{CH_2}CH_3$), 7.32(d, *J* = 8.8 Hz, 2H, ArH), 7.42 (d, *J* = 9.6 Hz, 1H, pyridazine-H), 8.07 (s, 1H, pyrazole-H), 8.14 (d, *J* = 8.8 Hz, 2H, ArH), 8.19 (d, *J* = 9.6 Hz, 1H, pyridazine-H); IR (KBr) ν (cm^{-1}): 3136, 3013, 2025, 1723, 1606, 1590, 1554, 1506, 1481, 1456, 1435, 1412, 1400, 1298, 1245, 1206, 1184, 1168, 1098, 1042, 1016, 935, 877, 771; Anal. calcd. for $C_{19}H_{18}N_4O_5$: C, 59.68; H, 4.74; N, 14.65; found: C, 59.64; H, 4.55; N, 14.45.

3-(3-trifluorophenoxy)-6-(4-ethoxycarbonyl-5-methyl-1H-pyrazol-1-yl) pyridazine(8h). White solid, yield 80%, mp.: 133–134°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.38 (t, *J* = 7.2 Hz, 3H, $CH_2\mathbf{CH_3}$), 2.96 (s, 3H, pyrazole-CH_3), 4.34 (q, *J* = 7.2 Hz, 2H, $\mathbf{CH_2}CH_3$), 7.43 (d, *J* = 9.6 Hz, 1H, pyridazine-H), 7.47 (d, *J* = 8.0 Hz, 1H, ArH), 7.52 (s, 1H, ArH), 7.54 (d, *J* = 8.0 Hz, 1H, ArH), 7.58 (t, *J* = 7.6 Hz, 1H, ArH), 8.08 (s, 1H, pyrazole-H), 8.20 (d, *J* = 9.6 Hz, 1H, pyridazine-H); IR (KBr) ν (cm^{-1}): 3181, 3145, 3060, 2992, 2931,1718, 1648, 1581, 1554, 1474, 1444, 1380, 771, 691; Anal. calcd. for $C_{18}H_{15}F_3N_4O_3$: C, 55.10; H, 3.85; N, 14.28; found: C, 55.24; H, 4.05; N, 14.39.

Herbicidal activity tests [20,21]. ***Inhibition of the root-growth of rape (Brassica campestris L.).*** The compounds to be tested are made into emulsions to aid dissolution. Rape seeds are soaked in distilled water for 5 h before being placed on a filter paper in a 6-cm Petri plate, to which 2 ml of inhibitor solution had been added in advance. Usually, 15 seeds are used on each plate. The plate is placed in a dark room and allowed to germinate for 72 h at 28(±1)°C. The lengths of 10 rape roots selected from each plate are measured and the means are calculated. The inhibition percentage is calculated relative to controls using distilled water instead of the inhibitor solution. There were two replicates for each treatment. The data of herbicidal activity are listed in Table 1.

Inhibition of the seedling growth of barnyard grass (Echinochloa crusgalli (L.) Beauv.). The compounds to be evaluated are made into emulsions to aid dissolution. Ten baryard grass seeds are placed into a 50-mL cup covered with a layer of grass beads (diameter = 0.5cm) and a piece of filter paper at the bottom, to which 5 mL of inhibitor solution had been added in advance. The cup is placed in a bright room, and the seeds were allowed to germinate for 72 h at 28(±1)°C. The height of the above-ground parts of the seedlings in each cup is measured and the means calculated. The inhibition percentage is calculated relative to controls using distilled water instead of the inhibitor solution. There were two replicates for each treatment. The data of herbicidal activity are listed in Table 1.

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Influence of Differently Ionized Species on Fragmentation Pathways and Energetics of a Potential Adenosine Receptor Antagonist Using a Triple Quadrupole and a Multistage LTQ-Orbitrap™ FTMS Instrument

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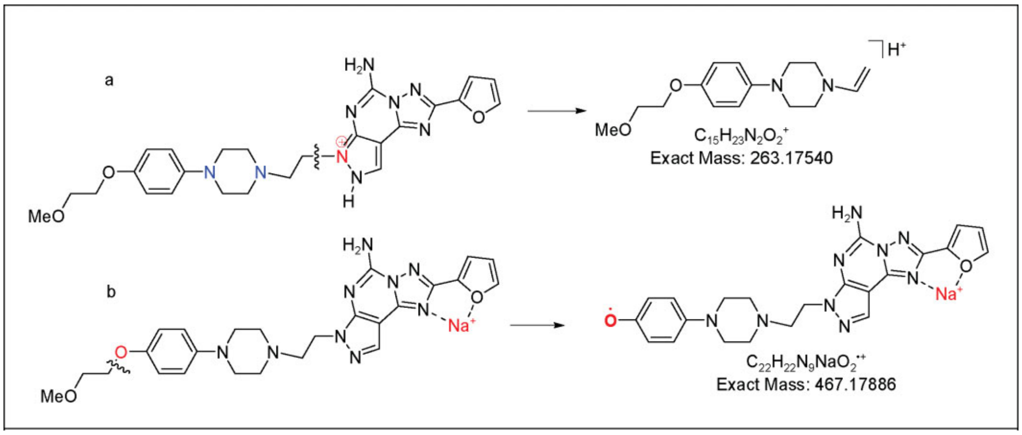

A systematic study was conducted to investigate the influence of differently ionized species on the fragmentation pathways and energetics of a piperazine-containing adenosine by using different cations or anions. Very different fragmentation mechanisms were observed in protonated- *versus* sodiated-molecules, which indicated that the proton is mobilized to promote the charge-direct fragmentation, whereas Na^+ cation was fixed at the heterotricyclic ring structure provoking charge-remote fragment ions. This finding was also supported by the results observed in the fragmentation behaviors in the deprotonated-molecule. The energetics of these fragment ions were also explored by using the breakdown curves obtained from the triple quadrupole and LTQ-Orbitrap™ instrument. The data indicated that the lowest energy pathways in the protonated-molecule $[M+H]^+$ involve breaking a C—N bond connecting an ethylene bridge and heterotricyclic ring structure. The lowest energy pathway is the cleavage of a C—O bond connecting the methoxy ethyl group and phenolic oxygen to form a distonic radical ion for a sodiated-molecule $[M+Na^+]$and a deprotonated-molecule $[M\text{-}H]^-$. The data suggest that by choosing the differently ionized species, one can probe different fragmentation channels that can provide additional structure information for an unknown impurity and possibly degradation product identification. In addition, by comparing the data obtained from triple quadrupole and LTQ-Orbitrap instruments, one can develop further understanding of the differences in the fragmentation behaviors due to the variations in the collision activation-dissociation process. From the side-by-side comparison with the breakdown curves obtained for both instruments, the difference in fragmentation behaviors caused by the difference in dissociation processes that occur in these two types of instruments can be probed.

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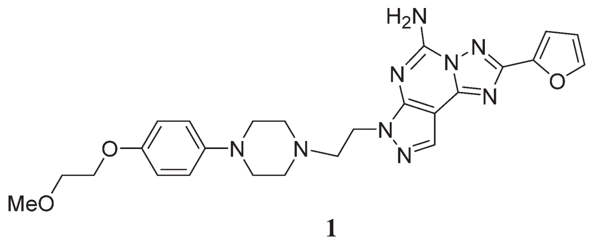
INTRODUCTION

LC/MS and LC/MS/MS techniques have become a widely used analytical tool for the identification of small molecule impurities in active pharmaceutical ingredients (API). With the increasing number of applications of LC/MS and MS/MS methods, a comprehensive understanding of small-molecule fragmentation pathways has become correspondingly more important. The newly designed LTQ-Orbitrap™ instrument has the capability of performing high-resolution (upto 100,000) and high-mass accuracy (<5 ppm, external calibration) with wide-dynamic range (>5000) mass measurements [1,2]. The instrument can also perform multistage MS/MS (MS^n) experiment that are essential for studying fragmentation pathways.

A potential adenosine receptor antagonist, **1**, was utilized as a model compound for this mass spectral fragmentation pathway study.



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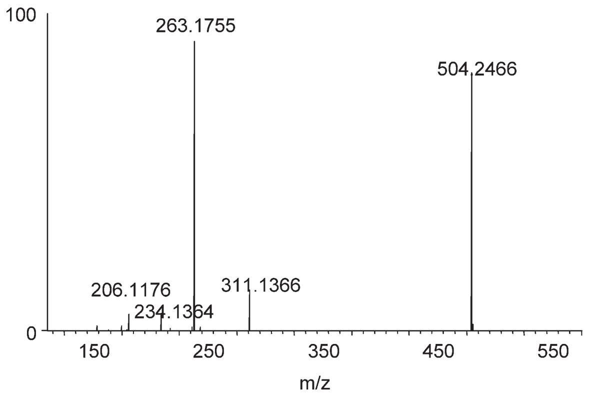


Figure 1. 30 eV MS/MS spectrum of the protonated-molecule at m/z 504 obtained from Orbitrap MS.

The fragmentation mechanisms and energetics of these types of compounds have not been explored previously. To identify potential impurities and degradation products in **1**, and related compounds, it is essential to understand the fragmentation pathways and energetics of this model compound. The LTQ-Orbitrap is a hybrid instrument that combines an LTQ ion trap instrument with an Orbitrap; the latter is used for high-mass accuracy analysis. All the ion activation processes occur in the LTQ ion trap portion of the instrument, and the resulting ions are then injected into the Orbitrap to achieve high-mass accuracy detection. In an ion trap, collisonal-activation of the precursor ion occurs *via* resonance excitation that couples with the tandem-in-time process of the ion trap, rather than tandem-in-space process of a beam instrument. This allows multistage tandem mass spectrometry for structural elucidation. Combining multistage MS/MS experiments with high-resolution detection obtained in the Orbitrap, one can obtain high-mass accuracy (<5 ppm) for every fragment ion. Consequently, we are able to determine the elemental composition of each fragment ion, allowing the derivation of plausible fragment structures. As a result, a detailed fragmentation pathway of a compound can be readily derived *via* these experiments. Themo Fisher Quantum triple quadrupole mass spectrometer is a beam instrument where collision activation of precursor ions occurs through tandem-in-space was used for comparison purposes [3,4]. The differences in fragmentation behavior of the model compound were illustrated clearly from the breakdown curves generated by both instruments.

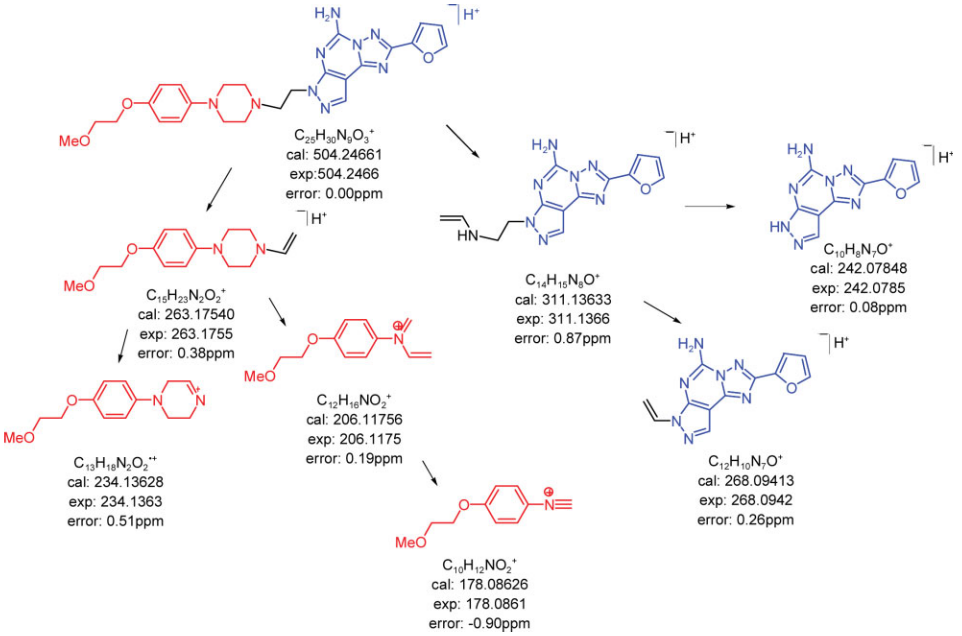
In this article, we discuss the influence of the different cations or anions on the fragmentation behavior of **1**, especially, the protonated, sodiated, and deprotonated adducts commonly observed in a routine LC/MS run. The different fragmentation behaviors observed from these varied approaches can assist the investigator in determining additional fragmentation channels that are structurally informative. By applying different approaches, the process can help an investigator to interpret the fragmentation patterns generated in unknown impurities and degradation products leading ultimately to the determination of the structure. Charge-remote fragmentation mechanism of the sodium adduct were also studied. The purpose was to provoke the charge-remote fragmentation by using the Na^+ cation instead of the protonated-molecule to gain access to different types of fragmentation channels. A similar approach has been successfully applied to other types of compounds previously [5,6].

RESULTS AND DISCUSSION1

Protonated-molecule. Figure 1 shows the 30 eV MS/MS spectrum of the protonated-molecule, 1, at m/z 504, obtained from the Orbitrap instrument. The most abundant fragment ion at m/z 263 was the result of the cleavage C—N bond with a neutral loss of 7*H*-pyrazolo[4,3-*e*]-[1,2,4]triazolo-[1,5-*c*]pyrimidin-5-yl amine moiety (a heterotricyclic moiety, see Scheme 1). The fragment ion at m/z 311 was the result of piperazine ring opening with a neutral loss of the methoxy-phenetole and a portion of the piperazine ring. MS^3 experiments were also conducted to further investigate the fragmentation pathway of this compound. Figure 2 shows the MS^3 spectra of the product ions at m/z 263 and m/z 311. As shown in Scheme 1, the fragment ion at m/z 263 yields two dominant fragment ions at m/z 206 generated by piperazine ring opening and 234 produced by the loss of the ethylene bridge. The fragment ion at m/z 206 undergoes further fragmentation to give an ion at m/z 178. The fragment ion at m/z 311 gave two major fragment ions at m/z 268 (the result of loss of a vinyl amine group) and 242 generated by cleavage at the C—N bond between the carbon of the ethylene linkage and the nitrogen on the tricyclic ring. The data show that all the fragment ions were the result of either the piperazine ring opening or the cleavage at either side of the ethylene linkage connecting the phenyl piperazine and hetero tricyclic moieties.

For comparison purposes, the 30 eV MS/MS spectrum of the protonated-molecule (m/z 504) generated by a

Scheme 1. Fragmentation pathways of the protonated-molecule at m/z 504 derived from MS^3 spectra obtained from the Orbitrap instrument at mass accuracy within 1 ppm. [Color scheme can be viewed in the online issue, which is available at www.interscience.wiley.com.]



triple quadrupole instrument is shown in Figure 3. The fragmentation patterns were similar to those obtained from the Orbitrap instrument except for the differences in the relative abundances of individual fragment ions. The MS/MS data suggested that preferential and selective cleavage was observed in the protonated-molecule obtained *via* the Orbitrap instrument, whereas extensive and nonselective cleavage was generated by the triple quadrupole instrument.

To illustrate energy effects on the fragmentation behavior more clearly, the breakdown curves obtained from both Orbitrap and triple quadrupole instruments are shown in Figure 4. It is clear that the breakdown curve obtained from the Orbitrap instrument changes dramatically with changing the collision energy from 20 to 35 eV. The intensity for the precursor ion decreases with increasing collision energy. At 35 eV collision energy, almost all the precursor ions underwent further fragmentation, the fragment ion at m/z 263 becoming the most dominant peak. The relative intensity of each fragment ion remained unchanged when the collision energy was increased from 35 to 60 eV. The major fragment ion at m/z 263 remained the dominant fragment ion, whereas all the other fragment ions were present at very low intensity. The data indicated that the m/z 263 ion was the low energy and preferred fragmentation channel. The collision activation dissociation process occurred in a linear ion trap, where the ion of interest collided multiple times with helium gas but could not accumulate enough internal energy to facilitate the higher energy fragmentation channels.

The breakdown curves obtained from the triple quadrupole instrument changed dramatically *via* changes of the collision energy as shown in Figure 4(b). The collision energy had a significant impact on the fragmentation channels. The precursor ion intensity decreases with the increase of the collision energy from 0 to 40 eV. Above 40 eV, the precursor ion intensity was less than 5%. Concurrently, the fragment ion intensity increased dramatically. At around 30 eV, the fragment ion at m/z 263 became the dominant fragmentation channel, which is consistent with the observation from Orbitrap instrument, where the m/z 263 is the lowest energy channel in the protonated-molecule. When the collision energy increased to around 40 eV, the fragment ions at m/z 84 and 206 became the dominant fragmentation channels. When the collision energy was increased to 50 eV, m/z 178 became the major fragment channel.

Based on the Scheme 1, it is clear that the fragment ions at m/z 84, 178, and 206 were the result of further dissociation of the fragment ion at m/z 263. The data suggest that in the triple quadrupole instrument, there is enough internal energy deposited into the molecule to promote higher energy fragmentation channels.

The breakdown curves obtained from both instruments also demonstrated that the dominant fragment ions, such as, m/z 263, 206, 178, and 84 contained the whole or partial piperazine ring. The fragment ions containing the 7*H*-pyrazolo[4,3-*e*][1,2,4]-triazolo[1,5-*c*]pyrimidin-5-yl amine, such as m/z 311, 268, and 242, were present in a very small amount. It is clear that in the

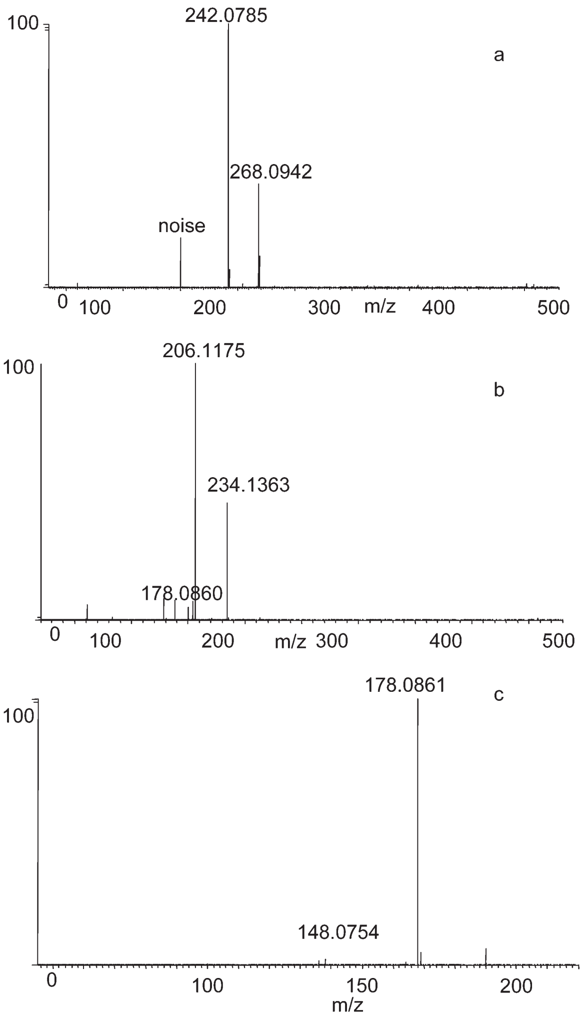


Figure 2. (a) 30 eV MS^3 spectrum of the protonated-molecule at m/z 504→m/z 311→ product, (b) 35 eV MS^3 spectrum of the protonated-molecule at m/z 504→m/z 263→ product, and (c) 30 eV MS^3 spectrum of the protonated-molecule at m/z 504→m/z 206→ product.

protonated-molecule, **1**, the preferred fragmentation channels involved the phenyl piperazine moiety.

Sodiated-molecule[M+Na$^+$]. Figure 5(a) shows the 20 eV MS/MS spectrum of the sodiated-molecule at m/z 526 in the Orbitrap MS instrument. Again, very selective and preferential cleavage was observed in the sodiated-molecule in the Orbitrap instrument. Only one fragment ion at m/z 467 was observed at collision energies ranging from 0 to 70 eV in the Orbitrap instrument. Based on the accurate mass data, the structure of this fragment ion can be determined as a nonconventional distonic radical cation (Scheme 2). This fragment ion was not observed for the protonated-molecule (Fig. 1 and Scheme 1). To explore the fragmentation behaviors of the sodiated-molecule, MS^3 experiments of the product ion at m/z 467 generated from the sodiated-molecule at m/z 526 were conducted [Fig. 5(b)]. The major fragment ions observed were m/z 333, 319, 290, and 264, in which, m/z 333, 290, and 264 correspond to fragment ions at m/z 311, 268, and 242 in the protonated-molecule. The fragment ion at m/z 319, the most dominant fragment in the 30 eV MS^3 spectrum using the Orbitrap MS, was not present for the protonated-molecule. This fragment ion was the result of piperazine ring opening in a different way from that of the m/z 333 ion. The fragmentation pathways derived from the MS/MS and

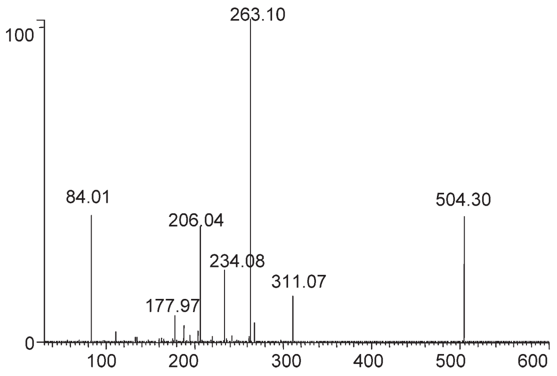


Figure 3. 30 eV MS/MS spectrum of the protonated-molecule at m/z 504 obtained from triple quadrupole instrument.

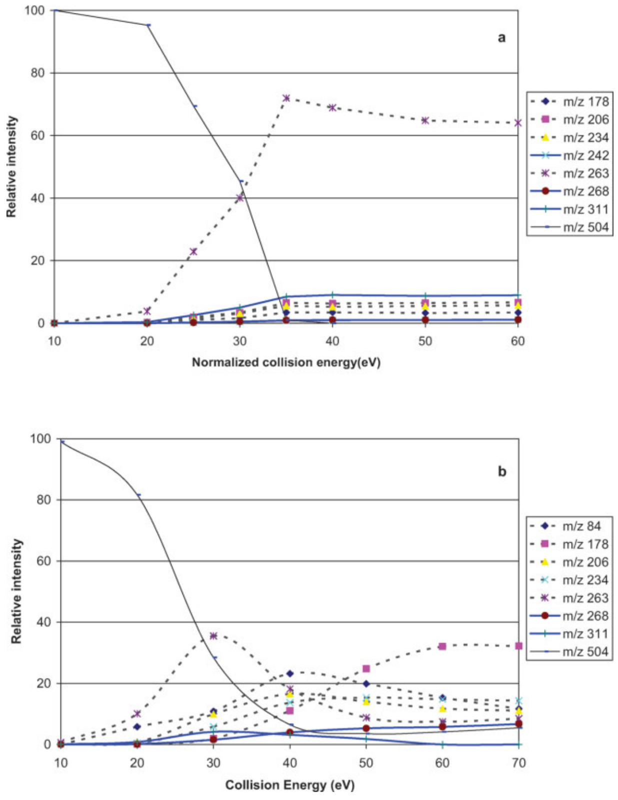


Figure 4. (a) Breakdown curve of $[M+H]^+$ from Orbitrap; (b) Breakdown curve of $[M+H]^+$ from triple quadrupole. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

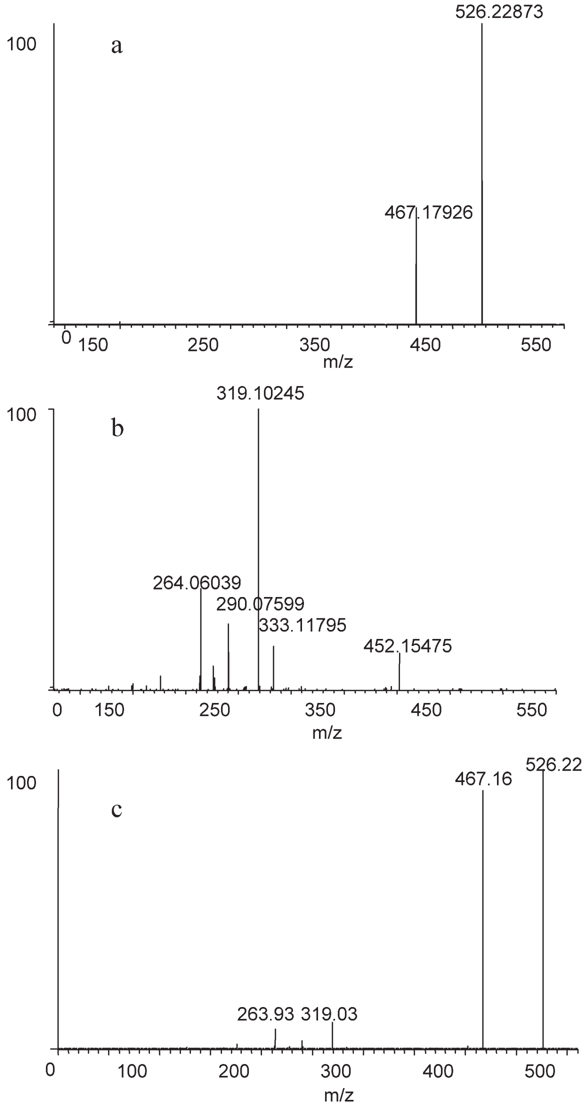


Figure 5. (a) 20 eV MS/MS spectra of [M+Na$^+$] at m/z 526 from the Orbitrap MS, (b) 35 eV MS^3 spectrum of [M+Na$^+$] at m/z 526→ m/z 467→products from the Orbitrap MS, (c) 30 eV MS/MS of [M+Na$^+$] at m/z 526 from the triple quadruple MS.

MS^3 experiments in the Orbitrap MS instrument are depicted in Scheme 2. It is worth noting that contrary to the fragmentation patterns observed for the protoned-molecule the major fragment ions in the MS^3 spectrum of the sodiated-molecule from the Orbitrap instrument all contain the intact 7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5-yl amine tricyclic ring moiety.

Figure 5(c) shows the 30 eV MS/MS spectrum of [M+Na$^+$] generated by a triple quadrupole instrument at 30 eV collision energy. The data showed the dominant fragment ion was observed at m/z 467, which is consistent with that obtained from Orbitrap instrument. However, in a triple quadrupole, we also observed several fragment ions at m/z 226, 264, 290, and 319, which were absent from the MS/MS spectrum generated in an Orbitrap instrument. Interestingly, all these ions were only observed in a MS^3 spectrum of the product ion at m/z 467 using the Orbitrap instrument.

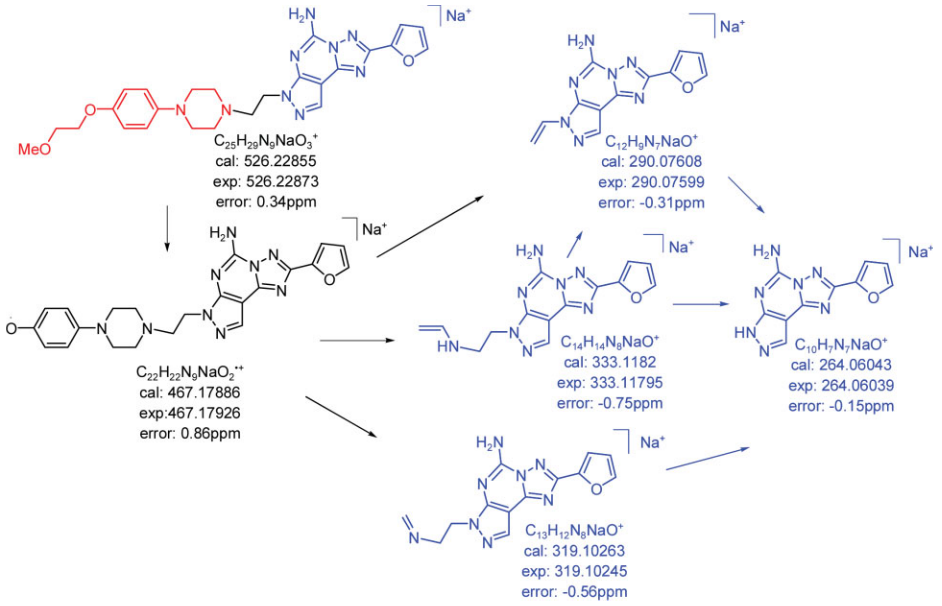
Figure 6(a,b) shows the breakdown curves generated by the Orbitrap and triple quadrupole instruments. The breakdown curves generated by the Orbitrap were very simple. Only one fragment ion at m/z 467 was generated at collision energy ranging from 0 to 80 eV with He as the collision gas. The data demonstrated that only one fragmentation channel opened during MS/MS experiment in Orbitrap and that forming the fragment ion at m/z 467 was the lowest energy process.

Figure 6(b) exhibits very interesting and different breakdown curves generated by the triple quadrupole instrument. Overall, the fragmentation behavior changed dramatically with increasing collision energy. At lower energy, the precursor ion intensity decreased with increasing collision energy. Only 50% of the precursor ion remained at collision energy of 30 eV; the dominant fragment ion observed at this collision energy was m/z 467, which indicated that this is the lowest energy channel. Many fragmentation channels were opened up when the fragment ion at m/z 319 became the major fragment ion at 40–50 eV collision energy. At a collision energy of 60 eV, the m/z 264 fragment ion was the most favored. The data clearly suggest that there were more internal energy deposited in the dissociation process in a triple quadrupole instrument, which opens up higher energy fragmentation channels.

The remarkable differences between breakdown curves obtained from the Orbitrap and triple quadrupole instruments for protonated- and sodiated-forms of **1** are the relative abundance of fragment ions at m/z 263 (protonated) and m/z 467 (sodiated). These differences are most likely caused by discrimination against certain fragment ions in competitive reaction channels in slow activation processes common in ion trap instruments [8,9]. Based on the study conducted by Futrell and coworkers [8], two different fragmentation pathways are competing with each other: the further dissociation of the lowest-energy fragmentation *via* high-energy fragmentation channel. The higher energy fragmentation pathway is strongly suppressed if it has a slower-activation process than that of the low-energy pathway(s). These observations were also consistent with the results of other ion-activation processes, such as surface-induced dissociation (SID) *vs.* collision induced dissociation (CID) reported by Laskin *et al.* [10]

We also wished to compare the fragmentation pathways obtained using the Orbitrap instrument (Schemes 1 and 2) and breakdown curves generated by triple quadrupole instrument [Figs. 4(b) and 6(b)] for both protonated- and sodiated-molecule, respectively. It is clear that all the dominant fragment ions in the protonated-

Scheme 2. Fragmentation pathways of [M+Na$^+$] from Orbitrap instrument with mass accuracy of 1 ppm. [Color scheme can be viewed in the online issue, which is available at www.interscience.wiley.com.]



molecules contain the piperazine moiety, whereas the major fragment ions in the sodiated-molecules contain a heterotricyclic moiety. The data may be explained by the proposed fragmentation mechanism shown in Scheme 3. In the protonated-molecule, the proton is freely mobilized in the molecule, which will promote charge-directed fragmentation. For example, when the proton is on a nitrogen atom of the tricyclic ring, it will weaken the C—N bond, which breaks to form the dominant fragment ion at m/z 263. The mobile proton model was also applied to explain the fragmentation behavior for protonated-peptides [11]. Conversely, for the sodiated-molecule, sodium cation is localized at the heterotricyclic moiety, which can provoke charge-remote fragment ions [12–14]. For example, the dominant fragment ion at m/z 467 was obtained through homolytic cleavage of a C—O bond to form the distonic radical cation, with 0.11 ppm mass accuracy. The data from deprotonated-negative ion [M-H]$^-$, as described in the next section, further supported this hypothesis.

Deprotonated-negative ion [M-H]$^-$. Figure 7(a,c) show the 30 eV MS/MS spectra of the deprotonated-molecule at m/z 502 obtained by Orbitrap and triple quadrupole instruments. Similar fragmentation patterns were observed in both instruments, with the major fragment ion at m/z 443, which is speculated to be a distonic radical ion formed *via* the breaking C—O bond, corresponding to m/z 467 ion in sodiated-molecule. Figure 7(b) shows the 35 eV MS^3 spectrum of the product ion at m/z 443, the major fragment ion from the precursor ion at m/z 502. The major fragment ions at m/z 295 and 252 were generated by the piperazine ring opening and C—C breaking in the ethylene moiety. The fragmentation pathways of the deprotonated-negative ion at m/z 502 are presented in Scheme 4. It is worth noting that

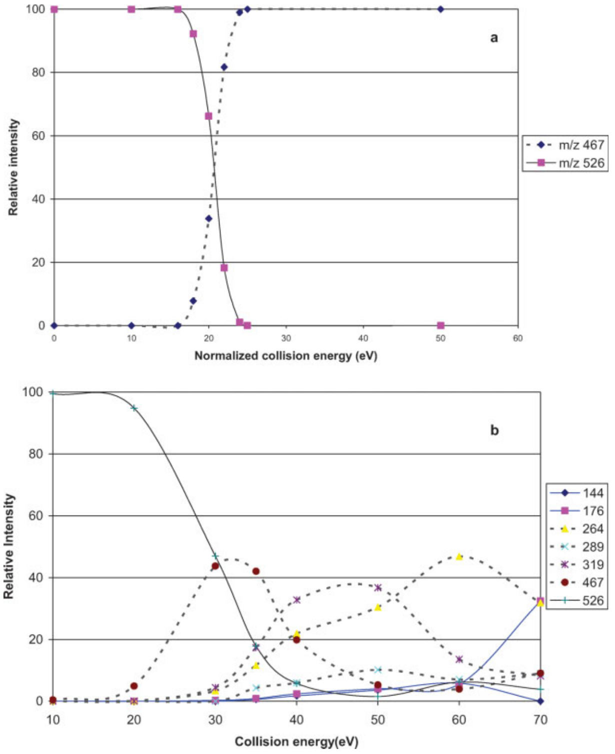
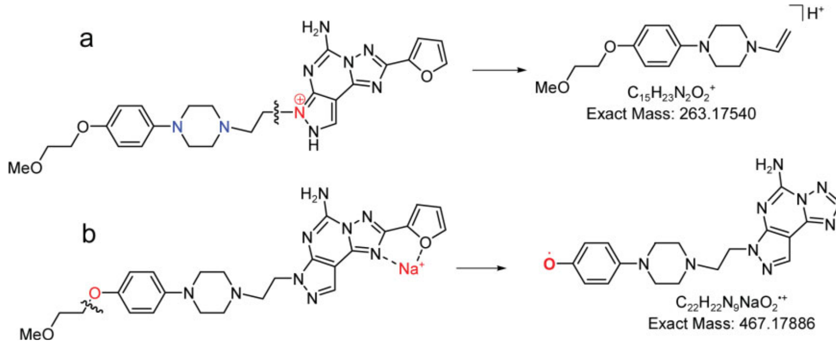


Figure 6. (a) Breakdown curve of [M+Na$^+$] from Orbitrap; (b) breakdown curve of [M+Na$^+$] from triple quadrupole. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Scheme 3. The proposed fragmentation mechanism diagram: (a) $[M+H]^+$: mobile proton-charge direct fragmentation; (b) $[M+Na^+]$: fixed charge–charge remote fragmentation. [Color scheme can be viewed in the online issue, which is available at www.interscience.wiley.com.]



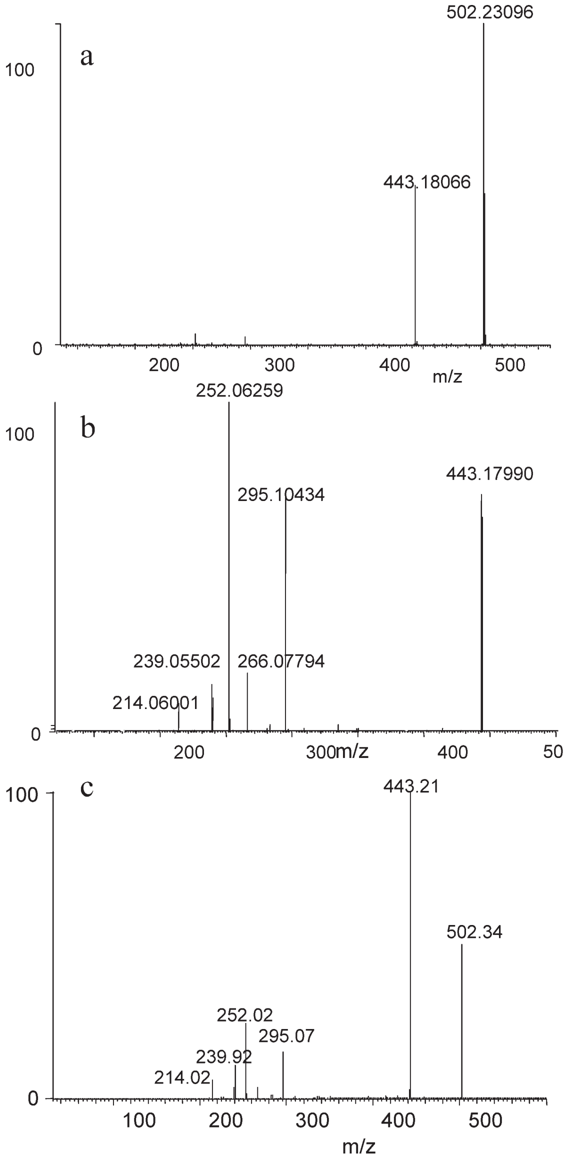
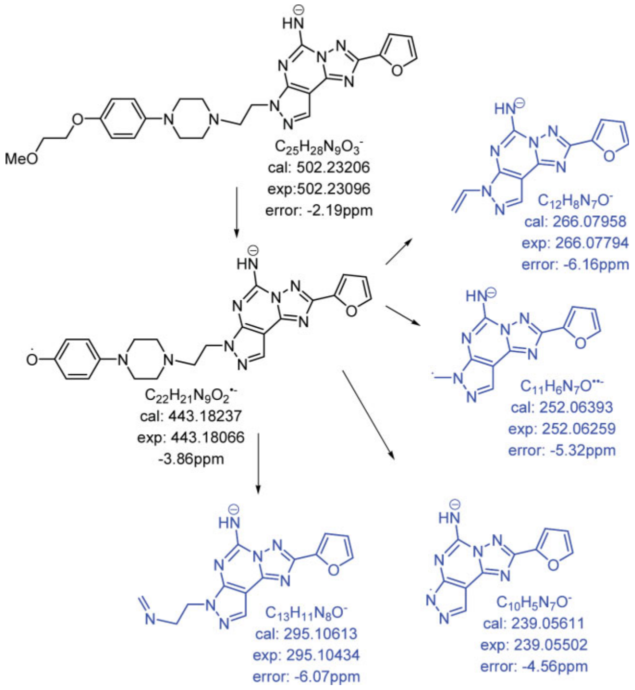


Figure 7. (a) 30 eV MS/MS spectra of $[M\text{-}H]^-$ from Orbitrap, (b) 35 eV MS^3 spectrum from Orbitrap, (c) 30 eV MS/MS spectra from triple quadrupole.

all the fragment ions from both MS/MS and MS^3 spectra contained a heterotricyclic moiety, which is similar to the behavior of the sodiated-molecule. The data suggest that the negative charge was located on the heterotricyclic moiety and all the fragment ions were again generated *via* charge-remote fragmentation mechanisms. This observation explains why the fragmentation patterns obtained from the deprotonated-molecule are similar to those obtained from the sodiated-molecule. A plausible hypothesis is that the only protons that can be removed in this molecule were those of the amino group connected to the tricyclic ring moiety, and the anion is localized/stabilized by the heterotricyclic ring moiety,

Scheme 4. Fragmentation pathways of $[M\text{-}H]^-$ from Orbitrap instrument. [Color scheme can be viewed in the online issue, which is available at www.interscience.wiley.com.]



which promotes the charge-remote fragment ions as seen in the sodiated-molecule. The data served to further confirm that the fragmentation mechanisms for protonated-molecule and sodiated-molecule are different. Fragment ions generated in protonated-molecules were through charge-direct fragmentation, whereas the fragment ions generated in sodiated-molecules were *via* charge-remote fragmentation.

CONCLUSIONS

Fragmentation patterns differed substantially for the protonated- and sodiated–molecules, whereas the fragmentation patterns between the sodiated- and deprotonated-molecules were similar, with all the dominant fragmentation ions containing the hetero tricyclic moiety. The data suggest that the proton is mobile in a protonated-molecule to produce the charge-direct fragment ions, whereas the sodiated- or deprotonated-ions were localized/stabilized in the heterotricyclic moiety, to promote the formation of charge-remote fragment ions.

Based on the differences in the breakdown curves generated for the triple quadrupole and Orbitrap instruments, it is clear that higher internal energy was deposited into the molecule in the triple quadrupole instrument, whereas less internal energy was deposited in the Orbitrap instrument. The lowest energy fragmentation channel for the protonated-molecule was the formation of the fragment ion at m/z 263 formed *via* the cleavage between C—N bond connecting an ethylene linkage and heterotricyclic moiety. The lowest energy fragmentation channel for the sodiated- and deprotonated-molecule was the formation of the fragment ion at m/z 467 or 443 due to the cleavage of the phenole ether linkage. The data suggest that the preferential and selective cleavages at C—N and C—O in the protonated, deprotonated, and sodiated are likely to be observed in other adenosine receptor antagonist related compounds. These characteristic fragmentation patterns observed in Orbitrap MS/MS spectra will provide additional evidence in solving the unknown impurities related to adenosine receptor antagonist compounds. By fragmenting differently ionized species adducts, one can get additional fragmentation information helpful in pinpointing the location of the oxidation or chemical modification sites in the unknown molecules. Combining the fragmentation information obtained in both ion trap and triple quadrupole instrument, one can derive a more comprehensive understanding of the molecular structure and its behavior.

EXPERIMENTAL

Ion trap experiments. Experiments were conducted using a Thermo LTQ-Orbitrap instrument equipped with a Surveyor HPLC system. The high resolution LC/MS and LC/MS^n spectra were acquired in the FTMS mode of the Orbitrap instrument at 30,000 mass resolution and 5 ppm mass accuracy to obtain the elemental composition of each fragment ion. The electrospray ionization needle was held at 4.5 kV, and a nitrogen sheath gas (10 units), and a nitrogen auxiliary gas (20 units) were used to stabilize the spray. The heated-capillary was set at 270°C. All MS/MS experiments were conducted in the linear ion trap. Helium was introduced into the ion trap to improve the trapping efficiency and also serves as the collision gas for CID. Consequently, only helium can be used as collision gas with the Orbitrap instrument. The operational pressure after introducing helium was $\sim 2 \times 10^{-5}$ Pa in the linear ion trap.

Triple quadrupole experiments. The experiments were conducted in a Thermo Quantum triple quadrupole mass spectrometer equipped with a Surveyor HPLC system. Argon was used as collision gas at 0.1 Torr in all MS/MS experiments. The electrospray ionization needle was held at 4 kV, and a nitrogen sheath gas (10 units) and a nitrogen auxiliary gas (20 units) were used to stabilize the spray. The heated-capillary was set at 270°C.

About 1 mg/mL of adenosine receptor antagonist (**1**), which was synthesized and well characterized previously [7], was dissolved in 50:50 acetonitrile: water. Sample solutions were introduced to the mass spectrometer through the LC system. The protonated, sodiated, and deprotonated-molecule were formed during the LC run without introducing additional Na cation.

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Preparation of 5-Nitro-2-amino[*b*]thiophenes and 1-(2-Amino-5-nitrophenyl)ethanones *via* Microwave Irradiation

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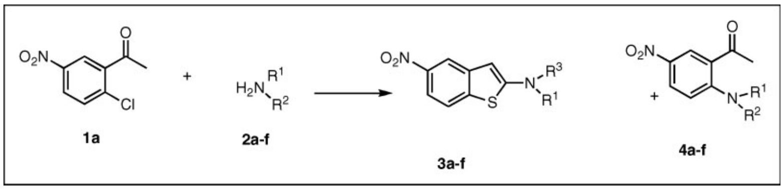

1a **2a-f** **3a-f** **4a-f**

1-(2-Chloro-5-nitrophenyl)ethanone) reacts with various amines in the presence of sulfur under microwave radiation to give the corresponding 2-aminobenzo[*b*]-thiophenes **3a–f** in good yields. The yields of **3a–f** are vastly superior to those obtained using conventional heating. Additionally, 1-(2-amino-5-nitrophenyl)ethanones **4a–f** were also obtained. A mechanism is proposed in which 2-amino thiophenes **3a–f** are formed by a S_NAr mechanism involving an intramolecular addition of sulfur of the intermediate thioamide to the 2-substituted carbon to give a Meisenheimer complex, which collapses to 2-aminothiophenes **3a–f**, and 2-amino ketones (**4a–f**) are formed by a parallel pathway involving nucleophilic addition amine to the 2-chloro position of **1** to form a Meisensheimer complex, which collapses to the amino ethanones.

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INTRODUCTION

In our continuing research on microwave-assisted synthesis of heterocycles [1], we directed our attention to preparing 2-aminobenzo[*b*]-thiophenes. Our interest in these heterocycles was piqued by their extensive use in the chemical and pharmaceutical industries. For example, 2-aminothiophenes are important precursors or intermediates in the preparation of coumarin dyes, biologically active chemicals, other fused heterocycles, *etc*. [2–4].

Before this study, 2-aminothiophenes were prepared primarily by the Gewald reaction [5], which involves treating an activated ketone, an activated nitrile and sulfur in the presence of morpholine as catalyst. Recently, the Gewald reaction was carried out using KF-alumina as catalyst [6] and microwave irradiation for heating. Cyclohexanone and cyclopentanone gave 2-amino products in very good yields (85–92%), whereas other cyclic ketones and various acyclic ketones gave modest yields (55–66%). All reactions were completed in 3.5–8.0 min. On the other hand, when the reactions were carried out using conventional heating (CH), the 2-aminothiphenes were obtained in comparable yields but a much longer time (3.5–7 h) was required [6].

Neckers and coworkers [7] reported a one-pot synthesis of 5-nitro-2-aminobenzo[*b*]thiophenes *via* a Willgerodt–Kindler (W-K) [8] using CH. Although the thiophenes were formed quickly (6–20 min), the yields were generally mediocre (4–47%). Furthermore, 2-chlorophenyl)ethanones that lacks a 5-nitro group failed to react. To see if these yields could be increased, we subjected the reactions to microwave irradiation and report the results herein.

RESULTS AND DISCUSSION

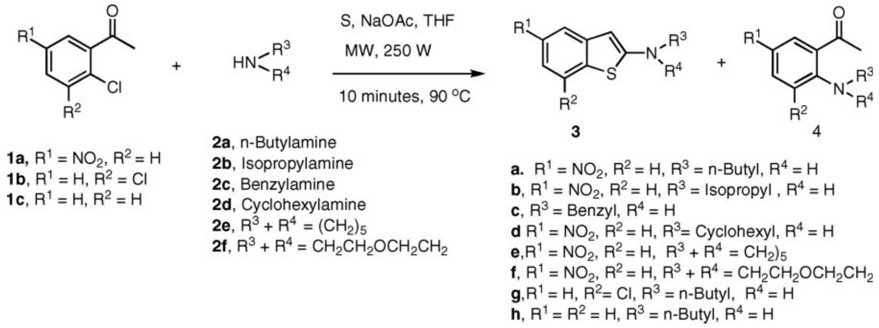
Equation (1) outlines the microwave-assisted reactions carried out in our laboratories for preparation of several 5-nitro-2-amino-benzo[*b*]thiophenes (**3a–f**). As shown, the reaction 5-nitro-1-(2-chlorophenyl)ethanone (**1**) with the appropriate amine (**2a–f**), elemental sulfur, NaOAc and DMF using microwave irradiation at 90–100°C for 10 min yielded thiophene analogs (**3a–f**) as major products along with minor amounts of 2-amino-5-nitroethanones (**4a–f**). The microwave yields as well as the yields of **3a–f** reported previously using CH [7] are listed in Table 1.

Considering first the relative yields of **3a–f** using microwave radiation (MV) *versus* CH, one sees that the yields from the former are significantly higher than those of the latter. For example, the ratio of the yields of **3b** and **3d** (entries 2 and 4) using MV *versus* CH was 60:14 and 52:19, respectively. Additionally, the ratio of the yields of the morpholino derivative **3f** was essentially the same (10 *vs.* 12%) (entry 6) in DMF. However, the MW reaction using NMM (entry 7) increased to 45%.

A possible mechanism for the formation of **3** and **4** is shown in Scheme 1. As shown, there are two parallel

Table 1

Reaction conditions and yields of compound **3a–f** and **4a–f.**



			Yield (%)					
			2-Aminothiophene			2-Aminoethanone		
	Ketone 1	Amine 2	3	MW[a]	Conventional[b]	4	MW[a]	Conventional[b]
1	**a**	**a**	**a**	71	36 (8, 60)	**a**	60	31 (8, 60)
2	**a**	**b**	**b**	60	14 (10,60)	**b**	62	30 (10, 60)
3	**a**	**c**	**c**	62	30 (10, 60)	**c**	52	52 (10, 60)
4	**a**	**d**	**d**	52	19 (6, 35)	**d**	65	65 (6, 35)
5	**a**	**e**	**e**	65	31 (15, 60)	**e**	10	12 (15, 60)
6	**a**	**e**	**f**	10	12 (20, 100)	**f**	48	10 (20, 100)
7	**a**	**e**	**f**	45[c]	–	**f**	25[c]	
8	**b**	**a**	**g**	0	0	**g**	0	0
9	**c**	**a**	**h**	0	0	**h**	0	0

[a] DMF used as solvent unless indicated otherwise. MW reactions were carried out at 90°C for 10 min.

[b] Respective time (minutes) and temperature (°C) for conventional reactions are given in parenthesis and ranged between 6 and 20 min and 35 and 100°C.

[c] NMM used as solvent.

pathways to the two products. One involves the reaction of 5-nitro-2-chloro ketone (**1**), amine (**2**), and sulfur proceeds *via* a W-K reaction to give the corresponding thioamide (**5**). Compound **5** then undergoes a substitution nucleophilic aromatic (S_NAr) intramolecular addition of sulfur to the 2-chloro-substituted carbon to give a Meisenheimer complex **6**, which then collapses to **3**. However, the starting ketone **1** can also proceed *via* a S_NAr pathway in which amine **2** adds intramolecularly to the 2-chloro carbon atom of **1** to form the resonance-stabilized Meisenheimer complex **7** and **8**. The complex then collapses to **4**. The stability of this complex probably allows this pathway to compete successfully with the addition of amine **2** to the C=O group in **1** giving an enamine, which is most likely the first step in the W-K mechanism [8,9].

In support of our proposed mechanism, the starting acetophenones **1b** and **Ic** (entries 8 and 9), which lack a 5-nitro group, failed to react by either pathway. Further, we were able to isolate the direct amination products **4a–f** by carrying out microwave-assisted reactions of **1a** with the amines **2a–f** in the absence of sulfur and solvent. As shown in Table 2, compounds **4a–f** were obtained in excellent yields (93–97%) using microwave irradiation at 90°C for only 5 min.

An added feature of this reaction is that various 2-aminoacetophenones are excellent precursors to various

Scheme 1

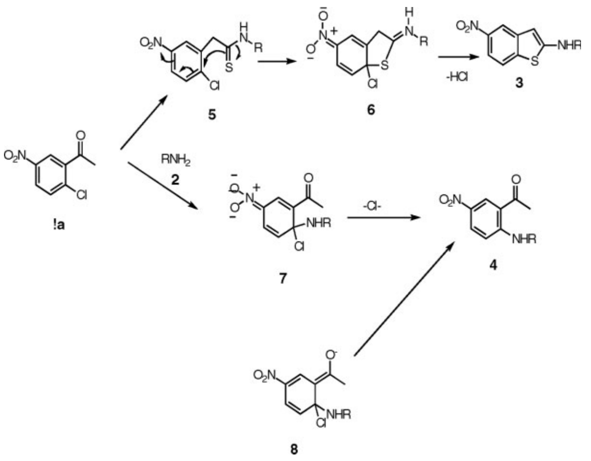
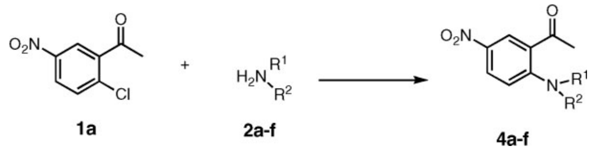


Table 2

Microwave-assisted synthesis of 5-nitro-2-aminoacetophenones (**4a–f**) using primary and secondary amines.[a]



Entry	Amine	Products [yield (%)][b]
1	*n*-Butylamine (**2a**)	**4a** (93)
2	Isopropylamine (**2b**)	**4b** (97)
3	Benzylamine (**2c**)	**4c** (92)
4	Cyclohexylamine (**2d**)	**4d** (94)
5	Pyrrolidine(**2e**)	**4e** (97)
6	Morpholine (**2f**)	**4f** (93)

[a] Reaction mixtures were subjected to microwave radiation at 90°C for 5 min.

[b] Product yields were determined by gravimetric analysis. Products were identified by NMR, IR, and elemental analyses.

biologically important compounds, such as azines [10], heterocyclic compounds [10], and repaglinide and related hypoglycemic benzoic acid derivatives [11].

EXPERIMENTAL

The ^{1}H and ^{13}C NMR were recorded on a 500 MHz Joel multinuclear NMR spectrometer; chemical shifts were referenced to TMS as internal standard. Microwave experiments were carried out in CEM-Driver microwave. All chemicals were purchased from Aldrich Chemicals and were used without further purification. Elemental analyses were performed by the SMU Analytical Services.

General procedure for the preparation of 5-nitro-2-amino[*b*]thiophenes (3a–f). In a typical experiment, 1-(2-chloro-5-nitrophenyl)-ethanone (**1**) (1 equiv) was mixed with amine 2 (2 equiv), sulfur (3 equiv), DMF or *N*-methylpyrrolidine as solvent, and base (sodium acetate or methylpyrrolidine) in a microwavable test tube. The tube was then capped and charged into a CEM microwave instrument, and the mixture was irradiated with 250 psi pressure and at a temperature for several minutes (see Table 1 for conditions). After cooling, the reaction mixture was dissolve in ethyl acetate and then washed with brine. The ethyl acetate layer was separated, dried over sodium sulfate, and evaporated under reduced pressure. The crude reaction mixture was purified by column chromatography using ethyl acetate–hexane (9:1, v/v) as eluent, and the compounds were identified by comparison of their ^{1}H and ^{13}C NMR spectral data with those previously reported [7].

General procedure for the preparation of 1-(2-amino-5-nitrophenyl)ethanones (4a–f). In a typical experiment, 1 equiv 1-(2-chloro-5-nitrophenyl)ethanone (**1**) and 2 equiv of the appropriate amine **2a–f** were placed in a microwavable test tube and then capped. The mixture was then placed in a CEM-driven microwave and heated at 90°C for 10 min. After cooling, the reaction mixture was worked up as described in the general procedure for the preparation of **3a–f**. The ^{1}H and ^{13}C NMR, IR spectral data, and elemental analyses for these novel compounds are shown later.

1-(2-(n-Butylamino)-5-nitrophenyl)ethanone (4a). This compound was obtained as light yellow solid, mp (46.8–48.3°C); IR: 637.1, 748.2, 904.3, 953.4, 1213.8, 1322.2, 1496.8, 1608.9, 1633.8, 2960.6, 3284.9 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 0.96 (t, J = 7.45 Hz, 3H, CH_3), 1.42–1.49 (m, 2H, CH_2), 1.64–1.71 (m, 2H, CH_2), 2.63 (s, 1H, CH_3), 3.26–3.30 (m, 2H, CH_2), 6.68 (d, J = 9.75 Hz, 1H, aromatic), 8.17 (dd, J = 2.3 Hz, 9.15 Hz, 1H, aromatic), 8.70 (d, J = 2.5 Hz, 1H, aromatic), 9.63 (br, 1H, NH). ^{13}C NMR (deuteriochloroform): δ 13.8 (CH_3), 20.2 (CH_2), 27.8 (CH_3), 30.8 (CH_2), 42.8 (CH_2), 111.5 (C), 115.7 (CH), 130.0 (CH), 130.1 (CH), 135.1 (C), 154.7 (C), 200.5 (CO). *Anal.* Calcd. for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.86; H, 7.01; N, 12.05.

1-(2-(Isopropylamino)-5-nitrophenyl)ethanone (4b). This compound was obtained as light orange solid, mp (68.3–71.4°C); IR: 676.1, 634.8, 831.2, 1172.3, 1114.5, 1236.4, 1338.0, 1440.3, 1486.9, 1527.8, 1580.9, 1604.4, 1642.7, 1690.2, 1708.9, 2973.5, 3249.2 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 1.29 (d, J = 6.30 Hz, 6H, —CH_3 X 2), 2.61 (S, 3H, CH_3), 3.78–3.82 (m, 1H, CH), 6.68 (d, J = 9.15 Hz, 1H, aromatic), 8.13 (dd, J = 2.3 Hz, 9.15 Hz, 1H, aromatic), 8.67 (d, J = 2.3 Hz, 1H, aromatic), 9.60 (br, 1H, NH). ^{13}C NMR (deuteriochloroform): δ 22.5 (CH_3), 27.9 (CH_3), 44.2 (CH), 111.8 (CH), 126.3 (C), 129.9 (CH), 130.3 (CH), 132.0 (CH), 153.8 (C), 200.4 (CO). *Anal.* Calcd. for $C_{15}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 10.36. Found: C, 60.86; H, 5.27; N, 10.45.

1-(2-(Benzyl)-5-nitrophenyl)ethanone (4c). This compound was obtained as light yellow solid, mp (89.1–91.5°C); IR: 696.7, 746.4, 819.7, 965.4, 1118.4, 1224.9, 1326.0, 1493.7, 1579.0, 1605.7, 1643.7, 3068.7, 3280.9 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.69 (s, 3H, CH_3), 4.54 (d, J = 5.65 Hz, 1H, CH_2), 6.68 (d, J = 9.20 Hz, 1H, aromatic), 7.28–7.37 (m, 5H, aromatic), 8.15 (d, J = 9.75 Hz, 1H, aromatic), 8.73 (d, J = 2.25 Hz, 1H, aromatic), 10.0 (br, 1H, NH). ^{13}H NMR (deuteriochloroform): δ 27.9 (CH_3), 47.1 (CH_2), 112.2 (CH), 116.3 (C), 127.0 (CH), 127.9 (CH), 129.1 (CH), 129.9 (CH), 130.0 (CH), 135.7 (C), 136.7 (C), 154.6 (C), 200.7 (CO). *Anal.* Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.86; H, 5.27; N, 10.45.

1-(2-Cyclohexylamino-5-nitrophenyl)ethanone (4d). This compound was obtained as light yellow solid, mp (124.3–126.1°C); IR: 654.97, 757.7, 834.5, 907.4, 953.2, 1115.3, 1225.0, 1315.7, 1442.2, 1492.5, 1529.5, 1579.4, 1603.7, 1649.2, 1708.0, 2852.8, 2927.2, 3254.1 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 1.31–1.46 (m, 5H, CH_2), 1.63–1.65 (m, 1H, CH_2), 1.78–1.79 (m, 2H, CH_2), 1.99–2.03 (m, 2H, CH_2), 2.65 (s, 3H, CH_3), 3.51–3.52 (m, 1H, CH), 6.71 (d, J = 9.70 Hz, 1H, aromatic), 8.15 (dd. J = 2.90 Hz, 9.70 Hz, 1H, aromatic), 8.71 (d, J = 2.90 Hz, 1H, aromatic), 9.75 (br, 1H, NH). ^{13}C NMR (deuteriochloroform): δ 24.4 (CH_2), 25.5 (CH_2), 27.9 (CH_3), 32.4 (CH_2), 51.1 (CH_2), 111.8 (CH), 115.6 (C), 129.9 (CH), 130.4 (CH), 134.8 (C), 153.8 (C), 200.5 (CO). *Anal.* Calcd. for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.16; H, 6.77; N, 10.48.

1-(5-Nitro-2-(pyrrolidin-1-yl)phenyl)ethanone (4e). This compound was obtained as a colorless solid, mp (149.8–

151.8°C); IR: 747.9, 802.1, 867.4, 914.7, 955.2, 1113.4, 1229.2, 1266.8, 1300.6, 1369.1, 1447.1, 1481.8, 1501.9, 1563.2, 1556.1, 1682.4, 2851.6 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ1.97−2.0 (m, 4H, NCH_2 X 2), 2.62 (s, 3H, CH_3) 3.17−3.19 (m, 4H, NCH_2 X 2), 6.70 (d, J = 9.75 Hz, 1H, aromatic), 8.08 (dd, J = 2.3 Hz, 9.2 Hz, 1H, aromatic), dd, J = 2.3 Hz, 1H, aromatic). ^{13}C NMR (deuteriochloroform): δ 25.8 (NCH_2), 29.0 (CH_3), 52.3 (OCH_2), 113.7 (CH), 124.2 (C), 126.8 (CH), 127.3 (CH), 135.6 (C), 150.8 (C), 198.4 (CO). *Anal*. Calcd. for $C_{14}H_{12}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.63; H, 6.07; N, 11.89.

1-(2-Morpholino)-5-nitrophenyl)ethanone (4f). This compound was obtained as light yellow solid, mp (61.1–63.6°C); IR: 601.3, 653.7, 739.2, 905.3, 931.3, 1263.7, 1043.5, 1107.8, 1229.4, 1342.6, 1452.6, 1503.8, 1576.2, 1598.0, 1684.7 cm^{-1}; 2859.5 ^{1}H NMR (deuteriochloroform): δ 2.63 (s, 3H, CH_3)), 3.15−3.17 (m, 4H, NCH_2 X 2), 3.84−3.86 (m, 4H, OCH_2 X 2), 2.63 (s, 3H, CH_3), 7.03 (d, J = 9.2 Hz, 1H, aromatic), 8.22 (dd, J = 2.4 Hz, 9.2 Hz, 1H, aromatic), 8.31 (d, J = 2.4 Hz, 1H, aromatic). ^{13}C NMR (deuteriochloroform): δ 28.7 (CH_3), 52.4 (NCH_2), 66.4 (OCH_2), 117.6 (CH), 127.2 (CH), 127.5 (CH), 131.8 (C), 141.0 (C), 155.3 (C), 200.7 (CO). Anal. Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.86; H, 5.67; N, 11.25.

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Regiospecific Synthesis of 3*H*-Pyrido[2,3-*b*][1,4]diazepin-4(5*H*)-ones *via* Haloform Reaction with the Isolation of N^3-[3-Oxo-4,4,4-trichloroalk-1-en-1-yl]-2,3-diaminopyridine Intermediates

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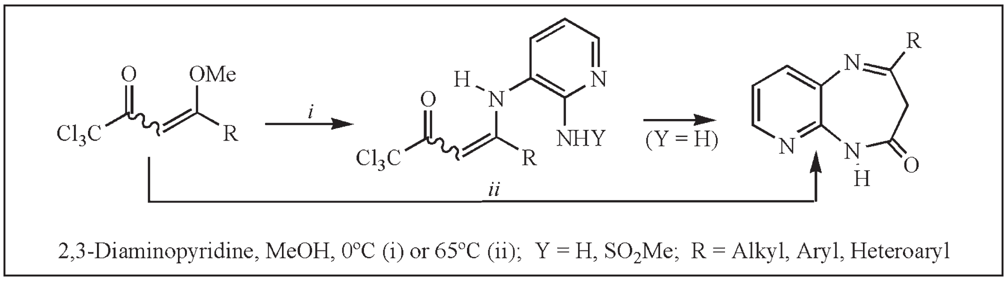

The synthesis of a novel series of analogous intermediates N^3-[1-alkyl(aryl/heteroaryl)-3-oxo-4,4,4-trichloroalk-1-en-1-yl]-2,3-diaminopyridines and N^2-(methanesulfonyl) [$Cl_3CC(O)CH{=}CRNH(C_5H_3N)$—NHY], where R = H, Me, C_6H_5, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4,4′-biphenyl, 1-naphthyl, 2-thienyl, 2-furyl, and Y = H, SO_2Me, is reported. A new corresponding series of 2-aryl/heteroaryl-3*H*-pyrido[2,3-*b*][1,4]diazepin-4(5*H*)-ones obtained from intramolecular cyclization reaction of the first series of trichloroacetyl enamines or from the direct cyclocondensation reaction of 4-methoxy-1,1,1-trichloalk-3-en-2-ones with 2,3-diaminopyridine, under mild conditions, is also demonstrated.

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INTRODUCTION

The reactions of 2,3-diaminopyridine with ethyl benzoylacetate and ethyl nicotinoylacetate were first reported in a communication in 1964 by Barchet and Merz [1]. However, no evidence was given in support of the first 2-phenyl-1,3-dihydro-4*H*-pyrido[2,3-*b*][1,4] diazepin-4-one structure assignment.

Three years later, Israel *et al.* [2] found that different reaction conditions resulted in the preferential formation of dihydropyrido[2,3-*b*][1,4]diazepin-2-one or the 4-one isomer from the reaction of 2,3-diaminopyridine with ethyl acetoacetate. This reaction when conducted in boiling xylene for 8 h with azeotropic removal of water, afforded 2-methylpyrido[2,3-*b*][1,4]diazepin-4-one as the major product. However, 1,3-dihydro-1-isopropenyl-2*H*-imidazo[4,5-b]pyridin-2-one was present in small yield. In the absence of solvent, the mixture of 2,3-diaminopyridine with an excess of ethyl acetoacetate at 185°C for 15 min furnished 4-methylpyrido[2,3-*b*][1,4]diazepin-2-one, which was obtained as an inseparable tautomeric mixture of 1,3- and 1,5-dihydro-4-methyl-2*H*-pyrido[2,3-*b*][1,4]diazepin-2-one.

Later, in 1969, Israel and Jones [3] studied the reaction of 2,3-diaminopyridine with ethyl benzoylacetate in boiling xylene, in an approximation of the incompletely defined conditions given by Barchet and Merz [1] and obtained and proved the isolation of the same pyridodiazepinone described firstly in 1964.

In the 1960s, the determination of the correct structure for a given pyridodiazepinone product from the reaction involving 2,3-diaminopyridine and β-ketoesters was difficult and laborious, and, in some instances, an impossible task. Contributing with the solution of this problem, Israel and Jones [3,4] developed the thermal conversion of pyridodiazepinones into imidazolones, which permitted the assignment of the correct structures to ambiguous products through the knowledge that the N1—C2 bond of the pyridodiazepinone was not cleaved during the course of the rearrangement reaction.

Recently, various diamine-ketoester condensations involving reactions of ethyl 2-oxocyclohexanecarboxylate [5] or ethyl 2-oxocyclopentanecarboxylate [6] (cyclic β-ketoesters) with nonsymmetrical diaminopyridines have been studied, and the results compared in a attempt to develop generalizations of predictive value regarding the direction of ring closure to form diazepinones, as well as, in search of novel tricyclic ring systems which may be of interest in obtaining clozapine and pirenzapine analogues with psychotropic properties.

Finally, in 2001 Savelli *et al.* [7] studied the reaction of 3-amino-2-(methylamino)pyridine with diethyl 1,3-acetonedicarboxylate to develop pyridodiazepinone derivatives. From the reaction mixture, Savelli separated dipyrido[1,2-*a*:2,3-*d*]imidazole derivatives as well as two isomeric pyrido[2,3-*b*]diazepinone derivatives in which the complex structural differentiation was achieved through NMR experiments and chemical evidence, but attempts to obtain the cited pyrido[2,3-*b*][1,4]diazepinone isomers as pure compounds have failed until now.

On the other hand, over the last few years, we have reported the synthesis of 2-trifluoro- and 2-trichloromethyl-3*H*-1,5-benzodiazepines from the reaction of 4-aryl-4-methoxy-1,1,1-haloalk-3-en-2-ones with *o*-phenylenediamine in good yields [8]. Next, we demonstrated that 4-phenyl-2-trichloromethyl-3*H*-1,5-benzodiazepine hydrogen sulfate possesses anxiolytic activity and produces motor in co-ordination similar to that observed in mice given diazepam [9]. In the same year, we also reported that some 4-substituted 2-trichloromethyl-3*H*-1,5-benzodiazepines presented an inhibitory effect on acetylcholinesterase and ATPDase activities from cerebral cortex of adult rats [10].

Recently, we have also reported an addition/elimination sequence leading to trichloroacetyl enamines from the reaction of *o*-phenylenediamine [8c] and *o*-aminophenol [11] with 4-alkyl(aryl)-1,1,1-trichloro-4-alkoxyalk-3-en-2-ones. Particularly, considering the importance of the development of new anticancer agents, in the last several years we have researched the possibility of using 4-alkoxy-1,1,1-trichloroalk-3-en-2-ones for the synthesis of new structures with promising chemotherapeutic potential. Thus, some acyclic trichloroacetyl enamines, derived from *o*-phenylenediamine and *o*-aminophenol, were submitted to *in vitro* antitumor screens and showed interesting results [11]. The best activity was obtained when the structure was derived from *o*-aminophenol and presented a *p*-bromophenyl substituent linked to the carbon-1 of the trichloromethylated enamino ketone.

In 2002, we showed the use of the trichloromethyl group as a convenient leaving group for the synthesis of 6-methyl- and 7-alkyl(aryl)-5H-thiazolo[3,2-*a*]pyrimidin-5-ones in 45–89% yields from the reaction of 4-alkyl(aryl)-1,1,1-trichloro-4-alkoxyalk-3-en-2-ones with 2-aminothiazole in refluxing ethanol [12]. In the mentioned work, it was only possible to isolate the non-substituted *N*-[3-oxo-4,4,4-trichlorobut-1-en-1-yl]-2-aminothiazole and all the other (1-substituted) enamino ketone intermediates *N*-[1-alkyl(aryl)-3-oxo-4,4,4-trichloroalk-1-en-1-yl]-2-aminothiazoles could be not isolated.

Recently, we have reported attempts to obtain *N*-[1-alkyl(aryl)-3-oxo-4,4,4-trichloroalk-1-en-1-yl]-2-aminopyridine intermediates by the reaction of 4-alkoxy-1,1,1-trichloroalk-3-en-2-ones with 2-aminopyridine [13]. However, when these reactions were carried out in dichloromethane as solvent, under mild conditions, the respective trichloroacetyl enamines were isolated only in very low yields (>10%). Surprisingly, when the same reactions were carried out in a molar ratio of 1:1 in anhydrous ethanol as solvent under reflux for 5 h, 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines were easily isolated in 45–81% yields instead of *N*-[1-alkyl(aryl)-3-oxo-4,4,4-trichloroalk-1-en-1-yl]-2-aminopyridine intermediates.

Surprisingly, since the first pyridodiazepinone was reported in 1964 [1], no publications have been found with the objective of carrying out a regiospecific and simultaneous introduction of trichloromethyl and substituted aryl groups at the pyrido[2,3-*b*][1,4]-diazepine derivatives starting from trichloromethyl substituted 1,3-diketones or 4-methoxy-1,1,1-trihaloalk-3-en-2-ones. In addition, there is no data on reactions involving simple 1,3-diketones, such as acetylacetone or benzoylacetone, with 2,3-diaminopyridine.

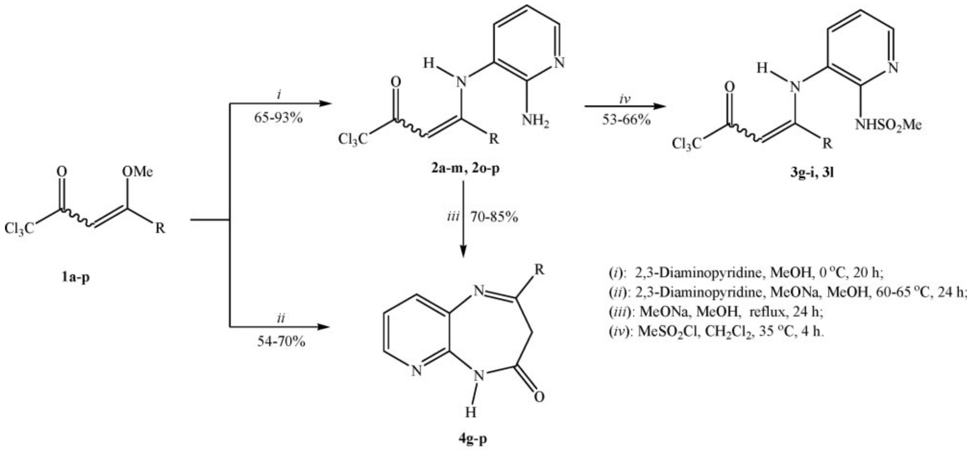
Only recently, we have communicated the first synthesis of 2-aryl(heteroaryl)-3*H*-pyrido[2,3-*b*][1,4]diazepin-4(5*H*)-ones from the direct cyclocondensation reaction of 4-methoxy-1,1,1-trichloroalk-3-en-2-ones (**1**) with 2,3-diaminopyridine [14].

Considering the biological importance of heterocyclic fused diazepinones and their derivatives and the fact that 2-aryl- and 2-heteroaryl-dihydropyridodiazepinone analogues and trichloroacetyl enamine intermediates have not yet been reported, it would be worthwhile to demonstrate a new synthetic application of β-aryl(heteroaryl)-β-methoxyvinyl trichloromethyl ketones. In addition, with the intention of carrying out future biological evaluations, it seemed desirable to develop a general method for the synthesis of pyridodiazepine derivatives (3*H*-1,5-benzodiazepine analogues), in which a trichloromethyl, carbonyl, aryl, or heteroaryl group could be introduced as substituent to this promising triaza fused heterocyclic family.

RESULTS AND DISCUSSION

Herein, the synthesis and isolation of a novel series of fifteen N^3-[1-aryl(heteroaryl)-3-oxo-4,4,4-trichloroalk-1-en-1-yl]-2,3-diaminopyridines and some N^3-[1-(aryl)-3-oxo-4,4,4-trichloroalk-1-en-1-yl]-N^2-(methanesulfonyl)-2,3-diaminopyridines and the regiospecific preparation of a series of 10 2-aryl(heteroaryl)-3*H*-pyrido[2,3-*b*][1,4]diazepin-4(5*H*)-ones from the intramolecular cyclization reaction of trichloroacetyl enamines, or direct cyclocondensation reaction of 4-substituted-4-methoxy-1,1,1-trichloroalk-3-en-2-ones with 2,3-diaminopyridine, is presented (Scheme 1).

Scheme 1



(*i*): 2,3-Diaminopyridine, MeOH, 0 °C, 20 h;
(*ii*): 2,3-Diaminopyridine, MeONa, MeOH, 60-65 °C, 24 h;
(*iii*): MeONa, MeOH, reflux, 24 h;
(*iv*): $MeSO_2Cl$, CH_2Cl_2, 35 °C, 4 h.

1-4	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**
R	Me	*n*-Pr	*i*-Pr	*i*-Bu	*i*-Pen	*n*-Hex	Ph	4-MePh	4-OMePh	4-FPh

1-4	**k**	**l**	**m**	**n**	**o**	**p**
R	4-ClPh	4-BrPh	4,4'-BiPh	1-Naphthyl	2-Furyl	2-Thienyl

A review of the literature has shown that 2-methyl- and 2-phenyl-3*H*-pyrido[2,3-*b*][1,4]diazepin-4(5*H*)-ones, obtained under hard reaction conditions in boiling xylene, would result from the interaction of the more nucleophilic 3-amino group of the 2,3-diaminopyridine with the keto carbonyl function of the β-keto-ester [2]. This direction of cyclization was also seen in the cyclocondensation reaction of 2,3-diaminopyridine with ethyl benzoylacetate under similar conditions [3].

An extension of the reaction of ketones **1** with 2,3-diaminopyridine, a nonsymmetrical heteroaromatic diamine, necessarily introduces the additional problem of two possible isomeric diazepine products. The formation of the pyridodiazepine system presumably will depend on whether the initial reaction of the more nucleophilic 3-amino function occurs at the β-olefinic carbon of the vinyl ketones **1** or at the carbonyl carbon.

The ketones **1a** [15b], **1b-f** [12], **1g-j** [15a], **1m-n** [14], and **1o-p** [15g] are readily available *CCC* synthetic blocks and were prepared from trichloroacetylation reactions of enol ethers generated *in situ* from the respective aryl- or heteroaryl methyl ketone acetals [15] with trichloroacetyl chloride, respectively.

Subsequently, a novel series of 15 N^3-[1-alkyl(aryl/heteroaryl)-3-oxo-4,4,4-trichloroalk-1-en-1-yl]-2,3-diaminopyridines **2a-m**, **2o-p** was obtained in 65–93% yields by the methoxy-amino exchange reaction of **1** with 2,3-diaminopyridine and its X-ray diffraction data is shown (Fig. 1). The best results were obtained when the reactions of compounds **1a-p** with 2,3-diaminopyridine were carried out in methanol at 0°C for 20 h.

Crystallographic data for compound **2g**, reported in this article, have been given to the Cambridge Crystallographic Data Center (CCDC 687399) [16].

Initially, to obtain other new protected pyridino-sulfonamides bearing the similarly interesting aryl substituents at the enamino function, four examples of these new aryl-enamino ketones **2** were employed to obtain the respective N^3-[1-aryl-3-oxo-4,4,4-trichloroalk-1-en-1-yl]-N^2-(methanesulfonyl)-2,3-diaminopyridines (**3g-i**, **3l**). Thus, the reactions of **2g-i**, **2l** with methanesulfonyl chloride were carried out in dichlomethane as solvent at

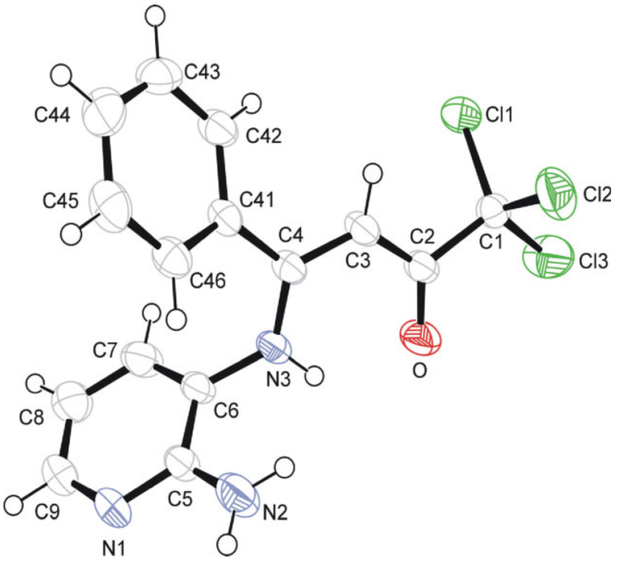


Figure 1. Perspective view of compound **2g**. Thermal ellipsoids correspond to 50% probability. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

35°C for 4 h. This procedure allowed for the easy attainment of sulfonamides **3g-i**, **3l** in 53–66% yields.

In this study, we also found that aryl- and heteroaryl-substituted trichloromethylated ketones **1g-p**, when treated directly with 2,3-diaminopyridine at a molar ratio of 1:1, respectively, in anhydrous methanol as solvent and in the presence of sodium methoxide under reflux for 24 h, regiospecifically produced 2-aryl(heteroaryl)-3*H*-pyrido[2,3-*b*][1,4]diazepin-4(5*H*)-ones (**4g-p**), which were easily isolated in 52–70% yields, as pure isomers. The above described conditions allowed us to regiospecifically obtain the diazepinones (**4**) instead of the analogous 2-aryl(heteroaryl)-4-trichloromethyl-4,5-dihydro-3*H*-pyrido[2,3-*b*][1,4]diazepin-4-ol or the respective 2-keto-pyridodiazepine isomers.

Although similar reaction conditions have been employed previously to synthesize 5*H*-thiazolo[2,3-*a*]pyrimidin-5-ones and 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones, we found in this case an unexpected reactivity of the 2-amino group of the π-deficient pyridine ring toward the carbonyl group of the 4-aryl(heteroaryl)-4-methoxy-1,1,1-trichloroalk-3-en-2-ones (**2**), promoting an efficient haloform reaction. Compound **4g** had only been synthesized previously by Israel et al. [3] and by Barchet and Merz [1] in 65% yield from the reaction of 2,3-diaminopyridine with ethyl benzoylacetate, but under difficult reaction conditions (boiling xylene for 4 h with azeotropic distillation of the formed water). Our procedure not only gave the same compound under milder conditions (refluxing methanol for 24 h) and in a similar yield (52%) but also increased the scope of the reaction with the possibility of introducing other aryl and heteroaryl substituents to this pyridodiazepinone system.

Complementarily, examples of enamino ketones (**2g-m, 2o-p**) were readily converted into **4g-m, 4g-p** by refluxing in methanol in the presence of sodium methoxide for 24 h with yields higher than 70% (Scheme 1).

We consider the one-pot reaction presented to be a useful and convenient alternative to obtain regiospecifically pyridodiazepinone system and, in summary, the use of this methodology allowed also the isolation of two new series of N^3-[1-alkyl(aryl/heteroaryl)-3-oxo-4,4,4-trichloroalk-1-en-1-yl]-2,3-diaminopyridines and N^3-[1-aryl-3-oxo-4,4,4-trichloroalk-1-en-1-yl]-N^2-(methanesulfonyl)-2,3-diaminopyridines, which have been prepared in an analytically pure form and in good yields, for future chemical and biological studies.

EXPERIMENTAL

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. All melting points were determined on a calibrated Electrothermal Melt-Temp 3.0 apparatus. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DPX 200 spectrometer (^{1}H at 200.13 MHz and ^{13}C at 50.32 MHz), 5mm sample tubes, 298 K, digital resolution ±0.01 ppm, in chloroform-d_1 (for **2, 3**) or DMSO-d_6 (for **4**) using TMS as internal reference. The CHN elemental analyses were performed on a Perkin Elmer 2400 CHN elemental analyzer (São Paulo University–USP/Brazil).

General procedure for the preparation of substituted N^3-[3-oxo-4,4,4-trichloroalk-1-en-1-yl]-2,3-aminopyridines (2a-m, 2o-p). To a stirred solutions of 2,3-diaminopyridine (0.327 g, 3 mmol) in 10 mL of dry methanol, 4-alkoxy-4-aryl(alkyl)-1,1,1-trichloroalk-3-en-2-ones (**1a-m, 1o-p**) (3 mmol) were added at 0°C. The mixtures were stirred for 20 h at 0°C. After the reaction time, yellow solids (**2a-m, 2o-p**) were filtered, washed with cold methanol and recrystallized from hexane (yields 65–93%).

N^3-[4-Oxo-5,5,5-trichloropent-2-en-2-yl]-2,3-diaminopyridine (2a). Yield 86%; mp 120–122°C; ^{1}H NMR, δ (ppm) = 11.5 (s, 1H, NH), 8.0 (d, 1H, J = 5, PyH6), 7.3 (d, 1H, J = 7.5, PyH4), 6.70 (dd, 1H, J = 5, J = 5, PyH5), 5.9 (s, 1H, H2), 4.8 (s, 2H, NH$_2$), 2.1 (s, 3H, Me); ^{13}C NMR, δ (ppm) = 181.7 (C=O), 161.6 (C1), 154.9 (PyC2), 147.6 (PyC6), 135.6 (PyC4), 118 (PyC3), 113.9 (PyC5), 96.7 (CCl$_3$), 88.9 (C2), 20.2 (Me). Anal. Calcd. for $C_{10}H_{10}Cl_3N_3O$ (mw 294.57): C, 40.77; H, 3.42; N,14.26%. Found: C, 40.56; H, 3.33; N, 14.17%.

N^3-[6-Oxo-7,7,7-trichlorohept-4-en-4-yl]-2,3-diaminopyridine (2b). Yield 65%; mp 147–149°C; ^{1}H NMR, δ (ppm) = 11.6 (s, 1H, NH), 8.0 (d, 1H, J = 5, PyH6), 7.3 (d, 1H, J = 7.5, PyH4), 6.72 (dd, 1H, J = 5, J = 5, PyH5), 6.0 (s, 1H, H2), 4.8 (s, 2H, NH$_2$), 2.2 (t, 2H, J = 8, CH$_2$), 1,1 (qui., 2H, J = 7, CH$_2$), 0.8 (t, 3H, J = 7, Me) ; ^{13}C NMR, δ (ppm) = 181.8 (C—O), 172.7 (C1), 155 (PyC2), 147.7 (PyC6), 135.8 (PyC4), 117.7 (PyC3), 113.8 (PyC5), 96.8 (CCl$_3$), 87.7 (C2), 34.5 (CH$_2$), 21.1 (CH$_2$), 13.6 (Me). Anal. Calcd. for $C_{12}H_{14}Cl_3N_3O$ (mw 322.62): C, 44.60; H, 4.37; N, 13.02%. Found: C, 44.72; H, 4.41; N, 12.87%.

N^3-[2-Methyl-5-oxo-6,6,6-trichlorohex-3-en-3-yl]-2,3-diaminopyridine (2c). Yield 90%; mp 160–162 °C; ^{1}H NMR, δ (ppm) = 11.4 (s, 1H,NH), 7.9 (d, 1H, J = 5, PyH6), 7.4 (d, 1H, J = 7.5, PyH4), 6.71 (dd, 1H, J = 5, J = 5, PyH5), 6.1 (s, 2H, NH$_2$), 5.9 (s, 1H, H-2), 2.6 (qui., 1H, CH), 1.1 (d, 6H, J = 7, 2Me); ^{13}C NMR, δ (ppm) = 182.3 (C=O), 179.1 (C1), 155.3 (PyC2), 147.5 (PyC6), 136 (PyC4), 117.5 (PyC3), 113.8 (PyC5), 96.7 (CCl$_3$), 84.3 (C2), 29.9 (CH), 21.6 (2Me). Anal. Calcd. for $C_{12}H_{14}Cl_3N_3O$ (mw 322.62): C, 44.60; H, 4.37; N, 13.02%. Found: C, 44.37; H, 4.17; N, 13.10%.

N^3-[2-Methyl-6-oxo-7,7,7-trichlorohept-4-en-4-yl]-2,3-diaminopyridine (2d). Yield 79%; mp 154–156°C; ^{1}H NMR, δ (ppm) = 11.5 (s, 1H, NH), 8.0 (d, 1H, J = 5, PyH6), 7.3 (d, 1H, J = 7.5, PyH4), 6.6 (dd, 1H, J = 5, J = 5, PyH5), 5.9 (s, 1H, H-2), 5.0 (s, 2H, NH$_2$), 2.2 (d, 4H, J = 8, CH$_2$), 1.8 (sex, 1H, CH), 0.8 (d, 6H, J = 7, 2Me); ^{13}C NMR, δ (ppm) = 181.3 (C=O), 171.7 (C1), 155.1 (PyC2), 147.2 (PyC6), 135.9 (PyC4), 117.6 (PyC3), 113.3 (PyC5), 96.7 (CCl$_3$), 88.4 (C2), 41.2 (CH$_2$), 27.4 (CH), 22.1 (Me). Anal. Calcd. for $C_{13}H_{16}C_{13}N_3O$ (mw 336.65): C, 46.38; H, 4.79; N, 12.48%. Found: C, 46.49; H, 4.75; N, 12.37%.

N^3-[2-Methyl-7-oxo-8,8,8-trichlorooct-5-en-5-yl]-2,3-diaminopyridine (2e). Yield 93%; mp 132–135°C; ^{1}H NMR, δ (ppm) = 11.4 (s, 1H, NH), 8.0 (d, 1H, J = 5, PyH6), 7.4 (d, 1H, J = 7.5, PyH4), 6.72 (dd, 1H, J = 5, J = 5, PyH5), 5.9 (s, 1H, H2), 5.4 (s, 2H, NH$_2$), 2.2 (t, 2H, J = 7, CH$_2$), 1.5 (t, 2H, *J* = 6, CH), 1.46–134 (m, 3H, CH_2 and CH), 0.8 (t, 3H, *J* = 7, 2Me); ^{13}C NMR, δ (ppm) = 181.8 (C=O), 173.4 (C1), 154.9 (PyC2), 147.6 (PyC6), 135.9 (PyC4), 117.7 (PyC3),113.8 (PyC5), 96.8 (CCl_3), 87.8 (C2), 36.9 (CH_2), 30.8 (CH), 27.8 (CH_2), 21.9 (Me). Anal. Calcd. for $C_{14}H_{18}Cl_3N_3O$ (mw 350.68): C, 47.95; H, 5.17; N 11.98%. Found: C,48.13; H, 5.26; N, 12.22%.

N^3-[9-Oxo-10,10,10-trichlorodec-7-en-7-il]-2,3-diaminopyridine (2f). Yield 81%; mp 121–123°C; ^{1}H NMR, δ (ppm) = 11.4 (s, 1H, NH), 8.0 (d, 1H, *J* = 5, PyH6), 7.3 (d, 1H, *J* = 7.5, PyH4), 6.74 (dd, 1H, *J* = 5, *J* = 5, PyH5), 5.9 (s, 1H, H2), 5.0 (s, 2H, NH_2), 2.2 (t, *J* = 8, 2H, CH_2), 1.50–1.46 (m, 2H, CH_2), 1.24–1.19 (m, 6H, 3CH_2), 0.8 (t, *J* = 7, 3H, Me); ^{13}C NMR, δ (ppm) = 181.9 (C=O), 172.9 (C1), 154.8 (PyC2), 147 (PyC6), 136.2 (PyC4), 118 (PyC3), 113.8 (PyC5), 96.8 (CCl_3), 87.9 (C2), 32.6 (CH_2), 31.1 (CH_2), 28.7 (CH_2), 27.7 (CH_2), 22.3 (CH_2), 13.9 (Me). Anal. Calcd. for $C_{15}H_{20}Cl_3N_3O$ (mw 364.70): C, 49.40; H, 5.53; N, 11.52%. Found: C, 49.63; H, 5.47; N, 11.57%.

N^3-[1-Phenyl-3-oxo-4,4,4-trichlorobut-1-en-1-yl]-2,3-diaminopyridine (2g). Yield 90%; mp 149–150°C; ^{1}H NMR, δ (ppm) = 11.4 (s, 1H, NH), 7.8 (d, 1H, *J* = 5, PyH6), 7.41–7.32 (m, 5H, Ph), 6.7 (d, 1H, *J* = 7.5, PyH4), 6.40 (dd, 1H, *J* = 5, *J* = 5, PyH5), 6.1 (s,1H, H2), 5.1 (s, 2H, NH_2); ^{13}C NMR, δ (ppm) = 182.3 (C=O), 167.6 (C1), 153.8 (PyC2), 144.8 (PyC6), 135.1 (PyC4), 133.9, 130.7, 128.7, 127.8 (4C, Ph), 119.9 (PyC3), 113.6 (PyC5), 96.6 (CCl_3), 91.3 (C2). Anal. Calcd. for $C_{15}H_{12}Cl_3N_3O$ (mw 356.64): C, 50.52; H, 3.39; N, 11.78%. Found: C, 50.32; H, 3.31; N, 11.83%.

N^3-[1-(4-Methylphenyl)-3-oxo-4,4,4-trichlorobut-1-en-1-yl]-2,3-diaminopyridine (2h). Yield 73%; mp 174–175°C; ^{1}H NMR, δ (ppm) = 12.0 (s, 1H, NH), 7.8 (d, 1H, *J* =5, PyH6), 7.2 (d, 2H, ^3J = 8, Ph), 6.8 (d, 1H, ^3J = 8, Ph), 6.7 (d, 1H, *J* = 7.5, PyH4), 6.44 (dd, 1H, *J* = 5, *J* = 5, PyH5), 5.8 (s, 1H, H2), 5.3 (s, 2H, NH_2), 2.3 (s, 3H, Me); ^{13}C NMR, δ (ppm) = 168.0 (C=O), 153.8 (C1), 146.1 (PyC6), 145.2 (PyC2), 134.9 (PyC4), 129.4, 129.2, 128.8, 127.8 (4C, Ph), 119.9 (PyC3), 113.6 (PyC6), 92.7 (C2), 91.1 (CCl_3), 21.3 (Me). Anal. Calcd. for $C_{16}H_{14}Cl_3N_3O$ (mw 370.67): C, 51.85; H, 3.81; N, 11.34%. Found: C, 51.70; H, 3.75; N, 11.13%.

N^3-[1-(4-Methoxyphenyl)-3-oxo-4,4,4-trichlorobut-1-en-1-yl]-2,3-diaminopyridine (2i). Yield 78%; mp 174–175°C; ^{1}H NMR, δ (ppm) = 11.5 (s, 1H, NH), 7.8 (d, 1H, *J* = 5, PyH6), 7.2 (d, 2H, ^3J = 9, Ph), 6.8 (d, 1H, ^3J = 9, Ph), 6.7 (d, 1H, *J* = 7.5, PyH4), 6.45 (dd, 1H, *J* = 5, *J* = 5, PyH5), 6.1 (s, 1H, H2), 4.9 (s, 2H, NH_2), 3.8 (s, 3H, OMe); ^{13}C NMR, δ (ppm) = 181.3 (C=O), 167.4 (C1), 161.5 (Ph), 153.7 (PyC2), 145.7 (PyC6), 134.6 (PyC4), 129.7, 125.8, 114.1 (3C, Ph), 120.1 (PyC3), 113.8 (PyC5), 96.8 (CCl_3), 90.8 (C2), 55.3 (OMe). Anal. Calcd. for $C_{16}H_{14}Cl_3N_3O_2$ (mw 386.67): C, 49.70; H, 3.65; N, 10.87%. Found: C, 49.95; H, 3.72; N, 10.60%.

N^3-[1-(4-Fluorophenyl)-3-oxo-4,4,4-trichlorobut-1-en-1-yl]-2,3-diaminopyridine (2j). Yield 80%; mp 146–148°C; ^{1}H NMR, δ (ppm) = 11.1 (s, 1H, NH), 7.8 (d, 1H, *J* = 5, PyH6), 7.3 (d, 2H, ^3J = 9, Ph), 7.0 (d, 2H, ^3J = 9, Ph), 6.8 (d, 1H, *J* = 7.5, PyH4), 6.4–6.3 (m, 1H, PyH5 and 2H, NH_2), 6.1 (s, 1H, H2); ^{13}C NMR, δ (ppm) = 182.2 (C=O), 166.5 (C1), 163.8 (d, $^1J_{CF}$ = 249.2, Ph), 153.8 (PyC2), 146.1 (PyC6), 134.8 (PyC4), 130.1 (d, $^3J_{CF}$ = 9, Ph), 129.9 (PyC3), 119.6 (d, $^2J_{CF}$ = 22, Ph), 116.0 (d, $^4J_{CF}$ = 3, Ph), 113.9 (PyC5), 96.6 (CCl_3), 91.3 (C2). Anal. Calcd. for $C_{15}H_{11}Cl_3FN_3O$ (mw 374.63): C, 48.09; H, 2.96; N, 11.22%. Found: C, 48.21; H, 3.03; N, 11.15%.

N^3-[1-(4-Chlorophenyl)-3-oxo-4,4,4-trichlorobut-1-en-1-yl]-2,3-diaminopyridine (2k). Yield 67%; mp 180–182°C; ^{1}H NMR, δ (ppm) = 11.4 (s, 1H, NH), 7.9 (d, 1H, *J* = 5, PyH6), 7.4 (d, 2H, ^3J = 8, Ph), 7.2 (d, 2H, ^3J = 8, Ph), 6.7 (d, 1H, *J* = 7.5, PyH4), 6.46 (dd, 1H, *J* = 5, *J* = 5, PyH5), 6.1 (s, 1H, H2), 4.8 (s, 2H, NH_2); ^{13}C NMR, δ (ppm) = 182.5 (C=O), 165.9 (C1), 153.3 (PyC2), 142.9 (PyC6), 137.2 (Ph), 135.9 (PyC4), 132.1, 129.3, 129.2 (3C, Ph), 120.8 (PyC3), 113.5 (PyC5), 96.4 (CCl_3), 92.3 (C2). Anal. Calcd. for $C_{15}H_{11}Cl_4N_3O$ (mw 391.08): C, 46.07; H, 2.84; N 10.74%. Found: C, 45.88; H, 2.87; N, 10.68%.

N^3-[1-(4-Bromophenyl)-3-oxo-4,4,4-trichlorobut-1-en-1-yl]-2,3-diaminopyridine (2l). Yield 93%; mp 182–184°C; ^{1}H NMR, δ (ppm) = 11.4 (s, 1H, NH), 7.9 (d, 1H, *J* = 5, PyH6), 7.4 (d, 2H, ^3J = 8, Ph), 7.2 (d, 2H, ^3J = 8, Ph), 6.7 (d, 1H, *J* = 7.5, PyH4), 6.47 (dd, 1H, *J* = 5, *J* = 5, PyH5), 6.1 (s, 1H, H2), 4.8 (s, 2H, NH_2); ^{13}C NMR, δ (ppm) = 179.9 (C=O), 165.9 (C1), 154.3 (PyC2), 143.1 (PyC6), 136.4 (PyC4), 133.6, 131.8, 129.9, 124.2 (4C, Ph), 120.2 (PyC3), 112.2 (PyC5), 96.6 (CCl_3), 90.2 (C2). Anal. Calcd. for $C_{15}H_{11}Cl_3BrN_3O$ (mw 435.53): C, 41.37; H, 2.55; N 9.65%. Found: C, 41.50; H, 2.47; N, 9.94%.

N^3-[1-(4,4′-Biphenyl)-3-oxo-4,4,4-trichlorobut-1-en-1-yl]-2,3-diaminopyridine (2m). Yield 71%; mp 171–173°C; ^{1}H NMR, δ (ppm) = 11.5 (s, 1H, NH), 7.9 (d, 1H, *J* = 5, PyH6), 7.6–7.4 (m, 9H, Ph), 6.8 (d, 1H, *J* = 7.5, PyH4), 6.5 (dd, 1H, *J* = 5, *J* = 5, PyH5), 6.2 (s, 1H, H2), 4.9 (s, 2H, NH_2); ^{13}C NMR, δ (ppm) = 182.2 (C=O), 167.3 (C1), 153.8 (PyC2), 146.2 (PyC6), 143.5, 139.4, 132.6, 128.9, 128.5, 128.1, 127.2, 126.9 (8C, Ph), 134.6 (PyC4), 119.8 (PyC3), 113.9 (PyC5),96.7 (CCl_3), 91.3 (C2). Anal. Calcd. for $C_{13}H_{10}Cl_3N_3O_2$ (mw 346.60): C, 45.05; H, 2.91; N, 12.12%. Found: C, 45.17; H, 3.13; N, 12. 25%.

N^3-[1-(2-Furyl)-3-oxo-4,4,4-trichlorobut-1-en-1-yl]-2,3-diaminopyridine (2o). Yield 75%; mp 167–169°C; ^{1}H NMR, δ (ppm) =11.4 (s, 1H, NH), 7.8 (bs, 1H, PyH6), 7.2 (d, 1H, *J* = 4, fr), 7.1 (t, 1H, *J* = 4, fr), 7.0 (d, 1H, *J* = 4, fr), 6.9 (d, 1H, *J* = 7.5, PyH4), 6.41 (dd, 1H, *J* = 5, *J* = 5, PyH5), 6.1 (s, 1H, H2), 4.8 (s, 2H, NH_2); ^{13}C NMR, δ (ppm) = 182.3 (C=O), 167.3 (C1), 153.7 (PyC2),146 (PyC6), 139.5 (fr), 132.6 (PyC4), 128.9, 128.1, 127.3 (3C, fr), 119.9 (PyC3), 114.1 (PyC5), 96.7 (CCl_3), 91.4 (C2). Anal. Calcd. for $C_{19}H_{14}Cl_3N_3O$ (mw 406.70): C, 56.11; H, 3.47; N, 10.33%. Found: C, 56.37; H, 3.46; N, 10.40%.

N^3-[1-(2-Thienyl)-3-oxo-4,4,4-trichlorobut-1-en-1-yl]-2,3-diaminopyridine (2p). Yield 79%; mp 175–177°C; ^{1}H NMR, δ (ppm) =11.4 (s, 1H, NH), 7.9 (d, 1H, *J* = 5, PyH6), 7.3 (d, 1H, *J* = 5, tn), 7.1 (d, 1H, *J* = 3, tn), 7.0 (d, 1H, *J* = 7, tn), 6.5 (d, 1H, *J* = 7.5, PyH4), 6.4 (dd, 1H, *J* = 5, *J* = 5, PyH5), 6.1 (s, 1H, H2), 5.2 (s, 2H, NH_2); ^{13}C NMR, δ (ppm) = 182.1 (C=O), 160.3 (C1), 154.6 (PyC2), 147.2 (PyC6), 135.8 (PyC4), 130.2, 127.7, 127.3 (3C, tn), 119.3 (PyC3), 114.1 (PyC5), 103.7 (CCl_3), 89.3 (C2). Anal. Calcd. for $C_{21}H_{16}Cl_3N_3O$ (mw 432.74): C, 58.29; H, 3.73; N, 9.71%. Found: C, 58.32; H, 3.76; N, 9.66%.

General procedure for the preparation of substituted N^3-[1-alkyl(aryl/heteroaryl)-3-oxo-4,4,4-trichloroalk-1-en-1-yl]-N^2-(methanesulfonyl)-2,3-diaminopyridines (3g-i, 3l). To a stirred solutions of N^3-[1-aryl(heteroaryl)-3-oxo-4,4,4-

trichlorobut-1-en-1-yl]-2,3-diaminopyridines (**2g-i, 2l**) (1 mmol) in 5 mL of dry dichloromethane, pure methanesulfonyl chloride (0.15 mL, 2 mmol) was added at room temperature. The mixtures were stirred for 4 more hours at 35°C. After the reaction time, the reactions were filtered and the organic solvent was removed under reduced pressure. The crude yellow solids (**3g-i, 3l**) were recrystallized from hexane (yields 53–66%).

N^3-[1-Phenyl-3-oxo-4,4,4-trichlorobut-1-en-1-yl]-N^2-(methanesulfonyl)-2,3-diamino-pyridine (3g). Yield 63%; mp 168–170°C; ^{1}H NMR, δ (ppm) =10.9 (s, 1H, NH), 8.3 (s, 1H, NH), 7.6 (d, 1H, J = 5, PyH6), 7.42–7.28 (m, 5H, Ph), 7.0 (d, 1H, J = 7.5, PyH4), 6.5 (dd, 1H, J = 5, J = 5, PyH5), 6.1 (s, 1H, H2), 2.8 (s, 3H, Me); ^{13}C NMR, δ (ppm) = 182.6 (C=O), 164.5 (C1), 145.1 (PyC6), 140.9 (PyC2), 135.1 (Ph), 133.9 (PyC4), 131.1 (PyC3), 129.2, 128.3, 124.8 (3C, Ph), 111.7 (PyC5), 96.3 (CCl_3), 93.8 (C2), 43.5 (Me). Anal. Calcd. for $C_{22}H_{18}Cl_3N_3O_3S$ (mw 510.82): C, 51.73; H, 3.55; N, 8.23%. Found: C, 52.01; H, 3.60; N, 8.33%.

N^3-[1-(4-Methylphenyl)-3-oxo-4,4,4-trichlorobut-1-en-1-yl]-N^2-(methanesulfonyl)-2,3-diaminopyridine (3h). Yield 53%; mp 174–176°C; ^{1}H NMR, δ (ppm) =11.0 (s, 1H, NH), 8.2 (s, 1H, NH), 7.61 (d, 1H, J = 5, PyH6), 7.28–7.20 (m, 4H, Ph), 7.0 (d, 1H, J = 7.5, PyH4), 6.52 (dd, 1H, J = 5, J = 5, PyH5), 6.2 (s, 1H, H2), 2.8 (s, 3H, Me), 3.3 (s, 3H, Me); ^{13}C NMR, δ (ppm) = 181.2 (C=O), 162.7 (C1), 155.1 (Ph), 145.9 (PyC2), 144.5 (PyC6), 129.6, 129, 127.2 (3C, Ph), 128.2 (PyC4), 122.4 (PyC3), 113.8 (PyC5), 95.1 (CCl_3), 89 (C2), 39.5 (Me), 21.7 (Me). Anal. Calcd. for $C_{23}H_{20}Cl_3N_3O_4S$ (mw 540.85): C 51.08% H 3.73% N 7.77%. Found: C, 50.92; H, 3.58; N, 7.69%.

N^3-[1-(4-Methoxyphenyl)-3-oxo-4,4,4-trichlorobut-1-en-1-yl]-N^2-(methanesulfonyl)-2,3-diaminopyridine (3i). Yield 66%; mp 180–182°C; ^{1}H NMR, δ (ppm) = 11.0 (s, 1H, NH), 8.1 (s, 1H, NH), 7.5 (d, 1H, J = 5, PyH6), 7.29 (d, 2H, ^3J = 7, Ph), 7.0 (s, 1H, J = 7.5, PyH4), 6.69 (d, 2H, ^3J = 7, Ph), 6.55 (dd, 1H, J = 5, J = 5, PyH5), 6.2 (s, 1H, H2), 3.8 (s, 1H, OMe), 2.8 (s, 3H, Me); ^{13}C NMR, δ (ppm) = 182.5 (C=O), 164.8 (C1), 152.1 (PyC6), 138.6 (PyC4), 134.9 (PyC2), 134.8, 132.9, 129.4, 128.5, 125.9 (5C, Ph), 124.2 (PyC3), 112.2 (PyC5), 96.3 (CCl3), 93.9 (C2), 53.4 (OMe), 39.4 (Me). Anal. Calcd. for $C_{22}H_{17}Cl_3FN_3O_3S$ (mw 528.81): C, 49.97; H, 3.24; N, 7.95%. Found: C, 50.12; H, 3.27; N, 8.01%.

N^3-[1-(4-Bromophenyl)-3-oxo-4,4,4-trichlorobut-1-en-1-yl]-N^2-(methanesulfonyl)-2,3-diaminopyridine (3l). Yield 61%; mp 177–179°C; ^{1}H NMR, δ (ppm) = 11.0 (s, 1H, NH), 7.8 (s, 1H, NH), 7.7 (bs, 1H, PyH6), 7.5 (bs, 2H, Ph), 7.2 (bs, 2H, Ph), 6.9 (bs, 1H, PyH4), 6.5 (bs, 1H, PyH5), 6.1 (s, 1H, H2), 2.8 (s, 3H, Me); ^{13}C NMR, δ (ppm) = 182.5 (C=O), 165.2 (C1), 153.1 (PyC6), 141.7 (PyC2), 136.3 (PyC4), 132.5, 132.2, 129.4, 125.6 (4C, Ph), 121.3 (PyC3), 113.3 (PyC5), 96.4 (CCl_3), 92.5 (C2), 52.5 (Me). Anal. Calcd. for $C_{22}H_{17}BrCl_3N_3O_3S$ (mw 589.72): C, 44.81; H, 2.91; N, 7.13%. Found: C, 44.99; H, 3.01; N, 7.19%.

General procedure for the preparation of substituted 2-aryl(heteroaryl)-3*H*-pyrido[2,3-*b*][1,4]diazepin-4(5*H*)-ones (4g-p).

Method A: From N^3-[1-aryl(heteroaryl)-3-oxo-4,4,4-trichlorobut-1-en-1-yl]-2,3-diaminopyridines (2g-p). To a stirred solutions of N^3-[1-aryl(heteroaryl)-3-oxo-4,4,4-trichlorobut-1-en-1-yl]-2,3-diaminopyridines (**2g-p**) (3 mmol) in 5 mL of dry ethanol, were added CH_3ONa (3 mmol). The reactions were carried out under reflux during 24 h. After the reaction time the solvent was removed under reduced pressure and the crude solid products were washed with water and then with chloroform, obtaining dark solids (**4g-p**), as pure compounds (yields 70–85%).

Method B: From 4-aryl(heteroaryl)-4-methoxy-1,1,1-trichlorobut-3-en-2-ones (1g-p). To a stirred solutions of 2,3-diaminopyridine (2 mmol, 0.218 g), in 6 mL of dry methanol, was added CH_3ONa (2 mmol). After 10 min, the respective 4-aryl(heteroaryl)-4-methoxy-1,1,1-trichlorobut-3-en-2-ones (**1g-p**) were added (2 mmol) in one portion and the solutions were stirred at 60–65°C during 24 h. After the reaction time the solvent was removed under reduced pressure and the crude solid products were washed with water and then with chloroform, obtaining dark solids (**4g-p**), as pure compounds (yields 52–70%).

2-Phenyl-3H-pyrido[2,3-b][1,4]-diazepin-4(5H)-one (4g). Yield 52%; mp 250–252°C. See ref. [3] yield 65%; mp 258°C; ^{1}H NMR, δ (ppm) = 10.9 (s, 1H, NH), 8.3 (d, 1H, J = 5, H7), 8.0 (bs, 2H, Ph), 7.8 (bs, 1H, H9), 7.5 (bs, 3H, Ph), 7.3 (bs, 1H, H8), 3.6 (s, 2H, H3); ^{13}C NMR, δ (ppm) = 166.1 (C=O), 159.3 (C2), 146 (C7), 142.4 (C5a), 136.7 (Ph), 136.3 (C9a), 134.4 (C9), 131.2 (Ph), 128.7 (Ph), 127.6 (Ph), 120 (C8), 40.2 (C3).

2-(4-Methylphenyl)-3H-pyrido[2,3-b][1,4]-diazepin-4(5H)-one (4h). Yield 55%; mp 257–259°C; ^{1}H NMR, δ (ppm) = 10.8 (s, 1H, NH), 8.3 (d, 1H, J = 5, H7), 7.9 (d, ^3J = 7, 2H, Ph), 7.8 (d, J = 7, 1H, H9), 7.35–7.33 (m, 3H, Ph and H8), 3.5 (s, 2H, H3), 2.3 (s, 3H, Me); ^{13}C NMR, δ (ppm) = 165.7 (C=O), 158.9 (C2), 145.4 (C7), 142.1 (C5a), 140.9 (Ph), 135.2 (C9), 134.2 (C9a), 133.9 (Ph), 128.9 (Ph), 127.3 (Ph), 119.5 (C8), 20.4 (Me). Anal. Calcd. for $C_{15}H_{13}N_3O$ (mw 251.29): C, 71.70; H 5.21; N 16.72%. Found: C, 71.83; H, 5.31; N, 16.75%.

2-(4-Methoxyphenyl)-3H-pyrido[2,3-b][1,4]-diazepin-4(5H)-one (4i). Yield 57%; mp 245–247°C; ^{1}H NMR, δ (ppm) = 11.0 (s, 1H, NH), 8.4 (d, 1H, J = 5, H7), 8.1 (d, ^3J = 8.5, 2H, Ph), 7.9 (d, J = 7, 1H, H9), 7.4 (bs, 1H, H8), 7.1 (d, 2H, ^3J = 8.5, Ph), 3.9 (s, 2H, OMe), 3.6 (s, 2H, H3); ^{13}C NMR, δ (ppm) = 166.0 (C=O), 161.8 (C2), 158.6 (Ph), 145.4 (C7), 142.4 (C5a), 136.1 (Ph), 134.6 (C9a), 129.6 (Ph), 129,1 (C9), 119.9 (C8), 114 (Ph), 55.3 (OMe), 40.6 (C3). Anal. Calcd. for $C_{15}H_{13}N_3O_2$ (mw 267.29): C, 67.41; H, 4.90; N, 15.72%. Found: C, 67.20; H,4.95; N, 15.83%.

2-(4-Fluorophenyl)-3H-pyrido[2,3-b][1,4]-diazepin-4(5H)-one (4j). Yield 60%; mp 252–254°C; ^{1}H NMR, δ (ppm) = 10.9 (d, 1H, NH), 8.3 (d, 1H, J = 5, H7), 8.1 (bs, 2H, Ph), 7.8 (bs, 1H, H9), 7.40–7.31 (m, 3H, Ph and H8), 3.6 (s, 2H, H3); ^{13}C NMR, δ (ppm) = 165.6 (C=O), 157.9 (C2), 156.5 (d, $^1J_{CF}$ = 250, Ph), 145.7 (C7), 142.1 (C5a), 135.8 (d, $^4J_{CF}$ = 22, Ph), 134.1 (C9a), 133.2 (C9), 129.9 (d, $^3J_{CF}$ = 9, Ph), 119.7 (C8), 115.3 (d, $^2J_{CF}$ = 22), 33.9 (C3). Anal. Calcd. for $C_{14}H_{10}FN_3O$ (mw 255.25): C, 65.88; H, 3.95; N 16.46%. Found: C, 66.02; H, 3.80; N, 16.37%.

2-(4-Chlorophenyl)-3H-pyrido[2,3-b][1,4]-diazepin-4(5H)-one (4k). Yield 64%; mp 262–264°C; ^{1}H NMR, δ (ppm) =10.8 (s, 1H, NH), 8.3 (d, 1H, J = 5, H7), 8.0 (d, ^3J = 8, 2H, Ph), 7.8 (d, J = 7, 1H, H9), 7.7 (d, ^3J = 8, 2H, Ph), 7.3 (bs, 1H, H8), 3.5 (s, 2H, H3); ^{13}C NMR, δ (ppm) = 165.9 (C=O), 158 (C2), 145.8 (C7), 143 (C5a), 138.3 (C9a), 135.9 (C9), 133.9 (Ph), 131.3 (Ph), 129.2 (Ph), 119.9 (C8). Anal. Calcd.

for $C_{14}H_{10}ClN_3O$ (mw 271.71): C, 61.89; H, 3.71; N, 15.47%. Found: C, 61.94; H, 3.68; N, 15.32%.

2-(4-Bromophenyl)-3H-pyrido[2,3-b][1,4]-diazepin-4(5H)-one (4l). Yield 53%; mp 266–268°C; ^{1}H NMR, δ (ppm) =10.6 (s, 1H, NH), 8.3 (d, 1H, $J = 5$, H7), 8.0 (bs, 2H, Ph), 7.8 (bs, 1H, H9), 7.7 (bs, 2H, Ph), 7.3 (bs, 1H, H8), 3.5 (s, 2H, H3); ^{13}C NMR, δ (ppm) = 165.5 (C=O), 158 (C2), 145.8 (C7), 142.1 (C5a), 135.9 (C9), 135.8 (C9a), 133.9, 131.3, 129.1, 124.7 (4C, Ph), 119.6 (C8). Anal. Calcd. for $C_{14}H_{10}BrN_3O$ (mw 316.16): C, 53.19; H, 3.19; N, 13.29%. Found: C, 53.02; H, 3.10; N, 13.17%.

2-(4,4′-Biphenyl)-3H-pyrido[2,3-b][1,4]-diazepin-4-one (4m). Yield 59%; mp 248–250°C; ^{1}H NMR, δ (ppm) =11.0 (s, 1H, NH), 8.3 (d, $J = 5$, 1H, H7), 8.0 (bs, $^3J = 8$, 2H, Ph), 7.9–7.8 (m, 2H, Ph and 1H, H9), 7.7 (d, $^3J = 8$, 2H, Ph), 7.5 (t, 2H, $^3J = 8$, Ph), 7.4 (t, 1H, $^3J = 8$, Ph), 7.3 (dd, $J = 5$, $J = 5$, 1H, H8), 3.6 (s, 2H, H3); ^{13}C NMR, δ (ppm) = 165.7 (C=O), 158.6 (C2), 145.6 (C7), 142.5 (C5a), 142.1 (Ph), 138.7 (C9a), 135.9 (C9), 135.5, 134.2, 128.5, 127.9, 127.6, 126.5, 126.4 (7C, Ph), 119.6 (C8). Anal. Calcd. for $C_{20}H_{15}N_3O$ (mw 313.36): C, 76.66; H, 4.82; N 13.41%. Found: C, 76.45; H, 4.71; N, 13.20%.

2-(1-Naphthyl)-3H-pyrido[2,3-b][1,4]-diazepin-4-one (4n). Yield 67%; mp 251–253°C; ^{1}H NMR, δ (ppm) = 8.5 (s, 1H, NH), 8.3 (d, 1H, $J = 5$, H7), 7.9 (bs, 2H, Ph), 7.8 (bs, 2H, Ph), 7.7–7.5 (m, 2H, OH and H9 and 2H, Ph), 7.2 (bs, 1H, Ph), 6.7 (bs, 1H, Ph), 6.3 (bs, 1H, H8), 3.6 (s, 2H, H3); ^{13}C NMR, δ (ppm) = 170.8 (Ph), 166.9 (C=O), 161.2 (C2), 148.5 (C7), 136.1 (C5a), 134.9 (C9), 132.8 (C9a), 131.2 (Ph), 127.7–124.9 (Ph), 113.8 (C8). Anal. Calcd. for $C_{18}H_{13}N_3O$ (mw 287.32): C, 75.25; H, 4.56; N, 14.62%. Found: C, 75.48; H, 4.85; N, 14.83%.

2-(2-Furyl)-3H-pyrido[2,3-b][1,4]-diazepin-4-one (4o). Yield 62%; mp 218–220°C; ^{1}H NMR, δ (ppm) =11.0 (s, 1H, NH), 8.3 (d, 1H, $J = 5$, H7), 8.20–8.18 (m, OH, 1H, fr), 7.8 (bs, 1H, H9), 7.7 (bs, 1H, fr), 7.5 (bs, 1H, fr), 7.4 (bs, 1H, H8), 3.6 (s, 2H, H3); ^{13}C NMR, δ (ppm) = 165.8 (C=O), 154.2 (C2), 145.8 (C7), 143.0 (fr), 136.1 (C9a), 134.1 (C9), 133.2 (fr), 131.6 (fr), 128.4 (fr), 120.1 (C8), 40.3 (C3). Anal. Calcd. for $C_{12}H_9N_3O_2$ (mw 227.22): C, 63.43; H, 3.99; N, 18.49%. Found: C, 63.57; H, 4.03; N, 18.55%.

2-(2-Thienyl)-3H-pyrido[2,3-b][1,4]-diazepin-4-one (4p). Yield 70%; mp 264–266°C; ^{1}H NMR, δ (ppm) =10.9 (s, 1H, NH), 8.3 (d, 1H, $J = 5$, H7), 7.9 (bs, 1H, H9), 7.6 (bs, 1H, tn), 7.4 (bs, 1H, tn), 7.0 (bs, 1H, H8), 6.9 (bs, 1H, tn), 3.6 (s, 2H, H3); ^{13}C NMR, δ (ppm) = 165.8 (C=O), 154.8 (C2), 145.8 (C7), 143 (tn), 142.5 (tn), 136.1 (C9), 134.1 (C9a), 133.2, 131.6, 128.4 (3C, tn), 120.1 (C8). Anal. Calcd. for $C_{12}H_9N_3OS$ (mw 243.28): C, 59.24; H, 3.73; N, 17.27%. Found: C, 59.37; H, 3.80; N, 17.32%.

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[16] Crystallographic data for compound **2g**, reported in this article, have been deposited with the Cambridge Crystallographic Data Center (CCDC 687399). Copies of the data can be obtained, free of charge, on application to CCDC 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Molecular Interaction between Free Base *meso*-Tetraarylporphyrins and *o*-Chloranil

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Mixing of *meso*-tetraarylporphyrins and *o*-chloranil leads to the formation of a $[H_2T(4\text{-}X)PP{:}(C_6Cl_4O_2)_2]$ molecular complex, that two nitrogen atoms of pyrrolenine in the porphyrin core act as electron donors to π^* orbital of a CO group in two acceptor molecules.

$$H_2T(4\text{-}X)PP + 2C_6Cl_4O_2 \rightarrow [H_2T(4\text{-}X)PP(C_6Cl_4O_2)_2]$$

Interaction of *meso*-tetraarylporphyrins ($H_2T(4\text{-}X)PP$, X=H, CH_3, OCH_3, Br) and *o*-chloranil ($C_6Cl_4O_2$) in chloroform at room temperature, with any ratio of the reactants leads to formation of $[H_2T(4\text{-}X)PP(C_6Cl_4O_2)_2]$ compounds as a sole yield. The significant UV-vis, ^{1}H NMR, and ^{13}C NMR spectral results suggested distortion of porphyrin core structure in the molecular complexes. Spectral data of the complexes revealed that the lone pair electron of a pyrrolenine nitrogen of porphyrin (σ-electron donor) occupy π^* orbital of a CO group in one *o*-chloranil molecule (π-electron acceptor).

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INTRODUCTION

The molecular interaction of free base porphyrins (as σ-electron donors) with σ- or π-acceptors has been of interest to chemists because of deformation of porphyrin core in the produced adducts. It is reported that the reaction between porphyrins and σ- or π-acceptors produces the molecular complexes with 1:1 or 1:2 (donor:acceptor) molar ratios [1–15]. In most of the studies, the selected acceptor molecules are σ-acceptors [3–15], and there are two works for the molecular complexation between porphyrins and π-acceptors of DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) and TCNE (tetracyanoethylene) [1,2]. The π-acceptors are weaker acids than σ-acceptors and formation of those molecular complexes with porphyrins is slow. Furthermore, the importance and complexity of electron transfer reactions in nature have lead many researchers to look always to study the fundamental chemistry of these processes in simplified model systems. Porphyrins are some of the most ubiquitous compounds found in nature, and they are important in a wide variety of biochemical processes from oxygen transport to the trapping and transduction of solar radiation into useful chemical energy [16–18]. The primary photochemical reaction of photosynthesis is involving electron transfer from a photo-excited chlorophyll molecule to a quinone [19]. This subject led us to investigate the formation of molecular complexes of quinones with free base *meso*-tetraarylporphyrins. In this article, spectroscopic evidences of molecular complexes of four derivatives of free base parasubstituted *meso*-tetraarylporphyrins (Figure 1) as σ-electron donors, with *o*-chloranil ($C_6Cl_4O_2$) as electron acceptor (Figure 2) has been studied. This work provides the first example of the molecular complexes of *meso*-tetraarylporphyrins containing N-to-O dative bond.

RESULTS AND DISCUSSION

The UV-vis spectra for titration of *o*-chloranil into H_2TPP with different molar ratios (*e.g.*, 1:0, 1:0.5, 1:1, 1:1.5, and 1:2) in $CHCl_3$ show a new absorption band at 444 nm and shrinking of 418 nm peak (Soret band), which are, respectively, belong to 1:2 molecular complex and H_2TPP with no evidence of formation of 1:1 adduct $[H_2TPP{:}(C_6Cl_4O_2)]$, Figure 3. The spectrum of the 1:1 $[H_2TPP{:}\ (C_6Cl_4O_2)]$ reaction mixture clearly demonstrates the superimposition of the H_2TPP and $[H_2TPP(C_6Cl_4O_2)_2]$ spectra, with no indication for the occurrence of a 1:1 adduct. While an excess amount of *o*-chloranil beyond the 1:2 molar ratios makes no measurable changes in the UV-vis spectra of $[H_2TPP(C_6Cl_4O_2)_2]$ molecular complex. For the interaction of other *meso*-tetraarylporphyrins were obtained similar UV-vis spectral results, Table 1. The spectral red shift for $[H_2T(4\text{-}OCH_3)PP(C_6Cl_4O_2)_2]$ when compared with that of $[H_2TPP(C_6Cl_4O_2)_2]$ is greater than the shifts in other $[H_2T(4\text{-}X)PP(C_6Cl_4O_2)_2]$ molecular complexes (Table 1). This could be attributed to a better π-resonance-type interaction produced by the lone pair of the methoxy groups.

Comparison of the ^{1}H NMR spectra of H_2TPP and $[H_2TPP(C_6Cl_4O_2)_2]$ reveals notable shifts, which are due

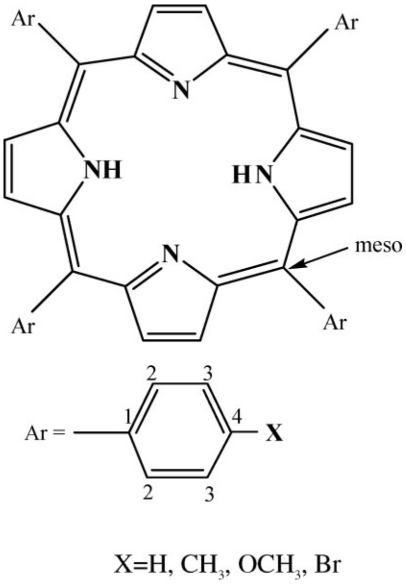

Figure 1. *meso*-Tetraarylporphyrins.

to the formation of $[H_2TPP(C_6Cl_4O_2)_2]$ complex (*o*-chloranil has no hydrogens), Figure 4. ^1H NMR spectra of different molar ratios of *o*-chloranil with the porphyrin (*e.g.*, 1:1 and 1:1.5), in $CDCl_3$ show a mixture of the free base porphyrin and the related 1:2 complex with no trace of 1:1 adduct. The protons of internal N—H in free base porphyrins are upfield (at −2.75 to −2.82 ppm) and the β-protons are downfield (at 8.85–8.89 ppm), Table 2. The aryl protons show a composition of two doublets, a doublet for the *ortho*-protons at about 8.08–8.24 ppm, and another for the *meta*-hydrogens at 7.27–7.77 ppm. The complexation of $H_2T(4\text{-}X)PP$ with *o*-chloranil was similar to molecular complexation of porphyrin with various acceptors [1–8] and showed a downfield shift of NH signals ($\Delta\delta$ = 3.08–3.20 ppm) and an upfield shift of β-hydrogens ($\Delta\delta$ = −0.23 to −0.40 ppm, Table 2. Also a downfield shift is observed for all the protons of the aryl ring, while β-hydrogens of pyrrole and *ortho*-aryl overlap to give a broad signal at 8.47 to 8.65 ppm, Table 2. All of these downfield or upfield changes were in the direction to decrease and increase of the ring current for the porphyrin macrocycle and the aryl rings, respectively [1–7]. The eight protons of meta-positions in aryl ring and four protons of the para in the molecular complex of $[H_2TPP(C_6Cl_4O_2)_2]$ is overlapped and showed a resonance at 7.99 to 8.07 ppm, Table 2.

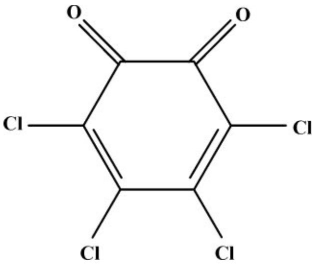

Figure 2. *o*-Chloranil.

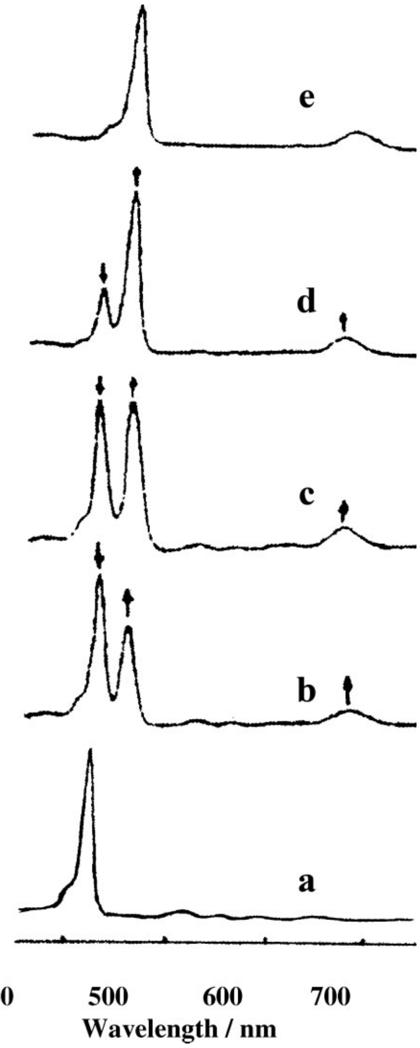

Figure 3. UV-vis spectra for the titration of H_2TPP with (a) 0.0; (b) 0.5; (c) 1.0; (d) 1.5; and (e) two equivalents of *o*-chloranil in chloroform solution. The concentration of H_2TPP for the spectra was $4.33 \times 10^{-6}M$.

The UV-vis and ^1H NMR spectra of the $H_4T(4\text{-}X)PP^{2+}$ were quite sensitive to the concentration of CF_3COOH, but an excess of *o*-chloranil had no effect on the UV-vis and ^1H NMR spectra of $[H_2T(4\text{-}X)PP(C_6Cl_4O_2)_2]$ molecular complexes [5,6,8]. In result, a diprotonated porphyrin species is not formed in our reaction system. The remarkable spectral correspondence between the $[H_2TPP(C_6Cl_4O_2)_2]$ and H_4TPP^{2+}

Table 1

UV-vis spectral results of the various *meso*-tetraarylporphyrins and $[H_2T(4\text{-}X)PP(C_6Cl_4O_2)_2]$ complexes in $CHCl_3$.

Compounds	Peaks(λ_{max}/nm)
H_2TPP	418(S), 516, 550, 590, 646
$[H_2TPP(C_6Cl_4O_2)_2]$	444(S) 659
$H_2T(4\text{-}CH_3)PP$	420(S), 517, 552, 592, 648
$[H_2T(4\text{-}CH_3)PP(C_6Cl_4O_2)_2]$	446(S) 668
$H_2T(4\text{-}OCH_3)PP$	420(S), 519, 556, 593, 653
$[H_2T(4\text{-}OCH_3)PP(C_6Cl_4O_2)_2]$	454(S) 690
$H_2T(4\text{-}Br)PP$	421(S), 514, 548, 591, 649
$[H_2T(4\text{-}Br)PP(C_6Cl_4O_2)_2]$	445(S) 666

S, Soret band.

suggested analogous saddled porphyrin core structures in these species [1–8,20].

^1H NMR and UV-vis spectral shifts for the molecular complexation of various *meso*-tetraarylporphyrins with *o*-chloranil indicate that π-resonance more than σ-induction effects are predominantly transmitted from aryl substituents to the porphyrin core in the molecular complexes (Tables 1 and 2).

^{13}C NMR spectrum of $[H_2TPP(C_6Cl_4O_2)_2]$ molecular complex shows 11 signals in regions: 123.1, 124.0, 128.5, 128.8, 129.8, 130.4, 135.0, 139.4, 140.3, 146.4, 154.5 ppm. ^{13}C NMR spectrum of free base H_2TPP is consisting to six signals. One broad signal for β-carbons (131.5 ppm) and five sharp lines ($C_{meso} = 120.5$, $C'_3 = 127.1$, $C'_4 = 128.1$, $C'_2 = 135.0$, $C'_1 = 142.6$) [1,2,5,6]. The α-carbons about 145 ppm is too broad and weak to be seen. The complexation of the porphyrin with *o*-chloranil was leaded to changes in the ^{13}C NMR spectrum of the porphyrin (123.1 (C_{meso}), 128.5 (C_β), 128.8 (C'_3), 130.4 (C'_4), 139.4 (C'_2), 140.3 (C'_1), and 146.4 (Cα) ppm). Complexation of the porphyrin with *o*-chloranil sharpens α and β-carbon signals. On the other hand, the complexation causes a small downfield shift in the lines of C_{meso}, C'_2, C'_3, C'_4 and an upfield shift of C_β and C'_1 signals of H_2TPP. The molecular complexation of the porphyrins with π-acceptors (DDQ and TCNE) or σ-acceptors ($BiCl_3$ and $SbCl_3$) have been made same changes in those ^{13}C resonances [1,2,5,6].

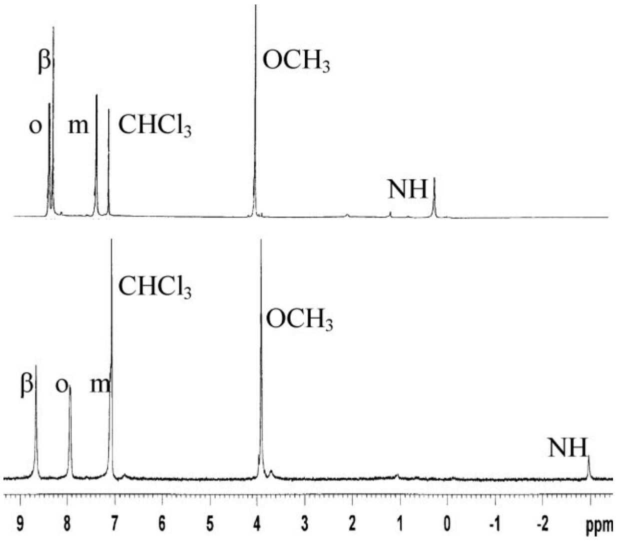

Figure 4. ^1H NMR spectra of (a) $H_2T(4\text{-}OCH_3)PP$ and (b) $[H_2T(4\text{-}OCH_3)PP(C_6Cl_4O_2)_2]$ in $CDCl_3$ at 20°C.

Considerable correspondences between UV-vis, ^1H NMR, and ^{13}C NMR spectral data (shifts and general features of spectra) in the adducts of the

Table 2

^1H NMR spectral data of various *meso*-tetraarylporphyrins and those molecular complexes.

Compounds	N—H	H_β	H_o	H_m	H_p or H_x
H_2TPP	−2.76	8.85	8.20,8.24	7.75,7.77	7.99,8.07
$[H_2TPP(C_6Cl_4O_2)_2]$	0.32	8.62	8.62,8.65	7.99,8.07	7.99,8.07
$\Delta\delta^a$	3.08	−0.23			
$H_2T(4\text{-}CH_3)PP$	−2.77	8.85	8.08,8.11	7.54,7.56	2.70
$[H_2T(4\text{-}CH_3)PP(C_6Cl_4O_2)_2]$	0.34	8.57	8.53,8.58	7.84,7.86	2.82
$\Delta\delta^a$	3.11	−0.28			
$H_2T(4\text{-}OCH_3)PP$	−2.75	8.86	8.10,8.14	7.27,7.31	4.10
$[H_2T(4\text{-}OCH_3)PP(C_6Cl_4O_2)_2]$	0.44	8.52	8.56,8.57	7.56,7.58	4.21
$\Delta\delta^a$	3.19	−0.34			
$H_2T(4\text{-}Br)PP$	−2.82	8.89	8.12	7.72	–
$[H_2T(4\text{-}Br)PP(C_6Cl_4O_2)_2]$	0.38	8.49	8.47	8.22	–
$\Delta\delta^a$	3.20	−0.40			

Multiplicity in all signals of the *meso*-tetraarylporphyrins and those molecular complexes are as follows: N—H (singlet); H_β (singlet); H_o (doublet); H_m (doublet); in H_2TPP, H_m and H_p (multiplet).

[a] Δδ is difference between the proton chemical shift for the porphyrin and the related molecular complex.

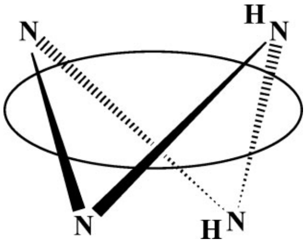

Figure 5. The deformation of the porphyrin core causes two pyrrolenine nitrogen atoms of pyrrole rings to be able act as the electron donors to two molecules of *o*-chloranil.

porphyrins with various acceptors [1–8] and [H_2T(4-X)PP($C_6Cl_4O_2$)$_2$] complexes strongly suggests a very similar porphyrin core structure in all of the mentioned species. This is logically corresponded to the proposed deformation of porphyrin pyrrole rings to provide suitable position for the N—Hs for formation of new bonds in above and below the plane of porphyrin, Figure 5.

In the FT-IR spectroscopy, the N—H stretching band of the free base *meso*-tetraarylporphyrins appears at 3320 cm^{-1} [21], and two stretching vibrations of the carbonyl groups in *o*-chloranil give one strong band at 1670 cm^{-1}, Figure 6(a,b). In the FT–IR spectra of the [H_2T(4-X)PP($C_6Cl_4O_2$)$_2$] complexes, the bands in 3320 and 1670 cm^{-1} regions are completely lost, Figure 6(c). The disappearance of the NH stretching band for the molecular complexes, [H_2T(4-X)PP($C_6Cl_4O_2$)$_2$], suggests the existence of an interamolecular hydrogen-bonding between N—H and *o*-chloranil [1,2]. Furthermore, the disappearance of the carbonyl band of *o*-chloranile upon the molecular complexation indicates that π*-orbital of CO group is as electron acceptor.

^{13}C NMR spectrum of *o*-chloranil has been showed that the resonances in the 131.9 ppm (C_α), 143.7 ppm (C_β), and 168.7 ppm (CO) regions [22] that upon the complexation with H_2TPP change to four signals (123.9, 129.8, 135.0, 154.5 ppm). These changes suggested a loss of symmetry upon the interaction of *o*-chloranil with H_2TPP.

The FT-IR and ^{13}C NMR results indicated that the *o*-chloranil has an electron acceptor role through only one of its carbonyl groups (π* orbital). The pyrrole rings of the H_2TPP tilt alternately up and downward and the two lone electron pairs of the pyrrolenine nitrogens in this noncoplanar configuration are much more accessible for being engaged with the empty π* orbital of CO groups in *o*-chloranil, from above and below the main plane of the porphyrin (Figure 7). The accepting of an electron pair of pyrrolenine nitrogen by a π* orbital of one carbonyl group is most consistent with ^{13}C NMR assignments of a complexed *o*-chloranil. The largest shift is relative to the carbon atom of CO group that acting as electron acceptor directly (C_1 = 129.8 ppm, shift = −38.9 ppm), Figure 7. In contrast, the C_α and C_β carbon atoms had the most distances from the interaction site and revealed as signals in the 123.9 and 135.0 ppm, respectively. These carbons showed a small shift −8.0 ppm (C_α) and −8.7 ppm(C_β), respectively. Furthermore, another CO group that had no interaction with the lone pair of the pyrrolenine nitrogen in the porphyrin had the most contribution in the accepting of electron and revealed at 154.5 ppm and showed −14.2 ppm shift relative to carbonyl group in free *o*-chloranil. The accepting of electron by a CO group causes the aromaticity property for the complexed *o*-chloranil molecule. In Figure 7, two adjacent nitrogen atoms acted as electron donors to two molecules of *o*-chloranil. This structure is

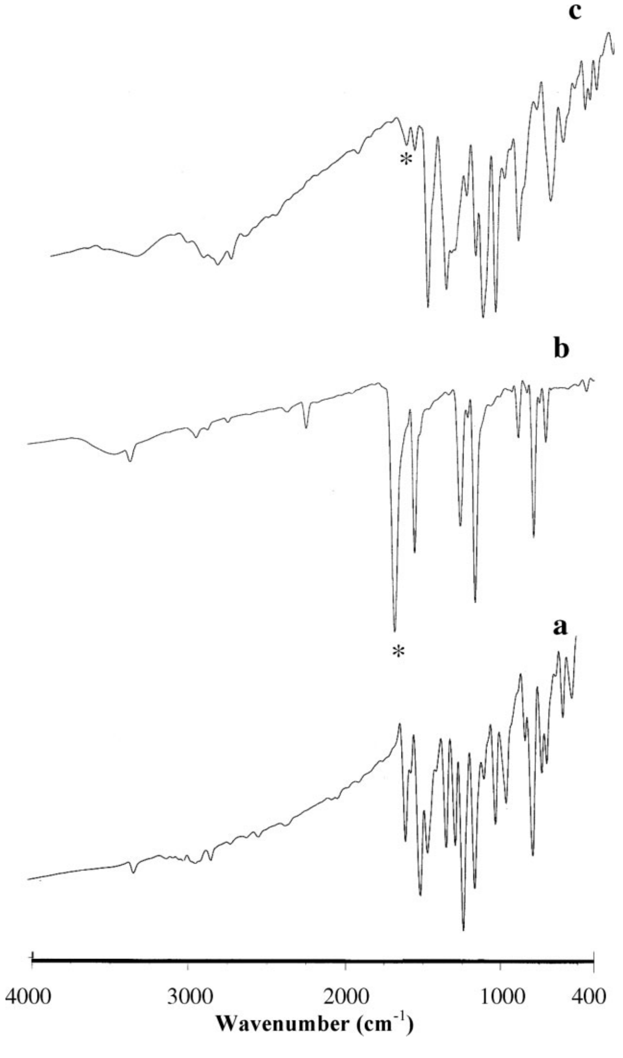

Figure 6. FT-IR spectra of (a) $H_2T(4\text{-}OCH_3)PP$ (b) o-Chloranil and (c) [$H_2T(4\text{-}OCH_3)PP(C_6Cl_4O_2)_2$]. *The band in1670 cm^{-1} region is completely lost.

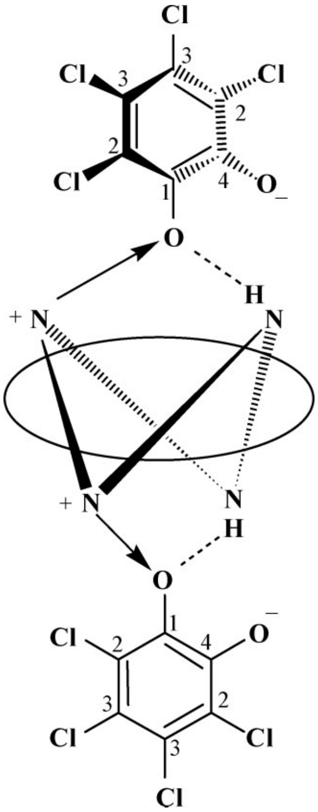

Figure 7. The proposed structure and bonding interactions for a $[H_2T(4\text{-}X)PP(C_6Cl_4O_2)_2]$ molecular complex.

similar to the proposed structure of diprotonated porphyrin, $[H_4TPP^{2+}].2Cl^-$, [23]. In diprotonated species, two molecules of HCl located above and below the porphyrin plane and two protons connected to two adjacent nitrogens. Furthermore, this structure is similar to the proposed structure for the 1:2 molecular complexation of porphyrins with various acceptors [1–4,7,8].

It was interest that there had no interaction between *p*-chloranil and the *meso*-tetraarylporphyrins under our experimental conditions. This may related to long distance between two carbonyl groups and the weakness of the electron accepting in *p*-chloranil or existence of four chloro atoms between two carbonyl groups in *p*-chloranil. If a carbonyl group of *p*-chloranil to acts as electron acceptor, the existence of four electronegative chloro atoms causes negative charge does not locate on oxygen of *p*-chloranil and in result does not produce an aromatic property in the *p*-chloranil ring.

Finally, a singlet for β-protons of *meso*-tetraarylporphyrins is in contrast to unsymmetrical pyrrole rings of the proposed structure in the molecular complex. This may related to a ring inversion of the tilted core conformation of the porphyrin that is probably fast on the NMR time scale [5,6,8].

CONCLUSIONS

Reaction of *meso*-tetraarylporphyrins ($H_2T(4\text{-}X)PP$) and *o*-chloranil ($C_6Cl_4O_2$), with any ratio of the reactants leads only to formation of $[H_2T(4\text{-}X)PP(C_6Cl_4O_2)_2]$ molecular complexes. The UV-vis, (^1H and ^{13}C) NMR spectral data suggest distortion of porphyrin core structure in the molecular complexes. In the produced molecular complexes, the lone electron of pyrrolenine nitrogen of the porphyrin occupies π^* orbital of a CO group in the *o*-chloranil molecule.

EXPERIMENTAL

All of the employed chemicals and solvents were obtained from Merck. The used pyrrole was purified by distillation before use. Chloroform solvent was distilled over K_2CO_3 before use. Syntheses of the *meso*-tetraarylporphyrins have carried out according to Adler and Gonsalves method [24].

The UV-vis spectra were recorded in $CHCl_3$ solution utilizing a GBC cintra 6 UV-Vis spectrophotometer, (1 cm optical path length was employed). A Bruker DPX 500 MHz spectrometer was used for ^1H NMR and ^{13}C NMR spectra of porphyrins and those molecular complexes in $CDCl_3$ solvent. The concentration of the molecular complexes in ^1H NMR spectra was 0.006*M*. The residual $CHCl_3$ in the conventional 99.8% atom $CDCl_3$ gives a signal at $\delta = 7.26$ ppm, which was used for calibration of the chemical shift scale. For FT-IR spectra, a Magna 550 Nicolet instrument was applied (using KBr pellets).

Mixing of *o*-chloranil (0.2 mmol) and *meso*-tetraarylporphyrin (0.1 mmol) in chloroform (20 mL) at room temperature after 7–8 days slowly produced green $[H_2T(4\text{-}X)PP(C_6Cl_4O_2)_2]$ complex. The needle crystals obtained after slow evaporation (3–4 days) of the solvent contained no excess of either *o*-chloranil or $H_2T(4\text{-}X)PP$. The results of elemental analyses for the molecular complexes formed from the porphyrins and *o*-chloranil, which were dried under vacuum oven for 12 h at 55–60°C, were consistent with $[H_2t(4\text{-}X)pp(C_6Cl_4O_2)_2]$.

$[H_2tpp(C_6Cl_4O_2)_2]$: $C_{56}H_{30}N_4O_4Cl_8$: calcd. C, 60.8; H, 2.7; N, 5.1 (found: C, 60.6; H, 2.5; N, 4.9).

$[H_2t(4\text{-}CH_3)pp(C_6Cl_4O_2)_2]$: $C_{60}H_{38}N_4O_4Cl_8$: calcd. C, 62.0; H, 3.3; N, 4.8 (found: C, 61.7; H, 3.0; N, 4.8).

$[H_2t(4\text{-}OCH_3)pp(C_6Cl_4O_2)_2]$: $C_{60}H_{38}N_4O_8Cl_8$: calcd. C, 58.7; H, 3.1; N, 4.6 (found: C, 58.5; H, 2.9; N, 4.8).

$[H_2t(4\text{-}Br)pp(C_6Cl_4O_2)_2]$: $C_{56}H_{26}N_4O_4Cl_8Br_4$: calcd. C, 47.3; H, 1.8; N, 3.9 (found: C, 47.4; H, 1.6; N, 4.0).

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Dicyanomethylene Compounds and Heterocyclization of Substituted Carbohydrazides

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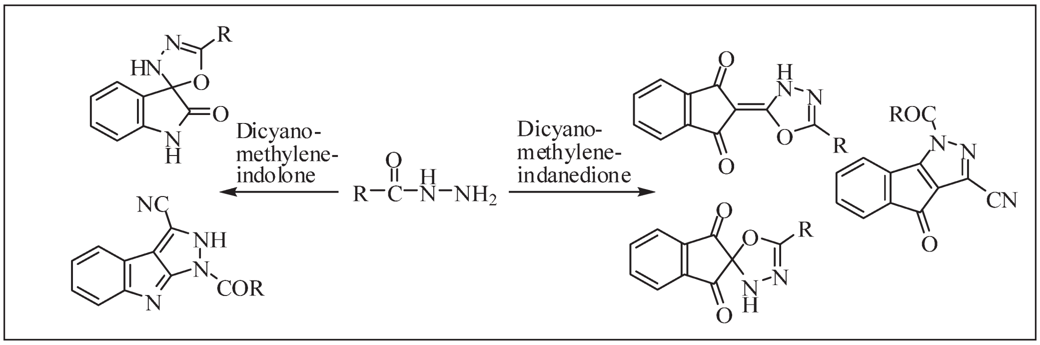

(1,3-Dioxo-2,3-dihydro-1*H*-inden-2-ylidene)propanedinitrile (**2**, in dimethylformamide solution), 3-(dicyanomethylene)-2-indolone (**3**, in ethanol/piperidine solution) act on substituted carbohydrazides **1a–e** forming the derivatives of oxadiazolylideneindene-1,3-diones **4a–e**, spiro(indene-2,2′-oxadiazole)-1,3-dione **5a–e**, cyloxoindenopyrazolecarbonitriles **6a–e**, spiro(indoline-3,2′-oxadiazol)-2-ones **11a–e**, and acylpyrazoloindoles **13a–e**. Rational for these conversions involving the nucleophilic addition on the dicyanomethylene carbon atom are presented.

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INTRODUCTION

In organic π-acceptors containing dicyanomethylene groups such as ethenetetracarbonitrile and (1,3-dioxo-2,3-dihydro-1*H*-inden-2-ylidene)propanedinitrile (**2**), the nitrile groups can be substituted by the nucleophilic nitrogen atom of primary aromatic [1–3] and secondary aliphatic amines [4,5]. Tertiary aromatic amines (like *N,N*-dimethylaniline) are prone to attack to the C=C double bond of **2** with their *para*-position, followed by release of HCN [3,6–10]. By reaction of acceptor **2** with tertiary cyclic amines, one can generate the iminium ions and formation of the α-cyanated amines [11]. Additionally, the reaction of **2** with arylazoaminopyrazoles [12,13], 2-mercaptobenzazoles [14], thiocarbohydrazide, and thiocarbazones [15] as well as *N*-arylisoindolines [16] have been reported. Closely analogous 3-(dicyanomethylene)-2-indolone (**3**) [17] which is a ylidene malononitrile like **2** reacted with thiobarbituric acid [18], *S,S*- and *N,S*-acetals [19], cyclohexanedione [20], and another active methylene systems to give spiroheterocyclic compounds [21,22]. The reaction of *N,N*′-diarylacetamidines with **2** afforded indenoazepine-6-ones [23]. In contrast, spiro[2,3-dihydro-indol-3,4′-pyridino]-5′-carbonitriles were obtained from the reaction of *N,N*′-diarylacetamidines with **3** [23].

Recently, we have reported an efficient transformation of substituted acylhydrazinecarbothioamides with **2** and **3** into oxoindenopyrrolylidenehydrazide, thiazoloindolylidenehydrazide, and pyrroloindolylidenehyrazide derivatives [24].

These intriguing transformations led us to investigate the reaction of carbohydrazides **1a–e** bearing a selection of aromatic and heterocyclic substitutions with acceptor systems **2** and **3** (Fig. 1).

RESULTS AND DISCUSSION

Dimethylformamide solutions of **2** and substituted carbohydrazides **1a–e** in a molar ratio of 2:1 were stirred at room temperature for 48 h. Concentration of the reaction mixture yielded reddish brown crystals from 2-(5-substituted-1,3,4-oxadiazol-2(3*H*)-ylidene)-1*H*-indene-1,3-(2*H*)-diones **4a–e** (51–57%). The remaining soluble materials were subjected to preparative layer chromatography to give 5′-substituted spiro(indene-2,2′-[1,3,4]-oxadiazole)-1,3-dione **5a–e** (13–17%) and 1-acyl-4-oxo-indeno[1,2-*c*]pyrazole-3-carbonitriles **6a–e** (11–15%).

The structures of **4a–e** were delineated from their spectroscopic properties and gross compositions. The products **4a–e** resulted from **1a–e** were found to be

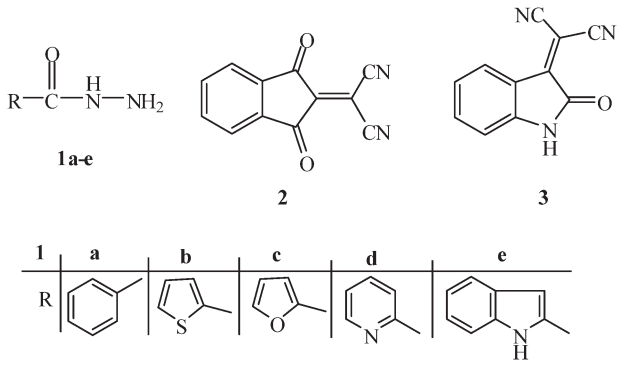
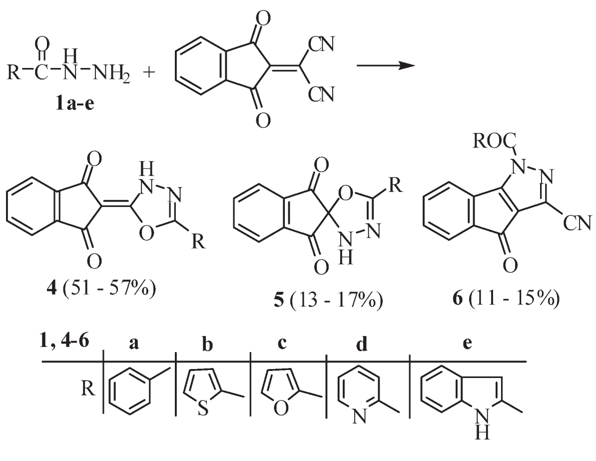


Figure 1. Substituted carbohydrazides and some electron acceptors.

formed by reacting one molecule of **1a–e** and one molecule of **2** *via* loss two molecules of HCN. The molecular ions in their EI-mass spectra confirm the molecular masses and the gross compositions. Furthermore, the following common features of the fragmentation patterns lend support to the assigned structures: Loss of RCO giving rise to the ion $m/z = 185$ common in the spectra of all five compounds. The resulting fragment ions undergo loss of 28 a.m.u. (dinitrogen or CO group). The ir spectra show characteristic absorptions for NH group in range 3330 to 3355 and carbonyl absorption at 1705–1720 cm^{-1} as expected for indane-1,3-dione ring system. Strong bands around 1080–1095 have to be assigned to C—O—C group [25].

The ^{1}H NMR spectra show the presence of a broad signal for 1H at $\delta = 12.57$–12.64 ppm due to oxadiazole-NH, and additionally, the expected signals for R groups. In the ^{13}C NMR spectrum of **4b**, the carbonyl groups resonate at 187.34 ppm. Further peaks at 91.64 (indene-C-2) [16], 154.55 (oxadiazole-C-5), and 174.26 (oxadiazole-C-2) lend support to the structures assigned to **4a–e** (Scheme 1).

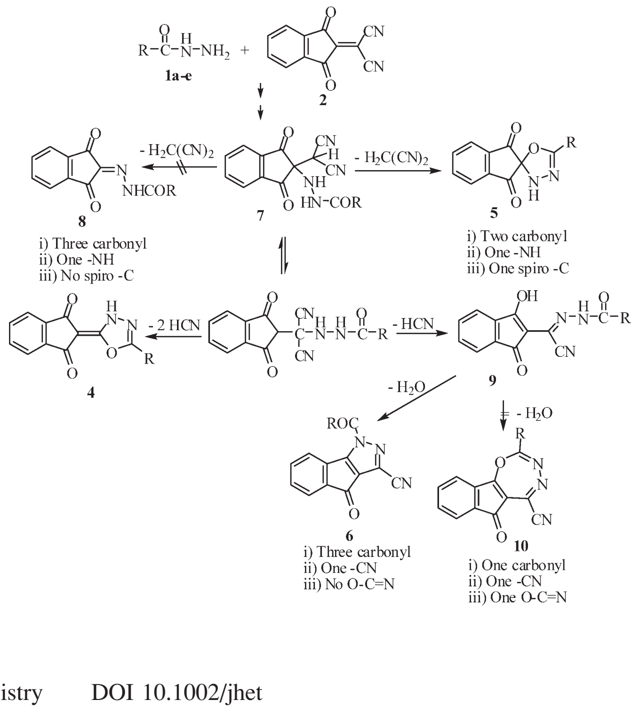
Scheme 1



Compounds **5a–e** show sharp absorptions characteristic of carbonyl group at 1725–1710, NH group at 3330–3315, C=N group at 1630–1620 cm^{-1}, as well as C—O—C group 1095–1080 cm^{-1}. The ^{1}H NMR spectrum (DMSO-d_6) of **5a** clearly shows the presence of oxadiazole-NH at ($\delta = 12.55$ ppm) and phenyl protons at ($\delta = 7.34$–8.12 ppm). The ^{13}C NMR of **5a** shows signals at $\delta = 103.67$ for (spiro-C-2,2′), 156.47 (C-5), and 187.42 (C-1,3), in addition to aryl carbons. The molecular formulae of compounds **5a–e** were supported by elemental analysis and mass spectra, which gave the expected molecular ion peaks. The alternative structure **8** (Scheme 2) based on the same elemental composition could be eliminated according to ir, ^{1}H NMR and ^{13}C NMR spectral data.

The results of combustion analysis and spectroscopic data suggested the presence of acyloxoindenopyrazole derivatives **6a–e** as one of the products from the reaction between **1a–e** and **2**. The gross formula, $C_{20}H_{10}N_4O_2$, **6e** was confirmed by the mass spectrum, which exhibited the molecular ion at *m*/*z* 338 (26%) and the fragmentation pattern at 312, 284, 144, 140, 104, 91, 77, and 65. The ir spectrum showed absorptions at 3365 (NH), 2220 (CN), and 1710, 1665 (CO). The ^{1}H NMR spectrum of **6e** displayed one broad singlet at 11.69 ppm for 1H (indole-NH) and another sharp singlet at 6.64 due to indole-CH in addition to the aromatic protons. In its ^{13}C NMR spectrum, C-3 and C-4 resonate at $\delta = 121.69$ and 189.31 ppm, respectively; further peaks are at $\delta = 99.91$ ppm (indole-CH), 105.06 (C-3a), 149.76 (C-8a), 167.72 acyl-CO, and cyano group at 118.11 ppm.

Scheme 2

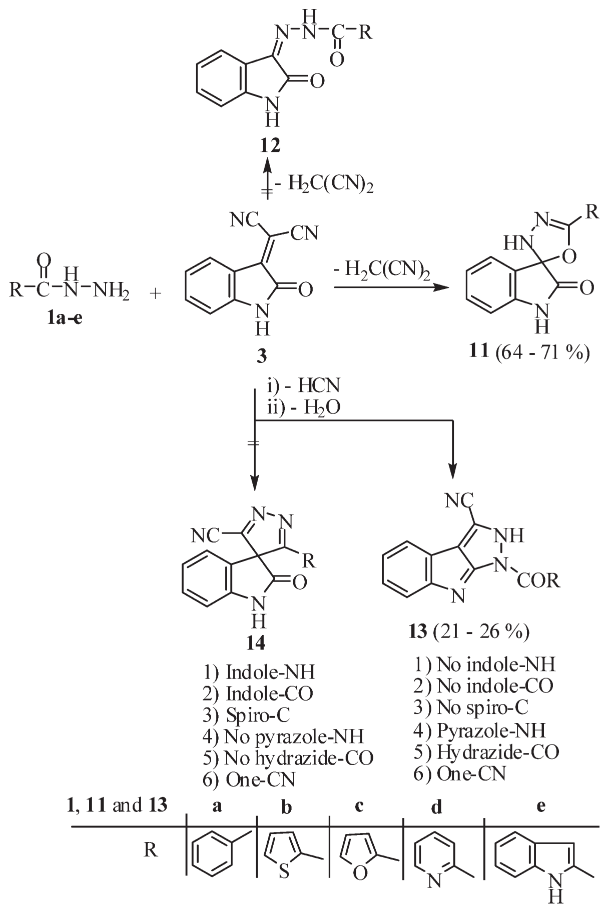


Compound **10** (Scheme 2) could be ruled out, owing to the presence of acyl-CO signals in the ^{13}C NMR spectra. A rational for the formation of the products **4–6** is presented in scheme 2. The carbohydrazides **1a–e** and **2** give the neutral adduct **7**. Elimination of a molecule of malononitrile afforded compounds **5**, whereas elimination two molecules of HCN gave compounds **4**. Elimination one molecule of HCN from the adduct **7** afforded the intermediate **9** followed by elimination a molecule of H_2O to give oxoindenopyrazole derivatives **6**.

Reflux of one mole of **1a–e** with two equivalents of 3-(dicyanomethylene)-2-indolone (**3**) in ethanol/piperidine resulted in pink coloration of the solution, which later became yellowish brown. The residue remaining after concentration was subjected to preparative layer chromatography to give 5′-substituted-spiro[indoline-3,2′-1,3,4-oxadiazol]-2-one **11a–e** (64–71%) and 1-(substituted-2-carbonyl)-1,2-dihydro-pyrazolo[3,4-*b*]-indole-3-carbonitrile **13a–e** (21–26%) (Scheme 3).

Compounds 11a–e. The EI-mass spectra of 11a–e are characterized by molecular ions of low intensity and loss of 28 a.m.u. (may be dinitrogen or carbonyl group) followed by loss of 144 a.m.u. from the molecular ion of 11e (probably indol-2-carbonyl). The ir spectrum showed absorption at 3325–3370 (NH's), 1720 (CO), 1090 (C-O-C). The ^{1}H NMR spectrum of 11e showed the presence of three broad signals with the ratio 1:1:1 centered at 9.81, 11.75, and 12.38 due to indolinone-NH, indole-NH, and oxadiazole -NH, respectively. Indole-CH resonate at 6.57 ppm in addition to the aromatic protons. Signals around 93.66 (spiro C-3 = C-2′), 101.96 (indole-CH), 154.84 (C-5′), and 177.90 (CO) in addition to the aromatic carbons.

Scheme 3



The alternative structure **12** was ruled out based on mp, ir, ^{1}H NMR and ^{13}C NMR spectral data. It has been reported that **1a** and isatine were ball-milled at room temperature for 3 h to give **12a** [26] after drying at 0.01 bar at 80°C. Also, **12a** was obtained during the reaction of **1a** with isatine under reflux in MeOH [27].

Recently, it has been reported that under acetylating condition, isatine-3-acylhydrazones were transformed into selectively acylated derivatives and into the corresponding 3-acetyl-1,3,4-oxadiazolines [28].

Compounds 13a–e. Substituted carbonyl-1,2-dihydropyrazolo[3,4-*b*]indole-3-carbonitrile **13a–e** (21–26%), the ir spectrum of **13b** shown absorption bands characteristic of NH group at 3395 cm^{-1}, strong cyano group at 2215, and one carbonyl absorption at 1660 cm^{-1}. ^{1}H NMR spectrum of **13b** clearly supports the presence of broad signals centered at 11.98 ppm due to pyrazole-NH, aromatic, and thiophene protons were also observed. The ^{13}C NMR spectrum of **13b** exhibited a signal at $\delta = 169.64$ for carbonyl group, 118.24 (CN), 102.36 (C-3a), and 148.66 (C-8a). Therefore, we will concentrate on the interplay between the formation of the products **13a–e** and alternative structure **14**. The a priori possible isomeric structures **14** were ruled out on the basis of ^{1}H NMR and ^{13}C NMR, which clearly support the presence of pyrazole-NH [29] and hydrazide-CO groups. Also, the spectral data showed the absence of indolone-CO, indolone-NH, and spiro-carbons [30].

EXPERIMENTAL

Mps were determined with a Gallenkamp melting point apparatus and were uncorected. The ir spectra were recorded with a Shimadzu 408 instrument using potassium bromide pellets. Five hundred Megahertz ^{1}H and 125 MHz ^{13}C NMR spectra were recorded on a Bruker AVANCE DRX 500 spectrometer. Chemical shifts are expressed as δ (ppm) with reference to tetramethylsilane as internal standard, br = broad, s =singlet, and m = multiplet. ^{13}C assignments (q = quaternary carbon atoms) were made with the aid DEPT 135/90 spectra. The mass spectra (70 eV, electron impact mode) were recorded on Varian MAT CH-7 instrument. Elemental analyses were carried out at the Microanalytical Center, Cairo University, Egypt. Preparative layer chromatography (PLC) was made using 48 cm × 20 cm glass plates covered with slurry applied and air dried 1.0 mm thick layers of Merck silica gel Pf_{254}. Zones were detected by indicator fluorescence quenching upon 254 nm exposure, removed from plates, and extracted with cold acetone

Starting materials. Substituted carbohydrazides 1a–e were prepared according to published procedures [31–36], as were 2-thiophene carbo-hydrazide (1b), mp 135–137°C (lit. [31] 134–136°C); furan-2-carbohydrazide (1c), mp 77–79 (lit. [32] 78°C); 2-pyridine carbohydrazide (1d), mp 136–138°C (lit. [33] 137°C); indole-2-carbohydrazide (1e), mp 243–245°C (lit. [34–36] 246°C) and phenyl carbohydrazide (1a) (Aldrich) was used as received. 2-(1,3-Dioxo-2,3-dihydro-1*H*-inden-2-ylidene)pro-panedinitrile(dicyanomethyleneindane-1,3-dione) (2) was prepared according chatterjee [37], yellow crystals, mp 282–284°C with decomposition, black preheated to 260°C (lit. [37] 280–285°C with decomp.). 3-(Dicyanomethylene)-2-indolone (3) was prepared according to Fatiadi [17], brick-red needles, mp 235–236°C (lit. [17] 235–237°C).

Reactions of carbohydrazides 1a–e with (2). To a solution of **2** (416 mg, 2.0 mmol) in dry dimethylformamide (DMF) (15 mL), a solution of **1a**–**e** (1.0 mmol each) in 5 mL of DMF was added drop wise over 5 min at room temperature with stirring and admission of air for 3 h and left standing for 48 h at room temperature. Reddish brown crystals were precipitated, filtered, and washed with small amount of cold ethanol, which contains 2-(5-substituted-1,3,4-oxadiazol-2-(3*H*)-ylidene)-1*H*-indene-1,3-(2*H*)-diones (**4a**–**e**). The filtration was concentrated to dryness and dissolved in a few mL of acetone and subjected to PLC using toluene/ethyl acetate (2:1) to afford two zones. The fastest migrating fraction contained compounds **5a**–**e** and the slowest migrating zone contained **6a**–**e**.

2-(5-Phenyl-1,3,4-oxadiazol-2-(3*H*)-ylidene)-1*H*-indene-1,3-(2*H*)-dione (4a). This compound was obtained as reddish brown crystals (acetonitrile), mp 247–249°C; ir: NH 3340, CO 1710, C=N 1630, Aryl and C=C 1605, C—O—C 1085 cm^{-1}. ^{1}H NMR: δ 7.38–8.18 (m, 9H, Ar—H), 12.64 (br, 1H, oxadiazole-NH); ^{13}C NMR: δ 91.57 (indene-C-2), 126.31, 128.41, 129.67, 135.86, 138.17 (Ar—CH), 141.27, 143.67 (Ar—C), 154.67 (C-5), 174.34 (C-2), 187.38 (CO); ms: *m*/*z* 290 (M^+, 31), 185 (52), 153 (13), 105 (100), 104 (76), 77 (68), 65 (55). Anal. Calcd. for $C_{17}H_{10}N_2O_3$: C, 70.34; H, 3.47; N, 9.65. Found: C, 70.57; H, 3.39; N, 9.73.

2-(5-(Thiophen-2-yl)-1,3,4-oxadiazol-2-(3*H*)-ylidene)-1*H*-indene-1,3-(2*H*)-dione (4b). This compound was obtained as reddish brown crystals (acetonitrile), mp 270–272°C; ir: NH 3330, CO 1715, C=N 1625, Aryl and C=C 1600, C—O—C 1080; ^{1}H NMR: δ 7.19–8.16 (m, 7H, Ar—H and thiophene-H), 12.62 (br, 1H, oxadiazole-NH); ^{13}C NMR: δ 91.64 (indene-C-2), 126.14, 127.49, 129.57, 130.12, 135.66 (Ar—CH), 141.39, 144.15 (Ar—C), 154.55 (C-5), 174.26 (C-2), 187.34 (CO); ms *m*/*z*: 296 (M^+, 25), 185 (44), 111 (65), 104 (100), 76 (76), 65 (44). Anal. Calcd. for $C_{15}H_8N_2O_3S$: C, 60.80; H, 2.72; N, 9.45; S, 10.82. Found: C, 61.02; H, 2.86; N, 9.28; S, 11.03.

2-(5-(Furan-2-yl)-1,3,4-oxadiazol-2-(3*H*)-ylidene)-1*H*-indene-1,3-(2*H*)-dione (4c). This compound was obtained as reddish brown crystals (methanol), mp 228–230°C; ir: NH 3345, CO 1720, C=N 1620, Aryl and C=C 1605, C—O—C 1090; ^{1}H NMR: δ 7.14–8.21 (m, 7H, Ar—H and furan-H), 12.59 (br, 1H, oxadiazole-NH); ^{13}C NMR: δ 91.65 (indene-C-2), 126.03, 126.33, 127.41, 134.88 (Ar—CH and furan-CH), 140.97, 142.85, 143.66, 145.54 (Ar—C and furan-C-2, C-5), 155.12 (C-5), 174.16 (C-2), 187.83 (CO); ms *m*/*z*: 280 (M^+, 41), 185 (37), 104 (77), 95 (100), 76 (56), 65 (66). Anal. Calcd. for $C_{15}H_8N_2O_4$: C, 64.29; H, 2.88; N, 10.00. Found: C, 64.11; H, 3.04; N, 9.83.

2-(5-(Pyridine-2-yl)-1,3,4-oxadiazol-2-(3*H*)-ylidene)-1*H*-indene-1,3-(2*H*)-dione (4d). This compound was obtained as reddish brown crystals (methanol), mp 262–264°C; ir: NH 3355, CO 1705, C=N 1630, Aryl and C=C 1610, C—O—C 1095; ^{1}H NMR: δ 7.54–8.43 (m, 8H, Ar—H and pyridine-H), 12.57 (br, 1H, oxadiazole-NH); ^{13}C NMR: δ 91.48 (indene-C-2), 126.33, 126.84, 126.87, 136.33 (Ar—CH and pyridine-CH), 141.44, 143.59 (Ar—C), 147.14, 149.34 (pyridine-C-2, C-6), 155.12 (C-5), 174.32 (C-2), 187.66 (CO); ms *m*/*z*: 291 (M^+, 24), 185 (29), 106 (58), 104 (67), 76 (66), 65 (100). Anal. Calcd. for $C_{16}H_9N_3O_3$: C, 65.98; H, 3.11; N, 14.43. Found: C, 66.17; H, 2.98; N, 14.27.

2-(5-(1*H*-Indol-2-yl)-1,3,4-oxadiazol-2-(3*H*)-ylidene)-1*H*-indene-1,3-(2*H*)-dione (4e). This compound was obtained as reddish brown crystals (methanol), mp 291–293°C; ir: NH 3385–3340, CO 1720, C=N 1625, Aryl and C=C 1590, C—O—C 1095; ^{1}H NMR: δ 6.58 (s, 1H, indole-CH), 7.09–8.13 (m, 8H, Ar—H), 11.69 (br, 1H, indole-NH), 12.61 (br, 1H, oxadiazole-NH); ^{13}C NMR: δ 91.76 (indene-C-2), 102.12 (indole-CH), 125.23 (indole-C-2), 126.27, 127.96, 135.78, 138.26 (Ar—CH), 140.22, 141.38, 142.57, 143.81 (Ar—C), 155.06 (C-5), 174.47 (C-2), 187.71 (CO); ms *m*/*z*: 329 (M^+, 39), 225 (23), 185 (34), 144 (41), 104 (74), 91 (57), 76 (100), 65 (69). Anal. Calcd. for $C_{19}H_{11}N_3O_3$: C, 69.30; H, 3.37; N, 12.76. Found: C, 69.13; H, 3.25; N, 12.95.

5′-Phenyl-3′*H*-spiro(indene-2,2′-[1,3,4]oxadiazole)-1,3-dione (5a). This compound was obtained as yellow crystals (ethanol), mp 206–208°C; ir: NH 3325, CO 1715, C=N 1625, Ar—C=C 1595, C—O—C 1090; ^{1}H NMR: δ 7.34–8.12 (m, 9H, Ar—H), 12.55 (br, 1H, oxadiazole-NH); ^{13}C NMR: δ 103.67 (C-2,2′), 126.27, 126.56, 128.31, 129.26, 130.44 (Ar—CH), 132.84, 134.71 (Ar—C), 156.47 (C-5′), 187.42 (C-1,3); ms *m*/*z*: 278 (M^+, 34), 250 (49), 145 (67), 105 (89), 104 (59), 77 (100), 65 (71); Anal. Calcd. for $C_{16}H_{10}N_2O_3$: C, 69.06; H, 3.62; N, 10.07. Found: C, 68.84; H, 3.73; N, 9.88.

5′-(Thiophen-2-yl)-3′*H*-spiro(indene-2,2′-[1,3,4]oxadi-azole)-1,3-dione (5b). This compound was obtained as yellow crystals (ethanol), mp 227–228°C; ir: NH 3315, CO 1710, C=N 1620, Ar—C=C 1600, C—O—C 1080; ^{1}H NMR: δ 7.23–8.15 (m, 7H, Ar—H and thiophene-H), 12.51 (br, 1H, oxadiazole-NH); ^{13}C NMR: δ 103.69 (C-2,2′), 126.36, 126.72, 127.94, 128.66, 130.46 (Ar—CH and thiophene-CH), 132.82, 134.66 (Ar—C and thiophene-C), 156.39 (C-5′), 187.47 (C-1,3); ms *m*/*z*: 284 (M^+, 41), 256 (17), 145 (46), 111 (100), 104 (73), 77 (64), 65 (55); Anal. Calcd. for $C_{14}H_8N_2O_3S$: C, 59.15; H, 2.84; N, 9.85; S, 11.28. Found: C, 58.89; H, 2.92; N, 10.03; S, 11.05.

5′-(Furan-2-yl)-3′*H*-spiro(indene-2,2′-[1,3,4]oxadiazole)-1,3-dione (5c). This compound was obtained as yellow crystals (acetonitrile), mp 189–190°C; ir: NH 3320, CO 1710, C=N 1625, C—O—C 1100, 1080; ^{1}H NMR: δ 7.26–8.15 (m, 7H, Ar—H and furan-H), 12.54 (br, 1H, oxadiazole-NH); ^{13}C NMR: δ 103.71 (C-2,2′), 125.97, 126.43, 126.42, 130.34 (Ar—CH and furan-CH), 134.26 (Ar—C), 140.96, 141.88 (furan-C-2, C-5), 156.47 (C-5′), 187.55 (C-1,3); ms *m*/*z*: 268 (M^+, 33), 240 (21), 145 (28), 104 (67), 95 (81), 77 (100), 65 (49); Anal. Calcd. for $C_{14}H_8N_2O_4$: C, 62.69; H, 3.01; N, 10.44. Found: C, 62.46; H, 2.94; N, 10.67.

5′-(Pyridin-2-yl)-3′*H*-spiro(indene-2,2′-[1,3,4]oxadiazole)-1,3-dione (5d). This compound was obtained as orange crystals (acetonitrile), mp 214–216°C, ir: NH 3330, CO 1715, C=N 1630, C—O—C 1095; ^{1}H NMR: δ 7.28–8.46 (m, 8H, Ar—H and pyridine-H), 12.50 (br, 1H, oxadiazole-NH); ^{13}C NMR: δ 103.55 (C-2,2′), 126.11, 126.47, 126.96, 130.54, 132.16 (Ar—CH and pyridine-CH), 134.71 (Ar—C), 147.93, 148.67 (pyridine-C2, C6), 156.79 (C-5′), 187.56 (C-1,3); ms *m/z*: 279 (M$^+$, 51), 251 (26), 145 (55), 106 (67), 104 (89), 78 (100), 77 (92), 65 (41); Anal. Calcd. for $C_{15}H_9N_3O_3$: C, 64.52; H, 3.25; N, 15.05. Found: C, 64.71; H, 3.36; N, 14.87.

5′-(1*H*-Indol-2-yl)-3′*H*-spiro(indene-2,2′-[1,3,4]oxadi-azole)-1,3-dione (5e). This compound was obtained as orange crystals (methanol), mp 283–285°C; ir: 3380-NH 3325, CO 1710, C=N 1630, C—O—C 1095; ^{1}H NMR: δ 6.61 (s, 1H, indole-H), 7.19–8.22 (m, 8H, Ar—H), 11.71 (br, 1H, indole-NH), 12.53 (br, 1H, oxadiazole-NH); ^{13}C NMR: δ 99.76 (indole-CH), 103.42 (C-2,2′), 122.87 (indole-CH-2), 125.88, 126.29, 126.44, 127.63, 128.41, 130.55 (Ar—CH), 132.77, 133.52, 134.89 (Ar—C), 156.36 (C-5′), 187.64 (C-1,3); ms *m/z*: 317 (M$^+$, 18), 289 (26), 144 (57), 145 (37), 116 (29), 104 (76), 91 (89), 77 (100), 65 (71); Anal. Calcd. for $C_{18}H_{11}N_3O_3$: C, 68.14; H, 3.49; N, 13.24. Found: C, 67.88; H, 3.36; N, 13.45.

1-Benzoyl-4-oxo-1,4-dihydroindeno[1,2-*c*]pyrazole-3-carbonitrile (6a). This compound was obtained as pale yellow crystals (acetonitrile), mp 273–275°C; ir: Ar—CH 3090, CN 2215, CO (1720, 1660), C=N 1620, Ar—C=C 1590; ^{1}H NMR: δ 7.31–8.21 (m, 9H, Ar—H); ^{13}C NMR: δ 105.12 (C-3a), 118.12 (CN), 121.75 (C-3), 126.76, 126.94, 127.85, 129.22, 130.12, 130.41 (Ar—CH), 132.18, 134.71 (Ar—C), 149.53 (C-8b), 167.54 (CO), 189.27 (C-4); ms *m/z*: 299 (M$^+$, 26), 273 (16), 245 (41), 140 (61), 105 (100), 104 (74), 77 (56), 65 (64); Anal. Calcd. for $C_{18}H_9N_3O_2$: C, 72.24; H, 3.03; N, 14.04. Found: C, 72.39; H, 2.89; N, 13.83.

4-Oxo-1-(thiophene-2-carbonyl)-1,4-dihydroindeno[1,2-*c*] pyrazole-3-carbonitrile (6b). This compound was obtained as pale yellow crystals (ethanol), mp 296–298°C; ir: Ar—CH 3105, CN 2220, CO (1715, 1665), C=N 1620, Ar—C=C 1590; ^{1}H NMR: δ 7.22–8.16 (m, 7H, Ar—H and thiophene-H); ^{13}C NMR: δ 104.96 (C-3a), 118.19 (CN), 121.71 (C-3), 126.75, 128.45, 129.97, 130.26, 130.54 (Ar—CH and thiophene-CH), 132.28 (Ar—C), 139.26 (thiophene-C), 149.67 (C-8b), 167.49 (CO), 189.34 (C-4); ms *m/z*: 305 (M$^+$, 22), 279 (19), 251 (46), 140 (41), 111 (100), 104 (83), 77 (69), 65 (59); Anal. Calcd. for $C_{16}H_7N_3O_2S$: C, 62.94; H, 2.31; N, 13.76; S, 10.50. Found: C, 63.19; H, 2.43; N, 13.54; S, 10.68.

1-(Furan-2-carbonyl)-4-oxo-1,4-dihydroindeno[1,2-*c*]-pyrazole-3-carbonitrile (6c). This compound was obtained as pale yellow crystals (ethanol), mp 265–267°C; ir: Ar—CH 3085, CN 2210, CO (1715, 1660), C=N 1615, Ar—C=C 1585, C—O—C 1085; ^{1}H NMR: δ 7.31–8.15 (m, 7H, Ar—H and furan-H); ^{13}C NMR: δ 105.09 (C-3a), 118.22 (CN), 121.68 (C-3), 125.94, 126.35, 128.90, 130.56 (Ar—C and furan-C), 141.18, 142.26 (furan-C-2, C-5), 149.74 (C-8b), 167.61 (CO), 189.28 (C-4); ms: *m/z* 289 (M$^+$, 39), 253 (22), 225 (32), 130 (29), 104 (74), 95 (81), 77 (100), 65 (61); $C_{16}H_7N_3O_3$: C, 66.44; H, 2.44; N, 14.53. Found: C, 66.27; H, 2.57; N, 14.71.

4-Oxo-1-picolinoyl-1,4-dihydroindeno[1,2-*c*]pyrazole-3-carbonitrile (6d). This compound was obtained as yellow crystals (acetonitrile), mp 284–286°C; ir: Ar—CH 3115, CN 2215, CO (1715, 1665), C=N 1620, Ar—C=C 1590; ^{1}H NMR: δ 7.28–8.49 (m, 8H, Ar—H and pyridine-H); ^{13}C NMR: δ 104.92 (C-3a), 118.12 (CN), 121.74 (C-3), 126.32, 126.53, 127.19, 127.44, 130.47, 132.22 (Ar—CH and pyridine-CH), 134.65 (Ar—C), 148.11, 148.72 (pyridine-C-2, C6), 149.79 (C-8b), 167.70 (CO), 189.29 (C-4); ms: *m/z* 300 (M$^+$, 28), 274 (9), 246 (19), 140 (38), 106 (100), 104 (91), 77 (83), 65 (54). Anal. Calcd. for $C_{17}H_8N_4O_2$: C, 68.00; H, 2.69; N, 18.66. Found: C, 67.78; H, 2.78; N, 18.83.

1-(1*H*-Indole-2-carbonyl)-4-oxo-1,4-dihydroindeno[1,2-*c*] pyrazole-3-carbonitrile (6e). This compound was obtained as yellow crystals (methanol), mp 311–313°C; ir: NH 3365, CN 2220, CO (1710, 1665), C=N 1625, Ar—C=C 1595; ^{1}H NMR: δ 6.64 (s, 1H, indole-H), 7.28–8.19 (m, 8H, Ar—H), 11.69 (br, 1H, indole-NH); ^{13}C NMR: δ 99.91 (indole-CH), 105.06 (C-3a), 118.19 (CN), 121.69 (C-3), 126.12, 126.22, 126.45, 126.86, 127.61, 128.22, 130.51 (Ar—CH), 132.69, 134.18, 134.87, 135.29 (Ar—C), 149.76 (C-8b), 167.72 (CO), 189.31 (C-4); ms: *m/z* 338 (M$^+$, 27), 312 (21), 284 (46), 144 (87), 140 (51), 104 (79), 91 (100), 77 (82), 65 (43); Anal. Calcd. for $C_{20}H_{10}N_4O_2$: C, 71.00; H, 2.98; N, 16.56. Found: C, 70.83; H, 3.11; N, 16.77.

Reaction of carbohydrazides 1a–e with 3. Carbohydrazides **1a–e** (1.0 mmol) were dissolved in 20 mL absolute ethanol with two drops of pipridine and added to the indolone **3** (1 mmol) in 25 mL absolute ethanol, the mixture was heated under reflux for 5 h (for runs **1a–c** with **3**), and 7 h (for runs **1d**,**e** with **3**), cooled to room temperature. Concentrated and subjected to PLC using toluene/ethyl acetate (4:1) to give numerous colored zones, the two intense of which were removed and extracted. The fastest migrating one contained substituted spiro(indoline-3,2′-[1,3,4]oxadiazol)-2-one **11a–e**, the second zone contained substituted carbonylpyrazolo[3,4-*b*]indole-3-carbonitrile **13a–e**. Extraction of the zones with acetone and crystallized.

5′-Phenyl-3′*H*-spiro(indoline-3,2′-[1,2,4]oxadiazol)-2-one (11a). This compound was obtained as yellow crystals (ethanol), mp 231–233°C; ir: NH's 3310–3380, CO 1710, C=N 1620, Ar and C=C 1600, C—O—C 1085; ^{1}H NMR: δ 7.22–7.82 (m, 9H, Ar—H), 9.89 (br, 1H, indolone-NH), 12.56 (br, 1H, oxadiazole-NH); ^{13}C NMR: δ 93.74 (C-3 = C-2′), 126.54, 127.17, 127.94, 128.76, 131.24, 132.16 (Ar—CH), 135.33, 138.19, 142.55 (Ar—C), 154.85 (C-5′), 177.98 (CO); ms: *m/z* 265 (M$^+$, 36), 237 (17), 132 (56), 119 (68), 105 (74), 91 (82), 77 (100), 65 (42); Anal. Calcd. for $C_{15}H_{11}N_3O_2$: C, 67.92; H, 4.18; N, 15.84. Found: C, 68.16; H, 4.02; N, 16.05.

5′-(Thiophen-2-yl)-3′*H*-spiro(indoline-3,2′-[1,2,4]oxadi-azol)-2-one (11b). This compound was obtained as yellow crystals (acetonitril), mp 259–261°C; ir: NH's 3330–3375, CO 1720, C=N 1625, Ar and C=C 1590, C—O—C 1080; ^{1}H NMR: δ 7.11–7.74 (m, 7H, Ar—H and thiophene-H), 9.93 (br, 1H, indolone-NH), 12.46 (br, 1H, oxadiazole-NH); ^{13}C NMR: δ 93.65 (C-3 = C-2′), 126.17, 127.37, 127.88, 129.17, 130.17, 131.44 (Ar—CH and thiophene-CH), 132.16, 137.95, 142.35 (Ar—C and thiophene-C), 155.12 (C-5′), 178.09 (CO); ms: *m/z* 271 (M$^+$, 37), 139 (42), 119 (25), 111 (100), 91 (63), 77 (87), 65 (56); Anal. Calcd. for $C_{13}H_9N_3O_2S$: C, 57.55; H, 3.34; N, 15.49; S, 11.82. Found: C, 57.77; H, 3.21; N, 15.26; S, 12.06.

5′-(Furan-2-yl)-3′*H*-spiro(indoline-3,2′-[1,2,4]oxadiazol)-2-one (11c). This compound was obtained as pale yellow crystals (ethanol), mp 218–219°C; ir: NH's 3315–3380, CO 1715, C=N 1620, Ar and C=C 1595, C—O—C 1085; ^{1}H NMR: δ 7.08–7.69 (m, 7H, Ar—H and furan-H), 9.90 (br, 1H, indolone-NH), 12.48 (br, 1H, oxadiazole-NH); ^{13}C NMR: δ 93.68 (C-3 = C-2′), 125.87, 126.82, 128.76, 129.97, 130.18 (Ar—CH and furan-CH), 132.76, 141.55, 141.96, 144.12 (Ar—C and furan-C-2, C-5), 155.29 (C-5′), 177.84 (CO); ms *m*/*z* 255 (M^+, 27), 227 (23), 142 (19), 119 (26), 85 (69), 91 (82), 77 (100), 65 (44); Anal. Calcd. for $C_{13}H_9N_3O_3$: C, 61.18; H, 3.55; N, 16.46. Found: C, 60.94; H, 3.64; N, 16.65.

5′-(Pyridin-2-yl)-3′*H*-spiro(indoline-3,2′-[1,2,4]oxadiazol)-2-one (11d). This compound was obtained as yellow crystals (acetonitril), mp 236–235°C; ir: NH's 3325–3380, CO 1725, C=N 1630, Ar and C=C 1600, C—O—C 1080; ^{1}H NMR: δ 7.24–8.46 (m, 8H, Ar—H and pyridine-H), 9.86 (br, 1H, indolone-NH), 12.49 (br, 1H, oxadiazole-NH); ^{13}C NMR: δ 93.75 (C-3 = C-2′), 126.26, 126.53, 127.79, 128.88, 130.16, 130.35 (Ar—CH and pyridine-CH), 132.19, 141.76 (Ar—C), 147.23, 148.89 (pyridine-C-2, C-6), 155.28 (C-5′), 178.05 (CO); ms: *m*/*z* 266 (M^+, 22), 160 (36), 132 (28), 119 (41), 106 (100), 91 (57), 77 (83), 65 (61); Anal. Calcd. for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04. Found: C, 62.92; H, 3.91; N, 20.88.

5′-(1H-Indol-2-yl)-3′*H*-spiro(indoline-3,2′-[1,2,4]oxadi-azol)-2-one (11e). This compound was obtained as orange crystals (methanol), mp 187–188°C; ir: NH's 3290–3370, CO 1720, C=N 1630, Ar and C=C 1605, C—O—C 1090; ^{1}H NMR: δ 6.57 (indole-CH), 7.02–7.74 (m, 8H, Ar—H), 9.81 (br, 1H, indolone-NH), 11.75 (br, 1H, indole-NH), 12.55 (br, 1H, oxadiazole-NH); ^{13}C NMR: δ 93.66 (C-3 = C-2′), 101.96 (indole-CH), 126.26, 127.53, 128.82, 129.96, 130.31, 130.45 (Ar—CH), 132.26, 135.26, 138.92, 141.22, 142.11 (Ar—C and indole-C-2), 154.89 (C-5′), 177.90 (CO); ms: *m*/*z* 304 (M^+, 33), 276 (31), 144 (28), 132 (26), 119 (54), 91 (100), 77 (67), 65 (41); Anal. Calcd. for $C_{17}H_{12}N_4O_2$: C, 67.10; H, 3.97; N, 18.41. Found: C, 66.87; H, 4.12; N, 18.18.

1-Benzoyl-1,2-dihydropyrazolo[3,4-*b*]indole-3-carbonitrile (13a). This compound was obtained as pale yellow crystals (methanol), mp 279–281°C; ir: NH 3410, CN 2210, CO 1665, C=N 1625, Ar and C=C 1590; ^{1}H NMR: δ 7.34–7.96 (m, 9H, Ar—H), 11.96 (br, 1H, pyrazole-NH); ^{13}C NMR: δ 101.86 (C-3a), 118.16 (CN), 126.37, 126.89, 128.85, 129.71, 130.16, 130.97, 132.12 (Ar—CH and C-3), 136.33, 138.91, 141.74, 142.23 (Ar—C), 150.33 (C-8a), 169.44 (CO); ms: *m*/*z* 286 (M^+, 54), 181 (37), 154 (42), 126 (18), 105 (62), 91 (75), 77 (100), 65 (64); Anal. Calcd. for $C_{17}H_{10}N_4O$: C, 71.32; H, 3.52; N, 19.57. Found: C, 71.55; H, 3.39; N, 19.35.

1-(Thiophene-2-carbonyl)-1,2-dihydropyrazolo[3,4-*b*]-indole-3-carbonitrile (13b). This compound was obtained as pale yellow crystals (acetonitrile), mp 295–297°C; ir: NH 3395, CN 2215, CO 1660, C=N 1630, Ar and C=C 1600; ^{1}H NMR: δ 7.23–7.90 (m, 7H, Ar—H and thiophene-H), 11.98 (br, 1H, pyrazole-NH); ^{13}C NMR: δ 102.05 (C-3a), 118.24 (CN), 126.56, 126.84, 128.33, 129.61, 130.23, 130.85, 132.26 (Ar—CH, thiophene-CH and C-3), 135.89, 142.33, 146.13 (Ar—C and thiophene-C-2), 149.98 (C-8a), 169.64 (CO); ms: *m*/*z* 292 (M^+, 28), 181 (12), 153 (31), 126 (24), 111 (100), 91 (47), 77 (63), 65 (55); Anal. Calcd. for $C_{15}H_8N_4OS$: C, 61.63; H, 2.76; N, 19.17; S, 11.16. Found: C, 61.84; H, 2.63; N, 18.91; S, 10.97.

1-(Furan-2-carbonyl)-1,2-dihydropyrazolo[3,4-*b*]indole-3-carbonitrile (13c). This compound was obtained as pale yellow crystals (ethanol), mp 261–263°C; ir: NH 3390, CN 2220, CO 1665, C=N 1625, Ar and C=C 1585, C—O—C 1090; ^{1}H NMR: δ 7.31–7.96 (m, 7H, Ar—H and furan-H), 11.95 (br, 1H, pyrazole-NH); ^{13}C NMR: δ 101.93 (C-3a), 117.97 (CN), 126.44, 128.57, 129.64, 130.26, 130.86, 132.42 (Ar—CH, furan-CH and C-3), 135.57, 141.84, 145.33, 147.87 (Ar—C and furan-C-2, C-5), 150.14 (C-8a), 169.36 (CO); ms: *m*/*z* 276 (M^+, 39), 181 (23), 154 (33), 126 (18), 95 (84), 91 (100), 77 (67), 65 (52); Anal. Calcd. for $C_{15}H_8N_4O_2$: C, 65.22; H, 2.92; N, 20.28. Found: C, 65.41; H, 3.05; N, 20.07.

1-Picolinyl-1,2-dihydropyrazolo[3,4-*b*]indole-3-carbonitrile (13d). This compound was obtained as yellow crystals (acetonitrile), mp 290–292°C; ir: NH 3405, CN 2220, CO 1655, C=N 1630, Ar and C=C 1610; ^{1}H NMR: δ 7.33–8.41 (m, 8H, Ar—H and pyridine-H), 11.93 (br, 1H, pyrazole-NH); ^{13}C NMR: δ 102.12 (C-3a), 118.27 (CN), 126.45, 127.44, 128.55, 129.79, 130.16, 131.26, 132.19 (Ar—CH, pyridine-CH and C-3), 135.76, 141.88 (Ar—C), 148.92, 150.12, 151.64 (pyridine-C-2, C-6 and C-8a), 169.77 (CO); ms: *m*/*z* 287 (M^+, 43), 181 (18), 154 (25), 126 (13), 106 (75), 91 (100), 77 (83), 65 (66); Anal. Calcd. for $C_{16}H_9N_5O$: C, 66.89; H, 3.16; N, 24.38. Found: C, 67.04; H, 3.02; N, 24.21.

1-(1*H*-Indole-2-carbonyl-1,2-dihydropyrazolo[3,4-*b*]indole-3-carbonitrile (13e). This compound was obtained as yellow crystals (methanol), mp 304–306°C; ir: NH's 3290–3415, CN 2215, CO 1660, Ar and C=C 1595; ^{1}H NMR: δ 6.62 (s, 1H, indole-H), 7.18–7.88 (m, 8H, Ar—H), 11.71 (br, 1H, indole-NH), 11.97 (br, 1H, pyrazole-NH); ^{13}C NMR: δ 101.94 (C-3a), 118.29 (CN), 123.87 (indole-CH), 126.37, 126.94, 128.54, 129.17, 130.29, 131.47, 132.31 (Ar—CH and C-3), 135.29, 138.77, 139.27, 140.81, 142.16 (Ar—C and indole-C-2), 149.93 (C-8a), 169.65 (CO); ms: *m*/*z* 325 (M^+, 46), 181 (27), 154 (28), 144 (86), 91 (92), 77 (100), 65 (55); Anal. Calcd. for $C_{19}H_{11}N_5O$: C, 70.15; H, 3.41; N, 21.53. Found: C, 69.93; H, 3.55; N, 21.31.

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1-Alkyl-2,3-dihydro-4(1*H*)-quinolinones by a Tandem Michael-S_NAr Annulation Reaction

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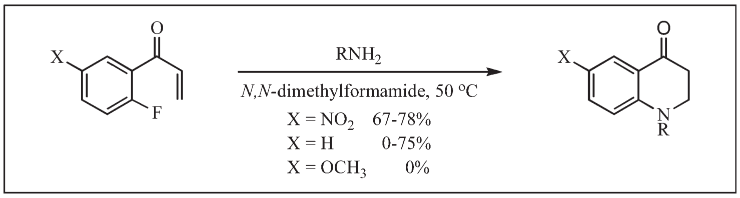

A tandem Michael-S_NAr annulation reaction has been developed for the synthesis of 1-alkyl-2,3-dihydro-4(1*H*)-quinolinones. Success in the reaction followed expected electronic effects for the final S_NAr ring closure. Treatment of doubly activated 1-(2-fluoro-5-nitrophenyl)-2-propen-1-one with primary amines in *N,N*-dimethylformamide at 50°C for 24 h provided 2,3-dihydro-4(1*H*)-quinolinones in 67–78% yields. Singly activated 1-(2-fluorophenyl)-2-propen-1-one reacted similarly, but failed to undergo the final ring closure with hindered or aromatic amines. Finally, 1-(2-fluoro-5-methoxyphenyl)-2-propen-1-one, with one activating and one deactivating group on the ring, gave only simple 1,4-addition products.

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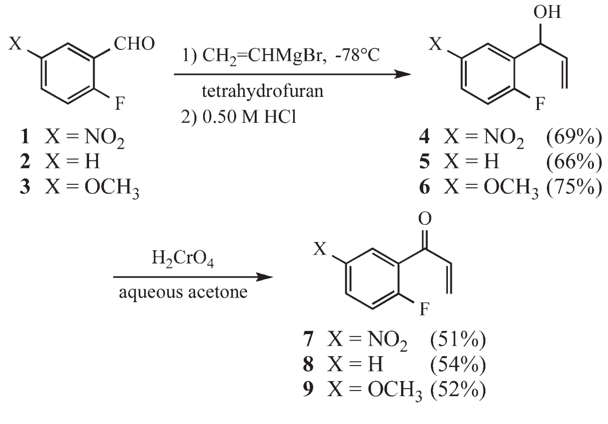
INTRODUCTION

Over the past several years, our work has led to a number of tandem cyclizations terminated by nucleophilic aromatic substitution reactions [2]. The current work extends these previous results to the preparation of 1-alkyl-2,3-dihydro-4(1*H*)-quinolinones by a sequential Michael-S_NAr process. Earlier approaches to these ring systems have involved Friedel-Crafts cyclizations of *N*-phenyl-β-alanine derivatives [3]; acid mediated ring opening-Friedel-Crafts reactions of 1-aryl-2-azetidinones [4]; acid or base promoted cyclizations of 2-aminochalcone derivatives [5]; or reaction of aromatic amines with iminium salts derived from reaction of *N,N*-dimethylacrylamide with trifluoromethanesulfonic anhydride [6]. These protocols gave modest to good yields, but generally subjected substrates to strongly acidic reagents. The current reaction provides a straightforward route to the title compounds in good yields under very mild reaction conditions. The target dihydroquinolinones are valuable building blocks for the synthesis of drugs used to treat pain [7], psychosis [8], and Alzheimer's disease [9] as well as several other medical afflictions [10].

RESULTS AND DISCUSSION

The synthesis of our cyclization substrates is shown in Scheme 1. The requisite aryl vinyl ketones were easily prepared in two steps from 2-fluoro-5-nitrobenzaldehyde (**1**) [11], 2-fluorobenzaldehyde (**2**), and 2-fluoro-5-methoxybenzaldehyde (**3**). Treatment of these aldehydes with vinylmagnesium bromide in tetrahydrofuran at −78°C gave alcohols **4**, **5**, and **6**, respectively. These alcohols were carried on directly to dihydroquinolinone precursors **7**, **8**, and **9** by Jones oxidation in 34–39% overall yields after chromatography [12].

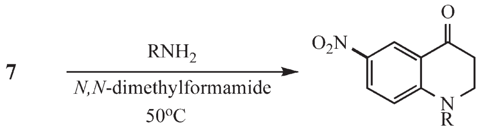
Scheme 1



In the planning stages, we anticipated that 1,4-addition to the unhindered side chain enone would precede nucleophilic attack on the aromatic ring. Because of this, however, bulky amines could pose a problem in the final S_NAr ring closure. Thus, precursor **7** was selected as our initial test case because this compound possessed two electron-withdrawing substituents positioned to facilitate the final ring-closing step. If the annulation proceeded

Table 1

Michael-S_NAr reaction of a doubly activated substrate.



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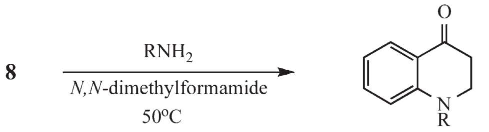
	R	Yield (%)
a	$C_6H_5CH_2$	69
b	$C_6H_5CH_2CH_2$	78
c	n-C_6H_{13}	67
d	i-$C_3H_7OCH_2CH_2CH_2$	75
e	i-C_4H_9	72
f	c-C_6H_{11}	77
g	t-C_4H_9	71
h	C_6H_5	72

Table 2

Michael-S_NAr reaction of a singly activated substrate.



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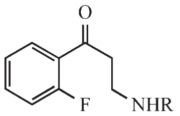
	R	Yield (%)
a	$C_6H_5CH_2$	61
b	$C_6H_5CH_2CH_2$	58
c	n-C_6H_{13}	74
d	i-$C_3H_7OCH_2CH_2CH_2$	70
e	i-C_4H_9	75
f	c-C_6H_{11}	54
g	t-C_4H_9	0[a]
h	C_6H_5	0[b]

[a] This reaction gave 3-(*tert*-butylamino)-1-(2-fluorophenyl)-1-propanone (**12a**) as the only product in 52% yield.

[b] This reaction gave 1-(2-fluorophenyl)-3-(phenylamino)-1-propanone (**12b**) as the only product in 65% yield.



12a R = t-C_4H_9
12b R = C_6H_5

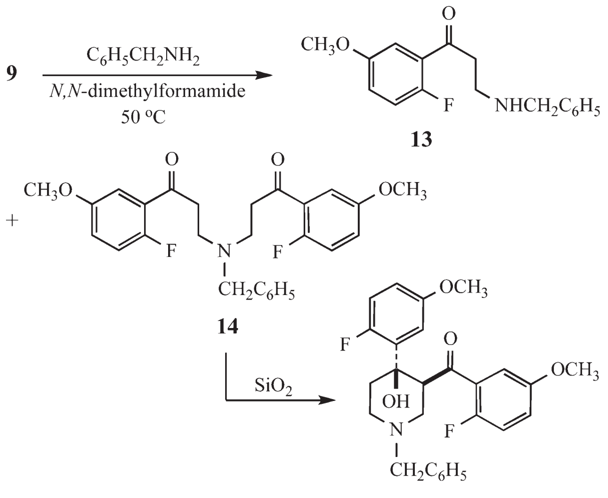
smoothly for **7**, we planned to further explore the scope of the reaction by studying compounds **8** and **9**, which vary the electronic nature of the aromatic moiety. Substrate **8** has a single activating group for the final S_NAr reaction; **9** has one activating and one deactivating group.

Experimentally, the Michael-S_NAr reaction was carried out by dissolving 1.00 equivalent of the aryl vinyl ketone in dry *N,N*-dimethylformamide, adding 1.25 equivalents of the amine and heating for 24 h at 50°C. Following workup, the products were easily isolated and purified by chromatography to give the target heterocycles in good yields. The use of *N,N*-dimethylformamide as the solvent was critical to the success of the reaction; methanol gave complex product mixtures and was not useful.

The results of our cyclization studies are summarized in Tables 1 and 2. Doubly activated substrate **7** reacted with α-branched as well as unbranched and aryl primary amines to give dihydroquinolinones in 67–78% yields. Singly activated precursor **8** was successful in most cases, but failed to cyclize with sterically hindered amines such as *tert*-butylamine and deactivated amines such as aniline. The methoxy-bearing substrate **9** afforded products derived only from 1,4-addition without the subsequent ring closure. Thus, under our standard conditions with benzylamine, **9** gave the expected 1:1 Michael adduct **13** in 12% yield (Scheme 2). More surprisingly, however, the reaction also produced piperidinol **15** in 42% yield. This product presumably arose from silica gel-promoted aldol ring closure of the 2:1 Michael adduct **14** during chromatography. Indeed, ^1H NMR analysis of the crude reaction mixture revealed that **14** was present before purification. The structure of **15** was deduced from spectral analysis and by comparison to calculated ^1H and ^{13}C NMR spectra [13], but the stereochemical assignment is tentative. The indicated relative stereochemistry places both aryl moieties in equatorial positions and allows hydrogen bonding between the C1 alcohol and the side chain carbonyl.

Thus, for success in the two-reaction sequence, the substrate must possess at least one electron-withdrawing group ortho or para to fluorine on the aromatic ring. Substrates incorporating an electron-donating group on the ring (even in the presence of a second withdrawing

Scheme 2



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substituent) fail to undergo the final ring closure. Additionally, the reacting partner must be an alkyl or aryl primary amine. Secondary amines give only complex product mixtures containing low yields of the 1,4-adduct.

The mechanism of dihydroquinolinone formation involves sequential Michael addition to the side chain enone followed by $\mathrm{S_NAr}$ ring closure. The fact that hindered and deactivated amines react with **8** to afford only the simple 1,4-addition product confirms this reaction sequence. Uncyclized structures resulting from an initial $\mathrm{S_NAr}$ reaction with the aromatic ring are not observed, nor are products resulting from attack at the carbonyl.

CONCLUSION

We have developed a new approach to the synthesis of 1-alkyl-2,3-dihydro-4(1*H*)-quinolinones based on a novel tandem Michael addition-$\mathrm{S_NAr}$ reaction. The required substrates are easily prepared in two steps from readily available precursors. The sequence gives good yields of the target ring system from substrates having either one or two electron withdrawing groups ortho or para to fluorine on the aromatic ring. Systems having one activating group are slightly less reactive while those incorporating an electron donating group give only Michael adducts and fail to close the final ring. We are pursuing further studies of this annulation procedure in systems bearing alkyl groups at the β-carbon of the Michael acceptor.

EXPERIMENTAL

All reactions were run under dry nitrogen. Vinylmagnesium bromide (1*M* in tetrahydrofuran) was purchased from Aldrich Chemical Company. *N*,*N*-Dimethylformamide from a freshly opened bottle was stored over 4 Å molecular sieves and syringed into reactions where it was used. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech 21521) with ultraviolet detection. The 0.5*M* hydrochloric acid, saturated sodium bisulfite, saturated sodium chloride, and 0.1*M* sodium hydroxide used in workup procedures were aqueous solutions. Preparative separations were performed by one of the following methods: (1) flash column chromatography [14] on silica gel (grade 62, 60–200 mesh) containing ultraviolet-active phosphor (Sorbent Technologies UV-5) packed into quartz columns or (2) preparative thin layer chromatography on 20-cm × 20-cm silica gel GF plates (Analtech 02015). Band elution for both methods was monitored using a hand-held ultraviolet lamp. Hexanes used in chromatography had a boiling range of 65–70°C. Melting points were uncorrected. Infrared spectra were run as thin films on sodium chloride disks and referenced to polystyrene. ^{1}H and ^{13}C Nuclear magnetic resonance spectra were measured in deuteriochloroform at 300 MHz and 75 MHz, respectively, using tetramethylsilane as the internal standard; coupling constants (*J*) are given in Hertz. Unless otherwise indicated, mass spectra (electron impact/direct probe) were obtained at 70 eV.

Representative procedure for the addition of vinylmagnesium bromide: (±)-1-(2-Fluoro-5-nitrophenyl)-2-propen-1-ol (4). The general procedure of Danishefsky and coworkers was used [11]. To a −78°C solution of 4.00 g (23.7 mmoles) of **1** [11] in 75 mL of anhydrous tetrahydrofuran was added 35.6 mL of 1*M* vinylmagnesium bromide in tetrahydrofuran (35.6 mmoles). The reaction mixture was stirred for 3.5 h at −78°C, then quenched by addition of 50 mL of 0.5*M* hydrochloric acid and ether extracted (three times). The combined ether extracts were washed with water (three times), saturated sodium chloride (one time), dried (magnesium sulfate), and concentrated under vacuum to give 3.09 g (66%) of **4** as a brown oil. This product was spectroscopically pure and was used without further purification. IR: 3382, 1530, 1353, 1254 cm^{-1}; ^{1}H NMR: δ 8.44 (dd, 1H, J = 6.1, 2.9), 8.18 (ddd, 1H, J = 9.0, 4.4, 2.9), 7.18 (t, 1H, J = 9.0), 6.02 (ddd, 1H, J = 17.2, 10.3, 6.0), 5.55 (d, 1H, J = 6.0), 5.43 (d, 1H, J = 17.2), 5.28 (d, 1H, J = 10.3), 2.53 (br s, 1H); ^{13}C NMR: δ 163.1 (d, J = 257.9), 144.7, 137.7, 131.8 (d, J = 16.0), 125.0 (d, J = 10.3), 123.8 (d, J = 6.6), 116.7, 116.4 (d, J = 24.6), 68.5 (d, J = 2.3); ms (30 eV): *m*/*z* 197 (M^{+}). Anal. Calcd. for $C_9H_8FNO_3$: C, 54.82; H, 4.06; N, 7.11. Found: C, 54.89; H, 4.10; N, 7.02.

(±)-1-Phenyl-2-propen-1-ol (5). This compound (3.10 g, 69%) was prepared as above from 3.66 g (29.6 mmoles) of **2** and 30 mL of 1*M* vinylmagnesium bromide (30.0 mmoles). It was used without further purification. IR: 3363, 1228 cm^{-1}; ^{1}H NMR: δ 7.43 (td, 1H, J = 7.4, 1.6), 7.25 (m, 1H), 7.14 (td, 1H, J = 7.6, 1.0), 7.02 (ddd, 1H, J = 10.3, 8.2, 1.0), 6.06 (ddd, 1H, J = 17.2, 10.3, 5.5), 5.50 (d, 1H, J = 5.5), 5.34 (d, 1H, J = 17.2), 5.19 (dd, 1H, J = 10.3, 1.2), 2.47 (br s, 1H); ^{13}C NMR: δ 159.9 (d, J = 246.6), 138.8, 129.6, (d, J = 13.3), 129.2, (d, J = 8.1), 127.6 (d, J = 3.7), 124.3 (d, J = 3.7), 115.3 (d, J = 22.1), 115.3, 69.1 (d, J = 2.9); ms (30 eV): *m*/*z* 152 (M^{+}). Anal. Calcd. for C_9H_9FO: C, 71.05; H, 5.92. Found: C, 71.08; H, 5.93.

(±)-1-(2-Fluoro-5-methoxyphenyl)-2-propen-1-ol (6). This compound (2.21 g, 75%) was prepared as above from 2.50 g (16.2 mmoles) of **3** and 24.5 mL of 1*M* vinylmagnesium bromide (24.5 mmoles). It was used without further purification. IR: 3402, 2839, 1272 cm^{-1}; ^{1}H NMR: δ 6.97 (m, 1H), 6.95 (t, 1H, J = 9.0), 6.76 (ddd, 1H, J = 9.0, 3.8, 3.3), 6.05 (ddd, 1H, J = 16.4, 10.0, 5.5), 5.48 (d, 1H, J = 5.5), 5.35 (dd, 1H, J = 17.3, 0.8), 5.20 (dt, 1H, J = 1.0, 1.1), 3.78 (s, 3H), 2.27 (br s, 1H); ^{13}C NMR: δ 155.8, 154.3 (d, J = 238.8), 138.7, 130.3 (d, J = 14.9), 115.9 (d, J = 23.5), 115.4, 114.2 (d, J = 8.3), 112.2 (d, J = 4.0), 69.2, 55.7; ms (30 eV): *m*/*z* 182 (M^{+}). Anal. Calcd. for $C_{10}H_{11}FO_2$: C, 65.93; H, 6.04. Found: C, 66.01; H, 6.10.

Representative procedure for oxidation to the enone: 1-(2-Fluoro-5-nitrophenyl)-2-propen-1-one (7). The general procedure of Danishefsky and coworkers was used [12]. To a solution of 3.09 g (15.7 mmoles) of **4** in 30 mL of acetone was added 8.10 mL of freshly prepared Jones reagent (*ca.*, 2.9*M*, 23.5 mmoles) [15]. After 15 min, 37.5 mL of ice water was added followed by 7.5 mL of saturated sodium bisulfite and the resulting mixture was extracted with ether (four times). The combined ether extracts were washed with water (three times), saturated sodium chloride (one time), dried (magnesium sulfate), and concentrated under vacuum. The resulting yellow oil was flash chromatographed on a 40 cm × 2.5 cm silica gel column eluted with 5–15% ether in hexanes to give 1.57 g (51%) of **7** as a light yellow oil that crystallized on standing, mp 50–52°C. IR: 1673, 1530, 1349, 1251 cm^{-1}; ^{1}H NMR: δ 8.65 (dd, 1H, J = 6.1, 2.9), 8.42 (ddd, 1H, J = 9.0, 4.1, 2.9), 7.35 (t, 1H, J = 9.0), 7.01 (ddd, 1H, J = 17.2, 10.3, 3.0), 6.45 (dt, 1H, $J = 17.2, 1.2$), 6.06 (dd, 1H, $J = 10.3, 1.2$); ^{13}C NMR: δ 187.1 (d, $J = 2.9$), 164.1 (d, $J = 264.3$), 144.4, 134.4 (d, $J = 5.9$), 132.2, 129.0 (d, $J = 11.0$), 127.0 (d, $J = 16.2$), 127.0 (d, $J = 5.2$), 118.0 (d, $J = 25.8$); ms (30 eV): *m/z* 195. Anal. Calcd. for $C_9H_6FNO_3$: C, 55.38; H, 3.08; N, 7.18. Found: C, 55.44; H, 3.11; N, 7.15.

1-Phenyl-2-propen-1-one (8). This compound was prepared as a colorless oil from 3.10 g (20.3 mmoles) of **5** and 10.5 mL of freshly prepared Jones reagent (*ca.*, 2.9*M*, 30.4 mmoles) [15]. The crude product was flash chromatographed on a 40 cm × 2.5 cm silica gel column eluted with 5% ether in hexanes to give 1.64 g (54%) of **8** as a colorless oil. IR: 1673, 1276 cm^{-1}; ^{1}H NMR: 7.75 (td, 1H, $J = 7.4, 1.8$), 7.51 (m, 1H), 7.24 (td, 1H, $J = 7.6, 1.0$), 7.14 (ddd, 1H, $J = 10.7, 8.4, 1.0$), 7.02 (ddd, 1H, $J = 17.2, 10.4, 3.1$), 6.39 (dt, 1H, $J = 17.2, 1.6$), 5.92 (dd, 1H, $J = 10.4, 1.6$); ^{13}C NMR: δ 189.6, 161.2 (d, $J = 254.0$), 135.5 (d, $J = 5.9$), 134.1 (d, $J = 8.8$), 130.9 (d, $J = 2.9$), 130.2, 128.3, 124.4 (d, $J = 2.9$), 116.5 (d, $J = 22.8$); ms (30 eV): *m/z* 150 (M$^+$). Anal. Calcd. for C_9H_7FO: C, 72.00; H, 4.67. Found: C, 72.04; H, 4.69.

1-(2-Fluoro-5-methoxyphenyl)-2-propen-1-one (9). This compound was prepared from 2.21 g (12.1 mmoles) of **6** and 6.86 mL of freshly prepared Jones reagent (*ca.*, 2.9*M*, 19.9 mmoles) [15]. The crude product was flash chromatographed on a 40 cm × 2.5 cm silica gel column eluted with 5% ether in hexanes to give 1.14 g (52%) of **9** as a colorless oil. IR: 2840, 1671, 1273 cm^{-1}; ^{1}H NMR: δ 7.24 (m, 1H), 7.10–6.99 (complex, 3H), 6.41 (dt, 1H, $J = 17.0, 1.6$), 5.91 (dd, 1H, $J = 10.4, 1.6$), 3.82 (s, 3H); ^{13}C NMR: δ 189.2, 155.9 (d, $J = 246.8$), 155.8, 135.4 (d, $J = 7.2$), 130.1, 126.3 (d, $J = 15.9$), 120.8 (d, $J = 8.6$), 117.4 (d, $J = 25.4$), 113.6 (d, $J = 2.9$), 55.9; ms (30 eV): *m/z* 180 (M$^+$). Anal. Calcd. for $C_{10}H_9FO_2$: C, 66.67; H, 5.00. Found: C, 66.71; H, 5.03.

Representative procedure for the tandem Michael-S$_N$Ar reaction using 7: 1-Benzyl-6-nitro-4(1*H*)-quinolinone (10a). To a solution of 78 mg (0.4 mmoles) of **5** in 3 mL of anhydrous *N,N*-dimethylformamide was added 53.5 mg (0.055 mL, 0.5 mmoles) of benzylamine and the solution was heated at 50°C for 22 h. The reaction mixture was cooled and added to 25 mL of saturated sodium chloride and extracted with ether (three times). The combined ether extracts were washed with water (one time), saturated sodium chloride (one time), dried (magnesium sulfate), and concentrated under vacuum to afford a dark yellow oil. The product was purified on a 20-cm × 20-cm preparative thin layer chromatography plate using 50–70% ether in hexanes to afford 78 mg (69%) of **7a** as a yellow solid, mp 118–121°C. IR: 1686, 1513, 1314 cm^{-1}; ^{1}H NMR: δ 8.77 (d, 1H, $J = 2.7$), 8.11 (dd, 1H, $J = 9.5, 2.7$), 7.43–7.28 (complex, 3H), 7.25 (d, 2H, $J = 7.0$), 6.74 (d, 1H, $J = 9.5$), 4.72 (s, 2H), 3.77 (t, 2H, $J = 7.1$), 2.83 (t, 2H, $J = 7.1$); ^{13}C NMR: δ 191.2, 154.5, 138.3, 135.2, 130.0, 129.2, 128.0, 126.5, 125.1, 118.1, 113.3, 55.4, 49.0, 37.1; ms: *m/z* 191 (M$^+$-C$_7$H$_7$). Anal. Calcd. for $C_{16}H_{14}N_2O_3$: C, 68.09; H, 4.96; N, 9.93. Found: C, 68.05; H, 4.95; N, 9.96.

6-Nitro-1-(2-phenylethyl)-4(1*H*)-quinolinone (10b). This compound (92 mg, 78%) was isolated as a yellow solid, mp 96–99°C. IR: 1687, 1517, 1317 cm^{-1}; ^{1}H NMR: δ 8.74 (s, 1H), 8.17 (d, 1H, $J = 9.2$), 7.38–7.18 (complex, 5H), 6.73 (d, 1H, $J = 9.2$), 3.76 (t, 2H, $J = 6.8$), 3.49 (t, 2H, $J = 7.0$), 2.98 (t, 2H, $J = 7.0$), 2.59 (t, 2H, $J = 7.0$); ^{13}C NMR: δ 191.3, 153.7, 137.9, 137.6, 129.9, 128.9, 128.7, 127.1, 125.4, 117.9, 112.5, 53.8, 49.2, 36.7, 33.2; ms: *m/z* 205 (M$^+$-C$_7$H$_7$). Anal. Calcd. for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.41; N, 9.46. Found: C, 68.94; H, 5.40; N, 9.49.

1-Hexyl-6-nitro-4(1*H*)-quinolinone (10c). This compound (74 mg, 67%) was isolated as a yellow oil. IR: 1688, 1515, 1317 cm^{-1}; ^{1}H NMR: δ 8.73 (d, 1H, $J = 2.7$), 8.17 (dd, 1H, $J = 9.4, 2.7$), 6.71 (d, 1H, $J = 9.4$), 3.68 (t, 2H, $J = 7.0$), 3.48 (t, 2H, $J = 7.4$), 2.76 (t, 2H, $J = 7.0$), 1.68 (quintet, 2H, $J = 7.4$), 1.41–1.33 (complex, 6H), 0.91 (t, 3H, $J = 6.8$); ^{13}C NMR: δ 191.3, 154.1, 137.4, 129.9, 125.3, 117.8, 112.6, 52.1, 48.7, 36.9, 31.5, 26.6 (2C), 22.5, 13.9; ms: *m/z* 205 (M$^+$-C$_5$H$_{11}$). Anal. Calcd. for $C_{15}H_{20}N_2O_3$: C, 65.21; H, 7.25; N, 10.14. Found: 65.34; 7.29; N, 10.06.

1-(3-Isopropoxypropyl)-6-nitro-4(1*H*)-quinolinone (10d). This compound (88 mg, 75%) was isolated as a yellow oil. IR: 1687, 1516, 1317 cm^{-1}; ^{1}H NMR: δ 8.70 (d, 1H, $J = 2.7$), 8.14 (dd, 1H, $J = 9.4, 2.7$), 6.84 (d, 1H, $J = 9.4$), 3.71 (t, 2H, $J = 7.0$), 3.63 (t, 2H, $J = 7.1$), 3.57 (septet, 1H, $J = 6.1$), 3.50 (t, 2H, $J = 6.0$), 2.75 (t, 2H, $J = 7.0$), 1.92 (quintet, 2H, $J = 7.0$), 1.18 (d, 6H, $J = 6.1$); ^{13}C NMR: δ 191.4, 154.3, 137.4, 129.8, 125.2, 117.7, 112.9, 71.8, 64.4, 48.9, 48.5, 36.9, 27.4, 22.0 (2C); ms: *m/z* 205 (M$^+$-C$_5$H$_{11}$O). Anal. Calcd. for $C_{15}H_{20}N_2O_4$; C, 61.64; H, 6.85; N, 9.59. Found: C, 61.76; H, 6.89; N, 9.53.

1-Isobutyl-6-nitro-4(1*H*)-quinolinone (10e). This compound (72 mg, 72%) was isolated as a yellow solid, mp 102–104°C. IR: 1686, 1520, 1315 cm^{-1}; ^{1}H NMR: δ 8.73 (d, 1H, $J = 2.7$), 8.14 (dd, 1H, $J = 9.4, 2.7$), 6.71 (d, 1H, $J = 9.4$), 3.71 (t, 2H, $J = 7.0$), 3.28 (d, 2H, $J = 7.4$), 2.76 (t, 2H, $J = 7.0$), 2.13 (nonet, 1H, $J = 6.6$), 1.04 (d, 6H, $J = 6.6$); ^{13}C NMR: δ 191.3, 154.4, 137.3, 129.8, 125.3, 117.6, 112.7, 59.6, 49.5, 36.8, 27.4, 20.3, 20.2; ms: *m/z* 205 (M$^+$-C$_3$H$_7$). Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.90; H, 6.45; N, 11.29. Found: C, 62.94; H, 6.45; N, 11.26.

1-Cyclohexyl-6-nitro-4(1*H*)-quinolinone (10f). This compound (84 mg, 77%) was isolated as a yellow solid, mp 174–177°C. IR: 1688, 1504, 1316 cm^{-1}; ^{1}H NMR: δ 8.77 (d, 1H $J = 2.5$), 8.16 (dd, 1H, $J = 9.5, 2.5$), 6.86 (d, 1H, $J = 9.5$), 3.81 (tt, 1H, $J = 11.5, 3.3$), 3.60 (d, 2H, $J = 7.0$), 2.70 (d, 2H, $J = 7.0$), 1.91 (m, 4H), 1.78 (m, 1H), 1.58 (m, 2H), 1.45 (m, 2H), 1.21 (m, 1H); ^{13}C NMR: δ 191.6, 154.3, 137.4, 129.9, 12.57, 118.5, 112.6, 57.4, 41.2, 37.3, 30.0 (2C), 25.8 (2C), 25.4; ms: *m/z* 274 (M$^+$). Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.69; H, 6.57; N, 10.22. Found: C, 65.70; H, 6.56; N, 10.20.

1-*tert*-Butyl-6-nitro-4(1*H*)-quinolinone (10g). This compound (70 mg, 71%) was isolated as a yellow solid, mp 132–134°C. IR: 1688, 1499, 1317 cm^{-1}; ^{1}H NMR: δ 8.81 (d, 1H, $J = 2.9$), 8.13 (dd, 1H, $J = 9.6, 2.9$), 7.19 (d, 1H, 9.6), 3.73 (t, 2H, $J = 6.6$), 2.70 (t, 2H, $J = 6.6$), 1.61 (s, 9H); ^{13}C NMR: δ 192.5, 155.2, 137.9, 127.9, 125.5, 121.2, 117.5, 57.7, 44.2, 38.9, 29.6 (3C); ms: *m/z* 233 (M$^+$-CH$_3$). Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.90; H, 6.45; N, 11.29. Found: C, 62.93; H, 6.44; N, 11.27.

6-Nitro-1-phenyl-4(1*H*)-quinolinone (10h). This compound (77 mg, 72%) was isolated as a yellow solid, mp 126–128°C. IR: 1688, 1498, 1314 cm^{-1}; ^{1}H NMR: δ 8.80 (d, 1H, $J = 2.7$), 8.00 (dd, 1H, $J = 9.4, 2.7$), 7.54 (t, 2H, $J = 7.5$), 7.41 (t, 1H, $J = 7.4$), 7.30 (d, 2H, $J = 7.4$), 6.59 (d, 1H, $J = 9.4$), 4.03 (t, 2H, $J = 6.9$), 2.93 (t, 2H, $J = 7.0$); ^{13}C NMR: δ 191.1, 154.5, 144.0, 138.9, 130.5, 129.3, 127.9, 126.1, 125.0, 118.4, 115.4, 50.6, 37.4; ms: *m*/*z* 268 (M^+). Anal. Calcd. for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.48; N, 10.45. Found: C, 67.18; H, 4.47; N, 10.42.

Representative procedure for the tandem Michael-S_NAr reaction using 8: 1-Benzyl-4(1*H*)-quinolinone (11a). This reaction was run using 75 mg (0.50 mmoles) of **8** and the general procedure given above for the preparation of **10a**. This compound (72 mg, 61%) was isolated as a light yellow solid, mp 111–114°C [16]. IR: 1673 cm^{-1}; ^1H NMR δ 7.93 (dd, 1H, *J* = 7.8, 1.8), 7.39–7.24 (complex, 6H), 6.72 (t, 1H, *J* = 8.0), 6.70 (d, 1H, *J* = 8.4), 4.57 (s, 2H), 3.60 (t, 2H, *J* = 7.0), 2.75 (t, 2H, *J* = 7.0); ^{13}C NMR: δ 193.5, 151.7, 137.2, 135.5, 128.8, 128.2, 127.4, 126.7, 119.8, 117.0, 113.4, 55.2, 49.4, 38.0; ms: *m*/*z* 146 (M^+-C_7H_7). Anal. Calcd. for $C_{16}H_{15}NO$: C, 81.01; H, 6.33; N, 5.91. Found: C, 80.97; H, 6.35; N, 5.89.

1-(2-Phenylethyl)-4(1*H*)-quinolinone (11b). This compound (73 mg, 58%) was isolated as a yellow oil. IR: 1673 cm^{-1}; ^1H NMR δ 7.91 (dd, 1H, *J* = 7.8, 1.8), 7.39 (ddd, 1H, *J* = 8.6, 7.2, 1.8), 7.36–7.18 (complex, 5H), 6.78 (d, 1H, *J* = 8.6), 6.71 (t, 1H, *J* = 7.2), 3.61 (t, 2H, *J* = 7.5), 3.41 (t, 2H, *J* = 7.0), 2.91 (t, 2H, *J* = 7.5), 2.59 (t, 2H, *J* = 7.0); ^{13}C NMR: δ 193.5, 150.8, 138.9, 135.4, 128.7, 128.6, 128.4, 126.5, 119.6, 116.4, 112.7, 53.3, 49.4, 37.7, 32.7; ms: *m*/*z* 160 (M^+-C_7H_7). Anal. Calcd. for $C_{17}H_{17}NO$: C, 81.27; H, 6.77; N, 5.58. Found: C, 81.21; H, 6.74; N, 5.62.

1-Hexyl-4(1*H*)-quinolinone (11c). This compound (90 mg, 78%) was isolated as a yellow oil. IR: 1677 cm^{-1}; ^1H NMR: δ 7.89 (dd, 1H, *J* = 7.8, 1.8), 7.35 (ddd, 1H, *J* = 8.6, 7.0, 1.8), 6.70 (d, 1H, *J* = 8.6), 6.67 (t, 1H, *J* = 7.8), 3.51 (t, 2H, *J* = 7.0), 3.34 (t, 2H, *J* = 7.6), 2.68 (t, 2H, *J* = 7.0), 1.61 (quintet, 2H, *J* = 7.6), 1.34 (m, 6H), 0.90 (distorted t, 3H, J = 6.8); ^{13}C NMR: δ 193.5, 151.4, 135.3, 128.3, 119.5, 116.1, 112.8, 51.5, 49.0, 37.8, 31.6, 26.8, 26.1, 22.6, 14.0; ms: *m*/*z* 160 (M^+-C_5H_{11}). Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.92; H, 9.09; N, 6.06. Found: C, 77.81; H, 9.04; N, 6.12.

1-(3-Isopropoxypropyl)-4(1*H*)-quinolinone (11d). This compound (86 mg, 70%) was isolated as a yellow oil. IR: 1674 cm^{-1}; ^1H NMR: δ 7.89 (dd, 1H, *J* = 7.8, 1.8), 7.35 (ddd, 1H, *J* = 8.5, 7.0, 1.8), 6.78 (d, 1H, *J* = 8.5), 6.67 (ddd, 1H, *J* = 7.8, 7.0, 1.8), 3.61–3.45 (complex, 7H), 2.68 (t, 2H, *J* = 7.0), 1.86 (quintet, 2H, *J* = 6.1), 1.17 (d, 6H, *J* = 6.1); ^{13}C NMR: δ 193.5, 151.4, 135.3, 128.2, 119.5, 116.2, 113.0, 71.6, 65.0, 49.1, 48.4, 37.8, 27.2, 22.1 (2C); ms: *m*/*z* 160 (M^+-$C_5H_{11}O$). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.87; H, 8.50; N, 5.67. Found: C, 72.96; H, 8.54; N, 5.64.

1-Isobutyl-4(1*H*)-quinolinone (11e). This compound (76 mg, 75%) was isolated as a yellow oil. IR: 1677 cm^{-1}; ^1H NMR δ 7.89 (dd, 1H, *J* = 7.8, 1.8), 7.34 (ddd, 1H, *J* = 8.6, 7.0, 1.8), 6.68 (d, 1H, *J* = 8.8), 6.67 (t, 1H, *J* = 7.8), 3.54 (t, 2H, *J* = 7.0), 3.10 (d, 2H, *J* = 7.4), 2.68 (t, 2H, *J* = 7.0), 2.07 (nonet 1H, *J* = 6.8), 1.01 (d, 6H, *J* = 6.6); ^{13}C NMR: δ 193.5, 151.7, 135.3, 128.3, 119.2, 116.0, 112.7, 59.6, 50.0, 37.8, 27.4, 20.4 (2C); ms: *m*/*z* 160 (M^+-C_3H_7). Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.85; H, 8.37; N, 6.90. Found: C, 76.90; H, 8.40; N, 6.83.

1-Cyclohexyl-4(1*H*)-quinolinone (11f). This compound (62 mg, 54%) was isolated as a yellow oil. IR: 1674 cm^{-1}; ^1H NMR δ 7.92 (dd, 1H, *J* = 7.8, 1.8), 7.35 (ddd, 1H, *J* = 8.6, 7.0, 1.8), 6.83 (d, 1H, *J* = 8.8), 6.67 (t, 1H, *J* = 7.8), 3.68 (tt, 1H, *J* = 11.1, 3.1), 3.43 (t, 2H, *J* = 7.0), 2.62 (t, 2H, *J* = 7.0), 1.85 (m, 4H), 1.74 (m, 1H), 1.45 (m, 4H), 1.15 (m, 1H); ^{13}C NMR: δ 193.9, 151.6, 135.3, 128.6, 120.1, 116.1, 112.7, 56.0, 41.5, 38.3, 29.8 (2C), 26.1 (2C), 25.7; ms: *m*/*z* 229 (M^+). Anal. Calcd for $C_{15}H_{19}NO$: C, 78.60; H, 8.30; N, 6.11. Found: C, 78.54; H, 8.34; N, 6.04.

3-(*tert*-Butylamino)-1-(2-fluorophenyl)-1-propanone (12a). This compound (58 mg, 52%) from *tert*-butylamine and **8** was isolated as a yellow oil. To prevent extraction of the product into the aqueous layer during workup, the reaction was diluted with water and made slightly basic with 0.1*M* NaOH before extraction with ether. Attempts to purify this material by chromatography resulted in extensive decomposition, and thus, characterization was carried out on the crude product. IR: 3454, 1685, 1269 cm^{-1}; ^1H NMR: δ 7.87 (td, 1H, *J* = 7.6, 1.8), 7.50 (m, 1H), 7.22 (t, 1H, *J* = 7.8), 7.12 (dd, 1H, *J* = 11.2, 8.0), 3.20 (td, 2H, *J* = 6.2, 3.3), 2.96 (t, 2H, *J* = 6.2), 1.71 (br s, 1H), 1.13 (s, 9H); ^{13}C NMR: δ 198.1, 162.0 (d, *J* = 254.7), 134.5 (d, *J* = 8.8), 130.5 (d, *J* = 2.9), 130.4, 124.4 (d, *J* = 3.4), 116.7 (d, *J* = 24.2), 50.5, 44.7 (d, *J* = 7.4), 37.3 (d, *J* = 2.2), 28.9 (3C); ms: *m*/*z* 123 (M^+-$C_6H_{14}N$).

1-(2-Fluorophenyl)-3-(phenylamino)-1-propanone (12b). This compound (79 mg, 65%) from aniline and **8** was isolated as a yellow solid, mp 69–71°C. IR: 3405, 1683, 1264 cm^{-1}; ^1H NMR: δ 7.88 (td, 1H, *J* =7.8, 1.8), 7.50 (m, 1H), 7.25–7.08 (complex, 5H), 6.70 (t, 1H, *J* = 7.2), 6.64 (dd, 1H, *J* = 7.6, 1.0), 4.09 (br s, 1H), 3.58 (t, 2H, *J* = 6.1), 3.28 (m, 2H); ^{13}C NMR: δ 197.4, 162.1 (d, *J* = 254.7), 147.7, 134.8 (d, *J* = 8.8), 130.5 (d, *J* = 2.2), 129.3, 124.5 (d, *J* = 3.7), 117.5, 116.8, 116.6 (d, *J* = 11.8), 112.9, 42.8, 38.5; ms: *m*/*z* 123 (M^+-$C_8H_{10}N$). Anal. Calcd. for $C_{15}H_{14}FNO$: C, 74.07; H, 5.76; N, 5.76. Found: C, 73.98; H, 5.79; N, 5.70.

Representative procedure for the tandem Michael-S_NAr reaction using 9: 1-(2-Fluoro-5-methoxyphenyl)-3-(benzylamino)-1-propanone (13) and (±)-(3*S,4*R**)-1-benzyl-3-(2-fluoro-5-methoxybenzoyl)-4-(2-fluoro-5-methoxyphenyl)-4-piperidinol (15).** This reaction was run using 75 mg (0.42 mmoles) of **9** and the general procedure given above for the preparation of **10a**. The reaction did not yield the dihydroquinolinone but yielded only products resulting from the initial conjugate addition without subsequent S_NAr ring closure. The 1:1 Michael addition product **13** (14 mg, 12%) was isolated as a yellow oil. IR: 3333, 2815, 1685, 1271 cm^{-1}; ^1H NMR: δ 7.32 (m, 5H), 7.25 (m, 1H), 7.04 (m, 2H), 3.83 (s, 2H), 3.81 (s, 3H), 3.22 (td, 2H, *J* = 6.2, 3.3), 3.02 (t, 2H, *J* = 6.2), 1.77 (br s, 1H); ^{13}C NMR: δ 197.7 (d, *J* = 4.4), 156.6 (d, *J* = 247.4), 155.7, 140.2, 128.4, 128.1, 126.9, 125.5 (d, *J* = 14.7), 121.5 (d, *J* = 8.8), 117.7 (d, *J* = 26.5), 112.7 (d, *J* = 2.9), 55.9, 54.0, 43.9, 43.8 (d, *J* = 7.4); ms: *m*/*z* 153 (M^+-$C_9H_{12}N$). Anal. Calcd. for $C_{17}H_{18}FNO_2$: C, 71.08; H, 6.27; N, 4.88. Found: C, 71.12; H, 6.29; N, 4.82.

This reaction also yielded piperidinol **15**, which results from the silica gel-promoted aldol ring closure of the 2:1 Michael addition product **14**. Compound **15** (82 mg, 42%) was isolated as a viscous yellow oil. IR: 3462, 2830, 1663 cm^{-1}; ^1H NMR: δ 7.39 (d, 2H, *J* = 7.4), 7.32 (t, 2H, *J* = 7.4), 7.25 (m, 2H), 6.97 (m, 2H), 6.91 (m, 1H), 6.77 (dd, 1H, *J* = 11.5, 8.9), 6.63 (dt, 1H, *J* = 8.9, 3.5), 4.89 (d, 1H, *J* = 2.3), 4.71 (dd, 1H, *J* = 11.1, 3.5), 3.76 (s, 3H), 3.69 (s, 3H), 3.68 (s, 2H), 3.03 (dd, 1H, *J* = 11.1, 3.5), 2.75 (complex, 3H), 2.72 (m, 1H), 1.65 (d, 1H, *J* = 13.7); ^{13}C NMR: δ 203.2 (d, *J* = 3.7), 156.1 (d, *J* = 250.3), 155.6, 155.5, 153.2 (d, *J* = 237.8), 138.3, 134.1 (d, *J*

= 14.0), 128.8, 128.2, 127.0, 125.3 (d, J = 13.9), 121.9 (d, J = 8.8), 117.7 (d, J = 25.8), 116.6 (d, J = 26.5), 113.9 (d, J = 8.8), 112.9 (d, J = 4.4), 112.6 (d, J = 2.2), 72.3 (d, J = 5.9), 62.0, 55.7, 55.6, 53.1 (t, J = 7.4), 51.4, 48.5, 36.2 (d, J = 2.9); ms (30 eV): m/z 467 (M^{+}). Anal. Calcd for $C_{27}H_{27}F_{2}NO_{4}$: C, 69.38; H, 5.78; N, 3.00. Found: C, 69.44; H, 5.81; N, 2.93. The ^{1}H and ^{13}C NMR spectra compare well with calculated spectra [12], but the stereochemical assignment is tentative.

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(±)-1,2-Dialkyl-5-nitro-2,3-dihydro-1*H*-indoles by a Tandem Reductive Amination-S$_N$Ar Reaction

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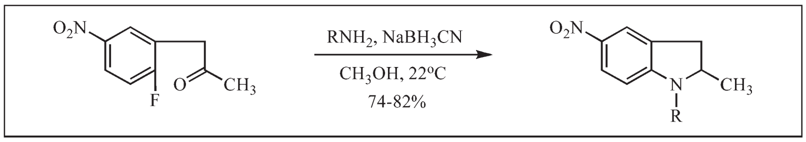

A tandem reductive amination-S$_N$Ar reaction has been applied to the synthesis of (±)-1,2-dialkyl-5-nitro-2,3-dihydro-1*H*-indoles. Treatment of a series of 2-fluoro-5-nitrobenzyl ketones with primary amines and sodium cyanoborohydride in methanol at room temperature provided good yields of the target heterocycles. The reaction is sensitive to steric hindrance and proceeds best with less hindered ketone substrates using primary amines that are unbranched at the α carbon.

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INTRODUCTION

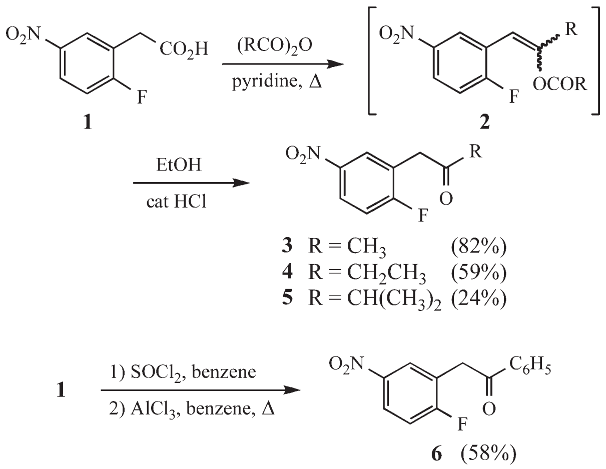
Over the past several years, our work has led to a number of reductive cyclizations that yield 1,2,3,4-tetrahydroquinolines [2]. Recently, we reported a tandem reductive amination-S$_N$Ar reaction for the preparation of substituted 6-nitro-1,2,3,4-tetrahydroquinolines [3]. In the current work, we have extended this sequence to the preparation of (±)-dialkyl-5-nitro-2,3-dihydro-1*H*-indoles. Earlier syntheses of dihydroindoles have involved photolysis of *N*-aryl enamines [4]; reduction of indoles with borane-trimethylamine [5]; base-catalyzed spirocyclization of aromatic imide imines [6]; base-catalyzed tandem hydroamination-aryne addition of chlorostyrenes [7]; and tandem S$_N$2-S$_N$Ar reaction of 2-(3-bromopropyl)-1-fluoro-4-nitrobenzene [2(b)]. Each of these mechanistically diverse routes provides access to a select group of dihydroindoles but none constitutes a general synthesis.

Dihydroindoles bearing a 1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl group in the C5 position have been shown to exhibit significant biological activity as nonsteroidal liver X receptor-α agonists [8]. Liver X receptors normally bind 24*S*,25-epoxycholesterol and have been found to play an important role in lipid metabolism [8]. These potent modulators of liver X receptor-α are currently being investigated for the treatment of dyslipidemia, atherosclerosis, and diabetes [9]. While the compounds prepared here possess a nitro group at C5, the nitro group could be readily transformed [10,11] to permit installation of the required substituent.

RESULTS AND DISCUSSION

The synthesis of our dihydroindole precursors is shown in Scheme 1. Dakin-West reaction of (2-fluoro-5-nitrophenyl)acetic acid (**1**) [2(b)] with a series of carboxylic acid anhydrides in pyridine followed by refluxing with acidic ethanol gave the 1-(2-fluoro-5-nitrophenyl)-2-propanone derivatives **3**, **4**, and **5** [12,13]. Yields of the ketone products correlated with the steric hindrance of the anhydride with acetic anhydride giving the highest yield (82%) and isobutyric anhydride the lowest (24%). Finally, the desoxybenzoin derivative **6** was prepared in 58% yield by a Friedel-Crafts reaction of (2-fluoro-5-nitrophenyl)acetyl chloride with benzene [14].

Scheme 1



3 R = CH$_3$ (82%)
4 R = CH$_2$CH$_3$ (59%)
5 R = CH(CH$_3$)$_2$ (24%)

6 (58%)

Our cyclization study sought to demonstrate the feasibility of preparing selected dihydroindoles from alkyl 2-fluoro-5-nitrobenzyl ketones and primary amines by a tandem reductive amination-S$_N$Ar sequence. Initially, we believed that the enolizability of the substrates might lead to competitive condensation reactions under the neutral to basic reaction conditions. Another potential problem was the strain associated with closing a benzo-fused five-membered ring [15]. Neither of these concerns, however, proved to be a significant deterrent to the success of the reaction.

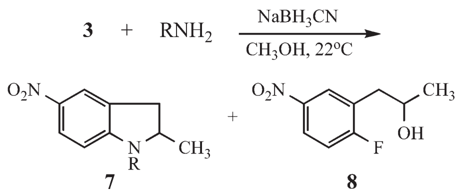
The reaction is run by dissolving 1.00 equivalent of the ketone in methanol, then adding 1.20 equivalents of the amine and 1.25 equivalents of sodium cyanoborohydride, and stirring at room temperature for 48 h. Optimum yields were obtained when two extra portions (0.18 equivalents each) of the amine and the reducing agent were added at 12-h intervals during the first 24 h. The major limitation of the current process is its sensitivity to the steric environment surrounding the ketone and amine functions. For example, the reaction was successful for substrates **3** ($R = CH_3$) and **4** ($R = CH_2CH_3$), but proceeded poorly for **5** ($R = CH(CH_3)_2$). The phenyl ketone **6** proved to be inert to the reaction conditions at 22°C, but gave a low yield of the heterocycle, along with three other products, at 65°C. Bulky amines, branched at the α-carbon, also gave lower yields.

The best results were achieved by reacting methyl ketone **3** with unbranched primary amines (see Table 1). These gave the target dihydroindoles **7a–e** in 74–82% yields. In each case, the ketone reduction product, 1-(2-fluoro-5-nitrophenyl)-2-propanol (**8**), was also isolated in 10–15% yield. More hindered amines, such as cyclohexylamine, gave dihydroindole **7f** in much lower yield (22%), with the remainder being alcohol **8** (20%), simple reductive amination product **9** (32%) and recovered **3** (14%). Isolation of **9** in this case suggests that reductive amination initiates the two-step sequence. Finally, *tert*-butylamine gave only alcohol **8** (20%) along with unreacted **3** (75%).

For more sterically congested substrates **4** and **5**, the yield of the dihydroindole decreased and the proportion of ketone reduction product (**11** and **13**, respectively) and unreacted ketone increased (see Tables 2 and 3). Ethyl ketone **4** gave the dihydroindoles in 60–64% yield, which is still synthetically useful. Isopropyl ketone **5**, however, afforded less than 25% yields and the desired products were difficult to separate from unreacted ketone and other minor by-products. Finally,

Table 1

Reductive cyclization of methyl ketone **3**.

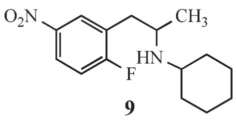


	R	Yield of **7** (%)[a]
Unbranched		
a	$C_6H_5CH_2$	78
b	$C_6H_5CH_2CH_2$	76
c	n-C_6H_{13}	82
d	i-$C_3H_7OCH_2CH_2CH_2$	74
e	i-C_4H_9	82
Branched		
f	c-C_6H_{11}	22[b]
g	t-C_4H_9	0[c]

[a] Each reaction also gave **8** in 10–13 % yield.

[b] This reaction also gave reductive amination product **9** in 32% yield, **8** in 20% yield, and unreacted **3** in 14% yield.

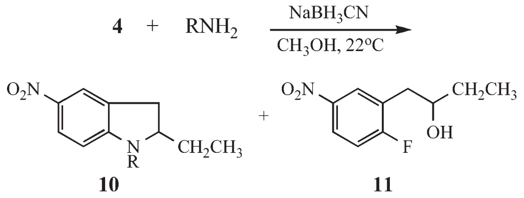
[c] This reaction gave **8** in 20% yield and unreacted **3** in 75% yield.



9

Table 2

Reductive cyclization of ethyl ketone **4**.

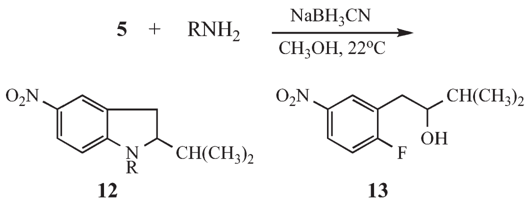


	R	Yield of **10** (%)[a]
a	$C_6H_5CH_2$	60
b	$C_6H_5CH_2CH_2$	62
c	n-C_6H_{13}	61
d	i-$C_3H_7OCH_2CH_2CH_2$	61
e	i-C_4H_9	64

[a] Each reaction also gave **11** in 18–20% yield and unreacted **4** in 10–12% yield.

Table 3

Reductive cyclization of isopropyl ketone **5**.

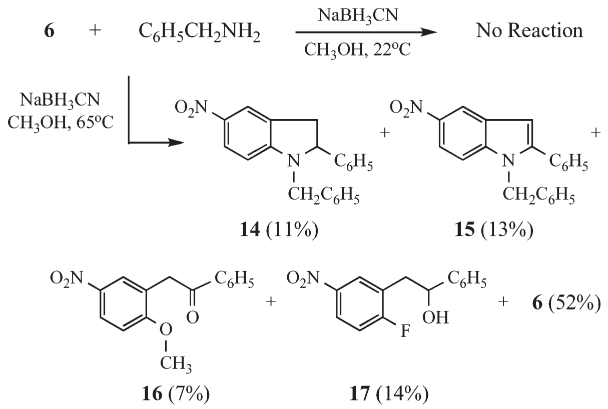


	R	Yield of **12** (%)
a	$C_6H_5CH_2$	17[a]
c	n-C_6H_{13}	22[b]

[a] This reaction also gave **13** in 15% yield and unreacted **5** in 58% yield.

[b] This reaction also gave **13** in 14% yield and unreacted **5** in 55% yield.

Scheme 2



phenyl ketone **6** and benzylamine in methanol reacted only under forcing conditions (65°C, 48 h) to give a low yield of the desired dihydroindole **14** (11%), along with indole **15** (13%) from α deprotonation of the intermediate imine and cyclization by the nitrogen of the delocalized anion, methoxyketone **16** (7%) from solvent addition to the activated ring, alcohol **17** (14%) and unreacted **6** (52%) (see Scheme 2).

CONCLUSION

We have developed an approach to the synthesis of (±)-1,2-dialkyl-5-nitro-2,3-dihydro-1*H*-indoles based on a tandem reductive amination-S_NAr reaction. The reaction gives good yields in many cases but is sensitive to steric hindrance in the ketone and amine reacting partners. Thus, while satisfactory conversions were achieved from substrates **3** and **4**, hindered ketone **5** gave low yields and aromatic ketone **6** was unreactive. Branching at the α-carbon of the amine also proved detrimental to the reaction. We are pursuing further studies of this transformation in systems bearing other electron withdrawing groups at C5 and C7 of the dihydroindole system.

EXPERIMENTAL

All reactions were run under dry nitrogen unless otherwise indicated. Methanol was used from a freshly opened bottle. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech 21521) with ultraviolet detection. Preparative separations were performed by one of the following methods: (1) flash column chromatography [16] on silica gel (grade 62, 60–200 mesh) containing ultraviolet-active phosphor (Sorbent Technologies UV-5) packed into quartz columns or (2) preparative thin layer chromatography on 20 cm × 20 cm silica gel GF plates (Analtech 02015). Band elution for both methods was monitored using a hand-held ultraviolet lamp. Hexanes used in chromatography had a boiling range of 65–70°C. Melting points were uncorrected. Infrared spectra were run as thin films on sodium chloride disks and referenced to polystyrene. ^{1}H and ^{13}C Nuclear magnetic resonance spectra were measured in deuteriochloroform at 300 MHz and 75 MHz, respectively, using tetramethylsilane as the internal standard; coupling constants (J) are given in Hz. Mass spectra (electron impact/direct probe) were obtained at 70 eV.

1-(2-Fluoro-5-nitrophenyl)-2-propanone (3). This compound was prepared from **1** and acetic anhydride on a 13.2 mmol scale by adapting the method described by Schtacher and Dayagi [12] for the synthesis of 1-(3-nitrophenyl)-2-propanone. The crude product was recrystallized from methanol to give 2.13 g (82%) of **3**, mp 113–114°C. ir: 1725, 1522, 1352, 1246 cm^{-1}; ^{1}H NMR: δ 8.19 (ddd, 1H, *J* = 8.8, 4.4, 2.7), 8.12 (dd, 1H, *J* = 6.2, 2.7), 7.22 (t, 1H, *J* = 8.8), 3.88 (d, 2H, *J* = 0.9), 2.31 (s, 3H); ^{13}C NMR: δ 202.7, 164.5 (d, *J* = 257.4), 144.2, 127.4 (d, *J* = 6.6), 124.9 (d, *J* = 10.3), 123.4, (d, *J* = 18.6), 116.2 (d, *J* = 24.9), 43.3, 29.7; ms: *m*/*z* 197 (M^+). Anal. Calcd. for $C_9H_8FNO_3$: C, 54.82; H, 4.06; N, 7.11. Found: C, 54.84; H, 4.07; N, 7.07.

1-(2-Fluoro-5-nitrophenyl)-2-butanone (4). This compound was prepared from **1** and propionic anhydride on a 13.2 mmol scale by adapting the method described by Schtacher and Dayagi [12] for the synthesis of 1-(3-nitrophenyl)-2-propanone. The crude product was flash chromatographed on a 30 cm × 2.5 cm silica gel column eluted with 5% ether in hexanes to give 1.53 g (59%) of **4**, mp 59–61°C. ir: 1721, 1529, 1351, 1248 cm^{-1}; ^{1}H NMR: δ 8.18 (ddd, 1H, *J* = 8.8, 4.5, 2.9), 8.13 (dd, 1H, *J* = 6.2, 2.9), 7.21 (t, 1H, *J* = 8.8), 3.85 (d, 2H, *J* = 0.8), 2.60 (q, 2H, *J* = 7.2), 1.12 (t, 3H, *J* = 7.2); ^{13}C NMR: δ 205.5, 164.5 (d, *J* = 257.7), 144.1, 127.7 (d, *J* = 6.6), 124.9 (d, *J* = 9.6), 123.6 (d, *J* = 19.1), 116.2 (d, *J* = 24.3), 42.0 (d, *J* = 1.5), 35.9, 7.7; ms: *m*/*z* 211 (M^+). Anal. Calcd. For $C_{10}H_{10}FNO_3$: C, 56.87; H, 4.74; N, 6.63. Found: C, 56.85; H, 4.73; N, 6.63.

1-(2-Fluoro-5-nitrophenyl)-3-methyl-2-butanone (5). This compound was prepared from **1** and isobutyric anhydride on an 11.5 mmol scale by adapting the method described by Schtacher and Dayagi [11] for the synthesis of 1-(3-nitrophenyl)-2-propanone. The crude product was flash chromatographed on a 30 cm × 2.5 cm silica gel column using 5% ether in hexanes to give 0.62 g (24%) of **5**, mp 46–48°C. ir: 1720, 1530, 1349, 1249 cm^{-1}; ^{1}H NMR: δ 8.18 (ddd, 1H, *J* = 8.8, 4.5, 2.9), 8.12 (dd, 1H, *J* = 6.2, 2.9), 7.20 (t, 1H, *J* = 8.8), 3.90 (s, 2H), 2.79 (septet, 1H, *J* = 6.8), 1.20 (d, 6H, *J* = 6.8); ^{13}C NMR: δ 208.8, 164.5 (d, *J* = 256.9), 144.3, 127.8 (d, *J* = 6.6), 124.8 (d, *J* = 10.7), 123.8 (d, *J* = 18.4), 116.1 (d, *J* = 24.3), 41.0, 40.1 (d, *J* = 1.5), 18.2; ms: *m*/*z* 182 (M^+-C_3H_7). Anal. Calcd. For $C_{11}H_{12}FNO_3$: C, 58.67; H, 5.33; N, 6.22. Found: C, 58.71; H, 5.34; N, 6.17.

3-(2-Fluoro-5-nitrophenyl)-1-phenyl-1-ethanone (6). **[Caution!** Benzene is a carcinogen. Thionyl chloride is an inhalation hazard and is highly toxic. Both should be handled carefully in a well-ventilated area.] In a round-bottomed flask protected by a drying tube (Drierite®), 2.97 g (1.82 mL, 25.0 mmol) of thionyl chloride was added to a solution of 2.49 g (12.5 mmol) of **1** in 40 mL of benzene and the mixture was stirred and heated under reflux for 3 h. Solvent and excess thionyl chloride were removed by distillation and the resulting acid chloride in 10 mL of benzene was added dropwise to a suspension of 2.00 g (15.0 mmol) of aluminum chloride in 40 mL of benzene [14]. The mixture was heated under reflux for 1 h, then cooled and quenched by addition to 10 mL of concentrated hydrochloric acid and 25 g of crushed ice. The product was extracted with 1:1 benzene:ether (two times) and the combined organic extracts were washed with saturated sodium chloride (one time), dried (magnesium sulfate), and concentrated under vacuum. The crude product was recrystallized from methanol to give 1.88 g (58%) of **6**, mp 89–90°C. ir: 1691, 1527, 1352, 1249 cm^{-1}; ^{1}H NMR: δ 8.21 (superimposed ddd and dd, 2H), 8.05 (superimposed dd, 2H), 7.64 (tt, 1H, *J* = 7.4, 1.2), 7.52 (t, 2H, *J* = 7.4), 7.24 (t, 1H, *J* = 8.2), 4.44 (d, 2H, *J* = 0.8); ^{13}C NMR: δ 194.5, 164.7 (d, *J* = 256.9), 144.1, 135.9, 133.8, 128.9, 128.3, 127.9 (d, *J* = 6.6), 125.0 (d, *J* = 10.3), 123.8 (d, *J* = 18.4), 116.2 (d, *J* = 24.3), 38.6 (d, *J* = 1.5); ms (30 eV): *m/z* 259 (M^{+}). Anal. Calcd. For $C_{14}H_{10}FNO_3$: C, 64.86; H, 3.86; N, 5.41. Found: C, 64.87; H, 3.86; N, 5.42.

Representative procedure for the reductive amination-nucleophilic substitution reaction with 3: (±)-1-Benzyl-2-methyl-5-nitro-2,3-dihydro-1*H*-indole (7a). To a stirred solution of 100 mg (0.51 mmol) of **3** and 64 mg (0.65 mL, 0.60 mmol) of benzylamine at 22°C was added 40 mg (0.64 mmol) of sodium cyanoborohydride. The reaction was stirred at 22°C for 48 h; two additional portions of 10 mg (0.09 mmol) of benzylamine and 6 mg (0.09 mmol) of sodium cyanoborohydride were added at 12-h intervals during the first 24 h. The crude reaction mixture was poured into saturated sodium chloride and extracted with ether (three times). The combined ether extracts were dried (magnesium sulfate), concentrated under vacuum, and purified by preparative thin layer chromatography using 20% ether in hexanes. The bright yellow band contained 106 mg (78%) of **7a** as a yellow solid, mp 94–95°C. ir: 1506, 1315 cm^{-1}; ^{1}H NMR: δ 8.00 (dd, 1H, *J* = 8.8, 2.4), 7.88 (m, 1H), 7.38–7.22 (complex, 5H), 6.23 (d, 1H, *J* = 8.8), 4.55 (d, 1H, *J* = 16.3), 4.35 (d, 1H, *J* = 16.3), 4.02 (m, 1H), 3.29 (ddd, 1H, *J* = 16.1, 9.1, 1.1), 2.72 (ddd, 1H, *J* = 16.1, 7.7, 0.9), 1.32 (d, 3H, *J* = 6.2); ^{13}C NMR: δ 156.8, 138.1, 136.7, 128.8, 128.5, 127.6, 127.0, 126.6, 120.6, 103.7, 59.7, 48.5, 35.8, 19.8; ms: *m/z* 268 (M^{+}). Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.64; H, 5.97; N, 10.45. Found: C, 71.64; H, 5.96; N, 10.42.

This reaction also produced 12 mg (12%) of 1-(2-fluoro-5-nitrophenyl)-2-propanol (**8**), mp 53–54.5°C. ir: 3385, 1527, 1350, 1245 cm^{-1}; ^{1}H NMR: δ 8.21 (dd, 1H, *J* = 6.2, 2.9), 8.13 (ddd, 1H, *J* = 8.8, 4.4, 2.9), 7.18 (t, 1H, *J* = 8.8), 4.13 (d of sextets, 1H, *J* = 6.2, 0.9), 2.91 (ddd, 1H, *J* = 13.8, 4.8, 1.3), 2.83 (ddd, 1H, *J* = 13.8, 7.5, 1.3), 1.61 (br s, 1H), 1.29 (d, 3H, *J* = 6.2); ^{13}C NMR: δ 164.8 (d, *J* = 256.2), 149.6, 128.3 (d, *J* = 18.3), 127.6 (d, *J* = 7.2), 124.1 (d, *J* = 10.3), 116.2 (d, *J* = 25.5), 67.4, 38.2, 23.3; ms: *m/z* 199 (M^{+}). Anal. Calcd. for $C_9H_{10}FNO_3$: C, 54.27; H, 5.03; N, 7.04. Found: C, 54.31; H, 5.05; N, 7.01.

(±)-2-Methyl-5-nitro-1-(2-phenylethyl)-2,3-dihydro-1*H*-indole (7b). This compound (110 mg, 76%) was isolated as a yellow oil. ir: 1508, 1315 cm^{-1}; ^{1}H NMR: δ 8.00 (dd, 1H, *J* = 8.8, 2.2), 7.83 (m, 1H), 7.34–7.16 (complex, 5H), 6.16 (d, 1H, *J* = 8.8), 3.91 (m, 1H), 3.47 (m, 2H), 3.19 (ddd, 1H, *J* = 16.3, 9.3, 0.9), 2.86 (m, 2H), 2.62 (ddd, 1H, *J* = 16.3, 7.5, 0.9), 1.26 (d, 3H, *J* = 6.2); ^{13}C NMR: δ 156.2, 138.6, 137.6, 128.7, 128.6, 128.4, 126.7, 126.6, 120.5, 103.0, 59.5, 46.2, 35.6, 33.5, 19.7; ms: *m/z* 282 (M^{+}). Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.34; H, 6.38; N, 9.93. Found: C, 72.27; H, 6.40; N, 9.88.

Alcohol **8** (12%) was also isolated.

(±)-1-Hexyl-2-methyl-5-nitro-2,3-dihydro-1*H*-indole (7c). This compound (110 mg, 82%) was isolated as a yellow oil. ir: 1508, 1314 cm^{-1}; ^{1}H NMR: δ 8.04 (dd, 1H, *J* = 8.8, 2.2), 7.84 (m, 1H), 6.20 (d, 1H, *J* = 8.8), 4.02 (m, 1H), 3.21 (m, 3H), 2.65 (ddd, 1H, *J* = 16.3, 7.5, 0.9), 1.56 (m, 2H), 1.40–1.23 (complex, 6H), 1.31 (d, 3H, *J* = 6.2), 0.90 (t, 3H, *J* = 7.0); ^{13}C NMR: δ 156.6, 137.4, 128.4, 126.8, 120.6, 103.0, 59.2, 44.3, 35.7, 31.5, 27.1, 26.8, 22.6, 19.8, 14.0; ms: *m/z* 262 (M^{+}). Anal. Calcd. for $C_{15}H_{22}N_2O_2$: C, 68.70; H, 8.40; N, 10.69. Found: 68.68; H, 8.45; N, 10.63.

Alcohol **8** (10%) was also isolated.

(±)-1-(3-Isopropoxypropyl)-2-methyl-5-nitro-2,3-dihydro-1*H*-indole (7d). This compound (105 mg, 74%) was isolated as a yellow oil that solidified upon standing at 10°C, mp 39–40°C. ir: 1507, 1316 cm^{-1}; ^{1}H NMR: δ 8.03 (dd, 1H, *J* = 8.8, 2.4), 7.84 (m, 1H), 6.29 (d, 1H, *J* = 8.8), 4.02 (m, 1H), 3.52 (septet, 1H, *J* = 6.2), 3.46–3.30 (complex, 4H), 3.23 (ddd, 1H, *J* = 16.1, 9.2, 1.1), 2.65 (ddd, 1H, *J* = 16.1, 7.5, 1.3), 1.82 (quintet, 2H, *J* = 6.8), 1.32 (d, 3H, *J* = 6.2), 1.16 (d, 6H, *J* = 6.1); ^{13}C NMR: δ 156.8, 137.4, 128.3, 126.7, 120.5, 103.2, 71.6, 64.8, 59.4, 41.2, 35.7, 27.9, 22.1, 22.0, 19.8; ms: *m/z* 278 (M^{+}). Anal. Calcd. for $C_{15}H_{22}N_2O_3$: C, 64.75; H, 7.91; N, 10.07. Found: C, 64.77; H, 7.94; N, 9.99.

Alcohol **8** (13%) was also isolated.

(±)-1-Isobutyl-2-methyl-5-nitro-2,3-dihydro-1*H*-indole (7e). This compound (96 mg, 82%) was isolated as a yellow oil. ir 1507, 1316 cm^{-1}; ^{1}H NMR: δ 8.02 (dd, 1H, *J* = 8.8, 2.4), 7.84 (m, 1H), 6.21 (d, 1H, *J* = 8.8), 4.01 (m, 1H), 3.25 (ddd, 1H, *J* = 16.2, 8.8, 2.4), 3.02 (d, 2H, *J* = 7.5), 2.66 (ddd, 1H, *J* = 16.2, 7.0, 1.3), 2.01 (septet, 1H, *J* = 7.0), 1.29 (d, 3H, *J* = 6.2), 0.98 (d, 3H, *J* = 6.8), 0.92 (d, 3H, *J* = 6.8); ^{13}C NMR: δ 157.0, 137.5, 128.1, 126.7, 120.6, 103.2, 59.9, 52.3, 35.6, 27.5, 20.5, 20.3, 19.6; ms: *m/z* 234 (M^{+}). Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.67; H, 7.69; N, 11.97. Found: C, 66.63; H, 7.73; N, 11.95.

Alcohol **8** (10%) was also isolated.

(±)-1-Cyclohexyl-2-methyl-5-nitro-2,3-dihydro-1*H*-indole (7f). This compound (29 mg, 22%) was isolated as a yellow oil. ir: 1506, 1313 cm^{-1}; ^{1}H NMR: δ 8.02 (dd, 1H, *J* = 8.8, 2.3), 7.83 (dt, 1H, *J* = 2.3, 1.4), 6.24 (d, 1H, *J* = 8.8), 4.14 (m, 1H), 3.30 (m, 2H), 2.61 (ddd, 1H, *J* = 16.2, 4.5, 0.8), 1.89 (m, 4H), 1.73 (m, 2H), 1.54 (m, 1H), 1.30 (m, 3H), 1.30 (d, 3H, *J* = 6.2); ^{13}C NMR: δ 155.3, 137.1, 128.5, 126.7, 120.8, 103.6, 57.2, 56.2, 36.0, 31.0, 30.1, 26.1, 26.0, 25.6, 23.2; ms: *m/z* 245 (M^{+}-CH$_3$). Anal. Calcd. for $C_{15}H_{20}N_2O_2$: C, 69.23; H, 7.69; N, 10.77. Found: C, 69.26; H, 7.71; N, 10.72.

This reaction also produced 45 mg (32%) of *N*-cyclohexyl-α-methyl-2-(2-fluoro-5-nitrophenyl)ethanamine (**9**) as a yellow oil. ir: 3323, 1528, 1350, 1244 cm^{-1}; ^{1}H NMR: δ 8.16 (dd, 1H, *J* = 6.2, 2.7), 8.11 (ddd, 1H, *J* = 9.0, 4.5, 2.7), 7.16 (t, 1H, *J* = 9.0), 3.11 (sextet, 1H, *J* = 6.3), 2.86 (dd, 1H, *J* = 13.5, 6.1), 2.64 (dd, 1H, *J* = 13.5, 7.2), 2.55 (tt, 1H, *J* = 10.3, 3.7), 1.85 (m, 2H), 1.70 (m, 2H), 1.60 (m, 1H), 1.32–1.15 (complex, 4H), 1.04 (d, 3H, *J* = 6.3), 1.01 (m, 2H); ^{13}C NMR: δ 164.8 (d, *J* = 256.2), 144.3, 128.7 (d, *J* = 17.7), 127.5 (d, *J* = 7.4), 123.8 (d, *J* = 10.3), 116.1 (d, *J* = 25.8), 53.5, 49.7, 36.7, 34.2, 33.9, 26.1, 25.1, 25.0, 20.9; ms: *m/z* 265 (M^{+}-CH$_3$). Anal. Calcd. for $C_{15}H_{21}FN_2O_2$: C, 64.29; H, 7.50; N, 10.00. Found: C, 64.38; H, 7.56; N, 9.95.

Alcohol **8** (20%) and unreacted **3** (14%) were also isolated.

Attempted preparation of (±)-1-*tert*-butyl-2-methyl-5-nitro-2,3-dihydro-1*H*-indole (7g). Treatment of **3** as above gave only alcohol **8** (20%) and unreacted **3** (75%).

Reductive amination-nucleophilic substitution reaction with 4: (±)-1-Benzyl-2-ethyl-5-nitro-2,3-dihydro-1*H*-indole (10a). This reaction was run on a 100 mg (0.47 mmol)-scale using the general procedure given above for the preparation of **7a**. This compound (80 mg, 60%) was obtained as a yellow solid, mp 47–48°C. ir: 1509, 1316 cm^{-1}; ^{1}H NMR: δ 8.00 (dd, 1H, *J* = 8.9, 2.3), 7.89 (m, 1H), 7.36–7.22 (complex, 5H), 6.23 (d, 1H, *J* = 8.9), 4.56 (d, 1H, *J* = 16.4), 4.36 (d, 1H, *J* = 16.4), 3.89 (m, 1H), 3.24 (dd, 1H, *J* = 16.5, 9.6), 2.81 (dd, 1H, *J* = 16.5, 3.1), 1.81 (sextet d, 1H, *J* = 7.4, 3.1), 1.58 (m, 1H), 0.90 (t, 3H, *J* = 7.4); ^{13}C NMR: δ 157.2, 138.0, 136.7, 128.8, 128.6, 127.5, 126.9, 126.7, 120.6, 103.5, 65.1, 48.7, 32.8, 26.2, 8.9; ms: *m/z* 191 (M^+-C_7H_7). Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.34; H, 6.38; N, 9.93. Found: C, 72.38; H, 6.41; N, 9.87.

This reaction also produced 19 mg (19%) of 1-(2-fluoro-5-nitrophenyl)-2-butanol (**11**), mp 37–38°C. ir: 3390, 1527, 1350, 1244 cm^{-1}; ^{1}H NMR: δ 8.23 (dd, 1H, *J* = 6.2, 2.9), 8.13 (ddd, 1H, *J* = 8.9, 4.2, 2.9), 7.18 (t, 1H, *J* = 8.9), 3.84 (m, 1H), 2.95 (ddd, 1H, *J* = 14.0, 4.1, 1.0), 2.79 (dd, 1H, *J* = 14.0, 8.4), 1.60 (br s, 1H), 1.58 (m, 2H), 1.02 (t, 3H, *J* = 7.4); ^{13}C NMR: δ 164.8 (d, *J* = 256.9), 144.0, 127.8 (d, *J* = 17.6), 127.6 (d, *J* = 7.4), 124.0 (d, *J* = 10.3), 116.1 (d, *J* = 25.8), 72.6, 36.2, 30.1, 9.8; ms: *m/z* 184 (M^+-C_2H_5). Anal. Calcd. For $C_{10}H_{12}FNO_3$: C, 56.34; H, 5.63; N, 6.57. Found: C, 56.40; H, 5.66; N, 6.51.

Unreacted **4** (12%) was also recovered.

(±)-2-Ethyl-5-nitro-1-(2-phenylethyl)-2,3-dihydro-1*H*-indole (10b). This compound (87 mg, 62%) was isolated as a yellow oil. ir: 1513, 1322 cm^{-1}; ^{1}H NMR: δ 8.00 (dd, 1H, *J* = 8.8, 2.1), 7.83 (m, 1H), 7.32–7.15 (complex, 5H), 6.15 (d, 1H, *J* = 8.8), 3.76 (m, 1H), 3.51 (ddd, 1H, *J* = 14.8, 9.0, 6.1), 3.42 (ddd, 1H, *J* = 14.8, 8.8, 6.8), 3.12 (dd, 1H, *J* = 16.4, 9.6), 2.89 (ddd, 1H, *J* = 14.6, 9.0, 6.8), 2.80 (ddd, 1H, *J* = 14.6, 8.8, 6.1), 2.70 (dd, 1H, *J* = 16.4, 7.4), 1.78 (sextet d, 1H, *J* = 7.4, 3.1), 1.50 (m, 1H), 0.88 (t, 3H, *J* = 7.4); ^{13}C NMR: δ 156.6, 138.6, 137.5, 128.6 (2C), 128.5, 126.7, 126.6, 120.5, 102.8, 64.8, 46.3, 33.4, 32.6, 26.0, 8.8; ms: *m/z* 205 (M^+-C_7H_7). Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.97; H, 6.76; N, 9.46. Found: C, 73.01; H, 6.74; N, 9.47.

Alcohol **11** (19%) and unreacted **4** (10%) were also isolated.

(±)-2-Ethyl-1-hexyl-5-nitro-2,3-dihydro-1*H*-indole (10c). This compound (80 mg, 61%) was isolated as a yellow oil. ir: 1511, 1313 cm^{-1}; ^{1}H NMR: δ 8.03 (dd, 1H, *J* = 8.9, 2.3), 7.83 (m, 1H), 6.19 (d, 1H, *J* = 8.9), 3.89 (m, 1H), 3.31–3.11 (complex, 3H), 2.73 (dd, 1H, *J* = 17.1, 8.0), 1.80 (m, 1H), 1.57 (m, 3H), 1.31 (m, 6H), 0.91 (t, 3H, *J* = 7.4), 0.90 (distorted t, 3H, *J* = 6.2); ^{13}C NMR: δ 157.0, 137.2, 128.4, 126.8, 120.4, 102.7, 64.6, 44.4, 32.6, 31.5, 27.0, 26.8, 26.0, 22.5, 14.0, 8.8; ms: *m/z* 205 (M^+-C_5H_{11}). Anal. Calcd. for $C_{16}H_{24}N_2O_2$: C, 69.57; H, 8.70; N, 10.14. Found: C, 69.63; H, 8.75; N, 10.06.

Alcohol **11** (20%) and unreacted **4** (10%) were also isolated.

(±)-2-Ethyl-1-(3-isopropoxypropyl)-5-nitro-2,3-dihydro-1*H*-indole (10d). This compound (84 mg, 61%) was isolated as a yellow oil. ir: 1515, 1315 cm^{-1}; ^{1}H NMR: δ 8.03 (dd, 1H, *J* = 8.8, 2.1), 7.84 (m, 1H), 6.28 (d, 1H, *J* = 8.8), 3.85 (m, 1H), 3.53 (septet, 1H, *J* = 6.2), 3.49–3.27 (complex, 4H), 3.18 (dd, 1H, *J* = 16.4, 9.4), 2.74 (dd, 1H, *J* = 16.4, 7.4), 1.82 (m, 3H), 1.55 (m, 1H), 1.15 (d, 6H, *J* = 6.2), 0.91 (t, 3H, *J* = 7.4); ^{13}C NMR: δ 157.2, 137.4, 128.3, 126.8, 120.4, 102.9, 71.6, 64.8, 64.7, 41.3, 32.6, 27.8, 26.0, 22.1, 22.0, 8.8; ms: *m/z* 205 (M^+-$C_5H_{11}O$). Anal. Calcd. for $C_{16}H_{24}N_2O_3$: C, 65.75; H, 8.22; N, 9.59. Found: C, 65.79; H, 8.24. N, 9.52.

Alcohol **11** (18%) and unreacted **4** (11%) were also isolated.

(±)-2-Ethyl-1-isobutyl-5-nitro-2,3-dihydro-1*H*-indole (10e). This compound (75 mg, 64%) was isolated as a yellow oil. ir: 1511, 1315 cm^{-1}; ^{1}H NMR: δ 8.02 (dd, 1H, *J* = 8.8, 2.3), 7.85 (m, 1H), 6.21 (d, 1H, *J* = 8.8), 3.88 (m, 1H), 3.20 (ddd, 1H, *J* = 16.4, 9.6, 1.0), 3.03 (m, 2H), 2.74 (ddd, 1H, *J* = 16.4, 6.6, 1.0), 2.02 (septet, 1H, *J* = 6.7), 1.78 (sextet d, 1H, *J* = 7.4, 3.1), 1.53 (m, 1H), 0.97 (d, 3H, *J* = 6.7), 0.91 (d, 3H, *J* = 6.7), 0.90 (t, 3H, *J* = 7.4); ^{13}C NMR: δ 157.4, 137.1, 128.2, 126.8, 120.5, 102.9, 65.1, 52.3, 32.5, 27.4, 25.9, 20.5, 20.3, 8.8; ms: *m/z* 205 (M^+-C_3H_7). Anal. Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.74; H, 8.06; N, 11.29. Found: C, 67.69; H, 8.04; N, 11.30.

Alcohol **11** (18%) and unreacted **4** (11%) were also isolated.

Reductive amination-nucleophilic substitution reaction with 5: (±)-1-Benzyl-2-isopropyl-5-nitro-2,3-dihydro-1*H*-indole (12a). This reaction was run on a 100 mg (0.44 mmol)-scale using the general procedure given above for the preparation of **7a**. This compound (22 mg, 17%) was isolated as a yellow oil following preparative thin layer chromatography using 15% ether in hexanes. ir: 1510, 1317 cm^{-1}; ^{1}H NMR: δ 8.01 (dd, 1H, *J* = 9.0, 2.3), 7.89 (m, 1H), 7.38–7.20 (complex, 5H), 6.29 (d, 1H, *J* = 9.0), 4.62 (d, 1H, *J* = 16.4), 4.33 (d, 1H, *J* = 16.4), 3.92 (ddd, 1H, *J* = 10.3, 7.6, 3.9), 3.03 (dd, 1H, *J* = 16.6, 10.2), 2.89 (dd, 1H *J* = 16.6, 7.6), 2.17 (sextet d, 1H, *J* = 6.8, 3.9), 0.91 (d, 3H, *J* = 6.8), 0.81 (d, 3H, *J* = 6.8); ^{13}C NMR: δ 157.7, 138.0, 136.4, 128.8, 127.7, 127.6, 127.1, 126.7, 120.6, 103.7, 68.0, 48.4, 28.3, 27.5, 18.6, 14.6; ms: *m/z* 205 (M^+-C_7H_7). Anal. Calcd. for $C_{18}H_{20}N$ for $C_{18}H_{20}N_2O_2$: C, 72.97; H, 6.76; N, 9.46. Found: C, 72.93; H, 6.72; N, 9.48.

This reaction also produced 15 mg (15%) of 1-(2-fluoro-5-nitrophenyl)-3-methyl-2-butanol (**13**) as a dark yellow oil. ir: 3427, 1526, 1347, 1245 cm^{-1}; ^{1}H NMR: δ 8.24 (dd, 1H, *J* = 6.2, 2.9), 8.13 (ddd, 1H, *J* = 8.8, 4.3, 2.9), 7.17 (t, 1H, *J* = 8.8), 3.66 (m, 1H), 2.96 (dd, 1H, *J* = 14.1, 2.0), 2.73 (dd, 1H, *J* = 14.1, 9.8), 1.77 (septet, 1H, *J* = 6.8), 1.48 (br s, 1H), 1.03 (d, 3H, *J* = 6.8), 1.02 (d, 3H, *J* = 6.8); ^{13}C NMR: δ 164.8 (d, *J* = 256.2), 144.1, 128.5 (d, *J* = 18.5), 127.6 (d, *J* = 7.4), 124.0 (d, *J* = 10.3), 116.1 (d, *J* = 25.0), 76.1, 33.9, 33.5, 18.7, 17.1; ms: *m/z* 184 (M^+-C_3H_7). Anal. Calcd. for $C_{11}H_{14}FNO_3$: C, 58.15; H, 6.17; N, 6.17. Found: C, 58.23; H, 6.19; N, 6.12.

Unreacted **5** (58%) was also recovered.

(±)-1-Hexyl-2-isopropyl-5-nitro-2,3-dihydro-1*H*-indole (12c). This compound (28 mg, 22%) was isolated as a yellow oil. ir: 1516, 1327 cm^{-1}; ^{1}H NMR: δ 8.03 (dd, 1H, *J* = 8.8, 2.1), 7.83 (m, 1H), 6.19 (d, 1H, *J* = 8.8), 4.12 (t, 1H, *J* = 7.8), 3.93 (ddd, 1H, *J* = 10.5, 7.3, 3.7), 3.30 (ddd, 1H, *J* = 14.8, 9.4, 6.3), 3.16 (ddd, 1H, *J* = 14.8, 9.4, 5.8), 3.06 (septet, 1H, *J* = 6.8), 2.98 (dd, 1H, *J* = 16.6, 9.9), 2.82 (dd, 1H, *J* = 16.6, 7.2), 2.16 (m, 1H), 1.76 (m, 1H), 1.57 (m, 1H), 1.32 (m, 4H), 0.95 (d, 3H, *J* = 6.8), 0.89 (m, 3H), 0.78 (d, 3H, *J* = 6.8); ^{13}C NMR: δ 157.3, 139.5, 128.5, 126.9, 120.4, 102.5, 67.9, 44.4, 43.6, 31.5, 28.5, 27.2, 26.8, 26.7, 22.6, 18.6, 14.4; ms: *m/z* 219 (M^+-C_5H_{11}). Anal. Calcd. for $C_{17}H_{26}N_2O_2$: C, 70.34; H, 8.97; N, 9.66. Found: C, 70.40; H, 9.01; N, 9.60.

Alcohol **13** (14%) and unreacted **5** (55%) were also isolated.

Reductive amination-nucleophilic aromatic substitution reactions with 6. Treatment of 100 mg (0.39 mmol) of **6** with 51.8 mg (0.48 mmol) of benzylamine using the general procedure given above for the preparation of **7a** afforded 98% recovery of unreacted **6**.

Repeating this reaction in methanol at 65°C for 48 h yielded four products, in addition to recovered **6**. These products were separated by preparative thin layer chromatography using 10% ether in hexanes to give: band 1: 16 mg (13%) of **15**; band 2: 13 mg (11%) of **14**; band 3: 52 mg (52%) of recovered **6**; band 4: 14 mg (14%) of **17**; and band 5: 7 mg (7%) of **16**. The physical and spectral data for these products were as follows:

1-Benzyl-2-phenyl-5-nitroindole (15). Viscous yellow oil; ir: 1513, 1332 cm^{-1}; ^{1}H NMR: δ 8.62 (d, 1H, *J* = 2.2), 8.05 (dd, 1H, *J* = 9.3, 2.2), 7.43 (apparent s, 5H), 7.30 (m, 1H), 7.28 (apparent t, 2H, *J* = 6.6), 7.20 (d, 1H, *J* = 8.8), 6.97 (dd, 2H, *J* = 8.2, 2.2), 6.80 (s, 1H), 5.41 (s, 2H); ^{13}C NMR: δ 145.0, 142.1, 140.6, 136.9, 131.3, 129.2, 129.0, 128.9, 128.8, 127.7, 127.5, 125.8, 117.6, 117.5, 110.4, 104.3, 48.0; ms: *m*/*z* 237 (M$^+$-C$_7$H$_7$). Anal. Calcd. for $C_{21}H_{16}N_2O_2$: C, 76.82; H, 4.88; N, 8.54. Found: C, 76.88; H, 4.91; N, 8.50.

(±)-1-Benzyl-2-phenyl-5-nitro-2,3-dihydro-1*H*-indole (14). Yellow solid, mp 137–139°C; ir: 1510, 1313 cm^{-1}; ^{1}H NMR: δ 8.09 (dd, 1H, *J* = 8.8, 2.2), 7.93 (s, 1H), 7.41–7.24 (complex, 8H), 7.12 (dd, 2H, *J* = 7.7, 2.2), 6.39 (d, 1H, *J* = 8.8), 4.88 (dd, 1H, *J* = 9.9, 7.7), 4.56 (d, 1H, *J* = 15.9), 4.01 (d, 1H, *J* = 15.9), 3.55 (dd, 1H, *J* = 16.5, 9.9), 3.08 (dd, 1H, *J* = 16.5, 8.2); ^{13}C NMR: δ 156.8, 141.0, 138.6, 136.0, 129.0, 128.8, 128.4, 128.2, 127.7, 127.5, 127.1, 126.8, 120.8, 103.9, 67.6, 48.4, 37.7; ms: *m*/*z* 239 (M$^+$-C$_7$H$_7$). Anal. Calcd. for $C_{21}H_{18}N_2O_2$: C, 76.36; H, 5.45; N, 8.48. Found: C, 76.38; H, 5.46; N, 8.45.

(±)-1-Phenyl-2-(2-fluoro-5-nitrophenyl) ethanol (17). Viscous yellow oil; ir: 3546, 3416, 1526, 1346, 1244 cm^{-1}; ^{1}H NMR: δ 8.13 (m, 2H), 7.41–7.28 (complex, 5H), 7.16 (t, 1H, *J* = 8.8), 4.99 (t, 1H, *J* = 6.6), 3.12 (d, 2H, *J* = 6.6), 2.00 (br s, 1H); ^{13}C NMR: δ 164.8 (d, *J* = 256.5), 144.0, 143.1, 128.7, 128.2, 127.8 (d, *J* = 6.9), 127.2 (d, *J* = 18.0), 125.7, 124.2 (d, *J* = 10.0), 116.1 (d, *J* = 25.5), 73.7, 38.4; ms: *m*/*z* 243 (M$^+$-H$_2$O). Anal. Calcd. for $C_{14}H_{12}FNO_3$: C, 64.37; H, 4.60; N, 5.36. Found: C, 64.44; H, 4.64; N, 5.29.

3-(2-Methoxy-5-nitrophenyl)-1-phenyl-1-ethanone (16). Light yellow solid, mp 118–120°C; ir: 2848, 1689, 1514, 1330 cm^{-1}; ^{1}H NMR: δ 8.22 (dd, 1H, *J* = 9.3, 2.7), 8.11 (d, 1H, *J* = 2.7), 8.03 (d, 2H, *J* = 7.7), 7.62 (t, 1H, *J* = 7.7), 7.51 (t, 2H, *J* = 7.7), 6.96 (d, 1H, *J* = 9.3), 4.36 (s, 2H), 3.88 (s, 3H) ^{13}C NMR: δ 196.0, 162.5, 141.3, 136.5, 133.4, 128.7, 128.2, 127.0, 125.1, 124.9, 110.0, 56.2, 39.9; ms: *m*/*z* 166 (M$^+$-C$_7$H$_5$O). Anal. Calcd. for $C_{15}H_{13}NO_4$: C, 66.42; H, 4.80; N, 5.17. Found: C, 66.44; H, 4.80; N, 5.19.

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[15] Strain in closing a benzo-fused five-membered ring was cited as a contributing factor in the low yields obtained for 2,3-dihydro-1*H*-indoles prepared by a tandem S$_N$2-S$_N$Ar reaction. This now appears unlikely. The primary problem in the S$_N$2-S$_N$Ar approach to this ring system is the tendency for the substrates to undergo elimination to the styrene in the presence of the basic amine nucleophile, see ref. 1(b).

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Efficient Synthesis of 5-(2-Hydroxyethyl)-2-phenylimino-1,3-thiazolidin-4-ones and 5-(2-Hydroxyethyl)-2-phenylamino-4,5-dihydro-1,3-thiazol-4-ones

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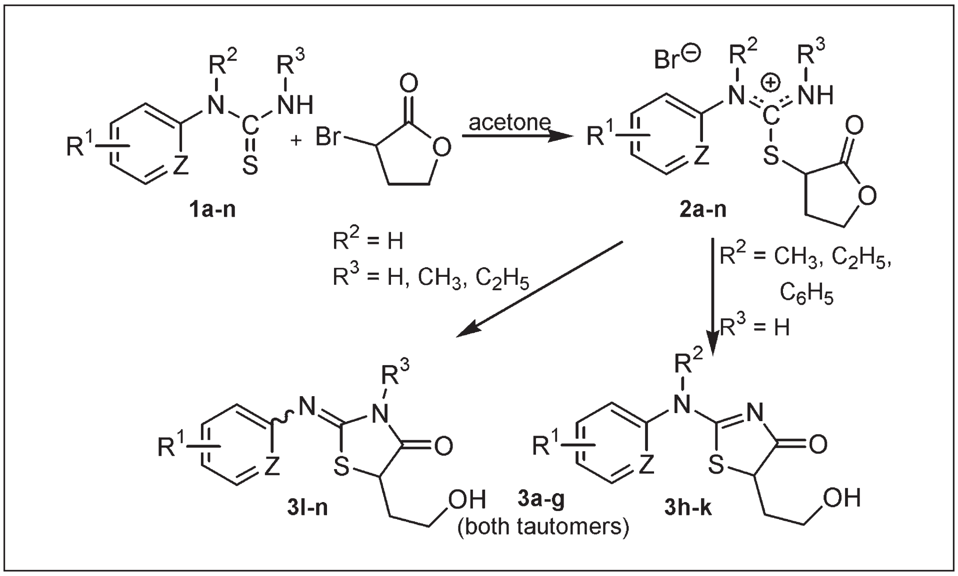
Dedicated to Professor Vladimír Macháček on the occasion of his 65th birthday.



A new method for the synthesis of substituted 5-(2-hydroxyethyl)-2-phenylimino-1,3-thiazolidin-4-ones and 5-(2-hydroxyethyl)-2-phenylamino-4,5-dihydro-1,3-thiazol-4-ones is described, starting from phenylthioureas and 3-bromotetrahydrofuran-2-one. The reaction proceeds under mild conditions, is very simple to perform, and is applicable to a relatively wide range of substituents in benzene nucleus. Some 1,3-thiazolidin-4-ones show dynamic NMR behavior in solution because of prototropy tautomerism and *E*-/*Z*-stereoisomerism.

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INTRODUCTION

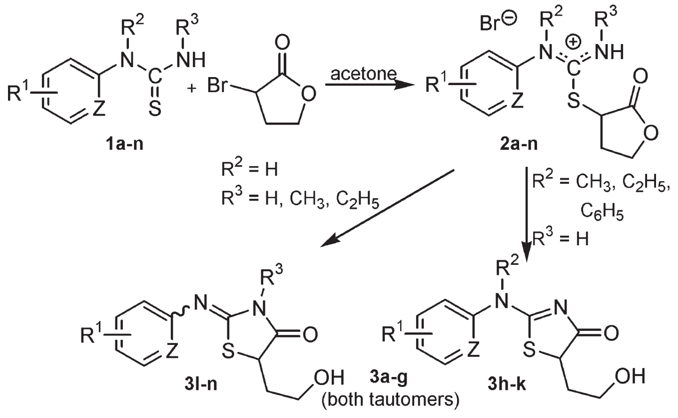
Natural [1] as well as synthetic heterocyclic compounds, containing a thiazole ring system often exhibit good antifungal [2], antibacterial [3], and anti-inflammatory [4] activity and are widely used in new pharmaceutical and agrochemical compounds. Also thiazolidine cycle belongs among pharmaceutically significant heterocycles representing an important group of per oral antidiabetics [5]. Thiazole skeleton is also present in many dyes and pigments [6].

There exist a lot of synthetic methods leading to thiazole or thiazolidine skeleton [7] from which those involving rearrangements of another heterocyclic rings represent new interesting alternative. Such rearrangements may provide fascinating routes to derivatives that can be obtained only with great difficulties—or not at all—by other procedures.

RESULTS AND DISCUSSION

Recently, we have found [8] that substituted *S*-(1-phenylpyrrolidin-2-on-3-yl) isothiuronium salts in weakly basic medium undergo an intramolecular transformation reaction. In this particular case, the γ-lactam ring is cleaved and a thiazolidine ring is formed, i.e. substituted 2-imino-5-[2-(phenylamino)ethyl]-1,3-thiazolidin-4-ones are obtained in very good yields. In this work, we extended the scope of this transformation replacing γ-lactam cycle by γ-lacton cycle. In the first step, we have prepared corresponding *S*-(2-oxotetrahydrofuran-3-yl)-*N*-(subst. phenyl) isothiuronium

Scheme 1



a: $R^1 = R^2 = R^3 = H$; $Z = CH$
b: $R^1 = 4\text{-}OCH_3$; $R^2 = R^3 = H$; $Z = CH$
c: $R^1 = 4\text{-}CH_3$; $R^2 = R^3 = H$; $Z = CH$
d: $R^1 = 4\text{-}Cl$; $R^2 = R^3 = H$; $Z = CH$
e: $R^1 = 4\text{-}Br$; $R^2 = R^3 = H$; $Z = CH$
f: $R^1 = 3\text{-}CF_3$; $R^2 = R^3 = H$; $Z = CH$
g: $R^1 = R^2 = R^3 = H$; $Z = N$
h: $R^1 = H$; $R^2 = CH_3$; $R^3 = H$; $Z = CH$
i: $R^1 = H$; $R^2 = C_2H_5$; $R^3 = H$; $Z = CH$
j: $R^1 = H$; $R^2 = C_6H_5$; $R^3 = H$; $Z = CH$
k: $R^1 = 4\text{-}OCH_3$; $R^2 = CH_3$; $R^3 = H$; $Z = CH$
l: $R^1 = 4\text{-}OCH_3$; $R^2 = H$; $R^3 = CH_3$; $Z = CH$
m: $R^1 = R^2 = H$; $R^3 = C_2H_5$; $Z = CH$
n: $R^1 = 4\text{-}Cl$; $R^2 = H$; $R^3 = CH_3$; $Z = CH$

bromides (**2a–n**) from substituted phenylthioureas (**1a–n**) and 3-bromotetrahydrofuran-2-one (α-bromo-γ-butyrolactone), which then underwent rearrangement in basic medium to give desired 5-(2-hydroxyethyl)-2-phenylimino-1,3-thiazolidin-4-ones (**3a–g**, **3l–n**) or 5-(2-hydroxyethyl)-2-phenylamino-4,5-dihydro-1,3-thiazol-4-ones (**3h–k**) (Scheme 1). In most cases, it was impossible to characterize pure isothiuronium salts by NMR because of their spontaneous cyclization giving **3a–n** in DMSO-d_6 solution.

The only exception was *S*-(2-oxotetrahydrofuran-3-yl)-*N*-(4-methoxyphenyl)isothiuronium bromide (**2b**) which was prepared in a pure form and characterized by ^{1}H, ^{13}C NMR, and microanalysis. The reason for enhanced reactivity of the other derivatives lies in the presence of electron-withdrawing group in the benzene nucleus or methyl group on nitrogen(s). All of these substituents facilitate rearrangement involving bicyclic tetrahedral intermediate.

Similar method [9] starting from substituted phenylthioureas and ethyl 3-bromo-5-methyl-2-oxo-tetrahydrofuran-3-carboxylate, ethyl 3-bromo-5,5-dimethyl-2-oxo-tetrahydrofuran-3-carboxylate, and ethyl 3-bromo-5-isobutoxymethyl-2-oxotetrahydrofuran-3-carboxylate giving spirocyclic 2-aza-3-amino or substituted amino-4-thia-7-oxa-8-methyl-8-substituted spiro[4.4]-2-nonene-1,6-diones was recently published. In this case, nitrogen atom of isothiuronium salt attacks ethoxycarbonyl group in position 3 instead of lactone carbonyl group.

Prepared 5-(2-hydroxyethyl)-2-phenylimino-1,3-thiazolidin-4-ones (**3a–g**, **3l–n**) 5-(2-hydroxyethyl)-2-phenylamino-4,5-dihydro-1,3-thiazol-4-ones (**3h–k**) were characterized by ^{1}H, ^{13}C NMR, and microanalyses and some of them also by X-ray diffraction (Figs. 1, 2) and mass spectroscopy.

Compounds **3a–f** carrying hydrogen atoms on both nitrogen atoms ($R^2 = R^3 = H$) exist in the form of two tautomers differing in the position of C=N double bond. Moreover, the tautomer with exocyclic double bond exists as a mixture of *E*- and *Z*-stereoisomers in the proportion depending on substitution of the benzene nucleus and temperature. This tautomerism and stereoisomerism, which can be seen in both ^{1}H and ^{13}C NMR spectra was previously studied for C-5 unsubstituted 2-phenyliminothiazolidin-4-ones by several authors [10].

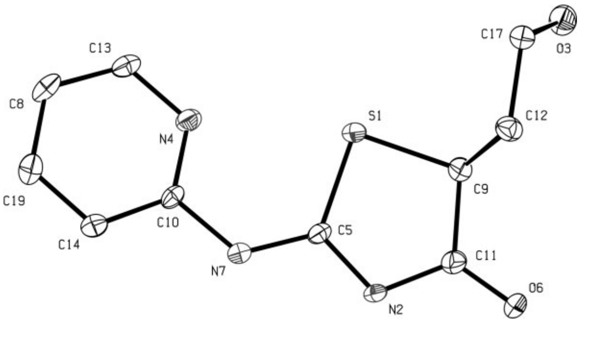


Figure 1. ORTEP view of compound **3g** (thermal ellipsoids at 40% probability).

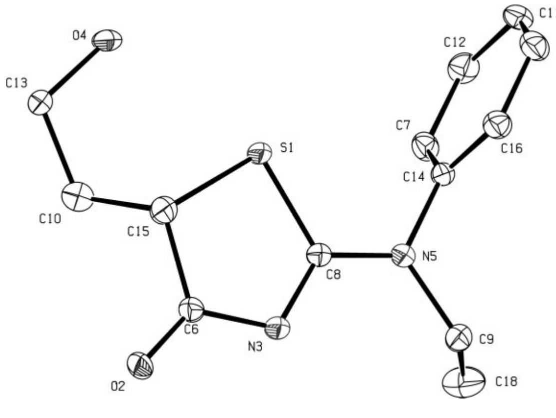


Figure 2. ORTEP view of compound **3i** (thermal ellipsoids at 40% probability).

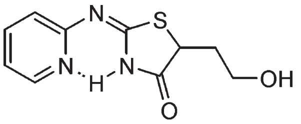


Figure 3. Intramolecular hydrogen bond in solution of **3g** in DMSO-d_6.

In the case of compounds **3h–k** ($R^2 = CH_3, C_2H_5, C_6H_5$; $R^3 = H$) and **3l–n** ($R^2 = H$; $R^3 = CH_3, C_2H_5$), prototropic tautomerism is absent due to C=N double bond fixation and stereoisomerism is possible only for **3l–n**. In both ^{1}H and ^{13}C NMR spectra of **3g**, there is only one set of signals. From this observation, it can be deduced that compound **3g** exists only as *E*-stereoisomer stabilized in solution by intramolecular hydrogen bond (Fig. 3). On the other hand, in crystal lattice two molecules of **3g** are connected by intermolecular hydrogen bonds ($N_{ring}—H\cdots N_{imino}$), which constrains *Z*-configuration of C=N double bond (Fig. 1).

EXPERIMENTAL

Starting arylthioureas **1a–n** were prepared and purified by known methods [11]. All other chemicals were purchased from commercial suppliers and used as received. Before use, solvents were dried and distilled. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 MHz instrument in DMSO-d_6 solution. Chemical shifts δ are referenced to solvent residual peak δ(DMSO-d_6) = 2.50 (^{1}H) and 39.6 ppm (^{13}C). Coupling constants *J* are quoted in Hz. ^{13}C NMR spectra were measured in a standard way and by means of the APT (attached proton test) pulse sequence to distinguish CH, CH_3, and CH_2, C_{quart}. Proton–proton connectivities were found by gs-COSY. Protonated carbon atoms were assigned by gs-HSQC spectra. All NMR experiments were performed with the aid of the manufacturer's software. The microanalyses were performed on an apparatus of Fisons Instruments, EA 1108 CHN. The mass spectra (EI) were recorded on an Agilent Technologies Co. gas chromatograph 6890N with a mass detector 5973 Network for samples dissolved in either ether or acetone.

X-ray Crystallography of 3g and 3i. The colorless single crystals of **3g** and **3i** were grown from DMSO solution. The X-ray diffraction data were collected at 150(2)K on a Nonius KappaCCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The structures were solved by direct methods (SIR92) [12]. All reflections were used in the structure refinement based on F2 by full-matrix least-squares technique (SHELXL97) [13].

Compound 3g. $C_{10}H_{11}N_3O_2S$; triclinic, space group P-1, $a = 5.7500(3)$, $b = 8.7980(3)$, $c = 10.9290(6)$ (Å), $\alpha = 90.703(4)°$, $\beta = 95.787(4)°$, $\gamma = 107.550(4)°$, $Z = 2$, $V = 523.93(4)$ Å^3, Dc = 1.504 g·cm^{-3}. Intensity data collected with $3.0 \leq \theta \leq 27.5°$; 2404 independent reflections measured; 2000 observed [$I > 2\sigma(I)$]. Final *R* index = 0.0589 (observed reflections), Rw = 0.1329 (all reflections), *S* = 1.112. CCDC 704421.

Compound 3i. $C_{13}H_{16}N_2O_2S$; monoclinic, space group P-21/c, $a = 9.3440(7)$, $b = 18.8800(1)$, $c = 7.5690(5)$ (Å), $\alpha = 90.000(5)°$, $\beta = 105.913(6)°$, $\gamma = 90.000(5)°$, $Z = 4$, $V = 1284.11(15)$ Å^3, Dc = 1.367 g·cm^{-3}. Intensity data collected with $3.0 \leq \theta \leq 27.5°$; 2849 independent reflections measured; 2406 observed [$I > 2\sigma(I)$]. Final *R* index = 0.0608 (observed reflections), Rw = 0.1481 (all reflections), *S* = 1.062. CCDC 704422.

Isothiuronium salts 2; General Procedure. To a hot solution of *N*-arylthiourea **1a–n** (5 mmol) in dry acetone 5 mmol (0.83 g) of 3-bromotetrahydrofuran-2-one was injected. Reaction mixture was refluxed for 5 min and left to stand at room temperature for 2 days. Then precipitated crystals were collected by filtration and submitted to cyclization. In the case of compounds **2d–g**, **2j**, **2l**, and **2n**, no crystals precipitated so that the solution was evaporated and resulting oil was submitted to cyclization without any further purification (yields are given only for **3d–g**, **3j**, **3l**, and **3n**). Crystalline isothiuronium salts **1a–c**, **1h**, **1i**, **1k**, and **1m** were characterized by melting point and by microanalysis. Only in the case of salt **1b**, it was possible to measure ^{1}H and ^{13}C NMR spectra immediately after its dissolution in DMSO-d_6. For all the other salts quick transformation to **3a–n** was observed during the measurement.

S-(2-Oxotetrahydrofuran-3-yl)-N-phenyl isothiuronium bromide (2a). Yield: 1.24g (78%); m.p. 153–155°C. *Anal.* Calcd. for $C_{11}H_{13}BrN_2O_2S$: C, 41.65; H, 4.13; N, 8.83; S, 10.11; Br, 25.19. Found: C, 41.74; H, 4.13; N, 9.01; S, 10.16; Br, 25.05.

S-(2-Oxotetrahydrofuran-3-yl)-N-(4-methoxyphenyl) isothiuronium bromide (2b). Yield: 0.77g (44%); m.p. 154–156°C; ^{1}H NMR (500 MHz): δ = 2.29 (m, 2H, CH_2), 3.65 (m, 2H, OCH_2), 3.82 (s, 3H, OCH_3), 4.72 (dd, *J* = 7.5 and 4.5 Hz, 1H, SCH), 7.16 (AA′XX′, *J* = 9 Hz, 2H, ArH), 7.37 (AA′XX′, *J* = 9 Hz, 2H, ArH), 10.79 (vbs, 3H, NH and NH_2).

^{13}C NMR (125 MHz): δ = 33.6 (CH_2), 47.5 (S—CH), 55.7 (OCH_3), 57.8 (O—CH_2), 115.3 (Ar C-3), 123.6 (Ar C-1), 129.6 (Ar C-2), 160.7 (Ar C-4), 174.1 (C=N), 175.0 (C=O). *Anal.* Calcd. for $C_{12}H_{15}BrN_2O_3S$: C, 41.51; H, 4.35; N, 8.07; S, 9.23; Br, 23.01. Found: C, 41.56; H, 4.29; N, 8.07; S, 9.08; Br, 22.99.

S-(2-Oxotetrahydrofuran-3-yl)-N-(4-methylphenyl) isothiuronium bromide (2c). Yield: 0.83g (50%); m.p. 160–164°C. *Anal.* Calcd. for $C_{12}H_{15}BrN_2O_2S$: C, 43.51; H, 4.56; N, 8.46; S, 9.68; Br, 24.12. Found: C, 43.71; H, 4.60; N, 8.26; S, 9.45; Br, 24.32.

S-(2-Oxotetrahydrofuran-3-yl)-N-phenyl-N-methyl isothiuronium bromide (2h). Yield: 1.3g (78%); m.p. 155–159°C. *Anal.* Calcd. for $C_{12}H_{15}BrN_2O_2S$: C, 43.51; H, 4.56; N, 8.46; S, 9.68; Br, 24.12. Found: C, 43.51; H, 4.86; N, 8.35; S, 9.90; Br, 24.03.

S-(2-Oxotetrahydrofuran-3-yl)-N-phenyl-N-ethyl isothiuronium bromide (2i). Yield: 1.59g (92%); m.p. 155–157°C. *Anal.* Calcd. for $C_{13}H_{17}BrN_2O_2S$: C, 45.23; H, 4.96; N, 8.11; S, 9.29; Br, 23.14. Found: C, 45.14; H, 5.11; N, 8.08; S, 9.03; Br, 23.20.

S-(2-Oxotetrahydrofuran-3-yl)-N-(4-methoxyphenyl)-N-methyl isothiuronium bromide (2k). Yield: 0.96g (53%); m.p. 164–167°C. *Anal.* Calcd. for $C_{13}H_{17}BrN_2O_3S$: C, 43.22; H, 4.74; N, 7.75; S, 8.87; Br, 22.12. Found: C, 43.06; H, 4.80; N, 7.66; S, 8.68; Br, 22.03.

S-(2-Oxotetrahydrofuran-3-yl)-N-phenyl-N′-ethyl isothiuronium bromide (2m). Yield: 1.3g (75%); m.p. 144–146°C. *Anal.* Calcd. for $C_{13}H_{17}BrN_2O_2S$: C, 45.23; H, 4.96; N, 8.11; S, 9.29; Br, 23.14. Found: C, 45.43; H, 5.08; N, 7.96; S, 9.10; Br, 23.14.

5-(2-Hydroxyethyl)-2-phenyliminothiazolidin-4-ones (3a-n); General Procedure. Isothiuronium salts (2 mmol) were dissolved in a minimum amount of aqueous ammonia (25%) and solution was stirred until precipitation of products. Crude products (yields 80–90%) were filtered off and recrystallized from water. Isothiuronium salts **2k–m** were quite insoluble in aqueous ammonia and stirring of suspension gave an oil which was extracted by dichloromethane. Extract was dried and evaporated to give oil solid which was characterized.

5-(2-Hydroxyethyl)-2-(phenylimino)-1,3-thiazolidin-4-one (3a). Yield: 0.44g (94%); m.p. 123–124°C; ^{1}H NMR (500 MHz): δ = 1.79 and 2.26 (2 × m, 2H, CH_2), 3.45 (m, 2H, OCH_2), 4.29 (m, 1H, S—CH), 4.74 (m, 1H, OH), 7.00 and 7.72 (2 × m, 2H, Ar H-2,6), 7.12 (m, 1H, Ar H-4), 7.36 (m, 2H, Ar H-3,5), 11.14, and 11.71 (2 × bs, 1H, NH); ^{13}C NMR (125 MHz): δ = 36.0 and 36.6 (CH_2), 47.7 and 52.1 (S—CH), 58.8 and 59.6 (O—CH_2), 120.5 and 121.6 (Ar C-2,6), 124.7 and 124.8 (Ar C-4), 129.1 and 129.4 (Ar C-3,5), 138.9 and 146.8 (Ar C-1), 177.5 and 178.5 (C=N), 190.6 (C=O). *Anal.* Calcd. for $C_{11}H_{12}N_2O_2S$: C, 55.91; H, 5.12; N, 11.86; S, 13.57. Found: C, 56.13; H, 5.32; N, 11.62; S, 13.35. EI-MS: *m/z* 236 [M^+], 218 [M^+—H_2O], 205, 192, 160, 151, 145, 135, 118 (100 %), 109, 101, 91, 77, 71, 65, 59, 51.

5-(2-Hydroxyethyl)-2-[(4-methoxyphenyl)imino]-1,3-thiazolidin-4-one (3b). Yield: 0.48g (91%); m.p. 124–126°C; ^{1}H NMR (500 MHz): δ = 1.76 and 2.27 (2 × m, 2H, CH_2), 3.52 (m, 2H, OCH_2), 3.74 (s, 3H, OCH_3), 4.26 (dt, *J* = 11.8 and 3.5 Hz, 1H, S—CH), 4.73 (m, 1H, OH), 6.94 (m, 2H, Ar H-3,5), 6.99 and 7.60 (2 × m, 2H, Ar H-2,6), 11.02 and 11.56 (2 × bs, 1H, NH); ^{13}C NMR (125 MHz): δ = 36.0 and 36.5 (CH_2), 48.4 and 52.0 (S—CH), 55.2 (OCH_3), 58.8 and 59.5 (O—CH_2), 114.0 and 114.4 (Ar C-3,5), 121.9 and 123.3 (Ar C-2,6), 131.9 (Ar C-1), 156.2 and 156.7 (Ar C-4), 176.6 (C=N), 190.3 (C=O). *Anal.* Calcd. for $C_{12}H_{14}N_2O_3S$: C, 55.12; H, 5.30; N, 10.52; S, 12.04. Found: C, 55.24; H, 5.26; N, 10.64; S, 12.01. EI-MS: *m/z* 266 [M^+], 248 [M—H_2O], 235, 222, 207, 191, 175, 165, 148, 133 (100%), 118, 105, 90, 78, 63, 55, 41.

5-(2-Hydroxyethyl)-2-[(4-methylphenyl)imino]-1,3-thiazolidin-4-one (3c). Yield: 0.43g (87%); m.p. 124–126°C; ^{1}H NMR (500 MHz): δ = 1.79 and 2.30 (2 × m, 2H, CH_2), 2.27 (s, 3H, CH_3), 3.52 (m, 2H, OCH_2), 4.27 (m, 1H, S—CH), 4.75 (m, 1H, OH), 6.91 and 7.14 (2 × AA′XX′, 2H, Ar H-2,6), 7.15 and 7.59 (2 × AA′XX′, 2H, Ar H-3,5), 11.08 and 11.64 (2 × bs, 1H, NH); ^{13}C NMR (125 MHz): δ = 20.3 (CH_3), 36.1 and 36.7 (CH_2), 48.1 and 52.1 (S—CH), 58.9 and 59.7 (O—CH_2), 120.4 and 121.7 (Ar C-2,6), 129.5 and 129.8 (Ar C-3,5), 134.0 (Ar C-4), 136.5 and 143.3 (Ar C-1), 177.1 and 179.4 (C=N), 190.6 (C=O). *Anal.* Calcd. for $C_{12}H_{14}N_2O_2S$: C, 57.58; H, 5.64; N, 11.19; S, 12.81. Found: C, 57.59; H, 5.69; N, 10.93; S, 12.74.

5-(2-Hydroxyethyl)-2-[(4-chlorophenyl)imino]-1,3-thiazolidin-4-one (3d). Overall yield: 1.7g (97%); m.p. 136–137°C; ^{1}H NMR (500 MHz): δ = 1.79 and 2.25 (2 × m, 2H, CH_2), 3.52 (m, 2H, OCH_2), 4.31 (m, 1H, S—CH), 4.75 (bs, 1H, OH), 6.96 and 7.37 (2 × AA′XX′, 2H, Ar H-2,6), 7.42 and 7.77 (2 × AA′XX′, 2H, Ar H-3,5), 11.26 and 11.80 (2 × bs, 1H, NH); ^{13}C NMR (125 MHz): δ = 35.8 and 36.5 (CH_2), 47.5 and 52.2 (S—CH), 58.7 and 59.6 (O—CH_2), 122.0 and 123.3 (Ar C-2,6), 128.6 (Ar C-4), 129.1 and 129.3 (Ar C-3,5), 137.1 and 146.7 (Ar C-1), 177.4 and 177.7 (C=N), 190.5 (C=O). *Anal.* Calcd. for $C_{11}H_{11}ClN_2O_2S$: C, 48.80; H, 4.10; N, 10.35; S, 11.84; Cl, 13.10. Found: C, 49.01; H, 4.27; N, 10.08; S, 11.60; Cl, 12.94.

5-(2-Hydroxyethyl)-2-[(4-bromophenyl)imino]-1,3-thiazolidin-4-one (3e). Overall yield: 1.21g; (61%) m.p. 140–141°C; ^{1}H NMR (500 MHz): δ = 1.81 and 2.26 (2 × m, 2H, CH_2), 3.50 (m, 2H, OCH_2), 4.31 (m, 1H, S—CH), 4.77 (bs, 1H, OH), 6.91 and 7.51 (2 × AA′XX′, 2H, Ar H-2,6), 7.56 and 7.67 (2 × AA′XX′, 2H, Ar H-3,5), 11.37 and 11.70 (2 × bs, 1H, NH); ^{13}C NMR (125 MHz): δ = 35.8 and 36.5 (CH_2), 47.5 and 52.1 (S—CH), 58.7 and 59.6 (O—CH_2), 116.7 (Ar C-4), 122.4 and 123.7 (Ar C-2,6), 132.0 and 132.3 (Ar C-3,5), 138.3 and 147.1 (Ar C-1), 176.6 (C=N), 190.6 (C=O). *Anal.* Calcd. for $C_{11}H_{11}BrN_2O_2S$: C, 41.92; H, 3.52; N, 8.89; S, 10.17; Br, 25.35. Found: C, 41.93; H, 3.71; N, 8.78; S, 10.40; Br, 24.98.

5-(2-Hydroxyethyl)-2-[(3-trifluoromethylphenyl)-imino]-1,3-thiazolidin-4-one (3f). Overall yield: 1.02g (53%); m.p. 130–131°C; ^{1}H NMR (500 MHz): δ = 1.83 and 2.26 (2 × m, 2H, CH_2), 3.52 (m, 2H, OCH_2), 4.34 (d, *J* = 6.0 Hz, 1H, S—CH), 4.78 (m, 1H, OH), 7.24 (m, 1H, Ar H-6), 7.48 (m, 1H, Ar H-4), 7.60 (m, 1H, Ar H-5), 7.89 and 8.22 (2 × m, 1H, Ar H-2), 11.02 and 11.56 (2 × bs, 1H, NH); ^{13}C NMR (125 MHz): δ = 35.6 and 36.4 (CH_2), 47.4 and 52.2 (S—CH), 58.6 and 59.6 (O—CH_2), 124.1 (q, *J* = 272 Hz, CF_3), 130.1 (q, *J* = 31.6 Hz, Ar C-3), 116.6 and 121.1 (Ar C-2), 117.8 and 120.8 (Ar C-5), 124.0 and 130.5 (Ar C-4), 125.2 and 130.6 (Ar C-6), 139.6 and 149.1 (Ar C-1), 176.9 and 178.3 (C=N), 190.6 (C=O). *Anal.* Calcd. for $C_{12}H_{11}F_3N_2O_2S$: C, 47.37; H, 3.64; N, 9.21; S, 10.54. Found: C, 47.56; H, 3.67; N, 9.42; S, 10.31.

5-(2-Hydroxyethyl)-2-[(2-pyridyl)imino]-1,3-thiazolidin-4-one (3g). Overall yield: 1.34g (84%); m.p. 187–188°C; ^{1}H NMR (500 MHz): δ = 1.82 and 2.22 (2 × m, 2H, CH_2), 3.58 (m, 2H, OCH_2), 4.10 (d, *J* = 7.0 Hz, 1H, S—CH), 4.78 (bs, 1H, OH), 7.11 (m, 2H, Ar H-4,6), 7.82 (m, 1H, Ar H-5), 8.42 (m, 1H, Ar H-3), 11.93 (bs, 1H, NH); ^{13}C NMR (125 MHz): δ = 35.9 (CH_2), 47.2 (S—CH), 58.9 (O—CH_2), 118.2 (Ar C-6), 119.8 (Ar C-4), 138.7 (Ar C-5), 146.9 (Ar C-3), 156.2 (Ar C-1), 165.3 (C=N), 180.7 (C=O). *Anal.* Calcd. for $C_{10}H_{11}N_3O_2S$: C, 50.62; H, 4.67; N, 17.71; S, 13.41. Found: C, 50.52; H, 4.44; N, 17.76; S, 13.64. EI-MS: *m/z* 237 [M^+], 206, 119 (100%), 78, 55, 44.

5-(2-Hydroxyethyl)-2-[(N-phenyl-N-methyl)amino]-4,5-dihydro-1,3-thiazol-4-one (3h). Yield: 0.40g (80%); m.p. 112–115°C; ^{1}H NMR (500 MHz): δ = 1.67 and 2.24 (2 × m, 2H, CH_2), 3.44 (m, 2H, OCH_2), 3.50 (s, 3H, NCH_3), 4.21 (d, *J* = 10.9 Hz, 1H, S—CH), 4.69 (bs, 1H, OH), 7.47 (m, 5H, Ar H-2,3,4,5,6); ^{13}C NMR (125 MHz): δ = 36.5 (CH_2), 41.8 (S—CH), 54.7 (NCH_3), 59.6 (O—CH_2), 127.1 (Ar C-2,6), 129.3 (Ar C-4), 130.0 (Ar C-3,5), 142.2 (Ar C-1), 181.9 (C=N), 189.3 (C=O). *Anal.* Calcd. for $C_{12}H_{14}N_2O_2S$: C, 57.58; H, 5.64; N, 11.19; S, 12.81. Found: C, 57.53; H, 5.56; N, 10.90; S, 12.76.

5-(2-Hydroxyethyl)-2-[(N-phenyl-N-ethyl)amino]-4,5-dihydro-1,3-thiazol-4-one (3i). Yield: 0.47g (90%); m.p. 158–160°C; ^{1}H NMR (500 MHz): δ = 1.12 (t, *J* = 7.1 Hz, 3H, CH_3), 1.67 and 2.26 (2 × m, 2H, CH_2), 3.46 (m, 2H, OCH_2), 4.01 (m, 2H, NCH_2), 4.23 (dd, *J* = 10.6 and 3.1 Hz, 1H, S—CH), 4.68 (t, *J* = 4.8 Hz, 1H, OH), 7.45 (m, 2H, Ar H-2,6), 7.52 (m, 3H, Ar H-3,4,5); ^{13}C NMR (125 MHz): δ =

12.6 (CH_3), 36.5 (CH_2), 49.0 (S—CH), 54.3 (NCH_3), 59.6 (O—CH_2), 128.2 (Ar C-2,6), 129.6 (Ar C-4), 130.0 (Ar C-3,5), 140.4 (Ar C-1), 181.7 (C=N), 189.5 (C=O). *Anal.* Calcd. for $C_{13}H_{16}N_2O_2S$: C, 59.07; H, 6.10; N, 10.60; S, 12.13. Found: C, 58.84; H, 5.92; N, 10.76; S, 12.31.

5-(2-Hydroxyethyl)-2-diphenylamino-4,5-dihydro-1,3-thiazol-4-one (3j). Overall yield: 1.66g (60%); m.p. 153–155°C; ^{1}H NMR (500 MHz): δ = 1.74 and 2.27 (2 × m, 2H, CH_2), 3.47 (m, 2H, OCH_2), 4.26 (dd, *J* = 7.5 and 3.0 Hz, 1H, S—CH), 4.73 (t, *J* = 5.0 Hz, 1H, OH), 7.33-7.63 (m, 10H, Ar H); ^{13}C NMR (125 MHz): δ = 36.1 (CH_2), 54.5 (S—CH), 59.4 (O—CH_2), 126.5 (Ar C-2,6), 128.5 (Ar C-4), 129.1 (Ar C-3,5), 129.9 (Ar C-1), 183.2 (C=N), 189.7 (C=O). *Anal.* Calcd. for $C_{17}H_{16}N_2O_2$: C, 65.36; H, 5.16; N, 8.97; S, 10.26. Found: C, 65.12; H, 5.27; N, 8.79; S, 10.44.

5-(2-Hydroxyethyl)-2-[(N-(4-methoxyphenyl)-N-methyl)amino]-4,5-dihydro-1,3-thiazol-4-one (3k). Yield: 0.44g (79%); m.p. 119–120°C; ^{1}H NMR (500 MHz): δ = 1.66 and 2.23 (2 × m, 2H, CH_2), 3.36 (s, 3H, NCH_3), 3.45 (m, 2H, OCH_2), 3.80 (s, 3H, OCH_3), 4.18 (dd, *J* = 10.5 and 3.0 Hz, 1H, S—CH), 4.76 (t, *J* = 5.5 Hz, 1H, OH), 7.05 (AA′XX′, *J* = 8.5 Hz, 2H, Ar H-2,6), 7.41 (AA′XX′, *J* = 8.5 Hz, 2H, Ar H-3,5); ^{13}C NMR (125 MHz): δ = 35.4 (CH_2), 41.7 (S—CH), 54.6 (NCH_3), 55.4 (OCH_3), 59.5 (O—CH_2), 114.8 (Ar C-2,6), 128.3 (Ar C-3,5), 134.8 (Ar C-1), 159.4 (Ar C-4), 182.1 (C=N), 189.2 (C=O). *Anal.* Calcd. for $C_{13}H_{16}N_2O_3S$: C, 55.70; H, 5.75; N, 9.99; S, 11.44. Found: C, 56.03; H, 5.96; N, 10.32; S, 11.76.

5-(2-Hydroxyethyl)-2-[(4-methoxyphenyl)imino]-3-methyl-1,3-thiazolidin-4-one (3l). Overall yield: 1.03g (57%); m.p. 101–103°C; ^{1}H NMR (500 MHz): δ = 1.83 and 2.28 (2 × m, 2H, CH_2), 3.16 (s, 3H, NCH_3), 3.43 and 3.51 (2 × m, 2H, OCH_2), 3.73 (s, 3H, OCH_3), 4.33 (dd, *J* = 9.7 and 3.5 Hz, 1H, S—CH), 4.76 (bs, 1H, OH), 6.91 (m, 4H, Ar H-2,3,5,6); ^{13}C NMR (125 MHz): δ = 29.2 (NCH_3), 35.8 (CH_2), 45.2 (S—CH), 55.1 (OCH_3), 58.4 (O—CH_2), 114.3 (Ar C-2,6), 122.0 (Ar C-3,5), 141.2 (Ar C-1), 154.4 (C=N), 156.0 (Ar C-4), 174.6 (C=O). *Anal.* Calcd. for $C_{13}H_{16}N_2O_3S$: C, 55.70; H, 5.75; N, 9.99; S, 11.44. Found: C, 55.81; H, 5.54; N, 10.37; S, 11.21. EI-MS: *m/z* 280 [M$^+$] (100 %), 265, 249, 236, 221, 207, 194, 179, 162, 147, 133, 119, 106, 90, 78, 64, 55, 45, 35.

5-(2-Hydroxyethyl)-2-(4-phenylimino)-3-ethyl-1,3-thiazolidin-4-one (3m). Yield: 0.17g (33%); oil; ^{1}H NMR (500 MHz): δ = 1.18 (t, *J* = 7.0 Hz, 3H, CH_3), 1.84 and 2.24 (2 × m, 2H, CH_2), 3.43-3.58 (m, 2H, OCH_2), 3.77 (q, *J* = 7.0 Hz, 2H, NCH_2), 4.34 (dd, *J* = 9.6 and 3.7 Hz, 1H, S—CH), 4.75 (bs, 1H, OH), 6.96 (d, *J* = 7.3 Hz, 2H, Ar H-2,6), 7.11 (t, *J* = 7.3 Hz, 1H, Ar H-4), 7.35 (t, *J* = 7.4 Hz, 2H, Ar H-3,5); ^{13}C NMR (125 MHz): δ = 12.3 (CH_3), 35.7 (CH_2), 37.4 (NCH_2), 45.3 (S—CH), 58.3 (O—CH_2), 121.0 (Ar C-2,6), 124.2 (Ar C-4), 129.2 (Ar C-3,5), 148.3 (Ar C-1), 154.0 (C=N), 174.4 (C=O). *Anal.* Calcd. for $C_{13}H_{16}N_2O_2S$: C, 59.07; H, 6.10; N, 10.60; S, 12.13. Found: C, 58.71; H, 5.96; N, 10.86; S, 11.88. EI-MS: *m/z* 264 [M$^+$] (100 %), 233, 221, 205, 192, 177, 163, 146, 131, 118, 104, 91, 77, 65, 55, 45, 35.

5-(2-Hydroxyethyl)-2-[(4-chlorophenyl)imino]-3-methyl-1,3-thiazolidin-4-one (3n). Overall yield: 1.15g (63%); m.p. 87–89°C; ^{1}H NMR (500 MHz): δ = 1.86 and 2.27 (2 × m, 2H, CH_2), 3.16 (s, 3H, NCH_3), 3.45 and 3.54 (2 × m, 2H, OCH_2), 4.36 (dd, *J* = 9.8 and 3.6 Hz, 1H, S—CH), 4.75 (t, *J* = 5.0 Hz, 1H, OH), 6.96 (AA′XX′, *J* = 8.5 Hz, 2H, Ar H-2,6) 7.40 (AA′XX′, *J* = 8.5 Hz, 2H, Ar H-3,5); ^{13}C NMR (125 MHz): δ = 29.0 (NCH_3), 35.3 (CH_2), 45.3 (S—CH), 58.1 (O—CH_2), 122.6 (Ar C-2,6), 128.0 (Ar C-4), 128.9 (Ar C-3,5), 147.0 (C-1), 155.6 (C=N), 174.3 (C=O). *Anal.* Calcd. for $C_{12}H_{13}ClN_2O_2S$: C, 50.61; H, 4.60; N, 9.84; S, 11.26. Found: C, 50.35; H, 4.63; N, 10.15; S, 11.02.

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Synthesis of Novel Pyrazole-Linked Norcantharidin Derivatives of Substituted Aromatic Amines with Efficient 1,3-Dipolar Cycloaddition

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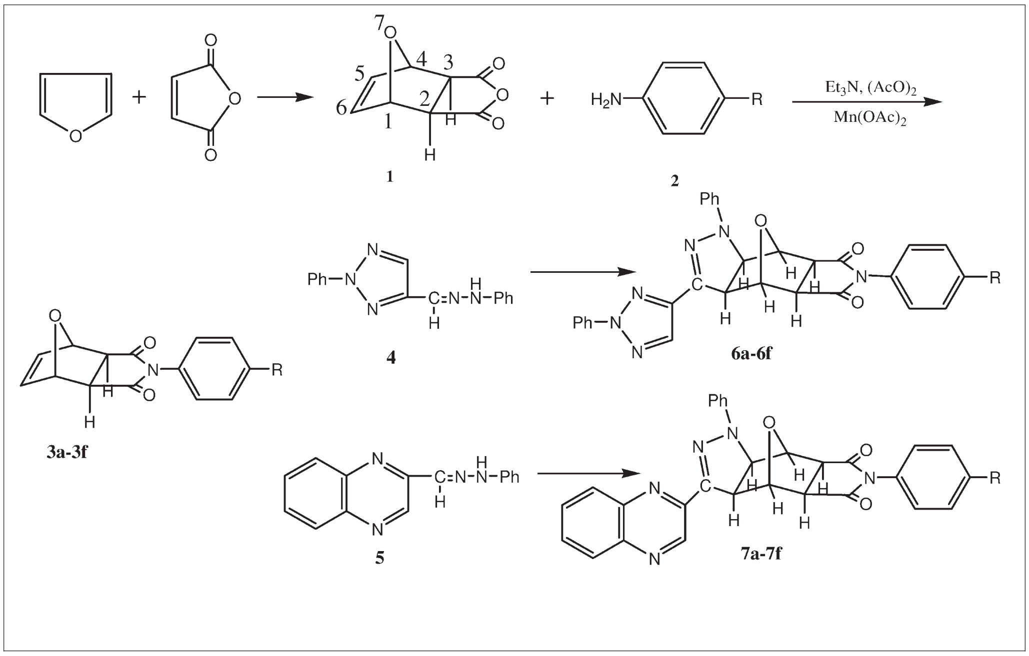

Highly efficient, practical and convenient synthesis of twelve compounds by the [3+2] 1, 3-dipolar cycloaddition reaction of norcantharidin derivatives of substituted aromatic amines with two hydrazines in the presence of chloramine-T.

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INTRODUCTION

Cantharidin (Figure 1), the principle active ingredient of Mylabris, a compound that has been used in China as a medicinal agent for 2000 years and for the treatment of cancer, particularly hepatoma [1]. Cantharidin is potentially attractive for the treatment of leukemia because it does not cause myelosuppression [2,3] and is effective against cells exerting the multidrug resistance phenotype [4]. Despite such qualities, the nephrotoxicity of cantharidin has prevented it from entering mainstream oncology. Norcantharidin (NCTD, Figure 1), the demethylated analogue of cantharidin, also possesses anticancer activity and stimulates the bone marrow, but without the urinary toxicity. Both agents are known protein phosphatase 1 (PP1) and protein phosphatase 2A (PP2A) inhibitors [5]. Pyrazoles [6,7] have been the subject of chemical and biological studies due to their interesting pharmacology including antipyretic, analgesic, anti-inflammatory potential herbicidal, fungicidal and leishmanicidal [8–11] properties. Stimulated by these findings, we combine pyrazoles with norcantharidin derivatives in one single molecule through 1,3-dipolar cycloaddition and we have successfully synthesized some compounds before [12]. With our sustained interest in the synthesis of norcantharidin derivatives we have achieved a facile 1,3-dipolar cycloaddition method by the use of chloramines-T. Chloramine-T, a versatile reagent in organic synthesis [13], was used in this article to generate nitrilimines *in situ* from hydrazines. Such type of compounds (Table 1) with versatile activities

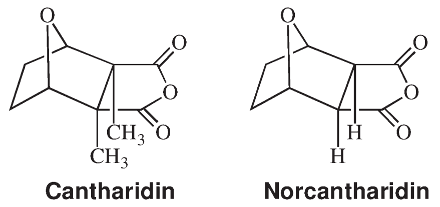


Figure 1. Chemical structures of cantharidin and noncantharidin.

may be of interest in chemistry, biochemistry and pharmacology [14].

RESULTS AND DISCUSSION

The precursor 5,6-dehydronorcantharidian derivatives **3a-3f** were synthesized by ‘‘one pot’’ method in good yield (Scheme 1) [12].

In this article, we have carried out the [4+2] cycloaddition of furan to maleic anhydride to obtain 5,6-dehydronorcantharidin **1**, then by "one pot" method, 5,6-dehydronorcantharidin reacted with substituted phenylamine **2a-2f** to give compounds **3a-3f**, after that, we carried out the [3+2] cycloaddition of **3a-3f** with **4**, **5** in the presence of chloramine-T respectively to obtain the target compounds **6a-6f**, **7a-7f** efficiently.

To identify the configuration of the pyrazoline with norcantharidin adducts (**6a-6f**, **7a-7f**), we have studied selective ^{1}H-^{1}HCOSY spectra, NOESY spectra of the compounds (take the example of **6a**). The exo-adduct (**6a-6f**, **7a-7f**) showed characteristic coupling for the bridge-head proton in the 400 MHz NMR spectrum which indicate that the protons involved are attached to the vicinal proton,[1] H-^{1}HCOSY spectrum showed cross peaks between C_2—H and C_3—H; between C_5—H and C_6—H; NOESY spectrum showed cross peaks between C_1—H and C_2—H; C_1—H and C_4—H; C_2—H and C_3—H; C_3—H and C_4—H; C_2—H and C_6—H; between C_3—H and C_5—H. This proves that the six protons are near in space and on the same side. The Diels-Alder adduct of furan with maleic anhydride has been shown to have the exo configuration exclusively; the endo isomer has never been reported [11]. This information combined with ^{1}H-^{1}HCOSY spectra and NOESY spectra data give us a definite configuration as we have proved before [12].

EXPERIMENTAL

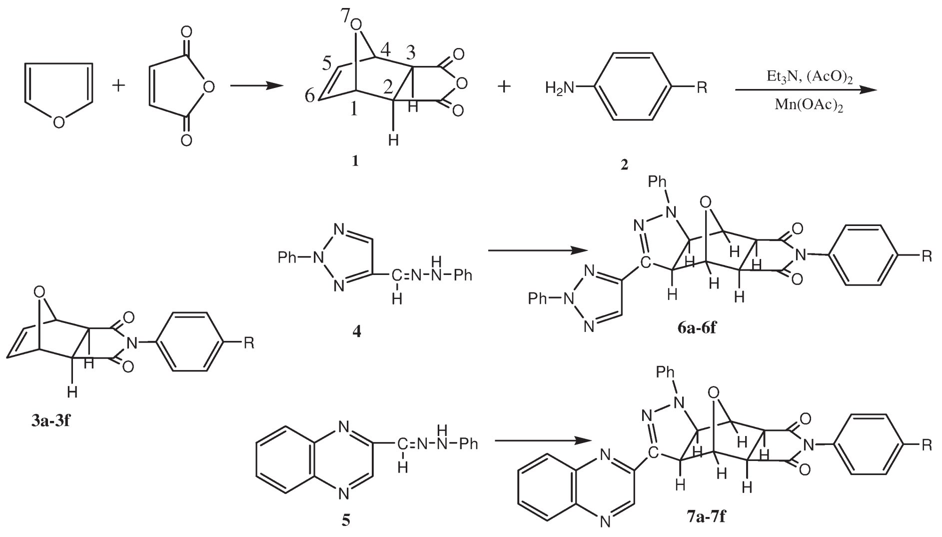
Melting points were obtained on a B-540 Bűchi melting point apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Brucker AM-400 M Hz spectrometer with

Table 1

Physical data of the compounds.

Compound	R_1	Time (h)	Mp (°C)	Yield (%)	Molecular formula	Analysis % Calcd./Found		
						C	H	N
6a	H	7	278	88.3	$C_{29}H_{22}N_6O_3$	69.31 69.30	4.41 4.44	16.72 16.71
6b	Cl	4	276	93.7	$C_{29}H_{21}ClN_6O_3$	64.87 64.87	3.94 3.95	15.65 15.63
6c	CH_3	3	280	89.4	$C_{30}H_{24}N_6O_3$	69.76 69.75	4.68 4.70	16.27 16.25
6d	OCH_3	5	256	89.7	$C_{30}H_{24}N_6O_4$	67.66 67.65	4.54 4.56	15.78 15.76
6e	OH	8	260	72.4	$C_{29}H_{22}N_6O_4$	67.17 67.18	4.28 4.29	16.21 16.20
6f	NO_2	4	239	85.2	$C_{29}H_{21}N_7O_5$	63.62 63.61	3.87 3.89	17.91 17.92
7a	H	5	299	83.5	$C_{29}H_{21}N_5O_3$	71.45 71.44	4.34 4.36	14.37 14.37
7b	Cl	4.5	293	85.4	$C_{29}H_{20}ClN_5O_3$	66.73 66.74	3.86 3.85	13.42 13.41
7c	CH_3	4	266	79.3	$C_{30}H_{23}N_5O_3$	71.84 71.85	4.62 3.64	13.96 13.95
7d	OCH_3	6	278	69.6	$C_{30}H_{23}N_5O_4$	69.62 69.63	4.48 4.47	13.53 13.53
7e	OH	8	298	90.7	$C_{29}H_{21}N_5O_4$	69.18 69.17	4.20 4.20	13.91 13.93
7f	NO_2	7	159	94.6	$C_{29}H_{20}N_6O_5$	65.41 65.42	3.79 3.80	15.78 15.77

Scheme 1



2a, 3a, 4a, 5a R=H; **2b, 3b, 4b, 5b** R=Cl; **2c, 3c, 4c, 5c** R=CH$_3$;
2d, 3d, 4d, 5d R=OCH$_3$; **2e, 3e, 4e, 5e** R=OH; **2f, 3f, 4f, 5f** R=NO$_2$;

SiMe$_4$ as the internal standard in CDCl$_3$. Mass spectra were made with a HP5989B analyzer. Element analyses were performed on a EA-1110 instrument.

“One-pot” method for the preparation of 3-acetyl-7-oxa-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid phenylamide 3a-3f. All this work we have done before [12].

General procedure for the preparation of the pyrazole-linked norcantharidin derivatives of substituted aromatic amines (6a-6f, 7a-7f). To a solution of 3-acetyl-7-oxa-bicyclo [2.2.1] hept-5-ene-2-carboxylic acid phenylamide **3a** (1 mmole) and 2-phenyl-4-((2-phenylhydrazono) methyl)-2H-1, 2, 3-triazole **4** (1 mmole) in ethanol (20 mL), add chloramine T (1.2 mmole) and the reaction mixture was refluxed in ethanol for 3–8 h which were monitored by thin-layer chromatography. Then washed with water (30 mL) and extracted with dichloromethane (30 mL). The extracts were dried over anhydrous sodium sulfate, concentrated *in vacuum* and the residue was recrystallized from menthol to give the compound **6a**. The synthesis of compounds **6b-6f, 7a-7f** was performed using the same method.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(phenyl)-4,8-epoxy-1-phenyl-3-(2-phenyl-**2H*****-1,2,3-triazol-4-yl)-4,4a,6,7a,8,8a-hexahydropyrrolo[3,4-f]indazole-5,7(*****1H,3aH*****)-dione (6a).*** This compound was obtained as yellow crystals, yield 88.3%, m.p. 278°C; ir (potassium bromide): 3473(N—C=O), 3064 (ArH), 1714 (C=O), 1597 (C=N), 1189 (C—O—C) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ: 8.53(s, 1H, H—C=N), 8.20–6.93 (M, 15H, Ar—H), 5.51 (s, 1H, C$_4$—H) 5.34 (s, 1H, C$_1$—H) 4.65–4.62 (d, J = 9.60 Hz, 1H, C$_5$—H), 4.21–4.18 (d, J = 9.60 Hz, 1H, C$_6$—H), 3.41–3.39 (d, J = 7.20 Hz, 1H, C$_3$—H), 3.30–3.28 (d, J = 7.20 Hz, 1H, C$_2$—H). ms (70 ev): m/z 502 (M$^+$). *Anal.* Calcd. for $C_{29}H_{22}N_6O_3$: C, 69.31; H, 4.41; N, 16.72. Found: C, 69.30; H, 4.43; N, 16.71.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(4-chlorophenyl)-4,8-epoxy-1-phenyl-3-(2-phenyl-**2H*****-1,2,3-triazol-4-yl)-4,4a,6,7a,8,8a-hexahydropyrrolo[3,4-f]indazole-5,7(*****1H,3aH*****)-dione (6b).*** This compound was obtained as yellow crystals, yield 93.7%, m.p. 276°C; ir (potassium bromide): 3448(N—C=O), 3058 (ArH), 1700 (C=O), 1596 (C=N), 1199 (C—O—C) cm^{-1}; ^{1}H NMR (CDCl$_3$)δ: 8.52(s, 1H, H—C=N), 8.21–6.93 (M, 14H, Ar—H), 5.50 (s, 1H, C$_4$—H) 5.34 (s, 1H, C$_1$—H) 4.66–4.64 (d, J = 9.20 Hz, 1H, C$_5$—H), 4.20–4.17 (d, J = 9.20 Hz, 1H, C$_6$—H), 3.41–3.39 (d, J = 7.20 Hz, 1H, C$_3$—H), 3.30–3.28 (d, J = 7.20 Hz, 1H, C$_2$—H). ms (70 ev): m/z 536 (M$^+$) 538 (M$^+$+2). *Anal.* Calcd. for $C_{29}H_{21}ClN_6O_3$: C, 64.87; H, 3.94; N, 15.65. Found: C, 64.87; H, 3.95; N, 15.63.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(p-tolyl)-4,8-epoxy-1-phenyl-3-(2-phenyl-**2H*****-1,2,3-triazol-4-yl)-4,4a,6,7a,8,8a-hexahydropyrrolo[3,4-f]indazole-5,7(*****1H,3aH*****)-dione (6c).*** This compound was obtained as yellow crystals, yield 89.4%, m.p. 280° C; ir (potassium bromide): 3482(N—C=O), 3057(ArH), 1717 (C=O), 1597 (C=N), 1202 (C—O—C) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ: 8.51(s, 1H, H—C=N), 8.20–6.92 (M, 14H, Ar—H), 5.50 (s, 1H, C$_4$—H) 5.33 (s, 1H, C$_1$—H) 4.65–4.63 (d, J = 9.20 Hz, 1H, C$_5$—H), 4.21–4.19 (d, J = 9.20 Hz, 1H, C$_6$—H), 3.41–3.39 (d, J = 7.20 Hz, 1H, C$_3$—H), 3.30–3.28 (d, J = 7.20 Hz, 1H, C$_2$—H), 2.37 (s, 3H, CH$_3$). ms (70 ev): m/z 516 (M$^+$). *Anal.* Calcd. for $C_{30}H_{24}N_6O_3$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.75; H, 4.70; N, 16.25.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(4-methoxyphenyl)-4,8-epoxy-1-phenyl-3-(2-phenyl-**2H*****-1,2,3-triazol-4-yl)-4,4a,6,7a,8,8a-hexahydropyrrolo[3,4-f]indazole-5,7(*****1H,3aH*****)-dione (6d).*** This compound was obtained as yellow crystals, yield 89.7%, m.p. 256°C; ir (potassium bromide): 3448 (N—C=O), 3062 (ArH), 1711 (C=O), 1596 (C=N), 1190 (C—O—C) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ: 8.54(s, 1H, H—C=N), 8.21–6.95 (M, 14H, Ar—H), 5.51 (s, 1H, C_4—H) 5.34 (s, 1H, C_1—H) 4.67–4.65 (d, J = 9.20 Hz, 1H, C_5—H), 4.21–4.19 (d, J = 9.20 Hz, 1H, C_6—H), 3.81 (s, 3H, OCH_3) 3.41–3.39 (d, J = 7.20 Hz, 1H, C_3—H), 3.31–3.29 (d, J = 7.20 Hz, 1H, C_2—H). ms (70 ev): m/z 532 (M^+). *Anal*. Calcd. for $C_{30}H_{24}N_6O_4$: C, 67.66; H, 4.54; N, 15.78 Found: C, 67.65; H, 4.56; N, 15.76.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(4-hydroxyphenyl)-4,8-epoxy-1-phenyl-3-(2-phenyl-*2H*-1,2,3-triazol-4-yl)-4,4a,6,7a,8,8a-hexahydropyrrolo[3,4-f]indazole-5,7(*1H,3aH*)-dione (6e). This compound was obtained as yellow crystals, yield 72.4%, m.p. 260°C; ir (potassium bromide): 3448(N—C=O), 3022 (ArH), 1708 (C=O), 1596 (C=N), 1186 (C—O—C) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.55(s, 1H, H—C=N), 8.21–6.95 (M, 14H, Ar—H), 5.50 (s, 1H, C_4—H) 5.33 (s, 1H, C_1—H) 4.67–4.64 (d, J = 9.20 Hz, 1H, C_5—H), 4.23–4.20 (d, J = 9.20 Hz, 1H, C_6—H), 3.42–3.40 (d, J = 7.20 Hz, 1H, C_3—H), 3.32–3.30 (d, J = 7.20 Hz, 1H, C_2—H). ms (70 ev): m/z 518 (M^+). *Anal*. Calcd. for $C_{29}H_{22}N_6O_4$: C, 67.17; H, 4.28; N, 16.21. Found: C, 67.18; H, 4.29; N, 16.20.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(4-nitrophenyl)-4,8-epoxy-1-phenyl-3-(2-phenyl-*2H*-1,2,3-triazol-4-yl)-4,4a,6,7a,8,8a-hexahydropyrrolo[3,4-f]indazole-5,7(*1H,3aH*)-dione (6f). This compound was obtained as yellow crystals, yield 85.2%, m.p. 239°C; ir (potassium bromide): 3448(N—C=O), 3062 (Ar—H), 1710 (C=O), 1596 (C=N), 1174 (C—O—C) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.54(s, 1H, H—C=N), 8.34–6.94 (M, 14H, Ar—H), 5.54 (s, 1H, C_4—H) 5.37 (s, 1H, C_1—H), 4.70–4.68 (d, J = 9.20 Hz, 1H, C_5—H), 4.26–4.24 (d, J = 9.20 Hz, 1H, C_6—H), 3.49–3.47 (d, J = 7.20 Hz, 1H, C_3—H), 3.38–3.36 (d, J = 7.20 Hz, 1H, C_2—H). ms (70 ev): m/z 547 (M^+). *Anal*. Calcd. for $C_{29}H_{21}N_7O_5$: C, 63.62; H, 3.87; N, 17.91 Found: C, 63.61; H, 3.89; N, 17.92.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(phenyl)-4,8-epoxy-1-phenyl-3-(quinoxalin-2-yl)-4,4a,6,7a,8,8a-hexahydropyrrolo[3,4-f]indazole-5,7(*1H,3aH*)-dione (7a). This compound was obtained as yellow crystals, yield 83.5%, m.p. 299°C; ir (potassium bromide): 3474(N—C=O), 3045 (ArH), 1714 (C=O), 1598 (C=N), 1227 (C—O—C) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 9.54 (s, 1H, H—C=N), 8.14–7.00 (M, 14H, Ar—H), 5.58 (s, 1H, C_4—H), 5.38 (s, 1H, C_1—H), 4.70–4.68 (d, J = 9.20 Hz, 1H, C_5—H), 4.26–4.24 (d, J = 9.20 Hz, 1H, C_6—H), 3.49–3.47 (d, J = 7.20 Hz, 1H, C_3—H), 3.38–3.36 (d, J = 7.20 Hz, 1H, C_2—H). ms (70 ev): m/z 487 (M^+). *Anal*. Calcd. for $C_{29}H_{21}N_5O_3$: C, 71.45; H, 4.34; N, 14.37. Found: C, 71.44; H, 4.36; N, 14.37.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(4-chlorophenyl)-4,8-epoxy-1-phenyl-3-(quinoxalin-2-yl)-4,4a,6,7a,8,8a-hexahydropyrrolo [3,4-f]indazole-5,7(*1H,3aH*)-dione (7b). This compound was obtained as yellow crystals, yield 85.4%, m.p. 293°C; ir (potassium bromide): 3448(N—C=O), 3065 (ArH), 1708 (C=O), 1560 (C=N), 1186 (C—O—C) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 9.55 (s, 1H, H—C=N), 8.14–7.01 (M, 13H, Ar—H), 5.58 (s, 1H, C_4—H), 5.37 (s, 1H, C_1—H), 4.70–4.68 (d, J = 9.20 Hz, 1H, C_5—H), 4.26–4.24 (d, J = 9.20 Hz, 1H, C_6—H), 3.48–3.46 (d, J = 7.20 Hz, 1H, C_3—H), 3.36–3.34 (d, J = 7.20 Hz, 1H, C_2—H).ms (70ev): m/z 523 (M^++2), 522 (M^++1) 521 (M^+). *Anal*. Calcd. for $C_{29}H_{20}ClN_5O_3$: C, 66.73; H, 3.86; N, 13.42. Found: C, 66.74; H, 3.85; N, 13.41.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(p-tolyl)-4,8-epoxy-1-phenyl-3-(quinoxalin-2-yl)-4,4a,6,7a,8,8a-hexahydropyrrolo[3,4-f] indazole-5,7(*1H,3aH*)-dione (7c). This compound was obtained as yellow crystals, yield 79.3%, m.p. 266°C; ir (potassium bromide): 3473(N—C=O), 3047 (ArH), 1715 (C=O), 1598 (C=N), 1226 (C—O—C) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 9.53 (s, 1H, H—C=N), 8.12–6.99 (M, 13H, Ar—H), 5.56 (s, 1H, C_4—H), 5.37 (s, 1H, C_1—H), 4.74–4.72 (d, J = 9.20 Hz, 1H, C_5—H), 4.38–4.36 (d, J = 9.20 Hz, 1H, C_6—H), 3.48–3.46 (d, J = 7.20 Hz, 1H, C_3—H), 3.33–3.31 (d, J = 7.20 Hz, 1H, C_2—H), 2.37 (s, 3H, CH_3).ms (70 ev): m/z 501 (M^+). *Anal*. Calcd. for $C_{30}H_{23}N_5O_3$: C, 71.84; H, 4.62; N, 13.96. Found: C, 71.85; H, 3.64; N, 13.95.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(4-methoxyphenyl)-4,8-epoxy-1-phenyl-3-(quinoxalin-2-yl)-4,4a,6,7a,8,8a-hexahydropyrrolo [3,4-f]indazole-5,7(*1H,3aH*)-dione (7d). This compound was obtained as yellow crystals, yield 69.6%, m.p. 278°C; ir (potassium bromide): 3448(N—C=O), 3043 (ArH), 1701 (C=O), 1560 (C=N), 1201 (C—O—C) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 9.56 (s, 1H, H—C=N), 7.40–6.56 (M, 13H, Ar—H), 5.57 (s, 1H, C_4—H), 5.39 (s, 1H, C_1—H), 4.74–4.72 (d, J = 9.20 Hz, 1H, C_5—H), 4.38–4.36 (d, J = 9.20 Hz, 1H, C_6—H), 3.81 (s, 3H, OCH_3), 3.48–3.46 (d, J = 7.20 Hz, 1H, C_3—H), 3.33–3.31 (d, J = 7.20 Hz, 1H, C_2—H). ms (70 ev): m/z 517(M^+). *Anal*. Calcd. for $C_{30}H_{23}N_5O_4$: C, 69.62; H, 4.48; N, 13.53. Found: C, 69.63; H, 4.47; N, 13.53.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(4-hydroxyphenyl)-4,8-epoxy-1-phenyl-3-(quinoxalin-2-yl)-4,4a,6,7a,8,8a-hexahydropyrrolo [3,4-f]indazole-5,7(*1H,3aH*)-dione (7e). This compound was obtained as yellow crystals, yield 90.7%, m.p. 298°C; ir (potassium bromide): 3476(N—C=O), 3062 (ArH), 1710 (C=O), 1598 (C=N), 1210 (C—O—C) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 9.55 (s, 1H, H—C=N), 8.14–7.01 (M, 13H, Ar—H), 5.58 (s, 1H, C_4—H), 5.37 (s, 1H, C_1—H), 4.70–4.68 (d, J = 9.20 Hz, 1H, C_5—H), 4.26–4.24 (d, J = 9.20 Hz, 1H, C_6—H), 3.48–3.46 (d, J = 7.20 Hz, 1H, C_3—H), 3.36–3.34 (d, J = 7.20 Hz, 1H, C_2—H).ms (70 ev): m/z 503 (M^+). *Anal*. Calcd. for $C_{29}H_{21}N_5O_4$: C, 69.18; H, 4.20; N, 13.91. Found: C, 69.17; H, 4.20; N, 13.93.

rel-(3aR,4S,4aR,7aS,8S,8aR)-6-(4-nitrophenyl)-4,8-epoxy-1-phenyl-3-(quinoxalin-2-yl)-4,4a,6,7a,8,8a-hexahydropyrrolo [3,4-f]indazole-5,7(*1H,3aH*)-dione (7f). This compound was obtained as yellow crystals, yield 94.6%, m.p. 159°C; ir (potassium bromide): 3442(N—C=O), 3045 (ArH), 1718 (C=O), 1598 (C=N), 1178 (C—O—C) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 9.54 (s, 1H, H—C=N), 8.34–6.93 (M, 13H, Ar—H), 5.61 (s, 1H, C_4—H), 5.40 (s, 1H, C_1—H), 4.80–4.78 (d, J = 9.20 Hz, 1H, C_5—H), 4.43–4.41 (d, J = 9.20 Hz, 1H, C_6—H), 3.57–3.55 (d, J = 7.20 Hz, 1H, C_3—H), 3.42–3.40 (d, J = 7.20 Hz, 1H, C_2—H).ms (70 ev): m/z 532 (M^+). *Anal*. Calcd. for $C_{29}H_{20}N_6O_5$: C, 65.41; H, 3.79; N, 15.78. Found: C, 65.42; H, 3.80; N, 15.77.

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One-Pot Synthesis of Quinazoline-2,4(1*H*,3*H*)-diones and 2-Thioxoquinazolinones with the Aid of Low-Valent Titanium Reagent

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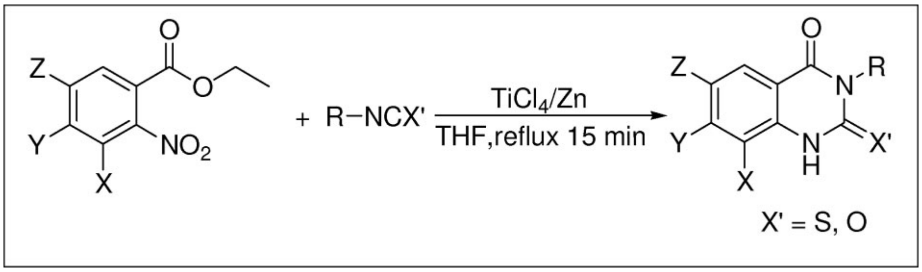

An efficient, convenient, one-pot synthesis of 2,4(1*H*,3*H*)-quinazolinediones and 2-thioxoquinazolinones was accomplished in good yields *via* the novel reductive cyclization of ethyl 2-nitrobenzoates with isocyanates or isothiocyanates mediated by $TiCl_4$/Zn system.

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INTRODUCTION

It has been reported that quinazolinones show antihypertonic, antirheumatic, antianaphylactic, antiasthmatic, tranquilizing, neuro-stimulating, and benzodiazepine binding activity [1,2]. The quinazolindione moiety, in particular, is widely found in natural purine based, alkaloids and many biologically active compounds [3]. For example, 3-substituted quinazolinones, such as SGB-1534 (**1**) and ketanserin (**2**) have been found to have antihypertensive activities mediated *via* α-adrenoceptor and serotonic receptor anatgonism [4], respectively. 6,7-Dimethoxy-1*H*-quinazoline-2,4-dione is a key intermediate for the production of the following medicines (Prazosin (Minipress) [5], Bunazosin (Detantol) [5], and Doxazosin (Cardenalin) [5]. 7-Chloro-1*H*-quinazoline-2,4-diones is also a key intermediate for the production of the medicines such as FK366 [6] and KF31327 [7].

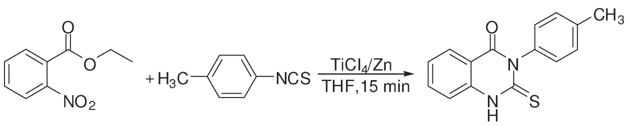
The quinazolinedione ring system can generally be prepared by the reaction of anthranilic acid with urea [8], anthranilamide with phosgene [9], and anthranilic acid with potassium cyanate [10] or chlorosulfonyl isocyanate [11]. However, these synthetic methods are considerably limited because of the usage of drastic conditions and uneasily starting materials. Different solid-phase combinatorial synthesis of quinazolinediones was reported in recent years, but these methods need long reaction times, multiple steps, or both [12]. Carbon dioxide reacted with 2-aminobenzonitriles assisted by excess amount of DBU or DBN to give corresponding 1*H*-quinazoline-2,4-diones has been reported [13]. However, the reaction time is too long (24 h). A recent report details the preparation of 2,4(1*H*,3*H*)-quinazolinediones and 2-thioxoquinazolines assisted by microwave [14], but the yields of this protocol were a little lower. It is found that all the methods mentioned earlier used amino-compounds other than nitro-compounds as starting materials. Therefore, we became interested in developing a novel and convenient synthetic method for the preparation of quinazolinedione derivatives start with nitro-compounds. Our initial studies showed that successful synthesis of various quinazolinediones from 2-nitrobenzamides and triphosgene [15]. As part of our ongoing research for novel synthesis of quinazolinediones derivatives, herein, we describe a new one-pot synthesis of quinazolinedione derivatives by treating ethyl *o*-nitrobenzoates with isothiocyanates or isocyanates under low-valent titanium reagent ($TiCl_4$/Zn).

RESULTS AND DISCUSSION

On the basis of our previous experience, we selected ethyl 2-nitrobenzoate **1a** and the 4-methylphenyl isothiocyanate **2a** as model substrates to optimize the experimental conditions for the proposed reductive cyclization reaction (Scheme 1). The results are summarized in Table 1.

As shown in Table 1, we briefly examined the effect of different temperatures and ratio of **1a**:$TiCl_4$/Zn. The

Scheme 1



1a **2a** **3a**

results obtained from these experiments indicated that the reaction temperatures had a significant influence on the success of this reaction. At room temperature or 40°C, no expected compound was detected (Table 1, entries 1 and 2). To our delight at refluxed the reaction proceeded smoothly in high yield (entry 4). To further evaluate the influence of the ratio of **1a**:$TiCl_4$/Zn, this reaction was carried out with different ratio. From the results it is obvious that the best ratio is 1:3.

Having established an optimal condition for the protocol, we performed a more detailed examination of the substrates. Thus, the behavior of a variety of substrates, which include different ethyl 2-nitrobenzoates as well as different isothiocyanates or isocyanates, was examined.

First of all, we performed the reaction of a variety of ethyl 2-nitrobenzoates **1** and isothiocyanates **2** *via* $TiCl_4$/Zn system (Scheme 2, Table 2).

As shown in Table 2, it can be seen that this protocol can be applied not only to aliphatic isothiocyanates but also to aromatic isothiocyanates with either electron-withdrawing groups (such as halide groups) or electron-donating groups (such as alkyl groups) under the same conditions. Furthermore, it was particularly noteworthy that the effects of substituted ethyl 2-nitrobenzoates were also investigated. 4-Chloro and 3-methyl substitution can also give moderate to good yields. However, the reductive cyclization was hindered by severe steric hindrance. For instance, no expected product was obtained when ethyl 2-nitrobenzoate was reacted with 2,6-di-*i*-pr-substituted aryl isothiocyanate.

A second part of the research was designed to synthesize quinazoline-2,4(1*H*,3*H*)-diones *via* the novel reductive cyclization of ethyl 2-nitrobenzoates with isocyanates under the same reaction conditions (Scheme 3, Table 3).

Table 1

Optimization for the reductive cyclization reaction.

Entry	Temperature (°C)	Ratio[a]	Isolated yield (%)
1	r.t.	1:3	0
2	40	1:3	0
3	60	1:3	10
4	Reflux	1:3	93
5	Reflux	1:1	0
6	Reflux	1:2	57
7	Reflux	1:4	83
8	Reflux	1:5	80

[a] Ratio of **1** and $TiCl_4$/Zn system.

Similarly, aryl isocyanates containing electron-donating and electron-withdrawing substituents were reacted well with ethyl 2-nitrobenzoate, therefore, we can conclude that the electronic nature of the substituents has no significant effect on this reaction, but severe steric hindrance still play an important part in this reaction. Good yields were also obtained when 3-methyl or 4-Cl-substituted ethyl 2-nitrobenzoates were used. Meanwhile, it was found that isocyanates showed similar reactivity trends with isothiocyanates.

The structures of products **3** and **5** were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and HRMS.

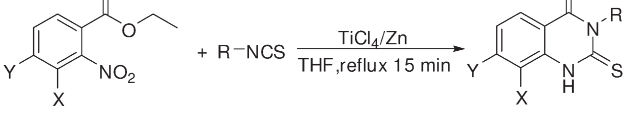
In conclusion, a series of quinazoline-2,4(1*H*,3*H*)-diones and 2-thioxoquinazolinones were synthesized induced by low-valent titanium reagent ($TiCl_4$/Zn). The protocol has been used for nitro-compounds other than amino-compounds as starting materials, which is very economic. Meanwhile, a variety of substrates can participate in the procedure with good yields. Furthermore, this method still has the advantages of short reaction time and convenient manipulation.

EXPERIMENTAL

THF was distilled from sodium-benzophenone immediately before use. All reactions were conducted under N_2 atmosphere. Melting points are uncorrected. IR spectra were recorded on Varian F-1000 spectrometer in KBr with absorptions in cm^{-1}. ^{1}H and ^{13}C NMR were determined on Varian-400 MHz spectrometer in DMSO-d_6 solution. *J* values are in Hz. Chemical shifts are expressed in ppm downfield from internal standard TMS.

General procedure for synthesis of thioxoquinazolineones 3. $TiCl_4$ (0.3 mL, 3 mmol) was added dropwise using a syringe to a stirred suspension of zinc powder (0.384 g, 6 mmol) in freshly distilled anhydrous THF (10 mL) at RT under a dry N_2 atmosphere. After completion of the addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to RT and a solution of ethyl 2-nitrobenzoates (1 mmol) and isothiocycanates (1 mmol) in THF (5 mL) was added dropwise. The reaction mixture was then refluxed for 15 min under N_2. After this period, the TLC analysis of the mixture showed the reaction to be completed. The reaction mixture was quenched with 5% HCl (15 mL) and extracted with $ClCH_2CH_2Cl$ (3 × 20 mL). The combined extracts were washed with water (3 × 20 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product was purified by recrystallization from 95% ethanol.

Scheme 2



1 **2** **3**

Table 2

Synthesis of 2-thioxoquinazolinones.

Entry	X	Y	R	Products	Yields (%)[a]
1	H	H	4-$CH_3C_6H_4$	**3a**	93
2	H	H	C_6H_5	**3b**	90
3	H	H	3-$CH_3C_6H_4$	**3c**	78
4	H	H	$C_6H_5CH_2$	**3d**	86
5	H	Cl	C_6H_5	**3e**	71
6	H	Cl	4-ClC_6H_4	**3f**	72
7	H	Cl	3-$CH_3C_6H_4$	**3g**	86
8	H	Cl	$C_6H_5CH_2$	**3h**	83
9	CH_3	H	C_6H_5	**3i**	86
10	CH_3	H	4-ClC_6H_4	**3j**	89
11	CH_3	H	3-ClC_6H_4	**3k**	82
12	H	H	2,6-di-*i*-PrC_6H_4	**3l**	0

[a] Isolated yield.

2-Thioxo-3-*p*-tolyl-2,3-dihydroquinazolin-4(1*H*)-one (3a). This compound was obtained as solid with mp >300°C (ref. 16; 304°C); IR (KBr) ν: 3244, 1661, 1621, 1532, 1488, 1408, 1269, 1232, 1200, 1023, 990, 807, 759, 709, 692 cm^{-1}. ^1H NMR (DMSO-d_6): 2.37 (s, 3H, CH_3), 7.13–7.15 (m, 2H, ArH), 7.26–7.28 (m, 2H, ArH), 7.35 (t, $J = 7.6$ Hz, 1H, ArH), 7.43–7.45 (m, 1H, ArH), 7.76–7.80 (m, 1H, ArH), 7.94–7.96 (m, 1H, ArH), 13.03 (s, 1H, NH).

3-Phenyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3b). This compound was obtained as solid with mp >300°C (ref. 17; 307°C); IR (KBr) ν: 3245, 1661, 1622, 1532, 1487, 1406, 1266, 1105, 988, 759, 691 cm^{-1}. ^1H NMR (DMSO-d_6): 7.26–7.28 (m, 2H, ArH), 7.33–7.37 (m, 1H, ArH), 7.38–7.42 (m, 1H, ArH), 7.45–7.50 (m, 3H, ArH), 7.76–7.80 (m, 1H, ArH), 7.96 (t, $J = 7.6$ Hz, 1H, ArH), 12.99 (s, 1H, NH).

2-Thioxo-3-*m*-tolyl-2,3-dihydroquinazolin-4(1*H*)-one (3c). This compound was obtained as solid with mp 282–284°C (ref. 18; 286–289°C); IR (KBr) ν: 3246, 1665, 1622, 1530, 1488, 1403, 1270, 1238, 1203, 913, 798, 772, 691 cm^{-1}.

3-Benzyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3d). This compound was obtained as solid with mp 233–234°C (ref. 19; 230–231°C); IR (KBr) ν: 3198, 3130, 1650, 1622, 1533, 1487, 1426, 1403, 1340, 1170, 1147, 1074, 958, 754, 707, 691 cm^{-1}.

7-Chloro-3-phenyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3e). This compound was obtained as solid with mp 286–288°C (ref. 20; 289 °C); IR (KBr) ν: 3185, 1661, 1616, 1528, 1479, 1385, 1337, 1276, 1260, 1217, 1191, 1123, 1075, 925, 861, 845, 751, 692 cm^{-1}. ^1H NMR (DMSO-d_6): 7.27–7.29 (m, 2H, ArH), 7.38–7.51 (m, 5H, ArH), 7.94–7.96 (m, 1H, ArH), 13.09 (s, 1H, NH).

7-Chloro-3-(4-chlorophenyl)-2-thioxo-2,3-dihydroqui-nazolin-4(1*H*)-one (3f). This compound was obtained as solid with mp 274–276°C (ref. 20; 273°C); IR (KBr) ν: 3195, 1657, 1617, 1530, 1491, 1386, 1279, 1257, 1219, 1193, 1090, 1022, 992, 924, 856, 815, 756, 680 cm^{-1}.

7-Chloro-2-thioxo-3-*m*-tolyl-2,3-dihydroquinazolin-4(1*H*)-one (3g). This compound was obtained as solid with mp 230–231°C (ref. 21; 230–232°C); IR (KBr) ν: 3193, 1659, 1617, 1525, 1479, 1385, 1258, 1192, 926, 880, 781, 757, 696 cm^{-1}. ^1H NMR (DMSO-d_6): 2.34 (s, 3H, CH_3), 7.06–7.08 (m, 2H, ArH), 7.21–7.23 (m, 1H, ArH), 7.34–7.38 (m, 2H, ArH), 7.44–7.45 (m, 1H, ArH), 7.93 (t, $J = 8.4$ Hz, 1H, ArH), 13.06 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 20.84, 114.99, 115.14, 124.39, 125.92, 128.77, 128.90, 129.16, 129.56, 133.31, 138.95, 139.92, 140.43, 159.13, 176.49.

HRMS [Found: m/z 302.0281 (M^+), calcd for $C_{15}H_{11}N_2OS^{35}Cl$: M, 302.0281].

3-Benzyl-7-chloro-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3h). This compound was obtained as solid with mp 258–260°C (ref. 21; 255–257°C); IR (KBr) ν: 3204, 1652, 1616, 1528, 1481, 1431, 1385, 1334, 1307, 1289, 1254, 1163, 1150, 1075, 948, 917, 862, 761, 726, 698 cm^{-1}. ^1H NMR (DMSO-d_6): 5.65 (s, 2H, CH_2), 7.22–7.26 (m, 1H, ArH), 7.28–7.33 (m, 4H, ArH), 7.37–7.40 (m, 1H, ArH), 7.44 (s, 1H, ArH), 7.96 (t, $J = 8.4$ Hz, 1H, ArH), 13.08 (s, 1H, NH).

HRMS [Found: m/z 302.0293 (M^+), calcd for $C_{15}H_{11}N_2OS^{35}Cl$: M, 302.0281].

8-Methyl-3-phenyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3i). This compound was obtained as solid with mp 152–153°C; IR (KBr) ν: 3263, 1692, 1617, 1524, 1492, 1469, 1409, 1240, 1213, 1090, 1016, 987, 795, 757, 735, 691 cm^{-1}. ^1H NMR (DMSO-d_6): 2.12 (s, 3H, CH_3), 6.15 (s, 2H, ArH), 6.57 (t, $J = 7.6$ Hz, 1H, ArH), 7.15 (d, $J = 7.2$ Hz, 1H, ArH), 7.38 (t, $J = 8.8$ Hz, 1H, ArH), 7.51 (d, $J = 7.6$ Hz, 1H, ArH), 7.65–7.69 (m, 1H, ArH), 8.04 (dd, $J_1 = 2.4$ Hz, $J_2 = 6.8$ Hz, 1H, ArH), 10.19 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 17.67, 114.57, 116.52, 116.74, 120.67, 120.73, 121.82, 123.18, 126.55, 133.19, 136.57, 147.77, 168.38.

HRMS [Found: m/z 268.0670 (M^+), calcd for $C_{15}H_{12}N_2OS$: M, 268.0670].

Scheme 3

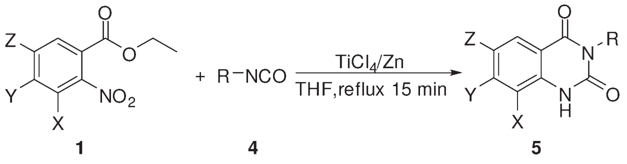


Table 3

Synthesis of quinazoline-2,4(1*H*,3*H*)-diones.

Entry	X	Y	Z	R	Products	Yield (%)[a]
1	H	H	H	4-ClC_6H_4	**5a**	81
2	H	H	H	3-ClC_6H_4	**5b**	89
3	H	H	H	4-$CH_3C_6H_4$	**5c**	84
4	H	H	H	3-$CH_3C_6H_4$	**5d**	92
5	H	Cl	H	3-ClC_6H_4	**5e**	75
6	H	Cl	H	3-$CH_3C_6H_4$	**5f**	90
7	CH_3	H	H	4-ClC_6H_4	**5g**	66
8	CH_3	H	H	3-ClC_6H_4	**5h**	77
9	CH_3	H	H	4-$CH_3C_6H_4$	**5i**	94
10	CH_3	H	H	3-$CH_3C_6H_4$	**5j**	90
11	CH_3	H	H	cyclohexy	**5k**	93
12	H	H	Cl	4-$CH_3C_6H_4$	**5l**	91
13	H	H	H	2,6-di-*i*-PrC_6H_4	**5m**	0

[a] Isolated yield.

3-(4-Chlorophenyl)-8-methyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3j). This compound was obtained as solid with mp 182–184°C; IR (KBr) ν: 3060, 1705, 1617, 1514, 1404, 1247, 1213, 1165, 1075, 808, 762, 701 cm^{-1}. ^1H NMR (DMSO-d_6): 2.57 (s, 3H, CH_3), 7.24–7.28 (m, 1H, ArH), 7.33–7.35 (m, 2H, ArH), 7.54–7.56 (m, 2H, ArH), 7.62 (d, J = 8.0 Hz, 1H, ArH), 7.83 (d, J = 7.6 Hz, 1H, ArH), 11.90 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 17.44, 116.56, 124.26, 124.58, 125.32, 129.04, 131.01, 132.69, 136.88, 138.03, 138.45, 159.79, 176.29.

HRMS [Found: m/z 302.0281 (M^+), calcd for $C_{15}H_{11}N_2OS^{35}Cl$: M, 302.0281].

General procedure for synthesis of quinazolinedione 5. $TiCl_4$ (0.3 mL, 3 mmol) was added dropwise using a syringe to a stirred suspension of zinc powder (0.384 g, 6 mmol) in freshly distilled anhydrous THF (10 mL) at RT under a dry N_2 atmosphere. After completion of the addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to RT and a solution of ethyl 2-nitrobenzoates (1 mmol) and isocyanates (1 mmol) in THF (5 mL) was added dropwise. The reaction mixture was then refluxed for 15 min under N_2. After this period, the TLC analysis of the mixture showed the reaction to be completed. The reaction mixture was quenched with 5% HCl (15 mL) and extracted with $ClCH_2CH_2Cl$ (3 × 20 mL). The combined extracts were washed with water (3 × 20 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product was purified by recrystallization from 95% ethanol.

3-(4-Chlorophenyl)quinazoline-2,4(1*H*,3*H*)-dione (5a). This compound was obtained as solid with mp 298–299°C (ref. 22; 301–302°C); IR (KBr) ν: 3201, 3070, 2938, 1732, 1674, 1493, 1448, 1406, 1282, 1156, 1090, 1016, 872, 825, 757, 741, 688 cm^{-1}. ^1H NMR (DMSO-d_6): 7.23 (d, J = 7.2 Hz, 2H, ArH), 7.38–7.39 (m, 2H, ArH), 7.54–7.55 (m, 2H, ArH), 7.71 (t, J = 8.0 Hz, 1H, ArH), 7.95 (d, J = 8.0 Hz, 1H, ArH), 11.59 (s, 1H, NH).

3-(3-Chlorophenyl)quinazoline-2,4(1*H*,3*H*)-dione (5b). This compound was obtained as solid with mp 265–266°C (ref. 23; 260.5–261.5°C); IR (KBr) ν: 3248, 3204, 3065, 2938, 1734, 1652, 1594, 1493, 1437, 1400, 1340, 1275, 1168, 731, 688 cm^{-1}. ^1H NMR (DMSO-d_6): 7.22–7.25 (m, 2H, ArH), 7.33–7.35 (m, 1H, ArH), 7.51–7.52 (m, 3H, ArH), 7.71 (t, J = 8.0 Hz, 1H, ArH), 7.94 (d, J = 8.0 Hz, 1H, ArH), 11.61 (s, 1H, NH).

3-*p*-Tolylquinazoline-2,4(1*H*,3*H*)-dione (5c). This compound was obtained as solid with mp 260–262°C (ref. 24; 265–266°C); IR (KBr) ν: 3199, 3129, 3069, 3005, 1721, 1665, 1608, 1512, 1490, 1448, 1288, 1153, 1023, 869, 815, 791, 754 cm^{-1}. ^1H NMR (DMSO-d_6): 2.37 (s, 3H, CH_3), 7.10–7.19 (m, 2H, ArH), 7.21–7.24 (m, 2H, ArH), 7.27–7.29 (m, 2H, ArH), 7.68–7.72 (m, 1H, ArH), 7.93 (d, J = 7.2 Hz, 1H, ArH), 11.54 (s, 1H, NH).

3-*m*-Tolylquinazoline-2,4(1*H*,3*H*)-dione (5d). This compound was obtained as solid with mp 256–258°C (ref. 23; 252–252.6°C); IR (KBr) ν: 3255, 1721, 1668, 1620, 1607, 1490, 1433, 1398, 1272, 1157, 922, 812, 785, 758, 697 cm^{-1}. ^1H NMR (DMSO-d_6): 2.36 (s, 3H, CH_3), 7.10–7.13 (m, 2H, ArH), 7.22–7.25 (m, 3H, ArH), 7.37 (t, J = 7.6 Hz, 1H, ArH), 7.71 (t, J = 8.0 Hz, 1H, ArH), 7.94 (d, J = 8.0 Hz, 1H, ArH), 11.56 (s, 1H, NH).

7-Chloro-3-(3-chlorophenyl)quinazolinee-2,4(1*H*,3*H*)-dione (5e). This compound was obtained as solid with mp >300°C (ref. 23; 312°C); IR (KBr) ν: 3232, 3188, 1736, 1656, 1616, 1594, 1480, 1432, 1370, 1169, 1089, 945, 867, 837, 759, 718 cm^{-1}. ^1H NMR (DMSO-d_6): 7.25–7.35 (m, 3H, ArH), 7.52–7.53 (m, 3H, ArH), 7.95 (d, J = 8.4 Hz, 1H, ArH), 11.74 (s, 1H, NH).

7-Chloro-3-*m*-tolylquinazoline-2,4(1*H*,3*H*)-dione (5f). This compound was obtained as solid with mp >300°C (ref.17; >300°C); IR (KBr) ν: 3230, 3185, 1736, 1652, 1593, 1429, 1370, 1262, 1159, 1089, 944, 871, 815, 726, 702 cm^{-1}. ^1H NMR (DMSO-d_6): 2.35 (s, 3H, CH_3), 7.10–7.13 (m, 2H, ArH), 7.24–7.29 (m, 3H, ArH), 7.37 (d, J = 7.6 Hz, 1H, ArH), 7.93–7.95 (m, 1H, ArH), 11.68 (s, 1H, NH).

3-(4-Chlorophenyl)-8-methylquinazoline-2,4(1*H*,3*H*)-dione (5g). This compound was obtained as solid with mp 282–284°C; IR (KBr) ν: 3327, 3233, 1721, 1655, 1534, 1493, 1405, 1225, 1092, 1059, 1019, 819, 760 cm^{-1}. ^1H NMR (DMSO-d_6): 2.39 (s, 3H, CH_3), 7.14 (t, J = 7.6 Hz, 1H, ArH), 7.33 (d, J = 8.8 Hz, 1H, ArH), 7.38–7.40 (m, 2H, ArH), 7.55–7.56 (m, 3H, ArH), 10.84 (s, 1H, NH).

HRMS [Found: m/z 286.0510 (M^+), calcd for $C_{15}H_{11}N_2O_2{}^{35}Cl$: M, 286.0509].

3-(3-Chlorophenyl)-8-methylquinazoline-2,4(1*H*,3*H*)-dione (5h). This compound was obtained as solid with mp 280–282°C; IR (KBr) ν: 3233, 3089, 1726, 1665, 1605, 1506, 1476, 1405, 1330, 1266, 1147, 1088, 898, 785, 753, 691 cm^{-1}. ^1H NMR (DMSO-d_6): 2.40 (s, 3H, CH_3), 7.15 (t, $J = 7.6$ Hz, 1H, ArH), 7.35–7.36 (m, 1H, ArH), 7.52–7.57 (m, 4H, ArH), 7.82 (d, $J = 8.0$ Hz, 1H, ArH), 10.86 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 17.87, 115.18, 123.01, 124.77, 126.06, 128.80, 128.96, 129.96, 131.08, 133.56, 136.94, 137.92, 138.85, 150.94, 150.97.

HRMS [Found: m/z 286.0510 (M^+), calcd for $C_{15}H_{11}N_2O_2{}^{35}Cl$: M, 286.0509].

8-Methyl-3-*p*-tolylquinazoline-2,4(1*H*,3*H*)-dione (5i). This compound was obtained as solid with mp 284–286°C; IR (KBr) ν: 3228, 3083, 1712, 1659, 1613, 1506, 1469, 1411, 1329, 1269, 1168, 1108, 1069, 887, 814, 790, 766 cm^{-1}. ^1H NMR (DMSO-d_6): 2.38 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 7.14 (t, $J = 7.6$ Hz, 1H, ArH), 7.18–7.20 (m, 2H, ArH), 7.28–7.30 (m, 2H, ArH), 7.54 (d, $J = 7.2$ Hz, 1H, ArH), 7.82 (d, $J = 8.0$ Hz, 1H, ArH), 10.78 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 17.83, 21.43, 115.17, 122.91, 124.67, 126.06, 129.39, 130.01, 133.81, 136.79, 138.13, 138.81, 151.17, 163.00.

HRMS [Found: m/z 266.1056 (M^+), calcd for $C_{16}H_{14}N_2O_2$: M, 266.1055].

8-Methyl-3-*m*-tolylquinazoline-2,4(1*H*,3*H*)-dione (5j). This compound was obtained as solid with mp 240–241°C; IR (KBr) ν: 3236, 1722, 1663, 1606, 1507, 1407, 1329, 1269, 1150, 803, 780, 759, 699 cm^{-1}. ^1H NMR (DMSO-d_6): 2.36 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 7.10–7.16 (m, 3H, ArH), 7.24–7.25 (m, 1H, ArH), 7.37 (t, $J = 7.6$ Hz, 1H, ArH), 7.54 (d, $J = 7.2$ Hz, 1H, ArH), 7.81 (d, $J = 8.0$ Hz, 1H, ArH), 10.80 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 17.17, 20.80, 114.49, 122.28, 124.04, 125.37, 126.03, 128.67, 128.78, 129.39, 135.69, 136.16, 138.26, 138.16, 150.44, 150.47.

HRMS [Found: m/z 266.1055 (M^+), calcd for $C_{16}H_{14}N_2O_2$: M, 266.1055].

3-Cyclohexyl-8-methylquinazoline-2,4(1*H*,3*H*)-dione (5k). This compound was obtained as solid with mp 244–245°C; IR (KBr) ν: 3222, 3189, 3079, 2935, 2852, 1703, 1650, 1607, 1506, 1474, 1417, 1376, 1329, 1276, 1188, 1116, 1081, 1023, 915, 793, 754 cm^{-1}. ^1H NMR (DMSO-d_6): 1.17 (t, $J = 12.8$ Hz, 1H, CH_2), 1.26–1.36 (m, 2H, CH_2), 1.58–1.67 (m, 3H, CH_2), 1.78–1.82 (m, 2H, CH_2), 2.33 (s, 3H, CH_3), 2.38–2.44 (m, 2H, CH_2), 4.71–4.77 (m, 1H, CH), 7.08 (t, $J = 7.2$ Hz, 1H, ArH), 7.46 (d, $J = 7.2$ Hz, 1H, ArH), 7.78 (d, $J = 7.6$ Hz, 1H, ArH), 10.53 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 16.95, 25.11, 25.99, 28.33, 52.85, 114.34, 122.12, 123.62, 125.25, 135.74, 137.78, 151.07, 162.34.

HRMS [Found: m/z 258.1367 (M^+), calcd for $C_{15}H_{18}N_2O_2$: M, 258.1368].

6-Chloro-3-*p*-tolylquinazoline-2,4(1*H*,3*H*)-dione (5l). This compound was obtained as solid with mp 291–293°C (ref. 25; 291–293°C); IR (KBr) ν: 3336, 1700, 1695, 1595, 1528, 1478, 1409, 1312, 1295, 1254, 1231, 1079, 815, 773, 743 cm^{-1}. ^1H NMR (DMSO-d_6): 2.37 (s, 3H, CH_3), 7.17–7.19 (m, 2H, ArH), 7.24–7.29 (m, 3H, ArH), 7.74–7.76 (m, 1H, ArH), 7.85–7.86 (m, 1H, ArH), 11.67 (s, 1H, NH).

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Synthesis and Characterization of Some 3-Acyl-4-amino-1-aryl-1*H*-pyrazoles

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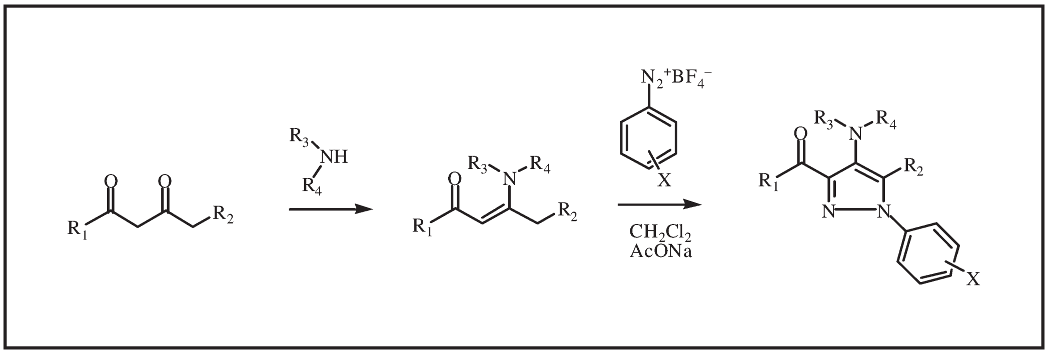

A series of 3-acyl-4-amino-1-aryl-1*H*-pyrazoles has been prepared by reaction of β-enaminones with benzenediazonium tetrafluoroborates substituted especially by fluorine-containing groups (F, CF_3, and OCF_3). The compounds prepared have been characterized by means of ^1H and ^{13}C NMR spectroscopy. In the case of reaction of 5-phenylaminohept-4-en-3-one with 2,6-dichloro-4-trifluoromethylbenzenediazonium tetrafluoroborate the product of azo coupling on phenylamino group of the corresponding pyrazole has been isolated and identified. The intermediate (4-(4-methoxyphenyldiazenyl)-5-methylaminohept-4-en-3-one) on the route from enaminone to pyrazole has been isolated.

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INTRODUCTION

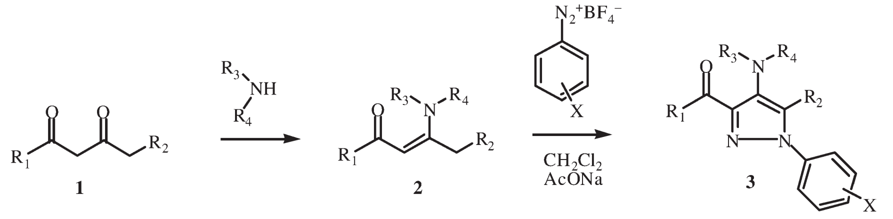
Fluorinated heterocycles represent an important class of compounds. These compounds are widely used as agrochemicals, pharmaceuticals, fluorinated polymers, and catalysts [1]. It has been proved that the introduction of a CF_3 group into heterocycle often leads to enhancement of biological effect compared with a parent compound, probably due to high lipophilicity of perfluoralkyl groups [2].

Compounds containing pyrazole moiety rank among the compounds having broad spectrum of biological activity [3]. A number of fluorine-containing pyrazoles found application as insecticides [4] (e.g., fiproles), herbicides [4] (e.g., pyrasulfotole, fluazolate, azimsulfurone), and fungicides [4] (e.g., penthiopyrad). Pyrazole ring is also an important pharmacophore. Celecoxib [5] (Celebrex) is an example of fluorinated pyrazole used in human medicine for treatment of osteoarthritis, rheumatoid arthritis, acute pain, painful menstruation and menstrual symptoms, and to reduce numbers of colon and rectum polyps in patients with familial adenomatous polyposis. Pyrazole derivatives so-called scorpionates work as metal ligands with promising perspective in homogeneous catalysis [6,7].

Great practical usability of pyrazole derivatives is reflected in interest in their syntheses. Stanovnik and Svete [8] published a review of the synthetic methods leading to pyrazoles. Probably, the most used method for synthesis of pyrazole skeleton is reaction of hydrazines with 1,3-difunctional compounds [8]. A drawback of the methods is the possibility of formation of regioisomers in the case of using of unsymmetrical 1,3-difunctional compounds. Kumar et al. [9] published a review dealing with a synthesis of trifluoromethylpyrazoles by reaction of corresponding trifluoromethyl-β-diketones with hydrazines. Pyrazoles are also obtainable from enaminones [10].

Combination of enaminones and diazonium salts is useful for preparation of some heterocyclic systems: pyridazinones [11], pyridazinium salts [12,13], and some boron-containing heterocycles [14,15]. We also developed a method for synthesis of substituted 3-acyl-4-amino-1-aryl-1*H*-pyrazoles using reaction of β-enaminones with substituted benzenediazonium tetrafluoroborates [16]. Advantages of the method are mild reaction conditions and easy performance. The method is applicable for diazonium salts substituted by both electron-donating and electron-withdrawing groups. The aim of this study was to prepare and characterize some

Scheme 1



1a: R_1 = Ph, R_2 = Me
1b: R_1 = R_2 = Ph
1c: R_1 = Et, R_2 = Me
1d: R_1 = cycloPr, R_2 = Et
1e: R_1 = CF_3, R_2 = *i*Pr

2a: R_1 = Ph, R_2 = Ph, R_3 = H, R_4 = Ph
2b: R_1 = Et, R_2 = Me, R_3 = H, R_4 = Ph
2c: R_1 = Et, R_2 = Me, R_3 = H, R_4 = antipyrine-4-yl
2d: R_1 = Ph, R_2 = Me, R_3 = H, R_4 = 3,4-diFPh
2e: R_1 = Ph, R_2 = Me, R_3 = H, R_4 = CH_2COOEt
2f: R_1 = Ph, R_2 = Me, R_3,R_4 = $(CH_2)_4$
2g: R_1 = CF_3, R_2 = *i*Pr, R_3 = H, R_4 = 3,4-diFPh
2h: R_1 = R_2 = Ph, R_3 = H, R_4 = Me
2i: R_1 = cycloPr, R_2 = Et, R_3 = H, R_4 = CH_2CH_2OH
2j: R_1 = Et, R_2 = Me, R_3 = H, R_4 = Me

3a: R_1 = Et, R_2 = Me, R_3 = H, R_4 = Ph, X = 4-F
3b: R_1 = Ph, R_2 = Me, R_3 = H, R_4 = 3,4-diFPh, X = 4-F
3c: R_1 = Ph, R_2 = Ph, R_3 = H, R_4 = Ph, X = 4-F
3d: R_1 = Et, R_2 = Me, R_3 = H, R_4 = antipyrine-4-yl, X = 4-F
3e: R_1 = Ph, R_2 = Ph, R_3 = H, R_4 = Me, X = 2-F
3f: R_1 = Ph, R_2 = Me, R_3 = H, R_4 = CH_2COOEt, X = 4-F
3g: R_1 = Ph, R_2 = Me, R_3,R_4 = $(CH_2)_4$, X = 3-CF_3
3h: R_1 = cycloPr, R_2 = Et, R_3 = H, R_4 = CH_2CH_2OH, X = 4-Me
3i: R_1 = Et, R_2 = Me, R_3 = H, R_4 = Me, X = 4-OMe
3j: R_1 = Et, R_2 = Me, R_3 = H, R_4 = Ph, X = 4-OCF_3

potentially biologically active pyrazoles with one or more fluorine atoms at various places of molecule and to explore extension of its applicability for other substituents at the amino group of the starting β-enaminones.

RESULTS AND DISCUSSION

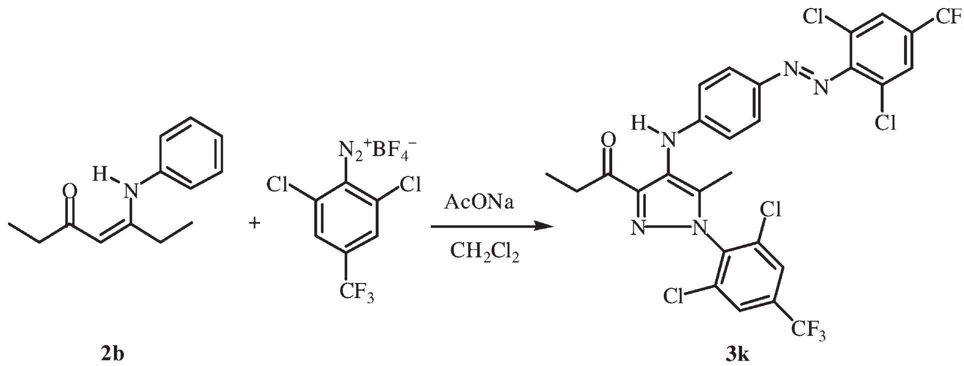
The pyrazoles have been synthesized according to the general Scheme 1. The starting components have been selected so that a series of the pyrazoles containing fluorine at various places of the molecule is prepared (fluorinated diazonium salts, diketones, and amines). For consideration of the applicability of the method some new amines for preparation of the β-enaminones have been used (aminoantipyrine, ethyl glycinate, 2-aminoethanol) and polysubstituted diazonium salt (from 2,6-dichloro-4-trifluoromethylaniline). For a review of the prepared pyrazoles see Scheme 1. Pyrazoles **3b,c,h** were prepared in relative good yields 65–79%. In the most cases, however, yields about 35% were obtained.

In the case of the reaction of 2,6-dichloro-4-trifluoromethylbenzenediazonium tetrafluoroborate with enaminone **2b**, a product of azo coupling on benzene ring of the group =C—NHC_6H_5 of pyrazole **3** has been isolated (Scheme 2). We have never observed formation of a product of this type for any previously used diazonium ions, including very reactive 4-nitrobenzenediazonium. Indeed 2,6-Dichloro-4-trifluoromethylbenzenediazonium is considerably more reactive than 4-nitrobenzenediazonium. For 2,6-dichloro-4-trifluoromethylbenzenediazonium was, from the kinetics of azo coupling with anion of pentane-2,4-dione, found the value [17] $\Sigma\sigma = 1.73$. Difference in the values of σ_p constants [18] between groups 4-NO_2 and 4-CF_3 is $\Delta\sigma = 0.24$, and the value of the reaction constant of azo coupling at position 4- of *N*,*N*-dimethylaniline is $\rho = 4.15$ [19] and at position 4- of *N*-methylaniline is $\rho = 3.98$ [20]. It results that, for azo coupling at position 4- of phenylamino group, 2,6-dichloro-4-trifluoromethylbenzenediazonium is about 10 times more reactive than 4-nitrobenzenediazonium.

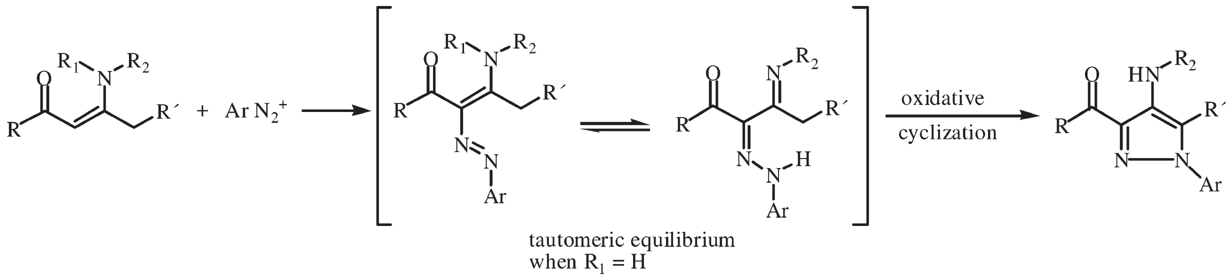
Because of no intermediate of the reaction has been detected, the sequence of the reaction stages of formation of the compound **3k** is unclear.

From the reaction mixture of enaminone **2g** and 4-methylbenzenediazonium tetrafluoroborate, only the

Scheme 2



Scheme 3



starting enaminone has been isolated after 24 h and no pyrazole was formed.

The mechanisms of the pyrazole formation by reaction of diazonium salts with β-enaminones is so far not clear. A hypothesis assumes the primary attack of diazonium ion at α-carbon of enaminone to form a product of azo coupling undergoing subsequently oxidative cyclization to pyrazole (Scheme 3). The hypothesis is supported by the fact that by the reaction of 5-methylaminohept-4-en-3-one (**2j**) with 4-methoxybenzenediazonium tetrafluoroborate at a molar ratio 1:1 of 4-methoxyphenyldiazenyl-5-methylaminohept-4-en-3-one (**4**) (tautomeric form assigned based on results of the structural study [21] performed for similar compounds) was isolated as the main product. Compound **4** exists in $CDCl_3$ solution as *Z* isomer (in analogy with similar compounds [21]) with traces of *E* isomer. Corresponding pyrazole **3i** was isolated as a by-product. Oxidative cyclization of hydrazones to pyrazoles by number of oxidative agents ($Pb(OAc)_4$, hypervalent iodine compounds, MnO_2...) is described in the literature [22–24]. An oxidative agent in the case of formation of pyrazoles **3** is unclear; it could be the second molecule of diazonium salt.

To eliminate possibility of oxidation of primarily formed azo compound (Scheme 3) by air oxygen, the reaction of enaminone **2b** with 4-fluorobenzenediazonium tetrafluoroborate has been performed in an inert atmosphere. After finishing the reaction, a test for diazonium salt was negative and pyrazole was isolated in 69% yield (without inert atmosphere 42.5%). Presence of fluorobenzene as a possible reduction product of diazonium salt in the reaction mixture has been proved by means of gas chromatography-mass spectrometry. Previously, anisol has been detected in the reaction of 4-methoxybenzenediazonium tetrafluoroborate with 3-phenylaminocyclopent-2-en-1-one [25].

The reaction of β-enaminones with benzenediazonium salts in a molar ratio of 1:2 is accompanied by a color change, i.e., after approximately 20–30 min the color of the reaction mixture changes from dark red to orange. When the reaction of 4-methoxybenzenediazonium tetrafluoroborate with 5-methylaminohept-4-en-3-one (**2j**) was stopped after the color change, the yield of pyrazole **3i** was 58%. Compound **4** was isolated in 18% yield. Gas chromatography-mass spectrometry analysis of the reaction mixture detected anisole. Extension of a reaction time to 2 h and subsequent ^{1}H NMR analysis of the reaction mixture proved pyrazole as practically a sole product.

CONCLUSIONS

The method developed and described by us [16] has been used for synthesis of pyrazole derivatives containing fluorine atoms. At the same time its usability in the case of presence of new nitrogen substitutions of the starting enaminone (2-hydroxyethyl, antipyrine-4-yl, pyrrolidine-1-yl, and ethoxycarbonylmethyl) was tested. While using 2,6-dichloro-4-trifluoromethylbenzenediazonium tetrafluoroborate, the product of attack of *N*-phenyl group of the starting enaminone has been isolated for the first time.

Attack of diazonium ion at α-carbon of β-enaminone has been proved to be the first step of our synthesis of pyrazoles. An oxidation agent is probably the second molecule of diazonium ion, being reduced to substituted benzene (4-fluorobenzenediazonium to fluorobenzene, 4-methoxybenzenediazonium to anisole). The mechanism of the pyrazole formation is currently under examination.

EXPERIMENTAL

Tetrahydrofuran (THF) was dried by refluxing with sodium benzophenone ketyl under inert atmosphere until blue–violet coloration took place. THF was freshly distilled under inert atmosphere before use. Dichloromethane was used commercially (Fluka), dried over molecular sieves, and stored in the bottle with Sure/Seal.

Diazonium tetrafluoroborates were freshly prepared before using standard procedures (diazotization of corresponding aniline and subsequent treatment of diazonium chloride by sodium tetrafluoroborate) and dried *in vacuo*. Anhydrous sodium acetate was purchased commercially and used without change.

NMR spectra were measured in $CDCl_3$ using the Bruker AVANCE 500 spectrometer operating at 500.13 MHz (^{1}H), 125.77 MHz (^{13}C).

Hexamethyldisiloxane was used as internal standard for ^{1}H ($\delta = 0.05$). The ^{13}C NMR spectra were standardized by means of the middle signal of the solvent multiplet ($\delta = 76.9$). The carbon spectra were measured by standard way with the broad-band decoupling of protons or by means of the APT pulse sequence.

Diketones **1a,b,d** and enaminones **2a,h,j** were prepared according to the procedure described in the literature [10]. Diketone **1c** was purchased commercially (Aldrich).

1,1,1-Trifluoro-6-methylheptane-2,4-dione (1e). The reaction has been performed in an inert atmosphere. Sodium hydride (9.6 g, 0.4 mol) and THF (240 mL) were added to a 500-mL four-necked flask equipped with reflux condenser, thermometer, magnetic stirrer, and dropping funnel. Methyl trifluoroacetate (25.61 g, 0.2 mol) was added dropwise for 30 min. Then, 4-methylpentane-2-one (20.03 g, 0.2 mol) was added under cooling for 30 min. The mixture was stirred under inert atmosphere at laboratory temperature overnight. Reaction was quenched by ethanol (10 mL) and the mixture was poured into a flask containing 10% HCl (120 mL). Aqueous layer was extracted by ethyl acetate (2 × 50 mL). Combined organic layers were washed by saturated aqueous sodium bicarbonate (1 × 150 mL), water (1 × 150 mL), and brine (1 × 150 mL), dried with sodium sulfate, and evaporated. Diketone has been purified through copper diketonate [16]. After complex decomposition by dilute sulfuric acid, the product was distilled, bp 153–154°C ([26] 136°C). Yield: 7.66 g (19.5%). ^{1}H NMR: δ 0.94 (d, 6H, J = 7.0 Hz, 2 × CH_3), 2.09 (sp, 1H, J = 6.5 Hz, CH), 2.26 (d, 2H, J = 7.5 Hz, CH_2), 5.87 (s, 1H, =C—H), 14.28 (brs, 1H, NH). ^{13}C NMR: δ 22.1 (CH_3), 26.3 (CH), 47.0 (CH_2), 96.0 (q, J = 1.8 Hz, =CH), 116.9 (q, J = 283.3, CF_3), 176.3 (q, J = 36.2 Hz, =C—OH), 196.3 (C=O).

5-Phenylaminohept-4-en-3-one (2b). A mixture of **1c** (6.61 g, 0.05 mol), aniline (4.65 g, 0.05 mol), and catalytic amount of TsOH in toluene (30 mL) has been boiled on an oil bath for 2.5 h. Reaction water was removed azeotropically. After completion of the reaction, volatile components were distilled off *in vacuo* and the rest was subjected to a vacuum distillation. Yield: 7.54 g (74%), bp 142–144°C/0.5 kPa. ^{1}H NMR: δ 1.04 (t, 3H, J = 7.5 Hz, CH_3), 1.13 (t, 3H, J = 7.5 Hz, CH_3), 2.31 (q, 2H, J = 7.5 Hz, CH_2), 2.36 (q, 2H, J = 7.5 Hz, CH_2), 5.20 (s, 1H, =C—H), 7.09–7.10 (m, 2H, Ph), 7.16–7.19 (m, 1H, Ph), 7.30–7.33 (m, 2H, Ph), 12.48 (brs, 1H, NH). ^{13}C NMR: δ 9.7 (CH_3), 12.3 (CH_3), 25.0 (CH_2), 35.1 (CH_2), 94.2 (=CH), 125.0, 125.5, 128.9 (3 × CH_{Ar}), 138.5, 165.8, 200.0 (3 × C_q). *Anal.* Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.65; H, 8.49; N, 6.96.

5-(1,5-Dimethyl-3-oxo-2-phenyl-1,2-dihydropyrazol-4-yl)-aminohept-4-en-3-one (2c). A mixture of **1c** (3.84 g, 0.03 mol) and 4-aminoantipyrine (4.06 g, 0.02 mol) has been stirred at laboratory temperature overnight. The mixture was then diluted by petroleum ether (70 mL). Separated oil solidified on standing. The solidified product was thoroughly washed with petroleum ether. Yield: 5.72 g (91.3%), mp 94–96.5°C. ^{1}H NMR: δ 1.04 (t, 3H, J = 7.5 Hz, CH_3), 1.10 (t, 3H, J = 7.5 Hz, CH_3), 2.21 (s, 3H, =C—CH_3), 2.30 (q, 2H, J = 7.5 Hz, CH_2), 2.34 (q, 2H, J = 7.5 Hz, CH_2), 3.05 (s, 3H, N—CH_3), 5.21 (s, 1H, =C—H), 7.25–7.29 (m, 1H, Ph), 7.36–7.38 (m, 2H, Ph), 7.42–7.45 (m, 2H, Ph), 11.54 (brs, 1H, NH). ^{13}C NMR: δ 9.6, 10.4, 11.5 (3 × CH_3), 25.0, 35.1 (2 × CH_2), 36.0 (CH_3), 94.0 (=C—H), 110.4 (C_q), 123.8, 126.6, 129.0 (3 × CH_{Ar}), 134.7, 150.9, 161.9, 168.0, 200.2 (5 × C_q). *Anal.* Calcd for $C_{18}H_{23}N_3O_2$: C, 68.98; H, 7.40; N, 13.41. Found: C, 69.23; H, 7.32; N, 13.48.

3-(3,4-Difluorophenylamino)-1-phenylpent-2-en-1-one (2d). A mixture of diketone **1a** (1.39 g, 7.9 mmol), 3,4-difluoroaniline (1.02 g, 7.9 mmol), and catalytic amount of TsOH in toluene (15 mL) has been boiled and water formed was removed azeotropically. After 3 h, solvent was distilled off and the rest was suspended in *n*-hexane. Solid product was isolated by suction and recrystallized from *n*-hexane. Yield: 1.12 g (49.3%), mp 54–57°C. ^{1}H NMR: δ 1.14 (t, 3H, J = 7.5 Hz, CH_3), 2.40 (q, 2H, J = 7.5 Hz, CH_2), 5.94 (s, 1H, =C—H), 6.89–6.92 (m, 1H, NPh), 7.02 (ddd, 1H, J = 10.9, 7.0, 2.7 Hz, NPh), 7.13 (dt, 1H, J = 8.8, 9.5 Hz, NPh), 7.40–7.47 (m, 3H, Ph), 7.89–7.91 (m, 2H, Ph), 12.98 (brs, 1H, NH). ^{13}C NMR: δ 12.4 (CH_3), 25.4 (CH_2), 92.5 (=CH), 114.7 (d, J = 18.5 Hz, NPh), 117.5 (d, J = 18.1 Hz, NPh), 121.5 (dd, J = 6.0, 3.4 Hz, NPh), 127.0, 128.2, 131.0 (3 × CH, Ph), 134.9 (dd, J = 7.7, 3.5 Hz, NPh), 139.7 (Ph), 148.3 (dd, J = 198.7, 13.5 Hz, NPh), 150.3 (dd, J = 200.7, 13.5 Hz, NPh), 167.2 (C_q), 189.42 (C=O). *Anal.* Calcd for $C_{17}H_{15}F_2NO$: C, 71.07; H, 5.26; N, 4.88. Found: C, 71.27; H, 5.01; N, 5.10.

3-(Ethoxycarbonylmethylamino)-1-phenylpent-2-en-1-one (2e). A mixture of ethyl glycinate hydrochloride (2.38 g, 17 mmol), **1a** (3 g, 17 mmol) and $NaHCO_3$ (1.43 g, 17 mmol) in ethanol (30 mL) has been refluxed for 5.5 h. The mixture was then cooled, filtered, and the solvent was distilled off. The residue was extracted with dichloromethane (20 mL), filtered, and the filtrate was evaporated. The residue was recrystallized from hexane–cyclohexane mixture. Yield: 3.90 g (87%), mp 69–71.5°C. ^{1}H NMR: δ 1.18 (t, 3H, J = 7.5 Hz, CH_3), 1.26 (t, 3H, J = 7.0 Hz, CH_3), 2.28 (q, 2H, J = 7.5 Hz, CH_2), 4.06 (d, 2H, J = 6.0 Hz, N—CH_2), 4.21 (q, 2H, J = 7.0 Hz, O—CH_2), 5.75 (s, 1H, =C—H), 7.34–7.40 (m, 3H, Ph), 7.83–7.85 (m, 2H, Ph), 11.55 (brs, 1H, NH). ^{13}C NMR δ: 11.9, 14.0 (2 × CH_3), 25.2, 44.3, 61.6 (3 × CH_2), 91.0 (=CH), 126.9, 128.0, 130.5 (3 × CH_{Ar}), 140.2, 168.6, 168.9 (3 × C_q), 188.8 (C=O). *Anal.* Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.12; H, 7.28; N, 5.26.

1-Phenyl-3-(pyrrolidine-1-yl)pent-2-en-1-one (2f). The procedure from Ref. [27] has been adopted. A mixture of diketone **1a** (2.05 g, 11.6 mmol), pyrrolidine (1.03 g, 14.4 mmol), and $CoCl_2 \cdot 6H_2O$ (0.14 g, 0.58 mmol) has been stirred at laboratory temperature for 72 h, then mixed with CH_2Cl_2 and filtered. Filtrate was evaporated and the residue was recrystallized from cyclohexane. Yield: 1.50 g (56.4%) mp 105–108°C. ^{1}H NMR: δ 1.24 (t, 3H, J = 7.5 Hz, CH_3), 1.96 (brs, 4H, 2 × CH_2), 3.12 (q, 2H, J = 7.5 Hz, CH_2), 3.33 (brs, 2H, CH_2), 3.56 (brs, 2H, CH_2), 5.55 (s, 1H, =C—H), 7.34–7.38 (m, 3H, Ph), 7.85–7.86 (m, 2H, Ph). ^{13}C NMR: δ 12.2 (CH_3), 24.4, 24.8, 25.4, 47.3, 48.7 (5 × CH_2), 91.5 (=CH), 127.2, 128.0, 130.1 (3 × CH_{Ar}), 143.1, 167.0 (2 × C_q), 187.0 (C=O). *Anal.* Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.60; H, 8.29; N, 6.14.

1,1,1-Trifluoro-5-methyl-4-(3,4-difluorophenylamino)hept-3-en-2-one (2g). A mixture of **1e** (2.94 g, 15 mmol), 3,4-difluoroaniline (1.94 g, 15 mmol), and catalytic amount of TsOH in toluene (10 mL) has been heated to 110°C for 3 h. The mixture solidified on cooling. The solidified mixture was subjected to column chromatography (silicagel/$CHCl_3$-EtOAc 6:1). Yield: 2.66 g (57.7%). Recrystallization from aqueous ethanol, mp 50–56°C. ^{1}H NMR: δ 0.86 (d, 6H, $J = 6.6$ Hz, 2 × CH_3), 1.80 (sp, 1H, $J = 6.8$ Hz, CH), 2.24 (d, 2H, $J = 7.4$ Hz, CH_2), 5.56 (s, 1H, =C—H), 6.90–6.94 (m, 1H, NPh), 7.02 (ddd, 1H, $J = 2.6, 6.9, 10.0$ Hz, NPh), 7.22 (dt, 1H, $J = 8.7, 9.8$ Hz, NPh), 12.54 (brs, 1H, NH). ^{13}C NMR: δ 22.1 (CH_3), 27.8 (CH), 40.8 (CH_2), 90.5 (=CH), 115.6 (d, $J = 18.8$ Hz, NPh), 117.2 (q, $J = 288.3$ Hz, CF_3), 117.9 (d, $J = 18.4$ Hz, NPh), 122.4 (dd, $J = 6.3, 3.6$ Hz, NPh), 133.2 (dd, $J = 7.5, 3.6$ Hz, NPh), 149.5 (dd, $J = 250.6, 12.4$ Hz, C—F), 150.1 (dd, $J = 251.9, 13.6$ Hz, C—F), 171.4, 177.1 (q, $J = 33.3$, C=O). *Anal.* Calcd for $C_{14}H_{14}F_5NO$: C, 54.73; H, 4.59; N, 4.56. Found: C, 55.11; H, 4.41; N, 4.77.

1-Cyclopropyl-3-(2-hydroxyethyl)hex-2-en-1-one (2i). A mixture of diketone **1d** (3.08 g, 0.02 mol) and ethanolamine (1.22 g, 0.02 mol) in toluene (10 mL) has been refluxed in the presence of catalytic amount of TsOH for 5.5 h. The mixture was then cooled and washed by water (10 mL). Organic phase was separated, dried by sodium sulfate, and solvent was evaporated. The residue was recrystallized from *n*-hexane. Yield: 2.5 g (63.4%), mp 68–71°C. ^{1}H NMR: δ 0.67–0.71 (m, 2H, cPr CH_2), 0.88–0.91 (m, 2H, cPr CH_2), 0.98 (t, 3H, $J = 7.0$ Hz, CH_3), 1.54–1.64 (m, 3H, cPr CH + CH_2), 2.17–2.20 (m, 2H, CH_2), 3.37 (q, 2H, $J = 5.7$ Hz, CH_2N), 3.71 (brt, 2H, $J = 5.6$ Hz, CH_2O), 3.85 (brs, 1H, OH), 5.13 (s, 1H, =C—H), 10.81 (brs, 1H, NH). ^{13}C NMR: δ 8.5 (CH_2), 13.8 (CH_3), 19.7 (CH), 21.1, 33.9, 44.7, 61.2 (4 × CH_2), 94.0 (=CH), 166.3 (=C—N), 196.6 (C=O). *Anal.* Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 67.31; H, 9.39; N, 7.23.

Pyrazoles synthesis. The following pyrazoles have been prepared according to the published procedure [16].

1-(4-Fluorophenyl)-5-methyl-4-phenylamino-3-propanoyl-1H-pyrazole (3a). This is prepared from enaminone **2b** and 4-fluorobenzenediazonium tetrafluoroborate. Chromatography silicagel/CH_2Cl_2, yield 42.5%, recrystallization from ethanol, mp 100–102°C. ^{1}H NMR: δ 1.16 (t, 3H, $J = 7.5$ Hz, CH_3), 2.10 (s, 3H, CH_3), 3.04 (q, 2H, $J = 7.5$ Hz, CH_2), 6.76–6.78 (m, 2H, Ph), 6.81–6.84 (m, 1H, Ph), 6.91 (brs, 1H, NH), 7.17–7.23 (m, 4H, Ph), 7.48–7.51 (m, 2H, Ph). ^{13}C NMR: δ 7.7, 12.0 (2 × CH_3), 32.0 (CH_2), 115.6 (CH_{Ar}), 116.2 (d, $J_{CF} = 23.0$ Hz, CH_{Ar}), 119.7 (CH_{Ar}), 126.6 (d, $J_{CF} = 8.7$ Hz, CH_{Ar}), 126.6 (C_q), 129.0 (CH_{Ar}), 131.6, 135.4 (d, $J_{CF} = 2.9$ Hz, C_q), 141.6, 144.5, 162.1 (d, $J_{CF} = 249.0$ Hz, C—F), 199.3 (C=O). *Anal.* Calcd for $C_{19}H_{18}FN_3O$: C, 70.57; H, 5.61; N, 12.99. Found: C, 70.77; H, 5.37; N, 12.99.

3-Benzoyl-1-(4-fluorophenyl)-4-(3,4-difluorophenylamino)-5-methyl-1H-pyrazole (3b). This compound is prepared from enaminone **2d** and 4-fluorobenzenediazonium tetrafluoroborate. Chromatography silicagel/CH_2Cl_2, yield 70%, recrystallization from ethanol, mp 190–193°C. ^{1}H NMR: δ 2.14 (s, 3H, CH_3), 6.50–6.51 (m, 1H, Ph), 6.56 (ddd, 1H, $J = 12.3, 6.7, 2.7$ Hz, Ph), 6.99 (dt, 1H, $J = 8.9, 9.9$ Hz, Ph), 7.09 (brs, 1H, NH), 7.18–7.22 (m, 2H, Ph), 7.42–7.45 (m, 2H, Ph), 7.50–7.55 (m, 3H, Ph), 8.30–8.31 (m, 2H, Ph). ^{13}C NMR: δ 11.8 (CH_3), 104.2 (d, $J_{CF} = 20.8$ Hz), 111.1 (dd, $J_{CF} = 5.4, 2.9$ Hz), 116.2 (d, $J_{CF} = 23.0$ Hz), 117.3 (d, $J_{CF} = 17.9$ Hz), 126.6 (d, $J_{CF} = 8.7$ Hz), 128.0, 128.1, 130.5, 131.9, 132.8, 135.3 (d, $J_{CF} = 3.1$ Hz), 136.8, 141.6 (dd, $J_{CF} = 8.2, 2.0$ Hz), 142.0, 144.3 (dd, $J_{CF} = 239.1, 12.8$ Hz), 150.6 (dd, $J_{CF} = 246.2, 13.8$ Hz), 162.2 (d, $J_{CF} = 249.2$ Hz), 189.2 (C=O). *Anal.* Calcd for $C_{23}H_{16}F_3N_3O$: C, 67.81; H, 3.96; N, 10.31. Found: C, 67.94; H, 4.04; N, 10.32.

3-Benzoyl-1-(4-fluorophenyl)-5-phenyl-4-phenylamino-1H-pyrazole (3c). This is prepared from enaminone **2a** and 4-fluorobenzenediazonium tetrafluoroborate. Chromatography silicagel/CH_2Cl_2, yield 79%, recrystallization from ethanol, mp 148–150°C. ^{1}H NMR: δ 6.56–6.61 (m, 3H, Ph), 6.86–6.89 (m, 2H, Ph), 6.97–7.00 (m, 2H, Ph), 7.10–7.13 (m, 5H), 7.26–7.28 (m, 2H, Ph), 7.42–7.46 (m, 2H), 7.50–7.53 (m, 2H), 8.31–8.33 (m, 2H). ^{13}C NMR: δ 115.8 (d, $J_{CF} = 23.0$ Hz, CH), 116.4, 119.7 (2 × CH), 127.3 (d, $J_{CF} = 8.7$ Hz, CH), 128.1, 128.2, 128.3 (3 × CH), 128.9, 128.9 (2 × C_q), 129.0, 130.4, 132.6 (3 × CH), 133.0 (C_q), 135.9 (d, $J_{CF} = 3.2$ Hz, C_q), 137.1, 141.9, 142.9 (3 ×C_q), 161.8 (d, $J_{CF} = 248.9$ Hz, C—F), 189.3 (C=O). *Anal.* Calcd for $C_{28}H_{20}FN_3O$: C, 77.58; H, 4.65; N, 9.69. Found: C, 77.55; H, 4.90; N, 9.71.

1-(4-Fluorophenyl)-5-methyl-4-(1,5-dimethyl-2-phenyl-1,2-dihydropyrazol-3-one-4-ylamino)-3-propanoyl-1H-pyrazole (3d). This compound is prepared from enaminone **2c** and 4-fluorobenzenediazonium tetrafluoroborate. Chromatography silicagel/$CHCl_3$-EtOAc 3:2, yield 37.2%, recrystallization from ethanol, mp 184–189.5°C. ^{1}H NMR: δ 1.08 (t, 3H, $J = 7.0$ Hz, CH_3), 1.91 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 2.89–2.95 (m, 5H, CH_2 + CH_3), 6.99–7.03 (m, 2H, Ph), 7.13–7.16 (m, 1H, Ph), 7.26–7.32 (m, 6H, Ph). ^{13}C NMR: δ 7.7, 9.9, 10.0 (3 × CH_3), 31.2 (CH_2), 35.7 (NCH_3), 112.9 (C_q), 115.5 (d, $J_{CF} = 23.0$ Hz, CH), 123.5 (CH), 124.5 (C_q), 126.3 (CH), 126.7 (d, $J_{CF} = 8.7$ Hz, CH), 128.7, 131.2, 134.4 (2 × C_q), 135.0 (d, $J_{CF} = 2.9$ Hz, C_q), 138.0, 150.9 (2 × C_q), 161.6 (d, $J_{CF} = 248.5$ Hz, C—F), 163.2 (C_q), 199.2 (C=O). *Anal.* Calcd for $C_{24}H_{24}FN_5O_2$: C, 66.50; H, 5.58; N, 16.16. Found: C, 66.67; H, 5.32; N, 15.92.

3-Benzoyl-1-(2-fluorophenyl)-4-methylamino-5-phenyl-1H-pyrazole (3e). This is prepared from enaminone **2h** and 2-fluorobenzenediazonium tetrafluoroborate. Chromatography silicagel/CH_2Cl_2, yield 39.5%, recrystallization from ethanol, mp 140–145°C. ^{1}H NMR: δ 2.54 (s, 3H, CH_3), 5.94 (brs, 1H. NH), 7.00–7.04 (m, 1H, Ph), 7.07–7.10 (m, 1H, Ph), 7.24–7.31 (m, 7H), 7.42–7.45 (m, 2H), 7.49–7.53 (m, 1H), 8.29–8.31 (m, 2H). ^{13}C NMR: δ 33.3 (CH_3), 116.4 (d, $J_{CF} = 19.7$ Hz, CH), 124.1 (d, $J_{CF} = 3.9$ Hz, CH), 127.7, 127.9, 128.2, 129.2 (3 × CH), 129.7 (C_q), 130.3 (CH), 130.4 (d, $J_{CF} = 7.7$ Hz, CH), 130.5, 132.1 (2 × CH), 137.9 (d, $J_{CF} = 9.9$ Hz, C_q), 138.7 (C_q), 157.0 (d, $J_{CF} = 253.4$ Hz, C—F), 190.0 (C=O). *Anal.* Calcd for $C_{23}H_{18}FN_3O$: C, 74.38; H, 4.88; N, 11.31. Found: C, 74.16; H, 5.17; N, 11.06.

3-Benzoyl-4-ethoxycarbonylmethylamino-1-(4-fluorophenyl)-5-methyl-1H-pyrazole (3f). The compound **3f** is prepared from enaminone **2e** and 4-fluorobenzenediazonium tetrafluoroborate. Chromatography silicagel/$CHCl_3$-EtOAc 6:1, yield 56%, oil. ^{1}H NMR: δ 1.21 (t, 3H, $J = 7.0$ Hz, CH_3), 2.31 (s, 3H, CH_3), 3.96 (s, 2H, CH_2), 4.17 (q, 2H, $J = 7.0$ Hz, CH_2), 6.02 (brs, 1H, NH), 7.15–7.18 (m, 2H), 7.41–7.44 (m, 4H), 7.50–7.53 (m, 1H), 8.28–8.29 (m, 2H). It was not possible to purify the compound sufficiently for elemental analysis.

3-Benzoyl-1-(3-trifluoromethylphenyl)-5-methyl-4-(pyrrolidine-1-yl)-1H-pyrazole (3g). This is prepared from enaminone **2f** and 3-trifluoromethylbenzenediazonium tetrafluoroborate. Chromatography silicagel/CH_2Cl_2, yield 38.3%, oil. ^{1}H NMR: δ 1.94–1.97 (m, 4H, CH_2 pyrr.), 2.37 (s, 3H, CH_3), 3.18–3.20 (m, 4H, CH_2, pyrr.), 7.44–7.47 (m, 2H), 7.53–7.56 (m, 1H), 7.60–7.62 (m, 1H), 7.64–7.66 (m, 1H), 7.69–7.71 (m, 1H), 7.77 (brs, 1H), 8.11–8.13 (m, 2H). ^{13}C NMR: δ 11.0 (CH_3), 25.9, 52.4 (2 × CH_2), 121.5 (q, J_{CF} = 3.9 Hz, CH), 123.3 (q, J_{CF} = 273.0 Hz, CF_3), 124.5 (q, J_{CF} = 3.7 Hz, CH), 127.8, 128.0, 129.7, 130.5 (4 × CH), 131.6 (q, J_{CF} = 33.2 Hz, C_q), 132.6 (CH), 134.5, 134.6, 137.9, 140.1, 145.1 (5 × C_q), 189.8 (C=O). *Anal*. Calcd for $C_{22}H_{20}F_3N_3O$: C, 66.16; H, 5.05; N, 10.52. Found: C, 66.08; H, 5.34; N, 10.34.

3-Cyclopropylcarbonyl-5-ethyl-4-(2-hydroxyethylamino)-1-(4-methylphenyl)-1H-pyrazole (3h). This is prepared from enaminone **2i** and 4-methylbenzenediazonium tetrafluoroborate. Chromatography silicagel/CH_2Cl_2-EtOAc 4:1, yield 65.7%, recrystallization from *n*-hexane, mp 112–114°C. ^{1}H NMR: δ 0.90–0.94 (m, 2H, cPr CH_2), 0.98 (t, 3H, *J* = 7.5 Hz, CH_3), 1.13–1.16 (m, 2H), 2.38 (s, 3H, CH_3Ph), 2.63 (q, 2H, *J* = 7.5 Hz, CH_2), 3.02 (tt, 1H, *J* = 4.6, 8.0 Hz, cPr CH), 3.16–3.18 (m, 2H, NCH_2), 3.60–3.62 (m, 2H, CH_2O), 4.63 (brs, 1H, OH), 7.24–7.29 (m, 4H, Ph). ^{13}C NMR: δ 11.4 (cPr CH_2), 12.9, 17.0 (2 × CH_3), 17.7 (CH_2), 21.0 (cPr CH), 50.4, 61.0 (2 × CH_2), 125.4, 129.6 (2 × CH_{Ar}), 131.8, 134.5, 137.0, 138.8, 140.9 (5 × C_q), 199.2 (C=O). *Anal*. Calcd for $C_{18}H_{23}N_3O_2$: C, 68.98; H, 7.40; N, 13.41. Found: C, 69.27; H, 7.45; N, 13.58.

1-(4-Methoxyphenyl)-4-methylamino-5-methyl-3-propanoyl-1H-pyrazole (3i). This is prepared from enaminone **2j** and 4-methoxybenzenediazonium tetrafluoroborate. Chromatography silicagel/CH_2Cl_2-EtOAc 4:1. Yield 62.9% mp 79–82°C ([16] 79–82°C).

1-(2-Trifluoromethoxyphenyl)-5-methyl-4-phenylamino-3-propanoyl-1H-pyrazole (3j). Prepared from enaminone **2b** and 2-trifluoromethoxybenzendiazonium tetrafluoroborate. Chromatography silicagel/CH_2Cl_2, yield 23% (in an inert atmosphere 34%). ^{1}H NMR: δ 1.16 (t, 3H, *J* = 7.4 Hz CH_3), 1.98 (s, 3H, CH_3), 3.04 (q, 2H, *J* = 7.4 Hz CH_2), 6.76–6.77 (m, 2H), 6.83–6.86 (m, 1H), 6.87 (brs, 1H, NH), 7.20–7.23 (m, 2H), 7.45–7.50 (m, 2H), 7.54–7.59 (m, 2H).

1-(2,6-Dichloro-4-trifluoromethyl)-4-[4-(2,6-dichloro-4-trifluoromethylphenyldiazenyl)phenylamino]-5-methyl-3-propanoyl-1H-pyrazole (3k). Prepared from enaminone **2b** and 2,6-dichloro-4-trifluoromethylbenzenediazonium tetrafluoroborate. Chromatography silicagel/CH_2Cl_2, yield 27.3%, recrystallization from ethanol, mp 192–194°C. ^{1}H NMR: δ 1.18 (t, 3H, *J* = 7.3 Hz, CH_3), 2.02 (s, 3H, CH_3), 3.05 (q, 2H, *J* = 7.3 Hz, CH_2), 6.81–6.83 (AA′, 2H), 7.03 (s, 1H, NH), 7.64 (s, 2H, CH_{Ar}), 7.81 (s, 2H, CH_{Ar}), 7.90–7.92 (XX′, 2H). ^{13}C NMR: δ 7.6, 10.3 (2 × CH_3), 32.4 (CH_2), 114.5 (C_q), 121.9 (q, J_{CF} = 273.5 Hz, CF_3), 122.5 (q, J_{CF} = 273.1 Hz, CF_3), 123.3 (C_q), 125.7 (CH), 125.9 (q, J_{CF} = 3.7 Hz, CH), 126.0 (q, J_{CF} = 3.5 Hz, CH), 127.6 (CH), 134.0 (q, J_{CF} = 34.6 Hz, 2 × C_q), 135.2 (C_q), 136.0 (C_q), 137.5 (C_q), 144.0 (C_q), 145.8 (C_q), 149.3 (C_q), 151.4 (C_q), 198.8 (C=O). *Anal*. Calcd for $C_{27}H_{17}Cl_4F_6N_5O$: C, 47.46; H, 2.51; N, 10.25. Found: C, 47.71; H, 2.21; N, 10.29.

4-Methoxyphenyldiazenyl-5-methylaminohept-4-en-3-one (4). The compound has been prepared by the same procedure as pyrazoles **3a–j** but the molar ratio of diazo:enaminone was 1:1. The reaction was performed for 24 h under inert atmosphere. Chromatography silicagel/CH_2Cl_2-EtOAc 4:1. Yield 45.2%, oil. ^{1}H NMR (major isomer only) δ: 1.14 (t, 3H, *J* = 7.5 Hz, CH_3), 1.25 (t, 3H, *J* = 7.5 Hz, CH_3), 2.99–3.03 (m, 4H, 2 × CH_2), 3.13 (s, 3H, N—CH_3), 3.83 (s, 3H, OCH_3), 6.92–6.94 (m, 2H, AA′), 7.53–7.55 (brm, 2H, XX′), 14.53 (brs, 1H, NH). ^{13}C NMR: (major isomer only) δ 9.4, 11.5, 21.8, 28.8, 32.7, 55.3, 114.1, 121.1, 127.0, 145.8, 158.6, 165.1, 200.4. *Anal*. Calcd for $C_{15}H_{21}N_3O_2$: C, 65.43; H, 7.69; N, 15.26. Found: C, 65.28; H, 7.40; N, 15.46.

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Synthesis of Novel Amide-Crownophanes and Schiff Base-Crownophanes Based on *p*-Phenylene, 2,6-Naphthalene, and 9,10-Anthracene

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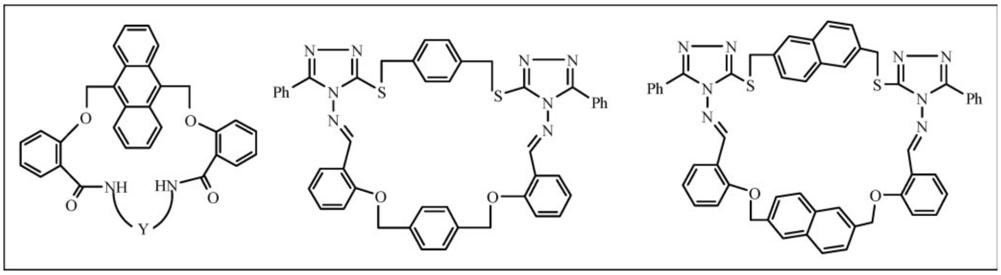

The novel macrocyclic diamides **11–13, 16–18** are obtained in 45–66% yields by the reaction of dipotassium salts **10a–c** and **15** with each of 1,4-di(bromomethyl)benzene **4**, 2,6-di(bromomethyl)naphthalene **6** and 9,10-di(bromomethyl)anthracene **8**, repectively, in boiling DMF. On the other hand, the new macrocyclic Schiff bases **28** and **29** are obtained in 44% and 42% yields by heating the appropriate bis-amines **25b**, **26b** with the corresponding bis-aldehydes **21**, **22**, respectively, in refluxing acetic acid under high-dilution conditions.

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INTRODUCTION

Over the past few decades, macrocyclic compounds have become important synthetic targets due to their wide applications in host-guest supramolecular chemistry. They have been shown to exhibit important applications, including selective ion separation and detection, molecular recognition, catalysis, biological applications as well as many other interesting applications in diverse fields of supramolecular chemistry [1–8]. In particular, macrocyclic polyethers with amide groups in the macrocyclic ring have attracted much attention. Insertion of these groups into the macrocyclic ring structure has been reported to affect the binding properties and selectivity of macrocyclic compounds with metal cation [9,10] as well as organic molecules [11–13]. Recently Kumar *et al.* [14–16] have reported that diamide-ester macrocyclic compounds showed extraordinary Ag^+ binding strength with a remarkable selectivity for Ag over other metal ions. Macrocyclic amides are also precursors in the preparation of azacrown ethers and cryptands [4,6,9,11]. Furthermore, some diamide-containing macrocycles have been utilized as new catalysts [17]. Moreover, a progressive interest was directed in the last few years to the synthesis of novel macrocyclic Schiff bases because they can be obtained by simple self-condensation of suitable formyl- or keto- and primary amine-precursors [18] and they can be functionalized by inserting appropriate groups in the aliphatic and/or aromatic chains of the precursors. They generally can contain additional donor groups (O, S, P, etc.) and this makes them good candidates for metal ion complexation and for mimicking biological systems.

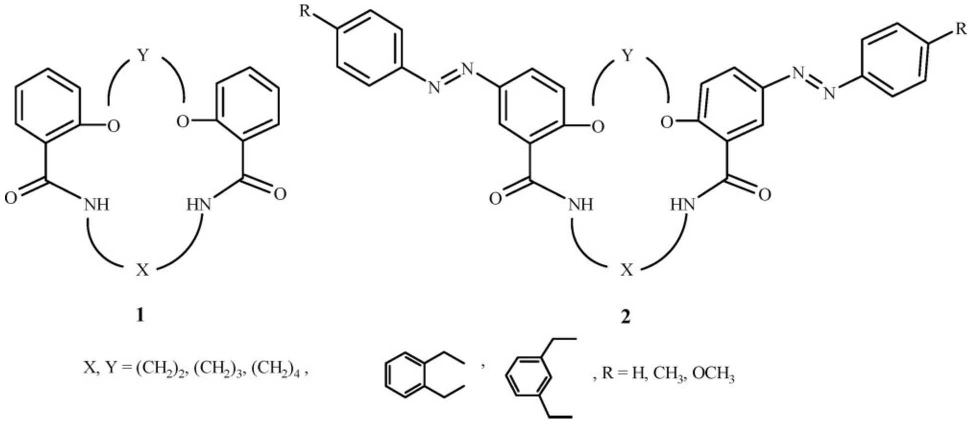
Furthermore, considerable attention has been focused on crown ethers bearing chromophores such as naphthalene and/or anthracene. They are promising analytical reagents for colorimetry and can be used for spectrophotometric determination of metal ions [19]. Anthracene is one of the most employed chromophores due to its ability to induce PET (photoinduced electron transfer) processes [20]. The naphthalene moiety is also a well-known fluorophore and its ability to block intersystem crossing in the first excited state is remarkable [21]. The detection of metal ions with a high specificity under physiologically relevant conditions is an important issue in the design of fluorescent chemosensors in biological and environmental applications [22].

We have investigated several synthetic approaches towards macrocyclic azacrown compounds where some of them showed useful application in ion selective electrodes and as spectrophotometric reagents [23].

Although up to now, many kinds of azacrownophanes were prepared, development of a mild and effective synthetic route to this type of macrocycles still remains an attractive and challenging subject for synthetic chemists. Here, we report on the synthesis of a new family of amide-crownophanes and Schiff base-crownophanes that use *p*-phenylene, 2,6-naphthalene or 9,10-anthracene as assembling units.

RESULTS AND DISCUSSION

Previously, we reported the synthesis of tribenzo- and tetra-benzosubstituted macrocyclic diamides **1** and their corresponding azo derivatives **2**, in which the arylazo groups act as chromophoric side arms, by the reaction of the potassium salts of the appropriate bis(phenols) with the corresponding dihalo compounds in refluxing DMF [23a,b,f,h].



1

2

In this study, we intended to insert the chromophoric units 2,6-naphthalene and 9,10-anthracene into the macrocyclic rings **1**. The insertion of *p*-phenylene unit into the macrocycles **1** was also investigated for a comparison study. For this purpose, the bis(bromomethyl) compounds **4**, **6**, and **8** were chosen as a key intermediate and could be readily obtained from the corresponding dimethyl derivatives **3**, **5**, and **7**, respectively, by bromination with Br_2 or *N*-bromosuccinimide (NBS) in CCl_4 according to reported methods [24] (Scheme 1).

Thus, the treatment of the bis(phenol)s **9** with ethanolic KOH afforded the corresponding dipotassium salt **10**. Alkylation of **10** with **4**, **6**, and **8** in boiling DMF led to the formation of the novel macrocyclic diamides **11–13** in 45–66% yield (Scheme 2). It is noteworthy that we were not able to isolate pure sample of **13a** by the reaction of **10a** with **8** under similar conditions.

We also studied the insertion of an additional 1,3-xyly unit into the macrocyclic ring **11–13** instead of the alkylene moieties, aiming at studying the effect of rigidity provided by these groups on the ability of the ligands to form stable complexes compared with other macrocyclic analogues. Thus, reacting the dipotassium salts **15** (obtained from the corresponding bis(phenol) **14** upon treatment with ethanolic KOH) with the corresponding bis(bromomethyl)arenes **4**, **6**, and **8** under similar conditions give the corresponding macrocyclic diamides **16–18** in 49–62% yields, respectively (Scheme 3).

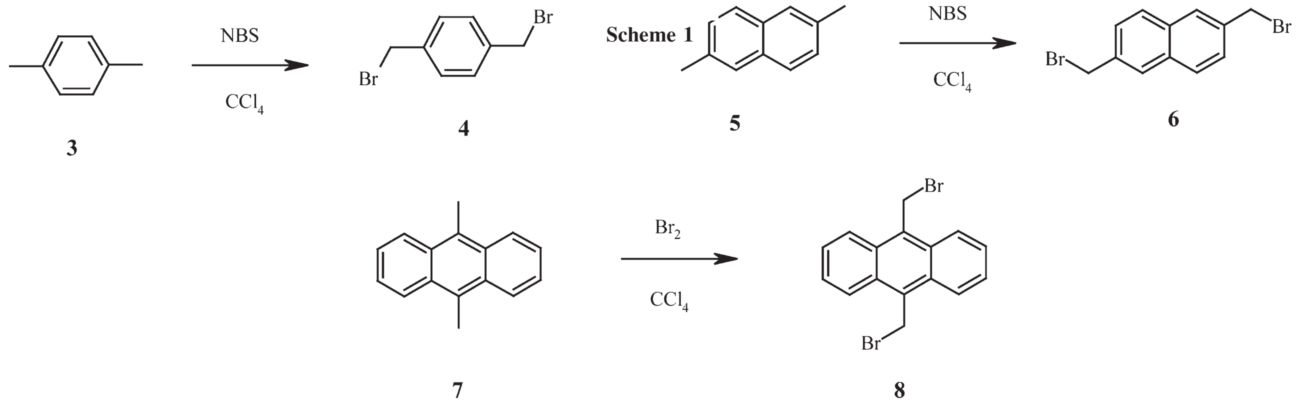
Our study was extended to include the insertion of chromophoric units into the macrocyclic Schiff base **19**. The latter compounds were recently obtained by cyclocondensation of the appropriate bis(carbonyl) ethers with the corresponding bis(amines) in glacial acetic acid under high-dilution conditions [23(f,l)].

To achieve this goal, the novel bis(aldehyde)s **21–23** as well as the novel bis(amine)s **25–27** were prepared as outlined in Schemes 4 and 5. Compounds **4**, **6**, and **8** serve as starting materials for the synthesis of **21–23**, **25–27**. Thus, reaction of **4**, **6**, and **8** with the potassium salt **20** (obtained upon treatment of salicylaldehyde with ethanolic potassium hydroxide) in refluxing DMF afforded the corresponding bis(aldehydes) **21–23** in 65–80% yield (Scheme 4).

On the other hand, reaction of **4**, **6** and **8** with 4-amino-1,2,4-triazol-3-thiones **24a,b** in ethanol/water mixture containing potassium hydroxide afforded the corresponding bis(4-amino-1,2,4-triazol-3-ylsulfanylmethyl)arenes **25–27** in 67–81% yield (Scheme 5).

The synthetic utility of the novel bis(aldehyde)s **21–23** and the bis(amine)s **25–27** as building blocks for novel macrocyclic Schiff bases containing *p*-phenylene, 2,6-naphthalene, or 9,10-anthracene groups incorporated into the ring system was then investigated. Thus, cyclocondensation of **21** with 1,4-bis(4-amino-5-phenyl-3-

Scheme 1



ylsulfanylmethyl)benzene (**25b**) in glacial acetic acid under high-dilution conditions gave the corresponding macrocyclic Schiff base **28** in 44% yield. Under similar conditions **22** reacted with **26b** to give the corresponding macrocyclic Schiff base **29** in 42% yield (Scheme 6).

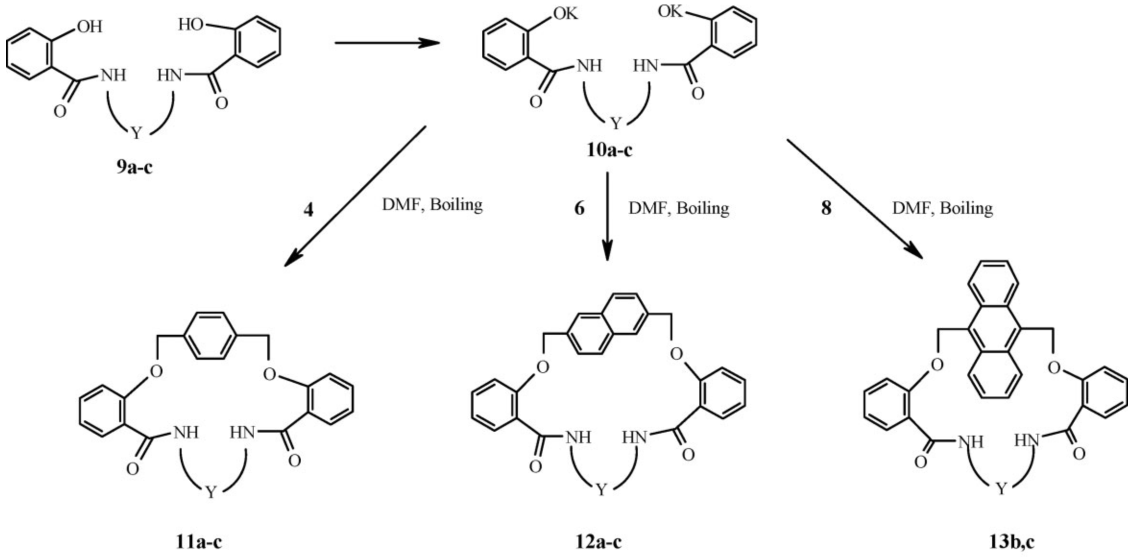
Unfortunately repeated attempts to react 9,10-bis(2-formylphenoxymethyl)anthracene **23** with with 9,10-bis(4-amino-5-phenyl-3-ylsulfanylmethyl)anthracene **27b** in refluxing acetic acid under high dilution conditions did not lead to the formation of the expected macrocyclic Schiff base **30**. Instead, the reaction gave 55% of another product which was characterized by ^{1}H NMR (DMSO), IR, and mass spectra as 9,10-bis(acetyloxymethyl)-anthracene **31**. The latter was obtained in 50% yield by heating only **23** in refluxing acetic acid (Scheme 7).

In conclusion, we prepared a new series of bis(4-amino-1,2,4-triazol-3-ylsulfanylmethyl)arenes as well as bis(2-formylphenoxymethyl)arenes and utilized them successfully as key intermediates for the synthesis of novel macrocyclic Schiff bases upon which fused triazole units and contain N, O, and S inside the macrocyclic ring as donor atoms. We also prepared a new series of amide-crownophanes by the reaction of the appropriate bis(phenol)s with the corresponding dihalo compounds. The novel macrocycles use *p*-phenylene, 2,6-naphthalene or 9,10-anthracene as assembling units. Some derivatives of the new dilactams as well as the new Schiff bases showed promising cation binding properties in a preliminary spectrophotometric study. This data will be published separately due to the large quantity of analytical data accumulated.

EXPERIMENTAL

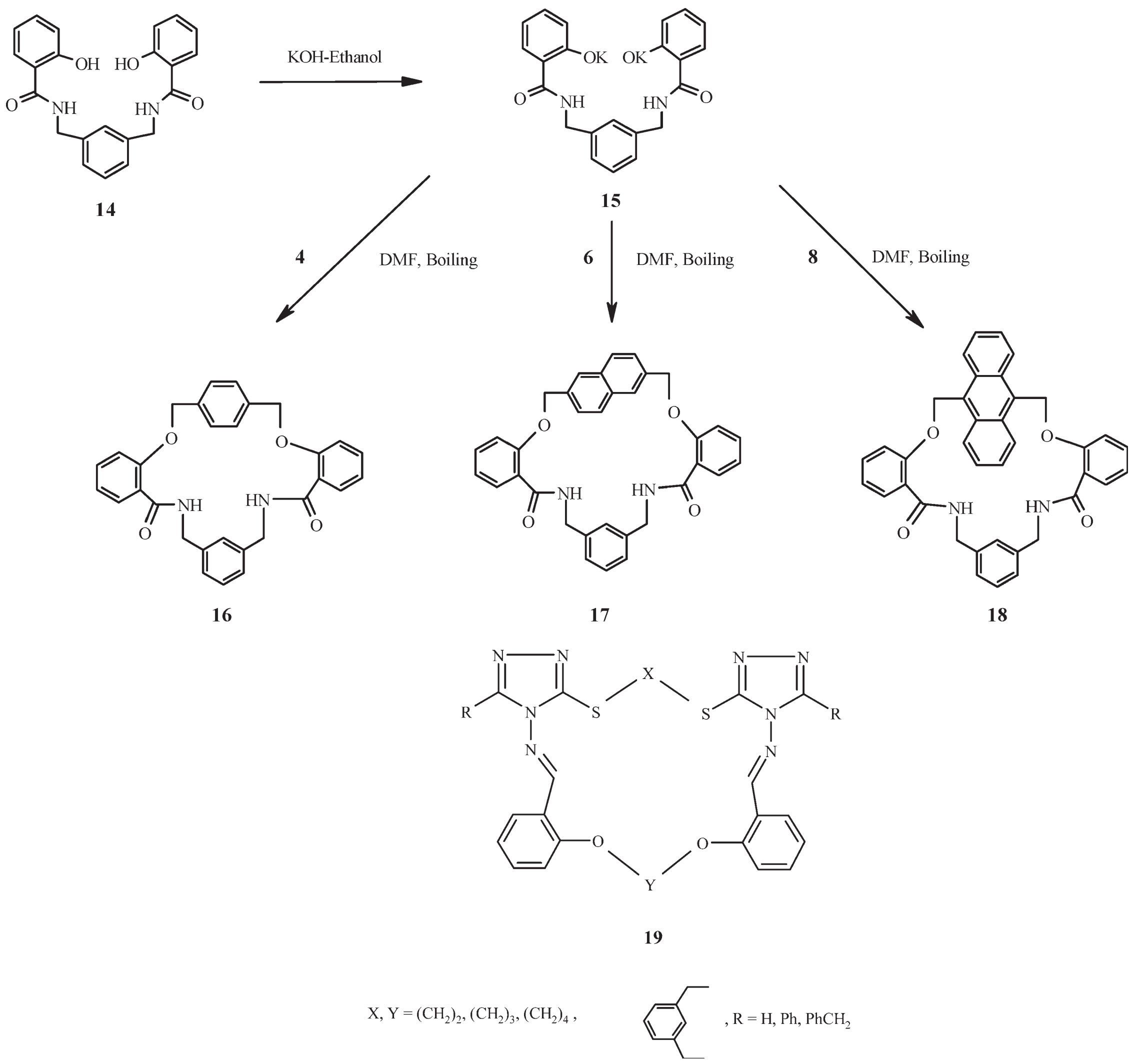
Melting points are uncorrected. IR spectra (KBr) were recorded on a Perkin-Elmer 1430 spectrophotometer. NMR

Scheme 2

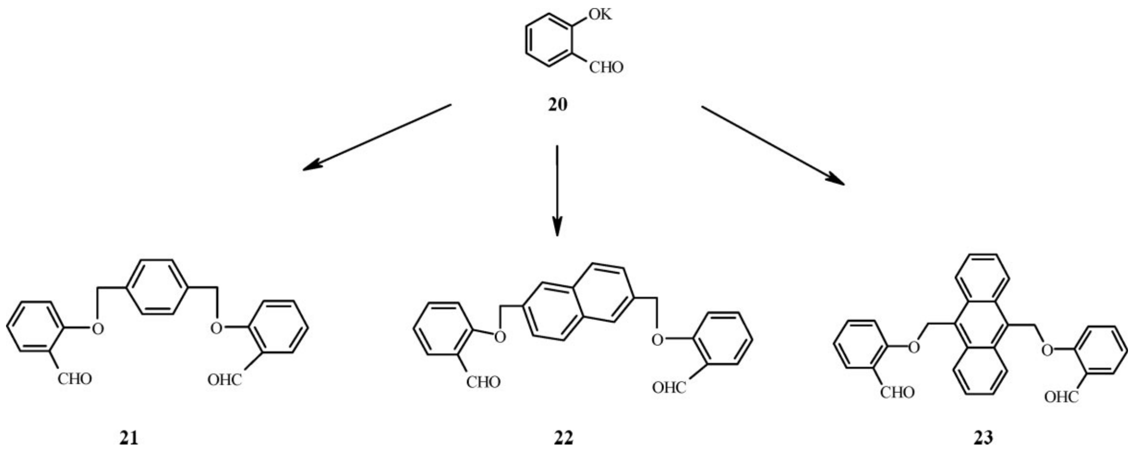


a, Y = $(CH_2)_2$, **b**, Y = $(CH_2)_3$, **c**, Y = $(CH_2)_4$

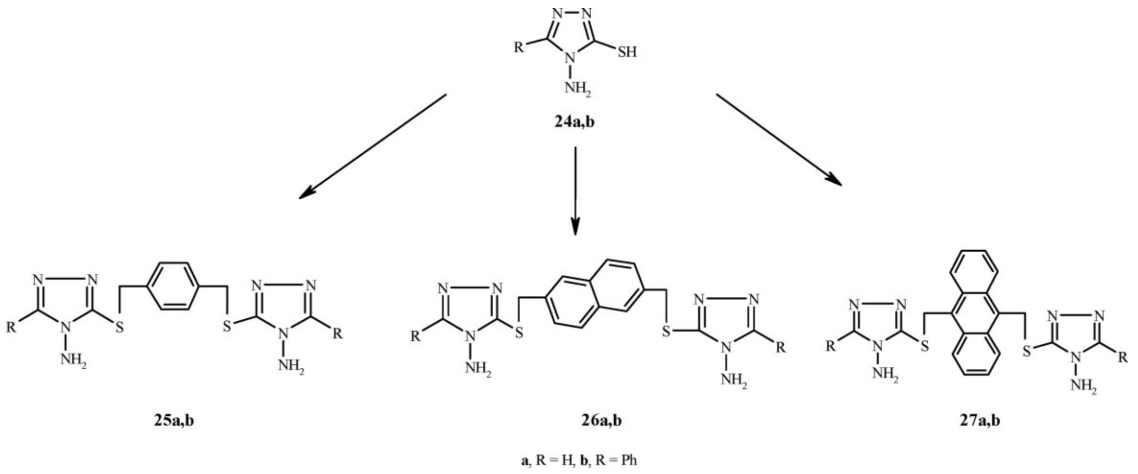
Scheme 3



Scheme 4



Scheme 5



spectra were measured with a Varian Mercury 300 (300 MHz ^{1}H NMR, 75 MHz ^{13}C NMR) spectrophotometer and chemical shifts are given in ppm from TMS. Mass spectra were recorded on GC MS-QP1000 EX (70 eV) or MS 5988 (15 eV) spectrometers. Elemental analyses were carried out at the Microanalytical Centre, Cairo University. 4-Aminotriazol-3-thione derivatives **24a**,**b** were prepared as reported [25].

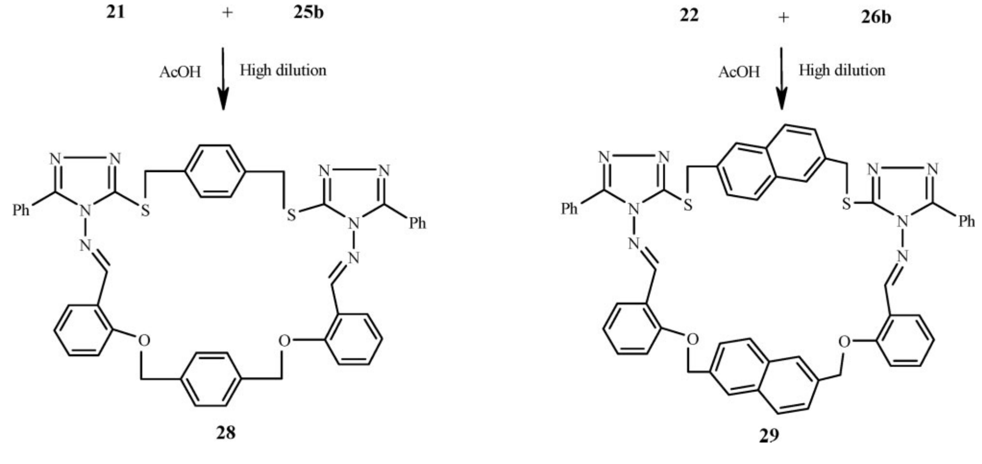
Preparation of dipotassium salts 10, 15, general procedure [28a,28s,28y]. To a solution of KOH (1.14 g, 10 mmol) in methanol (10 mL) was added the appropriate bis(phenol) **9a–c**, **14** (5 mmol). The mixture was stirred at room temperature for 10 min. The solvent was then removed *in vacuo*. The remaining solid was triturated with dry ether, collected, dried, and used in the next step without further purification.

Synthesis of macrocycles 11a–c, 12a–c, 13b,c, 16–18, general procedure. A solution of the appropriate potassium salt **10a–c**, **15** (10 mmol) and the appropriate dihalo compound **4**, **6**, **8** (10 mmol) in DMF (20 mL) was heated under reflux for 10 min. during which time KCl precipitated. The solvent was then removed *in vacuo* and the remaining material was washed with water (50 mL) and purified by crystallization from acetic acid unless otherwise noted.

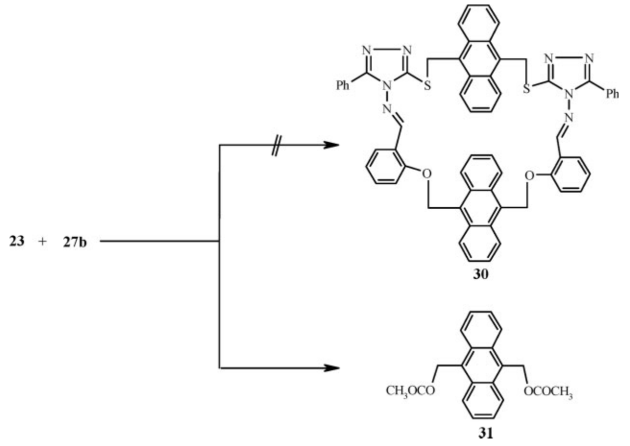
Macrocycle 11a. Reaction of **10a** with **4** produced **11a** as colorless crystals (64%), mp 253–254°C; IR: 3376 (NH), 1651 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.26 (s, 4H, CH_2NH), 5.20 (s, 4H, OCH$_2$), 7.02–7.57 (m, 14H, ArH's, NH); ^{13}C NMR (DMSO) δ 38.66 (CH$_2$N), 72.48 (OCH$_2$), 116.51, 121.49, 125.72, 129.35, 129.86, 131.90, 136.60, 155.77 (ArC's), 165.28 (C=O); MS (EI): *m/z* 402 (M$^+$, 2%), 282 (42.6%), 239 (15.1%), 162 (24.5%), 104 (100%). Anal. Calcd. for $C_{24}H_{22}O_4N_2$ (402.45): C, 71.63; H, 5.51; N, 6.96. Found: C, 71.80; H, 5.30; N, 7.20.

Macrocycle 11b. Reaction of **10b** with **4** produced **11b** as colorless crystals (62%), mp > 300°C; IR: 3376 (NH), 1648 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.06 (m, 2H, CH_2CH$_2$NH), 3.04 (m, 4H, CH_2NH), 5.17 (s, 4H, OCH$_2$), 7.06–7.83 (m, 14H, ArH's, NH); ^{13}C NMR (DMSO) δ 29.10 (CH$_2$CH$_2$NH), 37.20 (CH$_2$N), 71.20 (OCH$_2$), 109.26, 113.06, 120.86, 130.07, 130.32, 132.26, 136.50, 155.80 (ArC's), 164.30 (C=O); MS (EI): *m/z* 416 (M$^+$, 2.7%), 296 (47.8%),

Scheme 6



Scheme 7



178 (16.3%), 104 (100%). Anal. Calcd. for $C_{25}H_{24}O_4N_2$ (416.48): C, 72.10; H, 5.81; N, 6.73. Found: C, 72.30; H, 5.70; N, 6.70.

Macrocycle 11c. Reaction of **10c** with **4** produced **11c** as colorless crystals (61%), mp 291–292°C; IR: 3413, 3380 (NH), 1647 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.21 (s, 4H, *CH*$_2$CH$_2$NH), 3.19 (m, 4H, *CH*$_2$NH), 5.21 (s, 4H, OCH$_2$), 7.07–7.91 (m, 14H, ArH's, NH); ^{13}C NMR (DMSO) δ 26.87 (*C*H$_2$CH$_2$NH), 38.82 (CH$_2$N), 70.87 (OCH$_2$), 113.22, 120.93, 122.35, 130.88, 132.43, 136.39, 156.54 (ArC's), 164.21 (C=O); MS (EI): *m/z* 430 (M$^+$, 1.6%), 310 (49.4%), 173 (25.3%), 104 (100%). Anal. Calcd. for $C_{26}H_{26}O_4N_2$ (430.51): C, 72.54; H, 6.09; N, 6.51. Found: C, 72.70; H, 5.90; N, 6.20.

Macrocycle 12a. Reaction of **10a** with **6** produced **12a** as colorless crystals (54%), mp 197–199°C; IR: 3390 (NH), 1636 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.47 (m, 4H, *CH*$_2$NH), 5.32 (m, 4H, OCH$_2$), 7.33–7.84 (m, 14H, ArH's), 8.40 (brs, 2H, NH); MS (EI): *m/z* 453 (M$^+$+1, 2.5%), 369 (2.6%), 300 (17.5%), 247 (13.6%), 155 (4.2%). Anal. Calcd. for $C_{28}H_{24}O_4N_2$ (452.51): C, 74.32; H, 5.35; N, 6.19. Found: C, 74.50; H, 5.30; N, 6.20.

Macrocycle 12b. Reaction of **10b** with **6** produced **12b** as colorless crystals (66%), mp 287–289°C; IR: 3384 (NH), 1641 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.13 (m, 2H, *CH*$_2$CH$_2$NH), 2.79 (brs, 4H, *CH*$_2$NH), 5.38 (s, 4H, OCH$_2$), 7.03–8.16 (m, 16H, ArH's, NH); ^{13}C NMR (DMSO) δ 26.40 (*C*H$_2$CH$_2$NH), 37.28 (CH$_2$N), 73.26 (OCH$_2$), 114.93, 121.30, 122.32, 127.71, 128.66, 128.96, 130.82, 132.75, 133.20, 134.35, 156.96 (ArC's), 163.84 (C=O); MS (EI): *m/z* 466 (M$^+$, 15.6%), 346 (93.9%), 154 (100%), 121 (36.9%). Anal. Calcd. for $C_{29}H_{26}O_4N_2$ (466.54): C, 74.66; H, 5.62; N, 6.01. Found: C, 74.80; H, 5.30; N, 5.80.

Macrocycle 12c. Reaction of **10c** with **6** produced **12c** as colorless crystals (61%), mp 254–255°C; IR: 3426, 3385 (NH), 1642 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.68 (brs, 4H, *CH*$_2$CH$_2$NH), 2.85 (m, 4H, *CH*$_2$NH), 5.38 (s, 4H, OCH$_2$), 7.05–8.12 (m, 16H, ArH's, NH); ^{13}C NMR (DMSO) δ 26.76 (*C*H$_2$CH$_2$NH), 38.80 (CH$_2$N), 72.73 (OCH$_2$), 115.19, 121.10, 121.34, 123.76, 127.54, 128.56, 130.40, 132.27, 132.94, 134.42, 156.49 (ArC's), 164.35 (C=O); MS (EI): *m/z* 480 (M$^+$, 11.1%), 360 (100%), 223 (19.2%), 154 (55.7%), 121 (24.4%). Anal. Calcd. for $C_{30}H_{28}O_4N_2$ (480.57): C, 74.98; H, 5.87; N, 5.83. Found: C, 74.80; H, 5.50; N, 5.70.

Macrocycle 13b. Reaction of **10b** with **8** produced **13b** as yellow crystals (45%), mp 291–292°C; IR: 3388, 3421 (NH), 1640 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ −0.34 (brs, 2H, *CH*$_2$CH$_2$NH), 2.64 (m, 4H, *CH*$_2$NH), 6.37 (s, 4H, OCH$_2$), 7.14–8.52 (m, 18H, ArH's, NH); ^{13}C NMR (DMSO) δ 26.24 (*C*H$_2$CH$_2$NH), 36.41 (CH$_2$N), 64.23 (OCH$_2$), 113.74, 120.71, 121.20, 124.77, 126.65, 129.14, 130.04, 130.54, 132.54, 156.74 (ArC's), 163.56 (C=O); MS (EI): *m/z* 516 (M$^+$, 45.5%), 396 (100%), 314 (13.8%), 204 (81.1%), 178 (86.8%), 121 (73.5). Anal. Calcd. for $C_{33}H_{28}O_4N_2$ (516.60): C, 76.73; H, 5.46; N, 5.42. Found: C, 76.80; H, 5.30; N, 5.20.

Macrocycle 13c. Reaction of **10c** with **8** produced **13c** as yellow crystals (51%), mp 259–260°C; IR: 3402 (NH), 1650 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.28 (s, 4H, *CH*$_2$CH$_2$NH), 2.73 (m, 4H, *CH*$_2$NH), 6.30 (s, 4H, OCH$_2$), 7.14–8.50 (m, 18H, ArH's, NH). ^{13}C NMR (DMSO) δ 25.92 (*C*H$_2$CH$_2$NH), 37.10 (CH$_2$N), 63.19 (OCH$_2$), 113.88, 121.28, 124.68, 126.69, 128.95, 130.03, 131.13, 132.76, 156.78 (ArC's), 163.66 (C=O); MS (EI): *m/z* 530 (M$^+$, 14.9%), 410 (56.8%), 204 (75.6%), 121(100%). Anal. Calcd. for $C_{34}H_{30}O_4N_2$ (530.63): C, 76.96; H, 5.70; N, 5.28. Found: C, 76.80; H, 5.40; N, 5.20.

Macrocycle 16. Reaction of **15** with **4** produced **16** as colorless crystals [acetic acid-ethanol (1:1)] (62%), mp 281–282°C; IR: 3392 (NH), 1648 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.46 (m, 4H, *CH*$_2$NH), 5.15 (s, 4H, OCH$_2$), 7.09–7.93 (m, 16H, ArH's), 8.48 (br, 2H, NH); MS (EI): *m/z* 478 (M$^+$, 5.9%), 358 (25.7%), 254 (10.6%), 121 (55.9%), 104 (100%). Anal. Calcd. for $C_{30}H_{26}N_2O_4$ (478.55): C, 75.30; H, 5.48; N, 5.85. Found: C, 75.40; H, 5.70; N, 5.90.

Macrocycle 17. Reaction of **15** with **6** produced **17** as colorless crystals (ethanol) (49%), mp 258–259°C; IR: 3391 (NH), 1649 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.32 (m, 4H, CH$_2$NH), 5.31 (s, 4H, OCH$_2$), 6.50–7.97 (m, 18H, ArH's), 8.17 (br, 2H, NH); ^{13}C NMR (DMSO) δ 42.59 (CH$_2$N), 71.27 (OCH$_2$), 113.10, 120.96, 121.99, 123.36, 125.66, 126.87, 127.67, 128.19, 130.83, 132.55, 132.68, 133.33, 136.85, 156.74 (ArC's), 164.51 (C=O); MS (EI): *m/z* 528 (M$^+$, 9.4%), 408 (49.1%), 339 (25.7%), 288 (22%), 154 (100). Anal. Calcd. for $C_{34}H_{28}N_2O_4$ (528.61): C, 77.26; H, 5.34; N, 5.30. Found: C, 77.30; H, 5.30; N, 4.90.

Macrocycle 18. Reaction **15** with **8** produced **18** as yellow crystals [acetic acid-ethanol (1:1)] (51%), mp 245–246°C; IR: 3485, 3389 (NH), 1641 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.91 (m, 4H, *CH*$_2$NH), 6.18 (s, 4H, OCH$_2$), 6.50–8.39 (m, 20H, ArH's, NH); MS (EI): *m/z* 578 (M$^+$, 9.4%), 458 (13.7%), 338 (11.5%), 240 (17.6%), 205 (100%), 121 (51.5%). Anal. Calcd. for $C_{38}H_{30}N_2O_4$ (578.67): C, 78.87; H, 5.23; N, 4.84. Found: C, 78.80; H, 4.90; N, 4.90.

Synthesis of bis(aldehyde)s 21–23, general procedure. A solution of the potassium salt of salicylaldehyde 20 (20 mmol) and the dibromo compound **4**, **6**, **8** (10 mmol) in DMF (20 mL) was heated under reflux for 5 min. during which the potassium chloride precipitated. The solution was concentrated to small volume (ca. 2 mL) and then cold water (ca. 10 mL) was added. The solid obtained was collected and crystallized from acetic acid.

1,4-Bis(2-formylphenoxymethyl)benzene (21). Reaction of **20** with **4** produced **21** as colorless crystals (80%), mp 189–

190°C; IR: 2762, 2850 (CHO), 1686 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 5.30 (s, 4H, OCH_2), 7.06–7.73 (m, 12H, ArH's), 10.44 (s, 2H, CHO); ^{13}C NMR (DMSO) δ 69.77 (OCH_2), 114.15, 120.93, 124.73, 127.64, 127.86, 136.15, 136.22, 160.51 (ArC's), 189.05 (C=O); MS (EI): *m/z* 346 (M$^+$, 0.1%), 224 (38%), 179 (4.6%), 121.05 (11.7%), 104 (92.2%), 91 (100%). Anal. Calcd. for $C_{22}H_{18}O_4$ (346.38): C, 76.29; H, 5.24. Found: C, 76.30; H, 4.90.

2,6-Bis(2-formylphenoxymethyl)naphthalene (22). Reaction of **20** with **6** produced **22** as colorless crystals (65%), mp 191–192°C; IR: 2761, 2868 (CHO), 1674 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 5.45 (s, 4H, OCH_2), 7.07–8.05 (m, 14H, ArH's), 10.49 (s, 2H, CHO); ^{13}C NMR (DMSO) δ 69.98 (OCH_2), 114.13, 120.59, 120.63, 120.95, 125.84, 126.07, 127.83, 128.27, 134.33, 136.27, 160.53 (ArC's), 189.25 (C=O); MS (EI): *m/z* 396 (M$^+$, 0.9%), 275 (55.9%), 215 (0.9%), 169 (2.2%), 154 (100%). Anal. Calcd. for $C_{26}H_{20}O_4$ (396.45): C, 78.77; H, 5.09. Found: C, 78.70; H, 4.90.

9,10-Bis(2-formylphenoxymethyl)anthracene (23). Reaction of **20** with **8** produced **23** as yellow crystals (DMF) (70%), mp 248–249°C; IR: 2753, 2850 (CHO), 1682 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 6.28 (s, 4H, OCH_2), 7.14–8.51 (m, 16H, ArH's), 10.04 (s, 2H, CHO); MS (EI): *m/z* 446 (M$^+$, 2.5%), 325 (26%), 204 (100%), 121 (35.6%). Anal. Calcd for $C_{30}H_{22}O_4$ (446.51): C, 80.70; H, 4.97. Found: C, 80.60; H, 5.10.

Synthesis of bis(amine)s 25a,b–27a,b, general procedure. To a solution of **24a**, **b** (50 mmol) in aqueous ethanol (50 mL, 50%) containing KOH (50 mmol) was added the appropriate dibromo compound **4**, **6**, **8** (25 mmol). The reaction mixture was heated under reflux for 1 h. The solvent was then removed *in vacuo* and the remaining solid was collected and crystallized from the proper solvent.

1,4-Bis(4-amino-1,2,4-triazol-3-ylsulfanylmethyl)benzene (25a). Reaction of **24a** with **4** produced **25a** as colorless crystals (DMF/H_2O) (71%), mp 207–209°C; IR: 3333, 3092 (NH_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 4.35 (s, 4H, SCH_2), 6.02 (s, 4H, NH_2), 7.33 (s, 4H, ArH's), 8.44 (s, 2H, triazole H's); ^{13}C NMR (DMSO-*d6*) δ 34.73 (SCH_2), 128.95, 136.60, 146.19, 150.47 (ArC's, Triazole C's); MS (EI): *m/z* 334 (M$^+$, 0.4%), 218 (3.9%), 203 (8%), 183 (4%), 128 (4.9%), 116 (100%). Anal. Calcd. for $C_{12}H_{14}N_8S_2$ (334.43): C, 43.10; H, 4.22; N, 33.51. Found: C, 43.40; H, 4.30; N, 33.50.

1,4-Bis(4-amino-5-phenyl-1,2,4-triazol-3-ylsulfanylmethyl)benzene (25b). Reaction of **24b** with **4** produced **25b** as colorless crystals (dilute acetic acid) (81%), mp 214–215°C; IR: 3309, 3181 (NH_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 4.42 (s, 4H, SCH_2), 6.09 (s, 4H, NH_2), 7.42–7.99 (m, 14H, ArH's); ^{13}C NMR (DMSO-d_6) δ 34.93 (SCH_2), 126.85, 127.72, 128.37, 129.03, 129.54, 136.63, 152.85, 154.02 (ArC's, Triazole C's); MS (EI): *m/z* 486 (M$^+$, 2.6%), 294 (11.8%), 192 (100%), 121 (20.1%). Anal. Calcd. for $C_{24}H_{22}N_8S_2$ (486.63): C, 59.24; H, 4.56; N, 23.03. Found: C, 59.30; H, 4.30; N, 22.90.

2,6-Bis(4-amino-1,2,4-triazol-3-ylsulfanylmethyl)naphthalene (26a). Reaction of **24a** with **6** produced **26a** as colorless crystals (DMF/H_2O) (69%), mp 216–217°C; IR: 3325, 3109 (NH_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 4.53 (s, 4H, SCH_2), 6.04 (s, 4H, NH_2), 7.53–7.86 (m, 6H, ArH's), 8.44 (s, 2H, triazole H's); ^{13}C NMR (DMSO-*d6*) δ 35.68 (SCH_2), 120.81, 127.15, 127.44, 127.80, 131.94, 135.14, 146.10 (ArC's, Triazole C's); MS (EI): *m/z* 385 (M$^+$+1, 3.2%), 327 (2.6%), 268 (21.7%), 155 (29.2%), 116 (100%). Anal. Calcd. for $C_{16}H_{16}N_8S_2$ (384.49): C, 49.98; H, 4.19; N, 29.14. Found: C, 50.10; H, 4.30; N, 28.90.

2,6-Bis(4-amino-5-phenyl-1,2,4-triazol-3-ylsulfanylmethyl)-naphthalene (26b). Reaction of **24b** with **6** gave **26b** as colorless crystals (acetic acid) (74%), mp 240–241°C; IR: 3315, 3183 (NH_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 4.60 (s, 4H, SCH_2), 6.10 (s, 4H, NH_2), 7.48–7.98 (m, 16H, ArH's); ^{13}C NMR (DMSO-d_6) δ 35.33 (SCH_2), 120.71, 126.81, 127.29, 127.57, 127.86, 128.41, 129.57, 131.91, 135.17, 152.91, 154.03 (ArC's, Triazole C's). Anal. Calcd. for $C_{28}H_{24}N_8S_2$ (536.69): C, 62.66; H, 4.51; N, 20.88. Found: C, 62.40; H, 4.30; N, 21.00.

9,10-Bis(4-amino-1,2,4-triazol-3-ylsulfanylmethyl)anthracene (27a). Reaction of **24a** with **8** produced **27a** as yellow crystals (DMF/H_2O) (67%), mp 243–244°C; IR: 3332, 3281 (NH_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 5.46 (s, 4H, SCH_2), 6.14 (s, 4H, NH_2), 7.64–8.47 (m, 8H, ArH's), 8.55 (s, 2H, triazole H's); ^{13}C NMR (DMSO-*d6*) δ 29.40 (SCH_2), 124.79, 126.39, 128.90, 129.35, 146.39, 150.45 (ArC's, Triazole C's); MS (EI): *m/z* 434 (M$^+$, 2.2%), 318 (5.7%), 204 (18.2%), 116 (100%). Anal. Calcd. for $C_{20}H_{18}N_8S_2$ (434.55): C, 55.28; H, 4.18; N, 25.79. Found: C, 55.30; H, 4.30; N, 25.90.

9,10-Bis(4-amino-5-phenyl-1,2,4-triazol-3-ylsulfanylmethyl)-anthracene (27b). Reaction of **24b** with **8** produced **27b** as yellow crystals (DMF/H_2O) (75%), mp 233–235°C; IR: 3281, 3353 (NH_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 5.52 (s, 4H, SCH_2), 6.17 (s, 4H, NH_2), 7.53–8.52 (m, 18H, ArH's); MS (EI): *m/z* 586 (M$^+$, 9%), 394 (46.1%), 228 (25.8%), 192 (82%), 104 (100%). Anal. Calcd. for $C_{32}H_{26}N_8S_2$ (586.75): C, 65.51; H, 4.47; N, 19.10. Found: C, 65.30; H, 4.30; N, 18.90.

Synthesis of macrocyclic bis-Schiff bases 28, 29, and 9,10-bis(acetyloxymethyl)-anthracene 31, general procedure. To a solution of the appropriate bis aldehyde **21–23** (10 mmol) in glacial acetic acid (50 mL) was added a solution of the appropriate bis amine **25b**, **26b**, **27b** (10 mmol) in glacial acetic acid (50 mL). The reaction mixture was then heated under reflux for 2 h. The solution was concentrated to small volume (ca. 2 mL) and then cold water (ca. 15 mL) was added. The precipitate obtained was collected and recrystallized from acetic acid.

Macrocycle 28. Reaction of **21** with **25b** produced **28** as colorless crystals (44%), mp 248–249°C; ^{1}H NMR (DMSO-d_6) δ 4.43 (s, 4H, SCH_2), 5.24 (s, 4H, OCH_2), 7.14–7.99 (m, 26H, ArH's), 9.18 (s, 2H, CH=N). MS (EI): *m/z* 796 (M$^+$, 0.4%), 626 (0.3%), 561 (0.8%), 558 (0.8%), 486 (1.6%), 280 (22.4%), 222 (76.5%), 177 (24.9%), 104 (100%). Anal. Calcd. for $C_{46}H_{36}N_8O_2S_2$ (796.98): C, 69.33; H, 4.55; N, 14.06. Found: C, 69.40; H, 4.30; N, 14.30.

Macrocycle 29. Reaction of **22** with **26b** gave **29** as colorless crystals (42%), mp 254–255°C; ^{1}H NMR (DMSO-d_6) δ 4.60 (s, 4H, SCH_2), 5.38 (s, 4H, OCH_2), 7.17–8.03 (m, 30H, ArH's), 9.21 (s, 2H, CH=N). MS (EI): *m/z* 896 (M$^+$, 0.5%), 522 (0.9%), 448 (1.6%), 390 (2.1%), 330 (4%), 272 (65.5%), 154 (100%). Anal. Calcd. for $C_{54}H_{40}N_8O_2S_2$ (897.10): C, 72.30; H, 4.49; N, 12.49. Found: C, 72.40; H, 4.30; N, 12.20.

9,10-Bis(acetyloxymethyl)anthracene (31). Reaction of **23** with **27b** produced **31** as yellow crystals (55%), mp 214–215°C; 178 (35.29%); IR: 1729 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.02 (s, 6H, $OCOCH_3$), 6.15 (s, 4H, OCH_2), 7.65–8.45 (m, 8H, ArH's); MS (EI): *m/z* 322 (M$^+$, 30.71%), 263 (10.8%), 220 (100%), 204 (18.96%), 191 (53.41%). Anal. Calcd. for $C_{20}H_{18}O_4$ (322.36): C, 74.52; H, 5.63. Found: C, 74.80; H, 5.50.

Action of acetic acid on 27b. A solution of **27b** (10 mmol) in acetic acid (20 mL) was heated under reflux for 1 h. The solid obtained upon cooling was collected and crystallized from acetic acid to give **31** as yellow crystals (50%).

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Poly(ethyleneglycol): A Versatile and Recyclable Reaction Medium in Gaining Access to Benzo[4,5]imidazo[1,2-*a*]pyrimidines Under Microwave Heating

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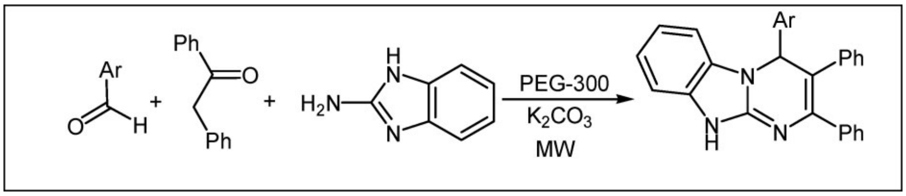

Polyethylene glycol is found to be a nontoxic and recyclable reaction medium for the microwave-assisted, one-pot, multicomponent reactions of aromatic aldehydes with 2-aminobenzimidazole and 1,2-diphenylethanone in the presence of potassium carbonate. This environmentally friendly microwave protocol offers ease of operation and enables recyclability of reaction media and synthesis of a variety of substituted benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives. It is an efficient, promising, and green synthetic strategy to construct benzo[4,5]imidazo[1,2-*a*]pyrimidine skeleton.

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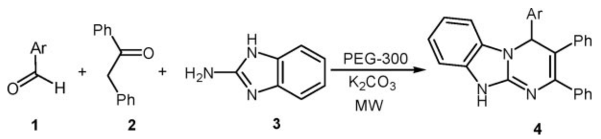
INTRODUCTION

The search for alternative reaction media to replace volatile and often toxic solvents commonly used in organic synthetic procedures is an important objective of significant environmental consequence [1]. Media considered include (a) the use of supercritical fluids [2] that have the advantage of facile solvent removal and easy recyclability but require high pressure; (b) fluorous-based systems [3] that have the advantage of being highly hydrophobic but expensive and for which the solvents are probably innocuous but have the disadvantage of being volatile; (c) more recently, environmentally benign solvents such as ionic liquids [4] and water [5]. Ionic liquids have a particularly useful set of properties, being nonvolatile and readily dissolving many transition metal catalysts but their preparation was not convenient, and volatile organic solvents were also used for the preparation. The use of water as solvent is probably the most desirable approach, but this is often not possible due to the hydrophobic nature of the reactants. It is customary to measure the efficiency of a catalyst by the number of cycles for which it can be reused. Similarly, the value of a new solvent medium primarily depends on its environmental impact, the ease with which it can be recycled, low vapor pressure, nonflammability, and high polarity for solubilization. In performing the majority of organic transformations, solvents play an important role in mixing the ingredients to make the system homogeneous and allow molecular interactions to be more efficient [6].

Recently, using polyethylene glycol (PEG) as a green reaction medium has become an important research area [7]. In addition to be a safe, readily available, and environmentally friendly solvent [8], PEG has also been recognized as an effective and recyclable reaction medium with unique properties and potentials for many organic reactions such as substitution, oxidation, and reduction. Under microwave irradiation (MW), PEG is rapidly heated to high temperature, enhancing molecular interactions more efficiently. Thus, it is clear that the combined approach of microwave superheating and PEG as a reaction medium could be considered a promising and green synthetic strategy for the construction of important heterocyclic skeleton.

Imidazo[1,2-*a*]pyrimidines are well-known compounds because of their pharmacological profiles as anti-cytomegalo-zoster and antivaricella-zoster virus [9]. The chemical modification of the imidazopyrimidine ring such as the introduction of different substituents or heteroatoms have allowed expansion of the research to structure–activity relationship to afford new insight into the molecular interaction at the receptor level. With an imidazo[1,2-*a*]pyrimidine parent nucleus, benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives showed a diverse range of biological properties such as antineoplastic activity [10], and acted as C3a receptor antagonists [11]

Scheme 1

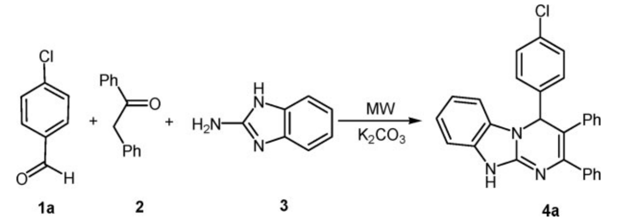


and new calcium antagonists [12]. Because of a range of biological activity they exhibited, these compounds have distinguished themselves as heterocycles of profound chemical and biological significance. Thus, the synthesis of these molecules has attracted considerable attention [13]. Recently, the synthesis of benzo[4,5] imidazo[1,2-*a*]pyrimidine derivatives were reported by Alvarez-Builla and coworkers *via* the reaction of an requisite arylmethyleneacetoacetate with 2-aminobenzimidazole [14]. The improved procedure for benzo[4,5]-imidazo[1,2-*a*]pyrimidines in ionic liquid through the condensation of aldehydes with β-ketoester and 2-aminobenzimidazole was described by Shaabani *et al*. [15]. However, the synthesis of new heterocyclic compounds containing benzoimidazopyrimidine scaffold and development of more rapid and efficient entry to this heterocycles are strongly desired. In connection with our previous studies [16], to modify benzoimidazopyrimidine scaffold, in this article we report a practical, inexpensive, rapid, and green microwave-promoted method for the synthesis of new heterocyclic compounds containing benzoimidazopyrimidine unit in PEG-300 using 1,2-diphenylethanone as potent precursor (Scheme 1).

RESULTS AND DISCUSSION

2-Aminobenzimidazole is a versatile and readily obtainable reagent, and its chemistry has received considerable attention in recent years due to the high nucleophilic reactivity of two nitrogen atoms [17]. Our strategy synthesizing the poly-substituted benzo[4,5]imidazo[1,2-*a*]pyrimidines was that 2-aminobenzimidazole was examined as starting material to react with aromatic aldehydes and 1,2-diphenylethanone under microwave heating. Initially, we screened various conditions for the one-pot, three-component reaction of equimolar amount of 2-aminobenzimidazole with 4-chlorobenzaldehyde and 1,2-diphenylethanone at 100°C in the presence of potassium carbonate under microwave irradiation (Scheme 2 and Table 1). Among various polar solvents tested, glacial acetic acid (HOAc), acetonitrile, ethanol, and water gave poor to moderate yields of the expected product (Table 1, entries 1−4). The best solvent was found to be PEG-300. In this solvent, benzo[4,5]imidazo[1,2-*a*]pyrimidines (**4a**) was obtained with the best yield (Table 1, entry 5). To further optimize the reaction conditions, the reaction was carried out at temperatures ranging from 90 to 130°C, with an increment of 10°C each time. The yield of product **4a** was increased and the reaction time was shortened as the temperature was increased from 90 to 120°C (Table 1, entries 5−8). However, further increase of the temperature to 130°C failed to improve the yield of product **4a** (Table 1, entry 9). Therefore, 120°C was chosen as the reaction temperature for all further microwave-assisted reactions.

Scheme 2



The use of these optimal microwave experimental conditions [PEG-300, 120°C] to the reactions of different aromatic aldehydes afforded good yields of benzo[4,5]imidazo[1,2-*a*]pyrimidines, with two phenyl groups presenting in positions 4 and 5 of the new forming pyrimidine nucleus, respectively. To test the scope of aromatic aldehydes, 2-aminobenzimidazole and 1,2-diphenylethanone were used as model substrates, and the results (Table 2, entries 1–11) indicated that aromatic aldehydes bearing functional groups such as chloro, bromo, or methoxy are suitable for the reaction. We have also observed electronic effects, that is, aromatic aldehydes with electron-withdrawing groups (Table 2, entries 1−4) reacted rapidly, while electron-rich groups (Table 2, entries 6−11) decreased the reactivity, requiring longer reaction times.

The use of PEG as a recyclable reaction medium in these reactions avoids the use of volatile and toxic organic solvents. In addition to the often referred advantages of using PEG-300 as solvent, this procedure has following remarkable features when compared to conventional method: (1) short reaction time, (2) clean reaction protocol, (3) high yielding.

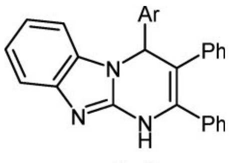
Table 1

Optimization for the synthesis of **4a** under MW.

Entry	Solvent	*T* (°C)	Time (min)	Yield (%)
1	HOAc	100	10	46
2	CH_3CN	100	10	34
3	Ethanol	100	10	57
4	Water	100	10	41
5	PEG-300	100	10	68
6	PEG-300	90	14	60
7	PEG-300	110	12	76
8	PEG-300	120	12	87
9	PEG-300	130	12	83

Table 2

Synthesis of compounds **4** under microwave irradiation.

Entry	Product	Ar	Time (min)	Yield (%)	mp (°C)
1	 **4a-4k**	**4a**, 4-Chlorophenyl (**1a**)	12	87	284–286
2		**4b**, 4-Bromophenyl (**1b**)	12	85	>300
3		**4c**, 2-Chlorophenyl (**1c**)	10	86	>300
4		**4d**, 2,4-Dichlorophenyl (**1d**)	10	84	>300
5		**4e**, Phenyl (**1e**)	14	82	274–276
6		**4f**, 4-Tolyl (**1f**)	14	80	295–297
7		**4g**, 4-Dimethylaminophenyl (**1g**)	16	78	>300
8		**4h**, Benzo[*d*][1,3]dioxol-5-yl (**1h**)	14	80	>300
9		**4i**, 4-Methoxyphenyl (**1i**)	14	79	250–252
10		**4j**, 3,4-Dimethoxyphenyl (**1j**)	16	75	267–268
11		**4k**, 3,4,5-Trimethoxyphenyl (**1k**)	18	76	296–298

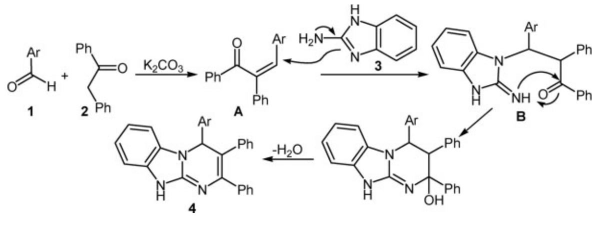
To prove that the use of PEG as solvent is practical, it has to be conveniently recyclable with minimal loss and decomposition. Because PEG is immiscible with aliphatic hydrocarbons, the desired product may be extracted with compounds such as cyclohexane [18], and the retained PEG phase may be reused. In the recycling study, the reaction between 4-chlorobenzaldehyde, 1,2-diphenylethanone, and 2-aminobenzimidazole in the presence of potassium carbonate could be repeated three times without reduction of the yield (84% ± 3%), although a weight loss of ~10% PEG was observed from cycle to cycle.

The formation of **4** is likely to proceed *via* initial condensation of aromatic aldehydes **1** with 1,2-diphenylethanone **2** to afford 3-aryl-1,2-diphenylprop-2-en-1-one **A,** which further undergoes *in situ* Michael addition reaction with 2-aminobenzimidazole **3** to yield intermediate **B**. The intermediate **B** is upon intramolecular cyclization and dehydration to generate final products 4 (Scheme 3).

In this study, all the products were characterized by melting point, IR, and ^{1}H NMR spectral data, as well as elemental analysis.

In conclusion, we have demonstrated that PEG is a convenient, inexpensive, nonionic liquid, nontoxic, and recyclable reaction medium for the efficient synthesis of 4,5-bis-aryl substituted benzo[4,5]imidazo[1,2-*a*]pyrimidines. Interestingly, we found a new multicomponent reaction of aromatic aldehydes with 1,2-diphenylethanone and 2-aminobenzimidazole in PEG-300, which provides a rapid and efficient route for the construction of benzo[4,5]imidazo[1,2-*a*]pyrimidine skeleton. This protocol offers a rapid and clean alternative and reduces reaction time. The recyclability of the reaction media makes reaction economically and potentially viable for commercial applications.

Scheme 3



EXPERIMENTAL

Microwave irradiation was carried out with a microwave oven Emrys^{TM} Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in the open capillaries and were uncorrected. IR spectra were taken on a FT-IR-Tensor 27 spectrometer in KBr pellets and reported in cm^{-1}. ^{1}H NMR spectra were measured on a Bruker DPX 400 MHz spectrometer using TMS as an internal standard and DMSO-d_6 as solvent. Elemental analysis was determined by using a Perkin-Elmer 240c elemental analysis instrument.

General procedure for the one-pot synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives under microwave irradiation conditions. Typically, in a 10-mL Emrys^{TM} reaction vial, aromatic aldehyde 1 (1 mmol), 1,2-diphenylethanone 2 (1 mmol), 2-aminobenzimidazole 3 (1 mmol), potassium carbonate (0.4 mmol), and PEG-300 (2 mL) were mixed and then capped. The mixture was irradiated for a given time at 120°C under microwave irradiation (initial power 100 W and maximum power 250 W). Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature. The precipitated product was filtered off and the filter liquor was extracted by diethyl ether. The residue left after evaporation of the solvent was added to the solid product isolated by filtration, and purified by flash chromatography (silica gel, petroleum ether: acetone = 10:1) to give rise to the pure product 4. The recovered PEG can be reused for a number of cycles without significant loss of activity.

4-(4-Chlorophenyl)-2,3-diphenyl-4,10-dihydrobenzo[4,5]-imidazo[1,2-*a*]pyrimidine (4a). ir (potassium bromide): 3055, 3025, 2820, 1625, 1578, 1408, 1279, 1088, 1011, 830, 774, 698 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.22 (s, 1H, NH), 7.40 (d, 2H, J = 8.4 Hz, ArH), 7.31 (d, 2H, J = 8.8 Hz, ArH), 7.26–7.24 (m, 6H, ArH), 7.15 (d, 1H, J = 8.0 Hz, ArH), 7.07–7.00 (m, 4H, ArH), 6.91–6.88 (m, 3H, ArH), 6.66

(s, 1H, CH). Anal. calcd. for $C_{28}H_{20}ClN_3$: C, 77.50; H, 4.65; N, 9.68. Found: C, 77.31; H, 4.67; N, 9.55.

4-(4-Bromophenyl)-2,3-diphenyl-4,10-dihydrobenzo[4,5]-imidazo[1,2-*a*]pyrimidine (4b). ir (potassium bromide): 3054, 3024, 2820, 1626, 1579, 1403, 1286, 1071, 1009, 841, 774, 699 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.19 (s, 1H, NH), 7.45 (d, 2H, J = 8.0 Hz, ArH), 7.33 (d, 2H, J = 8.4 Hz, ArH), 7.30–7.27 (m, 6H, ArH), 7.15 (d, 1H, J = 8.0 Hz, ArH), 7.07–7.00 (m, 4H, ArH), 6.92–6.89 (m, 3H, ArH), 6.65 (s, 1H, CH). Anal. calcd. for $C_{28}H_{20}BrN_3$: C, 70.30; H, 4.21; N, 8.78. Found: C, 70.46; H, 4.19; N, 8.69.

4-(2-Chlorophenyl)-2,3-diphenyl-4,10-dihydrobenzo[4,5]-imidazo[1,2-*a*]pyrimidine (4c). ir (potassium bromide): 3051, 3023, 2822, 1627, 1579, 1459, 1283, 1034, 913, 783, 697 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.25 (s, 1H, NH), 7.52 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.6 Hz, ArH), 7.28–7.24 (m, 8H, ArH), 7.18 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.6 Hz, ArH), 7.03–6.96 (m, 5H, ArH), 6.92–6.87 (m, 3H, ArH), 6.85 (s, 1H, CH). Anal. calcd. for $C_{28}H_{20}ClN_3$: C, 77.50; H, 4.65; N, 9.68. Found: C, 77.59; H, 4.64; N, 9.74.

4-(2,4-Dichlorophenyl)-2,3-diphenyl-4,10-dihydrobenzo [4,5]-imidazo[1,2-*a*]pyrimidine (4d). ir (potassium bromide): 3055, 3024, 2816, 1626, 1580, 1459, 1282, 1102, 1010, 843, 772, 696 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.25 (s, 1H, NH), 7.54 (d, 1H, J = 8.4 Hz, ArH), 7.45 (s, 1H, ArH), 7.34 (d, 1H, J = 8.0 Hz, ArH), 7.29 (d, 1H, J = 8.0 Hz, ArH), 7.24 (s, 5H, ArH), 7.04–6.97 (m, 5H, ArH), 6.93–6.89 (m, 3H, ArH), 6.88(s, 1H, CH). Anal. calcd. for $C_{28}H_{19}Cl_2N_3$: C, 71.80; H, 4.09; N, 8.97. Found: C, 71.72; H, 4.11; N, 8.90.

2,3,4-Triphenyl-4,10-dihydrobenzo[4,5]imidazo[1,2-*a*]-pyrimidine (4e). ir (potassium bromide): 3053, 3023, 2823, 1626, 1509, 1458, 1284, 1073, 829, 782, 700 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.14 (s, 1H, NH), 7.39(d, 2H, J = 7.2 Hz, ArH), 7.29–7.27 (m, 3H, ArH), 7.26–7.23 (m, 5H, ArH), 7.17 (d, 2H, J = 7.2 Hz, ArH), 7.05–6.98 (m, 4H, ArH), 6.90–6.87 (m, 3H, ArH), 6.57 (s, 1H, CH). Anal. calcd. for $C_{28}H_{21}N_3$: C, 84.18; H, 5.30; N, 10.52. Found: C, 84.24; H, 5.33; N, 10.49.

4-*p*-Tolyl-2,3-diphenyl-4,10-dihydrobenzo[4,5]imidazo-[1,2-*a*]pyrimidine (4f). ir (potassium bromide): 3051, 3022, 2825, 1626, 1574, 1459, 1282, 1179, 1009, 826, 774, 698 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.12 (s, 1H, NH), 7.29 (d, 2H, J = 8.0 Hz, ArH), 7.28–7.21 (m, 6H, ArH), 7.18 (d, 1H, J = 8.0 Hz, ArH), 7.06 (d, 2H, J = 7.6 Hz, ArH), 7.03–6.98 (m, 4H, ArH), 6.90–6.87 (m, 3H, ArH), 6.53 (s, 1H, CH), 2.18 (s, 3H, CH_3). Anal. calcd. for $C_{29}H_{23}N_3$: C, 84.23; H, 5.61; N, 10.16. Found: C, 84.31; H, 5.59; N, 10.21.

4-(4-Dimethylaminophenyl)-2,3-diphenyl-4,10-dihydro-benzo [4,5]imidazo[1,2-*a*]pyrimidine (4g). ir (potassium bromide): 3053, 3023, 2802, 1625, 1575, 1444, 1234, 1165, 1073, 827, 777, 698 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.05 (s, 1H, NH), 7.26–7.23 (m, 9H, ArH), 7.05–6.97 (m, 4H, ArH), 6.91–6.87 (m, 3H, ArH), 6.58 (d, 2H, J = 8.4 Hz, ArH), 6.39 (s, 1H, CH), 2.81 (s, 6H, CH_3). Anal. calcd. for $C_{30}H_{26}N_4$: C, 81.42; H, 5.92; N, 12.66. Found: C, 81.34; H, 5.95; N, 12.72.

4-Benzo[1,3]dioxol-5-yl-2,3-diphenyl-4,10-dihydrobenzo[4,5]-imidazo[1,2-*a*]pyrimidine (4h). ir (potassium bromide): 3051, 3018, 2824, 1627, 1573, 1460, 1237, 1039, 935, 853, 777, 698 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.13 (s, 1H, NH), 7.29–7.27 (m, 2H, ArH), 7.26–7.23 (m, 5H, ArH), 7.07–6.99 (m, 4H, ArH), 6.94–6.89 (m, 5H, ArH), 6.78 (d, 1H, J = 8.4 Hz, ArH), 6.50 (s, 1H, CH), 5.93 (d, 2H, J = 16 Hz, CH_2). Anal. calcd. for $C_{29}H_{21}N_3O_2$: C, 78.54; H, 4.77; N, 9.47. Found: C, 78.62; H, 4.75; N, 9.53.

4-(4-Methoxyphenyl)-2,3-diphenyl-4,10-dihydrobenzo[4,5]-imidazo[1,2-*a*]pyrimidine (4i). ir (potassium bromide): 3048, 3016, 2834, 1628, 1580, 1418, 1264, 1028, 856, 777, 701 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.14 (s, 1H, NH), 7.35 (d, 2H, J = 8.8 Hz, ArH), 7.29–7.26 (m, 5H, ArH), 7.25–7.20 (m, 2H, ArH), 7.06–6.98 (m, 4H, ArH), 6.91–6.87 (m, 3H, ArH), 6.81 (d, 2H, J = 8.8 Hz, ArH), 6.51 (s, 1H, CH), 3.65 (s, 3H, OCH_3). Anal. calcd. for $C_{29}H_{23}N_3O$: C, 81.09; H, 5.40; N, 9.78. Found: C, C, 81.01; H, 5.43; N, 9.69.

4-(3,4-Dimethoxyphenyl)-2,3-diphenyl-4,10-dihydrobenzo [4,5]imidazo[1,2-*a*]pyrimidine (4j). ir (potassium bromide): 3048, 3016, 2834, 1628, 1580, 1418, 1264, 1028, 856, 777, 701 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.09 (s, 1H, NH), 7.29–7.25 (m, 7H, ArH), 7.07–7.01 (m, 4H, ArH), 7.00–6.96 (m, 2H, ArH), 6.95–6.93 (m, 1H, ArH), 6.90 (d, 2H, J = 8.0 Hz, ArH), 6.84 (d, 1H, J = 8.4 Hz, ArH), 6.48 (s, 1H, CH), 3.65 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3). Anal. calcd. for $C_{30}H_{25}N_3O_2$: C, 78.41; H, 5.48; N, 9.14. Found: C, 78.52; H, 5.46; N, 9.20.

4-(3,4,5-Trimethoxyphenyl)-2,3-diphenyl-4,10-dihydrobenzo [4,5]imidazo[1,2-*a*]pyrimidine (4k). ir (potassium bromide): 3050, 3018, 2834, 1651, 1571, 1418, 1251, 1125, 1011, 828, 779, 701 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.13 (s, 1H, NH), 7.41 (d, 1H, J = 7.6 Hz, ArH), 7.30–7.28 (m, 6H, ArH), 7.08–7.01 (m, 4H, ArH), 6.96 (d, 1H, J = 7.6 Hz, ArH), 6.91 (d, 2H, J = 7.6 Hz, ArH), 6.78 (s, 2H, ArH), 6.47 (s, 1H, CH), 3.66 (s, 6H, OCH_3), 3.56 (s, 3H, OCH_3). Anal. calcd. for $C_{31}H_{27}N_3O_3$: C, 76.05; H, 5.56; N, 8.58. Found: 76.13; H, 5.54; N, 8.63.

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Formation of an Unusual Product in the Reaction of a 1,2,5-Thiadiazolidine 1,1-Dioxide-Derived Thioether with Sulfuryl Chloride

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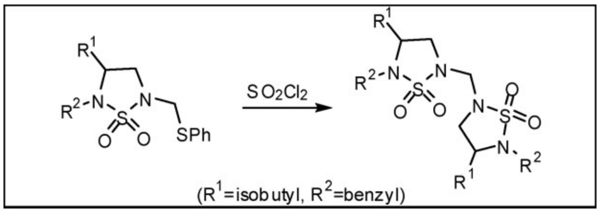

The treatment of a 1,2,5-thiadiazolidine 1,1-dioxide-derived phenylthiomethyl ether with sulfuryl chloride yielded an unexpected dimeric product whose structure was determined using X-ray crystallography. A plausible mechanism for the formation of this product is proposed.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a multifactorial inflammatory disorder characterized by alveolar wall destruction, enlargement of the air spaces, and airflow obstruction due to chronic bronchitis and emphysema [1–3]. The treatment of COPD is symptomatic [4,5], and there are no drugs capable of halting the relentless progression of the disorder. Although the pathogenesis of COPD is poorly understood, recent ground-breaking studies indicate that the disorder involves the close interplay of oxidative stress [6], alveolar septal cell apoptosis [7–9], extracellular matrix destruction arising from a protease/antiprotease imbalance [10,11], and chronic inflammation [12]. Proteases implicated in COPD include serine (neutrophil elastase), cysteine (cathepsin S), and metallo-(MMP-2, MMP-9, and MMP-12) proteases [13]. Agents capable of modulating the aberrant activity of these enzymes may be of potential therapeutic value [14–16].

We have previously described the design, synthesis, and *in vitro* biochemical evaluation of a new and general class of mechanism-based inhibitors of serine proteases (structure (I), Figure 1) [17,18], and have recently demonstrated that the time-dependent inactivation of these enzymes by (I) proceeds through the initial formation of a Michael acceptor (a sulfonyl imine), ultimately leading to the formation of an inactive enzyme-inhibitor complex (or complexes) [19]. A key step in the multistep synthesis of (I) was the synthesis of a substituted *N*-chloromethyl sulfohydantoin via a sulfuryl chloride-mediated cleavage of a phenylthiomethyl ether (Scheme 1).

Based on the successful development of (I), we reasoned that the replacement of the C=O group by a CH_2 group would generate a 1,2,5-thiadiazolidine 1,1-dioxide (cyclosulfamide) and transform (I) into a new class of noncovalent inhibitors (II) (Figure 1) [20]. Accordingly, the appropriate substituted 1,2,5-thiadiazolidine 1,1-dioxide-derived phenylthiomethyl ether intermediate was synthesized and then treated with sulfuryl chloride to obtain the *N*-chloromethyl derivative (Scheme 2). Surprisingly, work up of the reaction mixture and subsequent purification of the product by flash chromatography afforded a solid which did not exhibit the spectral characteristics of the expected *N*-chloromethyl compound. Instead, an interesting dimeric product (7) was obtained, the structure of which and the mechanism leading to it constitutes the subject of the present article.

RESULTS AND DISCUSSION

The structure of product (7) was established on the basis of the following data: the molecular weight of the compound was determined by ESI-MS to be 549, corresponding to the molecular formula $C_{27}H_{40}N_4O_4S_2$, which was in agreement with the elementary analysis of the product. The structure of (7) was established unambiguously via single crystal X-ray crystallography. An ORTEP [21] view (Figure 2) and X-ray crystal structure data (Table 1) are shown below [22].

A plausible mechanism depicting the formation of (7) is outlined in Figure 3, line (a), whereby the initial formation of a chlorosulfonium salt proceeds further along

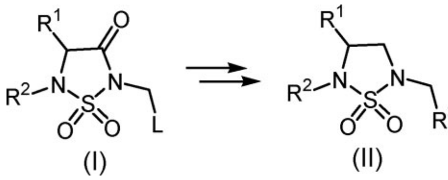


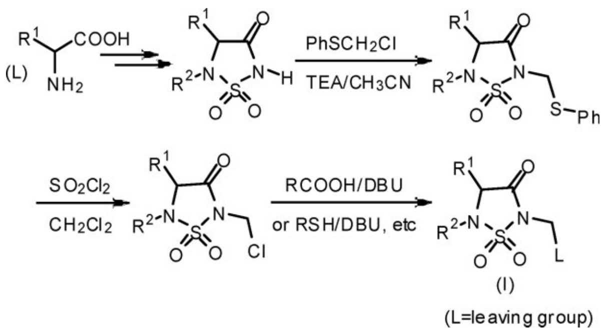
Figure 1. Design of noncovalent inhibitor (II).

two pathways: one leading to an iminium ion (A) [23], and the other leading to a sulfur ylide (B), probably favored by the high acidity of the methylene hydrogens in the moiety -N(SO_2N-)CH_2SClPh. This ylide subsequently undergoes rearrangement to α-chlorosulfide (C) in a process that is reminiscent of the Pummerer rearrangement [24,25]. When (C) dissociates into an ion pair (both ions are stabilized by resonance), anion (D) undergoes a Michael-type reaction with iminium ion (A) to afford the unusual dimeric product (7). The equilibrium leading to (A) will likely be more favorable for formation of (A) than (B), and hence more favorable for (A) than for (C) and (D). However, capture of (D) by (A) to produce (7) would shift the series of equilibria from (B) to (C) and (D), ultimately leading to (7).

It now becomes clear why such a dimeric product is not observed when the initial phenyl thiomethyl ether bears a carbonyl group at position 3 of the 1,2,5-thiadiazolidine 1,1-dioxide ring, but merely affords the chloromethyl derivative upon treatment with sulfuryl chloride (Figure 3, line (b)). The presence of a C=O group adjacent to nitrogen located at position 2 diminishes its nucleophilicity considerably (by virtue of being adjacent to a C=O group, as well as an SO_2 group), rendering path (a) in Figure 3 inoperative and blocking the formation of a dimer.

In summary, the structure of an unexpected dimeric product formed in the reaction of a 1,2,5-thiadiazolidine 1,1-dioxide-derived phenylthiomethyl ether with sulfuryl chloride was determined using X-ray crystallography. A plausible mechanism leading to the formation of this product is proposed.

Scheme 1

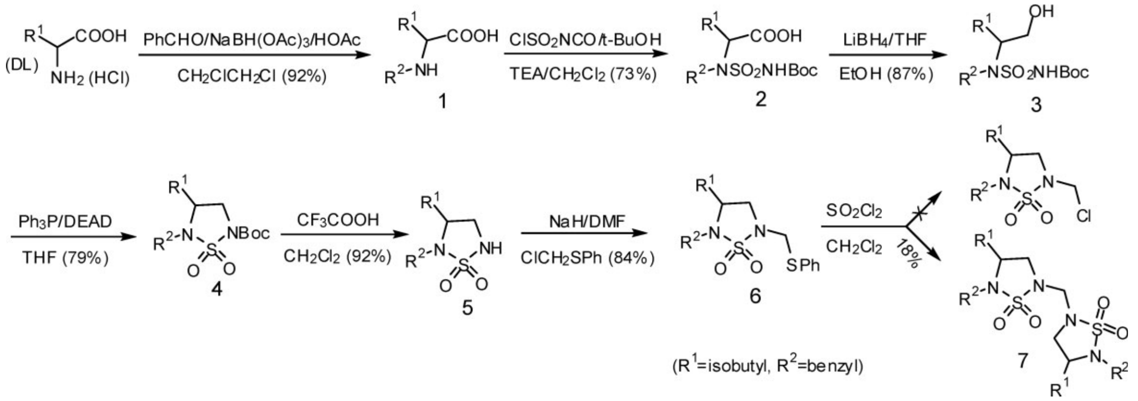


EXPERIMENTAL

General. The ^{1}H NMR spectra were recorded on a Varian XL-300 or XL-400 NMR spectrometer. Melting points were determined on a Mel-Temp apparatus and are uncorrected. IR spectra were taken with a Nicolet FT-IR-Avatar 360 spectrometer. MS spectra were recorded with VARIAN 1200L mass spectrometer. Elemental analysis data were obtained from Columbia Analytical Services (Tucson, AZ). Reagents and solvents were purchased from various chemical suppliers (Aldrich, Acros rganics, TCI America, and Bachem). Silica gel (230–450 mesh) used for flash chromatography was purchased from Sorbent Technologies, Atlanta, GA. Thin layer chromatography was performed using Analtech silica gel plates. The TLC plates were visualized using iodine and/or UV light.

Methyl 2-(Benzylamino)-4-methylpentanoate (1). DL-Leucine methyl ester hydrochloride (43.6 g; 240 mmol) was suspended in 250 mL 1,2-dichloroethane, and then benzaldehyde (30.8 g; 270 mmol) and acetic acid (19.2 g; 320 mmol) were added, followed by sodium triacetoxyborohydride (71.2 g; 335 mmol). The reaction was stirred at RT overnight. The reaction mixture was adjusted to pH 10 using 20% sodium hydroxide, and then two layers were separated. The aqueous layer was extracted with 2 × 100 mL diethyl ether and the organic layers were combined and dried over anhydrous sodium

Scheme 2



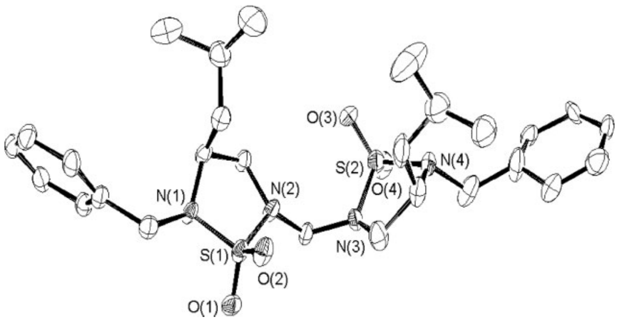


Figure 2. ORTEP drawing of compound **7** showing the 30% thermal ellipsoids. H atoms have been omitted for clarity.

sulfate. Removal of solvent yielded a crude product, which was purified by flash chromatography (silica gel/ethyl acetate/hexanes) to give compound **1** as a colorless oil (27.0 g, 48.6% yield). ir (neat): 3333 (NH), 1735 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.88 (dd, 6H, $2CH_3$, J = 6.6, 19.8 Hz), 1.48 (t, 2H, CH_2, J = 7.5 Hz), 3.31 (t, 1H, alpha-H, J = 7.5 Hz), 3.71 (dd, 2H, CH_2, J = 12.9, 60 Hz), 3.72 (s, 3H, OCH_3), 7.20–7.26 (m, 5H, phenyl protons); ms: m/z 258 (M^++Na, 27%), 236 (M^++1, 53%), 176 (M^+-C(O)OCH$_3$, 21%), 91 (phCH$_2^+$, 100%). Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.19; H, 9.28; N, 5.94.

Methyl 2-(Benzyl(*N*-(*tert*-butoxycarbonyl)sulfamoyl)-amino)-4-methylpentanoate (2). A solution of *N*-chlorosulfonyl isocyanate (14.9 g; 103 mmol) in 130 mL dry methylene chloride cooled in an ice bath was added dropwise to a solution of *t*-butyl alcohol (7.72 g; 103 mmol) in 130 mL dry methylene chloride with stirring. After 15 min stirring, the resulting solution was added dropwise to a solution of compound **1** (24.24 g; 103 mmol) and triethylamine (10.6 g; 103 mmol) in 130 mL dry methylene chloride under an ice bath. The ice bath was removed after the addition and the reaction stirred at RT for 6 h. The reaction mixture was washed with150 mL brine and the organic layer was dried over anhydrous sodium sulfate. Removal of the solvent yielded a crude product, which was purified by flash chromatography (silica gel/ethyl acetate/hexanes) to give compound **2** as a white solid (31.0 g, 72.6% yield), mp 95–96°C. ir (KBr pellet): 3355 (NH), 1740 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.68 (dd, 6H, $2CH_3$, J = 6.0, 94.5 Hz), 1.40–1.60 (m, 3H, CH & CH_2), 1.50 (s, 9H, t-Butyl protons), 3.70 (s, 3H, OCH_3), 4.65 (t, 1H, alpha-H, J = 7.5 Hz), 4.71 (dd, 2H, CH_2, J = 16.5, 122.1 Hz, CH_2), 7.25–7.45 (m, 5H, phenyl protons); ms: m/z 437 (M^++Na, 100%), 381 (M^+-OCH$_3$, 19%), 258 (M^+-SO$_2$NH-Boc+Na, 29%), 236 (M^+-SO$_2$NHBoc+1, 46%), 91 (PhCH$_2^+$, 19%). Anal. Calcd. for $C_{19}H_{30}N_2O_6S$: C, 55.05; H, 7.29; N, 6.76. Found: C, 55.13; H, 7.03; N, 6.62.

***tert*-Butyl *N*-Benzyl-*N*-(1-hydroxy-4-methylpentan-2-yl) sulfamoylcarbamate (3).** To a solution of compound **2** (27.21 g; 65.5 mmol) in 100 mL dry THF, a solution of 2*M* lithium borohydride in THF (32.8 mL; 65.6 mmol) was added dropwise, followed by the dropwise addition of 197 mL absolute ethanol. The reaction mixture was stirred at RT overnight. The reaction mixture was cooled in an ice bath and neutralized to pH 4 using 5% aqueous HCl solution, and then the solvent was completely removed. Two hundred and fifty millilitres of water was added and extracted with 3 × 300 mL ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate. Removal of the solvent yielded a crude product, which was purified by flash chromatography (silica gel/ethyl acetate/hexanes) to give compound **3** as a white solid (22.0 g, 86.7% yield), mp 107–109°C. ir (KBr pellet): 3217 (OH), 1733 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.82 (dd, 6H, $2CH_3$, J = 6.3, 38.4 Hz), 1.05–1.35 (m, 2H, CH_2), 1.48 (s, 9H, t-Butyl protons), 1.56–1.65 (m, 1H, CH), 2.82 (t, 1H, OH, J = 5.4 Hz), 3.55–3.70 (m, 2H, CH_2), 4.03–4.17 (m, 1H, CH), 4.50 (dd, 2H, CH_2, J = 15.9, 29.7 Hz), 7.18–7.45(m, 5H, phenyl protons); ms: m/z 409 (M^++Na, 100%), 353 (M^+-*t*-Butene+Na, 12%), 230 (M^+-SO$_2$NHBoc+Na, 35%), 91 (PhCH$_2^+$, 9%). Anal. Calcd. for $C_{18}H_{30}N_2O_5S$: C, 55.94; H, 7.82; N, 7.25. Found: C, 56.11; H, 8.12; N, 7.18.

***tert*-Butyl 5-Benzyl-4-isobutyl-1,2,5-thiadiazolidine-2-carboxylate 1,1-dioxide (4).** A solution of compound **3** (21.54 g; 55.7 mmol) in 170 mL dry THF was treated with triphenyl phosphine (29.22 g; 111.4 mmol) and diethyl azodicarboxylate (DEAD, 19.4 g; 111.4 mmol) with stirring at RT for 4 h. Removal of the solvent left a crude product, which was purified

Table 1

Crystal data and structure refinement parameters for **7**.

Empirical formula	$C_{27}H_{40}N_4O_4S_2$	Crystal habit	Needle
Formula weight	548.75	Crystal color	Colorless
Temperature	150 K	Θ range for data collection	2.04° to 26.00°
Diffractometer	Bruker Kappa APEX II		$-50 \leq h \leq 50$
Radiation	Mo Kα, 0.71073 Å	Limiting indices	$-7 \leq k \leq 7$
Crystal system	Monoclinic		$-34 \leq l \leq 34$
Space group	C2/c	Reflections collected/unique	50861/5705 [R(int) = 0.4278]
Unit cell dimensions	a = 40.714(7) Å	Completeness to θ = 26.00°	99.8%
	b = 6.2300(9) Å	Refinement method	Full-matrix least-squares on F^2
	c = 27.774(4) Å	Data/restraints/parameters	5705/0/367
	β = 124.547(9)°	Refinement threshold	$I > 2\sigma(I)$
Volume	5802.5(16) Å^3	Data > threshold	1681
Z	8	Goodness-of-fit on F2	1.021
Density (calculated)	1.256 Mg/m^3	Final R indices [$I > 2\sigma(I)$]	R1 = 0.0896, wR2 = 0.1829
Absorption coefficient	0.222 mm^{-1}	R indices (all data)	R1 = 0.3060, wR2 = 0.3004
F(000)	2352	Largest diff. peak and hole	0.491 and −0.400 e.Å^{-3}
Crystal size	0.43 × 0.06 × 0.05 mm^3		

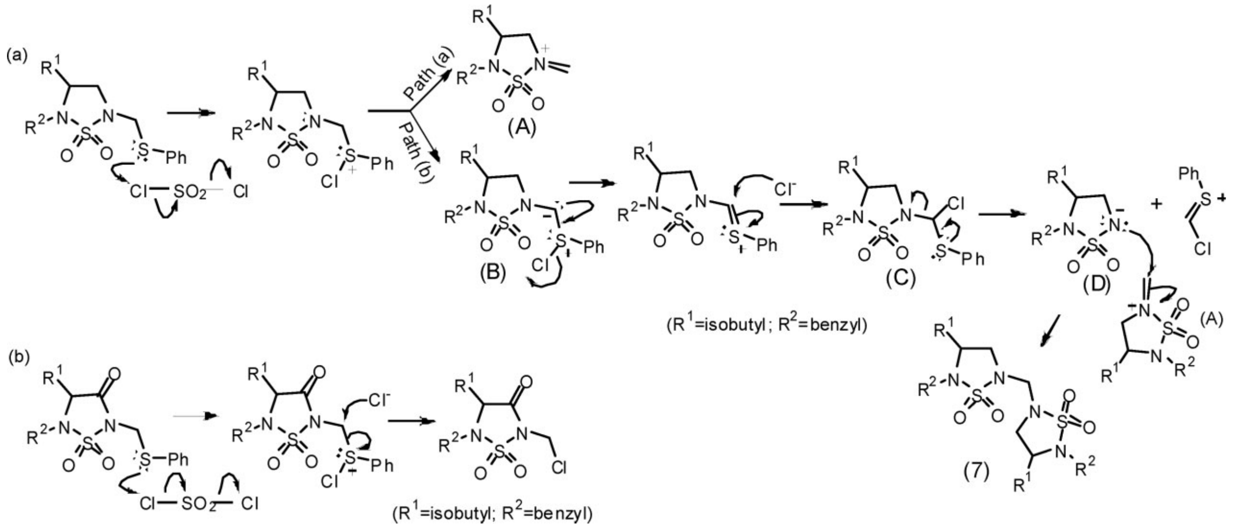


Figure 3. Postulated mechanism for the formation of compound **7**.

by flash chromatography (silica gel/ethyl acetate/hexanes) to give compound **4** as a white solid (16.19 g, 79.0% yield), mp 81–82°C. ir (KBr pellet): 1721 (C=O) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 0.79 (dd, 6H, 2CH$_3$, *J* = 6.3, 14.4 Hz), 1.35–1.60 (m, 3H, CH & CH$_2$), 1.56 (s, 9H, t-Butyl protons), 3.40–3.51 (m, 2H, CH$_2$), 3.80–3.88 (m, 1H, CH), 4.29 (dd, 2H, CH$_2$, *J* = 15.3, 48.3 Hz), 7.30–7.41 (m, 5H, phenyl protons); ms: *m*/*z* 391 (M$^+$+Na, 5%), 335 (M$^+$-t-Butene +Na, 42%), 176 (M$^+$-CH$_2$OH-SO$_2$NHBoc, 35%), 91 (PhCH$_2^+$, 100%). Anal. Calcd. for C$_{18}$H$_{28}$N$_2$O$_4$S: C, 58.67; H, 7.66; N, 7.60. Found: C, 58.85; H, 7.75; N, 7.53.

2-Benzyl-3-isobutyl-1,2,5-thiadiazolidine 1,1-dioxide (5). A solution of compound **4** (15.76 g; 42.8 mmol) in 40 mL dry methylene chloride was treated with trifluoroacetic acid (140 mL) at RT for 3 h. Removal of the solvent left a crude product, which was purified by flash chromatography (silica gel/ ethyl acetate/hexanes) to give compound **5** as a white solid (10.5 g, 91.5% yield), mp 60–62°C. ir (KBr pellet): 3225 (NH) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.80 (dd, 6H, 2CH$_3$, *J* = 6.3, 24.9 Hz), 1.38–1.58 (m, 3H, CH & CH$_2$), 3.12–3.20 (m, 1H, one proton of CH$_2$), 3.40–3.50 (m, 1H, one proton of CH$_2$), 3.50–3.60 (m, 1H, CH), 4.28(s, 1H, NH), 4.29 (dd, 2H, CH$_2$, *J* = 12.0, 45.6), 7.25-7.42 (m, 5H, phenyl protons); ms: *m*/*z* 291 (M$^+$+Na, 100%), 91 (PhCH$_2^+$, 20%). Anal. Calcd. for C$_{13}$H$_{20}$N$_2$O$_2$S: C, 58.18; H, 7.51; N, 10.44. Found: C, 58.09; H, 7.42; N, 10.20.

2-Benzyl-3-isobutyl-5-[(phenylsulfanyl)methyl]-1,2,5-thiadiazolidine 1,1-dioxide (6). A solution of compound **5** (0.97 g; 3.6 mmol) in 4 mL dry DMF was cooled in an ice bath, and then sodium hydride (0.23 g; 60% w/w; 5.8 mmol) was added with stirring. Ten minutes later, chloromethyl phenyl sulfide (0.80 g; 5.0 mmol) was added. The reaction was allowed to warm to room temperature and stirred for 2 h. DMF was removed by oil pump under 40°C. The residue was dissolved in 30 mL ethyl acetate and washed with 2 × 20 mL brine, and then the organic layer was dried over anhydrous sodium sulfate. Removal of the solvent left a crude product, which was purified by flash chromatography (silica gel/ ethyl acetate/ hexanes) to give compound **6** as a colorless oil (1.18 g, 84.0% yield). ^{1}H NMR (CDCl$_3$): δ 0.75 (dd, 6H, 2CH$_3$, *J* = 6.0, 20.7 Hz), 1.35–1.50 (m, 3H, CH & CH$_2$), 2.95 (dd, 1H, one proton of CH$_2$, *J* = 7.2, 9.0 Hz), 3.32–3.43 (m, 1H, CH), 3.65 (m, 1H), 3.65 (dd, 1H, one proton of CH$_2$, *J* = 7.2, 9.0 Hz), 4.38 (dd, 2H, CH$_2$, *J* = 7.8, 15.0 Hz), 4.45 (dd, 2H, CH$_2$, *J* = 13.8, 156.9 Hz), 7.23–7.53 (m, 10H, phenyl protons); ms: *m*/*z* 391 (M$^+$+1, 78%), 281 (M$^+$-PhSH, 100%). Anal. Calcd. for C$_{20}$H$_{26}$N$_2$O$_2$S$_2$: C, 61.50; H, 6.71; N, 7.17. Found: C, 61.34; H, 7.04; N, 7.16.

2,2′-Methylenebis(5-benzyl-4-isobutyl-1,2,5-thiadi-azolidine) 1,1,1′,1′-tetraoxide (7). To a solution of compound **6** (1.18 g; 3.0 mmol) in 4 mL dry methylene chloride in an ice bath, a solution of sulfuryl chloride (0.82 g; 6.0 mmol) in 2 mL dry methylene chloride was added with stirring. The reaction was allowed to warm to RT and stirred for 2 h. The solvent was removed and the residue was purified by flash chromatography (silica gel/ethyl acetate/hexanes) to give compound **7** as a white solid (0.15 g, 18.2% yield), mp 127–128°C. ^{1}H NMR (CDCl$_3$): δ 0.79 (dd, 12H, 4CH$_3$, *J* = 6.3, 24.0 Hz), 1.40–1.58 (m, 6H, 2CH & 2CH$_2$), 3.25 (dd, 2H, two protons of 2CH$_2$, *J* = 6.3, 9.6 Hz), 3.38–3.48 (m, 2H, 2CH), 3.72 (dd, 2H, two protons of 2CH$_2$, *J* = 6.9, 9.6 Hz), 4.26 (dd, 4H, 2CH$_2$, *J* = 14.7, 62.1 Hz), 4.60 (s, 2H, bridge CH$_2$), 7.25–7.41(m, 10H, phenyl protons); ms: *m*/*z* 549 (M$^+$+1, 76%), 281 (M$^+$-**5**, 100%), 91 (PhCH$_2^+$, 24%). Anal. Calcd. for C$_{27}$H$_{40}$N$_4$O$_4$S$_2$: C, 59.09; H, 7.35; N, 10.21. Found: C, 59.02; H, 7.15; N, 10.17.

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Synthesis and Characterization of New Phthalhydrazothiazole Derivatives: A Preliminary Investigation on Their Activity against Hepatocellular Carcinoma

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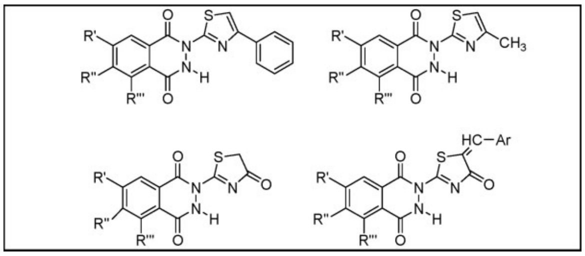

The synthesis of new 2-(4-substituted thiazol-2-yl)-2,3-dihydrophthalazine-1,4-diones, 2-(4-oxo-4,5-dihydro-thiazol-2-yl)-2,3-dihydrophthalazine-1,4-diones, and 2-(5-arylidene-4-oxo-4,5-dihydrothiazol-2-yl)-2,3-dihy-drophthalazine-1,4-diones is reported. The introduction of different substituents on the phthalazine, the thiazole and the thiazolinone has been studied. The new compounds have been characterized and evaluated for their antiproliferative activity against hepatocellular carcinoma, one of the most lethal tumors. The activity shown by some of these compounds towards liver tumor cells is encouraging.

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INTRODUCTION

Thiazoles play a prominent role in nature and have broad applications in agricultural and medicinal chemistry. As a matter of fact, thiazole derivatives show antitumor [1,2], anti-hypertensive [3], anti-inflammatory [4,5], anti-hyperlipidemic [6] and other biological properties [7,8].

Phthalazine derivatives, similarly to other members of the isomeric diazine series, have found wide application as therapeutic agents [9–21]. The synthesis and biological evaluation of semicarbazide derivatives that exhibit anticancer activity has been reported [22–24].

Moreover, a number of molecules bearing a tridentate ligand system, structurally related to thiazolophthalazines and thiazolinonephthalazines [25–32], show an inhibitory activity towards tumors; it has been shown that complexation of these compounds results in derivatives that are potent cytotoxic agents [33].

Following our interest in the synthesis and biological activity of heterocyclic compounds [34–39], we have synthesized several new 2-(4-substituted thiazol-2-yl)-2,3-dihydrophthalazine-1,4-diones, 2-(4-oxo-4,5-dihydro-thiazol-2-yl)-2,3-dihydrophthalazine-1,4-diones, and 2-(5-arylidene-4-oxo-4,5-dihydrothiazol-2-yl)-2,3-dihydrophthalazine-1,4-diones, in order to assess their capability of inhibiting tumor cell growth, and in particular their activity against hepatocellular carcinoma.

Hepatocellular carcinoma is one of the five most common cancers worldwide; it is one of the most common cancers in males in the world; it has an annual incidence worldwide of more than 500,000 cases and is very poorly treated with survival rates of only 23% at one year and less than 5% at five years [40].

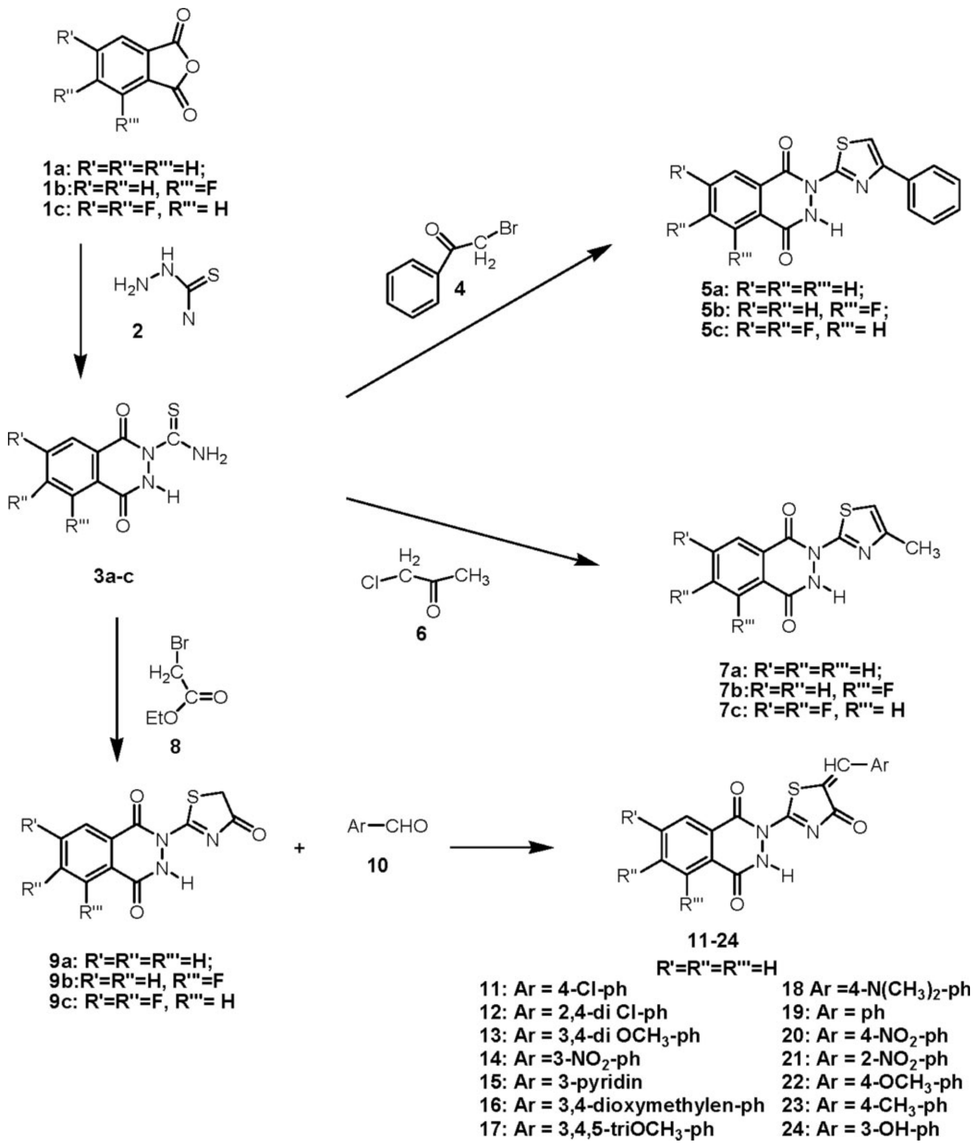
According to literature data, the highest diffusion is observed in China and eastern Asia, middle Africa and some countries of western Africa, while lower incidence is evident in Japan, Europe, and America. Nevertheless a rising trend is observed, due to the increasing of HCV infection [41]. The prognosis is generally poor, especially in the African and Chinese population, where survival time may be as short as eleven weeks from the onset of symptoms.

In this article, we investigate a straightforward and efficient synthesis of compounds containing thiazole and phthalazine moieties in the same molecule, as we consider this aspect particularly interesting.

RESULTS AND DISCUSSION

Several 2-(4-substituted thiazol-2-yl)-2,3-dihydrophtha-lazine-1,4-diones, 2-(4-oxo-4,5-dihydrothiazol-2-yl)-2,3-dihydrophthalazine-1,4-diones, and 2-(5-arylidene-4-oxo-4,5-dihydrothiazol-2-yl)-2,3-dihydrophthalazine-1,4-

Scheme 1



diones have been synthesized and their capability of inhibiting tumor cell growth investigated.

The first step in the synthetic pathway (Scheme 1) consists of the reaction of equimolecular amounts of phthalic anhydrides **1a–c** with thiosemicarbazide **2** in isopropanol, in the presence of catalytic amounts of acetic acid. By this method [39], 2-carbothioamidophthalazines **3a–c** can be prepared easily.

Compounds **3a–c** are then reacted either with α-halogen ketones or with α-halogen esters to form the substituted thiazole ring derivatives (**5a–c**, **7a–c**), and the thiazolinonic derivatives **9a–c,** respectively.

In the case of compound **3b** and its derivatives two possible regioisomers can be obtained. Apparently, according to chromatographic and spectral data, only one of the two possible isomers is formed, but the exact structure has not been investigated at this stage of the study.

Compounds **11–24** were obtained by reacting compound **9a** with different aryl aldehydes in acetic acid and acetic anhydride. All the obtained compounds were purified by crystallization from an appropriate solvent, and were fully characterized with the aid of ^{1}H NMR spectroscopy, mass spectrometry, and elemental analysis.

Compounds **5b–c**, **7a–c**, **9a–c**, **11–18** have been evaluated for their anti-proliferative activity towards the *FaO Reuber hepatoma* cell line, which maintains the characteristics of hepatocytes, both *in vivo* and *in vitro*, and retains the ability to undergo apoptosis [42].

To demonstrate the most promising structures and substitutions for biological activity, we investigated

Table 1

Percentage of cell vitality with respect to the control (NRU assay).

	Concentration (m*M*)					
Cp	1 (m*M*)	0.5 (m*M*)	0.25 (m*M*)	0.1 (m*M*)	0.05 (m*M*)	0.01 (m*M*)
7a	94.83	94.83	96.43	98.57	100	100
9a	60.02	64.86	91.35	93.87	97.69	98.01
5b	42.68	94.73	100	100	100	100
7b	98.71	100	100	100	100	100
9b	100	100	100	100	100	100
5c	100	100	100	100	100	100
7c	65.20	69.12	82.03	91.70	99.77	100
9c	100	100	100	100	100	100
11	62.17[a]	42.83[a]	36.53	44.41	94.84	95.12
12	40.68	38.20	41.68	58.08	74.94	100
13	100[b]	88.83	90.29	94.33	100	100
14	100	100	100	100	100	100
15	100	100	100	100	100	100
16	67.18	100	100	100	100	100
17	45.86	71.93	84.30	98.76	95.98	100
18	95.36	94.12	89.87	91.11	89.95	88.55

[a] Poorly soluble at 1 m*M* e 0.5 m*M*.

[b] Precipitates at 1 m*M*.

three different scaffolds, namely 2-(4-phenylthiazol-2-yl)-2,3-dihydrophthalazine-1,4-diones, 2-(4-thiazolinone-2-yl)-2,3-dihydrophthalazine-1,4-diones, and 2-(4-arylidenthiazolinone-2-yl)-2,3-dihydrophthalazine-1,4-diones.

Some of the tested compounds (Table 1) show a fairly good cytotoxic activity against FaO cells in the NRU assay.

Compound **11**, 2-[5-(4-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione shows the best activity with a 44% cell survival at a concentration of 0.1m*M*.

A similar behavior was observed in compound **12**, 2- [5-(2,4-dichlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione, indicating that the presence of one or two chlorine atoms, in the 5-arylidene moiety, increases activity against hepatoma cells.

It should be observed on the other hand that introduction of different substituents in the same scaffold generally leads to a decrease in biological activity, as observed for compounds **14, 15,** and **18**, which have a 3-nitrobenzylidene-, a 3-pyridylene-, and a 4-dimethylaminobenzylidene in position 5 of the thiazolidinone moiety, respectively.

In the case of compounds **16** and **17**, good activity is observed only at relatively high concentrations.

Compound **9a**, which contains an unsubstituted thiazolinonic cycle, showed a moderate biological activity.

The substitution of the thiazolinonic ring with a 4-phenylthiazole or 4-methylthiazole leads to a moderate increase in biological activity. This is particularly evident for compounds **5b** and **7c**, where one or two fluorine atoms are introduced in the phthalazine moiety, respectively.

Moreover, the presence of an opportunely functionalized aromatic moiety both in the thiazole and in the thiazolinone rings seems important for biological properties.

Thus activity is strongly influenced by the nature of the substituents, and the presence of halogen atoms both on the phthalazine and on 5-arylidenthiazolinone leads to an increase in activity.

These results give an indication towards the design of new and potentially more active compounds, and suggest that 2-(4-phenylthiazol-2-yl)-2,3-dihydrophthalazine-1,4-diones, 2-(4-thiazolinone-2-yl)-2,3-dihydrophthalazine-1,4-diones, and 2-(5-arylidenthiazolinone-2-yl)-2,3-dihydrophthalazine-1,4-diones could be considered promising scaffolds for cytotoxic compounds.

EXPERIMENTAL

Melting points were uncorrected and were determined on a Reichert Kofler thermopan apparatus. ^{1}H NMR spectra were recorded on a Bruker AMX (300 MHz) using tetramethylsilane (TMS) as internal standard (chemical shifts in δ values). Electron ionization (EI) mass spectra were obtained by a Fisons QMD 1000 mass spectrometer (70 eV, 200 μA, ion source temperature 200°C). The samples were introduced directly into the ion source. Elemental analyses were obtained on a Perkin-Elmer 240 B microanalyzer.

All synthesized compounds were purified by crystallization from an appropriate solvent (ethanol, ethanol/water or ethanol/acetic acid).

Compounds **3a–c** were prepared as reported in the literature [39].

General procedure for the synthesis of compounds 5a–c. The compounds **3a–c** (3 mmol) and 2-bromoacetophenone (3.5 mmol) in 100 mL of isopropanol suspension is refluxed, under vigorous stirring, until complete dissolution of reagents and for further 4 h. After cooling to room temperature, a solid is obtained, which is filtered off, washed with isopropyl ether several times, and dried.

The following listed compounds were synthesized using the same procedure.

2-(4-Phenylthiazol-2-yl)-2,3-dihydrophthalazine-1,4-dione (5a). Whitish solid, m.p. 300°C. MS m/z = 321, yield = 70%. ^{1}H NMR (DMSO-*d6*): δ 7.36 (t, 1H, phth., $J = 7.7$); 7.47 (t, 2H, phenyl, $J = 7.7$); 7.90 (s, 1H, C_5H-thiaz.); 7.96–8.05 (m, 4H, phth. + phenyl); 8.10 (d, 1H, phth., $J = 7.3$); 8.38 (d, 1H, phth., $J = 7.3$); 12.42 (s, 1H, NH, D_2O-exch.). *Anal.* Calcd for $C_{17}H_{11}N_3O_2S$: C, 63.54; H, 3.45; N, 13.08. Found: C, 63.71; H, 3.43; N, 13.13.

5- (or 8-) Fluoro-2-(4-phenylthiazol-2-yl)-2,3-dihydrophthalazine-1,4-dione (5b). Pale yellow solid, m.p. 210–211°C. MS m/z = 339, yield = 79%. ^{1}H NMR (DMSO-*d6*): δ 7.36 (t, 1H, phth., $J = 7.7$); 7.47 (t, 2H, phenyl, $J = 7.7$); 7.90 (s, 1H, C_5H-thiaz.); 7.96–8.05 (m, 3H, phenyl); 8.10 (d, 1H, phth. $J = 7.3$); 8.38 (d, 1H, phth. $J = 7.3$); 12.42 (s, 1H, NH, D_2O-exch.). *Anal.* Calcd for $C_{17}H_{10}FN_3O_2S$: C, 60.17; H, 2.97; N, 12.38. Found: C, 59.99; H, 2.96; N, 12.35.

6,7-Difluoro-2-(4-phenylthiazol-2-yl)-2,3-dihydrophthalazine-1,4-dione (5c). Beige solid, m.p. 229–231°C. MS m/z = 357, yield = 72%. ^{1}H NMR (DMSO-*d6*): δ· 7.42–7.44 (m, 1H, phth.); 7.51–7.55 (m, 2H, phenyl); 7.99 (s, 1H, C_5H-thiaz.); 8.04–8.07 (m, 2H, phenyl + phth.); 8.14 (t, 1H, phenyl, $J = 8.1$); 8.42 (t, 1H, phenyl, $J = 8.1$); 12.82 (s, 1H, NH, D_2O-exch.). *Anal.* Calcd for $C_{17}H_9F_2N_3O_2S$: C, 57.14; H, 2.54; N, 11.76. Found: C, 56.99; H, 2.55; N, 11.75.

General procedure for the synthesis of compounds 7a–c. A suspension of compounds **3a–c** (2.71 mmol) and chloroacetone (3.25 mmol) in 140 mL of isopropanol is refluxed, under vigorous stirring, until complete dissolution of reagents and then for further 5 h. The mixture is allowed to cool down to room temperature thus obtaining a solid, which is filtered off, washed with isopropyl ether several times, and dried. The following listed compounds were synthesized using the same procedure.

2-(4-Methylthiazol-2-yl)-2,3-dihydrophthalazine-1,4-dione (7a). Beige solid, m.p. 249–251°C. MS m/z = 259, yield = 52%. ^{1}H NMR (DMSO-*d6*): δ· 2.38 (s, 3H, CH_3); 7.08 (s, 1H, C_5H-thiaz.); 7.95–8.08 (m, 3H, phth.); 8.37 (d, 1H, phth. $J = 7.3$); 12.61 (s, 1H, NH, D_2O-exch.). *Anal.* Calcd for $C_{12}H_9N_3O_2S$: C, 55.59; H, 3.50; N, 16.21. Found: C, 55.80; H, 3.48; N, 16.15.

5- (or 8-) Fluoro-2-(4-methylthiazol-2-yl)-2,3-dihydrophthalazine-1,4-dione (7b). Beige solid, m.p. 243–245°C. MS m/z = 277, yield = 89%. ^{1}H NMR (DMSO-*d6*): δ· 2.13 (s, 3H, CH_3); 6.61 (s, 1H, C_5H-thiaz.); 7.76–7.96 (m, 2H, phth.); 7.98–8.03 (m, 1H, phth.); NH not detected. *Anal.* Calcd for $C_{12}H_8FN_3O_2S$: C, 51.98; H, 2.91; N, 15.15. Found: C, 52.19; H, 2.90; N, 15.11.

6,7-Difluoro-2-(4-methylthiazol-2-yl)-2,3-dihydrophtha-lazine-1,4-dione (7c). Beige solid, m.p. 254–258°C. MS m/z = 295, yield = 77%. ^{1}H NMR (DMSO-*d6*): δ· 2.27 (s, 3H, CH_3); 6.50 (s, 1H, C_5H-thiaz.); 7.65 (dd, 1H, phth., $J = 7.8, 2.4$); 8.00 (dd, 1H, phth., $J = 7.8, 2.7$); 10.72 (s, 1H, NH, D_2O-exch.). *Anal.* Calcd for $C_{12}H_7F_2N_3O_2S$: C, 48.81; H, 2.39; N, 14.23. Found: C, 48.55; H, 2.41; N, 14.17.

General procedure for the synthesis of compounds 9a-c. A mixture of compounds **3a–c** (0.013 mol) and ethyl bromoacetate (0.016 mol) were suspended in isopropanol (120 mL) and refluxed for 2 h. A white product was isolated by filtration and crystallized from acetic acid. The following listed compounds have been synthesized using the same procedure.

2-(4-Oxo-4,5-dihydrothiazol-2-yl)-2,3-dihydrophthalazine-1,4-dione (9a). White solid, m.p. 311–312°C. MS m/z = 261, yield = 93%. ^{1}H NMR (DMSO-*d6*): δ· 4.10 (s, 2H, CH_2-thiaz.); 7.83–7.91 (m, 4H, phth.); 12.52 (s, 1H, NH, D_2O-exch.). *Anal.* Calcd for $C_{11}H_7N_3O_3S$: C, 50.57; H, 2.70; N, 16.08. Found: C, 50.78; H, 2.68; N, 16.11.

5- (or 8-) Fluoro-2-(4-oxo-4,5-dihydrothiazol-2-yl)-2,3-dihydrophthalazine-1,4-dione (9b). White solid, m.p. 309°C d. MS m/z = 279, yield = 82%. ^{1}H NMR (DMSO-*d6*): δ· 3.85 (s, 2H, CH_2-thiaz.); 7.71–7.76 (m, 2H, phth.); 7.89–7.92 (m, 1H, phth.); 11.77 (s, 1H, NH, D_2O-exch.). *Anal.* Calcd for $C_{11}H_6FN_3O_3S$: C, 47.31; H, 2.17; N, 15.05. Found: C, 47.52; H, 2.18; N, 14.99.

6,7-Difluoro-2-(4-oxo-4,5-dihydrothiazol-2-yl)-2,3-dihydrophthalazine-1,4-dione (9c). Whitish solid, m.p. 298°C d. MS m/z = 297, yield = 84%. ^{1}H NMR (DMSO-*d6*): δ· 3.97 (s, 2H, CH_2-thiaz.); 8.15–8.26 (m, 2H, phth.); 11.88 (s, 1H, NH, D_2O-exch.). *Anal.* Calcd for $C_{11}H_5F_2N_3O_3S$: C, 44.45; H, 1.70; N, 14.14. Found: C, 44.21; H, 1.69; N, 14.18.

General procedure for the synthesis of 2-(5-arylidene-4-oxo-4,5-dihydrothiazol-2-yl)-2,3-dihydrophthalazine-1,4-dione derivatives (11–24). These derivatives were prepared starting from 2-(4-oxo-4,5-dihydrothiazol-2-yl)-2,3-dihydrophthalazine-1,4-dione (4 mmol) and the appropriate aryl aldehyde (4 mmol) in acetic acid (20 mL) and acetic anhydride (2 mL). The reaction mixture was stirred and heated to reflux for 30 min. A colored precipitate was obtained, which was filtered off and crystallized from the appropriate solvent. Compounds **11–24** were synthesized using this procedure.

2-[5-(4-Chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione (11). Light yellow solid, m.p. 346–347°C d. MS m/z = 383–385, yield = 64%. ^{1}H NMR (DMSO-*d6*): δ· 7.52 (d, 2H, aryl, $J = 8.5$); 7.58 (d, 2H, phth., $J = 7.3$); 7.76 (s, 1H, aryl—CH=); 7.90–7.97 (m, 4H, aryl + phth.); 11.80 (1H, s, NH, D_2O-exch.). *Anal.* Calcd for $C_{18}H_{10}ClN_3O_3S$: C, 56.33; H, 2.62; N, 10.95. Found: C, 56.14; H, 2.64; N, 10.90.

2-[5-(2,4-Dichlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione (12). Orange solid, m.p. 345–347°C d. MS m/z = 417–420, yield = 54%. ^{1}H NMR (DMSO-*d6*): δ· 7.52 (d, 2H, aryl, $J = 8.5$); 7.59 (d, 2H, phth., $J = 7.3$); 7.76 (s, 1H, aryl—CH=); 7.88–7.97 (m, 3H, aryl + phth.); 11.80 (1H, s, NH, D_2O-exch.). *Anal.* Calcd for $C_{18}H_9Cl_2N_3O_3S$: C, 51.69; H, 2.17; N, 10.05. Found: C, 51.92; H, 2.15; N, 10.10.

2-[5-(3,4-Dimethoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione (13). Yellow solid, m.p. 308–311°C d. MS m/z = 409, yield = 68%. ^{1}H NMR (DMSO-*d6*): δ· 3.76 (s, 3H, OCH_3); 3.78 (s, 3H, OCH_3); 6.84 (d, 1H, aryl, $J = 8.1$); 7.07 (d, 1H, aryl, $J = 8.1$); 7.24 (s, 1H, aryl); 7.73 (s, 1H, aryl—CH=); 7.76–7.94 (m, 4H, phth.); 11.78 (s, 1H, NH, D_2O-exch.). *Anal.* Calcd for $C_{20}H_{15}N_3O_5S$:

C, 58.67; H, 3.69; N, 10.26. Found: C, 58.55; H, 3.70; N, 10.30. *Anal.* Calcd for $C_{10}H_{10}OS$: C, 67.38; H, 5.65; S, 17.99. Found: C, 67.06; H, 5.75; S, 17.69.

2-[5-(3-Nitrobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione (14). Mustard colored solid, m.p. 320–323°C d. MS m/z = 394, yield = 49%. ^1H NMR (DMSO-d_6): δ· 7.72 (t, 1H, aryl, J = 8.1); 7.88–7.96 (m, 6H, phth. +aryl—CH=); 8.24 (d, 1H, phth., J = 7.3); 8.45 (s, 1H, aryl); 11.78 (s, 1H, NH, D_2O-exch.). *Anal.* Calcd for $C_{18}H_{10}N_4O_5S$: C, 54.82; H, 2.56; N, 14.21. Found: C, 55.01; H, 2.54; N, 14.26.

2-[5-(3-Pyridinylidene)-4-oxo-4,5-dihydrothiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione (15). Light yellow solid, m.p. 297–299°C d. MS m/z = 350, yield = 67%. ^1H NMR (DMSO-d_6): δ· 7.48 (t, 1H, pyr. J = 7.8); 7.80 (s, 1H, —CH=aryl); 7.83–7.94 (m, 5H, phth. + pyr.); 8.58 (dd, 1H, pyr, J = 4.6, 1.9); 8.82 (d, 1H, pyr., J = 1.9); 11.78 (s, 1H, NH, D_2O-exch.). *Anal.* Calcd for $C_{17}H_{10}N_4O_3S$: C, 58.28; H, 2.88; N, 15.99. Found: C, 57.98; H, 2.90; N, 16.04.

2-[5-(3,4-Dioxymethylenbenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione (16). Orange solid, m.p. 333°C d. MS m/z = 393, yield = 75%. ^1H NMR (DMSO-d_6): δ 6.09 (s, 2H, CH_2); 7.04 (d, 1H, aryl, J = 8.1); 7.13 (d, 1H, aryl, J = 8.1); 7.20 (s, 1H, aryl); 7.68 (s, 1H, —CH=aryl); 7.85–7.93 (m, 4H, phth.); 12.25 (s, 1H, NH, D_2O-exch.). *Anal.* Calcd for $C_{19}H_{11}N_3O_5S$: C, 58.01; H, 2.82; N, 10.68. Found: C, 57.62; H, 2.80; N, 10.72.

2-[5-(3,4,5-Trimethoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione (17). Yellow solid, m.p. 320–322°C d. MS m/z = 439, yield = 56%. ^1H NMR (DMSO-d_6): δ· 3.70 (s, 3H, OCH_3); 3.76 (s, 3H, OCH_3); 3.78 (s, 3H, OCH_3); 6.85 (s, 1H, aryl); 6.97 (s, 1H, aryl); 7.73 (s, 1H, aryl—CH=); 7.85–7.92 (m, 4H, phth.); 12.22 (s, 1H, NH, D_2O-exch.). *Anal.* Calcd for $C_{21}H_{17}N_3O_6S$: C, 57.40; H, 3.90; N, 9.56. Found: C, 57.19; H, 3.88; N, 9.53.

2-[5-(4-Dimethylaminobenzylidene)-4-oxo-4,5-di-hydro-thiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione (18). Yellow solid, m.p. 293–294°C d. MS m/z = 392, yield = 70%. ^1H NMR (DMSO-d_6): δ 3.37 (s, 6H, NCH_3); 6.74 (d, 2H, aryl, J = 8.1); 7.36 (d, 2H, aryl, J = 8.1); 7.62 (s, 1H, aryl—CH=); 7.89–7.92 (m, 4H, phth.); 11.78 (s, 1H, NH, D_2O-exch.). *Anal.* Calcd for $C_{20}H_{16}N_4O_3S$: C, 61.21; H, 4.11; N, 14.28. Found: C, 60.97; H, 4.09; N, 14.34.

2-(5-Benzylidene-4-oxo-4,5-dihydrothiazol-2-yl)-2,3-dihydrophthalazine-1,4-dione (19). Orange solid, m.p. 331–333°C d.MS m/z = 349, yield = 50%. ^1H NMR (DMSO-d_6): δ 7.50 (d, 2H, phenyl, J = 7.7); 7.60 (d, 2H, phth., J = 7.3); 7.80 (s, 1H, phenyl—CH=); 7.93–7.98 (m, 5H, phenyl + phth.); 11.79 (1H, s, NH, D_2O-exch.). *Anal.* Calcd for $C_{18}H_{11}N_3O_3S$: C, 61.88; H, 3.17; N, 12.03. Found: C, 62.12; H, 3.15; N, 11.98.

2-[5-(4-Nitrobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione (20). Dark yellow solid, m.p. 345–348°C d. MS m/z = 394, yield = 60%. ^1H NMR (DMSO-d_6): δ 7.82 (d, 2H, aryl, J = 8.8); 7.87 (s, 1H, aryl—CH=); 7.88–7.98 (m, 4H, phth.); 8.26 (d, 2H, aryl, J = 8.8); 11.78 (s, 1H, NH, D_2O-exch.). *Anal.* Calcd for $C_{18}H_{10}N_4O_5S$: C, 54.82; H, 2.56; N, 14.21. Found: C, 54.57; H, 2.55; N, 14.17.

2-[5-(2-Nitrobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione (21). Orange solid, m.p. 327°C d. MS m/z = 394, yield = 37%. ^1H NMR (DMSO-d_6): δ· 7.84–8.09 (m, 9H, phth. +aryl—CH=); 12.27 (s, 1H, NH, D_2O-exch.). *Anal.* Calcd for $C_{18}H_{10}N_4O_5S$: C, 54.82; H, 2.56; N, 14.21. Found: C, 54.88; H, 2.55; N, 14.18.

2-[5-(4-methoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione (22). Beige solid, m.p. 301–304°C d. MS m/z = 379, yield = 50%. ^1H NMR (DMSO-d_6): δ· 3.86 (s, 3H, OCH_3); 7.02 (d, 2H, aryl, J = 8.4); 7.51 (d, 2H, aryl, J = 8.8); 7.70 (s, 1H, aryl—CH=); 7.86–7.96 (m, 4H, phth.); 11.78 (s, 1H, NH, D_2O-exch.). *Anal.* Calcd for $C_{19}H_{13}N_3O_4S$: C, 60.15; H, 3.45; N, 11.08. Found: C, 59.88; H, 3.47; N, 11.06.

2-[5-(4-Methylbenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione (23). Yellow solid, m.p. 331–333°C d. MS m/z = 363, yield = 38%. ^1H NMR (DMSO-d_6): δ· 2.32 (s, 3H, CH_3); 7.28 (d, 2H, aryl, J = 8.1); 7.45 (d, 2H, aryl, J = 8.1); 7.72 (s, 1H, aryl—CH=); 7.76–7.97 (m, 4H, phth.); 11.79 (s, 1H, NH, D_2O-exch.). *Anal.* Calcd for $C_{19}H_{13}N_3O_3S$: C, 62.80; H, 3.60; N, 11.56. Found: C, 63.11; H, 3.59; N, 11.60.

2-[5-(3-Hydroxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl]-2,3-dihydrophthalazine-1,4-dione. (24). Yellow solid, m.p. 354°C d. MS m/z = 365, yield = 42%. ^1H NMR (DMSO-d_6): δ· 7.22 (d, 1H, aryl, J = 7.7); 7.35 (s, 1H, aryl); 7.44–7.49 (d, 2H, aryl+aryl-OH, D_2O-exch.); 7.52 (t, 1H, aryl, J = 7.7); 7.75 (s, 1H, —CH=aryl); 7.88–7.94 (m, 4H, phth.); 11.78 (s, 1H, NH, D_2O-exch.). *Anal.* Calcd for $C_{18}H_{11}N_3O_4S$: C, 59.17; H, 3.03; N, 11.50. Found: C, 58.97; H, 3.05; N, 11.45.

Biological assay. The FaO rat hepatoma cell line H-35 Reuber (ICLC ATL99001) was purchased from Interlab Line Collection (Servizio Biotecnologie, IST, Genoa, Italy). FaO cells were cultured in flasks (capacity 75 cm^2) containing 15 mL Dulbecco's modified Eagle's medium (DMEM plus Glutamax I, Invitrogen S.r.l., Milan, Italy) and then supplemented with 100 UI/mL penicillin, 0.1 mg/mL streptomycin and 10% foetal bovine serum (Mascia Brunelli, Milan, Italy). Cells were incubated at 37°C in 5% CO_2 and 95% O_2 atmosphere. All experiments were carried out 24 h after seeding. Before the assay, the cells were treated with a phosphate buffer (PBS) and the culture medium was substituted with DMEM without serum.

Cell vitality. The vitality of adhesive cells was determinated with the *Neutral Red Uptake* assay (NRU) as reported by Borenfreund and Puerner [43]. As far as the NRU assay is concerned, the Neutral Red solution (0.4% NR in H_2O) was diluted 1:80 with phosphate buffer (PBS) and incubated at 37°C overnight. Then the solution was centrifuged (2600 rpm) to remove micro crystals that are insoluble in coloring. Once treated, the culture medium was vacuumed and substituted with a NR solution. The cells were incubated in the NR solution at 37°C for 30 min to allow coloring incorporation of the lisosomes in the vital cells of the flask. The RN solution was removed, the cells were rapidly washed with 1% formaldehyde and a calcium chloride solution was added. To remove incorporated NR from vital cells, a mixture (solution) of 1% acetic acid in ethanol 50% was added. A sample collected from every well was read using a Perkin-Elmer, 540 nm spectrophotometer. The values obtained for the treated cells were expressed as percentages of the value obtained for the control cells. All experiments were repeated at lease three times and were made in triplicate.

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Convenient Synthesis of Some New Pyrazolo[1,5-*a*]pyrimidine, Pyridine, Thieno[2,3-*b*]pyridine, and Isoxazolo[3,4-*d*]pyridazine Derivatives Containing Benzofuran Moiety

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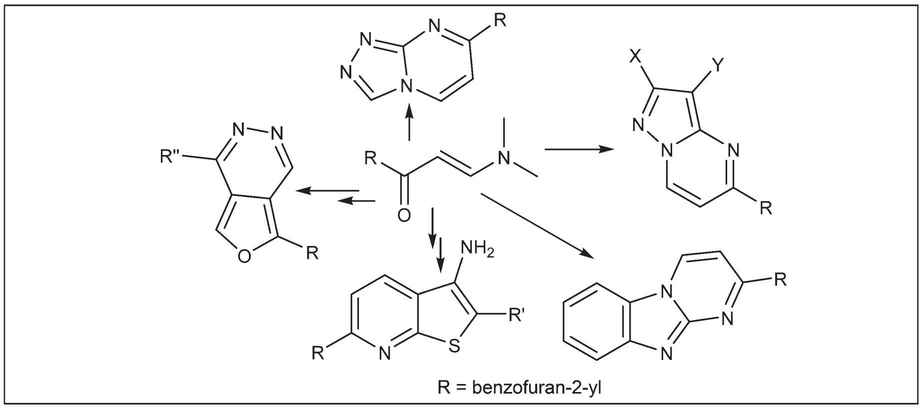

Pyrazolo[1,5-*a*]pyrimidines, pyrazoles, and thieno[2,3-*b*]pyridine were synthesized from sodium salt of 5-benzofuran-2-yl-3-hydroxypropenone and the appropriate of heterocyclic amines, diazonium chloride, and 1,3-dicarbonoyl compounds. Pyrimidino[4′,5′:4,5]thieno[2,3-*b*]pyridine, 1,2,3,4-tetrazolo[1″,5″:6′,1′]-pyrimidino[4′,5′:4,5]thieno[2,3-*b*]pyridine and pyridino[2″,3″:2′,3′]thieno[4,5-*d*]1,2,4-triazolo[4,3-*e*]pyrimidine derivatives were synthesized from 6-benzo[*d*]furan-2-yl-2-thioxohydropyridine-3-carbonitrile and each of formic acid or formamide. Structures of the newly synthesized were established by elemental analysis and spectral data.

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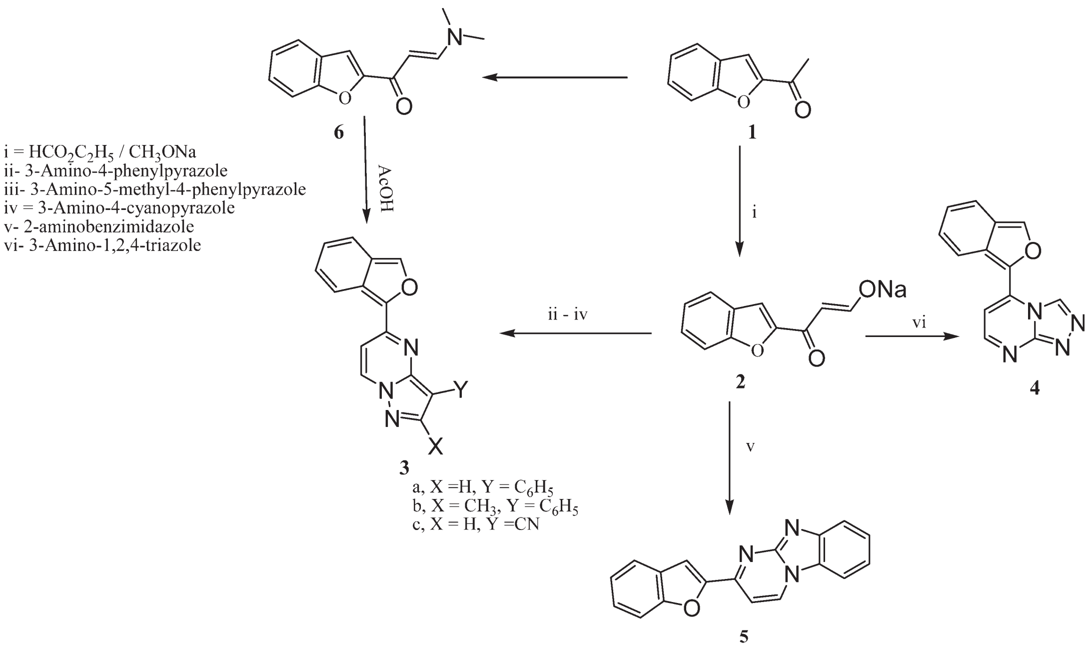
INTRODUCTION

Pyrazolo[1,5-*a*]pyrimidines are of considerable chemical and pharmacological importance as purine analogs [1]. The interesting biological activity has attracted the attention of many chemists to develop new efficient general procedures for the synthesis of pyrazolo[1,5-*a*]pyrimidines by using aminopyrazoles. The benzofuran moiety is incorporated in various natural products [2–5] and pharmaceuticals [6–9]. In addition, biological and medicinal activity of fused thienopyrimidines has stimulated much research in this field [10–21]. Our research has been devoted to the development of new classes of heterocyclic systems which incorporate the thienopyrimidine moiety in the hope that they may be biologically active. In continuation of our interest in the synthesis of heterocycles [22–26], we report herein, a convenient method for the synthesis of pyrazolo[1,5-*a*]pyrimidines, thieno[2,3-*b*]pyridines, pyrimidino[4′,5′:4,5]thieno[2,3-*b*]pyridine, isoxazolo[3,4-*d*]pyridazines, and pyridine containing benzofuran moiety as antimicrobial agents.

RESULTS AND DISCUSSION

Treatment of sodium salt of 5-benzofuran-2-yl-3-hydroxypropenone (**2**) with 3-amino-4-phenylpyrazole in piperidenium acetate yielded 5-benzofuran-2-yl-3-phenylpyrazolo[1,5-*a*]pyrimidine (**3a**). Structure of **3** was established on the basis of their elemental analysis, spectral data, and alternative synthetic route. Thus, treatment of 1-benzofuran-2-yl-3-dimethylamino-propenone [26] (**6**) with 3-amino-4-phenylpyrazole in boiling ethanol gave product identical in all respects (mp., mixed mp., and spectra) with **3a**. ^{1}H NMR spectrum of **3a** revealed multiple band at $\delta = 7.35–8.55$ (m, aromatic protons). Analogously, compound **2** was reacted with the appropriate 3-amino-4-methyl-5-phenylpyrazole, 3-amino-4-cyanopyrazole, 2-aminobenzimidazole or 3-aminotriazole gave 5-(1-benzofuran-2-yl)-3-methyl-2-phenylpyrazolo[1,5-*a*]pyrimidine (**3b**), 5-benzofuran-2-yl-3-cyanopyrazolo[1,5-*a*]pyrimidine (**3c**), 7-(benzofuran-2-yl)-[1,2,4]triazolo[4,3-*a*]pyrimidine (**4**), and 2-(1-benzofuran-2-yl)pyrimido[1,2-*a*]benzimidazole (**5**), respectively (Scheme 1).

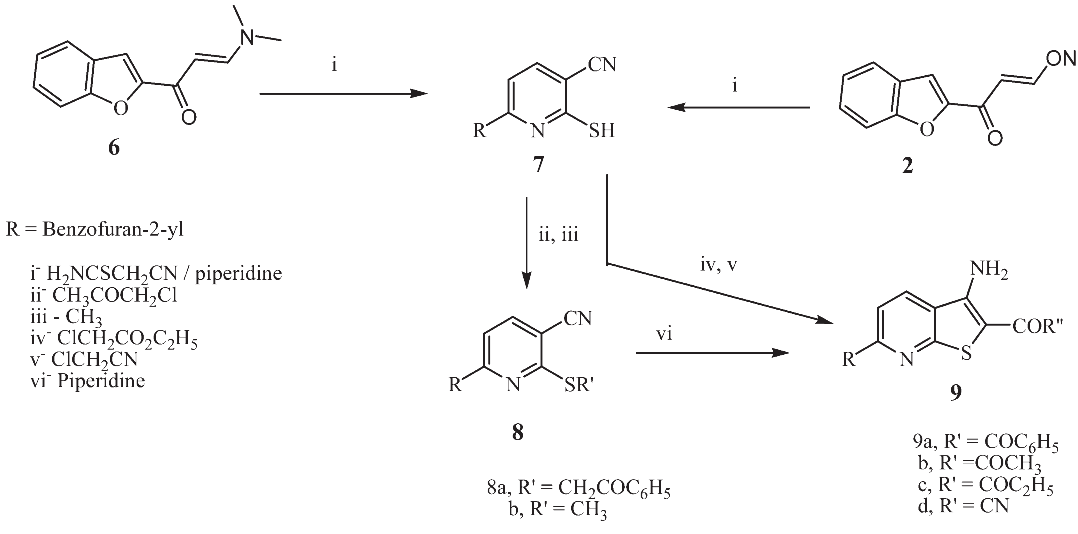
Scheme 1



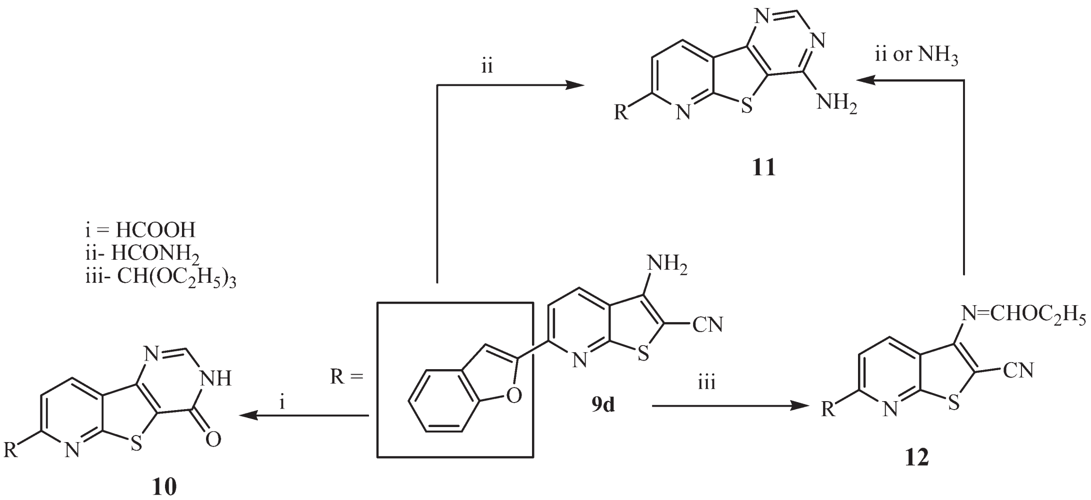
It has been found that 6-benzofuran-2-yl-2-sulfanylpyridine-3-carbonitrile (**7**), which prepared via reaction of **2** with cyanothioacetamide in presence of piperidenium acetate, reacted with ω-bromoacetophenone in *N,N*-dimethylformamide containing potassium hydroxide to afford the product corresponding to addition and dehydrobromination reactions. The IR spectrum of this product showed bands corresponding to CN and CO groups. Its ^{1}H NMR spectrum revealed the signals at δ = 4.09 (S, 2H, **SCH_2**) and 7.47–8.04 (m, 12H, ArH's). Based on the above-mentioned data, these reaction products could be formulated as 6-benzofyran-2-yl-2-(2-oxo-2-phenylethylthio)pyridine-3-carbonitrile (**8a**). Further confirmation of the structure of **8a** arose from their cyclization in boiling ethanol containing catalytic amount of piperidine to give the corresponding (3-amino-6-(benzofuran-2-yl)thieno[2,3-b]pyridin-2-yl)(phenyl)methanone (**9a**) (Scheme 2).

The IR spectrum of **9a** showed no band of the CN function while the band of the new NH_2 group was detected. On the other hand, the ^{1}H NMR spectrum of **9a** revealed absence of signals of the —SCH_2— group and the presence of the NH_2 protons. The earlier findings proved that the CN and the —SCH_2— groups were

Scheme 2



Scheme 3

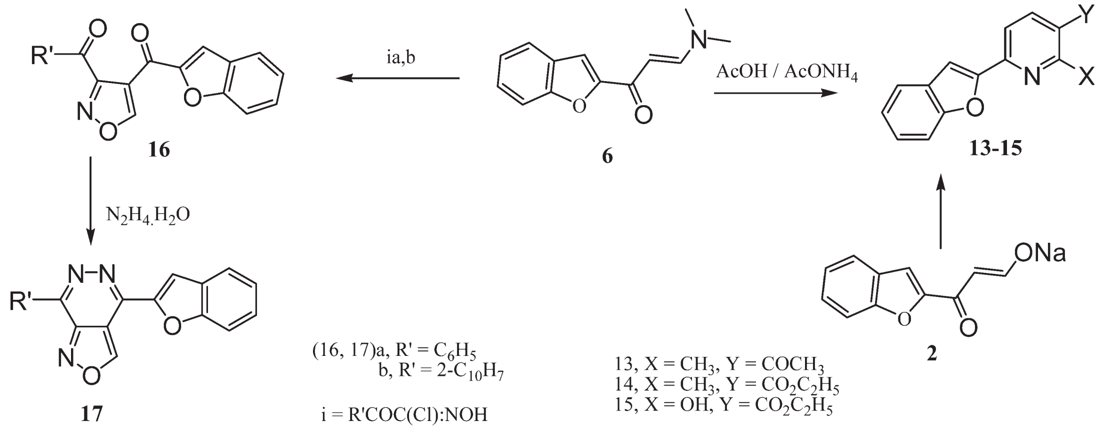


both involved in the cyclization step leading to **9a**. Compound **7** reacted also with each of iodomethane, chloroacetone, ethyl chloroacetate, and chloroacetonitrile in *N*,*N*-dimethylformamide containing potassium hydroxide to afford **8b** and **9b–d**, respectively. The reaction seemed to proceed through dehydrochlorination to give the intermediate **8c–d**, which underwent cyclization via addition of the $-SCH_2-$ hydrogen to the nitrile function to give **9b–d**, respectively. IR, ^1H NMR, and elemental analyses were the basis on which the structure of **9** was established. Thus, it has been found that **9d** reacted with each of formic acid, formamide, or triethyl orthoformate to give the corresponding 7-(1-benzofuran-2-yl)pyrido[2′,3′:4,5]-thieno[2,3-*b*]pyridin-4(3*H*)-one (**10**), 7-(1-benzofuran-2-yl)pyrido[2′,3′:4,5]thieno[2,3-*b*]pyridin-4-amine (**11**), and ethyl [6-(1-benzofuran-2-yl)-2-cyanothieno[2,3-*b*]pyridin-3-yl]imidoformate (**12**), respectively (Scheme 3). Structures of **10–12** were established on the basis of spectral data (IR, ^1H NMR) and elemental analysis. Thus, IR spectrum of **11** revealed bands at 3458 and 3216 (NH_2). IR spectrum of **12** revealed bands at 2248 (CN) and 1627 (C=N). Also, compound **17** reacted with ethanolic ammonia (or formamide) afforded a product identical in all aspects (mp., mixed mp., and spectra) with **11**.

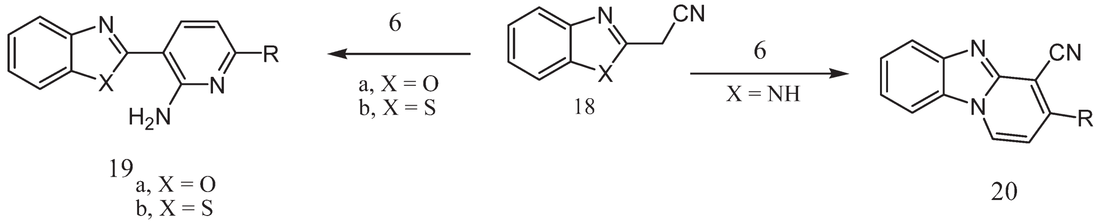
Treatment of 1-benzofuran-2-yl-3-dimethylamino-propenone (**6**) with the appropriate acetylacetone, ethyl acetoactate, or ethyl cyanoacetate, in boiling acetic acid containing ammonium acetate under reflux gave pyridine derivatives **13–15**, respectively (Scheme 4).

Compound **6** reacted with *N*-hydroxy-2-oxo-2-phenylethanimidoyl chloride in toluene containing triethylamine afforded 1-benzofuran-2-yl(3-benzoylisoxazol-4-yl)methanone (**16a**). Structure **16** was elucidated by elemental analysis, spectral data, and chemical transformation. ^1H NMR spectrum of **16a** showed signals at $\delta = 7.25–7.69$ (m, 8H, aromatic), 8.58–8.60 (d, 2H, $J = 4$ Hz, aromatic), and 8.74 (s, 1H, isoxazole H-5). Thus, treatment of **16a** with hydrazine hydrate gave 1-benzofuran-2-yl(3-benzoylisoxazol-4-yl)methanone (**17a**). Analogously, **6** reacted with *N*-hydroxy-2-oxo-2-(2-naphthyl)ethanimidoyl chloride

Scheme 4



Scheme 5



in toluene containing triethylamine afforded **16b**, which treated with hydrazine hydrate to give **17b**.

Also, treatment of 1-benzofuran-2-yl-3-dimethylamino-propenone (**6**) with each of benzoxazol-2-ylacetonitrile (**18a**) and benzthiazol-2-ylacetonitrile (**18b**) in boiling acetic acid containing ammonium acetate afforded 3-(benzo[d]oxazol-2-yl)-6-(benzofuran-2-yl)pyridin-2-amine (**19a**) and 3-(benzo[*d*]thiazol-2-yl)-6-(benzofuran-2-yl) pyridin-2-amine (**21b**) on the elemental analysis and spectral data. In contrast, benzimidazol-2-acetonitile reacted with **6** in ethanol gave 3-(1-benzofuran-2-yl)pyrido[1,2-*a*]benzimidazole-4-carbonitrile (**20**) in a good yield (Scheme 5).

Finally, treatment of sodium salt of 5-benzofuran-2-yl-3-hydroxypropenone **2** with the benzenediazonium chloride in ethanol containing sodium acetate as a buffer solution yielded 3-(1-benzofuran-2-yl)-3-oxo-2-(phenylhydrazono)propanal (**21**). Structure **21** was confirmed by elemental analysis, spectral data, and chemical transformation. ^{1}H NMR spectrum of **21** showed signal at δ = 7.26–7.93 (m, 10 H, ArH's), 9.98 (s, 1H, —CHO) and 14.39 (s, br., 1H, NH). Thus, **21** was reacted with hydrazine hydrate in boiling ethanol under reflux to give 3-(1-benzofuran-2-yl)-4*H*-pyrazol-4-one phenylhydrazone **22** (Scheme 6).

CONCLUSION

5-Benzofuran-2-yl-3-hydroxypropenone is used to synthesize different pyrazolo[1,5-*a*]pyrimidines, pyrazoles, and thieno[2,3-*b*]pyridine via its reaction with different heterocyclic amines, cyanothioacetamide, and diazonium chlorides, respectively. Pyrimidino[4′,5′:4,5]-thieno[2,3-*b*] pyridine, 7-(1-benzofuran-2-yl)pyrido-[2′,3′:4,5]thieno[2,3-*b*] pyridin-4(3*H*)-one, and 7-(1-benzofuran-2-yl)pyrido[2′,3′: 4,5]thieno[2,3-*b*]pyridin-4-amine were synthesized from 6-benzo[*d*]furan-2-yl-2-thioxohydropyridine-3-carbonitrile in good yields.

EXPERIMENTAL

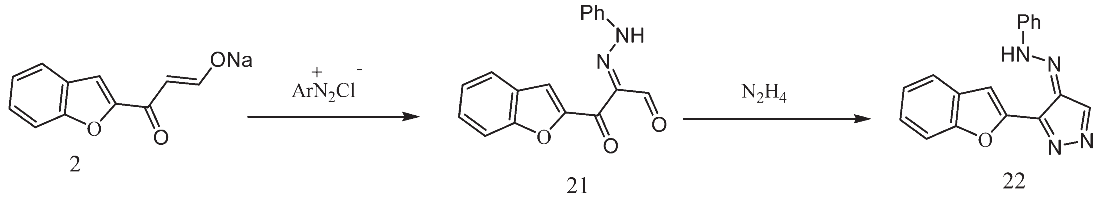
All melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu FTIR 8201 PC spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $(CD_3)_2SO$ solutions on a Varian Gemini 300 MHz spectrometer and chemical shifts are expressed in δ units using TMS as an internal reference. Elemental analyses and microorganism tests were carried out at the Microanalytical Center of the Cairo University.

Sodium salt of 5-benzofuran-2-yl-3-hydroxypropenone (2). In three-necked flask sodium methoxide (10 mmol) and ether (20 mL) was taken and 2-acetylbenzofuran (**1**) (10 mmol) with (10 mmol) of ethyl format was poured over it through a separating funnel with efficient stirring. The solid product was collected and used directly in the reactions.

Synthesis of 3a–c, 4, 5, 7, 13, 14, and ethyl 15. ***Method A.*** A solution of (10 mmol) sodium salt of sodium salt of 5-benzofuran-2-yl-3-hydroxypropenone **2**, (10 mmol), the appropriate 3-amino-4-phenyle, 3-amino-4-methyl-5-phenylpyrazole, 3-amino-4-cyanopyrazole, 3-aminopyrazole, 2-aminobenzimidazole, cyanothioacetamide, acetylacetone, ethyl acetoacetate, or ethyl cyanoacetate (10 mmol) and piperidine acetate (1 mL) in water (3 mL) was refluxed for 10 min. Acetic acid (1.5 mL) was added to the hot solution. The solid product was filtered off and recrystallized from the proper solvent gave products **3a–c**, **4**, **5**, **7**, **13–15**.

Method B. An equimolar amount of 1-benzofuran-2-yl-3-dimethylaminopropenone (**6**), the appropriate 3-amino-4-phenylpyrazole, 3-amino-4-methyl-5-phenylpyrazole, 3-amino-4-cyanopyrazole, 3-amino-1,2,4-triazole, 2-aminobenzimidazole, cyanothioacetamide, acetylacetone, ethyl acetoacetate, or ethyl cyanoacetate and ammonium acetate (5 mmol) in acetic acid

Scheme 6



(10 mL) was heated under reflux for 4 h. The resulting solid was collected and recrystallized from the proper solvent gave products **3a–c**, **4**, **5**, **7**, **13–15**.

5-Benzofuran-2-yl-2-phenylpyrazolo[1,5-*a*]pyrimidine (3a). This compound was obtained as yellow crystals (AcOH), mp 204–206°C, yield (73%); IR (cm^{-1}): 1635 (C=N), 1589 (C=C). ^{1}H NMR $(CD_3)_2SO$ δ = 7.35–8.55 (m, aromatic protons). ^{13}C NMR $(CD_3)_2SO$ δ = 102.23, 110.21, 122.6, 122.8, 123.52, 125.8, 125.9, 128.2, 128.6, 130, 131.2, 132, 133.1, 135.2, 140.1, 144.2, 146.2, 147.8. *Anal.* Calcd. for $C_{20}H_{13}N_3O$ (311.35): C, 77.16; H, 4.21; N, 13.50. Found: C, 76.92; H, 4.00; N, 13.65.

5-(1-Benzofuran-2-yl)-3-methyl-2-phenylpyrazolo[1,5-*a*] pyrimidine (3b). This compound was obtained as yellow crystals (AcOH), mp 215–217°C, yield (75%); IR (cm^{-1}): 3050 (CH, aromatic), 2920 (CH, aliphatic), 1635 (C=N), 1589 (C=C). ^{1}H NMR $(CD_3)_2SO$ δ = 2.51 (s, 3H, CH_3), 7.35–8.55 (m, 12 H, aromatic protons). *Anal.* Calcd. for $C_{21}H_{15}N_3O$ (325.37): C, 77.52; H, 4.65; N, 12.91. Found: C, 77.45; H, 4.56; N, 13.12.

5-Benzofuran-2-yl-2-cyanopyrazolo[1,5-*a*]pyrimidine (3c). This compound was obtained as pale yellow crystals (AcOH), mp 238–240°C, yield (76 %); IR (cm^{-1}): 3050 (CH, aromatic), 2920 (CH, aliphatic), 2229 (CN), 1635 (C=N), 1589 (C=C). ^{1}H NMR $(CD_3)_2SO$ δ = 7.32–8.91 (m, 11 H, aromatic protons), 8.97 (s, 1H, pyrazole H-5). ^{13}C NMR $(CD_3)_2SO$ δ = 84.1, 104.2, 112,3, 121.3, 122.6, 123.3, 128.5, 130.1, 130.7, 131.2, 136.2, 140.4, 148.8, 150, 152.2. *Anal.* Calcd. for $C_{15}H_8N_4O$ (260.26): C, 69.23; H, 3.10; N, 21.53. Found: C, 69.32; H, 3.00; N, 21.35.

2-(1-Benzofuran-2-yl)pyrimido[1,2-*a*]benzimidazole (4). This compound was obtained as pale yellow crystals (AcOH), mp 230–262°C, yield (64%); IR (cm^{-1}): 1616 (C=N), 1562 (C=C). ^{1}H NMR $(CD_3)_2SO$ δ = 7.36–7.955 (m, 5H, aromatic protons), 8.59 (s, 1H, triazole H-5), 8.99–9.01(d, *J* = 6H), pyrimidine ring). *Anal.* Calcd. for $C_{13}H_8N_4O$ (236.23): C, 66.10; H, 3.41; N, 23.72. Found: C, 66.25; H, 3.51; N, 23.54.

7-(1-Benzofuran-2-yl)[1,2,4]triazolo[4,3-*a*]pyrimidine (5). This compound was obtained as yellow crystals (AcOH), mp 205–207°C, yield (37%); IR (cm^{-1}): 3050 (CH, aromatic), 1635 (C=N), 1589 (C=C). ^{1}H NMR $(CD_3)_2SO$ δ = 7.34–8.53 (m, aromatic protons). *Anal.* Calcd. for $C_{18}H_{11}N_3O$ (285.31): C, 75.78; H, 3.89; N, 14.73. Found: C, 75.87; H, 3.98; N, 14.65.

6-Benzofuran-2-yl-2-sulfanylpyridine-3-carbonitrile (7). This compound was obtained as page crystals (EtOH), mp 200–202°C, yield (84%); IR (cm^{-1}): 3342 (NH), 2217 (CN). ^{1}H NMR $(CD_3)_2SO$ δ = 6.67–7.42 (m, 6H, aromatic proton), 8.21 (s, 1H, 5-H of the pyridinethione ring), 14.10 (b, 1H, SH). *Anal.* Calcd. for $C_{14}H_8N_2OS$ (252.30): C, 66.65; H, 3.20; N, 11.10.60; S, 12.71. Found: C, 66.72; H, 3.41; N, 11.28; S, 12.64.

1-[6-(1-Benzofuran-2-yl)-2-methylpyridin-3-yl]ethanone (13). This compound was obtained as colorless crystals (EtOH), mp 113–114°C, yield (37%); IR (cm^{-1}): 1685 (CO), 1639 (C=N), 1581 (C=C). ^{1}H NMR $(CD_3)_2SO$ δ = 2.50 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 7.31–8.38 (m, 7H, aromatic protons). ^{13}C NMR $(CD_3)_2SO$ δ = 24.4, 25.3, 106.3, 111.5, 118.4, 121.2, 123.4, 125, 128.2131, 137.5, 148.2, 151.3, 145,5, 155.8, 199.8. *Anal.* Calcd. for $C_{16}H_{13}NO_2$ (251.25): C, 76.48; H, 5.21; N, 5.57. Found: C, 76.64, H, 5.10; N, 5.75.

Ethyl 6-(1-benzofuran-2-yl)-2-methylnicotinate (14). This compound was obtained as colorless crystals (EtOH), mp 129–130°C, yield (37%); IR (cm^{-1}): 1715 (CO), 1639 (C=N), 1581 (C=C). ^{1}H NMR $(CD_3)_2SO$ δ = 1.29 (t, 3H, *J* = 7.5 Hz, CH_3), 2.77 (s, 3H, CH3), 4.26 (q, 2H, *J* = 7.5 Hz, CH_2), 7.27–839 (m, 7H, aromatic protons). ^{13}C NMR $(CD_3)_2SO$ δ = 14.2, 25.6, 60.8, 106.3, 111.5, 115.4, 121, 123.3, 125.2, 125.6, 128.3, 139.4, 148, 145.2, 156.2, 159.3, 164. ^{1}H NMR $(CD_3)_2SO$. *Anal.* Calcd. for $C_{17}H_{15}NO_3$ (281.31): C, 72.58; H, 5.37; N, 4.98. Found: C, 72.45; H, 5.45; N, 4.75.

Ethyl 6-(1-benzofuran-2-yl)-2-oxo-1,2-dihydro-pyridine-3-carboxylate (15). This compound was obtained as colorless crystals (AcOH), mp 182–184°C, yield (89%); IR (cm^{-1}): 3448 (NH), 1681 (CO), 1635 (C=N), 1589 (C=C). ^{1}H NMR $(CD_3)_2SO$ δ = 1.32 (t, 3H, *J* = 6 Hz, CH_3), 4.28 (q, 2H, *J* = 6 Hz, CH_2), 7.22–8.50 (m, 7H, aromatic protons), 9.26 (s, br., 1H, NH). *Anal.* Calcd. for $C_{16}H_{13}NO_4$ (283.28): C, 67.84; H, 4.63; N, 4.94. Found: C, 67.58; H, 4.50; N, 5.24.

Synthesis of 8a,b, 9b-d. A mixture of **7**(1.3 g, 10 mmol) and potassium hydroxide (0.6 g, 10 mmol) in *N,N*-dimethylformamide (20 mL) was stirred for 2 h at room temperature. The appropriate of ω-bromoacetophenone, methyl iodide, chloroacetone, ethyl chloroacetate, or chloroacetonitrile (10 mmol each) was added and stirring was continued for 2 h. The resulting solid was collected and recrystallized from the proper solvent to give **8a**, **8b**, and **9b–d**, respectively.

6-(1-Benzofuran-2-yl)-2-[(2-oxopropyl)thio]nicotino-nitrile (8a). This compound was obtained as pale yellow crystals (EtOH), mp 240–242°C, yield (92%); IR (cm^{-1}): IR: 2190 (CN). ^{1}H NMR $(CD_3)_2SO$ δ = 4.09 (S, 2H, SCH_2) and 7.47–8.04 (m, 12H, ArH's). ^{1}H NMR $(CD_3)_2SO$ δ = 52.8, 95.1, 106.3, 111.4, 113.2, 116, 121.2, 123.3, 125.6, 126.4, 127.6, 127.9, 130.1, 136.7, 151, 155.4, 160.3, 163.2, 198.8. *Anal.* Calcd. for $C_{22}H_{14}N_2O_2S$ (370.42): C, 71.33; H, 3.81; N, 7.56; S, 8.66. Found: C, 71.23; H, 3.75; N, 7.64; S, 8.65.

6-(1-Benzofuran-2-yl)-2-(methylthio)nicotinonitrile (8b). This compound was obtained as pale brown crystals (EtOH), mp 120–121°C, yield (81%); IR (cm^{-1}): 2198 (CN). ^{1}H NMR $(CD_3)_2SO$ δ = 2.47 (s, 3H, CH_3), 6.67–8.02 (m, 11H, aromatic proton), 8.21 (s, 1H, 5-H of the pyridinethione ring). *Anal.* Calcd. for $C_{15}H_{10}N_2OS$ (266.32): C, 67.65; H, 3.78; N, 10.52; S, 12.04. Found: C, 67.52; H, 3.82; N, 10.67; S, 12.19.

1-[3-Amino-6-(1-benzofuran-2-yl)thieno[2,3-*b*]pyridin-2-yl] ethanone (9b). This compound was obtained as pale yellow crystals (EtOH), mp 260–262°C, yield (37%); IR (cm^{-1}): 3316, 3124 (NH_2), 1596 (CO). ^{1}H NMR $(CD_3)_2SO$ δ = 2.38 (s, 3H, CH_3CO), 6.45 (br, 2H, NH_2), 7.16–7.73 (m, 6H, aromatic protons), 7.82 (s, 1H, 5-H of the thienopyridine ring). ^{13}C NMR $(CD_3)_2SO$ δ = 30.1, 106.4, 111.6, 115.4, 121.3, 122.6, 123.2, 125.6, 127.4, 127.8, 134.6, 148.2, 149.4, 154.3, 155.8, 156.6, 191.2. *Anal.* Calcd. for $C_{17}H_{12}N_2O_2S$ (308.35): C, 66.22; H, 3.92; N, 9.08; S, 10.40. Found: C, 66.10; H, 3.85; N, 8.89; S, 10.30.

Ethyl 3-amino-6-(1-benzofuran-2-yl)thieno[2,3-*b*]pyridine-2-carboxylate (9c). This compound was obtained as pale yellow crystals (Dioxan), mp 240–242°C, yield (68%); IR (cm^{-1}): 3481, 3351 (NH_2), 1731 (CO). ^{1}H NMR $(CD_3)_2SO$ δ = 1.29 (t, 3H, *J* = 7 Hz, CH3), 4.24 (q, 2H, *J* = 7 Hz, CH2), 6.21 (br, 2H, NH_2), 7.12–7.87 (m, 6H, aromatic protons), 7.99 (s, 1H, 5-H of the thienopyridine ring). ^{13}C NMR $(CD_3)_2SO$ δ = 13.8, 59.1, 105.6, 106.2, 111.4, 115.5, 121.2, 123.5, 125.4, 127.2, 128.1, 133.3, 148.4, 149.6, 154.3, 155.2, 155.8, 166.4. ^{1}H NMR $(CD_3)_2SO$. *Anal.* Calcd. for $C_{18}H_{14}N_2O_3S$ (338.38): C, 63.89; H, 4.17; N, 8.28; S, 9.48. Found: C, 63.95; H, 4.00; N, 8.45; S, 9.65.

3-Amino-6-(1-benzofuran-2-yl)thieno[2,3-*b*]pyridine-2-carbonitrile (9d). This compound was obtained as pale yellow crystals (EtOH), mp 160–162°C, yield (72%); IR (cm^{-1}): 3496, 3300 (NH_2), 2198 (CN). ^{1}H NMR $(CD_3)_2SO$ $\delta = 6.57$ (br, 2H, NH_2), 7.12 (m, 6H, aromatic protons), 8.31(s, 1H, 5-H of the thienopyridine ring). *Anal.* Calcd. for $C_{16}H_9N_3OS$ (291.33): C, 65.96; H, 3.11; N, 14.42; S, 11.01. Found: C, 66.12; H, 3.18; N, 14.30; S, 10.85.

(3-Amino-6-(benzofuran-2-yl)thieno[2,3-b]pyridin-2-yl)(phenyl)-methanone (9a). A solution of **8a** (1.85 g, 5 mmol) in ethanol (20 mL) containing piperidine (0.3 mL) was heated under reflux for 2 h. After cooling, the resulting solid was collected by filtration and recrystallized from dioxin/ethanol to give as pale yellow crystals (EtOH), mp 290–292°C, yield (78%); IR (cm^{-1}): 3408, 3300 (NH_2), 1685 (CO). ^{1}H NMR $(CD_3)_2SO$ $\delta = 16.21$ (br, 2H, NH_2), 7.52–7.87 (m, 11H, aromatic protons), 7.99 (s, 1H, 5-H of the thienopyridine ring). *Anal.* Calcd. for $C_{22}H_{14}N_2O_2S$ (370.42): C, 71.33; H, 3.81; N, 6.56; S, 8.66. Found: C, 71.34; H, 3.79; N, 7.64; S, 8.75.

7-(1-Benzofuran-2-yl)pyrido[2′,3′:4,5]thieno[2,3-*b*]pyridin-4(3*H*)-one (10). A mixture of **9c** (1.7 g, 10 mmol) and formic acid (99%, 20 mL) was heated under reflux for 7 h. After cooling, the reaction mixture was poured over ice (100 g) and the resulting solid was collected and recrystallized form *N*,*N*-dimethylformamide to give as page crystals mp > 300°C, yield (88%); IR (cm^{-1}): 3423 (NH), 1660 (CO). ^{1}H NMR $(CD_3)_2SO$ $\delta = 7.02$–7.99 (m, 6H, aromatic protons), 8.25 (s, 1H, 5-H of the thienopyridine ring), 8.57 (s, 1H, Proton on C-2 of pyrimidine ring), 12.56 (s, 1H, NH of pyrimidine ring). *Anal.* Calcd. for $C_{17}H_9N_3O_2S$ (319.34): C, 63.94; H, 2.84; N, 13.16; S, 10.04. Found: C, 64.12; H, 2.98; N, 13.25; S, 10.15.

7-(1-Benzofuran-2-yl)pyrido[2′,3′:4,5]thieno[2,3-*b*]pyridin-4-amine (11). Compound **9c** (1.7 g, 10 mmol) was heated with formamide (20 mL) at 180°C for 2 h. After cooling, the reaction mixture was poured over ice and the formed solid was collected by filtration and recrystallized form *N*,*N*-dimethylformamide to obtain as page crystals, mp 220–222°C, yield (78%); IR (cm^{-1}): 3458, 3216 (NH_2). ^{1}H NMR $(CD_3)_2SO$ $\delta =$ 6.79 (br, 2H, NH_2), 7.14–7.93 (m, 6H, aromatic protons), 8.01 (s, 1H, 5-H of the thienopyridine ring). *Anal.* Calcd. for $C_{17}H_{10}N_4OS$ (318.35): C, 64.14; H, 3.17; N, 17.60; S, 10.07. Found: C, 64.00; H, 3.27; N, 17.51; S, 10.24.

Ethyl [6-(1-benzofuran-2-yl)-2-cyanothieno[2,3-*b*]pyridin-3-yl]imidoformate (12). A mixture of **9c** (1.7 g, 10 mmol) and triethylorthoformate (20 mL) with catalytic amount of acetic acid were heated under reflux at 140°C for 6 h. The resulting dark brown solution was allowed to cool to room temperature and evaporated under vacuum. *n*-Hexane was added to the residue and the separated solid was filtered, washed with *n*-hexane and recrystallized from ethanol to obtain as pale yellow crystals, mp 180–182°C, yield (69%); IR (cm^{-1}): 2248 (CN), 1627 (C=N). ^{1}H NMR $(CD_3)_2SO$ $\delta = 1.22$ (t, 3H, $J =$ 7.5 Hz, CH_3), 4.33 (q, 2H, $J = 7.5$ Hz, CH_2), 6.73–7.98 (m, 6H, aromatic protons), 8.11 (s, 1H, 5-H of the thienopyridine ring), 8.66 (s, 1H, CH=N). ^{13}C NMR $(CD_3)_2SO$ $\delta = 13.2$, 62.4, 85.4, 106.1, 111.5, 115.2, 121.2, 123.4, 125.2, 125.6, 126.4, 127.2, 135.2, 147.4, 150, 154.2, 155.5, 165.4. *Anal.* Calcd. for $C_{19}H_{13}N_3O_2S$ (347.39): C, 65.69; H, 3.77; N, 12.10; S, 9.23. Found: C, 65.82; H, 3.51; N, 11.95; S, 9.32.

Synthesis of 1-phenyl-4-(1-benzofuran-2-ylcarbonyl)-3-substituted oxazoles 16a,b. An equimolar amounts of the appropriate hydroxamoyl chlorides, 1-(benzofuran-2-yl)-3-(dimethylamino)prop-2-en-1-one (**6**) (5 mmol), and triethylamine (5 mmol) in toluene (20 mL) were heated under reflux for 2 h. The solvent was evaporated under reduce pressure and triturated with petroleum ether 40–60°C then the resulting solid was collected and recrystallized from ethanol to give the oxazoles **16a** and **16b**, respectively.

1,3-Diphenyl-4-(1-benzofuran-2-ylcarbonyl)oxazoles (16a). This compound was obtained as colorless crystals (EtOH), mp 148–150°C, yield (91%); IR (cm^{-1}): 3058 (CH), 1685, 1639 (CO), 1612 (C=N), 1596 (C=C). ^{1}H NMR $(CD_3)_2SO$ $\delta =$ 7.38–8.02 (m, 10H, aromatic protons) and 10.26 (s, 1H, isoxazole H-5). ^{13}C NMR $(CD_3)_2SO$ $\delta = 111.3$, 117.4, 123.3, 123.8, 126.3, 128.6, 129.2, 130.5, 132.2, 138.2, 138.6, 157.3, 162.7, 173.6, 185.2, 187.9. *Anal.* Calcd. for $C_{19}H_{11}NO_4$ (317.29): C, 71.92; H, 3.49; N, 4.41. Found: C, 71.84; H, 3.75; N, 4.57.

1-Phenyl-4-(1-benzofuran-2-ylcarbonyl)-3-(2-naphthyl)oxazoles (16b). This compound was obtained as yellow crystals (AcOH), mp 214–216°C, yield (95%); IR (cm^{-1}): 3055 (CH), 1674, 1639 (CO), 1627 (C=N), 1554 (C=C). ^{1}H NMR $(CD_3)_2SO$ $\delta = 7.25$–7.69 (m, 8H, aromatic), 8.58–8.60 (d, 2H, $J = 4$ Hz, aromatic) and 9.92 (s, 1H, isoxazole H-5). *Anal.* Calcd. for $C_{23}H_{13}NO_4$ (367.35): C, 75.20; H, 3.57; N, 3.81. Found: C, 75.10; H, 3.45; N, 3.75.

Synthesis of 17a,b and 22. An equimolar amount of the appropriate isoxazoles **16a**, **16b**, or **21** and hydrazine hydrate (5 mmol) in ethanol (20 mL) was boiled under refluxed for 15 min. The resulting solid was collected and recrystallized from the proper solvent to give the oxazolo[3,4-*d*]pyridazines **17a**, **17b**, and **25**, respectively.

7-(1-Benzofuran-2-yl)-2,4-diphenyl-2H-oxazolo[3,4-*d*]pyridazine (17a). This compound was obtained as colorless crystals (AcOH), mp 178–181°C, yield (94%); IR (cm^{-1}): 3058 (CH), 1685, 1639 (CO), 1612 (C=N), 1596 (C=C). ^{1}H NMR $(CD_3)_2SO$ $\delta = 7.37$–8.53 (m, 12H, aromatic protons) and 10.32 (s, 1H, isoxazole H-5). ^{13}C NMR $(CD_3)_2SO$ $\delta = 105.2$, 113.2, 117.7, 122, 123.5, 124.8, 128.2, 128.7, 129.3, 131.3, 136.8, 141.2, 149.2, 149.6, 151.5, 154.8, 159.1. *Anal.* Calcd. for $C_{19}H_{11}N_3O_2$ (313.31): C, 72.84; H, 3.54; N, 13.41. Found: C, 72.65; H, 3.41; N, 13.50.

7-(1-Benzofuran-2-yl)-2-phenyl-2H-4-(2-naphthyl)oxazolo[3,4-*d*]pyridazines (17b). This compound was obtained as yellow crystals (AcOH), mp 240–242°C, yield (89%); IR (cm^{-1}): 3058 (CH), 1624 (C=N), 1569 (C=C). ^{1}H NMR $(CD_3)_2SO$ δ = 7.42–8.58 (m, 11, aromatic protons), 9.13 (s, 1H, aromatic proton) and 9.90 (s, 1H, isoxazole H-5). *Anal.* Calcd. for $C_{23}H_{13}N_3O_2$ (363.37): C, 76.02; H, 3.61; N, 11.56. Found: C, 76.15; H, 3.48; N, 11.68.

3-(1-Benzofuran-2-yl)-4H-pyrazol-4-one phenylhydrazone (22). This compound was obtained as yellow crystals (AcOH), mp 246–248°C, yield (88%); IR (cm^{-1}): 3309 (NH), 1624 (C=N), 1566 (C=C). ^{1}H NMR $(CD_3)_2SO$ $\delta = 7.26$–7.93 (m, 11H, aromatic protons) and 9.35 (s, 1H, NH). ^{13}C NMR $(CD_3)_2SO$ $\delta = 104.2$, 114.2, 114.5, 119.1, 123.3, 125.7, 126.3, 128.6, 130.8, 132.8, 140.5, 143.2, 149.2, 154.2. *Anal.* Calcd. for $C_{17}H_{12}N_4O$ (288.3): C, 70.82; H, 4.20; N, 19.43. Found: C, 70.89; H, 4.10; N, 19.21.

Synthesis of 19a, 19b, and 20. An equimolar amount of 1-benzfuran-2-yl-3-dimethylaminopropenone (**6**), the appropriate benzoxazol-2-ylacetonitrile, benzthiazole-2-ylacetonitrile or benzimidazole-2-ylacetonitrile and ammonium acetate (5 mmol) in acetic acid (10 mL) was heated under reflux for 4 h. The resulting solid was collected and recrystallized from the proper solvent gave products **19a**, **19b**, and **20**, respectively.

3-(Benzo[*d*]oxazol-2-yl)-6-(benzofuran-2-yl)pyridin-2-amine (19a). This compound was obtained as yellow crystals (DMF), mp 278–279°C, yield (68%); IR (cm^{-1}): 3421, 3298 (NH_2), 3055 (CH), 1627 (C=N), 1581 (C=C). ^{1}H NMR $(CD_3)_2SO$ $\delta = 6.21$ (s, br., 2H, NH_2), 6.07–7.98 (m, 11H, aromatic protons). MS: 329 [(5.2%), M^{+2}], 328 [(27%), M^{+1}], 327 [(100%), M^+)], 310 (41%), 208 (12.5%), 150 (12.4%). *Anal.* Calcd. for $C_{20}H_{13}N_3O_2$ (327.34): C, 73.38; H, 4.00; N, 12.84. Found: C, 73.24; H, 3.87; N, 12.74.

3-(Benzo[*d*]thiazol-2-yl)-6-(benzofuran-2-yl)pyridin-2-amine (19b). This compound was obtained as yellow crystals (DMF), mp 274–276°C, yield (74%); IR (cm^{-1}): 3398, 3286 (NH_2), 3055 (CH), 1620 (C=N), 1577 (C=C). ^{1}H NMR $(CD_3)_2SO$ $\delta = 2.42$ (s, 3H, CH_3), 3.25 (s, 3H, CH_3), 3.49 (t, 1H, $J = 7.5$ Hz, pyrazoline H-4), 6.21 (s, br., 2H, NH_2), 6.07–7.98 (m, 11H, aromatic protons). *Anal.* Calcd. for $C_{20}H_{13}N_3OS$ (343.40): C, 69.95; H, 3.82; N, 12.24; S, 9.34. Found: C, 70.15; H, 3.74; N, 12.45; S, 9.43.

3-(1-Benzofuran-2-yl)pyrido[1,2-*a*]benzimidazole-4-carbonitrile (20). This compound was obtained as yellow crystals (AcOH), mp 256–258°C, yield (65%); IR (cm^{-1}): 3124, 3055 (CH), 2241 (CN), 1635 (C=N), 1589 (C=C). ^{1}H NMR $(CD_3)_2SO$ $\delta = 7.11$ (s, 1H, furan, vinyl CH), 7.24–7.58 (m, 7H, aromatic proton), 8.0–8.10 (d, 2H, $J = 4$ Hz, aromatic) and 9.54 (d, 1H, $J = 4$ Hz, 1H). *Anal.* Calcd. for $C_{20}H_{11}N_3O$ (309.32): C, 77.66; H, 3.58; N, 13.58. Found: C, 77.54; H, 3.45; N, 13.75.

3-(1-Benzofuran-2-yl)-3-oxo-2-(phenylhydrazono)-propanal (21). Benzenediazonium chloride was added to a cold solution of **6** (5 mmol) in ethanolic sodium acetate solution (ethanol, 50 mL) and sodium acetate (0.65 g, 5 mmol) while stirring. The crude solid was collected and recrystallized from ethanol to obtain as reddish yellow crystals, mp 145–145°C, yield (90%); IR (cm^{-1}): 3320 (NH), 1739, 1647 (CO), 1624 (C=N), 1589 (C=C). ^{1}H NMR $(CD_3)_2SO$ $\delta = 7.26$–7.93 (m, 11H, aromatic protons) and 9.98 (s, 1H, CHO), 14.39 (s, br., 1H, NH). ^{13}C NMR $(CD_3)_2SO$ $\delta = 112.1$, 115.8, 118.3, 123.1, 125.7, 126.4, 127.4, 128.6, 130.5, 149.3, 150.5, 155.2, 155.7, 178.2, 192.6. *Anal.* Calcd. for $C_{17}H_{12}N_2O_3$ (292.29): C, 69.86; H, 4.14; N, 9.58. Found: C, 70.12; H, 4.00; N, 9.72.

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Synthesis of [1,2,4]Triazolo[3,4-*b*][1,3]thiazine-5-carboxylates *via* One-Pot Reaction of *N*-Substituted-hydrazino-carbothioamides with Diethyl Maleate

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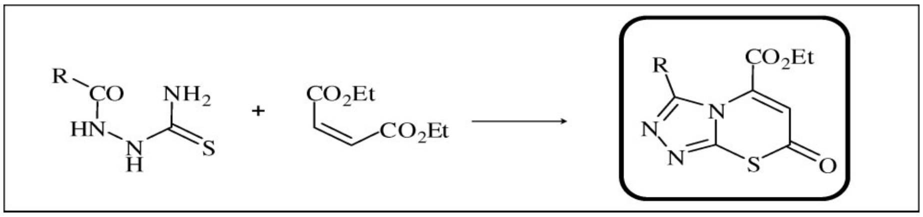

Diethyl maleate reacts with *N*-substituted-hydrazino-carbothioamides to form ethyl [1,2,4]triazolo[3,4-*b*][1,3]thiazine-5-carboxylates. Reaction proceeds *via* bicyclization and oxidation processes.

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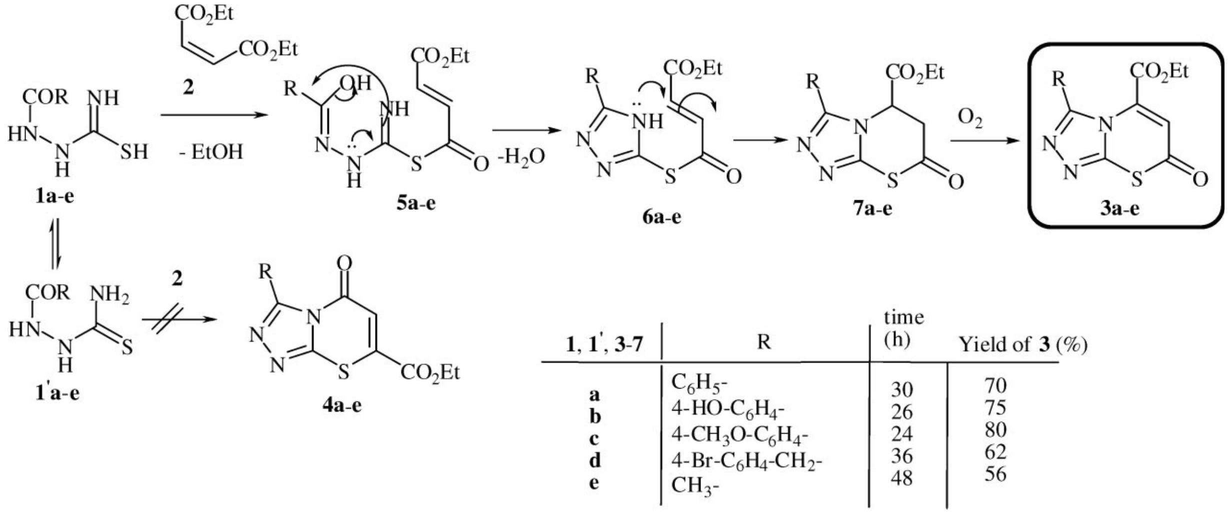
INTRODUCTION

Thioamides and their derivatives occupy a special place among *N*,*S*-containing compounds used in the synthesis of heterocyclic systems, due to their accessibility and the ability to act as difunctional nucleophiles. Reaction of acetylenecarboxylic acid derivatives with *N*,*S*-dinucleophiles provides the general approach for the construction of 1,3-thiazolidine and 1,3-thiazine systems, which are of great interest [1,2]. [1,2,4]Triazepine-3-thiones have been obtained during the reactions of *N*-substituted-hydrazino-carbothioamides with dimethyl acetylene-dicarboxylate and dibenzoyl acetylene under microwave irradiation [3]. The proton-coupled ^{15}N-NMR spectra of hydrazine-carbothioamides have been taken at the natural-abundance level in neutral, basic and acidic solutions at 25°C. The *N*-H proton-exchange reactions of the hydrazino-NH_2 groups in both compounds were found to be very rapid in the presence of acid, but quite slow in the presence of base [4]. Recent report has shown that various *N*-ethyl hydrazine-carbothioamides can undergo different cyclization reactions to give five member heterocycles, which showed a general stimulation effect on B-cells' response [5]. Recently Aly *et al.* [6] investigated the reaction between 2,3-diphenylcyclopropenone and ylidene-*N*-phenylhydrazine-carbothioamides. 1,3-Thiazines have shown wide biological activities. For example, they have shown potential CNS activity [7], potential analgesic, anti-inflammatory, activities [8], and activity as chemotherapeutic agents (i.e., leishmanicides) [9], in addition to their antifungal activity [10]. Our synthetic program has been concerned with the preparation of novel heterocycles efficiently [11–13]. On the basis of the aforementioned encouraging results, we have investigated the reaction of *N*-substituted-hydrazino-carbothioamides **1a**-**e** [14] with diethyl maleate (**2**) to synthesize heterocyclic systems, which might give prospective biological and/or pharmaceutical activities.

RESULTS AND DISCUSSION

Now we have reacted *N*-substituted-hydrazino-carbothioamides **1a**-**e** [14] with diethyl maleate (**2**); the reactions gave mainly the corresponding ethyl 7-oxo-3-substituted-7*H*-[1,2,4]triazolo[3,4-*b*][1,3]thiazine-5-carboxylates **3a-e** (Scheme 1). We chose compounds **1a-d** having aryl groups, whereas we used the methyl derivative **1e** to generalize the idea beyond benzenoid aromatics, to alkyl-substituted starting materials. The structural proof of **3a-e** was based upon the mass, ^{1}H-NMR, ^{13}C-NMR and IR spectra, and elemental analyses. The IR and ^{13}C-NMR spectra of **3a-e** supported the disappearance of any thione and/or NH group. Mass spectrometry and elemental analysis of **3a** proved its molecular formula to be $C_{14}H_{11}N_3O_3S$. The ^{1}H-NMR spectrum of **3a** showed three multiplets for the aromatic phenyl. Besides, the ester-ethyl protons appeared at δ_H 4.12 (q, 2 H, $J = 6.8$ Hz, CH_2) and 1.25 (t, 3 H, $J = 6.8$ Hz, CH_3). The H-6 proton in the ^{1}H-NMR spectrum of **3a** resonated at δ_H 6.82, whereas CH-6 appeared at δ_C 124.2. The ^{13}C-NMR spectrum supported the ^{1}H-NMR spectroscopic data by the distinctive appearance of the

Scheme 1. Reaction of *N*-substituted-hydrazino-carbothioamides **1a-e** with diethyl maleate (**2**). Condition: AcOH, reflux, 1-3d.



1, 1', 3-7	R	time (h)	Yield of 3 (%)
a	C_6H_5-	30	70
b	4-HO-C_6H_4-	26	75
c	4-CH_3O-C_6H_4-	24	80
d	4-Br-C_6H_4-CH_2-	36	62
e	CH_3-	48	56

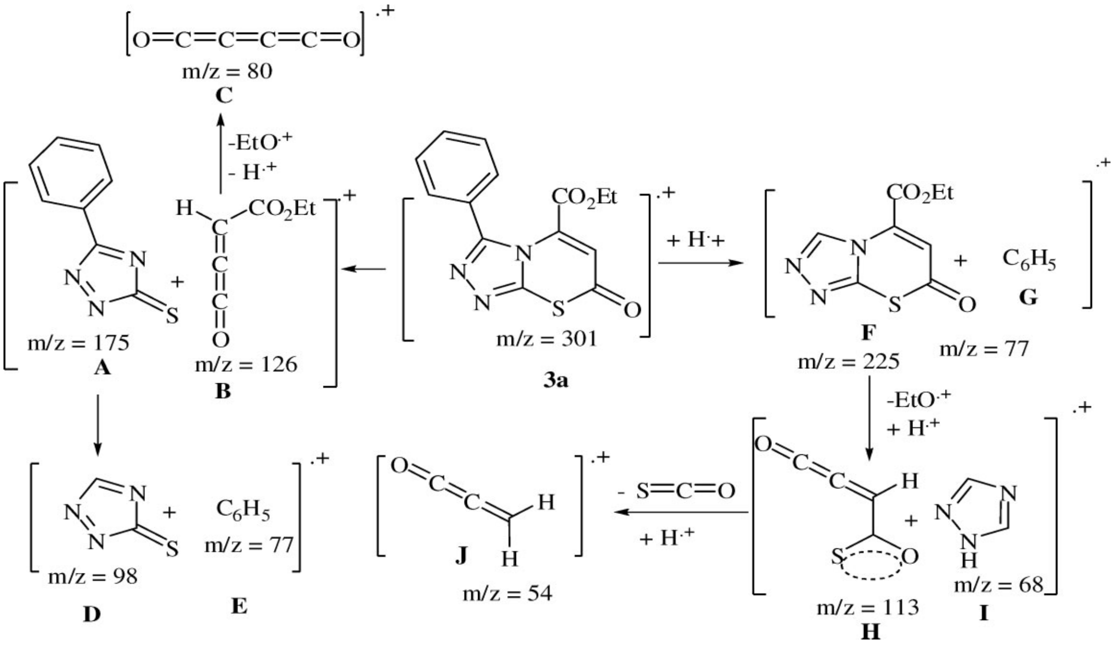
carbon signals representing the ethyl triazolo-thiazine-5-ester skeleton at δ_C 184.0 (C-7), 166.4 (CO-ester), 158.0 (C-3), 150.8 (C-8a), 131.0 (C-5) and 124.2 (CH-6). In **3b**, the mass spectrometry and elemental analysis proved the molecular formula to be $C_{14}H_{11}N_3O_4S$. The IR spectrum did not reveal any absorption due to C=S and/or NH groups, but an absorption band at ν_{max} 3490 cm^{-1} was assigned to the OH stretching. In the ^{1}H-NMR spectrum of **3b**, the OH proton absorbed at δ_H 9.20. Distinctive ^{13}C-NMR signals of **3b** appeared at δ_C 184.2 (C-7), 158.4 (C-3), 150.6 (C-8a), 149.0 (OH-Ar-C), 134.0 (Ar-C-1′), 131.6 (C-5), 128.6 (*ortho*-Ar CH), 120.6 (*meta*-Ar CH), 124.6 (CH-6). The ester carbon signals appeared at δ_C 166.1 (CO), 59.6 (CH_2), and 13.0 (CH_3). In the ^{13}C-NMR of **3d**, characteristic carbon signals appeared at δ_C 183.2, 166.2, 158.3, 150.6, 134.8, 132.0, 129.2, 126.8, 124.4, 122.2, 33.6, and 24.2, which were assigned to C-7, CO-ester, C-3, C-8a, Br-Ar-C, C-5, Ar-C-1′, *ortho*-Ar CH, CH-6, *meta*-Ar CH, 60.2 CH_2-ester, benzyl-CH_2 and CH_3-ester, respectively (Experimental part). The reaction of **1e** with **2** took the longest time of refluxing (2d) compared with other substituents. The ^{1}H-NMR spectrum of **3e** revealed the proton signals at δ_H 6.82 (s, 1 H, H-6), 4.17 (q, 2 H, $J = 6.7$ Hz, CH_2-ester), 2.20 (s, 3 H, C-3-CH_3), 1.21 (t, 3 H, $J = 6.7$, CH_3-ester), whereas the carbon signals appeared at δ_C 184.2 (C-7), 166.6 (CO-ester), 158.4 (C-3), 151.2 (C-8a), 132.0 (C-5), 124.2 (CH-6), 59.8 (CH_2-ester), 22.2 (CH_3), 24.4 (CH_3-ester).

The yield percentages of the obtained products increase in the presence of aromatic moiety. On the other hand, the methyl derivative **1e** gives a lower yield and the reaction requires more time than the other derivatives **1a-d**.

The reaction mechanism proceeds *via* the HN=C—SH tautomer **1** instead of the H_2N—C=S tautomer **1′**. Evidently attack by the SH group is faster than attack by the amine [6]. Accordingly, the reaction of **1a-e** with **2** can be described as due to nucleophilic attack of the thiol group to the ester carbon accompanied by elimination of one molecule of ethanol to form the intermediate **5** (Scheme 1). Thereafter, amidine-like nucleophilic attack on the amide is accompanied by water elimination to give **6** (Scheme 1). Nucleophilic attack of the terminal NH on the π-deficient double-bond produces the corresponding triazolo-dihydrothiazines **7** (Scheme 1). Ultimately, we propose that aerial oxidation of **7** gives the stable heterocyclic compounds **3** (Scheme 1). In HMBC studies of **3a-c**, the aromatic protons showed a correlation with the carbonyl ester, but not with the carbonyl in position-7. In methyl derivative **3e**, the methyl revealed a medium correlation with the carbonyl-ester, whereas no correlation was indicated with C-7. In an NOE experiment, irradiation of the methyl protons in **3e** (δ_H 2.20) showed enhancement the CH_2-ester protons. These data unambiguously exclude the formation of isomers **4a-e** (Scheme 1).

The 70-eV EI mass spectra of compounds **3a-e** are illustrated in the experimental section. All compounds **3a-e** exhibit the molecular peaks as intense base ion peaks. Most indicative is the appearance of the triazolethiones$^+$ and ethyl 4-oxobuta-2,3-dienoate$^+$ (Scheme 2). For example, the fragmentation pattern of **3a** showed ion peaks for **A**$^+$ and **B**$^+$ at m/z 175 (50) and 126 (28), respectively. An abundant peak resulting from loss of ethanol from **B**$^+$ leads to **C**$^+$, whereas loss of phenyl group gave species **D**$^+$ and **E**$^+$ (Scheme 2). The ion peak **H**$^+$ shows that it fragmented primarily *via* the loss of carbonoxysulfide from **H**$^+$ to give **J**$^+$ at m/z 54. Other species **F-J**$^+$ of **3a** appeared as shown in Scheme 2.

Scheme 2. Fragmentation patterns of compound **3a**.



CONCLUSION

In conclusion, *N*-substituted-hydrazino-carbothioamides react with diethyl maleate *via* initial *S*-acylation followed by cyclizative conjugate addition to the unsaturated ester. A second cyclization forms a triazole ring, and aerial oxidation occurs to afford the [1,2,4]triazolo-[3,4-*b*][1,3]thiazine-5-carboxylate products.

EXPERIMENTAL

Melting points are uncorrected values. ^{1}H-NMR and ^{13}C-NMR spectra (Bruker AM 400, ^{1}H: 400.13 MHz, ^{13}C: 100.6 MHz) were obtained from deuterio-chloroform and deuterio-DMSO solutions; the chemical shifts are given relative to internal standard TMS. For preparative thin layer chromatography (PLC), glass plates (20 × 48 cm) were covered with slurry of silica gel Merck PF$_{254}$ and air-dried using the solvents listed for development. Zones are detected by quenching of indicator fluorescence upon exposure to 254 nm UV light. Elemental analyses were carried in Assiut Microanalysis Center of Assiut University. Mass spectroscopy was performed at 70 eV with a Finnigan Mat 8430 spectrometer at the Institute of Organic Chemistry, TU-Braunschweig. Germany. The IR spectra were run on a Shimadzu 470 spectrometer using KBr pellets.

Starting materials. *N*-Substituted-hydrazino-carbothioamides **1a**-**e** were prepared according to literature [14].

General procedure. To a 250 cm^3 two-necked round bottom flask containing a solution of **1a**-**e** (2 mmol) in glacial acetic acid (50 mL), a solution of **2** (0.344 g, 2 mmol) in glacial acetic acid (10 mL) was added dropwise with stirring. The mixture was refluxed for 1-2 d (the reaction was monitored by TLC). The solvent was evaporated under vacuum, and the solid residue was dissolved in dry acetone (30 mL), and the solution was chromatographed on thin layer plates (silica gel) using toluene. All zones were extracted and the obtained products were recrystallized from the stated solvents.

Ethyl 3-phenyl-7-oxo-7*H*-[1,2,4]triazolo[3,4-*b*]-[1,3] thiazine-5-carboxylate (3a). Yellow crystals 0.42 (70%), mp 212°C (ethanol); ^{1}H-NMR (400 MHz, deuterio-chloroform): δ_H 7.90-7.80 (m, 2 H, Ar-H), 7.60-7.50 (m, 2 H, Ar-H), 7.46-7.41 (m, 1 H, Ar-H), 6.82 (s, 1 H, H-6), 4.12 (q, 2 H, $J = 6.8$ Hz, CH$_2$-ester), 1.25 (t, 3 H, $J = 6.8$ Hz, CH$_3$-ester); ^{13}C-NMR (100.6 MHz, deuterio-chloroform): δ_C 184.0 (C-7), 166.4 (CO-ester), 158.0 (C-3), 150.8 (C-8a), 131.4 (Ar-C-1′), 131.0 (C-5), 130.0 (*para*-Ar CH), 127.8 (*ortho*-Ar CH), 127.2, (*meta*-Ar CH), 124.2 (C-6), 60.0 (CH$_2$-ester), 24.2 (CH$_3$-ester); IR (KBr): ν_{max} 3086-3008 (w, Ar-CH), 1720 (s, CO-ester), 1700 (s, CO), 1625 (s, C=N), 1590 (m, C=C) cm^{-1}; λ_{max} (CH$_3$CN, nm, lg ε): 400 (3.8); ms (EI): m/z 301 [M$^+$] (100), 286 (14), 272 (18), 256 (38), 228 (22), 225 (30), 175 (50), 152 (24), 126 (28), 113 (32), 98 (20), 80 (16), 77 (34), 68 (24), 54 (22). *Anal.* Calcd for $C_{14}H_{11}N_3O_3S$ (301.33): C, 55.81; H, 3.68; N, 13.95; S, 10.64. Found: C, 56.00; H, 3.60; N, 13.86; S, 10.70.

Ethyl 3-(4′-hydroxyphenyl)-7-oxo-7*H*-[1,2,4]triazolo-[3,4-*b*][1,3]thiazine-5- carboxylate (3b). Yellow plates 0.47 g (75%), mp 234°C (ethanol); ^{1}H-NMR (400 MHz, deuterio-chloroform): δ_H 9.20 (s, 1 H, OH), 7.53-7.29 (m, 4 H, Ar-H), 6.74 (s, 1 H, H-6), 4.14 (q, 2 H, $J = 7.0$ Hz, CH$_2$-ester), 1.22 (t, 3 H, $J = 7.0$ Hz, CH$_3$-ester); ^{13}C-NMR (100.6 MHz, deuterio-chloroform): δ_C 184.2 (C-7), 166.1 (CO-ester), 158.4 (C-3), 150.6 (C-8a), 149.0 (Ar-C-OH), 134.0 (Ar-C-1′), 131.6 (C-5), 128.6 (*ortho*-Ar CH), 126.6, (*meta*-Ar CH), 124.6 (CH-6), 59.6 (CH$_2$-ester), 24.6 (CH$_3$-ester); IR (KBr): ν_{max} 3490 (s, OH), 3090-3010 (m, Ar-CH), 1724 (CO-ester), 1702 (CO), 1628 (s, C=N), 1596 (m, C=C) cm^{-1}; λ_{max} (CH$_3$CN, nm, lg ε): 410 (4.0); ms (EI): m/z 317 [M$^+$] (100), 300 (22), 286 (24), 256 (14), 234 (26), 225 (34), 190 (24), 175 (22), 160 (42), 152 (32), 126 (30), 113 (40), 98 (20), 94 (40), 80 (26), 77 (32), 68 (26), 54 (20). *Anal.* Calcd for $C_{14}H_{11}N_3O_4S$ (317.33): C, 52.99; H, 3.49; N, 13.24; S, 10.10. Found: C, 52.78; H, 3.40; N,13.10; S, 10.06.

Ethyl 3-(4′-methoxyphenyl)-7-oxo-7*H*-[1,2,4]triazolo-[3,4-*b*][1,3]thiazine-5-carboxylate (3c). Yellow crystals 0.53 g (80%), mp 298°C (acetonitrile); ^{1}H-NMR (400 MHz, deuterio-chloroform): δ_H 7.49-7.28 (m, 4 H, Ar-H), 6.80 (s, 1 H, H-6), 4.10 (q, 2 H, J = 6.9 Hz, CH_2-ester), 3.90 (s, 3 H, OCH_3), 1.25 (t, 3 H, J = 6.9 Hz, CH_3-ester); ^{13}C-NMR (100.6 MHz, deuterio-chloroform): δ_C 185.0 (C-7), 165.9 (CO-ester), 158.6 (C-3), 156.0 (CH_3O-C), 150.8 (C-8a), 134.2 (Ar-C-1′), 131.6 (C-5), 130.2 (*meta*-Ar CH), 125.2 (CH-6), 123.0 (*ortho*-Ar CH), 60.0 (CH_2-ester), 58.8 (OCH_3), 24.3 (CH_3-ester); IR (KBr): ν_{max} 3060-3007 (w, Ar-CH), 2996-2886 (aliph.-CH), 1722 (s, CO-ester), 1700 (s, CO), 1632 (s, C=N), 1590 (m, C=C) cm^{-1}; λ_{max} (CH_3CN, nm, lg ε): 418 (4.1); ms (EI): m/z 331 [M$^+$] (100), 316 (18), 300 (22), 286 (32), 258 (28), 226 (34), 205 (16), 174 (40), 126 (34), 113 (42), 108 (32), 99 (20), 80 (24), 77 (26), 68 (26), 54 (24). *Anal.* Calcd for $C_{15}H_{13}N_3O_4S$ (331.35): C, 54.37; H, 3.95; N, 12.68; S, 9.68. Found: C, 54.30; H, 3.98; N, 12.62; S, 9.72.

Ethyl 3-(4′-bromobenzyl)-7-oxo-7*H*-1,2,4-triazolo[3,4-*b*][1,3]thiazine-5-carboxylate (3d). Yellow crystals 0.47 g (62%), mp 290°C (ethyl acetate). ^{1}H-NMR (400 MHz, deuterio-DMSO): δ_H 7.46-7.10 (m, 4 H, Ar-H), 6.70 (s, 1 H, H-6), 4.07 (s, 2H, benzyl-CH_2), 4.14 (q, 2 H, J = 6.9 Hz, CH_2-ester), 1.21 (t, 3 H, J = 6.9, CH_3-ester); ^{13}C-NMR (100.6 MHz, deuterio-DMSO): δ_C 183.2 (C-7), 166.2 (CO-ester), 158.3 (C-3), 150.6 (C-8a), 134.8 (Br-C), 132.0 (C-5), 129.2 (Ar-C-1′), 126.8 (*ortho*-Ar CH), 124.4 (CH-6), 122.2 (*meta*-Ar CH), 60.2 (CH_2-ester), 33.6 (benzyl-CH_2), 24.2 (CH_3-ester); IR (KBr): ν_{max} 3082-3015 (w, Ar-CH), 2980-2880 (m, aliph.-CH), 1726 (s, CO-ester), 1700 (s, CO), 1612 (br, s, C=N), 1588 (m, C=C), 1112 (m, C—O) cm^{-1}; λ_{max} (CH_3CN, lg ε, nm): 388 (4.0); ms (EI): m/z 395 [M+1] (94), 393 [M-1] (100) 313 (32), 268 (28), 240 (26), 224 (45), 212 (28), 172 (40), 170 (55), 126 (18), 113 (24), 98 (30), 80 (22), 77 (40), 68 (22), 80 (22), 54 (18). *Anal.* Calcd for $C_{15}H_{12}BrN_3O_3S$ (394.24): C, 45.70; H, 3.07; Br, 20.27; N, 10.66; S, 8.13. Found: C, 45.60; H, 3.00; Br, 20.37; N, 10.50; S, 8.20.

Ethyl 3-methyl-7-oxo-7*H*-[1,2,4]triazolo[3,4-*b*]-[1,3]thiazine-5-carboxylate (3e). Pale yellow crystals 0.27 g (56%), mp 170°C (ethanol); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 6.82 (s, 1 H, H-6), 4.17 (q, 2 H, J = 6.7 Hz, CH_2-ester), 2.20 (s, 3 H, C-3-CH_3), 1.21 (t, 3 H, J = 6.7, CH_3-ester); ^{13}C-NMR (100.6 MHz, deuterio-chloroform): δ_C 184.2 (C-7), 166.6 (CO-ester), 158.4 (C-3), 151.2 (C-8a), 132.0 (C-5), 124.2 (CH-6), 59.8 (CH_2-ester), 22.2 (C-3-CH_3), 24.4 (CH_3-ester); IR (KBr): ν_{max} 3078-3000 (w, Ar-CH), 2980-2860 (m, aliph.-CH), 1718 (s, CO-ester), 1700 (s, CO), 1622 (s, C=N), 1590 (s, C=C) cm^{-1}; λ_{max} (CH_3CN, nm, lg ε): 390 (3.2); ms (EI): m/z 239 [M$^+$] (100), 194 (24), 166 (24), 151 (18), 126 (22), 113 (56), 80 (16), 64 (16), 54 (18). *Anal.* Calcd for $C_9H_9N_3O_3S$ (239.25): C, 45.18; H, 3.79; N, 17.56; S, 13.40. Found; C, 45.04; H, 3.70; N, 17.40; S, 13.40.

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Substituent-Dependence of Photophysical Properties of *trans*-2-Styrylpyridazin-3(2*H*)-ones

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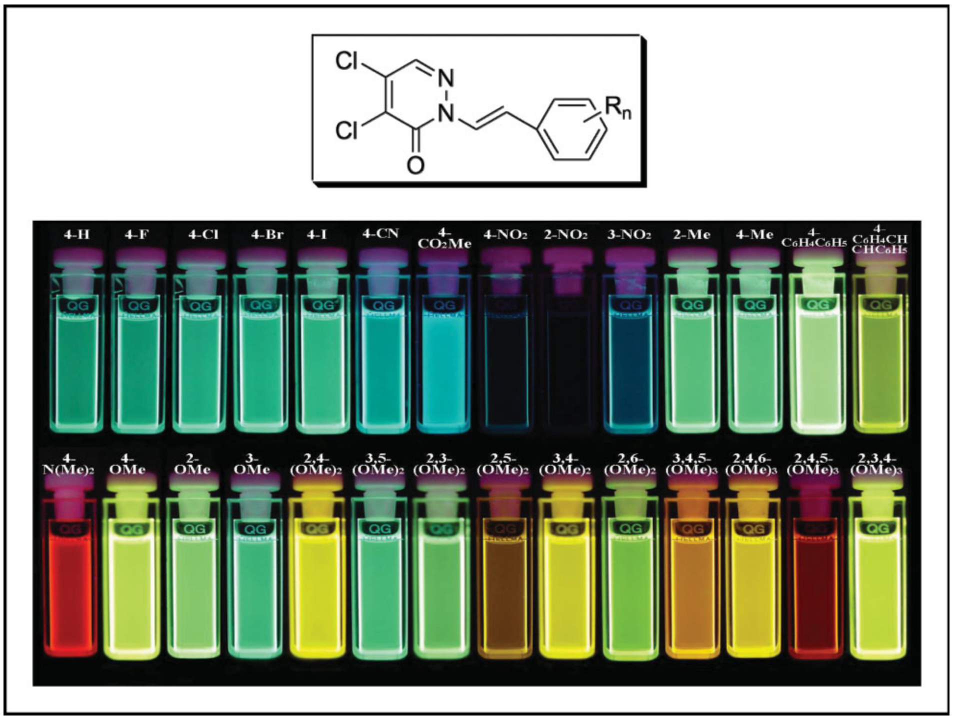

The photophysical behavior of *trans*-2-styrylpyridazin-3(2*H*)-ones **3** strongly depend on the number and the position of substituents in the phenyl ring in THF, methylene chloride, acetonitrile and methanol. The absorption spectra of **3** containing the electron-donating substituents at the *para*-position show the red-shift, whereas the spectra of **3** containing the electron-withdrawing substituents show the blue-shift. For the *trans*-2-(*p*-substituted-styryl)pyridazin-3(2*H*)-ones **3b**–**3h** and **3k**–**3o**, the magnitude of the solvatochromic shifts and the shape of the fluorescence spectra depend on the number and/or the position of substituents in benzene ring. The emission maximum of *trans*-2-styrylpyridazin-3(2*H*)-ones involving the electron-donating group is larger than one of *trans*-2-styrylpyridazin-3(2*H*)-ones involving the electron-withdrawing group in the phenyl ring. The magnitude of the emission maximum is roughly parallel to the relative electron-withdrawing ability of the substituents of the phenyl ring.

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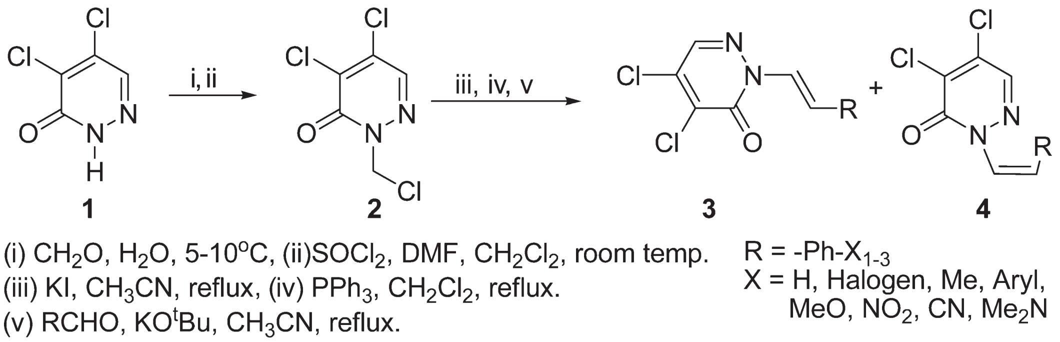
INTRODUCTION

The creation of luminescent molecules is an active field of research in supramolecular chemistry [1–8]. The chemosensors also have the advantages of possessing high sensitivity and selectivity, as well as providing on-line and real time analysis [9–25]. However, the development of a useful fluorescent probes is difficult because of the lack of flexible design strategies. The design also is largely empirical at present. Thus, the tuning of the photophysical properties introducing the substituent is very useful in this field.

Organic molecules that contain styryl moiety are an important fluorescent class and show a number of attractive photophysical and electro-optical properties

Scheme 1

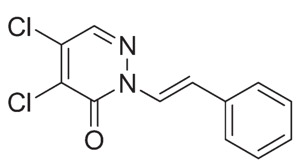


(i) CH_2O, H_2O, 5-10°C, (ii)$SOCl_2$, DMF, CH_2Cl_2, room temp.
(iii) KI, CH_3CN, reflux, (iv) PPh_3, CH_2Cl_2, reflux.
(v) RCHO, KO^tBu, CH_3CN, reflux.

R = -Ph-X_{1-3}
X = H, Halogen, Me, Aryl, MeO, NO_2, CN, Me_2N

[20,26–36]. The substitution of phenyl ring in stilbene with a heterocyclic acceptor (pyridine) significantly affected the photophysical and photochemical behavior, because of the involvement of the (nπ*) state [28,37]. According to the literature [26,28,38–40], the photophysical behavior and the torsional barrier of *trans*-stilbene derivatives depend on the nature of substituents and/or solvent polarity. Therefore, the fluorescent property could be tunable by the introduction of a suitable substituent on the phenyl ring in stilbene.

Recently, we reported the synthesis the photophysical properties and the potentiality for the application as spectroscopic or fluorescent probes for some *N*-styrylazinones containing Het-N—CH=CH—Ar (Het = hetetocycle) moiety [41]. The heterocycle-dependent photophysical behavior of *trans*-2-(2-arylvinyl)-4,5-dichloropyridazin-3(2*H*)-ones was also reported [42]. Because of the utility of C—Cl bond in 4,5-dichloropyridazin-3(2*H*)-one ring for the derivatization, we selected *trans*-4,5-dichloro-2-styrylpyridazin-3(2*H*)-one as parent fluorescence molecules, and studied on the dependence on the substituents of the phenyl ring about the photophysical properties of **3**. Here we report on the synthesis and tuning of the photophysical properties of some *trans*-2-styrylpyridazin-3(2*H*)-ones **3**.



trans-4,5-Dichloro-2-styrylpyridazin-3(2*H*)-one

RESULTS AND DISCUSSION

Synthesis. Various *trans*-2-(substituted-styryl)pyridazin-3(2*H*)-ones **3** were prepared according to the literature [41] using the synthetic sequence outlined in Scheme 1. Compound **2** [43] was reacted with benzaldehyde after treating potassium iodide and then triphenylphosphine to give *trans*-isomers **3** as the major product. Although *cis*-isomers **4** were formed as the minor product, it was not isolated since the *cis*-isomer changed slowly to *trans*-isomer at room temperature during the workup. The structures of **3** were established by NMR, IR and elemental analyses.

Absorption spectra. All the *trans*-2-styrylpyridazin-3(2*H*)-ones **3a–3aa** displays a single intense long wavelength absorption band in methylene chloride, tetrahydrofuran, acetonitrile and methanol. The absorption maxima are reported in Table 2. In general, the absorption maximum of **3** depends on substituent of *para*-position in benzene ring; that is, the electron-donating group shows the red-shift (e.g., **3o** vs. **3a**), whereas the electron-withdrawing group shows the blue-shift (e.g., **3f** vs. **3a**).

The substituted position also affects about absorption maximum of nitrophenyl derivatives, that is, the 4-nitro: the red-shift (**3h** *vs.* **3a**); the 2-nitro or 3-nitro group: the blue-shift (**3i/3j** *vs.* **3a**). The **3b** show the blue-shift in the absorption maximum due to the 4-fluoro group.

On the other hand, we investigated the dependence of an absorption spectrum on the position and the number of methoxy group. All methoxy compounds showed the red-shift compared with **3a** in the absorption spectrum. The magnitude of the bathochromic effect of 2-methoxy and 4-methoxy compounds (**3o** and **3p**) is larger than that of 3-methoxy derivative (**3q**) (Table 2 entries 15–17). For the dimethoxy derivatives, the bathochromic effect of 2,4-, 2,5-, 2,6-, and 3,4-dimethoxy compounds (**3r**, **3u**, **3w**, **3v**) is also larger than one of 3,5-and 2,3-dimethoxy derivatives (**3s, 3t**) (Table 2 entries 18–23). All four trimethoxy derivatives (**3x–3aa**) show much larger the bathochromic effect than mono- and dimethoxy derivatives. Among four trimethoxy derivatives, the magnitude of the bathochromic shift for 2,4,5- and 2,4,6-trimethoxy compounds (**3y** and **3z**) is especially large (Table 2 entries 25 and 26).

Table 1

Synthesis of *trans*-**3** from **2**.

Entry	**3,** R		Yield (%)[a]	Entry	**3,** R		Yield (%)[a]
1	**a**	C_6H_5—	47	15	**o**	4-$MeOC_6H_4$—	46
2	**b**	4-FC_6H_4—	45	16	**p**	2-$MeOC_6H_4$—	45
3	**c**	4-ClC_6H_4—	44	17	**q**	3-$MeOC_6H_4$—	43
4	**d**	4-BrC_6H_4—	51	18	**r**	2,4-$(MeO)_2C_6H_3$	43
5	**e**	4-IC_6H_4—	42	19	**s**	3,5-$(MeO)_2C_6H_3$—	44
6	**f**	4-NCC_6H_4—	41	20	**t**	2,3-$(MeO)_2C_6H_3$—	41
7	**g**	4-$(MeO_2C)C_6H_4$—	49	21	**u**	2,5-$(MeO)_2C_6H_3$—	42
8	**h**	4-$NO_2C_6H_4$—	58	22	**v**	3,4-$(MeO)_2C_6H_3$—	41
9	**i**	2-$NO_2C_6H_4$—	49	23	**w**	2,6-$(MeO)_2C_6H_3$—	47
10	**j**	3-$NO_2C_6H_4$—	54	24	**x**	3,4,5-$(MeO)_3C_6H_3$—	45
11	**k**	4-MeC_6H_4—	65	25	**y**	2,4,6-$(MeO)_3C_6H_2$—	42
12	**l**	4-$(C_6H_5)C_6H_4$—	43	26	**z**	2,4,5-$(MeO)_3C_6H_2$—	38
13	**m**	4-$(C_6H_5CHCH)C_6H_4$—	41	27	**aa**	2,3,4-$(MeO)_3C_6H_2$—	39
14	**n**	4-$(Me)_2NC_6H_5$—	51				

[a] Isolated yield.

In addition, the absorption spectra of **3** show hypsochromic and hyperchromic effects (exception for **3l**, **3m**, **3o**, **3s**, **3u**, **3w**, and **3y-3aa**) in acetonitrile comparing with the spectra in methylene chloride. The absorption spectra of **3** show hypsochromic and hyperchromic effects (exception for **3b**, **3d**, **3g-3l**, **3n, 3r**, and **3z**) in methanol comparing with the spectra in methylene chloride. The absorption spectra of **3** show bathochromic effect (exception for **3h**, **3k**, **3m**, **3p**, **3r**, **3u**, **3v**, **3z**, and **3aa**) and hyperchromic effect (exception for **3c**, **3e**, **3o**,

Table 2

The absorption maxima (nm) for *trans*-2-(substituted-styryl)pyridazin-3(2*H*)-ones **3** at room temperature.[a]

		λ_{max} (ε)			
Entry	**3**	CH_2Cl_2	THF	CH_3CN	MeOH
1	**3a**	371 (8657)	371 (8799)	365 (10410)	366 (8254)
2	**3b**	370 (7935)	371 (8017)	361 (10117)	364 (8172)
3	**3c**	371 (8090)	371 (7236)	363 (10104)	365 (7429)
4	**3d**	370 (6919)	370 (8596)	365 (9874)	365 (8780)
5	**3e**	370 (8837)	373 (8763)	367 (10110)	367 (8629)
6	**3f**	362 (7941)	364 (8009)	359 (8587)	357 (7030)
7	**3g**	369 (9209)	370 (9954)	363 (9349)	363 (8511)
8	**3h**	373 (7004)	372 (9546)	370 (9369)	378 (7310)
9	**3i**	362 (7358)	365 (8901)	358 (7952)	358 (7612)
10	**3j**	356 (7036)	361 (8750)	356 (8813)	353 (9042)
11	**3k**	379 (9820)	379 (8010)	373 (8350)	374 (8570)
12	**3l**	384 (9594)	382 (4797)	374 (5285)	376 (6154)
13	**3m**	396 (8898)	390 (9427)	387 (7948)	390 (7055)
14	**3n**	373 (6264)	439 (8509)	432 (8589)	437 (8272)
15	**3o**	389 (8684)	389 (8314)	382 (7115)	382 (8610)
16	**3p**	383 (8382)	382 (8755)	373 (8920)	366 (8254)
17	**3q**	373 (8699)	374 (8232)	367 (9164)	366 (8649)
18	**3r**	401 (8670)	401 (8794)	394 (8844)	397 (8748)
19	**3s**	373 (8857)	374 (8653)	368 (8499)	369 (7211)
20	**3t**	373 (7366)	376 (8024)	367 (9517)	368 (7556)
21	**3u**	395 (8435)	394 (7464)	386 (8096)	387 (8172)
22	**3v**	399 (8775)	397 (8842)	388 (8833)	390 (8970)
23	**3w**	392 (9180)	393 (8327)	385 (7635)	387 (8717)
24	**3x**	386 (7788)	387 (8118)	378 (8655)	378 (7310)
25	**3y**	411 (9237)	414 (8056)	405 (8620)	410 (8728)
26	**3z**	415 (8930)	413 (8357)	407 (6915)	408 (8213)
27	**3aa**	393 (8844)	394 (9618)	384 (8396)	387 (8992)

[a] Data were collected from sample solution prepared under atmosphere without degassing or inert gas bubbling.

Table 3

Maxima of fluorescence (λ_f), fluorescence band half-width ($\Delta\nu_{1/2}$), 0,0 transition ($\lambda_{0,0}$), Stokes shifts ($\Delta\nu_{st}$), and quantum yields of 2-styryl-pyridazin-3(2*H*)-ones **3** in tetrahydrofuran, methylene chloride, methanol, and acetonitrile.[a]

Compound	Solvent	λ_f[b](nm)	$\Delta\nu_{st}$ (cm^{-1})[c]	$\lambda_{0,0}$ (nm)[d]	$\Delta\nu_{1/2}$ (cm^{-1})	Quantum yield (Φ)[e]
3a	THF	492(513)	6629	435	3451	0.18
	CH_2Cl_2	492	6608	434	3407	0.41
	MeOH	494	7096	431	3432	0.18
	CH_3CN	496 (519)	7335	431	3383	0.12
3b	THF	492 (501)	6645	435	3355	0.18
	CH_2Cl_2	491	6697	434	3396	0.27
	MeOH	496	7329	431	3431	0.20
	CH_3CN	494	7233	431	3375	0.11
3c	THF	496 (517)	6773	435	3384	0.33
	CH_2Cl_2	491	6603	435	3401	0.18
	MeOH	492 (516)	7051	431	3487	0.09
	CH_3CN	495 (517)	7223	431	3404	0.09
3d	THF	493	6650	436	3404	0.05
	CH_2Cl_2	487	6472	434	3416	0.08
	MeOH	495	7175	433	3496	0.02
	CH_3CN	495	7203	431	3378	0.01
3e	THF	491	6423	440	3335	0.24
	CH_2Cl_2	491	6640	438	3324	0.19
	MeOH	499	7225	436	3335	0.04
	CH_3CN	496 (513)	7053	434	3271	0.06
3f	THF	482	6726	427	3648	0.18
	CH_2Cl_2	475	6588	423	3751	0.41
	MeOH	476	7003	443	3717	0.18
	CH_3CN	485	7092	421	3787	0.12
3g	THF	485	6387	431	3594	0.18
	CH_2Cl_2	476	6310	431	3567	0.27
	MeOH	484	6866	426	3661	0.20
	CH_3CN	486	6951	428	3575	0.11
3h	THF	479	6019	429	3718	0.33
	CH_2Cl_2	467	5409	425	3591	0.18
	MeOH	482	6554	424	3932	0.09
	CH_3CN	471	5821	423	3747	0.09
3i	THF	478	6455	421	3844	0.05
	CH_2Cl_2	472	6454	417	3889	0.08
	MeOH	471	6702	415	3837	0.02
	CH_3CN	480	7023	412	4098	0.01
3j	THF	463	6141	416	4072	0.24
	CH_2Cl_2	471	6875	417	3774	0.19
	MeOH	485	7689	418	3816	0.04
	CH_3CN	477	7111	416	3865	0.06
3k	THF	502	6480	444	3122	0.55
	CH_2Cl_2	502	6320	446	3177	0.42
	MeOH	504	6913	442	3148	0.51
	CH_3CN	505	7044	441	3710	0.35
3l	THF	514	6757	453	2883	0.83
	CH_2Cl_2	514	6568	457	2862	0.46
	MeOH	519	7309	479	2854	0.83
	CH_3CN	521	7474	449	2820	0.84
3m	THF	529	6720	477	2425	0.32
	CH_2Cl_2	531	6420	476	2408	0.27
	MeOH	536	6984	508	3002	0.16
	CH_3CN	535	7320	470	2741	0.33
3n	THF	619	6624	545	2121	0.11
	CH_2Cl_2	618	10664	532	2168	0.13
	MeOH	621	6793	572	2665	–
	CH_3CN	641	7753	535	16816	0.01
3o	THF	526	6711	466	2431	0.75
	CH_2Cl_2	527	6747	466	2492	0.83
	MeOH	532	7415	467	2503	0.74
	CH_3CN	531	7373	462	2543	0.69

(*Continued*)

Table 3
(*Continued*)

Compound	Solvent	$\lambda_f{}^b$(nm)	$\Delta\nu_{st}$ (cm^{-1})^c	$\lambda_{0,0}$ (nm)^d	$\Delta\nu_{1/2}$ (cm^{-1})	Quantum yield (Φ)^e
3p	THF	519	6910	455	2842	0.73
	CH_2Cl_2	519	6842	455	2457	0.78
	MeOH	523	7725	453	2797	0.81
	CH_3CN	523	7480	449	2742	0.64
3q	THF	500	6774	441	3220	0.46
	CH_2Cl_2	498	6745	440	3222	0.67
	MeOH	508	7544	438	3308	0.31
	CH_3CN	504	7423	436	3187	0.25
3r	THF	535	6260	484	2348	0.62
	CH_2Cl_2	537	6316	483	2400	0.85
	MeOH	540	6653	485	2816	0.30
	CH_3CN	541	7070	479	2755	0.52
3s	THF	505	6972	444	3189	0.39
	CH_2Cl_2	500	6847	442	3214	0.55
	MeOH	506	7374	438	3227	0.29
	CH_3CN	507	7541	437	4084	0.10
3t	THF	511	7043	444	3165	0.62
	CH_2Cl_2	513 (516)	7298	443	3148	0.77
	MeOH	507	7468	436	3386	0.04
	CH_3CN	514	7689	433	3307	0.02
3u	THF	536	6739	475	2716	0.21
	CH_2Cl_2	538	6729	476	2864	0.12
	MeOH	473	4709	438	4249	0.02
	CH_3CN	534	7332	433	6092	0.01
3v	THF	537	6581	482	2521	0.76
	CH_2Cl_2	536	6438	479	2491	0.78
	MeOH	544	7292	479	3082	0.17
	CH_3CN	541	7337	475	3047	0.24
3w	THF	524	6361	465	2602	0.95
	CH_2Cl_2	524	6441	467	2611	0.50
	MeOH	526	6862	465	2615	0.66
	CH_3CN	528	6991	461	2541	0.58
3x	THF	540	7355	475	3020	0.35
	CH_2Cl_2	546	7609	473	3091	0.35
	MeOH	573	9038	460	3614	0.03
	CH_3CN	574	8914	467	3409	0.15
3y	THF	537	5562	494	2390	0.69
	CH_2Cl_2	539	5808	495	2488	0.40
	MeOH	555	6372	497	2881	0.33
	CH_3CN	547	6863	490	2835	0.43
3z	THF	585	7104	509	2760	0.24
	CH_2Cl_2	585	7031	508	2857	0.16
	MeOH	538	5922	477	4155	–
	CH_3CN	601	8150	478	3878	0.01
3aa	THF	530	6513	472	2453	0.64
	CH_2Cl_2	532	6663	472	2426	0.91
	MeOH	535	7148	471	2614	0.18
	CH_3CN	535	7320	468	2623	0.55

[a] Fluorescence data were obtained from corrected spectra.

[b] The second vibronic band is given in parentheses.

[c] $\Delta\nu_{st} = \nu_{abs-}\ \nu_{f.}$

[d] The value of $\lambda_{0,0}$ was obtained from the intersection of normalized absorption and fluorescence spectra.

[e] Quantum yield of the emission is evaluated at 25°C, the quantum yield values is that relative to 9,10-diphenylanthracene (1.00×10^{-4} *M*) in acetonitrile (from 352 nm excitation wavelength, $\Phi = 0.95$).

3q, **3s**, **3u**, **3w**, and **3y-3aa**) in tetrahydrofuran comparing with the spectra in methylene chloride. However, the solvatochromic effect of these compounds is rather small, which indicate a small difference between the dipole moment of the Franck-Condon excited state and the ground state [44].

Emission spectra. The fluorescence maxima (λ_f), the half-bandwidth ($\Delta\nu_{1/2}$), the 0,0 transitions ($\lambda_{0,0}$), the

Stokes shift ($\Delta\nu_{st}$), and the fluorescence quantum yield (Φ) of all compounds **3** are reported in four solvents in Table 3. For the *trans*-2-(*p*-substituted-styryl)pyridazin-3(2*H*)-ones **3b–3h** and **3k–3o**, the magnitude of the solvatochromic shifts and the shape of the fluorescence spectra depend on the substituents in four solvents. In general, the emission maximum of **3** involving an electron-donating substituent is larger than one of **3** involving an electron-withdrawing. Among all *p*-substituted derivatives, compound **3n** shows the largest emission maximum and the lowest fluorescence efficiency in four solvents.

The magnitude of the emission maximum for *p*-substituted derivatives **3a–3h** and **3k–3o** is in the order **3n** (4-Me_2N) >**3m** (4-C_6H_5CHCH) >**3o** (4-MeO) >**3l** (4-C_6H) >**3k** (4-Me) >**3a** (4-H) >**3b** (4-F), **3c** (4-Cl), **3e** (4-I) >**3d** (4-Br) >**3g** (4-CO_2Me) >**3f** (4-CN) >**3h** (4-NO_2) in methylene chloride, **3n** (4-Me_2N) >**3m** (4-C_6H_5CHCH) >**3o** (4-MeO) >**3l** (4-C_6H_5) >**3k** (4-Me) >**3a** (4-H), **3e** (4-I) >**3d** (4-Br), **3c** (4-Cl) >**3b** (4-F) >**3g** (4-CO_2Me) >**3f** (4-CN) >**3h** (4-NO_2) in acetonitrile,**3n** (4-Me_2N) >**3m** (4-C_6H_5CHCH) >**3o** (4-MeO) >**3l** (4-C_6H_5) >**3k** (4-Me) >**3e** (4-I) >**3b** (4-F) >**3d** (4-Br) >**3a** (4-H) >**3c** (4-Cl) >**3g** (4-CO_2Me) >**3h** (4-NO_2) >**3f** (4-CN) in methanol and **3n** (4-Me_2N) >**3m** (4-C_6H_5CHCH) >**3o** (4-MeO) >**3l** (4-C_6H_5) >**3k** (4-Me) >**3c** (4-Cl) >**3d** (4-Br) >**3a** (4-H), **3b** (4-F) >**3e** (4-I) >**3g** (4-CO_2Me) >**3f** (4-CN) >**3h** (4-NO_2) in Tetrahydrofuran. The magnitude of the emission maximum for *p*-substituted derivatives is roughly parallel with the relative electron-withdrawing ability of the substitutents. According to the 0-0 transition energies (Table 3), the planar $^1t^*$ (ICT) state of **3a** (4-H) is stabilized by the electron-donating substituents (e.g., **3k**, **3n**, and **3o**) but destabilized by the electron-withdrawing substituents (e.g., **3b**, **3f**, **3g**, and **3h**) [26,38]. The number and the position of the substituents on the phenyl ring and/or the solvents affected about the magnitude of fluorescence band half-width ($\Delta\nu_{1/2}$) of all derivatives. Fluorescence band half-width increases due to the electron-withdrawing groups, whereas one of derivatives containing the electron-donating groups decreases. All derivatives are strongly fluorescent in methylene chloride, but the values of Φ_f decrease in more polar solvents. It depends on the substituents of the phenyl ring. The quantum yields of **3f–3j** decrease due to the strong electron-withdrawing substituents, whereas one of **3b–3e** and **3k–3aa** increases due to halogen at the para-position (for **3b–3e**) and the electron-donating substituents (for **3k–3aa**).

According to the literatures [26,45], the energies of the fluorescence maxima of benzene derivatives correlate better with the Hammett σ^+ than with the σ constants. The relationship of the energies of the fluorescence maxima for **3** and the Hammett σ^+ shows in the Figure 2. In four solvents, a nice linear relationship can be observed for *p*-substituted derivatives **3e–3h, 3k**, and **3o** except for **3l**.

For the **3h** (4-NO_2), **3i** (2-NO_2), and **3j** (3-NO_2), the magnitude of the solvatochromic shifts and the shape of the fluorescence spectra (Fig. 1) depend on the substituted position. The magnitude of the emission maximum for **3h–3j** is in the order **3i** (2-NO_2) >**3j** (3-NO_2) >**3h** (4-NO_2) in methylene chloride and acetonitrile, **3j** (3-NO_2) >**3h** (4-NO_2) >**3i** (2-NO_2) in methanol and **3h** (4-NO_2) >**3i** (2-NO_2) >**3j** (3-NO_2) in THF. The magnitude of the quantum yields for **3h**, **3i**, and **3j** is in the order **3h** (4-NO_2) >**3j** (3-NO_2) >**3i** (2-NO_2). According 0-0 transition energies (Table 3), the stability of the planar $^1t^*$ (ICT) state in the excited state for *trans*-2-(nitrostyryl)pyridazin-3(2*H*)-ones **3h-3j** depends on the substituted position of the nitro group and/or slightly the solvent. Among the *trans*-2-(*p*-substituted-styryl)pyridazin-3(2*H*)-ones, *p*-methoxy derivative **3o** shows the largest value of the emission maximum and the 0-0 transition energy in four solvents. Therefore, we have been investigated the dependence of the fluorescence spectra for mono-, di- and trimethoxystyryl derivatives on the position and the numbers of the methoxy group. Among the three monomethoxy derivatives, *p*-substituted derivative **3o** shows excellent emission maximum and the high fluorescence intensity in four solvents except for **3p** in methanol.

For the *trans*-2-(dimethoxystyryl)pyridazin-3(2*H*)-ones **3r-3w**, the emission maximum and the quantum yield depend very highly on the solvent and the substituted position (Table 3). Among six dimethoxy derivatives, compound **3v** [3,4-$(MeO)_2$] shows the highest quantum yield in tetrahydrofuran. For the *trans*-2-(trimethoxystyryl)pyridazin-3(2*H*)-ones **3x-3aa**, the number and the position of the methoxy group and/or the solvent affected about the magnitude of the solvatochromic shifts, the shape of the fluorescence spectra and the quantum yield.

In case of the *trans*-2-(methoxystyryl)pyridazin-3(2*H*)-ones **3o-3aa**, the magnitude of the solvatochromic shifts and the shape of the fluorescence spectra depend on the number and the substituted position of the methoxy group. These effects for the di- and trimethoxy derivatives **3r–3w, 3x–3aa** are larger than the monomethoxy derivatives **3p** and **3q** in polar solvents such as acetonitrile and methanol. Among the methoxy derivatives, the magnitude of the solvatochromic shifts and the shape of the fluorescence spectra for 2,5-dimethoxy derivative (**3u**) change dramatically in polar solvent such as methanol and acetonitrile. The magnitude of the fluorescence maxima for the trimethoxy derivatives **3x–3z** is larger than the magnitude of the mono- or dimethoxyphenyl derivatives **3p–3w** except for **3r**. In the case of

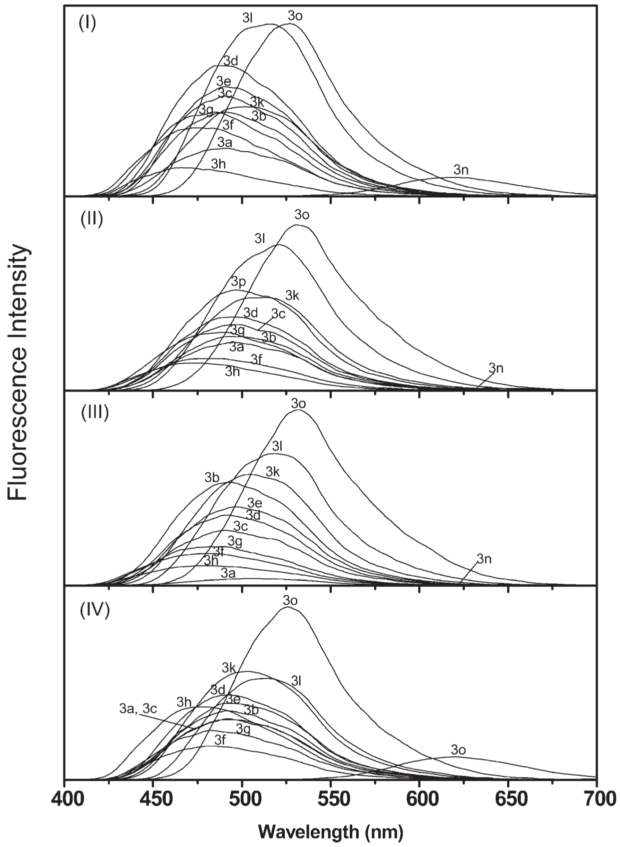


Figure 1. Normalized fluorescence spectra of *p*-substituted-2-styrylpyridazin-3(2*H*)-ones **3a-3h** and **3k-3o** in methylene chloride (I), acetonitrile (II), methanol (III), and tetrahydrofuran (IV).

dimethoxy derivatives **3r–3w**, the emission maximum strongly depends on the substitution position and the solvent. According to the 0-0 transition energies (Table 3), the stability of the planar $^1t^*$ (ICT) state for all methoxy compounds **3o–3aa** depends also on the substituted position and the number of the methoxy group and slightly the solvent. Especially, the methoxy group at the *para*-position should be more stabilized, whereas the methoxy group at the *meta*-position should be more destabilized.

CONCLUSIONS

The substituent-dependent photophysical behavior of the 28 *trans*-2-styryl-4,5-dichloropyridazin-3(2*H*)-ones **3** as novel fluorescent molecules has been elucidated. According to our observation, the absorption maximum of compounds **3** depends on the substituent, the substituted position of the benzene ring and the solvent polarity. In addition, the intensity of absorption spectra for compounds **3** depends on the solvent polarity.

The magnitude of the solvatochromic shifts and the shape of the fluorescence spectra for **3** depend on the substituents. In general, the emission maxima of *trans*-2-styrylpyridazin-3(2*H*)-ones involving the electron-donating group is larger than that of *trans*-2-styrylpyridazin-3(2*H*)-ones involving the electron-withdrawing group. The magnitude of the emission maximum is roughly parallel with the relative electron-withdrawing ability of the substitutents. According to the 0-0 transition energies (Table 3), the planar $^1t^*$ (ICT) state of the *trans*-2-(*p*-substituted-styryl)pyridazin-3(2*H*)-ones is stabilized by electron donating substituents but destabilized by electron withdrawing substituents. The number and the position of the substituents on the phenyl ring and/or the solvents also affected about the magnitude of fluorescence band half-width ($\Delta\nu_{1/2}$) of all derivatives. The quantum yield and fluorescent intensity of all compounds **3** depend on the number, the kind and the position of substituent in the phenyl ring and the solvent.

By introducing the suitable substituent in the phenyl ring of styryl moiety, *trans*-2-styrylpyridazin-3(2*H*)-ones **3** may use as a platform for fluorescence probes. These results may be a guide-line for the tuning of novel fluorescence molecules containing styryl moiety.

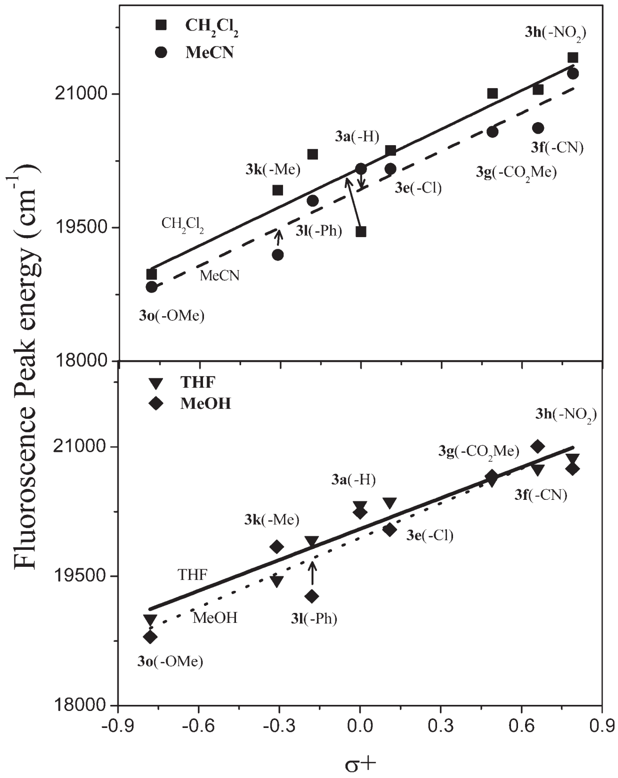


Figure 2. Correlation diagram of the energies of the fluorescence maxima against the Hammett σ^+ constants for *p*-substituted derivatives **3e-3h**, **3k**, **3l,** and **3o** in methylene chloride, tetrahydrofuran, methanol and acetonitrile.

Further dynamic, theoretical and application studies on these and the related systems would complement the current results and provide more insights into the photophysical behaviors of *trans*-*N*-styryl-nitrogen-heterocycles.

EXPERIMENTAL

General comments. Melting points were determined with a capillary apparatus and uncorrected. ^{1}H and ^{13} NMR spectra were recorded on a 300 MHz spectrometer with chemical shift values reported in δ units (ppm) relative to an internal standard TMS. IR spectra were obtained on an IR spectrophotometer. Elemental analyses were performed with a Perkin Elmer 240 C. Open-bed chromatography was carried out on silica gel (70–230 mesh, Merck) using gravity flow. The column was packed as slurries with the elution solvent.

Typical process of 4,5-dichloro-2-chloromethylpyridazin-3(2*H*)-one (2). A mixture of 4,5-dichloropyridazin-3(2*H*)-one (**1**, 60 g, 364 mmol) and distilled water (350 mL) was stirred for 10 min at room temperature. After adding formaldehyde solution (36%, 70 mL), the solution was refluxed for 1.5 h. After cooling to 5–10°C, the resulting precipitate was filtered, washed with cold water (0–5°C, 200 mL) and dried in air to give *N*-hydroxymethyl-4,5-dichloropyridazin-3(2*H*)-one. A solution of thionyl chloride (357 mmol) and dimethylformamide (360 mmol) in methylene chloride (50 mL) was added slowly to the mixture of *N*-hydroxymethyl-4,5-dichloropyridazin-3(2*H*)-one and methylene chloride (550 mL) for 30 min at room temperature with stirring. The resulting mixture was stirred for 2 h at room temperature. After cooling to 0°C, water (200 mL) was added slowly. The solution was neutralized to pH 6.7–7.4 by using saturated solution of $NaHCO_3$. The organic layer was separated and then dried over anhydrous magnesium sulfate. The resulting organic solution was evaporated under reduced pressure. The residue was washed with *n*-hexane (100 mL) to give 4,5-dichloro-2-chloromethylpyridazin-3(2*H*)-one (**2**, 71.2 g, 92%) as white color. White crystal (diethyl ether/*n*-hexane = 1:5, v/v). mp 69–70°C (lit. 43 mp 70–71°C). TLC (CH_2Cl_2) $R_f = 0.65$. IR (KBr) 3046, 2984, 1670, 1292, 1122, 964 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.83 (s, 2H), 7.88 ppm (s, 1H); ^{13}C NMR ($CDCl_3$) δ 58.40, 134.87, 137.23, 137.34, 155.58 ppm. Elemental analysis calcd. for $C_5H_3Cl_3N_2O$: C 28.13, H 1.42, N 13.12; found: C 28.10, H 1.41, N 13.09.

Typical process of synthesis for trans-4,5-dichloro-2-styrylpyridazin-3(2*H*)-one 3. A mixture of 2-chloromethyl-4,5-dichloropyridazin-3(2*H*)-one (**2**, 3 g, 14.055 mmol), sodium iodide (2.45 g, 14.76 mmol) and acetonitrile (50 mL) was refluxed for 10 h. After cooling to 30–40°C, triphenylphosphine (4.07 g, 15.51 mmol) was added to the reaction solution. The mixture was then refluxed for 6 h. After cooling to room temperature, the mixture was filtered by using Celite 545 and washed with methylene chloride (50 mL). The organic layer was concentrated under reduced pressure. After adding dichloromethane (100 mL) to the resulting mixture, the solution was stirred for 20 min. The solution was filtered and then concentrated under reduced pressure. After cooling to room temperature, the resulting precipitate was filtered, washed with excess diethyl ether and dried to give the product as thin yellow crystals. The product was used without further purification.

To a solution of crude ((4,5-dichloro-6-oxopyridazin-1(6*H*)-yl)methyl)triphenyl phosphonium iodide (8 g, 14.10 mmol) in acetonitrile (50 mL) was added benzaldehyde (1.5 g, 14.10 mmol) at 0–10°C. After stirring for 30 min, potassium *t*-butoxide (2.05 g, 95%, 17.21 mmol) was added. The resulting mixture was stirred for 2 h. The solution was concentrated under reduced pressure. After adding dichloromethane (100 mL) and then water (50 mL), the solution was stirred for 10 min, and neutralized to pH 6.7–7.4 by using saturated solution of $NaHCO_3$. The organic layer was separated and then dried over anhydrous magnesium sulfate. The resulting organic solution was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel. The column was eluted with methylene chloride/*n*-hexane (1:4, v/v). Fractions containing *trans*-isomer **3** were combined and evaporated to give pure *trans*-isomer **3**, respectively. The yields of all compounds **3** showed in Table 1.

(E)-4,5-Dichloro-2-styrylpyridazin-3(2H)-one (3a). Pale yellow crystal (diethyl ether:*n*-hexane = 1:2, v/v). mp 161–162°C. IR (KBr) 3108, 1664, 1592, 1300, 1238, 1134, 958, 898, 742, 696 cm^{-1}. ^{1}H NMR ($CDCl_3$); δ 7.25 $\sim$ 7.38 (m, 4H), 7.47 $\sim$ 7.50 (m, 2H), 7.86 (s, 1H), 8.10 (d, J = 14.35 Hz, 1H). ^{13}C NMR ($CDCl_3$); δ 122.21, 124.13, 127.02, 128.49, 128.88, 134.49, 134.56, 135.94, 136.04, 154.68. Anal. Calcd. for $C_{12}H_8Cl_2N_2O$: C, 53.96; H, 3.02; N, 10.49. Found: C, 53.94; H, 3.01; N, 10.51.

(E)-4,5-Dichloro-2-(4-fluorostyryl)pyridazin-3(2H)-one (3b). Pale yellow crystal (methylene chloride). mp 158–159°C. IR (KBr) 3096, 1664, 1596, 1520, 1240, 1138, 960, 858, 748 cm^{-1}. ^{1}H NMR ($CDCl_3$); δ 7.01 $\sim$ 7.09 (m, 2H), 7.24 (d, J = 14.58 Hz, 1H), 7.43 $\sim$ 7.48 (m, 2H), 7.87 (s, 1H), 8.04 (d, J = 14.34 Hz, 1H). ^{13}C NMR ($CDCl_3$); δ 115.78 (C—F), 116.07 (C—F), 121.02, 123.79 (C—F), 123.82 (C—F), 128.58 (C—F), 128.69 (C—F), 130.65 (C—F), 130.69 (C—F), 134.49, 136.00 (C—F), 136.11 (C—F), 154.66, 161.12, 164.42. Anal. Calcd. for $C_{12}H_7Cl_2FN_2O$: C, 50.55; H, 2.47; N, 9.83. Found: C, 50.56; H, 2.49; N, 9.84.

(E)-4,5-Dichloro-2-(4-chlorostyryl)pyridazin-3(2H)-one (3c). Light yellow crystal (methylene chloride). mp 177–178°C. IR (KBr) 3086, 1664, 1582, 1494, 1290, 960, 818 cm^{-1}. ^{1}H NMR ($CDCl_3$); δ 7.21 (d, J = 14.36 Hz, 1H), 7.27 $\sim$ 7.34 (m, 2H), 7.38 $\sim$ 7.43 (m, 2H), 7.87 (s, 1H), 8.08 (d, J = 14.35 Hz, 1H). ^{13}C NMR ($CDCl_3$); δ 120.80, 124.37, 128.14, 129.06, 133.03, 134.16, 134.52, 136.06, 136.20, 154.63. Anal. Calcd. for $C_{12}H_7Cl_3N_2O$: C, 47.79; H, 2.34; N, 9.29. Found: C, 47.78; H, 2.33; N, 9.25.

(E)-2-(4-Bromostyryl)-4,5-dichloropyridazin-3(2H)-one (3d). Light yellow crystal (methylene chloride). mp 183–184°C. IR (KBr) 3100, 1676, 1594, 1496, 1300, 1138, 963, 902, 820 cm^{-1}. ^{1}H NMR ($CDCl_3$); δ 7.20 (d, J = 14.35 Hz, 1H), 7.32 $\sim$ 7.36 (m, 2H), 7.46 $\sim$ 7.50 (m, 2H), 7.87 (s, 1H), 8.09 (d, J = 14.32 Hz, 1H). ^{13}C NMR ($CDCl_3$); δ 120.91, 122.37, 124.55, 128.43, 132.04, 133.55, 134.58, 136.05, 136.19, 154.63. Anal. Calcd. for $C_{12}H_7BrCl_2N_2O$: C, 41.65; H, 2.04; N, 8.10. Found: C, 41.66; H, 2.03; N, 8.08.

(E)-4,5-Dichloro-2-(4-iodostyryl)pyridazin-3(2H)-one (3e). Light yellow crystal (methylene chloride). mp 194–195°C. IR (KBr) 3122, 1680, 1596, 1298, 1234, 970, 900, 806, 760 cm^{-1}. ^{1}H NMR (CDCl$_3$); δ 7.17 ~ 7.24 (m, 3H), 7.69 (d, J = 8.42 Hz, 2H), 7.88 (s, 1H), 8.12 (d, J = 14.37 Hz, 1H). ^{13}C NMR (CDCl$_3$); δ 99.94, 121.01, 124.54, 128.61, 134.09, 134.59, 136.09, 136.25, 137.99, 154.66. Anal. Calcd. for $C_{12}H_7ICl_2N_2O$: C, 36.67; H, 1.80; N, 7.13. Found: C, 36.65; H, 1.79; N, 7.10.

(E)-2-(4-Cyanostyryl)-4,5-dichloropyridazin-3(2H)-one (3f). Light yellow crystal (methylene chloride). mp 226–227°C. IR (KBr) 3092, 2998, 2226, 1665, 1584, 1294, 1136, 962, 947, 895, 864, 824, 556 cm^{-1}. ^{1}H NMR (CDCl$_3$); δ 3.81 (s, 2OCH$_3$), 6.40 ~ 6.42 (t, J = 2.19 Hz, 1H), 6.62 (d, J = 2.21 Hz, 2H), 7.27 (d, J = 14.37 Hz, 1H), 7.56–7.59 (m, 2H), 7.64 ~ 7.67 (m, 2H), 7.91 (s, 1H), 8.19 (d, J = 14.38 Hz, 1H). ^{13}C NMR (CDCl$_3$); δ 111.57, 118.67, 119.97, 126.65, 127.38, 132.66, 134.83, 136.40, 136.62, 139.28, 154.73 ppm. Anal. Calcd. for $C_{13}H_7Cl_2N_3O$: C, 53.45; H, 2.42; N, 14.38. Found: C, 53.44; H, 2.42; N, 14.35.

(E)-4,5-Dichloro-2-(4-methoxycarbonylstyryl)pyridazin-3(2H)-one (3g). Light yellow crystal (methylene chloride). mp 212–214°C. IR(KBr) 3086, 3053, 3005, 2954, 1711, 1670, 1589, 1436, 1277, 1182, 112, 954 cm^{-1}. ^{1}H NMR (CDCl$_3$); δ 3.91 (s, OCH$_3$), 7.30 (d, J = 14.37 Hz, 1H), 7.54 ~ 7.57 (m, 2H), 7.90 (s, 1H), 8.02 ~ 8.05 (m, 2H), 8.20 (d, J = 14.35 Hz, 1H). ^{13}C NMR (CDCl$_3$); δ 52.17, 120.91, 125.82, 126.85, 129.77, 130.17, 134.70, 136.21, 136.38, 139.12, 154.72, 166.62 ppm. Anal. Calcd. for $C_{14}H_{10}Cl_2N_2O_3$: C, 51.72; H, 3.10; N, 8.62. Found: C, 51.71; H, 3.11; N, 8.60.

δ 7.32 (d, J = 14.38 Hz, 1H), 7.61 ~ 7.65 (m, 2H), 7.92 (s, 1H), 8.20 ~ 8.27 (m, 3H). ^{13}C NMR (CDCl$_3$); δ 119.47, 124.25, 127.19, 127.44, 134.86, 136.44, 136.69, 141.26, 147.32, 154.72. Anal. Calcd. for $C_{12}H_7Cl_2N_3O_3$: C, 46.18; H, 2.26; N, 13.46. Found: C, 46.16; H, 2.23; N, 13.47.

(E)-4,5-dichloro-2-(2-nitrostyryl)pyridazin-3(2H)-one (3i). Light yellow crystal (methylene chloride). mp 180–181°C. IR (KBr) 3108, 3068, 1668, 1596, 1520, 1340, 1300, 1280, 1146, 1122, 964, 950, 898, 738 cm^{-1}. ^{1}H NMR (CDCl$_3$); δ 7.45 ~ 7.50 (m, 1H), 7.61 ~ 7.66 (m, 1H), 7.70 ~ 7.73 (m, 1H), 7.80 (d, J = 14.15 Hz, 1H), 7.93 (s, 1H), 8.00 ~ 8.04 (m, 1H), 8.08 (d, J = 14.12 Hz, 1H). ^{13}C NMR (CDCl$_3$); δ 117.55, 125.07, 127.30, 128.59, 128.92, 130.38, 133.46, 134.72, 136.50, 136.64, 148.24, 154.79. Anal. Calcd. for $C_{12}H_7Cl_2N_3O_3$: C, 46.18; H, 2.26; N, 13.46. Found: C, 46.15; H, 2.24; N, 13.45.

δ 7.38 (d, J = 14.26 Hz, 1H), 7.59 ~ 7.64 (m, 1H), 7.88 ~ 7.91 (m, 1H), 8.08 ~ 8.15 (m, 2H), 8.23 (d, J = 14.38 Hz, 1H), 8.34 (s, 1H). ^{13}C NMR (CDCl$_3$); δ 119.34, 121.89, 123.06, 127.12, 130.78, 133.35, 134.01, 136.36, 136.92, 137.69, 148.83, 154.75. Anal. Calcd. for $C_{12}H_7Cl_2N_3O_3$: C, 46.18; H, 2.26; N, 13.46. Found: C, 46.13; H, 2.23; N, 13.42.

(E)-4,5-dichloro-2-(4-methylstyryl)pyridazin-3(2H)-one (3k). Light yellow crystal (methylene chloride). mp 179–180°C. IR (KBr) 3150, 2976, 1688, 1610, 1322, 1158, 980, 920, 832, 758 cm^{-1}. ^{1}H NMR (CDCl$_3$); δ 2.35 (s, CH$_3$), 7.15 (d, J = 7.97 Hz, 2H), 7.25 (d, J = 14.34 Hz, 1H), 7.38 (d, J = 8.08 Hz, 2H), 7.85 (s, 1H), 8.08 (d, J = 14.32 Hz, 1H). ^{13}C NMR (CDCl$_3$); δ 21.28, 122.22, 123.37, 126.94, 129.57, 131.69, 134.37, 135.80, 135.91, 138.59. Anal. Calcd. for $C_{13}H_{10}Cl_2N_2O$: C, 55.54; H, 3.59; N, 9.96. Found: C, 55.51; H, 3.58; N, 9.93.

(E)-2-(2-(biphenyl-4-yl)vinyl)-4,5-dichloropyridazin-3(2H)-one (3l). Light yellow crystal (methylene chloride). mp 212–213°C. IR (KBr) 3088, 1680, 1614, 1140, 972, 838, 760 cm^{-1}. ^{1}H NMR (CDCl$_3$); δ 7.31 ~ 7.38 (m, 2H), 7.42 ~ 7.47 (m, 2H), 7.55 ~ 7.63 (m, 6H), 7.92 (s, 1H), 8.16 (d, J = 14.31 Hz, 1H). ^{13}C NMR (CDCl$_3$); δ 121.99, 123.92, 126.84, 126.96, 127.43, 127.49, 128.77, 133.47, 134.34, 136.09, 136.26, 140.29, 141.25, 154.84. Anal. Calcd. for $C_{18}H_{12}Cl_2N_2O$: C, 62.99; H, 3.52; N, 8.16. Found: C, 62.98; H, 3.49; N, 8.15.

4,5-Dichloro-2-((E)-4-(E)-styrylstyryl)pyridazin-3(2H)-one (3m). Yellow crystal (methylene chloride). mp 224–225°C. IR (KBr) 3106, 1670, 1600, 1520, 1306, 1142, 968, 906, 820, 768, 698 cm^{-1}. ^{1}H NMR (CDCl$_3$); δ 7.12 (d, J = 4.01 Hz, 2H), 7.24 ~ 7.29 (m, 2H), 7.32 ~ 7.39 (m, 25H), 7.47 ~ 7.54 (m, 6H), 7.89 (s, 1H), 8.15 (d, J = 14.32 Hz, 1H). ^{13}C NMR (CDCl$_3$); δ 121.87, 123.93, 126.58, 126.98, 127.39, 127.81, 128.02, 128.71, 129.28, 133.86, 134.38, 136.07, 137.18, 137.67. Anal. Calcd. for $C_{20}H_{14}Cl_2N_2O$: C, 65.06; H, 3.82; N, 7.59. Found: C, 65.05; H, 3.81; N, 7.57.

(E)-4,5-dichloro-2-(4-(dimethylamino)styryl)pyridazin-3(2H)-one (3n). Deep red crystal (methylene chloride). mp 130–132°C. IR (KBr) 3134, 2962, 1678, 1620, 1540, 1522, 1380, 1200, 1248, 1236, 964, 914 cm^{-1}. ^{1}H NMR (CDCl$_3$); δ 2.99 (s, 6H), 6.68 (d, J = 8.86 Hz, 2H), 7.22 (d, J = 14.26 Hz, 1H), 7.39 (d, J = 8.84 Hz, 2H), 7.85 (s, 1H), 7.98 (d, J = 14.24 Hz, 1H). ^{13}C NMR (CDCl$_3$); δ 40.30, 112.25, 120.51, 122.36, 122.75, 128.27, 133.89, 135.33, 135.60, 150.59, 154.52. Anal. Calcd. for $C_{14}H_{13}Cl_2N_3O$: C, 54.21; H, 4.22; N, 13.55. Found: C, 54.19; H, 4.20; N, 13.52.

(E)-4,5-dichloro-2-(4-methoxystyryl)pyridazin-3(2H)-one (3o). Yellow crystal (methylene chloride). mp 177–178°C. IR (KBr) 3062, 2944, 1666, 1614, 1590, 1522, 1308, 1258, 1196, 1140, 1038, 960, 906, 812, 744 cm^{-1}. ^{1}H NMR (CDCl$_3$); δ 3.83 (s, OCH$_3$), 6.87 ~ 6.92 (m, 2H), 7.23 (d, J = 14.32 Hz, 1H), 7.41 ~ 7.4 5 (m, 2H), 7.86 (s, 1H), 8.01 (d, J = 14.29 Hz, 1H). ^{13}C NMR (CDCl$_3$); δ 55.34, 114.32, 121.95, 122.36, 127.09, 128.37, 134.25, 135.74, 135.88, 154.62, 159.95. Anal. Calcd. for $C_{13}H_{10}Cl_2N_2O_2$: C, 52.55; H, 3.39; N, 9.43. Found: C, 52.52; H, 3.38; N, 9.40.

(E)-4,5-dichloro-2-(2-methoxystyryl)pyridazin-3(2H)-one (3p). Light yellow crystal (methylene chloride). mp 133–135°C. IR (KBr) 3132, 2987, 1684, 1600, 1500, 1478, 1300, 1260, 1140, 1042, 966, 760 cm^{-1}. ^{1}H NMR (CDCl$_3$); δ 3.91 (s, OCH$_3$), 6.91 ~ 6.99 (m, 2H), 7.26 ~ 7.31 (m, 1H), 7.48 ~ 7.51 (m, 1H), 7.53 (d, J = 14.02 Hz, 1H), 7.89 (s, 1H), 8.87 (d, J = 14.32 Hz, 1H). ^{13}C NMR (CDCl$_3$); δ 55.50, 110.96, 118.06, 120.82, 123.42, 124.89, 128.31, 129.58, 134.33, 135.81, 135.90, 154.73, 157.45. Anal. Calcd. for $C_{13}H_{10}Cl_2N_2O_2$: C, 52.55; H, 3.39; N, 9.43. Found: C, 52.53; H, 3.37; N, 9.42.

(E)-4,5-dichloro-2-(3-methoxystyryl)pyridazin-3(2H)-one (3q). Pale yellow crystal (methylene chloride). mp 143–145°C. IR (KBr) 3126, 2988, 1676, 1602, 1504, 1478, 1264, 1134, 1046, 960, 900, 796, 740 cm^{-1}. ^{1}H NMR (CDCl$_3$); δ 3.84 (s, OCH$_3$), 6.84 ~ 6.88 (m, 1H), 7.01 ~ 7.02 (m, 1H), 7.08 ~ 7.11 (m, 1H), 7.24 ~ 7.31 (m, 2H), 7.89 (s, 1H), 8.12 (d, J = 14.32 Hz, 1H). ^{13}C NMR (CDCl$_3$); δ 55.33, 112.12, 114.34, 119.73, 122.15, 124.30, 129.88, 134.52, 135.92, 136.00, 136.12, 154.72, 159.95. Anal. Calcd. for $C_{13}H_{10}Cl_2N_2O_2$: C, 52.55; H, 3.39; N, 9.43. Found: C, 52.51; H, 3.38; N, 9.43.

(E)-4,5-dichloro-2-(2,4-dimethoxystyryl)pyridazin-3(2H)-one (3r). Yellow crystal (methylene chloride). mp 169–170°C. IR (KBr) 3066, 2982, 1660, 1620, 1592, 1516, 1460, 1298, 1280, 1216, 1156, 1134, 1040, 966, 898, 834 cm^{-1}. ^{1}H NMR ($CDCl_3$); δ 3.83 (s, OCH_3), 3.88 (s, OCH_3), 6.47 ~ 6.52 (m, 2H), 7.39 ~ 7.46 (m, 3H), 7.86 (s, 1H), 8.17 (d, J = 14.36 Hz, 1H). ^{13}C NMR ($CDCl_3$); δ 55.42, 55.51, 98.64, 105.08, 116.50, 118.10, 123.21, 129.30, 134.08, 135.52, 135.65, 154.62, 158.71, 161.23. Anal. Calcd. for $C_{14}H_{12}Cl_2N_2O_3$: C, 51.40; H, 3.70; N, 8.56. Found: C, 51.38; H, 3.70; N, 8.55.

δ 3.81 (s, 2OCH_3), 6.40 ~ 6.42 (t, J = 2.19 Hz, 1H), 6.62 (d, J = 2.21 Hz, 2H), 7.20 (d, J = 14.30 Hz, 1H), 7.86 (s, 1H), 8.09 (d, J = 14.29 Hz, 1H). ^{13}C NMR ($CDCl_3$); δ 55.43, 100.85, 104.99, 122.16, 124.40, 134.47, 135.98, 136.12, 136.41, 154.66, 161.03. Anal. Calcd. for $C_{14}H_{12}Cl_2N_2O_3$: C, 51.40; H, 3.70; N, 8.56. Found: C, 51.36; H, 3.69; N, 8.53.

(E)-4,5-dichloro-2-(2,3-dimethoxystyryl)pyridazin-3(2H)-one (3t). Yellow crystal (methylene chloride). mp 149–150°C. IR (KBr) 3066, 2962, 1674, 1592, 1482, 1276, 1076, 966 cm^{-1}. ^{1}H NMR ($CDCl_3$); δ 3.86 (s, OCH_3), 3.88 (s, OCH_3), 6.87 (dd, J = 1.28, 8.06 Hz, 1H), 7.05 (t, J = 7.96 Hz, 1H), 7.15 (dd, J = 1.27, 7.90 Hz, 1H), 7.54 (d, J = 14.46 Hz, 1H), 7.89 (s, 1H), 8.20 (d, J = 14.44 Hz, 1H). ^{13}C NMR ($CDCl_3$); δ 55.85, 60.96, 112.34, 117.20, 118.82, 124.27, 125.26, 128.72, 134.38, 135.95, 136.03, 147.46, 153.12, 154.75. Anal. Calcd. for $C_{14}H_{12}Cl_2N_2O_3$: C, 51.40; H, 3.70; N, 8.56. Found: C, 51.39; H, 3.68; N, 8.55.

(E)-4,5-dichloro-2-(2,5-dimethoxystyryl)pyridazin-3(2H)-one (3u). Yellow crystal (methylene chloride). mp 158–159°C. IR (KBr) 3068, 2974, 1664, 1594, 1506, 1300, 1228, 1046, 972, 896, 814, 742 cm^{-1}. ^{1}H NMR ($CDCl_3$); δ 3.80 (s, OCH_3), 3.85 (s, OCH_3), 6.83 (s, 2H), 7.02 (d, J = 1.93 Hz, 1H), 7.47 (d, J = 14.40 Hz, 1H), 7.86 (s, 1H), 8.23 (d, J = 14.38 Hz, 1H). ^{13}C NMR ($CDCl_3$); δ 55.80, 56.10, 112.20, 113.06, 114.83, 117.78, 124.10, 125.05, 134.29, 135.79, 135.90, 151.92, 153.63, 154.66. Anal. Calcd. for $C_{14}H_{12}Cl_2N_2O_3$: C, 51.40; H, 3.70; N, 8.56. Found: C, 51.38; H, 3.67; N, 8.53.

(E)-4,5-dichloro-2-(3,4-dimethoxystyryl)pyridazin-3(2H)-one (3v). Yellow crystal (methylene chloride). mp 163–164°C. IR (KBr) 3076, 2966, 1674, 1600, 1530, 1272, 1156, 1036, 958, 908, 814 cm^{-1}. ^{1}H NMR ($CDCl_3$); δ 3.90 (s, OCH_3), 3.93 (s, OCH_3), 6.84 (d, J = 7.97 Hz, 1H), 7.01 ~ 7.04 (m, 2H), 7.22 (d, J = 14.30 Hz, 1H), 7.85 (s, 1H), 8.01 (d, J = 14.28 Hz, 1H). ^{13}C NMR ($CDCl_3$); δ 55.94, 55.97, 109.01, 111.27, 120.81, 122.20, 122.48, 127.41, 134.25, 135.74, 135.90, 149.26, 149.67, 154.59. Anal. Calcd. for $C_{14}H_{12}Cl_2N_2O_3$: C, 51.40; H, 3.70; N, 8.56. Found: C, 51.39; H, 3.68; N, 8.55.

(E)-4,5-dichloro-2-(2,6-dimethoxystyryl)pyridazin-3(2H)-one (3w). Light yellow crystal (methylene chloride). mp 190°C. IR (KBr) 3060, 2964, 1660, 1590, 1480, 1258, 1136, 1106, 962, 776, 720 cm^{-1}. ^{1}H NMR ($CDCl_3$); δ 3.90 (s, 2OCH_3), 6.56 (d, J = 8.39 Hz, 2H), 7.19 (t, J = 8.37 Hz, 1H), 7.66 (d, J = 14.42 Hz, 1H), 7.86 (s, 1H), 8.63 (d, J = 14.42 Hz, 1H). ^{13}C NMR ($CDCl_3$); δ 55.84, 103.75, 111.99, 113.20, 126.91, 12916, 134.06, 135.53, 135.62, 154.73, 158.81. Anal. Calcd. for $C_{14}H_{12}Cl_2N_2O_3$: C, 51.40; H, 3.70; N, 8.56. Found: C, 51.37; H, 3.66; N, 8.54.

(E)-4,5-dichloro-2-(3,4,5-trimethoxystyryl)pyridazin-3(2H)-one (3x). Yellow crystal (methylene chloride). mp 149–150°C. IR (KBr) 3120, 2962, 1678, 1590, 1516, 1460, 1428, 1360, 1300, 1246, 1136, 1014, 952, 900 cm^{-1}. ^{1}H NMR ($CDCl_3$); δ 3.87 (s, OCH_3), 3.90 (s, 2OCH_3), 6.71 (s, 2H), 7.22 (d, J = 14.28 Hz, 1H), 7.88 (s, 1H), 8.04 (d, J = 14.26 Hz, 1H). ^{13}C NMR ($CDCl_3$); δ 56.22, 60.97, 104.18, 122.32, 123.55, 130.12, 134.46, 135.95, 136.11, 138.69, 153.52, 154.68. Anal. Calcd. for $C_{15}H_{14}Cl_2N_2O_4$: C, 50.44; H, 3.95; N, 7.84. Found: C, 50.43; H, 3.93; N, 7.82.

(E)-4,5-dichloro-2-(2,4,6-trimethoxystyryl)pyridazin-3(2H)-one (3y). Orange crystal (methylene chloride). mp 209–210°C. IR (KBr) 3058, 2950, 1650, 1600, 1580, 1458, 1334, 1232, 1196, 1120, 956 cm^{-1}. ^{1}H NMR ($CDCl_3$); δ 3.84 (s, OCH_3), 3.90 (s, 2OCH_3), 6.16 (s, 2H), 7.62 (d, J = 14.37 Hz, 1H), 7.88 (s, 1H), 8.51 (d, J = 14.37 Hz, 1H). ^{13}C NMR ($CDCl_3$); δ 55.36, 55.80, 90.62, 105.36, 113.45, 124.96, 133.86, 135.30, 135.45, 154.70, 159.78, 161.20. Anal. Calcd. for $C_{15}H_{14}Cl_2N_2O_4$: C, 50.44; H, 3.95; N, 7.84. Found: C, 50.41; H, 3.93; N, 7.83.

δ 3.89 (s, 2 OCH_3), 3.92 (s, OCH_3), 6.53 (s, 1H), 6.99 (d, J = 2.66 Hz, 1H), 7.47 (d, J = 14.38 Hz, 1H), 7.87 (s, 1H), 8.14 (d, J = 14.37 Hz, 1H). ^{13}C NMR ($CDCl_3$); δ 56.10, 56.45, 56.61, 97.40, 110.86, 115.04, 117.73, 123.03, 134.09, 135.59, 135.75, 143.38, 150.41, 152.41, 152.52, 154.64. Anal. Calcd. for $C_{15}H_{14}Cl_2N_2O_4$: C, 50.44; H, 3.95; N, 7.84. Found: C, 50.40; H, 3.93; N, 7.84.

(E)-4,5-dichloro-2-(2,3,4-trimethoxystyryl)pyridazin-3(2H)-one (3aa). Yellow crystal (methylene chloride). mp 127–128°C. IR (KBr) 3106, 2964, 1670, 1598, 1500, 1472, 1420, 1306, 1114, 1100, 970, 896 cm^{-1}. ^{1}H NMR ($CDCl_3$); δ 3.89 (s, 2 OCH_3), 3.93 (s, OCH_3), 6.69 (d, J = 8.77 Hz, 1H), 7.22 (d, J = 8.74 Hz, 1H), 7.426 (d, J = 14.43 Hz, 1H), 7.88 (s, 1H), 8.14 (d, J = 14.39 Hz, 1H). ^{13}C NMR ($CDCl_3$); δ 56.06, 60.88, 61.12, 107.76, 117.54, 121.48, 122.12, 123.66, 134.19, 135.73, 135.85, 142.51, 152.25, 154.07, 154.66. Anal. Calcd. for $C_{15}H_{14}Cl_2N_2O_4$: C, 50.44; H, 3.95; N, 7.84. Found: C, 50.43; H, 3.94; N, 7.85.

Absorption spectra, fluorescence spectra and quantum yield. UV spectra were measured on a Shimadzu PC-2401 double beam spectrophotometer. Absorption spectra were collected from sample solution prepared under atmosphere without degassing or inert gas bubbling. The concentration of the sample solution is 1.0×10^{-4} *M*. ^{b}(M^{-1} cm^{-1}).

Fluorescence spectra were recorded on a PerkinElmer LS50B spectrofluorometer at room temperature. Quantum yield of the emission is evaluated in acetonitrile at 25°C, the quantum yield values are that relative to 9,10-diphenylanthrancene (1.00×10^{-4} *M*) in acetonitrile (from 352 nm extraction, Φ = 0.95).

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Synthesis of 2,4,5-Triaryl-5*H*-chromeno[4,3-*b*]pyridines under Microwave Radiation

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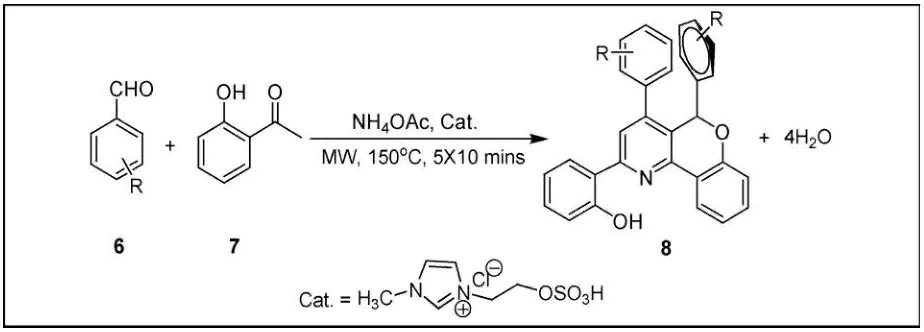

2,4,5-Triaryl-5*H*-chromeno[4,3-*b*]pyridines were synthesized from a three-component cascade reaction of 2′-hydroxyacetophenone, aromatic aldehyde, and ammonium acetate catalyzed by 2-1′-methylimidazolium-3-yl-1-ethyl sulfate under microwave irradiation. Nine new bonds and two new rings were formed in one-pot.

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INTRODUCTION

The synthesis of new heterocyclic compounds has been a subject of great interest due to their wide applicability. Among a large variety of heterocyclic compounds, heterocycles containing 5*H*-chromeno[4,3-*b*]pyridine are of interest because they show some important biological activities such as analgesic, anti-inflammation, and antibacterial [1,2]. Accordingly, the development of efficient synthetic strategies for the construction of this molecular architecture is of considerable importance from the standpoint of the material and organic chemistry.

By far, only two types of approach for obtaining 5*H*-chromeno[4,3-*b*]pyridines have been reported due to its complex structure. One was mainly based on the multistep intramolecular oxa- or diaza-Diels-Alder cycloadditions [1] with some shortcomings, such as low yields, high reaction temperature (180–200°C), long reaction time (48h) [3c], and requirement of toxic solvents. Moreover, unavailable starting material such as benzylidene-3-chromanone-4 (**1**, Fig. 1) [3a] or neutral 2-azadienes (**2**, Fig. 1) [3b] or 2-[2-(prop-2-ynyloxy)phenyl]-pyridine (**3**, Fig. 1) [3c] were required. In another method [4], it is the product of the primary 1,4-addition followed by the pyrone ring-opening, attacking of the NH_2 group to the carbonyl bound with the aromatic cycle and ring-closure involving the phenolic hydroxyl and CHO group (Fig. 2).

However, at least, two rings of product derived from starting materials in these methods. There were few of report about the synthesis of poly aryl-substituted 5*H*-chromeno[4,3-*b*]pyridines. To the best of our knowledge, aryl can improve the oil–water partition coefficient of drug, which serve as an important impact factor on the absorption and duration of drug *in vivo*, and it can also lengthen the conjugated system to improve the rigidity and luminescence potency of molecules. So, it is important to develop new efficient method to prepare poly aryl-substituted 5*H*-chromeno[4,3-*b*]pyridines.

The synthetic route used for the preparation of the title compound (**8**) *via* the one-pot, three-component reaction of aromatic aldehyde (**6**), 2′-hydroxyacetophenone (**7**), and ammonium acetate (1:1:5) under microwave-radiation is shown in Scheme 1. The new compound, 2-1′-methylimidazolium-3-yl-1-ethyl sulfate, was

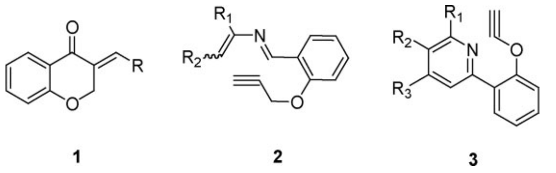


Figure 1. Three previous starting materials of 5*H*-chromeno[4,3-*b*] pyridines.

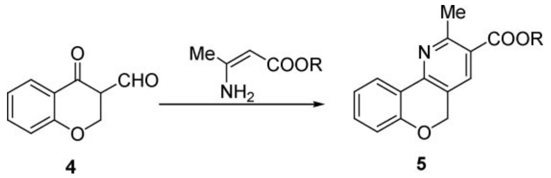


Figure 2. A previous method to construct 5*H*-chromeno[4,3-*b*] pyridines.

synthesized and used as catalyst to improve the selectivity of the reaction. Upto nine new bonds were formed with water as the only one by-product in this transformation. Only one benzene ring in the new 5*H*-chromeno[4,3-*b*]pyridine framework is derived from starting material.

RESULTS AND DISCUSSION

Initially, different reaction conditions were systematically tested based on the reaction of 4-cyanobenzaldehyde, 2′-hydroxyacetophenone, and ammonium acetate (1:1:5) (Table 1). It indicated that only the corresponding chalcone was detected when the amount of 2-1′-methylimidazolium-3-yl-1-ethyl sulfate was less than 3.2 mmol, which showed the importance of catalyst amount in controlling the selectivity of this multicomponent reaction. In addition, glycol is necessary to prevent the instantaneous partial charring of reactant caused by the catalyst. However, when the amount of glycol was up to 2 mL, the yield decreased due to the dilution of catalyst.

Under the optimal conditions, the reaction of a variety of aromatic aldehydes with 2′-hydroxyacetophenone and ammonium acetate was investigated. The product **8** was obtained with the yields ranging from 50 to 81% (Table 2). As can be seen from the results, the electronic nature and steric effect of substituted group in aromatic aldehyde influenced the yield. Substrates with electron-donated groups can enhance the yields.

The X-ray structure of **8h** [5] (Table 2, entry 8) was shown in Figure 3. The framework has a long conjugated system with many modifiable positions, which indicates its potential application in new drug discover or molecular electronics.

A reasonable mechanism for the formation of the products **8** was proposed (Scheme 2). The reaction proceeds *via* a simple and normal procedure: the tandem Aldol condensation-Michael addition-Aldol condensation-nucleophilic addition (Adn), and finally, the elimination (*E*)-cyclication.

In summary, we have developed a novel, simple, and efficient method to synthesize 2,4,5-triaryl-5*H*-chromeno[4,3-*b*]pyridines under microwave radiation. Besides the advantages that all the reactants were added at the beginning and the same reaction conditions were maintained throughout, the features of this process include as follows: (1) the starting materials are available; (2) the reaction has good atom-economy and environmental friendliness: nine new bonds (three C—N bonds, one C—O bond, three C—C single bonds, two C—C double bonds) and two new rings were formed in one-pot with water as the only one by-product during the whole process. Indeed, the present protocol provides a straightforward and effective pathway to afford triaryl-5*H*-chromeno[4,3-*b*]pyridines.

EXPERIMENTAL

Microwave radiation was carried out with a microwave oven Emrys^{TM} Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in the open capillaries and were uncorrected. IR spectra were obtained on a Bruker FT-IR spectrometer. ^{1}H NMR spectra were recorded at

Scheme 1. One-pot synthesis of 2,4,5-triaryl-5*H*-chromeno[4,3-*b*]pyridines.

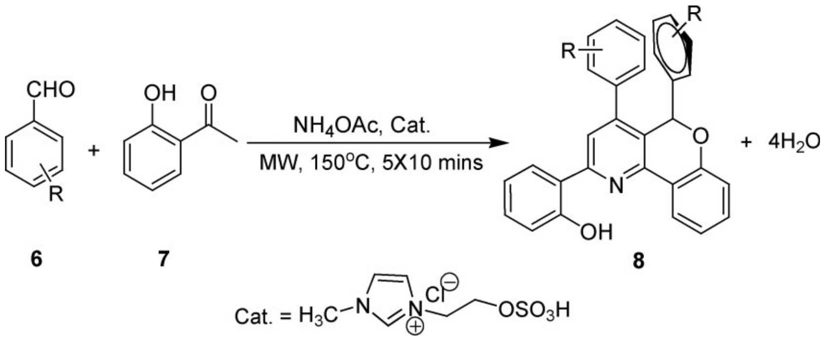


Table 1

Testing of different reaction conditions based on the model reaction.[a]

Entry	Amount of catalyst (mmol)	Amount of glycol (mL)	Time (min)	Yield (%)[b]
1	0.0	1.0	50	NP[c]
2	0.8	1.0	50	NP
3	1.6	1.0	50	NP
4	3.2	1.0	50	5
5	6.4	1.0	50	30
6	8.0	1.0	50	60
7	12.0	1.0	50	58
8	8.0	0.0	50	charring
9	8.0	0.5	50	charring
10	8.0	2.0	50	35
11	8.0	1.0	10	NP
12	8.0	1.0	20	NP
13	8.0	1.0	30	5
14	8.0	1.0	40	25
15	8.0	1.0	60	58

[a] Reaction conditions: 2.0 mmol of 4-cyanobenzaldehyde, 2.0 mmol of 2′-hydroxyacetophenone, 5 equiv. of ammonium acetate, $T = 150°C$, $P = 200$ W.

[b] Isolated yield.

[c] No desired products.

400 MHz on a Bruker DPX 400 or AV400 spectrometer using TMS as an internal standard and DMSO-d_6 as solvent. ^{13}C NMR spectra were recorded at 100.6 MHz. Mass was determined by using a TOF-MS high-resolution mass spectrometer. Elemental analyses were performed on a Perkin-Elmer-2400 elemental analyzer. Thin layer chromatography analysis was carried out on aluminium sheets of silica gel GF_{254}. All reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. Organic solvents were dried and/or distilled prior to use. The X-ray structure determination for complex **8h** was given by Smartapex Bruke diffractometer.

Table 2

Synthesis of compounds **8** under microwave radiation.[a]

Entry	R	Product	Time (min)	Yield (%)[b]
1	H	8a	50	65
2	4-CH_3	8b	50	68
3	4-OCH_3	8c	50	71
4	4-Br	8d	50	52
5	2,3-OCH_3	8e	50	68
6	4-CN	8f	50	49
7	4-Cl	8g	50	42
8	2-OCH_3	8h	50	60
9	3,4,5-OCH_3	8i	50	70
10	2-Cl	8j	50	45
11	3-Br	8k	50	63
12	2,4-Cl	8l	50	40
13	3,4-(OCH_2O)	8m	50	56
14	3-NO_2	8n	50	55

[a] Reaction conditions: 2.0 mmol aromatic aldehyde, 2.0 mmol 2′-hydroxyacetophenone, 5 equiv. of ammonium acetate, and 8.0 mmol of catalyst in 1 mL of glycol, $T = 150°C$, $P = 200$ W.

[b] Isolated yield.

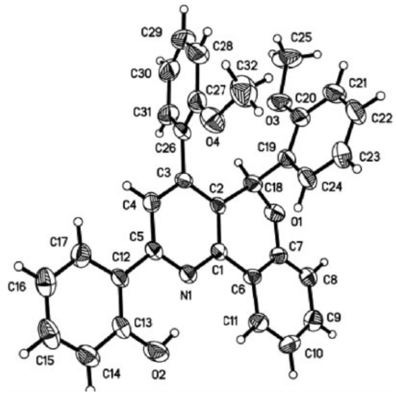


Figure 3. Single-crystal X-ray structure of compound **8h**.

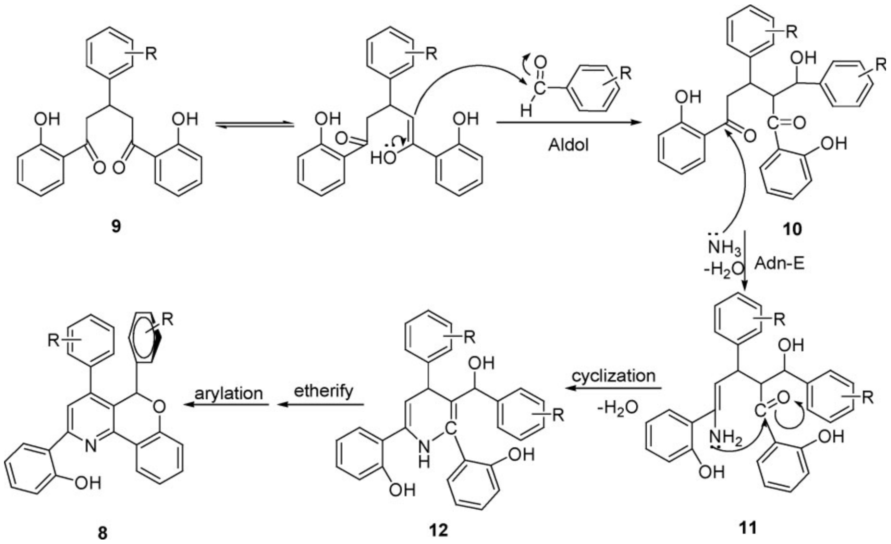
General procedure for the preparation of 2-1′-methylimidazolium-3-yl-1-ethyl sulfate. 1-Methylimidazole (0.3 mol) and chloroethanol (0.3 mol) were added in a flask containing 10 mL of $CHCl_3$, the mixture was refluxed for 8 h, removed $CHCl_3$ under vacuum, extracted the unreacted 1-methylimidazole with ether to give 1-methyl-3-(2-hydroxylethyl)imidazolium chloride, then chlorosulfonic acid was added dropwise at 0–5°C, when the mixture became solid, suitable single crystal was obtained after 3 days by recrystallized with DMF. Its structure was further confirmed by X-ray crystallographic analysis (Fig. 4). This solid inner salt reacted with chlorosulfonic acid continuously until it just became a ropy liquid to afford acidic ionic liquid 2-1′-methylimidazolium-3-yl-1-ethyl sulfate.

Procedure for the preparation of triaryl-5*H*-chromeno [4,3-*b*]pyridines. 2 mmol of aromatic aldehyde **1**, 2′-hydroxyacetophenone (**2**, 2 mmol), and ammonium acetate (5 equiv.) were added into a one-necked 50 mL round bottom flask containing 1 mL of glycol and 2 mL of 1-methyl-3-2′-hydroxylethylimidazolium chloride, the mixture was then radiated under microwave in a Emrys^{TM} Creator (Sweden) for 50 min (5 × 10 min). When the reaction was finished (monitored by TLC), distilled water was poured into, the deposition was then filtered, and recrystallized with DMF to give **8**.

2-(4,5-Diphenyl-5*H*-chromeno[4,3-*b*]pyridin-2-yl)phenol (8a). This compound was obtained as yellow crystal (DMF), mp 194.1–195.3°C; ir (potassium bromide): 3310, 3030, 1600, 1580, 1031; ^1H NMR: δ 13.80 (s, 1H, OH), 8.20 (d, 1H, J = 8.4 Hz, ArH), 8.14 (s, 1H, ArH), 8.01 (d, 1H, J = 8.0 Hz, ArH), 7.46 (m, 3H, ArH), 7.36 (m, 4H, ArH), 7.24 (m, 3H, ArH), 7.11 (t, 1H, ArH), 7.04 (t, 2H, ArH), 7.02 (d, 1H, J = 9.6 Hz, ArH), 6.97 (t, 2H, ArH), 6.50 (s, 1H, CH); ^{13}C NMR: δ 161.5, 159.2, 156.5, 153.2, 148.0, 141.2, 139.2, 135.0, 134.5, 131.5, 131.4, 131.3, 131.2, 131.0, 130.8, 130.3, 126.4, 125.5, 125.3, 124.5, 123.4, 122.9, 122.8, 120.9, 120.5; Anal. Calcd. for $C_{30}H_{21}NO_2$: C, 84.29; H, 4.95; N, 3.28. Found: C, 84.30; H, 4.96; N, 3.26; hrms: m/z calcd. for $C_{30}H_{21}NO_2$, 427.1572; found, 427.1554.

2-(4,5-Bis(4-methylphenyl)-5*H*-chromeno[4,3-*b*]pyridin-2-yl) phenol (8b). This compound was obtained as yellow crystal (DMF), mp 207.7–208.7°C; ir (potassium bromide): 3310, 3030, 2985, 1600, 1550, 1030; ^1H NMR: δ 14.70 (s, 1H, OH), 8.11 (dd, 1H, J_1 = 1.6 Hz, J_2 = 7.6 Hz, ArH), 7.85 (dd, 1H,

Scheme 2. A possible mechanism for the formation of **8**.



J_1 = 1.6 Hz, J_2 = 7.6 Hz, ArH), 7.80 (s, 1H, ArH), 7.33–7.37 (t, 1H, ArH), 7.24–7.28 (t, 1H, ArH), 7.18 (d, 2H, J = 7.6 Hz, ArH), 7.11–7.04 (m, 4H, ArH), 7.02 (s, 4H, ArH), 6.91–6.95 (t, 1H, ArH), 6.88–6.85 (dd, 1H, J_1 = 1.6 Hz, J_2 = 7.6 Hz, ArH), 6.38 (s, 1H, CH), 2.39 (s, 3H, CH_3), 2.25 (s, 3H, CH_3); ^{13}C NMR: δ 159.9, 156.9, 154.2, 149.8, 145.9, 138.7, 138.2, 136.1, 134.1, 131.9, 131.6, 129.2, 129.1, 128.2, 127.9, 126.3, 124.2, 123.3, 22.2, 122.1, 119.2, 118.9, 118.8, 118.5, 118.1, 21.1, 21.0; Anal. Calcd. for $C_{32}H_{25}NO_2$: C, 83.26; H, 6.77; N, 3.03. Found: C, 83.36; H, 6.76; N, 3.01; hrms: m/z calcd. for $C_{32}H_{25}NO_2$, 455.1885; found, 455.1871.

2-(4,5-Bis(4-methoxyphenyl)-5*H*-chromeno[4,3-*b*]pyridin-2-yl)phenol (8c). This compound was obtained as brown crystal (DMF), mp 191.2–192.4°C; ir (potassium bromide): 3310, 3030, 2985, 1610, 1540, 1020; ^{1}H NMR: δ 13.91 (s, 1H, OH), 8.18 (dd, 1H, J_1 = 1.6 Hz, J_2 = 7.6 Hz, ArH), 8.09 (s, 1H, ArH), 8.00 (dd, 1H, J_1 = 1.6 Hz, J_2 = 7.6 Hz, ArH), 7.39–7.32 (m, 2H, ArH), 7.26 (d, 2H, J = 7.6 Hz, ArH), 7.12–7.17 (t, 1H, ArH), 6.90–7.07 (m, 7H, ArH), 6.79–6.81 (d, 2H, J = 7.6 Hz, ArH), 6.45 (s, 1H, CH), 3.78 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3); ^{13}C NMR: δ 160.0, 159.5, 156.9, 154.1, 149.4, 145.9, 132.0, 131.6, 131.3, 129.7, 129.4, 129.3, 126.3, 124.2, 123.5, 122.3, 122.1, 119.3, 118.9, 118.8, 118.5, 118.1, 114.0, 113.8, 55.3, 55.1; *Anal.* Calcd. for $C_{32}H_{25}NO_4$: C, 78.83; H, 5.17; N, 2.87. Found: C, 78.72; H, 5.18; N, 2.89; hrms: m/z calcd. for $C_{32}H_{25}NO_4$, 487.1784; found, 487.1771.

2-(4,5-Bis(4-bromophenyl)-5*H*-chromeno[4,3-*b*]pyridin-2-yl) phenol (8d). This compound was obtained as yellow crystal (DMF), mp 221.5–222.5°C; ir (potassium bromide): 3310, 3030, 2980, 1600, 1550, 1010; ^{1}H NMR: δ 13.65 (s, 1H, OH), 8.21 (d, 1H, J = 9.6 Hz, ArH), 8.15 (s, 1H, ArH), 8.06 (d, 1H, J = 9.6 Hz, ArH), 7.67 (d, 2H, J = 8.0 Hz, ArH), 7.44 (d, 2H, J = 9.6 Hz, ArH), 7.33–7.41 (m, 2H, ArH), 7.29 (d, 2H, J = 8.0 Hz, ArH), 7.14–7.21 (t, 1H, ArH), 6.94–7.09 (m, 5H, ArH), 6.47 (s, 1H, CH); ^{13}C NMR: δ 155.2, 152.8, 149.1, 143.8, 141.4, 138.0, 135.0, 133.1, 131.0, 127.7, 127.3, 127.2, 127.0, 125.1, 124.9, 121.7, 119.6, 118.7, 118.3, 118.0, 117.6, 117.0, 114.4, 114.2, 113.9, 113.8, 113.4; Anal. Calcd. for $C_{30}H_{19}Br_2NO_2$: C, 61.56; H, 3.27; N, 2.39. Found: C, 61.66; H, 3.26; N, 2.37; hrms: m/z calcd. for $C_{30}H_{19}Br_2NO_2$, 584.9762; found, 584.9760.

2-(4,5-Bis(2,3-dimethoxyphenyl)-5*H*-chromeno[4,3-*b*]pyridin-2-yl)phenol (8e). This compound was obtained as yellow crystal (DMF), mp 223.7–225.2°C; ir (potassium bromide): 3310, 3030, 2986, 1600, 1560, 1030; ^{1}H NMR: δ 13.95 (s, 1H, OH), 8.23 (d, 1H, J = 8.0 Hz, ArH), 8.15 (s, 1H, ArH), 8.00 (d, 1H, J = 8.0 Hz, ArH), 7.33–7.41 (m, 2H, ArH), 7.13–7.18 (t, 1H, ArH), 6.10–7.08 (m, 6H, ArH), 6.84 (s, 1H, ArH), 6.77 (d, 1H, J = 8.0 Hz, ArH), 6.46 (d, 1H, J = 8.0 Hz, ArH), 6.44 (s, 1H, CH), 3.79 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3); ^{13}C NMR: δ 159.0, 155.3, 154.3, 153.0, 152.9, 147.0, 145.5, 145.0, 132.8, 132.3, 131.8, 131.0, 128.3, 124.8, 123.9, 122.9, 121.9, 121.6, 120.9, 119.9, 119.5, 118.5, 118.0, 61.0, 60.5, 56.5, 56.0; *Anal.* Calcd. for $C_{34}H_{29}NO_6$: C, 74.57; H, 5.34; N, 2.56. Found: C, 73.85; H, 6.36; N, 2.51; hrms: *m/z* calcd. for $C_{34}H_{29}NO_6$, 547.1995; found, 547.1975.

2-(4,5-Bis(4-cyanophenyl)-5*H*-chromeno[4,3-*b*]pyridin-2-yl) phenol (8f). This compound was obtained as yellow crystal (DMF), mp > 300°C; ir (potassium bromide): 3320, 3030, 2980, 2250, 1600, 1560, 1030; ^{1}H NMR: δ 13.50 (s, 1H, OH),

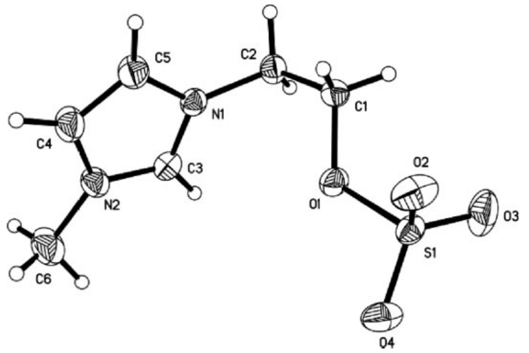


Figure 4. Single-crystal X-ray structure of 2-1′-methylimidazolium-3-yl-1-ethyl sulfate.

8.21 (d, 1H, $J = 8.0$ Hz, ArH), 8.19 (s, 1H, ArH), 8.03 (d, 1H, $J = 7.6$ Hz, ArH), 7.94 (d, 2H, $J = 8.0$ Hz, ArH), 7.71 (d, 2H, $J = 8.0$ Hz, ArH), 7.54 (d, 2H, $J = 8.0$ Hz, ArH), 7.37–7.41 (t, 2H, ArH), 7.30 (d, 2H, $J = 8.0$ Hz, ArH), 7.17–7.21 (t, 1H, ArH), 6.96–7.04 (t, 3H, ArH), 6.57 (s, 1H, CH); ^{13}C NMR: δ 159.2, 156.8, 154.0, 149.5, 148.3, 148.0, 147.9, 147.9, 145.7, 133.0, 132.9, 132.3, 130.3, 128.5, 124.0, 123.3, 123.0, 122.9, 122.2, 122.1, 121.9, 119.9, 119.8, 118.8, 118.2, 109.4, 109.0, 108.4, 101.9; *Anal.* Calcd. for $C_{32}H_{19}N_3O_2$: C, 80.49; H, 4.01; N, 8.80. Found: C, 80.59; H, 4.00; N, 8.78; hrms: *m*/*z* calcd. for $C_{32}H_{19}N_3O_2$, 477.1477; found, 477.1455.

2-(4,5-Bis(4-chlorophenyl)-5*H*-chromeno[4,3-*b*]pyridin-2-yl) phenol (8g). This compound was obtained as yellow crystal (DMF), mp 208.3–209.4°C; ir (potassium bromide): 3350, 3030, 2980, 1640, 1580, 1050; ^{1}H NMR: δ 13.62 (s, 1H, OH), 8.20 (d, 1H, $J = 8.0$ Hz, ArH), 8.13 (s, 1H, ArH), 8.01 (d, 1H, $J = 8.0$ Hz, ArH), 7.52 (d, 2H, $J = 8.0$ Hz, ArH), 7.29–7.35 (m, 6H, ArH), 7.11–7.20 (m, 3H, ArH), 6.94–7.04 (m, 3H, ArH), 6.48 (s, 1H, CH); ^{13}C NMR: δ 159.1, 157.0, 153.9, 148.9, 145.9, 137.9, 135.8, 134.2, 134.0, 133.0, 132.8, 130.9, 130.0, 129.5, 129.0, 128.6, 124.0, 123.2, 123.0, 121.9, 121.0, 119.0, 118.9, 118.3; *Anal.* Calcd. for $C_{30}H_{19}Cl_2NO_2$: C, 72.59; H, 3.86; N, 2.82. Found: C, 72.65; H, 3.85; N, 2.81; hrms: *m*/*z* calcd. for $C_{30}H_{19}Cl_2NO_2$, 495.0793; found, 495.0775.

2-(4,5-Bis(2-methoxyphenyl)-5*H*-chromeno[4,3-*b*]pyridin-2-yl)phenol (8h). This compound was obtained as yellow crystal (DMF), mp 244.5–245.5°C; ir (potassium bromide): 3310, 3030, 2985, 1600, 1550, 1050; ^{1}H NMR: δ 14.70 (s, 1H, OH), 8.11 (dd, $J_1 = 1.2$ Hz, $J_2 = 1.6$ Hz, 1H, ArH), 7.81 (dd, $J_1 = 1.6$ Hz, $J_2 = 1.6$ Hz, 1H, ArH), 7.81 (s, 1H, ArH), 7.56 (t, 1H, ArH), 7.31–7.33 (t, 1H, ArH), 7.08–7.18 (m, 6H, ArH), 6.78–6.98 (m, 4H, ArH), 6.75–6.79 (m, 2H, ArH), 6.39 (s, 1H, CH), 3.88 (s, 3H, OCH$_3$), 3.74 (s, 3H, OCH$_3$); ^{13}C NMR: δ 160.1, 159.7, 159.3, 156.9, 154.1, 149.8, 145.9, 132.9, 132.1, 131.1, 130.3, 129.6, 129.1, 128.0, 124.1, 123.6, 123.0, 122.5, 121.0, 119.9, 119.9, 118.5, 118.8, 114.8, 114.7, 60.5, 56.0; Anal. Calcd. for $C_{32}H_{25}NO_4$: C, 78.83; H, 5.17; N, 2.87. Found: C, 78.91; H, 5.16; N, 2.85; hrms: m/z calcd. for $C_{32}H_{25}NO_4$, 487.1784; found, 487.1768.

2-(4,5-Bis(3,4,5-trimethoxyphenyl)-5*H*-chromeno[4,3-*b*] pyridin-2-yl)phenol (8i). This compound was obtained as brown crystal (DMF), mp 236.1–237.9°C; ir (potassium bromide): 3300, 3030, 2980, 1600, 1550, 1050; ^{1}H NMR: δ 13.95 (s, 1H, OH), 8.22 (d, 1H, $J = 8.0$ Hz, ArH), 8.17 (s, 1H, ArH), 8.02 (d, 1H, $J = 8.0$ Hz, ArH), 7.53–7.59 (t, 1H, ArH), 7.34–7.44 (m, 1H, ArH), 6.94–7.22 (m, 4H, ArH), 6.60 (s, 1H, CH), 6.46 (d, 3H, $J = 11.2$ Hz, ArH), 3.56–3.61 (m, 18H, OCH$_3$); ^{13}C NMR: δ 159.4, 156.9, 154.4, 153.9, 150.1, 147.6, 145.6, 138.2, 135.2, 132.8, 132.3, 131.6, 128.4, 127.7, 123.5, 123.6, 122.3, 121.0, 120.0, 119.6, 119.6, 118.6, 118.2, 106.6, 106.5, 106.1, 60.6, 60.5, 60.3, 56.9, 56.4, 56.0; *Anal.* Calcd. for $C_{36}H_{33}NO_4$: C, 71.16; H, 5.47; N, 2.31. Found: C, 71.26; H, 5.46; N, 2.29; hrms: *m*/*z* calcd. for $C_{36}H_{33}NO_4$, 607.2206; found, 607.2217.

2-(4,5-Bis(2-chlorophenyl)-5*H*-chromeno[4,3-*b*]pyridin-2-yl) phenol (8j). This compound was obtained as yellow crystal (DMF), mp 196.9–197.7°C; ir (potassium bromide): 3350, 3010, 2990, 1630, 1580, 1010; ^{1}H NMR: δ 13.62 (s, 1H, OH), 8.16–8.21 (t, 1H, ArH), 8.13 (s, 1H, ArH), 8.09 (d, 1H, $J = 8.0$ Hz, ArH), 7.67–7.75 (m, 1H, ArH), 6.81–7.49 (m, 12H, ArH), 6.60 (d, 1H, $J = 9.6$ Hz, ArH), 6.58 (s, 1H, CH); ^{13}C NMR: δ 159.21, 157.7, 153.8, 153.7, 147.2, 145.6, 135.2, 135.1, 133.4, 133.1, 132.4, 131.3, 131.2, 131.1, 131.1, 130.7, 130.3, 130.2, 130.0, 128.6, 127.9, 123.5, 119.7, 118.2; *Anal.* Calcd. for $C_{30}H_{19}Cl_2NO_2$: C, 72.59; H, 3.86; N, 2.82. Found: C, 72.66; H, 3.87; N, 2.80; hrms: *m*/*z* calcd. for $C_{30}H_{19}Cl_2NO_2$, 495.0793; found, 495.0769.

2-(4,5-Bis(3-bromophenyl)-5*H*-chromeno[4,3-*b*]pyridin-2-yl) phenol (8k). This compound was obtained as brown crystal (DMF), mp 187.1–188.6°C; ir (potassium bromide): 3320, 3020, 2980, 1620, 1580, 1020; ^{1}H NMR: δ 14.70 (s, 1H, OH), 8.10 (dd, 1H, $J_1 = 1.6$ Hz, $J_2 = 7.6$ Hz, ArH), 7.85 (dd, 1H, $J_1 = 1.6$ Hz, $J_2 = 7.6$ Hz, ArH), 7.79 (s, 1H, ArH), 7.33–7.37 (t, 1H, ArH), 7.23–7.27 (t, 1H, ArH), 7.18 (d, 2H, $J = 7.6$ Hz, ArH), 7.01–7.11 (m, 8H, ArH), 6.90–6.94 (t, 1H, ArH), 6.82 (dd, 1H, $J_1 = 1.6$ Hz, $J_2 = 7.6$ Hz, ArH), 6.38 (s, 1H, CH); ^{13}C NMR: δ 159.2, 157.0, 154.2, 149.9, 145.7, 139.0, 137.0, 132.2, 129.7, 129.3, 129.1, 129.0, 129.0, 128.8, 128.5, 128.1, 124.1, 123.2, 123.0, 122.1, 121.1, 121.1, 119.8, 119.7, 118.6, 118.2; *Anal.* Calcd. for $C_{30}H_{19}Br_2NO_2$: C, 61.56; H, 3.27; N, 2.39. Found: C, 61.62; H, 3.26; N, 2.38; hrms: *m*/*z* calcd. for $C_{30}H_{19}Br_2NO_2$, 584.9762; found, 584.9753.

2-(4,5-Bis(2,4-dichlorophenyl)-5*H*-chromeno[4,3-*b*]pyridin-2-yl)phenol (8l). This compound was obtained as yellow crystal (DMF), mp 196.4–197.1°C; ir (potassium bromide): 3310, 3030, 2998, 1600, 1540, 1020; ^{1}H NMR: δ 13.65 (s, 1H, OH), 8.21 (d, 1H, $J = 8.0$ Hz, ArH), 8.15 (s, 1H, ArH), 8.02 (d, 1H, $J = 8.0$ Hz, ArH), 7.54 (d, 2H, $J = 8.0$ Hz, ArH), 7.29–7.41 (m, 6H, ArH), 7.11–7.21 (m, 3H, ArH), 6.94–7.04 (m, 3H, ArH), 6.50 (s, 1H, CH); ^{13}C NMR: δ 160.0, 159.5, 156.9, 154.1, 149.4, 145.9, 131.9, 131.6, 131.3, 129.7, 129.4, 129.3, 126.3, 124.2, 123.5, 122.3, 122.1, 119.3, 118.9, 118.2, 118.5, 118.1, 114.0, 113.7; *Anal.* Calcd. for $C_{30}H_{17}Cl_4NO_2$: C, 63.74; H, 3.03; N, 2.48. Found: C, 63.66; H, 3.04; N, 2.50; hrms: *m*/*z* calcd. for $C_{30}H_{17}Cl_4NO_2$, 564.9989; found, 564.9927.

2-(4-(Benzo[*d*][1,3]dioxol-5-yl)-5-(benzo[*d*][1,3]dioxol-6-yl)-5*H*-chromeno[4,3-*b*]pyridin-2-yl)phenol (8m). This compound was obtained as yellow crystal (DMF), mp 234.1–235.0°C; ir (potassium bromide): 3320, 3020, 2995, 1600, 1500, 1010; ^{1}H NMR: δ 13.85 (s, 1H, OH), 8.19 (d, 1H, $J = 8.0$ Hz, ArH), 8.09 (s, 1H, ArH), 7.81 (d, 1H, $J = 8.0$ Hz, ArH), 7.37 (t, 2H, ArH), 7.17 (t, 1H, ArH), 6.95–7.02 (m, 5H, ArH), 6.73–6.81 (m, 3H, ArH), 6.46 (d, 1H, $J = 8.0$ Hz, ArH), 6.43 (s, 1H, ArH), 6.09 (s, 2H, CH$_2$), 5.97 (s, 2H, CH$_2$); ^{13}C NMR: δ 159.2, 156.9, 154.0, 152.9, 149.3, 148.2, 148.0, 147.9, 133.9, 123.6, 122.1, 120.0, 118.9, 109.3, 109.0, 108.0; *Anal.* Calcd. for $C_{32}H_{21}NO_6$: C, 74.56; H, 4.11; N, 2.72. Found: C, 74.61; H, 4.10; N, 2.71; hrms: *m*/*z* calcd. for $C_{32}H_{21}NO_6$, 515.1369; found, 515.1360.

2-(4,5-Bis(3-nitrophenyl)-5*H*-chromeno[4,3-*b*]pyridin-2-yl) phenol (8n). This compound was obtained as yellow crystal (DMF), mp 186.2–197.7°C; ir (potassium bromide): 3350, 3010, 2995, 1600, 1530, 1040; ^{1}H NMR: δ 14.35 (s, 1H, OH), 8.50 (m, 1H, ArH), 8.25–8.35 (m, 3H, ArH), 8.17 (s, 1H, ArH), 8.00 (dd, 1H, $J_1 = 1.6$ Hz, $J_2 = 7.6$ Hz, ArH), 7.50–7.67 (m, 2H, ArH), 7.10–7.49 (m, 9H, ArH), 6.55 (s, 1H, CH); ^{13}C NMR: δ 155.3, 153.6, 148.8, 141.7, 135.8, 133.5, 129.3, 128.7, 128.1, 127.7, 125.5, 125.1, 121.8, 119.9, 119.3, 119.2, 118.5, 117.9, 116.7, 116.6, 114.5, 114.3, 114.0, 113.5; *Anal.* Calcd. for $C_{30}H_{19}N_3O_6$: C, 69.63; H, 3.70; N, 8.12. Found: C, 69.55; H, 3.71; N, 8.14; hrms: *m*/*z* calcd. for $C_{30}H_{19}N_3O_6$, 517.1274; found, 517.1360.

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[5] The single crystal growth was carried out in DMF at room temperature. X-ray crystallographic analysis was performed with a Smartapex Bruke diffractometer (graphite monochromator, MoKα radiation $\lambda = 0.71073$ Å). Crystal data for 8 h: Empirical formula $C_{32}H_{25}NO_4$, yellow, crystal dimension 0.16 × 0.10 × 0.08 mm, monoclinic, space group P2(1)/*n*, $a = 10.382$ (6) Å, $b = 15.694$ (9) Å, $c = 14.987$ (8) Å, $\alpha = 90.00°$, $\beta = 99.233$ (8)°, $\gamma = 90.00°$, $V = 2410$ (2) Å^3, Mr = 487.53, $Z = 7$, Dc = 1.344 Mg/m^3, $\lambda = 0.71073$ Å, μ (MoKα) = 0.088 mm^{-1}, F(000) = 1024, $S = 0.898$, $R_1 = 0.0558$, wR$_2$ = 0.0592. Crystallographic data for the structures of 8 h reported in this letter have been deposited with the Cambridge Crystallographic Date Centre as supplementary publication No. CCDC-655835.

New One-Step Synthesis of Pyrazolo[1,5-*a*]pyrimidine and Pyrazolo[1,5-*a*]quinazoline Derivatives via Multicomponent Reactions

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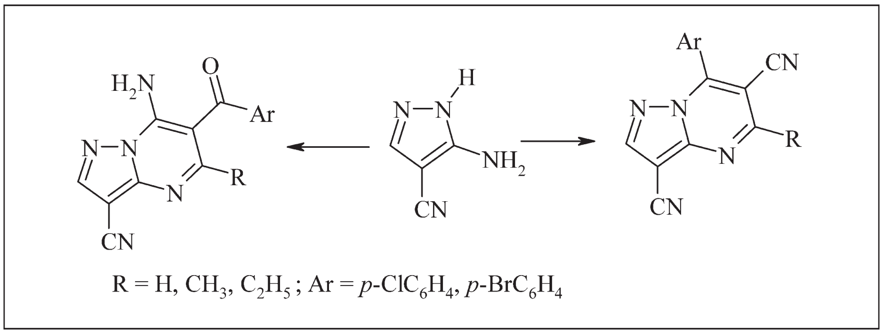

R = H, CH$_3$, C$_2$H$_5$; Ar = *p*-ClC$_6$H$_4$, *p*-BrC$_6$H$_4$

A series of pyrazolopyrimidine and pyrazoloquinozoline derivatives has been synthesized in one step by multicomponent reactions using, 5-aminopyrazole, *p*-substitutedbenzoylacetonitrile/dimedone and triethylorthoesters. pyrazolopyrimidine derivatives were also studied for their absorption and fluorescence maxima.

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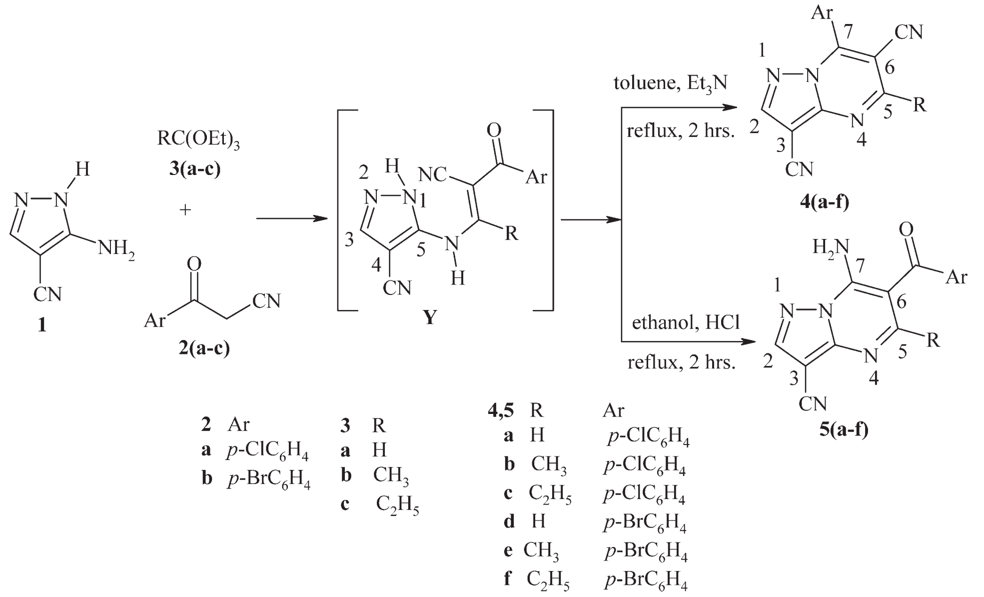
INTRODUCTION

Heterocyclic ring systems that containing the pyrazole ring fused to pyrimidine or quinazoline rings are interesting classes of compounds both chemically and biologically. For example, pyrazolopyrimidines display significant chemical properties [1–7]. In particular, pyrazolo[1,5-*a*]pyrimidines structural motif may be found in a large number of pharmaceutical agents with a diverse range of physiological activities, such as, antiepileptic agents [8], anxiolytics [9], antidepressants [10], agents for treatment of sleep disorders [11], and oncolytics [12,13]. Whereas, several naturally occurring and synthetic compounds containing the quinazoline derivatives exhibit a wide range of biological properties [14,15]. In recent years an increasing interest has been focused on synthesis of fluorescent compounds owing to their significant biological applications in the medicinal chemistry [16,17]. In particular, these compounds have important applications in the field of dyes [18] and are used in the security papers [19]. In literature the synthesis of pyrazolo[1,5-*a*]pyrimidines has been reported [20,21] by using Michael addition reaction of 5-aminopyrazoles with enol ether of reactive methylene compounds and triethylorthoesters. The title compounds could be synthesized in one pot in which the synthesis of enol ether is not required.

On the other hand, multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry. MCR strategies offer significant advantages over conventional linear type synthesis [22–24]. As a part of our continued interest [25–27] in the synthesis of novel heterocyclic compounds, we have reported the synthesis of pyrazolo[3,4-*b*]pyridines, pyrazolo[3,4-*b*]quinolines, pyrazolonaphthyridines and pyrazolopyridopyrimidines by Friedlander condensation of 5-aminopyrazole-4-carbaldehyde with various reactive methylene compounds and the synthesis of fused pyrimidines [28] by using 2-aminoheterocycles and cyclic β-formylesters in ammonium acetate at 120°C. We have also reported the study of fluorescence properties of benzo[*h*]quinolines and dipyrazolopyridines [29,30]. In our recent communications [31,32], we have reported the synthesis of chromenes, quinolines, and pyrazolo[3,4-*b*]pyridines by multicomponent reaction strategy. These literature reports and increasing importance of multicomponent reactions in organic chemistry encourage us to synthesize, pyrazolo[1,5-*a*]pyrimidine and pyrazolo[1,5-*a*] quinazoline derivatives using multicomponent reactions and study the photophysical properties of pyrazolopyrimidine derivatives.

Scheme 1



2	Ar
a	*p*-ClC$_6$H$_4$
b	*p*-BrC$_6$H$_4$

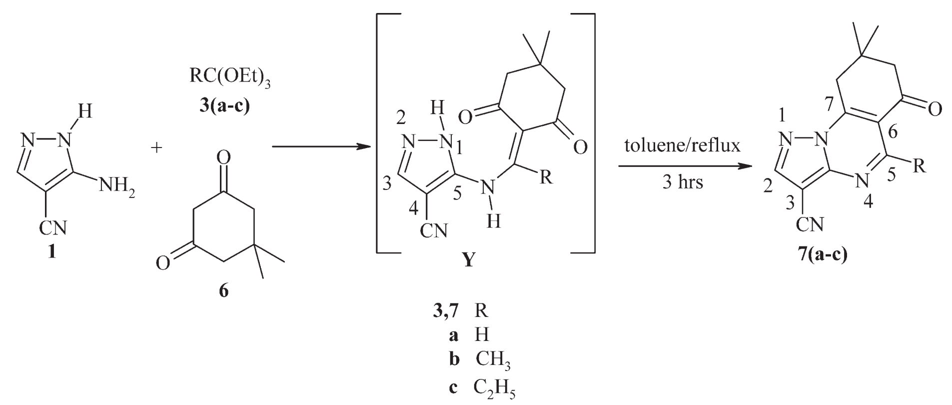
3	R
a	H
b	CH$_3$
c	C$_2$H$_5$

4,5	R	Ar
a	H	*p*-ClC$_6$H$_4$
b	CH$_3$	*p*-ClC$_6$H$_4$
c	C$_2$H$_5$	*p*-ClC$_6$H$_4$
d	H	*p*-BrC$_6$H$_4$
e	CH$_3$	*p*-BrC$_6$H$_4$
f	C$_2$H$_5$	*p*-BrC$_6$H$_4$

RESULTS AND DISCUSSION

The cyclocondensation of 5-amino-1*H*-pyrazole-4-carbonitrile **1**, *p*-substituted benzoylacetonitriles **2** and triethylorthoesters **3** by refluxing in toluene containing catalytic amount of triethylamine for 2 h, afforded compounds **4** in good yield. The structure of **4a** was confirmed by IR, ^{1}H-NMR, ^{13}C-NMR, mass spectroscopy and elemental analysis for example the IR spectrum of **4a** showed bands at 2237 cm^{-1} for CN stretching. The ^{1}H-NMR of compound **4a** showed a multiplets at δ 7.85–7.89 for four aromatic protons and the two singlets at δ 8.87 and δ 9.16 corresponding to C$_2$H and C$_5$H aromatic protons. The ^{13}C-NMR spectrum of this compound exhibits a peaks of tertiary carbons at δ 128, 129, 138, 161 and of quaternary carbons at δ 66, 106, 117, 167, 131, 133, 134. Mass Spectrum of **4a** showed characteristic peaks for M$^+$ and M+2 at 279 and 281 *m*/*z*, due to presence of chlorine. The elemental analysis obtained is in agreement with molecular formula. Analogously, the cyclocondensation of 5-amino-1*H*-pyrazole-4-carbonitrile **1**, *p*-substituted benzoylacetonitriles **2** and triethylorthoesters **3** by refluxing in ethanol in the presence of catalytic amount of hydrochloric acid for 2 h, afforded compounds **5** in good yield. The structure of **5a** was confirmed by IR, ^{1}H-NMR, ^{13}C-NMR, mass spectroscopy and elemental analysis for example the IR spectrum of **5a** showed the bands at 1621 and 2231 cm^{-1} for C=O and CN stretching respectively and two bands for NH$_2$ groups were appears at 3328–3425 cm^{-1}. The 1H-NMR of compound **5a** showed a multiplet

Scheme 2



3,7	R
a	H
b	CH$_3$
c	C$_2$H$_5$

Table 1

The absorbance, emission λ_{max}, and quantum yield of pyrazolopyrimidines (**4a-f** and **5a-f**).

Compd.	Absorbance λ_{max} (nm)	Emission λ_{max} (nm)	Quantum yield (Φ_F)
(**4a**)	293	322	0.110
(**4b**)	280	316	0.109
(**4c**)	296	332	0.111
(**4d**)	279	306	0.108
(**4e**)	267	304	0.107
(**4f**)	284	312	0.112
(**5a**)	336	393	0.113
(**5b**)	342	398	0.114
(**5c**)	345	400	0.116
(**5d**)	360	414	0.117
(**5e**)	338	402	0.103
(**5f**)	350	407	0.104

between δ 7.71 and 7.97 for four aromatic protons and the two singlets at δ 6.84 and δ 8.63 for C2H and C5H aromatic protons. The two broad singlets appeared at δ 7.01 and δ 8.48 corresponding to NH_2 protons. The NH_2 protons are splits in to two broad singlets due to formation of hydrogen bonding between hydrogen atom of NH_2 group and oxygen atom of C=O group. The 13C-NMR spectrum of this compound exhibits a peaks of tertiary carbons at δ 129, 131, 138, 160, and of quaternary carbons at δ 68, 115, 133, 138, 168. The cyanide and carbonyl carbon appears at δ 126 and 196. The mass spectrum of a showed M+ and M+2 at 297 and 299 *m*/*z*. The elemental analysis obtained is in agreement with the molecular formula. Similarly, the structures of bromo-derivatives 4d and 5d were confirmed. It was observed that, the cyclocondensation of intermediate Y with $-COCH_2-$ fragment of substrate 2 should give product 4 but cyclocondensation of Y with $-CH_2CN-$ fragment of substrate 2 should give product 5 [21,33].

It was interesting to note that the cyclocondensaton reaction in presence of basic medium at pH 9–10 led 7-(4-aryl)pyrazolo[1,5-*a*] pyrimidine-3,6-dicarbonitriles **4**, where the cyclization on carbonyl carbon takes place, whereas the similar cyclocondensation reaction when carried out in presence of acidic medium at pH 3-4 gave 7-amino-6-(4-aroyl)pyrazolo[1,5-*a*]pyrimidine-3-carbonitriles **5** in which the cyclization on nitrile carbon takes place [21,33]. The synthesis of pyrazolo[1,5-*a*]quinazolines **7** were also achieved in one step, by the cyclocondensation of 5-aminopyrazole **1**, dimedone **6** and triethyorthoesters **3** by refluxing in toluene for 3 h furnished the compound **7** in 75–80% yield. The structure of **7a** was confirmed by IR, ^{1}H-NMR, ^{13}C-NMR and elemental analysis for example the IR spectrum of **7a** showed bands at 2215, 1687 cm^{-1} for CN and carbonyl groups. The ^{1}H-NMR of compound **7a** showed a singlet at δ 1.25 for six methyl protons, singlet at δ 2.65 and δ 3.40 for four methylene protons, a singlet at 8.49 and 9.18 corresponding to C_2H and C_5H protons respectively. Further this structure was confirmed by ^{13}C-NMR which is in agreement with the structure proposed. Similarly, the structures of compound **7b** and **7c** were confirmed.

After synthesis of all these compounds, it was noted that the pyrazolo[1,5-*a*]pyrimidine derivatives showed good fluorescence properties. So, we further studied the photophysical properties of pyrazolopyrimidine derivatives **4** and **5**. It was observed that compounds **4** showed UV absorption in the range 267–296 nm and fluorescence maxima in the range of 304–332 nm. While the compounds **5** showed slightly better absorption and emission values. From Table 1. It is evident that the incorporation of amino group at C_7 position in compounds **5** markedly increases the absorption and emission properties compared with aryl group at C_7 position in compounds **4**. The compound **5d** showed good absorption and emission spectra as shown in Figure 1.

The reactions reported here represent new synthetic methods toward synthesis of novel pyrazolopyrimidine and pyrazoloquinozoline derivatives with simple workup and clean products in single step.

EXPERIMENTAL

Melting points were determined on a Gallenkamp Melting Point Apparatus, Mod. MFB-595 in open capillary tubes and are uncorrected. The ^{1}H and ^{13}C-NMR spectra were recorded on a Varian XL-300 spectrometer (300 MHz). Chemical shifts are reported in ppm from internal tetramethylsilane standard and are given δ-units. The solvents for NMR spectra was duteriochloroform unless otherwise stated. Infrared spectra were taken on Shimadzu IR-408, a Shimadzu FTIR instrument in potassium bromide pellets unless otherwise stated. UV Spectra were recorded on a Shimadzu UV-1601 UV–visible

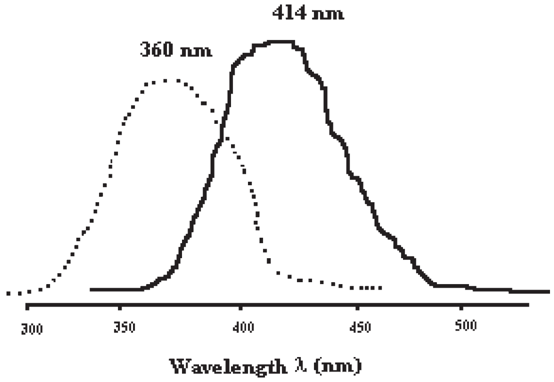


Figure 1. The absorption (dotted line) and emission spectra of compound **5d**.

Spectrophotometer. High-resolution mass spectra were obtained with a Mat 112 Varian Mat Bremen (70 eV) mass spectrometer. Compounds for UV scan were dissolved in methanol. Fluorescence spectra were recorded using RF-5301 PC Spectrofluorophotometer. Compounds for fluorescence measurements were dissolved in methanol. UV and fluorescence scans were recorded from 200 to 500 nm. Elemental analyses were performed on a Hosli CH-Analyzer and are within ±0.3 of the theoretical percentage. Solutions were concentrated in a rotary evaporator under reduced pressure. All reactions were monitored by thin layer chromatography, carried out on 0.2-mm silica gel 60 F_{254} (Merk) plates using UV light (254 and 366 nm) for detection. Common reagents-grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures.

General procedure for the synthesis of 7-(4-aryl) pyrazolo[1,5-*a*]pyrimidine-3,6-dicarbonitrile (4). A mixture of 5-aminopyrazole **1** (1.08 g, 10 mmole), aroylacetonitriles **2** (10 mmole), and triethylorthoesters **3** (10 mmole) in toluene (20 mL) containing catalytic amount of triethylamine (0.5 mL) was refluxed for 2–3 h. The completion of reaction was monitored by thin layer chromatography (TLC). Then the excess of solvent was removed under reduced pressure. The solid obtained was stirred in ethanol (10 mL), filtered, washed with ethanol, dried and recrystallized from suitable solvent furnished compounds **4** in good yield.

7-(4-Chlorophenyl)pyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile (4a). This compound was obtained as colorless prism (ethanol), 2.15 g (77%), mp 223–224°C; IR: (Potassium bromide): 2237, 1654, 1606, 1590, 1525, 1486, 1264, 1065, 1012, 827, 637 cm^{-1}; 1H-NMR: (CDCl3) δ 7.85–7.89 (m, 4H, Ar—H), 8.87 (s, 1H, Ar—H), 9.16 (s, 1H, Ar—H); 13C-NMR: (CDCl3) δ 66, 106, 117, 119, 128, 129, 131, 133, 134, 138, 161, 167. MS: (70 eV) *m*/*z* (%) 281 (90) (M+2), 279 (100) (M+), 271 (80), 258 (65), 244 (70), 233 (80), 207 (10), 181 (20), 153 (40), 122 (30), 93 (50), 78 (70), 63 (80), 44 (40). *Anal.* Calcd for $C_{14}H_6ClN_5$: C, 60.12; H, 2.16; N, 25.04. Found: C, 60.29; H, 2.45; N, 25.33.

7-(4-Chlorophenyl)-5-methylpyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile (4b). This compound was obtained as yellow prism (ethanol/DMF), 2.58 g (88 %), mp 228–230°C; IR: (Potassium bromide): 2246, 1615, 1596, 1489, 1464, 1381, 1098, 1018, 832, 643 cm^{-1}; ^{1}H-NMR: ($CDCl_3$) δ 2.81 (s, 3H, CH_3), 7.74 (d, 2H, *J* = 8.7 Hz, Ar—H), 7.84 (d, 2H, *J* = 8.7 Hz, Ar—H), 8.89 (s, 1H, Ar—H). *Anal.* Calcd for $C_{15}H_8ClN_5$: C, 61.34; H, 2.75; N, 23.84. Found: C, 61.13; H, 2.45; N, 23.61.

7-(4-Chlorophenyl)-5-ethylpyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile (4c). This compound was obtained as colorless prism (ethanol/DMF), 2.43 g (79%), mp 174–175°C; IR: (Potassium bromide): 2233, 1622, 1587, 1492, 1463, 1385, 1094, 1021, 838, 642 cm^{-1}; ^{1}H-NMR: ($CDCl_3$) δ 1.41 (t, 3H, *J* = 7.2 Hz, CH_3), 3.19 (q, 2H, *J* = 7.2 Hz, CH_2), 7.83 (d, 2H, *J* = 8.7 Hz, Ar—H), 7.95 (d, 2H, *J* = 8.4 Hz, Ar—H), 8.91 (s, 1H, Ar—H); MS: (70 eV) *m*/*z* (%) 309 (40) (M+2), 307 (100) (M+), 280 (40), 272 (80), 252 (20), 245 (30), 229 (10), 218 (10), 187 (30), 179 (20), 161 (50), 152 (30), 126 (30), 113 (10), 111 (40), 88 (10), 75 (60), 63 (50), 51 (55), 40 (40). *Anal.* Calcd for $C_{16}H_{10}ClN_5$: C, 62.45; H, 3.28; N, 22.76. Found: C, 62.67; H, 3.53; N, 22.55.

7-(4-Bromophenyl)pyrazolo[1,5-a]pyrimidine-3,6-dicarb onitrile (4d). This compound was obtained as colorless prism (ethanol), 2.78 g (86%), mp 246–248°C; IR: (Potassium bromide): 2239, 1656, 1610, 1587, 1521, 1482, 1262, 1068, 1018, 828, 639 cm^{-1}; ^{1}H-NMR: ($CDCl_3$) δ 7.85 (d, 2H, *J* = 8.5 Hz, Ar—H), 7.89 (d, 2H, *J* = 8.4 Hz, Ar—H), 8.85 (s, 1H, Ar—H), 9.12 (s, 1H, Ar—H); ^{13}C-NMR: ($CDCl_3$) δ 67, 108, 118, 121, 125, 127, 131, 134, 136, 140, 163, 168. MS: (70 eV) *m*/*z* (%) 326 (90) (M+2), 324 (100) (M+), 323 (80), 322 (60), 298 (10), 271 (10), 258 (10), 244 (20), 233 (10), 207 (10), 183 (20), 181 (10), 153 (40), 122 (60), 102 (70), 91 (60), 75 (80), 63 (70), 44 (60). *Anal.* Calcd for $C_{14}H_6BrN_5$: C, 51.88; H, 1.87; N, 21.61. Found: C, 51.54; H, 1.62; N, 21.41.

7-(4-Bromorophenyl)-5-methylpyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile (4e). This compound was obtained as yellow prism (ethanol/DMF), 2.77 g (82%), mp 142–143°C; IR: (Potassium bromide): 2243, 1611, 1592, 1485, 1460, 1383, 1097, 1016, 830, 641 cm^{-1}; ^{1}H-NMR: ($CDCl_3$) δ 2.83 (s, 3H, CH_3), 7.76 (d, 2H, *J* = 8.7 Hz, Ar—H), 7.86 (d, 2H, *J* = 8.7 Hz, Ar—H), 8.85 (s, 1H, Ar—H). *Anal.* Calcd for $C_{15}H_8BrN_5$: C, 53.28; H, 2.38; N, 20.71. Found: C, 53.51; H, 2.49; N, 20.39.

7-(4-Bromophenyl)-5-ethylpyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile (4f). This compound was obtained as yellow prism (ethanol/DMF), 2.67 g (76%), mp 194–196°C; IR: (Potassium bromide): 2234, 1622, 1587, 1491, 1461, 1382, 1093, 1016, 836, 646 cm^{-1}; ^{1}H-NMR: ($CDCl_3$) δ 1.40 (t, 3H, *J* = 7.2 Hz, CH_3), 3.18 (q, 2H, *J* = 7.2 Hz, CH_2), 7.83 (d, 2H, *J* = 8.7 Hz, Ar—H), 7.94 (d, 2H, *J* = 8.4 Hz, Ar—H), 8.91 (s, 1H, Ar—H). *Anal.* Calcd for $C_{16}H_{10}BrN_5$: C, 54.56; H, 2.86; N, 19.89. Found: C, 54.29; H, 2.66; N, 19.65.

General procedure for the synthesis of 7-Amino-6-(4-aroyl)pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (5). A mixture of 5-aminopyrazole **1** (1.08 g, 10 mmole), aroylacetonitriles **2** (10 mmole) and triethylorthoesters **3** (10 mmole) in absolute ethanol (20 mL) containing catalytic amount of hydrochloric acid (0.1*N*, 0.5 mL) was refluxed for 2–3 h. The completion of reaction was monitored by thin layer chromatography (TLC). The solid obtained on cooling was filtered, washed with ethanol, dried, and recrystallized from suitable solvent furnished compounds **5** in good yield.

7-Amino-6-(4-chlorobenzoyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (5a). This compound was obtained as colorless prism (DMF), 2.64 g (89%), mp 273–274°C; IR: (Potassium bromide): 3425, 3328, 2887, 2874, 2554, 2231, 1660, 1621, 1499, 1368, 1313, 1200, 1076, 1011, 899, 821, 726, 627. cm^{-1}; ^{1}H-NMR: ($CDCl_3$) δ 6.84 (s, 1H, Ar—H), 7.01 (bs, 1H, NH), 7.71 (d, 2H, *J* = 8.4 Hz, Ar—H), 7.97 (d, 2H, *J* = 8.4 Hz, Ar—H), 8.48 (bs, 1H, NH), 8.63 (s, 1H, Ar—H); ^{13}C-NMR: ($CDCl_3$) δ 68, 115, 126, 129, 131, 133, 138, 160, 164, 168, 169, 196. MS: (70 eV) *m*/*z* (%) 299 (70) (M+2), 297 (90) (M+), 275 (80), 243 (65), 236 (70), 233 (80), 205 (10), 173 (100), 151 (40), 119 (30), 91 (50), 74 (70), 61 (80), 42 (40). *Anal.* Calcd for $C_{14}H_8ClN_5O$: C, 56.48; H, 2.71; N, 23.52. Found: C, 56.29; H, 2.45; N, 23.33.

7-Amino-6-(4-chlorobenzoyl)-5-methylpyrazolo[1,5-a] pyrimidine-3-carbonitrile (5b). This compound was obtained as colorless prism (DMF), 2.43 g (78%), mp 275–277°C; IR: (Potassium bromide): 3427, 3330, 3086, 2888, 2524, 2235, 1660, 1623, 1400, 1367, 1310, 1200, 1069, 1011, 890, 820, 726, 626. cm^{-1}; ^{1}H-NMR: ($CDCl_3$) δ 2.35 (s, 3H, CH_3), 5.29 (bs, 2H, NH_2), 7.60 (s 1H, Ar—H), 7.62 (d, 2H, *J* = 8.7 Hz, Ar—H), 7.70 (d, 2H, *J* = 8.7 Hz, Ar—H). *Anal.* Calcd for

$C_{15}H_{10}Cl\,N_5O$: C, 57.79; H, 3.23; N, 22.47. Found: C, 57.63; H, 3.41; N, 22.61.

7-Amino-6-(4-chlorobenzoyl)-5-ethylpyrazolo[1,5-a]pyrimidine-3-carbonitrile (5c). This compound was obtained as colorless prism (DMF), 2.47 g (76%), mp 271–272°C; IR: (Potassium bromide): 3430, 3320, 3086, 2920, 2877, 2530, 2231, 1620, 1622, 1401, 1369, 1310, 1200, 1069, 1011, 890, 830, 710, 636. cm^{-1}; ^{1}H-NMR: ($CDCl_3$) δ 1.24 (t, 3H, J = 7.2 Hz, CH_3), 2.55 (q, 2H, J = 7.2 Hz, CH_2), 5.62 (bs, 2H, NH_2), 7.89 (d, 2H, J = 8.7 Hz, Ar—H), 7.98 (d, 2H, J = 8.4 Hz, Ar—H), 8.96 (s, 1H, Ar—H). *Anal.* Calcd for $C_{16}H_{12}ClN_5O$: C, 58.99; H, 3.71; N, 21.50. Found: C, 58.76; H, 3.53; N, 21.69.

7-Amino-6-(4-bromobenzoyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (5d). This compound was obtained as colorless prism (DMF), 2.87 g (84%), mp 289–290°C; IR: (Potassium bromide): 3426, 3329, 2889, 2877, 2559, 2232, 1661, 1623, 1496, 1363, 1310, 1201, 1077, 1012, 890, 823, 722, 628. cm^{-1}; ^{1}H-NMR: ($CDCl_3$) δ 6.86 (s, 1H, Ar—H), 7.12 (bs, 1H, NH), 7.77 (d, 2H, J = 8.2 Hz, Ar—H), 7.95 (d, 2H, J = 8.2 Hz, Ar—H), 8.52 (bs, 1H, NH), 8.65 (s, 1H, Ar—H); ^{13}C-NMR: ($CDCl_3$) δ 65, 120, 122, 123, 124, 128, 130, 133, 134, 165, 166, 192. MS: (70 eV) m/z (%) 344 (20) (M+2), 342 (90) (M+), 339 (30), 326 (10), 315 (60), 307 (10), 288 (10), 275 (10), 145 (25), 235 (20), 218 (60), 196 (65), 182 (45), 157 (10), 151 (05), 127 (20), 116 (15), 109 (100), 97 (60), 63 (40). *Anal.* Calcd for $C_{14}H_8BrN_5O$: C, 49.14; H, 2.36; N, 20.47. Found: C, 49.29; H, 2.48; N, 20.28.

7-Amino-6-(4-bromobenzoyl)-5-methylpyrazolo[1,5-a]pyrimidine-3-carbonitrile (5e). This compound was obtained as colorless prism (DMF), 2.77 g (78%), mp 292–293°C; IR: (Potassium bromide): 3429, 3331, 3089, 2890, 2221, 1660, 1619, 1400, 1369, 1315, 1200, 1069, 1013, 892, 823, 729, 628. cm^{-1}; ^{1}H-NMR: ($CDCl_3$) δ 2.37 (s, 3H, CH_3), 5.21 (bs, 2H, NH_2), 7.63 (s 1H, Ar—H), 7.65 (d, 2H, J = 8.7 Hz, Ar—H), 7.73 (d, 2H, J = 8.7 Hz, Ar—H). *Anal.* Calcd for $C_{15}H_{10}BrN_5O$: C, 50.58; H, 2.83; N, 19.66. Found: C, 50.73; H, 2.68; N, 19.53.

7-Amino-(4-bromobenzoyl)-5-ethylpyrazolo[1,5-a]pyrimidine-3-carbonitrile (5f). This compound was obtained as colorless prism (DMF), 2.73 g (74%), mp 277–278°C; IR: (Potassium bromide): 3433, 3316, 3086, 2921, 2879, 2530, 2233, 1620, 1623, 1401, 1363, 1319, 1200, 1069, 1011, 895, 830, 712, 630 cm^{-1}; ^{1}H-NMR: ($CDCl_3$) δ 1.21 (t, 3H, J = 7.2 Hz, CH_3), 2.59 (q, 2H, J = 7.2 Hz, CH_2), 5.62 (bs, 2H, NH_2), 7.85 (d, 2H, J = 8.7 Hz, Ar—H), 7.93 (d, 2H, J = 8.4 Hz, Ar—H), 8.91 (s, 1H, Ar—H). *Anal.* Calcd for $C_{16}H_{12}BrN_5O$: C, 51.91; H, 3.27; N, 18.92. Found: C, 51.77; H, 3.41; N, 18.73.

General procedure for the synthesis of 8,8-Dimethyl-6-oxo-6,7,8,9-tetrhydropyrazolo[1,5-*a*]quinazoline-3-carbo-nitrile (7). A mixture of 5-aminopyrazole **1** (1.08 g, 10 mmole), dimedone **2** (10 mmole) and triethylorthoesters **3** (10 mmole) was refluxed in toluene for about 3 h. Completion of reaction was monitored by thin layer chromatography (TLC). The excess of solvent was removed under reduced pressure. The solid obtained was stirred in ethanol (20 mL), filtered, washed with ethanol, dried, and recrystallized from suitable solvent furnished compounds **7** in good yield.

8,8-Dimethyl-6-oxo-6,7,8,9-tetrhydropyrazolo[1,5-a]quinazoline-3-carbonitrile (7a). This compound was obtained as colorless prism (ethanol), 1.96 g (82%), mp 162–163°C; IR: (Potassium bromide): 2215, 1687, 1609, 1537, 1367, 1310, 1261, 1175, 1096, 801, 683 cm^{-1}; ^{1}H-NMR: ($CDCl_3$) δ 1.25 (s, 6H, $2CH_3$), 2.65 (s, 2H, CH_2), 3.40 (s, 2H, CH_2), 8.49 (s, 1H, Ar—H), 9.18 (s, 1H, Ar—H); ^{13}C-NMR: 28, 32, 37, 50, 85, 111, 115, 149, 150, 151, 153, 193. *Anal.* Calcd for $C_{13}H_{12}N_4O$: C, 64.99; H, 5.03; N, 23.32. Found: C, 65.29; H, 5.16; N, 23.56.

5,8,8-Trimethyl-6-oxo-6,7,8,9-tetrhydropyrazolo[1,5-a] quinazoline-3-carbonitrile (7b). This compound was obtained as colorless prism (ethanol), 2.13 g (84%), mp 186–187°C; IR: (Potassium bromide): 2217, 1689, 1610, 1539, 1369, 1312, 1264, 1177, 1098, 802, 684 cm^{-1}; ^{1}H-NMR: ($CDCl_3$) δ 1.23 (s, 6H, $2CH_3$), 2.63 (s, 2H, CH_2), 2.79 (s, 3H, CH_3), 3.38 (s, 2H, CH_2), 8.47 (s, 1H, Ar—H), 9.17 (s, 1H, Ar—H). *Anal.* Calcd for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 65.97; H, 5.31; N, 22.41.

5-Ethyl-8,8-dimethyl-6-oxo-6,7,8,9-tetrhydropyrazolo[1,5-a] quinazoline-3-carbonitrile (7c). This compound was obtained as colorless prism (ethanol), 2.38 g (89%), mp 205–206°C; IR: (Potassium bromide): 2216, 1688, 1610, 1538, 1366, 131 0, 1266, 1176, 1098, 801, 685 cm^{-1}; ^{1}H-NMR: ($CDCl_3$) δ 1.27 (s, 6H, $2CH_3$), 1.43 (t, 3H, J = 7.2 Hz, CH_3), 2.66 (s, 2H, CH_2), 3.19 (q, 2H, J = 7.1 Hz, CH_2), 3.41 (s, 2H, CH_2), 8.50 (s, 1H, Ar—H). *Anal.* Calcd for $C_{15}H_{16}N_4O$: C, 67.15; H, 6.01; N, 20.88. Found: C, 67.29; H, 6.16; N, 20.56.

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Self Termination of Ring Opening Reaction of *p*-Substituted Phenol-Based Benzoxazines: An Obstructive Effect *via* Intramolecular Hydrogen Bond

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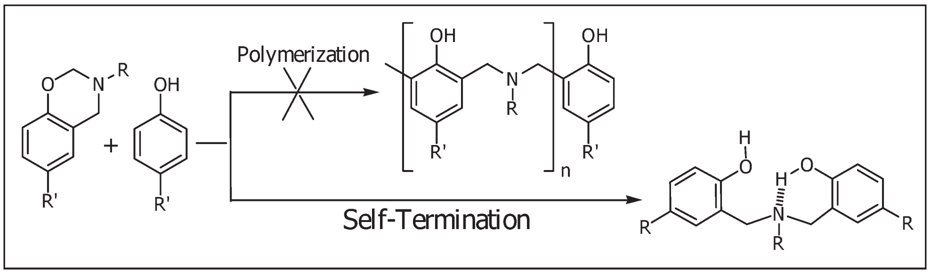

The ring opening polymerizations of *p*-substituted phenol-based benzoxazines are self-terminated as soon as dimers form. The polymerization of benzoxazine monomers does not proceed according to the theoretical mechanism even though the conditions, temperature, molar ratio, solvent polarity, and reactant ratio are varied. The speculated mechanism, involving the unique structure of a dimer with inter- and intramolecular hydrogen bonds, is applied to explain an obstructive effect on ring opening polymerization. In this article, we clarify an important case which the stereo structure of the compound controls the reaction and prevents the polymerization expected from the theoretical mechanism.

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INTRODUCTION

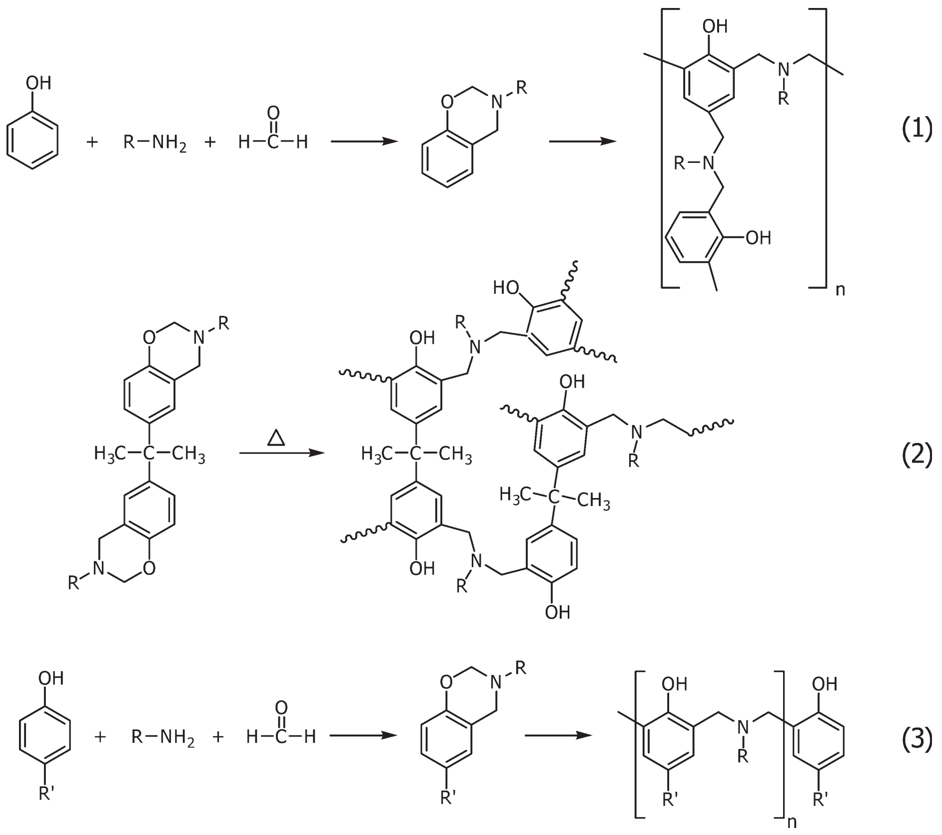
3,4-Dihydro-1,3-2*H*-benzoxazines are known as heterocyclic compounds obtained from *p*-substituted phenols, formaldehyde, and primary amines in a molar ratio of 1:2:1 *via* the Mannich reaction [1]. Theoretically, benzoxazines act as a monomer that undergoes the ring opening reaction to obtain a polymer chain with methylene-amine-Mannich bridges at both the ortho and para positions [2–6] [eq. (1), Scheme 1]. Kopf and Wagner [7] proposed the oxazine-derived phenolics as a potential precursor in synthesis of novolacs. Benzoxazines are reported as polybenzoxazines for the first time when Ning and Ishida [6] demonstrated novel phenolic resins obtained from a series of bisphenol A-based benzoxazine monomers. The success in polymeric material of bisphenol A-based polybenzoxazines might be related to the crosslink structure generated from the two hydroxyl groups belonging to a single bisphenol ring [eq. (2), Scheme 1] [6].

It is important to note that, although the reaction and mechanism of ring-opening benzoxazines [2] have been studied since 1952, *p*-substituted phenol-based benzoxazines and azamethylene phenols have rarely been reported. Based on the reverse Mannich reaction [8], *p*-substituted phenol should produce a high-molecular-weight linear polymer, since the aza-methylene linkage is occurred at only the ortho positions in the structure [eq. (3), Scheme 1].

Riess *et al.* [5] attempted the polymerization of phenol by using various conditions, which are the type of phenols, reaction temperatures, molar ratios, and phenol initiator concentrations. The reactions were done in bulk using NMR and vapor pressure methods to find that the degree of polymerization of the main products were about at the level of tetramer to hexamer. Although the reason why polymerization terminated was not clarified, the reaction was explained in terms of the kinetics and mechanisms [5].

Until now, there is no report about the linear polybenzoxazines even the mechanism insists the stepwise reaction to produce a chain of aza-methylene-phenol polymer. For the past few years, our group has paid attention onto the linear chain of polybenzoxazines, however, to our surprise the polymerization of *p*-substituted phenol-based benzoxazines does not proceed as expected. As will be describe here, the many reactions we have carried out allows us to conclude that the ring opening of *p*-substituted phenols provide neither linear oligomer nor polymer (Scheme 2), but only dimers.

Scheme 1



This article, thus, are to clarify (i) if indeed we never get the linear or cyclic compounds from the *p*-substituted based benzoxazine monomers as written in the formula, (ii) why the *p*-substituted based benzoxazine monomers give only dimer, and (iii) what obstructs the polymerization. By solving these questions, we are able not only to point out a rare example of a polymerization that could not proceed according to theory but also to design a synthesis pathway considering the factors involved at the monomer level.

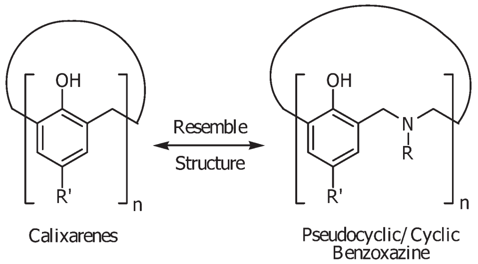
RESULTS AND DISCUSSION

Ring opening polymerization. Carboxylic acids and phenol derivatives are known as acid catalysts for the ring opening reaction of benzoxazines [5,9]. Ning and Ishida [6] reported that the ring opening is preferable in high-dielectric constant solvents such as methanol.

After the mixture of **1a** and *p*-cresol (molar ratio of 20:1) was refluxed in MeOH for 8 h, a white precipitate appeared. The TLC of the MeOH solution shows two spots at R_f for 0.48 and 0.56, referring to *p*-cresol and **1a**, respectively. This confirmed that only starting materials were present. However, the white precipitate gives an R_f for 0.30, implying a new product. The HPLC chromatograms exhibit the results corresponding to TLC. As shown in Figure 1, a new single sharp peak at (t_R) 3.430 min is observed for the white product, whereas those for **1a** and *p*-cresol are found at t_R 3.344 and 3.418 min, respectively.

From FTIR spectra (Fig. 2), the white product gives rise not only to the band at 3226 cm^{-1} but also to a broad band at 3100–2600 cm^{-1}. Lin-Vien *et al.* [10] reported a broad band at 3200–2600 cm^{-1} corresponding to the strong OH···N bond. Thus, we speculate that the white product with a free hydroxyl group in an open ring benzoxazine forms an intermolecular hydrogen bond with another free hydroxyl group and an intramolecular hydrogen bond with an aza group. The band at

Scheme 2



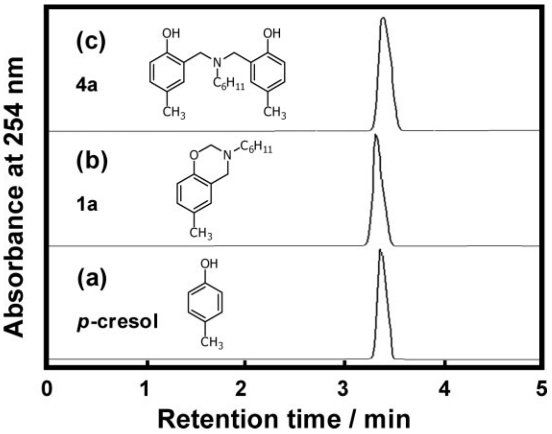


Figure 1. HPLC chromatograms of (a) *p*-cresol, (b) **1a**, and (c) **4a**.

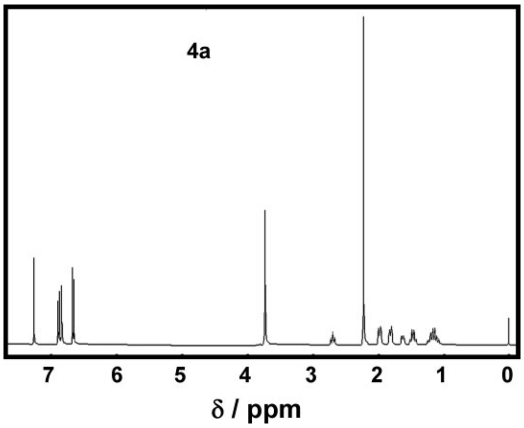


Figure 3. ^{1}H NMR spectrum of **4a**.

1502 cm^{-1} in both **1a** and the product corresponds to a vibrational mode of a trisubstituted benzene. It is important that no tetrasubstituted benzene band at 1485 cm^{-1} was observed. The ^{1}H NMR spectrum of **1a** shows two singlet peaks at $\delta_H = 4.07$ and 4.95 ppm, whereas that of the white precipitate (Fig. 3) shows a singlet resonance at $\delta_H = 3.75$ ppm belonging to methylene groups. This suggests the existence of the aza-methylene linkage in the product as a result of a ring opening reaction. If the product is a polymer, four species of aromatic protons could be observed; however, only three protons at δ_H 6.65 (d), 6.8 (s), and 6.90 (d) ppm resulted. Thus, we speculated that the product was not a polymer but rather a dimer as shown in **4a**.

Elemental analysis (EA) supports our conclusion. Elemental analysis is C 77.90, H 8.56, and N 4.16, which reflects exactly the dimer unit of **4a**.

Effect of solvent and temperature. Bruke *et al.* [4] reported the ring opening of benzoxazine monomer initiated by an intermolecular hydrogen bond with phenol derivatives. Riess *et al.* [5] proposed a mechanism catalyzed by dissociation of phenol. To overcome the termination at dimer, we concentrated on the optimal amount of *p*-cresol and solvent as well as reaction time and temperature.

Regardless of the variation of the molar ratio and solvents, the white precipitate was obtained. The characterization by TLC, HPLC, FTIR, ^{1}H NMR, and EA showed that the product was the dimer **4a**. In addition, it was found that the generation of **4a** is largely dependent on the amount of *p*-cresol (Fig. 4). When the molar ratio of the *p*-cresol increases, the yield of the dimer is increased. Unexpectedly, at 1:1, the yield is highest for all solvents. This implies that the reaction between **1a** and *p*-cresol might possibly be stoichiometric.

If *p*-cresol acts as an initiator in a reverse Mannich reaction, a generated open-ring intermediate should attack at the ortho position of either **1a** or *p*-cresol (see speculated mechanism). Thus, the product obtained should be a mixture of dimer and mono-oxazine compound as detailed in Scheme 3. However, the compound

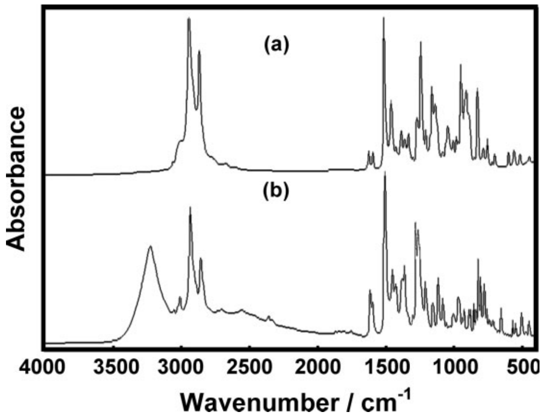


Figure 2. FTIR spectra of (a) **1a** and (b) **4a**.

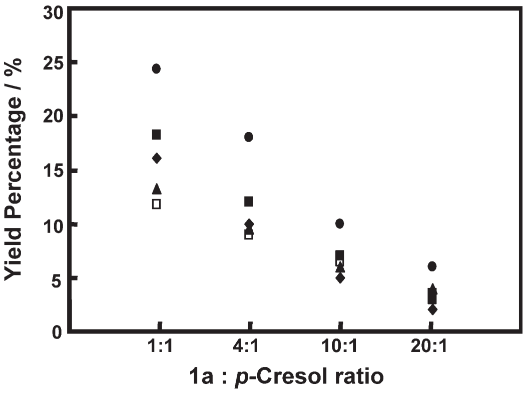
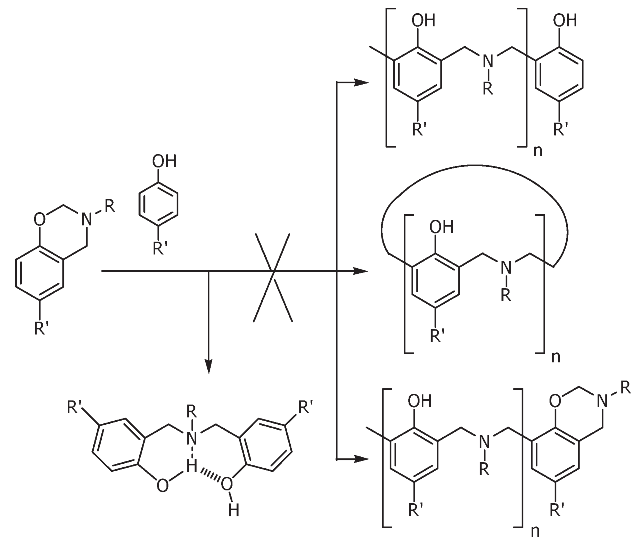


Figure 4. Yields of the product obtained from the reaction of **1a** and *p*-cresol carried out at the boiling point of each solvent; MeOH (◆), iso-PrOH (■), iso-BuOH (▲), cyclohexane (●), and xylene (□).

Scheme 3



obtained is a single component and its characterization does not correspond to the mono-oxazine product [11].

Figure 4 also implies that the yields of **4a** are increased for all molar ratios when the reactions have been carried out at low temperature. The yields from lower reaction temperatures, such as MeOH (bp 65°C) and cyclohexane (bp 80°C) are higher than those from higher reaction temperatures, such as iso-BuOH (bp 110°C) and mixed xylenes (bp 135°C).

Figure 5 implies two important results related to the optimum temperature and polarity effect. As expected, the highest yields are obtained at 65°C for every solvent. Considering the solvent polarity, the nonpolar ones (yield 40–60%) give higher yields than the polar ones (18–35%). This implies that the reaction is preferably carried out with nonpolar solvents (see speculated mechanism).

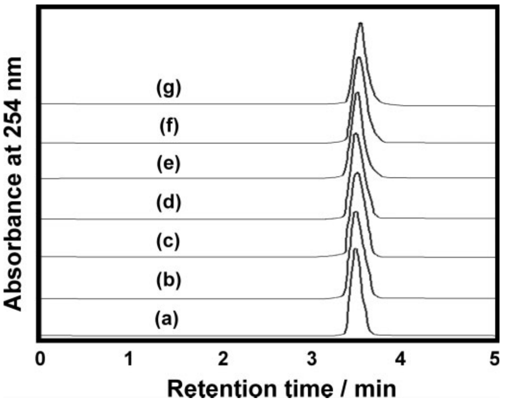


Figure 6. HPLC chromatograms of the product obtained from **1a** and *p*-cresol at 65°C in neat condition with various ratios; (a) 0.5:1, (b) 1:1, (c) 2:1, (d) 3:1, (e) 4:1, (f) 10:1, and (g) 20:1.

Neat liquid state reaction. It can be expected that the polymerization of *p*-substituted phenol-based benzoxazine might be favorable in neat condition. After heating the mixture of **1a** and *p*-cresol in various ratios to the molten state, the white powder precipitated soon after 30 min. Figure 6 shows that each product obtained exhibits only a single component with t_R 3.430 min. The NMR spectra of all products were same as shown in Figure 3, hence, we conclude that all products are **4a**.

Figure 7 shows the comparative studies between neat and solvent (xylene) conditions with a fixed molar ratio of **1a** and *p*-cresol of 1:1. Both reactions give the dimer in high yield (~90%) at 65°C. It is obvious that the neat condition also provides a stoichiometric reaction between **1a** and *p*-cresol. When the reactions are carried out at temperatures either lower or higher than 65°C, the yield is drastically decreased. This supports our speculation about the effect of temperature.

It is important to point out that when the reaction was carried out to satisfy the thermal initiation (above

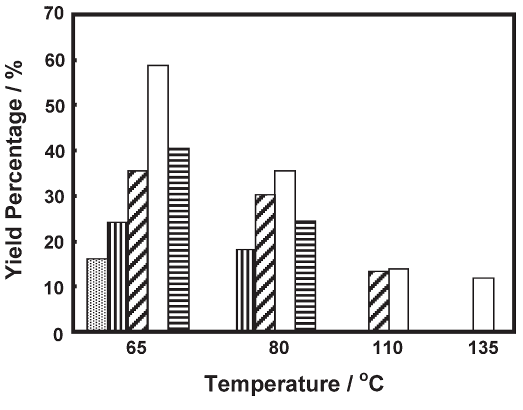


Figure 5. Yields of the product obtained from **1a** and *p*-cresol under various temperatures: 65, 80, 110, and 135°C in various solvents; MeOH ▒, iso-PrOH ▥, iso-BuOH ▨, xylene □, and cyclohexane ▤.

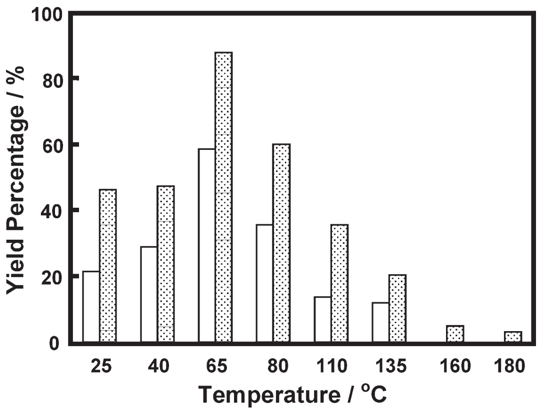


Figure 7. Yields of the product obtained from **1a** and *p*-cresol at various temperatures; 25, 40, 65, 80, 110, 135, 160, and 180°C in □ mixed xylenes and ▒ neat condition.

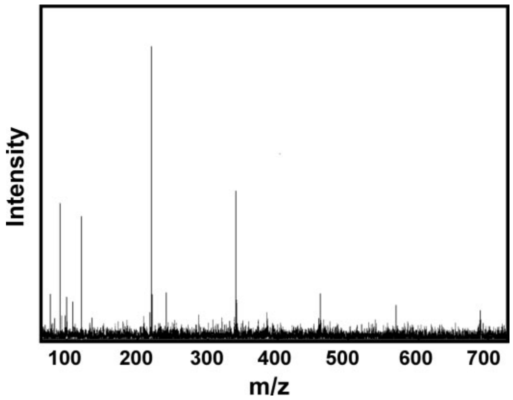


Figure 8. Mass spectrum of the mixture obtained from **1a** and *p*-cresol at 180°C.

140°C) condition as reported by Riess *et al.* [5], the precipitation of dimer **4a** is decreased to 2–3% (Fig. 7). Figure 7 also suggests that the reaction either in solution (mixed xylenes) or neat give maximum yield at the reaction temperature 65°C. At the same time, the neat liquid becomes a dark-brownish highly viscous liquid. A further study by LC-MS indicates the various fragments belonging to the dimer, appearing at m/z = 340, as well as other incomplete structures associated with the starting materials (Fig. 8). The trace fragments (m/z = 570 and 678) of higher molecular weight than dimer is also observed. These fragments could result from dimer aggregation or from trimer and tetramer. This implies that high temperature does not favor the polymerization but brings into play the competition between thermal dissociation of benzoxazine and chain propagation as reported by Riess *et al.* [5]

Reactivity of 1a and *p*-cresol. Figure 9 gives important information about the reactivity of **1a** and *p*-cresol as related to the reaction temperature. Generally, stoichiometric balance gives the highest yield with an equivalent molar ratio between the two reactants.

At high-reaction temperatures such as 110 and 135°C, our results indicate that even a lesser amount (stoichimetric imbalance) of *p*-cresol in the system, such as a molar ratio of **1a** and *p*-cresol of 2:1, 3:1, and 4:1, provides a yield of **4a** higher than that of equivalent molar quantities (stoichiometric balance).

It should be noted that the stoichiometric ratio 1:1 and the effectiveness of this stoichiometric ratio are different due to the reactivity of the reactive species. In this case, the reactive species are deactivated by heat [5]. Thus, the high yield of **4a** might result in the case of stoichiometric imbalance because the reactive species, **1a**, were always present in high concentration in the system.

In the case of low temperatures (65°C and 80°C), the yield from the reactant ratios in stoichiometric balance gives the maximum yield when compared with other ratios. This shows that there is no deactivation of **1a** at the low temperature, and the high yield is obtained as expected.

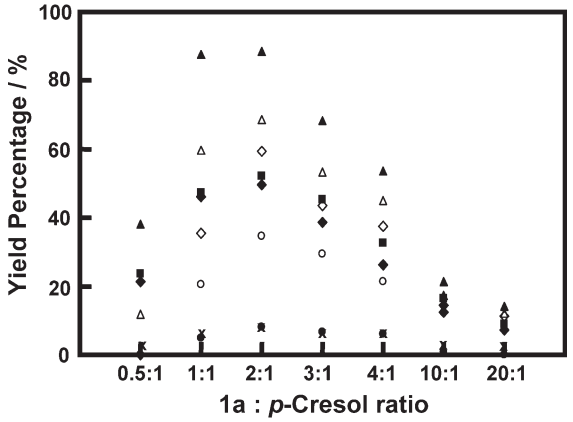


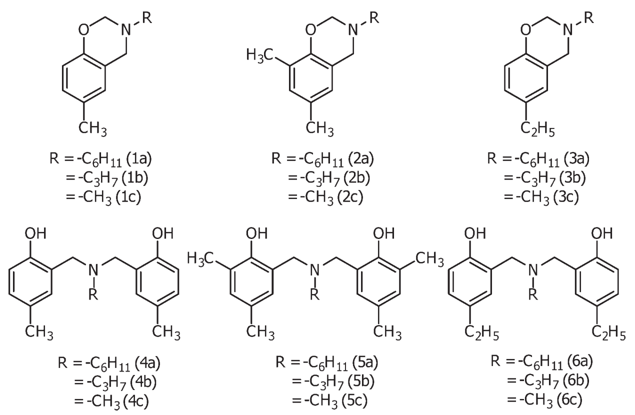
Figure 9. Yields of the product obtained from **1a** and *p*-cresol in various temperatures; 25 (◆), 40 (■), 65 (▲), 80 (△), 110 (◇), 135 (○), 160 (●), and 180°C (×) in neat condition.

Taking the above discussion into consideration, we speculated that without thermal degradation, the reactivity of *p*-cresol is ~0.8–0.9. This is strongly supported by the results that **4b–4c**, **5a–5c**, and **6a–6c** (Scheme 4) give similar yields (80–90%).

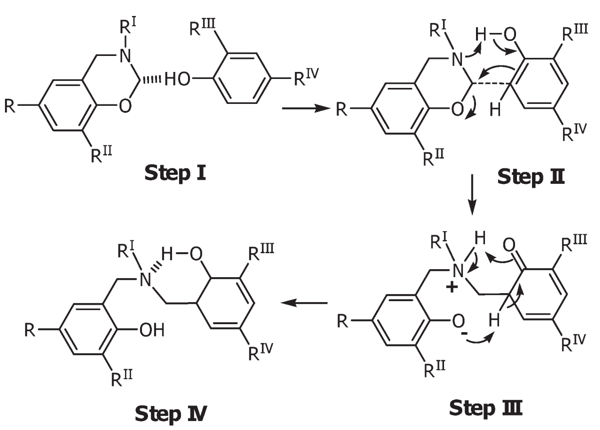
When we consider that there is no deactivation at 65°C, it is natural to expect that all molar ratios should give a yield of **4a** of 90%. However, Figure 9 shows that the yield of **4a** decreases significantly with an excess amount of **1a**. This implies that the reaction of **1a** and *p*-cresol could not proceed effectively. In other words, the ring opening reaction occurs only when the intermediate between **1a** and *p*-cresol is effectively formed.

Since only the dimer is obtained in every case, we conclude that the *p*-substituted phenol in the reaction does not provide a reactive site for another step in ring

Scheme 4



Scheme 5



opening polymerization. In fact, Riess *et al.* [5] reported that the *in situ* ring opening polymerization of *p*-substituted phenol initiated by disubstituted phenol (10%) gave a range of dimers to octamers as evaluated by NMR and vapor pressure methods. Although the structural characterization of the purified product in those cases was not reported in detail, the results support our speculation about some obstructive effects in polymerization.

It is known that the cyclization might be successful in dilute conditions [12]. Thus, an attempt was made to prepare cyclic compounds by using a mixture of **1a** and *p*-cresol (20:1) diluted in mixed xylenes to $5 \times 10^{-3} M$. These systems did not even give a white precipitate as in the previous reactions and the reactants remained in the solution.

Speculated mechanism. To explain why self termination occurs to prevent the polymerization, we combine our results with the mechanisms proposed by Burke *et al.* [4] and Riess *et al.* [5] We speculated that the reaction proceeded as follows. As shown in Scheme 5, intermolecular hydrogen bonding takes place between benzoxazine and the free ortho position in the phenol.

Here, the ring opening of benzoxazine requires some protonation from the phenol derivatives at the nitrogen atom of the oxazine ring to further react with the phenol derivative at ortho position. If the phenol derivative was an initiator, after generating the dimer, the hydroxyl group of one unit of the dimer would further attack another benzoxazine molecule. As a result, a linear polymer chain would be obtained. However, in our case, it is important to note that the reaction terminates as soon as the dimer is formed. This implies that phenol derivatives act as a reactant, not as an initiator, since the reaction does not give products other than dimer.

The effect of temperature and polarity might play an important role (Scheme 5). At this step, an effective ring opening requires thermal degradation, whereas the intermolecular hydrogen bonding between **1a** and *p*-cresol needs lesser thermal motion to maintain stability. Thus, the effect of temperature to drive the reaction provides a dilemma. This might be the reason why we found that the reaction can best proceed at a defined temperature (at 65°C) rather than at a higher or lower temperature (below or higher than 65°C).

In the case of solvent polarity, proton dissociation of phenol results when a polar solvent is used. However, at the same time, the hydrogen bond with the polar solvent will stabilize that proton. In contrast, nonpolar solvents promote the intermolecular hydrogen bonding between the benzoxazine and phenol derivatives. The significant yield of dimer in the nonpolar solvent might result from phenol dissociation rather than intermolecular hydrogen bonding. The effect of intermolecular hydrogen bonding is much enhanced as evidenced from experiments in the neat liquid state.

Stereo structure of dimer: A key factor for obstructive effect in polymerization. Previously, we detailed the unique stereo structure of benzoxazine dimer with strong inter- and intramolecular hydrogen bonds. The stabilization of a symmetrical compound through an intramolecular hydrogen bond inevitably gives us an asymmetric compound [11]. The X-ray structural analyses of dimers (**4a–4c**, **5a–5c**, and **6a–6c**) shows clearly that *p*-substituted based benzoxazines have inter- and intramolecular hydrogen bonds that stabilize the compounds [11,13,14]. Thus, after the single step of ring opening polymerization that produces the dimer, the stability of the network of inter- and intramolecular hydrogen bonding brings about the self termination. It can be concluded that stereo structure of dimer is the key factor to terminate the polymerization.

CONCLUSIONS

Although, in theory, a linear polymer can be obtained from the ring opening polymerization of *p*-substituted phenol-based benzoxazines, this work shows that in practice we will probably never achieve the polymer. Even when the reaction conditions were varied in terms of solvent, neat liquid state, reaction temperature, and concentration, the product was inevitably the dimer. Considering the factors involved in the ring opening reaction, our results show that, in the initial step, the hydrogen bonding between phenol derivatives and benzoxazine is primary when compare with phenol dissociation. Combining this with the previous X-ray structure analyses [11,13,14], we conclude that the obstructive effect of dimer in polymerization might result from the strong intramolecular hydrogen bond between the hydroxyl group of the phenol ring and the aza methylene group in the dimer.

Thus, the mechanism and the reaction assumed from the formula are not always practical. As shown here, the unique stereo structure of benzoxazine dimer leads to the self termination and obstructs the polymerization as clarified in Scheme 5.

EXPERIMENTAL

Chemicals. Paraformaldehyde was purchased from Sigma (St. Louis, MO). *p*-Cresol, 2,4-dimethylphenol, 4-ethylphenol, methylamine (40% w/v in water), cyclohexylamine, and propylamine, deuterated chloroform ($CDCl_3$), and anhydrous sodium sulfate were purchased from Fluka Chemicals (Buchs, Switzerland). HPLC grade tetrahydrofuran (THF), methanol, propan-2-ol, mixed xylenes, 2-methylpropan-1-ol, cyclohexane, sodium hydroxide, and diethyl ether were the products of Ajax chemicals (Australia). All chemicals were analytical grade and used as received.

Procedures. Benzoxazines, **1a**–**3c**, were prepared by using phenol, formaldehyde, and amine derivatives in the ratio of 1:2:1, respectively. *p*-Cresol was added into solution of cyclohexylamine and *p*-formaldehyde, then refluxed for 6 h. The crude product was washed and solvent was removed to obtain **1a**. Compounds **1b** and **1c** were prepared similarly but using propylamine and methylamine, respectively, instead of cyclohexylamine. In the preparation of **2a**–**2c** and **3a**–**3c**, 2,4-dimethylphenol and 4-ethylphenol were used as phenol derivatives, respectively. The ^{1}H nuclear magnetic resonance (NMR) spectrometers were a Bruker ACF with a proton frequency of 200 MHz. Fourier transform infrared spectra were measured at a resolution of 4 cm^{-1} by a Bruker Equinox55/S spectrophotometer equipped with deuterated triglycine (DTGS) detector under constant purge with dry air. High-performance liquid chromatography (HPLC) was done with a Hewlett Packard HP1100 HPLC and a diode array detector model G1315A #DE72002547 fixed at 254 nm. The samples were eluted through a Whatman Partisil 5, a silica gel column with an average pore diameter of 8.5 nm, and a surface area > 350 m^2/g by maintaining the flow rate at 1 mL/min throughout the experiment. Liquid chromatography mass spectrometer (LC-MS) was a Bruker Esquire-LC using methanol as a mobile phase. Elemental analysis (EA) was performed by a Perkin Elmer 2400 Series II CHNS/O analyzer with a combustion temperature of 975°C and a reduction temperature of 500°C.

Reaction of 1a and *p*-cresol in various solvents and temperatures. Benzoxazine **1a** (1.6 mmol) and *p*-cresol were reacted in molar ratios of 1:1, 4:1, 10:1, and 20:1 in various solvents (5 mL), methanol (MeOH), propan-2-ol (iso-PrOH), 2-methylpropan-1-ol (iso-BuOH), cyclohexane, and xylene. The mixtures of monomer **1a** and *p*-cresol in each solvent were reacted at room temperature (~25°C), 40, 65, 80, 110, 135, 160, and 180°C. The completion of the reaction was followed by thin layer chromatography (TLC) and the reaction was stopped after 8 h. The solvent was removed and the crude product was washed with diethyl ether several times before drying at 60°C for 6 h.

Reaction in neat liquid state under various temperatures. Mixtures of **1a** and *p*-cresol (0.5:1, 1:1, 2:1, 3:1, 4:1, 10:1, and 20:1) were prepared and stirred at room temperature (~25°C), 40, 65, 80, 110, 135, 160, and 180°C. The mixtures were allowed to react until viscous. The precipitates obtained from the reaction were collected, washed with diethyl ether before drying at 60°C for 6 h.

Similarly, **1b**–**1c**, **2a**–**2c**, and **3a**–**3c** were reacted with *p*-cresol, 2,4-dimethylphenol, and 4-ethylphenol, respectively. The compounds obtained were qualitatively analyzed by FTIR, ^{1}H NMR, HPLC, LC-MS, and EA. From structural analyses, the compounds obtained are proposed as shown in Scheme 3.

2,2′-[(Cyclohexylimino)di(methylene)]bis(4-methylphenol) (4a). 80% yield; $R_f = 0.30$ (5% MeOH in $CHCl_3$); clear and colorless solid; mp = 181°C; FTIR (KBr, cm^{-1}): 3226 (br, OH), 1500 (vs, C—C), 1449 (m, N—CH), 1249 (s, C—N), 1210 (m, C—N—C), 819 (s, C—N—C); ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ_H 1.1 (m, 2H, **CH$_2$**), 1.45 (m, 4H, **CH$_2$**), 1.82 (m, 4H, **CH$_2$**), 2.22 (s, 6H, **CH$_3$**—Ar), 2.70 (m, 1H, **CH**), 3.72 (s, 4H, Ar—**CH$_2$**—N), 6.68 (d, 2H, Ar—**H**), 6.85 (s, 2H, Ar—**H**), 6.90 (d, 2H, Ar—**H**). Anal. calcd. for $C_{22}H_{29}NO_2$: C, 77.88; H, 8.55; N, 4.13. Found: C, 77.90; H, 8.56; N, 4.16.

2,2′-[(Propylimino)di(methylene)]bis(4-methylphenol) (4b). 80% yield; $R_f = 0.22$ (5% MeOH in $CHCl_3$); clear and colorless solid; mp = 149°C; FTIR (KBr, cm^{-1}): 3251 (br, OH), 1501 (vs, C—C), 1467 (m, N—CH$_2$), 1276 (s, C—N), 1210 (s, C—N—C), 819 (s, C—N—C); ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ_H 0.87 (t, 3H, **CH$_3$**—CH$_2$—CH$_2$—N), 1.65 (m, 2H, CH$_3$—**CH$_2$**—CH$_2$—N), 2.22 (s, 6H, **CH$_3$**—Ar), 2.50 (t, 2H, CH$_3$—CH$_2$—**CH$_2$**—N), 3.70 (s, 4H, Ar—**CH$_2$**—N), 6.68 (d, 2H, Ar—**H**), 6.85 (s, 2H, Ar-**H**), 6.90 (d, 2H, Ar—**H**). Anal. calcd. for $C_{19}H_{25}NO_2$: C, 76.25; H, 8.36; N, 4.69. Found: C, 76.28; H, 8.31; N, 4.70.

2,2′-[(Methylimino)di(methylene)]bis(4-methylphenol) (4c). 90% yield; $R_f = 0.24$ (5% MeOH in $CHCl_3$); clear and colorless solid; mp = 163°C; FTIR (KBr, cm^{-1}): 3271 (br, OH), 1499 (vs, C—C), 1456 (m, N—CH$_3$), 1249 (s, C—N), 1209 (m, C—N—C), 815 (vs, C—N—C); ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ_H 2.23 (s, 6H, Ar—**CH$_3$**), 2.23 (s, 3H, N—**CH$_3$**), 3.69 (s, 4H, Ar—**CH$_2$**—N), 6.70 (d, 2H, Ar—**H**), 6.83 (s, 2H, Ar—**H**), 6.86 (d, 2H, Ar—**H**). Anal. calcd. for $C_{17}H_{21}NO_2$: C, 75.28; H, 7.75; N, 5.17. Found: C, 75.31; H, 7.77; N, 5.19.

2,2′-[(Cyclohexylimino)di(methylene)]bis(4,6-dimethylphenol) (5a). 90% yield; $R_f = 0.38$ (5% MeOH in $CHCl_3$); clear and colorless solid; mp = 152°C; FTIR (KBr, cm^{-1}): 3384 (br, OH), 1484 (vs, C—C), 1451 (m, N—CH), 1245 (m, C—N), 1199 (m, C—N—C), 858 (m, C—N—C); ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ_H 1.1 (m, 2H, **CH$_2$**), 1.45 (m, 4H, **CH$_2$**), 1.82 (m, 4H, **CH$_2$**), 2.20 (s, 6H, **CH$_3$**—Ar), 2.22 (s, 6H, **CH$_3$**—Ar), 2.70 (m, 1H, **CH**), 3.72 (s, 4H, Ar—**CH$_2$**—N), 6.70 (s, 2H, Ar—**H**), 6.85 (s, 2H, Ar—**H**). Anal. calcd. for $C_{24}H_{33}NO_2$: C, 78.47; H, 8.99; N, 3.82. Found: C, 78.49; H, 8.97; N, 3.85.

2,2′-[(Propylimino)di(methylene)]bis(4,6-dimethylphenol) (5b). 90% yield; $R_f = 0.43$ (5% MeOH in $CHCl_3$); clear and colorless solid; mp = 116°C; FTIR (KBr, cm^{-1}): 3298 (br, OH), 1483 (vs, C—C), 1450 (m, N—CH$_2$), 1250 (m, C—N), 1199 (vs, C—N—C), 852 (m, C—N—C); ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ_H 0.85 (t, 3H, **CH$_3$**—CH$_2$—CH$_2$—N), 1.65 (m, 2H, CH$_3$—**CH$_2$**—CH$_2$—N), 2.20 (s, 6H, **CH$_3$**—Ar), 2.22 (s, 6H, **CH$_3$**—Ar), 2.50 (t, 2H, CH$_3$—CH$_2$—**CH$_2$**—N), 3.65 (s, 4H, Ar—**CH₂**—N), 6.70 (s, 2H, Ar—**H**), 6.85 (s, 2H, Ar—**H**). Anal. calcd. for $C_{21}H_{29}NO_2$: C, 77.06; H, 8.87; N, 4.28. Found: C, 77.05; H, 8.86; N, 4.27.

2,2′-[(Methylimino)di(methylene)]bis(4,6-dimethylphenol) (5c). 80% yield; $R_f = 0.39$ (5% MeOH in $CHCl_3$); clear and colorless solid; mp = 123°C; FTIR (KBr, cm^{-1}): 3399 (br, OH), 1484 (vs, C—C), 1427 (m, N—CH_3), 1243 (m, C—N), 1214 and 1201 (m, C—N—C), 847 (m, C—N—C); ^1H NMR (200 MHz, $CDCl_3$, ppm): δ_H 2.22 (s, 12H, Ar—$\mathbf{CH_3}$), 2.25 (s, 3H, N—$\mathbf{CH_3}$), 3.68 (s, 4H, Ar—$\mathbf{CH_2}$—N), 6.72 (s, 2H, Ar—**H**), 6.81 (s, 2H, Ar—**H**). Anal. calcd. for $C_{19}H_{25}NO_2$: C, 76.26; H, 8.36; N, 4.68. Found: C, 76.27; H, 8.34; N, 4.69.

2,2′-[(Cyclohexylimino)di(methylene)]bis(4-ethylphenol) (6a). 80% yield; $R_f = 0.21$ (5% MeOH in $CHCl_3$); clear and colorless solid; mp = 170°C; FTIR (KBr, cm^{-1}): 3251 (br, OH), 1499 (vs, C—C), 1450 (m, N—CH), 1250 (s, C—N), 1207 (m, C—N—C), 818 (m, C—N—C); ^1H NMR (200 MHz, $CDCl_3$, ppm): δ_H 1.15 (t, 6H, $\mathbf{CH_3}$—CH_2—Ar), 1.15 (m, 2H, $\mathbf{CH_2}$), 1.45 (m, 4H, $\mathbf{CH_2}$), 1.82 (m, 4H, $\mathbf{CH_2}$), 2.52 (q, 2H, CH_3—$\mathbf{CH_2}$—Ar), 2.70 (m, 1H, **CH**), 3.72 (s, 4H, Ar—$\mathbf{CH_2}$—N), 6.72 (d, 2H, Ar—**H**), 6.87 (s, 2H, Ar—**H**), 6.94 (d, 2H, Ar—**H**). Anal. calcd. for $C_{24}H_{33}NO_2$: C, 78.47; H, 8.99; N, 3.82. Found: C, 78.51; H, 8.97; N, 3.79.

2,2′-[(Propylimino)di(methylene)]bis(4-ethylphenol) (6b). 80% yield; $R_f = 0.28$ (5% MeOH in $CHCl_3$); clear and colorless solid; mp = 132°C; FTIR (KBr, cm^{-1}): 3265 (br, OH), 1499 (vs, C—C), 1447 (m, N—CH_2), 1247 (s, C—N), 1205 (m, C—N—C), 819 (s, C—N—C); ^1H NMR (200 MHz, $CDCl_3$, ppm): δ_H 0.87 (t, 3H, $\mathbf{CH_3}$—CH_2—CH_2—N), 1.18 (t, 3H, $\mathbf{CH_3}$—CH_2—Ar), 1.65 (m, 2H, CH_3—$\mathbf{CH_2}$—CH_2—N), 2.52 (q, 2H, CH_3—$\mathbf{CH_2}$—Ar), 2.52 (t, 2H, CH_3—CH_2—$\mathbf{CH_2}$—N), 3.70 (s, 4H, Ar—$\mathbf{CH_2}$—N), 6.72 (d, 2H, Ar—**H**), 6.87 (s, 2H, Ar—**H**), 6.94 (d, 2H, Ar—**H**). Anal. calcd. for $C_{21}H_{29}NO_2$: C, 77.06; H, 8.87; N, 4.28. Found: C, 77.08; H, 8.89; N, 4.31.

2,2′-[(Methylimino)di(methylene)]bis(4-ethylphenol) (6c). 90% yield; $R_f = 0.34$ (5% MeOH in $CHCl_3$); clear and colorless solid; mp = 130°C; FTIR (KBr, cm^{-1}): 3301 (br, OH), 1499 (vs, C—C), 1460 (m, N—CH_3), 1251 (s, C—N), 1207 (m, C—N—C), 821 (s, C—N—C); ^1H NMR (200 MHz, $CDCl_3$, ppm): δ_H 1.17 (t, 6H, Ar—CH_2—$\mathbf{CH_3}$), 2.25 (s, 3H, N—$\mathbf{CH_3}$), 2.54 (q, 4H, Ar—$\mathbf{CH_2}$—CH_3), 3.72 (s, 4H, Ar—$\mathbf{CH_2}$—N), 6.73 (d, 2H, Ar—**H**), 6.87 (s, 2H, Ar—**H**), 6.94 (d, 2H, Ar—**H**). Anal. calcd. for $C_{19}H_{25}NO_2$: C, 76.26; H, 8.36; N, 4.68. Found: C, 76.24; H, 8.35; N, 4.65.

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Synthesis, Characterization, and Anti-Inflammatory Evaluation of 1,2,4-Oxadiazoles Combined with Thiosemicarbazide and 1,3,4-Oxadiazole Moieties

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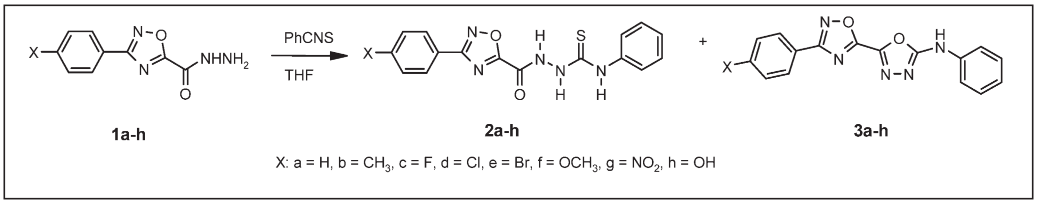

The reaction of 1,2,4-oxadiazole carbohydrazides **1a-h** with phenyl isothiocyanate led to an unexpected ring cyclisation of the thiosemicarbazide derivatives **2a-h**, giving compounds **3a-h** as side products. These two new series were preliminarily evaluated for their anti-inflammatory activity, using the carrageenin induced edema protocol.

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) have been used remarkably widely in the treatment of pain, fever, and inflammatory diseases, in particular rheumatoid arthritis [1–3]. However, severe side effects like gastrointestinal (GI) ulceration, bleeding, and nephrotoxicity are associated with the chronic use of NSAIDs [4,5]. Since most NSAIDs possess a carboxylic group or a 1,3-diketone moiety capable of forming an enol, they have the potential to have a topical effect on the stomach walls, leading to GI damage [6,7]. In addition, the inhibition of enzyme cyclooxygenases (COXs), which is the main NSAID action mechanism, also inhibits tissue prostraglandin production, undermining its physiological cytoprotective role in maintaining GI health [8–11].

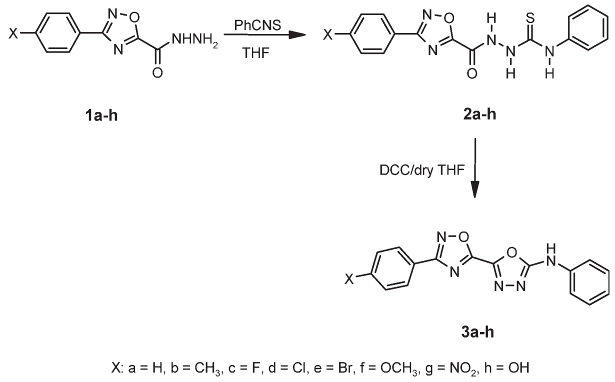
Substances containing heterocyclic and/or heteroaliphatic moieties have been found to exhibit a large spectrum of biological responses, including anti-inflammatory activity. It has been reported in the literature that certain compounds possessing 1,2,4-oxadiazole [12–14], 1,3,4-oxadiazole [15–19] or thiosemicarbazide [20–22] moieties exhibit significant anti-inflammatory properties. This led us to investigate the planning and synthesis of new series of substances whose structures fuse two of these groups with the consequent study of their biological responses. In our attempt to discover new and useful agents for the treatment of inflammation diseases, we selected the 1,2,4-oxadiazole ring as the main pharmacophoric group in our studies. Starting with 1,2,4-oxadiazole carbohydrazides **1a-h**, it was possible to introduce thiosemicarbazide and 1,3,4-oxadiazole residues at the C-5 position of the 1,2,4-oxadiazole ring, so as to obtain the designed substances. On the basis of the approach to the synthesis of 1,2,4-oxadiazole derivatives largely explored in our group, it was possible to synthesize compounds **1a-h**, which are the adequate starting materials for our purposes [23].

During the synthesis of the thiosemicarbazide derivatives **2a-h**, their spontaneous ring closure was observed, leading to 1,3,4-oxadiazole derivatives **3a-h**. To our best knowledge, this unusual outcome for this condensation reaction was never observed before and is possible due to the structural features of compounds **2a-h**. All isolated compounds were preliminary tested for their anti-inflammatory activity as part of our studies on new NSAIDs drugs.

RESULTS AND DISCUSSION

1,2,4-Oxadiazole hydrazides **1a-h** provided access to the designed heterogeneous chains and heterocyclic systems. Their synthesis was already described by our group and can be achieved in three easy and efficient steps [23]. Preparation of thiosemicarbazide derivatives has usually been carried out by condensation of hydrazides with appropriate isothiocyanates in a polar protic

Scheme 1



solvent under reflux. However, it was not possible to transform 1,2,4-oxadiazole hydrazides **1a-h** into their thiosemicarbazide derivatives **2a-h** under these conditions. First, educts were poorly soluble in ethanol or methanol even at their boiling points. Solubility was increased after addition of phenyl isothiocyanate and reflux. After reaction times, a complex mixture of products was observed when using TLC, but none of them could be isolated or identified. Access to the desired thiosemicarbazides **2a-h** was possible using dry THF as solvent and refluxing for only short periods of time (Scheme 1). Despite the satisfactory outcome, this methodology led to a result different from that usually reported in the literature. Thiosemicarbazide adducts **2a-h** have been formed in a mixture with their corresponding ring closed 1,3,4-oxadiazole derivatives **3a-h** as by-products in yields ranging from 2 to 10%, as determined after isolation (Tables 1 and 2).

Cyclisation of thiosemicarbazide moiety exclusively into the 1,3,4-oxadiazole nucleus has been reported under oxidative iodine-mediated conditions in the presence of base [24] or selective activation of the sulfur moiety by coupling reagents such as DCC [25] under reflux. No references to a spontaneous process have been found in the literature. This suggests that the ring closure process is possibly associated with the specific structural features of the thiosemicarbazides **2a-h**. In order to investigate the effect of the solvent on this cyclisation, the reaction of hydrazides **1a-h** with phenyl isothiocyanate was carried out in THF/MeOH 7:3. No difference in the results was observed, indicating that the reaction doesn't depend on using an aprotic or protic solvent. On the other hand, solutions of pure phenyl thiosemicarbazides **2a-h** in THF produce 1,3,4-oxadiazole derivatives **3a-h** very slowly at room temperature. By means of TLC control, traces of 1,3,4-oxadiazole were identified only after 10 days. Refluxing these solutions over several hours under argon, a mixture of decomposition products could be observed, confirming the thermal instability of the thiosemicarbazides. However, transformation into tetracyclic compounds **3a-h** was not increased, as observed by ^{1}H-NMR analysis. Hence, the cyclisation process should occur mainly during the formation of the thiosemicarbazides. Analysing the mechanism of this reaction, depicted in Scheme 2, it can be assumed that the formation of intermediate **A** is a critical step for understanding its outcome. After the breaking of the C=N bond, an electron pair of thiol group (pathway **a**) easily establishes the thiocarbonyl bond, leading to the thiosemicarbazide products **2a-h**, as normally described. Ring closure should otherwise occur as a consequence of a nucleophilic attack by the carbonyl oxygen on the carbon atom of the imine group, as shown in pathway **b**. However, this oxygen atom is usually not basic enough to undergo such a nucleophilic addition. It is reasonable to assume that the conjugated 3-aryl-1,2,4-oxadiazol-5-yl substituent attached to the

Table 1

Physical and pharmacological data for the derivatives N^1-[3-(4-substituted-aryl)-1,2,4-oxadiazol-5-yl carbonyl]-N^4-phenyl thiosemicarbazides **2a-h**.

Comp.	X	Molecular formula	Molecular weight	Yield (%)	M.p. (°C)	CFE, % inhibn ± S.E.M.[a,b]
2a	H	$C_{16}H_{13}N_5SO_2$	339	81	194–196	29.5 ± 7.2
2b	CH_3	$C_{17}H_{15}N_5SO_2$	353	75	192–193	28.9 ± 2.5
2c	F	$C_{16}H_{12}N_5SO_2F$	357	88	193–194	20.7 ± 2.5
2d	Cl	$C_{16}H_{12}N_5SO_2Cl$	373	82	193–194	23.5 ± 1.5
2e	Br	$C_{16}H_{12}N_5SO_2Br$	418	80	203–204	26.4 ± 2.5
2f	OCH_3	$C_{17}H_{15}N_5SO_3$	369	85	184–186	18.3 ± 1.8
2g	NO_2	$C_{16}H_{12}N_6SO_4$	384	90	211–212	30.7 ± 4.8
2h	OH	$C_{16}H_{13}N_5SO_3$	355	75	229–230	32.9 ± 3.2
Diclofenac sodium[c]				75.0 ± 5.7		

[a] Percentage of inhibition on carrageenin-induced rat paw edema at the dosis of 25 mg/kg. The result is the mean value ± S.E.M. for each test group.

[b] $P < 0.001$ and $P < 0.01$ represented a significant difference when compared with control group.

[c] At the dosis of 2 mg/kg.

Table 2

Physical and pharmacological data for derivatives 5-[3-(4-substituted-aryl)-1,2,4-oxadiazol-5-yl]-2-(*N*-phenylamino)-1,3,4-oxadiazoles **3a-h**.

Comp.	X	Molecular formula	Molecular weight	Yield (%)[a]	M.p. (°C)	CFE, %inhibn ± S.E.M.[b,c]
3°	H	$C_{16}H_{11}N_5O_2$	305	75 (10)	238–240	49.6 ± 5.8
3b	CH_3	$C_{17}H_{13}N_5O_2$	319	80 (9)	236–237	48.6 ± 2.8
3c	F	$C_{16}H_{10}N_5O_2F$	323	73 (7)	225–227	47.9 ± 2.3
3d	Cl	$C_{16}H_{10}N_5O_2Cl$	339	90 (8)	229–230	49.9 ± 4.9
3e	Br	$C_{16}H_{10}N_5O_2Br$	384	84 (6)	232–233	41.4 ± 5.7
3f	OCH_3	$C_{17}H_{13}N_5O_3$	335	93 (7)	225–227 (dec.)	39.2 ± 0.54
3g	NO_2	$C_{16}H_{10}N_6O_4$	350	85 (2)	259–260 (dec.)	61.3 ± 2.4
3h	OH	$C_{16}H_{11}N_5O_3$	321	89 (8)	218–220 (dec.)	59.2 ± 8.1
Diclofenac sodium[d]	75.0 ± 5.7					

[a] Values in parenthesis report the percentage of the compound obtained as side product after isolation in the reaction to obtain **2a-h**.

[b] Percentage of inhibition on carrageenin-induced rat paw edema at the dosis of 25 mg/kg. The result is the mean value ± S.E.M. for each test group.

[c] $P < 0.001$ and $P < 0.01$ represented a significant difference when compared with control group.

[d] At the dosis of 2 mg/kg.

carbonyl group acts as a good electron-donating group, enhancing the nucleophilicity of the oxygen atom. Thus, the reaction described by pathway **b** can take place in addition to the pathway **a**. Protons migration, elimination of the thiol group, and aromatisation of the five-membered ring should be a specially favoured and rapid process, owing to the direct conjugation between 1,3,4-oxadiazole and the other two aromatic rings.

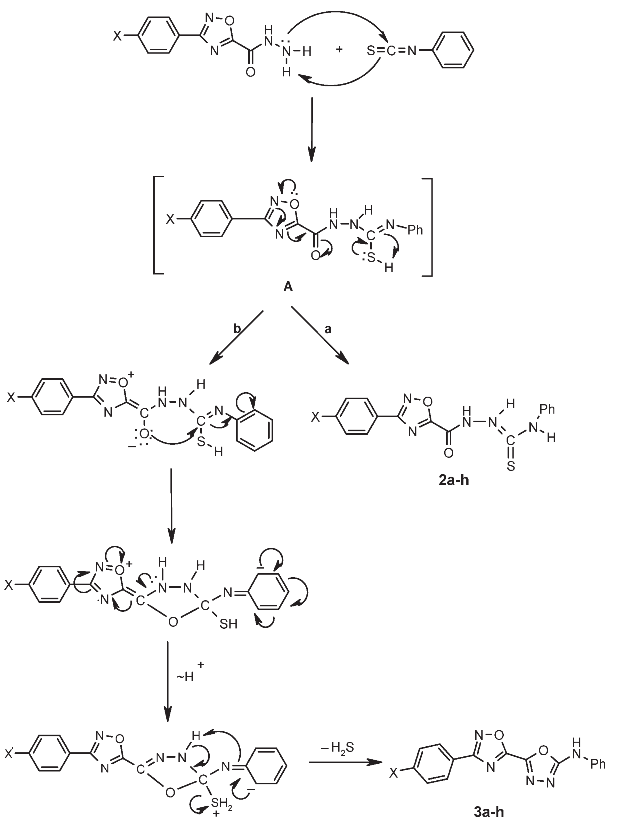
The nature of the para-substituents on the phenyl ring influences the quantity of products formed. The strong electron-withdrawing nitro-substituent doubtless affects the cyclisation reaction, since it decreases the stabilising effect of the aromatic rings on the carbonyl group, leading to only 2% of compound **3g** as a by-product. The other substituents seem to influence the ring closure process to almost the same extent, as suggested by the yields for isolated products (Table 2).

To obtain appropriate amounts of compounds **3a-h**, thiosemicarbazides **2a-h** were treated with DCC in dry THF, leading to the well known oxidative process of ring closure with good yields. The characterization and results of pharmacological tests for compounds **2a-h** and **3a-h** are given in Tables 1 and 2 as well as in the experimental protocols.

The anti-inflammatory activity of synthesized compounds **2a-h** and **3a-h** was evaluated using the carrageenin induced edema method [26]. The compounds were tested at a 25 mg/kg oral dose and compared with the standard drug diclofenac sodium in a dose of 2 mg/kg. Comparing the results in Tables 1 and 2 it can easily be concluded that compounds exhibiting the thiosemicarbazide moiety **2a-h** have a low level of activity. In contrast to these poor results, compounds **3a-h**, possessing the two oxadiazole rings directly linked to each other are more effective in edema inhibition. It was found that the presence of NO_2 and OH groups, in products **3g** and **3h** respectively, promotes better biological responses.

In the light of these results, we envisage introducing structural modifications in compounds **3a-h** to identify

Scheme 2



more potent substances, which can then be submitted to further biological studies.

In summary, a set of 16 new compounds were designed and synthesized to evaluate their anti-inflammatory profiles and to correlate them with molecular properties of these products. Although compounds bearing a thiosemicarbazide moiety **2a-h** are practically inactive, their derivatives **3a-h** showed better biological response to the carrageenin footpad edema (CFE) test, so that they can serve as models for designing a new series of derivatives, expected to be more effective as NSAIDs drugs. Compounds **3g** and **3h** were especially active, suggesting that groups capable of establishing hydrogen bonds should be crucial for the biological response. Studies of GI effects of these products were not carried out because of the limitation of their anti-inflammatory profiles.

The spontaneous ring closure of compounds bearing the thiosemicarbazide group **2a-h** leading to compounds **3a-h** was observed for the first time for this kind of transformation, constituting an interesting subject for further experimental and theoretical studies.

EXPERIMENTAL

Melting points were determined on a Gallenkamp capillary apparatus and are uncorrected. Infrared spectra were recorded using KBr discs on a Perkin-Elmer Paragon 500 FT-IR spectrometer. ^{1}H-NMR spectra were recorded on a Bruker DPX-200 spectrometer, with chemical shifts δ reported in ppm unities relative to the internal standard TMS. Mass spectra were obtained by using a Finnigam MAT 8200 or MAT 95 mass spectrometer. Values for High resolution mass spectrometry (HRMS) lie within the permitted limit intervals with resolution of 10,000. Reactions were generally run under an argon atmosphere. Elemental analysis was performed on a Carlo Erba EA 1110 elemental analyzer. Organic solutions were concentrated at vacuum on a rotary evaporator at room temperature or at 60°C. Column chromatography was performed with ICN Biomedicals silica gel 60, 32–63 μm.

Compounds **3**-(4-substitutedaryl)-1,2,4-oxadiazol-5-yl carbohydrazide (**1a-h**) were prepared by the procedure given in literature [23].

General procedure for the preparation of *N*^{1}-[3-(4-substitutedaryl)-1,2,4-oxadiazol-5-yl carbonyl]-*N*^{4}-phenyl thiosemicarbazides (2a-h). A solution of hydrazides **1a-h** (0.5 mmol) in 2.5 mL THF was gently heated at 50°C, then phenyl isothiocyanate (0.5 mmol, 0.068 g) was added and the reaction was allowed to proceed at reflux under inert atmosphere for 30 min before cooling to room temperature. Solvent was removed in vacuo and the crude products were recrystallized from THF/petroleum ether (30–60°C) to afford, after filtration, the thiosemicarbazides **2a-h** as main products, whose yields, melting points and results of biological evaluation are given in Table 1. The filtrate was concentrated and the residue was eluted on a silica gel column using CH_2Cl_2/MeOH 10:0.2 as eluent to give the secondary ring closed products **3a-h,** and their yields were reported in Table 2.

N^1-(3-Phenyl-1,2,4-oxadiazol-5-ylcarbonyl)-N^4-phenyl thiosemicarbazide (2a). IR ($\tilde{\nu}$, cm^{-1}): 3302, 3207 (N—H), 1683 (C=O), 1226 (C=S); ^{1}H-NMR (DMSO-d$_6$, ppm): 11.5 (s, 1H, CONH), 10.0 (s, 1H, CSNH), 9.85 (s, 1H, NH), 8.10–8.05 (m, 2H, ortho-oxadiazole ArH), 7.63–7.58 (m, 3H, ArH), 7.42–7.29 (m, 4H, ArH), 7.16 (t, 1H, *J* = 7.1 Hz, para-amino ArH); MS (m/z, %): 339 (M$^{+\bullet}$, 24), 305 (8), 204 (21), 193 (39), 135 (94), 77 (100); HRMS, Calc. (Found) for $C_{16}H_{13}N_5SO_2$: 339.07900 (339.07970); *Anal.* Calcd.: C, 56.62; H, 3.86; N, 20.64. Found: C, 56.69; H, 4.07; N, 20.84.

N^1-[3-(4-Tolyl)-1,2,4-oxadiazol-5-ylcarbonyl]-N^4-phenyl thiosemicarbazide (2b). IR ($\tilde{\nu}$, cm^{-1}): 3326, 3220, 3151 (N—H), 1689 (C=O), 1231 (C=S); ^{1}H-NMR (DMSO-d$_6$, ppm): 11.5 (s, 1H, CONH), 10.0 (s, 1H, CSNH), 9.84 (s, 1H, NH), 7.96 (d, 2H, AB-System, *J* = 8.0 Hz, ortho-oxadiazole ArH), 7.43–7.33 (m, 6H, ArH), 7.16 (t, 1H, *J* = 6.8 Hz, para-amino ArH), 2.48 (s, 3H, CH_3); MS (m/z, %): 353 (M$^{+\bullet}$, 21), 218 (12), 193 (27), 132 (81), 77 (100); HRMS, Calc. (Found) for $C_{17}H_{15}N_5SO_2$: 353.09465 (353.09573); *Anal.* Calcd.: C, 57.77; H, 4.28; N, 19.82. Found: C, 57.78; H, 4.29; N, 20.23.

N^1-[3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-ylcarbonyl]-N^4-phenylthiosemicarbazide (2c). IR ($\tilde{\nu}$, cm^{-1}): 3306, 3226, 3159 (N—H), 1688 (C=O), 1227 (C=S); ^{1}H-NMR (DMSO-d$_6$, ppm): 11.6 (s, 1H, CONH), 10.1 (s, 1H, CSNH), 9.84 (s, 1H, NH), 8.12 (dd, 2H, *J* = 8.4 Hz, ortho-oxadiazole ArH), 7.51–7.29 (m, 6H, ArH), 7.16 (t, 1H, *J* = 7.1 Hz, para-amino ArH); MS (m/z, %): 357 (M$^{+\bullet}$, 13), 222 (13), 193 (17), 136 (100), 77 (56); HRMS, Calc. (Found) for $C_{16}H_{12}N_5SO_2F$: 357.06957 (357.07017); *Anal.* Calcd.: C, 53.77; H, 3.38; N, 19.60. Found: C, 53.50; H, 3.49; N, 19.46.

N^1-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-ylcarbonyl]-N^4-phenyl thiosemicarbazide (2d). IR ($\tilde{\nu}$, cm^{-1}): 3325, 3221, 3158 (N—H), 1687 (C=O), 1232 (C=S); ^{1}H-NMR (DMSO-d$_6$, ppm): 11.6 (s, 1H, CONH), 10.1 (s, 1H, CSNH), 9.82 (s, 1H, NH), 8.08 (d, 2H, AB-System, *J* = 8.5 Hz, ortho-oxadiazole ArH), 7.70 (d, 2H, AB-System, *J* = 8.8 Hz, meta-oxadiazole ArH), 7.39–7.29 (m, 4H, ArH), 7.16 (t, 1H, *J* = 7.0 Hz, para-amino ArH); MS (m/z, %): 375 (M$^{+\bullet}$+2, 11), 373 (M$^{+\bullet}$, 25), 238 (13), 193 (48), 135 (100), 77 (79); HRMS, Calc. (Found) for $C_{16}H_{12}N_5SO_2{}^{35}Cl$: 373.04002 (373.03986); *Anal.* Calcd.: C, 51.41; H, 3.23; N, . Found: C, 51.49; H, 3.40; N, 18.80.

N^1-[3-(4-Bromophenyl)-1,2,4-oxadiazol-5-ylcarbonyl]-N^4-phenyl thiosemicarbazide (2e). IR ($\tilde{\nu}$, cm^{-1}): 3319, 3187, 3099 (N—H), 1688 (C=O), 1219 (C=S); ^{1}H-NMR (DMSO-d$_6$, ppm): 11.6 (s, 1H, CONH), 10.1 (s, 1H, CSNH), 9.83 (s, 1H, NH), 8.00 (d, 2H, AB-System, *J* = 8.4 Hz, ortho-oxadiazole ArH), 7.84 (d, 2H, AB-System, *J* = 8.7 Hz, meta-oxadiazole ArH), 7.42–7.29 (m, 4H, ArH), 7.16 (t, 1H, *J* = 6.9 Hz, para-amino ArH); MS (m/z, %): 419 (M$^{+\bullet}$+2, 11), 417 (M$^{+\bullet}$, 11), 284/282 (13/13), 196 (55), 135 (100), 77 (52); HRMS, Calc. (Found) for $C_{16}H_{12}N_5SO_2{}^{81}Br$: 418.98746 (418.98777); *Anal.* Calcd.: C, 45.94; H, 2.89; N, 16.74. Found: C, 45.90; H, 2.90; N, 16.85.

N^1-[3-(4-Methoxyphenyl)-1,2,4-oxadiazol-5-ylcarbonyl]-N^4-phenyl thiosemicarbazide (2f). IR ($\tilde{\nu}$, cm^{-1}): 3301, 3220, 3163 (N—H), 1686 (C=O), 1226 (C=S); ^{1}H-NMR (DMSO-d$_6$, ppm): 12.3 (s, 1H, CONH), 10.9 (s, 1H, CSNH), 10.7 (s, 1H, NH), 8.84 (d, 2H, AB-System, *J* = 9.1 Hz, ortho-oxadiazole ArH), 8.23 (m, 4H, ArH), 7.98 (broad m, 3H, ArH), 4.67 (s, 3H, OCH_3); MS (m/z, %): 369 (M$^{+\bullet}$, 4), 234

(13), 193 (6), 148 (100), 135 (67), 77 (48); HRMS, Calc. (Found) for $C_{17}H_{15}N_5SO_3$: 369.08956 (369.08884); *Anal.* Calcd.: C, 55.27; H, 4.09; N, 18.96. Found: C, 55.12; H, 4.05; N,19.05.

N^1-[3-(4-Nitrophenyl)-1,2,4-oxadiazol-5-ylcarbonyl]-N^4-phenyl thiosemicarbazide (2g). IR ($\tilde{\nu}$, cm^{-1}): 3329, 3223, 3157 (N—H), 1690 (C=O), 1220 (C=S); ^{1}H-NMR (DMSO-d$_6$, ppm): 11.6 (s, 1H, CONH), 10.1 (s, 1H, CSNH), 9.83 (s, 1H, NH), 8.46 (d, 2H, AB-System, J = 8.1 Hz, ortho-oxadiazole ArH), 8.33 (d, 2H, AB-System, J = 8.7 Hz, meta-oxadiazole ArH), 7.42–7.13 (m, 4H, ArH), 7.17 (t, 1H, J = 7.0 Hz, para-amino ArH); MS (m/z, %): 384 ($M^{+\bullet}$, 2), 249 (23), 135 (100), 77 (67); HRMS, Calc. (Found) for $C_{16}H_{12}N_6SO_4$: 384.06407 (384.06372); *Anal.* Calcd.: C, 49.99; H, 3.15; N, 21.86. Found: C, 50.02; H, 3.24; N, 21.89.

N^1-[3-(4-Hydroxyphenyl)-1,2,4-oxadiazol-5-ylcarbonyl]-N^4-phenyl thiosemicarbazide (2h). IR ($\tilde{\nu}$, cm^{-1}): 3289, 3183 (broad, N—H), 1694 (C=O), 1220 (C=S); ^{1}H-NMR (DMSO-d$_6$, ppm): 11.5 (s, 1H, CONH), 10.3 (s, 1H, OH), 10.0 (s, 1H, CSNH), 9.84 (s, 1H, NH), 7.90 (d, 2H, AB-System, J = 8.8 Hz, ortho-oxadiazole ArH), 7.42–7.29 (m, 4H, ArH), 7.16 (t, 1H, J = 7.1 Hz, para-amino ArH), 6.94 (d, 2H, AB-System, J = 8.8 Hz, meta-oxadiazole ArH); MS (m/z, %): 355 ($M^{+\bullet}$, 0.4), 220 (13), 134 (100), 77 (37); HRMS, Calc. (Found) for $C_{16}H_{13}N_5SO_3$: 355.07391 (355.07361); *Anal.* Calcd.: C, 54.07; H, 3.69; N, 19.71. Found: C, 53.91; H, 3.82; N, 19.67.

General procedure for the preparation of 5-[3-(4-substitutedaryl)-1,2,4-oxadiazol-5-yl]-2-(*N*-phenylamino)-1,3,4-oxadiazoles (3a-h). Thiosemicarbazides **2a-h** (0.5 mmol) were dissolved in 5 mL of dry THF together with DCC (0.75 mmol, 1.5 eq.), and the solution was refluxed under inert atmosphere for 2 h. After solvent evaporation under vacuum, crude products were digested in CH_2Cl_2/petroleum ether (30–60°C) 1:1, cooled in ice bath, filtered and washed with cold CH_2Cl_2/ petroleum ether 1:1. All products were purified by column chromatography on silica gel using CH_2Cl_2/MeOH 10:0.2 as eluent.

5-(3-Phenyl-1,2,4-oxadiazol-5-yl)-2-(N-phenylamino)-1,3,4-oxadiazole (3a). IR ($\tilde{\nu}$, cm^{-1}): 3172 (N—H), 1672 (C=C), 1638 (C=N); ^{1}H-NMR (DMSO-d$_6$, ppm): 11.3 (s, 1H, NH), 8.07 (broad s, 2H, ortho-oxadiazole ArH), 7.61 (broad d, 5H, J = 6.4 Hz, ArH), 7.39 (t, 2H, J = 7.6 Hz, meta-oxadiazole ArH), 7.07 (t, 1H, J = 7.1 Hz, para-amino ArH); MS (m/z, %): 305 ($M^{+\bullet}$, 100), 145 (18), 120 (46), 92 (15), 77 (71); HRMS, Calc. (Found) for $C_{16}H_{11}N_5O_2$: 305.09127 (305.09170); *Anal.* Calcd.: C, 62.95; H, 3.63; N, 22.94. Found: C, 62.80; H, 3.66; N, 23.15.

5-[3-(4-Tolyl)-1,2,4-oxadiazol-5-yl]-2-(N-phenylamino)-1,3,4-oxadiazole (3b). IR ($\tilde{\nu}$, cm^{-1}): 3258 (N—H), 1636 (C=C), 1621 (C=N); ^{1}H-NMR (DMSO-d$_6$, ppm): 11.3 (s, 1H, NH), 8.15 (dd, 2H, J = 5.2 Hz, ortho-oxadiazole ArH), 7.60 (d, 2H, AB-System, J = 7.6 Hz, ArH), 7.45 (m, 4H, ArH), 7.09 (t, 1H, J = 7.3 Hz, para-amino ArH), 2.39 (s, 3H, CH_3); MS (m/z, %): 319 ($M^{+\bullet}$, 100), 160 (13), 120 (13), 92 (6), 77 (13); HRMS, Calc. (Found) for $C_{17}H_{13}N_5O_2$: 319.10692 (319.10594); *Anal.* Calcd.: C, 63.94; H, 4.10; N, 21.93. Found: C, 63.96; H, 4.17; N, 21.93.

5-[3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl]-2-(N-phenylamino)-1,3,4-oxadiazole (3c). IR ($\tilde{\nu}$, cm^{-1}): 3286 (N—H), 1639 (C=C), 1614 (C=N); ^{1}H-NMR (DMSO-d$_6$, ppm): 11.3 (s, 1H, NH), 8.15 (dd, 2H, J = 5.2 Hz, ortho-oxadiazole ArH), 7.63 (d, 2H, AB-System, J = 7.6 Hz, ArH), 7.45 (m, 4H, ArH), 7.09 (t, 1H, J = 7.3 Hz, para-amino ArH); MS (m/z, %): 323 ($M^{+\bullet}$, 100), 163 (8), 120 (32), 92 (9), 77 (24); HRMS, Calc. (Found) for $C_{16}H_{10}N_5O_2F$: 323.08185 (323.08104); *Anal.* Calcd.: C, 59.44; H, 3.12; N, 21.66. Found: C, 59.32; H, 3.23; N, 21.79.

5-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-2-(N-phenylamino)-1,3,4-oxadiazole (3d). IR ($\tilde{\nu}$, cm^{-1}): 3290 (N—H), 1640 (C=C), 1613 (C=N); ^{1}H-NMR (DMSO-d$_6$, ppm): 11.3 (s, 1H, NH), 8.09 (d, 2H, AB-System, J = 8.5 Hz, ortho-oxadiazole ArH), 7.69 (d, 2H, AB-System, J = 8.8 Hz, meta-oxadiazole ArH), 7.62 (d, 2H, AB-System, J = 7.9 Hz, ortho-amino ArH), 7.40 (t, 2H, J = 7.6 Hz, meta-amino ArH), 7.08 (t, 1H, J = 7.3 Hz, para-amino ArH); MS (m/z, %): 341 ($M^{+\bullet}$+2, 35), 339 ($M^{+\bullet}$, 100), 181/179 (3/8), 120 (56), 92 (30), 77 (76); HRMS, Calc. (Found) for $C_{16}H_{10}N_5O_2{}^{35}Cl$: 339.05230 (339.05128); *Anal.* Calcd.: C, 56.56; H, 2.97; N, 20.61. Found: C, 56.70; H, 3.18; N, 20.70.

5-[3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl]-2-(N-phenylamino)-1,3,4-oxadiazole (3e). IR ($\tilde{\nu}$, cm^{-1}): 3292 (N—H), 1621 (C=C), 1584 (C=N); ^{1}H-NMR (DMSO-d$_6$, ppm): 11.3 (s, 1H, NH), 8.01 (d, 2H, AB-System, J = 8.3 Hz, ortho-oxadiazole ArH), 7.82 (d, 2H, AB-System, J = 8.6 Hz, meta-oxadiazole ArH), 7.61 (d, 2H, AB-System, J = 7.7 Hz, ortho-amino ArH), 7.40 (t, 2H, J = 7.5 Hz, meta-amino ArH), 7.07 (t, 1H, J = 7.4 Hz, para-amino ArH); MS (m/z, %): 385 ($M^{+\bullet}$+2, 99), 383 ($M^{+\bullet}$, 100), 227/225 (5/5), 120 (42), 92 (9), 77 (36); HRMS, Calc. (Found) for $C_{16}H_{10}N_5O_2{}^{79}Br$: 383.00179 (383.00193); *Anal.* Calcd.: C, 50.02; H, 2.62; N, 18.23. Found: C, 50.23; H, 2.80; N, 18.32.

5-[3-(4-Methoxyphenyl)-1,2,4-oxadiazol-5-yl]-2-(N-phenylamino)-1,3,4-oxadiazole (3f). IR ($\tilde{\nu}$, cm^{-1}): 3286 (N—H), 1639 (C=C), 1614 (C=N); ^{1}H-NMR (DMSO-d$_6$, ppm): 11.3 (s, 1H, NH), 8.03 (d, 2H, AB-System, J = 8.3 Hz, ortho-oxadiazole ArH), 7.60 (d, 2H, AB-System, J = 7.7 Hz, ortho-amino ArH), 7.40 (t, 2H, J = 7.5 Hz, meta-amino ArH), 7.14 (d, 2H, AB-System, J = 8.7 Hz, meta-oxadiazole ArH), 7.07 (t, 1H, para-amino ArH), 3.84 (s, 3H, OCH_3); MS (m/z, %): 335 ($M^{+\bullet}$, 100), 175 (4), 120 (10), 92 (6), 77 (15); HRMS, Calc. (Found) for $C_{17}H_{13}N_5O_3$: 335.10184 (335.10141); *Anal.* Calcd.: C, 60.89; H, 3.91; N, 20.88. Found: C, 60.64; H, 3.97; N, 20.89.

5-[3-(4-Nitrophenyl)-1,2,4-oxadiazol-5-yl]-2-(N-phenylamino)-1,3,4-oxadiazole (3g). IR ($\tilde{\nu}$, cm^{-1}): 3372 (N—H), 1611 (C=C), 1580 (C=N); ^{1}H-NMR (DMSO-d$_6$, ppm): 11.6 (s, 1H, NH), 8.45 (d, 2H, AB-System, J = 8.6 Hz, ortho-oxadiazole ArH), 8.34 (d, 2H, AB-System, J = 9.0 Hz, meta-oxadiazole ArH), 7.63 (d, 2H, AB-System, J = 7.9 Hz, ortho-amino ArH), 7.41 (t, 2H, J = 8.2 Hz, meta-amino ArH), 7.09 (t, 1H, J = 7.6 Hz, para-amino ArH); MS (m/z, %): 350 ($M^{+\bullet}$, 100), 190 (3), 120 (26), 92 (8), 77 (17); HRMS, Calc. (Found) for $C_{16}H_{10}N_6O_4$: 350.07635 (350.07591); *Anal.* Calcd.: C, 54.85; H, 2.88; N, 23.99. Found: C, 54.53; H, 2.99; N, 23.69.

5-[3-(4-Hydroxyphenyl)-1,2,4-oxadiazol-5-yl]-2-(N-phenylamino)-1,3,4-oxadiazole (3h). IR ($\tilde{\nu}$, cm^{-1}): 3298 (broad, N—H), 1626 (C=C); ^{1}H-NMR (DMSO-d$_6$, ppm): 11.2 (s, 1H, NH), 10.3 (s, 1H, OH), 7.90 (d, 2H, AB-System, J = 9.3 Hz, ortho-oxadiazole ArH), 7.61 (d, 2H, AB-System, J = 8.2 Hz, ortho-amino ArH), 7.39 (t, 2H, J = 7.4 Hz, meta-amino ArH), 7.07 (t, 1H, J = 7.3 Hz, para-amino ArH), 6.94 (d, 2H, AB-System, J = 8.8 Hz, meta-oxadiazole ArH); MS (m/z, %): 321 ($M^{+\bullet}$, 100), 161 (12), 120 (13), 92 (10), 77 (26); HRMS, Calc. (Found) for $C_{16}H_{11}N_5O_3$: 321.08619 (321.08603); *Anal.* Calcd.: C, 59.81; H, 3.45; N, 21.80. Found: C, 59.56; H, 3.63; N, 21.66.

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TMSCl-Mediated One-Pot, Three-Component Synthesis of 2*H*-Indazolo[2,1-*b*]phthalazine-triones

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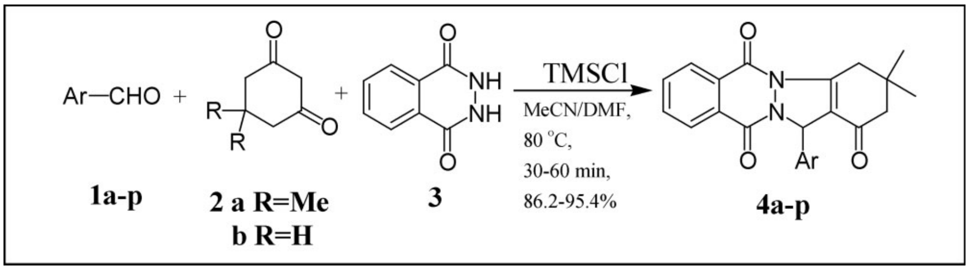

A simple, efficient, and cost-effective method for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione derivatives by a one-pot, three-component condensation reaction of phthalazide, dimedone, or 1,3-cyclohexanedione and aromatic aldehydes under CH_3CN/DMF (8:2) media at 80°C for 30–60 min in the presence of trimethylsilyl chloride (TMSCl) is described.

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INTRODUCTION

One-pot multicomponent reactions (MCRs) by virtue of their convergence, productivity, facile execution, and high yield have attracted considerable attention in recent years [1]. There have been tremendous developments in three- or four-component reaction specially the Biginelli [2], Passerini [3], Ugi [4], and Mannich [5] reactions, which have further led to renaissance of MCRs. Nevertheless, great efforts have been and still are being made to find and develop new MCRs.

The development of new synthetic methods for the efficient preparation of heterocycles containing phthalazine ring fragment (antihypoxic and antipyretic agent **I** and HAV 3C inhibitor **II**) is an interesting challenge because they show some pharmacological and biological activities [6–8]. Phthalazine derivatives were reported to possess anticonvulsant [8], cardiotonic [9], and vasorelaxant [10] activities. Therefore, a number of methods have been reported for the synthesis of phthalazine derivatives [11–19]. In recent years, the development of more economical and environmental friendly conversion processes is gaining interest in the chemical community (Figure 1).

In continuation of our work on the use of silica-supported reagents [20], TMSCl has attracted our interest. Among the various silicon-based acidic reagents, TMSCl has received considerable attention as an inexpensive and readily available reagent for various organic transformations [21]. Advantages such as its compatibility with many synthetically valuable nucleophiles (*e.g.*, organometalic reagents and cuprates) and its non-aggregation nature substantially simplify the analysis of the reaction mechanism. Because of this, it has been extensively used as a protecting group for various functional groups such as hydroxy and amino group [20(a),22] and as a promoter for cycloaddition and conjugate addition reactions [21(a)] under mild and convenient conditions to offer the products in excellent yield with high selectivity and one-pot cyclocondensation of dimedone, aldehydes, with/without urea or thiourea to form octahydroquinazolones and 1,8-dioxo-octahydro xanthenes in excellent yields [23]. However, to the best of our knowledge, there is no report on the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-triones using TMSCl as a reagent. In this communication, we report a TMSCl-mediated simple, efficient, and environmentally benign three-component condensation reaction of aromatic aldehydes **1a-p,** 5,5-dimethyl-1,3-cyclohexanedione **2a** or 1,3-cyclohexanedione **2b** and phthalhydrazide **3** in the preparation of 13-aryl-2,3,4,13-tetrahydroindazolo[1,2-*b*]phthalazine-1,6,11(13*H*)-trione or 3,4-dihydro-3,3-dimethyl-13-aryl-2*H*-indazolo[1,2-*b*]phthalazine-1,6,11(13*H*)-trione derivatives **4a-p** (Scheme 1).

RESULTS AND DISCUSSION

During the course of our studies directed towards the development of practical, and eco-friendly procedures [24], we developed the applicability of TMSCl for efficient, convenient, and facile synthesis of 13-aryl-

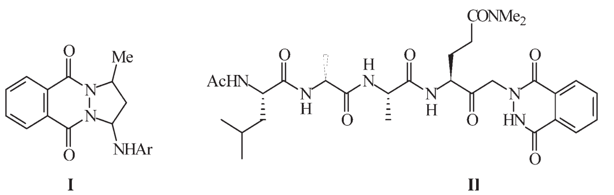


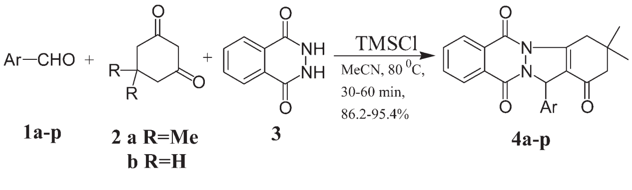
Figure 1. Antihypoxic and antipyretic agent **I** & HAV 3C inhibitor **II**.

2,3,4,13-tetrahydroindazolo[1,2-*b*]phthalazine-1,6,11(13*H*)-trione or 3,4-dihydro-3,3-dimethyl-13-aryl-2*H*-indazolo-[1,2-*b*]phthalazine-1,6,11(13*H*)-trione derivatives by a one-pot three-component condensation reaction of aromatic aldehydes **1a-p**, 5,5-dimethyl-1,3-cyclohexanedione **2a** or 1,3-cyclohexanedione **2b** and phthalhydrazide **3** in CH_3CN/DMF (8:2) at 80°C (Scheme 1).

Initially, a pilot reaction was attempted using benzaldehyde **1**, 5,5-dimethyl-1,3-cyclohexanedione **2a** and phthalhydrazide **3** in the presence of TMSCl (0.5 equiv) without any solvent. After 3 h, only 27% of 3,3-dimethyl-13-phenyl-2,3,4,13-tetrahydroindazolo[2,1-*b*]phthalazine-1,6,11-trione product **4a** was isolated. Increasing the amount of TMSCl (1.0 equiv) did not improve the product yield to a considerable amount. Subsequently, we investigated the effect of different solvents on the reaction rate as well as yield of the products. In protic solvents such as MeOH or EtOH, the reaction was very slow and resulted in lower product yield. Similar results were obtained in coordinating solvents such as THF, diethyl ether, and dimethyl ether. On the other hand, conducting the reactions in chlorinated solvents such as dichloromethane and chloroform improved both the reaction rates as well as product yields. After screening for different solvents, acetonitrile/DMF (8:2) came out as the solvent of choice, which not only afforded the products in good yield, but also with higher reaction rates (95% yield in 0.5 h). The formation of compound **4a** was evident from the appearance of $[M+H]^+$ peak at *m*/*z* 373 in mass spectrum (ESI), —C=O stretching at 1667 cm^{-1} in IR and the appearance of methine proton as singlet at δ 6.34 in ^1H NMR

To extend the scope of this catalytic transformation, the general applicability of this method was verified by reacting a number of substituted benzaldehydes with 5,5-dimethyl-1,3-cyclohexanedione **2a** or 1,3-cyclohexanedione **2b**. No observable substituent effect was noted for the various aromatic aldehydes.

Scheme 1



Aromatic aldehydes **1a-p**, 1,3-cyclohexanedione **2a-b** with phthalhydrazide **3** in the presence of TMSCl undergo a fast 1:1:1 addition reaction at 80°C in CH_3CN/DMF for 30–60 min to produce 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione derivatives **4a-p** (Scheme 1). The results were excellent in terms of yields and product purity in the presence of TMSCl instead of *p*-TSA24, compounds **4a-p** are stable solids whose structures are fully supported by IR, ^1H, and ^{13}C NMR spectroscopy's, mass spectrometry and elemental analysis.

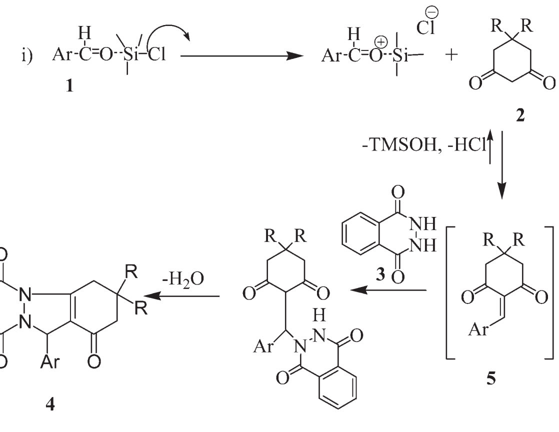
A feasible pathway (Scheme 2) might involve the role of TMSCl as a Lewis acid, which activated the aromatic aldehydes **1** by coordinating to the carbonyl group followed by the removal of TMSOH and HCl with enol form of 1,3-cyclohexanedione **2** to form a heterodienes **5**. Then, the subsequent Michael-type addition of the phthalhydrazide **3** followed by cyclization affords the corresponding products **4**.

In conclusion, we have successfully demonstrated a novel catalytic application of TMSCl for the efficient synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione derivatives. This simple procedure is efficient and can be applied to a wide variety of aromatic aldehydes. Shorter reaction times and excellent product yields make this catalytic system an alternative method for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione derivatives. Further application to explore this simple catalytic system is under progress.

EXPERIMENTAL

Melting points were measured with Fiescher-Johns melting point apparatus. ^1H NMR spectra were recorded with an AVANCE 300 Bruker (at 300 MHz) and Gemini 200 MHz spectrometers in $CDCl_3$. Chemical shifts relative to TMS as internal standard are given as δ values in ppm. ^{13}C NMR was

Scheme 2



recorded in $CDCl_3$ on a Varian (75 Hz) spectrometer. IR spectra were taken with a Perkin–Elmer 1725A FT-IR spectrophotometer. EI–MS mass spectra were measured at 70 eV (EI).

General procedure. A solution of benzaldehyde **1a** (10 m*M*), dimedone **2a** (10 m*M*) and phthalhydrazide **3** (12 m*M*), and CH_3CN/DMF (8 mL/2 mL) containing TMSCl (10 m*M*) was refluxed (80°C) till the reaction was completed (monitored by TLC). After completion, the reaction mass was poured into ice cold water, stirred, and filtered. The solid product **4a** obtained was filtered through a Buckner funnel, washed with hexane (2 × 5 mL) and dried. Spectral data for new compounds:

13-(2,4-Dichlorophenyl)-3,3-dimethyl-2,3,4,13-tetrahydro-indazolo[2,1-b]phthalazine-1,6,11-trione (4b). Pale yellow crystalline powder; Yield: 94.8%; mp 208–209°C. IR (KBr): $V_{\max}$ 2942, 1657, 1362, 1268, 711 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): $\delta = 1.24$ (s, 3H); 1.25 (s, 3H); 2.31 (s, 2H); 3.16–3.41 (dd, $J = 2.2$, 18.8 Hz, 2H); 6.57 (s, 1H); 7.28–7.36 (m, 2H, Ar); 7.46 (d, $J = 8.3$ Hz, 1H, Ar); 7.80–7.89 (m, 2H, Ar); 8.23–8.38 (m, 2H). LC/MS: $m/z = 441$ $[M+H]^+$. *Anal*. Calcd for $C_{23}H_{18}Cl_2N_2O_3$: C, 62.60; H, 4.11; N, 6.35%. Found: C, 62.53; H, 4.10, N, 6.35%.

13-(3-Hydroxyphenyl)-3,3-dimethyl-2,3,4,13-tetrahydro-indazolo[2,1-b]phthalazine-1,6,11-trione (4f). Light yellow crystalline powder, mp 257–258°C. Yield: 89.2%. ^1H NMR (200 MHz, DMSO-d_6): $\delta = 1.20$ (s, 6H); 2.27 (s, 2H); 3.11–3.41 (dd, $J = 1.4$, 18.8, 2H); 6.23 (s, 1H); 6.63–6.82 (m, 3H, Ar); 7.02–7.10 (t, $J = 8.0$, 1H, Ar); 7.84–7.89 (m, 2H, Ar); 8.16–8.32 (m, 2H, Ar); 9.02 (brs, 1H, OH). LC/MS: $m/z =$ 389 $[M+H]^+$. *Anal*. Calcd for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21%. Found: C, 71.11; H, 5.17; N, 7.21%.

3,3-Dimethyl-13-naphthalen-1-yl-2,3,4,13-tetrahydroindazolo[2,1-b]phthalazine-1,6,11-trione (4g). Pale yellow crystalline powder, Yield: 88.4%. mp 264–265°C. ^1H NMR (200 MHz, DMSO-d_6): $\delta = 1.19$ (s, 3H); 1.23 (s, 3H); 2.25 (s, 2H); 3.20–3.47 (dd, $J = 2.2$, 18.8 Hz, 2H); 7.12 (s, 1H); 7.36–7.59(m, 4H, Ar); 7.75–7.84 (m, 5H, Ar); 8.15–8.36 (m, 2H, Ar). LC/MS: $m/z = 423$ $[M+H]^+$. *Anal*. Calcd for $C_{27}H_{22}N_2O_3$; C, 76.76; H, 5.25; N, 6.63%. Found: C, 76.76; H, 5.24; N, 6.63%.

3,3-Dimethyl-13-(3,4,5-trimethoxyphenyl)-2,3,4,13-tetra-hydroindazolo[2,1-b]phthalazine-1,6,11-trione (4h). Pale yellow crystalline powder, mp 202–203°C; Yield: 86.2%. ^1H NMR (200 MHz, DMSO-d_6): $\delta = 1.24$ (s, 3H); 1.25 (s, 3H); 2.32 (s, 2H); 3.12–3.44 (dd, $J = 2.2$, 18.8, 2H); 3.77 (s, 3H); 3.82 (s, 6H); 6.34 (s, 1H); 6.57 (s, 2H, Ar); 7.82–7.86 (m, 2H, Ar); 8.26–8.34 (m, 2H, Ar).LC/MS: $m/z = 463$ $[M+H]^+$. *Anal*. Calcd for $C_{26}H_{26}N_2O_6C$, 67.52; H, 5.67; N, 6.06%. Found: C, 67.49; H, 5.62; N, 6.00%.

13-Phenyl-2,3,4,13-tetrahydroindazolo[2,1-b]phthalazine-1,6,11-trione (4i). Pale yellow crystalline powder, Yield: 93.8%. mp 224–225°C. IR (KBr): $V_{\max}$ 3290, 1685, 1512, 1479, 1181, 1125 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): $\delta =$ 2.18–2.45 (m, 4H); 3.19–3.61 (m, 2H); 6.34 (s, 1H); 7.23–7.41 (m, 5H, Ar); 7.83–7.88 (m, 2H, Ar); 8.09–8.32 (m, 2H, Ar). LC/MS: $m/z = 345$ $[M+H]^+$. *Anal*. Calcd for $C_{21}H_{16}N_2O_3$: C, 73.24; H, 4.68; N, 8.13%. Found: C, 73.20; H, 4.64; N, 8.13%.

13-(2,4-Dichlorophenyl)-2,3,4,13-tetrahydroindazolo[2,1-b]-phthalazine-1,6,11-trione (4j). Pale yellow crystalline powder, Yield: 94.0%; mp 274–275°C. IR (KBr): $V_{\max}$ 2943, 1659, 1362, 1265, 701 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): $\delta =$ 2.15–2.42 (m, 4H); 3.23–3.46 (m, 2H); 6.60 (s, 1H); 7.25–7.48 (m, 2H, Ar); 7.72–7.93 (m, 3H, Ar); 8.03–8.37 (m, 2H, Ar). LC/MS: $m/z = 413$ $[M+H]^+$. *Anal*. Calcd for $C_{21}H_{14}C_{l2}N_2O_3$: C, 61.03; H, 3.41; N, 6.78%. Found: C, 61.01; H, 3.42; N, 6.77%.

13-(2-Chlorophenyl)-2,3,4,13-tetrahydroindazolo[2,1-b]-phthalazine-1,6,11-trione (4k). Pale yellow crystalline powder, Yield: 91.1%; mp 250–252°C. IR (KBr): $V_{\max}$ 2925, 1660, 1366, 1270, 703 cm^{-1}. ^1H NMR (200 MHz, DMSO-d$_6$): $\delta = 2.22$–2.58 (m, 4H); 3.31–3.47 (m, 2H); 6.63 (s, 1H); 7.26–7.50 (m, 4H, Ar); 7.90–7.95 (m, 2H, Ar); 8.10–8.19 (m, 1H, Ar), 8.31–8.36 (m, 1H, Ar); LC/MS: $m/z = 379$ $[M+H]^+$. *Anal*. Calcd for $C_{21}H_{15}ClN_2O_3$: C, 66.58; H, 3.99; N, 7.40%. Found: C, 66.58; H, 3.88; N, 7.42%.

13-(4-Chlorophenyl)-2,3,4,13-tetrahydroindazolo[2,1-b]-phthalazine-1,6,11-trione (4l). Pale yellow crystalline powder, Yield: 92.0%; mp 272–273°C. IR (KBr): $V_{\max}$ 3290, 1685, 1512, 1479, 1181, 1125 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): $\delta = 2.23$–2.43 (m, 4H); 3.21–3.52 (m, 2H); 6.33 (s, 1H); 7.23–7.43 (m, 4H, Ar); 7.92–7.77 (m, 2H, Ar); 8.17–8.35 (m, 2H, Ar). LC/MS: $m/z = 379$ $[M+H]^+$. $\delta =$ (75 MHz, $CDCl_3$ + DMSO-d_6) 21.6, 23.8, 30.4, 60.5, 63.7, 117.7, 126.6, 127.8, 129.0, 132.6, 133.4, 134.2, 135.9, 152.7, 153.5, 155.1, 161.8, 167.3, 191.8. *Anal*. Calcd for $C_{21}H_{15}ClN_2O_3$: C, 66.58; H, 3.99; N, 7.40%. Found: C, 66.55; H, 3.99; N, 7.38%.

13-(3-Hydroxyphenyl)-2,3,4,13-tetrahydroindazolo[2,1-b]-phthalazine-1,6,11-trione (4m). Pale yellow crystalline powder, Yield: 89.4%; mp 267–268°C. ^1H NMR (200 MHz, DMSO-d_6): $\delta = 2.21$–2.43 (m, 4H); 3.20–3.61 (m, 2H); 6.24 (s, 1H); 6.66–6.82 (m, 3H, Ar); 7.10 (t, $J = 8.8$ Hz, 1H, Ar); 7.86–7.89 (m, 2H, Ar); 8.21–8.32 (m, 2H, Ar); 9.04 (brs, 1H). LC/MS: $m/z = 361$ $[M+H]^+$. *Anal*. Calcd for $C_{21}H_{16}N_2O_4$: C, 69.99; H, 4.48; N, 7.77%. Found: C, 69.98; H, 4.49; N, 7.77%.

13-Naphthalen-1-yl-2,3,4,13-tetrahydroindazolo[2,1-b]-phthalazine-1,6,11-trione (4n). Pale yellow crystalline powder, Yield: 88.9%; mp 260–262°C; ^1H NMR (200 MHz, DMSO-d_6): $\delta = 2.19$–2.38 (m, 4H); 3.22–3.62 (m, 2H); 7.10 (s, 1H); 7.34–7.64 (m, 4H, Ar); 7.75–7.89 (m, 4H, Ar); 8.09–8.11 (m, 1H, Ar); 8.29–8.34 (m, 1H, Ar); 8.47 (d, $J = 8.0$ Hz, 1H, Ar). LC/MS: $m/z = 395$ $[M+H]^+$. *Anal*. Calcd for $C_{25}H_{18}N_2O_3$: C, 76.13; H, 4.60; N, 7.10%. Found: C, 76.11; H, 4.61; N, 7.11%.

13-(4-Bromo-phenyl)-2,3,4,13-tetrahydroindazolo[2,1-b]-phthalazine-1,6,11-trione (4o). Pale yellow crystalline powder, Yield: 93.0%; mp 280–281°C. IR (KBr): $V_{\max}$ 2942, 1658, 1363, 1265, 703 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): $\delta = 2.21$–2.26 (m, 2H); 2.38–2.42 (m, 2H); 3.25–3.31 (dt, $J =$ 5.7 Hz, 1H); 3.48–3.54 (dt, $J = 5.7$ Hz, 1H); 6.30 (s, 1H); 7.34 (d, $J = 8.5$ Hz, 2H), 7.43 (d, $J = 8.5$ Hz, 2H, Ar); 7.88 (t, $J = 4.7$ Hz, 2H, Ar); 8.19 (t, $J = 4.7$ Hz, 1H, Ar), 8.31 (t, $J = 4.7$ Hz, 1H, Ar). δ_C (75 MHz, DMSO-d_6) 21.7, 23.9, 36.2, 63.7, 69.2, 117.7, 121.0, 126.6, 127.4, 128.4, 129.0, 129.7, 130.9, 133.7, 134.4, 136.8, 153.1, 155.3, 160.7, 165.7, 192.2. LC/MS: $m/z = 423$ $[M+H]^+$. *Anal*. Calcd for $C_{21}H_{15}BrN_2O_3$: C, 59.59; H, 3.57; N, 6.62%. Found: C, 59.59; H, 3.54; N, 6.61%.

13-(3-Methoxyphenyl)-2,3,4,13-tetrahydroindazolo[2,1-b]-phthalazine-1,6,11-trione (4p). Pale yellow crystalline powder, Yield: 88.2%; mp 210–211°C. IR (KBr): $V_{\max}$ 2942, 1658, 1366, 1427, 701 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 2.21$–2.46 (m, 4H); 3.19–3.65 (m, 2H); 3.79 (s, 3H, OMe); 6.30 (s, 1H); 6.81 (dd, $J = 8.0$ Hz, 1H, Ar); 6.94–6.96 (m, 2H, Ar); 7.24 (t, $J = 8.08$ Hz, 1H, Ar); 7.89–7.91 (m, 2H, Ar); 8.17–8.33 (m, 2H, Ar). LC/MS: $m/z = 375$ $[M+H]^+$. *Anal*. Calcd for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48%. Found: C, 70.55; H, 4.83; N, 7.48%.

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Synthesis and Biological Screening of Some Fluorinated Dibenzofuran Containing 3-Chlorochromones and Benzothiazepines

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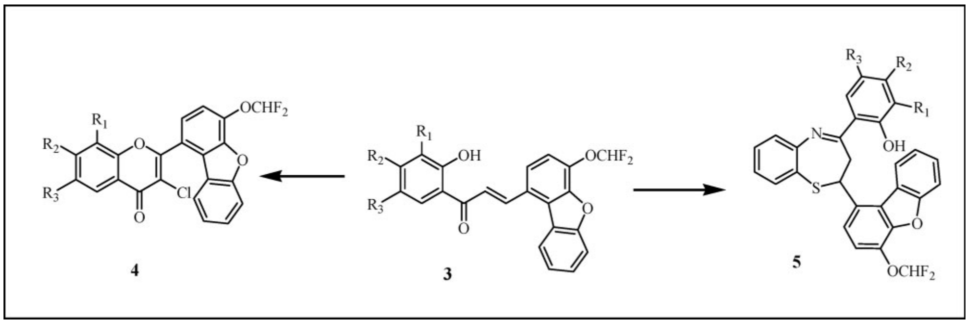

Variously substituted chalcones were synthesized from 4-difluoromethoxy-dibenzofuran-1-carboxaldehyde. These chalcones were converted into corresponding 3-chlorochromones and dihydro-benzothiazepines. Synthesized compounds were tested for their antifungal, antibacterial, antiviral and antioxidant activities.

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INTRODUCTION

In recent days, active research has been initiated on halogen containing heterocycles, particularly fluorine containing heterocycles. Incorporation of fluorine can alter the course of reaction as well as biological activities. Introduction of fluorine atom into an organic molecule largely enhances the pharmacological properties as compared with nonfluorinated analogues [1]. Despite the fact that fluorine has greater size than hydrogen, several studies have demonstrated that fluorine is a reasonable hydrogen mimic and exerts only a minor steric demand at receptor sites [2].

Fluorine containing organic compounds are associated with antimicrobial [3], antibacterial [4], and anticancer [5] activities. They also act as selective inhibitors of biosynthesis of aminergic neurotransmitters [6].

Dibenzofurans are associated with biological activities like antifungal [7], antibacterial [8], anti-inflammatory, and antiallergic [9].

Chalcones are versatile synthones and can be cyclized to give chromones [10], chlorochromones, and benzothiazepines [11]. Chalcones can be converted into 3-chlorochromones by using DMSO+$CuCl_2$ system [11,12].

Chalcones possess a broad spectrum of biological activities including antibacterial, anthelmintic, amoebicidal, antiulcer, antiviral, insecticidal, antiprotozoal, anticancer, cytotoxic, immunosuppressive, etc. [13,14].

Halogeno substituted chromones with heterocyclic substituent at 2-position are reported to have bronchodilatory [15], coronary spasmolytic [16], and antimicrobial properties [17,18].

1,4-Benzothiazepine derivatives are of considerable interest because of their biological activities as inhibitors of HIV-1 integrase [10], anti-tumor, antibiotics, enzyme inhibitors, muscle relaxant, anticonvulsant, sedatives, and hypnotics [19]. Some dihydrobenzothiazepines have excellent fungicidal activities [20]. Benzothiazepines are also associated with chemotherapeutic application such as antihypertension [21] and antibacterial activities [11,22]. Benzothiazepines have been reported as potent neuroleptic agents [23].

Biological activities associated with these molecules and importance of fluorine, prompted us to synthesize some fluorine containing chalcones, 3-chlorochromones and 1,4-benzothiazepines, and screen them for biological activities.

RESULT AND DISCUSSION

In this work, 2-hydroxy acetophenones **2** were treated with 4-difluoro-methoxy-dibenzofuran-1-carboxaldehyde **1** in presence of 40% KOH to afford corresponding 3-(4-(difluoromethoxy)dibenzofuran-1-yl)-1-(2-hydroxyphenyl) prop-2-en-1-one **3**. Compound **3** on treatment with copper

Table 1

Antioxidant activity results with test concentration 125 μg/mL.

Compd.	R_1	R_2	R_3	% AO activity
3a	H	H	H	−2.96
3f	H	Cl	H	5.65
4a	H	H	H	−2.71
4e	Cl	H	Cl	−23.26
5a	H	H	H	4.58
5b	H	H	Br	1.62

chloride in DMSO gave 3-chlorochromone **4** and with 2-aminothiophenol in alcohol gave benzothiazepine **5**.

The structures of compounds **3**, **4**, and **5** are confirmed by spectral analysis (IR, ^{1}H-NMR, and MS). The IR spectrum of compound **3a** shows a strong absorption band (cm^{-1}) at 3305 for —OH and 1633 for α, β-unsaturated carbonyl groups. The IR spectrum of compound **4a** shows no absorption band for —OH, whereas the band at 1650 is for carbonyl group of chromone. The IR spectrum of compound **5a** shows the absorption band at 3397 for —OH, whereas the band for carbonyl group is absent.

The ^{1}H-NMR spectra of **3a** shows a doublet at 8.40 δ for one proton (J = 15 Hz) for transcoupled protons of α, β-unsaturated carbonyl group. In ^{1}H-NMR spectrum of **4a**, the presence of triplet for one proton at 6.80 δ (J = 72.94 Hz) indicates coupling of proton of —$OCHF_2$ group with two fluorine atoms. The ^{1}H-NMR spectrum of **5a** shows three doublet of doublets at 3.21, 3.47, and 5.97 δ, which are the characteristic peaks of dihydrobenzothiazepine moiety.

The structures of all compounds are also confirmed by mass spectral analysis. The mass spectra shows M^+ peaks at corresponding masses of respective molecules.

Antioxidant activity. The antioxidant activity of some of the synthesized compounds was determined by DPPH method using Trolox as a reference standard. Amongst, the compounds screened for antioxidant activity none of the compounds showed promising activity as shown in Table 1.

Antimicrobial activity. The antimicrobial activity of some compounds was assessed against 24 hr culture of some selected bacteria and fungi. The bacteria used were *Escherichia coli* and *Staphylococcus aureus*; the fungi used were *Candida albicans* and *Aspergillus fumigatus*.

The antimicrobial activity was performed by agar well diffusion method at 100 and 1000 μg/mL conc. in DMSO. Nutrient agar and potato dextrose agar were used to culture the bacteria and fungi, respectively.

Amphotericin B and Vancomycin were used as standards for comparison of antifungal and antibacterial activities respectively. The activity is reported by measuring the diameter of the zone of inhibition. All the screened compounds were found inactive as shown in Table 2.

Antiviral activity. The antiviral activity of some of the compounds was determined against *Herpes Simplex virus-2* by CPE inhibition assay. Vero cells (African green monkey kidney cell line-ATCC # CCL-81) were cultivated as monolayers in 5% carbon dioxide at 37°C, in Dulbecco's modified Eagle medium (MEM) with 5% fetal bovine serum (FBS).

The diluted extracts (100 μg/mL) were transferred to the aspirated Vero cell monolayers. Cultures were incubated at 37°C for 60 minutes. 100 μL of virus (100 $TCID_{50}$) was added to each well. The tray was transferred to an environmental chamber (37°C).

Cultures were inspected periodically for virus-induced cytopathic effect (viral CPE). Absence of CPE indicated

Table 2

Antimicrobial activity results.

					Antifungal test models		Antibacterial test models		
Compd.	R_1	R_2	R_3	Conc. (μg/ml)	*C. albicans* ATCC 14503	*A. fumigatus* ATCC 16424	*S. aureus* 209P	E. coli ATCC 25922	Remark
3a	H	H	H	100	–	–	–	–	inactive
				1000	–	–	–	–	inactive
3f	H	Cl	H	100	–	–	–	–	inactive
				1000	–	–	–	–	inactive
4a	H	H	H	100	–	–	–	–	inactive
				1000	–	–	–	–	inactive
4e	Cl	H	Cl	100	–	–	–	–	inactive
				1000	–	–	–	–	inactive
5a	H	H	H	100	–	–	–	–	inactive
				1000	–	–	–	–	inactive
5b	H	H	Br	100	–	–	–	–	inactive
				1000	–	–	–	–	inactive
Amphotericin B (20 μg/ml)					22	24	18	–	–

Table 3

Antiviral activity results with test concentration 50 μg/mL.

Compd.	R_1	R_2	R_3	% CPE inhibition
3a	H	H	H	–
3f	H	Cl	H	–
4a	H	H	H	–
4e	Cl	H	Cl	–
5a	H	H	H	–
5b	H	H	Br	–
Scoring	**−0–25%**		**++26–50%**	
	+++51–75%		**++++76–100%**	

complete inactivation of the virus. Partial inhibition was considered to be a negative result. All the screened compounds were found inactive as shown in Table 3.

EXPERIMENTAL

All the recorded melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded on Perkin-Elmer FTIR spectrophotometer in KBr disc. ^{1}H-NMR spectra were recorded on Varian 300 MHz spectrometer and Bruker Avance II 400 MHz spectrometer in DMSO or $CDCl_3$ as a solvent and TMS as an internal standard. Peak values are shown in δ ppm. Mass spectra were recorded on a Q-T micromass 5630 mass spectrometer.

3-(4-(Difluoromethoxy)dibenzofuran-1-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one (3a–f). Equimolar amount of compound **1** (0.02 mol) and **2** (0.02 mol) were dissolved in 25 mL of alcohol in conical flask. To this reaction mixture 40% KOH (10 mL) was added. The reaction mixture was stirred at room temperature for 48 hr. The contents were then poured into crushed ice and neutralized with acetic acid. The yellow solid thus obtained was filtered and crystallized from alcohol to afford compounds **3**. The compounds synthesized by above procedure are listed in Table 4.

3-(4-(Difluoromethoxy)dibenzofuran-1-yl)-1-(2-hydroxyphenyl)-prop-2-en-1-one (3a). IR (KBr): 3305, 1633, 1589 and 1501, 1115 cm^{-1}; ^{1}H-NMR (DMSO): δ 6.75–8.22 (m, 12H, aromatic, olefinic, and —$OCHF_2$), 8.40 (d, 1H, $J = 15.00$ Hz, β to carbonyl), 12.61 (s, 1H, —OH); Mass: M$^+$ 380.

1-(5-Bromo-2-hydroxyphenyl)-3-(4-(difluoromethoxy)dibenzofuran-1-yl)prop-2-en-1-one (3b). IR (KBr): 3308, 1635, 1598 and 1515, 1125 cm^{-1}; ^{1}H-NMR (DMSO): δ 6.81–8.31 (m, 11H, aromatic, olefinic, and —$OCHF_2$), 8.43 (d, 1H, $J = 15.10$ Hz, β to carbonyl), 12.72 (s, 1H, —OH); Mass: M$^+$ 459.

3-(4-(Difluoromethoxy)dibenzofuran-1-yl)-1-(5-fluoro-2-hydroxyphenyl)prop-2-en-1-one (3c). IR (KBr): 3313, 1638, 1610 and 1519, 1177, 1130 cm^{-1}; ^{1}H-NMR (DMSO): δ 6.87–7.91 (m, 7H, aromatic, olefinic, and —$OCHF_2$), 8.13–8.20 (m, 3H, aromatic), 8.40–8.44 (m, 1H, aromatic) 8.55 (d, 1H, $J = 15.30$ Hz, β to carbonyl), 12.87 (s, 1H, —OH); Mass: M$^+$ 398.

1-(5-Chloro-2-hydroxyphenyl)-3-(4-(difluoromethoxy)dibenzofuran-1-yl)prop-2-en-1-one (3d). IR (KBr): 3311, 1636, 1601 and 1510, 1125, 1066 cm^{-1}; ^{1}H-NMR (DMSO): δ 6.72–7.75 (m, 7H, aromatic, olefinic, and —$OCHF_2$), 7.98–8.42 (m, 4H, aromatic) 8.48 (d, 1H, $J = 15.17$ Hz, β to carbonyl), 12.77 (s, 1H, —OH); Mass: M$^+$ 414 with isotopic peaks.

1-(3,5-Dichloro-2-hydroxyphenyl)-3-(4-(difluoromethoxy)dibenzofuran-1-yl) prop-2-en-1-one (3e). IR (KBr): 3320, 1642, 1125, 1076 cm^{-1}; ^{1}H-NMR (DMSO): δ 6.77–7.87 (m, 6H, aromatic, olefinic, and —$OCHF_2$), 7.98–8.42 (m, 3H, aromatic) 8.48–8.50 (m, 2H, aromatic, and β to carbonyl), 12.83 (s, 1H, —OH); Mass: M$^+$ 449 with isotopic peaks.

1-(4-Chloro-2-hydroxyphenyl)-3-(4-(difluoromethoxy)dibenzofuran-1-yl)prop-2-en-1-one (3f). IR (KBr): 3305, 1635, 1599 and 1496, 1125, 1063 cm^{-1}; ^{1}H-NMR (DMSO): δ 6.73–7.92 (m, 8H, aromatic, olefinic, and —$OCHF_2$), 8.21–8.42 (m, 4H, aromatic, and β to carbonyl), 12.97 (s, 1H, —OH); Mass: M$^+$ 414 with isotopic peaks.

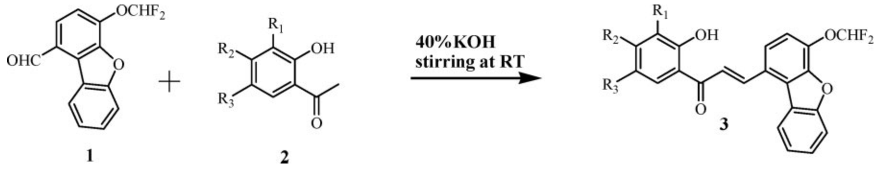
3-Chloro-2-(4-(difluoromethoxy)dibenzofuran-1-yl)-4*H*-chromon-4-one (4a–f). Compound **3** (0.001 mole) was dissolved in 15 mL DMSO. To this reaction mixture excess of $CuCl_2$ (2 gm) was added. The reaction mixture was heated under mild reflux for 3 hr and left overnight. Then 100 mL ice

Table 4

Physical and analytical data of synthesized compounds.

Compound	R_1	R_2	R_3	mp (°C)	Yield (%)	Elemental analysis Calcd. (Found) C	 H
3a	H	H	H	157	66	69.47 (69.45)	3.71 (3.73)
3b	H	H	Br	188	67	57.54 (57.53)	2.85 (2.86)
3c	H	H	F	182	65	66.34 (66.33)	3.29 (3.31)
3d	H	H	Cl	201	67	63.70 (63.68)	3.16 (3.16)
3e	Cl	H	Cl	191	61	58.82 (58.79)	2.69 (2.71)
3f	H	Cl	H	174	68	63.70 (63.68)	3.16 (3.19)
4a	H	H	H	184	49	64.02 (64.00)	2.69 (2.71)
4b	H	H	Br	200	52	53.74 (53.73)	2.05 (2.08)
4c	H	H	F	193	51	61.34 (61.32)	2.34 (2.32)
4d	H	H	Cl	216	55	59.08 (59.05)	2.25 (2.27)
4e	Cl	H	Cl	205	50	54.86 (54.85)	1.88 (1.90)
4f	H	Cl	H	215	55	54.86 (54.85)	1.88 (1.90)
5a	H	H	H	205	51	68.98 (68.96)	3.93 (3.94)
5b	H	H	Br	217	53	59.37 (59.35)	3.20 (3.21)
5c	H	H	F	193	51	66.53 (66.51)	3.59 (3.60)
5d	H	H	Cl	185	55	64.43 (64.40)	3.48 (3.50)
5e	Cl	H	Cl	213	50	60.44 (60.43)	3.08 (3.10)
5f	H	Cl	H	215	51	64.43 (64.40)	3.48 (3.50)

Scheme 1



cold water was added in it. The solid thus obtained was filtered and washed with dil. HCl and again with water. The product was crystallized from acetic acid to afford compounds **4.** The compounds synthesized by above procedure are listed in Table 4.

3-Chloro-2-(4-(difluoromethoxy)dibenzofuran-1-yl)-4*H*-chromon-4-one (4a). IR (KBr): 1650, 1128, 1072 cm^{-1}; ^{1}H-NMR (CDCl$_3$): δ 6.80 (t, 1H, J = 72.94 Hz, —OCHF$_2$), 7.15–8.13 (m, 10H, aromatic); Mass: M$^+$ 491 with isotopic peaks.

6-Bromo-3-chloro-2-(4-(difluoromethoxy)dibenzofuran-1-yl)-4*H*-chromon-4-one (4b). IR (KBr): 1647, 1135, 1065 cm^{-1}; ^{1}H-NMR (CDCl$_3$): δ 6.83 (t, 1H, J = 72.95 Hz, —OCHF$_2$) 7.25–7.77 (m, 8H, aromatic), 8.22 (d, 1H, aromatic); Mass: M$^+$ 491 with isotopic peaks.

3-Chloro-2-(4-(difluoromethoxy)dibenzofuran-1-yl)-6-fluoro-4*H*-chromon-4-one (4c). IR (KBr): 1658, 1169, 1132, 1078 cm^{-1}; ^{1}H-NMR (CDCl$_3$): δ 6.87 (t, 1H, J = 72.95 Hz, —OCHF$_2$) 7.35–7.92 (m, 8H, aromatic), 8.32 (m, 1H, aromatic); Mass: M$^+$ 430 with isotopic peaks.

3,6-Dichloro-2-(4-(difluoromethoxy)dibenzofuran-1-yl)-4*H*-chromon-4-one (4d). IR (KBr): 1652, 1135, 1075 cm^{-1}; ^{1}H-NMR (CDCl$_3$): δ 6.85 (t, 1H, J = 72.94 Hz, —OCHF$_2$), 7.25–7.74 (m, 8H, aromatic), 8.22(d, 1H, aromatic); Mass: M$^+$ 447 with isotopic peaks.

3,6,8-Trichloro-2-(4-(difluoromethoxy)dibenzofuran-1-yl)-4*H*-chromon-4-one (4e). IR (KBr): 1662, 1134, 1107, 1072, 1052, 1015 cm^{-1}; ^{1}H-NMR (CDCl$_3$): δ 6.97 (t, 1H, J = 72.96 Hz, —OCHF$_2$) 7.26–7.70 (m, 6H, aromatic), 7.81 (d, 1H, J = 2.48 Hz, aromatic), 8.26 (d, 1H, J = 2.48 Hz, aromatic); Mass: M$^+$ 481 with isotopic peaks.

3,7-Dichloro-2-(4-(difluoromethoxy)dibenzofuran-1-yl)-4*H*-chromon-4-one (4f). IR (KBr): 1655, 1125, 1080 cm^{-1}; ^{1}H-NMR (CDCl$_3$): δ 6.88 (t, 1H, J = 72.93Hz, —OCHF$_2$), 7.23–7.80 (m, 9H, aromatic), Mass: M$^+$ 447 with isotopic peaks.

2-(2-(4-(Difluoromethoxy)dibenzofuran-1-yl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol (5a–f). Compound **3** (0.001 mol) and 2-aminothiophenol (0.001 mol) were dissolved in 15 mL ethanol in 100 mL RBF. The reaction mixture was heated under reflux for 4 hr. Then 5 mL glacial acetic acid was added and heating was continued for further 4 hr. After completion of reaction, the contents were cooled to room temperature and poured into crushed ice. The solid thus obtained was separated by filtration and crystallized with alcohol to afford compounds **5.** The compounds synthesized by above procedure are listed in Table 4.

2-(2-(4-(Difluoromethoxy)dibenzofuran-1-yl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol. (5a). IR (KBr): 3397, 1598 and 1499, 1123 cm^{-1}; ^{1}H-NMR (CDCl$_3$): δ 3.21 (dd, 1H,) 3.47 (dd, 1H), 5.97 (dd, 1H), 6.81 (t, 1H, J = 72.97Hz, —OCHF$_2$), 6.99–7.90 (m, 14H, aromatic), 15.77 (s, 1H, —OH); Mass: M$^+$ 487.

4-Bromo-2-(2-(4-(difluoromethoxy)dibenzofuran-1-yl)-2,3-dihydrobenzo[b][1,4] thiazepin-4-yl)phenol (5b). IR (KBr): 3395, 1595 and 1518, 1116 cm^{-1}; ^{1}H-NMR (CDCl$_3$): δ 3.23 (dd, 1H), 3.49 (dd, 1H), 5.95 (dd, 1H), 6.84 (t, 1H, J = 72.95Hz, —OCHF$_2$), 7.02–7.85 (m, 13H, aromatic), 15.79(s, 1H, —OH); Mass: M$^+$ 566.

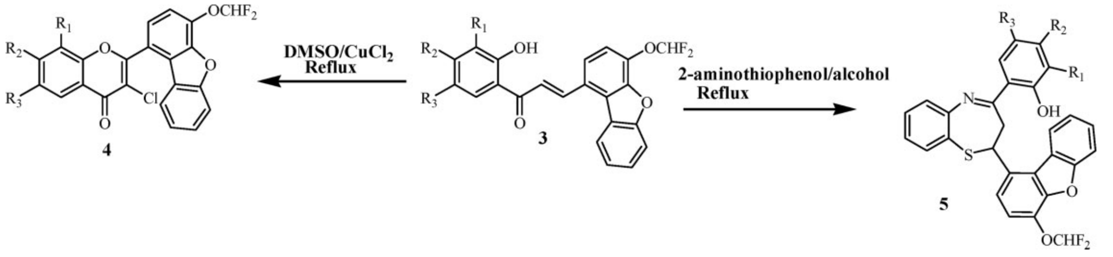
2-(2-(4-(Difluoromethoxy)dibenzofuran-1-yl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)-4-fluorophenol (5c). IR (KBr): 3398, 1170, 1145 cm^{-1}; ^{1}H-NMR (CDCl$_3$): δ 3.24 (dd, 1H), 3.50 (dd, 1H), 5.95 (dd, 1H), 6.85 (t, 1H, J = 72.96Hz, —OCHF$_2$), 7.32–8.20 (m, 13H, aromatic), 15.82 (s, 1H, —OH); Mass: M$^+$ 505.

4-Chloro-2-(2-(4-(difluoromethoxy)dibenzofuran-1-yl)-2,3-dihydrobenzo[b][1,4] thiazepin-4-yl)phenol. (5d). IR (KBr): 3390, 1590 and 1489, 1131, 1070 cm^{-1}; ^{1}H-NMR (CDCl$_3$): δ 3.23 (dd, 1H), 3.58 (dd, 1H), 6.00 (dd, 1H), 6.82 (t, 1H, J = 72.95 Hz, —OCHF$_2$), 7.15–7.98 (m, 13H, aromatic), 15.77(s, 1H, —OH); Mass: M$^+$ 521 with isotopic peaks.

2,4-Dichloro-2-(2-(4-(difluoromethoxy)dibenzofuran-1-yl)-2,3-dihydrobenzo[b] [1,4]thiazepin-4-yl)phenol (5e). IR (KBr): 3409, 1125, 1072 cm^{-1}; ^{1}H-NMR (CDCl$_3$): δ 3.29(dd, 1H), 3.47 (dd, 1H), 6.00 (dd, 1H), 6.85 (t, 1H, J = 72.96 Hz, —OCHF$_2$), 7.11–7.95 (m, 10H, aromatic),8.02 (d, 1H, aromatic), 8.23 (d, 1H, aromatic), 15.74 (s, 1H, —OH); Mass: M$^+$ 556 with isotopic peaks.

3-Chloro-2-(2-(4-(difluoromethoxy)dibenzofuran-1-yl)-2,3-dihydrobenzo[b][1,4] thiazepin-4-yl)phenol. (5f). IR (KBr): 3395, 1592 and 1501, 1131 cm^{-1}; ^{1}H-NMR (CDCl$_3$): δ 3.25 (dd, 1H), 3.49 (dd, 1H), 5.99 (dd, 1H), 6.82 (t, 1H, J = 72.95Hz, —OCHF$_2$), 7.21–8.06 (m, 13H, aromatic), 15.80 (s, 1H, —OH); Mass: M$^+$ 521 with isotopic peaks.

Scheme 2



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Utilization of 2-Benzo[*b*]furan Carboxylic Acid Hydrazide in the Synthesis of 1,3,4-Oxadiazole Derivatives

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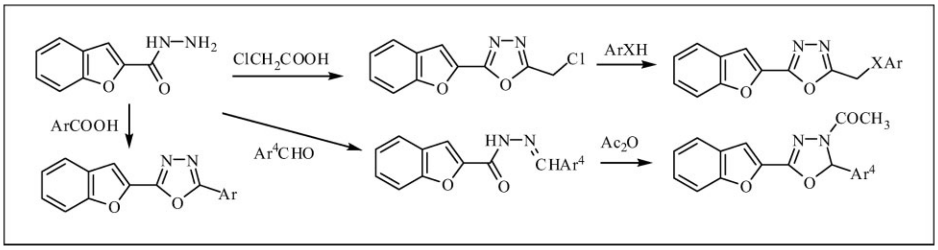

In this study, the synthesis of series of 2-benzo[*b*]furan-substituted 1,3,4-oxadiazole derivatives using readily available 2-benzo[*b*]furan carboxylic acid hydrazide as starting material has been investigated.

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INTRODUCTION

1,3,4-Oxadiazoles are five-membered aromatic heterocycles with great utility in synthetic, medicinal, and material chemistry [1–4]. The widespread use of 1,3,4-oxadiazoles as a scaffold in medicinal chemistry establishes this moiety as an important bioactive class of heterocycles. These molecules are also utilized as pharmacophores because of their favorable metabolic profile and ability to engage in hydrogen bonding. In particular, marketed antihypertensive agents, such as tiodazosin [5] and nesapidil [6], and antibiotics, such as furamizole [7], contain the oxadiazole nucleus. They are also useful as HIV integrase inhibitors and angiogenesis inhibitors [7,8]. 2,5-Disubstituted 1,3,4-oxadiazoles have also attracted significant interest because of their applications in organic light-emitting diodes, photoluminescence, polymers, and material science [9,10].

Several methods have been reported in the literature for the synthesis of 1,3,4-oxadiazoles. Most of these protocols are multistep in nature and generally involve the cyclization of diacylhydrazides or acylthiosemicarbazides and the oxidation of acylhydrozones [11] with a variety of reagents such as thionyl chloride, phosphorus oxychloride, or sulfuric acid, usually under harsh reaction conditions. Recently, a few efficient examples have been reported for the synthesis of 1,3,4-oxadiazoles by treatment of readily available carboxylic acids with acid hydrazides under acid conditions [12]. 1,3,4-Oxadiazoles by condensation of acid hydrazide and triethyl orthoalkanates under microwave irradiations have also been reported. This green protocol was catalyzed efficiently by solid-supported Nafion_NR50 [13].

2-Substituted benzo[*b*]furans [14,15] are widely distributed in nature and have a range of biological activities [16], for example, as insulin-sensitivity enhancers [17], inhibitors of tubulin polymerase [18], antagonists of the A1 adenosine receptor [19], inhibitors of testosterone 5R-reductase [20], and inhibitors of 5-lipoxygenase [21]. Recently, of particular interest is BPAP, which enhances impulse propagation mediated by the release of catecholamines and serotonin in the brain and so may slow progression of Parkinson's and Alzheimer's disease [22].

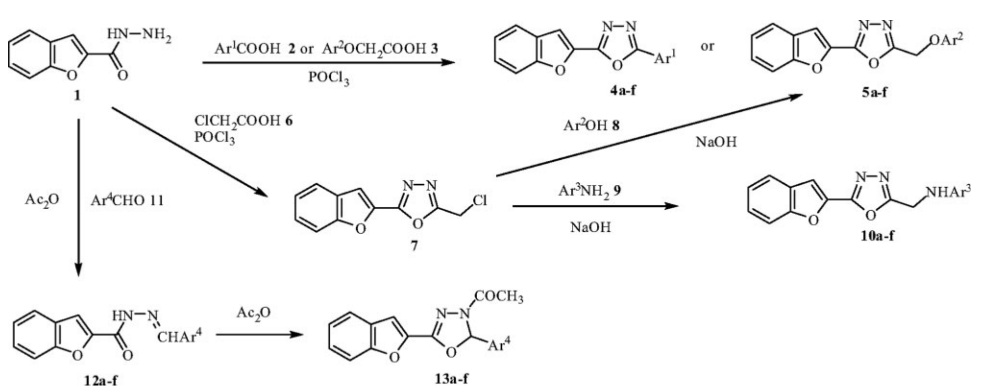
In previous reports, we demonstrated the use of 2-benzo[*b*]furan carboxylic acid and 2-benzo[*b*]furan carboxylic acid hydrazide as versatile building blocks for the synthesis of functionalized heterocycles [23]. We now report the investigations on the use of 2-benzo[*b*]furan carboxylic acid hydrazide (**1**) for the synthesis of 2,5-disubstituted 1,3,4-oxadiazole derivatives **4a–f**, **5a–f**, **10a–f**, and **13a–f** (Schemes 1).

RESULTS AND DISCUSSION

Scheme 1 outlines the synthetic sequences used in our laboratories for the preparation of the key intermediate **1** and its derivatives 1,3,4-oxadiazoles **4**, **5**, **10**, and **13**.

Synthesis of 2-aryl-5-(2-benzo[*b*]furan)-1,3,4-oxadiazoles 4a–f and 2-aryloxymethyl-5-(2-benzo[*b*]furan)-1,3,4-oxadiazoles 5a–f. Treatment of 2-benzofuroyl hydrazine (**1**) with 1 equiv of substituted benzoic acids (**2a–f**) in the presence of $POCl_3$ under reflux for 6 h produced 2,5-diaryl-substituted 1,3,4-oxadiazoles (**4a–f**) in high yields. However, the reaction of compound

Scheme 1



1 with aryloxyacetic acids (**3a–f**) need catalytic amounts of pyridine in reflux $POCl_3$ and longer time (8 h) to give the corresponding 1,3,4-oxadiazoles (**5a–f**) in higher yields (method A) (entries 7–12, Table 1).

Synthesis of 2-chloromethyl-5-(2-benzo[*b*]furan)-1,3,4-oxadiazole (7) and its utilization for the synthesis of 2-aryloxymethyl-5-(2-benzo[*b*]furan)-1,3,4-oxadiazoles (5a–f) and 2-arylaminomethyl-5-(2-benzo[*b*]furan)-1,3,4-oxadiazoles (10a–f). The reaction of acylhydrazine (**1**) with 2-chloroacetic acid in xylene in the presence of $POCl_3$ under reflux for 8 h gave compound **7** in 89% yield. Treatment of **7** with 1.1 equiv of substituted phenylamines (**9a–f**) gave 2-arylamine-methyl-5-(2-benzo[*b*]furan)-1,3,4-oxadiazoles (**10a–f**) (entries 13–18, Table 1), which cannot be synthesized by cyclization reaction of corresponding acids and acylhydrazines, and the reaction gave high yields. In examining the reactivity of 2-chloromethyl-5-(2-benzo[*b*]furan)-1,3,4-oxadiazole (**7**), the reaction of **7** with aryl-substituted phenols (**8**) was carried out in the

Table 1

Physical and analytical data of compounds.[a]

Entry	Compd.	Aryl	Yield[b] (%)	Molecular formula	Analysis (%) calcd./found		
					C	H	N
1	**4a**	C_6H_5	81	$C_{16}H_{10}N_2O_2$	73.27/73.05	3.84/3.92	10.68/10.51
2	**4b**	4-$CH_3OC_6H_4$	75	$C_{17}H_{12}N_2O_3$	69.86/69.64	4.14/4.10	9.58/9.45
3	**4c**	2-ClC_6H_4	81	$C_{16}H_9ClN_2O_2$	64.77/64.49	3.06/3.18	9.44/9.38
4	**4d**	4-ClC_6H_4	73	$C_{16}H_9ClN_2O_2$	64.77/64.95	3.06/3.13	9.44/9.25
5	**4e**	2-$NO_2C_6H_4$	83	$C_{16}H_9N_3O_4$	62.54/62.40	2.95/3.05	13.68/13.56
6	**4f**	4-$NO_2C_6H_4$	78	$C_{16}H_9N_3O_4$	62.54/62.74	2.95/2.86	13.68/13.49
7	**5a**	$C_6H_5OCH_2$	65(88)	$C_{17}H_{12}N_2O_3$	69.86/69.98	4.14/4.20	9.58/9.68
8	**5b**	4-$ClC_6H_4OCH_2$	68(93)	$C_{17}H_{11}ClN_2O_3$	62.49/62.31	3.39/3.48	8.57/8.68
9	**5c**	2-$CH_3C_6H_4OCH_2$	72(96)	$C_{18}H_{14}N_2O_3$	70.58/70.80	4.61/4.53	9.15/9.04
10	**5d**	4-$CH_3C_6H_4OCH_2$	60(77)	$C_{18}H_{14}N_2O_3$	70.58/70.35	4.61/4.69	9.15/9.26
11	**5e**	4-$CH_3OC_6H_4OCH_2$	63(88)	$C_{18}H_{14}N_2O_4$	67.17/67.07	4.45/4.38	8.58/8.69
12	**5f**	2-$NO_2C_6H_4OCH_2$	60(83)	$C_{17}H_{11}N_3O_5$	60.54/60.68	3.29/3.35	12.46/12.39
13	**10a**	C_6H_5	78	$C_{18}H_{16}N_3O_2$	70.09/70.28	4.50/4.41	14.42/14.55
14	**10b**	4-$CH_3C_6H_4$	86	$C_{18}H_{15}N_3O_2$	70.81/71.01	4.95/4.90	13.76/14.68
15	**10c**	4-$CH_3OC_6H_4$	80	$C_{18}H_{15}N_3O_3$	67.28/67.42	4.71/4.67	13.08/13.17
16	**10d**	4-ClC_6H_4	75	$C_{17}H_{12}ClN_3O_2$	62.68/62.56	3.71/3.78	12.90/11.78
17	**10e**	2-$NO_2C_6H_4$	76	$C_{17}H_{12}N_4O_4$	60.71/60.48	3.60/3.72	16.66/16.84
18	**10f**	4-$NO_2C_6H_4$	81	$C_{17}H_{12}N_4O_4$	60.71/60.98	3.60/3.72	16.66/16.84
19	**13a**	C_6H_5	70(78)	$C_{18}H_{14}N_2O_3$	70.58/70.76	4.61/4.55	9.15/9.06
20	**13b**	4-$CH_3OC_6H_4$	72(80)	$C_{19}H_{16}N_2O_4$	67.85/68.02	4.79/4.70	8.33/8.42
21	**13c**	2-ClC_6H_4	60(67)	$C_{18}H_{13}ClN_2O_3$	63.44/63.62	3.85/3.92	8.22/8.08
22	**13d**	4-ClC_6H_4	62(75)	$C_{18}H_{13}ClN_2O_3$	63.44/63.19	3.85/3.91	8.22/8.31
23	**13e**	3-$NO_2C_6H_4$	65(78)	$C_{18}H_{13}N_3O_5$	61.54/61.73	3.73/3.90	11.96/12.08
24	**13f**	4-$NO_2C_6H_4$	65(79)	$C_{18}H_{13}N_3O_5$	61.54/61.32	3.73/3.81	11.96/11.77

The values in parenthesis indicate the yields of method B for compounds **5** and **13**.

[a] Isolated yield.

[b] Yields of method A for compounds **5** and **13**.

presence of NaOH powder under reflux ethanol condition. Compounds **5a–f** could also be obtained in good yields (method B) (entries 7–12, Table 1).

One-pot synthesis of 3-acetyl-2-aryl-5-(2-benzo[*b*]-furan)-1,3,4-oxadiazolines (13a–f). First, the synthesis of 1,3,4-oxadiazoles **13a–f** were investigated through a two-step pathway. Treatment of **1** with aromatic aldehydes (**11a–f**) in the presence of catalytic amounts of Ac$_2$O under refluxing ethanol for 6 h gave 2-benzo[*b*]-furoyl hydrazones **12a–f**, which upon treatment in refluxing Ac$_2$O afforded 1,3,4-oxadiazolines **13a–f** in moderate total yields (entries 19–24, Table 1).

The ability of Ac$_2$O to promote both steps led us to investigate the one-pot synthesis of oxadiazolines **13a–f** starting from the same substrates. When acylhydrazine (**1**) and aromatic aldehydes (**11a–f**) were stirred in Ac$_2$O under reflux, the corresponding oxadiazolines **13a–f** were obtained in good yields after 2 h (entries 19–24, Table 1). It could be seen from Table 1 that the one-pot method was a more efficient way than the two-step procedures for the preparation of compounds **13a–f**.

In conclusion, the synthesis of series of 2-benzo[*b*]-furan-substituted 1,3,4-oxadiazole derivatives using readily available 2-benzo[*b*]furan carboxylic acid hydrazide as starting material has been investigated. These processes are highly efficient with good yields and use cheap and easily available aldehydes and acids.

EXPERIMENTAL

All reagents were obtained commercially and used without further purification. Melting points were determined on an XT-4 electrothermal micromelting point apparatus and uncorrected. IR spectra were recorded using KBr pellets on Nicolet AVATAR 36 FTIR spectrophotometer. For compounds **4a–f** and **5a–f**, NMR spectra were recorded on an Avanci-D2X-200 instrument using CDCl$_3$ as solvent and TMS as internal standard. For compounds **7**, **10a–f**, and **13a–f**, NMR spectra were recorded at 400 (^{1}H) and 100 (^{13}C) MHz, respectively, on a Varian Mercury plus-400 instrument using CDCl$_3$ as solvent and TMS as internal standard.

General procedure for the synthesis of 2-aryl-5-(2-benzo[*b*]furan)-1,3,4-oxadiazoles (4a–f). The mixture of 2-benzo[*b*]furan carboxylic acid hydrazide (**1**) (1 mmol), substituted benzoic acids (**2a–f**) (1 mmol), and POCl$_3$ (5 mL) was stirred under reflux condition for 6 h. The excess of POCl$_3$ was evaporated under reduced pressure. The residue was poured into ice water (50 mL). Then the precipitate was filtered and washed with aqueous solution of NaOH (1%) and subsequently with water. The solid was recrystallized from EtOH to give the products 2-aryl-5-(2-benzo[*b*]furan)-1,3,4-oxadiazoles (**4a–f**).

4a: m.p. 170–172°C; IR (KBr): 1633, 1579, 1506, 1210, 1058 cm^{-1}; ^{1}H NMR (200 Hz, CDCl$_3$): $\delta = 7.00$–8.14 (m, 10H, Ar-H); ^{13}C NMR (75 Hz, CDCl$_3$): $\delta = 164.5$, 159.8, 158.4, 144.1, 129.8, 128.1, 127.7, 127.1, 124.8, 124.6, 122.9, 121.2, 116.9, 110.4.

4b: m.p. 153–155°C; IR (KBr): 1639, 1580, 1501, 1209, 1052 cm^{-1}; ^{1}H NMR (200 Hz, CDCl$_3$): $\delta = 7.00$–8.14 (m, 9H, Ar-H), 3.80 (s, 3H, OCH$_3$); ^{13}C NMR (75 Hz, CDCl$_3$): $\delta = 164.5$, 161.2, 159.2, 144.5, 130.0, 128.2, 127.6, 126.9, 124.9, 124.2, 123.0, 116.3, 112.6, 110.7, 57.9.

4c: m.p. 126–128°C; IR (KBr): 1640, 1577, 1511, 1202, 1056 cm^{-1}; ^{1}H NMR (200 Hz, CDCl$_3$): $\delta = 7.15$–7.81 (m, 9H, Ar-H); ^{13}C NMR (75 Hz, CDCl$_3$): $\delta = 164.7$, 158.6, 156.4, 144.3, 139.8, 132.8, 129.5, 128.2, 127.7, 127.4, 124.9, 124.2, 122.9, 122.2, 116.7, 110.1.

4d: m.p. 177–179°C; IR (KBr): 1638, 1582, 1505, 1209, 1052 cm^{-1}; ^{1}H NMR (200 Hz, CDCl$_3$): $\delta = 7.00$–7.84 (m, 9H, Ar-H); ^{13}C NMR (75 Hz, CDCl$_3$): $\delta = 164.5$, 158.3, 156.4, 144.4, 136.8, 130.3, 127.6, 127.2, 124.5, 124.3, 122.3, 120.4, 116.4, 110.2.

4e: m.p. 140–142°C; IR (KBr): 1640, 1577, 1511, 1202, 1056 cm^{-1}; ^{1}H NMR (200 Hz, CDCl$_3$): $\delta = 7.16$–8.14 (m, 9H, Ar-H); ^{13}C NMR (75 Hz, CDCl$_3$): $\delta = 164.8$, 160.5, 158.6, 155.3, 147.3, 140.2, 130.8, 129.7, 128.4, 127.4, 124.6, 124.0, 122.8, 122.5, 116.9, 110.4.

4f: Yield 78%, m.p. 257–259°C; IR (KBr): 1638, 1582, 1505, 1209, 1052 cm^{-1}; ^{1}H NMR (200 Hz, CDCl$_3$): $\delta =$ 7.16–8.46 (m, 9H, Ar-H); ^{13}C NMR (75 Hz, CDCl$_3$): $\delta =$ 164.7, 158.8, 155.3, 147.5, 136.2, 135.2, 131.8, 129.3, 128.6, 124.9, 124.3, 122.3, 116.6, 110.6.

General procedure for the synthesis of 2-aryl-5-(2-benzo[*b*]furan)-1,3,4-oxadiazoles (5a–f).

Method A. The mixture of 2-benzo[*b*]furan carboxylic acid hydrazide (**1**) (1 mmol), substituted aryloxyacetic acids (**3a–f**) (1 mmol), pyridine (0.1 mL), and POCl$_3$ (5 mL) were stirred under reflux condition for 8 h. The excess of POCl$_3$ was evaporated under reduced pressure. The residue was poured into ice water (50 mL). Then the precipitate was filtered and washed with aqueous solution of NaOH (1%) and subsequently with water. The solid was recrystallized from EtOH to give the products 2-aryloxymethyl-5-(2-benzo[*b*]furan)-1,3,4-oxadiazoles (**5a–f**).

Method B. The mixture of 2-chloromethyl-5-(2-benzo[*b*]-furan)-1,3,4-oxadiazole (**7**) (1 mmol), substituted phenols (**8**) (1.1 mmol), and NaOH (1.1 mmol) in 10 mL ethanol were stirred at 80°C for 12 h. The mixture was poured into ice water (50 mL). Then the precipitate was filtered and washed with water (3 × 10 mL). The solid was recrystallized from EtOH to give the product 2-aryloxymethyl-5-(2-benzo[*b*]-furan)-1,3,4-oxadiazoles (**5a–f**).

5a: m.p. 184–186°C, IR (KBr): 1640, 1577, 1511, 1202, 1056 cm^{-1}; ^{1}H NMR (200 Hz, CDCl$_3$): $\delta = 7.01$–7.76 (m, 10H, Ar-H), 5.37 (s, 2H, CH$_2$); ^{13}C NMR (75 Hz, CDCl$_3$): $\delta = 164.4$, 161.2, 158.3, 157.8, 154.6, 129.8, 128.0, 127.7, 124.3, 122.8, 120.3, 114.0, 112.3, 110.5, 72.6.

5b: m.p. 130–132°C, IR (KBr): 1638, 1580, 1489, 1214, 1048 cm^{-1}; ^{1}H NMR (200 Hz, CDCl$_3$): $\delta = 7.10$–7.91 (m, 9H, Ar-H), 5.37 (s, 2H, CH$_2$); ^{13}C NMR (75 Hz, CDCl$_3$): $\delta =$ 164.6, 161.3, 158.3, 156.6, 154.8, 131.4, 130.9, 127.5, 126.5, 124.8, 123.2, 122.5, 114.1, 112.6, 110.3, 72.6.

5c: m.p. 187–189°C; IR (KBr): 1651, 1564, 1512, 1214, 1056 cm^{-1}; ^{1}H NMR (200 Hz, CDCl$_3$): $\delta = 6.88$–7.92 (m, 9H, Ar-H), 5.37 (s, 2H, CH$_2$), 2.36 (s, 3H, CH$_3$); ^{13}C NMR (75 Hz, CDCl$_3$): $\delta = 164.3$, 161.5, 158.6, 156.3, 154.1, 131.3, 131.4, 130.1, 127.7, 124.7, 124.8, 123.0, 122.1, 121.7, 112.6, 110.2, 72.9, 22.1.

5d: m.p. 137–139°C; IR (KBr): 1650, 1569, 1520, 1214, 1059 cm^{-1}; ^{1}H NMR (200 Hz, CDCl$_3$): $\delta = 6.94$–7.92 (m, 9H, Ar-H), 5.36 (s, 2H, CH_2), 2.35 (s, 3H, CH_3); ^{13}C NMR (75 Hz, $CDCl_3$): δ = 164.8, 160.4, 158.9, 156.9, 157.4, 131.1, 130.8, 128.1, 127.5, 124.0, 122.3, 120.8, 111.9, 110.3, 72.5, 22.2.

5e: m.p. 141–142°C; IR (KBr) 1639, 1567, 1501, 1208, 1052 cm^{-1}; ^{1}H NMR (200 Hz, $CDCl_3$): δ = 6.84–7.73 (m, 9H, Ar-H), 5.37 (s, 2H, CH_2), 3.77 (s, 3H, CH_3O); ^{13}C NMR (75 Hz, $CDCl_3$): 161.9, 160.3, 157.8, 156.9, 155.0, 154.0, 130.7, 128.8, 127.1, 126.0, 118.5, 115.7, 112.2, 111.2, 58.9, 56.1.

5f: m.p. 192–194°C; IR (KBr): 1652, 1580, 1508, 1206, 1056 cm^{-1}; ^{1}H NMR (200 Hz, $CDCl_3$): δ = 7.02–8.21 (m, 9H, Ar-H), 5.37 (s, 2H,CH_2); ^{13}C NMR (75 Hz, $CDCl_3$): δ = 164.9, 160.9, 158.8, 156.0, 155.8, 145.8, 132.3, 130.2, 127.3, 124.2, 124.0, 122.8, 121.1, 114.4, 112.2, 110.5, 70.7.

Synthesis of 2-chloromethyl-5-(2-benzo[*b*]furan)-1,3,4-oxadiazole (7). The mixture of 2-benzo[*b*]furan carboxylic acid hydrazide (**1**) (10 mmol), 2-chloroacetic acid (**6**) (11 mmol), xylene (10 mL), and $POCl_3$ (5 mL) were stirred under reflux for 8 h. The excess of $POCl_3$ and solvent were evaporated under reduced pressure. The residue was poured into ice water (50 mL). Then the precipitate was filtered and washed with aqueous solution of NaOH (1%) and subsequently with water. The solid was recrystallized from EtOH to give the product 2-chloromethyl-5-(2-benzo[*b*]furan)-1,3,4-oxadiazole (**7**).

Yield 89%, m.p. 149–151°C; IR (KBr): 3024, 1638, 1574 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d ,1H, *J* = 8.0 Hz, Ar-H), 7.63 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.58 (s, 1H, Ar-H),7.47 (t, *J* = 8.0 Hz, Ar-H), 7.34 (t, *J* = 8.0 Hz, Ar-H), 4.82 (s, 2H, CH_2).

General procedure for the synthesis of 2-arylamine-methyl-5-(2-benzo[*b*]furan)-1,3,4-oxadiazoles (10a–f). The mixture of 2-chloromethyl-5-(2-benzo[*b*]furan)-1,3,4-oxadiazole (**7**) (1 mmol), arylamines (**9**) (1.1 mmol), and NaOH (1.1 mmol) in 10 mL ethanol were stirred at 80°C for 12 h. The mixture was poured into ice water (50 mL). Then the precipitate was filtered and washed with water (3 × 10 mL). The solid was recrystallized from EtOH to give the product 2-aryloxymethyl-5-(2-benzo[*b*]furan)-1,3,4-oxadiazoles (**10a–f**).

10a: m.p. 204–205°C; IR (KBr): 3334, 1579, 1642, 1203, 1060 cm^{-1}; ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.63 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.57 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.74–7.40 (m, 2H, Ar-H), 7.34–7.23 (m, 1H, Ar-H), 7.21–6.85 (m, 5H, Ar-H), 4.30 (s, 1H, NH); ^{13}C NMR (100 Hz, $CDCl_3$): δ = 163.9, 158.0, 154.9, 146.5, 140.8, 128.7, 128.2, 126.8, 126.9, 124.5, 123.0, 115.2, 111.8, 109.5, 38.8.

10b: m.p. 150–151°C; IR (KBr): 3384, 1558, 1644, 1206, 1171 cm^{-1}; ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.65 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.58 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.46–7.40 (m, 2H, Ar-H), 7.33–7.25 (m, 1H, Ar-H), 7.01 (d, 2H, *J* = 8.0 Hz, Ar-H), 6.68 (d, 2H, *J* = 8.0 Hz, Ar-H), 4.35 (s, 2H, NH); 4.31 (s, 1H, NH), 2.23 (s, 3H, CH_3); ^{13}C NMR (100 Hz, $CDCl_3$): δ = 164.6, 158.3, 155.6, 143.9, 140.3, 129.9, 128.3, 127.1, 127.1, 124.0, 122.3, 113.4, 110.3, 39.4, 20.3.

10c: m.p. 128–130°C; IR (KBr): 3304, 1557, 1641, 1241, 1173 cm^{-1}; ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.64 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.54 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.45–7.39 (m, 2H, Ar-H), 7.31–7.28 (m, 1H, Ar-H), 6.72 (d, 2H, *J* = 8.0 Hz, Ar-H), 6.69 (d, 2H, *J* = 8.0 Hz, Ar-H), 4.32 (s, 1H, NH), 3.77 (s, 3H, CH_3O); ^{13}C NMR (100 Hz, $CDCl_3$): δ = 164.9, 159.3, 155.8, 154.8, 140.9, 136.7, 128.5, 127.9, 124.8, 123.0, 116.0, 113.9, 113.0, 110.8, 40.4, 23.6.

10d: m.p. 169–171°C; IR (KBr): 3352, 1511, 1640, 1170, 1089 cm^{-1}; ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.69 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.65 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.62–7.52 (m, 2H, Ar-H), 7.50–7.34 (m, 1H, Ar-H), 7.32–7.14 (m, 2H, Ar-H), 6.73–6.66 (m, 2H, Ar-H), 4.68 (s, 2H, CH_2), 4.33 (s, 1H, NH); ^{13}C NMR (100 Hz, $CDCl_3$): δ = 164.1, 158.5, 155.7, 144.8, 140.2, 129.3, 127.3, 127.1, 124.1, 123.9, 122.4, 114.4, 112.1, 110.5, 39.2.

10e: m.p. 200–202°C; IR (KBr): 3347, 1569, 1650, 1206, 1196 cm^{-1}; ^{1}H NMR (400 Hz, $CDCl_3$): δ = 8.24–7.75 (m, 2H, Ar-H), 7.68 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.67 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.63–7.52 (m, 2H, Ar-H), 7.51–7.35 (m, 1H, Ar-H), 7.20–6.98 (m, 2H, Ar-H), 4.68 (s, 2H, CH_2), 4.43 (s, 1H, NH); ^{13}C NMR (100 Hz, $CDCl_3$): δ = 163.4, 158.1, 154.9, 141.1, 138.4, 134.8, 132.9, 128.0, 123.8, 123.0, 122.6, 121.0, 117.6, 113.9, 111.7, 111.1, 39.8.

10f: m.p. 142–144°C; IR (KBr): 3351, 1571, 1652, 1210, 1200 cm^{-1}; ^{1}H NMR (400 Hz, $CDCl_3$): δ = 8.27–8.05 (m, 2H, Ar-H), 7.68 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.67 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.63–7.52 (m, 2H, Ar-H), 7.51–7.35 (m, 1H, Ar-H), 7.05–6.95 (m, 2H, Ar-H), 4.67 (s, 2H, CH_2), 4.43 (s, 1H, NH); ^{13}C NMR (100 Hz, $CDCl_3$): δ = 165.0, 158.8, 156.2, 154.6, 142.1, 137.5, 128.0, 124.5, 124.4, 123.0, 122.2, 114.8, 112.9, 111.1, 44.8.

General procedure for one-pot synthesis of 3-acetyl-2-aryl-5-(2-benzo[*b*]furan)-1,3,4-oxadiazolines (13a–f). The mixture of 2-benzo[*b*]furan carboxylic acid hydrazide (**1**) (1 mmol), aromatic aldehydes (**11a–f**) (1 mmol), and Ac_2O (5 mL) were stirred under reflux condition for 2 h. The excess of Ac_2O was evaporated under reduced pressure. The residue was recrystallized from benzene to give the product 2-aryl-5-(2-benzo[*b*]furan)-3-acetyl-1,3,4-oxadiazoline (**13a–f**).

13a: m.p. 150–151°C; IR (KBr): 1671, 1588, 1260, 1073 cm^{-1}; ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.66 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.59 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.52 (s, 1H, Ar-H), 7.49 (t, 1H, 8.0 Hz, Ar-H), 7.45 (t, 1H, *J* = 8.0 Hz, Ar-H), 7.29–7.43 (m, 5H, Ar-H), 7.13 (s, 1H, oxadiazoline-H), 2.42 (s, 3H, $COCH_3$); ^{13}C NMR (100 Hz, $CDCl_3$): δ = 167.9, 155.8, 149.1, 141.1, 135.8, 130.1, 128.8, 127.1, 127.0, 126.6, 123.9, 122.2, 111.9, 111.2, 92.7, 21.6.

13b: m.p. 153–155°C; IR (KBr): 1693, 1636, 1277, 1083 cm^{-1}; ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.66 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.57 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.51 (s, 1H, Ar-H), 7.47 (t, 1H, *J* = 8.8 Hz, Ar-H), 7.44 (t, 1H, *J* = 8.8 Hz, Ar-H), 6.80 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.34 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.10 (s, 1H, oxadiazoline-H), 2.40 (s, 3H, $COCH_3$), 3.73 (s, 3H, OCH_3); ^{13}C NMR (100 Hz, $CDCl_3$): δ = 167.8, 155.7, 148.7, 140.8, 135.8, 131.0, 128.4, 127.0, 126.7, 126.4, 123.7, 122.1, 111.7, 111.0, 92.3, 21.3.

13c: m.p. 192–194°C; IR (KBr): 1681, 1623, 1280, 1063 cm^{-1}; ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.65 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.60 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.50 (s, 1H, Ar-H), 7.48 (t, 1H, *J* = 8.8 Hz, Ar-H), 7.48 (t, 1H, *J* = 8.8 Hz, Ar-H), 7.17–7.40 (m, 5H, Ar-H), 7.16 (s, 1H, oxadiazoline-H), 2.45 (s, 3H, $COCH_3$); ^{13}C NMR (100 Hz, $CDCl_3$): δ = 167.9, 155.8, 149.3, 141.3, 136.3, 130.2, 128.4, 128.0, 126.9, 126.5, 123.6, 122.5, 111.6, 111.4, 92.9, 21.8.

13d: m.p. 118–120°C; IR (KBr): 1688, 1612, 1272, 1075 cm^{-1}; ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.69 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.59 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.54 (s, 1H, Ar-H), 7.49 (t, 1H, *J* = 8.0 Hz, Ar-H), 7.47 (t, 1H, *J* = 8.8 Hz, Ar-H), 7.23 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.47 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.15 (s, 1H, oxadiazoline-H), 2.43 (s, 3H, $COCH_3$); ^{13}C NMR (100 Hz, $CDCl_3$): δ = 167.9, 155.9, 149.0, 141.1, 136.2, 130.4, 129.1, 127.9, 126.8, 126.1, 123.9, 122.2, 111.7, 111.1, 92.7, 21.6.

13e: m.p. 158–160°C; IR (KBr): 1719, 1635, 1280, 1088 cm^{-1}; ^{1}H NMR (400 Hz, $CDCl_3$): δ = 8.20 (s, 1H, Ar-H), 8.34–7.75 (m, 3H, Ar-H), 7.69 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.59 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.56 (s, 1H, Ar-H), 7.51 (t, 1H, *J* = 8.8 Hz, Ar-H), 7.46 (t, 1H, *J* = 8.8 Hz, Ar-H), 7.16 (S, 1H, oxadiazoline-H), 2.43 (S, 3H, $COCH_3$); ^{13}C NMR (100 Hz, $CDCl_3$): δ = 167.9, 155.8, 149.2, 141.0, 136.0, 130.0, 129.1, 127.1, 127.0, 126.8, 124.2, 122.0, 111.8, 111.1, 92.5, 21.6.

13f: m.p. 144–146°C; IR (KBr): 1721, 1630, 1287, 1093 cm^{-1}; ^{1}H NMR (400 Hz, $CDCl_3$): δ = 8.28 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.68 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.60 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.55 (s, 1H, Ar-H), 7.50 (t, 1H, *J* = 8.8 Hz, Ar-H), 7.45 (t, 1H, *J* = 8.8 Hz, Ar-H), 7.55 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.15 (s, 1H, oxadiazoline-H), 2.44 (s, 3H, $COCH_3$); ^{13}C NMR (100 Hz, $CDCl_3$): δ = 167.9, 155.8, 149.2, 140.8, 136.2, 132.1, 128.8, 127.3, 126.5, 126.9, 123.9, 122.1, 111.6, 111.0, 92.5, 21.5.

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Microwave-Assisted Multicomponent Reaction for the Synthesis of New and Significative Bisfunctional Compounds Containing Two Furo[3,4-*b*]quinoline and Acridinedione Skeletons

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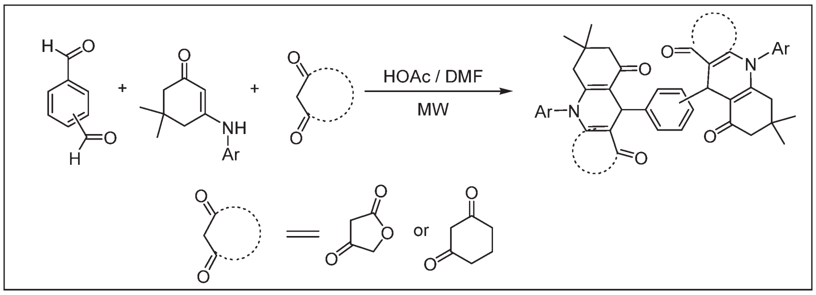

In this study, a series of new and significative bisfunctional compounds containing two furo[3,4-*b*]quinoline and acridinedione skeletons has been synthesized through a rapid one-pot three-component reaction of dialdehydes with *N*-aryl enaminones and cyclic-1,3-dicarbonyl compounds (tetronic acid and cyclohexane-1,3-dione) in mixed solvent of glacial acetic acid and *N*,*N*-dimethylformamide under microwave irradiation without catalyst. This method has the advantages of good yield and simple workup procedure.

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INTRODUCTION

Podophyllotoxin **1** (Figure 1) is an important lignan that inhibits microtubule assembly [1]. However, because attempts to use it for the treatment of human neoplasia were mostly unsuccessful and complicated by side effects, extensive structural modifications have been performed to obtain more potent and less toxic anticancer agents [2]. Among them, 4-aza podophyllotoxin derivative **2** (Fig. 1) has been reported to be a powerful DNA topoisomerase inhibitor, working through a mechanism of action entirely different from that of the parent, natural podophyllotoxin [3,4]. This suggests that substitution of the carbon atom at position 4 of podophyllotoxin by a nitrogen atom would bring about great changes in the biological profile. In view of the important biological properties of the azapodophyllotoxin, the modifications on the scaffold of aza-analogs may also bring significant changes in pharmacological activities.

The furoquinolines **A** as a kind of azapodophyllotoxin derivative have been synthesized by the reactions of single aldehydes with equivalent of appropriate cyclic-1,3-dicarbonyl compounds and *N*-aryl enaminones in our previous communications [5]. In addition, with a 1,4-dihydropyridine (1,4-DHP) parent nucleus, acridine-1,8-diones **B**, which showed interesting physical properties such as photoinitiators [6] have been prepared [7]. However, all these compounds contain only single furoquinoline skeleton or acridinedione unit. To the best of our knowledge, the compounds of type **C** and **D** including two furoquinoline skeletons or acridinedione units have been seldom reported (Fig. 1). With the aim to broaden the diversity of heterocyclic compound library and in continuation of our recent interest in the construction of heterocyclic scaffolds [8], we developed a facile, three-component reaction between dialdehydes, *N*-aryl enaminones, and cyclic-1,3-dicarbonyl compounds (tetronic acid and 1,3-cyclohexanedione) under microwave (MW) heating to afford a series of new polycyclic fused compounds **C** and **D**, including two furoquinoline skeletons or acridinedione units, respectively (Scheme 1).

RESULTS AND DISCUSSION

Enaminones and related compounds possessing the structural unit (N—C=C—Z, Z=COR, CO_2R, *etc.*) are versatile synthetic intermediates in organic chemistry that combine the ambient nucleophilicity of enamine and the electrophilicity of enones [9]. They are frequently applied in the preparation of heterocycles [10]. Our strategy of synthesizing the bisfunctional

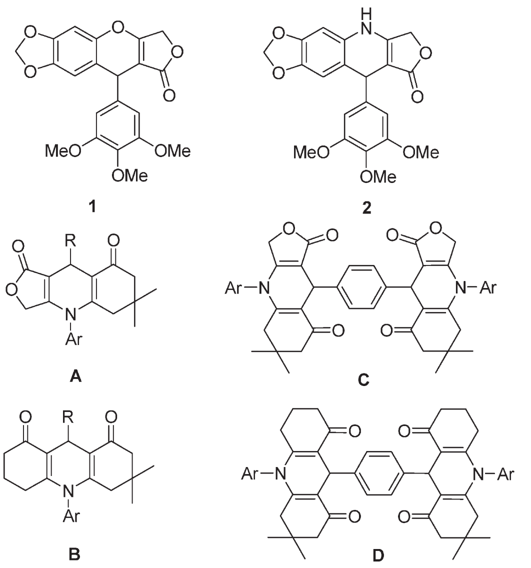
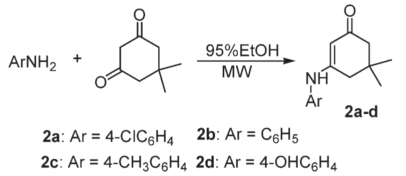


Figure 1. The podophyllotoxin derivatives and the unsymmetrical acridinediones.

compounds, furoquinolines of type **C** and acridinediones of type **D**, was through the reaction of a dialdehyde with a appropriate cyclic-1,3-dicarbonyl derivative and a preformed *N*-aryl enaminones. Representing aromatic amines with electron-rich group, 4-methylphenylamine electron-withdrawing group, 4-chlorobenzenamine, and 4-aminophenol, and phenylamine were selected for our study. The preparation of enaminones **2a–d** was commonly achieved by refluxing the reaction mixture in an aromatic solvent, with the removal of the produced water by azeotropic distillation [11]. We found that enaminones (**2a–d**) could be obtained in good to excellent yields by MW heating the mixture of the corresponding amine and 5,5-dimethyl-1,3-cyclohexanedione in EtOH (95%) at 100°C for 4–6 min (Scheme 2, Table 1) [5].

Choosing an appropriate solvent is of crucial importance for the successful microwave-assisted synthesis. To search for the optimal solvent, the microwave-assisted reaction of equimolar amount of terephthalaldehyde (**1a**) with 3-(*p*-tolylamino)-5,5-dimethylcyclohex-2-enone (**2c**) and tetronic acid (**3a**) was examined using

Scheme 2



ethylene glycol, glacial acetic acid (HOAc), *N*,*N*-dimethylformamide (DMF), and mixed solvent of glacial acetic acid and DMF as solvent at 100°C, respectively. All the reactions were carried out under microwave irradiation (initial power 100 W and maximum power 250 W; Table 2).

As shown in Table 2, the reactions using the mixed solvent (V_{HOAc}/V_{DMF}: 2:1) as the solvent resulted in higher yields and shorter reaction time than those using ethylene glycol, HOAc, DMF, and other mixed solvent as solvents. Thus, the mixed solvent (V_{HOAc}/V_{DMF}: 2:1) was used as the solvent for further optimization of reaction conditions, the same reaction was carried out at temperatures ranging from 80 to 140°C, with an increment of 10°C each time. The yield of product **4c** was increased, and the reaction time was shortened when the temperature was increased from 80 to 120°C. The yield leveled off when the temperature was further increased to 130 and 140°C. Therefore, the temperature of 120°C was chosen for all further microwave-assisted reactions (Table 3).

Under these optimal conditions [the mixed solvent (V_{HOAc}/V_{DMF}: 2:1, 2.0 mL), 120°C], the reactions of different dialdehydes, various *N*-aryl enaminones, and tetronic acid were performed. Initially, to test the scope of *N*-aryl enaminones substrates, dialdehydes and tetronic acid were used as model substrates (Table 4, entries 1–6), and the results indicated that *N*-aryl enaminones bearing functional groups such as chloro or methyl are suitable for the reaction. At the same time, we have also observed delicate electronic effects, that is, *N*-aryl enaminones with electron-rich groups (Table 4, entries 3 and 6) reacted rapidly, while electron-withdrawing groups on the benzene ring (Table 4, entries 1 and 4) decreased the reactivity, requiring longer reaction times.

Scheme 1

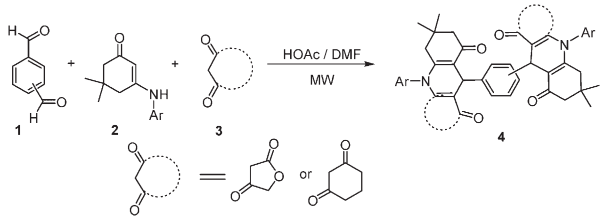


Table 1

Reaction times and yields for enaminones **2a**–**2d**.

Entry	Product	Time (min)	Yield (%)	m.p. (°C)
1	**2a**	4	89	207–209
2	**2b**	5	91	189–190
3	**2c**	5	93	206–208
4	**2d**	6	94	249–251

Table 2

Solvent optimization for the synthesis of **4c** under MW.

Entry	Solvent	Time (min)	Yield (%)
1	Ethylene glycol	14	80
2	HOAc	14	81
3	DMF	15	78
4	HOAc/DMF (3:1)	12	83
5	HOAc/DMF (2:1)	12	85
6	HOAc/DMF (1:1)	12	82

Table 3

Temperature optimization for the synthesis of **4c** under MW.

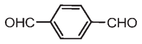
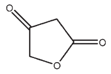
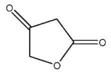
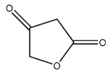
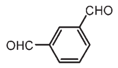
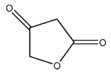
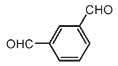
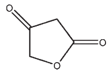
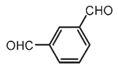
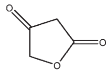
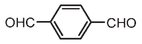
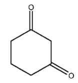
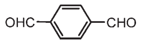
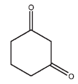
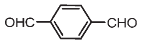
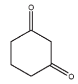
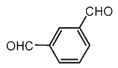
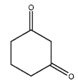
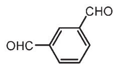
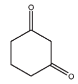
Entry	Temp (°C)	Time (min)	Yield (%)
1	80	18	70
2	90	16	81
3	100	12	85
4	110	10	89
5	120	8	92
6	130	8	90
7	140	6	86

To further expand the scope of this method, the replacement of tetronic acid (**3a**) with 1,3-cyclohexanedione (**3b**) was examined. To our delight, under the optimized conditions described earlier, the reactions proceeded smoothly as well (Table 4, entries 7–11). The new polycyclic-fused compounds including two acridinedione units were obtained without byproduct.

Additionally, to compare with microwave-assisted reactions, the same temperature and time were applied to synthesize the same product under classical heating (CH) conditions. The results listed in Table 4 show the specific activation of this reaction by MW heating. Simultaneously, the reaction yields were obviously increased. The difference in yields (MW > CH) may be a consequence of both thermal effects and specific effects induced by the microwave field [12,13]. The reactants in these multicomponent reactions (MCRs)

Table 4

The synthesis of compounds **4** at 120°C.

Entry	4	1	2	3	Time (min)	Yield[a] (%)	m.p. (°C)
1	**4a**		**2a**		14	85 (31)	>300
2	**4b**		**2b**		10	89 (44)	>300
3	**4c**		**2c**		8	92 (40)	>300
4	**4d**		**2a**		16	82 (32)	>300
5	**4e**		**2b**		10	86 (29)	>300
6	**4f**		**2c**		10	88 (35)	>300
7	**4g**		**2a**		12	84 (51)	>300
8	**4h**		**2c**		8	92 (46)	>300
9	**4i**		**2d**		7	87 (41)	>300
10	**4j**		**2c**		13	85 (38)	>300
11	**4k**		**2d**		10	90 (45)	>300

[a] Isolated yields under classical heating (CH) conditions.

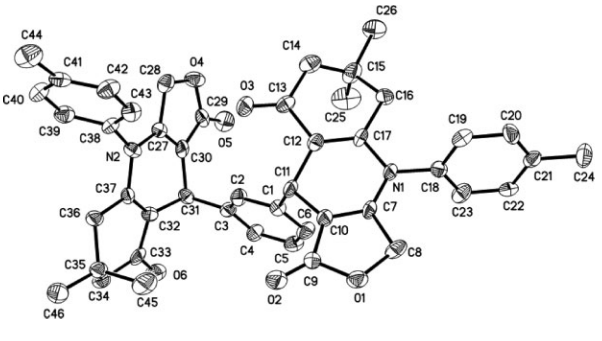


Figure 2. ORTEP diagram of **4f**.

contain dipoles and proceed via relatively polar intermediates, which enhance their interactions with MW and consequently benefit significantly from MW irradiation with respect to more efficient yield and product purity.

The mechanism of these reactions is similar to those we have previously reported [5,7], which includes sequential condensation, addition, cyclization, and elimination.

In this study, all the products were characterized by melting point, IR, ^{1}H NMR spectral data, and elemental analysis. Furthermore, the structure of **4f** was established by X-ray crystallographic analysis (Fig. 2) [14].

In summary, we have successfully combined the advantages of microwave technology with multicomponent reactions to facilitate the rapid construction of bisfuro[3,4-*b*]quinoline and bisacridinedione skeletons from readily obtainable and inexpensive materials. Particularly, valuable features of this method included the good to excellent yields and operational simplicity as well as increased safety for small-scale high-speed synthesis. In addition, this series of bisfunctional compounds containing two furo[3,4-*b*]quinoline and acridinedione skeletons may prove new classes of biologically active compounds for biomedical screening, which is in progress in our laboratory.

EXPERIMENTAL

Microwave irradiation was carried out with a microwave oven Emrys^{TM} Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in the open capillaries and were uncorrected. IR spectra were taken on a FTIR-Tensor 27 spectrometer in KBr pellets and reported in cm^{-1}. ^{1}H NMR spectra were measured on a Bruker DPX 400 MHz spectrometer using TMS as an internal standard and DMSO-d_6 as solvent. Elemental analysis was determined by using a Perkin-Elmer 240c elemental analysis instrument. HRMS (ESI) was determined by using micrOTOF-QII HRMS instrument (BRUKER). X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer.

General procedure for the one-pot synthesis of furo[3,4-*b*]quinoline and acridinedione derivative 4 under microwave irradiation conditions. Typically, in a 10-mL Emrys^{TM} reaction vial, dialdehyde 1 (1 mmol), *N*-aryl enaminones 2 (1 mmol), tetronic acid or 1,3-cyclohexanedione 3 (1 mmol), and HOAc/DMF (2:1, 2 mL) were mixed and then capped. The mixture was irradiated for a given time at 120°C under microwave irradiation (initial power 100 W and maximum power 250 W). Upon completion, monitored by TLC, the reaction mixture was filtered to give the crude product, which was further purified by recrystallization from EtOH (95%) to give pure furo[3,4-*b*]quinoline and acridinedione derivative **4**.

4-(4-Chlorophenyl)-9-(4-(4-(4-chlorophenyl)-1,3,4,5,6,7,8,9-octahydro-6,6-dimethyl-1,8-dioxofuro[3,4-b]quinolin-9-yl)-phenyl)-6,7-dihydro-6,6-dimethylfuro[3,4-b]quinoline-1,8(3H,4H,5H,9H)-dione (4a). This compound was obtained as pale yellow solid (95% ethanol), m.p. > 300°C; IR (potassium bromide, cm^{-1}): 1755 (C=O), 1682 (C=O); ^{1}H NMR: δ 7.68–7.60 (m, 8H, Ar-H), 7.25 (s, 4H, Ar-H), 4.75 (s, 1H, CH), 4.74 (s, 1H, CH), 4.63–4.59 (m, 2H, CH$_2$), 4.56–4.49 (m, 2H, CH$_2$), 2.23–2.09 (m, 8H, 4CH$_2$), 0.94–0.86 (m, 12H, 4CH$_3$). Anal. Calcd. for $C_{44}H_{38}Cl_2N_2O_6$: C, 69.38; H, 5.03; N, 3.68. Found: C, 71.08; H, 5.07; N, 3.66.

4-Phenyl-6,7-dihydro-9-(4-(1,3,4,5,6,7,8,9-octahydro-6,6-dimethyl-1,8-dioxo-furo[3,4-b]quinolin-9-yl)phenyl)-6,6-dimethylfuro[3,4-b]quinoline-1,8(3H,4H,5H,9H)-dione (4b). This compound was obtained as pale yellow solid (95% ethanol), m.p. > 300°C; IR (potassium bromide, cm^{-1}): 1756 (C=O), 1680 (C=O); ^{1}H NMR: δ 7.59–7.54 (m, 10H, Ar-H), 7.26 (s, 4H, Ar-H), 4.77 (s, 1H, CH), 4.75 (s, 1H, CH), 4.62–4.58 (m, 2H, CH$_2$), 4.51–4.45 (m, 2H, CH$_2$), 2.23–2.07 (m, 8H, 4CH$_2$), 0.93–0.85 (m, 12H, 4CH$_3$). Anal. Calcd. for $C_{44}H_{40}N_2O_6$: C, 76.28; H, 5.82; N, 4.04. Found: C, 76.41; H, 5.86; N, 4.15.

4-p-Tolyl-6,7-dihydro-9-(4-(1,3,4,5,6,7,8,9-octahydro-6,6-dimethyl-1,8-dioxo-4-p-tolylfuro[3,4-b]quinolin-9-yl)phenyl)-6,6-dimethyl-furo[3,4-b]quinoline-1,8(3H,4H,5H,9H)-dione (4c). This compound was obtained as pale yellow solid (95% ethanol), m.p. > 300°C; IR (potassium bromide, cm^{-1}): 1755 (C=O), 1681 (C=O); ^{1}H NMR: δ 7.44–7.40 (m, 8H, Ar-H), 7.24 (s, 4H, Ar-H), 4.76 (s, 2H, 2CH), 4.58 (d, 2H, *J* = 16.0 Hz, CH$_2$), 4.49 (d, 2H, *J* = 16.0 Hz, CH$_2$), 2.40 (s, 6H, 2CH$_3$), 2.21–2.09 (m, 8H, 4CH$_2$), 0.93 (s, 6H, 2CH$_3$), 0.89 (s, 6H, 2CH$_3$). Anal. Calcd. for $C_{46}H_{44}N_2O_6$: C, 76.64; H, 6.15; N, 3.89. Found: C, 76.69; H, 6.14; N, 3.83. HRMS (ESI): *m/z* calcd for: 743.3092 [M+Na]$^+$, found: 743.3099.

4-(4-Chlorophenyl)-9-(3-(4-(4-chlorophenyl)-1,3,4,5,6,7,8,9-octahydro-6,6-dimethyl-1,8-dioxofuro[3,4-b]quinolin-9-yl)phenyl)-6,7-dihydro-6,6-dimethylfuro[3,4-b]quinoline-1,8(3H,4H,5H,9H)-dione (4d). This compound was obtained as pale yellow solid (95% ethanol), m.p. > 300°C; IR (potassium bromide, cm^{-1}): 1756 (C=O), 1681 (C=O); ^{1}H NMR: δ 7.67 (s, 8H, Ar-H), 7.48 (s, 1H, Ar-H), 7.20–7.17 (m, 1H, Ar-H), 7.07 (d, 2H, *J* = 7.2 Hz, Ar-H), 4.82 (s, 2H, 2CH), 4.68 (d, 2H, *J* = 16.0 Hz, CH$_2$), 4.55 (d, 2H, *J* = 16.0 Hz, CH$_2$), 2.18–2.14 (m, 8H, Ar-H), 0.94 (s, 6H, 2CH$_3$), 0.85 (s, 6H, 2CH$_3$). Anal. Calcd. for $C_{44}H_{38}Cl_2N_2O_6$: C, 69.38; H, 5.03; N, 3.68. Found: C, 69.45; H, 5.00; N, 3.72.

4-Phenyl-6,7-dihydro-9-(3-(1,3,4,5,6,7,8,9-octahydro-6,6-dimethyl-1,8-dioxo-4-phenylfuro[3,4-b]quinolin-9-yl)phenyl)-6,6-dimethyl-furo[3,4-b]quinoline-1,8(3H,4H,5H,9H)-dione (4e). This compound was obtained as pale yellow solid (95%

ethanol), m.p. > 300°C; IR (potassium bromide, cm^{-1}): 1756 (C=O), 1680 (C=O); ^1H NMR: δ 7.60 (s, 10H, Ar-H), 7.49 (s, 1H, Ar-H), 7.21–7.18 (m, 1H, Ar-H), 7.08 (d, 2H, J = 7.6 Hz, Ar-H), 4.83 (s, 2H, 2CH), 4.67 (d, 2H, J = 16.4 Hz, CH_2), 4.49 (d, 2H, J = 16.4 Hz, CH_2), 2.23–2.09 (m, 8H, $4CH_2$), 0.92 (s, 6H, $2CH_3$), 0.84 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{44}H_{40}N_2O_6$: C, 76.28; H, 5.82; N, 4.04. Found: C, 76.34; H, 5.80; N, 4.08.

4-p-Tolyl-6,7-dihydro-9-(3-(1,3,4,5,6,7,8,9-octahydro-6,6-dimethyl-1,8-dioxo-4-p-tolylfuro[3,4-b]quinolin-9-yl)phenyl)-6,6-dimethyl-furo[3,4-b]quinoline-1,8(3H,4H,5H,9H)-dione (4f). This compound was obtained as pale yellow solid (95% ethanol), m.p. > 300°C; IR (potassium bromide, cm^{-1}): 1753 (C=O), 1679 (C=O); ^1H NMR: δ 7.47–7.39 (m, 9H, Ar-H), 7.21–7.17 (m, 1H, Ar-H), 7.06 (d, 2H, J = 7.2 Hz, Ar-H), 4.81 (s, 2H, 2CH), 4.65 (d, 2H, J = 16.0 Hz, CH_2), 4.48 (d, 2H, J = 16.4 Hz, CH_2), 2.41 (s, 6H, $2CH_3$), 2.22–2.08 (m, 8H, $4CH_2$), 0.92 (s, 6H, $2CH_3$), 0.83 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{46}H_{44}N_2O_6$: C, 76.64; H, 6.15; N, 3.89. Found: C, 76.34; H,5.99; N, 4.07. HRMS (ESI): m/z calcd for: 743.3092 $[M+Na]^+$, found: 743.3090.

10-(4-Chlorophenyl)-9-(4-(10-(4-chlorophenyl)-1,2,3,4,5,6,7,8,9,10-decahydro-3,3-dimethyl-1,8-dioxoacridin-9-yl)phenyl)-3,4,6,7-tetrahydro-3,3-dimethylacridine-1,8(2H,5H,9H,10H)-dione (4g). This compound was obtained as pale yellow solid (95% ethanol), m.p. > 300°C; IR (potassium bromide, cm^{-1}): 1639 (C=O); ^1H NMR: δ 7.68–7.44 (m, 8H, Ar-H), 7.16 (s, 4H, Ar-H), 5.06–5.01 (m, 2H, 2CH), 2.29–2.09 (m, 10H, $5CH_2$), 2.04–1.92 (m, 4H, $2CH_2$), 1.83–1.79 (m, 4H, $2CH_2$), 1.66–1.61 (m, 2H, CH_2), 0.89 (s, 6H, $2CH_3$), 0.70 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{48}H_{46}Cl_2N_2O_4$: C, 73.37; H, 5.90; N, 3.56. Found: C, 75.35; H, 6.00; N, 3.53.

10-p-Tolyl-3,4,6,7-tetrahydro-9-(4-(1,2,3,4,5,6,7,8,9,10-decahydro-3,3-dimethyl-1,8-dioxo-10-p-tolylacridin-9-yl)phenyl)-3,3-dimethyl-acridine-1,8(2H,5H,9H,10H)-dione (4h). This compound was obtained as pale yellow solid (95% ethanol), m.p. > 300°C; IR (potassium bromide, cm^{-1}): 1634 (C=O); ^1H NMR: δ 7.41–7.25 (m, 8H, Ar-H), 7.16 (s, 4H, Ar-H), 5.07–5.04 (m, 2H, 2CH), 2.42 (s, 6H, $2CH_3$), 2.29–2.13 (m, 10H, $5CH_2$), 2.05–1.92 (m, 4H, $2CH_2$), 1.83–1.78 (m, 4H, $2CH_2$), 1.64–1.60 (m, 2H, CH_2), 0.87 (s, 6H, $2CH_3$), 0.69 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{50}H_{52}N_2O_4$: C, 80.61; H, 7.04; N, 3.76. Found: C, 80.69; H, 7.06; N, 3.73.

10-(4-Hydroxyphenyl)-3,4,6,7-tetrahydro-9-(4-(1,2,3,4,5,6,7,8,9,10-decahydro-10-(4-hydroxyphenyl)-3,3-dimethyl-1,8-dioxoacridin-9-yl)phenyl)-3,3-dimethylacridine-1,8(2H,5H,9H,10H)-dione (4i). This compound was obtained as pale yellow solid (95% ethanol), m.p. > 300°C; IR (potassium bromide, cm^{-1}): 1635 (C=O); ^1H NMR: δ 9.96 (s, 2H, 2OH), 7.26–7.24 (m, 2H, Ar-H), 7.13–7.10 (m, 6H, Ar-H), 6.92 (s, 4H, Ar-H), 5.03 (s, 2H, 2CH), 2.28–2.12 (m, 10H, $5CH_2$), 2.03–1.97 (m, 4H, $2CH_2$), 1.86–1.79 (m, 4H, $2CH_2$), 1.69–1.60 (m, 2H, CH_2), 0.88 (s, 6H, $2CH_3$), 0.70 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{48}H_{48}N_2O_6$: C, 76.98; H, 6.46; N, 3.74. Found: C, 77.05; H, 6.43; N, 3.75.

10-p-Tolyl-3,4,6,7-tetrahydro-9-(3-(1,2,3,4,5,6,7,8,9,10-decahydro-3,3-dimethyl-1,8-dioxo-10-p-tolylacridin-9-yl)phenyl)-3,3-dimethyl-acridine-1,8(2H,5H,9H,10H)-dione (4j). This compound was obtained as pale yellow solid (95% ethanol), m.p. > 300°C; IR (potassium bromide, cm^{-1}): 1645 (C=O); ^1H NMR: δ 7.38–7.34 (m, 9H, Ar-H), 7.11–7.07 (m, 1H, Ar-H), 7.02–6.98 (m, 2H, Ar-H), 5.09 (s, 2H, 2CH), 2.41 (s, 6H, $2CH_3$), 2.21–2.14 (m, 8H, $4CH_2$), 2.09 (s, 2H, CH_2), 2.01–1.94 (m, 4H, $2CH_2$), 1.85–1.78 (m, 4H, $2CH_2$), 1.65–1.55 (m, 2H, CH_2), 0.88 (s, 6H, $2CH_3$), 0.70 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{50}H_{52}N_2O_4$: C, 80.61; H, 7.04; N, 3.76. Found: C, 82.49; H, 7.07; N, 3.77.

10-(4-Hydroxyphenyl)-3,4,6,7-tetrahydro-9-(3-(1,2,3,4,5,6,7,8,9,10-decahydro-10-(4-hydroxyphenyl)-3,3-dimethyl-1,8-dioxoacridin-9-yl)phenyl)-3,3-dimethylacridine-1,8(2H,5H,9H,10H)-dione (4k). This compound was obtained as pale yellow solid (95% ethanol), m.p. > 300°C; IR (potassium bromide, cm^{-1}): 1634 (C=O); ^1H NMR: δ 9.94 (s, 2H, 2OH), 7.34–7.23 (m, 5H, Ar-H), 7.10–6.96 (m, 3H, Ar-H), 6.91–6.89 (m, 4H, Ar-H), 5.09 (s, 2H, 2CH), 2.33–2.14 (m, 10H, $5CH_2$), 2.05–1.98 (m, 4H, $2CH_2$), 1.87–1.83 (m, 4H, $2CH_2$), 1.63–1.61 (m, 2H, CH_2), 0.89 (s, 6H, $2CH_3$), 0.72 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{48}H_{48}N_2O_6$: C, 76.98; H, 6.46; N, 3.74. Found: C, 77.03; H, 6.47; N, 3.77.

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[14] The single-crystal growth was carried out in ethanol at room temperature. X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Semens P4 diffractometer. Crystal data for **4f**: $C_{46}H_{44}N_2O_6$, $M = 720.83$, Triclinic, space group P-1, $a = 11.6215(14)$, $b = 13.3902(16)$, $c = 14.7823(19)$, $V = 2171.6(5)$ Å^3, $Z = 2$, $T = 298(2)$ K, $\mu = 0.073$ mm^{-1}, 10,857 reflections measured, 7481 unique reflections, $R = 0.0981$, $R_w = 0.1263$.

Friedel-Crafts Heteroarylation of (Hetero)arenes: A Facile Entry to 4-(Hetero)aryl Quinazolines and Quinolines

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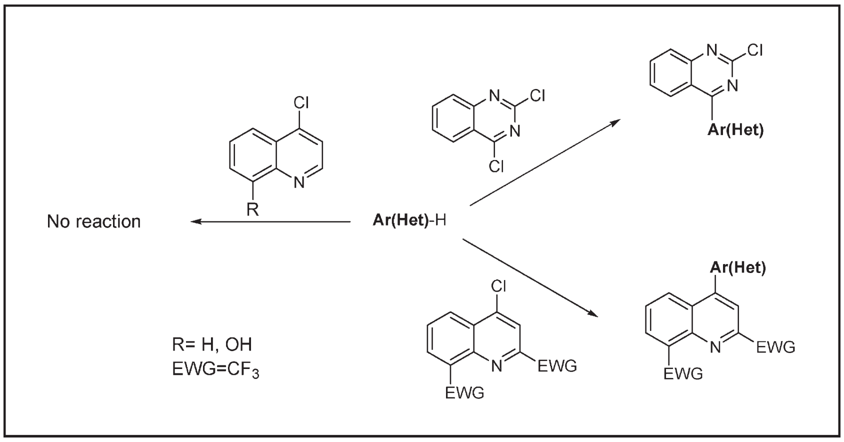

Anhydrous $AlCl_3$-mediated heteroarylation of various arenes and heteroarenes with 2,4-dichloro-quinazoline (**1**) and 4-chloroquinoline (**4**) afforded exclusively 4-aryl/heteroarylquinazolines (**3**) and 4-aryl/heteroarylquinolines (**5**), respectively. Compared with the available synthetic protocols, aluminum chloride induced C—C bond formation is direct and convenient to access bis-(hetero)aryl quinazolines and quinolines. The products were obtained in good to excellent yields by this method.

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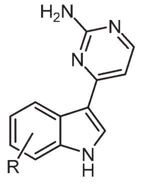
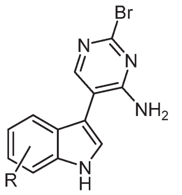
INTRODUCTION

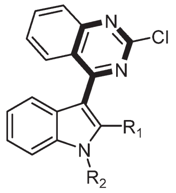
Biaryls and biheteroaryls are significant building blocks in a large number of natural products [1] and are also an important structural motif in a variety of biologically active compounds [2]. Pyrazinopyridine biheteroaryls have been reported as potent VEGFR-2 inhibitors [3]. The meridianins and related psammopemmin marine alkaloids containing 3-(2-aminopyrimidine)-indole motifs are potent protein kinase inhibitors [4] and possess antitumor activity [5]. The biheteroaryls have drawn a great attention in advanced materials including conductive polymers [6], liquid crystals [7], supramolecules [8], and molecular electronics [9]. Quinazolines and quinolines are of considerable interest because of their synthetic and therapeutic utility [10]. Biheteroaryls containing these scaffolds may have interesting biological and physicochemical properties. Important class of atropisomeric biaryl ligands with axial chirality, quinazolinap [11], and related ligands [12] containing nitrogen in one of the aryl rings have been used in various asymmetric reactions. These important biheteroaryls were earlier synthesized by metal-catalyzed reactions, which include palladium-catalyzed Suzuki-Miyaura cross coupling [13] between organoboronic acid and halides, nickel- or palladium-catalyzed Negishi coupling [14] of organozinc compounds with various halides, or Stille coupling [15] between stannanes and halides. These synthetic protocols require multistep reactions involving either pyrophoric organolithium reagents or toxic and expensive catalysts. Alternately, anhydrous $AlCl_3$-mediated heteroarylation of arenes [16] and heteroarenes could be a cheap, convenient, and straightforward synthetic methodology to access the bis-heteroaryls 1-(2-chloroquinazolin-4-yl)-naphthalen-2-ol (**3b**) and 2-chloro-4-(1H-indol-3-yl)quinazoline (**3g**), which are structurally similar to quinazolinap and meridianins, respectively. As a part of our ongoing program devoted to the diversity-oriented synthesis (DOS), we had reported synthesis and biological activity of some azaheterocycles and coumarine derivatives. In the continuation of our studies [17], herein we report a facile and direct synthesis of 4-aryl/heteroaryl quinazolines and 4-aryl/heteroaryl quinolines by $AlCl_3$-mediated direct C—C bond forming reactions.


R = H, OH, Br

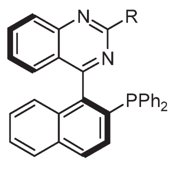
Meridianin


R = H, Br

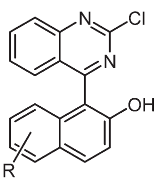
Psammopemmin


R_1, R_2= H

3g


R = H, alkyl, (hetero)aryl

Quinazolinap


R = H

3b

RESULTS AND DISCUSSION

The heteroarylation of arenes and heteroarenes with 2,4-dichloroquinazoline [18] was explored under Friedel-Crafts reaction conditions. When one equivalent of arene/heteroarene was reacted with one equivalent of 2,4-dichloroquinazoline in the presence of 1.2 equiv of anhydrous aluminum chloride using dichloroethane as solvent, 4-(hetero)aryl-substituted-2-chloroquinazolines were formed exclusively in good to excellent yields. The results are summarized in Table 1. Alternatively, on carrying out reactions at relatively lower temperature (40–45°C) for a longer duration of time (8–10 h), similar yield of the arylated and heteroarylated products could be obtained.

The heteroarylation proceeded well in the presence of various aryl and heteroaryl reactants. Arenes activated with electron donating groups were found to be effective for heteroarylation (entries 1–6). With 1,3,5-trimethoxybenzene as reactant, an excellent yield (85%) of the product **3e** was obtained in a short time (entry 5). Free phenolic hydroxyl groups were found to be well tolerated during the reaction and heteroarylation occurred at the ring carbon rather than oxygen (entries 1, 2, 3, and 6). With 2-hydroxynaphthalene (entry 2), a trace of 2,4-diarylquinazoline was formed along with the product **3b**. The structures of the products synthesized were established by analytical and spectroscopic data. The regioselectivity of the product **3a–d** were confirmed by NOESY experiment (Figure 1). In the ^{1}H NMR spectrum of compound **3a**, the signals at δ 3.49, 6.46, 7.01, and 7.68 were assigned for H-19, H-15, H-17, and H-4, which in ^{13}C NMR were appeared at δ 55.25, 104.00, 116.21, and 128.65, respectively.

The existence of correlations in the NOESY experiment of **3a** between the protons signals of H-19 and H-15, between the protons signals of H-19 and H-17 and the protons signals of H-15 and H-4 suggested that there is no substitution at C-15 and C-17, which is the confirmatory evidence of structure for the compound **3a**. Similarly, the connectivity in compound **3d** was confirmed from correlation between the proton signals at δ 6.61 (H-4) and δ 3.71 (H-7), between the protons signals of δ 6.67 (H-2) and δ 3.90 (H-8) and between the protons signals of δ 6.61 (H-4) and δ 3.90 (H-8) in the NOESY experiment of compound. A number of nitrogen-containing heteroarenes, e.g., pyrrole (entry 11), indoles (entries 7–10), and indolizines (entries 12–15) were used in the $AlCl_3$-induced reaction.

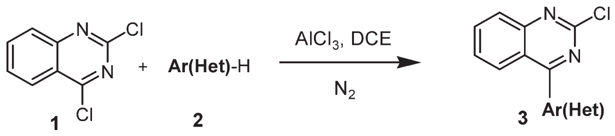
The reactivity toward indole and pyrrole derivatives (entries 7–15) were somewhat more than those of naphthyl derivatives which might be due to differences in their nucleophilicity. Similarly, with 1,3-dimethoxybenzene and *sym*-trimethoxybenzene, the arylation was completed within 2 h at 65–70°C, and the products were isolated in excellent yields (entries 4 and 5). The reaction of 2,4-dichloroquinazoline with various indolizines (fused pyrroles) (entries 12–15) were completed at 40–45°C within a few minutes. Imidazoles (entries 16 and 17), surprisingly, did not react under similar conditions. This is perhaps due to the formation of a metal-ionic complex with imidazole ($pK_a = 7.1$) resulting in a decrease of nucleophilicity. Thus, unlike pyrrole derivatives, the more basic imidazole system having an additional nitrogen atom deactivates the ring for arylation to occur.

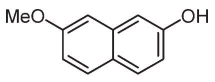
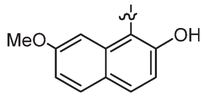
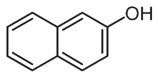
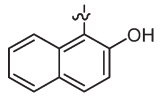
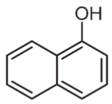
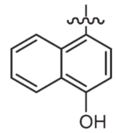
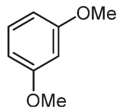
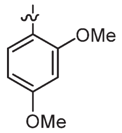
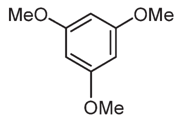
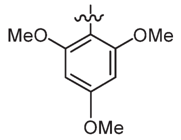
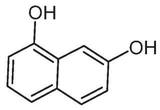
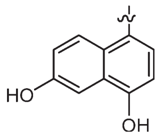
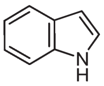
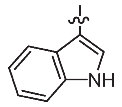
The arylation of 4-chloroquinoline derivatives with arenes and heteroarenes under similar conditions furnished 4-(hetero)aryl-substituted quinolines. The results are shown in Table 2. In the case of 4-chloro-2,8-bis(trifluoromethyl)quinoline, the reaction occurred in 72–80% yield at 60–65°C in 45–50 min for 1,3-dimethoxy-benzene and 1,3,5-trimethoxybenzene as nucleophiles. However, unsubstituted 4-chloroquinoline and 8-hydroxy quinoline failed to undergo arylation with arenes and heteroarenes.

The proposed mechanism is shown in Figure 2. The two chlorine atoms in 2,4-dichloroquinazoline are in different electronic environments, the chlorine at C-4 becomes more labile due to a greater electron withdrawing effect involving both the N atoms through mesomeric effects and hence can be easily replaced by a suitable nucleophile to give the regioselective product. A similar mechanism in the case of 4-chloro-2,8-bis(trifluoromethyl)quinoline may be invoked. Trifluoromethyl groups in the quinoline derivative make the reaction more facile by participating in decreasing the electron density at C-4 and thereby making this position more electrophilic for the nucleophilic attack.

Table 1

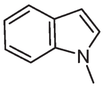
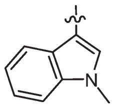
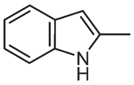
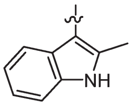
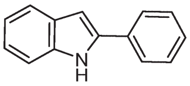
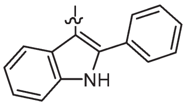
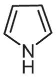
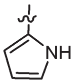
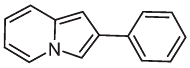
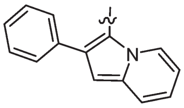
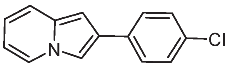
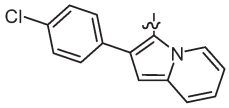
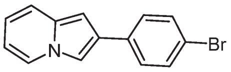
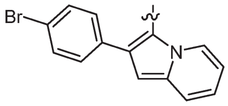
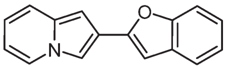
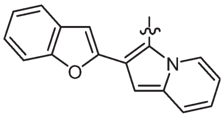
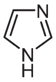
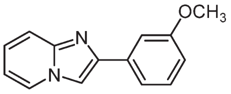
Regioselective $AlCl_3$-mediated synthesis of 4-(hetero)arylquinazolines.[a]



Entry	Substrate **2**; **Ar(Het)**-H	Temp. (°C)	Time	Product **3; Ar(Het)** =	Yield[b] (%)	m.p. (°C)
1	 **a**	75–80	3 h	 **a**	70	173–175
2	 **b**	75–80	3 h	 **b**	64	168–170
3	 **c**	75–80	3 h	 **c**	65	155–157
4	 **d**	65–70	2 h	 **d**	83	140–142
5	 **e**	65–70	1.5 h	 **e**	85	200–202
6	 **f**	75–80	3 h	 **f**	60	>250
7	 **g**	75–80	3 h	 **g**	77	175–177

(*Continued*)

Table 1
(*Continued*)

Entry	Substrate **2**; **Ar(Het)**-H	Temp. (°C)	Time	Product **3;** **Ar(Het)** =	Yield[b] (%)	m.p. (°C)
8	 **h**	75–80	2.5 h	 **h**	80	142–144
9	 **i**	75–80	2.5 h	 **i**	57	>250
10	 **j**	75–80	2.5 h	 **j**	50	260–262
11	 **k**	75–80	2.5 h	 **k**	85	107–109
12	 **l**	40–45	15 min	 **l**	80	192–194
13	 **m**	40–45	15 min	 **m**	85	218–220
14	 **n**	40–45	10 min	 **n**	85	190–192
15	 **o**	40–45	10 min	 **o**	80	146–148
16	 **p**	75–80	4 h	No reaction		
17	 **q**	75–80	4 h	No reaction		

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[a] Reaction stoichiometries: **1** (1.0 equiv), **2a–2q** (1.0 equiv), $AlCl_3$ (1.2 equiv).

[b] Isolated yield.

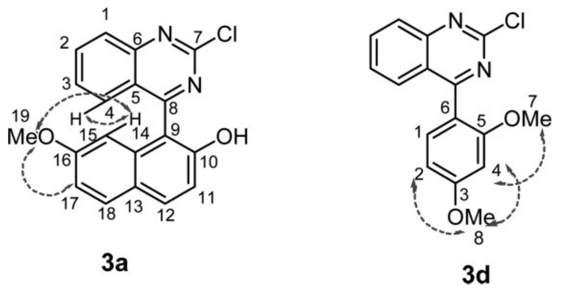


Figure 1. NOESY correlations in **3a** and **3d**.

CONCLUSIONS

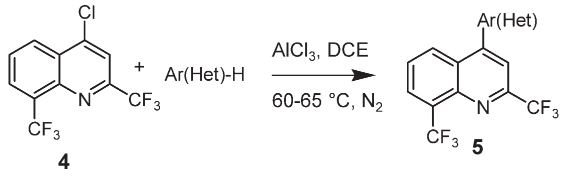
In conclusion, we have explored for the first time the scope and limitation of $AlCl_3$-mediated arylation and heteroarylation of mono and dichloroazarenes through a direct C—C bond forming reaction with arenes and heteroarenes. Suitably substituted chloroazarenes with single nitrogen atom such as 4-chloro-2,8-bis(trifluoromethyl)quinoline could be arylated regioselectively to furnish 4-arylquinolines. Similarly, arylation of 2,4-dichloroquinazoline leads to the formation 4-aryl and 4-heteroaryl quinazolines which are of biological importance. The biheteroaryls with ortho substituent are obtained in their racemic form, which after resolution could be separated into atropisomers, providing an easy route to access the P, N ligands. Surprisingly, demethylation and debromination of the product were not observed in any case in the presence of anhydrous aluminum chloride under the comparatively mild conditions.

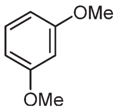
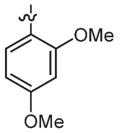
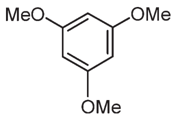
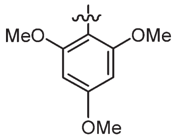
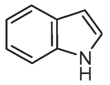
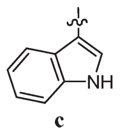
EXPERIMENTAL

General methods. All the reactions were performed under nitrogen atmosphere in oven-dried glass wares. The nucleophilic substrates **2a–q** used were either commercially available or prepared in laboratory. Aluminum chloride used was of commercial grade. A commercial grade dichloroethane stored

Table 2

$AlCl_3$-mediated synthesis of 4-(hetero)arylquinolines.[a]



Entry	Substrate **Ar(Het)-H**	Time	Product **5**; **Ar(Het)**=	Yield[b] (%)	m.p. (°C)
1	 **2d**	45 min	 **a**	80	105–107
2	 **2e**	50 min	 **b**	72	133–135
3	 **2g**	2.5 h	 **c**	68	141–143

[a] Reaction stoichiometries: **4** (1.0 equiv), **2d, 2e**, and **2g** (1.0 equiv), $AlCl_3$ (1.2 equiv).

[b] Isolated yield.

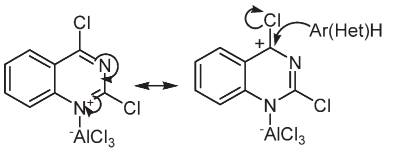


Figure 2. Proposed mechanism for the regioselective substitution in quinazoline.

over calcium chloride was used. Reaction progress was monitored by TLC aluminum sheets silica gel 60 F_{254}. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Supercon Magnet DPX-200 or DRX-300 spectrometers (operating at 200 and 300 MHz, respectively, for ^{1}H; 50 and 75 MHz, respectively, for ^{13}C) using $CDCl_3$ and DMSO-d_6 as solvent. Tetramethylsilane (δ 0.00 ppm) served as an internal standard in ^{1}H NMR and $CDCl_3$ (δ 77.23 ppm) in ^{13}C NMR. Splitting patterns are described as singlet (s), broad singlet (brs), doublet (d), triplet (t), and multiplet (m). Electrospray mass spectra (ES-MS) were recorded on a Micromass Quattro II triple quadruple mass spectrometer. High-resolution electron impact mass spectra (HREIMS) were obtained on JEOL MS route 600H instrument. Elemental analysis was performed on Vario EL-III C H N S analyzer. Column chromatography was performed over Merck silica gel (particle size: 60–120 mesh) obtained from Qualigens (India), or flash silica gel (particle size: 230–400 mesh).

General method for the preparation of 2,4-dichloroquinazoline 1

Step 1. A mixture of anthranilic acid (50 g, 0.36 mol) and urea (109 g, 1.82 mol) was heated [18a] in neat at 135–140°C using an air condenser for 3 h. The product mixture was poured into crushed ice (500 mL) with continuous stirring for 30 min. Quinazoline-2,4-dione thus obtained as solid was filtered, washed with water and used as such in the next step. Yield 74%; m.p. > 250°C.

Step 2. A mixture of quinazoline-2,4-dione (20 g, 0.12 mol) as obtained earlier and $POCl_3$ (98 g, 0.64 mol) was refluxed in the presence of *N*,*N*-dimethylaniline (8.5 g, 0.07 mol) for 5 h [18b]. The reaction mixture was allowed to cool to room temperature and poured cautiously into crushed ice (500 mL) with continuous stirring for 20 min. The precipitate obtained was filtered, washed with water, and finally purified column chromatography using 30% ethyl acetate/hexane as eluent. Yield 73%; m.p.: 115–116°C (116–117°C) [18b].

General method for the preparation of 4-(hetero)aryl quinazolines 3a–o. To the solution of 2,4-dichloroquinazoline **1** (1 mmol, 0.198 g) in 10 mL of dichloroethane under stirring, $AlCl_3$ (1.2 mmol, 0.158 g) was added and allowed to stir for 2–5 min. Nucleophilic substrate **2a–q** (1 mmol) (Table 1) were added and allowed to stir for completion of the reaction (see Table 1 for time and temperature). Reaction was monitored by TLC using 30% of ethyl acetate-hexane mixture. The reaction mixture was cooled to room temperature and poured into crushed ice (100 mL) with continuous stirring for 15–20 min. The products were obtained either by filtration through suction pump (**3b**, **3g**) or extracted with dichloromethane (3 × 30 mL). The organic layers were combined, washed with brine, and concentrated under reduced pressure after drying over Na_2SO_4. The crude products obtained were further purified by silica gel column chromatography using ethyl acetate-hexane as eluent.

1-(2-Chloroquinazolin-4-yl)-7-methoxynaphthalen-2-ol (3a). Yield 70%; m.p.: 173–175°C; IR (potassium bromide): 3450, 1597, 1351, 1183 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.49 (s, 3H), 6.46 (d, 1H, J = 2.2 Hz), 7.01 (dd, 1H, J = 8.9, 2.3 Hz), 7.14 (d, 1H, J = 8.8 Hz), 7.44–7.49 (m, 1H), 7.68 (d, 1H, J = 8.3 Hz), 7.72 (d, 1H, J = 8.9 Hz), 7.81 (d, 1H, J = 8.9 Hz), 7.89–7.95 (m, 1H), 8.05 (d, 1H, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.25 (CH_3), 104.00 (CH), 113.8, 116.21 (CH), 116.44 (CH), 122.92, 124.34, 128.05 (CH), 128.25 (CH), 128.65 (CH), 130.18 (CH), 132.90 (CH), 133.98, 135.86 (CH), 153.00, 154.64, 156.70, 158.87, 170.13; ES-MS (*m*/*z*): $[M+H]^+$ 337; HRMS -EI: found: 336.0665, calculated: 336.0666. Anal. Calcd. for $C_{19}H_{13}ClN_2O_2$: C, 67.76; H, 3.89; N, 8.32. Found: C, 67.61; H, 3.78; N, 8.23.

1-(2-Chloroquinazolin-4-yl)naphthalen-2-ol (3b). Yield 64%; m.p.: 168–170°C; IR (potassium bromide): 3455, 1580 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (d, 1H, J = 8.3 Hz), 7.26–7.32 (m, 2H), 7.34–7.39 (m, 1H), 7.42–7.48 (m, 1H), 7.61 (d, 1H, J = 8.1 Hz), 7.85 (d, 1H, J = 7.7 Hz), 7.90–7.96 (m, 2H), 8.09 (d, 1H, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 115.17, 118.69, 123.48, 123.89, 124.09, 127.24, 127.80, 127.97, 128.15, 128.26, 128.44, 131.78, 133.04, 135.27, 152.50, 153.28, 157.18, 171.31; ES-MS (*m*/*z*): $[M+H]^+$ 307; HRMS-EI: found: 306.0550, calculated: 306.0560. Anal. Calcd. for $C_{18}H_{11}ClN_2O$: C, 70.48; H, 3.61; N, 9.13. Found: C, 70.16; H, 3.70; N, 8.93.

4-(2-Chloroquinazolin-4-yl)naphthalen-1-ol (3c). Yield 65%; m.p.: 155–157°C; IR (potassium bromide): 3445, 1587 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.95 (d, 1H, J = 9.1 Hz), 7.26–7.40 (m, 4H), 7.47 (d, 1H, J = 9.0 Hz), 7.66 (d, 1H, J = 6.1 Hz), 7.78–7.83 (m, 1H), 7.93 (d, 1H, J = 6.0 Hz), 8.28 (d, 1H, J = 9.0 Hz), 9.95 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ 106.27, 121.53, 122.12, 122.46, 123.50, 123.76, 125.95, 126.36, 126.45, 126.79, 128.64, 131.28, 133.72, 151.25, 154.48, 155.53, 171.47; ES-MS (*m*/*z*): $[M+H]^+$ 307; HRMS-EI: found: 306.0558, calculated: 306.0559. Anal. Calcd. for $C_{18}H_{11}ClN_2O$: C, 70.48; H, 3.61; N, 9.13. Found: C, 70.17; H, 3.66; N, 9.01.

2-Chloro-4-(2,4-dimethoxyphenyl)quinazoline (3d). Yield 83%; m.p.: 140–142°C; IR (potassium bromide): 1611, 1209, 1161 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.71 (s, 3H), 3.90 (s, 3H), 6.61 (d, 1H, J = 2.2 Hz), 6.67 (dd, 1H, J = 8.4, 2.3 Hz), 7.41 (d, 1H, J = 8.4 Hz), 7.49–7.55 (m, 1H), 7.77 (dd, 1H, J = 8.0, 0.8 Hz), 7.85–7.90 (m, 1H), 7.99 (d, 1H, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.89, 56.01, 99.23, 105.64, 123.45, 127.70, 128.03, 128.65, 132.68, 135.00, 152.52, 158.66, 163.26, 171.21; FAB (*m*/*z*): 300, $[M+H]^+$ 301; HRMS-EI: found: 300.0663, calculated: 300.0666. Anal. Calcd. for $C_{16}H_{13}ClN_2O_2$: C, 63.90; H, 4.36; N, 9.31. Found: C, 63.95; H, 4.39; N, 9.29.

2-Chloro-4-(2,4,6-trimethoxyphenyl)quinazoline (3e). Yield 85%; m.p.: 200–202°C; IR (potassium bromide): 1610, 1215 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.64 (s, 6H), 3.89 (s, 3H), 6.25 (s, 2H), 7.47–7.53 (m, 1H), 7.66 (dd, 1H, J = 7.9, 0.6 Hz), 7.83–7.89 (m, 1H), 7.99 (d, 1H, J = 8.46 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.68 (OCH_3), 55.95 (OCH_3), 90.99, 106.72, 124.48, 127.59, 127.72, 134.70, 152.19, 157.22, 159.17, 163.07, 169.66. ES-MS (*m*/*z*): $[M+H]^+$ 331; HRMS-EI: found: 330.0769, calculated: 330.0771. Anal. Calcd. for $C_{17}H_{15}ClN_2O_3$: C, 61.73; H, 4.57; N, 8.47. Found: C, 61.49; H, 4.42; N, 8.15.

4-(2-Chloroquinazolin-4-yl)naphthalene-1,7-diol (3f). Yield 60%; m.p.: >250°C; IR (potassium bromide): 3452, 1585, 1352, 761 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 6.77–6.86 (m, 2H), 7.10 (d, 1H, J = 7.7 Hz), 7.27 (d, 1H, J = 9.1 Hz), 7.35 (d, 1H, J = 2.3 Hz), 7.45–7.58 (m, 2H), 7.88–7.89 (m, 2H), 9.6 (brs, 1H), 10.39 (brs, 1H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 104.43, 107.64, 119.96, 123.45, 123.63, 126.57, 127.09, 127.72, 128.12, 128.73, 135.90, 152.52, 154.39, 155.24, 156.35, 172.96, 175.22; ES-MS (m/z): [M+H]$^+$ 323; HRMS-EI: found: 322.0507, calculated: 322.0509. Anal. Calcd. for $C_{18}H_{11}ClN_2O_2$: C, 66.99; H, 3.44; N, 8.68. Found: C, 66.79; H, 3.41; N, 8.61.

2-Chloro-4-(1H-indol-3-yl)quinazoline (3g). Yield 77%; m.p.: 175–177°C; IR (potassium bromide): 1521, 1487, 1340 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$+DMSO-d_6): δ 7.27–7.30 (m, 2H), 7.54–7.57 (m, 1H), 7.61–7.67 (m, 1H), 7.88–7.94 (m, 1H), 7.97–8.02 (m, 2H), 8.26–8.29 (m, 1H), 8.45 (dd, 1H, J = 8.1, 0.6 Hz), 11.57 (NH); ^{13}C NMR (75 MHz, CDCl$_3$+DMSO-d_6): δ 111.91, 112.23, 121.12, 121.27, 121.40, 122.94, 126.03, 127.05, 127.25, 130.80, 133.98, 136.81, 152.17, 156.63, 166.35; FAB (m/z): 279, [M+H]$^+$ 280; HRMS-EI: found: 279.0494, calculated: 279.0485. Anal. Calcd. for $C_{16}H_{10}ClN_3$: C, 68.70; H, 3.60; N, 15.02. Found: C, 68.79; H, 3.68; N, 15.21.

2-Chloro-4-(1-methyl-1H-indol-3-yl)quinazoline (3h). Yield 80%; m.p.: 142–144°C; IR (potassium bromide): 1563, 1347, 735 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 3.93 (s, 3H), 7.28–7.36 (m, 2H), 7.38–7.43 (m, 1H), 7.55–7.61 (m, 1H), 7.78 (s, 1H), 7.84–7.89 (m, 1H), 7.97 (dd, 1H, J = 8.3, 0.7 Hz), 8.17–8.20 (m, 1H), 8.41 (dd, 1H, J = 8.6, 0.7 Hz); ^{13}C NMR (75 MHz, CDCl$_3$): δ 33.68 (CH$_3$), 109.96 (CH), 112.19 (C), 121.53 (C), 122.04 (CH), 122.12 (CH), 123.52 (CH), 127.00 (C), 127.29 (CH), 127.46 (CH), 128.05 (CH), 133.93 (CH), 134.33 (CH), 137.65 (C), 152.90 (C), 157.37 (C), 166.15 (C); ES-MS (m/z): [M+H]$^+$ 294; HRMS-EI: found: 293.0689, calcuated: 293.0719. Anal. Calcd. for $C_{17}H_{12}ClN_3$: C, 69.51; H, 4.12; N, 14.30. Found: C, 69.45; H, 4.10; N, 14.19.

2-Chloro-4-(2-methyl-1H-indol-3-yl)quinazoline (3i). Yield 57%; m.p.: >250°C; IR (potassium bromide): 1519, 1485, 1352 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$+DMSO-d_6): δ 2.60 (s, 3H), 7.05–7.21 (m, 2H), 7.42–7.45 (m, 2H), 7.51–7.58 (m, 1H), 7.87–8.01 (m, 2H), 8.12 (d, 1H, J = 8.3 Hz), 10.95 (brs, 1H); ^{13}C NMR (50 MHz, CDCl$_3$+DMSO-d_6): δ 13.67, 111.52, 119.62, 120.96, 122.18, 122.79, 127.26, 127.91, 128.18, 128.93, 134.88, 136.06, 139.67, 153.01, 157.41, 168.56; ES-MS (m/z): [M+H]$^+$ 294; HRMS-EI: found: 293.0718, calculated: 293.0719. Anal. Calcd. for $C_{17}H_{12}ClN_3$: C, 69.51; H, 4.12; N, 14.30. Found: C, 69.35; H, 4.22; N, 14.22.

2-Chloro-4-(2-phenyl-1H-indol-3-yl)quinazoline (3j). Yield 50%; m.p.: 260–262°C; IR (potassium bromide): 3223, 1598, 1345, 747 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$+DMSO-d_6): δ 7.09–7.15 (m, 1H), 7.23–7.28 (m, 4H), 7.32–7.39 (m, 3H), 7.55–7.82 (m, 2H), 7.73 (d, 1H, J = 8.2 Hz), 7.84–7.93 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$+DMSO-d_6): δ 106.57, 110.20, 117.70, 119.13, 120.14, 121.12, 125.47, 125.71, 126.32, 126.69, 126.96, 129.81, 133.24, 134.71, 138.15, 150.58, 154.79, 166.49; FAB (m/z): 355, [M+H]$^+$ 356. Anal. Calcd. for $C_{22}H_{14}ClN_3$: C, 74.26; H, 3.97; N, 11.81. Found: C, 74.59; H, 3.89; N, 11.75.

2-Chloro-4-(1H-pyrrol-2-yl)quinazoline (3k). Yield 85%; m.p.: 107–109°C; IR (potassium bromide): 3220, 1550 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.46–6.49 (m, 1H), 7.14–7.16 (m, 1H), 7.26–7.28 (m, 1H), 7.79–7.64 (m, 1H), 7.83–7.88 (m, 1H), 7.92 (dd, 4H, J = 8.3, 0.9 Hz), 8.53 (d, 1H, J = 8.5 Hz), 10.13 (s, NH); ^{13}C NMR (75 MHz, CDCl$_3$): δ 112.59, 117.33, 119.68, 123.99, 126.21, 127.85, 127.97, 128.34, 134.47, 153.26, 156.75, 159.41; ES-MS (m/z): [M+H]$^+$ 230; HRMS-EI: found: 229.0357, calculated: 229.0407. Anal. Calcd. for $C_{12}H_8ClN_3$: C, 62.76; H, 3.51; N, 18.30. Found: C, 62.41; H, 3.67; N, 18.54.

2-Chloro-4-(2-phenylindolizin-3-yl)quinazoline (3l). Yield 80%; m.p.: 192–194°C; IR (potassium bromide): 2366, 1598, 1350, 767 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.72–6.77 (m, 1H), 6.78 (s, 1H), 6.98–7.08 (m, 2H), 7.10–7.15 (m, 5H), 7.53–7.59 (m, 2H), 7.63–7.68 (m, 1H), 7.87 (d, 1H, J = 8.49 Hz), 8.99 (d, 1H, J = 7.2 Hz); ^{13}C NMR (75 MHz, CDCl$_3$): δ 101.55, 111.23, 114.25, 117.69, 119.95, 120.45, 123.43, 125.49, 125.70, 125.90, 127.24, 127.76, 133.15, 134.13, 134.22, 135.39, 151.99, 155.59, 161.36; ES-MS (m/z): [M+H]$^+$ 356; HRMS-EI: found: 355.0876, calculated: 355.0876. Anal. Calcd. for $C_{22}H_{14}ClN_3$: C, 74.26; H, 3.97; N, 11.81. Found: C, 73.95; H, 4.13; N, 11.49.

2-Chloro-4-[2-(4-chlorophenyl)indolizin-3-yl]quinazoline (3m). Yield 85%; m.p.: 218–220°C; IR (potassium bromide): 1597, 1349, 773 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.69–6.74 (m, 2H), 6.96–7.13 (m, 6H), 7.51 (d, 1H, J = 8.9 Hz), 7.53 (dd, 1H, J = 8.6, 0.6 Hz), 7.66–7.71 (m, 1H), 7.87 (d, 1H J = 8.5 Hz), 8.91 (dd, 1H, J = 7.2, 0.6 Hz); ^{13}C NMR (75 MHz, CDCl$_3$): δ 102.87, 112.90, 115.55, 119.18, 121.32, 122.07, 124.86, 127.29, 127.56, 128.41, 128.91, 130.32, 133.22, 134.04, 134.21, 134.89, 136.81, 153.53, 157.09, 162.54; ES-MS (m/z): [M+H]$^+$ 390; HRMS-EI: found: 389.0492, calcuated: 389.0487. Anal. Calcd. for $C_{22}H_{13}Cl_2N_3$: C, 67.71; H, 3.36; N, 10.77. Found: C, 67.46; H, 3.42; N, 10.63.

4-[2-(4-Bromophenyl)indolizin-3-yl]-2-chloroquinazoline (3n). Yield 85%; m.p.: 190–192°C; IR (potassium bromide): 1597, 1348, 772cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.70–6.75 (m, 2H), 6.97–7.02 (m, 3H), 7.09–7.15 (m, 1H), 7.22–7.25 (m, 2H), 7.50–7.55 (m, 2H), 7.67–7.73 (m, 1H), 7.88 (d, 1H, J = 8.3 Hz), 8.91 (dd, 1H, J = 7.1, 0.5 Hz); ^{13}C NMR (75 MHz, CDCl$_3$): δ 102.83, 112.94, 115.55, 119.22, 121.38, 121.45, 122.08, 124.90, 127.35, 127.64, 128.42, 130.66, 131.90, 134.05, 134.72, 134.94, 136.85, 157.15, 162.58; ES-MS (m/z): [M+H]$^+$ 434 (Br^{78}), 436(Br^{80}); HRMS-EI: found: 432.9950, calcuated: 432.9981. Anal. Calcd. for $C_{22}H_{13}BrClN_3$: C, 60.78; H, 3.01; N, 9.67. Found: C, 60.59; H, 3.29; N, 9.43.

4-(2-Benzofuran-2-yl-indolizin-3-yl)-2-chloroquinazoline (3o). Yield 80%; m.p.: 146–148°C; IR (potassium bromide): 1596, 1350 1172, 765 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.49 (s, 1H), 6.67–6.71 (m, 1H), 6.94–6.99 (m, 1H), 7.02–7.12 (m, 4H), 7.17–7.22 (m, 1H), 7.36–7.39 (m, 1H), 7.52 (d, 1H, J = 8.9 Hz), 7.72–7.79 (m, 2H), 7.99 (d, 1H, J = 8.3 Hz), 8.68 (d, 1H, J = 7.2 Hz); ^{13}C NMR (75 MHz, CDCl$_3$): δ 99.79, 103.04, 109.49, 111.60, 113.77, 117.96, 119.38, 120.36, 121.16, 121.49, 122.17, 122.87, 123.14, 126.27, 126.35, 127.39, 133.58, 135.01, 149.88, 151.95, 153.21, 155.61, 161.43; ES-MS (m/z): [M+H]$^+$ 396; HRMS-EI: found: 395.0831, calculated: 395.0825. Anal. Calcd. for $C_{24}H_{14}ClN_3O$: C, 72.82; H, 3.56; N, 10.62. Found: C, 72.53; H, 3.70; N, 10.45.

General method for the preparation of 4-(hetero)aryl quinolines 5a-c. 4-Chloro-2,8-bis(trifluoromethyl)quinoline **4** (1 mmol, 0.299 g) was added in 10 mL of dichloroethane. Under stirring, to it was added AlCl$_3$ (1.2 mmol, 0.158 g) and allowed to stirred for 2–5 min. Nucleophilic substrates **2d**, **2e**, and **2g** (1 mmol) (Table 2) were added and allowed to stirred at 60–65°C. The reaction mixture was cooled to room temperature and poured into ice-cold water (100 mL) with continuous stirring for 15–20 min. The products were obtained by extracting with dichloromethane (3 × 30 mL). The organic layers were combined, washed with brine and concentrated under reduced pressure after drying over Na_2SO_4. The crude products obtained further purified by silica gel column chromatography using ethyl acetate-hexane mixture.

4-(2,4-Dimethoxyphenyl)-2,8-bis-trifluoromethylquinoline (5a). Yield 80%; m.p.: 105–107°C; IR (potassium bromide): 1610, 1200, 1150 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.69 (s, 3H), 3.91 (s, 3H), 6.64–6.69 (m, 2H), 7.19 (d, 1H, $J = 8.5$ Hz), 7.54–7.62 (m, 1H), 7.72 (s, 1H), 7.92 (d, 1H, $J = 8.4$ Hz), 8.13 (d, 1H, $J = 7.1$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.70, 55.81, 99.23, 105.28, 118.33, 119.23, 126.61, 128.90, 128.97, 129.12, 131.21, 132.05, 144.16, 147.99, 148.45, 148.86, 157.97, 162.40; ES-MS (*m/z*): $[M+H]^+$ 402; HRMS-EI: found: 401.0848, calcuated: 401.0850. Anal. Calcd. for $C_{19}H_{13}F_6NO_2$: C, 56.87; H, 3.27; N, 3.49. Found: C, 57.02; H, 3.56; N, 3.24.

4-(2,4,6-Trimethoxyphenyl)-2,8-bis-trifluoromethylquinoline (5b). Yield 72%; m.p.: 133–135°C; IR (potassium bromide): 1613, 1194, 1143 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.64 (s, 6H), 3.89 (s, 3H), 6.24 (s, 2H), 7.10 (d, 1H, $J = 8.2$ Hz), 7.23 (s, 1H), 7.53–7.62 (m, 1H), 7.89 (d, 1H, $J = 8.3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.67, 55.98, 91.10, 106.70, 118.36, 119.21, 126.58, 128.87, 128.89, 130.99, 132.01, 144.12, 147.95, 148.39, 148.84, 159.10, 168.90; ES-MS (*m/z*): $[M+H]^+$ 432; HRMS-EI: found: 431.0955, calcuated: 431.0955. Anal. Calcd. for $C_{20}H_{15}F_6NO_3$: C, 55.69; H, 3.51; N, 3.25. Found: C, 55.51; H, 3.58; N, 2.97.

4-(1H-Indol-3-yl)-2,8-bis-trifluoromethylquinoline (5c). Yield 66%; m.p.: 145–147°C; IR (potassium bromide): 1611, 1522, 1403, 778 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21–7.27 (m, 2H), 7.52–7.58 (m, 2H), 8.01–8.13 (m, 1H), 8.26 (m, 1H), 8.27–8.29 (m, 1H), 8.39 (s, 1H), 11.53 (brs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 111.89, 112.30, 118.21, 119.03, 120.99, 121.19, 121.31, 123.01, 126.11, 127.25, 128.63, 128.96, 130.99, 131.93, 136.71, 145.62, 147.89, 148.36, 148.67; ES-MS (*m/z*): $[M+H]^+$ 381; HRMS-EI: found: 380.0739, calculated: 380.0746. Anal. Calcd. for $C_{19}H_{10}F_6N_2$: C, 60.01; H, 2.65; N, 7.37. Found: C, 59.73; H, 2.55; N, 7.26.

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An Efficient Two-Step Synthesis of Novel Thiazolo[2,3-*b*]pyrazolo[3,4-*f*][1,3,5]triazepines

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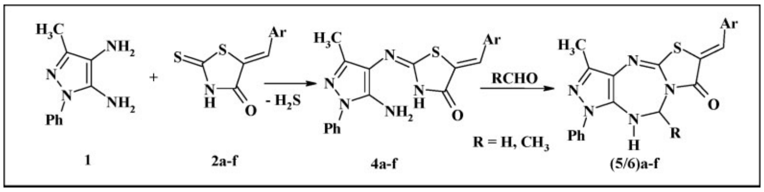

In an attempt to carry out a straightforward synthesis of thiazolopyrazolodiazepines from the reaction of 4,5-diamino-3-methyl-1-phenylpyrazole **1** with arylidene derivatives of rhodanine **2**, the unplanned (Z)-2′-[(5-amino-3-methyl-1-phenylpyrazol-4-yl)imino]-5-arylidenethiazolidin-4-ones **4** were obtained as unique products. Nevertheless, the treatment of these compounds with aliphatic aldehydes in dimethylformamide provided the novel thiazolo[2,3-*b*]pyrazolo[3,4-*f*][1,3,5]triazepines **5** and **6** in good to excellent yields. All the structures of the obtained compounds were assigned on the basis of IR, 1D and 2D NMR measurements, mass spectrometry, and microanalysis.

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INTRODUCTION

In recent years, the synthesis and pharmacological properties of diverse systems containing heterocycles fused to a seven-membered diazepine ring have appeared in the literature [1]. Particularly, good CNS activity was reported for various pyrazolodiazepines [2], some of them acting as psychotropic agents [3].

It is known that the interaction of *ortho*-diamines with α,β-unsaturated carbonyl compounds constitutes one of the more expeditious procedures yielding diazepine systems fused to aromatic rings [4]. In this sense, we have successfully carried out several reactions between 4,5-diaminopyrazoles and diaminopyrimidines with chalcones and β-dimethylaminopropiophenone hydrochlorides as versatile approaches for the synthesis of new pyrazolo- and pyrimidodiazepine derivatives, respectively [5].

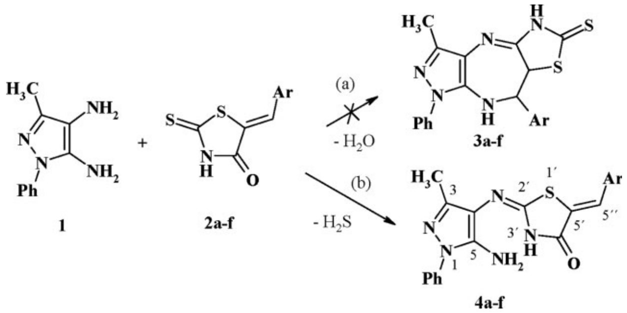
RESULTS AND DISCUSSION

Continuing with our studies directed toward the development of synthetic methodologies leading to fused pyrazole systems and in an attempt to obtain the new thiazolopyrazolodiazepines **3** for biological testing, we prepared a series of (Z)-arylidene derivatives of rhodanine **2a–f** (α,β-unsaturated carbonyl compounds) [6] to be reacted with 4,5-diamino-3-methyl-1-phenylpyrazole **1** as a direct procedure for the synthesis of our target compounds **3**, Scheme 1, approach (a).

To obtain the expected diazepines **3**, a mixture of diaminopyrazole **1** (1.5 mmol) and (Z)-5-(nitrobenzylidene)-2-thioxothiazolidin-4-one (**2a**) (Ar = 4-$NO_2C_6H_4$) (1.5 mmol) was heated at reflux for 15 h in the presence of ethanol (20 mL) as solvent and triethylamine (1 mL) as catalyst, according to previously reported procedures [7]. This reaction afforded a yellow solid, which after spectroscopic analysis (IR, ^{1}H and ^{13}C NMR and mass spectrum), corresponded unexpectedly to the imine compound **4a** (Ar = 4-$NO_2C_6H_4$) in 87% isolated yield, Scheme 1, approach (b), but not to the cyclo-condensed product **3a**.

The yellow solid exhibited all the signals expected for the proposed structure (**4a**). The IR spectrum showed mainly absorption bands at 3410, 3285, and 1700 cm^{-1} assigned to NH, NH_2, and C=O functionalities, respectively. The ^{1}H NMR of this compound features the following main signals: a broad singlet (2H) at 5.72 ppm assigned to the 5-NH_2 group, a singlet (1H) at 7.64 ppm assigned to 5″-H, and a broad singlet (1H) at 11.04 ppm assigned to 3′-NH. In fact, an H,H-NOESY effect was observed between both 5-NH_2 and 3′-NH groups in agreement with the proposed conformational structure. Without including the methyl carbon atoms, the relevant feature in

Scheme 1

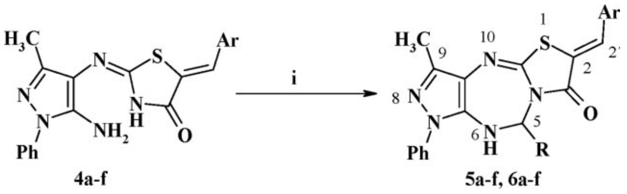


the ^{13}C NMR spectrum of this compound is that all signals appear at aromatic field (120.5–162.3 ppm), which is consistent with the proposed structure (**4a**). Finally, the molecular ion (*m*/*z* = 420), showed in mass spectrum confirmed that the formation process of this solid effectively involved the loss of a molecule of H_2S but not the loss of a molecule of H_2O, as expected for the synthesis of our compound **3**.

To evaluate the general character of this unplanned reaction, this approach was extended to the other 5-arylidene-2-thioxothiazolidin-4-ones (**2b–f**) with similar results, that is, yielding compounds **4b–f** as unique products involving in all the cases the loss of a molecule of H_2S, as shown in Scheme 1 and Table 1.

Trying to overcome the aforementioned failed attempt to obtain compounds **3**, we rationalized that according to NOESY experiments both 5-NH_2 and 3′-NH groups in **4** are certainly spatially nearby. Therefore, we considered the possibility of completing the cyclization process by treatment of compounds **4** with aldehydes, toward the formation of a novel, although slightly different from **3**, no less interesting triazepine system **5**. In this sense, the heating of compounds **4a–f** with an excess of formaldehyde in DMF at 70°C enabled us to obtain the novel pyrazolo[3,4-*f*]thiazolo[2,3-*b*][1,3,5]triazepines (**5a–f**) in 70 to 92% yield, as shown in Scheme 2 and Table 2.

Scheme 2. i = HCHO for **5a–f** (R = H). i = CH_3CHO for **6a–f** (R = CH_3).



In the ^{1}H NMR spectra of compounds **5**, the proton 2′-H appears as a singlet at δ = 7.65–7.77 ppm. The signals for the 9-CH_3 protons of the pyrazole ring result in a singlet at δ = 2.19–2.22 ppm. The two protons, 5-H and 6-NH, of the triazepine ring appear coupled between them, and the coupling constants are in the range of *J* = 6.2–6.4 Hz.

The analysis of ^{13}C, DEPT-135, and two-dimensional heteronuclear NMR spectra provided the final structural elucidation of compounds **5**. Thus, the signal for C-5 is in the range of δ = 56.4–63.9 ppm. The HMBC experiments for all derivatives indicate three-bond correlations between 5-H and quaternary carbons C-10a and C-6a. Mass spectra of compounds **5** show well-defined molecular ions with a characteristic fragmentation pattern involving the loss of phenyl group.

The extension of this procedure to acetaldehyde provided the analog triazepine systems **6a–f** also in good yields, as shown in Table 2. It is worth mentioning that when the compounds **4** were treated with aryl aldehydes (*i.e.* benzaldehyde, 4-methylbenzaldehyde and 4-chlorobenzadehyde), under the same reaction conditions, the reaction was not observed. Probably, steric effects could be related to such lack of reactivity, and therefore, this procedure is limited to aliphatic aldehydes. In short, we have not yet concluded an explanation why monoamines reacts with the arylidene derivatives **2** involving the C=O functionality through its α,β-unsaturated moiety as previously reported [8], while the analog diamine **1** reacted exclusively by the C=S functionality without participation of the α,β-unsaturated moiety. Currently, we are working in other cases to try to give a satisfactory explanation to this matter.

In summary, we have developed a new and versatile indirect two-step method for the synthesis of novel thiazolopyrazolotriazepines **5** and **6**, *via* the initially unplanned iminopyrazoles **4**, followed by treatment with

Table 1

Physical and analytical data of compounds **4a–f**.

Compound	Ar	m.p. (°C)	Yield
4a	4-$O_2NC_6H_4$	287–288	87
4b	4-BrC_6H_4	265–267	82
4c	4-ClC_6H_4	261–263	70
4d	4-FC_6H_4	267–269	71
4e	4-$CH_3C_6H_4$	189–190	65
4f	4-$CF_3C_6H_4$	286–288	62

Table 2

Physical and analytical data of compounds (**5**/**6**)**a–f**.

Compound	Ar	m.p. (°C)	Yield (%)
(5/6)a	4-$O_2NC_6H_4$	291–293/262–264	72/92
(5/6)b	4-BrC_6H_4	248–250/262–264	70/94
(5/6)c	4-ClC_6H_4	310–312/254–256	70/88
(5/6)d	4-FC_6H_4	265–267/209–211	92/93
(5/6)e	4-$CH_3C_6H_4$	246–248/264–266	90/92
(5/6)f	4-$CF_3C_6H_4$	222–224/231–233	88/85

aliphatic aldehydes. The chemical and biological potential of the triazepines **5** and **6** described herein are currently under investigation.

EXPERIMENTAL

Melting points were measured using a Stuart SMP3 melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FTIR 8400 instrument. The ^{1}H and ^{13}C NMR spectra were run on a Bruker DPX 400 spectrometer operating at 400 and 100 MHz, respectively, using dimethyl sulfoxide-d_6 as solvent and tetramethylsilane as internal standard. The mass spectra were scanned on a Hewlett Packard HP Engine-5989 spectrometer (equipped with a direct inlet probe) operating at 70 eV. High-resolution mass spectra (HRMS) were recorded in a Waters Micromass AutoSpec NT spectrometer (STIUJA). The elemental analyses have been obtained using a LECO CHNS-900 and a Thermo Finnigan FlashEA1112 CHNS-O (STIUJA) elemental analyzers. Thin layer chromatography (TLC) was performed on a 0.2-mm precoated plates of silica gel 60GF$_{254}$ (Merck). The benzylidene derivatives of rhodanine were obtained according to methodology described in the work [6c].

General procedure for the synthesis of (Z)-2′-[(5-amino-3-methyl-1-phenylpyrazol-4-yl)imino]-5′-arylidenethiazolidin-4-ones (4a–f). To a mixture of 4,5-diamino-3-methyl-1-phenylpyrazole **1** (1.5 mmol), ethanol (20 mL) and triethylamine (1 mL) was added to the corresponding 5-arylidene-2-thioxothiazolidin-4-one (1.5 mmol). The mixture was refluxed for 15 h. The formed precipitate was filtered off and washed with ethanol and recrystallized from ethanol.

(Z)-2′-[(5-Amino-3-methyl-1-phenylpyrazol-4-yl)imino]-5′-(4-nitrobenzylidene)thiazolidin-4-one (4a). This compound was obtained as yellow solid (ethanol); IR (KBr): (NH, NH$_2$) 3410 and 3285, C=O 1700 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.07 (s, 3H, 3-CH$_3$), 5.72 (s, 2H, NH$_2$), 7.34 (t, 1H, H$_p$-Ph, J = 7.5 Hz), 7.48 (t, 2H, H$_m$-Ph, J = 8.2 Hz), 7.50 (d, 2H, H$_o$-Ar, J = 8.2 Hz), 7.62 (d, 2H, H$_o$-Ph, J = 8.6 Hz), 7.64 (s, 1H, H-5″), 7.67 (d, 2H, H$_m$-Ar, J = 8.2 Hz), 11.04 ppm (s, 1H, 3′-NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.3 (3-CH$_3$), 120.5 (C-4), 122.5 (C$_o$), 126.3 (C$_p$), 128.2 (C-5′), 128.5 (C-5″), 129.0 (C$_i$-Ar), 129.2 (C$_m$-Ph), 131.1 (C$_o$-Ar), 132.2 (C$_m$-Ar), 134.0 (C$_p$-Ar), 139.0 (C$_i$-Ph), 143.3 (C-5), 144.9 (C-2′), 147.0 (C-3), 162.3 ppm (C-4′); ms (EI, 70 eV) m/z (%): 420 (M$^+$, 100), 213 (39). *Anal.* Calcd for $C_{20}H_{16}N_6O_3S$: C, 57.13; H, 3.84; N, 19.99. Found: C, 57.01; H, 3.79; N, 19.91.

(Z)-2′-[(5-Amino-3-methyl-1-phenylpyrazol-4-yl)imino]-5′-(4-bromobenzylidene)thiazolidin-4-one (4b). This compound was obtained as yellow solid (ethanol); IR (KBr): (NH, NH$_2$) 3442 and 3288, C=O 1698 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.05 (s, 3H, 3-CH$_3$), 5.68 (s, 2H, NH$_2$), 7.34 (t, 1H, H$_p$-Ph, J = 7.6 Hz), 7.49 (d, 2H, H$_m$-Ph, J = 8.3 Hz), 7.50 (d, 2H, Ho-Ar, J = 8.0 Hz), 7.63 (d, 2H, H$_o$-Ph, J = 8.7 Hz), 7.64 (s, 1H, H-5″), 7.68 (d, 2H, H$_m$-Ar, J = 8.0 Hz), 10.88 ppm (s, 1H, 3′-NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.4 (3-CH$_3$), 120.3 (C-4), 122.4 (C$_o$-Ph), 122.9 (C$_i$-Ar), 126.2 (C$_p$-Ph), 128.0 (C-5″), 128.4 (C-5″), 129.1 (C$_m$-Ph), 131.3 (C$_o$-Ar), 132.2 (C$_m$-Ar), 133.1 (C$_p$-Ar), 139.0 (C$_i$-Ph), 143.2 (C-5), 143.5 (C-2′), 144.9 (C-3), 161.8 ppm (C-4′); ms (EI, 70 eV) m/z (%): 455 (M$^+$, 100), 213 (58). *Anal.* Calcd for $C_{20}H_{16}BrN_5OS$: C, 52.87; H, 3.55; N, 15.41. Found: C, 52.89; H, 3.49; N, 15.39.

(Z)-2′-[(5-Amino-3-methyl-1-phenylpyrazol-4-yl)imino]-5′-(4-chlorobenzylidene)thiazolidin-4-one (4c). This compound was obtained as yellow solid (ethanol); IR (KBr): (NH, NH$_2$) 3410 and 3285, C=O 1700 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.05 (s, 3H, 3-CH$_3$), 5.68 (s, 2H, NH$_2$), 7.33 (t, 1H, H$_p$-Ph, J = 7.6 Hz), 7.49 (d, 2H, H$_m$-Ph, J = 8.3 Hz), 7.50 (d, 2H, H$_o$-Ar, J = 8.3 Hz), 7.62 (d, 2H, H$_o$-Ph, J = 8.6 Hz), 7.64 (s, 1H, H-5″), 7.68 (d, 2H, H$_m$-Ar, J = 8.3 Hz), 10.96 ppm (s, 1H, 3′-NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.3 (3-CH$_3$), 120.8 (C-4), 122.4 (C$_o$-Ph), 123.0 (C$_i$-Ar), 126.2 (C$_p$-Ph), 128.1 (C-5′), 128.4 (C-5″), 129.1 (C$_m$-Ph), 131.1 (C$_o$-Ar), 132.5 (C$_m$-Ar), 132.8 (C$_p$-Ar), 138.9 (C$_i$-Ph), 143.2 (C-5), 144.0 (C-2′), 144.9 (C-3), 162.0 ppm (C-4′); ms (EI, 70 eV) m/z (%): 409 (M$^+$, 100), 213 (39). *Anal.* Calcd for $C_{20}H_{16}ClN_5OS$: C, 58.61; H, 3.93; N, 17.09. Found: C, 58.56; H, 3.99; N, 17.00.

(Z)-2′-[(5-Amino-3-methyl-1-phenylpyrazol-4-yl)imino]-5′-(4-fluorobenzylidene)thiazolidin-4-one (4d). This compound was obtained as yellow solid (ethanol); IR (KBr): (NH, NH$_2$) 3425 and 3290, C=O 1680 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.07 (s, 3H, 3-CH$_3$), 5.71 (s, 2H, NH$_2$), 7.34 (t, 1H, H$_p$-Ph, J = 6.2 Hz), 7.52 (d, 2H, H$_m$-Ph, J = 7.4 Hz), 7.55 (d, 2H, H$_o$-Ar, J = 8.7 Hz), 7.60 (d, 2H, H$_o$-Ph, J = 8.7 Hz), 7.69 (s, 1H, H-5″), 7.70 (dd, 2H, H$_m$-Ar, J = 5.29 Hz, J = 8.7 Hz), 10.89 ppm (s, 1H, 3′-NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.3 (3-CH$_3$), 120.7 (C-4), 122.9 (C$_o$-Ph), 122.9 (C$_i$-Ar), 125.9 (C$_p$-Ph), 128.8 (C-5′), 129.0 (C-5″), 129.1 (C$_m$-Ph), 132.3 (d, $^3J_{C-F}$ = 8.0 Hz, C$_o$-Ar), 133.9 (d, $^2J_{C-F}$ = 22.0 Hz, C$_m$-Ar), 139.3 (d, $^1J_{C-F}$ = 242.0 Hz, C$_p$-Ar), 140.2 (C$_i$-Ph), 143.4 (C-5), 144.8 (C-2′), 144.9 (C-3), 163.2 ppm (C-4′); ms (EI, 70 eV) m/z (%): 393 (M$^+$, 100), 213 (47). *Anal.* Calcd for $C_{20}H_{16}FN_5OS$: C, 61.06; H, 4.10; N, 17.80. Found: C, 61.10; H, 4.02; N, 17.75.

(Z)-2′-[(5-Amino-3-methyl-1-phenylpyrazol-4-yl)imino]-5′-(4-methylbenzylidene)thiazolidin-4-one (4e). This compound was obtained as yellow solid (ethanol); IR (KBr): (NH, NH$_2$) 3446 and 3286, C=O 1695 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.07 (s, 3H, 3-CH$_3$), 2.31 (s, 3H, CH$_3$Ar), 5.68 (s, 2H, NH$_2$), 7.29 (d, 2H, H$_o$-Ar, J = 8.1 Hz), 7.33 (t, 1H, H$_p$-Ph, J = 7.4 Hz), 7.43 (d, 2H, H$_m$-Ar, J = 8.1 Hz), 7.45 (d, 2H, H$_m$-Ph, J = 7.4 Hz), 7.51 (d, 2H, H$_o$-Ph, J = 6.4 Hz), 7.63 (s, 1H, H-5″), 10.82 ppm (s, 1H, 3′-NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.4 (3-CH$_3$), 21.0 (CH$_3$Ar), 120.9 (C-4), 122.4 (C$_o$-Ph), 122.6 (C$_i$-Ar), 126.3 (C$_p$-Ph), 127.4 (C-5′), 127.6 (C$_p$-Ar), 127.9 (C$_m$-Ph), 129.2 (C-5″), 129.6 (C$_o$-Ar), 131.0 (C$_m$-Ar), 140.4 (C$_i$-Ph) 143.2 (C-5), 143.6 (C-2′), 144.9 (C-3), 162.4 ppm (C-4′); ms (EI, 70 eV) m/z (%): 389 (M$^+$, 100), 213 (69), 148 (32). *Anal.* Calcd for $C_{21}H_{19}N_5OS$: C, 64.76; H, 4.92; N, 17.98. Found: C, 64.70; H, 4.90; N, 17.95.

(Z)-2′-[(5-Amino-3-methyl-1-phenylpyrazol-4-yl)imino]-5′-(4-trifluoromethylbenzylidene)-thiazolidin-4-one (4f). This compound was obtained as yellow solid (ethanol); IR (KBr): (NH, NH$_2$) 3449 and 3296, C=O 1700 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.07 (s, 3H, 3-CH$_3$), 5.70 (s, 2H, NH$_2$), 7.34 (t, 1H, H$_p$-Ph, J = 7.6 Hz), 7.50 (d, 2H, H$_m$-Ph, J = 7.7 Hz), 7.64 (d, 2H, H$_o$-Ph, J = 7.7 Hz), 7.74 (s, 1H, H-5″), 7.77 (d, 2H, H$_m$-Ar, J = 8.3 Hz), 7.84 (d, 2H, H$_o$-Ar, J = 8.3 Hz), 10.97 ppm (s, 1H, 3′-NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ

11.3 (3-CH$_3$), 120.3 (C-4), 122.4 (C$_o$-Ph), 122.7 (C$_i$-Ar), 126.0 (C$_p$-Ph), 126.0 (q, $^3J_{C-F}$ = 5.2 Hz, C$_m$-Ar), 127.4 (C-5′), 127.9 (C$_m$-Ph), 128.5 (q, $^1J_{C-F}$ = 268.0 Hz, CF$_3$), 128.9 (q, $^2J_{C-F}$ = 31.2 Hz C$_p$-Ar), 129.2 (C$_{o'}$), 130.0 (C-5″), 138.9 (C$_i$-Ar), 143.2 (C-5), 143.5 (C-2′), 144.9 (C-3), 162.3 ppm (C-4′); ms (EI, 70 eV) *m*/*z* (%): 443 (M$^+$, 100), 213 (77), 145 (40). *Anal.* Calcd for $C_{21}H_{16}F_3N_5OS$: C, 56.88; H, 3.64; N, 15.79. Found: C, 56.82; H, 3.65; N, 15.84.

General procedure for the synthesis of (Z)-2-arylidene-9-methyl-7-phenyl-5-*R*-5,6-dihydropyrazolo[3,4-*f*][1,3]thiazolo [2,3-*b*][1,3,5]triazepin-3-ones (5a–f and 6a–f). A mixture of 2-(5-amino-3-methyl-1-phenylpyrazol-4-ylimino)-5-arylidenethiazolidin-4-one **4** (1 mmol), formaldehyde or acetaldehyde (2 mmol), and DMF (2.0 mL) was heated at 70°C for 2 h. The formed products were precipitated by adding water, filtered off under vacuum, washed with water and recrystallized from ethanol.

(Z)-9-Methyl-2-(4-nitrobenzylidene)-7-phenyl-5,6-dihydropyrazolo[3,4-f]thiazolo[2,3-b][1,3,5]triazepin-3-ona (5a). This compound was obtained as brown solid (ethanol); IR (KBr): NH 3371, C=O 1690 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.19 (s, 3H, 9-CH$_3$), 5.04 (d, 2H, H-5, J = 6.3 Hz), 7.18 (t, 1H, 6-NH, J = 6.2 Hz), 7.34 (t, 1H, H$_p$-Ph, J = 7.6 Hz), 7.48 (t, 2H, H$_m$-Ph, J = 8.4 Hz), 7.61 (d, 2H, H$_o$-Ph, J = 8.7 Hz), 7.77 (s, 1H, H-2′), 7.82 (d, 2H, H$_o$-Ar, J = 8.1 Hz), 8.30 ppm (d, 2H, H$_m$-Ar, J = 8.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.1 (9-CH$_3$), 56.5 (C-5), 118.2 (C-9a), 122.5 (C$_o$-Ph), 124.1 (C$_m$-Ar), 125.9 (C-2′), 126.5 (C$_p$-Ph), 128.6 (C-2), 129.0 (C$_m$-Ph), 130.5 (C$_o$-Ar), 138.4 (C-6a), 138.5 (C$_i$-Ph), 139.9 (C$_i$-Ar), 142.5 (C-10a), 145.5 (C-9), 146.7 (C$_p$-Ar), 164.8 ppm (C-3); ms (EI, 70 eV) *m*/*z* (%): 432 (M$^+$, 100), 225 (27), 131 (28). *Anal.* Calcd for $C_{21}H_{16}N_6O_3S$: C, 58.32; H, 3.73; N, 19.43. Found: C, 58.36; H, 3.67; N, 19.50.

(Z)-2-(4-Bromobenzylidene)-9-methyl-7-phenyl-5,6-dihydropyrazolo[3,4-f]thiazolo[2,3-b][1,3,5]triazepin-3-one (5b). This compound was obtained as red solid (ethanol); IR (KBr): NH 3394, C=O 1682 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.20 (s, 3H, 9-CH$_3$), 5.02 (d, 2H, H-5, J = 6.0 Hz), 7.15 (t, 1H, 6-NH, J = 6.0 Hz), 7.34 (t, 1H, H$_p$-Ph, J = 7.5 Hz), 7.48 (t, 2H, H$_m$-Ph, J = 8.2 Hz), 7.53 (d, 2H, H$_o$-Ar, J = 8.0 Hz), 7.61 (d, 2H, H$_o$-Ph, J = 8.6 Hz), 7.66 (s, 1H, H-2′), 7.70 ppm (d, 2H, H$_m$-Ar, J = 8.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.1 (9-CH$_3$), 56.4 (C-5), 118.3 (C-9a), 122.4 (C$_o$-Ph), 122.9 (C$_p$-Ar), 124.7 (C-2′), 126.4 (C$_p$-Ph), 127.4 (C-2), 129.0 (C$_m$-Ph), 131.5 (C$_i$-Ar), 132.1 (C$_o$-Ar), 132.8 (C$_m$-Ar), 138.4 (C-6a), 138.5 (C$_i$-Ph), 143.1 (C-10a), 145.4 (C-9), 165.1 ppm (C-3); ms (EI, 70 eV) *m*/*z* (%): 465 (M$^+$, 83), 225 (52), 212 (52), 77 (100). *Anal.* Calcd for $C_{21}H_{16}BrN_5OS$: C, 54.09; H, 3.46; N, 15.02. Found: C, 54.00; H, 3.39; N, 15.10.

(Z)-2-(4-Chlorobenzylidene)-9-methyl-7-phenyl-5,6-dihydropyrazolo[3,4-f]thiazolo[2,3-b][1,3,5]triazepin-3-one (5c). This compound was obtained as red solid (ethanol); IR (KBr): NH 3382, C=O 1704 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.21 (s, 3H, 9-CH$_3$), 5.02 (d, 2H, H-5, J = 5.9 Hz), 7.21 (t, 1H, 6-NH, J = 5.9 Hz), 7.33 (t, 1H, H$_p$-Ph, J = 7.6 Hz), 7.48 (t, 2H, H$_m$-Ph, J = 8.3 Hz), 7.60 (d, 2H, H$_o$-Ar, J = 8.2 Hz), 7.62 (d, 2H, H$_o$-Ph, J = 8.7 Hz), 7.64 (d, 2H, H$_m$-Ar, J = 8.3 Hz), 7.71 ppm (s, 1H, H-2′); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.2 (9-CH$_3$), 56.5 (C-5), 118.3 (C-9a), 122.5 (C$_o$-Ph), 124.6 (C-2′), 124.7 (C$_p$-Ar), 126.4 (C$_p$-Ph), 127.3 (C-2), 129.0 (C$_m$-Ph), 129.3 (C$_o$-Ar), 131.5 (C$_m$-Ar), 132.6 (C$_i$-Ar), 134.1 (C$_i$-Ph), 138.5 (C-10a), 143.2 (C-6a), 145.4 (C-9), 165.1 ppm (C-3); ms (EI, 70 eV) *m*/*z* (%): 421 (M$^+$, 100), 225 (30), 168 (40). *Anal.* Calcd for $C_{21}H_{16}ClN_5OS$: C, 59.78; H, 3.82; N, 16.60. Found: C, 59.75; H, 3.76; N, 16.50.

(Z)-2-(4-Fluorobenzylidene)-9-methyl-7-phenyl-5,6-dihydropyrazolo[3,4-f]thiazolo[2,3-b][1,3,5]triazepin-3-one (5d). This compound was obtained as orange solid (ethanol); IR (KBr): NH 3304, C=O 1677 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.21 (s, 3H, 9-CH$_3$), 5.03 (d, 2H, H-5, J = 6.2 Hz), 7.13 (t, 1H, 6-NH, J = 6.2 Hz), 7.35 (t, 1H, H$_p$-Ph, J = 7.5 Hz), 7.37 (d, 2H, H$_o$-Ar, J = 8.9 Hz), 7.48 (t, 2H, H$_m$-Ph, J = 8.3 Hz), 7.61 (d, 2H, H$_o$-Ph, J = 8.7 Hz), 7.63 (dd, 2H, H$_m$-Ar, J_F = 5.38 Hz, J = 8.9 Hz), 7.72 ppm (s, 1H, H-2′); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.1 (9-CH$_3$), 56.4 (C-5), 116.3 (d, $^3J_{C-F}$ = 8.0 Hz, C$_o$-Ar), 118.4 (C-9a), 122.5 (C$_o$-Ph), 123.5 (C-6a), 126.4 (C$_p$-Ph), 127.6 (C-2′), 128.9 (C$_m$-Ph), 130.3 (C$_i$-Ar), 132.1 (d, $^2J_{C-F}$ = 22.0 Hz, C$_m$-Ar), 138.5 (C$_i$-Ph), 143.3 (C-9), 145.4 (C-10a), 161.1 (C-2), 162.4 (d, $^1J_{C-F}$ = 248.0 Hz, C$_p$-Ar), 165.2 ppm (C-3); ms (EI, 70 eV) *m*/*z* (%): 405 (M$^+$, 100), 225 (31), 152 (66). *Anal.* Calcd for $C_{21}H_{16}FN_5OS$: C, 62.21; H, 3.98; N, 17.27. Found: C, 62.27; H, 3.99; N, 17.37.

(Z)-9-Methyl-2-(4-methylbenzylidene)-7-phenyl-5,6-dihydropyrazolo[3,4-f]thiazolo[2,3-b][1,3,5]triazepin-3-one (5e). This compound was obtained as orange solid (ethanol); IR (KBr): NH 3357, C=O 1708 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.22 (s, 3H, 9-CH$_3$), 2.37 (s, 3H, CH$_3$Ar), 5.03 (d, 2H, H-5, J = 6.0 Hz), 6.82 (t, 1H, 6-NH, J = 6.0 Hz), 7.32 (t, 1H, H$_p$-Ph, J = 7.3 Hz), 7.34 (t, 2H, H$_m$-Ph, J = 7.1 Hz), 7.46 (d, 2H, H$_o$-Ph, J = 8.3 Hz), 7.48 (d, 2H, H$_o$-Ar, J = 7.7 Hz), 7.61 (d, 2H, H$_m$-Ar, J = 7.7 Hz), 7.65 ppm (s, 1H, H-2′); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.4 (9-CH$_3$), 21.3 (CH$_3$Ar), 57.1 (C-5), 118.9 (C-10a), 123.0 (C$_m$-Ar), 123.5 (C$_i$-Ar), 126.8 (C$_p$-Ph), 129.3 (C-2′), 129.3 (C$_o$-Ph), 130.1 (C$_o$-Ar), 130.2 (C$_m$-Ph), 131.6 (C$_i$-Ph), 139.2 (C-2), 139.4 (C-6a), 140.2 (C$_p$-Ar), 143.9 (C-10a), 145.9 (C-9), 165.7 ppm (C-3); ms (EI, 70 eV) *m*/*z* (%): 401 (M$^+$, 71), 225 (21), 148 (100), 77 (100). *Anal.* Calcd for $C_{22}H_{19}N_5OS$: C, 65.82; H, 4.77; N, 17.44. Found: C, 65.72; H, 4.71; N, 17.38.

(Z)-9-Methyl-7-phenyl-2-(4-trifluoromethylbenzylidene)-5,6-dihydropyrazolo[3,4-f]thiazolo[2,3-b][1,3,5]triazepin-3-one (5f). This compound was obtained as orange solid (ethanol); IR (KBr): NH 3341, C=O 1689 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.22 (s, 3H, 9-CH$_3$), 5.81 (m, 2H, H-5), 7.14 (t, 1H, 6-NH), 7.33 (t, 1H, H$_p$-Ph, J = 7.5 Hz), 7.48 (t, 2H, H$_m$-Ph, J = 7.9 Hz), 7.58 (d, 2H, H$_o$-Ph, J = 8.3 Hz), 7.75 (s, 1H, H-2′), 7.80 (d, 2H, H$_o$-Ar, J = 8.3 Hz), 7.85 ppm (d, 2H, H$_m$-Ar, J = 8.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.2 (9-CH$_3$), 63.6 (C-5), 118.8 (C-9a), 123.1 (C$_o$-Ph), 125.7 (q, $^3J_{C-F}$ = 5.6 Hz C$_m$-Ar), 125.9 (q, $^1J_{C-F}$ = 274.0 Hz, CF$_3$,), 126.4 (q, $^2J_{C-F}$ = 30.6 Hz, C$_p$-Ar), 126.5 (C$_p$-Ph), 126.6 (C-2′), 129.2 (C-6a), 129.5 (C$_i$-Ar), 130.6 (C$_m$-Ph), 132.4 (C$_o$-Ar), 138.1 (C$_i$-Ph), 138.9 (C-2), 142.2 (C-10a), 145.8 (C-9), 165.05 ppm (C-3); ms (EI, 70 eV) *m*/*z* (%): 455 (M$^+$, 100), 225 (20), 77 (34). *Anal.* Calcd for $C_{22}H_{16}F_3N_5OS$: C, 58.02; H, 3.54; N, 15.38. Found: C, 58.11; H, 3.60; N, 15.48.

(Z)-5,9-Dimethyl-2-(4-nitrobenzylidene)-7-phenyl-5,6-dihydropyrazolo[3,4-f]thiazolo[2,3-b][1,3,5]triazepin-3-one (6a). This compound was obtained as red solid (ethanol); IR (KBr): NH 3318, C=O 1691 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.35 (d, 3H, 5-CH$_3$, J = 7.0 Hz), 2.21 (s, 3H, 9-CH$_3$), 5.81 (m, 1H, H-5), 7.16 (d, 1H, 6-NH, J = 6.1 Hz), 7.34 (t, 1H, H$_p$-Ph, $J = 7.9$ Hz), 7.48 (t, 2H, H$_m$-Ph, $J = 7.0$ Hz), 7.58 (d, 2H, H$_o$-Ph, $J = 7.9$ Hz), 7.76 (s, 1H, H-2′), 7.83 (d, 2H, H$_o$-Ar, $J = 7.9$ Hz), 8.29 ppm (d, 2H, H$_m$-Ar, $J = 7.9$ Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.6 (9-CH$_3$), 21.0 (5-CH$_3$), 63.7 (C-5), 118.7 (C-9a) 123.1 (C$_o$-Ph), 124.7 (C$_m$-Ar), 126.4 (C-2′), 127.1 (C$_p$-Ph), 128.7 (C-2), 129.6 (C$_m$-Ph), 131.0 (C$_o$-Ar), 136.5 (C-6a), 138.9 (C$_i$-Ph), 140.5 (C$_p$-Ar), 141.9 (C-10a), 145.80 (C-9), 147.3 (C$_i$-Ar), 164.9 ppm (C-3); ms (EI, 70 eV) *m/z* (%): 446 (M$^+$, 100), 413 (30), 239 (20). *Anal.* Calcd for $C_{22}H_{18}N_6O_3S$: C, 59.18; H, 4.06; N, 18.82. Found: C, 59.10; H, 4.01; N, 18.90.

(Z)-2-(4-Bromobenzylidene)-5,9-dimethyl-7-phenyl-5,6-dihydropyrazolo[3,4-f]thiazolo[2,3-b][1,3,5]triazepin-3-one (6b). This compound was obtained as yellow solid (ethanol); IR (KBr): NH 3298, C=O 1688 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.35 (d, 3H, 5-CH$_3$, $J = 5.6$ Hz), 2.23 (s, 3H, 9-CH$_3$), 5.84 (m, 1H, H-5), 6.81 (d, 1H, 6-NH, $J = 6.2$ Hz), 7.33 (t, 1H, H$_p$-Ph, $J = 7.1$ Hz), 7.48 (t, 2H, H$_m$-Ph, $J = 7.3$ Hz), 7.52 (d, 2H, H$_o$-Ar, $J = 8.0$ Hz), 7.62 (d, 2H, H$_o$-Ph, $J = 8.2$ Hz), 7.65 (s, 1H, H-2′), 7.74 ppm (d, 2H, H$_m$-Ar, $J = 8.0$ Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.3 (9-CH$_3$), 20.9 (5-CH$_3$), 63.9 (C-5), 118.2 (C-9a), 122.3 (C$_o$-Ph), 123.0 (C$_p$-Ar), 124.6 (C-2′), 127.4 (C$_p$-Ph), 127.8 (C-2), 128.6 (C$_m$-Ph), 131.7 (C$_i$-Ar), 132.1 (C$_o$-Ar), 132.8 (C$_m$-Ar), 138.8 (C-6a), 139.3 (C$_i$-Ph), 143.1 (C-10a), 145.4 (C-9), 165.2 ppm (C-3); ms (EI, 70 eV) *m/z* (%): 479 (M$^+$, 100), 481 (98), 239 (50), 168 (44), 77 (75). *Anal.* Calcd for $C_{22}H_{18}BrN_5OS$: C, 55.01; H, 3.78; N, 14.58. Found: C, 55.09; H, 3.83; N, 14.67.

(Z)-2-(4-Chlorobenzylidene)-5,9-dimethyl-7-phenyl-5,6-dihydropyrazolo[3,4-f]thiazolo[2,3-b][1,3,5]triazepin-3-one (6c). This compound was obtained as yellow solid (ethanol); IR (KBr): NH 3296, C=O 1687 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.35 (d, 3H, 5-CH$_3$, $J = 6.6$ Hz), 2.23 (s, 3H, 9-CH$_3$), 5.82 (m, 1H, H-5), 7.13 (d, 1H, 6-NH, $J = 5.0$ Hz), 7.34 (t, 1H, H$_p$-Ph, $J = 7.2$ Hz), 7.49 (t, 2H, H$_m$-Ph, $J = 7.4$ Hz), 7.59 (d, 2H, H$_o$-Ph, $J = 8.2$ Hz), 7.62 (d, 2H, H$_o$-Ar, $J = 8.2$ Hz), 7.63 (d, 2H, H$_m$-Ar, $J = 8.2$ Hz), 7.71 ppm (s, 1H, H-2′); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.1 (9-CH$_3$), 20.5 (5-CH$_3$), 56.5 (C-5), 118.4 (C-9a), 122.6 (C$_o$-Ph), 124.3 (C-2′), 126.6 (C$_p$-Ar), 127.4 (C$_p$-Ph), 129.1 (C-2), 129.3 (C$_m$-Ph), 131.3 (C$_o$-Ar), 132.6 (C$_m$-Ar), 134.1 (C$_i$-Ar), 135.9 (C$_i$-Ph), 138.5 (C-10a), 142.0 (C-6a), 145.2 (C-9), 164.7 ppm (C-3); ms (EI, 70 eV) *m/z* (%): 435 (M$^+$, 100), 239 (52), 168 (47), 77 (86). *Anal.* Calcd for $C_{22}H_{18}ClN_5OS$: C, 60.62; H, 4.16; N, 16.06. Found: C, 60.55; H, 4.23; N, 16.15.

(Z)-5,9-Dimethyl-2-(4-fluorobenzylidene)-7-phenyl-5,6-dihydropyrazolo[3,4-f]thiazolo[2,3-b][1,3,5]triazepin-3-one (6d). This compound was obtained as yellow solid (ethanol); IR (KBr): NH 3398, C=O 1692 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.35 (d, 3H, 5-CH$_3$, $J = 6.6$ Hz), 2.23 (s, 3H, 9-CH$_3$), 5.83 (m, 1H, H-5), 7.12 (d, 1H, 6-NH, $J = 5.0$ Hz), 7.34 (t, 1H, H$_p$-Ph, $J = 6.1$ Hz), 7.38 (d, 2H, H$_o$-Ar, $J = 8.7$ Hz), 7.49 (t, 2H, H$_m$-Ph, $J = 8.1$ Hz), 7.61 (d, 2H, H$_o$-Ph, $J = 7.4$ Hz), 7.68 (dd, 2H, H$_m$-Ar, $J = 8.7$ Hz, $J = 5.38$ Hz), 7.72 ppm (s, 1H, H-2′); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.1 (9-CH$_3$), 20.5 (5-CH$_3$), 63.1 (C-5), 116.2 (d, $^2J_{C-F} = 21.0$ Hz, C$_o$-Ar), 118.4 (C-9a), 122.6 (C$_o$-Ph), 123.1 (C-6a), 127.7 (C-2′), 127.8 (C$_p$-Ph), 128.6 (C-2), 129.1 (C$_m$-Ph), 131.0 (C$_i$-Ar), 132.1 (d, $^3J_{C-F} = 9.0$ Hz, C$_m$-Ar), 138.5 (C$_i$-Ph), 142.2 (C-10a), 145.2 (C-9), 162.4 (d, $^1J_{C-F} = 248.0$ Hz, C$_p$-Ar), 164.8 (C-3); ms (EI, 70 eV) *m/z* (%): 419 (M$^+$, 100), 239 (49), 152 (66), 77 (86). *Anal.* Calcd for $C_{22}H_{18}FN_5OS$: C, 62.99; H, 4.33; N, 16.70. Found: C, 62.91; H, 4.39; N, 16.78.

(Z)-5,9-Dimethyl-2-(4-methylbenzyliden)-7-phenyl-5,6-dihydropyrazolo[3,4-f]thiazolo[2,3-b][1,3,5]triazepin-3-one (6e). This compound was obtained as yellow solid (ethanol); IR (KBr): NH 3442, C=O 1701 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.35 (d, 3H, 5-CH$_3$, $J = 6.4$ Hz), 2.24 (s, 3H, 9-CH$_3$), 2.39 (s, 3H, CH$_3$Ar), 5.83 (m, 1H, H-5), 7.10 (d, 1H, 6-NH, $J = 5.0$ Hz), 7.34 (t, 1H, H$_p$-Ph, $J = 6.2$ Hz), 7.35 (t, 2H, H$_m$-Ph, $J = 7.4$ Hz), 7.38 (d, 2H, H$_o$-Ph, $J = 8.5$ Hz), 7.49 (d, 2H, H$_o$-Ar $J = 7.7$ Hz), 7.61 (d, 2H, H$_m$-Ar, $J = 7.7$ Hz), 7.67 ppm (s, 1H, H-2′); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.1 (9-CH$_3$), 20.5 (5-CH$_3$), 21.3 (CH$_3$Ar), 62.9 (C-4), 118.5 (C-9a), 124.2 (C$_m$-Ar), 125.5 (C$_i$-Ar), 126.7 (C$_p$-Ph), 128.4 (C-2′), 129.3 (C$_o$-Ph), 130.1 (C$_o$-Ar), 131.2 (C$_m$-Ph), 131.6 (C$_i$-Ph), 139.7 (C-2), 141.0 (C-6a), 141.2 (C$_p$-Ar), 142.5 (C-10a), 145.2 (C-9), 165.7 ppm (C-3); ms (EI, 70 eV) *m/z* (%): 415 (M$^+$, 100), 239 (46), 148 (57), 77 (73). *Anal.* Calcd for $C_{23}H_{21}N_5OS$: C, 66.48; H, 5.09; N, 16.85. Found: C, 66.39; H, 5.17; N, 16.84.

(Z)-5,9-Dimethyl-7-phenyl-2-(4-trifluoromethylbenzyli-dene)-5,6-dihydropyrazolo[3,4-f]thiazolo[2,3-b][1,3,5]tri-azepin-3-one (6f). This compound was obtained as orange solid (ethanol); IR (KBr): NH 3341, C=O 1689 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.35 (d, 3H, 5-CH$_3$, $J = 6.5$ Hz), 2.21 (s, 3H, 9-CH$_3$), 5.04 (m, 1H, H-5), 7.17 (s, 1H, 6-NH), 7.34 (t, 1H, H$_p$-Ph, J =7.3 Hz), 7.49 (t, 2H, H$_m$-Ph, $J = 7.8$ Hz), 7.63 (d, 2H, H$_o$-Ph, $J = 8.3$ Hz), 7.77 (s, 1H, H-2′), 7.81 (d, 2H, H$_o$-Ar, $J = 8.3$ Hz), 7.87 ppm (d, 2H, H$_m$-Ar, $J = 8.3$ Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.1 (9-CH$_3$), 21.0 (5-CH$_3$), 56.5 (C-5), 118.8 (C-9a), 122.2 (C$_o$-Ph), 125.3 (q, $^3J_{C-F} = 4.3$ Hz, C$_m$-Ar), 125.8 (q, $^2J_{C-F} = 31.6$ Hz, C$_p$-Ar), 126.0 (q, $^1J_{C-F} = 276.0$ Hz, CF$_3$), 126.5 (C$_p$-Ph), 126.6 (C-2′), 127.0 (C-5a), 128.7 (C$_i$-Ar), 128.9 (C$_m$-Ph), 130.2 (C$_o$-Ar), 137.6 (C$_i$-Ph), 138.5 (C-2), 142.8 (C-10a), 145.5 (C-9), 164.9 ppm (C-3); ms (EI, 70 eV) *m/z* (%): 469 (M$^+$, 100), 239 (23), 145 (17). *Anal.* Calcd for $C_{23}H_{18}F_3N_5OS$: C, 58.84; H, 3.86; N, 14.92. Found: C, 58.91; H, 3.79; N, 14.99.

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Unusual Retention of Isoxazole Ring under the Influence of 3-(Substituted nitrophenyl)-2-Isoxazoline during Catalytic Hydrogenation of Isoxazoline-Substituted Isoxazole Systems

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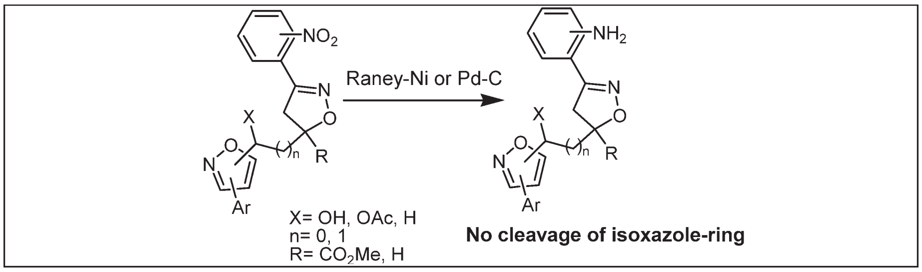
Dedicated to Professor Raymond C. F. Jones on the occasion of his 60th birthday.



The cleavage of the isoxazole ring during the Raney-Ni-promoted catalytic hydrogenation is prevented under the influence of 3-(substituted nitrophenyl)-2-isoxazoline in isoxazoline-substituted isoxazole systems produced *via* 1,3-dipolar cycloaddition either on the Baylis–Hillman derivatives or Grignard products. Unexpectedly, the hydrogenations in these diastereomeric compounds were observed to exclusively yield products, wherein the methoxycarbonyl and the hydroxyl or the acetyl groups exist *syn* to each other.

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INTRODUCTION

The catalytic hydrogenation of isoxazole and 2-isoxazoline heterocyclic systems in the presence of heterogeneous catalysts is relatively old and well-studied subject of synthetic organic chemistry [1]. Recently, we have discovered that the 2-isoxazoline system containing a 2-,3- or 4-nitrophenyl group at 3-position does not undergo ring cleavage under catalytic hydrogenation [2]. In our program to carry out Baylis–Hillman reaction-assisted synthesis of cyclic compounds [3], based on the aforementioned observation, we envisaged the synthesis of the spiroisoxazoline **III** from **I** (Figure 1). Substrate **I** was to be readily generated *via* 1,3-dipolar cycloaddition of appropriate benzonitrile oxide on the Baylis–Hillman adduct of substituted 3-isoxazolecarbaldehyde. In principle, a Raney-Ni-promoted hydrogenation would result in chemoselective ring cleavage of **I** to afford **II**, which may undergo intramolecular cyclization to produce the spiro-derivative. Spiroisoxazoline class of compounds has stimulated great interest in medicinal and biological chemistry [4]. Moreover, naturally occurring spiroisoxazolines have been found useful in different biomedical areas [5].

Therefore, we initiated the investigation by synthesizing **I** *via* 1,3-dipolar cycloaddition of the nitro-substituted benzonitrile oxide to the Baylis–Hillman adduct of 3-isoxazolecarbaldehyde and subjecting it to catalytic hydrogenation in the presence of Raney-Ni. Unexpectedly, analysis of the product isolated after work-up of the reaction revealed that instead of cleavage of the isoxazole ring, only the nitro group present on the phenyl group of the isoxazoline ring was reduced to amino group. A careful literature survey revealed that several reports described the Pd-on-carbon-promoted hydrogenation of the isoxazole derivatives without cleavage of the ring [6], but there exists no report exemplifying the retention of the isoxazole ring during Raney-Ni-promoted catalytic hydrogenation. This prompted us to systematically investigate the catalytic hydrogenation of derivatives wherein the isoxazole ring carry 3-(substituted nitrophenyl)-2-isoxazoline as substituent. It was observed that the cleavage of the isoxazole ring was invariably prevented during the catalytic hydrogenation because of the influence of 3-(substituted nitrophenyl)-2-isoxazoline in an isoxazoline-substituted isoxazole derivative. The details of this study are presented in this communication.

RESULTS AND DISCUSSION

The Baylis–Hillman adducts (**1a–c**) of substituted 3-isoxazolecarbaldehydes were prepared according to the

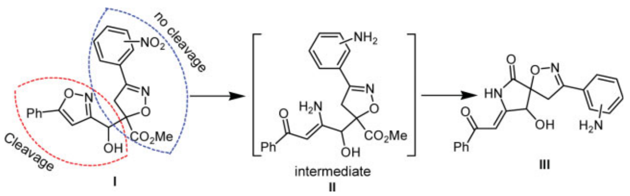
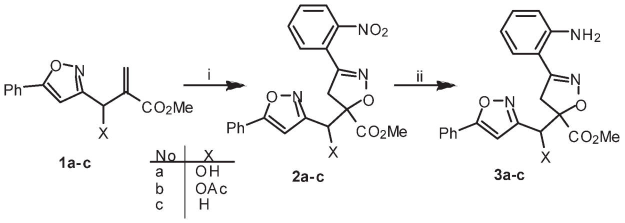


Figure 1. Possible route to spiroisoxazoline from isoxazoline-substituted isoxazole system. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

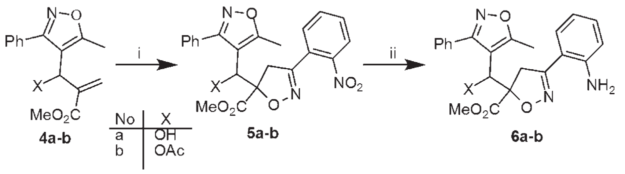
literature procedure [7] and subjected to 1,3-dipolar cycloaddition with 2-nitrobenzonitrile oxide. The required benzonitrile oxide was generated *in situ* from corresponding 2-nitrophenyl methylhydroximinoyl chloride by treating it with triethyl amine in dry ether. This reaction yielded **2a–c** as diastereomeric mixtures (1:1) in 78–83% yields. Hydrogenation of **2a** in the presence of Raney-Ni in methanol on a Parr assembly led to completion of reaction in 3 h. Unexpectedly, the spectral analysis of the isolated product (67% yield) led us to establish the structure as **3a** as a single diastereomer (Scheme 1). At this stage, the likelihood was that both the diastereomer were formed during the reaction, but we isolated only one of them. Consequently, ^{1}H NMR of the crude product was recorded. This spectrum also indicated the presence of a single diastereomer. Assuming that the period of reaction was insufficient to affect the cleavage of the isoxazole ring, the hydrogenation was repeated by continuing it for longer duration (*ca.* 24 h). The product isolated even after 24 h of the reaction time, however, was found to be **3a**. This led us to examine the hydrogenation using Pd-on-carbon as the catalyst. Interestingly, under this condition too, the compound **2a** was transformed to **3a** in 65% yield. To evaluate the outcome of these reactions with other substrates, compounds **2b** and **2c** were subjected to similar reactions. Both substrates behaved in an identical fashion to furnish corresponding products **3b** and **3c** as a single diastereomer in 63–66% yields.

This unusual observation generated interest to study hydrogenation in similar substrates afforded from the Baylis–Hillman adducts of substituted 4- and 5- isoxazole-carbaldehydes [8,9]. Accordingly, compounds **5a,b** were prepared in 83–92% yields from the Baylis–Hillman adduct **(4a)** of 3-phenyl-5-methyl-4-isoxazolecarbaldehyde and corresponding acetate **4b** through 1,3-dipolar cycloaddition. These compounds upon hydrogenation in the presence of Raney-Ni resulted in **6a,b** (Scheme 2) as single diastereomer in 66–92% yields. The relative stereochemistry delineated *via* X-ray crystallographic analysis of a single crystal of compound **6b** indicated that the acetyl group is placed *syn* to the ester group (Figure 2) [10].

Scheme 1. Reagents and conditions: (i) (2-NO$_2$C$_6$H$_4$)—C(=NOH)Cl, Et$_3$N, Et$_2$O, −78°C to rt, 12 h. (ii) Raney-Ni or Pd on carbon, H$_2$, MeOH, rt, 40 psi, 3 h.



Scheme 2. Reagents and conditions: (i) (2-NO$_2$C$_6$H$_4$)—C(=NOH)Cl, Et$_3$N, Et$_2$O, −78°C to rt, 12 h. (ii) Raney-Ni, H$_2$, MeOH, rt, 40 psi, 3 h.



In the next stage, the Baylis–Hillman derivatives **7a–c** and **8a** afforded from substituted 5-isoxazolecarbaldehydes were subjected to the cycloaddition with 2-nitrobenzonitrile oxide to furnish **9a–c** and **10a**, respectively, as diastereomeric mixtures (1:1) in 82–89% yields. Hydrogenation of **9a–c** and **10a** in the presence of Raney-Ni yielded **13a–c** and **14a**, respectively, in 63–71% yields (Scheme 3).

Next, to investigate whether the position of the nitro group in the phenyl ring has any effect on the outcome of the product, we prepared compounds **11a** and **12a** and carried out Raney-Ni-promoted hydrogenation.

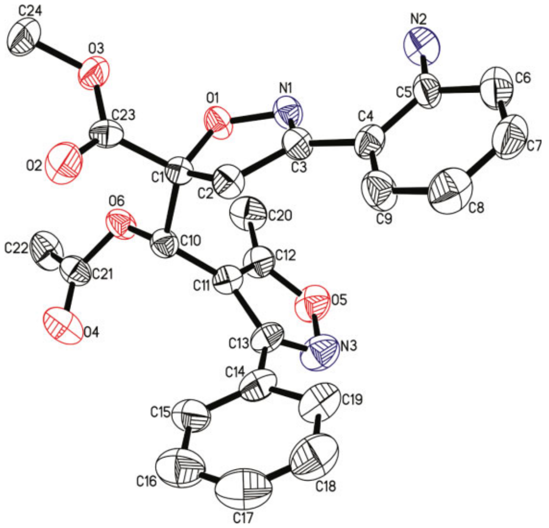
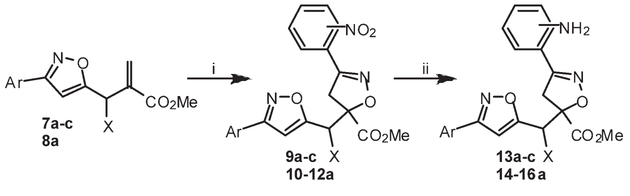


Figure 2. Ortep diagram of compound **6b** showing retention of both isoxazole and isoxazoline ring during catalytic hydrogenation [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Scheme 3. Reagents and conditions: (i) (2,3 or 4-$NO_2C_6H_4$)—C(=NOH)Cl, Et_3N, Et_2O, −78°C to rt, 12 h. (ii) Raney-Ni or Pd on carbon, H_2, MeOH, rt, 40 psi, 3–5 h.



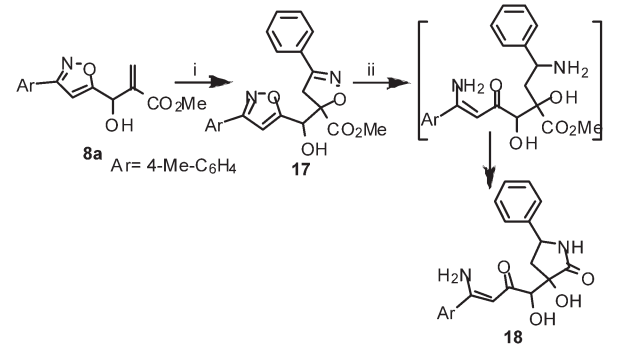
No	X
a	OH
b	OAc
c	H

No	Ar	NO2/NH2
7,9,13	Ph	2
8,10,14	4-Me-C6H4	2
11,15	Ph	3
12,16	Ph	4

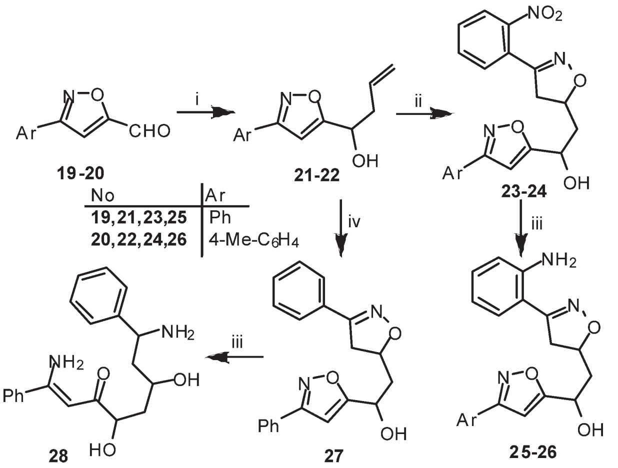
Gratifyingly, these substrates were also transformed to products **15a** and **16a**. In the absence of evidence, it is difficult to comment on the observed stereoselectivity; it is assumed that during hydrogenation reaction, inversion of one of the diastereomer occurs to produce the product with syn-stereochemistry only.

Earlier, we have observed that replacing the nitro-substituted phenyl with phenyl group at 3-position of the 2-isoxazoline makes it prone to ring cleavage during the catalytic hydrogenation [2]. In view of this observation, we decided to evaluate the effect of catalytic hydrogenation in the system where the nitrophenyl group was replaced by phenyl group. Hence, in a model study, compound **17** was prepared from reaction between compound **8a** and benzonitrile oxide. The Raney-Ni-mediated hydrogenation of **17** yielded a product, which was analyzed to be the 2-pyrrolidone **18** (Scheme 4). The formation of compound **18** from **17** implied that during catalytic hydrogenation, cleavage of both the isoxazole and the 2-isoxazoline rings ensued. This result made it apparent that presence of a nitro-substituted phenyl moiety at the 3-position of the 2-isoxazoline protected the isoxazole from ring cleavage during the catalytic hydrogenation of an isoxazoline-substituted isoxazole system.

Scheme 4. Reagents and conditions: (i) C_6H_5—C(=NOH)Cl, Et_3N, Et_2O, −78°C to rt, 12 h. (ii) Raney-Ni, H_2, MeOH, rt, 40 psi, 3 h.



Scheme 5. Reagent and conditions: (i) allyl bromide, Mg, Et_2O, rt, 3 h. (ii) (2-NO_2)C_6H_4C(=NOH)Cl, Et_3N, Et_2O, −78°C, 12 h. (iii) Raney-Ni, H_2, rt, 40 psi, 3–5 h. (iv) C_6H_5C(=NOH)Cl, Et_3N, Et_2O, −78°C, 12 h.



No	Ar
19,21,23,25	Ph
20,22,24,26	4-Me-C6H4

With the objective to find whether this phenomenon was restricted to the system wherein both the rings were separated by a methylene bridge or extend to a system wherein the two rings are separated by ethylene spacer compounds **23–24** were prepared. Grignard reaction of **19–20** with allylbromide resulted in the formation of **21–22** in good yields (Scheme 5). 1,3-Dipolar cycloaddition reaction of 2-nitrobenzonitrile oxide on the double bond of the allyl moiety furnished the required derivatives **23–24**. Hydrogenation of compounds **23–24** in the presence of Raney-Ni in methanol at room temperature in the Parr assembly yielded compounds **25–26**, respectively. Simultaneously, 1,3-dipolar cycloaddition of benzonitrile oxide on **21** was accomplished to afford the product **27**. As expected, hydrogenation of **27** in the presence of Raney-Ni at room temperature for 3 h led to the cleavage of isoxazole and isoxazoline ring leading to **28**. This study further substantiate that the presence of a 2-isoxazoline ring bearing a nitro-phenyl substitution at 3-position protect the isoxazole ring from hydrogenolysis.

On suggestion from one of the reviewers that the production of aniline derivatives during the hydrogenation would be poisoning the catalyst to prevent further reaction, hydrogenations of different substrates in the presence of aniline were investigated. Hydrogenating a simpler isoxazole derivative **29** in the presence of aniline

Scheme 6. Reagent and conditions: (i) Aniline, Raney-Ni, H_2, rt, 40 psi, 5 h. (ii) Aniline, Raney-Ni, H_2, rt, 40 psi, 1 h then added **29**, 5 h.

and Raney-Ni furnished **30** in 67% yield (Scheme 6). Alternatively, a mixture of aniline and Raney-Ni was maintained under hydrogen atmosphere for 1 h followed by addition of **29**. This reaction too resulted in the formation of **30** in 5 h. Similar study was also performed with compound **27**. Here too, the hydrogenolyzed product **28** was isolated in 62% yield. This study delineated that the presence of aniline in the hydrogenation mixture does not affect the activity of the catalyst.

CONCLUSIONS

In summary, we have disclosed an interesting observation wherein the cleavage of the isoxazole ring during the catalytic hydrogenation is influenced by the substitutions present on the 3-position of the 2-isoxazoline ring in isoxazoline-substituted isoxazole systems. Further work toward exploring applications of the intermediates resulting from the study for the synthesis of heterocyclic systems is underway.

EXPERIMENTAL

Melting points are uncorrected and were determined in capillary tubes on an apparatus containing silicon oil. IR spectra were recorded using Perkin Elmer's Spectrum RX I FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded either on a Bruker DPX-200 FT or Bruker Avance DRX-300 spectrometers, using TMS as an internal standard (chemical shifts in δ values, *J* in Hz). The ESMS were recorded on MICROMASS LCMS system and FABMS were recorded on JEOL/ SX-102 spectrometer. Elemental analyses were performed on Carlo Erba's 108 or Elementar's Vario EL III microanalyzer. The HRMS spectra were recorded as EI-HRMS. Compounds **2, 5, 9–12** existed as 1:1 diastereomeric mixtures.

General procedure for the synthesis of compounds 2a–c, 5a–b, 9a–c, 10–12a, 17, 23–24, and 27: as exemplified for the compound 2a. To a stirred solution of compound **1a** (2.0 g, 7.7 mmol) and 2-nitrophenyl methylhydroximinoyl chloride (1.85 g, 9.3 mmol) in anhydrous diethylether (15 mL) was added dropwise a solution of Et_3N (1.5 mL, 11.1 mmol) in anhydrous diethylether (5 mL) at −78°C. The reaction was allowed to continue at room temperature for 24 h. Thereafter, the reaction mixture was quenched with water (30 mL) and the ether layer was separated. The aqueous layer was again extracted with diethylether. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated to obtain the crude oily residue. The crude product was then purified by column chromatography over silica gel (60–120 mesh) using hexane/ethyl acetate (70:30, v/v) as the eluent to afford 2.58 g (79%) of **2a** as a brown solid.

Methyl 5-[hydroxy-(5-phenylisoxazol-3-yl)-methyl]-3-(2-nitrophenyl)-4,5-dihydro-isoxazole-5-carboxylate (2a). Mp 120–122°C, IR (potassium bromide): 1741 (CO_2Me), 3449 (OH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.69 (d, 1H, 1H of CH_2, *J* = 17.7 Hz), 3.81–3.93 (m, 9H, CH_2, 1H of CH_2 and 2 × CO_2CH_3), 5.49 (d, 1H, C*H*OH, *J* = 5.8 Hz), 5.56 (s, 1H, C*H*OH), 6.74 (s, 1H, =CH), 6.77 (s, 1H, =CH), 7.45–7.46 (m, 8H, 2 × 4ArH), 7.60–7.68 (m, 4H, 2 × 2ArH), 7.80–7.81 (m, 4H, 2 × 2ArH), 8.06–8.11 (m, 2H, ArH); ^{13}C NMR (deuteriochloroform): δ 42.5, 43.3, 53.9, 69.2, 90.5, 91.8, 99.4, 124.6, 124.8, 125.3, 126.3, 127.4, 128.4, 128.8, 129.4, 130.8, 131.0, 131.5, 134.0, 134.9, 148.1, 156.6, 162.8, 170.0, 170.9; ms: (electron spray+) *m*/*z* 424.2 (M^{+} + 1). *Anal.* Calcd for $C_{21}H_{17}N_3O_7$: C, 59.57; H, 4.05; N, 9.93. Found: C, 59.48; H, 4.11; N, 9.98.

Methyl 5-[acetoxy-(5-phenylisoxazol-3-yl)-methyl]-3-(2-nitrophenyl)-4,5-dihydroisoxazole-5-carboxylate (2b). This compound was obtained in 83% yield as a white solid, mp 133–135°C; IR (potassium bromide): 1756 (CO_2Me and OAc) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.22 (s, 3H, $OCOCH_3$), 2.25 (s, 3H, $OCOCH_3$), 3.80–4.01 (m, 10H, 2 × CH_2 and 2 × CO_2CH_3), 6.67 (s, 1H, =CH), 6.68 (s, 1H, =CH), 7.40–7.49 (m, 8H, 2 × 3ArH and 2 × CHOAc), 7.60–7.68 (m, 6H, 2 × 3ArH), 7.79–7.86 (m, 4H, 2 × 2ArH), 8.07–8.13 (m, 2H, 2 × 1ArH); ^{13}C NMR (deuteriochloroform): δ 21.1, 21.3, 42.6, 43.3, 54.0, 54.2, 67.8, 89.3, 90.0, 102.9, 103.7, 124.6, 124.7, 125.4, 127.1, 127.4, 128.7, 128.9, 129.4, 130.5, 130.7, 131.6, 134.0, 134.2, 148.1, 156.2, 156.3, 163.1, 166.1, 166.3, 168.2, 168.8, 169.5, 169.9, 171.2; ms: (electron spray+) *m*/*z* 466.1 (M^{+} + 1). *Anal.* Calcd for $C_{23}H_{19}N_3O_8$: C, 59.36; H, 4.11; N, 9.03. Found: C, 59.13; H, 4.21; N, 8.96.

Methyl 3-(2-nitrophenyl)-5-(5-phenylisoxazol-3-ylmethyl)-4,5-dihydroisoxazole-5-carboxylate (2c). This compound was obtained in 78% yield as yellow oil; IR (neat): 1744 (CO_2Me) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.47 (d, 1H, 1H of CH_2, *J* = 17.4 Hz), 3.66 (d, 2H, CH_2, *J* = 6.1 Hz), 3.86 (d, 1H, 1H of CH_2, *J* = 17.4 Hz), 3.93 (s, 3H, CO_2CH_3), 6.63 (s, 1H, =CH), 7.45–7.50 (m, 3H, ArH), 7.61–7.71 (m, 3H, ArH), 7.81–7.84 (m, 2H, ArH), 8.10 (d, 1H, ArH, *J* = 7.2 Hz); ^{13}C NMR (deuteriochloroform) δ= 33.5, 45.5, 53.7, 87.8, 102.6, 124.3, 124.5, 125.1, 127.0, 128.8, 129.0, 130.2, 131.2, 133.9, 147.7, 155.9, 162.9, 167.1, 167.2, 170.2; ms: (electron spray+) *m*/*z* 408.1 (M^{+} + 1). *Anal.* Calcd for $C_{21}H_{17}N_3O_6$: C, 61.91; H, 4.21; N, 10.31. Found: C, 61.78; H, 4.29; N, 10.26.

Methyl 5-[hydroxy-(5-methyl-3-phenylisoxazol-4-yl)-methyl]-3-(2-nitrophenyl)-4,5-dihydroisoxazole-5-carboxylate (5a). This compound was obtained in 92% yield as pale yellow oil; IR (neat): 1744 (CO_2Me), 3382 (OH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.64 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 3.07 (d, 1H, 1H of CH_2, *J* = 17.4 Hz), 3.36 (d, 1H, 1H of CH_2, *J* = 17.4 Hz), 3.45 (d, 1H, 1H of CH_2, *J* = 17.4 Hz), 3.53 (d, 1H, 1H of CH_2, *J* = 17.4 Hz), 3.61 (s, 6H, 2 × CO_2CH_3), 5.26 (s, 1H, C*H*OH), 5.40 (s, 1H, C*H*OH), 7.21–7.42 (m, 2H, 2 × 1ArH), 7.43–7.57 (m, 10H, 2 × 5ArH), 7.60–7.69 (m, 4H, 2 × 2ArH), 8.02–8.07 (m, 2H, 2 × 1ArH); ^{13}C NMR (deuteriochloroform): δ 13.0, 13.1, 41.7, 43.6, 53.2, 53.3, 67.3, 67.7, 92.7, 92.8, 110.0, 124.2, 124.9, 128.7, 128.9, 129.0, 129.2, 129.7, 130.9, 131.1, 133.7, 147.6, 155.9, 162.3, 169.5, 170.4; ms: (electron spray+) *m*/*z* 438.1 (M^{+} + 1). *Anal.* Calcd for $C_{22}H_{19}N_3O_7$: C, 60.41; H, 4.38; N, 9.61. Found: C, 60.63; H, 4.47; N, 9.49.

Methyl 5-[acetoxy-(5-methyl-3-phenylisoxazol-4-yl)-methyl]-3-(2-nitrophenyl)-4,5-dihydroisoxazole-5-carboxylate (5b). This compound was obtained in 83% as a pale yellow solid, mp. 74–76°C; IR (potassium bromide): 1752 (CO_2Me and OAc) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.19 (s, 3H, $OCOCH_3$), 2.26 (s, 3H, $OCOCH_3$), 2.72 (s, 3H, CH_3), 2.74 (s, 3H, CH_3), 3.26–3.50 (m, 4H, 2 × CH_2), 3.78 (s, 6H, 2 ×

CO_2CH_3), 6.37 (s, 1H, CHOAc), 6.42 (s, 1H, CHOAc), 7.12 (d, 1H, ArH, J = 7.6 Hz), 7.47–7.54 (m, 7H, 2 × 3ArH and ArH), 7.62–7.73 (m, 8H, 2 × 4ArH), 8.08 (d, 2H, 2 × 1ArH, J = 7.6 Hz); ^{13}C NMR (deuteriochloroform): δ 13.5, 13.7, 20.9, 21.0, 43.9, 44.1, 53.3, 53.8, 68.7, 69.3, 91.2, 91.5, 108.0, 108.7, 124.4, 125.4, 129.2, 129.6, 129.9, 130.3, 131.4, 131.7, 134.1, 134.3, 147.8, 148.2, 155.6, 162.2, 162.6, 169.7, 170.0, 171.7, 172.0; ms: (electron spray+) m/z 480.1 (M^+ + 1). *Anal.* Calcd for $C_{24}H_{21}N_3O_8$: C, 60.12; H, 4.41; N, 8.76. Found: C, 59.98; H, 4.53; N, 8.69.

Methyl 5-[hydroxy(3-phenylisoxazol-5-yl)methyl]-3-(2-nitrophenyl)-4,5-dihydroisoxazole-5-carboxylate (9a). This compound was obtained in 82% as yellow oil; IR (neat): 1744 (CO_2Me), 3336 (OH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.64–3.85 (m, 4H, 2 × CH_2), 3.89 (s, 3H, CO_2CH_3), 3.93 (s, 3H, CO_2CH_3), 5.47 (s, 1H, C*H*OH), 5.56 (s, 1H, C*H*OH), 6.75 (s, 1H, =CH), 6.78 (s, 1H, =CH), 7.46–7.52 (m, 6H, 2 × 3ArH), 7.58–7.72 (m, 4H, 2 × 2ArH), 7.78–8.04 (m, 6H, 2 × 3ArH), 8.06–8.09 (m, 2H, 2 × 1ArH); ^{13}C NMR (deuteriochloroform): δ 41.7, 43.9, 53.9, 54.0, 68.7, 69.0, 90.6, 91.5, 102.2, 124.4, 125.2, 127.3, 128.8, 129.4, 130.5, 130.6, 131.5, 131.6, 134.0, 134.2, 148.2, 156.6, 162.9, 169.6, 169.9; ms: (electron spray+) m/z 424.0 (M^+ + 1). *Anal.* Calcd for $C_{21}H_{17}N_3O_7$: C, 59.57; H, 4.05; N, 9.93. Found: C, 59.38; H, 4.17; N, 10.01.

Methyl 5-[(acetyloxy)(3-phenylisoxazol-5-yl)methyl]-3-(2-nitrophenyl)-4,5-dihydroisoxazole-5-carboxylate (9b). This compound was obtained in 86% as yellow oil; IR (neat): 1757 (CO_2Me and OAc) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.20 (s, 3H, $OCOCH_3$), 2.25 (s, 3H, $OCOCH_3$), 3.72–4.02 (m, 10H, 2 × CH_2 and 2 × CO_2CH_3), 6.62 (s, 1H, CHOAc), 6.70 (s, 1H, CHOAc), 6.72 (s, 1H, =CH), 6.83 (s, 1H, =CH), 7.46–7.48 (m, 6H, 2 × 3ArH), 7.64–7.70 (m, 4H, 2 × 2ArH), 7.77–8.05 (m, 6H, 2 × 3ArH), 8.10–8.13 (m, 2H, 2 × 1ArH); ^{13}C NMR (deuteriochloroform): δ 21.0, 21.4, 42.4, 43.4, 54.1, 54.2, 67.8, 89.1, 90.0, 103.5, 103.9, 124.4, 124.5, 125.4, 127.2, 127.3, 128.6, 128.8, 129.4, 130.7, 130.8, 131.6, 134.1, 134.2, 148.2, 156.1, 156.2, 163.0, 166.1, 166.3, 168.3, 168.9, 169.5, 169.6, 171.5; ms: (electron spray+) m/z 466.0 (M^+ + 1). *Anal.* Calcd for $C_{23}H_{19}N_3O_8$: C, 59.36; H, 4.11; N, 9.03. Found: C, 59.21; H, 4.01; N, 9.12.

Methyl 3-(2-nitrophenyl)-5-[(3-phenylisoxazol-5-yl)methyl]-4,5-dihydroisoxazole-5-carboxylate (9c). This compound was obtained in 87% as brown oil; IR (neat): 1743 (CO_2Me) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.45 (d, 1H, 1H of CH_2, J = 17.4 Hz), 3.64 (s, 2H, CH_2), 3.85 (d, 1H, 1H of CH_2, J = 17.4 Hz), 3.91 (s, 3H, CO_2CH_3), 6.62 (s, 1H, =CH), 7.45–7.48 (m, 4H, ArH), 7.58–7.72 (m, 2H, ArH), 7.79–7.81 (m, 2H, ArH), 8.11 (d, 1H, ArH, J = 7.3 Hz); ^{13}C NMR (deuteriochloroform): δ 33.9, 45.6, 54.0, 88.1, 102.8, 124.6, 125.4, 127.3, 129.1, 129.4, 130.6, 131.5, 131.6, 134.2, 148.1, 156.2, 163.2, 167.4, 170.6; ms: (electron spray+) m/z 408.1 (M^+ + 1). *Anal.* Calcd for $C_{21}H_{17}N_3O_6$: C, 61.91; H, 4.21; N, 10.31. Found: C, 62.13; H, 4.12; N, 10.39.

Methyl 5-{hydroxy[3-(4-methylphenyl)isoxazol-5-yl]methyl}-3-(2-nitrophenyl)-4,5-dihydroisoxazole-5-carboxylate (10a). This compound was obtained in 89% as pale yellow oil; IR (neat): 1742 (CO_2Me), 3371 (OH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.40 (s, 6H, 2 × $ArCH_3$), 3.63–3.84 (m, 4H, 2 × CH_2), 3.88 (s, 3H, CO_2CH_3), 3.93 (s, 3H, CO_2CH_3), 5.46 (s, 1H, C*H*OH), 5.55 (s, 1H, C*H*OH), 6.72 (s, 1H, =CH), 6.74 (s, 1H, =CH), 7.24–7.28 (m, 4H, 2 × 2ArH), 7.48–7.51 (m, 2H, 2 × 1ArH), 7.61–7.71 (m, 8H, 2 × 4ArH), 8.05–8.09 (m, 2H, 2 × 1ArH); ^{13}C NMR (deuteriochloroform): δ 21.8, 41.7, 43.9, 53.9, 54.0, 68.7, 69.0, 90.6, 91.5, 102.1, 102.2, 124.5, 125.3, 125.9, 126.1, 127.2, 130.0, 131.5, 131.6, 134.0, 134.2, 140.8, 148.1, 156.6, 162.8, 169.3, 169.6, 170.3; ms: (electron spray+) m/z 438.1 (M^+ + 1). *Anal.* Calcd for $C_{22}H_{19}N_3O_7$: C, 60.41; H, 4.38; N, 9.61. Found: C, 60.58; H, 4.29; N, 9.70.

Methyl 5-[hydroxy-(3-phenylisoxazol-5-yl)-methyl]-3-(3-nitrophenyl)-4,5-dihydroisoxazole-5-carboxylate (11a). This compound was obtained in 79% as a pale yellow solid, mp 138–140°C; IR (potassium bromide): 1744 (CO_2Me), 3421 (OH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.68–3.91 (m, 4H, 2 × CH_2), 3.92 (s, 3H, CO_2CH_3), 3.93 (s, 3H, CO_2CH_3), 5.51 (s, 1H, C*H*OH), 5.58 (s, 1H, C*H*OH), 7.08 (s, 1H, =CH), 7.14 (s, 1H, =CH), 7.38–7.42 (m, 4H, 2 × 2ArH), 7.48–7.54 (m, 6H, 2 × 3ArH), 7.61–7.66 (m, 4H, 2 × 2ArH), 7.93–7.99 (m, 2H, 2 × 1ArH), 8.03–8.05 (m, 2H, 2 × 1ArH); ^{13}C NMR (deuteriochloroform): δ 42.3, 43.6, 53.9, 69.2, 91.2, 91.9, 104.3, 124.7, 125.3, 126.3, 127.6, 129.9, 131.5, 132.3, 134.0, 148.0, 148.2, 156.6, 162.6, 167.2, 169.9, 170.3; ms: (electron spray+) m/z 424.1 (M^+ + 1). *Anal.* Calcd for $C_{21}H_{17}N_3O_7$: C, 59.57; H, 4.05; N, 9.93. Found: C, 59.69; H, 4.19; N, 9.84.

Methyl 5-[hydroxy-(3-phenylisoxazol-5-yl)-methyl]-3-(4-nitrophenyl)-4,5-dihydroisoxazole-5-carboxylate (12a). This compound was obtained in 79% as pale yellow oil; IR (neat): 1742 (CO_2Me), 3464 (OH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.71 (d, 1H, 1H of CH_2, J = 17.1 Hz), 3.83–3.95 (m, 9H, CH_2, 1H of CH_2 and 2 × CO_2CH_3), 5.49 (s, 1H, C*H*OH), 5.58 (s, 1H, C*H*OH), 6.76 (s, 1H, =CH), 6.79 (s, 1H, =CH), 7.46–7.53 (m, 8H, 2 × 4ArH), 7.61–7.72 (m, 4H, 2 × 2ArH), 7.79–7.82 (m, 4H, 2 × 2ArH), 8.08–8.13 (m, 2H, 2 × 1ArH); ^{13}C NMR (deuteriochloroform): δ 41.7, 43.6, 53.8, 54.1, 68.9, 69.1, 90.6, 91.3, 102.6, 103.1, 124.5, 124.7, 125.4, 127.0, 128.8, 129.2, 130.5, 130.7, 131.4, 131.7, 134.1, 134.3, 148.2, 156.9, 163.7, 169.9, 170.3; ms: (electron spray+) m/z 424.1 (M^+ + 1). *Anal.* Calcd for $C_{21}H_{17}N_3O_7$: C, 59.57; H, 4.05; N, 9.93. Found: C, 59.43; H, 3.89; N, 9.97.

Methyl 5-{hydroxy[3-(4-methylphenyl)isoxazol-5-yl]methyl}-3-phenyl-4,5-dihydroisoxazole-5-carboxylate (17). This compound was obtained in 85% as a white solid, mp. 118–120°C; IR (potassium bromide): 1744 (CO_2Me), 3438 (OH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.40 (s, 6H, 2 × $ArCH_3$), 3.67–3.95 (m, 10H, 2 × CH_2 and 2 × CO_2CH_3), 5.55 (s, 1H, C*H*OH), 5.56 (s, 1H, C*H*OH), 6.68 (s, 1H, =CH), 6.69 (s, 1H, =CH), 7.24–7.28 (m, 6H, 2 × 3ArH), 7.37–7.43 (m, 4H, 2 × 2ArH), 7.15–7.19 (m, 2H, 2 × 1ArH), 7.63–7.70 (m, 6H, 2 × 3ArH); ^{13}C NMR (deuteriochloroform): δ 21.8, 21.9, 38.9, 41.9; 53.8, 68.9, 69.0, 90.0, 91.0, 102.0, 126.0, 127.2, 127.4, 128.6, 128.9, 129.2, 130.1, 131.2, 140.8, 141.3, 157.9, 162.8, 169.4, 169.7; ms: (electron spray+) m/z 393.1 (M^+ + 1). *Anal.* Calcd for $C_{22}H_{20}N_2O_5$: C, 67.34; H, 5.14; N, 7.14. Found: C, 67.47; H, 5.01; N, 7.21.

2-[3-(2-Nitrophenyl)-4,5-dihydroisoxazol-5-yl]-1-(3-phenylisoxazol-5-yl)ethan-1-ol (23). This compound was obtained in 69% as yellow oil; IR (neat): 3414 (OH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.38–2.56 (m, 2H, CH_2), 3.00–3.14 (m, 1H, 1H of CH_2), 3.37–3.46 (m, 1H, 1H of CH_2), 5.01–5.28 (m, 1H, C*H*OH), 5.22–5.25 (m, 1H, C*H*CH_2), 6.62 (s, 1H, =CH), 7.44–7.46 (m, 3H, ArH), 7.57–7.70 (m, 3H, ArH), 7.79–7.82 (m, 2H, ArH), 8.06–8.09 (m, 1H, ArH); ^{13}C NMR (deuteriochloroform): δ 40.7, 42.9, 65.3, 78.4, 99.5, 124.9, 125.4, 126.8, 128.8, 129.0, 130.1, 130.8, 131.0, 141.6, 156.0, 162.4, 174.6; ms: (electron spray+) *m*/*z* 380.0 (M$^+$ + 1). *Anal.* Calcd for $\mathrm{C_{20}H_{17}N_3O_5}$: C, 63.32; H, 4.52; N, 11.08. Found: C, 63.49; H, 4.47; N, 11.34.

1-[3-(4-Methylphenyl)isoxazol-5-yl]-2-[3-(2-nitrophenyl)-4,5-dihydroisoxazol-5-yl]ethan-1-ol (24). This compound was obtained in 74% as pale yellow oil; IR (neat): 3382 (OH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.28–2.49 (m, 5H, CH$_2$ and ArCH$_3$), 2.97–3.18 (m, 1H, 1H of CH$_2$), 3.35–3.51 (m, 1H, 1H of CH$_2$), 5.01–5.16 (m, 1H, C*H*OH), 5.21–5.24 (m, 1H, C*H*CH$_2$), 6.60 (s, 1H, =CH), 7.24–7.28 (m, 1H, ArH), 7.55–7.61 (m, 2H, ArH), 7.62–7.72 (m, 3H, ArH), 8.08 (d, 2H, ArH, *J* = 7.7 Hz); ^{13}C NMR (deuteriochloroform): δ 21.7, 40.9, 41.3, 64.8, 79.5, 99.6, 125.0, 125.3, 126.5, 128.3, 129.2, 130.3, 130.6, 131.4, 141.2, 157.1, 162.1, 174.3; ms: (electron spray+) *m*/*z* 394.0 (M$^+$ + 1). *Anal.* Calcd for $\mathrm{C_{21}H_{19}N_3O_5}$: C, 64.12; H, 4.87; N, 10.68. Found: C, 63.91; H, 5.03; N, 10.47.

2-(3-Phenyl-4,5-dihydroisoxazol-5-yl)-1-(3-phenylisoxazol-5-yl)ethan-1-ol (27). This compound was obtained in 66% as a white solid, mp 135–137°C; IR (potassium bromide): 3380 (OH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.31–2.38 (m, 2H, CH$_2$), 3.10–3.20 (m, 1H, 1H of CH$_2$), 3.52–3.61 (m, 1H, 1H of CH$_2$), 4.98–5.16 (m, 1H, C*H*OH), 5.25–5.28 (m, 1H, C*H*CH$_2$), 6.60 (d, 1H, =CH, *J* = 2.1 Hz), 7.41–7.48 (m, 5H, ArH), 7.67–7.70 (m, 3H, ArH); 7.80–7.83 (m, 2H, ArH); ^{13}C NMR (deuteriochloroform): δ 40.8, 41.3, 64.8, 77.9, 99.7, 126.9, 127.0, 128.79, 129.0, 129.3, 129.4, 130.3, 130.5, 130.6, 157.3, 162.6, 174.8; ms: (electron spray+) *m*/*z* 335.0 (M$^+$ + 1). *Anal.* Calcd for $\mathrm{C_{20}H_{18}N_2O_3}$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.92; H, 5.21; N, 8.55.

General procedure for the synthesis of compounds 3a–c, 6a–b, 13a–c, 14–16a, 18, 25–26, and 28: as exemplified for the compound 3a. A mixture of compound **2a** (1.5 g, 3.56 mmol) and Raney-Ni (100 mg wet) in methanol (10 mL) was subjected to hydrogenation in the Parr assembly at 40 psi. The reaction was allowed to continue for 3 h. Thereafter, the catalyst was removed by filtration of the reaction mixture through a celite bed with methanol. The filtrate was evaporated to obtain an oily residue, which was taken in ethyl acetate (2 × 20 mL) and washed with water (30 mL). The organic layers were collected, dried over anhydrous $\mathrm{Na_2SO_4}$, and the solvent was evaporated *in vacuo* to obtain a crude oily product, which was purified by column chromatography over silica gel (60–120 mesh). Elution with hexane: ethyl acetate (70:30, v/v) gave 0.93 g (67%) of compound **3a** as a brown solid.

The Pd-on-carbon-promoted hydrogenations were performed in similar fashion on a Parr assembly.

Methyl 3-(2-aminophenyl)-5-[hydroxy(phenylisoxazol-3-yl)methyl]-4,5-dihydroisoxazole-5-carboxylate (3a). Mp 83–85°C; IR (potassium bromide): 1745 (CO$_2$Me), 3352 (NH), 3461 (OH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.81 (d, 1H, 1H of CH$_2$, *J* = 17.1 Hz), 3.88 (s, 3H, CO$_2$CH$_3$), 3.98 (d, 1H, 1H of CH$_2$, *J* = 17.1 Hz), 5.54 (s, 1H, CHOH), 6.67–6.74 (m, 3H, =CH and ArH), 7.16–7.24 (m, 2H, ArH), 7.45–7.48 (m, 3H, ArH), 7.78–7.83 (m, 2H, ArH); ^{13}C NMR (deuteriochloroform): δ 42.5, 53.9, 69.2, 91.8, 99.4, 125.3, 126.3, 127.4, 128.5, 129.4, 130.9, 131.5, 134.0, 148.1, 156.6, 162.8, 170.0, 170.9; ms: (electron spray+) *m*/*z* 394.2 (M$^+$ + 1). *Anal.* Calcd for $\mathrm{C_{21}H_{19}N_3O_5}$: C, 64.12; H, 4.87; N, 10.68. Found: C, 63.98; H, 4.95; N, 10.73.

Methyl 5-[acetoxy-(5-phenylisoxazol-3-yl)-methyl]-3-(2-amino-phenyl)-4,5-dihydromisoxazole-5-carboxylate (3b). This compound was obtained in 63% as yellow oil; IR (neat): 1743 (CO$_2$Me), 3358 (NH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.17 (s, 3H, OCOCH$_3$), 3.53–3.67 (m, 3H, CH$_2$ and 1H of CH$_2$), 3.86 (s, 3H, CO$_2$CH$_3$), 4.03 (d, 1H, 1H of CH$_2$, *J* = 17.0 Hz), 5.59 (s, 2H, NH$_2$), 6.56 (s, 1H, =CH), 6.69–6.75 (m, 2H, ArH), 7.12–7.23 (m, 2H, ArH), 7.45–7.47 (m, 3H, ArH), 7.78–7.79 (m, 2H, ArH); ^{13}C NMR (deuteriochloroform): δ 34.0, 44.8, 53.8, 85.6, 102.4, 110.8, 116.4, 117.0, 127.2, 129.3, 130.1, 130.5, 131.7, 147.3, 158.5, 163.1, 167.6, 171.1; ms: (electron spray+) *m*/*z* 436.1 (M$^+$ + 1). *Anal.* Calcd for $\mathrm{C_{23}H_{21}N_3O_6}$: C, 63.44; H, 4.86; N, 9.65. Found: C, 63.68; H, 5.07; N, 9.56.

Methyl 3-(2-amino-phenyl)-5-[hydroxy-(5-methyl-3-phenylisoxazol-4-yl)-methyl]-4,5-dihydro-isoxazole-5-carboxylate (6a). This compound was obtained in 66% as yellow oil; IR (neat): 1731 (CO$_2$Me), 3466 (NH and OH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.66 (s, 3H, CH$_3$), 3.21 (d, 1H, 1H of CH$_2$, *J* = 17.0 Hz), 3.44 (d, 1H, 1H of CH$_2$, *J* = 17.0 Hz), 3.60 (s, 3H, CO$_2$CH$_3$), 5.40 (s, 1H, C*H*OH), 6.64–6.74 (m, 3H, ArH), 7.15–7.21 (m, 1H, ArH), 7.50–7.54 (m, 3H, ArH), 7.55–7.59 (m, 2H, ArH); ^{13}C NMR (deuteriochloroform): δ 13.2, 30.3, 43.1, 53.7, 69.4, 88.7, 107.9, 110.1, 117.4, 117.9, 129.1, 129.5, 130.6, 131.7, 133.0, 147.1, 157.4, 163.2, 169.9, 170.6; ms: (electron spray+) *m*/*z* 408.1 (M$^+$ + 1). *Anal.* Calcd for $\mathrm{C_{22}H_{21}N_3O_5}$: C, 64.86; H, 5.20; N, 10.31. Found: C, 64.98; H, 5.08; N, 10.43.

Methyl 5-[acetoxy-(5-methyl-3-phenylisoxazol-4-yl)-methyl]-3-(2-amino-phenyl)-4,5-dihydro-isoxazole-5-carboxylate (6b). This compound was obtained in 92% as a white solid, mp. 180–182°C; IR (potassium bromide) 1756 (CO$_2$Me and OAc), 3346 (NH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.16 (s, 3H, OCOCH$_3$), 2.70 (s, 3H, CH$_3$), 3.00 (d, 1H, 1H of CH$_2$, *J* = 17.0 Hz), 3.39 (d, 1H, 1H of CH$_2$, *J* = 17.0 Hz), 3.77 (s, 3H, CO$_2$CH$_3$), 5.49 (s, 2H, NH$_2$), 6.38 (s, 1H, CHOAc), 6.62–6.71 (m, 3H, ArH), 7.15–7.20 (m, 1H, ArH), 7.53–7.55 (m, 3H, ArH), 7.59–7.63 (m, 2H, ArH); ^{13}C NMR (deuteriochloroform): δ 13.4, 20.9, 30.1, 43.4, 53.7, 69.6, 88.9, 107.9, 110.1, 116.4, 116.7, 129.4, 129.6, 130.4, 131.8, 132.9, 147.2, 157.4, 162.5, 169.7, 170.6, 171.8; ms: (electron spray+) *m*/*z* 449.9 (M$^+$ + 1). HR-EIMS Calcd for $\mathrm{C_{24}H_{23}N_3O_6}$: 449.1587. Found: 449.1566.

Methyl 3-(2-aminophenyl)-5-[hydroxy(3-phenylisoxazol-5-yl)methyl]-4,5-dihydroisoxazole-5-carboxylate (13a). This compound was obtained in 67% as brown oil; IR (neat): 1742 (CO$_2$Me), 3350 (NH), 3464 (OH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.77–3.94 (m, 5H, CH$_2$ and CO$_2$CH$_3$), 5.54 (brs, 3H, C*H*OH and NH$_2$), 6.67–6.74 (m, 3H, =CH and ArH), 7.16–7.23 (m, 2H, ArH), 7.45–7.46 (m, 3H, ArH), 7.76–7.79 (m, 2H, ArH); ^{13}C NMR (deuteriochloroform): δ 40.6, 53.9, 69.0, 89.0, 102.0, 110.9, 116.5, 117.2, 127.3, 128.9, 129.4, 130.3, 130.7, 131.8, 147.2, 159.1, 162.8, 169.6, 170.0; ms: (electron spray+) *m*/*z* 394.1 (M$^+$ + 1). *Anal.* Calcd for $\mathrm{C_{21}H_{19}N_3O_5}$: C, 64.12; H, 4.87; N, 10.68. Found: C, 64.31; H, 4.72; N, 10.79.

Methyl 3-(2-aminophenyl)-5-{hydroxy[3-(4-methylphenyl)isoxazol-5-yl]methyl}-4,5-dihydroisoxazole-5-carboxylate (14a). This compound was obtained in 63% as colorless oil; IR (neat): 1741 (CO$_2$Me), 3352 (NH), 3461(OH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.40 (s, 3H, ArCH$_3$), 3.78 (d, 1H, 1H of CH_2, $J = 17.1$ Hz), 3.87 (s, 3H, CO_2CH_3), 3.97 (d, 1H, 1H of CH_2, $J = 17.1$ Hz), 5.53 (brs, 3H, C*H*OH and NH_2), 6.68–6.74 (m, 3H, =CH and ArH), 7.16–7.24 (m, 4H, ArH), 7.69 (d, 2H, ArH, $J = 7.8$ Hz); ^{13}C NMR (deuteriochloroform): δ 21.8, 40.5, 53.9, 69.0, 89.1, 101.9, 110.9, 116.5, 117.2, 126.0, 127.2, 130.1, 130.3, 131.7, 140.8, 147.2, 159.1, 162.8, 169.5, 170.0; ms: (electron spray+) *m*/*z* 408.1 ($M^+ + 1$); *Anal.* Calcd for $C_{22}H_{21}N_3O_5$: C, 64.86; H, 5.20; N, 10.31. Found: C, 64.67; H, 5.09; N, 10.43.

Methyl 3-(3-aminophenyl)-5-[hydroxy-(3-phenylisoxazol-5-yl)-methyl]-4,5-dihydro-isoxazole-5-carboxylate (15a). This compound was obtained in 73% as a brown solid, mp. 114–116°C; IR (potassium bromide): 1721 (CO_2Me), 3321 (NH), 3456 (OH) cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.72–3.88 (m, 5H, CH_2 and CO_2CH_3), 5.31 (s, 1H, C*H*OH), 5.46 (s, 2H, NH_2), 6.62–6.67 (m, 2H, =CH and ArH), 6.87–6.93 (m, 2H, ArH), 7.06–7.12 (m, 1H, ArH), 7.31–7.38 (m, 3H, ArH), 7.69–7.70 (m, 2H, ArH); ^{13}C NMR (deuteriochloroform): δ 40.5, 52.0, 67.6, 88.1, 100.2, 111.7, 116.2, 116.4, 125.6, 127.6, 127.7, 128.4, 128.8, 145.4, 155.9, 161.1, 168.3; ms: (electron spray+) *m*/*z* 394.1 ($M^+ + 1$); *Anal.* Calcd for $C_{21}H_{19}N_3O_5$: C, 64.12; H, 4.87; N, 10.68. Found: C, 64.37; H, 4.98; N, 10.49.

Methyl 3-(4-aminophenyl)-5-[hydroxy-(3-phenylisoxazol-5-yl)-methyl]-4,5-dihydro-isoxazole-5-carboxylate (16a). This compound was obtained in 69% as yellow oil; IR (neat): 1745 (CO_2Me), 3345 (NH), 3442 (OH) cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.83 (d, 2H, 1H of CH_2, $J = 17.0$ Hz), 3.89 (s, 3H, CO_2CH_3), 4.00 (d, 2H, 1H of CH_2, $J = 17.0$ Hz), 5.55 (s, 1H, C*H*OH), 6.73–6.75 (m, 3H, =CH and ArH), 7.19 (d, 2H, ArH, $J = 7.5$ Hz), 7.47–7.49 (m, 3H, ArH), 7.80–7.85 (m, 3H, ArH); ^{13}C NMR (deuteriochloroform): δ 41.3, 53.2, 67.9, 88.7, 101.4, 111.3, 115.1, 114.9, 125.4, 126.4, 127.0, 128.1, 128.4, 129.6, 144.7, 156.7, 161.8, 168.5, 170.2; ms: (electron spray+) *m*/*z* 394.2 ($M^+ + 1$). *Anal.* Calcd for $C_{21}H_{19}N_3O_5$: C, 64.12; H, 4.87; N, 10.68. Found: C, 64.27; H, 4.73; N, 10.79.

3-[(Z)-4-Amino-1-hydroxy-4-(4-methylphenyl)-2-oxobut-3-enyl]-3-hydroxy-5-phenylpyrrolidin-2-one (18). This compound was obtained in 85% as a pale yellow solid, mp. 90–92°C; IR (potassium bromide): 1685 (CONH), 1721 (CO), 3426 (OH and NH) cm^{-1}; ^1H NMR (deuteriochloroform): δ 2.42 (s, 6H, 2 × $ArCH_3$), 3.48 (d, 1H, 1H of CH_2, $J = 17.1$ Hz), 3.72 (d, 1H, 1H of CH_2, $J = 17.1$ Hz), 3.83–3.96 (m, 2H, CH_2), 4.26 (s, 2H, 2 × ArCH), 4.36 (brs, 1H, 1H of NH_2), 4.75 (s, 1H, C*H*OH), 4.82 (s, 1H, C*H*OH), 5.34 (brs, 1H, 1H of NH_2), 5.64 (brs, 1H, 1H of NH_2), 5.67 (brs, 1H, 1H of NH_2), 5.74 (s, 1H, =CH), 5.81 (s, 1H, =CH), 7.37–7.51 (m, 14H, 2 × 7ArH), 7.60–7.72 (m, 4H, 2 × 2ArH), 9.89 (brs, 1H, NH), 8.96 (brs, 1H, NH); ^{13}C NMR (deuteriochloroform): δ 21.5, 21.8, 33.4, 33.5, 39.9, 41.3, 89.4, 89.5, 93.9, 94.1, 103.1, 103.4, 126.1, 126.3, 127.4, 127.8, 128.2, 128.8, 129.2, 130.3, 131.2, 140.4, 141.5, 157.6, 157.7, 162.4, 162.7, 179.3, 179.5, 190.4, 190.6; ms: (electron spray+) *m*/*z* 367.1 ($M^+ + 1$). *Anal.* Calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.69; H, 6.19; N, 7.57.

2-[3-(2-Aminophenyl)-4,5-dihydroisoxazol-5-yl]-1-(3-phenylisoxazol-5-yl)ethan-1-ol (25). This compound was obtained in 63% as a yellow solid, mp 110–112°C; IR (potassium bromide): 3431 (OH and NH_2) cm^{-1}; ^1H NMR (deuteriochloroform): δ 2.27–2.36 (m, 2H, CH_2), 3.16–3.29 (m, 1H, 1H of CH_2), 3.60–3.69 (m, 1H, 1H of CH_2), 4.90–4.96 (m, 1H, C*H*OH), 5.24–5.26 (m, 1H, C*H*CH_2), 6.62 (d, 1H, =CH, $J = 3.5$ Hz), 6.70–6.77 (m, 2H, ArH), 7.15–7.23 (m, 2H, ArH); 7.46–7.48 (m, 3H, ArH), 7.80–7.82 (m, 2H, ArH); ^{13}C NMR (deuteriochloroform): δ 40.8, 41.2, 64.9, 78.6, 99.6, 111.8, 116.2, 116.6, 117.0, 126.1, 126.9, 129.8, 131.0, 131.3, 140.6, 147.1, 162.5, 174.5; ms: (electron spray+) *m*/*z* 350.1 ($M^+ + 1$). *Anal.* Calcd for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.62; H, 5.19; N, 12.28.

2-[3-(2-Aminophenyl)-4,5-dihydroisoxazol-5-yl]-1-[3-(4-methylphenyl)isoxazol-5-yl]ethan-1-ol (26). This compound was obtained in 62% as a brown solid mp 158–160°C; IR (potassium bromide): 3374 (OH and NH_2) cm^{-1}; ^1H NMR (deuteriochloroform): δ 2.24–2.33 (m, 2H, CH_2), 2.40 (s, 3H, $ArCH_3$), 3.19–3.29 (m, 1H, 1H of CH_2), 3.56–3.69 (m, 1H, 1H of CH_2), 4.63–4.94 (m, 1H, C*H*OH), 5.21–5.24 (m, 1H, C*H*CH_2), 5.63 (brs, 2H, NH_2), 6.58 (d, 1H, =CH, $J = 1.2$ Hz), 6.66–6.76 (m, 2H, ArH), 7.13–7.19 (m, 2H, ArH); 7.22–7.28 (m, 2H, ArH), 7.69 (d, 2H, ArH, $J = 8.0$ Hz); ^{13}C NMR (75 MHz, deuteriochloroform): δ= 21.7, 40.6, 42.5, 65.2, 78.0, 99.7, 111.6, 116.1, 116.8, 116.9, 126.2, 127.0, 129.9, 131.1, 131.2, 140.5, 147.0, 158.9, 162.6, 173.9; ms: (electron spray+) *m*/*z* 364.1 ($M^+ + 1$). HR-EIMS Calcd for $C_{21}H_{21}N_3O_3$: 363.1583. Found: 363.1577.

1,8-Diamino-4,6-dihydroxy-1,8-diphenyloct-1-en-3-one (28). This compound was obtained in 63% as a brown solid, mp 118–120°C; IR (potassium bromide): 3410 (OH and NH_2) cm^{-1}; ^1H NMR (deuteriochloroform): δ 1.71 (brs, 1H, OH), 1.79–2.06 (m, 4H, 2 × CH_2), 3.71 (brs, 5H, OH and 2 × NH_2), 4.15–4.22 (m, 1H, C*H*OH), 4.37–4.39 (m, 1H, C*H*OH), 4.48–4.50 (m, 1H, C*H*NH_2), 5.53 (s, 1H, =CH), 7.33–7.57 (m, 10H, ArH); ^{13}C NMR (deuteriochloroform): δ 29.6, 30.7, 49.5, 52.9, 90.3, 126.4, 127.6, 128.6, 128.9, 129.3, 129.6, 129.9, 130.0, 134.2, 175.2; ms: (electron spray+) *m*/*z* 341.1 ($M^+ + 1$). *Anal.* Calcd for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.75; H, 7.03; N, 8.31.

(Z)-4-Amino-1-hydroxy-4-phenylbut-3-en-2-one (30). This compound was obtained in 67% as yellow oil; IR (neat): 1703 (CO), 3407 (OH and NH_2) cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.61 (brs, 1H, OH), 4.26 (s, 2H, CH_2), 5.36 (s, 1H, =CH), 7.40–7.61 (m, 5H, ArH), 9.69 (brs, 2H, NH_2); ms: (electron spray+) *m*/*z* 178.1 ($M^+ + 1$). *Anal.* Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.83; H, 6.41; N, 7.62.

General procedure for the synthesis of compounds 21–22: as exemplified for the compound 21. To the stirred suspension of Mg (0.42 g, 17.34 mmol) in anhydrous diethyl ether (30 mL), allyl bromide (1.5 mL, 17.34 mmol) was added under nitrogen atmosphere at room temperature and the mixture was stirred for 1 h. Thereafter, the resulting Grignard reagent was added to the stirred solution of appropriate aldehydes from **19** (1.5 g, 8.67 mmol) in anhydrous diethyl ether (40 mL) dropwise *via* cannula under nitrogen atmosphere, and the reaction was continued for additional 5 h. After completion, the reaction mixture was decomposed with cold H_2O maintaining the pH at 5–6 with dil. HCl. The resulting mixture was extracted with diethyl ether (3 × 30 mL). The organic layers were combined, dried with anhydrous Na_2SO_4, and evaporated to yield crude product, which was purified *via* silica gel chromatography using hexane: EtOAc (80:20, v/v) to afford 1.4 g (75%) of compound **21** as yellow oil.

1-(3-Phenylisoxazol-5-yl)but-3-en-1-ol (21). IR (neat): 3411 (OH) cm^{-1}; ^1H NMR (deuteriochloroform): δ 2.65–2.76

(m, 2H, C*H*$_2$CH), 4.94, 4.99 (dd, 1H, C*H*OH, $J_1 = 6.7$ Hz, $J_2 = 16.7$ Hz), 5.21–5.30 (m, 2H, =CH$_2$), 5.73–5.93 (m, 1H, =C*H*CH$_2$), 6.54 (d, 1H, =CH, $J = 0.9$ Hz), 7.42–7.49 (m, 3H, ArH), 7.78–7.82 (m, 2H, ArH); ^{13}C NMR (deuteriochloroform): δ 40.7, 66.9, 98.8, 120.6, 126.2, 126.7, 127.2, 129.4, 133.0, 141.3, 162.1, 174.7; ms: (electron spray+) *m/z* 216.1 ($M^+ + 1$). *Anal.* Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.31; H, 5.97; N, 6.63.

1-[3-(4-Methylphenyl)isoxazol-5-yl]but-3-en-1-ol (22). This compound was obtained in 90% as pale yellow oil; IR (neat): 3384 (OH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.40 (s, 3H, ArCH$_3$), 2.65–2.75 (m, 2H, C*H*$_2$CH), 4.91–5.00 (m, 1H, C*H*OH), 5.20–5.30 (m, 2H, =CH$_2$), 5.73–5.90 (m, 1H, =C*H*CH$_2$), 6.51 (d, 1H, =CH, $J = 1.0$ Hz), 7.26 (d, 2H, ArH, $J = 8.0$ Hz), 7.69 (d, 2H, ArH, $J = 8.0$ Hz); ^{13}C NMR (deuteriochloroform): δ 21.7, 40.5, 66.6, 99.3, 120.1, 126.3, 127.0, 129.9, 132.7, 140.4, 162.5, 174.3; ms: (electron spray+) *m/z* 230.1 ($M^+ + 1$). *Anal.* Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.19; H, 6.72; N, 6.01.

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[10] Crystal data of compound **6b**: $C_{24}H_{23}$ N_3O_6 (from methanol), $M = 449.45$, Orthorhombic, Pna2 (1), $a = 18.34(3)$, $b = 9.076$ (214.746(2), $c = 8.374(1)$ Å, $V = 2264.7(6)$ Å^3, $Z = 4$, $D_c = 1.318$ g cm^{-3}, μ (Mo–K$_\alpha$) = 0.096 mm^{-1}, F (000) = 944, colorless block, dimension 0.275 mm × 0.25 mm × 0.15 mm, 2804 reflections measured ($R_{\text{int}} = 0.0234$), 2436 unique, $wR_2 = 0.1112$, conventional $R = 0.0517$ on F values of 1235 reflections with $I > 2\sigma(I)$, $(\Delta/\sigma)_{\max} = 000$), $S = 0.999$ for all data and 184 parameters. Unit cell determination and intensity data collection (2θ = 50°) was performed on a Bruker P4 diffractometer at 293 (2) K. Structure solutions by direct methods and refinements by full-matrix least-squares methods on F^2. Programs: XSCANS (Siemens Analytical X-ray Instrument: Madison, WI, USA, 1996) for data collection and data processing; SHELXTL-NT (Bruker AXS: Madison, Wisconsin, USA, 1997) for structure determination, refinements and molecular graphics. Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (CCDC deposition no.: 715052). This is CDRI communication no. 7689.

A Convenient Approach to the Canthin-4-one Ring System: Total Synthesis of the Alkaloids Tuboflavine and Norisotuboflavine

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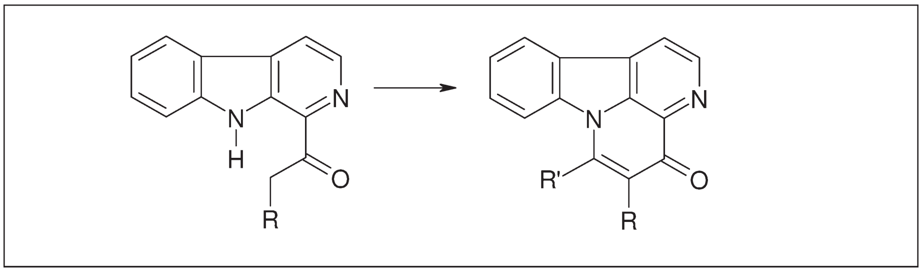

Canthin-4-one, as well as 5- and 6-alkylcanthin-4-ones are readily available through reaction of 1-acyl-β-carbolines with Bredereck's reagent or dimethylacetamide acetals in anhydrous DMF. The intermediate enaminoketones readily undergo cyclization to the canthin-4-ones. The alkaloids tuboflavine and norisotuboflavine were prepared following this methodology.

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INTRODUCTION

Considerable time ago, we published [1] the first total synthesis of the alkaloid annomontine (**3**), a aminopyrimidyl β-carboline from *Annona montana* [2] and *Annona foetida*, showing antileishmanial activity [3]. Readily available 1-acetyl-β-carboline (**1**) [1,4] was reacted with Bredereck's reagent (*tert*-butoxy-bis(dimethylamino)methane) in DMF to give a postulated enaminoketone **2**, which was, without further purification and characterization, converted to the alkaloid **3** by heating with guanidinium carbonate. To our surprise, construction of the aminopyrimidine ring was only possible with guanidinium carbonate under drastic conditions. Free guanidine and other guanidinium salts (hydrochloride, thiocyanate) did not give the desired product. This was in contrast to reports in literature describing an easy conversion of enaminoketones to aminopyrimidines with guanidine or various guanidinium salts [5,6].

RESULTS AND DISCUSSION

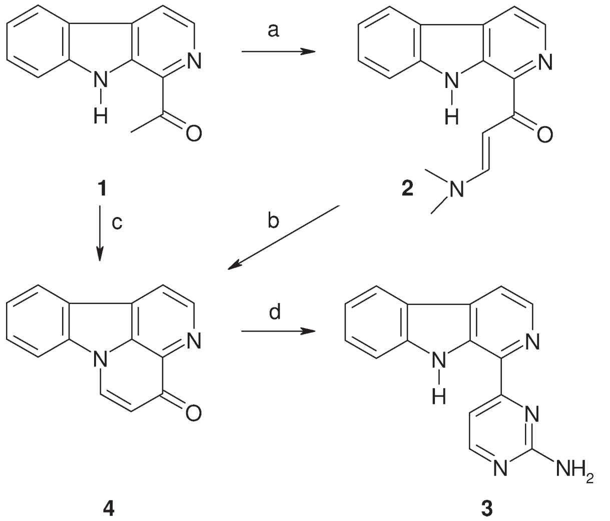
In a reinvestigation of the synthesis described above we intended to isolate the putative intermediate **2**. To our surprise we found that the progress of the reaction strongly depends on the water content of the solvent DMF. Reaction of **1** with Bredereck's reagent in commercially available DMF (water content about 1500 ppm) gave the expected enaminoketone **2**. In contrast, reaction in anhydrous DMF (water content about 50 ppm, as determined by Karl-Fischer titration) gave another product which was unambiguously identified as canthin-4-one (**4**) on the basis of spectroscopic and literature data [7]. Obviously, this product is formed by nucleophilic attack of the indole nitrogen at the enaminoketone moiety, followed by elimination of dimethylamine. In fact, heating of pure enaminoketone **2** in anhydrous DMF in the presence of a catalytic amount of potassium *tert*-butoxide resulted in a clean conversion to canthin-4-one (**4**), whereas heating of **2** in DMF without base for a prolonged time gave only traces of **4**. In the original reaction leading to **4**, the catalytic amount of alkoxide essential for the cyclization is obviously provided by heterolytic cleavage of Bredereck's reagent [8]. So the presence of alkoxide is essential for the cyclization of **2** to canthin-4-one (**4**), obviously by enhancing the nucleophilicity of the indole nitrogen by deprotonation. In wet DMF the alkoxide generated from Bredereck's reagent is likely to be hydrolyzed by water.

Canthin-4-one (**4**) could easily be converted to annomontine (**3**) by heating with guanidinium carbonate in DMF. This ring transformation is obviously initiated by nucleophilic attack of guanidine at the 6-position to affect ring opening, followed by cyclization to the aminopyrimidine ring system (Scheme 1).

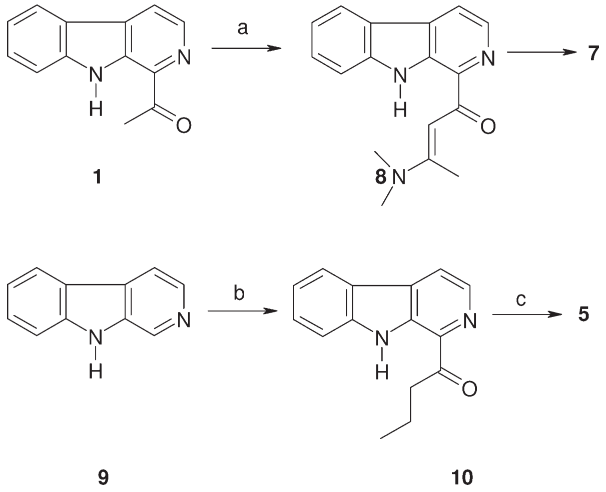
So we found, by chance, a new entry to the canthin-4-one ring system.

Canthin-4-ones represent a small class of three alkaloids isolated from *Pleiocarpa* species (Apocynaceae). Tuboflavine (**5**), isotuboflavine (**6**), and nor-

Scheme 1. Reagents: (a) Bredereck's reagent, wet DMF, reflux; (b) *tert.*-BuOK (cat.), anhydrous DMF, reflux; (c) Bredereck's reagent, anhydrous DMF, reflux; (d) guanidinium carbonate, DMF, reflux.



Scheme 2. Reagents: (a) *N,N*-dimethylacetamide dimethylacetal, anhydrous DMF, 130°C; (b) butyraldehyde, $H_2O/AcOH/H_2SO_4$, then $FeSO_4$, *tert.*-BuOOH/H_2O; (c) Bredereck's reagent, anhydrous DMF, reflux.



isotuboflavine (**7**) were isolated from *Pleiocarpa mutica* [9], **5** was also found in *Pleiocarpa tubicina* [10] (Fig. 1).

Up to now several multi-step syntheses of the alkaloids tuboflavine [11], isotuboflavine [7], norisotuboflavine [7,12], and of unsubstituted canthin-4-one [7] have been published, but none of these offer overall yields higher than 1%. So these total syntheses could only serve as proofs for the structures of the alkaloids, but do not represent efficient approaches to the canthin-4-one ring system.

In order to elucidate the scope of this new anellation protocol, we worked out total syntheses of the alkaloids norisotuboflavine (**7**) and tuboflavine (**5**) following the strategy described above.

Condensation of 1-acetyl-β-carboline (**1**) with *N,N*-dimethylacetamide dimethylacetal in refluxing anhydrous DMF gave, presumably via an intermediate enamine **8**, the alkaloid norisotuboflavine (**7**) in 52% yield.

For the synthesis of tuboflavine (**5**) we prepared the starting material 1-butanoyl-β-carboline (**10**) by *Minisci* –type acylation [13] of norharmane (**9**) with butyraldehyde and *tert*-butyl hydroperoxide/$FeSO_4$ in acidic medium. As we had demonstrated earlier [4], homolytic acylation occurs in a regioselective manner at C-1 with β-carbolines. Diacylated products could only be detected in traces by mass spectroscopy. Condensation of **10** with Bredereck's reagent in refluxing anhydrous DMF readily gave the expected alkaloid **5** in 74% yield (Scheme 2).

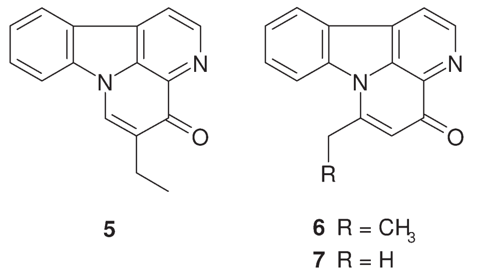


Figure 1. Canthin-4-one alkaloids from *Pleiocarpa* species: tuboflavine (**5**), isotuboflavine (**6**), norisotuboflavine (**7**).

In a preliminary screening for antimicrobial activities canthin-4-one (**4**) and norisotuboflavine (**7**) showed strong antibacterial and antifungal activities, whereas tuboflavine (**5**) was inactive.

In conclusion, we have worked out a simple and efficient approach to canthin-4-one as well as 5- and 6-alkylated derivatives thereof, starting from readily available 1-acyl-β-carbolines. Work on further modifications of the canthin-4-one ring system is in progress.

EXPERIMENTAL

General. Elemental analyses were performed on a Carlo Erba CHNO Elemental Analyser. FTIR spectra were recorded as KBr discs on a Pye-Unicam PU-9800 spectrometer, mass spectra on a Finnigan MAT-8430 spectrometer; nmr spectra were recorded with tetramethylsilane as internal standard on a Bruker AM-400 (400.1 MHz ^1H, 100.5 MHz ^{13}C) spectrometer, *J* values are given in Hz. Flash column chromatography was carried out on Merck Kieselgel 60 (230–400 mesh).

Commercially available reagent grade DMF (dimethylformamide) was purified by distillation; "anhydrous" DMF (water content about 50 ppm) was prepared by distillation followed by storage over activated molecular sieves 4 Å. The water content was determined by Karl-Fischer titration using a Mitsubishi MCI Moisturemeter, model CA-05.

1-(3-Dimethylamino)prop-2-enoyl-β-carboline (2). *tert*-Butoxy-bis(dimethylamino)methane [166 mg (0.95 mmole)] was added to a solution of 105 mg (0.50 mmole) 1-acetyl-β-carboline (**1**) in 8 mL DMF (water content 1580 ppm, equivalent to 0.7 mmole H_2O). The mixture was refluxed under nitrogen for 1 h. After evaporation the residue was purified by flash column chromatography (CH_2Cl_2:ethanol, 14:1, v/v) to give 89 mg (67%) **2** as a brown oil that crystallized overnight, mp 178°C; IR: 3422, 1638, 1625, 1537, 1412, 1243, 1101 cm^{-1}; ^1H NMR (deuteriochloroform) δ 10.82 (s, 1H, NH), 8.49 (d, 1H, *J* = 5.1 Hz, 3-H), 8.13 (d, 1H, *J* = 8.7 Hz, 5-H), 8.06 (d, 1H, *J* = 5.0 Hz, 4-H), 7.96 (d, 1H, *J* = 12.7 Hz, 3'-H), 7.55 (m, 2H, 7-H, 8-H), 7.27 (m, 1H, 6-H), 6.74 (d, 1H, *J* = 12.5 Hz, 2'-H), 3.19 (s, 3H, N-CH_3), 3.04 (s, 3H, N-CH_3); ^{13}C nmr (deuteriochloroform) δ 189.3 (C=O), 154.1 (C-3'), 140.9 (C-8a), 138.2 (C-4b), 137.5 (C-3), 135.9 (C-9a), 130.9 (C-4a), 128.6 (C-7), 121.6 (C-5), 120.7 (C-1), 119.9 (C-6), 117.3 (C-4), 111.8 (C-8), 91.5 (C-2'), 45.2 (CH_3), 37.5 (CH_3); ms (EI) m/z 265 (M^+, 17), 235 (15), 222 (48), 221 (100), 220 (19), 182 (19), 98 (26). Hr-ms: Calcd. for $C_{16}H_{15}N_3O$: 265.1215, found: 265.1210.

Canthin-4-one (4) from 1-acetyl-β-carboline (1). Under nitrogen 214 mg (1.23 mmol) *tert*-butoxy-bis-(dimethylamino) methane were added dropwise to a stirred solution of 200 mg (0.95 mmol) (**1**) [1,4] in 20 mL anhydrous DMF (water content about 55 ppm). The mixture was refluxed under nitrogen for 3 h. The solvent was evaporated under reduced pressure and the residue was dissolved in 60 mL ethyl acetate. The organic layer was washed with water (40 mL) and dried with Na_2SO_4. After evaporation the residue was purified by flash column chromatography (CH_2Cl_2:ethanol, 14:1, v/v) to give 156 mg (74%) **4** as a yellow solid. Recrystallization from CH_2Cl_2- heptane gave yellow needles, mp 264°C (lit. [7]: mp (diethyl ether) 270°C); IR: 1645, 1615, 1554, 1506, 1438, 1294, 1223, 1193 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.98 (d, 1H, *J* =4.6 Hz, 2-H), 8.97 (d, 1H, *J* = 7.7 Hz, 6-H), 8.47 (d, 1H, *J* = 4.8 Hz, 1-H), 8.38 (d, 1H, *J* = 7.7 Hz, 11-H), 8.18 (d, 1H, *J* = 8.2 Hz, 8-H), 7.79 (dd, 1H, *J* = 7.3, 8.4 Hz, 9-H), 7.53 (dd, 1H, *J* = 7.7, 7.3 Hz, 10-H), 6.52 (d, 1H, *J* = 7.7 Hz, 5-H); ^{13}C NMR (DMSO-d_6) δ 178.7 (C=O), 147.2 (C-2), 139.4 (C-7a), 138.9 (C-3a), 135.0 (C-11c), 134.3 (C-6), 133.7 (C-11b), 131.5 (C-9), 125.1 (C-10), 124.6 (C-11), 124.3 (C-11a), 119.9 (C-1), 117.1 (C-5), 112.7 (C-8); ms (EI) m/z 220 (M^+, 100), 192 (28), 165 (12), 139 (8); Anal. Calcd. for $C_{14}H_8N_2O$: C, 76.35; H, 3.66; N, 12.72. Found: C, 76.02; H, 3.27; N, 12.48.

Canthin-4-one (4) from enaminoketone 2. A catalytic amount (ca. 3 mg) of potassium *tert*-butoxide was added to a refluxing solution of 89 mg (0.34 mmol) **2** in 5 mL anhydrous DMF under nitrogen. Refluxing was continued for 4 h. After cooling to room temperature 20 mL 10% $NaHCO_3$-solution were added and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed 3 times with water and dried with $MgSO_4$. After evaporation 59 mg (80%) of pure canthin-4-one (**4**) was obtained.

Annomontine (3). Canthin-4-one (**4**) [100 mg (0.45 mmol)] was dissolved in 10 mL DMF, then 244 mg (1.35 mmol) guanidinium carbonate was added and the mixture was refluxed under nitrogen for 7 h. The solvent was evaporated under reduced pressure and the residue was dissolved in 40 mL ethyl acetate. The organic layer was washed with 30 mL water and dried with Na_2SO_4. After evaporation the residue was purified by flash column chromatography (CH_2Cl_2:ethanol, 14:1, v/v) to give 70 mg (59%) **3** as a yellow solid. The product was identified by comparison with an authentic sample. The spectroscopic data were in full accordance with those described in lit. [1].

Norisotuboflavine (7). Under nitrogen 231 mg (1.74 mmol) *N*,*N*-dimethylacetamide dimethylacetal were added dropwise to a stirred solution of 200 mg (0.95 mmol) 1-acetyl-β-carboline (**1**) in 20 mL anhydrous DMF. The mixture was heated under nitrogen at 130°C for 24 h. The solvent was evaporated under reduced pressure and the residue was dissolved in 60 mL ethyl acetate. The organic layer was washed with water (40 mL) and dried with Na_2SO_4. After evaporation the residue was purified by flash column chromatography (CH_2Cl_2:ethanol, 14:1, v/v) to give 115 mg (52%) **7** as a yellow solid. Recrystallization from CH_2Cl_2-heptane gave pale yellow needles, mp 294°C (lit. [7,9,11]: mp (diethyl ether) 298–300°C, (methanol) 282–284°C, (methanol) 294–296°C); IR: 1633, 1607, 1496, 1428, 1289, 1220 cm^{-1}; ^1H NMR (deuteriochloroform) δ 8.92 (d, 1H, *J* = 4.7 Hz, 2-H), 8.08 (d, 1H, *J* = 7.7 Hz, 11-H), 7.99 (d, 1H, *J* = 4.7 Hz, 1-H), 7.83 (d, 1H, *J* = 8.4 Hz, 8-H), 7.60 (m, 1H, 9-H), 7.42 (dd, 1H, *J* = 7.5, 7.6 Hz, 10-H), 6.35 (s, 1H, 5-H), 2.87 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ 178.8 (C=O), 147.0 (C-6), 146.7 (C-2), 140.1 (C-7a), 138.5 (C-3a), 135.4 (C-11c), 133.4 (C-11b), 130.9 (C-9), 125.4 (C-11a), 124.6 (C-10), 123.7 (C-11), 118.2 (C-1), 117.6 (C-5), 114.4 (C-8), 21.3 (CH_3); ms (EI) m/z 234 (M^+, 100), 217 (15), 195 (25), 168 (62), 139 (22) and 113 (27); Anal. Calcd. for $C_{15}H_{10}N_2O$: C, 76.91; H, 4.30; N, 11.96. Found: C, 77.05; H, 4.00; N, 11.78.

1-Butanoyl-β-carboline (10). Norharmane (**9**) [200 mg (1.19 mmol)] was suspended in an ice-cooled mixture of water (3 mL), glacial acetic acid (3 mL) and conc. sulfuric acid (0.6 mL) by means of ultrasound irradiation. 0.50 g (6.9 mmol) butyraldehyde were added. Then a solution of 1.0 g (3.6 mmol) $FeSO_4 \times 7\ H_2O$ in 3.6 mL water and 0.5 mL (3.6 mmol) *tert*-BuOOH (70% solution in water) were added simultaneously under stirring. After 1 h at 0°C the mixture was poured into water (100 mL), neutralized with solid K_2CO_3 and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried with Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (ethyl acetate:hexane, 1:4, v/v) to give 180 mg (64%) **10** as pale yellow crystals, mp 152°C; IR: 3401, 1663, 1490, 1452, 1430, 1317, 1200, 1137 cm^{-1}; ^1H NMR (deuteriochloroform) δ 10.34 (s, 1H, N—H), 8.52 (d, 1H, *J* = 4.9 Hz, 3-H), 8.14 (d, 1H, *J* = 7.9 Hz, 5-H), 8.13 (d, 1H, *J* = 4.9 Hz, 4-H), 7.53 (m, 2H, 7-H, 8-H), 7.32 (m, 1H, 6-H), 3.39 (m, 2H, 2'-H), 1.88 (m, 2H, 3'-H), 1.08 (t, 3H, *J* = 7.4 Hz, CH_3); ^{13}C NMR (deuteriochloroform) δ 205.4 (C=O), 141.1 (C-8a), 138.1 (C-3), 135.9 (C-9a), 135.5 (C-1), 131.5 (C-4a), 129.2 (C-7), 121.8 (C-5), 120.6 (C-6, C-4b), 118.9 (C-4), 111.9 (C-8), 39.6 (C-2'), 17.8 (C-3'), 14.0 (C-4'); ms (EI) m/z 238 (M^+, 42), 223 (35), 210 (38), 195 (20), 182 (50), 168 (100), 140 (40), and 91 (32); Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.97; H, 5.68; N, 11.49.

Tuboflavine (5). Under nitrogen 154 mg (0.89 mmol) *tert*-butoxy-bis(dimethylamino)methane was added dropwise to a stirred solution of 100 mg (0.42 mmol) 1-butanoyl-β-carboline (**10**) in 15 mL anhydrous DMF. The mixture was refluxed under nitrogen for 6 h. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (CH_2Cl_2:ethanol, 19:1, v/v) to give 77 mg

(74%) **5** as a yellow solid. Recrystallization from CH_2Cl_2-heptane gave yellow needles, mp 217°C (lit. [10,12]: mp 207–208°C, 216°C (acetone-hexane)); IR: 1610, 1573, 1510, 1470, 1438, 1345, 1292, 1166 cm^{-1}; ^{1}H NMR (CF_3COOD) δ 9.23 (d, 1H, $J = 5.9$ Hz, 2-H), 8.90 (d, 1H, $J = 5.9$ Hz, 1-H), 8.82 (s, 1H, 6-H), 8.51 (d, 1H, $J = 8.0$ Hz, 11-H), 8.11 (m, 2H, 8-H, 9-H), 7.81 (m, 1H, 10-H), 2.94 (q, 2H, $J = 7.5$ Hz, 1'-H), 1.45 (t, 3H, $J = 7.5$ Hz, 2'-H); ^{13}C NMR (CF_3COOD) δ 173.5 (C=O), 144.7 (C-7a), 143.3 (C-3a), 140.5 (C-2), 136.5 (C-6), 134.7 (C-11c), 133.6 (C-11b), 133.5 (C-9), 127.8 (C-10), 126.5 (C-11), 126.4 (C-11a), 122.4 (C-5), 119.9 (C-1), 112.3 (C-8), 20.9 (C-1'), 10.9 (C-2'); ms (EI) m/z 248 (M^+, 100), 247 (99), 192 (25), 151 (30), 91 (24); Anal. Calcd. for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.07; H, 4.85; N, 11.27.

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Junjappa-Ila Annulation: α-Oxoketene Dithioacetal Mediated Synthesis of Substituted Benzotriazoles

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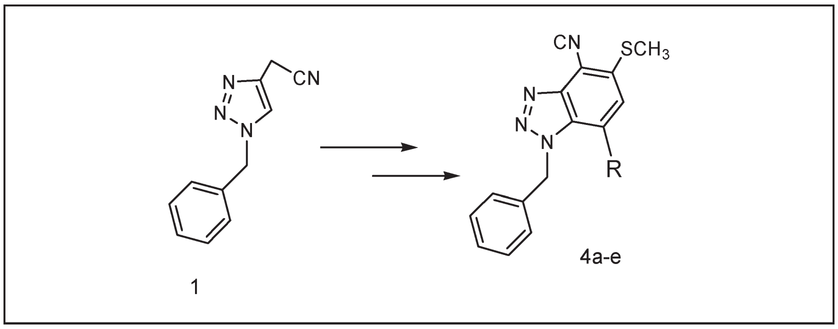

2-(1-Benzyl-1*H*–1,2,3-triazole-4-yl)-3-methylsulfanyl-5-oxo-5-substituted-*pent*-2-enenitrile **3a-e** were obtained in good yields by condensation of (1-benzyl-1*H*-1,2,3-triazole-4-yl)acetonitrile **(1)** with various α-oxoketene dithioacetals **2a-e** in the presence of sodium hydride. The intermediates **3a-e** underwent facile acid-induced cyclization in the presence of PTSA to afford the corresponding benzotriazoles **4a-e** in moderate yields.

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INTRODUCTION

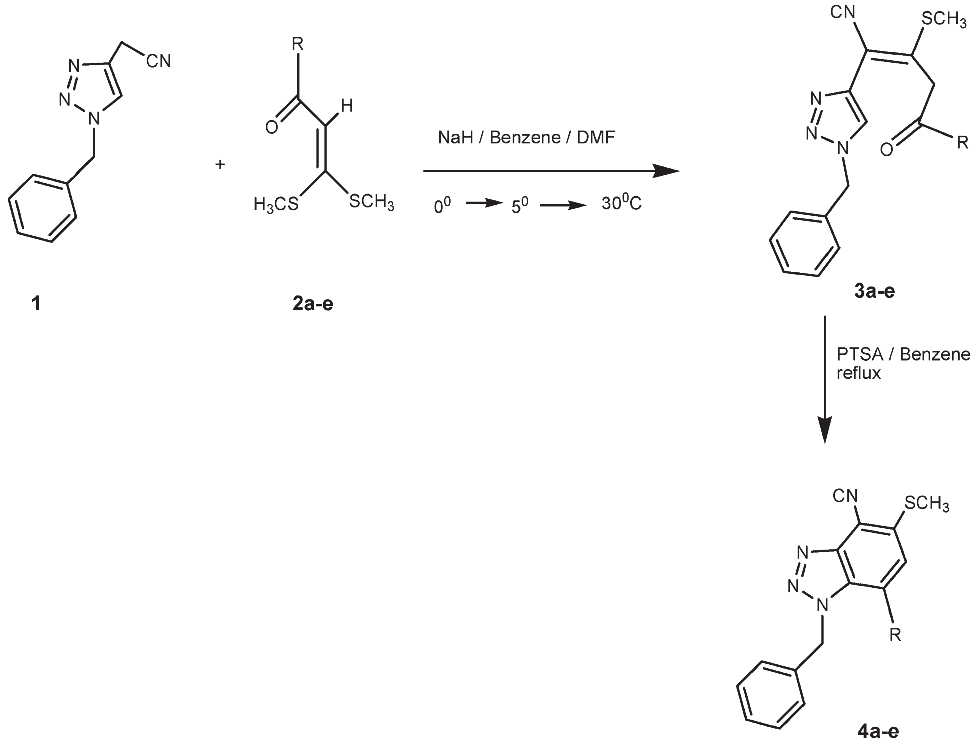
The α-oxoketene dithioacetals owe their potential synthetic application to their varied intrinsic chemical properties. The presence of carbonyl functionality and its position in conjugation with double bond carrying bis(alkylthio)group at the β-position place them among the versatile 1,3-dielectrophilic 3-carbon equivalents. The [3+3] benzoannulation methodologies involving the reaction of allyl anions with α-oxoketene dithioacetals, developed by Junjappa and coworkers [1–3], has emerged as a versatile method for the construction of a wide variety of aromatics, heteroaromatics, and benzoheterocycles. These benzoannulation methodologies have became the subject of intense investigation due to the easy availability of 1,3-dielectrophilic synthons, wide structural variants of allyl anions and a high degree of regiocontrol observed in these reactions.

In continuation of our studies on JI annulation and Heteroaromatic annulation reaction [4] on triazole chemistry [5] and in view of the pharmacological significance of benzotriazoles [6–9], we became interested in the corresponding benzotriazole group of compounds and found that the method developed by Junjappa and Ila to construct an aromatic ring over the preconstructed triazole ring would be an efficient route for the synthesis of benzotriazole. Interestingly, the literature survey revealed that entire benzotriazole chemistry has been confined to construct a triazole ring over the appropriately substituted benzene ring [10–13]. We therefore deemed it interesting to attempt the construction of benzotriazoles from the preconstructed triazole ring with required substitution. We have successfully achieved this goal and present our results in this communication.

DISCUSSION

The required α-oxoketene dithioacetals **2a-e** were prepared as described in the literature [14,15] and (1-benzyl-1*H*-1,2,3-triazol-4-yl]acetonitrile **1** was prepared from 1-benzyl-4-chloromethyl-1*H*-1,2,3-triazole [16]. The reaction of (1-benzyl-1*H*-1,2,3-triazol-4-yl)-acetonitrile **1** with various α-oxoketene dithioacetals **2a-e** in the presence of sodium hydride in dry dimethyl formamide and benzene mixture (50:50) afforded the corresponding 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl]-3-methylsulfanyl-5-oxo-5-substituted-*pent*-2-enenitrile **3a-e** in good yields (60–75%) (Scheme 1). Evolution of methanethiol (MeSH) was observed during the course of the reaction. Formation of this conjugate adduct was ascertained by spectral and analytical data. The presence of a sharp band in the region 1675–1746 cm^{-1} due to the carbonyl group and a sharp band around 2200 cm^{-1}, due to cyano group supports the formation of the adduct. The ^1H NMR spectra exhibited two sets of characteristic methylene

Scheme 1. a, R = Ph; b, R = *p*BrPh; c, R = *p*ClPh; d, R = *p*CH_3Ph; and e, R = 1-Naphthyl.



protons as singlets in the region δ 4.9–5.1 and δ 5.4–5.6 for $COCH_2$ and N—CH_2 respectively depending upon the alkyl/aryl substituents. The C5—H of the triazole ring in all the synthesized intermediates resonated around δ 7.6. The ^{13}C NMR spectra of the compound **3** also confirmed the formation of the intermediates, where characteristic carbonyl carbon resonated in the region δ 180.2 and the adjacent methylene carbon at around δ 44.07. These intermediates **3a-e** underwent facile acid-induced cyclization in presence of PTSA to furnish corresponding 1-benzyl-5-methylsulfanyl-7-substituted-1*H*-1,2,3-benzotriazole-4-carbonitrile **4a-e** in moderate yields (40–60%). The absence of carbonyl band in IR spectra, C5—H of triazole and carbonyl-methylene protons in ^1H NMR spectra confirms the cyclization. Similarly the carbonyl carbon and one of methylene carbon also disappeared in ^{13}C NMR spectra, confirming the formation of cyclized product **4**. Its application for functionally substituted benzotriazoles and other heterocycles is in progress.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on Nicolet Impact-410 FT-IR spectrophotometer, using KBr pellet technique. ^1H NMR and ^{13}C NMR experiments were performed at 300 MHz on Bruker AC-300F spectrometer (TMS as internal standard). Mass spectra were recorded on EI-70 EV instrument. Elemental analyses were carried out using Heraus CHN rapid analyzer.

(1-Benzyl-1*H*-1,2,3-triazole-4-yl)acetonitrile (1). A mixture of 1-benzyl-4-chloromethyl-1*H*-1,2,3-triazole (20.9 g, 0.1 mol) [16] and sodium cyanide (0.3 mol) in aq. ethanol (85%, 120 mL) was refluxed for 12 h (TLC). The reaction mixture was cooled, poured into water (200 mL), and extracted twice with benzene (100 mL). The benzene extract was washed thrice with water (200 mL), dried over anhydrous sodium sulfate and passed through silica bed. The filtrate was concentrated under reduced pressure to yield residual golden yellow oil in good yield (75%), which solidifies on cooling as needles. Pale brown solid, Yield 60%, mp 65–67°C; ir (KBr) ν cm^{-1}: 3066, 2922, 2229, 1412, 1129, 710; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.86 (s, 2H, CH_2CN), 5.54(s, 2H, CH_2-N), 7.28–7.53(m, 5H, Ar-H), 7.30(s, 1H, C5—H of triazole); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.5, 52.8, 112.6, 125.5, 128.4, 128.6, 129.2, 134.7. Anal. calcd for $C_{11}H_{10}N_4$: C, 66.65; H, 5.08; N, 28.26. Found: C, 66.61; H, 5.01; N, 28.29%

General procedure for the preparation of 2-(1-benzyl-1*H*-1,2,3-triazole-4-yl)-3-methylsulfanyl-5-oxo-5-substituted-*pent*-2-enenitrile (3a-e). To a suspension of NaH (60%, 0.88 g, 22 mmol) in dry benzene (20 mL) and dry DMF (20 mL) under stirring, a solution of (1-benzyl-1*H*-1,2,3-triazol-4-yl) acetonitrile **1** (2 g, 10 mmol) in dry benzene (10 mL) was added at 0°C over a period of 15 minutes and further stirred at 0–5°C for 15 min. Solution of α-oxoketene dithioacetal **2a-e** (10 mmol) in dry DMF (10 mL) was added slowly over 10 min to this mixture with stirring at 0–5°C. The reaction mixture was stirred at room temperature for 4–5 h. The solution was poured into aqueous ammonium chloride solution (8%, 200 mL), and extracted twice with benzene (50 mL). The collective benzene extract was washed thrice with water

(100 mL), dried over anhydrous sodium sulfate, passed through a silica bed and concentrated. After standing for 2 h, the crystallized material was separated by filtration and washed with a mixture of benzene and hexane (1:1) to afford **3a-e**.

2-(1-Benzyl-1H-1,2,3-triazole-4-yl)-3-methylsulfanyl-5-oxo-5-phenyl-*pent*-2-enenitrile (3a). Colorless solid, yield 70%, mp 114–116°C; ir (KBr) ν cm^{-1}: 3136, 2930, 2214, 1680, 1610, 1574, 1471; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.55 (s, 3H, SCH$_3$), 5.46 (s, 2H, NCH$_2$), 5.03 (s, 2H, COCH$_2$), 7.03–7.84 (m, 11H, C5—H of triazole, ArH); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 15.4, 44.07, 61.20, 96.3, 119.7, 127.8, 128.4, 128.6, 130.2, 132.4, 142.0, 165.4, 190.2. Anal. calcd for $C_{21}H_{18}N_4OS$: C, 67.36; H, 4.85; N, 14.96. Found: C, 67.24; H, 4.79; N, 14.99%.

2-(1-Benzyl-1H-1,2,3-triazole-4-yl)-5-(4-bromophenyl)-3-methylsulfanyl-5-oxo-*pent*-2-enenitrile (3b). Colorless solid, yield 75%, mp 140–142°C; ir (KBr) ν cm^{-1}: 3143, 2925, 2213, 1680, 1677, 1610, 1579, 1492; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.58 (s, 3H, SCH$_3$), 5.40 (s, 2H, NCH$_2$), 4.95 (s, 2H, COCH$_2$), 7.37–7.90 (m, 10H, C5—H of triazole, ArH); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 14.8, 46.6, 58.8, 107.0, 125.5, 125.7, 127.5, 128.4, 128.6, 129.2, 129.4, 130.8, 136.4, 144.3, 163.4, 184.5. Anal. calcd for $C_{21}H_{17}BrN_4OS$: C, 55.64; H, 3.78; N, 12.36. Found: C, 55.58; H, 3.65; N, 12.45%.

2-(1-Benzyl-1H-1,2,3-triazole-4-yl)-5-(4-chlorophenyl)-3-methylsulfanyl-5-oxo-*pent*-2-enenitrile (3c). Colorless solid, yield 65%, mp 152–154°C; ir (KBr) ν cm^{-1}: 3139, 2923, 2209, 1678, 1587, 1468; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.48 (s, 3H, SCH$_3$), 5.55 (s, 2H, NCH$_2$), 5.00 (s, 2H, COCH$_2$), 6.72–7.76 (m, 10H, C5—H of triazole, ArH); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 15.2, 47.1, 61.5, 99.7, 119.0, 125.5, 128.4, 128.6, 129.2, 129.4, 130.0, 135.5, 137.7, 142.0, 164.8, 190.0. Anal. calcd for $C_{21}H_{17}ClN_4OS$: C, 61.68; H, 4.19; N, 13.70. Found: C, 61.56; H, 4.10; N, 13.82%.

2-(1-Benzyl-1H-1,2,3-triazole-4-yl)-5-(4-methylphenyl)-3-methylsulfanyl-5-oxo-*pent*-2-enenitrile (3d). Colorless solid, yield 60%, mp 139–141°C; ir (KBr) ν cm^{-1}: 3129, 2914, 2210, 1673, 1570, 1260; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.53 (s, 3H, SCH$_3$), 5.46 (s, 2H, NCH$_2$), 4.99 (s, 2H, COCH$_2$), 7.07–7.72 (m, 10H, C5—H of triazole, ArH); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 15.3, 20.5, 46.9, 59.8, 109.1, 125.5, 128.4, 128.5, 128.7, 129.2, 129.4, 134.4 137.7, 165.4, 190.0. Anal. calcd for $C_{22}H_{20}N_4OS$: C, 68.02; H, 5.19; N, 14.42. Found: C, 67.93; H, 5.09; N, 14.54%.

2-(1-Benzyl-1H-1,2,3-triazole-4-yl)-3-methylsulfanyl-5-(1-naphthyl)-5-oxo-*pent*-2-enenitrile (3e). Colorless solid, yield 65%, mp 146–148°C; ir (KBr) ν cm^{-1}: 3142, 2932, 2219, 1668, 1574, 1460; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.42 (s, 3H, SCH$_3$), 5.35 (s, 2H, NCH$_2$), 4.90 (s, 2H, COCH$_2$), 7.06–8.74 (m, 13H, C5—H of triazole, ArH); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 15.7, 47.7, 62.0, 102.3, 123.7, 125.5, 126.6, 127.6, 128.2, 128.4, 128.6, 129.9, 134.4, 144.9, 164.0, 186.5. Anal. calcd for $C_{25}H_{20}N_4OS$: C, 70.73; H, 4.75; N, 13.20. Found: C, 70.61; H, 4.68; N, 13.31%.

General procedure for the preparation of 1-benzyl-5-methylsulfanyl-7-substituted-1*H*-1,2,3-benzotriazole-4-carbonitrile (4a-e). A solution of 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-3-methylsulfanyl-5-oxo-5-substituted-*pent*-2-enenitrile 3a-e (2.5 mmol) and PTSA (1 g, 5.3 mmol) in benzene was refluxed for 4–6 h. The reaction mixture (monitored by TLC) was concentrated and dissolved in chloroform and poured into aqueous sodium bicarbonate solution (6%, 150 mL). The organic layer was separated, washed thrice with water (100 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to yield the greenish yellow oil, which was purified by column chromatography using a benzene-hexane mixture (45:55–80: 20v/v) as eluent to furnish 4a-e.

1-Benzyl-5-methylsulfanyl-7-phenyl-1H-1,2,3-benzotriazole-4-carbonitrile (4a). Yellow solid, yield 50%, mp 180–182°C; ir (KBr) ν cm^{-1}: 3140, 2923, 2219, 1572, 1498; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.58 (s, 3H, SCH$_3$), 5.40 (s, 2H, NCH$_2$), 7.06–7.82 (m, 11H, ArH); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 17.4, 61.1, 123.7, 125.5, 125.7, 126.4, 127.1, 127.6, 128.4, 128.6, 129.2, 129.4, 130.5, 130.7, 133.4, 139.0, 144.3. Anal. calcd for $C_{21}H_{16}N_4S$: C, 70.76; H, 4.52; N, 15.72. Found: C, 70.67; H, 4.67; N, 15.80%.

1-Benzyl-7-(4-bromophenyl)-5-methylsulfanyl-1H-1,2,3-benzotriazole-4-carbonitrile (4b). Green solid, yield 58%, mp 191–193°C; ir (KBr) ν cm^{-1}: 3134, 2924, 2211, 1583, 1486; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.50 (s, 3H, SCH$_3$), 5.65 (s, 2H, NCH$_2$), 7.02–7.94 (m, 10H, ArH); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 17.9, 61.7, 124.2, 124.4, 124.6, 126.1, 126.5, 127.8, 128.3, 128.6, 129.5, 131.5, 132.9, 139.7, 142.9. Anal. calcd for $C_{21}H_{15}BrN_4S$: C, 57.94; H, 3.47; N, 12.87. Found: C, 57.89; H, 3.35; N, 12.95%.

1-Benzyl-7-(4-chlorophenyl)-5-methylsulfanyl-1H-1,2,3-benzotriazole-4-carbonitrile (4c). Pale yellow solid, yield 60%, mp 187–189°C; ir (KBr) ν cm^{-1}: 3135, 2926, 2219, 1584, 1468; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.54 (s, 3H, SCH$_3$), 5.60 (s, 2H, NCH$_2$), 7.03–8.02 (m, 10H, ArH); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 16.5, 60.0, 108.4, 125.4, 125.6, 127.1, 128.2, 129.8, 132.0, 135.5, 137.4, 139.4. Anal. calcd for $C_{21}H_{15}ClN_4S$: C, 64.53; H, 3.87; N, 14.33. Found: C, 64.42; H, 3.78; N, 14.44%.

1-Benzyl-7-(4-methylphenyll)-5-methylsulfanyl-1H-1,2,3-benzotriazole-4-carbonitrile (4d). Pale yellow solid, yield 50%, mp 156–158°C; ir (KBr) ν cm^{-1}: 3132, 2920, 2214, 1580, 1466; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.48 (s, 3H, SCH$_3$), 5.41 (s, 2H, NCH$_2$), 7.05–7.69 (m, 10H, ArH); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 17.9, 60.5, 111.2, 123.9, 125.2, 125.4, 126.9, 127.1, 128.6, 137.0, 141.9. Anal. calcd for $C_{22}H_{18}N_4S$: C, 71.32; H, 4.90; N, 15,12. Found: C, 71.21; H, 4.80; N, 15.20%.

1-Benzyl-5-methylsulfanyl-7-(1-naphthyl)-1H-1,2,3-benzotriazole-4-carbonitrile (4e). Pale green solid, yield 40%, mp 170–172°C; ir (KBr) ν cm^{-1}: 3133, 2922, 2211, 1590, 1458; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.61 (s, 3H, SCH$_3$), 5.34 (s, 2H, NCH$_2$), 7.14–7.84 (m, 13H, ArH); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 16.4, 59.7, 114.4, 125.7, 127.1, 128.6, 129.2, 132.6, 137.3, 140.8. Anal. calcd for $C_{25}H_{18}N_4S$: C, 73.87; H, 4.46; N, 13.78. Found: C, 73.79; H, 4.51; N, 13.80%.

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Facile and Selective Solvent-Free Synthesis of 2-Isoxazolines under Microwave Irradiation

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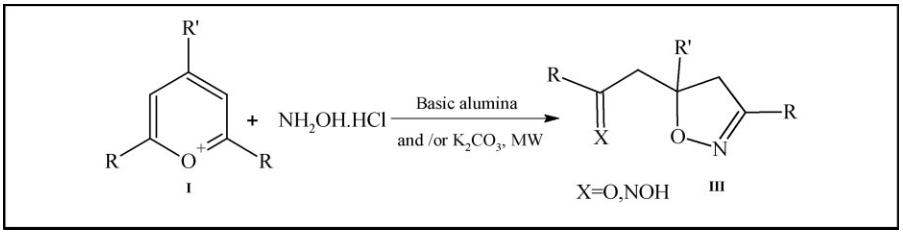

Triarylpyrylium perchlorates are readily and selectively converted into corresponding 2-isoxazolines in good yield and short reaction time using solventless conditions.

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INTRODUCTION

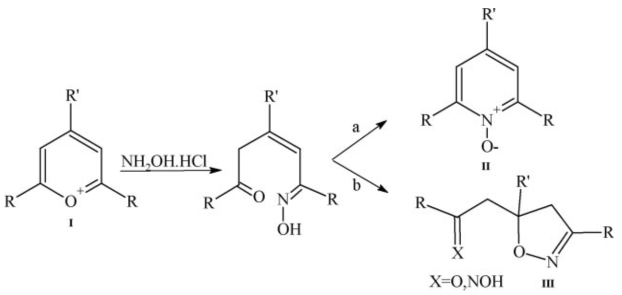
Isoxazoline heterocycles have been employed for a wide variety of uses in chemistry. These ring systems represent a class of unique pharmacophores, which are observed in many therapeutic agents and are versatile intermediates for the synthesis of complex natural products and are found in GPII/IIIa inhibitors and human leukocyte elastase inhibitors [1]. Besides being potential pharmaceutical agents, the isoxazolines have found numerous applications in synthesis through reductive cleavage of the N—O bond to give 1,3-amino alcohols [2]. Typically, 1,3-dipolar cycloaddition between nitrile oxide and alkene are used for synthesis of isoxazoline derivatives [3]. An alternative synthetic route could be offered for preparation of some 2-isoxazolines on treatment of a suspension of some 2,4,6-triarylpyrylium salts in aqueous ethanol with hydroxylamine in the presence of sodium hydroxide [4–6].

Mechanistic studies [5b,6] demonstrated that in the presence of bases the reaction proceeded, after initial attacked of the nucleophile and the ring opening to the δ-oxo-α,β-unsaturated ketoximes, not *via* path (a) but through Michael addition (path b) of two competing intramolecular cyclizations (Scheme 1). Even though this reaction is well studied in solution phase, however, solid supports procedures remain unexplored. The solvent-free use of supported reagents in combination with microwave irradiation provide ideal reaction conditions with special attributes such as reduced reaction time, easier work-up procedure, and enhanced selectivity and reactivity [7,8]. In connection with this trend and in continuation with our studies to develop selective, preparative, and synthetically useful methodology for preparation [9], application [10], and other transformation of pyrylium and thiopyrylium salts [11,12], herein, we report our results for a solvent-free microwave reaction protocol that leads to a facile preparation of 2-isoxazolines from the corresponding pyrylium salts.

RESULTS AND DISCUSSION

In efforts to improve the conversion of triarylpyryliums to corresponding 2-isoxazolines, these transformations were studied on solid materials such as silica gel, basic alumina, and nontraditional solid support material, such as K_2CO_3, which couple poorly with microwaves. Before introducing general protocol, preliminary tests were carried out to survey the requisite reaction conditions and establish the modifications required for this methodology. Triphenylpyrylium perchlorate was chosen as the model compound to identify and optimize the ideal solid support. In the cases of basic alumina and K_2CO_3 as solid support 2-isoxazolines obtained as sole product in comparable yields under microwave irradiation. More importantly, isolation of the product was more simplified and environmentally acceptable especially in the case of K_2CO_3, in which only washing the reaction mixture with water gave pure product. The same reaction in the presence of silica gel showed less selectivity toward 2-isoxazoline. Other attempts in the absence of solid phases were not successful and noticeable amount of starting materials remained intact. With these experiments, we have demonstrated that the traditional solid supports with soft acidic surface is less selective and effective, whereas solid supports with soft basic surface and nontraditional ones are moderately

Scheme 1



effective and perform the high selectivity toward desired product. Following these tests, the relative molar ratio of reactants and the amounts of solid support were also optimized under suitable microwave power. For elucidating the relative importance of this method and other effects in determining the selectivity course of these conversions, we proceeded to develop the solid support route to other triarylpyrylium perchlorates which contains electron donor and withdrawing group in para position of substituted phenyl rings and the results compared with those obtain from traditional method (in EtOH solvent). The data in Table 1 clearly showed that in the all cases (**Ia–g**) the reactions exhibit high regioselectivity toward corresponding 2-isoxazolines derivatives as favored products in very short reaction times. The long reaction time (*e.g.*, 18 h for model compound) which is one of the main drawbacks of traditional method overcomes in this method. The products undergo elimination of phenacyl in presence of sodium hydroxide as base in solvent so here; any attempt to increase the rate of the reaction at elevated temperature will decrease the yields [5a]. The formation of the oximes **IIId–f** may be described by considering the fact that the completion of these reactions in the presence of extra amount of hydroxylamine need more power of microwave irradiation and also more reaction times in comparison with the others. Interestingly, unlike to those obtained from trialkyl pyrylium [6a] these oximes were obtained as single E-isomer. This is also in accordance with the general trend in oximes, namely prevalence of the configuration in which the bulkier R group is opposite to hydroxyl group [13]. Pyryliums carrying *N*,*N*-dimethyl substituents in para position of 4-phenyl rings (**Ih**) do not react completely and selectively with hydroxylamine under these conditions and typical reaction times.

In conclusion, a new and general procedure for the construction of 2-isoxazoline derivatives (**IIIa–g**) from readily available starting material has been developed. We believe present solvent-free procedure under microwave irradiation; provide efficient, selective, and environmentally friendly methodology for conversion of triarylpyrylium perchlorates in which desired products can be obtained by simple filtration and washings without the need for a chromatographic workup.

EXPERIMENTAL

Chemicals were purchased from Fluka, Merck, and Aldrich chemical companies. All yields refer to isolated products. Monitoring of the reactions was accomplished by TLC. A domestic Butan microwave oven (1000 W) was used. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were obtained on a Bomen.MB:102 FTIR spectrophotometer in KBr disks. ^{1}H NMR spectra were recorded on 400 MHz Brucker using $CDCl_3$ as the solvent and TMS as the internal standard.

Syntheses. All triarylpyrylium perchlorates were synthesized from the corresponding aldehydes and ketones by the

Table 1

The results for solvent-free microwave-assisted preparation of 2-isoxazoline derivatives (**III**).

					Yield (%)[b]		
Entry	R	R′	X	Time (MW power)[a]	Basic alumina	K_2CO_3	EtOH[c]
a	Ph	Ph	O	3 (300) + 0.5 (400)	84	86	74
b	Ph	4-$CH_3C_6H_4$	O	3(300)	79	85	49
c	4-$CH_3OC_6H_4$	Ph	O	3 (300) + 0.5 (400)	80	89	67
d	Ph	4-$CH_3OC_6H_4$	NOH	4.5 (300) + 1 (400)	76	81	63
e	Ph	4-$NO_2C_6H_4$	NOH	4 (300) + 1 (400)	79	81	41
f	Ph	4-BrC_6H_4	NOH	4 (300) + 1 (400)	67	80	43
g	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4$	O	3 (300) + 0.5 (400)	79	87	69
h	Ph	4-$(CH_3)_2NC_6H_4$	–	4.5 (300) + 1 (400)[d]	–	–	–

[a] The time and microwave power units are minute and watt, respectively.
[b] Based on the isolated products.
[c] After at least 18 h products were isolated as x = O.
[d] A mixture of unidentified products obtained.

method previously described [14,15]. The isoxazolines IIIa and IIIf were identical with samples (IR, m.p.) prepared from the pervious method [5].

General procedure. ***In ethanol.*** 2,4,6-Triarylpyrylium perchlorate (0.5 mmol) was suspended in ethanol (10 ml). To the stirred suspension was added an aqueous of hydroxylamine hydrochloride (2.5 mmol) and excess sodium hydroxide. The suspension was stirred for 18 h at room temperature. The products was extracted and purified by chromatography (PLC) and then recrystalized from suitable solvents.

Solvent free. Triarylpyrylium perchlorate (1 mmol) was added to 1 g of basic alumina and/or K_2CO_3 in a mortar (this ratio was optimized under our experimental condition), after homogenizing 5 mmol of hydroxylamine gradually added in portion and the mixtures were grinded for further homogenization, then irradiated in different energy and required reaction times (Table 1). The reactions were monitored by TLC using a 30:70 mixture of ether:*n*-hexane as an eluent. After completion of the reaction, the mixtures were washed with water in the case of K_2CO_3 then the products were isolated by filtration. In the case of basic alumina, the reaction mixture diluted with CH_2Cl_2 then washed with water and dried (using $MgSO_4$). Evaporation of the solvent under vacuum provided a residue which was purified by PLC to afford the desired 2-isoxazolines or their oxime derivatives.

2-(3,5-Diphenyl-4,5-dihydro-isoxazol-5-yl)-1-phenyl-ethanone (IIIa). White crystals, m.p.: 123–124°C. IR (ν max/cm^{-1}): 1340, 1370, 1450, 1680. ^{1}H NMR: 7.3–7.88 (15H, m, Ar), 4.12 (1H, d, $^2J = 17$, CH_AH_B), 3.75 (1H, d, $^2J = 17$, CH_AH_B), 3.74 (2H, s, $COCH_2$). *Anal.* Calcd. for ($C_{23}H_{19}NO_2$): C, 80.91; H, 5.61; N, 4.10. Found: C, 80.95; H, 5.90; N, 4.02.

1-Phenyl-2-(3-phenyl-5-p-tolyl-4,5-dihydro-isoxazol-5-yl)-ethanone (IIIb). White crystals, m.p.: 134–135°C. IR (ν max/cm^{-1}): 1340, 1370, 1430, 1450, 1680. ^{1}H NMR: 7.17–7.90 (14H, m, Ar), 4.10 (1H, d, $^2J = 17$, CHAHB), 3.77 (2H, s, $COCH_2$), 3.71 (1H, d, $^2J = 17$, CH_AH_B), 2.31 (3H, s, CH_3). *Anal.* Calcd. for ($C_{24}H_{21}NO_2$): C, 81.10; H, 5.95, N, 3.94. Found: C, 80.84; H, 6.02; N, 4.03.

1-(4-Methoxy-phenyl)-2-[3-(4-methoxy-phenyl)-5-phenyl-4,5-dihydro-isoxazol-5-yl] ethanone (IIIc). White crystals, m.p.: 136–137°C. IR (ν max/cm^{-1}): 1340, 1370, 1430, 1450, 1680. ^{1}H NMR: 6.90–7.80 (13H, m, Ar), 4.10 (1H, d, $^2J = 17$, CH_AH_B), 3.9 (3H, s, OCH_3), 3.8 (3H, s, OCH_3), 3.70 (1H, d, $^2J = 17$, CH_AH_B), 3.67 (2H, s, $COCH_2$). *Anal.* Calcd. for ($C_{25}H_{23}NO_4$): C, 74.80; H, 5.77; N, 3.49. Found: C, 74.68; H, 5.93; N, 3.69.

2-[5-(4-Methoxy-phenyl)-3-phenyl-4,5-dihydro-isoxazol-5-yl]-1-phenyl-ethanone oxime (IIId). White crystals, m.p.: 150–151°C. IR (ν max/cm^{-1}): 1340, 1380, 1430, 1450, 3260 (broad), 3585. ^{1}H NMR: 8.90 (1H, oxime proton), 6.89–7.91(14H, m, Ar), 4.10 (1H, d, $^2J = 17$, CH_AH_B), 3.73 (1H, d, $^2J = 17$, CH_AH_B), 3.83 (1H, d, $^2J = 13.9$, $COCH_AH_B$), 3.81 (1H, d, $^2J = 13.9$, $COCH_AH_B$), 3.80 (3H, s, OCH_3). *Anal.* Calcd. for ($C_{24}H_{22}N_2O_3$): C, 74.60; H, 5.73; N, 7.25. Found: C, 74.48; H, 5.85; N, 7.34.

2-[5-(4-Nitro-phenyl)-3-phenyl-4,5-dihydro-isoxazol-5-yl]-1-phenyl-ethanone oxime (IIIe). White crystals, m.p.: 154–155°C. IR (ν max/cm^{-1}): 1340, 1380, 1430, 1450, 3260 (broad), 3585. ^{1}H NMR: 8.89 (1H, oxime proton), 7.20–8.20 (14H, m, Ar), 4.12 (1H, d, $^2J = 16.9$, CH_AH_B), 3.83 (1H, d, $^2J = 16.9$, CH_AH_B), 3.88 (1H, d, $^2J = 13.9$, $COCH_AH_B$), 3.81 (1H, d, $^2J = 13.9$, $COCH_AH_B$). *Anal.* Calcd. for ($C_{23}H_{19}N_3$O4): C, 68.82; H, 4.77; N, 10.47. Found: C, 68.58; H, 4.84; N, 10.71.

2-[5-(4-bromo-phenyl)-3-phenyl-4,5-dihydro-isoxazol-5-yl]-1-phenyl-ethanone oxime (IIIf). White crystals, m.p.: 164–165°C. IR (ν max/cm^{-1}): 1340, 1380, 1430, 1450, 3327 (broad). ^{1}H NMR: 9 (1H, oxime proton), 7.40–7.60 (14H, m, Ar), 3.78 (1H, d, $^2J = 16.6$, CH_AH_B), 3.71 (1H, d, $^2J = 13.4$, $COCH_AH_B$), 3.42 (1H, d, $^2J = 13.4$, $COCH_AH_B$) 3.38 (1H, d, $^2J = 16.6$, CHAHB). *Anal.* Calcd. for ($C_{23}H_{19}N_2O_2Br$): C, 63.43; H, 4.40; N, 6.44; Br, 18.36. Found: C, 64.12; H, 4.54; N, 6.12; Br, 17.82.

1-(4-Methoxy-phenyl)-2-[3-(4-methoxy-phenyl)-5-p-tolyl-4,5-dihydro-isoxazol-5-yl] ethanone (IIIg). White crystals, m.p.: 124–128°C. IR (ν max/cm^{-1}): 1340, 1370, 1430, 1450, 1680. ^{1}H NMR: 6.70–8.00 (12H, m, Ar), 4.05 (1H, d, $^2J = 16.5$, CH_AH_B), 3.77 (6H, s, OCH_3), 3.70 (1H, d, $^2J = 16.5$, CH_AH_B), 3.70 (2H, s, $COCH_2$), 2.37 (3H, s, CH_3). *Anal.* Calcd. for ($C_{25}H_{23}NO_4$): C, 78.17; H, 6.31; N, 3.51. Found: C, 78.20; H, 6.44; N, 3.50.

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Ring Transformation of Spirocyclopropanepyrazoles into Pyrano[2,3-*c*]pyrazoles

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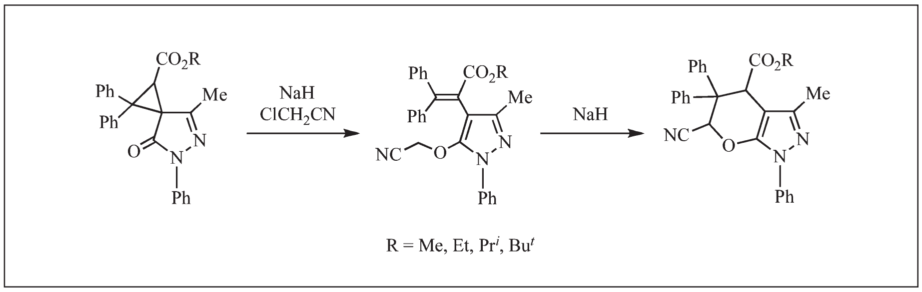

An approach to pyrano[2,3-*c*]pyrazoles starting from spirocyclopropanepyrazoles *via* a ring-opening/cyanomethylation and intramolecular cyclization is described. Reactions of spirocyclopropanepyrazoles **1a**-**d** with chloroacetonitrile in the presence of sodium hydride gave the corresponding cyanomethoxypyrazoles **4a**-**d**. Treatment of **4a**-**d** with sodium hydride at room temperature caused intramolecular Michael addition reaction to afford the corresponding pyrano[2,3-*c*]pyrazoles **5a**-**d**.

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INTRODUCTION

In many biologically active compounds, the pyrazole core is a privileged substructure. Compounds containing this ring system are known to display diverse pharmacological activities such as analgesic, antidepressant, antibacterial, plant growth regulatory, anti-inflammatory and antihyperglycemic activities [1–10]. In this context, the synthesis of pyrazole derivatives continues to attract attention and provides an interesting challenge [11–16]. In connection with our current research interests in this area, we have reported the synthesis of 1-acyl-1,2-dihydro-3*H*-pyrazol-3-ones through Lewis acid-mediated rearrangement of 3-acyloxypyrazoles [17]. More recently, we have also discussed the efficient method for the preparation of spirocyclopropanepyrazoles [18].

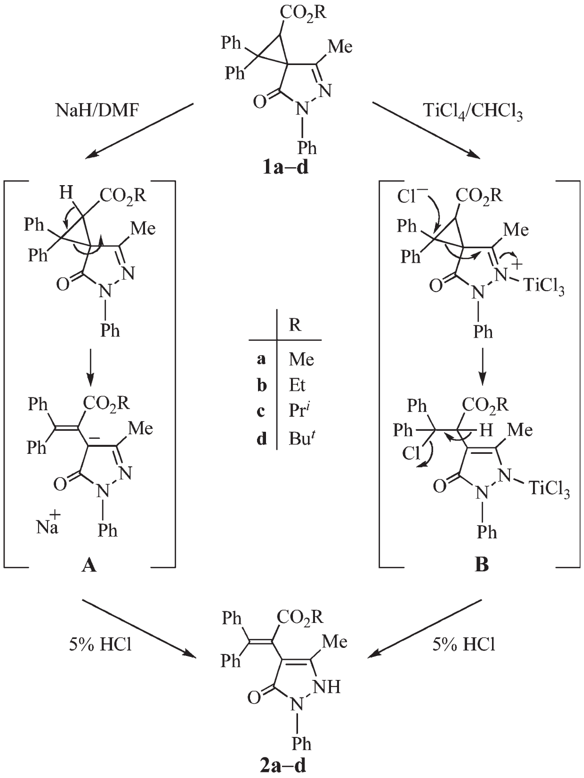
Some heterocyclic compounds containing condensed pyrazoles such as pyrano[2,3-*c*]pyrazoles possess a wide spectrum of pharmacological action, including analgesic, anti-inflammatory, vasodilating and antihypertensive activities [19–21]. Hence, the preparation and biological properties of new substituted pyrano[2,3-*c*]pyrazoles are of interest [22–36]. For these reasons, we focused our attention on the development of a new method for the preparation of pyrano[2,3-*c*]pyrazoles starting from spirocyclopropanepyrazoles and now report the results of our investigation, a ring-opening/cyanomethylation and intramolecular cyclization of them in the presence of a base such as sodium hydride.

RESULTS AND DISCUSSION

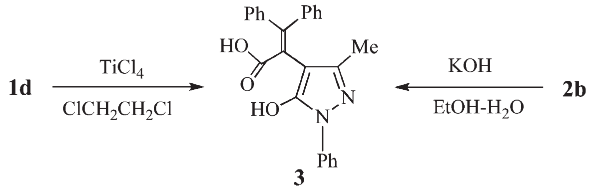
The starting materials, spiro compounds **1a-d**, were prepared by treatment of 2,4-dihydro-5-methyl-2-phenyl-4-(diphenylmethylene)-3*H*-pyrazol-3-one and α-chloro esters according to our previous investigation [18]. When a mixture of **1a-d** and sodium hydride in *N*,*N*-dimethylformamide was stirred at room temperature for 1 h, pyrazol-3-ones **2a-d** were obtained in excellent yields (Scheme 1 and Table 1). The IR spectra of **2a-d** display bands near 3100 cm^{-1} due to the secondary amino group and in the range of 1650–1690 cm^{-1} due to the two carbonyl groups. The ^{1}H NMR spectra of **2a-d** in deuteriochloroform exhibit a D_2O exchangeable signal near δ 10 attributable to the secondary amino proton. The ^{13}C NMR spectra of **2a-d** show two signals near δ 120 and 150 due to the olefin carbons, whereas those of **1a-d** show three signals near δ 50 due to the spirocyclopropane carbons. Elemental analyses and spectral data of **2a-d** are consistent with the proposed structures (see experimental section).

Fortunately, we found the reaction condition under which ring-opening products **2a-c** could be isolated in the presence of a Lewis acid. Titanium(IV) chloride-catalyzed ring-opening reactions have already been reported in the literature [37–39]. Subsequently, thermal treatment of **1a-c** with titanium(IV) chloride in chloroform caused ring opening of cyclopropane to give the corresponding pyrazol-3-ones **2a-c** in good yields. The

Scheme 1



Scheme 2



melting points and IR spectra of these compounds **2a**-**c** coincided with those of samples prepared from **1a**-**c** and sodium hydride as described above. Interestingly, in the case of the reaction of **1d** as the substrate, the expected product **2d** could not be produced but instead the carboxylic acid **3** was obtained in 93% yield (Scheme 2 and see "Experimental" section). To confirm the structure of **3**, we carried out the hydrolysis of compound **2b**. Thus, thermal treatment of **2b** with potassium hydroxide in aqueous ethanol afforded the carboxylic acid **3** (73%), which was confirmed by direct comparison with an authentic sample prepared from **1d** and titanium(IV) chloride. Although the detailed mechanism for the formation of **3** is not clear at present, this is probably because the metal complex containing chelate ring coordinated by both carboxyl and hydroxyl groups would be easily formed as an intermediate in this reaction.

Table 1

Synthesis of compounds **2a-d** according to Scheme 1.

Entry	Substrate	Product	Yield (%)
1	**1a**	**2a**	99[a] 99[b]
2	**1b**	**2b**	99[a] 99[b]
3	**1c**	**2c**	99[a] 99[b]
4	**1d**	**2d**	86[a] 0[b]

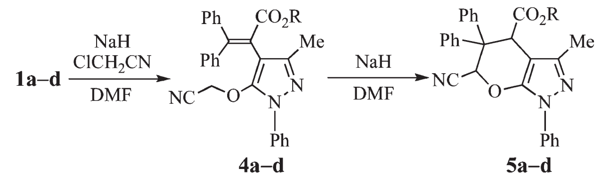
[a] NaH/DMF, r.t., 1 h.

[b] $TiCl_4/CHCl_3$, reflux, 1h.

The formation of the pyrazole-3-ones **2** could be explained by possible mechanism presented in Scheme 1. Thus, the reaction of spiro compounds **1** with sodium hydride probably causes the ring opening of cyclopropane *via* deprotonation to give the sodium salts **A** of pyrazole, which could then undergo protonation of **A** to afford the pyrazoles **2**. On the other hand, treatment of **1** with titanium(IV) chloride probably causes ring opening reaction *via* an attack of chloride ion to cyclopropane ring, giving the intermediate chlorine-containing compound **B**. The pyrazol-3-ones **2** would then be produced easily from **B** through an elimination of hydrogen chloride.

Based on these results, we hypothesized if a cyanomethylation of sodium salts **A** of pyrazole could undergo readily under an appropriate reaction condition, the synthesis of cyanomethylated pyrazoles would be possible. Thus, we carried out the cyanomethylation of spiro compounds **1** with chloroacetonitrile by use of a sodium hydride/*N*,*N*-dimethylformamide system. Contrary to our expectation, when a mixture of **1a-d** and sodium hydride in *N*,*N*-dimethylformamide was stirred at room temperature for 1 h and then the reaction mixture was treated with chloroacetonitrile at 60°C for 1 h, the *O*-cyanomethylated pyrazoles **4a-d** were obtained in moderate to good yields (Scheme 3 and entries 1–4 in Table 2). By comparison of the NMR, mass spectra and elemental analyses of **4a-d** it seems that the structural assignments given to these compounds are correct. In this reaction, *C*- and/or *N*-cyanomethylated pyrazoles were not detected.

Scheme 3



a: R = Me, **b**: R = Et, **c**: R = Pr^i, **d**: R = Bu^t

Table 2

Synthesis of compounds **4a-d** and **5a-d** according to Scheme 3.

Entry	Substrate	Product	Yield (%)
1	**1a**	**4a**	67
2	**1b**	**4b**	58
3	**1c**	**4c**	76
4	**1d**	**4d**	85
5	**4a**	**5a**	35
6	**4b**	**5b**	61
7	**4c**	**5c**	56
8	**4d**	**5d**	58

To confirm the *O*-cyanomethylated pyrazoles **4**, we next examined the conversion of **4** into the fused pyrazole derivatives in the presence of a base. After some optimization, the best result was obtained when **4a-d** were treated with sodium hydride in *N,N*-dimethylformamide at room temperature, the expected pyrano[2,3-*c*]pyrazoles **5a-d** was isolated in moderate yields (Scheme 3 and entries 5–8 in Table 2). Although, we tested the reactions under the other conditions such as a potassium *tert*-butoxide/*N,N*-dimethylformamide and potassium *tert*-butoxide/*tert*-butyl alcohol system, those attempts were unacceptable with respect to yield. It makes us believe that the intramolecular Michael addition reaction of **4** can only be promoted by using a sodium hydride/*N,N*-dimethylformamide system.

The IR spectra of **5a-d** display bands near 2250 cm^{-1} due to a nonconjugated cyano group and near 1730 cm^{-1} due to a carbonyl group. The ^{1}H NMR spectra of **5a-d** in deuteriochloroform exhibit a signal near δ 5.0 attributable to the 4-methine proton and a signal near δ 6.0 attributable to the 6-methine proton. The ^{13}C NMR spectra of **5a-d** show a signal near δ 50 due to the 4-methine carbon, a signal near δ 60 due to the 5-quaternary carbon and a signal near δ 70 due to the 6-methine carbon, whereas those of **4a-d** show a signal near δ 40 due to the methylene carbon and two signals near δ 120 and 150 due to the olefin carbons. Elemental analyses and spectral data of **4** and **5** are consistent with the assigned structures (see experimental section). In addition, for products **5a-d**, a clear nuclear Overhauser effect was not observed between 4-methine proton and 6-methine proton of trans configuration. These results indicate that *trans*-pyrano[2,3-*c*]pyrazoles are more stable than *cis*-pyrano[2,3-*c*]pyrazoles.

Finally, on the basis of these results, we have tried to directly construct pyrano[2,3-*c*]pyrazoles **5** starting from sipro compounds **1** in a one-pot process. To optimize the yield of **5**, we carried out several further experiments on **1**, testing different reaction conditions, e.g. time, solvent and substrate/base molar ratio. The results are summarized in Table 3. After a mixture of 1.0 equivalent of **1a-d** and 1.0 equivalent of sodium hydride in *N,N*-dimethylformamide was stirred at room temperature for 1 h, the reaction mixture was treated with 1.0 equivalent of chloroacetonitrile at 60°C for 1 h and then with 0.5 equivalent of sodium hydride at room temperature, the corresponding pyrano[2,3-*c*]pyrazoles **5a-d** were obtained in moderate yields (Table 3).

In conclusion, we have developed a novel method for the construction of pyrano[2,3-*c*]pyrazole derivatives **5a-d**, proceeding by a ring-opening/cyanomethylation and intramolecular cyclization when spirocyclopropane-pyrazoles **1a-d** are treated with chloroacetonitrile in the presence of sodium hydride. This methodology offers significant advantages with regard to the supply of pyrano[2,3-*c*]pyrazoles, which may exhibit biological activities such as analgesic, anti-inflammatory, vasodilating and antihypertensive activities. Functionalized pyrano[2,3-*c*]pyrazoles are important synthons in organic synthesis and for the preparation of biologically active compounds with interest in medicinal chemistry. Further studies on the synthesis of new substituted pyrano[2,3-*c*]pyrazoles are under way.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded on a JASCO FT/IR-4100 spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-A500 spectrometer at 500 and 125 MHz, respectively. The ^{1}H and ^{13}C chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane as internal standard. The positive FAB mass spectra were obtained on a JEOL JMS-700T spectrometer. The elemental analyses were performed on a YANACO MT-6 CHN analyzer.

General Procedure for the Preparation of Ring-Opening Products 2a-d from 1a-d. Procedure A. To an ice-cooled and stirred solution of **1a-d** [18] (1 mmole) in *N,N*-dimethylformamide (5 mL) was added 60% sodium hydride (0.04 g, 1 mmole). After the mixture was stirred at room temperature for 1 h, the solvent was removed *in vacuo*. A 5% hydrochloric acid solution (20 mL) was added to the residue with stirring and ice-cooling. The resulting mixture was extracted with chloroform (60 mL). The extract was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with chloroform-acetone (4:1) as the eluent to afford **2a** (0.404 g, 99%),

Table 3

Synthesis of pyrano[2,3-*c*]pyrazoles **5a-d** starting from **1a-d**.

Entry	Substrate	Product	Yield (%)
1	**1a**	**5a**	28
2	**1b**	**5b**	47
3	**1c**	**5c**	44
4	**1d**	**5d**	59

2b (0.420 g, 99%), **2c** (0.436 g, 99%) and **2d** (0.388 g, 86%), respectively.

Procedure B. To an ice-cooled and stirred solution of **1a**-**c** (1 mmole) in chloroform (5 mL) was added titanium(IV) chloride (0.38 g, 2 mmoles). After the mixture was refluxed for 1 h, a 5% hydrochloric acid solution (20 mL) was added to the reaction mixture with stirring and ice-cooling. After work-up as described above, **2a** (0.406 g, 99%), **2b** (0.419 g, 99%) and **2c** (0.435 g, 99%) were obtained.

Methyl 2-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-3,3-diphenylacrylate (2a). This compound was obtained as pale yellow needles, mp 141–143°C (chloroform-petroleum ether); IR (potassium bromide): ν 3060 (NH), 1714, 1685, 1656 cm^{-1} (C=O); ^1H NMR (deuteriochloroform): δ 1.32 (s, 3H, 5-Me), 3.37 (s, 3H, CO_2Me), 6.72 (d, J = 7.3 Hz, 2H, Ph-H), 6.99 (d, J = 3.7 Hz, 2H, Ph—H), 7.15–7.44 (m, 9H, Ph—H), 7.79 (d, J = 7.9 Hz, 2H, Ph—H), 10.33 ppm (s, 1H, NH); ^{13}C NMR (deuteriochloroform): δ 12.0 (5-Me), 52.3 ($CO_2\mathit{Me}$), 107.9 (C-4), 118.0, 121.6 (Ph—C), 122.2 ($Ph_2C{=}\mathit{C}{-}CO_2Me$), 124.6, 125.0, 127.9, 128.0, 128.1, 128.5, 128.7, 128.9, 129.1, 130.4, 137.1, 141.2, 142.4 (Ph—C), 149.1 (C-5), 150.2 ($Ph_2\mathit{C}{=}C{-}CO_2Me$), 162.7, 172.9 ppm (C=O); ms: m/z 411 $[M+H]^+$. *Anal.* Calcd. for $C_{26}H_{22}N_2O_3{\cdot}0.2H_2O$: C, 75.42; H, 5.45; N, 6.77. Found: C, 75.59; H, 5.45; N, 6.75.

Ethyl 2-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-3,3-diphenylacrylate (2b). This compound was obtained as pale yellow needles, mp 149–151°C (chloroform-petroleum ether); IR (potassium bromide): ν 3110 (NH), 1711, 1680, 1656 cm^{-1} (C=O); ^1H NMR (deuteriochloroform): δ 0.69, 0.91 (t, J = 7.1 Hz, 3H, $CO_2CH_2\mathit{Me}$), 1.31, 1.62 (s, 3H, 5-Me), 3.90, 3.96 (q, J = 7.1 Hz, 2H, $CO_2C\mathit{H_2}Me$), 6.68 (d, J = 7.3 Hz, 2H, Ph—H), 6.97–7.45 (m, 11H, Ph—H), 7.70–7.83 (m, 2H, Ph—H), 8.43, 10.47 ppm (s, 1H, NH); ^{13}C NMR (deuteriochloroform): δ 12.0 (5-Me), 13.1, 13.3 ($CO_2CH_2\mathit{Me}$), 61.7 ($CO_2\mathit{C}H_2Me$), 108.0 (C-4), 117.9, 118.9, 121.5 (Ph—C), 122.4 ($Ph_2C{=}\mathit{C}{-}CO_2CH_2Me$), 124.4, 127.8, 128.0, 128.1, 128.5, 128.9, 129.0, 129.3, 130.4, 137.2, 141.3, 142.7 (Ph—C), 149.3 (C-5), 150.2 ($Ph_2\mathit{C}{=}C{-}CO_2CH_2Me$), 162.8, 172.5 ppm (C=O); ms: m/z 425 $[M+H]^+$. *Anal.* Calcd. for $C_{27}H_{24}N_2O_3$: C, 76.39; H, 5.70; N, 6.60. Found: C, 76.46; H, 5.78; N, 6.42.

Isopropyl 2-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-3,3-diphenylacrylate (2c). This compound was obtained as pale yellow needles, mp 196–198°C (chloroform-petroleum ether); IR (potassium bromide): ν 3126 (NH), 1706, 1671, 1644 cm^{-1} (C=O); ^1H NMR (deuteriochloroform): δ 0.85, 0.91 (d, J = 6.4 Hz, 6H, $CO_2CH\mathit{Me_2}$), 1.32, 1.74 (s, 3H, 5-Me), 4.78, 4.84 (sep, J = 6.4 Hz, 1H, $CO_2C\mathit{H}Me_2$), 6.69 (d, J = 7.3 Hz, 1.2H, Ph—H), 6.97–6.99 (m, 1.2H, Ph—H), 7.13–7.46 (m, 10.6H, Ph—H), 7.73 (d, J = 7.6 Hz, 0.8H, Ph—H), 7.82 (d, J = 7.6 Hz, 1.2H, Ph—H), 8.74, 10.35 ppm (s, 1H, NH); ^{13}C NMR (deuteriochloroform): δ 12.7, 13.4 (5-Me), 20.9, 21.01, 21.09, 21.11 ($CO_2CH\mathit{Me_2}$), 69.5, 70.1 ($CO_2\mathit{C}HMe_2$), 108.3, 118.0 (C-4), 118.8, 121.5, 122.9 (Ph—C), 123.2, 124.4 ($Ph_2C{=}\mathit{C}{-}CO_2CHMe_2$), 124.8, 125.8, 127.6, 127.8, 127.9, 128.0, 128.1, 128.3, 128.4, 128.6, 128.8, 128.9, 129.0, 129.4, 130.4, 137.3, 138.7, 141.2, 141.4, 142.7 (Ph—C), 146.3, 147.0 (C-5), 149.4, 149.7 ($Ph_2\mathit{C}{=}C{-}CO_2CHMe_2$), 162.8, 171.5, 171.8 ppm (C=O); ms: m/z 439 $[M+H]^+$. *Anal.* Calcd. for $C_{28}H_{26}N_2O_3$: C, 76.69; H, 5.98; N, 6.39. Found: C, 76.68; H, 6.03; N, 6.33.

tert-*Butyl 2-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-3,3-diphenylacrylate (2d).* This compound was obtained as colorless needles, mp 175–177°C (chloroform-petroleum ether); IR (potassium bromide): ν 3106 (NH), 1706, 1683, 1656 cm^{-1} (C=O); ^1H NMR (deuteriochloroform): δ 1.14, 1.16 (s, 9H, CO_2CMe_3), 1.29, 1.69 (s, 3H, 5-Me), 6.65 (d, J = 7.3 Hz, 1.35H, Ph—H), 6.94–6.96 (m, 1.35H, Ph—H), 7.11–7.46 (m, 10.3H, Ph—H), 7.77 (d, J = 7.9 Hz, 0.65H, Ph—H), 7.85 (d, J = 7.9 Hz, 1.35H, Ph—H), 9.26, 10.74 ppm (s, 1H, NH); ^{13}C NMR (deuteriochloroform): δ 11.9, 13.4 (5-Me), 27.2, 27.4, 27.5 ($CO_2C\mathit{Me_3}$), 82.3, 83.8 ($CO_2\mathit{C}Me_3$), 97.6, 108.3 (C-4), 117.8, 118.8, 121.4 (Ph—C), 124.0 ($Ph_2C{=}\mathit{C}{-}CO_2CMe_3$), 124.1, 124.7, 125.7, 127.5, 127.7, 127.8, 127.9, 128.0, 128.2, 128.3, 128.7, 128.8, 128.9, 129.3, 129.6, 129.7, 130.6, 137.5, 138.8, 140.4, 141.2, 141.6, 142.9, 145.4 (Ph—C), 146.0, 149.4 (C-5), 149.5, 150.4 ($Ph_2\mathit{C}{=}C{-}CO_2CMe_3$), 162.9, 171.3, 171.5, 176.3 ppm (C=O); ms: m/z 453 $[M+H]^+$. *Anal.* Calcd. for $C_{29}H_{28}N_2O_3{\cdot}0.5H_2O$: C, 75.47; H, 6.33; N, 6.07. Found: C, 75.51; H, 6.27; N, 6.06.

The Preparation of Carboxylic Acid Derivative 3 from 1d and/or 2b. Procedure A. To an ice-cooled and stirred solution of **1d** [18] (0.45 g, 1 mmole) in 1,2-dichloroethane (5 mL) was added titanium(IV) chloride (0.38 g, 2 mmoles). After the mixture was refluxed for 4 h, a 5% hydrochloric acid solution (20 mL) was added to the reaction mixture with stirring and ice-cooling. The precipitate was collected by filtration, washed with water, dried and recrystallized from chloroform-methanol to yield **2-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-3,3-diphenylacrylic acid** (**3**) (0.37 g, 93%) as colorless needles, mp 277–279°C; IR (potassium bromide): ν 3448 (OH), 1676 cm^{-1} (C=O); ^1H NMR (dimethyl sulfoxide-d_6): δ 1.67 (s, 3H, 3-Me), 7.05–7.07 (m, 2H, Ph—H), 7.17–7.24 (m, 6H, Ph—H), 7.39–7.42 (m, 5H, Ph—H), 7.63–7.65 (m, 2H, Ph—H), 11.04, 12.21 ppm (s, 2H, 2×OH); ^{13}C NMR (dimethyl sulfoxide-d_6): δ 12.2 (3-Me), 118.3 (C-4), 124.3 ($Ph_2C{=}\mathit{C}{-}CO_2H$), 124.6, 127.4, 127.6, 127.7, 127.8, 128.8, 129.0, 129.6, 137.4, 141.8 (Ph—C), 142.2 (C-3), 147.1 (C-5), 147.5 ($Ph_2\mathit{C}{=}C{-}CO_2H$), 169.9 ppm (C=O); ms: m/z 397 $[M+H]^+$. *Anal.* Calcd. for $C_{25}H_{20}N_2O_3$: C, 75.74; H, 5.09; N, 7.07. Found: C, 75.62; H, 5.13; N, 6.91.

Procedure B. After a mixture of **2b** (0.42 g, 1 mmole) and potassium hydroxide (0.56 g, 10 mmoles) in ethanol (5 mL) and water (2 mL) was refluxed for 8 h, the solvent was removed *in vacuo*. A 10% hydrochloric acid solution (20 mL) was added to the residue with stirring and ice-cooling. The precipitate was collected by filtration, washed with water, dried and recrystallized from chloroform-methanol to yield **3** (0.289 g, 73%).

General Procedure for the Preparation of Cyanomethoxypyrazoles 4a-d from 1a-d and chloroacetonitrile. To an ice-cooled and stirred solution of **1a**-**d** (5 mmoles) in *N*,*N*-dimethylformamide (15 mL) was added 60% sodium hydride (0.20 g, 5 mmoles). After the mixture was stirred at room temperature for 1 h, chloroacetonitrile (0.76 g, 10 mmoles) was added to the reaction mixture with stirring and then the resulting mixture was stirred at 60°C for 1 h. After the solvent was removed *in vacuo*, a 5% hydrochloric acid solution (20 mL) was added to the residue with stirring and ice-cooling. The resulting mixture was extracted with chloroform (60 mL). The extract was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with chloroform as the eluent to afford **4a**-**d**.

Methyl 2-[5-(cyanomethoxy)-3-methyl-1-phenyl-1H-pyrazol-4-yl]-3,3-diphenylacrylate (4a). This compound was obtained as colorless prisms (1.51 g, 67%), mp 120–122°C (acetone-petroleum ether); IR (potassium bromide): ν 2251 (CN), 1712 cm^{-1} (C=O); ^{1}H NMR (deuteriochloroform): δ 2.05 (s, 3H, 3-Me), 3.55 (s, 3H, CO_2Me), 4.62 (s, 2H, OCH_2CN), 7.08–7.10 (m, 2H, Ph—H), 7.20–7.30 (m, 6H, Ph—H), 7.34–7.43 ppm (m, 7H, Ph—H); ^{13}C NMR (deuteriochloroform): δ 13.3 (3-Me), 52.1 (CO_2*Me*), 57.9 (O*C*H_2CN), 105.1 (C-4), 114.0 (CN), 121.5 (Ph_2C=*C*—CO_2Me), 122.7, 127.3, 128.1, 128.4, 128.6, 129.1, 129.2, 137.6, 140.5, 141.5 (Ph—C), 148.3 (C-3), 148.4 (C-5), 150.8 (Ph_2*C*=C—CO_2Me), 170.2 ppm (C=O); ms: m/z 450 $[M+H]^+$. *Anal.* Calcd. for $C_{28}H_{23}N_3O_3$: C, 74.82; H, 5.16; N, 9.35. Found: C, 74.98; H, 5.22; N, 9.29.

Ethyl 2-[5-(cyanomethoxy)-3-methyl-1-phenyl-1H-pyrazol-4-yl]-3,3-diphenylacrylate (4b). This compound was obtained as colorless prisms (1.35 g, 58%), mp 98–100°C (acetone-petroleum ether); IR (potassium bromide): ν 2244 (CN), 1713 cm^{-1} (C=O); ^{1}H NMR (deuteriochloroform): δ 0.95 (t, J = 7.1 Hz, 3H, CO_2CH_2*Me*), 2.06 (s, 3H, 3-Me), 4.02 (q, J = 7.1 Hz, 2H, CO_2*C*H_2Me), 4.64 (s, 2H, OCH_2CN), 7.09–7.10 (m, 2H, Ph—H), 7.20–7.44 ppm (m, 13H, Ph—H); ^{13}C NMR (deuteriochloroform): δ 13.4 (3-Me), 13.6 (CO_2CH_2*Me*), 57.9 (O*C*H_2CN), 61.2 (CO_2*C*H_2Me), 105.1 (C-4), 114.0 (CN), 121.9 (Ph_2C=*C*—CO_2CH_2Me), 122.7, 127.3, 128.1, 128.2, 128.4, 128.5, 129.2, 129.9, 137.6, 140.5, 141.7 (Ph—C), 148.36 (C-3), 148.43 (C-5), 150.5 (Ph_2*C*=C—CO_2CH_2Me), 169.8 ppm (C=O); ms: m/z 464 $[M+H]^+$. *Anal.* Calcd. for $C_{29}H_{25}N_3O_3$: C, 75.14; H, 5.44; N, 9.07. Found: C, 75.14; H, 5.52; N, 9.04.

Isopropyl 2-[5-(cyanomethoxy)-3-methyl-1-phenyl-1H-pyrazol-4-yl]-3,3-diphenylacrylate (4c). This compound was obtained as colorless needles (1.54 g, 65%), mp 143–145°C (acetone-petroleum ether); IR (potassium bromide): ν 2244 (CN), 1716 cm^{-1} (C=O); ^{1}H NMR (deuteriochloroform): δ 0.97 (d, J = 6.4 Hz, 6H, CO_2CH*Me_2*), 2.09 (s, 3H, 3-Me), 4.68 (s, 2H, OCH_2CN), 4.88 (sep, J = 6.4 Hz, 1H, CO_2*CH*Me_2), 7.19–7.23 (m, 2H, Ph—H), 7.25–7.30 (m, 6H, Ph—H), 7.33–7.35 (m, 3H, Ph—H), 7.37–7.43 ppm (m, 4H, Ph—H); ^{13}C NMR (deuteriochloroform): δ 13.4 (3-Me), 21.2 (CO_2CH*Me_2*), 58.0 (O*C*H_2CN), 69.0 (CO_2*C*HMe_2), 105.0 (C-4), 114.0 (CN), 122.2 (Ph_2C=*C*—CO_2CHMe_2), 122.7, 127.3, 128.1, 128.3, 128.4, 129.1, 129.3, 129.9, 137.5, 140.5, 141.6 (Ph—C), 148.3 (C-3), 148.4 (C-5), 149.9 (Ph_2*C*=C—CO_2CHMe_2), 169.3 ppm (C=O); ms: m/z 478 $[M+H]^+$. *Anal.* Calcd. for $C_{30}H_{27}N_3O_3$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.43; H, 5.77; N, 8.75.

tert-*Butyl 2-[5-(cyanomethoxy)-3-methyl-1-phenyl-1H-pyrazol-4-yl]-3,3-diphenylacrylate (4d).* This compound was obtained as colorless needles (2.09 g, 85%), mp 85–87°C (diethyl ether-petroleum ether); IR (potassium bromide): ν 2251 (CN), 1711 cm^{-1} (C=O); ^{1}H NMR (deuteriochloroform): δ 1.24 (s, 9H, CO_2CMe_3), 2.13 (s, 3H, 3-Me), 4.70 (s, 2H, OCH_2CN), 7.06–7.08 (m, 2H, Ph—H), 7.19–7.21 (m, 3H, Ph—H), 7.25–7.29 (m, 3H, Ph—H), 7.34–7.42 ppm (m, 7H, Ph—H); ^{13}C NMR (deuteriochloroform): δ 13.5 (3-Me), 27.6 (CO_2C*Me_3*), 58.0 (O*C*H_2CN), 81.9 (CO_2*C*Me_3), 105.1 (C-4), 114.1 (CN), 122.8 (Ph—C), 123.4 (Ph_2C=*C*—CO_2CMe_3), 127.2, 128.0, 128.2, 129.1, 129.4, 129.8, 137.7, 140.6, 141.7 (Ph—C), 148.4 (C-3), 148.5 (C-5), 149.5 (Ph_2*C*=C—CO_2CMe_3), 168.6 ppm (C=O); ms: m/z 492 $[M+H]^+$. *Anal.* Calcd. for $C_{31}H_{29}N_3O_3 \cdot 0.3CH_3CH_2OCH_2CH_3$: C, 75.27; H, 6.28; N, 8.18. Found: C, 75.26; H, 6.47; N, 8.01.

General Procedure for the Preparation of Pyrano[2,3-*c*]pyrazoles 5a-d from 4a-d. To an ice-cooled and stirred solution of **4a**-**d** (1 mmole) in *N,N*-dimethylformamide (5 mL) was added 60% sodium hydride (0.02 g, 0.5 mmole). After the mixture was stirred at room temperature for 48 h, a 5% hydrochloric acid solution (20 mL) was added to the reaction mixture with stirring and ice-cooling. The resulting mixture was extracted with chloroform (60 mL). The extract was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with chloroform as the eluent to give **5a**-**d**.

Methyl 6-cyano-3-methyl-1,5,5-triphenyl-1,4,5,6-tetrahydropyrano[2,3-c]pyrazole-4-carboxylate (5a). This compound was obtained as colorless prisms (0.155 g, 35%), mp 218–220°C (chloroform-petroleum ether); IR (potassium bromide): ν 2255 (CN), 1740 cm^{-1} (C=O); ^{1}H NMR (deuteriochloroform): δ 2.28 (s, 3H, 3-Me), 3.26 (s, 3H, CO_2Me), 4.40 (s, 1H, 4-H), 6.54 (s, 1H, 6-H), 7.15–7.38 (m, 13H, Ph—H), 7.59–7.61 ppm (m, 2H, Ph—H); ^{13}C NMR (deuteriochloroform): δ 12.6 (3-Me), 47.3 (C-4), 50.5 (C-5), 52.2 (CO_2*Me*), 71.2 (C-6), 96.3 (C-3a), 115.4 (CN), 120.4, 126.3, 128.0, 128.3, 129.1, 137.8, 139.4, 140.5, (Ph—C), 145.2 (C-3), 148.1 (C-7a), 171.8 ppm (C=O); ms: m/z 450 $[M+H]^+$. *Anal.* Calcd. for $C_{28}H_{23}N_3O_3$: C, 74.82; H, 5.16; N, 9.35. Found: C, 74.96; H, 5.26; N, 9.34.

Ethyl 6-cyano-3-methyl-1,5,5-triphenyl-1,4,5,6-tetrahydropyrano[2,3-c]pyrazole-4-carboxylate (5b). This compound was obtained as pale yellow prisms (0.282 g, 61%), mp 187–189°C (chloroform-petroleum ether); IR (potassium bromide): ν 2255 (CN), 1723 cm^{-1} (C=O); ^{1}H NMR (deuteriochloroform): δ 0.87 (t, J = 7.3 Hz, 3H, CO_2CH_2*Me*), 2.29 (s, 3H, 3-Me), 3.62–3.69 (m, 1H, CO_2*C*H_2Me), 3.75–3.82 (m, 1H, CO_2*C*H_2Me), 4.39 (s, 1H, 4-H), 6.59 (s, 1H, 6-H), 7.17–7.38 (m, 13H, Ph—H), 7.59–7.62 ppm (m, 2H, Ph—H); ^{13}C NMR (deuteriochloroform): δ 12.7 (3-Me), 13.7 (CO_2CH_2*Me*), 47.2 (C-4), 50.5 (C-5), 61.3 (CO_2*C*H_2Me), 65.8 (C-6), 96.4 (C-3a), 115.5 (CN), 120.3, 126.2, 127.9, 128.2, 128.4, 129.1, 137.8, 139.6, 140.6 (Ph—C), 145.1 (C-3), 148.1 (C-7a), 171.5 ppm (C=O); ms: m/z 464 $[M+H]^+$. *Anal.* Calcd. for $C_{29}H_{25}N_3O_3 \cdot 0.5CH_3CH_2OCH_2CH_3$: C, 74.38; H, 6.04; N, 8.39. Found: C, 74.53; H, 6.03; N, 8.39.

Isopropyl 6-cyano-3-methyl-1,5,5-triphenyl-1,4,5,6-tetrahydropyrano[2,3-c]pyrazole-4-carboxylate (5c). This compound was obtained as colorless prisms (0.267 g, 56%), mp 188–189°C (chloroform-petroleum ether); IR (potassium bromide): ν 2254 (CN), 1718 cm^{-1} (C=O); ^{1}H NMR (deuteriochloroform): δ 0.62, 1.11 (d, J = 6.4 Hz, 6H, CO_2CH*Me_2*), 2.30 (s, 3H, 3-Me), 4.36 (s, 1H, 4-H), 4.58 (sep, J = 6.4 Hz, 1H, CO_2*CH*Me_2), 6.65 (s, 1H, 6-H), 7.17–7.38 (m, 13H, Ph—H), 7.59–7.61 ppm (m, 2H, Ph—H); ^{13}C NMR (deuteriochloroform): δ 12.7 (3-Me), 21.0, 21.5 (CO_2CH*Me_2*), 47.1 (C-4), 50.3 (C-5), 69.0 (CO_2*C*HMe_2), 71.2 (C-6), 96.6 (C-3a), 115.5 (CN), 120.4, 126.2, 127.9, 128.2, 128.5, 129.1, 137.8, 139.7, 140.7 (Ph—C), 145.0 (C-3), 148.1 (C-7a), 171.1 ppm (C=O); ms: m/z 478 $[M+H]^+$. *Anal.* Calcd. for $C_{30}H_{27}N_3O_3$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.50; H, 5.84; N, 8.72.

tert-*Butyl 6-cyano-3-methyl-1,5,5-triphenyl-1,4,5,6-tetrahydropyrano[2,3-c]pyrazole-4-carboxylate (5d).* This compound was obtained as pale yellow prisms (0.287 g, 58%), mp 225–227°C (chloroform-petroleum ether); IR (potassium bromide): ν 2251 (CN), 1723 cm^{-1} (C=O); ^{1}H NMR (deuteriochloroform): δ 1.07 (s, 9H, CO_2CMe_3), 2.33 (s, 3H, 3-Me), 4.32 (s, 1H, 4-H), 6.61 (s, 1H, 6-H), 7.20–7.38 (m, 13H, Ph—H), 7.60–7.62 ppm (m, 2H, Ph—H); ^{13}C NMR (deuteriochloroform): δ 12.8 (3-Me), 27.5 ($CO_2C\mathit{Me}_3$), 47.6 (C-4), 50.4 (C-5), 71.2 (C-6), 82.1 ($CO_2\mathit{C}Me_3$), 96.9 (C-3a), 115.6 (CN), 120.3, 126.2, 127.8, 128.1, 128.2, 128.7, 129.1, 137.9, 140.0, 140.9 (Ph—C), 145.1 (C-3), 148.1 (C-7a), 170.6 ppm (C=O); ms: m/z 492 $[M+H]^+$. *Anal*. Calcd. for $C_{31}H_{29}N_3O_3$: C, 75.74; H, 5.95; N, 8.55. Found: C, 75.74; H, 6.03; N, 8.51.

General Procedure for the Preparation of Pyrano[2,3-*c*]pyrazoles 5a-d from 1a-d and Chloroacetonitrile. To an ice-cooled and stirred solution of **1a-d** (1 mmole) in *N*,*N*-dimethylformamide (5 mL) was added 60% sodium hydride (0.04 g, 1 mmole). After the mixture was stirred at room temperature for 1 h, chloroacetonitrile (0.075 g, 1 mmole) was added to the reaction mixture with stirring and then the resulting mixture was stirred at 60°C for 1 h. To an ice-cooled and stirred solution of the reaction mixture was added 60% sodium hydride (0.04 g, 1 mmole). After the mixture was stirred at room temperature for 48 h, a 5% hydrochloric acid solution (20 mL) was added to the reaction mixture with stirring and ice-cooling. The resulting mixture was extracted with chloroform (60 mL). The extract was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with chloroform as the eluent to form **5a** (0.127 g, 28%), **5b** (0.219 g, 47%), **5c** (0.208 g, 44%), and **5d** (0.292 g, 59%), respectively.

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Synthesis and Characteristic of 5,6-Dinitro and 5,6-Diaminobenzimidazolone-2

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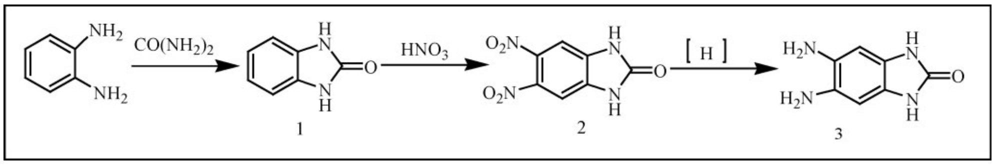

5,6-Dinitro and 5,6-diaminobenzimidazolone-2 can be synthesized at a sufficiently high purity and yield to permit its large scale production in an economically feasible manner. The results of our studies derived optimum conditions for the nitration process necessary to obtain pure 5,6-dinitriobenzimidazolone-2.

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INTRODUCTION

Connected mostly with their ability to form strong hydrogen bonds, benzimidazolone-2 and its derivatives have invoked considerable interest, and they are useful chemicals mainly as the intermediates in production of pharmaceuticals, pesticides, and pigment. 5,6-Dinitrobenzimidazolone-2 possess a variety of biological activities [1] and is explored for corrosion inhibitor [2]. 5,6-diaminobenzimidazolone-2 is widely used in diverse applications such as organic pigments and pharmaceuticals [3].

According to the refs. 4 and 5,5,6-dinitriobenzimidazolone-2 can be obtained by nitration of benzimidazolone-2 or 5-nitrobenzimidazolone-2, and 5,6-diaminobenzimidazolone-2 can be synthesized by reduction of 5,6-dinitriobenzimidazolone (Scheme 1). If pure compounds can obtain by the first method, it has a remarkable advantage in terms of cost.

Although there are some references to the synthesis of two compounds in the literature, very few data were reported. Moreover, the results of our investigations show their purity should be important, since impurities in the substrates can cause a substantial deterioration of the properties of the pigments.

In this article, we provide a process for preparing 5,6-dinitro and 5,6-diaminobenzimidazolone-2 and study the optimum conditions for the nitration reaction. The results indicate two compounds can be synthesized with high purity and yield, which permit a large scale production in an economically feasible manner.

RESULTS AND DISCUSSION

The nitration of bezimidazolone-2 is a key process in the overall reaction, since impure 5,6-dinitrobenzimidazolone-2 can cause a substantial deterioration of the properties of following products. In this article, our special concern is the optimum conditions for the nitric process.

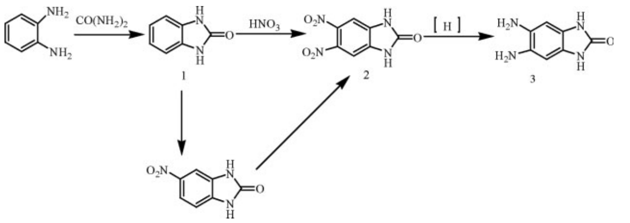
In the nitration reaction, the concentration and the dosage of nitric acid were two important factors. The by-product, 5-nitrobenzimidazolone-2, could be formed when the concentration of nitric acid was lower than 80%. It was found that the preferred concentration of nitric acid was 90% (fuming) [6], and pure 5,6-dinitriobenzimidazolone could be obtained by nitration of benzimidazolone-2 using a excess of fuming nitric acid (1.07:1–1.20:1).

Furthermore, bezimidazolone-2 is soluble in 98% sulfuric acid, and there is a disadvantage of being able to sulfonate starting material. The disadvantage is rarely serious, for nitration is generally a more rapid process than sulfonation, and pure 5,6-dinirtobezimidazolone-2 can be obtained by purified.

To obtain the optimal conditions of the nitration reaction, we designed the L_3^3 orthogonal test, and selected values of D.V.S (Dehydrating value of sulfuric acid), reaction temperature, and reaction time were chosen. The results are shown in Table 1.

The nitrating mixture employed can be characterized by the D.V.S. value. The D.V.S. value is defined as the actual sulfuric acid divided by the total water present

Scheme 1. Synthesis of 5,6-dinitro and 5,6-diaminobenzimidazolone-2.



when nitration is completed, both values being on a weight basis. Hence, water introduced with the reactants-mixed acid and formed in the reaction are both accounted for in the D.V.S. The relationship can be calculated from the equations:

$$\text{D.V.S.} = \frac{\text{Wt. of } H_2SO_4 \text{ used}}{\text{Wt. of } H_2O \text{ at end of reaction}} = \frac{m_{H_2SO_4}}{m_{H_2O}}$$

The results listed in Table 1 show that the higher D.V.S. is, the higher yield is obtained. A 73.75% yield is corresponding to D.V.S. 20. Intuitively, it would seem that the rate of reaction could be increased by increasing concentration sulfuric acid, since an increase in sulfuric acid concentration generates a corresponding increase in nitronium ion activity. Whereas using a significant excess of strong acid would raise the cost of the method, since the acid should be regenerated and purified. Otherwise, the presence of more water in the mixed acid can affect the reaction by (a) increasing the NO_x produced, which increases reaction instability and (b) decreasing the nitrating strength of the acid which, in turn, lowers product yield. Moreover, the results listed in Figure 1 has shown that if D.V.S. exceed 15, the product is low in other by-product impurities without 5-nitrobenzimidazolone-2 and can gain 97% or greater based on HPLC (Fig. 1) by purification. So, this value should be in the range 16–20, more preferably about 20.

Table 1

Parameters and results of the nitration reaction of benzimidazolone-2.[a]

D.V.S.	98% of H_2SO_4 (g)	90% of HNO_3 (g)	Reaction temperature (°C)	Reaction time (h)	Yield[b] (%)
20	44.82	4.02	0–5	2	73.75
20	44.82	4.02	5–10	5	67.35
20	44.82	4.02	10–15	8	66.30
18	37.74	4.02	0–5	5	71.38
18	37.74	4.02	5–10	8	65.13
18	37.74	4.02	10–15	2	69.22
16	31.51	4.02	0–5	8	65.19
16	31.51	4.02	5–10	2	74.05
16	31.51	4.02	10–15	5	60.94

[a] Reaction conditions: benzimidazolone-2, 3.35 g (dissolved in 22.5 g 98% sulfuric acid); the mole ratio of actual nitric acid to theoretical acid, 1.15.

[b] Isolated yield.

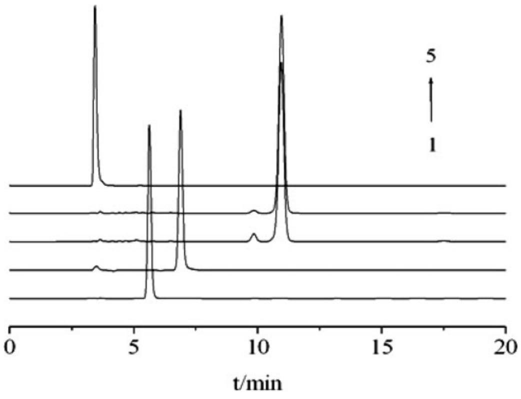


Figure 1. The chromatograms of (1) benzimidazolone-2 ($R_f = 5.62$, ≥99%); (2) 5-nitrobenzimidazolone-2 ($R_f = 6.88$, ≥99%, purchased from Aldrich); (3) 5,6-dinitrobenzimidazolone-2 (crude, $R_f = 10.95$, ≥93%); (4) 5,6-dinitrobenzimidazolone-2 (pure, $R_f = 10.95$, ≥97%); (5) 5,6-diaminobenzimidazolone-2 ($R_f = 3.42$, ≥98%).

As the nitration reaction is highly exothermic, it is necessary by using cooling techniques. As regards reaction temperature, pure product by further recrystallization can be obtained below 15°C, and the reaction temperature preferably being in the range of from about 0 to about 5°C. Eventually, it could be shown from Figure 1 that two by-product impurities ($R_f = 9.84$ and $R_f = 17.50$) were formed and have a certain relation. When the reaction time is extended, the product ($R_f = 9.84$) is slowly decreased, and another is increased. Both of them are inevitably formed, however, the total will be less below 5°C. Preferably, the reaction temperature is below 5°C by means of controlling the dropping rate. Immediately after the addition of the mixed acid was complete, the cold solution was poured into ice-water.

The results of our investigations indicated the purity of 5,6-dinitriobenzimidazolone-2 did not affect its reduction process. 5,6-Diaminobenzimidazolone-2 was easily oxidized by oxygen, so the reduction of 5,6-dinitriobenzimidazolone-2 should be under nitrogen, and the light yellow 5,6-diaminobenzimidazolone-2(HPLC 98%) could be obtained.

EXPERIMENTAL

All the reagents were reagent grade and were used without further purification unless otherwise noted. Melting points were determined on a SPSIC WRS-1B digital melting point apparatus which is uncorrected. Infrared spectra were recorded as KBr pellets for all the samples on a Perkin Elmer FT-IR instrument. Nuclear Magnetic Resonance spectra were recorded as indicated on a Varian INOVA600 spectrometer operating at 600 MHz for ^{1}H nuclei and 150 MHz for ^{13}C nuclei. Chemical shifts are reported downfield from TMS, and coupling constants are given in hertz. Mass spectra were obtained on Perkin Elmer Mass Spectrometer. The elemental analysis was carried out using Flashea 1112Series CHNS-O Analyzer and the METTLER TOLEDO MX5 (Max5.1 g d = 1 μg) weighting device. Quantitative analyses were carried out over a Shimadzu LC−20A HPLC (Column: Ultimate XB-C18 150 × 4.6 mm, 5 μm).

Benzimidazolone-2 (1). Following a literature procedure, a mixture of 54 g (0.5 mol) *o*-phenylenediamine, 34 g (0.57 mol) urea, and 95 mL glycol were stirring under nitrogen for 1 h at 130–140°C, and then heated in an oil bath at a maximum temperature of 170°C for 7 h [7]. The solution was cooled down to 40–50°C, and ~35 mL of 95% ethanol were added with stirring for 10 min, then ~100 mL of water were added. The precipitate was recovered by suction filtration and slurried with successive batches of water and 95% ethanol. The residue was dried at 100°C to give 60.2 g of white benzimidazolone-2 (1). Yield 89.9%. M.P.: 317.7–318.6°C; HPLC ≥ 99%, IR: 3128.74, 3021.52, 1741.41, 1484.26, 736.67 cm^{-1}; ^{1}H NMR (DMSO, 600 MHz): δ 6.87(s, 4H), 10.54 (s, 2H); ^{13}C NMR (DMSO, 150 MHz): δ 109.133, 121.060, 130.311, 155.934. Anal. calc. for $C_7H_6ON_2$: C 62.69, H 4.48, N 20.90; found: C 62.79, H 4.60, N 20.59.

5,6-Dinitrobenzimidazolone-2 (2). According to a variation of the method of literature, 5,6-dinitrobenzimidazolone-2 was prepared. Benzimidazolone-2 (67 g, 0.50 mol) was dissolved in 450 g 98% sulfuric acid. The colorless solution was cooled to 0–5°C in an ice bath and 80 g (1.14 mol) of 90% fuming nitric acid in 470 g 98% sulfuric acid was added dropwise to the cooled, stirred solution. The reaction temperature was not allowed to go above 5°C during the addition. After the addition of the nitric acid was complete, the cold solution was poured onto 3 kg of ice rapidly. The yellow precipitate was collected *via* filtration and washed thoroughly four times with 1-L portions of cold water. After drying at 100°C, 101.6 g yellow 5,6-dinitrobenzimidazolone-2 was obtained (HPLC 93%). Yield 90.7%. The crude 2 was recrystallized from 60% aqueous acetone to afford 80 g pure 2. M.P. > 300°C, HPLC ≥ 97%, IR: 3289.9, 3073.67, 1721.95, 1629.54, 1537.29, 1332.22, 883.59 cm^{-1}; ^{1}H NMR (DMSO, 600MHz): δ 7.65 (s, 2H), 11.78 (s, 2H); ^{13}C NMR (DMSO, 150 MHz): δ 105.560, 133.255, 137.810, 156.120; MS: 224. Anal. calc. for $C_7H_4O_5N_4$: C 37.50, H 1.79, N 35.71; found: C 37.65, H 2.00, N 35.62.

5,6-Diaminobenzimidazolone-2 (3). A mixture of 112 g (0.5 mol) of crude 2, 224 g (4 mol) of iron dust, and 1.2 L of 85% ethanol were heated to boiling on an oil bath, the stirrer was started, and a solution of 75 mL concentrated hydrochloric acid in 300 mL 85% ethanol was added dropwise. The mixture was refluxed for 5 h beyond the final addition of hydrochloric acid, and then the hot mixture was made just alkaline to pH paper by the addition of potassium hydroxide pellets. Without allowing the mixture to cool, the iron was removed by filtration and the hot ethanol was used to wash the iron residue. Hydrochloric acid (15%) was added until the filtrate was 4–5 to pH paper, and then the mixture was chilled to 0°C for 12 h. The resulting precipitate was filtered, washed with water, and dried for about 24 h under vacuum with slight nitrogen flow at 80°C to give 75 g (91.4%) of tan 5,6-diaminobenzimidazolone-2 (3). The crude 3 was purified to afford 72 g (87.8%) of light yellow pure 3. M.P.: > 300°C; HPLC ≥ 98%; IR: 3407.18, 3366.27, 3106.60, 1682.70, 850.39 cm^{-1}; ^{1}H NMR (DMSO, 600 MHz): δ 4.07 (s, 2H), 6.23 (s, 2H), 9.81(s, 2H); ^{13}C NMR (DMSO, 150 MHz): δ 96.910, 121.410, 129.550, 155.440; MS: 164. Anal. calc. for $C_7H_8ON_4$: C 51.22, H 4.88, N 34.15; found: C 50.40, H 5.67, N 33.44.

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Ionic Liquid Catalyzed Expeditious Synthesis of 2-Aryl-2,3-dihydroquinolin-4(1*H*)-ones and 2-Aryl-2,3-dihydro-4*H*-chromen-4-ones under Microwave Irradiation

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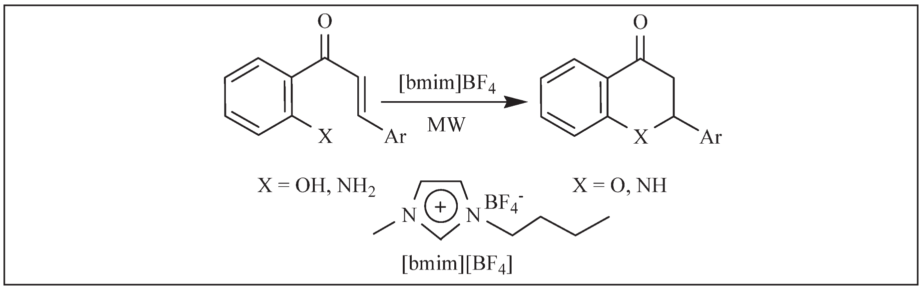

A facile and convenient synthesis of 2-aryl-2,3-dihydroquinolin-4(1*H*)-one and 2-aryl-2,3-dihydro-4*H*-chromen-4-one has been described using ionic liquid catalyzed intramolecular cyclization of the corresponding 2′-aminochalcones and 2′-hydroxychalcones, respectively. The rapid and fairly general protocol affords product in good yield. Ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate, was recovered and reused without loosing its efficiency.

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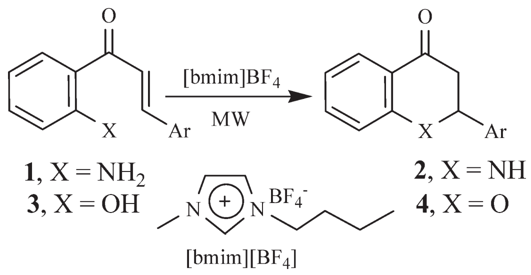
INTRODUCTION

Naturally occurring 2-aryl-2,3-dihydro-quinolin-4(1*H*)-ones and 2-aryl-2,3-dihydro-4*H*-chromen-4-ones are valuable precursors [1] for the synthesis of medicinally important compounds [2]. Because of their diverse biological activities such as hypertensive, antibacterial, antitumor, antifungal, antiinflammatory, etc., synthesis of these compounds has generated significant interest among chemists and biologists. Thus, the synthesis of these compounds has been fuelled due to diverse biological importance and presence of these moieties in various natural products [3]. The common method for the synthesis of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones and 2-aryl-2,3-dihydro-4*H*-chromen-4-ones is intramolecular cyclization of 2′-hydroxy and 2′-amino chalcones, respectively. Their synthesis following this strategy have been accomplished by using Lewis acid as catalyst, e.g. silica gel supported $TaBr_5$, K-10 Clay, orthophosphoric acid, sulphuric acid, acetic acid, 30% TFA over silica gel, silica gel [4]. Intramolecular cyclization by basic catalysts such as alumina supported-$CeCl_3{\cdot}7H_2O$-NaI, NaOH [5] is well documented in literature. Other methods like thermolysis [6], electrolysis [7], ZnO supported metal oxide [8], light [9], Ni/Zn/K halides [10] were also employed for the cyclization. Many of the reported methods for the synthesis of these biologically important heterocyclic compounds involve the use of toxic fine chemicals, requires stoichiometric amount of catalysts and afford products in low yields. Therefore, the search continues for an efficient method in terms of operational simplicity and economical viability.

In the last decade, ionic liquids have gained increasing attention of synthetic organic chemists in various organic transformations because of their tunable chemical and physical properties and catalytic behaviour [11–14]. Ionic liquids are salts that contain organic cations and inorganic or organic anions, and are liquid at or close to ambient temperature. In contrast to conventional polar organic solvents such as THF, DMF and DMSO, ionic liquids are nonflammable, nonvolatile and stable to atmospheric conditions. Among all, imidazolium-based ionic liquids with tetrafluoroborate and hexafluorophosphate anions are the most studied ionic liquids for organic synthesis.

Microwave-assisted organic synthesis offers many advantages including faster and cleaner reaction, high product yield, and operational simplicity [15]. Several methods have been developed for performing reactions with microwave irradiation in solution and under solvent free conditions [16], but a homogeneous mixture is preferred to obtain uniform heating. The excellent dielectric properties of ionic liquids offer added advantages when used as solvent in microwave-assisted organic reactions [17]. Ionic liquids couple very efficiently with

Scheme 1



microwave through an ionic conduction mechanism [18]. Nucleophilic aromatic substitution reactions have been reported with and without solvent under microwave irradiations [19]. In continuation of our study on the development of new cost effective methodologies utilizing this unconventional energy source, we herein report an ionic liquid catalyzed intramolecular cyclization of 2′-aminochalcones and 2′-hydroxychalcones with enhanced yields and efficiency under microwave irradiation to obtain 2-aryl-2,3-dihydro-quinolin-4(1*H*)-ones and 2-aryl-2,3-dihydro-4*H*-chromen-4-ones, respectively (Scheme 1).

RESULTS AND DISCUSSION

Our initial attempts under conventional conditions to cyclize 2′-aminochalcones and 2′-hydroxychalcones using 1-butyl-3-methylimidazolium tetrafluoroborate [bmim]BF_4 failed at room temperature. On heating the reaction mixture for 48 h at 135°C, very little product was produced. Further heating at this temperature generated more impurities. Encouraged by reported efficient coupling of ionic liquids with microwave [18], we next investigated this intramolecular cyclization under microwave irradiation. After several attempts, it was realized that intermittent microwave exposure for 20 s (total microwave exposer time 120 s) followed by cooling (20 s) is optimum in terms of efficient intramolecular cyclization and product yield. Among ionic liquids, [bmim]BF_4 is found to be best choice for the efficient intramolecular cyclization with shorter reaction time and good yield. After standardizing the reaction conditions for this reaction, cyclization of substituted 2′-aminochalcones **1a–g** to the corresponding 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones **2a–g** were achieved satisfactorily (Table 1).

Encouraged by the successful cyclization of 2′-aminochalcones, we next explored the intramolecular cyclization of analogues 2′-hydroxychalcones **3a–g** to prepare 2-aryl-2,3-dihydro-4*H*-chromen-4-ones **4a–g**. Microwave exposure (1.0–1.5 min) of a thick paste of 2′-hydroxychalcones **3a–g** in [bmim]BF_4 led to the formation of 2-aryl-2,3-dihydro-4*H*-chromen-4-ones **4a–g** in moderate yields (Table 2). In all the cases, some unreacted 2′-hydroxychalcones was recovered along with the product. Further increasing the amount of [bmim]BF_4 and prolonging microwave irradiation does not improve the product yield.

To determine if the ionic liquid, [bmim]BF_4 was an essential factor to promote this intramolecular cyclization, the cyclization of **2a** as a model reaction was carried out in polar organic solvents such as DMF and DMSO under microwave irradiation. This resulted in poor yield of product along with unchanged starting material. Ionic liquids are known to couple efficiently with microwave energy to accelerate the reaction. Further, ionic liquids are reported to stabilize the charged species formed as intermediate in different reactions and enhance the nucleophilicity of various nucleophiles [20]. It is expected that enhanced stability of the polar activated complex formed during intramolecular cyclization (Figure 1) and enhanced nucleophilicity of amino or hydroxyl group by ionic liquid along with the effect of microwave radiations are probable reasons for the increased reaction rate. It is also worth to mention that in absence of ionic liquid reaction did not proceed under

Table 1

Synthesis of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones.

Substrate (**1**)	Ar	Product[a] (**2**)	Time (min)	Yield[b] (%)
1a	C_6H_5	**2a**	2.0	89[c]
1b	4-ClC_6H_4	**2b**	2.0	85
1c	4-MeC_6H_4	**2c**	2.0	87
1d	4-$(C_6H_5CH_2O)C_6H_4$	**2d**	2.0	84
1e	2,6-$Cl_2C_6H_3$	**2e**	2.0	82
1f	2-Furyl	**2f**	2.0	88

[a] All the products gave satisfactory NMR (^1H and ^{13}C) and Mass data.
[b] Isolated yield.
[c] **2a** was obtained in 81% when ionic liquid was recycled and reused.

Table 2

Synthesis of 2-aryl-2,3-dihydro-4*H*-chromen-4-one.

Substrate (**3**)	Ar	Product[a] (**4**)	Time (min)	Yield[b] (%)
3a	C_6H_5	**4a**	1.0	58
3b	4-MeC_6H_4	**4b**	1.0	57
3c	4-$MeOC_6H_4$	**4c**	1.0	52
3d	4-FC_6H_4	**4d**	1.5	51
3e	4-ClC_6H_4	**4e**	1.5	49
3f	2,6-$Cl_2C_6H_3$	**4f**	1.5	55
3g	2-Furyl	**4g**	1.5	51

[a] All the products gave satisfactory NMR (^1H and ^{13}C) and mass data.
[b] Isolated yield.

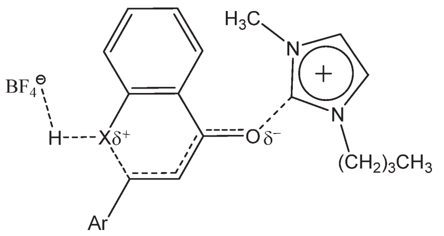


Figure 1. Proposed activated complex of [Bmim] BF_4 catalyzed intramolecular cyclization of 2′-amino/2′-hydroxychalcones.

microwave irradiation. Results of this intramolecular cyclization in other ionic liquids were also poor. Thus [bmim]BF_4 and microwave irradiation plays very important role in this rapid intramolecular cyclization.

The slow reactivity of 2′-hydroxychalcones relative to 2′-aminochalcones can be rationalized from the corresponding activation energy (E_{act}) values. For example, the transition states corresponding to the cyclization process of **1a** and **3a** are optimized using *ab initio* quantum chemical method (HF/6-31G**). The E_{act} value for the cyclization of **1a** is found to be 57 kcal/mol, whereas for cyclization of **3a** the value is 117.886 kcal/mol. To find out the exact reason of this difference in E_{act} between the two types of chalcone derivatives we used conceptual density functional theory (DFT) based local reactivity descriptors. As both types of chalcones have same number of electrons (if *R* remains same) local nucleophilicity of the N_{NH_2} (*N*-atom of the NH_2 group) and O_{OH} (*O*-atom of OH group) should be an ideal descriptor to reveal the relative electron donating ability of the two atoms during cyclization process [21]. One such descriptor is condensed local softness (S_{k}^-) [22]. The S_{k}^- values generated using the same HF/6-31G** method were 0.37 and 0.29 for N_{NH_2} and O_{OH}, respectively. These values clearly demonstrate that *N*-atom of the NH_2 group is more nucleophilic than *O*-atom of the OH group, favouring cyclization by lowering the activation energy values.

In conclusion, this article describes a practical and facile way to make 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones and 2-aryl-2,3-dihydro-4*H*-chromen-4-ones in moderate to good yields. Relatively faster cyclization of 2′-aminochalcone in comparison with 2′-hydroxychalcone has been explained using theoretical calculations. A plausible explanation for the ionic liquid-mediated expeditious cyclizations of 2′-aminochalcones and 2′-hydroxychalcones under the influence of microwave irradiation has also been provided. When compared with literature procedures, this method has the advantages of simple reaction procedure, shorter reaction time, and reuse of [bmim]BF_4 as a catalyst.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a MPA120-Automated Melting Point apparatus and are uncorrected. IR spectra were recorded with a JASCO IR-Report-100. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Bruker-400 instrument in $CDCl_3$ solution with TMS as an internal standard. Column chromatography was performed on silica gel (100–200 mesh, S. D. Fine, Pilani, India). Amino- and hydroxychalcones were prepared using the appropriate aldehyde and the corresponding *o*-substituted acetophenones [23]. The 2-aminoacetophenone and 2-hydroxyacetophenone (Sigma-Aldrich) were used as purchased. Aromatic aldehydes were obtained from E-Merck (India) Ltd. [bmim]BF_4 was prepared according to literature procedure [24]. Theoretical calculations were performed using Gaussian 03 Rev E.0.1 software. Reactions were performed in a domestic LG microwave MG607APR model (900 W).

Preparation of 2-aryl-2,3-dihydro-4(1*H*)-quinolinones (2a-g). A neat mixture of 2′-aminochalcone (1 mmol) and [bmim]BF_4 (50 mg) was subjected to microwave irradiation at 50% power for 2 min with intermittent heating (20 s) and cooling (20 s). After completion of reaction, as indicated by TLC, the product was extracted into diethyl ether (3 × 5 mL). Combined diethyl ether layer was distilled off under reduced pressure. The residue so obtained was percolated through a bed of silica gel using hexane:ethyl acetate (8:2) as eluent to afford pure product.

2-Phenyl-2,3-dihydro-4(1*H*)-quinolinone (2a). mp 149–152°C, lit. [25]149–150°C; IR (KBr): 3325 (NH), 1690 cm^{-1}(C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.87$ (d, $J = 7.6$ Hz, 1H), 7.47–7.32 (m, 6H), 6.80 (dd, $J = 7.2, 7.6$ Hz, 1H), 6.71 (d, $J = 8.4$ Hz, 1H), 4.76 (dd, $J = 4.0, 13.6$ Hz, 1H), 4.52 (br s, 1H, NH), 2.88 (dd, $J = 13.6, 16.4$ Hz, 1H), 2.77 (dd, $J = 3.6, 16.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta =$ 193.41, 151.70, 141.17, 135.55, 129.15, 128.63, 127.78, 126.77, 119.21, 118.62, 116.05, 58.66, 46.59.

2-(4′-Chlorophenyl)-2,3-dihydro-4(1*H*)-quinolinone (2b). mp 168–170°C, lit. [25] 167–168°C; IR (KBr): 3300 (NH), 1640 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.85$ (d, $J = 7.6$ Hz, 1H), 7.41–7.32 (m, 5H), 6.79 (dd, $J = 7.20, 7.24$ Hz, 1H), 6.72 (d, $J = 8.4$ Hz, 1H), 4.73 (dd, $J = 4.16, 13.20$ Hz, 1H), 4.52 (br s, 1H, NH), 2.83 (dd, $J = 16.20, 18.00$ Hz, 1H), 2.74 (dd, $J = 2.40, 16.20$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta =$ 192.98, 151.50, 139.72, 135.64, 134.33, 129.32, 128.13, 127.74, 123.66, 122.08, 119.23, 118.84, 116.13, 58.00, 46.55.

2-(p-Tolyl)-2,3-dihydro-4(1*H*)-quinolinone (2c). mp 148–149°C, lit. [25] 149°C; IR (KBr): 3300 (NH), 1640 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.85$ (d, $J = 8.0$ Hz, 1H), 7.34–7.19 (m, 5H), 6.79–6.75 (m, 1H), 6.70 (d, $J = 8.0$ Hz,1H), 4.69 (dd, $J = 3.40, 13.60$ Hz, 1H), 4.57 (br s, 1H, NH), 2.85 (dd, $J = 13.80, 16.20$ Hz, 1H), 2.72 (dd, $J = 2.40, 16.4$ Hz, 1H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 193.52$, 151.66, 138.25, 136.49, 135.38, 129.60, 127.56, 126.52, 118.95, 118.31, 115.94, 58.16, 46.44, 21.13.

2-(4′-Benzyloxyphenyl)-2,3-dihydro-4(1*H*)-quinolinone (2d). [25e] mp 130–133°C; IR (KBr): 3325 (NH), 1648 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.85$ (d, $J = 5.6$ Hz, 1H), 7.44–7.32 (m, 8H), 6.99 (d, $J = 8.8$ Hz, 2H), 6.78 (dd, $J = 7.6$ Hz, 1H), 6.68 (d, $J = 8.4$ Hz, 1H), 5.01 (s, 2H), 4.68 (dd, $J = 3.60, 14.0$ Hz, 1H), 4.46 (br s, 1H, NH), 2.85 (ddd, $J = 3.73, 13.84, 17.90$ Hz, 1H), 2.73 (dd, $J = 3.13, 16.15$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 193.59$, 158.99, 151.73, 136.94, 135.48, 133.50, 128.77, 128.19, 128.00, 127.76, 127.57, 119.18, 118.52, 116.01, 115.40, 70.25, 58.06, 46.66.

2-(2′,6′-Dichlorophenyl)-2,3-dihydro-4(1*H*)-quinolinone (2e). Viscous liquid lit. [25]; IR (KBr): 3315 (NH), 1640 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.89 (d, J = 8.0 Hz, 1H), 7.38–7.20 (m, 4H), 6.76 (t, J = 7.8 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 5.74 (dd, J = 4.04, 15.24 Hz, 1H), 4.40 (br s, 1H, NH), 3.65 (dd, J = 15.42, 16.40 Hz, 1H), 2.59 (dd, J = 4.00, 16.40 Hz, 1H); ^{13}C NMR (CDCl$_3$): δ = 193.03, 151.28, 135.87, 135.52, 133.87, 130.09, 129.98, 127.94, 118.62, 118.21, 115.99, 54.17, 40.06.

2-(Furan-2-yl)-2,3-dihydro-4(1*H*)-quinolinone(2f). [25d,e] Viscous liquid; IR (KBr): 3325 (NH), 1690 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.85 (d, J = 8.0 Hz, 1H), 7.38–7.26 (m, 2H), 6.79–6.69 (m, 2H), 6.32 (d, J = 1.39 Hz, 1H), 6.25 (d, J = 1.53 Hz, 1H), 4.84–4.78 (m, 2H), 3.07–2.92 (m, 2H); ^{13}C NMR (CDCl$_3$): δ = 192.72, 153.48, 150.61, 142.59, 135.54, 127.56, 119.34, 118.69, 116.14, 113.25, 110.49, 50.72, 42.07.

Preparation of 2-aryl-2,3-dihydro-4*H*-chromen-4-one (4a-g). A neat mixture of 2′-hydroxychalcone (1 mmol) and [bmim]BF$_4$ (50 mg) was subjected to microwave irradiation at 50% power for 2 min with intermittent heating (20 s) and cooling (20 s). After completion of reaction, as indicated by TLC, the product was extracted into diethyl ether (3 × 5 mL). The combined organic phase was distilled off under reduced pressure. The residue so obtained was percolated through a bed of silica gel using hexane:ethyl acetate (8:2) as eluent to afford pure product.

2-Phenyl-2,3-dihydro-4*H*-chromen-4-one (4a). mp 75–76°C, lit. [25] 77–78 °C; IR (KBr): 1685 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.94 (dd, J = 1.28,7.8 Hz, 1H), 7.53–7.38 (m, 6H), 7.07–7.04 (m, 2H), 5.48 (dd, J = 2.8, 13.36 Hz, 1H), 3.09 (dd, J = 13.6, 16.8 Hz, 1H), 2.89 (dd, J = 2.8, 16.8 Hz, 1H); ^{13}C NMR (CDCl$_3$): δ = 191.92, 161.53, 138.72, 136.16, 128.82, 128.74, 127.03, 126.12, 121.59, 120.92, 118.10, 79.57, 43.64.

2-(p-Tolyl)-2,3-dihydro-4*H*-chromen-4-one (4b). mp 82–83°C, lit. [25] 83–84°C; IR (KBr):1680 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.9 (dd, J = 2.0, 6.0 Hz, 1H), 7.5 (dd, J = 7.6, 11.2 Hz, 1H), 7.3 (dd, J = 1.6, 8.0 Hz, 2H,), 7.24 (d, J = 7.2 Hz, 2H), 7.0 (d, J = 7.2 Hz, 2H), 5.45 (d, J = 13.6 Hz, 1H,), 3.09 (dd, J = 2.4, 15.2 Hz,1H), 2.8 (dt, J = 2.4, 16.8 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (CDCl$_3$): δ = 192.12, 161.64, 138.69, 136.12, 135.77, 129.48, 127.03, 126.18, 121.52, 120.95, 118.14, 79.53, 44.56, 21.17.

2-(4′-Methoxyphenyl)-2,3-dihydro-4*H*-chromen-4-one (4c). mp 87–88°C, lit. [25] 88-89 °C; IR (KBr): 1690 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.93 (d, J = 7.8 Hz, 1H), 7.50 (dd, J = 1.4, 7.52 Hz, 1H), 7.41 (d, J = 8.6 Hz, 2H), 7.06–7.02 (m, 2H), 6.96 (d, J = 8.6 Hz, 2H), 5.43 (dd, J = 2.72, 13.36 Hz, 1H), 3.83 (s, 3H,), 3.11 (dd, J = 13.44, 16.88 Hz, 1H), 2.86 (dd, J = 2.76, 16.84 Hz, 1H); ^{13}C NMR (CDCl$_3$): δ = 192.23, 161.64, 159.99, 136.15, 130.78, 127.73, 127.03, 121.52, 120.92, 118.13, 114.21, 79.35, 55.36, 44.46.

2-(4′-Fluorophenyl)-2,3-dihydro-4*H*-chromen-4-one (4d). mp 96–98°C, lit. [26] 79–80°C; IR (KBr): 1690 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.94 (d, J = 7.62 Hz, 1H), 7.53-7.40 (m, 3H), 7.15-7.02 (m, 3H), 6.97–6.95 (m, 1H), 5.44 (dd, J = 14.8, 17.2 Hz, 1H), 3.09 (dd, J = 3.6, 13.2, Hz, 1H), 2.92–2.85 (m, 1H); ^{13}C NMR (CDCl$_3$): δ = 192.31, 161.68, 159.38, 136.29, 130.60, 128.08, 128.03, 127.05, 121.78, 120.94, 118.15, 79.41, 44.47.

2-(4′-Chlorophenyl)-2,3-dihydro-4*H*-chromen-4-one (4e). mp 95–96°C, lit. [25] 94–95°C; IR (KBr): 1690 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.93 (dd, J = 1.76, 7.72 Hz, 1H), 7.54–7.49 (m, 1H), 7.42–7.41 (m, 4H), 7.09–7.04 (m, 2H), 5.47 (dd, J = 3.0, 12.08 Hz, 1H), 3.04 (dd, J = 3.48, 13.24 Hz, 1H), 2.88 (dd, J = 3.12, 16.84 Hz, 1H); ^{13}C NMR (CDCl$_3$): δ = 191.51, 161.30, 137.27, 136.29, 134.59, 129.04, 127.50, 127.09, 121.81, 120.89, 118.08, 78.81, 44.58.

2-(2′,6′-Dichlorophenyl)-2,3-dihydro-4*H*-chromen-4-one (4f). [25c,e] mp 148–149°C; IR (KBr): 1680 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.97 (d, J = 7.85 Hz, 1H), 7.54–7.50 (m, 1H), 7.41–7.38 (m, 2H), 7.29–7.24 (m, 1H), 7.10–7.03 (m, 2H), 6.30 (dd, J = 2.8, 14.8 Hz, 1H), 3.79 (dd, J = 3.33, 17.11 Hz, 1H), 2.70 (dd, J = 3.02, 17.02 Hz, 1H); ^{13}C NMR (CDCl$_3$): δ = 189.22, 159.12, 134.07, 133.01, 130.29, 128.10, 127.53, 125.03, 119.40, 118.43, 115.91, 73.71, 37.37.

2-(Furan-2′-yl)-2,3-dihydro-4*H*-chromen-4-one (4g). mp 74–75°C, lit. [27] 80°C; IR (KBr): 1680 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.92 (d, J = 8.0 Hz, 1H), 7.51–7.48 (m, 2H), 7.06-7.01 (m, 2H), 6.46 (d, J = 3.24 Hz, 1H), 6.40 (d, J = 3.05 Hz, 1H), 5.55 (dd, J = 3.28, 11.53 Hz, 1H), 3.27 (dd, J = 11.56, 17.05 Hz, 1H), 2.98 (dd, J = 3.50, 16.92 Hz, 1H); ^{13}C NMR (CDCl$_3$): δ = 191.24, 160.74, 150.89, 143.43, 136.24, 126.95, 121.73, 120.93, 118.12, 110.51, 109.34, 72.27, 40.80.

General procedure for recovery and reuse of ionic liquid. After extracting the product using diethyl ether, the recovered ionic liquid was dried under reduced pressure. The flask containing recovered ionic liquid (50 mg) was again charged with 2′-aminochalcone (1 mmol) and following the aforementioned general procedure, 2-phenyl-2,3-dihydro-4(1*H*)-quinolinone **2a** was isolated in 81% yield.

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Hafnium (IV) Bis(perfluorooctanesulfonyl)amide-Catalyzed One-Pot Synthesis of Substituted Quinolines in Fluorous Media

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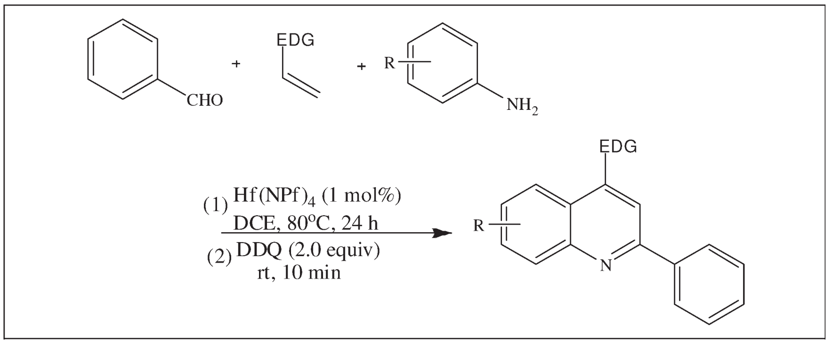

Hafnium (IV) bis(perfluorooctanesulfonyl)amide (Hf(NPf)$_4$) catalyzed the one-pot synthesis of substituted quinolines in fluorous media. By simple phase separation, the fluorous phase containing the catalyst can be used several times.

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INTRODUCTION

Quinolines and their derivatives are very important synthons of many natural products and semisynthetic biologically active compounds. Many multisubstituted quinolines are important pharmaceutical compounds, and they exhibit a wide spectrum of biological activity [1]. Methods introduced by Skraup [2], Doebner and Miller [3], Conrad and Limbach [4], Combes [5], and Pfitzinger [6] are some of the classic ways to synthesize quinolines. A number of general synthetic methods have also been reported [7]. However, all of these methods have problems, including drastic reaction conditions, low yields, and severe side reactions. Therefore, development of a more practical and economical method for synthesis of quinolines is highly desirable. Recently, Shindoh *et al*. reported that triflic imide could catalyze the auto-tandem synthesis of quinolines by three-component reactions followed by oxidation reactions [8]. However, the catalyst triflic imide could not be recycled.

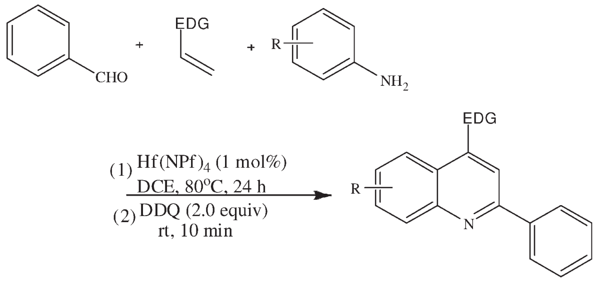
There has been rapidly increasing interest in the design and the synthesis of compounds that exhibit high affinities for ''fluorous'' phases since the technique of ''fluorous biphasic system'' (FBS) was described by Horváth and Rábai [9,10]. The technique of FBS, as a phase-separation and catalyst immobilization technique, has become one of the most important methods for facile catalyst separation from the reaction mixture and recycling of the catalyst [11]. In this catalytic system, the metalic catalyst coordinated by perfluoroalkylated ligands can be retained in the fluorous phase after the reaction. Recently, novel Lewis acids of lanthanide tris (perfluorooctanesulfonyl)methide {Ln[C(SO$_2$Rf$_8$)]$_3$, Rf$_8$ = (CF$_2$)$_7$CF$_3$, Ln(CPf$_3$)$_3$} [12], lanthanide bis(perfluorooctanesulfonyl)amide {Ln[N(SO$_2$Rf$_8$)$_2$]$_3$, Ln(NPf$_2$)$_3$} [13], and lanthanide perfluorooctanesulfonate [Ln(O-SO$_2$Rf$_8$)$_3$, Ln(OPf)$_3$] [14,15] received special interest because they have the characteristics of low hygroscopicity, ease of handling, robustness for the reuse, and high solubility in fluorous solvent.

During our studies to explore the utility of fluorinated Lewis acid catalysts in fluorous solvents [15], we found that the three component reaction of aldehydes, anilines, and electron-rich olefins followed by oxidation can proceed smoothly to afford quinolines in the presence of hafnium bis(perfluorooctanesulfonyl)amide [Hf(NPf)$_4$] in a FBS system (Scheme 1). Concurrently, we also found that the catalytic system could be reused by simple phase separation.

RESULTS AND DISCUSSION

Initially, the effect of catalyst loading and cosolvents using was examined. The results were summarized in Table 1. A mixture of benzaldehyde (1.2 equiv), aniline (1.2 equiv), and allyltriisopropylsilane (1 equiv) in the presence of Hf(NPf)$_4$ (1 mol%) in DCE (2 mL) and

Scheme 1



perfluorodecalin($C_{10}F_{18}$, *cis* and *trans*-mixture) (2 mL) was stirred at 80°C for 24 h, then the mixture was cooled to ambient temperature, followed by addition of 2,3-dichloro-5,6-dicyano-1,2-benzoquinone (DDQ, 2 equiv), and the reaction mixture was stirred in the same temperature for 10 min to afford the product in 76% yield (Table 1, entry 1). Although the catalyst loading was decreased from 1 to 0.5, and 0.25 mol %, lower product yields of 50, and 22% were obtained (Table 1, entries 2 and 3), and no reaction was observed in the absence of $Hf(NTf)_4$ (Table 1, entry 4). Several other cosolvents, such as MeCN, PhMe, H_2O, and THF, were tested, and less effective and lower product yields of 10–67% were obtained (Table 1, entries 5–8). DCE proved to be the most efficient one and was selected to be the reaction cosolvent for the subsequent exploration.

With the optimum reaction conditions in hands, we next investigated the scope of the reaction using different reactants. As shown in Table 2, several different substituted anilines and two kinds of electron-rich olefins were tested. The reactions of different reactants afforded the corresponding substituted quinolines in moderate to good yields. The substituents on the aniline had no obvious effect on the conversion. The reactivity of electron-rich olefin allyltriisopropylsilane (Table 2, entries 1–5) is higher than styrene (Table 2, entries 6–10). It may be caused by the different electron effect of the two electron-rich olefins. When the reaction was finished, the reaction mixture was cooled to room temperature, and the fluorous phase with $Hf(NPf)_4$ can be separated from the organic layer and return to the bottom layer. The recycle results (Table 2, entry 1) indicate that the catalyst does not lose its activity and can be reused without significant loss in activity up to four cycles. When the reaction was finished, the reaction mixture was cooled to room temperature, and the fluorous phase with $Hf(NPf)_4$ can be separated from the organic layer and return to the bottom layer. Based on GC-MS and ^{19}F NMR data, no distribution of $Hf(NPf)_4$ was found in organic layer and only a trace amount of perfluorodecalin leached to organic phase can be detected.

According to the literatures [8], $Hf(NPf)_4$ catalyzes the reaction as a mild Lewis acid. The reaction may proceed via 1,2,3,4-tetrahydroquinolines as intermediates formed by the reaction of the aldehyde, aniline, and electron-rich olefin. Subsequently, the intermediates were further oxidized by DDQ to give the product quinoline. These reactions take place as a one-pot reaction.

In conclusion, $Hf(NPf)_4$ is demonstrated to be new and highly effective catalyst for one-pot synthesis of substituted quinolines in FBS. By simple phase separation of the fluorous phase containing the catalyst, the reaction can be repeated many times. Further study on the application of FBS to other reactions, which can be promoted by such Lewis acids, is under way in this laboratory.

EXPERIMENTAL

Chemicals used were obtained from commercial suppliers and used without further purifications. ^1H NMR and ^{19}F NMR spectra were recorded with a Bruker Advance RX500 spectrometer. Mass spectra were recorded on a Saturn 2000GC/MS instrument. Inductively coupled plasma (ICP) spectra were measured on an Ultima2C apparatus. Elemental analyses were performed on a Yanagimoto MT3CHN recorder.

Typical procedure for preparation of $Hf(NPf)_4$. $Hf(NPf)_4$ was prepared according to the literatures [13]. Anhydrous methanol (10 mL) was added by $HN(SO_2C_8F_{17})_2$ (0.981 g, 1 mmol) and Hafnium (IV) chloride (0.080 g, 0.25 mmol), which was stirred continuously at 50°C for 16 h. After being cooled to room temperature, the mixture was evaporated and dried at 80°C /0.01 mmHg for 16 h to give white powders of Hafnium (IV) bis(perfluorooctanesulfonyl)amide complex in 96% yield (0.984 g). ICP: Calcd. for $C_{64}O_{16}N_4F_{136}S_8Hf$: Hf, 4.35%. Found: Hf, 4.33%. *Anal.* Calcd for $Hf[N(SO_2C_8F_{17})_2]_4$: C,18.75. Found: C, 18.65.

Typical procedure for the preparation of quinolines. A mixture of benzaldehyde (0.133 g, 1.2 mmol), aniline (0.116 g,

Table 1

Effect of catalyst loading and reaction solvent.[a]

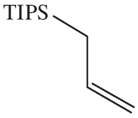
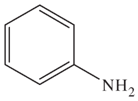
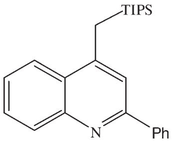
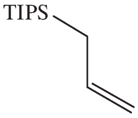
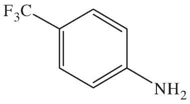
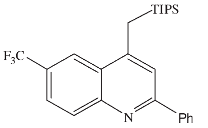
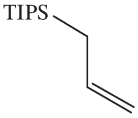
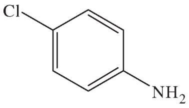
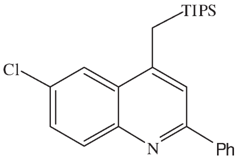
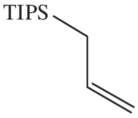
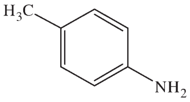
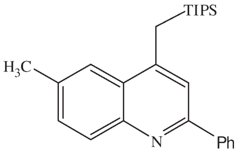
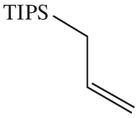
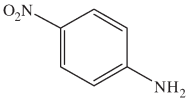
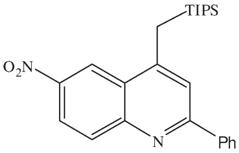
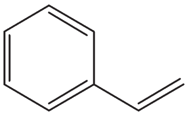
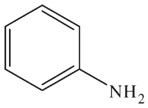
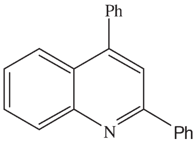
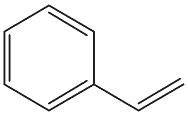
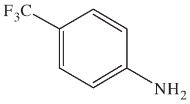
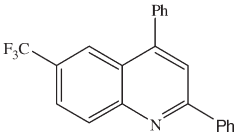
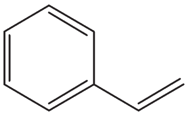
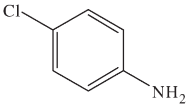
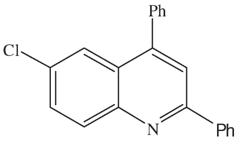
Entry	Catalyst loading (mol %)	Cosolvent	Yield (%)[b]
1	1	DCE	76
2	0.5	DCE	50
3	0.25	DCE	22
4	–	DCE	–
5	1	PhMe	65
6	1	H_2O	10
7	1	THF	56
8	1	MeCN	67

[a] The reaction condition: $Hf(NPf)_4$ (0.041 g, 0.01 mmol), benzaldehyde (0.133 g, 1.2 mmol), aniline (0.116 g, 1.2 mmol) and allyltriisopropylsilane (0.198 g, 1 mmol), Cosolvent (2 mL) and perfluorodecalin ($C_{10}F_{18}$, *cis* and *trans*-mixture, 2 mL), 80°C, 24 h; DDQ, 0.454 g, 2 mmol.

[b] Isolated yields.

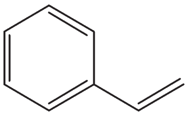
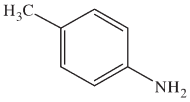
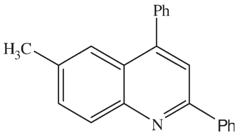
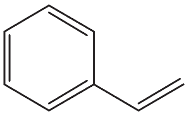
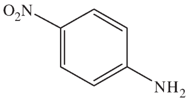
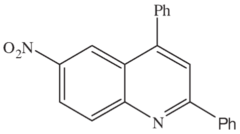
Table 2

Hf(NPf)$_4$-catalyzed preparation of quinolines.[a]

Entry	Electron-rich olefins	Anilines	Product	Yield (%)[b]
1				76, 74, 74, 73
2				81
3				79
4				69
5				82
6				59
7				65
8				63

(*Continued*)

Table 2
(*Continued*)

Entry	Electron-rich olefins	Anilines	Product	Yield (%)[b]
9				65
10				73

[a] The reaction condition: Hf(NPf)$_4$ (0.041 g, 0.01 mmol), benzaldehyde (0.133 g, 1.2 mmol), aniline (1.2 mmol) and electron-rich olefins (1 mmol), DCE (2 mL) and perfluorodecalin ($C_{10}F_{18}$, *cis* and *trans*-mixture, 2 mL), 80°C, 24 h; DDQ, 0.454 g, 2 mmol.
[b] Isolated yields base on the starting alcohol.

1.2 mmol), and allyltriisopropylsilane (0.198 g, 1 mmol) in the presence of Hf(NPf)$_4$ (0.041 g, 0.01 mmol) in DCE (2 mL) and perfluorodecalin($C_{10}F_{18}$, *cis* and *trans*-mixture, 2 mL). The mixture was stirred at 80°C for 24 h, then the mixture was cooled to ambient temperature, followed by addition of DDQ (0.454 g, 2 mmol), and the reaction mixture was stirred in the same temperature for 10 min. Then, the fluorous layer on the bottom was separated for the next reaction. The reaction mixture (organic phase) was filtered through a short pad of celite. The organic layer was added saturated aqueous solution of $NaHCO_3$, and the aqueous phase was extracted twice with $CHCl_3$. Combined organic layers were washed with saturated aqueous solution of $NaHCO_3$, dried over MgSO4, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography on silica gel column to afford the product (eluent: CH_2Cl_2/MeOH = 90/10). Selected data: 6-Trifluoromethyl-4-(triisopropylsilyl)methyl-2-phenylquinoline, colorless solid; mp 103–105°C; 1H NMR(500 MHz, CDCl3) $\delta = 1.10$ (d, $J = 10.5$ Hz, 18 H), 1.19–1.12 (m, 3H), 2.75 (s, 2H), 7.46–8.22 (m, 8H), 8.37 (s, 1H). MS (EI) m/z 444 (*M*+).

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Dimethylformamide Dimethyl Acetal as a Building Block in Heterocyclic Synthesis

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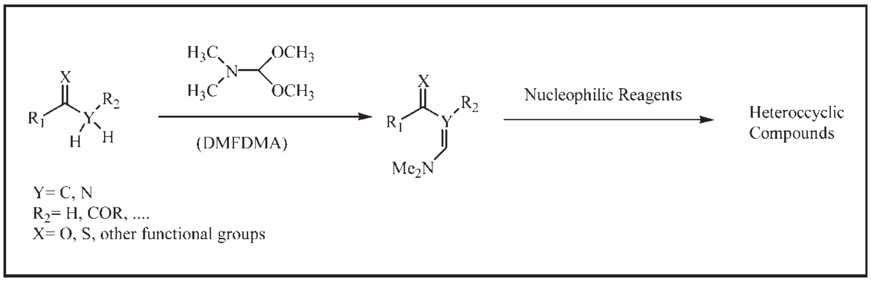

This review focuses on the use of dimethylformamide dimethyl acetal in the preparation of heterocyclic compounds *via* formylation of active methylene groups, methyl groups to give enamines, and formylation of amino groups to give amidines. These compounds are found to be useful intermediates in the formation and modification of heterocyclic compounds.

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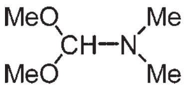
Contents

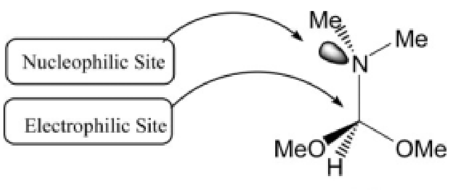
1. INTRODUCTION

N,*N*-dimethylformamide dimethyl acetal (DMFDMA) (**1**) is also called 1,1-dimethoxy-*N*,*N*-dimethylmethylamine and 1,1-dimethoxytrimethylamine. The molecular formula $(CH_3)_2NCH(OCH_3)_2$ and molecular weight 119.16. The Chemical Abstract Number is 4637-24-5.



(**1**)

DMFDMA (**1**) is a very important reagent in organic synthesis because of its higher reactivity. The DMFDMA molecule possesses a carbon atom attached to three electron withdrawing groups (2MeO and NMe_2) such that the carbon atom carries partial positive charge. While the nitrogen atom is attached to two methyl groups, the partially positive carbon atom, and carries a lone pair of electrons so that it ‘‘looks’’ like methyl amine. Therefore, DMFDMA carries two sites of reactivity, an electrophilic site and a nucleophilic site, respectively.



(**1**)

The main application of DMFDMA has been not only for functional group transformations but it may also be regarded as a one-carbon synthon in construction of the carbon skeletons.

Literatures referenced [1–10] highlight the methods of preparation and the major classes of reactions in which formamide acetals have been reported.

It has been found that reactions involving DMFDMA can be divided into two main categories, namely, methylation and formylation. DMFDMA acts as methylating agent [11,12] so that it has been used in the synthesis of methyl esters from acids, methyl ethers and thioethers from phenols and aromatic or heterocyclic thiols, and the methylation of active methines as shown in Scheme 1.

DMFDMA acts as formylating agent, so that it has been used in the synthesis of enamines from active methylenes and active methyl groups, and amidines from amines and amides or thioamide groups [12] as shown in Scheme 2.

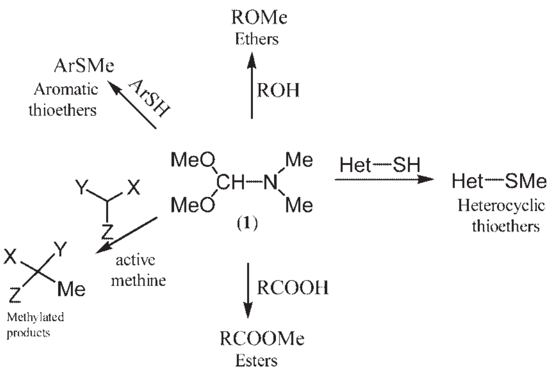
DMFDMA can also be used for cyclization of two functional groups to give heterocyclic compounds [11].

We will concentrate our review on the use of DMFDMA (**1**) for the preparation of heterocyclic compounds.

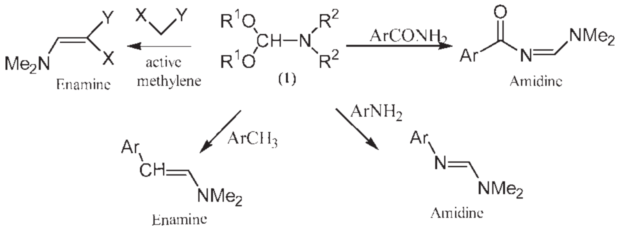
2. PREPARATION OF HETEROCYCLIC COMPOUNDS THROUGH THE FORMYLATION OF THE METHYLENE GROUP USING DMFDMA

2.1. Methylene of ethyl group. 4-Halopropiophenone (**2a–c**) condensed with DMFDMA to give the corresponding enamines (**3a–c**). 2,6-Bis(4-bromophenyl)-5-methylpyrimidine (**4**) was obtained by treatment of compound (**3a**) with *p*-bromobenzamidine. Compounds (**3a–c**) were subsequently treated with (4-sulfamoylphenyl)-hydrazine hydrochloride to provide pyrazoles (**5**), as in Scheme 3 [13,14]. The enamines (**3a–c**) are easily converted to the chloropropiniminium salt by the reaction with phosphorous oxychloride in dichloromethane which in turn is converted to the 2,3,4-trisubstituted pyrrole (**5′**) by condensation with ethyl *N*-methylglycinate in the presence of sodium hydride and DMF [15].

Scheme 1



Scheme 2



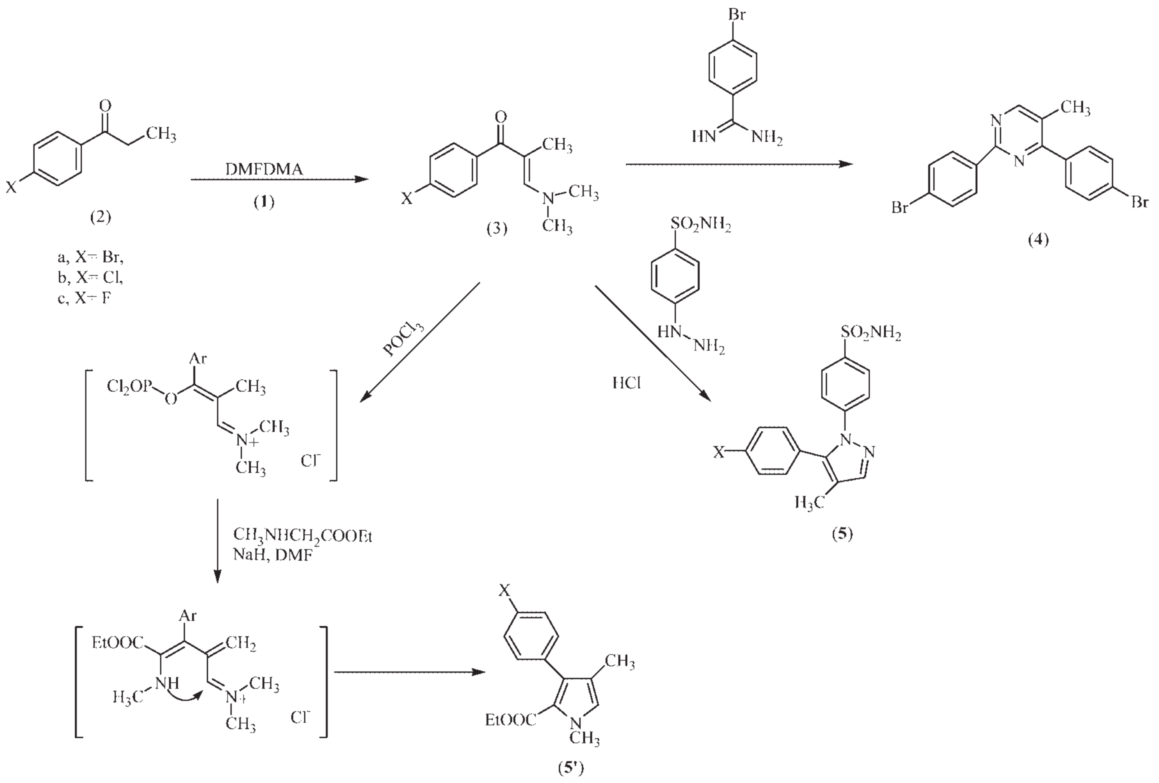
2.2. Active methylene group. DMFDMA was condensed with carbonyl compounds (**6**) yielding the corresponding enaminone (**7**), which reacted with cyanothioacetamide to yield polyfunctionaly substituted pyridines (**8**) [16–18]. Also the treatment of enaminone (**7**) with malononitrile dimer afforded 1,6-naphthyridine derivatives (**9**) [19], whereas treatment of the enaminones (**7**) with thiourea in the presence of sodium ethoxide affoded the corresponding 4,5-disubstituted pyrimidine-2-thiones (**10**) [20]. Although the treatment of enaminones (**7**) with hydrazine hydrate, phenyl, or alkyllhydrazine and hydroxylamine afforded 3,4-disubstituted azoles (**11**) as in Scheme 4 [21,22].

Consequently α-aryl or α-benzoylacetonitriles (**12a–c**) condensed with DMFDMA to afford enaminonitrile (**13a–c**). The reaction of enaminonitrile (**13a**) with 5-aminopyrazole afforded (**14**). Ring closure of enaminonitriles (**13a–c**) with hydrazine hydrate, and its derivatives and hydroxylamine in ethanol gave compounds (**15**) [23,24]. Although the reaction of enamine (**13c**) with hydrazine derivatives in the presence of HCl afforded 1-substituted-3-cyano-5-arylpyrazoles (**16**) as in Scheme 5 [14,25–27].

Also imidazo[1,2-*a*]pyridine derivative (**19**) could be obtained *via* reaction of (**17**) with DMFDMA. The reaction proceeds *via* the intermediate enamine derivative (**18**) as in Scheme 6 [28].

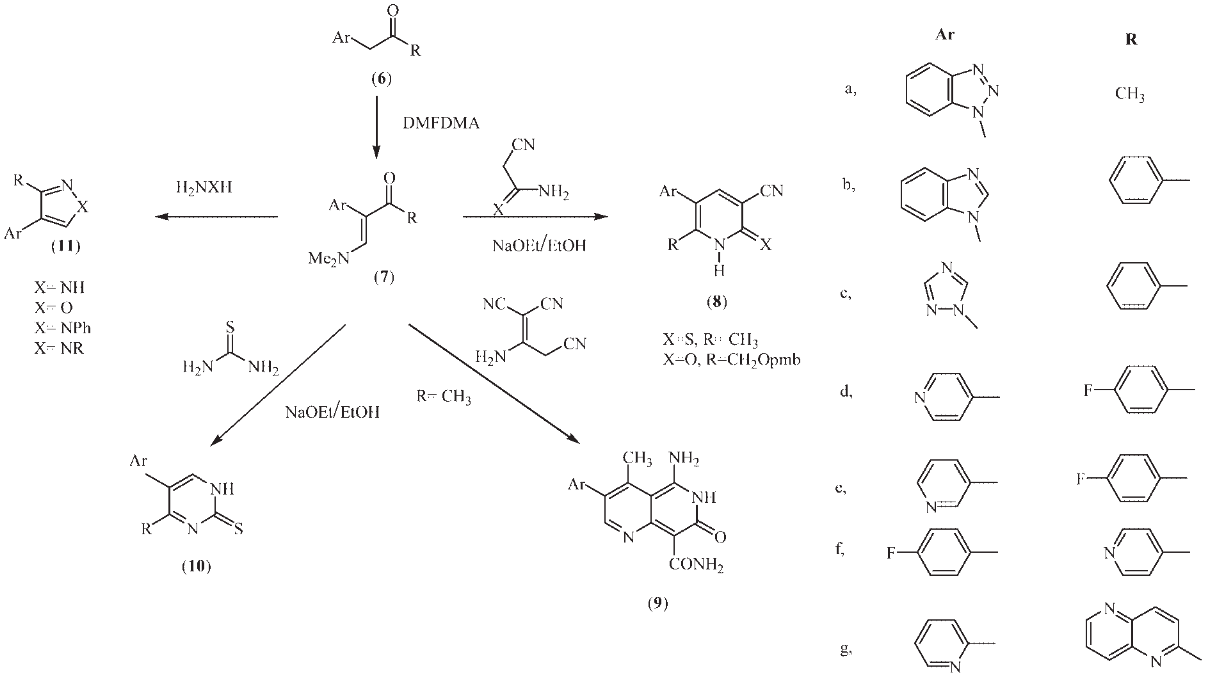
α-Phthaloylaminoacetophenone derivatives (**21a–c**) were obtained by the reaction of α-bromo- or α-chloroacetophenones (**20**) with phthalimide potassium salt in DMF. Reaction of (**21**) with 1.2 equivalents of DMFDMA gave the enamines (**22**), which on treatment with excess and one equivalent of hydrazine derivatives, produce (**23**) and (**24**), respectively, as in Scheme 7 [29,30].

Scheme 3

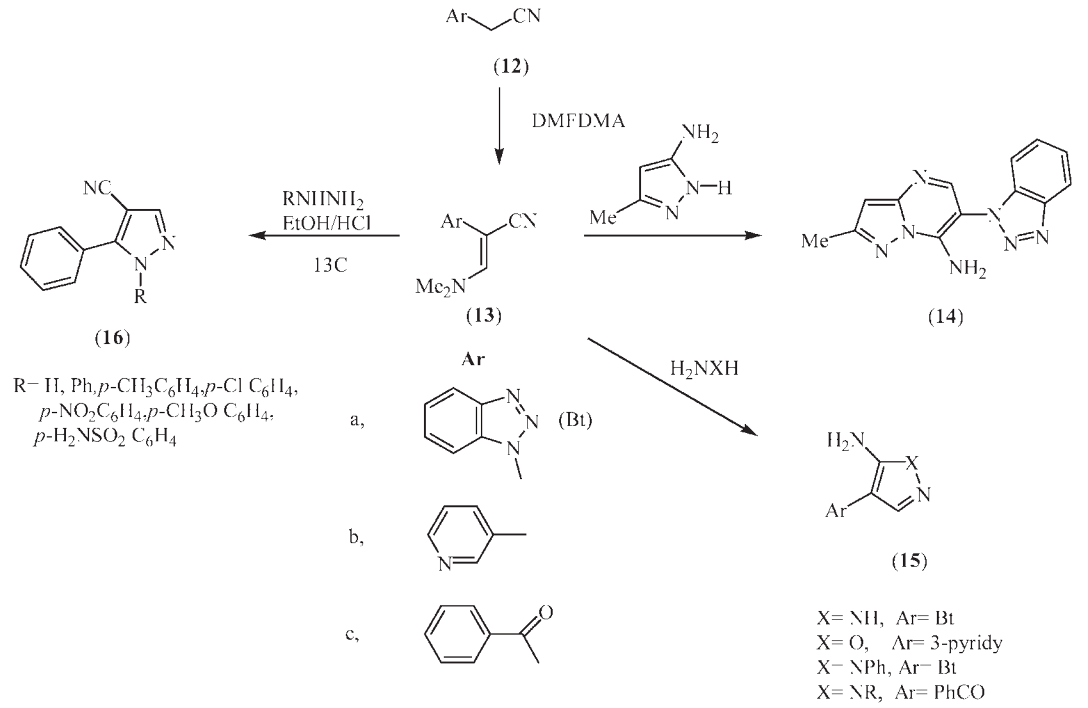


Refluxing of compound (**25**) with DMFDMA provided the enaminones (**26**), which were directly allowed to react with binucleophiles such as substituted guanidine and amino azoles (3-aminopyrazoles, 3-amino-1,2,4-triazole) to give the desired compounds (**27a,b**) and (**28a–d**), respectively, as in Scheme 8 [31,32].

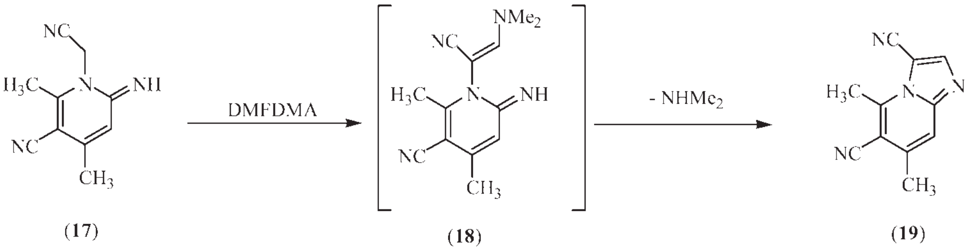
Scheme 4



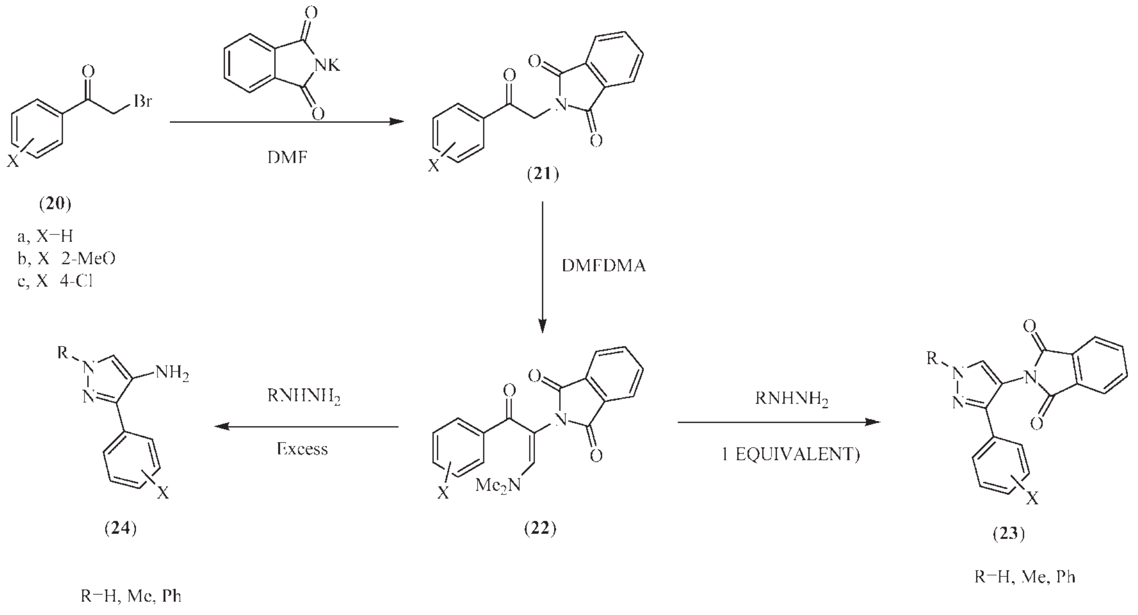
Scheme 5



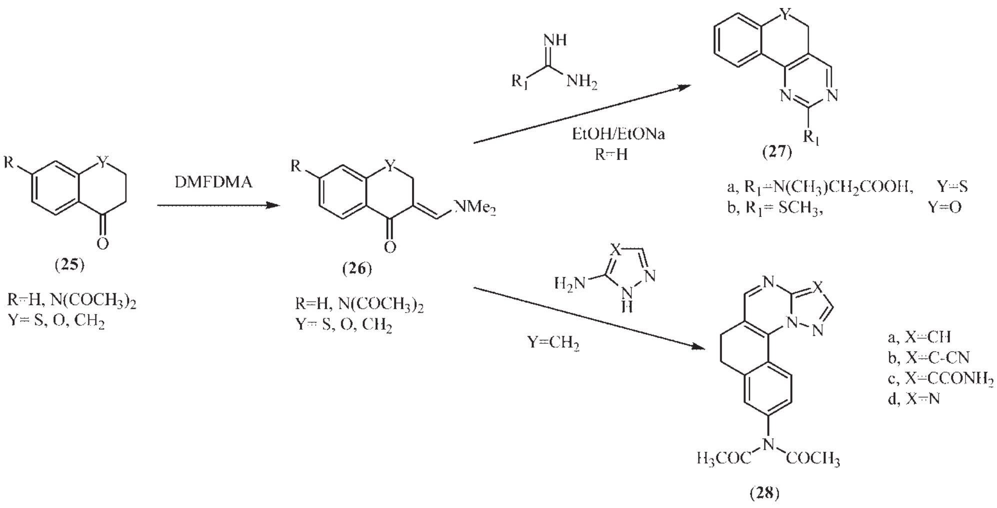
Scheme 6



Scheme 7



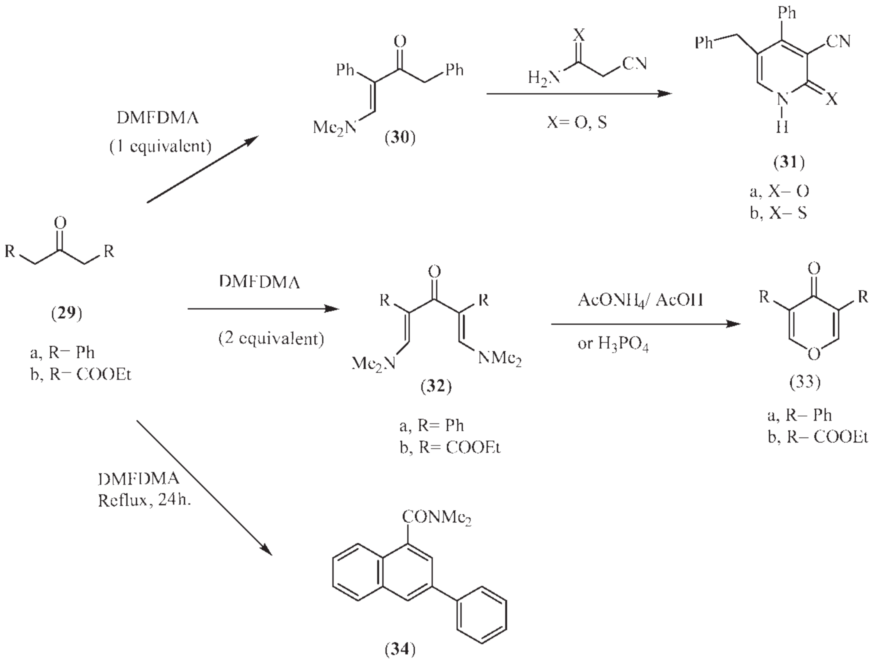
Scheme 8



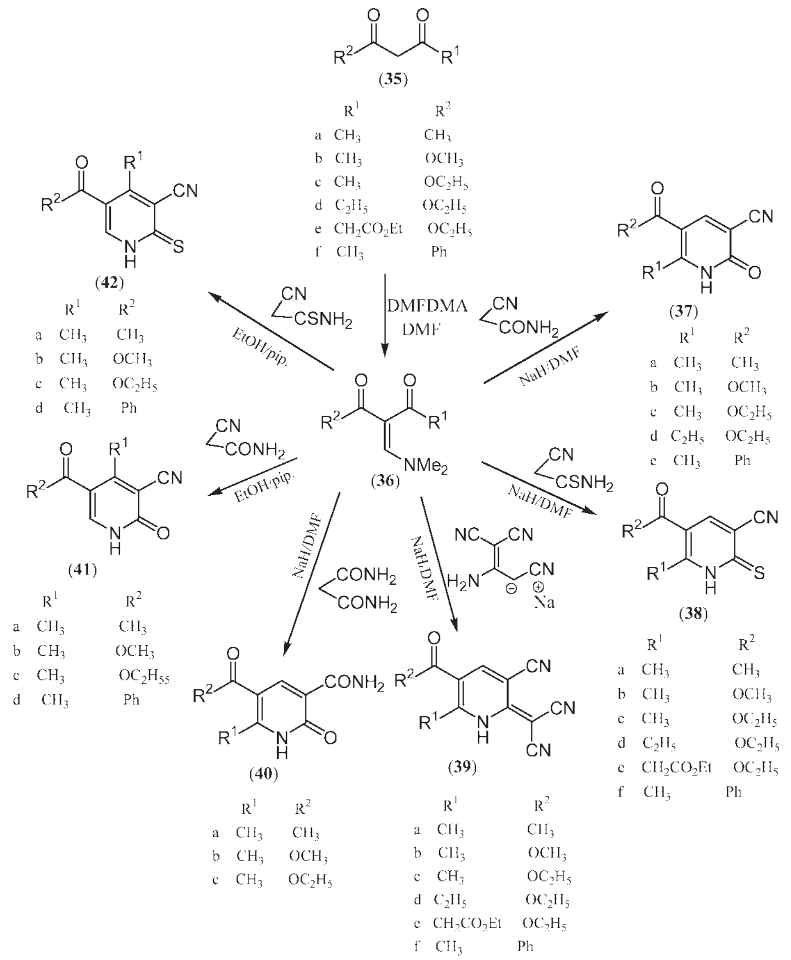
1,3-Diphenylacetone (**29a**) reacted with an equimolecular amount of DMFDMA to give the enaminone (**30**) which condensed with cyanoacetamide and with cyanothioacetamide to yield 2-oxo- and 2-thioxo-pyridine-3-carbonitrile derivatives (**31**). The 1,3-disubstituted acetones (**29a,b**) reacted with two molar equivalents of DMFDMA to give the dienaminones (**32**) which in turn reacted with an acetic acid ammonium acetate mixture or phosphoric acid to afford 3,5-disubstituted-pyrane-4-ones (**33a,b**) [33,34]. A mixture of 1,3-diphenylacetone and DMFDMA were left under reflux for 24 h to give the dimethylamide (**34**) as in Scheme 9 [35].

Abu-Shanab et al. [36–39] reported that, the reaction of 1,3-dicarbonyl compounds (**35a–f**) with DMFDMA in anhydrous DMF afforded the corresponding enaminones (**36a–f**) which reacted directly with the following nucleophiles using sodium hydride as a base in anhydrous DMF. Cyanoacetamide afforded 5,6-disubstituted-3-cyanopyridine-2(1*H*)-ones (**37a–d,f**). Cyanothioacetamide afforded 5,6-disubstituted-3-cyanopyridine-2(1*H*)-thiones (**38a–f**). Anion of malononitrile dimmer afforded 5,6-disubstituted-3-cyano-2-(dicyanomethylidene)-1,2-dihydropyridines (**39a–f**). Malonamide afforded 5,6-disubstituted-3-carboxamidopyridine-2(1*H*)-ones (**40a–c**). On the

Scheme 9

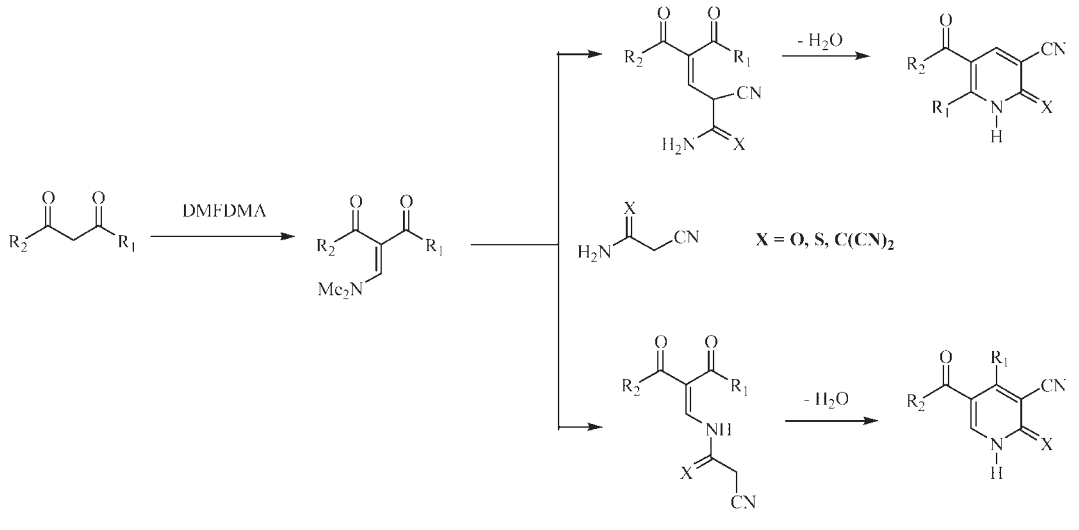


Scheme 10

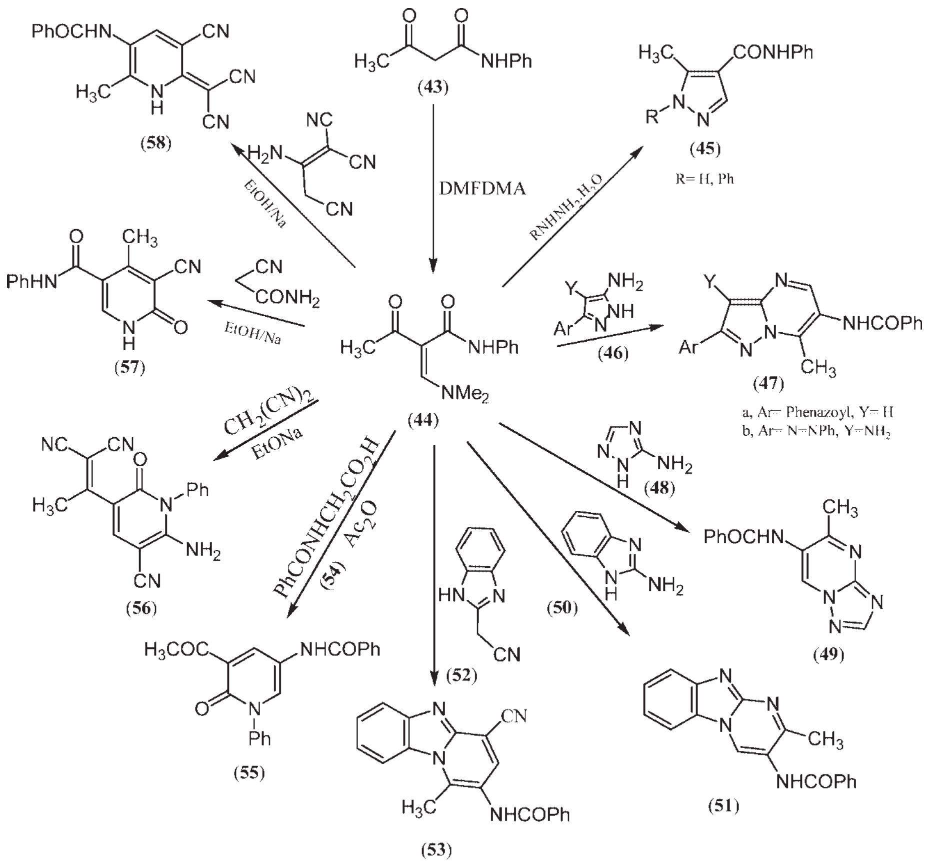


other hand, reactions analogous to those reported earlier, but using ethanol as a solvent and piperidine as a base, enaminones (**36**) reacted with the following nucleophiles: Cyanoacetamide to give 4,5-disubstituted-3-carboxamidopyridine-2(1*H*)-ones (**41a–c**). Cyanothioacetamide to give 4,5-disubstituted-3-carboxamidopyridine-2(1*H*)-thiones (**42a–d**) as in Scheme 10.

The structure of these compounds has been confirmed by X-ray crystallography [36,37]. The mechanism for the formation of the above products is as shown in the following.



Scheme 11



Also the reaction of DMFDMA with acetoacetanilide (**43**) gave enamine (**44**). Treatment of **44** with hydrazine hydrate and phenylhydrazine afforded pyrazoles (**45**). Pyrazolo[1,5-*a*]pyrimidines (**47**) were isolated when enamine (**44**) was reacted with pyrazoles (**46**). Enamine (**44**) reacted with 1,2,4-triazole (**48**) to produce triazolo[1,5-*a*]pyrimidine (**49**). 2-Aminobenzimidazole (**50**) reacted with (**44**) to give the pyrimido[1,2-*a*]benzimidazole (**51**). The reaction of enamine (**44**) with compound (**52**) afforded (**53**) and with hippuric acid (**54**) afforded the pyridine (**55**). Also the reaction of (**44**) with malononitrile, cyanoacetamide, and malononitrile dimer afforded (**56**), (**57**), and (**58**), respectively, as shown in Scheme 11 [40–47].

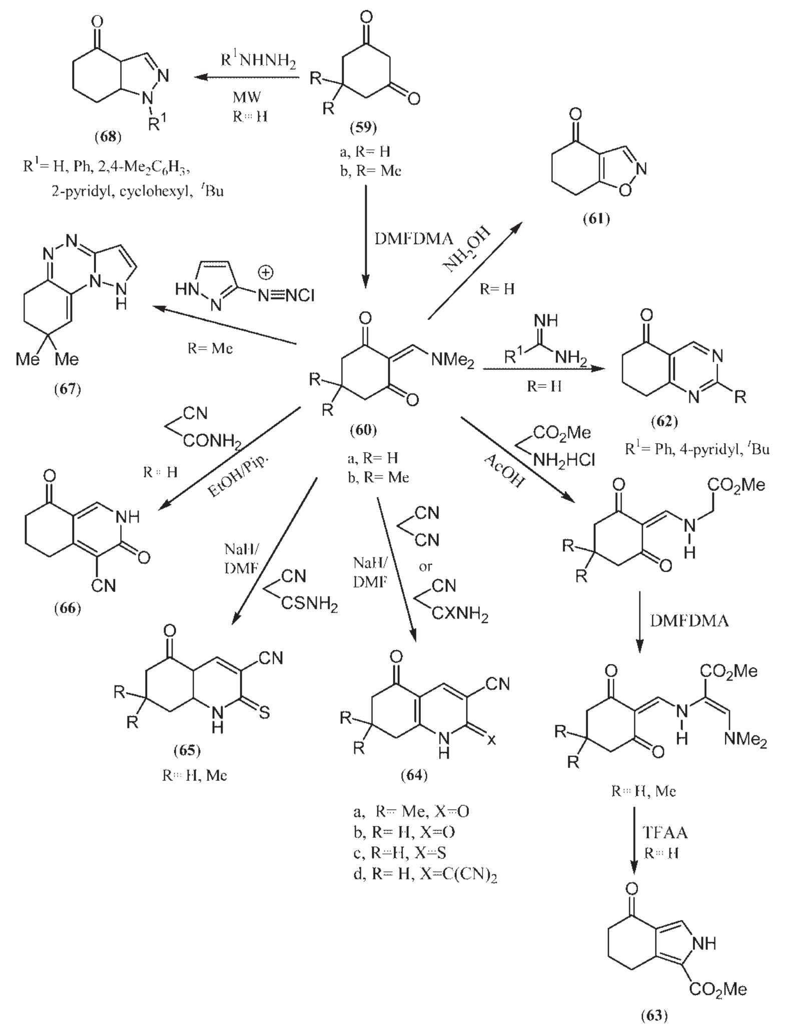
Further reactions for the preparation of heterocyclic compounds using DMFDMA are the condensation of 1,3-cyclohexanedione (**59a**) and 5,5-dimethyl-1,3-cyclohexanedione (**59b**) with DMFDMA to give the corresponding enaminones (**60a,b**). These compounds are also potentially valuable for the preparation of different types of heterocycles (**61–67**) as outlined in Scheme 12 [36,37,48–50]. Microwave irradiation of 1,3-cyclohexanedione (**59a**) with hydrazine hydrate and its derivatives afforded the corresponding pyrazole derivatives (**68**) [51]. The structure of these compounds has been confirmed by X-ray crystallography [36,37].

Diethyl ester (**69**) when refluxed with DMFDMA gave enamine (**70**), which was refluxed in DMF and ammonium acetate as a source of ammonia, the β-carboline (**71**) isolated Scheme 13 [52].

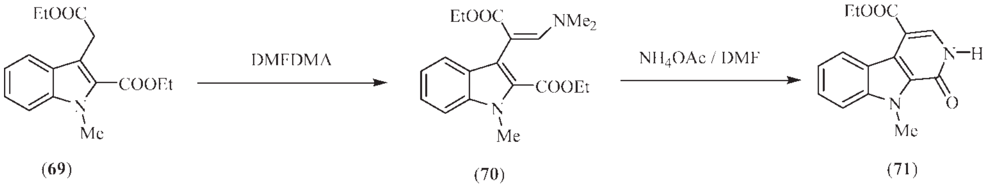
Enamines (**73a–c**) was obtained from (**72a–c**) with DMFDMA and converted directly to quinolinecarboxylic acid esters (**74**) by treatment with the requisite amines. Compounds (**75**) were prepared by reaction of (**73b**) with hydrogen sulfide in ethanol [53–55]. Also compound (**73a**) reacted with aryl hydrazine provided pyrazole (**76**) as shown in Scheme 14 [56,57].

Treatment of compounds (**77**) with excess DMFDMA gave compounds (**78**), which was cyclized to pyrrole ring (**79**) under various condition, EtOH in the presence of HCl (method A), AcOH (method B), AcOH and Ac_2O (method C), and $(CF_3CO)_2O$ (method D) as shown in Scheme 15 [58–60].

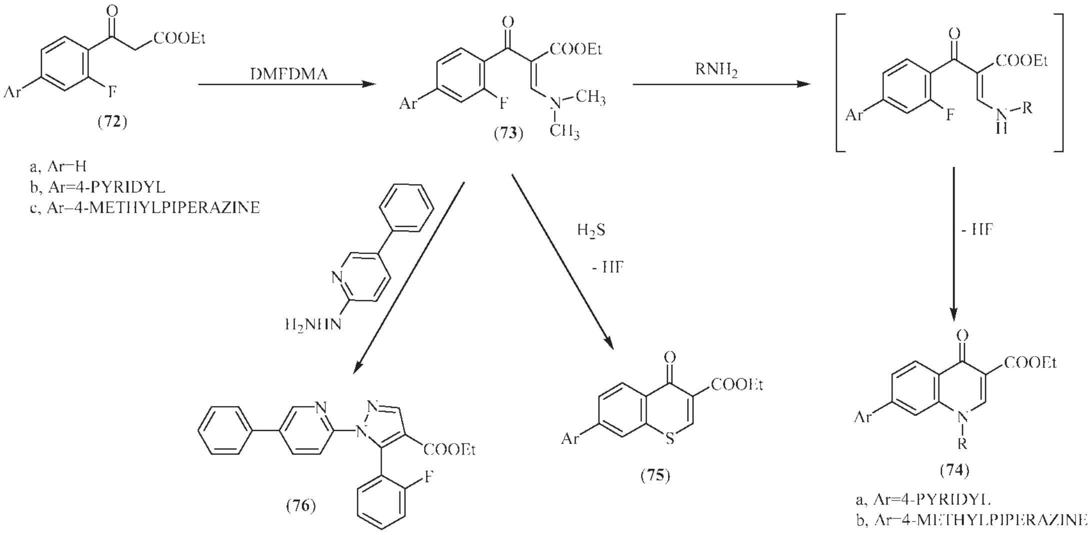
Scheme 12



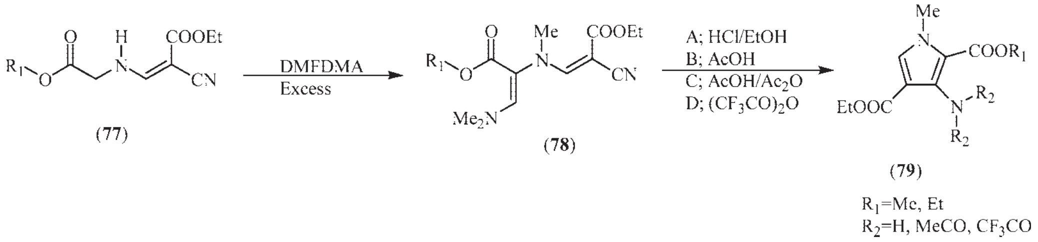
Scheme 13



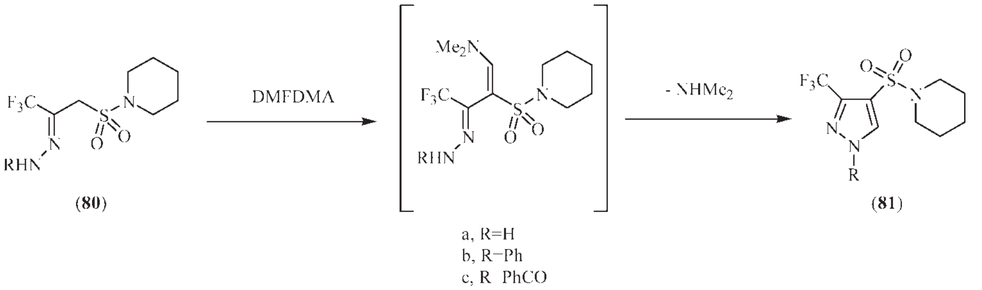
Scheme 14



Scheme 15



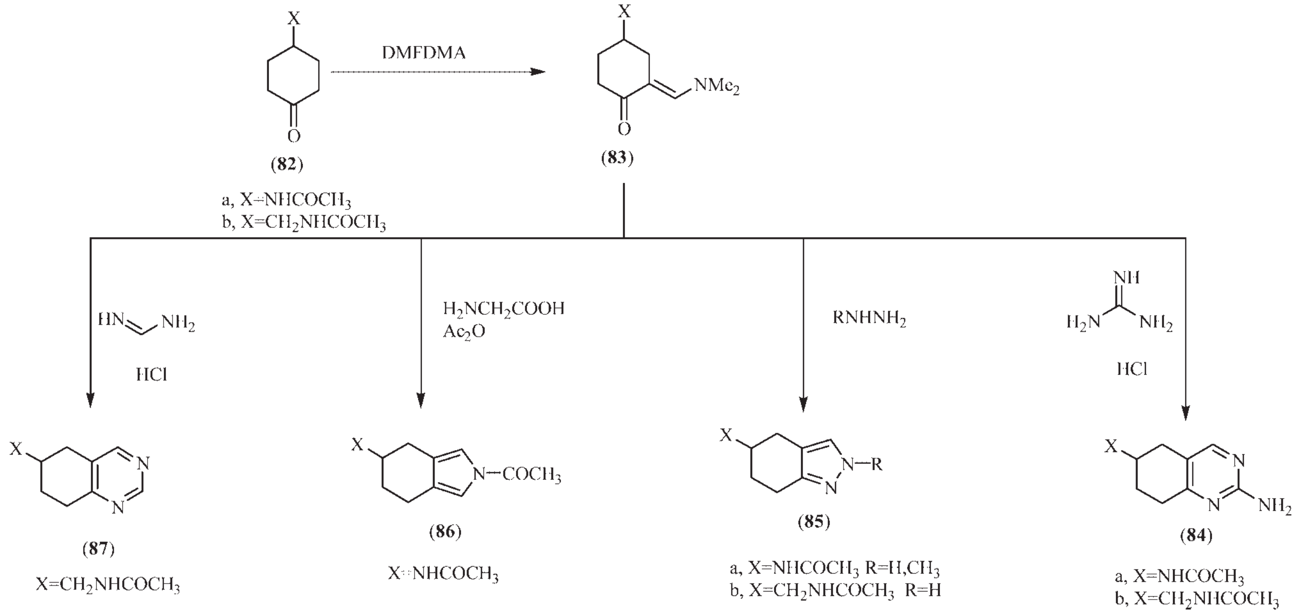
The reaction of hydrazones (**80**) with DMFDMA afforded 3-trifluoromethylpyrazole-4-sulfonamides (**81**) [61].



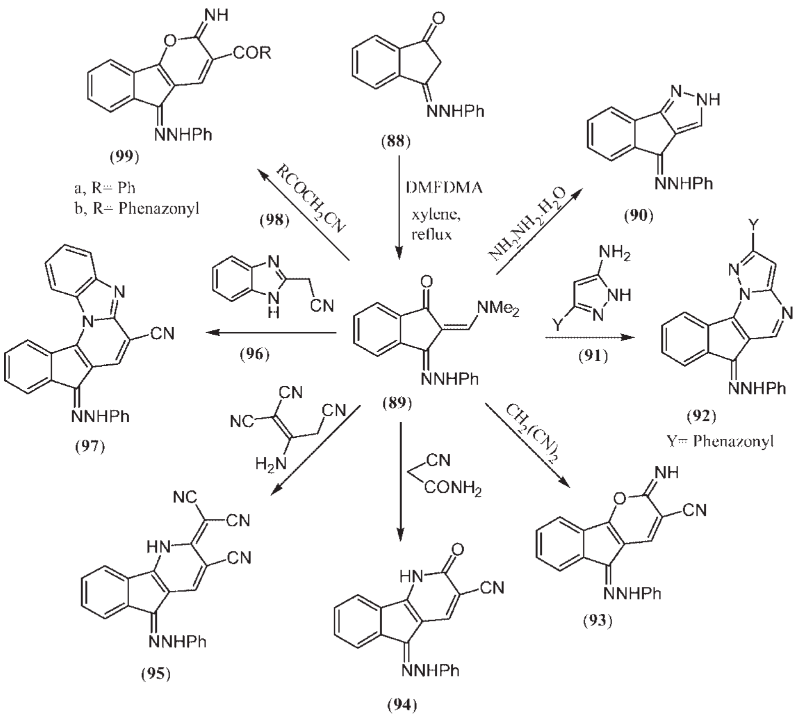
Condensation of 4-substituted cyclohexanones (**82a,b**) with DMFDMA provided enamino ketones (**83a,b**), which reacted with guanidine hydrochloride, hydrazine hydrate, *N*-methylhdrazine, glycine, and formamidine hydrochloride afforded heterocyclic compounds (**84a,b**), (**85a,b**), (**86**), and (**87**), respectively, as shown in Scheme 16 [18,62–67].

Also 3-(phenylhydrazono)indan-1-one (**88**) when reacted with DMFDMA gave the enaminone (**89**), which reacted with hydrazine hydrate to yield the indenopyrazole derivative (**90**). Treatment of (**89**) with pyrazole (**91**) gave the indenofluorene derivative (**92**). The reaction of compound (**89**) with malononitrile gave indenopyran derivative (**93**). When (**89**) reacts with cyanoacetamide, the

Scheme 16



Scheme 17

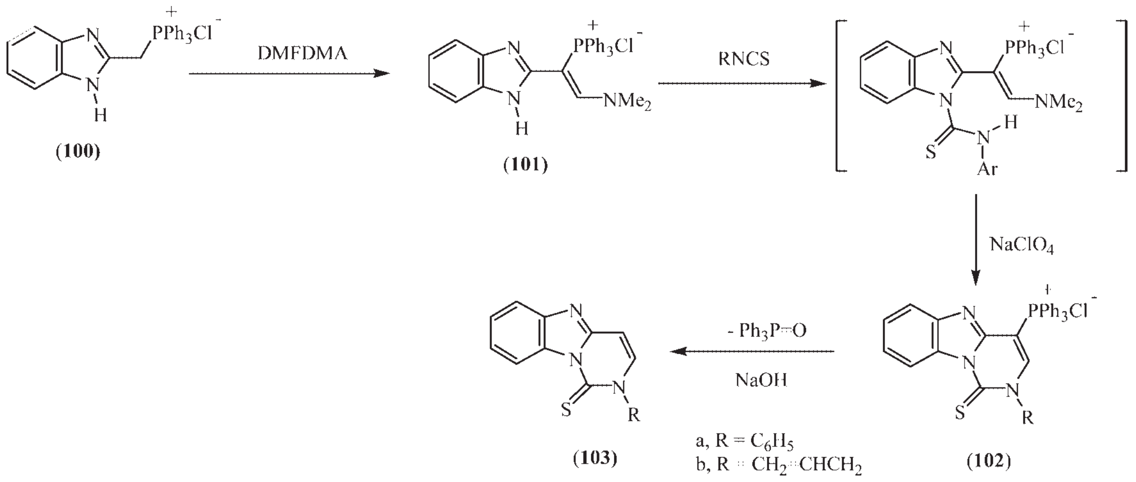


indenopyridine derivative (**94**) was formed. Also, compound (**89**) was reacted with malononitrile dimer to afford the trinitrile (**95**). Enaminone (**89**) reacted with compound (**96**) to afford the diazaindenofluorene derivative (**97**). The ω-cyano compounds (**98**) when reacted with (**89**) afforded compounds (**99a,b**) as shown in Scheme 17 [68].

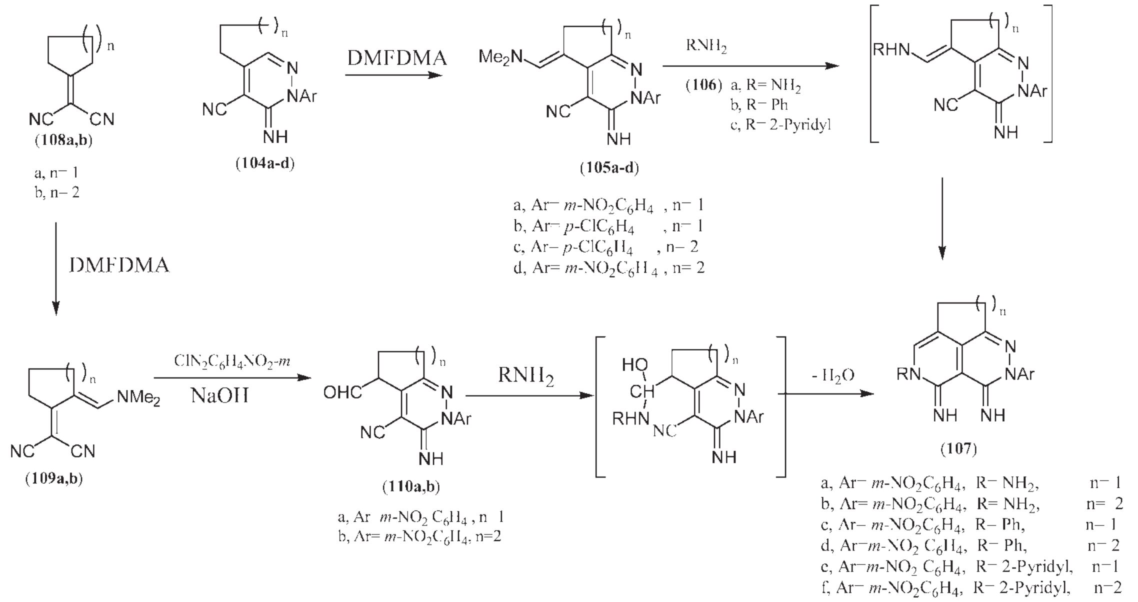
Treatment of the available phosphonium salt (**100**) with DMFDMA gives 2-vinylbenzimidazole derivatives (**101**) which on heating with phenyl or allyl isothiocyanate and sodium perchlorate afforded compounds (**102a,b**) followed by treatment with sodium hydroxide resulting thioxopyrimido[3,4-a]benzimidazoles (**103a,b**) as shown in Scheme 18 [69–72].

DMFDMA reacts with (**104a–d**) to give enamines (**105a–d**), which on treatment with hydrazine hydrate (**106a**) and aromatic amines (**106b,c**) gives pyridopyridazine derivatives (**107a–f**). The latter (**107a,b**) can also be prepared by treatment of (**108a,b**) with DMFDMA to give the corresponding enamines (**109a,b**) followed by coupling with diazonium salt of *m*-nitroaniline in sodium hydroxide to give the corresponding aldehyde derivatives (**110a,b**) followed by treatment with hydrazine hydrate and aromatic amines (Scheme 19) [73].

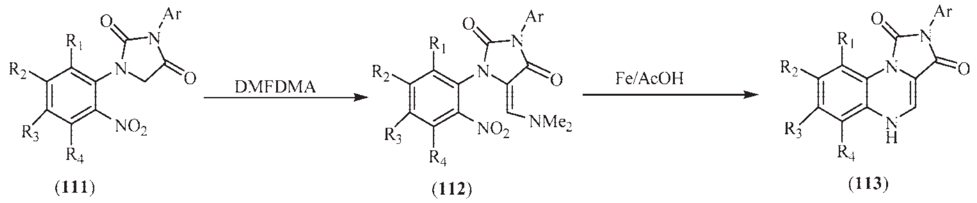
Scheme 18



Scheme 19

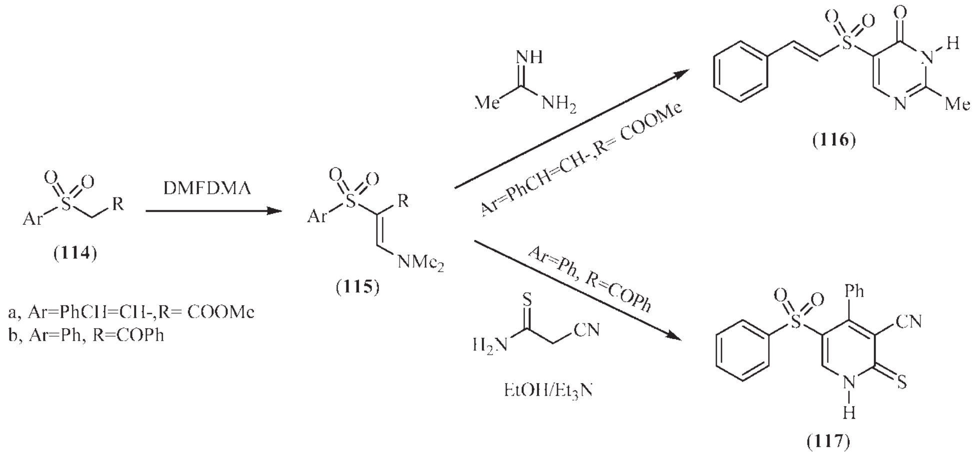


Imidazoquinoxalines (**113**) are biologically useful compounds, which can be prepared by the reaction of (**111**) with DMFDMA to give (**112**) followed by reductive cyclization using powdered Fe in AcOH [74].

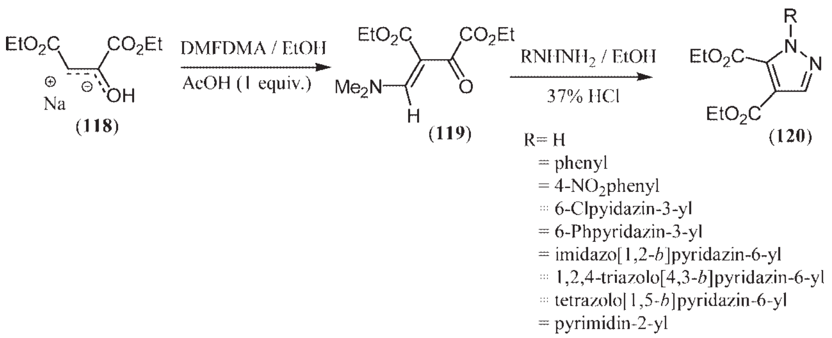


The treatment of compounds (**114a,b**) with DMFDMA afforded the corresponding arylsulfonylenamines (**115a,b**). Compound **115a** reacted with acetamidine to yield 5-styrylsulfonylpyrimidinone (**116**) [75]. Also compound **115b** reacted with cyanothioacetamide to give polysubstituted pyridine-2(1*H*)-thione in a good yield as shown in Scheme 20 [76].

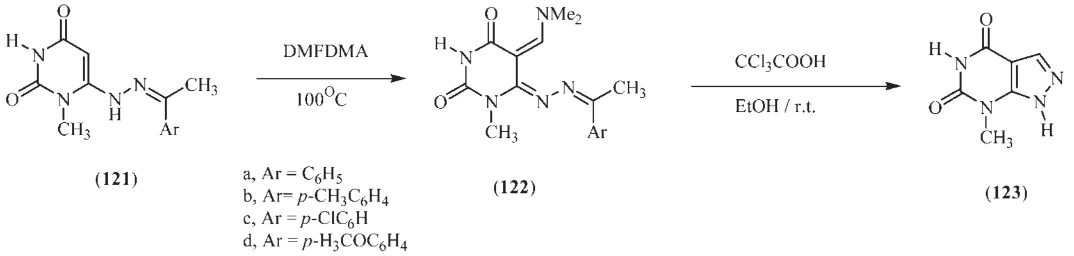
Scheme 20



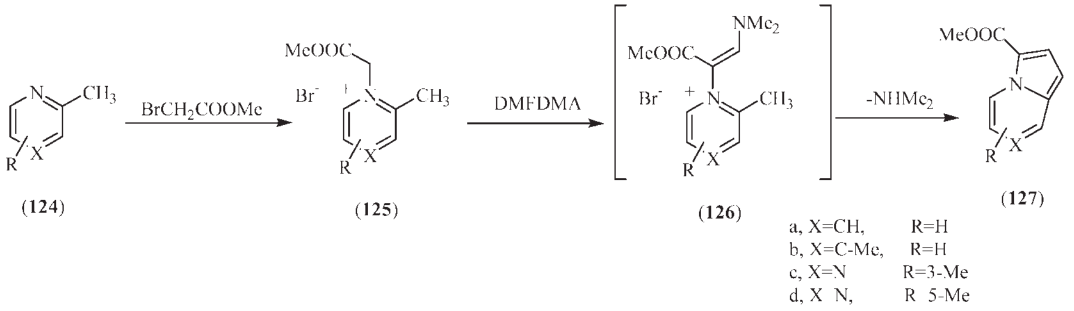
Enaminone (**119**) was prepared from the sodium salt of diethyl 2-oxosuccinate (**118**) by treatment with DMFDMA. Acid-catalyzed cyclocondensations of compound (**119**) were performed with hydrazine derivatives to give the corresponding 1-substituted diethyl 1*H*-pyrazole-4,5-dicarboxylates (**120**) [77].



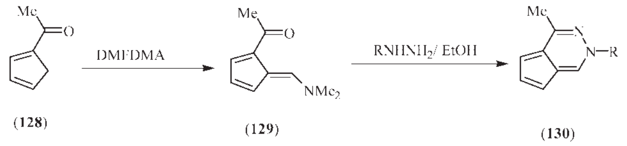
Heating of 6-(α-methylbenzylidenhydrazino)-1-methyluracils (**121a–d**) with an excess of DMFDMA at 100°C for 1 h led to the formation of enamines (**122a–d**) in good yields. Treatment of the products with trichloroacetic and hydrochloric acids (ethanol, room temperature, 15 min) gave rise to a ring closure with the loss of one mole of acetophenone and dimethylamine, affording 7-methylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*)-dione (**123**) [78].



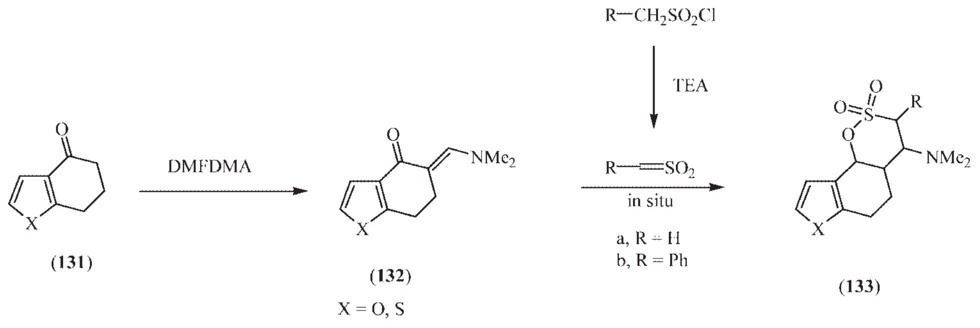
Quaternary salts (**125a–d**), which were prepared from (**124a–d**) and methyl bromoacetate, were treated with DMFDMA to afford fused heterocyclic compounds (**127a–d**) [26].



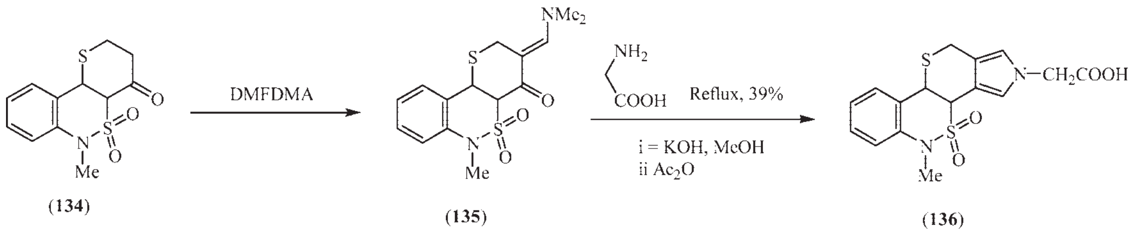
Also when the enamine and carbonyl functions are separated by a carbon, as in compound (**129**), which was prepared from compound (**128**) with DMFDMA, the reaction of (**129**) with a hydrazines gives a fused pyridazine ring, as cyclopenta[*d*]pyridazines (**130**) [79].



Treatment of compound (**131**) with DMFDMA afforded enaminones (**132**). A mixture of methanesulphonyl (or phenyl methylsulphonyl) chloride and triethyl amine produces a sulphene, RCH=SO_2 (R = H, Ph), which cyclizes enaminones (**132**) *in situ* at low temperature to an oxathiin ring (**133**) in high yields [80–85].

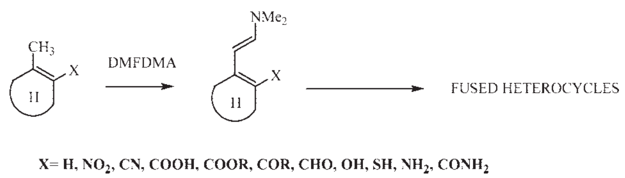


Reaction of (**134**) with DMFDMA afforded 2-keto-enamine (**135**) which reacts with glycine in alkali medium to form a pyrrole ring (**136**) [83].



3. PREPARATION OF HETEROCYCLIC COMPOUNDS THROUGH THE FORMYLATION OF THE METHYL GROUP USING DMFDMA

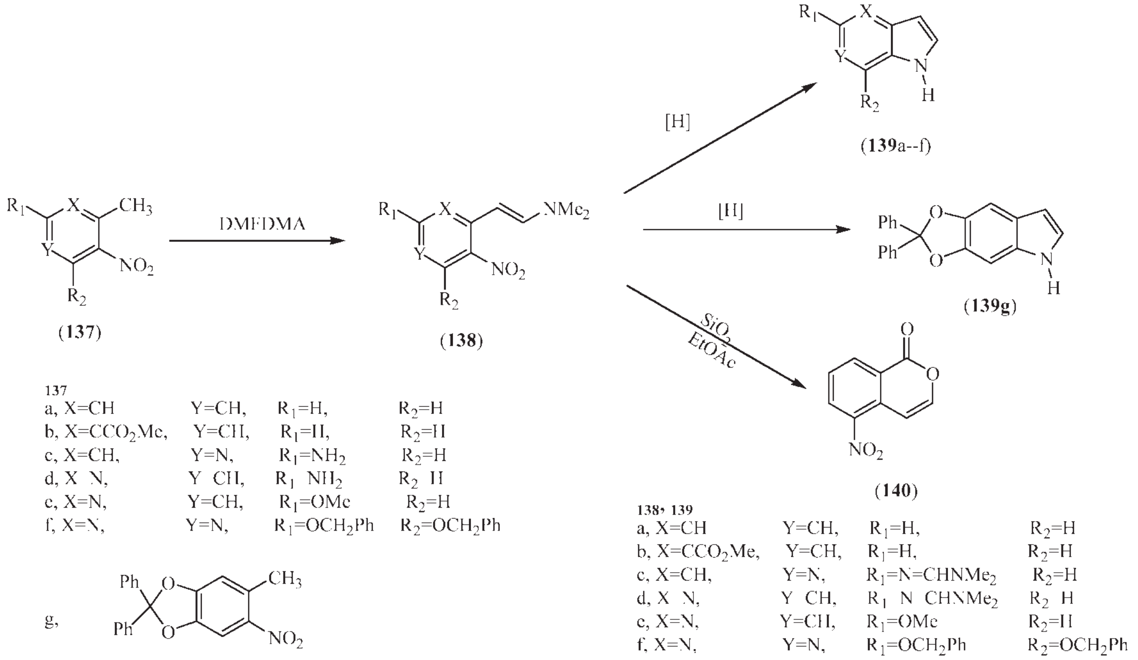
3.1. Ring methyl group. Abu-Shanab et al. reported the cyclization of the methyl group of azine compounds with different functional groups to give fused heterocycles using different organic reagents; DMFDMA is one of them [86].



Microwave irradiation of nitrotoluene (**137a**) with DMFDMA in the presence of anhydrous CuI gave the corresponding enamine (**138a**). Treatment of compounds (**137b–f**) with DMFDMA provided enamine (**138b–f**). Reductive cyclization of enamines (**138a–f**) using H_2/Pd-C or Fe/AcOH or zinc in acetic acid or hydrazine hydrate in the presence of Raney-Ni as a catalyst gave compounds (**139a-f**). Also, treatment of enamine (**138b**) with silica gel provides sufficient acid catalysis to hydrolyze the enamine and cyclises the intermediate enol to the isocoumarine (**140**) as shown in Scheme 21 [4,87–101].

Treatment of pyridazinones (**141a–d**) with DMFDMA in dry DMF afforded (*E*)-dimethylaminoethylenes (**142a–d**) in good yields. Compounds (**142a–c**) reacted with aromatic amines in glacial acetic acid to yield the 2,7-diarylpyrido[3,4-*c*]pyridazinones (**143a–g**). The 1-unsubstituted pyrido[3,4-*c*]pyridazinones (**143h–j**) were also formed on treatment of (**142a–c**) with ammonium acetate in acetic acid. Compound (**142a**) also reacted with 5-methylpyrazol-3-amine (**144**) and with hydrazine hydrate to yield pyrido[3,4-*c*]pyridazinones (**143k,l**), respectively. Refluxing (**142a–c**) in HOAc-HCl afforded carboxylic acids that may be formulated as (**145a–c**) as shown in Scheme 22 [102,103].

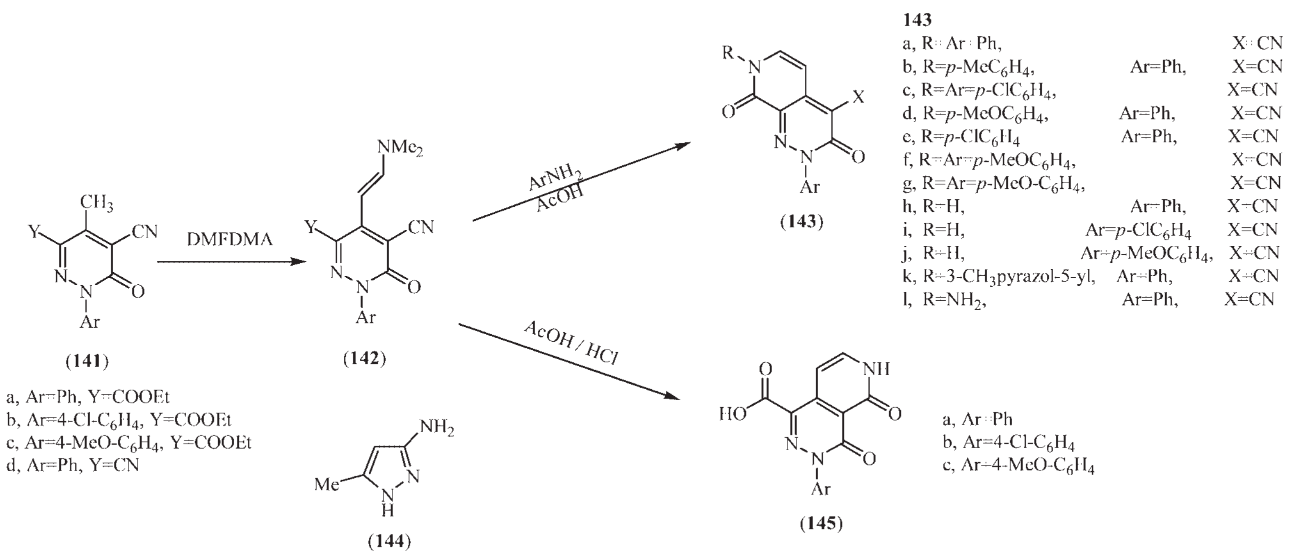
Scheme 21



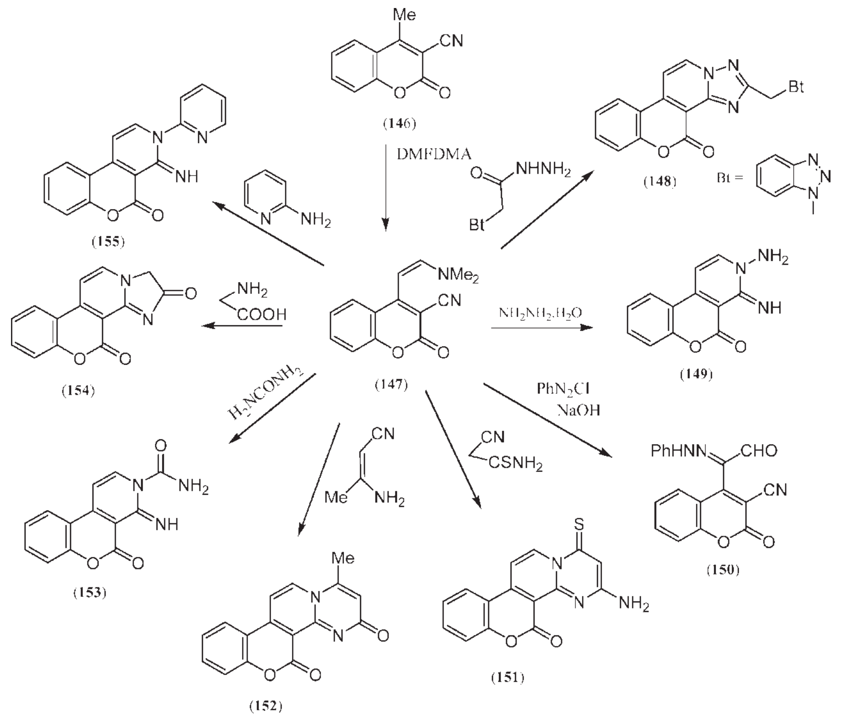
Also the treatment of 3-cyano-4-methylcoumarin (**146**) with DMFDMA in dry xylene afforded the (*E*)-dimethylaminoethylene derivative (**147**). Fusion of enamine (**146**) with benzotriazol-1-yl-acetic acid hydrazide afforded the corresponding [1,2,4]triazolo[1,5-*a*]pyrido[3′,4′-*c*]coumarin (**148**). Reaction of enamine (**147**) with hydrazine hydrate gave compound (**149**). Enamine (**147**) was also coupled with benzenediazonium chloride to afford 2-oxo-4-[2-oxo-1-(phenylhydrazono)-ethyl]-2*H*-chromene-3-carbonitrile (**150**). Treatment of (**147**) with cyanothioacetamide, 3-aminocrotononitrile, urea, glycine, and 2-aminopyridine affords fused heterocyclic compounds (**151–155**), respectively, as shown in Scheme 23 [104–106].

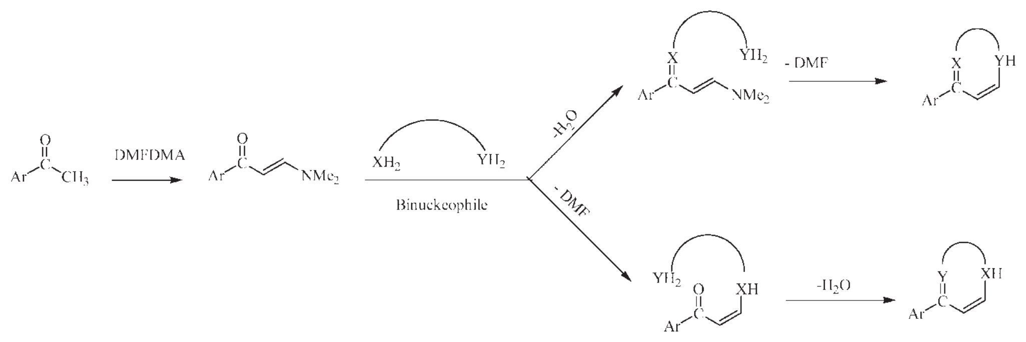
3.2. Methyl of acetyl group. In the acetyl group, the presence of the methyl group beside the carbonyl useful to give heterocyclic compounds using DMFDMA and different binucleophilic reagents. The general mechanism for this reaction is as shown in the following. The products of this reaction depend on the conditions under which the reactions were carried out and the type of the binucleophile used.

Scheme 22



Scheme 23



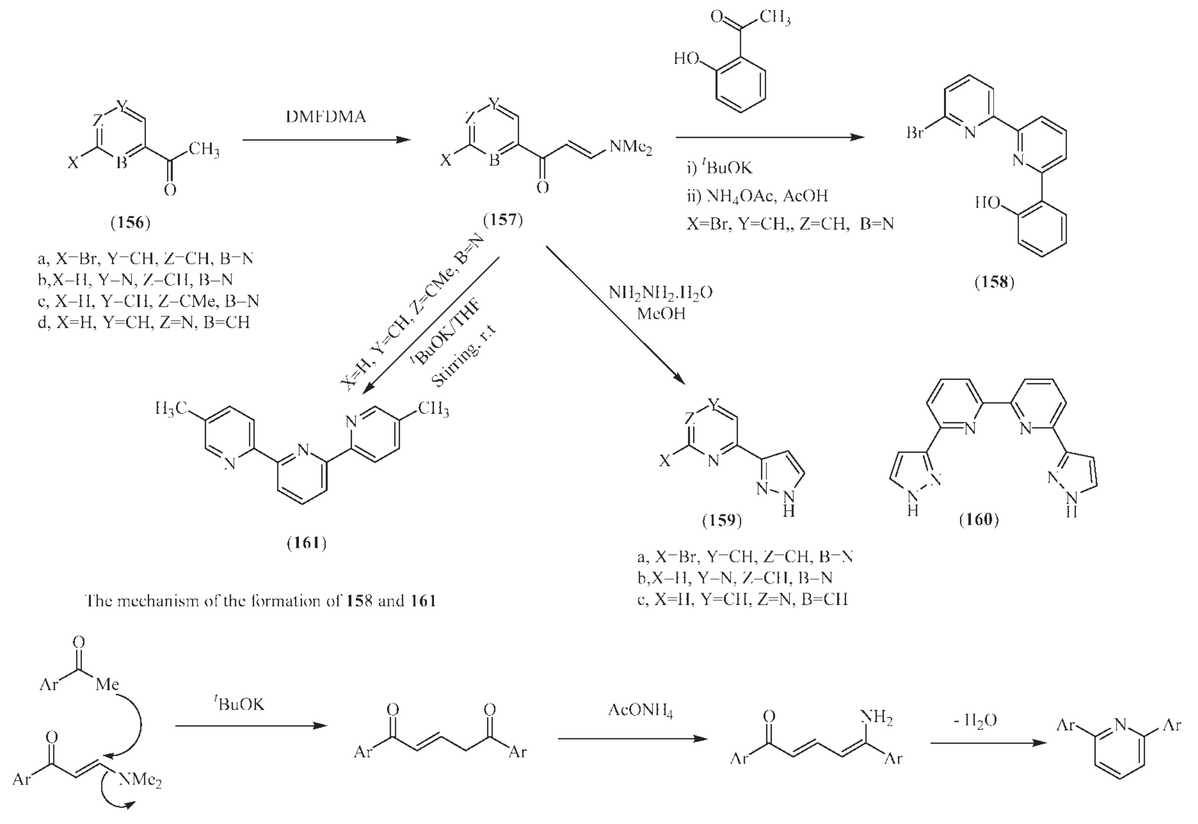


Reaction of acetyl azines (**156a–d**) with DMFDMA gave the corresponding enamines (**157a–d**). Compound (**157a**) reacted with 2-hydroxyacetophenone to afford 2,2′-bipyridine (**158**). When (**157a,b,d**) is reacted with hydrazine hydrate in hot methanol in a Schlenk tube, the pyrazolyl ring (**159a–c**) is formed. Also compound (**160**) is obtained similarly [107,108]. Also the reaction of (**157c**) with (**156c**) using potassium *t*-butoxide as a base gives 5,5’-dimethylterpyridine (**161**) as shown in Scheme 24 [109–112].

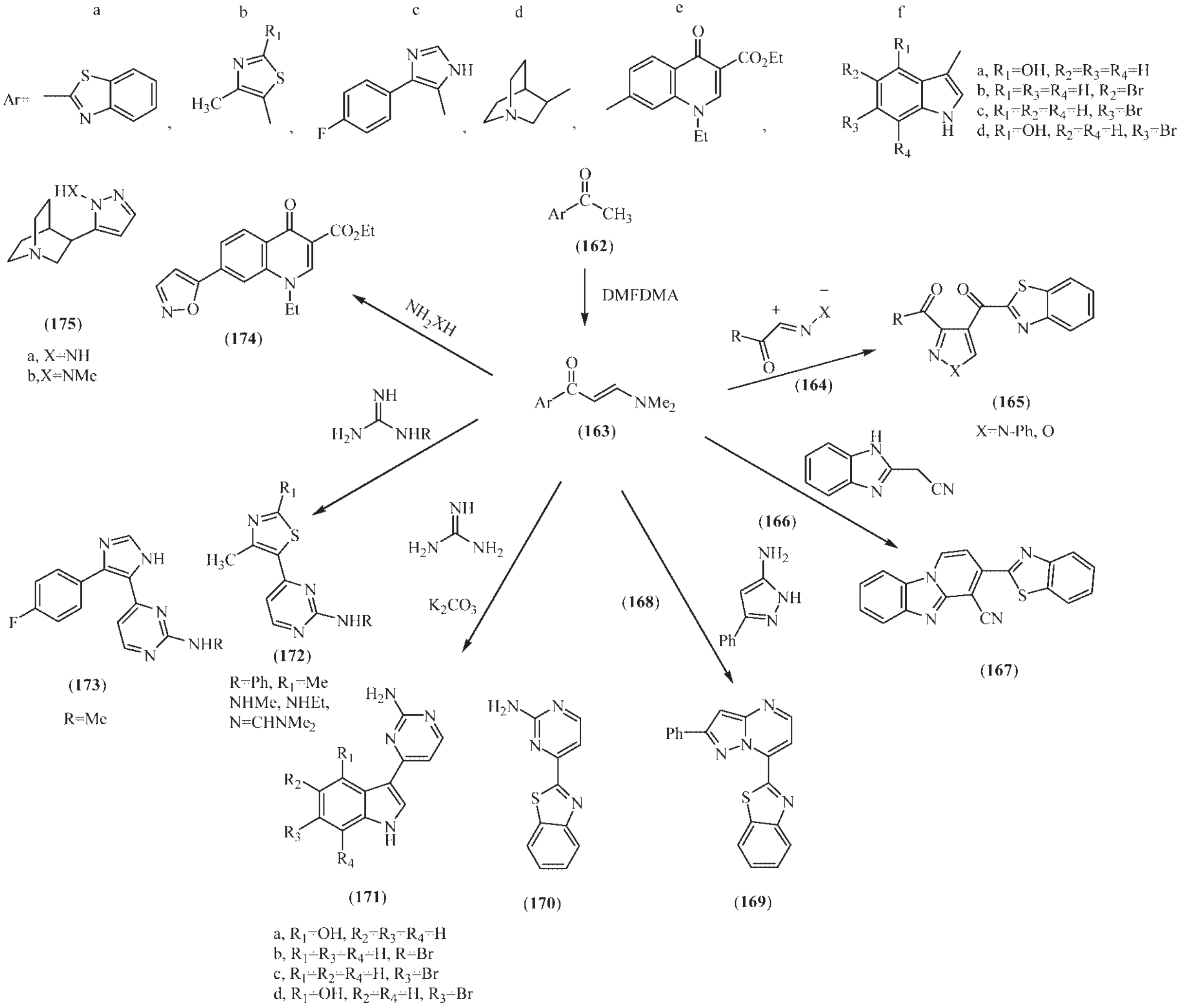
Also the treatment of some heterocyclic acetyl compounds (**162a–f**) with DMFDMA afforded *E*-1-heteroaryl-3-(*N*,*N*-dimethylamino)-2-propen-1-ones (**163a–f**). Cycloaddition of some nitrilimines and nitriles oxides (**164**) with the enaminone (**163a**) gave (**165**). Also the compound (**163a**) reacted with 1*H*-2-benzimidazoleacetonitrile (**166**) gave pyrido[1,2-*a*]benzimidazole (**167**). Also the enaminone (**163a**) reacted with 5-amino-3-phenylpyrazole (**168**) to yield pyrazolo[1,5-*a*]pyrimidine (**169**). Reaction of guanidine nitrate with (**163a,f**) afforded 2-amino-4-[2-benzothiazolyl]pyrimidine (**170, 171**), respectively. The reaction of (**163b,c**) with N-substituted guanidine carbonate at elevated temperature in alcoholic alkali afforded 2-[*N*-phenylamino]-4-[5-(2-substituted-4-methyl)thiazolyl]pyrimidine **172** and **173**, respectively. The treatment of **163c,d** with hydroxylamine or with alkylhydrazine afforded **174** and **175**, respectively, as shown in Scheme 25 [54,113–122].

Also, treatment of acetophenone and its derivatives (**176a–j**) with DMFDMA afforded 3-*N*,*N*-dimethylamino-1-aryl-prop-2-en-1-one (**177a–j**) in very good yield [123]. The reaction of enaminones (**177a–j**) with different nucleophiles afforded different heterocycles. Reaction of enaminone (**177a**) with 2-methoxyacetophenone

Scheme 24



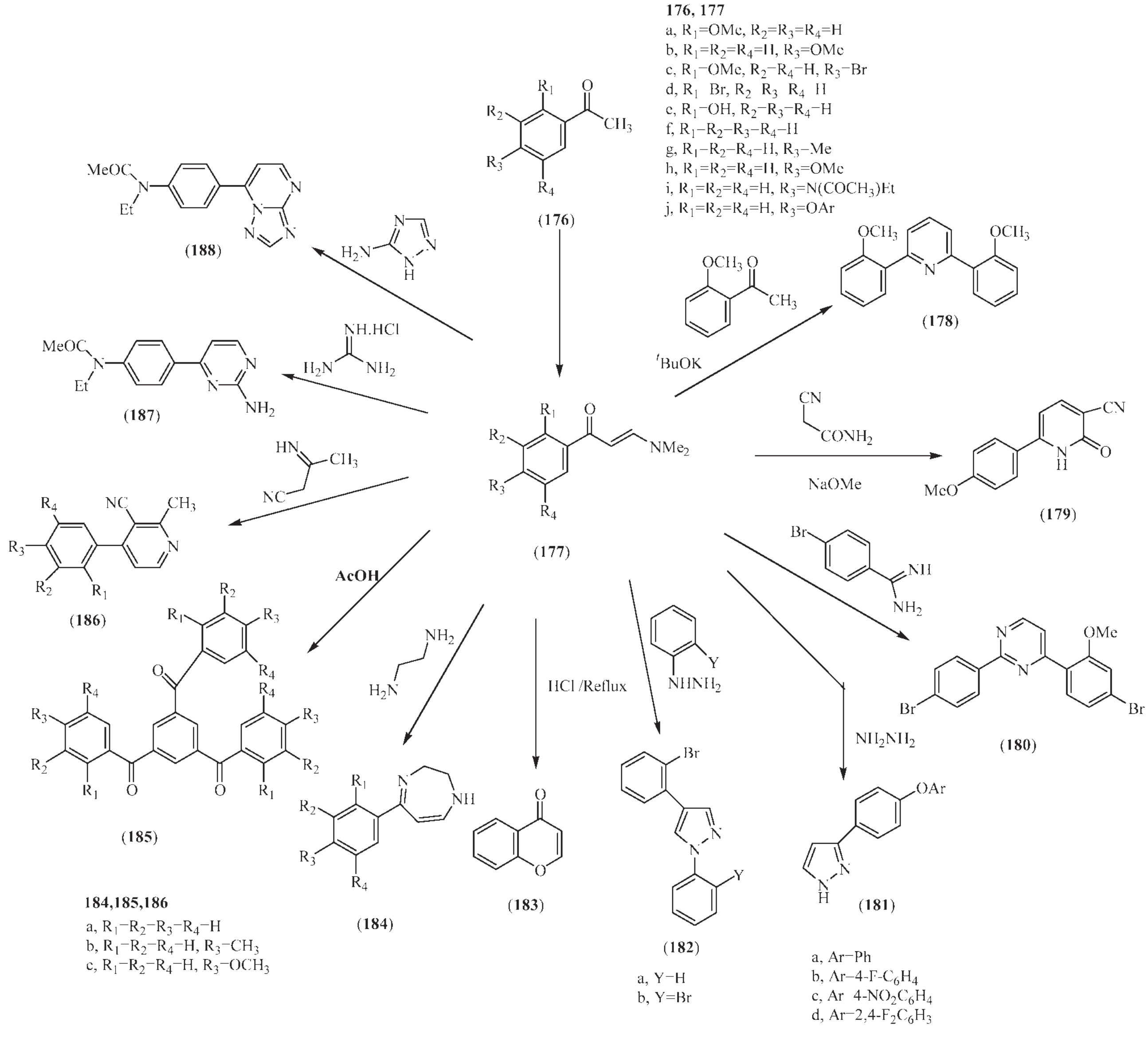
Scheme 25



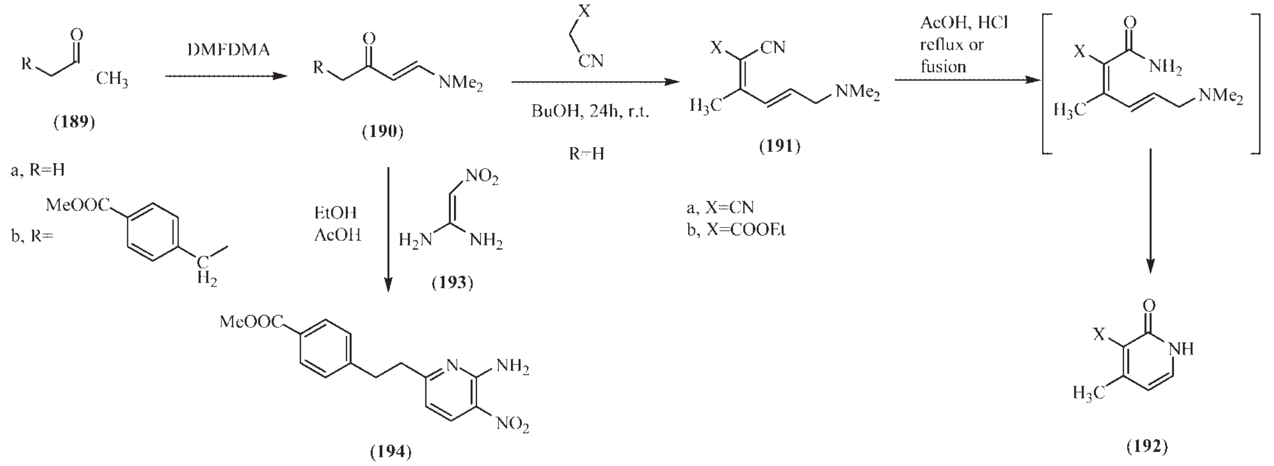
(**176a**) in the presence of potassium *t*-butoxide afforded pyridine derivative (**178**) [124]. The treatment of the dimethylaminopropenone (**177b**) with cyanoacetamide afforded pyridine-2(1*H*)-one (**179**) [125]. Formation of the pyrimidine ring (**180**) was achieved by the base-promoted condensation between 4-bromobenzamidine and 3-dimethylamino-1-(4-bromo-2-methoxyphenyl)-prop-2-en-1-one (**177c**) [126–128]. Enaminoketone (**177d**) was reacted with phenylhydrazine derivatives affording diarylpyrazoles (**182a,b**) [66,129]. Treatment of enaminone (**177e**) with hydrochloric acid under reflux gave 4*H*-benzopyran-4-one (**183**) [130,131]. The reaction of ethylenediamine with enaminones (**177f–h**) afforded the diazepenes (**184a–c**). Refluxing of enaminones (**177f–h**) in acetic acid gave (**185a–c**). The reaction of (**177f–h**) with 3-aminocrotononitrile afforded the pyridine derivatives (**186a–c**) [132]. 2-Amino-4-[4(*N*-acetyl-*N*-ethyl)aminophenyl]pyrimidine (**187**) was obtained by condensation of enaminone (**177i**) with guanidine hydrochloride. Enaminone (**177i**) reacted with 3-amino-1,2,4-triazole to give 1,2,4-triazolo[1,5-*a*]pyrimidine (**188**) [32,133] as shown in Scheme 26.

1-*N*,*N*-Dimethylaminobut-1-en-3-one (**190a**) and its derivatives (**190b**) were obtained by the reaction of acetone and its derivative (**189a,b**) with DMFDMA. The reaction of (**190a**) with either malononitrile or ethyl cyanoacetate afforded (**191a,b**) which was then refluxed in an acetic acid hydrochloric acid mixture to afford 3-substituted 4-methylpyridine-2(1*H*)-one (**192a,b**) in a good yield [134,135]. Treatment of phenethyl enaminone

Scheme 26

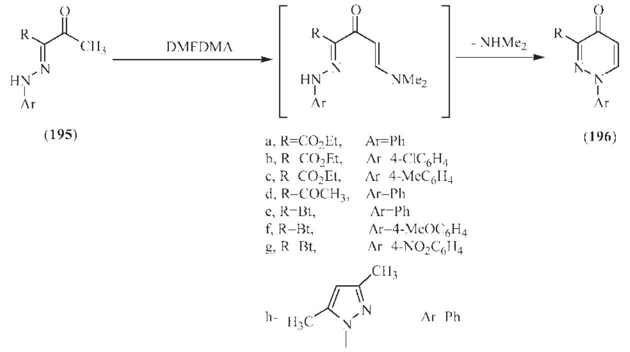


Scheme 27



(**190b**) with 2-nitroethene-1,1-diamine (**193**) gave pyridine (**194**) as shown in Scheme 27 [136].

Consequently arylhydrazones (**195a–h**) were condensed with DMFDMA to yield the pyrazolylpyridazine (**196a–h**) in good yields [137–139].

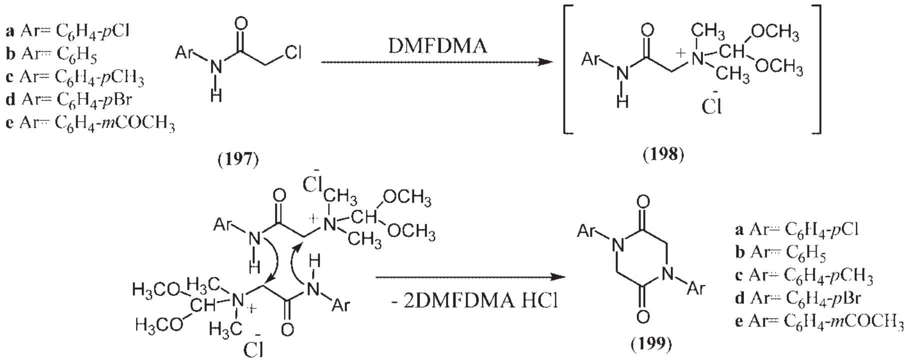


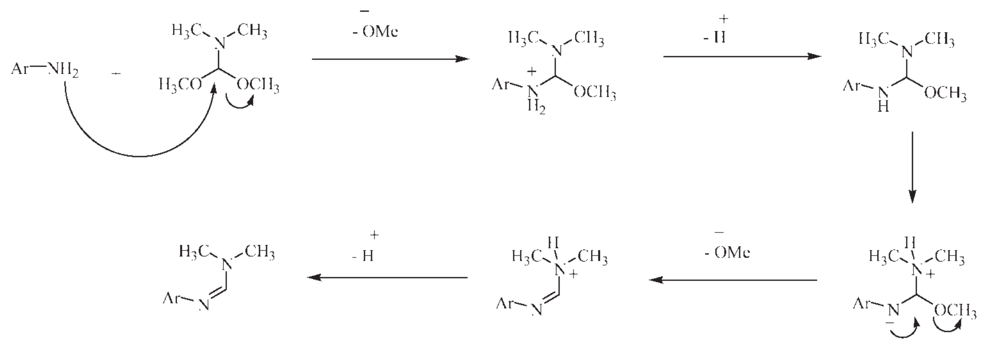
DMFDMA was found to react with α-chloroacetanildes (**197a–e**) to give the unexpected products 1,6-diarylpyrazine-2,5-diones (**199a–e**). Scheme 28 shows a possible alternative pathway, in which DMFDMA acts as a nucleophile which attacks the carbon carrying the chlorine in α-chloroacetamides (**197a–e**) to afford the salt (**198a–e**); dimerization with elimination of DMFDMA salt then gives 1,4-diarylpiperazine-2,5-diones (**199a–e**) [140].

4. PREPARATION OF HETEROCYCLIC COMPOUNDS THROUGH THE FORMYLATION OF THE AMINO GROUP USING DMFDMA TO GIVE AMIDINES

The reaction of the amino group with DMFDMA is easier and faster than the methyl and methylene groups because the amino group contains free lone pair of electrons, which make it a very good nucleophile. So that the reaction is nucleophilic substitution followed by elimination of methanol molecule to give the corresponding *N,N*-dimethylaminoamidine by the effect of NMe$_2$ group as shown in the following reaction mechanism.

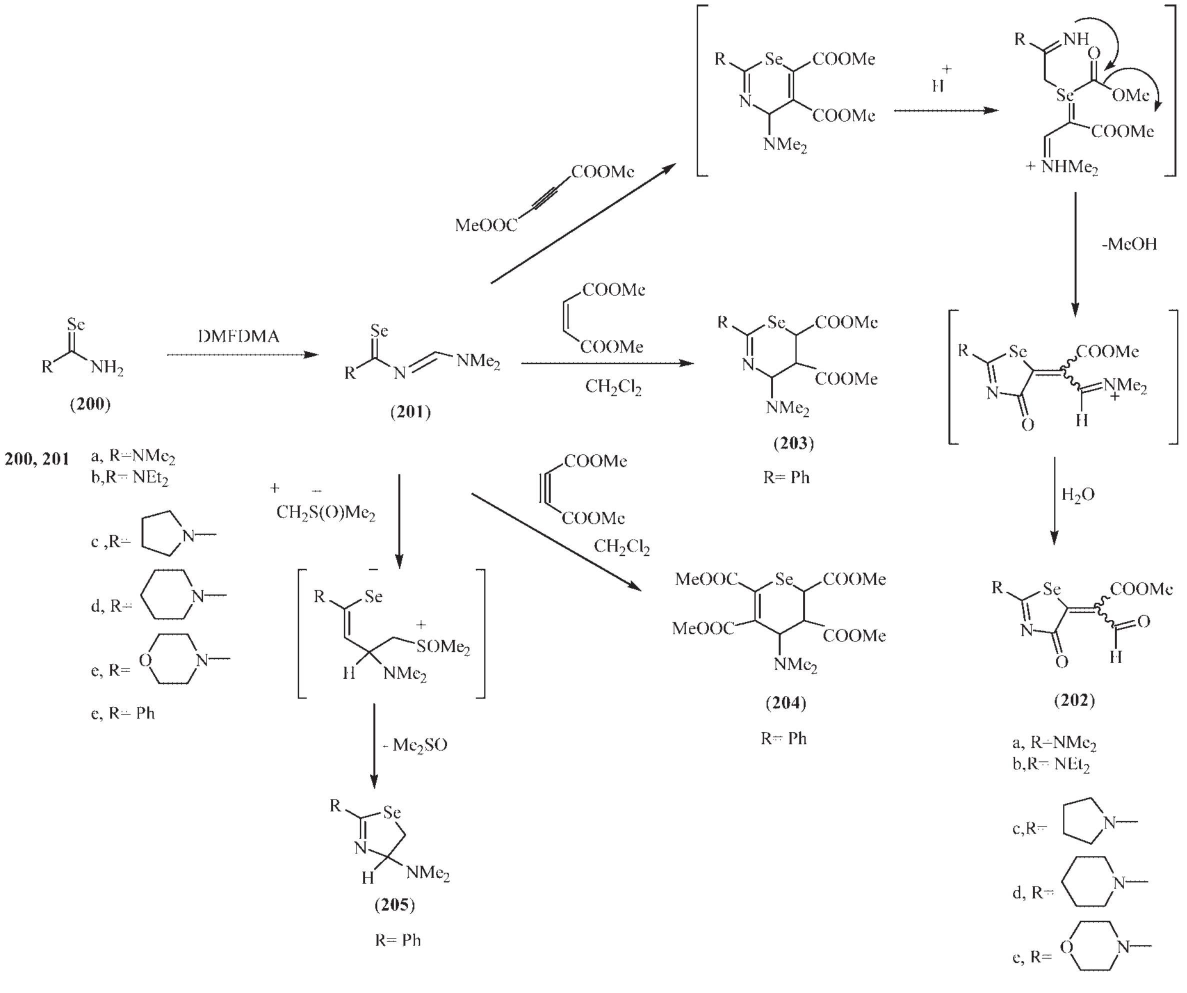
Scheme 28



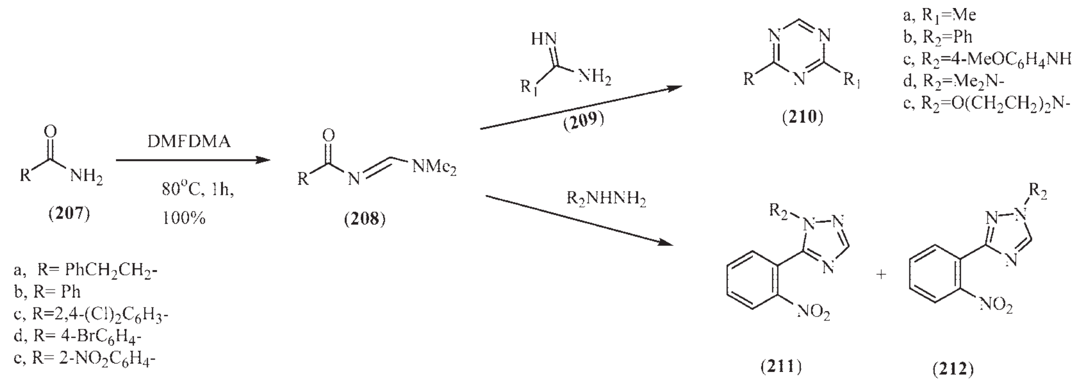


4.1. Amino of selenoamide group. Condensation of *N*,*N*-disubstituted selenourea (**200a–e**) with DMFDMA (1.5 equiv) at room temperature for 6 h afforded selenoazadienes (**201a–e**) in high yields. The presence of the selenium atom facilitates the cycloaddition reactions as a result of the presence of the vacant d-orbital which make it act as a Lewis acid. Interestingly, the reaction did not give the expected Diels-Alder adduct but a mixture of *E*/*Z* isomers of (**202**) was obtained. The reaction was carried out as shown in Scheme 29 [141]. The reactivity of the *N*-selenoacylamidine (**201e**) as 4π heterodienic system in [4 + 2] cycloaddition reactions with electrophilic dienophiles was investigated. Thus (**201e**) was quenched with an excess of methyl acrylate

Scheme 29



Scheme 30



affording 5,6-dihydro-4*H*-1,3-selenazine (**203**). The addition of dimethyl acetylenedicarboxylate (DMAD) afforded the 4*H*-selenopyran (**204**). Treatment of the trimethylsulfoxonium iodide with the *N*-selenoacylamidine (**201e**) gave the selenazol-2-ines (**205**) as shown in Scheme 29 [142].

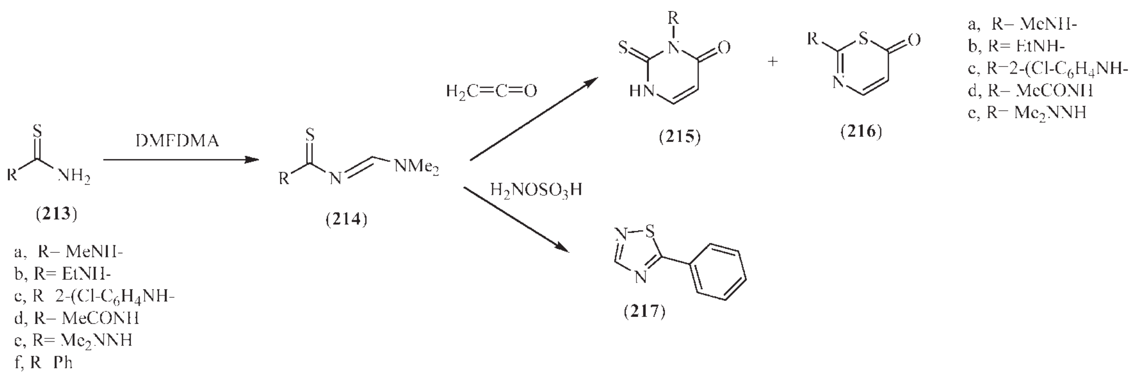
4.2. Amino of amide group. *N*′-Acyl-*N*,*N*-dimethylamidines (**208a–e**) were prepared in excellent yields by heating amides (**207a–e**) with DMFDMA. *N*′-Acyl-*N*,*N*-dimethylamidines (**208a–e**) were condensed with amidines or guanidines (**209a–e**) in aprotic solvent to give s-triazines (**210a–e**). Also 2-(2-nitrophenyl)-1,3,4-triazoles (**211**) and (**212**) were synthesized from treatment of (**208e**) with hydrazine derivatives Scheme 30 [143–146].

4.3. Amino of thioamide group. Treatment of thioamide (**213a–f**) with DMFDMA gave 2,4-diamino-1-thia-3-azabutadienes (**214a–f**). Thioxopyrimidinones (**215a–e**) and thiazinones (**216a–e**) were obtained from treatment of (**214a–e**) with ketene by [4 + 2] cycloaddition reaction [147]. 5-Phenyl-1,2,4-thiadiazole (**217**) was also synthesized from reaction of [dimethyl (amino)methylene]thiobenzamide (**214f**) with hydroxylamine-*O*-sulfonic acid at room temperature as shown in Scheme 31 [148].

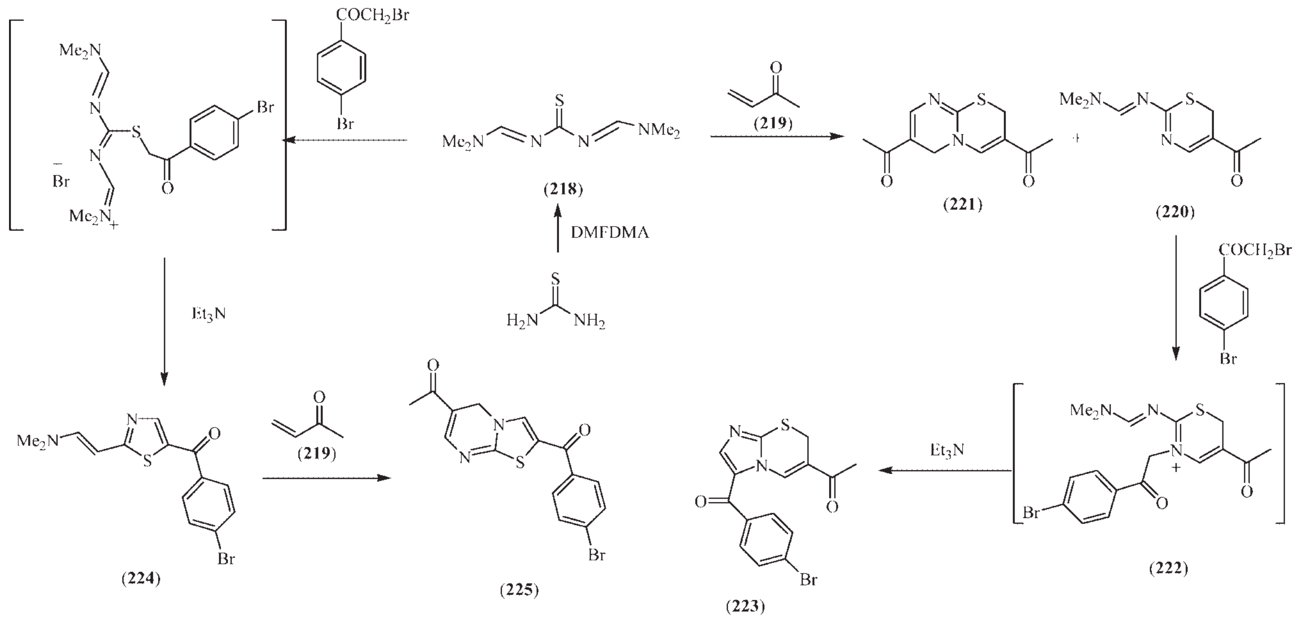
The reaction of thiourea with excess of DMFDMA in boiling dichloromethane afforded polyheteropolyene (**218**). The [4 + 2] cycloaddition reaction with methyl vinyl ketone (**219**), the thiazine (**220**), and pyrimido[2,1-*b*][1,3]thiazine (**221**) were formed. The alkylation of thiazine (**220**) by *p*-bromophenacyl bromide affected the endocyclic nitrogen atom providing the *N*-alkylated unisolated salt (**222**). Subsequent treatment with triethylamine afforded imidazo[2,1-*b*][1,3]thiazine (**223**). The reaction between polyheteropolyene (**218**) and *p*-bromophenacyl bromide afforded the corresponding S-alkyl bromide salt. This intermediate was deprotonated *in situ* by addition of triethylamine. Annulation proceeded spontaneously followed by loss of dimethylamine to provide thiazole derivative (**224**). The [4 + 2] cycloaddition reaction between thiazole (**224**) and methyl vinyl ketone (**219**) gave 5*H*-thiazolo[3,2-*a*]pyrimidine (**225**) as shown in Scheme 32 [149].

4.4. Amino group attached to the ring. Treatment of 2-aminoheterocyclic compounds (**226a–c**) with DMFDMA gave the corresponding amidines (**227a–c**). The treatment of (**227a–c**) with (*R*,*S*) isomer of *N*-trifluoroacetyl-5-bromo-4-oxonorvaline methyl ester (**228**) gave (**230a,b**) *via* the intermediate (**229**) as shown in

Scheme 31

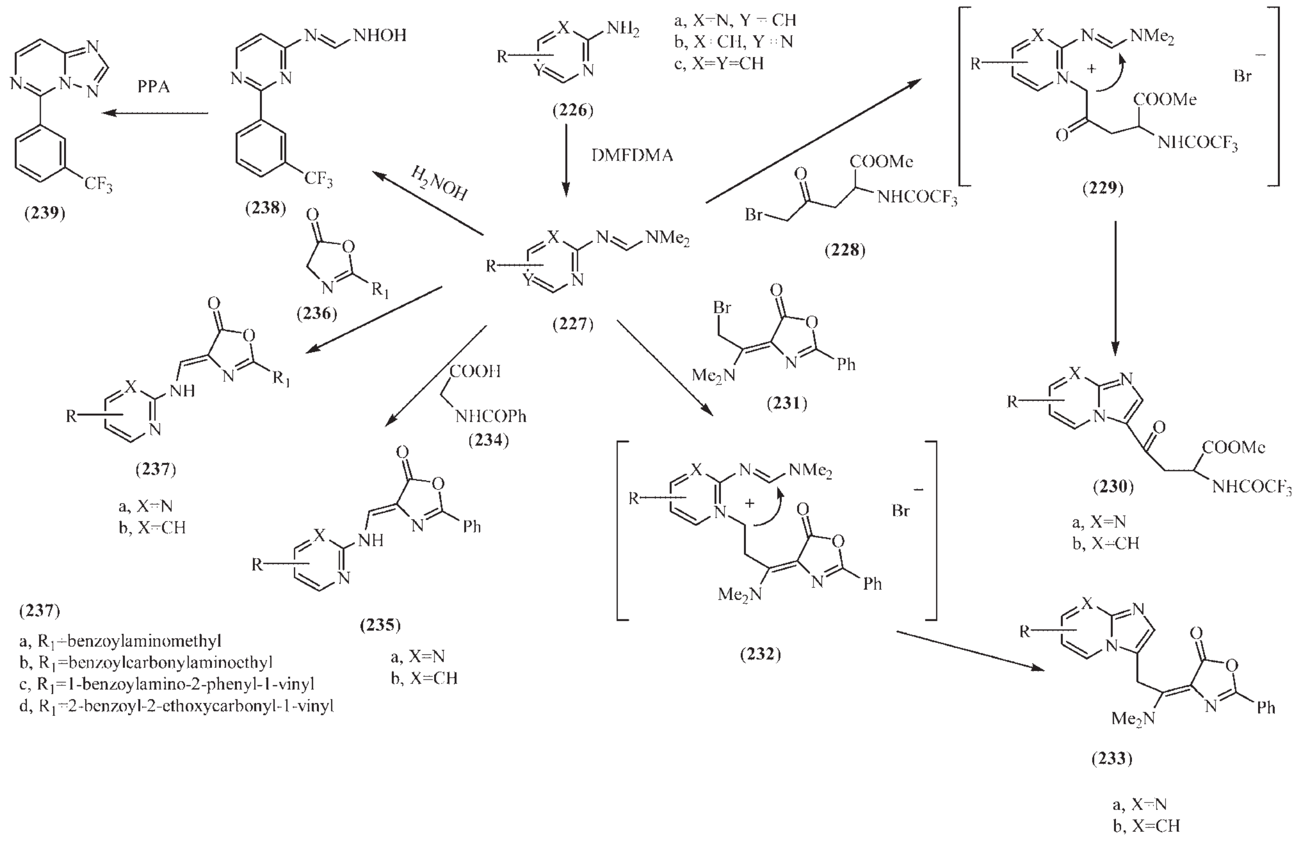


Scheme 32

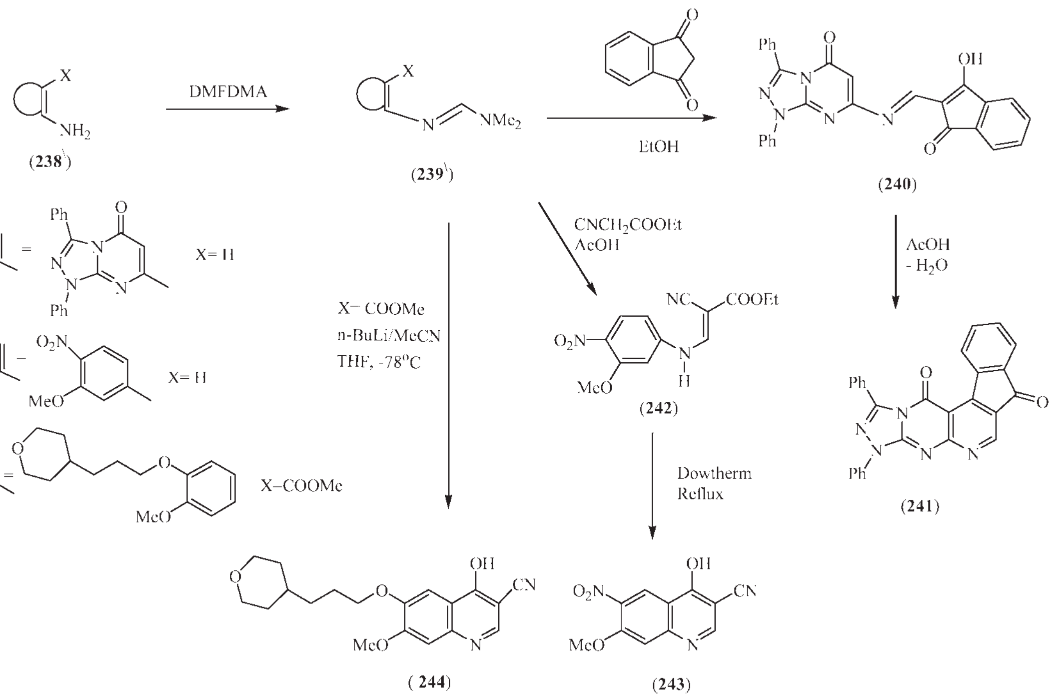


Scheme 33 [150]. Also the reaction of (**227a–c**) with 4-(2-bromo-1-dimethylaminoethylidene)-2-phenyl-5(4*H*)-oxazolone (**231**) in acetonitrile or DMF, the quaternary salt (**232**) was formed, which was cyclized into (**233a–c**) [151]. The reaction of (**227a–c**) with either huppuric acid (**234**) or oxazolones (**236**) afforded 2-substituted-4-

Scheme 33



Scheme 34



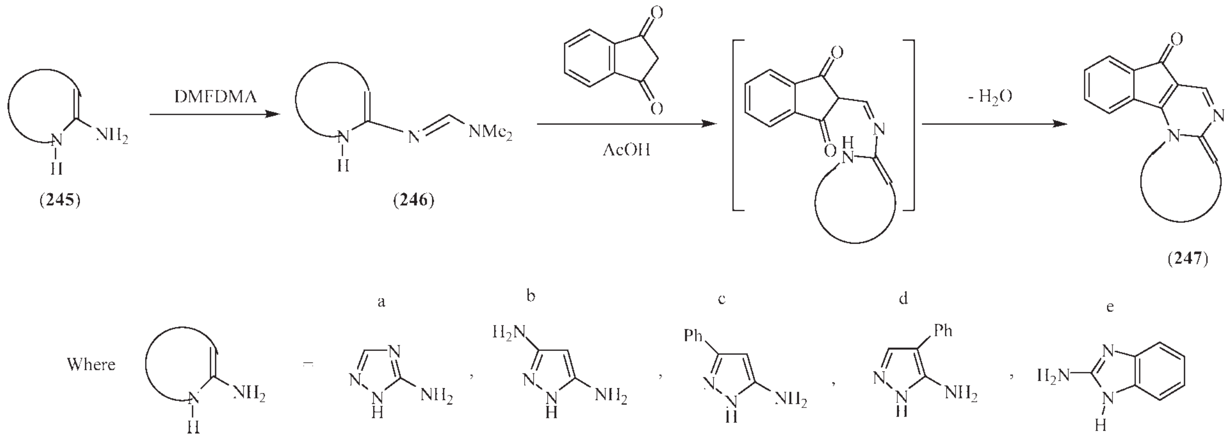
heteroarylaminomethylene-5(4*H*)-oxazolones (**235a–c**) and (**237**), respectively [152]. Triazolo[1,5-*c*]pyrimidine (**239**) was prepared by treatment of (**227b**) with hydroxylamine to give compound (**238**) followed by treatment with polyphosphric acid as is also shown in Scheme 33 [153,154].

Reaction of amino compounds (**238′a–c**) with DMFDMA yields the corresponding formamidine compounds (**239′a–c**). Treatment of compound (**239′a**) with indene-1,3(2*H*)-dione in boiling ethanol leads to the formation of acyclic structure (**240**), which is converted into cyclic compound (**241**) when boiled in glacial acetic acid [155]. Reaction of (**239b**) with ethyl cyanoacetate gave (**242**) as a mixture of isomers, which on thermal cyclization gave the 4-hydroxyquinoline (**243**). Hydroxyquinoline (**244**) was accomplished by treating (**239′c**) with the lithium anion of CH_3CN in THF at –78°C followed by quenching with AcOH, and warming to room temperature as shown in Scheme 34 [156].

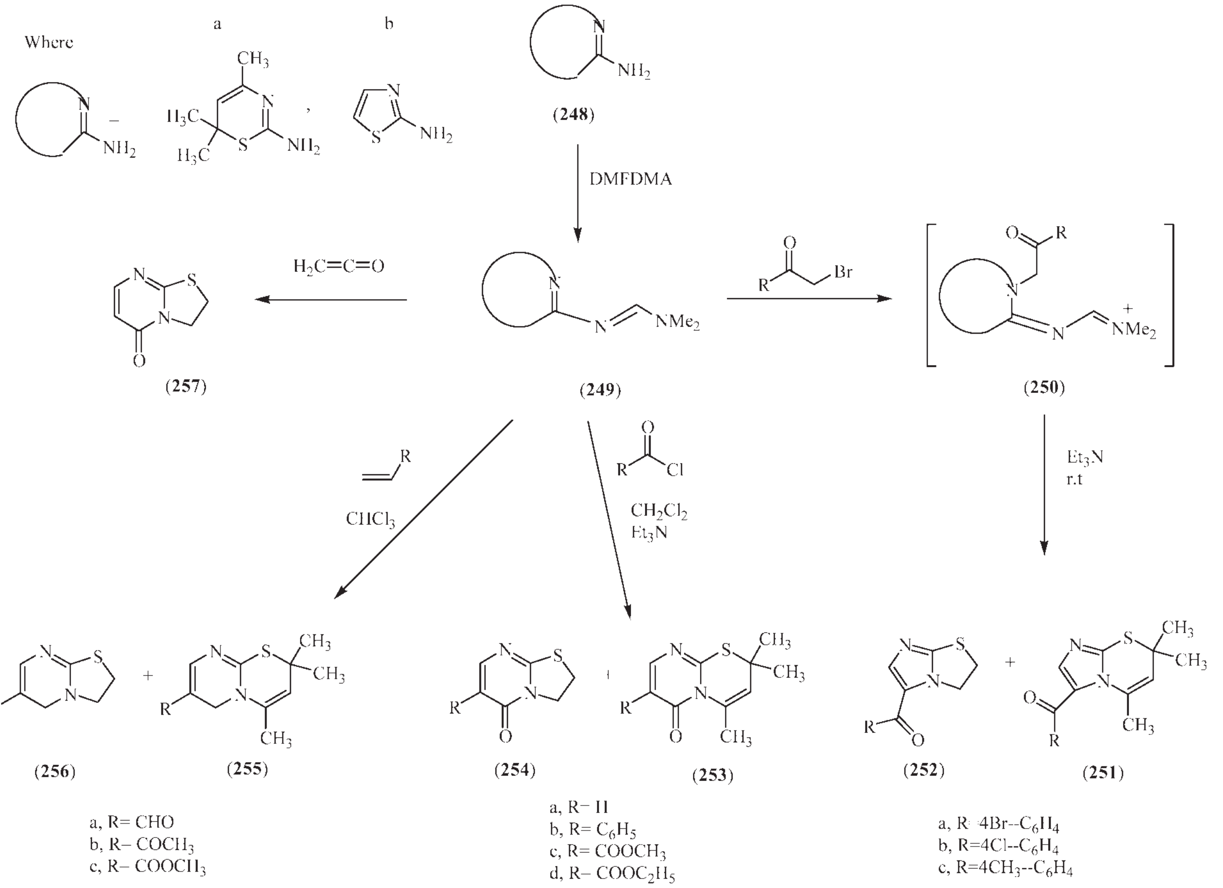
Also condensation of compounds (**246a–e**), which were prepared by reaction of (**245a–e**) with DMFDMA and indene-1,3-dione in boiling acetic acid leads to the formation of compounds (**247a–e**) as shown in Scheme 35 [155].

Treatment of 2-amino-4,6,6-trimethyl-6*H*-1,3-thiazine (**248a**) 2-aminothiazoline (**248b**) with DMFDMA

Scheme 35

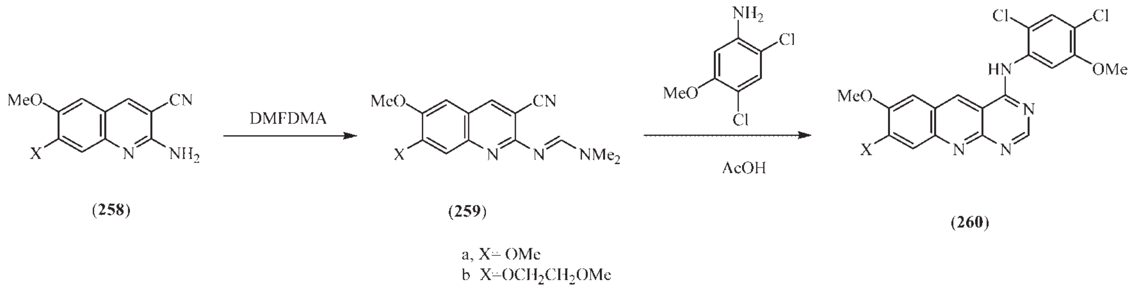


Scheme 36



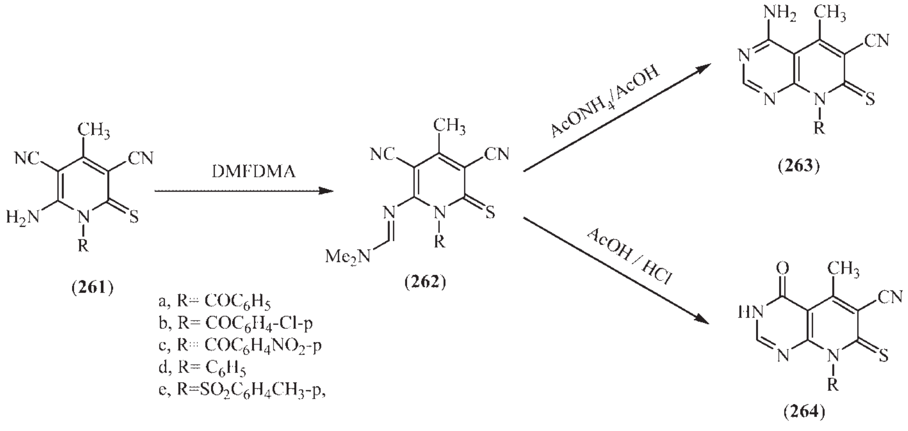
afforded (**249a,b**). Alkylation of compound (**249a,b**) with arylacyl bromides affected the intracyclic *N*-alkyl amidinium bromides (**250**). These salts transformed into 7*H*-imidazo[2,1-*b*][1,3]thiazines (**251**) imidazo[2,1-*b*]thiazoles (**252**), respectively, by addition of Et_3N. 2*H*,6*H*-Pyrimido[2,1-*b*][1,3]thiazin-6-ones (**253**) and (**254**) can be prepared from compounds (**249a,b**) with acid chlorides. 2*H*,6*H*-Pyrimido[2,1-*b*][1,3]thiazine derivatives (**255**) and thiazolo[3,2-*a*]pyrimidines (**256**) were obtained by the reaction of amidines (**249a,b**) with acrylic dienophiles in $CHCl_3$. Cycloaddition of amidine (**249b**) with ketene gave 6-unsubstituted thiazolo[3,2-*a*]pyrimidin-5-ones (**257**) as shown in Scheme 36 [157,158].

Treatment of quinoline derivatives (**258a,b**) with DMFDMA gave the corresponding amidines (**259a,b**). Subsequent addition of 2,4-dichloro-5-methoxyaniline in acetic acid provided the desired tricyclic derivatives (**260a,b**) as shown in the following [159].



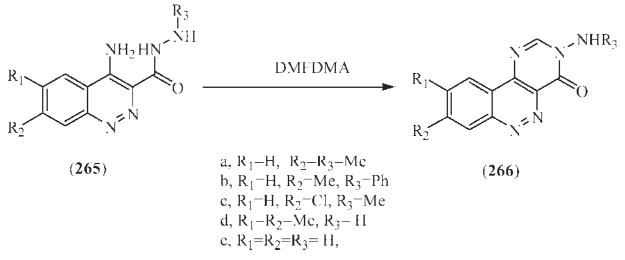
Also the treatment of 6-amino-3,5-dicyano-6-methyl-*N*-substitutedpyridine-2(1*H*)-thione (**261**) with DMFDMA in dry dioxane afforded the corresponding amidine (**262**) which on boiling with ammonium acetate in

Scheme 37

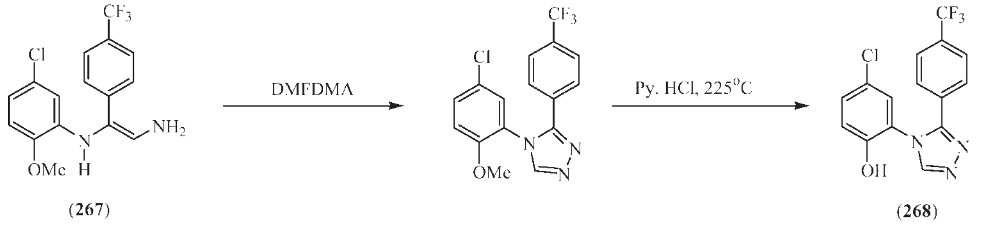


acetic acid and hydrochloric acid in acetic acid afforded pyrido[2,3-*d*]pyrimidine derivatives (**263**) and (**264**), respectively, as shown in Scheme 37 [160].

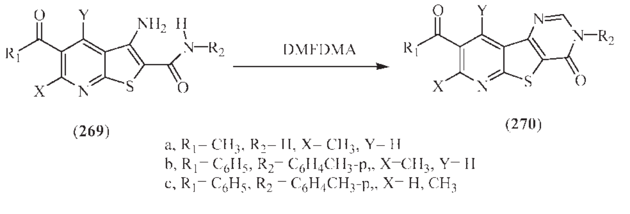
4.5. Cyclization of two amino groups by DMFDMA. Hydrazides (**265a–e**) were converted to 3-aminopyrimido[5,4-*c*]cinnolines (**266a–e**) by refluxing with DMFDMA in diethylene glycol dimethyl ether [161,162].



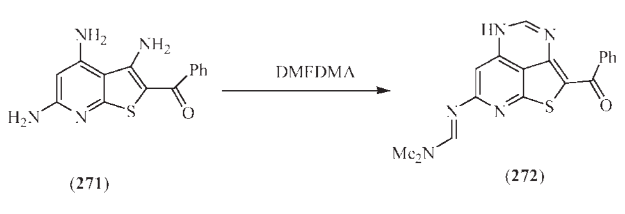
4-Chloro-2-[3-[4-(trifluoromethyl)phenyl]-4*H*-dihydro-1,2,4-triazol-4-yl]phenyl-phenol (**268**) was obtained by cyclization of compound (**267**) with DMFDMA to give triazole ring followed by hydrolysis [163].



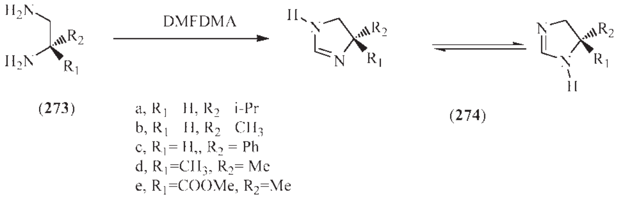
Thieno[2,3-*b*]pyridine derivatives (**269a–c**) on treatment with DMFDMA afforded a product that is formulated as pyrido[2,3-*b*]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (**270a–c**) [38,39,164].



Also, treatment of thieno[2,3-*b*]pyridine (**271**) when treated with DMFDMA afforded the tricyclic compound (**272**) [165].



Imidazolines (**273a–e**) were prepared from the treatment of diamines (**274a–e**) with DMFDMA [166].



5. CONCLUSIONS

The reactions considered in this review clearly demonstrate the high synthetic potential of DMFDMA. Many biologically active heterocyclic compounds have been obtained based on this reagent. This suggests that DMFDMA can be particularly used in the synthesis of functionalized carbo- and heterocyclic compounds used in the design of novel highly effective pharmaceuticals with a broad spectrum of bioresponses. The great interest of chemists in such reagent is confirmed by the facts that many articles cited in this review are recently obtained, along with a multitude of patents.

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An Efficient Method for Synthesis of Pyrano[3,2-*c*]pyridine Derivatives under Microwave Irradiation

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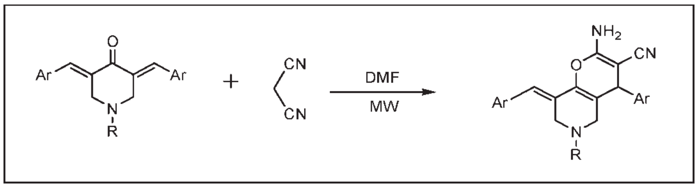

A series of pyrano[3,2-*c*]pyridine derivatives were synthesized *via* reactions of 3,5-dibenzylidene-piperidin-4-one and malononitrile in *N*,*N*-dimethylformamide under microwave irradiation. It is a simple, efficient, and promising synthetic method to construct pyrano[3,2-*c*]pyridine skeleton.

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INTRODUCTION

Since the cytotoxic activity of (*E*)-3,5-bis (benzylidene)-4-piperidones **1** (Fig. 1) and their specificity toward leukemia cell lines with IC$_{50}$ values <10 μ*M* have been reported [1] in 1992, the design and synthesis of their derivatives have been an object of big interest because of their potential application. The practice of incorporating chalcones into heterocyclic nitrogenous ring has been noticed recently [2–6]. The studies show that compound **2** is potential broad-spectrum antitumor agents [4].

Microwave irradiation (MWI) of organic reactions has rapidly gained popularity because it accelerates a variety of synthetic transformations [7] and have the prominent advantages of short reaction time and high yield [8].

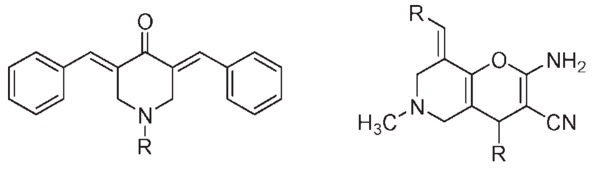
It is well known that the 2-amino-3-cyanopyrans was obtained by the reaction of chalcones with malononitrile, and several articles on this topic can be found in the literature [9]. However, there are few reports for the synthesis of **2**. These methods generally required long reaction time [4,5] or used EtONa [6] as catalyst. To provide vast new compounds for biomedical screening, a simple and efficient method for the synthesis of these molecules is urgently required.

In continuation of our recent interest in the construction of heterocyclic scaffolds [10], we herein describe a practical, inexpensive, rapid microwave-assisted method for the preparation of pyrano[3,2-*c*] pyridine derivatives *via* reactions of 3,5-dibenzylidenepiperidin-4-one and malononitrile in *N*,*N*-dimethylformamide (DMF) (Scheme 1).

RESULTS AND DISCUSSION

To explore conditions of the reaction of 3,5-dibenzylidenepiperidin-4-one **3** and malononitrile **4** in DMF (Scheme 1) under MWI, various reaction conditions were investigated, including solvent and temperature. To search for the optimal reaction solvent, the reaction of 3,5-bis(4-chlorobenzylidene)-1-methylpiperidin-4-one (**3c**) and malononitrile **4**, was examined in ethylene glycol, DMF, glacial acetic acid, and ethanol, respectively (Table 1, entries 1–4) under MWI at the maximum power of 200 W. As shown in Table 1, the reaction in DMF resulted in higher yields and shorter reaction time than others. So DMF was chosen as the appropriate solvent. To further optimize the reaction condition, the same reaction was carried out in DMF at temperatures ranging from 90 to 140°C (Table 1, entries 5–9), with an increment of 10°C each time. As shown in Table 1, the yields of product was increased and the reaction time was shortened when the temperature was increased from 90 to 120°C, however, further increase of the temperature from 130 to 140°C failed to improve the yield (Table 1, entries 9 and 10). Therefore, 120°C was chosen as the most suitable temperature for all further microwave-assisted reactions.

Based on these optimized conditions [DMF, 120°C, 200 W (maximum power)], reactions of different 3,5-dibenzylidenepiperidin-4-ones and malononitrile were performed, a series of pyrano[3,2-*c*]pyridine derivatives were synthesized with good yields. The results (Table 2, entries 1–12) indicated that for 3,5-dibenzylidenepiperidin-4-one bearing different functional groups such as



1 2

Figure 1. 3,5-Dibenzylidenepiperidin-4-one and its derivatives.

chloro, bromo, fluoro, nitro, or methyl the reaction proceeded smoothly in all cases. We have also observed the electronic effects: that is, 3,5-dibenzylidenepiperidin-4-one with electron-withdrawing groups (Table 2, entries 3–6) reacted rapidly, whereas electron-rich groups (Table 2, entry 2) decreased the reactivity, requiring longer reaction time.

A possible mechanism for the formation of the product **5** is outlined in Scheme 2. We proposed that the formation of **5** proceeds *via* an initial Michael addition reaction of chalcones and malononitrile to afford intermediate **6**, which then cyclized to give compound **5**.

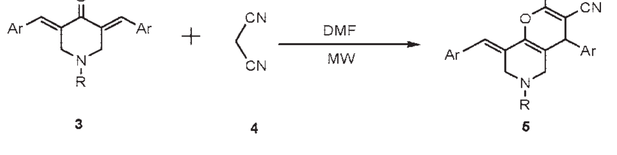
The structures of all the synthesized compounds were established on the basis of their spectroscopic data. The IR spectrum of compound **5b** showed strong absorptions at 3389 cm^{-1} and 3295 cm^{-1} due to the NH$_2$ group, 2178 cm^{-1} due to the CN group. The ^{1}H NMR spectrum of **5b** showed a broad singlet at δ 6.76 due to the —NH$_2$ proton and a singlet at δ 6.87 due to the =CH proton. In the IR spectrum of compound **5h**, the appearance of bands at 3329 cm^{-1}, 3279 cm^{-1}, and 2192 $^{-1}$ due to the NH$_2$ and CN triple bound. The appearance of a broad singlet at δ 6.90 due to the NH$_2$ protons and a singlet at δ 6.92 due to =CH in the ^{1}H NMR spectrum further confirmed the structure of product.

In conclusion, we have developed a simple and efficient method for the synthesis of pyrano[3,2-*c*]pyridine derivatives. The protocol includes particularly valuable features of excellent yield, shorten reaction time, reduced environmental impact, and straightforward procedure.

EXPERIMENTAL

All reactions were performed in a monomodal Emrys^{TM} Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in open capillaries and are uncorrected.

Scheme 1



3 4 5

Table 1

Optimization for the synthesis of **5c**.

Entry	Solvent	*T* (°C)	Time (min)	Yield (%)
1	HOAc	100	8	45
2	Glycol	100	8	86
3	DMF	100	8	91
4	EtOH	100	8	83
5	DMF	90	8	90
6	DMF	110	7	92
7	DMF	120	6	94
8	DMF	130	6	92
9	DMF	140	6	90

IR spectra were recorded on an FTIR-tensor 27 spectrometer. ^{1}H NMR spectra were measured on a DPX 400 MHz spectrometer using TMS as an internal standard and DMSO-d_6 as solvent. Elemental analysis was determined by using a PerkinElmer 240c elemental analysis instrument.

General procedure for the synthesis of compound 3N. In a 50 mL reaction vial, a mixture of 4-piperidone (10 mmol), the appropriate aldehyde (20 mmol), 1 mL 10% NaOH and 30 mL 95% EtOH was stirred at room temperature for 0.5–2 h. The separated solid was then filtered.

General procedure for the synthesis of compound 5 under MWI. In a 10 mL reaction vial, the 3,5-dibenzylidenepiperidin-4-one 3 (1 mmol), malononitrile (1.1 mmol), and DMF (2 mL) were mixed and then capped. The mixture was irradiated at 200 W (initial power 150 W, maximum power 200 W) at 120°C for a given time. On completion (the reaction was monitored by TLC), the reaction mixture was cooled to room temperature and poured into water (70 mL), filtered to give the crude product, which was further purified by recrystallization from 95% EtOH to give pure product.

2-Amino-8-benzylidene-5,6,7,8-tetrahydro-6-methyl-4-phenyl-4H-pyrano[3,2-c]pyridine-3-carbonitrile (5a). IR (KBr) 3338, 3284, 2189, 1683, 1640, 1619, 1594, 1489, 1453, 1415, 1399, 1326, 1272, 1218, 1171, 1110, 1050, 917, 904, 878, 766, 756, 699 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 7.43–7.35 (m, 4H, ArH), 7.31–7.22 (m, 6H, ArH), 6.93 (s, 1H, =CH), 6.84 (brs, 2H, NH$_2$), 4.06 (s, 1H, CH), 3.48 (d, 1H, J = 14.4 Hz, CH$_2$), 3.28 (d, 1H, J = 14.4 Hz, CH$_2$), 3.00 (d, 1H, J = 16.0 Hz, CH$_2$), 2.57 (d, 1H, J = 16.0 Hz, CH$_2$), 2.15 (s, 3H, CH$_3$). ^{13}C NMR (DMSO-d_6): δ = 159.79, 143.49, 139.15, 135.93, 128.96, 128.69, 128.49, 127.60, 127.46, 127.14, 121.43, 120.44, 113.23, 112.71, 55.86, 54.56, 54.08, 44.50, 41.07. Anal. Calcd for $C_{23}H_{21}N_3O$: C, 77.72; H, 5.96; N, 11.82; found C, 77.83; H, 5.94; N, 11.79.

8-(4-Methylbenzylidene)-2-amino-4-(4-methylphenyl)-5,6,7,8-tetrahydro-6-methyl-4H-pyrano[3,2-c]pyridine-3-carbonitrile (5b). IR (KBr) 3389, 3295, 2178, 1682, 1644, 1604, 1511, 1461, 1448, 1416, 1395, 1323, 1269, 1205, 1171, 1101, 1055, 911, 812 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 7.22 (d, 2H, J = 8.0 Hz ArH), 7.17–7.13 (m, 4H, ArH), 7.09 (d, 2H, J = 8.0 Hz, ArH), 6.87 (s, 1H, =CH), 6.76 (brs, 2H, NH$_2$), 3.99 (s, 1H, CH), 3.46 (d, 1H, J = 14.8 Hz, CH$_2$), 3.28 (d, 1H, J = 17.2 Hz, CH$_2$), 2.96 (d, 1H, J = 16.4 Hz, CH$_2$), 2.53 (d, 1H, J = 17.6 Hz, CH$_2$), 2.31 (s, 3H, CH$_3$), 2.29 (s, 3H, CH$_3$), 2.14 (s, 3H, CH$_3$). ^{13}C NMR (DMSO-d_6): δ = 159.72, 140.55, 139.08, 136.53, 136.21, 133.09, 129.23, 129.09, 128.92, 127.50,

Table 2

Synthesis of compounds **5** under microwave irradiation.

Entry	Product	R	Ar	Time/min	Yield (%)	Mp/°C
1	**5a**	Methyl	C_6H_5	6	93	200–202
2	**5b**	Methyl	$4\text{-}CH_3C_6H_4$	9	92	215–217 (214–215)[a]
3	**5c**	Methyl	$4\text{-}ClC_6H_4$	6	94	238–240
4	**5d**	Methyl	$3\text{-}NO_2C_6H_4$	7	91	225–227
5	**5e**	Methyl	$4\text{-}NO_2C_6H_4$	7	92	238–240
6	**5f**	Methyl	$4\text{-}BrC_6H_4$	7	93	245–246
7	**5g**	Benzyl	C_6H_5	6	94	226–228
8	**5h**	Benzyl	$4\text{-}ClC_6H_4$	7	94	243–245
9	**5i**	Benzyl	$4\text{-}FC_6H_4$	7	93	235–237
10	**5j**	Benzyl	$3\text{-}NO_2C_6H_4$	7	90	225–227
11	**5k**	Benzyl	$4\text{-}NO_2C_6H_4$	7	89	233–236
12	**5l**	Benzyl	$4\text{-}BrC_6H_4$	7	92	242–244

[a] Literature melting point.

126.80, 121.28, 120.48, 112.93, 55.99, 54.56, 54.17, 44.52, 40.70, 20.79, 20.65. Anal. Calcd for $C_{25}H_{25}N_3O$: C, 78.30, H, 6.57; N, 10.96; found C, 78.39; H, 6.56; N, 10.92.

8-(4-Chlorobenzylidene)-2-amino-4-(4-chlorophenyl)-5,6,7,8-tetrahydro-6-methyl-4H-pyrano[3,2-c]pyridine-3-carbonitrile (5c). IR (KBr) 3365, 3289, 2180, 1681, 1645, 1605, 1489, 1461, 1449, 1413, 1393, 1321, 1267, 1207, 1169, 1092, 1056, 1014, 986, 911, 817, 737, 697 cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.48–7.43 (m, 4H, ArH), 7.26 (m, 4H, ArH), 6.92 (brs, 2H, NH_2), 6.89 (s, 1H, =CH), 4.12 (s, 1H, CH), 3.46 (d, 1H, J = 13.6 Hz, CH_2), 3.28 (d, 1H, J = 14.8 Hz, CH_2), 3.00 (d, 1H, J = 16.0 Hz, CH_2), 2.55 (d, 1H, J = 16.0 Hz, CH_2), 2.16 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ = 159.79, 142.43, 139.23, 134.78, 131.76, 131.72, 130.71, 129.47, 128.70, 128.51, 128.13, 120.36, 120.19, 113.25, 55.54, 54.39, 53.92, 44.40, 40.39. Anal. Calcd for $C_{23}H_{19}Cl_2N_3O$: C, 65.10, H, 4.51; N, 9.90; found C, 65.01; H, 4.53; N, 9.94.

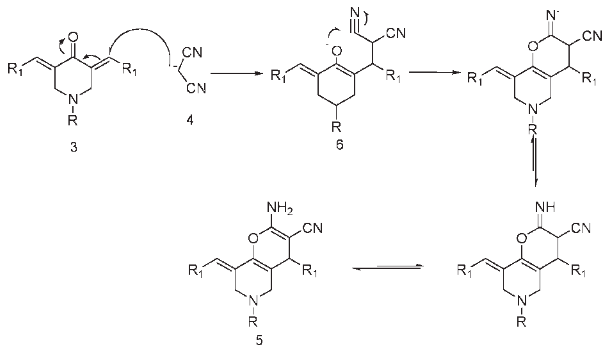
8-(3-Nitrobenzylidene)-2-amino-5,6,7,8-tetrahydro-6-methyl-4-(3-nitrophenyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (5d). IR (KBr) 3359, 3267, 2190, 1676, 1639, 1596, 1522, 1456, 1416, 1348, 1266, 1174, 1116, 1052, 984, 899, 818, 738, 714, 682 cm^{-1}. ^1H NMR (DMSO-d_6): δ 8.19–8.14 (m, 2H, ArH), 8.09 (s, 1H, ArH) 8.06 (s, 1H, ArH), 7.75–7.69 (m, 4H, ArH), 7.05 (brs, 3H, NH_2, and =CH), 4.41 (s, 1H, CH), 3.53 (d, 1H, J = 14.0 Hz, CH_2), 3.28 (d, 1H, J = 14.8 Hz, CH_2), 3.09 (d, 1H, J = 16.4 Hz, CH_2), 2.59 (d, 1H, J = 16.0 Hz, CH_2), 2.17 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ = 159.98, 148.06, 147.94, 145.66, 139.42, 137.45, 135.14, 134.46, 130.48, 130.09, 129.62, 123.37, 122.41, 122.04, 121.84, 119.98, 119.84, 113.67, 55.07, 54.14, 53.60, 44.25, 40.48. Anal. Calcd for $C_{23}H_{19}N_5O_5$: C, 62.02, H, 4.30; N, 15.72; found C, 62.17; H, 4.28; N, 15.66.

8-(4-Nitrobenzylidene)-2-amino-5,6,7,8-tetrahydro-6-methyl-4-(4-nitrophenyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (5e). IR (KBr) 3365, 3293, 2182, 1688, 1642, 1593, 1521, 1458, 1418, 1392, 1340, 1273, 1172, 1097, 1055, 907, 868, 809, 716 cm^{-1}. ^1H NMR (DMSO-d_6): δ 8.26 (d, 4H, J = 8.0 Hz, ArH), 7.54 (d, 4H, J = 8.8 Hz, ArH) 7.06 (brs, 2H, NH_2), 7.03 (s, 1H, =CH), 4.36 (s, 1H, CH), 3.53 (d, 1H, J = 14.4 Hz, CH_2), 3.48–3.43 (m, 1H, CH_2), 3.08 (d, 1H, J = 16.4 Hz, CH_2), 2.56 (d, 1H, J = 16.4 Hz, CH_2), 2.17 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ = 159.91, 150.84, 146.75, 145.93, 142.74, 139.46, 130.70, 130.09, 128.98, 124.10, 123.70, 120.07, 119.95, 114.32, 56.01, 54.75, 54.25, 53.81, 44.30, 40.69. Anal. Calcd for $C_{23}H_{19}N_5O_5$: C, 62.02, H, 4.30; N, 15.72; found C, 61.92; H, 4.32; N, 15.77.

8-(4-Bromobenzylidene)-2-amino-4-(4-bromophenyl)-5,6,7,8-tetrahydro-6-methyl-4H-pyrano[3,2-c]pyridine-3-carbonitrile (5f). IR (KBr) 3364, 3283, 2181, 1681, 1644, 1590, 1486, 1459, 1409, 1391, 1321, 1267, 1169, 1104, 1074, 1010, 910, 895, 828, 814, 734 cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.61–7.56 (m, 4H, ArH), 7.23–7.18 (m, 4H, ArH), 6.89 (brs, 2H, NH_2), 6.87 (s, 1H, =CH), 4.11 (s, 1H, CH), 3.46 (d, 1H, J = 14.0 Hz, CH_2), 3.26 (d, 1H, J = 14.0 Hz, CH_2), 3.00 (d, 1H, J = 16.4 Hz, CH_2), 2.53 (d, 1H, J = 16.4 Hz, CH_2), 2.16 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ = 159.72, 142.77, 139.18, 135.05, 131.55, 131.36, 130.93, 129.78, 128.11, 120.35, 120.30, 120.18, 120.11, 113.16, 55.39, 54.32, 53.85, 44.33, 40.40. Anal. Calcd for $C_{23}H_{19}Br_2N_3O$: C, 53.83, H, 3.73; N, 8.19; found C, 53.96; H, 3.70; N, 8.15.

2-Amino-6-benzyl-8-benzylidene-5,6,7,8-tetrahydro-4-phenyl-4H-pyrano[3,2-c]pyridine-3-carbonitrile (5g). IR (KBr) 3299, 3259, 2189, 1684, 1639, 1618, 1592, 1491, 1453, 1400, 1374, 1349, 1269, 1218, 1169, 1100, 1075, 1042, 919, 878, 746, 696 cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.37–7.32 (m, 4H, ArH), 7.29–7.25 (m, 2H, ArH), 7.23–7.19 (m, 4H, ArH), 7.18–7.16 (m, 3H, ArH), 7.09–7.07 (m, 2H, ArH), 6.95 (s, 1H, =CH), 6.86 (brs, 2H, NH_2), 4.01 (s, 1H, CH), 3.63 (d, 1H, J = 14.4 Hz,

Scheme 2



CH_2), 3.45 (m, 3H, CH_2), 3.07 (d, 1H, J = 16.0 Hz, CH_2), 2.69 (d, 1H, J = 16.0 Hz, CH_2). ^{13}C NMR (DMSO-d_6): δ = 159.79, 143.48, 139.47, 137.74, 135.89, 128.87, 128.64, 128.38, 128.00, 127.56, 127.10, 126.91, 121.83, 120.39, 112.87, 59.89, 56.05, 52.26, 51.69, 41.07. Anal. Calcd for $C_{29}H_{25}N_3O$: C, 80.72, H, 5.84; N, 9.74; found C, 80.86; H, 5.83; N, 9.70.

8-(4-Chlorobenzylidene)-2-amino-6-benzyl-4-(4-chlorophenyl)-5,6,7,8-tetrahydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (5h). IR (KBr) 3329, 3279, 2192, 1683, 1649, 1598, 1489, 1411, 1395, 1375, 1325, 1265, 1214, 1169, 1091, 1049, 1013, 917, 884, 826, 753, 700 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 7.43–7.39 (m, 4H, ArH), 7.23–7.17 (m, 7H, ArH), 7.07–7.06 (m, 2H, ArH), 6.92 (s, 1H, =CH), 6.90 (brs, 2H, NH_2), 4.07 (s, 1H, CH), 3.61 (d, 1H, J = 14.8 Hz, CH_2), 3.46–3.42 (m, 3H, CH_2), 3.06 (d, 1H, J = 16.8 Hz, CH_2), 2.66 (d, 1H, J = 16.0 Hz, CH_2). ^{13}C NMR (DMSO-d_6): δ = 159.78, 142.45, 139.46, 137.69,134.73, 131.70, 130.62, 129.45 128.66, 128.60, 128.42, 127.99, 127.74, 126.94, 120.79, 120.19, 112.86, 112.72, 59.65, 55.60, 51.81, 51.61, 40.30. Anal. Calcd for $C_{29}H_{23}Cl_2N_3O$: C, 69.60, H, 4.63; N, 8.40; found C, 69.75; H, 4.62; N, 8.37.

8-(4-Fluorobenzylidene)-2-amino-6-benzyl-4-(4-fluorophenyl)-5,6,7,8-tetrahydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (5i). IR (KBr) 3334, 3298, 2197, 1684, 1650, 1602, 1507, 1417, 1398, 1375, 1267, 1225, 1157, 1091, 916, 831, 780, 756, 697 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 7.25–7.20 (m, 4H, ArH), 7.19–7.14 (m, 7H, ArH), 7.08–7.06 (m, 2H, ArH), 6.92 (s, 1H, =CH), 6.83 (brs, 2H, NH_2), 4.05 (s, 1H, CH), 3.59 (d, 1H, J = 14.0 Hz, CH_2), 3.45 (s, 2H, CH_2), 3.40 (d, 1H, J = 14.4 Hz, CH_2), 3.05 (d, 1H, J = 16.0 Hz, CH_2), 2.65 (d, 1H, J = 16.0Hz, CH_2). ^{13}C NMR (DMSO-d_6): δ = 162.28, 159.72, 139.63, 139.37, 137.69, 132.28, 130.93, 130.85, 129.49, 129.40, 128.62, 127.99, 126.94, 120.86, 120.32, 115.51, 115.43, 115.30, 115.21, 112.66, 59.75, 55.84, 51.98, 51.57. Anal. Calcd for $C_{29}H_{23}F_2N_3O$: C, 74.50; H, 4.96; N, 8.99; found C, 74.66; H, 4.93; N, 8.95.

8-(3-Nitrobenzylidene)-2-amino-6-benzyl-5,6,7,8-tetrahydro-4-(3-nitrophenyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (5j). IR (KBr) 3337, 3293, 2184, 1679, 1647, 1596, 1522, 1465, 1399, 1351, 1263, 1218, 1159, 1085, 914, 815, 739, 695, 685 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 8.16–8.17 (m, 1H, ArH), 8.12–8.10 (m, 1H, ArH), 8.03 (brs, 2H, NH_2), 7.70–7.65 (m, 4H, ArH), 7.12–7.11 (m, 3H, ArH), 7.07 (s, 1H, =CH), 7.06–7.04 (m, 4H, ArH), 4.35 (s, 1H, CH), 3.66 (d, 1H, J = 14.4 Hz, CH_2), 3.54 (d, 1H, J = 15.2 Hz, CH_2), 3.49–3.34 (m, 2H, CH_2), 3.13 (d, 1H, J = 16.4 Hz, CH_2), 2.69 (d, 1H, J = 16.0 Hz, CH_2). ^{13}C NMR (DMSO-d_6): δ = 159.78, 142.45, 139.46, 137.69, 134.73, 131.70, 130.62, 129.45, 128.66, 128.60, 128.42, 127.99, 127.74, 126.93, 120.79, 112.87, 59.65, 56.01, 55.60, 51.89, 51.81, 51.62, 40.29. Anal. Calcd for $C_{29}H_{23}N_5O_5$: C, 66.79; H, 4.45; N, 13.43; found C, 66.96; H, 4.42; N, 13.39.

8-(4-Nitrobenzylidene)-2-amino-6-benzyl-5,6,7,8-tetrahydro-4-(4-nitrophenyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (5k). IR (KBr) 3329, 3301, 2200, 1681, 1650, 1591, 1517, 1421, 1398, 1340, 1269, 1218, 1168, 1108, 920, 895, 859, 811, 748, 700 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 8.24–8.19 (m, 4H, ArH), 7.51–7.48 (m, 4H, ArH), 7.15 (s, 1H, =CH), 7.14–7.13 (m, 2H, ArH), 7.08–7.06 (m, 3H, ArH), 7.05 (brs 2H, NH_2), 4.31 (s, 1H, CH), 3.69 (d, 1H, J = 14.8 Hz, CH_2), 3.53 (d, 1H, J = 14.8 Hz, CH_2), 3.48 (s, 2H, CH_2), 3.13 (d, 1H, J = 16.4 Hz, CH_2), 2.66 (d, 1H, J = 15.6 Hz, CH_2). ^{13}C NMR (DMSO-d_6): δ = 159.90, 150.89, 146.73, 145.92, 142.73, 139.70, 137.52, 130.34, 130.01, 128.97, 128.57, 127.98, 126.95, 124.03, 123.60, 113.88, 59.42, 54.85, 51.58, 40.59. Anal. Calcd for $C_{29}H_{23}N_5O_5$: C, 66.79; H, 4.45; N, 13.43; found C, 66.64; H, 4.47; N, 13.48.

8-(4-Bromobenzylidene)-2-amino-6-benzyl-4-(4-bromophenyl)-5,6,7,8-tetrahydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (5l). IR (KBr) 3326, 3293, 2196, 1681, 1644, 1594, 1485, 1407, 1392, 1373, 1322, 1267, 1170, 1098, 1071, 1010, 917, 887, 815, 749, 696 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 751–7.48 (m, 4H, ArH), 7.14–7.12 (m, 5H, ArH), 7.10 (m, 2H, ArH) 7.02–7.00 (m, 2H, ArH), 6.86 (brs, 2H, NH_2), 6.84 (s, 1H, =CH), 3.99 (s, 1H, CH), 3.56 (d, 1H, J = 14.4 Hz, CH_2), 3.40–3.36 (m, 3H ,CH_2), 3.00 (d, 1H, J = 16.0 Hz, CH_2), 2.60 (d, 1H, J = 16.0 Hz, CH_2). ^{13}C NMR (DMSO-d_6): δ = 159.77, 142.87, 139.46, 137.69, 135.06, 131.59, 131.34, 130.92, 129.83, 128.60, 128.01, 120.32, 120.23, 112.84, 59.62, 55.48, 51.75, 51.67, 40.36. Anal. Calcd for $C_{29}H_{23}Br_2N_3O$: C, 59.10, H, 3.94; N, 7.13; found C, 58.95; H, 3.95; N, 7.16.

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A Facile Route to the Synthesis of 1,4-Pyranonaphthoquinone Derivatives under Microwave Irradiation without Catalyst

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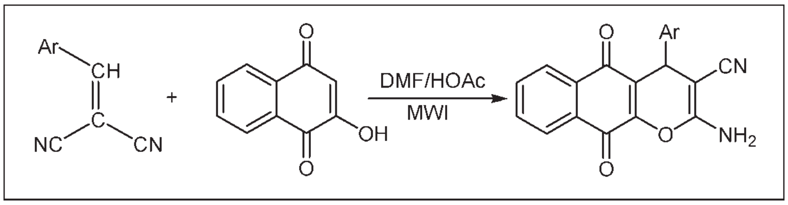

A series of 1,4-pyranonaphthoquinone derivatives were synthesized *via* the reaction of arylidenemalononitrile and 2-hydroxynaphthalene-1,4-dione in the mixed solvent of N,N-dimethylformamide and glacial acetic acid (HOAc) under microwave irradiation without catalyst. This protocol has the notable advantages of short reaction time, high yield, and convenient operation.

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INTRODUCTION

Organic reactions under microwave irradiation (MWI) have attracted considerable attention in the past decade for the efficient and friendly synthesis of various organic compounds [1]. More attractively, many reactions that typically required hours or days with conventional heating could be realized in several minutes utilizing MWI [2]. The use of MWI for the formation of carbon-heteroatom and carbon-carbon bonds has been successfully demonstrated [3].

Pyran derivatives are important compounds, which exhibit antibacterial activity [4,5], antiproliferation [6] and antitumor activities [7], hypotensive effect [8], antiallergic effect [9,10], and biological activities of local anesthetic and antiarrhythmic [11]. Derivatives of 1,4-naphthoquinone possess potent and versatile biological activity, such as antiallergic and anticancer activities [12]. And they are also used as inhibitors of KB cells [13]. Derivatives of 1,4-pyranonaphthoquinone, possessing both pyran ring and 1,4-naphthoquinone motif were evaluated against human cancer cell lines, which are KB (human epidermoid carcinoma), HeLa (human cervical carcinoma) and $HepG_2$ (human hepatocellular carcinoma) cell lines employing the MTT colorimetric method [14].

Due to their diverse biological activities, several groups [15] have been interested in the synthesis of derivatives of this structural type. For example, Abboub and coworkers [15a] have reported the reaction of 2-hydroxynaphthalene-1,4-dione and arylidenemalononitrile in methanol with Et_3N as catalyst under reflux condition. However, this protocol has drawbacks such as: (a) narrow application scope of substrates, (b) poor to moderate yields, (c) prolonged reaction time, (d) drastic reaction conditions and tedious work up. Therefore, the development of a relatively convenient method to prepare these compounds is still desirable.

Herein, we wish to report an efficient synthetic route to 1,4-Pyranonaphthoquinone derivatives by the reaction of arylidenemalononitrile and 2-hydroxynaphthalene-1,4-dione. The reaction was carried out in the mixed solvent of DMF and HOAc under MWI without catalyst (Scheme 1).

RESULTS AND DISCUSSION

Choosing an appropriate solvent is of crucial importance for successful MW promoted synthesis in view of a rapid rise of temperature in the reaction mixture. To search for the optimum solvent, different organic solvents such as ethanol, HOAc, DMF and mixed solvent of DMF, and HOAc were tested in the synthesis of **3c** at 100°C under MW irradiation (initial power 200 W and maximum power 250 W). As shown in Table 1, we could see the reaction in the mixed solvent of DMF and

Scheme 1

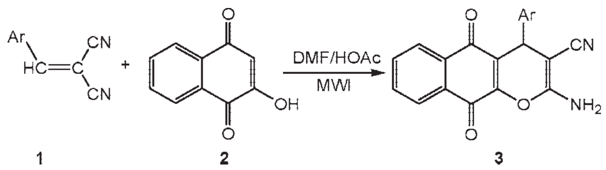


Table 2

Temperature optimization of synthesis **3c**.

Entry	Temp (°C)	Time (min)	Yield (%)
1	100	6	83
2	110	5	86
3	120	5	90
4	130	4	95
5	140	4	95
6	150	3	93

HOAc (the preferred volume ratio is 2:1) gave the best result (Table 1, Entry 5).

Moreover, to further optimize the reaction temperature, the synthesis of **3c** was performed in the mixed solvent of DMF and HOAc (2:1, V/V) at the temperatures ranging from 100 to 150°C in the increment of 10°C each time at 250 W. As illustrated in Table 2, when the temperature was increased from 100 to 130°C, the yield of **3c** obviously improved. However, no significant increase in the yield of **3c** was observed as the reaction temperature was raised from 130 to 150°C. Therefore, the temperature of 130°C was chosen for all further microwave-assisted reactions.

Under these optimized reaction conditions [mixed solvent (V_{DMF}/V_{HOAc}: 2:1, 1.5 mL), 130°C], a series of compounds **3** were synthesized with this simple procedure. The results were summarized in Table 3. As shown in Table 3, the applicability of this methodology is broad, not only to arylidenemalononitrile either with electron-donating groups or with electron-withdrawing groups, but also to heterocyclic arylidenemalononitrile (Table 3, entry 15). Therefore, we concluded that the electronic nature of the substituent has no significant effect on this reaction.

The proposed mechanism of this reaction may undergo a simple addition and cyclization progress (Scheme 2). The addition between arylidenemalononitrile **1** and 2-hydroxynaphthalene-1,4-dione **2** occurs to generate **4**, which subsequently undergoes intramolecular cyclization and isomerisation to afford final products **3**.

All the products were characterized by Mp, IR, ^{1}H NMR, and ^{13}C NMR spectral data, as well as by elemental analysis. The IR spectrum of compound **3b** showed strong absorptions at 3413 and 3329 cm^{-1} due to libration of NH_2 group, 2196 cm^{-1} due to CN group, 1662 and 1636 cm^{-1} due to C=O groups. The ^{1}H NMR spectrum of **3b** showed a singlet at δ 7.36 corresponding to proton from NH_2, and a singlet at δ 4.65 due to CH.

In summary, we have developed a rapid and facile method for the synthesis of highly functionalized 1,4-pyranonaphthoquinone derivatives of potential biological importance in excellent yields. Particularly, this protocol offers increased safety for small-scale high-speed synthesis, and the series of 1,4-pyranonaphthoquinone derivatives may provide expansive foreground for biomedical scopes.

Table 1

Solvent optimization of synthesis **3c**.

Entry	Solvent	Time (min)	Yield (%)
1	Ethanol	10	72
2	HOAc	7	74
3	DMF	8	70
4	DMF/HOAc(1:1)	6	76
5	DMF/HOAc(2:1)	6	83
6	DMF/HOAc(3:1)	6	78

EXPERIMENTAL

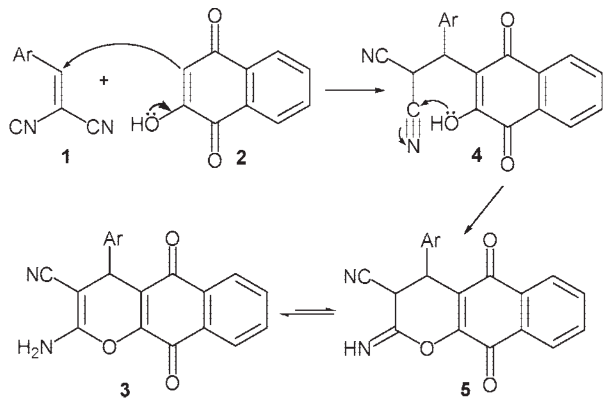
MWI was carried out with an Emrys™ Creator microwave oven from Personal Chemistry, Uppsala, Sweden. Melting points were determined in open capillaries and were uncorrected. IR spectra were recorded on a FTIR-Tensor 27 spectrometer in KBr. ^{1}H NMR spectra were measured on a DPX 400 MHz spectrometer using TMS as an internal standard and DMSO-d_6 as solvent. ^{13}C NMR spectra were measured on a DPX 100 MHz spectrometer using TMS as an internal standard and DMSO-d_6 as solvent. Elemental analysis was

Table 3

Physical data of products **3**.

Entry	Product	Ar	Time (min)	Yield (%)	Mp (°C)
1	**3a**	4-FC_6H_4	5	92	286–288
2	**3b**	4-ClC_6H_4	5	93	278–280
3	**3c**	4-BrC_6H_4	4	95	291–294
4	**3d**	4-$CH_3OC_6H_4$	6	81	257–259
5	**3e**	4-$CH_3C_6H_4$	6	83	254–257
6	**3f**	4-$NO_2C_6H_4$	4	94	247–248
7	**3g**	2-ClC_6H_4	5	90	>300
8	**3h**	3-$NO_2C_6H_4$	5	84	295–297
9	**3i**	3,4-$OCH_2OC_6H_3$	5	87	281–283
10	**3j**	2,4-$Cl_2C_6H_3$	4	86	293–295
11	**3k**	3,4-$(CH_3O)_2C_6H_3$	6	81	270–272
12	**3l**	4-OH-3-$NO_2C_6H_3$	4	80	237–239
13	**3m**	C_6H_5	5	88	>300
14	**3n**	3,4,5-$(CH_3O)_3C_6H_2$	6	85	290–293
15	**3o**	Thien-2-yl	6	82	274–276

Scheme 2



determined with a Perkin-Elmer 240c elemental analysis instrument.

General procedure for 2-arylidenemalononitrile (1). A mixture of aromatic aldehyde (5 mmol), malononitrile (5 mmol), and ethanol (2 mL) was added to a 10 mL reaction vessel of the monomodal Emrys™ Creator microwave synthesizer and allowed to react under MWI at 150 W power and 100°C for 2–3 min. The reaction mixture was cooled to room temperature, then filtered to give the crude product, which was further purified by recrystallization from EtOH (95%).

General procedure for 2-Amino-5,10-dihydro-5,10-dioxo-4-aryl-4*H*-benzo-[*g*]chromene-3-carbonitrile derivatives (3). The reactions were performed in a 10 mL Emrys™ reaction vial, arylidenemalononitrile **1** (1 mmol), 2-hydroxynaphthalene-1,4-dione **2** (1 mmol), and DMF/HOAc (1.5 mL) (2:1, V/V) were mixed and then capped. The mixture was irradiated for a given time at 130°C under MWI (initial power 200 W and maximum power 250 W). Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature, then filtered to give the crude product, which was further purified by recrystallization from EtOH (95%) to give pure 2-amino-5,10-dihydro-5,10-dioxo-4-aryl-4*H*-benzo[*g*]chromene-3-carbonitrile derivatives **3**.

2-Amino-4-(4-fluorophenyl)-5,10-dihydro-5,10-dioxo-4*H*-benzo [*g*]chromene-3-carbonitrile (3a). This compound was obtained according to above general procedure; ir (potassium bromide): 3407, 3324, 2210, 1667, 1635 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 8.06–8.04 (m, 1H, ArH), 7.88–7.83 (m, 3H, ArH), 7.38 (t, 2H, *J* = 5.6 Hz, ArH), 7.35 (s, 2H, NH$_2$), 7.13 (t, 2H, *J* = 8.8 Hz, ArH), 4.65 (s, 1H, CH); ^{13}C NMR (100 MHz) (δ, ppm): 182.55, 176.81, 162.37, 159.96, 158.28, 148.92, 139.82, 134.49, 134.12, 130.99, 130.64, 129.73, 129.65, 121.62, 119.24, 115.35, 57.33, 35.79. Anal. Calcd. for $C_{20}H_{11}FN_2O_3$: C, 69.36; H, 3.20; N, 8.09. Found: C, 69.54; H, 3.19; N, 8.11.

2-Amino-4-(4-chlorophenyl)-5,10-dihydro-5,10-dioxo-4*H*-benzo [*g*]chromene-3-carbonitrile (3b). This compound was obtained according to above general procedure; ir (potassium bromide): 3413, 3329, 2196, 1662, 1636 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 8.06–8.05 (m, 1H, ArH), 7.88–7.84 (m, 3H, ArH), 7.38 (s, 4H, ArH), 7.36 (s, 2H, NH$_2$), 4.65 (s, 1H, CH); ^{13}C NMR (100 MHz) (δ, ppm): 182.53, 176.78, 158.31, 149.03, 142.59, 134.51, 134.14, 131.67, 130.98, 130.63, 129.65, 128.47, 126.03, 125.78, 121.37, 119.16, 57.07, 36.98. Anal. Calcd. for $C_{20}H_{11}ClN_2O_3$: C, 66.22; H, 3.06; N, 7.72. Found: C, 66.43; H, 3.05; N, 7.74.

2-Amino-4-(4-bromophenyl)-5,10-dihydro-5,10-dioxo-4*H*-benzo [*g*]chromene-3-carbonitrile (3c). This compound was obtained according to above general procedure; ir (potassium bromide): 3406, 3326, 2194, 1665, 1603 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 8.07–8.04 (m, 1H, ArH), 7.89–7.83 (m, 3H, ArH), 7.50 (d, 2H, *J* = 8.4 Hz, ArH), 7.39 (s, 2H, NH$_2$), 7.31 (d, 2H, *J* = 8.4 Hz, ArH), 4.63 (s, 1H, CH); ^{13}C NMR (100 MHz) (δ, ppm): 182.52, 176.78, 158.30, 149.04, 143.01, 134.51, 134.14, 131.40, 130.97, 130.63, 130.02, 126.04, 125.78, 121.31, 120.20, 119.15, 57.00, 36.06. Anal. Calcd. for $C_{20}H_{11}BrN_2O_3$: C, 58.99; H, 2.72; N, 6.88. Found: C, 59.16; H, 2.73; N, 6.86.

2-Amino-5,10-dihydro-4-(4-methoxyphenyl)-5,10-dioxo-4*H*-benzo[*g*]chromene-3-carbonitrile (3d). This compound was obtained according to above general procedure; ir (potassium bromide): 3396, 3329, 2204, 1672, 1635 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 8.06–8.04 (m, 1H, ArH), 7.87–7.83 (m, 3H, ArH), 7.30 (s, 2H, NH$_2$), 7.22 (d, 2H, *J* = 8.4 Hz, ArH), 6.86 (d, 2H, *J* = 8.8 Hz, ArH), 4.56 (s, 1H, CH), 3.71 (s, 3H, OCH$_3$); ^{13}C NMR (100 MHz) (δ, ppm): 182.58, 176.88, 158.29, 148.55, 135.64, 134.49, 134.09, 131.02, 130.56, 128.82, 128.29, 126.02, 125.76, 122.25, 119.37, 113.93, 57.70, 55.04, 35.67. Anal. Calcd. for $C_{21}H_{14}N_2O_4$: C, 70.39; H, 3.94; N, 7.82. Found: C, 70.62; H, 3.95; N, 7.87.

2-Amino-5,10-dihydro-5,10-dioxo-4-*p*-tolyl-4*H*-benzo[*g*]-chromene-3-carbonitrile (3e). This compound was obtained according to above general procedure; ir (potassium bromide): 3404, 3327, 2197, 1662, 1603 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 8.06–8.04 (m, 1H, ArH), 7.87–7.83 (m, 3H, ArH), 7.32 (s, 2H, NH$_2$), 7.19 (d, 2H, *J* = 8.0 Hz, ArH), 7.11 (d, 2H, *J* = 7.6 Hz, ArH), 4.57 (s, 1H, CH), 2.25 (s, 3H, CH$_3$); ^{13}C NMR (100 MHz) (δ, ppm): 182.53, 176.86, 158.29, 148.73, 140.63, 136.25, 134.51, 134.10, 131.01, 130.58, 129.12, 127.56, 126.03, 125.77, 122.16, 119.33, 57.59, 36.09, 20.59. Anal. Calcd. for $C_{21}H_{14}N_2O_3$: C, 73.68; H, 4.12; N, 8.18. Found: C, 73.88; H, 4.11; N, 8.20.

2-Amino-5,10-dihydro-4-(4-nitrophenyl)-5,10-dioxo-4*H*-benzo [*g*]chromene-3-carbonitrile (3f). This compound was obtained according to above general procedure; ir (potassium bromide): 3421, 3328, 2201, 1673, 1604 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 8.21–8.19 (m, 1H, ArH), 8.11 (d, 1H, *J* = 8.4 Hz, ArH), 8.06 (d, 1H, *J* = 7.6 Hz, ArH), 7.88–7.84 (m, 4H, ArH), 7.63 (t, 1H, *J* = 8.0 Hz, ArH), 7.49 (s, 2H, NH$_2$), 4.88 (s, 1H, CH); ^{13}C NMR (100 MHz) (δ, ppm): 182.56, 176.75, 158.46, 149.37, 147.94, 145.81, 134.77, 134.47, 134.14, 130.97, 130.05, 126.02, 125.79, 122.49, 120.58, 119.01, 56.63, 36.33. Anal. Calcd. for $C_{20}H_{11}N_3O_5$: C, 64.35; H, 2.97; N, 11.26. Found: C, 64.51; H, 2.96; N, 11.29.

2-Amino-4-(2-chlorophenyl)-5,10-dihydro-5,10-dioxo-4*H*-benzo[*g*]chromene-3-carbonitrile (3g). This compound was obtained according to above general procedure; ir (potassium bromide): 3434, 3327, 2192, 1663, 1635 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 8.08–8.06 (m, 1H, ArH), 7.87–7.84 (m, 3H, ArH), 7.45–7.40 (m, 2H, ArH), 7.37 (s, 2H, NH$_2$), 7.26–7.24 (m, 2H, ArH), 5.15 (s, 1H, CH); ^{13}C NMR (100 MHz) (δ, ppm): 182.39, 176.78, 158.40, 149.52, 140.92, 134.57, 134.15, 132.01, 130.93, 130.57, 130.50, 129.38, 128.67, 127.79, 126.06, 125.80, 121.29, 118.77, 56.33, 33.55. Anal. Calcd. for $C_{20}H_{11}ClN_2O_3$: C, 66.22; H, 3.06; N, 7.72. Found: C, 66.41; H, 3.07; N, 7.70.

2-Amino-5,10-dihydro-4-(3-nitrophenyl)-5,10-dioxo-4*H*-benzo[*g*] chromene-3-carbonitrile (3h). This compound was obtained according to above general procedure; ir (potassium bromide): 3421, 3328, 2202, 1671, 1639 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 8.21–8.18 (m, 1H, ArH), 8.11 (d, 1H, *J* = 7.6 Hz, ArH), 8.07 (d, 1H, *J* = 7.6 Hz, ArH), 7.87–7.84 (m, 4H, ArH), 7.63 (t, 1H, *J* = 8.0 Hz, ArH), 7.49 (s, 2H, NH$_2$), 4.88 (s, 1H, CH); ^{13}C NMR (100 MHz) (δ, ppm): 182.57, 176.76, 158.44, 149.37, 147.93, 145.82, 134.79, 134.47, 134.14, 130.96, 130.73, 130.05, 126.02, 125.79, 122.49, 122.16, 120.54, 119.03, 56.59, 36.32. Anal. Calcd. for $C_{20}H_{11}N_3O_5$: C, 64.35; H, 2.97; N, 11.26. Found: C, 64.51; H, 2.98; N, 11.23.

2-Amino-4-(benzo[*d*][1,3]dioxol-5-yl)-5,10-dihydro-5,10-dioxo-4*H*-benzo[*g*]chromene-3-carbonitrile (3i). This compound was obtained according to above general procedure; ir (potassium bromide): 3427, 3396, 2207, 1673, 1637 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 8.06–8.04 (m, 1H, ArH), 7.89–7.83 (m, 3H, ArH), 7.29 (s, 2H, NH$_2$), 6.89–6.86 (m, 1H, ArH), 6.83 (d, 1H, *J* = 8.0 Hz, ArH), 6.78 (d, 1H, *J* = 7.6 Hz, ArH), 5.97 (s, 2H, CH$_2$), 4.55 (s, 1H, CH); ^{13}C NMR (100 MHz) (δ, ppm): 182.59, 176.84, 158.21, 148.82, 147.39, 146.23, 137.66, 134.45, 134.07, 131.04, 130.67, 126.00, 125.77, 121.75, 120.98, 119.29, 112.71, 108.13, 100.97, 57.70, 36.12. Anal. Calcd. for $C_{21}H_{12}N_2O_5$: C, 67.74; H, 3.25; N, 7.52. Found: C, 67.94; H, 3.26; N, 7.50.

2-Amino-4-(2,4-dichlorophenyl)-5,10-dihydro-5,10-dioxo-4*H*-benzo[*g*]chromene-3-carbonitrile (3j). This compound was obtained according to above general procedure; ir (potassium bromide): 3467, 3341, 2202, 1671, 1632 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 8.08–8.06 (m, 1H, ArH), 7.88–7.85 (m, 3H, ArH), 7.60–7.58 (m, 1H, ArH), 7.49 (d, 1H, *J* = 8.4 Hz, ArH), 7.42 (s, 2H, NH$_2$), 7.33 (d, 1H, *J* = 8.4 Hz, ArH), 5.14 (s, 1H, CH); ^{13}C NMR (100 MHz) (δ, ppm): 182.43, 176.73, 158.37, 149.63, 140.21, 134.57, 134.20, 132.92, 132.26, 131.94, 130.89, 130.59, 128.66, 127.97, 126.07, 125.80, 120.70, 118.69, 55.77, 33.15. Anal. Calcd. for $C_{20}H_{10}Cl_2N_2O_3$: C, 60.48; H, 2.54; N, 7.05. Found: C, 60.67; H, 2.55; N, 7.02.

2-Amino-5,10-dihydro-4-(3,4-dimethoxyphenyl)-5,10-dioxo-4*H*-benzo[*g*]chromene-3-carbonitrile (3k). This compound was obtained according to above general procedure; ir (potassium bromide): 3418, 3324, 2195, 1688, 1632 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 8.06–8.04 (m, 1H, ArH), 7.90–7.83 (m, 3H, ArH), 7.28 (s, 2H, NH$_2$), 6.88–6.86 (m, 2H, ArH), 6.80 (d, 1H, *J* = 8.4 Hz, ArH), 4.56 (s, 1H, CH), 3.72 (s, 3H, OCH$_3$), 3.70 (s, 3H, OCH$_3$); ^{13}C NMR (100 MHz) (δ, ppm): 182.62, 176.91, 158.27, 148.66, 148.63, 147.96, 136.22, 134.47, 134.06, 131.07, 130.62, 126.01, 125.78, 122.04, 119.89, 119.38, 111.95, 111.68, 57.70, 55.62, 55.52, 36.05. Anal. Calcd. for $C_{22}H_{16}N_2O_5$: C, 68.04; H, 4.15; N, 7.21. Found: C, 68.26; H, 4.16; N, 7.23.

2-Amino-5,10-dihydro-4-(4-hydroxy-3-nitrophenyl)-5,10-dioxo-4*H*-benzo[*g*]chromene-3-carbonitrile (3l). This compound was obtained according to above general procedure; ir (potassium bromide): 3446, 3350, 2197, 1667, 1642 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 10.95 (s, 1H, OH), 8.06–8.04 (m, 1H, ArH), 7.90–7.83 (m, 4H, ArH), 7.53 (d, 1H, *J* = 8.4 Hz, ArH), 7.41 (s, 2H, NH$_2$), 7.07(d, 1H, *J* = 8.8 Hz, ArH), 4.68 (s, 1H, CH); ^{13}C NMR (100 MHz) (δ, ppm): 182.60, 176.82, 158.37, 150.96, 149.01, 136.73, 134.87, 134.59, 134.47, 134.11, 131.02, 130.68, 125.99, 125.79, 124.03, 120.98, 119.15, 119.10, 56.89, 35.46. Anal. Calcd. for $C_{20}H_{11}N_3O_6$: C, 61.70; H, 2.85; N, 10.79. Found: C, 61.90; H, 2.84; N, 10.82.

2-Amino-5,10-dihydro-5,10-dioxo-4-phenyl-4*H*-benzo[*g*]-chromene-3-carbonitrile (3m). This compound was obtained according to above general procedure; ir (potassium bromide): 3401, 3325, 2200, 1671, 1636 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 8.07–8.05 (m, 1H, ArH), 7.90–7.83 (m, 3H, ArH), 7.34 (s, 2H, NH$_2$), 7.31 (d, 4H, *J* = 4.4 Hz, ArH), 7.23–7.22 (m, 1H, ArH), 4.61 (s, 1H, CH); ^{13}C NMR (100 MHz) (δ, ppm): 182.53, 176.84, 158.37, 148.91, 143.55, 134.51, 134.12, 131.03, 130.63, 128.56, 127.65, 127.05, 126.05, 125.79, 122.04, 119.27, 57.54, 36.50. Anal. Calcd. for $C_{20}H_{12}N_2O_3$: C, 73.16; H, 3.68; N, 8.53. Found: C, 73.38; H, 3.69; N, 8.51.

2-Amino-5,10-dihydro-4-(3,4,5-trimethoxyphenyl)-5,10-dioxo-4*H*-benzo[*g*]chromene-3-carbonitrile (3n). This compound was obtained according to above general procedure; ir (potassium bromide): 3418, 3327, 2196, 1662, 1634 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 8.07–8.05 (m, 1H, ArH), 7.92–7.84 (m, 3H, ArH), 7.30 (s, 2H, NH$_2$), 6.57–6.55 (m, 2H, ArH), 4.57 (s, 1H, CH), 3.74 (s, 6H, 2OCH$_3$), 3.62 (s, 3H, OCH$_3$); ^{13}C NMR (100 MHz) (δ, ppm): 182.64, 176.88, 158.29, 152.87, 149.00, 139.28, 136.59, 134.43, 134.04, 131.08, 130.72, 125.99, 125.82, 121.48, 119.35, 105.13, 59.89, 57.54, 55.99, 36.76. Anal. Calcd. for $C_{23}H_{18}N_2O_6$: C, 66.02; H, 4.34; N, 6.70. Found: C, 66.24; H, 4.35; N, 6.72.

2-Amino-5,10-dihydro-5,10-dioxo-4-(thiophen-2-yl)-4*H*-benzo[*g*]chromene-3-carbonitrile (3o). This compound was obtained according to above general procedure; ir (potassium bromide): 3409, 3328, 2196, 1665, 1638 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 8.05–8.04 (m, 1H, ArH), 7.98–7.96 (m, 1H, ArH), 7.88–7.86 (m, 2H, ArH), 7.49 (s, 2H, NH$_2$), 7.40 (d, 1H, *J* = 4.0 Hz, ArH), 7.01 (d, 1H, *J* = 3.2 Hz, ArH), 6.95 (t, 1H, *J* = 2.8 Hz, ArH), 4.97 (s, 1H, CH); ^{13}C NMR (100 MHz) (δ, ppm): 182.38, 176.81, 158.93, 148.18, 147.10, 134.69, 134.29, 130.91, 130.48, 127.18, 126.16, 125.92, 125.41, 125.35, 121.87, 119.19, 57.10, 31.17. Anal. Calcd. for $C_{18}H_{10}N_2O_3S$: C, 64.66; H, 3.01; N, 8.38; S, 9.59. Found: C, 64.83; H, 3.00; N, 8.35; S, 9.61.

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Utility of *p*-Phenylenediformamidine in the Synthesis of Bisazoles and Phenanthroline

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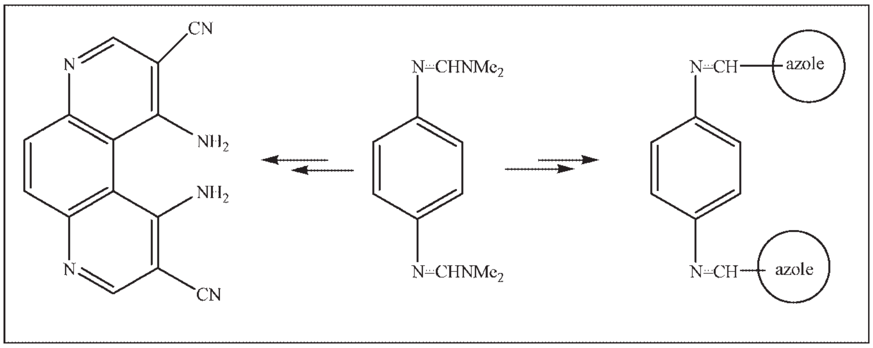

p-Phenylenediformamidine **1** is readily obtained upon treating *p*-phenylenediamine with dimethylformamide dimethyl acetal (DMFDMA) by heating or by microwave irradiation. Compound **1** was treated with active methylene nitriles followed by hydrazine hydrate derivatives to give bisaminopyrazole derivatives. Other bisazoles can be obtained by reacting **1** with aminoazole derivatives. Cyclization of Bis [2-(*p*-phenelyeneimino)malononitrile] to 1,10-diaminophenanthroline-2,9-dicarbonitrile is also reported.

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INTRODUCTION

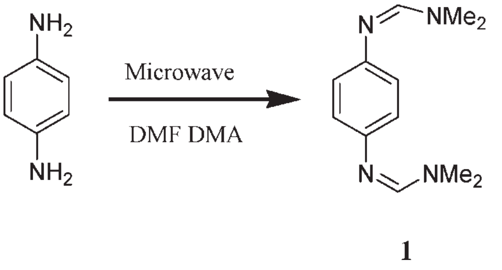
Heterocyclic compounds have attracted considerable interest. A lot of attention has been directed toward the synthesis of polyfunctionally substituted azoles because of their biological and pharmaceutical activities. For example, pyrazoles have shown many interesting biological and pharmacological properties such as inhibitors of p 38 MAP kinase [1] anti-tumor CDK inhibitors [2], potent inhibitors of type II topoisomerases [3]. Thiazolediamides are used as potent g-secretase [4], also as vanilloid receptor 1 (TRPV 1) antagonists [5]. Both imidazole and triazole potent CB_1 receptor antagonists related to SR141716 [6]. 4-Triazole-modified zanamivir analogs exert moderate inhibition against AIV (H5N1) [7]. Carroll *et al.* [8] reported that the heterocyclic replacement on substituted benzene ring showed a progressive loss of P2X-, potency in the order tetrazole > triazole > imidazole > pyrazole. He rationalized this result to overall electron density of the core heterocycle and P2X-, potency. Furthermore, phenylenediformamidine showed good acaricidal and insecticidal activity [9]. A combination of phenylenediformamidine and azoles in one system seemed to be useful. Thus, design of a simple and an efficient approach to the polyfunctionally substituted heterocycles on benzene ring is one of our goals. In conjugation with our previous work [10], here we report on the synthesis of bisazole using *p*-phenylenediformamidine as starting material.

RESULTS AND DISCUSSION

p-Phenylenediamine readily reacts with dimethylformamide dimethylacetal, DMFDMA, to give *N.N'*-*p*-phenylenediformamidine **1**, which agree with the literature in this data [11]. Formamidine, **1** could also be obtained by Vilsmeier reaction [12,13]. Synthesis of *p*-phenylenediformamidine **1** using microwave irradiation has not been described before. In this article, we have obtained *p*-phenylenediformamide **1** in an excellent yield and short time upon irradiating a mixture of *p*-phenylenediamine, DMFDMA, and xylene at 160°C (cf. Scheme 1). The reaction product was established based on mass spectrometry which showed *m*/*z* 260 (M^+). ^{1}H NMR revealed the presence of NMe_2 and aromatic protons as a singlet at d 3.49 and d 6.78 ppm, respectively. This NMR data confirm the symmetry in the molecule. Furthermore, the CH protons appeared at d 7.64 ppm.

Chemical reactivity of *p*-phenylenediformamidine **1** toward different active methylene has been investigated. Thus, compound **1** reacted with **2a–c** in glacial acetic acid to give the same reaction product **3**. This result prompted us to investigate the behavior of **1** in acetic

Scheme 1



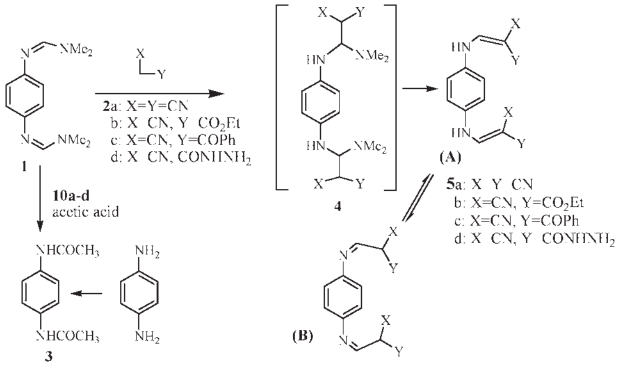
acid as a blank experiment. We also obtained here the same result as that obtained from its reaction with each of compounds **2a–c**. This supported our believing that the acetylation reaction had taken place between the solvent (acetic acid) and *p*-phenylenediformamidine **1**. This result was confirmed by refluxing *p*-phenylenediamine in glacial acetic acid which afforded the acetylated product **3**. Thus, the reaction of **2a–d** with *p*-phenylenediformamidine **1** in pyridine afforded the target products **5a–d**. The formation of these products are believed to proceed *via* addition of active methylene to the imine double bond to give the nonisolable intermediate **4** followed by loss of two molecules of dimethylamine. ^{1}H NMR spectrum of structure **5a** showed the low field signals as a doublet at d 8.45 ppm corresponding to CH protons, while aromatic protons appeared as a singlet at d 7.44 ppm. These data confirm the symmetry in the molecule. Signal at d 11.13 ppm was assigned to the NH protons. This signal underwent a facile hydrogen deuterium exchange upon addition of deuterium oxide. The NOE experiment showed the irradiation of NH protons enhancing the CH protons while the aromatic protons was not affected revealing the special proximity of NH and CH protons. The ^{13}C NMR spectrum revealed a low field signal at d 156.41 ppm and a high field signal at d 52.52 ppm corresponding to the imine carbon and ethylenic carbon, respectively. Other carbons appeared at expected positions. On the other hand, a structure of compound **5b** was established based on ^{1}H NMR which showed a triplet at d 1.27 ppm (J = 7.2 Hz) and quartet at d 4.21 ppm (J = 7.2 Hz) corresponding to methyl group and methylene group, respectively. Aromatic protons appeared at d 7.52 ppm as a singlet. Other synthetic method for **5b** [14] and **5a** [15] had been described *via* condensation of ethoxymethylene-malononitrile or ethoxymethylenethyl cyanoacetate with *p*-phenylenediamine. Similarly **5c** and **d** were elucidated (Scheme 2).

Enamine of **5a–d** (form A) may be tautomerized to the corresponding imine (form B). Thus, phenylenimino derivatives **5a–c** reacted with nucleophilic reagent, hydrazine hydrate, or phenyhydrazine, to afford the intermediate **6.** This could be formed *via* addition of the amino group of the hydrazine hydrate to the cyano function followed by further addition in case of **5a** and condensation in case of **5b** and **5c** to loss ethanol or water molecule, respectively, to give the final isolated product **7**, **8**, and **9.** An independent method for preparation of **9** took place through heating of **5d** for a long time in a basic medium. The obtained product was confirmed by mixing melting point and IR spectrum. The reaction product **9** is believed to proceed through intramolecular cyclization of **5d** through addition of amino group to cyano function. Reaction of **5a** and **5b** with phenylhydrazine produce the corresponding compounds **10** and **11**, respectively. The compounds **10** and **11** formed through addition of amino group of phenylhydrazine to the cyano function followed by addition to the second cyano group in case of **5a** or lose of ethanol in case of **5b** to cyclized to **10** and **11**, respectively. The structure of the reaction products are established based on the elemental analysis and spectral data. IR spectra in all cases revealed the absence of the cyano group and the presence of amino group. ^{1}H NMR confirms the presence of the imine protons, amino group, and NH. In addition, the absence of ethyl group was observed. Phenyl protons in **10** and **11** appeared at high field than those of corresponding **7** and **8** reflecting shielding effect of sp^3 nitrogen on aromatic protons (cf. experimental part) (Scheme 3).

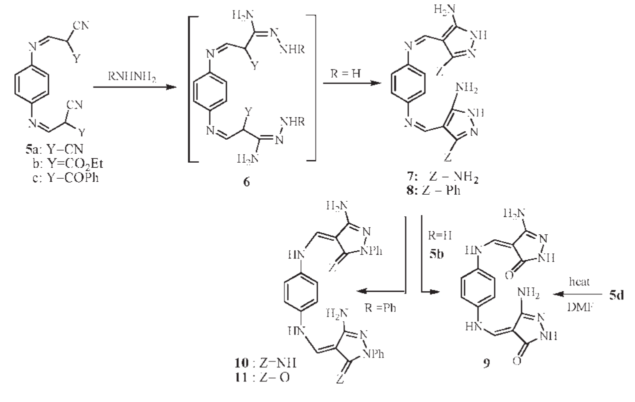
Moreover, bisazole derivatives **12–16** could be synthesized by direct treatment of *p*-phenylenedi-formamidine **1** with different heteroamines, for example, aminotriazole, aminoimidazole, aminothiazole, and aminobenzimidazole. The reaction products are believed to be formed through the addition of the nucleophilic amino group to the imine double bond to give the nonisolated intermediate **A** followed by loss of two molecules of dimethylamine to afford the final isolated products **B**, **12–16** (Scheme 4). The structure of the reaction products were confirmed by elemental analysis and spectral data as indicated in the experimental section.

Trials to cyclize **5a** to phenanthrolinedicarbonitrile derivative **17** or **18** in polyphosphoric acid or ionic

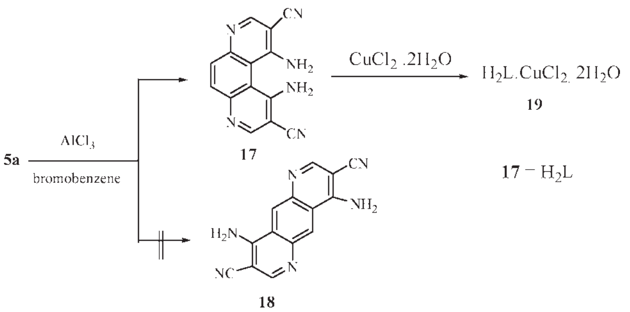
Scheme 2



Scheme 3

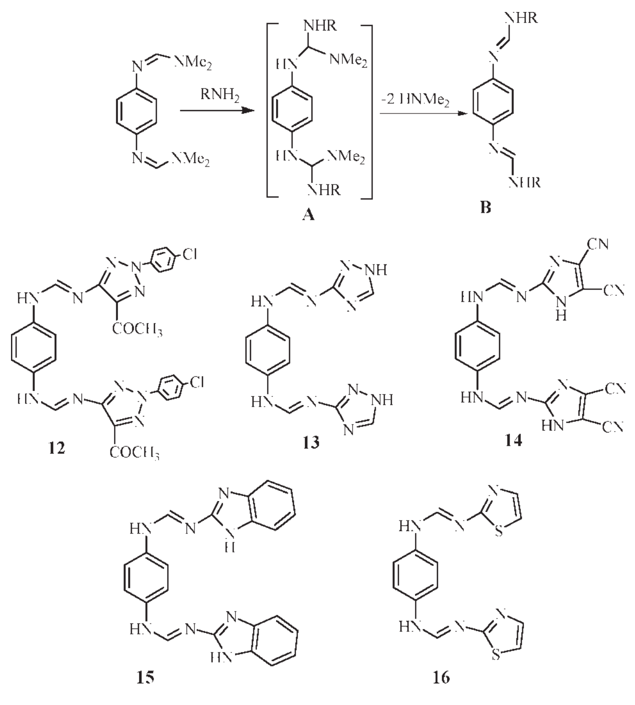


Scheme 5



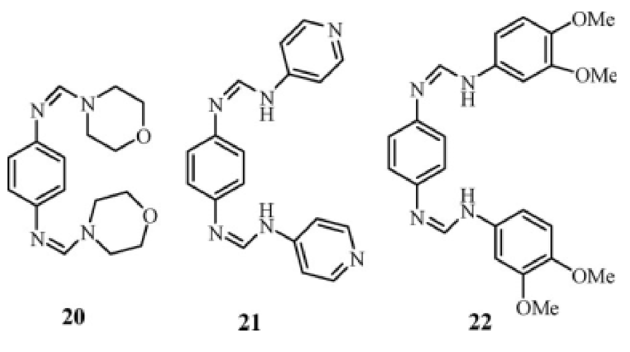
liquid (pyridinium hydrochloride) or by microwave irradiation for a long time has failed. An extension of Gould-Jacobs reaction [16–21] approach for cyclization of **5a** to **17**, a mixture of compound **5a** and anhydrous aluminum chloride has been heated under reflux in bromobenzene to give a product characterized **17** or **18**. The latter compound **18** is ruled out based on the NOE experiment which showed the protons of amino groups in opposite to the benzene protons. Where the irradiation of NH_2 protons has no effect on benzene ring protons which agree with compound **17**. In addition, the reaction product was established as 1,10-diaminophenanthroline-2,9-dicarbo-nitrile **17** based on elemental analysis and spectral data. ^{1}H NMR reveals the presence of amino protons at 11.12 ppm (D_2O-exchange), two protons of pyridine rings at 8.45 ppm, and a singlet proton at 7.47 ppm represent the symmetrical two protons of benzene ring. Bidentate **17** (H_2L) could also be confirmed by using as a ligand. Thus, compound **17** was uptake Cu(II) from its solution, which support that the two amino groups are in the same side, to give the complex **19**. Complex product **19** was established based on its elemental analysis and spectral data. IR reveals the presence of a broad band at 3440 cm^{-1} refers to presence of water molecules. IR also reveals the presence of amino and cyano bands at 3297, 3219, and 2215 cm^{-1}, respectively. In continuation of complex structure elucidation, energy-dispersive spectroscopy (EDS) reveals the presence of Cu(II). In addition to chlorine, carbon, hydrogen, and oxygen appeared clearly in the EDS chart. Furthermore, the electron spin resonance (ESR) confirmed the formation of the complex, where the π-band ESR spectrum of the Cu(II) complex at room temperature is of axial type consistent with d_{x2}-d_{y2} ground state (Scheme 5).

Scheme 4



Investigation of reactivity of **1** toward aliphatic, heteroaromatic, and aromatic amines was also studied. Thus, compound **1** reacted with morpholine, 4-aminopyridine, and 3,4-dimethoxyaniline in pyridine to give the N-substituted amine derivatives **20–22**, respectively (Scheme 6). This reaction is believed to be proceed through loss of two dimethylamine molecules.

Scheme 6



EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded in KBr disks using a Perkin-Elmer System 2000 FT-IR spectrophotometer. ^1H and ^{13}C-NMR spectra were recorded on a Bruker DPX 400, 400MHz super-conducting NMR spectrometer in DMSO-d_6 as solvent and TMS as internal standard; chemical shifts are reported in d units (ppm). Mass spectra were measured on a VG Autospec-Q (high resolution, high performance, tri-sector GC/MS/MS). Microanalyses were performed on a LECO CHNS-932 Elemental Analyzer. Microwave experiments were conducted using a microwave oven DAEWOO, edition II (KOR-8667).

Preparation of *N,N'*-Phenylenediformamidine (1). ***Method A.*** To a solution of *p*-pheneylenediamine 1.08 g (0.01 mol) in xylene (30 mL), dimethylformamide dimethylacetal (DMFDMA), 1.19 g (0.01 mol) was added. The reaction mixture was heated under reflux for 3 h. The solid product so formed after cooling was collected by filtration and crystallized from xylene.

Method B. To a solution of *p*-pheneylenediamine 1.08 g (0.01 mol) in xylene (5 mL), dimethylformamide dimethylacetal (DMFDMA), 1.19 g (0.01 mol) was added. The reaction mixture was irradiated for 15 min in microwave at 160°C. The solid product so formed was collected by filtration and crystallized from xylene. Melting point 116–119°C (ref. [14] mp 119–120°C; ref. [12,13] mp 120.5–121°C).

Compound **1** was obtained as yellowish white crystals 1.8 g (82%), while in case of microwave synthesis 1.98 g (91%) was obtained, from xylene, mp 116–119°C; ir: 1655 cm^{-1} (C=N); ^1H NMR: δ 7.64 (s, 2H, CH=), 6.78 ppm (s, 4H, C_6H_4), 3.49 (s, 12H. 4Me) ^{13}C NMR: δ 153.74 (—CH=), 147.52, 121.76 (aromatic carbons), 39.86 (Me); ms: *m/z* 218 (M^+, 100%). Anal. Calcd. for $C_{12}H_{18}N_4$ (218.30): C, 66.02; H, 8.31; N, 25.67. Found: C, 65.98; H, 8.06; N, 25.76.

General procedure for ylidene synthesis (5a–d). ***Method A.*** To a solution of (**1**) 2.18 g (0.01 mol) in ethanol (30 mL), active methylene compound (**2a**) or (**2b**) or (**2c**) or (**2d**) (0.01 mol) was added. The reaction mixture was heated under reflux for 3 h. The obtained product after cooling was collected by filtration and crystallized from the proper solvent.

Method B. To a solution of (**1**) 2.18 g (0.01 mol) in DMF (5 mL), active methylene compound (**2a**) or (**2b**), (0.01 mol), was added. The reaction mixture was irradiated for 30 min in microwave at 160°C in the case of (**2a**) and 155°C in the case of (**2b**). The obtained product after cooling was collected by filtration and crystallized from the proper solvent.

Bis [2-(*p*-phenelyeneimino)malononitrile] (5a). This compound was obtained as yellow crystals 1.62 g (62%) while in case of microwave synthesis 2.16 g (83%) was obtained), from acetone, mp > 300°C; ir: 3299, 3224 (2NH), 2223, 2210 (CN), 1655 cm^{-1} (C=N); ^1H NMR: δ 11.15 (br, 2H, 2NH), 8.49 (d, 2H, CH=), 7.44 ppm (s, 4H, C_6H_4). ^{13}C NMR: δ 156.41 (—CH=), 137.21, 119.81 (aromatic carbons), 117.37, 115.12 (CN), 52.52 (ethylenic carbon); ms: *m/z* 260 (M^+, 100%). Anal. Calcd. for $C_{14}H_8N_6$ (260.25): C, 64.61; H, 3.10; N, 32.29. Found: C, 64.95; H, 3.06; N, 31.99.

Bis[(Ethyl 2-cyano-2-(*p*-phenyleneimino) acetate] (5b). This compound was obtained as yellow crystals 1.77 g (50%) from acetone, mp > 300°C; ir: 3337 (br, 2NH), 2209 (CN), 1667 cm^{-1} (C=N); ^1H NMR: δ 10.77 (br, 2H, 2NH), 8.47 (d, 2H, CH=), 7.52 ppm (s, 4H, C_6H_4), 4.21 (q, 4H, $2CH_2$—, J = 7.2 Hz), 1.27 (t, 6H, 2Me, J = 7.2 Hz). ^{13}C NMR: δ 167.15, 165.58 (2CO), 153.32 (2—CH=), 137.82, 136.51, 119.93, 119.84, 119.74, 119.16 (aromatic carbons), 117.00 (CN), 75.01, 74.19 (ethylenic carbons); 61.31 (CH_2), 15.22 (Me); ms: *m/z* 354 (M^+, 100%). Anal. Calcd. for $C_{18}H_{18}N_4O_4$ (354.36): C, 61.01; H, 5.12; N, 15.81. Found: C, 61.36; H, 5.42; N, 16.18.

Bis[(3-oxo-3-phenyl-2-(*p*-pheneyleneimino) propanenitrile] (5c). This compound was obtained as red crystals 2.72 g (65%) from acetone, mp > 300°C; ir: 3449, 3349 (NH), 2204 (CN), 1703 cm^{-1} (CO); ^1H NMR: δ 10.52 (br, 2H, 2NH), 8.40 (d, 2H, CH=), 7.51–6.59 ppm (m, 14H, C_6H_4, $2C_6H_5$). ^{13}C NMR: δ 190.54 (CO), 153.65, 152.96, 147.98, 140.19, 130.70, 128.44, 128.22, 126.54, 121.22, 119.08 (aromatic carbons), 114.57 (CN), 87.15 (ethylenic carbons); ms: *m/z* 446 (M^+, 10%). Anal. Calcd. for $C_{26}H_{18}N_4O_2$ (418.45): C, 74.63; H, 4.34; N, 13.39. Found: C, 74.63; H, 4.01; N, 13.77.

Bis[2-cyano-2-(*p*-pheneyleneimino)acetamide] (5d). This compound was obtained as red crystals 1.79 g (55%) from acetone, mp > 300°C; ir: br, 3343 (NH & NH_2), 2210 (CN), 1670 cm^{-1} (CO). ^1H NMR: δ 10.93, 5.59 (br, 8H, 4NH, $2NH_2$), 8.45 (d, 2H, 2CH=), 7.39 ppm (s, 4H, C_6H_4); ms: *m/z* 296. (M^+, 10%). Anal. Calcd. for $C_{14}H_{14}N_8O_2$ (326.31): C, 51.53; H, 4.32; N, 34.34. Found: C, 51.78; H, 4.53; N, 34.34.

General procedure for synthesis of bisazoles (7, 8, 10, 11). To a solution of (**5a**) or (**5b**) or (**5c**), (0.01 mol), in DMF (30 mL) an equivalent amount of hydrazine hydrate or phenyl hydrazine was added. The reaction mixture was heated under reflux for 3 h. The obtained product after cooling was collected by filtration and washed by ethanol (3 × 10 mL). The obtained product was crystallized from the proper solvent.

***N*^{1},*N*^{4}-Bis[(3,5-diamino-4*H*-pyrazol-4-ylidene)methyl)benzene-1,4-diamine (7).** This compound was obtained as yellow crystals 2.10 g (65%) from acetone, mp 150–151°C; ir: 3164, 3112 cm^{-1} (NH & NH_2). ^1H NMR: δ 10.06 (br, 8H, $4NH_2$), 8.15 (s, 2H, 2CH=), 8.01 (s, 2H, 2NH), 7.91 ppm (m, 4H, C_6H_4); ms: *m/z* 324 (M^+, 6%). Anal. Calcd. for $C_{14}H_{16}N_{10}$ (324.34): C, 51.84; H, 4.97; N, 43.18. Found: C, 52.01; H, 5.12; N, 43.44.

***N*^{1},*N*^{4}-Bis[(3-amino-5-phenyl-4*H*-pyrazol-4-ylidene)methyl] benzene-1,4-diamine (8).** This compound was obtained as brown crystals 2.45 g (55%) from acetone, mp > 300°C; ir: 3211, 3114 (NH & NH_2); 1617 cm^{-1} (C=N). ^1H NMR: δ 10.14 (br, 4H, $2NH_2$), 9.44 (br, 2H, 2NH), 8.16 (s, 2H, 2CH=), 7.56–8.01 ppm (m, 14H, C_6H_4, $2C_6H_5$); ms: *m/z* 446 (M^+, 12%). Anal. Calcd. for $C_{26}H_{22}N_8$ (446.51): C, 69.94; H, 4.97; N, 25.10. Found: C, 70.11; H, 5.12; N, 24.98.

Synthesis of *N*^{1},*N*^{4}-bis(3-amino-4-methylidene-1*H*-pyrazol-5(4*H*)-one)benzene-1,4-diamine (9). ***Method A.*** To a solution of (**5b**) 3.54 g (0.01 mol) in DMF (30 mL), hydrazine hydrate 0.75 g (0.015 mol) was added. The reaction mixture was heated under reflux for 3 h. The obtained product after cooling was collected by filtration and washed by cold ethanol (3 × 10 mL). The obtained product was crystallized from the proper solvent.

Method B. A solution of (**5d**) 3.26 g (0.01 mol) was heated under reflux in DMF (30 mL) for 3 h. The obtained product after cooling was collected by filtration and washed by cold ethanol (3 × 10 mL). This compound was obtained as brown crystals 1.96 g (60%) from acetone, mp 163–164°C; ir: 3211, 3114 (NH & NH_2); 1668 (CO), 1617 cm^{-1} (C=N). ^1H NMR:

δ 10.04 (br, 2H, 2NH), 9.45 (br, 2H, 2NH), 8.14 (d, 2H, 2CH=), 8.01 (br, 4H, 2NH_2), 8.01 ppm (s, 4H, C_6H_4). Anal. Calcd. for $C_{14}H_{14}N_8O_2$ (326.31): C, 51.53; H, 4.32; N, 34.34. Found: C, 51.38; H, 4.03; N, 34.54.

***N^1,N^4*-Bis[(3-amino-5-imino-1-phenyl-1*H*-pyrazol-4(5*H*)-ylidene)methyl]benzene-1,4-diamine (10).** This compound was obtained as brown crystals 3.38 g (71%) from DMF/EtOH (1:1), mp > 300°C; ir: 3435, 3224 (br, NH & NH_2); 1667 cm^{-1} (C=N). ^1H NMR: δ 10.90 (br, 4H, 2NH_2), 10.60 (br, 2H, 2NH), 8.58 (m, 10H, 2C_6H_5), 7.09,7.07 (d, 2H, $J = 8$ Hz, C_6H_4), 6.54, 6.52 (d, 2H, $J = 8$ Hz, C_6H_4), 6.65 (d, 2H, 2CH=), 5.17 (br, 2H, 2NH). Anal. Calcd. for $C_{26}H_{24}N_{10}$ (476.54): C, 65.53; H, 5.08; N, 29.39. Found: C, 65.35; H, 4.97; N, 29.53.

***N^1,N^4*-Bis[(3-amino-5-oxo-1-phenyl-1,4*H*-pyrazol-4(5*H*)-ylidene)methyl]benzene-1,4-diamine (11).** This compound was obtained as brown crystals 3.45 g (72%) from DMF/EtOH (1:1), mp > 300°C; ir: 3274, 3182 (br, NH & NH_2); 1696, 1666 cm^{-1} (CO). ^1H NMR: δ 10.83, 10.77, 10.73 (br, 6H, 2NH & 2NH_2), 8.47–8.28, 7.54–7.49 (m, 10H, 2C_6H_5), 7.40 (s, 4H, C_6H_4), 7.95 (d, 2H, 2CH=). Anal. Calcd. for $C_{26}H_{22}N_8O_2$ (478.51): C, 65.26; H, 4.63; N, 23.42. Found: C, 65.04; H, 4.57; N, 23.56.

General procedure for synthesis bisazoles (12–16). To a solution of (**1**) 2.18 g (0.01 mol) in pyridine (20 mL), heteroamines (0.01 mol) was added. The reaction mixture was heated under reflux for 3 h. The reaction mixture was poured on ice-cold water. The obtained product was collected by filtration and washed by ethanol (3 × 10 mL). The obtained product was crystallized from the proper solvent.

***N^1,N^4*-Bis(5-acetyl-2-(4-chlorophenyl)-2*H*-1,2,3-triazol-4-yl) phenylenediformamidine (12).** This compound was obtained as yellow crystals 3.91 g (65%) from DMF/EtOH (1:1), mp > 300°C; irir: 3480, 3382 (NH); 1617 cm^{-1} (C=N). ^1H NMR: δ 8.00, 7.98 (d, 4H, C_6H_4, $J = 8.0$ Hz), 7.67, 7.66 (d, 4H, C_6H_4, $J = 8.4$ Hz), 7.64 (s, 4H, C_6H_4), 6.75 (d, 2H, 2CH=), 6.36 (s, 2H, 2NH), 2.59 ppm (s, 6H, 2Me). ^{13}C NMR: δ 193.40, 154.91 (triazole carbons), 146.00, 137.95, 132.62, 132.37, 130.16, 120.29 (Ar-carbons), 27.17 (Me); ms: *m*/*z* 601 (M^+, 30%). Anal. Calcd. for $C_{28}H_{22}Cl_2N_{10}O_2$ (601.45): C, 55.92; H, 3.69; N, 23.29. Found: C, 56.11; H, 3.92; N, 23.63.

***N^1,N^4*-Bis(1*H*-1,2,4-triazol-3-yl)phenylenediformamidine (13).** This compound was obtained as yellowish brown crystals 1.96 g (66%) from acetic acid, mp 262–263°C; ir: 3439, 3288, 3259 (NH), 1684, 1663 cm^{-1} (C=N). ^1H NMR: δ 13.34, 11.51 (s, 4H, 4NH); 7.70 (s, 1H, triazole-H), 7.52 (d, 2H, 2CH=), 7.47 (S, 4H, C_6H_4). ^{13}C NMR: δ 168.70 (CH=N), 160.09, 149.39 (triazole carbons), 135.46, 120.19 (aromatic carbons); ms: *m*/*z* 296 (M^+, 30%). Anal. Calcd. for $C_{12}H_{12}N_{10}$ (296.29): C, 48.64; H, 4.08; N, 47.27. Found: C, 48.43; H, 3.92; N, 47.42.

***N^1,N^4*-Bis(4,5-dicyano-1*H*-imidazole-2-yl)phenylenediformamidine (14).** This compound was obtained as brown crystals 2.17 g (55%) from acetone, mp > 300°C; ir: 3434, 3248 (NH); 2231 (CN), 1666 cm^{-1} (C=N). ^1H NMR: δ 11.59 (s, 2H, 2 imidazole-NH), 10.21 (br, 2H, 2NH) 7.97 (d, 2H, 2CH=), 7.59 (s, 4H, C_6H_4). ^{13}C NMR: δ 160.83, 168.70 (2CH=N), 133.92, 117.60 (Ar-carbons), 135.71, 135.05, 121.74, 121.31, 121.22, 121.16 (imidazole carbons), 119.97, 119.93, 119.63, 119.03 (4CN); ms: *m*/*z* 394 (M^+, 8%). Anal. Calcd. for $C_{18}H_{10}N_{12}$ (394.35): C, 54.82; H, 2.56; N, 42.62. Found: C, 54.78; H, 2.72; N, 42.63.

***N^1,N^4*-Bis(1*H*-benzo[*d*]imidazol-2-yl)phenylenediformamidine (15).** This compound was obtained as yellow crystals 2.72 g (69%) from DMF, mp 296–298°C; ir: 3381, 3178 (NH), 1664 cm^{-1} (C=N). ^1H NMR: δ 11.87 (br, 2H, 2NH), 10.14 (br, 2H, 2NH), 8.58, 8.57 (d, 4H, 2benzimidazole-H) 7.38, 7.36 (m, 4H, 2 benzimidazole-H), 7.92 (d, 2H, 2CH=), 7.04 (s, 4H, C_6H_4). ^{13}C NMR: δ 158.69 (CH=N), 152.14, 143.72, 121.51, 110.68 (benzimidazole carbons), 134.75, 117.63 (Phenyl carbon); ms: *m*/*z* (M^+, 72%). Anal. Calcd. for $C_{22}H_{18}N_8$ (394.43): C, 66.99; H, 4.60; N, 28.41. Found: C, 66.88; H, 4.78; N, 28.63.

***N^1,N^4*-Bis(thiazol-2-yl)phenylenediformamidine (16).** This compound was obtained as brown crystals 1.98 g (60%) from acetone, mp > 300°C; ir: 3248 (NH); 1665 cm^{-1} (C=N). ^1H NMR: δ 10.16 (br, 2H, 2NH) 7.75, 7.73 (d, 2H, $J = 8$Hz, thiazole-H), 7.40(d, 2H, 2CH=), 7.16 (s, 4H, C_6H_4), 6.53, 6.51 ppm (d, 2H, $J = 8$ Hz, thiazole-H). ^{13}C NMR: δ 159.66 (2CH=N), 169.67, 139.46, 118.11 (thiazole carbons), 134.74, 117.56 ppm (phenyl carbons); ms: *m*/*z* 328 (M^+, 64%). Anal. Calcd. for $C_{14}H_{12}N_6S_2$ (328.42): C, 51.20; H, 3.68; N, 25.59; S, 19.53. Found: C, 51.01; H, 3.44; N, 25.84; S, 19.78.

Synthesis of 1,10-diaminophenanthroline-2,9-dicarbo-nitrile (17). A mixture of (**5a**) 2.6 g (0.01 mol) in bromobenzene and resublimed aluminum chloride (0.01 mol) was heated under reflux for 6 h. After cooling, the reaction mixture was poured onto cold water (40 mL) containing 2 mL of concentrated hydrochloric acid, and left to stand for 2 h. The obtained product was collected by filtration and washed by water (3 × 30 mL) and ethanol (3 × 10 mL). NOE experiment has been done via irradiation of amino protons at δ 11.04 ppm enhanced the pyridine protons at δ 8.38 ppm and vice versa while, the aromatic protons was not affected. This compound was obtained as pale green crystals 1.95 g (75%), from DMF/EtOH, mp > 300°C; ir: 3320, 3224 (NH_2), 2211, 2210 cm^{-1} (CN); ^1H NMR: δ 11.04 (br, 4H, 2NH_2, D_2O-exchange), 8.38 (s, 2H, pyridine-H), 7.47 ppm (s, 2H, C_6H_2). ^{13}C NMR: δ 136.74, 131.15, 121.51 (aromatic carbons), 117.00, 117.21(CN), 155.65, 149.98, 87.78 (pyridine carbons); ms: *m*/*z* 260 (M^+, 100%). Anal. Calcd. for $C_{14}H_8N_6$ (260.25): C, 64.61; H, 3.10; N, 32.29. Found: C, 64.65; H, 3.11; N, 32.01.

General procedure for synthesis of bisazoles (19–21). To a solution of (**1**) 2.18 g (0.01 mol) in pyridine (20 mL), morpholine or 4-aminopyridine or 3,4-dimethoxyaniline (0.01 mol) was added. The reaction mixture was heated under reflux for 3 h. The reaction mixture was poured onto ice-cold water. The obtained product was collected by filtration and washed by ethanol (3 × 10 mL). The obtained product was crystallized from the proper solvent.

Preparation of complex (19). To a solution of (**17**) 2.6 g (0.01 mol) in DMF (20 mL), $CuCl_2{\cdot}2H_2O$, 4.12g (0.01 mol) solution was added. The reaction mixture was heated under reflux for 5 h. The solvent was evaporated and the solid product, so formed, after cooling and water addition was collected by filtration and washed by ether (3 × 10 mL) and crystallized from DMF. Compound **19** was obtained as brown crystals 3.75 g (87%), mp > 250°C; ir: 3440 (OH, water), 3297, 3219 (NH_2), 2215 cm^{-1} (CN). ^1H NMR: δ 11.15, 11.12 (s, 4H, 2NH_2), 8.48, 8.46 (s, 2H, pyridine-H), 7.43 (s, 2H, C_6H_4). Anal. Calcd. for $C_{14}H_{12}Cl_2Cu\ N_6O_2$

(430.74) C, 39.04; H, 2.81; N, 19.51. Found: C, 39.14; H, 2.96; N, 19.46.

***N*¹,*N*⁴-Bis(*N*-morpholino)phenylenediformamidine (20).** This compound was obtained as pale white crystals 1.97 g (65%) from ethanol, mp 234–236°C; ir: 2984, 2962, 2901 (CH-aliphatic), 1625 $\mathrm{cm^{-1}}$ (C=N). ^{1}H NMR: δ 7.72 (s, 2H, 2CH=), 6.81 (s, 4H, C_6H_4), 3.43 (t, 8H, morpholine-H), 2.50 (t, 8H, morpholine-H). ^{13}C NMR: δ 159.70 (CH=N), 145.46, 121.19 (aromatic carbons), 61.21, 49.45 (morphiline carbons); ms: *m/z* 302 (M^+, 60%). Anal. Calcd. for $C_{16}H_{22}N_4O_2$ (302.37) C, 63.55; H, 7.33; N, 18.53. Found: C, 63.52; H, 7.30; N, 18.60.

***N*¹,*N*⁴-Bis(pyridin-4-yl)phenylenediformamidine (21).** This compound was obtained as brown crystals 2.06 g (65%) from ethanol, mp 174–177°C; ir: 3170 (NH), 1660 $\mathrm{cm^{-1}}$ (C=N). ^{1}H NMR: δ 10.10 (br, 2H, 2NH); 8.76, 7.15 (m, 8H, 2 pyridine-H), 8.20 (d, 2H, 2CH=), 7.54 (s, 4H, C_6H_4). ^{13}C NMR: δ 162.70 (CH=N), 156.61, 149.36 110.01 (pyridine carbons), 145.30, 121.19 (aromatic carbons); ms: *m/z* 316 (M^+, 6%). Anal. Calcd. for $C_{18}H_{16}N_6$ (316.36) C, 68.34; H, 5.10; N, 26.56. Found: C, 68.29; H, 5.09; N, 26.51.

***N*¹,*N*⁴-Bis(3,4-dimethoxyphenyl)phenylenediformamidine (22).** This compound was obtained as pale white crystals 2.74 g (63%) from ethanol, mp > 300°C; ir: 3300 (NH), 1662 $\mathrm{cm^{-1}}$ (C=N). ^{1}H NMR: δ 10.71 (br, 2H, 2NH), 7.52 (d, 2H, 2CH=), 7.31 (s, 4H, C_6H_4), 6.10–6.72 (m, 6H, $2C_6H_3$), 3.62 (s, 12H, 4MeO); ms: *m/z* 434 (M^+, 60%); Anal. Calcd. for $C_{24}H_{26}N_4O_4$ (434.49) C, 66.34; H, 6.03; N, 12.89. Found: C, 66.44; H, 5.98; N, 12.60.

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Diastereoselective Synthesis of γ-Dispiroiminolactone Bearing Naphthalene or Bipyridine Pendant Groups

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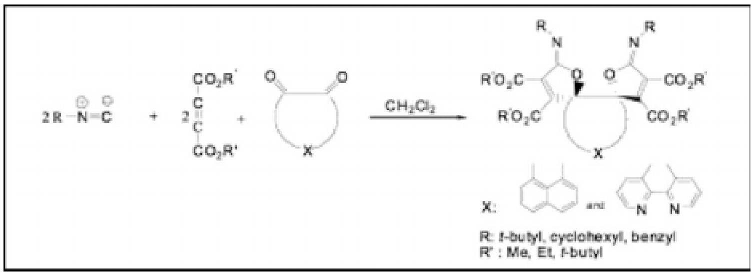

Diastereoselective γ-dispiroiminolactone products **4a–m** were obtained from a condensation of the highly reactive 1:1 intermediate of isocyanides and acetylenic esters with aromatic α-dicarbonyls compounds **3a, b**.

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INTRODUCTION

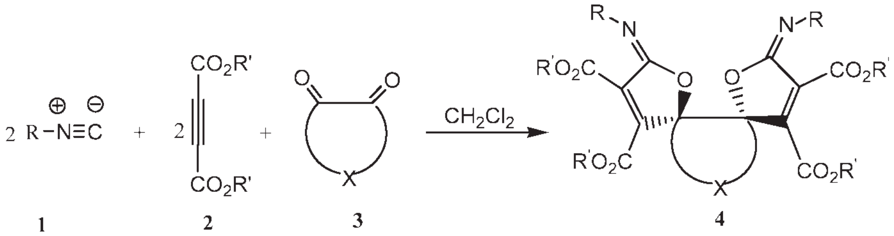
γ-Spirolactones and iminolactones are heterocyclic compounds obtained via ''one pot'' multicomponents condensation reaction [1,2]. They are generally used as precursors for the preparation of a wide range of compounds including antibacterial agents [3a]. Moreover, the ease of hydrolysis of iminolactones to spirolactones affords a number of biologically active natural products such as kijanolide, tetranolide, and chlorothricolide [3b–d]. Multicomponent reactions [4,5] are commonly used approaches for production of iminolactones by virtue of their convergence, facile execution, and generally proceed with high yields [1,2]. Recently, we have reported a series of iminolactones from the reaction of isocyanide with activated acetylenic esters in the presence of carbonyl compounds [6–8]. Intimately related condensation is the reaction of isocyanide with acetylenic diesters and carbonyl compounds affording *gama*-spiroiminolactones [1,2,9]. Continuing with our investigation of this reaction with activated α-diketones, we examined the reaction of 1,2-dicarbonyl groups of acenaphthenequinone and phendione with acetylenic esters in the presence of variety isocyanides and successfully prepared the γ-dispiroiminolactone derivatives reported herein.

RESULTS AND DISCUSSION

The reaction of alkyl isocyanides with dialkyl acetylenedicarboxylates in the presence of 1,2-diketones, acenaphthenequinone and phendione afford new γ-dispiroiminolactone products **4a–m** (Scheme 1). Such condensation reaction generally yields the γ-spiroiminolactone analogues [8–11]. For example, when the α-ketoester or α-ketoamide is used, the carbonyl of the ester or the amide functionality is not involved in the reaction [10]. This reaction is molar ratio dependent and influenced by the ratio of the dicarbonyl compounds to the isocyanide and the dialkyl acetylenedicarboxylate. The reaction of the preformed highly reactive zwitterionic intermediate with activated α-dicarbonyl ketone at 1:1:1 molar ratio of reactants **1**, **2**, and **3** favors γ-spiroiminolactones, whereas at 2:2:1 molar ratio the reaction yields γ-dispiroiminolactones [12]. We utilized the 2:2:1 molar ratio of reactants resulting in the participation of both carbonyl groups and the formation of γ-dispiroiminolactone products, **4a–f** and **4g–m** from acenaphthenequinone and phendione, respectively. The products are obtained as diastereoselective racemic mixture based on NMR and X-ray data (see Experimental section).

The reported products **4a–m** are stable solids and their structures determined by IR, ^{1}H, ^{13}C NMR, and

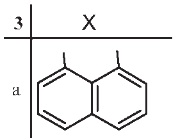
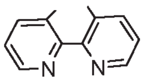
Scheme 1



1 2 3 4

1	R
a	*t*-butyl
b	cyclohexyl
c	benzyl

2	R'
a	Me
b	Et
c	*t*-butyl

3	X
a	
b	

4	3	R	R'	(%) yield
a	a	benzyl	Me	93
b	a	cyclohexyl	Me	88
c	a	cyclohexyl	Et	80
d	a	t-butyl	Me	91
e	a	*t*-butyl	Et	96
f	a	*t*-butyl	*t*-butyl	91
g	b	benzyl	Me	80
h	b	benzyl	Et	94
i	b	benzyl	*t*-butyl	79
j	b	cyclohexyl	Me	74
k	b	cyclohexyl	Et	84
l	b	cyclohexyl	*t*-butyl	79
m	b	*t*-butyl	Et	90

Mass spectrometry with **4a** and **4h** structurally authenticated by single X-ray single crystal diffraction. The ^{1}H NMR spectrum of compound **4a** exhibited two singlets arising from the methyl of the ester groups [δ 3.38 ppm (6H, s, 2OMe), 3.90 ppm (6H, s, 2OMe)] and one singlet [δ 4.55 ppm (4H, s, 2CH$_2$)] due to the methylene of the benzyl groups. The aromatic region of ^{1}H NMR spectrum clearly accounts for the protons associated with the aromatics of benzyl and naphthal moieties. The ^{13}C NMR data displays 19 distinct signals consistent with the structure of **4a**. The characteristic signal resulting from the spiro carbon was identified at δ 101.18 ppm. In addition, FTIR spectrum of compound **4a** showed strong absorptions at 1749 and 1733 cm^{-1} relevant to the ester groups and 1683 cm^{-1} attributed to C=N (see Experimental section). The mass spectrum of compound **4a** displayed a molecular ion peak of 700 (*m*/*z*). Single crystal of compound **4a** was grown from dichloromethane/ethanol (1:3) solution and the X-ray structure is in agreement with the NMR data for γ-dispiroiminolactone (Fig. 1).

Pertinent structural information is deduced from solution NMR for these class of compounds (**4a–m**). For example, the benzylic methylene proton signals for the compounds derived from the benzyl cyanide are diagnostic of the symmetry of the molecules. The mode of splitting is associated with spatial arrangement of the α-diketonic derived building block. The products bearing acenaphthenequinone derived moiety (**4a–f**) display one singlet accounting for four magnetically equivalent protons for the benzylic methylenes (C$_2$ symmetry). On the other hand for the products bearing pyridyl (**4g–m**), the benzylic methylene protons appear as an AB-quartet. The NMR mode of splitting is related to the lack of C$_2$ symmetry in the molecule associated with the formation of nonaromatic six-membered ring. Variable temperature ^{1}H NMR was performed on the model compounds, **4a** and **4h** and no dynamic effect was observed reflecting the structural rigidity of these compounds. The stereochemistry of all reported products are comparable with compound **4a** or **4h** obtained as racemate.

It is noteworthy to mention that the solvent has an effect on the reaction yield with good yields could be obtained using nonpolar solvents, such as benzene and toluene. However, some of the products in this work (e.g., **4a–i**) were obtained from a reaction using dichloromethane at 38°C for 27 h. Optimization of the reaction conditions was investigated and higher yields were obtained using dichloromethane and benzene mixture (1:4) at 75°C for 48 h. All the synthesized products,

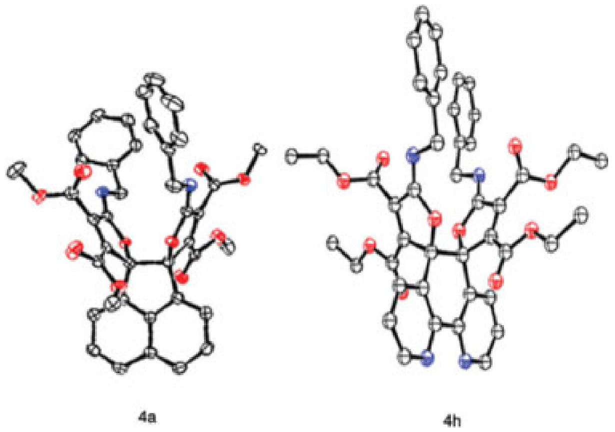
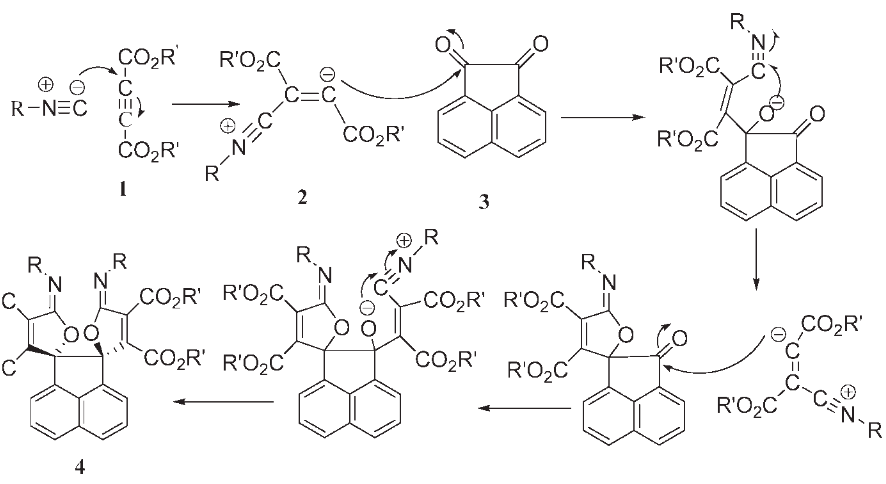


Figure 1. X-ray structure of **4a** and **4h** as model compounds. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Scheme 2



4a–f were fully characterized and the formation can be rationalized by the mechanism shown in Scheme 2.

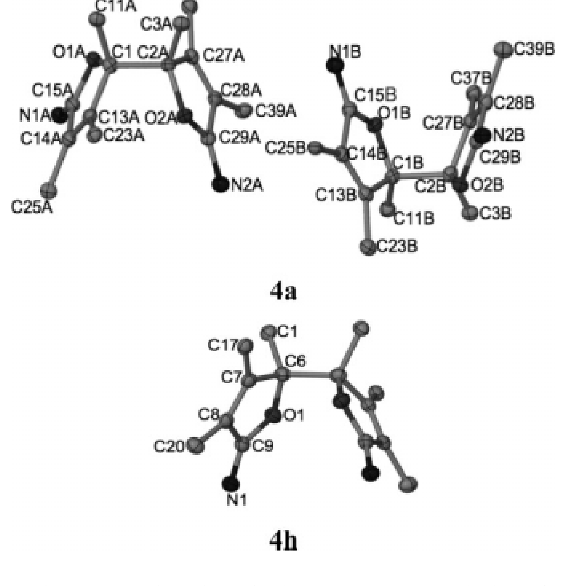
EXPERIMENTAL

Starting materials, dialkyl acetylenedicarboxylates; *tert*-butyl, cyclohexyl, and benzyl isocyanides; acenaphthenequinone and phendione were purchased from Fluka, Buchs, and Switzerland, and used as received. Melting point and IR spectra were measured on an Electrothermal 9100 apparatus and on Shimadzu IR-470 spectrometer. Elemental analysis for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. The ^{1}H and ^{13}C NMR spectra were measured using Bruker DRX-500 AVANCE instrument in $CDCl_3$ at 300.1 and 75.5 MHz, respectively. Mass spectra were recorded on a Shimadzu GC/MS QP 1100 EX mass spectrometer operating at an ionization potential of 70 ev. X-ray diffracted intensities were measured from single crystals at 100 K on an Oxford Diffraction Gemini-R Ultra CCD diffractometer using monochromatized Cu-Kα (λ = 1.54178 Å). A partial projections of the heterocyclic rings with their atomic numbering are depicted in Figure 2. The interatomic distances and angles for each heterocyclic ring in compounds **4a** and **4h** are depicted in Table 1 and 2.

General procedures. The solution of alkyl isocyanide (1 mmol) in 3 mL of CH_2Cl_2 was slowly added dropwise to the mixture of acenaphthenequinone (0.5 mmol) and DMAD (1 mmol) in 20 mL of dry CH_2Cl_2 for 5 min at room temperature. The reaction mixture was heated to 38°C for 28 h. The crude product was collected by filtration and crystallized from dichloromethane-methanol (1:3) and washed with cold diethyl ether (2 × 5 mL).

Bis(Dimethyl-5-benzyl-5H-6H′)-dispiro[furan-2,5′-acenaphthenequinone]-3,3′,4,4′-tetracarboxylate (4a). Light brown powder, yield: 0.32 g (91%), m.p. 203–205°C, IR (KBr) (υ_{max}, cm^{-1}): 1744 and 1729 (4C=O), 1689 (2C=N). ^{1}H NMR: (300 MHz, $CDCl_3$): δ_H 3.38 (6H, s, 2OMe), 3.90 (6H, s, 2OMe), 4.55 (4H, s, $2CH_2$ of benzyl), 7.22–7.32 (10H, m, 10CH), 7.34 (2H, d, J = 7.0 Hz, 2CH), 7.64 (2H, t, J = 7.0 Hz, 2CH), 7.93 (2H, d, J = 8.0 Hz, 2CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 51.72 ($2NCH_2$), 52.53 and 53.36 (4OMe), 101.18 (2Cspiro), 120.33, 126.86, 126.91, 127.92, 127.75, 128.36, 128.51, 130.64, 134.90, 136.37, 138.70, and 144.10 (C=C$_{iminolactone}$ and C$_{arom}$), 156.26 (N=C$_{iminolactone}$), 160.29 and 161.35 (4C=O of esters). MS (m/z, %): 701 (M^{+} + 1) (1), 700 (M^{+} +3), 684 (1), 669 (1), 641 (2), 609 (6), 577 (1), 533 (3), 121 (4), 105 (3), 91 (100). Anal. Calcd for $C_{40}H_{32}N_2O_{10}$ (700.69): C, 68.57; H, 4.60; N, 4.00%; Found: C, 68.39; H, 4.58; N, 4.03%.

Bis(Dimethyl-5-cyclohexyl-5H-6H′)-dispiro[furan-2,5′-acenaphthenequinone]-3,3′,4,4′-tetracarboxylate (4b) Yellow powder, yield: 0.31 g (91%), m.p. 233–236°C, IR (KBr) (λ_{max}, cm^{-1}): 1749 and 1738 (4C=O), 1695 (2C=N). ^{1}H NMR: (300 MHz, $CDCl_3$): δ_H 1.19–1.77 (20H, m, $10CH_2$), 3.43 (6H, s, 2OMe), 3.55 (1H, m, N—CH), 3.94 (6H, s, 2OMe), 7.37 (2H, d, J = 7.0 Hz, 2CH), 7.63 (2H, t, J = 7.1 Hz, 2CH), 7.91 (2H, d, J = 7.0 Hz, 2CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_c 24.82, 25.52 and 32.83 ($5CH_2$ of cyclohexyl), 52.54 and 53.24 (4OMe), 57.35 (2N—*C*H), 100.23 (2C$_{spiro}$), 120.10,



4a

4h

Figure 2. Asymmetric unit projections and atoms numbering of each heterocyclic ring in the structures of compounds **4a** and **4h**.

126.65, 128.46, 130.50, 135.51, 136.85, 137.70, and 143,33 (C=C$_{\text{iminolactone}}$ and C$_{\text{arom}}$), 154.98 (2C=N$_{\text{iminolactone}}$), 160.15 and 161.66 (4C=O of esters). MS (*m*/*z*, %): 685 (M$^+$ +1, 10), 684 (M$^+$, 18), 602 (12), 543 (16), 417 (3), 83 (44), 59 (17), 55(100). Anal. Calcd for $C_{38}H_{40}N_2O_{10}$ (684.73): C, 66.65; H, 5.89; N, 4.09%; Found: C, 65.87; H, 6.02; N, 4.15%.

Bis(Diethyl-5-cyclohexyl-5H-6H′)-dispiro[furan-2,5′-acenaphthenequinone]-3,3′,4,4′-tetracarboxylate (4c) Pale white powder, yield: 0.36 g (96%), m.p. 230–233°C, IR (KBr) ($\upsilon_{\max}$, cm^{-1}): 1742 and 1733 (4C=O), 1683 (2C=N). ^{1}H NMR: (300 MHz, CDCl$_3$): δ_H 0.51 (3H, t, *J* = 5.4 Hz, 2OCH2*CH*$_3$), 1.14–1.75 (20H, m, 10CH$_2$), 1.35 (3H, t, *J* = 5.4 Hz, 2OCH$_2$CH$_3$), 3.68 (1H, m, N—CH), 4.37 (4H, m, 2OCH$_2$), 4.41 (4H, m, 2OCH$_2$), 7.35 (2H, d, *J* = 7.0 Hz, 2CH), 7.59 (2H, t, *J* = 7.0 Hz, 2CH), 7.86 (2H, d, *J* = 7.0 Hz, 2CH). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ_c 12.75 and 13.93 (4OCH$_2$*C*H$_3$), 24.83, 25.63 and 33.10 (5CH$_2$ of cyclohexyl), 57.1 (2N*C*Me$_3$), 61.16 and 62.37 (4O*C*H$_2$CH$_3$), 100.39 (2C$_{\text{spiro}}$), 119.85, 126.15, 128.28, 130.45, 134.00, 136.19, 137.93, and 142.93 (C=C$_{\text{iminolactone}}$ and C$_{\text{arom}}$), 154.10 (2C=N$_{\text{iminolactone}}$), 159.77 and 161.58 (4C=O of esters). MS (*m*/*z*, %): 742 (M$^+$ +2, 3), 741 (M$^+$ +1, 6), 740 (M$^+$, 13), 658 (8), 613 (4), 585 (38), 83 (35), 55 (100). Anal. Calcd for $C_{42}H_{48}N_2O_{10}$ (740.33): C, 68.09; H, 6.53; N, 3.78%; Found: C, 68.15; H, 6.49; N, 3.83%.

Bis(Dimethy-5-tert-butylimino-5H-6H′)-dispiro[furan-2,5′-acenaphthenequinone]-3,3′,4,4′-tetracarboxylate (4d). Yellow crystals, yield: 0.59 g (93%), m.p. 207–210°C, IR (KBr) ($\lambda_{\max}$, cm^{-1}): 1749 and 1733 (4C=O), 1683 (2C=N). ^{1}H NMR: (300 MHz, CDCl$_3$): δ_H 1.27 (18H, s, 2C*Me*$_3$), 3.34 and 3.91 (6H, 2s, 4OMe), 7.30 (2H, d, *J* = 7.0 Hz, 2CH), 7.60 (2H, t, *J* = 7.4 Hz, 2CH), 7.89 (2H, d, *J* = 8.2Hz, 2CH). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ_c 29.40 (2C*Me*$_3$), 52.07 and 52.98 (4OMe), 55.03 (N*C*Me$_3$), 100.81 (2C$_{\text{spiro}}$), 119.23, 126.21, 128.31, 130.30, 137.34, 137.53, 137.85, and 141.56 (C=C$_{\text{iminolactone}}$ and C$_{\text{arom}}$), 151.57 (2C=N$_{\text{iminolactone}}$), 160.17 and 162.41 (4C=O of esters). MS (*m*/*z*, %): 632 (M$^+$, 3), 576 (31), 561 (5), 502 (7), 444 (13), 429 (8), 419 (4), 397 (5), 297 (4), 213 (27), 57 (100). Anal. Calcd for $C_{34}H_{36}N_2O_{10}$ (632.24): C, 64.55; H, 5.74; N, 4.43%; Found: C, 64.48; H, 5.80; N, 4.21%.

Bis(Diethyl-5-tert-butylimino-5H-6H′)-dispiro[furan-2,5′-acenaphthenequinone]-3,3′,4,4′-tetracarboxylate (4e). Yellow crystals, yield: 0.39 g (88%), m.p. 197–200°C, IR (KBr) ($\upsilon_{\max}$, cm^{-1}): 1747 and 1731 (4C=O), 1680 (2C=N), ^{1}H NMR: (300 MHz, CDCl$_3$): δ_H 1.27 (18H, s, 2C*Me*$_3$), 1.30 (6H, t, *J* = 7.1 Hz, 2OCH$_2$*CH*$_3$), 1.37 (6H, t, *J* = 7.0 Hz, 2OCH$_2$*CH*$_3$), 4.33 (4H, m, 2OCH$_2$), 4.43 (4H, m, 2OCH$_2$), 7.28 (2H, d, *J* = 6.9 Hz, 2CH), 7.56 (2H, t, *J* = 7.4 Hz, 2CH), 7.85 (2H, d, *J* = 8.2 Hz, 2CH). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ_c 12.6 and 14.1 (4OCH$_2$*C*H$_3$), 29.5 (2C*Me*$_3$), 54.9 (2N*C*Me$_3$), 126.95, 128.25, 130.35, 137.65, 137.97, 138.37, and 141.76 (C=C$_{\text{iminolactone}}$ and C$_{\text{arom}}$), 151.75 (2C=N$_{\text{iminolactone}}$), 159.80 and 162.06 (4C=O of esters). MS (*m*/*z*, %): 689 (M$^+$ +1, 4), 688 (M$^+$, 8), 632 (98), 576 (17), 559 (64), 503 (36), 385 (36), 57 (100). Anal. Calcd for $C_{38}H_{44}N_2O_{10}$ (688.30): C, 66.26; H, 6.44; N, 4.07%; Found: C, 66.50; H, 6.51; N, 3.89%.

Bis(Di-tert-butyl-5-tert-butylimino-5H-6H′)-dispiro[furan-2,5′-acenaphthenequinone]-3,3′,4,4′-tetracarboxylate (4f). Yellow crystals, yield: 0.32 g (80%), m.p. 210–213°C, IR (KBr) ($\upsilon_{\max}$, cm^{-1}): 1743 and 1726 (4C=O), 1678 (2C=N). ^{1}H NMR: (300 MHz, CDCl$_3$): δ_H 0.80 (18H, s, 2CMe$_3$), 1.25 (18H, s, 2NCMe$_3$), 1.60 (18H, s, 2CMe$_3$), 7.53 (2H, d, *J* = 6.9 Hz, 2CH), 7.69 (2H, t, *J* = 7.0 Hz, 2CH), 7.97 (2H, d, *J* = 8.0 Hz, 2CH). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ_c 27.13 and 28.14 (4OCMe$_3$), 29.53 (2NCMe$_3$), 54.89 (2N*C*Me$_3$), 82.00 and 83.05 (4O—*C*Me$_3$), 99.86 (2C$_{\text{spiro}}$), 122.76, 126.57, 128.42, 130.63, 134.36, 137.82, 139.34, and 142.86 (C=C$_{\text{iminolactone}}$ and C$_{\text{arom}}$), 158.64 (2C=N$_{\text{iminolactone}}$), 160.77 and 161.40 (4C=O of esters). MS (*m*/*z*, %): 643 (6), 531 (7), 476 (5), 358 (4), 314 (9), 234 (5), 57 (100). Anal. Calcd for $C_{46}H_{60}N_2O_{10}$ (800): C, 69.00; H, 7.50; N, 3.50%; Found: C, 70.13; H, 7.61; N, 3.42%. Anal. Calcd for $C_{46}H_{60}N_2O_{10}$ (800.98): C, 68.98; H, 7.55; N, 3.50%; Found: C, 69.30; H, 7.60; N, 3.53%.

Bis(dimethyl 5-benzylimino-5H,6H′)-dispiro(furan-2,5′-[1,10] phenanthroline)-3,3′,4,4′-tetracarboxylate (4g). Brown powder; yield: 0.29 g (80%), m.p. 94–97°C, IR (KBr) ($\upsilon_{\max}$, cm^{-1}): 1740 and 1732 (4C=O), 1687 (2C=N). ^{1}H NMR (300.1 MHz, CDCl$_3$): δ_H 3.29 (6H, s, 2 OMe), 3.84 (6H, s, 2 OMe), 4.71 (4H, AB quartet, 2 CH$_2$ of benzyl), 7.21–7.31 (14H, m, 14 CH$_{\text{arom}}$), 8.86 (2H, dd, J_1 = 4.0, J_2 = 2.0 Hz, 2 CH$_{\text{arom}}$). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ_C 52.37 (2 NCH$_2$), 52.78 and 53.26 (4 OMe), 91.32 (2 C$_{\text{spiro}}$), 124.36, 126.86, 127.94, 128.18, 128.31, 133.10, 133.66, 139.07, 146.73, 150.53, and 151.28 (C=C$_{\text{iminolactone ring}}$ and C$_{\text{arom}}$), 155.09 (2C=N$_{\text{iminolactone}}$), 160.06 and 160.87 (4C=O of esters). MS (*m*/*z*, %): 729 (M$^+$ +1, 2), 728 (M$^+$, 3), 669 (8), 610 (17), 587 (3), 452 (11), 321 (8), 179 (8), 91 (58). Anal. Calcd for $C_{40}H_{32}N_4O_{10}$ (728.70): C, 65.93; H, 4.43; N, 7.69%; Found: C, 65.78; H, 4.52; N, 7.57%.

Bis(diethyl 5-benzylimino-5H,6H′)-dispiro(furan-2,5′-[1,10] phenanthroline)-3,3′,4,4′-tetracarboxylate (4h). Pale yellow powder; yield: 0.37 g (94%), m.p. 176–179°C, IR (KBr) ($\upsilon_{\max}$, cm^{-1}): 1737 and 1733 (4C=O), 1686 (2C=N); ^{1}H NMR (300.1 MHz, CDCl$_3$): δ_H 0.87 (6H, t, *J* = 7.1 Hz, 2 OCH$_2$*CH*$_3$), 1.28 (6H, t, *J* = 7.1 Hz, 2 OCH$_2$*CH*$_3$), 3.82 (4H, ABX$_3$ system, 2 O*CH*$_2$CH$_3$), 4.34 (4H, ABX$_3$ system, 2 O*CH*$_2$CH$_3$), 4.71 (4H, AB quartet, 2 CH$_2$ of benzyl), 7.24–7.38 (14H, m, 14 CH$_{\text{arom}}$), 8.93 (2H, t, *J* = 6.2 Hz, 2 CH$_{\text{arom}}$). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ_C 13.36 and 13.92 (4 OCH$_2$*C*H$_3$), 52.22 (2 N*C*H$_2$), 62.30 and 62.56 (4 O*C*H$_2$CH$_3$), 91.34 (2 C$_{\text{spiro}}$), 124.67, 126.83, 127.96, 128.08, 128.29, 128.67, 133.91, 139.23, 146.25, 150.86, and 151.81 (C=C$_{\text{iminolactone ring}}$ and C$_{\text{arom}}$), 155.26 (2C=N$_{\text{iminolactone}}$), 159.62 and 160.56 (4C=O of esters). MS (*m*/*z*, %): 784 (M$^+$, 8), 694 (12), 132 (4), 91 (100), 65 (4), 44 (4). Anal. Calcd for $C_{44}H_{40}N_4O_{10}$ (784.81): C, 67.34; H, 5.14; N, 7.14%; Found: C, 67.46; H, 5.23; N, 7.02%.

Bis(di-tert-butyl 5-benzylimino-5H,6H′)-dispiro(furan-2,5′-[1,10]phenanthroline)-3,3′,4,4′-tetracarboxylate (4i). Light brown crystals; yield: 0.35 g (79%), m.p. 138–141°C, IR (KBr) ($\upsilon_{\max}$, cm^{-1}): 1738 and 1718 (4C=O), 1687 (2C=N); ^{1}H NMR (300.1 MHz, CDCl$_3$): δ_H 1.09 (18H, s, 2 C*Me*$_3$), 1.53 (18H, s, 2 C*Me*$_3$), 4.74 (4H, AB quartet, 2 CH$_2$ of benzyl), 7.28–7.44 (14H, m, CH$_{\text{arom}}$), 9.02 (2H, d, *J* = 3.7 Hz, 2 CH$_{\text{arom}}$). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ_C 27.32 and 27.92 (4 OC*Me*$_3$), 51.79 (2 N—CH$_2$), 84.74 and 85.89 (4 O*C*Me$_3$), 91.83 (2 C$_{\text{spiro}}$), 125.10, 126.75, 127.69, 127.86, 128.04, 128.34, 128.83, 133.12, 138.85, 144.59, and 151.35 (C=C$_{\text{iminolactone ring}}$ and C$_{\text{arom}}$), 158.77 (2C=N$_{\text{iminolactone}}$), 160.16 and 161.69 (4C=O of esters). MS (*m*/*z*, %): 896 (M$^+$, 4), 795 (2), 704 (3), 670 (16), 537 (8), 444 (4), 200 (1), 105 (5), 91 (15), 56 (43), 44 (77), 41 (100). Anal. Calcd for $C_{52}H_{56}N_4O_{10}$ (897.02): C, 69.63; H, 6.29; N, 6.25%; Found: C, 69.65; H, 6.36; N, 6.21%.

Table 1

Interatomic distances (*l*, Å) and bond angles (ϕ, °) around the heterocyclic rings in compound **4a**.

O(1A)-C(15A)	1.375 (3)
O(1A)-C(1A)	1.455 (3)
O(2A)-C(29A)	1.373 (3)
O(2A)-C(2A)	1.455 (3)
N(1A)-C(15A)	1.254 (3)
N(2A)-C(29A)	1.260 (3)
C(1A)-C(13A)	1.513 (3)
C(1A)-C(11A)	1.515 (3)
C(1A)-C(2A)	1.605 (3)
C(2A)-C(3A)	1.509 (3)
C(2A)-C(27A)	1.518 (3)
C(15A)-O(1A)-C(1A)	109.72 (16)
C(29A)-O(2A)-C(2A)	110.08 (16)
O(1A)-C(1A)-C(13A)	103.36 (16)
O(1A)-C(1A)-C(11A)	112.28 (17)
C(13A)-C(1A)-C(11A)	116.41 (18)
O(1A)-C(1A)-C(2A)	109.10 (17)
C(13A)-C(1A)-C(2A)	111.96 (18)
C(11A)-C(1A)-C(2A)	103.78 (17)
O(2A)-C(2A)-C(3A)	114.32 (18)
O(2A)-C(2A)-C(27A)	102.95 (16)
C(3A)-C(2A)-C(27A)	112.53 (17)
O(2A)-C(2A)-C(1A)	108.03 (16)
C(3A)-C(2A)-C(1A)	104.42 (17)
C(27A)-C(2A)-C(1A)	114.84 (18)
N(1A)-C(15A)-O(1A)	126.8 (2)
N(1A)-C(15A)-C(14A)	125.2 (2)
O(1A)-C(15A)-C(14A)	108.00 (18)
C(28A)-C(27A)-C(37A)	128.1 (2)
C(28A)-C(27A)-C(2A)	109.55 (19)
C(37A)-C(27A)-C(2A)	122.29 (19)
C(27A)-C(28A)-C(29A)	109.1 (2)
C(27A)-C(28A)-C(39A)	131.5 (2)
C(29A)-C(28A)-C(39A)	119.43 (19)
N(2A)-C(29A)-O(2A)	126.9 (2)
N(2A)-C(29A)-C(28A)	125.5 (2)
O(2A)-C(29A)-C(28A)	107.58 (19)
O(1B)-C(15B)	1.374 (3)
O(1B)-C(1B)	1.449 (3)
O(2B)-C(29B)	1.375 (3)
O(2B)-C(2B)	1.447 (3)
N(1B)-C(15B)	1.251 (3)
N(2B)-C(29B)	1.259 (3)
C(1B)-C(11B)	1.512 (3)
C(1B)-C(13B)	1.525 (3)
C(1B)-C(2B)	1.616 (3)
C(2B)-C(3B)	1.507 (3)
C(2B)-C(27B)	1.517 (3)
C(15B)-O(1B)-C(1B)	109.60 (16)
C(29B)-O(2B)-C(2B)	109.70 (16)
O(1B)-C(1B)-C(11B)	112.61 (18)
O(1B)-C(1B)-C(13B)	103.22 (17)
C(11B)-C(1B)-C(13B)	117.29 (19)
O(1B)-C(1B)-C(2B)	108.59 (17)
C(11B)-C(1B)-C(2B)	103.50 (18)
C(13B)-C(1B)-C(2B)	111.59 (18)
O(2B)-C(2B)-C(3B)	114.58 (17)
O(2B)-C(2B)-C(27B)	103.43 (17)
C(3B)-C(2B)-C(27B)	113.43 (18)
O(2B)-C(2B)-C(1B)	109.00 (17)
C(3B)-C(2B)-C(1B)	104.30 (18)
C(27B)-C(2B)-C(1B)	112.27 (18)
N(1B)-C(15B)-O(1B)	126.7 (2)
N(1B)-C(15B)-C(14B)	125.3 (2)
O(1B)-C(15B)-C(14B)	107.94 (18)
C(28B)-C(27B)-C(37B)	124.5 (2)
C(28B)-C(27B)-C(2B)	109.39 (19)
C(37B)-C(27B)-C(2B)	126.04 (19)
C(27B)-C(28B)-C(29B)	108.5 (2)
C(27B)-C(28B)-C(39B)	129.3 (2)
C(29B)-C(28B)-C(39B)	121.8 (2)
N(2B)-C(29B)-O(2B)	125.4 (2)
N(2B)-C(29B)-C(28B)	126.4 (2)
O(2B)-C(29B)-C(28B)	108.13 (19)

The interatomic distances and angles for each heterocyclic ring in compound **4a** is depicted in Table 1.

Bis(dimethyl 5-cyclohexylimino-5H,6H′)-dispiro(furan-2,5′-[1,10]phenanthroline)-3,3′,4,4′-tetracarboxylate (4j). Pale yellow crystals; yield: 0.26 g (74%), m.p. 148–151°C, IR (KBr) (υ_{max}, cm^{-1}): 1681 and 1723 (4C=O), 1643 (2C=N). ^{1}H NMR (300.1 MHz, CDCl$_3$): δ_H 1.19–1.78 (20H, m, 10 CH$_2$ of cyclohexyl), 3.30 (6H, s, 2 OMe), 3.69 (2H, m, 2 NC*H*), 3.87 (6H, s, 2 OMe), 7.43 (2H, dd, J_1 = 4.0, J_2 = 7.5 Hz, 2 CH$_{arom}$), 7.63 (2H, d, J = 7.5 Hz, 2 CH$_{arom}$), 8.91 (2H, dd, J_1 = 9.2, J_2= 4.0 Hz, 2CH$_{arom}$). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ_C 24.69, 25.61 and 33.01 (10 *C*H$_2$ of cyclohexyl), 52.66 and 53.11 (4 OMe), 57.45 (2 N*C*H), 90.86 (2 C$_{spiro}$), 124.45, 128.97, 133.13, 134.35, 145.86, 150.59, and 151.16 (C=C$_{iminolactone\ ring}$ and C$_{arom}$), 152.53 (2C=N$_{iminolactone}$), 160.24 and 161.64 (4C=O of esters). MS (*m*/*z*, %): 714 (M$^+$ +2, 4), 713 (M$^+$ +1, 13), 712 (M$^+$, 27), 644 (6), 630 (5), 629 (12), 378 (10), 252 (17), 170 (27), 83 (43), 67 (33), 55 (100). Anal. Calcd for $C_{38}H_{40}N_4O_{10}$ (712.74): C, 64.04; H, 5.66; N, 7.86%; Found: C, 63.96; H, 5.70; N, 7.81%.

Bis(diethyl 5-cyclohexylimino-5H,6H′)-dispiro(furan-2,5′-[1,10]phenanthroline)-3,3′,4,4′-tetracarboxylate (4k). Brown crystals; yield: 0.32 g (84%), m.p. 65–68°C, IR (KBr) (υ_{max}, cm^{-1}): 1742 and 1730 (4C=O), 1685 (2C=N). ^{1}H NMR (300.1 MHz, CDCl$_3$): δ_H 0.80 (6H, t, J = 7.2 Hz, 2 OCH$_2$C*H*$_3$), 1.25 (6H, t, J = 7.2 Hz, 2 OCH$_2$C*H*$_3$), 1.21–2.14 (20H, m, 10 CH$_2$ of cyclohexyl), 3.59 (2H, m, 2 NC*H*), 3.78 (4H, m, 2 OC*H*$_2$CH$_3$), 4.30 (4H, m, 2 OC*H*$_2$CH$_3$), 7.37 (2H, dd, J_1 = 4.0, J_2 = 7.0 Hz, 2 CH$_{arom,}$), 7.53 (2H, d, J = 7.0 Hz, 2 CH$_{arom}$), 8.82 (2H, d, J = 4.0 Hz, 2 CH$_{arom}$). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ_C 13.32 and 13.91 (4 OCH$_2$*C*H$_3$), 24.34, 24.66, 25.60, 32.94, and 33.11 (10 *C*H$_2$ of cyclohexyl), 57.27 (2 N*C*H), 61.49 and 62.20 (4 O*C*H$_2$CH$_3$), 90.74 (2 C$_{spiro}$), 124.46, 129.32, 133.27, 133.54, 146.16, 150.15, and 151.03 (C=C$_{iminolactone\ ring}$ and C$_{arom}$), 152.87 (2C=N$_{iminolactone}$), 159.87 and 160.63 (4C=O of esters). MS (*m*/*z*, %): 769 (M$^+$ +1, 40), 768 (M$^+$, 82), 686 (36), 604 (27), 407 (14), 83 (29), 55 (100). Anal. Calcd for $C_{42}H_{48}N_4O_{10}$ (768.85): C, 65.61; H, 6.29; N, 7.29%; Found: C, 65.70; H, 6.32; N, 7.25%.

Bis(di-tert-butyl 5-cyclohexylimino-5H,6H′)-dispiro(furan-2,5′-[1,10]phenanthroline)-3,3′,4,4′-tetracarboxylate (4l). Pale yellow crystals; yield: 0.34 g (79%), m.p. 202–205°C, IR (KBr) (υ_{max}, cm^{-1}): 1744 and 1735 (4C=O), 1686 (2C=N); ^{1}H NMR (300.1 MHz, CDCl$_3$): δ_H 1.00 (18H, s, 2 C*Me*$_3$), 1.52 (18H, s, 2 C*Me*$_3$), 1.29–1.80 (20H, m, 10 CH$_2$ of cyclohexyl), 3.68 (2H, m, 2 NC*H*), 7.41 (2H, dd, J_1 = 4.7, J_2 = 7.9 Hz, 2 CH$_{arom}$), 7.64 (2H, dd, J_1 = 1.4, J_2 = 7.sz9 Hz, 2

Table 2

Interatomic distances (l, Å) and bond angles (ϕ, °) around the heterocyclic rings in compound **4h**.

O(1)-C(9)	1.380 (2)
O(1)-C(6)	1.456 (2)
N(1)-C(9)	1.257 (2)
C(6)-C(7)	1.527 (2)
C(6)-C(6)#1	1.565 (4)
C(9)-O(1)-C(6)	110.31 (13)
O(1)-C(6)-C(1)	108.71 (15)
O(1)-C(6)-C(7)	102.58 (14)
C(1)-C(6)-C(7)	112.03 (15)
O(1)-C(6)-C(6)#1	106.49 (13)
C(1)-C(6)-C(6)#1	114.00 (11)
C(7)-C(6)-C(6)#1	112.16 (18)
C(8)-C(7)-C(17)	127.54 (17)
C(7)-C(8)	1.330 (3)
C(7)-C(17)	1.477 (3)
C(8)-C(9)	1.463 (3)
C(8)-C(20)	1.497 (3)
C(8)-C(7)-C(6)	109.69 (16)
C(17)-C(7)-C(6)	122.72 (16)
C(7)-C(8)-C(9)	109.27 (16)
C(7)-C(8)-C(20)	130.36 (17)
C(9)-C(8)-C(20)	119.76 (16)
N(1)-C(9)-O(1)	126.46 (17)
N(1)-C(9)-C(8)	125.66 (17)
O(1)-C(9)-C(8)	107.87 (15)

The interatomic distances and angles for each heterocyclic ring in compound **4h** is depicted in Table 2.

CH_{arom}), 8.89 (2H, dd, $J_1 = 1.4$, $J_2 = 4.7$ Hz, 2 CH_{arom}). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 24.37, 24.47, 25.77, 32.96, and 33.23 (10 CH_2 of cyclohexyl), 27.29 and 27.96 (4 $OCMe_3$), 56.40 (2 NCH), 83.49 and 83.65 (4 $OCMe_3$), 90.51(2 C_{spiro}), 124.53, 130.10, 132.08, 133.71, 147.66, 149.78, and 150.71 ($C{=}C_{iminolactone\ ring}$ and C_{arom}), 153.03 ($2C{=}N_{iminolactone}$), 159.31 and 159.86 (4C=O of esters). MS (m/z, %): 880 (M^+, 2), 781 (4), 442 (2), 399 (3), 343 (3), 272 (4), 229 (3), 98(6), 83 (8), 57 (49), 44 (61). Anal. Calcd for $C_{50}H_{64}N_4O_{10}$ (881.06): C, 68.16; H, 7.32; N, 6.36%; Found: C, 68.07; H, 7.35; N, 6.40%.

Bis(diethyl 5-tert-butylimino-5H, 6H′)-dispiro(furan-2,5′-[1,10]phenanthroline)-3,3′,4,4′-tetracarboxylate (4m). Brown crystals; yield: 0.31 g (90%), m.p. 50–53°C, IR (KBr) (υ_{max}, cm^{-1}): 1738 and 1729 (4C=O), 1689 (2C=N); ^1H NMR (300.1 MHz, $CDCl_3$): δ_H 0.89 (6H, br s, 2 OCH_2CH_3), 1.23 (6H, br s, 2 OCH_2CH_3), 1.41 (18H, s, 2 CMe_3), 3.76 (4H, q, $J = 7.0$ Hz, 2 OCH_2CH_3), 4.31 (4H, q, $J = 7.0$ Hz, 2 OCH_2CH_3), 7.29–7.58 (4H, m, 4 CH_{arom}), 7.82 (2H, d, $J = 6.5$ Hz, 2 CH_{arom}). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 13.37 and 13.84 (4 OCH_2CH_3), 29.53 (2 CMe_3), 55.25 (2 $NCMe_3$), 61.97 and 62.10 (4 OCH_2CH_3), 93.35 (2 C_{spiro}), 123.52, 125.59, 128.98, 130.33, 131.31, 133.42, 149.67, and 150.52 ($C{=}C_{iminolactone\ ring}$ and C_{arom}), 150.79 ($2C{=}N_{iminolactone}$), 159.92 and 161.01 (4C=O of esters). MS (m/z, %): 717 ($M^+ +1$, 28), 716 (M^+, 47), 702 (11), 660 (55), 603 (100), 515 (12), 406 (15), 297 (10), 57 (71). Anal. Calcd for $C_{38}H_{44}N_4O_{10}$ (716.78): C, 63.67; H, 6.19; N, 7.82%; Found: C, 63.60; H, 6.23; N, 7.78%.

Crystal/refinement details for 4a. $C_{40}H_{32}N_2O_{10}$, M = 700.68, $F(000) = 2928$ e, orthorhombic, $P2_12_12_1$ (No. 19), $Z = 8$, $T = 100(2)$ K, $a = 15.7294(1)$, $b = 20.0784(1)$, $c = 21.5051(1)$ Å, $V = 6791.77(6)$ Å^3; $D_c = 1.370$ g cm^{-3}; $\mu_{Cu} = 0.825$ mm^{-1}; $\sin\theta/\lambda_{max} = 0.5981$; N(unique) = 6631 (merged from 92696, $R_{int} = 0.0364$, $R_{sig} = 0.0148$), N_o ($I > 2\delta(I)$) = 6039; $R = 0.0324$, $wR2 = 0.0850$ ($A,B = 0.07, 0.67$), GOF = 1.002; $|\Delta_{\rho max}| = 0.26(4)$ e Å^{-3}. CCDC 662911.

Crystal/refinement details for 4h. $C_{44}H_{40}N_4O_{10}$, M = 784.80, $F(000) = 1648$ e, monoclinic, $C2/c$ (No. 15), $Z = 4$, $T = 100(2)$ K, $a = 17.6425(2)$, $b = 14.3501(1)$, $c = 16.1083(2)$ Å, $\beta = 109.573(1)°$, $V = 3842.51(7)$ Å^3; $D_c = 1.357$ g cm^{-3}; $\mu_{Cu} = 0.803$ mm^{-1}; $\sin\theta/\lambda_{max} = 0.5970$; N(unique) = 3399 (merged from 43440, $R_{int} = 0.0483$, $R_{sig} = 0.0319$), N_o ($I > 2\delta(I)$) = 2349; $R = 0.0439$, $wR2 = 0.1107$ ($A,B = 0.078, 0$), GOF = 1.002; $|\Delta_{\rho max}| = 0.68(5)$ e Å^{-3}. CCDC 662912.

CCDC numbers 662911 and 662912 contains the crystallographic data for compounds **4a** and **4h**. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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An Efficient and Stereoselective Synthesis of Pyrazolo[4,3-*c*]pyridine Derivatives under Microwave Heating

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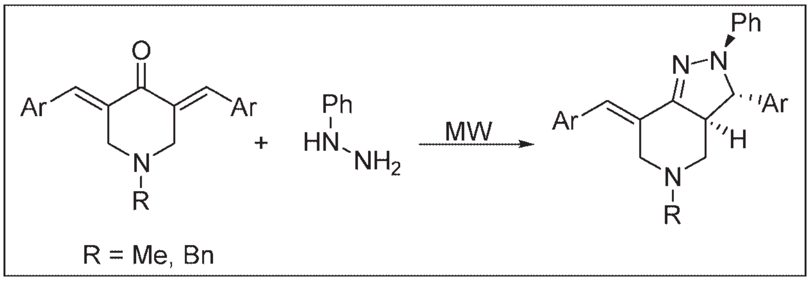

A practical, inexpensive, and rapid method for the stereoselective synthesis of pyrazolo[4,3-*c*]pyridine derivatives *via* microwave-assisted reactions of 3,5-diarylidenepiperidin-4-ones with phenylhydrazine in ethylene glycol. This method has the advantages of good yield, operational simplicity, and simple purification procedure.

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INTRODUCTION

In recent years, microwave-assisted organic synthesis has received much attention [1] because of its shorter reaction times and formation of cleaner products compared with conventional heating. It is clear that the application of microwave technology to rapid synthesis of biologically significant molecules would be of great value for library generation [2]. This technology has recently been recognized as a useful tool for a drug-discovery program [3]. In addition, microwave-assisted synthesis of pyrazoles and pyrazolines *via* the cyclocondensation of phenylhydrazine with α,β-unsaturated ketones has been reported [4]. In conjunction with our continuous interest in combinatorial synthesis [5], we explore the use of microwave irradiation as a heating source in the synthesis of pyrazolo[4,3-*c*]pyridine derivatives.

Five and six-membered nitrogen-containing heterocycles are abundant in nature and exhibit diverse and important biological properties [6]. Pyrazolopyridine derivatives are the important heterocyclic compounds, which exhibit a diverse range of biological properties such as new inhibitors of xanthine oxidases [7], as Polo-like kinase 1 inhibitors [8], and HIF-1alpha prolyl hydroxylase inhibitors [9]. They also have proved to be active against Gram positive and Gram negative bacteria [10] and also as compounds for the inhibition of cholesterol formation [11]. Because of their biological activities, these compounds have distinguished themselves as heterocycles of profound chemical and biological significance. As a result, the synthesis of these molecules has attracted considerable attention.

The pyrazolo[4,3-*c*]pyridine derivatives were, previously, mostly synthesized through the reaction of α,β-unsaturated ketones with substituted hydrazine in different reaction conditions such as (i) catalyzed by NaOEt in HOEt for 10 h [12], (ii) in refluxing MeOH for 4 h [13], (iii) in refluxing EtOH for 6 h [14], and (iv) catalyzed by Et_3N in refluxing EtOH [15]. However, the continued development of a facile and versatile method to pyrazolo[4,3-*c*]pyridine derivatives is still desired.

With the aim to develop more efficient synthetic processes, reduce the number of separate reaction steps, and minimize byproducts, and in continuation of our recent interest in the construction of heterocyclic scaffolds [16], we herein describe a practical, inexpensive, and rapid method for the stereoselective synthesis of pyrazolo[4,3-*c*]pyridine derivatives **3** *via* microwave-assisted (MW) reactions of 3,5-diarylidenepiperidin-4-ones **1** with phenylhydrazine **2** in ethylene glycol (Scheme 1).

RESULTS AND DISCUSSION

To explore the scope and versatility of this method, various reaction conditions were investigated, including solvent and temperature variations. Highlighted in

Scheme 1

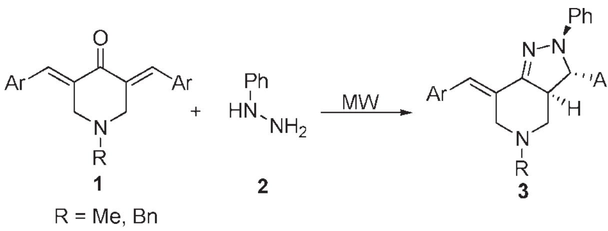


Table 1

Optimization of reaction conditions of compound **3a**.

Entry	Solvent	*T* (°C)	Time (min)	Yield (%)
1	Glycol	100	12	64
2	HOAc	100	16	35
3	EtOH	100	14	58
4	None	100	12	47
5	DMF	100	16	55
6	Glycol	90	16	61
7	Glycol	110	10	81
8	Glycol	120	8	89
9	Glycol	130	8	85
10	Glycol	140	8	88

Table 1 for compound **3a**, for example, is the influence of solvent on the reaction yield. The MW-assisted reaction of 3,5-bis(4-chlorobenzylidene)-1-methylpiperidin-4-one (**1a**, 1.0 mmol) with phenylhydrazine (**2**, 1.0 mmol) was examined using glycol, glacial acetic acid (HOAc), ethanol, and *N,N*-dimethylformamide (DMF) as solvent (1.0 mL) and solvent-free at 100°C, respectively. All the reactions were carried out at the maximum power of 200 W. The results were summarized in Table 1.

It was shown in Table 1 that the reaction using glycol as solvent gave the best result (Table 1, entry 8). So glycol was chosen as the reaction solvent. To further optimize reaction conditions, the same reaction was carried out in glycol at temperatures ranging from 90 to 140°C, with an increment of 10°C each time. The yield of product **3a** was increased and the reaction time was shortened as the temperature was increased from 90°C to 120°C (Table 1, entries 6–8). However, further increase of the temperature to 130–140°C failed to improve the yield of product **3a** (Table 1, entries 9–10). Therefore, 120°C was chosen as the reaction temperature for all further microwave-assisted reactions.

The use of these optimal microwave experimental conditions [glycol, 120°C, 200 W (Maximum power)] to the reactions of different 3,5-diarylidenepiperidin-4-ones afforded good yields of pyrazolo[4,3-*c*]pyridine. As shown in Table 2, at the beginning, we made a search for the 3,5-diarylidenepiperidin-4-ones substrate scope, phenylhydrazine **2** were used as model substrates (Table 2, entries 1–9 and 11–12), and the results indicated that 3,5-diarylidenepiperidin-4-ones bearing either electron donating or electron withdrawing functional groups such as nitro, chloro, hydroxyl, or methoxy were able to affect the synthesis of compounds **3**. Moreover, the heterocyclic3,5-diarylidenepiperidin-4-one such as thiophen-2-yl group (Table 2, entry 10) still displayed high reactivity under this standard condition.

Additionally, to demonstrate the microwave effects, the same temperature was applied to synthesize some of the products under classical heating (CH) conditions. The results listed in Table 3 showed the specific activation of this reaction by microwave heating. Simultaneously, the reaction times was strikingly shortened to minutes from hours required in traditional heating condition, and the yields were increased obviously too. The difference in yields (MW > CH) may be a consequence of both thermal effects and specific effects induced by the microwave field [17]. The reactants in these reactions contain dipoles and proceed *via* relatively polar

Table 2

The reaction times, melting points, and yields of products.

Entry	Product	Ar	R	Time (min)	Mp: (lit) (°C)	Yield[a] (%)
1	**3a**	4-Chlorophenyl	Me	8	173–174	89
2	**3b**	4-Bromophenyl	Me	8	170–172	93
3	**3c**	3-Nitrophenyl	Me	9	201–203	91
4	**3d**	2-Chlorophenyl	Me	10	227–228	88
5	**3e**	Phenyl	Me	8	159–160 (147–148) [14]	90 (72) [14]
6	**3f**	4-Tolyl	Me	9	171–173 (175–176) [12(a)]	87 (53) [12(a)]
7	**3g**	4-Dimethylaminophenyl	Me	8	226–228	88
8	**3h**	4-Methoxyphenyl	Me	11	201–202 (192–193) [12(a)]	85 (51) [12(a)]
9	**3i**	3,4-Dimethoxyphenyl	Me	12	173–175	83
10	**3j**	Thiophen-2-yl	Me	12	176–177 (169–170) [12(a)]	88 (36) [12(a)]
11	**3k**	Phenyl	Benzyl	8	171–173 (155–157) [14]	90 (25) [14]
12	**3l**	4-Methoxyphenyl	Benzyl	10	168–170 (157–158) [14]	92 (42) [14]

[a] Isolated yields under microwave heating conditions.

Table 3

The synthesis of some of compound **3** using conventional heating.

Entry	Product	Time (h)	Yield (%)
1	**3a**	2	84
2	**3c**	2	69
3	**3e**	2	74
4	**3f**	2	79
5	**3k**	2	72

intermediates, which enhance their interactions with MW and consequently benefit significantly from MW irradiation.

The structures of all the synthesized compounds were established on the basis of their spectroscopic data. The structural elucidation and the attribution of the relative stereochemistry rest upon NMR analysis and was unequivocally confirmed by X-ray diffraction of single crystals obtained by slow evaporation of the solvent in the case of **3j** (Fig. 1) [18]. The *anti* and *syn* isomers were identified by the coupling constants (J) of the vicinal protons adjacent to N-Ph and CH_2 in their ^1H NMR spectra. The coupling constants (J) of *anti* isomer is higher than that of the *syn* one [19]. The ^1H NMR spectrum of **3a** showed two doubles at $\delta = 4.83$, 3.78 from CH proton, and the corresponding coupling constant is $J = 12.4$; it is indicated that compounds **3** were *anti* configuration. Furthermore, because of exclusion between crowded aryl systems adjacent to N=C and CH, the molecule structure **3** is thermodynamic stable configuration (Fig. 2).

In summary, we have developed an efficient and improved stereoselective reactions of 3,5-diarylidenepiperidin-4-ones with phenylhydrazine **2** under mild conditions and have shown its application in the microwave-assisted synthesis of a wide range of pyrazolo[4,3-*c*]pyridine derivative in excellent yields. In light of its operational simplicity, simple purification procedure, and increased safety for small-scale high-speed synthesis, this protocol is superior to the existing methods.

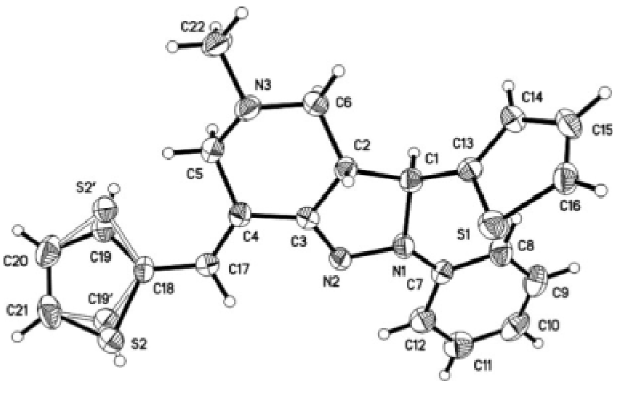
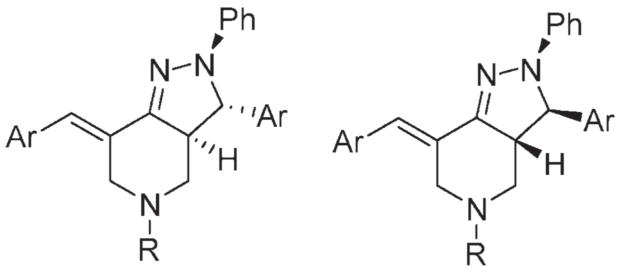


Figure 1. ORTEP diagram of **3j**.



3 3'

Figure 2. The structures of *anti* and *syn* isomers **3** and **3′**.

EXPERIMENTAL

Microwave irradiation was carried out with a microwave oven Emrys^{TM} Creator from Personal Chemistry (Uppsala, Sweden). Melting points were determined in the open capillaries and were uncorrected. IR spectra were taken on a FT-IR-Tensor 27 spectrometer in KBr pellets and reported in cm^{-1}. ^1H NMR spectra were measured on a Bruker DPX 400 MHz spectrometer using TMS as an internal standard and DMSO-d_6 as solvent. HRMS (ESI) was determined by using micrOTOF-Q·HRMS/MS instrument (BRUKER). X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer.

General procedure for the one-pot synthesis of pyrazolo[4,3-*c*]pyridines 3 under microwave irradiation conditions. Typically, in a 10 mL Emrys^{TM} reaction vial, 3,5-bis(4-chlorobenzylidene)-1-methylpiperidin-4-one (**1a**, 1.0 mmol), phenylhydrazine (**2**, 1.0 mmol), and glycol (1.0 mL) were mixed and then capped. The mixture was kept for a given time at 120°C under microwave irradiation (initial power 100 W and maximum power 200 W). Upon completion, monitored by TLC, the reaction mixture was filtered to give the crude product, which was further purified by recrystallization from EtOH (95%) to give pure pyrazolo[4,3-*c*]pyridines **3**.

7-(4-Chlorobenzylidene)-3-(4-chlorophenyl)-3,3a,4,5,6,7-hexahydro-5-methyl-2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridine (3a). IR (KBr): 2763, 1598, 1489, 1281, 1091, 1013, 889, 824, 756 cm^{-1}.

^1H NMR (DMSO-d_6, 400 MHz) δ: 7.49–7.38 (m, 8H, ArH), 7.16 (t, $J = 7.8$ Hz, 3H, =CH, and ArH), 6.94 (d, $J = 8.0$ Hz, 2H, ArH), 6.81 (t, $J = 7.6$ Hz, 1H, ArH), 4.83 (d, $J = 12.4$ Hz, 1H, CH), 3.78 (d, $J = 12.0$ Hz, 1H, CH_2), 3.17−3.03 (m, 3H, CH, and CH_2), 2.47 (d, $J = 8.0$ Hz, 1H, CH_2), 2.30 (s, 3H, CH_3); HRMS (ESI): *m*/*z* calcd for: 448.1342 $[M + H]^+$, found: 448.1369.

7-(4-Bromobenzylidene)-3-(4-bromophenyl)-3,3a,4,5,6,7-hexahydro-5-methyl-2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridine (3b). IR (KBr): 2840, 1599, 1486, 1382, 1284, 1178, 1072, 1010, 889, 821 cm^{-1}.

^1H NMR (DMSO-d_6, 400 MHz) δ: 7.68–7.57 (m, 5H, ArH), 7.42–7.32 (m, 3H, =CH, and ArH), 7.16 (t, $J = 7.8$ Hz, 3H, ArH), 7.02–6.93 (m, 2H, ArH), 6.81 (t, $J = 7.4$ Hz, 1H, ArH), 4.82 (d, $J = 12.8$ Hz, 1H, CH), 3.79–3.70 (m, 1H, CH_2), 3.16–3.03 (m, 3H, CH_2), 2.48–2.37 (m, 1H, CH), 2.30 (s, 3H, CH_3).

HRMS (ESI): *m*/*z* calcd for: 536.0332 $[M + H]^+$, found: 536.0337.

7-(3-Nitrobenzylidene)-3,3a,4,5,6,7-hexahydro-5-methyl-3-(3-nitrophenyl)-2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridine (3c). IR (KBr): 2950, 2796, 1597, 1525, 1498, 1351, 1298, 1097, 1034, 882, 746, 693 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.31 (s, 1H, ArH), 8.21–8.17 (m, 3H, ArH), 7.94 (d, *J* = 8.0 Hz, 1H, ArH), 7.83 (d, *J* = 8.0 Hz, 1H, ArH), 7.72 (t, *J* = 7.8 Hz, 2H, ArH), 7.34 (s, 1H, =CH), 7.18 (t, *J* = 8.0 Hz, 2H, ArH), 6.97 (d, *J* = 7.6 Hz, 2H, ArH), 6.84 (t, *J* = 7.4 Hz, 1H, ArH), 5.11 (d, *J* = 12.4 Hz, 1H, CH), 3.81 (t, *J* = 14.4 Hz, 1H, CH_2), 3.25–3.21 (m, 2H, CH_2), 3.15–3.12 (m, 1H, CH_2), 2.60–2.54 (m, 1H, CH), 2.32 (s, 3H, CH_3).

HRMS (ESI): *m*/*z* calcd for: 470.1823 $[M + H]^+$, found: 470.1804.

7-(2-Chlorobenzylidene)-3-(2-chlorophenyl)-3,3a,4,5,6,7-hexahydro-5-methyl-2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridine (3d). IR (KBr): 2939, 1597, 1491, 1288, 1146, 1049, 998, 755 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.58–7.55 (m, 3H, ArH), 7.40–7.35 (m, 5H, ArH), 7.22–7.16 (m, 3H, CH, and ArH), 6.88–6.82 (m, 3H, ArH), 5.22 (d, *J* = 12.0 Hz, 1H, CH), 3.62 (d, *J* = 12.0 Hz, 1H, CH_2), 3.25–3.10 (m, 3H, CH_2), 2.59–2.57 (m, 1H, CH), 2.28 (s, 3H, CH_3).

HRMS (ESI): *m*/*z* calcd for: 448.1342 $[M + H]^+$, found: 448.1342.

7-Benzylidene-3,3a,4,5,6,7-hexahydro-5-methyl-2,3-diphenyl-2*H*-pyrazolo[4,3-*c*]pyridine (3e). IR (KBr): 2942, 2843, 1597, 1498, 1321, 1287, 1236, 1134, 1030, 1003, 889, 750 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.46–7.31 (m, 10H, ArH), 7.21 (s, 1H, =CH), 7.16–7.12 (m, 2H, ArH), 6.96 (d, *J* = 8.0 Hz, 2H, ArH), 6.79 (t, *J* = 7.2 Hz, 1H, ArH), 4.78 (d, *J* = 12.8 Hz, 1H, CH), 3.82 (d, *J* = 14.0 Hz, 1H, CH_2), 3.16–3.10 (m, 2H, CH_2), 3.07–3.03 (m, 1H, CH), 2.47 (d, *J* = 8.0 Hz, 1H, CH_2), 2.30 (s, 3H, CH_3).

HRMS (ESI): *m*/*z* calcd for: 380.2122 $[M+H]^+$, found: 380.2119.

7-(4-Methylbenzylidene)-3,3a,4,5,6,7-hexahydro-3-(4-methylphenyl)-5-methyl-2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridine (3f). IR (KBr): 2781, 1599, 1508, 1498, 1272, 1030, 977, 815, 749 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.57 (s, 1H, =CH), 7.40 (d, *J* = 8.0 Hz, 1H, ArH), 7.33–7.11 (m, 10H, ArH), 6.95 (d, *J* = 8.0 Hz, 1H, ArH), 6.78 (t, *J* = 7.4 Hz, 1H, ArH), 4.71 (d, *J* = 12.4 Hz, 1H, CH), 3.80 (t, J = 8.0 Hz, 1H, CH_2), 3.73 (d, *J* = 4.0 Hz, 1H, CH_2), 3.13–3.09 (m, 2H, CH_2), 2.45–2.35 (m, 1H, CH), 2.33 (t, *J* = 10.0 Hz, 9H, CH_3).

HRMS (ESI): *m*/*z* calcd for: 408.2435 $[M+H]^+$, found: 408.2418.

7-(4-(Dimethylamino)benzylidene)-3,3a,4,5,6,7-hexahydro-5-methyl-2-phenyl-2H-pyrazolo[4,3-c]pyridin-3-yl)-*N*,*N*-dimethylbenzenamine (3g). IR (KBr): 2870, 1595, 1521, 1443, 1357, 1282, 1168, 1045, 977, 817 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.22 (t, *J* = 9.4 Hz, 4H, ArH), 7.11 (t, *J* = 7.8 Hz, 3H, =CH, and ArH), 6.98 (d, *J* = 7.6 Hz, 2H, ArH), 6.76–6.72 (m, 5H, ArH), 4.55 (d, *J* = 12.8 Hz, 1H, CH), 3.84 (d, *J* = 14.0 Hz, 1H, CH_2), 3.82–3.06 (m, 3H, CH_2), 2.95 (s, 6H, CH_3), 2.89 (s, 6H, CH_3), 2.43–2.37 (m, 1H, CH), 2.31 (s, 3H, CH_3).

HRMS (ESI): *m*/*z* calcd for: 466.2966 $[M + H]^+$, found: 466.2968.

7-(4-Methoxybenzylidene)-3,3a,4,5,6,7-hexahydro-3-(4-methoxyphenyl)-5-methyl-2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridine (3h). IR (KBr): 2945, 2834, 1598, 1510, 1250, 1031, 833, 754 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.37–7.31 (m, 4H, ArH), 7.13 (t, *J* = 7.8 Hz, 3H, =CH, and ArH), 7.00–6.95 (m, 6H, ArH), 6.78 (t, *J* = 7.2 Hz, 1H, ArH), 4.68 (d, *J* = 12.8 Hz, 1H, CH), 3.79(t, *J* = 14.0 Hz, 7H, CH_2, and OCH_3), 3.13–2.99 (m, 3H, CH, and CH_2), 2.44 (t, *J* = 10.0 Hz, 1H, CH_2), 2.30 (s, 3H, CH_3).

HRMS (ESI): *m*/*z* calcd for: 440.2333 $[M+H]^+$, found: 440.2338.

7-(3,4-Dimethoxybenzylidene)-3,3a,4,5,6,7-hexahydro-3-(3,4-dimethoxyphenyl)-5-methyl-2-phenyl-2*H*-pyrazolo[4,3-*c*] pyridine (3i). IR (KBr): 2944, 1597, 1513, 1496, 1261, 1141, 1032, 897, 749 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.14 (t, *J* = 7.8 Hz, 3H, =CH, and ArH), 7.02–6.97 (m, 7H, ArH), 6.92 (d, *J* = 1.6 Hz, 1H, ArH), 6.79 (t, *J* = 7.2 Hz, 1H, ArH), 4.65 (d, *J* = 12.8 Hz, 1H, CH), 3.85 (d, *J* = 16.0 Hz, 1H, CH_2), 3.77 (d, *J* = 16.0 Hz, 12H, OCH_3), 3.17–3.10 (m, 2H, CH_2), 3.05–3.01 (m, 1H, CH_2), 2.46–2.41 (m, 1H, CH), 2.32 (s, 3H, CH_3).

HRMS (ESI): *m*/*z* calcd for: 500.2549 $[M + H]^+$, found: 500.2563.

7-(Thiophen-2-ylmethylene)-3,3a,4,5,6,7-hexahydro-5-methyl-2-phenyl-3-(thiophen-2-yl)-2*H*-pyrazolo[4,3-*c*]pyridine (3j). IR (KBr): 2781, 1596, 1489, 1382, 1280, 1134, 1027, 912, 857 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.70 (d, *J* = 4.0 Hz, 1H, ArH), 7.50 (d, *J* = 4.0 Hz, 1H, ArH), 7.42 (s, 1H, =CH), 7.32 (d, *J* = 4.0 Hz, 1H, ArH), 7.27 (d, *J* = 4.0 Hz, 1H, ArH), 7.18 (d, *J* = 16.0 Hz, 3H, ArH), 7.09–7.04 (m, 3H, ArH), 6.85 (t, *J* = 6.0 Hz, 1H, ArH), 5.10 (d, *J* = 12.8 Hz, 1H, CH), 3.99 (d, *J* = 16.0 Hz, 1H, CH_2), 3.27–3.19 (m, 1H, CH), 3.04 (d, *J* = 12.0 Hz, 2H, CH_2), 2.47 (s, 1H, CH_2), 2.39 (s, 3H, CH_3).

HRMS (ESI): *m*/*z* calcd for: 392.1250 $[M + H]^+$, found: 392.1238.

5-Benzyl-7-benzylidene-3,3a,4,5,6,7-hexahydro-2,3-diphenyl-2*H*-pyrazolo[4,3-*c*]pyridine (3k). IR (KBr): 2891, 2811, 1596, 1498, 1452, 1375, 1281, 1118, 1032, 918, 883, 748 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.44–7.11 (m, 18H, =CH, and ArH), 6.95 (d, *J* = 7.6 Hz, 2H, ArH), 6.78 (t, *J* = 7.4 Hz, 1H, ArH), 4.77 (d, *J* = 12.8 Hz, 1H, CH), 3.91 (d, *J* = 13.6 Hz, 1H, CH_2), 3.65 (s, 2H, CH_2), 3.24–3.14 (m, 3H, CH_2), 2.61–2.57 (m, 1H, CH).

HRMS (ESI): *m*/*z* calcd for: 456.2435 $[M+H]^+$, found: 456.2415.

7-(4-Methoxybenzylidene)-5-benzyl-3,3a,4,5,6,7-hexahydro-3-(4-methoxyphenyl)-2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridine (3l). IR (KBr): 2835, 1597, 1497, 1300, 1250, 1179, 1032, 992, 830 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.34–7.10 (m, 12H, =CH, and ArH), 6.96–6.92 (m, 6H, ArH), 6.77 (t, *J* = 6.0 Hz, 1H, ArH), 4.68 (d, *J* = 12.8 Hz, 1H, CH), 3.91 (d, *J* = 12.0 Hz, 1H, CH_2), 3.80–3.59 (m, 9H, CH_2, and OCH_3), 3.20–3.07 (m, 3H, CH, and CH_2).

HRMS (ESI): *m*/*z* calcd for: 516.2646 $[M + H]^+$, found: 516.2654.

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[18] The single-crystal growth was carried out in ethanol at room temperature. X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Semens P4 diffractometer. Crystal data for **3j**: $C_{22}H_{21}N_3S_2$, $M = 391.54$, Monoclinic, space group P2(1)/n, $a = 8.0414(10)$, $b = 29.939(3)$, $c = 8.51360(11)$, $\alpha = 90$, $\beta = 107.308(2)$, $\gamma = 90°$, $V = 1956.9(3)$ $\mathrm{\AA}^3$, $Z = 4$, $T = 298(2)$ K, $\mu = 0.284$ mm^{-1}, 10238 reflections measured, 3418 unique reflections, $R = 0.0727$, $R_w = 0.0878$.

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Divergent Reactivity in Tandem Reduction–Michael Ring Closures of Five- and Six-Membered Cyclic Enones

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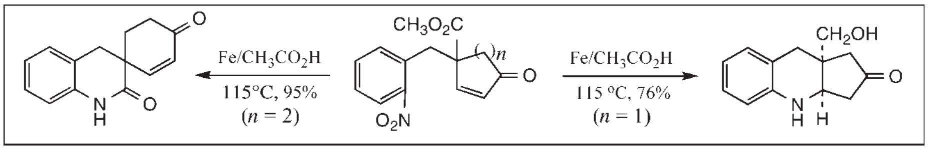

In this study, methyl (±)-1-(2-nitrobenzyl)-4-oxo-2-cyclohexene-1-carboxylate and methyl (±)-(2-nitrobenzyl)-4-oxo-2-cyclopentene-1-carboxylate were prepared and subjected to reductive cyclization under dissolving metal conditions. The two reactants showed divergent behavior with the six-ring substrate reacting at the ester carbonyl and the five-ring substrate closing on the enone double bond. The difference in reactivity is attributed to the conformational flexibility, relative reactivity, and steric environment of C4-substituted six- and five-membered cyclic enones.

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INTRODUCTION

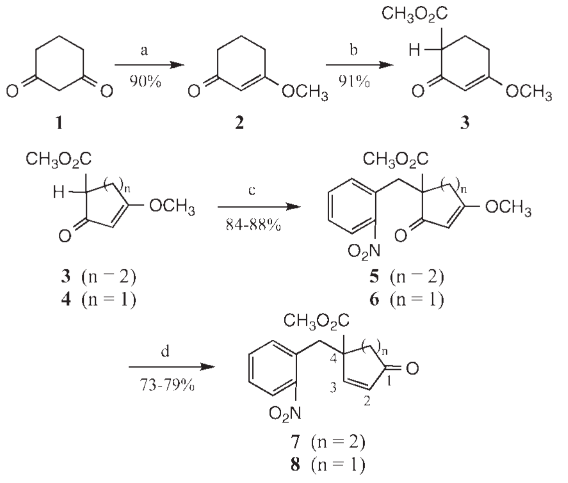
The reductive cyclization of 2-nitrobenzyl ketones under dissolving metal conditions is well established as a route to the synthesis of indoles [1,2]. Earlier work from our laboratory studied a tandem reduction–Michael addition variant of this reaction as a route to the synthesis of 1,2,3,4-tetrahydroquinoline-2-acetic esters [3], and we have recently used this reaction to synthesize 1,2,3,9-tetrahydro-4*H*-carbazol-4-one [4]. In this investigation, we sought to expand the scope of the tandem reduction–Michael sequence to access functionalized linear-fused tricyclic systems. For this study, we prepared six- and five-membered cyclic enones substituted at C4 by a methyl ester and a 2-nitrobenzyl group, and subjected each to mild reduction using iron in acetic acid. To our surprise, divergent reactivity was observed from the cyclohexenone and cyclopentenone substrates, resulting in two relatively uncommon ring systems. In addition, a mechanistically novel competitive ester reduction process was observed. Thus, we report our findings in this area.

RESULTS AND DISCUSSION

The syntheses of our cyclization substrates are summarized in Scheme 1. Ketoester **3** was prepared from 1,3-cyclohexanedione (**1**) by Lewis acid-catalyzed enol ether formation to give **2** [5] followed by kinetic deprotonation [6] and reaction with methyl cyanoformate [7]. In this case, we found that methyl cyanoformate gave better yields of the ketoester than methyl chloroformate with easier purification of the product. Ketoester **4** was prepared as previously described [8]. Alkylation of **3** and **4** with 2-nitrobenzyl bromide [9] using potassium carbonate and catalytic 18-crown-6 in acetonitrile under anhydrous conditions [10] gave products **5** and **6**, respectively. Reduction of the enone carbonyls in **5** and **6** with sodium borohydride in the presence of cerium(III) chloride [11], followed by treatment with aqueous acid resulted in 1,3-carbonyl transposition to give substrates **7** and **8**.

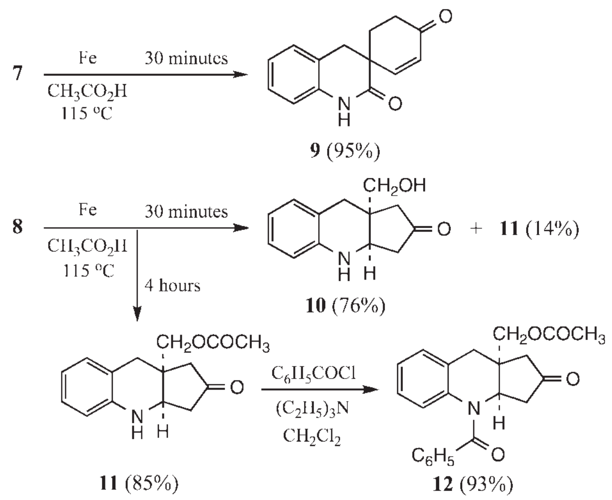
The results of our reduction-cyclization study are outlined in Scheme 2. In each case, the reaction was

Scheme 1 [a]



[a] Key: (a) CH_3OH, $CeCl_3{\cdot}7H_2O$-SiO_2, 22°C; (b) *i.* $LiN(i\text{-}C_3H_7)_2$, tetrahydrofuran, -78°C; *ii.* CH_3O_2CCN, -78°C → 22°C; (c) K_2CO_3, 18-crown-6, CH_3CN, 2-nitrobenzyl bromide, 82°C; (d) *i* $NaBH_4$, $CeCl_3{\cdot}7H_2O$, CH_3OH, 22 °C; *ii.* 3 M HCl.

Scheme 2



complete in 30 min and led predominantly to a single product. For cyclohexenone **7**, the expected reduction-Michael addition was not observed, but instead, reduction of the nitro group was followed by addition of the aniline nitrogen to the ester to give the spiro-fused 3,4-dihydro-2(1*H*)-quinolinone derivative **9** in 95% yield. For cyclopentenone **8**, the reduction–Michael sequence proceeded as planned, but was accompanied by reduction of the ester to afford **10** in 76% yield. Extended reaction times (4 h) led to further acylation of the primary alcohol in **10** to give **11**. The *cis* stereochemistry of the ring junction was confirmed by the conversion of **11** to its solid *N*-benzoyl derivative **12** and single crystal X-ray analysis (Fig. 1).

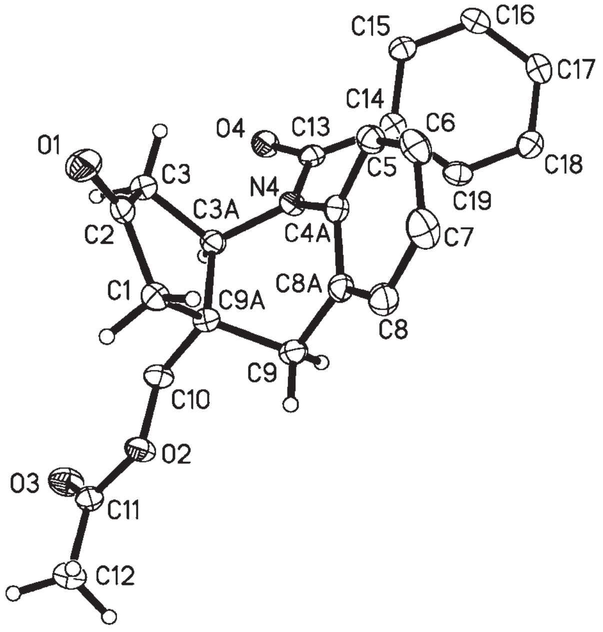
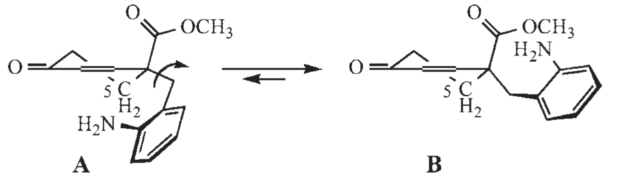


Figure 1. Molecular structure of compound **12**, with thermal ellipsoids drawn at the 50% probability level. Hydrogen atoms on C10 and on the aromatic rings have been removed for clarity.

Scheme 3



Examination of molecular models provides some insight into the observed difference in reactivity. Following reduction of the nitro function in **7**, alignment of the amino group for addition to the enone would result in steric repulsion between the C5 methylene of the cyclohexenone and the aromatic ring as in **A** (Scheme 3). Rotation about the benzylic bond to minimize this interaction would then lead to conformation **B**, which is more prone to react at the ester carbonyl. By comparison, similar steric interference is not present in cyclopentenone **8**. Furthermore, the five-membered cyclic enone should be more reactive due to strain. Eclipsing interactions that develop in the five-membered ring of **10** during addition should not significantly deter cyclization since the starting enone also possesses considerable torsional strain. The eclipsing in the cyclized product is clearly visible in the X-ray structure of **12** (Fig. 1).

The preference for the *cis* stereochemistry of the ring junction in **10** is in accord with both strain and stereoelectronic considerations. The *cis*-fused stereochemistry would be expected based on strain arguments, with the *cis*-fused ring junction preferred over the more strained *trans* [12]. Stereoelectronically, it is well established that the *cis*-fused isomer is strongly favored in nucleophilic ring closures on pre-existing rings via an axial attack that permits a chair-like transition state [13]. Although, a true chair transition state is not possible due to the aromatic sp^2 carbons, pseudoaxial attack would still be expected to afford a *cis* product.

The reduction of the ester group in **8** is also an interesting observation. The reduction is analogous to the classical Bouveault-Blanc reaction [14], but would not be expected to occur with iron as the electron source [15]. In our substrates, the α,β-unsaturated ketone is the functional group most susceptible to reduction under dissolving metal conditions [16], and we believe that this moiety is the key to reduce the ester.

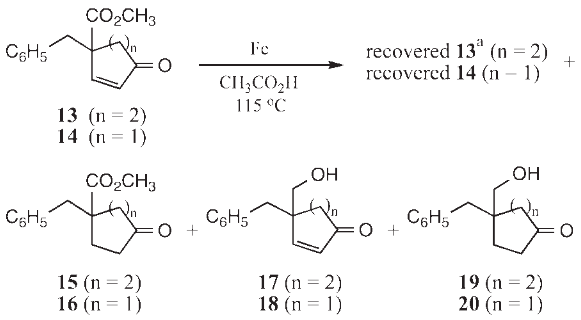
To explore this process without interference from the amino group, methyl (±)-1-benzyl-4-oxo-2-cyclohexene-1-carboxylate (**13**) and methyl (±)-1-benzyl-4-oxo-2-cyclopentene-1-carboxylate (**14**) were prepared using the method described for the nitro-bearing substrates. Treatment of **13** with iron in acetic acid for 24 h yielded a

33:67 mixture (by NMR) of starting material **13** and the double bond reduction product **15**. This ratio varied little with longer reaction times or increased amounts of iron. Similar reaction of **14** gave more interesting results, and the reaction was considerably faster. Exposure of **14** to iron in refluxing acetic acid gave nearly complete conversion to alcohol **18** in 15 min. Prolonged treatment (2 h) under the same conditions gave a 67:33 mixture (by NMR) of **18**:**20**, as the acetates, in 95% yield. These results are summarized in Scheme 4.

Mechanistically, the reduction of **13** and **14** is initiated by protonation of the enone carbonyls followed by the addition of two electrons to each conjugated system [16] to give anions **21** and **22**, respectively (Scheme 5). In **21**, the six-membered ring is conformationally flexible making the ester at C4 less accessible to attack by the anionic center at C3. Thus, protonation and tautomerization occur to give **15**. In the more rigid structure **22**, the C3 anion is closer to the C4 ester and cyclization occurs to afford the strained cyclopropanone hemiketal **23**. Under the acidic conditions of the reaction, **23** would undergo rapid proton and enol-assisted three-ring opening [17], as in **24**, followed by the loss of methanol to give aldehyde **25**. Further reduction of **25** would then afford alcohol **18** and, eventually, **20**.

The systems resulting from these ring closures have minimal precedent in the literature. The 3,3-dialkyl-3,4-dihydro-2(1*H*)-quinolinone scaffold of **9** is found in some antidepressants [18], but spiro-fused compounds have not been extensively investigated [19]. The 2,3,3a,4,9,9a-hexahydro-1*H*-cyclopenta[*b*]quinoline system has been reported [20] and is known to exhibit some antipsychotic activity [21], but structures with the functional group arrangement of **10** are unknown.

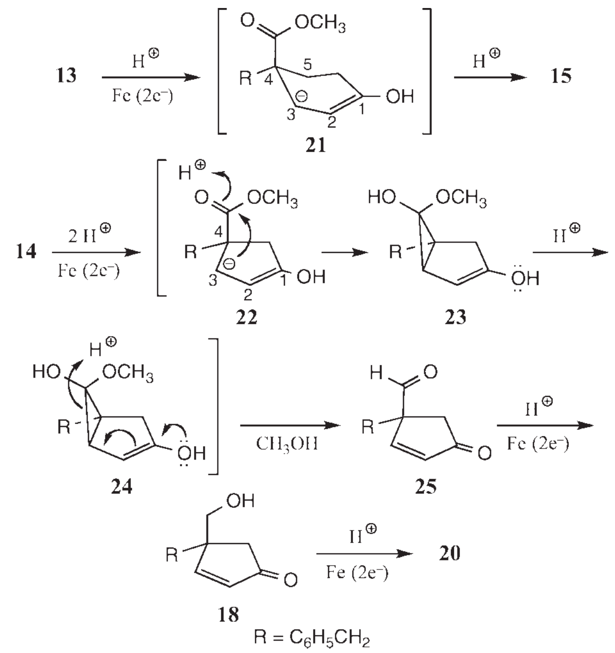
Scheme 4



Substrate	time (hours)	**13**	**15**	**17**	**19**
13 (n = 2)	24	33	67	0	0
		14	**16**	**18**	**20**
14 (n = 1)	0.25	10[b]	0	72[b]	trace
	2	0	0	67[c]	33[c]

[a] Percentages listed are from the ^{1}H NMR. [b] Isolated yields. [c] Products detected were the acetates of the indicated alcohols.

Scheme 5



CONCLUSIONS

Divergent behavior has been observed in the dissolving metal reduction–Michael reaction of two substrates differing only in the size of the ring incorporating the Michael acceptor. The disparate reaction pathways can be attributed to the differences in strain and steric environment of the enone acceptor as well as the alignment of the reacting functionality in the two systems. The reaction is clean and offers an efficient route to a relatively rare ring skeleton from each substrate. The reduction of the ester functionality in the five-membered ring substrate is novel and likely involves the participation of the enone moiety.

EXPERIMENTAL

Commercial reagents and solvents were used as received. Tetrahydrofuran was dried over potassium hydroxide pellets and distilled from lithium aluminum hydride before use. The hydrochloric acid (3*M*), ammonium chloride (saturated), sodium bicarbonate (saturated), and sodium chloride (saturated) used in workup procedures refer to aqueous solutions. All reactions were run under dry nitrogen in oven-dried glassware. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech 21521). Preparative separations were performed using flash column chromatography [22] on silica gel (grade 62, 60–200 mesh) mixed with ultraviolet-active phosphor (Sorbent Technologies No. UV-5) or thin layer chromatography on 20 cm × 20 cm silica gel GF plates (Analtech 02015); band elution was monitored using a hand-held ultraviolet lamp. Hexanes used in chromatography had a boiling range of 65–70°C. Melting points were uncorrected. Infrared spectra were run as thin films on sodium chloride disks and were referenced to polystyrene. ^{1}H- and ^{13}C-NMR spectra were measured in deuteriochloroform at 300 MHz and 75 MHz, respectively, using tetramethylsilane as the internal standard; coupling constants (J) are reported in Hertz. Low-resolution mass spectra (electron impact/direct probe) were run at 30 eV.

3-Methoxy-2-cyclohexen-1-one (2). The procedure of Sabitha *et al*. [5] was modified. A mixture of 20.0 g of silica gel (Alfa-Aesar, 220–440 mesh) and 3.60 g (9.60 mmoles) of cerium(III) chloride heptahydrate in 60 mL of dry acetonitrile was stirred for 12 h at 22°C. The acetonitrile was removed under vacuum and a solution of 5.00 g (44.6 mmoles) of **1** in 20 mL of methanol was added. The mixture was stirred for 72 h at 22°C and filtered with ethyl acetate. The filtrate was concentrated under reduced pressure, and the crude product was purified by flash chromatography on a 30 cm × 2.5 cm silica gel column eluted with 50% ethyl acetate in hexanes to give 3.70 g (90%) of **2** as a colorless oil. IR: 1671, 1645, 1605 cm^{-1}; ^{1}H-NMR: δ 5.37 (s, 1H), 3.70 (s, 3H), 2.42 (t, 2H, J = 6.4), 2.35 (t, 2H, J = 6.9), 1.98 (quintet, 2H, J = 6.6); ^{13}C-NMR: δ 199.4, 178.4, 102.1, 55.4, 36.5, 28.6, 21.0.

Methyl (±)-4-methoxy-2-oxo-3-cyclohexene-1-carboxylate (3). To a stirred solution of 2.88 g (4.00 mL, 28.6 mmoles) of diisopropylamine in 30.0 mL of tetrahydrofuran at −78°C, was slowly added 17.0 mL of 1.75*M* *n*-butyllithium in hexanes (30.0 mmoles). After 30 min, a solution of 3.00 g (23.8 mmoles) of **2** in 20.0 mL of tetrahydrofuran was added dropwise and stirring was continued at −78°C for 30 min. A solution of 3.40 g (40.0 mmoles) of methyl cyanoformate in 10 mL of tetrahydrofuran was then added dropwise and the reaction was stirred for 1 h at −78°C. The reaction mixture was slowly warmed to 22°C, stirred for 30 min, cautiously added to saturated ammonium chloride and extracted with ether. The ether extracts were washed with saturated sodium bicarbonate (one time), water (one time), and saturated sodium chloride (one time), and then dried (magnesium sulfate) and concentrated under vacuum. The crude product was purified by flash chromatography on a 100 cm × 2.5 cm silica gel column eluted with 30% ethyl acetate in hexanes to give 0.60 g (20%) of **2** and 3.20 g (73%) of **3**. The yield of **3** was 91% based on recovered starting material. IR: 1740, 1656, 1606 cm^{-1}; ^{1}H-NMR: δ 5.41 (s, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.35 (dd, 1H, J = 9.2, 5.3), 2.57 (m, 1H), 2.46 (m, 1H), 2.36 (m, 1H), 2.17 (m, 1H); ^{13}C-NMR: δ 193.5, 178.4, 170.6, 101.6, 55.8, 52.2, 52.0, 27.0, 24.0; ms: m/z 184 (M$^+$); *Anal*. Calcd. for $C_9H_{12}O_4$: C, 58.70; H, 6.52. Found: C, 58.77; H, 6.55.

Methyl (±)-4-methoxy-2-oxo-3-cyclopentene-1-carboxylate (4). This compound was prepared by the method of Fuchs and McGarrity [8]. The spectral data matched those reported.

Representative procedure for alkylation of 3 with 2-nitrobenzyl bromide: Methyl (±)-4-methoxy-1-(2-nitrobenzyl)-2-oxo-3-cyclohexene-1-carboxylate (5). The general procedure of Makosza and Tyrala [10] was used. A 100-mL three-necked, round-bottomed flask equipped with an addition funnel, a reflux condenser, and a magnetic stir bar was charged with 35 mL of dry acetonitrile, 4.87 g (35.2 mmoles) of anhydrous potassium carbonate, and 10 mg of 18-crown-6. Stirring was initiated and a solution of 2.16 g (11.7 mmoles) of **3** in 10 mL of acetonitrile was added dropwise at 22°C. The resulting blue solution was stirred for 10 min and a solution of 2.80 g (13.0 mmoles) of 2-nitrobenzyl bromide [9] in 10 mL of acetonitrile was added dropwise. The reaction was refluxed for 18 h at which time thin layer chromatography indicated complete consumption of **3**. The crude reaction mixture was cooled, diluted with ether, vacuum filtered, and concentrated under vacuum. The resulting dark yellow oil was purified by flash chromatography on a 100 cm × 2.5 cm silica gel column eluted with 20–30% ether in hexanes to give 3.30 g (88%) of **5** as a light yellow oil. IR: 1729, 1660, 1609, 1526, 1384, 1350 cm^{-1}; ^{1}H-NMR: δ 7.82 (dd, 1H, J = 8.2, 6.6), 7.47 (td, 1H, J = 7.5, 1.5), 7.36 (td, 1H, J = 7.9, 1.6), 7.35 (d, 1H, J = 7.0), 5.41 (d, 1H, J = 1.5), 3.87 (d, 1H, J = 14.1), 3.68 (s, 3H), 3.67 (s, 3H), 3.57 (d, 1H, J = 14.1), 2.59 (m, 1H), 2.39 (m, 1H), 2.27 (m 1H), 1.77 (m, 1H); ^{13}C-NMR: δ 193.9, 177.7, 171.1, 150.9, 133.4, 133.3, 131.5, 127.9, 124.7, 101.9, 57.0, 55.8, 52.7, 34.7, 28.3, 26.3; ms: m/z 319 (M$^+$). *Anal*. Calcd. for $C_{16}H_{17}NO_6$: C, 60.19; H, 5.33; N, 4.39. Found: C, 60.29; H, 5.36; N, 4.35.

Methyl (±)-4-methoxy-1-(2-nitrobenzyl)-2-oxo-3-cyclopentene-1-carboxylate (6). This compound (3.00 g, 84%) was obtained as a light yellow oil. IR: 1740, 1699, 1596, 1526, 1359 cm^{-1}; ^{1}H-NMR: δ 7.86 (dd, 1H, J = 8.1, 1.5), 7.47 (td, 1H, J = 7.5, 1.5), 7.38 (td, 1H, J = 7.9, 1.6), 7.35 (dd, 1H, J = 7.7, 1.5), 5.26 (t, 1H, J = 1.1), 3.80 (s, 3H), 3.75 (d, 1H, J = 14.6), 3.75 (s, 3H), 3.52 (d, 1H, J = 14.6), 3.17 (dd, 1H, J = 17.9, 1.1), 2.48 (dd, 1H, J = 17.9, 1.1); ^{13}C-NMR: δ 200.3, 191.0, 170.8, 150.5, 132.7, 132.2, 131.4, 128.0, 124.7, 102.0, 59.8, 59.1, 53.1, 37.0, 33.7; ms: m/z 305 (M$^+$). *Anal*. Calcd. for $C_{15}H_{15}NO_6$: C, 59.02; H, 4.92; N, 4.59. Found: C, 59.13; H, 4.96; N, 4.53.

Representative procedure for 1,3-carbonyl tranposition: Methyl (±)-1-(2-nitrobenzyl)-4-oxo-2-cyclohexene-1-carboxylate (7). The procedure of Luche was modified [11]. A 250-mL three-necked, round-bottomed flask equipped with a reflux condenser and a magnetic stir bar was charged with 20 mL of methanol followed by 4.60 g (12.4 mmoles) of cerium(III) chloride heptahydrate. The mixture was stirred for 10 min and a solution of 2.50 g (7.84 mmoles) of **5** in 10 mL of methanol was added dropwise. After 5 min, 1.25 g (32.9 mmoles) of sodium borohydride was added in small portions over a period of 20 min. (Note: Frothing is a problem if the added portions of sodium borohydride are too large). The reaction mixture was stirred for 15 min at which time 12 mL of 3*M* hydrochloric acid was added. After 20 min, the mixture was concentrated under vacuum to one-third its volume and extracted with ether (three times). The combined ether extracts were washed with water (three times) and saturated sodium chloride (one time), then dried (magnesium sulfate) and concentrated under vacuum. The resulting dark brown liquid was purified by flash chromatography on a 50 cm × 2.5 cm silica gel column eluted with 20–30% ether in hexanes to give 1.78 g (79%) of **7** as thick yellow oil. IR: 1732, 1685, 1609, 1528, 1351 cm^{-1}; ^{1}H-NMR: δ 7.92 (dd, 1H, J = 8.1, 1.5), 7.55 (td, 1H, J = 7.5, 1.3), 7.43 (td, 1H, J = 8.1, 1.5), 7.27 (dd, 1H, J = 7.7, 1.5), 6.82 (d, 1H, J = 10.4), 6.02 (d, 1H, J = 10.4), 3.70 (s, 3H), 3.66 (d, 1H, $J = 13.8$), 3.50 (d, 1H, $J = 13.8$), 2.45 (m, 2H), 2.36 (m, 1H), 2.06 (m, 1H); ^{13}C-NMR: δ 197.8, 172.8, 150.2, 149.0, 133.0, 132.7, 130.3, 129.7, 128.5, 125.2, 52.8, 48.6, 39.5, 34.4, 30.9; ms: *m*/*z* 289 (M^+). *Anal.* Calcd. for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.19; N, 4.84. Found: C, 62.40; H, 5.24; N, 4.76.

Methyl (±)-1-(2-nitrobenzyl)-4-oxo-2-cyclopentene-1-carboxylate (8). This compound (1.65 g, 73%) was obtained as yellow crystals, mp 103–105°C. IR: 1712, 1679, 1608, 1526, 1352 cm^{-1}; ^{1}H-NMR: δ 7.86 (dd, 1H, $J = 8.2, 1.3$), 7.52 (td, 1H, $J = 7.5, 1.3$), 7.47 (d, 1H, $J = 5.7$), 7.39 (td, 1H, $J = 8.1, 1.5$), 7.29 (dd, 1H, $J = 7.7, 1.5$), 6.08 (d, 1H, $J = 5.7$), 3.65 (s, 3H), 3.50 (d, 1H, $J = 13.7$), 3.17 (d, 1H, $J = 13.7$), 2.36 (d, 1H, $J = 18.7$), 2.18 (d, 1H, $J = 18.7$); ^{13}C-NMR: δ 208.7, 167.3 (2C), 150.1, 134.9, 133.4, 132.6, 131.2, 128.1, 125.0, 67.7, 52.3, 42.6, 36.5; ms: *m*/*z* 275 (M^+). *Anal.* Calcd. for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.73; N, 5.09. Found: C, 61.13; H, 4.74; N, 5.09.

(±)-1′,4′-Dihydrospiro[2-cyclohexene-1,3′(2′*H*)-quinoline]-2′,4-dione (9). The procedure of Bunce *et al.* was used [1]. A mixture of 500 mg (1.73 mmoles) of **7**, 25 mL of acetic acid, and 773 mg (13.8 mmoles, 8.0 equiv) of iron powder (>100 mesh) was heated with stirring at 115°C (oil bath) until thin layer chromatography indicated complete consumption of starting material (*ca.* 30 min). The reaction mixture was cooled, diluted with 50 mL of water, and extracted with ether (three times). The combined ether layers were washed with water (one time), saturated sodium bicarbonate (three times), saturated sodium chloride (one time), then dried (magnesium sulfate) and concentrated under vacuum to give 373 mg (95%) of **9** as a pale white solid, mp 212–215°C. IR: 3195, 1667 cm^{-1}; ^{1}H-NMR: δ 8.69 (br s, 1H), 7.21 (complex, 2H), 7.05 (td, 1H, $J = 7.5, 1.3$), 6.82 (obscured, 1H) 6.81 (d, 1H, $J = 10.3$), 6.14 (d, 1H, $J = 10.3$), 3.13 (d, 1H, $J = 15.9$), 2.99 (d, 1H, $J = 15.9$), 2.73 (ddd, 1H, $J = 17.1, 8.4, 4.9$), 2.49 (ddd, 1H, $J = 17.1, 8.4, 4.9$), 2.34 (ddd, 1H, $J = 13.4, 8.4, 4.9$), 1.98 (ddd, 1H, $J = 13.4, 8.4, 4.9$); ^{13}C-NMR: δ 198.2, 172.1, 148.9, 136.1, 130.7, 128.6, 128.2, 123.7, 121.1, 115.2, 42.6, 36.6, 33.6, 29.4; ms: *m*/*z* 227 (M^+). *Anal.* Calcd. for $C_{14}H_{13}NO_2$: C, 74.01; H, 5.73; N, 6.17. Found: C, 74.00; H, 5.71; N, 6.20.

(±)-(3a*R, 9a*R**)-9a-Hydroxymethyl-1,3,3a,4,9,9a-hexahydro-2*H*-cyclopenta[*b*]quinolin-2-one (10).** The procedure used to prepare **9** was followed using 200 mg (0.73 mmoles) of **8** and 325 mg (5.84 mmoles) of iron powder in 12 mL of acetic acid. After 30 min at 115°C, workup and preparative thin layer chromatography using 40% ether in hexanes gave 120 mg (76%) of **10** as a light yellow oil. IR: 3395, 1733 cm^{-1}; ^{1}H-NMR: δ 7.01 (td, 1H, $J = 7.3, 1.2$), 6.98 (dd, 1H, $J = 7.5, 0.8$), 6.64 (td, 1H, $J = 7.3, 1.2$), 6.48 (dd, 1H, $J = 7.9, 0.8$), 3.92 (br s, 1H), 3.94 (t, 1H, $J = 6.4$), 3.59 (d, 1H, $J = 10.9$), 3.55 (d, 1H, $J = 10.9$), 2.74 (d, 1H, $J = 16.7$), 2.69 (obscured, 2H), 2.65 (d, 1H, $J = 16.7$), 2.37 (d, 1H, $J = 18.7$), 2.17 (dd, 1H, $J = 18.7, 1.6$), 2.20 (m, 1H); ^{13}C-NMR: δ 216.6, 141.7, 129.6, 127.4, 117.5, 117.4, 113.4, 66.6, 52.0, 46.4, 45.9, 41.3, 31.3; ms: *m*/*z* 217 (M^+). *Anal.* Calcd. for $C_{13}H_{15}NO_2$: C, 71.89; H, 6.91; N, 6.45. Found: C, 71.96; H, 6.95; N, 6.40. This reaction also gave 26 mg (14%) of compound **11**.

(±)-(3a*R, 9a*R**)-9a-Acetoxymethyl-1,3,3a,4,9,9a-hexahydro-2*H*-cyclopenta[*b*]quinolin-2-one (11).** The procedure used to prepare **9** was followed using 500 mg (1.82 mmoles) of **8** and 812 mg (14.6 mmoles) of iron powder in 30 mL of acetic acid. After 4 h at 115°C, workup and flash chromatography on a 25 cm × 2 cm silica gel column using 15% ether in hexanes gave 400 mg (85%) of **10** as a tan oil. IR: 3394, 1740 cm^{-1}; ^{1}H-NMR: δ 7.05 (m, 2H), 6.66 (td, 1H, $J = 7.5, 1.3$), 6.50 (dd, 1H, $J = 7.8, 0.8$), 4.10 (br s, 1H), 4.08 (d, 1H, $J = 11.4$), 4.02 (d, 1H, $J = 11.4$), 3.92 (t, 1H, $J = 6.4$), 2.80 (d, 1H, $J = 16.5$), 2.70 (d, 1H, $J = 16.5$), 2.70 (m, 1H), 2.27 (m, 2H), 2.21 (dd, 1H, $J = 5.4, 1.1$), 2.06 (s, 3H); ^{13}C-NMR: δ 214.9, 170.8, 141.4, 129.7, 127.6, 117.7, 116.8, 113.5, 67.6, 52.4, 46.3, 46.0, 39.6, 31.5, 20.8; ms: *m*/*z* 259 (M^+). *Anal.* Calcd. for $C_{15}H_{17}NO_3$: C, 69.50; H, 6.56; N, 5.41. Found: C, 69.52; H, 6.55; N, 5.39.

(±)-(3a*R, 9a*R**)-9a-Acetoxymethyl-4-benzoyl-1,3,3a,4,9,9a-hexahydro-2*H*-cyclopenta[*b*]quinolin-2-one (12).** To a stirred solution of 200 mg (0.77 mmoles) of **11** and 85.6 mg (0.85 mmoles) of triethylamine in 20 mL of dichloromethane, a solution of 120 mg (0.85 mmoles) of benzoyl chloride in 1 mL of dichloromethane was slowly added over a period of 5 min. The reaction mixture was stirred at 22°C for 2 h at which time thin layer chromatography confirmed the absence of starting material. The reaction mixture was poured into cold water and the dichloromethane layer was separated. The organic phase was washed with cold water (two times), dried (magnesium sulfate) and concentrated under vacuum. The resulting residue was passed through a small plug of silica gel with 30% ether in hexanes to give 260 mg (93%) of **12** as a light yellow solid, mp 108–110°C. IR: 1744, 1643 cm^{-1}; ^{1}H-NMR: δ 7.38–7.21 (complex, 6H), 7.07 (td, 1H, $J = 7.5, 1.1$), 6.93 (t, 1H, $J = 7.5$), 6.49 (d, 1H, $J = 7.9$), 5.19 (dd, 1H, $J = 9.0, 4.4$), 4.28 (d, 1H, $J = 10.9$), 4.20 (d, 1H, $J = 10.9$), 3.04 (ddd, 1H, $J = 19.4, 9.0, 1.8$), 2.94 (d, 1H, $J = 14.1$), 2.73 (d, 1H, $J = 14.1$), 2.29 (ddd, 1H, $J = 19.4, 4.4, 1.8$), 2.20 (dd, 1H, $J = 18.5, 1.8$), 2.10 (s, 3H), 2.06 (dd, 1H, $J = 18.5, 1.8$); ^{13}C-NMR: δ 214.1, 170.7, 169.8, 138.1, 134.8, 130.8, 130.6, 129.1, 129.0, 128.1, 127.4, 126.9, 126.1, 71.1, 57.4, 47.9, 45.6, 45.2, 34.6, 20.7; ms: *m*/*z* 363 (M^+). *Anal.* Calcd. for $C_{22}H_{21}NO_4$: C, 72.73; H, 5.79; N, 3.86. Found: C, 73.71; H, 5.79; N, 3.88.

X-ray crystallographic analysis of 12. Flat, elongated rods of **12** were obtained by slow diffusion of pentane into an ether solution of the compound. A sample measuring 0.4 mm × 0.4 mm × 0.1 mm, which was cut from a longer rod, was immersed in polyisobutylene and placed in a nylon loop under a nitrogen cold stream. X-ray intensity data were measured at 115(2) K on a Bruker SMART Apex II diffractometer. Graphite-monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å, fine-focus sealed tube) was used with the CCD detector placed 6.0 cm from the sample. Data frames were collected in a series of ϕ and ω scans with 0.5° scan widths and 30-s exposure times. Data integration used the Bruker SAINT software package [23]. Data were corrected for absorption effects using the multiscan technique (SADABS) [24]. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 using the Bruker SHELXTL software suite [25]. Non-hydrogen atoms were assigned anisotropic temperature factors. Hydrogen atoms were placed in calculated positions based on the geometry at carbon (riding model). Refined formula: $C_{22}H_{21}NO_4$, $M = 363.40$, monoclinic, space group $P2_1/n$, $a = 11.1983(2)$ Å, $b = 8.18310(10)$ Å, $c = 19.7453(3)$ Å, $\beta = 101.7010(10)°$, $U = 1771.80(5)$ Å^3, $Z = 4$, $D_c = 1.362$ g/cm, $\mu = 0.094$ mm^{-1},

T = 115(2) K, $2\theta_{max}$ = 50.6°, completeness to $2\theta_{max}$ = 100.0%, 13372 total reflections, 3227 independent (R_{int} = 0.0248), 2619 observed [$I > 2\sigma(I)$]. Final $R1$ [$I > 2\sigma(I)$] = 0.0336, $wR2$ (all data) = 0.0833, largest difference peak and hole 0.225 and −0.194 e$Å^{-3}$. CCDC 692896 contains the supplementary crystallographic data for compound **12**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Methyl (±)-4-benzyl-2-oxo-3-cyclohexene-1-carboxylate (13). The procedure used to prepare **5** was followed using 1.08 g (5.85 mmoles) of **3** and 1.11 g (6.5 mmoles) of benzyl bromide. Following flash chromatography, 1.52 g (95%) of methyl (±)-1-benzyl-4-methoxy-2-oxo-3-cyclohexene-1-carboxylate was isolated as a white solid, mp 68–70°C. IR: 1729, 1660, 1610 cm^{-1}; ^{1}H-NMR: δ 7.28–7.17 (complex, 3H), 7.14 (m, 2H), 5.41 (d, 1H, J = 1.2), 3.71 (s, 3H), 3.66 (s, 3H), 3.32 (d, 1H, J = 13.7), 3.23 (d, 1H, J = 13.7), 2.63 (m, 1H), 2.29 (m, 2H), 1.80 (m, 1H); ^{13}C-NMR: δ 194.4, 177.8, 171.5, 136.5, 130.4, 128.1, 126.7, 101.9, 56.9, 55.7, 52.4, 40.0, 28.1, 26.3; ms (30 eV): m/z 274 (M^+); *Anal.* Calcd. for $C_{16}H_{18}O_4$: C, 70.07; H, 6.57. Found: C, 70.12; H, 6.59.

Reduction and carbonyl transposition were carried out as described for the preparation of **7** using 1.52 g (5.56 mmoles) of the benzylated product from the earlier procedure. Following flash chromatography, 1.22 g (90%) of **13** was isolated as a colorless oil. IR: 1732, 1682 cm^{-1}; ^{1}H-NMR: δ 7.32–7.22 (complex, 3H), 7.09 (dd, 1H, J = 7.8, 1.8), 6.95 (d, 1H, J = 10.3), 6.02 (d, 1H, J = 10.3), 3.69 (s, 3H), 3.08 (s, 2H), 2.47 (m, 2H), 2.40 (m, 1H), 2.07 (m, 1H); ^{13}C-NMR: δ 198.3, 173.2, 150.3, 135.4, 129.8, 129.2, 128.4, 127.2, 52.3, 49.0, 44.5, 34.5, 30.5; ms: m/z 244 (M^+); *Anal.* Calcd. for $C_{15}H_{16}O_3$: C, 73.77; H, 6.56. Found: C, 73.81; H, 6.60.

Methyl (±)-4-benzyl-2-oxo-3-cyclopentene-1-carboxylate (14). The procedure used to prepare **5** was followed using 0.99 g (5.85 mmoles) of **4** and 1.11 g (6.50 mmoles) of benzyl bromide. Following flash chromatography, 1.46 g (96%) of methyl (±)-1-benzyl-4-methoxy-2-oxo-3-cyclopentene-1-carboxylate was isolated as white solid, mp 96–98°C. IR: 1741, 1699, 1597 cm^{-1}; ^{1}H-NMR: δ 7.27–7.17 (complex, 3H), 7.13 (m, 2H), 5.18 (s, 1H), 3.76 (2s, 6H), 3.30 (d, 1H, J = 14.1), 3.25 (d, 1H, J = 14.1), 3.11 (dd, 1H, J = 17.7, 1.0), 2.61 (dd, 1H, J = 17.7, 1.0); ^{13}C-NMR: δ 200.6, 190.3, 171.0, 136.2, 130.0, 128.2, 126.9, 102.3, 60.1, 59.0, 52.9, 39.1, 36.5; ms: m/z 260 (M^+). *Anal.* Calcd for $C_{15}H_{16}O_4$: C, 69.23; H, 6.15. Found: C, 69.29; H, 6.17.

Reduction and carbonyl transposition were carried out as described for the preparation of **7** using 1.46 g (5.62 mmoles) of the benzylated product from the earlier procedure. Following flash chromatography, 1.16 g (90%) of **14** was isolated as a colorless oil. IR: 1710, 1677 cm^{-1}; ^{1}H-NMR: δ 7.54 (d, 1H, J = 5.7), 7.32–7.20 (complex, 3H), 7.13 (m, 2H), 6.14 (d, 1H, J = 5.7), 3.62 (s, 3H), 2.97 (d, 1H, J = 13.3), 2.84 (d, 1H, J = 13.3), 2.29 (s, 2H); ^{13}C-NMR: δ 209.0, 168.2 (2C), 136.4, 134.7, 130.2, 128.3, 126.8, 67.3, 51.7, 43.0, 41.5; ms: m/z 230 (M^+). *Anal.* Calcd. for $C_{14}H_{14}O_3$: C, 73.04; H, 6.09. Found: C, 73.10; H, 6.12.

Reduction of 13 with iron and acetic acid: Methyl 1-benzyl-4-oxocyclohexane-1-carboxylate (15). The procedure used to prepare **9** was followed using 500 mg (2.05 mmoles) of **13** and 915 mg (16.4 mmoles) of iron powder in 35 mL of acetic acid. After 24 h, workup gave 450 mg of an inseparable 33:67 mixture of **13**:**15**. The spectral data for **15** were: IR: 1727, 1702 cm^{-1}; ^{1}H-NMR: δ 7.36–7.27 (complex, 3H), 7.12 (m, 2H), 3.77 (s, 3H), 2.96 (s, 2H), 2.56–2.33 (complex, 6H), 1.78 (m, 2H); ^{13}C-NMR: δ 210.4, 174.8, 129.4, 128.1, 127.9, 126.6, 51.6, 47.5, 45.6, 38.1, 33.1. The use of more iron and longer reaction times failed to significantly alter this product ratio.

Reduction of 14 with iron and acetic acid: (±)-4-Benzyl-4-hydroxymethyl-2-cyclopenten-1-one (18). The procedure used to prepare **9** was followed using 500 mg (2.17 mmoles) of **14** and 969 mg (17.3 mmoles) of iron powder in 35 mL of acetic acid. After 15 min, workup and preparative thin layer chromatography gave 320 mg (72%) of **18** as a colorless oil. IR: 3416, 1711, 1677 cm^{-1}; ^{1}H-NMR: δ 7.53 (d, 1H, J = 5.7), 7.30–7.21 (complex, 3H), 7.10 (d, 2H, J = 6.8), 6.11 (d, 1H, J = 5.7), 3.60 (d, 1H, J = 10.7), 3.58 (d, 1H, J = 10.7), 2.96 (d, 1H, J = 13.5), 2.81 (d, 1H, J = 13.5), 2.62 (br s, 1H), 2.29 (d, 1H, J = 18.6), 2.26 (d, 1H, J = 18.6); ^{13}C-NMR: δ 209.5, 168.7, 136.3, 134.4, 130.1, 128.2, 126.7, 67.0, 51.8, 42.9, 41.3; ms: m/z 111 (M^+-C_7H_7). *Anal.* Calcd. for $C_{13}H_{14}O_2$: C, 77.23; H, 6.93. Found: C, 77.29; H, 6.97. This reaction also afforded 10% of recovered **14**.

Upon prolonged heating for 2 h, the reaction gave 450 mg of an inseparable 67:33 mixture of **18**:**20** as the acetates. The spectral data for **18** (acetate): IR: 1743, 1715 cm^{-1}; ^{1}H-NMR: δ 7.46 (d, 1H, J = 5.7), 7.33–7.17 (complex, 3H), 7.09 (m, 2H), 6.13 (d, 1H, J = 5.7), 4.17 (d, 1H, J = 10.9), 4.00 (d, 1H, J = 10.9), 2.96 (d, 1H, J = 13.7), 2.84 (d, 1H, J = 13.6), 2.31 (s, 2H), 2.06 (s, 3H); ^{13}C-NMR: δ 207.6, 170.6, 166.7, 135.5, 134.6, 130.0, 128.4, 127.0, 67.7, 49.4, 43.0, 42.0, 20.7. The spectral data for **20** (acetate): 1743 cm^{-1}; ^{1}H-NMR: δ 7.34–7.18 (complex, 3H), 7.10 (m, 2H), 3.98 (d, 1H, J = 11.1), 3.89 (d, 1H, J = 11.1), 2.79 (s, 2H), 2.39–2.21 (complex, 2H), 2.33 (s, 2H), 2.10 (s, 3H), 1.93 (m, 2H); ^{13}C-NMR: δ 217.5, 170.7, 136.6, 130.0, 128.3, 126.7, 68.4, 47.0, 43.6, 42.3, 36.3, 30.2, 20.8.

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New Access to the One-Pot Solvent-Free Synthesis of 4,5-Dihydro-pyrido[2,3-*b*][1,4]diazepines and 2,3-Dihydro-benzo[*b*][1,4]diazepines by Microwave Irradiation

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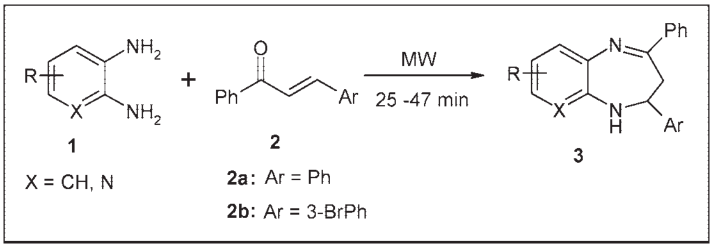

A series of diversely substituted pyridodiazepines and benzodiazepines have been synthesized in solvent and catalyst free microwave condition from aryl/heteroaryl diamines and β-aryl vinyl ketones. The yields of the reactions varied with the substituents attached to the aryl/heteroaryl diamines. This common protocol is equally effective for the synthesis of pyridodiazepines and benzodiazepines with pharmacological interest, though in case of pyridodiazepines required time is comparatively higher than benzodiazepines.

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INTRODUCTION

The pyridodiazepines and benzodiazepines are important class of compounds for their versatile use in biological [2] and therapeutic purpose [3]. Different substituted benzodiazepines are effective as tranquilizing, anti-inflammatory, and anticonvulsant agents. These compounds are also important synthons for the synthesis of oxadiazol, triazol [4] like various fused heterocyclic ring benzodiazepine derivatives. In industry, benzodiazepine derivatives are used as dyes in photography [5].

For the considerable applications in medicinal chemistry, scientific community has a continuous drive for efficient synthetic methods of such compounds. So far the different methods, which have been developed for the synthesis of benzodiazepines include the condensation of 1,2-diamines with α,β-unsaturated carbonyl compounds [6], ketones and β-haloketones [7] in the presence of Al_2O_3-P_2O_5 [8], $SbCl_3$-Al_2O_3 [9], polyphosphoroic acid-SiO_2 [10], $Yb(Otf)_3$ [11], BF_3-etherate [12], MgO-$POCl_3$ [13], Zn $[L\text{-proline}]_2$ [14], Amberlyst-15 [15], $NaBH_4$ [16], ionic liquid [17], and AcOH [18]. Recently, alum $[KAl(SO_4)_2{\cdot}12H_2O]$ is also used as a catalyst for the synthesis of benzodiazepines [19]. However, all these reactions are carried out under hazardous reaction conditions and in the presence of a catalyst. Among all the available reports, there are very few examples for the synthesis of pyridodiazepines [20]. But according to our knowledge, there is no report for the synthesis of pyridodiazepines under microwave conditions.

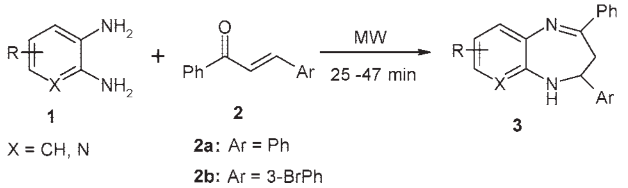
Nowadays, different organic synthesis has been carried out under microwave irradiation because of its very slight environmental impact and short reaction time [21]. This technique has been widely used in recent years for different organic transformations, including the synthesis of a wide range of heterocyclic compounds [22].

RESULTS AND DISCUSSION

In recent past, we have successfully exploited this microwave technique to develop new methodologies including the synthesis of different heterocyclic backbone [23]. Herein, we report the synthesis of pyridodiazepines and benzodiazepines by reacting heteroaryl/aryl diamines with β-aryl vinyl ketones in solid phase without using any catalyst and solvent under microwave irradiation (Scheme I). Previously microwave reactions for the synthesis of benzodiazepines from *o*-phenylenediamines with various ketones are carried out using Al_2O_3/P_2O_5 [8] or AcOH [18] catalyst. But in the present procedure benzodiazepines are synthesized in quite good yield without any catalyst.

In one representative procedure, pyridine-2,3-diamine (2 mmol) and β aryl vinyl ketone (2 mmol) are mixed thoroughly in solid phase and irradiated at 400 W for

Scheme 1. Synthesis of pyridodiazepines and benzodiazepines from 2,3-diaminopyridine and 1,2-diaminobenzene with β-aryl vinyl ketones (for R, X and Ar see Table 1).



27 min (Scheme 1, Table 1) in a microwave oven to afford 2,4-diphenyl-4,5-dihydro-3*H*-pyrido[2,3-b][1,4] diazepine (**3a**) in 80% yield, and no isomerisation product is obtained. The pyridodiazepines [3(**a**, **c**, **f** and **h**)] and benzodiazepines [24] [3(**b**, **d**, **e**, **g**, **i** and **j**)] are synthesized using this procedure with variable time, and power for each set of reaction and are also characterized by spectroscopic studies (Table 1).

In case of diaminopiridines the overall time for the microwave irradiation is higher than the unsubstituted 1,2-phenylenediamine to afford the respective diazepines. Similar trend is also observed in case of substituted 1,2-phenylenediamine. Here, both bromo (entries c, d, h and i) and nitro (entries e and j) groups may reduce the nucleophilicity of the amine group attached with the aromatic ring. This effect is very much pronounced in case of nitro group, which also affects the yield of the compounds **3e** and **3j**. The overall yield of the other diazepine compounds are varied from moderate to good, depending upon the reactivity of the starting diamines. The ^{1}H NMR spectra of the nitro group containing benzodiazepines (**3e** and **3j**) may tautomerise to the quinoid form of the compounds resulting the disappearance of N—*H* peak.

All these reactions probably proceed through Michael addition of amine to the β position of α,β-unsaturated ketone followed by condensation and dehydration (Scheme 2). In the case of 2,3 diaminopyridine, probably nucleophilic attack takes place through comparatively less reactive 2-amino group to the double bond of α,β-unsaturated ketone followed by cyclization of the more reactive amino group with the keto group to achieve only the substituted 4,5-dihydropyridodiazepine [23a,25]. The other isomer like substituted 2,3-dihydropyridodiazepine is not obtained under this reaction condition. The appearance of N*H* proton at δ 5.14 ppm in pyridodiazepine (**3a**) (more downfield because of amidine system *i.e* conjugated with pyridine ring "N") comparing with benzdiazepine (**3g**) with N*H* proton at 3.77 ppm also support the formation of 4,5 dihydropyridodiazepine. Formation of minor amount (5%) of aryl substituted benzimidazole (**4**) [26] by thermally induced ring contraction also favors the suggested mechanism in case of 1,2-phenylenediamine (**1a**) and β aryl vinyl ketone (**2b**) [27].

In conclusion we have developed a general straightforward method under microwave irradiation for the efficient synthesis of 4,5-dihydro-3*H*-pyrido[2,3-b][1,4] diazepines and 2,3-dihydro-1*H*-benzo[b][1,4]diazepines. Major advantage of this reaction is that same solvent and catalyst free condition is effective for both aryl and heteroaryl diamines. By this method different diazepines of pharmacological interest can be synthesized by varying the substituents at diamines, as well as the other substituted phenyl rings.

EXPERIMENTAL

General reaction procedure for the synthesis of 2,4 substituted-4,5-dihydro-3*H*-pyrido[2,3-*b*][1,4]diazepine/2,4 substituted-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine using β aryl vinyl ketone. A mixture of pyridine-2,3-diamine (218 mg, 2.0 mmol) (1a) and β aryl vinyl ketone (416 mg, 2.0 mmol) (2a) was thoroughly grinded and taken in an open-mouthed conical flask and then irradiated at 400 W for 27 min (Scheme 1, Table 1) in a domestic microwave oven (SANYO 800G). The residue was dissolved in water and then extracted with $CHCl_3$. The organic layer was evaporated under reduced pressure. The crude product was then purified by column chromatography (silica gel, 100–200 mesh) to afford a pure yellow colored 2,4-diphenyl-4,5-dihydro-3*H*-pyrido[2,3-b][1,4]diazepine (3a) in 80% yield using 5% ethyl acetate-petroleum ether as eluent.

Representative spectral data of all compounds.

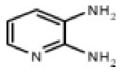
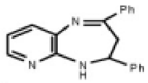
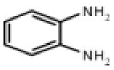
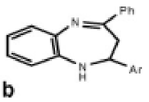
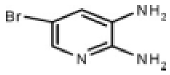
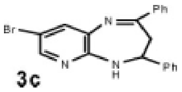
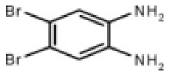
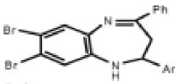
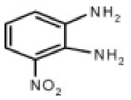
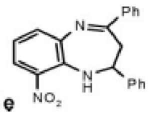
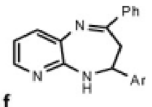
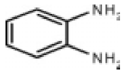
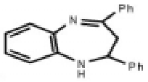
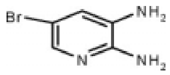
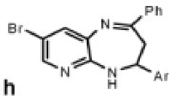
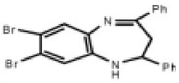
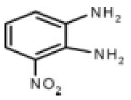
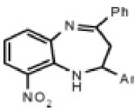
2,4-Diphenyl-4,5-dihydro-3H-pyrido[2,3-b][1,4]diazepine (3a). Yield: 80%; mp 126–128°C; IR: 3230, 3058, 2917, 2849, 1610, 1579, 1445, 1363, 1234, 1101, 915 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm): 8.03 (d, 1H, $J = 4.7$ Hz), 7.78 (d, 2H, $J = 7.2$ Hz), 7.66 (d, 1H, $J = 7.7$ Hz), 7.39 (m, 7H), 7.29 (m, 1H), 6.89 (q, 1H, $J = 7.7$ Hz), 5.16 (m, 1H), 5.14 (s, 1H), 3.37 (d, 1H, $J = 13.9$ Hz), 3.09 (q, 1H, $J = 13.9$ Hz); ms (HRMS-ESI): m/z (%): Calculated for $C_{20}H_{18}N_3$ is 300.1484, found 300.1477 [(M+H)$^+$, 100], 301.1532 [(M+2H)$^+$, 23]. *Anal.* Calcd. for $C_{20}H_{17}N_3$: C, 80.24; H, 5.72; N, 14.04. Found: C, 80.29; H, 5.77; N, 13.98.

2-(3-Bromo-phenyl)-4-phenyl-2,3-dihydro-1H-benzo[b]-[1,4]diazepine (3b). Yield: 82%; mp 90–92°C; IR: 3359, 3057, 2916, 1679, 1608, 1569, 1473, 1428, 1296, 1070, 996 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm): 7.81 (d, 2H, $J =$ 8.1 Hz), 7.56 (s, 1H), 7.39 (m, 6H), 7.17 (t, 1H, $J = 7.8$ Hz), 7.05 (m, 2H), 6.82 (d, 1H, $J = 7.5$ Hz), 5.17 (q, 1H, $J = 8.4$ Hz), 3.73 (bs, 1H), 3.21 (dd, 1H, $J = 4.0$, 13.5 Hz), 3.02 (dd, 1H, $J = 8.5$, 13.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δc (ppm): 167.4, 147.4, 139.8, 139.4, 138.3, 131.5, 130.8, 130.7, 129.6, 129.3, 129, 128.8, 128.5, 127.4, 126.9, 125, 123.2, 122.1, 121.1, 70.6, 37.7; ms (HRMS-ESI): m/z (%): Calculated for $C_{21}H_{17}BrN_2$ is 377.0625, found 377.0617 [M$^+$, 100], 379.0558 [(M+2H)$^+$, 80]. *Anal.* Calcd. for $C_{21}H_{17}BrN_2$: C, 66.85; H, 4.54; N, 7.42. Found: C, 66.79; H, 4.69; N, 7.47.

8-Bromo-2,4-diphenyl-4,5-dihydro-3H-pyrido[2,3-b][1,4]-diazepine (3c). Yield: 72%; mp 152–153°C; IR: 3235, 3062, 2928, 2844, 1606, 1578, 1432, 1224, 912 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm): 8.00 (s, 1H), 7.78 (d, 3H, $J =$ 6.8 Hz), 7.42 (t, 1H, $J = 7.2$ Hz), 7.38 (d, 2H, $J = 7.2$ Hz),

Table 1

Pyridodiazepines and benzodiazepines synthesis under microwave irradiation.

Entry	Substrate (**1**)	β-aryl vinyl ketones (**2**)	MW condition (Watt. min)	Products [24] (**3**)	Yield (%)[a]
a		**2a**	400, 35	 **3a**	80
b		**2b**	400, 27	 **3b**	82
c		**2a**	400, 37	 **3c**	72
d		**2b**	400, 35	 **3d**	65
e		**2a**	400, 47	 **3e**	35
f		**2b**	400, 40	 **3f**	70
g		**2a**	400, 25	 **3g**	85
h		**2b**	400, 38	 **3h**	65
i		**2a**	400, 32	 **3i**	68
j		**2b**	400, 45	 **3j**	32

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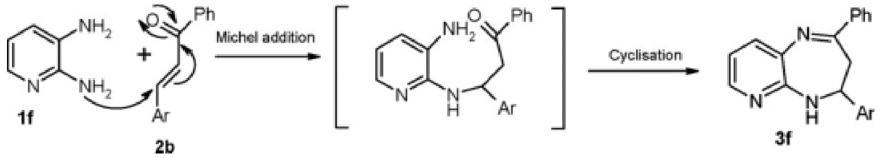
[a] Chromatographically isolated pure materials.

Scheme 2. Probable mechanism for the synthesis of pyridodiazepines and benzodiazepines.



7.34 (t, 4H, $J = 7.1$ Hz), 7.29 (t, 1H, $J = 7.1$ Hz), 5.22 (bs, 1H), 5.11 (m, 1H), 3.38 (d, 1H, $J = 14.0$ Hz), 3.07 (dd, 1H, $J = 8.7$, 13.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δc (ppm): 168.2, 150.0, 146.6, 144.0, 140.3, 139.2, 132.2, 131.0, 129.4, 128.9, 128.7, 127.5, 126.3, 109.8, 66.1, 39.8; ms (HRMS-ESI): m/z (%): Calculated for $C_{20}H_{16}BrN_3$ is 378.0625, found 378.0921 [M^+, 100], 380.0891 [$(M+2H)^+$, 93]. *Anal.* Calcd. for $C_{20}H_{16}BrN_3$: C, 63.50; H, 4.26; N, 11.11. Found: C, 63.41; H, 4.35; N, 11.21.

7,8-Dibromo-2-(3-bromo-phenyl)-4-phenyl-2,3-dihydro-1H-benzo[b][1,4]diazepine (3d). Yield: 65%; mp 88–89°C; IR: 3356, 2922, 2863, 1658, 1568, 1248, 1021, 910 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm): 7.77 (d, 2H, $J = 7.1$ Hz), 7.52 (s, 1H), 7.37 (m, 6H), 7.19 (m, 2H), 5.13 (m, 1H), 3.80 (bs, 1H), 3.21 (dd, 1H, $J = 3.7$, 16.6 Hz), 3.03 (q, 1H, $J = 13.3$ Hz); ms (HRMS-ESI): m/z (%): Calculated for $C_{21}H_{15}Br_3N_2Na$ is 558.8683, found 558.8696 [$(M+Na)^+$, 50], 560.8768 [$(M+2H+Na)^+$, 10], 556.8659 [$(M\text{-}2H+Na)^+$, 100], 554.8785 [$(M\text{-}4H+Na)^+$, 50]. *Anal.* Calcd. for $C_{21}H_{15}Br_3N_2$: C, 47.14; H, 2.83; N, 5.24. Found: C, 47.22; H, 2.69; N, 5.32.

9-Nitro-2,4-diphenyl-2,3-dihydro-1H-benzo[b][1,4]-diazepine (3e). Yield: 35%; mp 86–88°C; IR: 3062, 2934, 2846, 1680, 1586, 1445, 1218, 1056, 982 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm): 7.98 (m, 4H), 7.59 (m, 1H), 7.52 (d, 1H, $J = 8.4$ Hz), 7.44 (m, 2H), 7.42 (m, 1H), 7.40 (m, 2H), 7.32 (t, 2H, $J = 7.9$ Hz), 6.57 (q, 1H, $J = 8.9$ Hz), 4.87 (dd, 1H, $J = 8.7$, 18.9 Hz), 3.87 (dd, 1H, $J = 4.9$, 17.9 Hz); ms (FIA-MS): m/z (%): 347 [$(M+4H)^+$, 10], 328.2 [$(M+3H\text{-}H_2O)^+$, 100], 209.2 (70); *Anal.* Calcd. For $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.99; N, 12.24. Found: C, 72.95; H, 5.65; N, 12.23.

4-(3-Bromo-phenyl)-2-phenyl-4,5-dihydro-3H-pyrido[2,3-b][1,4] diazepine (3f). Yield: 70%; mp 138–140°C; IR: 3242, 3068, 2910, 1665, 1575, 1448, 1226, 1120, 924 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm): 8.03 (s, 1H), 7.77 (d, 2H, $J = 6.8$ Hz), 7.66 (d, 1H, $J = 7.7$ Hz), 7.54 (s, 1H), 7.39 (m, 5H), 7.18 (t, 1H, $J = 7.8$ Hz), 6.92 (dd, 1H, $J = 7.7$ Hz), 5.17 (m, 1H), 5.12 (bs, 1H), 3.33 (dd, 1H, $J = 2.8$, 13.8 Hz), 3.10 (dd, 1H, $J = 8.2$, 13.9 Hz); ms (FIA-MS): m/z (%): 378.1 [M^+, 100], 380.1 [$(M+2H)^+$, 80], 196.2. *Anal.* Calcd. for $C_{20}H_{16}BrN_3$: C, 63.50; H, 4.26; N, 11.11. Found: C, 63.57; H, 4.30; N, 11.02.

2,4-Diphenyl-2,3-dihydro-1H-benzo[b][1,4]diazepine (3g). Yield: 85%; mp 112–114°C; IR: 3336, 3020, 2925, 1610, 1580, 1470, 1238, 1125, 940 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm): 7.84 (d, 2H, $J = 7.9$ Hz), 7.35 (m, 9H), 7.04 (m, 2H), 6.82 (d, 1H, $J = 7.6$ Hz), 5.18 (q, 1H, $J = 9.1$ Hz), 3.77 (bs, 1H), 3.24 (dd, 1H, $J = 3.8$, 13.5 Hz), 3.05 (q, 1H, $J = 13.5$ Hz); ms (FIA-MS): m/z (%): 299.3 [$(M+H)^+$, 100], 284.2, 195.2. *Anal.* Calcd. for $C_{21}H_{18}N_2$: C, 84.53; H, 6.08; N, 9.39. Found: C, 84.58, H, 6.17; N, 9.33.

8-Bromo-4-(3-bromo-phenyl)-2-phenyl-4,5-dihydro-3H-pyrido[2,3-b][1,4]diazepine (3h). Yield: 65%; mp 130–132°C; IR: 3239, 3056, 2922, 2852, 1669, 1573, 1472, 1214, 1071, 900 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm): 8.04 (s, 1H), 7.79 (s, 1H), 7.76 (d, 2H, $J = 7.1$ Hz), 7.52 (s, 1H), 7.39 (m, 4H), 7.32 (d, 1H, $J = 7.8$ Hz), 7.19 (t, 1H, $J = 7.8$ Hz), 5.13 (m, 1H), 5.12 (bs, 1H), 3.34 (d, 1H, $J = 13$ Hz), 3.09 (dd, 1H, $J = 8.9$, 13.9 Hz); ms (FIA-MS): m/z (%): 458.1 [$(M+H)^+$, 97], 458.9 [$(M+2H)^+$, 25], 459.8 [$(M+3H)^+$, 35], 456.0 [$(M-H)^+$, 100], 454.1 [$(M-3H)^+$, 50], 356.1 (45), 276.1 (15), 188.1 (40); *Anal.* Calcd. for $C_{20}H_{15}Br_2N_3$: C, 52.55; H, 3.31; N, 9.19. Found: C, 52.49; H, 3.36; N, 9.23.

7,8-Dibromo-2,4-diphenyl-2,3-dihydro-1H-benzo[b][1,4]-diazepine (3i). Yield: 68%; mp 71–72°C; IR: 3360, 2918, 2850, 1608, 1574, 1451, 1272, 1112, 1025, 885 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm): 7.80 (d, 2H, $J = 6.9$ Hz), 7.58 (s, 1H), 7.36 (m, 8H), 7.06 (s, 1H), 5.12 (m, 1H), 3.83 (bs, 1H), 3.26 (dd, 1H, $J = 3.6$, 13.6 Hz), 3.03 (dd, 1H, $J = 8.9$, 13.66 Hz); ms (HRMS): m/z (%): Calcd for $C_{21}H_{16}Br_2N_2$ is 456.9766, found 456.9735 [M^+, 100], 458.9732 [$(M+2H)^+$, 50], 454.9669 [$(M-2H)^+$, 50]. *Anal.* Calcd. for $C_{21}H_{16}Br_2N_2$: C, 55.29; H, 3.54; N, 6.14. Found: C, 55.23; H, 3.62, N, 6.21.

2-(3-Bromophenyl)-9-nitro-4-phenyl-2,3-dihydro-1H-benzo[b][1,4]diazepine (3j). Yield: 32%; mp 94–96°C; IR: 3068, 2922, 2851, 1685, 1595, 1529, 1473, 1207, 1073 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm): 8.03 (d, 2H, $J = 8.3$ Hz), 7.97 (t, 1H, $J = 8.4$ Hz), 7.59 (d, 1H, $J = 9.2$ Hz), 7.56 (m, 1H), 7.49 (m, 3H), 7.42 (d, 2H, $J = 7.0$ Hz), 7.34 (m, 1H), 7.18 (t, 1H, $J = 7.8$ Hz), 6.52 (q, 1H, $J = 8.5$ Hz), 4.83 (dd, 1H, $J = 9.1$, 16.9 Hz), 3.87 (dd, 1H, $J = 5.1$, 17.9 Hz); ms (FIA-MS): m/z (%): 421.2 [$(M-H)^+$, 20], 408.3 (30), 406.1 (20), 279.2 (100), 262.3 (80). *Anal.* Calcd. for $C_{21}H_{16}BrN_3O_2$: C, 59.73; H, 3.82; N, 9.95. Found: C, 59.37; H, 4.37; N, 9.81.

2-(3-Bromo-phenyl)-1H-benzoimidazole (4). Yield: 5%; mp 245–247°C; IR: 3342, 3121, 1621, 1534, 1012 cm^{-1}; ^{1}H NMR ($CDCl_3$ + d_6-DMSO, 400 MHz): δ (ppm): 8.41 (s, 1H), 8.17 (d, 1H, $J = 7.8$ Hz), 7.76 (d, 1H, $J = 8.1$ Hz), 7.56 (d, 1H, $J = 7.9$ Hz), 7.50 (d, 1H, $J = 7.45$ Hz), 7.38 (t, 1H, $J = 7.9$ Hz), 7.23 (m, 2H); ms (FIA): m/z (%): 273.0 (M^+, 98), 275.0 [$(M+2)^+$, 100].

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Unsymmetrically Substituted Furoxans. Part 19. Methyl and Phenylfuroxansulfonic Acids and Related Sulfonamides

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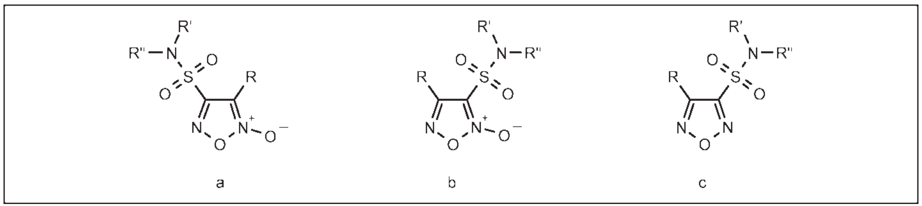

Synthesis, structural characterization, and acid dissociation constants (pK_a) of a series of methyl- and phenyl-substituted furoxansulfonic acids and related sulfonamide derivatives, as well as their furazan analogues are described. The ability of furoxans to dilate rat aorta strips precontracted with phenylephrine is reported as an example of their NO-dependent pharmacological properties.

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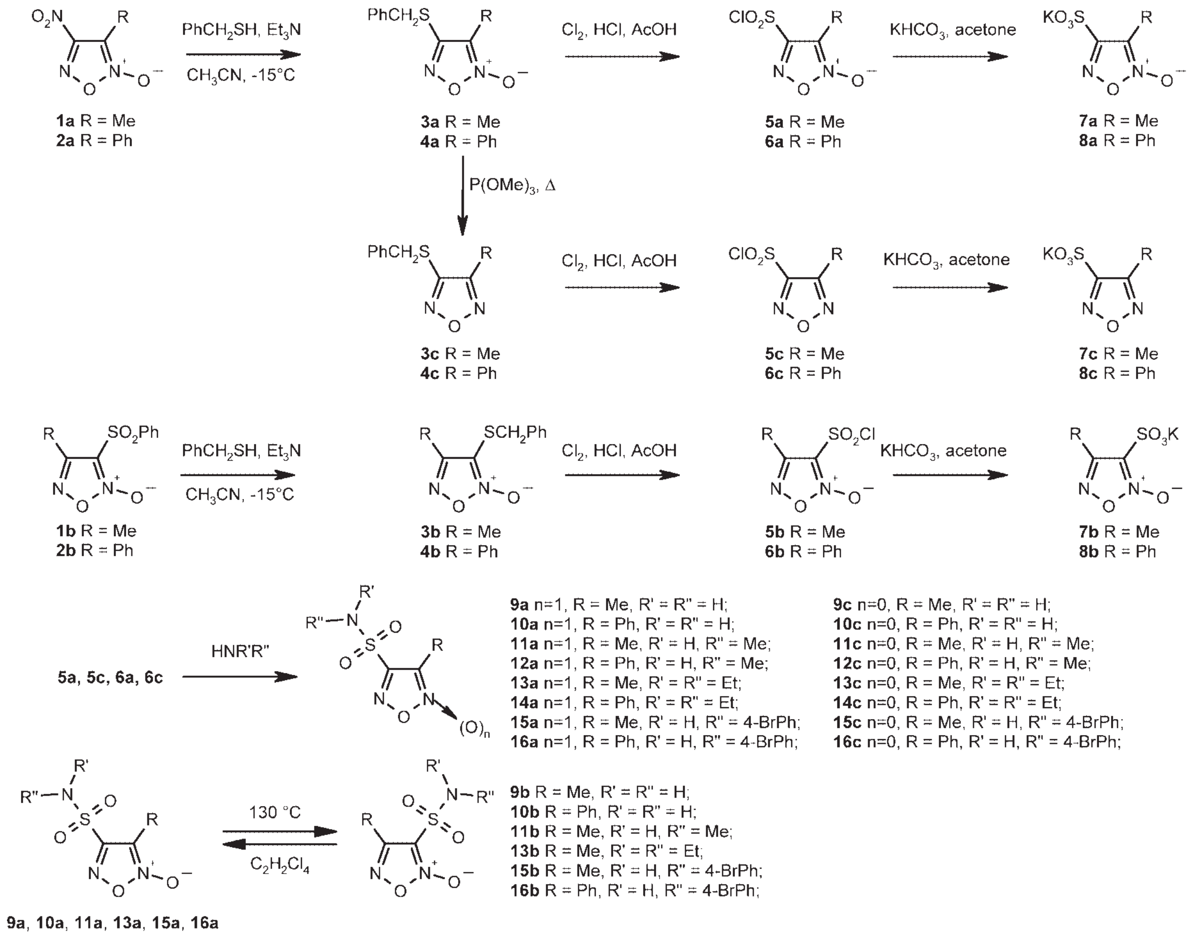
INTRODUCTION

The interest in furoxan (1,2,5-oxadiazole 2-oxide) derivatives is continuously expanding as it was shown that these products are able to release nitric oxide (NO) in physiological conditions, in the presence of thiol cofactors [1,2]. Consequently, they display a variety of pharmacological actions typical of NO [2,3]. A number of functional groups have been introduced into the simple furoxan ring, and their chemistry has been recently reviewed [4]. In previous works, we described the synthesis and chemical properties of many unsymmetrically substituted furoxans [5]. Currently we are using a number of them to design new NO-donor hybrid drugs [6,7], namely polyvalent products obtained by linking an appropriate drug, or a crucial part of it, with a NO-donor moiety through a suitable spacer. A paramount problem that must be addressed in this approach is the ''balance'' in the final hybrid of the activity deriving from its ability to release NO and the activity due to the presence of the native drug. The furoxan system seems to be a flexible NO-donor moiety for this scope as its NO-release profile can be easily modulated by changing the kind of substituent at heteroring. Surprisingly, a search in literature showed that no furoxan derivatives bearing either sulfonic or sulfonamide functions have been so far described. In this article, we report the synthesis, structural characterization, and ionization constants (pK_a) of a series of methyl- and phenyl-substituted furoxansulfonic acids and related sulfonamides, as well as their furazan analogues (1,2,5-oxadiazoles), devoid of the capacity to release NO. The ability of the furoxan derivatives to dilate rat aorta strips precontracted with phenylephrine is also discussed, as an example of their NO-dependent pharmacological properties.

RESULTS AND DISCUSSION

Chemistry. The synthesis of sulfonic acids both of the furoxan and the furazan series, and of the related sulfonamides is outlined in Scheme 1. The action of benzyl mercaptane on 4-nitro-substituted furoxans **1a**, **2a**, and 3-phenylsulfonyl-substituted furoxans **1b**, **2b** in acetonitrile solution, in the presence of triethylamine, afforded the corresponding benzylthiofuroxan derivatives **3a, 4a** and **3b, 4b**. Corresponding furazan analogues **3c, 4c** were obtained by action of refluxing trimethyl phosphite on **3a** and **4a**, respectively. All these sulphur intermediates were transformed in the related sulfonyl chlorides **5a-c**, **6a-c** by action of chlorine in acetic acid solution in presence of hydrochloric acid. In this reaction, benzyl chloride formed in equimolar amount with the expected sulfonyl chlorides. Solid sulfonyl chlorides **6a** and **6c** were purified by crystallization. All the attempts to isolate **5a-c** and **6b** failed due to their thermal and hydrolytic instability. Consequently, these compounds were used for further reactions in mixture with benzyl chloride. All sulfonyl chlorides afforded the final sulfonic acid potassium salts **7a-c**, **8a-c**, when treated with 1*N* $KHCO_3$ in acetone solution. Sulfonamides derivatives of 3-phenyl and 3-methylfuroxan series **9a-16a** and related furazans **9c-16c** were obtained by action of the appropriate amines on the

Scheme 1



corresponding sulfonyl chlorides in CH_2Cl_2, or in water solution when ammonia or methylamine were used. This synthetic approach failed in the preparation of the sulfonamide isomers of the 4-phenyl and 4-methylfuroxans series owing to the decomposition of the related sulfonyl chlorides in the presence of amine reagents. Consequently, we obtained the sulfonamides **9b**, **10b**, **11b**, **13b**, **15b**, and **16b** by thermal isomerization of the corresponding 3-phenyl and 3-methyl isomers at 130°C in 1,1,2,2-tetrachloroethane ($Cl_2CHCHCl_2$) solution. After solvent removal the mixtures of isomers were separated by HPLC. This separation failed in the case of **12a/12b** and **14a/14b** mixtures. The equilibrium constants (NMR or HPLC detection) between the isomer pair of sulfonamides, determined at 130°C in $Cl_2CHCHCl_2$, are listed in Table 1. In some cases the equilibrium was approached from both sides. In all cases the isomers bearing the sulfonamido groups from the opposite side of the exocyclic oxygen are favoured. ^1H and ^{13}C NMR spectra (Experimental) are in keeping with the structural assignments. In particular, in the case of the furoxan isomers they satisfy the rule that both in ^1H and in ^{13}C NMR spectra, the 3-CH_3 resonance signal is upfield with respect to the one of 4-CH_3 [8,9] and that in the ^{13}C NMR spectra the resonances of C(1) and C(4) carbons of the 3-Ph group appear upfield with respect to the corresponding resonances of the 4-Ph group [10]. Finally the chemical shift of C3 and C4 carbon atoms of the furoxan ring are in keeping with those observed in aryl- and alkylsulfonyl furoxans [9,11].

Ionization constants. The pK_a values of sulfonamide derivatives both of the furoxan and of the furazan series were measured by potentiometric technique using a Sirius GLpK_a apparatus. These values are listed in Table 1. The high acid strength of all the sulfonic acids, which are in keeping with the electron withdrawing properties of the furazan and furoxan rings [12], did not allow the detection of their dissociation constants with this technique. Some interesting structural considerations can be derived from the analysis of Table 1. In a pair of isomers the product bearing the sulfonamide function at the 4-position is always just a little less acid than the other isomer or displays the same acidity. The related furazans are always less acidic than the related furoxans. In

Table 1

Physicochemical parameters and pharmacological activities of furoxan and furazan sulfonic acids (**7, 8**) and related sulfonamides (**9–16**).

Comp.	Molecular formula	mp (crystallization solvent)	pK_a ± SD	Thermal isomerization equilibrium K ([a]/[b])	Vasodilator activity	
					EC_{50} ± SE (μ*M*)	EC_{50} ± SE (μ*M*) + 1 μ*M* ODQ
7a	$C_3H_3KN_2O_5S$	>280°C dec. (H_2O)	ND		ND[d]	ND[d]
7b	$C_3H_3KN_2O_5S$	277–279°C dec. (H_2O)	ND		24 ± 6	ND[d]
7c	$C_3H_3KN_2O_4S$	>270°C dec. without melting (H_2O)	ND		–	–
8a	$C_8H_5KN_2O_5S$	214–215°C dec. (H_2O)	ND		37 ± 4	ND[d]
8b	$C_8H_5KN_2O_5S$	250–255°C dec. (H_2O)	ND		4.3 ± 0.8	ND[d]
8c	$C_8H_5KN_2O_4S\cdot 3/4H_2O$	255–260°C dec. (H_2O)	ND		–	–
9a	$C_3H_5N_3O_4S$	93–93.5°C ($ClCH_2CH_2Cl$)	6.85 ± 0.01	2.05[b]	ND[d]	ND[d]
9b	$C_3H_5N_3O_4S$	117–118°C ($ClCH_2CH_2Cl$)	6.80 ± 0.01		27 ± 3	ND[d]
9c	$C_3H_5N_3O_3S$	81–82°C ($ClCH_2CH_2Cl/CCl_4$)	7.06 ± 0.02		–	–
10a	$C_8H_7N_3O_4S\cdot 1/2H_2O$	147–148°C (H_2O)	6.88 ± 0.01	1.94[c]	1.4 ± 0.2	ND[d]
10b	$C_8H_7N_3O_4S$	112–114°C (H_2O)	6.76 ± 0.01		0.61 ± 0.11	96 ± 16
10c	$C_8H_7N_3O_3S$	149.5–151°C (H_2O)	7.16 ± 0.01		–	–
11a	$C_4H_7N_3O_4S$	77–78°C (CCl_4)	8.03 ± 0.01	2.11[b]	21 ± 3	ND[d]
11b	$C_4H_7N_3O_4S$	48–50°C (CCl_4)	8.10 ± 0.01		2.4 ± 0.3	ND[d]
11c	$C_4H_7N_3O_3S$	55–55.5°C (CCl_4)	8.43 ± 0.01		–	–
12a	$C_9H_9N_3O_4S$	108–109°C (H_2O)	8.12 ± 0.01[a]		0.15 ± 0.02	10 ± 1
12c	$C_9H_9N_3O_3S$	94–95°C (H_2O)	8.58 ± 0.01[a]		–	–
13a	$C_7H_{13}N_3O_4S$	54–55°C (hexane)	–	3.30[b]	7.3 ± 0.7	ND[d]
13b	$C_7H_{13}N_3O_4S$	92–93°C (hexane)	–		0.087 ± 0.011	11 ± 3
13c	$C_7H_{13}N_3O_3S$	liquid	–		–	–
14a	$C_{12}H_{15}N_3O_4S$	64–65°C (hexane)	–		0.070 ± 0.014	6.5 ±1.1
14c	$C_{12}H_{15}N_3O_3S$	liquid	–		–	–
15a	$C_9H_8BrN_3O_4S\cdot 1/2H_2O$	126–127°C (CCl_4)	4.56 ± 0.01[a]	1.52[b]	[e]	[e]
15b	$C_9H_8BrN_3O_4S$	114.5–115.5°C (CCl_4)	4.43 ± 0.01[a]		[e]	[e]
15c	$C_9H_8BrN_3O_3S$	96.5–97.5°C (CCl_4)	5.15 ± 0.01[a]		[e]	[e]
16a	$C_{14}H_{10}BrN_3O_4S$	149–150°C (CCl_4)	4.72 ± 0.01[a]	2.15[c]	[e]	[e]
16b	$C_{14}H_{10}BrN_3O_4S$	158–159°C (CCl_4)	4.51 ± 0.01[a]		[e]	[e]
16c	$C_{14}H_{10}BrN_3O_3S$	131–132°C (CCl_4)	5.20 ± 0.2[a]		[e]	[e]

[a] Potentiometric titrations were performed in water containing methanol as a cosolvent in different ratios depending on the solubility of compounds: pK_a values were determined by extrapolation at 0% methanol using the Yasuda-Shedlovsky procedure (experimental).

[b] NMR determination.

[c] HPLC determination.

[d] EC_{50} could not be calculated as the relaxation at maximum concentration tested (100 μ*M*) did not reach 50%.

[e] The product completely relaxed the contracted tissue in a concentration independent manner; the tissue did not recover its contractility.

all the series, the presence on sulfonamide function of the *p*-bromophenyl group increases the acidity while the presence of the methyl group decreases it. This is in accordance with the ability of the former to delocalize the negative charge of the conjugated anion and with the opposite effect exerted by the latter.

Vasodilator activity. Furoxan derivatives display vasodilator properties. It is commonly accepted that this is due to their ability to release NO under the action of vessel intracellular thiols. The NO produced activates soluble guanylate cyclase (sGC) and this induces a series of events whose final result is dilation of the vessel [13]. All furoxansulfonamides described in this work were able to relax rat aorta strips precontracted with phenylephrine in a concentration dependent manner. The vasodilator potencies EC_{50}, namely the molar concentration able to induce 50% of the relaxing effect to the contracted tissue are reported in Table 1. When the experiments were repeated in the presence of 1 μ*M* 1*H*-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (ODQ), a decrease in the potencies was observed, in keeping with a NO-induced activation of the sGC as the mechanism, which underlies this effect. Products bearing a *p*-bromophenyl moiety behaved differently. They completely relaxed the contracted tissue in a concentration independent manner, both in the presence and in the absence of ODQ. In addition, the tissue did not recover its contractility in spite of extensive washing. It is worthy of note that also the furazan analogues **15c** and **16c** display similar behavior. This indicates that the vasodilator activity of these specific products is not NO dependent but probably connected with their tissue toxicity.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 at 300 and 75 MHz, respectively, using $SiMe_4$ as the internal standard. Low resolution mass spectra were recorded with a Finnigan-Mat TSQ-700. Melting points were determined with a capillary apparatus (Buchi 540). Flash column chromatography was performed on silica gel (Merck Kieselgel 60, 230–400 mesh ASTM), using the indicated eluents; PE stands for 40–60 petroleum ether. The progress of the reactions was followed by thin layer chromatography (TLC) on 5 × 20 cm plates with a layer thickness of 0.2 mm. Anhydrous magnesium sulfate was used as the drying agent for the organic phases. Organic solvents were removed under vacuum at 30°C. Preparative HPLC was performed on a LiChrospher® C18 column (250 × 25 mm, 10 μm) (Merck Darmstadt, Germany) with a Varian ProStar mod-210 with Varian UV detector mod-325. Elemental analyses (C, H, N) were performed by REDOX (Monza). Compounds **1a** [14], **2a** [15], **1b** [9], and **2b** [16] were synthesized as described elsewhere.

General procedure for preparation of benzylthiofuroxans (3a,b and 4a,b). To a stirred solution of appropriate furoxan derivative (24 mmol) in CH_3CN (25 mL), cooled at −15°C, Et_3N (3.4 mL, 24 mmol) was added. To the obtained solution benzylmercaptane (2.5 mL, 24 mmol) was added in one portion and the reaction was stirred at −15°C for 30 min. The cooling bath was removed and the reaction mixture was allowed to stir at room temperature for an additional 30 min. Benzylthiofuroxans were isolated as described.

4-Benzylthio-3-methylfuroxan (3a). The reaction mixture was diluted with CH_2Cl_2. The organic solvent was washed with H_2O, 1*N* HCl, $NaHCO_3$ saturated solution, brine, dried, and evaporated. The obtained oil was solidified by treating with PE at 0°C. The obtained solid was filtered, washed with cold PE, and crystallized from hexane to give the title compound as a white solid, yield 54%, mp 48–49°C (hexane); ^{1}H NMR ($CDCl_3$): δ 2.00 (s, 3H, CH_3), 4.38 (s, 2H, CH_2), 7.31–7.38 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$): δ 7.5 (3-CH_3), 35.2, 112.5 (*C*3 fx), 128.1, 128.8, 129.1, 135.4, 154.8 (*C*4 fx); ms: *m/z* 222 (M^+). *Anal.* Calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60. Found: C, 54.35; H, 4.51; N, 12.73.

3-Benzylthio-4-methylfuroxan (3b). The reaction mixture was diluted with CH_2Cl_2. The organic solvent was washed with H_2O, 1*N* HCl, $NaHCO_3$ saturated solution, brine, dried, and evaporated. The obtained oil was purified by flash chromatography (eluent 8/2 PE/CH_2Cl_2) to give the title compound as a colorless oil, yield 79%; ^{1}H NMR ($CDCl_3$): δ 1.90 (s, 3H, CH_3), 4.08 (s, 2H, CH_2), 7.14–7.18 (m, 2H) 7.24–7.31 (m, 3H) (C_6H_5); ^{13}C NMR ($CDCl_3$): δ 10.9 (4-CH_3), 34.9, 111.2 (*C*3 fx), 128.0, 128.7, 128.9, 135.4, 157.1 (*C*4 fx); ms: *m/z* 222 $(M)^+$. *Anal.* Calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60. Found: C, 54.26; H, 4.46; N, 12.42.

4-Benzylthio-3-phenylfuroxan (4a). The product precipitated from the reaction mixture. It was filtered, washed with cold CH_3CN, and crystallized from EtOH to give the title compound as a white solid, yield 57%, mp 111–113°C (EtOH); ^{1}H NMR ($CDCl_3$): δ 4.45 (s, 2H, CH_2), 7.31–7.49 (m, 8H), 7.83–7.87 (m, 2H) ($2C_6H_5$); ^{13}C NMR ($CDCl_3$): δ 35.5, 114.1 (*C*3 fx), 122.4 (*C*1 Ph), 127.3, 128.1, 128.8, 129.0, 129.3, 130.7 (*C*4 Ph), 135.0, 154.1 (*C*4 fx); ms: *m/z* 284 $(M)^+$. *Anal.* Calcd. for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85. Found: C, 63.58; H, 4.23; N, 9.84.

3-Benzylthio-4-phenylfuroxan (4b). The organic solvent was removed and the obtained oil was purified by flash chromatography (eluent 7/3 PE/CH_2Cl_2) to give the title compound as a colorless oil, yield 85%; ^{1}H NMR (DMSO-d_6): δ 4.16 (s, 2H, CH_2), 7.07–7.25 (m, 5H) 7.39–7.51 (m, 3H), 7.59–7.61 (m, 2H) ($2C_6H_5$); ^{13}C NMR ($CDCl_3$): δ 34.7, 110.6 (*C*3 fx), 126.1 (*C*1 Ph), 127.7, 128.0, 128.7, 128.8, 131.0, 135.5, 157.7 (*C*4 fx); ms: *m/z* 284 $(M)^+$. *Anal.* Calcd. for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85. Found: C, 63.15; H, 4.28; N, 9.87.

General procedure for preparation of benzylthiofurazans (3c and 4c). A solution of appropriate furoxan (45 mmol) in $P(OMe)_3$ (30 mL, 0.25 mol) was heated at reflux for 12 h. The reaction was cooled and poured into an ice/4*N* HCl (80 mL) mixture. The precipitate formed was filtered, washed with cold water and crystallized from MeOH to give the title compound as a white crystalline solid.

3-Benzylthio-4-methylfurazan (3c). Yield: 77%, mp 28–28.5°C (MeOH); ^{1}H NMR ($CDCl_3$): δ 2.23 (s, 3H, CH_3), 4.39 (s, 2H, CH_2), 7.25–7.41 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$): δ 8.0, 36.8, 128.0, 128.8, 129.1, 135.7, 149.8, 152.2; ms: *m/z* 206 (M^+). *Anal.* Calcd. for $C_{10}H_{10}N_2OS$: C, 58.23; H, 4.89; N, 13.58. Found: C, 58.20; H, 5.00; N, 13.60.

3-Benzylthio-4-phenylfurazan (4c). Yield 81%, mp 65.5–66.5°C (MeOH); ^{1}H NMR ($CDCl_3$): δ 4.49 (s, 2H, CH_2), 7.25–7.49 (m, 8H), 7.80–7.82 (m, 2H) ($2C_6H_5$); ^{13}C NMR ($CDCl_3$): δ 37.3, 125.3, 128.0, 128.0, 128.8, 129.0, 129.2, 130.7, 135.4, 151.1, 152.3; ms: *m/z* 268 (M^+). *Anal.* Calcd. for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44. Found: C, 67.24; H, 4.49; N, 10.45.

General procedure for preparation of sulfonylchlorides (5a-c and 6a-c). To the suspension/solution of benzylthioderivatives in acetic acid 4*N* HCl (0.5 mL) was added and chlorine was bubbled through reaction mixture for 2 h. After this time reaction, the mixture was stirred at room temperature for 1 h, then it was poured into H_2O and extracted with PE. The organic phase was washed with H_2O (3×), brine, dried, and evaporated. The obtained products were crystallized from hexane (in case of solids **6a** and **6c**) or used directly for further reaction in mixture with benzylchloride (1/1 molar ratio).

3-Phenylfuroxan-4-sulfonyl chloride (6a). White solid, yield 80%, mp 94–96°C (hexane); ^{1}H NMR ($CDCl_3$): δ 7.56–7.61 (m, 3H), 7.75–7.79 (m, 2H) (C_6H_5); ^{13}C NMR ($CDCl_3$) δ: 110.8 (*C*3 fx), 119.3 (*C*1 Ph), 129.1, 129.4, 132.1 (*C*4 Ph), 158.2 (*C*4 fx); ms: *m/z* 260/262 (M^+). *Anal.* Calcd. for $C_8H_5ClN_2O_4S$: C, 36.86; H, 1.93; N, 10.75. Found: C, 37.05; H, 1.99; N, 10.75.

3-Phenylfurazan-4-sulfonyl chloride (6c). White solid, yield 58%, mp 52–53°C (hexane); ^{1}H NMR ($CDCl_3$): δ 7.54–7.67 (m, 3H), 7.76–7.82 (m, 2H) (C_6H_5); ^{13}C NMR ($CDCl_3$) δ: 122.0, 129.3, 129.4, 132.2, 151.5, 156.9; ms: *m/z* 244/246 (M^+). *Anal.* Calcd. for $C_8H_5ClN_2O_3S$: C, 39.27; H, 2.06; N, 11.45. Found: C, 39.34; H, 2.21; N, 11.30.

General procedure for preparation of sulfonic acid potassium salts (7a-c and 8a-c). To a solution of the appropriate sulfonylchloride (2.5 mmol) in acetone (20 mL) 1*N* $KHCO_3$ (7.5 mL, 7.5 mmol) was added at 0°C. The reaction was allowed to reach room temperature and stirred for 2 h. The organic solvent was evaporated, the residue was dissolved in H_2O and the resulting solution was washed with CH_2Cl_2 (2×), filtered, and evaporated. The obtained solid was crystallized from water to give the title compound as a white solid.

Potassium 3-methylfuroxan-4-sulfonate (7a). White solid, yield 38% (for two synthetic steps), mp > 280°C dec. (H_2O); ^{1}H NMR (D_2O): δ 2.31 (s, 3H, CH_3); ^{13}C NMR (D_2O): δ 7.7 (3-CH_3), 114.9 (*C*3 fx), 160.5 (*C*4 fx). *Anal.* Calcd. for $C_3H_3KN_2O_5S$: C, 16.51; H, 1.39; N, 12.83. Found: C, 16.46; H, 1.41; N, 12.76.

Potassium 4-methylfuroxan-3-sulfonate (7b). White solid, yield 15% (for two synthetic steps), mp 277–280°C dec. (H_2O); ^{1}H NMR (D_2O): δ 2.47 (s, 3H, CH_3); ^{13}C NMR (D_2O): δ 12.1 (4-CH_3), 120.2 (*C3* fx), 154.4 (*C4* fx). *Anal.* Calcd. for $C_3H_3KN_2O_5S$: C, 16.51; H, 1.39; N, 12.83. Found: C, 16.45; H, 1.50; N, 12.65.

Potassium 3-methylfurazan-4-sulfonate (7c). White solid, yield 34% (for two synthetic steps), mp > 270°C dec. without melting (H_2O); ^{1}H NMR (D_2O): δ 2.06 (s, 3H, CH_3); ^{13}C NMR (D_2O): δ 8.4, 150.8, 157.5. *Anal.* Calcd. for $C_3H_3KN_2O_4S$: C, 17.82; H, 1.50; N, 13.85. Found: C, 17.71; H, 1.52; N, 13.66.

Potassium 3-phenylfuroxan-4-sulfonate (8a). White solid, yield 45%, mp 214–215°C (H_2O); ^{1}H NMR (D_2O): δ 7.58–7.60 (m, 3H), 7.86–7.90 (m, 2H) (C_6H_5); ^{13}C NMR (D_2O): δ 116.0 (*C3* fx), 121.7 (*C1* Ph), 129.4, 129.6, 132.0 (*C4* Ph), 159.7 (*C4* fx). *Anal.* Calcd. for $C_8H_5KN_2O_5S$: C, 34.28; H, 1.80; N, 9.99. Found: C, 34.05; H, 1.79; N, 9.83.

Potassium 4-phenylfuroxan-3-sulfonate (8b). White solid, yield 35% (for two synthetic steps), mp 250–255°C (H_2O); ^{1}H NMR (D_2O): δ 7.55–7.65 (m, 3H), 7.76–7.79 (m, 2H) (C_6H_5); ^{13}C NMR (D_2O): δ 119.4 (*C3* fx), 126.1 (*C1* Ph), 129.3, 129.7, 132.1 (*C4* Ph), 156.4 (*C4* fx). *Anal.* Calcd. for $C_8H_5KN_2O_5S$: C, 34.28; H, 1.80; N, 9.99. Found: C, 34.28; H, 1.93; N, 9.97.

Potassium 3-phenylfurazan-4-sulfonate (8c). White solid, yield 75%, mp 255–260°C (H_2O); ^{1}H NMR (D_2O): δ 7.55–7.64 (m, 3H), 7.92–7.95 (m, 2H) (C_6H_5); ^{13}C NMR (D_2O): δ 124.4, 129.6, 129.7, 132.0, 153.1, 156.6. *Anal.* Calcd. for $C_8H_5KN_2O_4S$ $\frac{3}{4}H_2O$: C, 34.58; H, 2.35; N, 10.08. Found: C, 34.50; H, 2.17; N, 10.07.

General procedure for preparation of sulfonylamides (9a, 9c, 10a, and 10c) and *N*-methyl sulfonylamides (11a, 11c, 12a, and 12c). An appropriate sulfonylchloride derivative was added to the vigorously stirred concentrated solution of amine in H_2O at −10°C. The ice-salt bath was removed and the reaction was stirred for 2 h at room temperature. Then reaction mixture was cooled again, the pH was adjusted to one with concentrated HCl and the product was purified as described.

3-Methylfuroxan-4-sulfonamide (9a). The acidified mixture was extracted with EtOAc. The organic phase was washed with H_2O, brine, dried, and evaporated. The resulting oil was purified by flash chromatography (eluent 8/2 PE/EtOAc) to give the colorless oil, which solidified at −78°C. The title compound was crystallized from 1,2-dichloroethane. White solid, yield 50% (for two synthetic steps), mp 93–93.5°C (1,2-dichloroethane); ^{1}H NMR (DMSO-d_6): δ 2.27 (s, 3H, CH_3), 8.67 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6): δ 7.7 (3-CH_3), 110.9 (*C3* fx), 160.2 (*C4* fx); ms: *m/z* 179 (M^+). *Anal.* Calcd. for $C_3H_5N_3O_4S$: C, 20.11; H, 2.81; N, 23.45. Found: C, 20.07; H, 2.86; N, 23.34.

3-Methylfurazan-4-sulfonamide (9c). The acidified mixture was extracted with EtOAc. The organic phase was washed with H_2O, brine, dried, and evaporated. The resulting oil was purified by flash chromatography (eluent 8/2 PE/EtOAc) to give the colorless oil, which solidified at −78°C. The title compound was crystallized from 1,2-dichloroethane/CCl_4 mixture. White solid, yield 34% (for two synthetic steps), mp 81–82°C (1,2-dichloroethane/CCl_4); ^{1}H NMR (DMSO-d_6): δ 2.54 (s, 3H, CH_3), 8.66 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6): δ 8.1, 149.6, 157.8; ms: *m/z* 164 [$(M+H)^+$]. *Anal.* Calcd. for $C_3H_5N_3O_3S$: C, 22.08; H, 3.09; N, 25.75. Found: C, 22.10; H, 3.08; N, 25.50.

3-Phenylfuroxan-4-sulfonamide (10a). Product precipitated from acidified reaction mixture. It was filtered, washed with cold H_2O, and crystallized from H_2O to give the title compound as a white solid, yield 75%, mp 147–148°C (H_2O); ^{1}H NMR (DMSO-d_6): δ 7.57–7.64 (m, 3H), 7.85–7.90 (m, 2H) (C_6H_5), 8.81 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6): δ 112.7 (*C3* fx), 121.0 (*C1* Ph), 128.7, 128.8, 131.0 (*C4* Ph), 159.7 (*C4* fx); ms: *m/z* 242 [$(M+H)^+$]. *Anal.* Calcd. for $C_8H_7N_3O_4S$ $\frac{1}{2}H_2O$: C, 38.40; H, 3.22; N, 16.79. Found: C, 38.45; H, 3.34; N, 16.42.

3-Phenylfurazan-4-sulfonamide (10c). The product precipitated from acidified reaction mixture. It was filtered, washed with cool water, and crystallized from H_2O to give the title compound as a white solid, yield 72%, mp 149.5–151°C (H_2O); ^{1}H NMR (DMSO-d_6): δ 7.57–7.68 (m, 3H), 7.89–7.97 (m, 2H) (C_6H_5), 8.92 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6): δ 123.3, 129.1 (two signals overlapped), 131.5, 151.9, 157.3; ms: *m/z* 225 [$(M+H)^+$]. *Anal.* Calcd. for $C_8H_7N_3O_3S$: C, 42.66; H, 3.13; N, 18.65. Found: C, 42.62; H, 3.19; N, 18.54.

***N*-Methyl-3-methylfuroxan-4-sulfonamide (11a).** The acidified reaction mixture was extracted with CH_2Cl_2. The organic solvent was washed with H_2O, brine, dried, and evaporated. The obtained solid was crystallized from CCl_4 to give the title compound as a white solid, yield 61% (for two synthetic steps), mp 77–79°C (CCl_4); ^{1}H NMR ($CDCl_3$): δ 2.13 (s, 3H, CH_3), 3.01 (d, 3H, CH_3), 5.19 (broad s., 1H, NH); ^{13}C NMR ($CDCl_3$): δ 8.0 (3-CH_3), 30.2, 110.3 (*C3* fx), 157.9 (*C4* fx); ms: *m/z* 193 (M^+). *Anal.* Calcd. for $C_4H_7N_3O_4S$: C, 24.87; H, 3.65; N, 21.75. Found: C, 24.79; H, 3.77; N, 21.41.

***N*-Methyl-3-methylfurazan-4-sulfonamide (11c).** The acidified reaction mixture was extracted with EtOAc. The organic solvent was washed with H_2O, brine, dried, and evaporated. The obtained oil was purified by flash chromatography (eluent 9/1 PE/EtOAc) to give the colorless oil, which solidified by treating with PE at −78°C. The obtained solid was crystallized from CCl_4 to give the title compound as a white solid, yield 32% (for two reaction steps), mp 55–55.5°C (CCl_4); ^{1}H NMR (DMSO-d_6): δ 2.53 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 8.79 (br.s., 1H, NH); ^{13}C NMR (DMSO-d_6): δ 8.2, 28.6, 149.9, 155.2; ms: *m/z* 178 [$(M+H)^+$]. *Anal.* Calcd. for $C_4H_7N_3O_3S$: C, 27.12; H, 3.98; N, 23.72. Found: C, 27.11; H, 4.01; N, 23.60.

***N*-Methyl-3-phenylfuroxan-4-sulfonamide (12a).** The acidified reaction mixture was kept at 4°C overnight. The next day a precipitate formed, was filtered, washed with cold H_2O, and crystallized from H_2O to give the title compound as a white solid, yield 77%, mp 108–109°C (H_2O); ^{1}H NMR ($CDCl_3$): δ 3.02 (d, 3H, CH_3), 5.04–5.13 (m, 1H, NH), 7.54–7.56 (m, 3H), 7.93–7.96 (m, 2H) (C_6H_5); ^{13}C NMR ($CDCl_3$): δ 30.7, 112.5 (*C3* fx), 120.6 (*C1* Ph), 128.5, 129.1, 131.5 (*C4* Ph), 157.4 (*C4* fx); ms: *m/z* 255 (M^+). *Anal.* Calcd. for $C_9H_9N_3O_4S$: C, 42.35; H, 3.55; N, 16.46. Found: C, 42.31; H, 3.57; N, 16.43.

***N*-Methyl-3-phenylfurazan-4-sulfonamide (12c).** The product precipitated from acidified reaction mixture was filtered, washed with cold H_2O, and crystallized from H_2O to give the title compound as a white solid, yield 84%, mp 94–95°C (H_2O); ^{1}H NMR (DMSO-d_6): δ 2.79 (s, 3H, CH_3), 7.59–7.68 (m, 3H), 7.91–7.94 (m, 2H) (C_6H_5), 9.11 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6): δ 29.1, 123.2, 129.0, 129.1, 131.5, 152.2, 155.0; ms: *m/z* 239 (M^+). *Anal.* Calcd. for $C_9H_9N_3O_3S$: C, 45.18; H, 3.79; N, 17.56. Found: C, 45.27; H, 3.66; N, 17.52.

General procedure for preparation *N,N*-diethylsulfonamides (13a, 13c 14a, and 14c). To the solution of corresponding sulfonylchloride (1.9 mmol) in CH_2Cl_2 (15 mL) a solution of Et_2NH (0.50 mL, 4.8 mmol) in CH_2Cl_2 (10 mL) was added dropwise at 0°C. The ice bath was removed and the reaction was stirred at room temperature for 1 h. The obtained solution was washed with 1*N* HCl, H_2O, $NaHCO_3$ saturated solution, brine, dried, and evaporated. The obtained oil was purified by flash chromatography with the indicated eluents.

***N,N*-Diethyl-3-methylfuroxan-4-sulfonamide (13a).** The obtained oil was purified by flash chromatography (eluent 7/3 PE/CH_2Cl_2) to give a solid, which was crystallized from hexane to give the title compound as a white solid, yield 36% (for two reaction steps), mp 54–55°C (hexane); ^1H NMR ($CDCl_3$): δ 1.30 (t, 6H, 2C*H*$_3$), 2.35 (s, 3H, C*H*$_3$), 3.49 (q, 4H, 2C*H*$_2$); ^{13}C NMR ($CDCl_3$): δ 8.1 (3-CH_3), 14.4, 43.4, 110.4 (*C*3 fx), 158.7 (*C*4 fx); ms: *m/z* 235 (M^+). *Anal.* Calcd. for $C_7H_{13}N_3O_4S$: C, 35.74; H, 5.57; N, 17.86. Found: C, 35.97; H, 5.59; N, 17.69.

***N,N*-Diethyl-3-methylfurazan-4-sulfonamide (13c).** The obtained oil was purified by flash chromatography (eluent 8/2 PE/CH_2Cl_2) to give the title compound as colorless oil, yield 35% (for two reaction steps); ^1H NMR ($CDCl_3$): δ 1.16 (t, 6H, 2C*H*$_3$), 2.54 (s, 3H, C*H*$_3$), 3.39 (q, 4H, 2C*H*$_2$); ^{13}C NMR ($CDCl_3$): δ 8.4, 14.2, 42.8, 150.6, 156.5; ms: *m/z* 219 (M^+). *Anal.* Calcd. for $C_7H_{13}N_3O_3S$: C, 38.35; H, 5.98; N, 19.16. Found: C, 38.40; H, 5.99; N, 19.06.

***N,N*-Diethyl-3-phenylfuroxan-4-sulfonamide (14a).** The obtained oil was purified by flash chromatography (eluent 7/3 PE/CH_2Cl_2) to give a pale yellow oil, which became solid on standing. The title product was obtained by crystallization from hexane, yield 57%, mp 64–65°C (hexane); ^1H NMR (CDCl3): δ 1.28 (t, 6H, 2C*H*$_3$), 3.48 (q, 4H, 2C*H*$_2$), 7.50–7.54 (m, 3H), 7.94–7.97 (m, 2H) (C_6*H*$_5$); ^{13}C NMR ($CDCl_3$): δ 14.7, 44.0, 112.7 (*C*3 fx), 120.9 (*C*1 Ph), 128.6, 129.0, 131.3 (*C*4 Ph), 157.9 (*C*4 fx);. ms: *m/z* 298 [$(M+H)^+$]. *Anal.* Calcd. for $C_{12}H_{15}N_3O_4S$: C, 48.47; H, 5.08; N, 14.13. Found: C, 48.30; H, 5.00; N, 13.92.

***N,N*-Diethyl-3-phenylfurazan-4-sulfonamide (14c).** The obtained oil was purified by flash chromatography (eluent 9/1 PE/CH_2Cl_2) to give the pale yellow oil, which was further purified with HPLC (75/25 CH_3CN/H_2O) to give the title compound as a colorless oil, yield 84%; ^1H NMR ($CDCl_3$): δ 1.29 (t, 6H, 2C*H*$_3$), 3.49 (q, 4H, 2C*H*$_2$), 7.49–7.59 (m, 3H), 7.98–8.00 (m, 2H) (C_6*H*$_5$); ^{13}C NMR ($CDCl_3$): δ 14.3, 43.3, 123.1, 129.0, 129.1, 131.5, 152.3, 154;. ms: *m/z* 281 (M^+). *Anal.* Calcd. for $C_{12}H_{15}N_3O_3S$: C, 51.23; H, 5.37; N, 14.93. Found: C, 50.91; H, 5.42; N, 15.10.

General procedure for preparation *N*-(4-bromophenyl)-sulfonamides (15a, 15c 16a, and 16c). To a solution of the appropriate sulfonylchloride (1.2 mmol) in CH_2Cl_2 (15 mL) *p*-bromoaniline (0.50 g, 2.9 mmol) was added and the reaction was stirred at room temperature for 4 days. The obtained solution was diluted with CH_2Cl_2 washed with 1*N* HCl, H_2O, brine, dried, and evaporated. The obtained solids were crystallized from CCl_4 to give the title compounds as white solids.

***N*-(4-Bromophenyl)-3-methylfuroxan-4-sulfonamide (15a).** Yield 50% (for two reaction steps), mp 126–127°C (CCl_4); ^1H NMR ($CDCl_3$): δ 2.20 (s, 3H, C*H*$_3$), 7.17–7.22 (m, 3H), 7.48–7.53 (m, 2H), (C_6*H*$_4$ + N*H*); ^{13}C NMR ($CDCl_3$): δ 8.0 (3-CH_3), 110.3 (*C*3 fx), 121.4, 125.7, 132.9, 132.9, 157.4 (*C*4 fx); ms: *m/z* 333/335 (M^+). *Anal.* Calcd. for $C_9H_8BrN_3O_4S$ $^1/_2H_2O$: C, 31.50; H, 2.64; N, 12.25. Found: C, 31.25; H, 2.34; N, 11.86.

***N*-(4-Bromophenyl)-3-methylfurazan-4-sulfonamide (15c).** Yield 42% (for two reaction steps), mp 96.5–97.5°C (CCl_4); ^1H NMR (DMSO-d$_6$): δ 2.48 (s, 3H, C*H*$_3$), 7.14–7.19 (m, 2H), 7.55–7.60 (m, 2H), (C_6*H*$_4$), 11.69 (broad s., 1H, N*H*); ^{13}C NMR (DMSO-d$_6$): δ 8.1, 118.1, 123.5, 132.3, 134.9, 150.0, 155.1; ms: *m/z* 317/319 (M^+). *Anal.* Calcd. for $C_9H_8BrN_3O_3S$: C, 33.98; H, 2.53; N, 13.20. Found: C, 33.93; H, 2.44; N, 13.14.

***N*-(4-Bromophenyl)-3-phenylfuroxan-4-sulfonamide (16a).** Yield 76%, mp 149–150°C (CCl_4); ^1H NMR ($CDCl_3$): δ 7.03 (s, 1H, N*H*), 7.11 (d, 2H), 7.43 (d, 2H) (C_6*H*$_4$), 7.53–7.54 (m, 3H), 7.79–7.82 (m, 2H) (C_6*H*$_5$); ^{13}C NMR ($CDCl_3$): δ 112.3 (*C*3 fx), 120.1, 121.0 (*C*1 Ph), 125.3, 128.6, 129.2, 131.5 (*C*4 Ph), 132.7, 133.1, 156.8 (*C*4 fx); ms: *m/z* 395/397 (M^+). *Anal.* Calcd. for $C_{14}H_{10}BrN_3O_4S$: C, 42.44; H, 2.54; N, 10.61. Found: C, 42.15; H, 2.55; N, 10.45.

***N*-(4-Bromophenyl)-3-phenylfurazan-4-sulfonamide (16c).** Yield 79%, mp 131–132°C (CCl_4); ^1H NMR (DMSO-d$_6$): δ 7.19 (d, 2H), 7.48 7.71 (m, 5H), 7.78–7.87 (m, 2H) (C_6*H*$_5$ + C_6*H*$_4$), 11.94 (broad s. 1H, N*H*); ^{13}C NMR (DMSO-d$_6$): δ 118.0, 122.8, 123.5, 129.0, 129.2, 131.5, 132.2, 135.2, 152.3, 154.9; ms: *m/z* 379/381 (M^+). *Anal.* Calcd. for $C_{14}H_{10}BrN_3O_3S$: C, 44.23; H, 2.65; N, 11.05. Found: C, 44.10; H, 2.64; N, 11.03.

General procedure for thermal isomerization of furoxansulfonamides (9b, 10b, 13b, 15b, 16b). A solution of the appropriate 3-methyl or 3-phenyl sulfonamide derivative in $Cl_2CHCHCl_2$ was heated at 130°C for 24 h. The solvent was evaporated and the obtained mixture of isomers was separated by HPLC with the eluent indicated. Analytically pure samples of 4-methyl and 4-phenyl substituted furoxansulfonamides were obtained by crystallization.

4-Methylfuroxan-3-sulfonamide (9b). HPLC (70/30 CH_3CN/H_2O + 0.1% CF_3COOH; 20 mL/min), second eluted. The obtained solid was crystallized from 1,2-dichloroethane to give the title compound as a white crystalline solid, mp 117–118°C (1,2-dichloroethane); ^1H NMR (DMSO-d$_6$): δ 2.45 (s, 3H, C*H*$_3$), 8.29 (s, 2H, N*H*$_2$); ^{13}C NMR (DMSO-d$_6$): δ 12.5 (4-CH_3), 119.1 (*C*3 fx), 153.2 (*C*4 fx); ms: *m/z* 179 (M^+). *Anal.* Calcd. for $C_3H_5N_3O_4S$: C, 20.11; H, 2.81; N, 23.45. Found: C, 20.19; H, 2.70; N, 23.41.

4-Phenylfuroxan-3-sulfonamide (10b). HPLC (40/60 CH_3CN/H_2O + 0.1% CF_3COOH; 20 mL/min), second eluted. The obtained solid was crystallized from H_2O to give the title compound as a white crystalline solid, mp 112–114°C (H_2O); ^1H NMR ($CDCl_3$): δ 5.56 (s, 1H, N*H*), 7.50–7.61 (m, 3H), 7.73–7.75 (m, 2H) (C_6*H*$_5$); ^{13}C NMR (DMSO-d$_6$): δ 118.4 (*C*3 fx), 125.3 (*C*1 Ph), 128.4, 129.3, 131.1 (*C*4 Ph), 154.8 (*C*4 fx); ms: *m/z* 241 (M^+). *Anal.* Calcd. for $C_8H_7N_3O_4S$: C, 39.83; H, 2.92; N, 17.42. Found: C, 39.90; H, 2.94; N, 17.41.

***N*-Methyl-4-methylfuroxan-3-sulfonamide (11b).** HPLC (25/75 CH_3CN/H_2O + 0.1% CF_3COOH), second eluted. The obtained solid was crystallized from CCl_4 to give the title compound as a white solid, mp 48–50°C (CCl_4); ^1H NMR ($CDCl_3$): δ 2.55 (s, 3H, C*H*$_3$), 2.83 (d, 3H, C*H*$_3$), 5.47 (broad s., 1H, N*H*); ^{13}C NMR ($CDCl_3$): δ 12.2 (4-CH_3), 29.5, 117.2 (*C*3 fx), 152.9 (*C*4 fx); ms: *m/z* 193 (M^+). *Anal.* Calcd. for $C_4H_7N_3O_4S$: C, 24.87; H, 3.65; N, 21.75. Found: C, 24.83; H, 3.67; N, 21.51.

***N,N*-Diethyl-4-methylfuroxan-3-sulfonamide (13b).** HPLC (40/60 CH_3CN/H_2O; 20mL/min), second eluted. The obtained solid was crystallized from hexane to give the title compound as a white solid, mp 92–93°C (hexane); ^{1}H NMR ($CDCl_3$): δ 1.22 (t, 6H, 2C*H*$_3$), 2.53 (s, 3H, C*H*$_3$), 3.45 (q, 4H, 2C*H*$_2$); ^{13}C NMR ($CDCl_3$): δ 12.5 (4-*C*H$_3$), 14.4, 43.5, 118.5 (*C*3 fx), 152.7 (*C*4 fx); ms: *m*/*z* 235 (M^+). *Anal.* Calcd. for $C_7H_{13}N_3O_4S$: C, 35.74; H, 5.57; N, 17.86. Found: C, 35.69; H, 5.56; N, 17.72.

***N*-(4-Bromophenyl)-4-methylfuroxan-3-sulfonamide (15b).** HPLC (70/30 CH_3CN/H_2O + 0.1% CF_3COOH; 20 mL/min), second eluted. The obtained solid was crystallized from CCl_4 to give the title compound as a white solid, mp 114.5–115.5°C (CCl_4); ^{1}H NMR ($CDCl_3$): δ 2.38 (s, 3H, C*H*$_3$), 7.11 (d, 2H), 7.43–7.50 (m, 3H) (C$_6$*H*$_4$ + N*H*); ^{13}C NMR ($CDCl_3$): δ 12.1 (4-*C*H$_3$), 117.2 (*C*3 fx), 125.2, 132.4, 133.1, 152.8 (*C*4 fx); ms: *m*/*z* 333/335 (M^+). *Anal.* Calcd. for $C_9H_8BrN_3O_4S$: C, 32.35; H, 2.41; N, 12.58. Found: C, 32.42; H, 2.42; N, 12.57.

***N*-(4-Bromophenyl)-4-phenylfuroxan-3-sulfonamide (16b).** HPLC (60/40 CH_3CN/H_2O + 0.1% CF_3COOH; 20 mL/min) second eluted. The obtained solid was crystallized from CCl_4 to give the title compound as a white solid, mp 158–159°C (CCl_4); ^{1}H NMR ($CDCl_3$): δ 7.02–7.07 (m, 2H), 7.41–7.60 (m, 7H) (C$_6$*H*$_5$, C$_6$*H*$_4$), 7.26 (s, 1H, N*H*); ^{13}C NMR ($CDCl_3$): δ 117.2, 121.3 (*C*3 fx), 124.4 (*C*1 Ph), 124.9, 128.7, 129.2, 131.8 (*C*4 Ph), 132.5, 133.0, 155.3 (*C*4 fx); ms: *m*/*z* 396/398 [$(M+H)^+$]. *Anal.* Calcd. for $C_{14}H_{10}BrN_3O_4S$: C, 42.44; H, 2.54; N, 10.61. Found: C, 42.31; H, 2.62; N, 10.54.

Ionization constants measurements. The ionization constants were determined by a potentiometric method using GLpK_a apparatus (Sirius Analytical Instruments, Forest Row, East Sussex, UK). The titrations were carried out under nitrogen atmosphere, at constant ionic strength ($I = 0.15M$ KCl) and temperature ($t = 25.0 \pm 0.5$°C). Ionization constants of **9a-c**, **10a-c**, and **11a-c**, were determined by at least three aqueous titration: solutions of the compounds (20 mL, about 1 m*M*) were initially acidified to pH 1.8 with 0.5*N* HCl and the solutions were then titrated with standardized 0.5*N* KOH to pH 10.0. Because of the low aqueous solubility, compounds of **12a**, **12c**, **15a-c**, and **16a-c** required titrations in methanol–water mixtures according to the following procedure. At least five different hydro-organic solutions of the compounds (20 mL, about 1 m*M* in 15–65 Wt % methanol) were titrated with the same protocol aforementioned. The apparent ionization constants in water–methanol mixtures (p_sK_as) were obtained and aqueous pK_a values were determined by extrapolation at 0% methanol using the Yasuda-Shedlovsky procedure [17].

Vasodilator activity. Thoracic aortas were isolated from male Wistar rats weighing 180–200 g. As few animals as possible were used. The purposes and the protocols of our studies have been approved by the Ministero della Salute, Rome, Italy. Experiments were performed according to procedures described earlier [18]. Results are expressed as $EC_{50} \pm$ SE (μ*M*). Responses were recorded by an isometric transducer connected to the MacLab System PowerLab (ADInstruments, Bella Vista, Australia). Addition of the drug vehicle (DMSO) had no appreciable effect on contraction level.

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Synthesis and Antifungal Evaluation of Hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones and Their Thioanalogs

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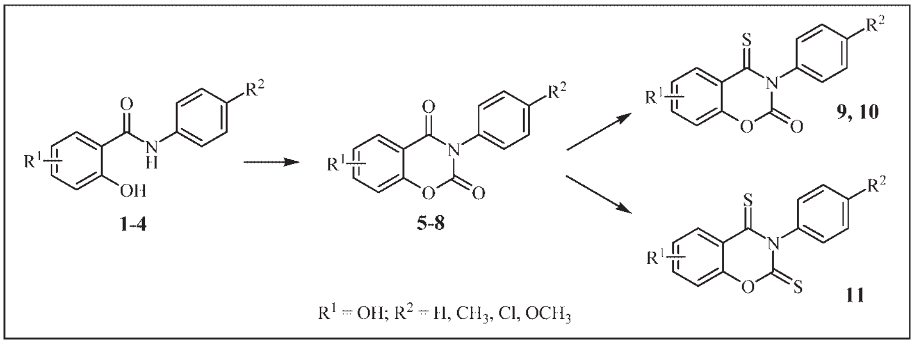

A series of substituted 5-, 6-, 7-, and 8-hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones (**5–8**) was synthesized by cyclization of corresponding dihydroxy-*N*-phenylbenzamides (**1–4**) with methyl chloroformate. The starting compounds **1–4** were prepared by the reaction of the respective dihydroxybenzoic acid, aniline and phosphorus trichloride *via* microwave irradiation. Thionation of compounds **8a–d** employing Lawesson's reagent was used to prepare 5-hydroxy-3-phenyl-4-thioxo-3,4-dihydro-2*H*-1,3-benzoxazin-2-ones (**10a–d**) and 5-hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones (**11a–d**). The position of sulfur in monothionated derivatives **9c** and **10a–d** was confirmed by 2D NMR methods. Attempts to prepare dithionated derivatives from the isomeric 6-, 7- or 8-hydroxy compounds **5–7** failed. All compounds were tested for their *in vitro* antifungal activity against eight test strains. Compounds **1–4** showed moderate activity and the cyclization to corresponding hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones (**5–8**) resulted in a decrease in antifungal activity. No antifungal activity was observed in thionated compounds **9c** and **10–11**.

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INTRODUCTION

Salicylanilides and their derivatives [1] are paid great attention to, particularly from the viewpoint of their antibacterial, antifungal, and other activities [2]. The most important analogs include benzoxazinediones [3] and thiosalicylanilides [4].

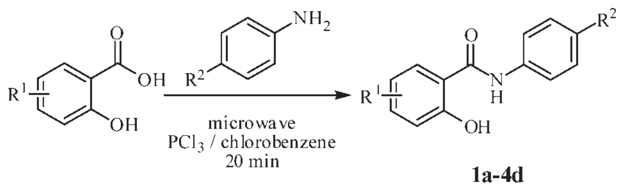
This article focuses on the synthesis of novel salicylanilide derivatives, dihydroxy-*N*-phenylbenzamides, which include two hydroxyl groups in the acyl moiety of the molecule, and their cyclic analogs hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones. Until now, the synthesized substances included mainly dihydroxy-*N*-phenylbenzamides with hydroxyl groups in positions 2 and 6, which were tested as anthelmintics and plant-protecting agents [5]. Resorantel, *N*-(4-bromophenyl)-2,6-dihydroxybenzamide, was introduced into practice as a veterinary anthelmintic agent [6]. As to the cyclic analogs, 5-hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones were patented as fungicidally active agents against rice blast pathogen *Pyricularia oryzae* (*Magnaporthe grisea*) [7].

In the obtained derivatives an attempt was made to prepare the corresponding mono- and dithionated analogs.

RESULTS AND DISCUSSION

Chemistry. The starting dihydroxy-*N*-phenylbenzamides **1a–4d** were synthesized by the microwave-assisted reaction of dihydroxybenzoic acid, appropriate aniline

Scheme 1



R^1 = OH; R^2 = H, CH_3, Cl, OCH_3

and PCl_3 at 135°C for 20 min (Scheme 1). The crude reaction mixtures were purified by column chromatography on silica gel using acetone-hexane (1:5). The products were recrystallized from ethanol-water mixture. For the details of compounds **1a–4d** see Table 1.

For the sake of comparison, when the reaction was carried out using conventional oil bath heating, the reaction was completed in 3 h [2a,f]. The use of a microwave oven resulted in shortening of reaction times, as described by other authors [2d,13], but not in an increase of yields. The use of column chromatography before crystallization has a significant influence on practical yields.

The synthesis of hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones **5a–8d** was based on literature reports describing cyclization reactions of salicylanilides with methyl chloroformate [3a], ethyl chloroformate [3e], or triphosgene [14]. In our experiments, the cyclization reagent was methyl chloroformate in pyridine (Scheme 2). After 2–h refluxing followed by 10–h stirring at room temperature, the reaction mixture was acidified to pH ≈ 6 with 5% HCl. The resulting white heterogeneous mixture was cooled to obtain crystalline compounds. Recrystallization from ethanol gave products **5a–8d** in the yields of 77–94% (Table 1).

Further experiments concerned thionation of hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones **5a–8d**. The published methods include thionation using P_2S_5, either in solution [15] or in melt [3f], and Lawesson's reagent [16]. For the synthesis of hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones, we made use melting of compounds **5a–8d** with Lawesson's reagent at 190–200°C for 4 min. Starting from 5-hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones **8a–d**, this treatment afforded 5-hydroxy-3-phenyl-4-thioxo-3,4-dihydro-2*H*-1,3-benzoxazin-2-ones **10a–d** and 5-hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones **11a–d**, which were separated by column chromatography on silica gel (Scheme 3).

Monothionated analogs **10a–d** and dithionated analogs **11a–d** were prepared in the yields of 31–42% and 24–33%, respectively. The yields were essentially the same as in the case of thionation with P_2S_5 [3d]. In the case of compounds **5–7** with hydroxyl group in position 8, 7 or 6, we did not succeed to isolate any desired product; except for compound **6c**, which gave only monothionation product **9c** in a 5% yield. Attempts to prepare desired thioxo derivatives using P_2S_5 instead of Lawesson's reagent also failed.

For monothionated compounds **9c** and **10a–d**, the presence of sulfur in position four was unequivocally corroborated by 2D NMR (gHMQC and gHSCQ experiments). All gHSQC correlations are shown in Figure 1.

***In vitro* antifungal activity.** All compounds were tested for their *in vitro* antifungal activity [17] against eight test strains. All experiments were performed in comparison with fluconazole, a known antifungal agent. Some compounds were not sufficiently soluble in the testing medium RPMI 1640 and precipitated during the testing period, therefore their minimum inhibitory concentrations MICs could not be determined accurately. The activities of the substances are shown in Table 2. Only compounds with MICs ≤ 125 μmol/L for at least one tested strain were included.

All compounds presented in Table 2 exhibited activities against *Aspergillus fumigatus* and *Absidia corymbifera* higher than or comparable with that of fluconazole. Generally, 2,3-dihydroxy derivatives **1** and 2,6-dihydroxy derivatives **4** were the most active compounds. As for the effect of the substituent in the aniline moiety, chloro substitution increased antifungal activity. Only compound **4c** was more active than fluconazole against *Trichophyton mentagrophytes* (MIC = 1.95 μmol/L after 120 h).

The cyclization of compounds **1–4** to corresponding 3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones **5–8** results in a decrease of antifungal activity. Only compound **5c** retained activity against at least one strain, *Candida glabrata*. No antifungal activity was observed in thionated compounds **9c** and **10a–11d** (Table 2).

CONCLUSIONS

We have described a convenient microwave-assisted method for the synthesis of dihydroxy-*N*-phenylbenzamides **1–4**, which were transformed into hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones **5–8** by a reaction with methyl chloroformate. We have been successful in thionation of benzoxazines with a free hydroxyl group in position five only, *i.e.* derivatives **8a–d**. In the case of derivatives **5–7**, attempts to prepare dithioxo-analogs failed, both with the use of P_2S_5 and Lawesson's reagent. The prepared compounds showed only moderate antifungal activity in comparison with the standard fluconazole. Cyclization of dihydroxy-*N*-phenylbenzamides **1–4** to produce benzoxazines **5–8** markedly decreased the activity and transformation to mono- and dithionated analogs destroyed the activity.

Table 1

Physical and analytical data of compounds **1a–11d**.

Compound	R^1	R^2	Mp (°C)	Yield (%)	Molecular formula	Analysis % Calcd./Found			
						C	H	N	S
1a	3-OH	4-H	113–114	75	$C_{13}H_{11}NO_3$	68.11	4.84	6.11	–
						68.23	4.96	6.22	–
1b	3-OH	4-CH_3	161–163	81	$C_{14}H_{13}NO_3$	69.12	5.39	5.76	–
						69.31	5.52	5.88	–
1c	3-OH	4-Cl	137–139	69	$C_{13}H_{10}ClNO_3$	59.22	3.82	5.31	–
						59.41	3.96	5.36	–
1d	3-OH	4-OCH_3	129–130	77	$C_{14}H_{13}NO_4$	64.86	5.05	5.40	–
						64.98	5.20	5.44	–
2a	4-OH	4-H	132–134 [8,9]	66	$C_{13}H_{11}NO_3$	68.11	4.84	6.11	–
						68.26	5.02	6.19	–
2b	4-OH	4-CH_3	164–166 [9]	71	$C_{14}H_{13}NO_3$	69.12	5.39	5.76	–
						69.36	5.49	5.82	–
2c	4-OH	4-Cl	166–168	55	$C_{13}H_{10}ClNO_3$	59.22	3.82	5.31	–
						59.38	4.05	5.39	–
2d	4-OH	4-OCH_3	191–193 [9]	62	$C_{14}H_{13}NO_4$	64.86	5.05	5.40	–
						65.03	5.14	5.43	–
3a	5-OH	4-H	176–178 [10,11]	58	$C_{13}H_{11}NO_3$	68.11	4.84	6.11	–
						68.23	4.91	6.20	–
3b	5-OH	4-CH_3	208–210	71	$C_{14}H_{13}NO_3$	69.12	5.39	5.76	–
						69.01	5.66	5.87	–
3c	5-OH	4-Cl	204–207	59	$C_{13}H_{10}ClNO_3$	59.22	3.82	5.31	–
						59.15	3.94	5.38	–
3d	5-OH	4-OCH_3	113–114 [10]	63	$C_{14}H_{13}NO_4$	64.86	5.05	5.40	–
						64.95	5.18	5.38	–
4a	6-OH	4-H	195–197 [5b,12]	72	$C_{13}H_{11}NO_3$	68.11	4.84	6.11	–
						68.22	4.96	6.16	–
4b	6-OH	4-CH_3	201–203 [12]	76	$C_{14}H_{13}NO_3$	69.12	5.39	5.76	–
						68.88	5.51	5.81	–
4c	6-OH	4-Cl	225–228 [5a]	63	$C_{13}H_{10}ClNO_3$	59.22	3.82	5.31	–
						59.40	3.89	5.41	–
4d	6-OH	4-OCH_3	213–215 [12]	55	$C_{14}H_{13}NO_4$	64.86	5.05	5.40	–
						64.96	5.26	5.50	–
5a	8-OH	4-H	276–278.5	88	$C_{14}H_9NO_4$	65.88	3.55	5.49	–
						65.96	3.77	5.58	–
5b	8-OH	4-CH_3	243–245	91	$C_{15}H_{11}NO_4$	66.91	4.12	5.20	–
						67.09	4.22	5.22	–
5c	8-OH	4-Cl	255–257	90	$C_{14}H_8ClNO_4$	58.05	2.78	4.84	–
						57.87	2.91	4.84	–
5d	8-OH	4-OCH_3	245–247	89	$C_{15}H_{11}NO_5$	63.16	3.89	4.91	–
						63.29	4.11	4.88	–
6a	7-OH	4-H	283–286	81	$C_{14}H_9NO_4$	65.88	3.55	5.49	–
						65.59	3.62	5.49	–
6b	7-OH	4-CH_3	282–285	86	$C_{15}H_{11}NO_4$	66.91	4.12	5.20	–
						66.98	4.29	5.23	–
6c	7-OH	4-Cl	250–252	77	$C_{14}H_8ClNO_4$	58.05	2.78	4.84	–
						58.31	2.86	4.76	–
6d	7-OH	4-OCH_3	262–265	84	$C_{15}H_{11}NO_5$	63.16	3.89	4.91	–
						63.21	3.97	5.06	–
7a	6-OH	4-H	266–269	89	$C_{14}H_9NO_4$	65.88	3.55	5.49	–
						65.71	3.82	5.53	–
7b	6-OH	4-CH_3	269–272	87	$C_{15}H_{11}NO_4$	66.91	4.12	5.20	–
						66.59	4.24	5.23	–
7c	6-OH	4-Cl	233–235	83	$C_{14}H_8ClNO_4$	58.05	2.78	4.84	–
						57.81	2.75	4.84	–
7d	6-OH	4-OCH_3	275–278	90	$C_{15}H_{11}NO_5$	63.16	3.89	4.91	–
						62.91	3.98	4.84	–
8a	5-OH	4-H	172–173 [6]	87	$C_{14}H_9NO_4$	65.88	3.55	5.49	–
						65.95	3.76	5.63	–
8b	5-OH	4-CH_3	179–181 [6]	89	$C_{15}H_{11}NO_4$	66.91	4.12	5.20	–
						66.68	4.29	5.26	–

Table 1
(*Continued*)

Compound	R^1	R^2	Mp (°C)	Yield (%)	Molecular formula	Analysis % Calcd./Found C	H	N	S
8c	5-OH	4-Cl	232–234 [6]	93	$C_{14}H_8ClNO_4$	58.05	2.78	4.84	–
						57.89	3.09	4.86	–
8d	5-OH	4-OCH_3	212–214	85	$C_{15}H_{11}NO_5$	63.16	3.89	4.91	–
						63.20	4.04	5.07	–
9c	7-OH	4-Cl	258–261	5	$C_{14}H_8ClNO_3S$	55.00	2.64	4.58	10.49
						55.22	2.74	4.60	10.40
10a	5-OH	4-H	178–179	42	$C_{14}H_9NO_3S$	61.98	3.34	5.16	11.82
						62.02	3.46	5.09	12.20
10b	5-OH	4-CH_3	206–209	37	$C_{15}H_{11}NO_3S$	63.14	3.89	4.91	11.24
						63.05	4.09	4.65	11.51
10c	5-OH	4-Cl	218–220	39	$C_{14}H_8ClNO_3S$	55.00	2.64	4.58	10.49
						54.89	2.74	4.52	10.68
10d	5-OH	4-OCH_3	185–187	31	$C_{15}H_{11}NO_4S$	63.77	5.02	4.65	10.64
						63.81	5.12	4.53	10.89
11a	5-OH	4-H	192–193	32	$C_{14}H_9NO_2S_2$	58.52	3.16	4.87	22.32
						58.66	3.25	4.65	22.46
11b	5-OH	4-CH_3	179–180	24	$C_{15}H_{11}NO_2S_2$	59.78	3.68	4.65	21.28
						59.81	3.78	4.55	21.24
11c	5-OH	4-Cl	166–167	27	$C_{14}H_8ClNO_2S_2$	52.25	2.51	4.35	19.93
						52.16	2.55	4.35	20.21
11d	5-OH	4-OCH_3	150–152	33	$C_{15}H_{11}NO_3S_2$	56.77	3.49	4.41	20.20
						56.88	3.57	4.42	20.51

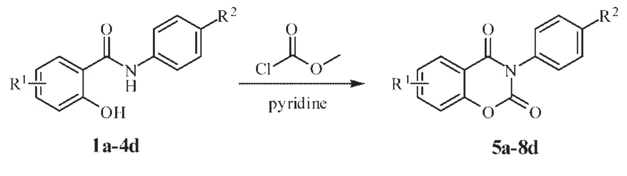
EXPERIMENTAL

The starting compounds were purchased from Sigma-Aldrich Company. Melting points were taken on a Büchi Melting Point B-545 apparatus and are uncorrected. IR spectra were taken on a Nicolet Impact 400 spectrometer in KBr pellets. The NMR spectra was recorded on a Varian Mercury-Vx BB 300 (300 MHz) and Bruker AC 250 (250 MHz). The samples were dissolved in hexadeuteriodimethyl sulfoxide (DMSO-d_6) or deuteriochloroform ($CDCl_3$). Chemical shifts were recorded as δ values, and were indirectly referenced to tetramethylsilane *via* the solvent signal. The elemental analyses were performed with a Perkin-Elmer 2400 CHNS/O analyzer. Microwave experiment was performed on a Millestone-MicroSYNTH (MLS ETHOS 1600 URM) instrument at 600 W output power. Column chromatography was carried out on silica gel 60 from E. Merck and purifications were monitored by TLC (UV detection) on aluminum sheets coated with silica gel 60 F_{254} (Merck).

General method for preparation of dihydroxy-*N*-phenylbenzamides (1a–4d) *via* microwave irradiation. A mixture of dihydroxybenzoic acid (3.08 g, 20 mmol) and respective aniline (30 mmol) in chlorobenzene (120 mL) was stirred. PCl_3 (0.87 mL, 10 mmol) was added, and the mixture was stirred and irradiated in a microwave reactor at 600 W for 20 min. The mixture was than cooled to room temperature and evaporated at reduced pressure. The crude product was purified by chromatography on a silica-gel column using acetone-hexane (1:5). The product was recrystallized from an ethanol/water mixture. For details see Table 1.

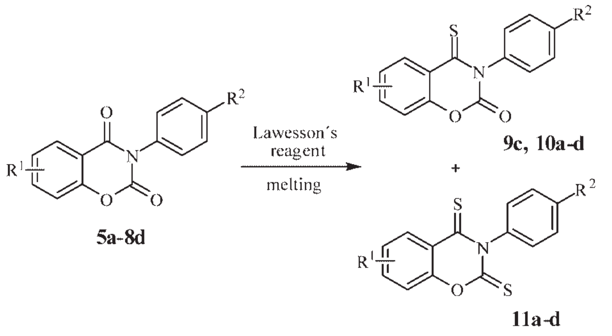
General method for preparation of hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones (5a–8d). Methyl chloroformate (0.5 mL, 6 mmol) was added dropwise to a stirred solution of dihydroxy-*N*-phenylbenzamide 1a–4d (5 mmol) in dry pyridine (40 mL) at 0°C. The mixture was heated on an oil bath for 2 h. After 10–h stirring at room temperature, the pH of the reaction mixture was adjusted to pH ≈ 6 (HCl aq., 5%). The resulting white heterogeneous mixture was cooled to obtain crystalline compound. The product was filtered off and recrystallized from ethanol. For details see Table 1.

Scheme 2



R^1 = OH; R^2 = H, CH_3, Cl, OCH_3

Scheme 3



R^1 = OH; R^2 = H, CH_3, Cl, OCH_3

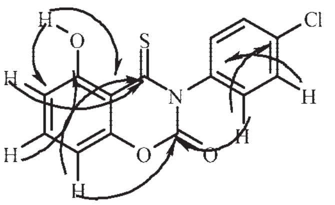


Figure 1. gHSCQ correlations present in **10c**.

Preparation of hydroxy-3-phenyl-4-thioxo-3,4-dihydro-2*H*-1,3-benzoxazin-2-ones (9c, 10a–d) and hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones (11a–d). 5-Hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dione **5a–8d** (4 mmol) was melted with Lawesson's reagent (4 mmol) for 4 min at 190–200°C. After cooling to room temperature, the melt was dissolved in chloroform, washed with aq. $NaHCO_3$ (5%, 1 × 100 mL), water (1 × 100 mL) and the solvent was evaporated under reduced pressure. Column chromatography on silica gel using toluene-hexane (1:1) was performed to obtain 3-(4-chlorophenyl)-7-hydroxy-4-thioxo-3,4-dihydro-2*H*-1,3-benzoxazin-2-one (**9c**), 5-hydroxy-3-phenyl-4-thioxo-3,4-dihydro-2*H*-1,3-benzoxazin-2-ones **10a–d** (lower R_f) and 5-hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones **11a–d** (higher R_f) as orange-yellow solids. For details see Table 1.

***In vitro* antifungal susceptibility testing.** The broth microdilution test M27-A [17] was used for the assessment of *in vitro* antifungal activity of the synthesized compounds against *Candida albicans* ATCC 44859 (CA), *Candida tropicalis* 156 (CT), *Candida krusei* E28 (CK), *Candida glabrata* 20/I (CG), *Trichosporon asahii* 1188 (TA), *Trichophyton mentagrophytes* 445 (TM), *Aspergillus fumigatus* 231 (AF), and *Absidia corymbifera* 272 (AC). Fluconazole was used as the reference drug. The procedure was performed with two-fold dilution of the compounds in RPMI 1640 medium (Sevapharma, Prague, Czech Republic) buffered to pH 7.0 with 0.165 *M* of 3-morpholinopropane-1-sulfonic acid. Drug-free controls were included. The minimum inhibitory concentrations (MICs) were defined as 80% (IC_{80}) and higher reduction of growth in comparison with control. The values of MICs were determined after 24 h and 48 h of static incubation at 35°C. For *T. mentagrophytes*, the final MICs were determined after 72 h and 120 h of incubation. The results for selected substances are summarized in Table 2.

2,3-Dihydroxy*-N-*phenylbenzamide (1a). IR (KBr): CO 1642 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 6.78 (t, *J* = 7.8 Hz, 1 H, *H-5*), 6.99 (dd, *J* = 1.5 Hz, *J* = 7.8 Hz, 1 H, *H-4*), 7.12–7.18 (m, 1 H, *H-4′*), 7.34–7.40 (m, 2 H, *H-3′*, *H-5′*), 7.45 (dd, *J* = 1.5 Hz, *J* = 7.8 Hz, 1 H, *H-6*), 7.67–7.72 (m, 2 H, *H-2′*, *H-6′*), 9.43 (bs, 1 H, *OH*), 10.36 (bs, 1 H, *NH*), 11.69 (bs, 1 H, O*H*); ^{13}C (75 MHz, DMSO): δ 117.2, 118.6, 118.7, 119.2, 121.5, 124.6, 128.9, 138.2, 146.4, 148.6, 168.0.

2,3-Dihydroxy*-N-*(4-methylphenyl)benzamide (1b). IR (KBr): CO 1653 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 2.26 (s, 3 H, *CH_3*), 6.40 (t, *J* = 2.1 Hz, 1 H, *H-5*), 6.76 (d, *J* = 2.1 Hz, 2 H, *H-4*, *H-6*), 7.08–7.15 (m, 2 H, *H-3′*, *H-5′*), 7.59–7.66 (m, 2 H, *H-2′*, *H-6′*), 9.56 (bs, 2 H, *OH*), 10.00 (bs, 1 H, *NH*); ^{13}C NMR (75 MHz, DMSO): δ 20.7, 117.1, 118.3, 119.1, 119.5, 120.9, 124.7, 128.3, 138.7, 146.6, 148.9, 168.5.

N-*(4-Chlorophenyl)-2,3-dihydroxybenzamide (1c).* IR (KBr): CO 1647 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 6.78 (t, *J* = 7.8 Hz, 1 H, *H-5*), 6.98 (dd, *J* = 1.5 Hz, *J* = 7.8 Hz, 1 H, *H-4*), 7.39 (d, *J* = 1.5 Hz, 1 H, *H-6*), 7.40–7.46 (m, 2 H, *H-3′*, *H-5′*), 7.70–7.77 (m, 2 H, *H-2′*, *H-6′*), 9.46 (bs, 1 H, *OH*), 10.43 (bs, 1 H, *NH*), 11.46 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 117.5, 118.6, 118.7, 119.2, 122.9, 128.1, 128.8, 137.3, 146.4, 148.3, 167.9.

2,3-Dihydroxy*-N-*(4-methoxyphenyl)benzamide (1d). IR (KBr): CO 1640 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 3.75 (s, 3 H, *OCH_3*), 6.76 (t, *J* = 8.1 Hz, 1 H, *H-5*), 6.91–6.98 (m, 2 H, *H-3′*, *H-5′*), 6.98 (d, *J* = 1.5 Hz, 1 H, *H-4*), 7.45 (dd, *J* = 1.5 Hz, *J* = 8.1 Hz, 1 H, *H-6*), 7.54–7.61 (m, 2 H, *H-2′*, *H-6′*), 9.35 (bs, 1 H, *OH*), 10.25 (bs, 1 H, *NH*), 11.93 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 55.4, 114.0, 116.6, 118.2, 118.5, 119.2, 123.4, 131.0, 146.4, 149.1, 156.3, 168.0.

Table 2

In vitro antifungal activity (MIC, μmol/L) of the selected compounds compared with standard fluconazole.

Comp.	CA 24 h/48 h	CT 24 h/48 h	CK 24 h/48 h	CG 24 h/48 h	TA 24 h/48 h	AF 24 h/48 h	AC 24 h/48 h	TM 72 h/120 h
1a	15.63/62.5	7.81/15.63	62.5/62.5	7.81/15.63	62.5/125	62.5/250	125/125	31.25/31.25
1b	31.25/62.5	7.81/15.62	31.25/62.5	7.8/15.62	62.5/125	125/125	62.5/62.5	31.25/31.25
1c	7.81/31.25	3.91/7.81	15.63/31.25	3.91/7.81	31.25/62.5	31.25/62.5	62.5/31.25	7.81/15.63
1d	31.25/62.5	62.5/62.5	31.25/62.5	62.5/62.5	31.25/62.5	62.5/250	15.62/15.62	31.25/31.25
2c	62.5/125	250/250	250/250	250/250	250/250	125/250	250/250	31.25/62.5
3c	31.25/62.5	125/125	125/250	125/250	250/250	125/250	125/250	31.25/31.25
4a	250/250	250/250	125/250	125/250	62.5/250	62.5/250	125/250	31.25/31.25
4b	15.63/31.25	62.5/62.5	31.25/31.25	62.5/62.5	31.25/62.5	31.25/62.5	62.5/62.5	7.81/15.63
4c	3.91/7.81	15.63/31.25	7.81/7.81	15.63/31.25	7.81/15.63	15.63/31.25	31.25/62.5	1.95/1.95
5b	125/125	125/250	125/125	15.62/31.25	62.5/125	125/250	125/125	31.25/31.25
5c	15.62/31.25	31.25/62.5	31.25/31.25	3.91/3.91	31.25/62.5	62.5/125	15.62/31.25	62.5/62.5
8b	125/125	125/125	125/125	250/250	62.5/125	62.5/125	125/125	31.25/31.25
8c	125/>125	>125/>125	>125/>125	>125/>125	7.81/15.63	>125/>125	>125/>125	7.81/7.81
11c	>125/>125	>125/>125	>125/>125	>125/>125	>125/>125	>125/>125	>125/>125	15.62/31.25
FLU	0.06/0.12	0.12/>125	3.91/15.62	0.98/3.91	0.24/0.48	>125/>125	>125/>125	1.95/3.91

CA, *Candida albicans* ATCC 44859; CT, *Candida tropicalis* 156; CK, *Candida krusei* E28; CG, *Candida glabrata* 20/I; TA, *Trichosporon asahii* 1188; AF, *Aspergillus fumigatus* 231; AC, *Absidia corymbifera* 272; TM, *Trichophyton mentagrophytes* 445.

2,4-Dihydroxy-N-phenylbenzamide (2a). IR (KBr): CO 1635 cm^{-1}; ^{1}H NMR (75 MHz, DMSO): δ 6.34 (d, $J = 2.4$ Hz, 1 H, *H-3*), 6.39 (dd, $J = 2.4$ Hz, $J = 8.7$ Hz, 1 H, *H-5*), 7.08–7.15 (m, 1 H, *H-4′*), 7.31–7.39 (m, 2 H, *H-3′*, *H-5′*), 7.64–7.70 (m, 2 H, *H-2′*, *H-6′*), 7.90 (d, $J = 8.7$ Hz, 1 H, *H-6*), 10.15 (bs, 1 H, *OH*), 10.20 (bs, 1 H, *OH*), 12.28 (bs, 1 H, *NH*); ^{13}C NMR (75 MHz, DMSO): δ 103.1, 107.7, 108.0, 121.4, 124.2, 128.9, 130.6, 138.4, 161.9, 162.8, 167.5.

2,4-dihydroxy-N-(4-methylphenyl)benzamide (2b). IR (KBr): CO 1636 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 2.27 (s, 3 H, CH_3), 6.31 (d, $J = 2.1$ Hz, 1 H, *H-3*), 6.36 (dd, $J = 2.1$ Hz, $J = 8.7$ Hz, 1 H, *H-5*), 7.12–7.20 (m, 2 H, *H-3′ H-5′*) 7.51–7.57 (m, 2 H, *H-2′*, *H-6′*), 7.88 (d, $J = 8.7$ Hz, 1 H, *H-6*), 10.01 (bs, 1 H, *NH*), 10.17 (bs, 1 H, *OH*), 12.36 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 20.7, 103.1, 107.6, 107.8, 121.5, 129.3, 130.4, 133.3, 135.8, 162.0, 162.7, 167.5.

N-(4-Chlorophenyl)-2,4-dihydroxybenzamide (2c). IR (KBr): CO 1647 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 6.33 (d, $J = 2.1$ Hz, 1 H, *H-3*), 6.38 (dd, $J = 2.1$ Hz, $J = 8.8$ Hz, 1 H, *H-5*), 7.36–7.43 (m, 2 H, *H-3′ H-5′*), 7.69–7.75 (m, 2 H, *H-2′*, *H-6′*), 7.87 (d, $J = 8.8$ Hz, 1 H, *H-6*), 10.23 (bs, 2 H, *OH*), 12.14 (bs, 1 H, *NH*); ^{13}C NMR (75 MHz, DMSO): δ 103.0, 107.8, 108.0, 122.8, 127.8, 128.8, 130.7, 137.5, 161.7, 162.8, 167.5.

2,4-Dihydroxy-N-(4-methoxyphenyl)benzamide (2d). IR (KBr): CO 1640 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 3.74 (s, 3 H, OCH_3), 6.31 (d, $J = 2.4$ Hz, 1 H, *H-3*), 6.37 (dd, $J = 2.4$ Hz, $J = 8.7$ Hz, 1 H, *H-5*), 6.90–6.96 (m, 2 H, *H-3′*, *H-5′*), 7.52–7.58 (m, 2 H, *H-2′*, *H-6′*), 7.89 (d, $J = 8.7$ Hz, 1 H, *H-6*), 10.04 (bs, 1 H, *OH*), 10.17 (bs, 1 H, *OH*), 12.47 (bs, 1 H, *NH*); ^{13}C NMR (75 MHz, DMSO): δ 55.4, 103.1, 107.5, 107.6, 114.0, 123.1, 130.1, 13102, 156.1, 162.3, 162.7, 167.6.

2,5-Dihydroxy-N-phenylbenzamide (3a). IR (KBr): CO 1635 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 7.02 (d, $J = 8.7$ Hz, 1 H, *H-3*), 7.10–7.17 (m, 1 H, *H-4′*), 7.22 (dd,1 H, $J = 2.7$ Hz, $J = 8.7$ Hz, *H-4*), 7.34-7.41 (m, 2 H, *H-3′*, *H-5′*), 7.67–7.74 (m, 3 H, *H-6*, *H-2′*, *H-6′*), 9.78 (bs, 1 H, *OH*), 10.40 (bs, 1 H, *NH*), 11.79 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 118.1, 118.3, 121.0, 122.0, 124.5, 127.4, 129.0, 138.3, 142.6, 155.6, 169.7.

2,5-Dihydroxy-N-(4-methylphenyl)benzamide (3b). IR (KBr): CO 1636 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 2.27 (s, 3 H, CH_3), 6.80 (d, $J = 8.7$ Hz, 1 H, *H-3*), 6.87 (dd, $J = 3.0$ Hz, $J = 8.7$ Hz, 1 H, *H-4*), 7.12–7.17 (m, 2 H, *H-3′*, *H-5′*), 7.36 (d, $J = 3.0$ Hz, 1 H, *H-6*), 7.54–7.59 (m, 2 H, *H-2′*, *H-6′*), 9.10 (bs, 1 H, *OH*), 10.32 (bs, 1 H, *NH*), 11.10 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 20.7, 114.7, 118.0, 118.1, 120.9, 121.3, 129.4, 133.3, 136.0, 149.9, 150.9, 166.0.

N-(4-Chlorophenyl)-2,5-dihydroxybenzamide (3c). IR (KBr): CO 1635 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 6.82 (d, $J = 8.7$ Hz, 1 H, *H-3*), 6.88 (dd, $J = 2.7$ Hz, $J = 9.0$ Hz, 1 H, *H-4*), 7.33 (d, $J = 2.7$ Hz, 1 H, *H-6*), 7.36–7.44 (m, 2 H, *H-3′*, *H-5′*), 7.71–7.78 (m, 2 H, *H-2′ H-6′*), 9.14 (bs, 1 H, *OH*), 10.48 (bs, 1 H, *NH*), 10.95 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 114.8, 118.1, 118.3, 121.4, 122.3, 127.8, 128.9, 137.6, 149.9, 150.6, 166.1.

2,5-Dihydroxy-N-(4-methoxyphenyl)benzamide (3d). IR (KBr): CO 1637 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 3.75 (s, 3 H, OCH_3), 6.81 (d, $J = 8.7$ Hz, 1 H, *H-3*), 6.89 (dd, $J = 2.7$ Hz, $J = 8.7$ Hz, 1 H, *H-4*), 6.91–6.96 (m, 2 H, *H-3′ H-5′*), 7.38 (d, $J = 2.7$ Hz, 1 H, *H-6*),7.56–7.62 (m, 2 H, *H-2′*, *H-6′*), 9.09 (bs, 1 H, *OH*), 10.28 (bs, 1 H, *NH*), 11.19 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 55.4, 114.1, 114.5, 117.7, 118.0, 121.3, 122.7, 131.5, 149.8, 151.2, 156.1, 166.1.

2,6-Dihydroxy-N-phenylbenzamide (4a). IR (KBr): CO 1654 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 6.41 (d, $J = 8.4$ Hz, 2 H, *H-3*, *H-5*), 7.10–7.15 (m, 1 H, *H-4′* 7.19 (t, $J = 8.4$ Hz, 1 H, *H-4*), 7.32–7.38 (m, 2 H, *H-3′*, *H-5′*), 7.61–7.65 (m, 2 H, *H-2′*, *H-6′*), 10.73 (bs, 1 H, *NH*), 12.24 (bs, 2 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 104.3, 107.6, 121.2, 124.7, 129.2, 133.8, 13.7, 159.8, 168.3.

2,6-Dihydroxy-N-(4-methylphenyl)benzamide (4b). IR (KBr): CO 1651 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 2.28 (s, 3 H, CH_3), 6.43 (d, $J = 8.4$ Hz, 2 H, *H-3*, *H-5*), 7.16–7.22 (m, 3 H, *H-4*, *H-3′*, *H-5′*), 7.50–7.56 (m, 2 H, *H-2′*, *H-6′*), 10.69 (bs, 1 H, *NH*), 12.34 (bs, 2 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 20.7, 104.1, 107.6, 121.2, 129.5, 133.8, 133.9, 135.1, 159.9, 168.3.

N-(4-Chlorophenyl)-2,6-dihydroxybenzamide (4c). IR (KBr): CO 1648 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 6.42 (d, $J = 8.1$ Hz, 2 H, *H-3*, *H-5*), 7.19 (t, $J = 8.1$ Hz, 1 H, *H-4*), 7.39–7.45 (m, 2 H, *H-3′*, *H-5′*), 7.66–7.72 (m, 2 H, *H-2′ H-6′*), 10.74 (bs, 1 H, *NH*), 11.97 (bs, 2 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 105.1, 107.5, 122.6, 128.2, 129.0, 133.7, 136.8, 159.5, 168.1.

2,6-Dihydroxy-N-(4-methoxyphenyl)benzamide (4d). IR (KBr): CO 1652 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 3.75 (s, 3 H, OCH_3), 6.42 (d, $J = 8.1$ Hz, 2 H, *H-3*, *H-5*), 6.90–6.97 (m, 2 H, *H-3′*, *H-5′*), 7.20 (t, $J = 8.1$ Hz, 1 H, *H-4*), 7.52–7.58 (m, 2 H, *H-2′*, *H-6′*), 10.63 (bs, 1 H, *NH*), 12.40 (bs, 2 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 55.4, 103.8, 107.6, 114.2, 122.9, 130,5, 133.8, 156.4, 160.0, 168.1.

8-Hydroxy-3-phenyl-2H-1,3-benzoxazine-2,4(3H)-dione (5a). IR (KBr): CO 1785, 1676 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 7.24 (t, $J = 7.8$ Hz, 1 H, *H-6*), 7.31 (dd, $J = 1.8$ Hz, $J = 7.8$ Hz, 1 H, *H-7*), 7.40 (dd, $J = 1.8$ Hz, $J = 7.8$ Hz, 1 H, *H-5*), 7.42–7.54 (m, 5 H, *H-2′*, *H-3′*, *H-4′*, *H-5′*, *H-6′*), 10.54 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 116.1, 116.9, 122.2, 125.4, 128.8, 129.2, 135.6, 141.7, 145.2, 147.7, 161.1.

8-Hydroxy-3-(4-methylphenyl)-2H-1,3-benzoxazine-2,4(3H)-dione (5b). IR (KBr): CO 1753, 1701 cm^{-1}; ^{1}H NMR (250 MHz, DMSO): δ 2.37 (s, 3 H, CH_3), 7.23 (t, $J = 7.5$ Hz, 1 H, *H-6*), 7.25–7.34 (m, 5 H, *H-7*, *H-2′*, *H-3′*, *H-5′*, *H-6′*), 7.39 (dd, $J = 1.8$ Hz, $J = 7.5$ Hz, 1 H, *H-5*), 10.49 (bs, 1 H, *OH*); ^{13}C NMR (63 MHz, DMSO): δ 20.5, 115.5, 116.5, 121.8, 124.9, 128.0, 129.2, 132.4, 137.9, 141.2, 144.7, 147.3, 160.7.

3-(4-Chlorophenyl)-8-hydroxy-2H-1,3-benzoxazine-2,4(3H)-dione (5c). IR (KBr): CO 1742, 1699 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 7.24 (t, $J = 7.8$ Hz, 1 H, *H-6*), 7.30 (dd, $J = 1.8$ Hz, $J = 7.8$ Hz, 1 H, *H-7*), 7.39 (dd, $J = 1.8$ Hz, $J = 7.8$ Hz, 1 H, *H-5*), 7.44–7.50 (m, 2 H, *H-3′*, *H-5′*), 7.54–7.61 (m, 2 H, *H-2′*, *H-6′*), 10.55 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 116.0, 116.9, 122.3, 125.4, 129.3, 130.8, 133.5, 134.5, 141.6, 145.2, 147.6, 161.1.

8-Hydroxy-3-(4-methoxyphenyl)-2H-1,3-benzoxazine-2,4(3H)-dione (5d). IR (KBr): CO 1766, 1704 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 3.81 (s, 3 H, OCH_3), 7.00–7.07 (m, 2 H, *H-3′*, *H-5′*), 7.23 (t, $J = 7.8$ Hz, 1 H, *H-6*), 7.27–7.36 (m, 3 H, *H-7*, *H-2′*, *H-6′*), 7.39 (dd, $J = 1.8$ Hz, $J = 7.8$ Hz, 1 H, *H-5*), 10.48 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 55.6, 114.4, 116.1, 116.9, 122.1, 125.3, 128.0, 129.9, 141.6, 145.2, 147.9, 159.4, 161.3.

7-Hydroxy-3-phenyl-2H-1,3-benzoxazine-2,4(3H)-dione (6a). IR (KBr): CO 1770, 1699 cm^{-1}; ^{1}H NMR (300 MHz, DMSO):

δ 6.74 (d, J = 2.1 Hz, 1 H, *H-8*), 6.86 (dd, J = 2.1 Hz, J = 8.7 Hz, 1 H, *H-6*), 7.38-7.52 (m, 5 H, *H-2′*, *H-3′*, *H-4′*, *H-5′*, *H-6′*), 7.82 (d, J = 8.7 Hz, 1 H, *H-5*), 11.08 (bs, H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 101.9, 106.3, 114.1, 129.2, 129.5, 130.9, 133.4, 134.4, 148.0, 154.6, 160.3, 164.9.

7-Hydroxy-3-(4-methylphenyl)-2**H*****-1,3-benzoxazine-2,4(3*****H*****)-dione (6b).*** IR (KBr): CO 1771, 1698 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 2.37 (s, 3 H, CH_3), 6.73 (d, J = 2.1 Hz, 1 H, *H-8*), 6.85 (dd, J = 2.1 Hz, J = 8.7 Hz, 1 H, *H-6*), 7.23–7.31 (m, 4 H, *H-2′*, *H-3′*, *H-5′*, *H-6′*), 7.81 (d, J = 8.7 Hz, 1 H, *H-5*), 11.07 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 21.0, 101.8, 106.4, 114.0, 128.6, 129.5, 129.6, 132.8, 138.2, 148.3, 154.5, 160.4, 164.8.

3-(4-Chlorophenyl)-7-hydroxy-2H-1,3-benzoxazine-2,4(3H)-dione (6c). IR (KBr): CO 1766, 1703 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 6.74 (d, J = 2.1 Hz, 1 H, *H-8*), 6.86 (dd, J = 2.1 Hz, J = 8.5 Hz, 1 H, *H-6*), 7.41–7.47 (m, 2 H, *H-3′*, *H-5′*), 7.53–7.59 (m, 2 H, *H-2′ H-6′*), 7.81 (d, J = 8.5 Hz, 1 H, *H-5*), 11.10 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 101.9, 106.3, 114.1, 129.2, 129.5, 130.9, 133.4, 134.4, 148.0, 154.6, 160.3, 164.9.

7-Hydroxy-3-(4-methoxyphenyl)-2H-1,3-benzoxazine-2,4(3H)-dione (6d). IR (KBr): CO 1766, 1704 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 3.80 (s, 3 H, OCH_3), 6.73 (d, J = 2.1 Hz, 1 H, *H-8*), 6.85 (dd, J = 2.1 Hz, J = 8.7 Hz, 1 H, *H-6*), 6.99–7.05 (m, 2 H, *H-3′*, *H-5′*), 7.27-7.32 (m, 2 H, *H-2′*, *H-6′* 7.81 (d, J = 8.7 Hz, 1 H, *H-5*), 11.05 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 56.0, 102.3, 106.9, 114.5, 114.8, 128.5, 130.0, 130.4, 148.8, 155.0, 159.8, 161.0, 165.3.

6-Hydroxy-3-phenyl-2H-1,3-benzoxazine-2,4(3H)-dione (7a). IR (KBr): CO 1735, 1680 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 7.24 (dd, J = 2.4 Hz, J = 8.7 Hz, 1 H, *H-7*), 7.28 (d, J = 2.4 Hz, 1 H, *H-5*), 7.35 (d, J = 8.7 Hz, 1 H, *H-8*), 7.38–7.54 (m, 5 H, *H-2′*, *H-3′*, *H-4′*, *H-5′*, *H-6′*), 11.05 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 111.3, 115.4, 117.8, 124.2, 128.8, 129.2, 135.6, 145.8, 148.0, 154.7, 160.9.

6-Hydroxy-3-(4-methylphenyl)-2H-1,3-benzoxazine-2,4(3H)-dione (7b). IR (KBr): CO 1749, 1683 cm^{-1}; ^{1}H NMR (DMSO): δ 2.37 (s, 3 H, CH_3), 7.23 (dd, J = 3.0 Hz, J = 8.7 Hz, 1 H, *H-7*), 7.26–7.35 (m, 6 H, *H-5*, *H-8*, *H-2′*, *H-3′*, *H5′*, *H6′*), 10.04 (bs, 1 H, *OH*); ^{13}C NMR (DMSO): δ 21.0, 111.3, 115.4, 117.8, 124.2, 128.5, 129.7, 132.9, 138.3, 145.8, 148.0, 154.7, 160.9.

3-(4-Chlorophenyl)-6-hydroxy-2H-1,3-benzoxazine-2,4(3H)-dione (7c). IR (KBr): CO 1749, 1685 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 7.20–7.24 (m, 2 H, *H-5*, *H-7*), 7.34 (d, J = 8.3 Hz, 1 H, *H-8*), 7.42–7.47 (m, 2 H, *H-3′*, *H-5′*), 7.54–7.59 (m, 2 H, *H-2′*, *H-6′*), 10.15 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 110.8, 114.8, 117.4, 123.9, 128.8, 130.3, 133.1, 133.9, 145.3, 147.3, 154.2, 160.3.

6-Hydroxy-3-(4-methoxyphenyl)-2H-1,3-benzoxazine-2,4(3H)-dione (7d). IR (KBr): CO 1751, 1704 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 3.81 (s, 3 H, OCH_3), 7.00–7.06 (m, 2 H, *H-3′*, *H-5′*), 7.23 (dd, J = 2.7 Hz, J = 8.7 Hz,1 H, *H-7*), 7.27 (d, J = 2.7 Hz, 1 H, *H-5*), 7.28–7.35 (m, 3 H, *H-8*, *H-2′*, *H-6′*), 10.04 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 55.6, 111.3, 114.4, 115.4, 117.8, 124.2, 128.0, 129.8, 145.8, 148.2, 154.7, 159.4, 161.0.

5-Hydroxy-3-phenyl-2H-1,3-benzoxazine-2,4(3H)-dione (8a). IR (KBr): CO 1761, 1662 cm^{-1}; ^{1}H NMR (250 MHz, DMSO): δ 6.88 (d, J = 8.3 Hz, 1 H, *H-6*), 6.92 (d, J = 8.3 Hz, 1 H, *H-8*), 7.44–7.57 (m, 5 H, *H-2′*, *H-3′*, *H-4′*, *H-5′*, *H-6′*), 7.69 (t, J = 8.3 Hz, 1 H, *H-7*), 10.78 (bs, 1 H, *OH*); ^{13}C NMR (63 MHz, DMSO): δ 100.9, 105.9, 112.0, 128.2, 128.7, 128.8, 133.9, 136.9, 146.7, 152.3, 159.1, 164.3.

5-Hydroxy-3-(4-methylphenyl)-2H-1,3-benzoxazine-2,4(3H)-dione (8b). IR (KBr): CO 1752, 1667 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 2.38 (s, 3 H, CH_3), 6.88 (dd, J = 0.9 Hz, J = 8.3 Hz, 1 H, *H-6*), 6.93 (dd, J = 0.9 Hz, J = 8.3 Hz, 1 H, *H-8*), 7.29–7.35 (m, 4 H, *H-2′*, *H-3′*, *H-5′*, *H-6′*), 7.69 (t, J = 8.3 Hz, 1 H, *H-7*), 10.79 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, DMSO): δ 21.0, 101.5, 106.4, 112.5, 128.5, 129.8, 31.8, 137.4, 138.7, 147.3, 152.8, 159.7, 165.0.

3-(4-Chlorophenyl)-5-hydroxy-2H-1,3-benzoxazine-2,4(3H)-dione (8c). IR (KBr): CO 1757, 1666 cm^{-1}; ^{1}H NMR (250 MHz, DMSO): δ 6.84–6.95 (m, 2 H, *H-6*, *H-8*), 7.44–7.52 (m, 2 H, *H-3′ H-5′*), 7.54–7.62 (m, 2 H, *H-2′*, *H-6′*), 7.68 (t, J = 8.3 Hz, 1 H, *H-7*), 10.68 (bs, 1 H, *OH*); ^{13}C NMR (63 MHz, DMSO): δ 101.7, 106.7, 112.9, 129.6, 131.0, 133.5, 134.2, 137.7, 147.3, 153.0, 159.9, 164.9.

5-Hydroxy-3-(4-methoxyphenyl)-2H-1,3-benzoxazine-2,4(3H)-dione (8d). IR (KBr): CO 1765, 1679 cm^{-1}; ^{1}H NMR (DMSO): δ 3.81 (s, 3 H, OCH_3), 6.87 (dd, J = 0.9 Hz, J = 8.2 Hz, 1 H, *H-6*), 6.92 (dd, J = 0.9 Hz, J = 8.2 Hz, 1 H, *H-8*), 7.02–7.08 (m, 2 H, *H-3′*, *H-5′*), 7.33–7.39 (m, 2 H, *H-2′*, *H-6′*), 7.69 (t, J = 8.2 Hz, 1 H, *H-7*), 10.81 (bs, 1 H, *OH*); ^{13}C NMR (DMSO): δ 55.6, 101.5, 106.4, 112.4, 114.5, 126.8, 129.8, 137.4, 147.4, 152.8, 159.6, 159.7, 165.2.

3-(4-Chlorophenyl)-7-hydroxy-4-thioxo-3,4-dihydro-2H-1,3-benzoxazin-2-one (9c). IR (KBr): CO 1733 cm^{-1}; ^{1}H NMR (300 MHz, Me$_2$CO-d_6): δ 6.72 (d, J = 2.1 Hz, 1 H, *H-8*), 6.93 (dd, J = 2.1 Hz, J = 9.0 Hz, 1 H, *H-6*), 7.43–7.47 (m, 2 H, *H-3′*, *H-5′*), 7.53–7.57 (m, 2 H, *H-2′*, *H-6′*), 8.27(d, J = 9.0 Hz, 1 H, *H-5*), 10.10 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, Me$_2$CO-d_6): δ 102.0, 115.4, 129.8, 130.1, 130.3, 131.4, 134.6, 139.8, 145.6, 152.6, 165.7, 192.6.

5-Hydroxy-3-phenyl-4-thioxo-3,4-dihydro-2H-1,3-benzoxazin-2-one (10a). IR (KBr): CO 1759 cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$): δ 6.79 (dd, J = 1.0 Hz, J = 8.5 Hz, 1 H, *H-6*), 6.95 (dd, J = 1.0 Hz, J = 8.5 Hz, 1 H, *H-8*), 7.23–7.28 (m, 2 H, *H-2′* H-6′), 7.52–7.63 (m, 4 H, *H-3′*, *H-4′*, *H-5′*, *H-7*), 12.86 (bs, 1 H, *OH*); ^{13}C NMR (63 MHz, CDCl$_3$): δ 106.1, 107.8, 115.2, 128.1, 129.7, 130.1, 137.0, 137.4, 144.5, 149.6, 161.8, 192.5.

5-Hydroxy-3-(4-methylphenyl)-4-thioxo-3,4-dihydro-2H-1,3-benzoxazin-2-one (10b). IR (KBr): CO 1751 cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$): δ 2.46 (s, 3 H, CH_3), 6.78 (dd, J = 1.0 Hz, J = 8.4 Hz, 1 H, *H-6*), 6.94 (dd, J = 1.0 Hz, J = 8.4 Hz, 1 H, *H-8*), 7.08–7.17 (m, 2 H, *H-3′*, *H-5′*), 7.34–7.42 (m, 2 H, *H-2′*, *H-6′*), 7.55 (t, J = 8.4 Hz, 1 H, *H-7*), 12.89 (bs, 1 H, *OH*); ^{13}C NMR (63 MHz, CDCl$_3$): δ 21.4, 106.1, 107.8, 115.2, 127.7, 130.8, 134.8, 136.9, 139.9, 144.5, 149.6, 161.8, 192.6.

3-(4-Chlorophenyl)-5-hydroxy-4-thioxo-3,4-dihydro-2H-1,3-benzoxazin-2-one (10c). IR (KBr): CO 1752 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.79 (dd, J = 1.2 Hz, J = 8.5 Hz, 1 H, *H-6*), 6.95 (dd, J = 1.2 Hz, J = 8.5 Hz, 1 H, *H-8*), 7.16–7.21 (m, 2 H, *H-2′ H-6′*), 7.51–7.60 (m, 3 H, *H-7*, *H-3′*, *H-5′*), 12.76 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, CDCl$_3$): δ 106.1, 107.7, 115.3, 129.6, 130.4, 135.7, 135.8, 137.2, 144.3, 149.5, 161.8, 192.2.

5-Hydroxy-3-(4-methoxyphenyl)-4-thioxo-3,4-dihydro-2H-1,3-benzoxazin-2-one (10d). IR (KBr): CO 1766 cm^{-1}; ^{1}H NMR

(300 MHz, $CDCl_3$): δ 3.87 (s, 3 H, *OCH_3*), 6.78 (dd, *J* = 1.2 Hz, *J* = 8.5 Hz, 1 H, *H-6*), 6.94 (dd, *J* = 1.2 Hz, *J* = 8.5 Hz, 1 H, *H-8*), 7.02–7.09 (m, 2 H, *H-3′*, *H-5′*), 7.12–7.19 (m, 2 H, *H-2′*, *H-6′*), 7.55 (t, *J* = 8.5 Hz, 1 H, *H-7*), 12.90 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.5, 106.0, 107.8, 115.1, 115.3, 129.1, 129.8, 136.9, 144.7, 149.5, 160.2, 161.7, 192.8.

5-Hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dithione (11a). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.85 (dd, *J* = 1.2 Hz, *J* = 8.4 Hz, 1 H, *H-6*), 6.94 (dd, *J* = 1.2 Hz, *J* = 8.4 Hz, 1 H, *H-8*), 7.19–7.23 (m, 2 H, *H-2′*, *H-6′*), 7.49–7.62 (m, 4 H, *H-7*, *H-3′ H-4′*, *H-5′*), 12.74 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 105.7, 109.2, 115.4, 128.1, 129.4, 130.2, 137.5, 141.5, 149.9, 161.6, 177.0, 187.9.

5-Hydroxy-3-(4-methylphenyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-dithione (11b). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.46 (s, 3 H, *CH_3*), 6.84 (dd, *J* = 0.9 Hz, *J* = 8.1 Hz, 1 H, *H-6*), 6.95 (dd, *J* = 0.9 Hz, *J* = 8.1 Hz, 1 H, *H-8*), 7.06–7.11 (m, 2 H, *H-3′*, *H-5′*), 7.35–7.40 (m, 2 H, *H-2′*, *H-6′*), 7.58 (t, *J* = 8.1 Hz, 1 H, *H-7*), 12.76 (s, 1 H, *OH*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4, 105.7, 109.2, 115.4, 127.7, 130.9, 137.4, 139.0, 139.7, 149.9, 161.6, 177.2, 188.0.

3-(4-Chlorophenyl)-5-hydroxy-2*H*-1,3-benzoxazine-2,4(3*H*)-dithione (11c). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.84 (dd, *J* = 1.0 Hz, *J* = 8.3 Hz, 1 H, *H-6*), 6.95 (dd, *J* = 1.0 Hz, *J* = 8.3 Hz, 1 H, *H-8*), 7.11–7.20 (m, 2 H, *H-2′*, *H-6′*), 7.48–7.57 (m, 2 H, *H-3′*, *H-5′*), 7.59 (t, *J* = 8.3 Hz, 1 H, *H-7*), 16.64 (s, 1 H, *OH*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 105.8, 109.2, 115.6, 129.7, 130.6, 135.5, 137.6, 139.9, 149.9, 161.7, 176.8, 188.8.

5-Hydroxy-3-(4-methoxyphenyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-dithione (11d). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.88 (s, 3 H, *OCH_3*), 6.83 (dd, *J* = 1.2 Hz, *J* = 8.3 Hz, 1 H, *H-6*), 6.94 (dd, *J* = 1.2 Hz, *J* = 8.3 Hz, 1 H, *H-8*), 7.03–7.14 (m, 4 H, *H-2′*, *H-3′*, *H-5′*, *H-6′*), 7.58 (t, *J* = 8.3 Hz, 1 H, *H-7*), 12.78 (bs, 1 H, *OH*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.4, 105.7, 109.2, 115.3, 115.4, 129.1, 134.2, 137.4, 149.9, 160.0, 161.5, 177.4, 188.2.

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Highly Soluble Perylene Tetracarboxylic Diimides (PDI)-Tetrathiafulvalene (TTF) Dyad and TTF-PDI-TTF Triad

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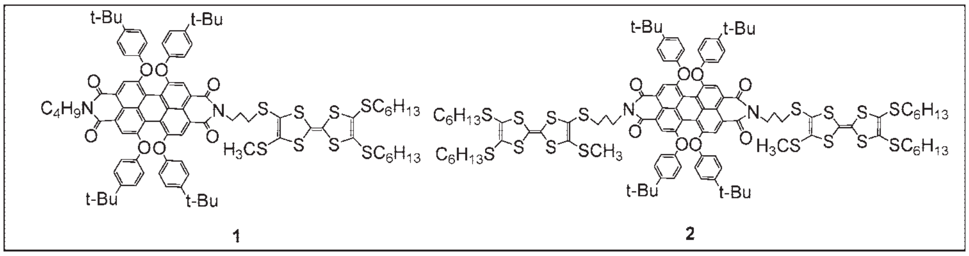

Two highly soluble donor-σ-acceptor and donor-σ-accepter-σ-donor type fluorescence switches consisting tetrathiafulvalene (TTF) and 3,4,9,10-perylene tetracarboxylic diimides (PDI) were synthesized. The structure of the dyad and triad as well as their intermediates was characterized by ^{1}H NMR, ^{13}C NMR MS, elemental analysis. Their fluorescence behavior could be modulated by oxidization and reduction of the TTF unit using either chemical or electrochemical method.

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INTRODUCTION

Perylene diimide (PDI) [1–7] has been used in donor-acceptor supramolecules due to their optical, redox, and stability properties. Tetrathiafulvalene (TTF) and its derivatives [8–11] are well known for their π-electron-donor properties. They have been extensively investigated as building blocks in electrical conductors and superconductors [12]. Some electron donor–acceptor supramolecules with TTF units have been prepared for studies related to intramolecular photoinduced electron transfer processes, intramolecular charge-transfer (ICT) interactions and construction of molecular rectifiers [13–16].

However, the research of PDI-TTF type donor-acceptor system was confined because of the poor solubility of perylene diimide (PDI). Thus, we interested in the introduction of tetra-substituent tetra-butylphenoxy group to the bay region of PDIs to improve its solubility. In this article, electron donor-σ-acceptor dyad **1** and donor-σ-acceptor-σ-donor triad **2** containing PDI and TTF unit were synthesized and characterized (Scheme 1). The TTF unit is linked to PDI unit and the PDI unit is modified by *tert*-butylphenol to increase its solubility. TTF-type compounds are able to exist in three different stable redox states (TTF, TTF$^{\bullet+}$, TTF^{2+}). Therefore, the donating ability of TTF could be tuned by either chemical or electrochemical reversible redox reactions. And the optical absorption, fluorescent spectra, chemical, and electrochemical methods shows that two novel fluorescence switches were established.

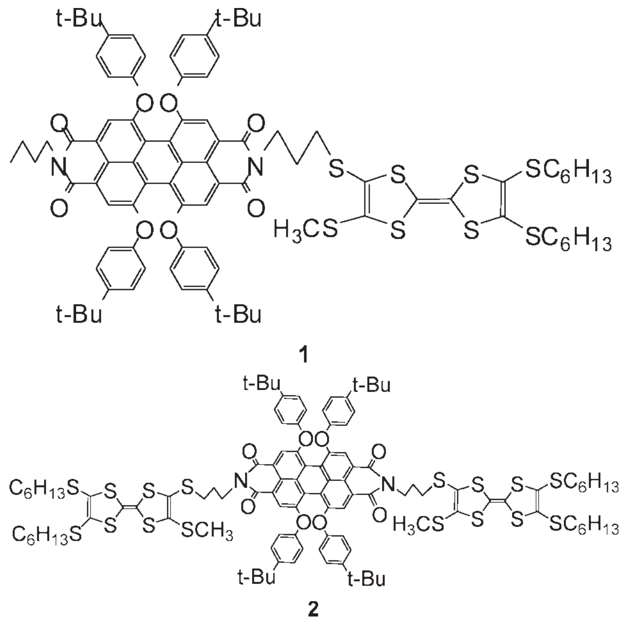
RESULTS AND DISCUSSION

The target compound **1** and **2** were synthesized starting from *N*-hexyl-1,6,7,12-tetra(4-*tert*-butylphenoxy)-perylene-3,4-anhydride-9,10-tetracarboxylicimide (**4**) and 1,6,7,12-tetrakis(4-*tert*-butylphenoxy)-3,4,9,10-perylene-tetracarboxy-anhydride (**5**) (Scheme 2).

Compounds **4**, **5**, and **6** were prepared by method previously reported [17–20]. The amino TTF **7** was synthesized through ammonization of TTF **6** with the presence of $LiAlH_4$ in THF. The reaction of compound **4** and amino TTF **7** led to dyad **1** (yield, 45%). The way to get compound **2** was just like the reaction to get compound **1**. Amino TTF **7**, compound **6** together with imidazole were heated to 175–180°C for 48 h, and compound **2** was finally achieved with a yield of 40% after column chromatography on silica gel (CH_2Cl_2: ethyl acetate = 1:1).

With tetrasubstitutions of p-t-butylphenoxy at the bay region, compound **1** and **2** were highly soluble in common organic solvents like CH_2Cl_2, $CHCl_3$, ethyl acetate, acetone, DMF, toluene, pyridine, and acetonitrile, slightly soluble in methanol, and insoluble in hexane and petroleum ether. The UV-vis spectra of dyad **1** and triad **2** were measured in CH_2Cl_2 (1.0×10^{-5} M) with CARY 100 Conc UV-vis spectrophotometer (Fig. 1).

Scheme 1. Structure of dyad **1** and triad **2**.



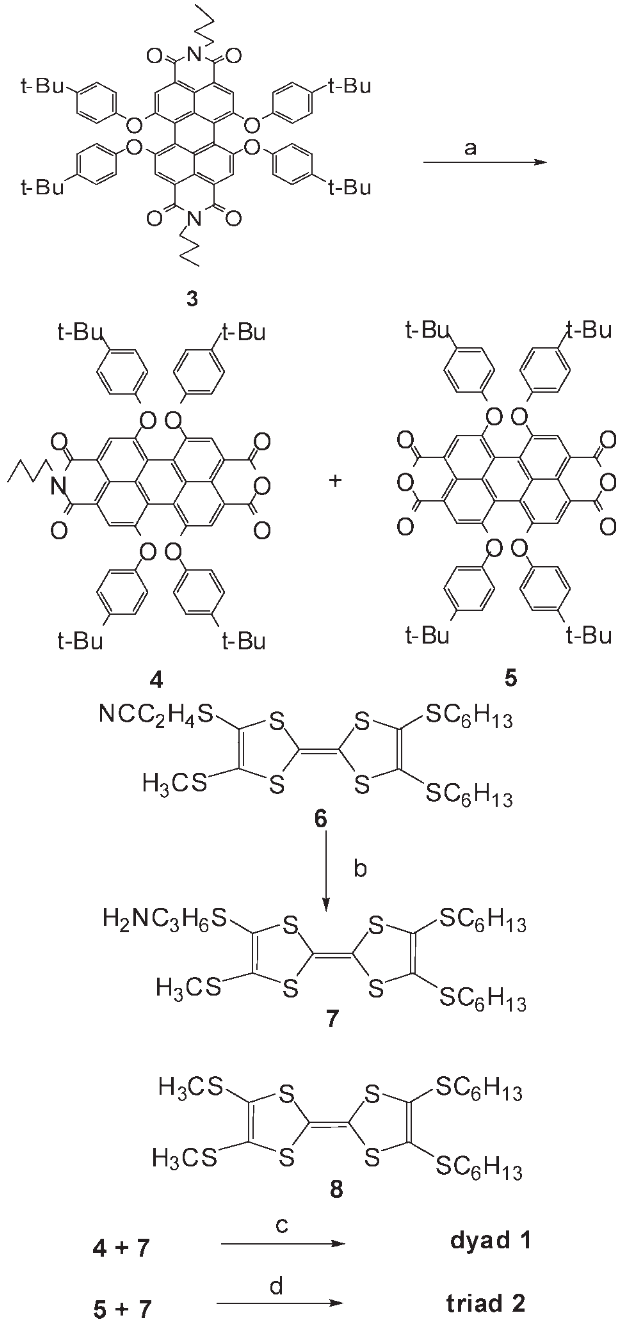
For comparison, the UV-vis spectra of model compound **3** and **8** (1.0×10^{-5} M in CH_2Cl_2) were also given. Their spectral data were listed in Table 1.

The absorption spectra of **1**, **2**, **3** showed a wide absorption between 300 and 650 nm with identical absorption maximum at about 451, 537, 577 nm. Compared with PDI **3**, compound **1** and **2** have a new band at about 331 nm which is coincide with the absorption of TTF **8**. The UV-vis absorption spectra of **1** and **2** were almost summation of the spectra of donor **8** and acceptor **3** and no new band or unique spectroscopic shoulder was observed, this implying neglectable ground state electronic interaction between perylene diimide and TTF unit.

The electrochemical characterization of **1**, **2** and reference compounds **3**, **8** were tested by cyclic voltammetry (CV) and their voltammetric data were listed in Table 2. All the experiments were performed in dichloromethane, using *n*-Bu_4NPF_6 (10^{-1} M) as the supporting electrolyte, platinum as the working and counter electrodes, and Ag/AgCl as the reference electrode; the scan rate was 50 mV s^{-1}. Dyad **1** and triad **2** show almost the same reduction potentials at about −0.90 and −0.60 V, which were ascribed to the successive formation of the anion radical PDI^- and dianion PDI^{2-}. In positive direction, **1** and **2** exhibited two one-electron reversible oxidation waves at about +0.58, +0.91, and +1.37 V, corresponding to the successive generation of the cation radical $TTF^{\bullet+}$, dication TTF^{2+} and cation radical PDI^+. Comparison of different values for dyad **1** and triad **2** with reference compounds **3** and **8** suggested that no significant interaction takes place between both electroactive moieties in the ground state. This result was coincident with that of the UV-vis absorption.

Fluorescence spectra of **1**, **2**, and **3** were carried out with a CARY Eclipse Fluorescence Spectrophotometer in a 1 cm quartz cell (Fig. 2). Compared to compound **3**, dyad **1** and triad **2** show a rather weak fluorescence. The fluorescence quantum yield ϕ_f (λ_{exc} = 540 nm) of

Scheme 2. Synthetic procedure for compound **1** and **2**: (a) KOH, isopropanol/H_2O, N_2, reflux; (b) $LiAlH_4$, THF, N_2; (c) imidazole, reflux in *m*-cresol for 24 h, yield: 6, 45%; 7, 10%; (d) imidazole, reflux in *m*-cresol for 48 h, yield 40%.



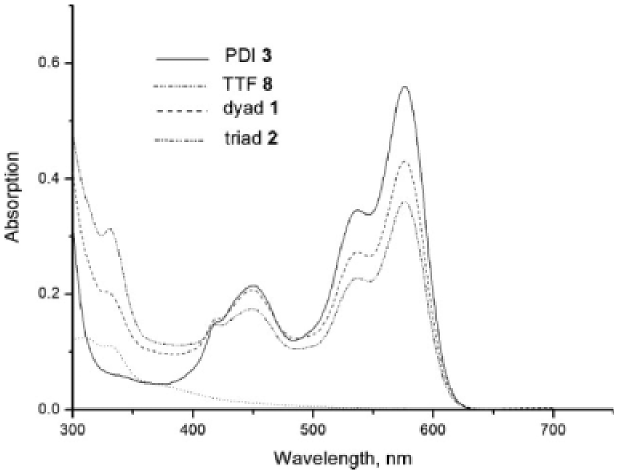


Figure 1. Absorption spectrum of compounds **1**, **2**, **3**, and **8** (1.0×10^{-5} M in CH_2Cl_2).

1 and **2** was 0.172 and 0.087 compared to PDI **3** ($\phi_f = 1$). This weakly fluorescence emission of **1** and **2** could be attributed to a photoinduced electron transfer (PET) reaction between PDI and TTF unit in the dyad and triad for two major reasons: (1) ΔG values of **1** and **2** calculated using the Rehm-Weller equation [21] for the photoinduced electron transfer reactions were −1.03 and −1.04 eV, thus these reactions are thermodynamically favorable; (2) there was no spectral overlap between the absorption spectrum of TTF unit and Fluorescence spectrum of PDI unit. Hence, the energy transfer process was prohibited according to Förster mechanism [4].

Figure 3 was fluorescence spectra of **1** and **2** after addition of different amount of Fe^{3+} and further reduction by $Na_2S_2O_3$ (1.0×10^{-5} M in CH_2Cl_2, $\lambda_{ex} = 540$ nm). It is known that TTF and its analogues can be oxidized stoichiometrically by Fe^{3+}. As TTF being oxidized to corresponding cation radical and dication species, the fluorescence of compound **1** and **2** both increased gradually after Fe^{3+} was added. The maximum fluorescent intensity of dyad **1** increased by 245% after reaction with 1.0 equiv of Fe^{3+} and the maximum fluorescent intensity of triad **2** increased by 663% after 2.0 equiv of Fe^{3+} was added. As expected, after react with excess sodium thiosulfate ($Na_2S_2O_3$) to the former chemically oxidized solution, both absorption and fluorescence spectrum of compound **1** and **2** restored (see Fig. 3). This is because the radical cation of TTF unit (TTF^{2+}) of compound **1** and **2** transferred into neutral unit after adding of $Na_2S_2O_3$. This indicates that the fluorescence of dyad **1** and triad **2** could be modulated by reversible chemical oxidation and reduction of TTF unit.

Table 1

The absorption data of compounds **1**, **2**, **3**, and **8** (1.0×10^{-5} M in CH_2Cl_2).

Compound	Absorption nm, $\varepsilon \times 10^5$ M^{-1} cm^{-1}
1	329(0.20), 448(0.21), 537(0.27), 577(0.43)
2	331(0.31), 449(0.17), 536(0.23), 577(0.37)
3	451(0.21), 537(0.34), 578(0.56)
8	312(0.12), 332(0.11)

Table 2

Oxidation potentials of compounds **1**, **2**, **3**, and **8** in dichloromethane (1.0×10^{-3} M).

	$E_{1/2}$ (V)				
Compound	PDI^{2-}	PDI^{-}	$TTF^{\bullet+}$	TTF^{2+}	PDI^{+}
3	−0.91	−0.60			1.37
8			0.54	0.91	
1	−0.90	−0.60	0.58	0.93	1.38
2	−0.89	−0.61	0.56	0.92	1.40

The fluorescence of dyad **1** and triad **2** could also be modulated by reversible electrochemical oxidation and reduction of TTF unit (see Fig. 4). Oxidation of compound **1** and **2** (1.0×10^{-5} M) containing n-Bu_4NPF_6 (1.0×10^{-1} M) was performed by applying an oxidation potential of 0.60 V (vs. Ag wire) to the solution. Figure 4 show that the oxidation led to the increase at 600 nm. This is similar to the fluorescence spectral variation observed after chemical oxidation which is discussed above. The application of a reduction potential of 0.1 V (vs. Ag wire) to former electrochemically oxidized solution for 5 min also led to the transformation of TTF^{2+} into neutral unit. Consequently, the fluorescence of dyad **1** and triad **2** restored (Fig. 4). As a result, electrochemically oxidization and reduction could also modulate the fluorescence of both dyad **1** and triad **2**.

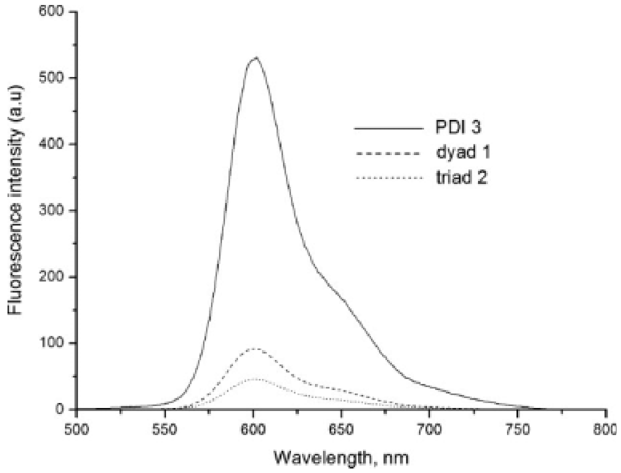


Figure 2. Fluorescence spectrum of compounds **1**, **2**, and **3** (1.0×10^{-5} M in CH_2Cl_2, $\lambda_{ex} = 540$ nm).

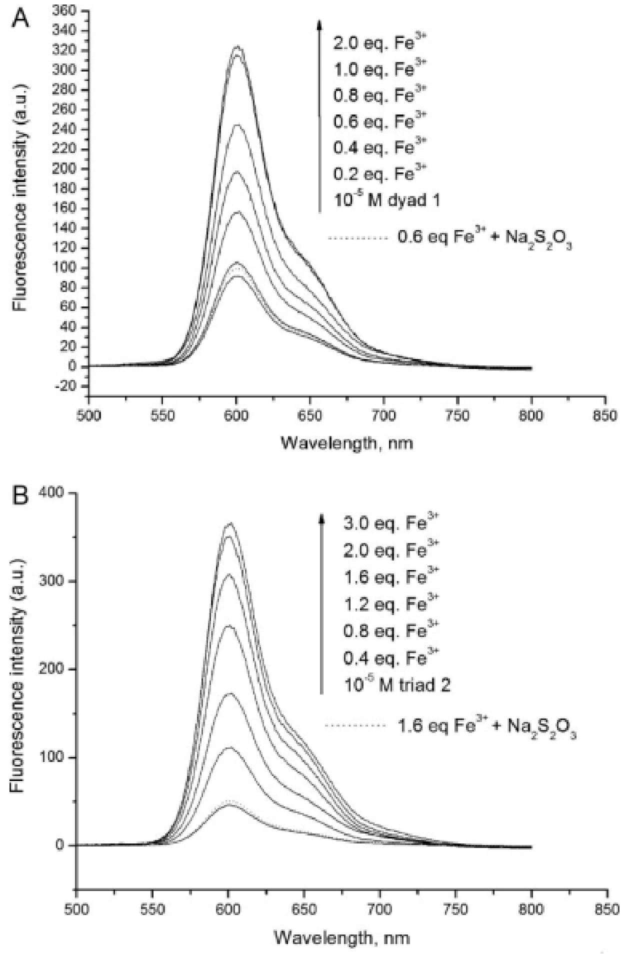


Figure 3. Fluorescence spectrum of dyad **1** (A) and triad **2** (B) (1.0×10^{-5} M in CH_2Cl_2, $\lambda_{ex} = 540$ nm) in the presence of different amounts of $Fe(ClO_4)_3$ and further reduction by $Na_2S_2O_3$.

CONCLUSIONS

We have designed and synthesized a new donor-σ-accepter (D-σ-A) type molecular fluorescence switches dyad **1** and a new donor-σ-accepter-σ-donor (D-σ-A-σ-D) type molecular fluorescence switch triad **2** containing PDI and TTF units. Compound **1** and **2** both have excellent solubility in most organic solvents because of the tetra-substituted p-t-butylphenoxy at the bay region. What's more, their fluorescent behavior could be modulated by reversible oxidation and reduction of TTF unit either chemically or electrochemically.

EXPERIMENTAL

***N*-Hexyl-1,6,7,12-tetra(4-*tert*-butylphenoxy)-perylene-3,4-anhydride-9,10-tetracarboxylicImide (4) and 1,6,7,12-tetra(4-*tert*-butylphenoxy)-perylene-3,4,9,10-tetracarboxylicbisanhydride (5).** *N,N′*-Dihexyl-1,6,7,12-tetra(4-*tert*-butylphenoxy)-perylene-3,4,9,10-tetracarboxylicdiimide (2.2 g, 2.0 mmol) with KOH (6 g,10 mmol) in isopropylalcohol (60 mL) and H_2O (6 mL) were heated to reflux temperature under argon for 10 h, followed by acidic work up and thorough washing and drying, yielded a mixture (1.0 g) of perylenemonooctylimide (**4**) and perylenebisanhydride (**5**) in a ratio of about 7:3. Compound **4** and **5** were separated by column chromatography on a silica gel with CH_2Cl_2/petroleumether (1:1). Compound (**4**): mp > 300°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.25 (s, 4H, H_{per}), 7.25 (d, J = 8.45 Hz, 8H, H_{ar}), 6.85 (d, J = 8.84 Hz, 8H, H_{ar}), 4.15 (t, J = 7.6 Hz, 2H, N—CH_2), 1.65 (m, 4H), 1.3 (s, 36H, 4—$C(CH_3)_3$), 0.85 (t, J = 6.4 Hz, 3H, —CH_3).Compound (**5**): mp > 300°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.28 (s, 4H, H_{per}), 7.25 (d, J = 8.46 Hz, 8H, H_{ar}), 6.85 (d, J = 8.76 Hz, 8H, H_{ar}), 1.3 (s, 36H, 4-$C(CH_3)_3$).

4-Methyl-5-aminopropyl-4,5-bishexylenetetrathiafulvalene (7). $LiAlH_4$ (21 mg, 0.55 mmol) which is dissolved in 5 mL anhydrous degassed THF was added dropwise to a stirred solution of compound **6** (114 mg, 0.2 mmol) in anhydrous degassed THF (20 mL) under N_2. The mixture was refluxed for 2 h. After cooling, THF was evaporated *in vacuo* and

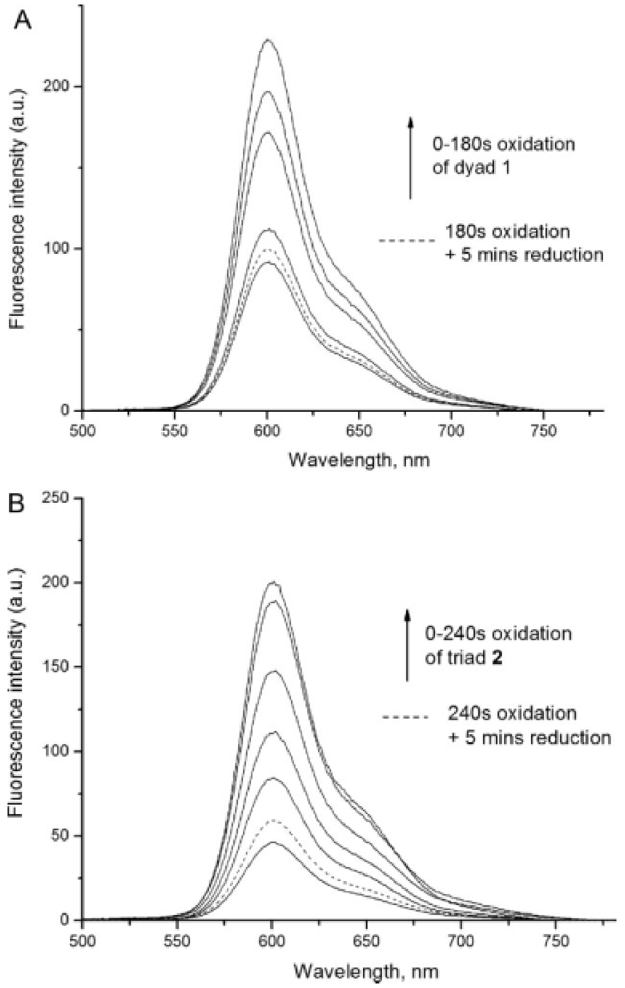


Figure 4. Fluorescence spectrum of dyad **1** (A) and triad **2** (B) (10^{-5} M in CH_2Cl_2, $\lambda_{ex} = 540$ nm, containing 10^{-1} M n-Bu_4NPF_6) after oxidation of 0.60 V (vs. Ag wire) for different period and further reduction of 0.1 V (vs. Ag wire) for 5 min (scan rate was 50 mV s^{-1}).

CH_2Cl_2 (20 mL) and H_2O (10 mL) was added. The two phases were separated and the organic phase was washed with H_2O. Column chromatography (silica gel, CH_2Cl_2: MeOH = 4:1) after drying ($MgSO_4$) give compound **7** (67mg). Yield: 60%. ^1H NMR ($CDCl_3$): δ 2.82 (m, 6H, —SCH_2—), 2.68 (m, 2H, —CH_2N), 2.40 (s, 3H, —SCH_3), 2.08 (s, 2H, NH_2) 2.01 (m, 2H, —CH_2—), 1.85 (m, 4H, —CH_2—), 1.42 (m, 4H, —CH_2—), 1.20–1.30 (m, 8H, —CH_2—), 0.86 (t, J = 6.8 Hz, 6H, —CH_3).

Perylene-TTF dyad 1. *N*-Hexyl-1,6,7,12-tetra(4-*tert*-butylphenoxy)-perylene-3,4-anhydride-9,10-tetracarboxylicimide (**4**) (208mg, 0.2 mmol), amino-TTF **7** (110mg, 0.2 mmol) and imidazole (0.5 g) are added to 30 mL of *m*-cresol. The reaction mixture was heated to 175–180°C under dry nitrogen for 48 h with stirring. After the reaction mixture was cooled to room temperature, it was evaporated *in vacuo* to remove *m*-cresol. The residue was washed by methanol to remove excess *m*-cresol and TTF **7**. Then the residue was washed with hot 1% NaOH solution and hot water three times, respectively. After drying, the residue was purified by chromatography on silica gel using a mixture of dichloromethane-petroleum ether (1:1) as eluent, to give a purple solid of dyad **1** (yield: 45%, 144 mg). mp $>$ 300°C; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.20 (s, 4H, Hper), 7.22 (d, J = 8.45 Hz, 8H, H_{ar}), 6.80 (d, J = 8.84 Hz, 8H, H_{ar}), 4.20–4.28 (m, 4H, N—CH_2), 2.75 (m, 6H, S—CH_2—), 2.71 (m, 2H) 2.38 (s, 3H, —SCH_3), 2.05 (m, 4H, —CH_2), 1.70 (m, 4H), 1.45 (m, 4H, CH_2), 1.28–1.35 (m, 44H), 0.88 (t, J = 6.4 Hz, 6H, —CH_3). 0.82 (t, J = 6.4 Hz, 3H, —CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.9, 155.7, 152.5, 147.2, 131.5, 127.4, 126.5, 122.3, 120.5, 119.7, 119.2, 110.1, 39.3, 36.7, 34.4, 31.6, 29.8, 29.3, 28.2, 27.7, 27.1, 22.5, 21.7, 19.4, 14.2, 13.8; MS(MALDI-TOF): *m*/*z* 1592.3 $[M]^+$ (calcd for $C_{90}H_{100}N_2O_8S_8$ 1592.5); Anal. Calcd (%) for $C_{90}H_{100}N_2O_8S_8$: C 67.80, H 6.32, N 1.76; Found C 67.71, H 6.38, N 1.72

TTF-Perylene-TTF triad 2. 1,6,7,12-tetra(4-*tert*-butylphenoxy)-perylene-3,4,9,10-tetracarboxylicbisanhydride **5** (100 mg, 0.1 mmol), amino-TTF **7** (230 mg, 0.4 mmol) and imidazole (0.5 g) are added to 30 mL of *m*-cresol. The reaction mixture was heated to 175–180°C under dry nitrogen for 48 h with stirring. After the reaction mixture was cooled to room temperature, it was evaporated *in vacuo* to remove *m*-cresol. The residue was washed by methanol to remove excess *m*-cresol and TTF **7**. Then the residue was washed by hot 1% NaOH solution and hot water three times, respectively. After drying, the residue was purified by chromatography on silica gel using a mixture of dichloromethane-ethyl acetate (1:1) as eluent, to give a purple solid of triad **2** (yield: 40%, 84 mg). mp $>$ 300°C; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.28 (s, 4H, H_{per}), 7.23 (d, J = 8.38 Hz, 8H, H_{ar}), 6.85 (d, J = 8.62 Hz, 8H, H_{ar}), 4.20–4.25 (m, 4H, N—CH_2), 2.94 (m, 8H, S—CH_2—), 2.59 (s, 6H, —SCH_3), 2.01 (m, 8H, —CH_2), 1.65 (m, 8H), 1.45 (m, 8H, CH_2), 1.28–1.35 (m, 52H), 0.85 (t, J = 6.4 Hz, 12H, —CH_3). ^{13}C NMR ($CDCl_3$, 100MHz): δ 163.3, 156.2, 152.9, 147.2, 131.3, 127.6, 126.8, 122.1, 120.6, 119.8, 119.1, 110.5, 39.2, 34.4, 31.7, 29.9, 28.3, 27.6, 27.2, 22.5, 19.6, 14.1; MS (MALDI-TOF): *m*/*z* 2090.2 $[M]^+$ (calcd for $C_{108}H_{126}N_2O_8S_{16}$ 2090.5); Anal. Calcd (%) for $C_{108}H_{126}N_2O_8S_{16}$: C 61.97, H 6.07, N 1.34; Found C 61.91, H 6.02, N 1.38.

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[21] (a) Rehm, D.; Weller, A. Isr J Chem 1970, 8, 259; (b) For dyad **1**: $\Delta G_{PET} = -E_{ex} + E_{ox} - E_{red} - e^2/\varepsilon r$, $E_{ox} = +0.58$ eV, $E_{red} = -0.60$ eV, $\lambda_{ex} = 540$, $e^2/\varepsilon r = -0.1$ eV; For triad **2**: $E_{ox} = +0.56$ eV, $E_{red} = -0.61$ eV, $\lambda_{ex} = 540$, $e^2/\varepsilon r = -0.1$ eV.

An Efficient and Direct Synthesis of 2-Thiopyridines *via* Microwave-Assisted Three-Component Reaction

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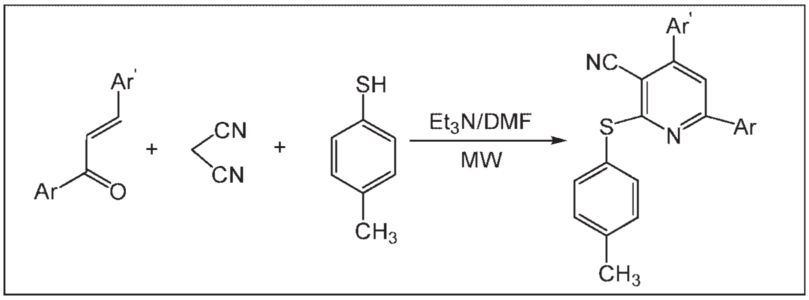

A series of 2-*p*-tolylthiopyridine derivatives was directly synthesized *via* three-component reactions of chalcones, malononitrile, and 4-methylbenzenethiol catalyzed by Et_3N in DMF under microwave irradiation. It is an efficient and promising synthetic strategy to construct 2-thiopyridine skeleton with the advantage of short time, excellent yield, and convenient operation.

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INTRODUCTION

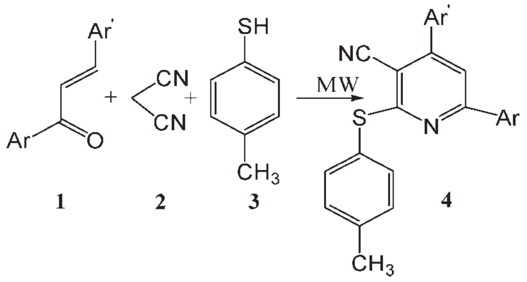
The pyridine nucleus, as the key constituent in a range of bioactive compounds, is one of the most well-known systems among the naturally occurring heterocycles [1]. Polysubstituted pyridines including the related 2-thiopyridines are prominent building blocks, exhibit antibacterial [2,3], pesticidal [4], antifungal [4,5], and acaricidal properties [5] and may have potential ability to form complexes with transition metals. Thus, the synthesis of pyridines and their analogs has attracted much attention. The majority of synthetic methods to the target compounds start from the condensation of α,β-unsaturated ketones or β-diketones with cyanothioacetamide, and then formed 2-alkylthio-pyridines by the reaction of the iodoalkane [6]. However, even these methods are still not satisfactory because of the narrow scope of substituted alkylthiopyridines produced and the multistep synthesis. Therefore, the development of a simple, one-pot, and directed synthetic route, which provides diverse of 2-thiopyridine compounds, is strongly desired for this important class of heterocycles.

As a part of our ongoing development of efficient protocols for the preparation of polysubstituted heterocycles [7] from common intermediates, we recently discovered technically simple microwave (MW) conditions for the synthesis of new 2-(*p*-tolylthio)-4,6-diarylpyridine-3-carbonitrile derivatives using α,β-unsaturated ketones as starting materials (Scheme 1).

RESULTS AND DISCUSSION

To choose the most appropriate medium in this heterocyclization reaction, the MW-assisted reaction of 3-(4-bromophenyl)-1-*p*-tolylprop-2-en-1-one (**1a**), malononitrile (**2**), and 4-methylbenzenethiol (**3**) was examined using the solvent of HOAc, glycol, THF, DMF, and EtOH as solvent at 100°C, respectively. The results are summarized in Table 1, the reaction in DMF gave the best yield. Therefore, DMF was chosen as the solvent of this reaction. Moreover, to further improve the reaction yields, different bases were examined for their ability to promote this reaction at 100°C. As shown in Table 2, the Et_3N afforded the target product **4a** in an 85% yield. Finally, to further optimize the reaction temperature, the synthesis of **4a** was performed in the presence of Et_3N at the temperatures ranging from 100 to 130°C. As illustrated in Table 3, the yield of product **4a** was increased and the reaction time was shortened as the temperature was increased from 100 to 120°C. The yield decreased slightly when the temperature was further increased from 120 to 130°C. So, the temperature of 120°C was chosen for all further microwave-assisted reactions.

Scheme 1



Under these optimized reaction conditions, we synthesized a series of products **4** using this simple procedure. The results are summarized in Table 4 (Entries 1–14). This methodology is applicable to aromatic and heteroaromatic chalcones. Furthermore, the electronic effect with various substituents on the chalcones was studied and had no significant effect on this reaction.

A mechanism for the formation of the products **4** is outlined in Scheme 2. The reaction occurs via initial formation of compounds **5** afforded by Michael addition reaction of chalcones and malononitrile followed by the thiolate nucleophilic attack in the presence of Et_3N. The intermediate **5** cyclizes to dihydropyridine **6** and subsequent afford the fully aromatized compound **4** with the loss of hydrogen. This type of oxidation is well precedented [8b,9]. In this study, all the products were characterized by mp, IR, and ^{1}H NMR spectral data and elemental analysis.

In summary, we demonstrated a rapid and direct method that offers a simple and efficient route for the one-pot, three-component synthesis of highly functionalized 2-thiopyridine derivatives in excellent yields. Particularly valuable features of this method include operational simplicity and increased safety for small-scale high-speed synthesis.

EXPERIMENTAL

Microwave irradiation was carried out with an Emrys^{TM} Creator microwave oven from Personal Chemistry, Uppsala, Sweden. Melting points were determined in open capillaries and were uncorrected. IR spectra were recorded on a FT-IR-Tensor 27 spectrometer in KBr. ^{1}H NMR spectra were measured on a DPX 400 MHz spectrometer using TMS as an internal standard and DMSO-d_6 as solvent. Elemental analyses were determined with a Perkin-Elmer 240c elemental analysis instrument.

Table 1

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

Entry	Solvent	Time (min)	Yield (%)
1	THF	12	25
2	Glycol	12	28
3	EtOH	12	24
4	HOAc	12	40
5	DMF	12	55

Table 2

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

Entry	Base	Time (min)	Yield (%)
1	NaOH	12	70
2	K_2CO_3	12	72
3	DMAP	12	75
4	Piperidine	12	78
5	Et_3N	12	85

General procedure for 2-(*p*-Tolylthio)-4,6-diphenylpyridine-3-carbonitrile derivatives (4). The reactions were performed in a 10 mL Emrys^{TM} reaction vial. Chalcones **1** (1 mmol), malononitrile **2** (1 mmol), and 4-methylbenzenethiol **3** (1 mmol) in DMF in the presence of Et_3N were mixed and then capped. The mixture was heated for a given time at 120°C under microwave irradiation (initial power 200 W and maximum power 250 W). Upon complete consumption of starting materials, as monitored by TLC, the reaction mixture was cooled to room temperature, and then filtered to give the crude product, which was further purified by recrystallization from EtOH (95%) to give pure target products **4**.

2-(*p*-Tolylthio)-4-(4-bromophenyl)-6-*p*-tolylpyridine-3-carbonitrile 4a. This compound was obtained according to the above general procedure; IR (potassium bromide): 3017, 2917, 2210, 1572, 1522, 1491, 1368, 1008, 820, 803, 761 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.92 (s, 1H, PyH),7.79 (t, J = 7.6 Hz, 4H, ArH), 7.68 (d, J = 8.4 Hz, 2H, ArH), 7.56 (d, J = 8.4 Hz, 2H, ArH), 7.38 (d, J = 8.0 Hz, 2H, ArH), 7.20 (d, J = 8.0 Hz, 2H, ArH), 2.44 (s, 3H, CH_3), 2.32 (s, 3H, CH_3); Anal. Calcd. for $C_{26}H_{19}BrN_2S$: C, 66.24; H, 4.06; N, 5.94; Found: C, 66.45; H, 4.10; N, 5.90.

2-(*p*-Tolylthio)-4-(4-chlorophenyl)-6-*p*-tolylpyridine-3-carbonitrile 4b. This compound was obtained according to above general procedure; IR (potassium bromide): 3063, 2918, 2210, 1595, 1523, 1367, 1093, 821, 801, 760 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.92 (s, 1H, PyH),7.79 (t, J = 7.6 Hz, 4H, ArH), 7.68 (d, J = 8.4 Hz, 2H, ArH), 7.56 (d, J = 8.4 Hz, 2H, ArH), 7.38 (d, J = 8.0 Hz, 2H, ArH), 7.20 (d, J = 8.0 Hz, 2H, ArH), 2.44 (s, 3H, CH_3), 2.32 (s, 3H, CH_3). Anal. Calcd. For $C_{26}H_{19}ClN_2S$: C, 73.14; H, 4.49; N, 6.56; Found: C, 73.29; H, 4.52; N, 6.63.

Table 3

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

Entry	Temp (°C)	Time (min)	Yield (%)
1	100	12	85
2	105	11	86
3	110	10	88
4	115	10	89
5	120	9	95
6	125	9	94
7	130	9	94

Table 4

Physical data of products **4**.

Entry	Product	Chalcones	Time (min)	Yield (%)	Mp (°C)
1	**4a**	3-(4-Bromophenyl)-1-*p*-tolylprop-2-en-1-one	9	95	254–255
2	**4b**	3-(4-Chlorophenyl)-1-*p*-tolylprop-2-en-1-one	8	93	195–196
3	**4c**	3-(4-Nitrophenyl)-1-*p*-tolylprop-2-en-1-one	9	92	266–268
4	**4d**	3-(3,4-Dimethoxyphenyl)-1-*p*-tolylprop-2-en-1-one	10	90	174–175
5	**4f**	3-(Benzo[*d*][1,3]dioxol-6-yl)-1-*p*-tolylprop-2-en-1-one	9	93	212–215
6	**4e**	3-(4-Bromophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one	8	94	221–223
7	**4g**	1-(4-Methoxyphenyl)-3-phenylprop-2-en-1-one	9	89	195–196
8	**4h**	3-(4-(Dimethylamino)phenyl)-1-(4-methoxyphenyl)prop-2-en-1-one	9	90	182–184
9	**4i**	3-(3,4-Dimethoxyphenyl)-1-phenylprop-2-en-1-one	10	91	245–248
10	**4j**	1-(4-Fluorophenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one	7	94	183–184
11	**4k**	1-(4-Fluorophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one	7	94	201–202
12	**4l**	1-(4-Chlorophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one	8	93	195
13	**4m**	3-(3,4-Dimethoxyphenyl)-1-(pyridin-2-yl)prop-2-en-1-one	7	90	189–190
14	**4n**	3-(4-Bromophenyl)-1-(pyridin-2-yl)prop-2-en-1-one	7	90	191–192

2-(*p*-Tolylthio)-4-(4-nitrophenyl)-6-*p*-tolylpyridine-3-carbonitrile 4c. This compound was obtained according to the above general procedure; IR (potassium bromide): 3071, 2207, 1604, 1567, 1526, 1353, 1018, 859, 820, 808 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.44 (d, J = 8.4 Hz, 2H, ArH), 8.05 (d, J = 8.0 Hz, 2H, ArH), 8.00 (s, 1H, PyH), 7.79 (d, J = 8.0 Hz, 2H, ArH), 7.57 (d, J = 8.0 Hz, 2H, ArH), 7.39 (d, J = 8.0 Hz, 2H, ArH), 7.22 (d, J = 8.0 Hz, 2H, ArH), 2.44 (s, 3H, CH_3), 2.33 (s, 3H, CH_3). Anal. Calcd. for $C_{26}H_{19}N_3O_2S$: C, 71.38; H, 4.38; N, 9.60; Found: C, 71.54; H, 4.40; N, 9.65.

2-(*p*-Tolylthio)-4-(3,4-dimethoxyphenyl)-6-*p*-tolylpyridine-3-carbonitrile 4d. This compound was obtained according to the above general procedure; IR (potassium bromide): 3003, 2935, 2214, 1604, 1569, 1523, 1506, 1270, 1140, 1022, 800, 662 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.84 (s, 1H, PyH), 7.73 (d, J = 8.0 Hz, 2H, ArH), 7.51 (d, J = 8.0 Hz, 2H, ArH), 7.35–7.29 (m, 4H, ArH), 7.17–7.11 (m, 3H, ArH), 3.83 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 2.39 (s, 3H, CH_3), 2.28 (s, 3H, CH_3). Anal. Calcd. for $C_{28}H_{24}N_2O_2S$: C, 74.31; H, 5.35; N, 6.19; Found: C, 74.11; H,5.51; N, 6.32.

2-(*p*-Tolylthio)-4-(benzo[*d*][1,3]dioxol-6-yl)-6-*p*-tolylpyridine-3-carbonitrile 4e. This compound was obtained according to the above general procedure; IR (potassium bromide): 2918, 2214, 1566, 1525, 1502, 1376, 1251, 1042, 816 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.85 (s, 1H, PyH), 7.77 (d, J = 8.0 Hz, 2H, ArH), 7.55 (d, J = 8.0 Hz, 2H, ArH), 7.39–7.37 (m, 3H, ArH), 7.30–7.27 (m, 1H, ArH), 7.19 (d, J = 8.0 Hz, 2H, ArH), 7.14 (d, J = 7.6 Hz, 2H, ArH), 6.16 (s, 2H, OCH_2O), 2.43 (s, 3H, CH_3), 2.32 (s, 3H, CH_3). Anal. Calcd. for $C_{27}H_{20}N_2O_2S$: C, 74.29; H, 4.62; N, 6.42; Found: C, 74.31; H, 4.76; N, 6.53.

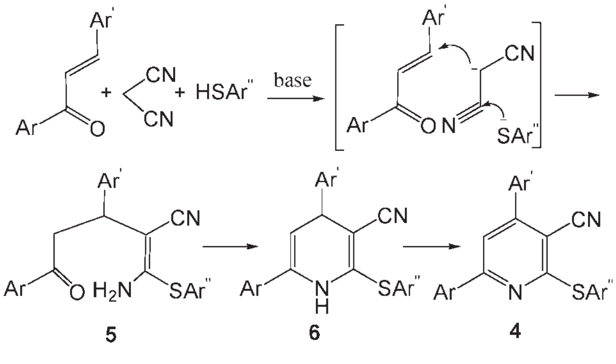
2-(*p*-Tolylthio)-4-(4-bromophenyl)-6-(4-methoxyphenyl)-pyridine-3-carbonitrile 4f. This compound was obtained according to the above general procedure; IR (potassium bromide): 3065, 2961, 2212, 1600, 1574, 1519, 1489, 1421, 1256, 1176, 1024, 1009, 983, 839, 820, 810 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.87 (s, 1H, PyH), 7.84–7.81 (m, 4H, ArH), 7.71 (d, J = 8.4 Hz, 2H, ArH), 7.56 (d, J = 8.0 Hz, 2H, ArH), 7.39 (d, J = 7.6 Hz, 2H, ArH), 6.93 (d, J = 9.2 Hz, 2H, ArH), 3.81 (s, 3H, OCH_3), 2.44 (s, 3H, CH_3). Anal. Calcd. for $C_{26}H_{19}BrN_2OS$: C, 64.07; H, 3.93; N, 5.75; Found: C, 64.26; H, 3.85; N, 5.89.

2-(*p*-Tolylthio)-6-(4-methoxyphenyl)-4-phenylpyridine-3-carbonitrile 4g. This compound was obtained according to the above general procedure; IR (potassium bromide): 3015, 2976, 2214, 1608, 1568, 1525, 1491, 1406, 1368, 1310, 1168, 1022, 834, 808, 773, 757, 698 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.88–7.86 (m, 3H, ArH, PyH), 7.77–7.75 (m, 2H, ArH), 7.61–7.57 (m, 5H, ArH), 7.39 (d, J = 8.0 Hz, 2H, ArH), 6.93 (d, J = 8.8 Hz, 2H, ArH), 3.81 (s, 3H, OCH_3), 2.45 (s, 3H, CH_3). Anal. Calcd. for $C_{26}H_{20}N_2OS$: C, 76.44; H, 4.93; N, 6.86; Found: C, 76. 04; H, 4.96; N, 6.88.

2-(*p*-Tolylthio)-4-(4-(dimethylamino)phenyl)-6-(4-methoxyphenyl)pyridine-3-carbonitrile 4h. This compound was obtained according to the above general procedure; IR (potassium bromide): 3070, 3014, 2889, 2208, 1610, 1567, 1506, 1406, 1365, 1310, 1246, 1202, 1167, 1060, 836, 808, 735 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.84 (d, J = 9.2 Hz, 2H, ArH), 7.77 (s, 1H, PyH), 7.65(d, J = 8.8 Hz, 2H, ArH), 7.55 (d, J = 8.0 Hz, 2H, ArH), 7.37 (d, J = 8.0 Hz, 2H, ArH), 6.92 (d, J = 9.2 Hz, 2H, ArH), 6.86 (d, J = 9.2 Hz, 2H, ArH), 3.80 (s, 3H, OCH_3), 3.02 (s, 6H, $N(CH_3)_2$), 2.43 (s, 3H, CH_3). Anal. Calcd. for $C_{28}H_{25}N_3OS$: C, 74.47; H, 5.58; N, 9.31; Found: C, 74.27; H, 5.65; N, 9.57.

2-(*p*-Tolylthio)-4-(3,4-dimethoxyphenyl)-6-phenylpyridine-3-carbonitrile 4i. This compound was obtained according to the above general procedure; IR (potassium bromide): 3034, 2998, 2210, 1606, 1570, 1551, 1491, 1368, 1266, 1252, 1172,

Scheme 2



1024, 828, 813, 781, 758, 691 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.96–7.93 (m, 3H, ArH, PyH), 7.56 (d, J = 8.0 Hz, 2H, ArH), 7.40–7.35 (m, 4H, ArH), 7.25 (t, J = 8.8 Hz, 2H, ArH), 7.17 (d, J = 8.0 Hz, 1H, ArH), 3.87 (s, 3H, OCH$_3$), 3.86 (s, 3H, OCH$_3$), 2.45 (s, 3H, CH$_3$). Anal. Calcd. for $C_{27}H_{22}N_2O_2S$: C, 73.95; H, 5.06; N, 6.39; Found: C, 73.86; H, 5.16; N, 6.59.

2-(*p*-Tolylthio)-6-(4-fluorophenyl)-4-(3,4-dimethoxyphenyl) pyridine-3-carbonitrile 4j. This compound was obtained according to the above general procedure; IR (potassium bromide): 3004, 2955, 2207, 1600, 1573, 1524, 1506, 1263, 1219, 1151, 1029, 824, 808; ^{1}H NMR (DMSO-d_6): δ 7.96–7.93 (m, 3H, ArH, PyH), 7.56 (d, J = 8.0 Hz, 2H, ArH), 7.40–7.35 (m, 4H, ArH), 7.25 (d, J = 8.8 Hz, 2H, ArH), 7.17 (d, J = 8.4 Hz, 2H, ArH), 3.87 (s, 3H, OCH$_3$), 3.81 (s, 3H, OCH$_3$), 2.44 (s, 3H, CH$_3$). Anal. Calcd. for $C_{27}H_{21}FN_2O_2S$: C, 71.03; H, 4.64; N, 6.14; Found: C, 71.15; H, 4.67; N, 6.20.

2-(*p*-Tolylthio)-6-(4-fluorophenyl)-4-(4-methoxyphenyl)-pyridine-3-carbonitrile 4k. This compound was obtained according to the above general procedure; IR (potassium bromide): 2918, 2214, 1600, 1571, 1524, 1515, 1373, 1255, 1154, 1034, 827, 799 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.96–7.92 (m, 3H, ArH, PyH), 7.75 (d, J = 8.8 Hz, 2H, ArH), 7.56 (d, J = 8.4 Hz, 2H, ArH), 7.38 (d, J = 8.0 Hz, 2H, ArH), 7.24 (t, J = 8.8 Hz, 2H, ArH), 7.15 (d, J = 8.8 Hz, 2H, ArH), 3.86 (s, 3H, OCH$_3$), 2.44 (s, 3H, CH$_3$). Anal. Calcd. for $C_{26}H_{19}FN_2OS$: C, 73.22; H, 4.49; N, 6.57; Found: C, 73.21; H, 4.48; N, 6.80.

2-(*p*-Tolylthio)-6-(4-chlorophenyl)-4-(4-methoxyphenyl)-pyridine-3-carbonitrile 4l. This compound was obtained according to the above general procedure; IR (potassium bromide): 3061, 2934, 2211, 1609, 1577, 1524, 1491, 1369, 1255, 1182, 1090, 1034, 1010, 829, 803 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.94 (s, 1H, PyH),7.89 (d, J = 8.8 Hz, 2H, ArH), 7.75 (d, J = 8.8 Hz, 2H, ArH), 7.55 (d, J = 8.0 Hz, 2H, ArH), 7.46 (d, J = 8.4 Hz, 2H, ArH), 7.38 (d, J = 8.0 Hz, 2H, ArH), 7.16 (d, J = 8.8 Hz, 2H, ArH), 3.86 (s, 3H, OCH$_3$), 2.44 (s, 3H, CH$_3$). Anal. Calcd. for $C_{26}H_{19}ClN_2OS$: C, 70.50; H, 4.32; N, 6.32; Found: C, 70.29; H, 4.50; N, 6.20.

2-(*p*-Tolylthio)-4-(3,4-dimethoxyphenyl)-6-(pyridin-2-yl) pyridine-3-carbonitrile 4m. This compound was obtained according to the above general procedure; IR (potassium bromide): 2932, 2834, 2213, 1560, 1511, 1269, 1142, 1025, 866, 800 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.70 (d, 1H, J = 4.4 Hz, PyH), 8.22 (s, 1H, PyH), 7.86 (t, J = 8.0 Hz, 1H, PyH), 7.68 (d, J = 8.0 Hz, 1H, PyH), 7.59 (d, J = 8.0 Hz, 2H, ArH), 7.48 (t, J = 8.0 Hz, 1H, PyH), 7.42–7.36 (m, 3H, ArH), 3.87 (s, 3H, OCH$_3$), 3.86 (s, 3H, OCH$_3$), 2.45 (s, 3H, CH$_3$). Anal. Calcd. for $C_{26}H_{21}N_3O_2S$: C, 71.05; H, 4.82; N, 9.56; Found: C, 71.20; H, 4.85; N, 9.57.

2-(*p*-Tolylthio)-4-(4-bromophenyl)-6-(pyridin-2-yl)pyridine-3-carbonitrile 4n. This compound was obtained according to the above general procedure; IR (potassium bromide): 3053, 2217, 1592, 1574, 1523, 1490, 1372, 1294, 1278, 1059, 1010, 806 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.70–8.69 (m, 1H, PyH), 8.20 (s, 1H, PyH), 7.89–7.86 (m, 1H, PyH),7.83 (d, J = 8.4 Hz, 2H, ArH), 7.71 (d, J = 8.4 Hz, 2H, ArH), 7.67 (d, J = 8.0 Hz, 2H, ArH), 7.59 (d, J = 8.0 Hz, 2H, ArH), 7.51–7.59 (m, 1H, PyH), 7.41 (d, J = 8.0 Hz, 2H, ArH), 2.45 (s, 3H, CH$_3$). Anal. Calcd. for $C_{24}H_{16}BrN_3S$: C, 62.89; H, 3.52; N, 9.17; Found: C, 63.01; H, 3.65; N, 9.29.

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An Efficient and Convenient Multicomponent Reaction for the Synthesis of 2-Methyl-4,6-Diarylpyrimidine Under Solvent-Free Conditions

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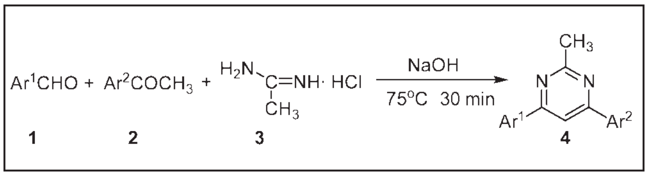

An efficient and convenient method for the preparation of 2-methyl-4,6-diarylpyrimidine derivatives by the multicomponent reactions of aromatic aldehydes, aromatic ketones, and acetamidine hydrochloride in the presence of sodium hydroxide under solvent-free conditions was reported. This method has the advantages of excellent yields, mild reaction conditions, easy workup, and environmentally friendly procedure.

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INTRODUCTION

In recent years, multicomponent reactions (MCRs) have emerged as a powerful strategy to construct useful molecules from simple starting materials [1]. Molecules synthesized by this method continue attracting the attention of medicinal and synthetic chemists [2]. The pyrimidines and their derivatives, as the important heterocyclic compounds, are an integral part of various natural products [3] and serve as a building block for various pharmaceuticals and biopolymers. It also has very good coordinating ability similar to pyridyl ligands in supramolecular metallogrid-like architecture [4]. In addition, pyrimidines are pharmacologically active and display anticonvulsant [5], anti-inflammatory [6], antibacterial [7], and antimycotic [8] activities. Therefore, synthesis of pyrimidine derivatives is always an important field for chemists. Some MCRs for the synthesis of pyrimidines or their derivatives have been reported [9].

Solvent-free organic synthesis is a well-established method for the synthesis of organic molecules [10] because it has some advantages, such as high efficiency and selectivity, easy separation and purification, and mild reaction conditions. As part of our continued interest in the development of highly expedient methods for the synthesis of organic compounds [11], herein, we would like to report a MCR for the synthesis of 2-methyl-4,6-diarylpyrimidine derivatives under solvent-free conditions.

RESULTS AND DISCUSSION

The first step of this synthetic approach consists of finding out the optimized reaction conditions. The optimization was begun by studying the effect of various solvents and solvent-free conditions on the model reaction of 4-chlorobenzaldehyde, acetophenone, and acetamidine hydrochloride in the presence of some different catalysts. As the data in Table 1 indicated, the results of reaction were quite different. When the reaction was carried out in solvent conditions using piperidine ($C_5H_{11}N$), triethylamine (Et_3N), and NaOH as catalyst, the results of reactions were not satisfying. We probably thought that acetamidine hydrochloride is the inorganic salt and does not easily dissolve in the organic solvents, so the reactions do not put out well. Then, the reaction was carried out under solvent-free conditions at 75°C. When piperidine ($C_5H_{11}N$) or triethylamine (Et_3N) was used as catalyst, the reaction was unsatisfactory. When the NaOH was chosen as catalyst, the reaction could be carried out smoothly, and the 4-(4-chlorophenyl)-2-methyl-6-phenylpyrimidine **4a** could be obtained with high yields (96%). We also investigated the reaction outcome using different amounts of NaOH. By increasing the quantity of NaOH from 0.05 to 0.3 g, the reaction gave different outcomes, resulting in the isolation of **4a** in about 85, 96, 92, and 90% yields, respectively. Higher loading of the catalyst did not improve the yields of the reaction. Perhaps, more NaOH could turn the reagents into solid more quickly, which hindered the reaction from completion.

With this optimum condition in hand, we synthesized 2-methyl-4,6-diarylpyrimidine derivatives under solvent-free conditions. The procedure of reaction was very facile: the mixture of aromatic aldehydes, aromatic ketones, and acetamidine hydrochloride was put into a flask, in

Table 1

Synthesis of **4a** under different conditions in the presence of different catalysts.[a]

Entry	Solvent	Amount	Yields[b] (%)
1	MeOH	$C_5H_{11}N$ (0.05 mL)	Trace
2	MeOH	Et_3N (0.05 mL)	Trace
3	MeOH	NaOH (0.1 g)	<5
4	EtOH	$C_5H_{11}N$ (0.05 mL)	Trace
5	EtOH	Et_3N (0.05 mL)	Trace
6	EtOH	NaOH (0.1 g)	<5
7	CH_3CN	$C_5H_{11}N$ (0.05 mL)	0
8	CH_3CN	Et_3N (0.05 mL)	0
9	CH_3CN	NaOH (0.1 g)	0
10	DMF	$C_5H_{11}N$ (0.05 mL)	0
11	DMF	Et_3N (0.05 mL)	0
12	DMF	NaOH (0.1 g)	0
13	Neat	$C_5H_{11}N$ (0.05 mL)	Trace
14	Neat	Et_3N (0.05 mL)	Trace
15	Neat	NaOH (0.05 g)	85
16	Neat	NaOH (0.1 g)	96
17	Neat	NaOH (0.2 g)	92
18	Neat	NaOH (0.3 g)	90

[a] Reagents and conditions: 4-chlorobenzaldehyde, **1** (2 mmol), acetophenone aldehydes **2** (2 mmol), acetamidine hydrochloride **3** (2 mmol).

[b] Isolated yields.

the presence of 0.1 g NaOH as catalyst, and let them at 75°C under solvent-free conditions, a series of 2-methyl-4,6-diarylpyrimidine derivatives could be prepared with high yield. The results of the reactions are summarized in Table 2.

The reaction was efficiently completed under solvent-free conditions. From Table 2, we could find that the aldehydes or ketones bearing either electron-withdrawing or electron-donating groups perform well in this reaction. Therefore, we concluded that the electronic nature of the substituents has no significant effect on this reaction. The structure of each product **4a–w** was established on the basis of spectroscopic data, particularly ^{1}H NMR analysis and HRMS spectra.

In conclusion, we have successfully developed an efficient and facile method to prepare a variety of 2-methyl-4,6-diarylpyrimidine derivatives *via* the MCRs of different aromatic aldehydes, aromatic ketones, and acetamidine hydrochloride under solvent-free conditions. In this reaction, we found that NaOH was an excellent catalyst, because the reaction could be efficiently completed when it existed, and that do not consider the quality of substituent groups. Because no toxic organic solvent was used, the simplicity of the reaction procedure coupled with excellent yields, making this method one of the most efficient methods for the synthesis of these kinds of heterocyclic compounds.

EXPERIMENTAL

Melting points were determined on XT-5 microscopic melting-point apparatus and were uncorrected. IR spectra were recorded on a FT Bruker Tensor 27 spectrometer. ^{1}H NMR spectra were obtained from solution in DMSO-d_6 with Me$_4$Si as an internal standard using a Bruker-400 spectrometer. Microanalyses were carried out using a Perkin-Elmer 2400 II analyzer. HRMS spectra were obtained with a Bruker micrOTOF-Q 134 instrument.

General procedure for the synthesis of 2-methyl-4,6-diarylpyrimidine derivatives. The mixture of aromatic aldehydes **1** (2 mmol), aromatic ketones **2** (2 mmol), acetamidine hydrochloride **3** (2 mmol), and NaOH (0.1 g) was put in a reaction flask and let at 75°C for about 30 min. After completing the reaction, the reaction mixture was poured into water (0.5% HCl) and then washed with water thoroughly. The product was filtered, dried, and recrystallized from 95% ethanol.

4-(4-Chlorophenyl)-2-methyl-6-phenylpyrimidine (4a). This compound was obtained as white crystals, mp 95–96°C; IR: (KBr, ν, cm^{-1}): 3054, 2842, 1585, 1570, 1533, 1441, 1393, 1234, 1183, 1159, 1119, 1089, 1031, 1013, 1001, 990, 907, 867, 834, 779, 753, 713, 686, 642, 602, 582 cm^{-1}; ^{1}H NMR: (400 Hz, DMSO-d_6), (δ, ppm): 2.73 (3H, s, CH$_3$), 7.56–7.58 (3H, m, ArH), 7.62 (2H, d, $J = 8.0$ Hz, ArH), 8.33–8.36 (3H, m, ArH), 8.40 (2H, $J = 8.0$ Hz, ArH). *Anal.* Calcd for $C_{17}H_{13}ClN_2$: C, 72.73; H, 4.67; N, 9.98. Found: C, 72.60; H, 4.70; N, 9.94. HRMS *m/z* calculated for $C_{17}H_{13}ClN_2$ [M + H]: 281.0846; found: 281.0845.

4-(4-Fluorophenyl)-2-methyl-6-phenylpyrimidine (4b). This compound was obtained as white crystals, mp 100–102°C, Lit. [12] 108–109°C; IR: (KBr, ν, cm^{-1}): 3042, 2932, 1602, 1578, 1534, 1509, 1417, 1394, 1369, 1297, 1227, 1163, 1099, 1074,

Table 2

Synthesis of 2-methyl-4,6-diarylpyrimidine derivatives under solvent-free conditions.

Entry	Ar^1	Ar^2	Product	Yields
1	4-ClC_6H_4	C_6H_5	**4a**	96
2	4-FC_6H_4	C_6H_5	**4b**	95
3	4-$CH_3C_6H_4$	C_6H_5	**4c**	89
4	4-$CH_3OC_6H_4$	C_6H_5	**4d**	90
5	4-FC_6H_4	4-$CH_3OC_6H_4$	**4e**	92
6	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	**4f**	90
7	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	**4g**	84
8	3-ClC_6H_4	4-$CH_3OC_6H_4$	**4h**	87
9	3,4-$(CH_3)_2C_6H_3$	4-$CH_3OC_6H_4$	**4i**	90
10	3,4-$(CH_3O)_2C_6H_3$	4-$CH_3OC_6H_4$	**4j**	80
11	4-FC_6H_4	3-ClC_6H_4	**4k**	92
12	4-$CH_3C_6H_4$	3-ClC_6H_4	**4l**	88
13	4-FC_6H_4	4-$CH_3C_6H_4$	**4m**	87
14	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	**4n**	86
15	4-FC_6H_4	4-ClC_6H_4	**4o**	89
16	4-ClC_6H_4	4-ClC_6H_4	**4p**	90
17	4-$CH_3C_6H_4$	4-ClC_6H_4	**4q**	92
18	4-$CH_3OC_6H_4$	4-ClC_6H_4	**4r**	90
19	3,4-$(CH_3)_2C_6H_3$	4-ClC_6H_4	**4s**	80
20	3,4-$(CH_3O)_2C_6H_3$	4-ClC_6H_4	**4t**	84
21	3-ClC_6H_4	4-ClC_6H_4	**4u**	94
22	3,4-$Cl_2C_6H_3$	4-ClC_6H_4	**4v**	88
23	4-BrC_6H_4	4-ClC_6H_4	**4w**	83

1012, 841, 777, 756, 720, 690, 648 cm^{-1}; ^{1}H NMR: (400 Hz, DMSO-d_6), (δ, ppm): 2.75 (3H, s, CH_3), 7.40 (2H, d, J = 8.8 Hz, J = 8.8 Hz, ArH), 7.57 (3H, t, J =3.6 Hz, J = 2.8 Hz, ArH), 8.33–8.36 (2H, m, ArH), 8.41–8.45 (3H, m, ArH). *Anal.* Calcd for $C_{17}H_{13}FN_2$: C, 77.25; H, 4.96; N, 10.60. Found: C, 77.40; H, 4.94; N, 10.56. HRMS *m/z* calculated for $C_{17}H_{13}FN_2$ [M + H]: 265.1141; found: 265.1146.

2-Methyl-4-phenyl-6-*p*-tolylpyrimidine (4c). This compound was obtained as white crystals, mp 99–100°C; IR: (KBr, ν, cm^{-1}): 3034, 2920, 1572, 1528, 1448, 1390, 1367, 1344, 1305, 1235, 1186, 1122, 1077, 1021, 989, 904, 875, 834, 818, 782, 759, 717, 698, 648 cm^{-1}; ^{1}H NMR: (400 Hz, DMSO-d_6), (δ, ppm): 2.40 (3H, s, CH_3), 2.74 (3H, s, CH_3), 7.37 (2H, d, J = 8.0 Hz, ArH), 7.56 (3H, t, J = 3.6 Hz, J = 3.6 Hz, ArH), 8.25 (2H, d, J = 8.0 Hz, ArH), 8.32–8.34 (2H, m, ArH), 8.36 (1H, s, ArH). *Anal.* Calcd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.19; N, 10.76. Found: C, 83.20; H, 6.17; N, 10.72. HRMS *m/z* calculated for $C_{18}H_{16}N_2$ [M + H]: 261.1392; found: 261.1390.

4-(4-Methoxyphenyl)-2-methyl-6-phenylpyrimidine (4d). This compound was obtained as white crystals, mp 94–96°C, Lit. [13] 103–104°C; IR: (KBr, ν, cm^{-1}): 2965, 2842, 1602, 1573, 1441, 1368, 1295, 1255, 1185, 1170, 1030, 987, 874, 829, 783, 763, 727, 698, 589 cm^{-1}; ^{1}H NMR: (400 Hz, DMSO-d_6), (δ, ppm): 2.72 (3H, s, CH_3), 3.85 (3H, s, OCH_3), 7.10 (2H, d, J = 8.8 Hz, ArH), 7.56 (3H, t, J = 2.8 Hz, J = 3.2 Hz, ArH), 8.32 (5H, d, J = 6.4 Hz, ArH). *Anal.* Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14. Found: C, 78.19; H, 5.86; N, 10.18. HRMS *m/z* calculated for $C_{18}H_{16}N_2O$ [M + H]: 277.1341; found: 277.1338.

4-(4-Fluorophenyl)-6-(4-methoxyphenyl)-2-methylpyrimidine (4e). This compound was obtained as white crystals, mp 107–109°C; IR: (KBr, ν, cm^{-1}): 3041, 3005, 2972, 2938, 2937, 1602, 1509, 1414, 1371, 1299, 1259, 1173, 1096, 1030, 846, 822, 764 cm^{-1}; ^{1}H NMR: (400 Hz, DMSO-d_6), (δ, ppm): 2.71 (3H, s, CH_3), 3.85 (3H, s, OCH_3), 7.10 (2H, d, J = 8.8 Hz, ArH), 7.39 (2H, t, J = 8.8 Hz, J = 8.8 Hz, ArH), 8.32 (3H, d, J = 6.8 Hz, ArH), 8.38–8.42 (2H, dd, J = 5.6 Hz, J = 5.6 Hz, ArH). *Anal.* Calcd for $C_{18}H_{15}FN_2O$: C, 73.45; H, 5.14; N, 9.52. Found: C, 73.51; H, 5.15; N, 9.50. HRMS *m/z* calculated for $C_{18}H_{15}FN_2O$ [M + H]: 295.1247; found: 295.1248.

4-(4-Methoxyphenyl)-2-methyl-6-*p*-tolylpyrimidine (4f). This compound was obtained as white crystals, mp 119–120°C; IR: (KBr, ν, cm^{-1}): 3014, 2968, 2971, 2840, 1609, 1585, 1525, 1456, 1442, 1410, 1371, 1340, 1303, 1256, 1172, 1113, 1024, 827, 776, 759, 574 cm^{-1}; ^{1}H NMR: (400 Hz, DMSO-d_6), (δ, ppm): 2.40 (3H, s, CH_3), 2.71 (3H, s, CH_3), 3.86 (3H, s, OCH_3), 7.09 (2H, d, J = 8.8 Hz, ArH), 7.36 (2H, d, J = 8.0, Hz, ArH), 8.23 (2H, d, J = 8.0 Hz, ArH), 8.28 (1H, s, ArH), 8.32 (2H, d, J = 8.4 Hz, ArH). *Anal.* Calcd for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.70; H, 6.27; N, 9.62. HRMS *m/z* calculated for $C_{19}H_{18}N_2O$ [M + H]: 291.1497; found: 291.1499.

4,6-Bis(4-methoxyphenyl)-2-methylpyrimidine (4g). This compound was obtained as white crystals, mp 159–160°C; IR: (KBr, ν, cm^{-1}): 3006, 2969, 2939, 2839, 1606, 1525, 1455, 1416, 1374, 1302, 1255, 1171, 1113, 1026, 830, 777, 636, 575 cm^{-1}; ^{1}H NMR: (400 Hz, DMSO-d_6), (δ, ppm): 2.69 (3H, s, CH_3), 3.85 (6H, s, 2 × OCH_3), 7.09 (4H, d, J = 8.8 Hz, ArH), 8.25 (1H, s, ArH), 8.32 (4H, d, J = 8.8 Hz, ArH). *Anal.* Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.62; H, 5.89; N, 9.18. HRMS *m/z* calculated for $C_{19}H_{18}N_2O_2$ [M + H]: 307.1447; found: 307.1446.

4-(3-Chlorophenyl)-6-(4-methoxyphenyl)-2-methylpyrimidine (4h). This compound was obtained as white crystals, mp 85–86°C; IR: (KBr, ν, cm^{-1}): 3066, 2974, 2938, 2842, 1608, 1572, 1511, 1462, 1420, 1364, 1292, 1240, 1192, 1174, 1027, 831, 802, 691, 590 cm^{-1}; ^{1}H NMR: (400 Hz, DMSO-d_6), (δ, ppm): 2.71 (3H, s, CH_3), 3.86 (3H, s, OCH_3), 7.10 (2H, d, J = 8.8 Hz, ArH), 7.57–7.63 (2H, m, ArH), 8.30 (1H, d, J = 7.2 Hz, ArH), 8.34 (2H, d, J = 8.8 Hz, ArH), 8.39 (2H, s, ArH). *Anal.* Calcd for $C_{18}H_{15}ClN_2O$: C, 69.57; H, 4.86; N, 9.01. Found: C, 69.66; H, 4.84; N, 9.05. HRMS *m/z* calculated for $C_{18}H_{15}ClN_2O$ [M + H]: 311.0951; found: 311.0951.

4-(3,4-Dimethylphenyl)-6-(4-methoxyphenyl)-2-methylpyrimidine (4i). This compound was obtained as white crystals, mp 92–93°C; IR: (KBr, ν, cm^{-1}): 3010, 2966, 2938, 2919, 2841, 1610, 1574, 1455, 1410, 1360, 1339, 1303, 1243, 1171, 1113, 1025, 874, 828, 805, 761, 578 cm^{-1}; ^{1}H NMR: (400 Hz, DMSO-d_6), (δ, ppm): 2.30 (3H, s, CH_3), 2.34 (3H, s, CH_3), 2.71 (3H, s, CH_3) 3.85 (3H, s, OCH_3), 7.09 (2H, d, J = 9.2 Hz, ArH), 7.30 (1H, d, J = 7.6 Hz, ArH), 8.05 (1H, d, J = 8.0 Hz, ArH), 8.20 (1H, s, ArH), 8.27 (1H, s, ArH), 8.31 (2H, d, J = 8.8 Hz, ArH). *Anal.* Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.78; H, 6.65; N, 9.16. HRMS *m/z* calculated for $C_{20}H_{20}N_2O$ [M + H]: 305.1654; found: 305.1654.

4-(3,4-Dimethoxyphenyl)-6-(4-methoxyphenyl)-2-methylpyrimidine (4j). This compound was obtained as white crystals, mp 116–117°C; IR: (KBr, ν, cm^{-1}): 3086, 2997, 2960, 2931, 2833, 1574, 1510, 1439, 1362, 1345, 1293, 1251, 1172, 1117, 1095, 1020, 883, 832, 803, 765, 616, 575 cm^{-1}; ^{1}H NMR: (400 Hz, DMSO-d_6), (δ, ppm): 2.70 (3H, s, CH_3), 3.85 (6H, s, 2 × OCH_3), 3.90 (3H, s, CH_3), 7.09–7.12 (3H, dd, J = 4.4 Hz, J = 4.4 Hz, ArH), 7.86 (1H, d, J = 2.0 Hz, ArH), 7.96 (1H, dd, J = 2.0 Hz, J = 2.0 Hz, ArH), 8.26 (1H, s, ArH), 8.32 (2H, d, J = 8.8 Hz, ArH). *Anal.* Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.55; H, 5.97; N, 8.29. HRMS *m/z* calculated for $C_{20}H_{20}N_2O_3$ [M + H]: 337.1552; found: 337.1555.

4-(3-Chlorophenyl)-6-(4-fluorophenyl)-2-methylpyrimidine (4k). This compound was obtained as white crystals, mp 105–106°C; IR: (KBr, ν, cm^{-1}): 3020, 2925, 1582, 1537, 1505, 1365, 1296, 1221, 1158, 1126, 1096, 1013, 990, 869, 854, 832, 791, 764, 715, 688, 653 cm^{-1}; ^{1}H NMR: (400 Hz, DMSO-d_6), (δ, ppm): 2.71 (3H, s, CH_3), 7.37 (2H, t, J = 8.8 Hz, J = 8.8 Hz, ArH), 7.58 (2H, t, J = 8.8 Hz, J = 8.8 Hz, ArH), 8.27 (1H, d, J = 7.2 Hz, ArH), 8.37–8.41 (4H, m, ArH). *Anal.* Calcd for $C_{17}H_{12}ClFN_2$: C, 68.35; H, 4.05; N, 9.38. Found: C, 68.45; H, 4.07; N, 9.34. HRMS *m/z* calculated for $C_{17}H_{12}ClFN_2$ [M + H]: 299.0751; found: 299.0751.

4-(3-Chlorophenyl)-2-methyl-6-*p*-tolylpyrimidine (4l). This compound was obtained as white crystals, mp 76–77°C; IR: (KBr, ν, cm^{-1}): 3025, 2930, 1612, 1569, 1511, 1364, 1238, 1181, 1126, 1068, 989, 834, 815, 799, 761, 714, 690, 655, 646 cm^{-1}; ^{1}H NMR: (400 Hz, DMSO-d_6), (δ, ppm): 2.40 (3H, s, CH_3), 2.74 (3H, s, CH_3), 7.37 (2H, d, J = 8.0 Hz, ArH), 7.57–7.64 (2H, m, ArH), 8.27 (2H, d, J = 8.4 Hz, ArH), 8.31 (1H, d, J = 7.6 Hz, ArH), 8.41 (2H, d, J = 9.2 Hz, ArH). *Anal.* Calcd for $C_{18}H_{15}ClN_2$: C, 73.34; H, 5.13; N, 9.50. Found: C, 73.45; H, 5.15; N, 9.47. HRMS *m/z* calculated for $C_{18}H_{15}ClN_2$ [M + H]: 295.1002; found: 295.1004.

4-(4-Fluorophenyl)-2-methyl-6-*p*-tolylpyrimidine (4m). This compound was obtained as white crystals, mp 95–96°C; IR: (KBr, ν, cm^{-1}): 3020, 2924, 1591, 1584, 1536, 1507, 1445, 1411, 1362, 1226, 1162, 1123, 1097, 1013, 847, 826, 814, 760, 642 cm^{-1}; ^{1}H NMR: (400 Hz, DMSO-d_6), (δ, ppm): 2.39 (3H, s, CH_3), 2.72 (3H, s, CH_3), 735–7.41 (4H, m, ArH), 8.24 (2H, d, $J = 8.0$ Hz, ArH), 8.35 (1H, s, ArH), 8.38–8.42 (2H, dd, $J = 5.6$ Hz, $J = 5.6$ Hz, ArH).

Anal. Calcd for $C_{18}H_{15}FN_2$: C, 77.68; H, 5.43; N, 10.07. Found: C, 77.57; H, 5.40; N, 10.11. HRMS *m*/*z* calculated for $C_{18}H_{15}FN_2$ [M + H]: 279.1298; found: 279.1296.

2-Methyl-4,6-dip-tolylpyrimidine (4n). This compound was obtained as white crystals, mp 130–131°C, Lit. [14] 137–139°C; IR: (KBr, ν, cm^{-1}): 3026, 2920, 1582, 1508, 1444, 1408, 1365, 1240, 1208, 1122, 1017, 826, 813, 758, 600 cm^{-1}; ^{1}H NMR: (400 Hz, DMSO-d_6), (δ, ppm): 2.40 (6H, s, 2 × CH_3), 2.73 (3H, s, CH_3), 7.37 (4H, d, $J = 8.0$ Hz, ArH), 8.24 (4H, d, $J = 8.0$ Hz, ArH), 8.32 (1H, s, ArH). *Anal*. Calcd for $C_{19}H_{18}N_2$: C, 83.18; H, 6.61; N, 10.21. Found: C, 83.27; H, 6.59; N, 10.24. HRMS *m*/*z* calculated for $C_{19}H_{18}N_2$ [M + H]: 275.1548; found: 275.1549.

4-(4-Chlorophenyl)-6-(4-fluorophenyl)-2-methylpyrimidine (4o). This compound was obtained as white crystals, mp 148–149°C; IR: (KBr, ν, cm^{-1}): 3044, 2972, 2950, 2851, 1600, 1548, 1509, 1491, 1415, 1391, 1364, 1229, 1162, 1088, 1012, 829, 762, 590 cm^{-1}; ^{1}H NMR: (400 Hz, DMSO-d_6), (δ, ppm): 2.74 (3H, s, CH_3), 7.40 (2H, t, $J = 8.8$ Hz, $J = 8.8$ Hz, ArH), 7.63 (2H, d, $J = 8.4$ Hz, ArH), 8.37 (1H, s, ArH), 8.39–8.45 (4H, m, ArH). *Anal*. Calcd for $C_{17}H_{12}ClFN_2$: C, 68.35; H, 4.05; N, 9.38. Found: C, 68.21; H, 4.07; N, 9.35. HRMS *m*/*z* calculated for $C_{17}H_{12}ClFN_2$ [M + H]: 299.0751; found: 299.0740.

4,6-Bis(4-chlorophenyl)-2-methylpyrimidine (4p). This compound was obtained as white crystals, mp 144–146°C; IR: (KBr, ν, cm^{-1}): 3057, 2978, 2955, 2859, 1565, 1529, 1488, 1365, 1291, 1232, 1172, 1120, 1091, 1012, 827, 804, 763, 726 cm^{-1}; ^{1}H NMR: (400 Hz, DMSO-d_6), (δ, ppm): 2.72 (3H, s, CH_3), 7.61 (4H, d, $J = 8.4$ Hz ArH), 8.35 (4H, d, $J = 8.4$ Hz, ArH), 8.42 (1H, s, ArH). *Anal*. Calcd for $C_{17}H_{12}Cl_2N_2$: C, 64.78; H, 3.84; N, 8.89. Found: C, 64.65; H, 3.82; N, 8.85. HRMS *m*/*z* calculated for $C_{17}H_{12}Cl_2N_2$ [M + H]: 315.0456; found: 315.0464.

4-(4-Chlorophenyl)-2-methyl-6-*p*-tolylpyrimidine (4q). This compound was obtained as white crystals, mp 120–121°C; IR: (KBr, ν, cm^{-1}): 3025, 2950, 2922, 2830, 1580, 1509, 1491, 1407, 1237, 1212, 1188, 1121, 1099, 1089, 1011, 825, 813, 778, 758, 708 cm^{-1}; ^{1}H NMR: (400 Hz, DMSO-d_6), (δ, ppm): 2.40 (3H, s, CH_3), 2.73 (3H, s, CH_3), 7.37 (2H, d, $J = 8.4$ Hz, ArH), 7.62 (2H, d, $J = 8.4$ Hz, ArH), 8.25 (2H, d, $J = 8.4$ Hz, ArH), 8.37 (3H, d, $J = 8.8$ Hz, ArH).

Anal. Calcd for $C_{18}H_{15}ClN_2$: C, 73.34; H, 5.13; N, 9.50. Found: C, 73.46; H, 5.15; N, 9.47. HRMS *m*/*z* calculated for $C_{18}H_{15}ClN_2$ [M + H]: 295.1002; found: 295.1009.

4-(4-Chlorophenyl)-6-(4-methoxyphenyl)-2-methylpyrimidine (4r). This compound was obtained as white crystals, mp 120–121°C; IR: (KBr, ν, cm^{-1}): 3055, 2974, 2935, 2834, 1610, 1586, 1530, 1513, 1491, 1454, 1412, 1368, 1288, 1257, 1235, 1169, 1119, 1097, 1024, 1010, 819, 779, 761, 594, 575 cm^{-1}; ^{1}H NMR: (400 Hz, DMSO-d_6), (δ, ppm): 2.71 (3H, s, CH_3), 3.85 (3H, s, OCH_3), 7.09 (2H, d, $J = 8.4$ Hz, ArH), 7.61 (2H, d, $J = 8.4$ Hz, ArH), 8.31 (1H, s, ArH), 8.33–8.37 (4H, t, $J = 7.2$ Hz, $J = 7.2$ Hz, ArH).

Anal. Calcd for $C_{18}H_{15}ClN_2O$: C, 69.57; H, 4.86; N, 9.01. Found: C, 69.45; H, 4.84; N, 9.04. HRMS *m*/*z* calculated for $C_{18}H_{15}ClN_2O$ [M + H]: 311.0951; found: 311.0948.

4-(4-Chlorophenyl)-6-(3,4-dimethylphenyl)-2-methylpyrimidine (4s). This compound was obtained as white crystals, mp 96–97°C; IR: (KBr, ν, cm^{-1}): 2967, 2942, 2920, 2855, 1581, 1530, 1490, 1443, 1407, 1369, 1340, 1283, 1244, 1132, 1104, 1086, 1023, 1011, 873, 832, 788, 763, 583 cm^{-1}; ^{1}H NMR: (400 Hz, DMSO-d_6), (δ, ppm): 2.29 (3H, s, CH_3), 2.33 (3H, s, CH_3), 2.71 (3H, s, CH_3), 7.30 (1H, d, $J = 8.0$ Hz, ArH), 7.61(2H, d, $J = 8.8$ Hz, ArH), 8.06 (1H, d, $J = 8.0$ Hz, ArH), 8.12 (1H, s, ArH), 8.34 (2H, d, $J = 2.4$ Hz, ArH), 8.36 (1H, s, ArH).

Anal. Calcd for $C_{19}H_{17}ClN_2$: C, 73.90; H, 5.55; N, 9.07. Found: C, 73.81; H, 5.57; N, 9.11. HRMS *m*/*z* calculated for $C_{19}H_{17}ClN_2$ [M + H]: 309.1159; found: 309.1159.

4-(4-Chlorophenyl)-6-(3,4-dimethoxyphenyl)-2-methylpyrimidine (4t). This compound was obtained as white crystals, mp 135–137°C; IR: (KBr, ν, cm^{-1}): 3002, 2973, 2959, 2934, 2831, 1584, 1489, 1440, 1410, 1324, 1268, 1216, 1178, 1134, 1096, 1025, 843, 822, 808, 785, 767, 622, 612, 580 cm^{-1}; ^{1}H NMR: (400 Hz, DMSO-d_6), (δ, ppm): 2.72 (3H, s, CH_3), 3.85 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 7.11(1H, d, $J = 8.4$ Hz, ArH), 7.62 (2H, d, $J = 8.8$ Hz, ArH), 7.87 (1H, d, $J = 2.0$ Hz, ArH), 7.97–7.99 (1H, dd, $J = 2.0$ Hz, J =2.0 Hz, ArH), 8.36 (2H, s, ArH), 8.38 (1H, s, ArH). *Anal*. Calcd for $C_{19}H_{17}Cl_2N_2O_2$: C, 66.96; H, 5.03; N, 8.22. Found: C, 66.82; H, 5.05; N, 8.18. HRMS *m*/*z* calculated for $C_{19}H_{17}ClN_2O_2$ [M + H]: 341.1057; found: 341.1057.

4-(3-Chlorophenyl)-6-(4-chlorophenyl)-2-methylpyrimidine (4u). This compound was obtained as white crystals, mp 111–113°C; IR: (KBr, ν, cm^{-1}): 3006, 2977, 2963, 2835, 1580, 1491, 1408, 1366, 1294, 1266, 1235, 1178, 1127, 1090, 1013, 845, 833, 812, 793, 766, 734, 695, 689, 654, 642 cm^{-1}; ^{1}H NMR: (400 Hz, DMSO-d_6), (δ, ppm): 2.73 (3H, s, CH_3), 7.56–7.62 (4H, m, ArH) 8.30 (1H, d, $J = 7.2$ Hz, ArH), 8.37 (3H, d, $J = 8.8$ Hz, ArH), 8.47 (1H, s, ArH). *Anal*. Calcd for $C_{17}H_{12}Cl_2N_2$: C, 64.78; H, 3.84; N, 8.89. Found: C, 64.59; H, 3.86; N, 9.92. HRMS *m*/*z* calculated for $C_{17}H_{12}Cl_2N_2$ [M + H]: 315.0456; found: 315.0451.

4-(4-Chlorophenyl)-6-(3,4-dichlorophenyl)-2-methylpyrimidine (4v). This compound was obtained as white crystals, mp 178–179°C; IR: (KBr, ν, cm^{-1}): 3021, 2992, 2978, 2850, 1595, 1575, 1491, 1472, 1405, 1387, 1339, 1398, 1233, 1139, 1088, 1026, 1011, 866, 850, 824, 765, 752, 699, 675 cm^{-1}; ^{1}H NMR: (400 Hz, DMSO-d_6), (δ, ppm): 2.73 (3H, s, CH_3), 7.62 (2H, d, $J = 8.4$ Hz, ArH), 7.81 (1H, d, $J = 8.4$ Hz, ArH), 8.32 (1H, d, $J = 8.4$ Hz, ArH), 8.37 (2H, d, $J = 8.4$ Hz, ArH), 8.50 (1H, s, ArH), 8.59 (1H, s, ArH). *Anal*. Calcd for $C_{17}H_{11}Cl_3N_2$: C, 58.40; H, 3.17; N, 8.01. Found: C, 58.56; H, 3.19; N, 8.04. HRMS *m*/*z* calculated for $C_{17}H_{11}Cl_3N_2$ [M + H]: 349.0066; found: 349.0053.

4-(4-Bromophenyl)-6-(4-chlorophenyl)-2-methylpyrimidine (4w). This compound was obtained as white crystals, mp 142–144°C; IR: (KBr, ν, cm^{-1}): 2968, 2943, 2921, 2856, 1582, 1526, 1485, 1439, 1407, 1388, 1365, 1241, 1292, 1232, 1097, 1088, 1069, 1010, 825, 805, 762 cm^{-1}; ^{1}H NMR: (400 Hz, DMSO-d_6), (δ, ppm): 2.72 (3H, s, CH_3), 7.60 (2H, d, $J =$ 8.8 Hz, ArH), 7.74 (2H, d, $J = 8.8$ Hz, ArH), 8.27 (2H, d, $J = 8.4$ Hz, ArH), 8.34 (2H, d, $J = 8.4$ Hz, ArH), 8.42 (1H, s, ArH). *Anal*. Calcd for $C_{17}H_{12}BrClN_2$: C, 56.77; H, 3.36; N, 7.79. Found: C, 56.65; H, 3.34; N, 7.75. HRMS *m/z* calculated for $C_{17}H_{12}ClBrN_2$ [M + H]: 358.9951; found: 358.9951.

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Ethyl {4-[2-(Saccharin-2-yl)acetylsulfamoyl]phenylazo}cyanoacetate in the Synthesis of Polyfunctionally Heteroaromatic Derivatives

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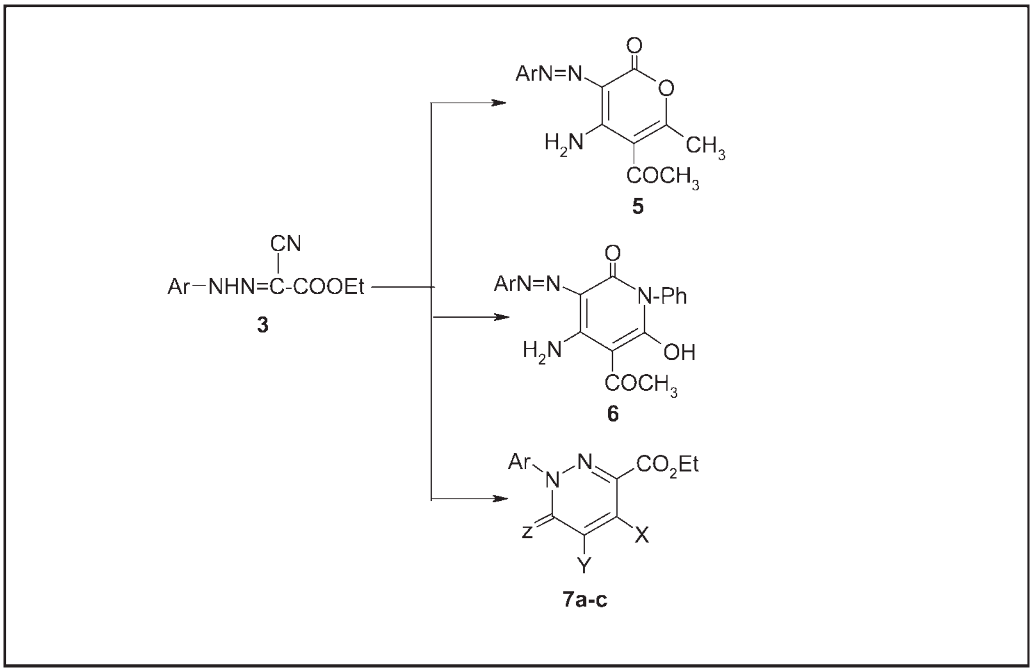

An efficient and direct one-pot reaction of ethyl saccharinylcyanoacetate derivative **3** with a variety of active methylene reagents and nitrogen nucleophiles afforded novel series of polyfunctionally substituted heteroaromatic derivatives **5–13**, respectively. The pyrazole derivative **13** was seemed to be the excellent precursors for the synthesis of pyrazolo[1,5-a]pyrimidine derivatives **14–24**. The antimicrobial screening of some synthesized products was evaluated against some selected bacteria and fungi. The structures of the synthesized derivatives were established by elemental and spectral data.

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INTRODUCTION

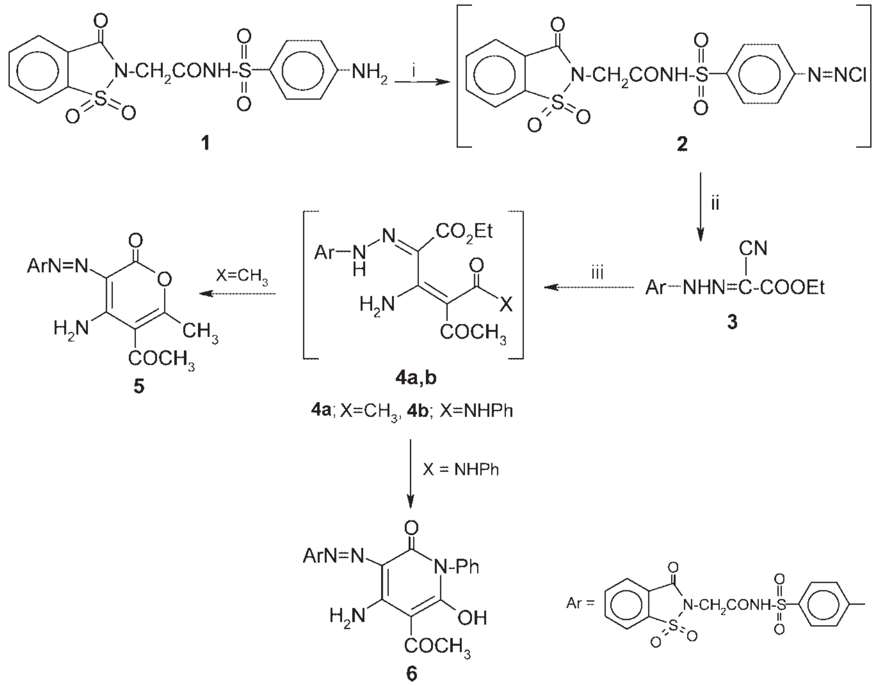
The increasing medicinal potential of both saccharine and sulfonamide derivatives as intermediate to biologically active compounds [1–5] and in continuation of our efforts [6,7] in the synthesis of heterocyclic systems incorporating saccharinyl and sulfonamide moieties as potential pharmaceuticals. We reported here on the utility of ethyl saccharinylcyanoacetate **3** as building blocks for synthesis of new polyfunctionally substituted heteroaromatic derivatives of pyran, pyridine, pyridazine, triazine, pyrimidine, and their analogues of sulfonamido moiety of promising therapeutic applications [8–13].

RESULTS AND DISCUSSION

The key starting material ethyl {4-[2-(saccharin-2-yl)-acetylsulfamoyl]phenylazo}cyanoacetate (**3**) was prepared by diazotization of the sulfanilamide derivative **1** followed by coupling the resulting intermediate **2** with ethyl cyanoacetate in ethanolic sodium acetate solution at 0–5°C. The structure of compound **3** was established on the basis of its elemental analysis and spectral data. Thus, its IR spectrum showed bands at 3320 and 3290 cm^{-1} for νNH groups, 2220 cm^{-1} for νCN, and at 1725, 1680 cm^{-1} for carbonyl groups. The ^{1}H NMR spectrum showed signals as triplet at $\delta = 1.53$ for methyl proton, quartet at 4.50, singlet at $\delta = 4.85$ for two methylene protons, multiplets at $\delta = 7.21$–8.35 for aromatic protons and two singlet at $\delta = 8.53$, 9.01 for 2NH protons, which disappeared upon addition of D$_2$O to the NMR sample (Scheme 1).

The reactivity of compound **3** toward 1,3-dicarbonyl compounds was investigated with respect to the synthesis of highly substituted pyran and pyridine. Thus, the reaction of equimolar amounts of compound **3** and acetylacetone and/or acetoacetanilide derivative in refluxing

Scheme 1. (i) $NaNO_2/AcOH/HCl$; (ii) $NCCH_2COOEt$, AcONa; (iii) $CH_3COCH_2COCH_3$ or $CH_3COCH_2CONHPh$, dioxane, Et_3N.



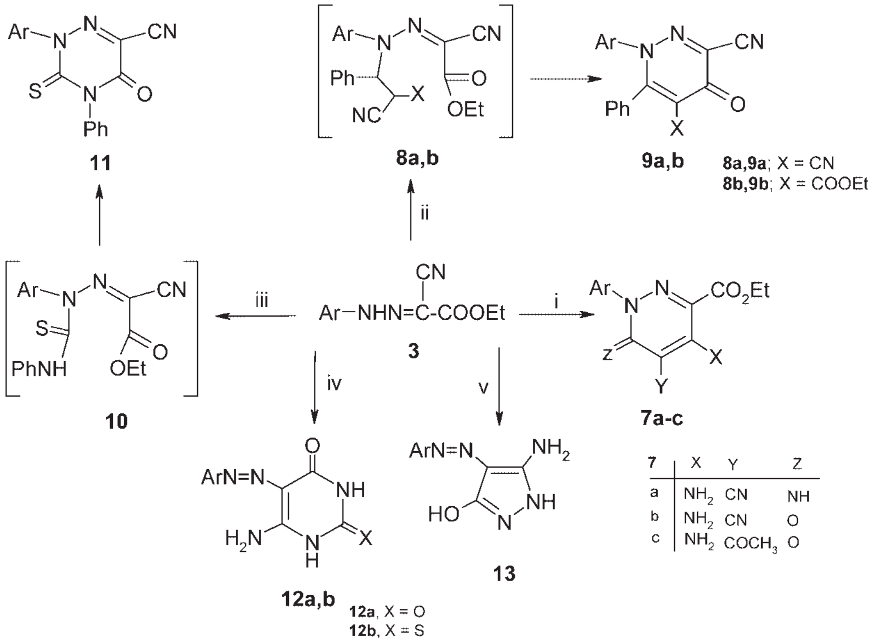
1,4-dioxane containing a few drops of triethylamine afforded 4-(5-acetyl-4-amino-6-methyl-2-oxo-2*H*-pyran-3-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (**5**) and 4-(5-acetyl-4-amino-6-hydroxy-2-oxo-1-phenyl-1,2-dihydropyridin-3-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]-benzenesulfonamide (**6**), respectively. In a similar manner, the treatment of compound **3** with malononitrile or ethyl cyanoacetate and/or ethyl acetoacetate afforded the pyridazine derivatives **7a–c**, respectively (Scheme 2). Moreover, the reaction of compound **3** with 2-benzylidenemalononitrile and/or ethyl 2-cyano-3-phenylacrylate in refluxing 1,4-dioxane containing a few drops of triethylamine yielded the pyridazine derivatives **9a,b**.

The formation of compounds **9a,b** are assumed to proceed *via* Michael-type addition of the NH of the hydrazone moiety in **3** to the activated α,β-unsaturated center of substituted cinnamonitriles, yielding a cyclic Michael adducts **8a,b**, which are cyclized followed by the aromatization to the final products **9a,b** *via* elimination of an ethanol molecule and subsequent dehydrocyanation. The reaction of compound **3** with phenyl isothiocyanate afforded 4-(6-cyano-5-oxo-4-phenyl-3-thioxo-4,5-dihydro-3*H*-[1,2,4]triazin-2-yl)-*N*-[2-(saccharin-2-yl)-acetyl]benzenesulfonamide(**11**). Compound **11** was assumed to be formed *via* an initial nucleophilic attack of NH group of compound **3** on the isothiocyanate moiety giving the adduct **10**, which cyclized *via* the elimination of ethanol molecule to give compound **11**. The structure of compound **11** was assigned on the basis of their elemental analysis and spectral data. Its IR spectrum showed bands at 3290 cm^{-1} for νNH, 2215 cm^{-1} for νCN, and 1685–1675 cm^{-1} for νCO.

As an extension of such synthetic route, the behavior of hydrazonoester **3** toward some nitrogen nucleophiles was investigated with the aim of synthesizing a biologically active substituted pyrimidine and pyrazole derivatives. Thus, the reaction of compound **3** with equimolar amounts of urea or thiourea, in refluxing ethanolic sodium ethoxide solution gave the corresponding pyrimidine derivatives **12a,b**. While the reaction of compound **3** with hydrazine hydrate in refluxing absolute ethanol yielded, 4-(5-amino-3-hydroxy-1*H*-pyrazol-4-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (**13**). The structure of compound **13** was assigned on the basis of elemental analysis and spectral data which agree with the proposed structure (Scheme 2). 5-Aminopyrazole **13** has been emphasized as a new synthetic auxiliary used for the preparation of pyrazolo[1,5-a]pyrimidine derivatives [14,15], which associated with a great applications in pharmaceutical fields [16–19] and dyestuff industry [20,21]. Thus, the reaction of compound **13** with acetylacetone in refluxing glacial acetic acid afforded 4-(5,7-dimethyl-2-hydroxypyrazolo[1,5-a]pyrimidin-3-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (**14**). Reaction of compound **13** with aromatic aldehydes *viz* benzaldehyde and 4-methoxybenzaldehyde in absolute ethanol yielded Schiff bases **15a,b,** respectively (Scheme 3).

The study was extended to investigate the behavior of Schiff bases toward some active methylene compounds. Thus, the treatment of **15a,b** with malononitrile afforded

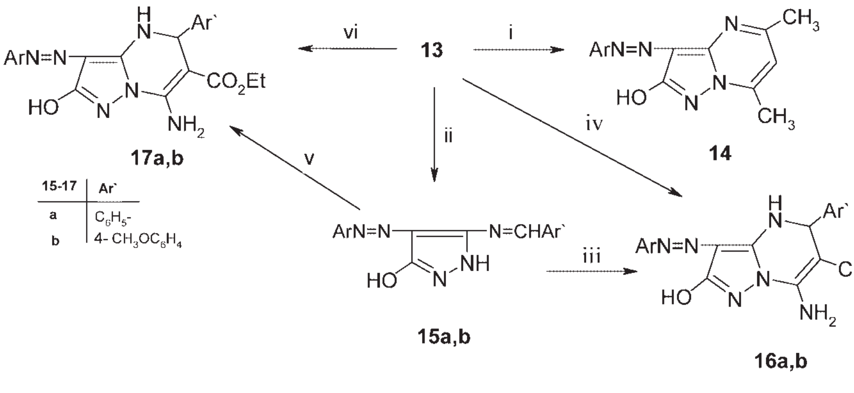
Scheme 2. (i) $NCCH_2CN$ or $NCCH_2CO_2Et$ or $CH_3COCH_2CO_2Et$, dioxane, Et_3N; (ii) $PhCH{=}C(CN)_2$ or $PhCH{=}C(CN)CO_2Et$, dioxane, Et_3N; (iii) PhNCS, dioxane, Et_3N; (iv) H_2NCONH_2 or H_2NCSNH_2, NaOEt; (v) $N_2H_4{\cdot}H_2O$, EtOH.



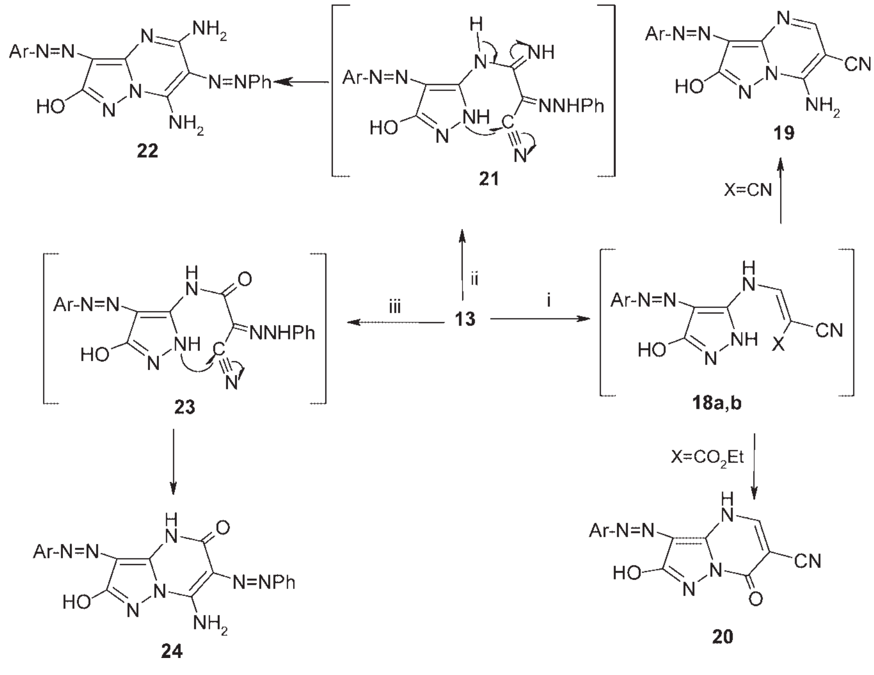
the pyrazolo[1,5-a]pyrimidines **16a,b**, which also obtained authentically, from the reaction of compound **13** with β-aryl-α-cyanoacrylonitrile derivatives in refluxing 1,4-dioxane, which are identical in all respects (m.p., m.m.p., and spectral data). The formation of compounds **16a,b** are assumed to proceed *via* initial addition of the active methylene of malononitrile to the double bond of the Schiff bases **15a,b** to form the non-isolable Michael adduct, which also formed *via* the initial attack of the exocyclic amino group of compound **13** on the activated double bond of acrylonitrile derivatives. This Michael adduct undergoes intramolecular cyclization to give compounds **16a,b**. Additionally, the reaction of Schiff bases **15a,b** with ethyl cyanoacetate yielded pyrazolo[1,5-a]pyrimidines **17a,b** which also obtained *via* independent synthesis from the reaction of compound **13** with β-aryl-α-cyanoacrylate derivatives, which are identical in all respects (m.p., m.m.p., and spectral data) (Scheme 3). Also, the treatment of compound **13** with ethoxymethylenemalononitrile and/or ethyl ethoxymethylenecyanoacetate in refluxing dimethylformamide containing a few drops of piperidine afforded the pyrazolopyrimidine derivatives **19** and **20**, respectively (Scheme 4).

The reaction of compound **13** with 2-phenylhydrazonomalononitrile [22] in refluxing absolute ethanol containing a few drops of pyridine afforded 4-(5,7-diamino-2-hydroxy-6-phenylazopyrazolo[1,5-a]pyrimidin-3-ylazo)-*N*-

Scheme 3. (i) $CH_3COCH_2COCH_3$, AcOH; (ii) Ar′CHO, EtOH; (iii) $CH_2(CN)_2$, EtOH, piperidine; (iv) Ar̀CH=C(CN)$_2$, 1,4-dioxane; (v) $NCCH_2CO_2Et$, EtOH, piperidine; (vi) Ar̀CH=C(CN)CO_2Et, 1,4-dioxane.



Scheme 4. (i) $EtOCH{=}C(X)CN$, DMF, piperidine; (ii) $PhNHN{=}C(CN)_2$, EtOH, pyridine; (iii) $PhNHN{=}C(CN)CO_2Et$, EtOH, pyridine.



[2-(saccharin-2-yl)acetyl]benzenesulfonamide (**22**). The formation of compound **22** was assumed *via* the condensation of the 5-NH_2 group of the pyrazole ring with the cyano group of malononitrile derivative to yield the intermediate **21**, in which internal nucleophilic attack of 1-NH group of the pyrazole ring on the other cyano group followed by a migration of 5-NH proton of the pyrazole ring to the nitrogen atom of imino group to yield the nonisolable adduct, which tautomerized forming the isolable product **22**. While, the reaction of compound **13** with ethyl 2-phenylhydrazonocyanoacetate [23] gave nonisolable intermediate **23**, which cyclized to afford 4-(7-amino-2-hydroxy-5-oxo-6-phenylazo-4,5-dihydropyrazolo[1,5-a]pyrimidin-3-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (**24**) (Scheme 4). The structures of the synthesized compounds were assigned on the basis of elemental analysis and spectral data (*c.f.*, experimental).

The antimicrobial activity. The antimicrobial activities of some synthesized compounds were screened *in vitro* using the hole plate and filter paper methods [24] for their antibacterial activity against *Escherichia coli* and *Pseudomonas aeruginosa* as gram-negative bacteria and *Staphylococcus aureus* as gram-positive bacteria.

Whereas the antifungal activity was tested against *Aspergillus niger* and *Fusarium oxysporium*. Ampicillin as an antibacterial agent and Clotrimazole as an antifungal were used as a reference drugs to evaluate the potency of the tested compounds under the same conditions. The minimal inhibitory concentration (MIC) values listed in Table 1 show that all the tested compounds have a similar or highest degree of inhibition area against the organisms relative to the reference drugs used.

EXPERIMENTAL

Melting points are uncorrected. IR spectra in KBr were recorded on a Perkin–Elmer 298 spectrophotometer.^{1}H and ^{13}C NMR spectra were obtained on an Varian Gemini 200 MHz instrument using TMS as internal reference with chemical shifts expressed as δ ppm. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 instrument (70 eV EI mode).

^{13}C NMR values of saccharinylsulfonamide moiety for compounds **5–24** are the same as in compound **3** with $\delta \pm 0.1–0.5$ ppm.

Ethyl {4-[2-(saccharin-2-yl)acetylsulfamoyl]phenylazo}-cyanoacetate (3). A cold solution of diazonium chloride **2** (30 mmol) [prepared from the addition of a cold solution of sodium nitrite (0.69 g, 10 mmol) in H_2O (5 mL) to a cold solution of compound **1** (3.95 g, 10 mmol) in concentrated hydrochloric acid (10 mL) and glacial acetic acid (10 mL) at 0–5°C] was added dropwise to a solution of ethyl cyanoacetate (30 mmol) in ethanol (30 mL) containing sodium acetate (5.0 g). After the complete addition of the diazonium chloride, the reaction mixture was stirred at room temperature overnight. The precipitated product which separated upon dilution with cold water (40 mL) was filtered off, washed with water (3 × 30 mL), dried and recrystallized from *n*-butanol to give **3**. Yield, 3.79 g (73%); m.p. 141–143°C; IR: ν = 3320, 3290 (NH), 2220 (CN), 1725, 1680 (CO), 1350, 1130 cm^{-1} (SO_2); ^{1}H NMR ($CDCl_3$): δ = 1.53 (t, 3H, CH_3), 4.50 (q, 2H, CH_2), 4.85 (s, 2H, CH_2), 7.21–8.35 (m, 8H, ArH), 8.53, 9.01 (2s, 2H, 2NH, exchangeable); ^{13}C NMR: δ = 14.5 (CH_3), 36.3

Table 1

In vitro antimicrobial activity of the tested compounds.

	E. coli		*P. aeruginosa*		*S. aureus*		*A. niger*		*F. oxysporium*	
Compound No	A	MIC	A	MIC	A	MIC	A	MIC	A	MIC
5	++	125	++	125	++	250	++	250	++	125
6	++	250	+	125	+++	250	+	250	++	500
7a	+++	500	++	250	++	125	++	250	+	125
9b	+++	125	++	250	+++	500	++	500	++	125
11	++	125	++	125	+	125	++	250	+++	125
12b	++	125	++	250	+++	250	++	125	++	250
13	++	250	++	125	++	125	++	125	+	250
16a	++	125	++	250	++	250	+	125	++	250
17b	++	125	++	250	++	125	++	250	++	250
19	++	250	+++	500	++	250	+	125	++	500
22	++	250	+++	125	++	125	+	125	+	250
24	++	125	+	250	++	250	+	250	+	250
Ampicillin	++	125	+++	250	++	125	−	−	−	−
Clotrimazole	−	−−	−	−	−	−	+++	125	+++	250

A, antimicrobial activity of tested compounds; MIC, minimum inhibitory concentration; −, inactive; +, > 5 mm, slightly active; ++, > 7 mm, moderately active; +++, > 9 mm, highly active.

(CH_2), 52.6 (CH_2CH_3), 65.3 (C-CN),108.2 (CN), 150.4 (CO), 118.3, 118.9, 120.3, 120.6, 129.2, 141.3 (phenyl ring), 125.3, 126.3, 127.1, 129.5, 130.1, 131.5 (phenyl ring), 146.5, 155.4 (2CO) (saccharinylsulfonamide moiety); Anal. Calcd. for $C_{20}H_{17}N_5O_8S_2$ (519.51): C, 46.24; H, 3.30; N, 13.48%. Found: C, 46.51; H, 3.50; N, 13.10%.

4-(5-Acetyl-4-amino-6-methyl-2-oxo-2*H*-pyran-3-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (5). A mixture of compound **3** (1.04 g, 2 mmol) and acetylacetone (2 mmol) in 1,4-dioxane (25 mL) containing a catalytic amount of Et_3N (0.4 mL) was heated under reflux for 8 h. The reaction mixture was concentrated *in vacuo* and the formed solid product was collected by filtration and recrystallized from ethanol to give **5**. Yield, 0.70 g (61%); m.p. 166–168°C; IR: ν = 3405–3240 (multiple bands, NH_2, NH), 1710, 1690, 1680 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 1.95 (s, 3H, CH_3), 2.10 (s, 3H, CH_3CO), 4.75 (s, 2H, CH_2), 5.85 (br s, 2H, NH_2), 7.25–8.12 (m, 8H, ArH), 8.30 (s, 1H, NH, exchangeable); ^{13}C NMR: δ = 16.2 (CH_3), 20.1 (CH_3CO), 81.3 (C-5), 89.5 (C-3), 136.3 (C-4), 141.4 (C-6), 161.2 (CO), 165.7 (C-2); Anal. Calcd. for $C_{23}H_{19}N_5O_9S_2$ (573.56): C, 48.16; H, 3.34; N, 12.21%. Found: C, 48.32; H, 3.50; N, 12.01%.

4-(5-Acetyl-4-amino-6-hydroxy-2-oxo-1-phenyl-1,2-dihydropyridin-3-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (6). A mixture of compound **3** (1.04 g, 2 mmol) and acetoacetanilide (2 mmol) in 1,4-dioxane (25 mL) containing a catalytic amount of Et_3N (0.4 mL) was heated under reflux for 8 h. The reaction mixture was concentrated *in vacuo* and the formed solid was collected by filtration and recrystallized from 1,4-dioxane to give **6**. Yield, 0.87 g (67%); m.p. 183–185°C; IR: ν = 3495–3200 (multiple bands, OH, NH_2, NH), 1705, 1680, 1675 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 1.95 (s, 3H, CH_3), 4.10 (s, 2H, CH_2), 5.95 (br s, 2H, NH_2), 7.30–8.3 (m, 13H, ArH), 8.35, 8.50 (2s, 2H, NH, and OH, exchangeable); Anal. Calcd. for $C_{28}H_{22}N_6O_9S_2$ (650.64): C, 51.69; H, 3.41; N, 12.92%. Found: C, 51.41; H, 3.19; N, 12.75%.

General procedure for the preparation of compounds 7a–c. A mixture of compound **3** (1.04 g, 2 mmol) and active methylene compounds *viz* malononitrile, ethyl cyanoacetate, and ethyl acetoacetate (2 mmol) in 1,4-dioxane (25 mL) containing a catalytic amount of Et_3N (0.4 mL) was heated under reflux for 10 h. The reaction mixture was cooled to room temperature, poured into crushed ice (20 g), and neutralized with diluted HCl. The resulting solid product was filtered off and recrystallized from proper solvent to give the compounds **7a–c**.

Ethyl 4-amino-5-cyano-6-imino-1-{4-[2-(saccharin-2-yl)acetylsulfamoyl]phenyl}-1,6-dihydropyridazine-3-carboxylate (7a). Yield, 0.69 g (59%) (DMF-H_2O); m.p. 173–175°C; IR: ν = 3310–3200 (NH_2, NH), 2215 (CN), 1730, 1680 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ = 1.65 (t, 3H, CH_3), 4.60 (q, 2H, CH_2), 4.80 (s, 2H, CH_2), 5.95 (s, 2H, NH_2), 7.18–8.15 (m, 8H, ArH), 8.20, 8.95 (2s, 2H, 2NH, exchangeable); Anal. Calcd. for $C_{23}H_{19}N_7O_8S_2$ (585.57): C, 47.18; H, 3.27; N, 16.74%. Found: C, 47.37; H, 3.51; N, 16.41%.

Ethyl 4-amino-5-cyano-6-oxo-1-{4-[2-(saccharin-2-yl)acetylsulfamoyl]phenyl}-1,6-dihydropyridazine-3-carboxylate (7b). Yield, 0.71 g (61%) (*n*-butanol); m.p. 220–222°C; IR: ν = 3340–3210 (NH_2, NH), 2220 (CN), 1725, 1680 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 1.45 (t, 3H, CH_3), 4.45 (q, 2H, CH_2), 4.75 (s, 2H, CH_2), 5.90 (br s, 2H, NH_2), 7.30–8.41 (m, 8H, ArH), 8.75 (s, 1H, NH, exchangeable); ^{13}C NMR: δ = 12.3 (CH_3), 50.3 (CH_2), 80.1 (C-5), 112.3 (CN), 140.2 (C-3), 150.2 (CO), 152.5 (C-6), 156.7 (C-4); Anal. Calcd. for $C_{23}H_{18}N_6O_9S_2$ (586.56): C, 47.10; H, 3.09; N, 14.33%. Found: C, 47.39; H, 3.34; N, 14.10%.

Ethyl 5-acetyl-4-amino-6-oxo-1-{4-[2-(saccharin-2-yl)acetylsulfamoyl]phenyl}-1,6-dihydropyridazine-3-carboxylate (7c). Yield, 0.86 g (71%) (1,4-dioxane); m.p. 212–214°C; IR: ν = 3230 (NH), 2225–2220 (CN), 1680–1675 cm^{-1} (CO); MS: *m*/*z* = 603 (M^+); Anal. Calcd. for $C_{24}H_{21}N_5O_{10}S_2$ (603.58): C, 47.76; H, 3.51; N, 11.60%. Found: C, 47.93; H, 3.75; N, 11.85%.

General procedure for the preparation of compounds 9a,b. A mixture of compound **3** (1.04 g, 2 mmol) and benzylidenemalononitrile or ethyl α-cyanocinnamate (2 mmol) in 1,4-dioxane (20 mL) containing a catalytic amount of triethylamine (0.4 mL) was heated under reflux for 9 h. The reaction mixture was cooled at room temperature, poured onto ice (20 g), and neutralized with diluted HCl. The formed solid product was filtered off and recrystallized from proper solvent to give **9a,b**.

4-(3,5-Dicyano-4-oxo-6-phenyl-4*H*-pyridazin-1-yl)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (9a). Yield, 0.88 g (73%) (benzene); m.p. 241–243°C; IR: ν = 3310 (NH), 2220–2215 (CN), 1705, 1680–1670, cm^{-1} (CO); ^{1}H NMR (DMSO-d$_6$): δ = 4.60 (s, 2H, CH$_2$), 7.40–8.31 (m, 13H, ArH), 8.45 (s, 1H, NH, exchangeable); Anal. Calcd. for $C_{27}H_{16}N_6O_7S_2$ (600.58): C, 54.00; H, 2.69; N, 13.99%. Found: C, 54.26; H, 2.81; N, 13.79%.

Ethyl 6-cyano-5-oxo-3-phenyl-2-{4-[2-(saccharin-2-yl)acetylsulfamoyl]phenyl}-2,5-dihydropyridazine-4-carboxylate (9b). Yield, 0.90 g (69%) (ethanol); m.p. 193–195°C; IR: ν = 3290 (NH), 2215 (CN), 1725, 1705, 1680 cm^{-1} (CO); ^{1}H NMR (CDCl$_3$): δ = 1.55 (t, 3H, CH$_3$), 4.30 (q, 2H, CH$_2$), 4.50 (s, 2H, CH$_2$), 7.20–8.35 (m, 13H, ArH), 8.40 (s, 1H, NH, exchangeable); Anal. Calcd. for $C_{29}H_{21}N_5O_9S_2$ (647.64): C, 53.78; H, 3.27; N, 10.81%. Found: C, 53.95; H, 3.51; N, 10.59%.

4-(6-Cyano-5-oxo-4-phenyl-3-thioxo-4,5-dihydro-3*H*-[1,2,4]triazin-2-yl)-*N*-[2-saccharin-2-yl]acetyl]benzenesulfonamide (11). A mixture of compound **3** (1.04 g, 2 mmol) and phenyl isothiocyanate (2 mmol) in 1,4-dioxane (20 mL) containing triethylamine (0.4 mL) was heated under reflux for 6 h. The reaction mixture was cooled at room temperature, poured onto cold water (40 mL) and neutralized with dilute HCl. The solid product that formed was collected by filtration and recrystallized from ethanol to give **11**. Yield, 0.93 g (76%); m.p. 211–213°C; IR: ν = 3290 (NH), 2215 (CN), 1685–1675 cm^{-1} (CO); ^{1}H NMR (CDCl$_3$): δ = 4.55 (s, 2H, CH$_2$), 7.12–8.25 (m, 13H, ArH), 8.35 (s, 1H, NH, exchangeable); Anal. Calcd. for $C_{25}H_{16}N_6O_7S_3$ (608.63): C, 49.34; H, 2.65; N, 13.81%. Found: C, 49.10; H, 2.31; N, 13.96%.

General procedure for the preparation of compounds 12a,b. To a solution of compound **3** (1.04 g, 2 mmol) in ethanolic sodium ethoxide solution (25 mL) [prepared by dissolving sodium metal (2.0 g) in absolute ethanol (20 mL)], urea or thiourea (2 mmol) was added. The reaction mixture was heated under reflux for 8 h. The solvent was evaporated *in vacuo* and the residue was triturated with cold water. The solid formed was collected by filtration and recrystallized from proper solvent to give **12a,b**.

4-(6-Amino-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (12a). Yield, 0.73 g (68%) (DMF); m.p. 251–253°C; IR: ν = 3400–3230 (NH$_2$, NH), 1680–1675 cm^{-1} (CO); ^{1}H NMR (CDCl$_3$): δ = 4.61 (s, 2H, CH$_2$), 5.85 (br s, 2H, NH$_2$), 7.25–8.05 (m, 8H, ArH), 8.10–8.50 (br s, 3H, 3NH, exchangeable); Anal. Calcd. for $C_{19}H_{15}N_7O_8S_2$ (533.50): C, 42.78; H, 2.83; N, 18.38%. Found: C, 42.96; H, 2.98; N, 18.10%.

4-(6-Amino-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (12b). Yield, 0.80 g (73%); (1,4-dioxane); m.p. 230–232°C; IR: ν = 3395–3200 (NH$_2$, NH), 1685–1680 cm^{-1} (CO), 1260 cm^{-1} (CS); ^{1}H NMR (CDCl$_3$): δ = 4.65 (s, 2H, CH$_2$), 5.90 (br s, 2H, NH$_2$), 7.30–8.20 (m, 8H, ArH), 8.30–9.00 (br s, 3H, 3NH, exchangeable); Anal. Calcd. for $C_{19}H_{15}N_7O_7S_3$ (549.56): C, 41.52; H, 2.75; N, 17.84%. Found: C, 41.20; H, 2.49; N, 17.98%.

4-(5-Amino-3-hydroxy-1*H*-pyrazol-4-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (13). A mixture of compound **3** (5.19 g, 10 mmol) and hydrazine hydrate (0.6 g, 12 mmol) in absolute ethanol (25 mL) was heated under reflux for 2 h. The solid product which formed after cooling was filtered off and recrystallized from 1,4-dioxane to give **13**. Yield, 3.94 g (78%); m.p. 207–209°C; IR: ν = 3450–3200 (OH, NH$_2$, NH), 1675 cm^{-1} (CO); ^{1}H NMR (CDCl$_3$): δ = 4.50 (s, 2H, CH$_2$), 5.80 (br s, 2H, NH$_2$), 7.15–8.25 (m, 8H, ArH), 8.30–9.10 (br s, 3H, 2NH, and OH, exchangeable); ^{13}C NMR: δ 62.3 (C-4), 153.3 (C-5), 156.2 (C-3); Anal. Calcd. for $C_{18}H_{15}N_7O_7S_2$ (505.49): C, 42.77; H, 2.99; N, 19.40%. Found: C, 42.50; H, 2.71; N, 19.67%.

4-(5,7-Dimethyl-2-hydroxypyrazolo[1,5-a]pyrimidin-3-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (14). A mixture of compound **13** (1.01 g, 2 mmol) and acetylacetone (3 mmol) in glacial acetic acid (20 mL) was refluxed for 5 h. The reaction mixture was cooled, the separated solid was filtered off, washed with water and recrystallized from 1,4-dioxane to give **14**. Yield, 0.83 g (73%); m.p. 196–198°C; IR: ν = 3420–3290 (OH, NH), 1675 cm^{-1} (CO); ^{1}H NMR (CDCl$_3$): δ = 1.2–1.4 (br s, 6H, 2CH$_3$), 4.55 (s, 2H, CH$_2$), 7.13–8.10 (m, 9H, ArH), 8.30–8.50 (br s, 2H, NH, and OH, exchangeable); Anal. Calcd. for $C_{23}H_{19}N_7O_7S_2$ (569.57): C, 48.50; H, 3.36; N, 17.21%. Found: C, 48.28; H, 3.12; N, 17.36%.

General procedure for the preparation of compounds 15a,b. A mixture of compound **13** (1.01 g, 2 mmol), benzaldehyde and/or 4-methoxybenzaldehyde (2 mmol) in absolute ethanol (25 mL) was heated under reflux for 5 h. The reaction mixture was cooled and the formed solid was filtered off and recrystallized to give **15a,b**.

4-[5-(Benzylideneamino)-3-hydroxy-1*H*-pyrazol-4-ylazo]-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (15a). Yield, 0.80 g (67%) (ethanol); m.p. 174–176°C; IR: ν = 3490–3290 (OH, NH), 1670 cm^{-1} (CO); ^{1}H NMR (CDCl$_3$): δ = 4.60 (s, 2H, CH$_2$), 7.25–8.30 (m, 14H, ArH, and benzylic proton), 8.40, 8.60, 9.10 (3s, 3H, 2NH, and OH, exchangeable); Anal. Calcd. for $C_{25}H_{19}N_7O_7S_2$ (593.59): C, 50.58; H, 3.23; N, 16.52%. Found: C, 50.74; H, 3.49; N, 16.23%.

4-{3-Hydroxy-5[(4-methoxybenzylidene)amino]-1*H*-pyrazolo-4-ylazo}-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (15b). Yield–0.79 g (63%) (ethanol); m.p. 213–215°C; IR: ν = 3480–3210 (OH, NH), 1675 cm^{-1} (CO); Anal. Calcd. for $C_{26}H_{21}N_7O_8S_2$ (623.62): C, 50.08; H, 3.39; N, 15.72%. Found: C, 50.30; H, 3.63; N, 15.42%.

General procedure for the preparation of compounds 16a,b. Method A: A mixture of compounds **15a** or **15b** (2 mmol) and malononitrile (0.13 g, 2 mmol) in absolute ethanol (20 mL) containing piperidine (0.4 mL) was heated under reflux for 8 h. The separated solid was filtered off and recrystallized from 1,4-dioxane to give **16a,b**. Yield, 0.73 g (61% for **16a**) and 0.86 g (62% for **16b**).

Method B: A mixture of compound **13** (1.01 g, 2 mmol) and arylidene malononitriles (2 mmol) in 1,4-dioxane (25 mL) containing a few drops of piperidine (0.4 mL) was refluxed for 10 h. The obtained solid after cooling was recrystallized from 1,4-dioxane to give **16a,b**. Yield, 0.82 g (69% for **16a**) and 0.98 g (71% for **16b**).

4-(7-Amino-6-cyano-2-hydroxy-5-phenyl-4,5-dihydropyrazolo[1,5-a]pyrimidin-3-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (16a). m.p. 165–167°C, IR: ν = 3505–3200 (OH, NH$_2$, NH), 2215 (CN), 1680 cm^{-1} (CO); ^{1}H NMR (CDCl$_3$): δ = 4.50 (s, 2H, CH$_2$), 5.10 (s, 1H, CH), 5.70 (br s, 2H, NH$_2$), 7.21–8.11 (m, 13H, ArH), 8.20–9.10 (br s, 3H, 2NH, OH, exchangeable); ^{13}C NMR: δ = 36.3 (C-5), 47.8 (C-6), 60.1 (C-3), 110.3 (CN), 150.1 (C-3a), 151.2 (C-7), 156.3 (C-2), 120.1, 120.4, 123.2, 123.6, 124.2, 129.3 (phenyl ring); Anal. Calcd. for $C_{28}H_{21}N_9O_7S_2$ (659.65): C, 50.98; H, 3.21; N, 19.11%. Found: C, 50.63; H, 3.08; N, 19.37%.

4-[7-Amino-6-cyano-2-hydroxy-5-(4-methoxyphenyl)-4,5-dihydropyrazolo[1,5-a]pyrimidin-3-ylazo]-*N*-[2–(saccharin-2-yl)acetyl]benzenesulfonamide (16b). m.p. 190–192°C, IR: ν = 3490–3210 (OH, NH_2, NH), 2220 (CN), 1675 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ = 3.90 (s, 3H, OCH_3), 4.55 (s, 2H, CH_2), 4.95 (s, 1H, CH), 5.75 (br s, 2H, NH_2), 7.20–8.15 (m, 12H, ArH), 8.30–9.10 (br s, 3H, 2NH, OH, exchangeable); Anal. Calcd. for $C_{29}H_{23}N_9O_8S_2$ (689.68): C, 50.50; H, 3.36; N, 18.28%. Found: C, 50.76; H, 3.60; N, 18.10%.

General procedure for the preparation of compounds 17a,b. Method A: A mixture of compounds **15a** or **15b** (2 mmol) and ethyl cyanoacetate (2 mmol) in absolute ethanol (20 mL) containing piperidine (0.4 mL) was heated under reflux for 8 h. The formed solid was filtered off and recrystallized from *n*-butanol to give **17a,b**. Yield, 0.91 g (64% for **17a**) and 0.89 g (60% for **17b**).

Method B: A mixture of compound **13** (1.01 g, 2 mmol) and β-aryl-α-cyanoacrylate derivatives (2 mmol) in 1,4-dioxane (20 mL) containing piperidine (0.3 mL) was refluxed for 10 h. The resulting solid was filtered off and recrystalized from *n*-butanol to give **17a,b**. Yield, 1.02 g (72% for **17a**) and 1.08 g (73% for **17b**).

Ethyl 7-amino-2-hydroxy-5-phenyl-3-{4-[2-(saccharin-2-yl)acetylsulfamoyl]phenylazo}-4,5-dihydropyrazolo[1,5-a]pyrimidine-6-carboxylate (17a). m.p. 236–238°C, IR: ν = 3490–3180 (OH, NH_2, NH), 1730, 1675 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ = 1.60 (t, 3H, CH_3), 4.45 (q, 2H, CH_2), 4.65 (s, 2H, CH_2), 5.20 (s, 1H, CH), 5.70 (br s, 2H, NH_2), 7.20–8.15 (m, 13H, ArH), 8.50–9.55 (br s, 3H, 2NH, and OH, exchangeable); Anal. Calcd. for $C_{30}H_{26}N_8O_9S_2$ (706.71): C, 50.99; H, 3.71; N, 15.86%. Found: C, 50.81; H, 3.50; N, 15.97%.

Ethyl 7-amino-2-hydroxy-5-(4-methoxyphenyl)-3-{4-[2-(saccharin-2-yl)acetylsulfamoyl]phenylazo}-4,5-dihydropyrazolo[1,5-a]pyrimidine-6-carboxylate (17b). m.p. 203–205°C, IR: ν = 3490–3190 (OH, NH_2, NH), 1725, 1670 cm^{-1} (CO); ^{1}H NMR (DMSO-d$_6$): δ = 1.70 (t, 3H, CH_3), 3.95 (s, 1H, OCH_3), 4.40 (q, 2H, CH_2), 4.60 (s, 2H, CH_2), 5.15 (s, 1H, CH), 5.75 (br s, 2H, NH_2), 7.15–8.20 (m, 12H, ArH), 8.25–9.50 (br s, 3H, 2NH, and OH, exchangeable); Anal. Calcd. for $C_{31}H_{28}N_8O_{10}S_2$ (736.73): C, 50.54; H, 3.83; N, 15.21%. Found: C, 50.35; H, 3.60; N, 15.36%.

4-(7-Amino-6-cyano-2-hydroxypyrazolo[1,5-a]pyrimidin-3-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (19). A mixture of **13** (1.01 g, 2 mmol) and ethoxymethylenemalononitrile (0.22 g, 2 mmol) in DMF (25 mL) containing a few drops of piperidine (0.3 mL) was heated under reflux for 4 h. The reaction mixture was cooled and the formed solid was filtered off and recrystallized from 1,4-dioxane to give **19**. Yield, 0.67 g (58%); m.p. 211–213°C; IR: ν = 3480–3190 (OH, NH_2, NH), 2215 (CN), 1675 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ = 4.60 (s, 2H, CH_2), 5.95 (br s, 2H, NH_2), 7.15–8.20 (m, 9H, ArH), 8.60–9.10 (br s, 2H, NH, and OH, exchangeable); ^{13}C NMR: δ = 35.6 (C-6), 82.1 (C-3), 111.2 (CN), 140.2 (C-3a), 150.3 (C-5), 153.1 (C-7), 156.3 (C-2); Anal. Calcd. for $C_{22}H_{15}N_9O_7S_2$ (581.54): C, 45.44; H, 2.60; N, 21.68%. Found: C, 45.65; H, 2.81; N, 21.45%.

4-(6-Cyano-2-hydroxy-7-oxo-4,7-dihydropyrazolo[1,5-a]pyrimidin-3-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (20). A mixture of **13** (1.01 g, 2 mmol) and ethyl ethoxymethylenecyanoacetate (0.34 g, 2 mmol) in DMF (20 mL) containing a few drops of piperidine (0.4 mL) was refluxed for 4 h. The reaction mixture was cooled and the formed solid was filtered off and recrystallized from DMF to give **20**. Yield, 0.65 g (56%); m.p. 196–198°C; IR: ν = 3490–3180 (OH, NH), 2210 (CN), 1680–1675 cm^{-1} (CO); ^{1}H NMR (DMSO-d$_6$): δ = 4.55 (s, 2H, CH_2), 7.15–8.10 (m, 9H, ArH), 8.60–9.10 (br s, 3H, 2NH, and OH, exchangeable); Anal. Calcd. for $C_{22}H_{14}N_8O_8S_2$ (582.53): C, 45.36; H, 2.42; N, 19.24%. Found: C, 45.53; H, 2.61; N, 19.41%.

4-(5,7-Diamino-2-hydroxy-6-phenylazopyrazolo[1,5-a]pyrimidin-3-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (22). A mixture of **13** (1.01 g, 2 mmol) and 2-phenylhydrazonomalononitrile (0.34 g, 2 mmol) in absolute ethanol (20 mL) containing a few drops of pyridine (0.4 mL) was heated under reflux for 6 h, then allowed to cool at room temperature. The precipitated solid was filtered off, washed with water (3 × 30 mL) and recrystallized from *n*-butanol to give **22**. Yield, 0.85 g (63%); m.p. 186–188°C; IR: ν = 3495–3180 (OH, NH_2, NH), 1670 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ = 4.61 (s, 2H, CH_2), 5.85–6.10 (br s, 4H, 2NH_2), 7.10–8.15 (m, 13H, ArH), 8.50–8.75 (br s, 2H, NH, and OH, exchangeable); Anal. Calcd. for $C_{27}H_{21}N_{11}O_7S_2$ (675.66): C, 48.00; H, 3.13; N, 22.80%. Found: C, 48.26; H, 3.36; N, 22.51%.

4-(7-Amino-2-hydroxy-5-oxo-6-phenylazo-4,5-dihydropyrazolo[1,5-a]pyrimidin-3-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (24). A mixture of **13** (1.01 g, 2 mmol) and ethyl 2-phenylhydrazonocyanoacetate (0.43 g, 2 mmol) in absolute ethanol (20 mL) containing a few drops of pyridine (0.5 mL) was heated under reflux for 6 h, then allowed to cool at room temperature. The formed solid was filtered off, washed with water (3 × 30 mL) and recrystallization from DMF to give **24**. Yield, 0.82 g (61%); m.p. 201–203°C; IR: ν = 3490–3200 (OH, NH_2), 1680–1675 cm^{-1} (CO); ^{1}H NMR (DMSO = d$_6$): δ = 4.50 (s, 2H, CH_2), 5.85 (br s, 2H, NH_2), 7.26–8.20 (m, 13H, ArH), 8.40–9.10 (br s, 3H, 2NH, and OH, exchangeable); ^{13}C NMR: δ = 67.1 (C-6), 68.5 (C-3), 131.5 (C-3a), 148.5 (C-7), 152.1 (C-2), 154.2 (C-5), 120.1, 120.9, 121.2, 121.8, 122.5, 123.1 (phenyl ring); Anal. Calcd. for $C_{27}H_{20}N_{10}O_8S_2$ (676.64): C, 47.93; H, 2.98; N, 20.70%. Found: C, 47.75; H, 2.71; N, 20.50%.

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Efficient Synthesis of Benzothieno[3,2-*d*]-1,2,4-triazolo [1,5-*a*]pyrimidin-5(1*H*)-ones *via* a Tandem aza-Wittig/ Heterocumulene-Mediated Annulation

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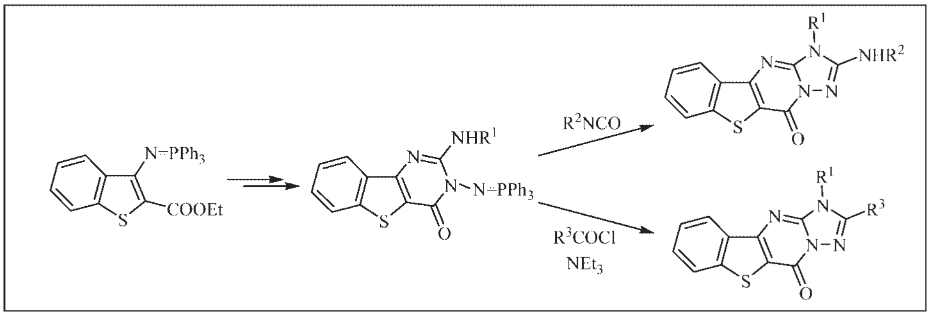

The carbodiimides **2**, obtained from reactions of iminophosphorane **1** with isocyanates, reacted with hydrazine to give selectively 3-amino-2-arylaminobenzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones **4**. Reactions of **4** with triphenylphosphine, hexachloroethane, and Et_3N produced iminophosphoranes **5**. A tandem aza-Wittig reaction of iminophosphorane **5** with isocyanate, acyl chloride generated benzothieno[3,2-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-5(1*H*)-ones **7** and **9** in satisfactory yields. The effects of the nucleophiles on cyclization have been investigated.

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INTRODUCTION

Thienopyrimidines are very important heterocycles because of their significant antifungal and antibacterial activities [1–4] as well as their good anticonvulsant and angiotensin or H_1 receptor antagonistic activities [5–7]. The chemistry of thienopyrimidinones have also received attention because of their starting materials, 2-amino-3-carboxythiophenes, which can be conveniently synthesized. On the other hand, heterocycles containing 1,2,4-triazole nucleus also exhibit various biological activities; several of them have been used as fungicidal, bactericidal, insecticidal, antitumor, and anti-inflammatory agents [8–13]. The introduction of a triazole ring into the thienopyrimidine system is expected to influence the biological activities significantly.

The aza-Wittig reactions of iminophosphoranes have received increasing attention in view of their useful utilities in the synthesis of nitrogen heterocyclic compounds under mild conditions [14,15]. Recently, we have been interested in the synthesis of triazolo-quinazolinones, thienopyrimidinones, and imidazolinones *via* aza-Wittig reaction, with the aim of evaluating their fungicidal activities [16–20]. Reported herein is a new efficient synthesis of 2-substituted benzothieno[3,2-*d*]-1,2,4-triazolo[1,5-*a*] pyrimidin-5(1*H*)-one **7** and **9** from easily accessible iminophosphorane **1** [21].

RESULTS AND DISCUSSION

Carbodiimides **2**, obtained from aza-Wittig reactions of iminophosphorane **1** with aromatic or alkyl isocyanates, reacted with hydrazine to give selectively 2-arylamino-3-aminobenzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones **4** in 80–87% yields at room temperature (Table 1, Scheme 1).

The formation of **4** can be rationalized in terms of an initial nucleophilic addition of hydrazine to give intermediate **3** which directly cyclized across the strong nucleophilic hydrazine group rather than the aryl(alkyl)-amine one. Compounds **4** were further converted to functionalized iminophosphoranes **5** *via* reaction with triphenylphosphine, hexachloroethane, and Et_3N in 72–78% yields (Table 1, Scheme 1).

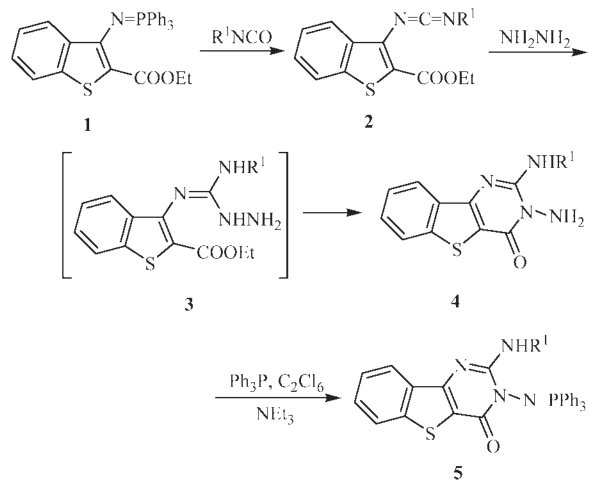
Table 1

Physical and analytical data of compounds **7**.

							Analysis % (Calcd./Found)		
Comp.	R^1	R^2 or R^3	Time (hours)	Mp (°C)	Yield %[a]	Molecular Formula	C	H	N
4a	Ph		2	246–247	80	$C_{16}H_{14}N_4OS$	62.32	3.92	18.17
							62.08	3.74	18.37
4b	4-ClC_6H_4		2	>300	82	$C_{16}H_{11}ClN_4OS$	56.07	3.23	16.34
							56.29	3.12	16.57
4c	4-$CH_3C_6H_4$		2	>300	83	$C_{17}H_{14}N_4OS$	63.33	4.38	17.38
							63.12	4.16	17.25
4d	i-Pr		2	207–208	79	$C_{13}H_{14}N_4OS$	56.91	5.14	20.42
							56.79	5.43	20.11
4e	n-Bu		2	199–201	77	$C_{14}H_{16}N_4OS$	58.31	5.59	11.12
							58.19	5.33	11.22
5a	Ph		6	258–260	74	$C_{34}H_{25}N_4OPS$	71.82	4.43	9.85
							71.78	4.54	9.77
5b	4-ClC_6H_4		6	260–261	72	$C_{34}H_{24}ClN_4OPS$	67.71	4.01	9.29
							67.58	4.24	9.17
5c	4-$CH_3C_6H_4$		6	259–261	78	$C_{35}H_{27}N_4OPS$	72.15	4.67	9.62
							72.02	4.84	9.52
5d	i-Pr		6	207–208	77	$C_{31}H_{27}N_4OPS$	69.65	5.09	10.48
							69.82	5.24	10.42
5e	n-Bu		6	202–204	75	$C_{32}H_{29}N_4OPS$	70.05	5.33	10.21
							70.22	5.45	10.05
7a	4-$CH_3C_6H_4$	Ph	4	>300	84	$C_{24}H_{17}N_5OS$	68.07	4.05	16.54
							68.19	4.11	16.37
7b	Ph	Ph	4	>300	82	$C_{23}H_{15}N_5OS$	67.47	3.69	17.10
							67.60	3.73	17.00
7c	4-$CH_3C_6H_4$	4-ClC_6H_4	4	>300	86	$C_{24}H_{16}ClN_5OS$	62.95	3.52	15.29
							63.08	5.57	15.14
7d	4-ClC_6H_4	4-ClC_6H_4	4	>300	85	$C_{23}H_{13}ClN_5OS$	57.75	2.74	14.64
							57.88	2.67	14.69
7e	Ph	4-ClC_6H_4	4	>300	84	$C_{23}H_{14}ClN_5OS$	62.23	3.18	15.78
							62.38	3.23	15.69
7f	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	4	>300	85	$C_{25}H_{19}N_5OS$	68.63	4.38	16.01
							68.75	4.44	15.86
7g	4-ClC_6H_4	4-$CH_3C_6H_4$	4	298–299	83	$C_{24}H_{16}ClN_5OS$	62.05	3.52	15.29
							62.18	3.54	15.16
7h	Ph	4-$CH_3C_6H_4$	4	290–291	86	$C_{24}H_{17}N_5OS$	68.07	4.05	16.54
							68.18	3.96	16.65
7i	4-ClC_6H_4	i-Pr	8	>300	76	$C_{20}H_{16}ClN_5OS$	58.60	3.93	17.09
							58.48	4.05	16.98
7j	4-ClC_6H_4	n-Bu	8	282–284	74	$C_{21}H_{18}ClN_5OS$	59.50	4.28	16.52
							59.58	4.45	16.35
7k	i-Pr	i-Pr	8	>300	77	$C_{17}H_{19}N_5OS$	59.80	5.61	20.51
							59.88	5.85	20.39
7l	i-Pr	Ph	8	>300	80	$C_{20}H_{17}N_5OS$	63.98	4.56	18.65
							64.05	4.75	18.50
7m	Ph	4-$CH_3C_6H_4$	4	>300	83	$C_{21}H_{19}N_5OS$	64.76	4.92	17.98
							64.68	5.15	17.89
7n	n-Bu	4-$CH_3C_6H_4$	8	>300	67	$C_{22}H_{21}N_5OS$	65.49	5.25	17.36
							65.54	5.45	17.19
7o	n-Bu	i-Pr	8	>300	72	$C_{18}H_{21}N_5OS$	60.82	5.95	19.70
							60.92	6.25	19.57
7p	n-Bu	Ph	8	294–296	82	$C_{21}H_{19}N_5OS$	64.76	4.92	17.98
							64.85	5.13	17.79
9a	n-Bu	CH_3	24	187–189	72	$C_{16}H_{19}N_4OS$	61.52	5.16	17.93
							61.59	5.03	17.97
9b	n-Bu	Ph	24	212–214	65	$C_{21}H_{18}N_4OS$	67.36	4.85	14.96
							67.39	4.67	14.98
9c	Ph	CH_3	24	>300	74	$C_{18}H_{12}N_4OS$	65.04	3.64	14.86
							65.29	3.77	14.65
9d	Ph	Ph	24	277–279	62	$C_{23}H_{14}N_4OS$	70.03	3.58	14.20
							70.22	3.67	14.01

[a] Yields based on iminophosphorane **1** or **5**.

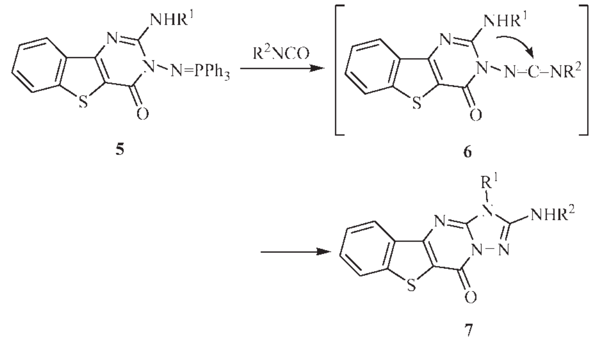
Scheme 1



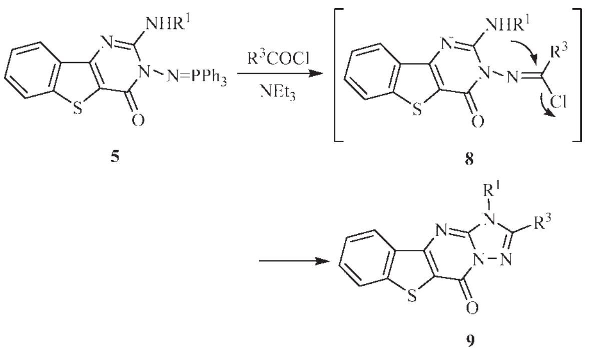
When iminophosphoranes **5** in anhydrous CH_2Cl_2 were treated with isocyanate at room temperature, the color of the reaction mixture quickly turned red, disappearing after few minutes, and 2-aminobenzothieno[3,2-*d*]-1,2,4-triazolo-[1,5-*a*]pyrimdin-5(1*H*)-ones **7** were isolated as crystalline solids in good yields (67–86%, Table 1, Scheme 2). Presumably, the conversion of **5** into **7** involves initial aza-Wittig reaction between the iminophosphorane **5** and the isocyanate to give a carbodiimide **6** as highly reactive intermediate, which easily undergoes ring closure across the amino group to give the otherwise not readily available 2-amino substituted benzothieno[3,2-*d*]-1,2,4-triazolo[1,5-*a*] pyrimidin-5(1*H*)-ones **7**. It is noteworthy that the reaction can be easily carried out at room temperature under mild, neutral condition, and the separation of **7** from the reaction mixture was also easily carried out by simple filtration.

Iminophosphorane **5** reacted with acyl chlorides in the presence of Et_3N in CH_2Cl_2 at room temperature to give 2-substituted benzothieno[3,2-*d*]-1,2,4-triazolo[1,5-*a*] pyrimidin-5(1*H*)-ones **9** in good yields (62–74%, Table 1, Scheme 3). The formation of **9** can be viewed as an initial aza-Wittig reaction between the iminophosphorane **5** and acyl chloride in the presence of Et_3N affording the intermediate imidoyl chloride **8**, which undergoes cyclization to give **9**.

Scheme 2



Scheme 3



The structure of the synthesized compound **5**, **7**, **9** were confirmed by their spectral data. For example, the IR spectra of **7k** revealed C=O absorption bands at 1672 cm^{-1}. The ^1H NMR spectral data of **7k** show the signals of —NH at 9.89 ppm as singlet. The Ar—H signals appeared at 7.50–8.34 (m, 4H, Ar—H). The MS spectrum of **7k** shows an obvious molecule ion peak at m/z 341 with 34% abundance.

In summary, we have developed an efficient synthesis of 2-substituted benzothieno[3,2-*d*]-1,2,4-triazolo[1,5-*a*] pyrimidin-5(1*H*)-one. Due to the easily accessible and versatile starting material, this method has the potential in the synthesis of many biologically and pharmaceutically active thienopyrimidinones derivatives.

EXPERIMENTAL

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

Preparation of compounds 4. To a solution of imino-phosphorane 1 (1.44 g, 3 mmol) in anhyd. CH_2Cl_2 (10 mL) was added isocyanate (3 mmol) under N_2 at r.t. After the reaction mixture was left unstirred for 8–12 h at 0–5°C, the solvent was removed off under reduced pressure and Et_2O/petroleum ether (1:2, 12 mL) was added to precipitate triphenylphosphine oxide. Removal of the solvent gave carbodiimides 2, which were used directly without further purification. To the solution of 2 prepared above in CH_2Cl_2 (10 mL) was added hydrazine (0.18 g, 3 mmol). The mixture was stirred for 2 h at r. t. and filtered to give 4.

3-Amino-2-phenylamino-benzo[4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (4a). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm): 4.65 (s, 1H, NH), 4.72 (s, 2H, NH_2), 7.15–8.06 (m, 9H, Ar—H). IR

(KBr): 3412 (NH), 1674 (C=O), 1530, 1380, 698 cm^{-1}. MS: *m/z* (%) 308 (47, M$^+$), 292 (33), 200 (19), 145 (28), 77 (87).

3-Amino-2-(4-chlorophenylamino)-benzo[4,5]thieno[3,2-d] pyrimidin-4(3*H*)-one (4b). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm): 4.71 (s, 1H, NH), 4.86 (s, 2H, NH$_2$), 7.43–7.68 (m, 6H, Ar—H), 7.87 (d, J = 8.0 Hz, 1H, Ar—H), 8.25 (d, J = 7.6 Hz, 1H, Ar—H). IR (KBr): 3428 (NH), 1676 (C=O), 1531, 1385, 693 cm^{-1}. MS: *m/z* (%) 342 (35, M$^+$), 327 (24), 200 (34), 146 (43), 77 (26).

3-Amino-2-(4-methylphenylamino)-benzo[4,5]thieno[3,2-*d*] pyrimidin-4(3*H*)-one (4c). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm): 2.66 (s, 3H, CH$_3$), 4.73 (s, 1H, NH), 4.77 (s, 2H, NH$_2$), 7.23–8.46 (m, 8H, Ar—H). IR (KBr): 3420 (NH), 1678 (C=O), 1531, 1377, 693 cm^{-1}. MS: *m/z* (%) 322 (52, M$^+$), 306 (47), 200 (34), 146 (52), 77 (47).

3-Amino-2-isopropylamino-benzo[4,5]thieno[3,2-d]pyrimidin-4(3*H*)-one (4d). ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 1.16 (d, J = 6.4 Hz, 6H, 2CH$_3$), 3.40–3.60 (m, 1H, NCH), 4.66 (d, J = 6.8 Hz, 1H, NH), 4.74 (s, 2H, NH$_2$), 7.40–7.61 (m, 2H, Ar—H), 7.83 (d, J = 8.4 Hz, 1H, Ar—H), 8.15 (d, J = 7.6 Hz, 1H, Ar—H). IR (KBr): 3417 (NH), 1676 (C=O), 1535, 1371, 694 cm^{-1}. MS: *m/z* (%) 274 (47, M$^+$), 258 (17), 200 (47), 146 (44), 77 (45).

3-Amino-2-butylamino-benzo[4,5]thieno[3,2-*d*]pyrimidin-4-(3*H*)-one (4e). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm): 0.92 (t, J = 7.0 Hz, 3H, CH$_3$), 1.20–1.37 (m, 4H, CH$_2$), 3.55 (m, 2H, NCH$_2$), 4.61 (s, 1H, NH), 4.75 (s, 2H, NH$_2$), 7.43–7.58 (m, 2H, Ar—H), 7.85 (d, J = 8.0 Hz, 1H, Ar—H), 8.26 (d, J = 7.6 Hz, 1H, Ar—H). IR (KBr): 3411 (NH), 1676 (C=O), 1533, 1372, 694 cm^{-1}. MS: *m/z* (%) 288 (58, M$^+$), 272 (31), 200 (55), 146 (37), 77 (58).

Preparation of iminophosphorane 5. To a mixture of **4** (8 mmol), PPh$_3$ (3.14 g, 12 mmol) and C$_2$Cl$_6$ (2.84 g, 12 mmol) in dry CH$_3$CN (40 mL), was added dropwise NEt$_3$ (2.42 g, 24 mmol) at room temperature. The color of the reaction mixture quickly turned yellow and the mixture was stirred 4–6 h at room temperature. After completion of the reaction (monitored with TLC), the solvent was removed under reduced pressure and the residue was recrystallized from EtOH to give iminophosphoranes **5**.

2-Phenylamino-3-(triphenylphosphoranylidene)aminobenzo[4,5]thieno[3,2-d]pyrimidin-4(3*H*)-one (5a). ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 4.66 (s, 1H, NH), 7.09–8.25 (m, 24H, Ar—H). IR (KBr): 3420 (NH), 1670 (C=O), 1533, 1381, 696 cm^{-1}. MS: *m/z* (%) 568 (52, M$^+$), 292 (20), 276 (57), 200 (13), 145 (24), 77 (50).

2-(4-Chlorophenyl)amino-3-(triphenylphosphoranylidene) amino-benzo[4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (5b). ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 4.73 (s, 1H, NH), 7.20–8.30 (m, 23H, Ar—H). IR (KBr): 3428 (NH), 1676 (C=O), 1531, 1385, 693 cm^{-1}. MS: *m/z* (%) 602 (32, M$^+$), 327 (9), 276 (26), 200 (12), 146 (51), 77 (22).

2-(4-Methylphenyl)amino-3-(triphenylphosphoranylidene) amino-benzo[4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (5c). ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 2.55 (s, 3H, CH$_3$), 4.78 (s, 1H, NH), 7.23–8.46 (m, 23H, Ar—H). IR (KBr): 3434 (NH), 1668 (C=O), 1529, 1378, 690 cm^{-1}. MS: *m/z* (%) 582 (56, M$^+$), 306 (31), 200 (14), 146 (55), 77 (83).

2-(Isopropylamino)-3-(triphenylphosphoranylidene) aminobenzo[4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (5d). ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 1.17 (d, J = 6.4 Hz, 6H, 2CH$_3$), 3.94 (m, 1H, NCH), 4.60 (s, 1H, NH), 7.23–8.20 (m, 19H, Ar—H). IR (KBr): 3430 (NH), 1673 (C=O), 1531, 1377, 696 cm^{-1}. MS: *m/z* (%) 534 (47, M$^+$), 272 (37), 200 (37), 146 (68), 77 (79).

2-(Butylamino)-3-(triphenylphosphoranylidene)aminobenzo [4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (5e). ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 0.90 (t, J = 7.0 Hz, 3H, CH$_3$), 1.22–1.37 (m, J = 7.0 Hz, 4H, 2CH$_2$), 3.50(m, 2H, NCH$_2$), 4.61 (s, 1H, NH), 7.27–8.22 (m, 19H, Ar—H). IR (KBr): 3431 (NH), 1671 (C=O), 1529, 1376, 697 cm^{-1}. MS: *m/z* (%) 548 (58, M$^+$), 286 (25), 200 (56), 146 (52), 77 (71).

General procedure for the preparation of 2-arylamino benzothieno[3,2-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-5(1*H*)-ones 7a–7p. To a solution of iminophosphorane 5 (1 mmol) in anhyd. CH$_2$Cl$_2$ (15 mL) was added aromatic isocyanate (1 mmol) under N$_2$ at r.t. The color of the reaction mixture became red, then decolorized after few minutes. The colorless solution was stirred at r.t for 4–8 h. The white precipitated solid was collected by filtration and recrystallized from CH$_2$Cl$_2$—EtOH to give 7a–7p.

1-(4-Methylphenyl)-2-phenylamino-benzo[4,5]thieno[3,2-*d*] [1,2,4]triazolo[1,5-a]pyrimidin-5(1*H*)-one (7a). ^{1}H NMR (400 MHz, CDCl$_3$/TFA) δ (ppm): 2.54 (s, 3H, CH$_3$), 6.72–8.07 (m, 13H, Ar—H). IR (KBr): 3409 (NH), 1671 (C=O), 1575, 1487, 737 cm^{-1}. MS: *m/z* (%) 422 (43, M$^+$), 277 (62), 201 (28), 146 (86), 91 (77), 77 (58).

1-Phenyl-2-phenylamino-benzo[4,5]thieno[3,2-*d*][1,2,4] tri-azolo[1,5-*a*]pyrimidin-5(1*H*)-one (7b). ^{1}H NMR (400 MHz, CDCl$_3$/TFA) δ (ppm): 7.10–8.13 (m, 14H, Ar—H). IR (KBr): 3412 (NH), 1671 (C=O), 1577, 1490, 744 cm^{-1}. MS: *m/z* (%) 408 (67, M$^+$), 277 (78), 201 (22), 146 (93), 77 (100).

2-(4-Chloro-phenylamino)-1-(4-methylphenyl)-benzo[4,5]-thieno[3,2-*d*][1,2,4]triazolo[1,5-a]pyrimidin-5(1*H*)-one (7c). ^{1}H NMR (400 MHz, CDCl$_3$/TFA) δ (ppm): 2.55 (s, 3H, CH$_3$), 6.88–8.03 (m, 12H, Ar—H). IR (KBr): 3421 (NH), 1672 (C=O), 1572, 1496, 743 cm^{-1}. MS: *m/z* (%) 457 (23, M$^+$), 277 (64), 200 (35), 146 (90), 91 (77), 77 (76).

1-(4-Chlorophenyl)-2-(4-chloro-phenylamino)-benzo[4,5]-thieno[3,2-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5(1*H*)-one (7d). ^{1}H NMR (400 MHz, CDCl$_3$/TFA) δ (ppm): 6.82–8.09 (m, 12H, Ar—H). IR (KBr): 3420 (NH), 1673 (C=O), 1574, 1492, 742 cm^{-1}. MS: *m/z* (%) = 477 (34, M$^+$), 277 (75), 201 (19), 145 (89), 77 (63).

2-(4-Chloro-phenylamino)-1-phenyl-benzo[4,5]thieno[3,2-*d*] [1,2,4]triazolo[1,5-*a*]pyrimidin-5(1*H*)-one (7e). ^{1}H NMR (400 MHz, CDCl$_3$/TFA) δ (ppm): 7.19–8.08 (m, 13H, Ar—H). IR (KBr): 3421 (NH), 1673 (C=O), 1573, 1490, 743 cm^{-1}. MS: *m/z* (%) = 442 (50, M$^+$), 277 (67), 201 (32), 145 (87), 77 (61).

1-(4-Methylphenyl)-2-(4-methyl-phenylamino)-benzo[4,5]-thieno[3,2-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5(1*H*)-one (7f). ^{1}H NMR (400 MHz, CDCl$_3$/TFA) δ (ppm): 1.80 (s, 3H, CH$_3$), 2.54 (s, 3H, CH$_3$), 6.72–8.02 (m, 12H, Ar—H). IR (KBr): 3419 (NH), 1671 (C=O), 1575, 1493, 742 cm^{-1}. MS: *m/z* (%) 436 (29, M$^+$), 277 (64), 201 (19), 146 (84), 91 (73), 77 (89).

1-(4-Chlorolphenyl)-2-(4-methyl-phenylamino)-benzo[4,5] thieno[3,2-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5(1*H*)-one (7g). ^{1}H NMR (400 MHz, CDCl$_3$/TFA) δ (ppm): 2.41 (s, 3H, CH$_3$), 7.40–8.00 (m, 12H, Ar—H). IR (KBr): 3422 (NH), 1672 (C=O), 573, 1490, 744 cm^{-1}. MS: *m/z* (%) 457 (65, M$^+$), 277 (58), 200 (31), 146 (82), 91 (67), 77 (78).

2-(4-Methyl-phenylamino)-1-phenyl-benzo[4,5]thieno[3,2-*d*][1,2,4]triazolo[1,5-a]pyrimidin-5(1*H*)-one (7h). ^{1}H NMR (400 MHz, $CDCl_3$/TFA) δ (ppm): 2.03 (s, 3H, CH_3), 6.76–8.06 (m, 13H, Ar—H). IR (KBr): 3412 (NH), 1671 (C=O), 1577, 1491, 742 cm^{-1}. MS: *m/z* (%) 423 (54, M^+), 277 (56), 201 (25), 146 (85), 91 (66), 77 (79).

1-(4-Chlorophenyl)-2-isopropylamino-benzo[4,5]thieno-[3,2-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5(1*H*)-one (7i). ^{1}H NMR (400 MHz, $CDCl_3$/TFA) δ (ppm): 1.33 (d, *J* = 7.0 Hz, 6H, 2CH_3), 4.09 (d, *J* = 6.9 Hz, 1H, NCH), 7.37–8.14 (m, 8H, Ar—H). IR (KBr): 3414 (NH), 1672 (C=O), 1567, 1489, 743 cm^{-1}. MS: *m/z* (%) 409 (46, M^+), 277 (46), 201 (22), 145 (100), 77 (69).

2-Butylamino-1-(4-chlorophenyl)-benzo[4,5]thieno[3,2-*d*]-[1,2,4]triazolo[1,5-a]pyrimidin-5(1*H*)-one (7j). ^{1}H NMR (400 MHz, $CDCl_3$/TFA) δ (ppm): 0.93 (t, *J* = 7.0 Hz, 3H, CH_3), 1.31–1.38 (m, 2H, CH_2), 1.60–1.69 (m, 2H, CH_2), 3.44 (t, *J* = 6.9 Hz, 2H, NCH_2), 7.47–8.13 (m, 8H, Ar—H). IR (KBr): 3415 (NH), 1673 (C=O), 1566, 1488, 742 cm^{-1}. MS: *m/z* (%) 423 (59, M^+), 277 (67), 200 (24), 146 (88), 77 (75).

1-Isopropyl-2-isopropylamino-benzo[4,5]thieno[3,2-*d*]-[1,2,4]triazolo[1,5-*a*]pyrimidin-5(1*H*)-one (7k). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.35 (d, *J* = 7.0 Hz, 6H, 2CH_3), 1.75 (d, *J* = 7.0 Hz, 6H, 2CH_3), 4.05 (t, *J* = 6.9 Hz, 1H, NCH), 4.70 (s, 1H, NCH), 7.50–8.34 (m, 4H, Ar—H), 9.89 (s, 1H, NH). IR (KBr): 3411 (NH), 1672 (C=O), 1574, 1490, 741 cm^{-1}. MS: *m/z* (%) 341 (34, M^+), 277 (55), 201 (37), 146 (73), 77 (65).

1-Isopropyl-2-phenylamino-benzo[4,5]thieno[3,2-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5(1*H*)-one (7l). ^{1}H NMR (400 MHz, $CDCl_3$/TFA) δ (ppm): 1.86 (d, *J* = 7.2 Hz, 6H, 2CH_3), 4.80–4.91 (m, 1H, CH), 6.90–8.35 (m, 9H, Ar—H). IR (KBr): 3416 (NH), 1672 (C=O), 1577, 1493, 743 cm^{-1}. MS: *m/z* (%) 375 (42, M^+), 277 (57), 201 (18), 146 (86), 77 (67).

1-Isopropyl-2-(4-methyl-phenylamino)-benzo[4,5]thieno-[3,2-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5(1*H*)-one (7m). ^{1}H NMR (400 MHz, $CDCl_3$/TFA) δ (ppm): 1.86 (d, *J* = 7.0 Hz, 6H, 2CH_3), 2.10 (s, 3H, Ar—CH_3), 4.83 (d, *J* = 6.9 Hz, 1H, NCH), 6.97–8.37 (m, 8H, Ar—H). IR (KBr): 3415 (NH), 1670 (C=O), 1576, 1490, 742 cm^{-1}. MS: *m/z* (%) 389 (59, M^+), 277 (77), 201 (16), 146 (92), 91 (71), 77 (86).

1-Butyl-2-(4-methyl-phenylamino)-benzo[4,5]thieno[3,2-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5(1*H*)-one (7n). ^{1}H NMR (400 MHz, $CDCl_3$/TFA) δ (ppm): 1.02 (t, *J* = 7.0 Hz, 3H, CH_3), 1.48–1.43 (m, 2H, CH_2), 1.91–1.98 (m, 2H, CH_2), 2.34 (s, 3H, Ar—CH_3), 4.47 (t, *J* = 6.9 Hz, 2H, NCH_2), 7.22–8.43 (m, 8H, Ar—H). IR (KBr): 3418 (NH), 1676 (C=O), 1572, 1495, 749 cm^{-1}. MS: *m/z* (%) 403 (67, M^+), 277 (69), 201 (21), 146 (80), 91 (68), 77 (79).

1-Butyl-2-(isopropylamino)-benzo[4,5]thieno[3,2-d][1,2,4]-triazolo[1,5-*a*]pyrimidin-5(1*H*)-one (7o). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.98 (t, *J* = 7.0 Hz, 3H, CH_3), 1.35 (t, *J* = 7.0 Hz, 6H, 2CH_3), 1.40–1.49 (m, 2H, CH_2), 1.80–1.88 (m, 2H, CH_2),4.00–4.15 (m, 1H, NCH), 4.22 (t, *J* = 6.9 Hz, 2H, NCH_2), 7.55–8.33 (m, 4H, Ar—H), 9.83 (s, 1H, NH). IR (KBr): 3413 (NH), 1671 (C=O), 1571, 1493, 733 cm^{-1}. MS: *m/z* (%) 355 (55, M^+), 277 (64), 200 (26), 146 (89), 77 (67).

1-Butyl-2-phenylamino-benzo[4,5]thieno[3,2-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5(1*H*)-one (7p). ^{1}H NMR (400 MHz, $CDCl_3$/TFA) δ (ppm): 1.01 (t, *J* = 7.0 Hz, 3H, CH_3), 1.40–1.47 (m, 2H, CH_2), 1.85–1.99 (m, 2H, CH_2), 4.41 (q, *J* = 6.9 Hz, 2H, NCH_2), 7.23–8.40 (m, 9H, Ar—H). IR (KBr): 3418 (NH), 1675 (C=O), 1576, 1492, 742 cm^{-1}. MS: *m/z* (%) 389 (63, M^+), 277 (62), 201 (26), 146 (88), 77 (74).

General procedure for the preparation of 2-substituted benzothieno[3,2-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-5(1*H*)-ones 9a–9d. To a solution of iminophosphorane 5 (2 mmol) in anhyd. CH_2Cl_2 (10 mL) were added acyl chloride (2 mmol) and Et_3N (0.20 g, 2 mmol) under N_2 at r.t. The solution was stirred at r.t for 24 h. The white precipitated ammonium salt was separated by filtration and the filtrate was concentrated to dryness. The residue was recrystallized from CH_2Cl_2—EtOH to give 9a–9d.

1-Butyl-2-methyl-benzo[4,5]thieno[3,2-*d*][1,2,4]triazolo-[1,5-*a*]pyrimidin-5(1*H*)-one (9a). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.02 (t, *J* = 7.0 Hz, 3H, CH_3), 1.40–1.49 (m, 2H, CH_2), 1.81–1.88 (m, 2H, CH_2), 2.57 (s, 3H, CH_3), 4.13 (t, *J* = 6.9 Hz, 2H, NCH_2), 7.42–8.26 (m, 4H, Ar—H). IR (KBr): 1672 (C=O), 1572, 1493, 740 cm^{-1}. MS: *m/z* (%) 312 (57, M^+), 277 (69), 201 (17), 145 (60), 77 (86).

1-Butyl-2-phenyl-benzo[4,5]thieno[3,2-*d*][1,2,4]triazolo-[1,5-*a*]pyrimidin-5(1*H*)-one (9b). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.92 (t, *J* = 7.0 Hz, 3H, CH_3), 1.30–1.39 (m, 2H, CH_2), 1.80–1.88 (m, 2H, CH_2), 4.30 (t, *J* = 6.9 Hz, 2H, NCH_2), 7.48–8.33 (m, 9H, Ar—H). IR (KBr): 1674 (C=O), 1573, 1495, 745 cm^{-1}. MS: *m/z* (%) 374 (65, M^+), 277 (68), 200 (24), 146 (87), 77 (83).

2-Methyl-1-phenyl-benzo[4,5]thieno[3,2-*d*][1,2,4]triazolo-[1,5-*a*]pyrimidin-5(1*H*)-one (9c). ^{1}H NMR (400 MHz, $CDCl_3$/TFA) δ (ppm): 2.42 (t, *J* = 7.2 Hz, 3H, CH_3), 7. 44 –7. 99 (m, 9H, Ar—H). IR (KBr): 1671 (C=O), 1571, 1491, 741 cm^{-1}. MS: *m/z* (%) 332 (57, M^+), 277 (68), 201 (31), 146 (92), 77 (65).

1-Phenyl-2-phenyl-benzo[4,5]thieno[3,2-d][1,2,4]triazolo-[1,5-*a*]pyrimidin-5(1*H*)-one (9d). H NMR (400 MHz, $CDCl_3$/TFA) δ (ppm): 7.48–8.33 (m, 14H, Ar—H). IR (KBr): 1673 (C=O), 1575, 1494, 737 cm^{-1}. MS: *m/z* (%) 394 (100, M^+), 277 (64), 201 (25), 145 (73), 77 (76).

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The Boulton–Katritzky Rearrangement of Isocarboxazid

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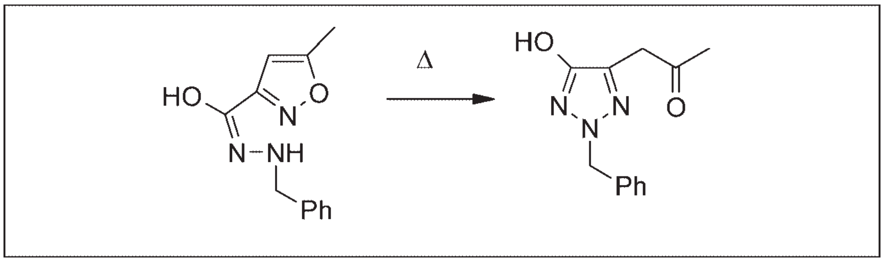

Isocarboxazid rearranges on heating to 5-acetonyl-2-benzyl-4-hydroxy-1,2,3-triazole in DMF at 150°C, in the ionic liquid, [bmin]HSO_4^- at 100°C or as a melt at 105°C. This is the first reported example of the Boulton–Katritzky rearrangement of an acyl hydrazide.

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INTRODUCTION

Control of process impurity formation is a critical aspect of pharmaceutical process research and development. Current guidelines by the ICH (International Committee on Harmonization) state that known impurities in the drug substance are acceptable at levels of 0.2%. Satisfactory levels of unknown impurities are 0.1% [1]. The melding of a mechanistic knowledge of impurity pathways coupled with solid process development has led to a generalized approach for statistical process control and control of impurity formation [2]. The necessity to characterize impurities and to synthesize quantities for analytical method development has afforded new synthetic methodology [3]. When an understanding of reactivity is required to elucidate potential degradation pathways in the drug product, experimental and computational methods have proven to be useful to accomplish this goal [4].

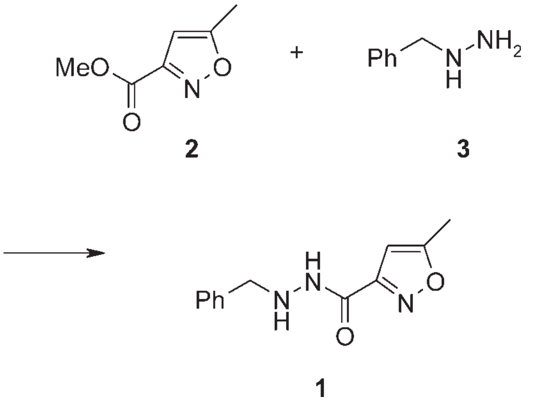
Isocarboxazid (**1**) is a monoamine oxidase inhibitor [5] and is used in the treatment of clinical depression [6]. The use of this compound in treatment is limited by side effects and its incompatibility with certain foods and the manifestation of the so-called ‘‘cheese effect’’ [7]. In the USP (United States Pharmacopoeia), the isocarboxazid (**1**) monograph requires a TLC test at a limit of 0.5% of two impurities: methyl 5-methylisoxazole-3-carboxylate (**2**) and 5-amino-1-benzyl-3-methylpyrazole (**6**). The respective visualization of these substances is done by short-wavelength ultraviolet light and by a spray of ferric chloride and potassium ferricycanide [8]. Isocarboxazid (**1**) is prepared by the reaction of the isoxazole ester **2** with benzylhydrazine (**3**) (Scheme 1) [9]. As a result of our efforts to characterize the pathway by which pyrazole **6** was formed, some interesting results on the thermolysis of isocarboxazid (**1**) were obtained. We wish to report on these findings.

RESULTS AND DISCUSSION

Although β-ketonitriles are known to have a propensity to dimerize and trimerize [10] and we are speculating about possible ways to form pyrazole **6**, we envisioned that a likely path for the formation of pyrazole **6** would be by loss of *N*-(benzylamino)isocyanate from the acidic α nitrogen of isocarboxazid (**1**) followed by isoxazole ring opening and formation of 3-oxobutanenitrile (**4**). Reaction of nitrile **4** with benzylhydrazine (**3**) would afford pyrazole **6** via the intermediacy of hydrazone **5** (Scheme 2). Many years ago, Gardener has commented on the formation of pyrazoles from isoxazole hydrazides and has indicated that their formation can be mitigated if the hydrazide-forming reaction is done at room temperature or under conditions by which the hydrazides will crystallize [11]. Alternatively, the route for the preparation of isocarboxazid (**1**) might be fundamentally flawed and the route could involve elimination of 3-oxobutanenitrile (**4**) in competition with loss of methanol.

Facile isoxazole ring opening of 3-acylisoxazoles is evident in the fact that when 3-acetyl-5-methylisoxazole (**7**) is reacted with sodium methoxide, nitrile **4** is formed. Nitrogen–oxygen bond cleavage of the isoxazole ring is initiated by the elimination of a neutral molecule, methyl acetate [12]. This chemistry parallels established behavior of isoxazole-3-yl lithium intermediates [13]. The enolate of nitrile **4** can be trapped with

Scheme 1. Synthesis of isocarboxazid (**1**).

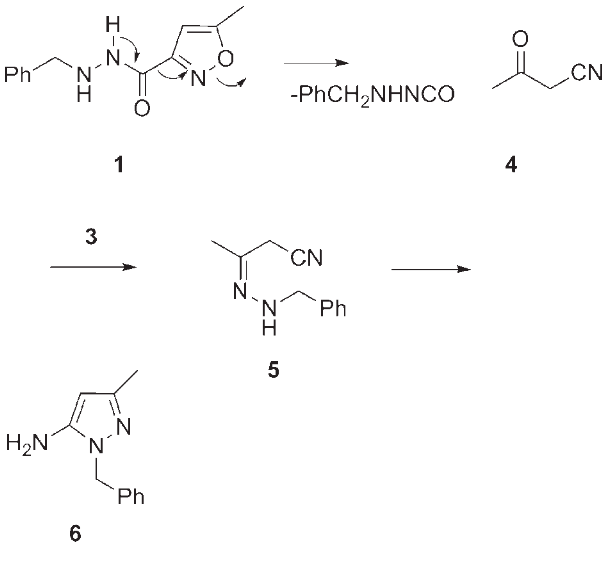


acetyl chloride and this route was used to prepare the (*E*) and (*Z*) isomers of 3-acetoxybut-2-ene nitrile (**8**) (Scheme 3) [14].

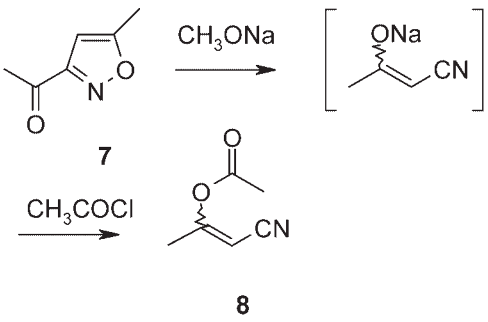
Unimolecular reactions of isocarboxazid (**1**) are known. As reported in the patent literature, isocarboxazid (**1**) rearranges to 5-acetonyl-2-benzyl-4-hydroxy-1,2-3-triazole (**9**) in refluxing toluene after an overnight hold in a 64% yield. No spectral data or purity assessment of the triazole **9** was reported [15]. We have repeated this experiment and found that the reaction follows first-order kinetics with $t_{1/2}$ of ~29 h (Scheme 4).

A significantly better conversion is observed when the rearrangement is conducted in DMF or in an ionic liquid at 150°C [16]. At 100°C in the ionic liquid, [bmin]HSO_4^-, close to the temperature of refluxing toluene, the reaction is essentially complete in 3 h as determined by HPLC analysis. Isocarboxazid (**1**) melts between 103 and 107°C and a 24% conversion to triazole **9** was observed when isocarboxazid (**1**) was heated at 105°C in a reaction vial for 2 h. For this drug substance, a validated HPLC method showed limits of detection (LOD) of 15 μg for the triazole **9** and 7.5 μg for the pyrazole **6** and no triazole **9** or pyrazole **6** was detected in the crude isocarboxazid (**1**).

Scheme 2. Thermal degradation of isocarboxazid (**1**) to nitrile **4**.



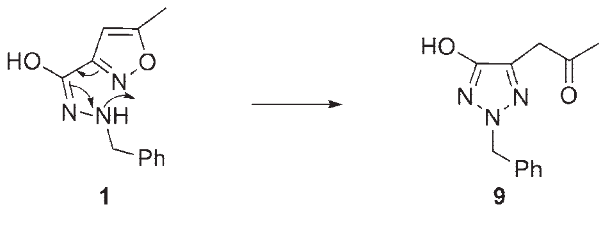
Scheme 3. Base-catalyzed ring opening of isoxazole **7**.



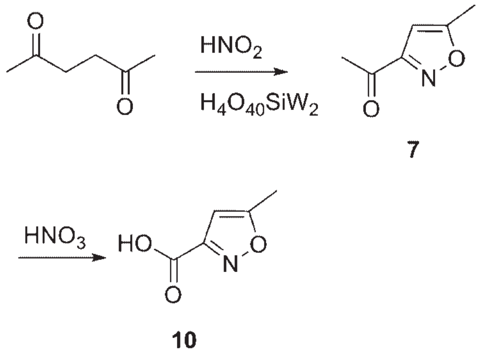
By analogy with the Boulton–Katritzky rearrangement of monoazoles, the driving force for this reaction would be the formation of the more aromatic triazole ring as opposed to the isoxazole ring [17]. In general, 1,2,4-oxadiazoles are the heterocycle involved in this rearrangement, although it has been observed in the case of an isoxazole [18]. Because of the increased acidity of the α-hydrogens of the hydrazide as opposed to an amide [19], we favor that the rearrangement occurs from the enol or imidic acid tautomer of the hydrazide. The rate acceleration that is observed in the ionic liquid as opposed to the nonpolar solvent toluene would support such an assertation. Nucleophilic attack of nitrogen on nitrogen followed by isoxazole nitrogen–oxygen bond cleavage would afford triazole **9**.

The expired Roche patent for the preparation of isocarboxazid (**1**) involves a purification of isocarboxazid (**1**) by the formation of a hydrochloride salt. Free-basing of the salt yields isocarboxazid (**1**) [9]. In a control experiment, we have found that isocarboxazid (**1**) is unstable in base and we would offer that pyrazole **6** originates, when isocarboxazid (**1**) is regenerated by treatment of the hydrochloride with base. For our current process, which is the result of additional development studies, the process has been refined and does not involve the formation of a hydrochloride salt.

Scheme 4. Thermolysis of isocarboxazid (**1**).



Scheme 5. Synthesis of isoxazole acid (**10**).



3-Oxobutanenitrile (**4**) or any precursors are not present in the starting ester **2** as both the isoxazole ester **2** and 5-methylisoxazole-3-carboxylic acid (**10**) are of exceptional quality [9,20]. Isoxazole acid (**10**) was prepared by the nitric acid oxidation of 2,5-hexanedione [20]. We have found that the violent exotherm of this oxidation [12] can be tempered when 3-acetyl-5-methylisoxazole (**7**) is prepared *in situ* by a heteropoly acid-catalyzed nitrosation with nitrous acid. When nitric acid is added to this reaction mixture, no uncontrolled exotherm is observed (Scheme 5). No yield improvement has yet been realized, however, as the heteropolyacid may also catalyze an aldol reaction or cyclization to 2,5-dimethylfuran.

An authentic sample of 5-amino-1-benzyl-3-methylpyrazole (**6**) was prepared by an adaptation of the Magnus β-ketonitrile process for the synthesis of 3-oxobutanenitrile (**4**) [21]. The procedure entails the reaction of β-ketonitrile **4** with benzylhydrazine (**3**), followed by ring closure of hydrazone **5** in a mixture of ethanol and hydrochloric acid [22]. The basis of this nitrile **4** process involves reaction of the enolate of acetonitrile with ethyl acetate and an inverse addition of the enolate suspension to an acetic acid solution of benzylhydrazine (**3**) [21]. Magnus' laboratory procedure involves the use of DMSO to solubilize the enolate. However, we found that stiff plastic tubing outfitted with standard adapters could accomplish this transfer in much the same way as the enolate suspension was transferred in the Magnus plant process. Although the yield was only 25%, byproducts could be readily removed from the relatively soluble pyrazole **6** and the pyrazole **6** was isolated as its hydrochloride salt **6a**. For comparison's sake, chromatography of the reaction mixture afforded the free base and the ^{1}H NMR spectrum agreed with the published values for this compound [23].

In conclusion, our requirement to control the formation of pyrazole **6** led to a more detailed investigation of the thermal rearrangement of isocarboxazid (**1**) to triazole **9**. By analogy with the Boulton–Katritzky rearrangement of monoazoles, the reaction would appear to proceed through the enol tautomer of the hydrazide. There is increased interest in monoamine oxidase inhibitors [24] and the crystal structures of monoamine oxidase A [25] and monoamine oxidase B [26] as well as the crystal structure of isocarboxazid (**1**) [27] have been solved. Combinatorial routes to 3-acylisoxazoles have been described [12,28]. The unmasking of a ketone functionality in this pericyclic rearrangement may have biochemical implications. The recent work of Edmonson and others have suggested that an aldehyde group may play a role in the inhibition of monoamine oxidase by arylalkylhydrazine-based therapeutics [26].

EXPERIMENTAL

Isocarboxazid (**1**) was a product of internal manufacture. An authentic sample of 5-amino-1-benzyl-3-methylpyrazole hydrochloride (**6a**) was obtained form the U.S. Pharmacopoeia, Rockville, MD [29]. The validated HPLC method consisted of gradient elution with a variable composition of 25 m*M* phosphate buffer and acetonitrile. The flow rate was 1.0 mL per minute. The initial conditions of the method consisted of 80% aqueous buffer and 20% acetonitrile. This condition was maintained for 10 min and over a 10 min period was changed to 60% buffer and 40% acetonitrile. After a further 10 min period, the conditions were changed to 50% aqueous buffer and 50% acetonitrile. The column temperature was maintained at 40°C and the wavelength was 232 nm. The buffer was prepared by dissolving 3.40 g of potassium hydrogen phosphate in 1 L of distilled water and by adjusting the pH to 2.5 with phosphoric acid. The column had dimensions of 250 mm × 4.6 mm and contained Luna C18(2), 5 μ, 100 Å packing. The column manufacturer was Phenomenex. The injection volume was 10 μL.

The respective retention times are 19.4 min for isocarboxazid (**1**), 15.9 min for the triazole **9**, 10.9 min for the isoxazole ester **2**, 6.9 min for the pyrazole **6**, 5.6 min for the isoxazole acid **10**, and 3.5 min for 5-methylisoxazole-3-carboxylic acid hydrazide (**11**). Similar retention time behavior is observed when 0.1% trifluoroacetic acid (v/v) is used as the aqueous phase.

For the validated method, 20 mg of isocarboxazid (**1**) was dissolved in 5.0 mL of acetonitrile in a 100 mL volumetric flask. The diluent was 0.1% trifluoroacetic acid (v/v) and the solution was diluted to volume with diluent. Serial dilutions of this solution allowed for the determination of the LOD from six replicate injections. The LOD of the known compounds was determined in a similar manner. The LOD for isocarboxazid (**1**), triazole **9**, isoxazole ester **2**, pyrazole **6**, isoxazole acid **10**, and isoxazole hydrazide **11** was 30, 15, 15, 7.5, 15, and 15 μg, respectively.

5-Acetonyl-2-benzyl-4-hydroxy-1,2,3-triazole (9). Under a nitrogen purge, isocarboxazid (**1**) (50.00 g) and 150 mL of anhydrous DMF were combined and heated to 150°C. When first at temperature, HPLC analysis showed the reaction to be 85% complete. After 2 h at 150°C, the conversion was essentially 100% and the triazole **9** was the only component present by HPLC. The reaction mixture was cooled and was added to 2.5 L of distilled water. Gummy material, which was associated with a white solid formed and the solution was decanted. The solid was washed with water. The solid was dissolved in 500 mL of isopropanol (IPA) and the IPA was evaporated to a minimum volume and was filtered. There was obtained 13.86 g of the triazole **9** as a pale yellow solid in a 27.4% yield and the solid was 100% pure by HPLC analysis. The crude solid was recrystallized from a 10:1 mixture of cyclohexane and IPA. Pure triazole **9** as a white solid was obtained in a 90.2% yield. The triazole **9** had melting point 95–96°C; IR (potassium bromide): 3033–2983 (br, OH), 1717 (C=O), 1226, 1180 cm^{-1}; ^{1}H NMR (deuteriochloroform) δ 2.29 (s, 3H, CH_3), 3.85 (s, 2H, CH_2), 5.32 (s, 2H, CH_2), 7.27–7.36 (m, 5H aromatic), 9.24 (b, 1H, OH); ms: *m/z* 232 (M + 1), 175 (M +1-CH_3COCH_2), 132; Anal. Calcd for $C_{12}H_{13}N_3O_2$ (231.26): C, 62.33; H, 5.67; N, 18.17. Found: C, 62.44; H, 5.74; N, 18.32.

Thermolysis of isocarboxazid (1) in [bmin] HSO_4^-. Isocarboxazid (**1**) (21.55 g) and 67.55 g of 1-butyl-3-methylimidazolium hydrogen sulfate were combined and heated to 150°C. At temperature, the reaction was essentially complete as evident by HPLC analysis. The reaction was cooled and the product was extracted with 5 × 150 mL of MTBE. The MTBE layer was isolated by vacuum decantation using a suction flask and the ionic liquid remained in the flask. After evaporation, there was obtained 11.41 g of the triazole **9** as a white solid in a 52.9% yield. The ionic liquid phase was extracted with 2 × 150 mL of ethyl acetate and 6.96 g of the remaining 10.14 g of triazole **9** was obtained. 20% IPA in ethyl acetate (150 mL) was used to extract the remaining amount of triazole **9**. After evaporation, 4.30 g of solid was obtained. The total mass balance was 105% with the overage being the ionic liquid, which was extracted when ethyl acetate or a mixture of IPA and ethyl acetate was used. No triazole **9** was detected in the ionic liquid phase. The ionic liquid was heated at 100°C for an overnight hold to remove solvent.

The ionic liquid was used in a recycle with 20.00 g of isocarboxazid (**1**) at 100°C. The reaction was monitored by HPLC once the reaction mixture reached temperature and every hour afterward. The reaction was 100% complete in 3 h.

Thermolysis of isocarboxaxzid (1) in toluene. Isocarboxazid (**1**) (50.00 g) and 150 mL of anhydrous toluene were combined under a nitrogen purge and the batch was heated to reflux. The solution was monitored periodically by HPLC over a time period of 60 h and the disappearance of isocarboxazid (**1**) was ascertained by this method. At an 88% conversion to triazole **9**, there was 4.6% of a polar impurity present along with <2.0% of other components.

Thermolysis of neat isocarboxazid (1). 20 mg of isocarboxazid (**1**) was heated at 105°C in a reaction vial for 2 h. The extent of the rearrangement was determined by HPLC. Triazole **9** was present to the extent of 24.4% by HPLC and trace levels (<0.2%) were observed for five unknowns.

5-Amino-1-benyzl-3-methylpyrazole hydrochloride (6a). Under a nitrogen purge, potassium *tert*-butoxide (87.90 g, 0.783 mol) and 825 mL of anhydrous tetrahydrofuran were combined in a 2 L flask with a mechanical stirrer. A mixture of 69.0 mL (62.2 g, 0.706 mol) of ethyl acetate and 45.0 mL (35.4 g, 0.862 mol) of acetonitrile was added over a 30 min period and the temperature was maintained below 30°C. The light beige suspension was stirred for 1 h at room temperature.

Benzylhydrazine dihydrochloride (**3a**) (55.65 g, 0.285 mol), 150 mL of ethanol, and 75 mL of concentrated ammonium hydroxide was added to a separate 3 L flask. Glacial acetic acid (225 mL) was added. The pH of the solution was 5 by paper and the suspension was cooled to 30°C. Under vacuum, the enolate suspension was transferred to the flask containing benzylhydrazine (**3**) with 1.0 cm (outer diameter) stiff plastic tubing, which had fitted into two standard 29/42 tubing adapters. The addition time was <5 min and the temperature was maintained at <30°C. The vessel was rinsed with 150 mL of THF. The suspension was stirred at room temperature for 22.5 h.

The solvent was removed under 10 mm of vacuum and a temperature of <45°C. Ethanol (500 mL) was added and this was followed by the addition of 120 mL of concentrated hydrochloric acid. The reaction mixture was refluxed for 24 h [22]. The reaction mixture was cooled and sodium carbonate was added. The pH of the solution was 5 to wet paper. The batch was filtered and washed with ethanol (2 × 300 mL). The filtrate was evaporated at 40–45°C under vacuum. After 500 mL of ethanol was removed, a white solid formed. The suspension was filtered and washed with ethanol. The concentration and filtration was repeated twice. To the residue was added 550 mL of isopropanol. The slurry was cooled, filtered, and washed with 2 × 50 mL of IPA. Concentrated hydrochloride acid (25 mL) was added. The slurry was cooled in an ice-bath, filtered, and dried. There was obtained in two crops, 16.16 g of 5-amino-1-benzy-3-methylpyrazole hydrochloride (**6a**) as a white solid in a 25.3% yield. Pyrazole hydrochloride **6a** had mp 221–223°C and the purity by HPLC was 100%.The melting point of the USP reference standard was 223–227°C [29].

5-Amino-1-benzyl-3-methylpyrazole (6). Using a similar protocol, the free base **6** was isolated in a 29% yield after chromatography on silica gel and with an eluent consisting of a mixture of 60% ethyl acetate and 40% heptane. Pyrazole **6** had mp 64–66°C (lit mp 67–70.5°C [23]) and ^{1}H NMR (deuteriochloroform) δ 2.14 (s, 3H), 3.46 (b, 2H), 4.92 (s, 2H), 5.40 (s, 1H), 7.15–7.36 (m, 5H, aromatic). The ^{1}H NMR agrees with the reported values [23]. Pyrazole **6** was freely soluble in IPA, the recrystallization solvent for isocarboxazid (**1**). The addition of hydrochloric acid causes the hydrochloride **6a** to precipitate from solution. Pyrazole **6a** had mp 223–227°C.

5-Methylisoxazole-3-carboxylic acid (10). 2,5-Hexanedione (42.8 g; 0.375 mol), 0.54 g (0.05 mol %) of silicotungstic acid, 17.9 mL (0.34 mol) of concentrated sulfuric acid, and 80 mL of water were combined and cooled to 5°C. Sodium nitrite (65.0; 0.94 mol) was added over a 100 min period and the temperature was maintained below 40°C. Copious gas evolution was observed with some nitrogen dioxide vapors. The mixture was held overnight. The reaction mixture was filtered and washed with ~5 mL of water. The filtrate contained two phases.

The reaction mixture was heated to between 75 and 80°C. 70% Nitric acid (85 mL, 1.3 mol) was added slowly over a 1 h period. The heat was shut off after the addition of 15 mL nitric acid. The batch temperature was maintained at 100–102°C for 19.5 h. The reaction was cooled to 15°C and the product was isolated by filtration. After drying to a constant weight, there was obtained 21.33 g of 5-methylisoxazole-3-carboxylic acid (**10**) as a white solid in a 45% yield. The purity by HPLC was 99% (Zorbax-SC-Cyano column, eluent: 95% 25 m*M* phosphate buffer and 5% methanol, flow rate: 1.0 mL per min) and the melting point was 171–173°C (decomposition). A reference standard, which was prepared by the Cusmano method [20] and was recrystallized from acetone had a melting point of 172–173°C with decomposition.

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Synthesis of Novel Naphth[1,2-f][1,4]oxazepine-3,4-dione Heterocycles

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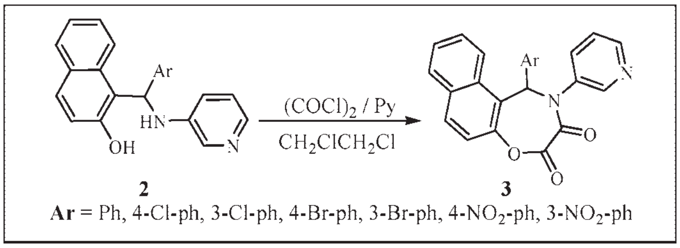

A number of *N*-heteroaryl aminonaphthols (Betti bases) were prepared from the reaction of 2-naphthol, 3-aminopyridine, and aromatic aldehydes. Subsequent condensation of the prepared Betti bases with oxalyl chloride afforded the novel naphth[1,2-f][1,4]oxazepine-3,4-dione heterocycles in moderate to high yields.

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INTRODUCTION

Although Betti's classical procedure for the preparation of 1-(α-aminobenzyl)-2-naphthol (Betti base) was published more than a century ago [1], the possibilities of the application of this versatile synthon in the ring-closure reactions to give naphthalene-condensed heterocyclic derivatives have not been thoroughly investigated. A few publications that have been appeared on this topic focus on the transformation reactions of the Betti base analog aminonaphthols with phosgene, ethyl benzimidate, 2-carboxybenzaldehyde, levulinic acid, salicylaldehyde/acetaldehyde, salicylaldehyde/formalin, benzaldehyde derivatives, and bis-aldehydes/NaBH$_3$CN to naphthoxazine derivatives [2–6]. Traditionally, the Betti base derivatives synthesis is carried out in organic solvents, such as, EtOH, MeOH, and Et$_2$O, at room temperature for long time or thermally under solvent-less conditions. As such, utilization of environmental friendly water as solvent not only provides the product in an easy work-up procedure but also is in accord with green sustainable chemistry principles [7–13].

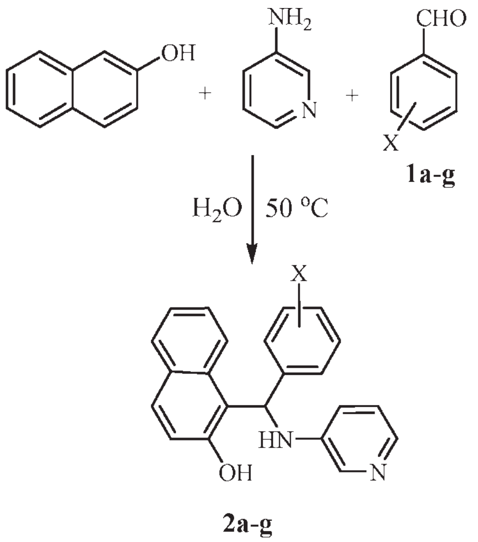
There are many methods for the synthesis of oxazepine ring systems [14]. In the reported synthetic approaches to the aryl-fused derivatives of 1,4-oxazepines, several bifunctional keto acids were used in Ugi condensation reaction [15]. Similarly, a number of 1,4-benzoxazepin-3-ones were obtained via Ugi three-component condensations using bifunctional starting materials containing aldehyde and carboxylic acid [16]. A synthetic procedure was also developed for the preparation of oxazepinedione derivatives by lactonization of some amides obtained from condensation of either 2-acetoxybenzoic acid chloride or the proper acethoxynaphthonic acid chloride with cyclic amino acids [17]. Oxazepine derivatives were described as effective protease inhibitors [18], integrin antagonists, squalene synthase [19], reverse transcriptase inhibitors [20], and antihistamines, which can be used for the efficient therapy of some allergic and dermatological infections [21]. To the best of our knowledge, synthesis of dioxo-1,4-naphthoxazepine via condensation of aminonaphthols (Betti bases) with oxalyl chloride has not been previously reported in literature.

Our very recently reported results on the successful uncatalyzed quantitative preparation of aminonaphthols (Betti bases) via one-pot three-component reaction of 2-naphthol, aromatic aldehydes, and heteroaryl amines, such as 2-aminopyrimidine, 2-aminopyrazine, and 2-aminopyridine [22] prompted us to utilize these bases in the synthesis of the novel dioxo-1,4-naphthoxazepines.

RESULTS AND DISCUSSION

Condensation of Betti bases containing the heteroaryls, such as 2-aminopyrimidine, 2-aminopyrazine, and 2-aminopyridine with oxalyl chloride failed to produce any product with the oxazepinedione structure. It was concluded that the Betti bases containing the very poor electron nature of 2-aminopyrimidine, 2-aminopyrazine, and 2-aminopyridine might have been responsible for

Scheme 1



X = **a**: H, **b**: 4-Cl, **c**: 3-Cl, **d**: 4-Br, **e**: 3-Br, **f**: 4-NO_2, **g**: 3-NO_2

the lack of expected reactivity. Therefore, it was decided to prepare the Betti bases obtained from one-pot condensation of 3-aminopyridine, 2-naphthol with different aromatic aldehydes. These aminonaphthols containing the 3-aminopyridine moiety with partially less electron deficiency with respect to the previously prepared heteroaryl amines were expected to successfully furnish the relevant oxazepine derivatives.

As the model reaction, the one-pot reaction of benzaldehyde, 2-naphthol, and 3-aminopyridine was carried out under our previously reported conditions. It was found that at least 2 h is needed for reaction to be completed at room temperature. The best result was obtained at 50°C, because the reaction was completed during 5 min. Therefore, three-component reactions of 2-naphthol, 3-aminopyridine, and aromatic aldehydes **1a–g** in water afforded aminonaphthol derivatives **2a–g** with excellent yields (Scheme 1). Reaction times and yields of the synthesized Betti base derivatives **2a–g** are presented in Table 1.

Identification of **2a–g** was carried out on the basis of spectroscopic information and elemental analysis. The ^{1}H NMR spectra of compounds **2a–g** show a sharp singlet for the hydroxyl group at δ 10.2 ppm, a doublet for NH proton at δ 6.7 ppm, and a doublet for methine proton at δ 6.5 ppm. D_2O is traditionally added into the NMR tube of compounds containing the OH or NH group to find the relevant signals and their coupling effects. Upon addition of D_2O into the **2a** NMR sample tube, the δ 10.2 ppm and δ 6.7 ppm signals disappeared and the proton of methine located at δ 6.5 ppm moiety collapsed into a singlet. The IR spectra of compounds **2a–g** display two absorption bands at 3373–3406 cm^{-1} for OH and NH groups. Compounds **2a–g** exhibit the expected parent ion peaks with medium intensity in the Mass spectra.

When the newly synthesized *N*-heteroaryl-substituted aminonaphthols **2a–g** were treated with oxalyl chloride in the presence of pyridine in dry 1,2-dichloroethane as solvent, the corresponding novel naphthoxazepine-condensed 1,4-naphthoxazepine-3,4-diones **3a–g** were obtained (Scheme 2).

Identification of **3a–g** was carried out on the basis of ^{1}H NMR, ^{13}C NMR, IR, Mass spectra, and elemental analysis. The absence of OH and NH protons in the ^{1}H NMR and IR spectra confirms the transformation of the starting aminonaphthols into the products by bonding of the oxalyl chloride sp^2 carbons to the hydroxyl and *N*-substituted groups. IR absorption bands appearing at 1633 and 1725 cm^{-1} reveals the presence of lactam and lactone carbonyl groups, respectively. The oxazepine-dione ring methine proton appears as a singlet at δ 6.5 ppm and the other protons are displayed in the aromatic regions. Mass spectra of **3a–g** reveal the presence of the molecular ion peaks and other fragments consistent with the assigned structures.

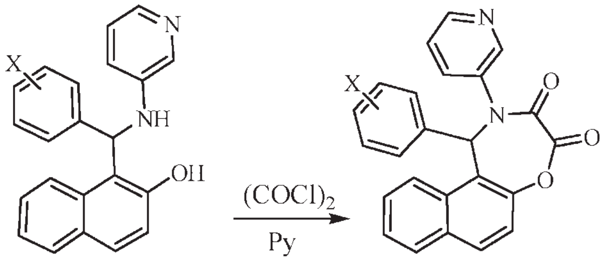
In summary, we have successfully developed a fast, convenient, and efficient method for the synthesis of new *N*-substituted-aminonaphthol (Betti base) derivatives in water. When compared with other previously reported procedures in literatures, this method with the advantages, such as omitting organic solvent, generality

Table 1

Reaction times, yields, and melting points of the products **2** in H_2O.

Compound	Aldehyde	Time (min)	Mp (°C)	Yield (%)
2a	Benzaldehyde	5	187–189	90
2b	4-Chlorobenzaldehyde	25	157–159	92
2c	3-Chlorobenzaldehyde	30	144–145	91
2d	4-Bromobenzaldehyde	50	162–164	95
2e	3-Bromobenzaldehyde	55	149–150	94
2f	4-Nitrrobenzaldehyde	10	179–180	97
2g	3-Nitrrobenzaldehyde	15	190–192	93

Scheme 2



2a-g **3a-g**

X – **a**: H, **b**: 4-Cl, **c**: 3-Cl, **d**: 4-Br, **e**: 3-Br, **f**: 4-NO_2, **g**: 3-NO_2

and simplicity of procedure, lower reaction time, elimination of acid catalyst, and obtaining excellent yields are worth noting. Moreover, we have developed a convenient synthetic strategy to novel naphthoxazepine-condensed derivatives 1,4-naphthoxazepine-3,4-diones. To the best of our knowledge, the synthesis of seven-membered rings consisting of 1,4-naphthoxazepine-3,4-diones have not been previously reported.

EXPERIMENTAL

All commercially available chemicals and reagents were used without further purification. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 4300 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 on Bruker DRX-500 AVANCE spectrometers. Chemical shifts (δ) are reported in ppm and are referenced to the NMR solvent. Mass spectra of the products were obtained with a HP (Agilent technologies) 5937 Mass Selective Detector. Elemental analyses were carried out by a CHN-O-Rapid Heraeus elemental analyzer (Wellesley, MA).

General procedure for the synthesis of 1-(X-substituted-phenyl(pyridine-3-ylamino)methyl)naphthalene-2-ol (2a–g). To a stirring suspension of 2-naphthol (1.44 g, 10 mmol) in water (15 mL), the appropriate aromatic aldehyde (10 mmol) and 3-aminopyridine (10 mmol) was added. The reaction mixture was stirred at 50°C for the appropriate time (see Table 1). Then water was decanted and the white precipitated product was separated upon addition of ethanol (10 mL) to the mixture with stirring, while cooling to 0–5°C. The precipitate was filtered, washed with cold EtOH, dried, and purified by recrystallization from EtOH to give the colorless crystals of **2a–g**.

1-(Phenyl(pyridine-3-ylamino)methyl)naphthalene-2-ol (2a). IR (potassium bromide): 3394, 3068, 2900, 1625, 1240, 804 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.55 (d, J = 6.6 Hz, 1H, methine-H), 6.72 (d, J = 6.6 Hz, 1H, NH), 7.00–8.15 (m, 15H, NPh-H, Ph-H, and Pyridine-H), 10.25 (s, 1H, OH) ppm; ^{1}H NMR (500 MHz, DMSO-d6 + D_2O): δ 6.57 (s, 1H, methine-H), 7.01–8.09 (m, 15H, NPh-H, Ph-H, and Pyridine-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 53.39, 119.08, 119.17, 119.56, 123.26, 124.34, 124.94, 126.91, 127.32, 127.59, 129.06, 129.45, 129.70, 130.19, 133.08, 136.73, 138.11, 143.11, 145.44, 153.88 ppm; ms: m/z (%) 326 (10) [M$^+$], 231 (100), 202 (50), 94 (40). *Anal.* Calcd for $C_{22}H_{18}N_2O$: C, 80.98; H, 5.52; N, 8.58%. Found: C, 80.87; H, 5.60; N, 8.49%.

1-(4-Chlorophenyl(pyridine-3-ylamino)methyl)naphthalene-2-ol (2b). IR (potassium bromide): 3373, 3051, 2917, 1627, 1299, 806 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.60 (d, J = 6.6 Hz, 1H, methine-H), 6.72 (d, J = 6.6 Hz, 1H, NH), 7.02–8.12 (m, 14H, NPh-H, Ph-H, and Pyridine-H), 10.25 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 52.86, 119.07, 119.21, 119.26, 123.33, 124.36, 124.69, 127.08, 128.99, 129.42, 129.51, 129.66, 130.39 131.83, 132.95, 136.76, 138.26, 142.27, 145.27, 153.85 ppm; ms: m/z (%) 360 (15) [M+], 265 (90), 231 (100), 202 (50), 144 (15), 94 (30). *Anal.* Calcd for $C_{22}H_{17}ClN_2O$: C, 73.23; H, 4.71; N, 7.76%. Found: C, 73.19; H, 4.64; N, 7.80%.

1-(3-Chlorophenyl(pyridine-3-ylamino)methyl)naphthalene-2-ol (2c). IR (potassium bromide): 3404, 3051, 2906, 1625, 1292, 815 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.57 (d, J = 6.8 Hz, 1H, methine-H), 6.74 (d, J = 6.8 Hz, 1H, NH), 7.02–8.13 (m, 14H, NPh-H, Ph-H, and Pyridine-H), 10.28 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 52.97, 119.10, 119.17, 119.24, 123.39, 124.37, 124.52, 126.29, 127.15, 127.23, 127.32, 129.55, 129.61, 130.48, 130.96, 132.93, 133.81, 136.77, 138.35, 145.16, 145.95, 153.90 ppm; ms: m/z (%) 360 (15) [M$^+$], 265 (60), 231 (100), 216 (75), 202 (30), 144 (85), 94 (25). *Anal.* Calcd for $C_{22}H_{17}ClN_2O$: C, 73.23; H, 4.71; N, 7.76%. Found: C, 73.16; H, 4.68; N, 7.72%.

1-(4-Bromophenyl(pyridine-3-ylamino)methyl)naphthalene-2-ol (2d). IR (potassium bromide): 3373, 3051, 2915, 1627, 1249, 806 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.53 (d, J = 6.3 Hz, 1H, methine-H), 6.71 (d, J = 6.3 Hz, 1H, NH), 7.02–8.12 (m, 14H, NPh-H, Ph-H, and Pyridine-H), 10.26 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 52.93, 119.10, 119.25, 120.33, 123.35, 124.38, 124.60, 124.72, 127.10, 129.52, 129.67, 129.82, 130.41, 131.91, 132.96, 136.78, 138.28, 142.75, 145.29, 153.87 ppm; ms: m/z (%) 404 (15) [M$^+$], 406 (15) [M$^+$], 311 (80), 231 (100), 202 (80), 144 (25), 94 (50). *Anal.* Calcd for $C_{22}H_{17}BrN_2O$: C, 65.18; H, 4.19; N, 6.91%. Found: C, 65.21; H, 4.11; N, 6.89%.

1-(3-Bromophenyl(pyridine-3-ylamino)methyl)naphthalene-2-ol (2e). IR (potassium bromide): 3394, 3053, 2923, 1625, 1238, 817 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.59 (d, J = 6.3 Hz, 1H, methine-H), 6.75 (d, J = 6.3 Hz, 1H, NH), 7.02–8.15 (m, 14H, NPh-H, Ph-H, and Pyridine-H), 10.32 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 52.96, 119.10, 119.15, 119.25, 122.51, 123.39, 124.37, 126.67, 127.21, 129.55, 129.60, 130.13, 130.21, 130.48, 131.25, 131.90, 132.94, 136.78, 138.36, 145.16, 146.19, 153.94 ppm; ms: m/z (%) 404 (100) [M$^+$], 406 (100) [M$^+$], 311 (10), 231 (20), 202 (8), 144 (15), 95 (25). *Anal.* Calcd for $C_{22}H_{17}BrN_2O$: C, 65.18; H, 4.19; N, 6.91%. Found: C, 65.14; H, 4.16; N, 6.97%.

1-(4-Nitrophenyl(pyridine-3-ylamino)methyl)naphthalene-2-ol (2f). IR (potassium bromide): 3406, 3087, 2916, 1627, 1514, 1346, 1244, 827 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.68 (d, J = 6.3 Hz, 1H, methine-H), 6.81 (d, J = 6.3 Hz, 1H, NH), 7.06–8.19 (m, 14H, NPh-H, Ph-H, and Pyridine-H), 10.35 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 53.29, 119.08, 119.11, 119.14, 119.37, 123.47, 124.28, 124.44, 127.37, 128.69, 129.58, 129.64, 130.76, 132.92, 136.86, 138.53, 145.17, 147.01, 151.70, 153.93 ppm; ms: *m*/*z* (%) 371 (12) [M$^+$], 260 (30), 231 (100), 202 (50), 144 (15), 94 (22). *Anal.* Calcd for $C_{22}H_{17}N_3O_3$: C, 71.16; H, 4.58; N, 11.32%. Found: C, 71.20; H, 4.57; N, 11.22%.

1-(3-Nitrophenyl(pyridine-3-ylamino)methyl)naphthalene-2-ol (2g). IR (potassium bromide): 3390, 3078, 2925, 1622, 1527, 1348, 1236, 804 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 6.71 (d, *J* = 6.7 Hz, 1H, methine-H), 6.93 (d, *J* = 6.7 Hz, 1H, NH), 7.10–8.23 (m, 14H, NPh-H, Ph-H, and Pyridine-H), 10.40 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d$_6$): δ 53.01, 118.75, 119.21, 120.07, 122.09, 122.46, 123.49, 124.22, 124.71, 127.45, 129.59, 129.64, 130.60, 130.80, 132.91, 134.32, 136.07, 137.90, 145.28, 145.81, 148.71, 154.10 ppm; ms: *m*/*z* (%) 371 (12) [M$^+$], 276 (50), 260 (65), 231 (100), 202 (75), 144 (90), 94 (85). *Anal.* Calcd for $C_{22}H_{17}N_3O_3$: C, 71.16; H, 4.58; N, 11.32%. Found: C, 71.11; H, 4.50; N, 11.25%.

General procedure for the synthesis of 1-(X-substituted-phenyl)-2-(pyridin-3-yl)-1,2-dihydronaphth[1,2-f][1,4]oxazepine-3,4-diones (3a–g). Oxalyl chloride (1.2 mmol) was added dropwise with ice cooling to a stirring solution of 1-(X-substituted-phenyl(pyridine-3-ylamino)methyl)naphthalene-2-ol **2a–g** (1 mmol) in dry 1,2-dichloroethane (15 mL) containing pyridine (2.4 mmol) under argon atmosphere. The mixture was stirred for 30 min at 0–5°C, then 30 min at room temperature, and refluxed for an additional 45 min. The solvent was then removed under reduce pressure to give a solid compound. It was then triturated in saturated sodium bicarbonate solution (15 mL), filtered, washed with distilled water, and dried. The crude product was recrystallized from EtOH to give colorless crystals of **3a–g**.

1-Phenyl-2-(pyridine-3-yl)-1,2-dihydronaphth[1,2-f][1,4]oxazepine-3,4-dione (3a). Yield: 85%; mp: 232–234°C; IR (potassium bromide): 1718, 1635 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 6.23 (s, 1H, methine-H), 7.22–8.62 (m, 15H, NPh-H, Ph-H, and Pyridine-H) ppm; ^{13}C NMR (125 MHz, DMSO-d$_6$): δ 65.41, 114.75, 117.35, 122.69, 124.23, 125.86, 128.06, 128.17, 129.18, 129.42, 129.54, 129.73, 131.28, 131.47, 136.41, 137.54, 139.39, 147.53, 149.50, 149.48, 149.53, 150.00 ppm; ms: *m*/*z* (%) 380 (5) [M$^+$], 352 (35), 231 (100), 202 (45). *Anal.* Calcd for $C_{24}H_{16}N_2O_3$: C, 75.79; H, 4.21; N, 7.37%. Found: C, 75.70; H, 4.25; N, 7.40%.

1-(4-Chlorophenyl)-2-(pyridine-3-yl)-1,2-dihydronaphth[1,2-f][1,4]oxazepine-3,4-dione (3b). Yield: 83%; mp: 245–246°C; IR (potassium bromide): 1718, 1635 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 6.73 (s, 1H, methine-H), 7.32–8.55 (m, 14H, NPh-H, Ph-H, and Pyridine-H) ppm; ^{13}C NMR (125 MHz, DMSO-d$_6$): δ 62.81, 115.42, 117.54, 124.06, 124.86, 126.33, 128.44, 129.20, 129.60, 130.03, 130.28, 131.48, 131.66, 131.66, 134.11, 136.61, 137.47, 139.75, 147.31, 149.41, 149.43, 149.94 ppm; ms: *m*/*z* (%) 415 (10) [M$^+$], 386 (15), 279 (40), 231 (50), 202 (20), 167 (90), 149 (100). *Anal.* Calcd For $C_{24}H_{15}ClN_2O_3$: C, 69.48; H, 3.62; N, 6.75%. Found: C, 69.51; H, 3.55; N, 6.70%.

1-(3-Chlorophenyl)-2-(pyridine-3-yl)-1,2-dihydronaphth[1,2-f][1,4]oxazepine-3,4-dione (3c). Yield: 76%; mp: 222–223°C; IR (potassium bromide): 1724, 1639 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 6.74 (s, 1H, methine-H), 7.28–8.56 (m, 14H, NPh-H, Ph-H, and Pyridine-H) ppm; ^{13}C NMR (125 MHz, DMSO-d$_6$): δ 62.82, 115.22, 117.57, 124.03, 124.85, 126.38, 127.00, 128.17, 128.54, 129.20, 129.61, 129.64, 131.49, 131.76, 132.08, 134.33, 136.60, 137.40, 143.09, 147.41, 149.40, 149.43, 149.48, 149.90 ppm; ms: *m*/*z* (%) 415 (10) [M$^+$], 386 (50), 265 (90), 231 (100), 202 (50). *Anal.* Calcd For $C_{24}H_{15}ClN_2O_3$: C, 69.48; H, 3.62; N, 6.75%. Found: C, 69.42; H, 3.59; N, 6.80%.

1-(4-Bromophenyl)-2-(pyridine-3-yl)-1,2-dihydronaphth[1,2-f][1,4]oxazepine-3,4-dione (3d). Yield: 80%; mp: 225–227°C; IR (potassium bromide): 1720, 1637 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 6.71 (s, 1H, methine-H), 7.25-8.54 (m, 14H, NPh-H, Ph-H, and Pyridine-H) ppm; ^{13}C NMR (125 MHz, DMSO-d$_6$): δ 62.88, 115.36, 117.53, 122.77, 124.05, 124.88, 126.33, 128.45, 129.19, 129.60, 130.57, 131.48, 131.67, 132.95, 136.60, 137.47, 140.14, 147.30, 149.40, 149.41, 149.43, 149.92 ppm; ms: *m*/*z* (%) 458 (5)[M$^+$], 460 (5) [M$^+$], 430 (12), 432 (12), 309 (25), 311 (25), 231 (90), 202 (25), 167 (80), 149 (100). *Anal.* Calcd for $C_{24}H_{15}BrN_2O_3$: C, 62.74; H, 3.26; N, 6.10%. Found: C, 62.70; H, 3.33; N, 6.14%.

1-(3-bromophenyl)-2-(pyridine-3-yl)-1,2-dihydronaphth[1,2-f][1,4]oxazepine-3,4-dione (3e). Yield: 78%; mp: 220–222°C; IR (potassium bromide): 1724, 1639 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 6.73 (s, 1H, methine-H), 7.26–8.56 (m, 14H, NPh-H, Ph-H, and Pyridine-H) ppm; ^{13}C NMR (125 MHz, DMSO-d$_6$): δ 62.78, 115.20, 117.56, 122.92, 124.02, 124.86, 126.39, 127.37, 128.55, 129.18, 129.63, 131.00, 131.49, 131.78, 132.34, 132.52, 136.61, 137.39, 143.28, 147.41, 149.41, 149.45, 149.48, 149.89 ppm; ms: *m*/*z* (%) 458 (5)[M$^+$], 460 (5)[M$^+$], 430 (12), 432 (12), 309 (50), 311 (50), 231 (90), 202 (50), 167 (40), 149 (100). *Anal.* Calcd for $C_{24}H_{15}BrN_2O_3$: C, 62.74; H, 3.26; N, 6.10%. Found: C, 62.80; H, 3.21; N, 6.02%.

1-(4-Nitrophenyl)-2-(pyridine-3-yl)-1,2-dihydronaphth[1,2-f][1,4]oxazepine-3,4-dione (3f). Yield: 78%; mp: 205–207°C; IR (potassium bromide): 1720, 1633, 1519, 1348 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 6.92 (s, 1H, methine-H), 7.48–8.55 (m, 14H, NPh-H, Ph-H, and Pyridine-H) ppm; ^{13}C NMR (125 MHz, DMSO-d$_6$): δ 62.59, 114.85, 117.61, 123.97, 124.93, 125.25, 126.43, 128.60, 129.15, 129.66, 129.83, 129.85, 131.50, 131.98, 136.64, 137.34, 147.50, 147.68, 148.30, 149.30, 149.57, 149.92 ppm; ms: *m*/*z* (%) 425 (6) [M$^+$], 397 (18), 279 (50), 260 (47), 231 (80), 202 (30), 167 (90), 149 (100). *Anal.* Calcd For $C_{24}H_{15}N_3O_5$: C, 67.76; H, 3.53; N, 9.88%. Found: C, 67.80; H, 3.52; N, 9.87%.

1-(3-Nitrophenyl)-2-(pyridine-3-yl)-1,2-dihydronaphth[1,2-f][1,4]oxazepine-3,4-dione (3g). Yield: 80%; mp: 202–203°C; IR (potassium bromide): 1725, 1638, 1524, 1349 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 6.95 (s, 1H, methine-H), 7.46–8. (m, 14H, NPh-H, Ph-H, and Pyridine-H) ppm; ^{13}C NMR (125 MHz, DMSO-d$_6$): δ 62.49, 114.83, 117.60, 123.04, 123.99, 124.57, 124.88, 126.45, 128.65, 129.14, 129.20, 129.67, 131.50, 131.73, 132.02, 134.94, 136.84, 137.23, 142.63, 147.57, 148.91, 149.29, 149.59, 150.09 ppm; ms: *m*/*z* (%) 425 (5) [M$^+$], 397 (15), 279 (60), 260 (50), 231 (85), 202 (30), 167 (92), 149 (100). *Anal.* Calcd for $C_{24}H_{15}N_3O_5$: C, 67.76; H, 3.53; N, 9.88%. Found: C, 67.69; H, 3.50; N, 9.92%.

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Synthesis of Functionalized 1,2,3-Triazole Derivatives of 2-Indolones from Morita-Baylis-Hillman Adducts of Isatin *via* ''Click Chemistry''

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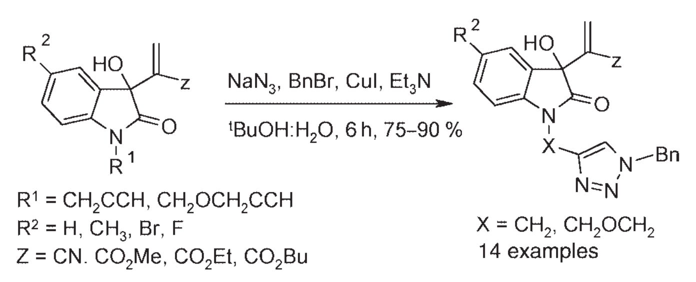

$R^1 = CH_2CCH, CH_2OCH_2CCH$
$R^2 = H, CH_3$, Br, F
Z = CN. CO_2Me, CO_2Et, CO_2Bu
$X = CH_2, CH_2OCH_2$
14 examples

A short and efficient regioselective synthesis of a number of 1,4-disubstituted-1,2,3-triazole derivatives of oxindoles from *N*-terminal alkyne and alkynyl ether derivatives of Morita-Baylis-Hillman (MBH) adducts of isatin with *in situ* generated alkyl azide and copper(I) iodide as a catalyst in 1:1 mixture of *t*-BuOH:water as a solvent system has been achieved. The synthetic procedure tolerates most of the functional groups present in the MBH adducts and circumvents the problems associated with the isolation of potentially toxic and explosive organic azides.

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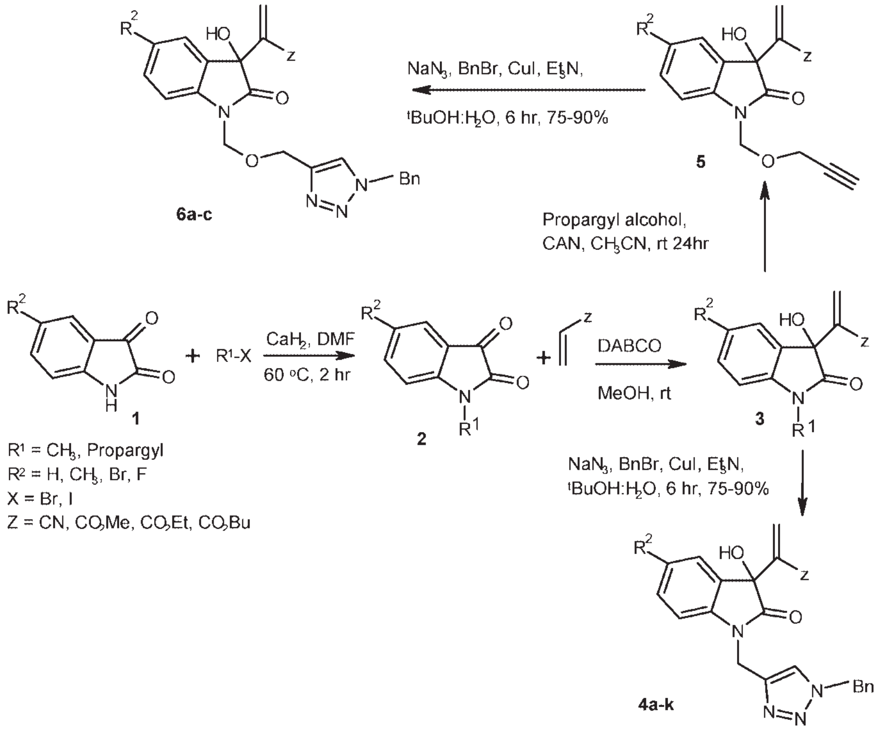
INTRODUCTION

Oxindoles derivatized as 1,2,3-triazole are elegant synthetic targets in organic synthesis due to their significant biological activities [1]. Recently, click chemistry has been emerged as a fast and efficient method for the synthesis of novel diverse chemical entities and the generation of large number of drug-like molecules with triazole scaffolds [2]. The triazole scaffolds are considered as significant synthetic targets due to their significant biological activities, such as antibacterial [3], anti-HIV [4], and anti-allergic [5]. Hence, a number of synthetic routes have been developed for the preparation of these structural frameworks [6–9]. As a result, there has been considerable interest in developing efficient synthetic methods for these compounds with oxindole as core structure. The Morita-Baylis-Hillman (MBH) adduct and their derivatives, such as halides, acetates, ethers, etc. play an important role as synthons for a number of potential synthetic intermediates and natural product syntheses [10]. As part of our on going research on novel synthetic applications of MBH adducts [11–13], particularly for the construction of novel oxindole derivatives [14–18], we were interested to explore the synthesis of title compounds using the versatile ''click chemistry'' reaction methodology. Several methods have been reported for the synthesis of 1,2,3-triazoles and 1,3-dipolar cycloaddition of azides to alkynes [19–21]. Recently, Sharpless and coworkers have reported a high yielding synthesis of triazoles using a Cu(I) catalyst with an excellent 1,4-regioselectivity. The metal-catalyzed reaction discovered simultaneously and independently in the Sharpless and Meldal laboratories [22] constitutes a substantial improvement of the classical Huisgen-type thermal 1,3-dipolar cycloaddition, which usually afford a mixture of 1,4- and 1,5-disubstituted triazoles. Fokin and coworkers have developed a multicomponent variant for the synthesis of trizoles both in conventional [23] and microwave irradiation [24] methods. Although *N*-propargyl isatins obtained from Friedel-Crafts alkylation of 2-napthol with isatin have been used for the 1,3-dipolar cycloaddition with alkyl azides [25], however, the reaction with *N*-alkyne and *N*-alkynyl ether derivatives of MBH adducts of isatin are unknown. Thus, herein, we report an efficient, safe, and one-pot synthesis of 1,4-disubstituted-1,2,3-triazole derivatives of oxindoles from the 1,3-dipolar cycloaddition reaction of *N*-propargyl MBH adduct of isatin with *in situ* generated alkyl azide and copper iodide as catalyst in 1:1 mixture of *t*-BuOH and water as a solvent. The reaction condition was fully compatible and environmentally benign. A detailed study

Scheme 1



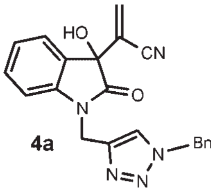
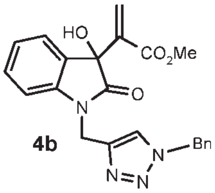
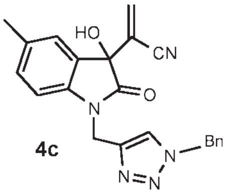
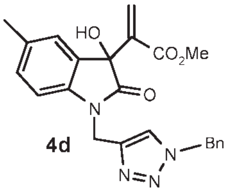
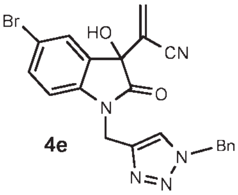
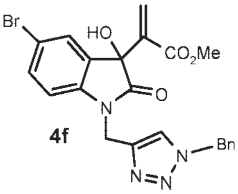
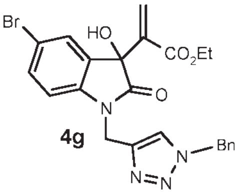
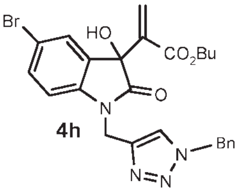
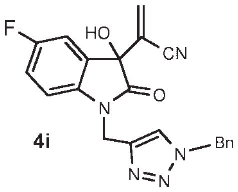
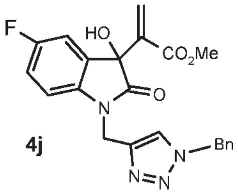
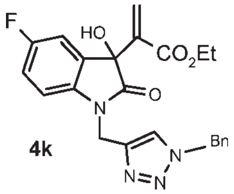
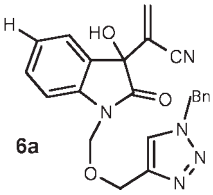
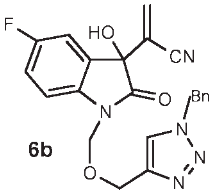
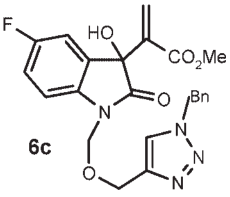
on the 1,3-dipolar cycloaddition reaction of *N*-terminal alkynes **3** and **5** with alkyl azides to afford highly functionalized triazole derivatives is the subject matter of this article (Scheme 1).

RESULTS AND DISCUSSION

The starting material *N*-terminal alkynes of isatin were prepared from the alkylation reaction of isatin with propargyl bromide and CaH_2 as a base in DMF at 60°C for 1 hr. Further, the corresponding MBH adducts were prepared following reported procedure [26]. The other substrate namely, *N*-propargyl ether derivative of MBH adduct was prepared from the *N*-methylated MBH adduct of isatin with propargyl alcohol and cerium ammonium nitrate (CAN) in acetonitrile at room temperature [11].

Initially, we carried out a reaction of alkyne **3** with 1.2 equivalents of sodium azide, 2.6 equivalents of triethylamine, and 2.2 equivalents of benzyl bromide in the presence of 2.5 mol % CuI in PEG-400. The reaction did not proceed and attempts to carry out the reaction with other solvent such as H_2O also did not yield fruitful results. However, the use of a mixture of $^tBuOH:H_2O$ (1:1 v/v) as solvent drove the reaction to form the desired 1,4-disubstituted 1,2,3-bistriazole product in excellent yield (Scheme 1, Table 1, entry 1). The click chemistry reaction, under mild conditions, constituted the Cu(I) catalyzed alkyne–azide [3+2]-cycloaddition furnished pharmaceutically important 1,4-disubstituted 1,2,3-triazole indolones in excellent yields (Scheme 1, Table 1). This investigation offers a mild and efficient method for the preparation of 1,2,3-triazoles using CuI as catalyst for the 1,3-dipolar cycloaddition of terminal alkynes with alkyl azides. The copper(I) readily inserts into terminal alkynes in the presence of a base, which proceeds *via* the intriguing six-membered ring [22,27]. The triazole was formed in a regioselective manner, with no contamination of 1,5-regioisomer. To demonstrate the methodology applicable to a variety of substrates having bromo, fluorine, and alkyl substitutions, synthesis of several triazole derivatives of oxindoles have been achieved and the results are collected in Table 1. The structure of 1,4-disubstituted 1,2,3-triazoles obtained is in good agreement with those described in the previous reports on the synthesis of substituted triazoles *via* three component coupling reaction [28]. The results revealed that the reaction was dependent on the nature of substituents on the isatin as evident from the comparison of the yields of products (**4a–k** and **6a–c**) due to electronic effects. The yields of the products decreased when electron donating groups were present on the isatin (entries 3 and 4). The yield of the products increased when electron-withdrawing groups were present on the isatin (entries 5, 6, 9, and 10). The substitution in ester group from Me → Et → Bu (entries 6, 7, 8, 10, and 11) afforded decreased yields.

Table 1
Synthesis of 1,2,3-triazole derivatives of oxindole.

Entry	Substrate (R^2)	Product	Yield (%)[a]
1	H	 4a	80
2	H	 4b	82
3	Me	 4c	73
4	Me	 4d	71
5	Br	 4e	82
6	Br	 4f	84
7	Br	 4g	78
8	Br	 4h	75
9	F	 4i	86
10	F	 4j	88
11	F	 4k	77
12	H	 6a	79
13	F	 6b	82
14	F	 6c	80

[a] Isolated yield.

All the new compounds were characterized thoroughly by spectroscopic methods (IR, ^{1}H, ^{13}C NMR, and ESI-mass spectra).

It is noteworthy that these reactions were efficiently performed in a neutral aqueous solution (water:^{t}BuOH) at an ambient temperature (RT). Molar equivalents of the halide, sodium azide, and alkyne were used in the mild 1,3-dipolar cycloaddition reaction. The method avoid the problems associated during the isolation of organic azides, and complements the reported method for the preparation of 1,2,3-triazoles. The operational simplicity of this method makes it attractive for preparative applications as well as a library compounds for drug discovery.

In conclusion, we have demonstrated an efficient synthetic procedure for the synthesis of highly functionalized 1,2,3-triazole derivatives of 2-indolones *via* a copper(I) catalyzed 1,3-dipolar cycloaddition of *N*-terminal alkyne derivative of MBH adduct of isatin with *in situ* generated alkyl azides. Further studies on this reagent system are in progress.

EXPERIMENTAL

General. IR measurements were done as KBr pellets for solids using PerkinElmer Spectrum RXI FTIR. The ^{1}H and ^{13}C NMR spectra were recorded in CDCl$_3$ with, Bruker 500 MHz and Bruker 300.1 MHz high resolution NMR spectrometer. CDCl$_3$ was used as the solvent for the NMR spectral measurements and spectra were recorded in ppm with TMS as internal standard. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), multiplet (m), and broad (br). The mass were analyzed by using a Electrospray Ionization method with Thermo Finnigan Mass spectrometer. Melting points were determined in capillary tubes and are uncorrected. Analytical TLC was performed on precoated plastic sheets of silica gel G/UV-254 of 0.2-mm thickness (Macherey-Nagel, Germany).

Typical experimental procedure (4b). A mixture of *N*-propargyl derivative of MBH adduct (100 mg, 0.35 mmol), sodium azide (27 mg, 0.42 mmol), benzyl bromide (66 mg, 0.38 mmol), triethylamine (92 mg, 0.91 mmol), and CuI (2.5 mol %) in 3 mL of *t*-butanol:water (1:1) was stirred at room temperature for 6 h. After completion of the reaction (monitored by TLC), the catalyst was filtered off through a pad of celite® and the product was extracted with ether (2 × 20 mL). The combined organic layer was dried (anhyd. Na$_2$SO$_4$), filtered, and removed under vacuum. The crude product was purified by silica gel column chromatography using hexane–ethyl acetate (7:3) solvent mixture to afford pure triazole derivatives.

2-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-3-hydroxy-2-oxoindolin-3-yl)acrylonitrile (4a). White solid: R_f (60% EA/hexane) 0.25; IR (KBr): 3378, 1612, 1487, 1332, 1177 cm^{-1}; ^{1}H NMR (CDCl$_3$/TMS, 300.1 MHz): δ 2.39 (brs, 1H), 4.86 (d, J = 15.8 Hz, 1H), 5.10 (d, J = 15.9 Hz, 1H), 5.38 (AB quartet, J = 14.2 Hz, 2H), 6.13 (s, 1H), 6.39 (s, 1H), 6.74–7.13 (m, 4H), 7.26–7.31 (m, 5H), 7.54 (s, 1H). ^{13}C NMR (CDCl$_3$/TMS, 75.3 MHz): 34.9, 52.5, 54.2, 76.2, 108.9, 112.1, 114.3, 122.7, 122.3, 122.6, 124.4, 128.0, 128.2, 128.9, 129.0, 131.0, 141.2, 164.3, 176.1. MS (EI) m/z 372 (M$^+$).

Methyl 2-(1-((1-benzyl-1H-1,2,3-triazol-4-y2l)methyl)-3-hydroxy-2-oxoindolin-3-yl) acrylate (4b). White solid: R_f (60% EA/hexane) 0.25; IR (KBr): 3383, 1718, 1612, 1490, 1327, 1171 cm^{-1}; ^{1}H NMR (CDCl$_3$/TMS, 300.1 MHz): δ 3.32 (brs, 1H), 3.49 (s, 3H), 4.92 (d, J = 15.8 Hz, 1H), 5.17 (d, J = 15.8 Hz, 1H), 5.45 (AB quartet, J = 13.7 Hz, 2H), 6.46 (s, 1H), 6.57 (s, 1H), 6.97–7.32 (m, 9H), 7.36 (s, 1H); ^{13}C NMR (CDCl$_3$/TMS, 75.3 MHz): 36.0, 51.8, 54.2, 76.0, 109.8, 122.9, 123.1, 123.7, 128.0, 128.1, 128.7, 129.0, 129.4, 130.2, 134.4, 139.0, 142.9, 143.1, 164.9, 176.0. MS (EI) m/z 405 (M$^+$).

2-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-3-ydroxy-5-methyl-2-oxoindolin-3-yl)acrylonitrile (4c). White solid: R_f (60% EtOAc/hexane) 0.34; IR (KBr): 3371, 2221, 1719, 1608, 1483, 1330, 1169 cm^{-1}; ^{1}H NMR (CDCl$_3$/TMS, 300.1 MHz): δ 2.30 (s, 1H), 4.37 (brs, 1H), 4.88 (d, J = 15.7 Hz, 1H), 5.06 (d, J = 15.7 Hz, 1H), 5.40 (AB quartet, J = 13.8 Hz, 2H), 6.16 (s, 1H), 6.40 (s, 1H), 6.90 (d, J = 7.9 Hz, 1H), 7.13–7.19 (m, 4H), 7.29–7.34 (m, 3H), 7.51 (s, 1H); ^{13}C NMR (CDCl$_3$/TMS, 75.3 MHz): 20.9, 33.0, 36.0, 54.2, 54.8, 76.5, 105.3, 110.1, 117.9, 122.6, 122.8, 125.2, 127.0, 128.0, 128.7, 129.0, 131.2, 131.3, 139.5, 142.9, 176.0. MS (EI) m/z 386 (M$^+$).

Methyl 2-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-3-hydroxy-5-methyl-2-oxoindolin-3-yl)acrylate (4d). White solid: R_f (60% EA/hexane) 0.25; IR (KBr): 3387, 1721, 1612, 1492, 1322, 1168 cm^{-1}; ^{1}H NMR (CDCl$_3$/TMS, 300.1 MHz): δ 2.03 (brs, 1H), 2.62 (s, 3H), 3.48 (s, 3H), 5.01 (AB quartet, J = 12.4 Hz, 2H), 5.38 (d, J = 14.8 Hz, 1H), 5.45 (d, J = 14.8 Hz, 1H), 6.49 (s, 1H), 6.56 (s, 1H), 6.82 (d, J = 7.8 Hz, 1H), 6.95–7.11 (m, 3H), 7.24–7.31 (m, 4H), 7.64 (s, 1H). ^{13}C NMR (CDCl$_3$/TMS, 125 MHz): 20.9, 36.0, 51.8, 54.2, 75.8, 109.5, 122.8, 124.4, 127.8, 127.9, 128.0, 128.3, 128.6, 129.01, 129.2, 130.4, 132.7, 134.4, 138.9, 140.6, 143.0, 164.9, 176.6. MS (EI) m/z 419 (M$^+$).

2-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-5-bromo-3-hydroxy-2-oxoindolin-3-yl)acrylonitrile (4e). White solid: R_f (60% EA/hexane) 0.25; IR (KBr): 3381, 1614, 1495, 1323, 1166 cm^{-1}; ^{1}H NMR (CDCl$_3$/TMS, 300.1 MHz): δ 2.00 (brs, 1H), 4.90 (d, J = 15.8 Hz, 1H), 4.99 (d, J = 15.7 Hz, 1H), 5.41 (AB quartet, J = 14.3 Hz, 2H), 6.20 (s, 1H), 6.44 (s, 1H), 6.91 (d, J = 8.8 Hz, 1H), 7.07–7.14 (m, 2H), 7.30–7.35 (m, 3H), 7.42–7.44 (m, 2H), 7.50 (s, 1H); ^{13}C NMR (CDCl$_3$/TMS, 75.3 MHz): 35.3, 52.1, 54.2, 76.1, 112.0, 122.1, 122.6, 126.2, 126.9, 128.0, 128.7, 128.6, 128.9, 130.2, 132.7, 133.9, 138.4, 142.2, 142.7, 175.4. MS (EI) m/z 450 (M$^+$), 452 (M + 2).

Methyl 2-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-5-bromo-3-hydroxy-2-oxoindolin-3-yl) acrylate (4f). White solid: R_f (60% EtOAc/hexane) 0.30; IR (KBr): 3371, 2221, 1719, 1608, 1483, 1330, 1169 cm^{-1}; ^{1}H NMR (CDCl$_3$/TMS, 300.1 MHz): δ 2.03 (s, 1H), 3.51 (s, 1H), 4.85 (d, J = 15.8 Hz, 1H), 5.09 (d, J = 15.9 Hz, 1H), 5.41 (AB quartet, J = 12.5 Hz, 2H), 6.51 (s, 1H), 6.58 (s, 1H), 6.82 (d, J = 8.2 Hz, 1H), 7.26–7.43 (m, 7H), 7.61 (s, 1H); ^{13}C NMR (CDCl$_3$/TMS, 75.3 MHz): 35.8, 51.8, 54.2, 76.5, 111.3, 122.1, 122.8, 126.8, 126.9, 128.0, 128.4, 128.6, 128.9, 129.1, 132.7, 134.2, 138.4, 142.0, 142.4, 165.4, 175.4. MS (EI) m/z 483 (M$^+$), 485 (M + 2).

Ethyl 2-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-5-bromo-3-hydroxy-2-oxoindolin-3-yl)acrylate (4g). White solid: R_f (60% EA/hexane) 0.25; IR (KBr): 3369, 1724, 1617, 1484, 1318, 1183 cm^{-1}; ^{1}H NMR (CDCl$_3$/TMS, 300.1 MHz): δ 1.09

(t, $J = 3.24$ Hz, 3H), 2.03 (brs, 1H,), 3.95 (q, $J = 4.5$, 11.8 Hz, 2H), 4.92 (d, $J = 15.8$ Hz, 1H), 5.09 (d, $J = 15.9$ Hz, 1H), 5.45 (AB quartet, $J = 11.9$ Hz, 2H), 6.48 (s, 1H), 6.60 (s, 1H), 6.79–7.01 (m, 3H), 7.26–7.38 (m, 5H), 7.60 (s, 1H). MS (EI) *m/z* 266 (M^{+});^{13}C NMR ($CDCl_3$/TMS, 125 MHz): 13.8, 14.1, 22.6, 22.9, 29.6, 34.6, 52.7, 54.3, 61.1, 75.7, 111.4, 115.7, 122.8, 125.0, 127.0, 128.1, 128.2, 128.7, 129.0, 135.2, 138.4, 142.0, 164.3, 175.4. MS (EI) *m/z* 497 (M^{+}), 499 (M + 2).

Butyl 2-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-5-bromo-3-hydroxy-2-oxoindolin-3-yl)acrylate (4h). White solid: R_f (60% EA/hexane) 0.25; IR (KBr): 3383, 1718, 1612, 1490, 1327, 1171 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 0.88 (t, $J = 7.2$ Hz, 3H), 1.19–1.29 (m, 4H), 3.89 (t, $J = 6.9$ Hz, 2H), 4.08 (brs, 1H), 4.91 (d, $J = 15.6$ Hz, 1H), 5.08 (d, $J = 15.9$ Hz, 1H), 5.44 (AB quartet, $J = 12.1$ Hz, 2H), 6.47 (s, 1H), 6.61 (s, 1H), 6.84 (d, 1H, $J = 8.1$ Hz), 7.24–7.38 (m, 7H), 7.61 (s, 1H). MS (EI) *m/z* 266 (M^{+});^{13}C NMR ($CDCl_3$/TMS, 125 MHz): 13.6, 18.9, 19.0, 29.6, 30.2, 36.0, 43.3, 54.3, 64.9, 75.7, 111.4, 115.7, 122.8, 127.0, 128.1, 128.2, 128.6, 128.7 (C), 129.0, 129.3, 132.6, 134.3, 138.4, 142.0, 164.4, 175.5. MS (EI) *m/z* 525 (M^{+}), 527 (M + 2).

2-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-5-fluoro 3-hydroxy-2-oxoindolin-3-yl)acrylonitrile (4i). White solid: R_f (60% EtOAc/hexane) 0.32; IR (KBr): 3386, 2243, 1726, 1619, 1490, 1343, 1171 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.02 (brs, 1H), 4.89 (d, $J = 15.8$ Hz, 1H), 4.99 (d, $J = 15.8$ Hz, 1H), 5.40 (d AB quartet, $J = 13.3$ Hz, 2H), 6.17 (s, 1H), 6.43 (s, 1H), 6.96–7.09 (m, 3H), 7.22 (d, $J = 3.3$ Hz, 1H), 7.26–7.34 (m, 4H), 7.51 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): 35.8, 52.0, 54.2, 76.5, 109.2, 112.4, 115.5, 122.1 122.7, 123.5, 128.0, 128.7, 129.0, 131.9, 134.0, 140.1, 141.8, 142.5, 143.3, 173.8. MS (EI) *m/z* 390 (M^{+}).

Methyl 2-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-5-fluoro-3-hydroxy-2-oxoindolin-3-yl)acrylate (4j). White solid: R_f (60% EtOAc/hexane) 0.28; IR (KBr): 3362, 2217, 1722, 1612, 1490, 1334 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.50 (s, 3H), 4.65 (brs, 1H), 4.86 (d, $J = 15.9$ Hz, 1H), 5.08 (d, $J = 15.9$ Hz, 1H), 5.41 (AB quartet, $J = 10.0$ Hz, 2H), 6.46 (s, 1H), 6.51 (s, 1H), 6.83–6.95 (m,3H), 7.21 (d, $J = 3.0$ Hz, 1H), 7.26–7.39 (m, 3H), 7.62 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): 35.9, 51.8, 54.2, 75.9, 110.1, 122.8, 128.0, 128.3, 128.6, 128.9, 129.2, 129.7, 130.0, 134.3, 138.5, 139.0, 142.5, 143.2, 164.7, 175.7. MS (EI) *m/z* 423 (M^{+}).

Ethyl 2-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-5-fluoro-3-hydroxy-2-oxoindolin-3-yl)acrylate (4k). White solid: R_f (60% EA/hexane) 0.31; IR (KBr): 3371, 1718, 1630, 1469, 1318, 1183 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.07 (t, 3H, $J = 7.1$ Hz), 2.48 (brs, 1H), 3.92 (q, $J = 4.3$, 11.2 Hz, 2H), 4.85(d, $J = 15.9$ Hz, 1H), 5.04 (d, $J = 15.9$ Hz, 1H), 5.39 (AB quartet, $J = 9.3$ Hz, 2H), 6.44 (s, 1H), 6.50 (s, 1H), 6.82–6.92 (m, 5H), 7.28–7.34 (m, 3H), 7.64 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): 14.2, 22.4, 33.8, 51.8, 53.9, 62.0, 75.5, 96.0, 99.2, 109.6, 113.8, 113.9, 115.4, 122.4, 128.3, 128.6, 128.8, 129.0, 129.4, 134.2, 138.4, 142.0, 164.1, 172.0. MS (EI) *m/z* 437 (M^{+}).

2-(1-(((1-benzyl-1H-1,2,3-triazol-4-l)methoxy)methyl)-3-hydroxy-2-oxoindolin-3-yl) acrylonitrile (6a). White solid: R_f (60% EA/hexane) 0.29; IR (KBr): 3377, 1615, 1473, 1117 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.43 (s, 1H, brs), 3.51 (s, 3H), 3.94–5.49 (m, 6H), 6.45 (s, 1H), 6.49 (s, 1H), 6.35–6.98 (m, 9H), 7.38 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): 30.1, 52.3, 53.9, 68.1, 74.2, 112.2, 114.9, 116.3, 125.9, 127.6, 128.1, 128.5, 129.4, 133.0, 135.5, 138.3, 138.6, 164.7, 177.1. MS (EI) *m/z* 402 (M^{+}).

2-(1-(((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy) methyl)-5-fluoro-3-hydroxy-2-oxoindolin-3-yl)acrylonitrile (6b). White solid: R_f (60% EA/hexane) 0.29; IR (KBr): 3382, 1621, 1486, 1112 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 4.63 (d, $J = 13.2$ Hz, 1H), 4.72 (d, $J = 13.1$ Hz, 1H), 5.06 (d, $J = 11.4$ Hz, 1H), 5.36 (AB quartet, $J = 9.8$ Hz, 2H), 5.53 (d, $J = 11.4$ Hz, 1H), 5.84 (brs, 1H), 6.25 (s, 1H), 6.58 (s, 1H), 6.78–6.81 (m, 4H), 7.00–7.12 (m, 4H), 7.35 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): 35.7, 53.2, 53.9, 69.7, 76.1, 111.5, 113.4, 115.8, 116.1, 123.3, 128.6, 128.1, 128.7, 128.9, 132.4, 134.7, 137.9, 138.3, 144.0, 164.4, 175.6. MS (EI) *m/z* 420 (M^{+}).

Methyl2-(1-(((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy) methyl)-5-fluoro-3-hydroxy-2-oxoindolin-3-yl) acrylate (6c). White solid: R_f (60% EA/hexane) 0.29; IR (KBr): 3386, 1722, 1617, 1483, 1110 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.50 (s, 3H), 4.60 (d, $J = 12.6$ Hz, 1H), 4.68 (d, $J = 12.8$ Hz, 1H), 5.11 (d, $J = 11.2$ Hz, 1H), 5.29 (d, $J = 11.3$ Hz, 1H), 5.40–5.51 (m, 2H), 5.71 (s, 1H, br), 6.61 (s, 1H), 6.83 (s, 1H), 6.83–6.93 (m, 3H), 7.30–7.36 (m, 3H), 7.14–7.17 (s, 2H), 7.42 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): 14.8, 35.9, 51.8, 53.9, 69.7, 75.8, 110.5, 111.7, 115.8, 116.1, 123.3, 127.9, 128.4, 128.6, 128.9, 131.4, 134.2, 138.1, 138.3, 144.0, 164.8, 176.9. MS (EI) *m/z* 453 (M^{+}).

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Near-Infrared Bis(indolium heptamethine cyanine) Dyes with a Spacer Derived from Oligo(ethylene glycol)

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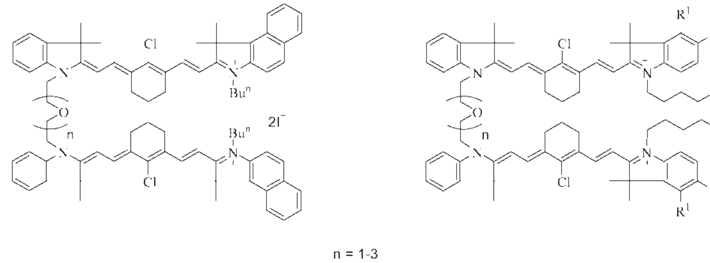

n = 1-3
$R^1 = R^2 = H$
$R^1R^2 = (CH{=}CH)_2$

Synthesis of a series of near-infrared dimeric dyes is presented. The intramolecular dimers contain two chromophores linked with a conformationally flexible ether or oligoether bridge. Optical properties of the dyes are discussed.

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INTRODUCTION

Currently, there is substantial interest in dimeric dyes in which two chromophoric subunits are linked by a conformationally flexible chain. Under low concentration conditions in aqueous solution, these bichromophoric molecules tend to exist in an intramolecular clam-shell conformation with the two chromophores in close proximity to each other. The intermolecular aggregation of such intramolecular foldamers becomes important with the increase in concentration. Normally, these are H-type stacking interactions characterized by hypsochromic absorption and low fluorescence quantum yield as compared to the characteristics of non-interacting dye molecules. In general, the stacking interactions are less important in solvents of low polarity. Several dimeric dyes have been designed as non-covalent labels for the detection of nucleic acids [2,3] and proteins [4–7]. More specifically, upon binding with a biopolymer, the intramolecular complex of a dimeric cyanine undergoes dissociation and the clam-shell of the inner complex opens up. Binding of the open form of the dimeric dye usually results in a batochromic shift in absorption and a greatly increased quantum yield of fluorescence. Several bichromophoric squaraines have been developed as cation-specific chemosensors [8–11]. These dimeric dyes bind metal cations and the resulting complexes show different spectral properties in comparison to non-complexed dyes. Finally, several bichromophoric cyanine dyes have been used as agents for latent fingerprint detection [5,12]. These dimeric dyes exhibit strongly enhanced fluorescence upon interaction with the hydrophobic fats of fingerprints that results in a clear fluorescence image of the fingerprint.

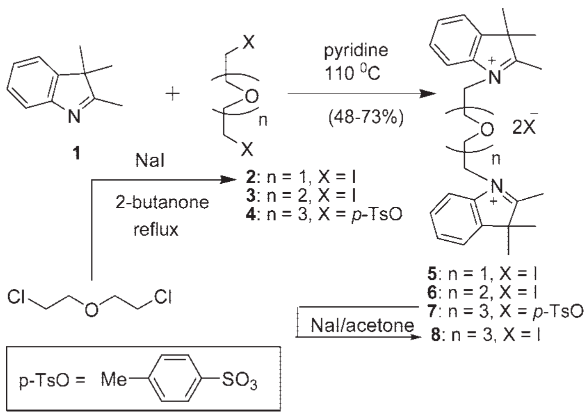
Synthesis of dimeric dyes **14–16** and **21–26** with an ether or oligoether linker in the molecule is described in this report. The molecules were designed as improved non-covalent labels for nucleic acids and proteins. The presence of oxygen atom(s) in the bridge linking the two dye moieties results in an increased solubility of the bifunctional molecules in water and aqueous buffers in comparison to the more hydrophobic analogs containing a polymethylene linker. The dimeric dyes **21–26** are additionally substituted with hydrophilic sulfonatobutyl groups. These dyes are bifunctional heptamethine cyanines that absorb and fluoresce in the near-infrared region (>700 nm). Few biomolecules absorb and fluoresce within the near-infrared region, and as a result Raman and Rayleigh light scattering are greatly reduced in this region. Consequently, improved signal-to-noise ratios are typically observed in the near-infrared region. In addition, typical impurities need not be considered because such species are not detected at wavelengths longer than 700 nm. All bis-dyes contain indolium moieties as end-heterocyclic subunits because such derivatives are relatively stable in solution [13].

RESULTS AND DISCUSSION

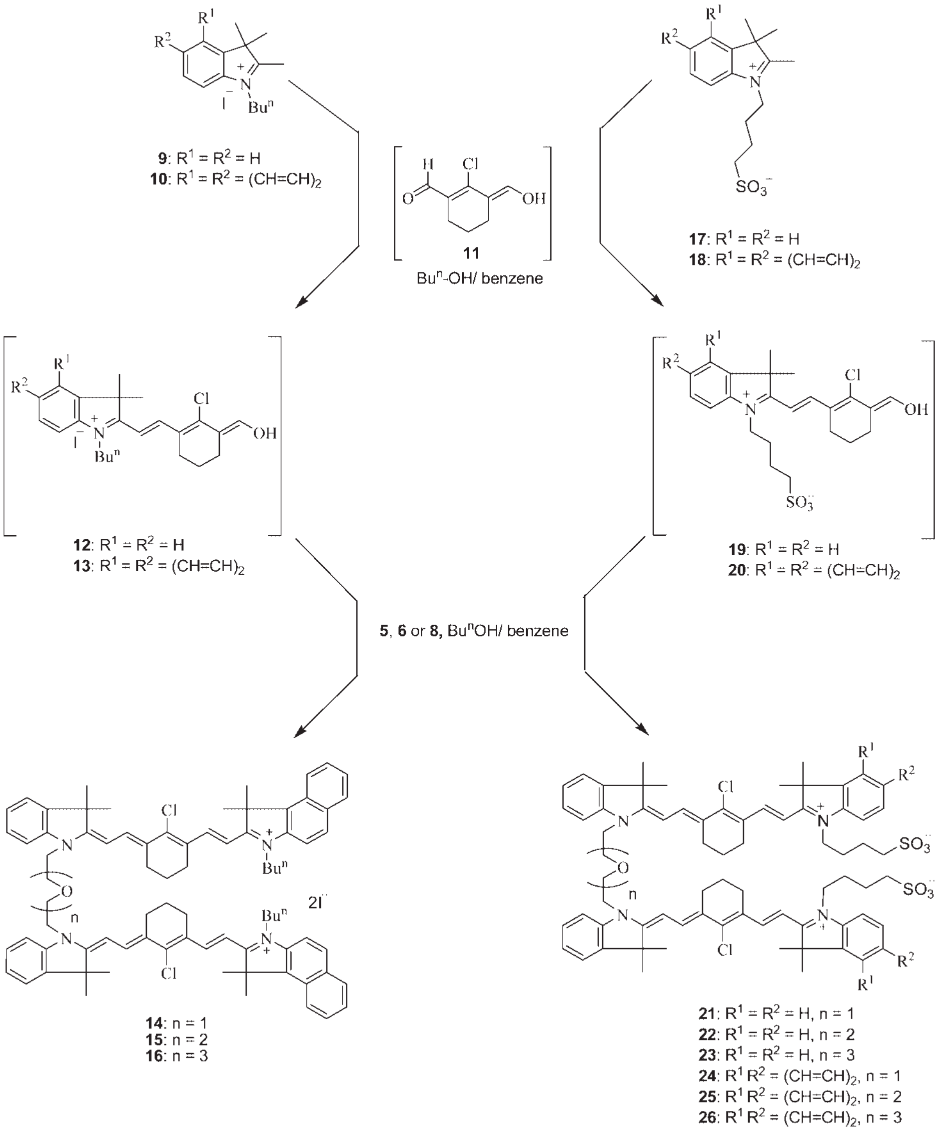
The key intermediate products are bis-indolium salts **5**–**7** (Scheme 1).

These compounds were obtained by quaternization of indolenine **1** with α,ω-diiodo-substituted ethers **2**, **3** or α,ω-bis-tosylate derivative **4**. In the latter case, the resultant bis-tosylate salt **7** was transformed into a more reactive diodide salt **8** by treatment with sodium iodide in acetone. The application of the intermediate dimeric salts **5**, **6**, and **8** in the synthesis of dimeric near-infrared cyanines **14**–**16** and **21**–**26** is shown in Scheme 2. The successful strategy for the synthesis of *N*-butyl derivatives **14**–**16** involved quaternization of 2,3,3-trimethylindole-nine and 2,3,3-trimethylbenzo[*e*]indolenine with *n*-butyl iodide followed by condensation of the

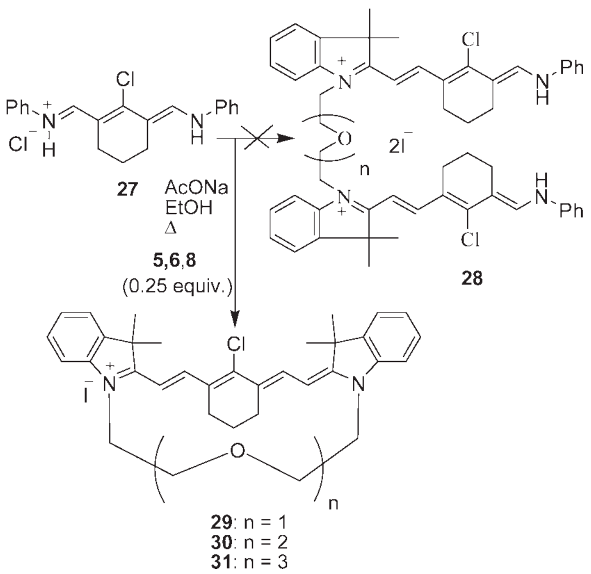
Scheme 1



Scheme 2



Scheme 3



resultant indolium salts **9** and **10** with a dialdehyde **11**. The condensation reaction was conducted in a mixture of *n*-butanol and benzene with azeotropic removal of water.

Under these conditions, the formation of mono-condensation products **12** or **13** is strongly favored [14]. Crude products **12** and **13**, without purification, were then allowed to react with dimeric salts **5**, **6,** and **8** to furnish the corresponding final dyes **14–16**. In a similar way, quaternization of 2,3,3-indolenine or its benzo counterpart with 1,4-butanesultone yielded the respective 4-sulfonatobutyl inner salts **17** and **18** that were subsequently used for mono-condensation with dialdehyde **11**. The resultant products **19** and **20** were subjected to condensation with dimeric indolium salts **5**, **6,** and **8** to furnish the desired corresponding dimeric cyanines **21–26**.

A bis-anilinium derivative of the bis-aldehyde **11** [15] (**27**, structure in Scheme 3) is normally used in the synthesis of cyanine dyes by the reaction with methyl-substituted cationic heterocycles. The anilinium derivative **27** is more stable than the parent compound **11** and is easily purified by crystallization. The initial synthesis plan called for condensation of excess **27** with a dimeric salt **5**, **6,** or **8** followed by condensation of the expected product **28** with the indolium salt **9** or analogs. This approach failed because compound **28** ($n = 1–3$) was not formed. A detailed separation analysis showed the presence of the corresponding cyanine dye **29–31** in which the terminal indolium subunits are bridged by an ether moiety. By contrast, the half-dyes **12**, **13** and **19**, **20** were the major products of the reactions conducted with bis-aldehyde **11**. The procedure is simple in that crude bis-aldehyde **11** and crude half-dyes **12**, **13**, **19,** and **20** can be used for the condensation reaction. The final dimeric dyes, however, must be purified by chromatography. The final yields of these highly polar products are quite low, even for the optimized procedures described in the experimental section. Nevertheless, the described preparations are inexpensive and highly reproducible, and the final dyes are analytically pure, as judged by the results of the elemental, thin-layer-chromatographic, and spectral analyses.

The near-infrared spectra of dyes **14–16** and **21–26** are listed in Table 1. As can be seen, for the spectra of **14–16** taken in methanol, the maximum absorption wavelengths decrease in the order **14** > **15** > **16**, and these decreases parallel the increases in the length of the linker joining two terminal dye subunits in these dimeric compounds. A similar pattern is observed in the spectra of the individual series of NIR dyes **21–23**, and **24–26**. The differences between the shortest and the longest absorption wavelengths are remarkably similar (about 20 ± 1 nm) for each individual series of dyes. These large differences cannot be due to an electronic effect of the linker on the absorption because the corresponding monomeric dyes that are N-substituted with ethyl, butyl, or 2-hydroxyethyl groups all show similar absorption within 1 nm in methanol [7,16]. It can be suggested that the spectral differences reflect different foldamers in which two dye subunits are in close proximity to each other. More specifically, it appears that the length of the linker dictates the stereochemistry of the foldamer.

It was of interest to compare spectral properties of the ether-linked NIR dyes with those of their oligomethylene-linked analogs, a limited number of which have been published by us previously [5–7]. A striking difference is the lack of correlation between the maximum absorption wavelength and the length of the polymethylene chain. Thus, the analogs of **21–23** containing 4, 6, 8, and 10 methylene (CH_2) units show absorption in methanol at 783 nm, 787 nm, 780 nm, and 787 nm, respectively. Yagi *et al.* [9] and Liang *et al.* [17] have synthesized a series of bichromophoric squarains containing intramolecular polymethylene chains of various length and reported their spectra. It escaped their attention, however, that, as in our analysis, there is no correlation between the length of a polymethylene linker and absorption wavelengths of the bichromophoric squaraines. The spectral differences between bichromophoric molecules containing polymethylene and ether chains can be explained in terms of their different conformational flexibility with the latter linkers showing more conformational freedom. This conclusion is strongly supported by conformational analysis of polyethylene $(CH_2CH_2)_n$, polyoxyethylene $(OCH_2CH_2)_n$, and related low molecular-weight molecules [18].

Table 1

Vis-NIR spectra of dyes **14–16**, and **21–26** taken in methanol.

Linker, No (C + O)	Dye	λ_{max}	Dye	λ_{max}	Dye	λ_{max}
5	**14**	817	**21**	794	**24**	818
8	**15**	799	**22**	776	**25**	802
11	**16**	797	**23**	775	**26**	797

We conducted conformational studies of dimeric dyes **14–16**. The conformations were computer-simulated in an aqueous environment and *in vacuo*, resembling conditions in solvents of high and low polarity, respectively. The technical aspects of the calculations are given in the experimental section. A general result is that there are a number of computed low-energy structures in an aqueous environment that contain the two cyanine subunits in close proximity to each other, strongly suggesting attractive hydrophobic interactions between these two subunits (not shown). By contrast, low-energy conformations of **14–16** in the absence of water contain an unfolded ether bridge and the two cyanine subunits away from each other. When the closed-shell conformations, as obtained from computing the structures in an aqueous environment, were taken as the starting structures for computation in the absence of water, all conformations opened-up, losing the presumed intramolecular interactions. The computed energy differences between the more stable solvated structures and the conformations in the absence of water are in the range of 70–100 kcal/mol. Compound **16** was selected for a detailed analysis. The molecular modeling work generated a number of water-induced conformations of **16** in which the two cyanine subunits are in close proximity to each other. Some of these structures are consistent with partial stacking of the planar portions of the dyes, suggesting a π–π interaction. Other computer-generated low-energy conformations of **16** in aqueous environment are consistent with hydrophobic interactions, but not stacking, between the cyanine chromophores. We have also conducted similar calculations for the analog of **16** in which the ether linkage is replaced by an eleven-methylene bridge. Despite the similar lengths of the two linkages, the number of low-energy conformations is larger for **16** than for its polymethylene analog. These computational results are consistent with the greater conformational flexibility of **16** in comparison to its analog containing an all-carbon bridge, as discussed earlier.

We have conducted preliminary binding studies of **14–16** and **21–26** with human serum albumin (HSA) and calf thymus DNA. All compounds bind with the protein, albeit the absorption and fluorescence differences between the compounds in the absence and presence of HSA are highly structure dependent. On the other hand, only the cationic molecules **14–16** bind with DNA as evidenced by the observed spectral changes. Molecules **21–26** that contain a zero net charge do not interact with anionic DNA. Complete biophysical studies will be reported in due course.

EXPERIMENTAL

General. Where applicable, products were purified on a chromatotron with silica gel-coated rotors. Melting points are greater than 300°C in all cases. All ^{1}H NMR spectra were taken at 400 MHz. Near-infrared (NIR) spectra were taken in methanol or dichloromethane for solutions with absorptivities <1.0. The intermolecular aggregation of cyanine dyes is negligible under such conditions.

Dimeric indolium salts 5, 6, 8. Bis(2-iodoethyl) ether (**2**) was prepared by refluxing bis(2-chloroethyl) ether with sodium iodide in 2-butanone for 24 h as reported previously [19]. A mixture of 2,3,3-trimethylindolenine (**1**, 0.48 g, 3 mmol), a diiodo derivative **2** or **3** (1.5 mmol), and pyridine (one drop) was heated to 110°C for 4 days to give the respective bis-salt **5** or **6**. In a similar way, product **7** was obtained by treatment of **1** with a bis-tosylate derivative **4**. Crude bis-tosylate salt **7** in acetone (10 mL) was treated with a saturated solution of sodium iodide (0.30 g, 2 mmol) in methanol, and the mixture was heated under reflux for 2 h. Cooling of the mixture to 0°C for several hours caused precipitation of sodium *p*-tosylate, leaving bis-indolium diiodide **8** in solution. The diiodides **5**, **6**, and **8** were purified by silica gel chromatography eluting with methanol/ethyl acetate (1:3).

***N,N′*-(3-Oxopentane-1,5-diyl)-bis(2,3,3-trimethyl-3*H*-indolium) diiodide 5.** This compound was obtained in a 63% yield; ^{1}H NMR (DMSO-d_6): $\delta = 1.26$ (s, 12H), 3.18 (s, 6H), 4.35 (t, $J = 5$Hz, 4H), 5.02 (t, $J = 5$Hz, 4H), 7.41 (m, 8H). Anal. Calcd for $C_{26}H_{34}I_2N_2O_2$: C, 48.46; H, 5.32; N, 4.35. Found: C, 48.28; H, 4.98; N, 4.29.

***N,N′*-(3,6-Dioxaoctane-1,8-diyl)-bis(2,3,3-trimethyl-3*H*-indolium) diiodide 6.** This compound was obtained in a 58% yield; ^{1}H NMR (DMSO-d_6): $\delta = 1.49$ (s, 12H), 2.76 (s, 6H), 3.66 (t, $J = 5$Hz, 4H), 3.79 (t, $J = 5$Hz, 4H), 4.67 (t, $J = 5$Hz, 4H), 7.61 (m, 4H), 7.85 (d, $J = 8$Hz, 2H), 7.92 (d, $J = 8$Hz, 2H). HR-MS (ESI). Calcd for $(C_{28}H_{38}N_2O_2)^{2+}$: $m/z = 217.1464$. Found: $m/z = 217.1456$. Anal Calcd for $C_{28}H_{38}I_2N_2O_2$: C, 48.84; H, 5.56; N, 4.07. Found: C, 48.95; H, 5.62; N, 4.03.

***N,N′*-(3,6,9-Trioxaundecane-1,11-diyl)-bis(2,3,3-trimethyl-3*H*-indolium) diiodide 8.** This compound was obtained in a 73% yield; ^{1}H NMR (DMSO-d_6): $\delta = 1.50$ (s, 12H), 2.35 (s, 6H), 3.25 (t, $J = 5$Hz, 4H), 3.34 (t, $J = 5$Hz, 4H), 3.83 (t, J

= 5Hz, 4H), 4.71 (t, J = 5Hz, 4H), 7.59 (m, 4H), 7.84 (d, J = 8Hz, 2H), 7.98 (d, J = 8Hz, 2H); ^{13}C NMR (DMSO-d_6): δ = 14.8, 21.9, 47.9, 54.2, 66.6, 69.4, 69.6, 115.6, 123.5, 128.8, 129.3, 140.8, 141.6, 189.1. HR-MS (ESI). Calcd for $(C_{30}H_{42}N_2O_3)^{2+}$: m/z = 239.1592. Found: m/z = 239.1592.

Near-infrared dyes 14–16 and 21–26. A mixture of bisaldehyde **11** [14] (173 mg, 1 mmol), a quaternary salt [5,19] **9**, **10**, **17**, or **18** (1 mmol), *n*-butanol (50 mL), and benzene (15 mL) was stirred at 23°C for 2 h. The resultant crude product **12**, **13**, **19**, or **20**, without isolation, was treated in the same flask with a dimeric salt **5**, **6**, or **8** (0.5 mmol) and the mixture was heated under reflux for an additional 12 h. The product was isolated by concentration of the mixture on a rotary evaporator followed by chromatography eluting with dichloromethane/methanol (10:1 for **14–16** and 9:1 for **21–26**).

3‴-Oxapentane-1‴,5‴-diyl[bis[2-[7′-(3″-butyl-1″,1″-dimethylbenzo[*e*]indolin-2″-ylidene)-4′-chloro-3′,5′-trimethylene-1′,3′,5′-heptatrien-1′-yl]-3,3-dimethyl-3*H*-indol-1-ium]] diiodide 14. This compound was obtained in a 17% yield; ^{1}H NMR (CDCl$_3$): δ = 1.02 (t, J = 6Hz, 6H), 1.54 (m, 4H), 1.68 (s, 12H), 1.90 (m, 4H), 1.94 (m, 4H), 2.02 (s, 12H), 2.74 (m, 8H), 4.05 (m, 4H), 4.36 (m, 8H), 6.20 (d, J = 11Hz, 2H), 6.32 (d, J = 11Hz, 2H), 7.09 (d, J = 6Hz, 2H), 7.18 (t, J = 6Hz, 2H), 7.26 (t, J = 6Hz, 2H), 7.34 (d, J = 6Hz, 2H), 7.44 (d, J = 6Hz, 2H), 7.48 (t, J = 6Hz, 2H), 7.63 (t, J = 6Hz, 2H), 7.96 (m, 4H), 8.13 (d, J = 6Hz, 2H), 8.28 (d, J = 11Hz, 2H), 8.48 (d, J = 11Hz, 2H); NIR: λ_{max} = 817 nm. Anal. Calcd for $C_{80}H_{90}Cl_2I_2N_4O\cdot 2H_2O$: C, 64.73; H, 6.38; N, 3.77. Found: C, 64.85; H, 6.22; N, 3.85.

3‴,6‴-Dioxaoctane-1‴,8‴-diyl[bis[2-[7′-(3″-butyl-1″,1″-dimethylbenzo[*e*]indolin-2″-ylidene)-4′-chloro-3′,5′-trimethylene-1′,3′,5′-heptatrien-1′-yl]-3,3-dimethyl-3*H*-indol-1-ium]] diiodide 15. This compound was obtained in a 26% yield; ^{1}H NMR (CDCl$_3$): δ = 1.02 (t, J = 7Hz, 6H), 1.54 (m, 4H), 1.73 (s, 12H), 1.90 (m, 4H), 1.97 (m, 4H), 2.01 (s, 12H), 2.76 (m, 8H), 3.56 (s, 4H), 3.92 (m, 4H), 4.32 (m, 4H), 4.41 (m, 4H), 6.29 (d, J = 14Hz, 2H), 6.34 (d, J = 14Hz, 2H), 7.24 (m, 4H), 7.40 (m, 6H), 7.49 (t, J = 6Hz, 2H), 7.62 (t, J = 6Hz, 2H), 7.94 (m, 4H), 8.13 (d, J = 8Hz, 2H), 8.32 (d, J = 14Hz, 2H), 8.45 (d, J = 14Hz, 2H); NIR: λ_{max} = 799 nm. Anal. Calcd for $C_{82}H_{94}Cl_2I_2N_4O_2\cdot 2H_2O$: C, 64.43; H, 6.46; N, 3.66. Found: C, 64.44; H, 6.48; N, 3.64.

3‴,6‴,9‴-Trioxaundecane-1‴,11‴-diyl[bis[2-[7′-(3″-butyl-1″,1″-dimethylbenzo[*e*]indolin-2″-ylidene)-4′-chloro-3′,5′-trimethylene-1′,3′,5′-heptatrien-1′-yl]-3,3-dimethyl-3*H*-indol-1-ium]] diiodide 16. This compound was obtained in a 12% yield; ^{1}H NMR (CDCl$_3$): δ = 1.02 (t, J = 6Hz, 6H), 1.53 (m, 4H), 1.72 (s, 12H), 1.94 (m, 8H), 2.02 (s, 12H), 2.77 (m, 4H), 3.56 (m, 12H), 3.96 (m, 4H), 4.38 (m, 8H), 6.28 (d, J = 14Hz, 2H), 6.33 (d, J = 14Hz, 2H), 7.22 (m, 4H), 7.35 (m, 4H), 7.48 (m, 4H), 7.63 (m, 2H), 7.95 (m, 4H), 8.13 (m, 2H), 8.31 (d, J = 14Hz, 2H), 8.47 (d, J = 14Hz, 2H); NIR: λ_{max} = 797 nm. Anal. Calcd for $C_{84}H_{98}Cl_2I_2N_4O_3\cdot 4H_2O$: C, 62.73; H, 6.64; N, 3.48. Found: C, 62.88; H, 6.42; N, 3.38.

3⁗-Oxapentane-1⁗,5⁗-diyl[bis[2-[7′-[1″-(4‴-sulfonatobutyl)-3″,3″-dimethylindolin-2″-ylidene]-4′-chloro-3′,5′-trimethylene-1′,3′,5′-heptatrien-1′-yl]-3,3-dimethyl-3*H*-indol-1-ium]] diiodide 21. This compound was obtained in a 16% yield; ^{1}H NMR (DMSO-d_6): δ = 1.58 (s, 12H), 1.66 (s, 12H), 1.76 (m, 16H), 2.50 (m, 4H), 2.69 (m, 4H), 3.84 (m, 4H), 4.28 (m, 8H), 6.19 (d, J = 13Hz, 2H), 6.46 (d, J = 14Hz, 2H), 7.25 (m, 8H), 7.44 (m, 2H), 7.55 (m, 4H), 7.65 (d, J = 7Hz, 2H), 8.13 (d, J = 14Hz, 2H), 8.28 (d, J = 13Hz, 2H); NIR: λ_{max} = 794 nm. Anal. Calcd for $C_{72}H_{84}Cl_2N_4O_7S_2\cdot 5H_2O$: C, 64.41; H, 7.06; N, 4.17. Found: C, 64.29; H, 6.82; N, 4.02.

3⁗,6⁗-Dioxaoctane-1,8-diyl[bis[2-[7′-[1″-(4‴-sulfonatobuty-l)-3″,3″-dimethylindolin-2″-ylidene]-4′-chloro-3′,5′-trimethylene-1′,3′,5′-heptatrien-1′-yl]-3,3-dimethyl-3*H*-indol-1-ium]] diiodide 22. This compound was obtained in a 14% yield; ^{1}H NMR (DMSO-d_6): δ = 1.62 (s, 12H), 1.68 (s, 12H), 1.78 (m, 16H), 2.71 (m, 8H), 3.38 (m, 4H), 3.45 (s, 4H), 4.20 (m, 4H), 4.30 (m, 4H), 6.35 (d, J = 13Hz, 2H), 6.44 (d, J = 14Hz, 2H), 7.27 (m, 6H), 7.44 (m, 6H), 7.62 (m, 4H), 8.24 (d, J = 13Hz, 2H), 8.27 (d, J = 14Hz, 2H); NIR: λ_{max} = 776 nm. Anal. Calcd for $C_{74}H_{88}Cl_2N_4O_8S_2\cdot 5H_2O$: C, 64.08; H, 7.12; N, 4.04. Found: C, 63.97; H, 6.94; N, 3.81.

3⁗,6⁗,9⁗-Trioxaundecane-1⁗,11⁗-diyl[bis[2-[7′-[1″-(4‴-sulfonatobutyl)-3″,3″-dimethylindolin-2″-ylidene]-4′-chloro-3′,5′-trimethylene-1′,3′,5′-heptatrien-1′-yl]-3,3-dimethyl-3*H*-indol-1-ium]] diiodide 23. This compound was obtained in a 12% yield; ^{1}H NMR (DMSO-d_6): δ = 1.62 (s, 12H), 1.65 (s, 12H), 1.73 (m, 16H), 2.59 (m, 8H), 3.27 (m, 4H), 3.37 (m, 4H), 3.71 (m, 4H), 4.24 (m, 4H), 4.36 (m, 4H), 6.35 (d, J = 14Hz, 2H), 6.39 (d, J = 15Hz, 2H), 7.41 (m, 16H), 8.20 (d, J = 14Hz, 2H), 8.25 (d, J = 15Hz, 2H); NIR: λ_{max} = 775 nm. Anal. Calcd for $C_{76}H_{92}Cl_2N_4O_9S_2\cdot 5H_2O$: C, 63.80; H, 7.18; N, 3.91. Found: C, 64.01; H, 6.92; N, 3.81.

3⁗-Oxapentane-1⁗,5⁗-diyl[bis[2-[7′-[3″-(4‴-sulfonatobutyl)-1″,1″-dimethylbenzo[*e*]indolin-2″-ylidene]-4′-chloro-3′,5′-trimethylene-1′,3′,5′-heptatrien-1′-yl]-3,3-dimethyl-3*H*-indol-1-ium]] diiodide 24. This compound was obtained in a 26% yield; ^{1}H NMR (DMSO-d_6): δ = 1.56 (m, 4H), 1.59 (s, 12H), 1.79 (m, 4H), 1.93 (s, 12H), 1.95 (m, 4H), 2.52 (m, 8H), 2.74 (m, 4H), 3.84 (m, 4H), 4.28 (m, 4H), 4.42 (m, 4H), 6.16 (d, J = 14Hz, 2H), 6.55 (d, J = 15Hz, 2H), 7.16 (m, 2H), 7.25 (m, 2H), 7.55 (m, 4H), 7.67 (m, 2H), 7.88 (m, 2H), 8.10 (m, 6H), 8.31 (m, 2H), 8.41 (d, J = 15Hz, 2H); NIR: λ_{max} = 818 nm. Anal. Calcd for $C_{80}H_{88}Cl_2N_4O_7S_2\cdot 5H_2O$: C, 66.60; H, 6.84; N, 3.88. Found: C, 66.58; H, 6.70; N, 3.66.

3⁗,6⁗-Dioxaoctane-1⁗,8⁗-diyl[bis[2-[7′-[3″-(4‴-sulfonatobutyl)-1″,1″-dimethylbenzo[*e*]indolin-2″-ylidene]-4′-chloro-3′,5′-trimethylene-1′,3′,5′-heptatrien-1′-yl]-3,3-dimethyl-3*H*-in-dol-1-ium]] diiodide 25. This compound was obtained in a 25% yield; ^{1}H NMR (DMSO-d_6): δ = 1.64 (s, 12H), 1.81 (m, 4H), 1.93 (s, 12H), 1.98 (m, 4H), 2.51 (m, 8H), 2.66 (m, 4H), 2.74 (m, 4H), 3.47 (s, 4H), 3.72 (m, 4H), 4.24 (m, 4H), 4.41 (m, 4H), 6.24 (d, J = 14Hz, 2H), 6.53 (d, J = 14Hz, 2H), 7.18 (m, 2H), 7.25 (m, 2H), 7.33 (m, 2H), 7.54 (m, 4H), 7.65 (m, 2H), 7.85 (m, 2H), 8.08 (m, 4H), 8.18 (d, J = 14Hz, 2H), 8.27 (m, 2H), 8.40 (d, J = 14Hz, 2H); NIR: λ_{max} = 802 nm. Anal. Calcd for $C_{82}H_{92}Cl_2N_4O_8S_2\cdot 2H_2O$: C, 68.74; H, 6.75; N, 3.91. Found: C, 68.43; H, 6.79; N, 3.82.

3⁗,6⁗,9⁗-Trioxaundecane-1⁗,11⁗-diyl[bis[2-[7′-[3″-(4‴-sulfonatobutyl)-1″,1″-dimethylbenzo[*e*]indolin-2″-ylidene]-4′-chloro-3′,5′-trimethylene-1′,3′,5′-heptatrien-1′-yl]-3,3-dimethyl-3*H*-indol-1-ium]] diiodide 26. This compound was obtained in a 12% yield; ^{1}H NMR (DMSO-d_6): δ = 1.66 (s, 12H), 1.83 (m, 12H), 1.95 (s, 12H), 2.69 (m, 4H), 2.77 (m, 4H), 3.40 (m, 8H), 3.76 (m, 4H), 4.35 (m, 4H), 4.42 (m, 4H), 6.33 (d, J = 14Hz, 2H), 6.53 (d, J = 15Hz, 2H), 7.22 (m, 2H), 7.36 (m, 4H), 7.56 (m, 4H), 7.69 (m, 2H), 7.89 (m, 2H), 8.12 (m, 4H), 8.18 (d, J = 14Hz, 2H), 8.32 (m, 2H), 8.33 (d,

J = 15Hz, 2H); NIR: λ_{max} = 797 nm in methanol. Anal. Calcd for $C_{84}H_{96}Cl_2N_4O_9S_2{\cdot}4H_2O$: C, 66.91; H, 6.92; N, 3.70. Found: C, 66.61; H, 6.65; N, 3.63.

Macrocyclic dyes 29–31. A mixture of Vilsmeier-Haack reagent **27** [15] (360 mg, 1 mmol), sodium acetate (82 mg, 1 mmol), and a dimeric salt, **5**, **6,** or **8** (732 mg, 1 mmol) in ethanol (30 mL) was stirred at 35°C for 1 h. The crude dye **29**–**31** was purified by chromatography eluting with dichloromethane/methanol (10:1) and then crystallized from ethanol/hexanes.

***N,N''*-(3''',5'''-Oxapentane-1''',5'''-diyl)-[2-[7'-(3'',3''-dimethylindolin-2''-ylidene)-4'-chloro-3',5'-trimethylene-1',3',5'-heptatrien-1'-yl]-3,3-dimethyl-3*H*-indol-1-ium] iodide 29.** This compound was obtained in a 10% yield; ^{1}H NMR (DMSO-d_6): δ = 1.57 (s, 12H), 1.62 (m, 2H), 2.66 (m, 4H), 3.91 (m, 4H), 4.46 (m, 4H), 6.31 (d, J = 14Hz, 2H), 7.24 (m, 2H), 7.36 (m, 4H), 7.57 (m, 2H), 8.18 (d, J = 14Hz, 2H). HR-MS (ESI). Calcd for $(C_{34}H_{38}ClN_2O)^+$: m/z = 525.2667. Found: m/z = 525.2687.

***N,N''*-(3''',6'''-Dioxaoctane-1''',8'''-diyl)-[2-[7'-(3'',3''-dimethylindolin-2''-ylidene)-4'-chloro-3',5'-trimethylene-1',3',5'-heptatrien-1'-yl]-3,3-dimethyl-3*H*-indol-1-ium] iodide 30.** This compound was obtained in a 20% yield; ^{1}H NMR (DMSO-d_6): δ = 1.57 (s, 12H), 1.84 (m, 2H), 2.63 (m, 4H), 3.52 (s, 4H), 3.72 (m, 4H), 4.29 (m, 4H), 6.32 (d, J = 14Hz, 2H), 7.24 (m, 2H), 7.38 (m, 4H), 7.58 (m, 2H), 8.14 (d, J = 14Hz, 2H); Anal. Calcd. for $C_{36}H_{42}ClIN_2O_2{\cdot}H_2O$: C, 60.46; H, 6.20; N, 3.91. Found: C, 60.61; H, 6.11; N, 3.85.

***N,N''*-(3''',6''',9'''-Trioxaundecane-1''',11'''-diyl)- [2-[7'-(3'',3''-dimethylindolin-2''-ylidene)-4'-chloro-3',5'-trimethylene-1',3',5'-heptatrien-1'-yl]-3,3-dimethyl-3*H*-indol-1-ium] iodide 31.** This compound was obtained in a 32% yield; ^{1}H NMR (CDCl$_3$): δ = 1.54 (s, 12H), 2.00 (m, 2H), 2.72 (m, 4H), 3.72 (m, 4H), 3.81 (m, 4H), 3.99 (m, 4H), 4.53 (m, 4H), 5.96 (d, J = 15Hz, 2H), 7.24–7.46 (m, 8H), 8.52 (d, J = 15Hz, 2H); NIR: λ_{max} = 777 nm. Anal Calcd. for $C_{38}H_{46}ClIN_2O_3{\cdot}2H_2O$: C, 58.72; H, 6.48; N, 3.60. Found: C, 58.92; H, 6.19; N, 3.48.

Molecular modeling. Energy minimizations were performed using SYBYL (running on SGI O$_2$ station) using MMFF94 force field and the minimum energy change of 0.01 kcal/mol per Å as a convergence criterion. Charges were calculated using the MMFF94 method as implemented in SYBYL. The molecules in aqueous environment were minimized using the Molecular Silverware option in SYBYL, which resulted in change of energy (E_{min}) and in the conformation of dyes. The values of E_{min} decreased of about 70–100 kcal/mol when the environment was changed from vacuum to aqueous solution. In vacuum, the structures are opened, and in water, the individual cyanine moieties of the dimeric molecules are close to each other in all cases studied.

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A Simple, Efficient, One-Pot Three-Component Domino Synthesis of Hantzsch Pyridines under Solvent-Free Condition

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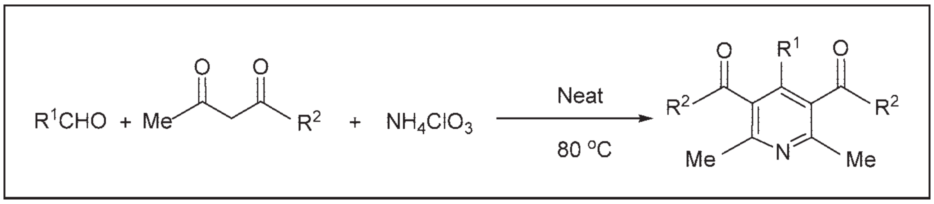

In this article, efficient and simple preparation of Hantzsch pyridine derivatives by reaction of various aldehydes and β-dicarbonyls in the presence of ammonium chlorate under solvent-free condition at 80°C is reported. The advantages of this system are the one-step procedure, high yields of the products, and the ability to carry out large-scale reactions.

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INTRODUCTION

Pyridine bases, as representative heteroaromatic ring compounds, are produced for applications in herbicides, insecticides, vitamins, nicotinic acid and nicotinic amide, pharmaceuticals, and adhesives [1]. For example, there are many bioactive pyridine compounds, such as the prosthetic pyridine nucleotide (NADP) [2], pyridoxine (vitamin B_6), and nicotine [3], and also many pharmaceuticals [4] and agrochemicals [5] possessing a pyridine nucleus. Pyridine is used as a basic solvent as well as a catalyst in industrially important organic reactions [6]. Thus, new construction methods for multisubstituted pyridines are still intriguing studies [7,8].

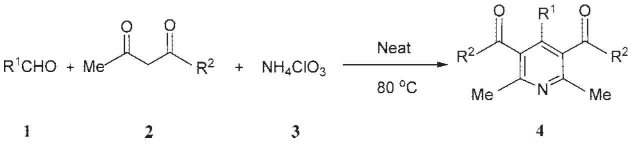
On the other hand, the synthesis of heteroaromatics by oxidative dehydrogenation is of fundamental importance in organic chemistry. These ubiquitous features always encourage synthetic chemist to explore improved protocols for the synthesis as well as the oxidation of 1,4-dihydropyridines. Oxidation of 1,4-dihydropyridines is one of the possible ways for the synthesis of the corresponding pyridines. Aromatization of 1,4-dihydropyridines has received considerable attention because of the fact that 1,4-dihydropyridine-based calcium channel blockers are oxidatively converted to pyridine derivatives by the action of cytochrome P-450 in the liver [9,10]. In addition, the corresponding pyridine derivatives show antihypoxic and anti-ischemic activities and are used in the treatment of atherosclerosis [11]. Additionally, dihydropyridines are often produced in a synthetic sequence and have to be oxidized to pyridines [12]. Numerous reagents and procedures have been recommended for this purpose, such as pyridinium chlorochromate (PCC) [13], N_2O_4 complex of 18-crown-6 [14], *tert*-butylhydroperoxide [15], photochemical oxidation [16], vanadium(V) salts [17], and biomimetic catalyzed oxidation [18].

Despite these intensive efforts, most of the reported oxidation procedures require long reaction time, use of the strong oxidants in large excess, and afford products with only modest yields. In particular, the aromatization reactions with these reagents lead to dealkylation of the 4-position or formation of side products.

It is well known in the protocol of green chemistry that its main objective is to perform reactions under solventless conditions using heterogeneous catalysts to generate environmentally friendly chemical transformations [19]. In addition, it is important to note that an ideal synthesis is considered as one in which a target molecule is produced quantitatively in one step, from available and inexpensive raw materials [20].

Ammonium acetate has been used for the synthesis of dihydropyridine [21] and pyridine derivatives. 4-Substituted Hantzsch 1,4-dihydropyridines were synthesized by replacing ammonium acetate with ammonia in a classical method, in which the products can be subsequently oxidized to corresponding pyridines. To the best of our knowledge, only two articles reported the continuous synthesis of Hantzsch pyridines by a mixture of bentonite clay, β-ketoester, aldehyde, and ammonium nitrate as the source of ammonia and oxidizing species [22,23]. These results are intriguing as they are somehow contradictory. In one of these reports [22], in the absence of solvent, the alkylated pyridine was isolated from the oxidation of 4-isopropyl dihydropyridine as the major product. On the other hand, dealkylated pyridine was isolated from the oxidation of 4-propyl or 4-phenyl dihydropyridines in substantial yield that this

Scheme 1



observation contrasts with the presented results in the second report [23], such as they do not mention the presence of this case of pyridine in the final mixtures.

In the Vilsmeier–Haack reaction progress, Jutz et al. [24] have demonstrated that the cyclization of the intermediate iminium salts formed by the multiple iminoalkylations of certain alkenes, in the presence of ammonium acetate, leads to the formation of substituted pyridines and naphthyridines. Thomas and Asokan [25] envisaged that a similar ammonium acetate-induced cyclization of the intermediates formed by the treatment of α-hydroxyketenedithioacetals would afford a useful method for the synthesis of substituted pyridines with moderate yields.

In this research, we report that the ammonium chlorate can be used as both ammonia and oxidizing agent source for the direct synthesis and oxidation of Hantzsch 1,4-dihydropyridines to pyridines.

RESULTS AND DISCUSSION

As a part of our current studies on multicomponent reaction (MCR) involving synthesis of dihydropyrimidinones [26] and our interest in the chemistry of dihydropyridines [18], we have investigated the one-pot synthesis of pyridine derivatives (Scheme 1).

The synthetic method for the preparation of substituted pyridine derivatives (**4**) was relatively easy and simple, and the compounds could be obtained in one step. The optimized reaction conditions were subsequently applied to the reaction between various aliphatic or aromatic aldehydes and β-dicarbonyls in the presence of ammonium chlorate in solvent-free conditions at 80°C. In all cases, the desired pyridine derivatives were obtained in high to excellent yields. Both electron-rich and electron-deficient aromatic aldehydes as well as heterocyclic ones worked well. Aliphatic aldehydes afforded equally good results. Many of the pharmacologically significant substitution patterns can be introduced with good efficiency (Table 1).

In a typical procedure, 2 mmol of aldehyde, 4 mmol of β-dicarbonyl, and 3 mmol of ammonium chlorate were mixed in solvent-free conditions at 80°C for 40–300 min. After work-up, the corresponding pyridines were isolated with excellent yields (**4a**–**4s**). One advantage of this method is its large-scale applicability. Pyridines were prepared on a 50-mmol scale, and the results were comparable with the small-scale experiments.

According to the literature, the thermal decomposition of NH_4ClO_3 begins at 50°C, which possibly includes equilibrium formation of ammonia and chloric acid according to Scheme 2 [28]. This process is probably accelerated by water formed in reaction. Thus, formed ammonia acts as a nitrogen nucleophile in Hantzsch dihydropyridine synthesis while chloric acid as an actual oxidant. However, it cannot be excluded that the product, substituted pyridine, is formed by the oxidation of intermediates different than 1,4-dihydropyridines.

Based on the evidences from the reaction and previous suggestions on such a system as shown in Scheme 1, our rationalization about the proposed mechanism includes thermal decomposition of ammonium chlorate to NH_3 and $HClO_3$ that these lead to Hantzsch dihydropyridine synthesis and its oxidation of the products with chloric acid to corresponding pyridines.

CONCLUSIONS

In conclusion, we have developed a simple and efficient synthetic protocol for the synthesis of a wide variety of Hantzsch pyridine derivatives under solvent-free conditions. Mild reaction conditions, cost efficiency, simplicity in operation, and large-scale applicability are some significant features of this protocol.

EXPERIMENTAL

All chemicals were purchased from Merck, Fluka, and Sigma-Aldrich chemical companies. The reactions were monitored by TLC. The products were isolated and identified by comparison of their physical and spectral data with authentic samples. IR spectra were recorded on FTIR JASCO-680. The ^{1}H NMR spectra were obtained on a Brüker-instrument DPX-300 MHz and melting points determined on a Barnstead Electrothermal (BI 9300) apparatus.

General procedure for the preparation of the Hantzsch pyridines. All reactions were carried out in a 25-mL round bottomed flask equipped with a magnetic stirring bar. A mixture of aldehyde (2 mmol), β-dicarbonyl (4 mmol), and ammonium chlorate (3 mmol) was heated at 80°C. After completion of the reaction, as monitored by TLC, the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The solvent was evaporated off, and the crude product was purified by silica gel plate or silica gel column (eluent: *n*-hexane–EtOAc). The products were characterized by IR, ^{1}H NMR, and *via* comparison of their melting points with the reported ones.

Spectral and physical data for selected compounds ***Diethyl 4-(2,4-dichlorophenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (4i).*** mp: 58–60°C, R_f (*n*-hehaxe/EtOAc, 5:1) = 0.55. IR (KBr): υ (cm^{-1}) = 2982, 2905, 1720, 1585, 1472, 1412, 1375, 1264, 1242, 1143, 1105, 1051, 837, 758; ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.05 (t, 6H), 2.11 (s, 6H), 3.89 (q, 4H),

Table 1

The one-pot synthesis of pyridine derivatives.[a]

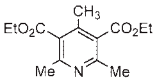
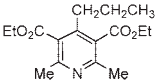
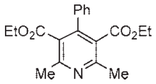
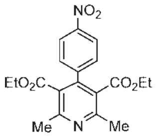
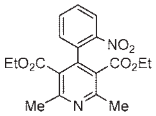
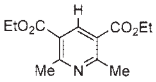
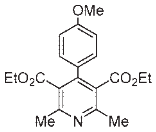
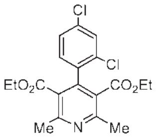
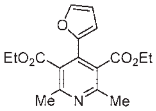
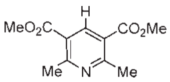
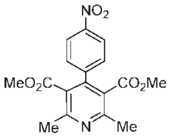
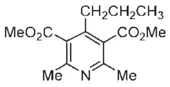
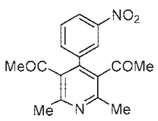
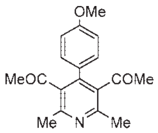
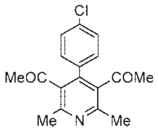
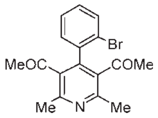
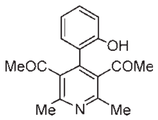
Entry products	R^1	R^2	Products	Time (min)	Yields[b] (%)	mp (°C)
4a	CH_3	OEt		70	90	Oily [27b]
4b	$(CH_3)_2CH$	OEt		75	95	70–72 [27e]
4c	$CH_3(CH_2)_2$	OEt		60	90	Oily [27a]
4d	C_6H_5	OEt		50	94	62–63 [27b]
4e	$4\text{-}NO_2\text{—}C_6H_4$	OEt		75	89	113–115 [27b]
4f	$2\text{-}NO_2\text{—}C_6H_4$	OEt		180	94	75–76 [27f]
4g	$C_6H_5\text{—}CHCH_3$	OEt		80	95	70–72 [27d]
4h	$4\text{-}CH_3O\text{—}C_6H_4$	OEt		40	94	49–50 [27a]
4i	$2,4\text{-}(Cl)_2\text{—}C_6H_3$	OEt		130	91	62–64
4j	2-Furyl	OEt		85	96	39–41 [27c]
4k	H	OMe		200	92	100–102 [27h]
4l	$4\text{-}NO_2\text{—}C_6H_4$	OMe		200	97	90–93 [27g]

Table 1
(*Continued*)

Entry products	R^1	R^2	Products	Time (min)	Yields^b (%)	mp (°C)
4m	$CH_3(CH_2)_2$	OMe		180	85	Oily [27h]
4n	3-NO_2-C_6H_4	Me		300	92	125–127 [27i]
4o	4-CH_3O-C_6H_4	Me		200	87	163–164 [27i]
4p	4-Cl-C_6H_4	Me		250	80	174–176 [27i]
4q	2-Br-C_6H_4	Me		160	89	190–192
4r	2-OH-C_6H_4	Me		130	90	140–142

[a] Characterized by spectral analysis and comparison with these reported in the literature [27].
[b] Isolated yields.

6.91 (q, 1H), 7.06–7.13 (m, 2H). Anal. Calcd. for $C_{19}H_{19}Cl_2NO_4$: C, 57.59; H, 4.83; N, 3.53; found: C, 57.5; H, 4.7; N 3.4.

3,5-Diacetyl-4-(2-bromophenyl)-2,6-dimethylpyridine (4q). mp: 190–192°C, R_f (CCl_4/EtOAc, 5:1) = 0.57. IR (KBr): υ (cm^{-1}) = 2975, 2900, 1695, 1620, 1456, 1405, 1378, 1260, 1225, 1140, 1110, 1045, 720; ^1H NMR ($CDCl_3$): δ (ppm) = 2.10 (s, 6H), 2.59 (s, 6H), 6.91–7.34 (m, 4H). Anal. Calcd. for $C_{17}H_{16}BrNO_2$: C, 58.97; H, 4.66; N, 4.05; found: C, 58.8; H, 4.5; N, 3.9.

3,5-Diacetyl-4-(2-hydroxyphenyl)-2,6-dimethylpyridine (4r). mp: 140–142°C, R_f (CCl_4/EtOAc, 5:1) = 0.52. IR (KBr): υ (cm^{-1}) = 3410, 3015, 2985, 2920, 1690, 1615, 1585, 1470, 1402, 1320, 1265, 1172, 1115, 1040, 905, 812, 740; ^1H NMR ($CDCl_3$): δ (ppm) = 1.95 (s, 6H), 2.50 (s, 6H), 4.01 (br, 1H), 6.80–7.42 (m, 4H). Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94; found: C, 71.9; H, 5.9; N, 4.8.

Scheme 2

$$NH_4ClO_3 \rightleftharpoons NH_3 + HClO_3$$

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Synthesis and Potent Antifungal Activity Against *Candida* Species of Some Novel 1*H*-Benzimidazoles

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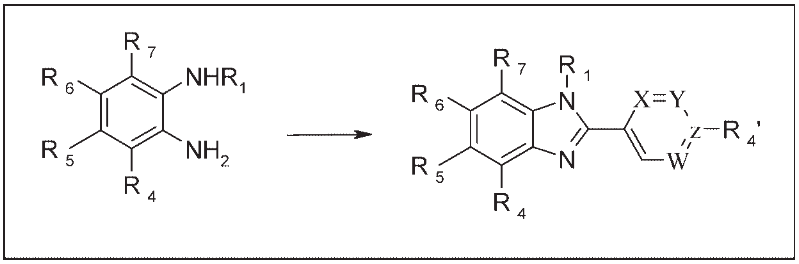

A series of 47 novel N^1-alkylated-2-aryl-5(6)-substituted-1*H*-benzimidazoles and their three novel indole analogues were synthesized and evaluated for *in vitro* antifungal activities against *Candida* species by the tube dilution method. The results showed that compounds **79** and **80**, having pyridine at the position C-2, of benzimidazoles exhibited the greatest activity with MIC values of 6.25–3.12 μg/mL. Indole analogues **108–110** have no inhibitory activity.

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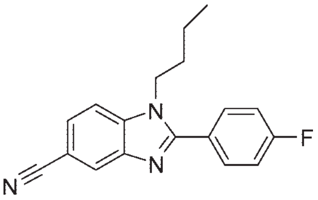
INTRODUCTION

We have already reported the synthesis and potent antifungal evaluation of a series of 2-substituted-phenyl-1*H*-benzimidazole-5-carbonitriles [1]. The study revealed that among the synthesized benzimidazoles compound **I** exhibited greatest antifungal activity with the MIC of 3.12 μg/mL against *Candida albicans*, *Candida krusei*, *Candida glabrata*, and *Candida parapsilosis* (Fig. 1).



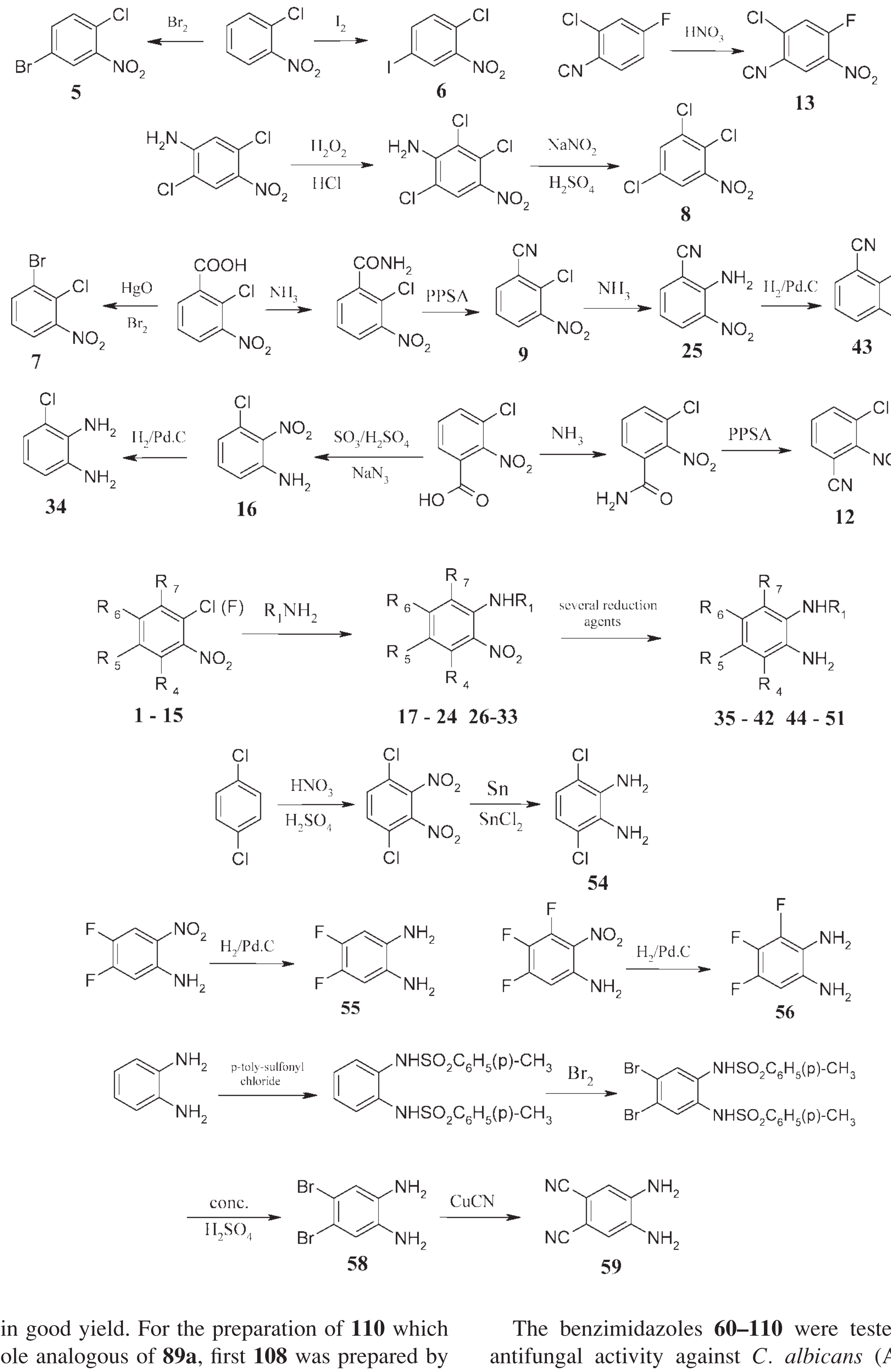
I

We planned to modify the structure of compound **I** in order to find more potent new antifungal agents.

RESULTS AND DISCUSSION

Noncommercial starting material *o*-phenylenediamines were prepared according to the literature methods, which are given in Scheme 1. The synthetic pathways for preparation of the targeted benzimidazoles listed in Table 1 are shown in Schemes 2 and 3. Nucleophilic displacement of the chloro group of **1–15** (Table 2), by the reaction with several amines in *N,N*-dimethylformamide gave **16–33** (Table 3). Their reduction with hydrogen gas by using palladium carbon or tin/hydrochloric acid produced **34–59** (Table 4). Condensation of these derivatives with the sodium metabisulfite adduct of appropriate benzaldehydes gave the targeted benzimidazoles **60–73**, **75**, **78–80**, **83**, **84**, **90–97**, **99–102**, **104** [1]. Heck and Nolley [23] reaction of **73** with (trimethylsilyl)acetylene led to **74a**, whose silyl group was cleaved to yield 5-ethynylbenzimidazole **74**. **77** was prepared by diazotation of **76**, followed by treatment with sodium azide. Acylation of 3-amino-4-(butylamino)benzonitrile with 4-pyridazine and pyrazine carbonyl chlorides gave the corresponding monoamide derivatives **81a** and **82a**, following this cyclization of these compounds with glacial acetic acid and anhydrous sodium acetate afforded **81** and **82**. The nitrile group of **I** was converted to carboxyaldehyde **85**, by using diisobutylaluminum hydride (DIBAL), in a moderato yield, and aldehyde group was transformed to the oxime ether **86**. The 1,2,4-oxadiazol-3-yl-1*H*-benzimidazole **88** was obtained by reaction of **I** first with hydroxylamine to amidoxime **87** and subsequently with acetic anhydride. In addition, another 1*H*-benzimidazole-5-carbonitrile **89a** reacted with sodium azide at high temperature to yield 5-substituted 1*H*-tetrazole **89**. Benzylic cleavage of **97** afforded **98** by reduction with hydrogen gas. Alkylation of tautomeric imidazole NH of **99–102** with butyl bromide in *N,N*-dimethylformamide gave **103**,

Scheme 1. Synthesis of noncommercial *o*-phenylenediamines.

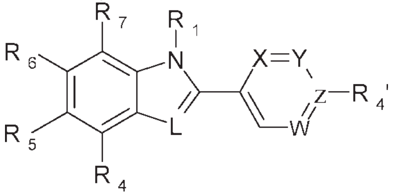


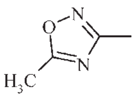
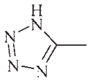
105–107 in good yield. For the preparation of **110** which is the indole analogous of **89a**, first **108** was prepared by the well-known Fischer indole synthesis method (Scheme 3) [24]. Alkylation of this compound gave **109**, then bromine was converted to the nitrile with copper(I) cyanide.

The benzimidazoles **60–110** were tested *in vitro* for antifungal activity against *C. albicans* (ATCC 10231), *C. krusei* (ATCC 6258), *C. parapsilosis* (ATCC 22019), and *C. glabrata* (Clinical isolate) by the tube dilution method [25] and the MIC values are listed in Table 1.

Table 1

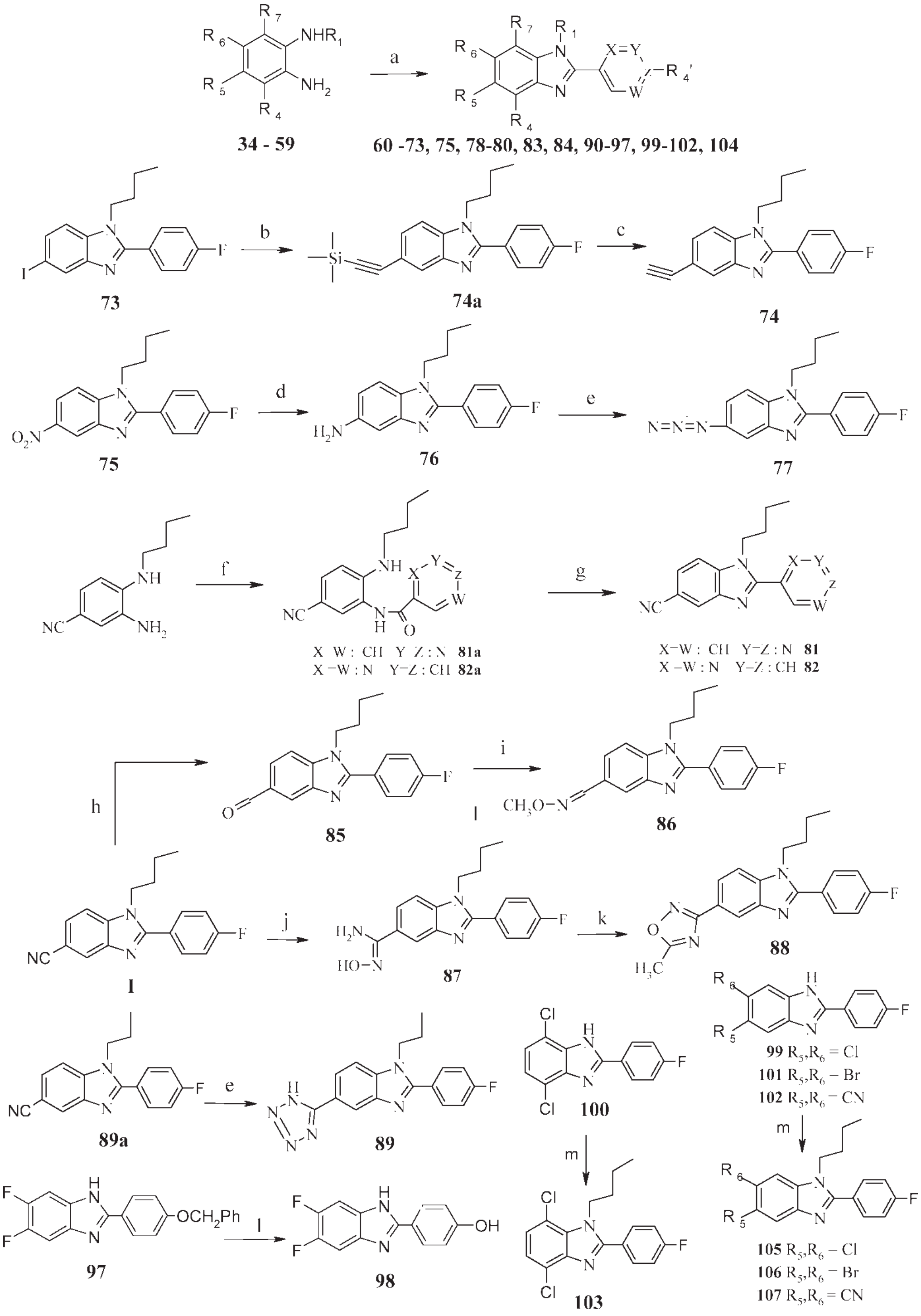
In vitro antifungal activities and formulas of **60–110**.



No	R_1	R_7	R_6	R_5	R_4	$R_{4'}$	L	X	Y	Z	W	MIC$_{100}$ (μg/mL) *C a*	*C k*	*C p*	*C g*
60		Cl				F	N	CH	CH	CH	CH	>50	>50	>50	>50
61		CN				F	N	CH	CH	CH	CH	>50	>50	>50	>50
62				CF_3		F	N	CH	CH	CH	CH	12.5	12.5	6.25	12.5
63	butyl	Cl					N	CH	CH	CH	CH	>50	>50	>50	>50
64	butyl	Cl				F	N	CH	CH	CH	CH	>50	>50	>50	>50
65	butyl	Br				F	N	CH	CH	CH	CH	>50	>50	>50	>50
66	butyl	CN				F	N	CH	CH	CH	CH	>50	>50	>50	>50
67	butyl		Cl			F	N	CH	CH	CH	CH	>50	>50	>50	>50
68	butyl		CN			F	N	CH	CH	CH	CH	>50	>50	>50	>50
69	butyl			F		F	N	CH	CH	CH	CH	>50	>50	>50	>50
70	butyl			Cl		F	N	CH	CH	CH	CH	>50	>50	>50	>50
71	butyl			Cl			N	CH	CH	N	CH	>50	>50	>50	>50
72	butyl			Br		F	N	CH	CH	CH	CH	>50	>50	>50	>50
73	butyl			I		F	N	CH	CH	CH	CH	>50	>50	>50	>50
74	butyl			$HC{\equiv}C—$		F	N	CH	CH	CH	CH	>50	>50	>50	>50
75	butyl			NO_2		F	N	CH	CH	CH	CH	>50	>50	>50	>50
76	butyl			NH_2		F	N	CH	CH	CH	CH	>50	>50	>50	>50
77	butyl			N_3		F	N	CH	CH	CH	CH	>50	>50	>50	>50
78	butyl			NC			N	N	CH	CH	CH	>50	>50	>50	>50
79	butyl			NC			N	CH	N	CH	CH	6.25	25	12.5	25
80	butyl			NC			N	CH	CH	N	CH	6.25	12.5	3.12	25
81	butyl			NC			N	CH	N	N	CH	25	25	12.5	25
82	butyl			NC			N	N	CH	CH	N	>50	>50	>50	>50
83	pentyl			NC			N	CH	CH	CH	CH	25	>50	25	>50
84	butyl		Cl	NC		F	N	CH	CH	CH	CH	>50	>50	>50	>50
85	butyl			CHO		F	N	CH	CH	CH	CH	>50	>50	>50	>50
86	butyl			MeO—N=CH—		F	N	CH	CH	CH	CH	>50	>50	>50	>50
87	butyl					F	N	CH	CH	CH	CH	>50	>50	>50	>50
88	butyl					F	N	CH	CH	CH	CH	>50	>50	>50	>50
89	propyl					F	N	CH	CH	CH	CH	>50	>50	>50	>50
90	butyl			CH_3CO		F	N	CH	CH	CH	CH	>50	>50	>50	>50
91	butyl				CN	F	N	CH	CH	CH	CH	>50	>50	>50	>50
92		Br		F_3C			N	CH	CH	CH	CH	>50	>50	>50	>50
93			F	F			N	CH	CH	CH	CH	25	25	3.12	25
94			F	F		F	N	CH	CH	CH	CH	12.5	25	6.25	12.5
95		F	F	F			N	CH	CH	CH	CH	>50	>50	>50	>50
96			F	F			N	CH	CH	N	CH	>50	>50	>50	>50
97			F	F		OBn	N	CH	CH	CH	CH	>50	>50	>50	>50
98			F	F		OH	N	CH	CH	CH	CH	>50	>50	>50	>50
99			Cl	Cl		F	N	CH	CH	CH	CH	>50	>50	>50	>50
100		Cl			Cl	F	N	CH	CH	CH	CH	>50	>50	>50	>50
101			Br	Br		F	N	CH	CH	CH	CH	>50	>50	>50	>50
102			NC	NC		F	N	CH	CH	CH	CH	>50	>50	>50	>50
103	butyl	Cl			Cl	F	N	CH	CH	CH	CH	>50	>50	>50	>50
104	butyl	Cl		Cl		F	N	CH	CH	CH	CH	>50	>50	>50	>50
105	butyl		Cl	Cl		F	N	CH	CH	CH	CH	>50	>50	>50	>50
106	butyl		Br	Br		F	N	CH	CH	CH	CH	25	25	25	25
107	butyl		NC	NC		F	N	CH	CH	CH	CH	>50	>50	>50	>50
108				Br		F	CH	CH	CH	CH	CH	>50	>50	>50	>50
109	propyl			Br		F	CH	CH	CH	CH	CH	>50	>50	>50	>50
110	propyl			NC		F	CH	CH	CH	CH	CH	>50	>50	>50	>50
I	butyl			NC		F	N	CH	CH	CH	CH	1.56	12.5	1.56	25
Flu												1.56	25	3.12	25

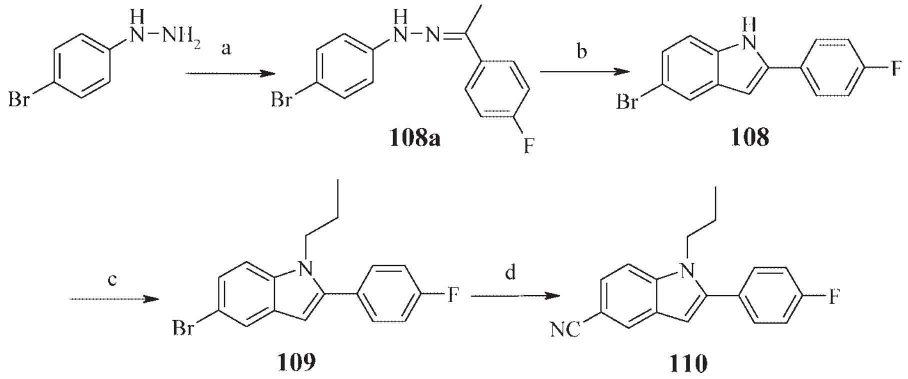
MIC$_{100}$ = Minimum inhibitory concentrations, *C a*, *Candida albicans*; *C k*, *Candida krusei*; *C p*, *Candida parapsilosis*; *C g*, *Candida glabrata*; I, formula in Figure 1; Flu, Fluconazole.

Scheme 2. Synthesis of benzimidazoles **60–107**. Reagents (a) $Na_2S_2O_5$ adduct of the corresponding benzaldehydes; (b) (Trimethylsilyl)-acetylen; (c) KOH/MeOH; (d) $SnCl_2$/HCl; (e) $NaNO_2$-HCl/NaN_3; (f) For **81a**: 4-Pyridazinecarboxylic acid and HBTU; For **82a**: Pyrazinecarbonyl chloride; (g) Glacial acetic acid/anhydrous Na-acetate; (h) DIBAL; (i) Methoxyl-amine HCl; (j) $NH_2OH{\cdot}HCl$, *i*-Pr_2NEt; (k) $(CH_3CO)_2O$; (l) Pd.C/H_2; and (m) Butyl bromide/NaH.



The synthesized compounds and reference drugs were dissolved in dimethyl sulfoxide-water (50%) at a concentration of 400 µg/mL. The concentration was adjusted to 100 µg/mL by fourfold dilution with media culture and fungi solution at the first tube. Data was not taken for the initial solution because of the high concentration (12.5%).

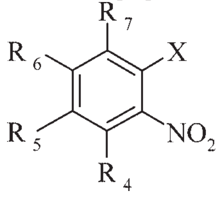
Scheme 3. Synthesis of indole analogues **108–110**. Reagents (a) 4′-fluoroacetophenone, trimethylamine; (b) PPA; (c) Propyl bromide, NaH; and (d) CuCN, *N*-methyl-2-pyrrolidone.



The result demonstrates that some of the benzimidazoles in this series showed the good activity profiles versus some *Candida* species. Among of them, compounds **79** and **80** exhibited the greatest activity with MIC values of 6.25–3.12 μg/mL. These compounds are having pyridine moiety at the position of C-2 instead of phenyl in compound **I** (Fig. 1). Replacement of phenyl moiety to 4-pyridazine (**81**) or pyrazine (**82**) caused to reduce inhibitory activity. Most of the other electron withdrawing group which could be the bioequivalence of cyano at the position of C-5 were tested, however, as no better result were found with them, cyano group was accepted

Table 2

Formulas and some properties of **1–15.**

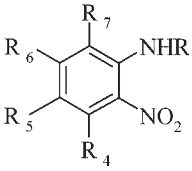


Comp	R_7	R_6	R_5	R_4	X	Formulas	References, physical and spectral data
1	Cl				Cl	$C_6H_3Cl_2NO_2$	Commercial
2		Cl			Cl	$C_6H_3Cl_2NO_2$	Commercial
3			F		Cl	$C_6H_3ClFNO_2$	Commercial
4			Cl		Cl	$C_6H_3Cl_2NO_2$	Commercial
5			Br		Cl	$C_6H_3BrClNO_2$	mp 69°C, ref. 2, 71–72°C
6			I		Cl	$C_6H_3ClINO_2$	mp 74°C, ref. 3, 74.5°C; ^{1}H NMR: δ 7.28 (d, 1H, J = 8.4 Hz), 7.82 (dd, 1H, J = 2, 8.6 Hz), 8.17 (d, 1H, J = 2 Hz)
7	Br				Cl	$C_6H_3BrClNO_2$	ref. 4
8	Cl		Cl		Cl	$C_6H_2Cl_3NO_2$	ref. 5
9	CN				Cl	$C_7H_3ClN_2O_2$	ref. 6
10		CN			Cl	$C_7H_3ClN_2O_2$	ref. 1
11			CN		Cl	$C_7H_3ClN_2O_2$	Commercial
12				CN	Cl	$C_7H_3ClN_2O_2$	mp 65°C,[a] ref. 7 mp 85°C; IR (potassium bromide): 2240 (CN) cm^{-1}; ^{1}H NMR: δ 7.57 (t, 1H, J = 7.6 Hz), 7.69 (dd, 1H, J = 1.2, 7.6 Hz), 7.75 (dd, 1H, J = 1.2, 8.5 Hz)
13		Cl	CN		F	$C_7H_2ClFN_2O_2$	ref. 8, mp 83°C, ref. 9, 84–85°C
14			$COCH_3$		Cl	$C_8H_6ClNO_3$	Commercial
15			NO_2		Cl	$C_6H_3ClN_2O_4$	Commercial

[a] Melting point is not in agreement with the data given in ref. 7. However, our elemental analysis result confirms the structure. *Anal.* Calcd for $C_7H_3ClN_2O_2$: C, 46.05; H, 1.66; N, 15.34. Found C, 45.62; H, 1.695; N, 15.17.

Table 3

Formulas and some properties of **16–33**.

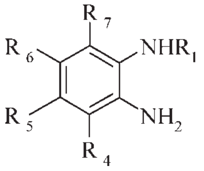


No	R_1	R_7	R_6	R_5	R_4	Formulas	References, physical and spectral data
16	H				Cl	$C_6H_5ClN_2O_2$	mp 108–109, ref. 10 mp 108–108.5; ^{1}H NMR: δ 6.7 (dd, 1H, *J* = 1.2, 8.4 Hz), 6.82 (dd, 1H, *J* = 1.2, 8.5 Hz), 7.16 (t, 1H, *J* = 8.3)
17	*n*-butyl	Cl				$C_{10}H_{13}ClN_2O_2$	Oily; ^{1}H NMR: δ 0.93 (t, 3H), 1.39 (m, 2H), 1.58 (m, 2H), 3.41 (q, 2H), 6.67 (br.s, 1H), 6.72 (t, 1H), 7.48 (dd, 1H, *J* = 1.6, 8.2 Hz), 7.91 (dd, 1H, *J* = 1.6, 8.4 Hz); ms: *m*/*z* 229 (100), 231 (33)
18	*n*-butyl		Cl			$C_{10}H_{13}ClN_2O_2$	Oily, ref. 11
19	*n*-butyl			F		$C_{10}H_{13}FN_2O_2$	ref. 12
20	*n*-butyl			Cl		$C_{10}H_{13}ClN_2O_2$	ref. 1
21	*n*-butyl			Br		$C_{10}H_{13}BrN_2O_2$	Purification: ethyl acetate:hexane (10:90) cc; Oily; ^{1}H NMR: δ 0.98 (t, 3H), 1.48 (m, 2H), 1.71 (m, 2H), 3.28 (q, 2H), 6.75 (d, 1H, *J* = 8.8), 7.48 (dd, 1H, *J* = 2.4, 8.8 Hz), 8.03 (br.t, 1H), 8.31 (d, 1H, *J* = 2.4 Hz); ms: *m*/*z* 273 (100), 275 (100)
22	*n*-butyl			I		$C_{10}H_{13}IN_2O_2$	Purification: ethyl acetate:hexane (10:90) cc; Oily; ^{1}H NMR: δ 0.985 (t, 3H), 1.48 (m, 2H), 1.70 (m, 2H), 3.28 (q, 2H), 6.64 (d, 1H, *J* = 9.2 Hz), 7.61 (dd, 1H, *J* = 2, 9.2 Hz), 8.04 (br.t, 1H), 8.46 (d, 1H, *J* = 2Hz); ms: *m*/*z* 321
23	*n*-butyl	Br				$C_{10}H_{13}BrN_2O_2$	Purification: ethyl acetate:hexane (20:80) cc; Oily; ^{1}H NMR: δ 0.92 (t, 3H), 1.38 (m, 2H), 1.58 (m, 2H), 3.25 (q, 2H), 6.05 (br.s, 1H), 6.68 (t, 1H), 7.67 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.87 (dd, *J* = 1.6, 8.4 Hz, 1H); ms: *m*/*z* 273 (100), 275 (100)
24	*n*-butyl	Cl		Cl		$C_{10}H_{12}Cl_2N_2O_2$	Purification: ethyl acetate:hexane (10:90) cc; Oily; ^{1}H NMR: δ 0.93 (t, 3H), 1.37 (m, 2H), 1.58 (m, 2H), 3.4 (q, 2H), 6.72 (br.s, 1H), 7.49 (d, 1H), 7.94 (d, 1H); ms: *m*/*z* 263 (100), 265 (61), 267(11)
25	H	CN				$C_7H_5N_3O_2$	mp 133–135°C, ref. 13 mp 129–130°C; ^{1}H NMR (Deuteriochloroform + D_2O): δ 6.79 (t, 1H, *J* = 8 Hz), 7.7 (dd, 1H, *J* = 1.2, 7.6 Hz), 8.4 (dd, 1H, *J* = 1.6, 8 Hz)
26	*n*-butyl	CN				$C_{11}H_{13}N_3O_2$	Purification: ethyl acetate:hexane (40:60) cc; mp 37°C; ^{1}H NMR: δ 0.96 (t, 3H), 1.46 (m, 2H), 1.72 (m, 2H), 3.83 (q, 2H), 6.68 (t, 1H), 7.17 (dd, 1H), 8.35 (dd, 1H), 8.46 (br.s, 1H); ms: *m*/*z* 220 (100)
27	*n*-butyl		CN			$C_{11}H_{13}N_3O_2$	Purification: Cryst. ethanol; mp 83–85°C; ^{1}H NMR: δ 1.02 (t, 3H), 1.48 (m, 2H), 1.72 (m, 2H), 3.30 (q, 2H), 6.85 (dd, 1H), 7.15 (d, 1H, *J* = 1.5 Hz), 8.03 (br.s, 1H), 8.26 (d, 1H, *J* = 8.4); ms: *m*/*z* 220 (100)
28	*n*-butyl			CN		$C_{11}H_{13}N_3O_2$	ref. 1
29	*n*-pentyl			CN		$C_{12}H_{15}N_3O_2$	Purification: Cryst. ethanol; ^{1}H NMR: δ 0.95 (t, 3H), 1.47 (m, 4H), 1.73 (m, 2H), 3.35 (q, 2H), 6.92 (d, *J* = 9.1, 1H), 7.58 (dd, 1H), 8.41 (br.s, 1H), 8.51 (d, 1H, *J* = 1.3)
30	*n*-butyl				CN	$C_{11}H_{13}N_3O_2$	Purification: ethyl acetate:hexane (40:60) cc; mp 82–84°C; ^{1}H NMR: δ 0.98 (t, 3H), 1.46 (m, 2H), 1.71 (m, 2H), 3.32 (q, 2H), 7.08 (d, 1H), 7.12 (d, 1H), 7.46 (t, 1H), 8.13 (br.s, 1H); ms: *m*/*z* 220 (100)
31	*n*-butyl		Cl	CN		$C_{11}H_{12}ClN_3O_2$	Purification: Cryst. ethanol; mp 83°C; ^{1}H NMR: δ 1.02 (t, 3H), 1.49 (m, 2H), 1.75 (m, 2H), 3.34 (q, 2H), 6.94 (s, 1H), 8.38 (s, 1H), 8.5 (s, 1H); ms: *m*/*z* 254 (100), 256 (33)
32	*n*-butyl			$COCH_3$		$C_{12}H_{16}N_2O_3$	ref. 14
33	*n*-butyl			NO_2		$C_{10}H_{13}N_3O_4$	ref. 15

as a best pharmacophore at this position. Moreover, changing the position of cyano group from C-5, to C-4 (**91**), C-6 (**68**), and C-7 (**66**), did not give better result. In addition, this cyano group was converted to the aldehyde (**85**), oxime (**86**), oxadiazole (**88**), and tetrazole (**89**), unfortunately activity was reduced again. Because we have already reported that, the best group was butyl at position N-1, no more modifications have been done in this study, only compound **83** with *n*-pentyl group was prepared, which also caused to reduce activity. Among the halogenated compounds, the best results were obtained with **93** against *C. parapsilosis* with the MIC

Table 4

Formulas and some properties of **34–59**.



Com	R_1	R_7	R_6	R_5	R_4	Formulas	References, physical and spectral data
34		Cl				$C_6H_7ClN_2$	Oily; ^{1}H NMR: δ 3.45 (br.s, 2H), 3.75 (br.s, 2H), 6.62 (m, 2H), 6.814 (m, 1H); ms: *m/z* 143 (100), 145 (31)
35	*n*-butyl	Cl				$C_{10}H_{15}ClN_2$	Purification: ethyl acetate:hexane (20:80) cc; Oily; ^{1}H NMR: δ 0.94 (t, 3H), 1.43 (m, 2H), 1.56 (m, 2H), 2.92 (t, 2H), 3.95 (br.s, 1H), 6.59 (dd, 1H, *J* = 1.6, 7.2 Hz), 6.76 (m, 2H); ms: *m/z* 199 (100), 201 (36)
36	*n*-butyl		Cl			$C_{10}H_{15}ClN_2$	^{1}H NMR: δ 0.98 (t, 3H), 1.47 (m, 2H), 1.64 (m, 2H), 3.1 (t, 2H), 3.2 (br.s), 6.61 (m, 3H); ms: *m/z* 199 (100), 201 (32)
37	*n*-butyl			F		$C_{10}H_{15}FN_2$	ref. 12
38	*n*-butyl			Cl		$C_{10}H_{15}ClN_2$	ref. 1
39	*n*-butyl			Br		$C_{10}H_{15}BrN_2$	Oily; ^{1}H NMR: δ 0.97 (t, 3H), 1.47 (m, 2H), 1.64 (m, 2H), 3.06 (t, 2H), 3.32 (br.s, 3H), 6.50 (d, 1H, *J* = 8.8), 6.83 (d, 1H, *J* = 2Hz), 6.89 (dd, 1H, *J* = 2.4, 8.4 Hz); ms: *m/z* 243 (100), 245 (100)
40	*n*-butyl			I		$C_{10}H_{15}IN_2$	Oily; ^{1}H NMR: δ 0.96 (t, 3H), 1.46 (m, 2H), 1.63 (m, 2H), 3.06 (t, 2H), 3.32 (br.s, 3H), 6.39 (d, 1H, *J* = 8.8), 6.98 (d, 1H, *J* = 2 Hz), 7.09 (dd, 1H, *J* = 2.1, 8.4 Hz); ms: *m/z* 291 (100)
41	*n*-butyl	Br				$C_{10}H_{15}BrN_2$	Oily; ^{1}H NMR: δ 0.91 (t, 3H), 1.45 (m, 2H), 1.58 (m, 2H), 2.91 (t, 2H), 3.28 (br.s, 1H), 3.98 (br.s, 2H), 6.64 (dd, 1H, *J* = 1.2, 7.6 Hz), 6.74 (t, 1H, *J* = 7.9 Hz), 6.91 (dd, 1H, *J* = 1.6, 8 Hz); ms: *m/z* 243 (100), 245 (100)
42	*n*-butyl	Cl		Cl		$C_{10}H_{14}Cl_2N_2$	Waxy; ^{1}H NMR: δ 0.92 (t, 3H), 1.38 (m, 2H), 1.92 (m, 2H), 3.43 (t, 2H), 6.72 (d, 1H, *J* = 1.2), 6.82 (d, 1H, *J* = 1.2); ms: *m/z* 233 (100), 235 (63), 237 (11)
43		CN				$C_7H_7N_3$	^{1}H NMR: δ 3.43 (br.s, 2H), 4.11 (br.s, 2H), 6.67 (t, *J* = 8 Hz, 1H), 6.84 (d, *J* = 8 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H); ms: *m/z* 134 (100)
44	*n*-butyl	CN				$C_{11}H_{15}N_3$	Oily; ^{1}H NMR (Deuteriochloroform + D_2O): δ 0.94 (t, 3H), 1.43 (m, 2H), 1.58 (m, 2H), 3.19 (t, 2H), 3.28 (br.s, 1H), 3.66 (br.s, 2H), 6.85 (m, 2H), 6.95 (dd, 1H, *J* = 1.6, 7.6 Hz); ms: *m/z* 190 (100)
45	*n*-butyl		CN			$C_{11}H_{15}N_3$	ms: *m/z* 190 (100)
46	*n*-butyl			CN		$C_{11}H_{15}N_3$	ref. 1
47	*n*-pentyl			CN		$C_{12}H_{17}N_3$	Not isolated, because it was immediately getting black colored
48	*n*-butyl				CN	$C_{11}H_{15}N_3$	mp 76–78°C; ^{1}H NMR: δ 0.97 (t, 3H), 1.44 (m, 2H), 1.65 (m, 2H), 3.09 (t, 2H), 4.28 (br.s), 6.78 (m, 2H), 6.91 (m, 1H); ms: *m/z* 190 (100)
49	*n*-butyl		Cl	CN		$C_{11}H_{14}ClN_3$	^{1}H NMR: δ 0.98 (t, 3H), 1.44 (m, 2H), 1.7 (m, 2H), 3.2 (t, 2H), 6.6 (s, 1H), 6.9 (s, 1H); ms: *m/z* 224 (100), 226 (33)
50	*n*-butyl			$COCH_3$		$C_{12}H_{18}N_2O$	ref. 14
51	*n*-butyl			NO_2		$C_{10}H_{15}N_3O_2$	ref. 15
52				CF_3		$C_7H_7F_3N_2$	Commercial
53		Br		CF_3		$C_7H_6BrF_3N_2$	Commercial
54		Cl			Cl	$C_6H_6Cl_2N_2$	refs. 16, and 17
55			F	F		$C_6H_6F_2N_2$	refs. 18, and 19
56		F	F	F		$C_6H_5F_3N_2$	refs. 19, and 20
57			Cl	Cl		$C_6H_6Cl_2N_2$	Commercial
58			Br	Br		$C_6H_6Br_2N_2$	ref. 21
59			CN	CN		$C_8H_6N_4$	ref. 22

values of 3.12 μg/mL. Dramatically reduced antifungal activity was also seen by changing the benzimidazole ring to indoles with similar substitutions (**108–110**). Further studies are needed to confirm these preliminary results and *in vivo* and mode of action studies are required to optimize the effectiveness of this series of compounds.

EXPERIMENTAL

Mp were measured with a capillary melting point apparatus Electrothermal 9100 and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded with VARIAN Mercury 400 FT-NMR spectrophotometer, δ scale (ppm) in deuteriochloroform, if not stated otherwise. LC/MS analyses were performed with Waters Alliance (equipped with a diode array UV detection monitoring at 254 nm) and Micromass ZQ by using ESI(+) method, if not stated otherwise. Elemental analyses were taken on a Leco 932 CHNS analyser; cc, column chromatography. Compound **89a** was synthesized as described in our previous study [1].

3-Chloro-2-nitrobenzonitrile (12). The mixture of 0.5 g (2.48 mmol) of 3-chloro-2-nitrobenzoic acid toluene (3 mL) and thionyl chloride (2 mL) were heated at 80°C for 4 h. Excess of thionyl chloride and solvent were evaporated, then the residue was stirred in ammonium hydroxide (5 mL) at room temperature for 1 h. The formed precipitate 3-chloro-2-nitrobenzamide was collected. The solid (0.46 g, 2.3 mmol) was added to a solution of PPSA (20 mL), and the mixture was refluxed for 48 h. The reaction mixture was directly carried out to a long silica gel column and eluted with hexanes (200 mL), then dichloromethane. Concentration of the dichloromethane gave the desired nitrile, as a white solid, 0.14 g (33.4%). Then eluting with 5% methanol in dichloromethane recovered 0.16 g of starting material. See Table 2 for spectral data.

2-Amino-3-nitrobenzonitrile (25). The mixture of **9** (0.3 g, 1.65 mmol) and saturated ethanolic ammonia solution (30 mL) were heated in a sealed tube at 120°C for 5 h, ethanol was removed, and washing with water of the residue gave pure compound, 0.2 g (74 %). See Table 3 for spectral data.

General procedure for synthesis of (17–24, 26–33). To a solution of **1–15** (5 mmol) in ethanol (5 mL), butyl or pentyl amine (15 mmol) was added and heated under reflux until the starting material was consumed (determined by TLC, 8–48 h). The mixture was cooled, water was added. The resultant yellow residue was crystallized from ethanol or purified by cc by using the mixture of ethyl acetate-hexane (30–40:70–60) as eluent (Table 3).

General procedure for synthesis of (34, 37, 38, 43–51, 55, 56). Appropriate nitro derivatives (3 mmol) in ethanol (30 mL) were reduced by hydrogenation using 40 psi of H_2 and 10% Pd-C until cessation of H_2 uptake. The catalyst was filtered off on a bed of Celite, washed with ethanol, and the filtrate was concentrated. This procedure was carried out at the atmospheric pressure for compound **33** (Table 4).

General procedure for synthesis of (35, 36, 39–42, 54). Compound **17**, **20–23** (1 mmol), tin(II) chloride dihydrate (0.75 g, 3.33 mmol), a granule tin in the mixture of ethanol (3 mL), hydrochloric acid (3 mL), (for 20 HBr and for 21 sulfuric acid were used without tin(II) chloride), and 1.5 mL water were stirred at room temperature for 6–7 h. For compound 40, the reaction mixture was heated under reflux for 3 h. Then, water and ethyl acetate were added. The pH was rendered basic by addition of an ammonium solution. The slurry was filtered on a Buchner, the resulting solid was washed with ethyl acetate. The combined organic phases were concentrated (Table 4).

General procedure for synthesis of 60–73, 75, 78–80, 83, 84, 90–97, 99–102, 104. The corresponding benzaldehydes (7.5 mmol) were dissolved in 25 mL ethanol and sodium metabisulfite (0.8 g) in 5 mL H_2O was added in portions. The reaction mixture was stirred vigorously and more ethanol was added. The mixture was kept in a refrigerator for a several hours. The precipitate was filtered and dried (yield over 93%). The mixture of these salts (0.5 mmol) and **34–59** (0.5 mmol) in *N*,*N*-dimethylformamide (1 mL) were heated at 120°C for 4 h. The reaction mixture was cooled, poured into water, and the solid was filtered.

7-Chloro-2-(4-fluorophenyl)-1H-benzimidazole (60). Purification, cc, ethyl acetate-hexane (1:3), mp 208°C, yield 56%. ^{1}H NMR δ (DMSO-d_6): 7.18 (t, 1H), 7.26 (dd, 1H, J = 0.8, 6.4 Hz), 7.4 (t, 2H), 7.52 (d, 1H, J = 6 Hz), 8.25 (br.s, 2H); ms: *m/z* 247 (M +1, 100), 249 (M +3, 34). *Anal.* Calcd for $C_{13}H_8ClFN_2$ HOH: C, 59.00; H, 3.81; N, 10.58. Found C, 58.96; H, 3.80; N, 10.54.

2-(4-Fluorophenyl)-1H-benzimidazole-7-carbonitrile (61). Purification, cc, ethyl acetate-hexane (1:1), mp 224–225°C, yield 47.4%. ^{1}H NMR δ (DMSO-d_6): 7.35 (t, 1H), 7.43 (t, 2H), 7.67 (d, 1H, J = 7.2 Hz), 7.86 (d, 1H, J = 7.2 Hz), 8.26 (br.s, 2H), 13.5 (br.s, 1H); ms: *m/z* 238 (M +1, 100). *Anal.* Calcd for $C_{14}H_8FN_3$ 0.1 HOH: C, 70.35; H, 3.46; N, 17.57. Found C, 70.44; H, 3.48; N, 17.15.

2-(4-Fluorophenyl)-5-(trifluoromethyl)-1H-benzimidazole (62). Purification, cc, ethyl acetate-hexane (1:1), mp 178–180°C, yield 46.4%. ^{1}H NMR δ (DMSO-d_6): 7.45 (m, 2H), 7.54 (dd, 1H, J = 1.2, 8.8 Hz), 7.79 (d, 1H, J = 8 Hz), 7.96 (s, 1H), 8.26 (m, 2H), 13.35 (br.s, 1H); ms: *m/z* 281 (M +1, 100). *Anal.* Calcd for $C_{14}H_8F_4N_2$: C, 60.00; H, 2.88; N, 10.00. Found C, 59.63; H, 2.89; N 9.93.

1-Butyl-7-chloro-2-phenyl-1H-benzimidazole (63). Purification, cc, ethyl acetate-hexane (1:4), oily, yield 51.5%. ^{1}H NMR δ: 0.8 (t, 3H), 1.18 (m, 2H), 1.76 (m, 2H), 4.49 (t, 2H), 7.2 (t, 1H), 7.26 (dd, 1H, J = 1.2, 7.4 Hz), 7.53 (m, 3H), 7.67 (m, 2H), 7.71 (dd, 1H, J = 1.2, 8 Hz); ms: *m/z* 285(M +1, 100), 287 (M +3, 36). *Anal.* Calcd for $C_{17}H_{17}ClN_2$: C, 71.69; H, 6.02; N, 9.84. Found C, 71.24; H, 6.15; N, 9.77.

1-Butyl-7-chloro-2-(4-fluorophenyl)-1H-benzimidazole (64). Purification, cc, ethyl acetate-hexane (1:3), mp 60°C, yield 32%. ^{1}H NMR δ: 0.8 (t, 3H), 1.18 (m, 2H), 1.75 (m, 2H), 4.46 (t, 2H), 7.25 (m, 4H), 7.66 (m, 3H); ms: *m/z* 303 (M +1, 100), 305 (M +3, 35). *Anal.* Calcd for $C_{17}H_{16}ClFN_2$: C, 67.44; H, 5.33; N, 9.25. Found C, 67.29; H, 5.27; N, 9.23.

7-Bromo-1-butyl-2-(4-fluorophenyl)-1H-benzimidazole (65). Purification, cc, ethyl acetate-hexane (1:1), mp 62°C, yield 53%. ^{1}H NMR δ: 0.79 (t, 3H), 1,18 (m, 2H), 1.73 (m, 2H), 4.48 (t, 2H), 7.15 (t, 1H), 7.24 (m, 2H), 7.46 (d, 1H, J = 8 Hz), 7.66 (m, 2H), 7.74 (d, 1H, J = 8.4 Hz); ms: *m/z* 347 (M +1, 100), 349 (M +3, 100). *Anal.* Calcd for $C_{17}H_{16}BrFN_2$ 0.2 HOH: C, 58.20 H; 4.71; N, 7.98. Found C, 58.11; H, 4.47; N, 8.08.

1-Butyl-2-(4-fluorophenyl)-1H-benzimidazole-7-carbonitrile (66). Purification, cc, ethyl acetate-hexane (2:8), mp 53–54°C, yield 40.5%. ^{1}H NMR δ: 0.86 (t, 3H), 1.3 (m, 2H), 1.85 (m, 2H), 4.54 (t, 2H), 7.29 (m, 2H), 7.44 (t, 1H), 7.71 (d, 1H, J = 7.2 Hz), 7.77 (m, 2H), 8.15 (d, 1H, J = 8.4 Hz); ^{13}C NMR δ: 164.2 (d, J = 250 Hz), 155.1, 143.8, 134.6, 131.75 (d, J = 8.3 Hz), 129.4, 125.7 (d, J = 2.5 Hz), 125.5, 123.0, 117.1, 116.4 (d, J = 22.1 Hz), 95.1, 45.4, 33.3, 19.5, 13.67; ms: *m/z* 294 (M +1, 100). *Anal.* Calcd for $C_{18}H_{16}FN_3$: C, 73.70; H, 5.50; N, 14.32. Found C, 73.84; H, 5.61; N, 14.09.

1-Butyl-6-chloro-2-(4-fluorophenyl)-1H-benzimidazole (67). Purification, cc, ethyl acetate-hexane (1:2), mp 100–

101°C, yield 39.7%. ^{1}H NMR δ: 0.88 (t, 3H), 1.27 (m, 2H), 1.75 (m, 2H), 4.16 (t, 2H), 7.19–7.28 (m, 3H), 7.39 (d, 1H, J = 1.6 Hz), 7.65–7.73 (m, 3H); ^{13}C NMR δ: 165.2 (d, J = 249 Hz), 153.8, 141.9, 136.5, 131.5 (d, J = 8.4 Hz), 128.7, 126.6, 123.3, 121, 116.2 (d, J = 22 Hz), 110.4, 44.9, 31.9, 20.1, 13.7; ms: *m/z* 303 (M +1, 100) 305 (M +3, 40). *Anal.* Calcd for $C_{17}H_{16}ClFN_2$: C, 67.44; H, 5.33; N, 9.25. Found C, 67.47; H, 5.31; N, 9.17.

1-Butyl-2-(4-fluorophenyl)-1H-benzimidazole-6-carbonitrile (68). Purification, cc, ethyl acetate-hexane (1:3), mp 128°C, yield 72% [26]. ^{1}H NMR δ: 0.88 (t, 3H), 1.28 (m, 2H), 1.79 (m, 2H), 4.23 (t, 2H), 7.25 (m, 2H), 7.55 (d, 1H, J = 8.4 Hz), 7.71 (m, 2H), 7.74 (s, 1H), 7.84 (d, 1H, J = 8 Hz); ^{13}C NMR δ: 164.2 (d, J = 250 Hz), 156.2, 146.2, 135.5, 131.5 (d, J = 8.4 Hz), 126.2, 125.9, 121.1, 120.1, 116.4 (d, J = 18 Hz), 115.3, 105.8, 45.2, 32.1, 20.2, 13.7; ms: *m/z* 294(M +1,100). *Anal.* Calcd for $C_{18}H_{16}FN_3$: C, 73.70; H, 5.50; N, 14.32. Found C, 73.48; H, 5.56; N, 14.15.

1-Butyl-5-fluoro-2-(4-fluorophenyl)-1H-benzimidazole (69). Purification, cc, ethyl acetate-hexane (1:3), mp 82–83°C, yield 29%. ^{1}H NMR δ: 0.86 (t, 3H), 1.26 (m, 2H), 1.77 (m, 2H), 4.19 (t, 2H), 7.06 (m, 1H), 7.25 (m, 2H), 7.32 (m, 1H), 7.46 (dd, 1H, J = 2, 9.4 Hz), 7.67 (m, 2H); ms: *m/z* 287(M +1, 100). *Anal.* Calcd for $C_{17}H_{16}F_2N_2$: C, 71.31; H, 5.63; N, 9.78. Found C, 71.26; H, 5.49; N, 9.84.

1-Butyl-5-chloro-2-(4-fluorophenyl)-1H-benzimidazole (70). Purification, cryst., ethyl acetate-hexane, mp 81–82°C, yield 31.5%. ^{1}H NMR δ: 0.87 (t, 3H), 1.25 (m, 2H), 1.76 (m, 2H), 4.18 (t, 2H), 7.18–7.37 (m, 4H), 7.68 (m, 2H), 7.77 (d, 1H, J = 2 Hz); ^{13}C NMR δ: 163.9 (d, J = 250 Hz), 154.1, 144.1, 134.4, 131 (d, J = 8.3 Hz), 128.2, 126.6, 123.4, 119.9, 116.2 (d, J = 21 Hz), 111.1, 44.9, 32, 20.1, 13.7; ms: *m/z* 303 (M +1, 100) 305 (M +3, 40). *Anal.* Calcd for $C_{17}H_{16}ClFN_2$: C, 67.44; H, 5.33; N, 9.25. Found C, 67.33; H, 5.25; N, 9.24.

1-Butyl-5-chloro-2-(pyridin-4-yl)-1H-benzimidazole (71). Purification, cryst., ethyl acetate-hexane, mp 96–98°C, yield 34%. ^{1}H NMR δ: 0.82 (t, 3H), 1.22 (m, 2H), 1.74 (m, 2H), 4.18 (t, 2H), 7.25 (dd, 1H, J = 2, 8.6 Hz), 7.29 (dd, 1H, J = 0.8, 8.8 Hz), 7.6 (dd, 2H, J = 1.6, 4.6 Hz), 7.75 (t, 1H), 8.75 (dd, 2H, J = 1.6, 4.4 Hz); ms: *m/z* 286 (M +1, 100), 288 (M +3, 35). *Anal.* Calcd for $C_{16}H_{16}ClN_3$ 0.25 HOH: C, 66.2; H, 5.73; N, 14.48. Found C, 66.4; H, 5.56; N, 14.29.

1-Butyl-5-bromo-2-(4-fluorophenyl)-1H-benzimidazole (72). Purification, ethyl acetate-hexane (2:8), mp 77–79°C, yield 84% [27]. ^{1}H NMR δ: 0.86 (t, 3H), 1.25 (m, 2H), 1.75 (m, 2H), 4.18 (t, 2H), 7.19–7.31 (m, 3H), 7.4 (dd, 1H, J = 1.6, 8.8 Hz), 7.68 (m, 2H), 7.92 (d, 1H, J = 1.2 Hz); ^{13}C NMR δ: 164.2 (d, J = 249 Hz), 153.9, 144.6, 134.8, 131.5 (d, J = 8.4 Hz), 126.6, 126, 123, 116.4 (d, J = 22 Hz), 115.6, 111.55, 44.9, 32, 20.1, 13.7; ms: *m/z* 347 (M +1, 100) 349 (M +3, 100). *Anal.* Calcd for $C_{17}H_{16}BrFN_2$: C, 58.80; H, 4.64; N, 8.07. Found C, 58.51; H, 4.68; N, 8.13.

1-Butyl-5-iodo-2-(4-fluorophenyl)-1H-benzimidazole (73). Purification, ethyl acetate-hexane (2:8), mp 125–126°C, yield 88%. ^{1}H NMR δ: 0.86 (t, 3H), 1.25 (m, 2H), 1.75 (m, 2H), 4.18 (t, 2H), 7.15–7.29 (m, 3H), 7.58 (d, 1H, J = 8.8 Hz), 7.69 (m, 2H), 8.14 (s, 1H); ms: *m/z* 395 (M +1, 100). *Anal.* Calcd for $C_{17}H_{16}FIN_2$: C, 51.79; H, 4.09; N, 7.11. Found C, 51.72; H, 4.24; N,7.20.

1-Butyl-5-nitro-2-(4-fluorophenyl)-1H-benzimidazole (75). Purification, cc, ethyl acetate-hexane (3:7), mp 160–162°C, yield 62%. ^{1}H NMR δ: 0.86 (t, 3H), 1.27 (m, 2H), 1.77 (m, 2H), 4.26 (t, 2H), 7.25 (m, 2H), 7.45 (d, 1H, J = 9.2 Hz), 7.71 (m, 2H), 8.21 (dd, 1H, J = 2.4, 9 Hz), 8.64 (d, 1H, J = 2.4 Hz); ms: *m/z* 314 (M +1, 100). *Anal.* Calcd for $C_{17}H_{16}FN_3O_2$: C, 65.17; H, 5.15; N, 13.41. Found C, 65.37; H, 5.20; N, 13.35.

1-Butyl-2-(pyridin-2-yl)-1H-benzimidazole-5-carbonitrile (78). Purification, cc, ethyl acetate-hexane (1:1), mp 117–119°C, yield 38%. ^{1}H NMR δ: 0.93 (t, 3H), 1.37 (m, 2H), 1.85 (m, 2H), 4.85 (t, 2H), 7.41 (m, 1H), 7.51 (d, 1H, J = 8.8 Hz), 7.57 (dd, 1H, J = 1.6, 8.2 Hz), 7.88 (td, 1H, J = 1.6, 8 Hz), 8.14 (d, 1H, J = 0.8 Hz), 8.39 (d, 1H, J = 7.6 Hz), 8.72 (dd, 1H, J = 1, 4 Hz); ^{13}C NMR δ: 152.5, 150.0, 149.0, 142.3, 139.5, 137.2,126.5, 125.3, 125.2, 124.6, 120.1, 111.4, 105.8, 45.9, 32.3, 20.2, 13.8; ms: *m/z* 277 (M +1, 100). *Anal.* Calcd for $C_{17}H_{16}N_4$ 0.15 $C_4H_8O_2$: C, 73.01; H, 5.98; N, 19.35. Found C, 73.42; H, 5.88; N, 19.12.

1-Butyl-2-(pyridin-3-yl)-1H-benzimidazole-5-carbonitrile (79). Purification, cc, ethyl acetate-hexane (2:1), mp 130–131°C, yield 52%. ^{1}H NMR δ: 0.85 (t, 3H), 1.26 (m, 2H), 1.77 (m, 2H), 4.25 (t, 2H), 7.44–7.59 (m, 3H), 8.06 (d, 1H, J = 7.6 Hz), 8.10 (s, 1H), 8.77 (d, 1H, J = 4.8 Hz), 8.94 (d, 1H, J = 1.2 Hz); ^{13}C NMR δ: 153.4, 151.5, 149.8, 142.9, 138.6, 137.1, 126.6, 126.3, 125.4, 123.9, 119.9, 111.6, 106.2, 45.2, 32.2, 20.1, 13.7; ms: *m/z* 277(M +1, 100). *Anal.* Calcd for $C_{17}H_{16}N_4$: C, 73.87; H, 5.84; N, 20.27. Found C, 73.76; H, 5.82; N, 20.01.

1-Butyl-2-(pyridin-4-yl)-1H-benzimidazole-5-carbonitrile (80). Purification, cc, chloroform-isopropanol (10:2), mp 135–137°C, yield 47%. ^{1}H NMR δ (DMSO-d_6): 0.74 (t, 3H), 1.12 (m, 2H), 1.62 (m, 2H), 4.41 (t, 2H), 7.74 (dd, 1H, J = 1,6, 8.4 Hz), 7.83 (dd, 2H, J = 1.6, 4.4 Hz), 7.95 (d, 1H, J = 8.8 Hz), 8.3 (d, 1H, J = 1.4 Hz), 8.82 (dd, 2H, J = 1.6, 4.4 Hz); ^{13}C NMR δ (DMSO-d_6): 153.5, 151.1, 142.6, 139.4, 137.8, 127, 125.4, 124.1, 120.4, 113.6, 105.4, 44.9, 31.9, 19.8, 13.9; ms: *m/z* 277(M +1, 100). *Anal.* Calcd for $C_{17}H_{16}N_4$. 0.5 HOH: C, 71.55; H, 6.00; N, 19.63. Found C, 71.28; H, 5.73; N, 19.33.

1-Pentyl-2-phenyl-1H-benzimidazole-5-carbonitrile (83). Purification, cc, ethyl acetate-hexane (1:3), mp 124–125°C, yield 17.5%. ^{1}H NMR δ: 0.83 (t, 3H), 1.24 (m, 4H), 1.8 (m, 2H), 4.25 (t, 2H), 7.47 (d, 1H, J = 7.6 Hz), 7.56 (m, 4H), 7.7 (m, 2H), 8.13 (d, 1H, J = 0.8 Hz); ^{13}C NMR δ: 156.4, 142.9, 138.5, 130.6, 129.8, 129.4, 129.1, 126.2, 125.2, 120.1, 111.3, 105.7, 45.2, 29.6, 28.9, 22.2, 14.0; ms: *m/z* 290 (M +1, 100). *Anal.* Calcd for $C_{19}H_{19}N_3$: C, 78.86; H, 6.62; N, 14.52. Found C, 78.66; H, 6.72; N, 14.39.

1-Butyl-6-chloro-2-(4-fluorophenyl)-1H-benzimidazole-5-carbonitrile (84). Purification, cc, ethyl acetate-hexane (1:4), mp 138°C, yield 34%. ^{1}H NMR δ: 0.89 (t, 3H), 1.28 (m, 2H), 1.77 (m, 2H), 4.21 (t, 2H), 7.27 (t, 2H), 7.53 (s, 1H), 7.7 (m, 2H), 8.1 (s, 1H); ^{13}C NMR δ: 164.1 (d, J = 251 Hz), 156.0, 141.3, 138.9, 131.3 (d, J = 8.4 Hz), 130.2, 126.1, 125.4 (d, J = 3.1 Hz), 116.9, 116.3 (d, J = 22 Hz), 111.7, 107.0, 45.0, 31.7, 19.8, 13.4; ms: *m/z* 328 (M +1, 100) 330 (M +3, 35). *Anal.* Calcd for $C_{18}H_{15}ClFN_3$: C, 65.96; H, 4.61; N, 12.82. Found C, 65.75; H, 4.59; N, 12.87.

1-[1-Butyl-2-(4-fluorophenyl)-1H-benzimidazol-5-yl]ethanone (90). Purification, cc, ethyl acetate-hexane (1:3), mp 75–77°C, yield 21.5%. ^{1}H NMR δ: 0.88 (t, 3H), 1.27 (m, 2H), 1.83 (m, 2H), 2.68 (s, 3H), 4.35 (t, 2H), 7.28 (m, 2H), 7.56 (d, 1H, J = 8.4 Hz), 7.85 (m, 2H), 8.11 (d, 1H, J = 8.8 Hz), 8.46

(s, 1H); ^{13}C NMR δ: 198.1, 163.9 (d, $J = 250$ Hz), 154.8, 142.8, 139.1, 132.5, 131.4 (d, $J = 8.5$ Hz), 126.4 8 (d, $J = 3.4$ Hz), 123.2, 121.8, 116.3 (d, $J = 22$ Hz), 110.3, 44.9, 32.1, 26.9, 20.1, 13.7; ms: *m/z* 311 (M +1,100). *Anal.* Calcd for $C_{19}H_{19}FN_2O$: C, 73.53; H, 6.17; N, 9.03. Found C, 73.82; H, 6.53; N, 8.58.

1-Butyl-2-(4-fluorophenyl)-1H-benzimidazole-4-carbonitrile (91). Purification, cc, ethyl acetate-hexane (2:8), mp 83–84°C, yield 44.5%. ^{1}H NMR δ: 0.87 (t, 3H), 1.26 (m, 2H), 1.76 (m, 2H), 4.24 (t, 2H), 7.25 (m, 2H), 7.35 (t, 1H), 7.63 (dd, 2H, J = 1.6, 7.6 Hz), 7.74 (m, 2H); ^{13}C NMR δ: 164.1 (d, $J = 250$ Hz), 155.2, 144.1, 136.1, 131.8 (d, $J = 8.4$ Hz), 127.5, 126 (d, $J = 3.1$ Hz), 122.6, 117.0, 116.4 (d, $J = 21.3$ Hz), 115.0, 103.3, 45.1, 32.0, 20.0, 13.6; ms: *m/z* 294 (M +1,100). *Anal.* Calcd for $C_{18}H_{16}FN_3$: C, 73.70; H, 5.50; N, 14.33. Found C, 74.19; H, 5.74; N, 13.94.

7-Bromo-5-(trifluoromethyl)-2-phenyl-1H-benzimidazole (92). Purification, cc, ethyl acetate-hexane (1:1), mp 179–181°C, yield 59%. ^{1}H NMR δ (DMSO-d_6): 7.57 (m, 3H), 7.72 (s, 1H), 7.88 (s, 1H), 8.2 (d, 2H, $J = 5.2$ Hz), 13.98 (br.s, 1H); ms: *m/z* 341 (M +1,100) 343 (M +3,100). *Anal.* Calcd for $C_{14}H_8BrF_3N_2$: C, 49.29; H, 2.36; N, 8.21. Found C, 49.1; H, 2.41; N, 8.17.

5,6-Difluoro-2-phenyl-1H-benzimidazole (93). Purification, cc, ethyl acetate-hexane (1:1), mp 213–215°C, yield 77%. ^{1}H NMR δ (DMSO-d_6): 7.43 (m, 5H), 7.99 (d, 2H, $J = 6.8$ Hz), 13.03 (br.s, 1H); ms: *m/z* 231 (M +1,100). *Anal.* Calcd for $C_{13}H_8F_2N_2$: C, 67.82; H, 3.50; N, 12.17. Found C, 68.00; H, 3.57; N, 11.98.

5,6-Difluoro-2-(4-fluorophenyl)-1H-benzimidazole (94). Purification, cc, ethyl acetate-hexane (1:2), mp 207–209°C, yield 81%. ^{1}H NMR δ (DMSO-d_6): 7.4 (m, 2H), 7.64 (t, 2H), 8.17 (m, 2H); ms: *m/z* 249 (M +1,100). *Anal.* Calcd for $C_{13}H_7F_3N_2$: C, 62.91; H, 2.84; N, 11.29. Found C, 63.04; H, 2.84; N, 11.28.

5,6,7-Trifluoro-2-phenyl-1H-benzimidazole (95). Purification, cryst., ethyl acetate-hexane, mp 215–216°C, yield 77%. ^{1}H NMR δ (DMSO-d_6): 7.4–7.66 (m, 4H), 8.17 (dd, 2H, J = 1.2, 8 Hz); ms: *m/z* 249 (M +1,100). *Anal.* Calcd for $C_{13}H_7F_3N_2$. 0.5 HOH: C, 60.70; H, 3.13; N, 10.89. Found C, 60.75; H, 3.06; N, 10.96.

5,6-Difluoro-2-(pyridin-4-yl)-1H-benzimidazole (96). Purification, cc, ethyl acetate-ethanol (95:5) mp > 300°C, yield 61.5%. ^{1}H NMR δ (DMSO-d_6): 7.71 (br.s, 2H), 8.04 (m, 2H), 8.74 (m, 2H), 13.5 (br.s, 1H); ms: *m/z* 232 (M +1,100). *Anal.* Calcd for $C_{12}H_7F_2N_3$: C, 62.34; H, 3.05; N, 18.17. Found C, 62.77; H, 3.29; N, 17.65.

2-[4-(Benzyloxy)phenyl]-5,6-difluoro-1H-benzimidazole (97). Purification, cc, ethyl acetate-hexane (1:2), mp 215–217°C, yield 33.7%. ^{1}H NMR δ (DMSO-d_6): 5.17 (s, 2H), 7.16 (d, 2H, $J = 9.2$ Hz), 7.32–7.52 (m, 6H), 7.64 (m, 1H), 8.05 (d, 2H, $J = 8.8$ Hz), 12.98 (s, 1H); ms: *m/z* 337 (M +1,100). *Anal.* Calcd for $C_{20}H_{14}F_2N_2O$. 0.1 $C_4H_8O_2$. 0.25 HOH: C, 70.07; H, 4.41; N, 8.01. Found C, 70.04; H, 4.13; N, 8.14.

5,6-Dichloro-2-(4-fluorophenyl)-1H-benzimidazole (99). Purification, cryst., ethyl acetate-hexane, mp 278–280°C, yield 69.5%. ^{1}H NMR δ: 7.19 (m, 2H), 7.58 (s, 1H), 7.82 (s, 1H), 8.17 (m, 2H); ms: *m/z* 281 (M +1,100) 283 (M +3, 63) 285 (M +5, 13). *Anal.* Calcd for $C_{13}H_7Cl_2FN_2$: C, 55.54; H, 2.51; N, 9.97. Found C, 55.52; H, 2.46; N, 9.92.

4,7-Dichloro-2-(4-fluorophenyl)-1H-benzimidazole (100). Purification, cc, ethyl acetate-hexane (2:8), mp 242°C, yield 71.4%. ^{1}H NMR δ (DMSO-d_6): 7.31 (s, 2H), 7.43 (t, 2H), 8.38 (m, 2H), 13.48 (br.s, 1H); ms: *m/z* 281 (M +1, 100) 283 (M +3, 72) 285 (M +5, 15). *Anal.* Calcd for $C_{13}H_7Cl_2FN_2$. 0.25 $C_4H_8O_2$. 0.4 HOH: C, 54.18; H, 3.18; N, 9.03. Found C, 54.03; H, 3.07; N, 9.07.

5,6-Dibromo-2-(4-fluorophenyl)-1H-benzimidazole (101). Purification, cryst., ethanol, mp 273–275°C, yield 68.4%. ^{1}H NMR δ (DMSO-d_6): 7.4 (m, 2H), 7.96 (s, 2H), 8.2 (m, 2H); ms: *m/z* 369 (M +1, 50), 371 (M +3, 100), 373 (M +5, 48). *Anal.* Calcd for $C_{13}H_7Br_2FN_2$ 0.25 HOH: C, 41.69; H, 2.02; N, 7.48. Found C, 41.50; H, 1.99; N, 7.61.

2-(4-Fluorophenyl)-1H-benzimidazole-5,6-dicarbonitrile (102). Purification, cc, (1) ethyl acetate-hexane (1:1), (2) ethyl acetate, (3) ethyl acetate-ethanol (95:5), mp > 300°C, yield 59.8%. ^{1}H NMR δ (DMSO-d_6): 7.48 (t, 2H), 8.31 (m, 2H), 8.44 (s, 2H); ms: *m/z* 263 (M +1,100). *Anal.* Calcd for $C_{15}H_7FN_4$. 0.75 HOH: C, 65.33; H, 3.11; N, 20.32. Found C, 64.94; H, 3.76; N, 20.53.

1-Butyl-5,7-dichloro-2-(4-fluorophenyl)-1H-benzimidazole (104). Purification, cc, (1) dichloro-methane-hexane (2:8) (2) ethyl acetate-ethanol (1:9), mp 58°C, yield 27.3%. ^{1}H NMR δ: 0.81 (t, 3H), 1.17 (m, 2H), 1.74 (m, 2H), 4.44 (t, 2H), 7.25 (m, 3H), 7.65 (m, 3H); ^{13}C NMR δ: 163.8 (d, $J = 250$ Hz), 155.8, 145.6, 131.6 (d, $J = 8.4$ Hz), 130.1, 128.0, 126.0 (d, $J = 3.8$ Hz), 124.5, 118.6, 116,8, 116.1 (d, $J = 22$ Hz), 45.7, 34.0, 19.4, 13.4; ms: *m/z* 337 (M +1, 100) 339 (M +3, 60) 341 (M +5, 11). *Anal.* Calcd for $C_{17}H_{15}Cl_2FN_2$: C, 60.55; H, 4.48; N, 8.31. Found C, 60.14; H, 4.44; N, 8.32.

1-Butyl-5-trimethylsilanylethylnyl-2-(4-fluorophenyl)-1H-benzimidazole (74a). To the mixture of **73** (0.69 mmol, 0.272 g) and (trimethylsilyl)acetylene (0.081g) in *N,N*-dimethyl formamide (1 mL) and triethylamine (1 mL) 10 mg of bis(triphenyl-phosphine)palladium (II) chloride and 2 mg of copper(I) iodide were added, and the mixture was stirred for 4.5 h at 45°C. The solvent was then removed *in vacuo* and the resulting residue was dissolved in acetonitrile and ether and washed with water. The solvent was removed *in vacuo*. The crude product was used without purification, yield 0.100 g. ms: *m/z* 365 (M +1, 100).

1-Butyl-5-ethynyl-2-(4-fluorophenyl)-1H-benzimidazole (74). 0.1 g (0.27 mmol) of **74a** and 1*N* potassium hydroxide (0.5 mL) was added 2.5 mL methanol. The mixture was stirred for 1.5 h at 25°C. The solvent was then removed *in vacuo*. The residue was purified by cc chloroform-ethyl acetate (20:0.5), mp 114–115°C, yield 31%. ^{1}H NMR δ: 0.86 (t, 3H), 1.26 (m, 2H), 1.76 (m, 2H), 3.06 (s, 1H), 4.19 (t, 2H), 7.24 (m, 2H), 7.34 (d, 1H, $J = 8.8$ Hz), 7.45 (dd, 1H, J = 1.6, 8.2 Hz), 7.69 (m, 2H), 7.96 (s, 1H); ^{13}C NMR δ: 163.7 (d, $J = 249$ Hz), 153.9, 142.8, 135.9, 131.24 (d, $J = 8.4$Hz), 126.9, 126.5 (d, $J = 2.8$ Hz), 124.1, 116.0, 116.02 (d, $J = 22.1$ Hz), 110.2, 84.4, 75.7, 44.6, 31.9, 19.9, 13.5; ms: *m/z* 293 (M +1, 100). *Anal.* Calcd for $C_{19}H_{17}FN_2$: C, 78.05; H, 5.86; N, 9.58. Found C, 77.69; H, 5.88; N, 9.46.

5-Amino-1-butyl-2-(4-fluorophenyl)-1H-benzimidazole HCl (76). Compound **75** (0.24 g, 0.767 mmol), tin(II) chloride dihydrate (0.375 g, 1.66 mmol), a granule tin in the mixture of ethanol (2 mL), hydrochloric acid (2 mL), and 1 mL water were stirred at 50°C for 2 h. Then water was added, pH was rendered basic by addition of dilute sodium hydroxide solution, extracted with ethyl acetate. The slurry was filtered on a Buchner, the resulting solid was washed with ethyl acetate.

The combined organic phases was concentrated, crystallization of crude product from ethanolic hydrogen chloride gave **76**, mp 265–267°C, yield 57.1%. ^{1}H NMR δ (DMSO-d_6): 0.75 (t, 3H), 1.16 (m, 2H), 1.68 (m, 2H), 4.36 (t, 2H), 7.29 (d, 1H, J = 8.4 Hz), 7.55 (m, 3H), 7.95 (m, 3H); ms: m/z 284 (M +1, 100). *Anal.* Calcd for $C_{17}H_{18}FN_3$. HCl: C, 63.85; H, 5.99; N, 13.14. Found C, 63.59; H, 5.96; N, 12.98.

5-Azido-1-butyl-2-(4-fluorophenyl)-1H-benzimidazole (77). A cooled solution of **76** (0.16 g, 0.5 mmol) was dissolved in 2 mL of aqueous 9*M* HCl and slowly a sodium nitrite aqueous solution (0.76 mL, 1.2 mmol) was added. The reaction temperature was not allowed to rise above 5°C. The mixture was stirred in an ice bath for 1 h. A solution of 0.6 mL of sodium azide (1.7 mmol) and sodium acetate (0.25g) was added at 0°C and stirred for 1 h. Then, the mixture was allowed to warm to room temperature and stirred for 1 h. Potassium carbonate is added to neutralize the mixture and extracted with ethyl acetate. The solvent was then removed *in vacuo*, the residue was chromatographed by using ethyl acetate-hexane (2:8), mp 85–87°C, yield 25.2%. ^{1}H NMR δ: 0.87 (t, 3H), 1.27 (m, 2H), 1.77 (m, 2H), 4.19 (t, 2H), 6.99 (dd, 1H, J = 2, 8.6 Hz), 7.23 (m, 2H), 7.36 (d, 1H, J = 8.8 Hz), 7.46 (d, 1H, J = 2 Hz), 7.69 (m, 2H); ^{13}C NMR δ: 163.9 (d, J = 249 Hz), 154.2, 144.2, 135.2, 133.6, 131 (d, J = 8.2 Hz), 126.8, 116.3 (d, J = 21.4 Hz), 115, 111.3, 109.9, 44.9, 32.1, 20.1, 13.7; ms: m/z 310 (M +1, 100). *Anal.* Calcd for $C_{17}H_{16}FN_5$: C, 66.00; H, 5.21; N, 22.64. Found C, 66.09; H, 5.28; N, 22.32.

N-[2-(butylamino)-5-cyanophenyl]pyridazine-4-carboxamide (81a). A mixture of 4-pyridazinecarboxylic acid (0.11 g, 0.89 mmol), triethylamine (0.41 mL), 3-amino-4-butylaminobenzonitrile (0.18 g, 0.95 mmol), and *O*-(Benzotriazol-1-yl)-*N*,*N*,*N′*,*N′*-tetramethyl-uronium hexafluorophosphate (HBTU) (0.366 g, 0.96 mmol) in *N*,*N*-dimethylformamide (1 mL) was stirred at room temperature for 20 h, water was added to the reaction mixture, then extracted with ethyl acetate and evaporated. The residue was purified by cc (4:1 toluene/methanol), to give **81a** as a white solid (6.75 g, 71%); mp 214–215°C; ^{1}H NMR (DMSO-d_6) δ: 0.89 (t, 3H), 1.35 (m, 2H), 1.51 (m, 2H), 3.15 (q, 2H), 6.38 (t, 1H, J = 6 Hz, deuterium oxide-exchangeable), 6.76 (d, 1H), 7.52 (m, 2H), 8.14 (m, 1H), 9.51 (d, 1H, J = 5.2 Hz), 9.68 (s, 1H), 10.1 (s, 1H, deuterium oxide-exchangeable), ms: m/z 296 (M +1, 100).

1-Butyl-2-(pyridazin-4-yl)-1H-benzimidazole-5-carbonitrile (81). 0.1 g (0.33 mmol) of **81a** and 0.1 g of sodium acetate was dissolved in 1 mL glacial acetic acid. The mixture was stirred for 4.5 h at 100°C. Then poured into ice-water and filtered. The precipitate was purified by silicagel cc (ethyl acetate-ethanol, 10:0.1), mp 148°C, yield 38%. ^{1}H NMR δ: 0.94 (t, 3H), 1.36 (m, 2H), 1.87 (m, 2H), 4.35 (t, 2H), 7.57 (d, 1H, J = 8 Hz), 7.66 (dd, 1H, J = 1.6, 8.6 Hz), 7.91 (dd, 1H, J = 2.4, 5.6 Hz), 8.20 (s, 1H), 9.47 (dd, 1H, J = 0.8, 5.8 Hz), 9.63 (m, 1H); ms: m/z 278 (M +1, 100). *Anal.* Calcd for $C_{16}H_{15}N_5$: C, 69.30; H, 5.45; N, 25.25. Found C, 69.81; H, 5.80; N, not available.

N-[2-(butylamino)-5-cyanophenyl]pyrazine-2-carboxamide (82a). 0.124 g (1 mmol) of pyrazinecarboxylic acid, thionyl chloride (2 mL), and toluene (5 mL) were heated at reflux for 4 h. After removal of the solvent, a mixture of 3-amino-4-butylaminobenzonitrile 0.189 g (1 mmol), dichloromethane (5 mL), and pyridine (0.5 mL) were added, the residue and the whole was stirred and reflux overnight. The reaction mixture was evaporated, washed with sodium carbonate solution (5%), extracted with ethyl acetate, and washed with water. The organic layer was dried over sodium sulfate, and evaporated. The residue was purified by silicagel cc (ethyl acetate-hexane, 50%), mp 130–133°C, yield 0.11 g, 37.28%. ^{1}H NMR (DMSO-d_6): δ 0.87 (t, 3H), 1.33 (m, 2H), 1.49 (m, 2H), 3.12 (q, 2H), 6.16 (t, 1H, J = 5.6 Hz, deuterium oxide-exchangeable), 6.74 (m, 1H), 7.48 (m, 2H), 8.84 (m, 1H), 8.91 (d, 1H, J = 2.8 Hz), 9.23 (d, 1H, J = 1.6 Hz), 10.16 (s, 1H, deuterium oxide-exchangeable); ^{13}C NMR (DMSO-d_6): δ 163.4, 148.5, 148.2, 145.7, 144.6, 143.9, 132.7, 131.6, 122.86, 120.7, 111.25, 95.8, 42.69, 31.1, 20.3, 14.4; ms: m/z 296 (M +1, 100).

1-Butyl-2-(pyrazin-2-yl)-1H-benzimidazole-5-carbonitrile (82). 0.1 g (0.33 mmol) of **82a** and 0.1 g of sodium acetate was dissolved in 1 mL glacial acetic acid. The mixture was stirred for 4.5 h at 100°C. Then poured into ice-water and filtered. The precipitate was purified by silicagel cc (ethyl acetate-hexane 1:1), mp 174–175°C, yield 33%. ^{1}H NMR δ (DMSO-d_6): 0.87 (t, 3H), 1.3 (m, 2H), 1.77 (m, 2H), 4.82 (t, 2H), 7.77 (d, 1H, J = 8 Hz), 7.98 (d, 1H, J = 8.4 Hz), 8.37 (s, 1H), 8.84 (dd, 2H, J = 2.4, 10.2 Hz), 9.51 (s, 1H); ^{13}C NMR δ (DMSO-d_6): 150.3, 146.1, 145.9, 145.5, 144.3, 142.1, 139.9, 127.3, 125.6, 120.3, 113.5, 105.6, 45.7, 32.4, 20.0, 14.1; ms: m/z 278 (M +1, 100). *Anal.* Calcd for $C_{16}H_{15}N_5$: C, 69.30; H, 5.45; N, 25.25. Found C, 69.00; H, 5.44; N, 24.84.

1-Butyl-2-(4-fluorophenyl)-1H-benzimidazol-5-carboxaldehyde (85). To a solution of **I** (0.293 g, 1 mmol) in dry dichloromethane (20 mL), 3 mL of DIBAL (1.0*M* solution in dichloromethane) was added and the mixture was heated at reflux for 3h under nitrogen atmosphere. Cool dilute sulfuric acid (15 mL) was added and stirred overnight, dichloromethane was removed and the residue was neutralized with dilute sodium carbonate solution, then extracted with ethyl acetate and evaporated. The residue was purified by silicagel cc (ethyl acetate-hexane 2:3), mp 85–86°C, yield 31.5%. ^{1}H NMR δ: 0.885 (t, 3H), 1.29 (m, 2H), 1.79 (m, 2H), 4.26 (t, 2H), 7.26 (m, 2H), 7.52 (d, 1H, J = 8.4 Hz), 7.72 (m, 2H), 7.9 (dd, 1H, J = 1.2, 8.8 Hz), 8.27 (s, 1H), 10.1 (s, 1H); ^{13}C NMR δ: 192.3, 164.05 (d, J = 250 Hz), 155.2, 143.1, 140.1, 132.2, 131.5 (d, J = 9.1 Hz), 126.3 (d, J = 1.1Hz), 124.3, 123.45, 116.3 (d, J = 22 Hz), 110.9, 45.1, 32.1, 20.1, 13.7; ms: m/z 297 (M +1, 100). *Anal.* Calcd for $C_{18}H_{17}FN_2O$: C, 72.96; H, 5.78; N, 9.45. Found C, 73.05; H, 6.01; N, 9.10.

1-Butyl-2-(4-fluorophenyl)-1H-benzimidazole-5-carbaldehyde O-methyloxime (86). A solution of **85** (0.1 g, 0.33 mmol) and of methoxylamine hydrochloride (0.028 g, 0.33 mmol) in 1 mL of pyridine and 3 mL of absolute ethanol was refluxed for 3 h. Solvent was removed *in vacuo*, water was added and extracted with ethyl acetate and evaporated. The residue was crystallized from ethanol, mp 104–105°C, yield 38.3%. ^{1}H NMR δ (DMSO-d_6): 0.78 (t, 3H), 1.17 (m, 2H), 1.67 (m, 2H), 3.93 (s, 3H), 4.32 (t, 2H), 7.45 (t, 2H), 7.65 (dd, 1H, J = 1.4, 8.5 Hz), 7.71 (d, 1H, J = 8.5 Hz), 7.86 (m, 2H), 7.91 (s, 1H), 8.36 (s, 1H); ms: m/z 326 (M +1, 100). *Anal.* Calcd for $C_{19}H_{20}FN_3O$: C, 70.12; H, 6.20; N, 12.92. Found C, 70.34; H, 6.30; N, 12.61.

1-Butyl-2-(4-fluorophenyl)-N′-hydroxy-1H-benzimidazole-5-carboximidamide (87). To a stirring solution of compound **I** (1 mmol, 0.293 g) in ethanol (50 mL) was added hydroxylamine hydrochloride (1.43 mmol, 0.1 g) followed by *N*,*N*,-diisopropylethylamine (1.43 mmol, 0.184 g). The solution was heated to reflux and after 6 h, it was concentrated. Residue was washed with water and crystallized from ethanol, mp 230–233°C, yield 66%. ^{1}H NMR δ (DMSO-d_6): 0.72 (t, 3H), 1.1 (m, 2H), 1.6 (m, 2H), 4.26 (t, 2H), 5.84 (s, 2H), 7.40 (t, 2H), 7.62 (m, 2H), 7.81 (m, 2H), 7.95 (s, 1H), 9.54 (s, 1H); ms: *m*/*z* 327 (M +1, 100). *Anal.* Calcd for $C_{18}H_{19}FN_4O\cdot0.4$ HOH.$\cdot$0.25 C_2H_6O: C, 64.38; H, 6.22; N, 16.23. Found C, 64.46; H, 5.79; N, 15.93.

1-Butyl-2-(4-fluorophenyl)-5-(5-methyl-1,2,4-oxadiazol-3-yl)-1H-benzimidazole (88). To a stirring solution of **87** (0.070 g, 0.214 mmol) in 1,2-dichloroethane was added acetic anhydride (1 g, 0.97 mL, 10.2 mmol) and then the mixture was heated to 75°C. After 10 h, the reaction was cooled to room temperature and concentrated under reduced pressure. Water was added and the mixture was made alkaline with dilute sodium carbonate solution, then extracted with ethyl acetate. The organic layer was washed with water and evaporated, the residue was purified by cc eluting with first ethyl acetate-hexane 50%, later ethyl acetate-ethanol (99:1) to give **88** (0.025 g, 33.3%), mp 120–122°C, ^{1}H NMR δ: 0.86 (t, 3H), 1.27 (m, 2H), 1.78 (m, 2H), 2.66 (s, 3H), 4.22 (t, 2H), 7.23 (t, 2H), 7.47 (d, 1H, $J = 8$ Hz), 7.71 (m, 2H), 8.03 (d, 1H, $J = 8.8$ Hz), 8.51 (s, 1H); ms: *m*/*z* 351 (M +1, 100). *Anal.* Calcd for $C_{20}H_{19}FN_4O\cdot0.1$ $C_4H_8O_2$: C, 68.21; H, 5.56; N, 15.59. Found C, 68.35; H, 5.54; N, 15.36.

2-(4-Fluorophenyl)-1-propyl-5-(1H-tetrazol-5-yl)-1H-benzimidazole (89). A mixture of **89a** (0.1 g, 0.358 mmol), sodium azide (0.11 g, 1.7 mmol), and ammonium chloride (0.11 g, 2.056 mmol) in *N*,*N*-dimethylformamide (1 mL) was stirred at 145°C for 24 h. After cooling, the mixture was diluted with water, acidified to pH 3 with dilute HCl and extracted with ethyl acetate. The organic layer was washed with water and evaporated. The residue was purified by c.c. eluting with first ethyl acetate, later ethyl acetate-ethanol (9:1) to give **89**, mp 126–128°C, yield 19.1%. ^{1}H NMR δ: 0.68 (t, 3H), 1.64 (m, 2H), 4.26 (t, 2H), 7.39 (t, 2H), 7.83 (m, 3H), 7.97 (d, 1H, $J =$ 7.6 Hz), 8.32 (s, 1H); ^{13}C NMR δ (DMSO-d_6): 163.7 (d, $J =$ 250 Hz), 163.15, 156.7, 154.5, 143.1, 138.0, 132.3 (d, $J = 9.2$ Hz), 127.1, 122.2, 119.2, 118.5, 116.7 (d, $J = 22$ Hz), 112.7, 46.4, 23.1, 11.4; ms: *m*/*z* 323 (M +1,100). *Anal.* Calcd for $C_{17}H_{15}FN_6$. HOH: C, 59.99; H, 5.03; N, 24.69. Found C, 60.03; H, 5.07; N, 24.41.

5,6-Difluoro-2-(4-hydroxyphenyl)-1H-benzimidazole (98). Compound **97** (0.12 g, 0.357 mmol) in ethanol (10 mL) were reduced by hydrogenation using 40 psi of H_2 and 10% Pd-C until cessation of hydrogen uptake. The catalyst was filtered off on a bed of Celite, washed with ethanol, and the filtrate was concentrated. The residue was crystallized from ethanol, mp 286–287°C, yield 43.2%. ^{1}H NMR δ (DMSO-d_6): 6.88 (d, 2H, $J = 8.4$ Hz), 7.47 and 7.6 (br.s, 2H), 7.94 (d, 2H, $J = 8.8$ Hz), 10.0 (s, 1H), 12.87 (s, 1H); ms: *m*/*z* 247 (M +1,100). *Anal.* Calcd for $C_{13}H_8F_2N_2O\cdot0.5C_4H_8O_2$: C, 62.07; H, 4.17; N, 9.65. Found C, 62.55; H, 4.29; N, 9.37.

General procedure for synthesis of 103, 105–107. A mixture of **99–102** (1 mmol), *n*-butylbromide (1 mmol), and sodium hydride (95%, 1.25 mmol) in *N*,*N*-dimethylformamide (1mL) was stirred at 60°C for 5 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate, and concentrated *in vacuo*.

1-Butyl-4,7-dichloro-2-(4-fluorophenyl)-1H-benzimidazole (103). Purification, cc, ethyl acetate-hexane (2:8), mp 93–94°C, yield 52.5%. ^{1}H NMR δ: 0.81 (t, 3H), 1.18 (m, 2H), 1.74 (m, 2H), 4.46 (t, 2H), 7.22 (m, 4H), 7.67 (m, 2H); ms: *m*/*z* 337 (M +1, 100) 339 (M +3, 63), 341 (M +5, 13). *Anal.* Calcd for $C_{17}H_{15}Cl_2FN_2$: C, 60.54; H, 4.48; N, 8.31. Found C, 60.73; H, 4.58; N, 8.29.

1-Butyl-5,6-dichloro-2-(4-fluorophenyl)-1H-benzimidazole (105). Purification, cc, ethyl acetate-hexane (1:3), mp 85–86°C, yield 70.5%. ^{1}H NMR δ: 0.88 (t, 3H), 1.26 (m, 2H), 1.76 (m, 2H), 4.17 (t, 2H), 7.24 (m, 2H), 7.51 (s, 1H), 7.68 (m, 2H), 7.87 (s, 1H); ms: *m*/*z* 337 (M +1, 100) 339 (M +3, 57). 341 (M +5, 13). *Anal.* Calcd for $C_{17}H_{15}Cl_2FN_2$: C, 60.55; H, 4.48; N, 8.31. Found C, 60.5; H, 4.39; N, 8.31.

1-Butyl-5,6-dibromo-2-(4-fluorophenyl)-1H-benzimidazole (106). Purification, cryst., ethanol, mp 100–101°C, yield 72.8%. ^{1}H NMR δ: 0.87 (t, 3H), 1.26 (m, 2H), 1.75 (m, 2H), 4.15 (t, 2H), 7.23 (m, 2H), 7.68 (m, 3H), 8.05 (s, 1H); ^{13}C NMR δ: 165.0, 162.6, 154.5, 143.4, 135.8, 131.3, 131.2, 126.0, 125.9, 124.3, 117.9, 117.6, 116.2, 116.0, 114.6, 44.8, 31.7, 19.8, 13.4. ms: *m*/*z* 425 (M +1, 51), 427 (M +3, 100), 429 (M +5, 50). *Anal.* Calcd for $C_{17}H_{15}Br_2FN_2$: C, 47.92; H, 3.55; N, 6.57. Found C, 47.52; H, 3.45; N, 6.73.

1-Butyl-2-(4-fluorophenyl)-1H-benzimidazole-5,6-dicarbonitrile (107). Purification, cc, ethyl acetate-hexane (3:7), mp 158–160°C, yield 36.6%. ^{1}H NMR δ (DMSO-d_6): 0.76 (t, 3H), 1.14 (m, 2H), 1.64 (m, 2H), 4.4 (t, 2H), 7.49 (t, 2H), 7.91 (m, 2H), 8.57 (s, 1H), 8.75 (s, 1H); ms: *m*/*z* 319 (M +1, 100). *Anal.* Calcd for $C_{19}H_{15}FN_4$. 0.15 $C_4H_8O_2$: C, 71.0; H, 4.92; N, 16.89. Found C, 71.16; H, 4.95; N, 16.78.

1-(4-Fluorophenyl)ethanone (4-bromophenyl) hydrazone (108a). A mixture of 4-bromo-phenylhidrazine HCl (1.12 g, 5 mmol), 4′-fluoroacetophenone (0.69 g, 5 mmol), and triethylamine (1 mL) in ethanol (10 mL) was heated to 80°C for 3 h. The mixture was allowed to cool and water was added. The resultant precipitate was filtered and dried under vacuum, yield 1.34 g, 87.3%.

5-Bromo-2-(4-fluorophenyl)-1H-indole (108). Compound **108a** (0.92 g, 3 mmol) in polyphosphoric acid (25 g) was heated to 120°C for 4 h. After cooling to room temperature, the resultant reaction solution was poured into a mixture of ice and water, and the solution was basified with 10% sodium hydroxide solution. The resultant precipitate was filtered, washed with water, crystallized from ethanol, mp 178–179°C, ref. 28; 180°C, yield 85%. ^{1}H NMR δ (DMSO-d_6): 6.87 (s, 1H), 7.21 (dd, 1H, $J = 2$, 8.8 Hz), 7.33 (m, 3H), 7.71 (s, 1H), 7.91 (m, 2H), 11.77 (s, 1H); ^{13}C NMR δ (DMSO-d_6): 162.9, 160.4, 138.1, 135.6, 130.4, 128.2, 127.2, 127.1, 123.8, 121.9, 115.9, 115.7, 113.1, 111.7, 98.1; ms [ESI(−)]: *m*/*z* 288 (M −1, 100) 290 (M +2, −1, 100). *Anal.* Calcd for $C_{14}H_9BrFN$: C, 57.95; H, 3.13; N, 4.83. Found C, 57.73; H, 3.04s; N, 4.98.

5-Bromo-2-(4-fluorophenyl)-1-propyl-1H-indole (109). A solution of **108** (0.58 g, 2 mmol) and sodium hydride (0.072 g, 3 mmol) was stirred in dry *N*,*N*-dimethylformamide (3 mL) at 0°C for 30 min, and then propyl bromide (0.30 g, 2.5 mmol) was added dropwise and the resulting mixture was stirred at room temperature for 16 h and then poured into ice-water and extracted with ethyl acetate (3 × 10). The organic phase was washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was crystallized from ethyl acetate-hexane, yield 63.3%, mp 55–56°C; ^{1}H NMR δ (DMSO-

d_6): 0.63 (t, 3H), 1.53 (m, 2H), 4.14 (t, 2H), 6.51 (s, 1H), 7.28 (dd, 1H, $J = 2$, 8.4 Hz), 7.36 (m, 2H), 7.55 (d, 1H, $J = 8.8$ Hz), 7.59 (m, 2H), 7.75 (d, 1H, $J = 2$ Hz); ms: m/z 332 (M +1, 100) 334 (M +3, 100). *Anal.* Calcd for $C_{17}H_{15}BrFN$: C, 61.46; H, 4.55; N, 4.22. Found C, 61.43; H, 4.56; N, 4.38.

5-Cyano-2-(4-fluorophenyl)-1-propyl-1H-indole (110). A mixture of **109** (0.332 g, 1 mmol) and cuprous cyanide (0.270 g, 3 mmol) in 5 mL of 1-methyl-2-pyrrolidinone was heated at 120°C for 6 h in a Parr Digestion Bomb. The mixture was cooled to room temperature and washed with 10 mL water, by stirring with water for 15 min and decanting the water layer. The washed reaction mixture was mixture with 8 mL of ethylenediamine and 5 mL of water. The resultant precipitate was filtered, washed with 15 mL of 10% sodium cyanide solution then water and dried. Crude product was purified by using cc (ethyl acetate-hexane 1:3), mp 141-143°C, yield 23.7%. ^1H NMR δ (DMSO-d_6): 0.63 (t, 3H), 1.52 (m, 2H), 4.20 (t, 2H), 6.67 (s, 1H), 7.37 (t, 2H), 7.52 (dd, 1H, $J = 1.4$, 8.6 Hz), 7.61 (m, 2H), 7.77 (d, 1H, $J = 8.6$ Hz), 8.09 (d, 1H, $J = 1$ Hz); ms: m/z 279 (M +1,100). *Anal.* Calcd for $C_{18}H_{15}FN_2$. 0.15 HOH: C, 76.93; H, 5.49; N, 9.96. Found C, 77.04; H, 5.76; N, 9.47.

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About the Reaction of β-Dimethylamino-α,β-enones with Active Methylene Nitriles

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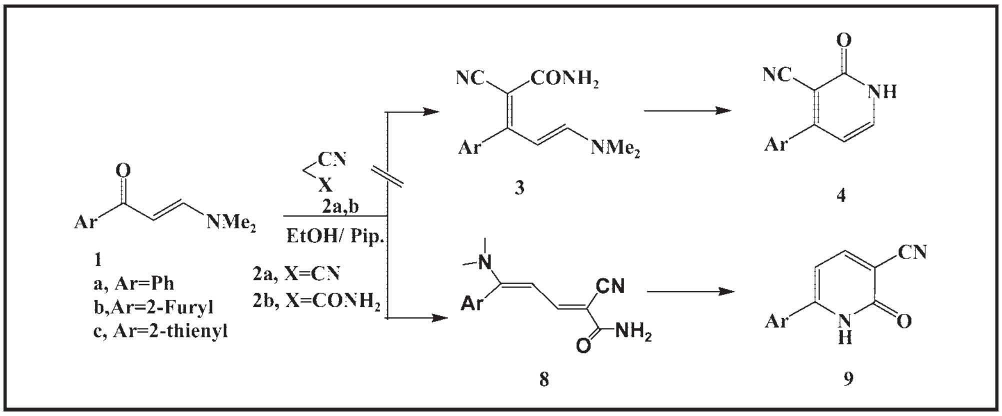

The reaction of 3-dimethylamino-1-arylpropenone derivatives with active methylene nitriles was reinvestigated and a plausible mechanism to account for the results is suggested. X-ray crystallographic study supported the suggested mechanism. Based on these findings, the reaction of 3-acetylamino-4-dimethylaminobut-3-en-2-one with malononitrile was also reinvestigated and the correct structures verified.

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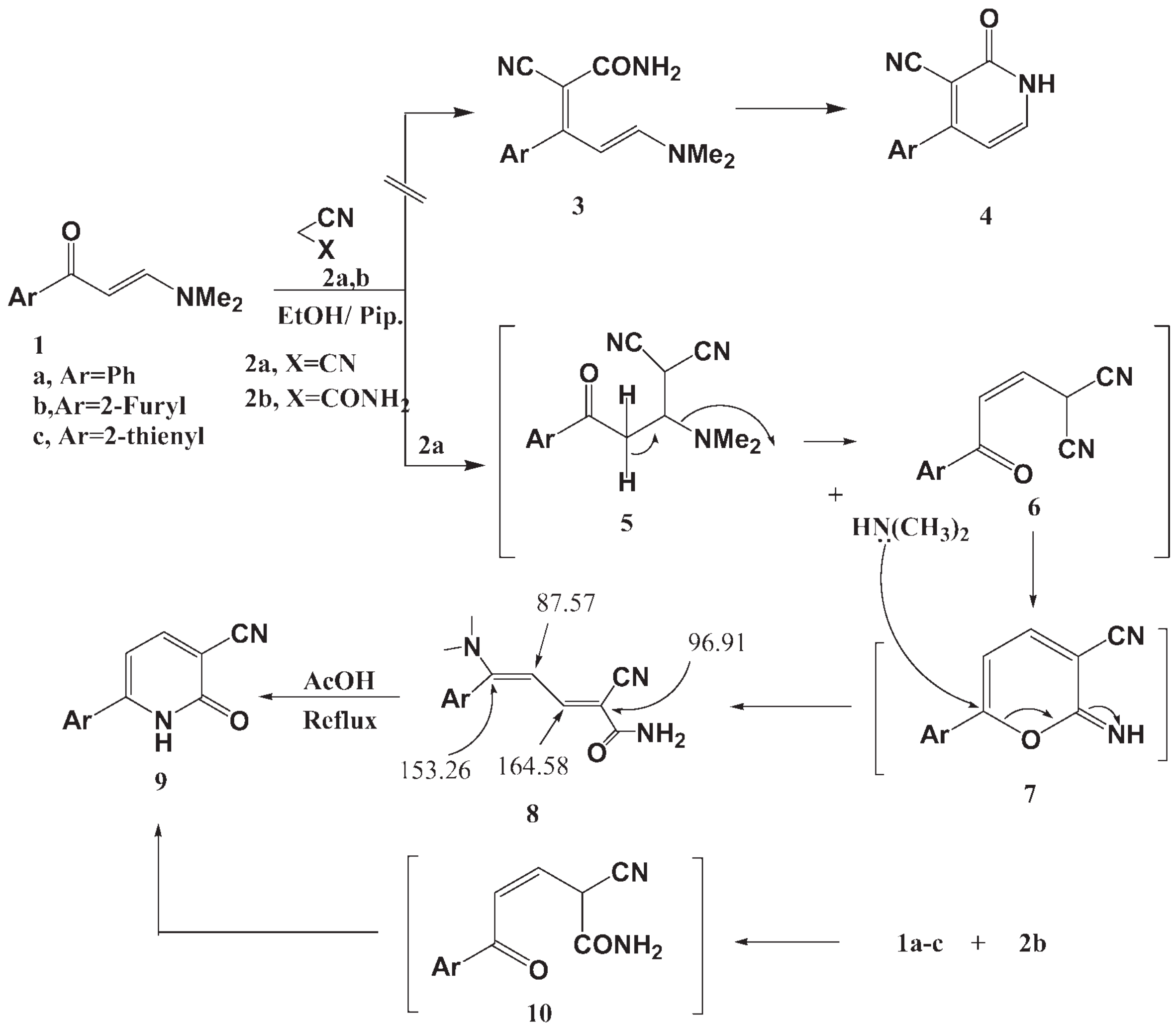
INTRODUCTION

In the past 2 decades, we have been involved in a program aiming to develop new simple routes for the synthesis of heterocyclic compounds of biological interest to be evaluated as biodegradable agrochemicals [1–5]. Pyridines and pyridones represent an important class of these compounds because of their pharmaceutical applications [6–8]. The reaction of enaminones with active methylene nitriles represents one of the strategies for the preparation of 2-1*H*-pyridone [9–11]. 3-Dimethylamino-1-arylpropenones **1a–c** have been extensively used in the last years by Elnagdi and coworkers for the synthesis of pyridones [12–14]. The reaction of **1a–c** with active methylene nitriles (namely malononitrile **2a** and cyanoacetamide **2b**; Scheme 1) in all these and other publications was based on the idea of a Knoevenagel condensation of the active methylene in **2a** or **2b** with the carbonyl groups of **1a–c**. In one article, it was assumed that malononitrile **2a** is first hydrolyzed to cyanoacetamide by the water present in the solvent [12], which then condenses with the carbonyl group of **1a–c** to afford **3a–c**. In the other article, it was assumed that the condensation takes place first and then the water resulting from the condensation hydrolyzes one of the cyano groups in the products of **2a** but do nothing with the products of **2b** to afford the amides **3a–c** [13]. Then, compounds **3a–c** were cyclized to afford the 2-1*H*-pyridones **4a–c**. These assumptions attracted our attention and raised our doubt in the structures of these products. The NMe$_2$ group is a very good leaving group and the active methylene reagent must substitute it easier and faster than to condense with the carbonyl group. Furthermore, the hydrolysis of a cyano group by the traces of water present in the solvent (ethanol and few drops of piperidine as catalyst), or that resulting from the condensation seemed far unlikely to occur. On the basis of these reservations, we decided to reinvestigate this reaction.

RESULTS AND DISCUSSION

Thus, the enaminone compounds **1a–c** were prepared and allowed to react with the active methylene compounds **2a**,**b** according to the method and under the same reaction conditions reported by Elnagdi and coworkers [12]. In our hands, we could isolate the 2-cyano-5-dimethylamino-5-arylpenta-2,4-dienoic amide derivatives **8a–c** from the reaction of **1a–c** with malononitrile **2a**. The mass spectra of these compounds showed

Scheme 1



5-9 : a, Ar=Ph ; b, Ar=2-Furyl ; c, Ar=2-thienyl

m/*z* = 241, 231, and 247, respectively. These masses reveal that 1:1 adducts were obtained and correspond to molecular formulae $C_{14}H_{15}N_3O$, $C_{12}H_{13}N_3O_2$, and $C_{12}H_{13}N_3OS$, respectively, as reported previously [12]. However, the cyclization of these compounds upon reflux in acetic acid led to the 2-1*H*-pyridone derivatives **9a–c**. The ^{1}H NMR spectrum of **9a** revealed two doublets; each integrated for 1H at $\delta = 6.72$ and 8.20 with equal *j* value of 8 Hz, which could be attributed to the pyridone **9a** H-5 and H-4, respectively. A pyridone structure like the claimed **4a** should have revealed these proton signals for H-5 and H-6 at slightly up field values $\delta \approx 5.8$ and 7.3 ppm. Thus, structures **9a–c** were assigned to these reaction products rather than **4a–c** (*cf.* Experimental).

The formation of the enaminones **8a–c** from the reaction of **1a–c** with **2a** is assumed to take place *via* the sequence depicted in Scheme 1. The active methylene group of malononitrile undergoes addition to the double bond of **1** to give the intermediate **5**, followed by elimination of dimethyl amine to afford 2-(3-oxo-3-aryl-propenyl)-malononitrile **6**, which directly undergoes ring closure *via* its enolized form to afford the iminopyran **7**. This newly born iminopyran is attacked by the dimethyl amine (which is still present in the reaction medium) and undergoes ring opening to afford the isolated 2-cyano-5-dimethylamino-5-arylpenta-2,4-dienoic amides **8a–c**. The ring opening of iminopyran under the effective ammonia and amines is well established in the literature [10]. Elemental analyses and spectral data are

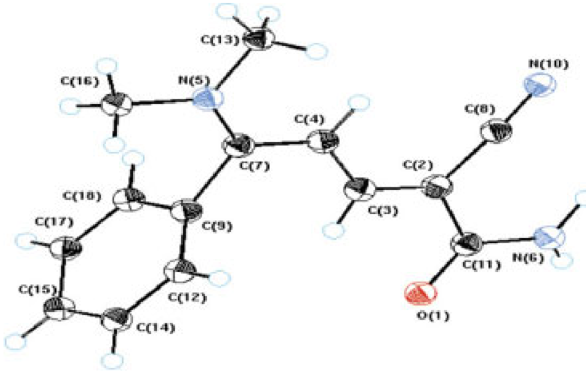


Figure 1. Crystal structure of compound **8a**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

in complete agreement with structures **8a–c** (*cf*. Experimental).

The X-ray crystallographic picture [15] afforded an unambiguous evidence of structure **8a** (Fig. 1; *cf*. experimental). It shows that the N(Me)$_2$ attached to the same carbon atom (C7) carrying the phenyl group and the other terminus carrying the cyano and the amide group on (C2) as shown in Figure 1 and Scheme 1, which affords a conclusive evidence to the pyridone structures **9**.

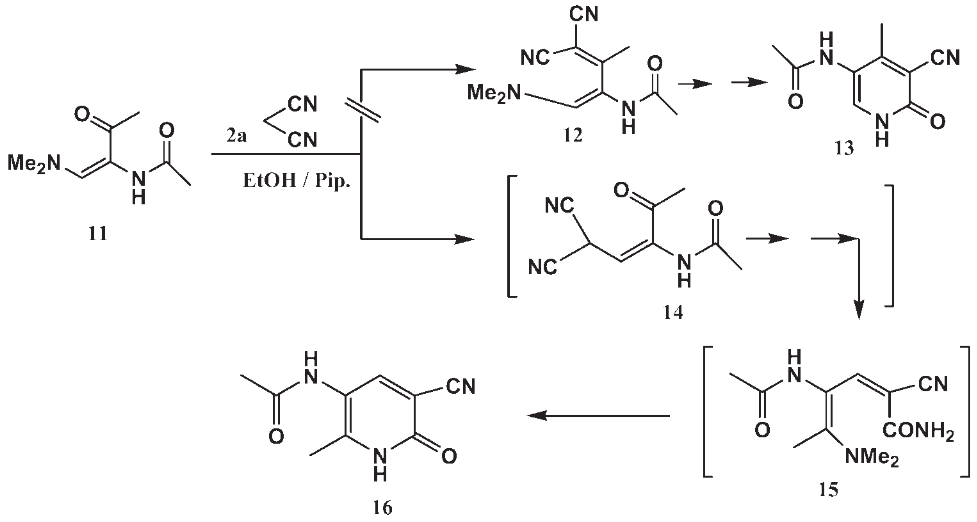
These compounds could be readily cyclized upon reflux in acetic acid to afford the 2-1*H*-pyridinone derivatives **9a–c**, respectively, *via* elimination of dimethyl amine.

The reaction of **1a–c** with cyanoacetamide **2b** afforded the same 2-1*H*-pyridinones **9a–c**, respectively, which represents further evidence to this suggested mechanism. It is apparent that **2b** followed the same addition elimination sequence to afford the intermediate 2-cyano-5-oxo-5-arylpent-3-enoic acid amide **10** (analogous to **6** in the above sequence), which undergoes directly the cyclization *via* elimination of water without passing through the step of the iminopyran, since the amide group is initially present. The identity of the products obtained from the reactions of **1a–c** with either **2a** or **2b** was deduced from the typical melting points and spectral data. It should be also clear that Elnagdi and coworkers [12] have reported that they obtained the same products from the reaction of **2b** with **1a–c**.

Furthermore, Elnagdi and coworkers [13] have reported the reaction of 3-acetylamino-4-dimethylamino-but-3-en-2-one **11** (obtained from the reaction of acetylaminoacetone with DMFDMA) with malononitrile **2a** and assumed the same scenario of condensation to give **12**, which is cyclized to **13** (Scheme 2).

Reinvestigation of this reaction showed that it follows the same mechanistic way shown in Scheme 1. Malononitrile substitutes the dimethylamnino group to give the intermediate **14** followed by cyclization and ring opening of the formed iminopyran to afford **15**, which readily eliminates dimethylamine to afford the final isolable 2-1*H*-pyridinone derivative **16** (in a Dimroth-type rearrangement). Although the claimed structure **13** and our structure **16** have almost the same elemental and spectral data, however, the δ value given by Elnagdi and coworkers [13] to the pyridinone H is 7.95 ppm, which better fits to the H-4 rather than the H-6. A structure like **13** would have revealed this H-6 signal much up field at ≈6–7 ppm. The ^{13}C NMR data given in [13] are wrongly interpreted. They assigned the value 116.64 ppm to the C-4, which points out that no methyl group is attached to this carbon, because attached methyl group at the fourth position would have shifted this

Scheme 2



value dramatically low field (>150 ppm); and the same words can be said on the value given to C-6 δ = 148.54, which is too much down field value to a simple CH ($\approx$90–100 ppm) and this means that the methyl group is attached to this carbon (C-6).

Finally, this confusion of the structures can be excused based on the similarity of analyses and the tiny differences in the spectral interpretation. However, the claim that the pyridinone obtained from this reaction underwent a Michael addition with ylidenemalononitriles to afford diaminoisoquinolines [13] requires revision.

CONCLUSION

Thus, we could suggest a conceivable mechanism that explains the behavior of active methylene nitriles with enaminones and could correct some literature wrong structures.

EXPERIMENTAL

Melting points were measured on an Electrothermal (9100) apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin Elmer 1430 spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were taken on a Varian Gemini 300 MHz spectrometer in DMSO-d_6 using TMS as an internal standard and chemical shifts are expressed in δ ppm values. Mass spectra were taken on a Shimadzu GCMS-GB 1000 PX (70 eV). Elemental analyses were carried out at the Microanalytical Center at Cairo University. X-ray data [15] were collected using KappaCCD on a Bruker Nonius apparatus. The structure was solved by direct methods and expanded using Fourier technique *SIR*92 [16]. The structure was refined using maXus [17]. Nonhydrogen atoms are refined anisotropically and the hydrogen atoms were refined according to the theoretical models.

Reaction of the enaminones 1a–c with malononitrile 2a: Preparation of compounds 8a–c. To a mixture of each of enaminone **1a–c** (10 mmol) and malononitrile (0.66 g; 10 mmol) in ethanol (15 mL) was added few drops of piperidine, which acts as catalyst. The reaction mixture was refluxed for 2 h and then left to cool to room temperature. The solid products thus precipitated were collected by filtration and crystallized from the proper solvent.

2-Cyano-5-dimethylamino-5-phenylpenta-2,4-dienoic acid amide 8a. Canary yellow crystals, yield (1.8 g, 75%); mp 260–262°C (Dioxan) (Lit. 254–256 [12]); $\upsilon_{\max}$ = 3435 and 3284 (NH$_2$), 2193 (CN) and 1665 cm^{-1} (CO); MS: *m*/*z* = 241 [M$^+$]; δ_H = 2.92 (s, 6H, 2 CH$_3$), 5.65 (d, *j* = 12.75 Hz, 1H, CH), 6.77 (s, 2H, NH$_2$), 7.13 (d, *j* = 12.75 Hz, 1H, CH), 7.24–7.55 (m, 5H, Ph). δ_C = 165.08 (s)(amide CO), 164.58 (d)(C-3), 153.26 (s)(C-5), [133.98(s), 129.56(d), 128.76(d), 128.72(d); Phenyl C's], 118.90(s)(CN), 96.91 (s)(C-2), 87.57(d)(C-4), 41.92 (q).

X-ray crystallographic data using *SIR*92 [16] program to solve structure: pale yellow crystals, $C_{14}H_{15}N_3O$ (M_r = 241.294 g mol^{-1}), orthorhombic prismatic, space group Pna-2(1), a = 10.0108(5) Å, b = 18.4003(9) Å, c = 7.1902(3) Å, α[°] = 90.00, β[°] = 90.00, γ[°] = 90.00; V[Å^3] = 1324.45(11). Z = 4, D_x = 1.210 Mg m^{-3}, μ(Mo Kα) = 0.08 nm^{-1}; fine-focus sealed tube. Data were collected using KappaCCD. T[°K] = 298, with graphite monochromator with Mo Kα radiation (λ = 0.71073 Å) min. 91.5%; max 98.2%. Measured reflections 2646, total independent reflections are 1898 were counted with observed reflections 582. R_{int} = 0.024. R(all) = 0.218, R(gt) = 0.101, wR(ref) = 0.197 and wR(all) = 0.224.

Anal. Calcd. for $C_{14}H_{15}N_3O$: (241.12): C, 69.69; H, 6.27; N, 17.41. Found: C, 69.55; H, 6.10; N, 17.30.

2-Cyano-5-dimethylamino-5-furan-2-yl-penta-2,4-dienoic acid amide 8b. Reddish brown crystals, yield (1.75 g, 76%); mp 243–244°C (Dioxan) (Lit 238–240 [12]); $\upsilon_{\max}$ = 3330 and 3290 (NH$_2$), 2187 (CN) and 1665 cm^{-1} (C=O); MS: *m*/*z* = 231 [M$^+$]; δ_H = 2.95 (s, 6H, 2 CH$_3$), 5.6 (d, *j* = 12.62 Hz, 1H, CH), 6.72 (d, 1H, furan H), 6.78 (d, 1H, furan H), 6.9 (br.s., 2H, NH$_2$), 7.55 (d, *j* = 12.62 Hz, 1H, CH), 7.75 (dd, 1H, furan H).

Anal. Calcd. for $C_{12}H_{13}N_3O_2$: (231.25): C, 62.33; H, 5.67; N, 18.17. Found: C, 62.10; H, 5.60; N, 18.20.

2-Cyano-5-dimethylamino-5-thiophen-2-yl-penta-2,4-dienoic acid amide 8c. Yellow crystals, yield (1.9 g, 78%); mp 253–254°C (Dioxan) (Lit. 250–252 [12]; $\upsilon_{\max}$ = 3403 and 3328 (NH$_2$), 2196 (CN) and 1669 cm^{-1} (CO); MS: *m*/*z* = 247 [M$^+$]; δ_H = 2.96 (s, 6H, 2 CH$_3$), 5.65 (d, *j* = 12.65 Hz, 1H, CH), 6.90 (br.s., 2H, NH$_2$), 7.15 (d, 1H, thiophene H), 7.25 (dd, 1H, thiophene H), 7.35 (d, 12.65 Hz, 1H, CH), 7.85 (d,1H, thiophene H).

Anal. Calcd. for $C_{12}H_{13}N_3OS$: (247.32): C, 58.28; H, 5.30; N, 16.99; S, 12.97. Found: C, 58.25; H, 5.35; N, 16.85; S, 12.85.

Cyclization of compounds 8a–c: Synthesis of the 2-1*H*-pyridones 9a–c. Each of compounds **8a–c** (10 mmol) was refluxed in glacial acetic acid (15 mL) for 30 min. The solvent was reduced to one-third of its volume under reduced pressure and left to cool overnight. The solid precipitates that appeared were collected by filtration and crystallized from the proper solvent.

2-Oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile 9a. Pale yellow crystals, yield (1.7 g, 87%); mp 291–292°C (AcOH) (Lit. 158°C [12]); $\upsilon_{\max}$ = 3220, 3151 (NH), 2222 (CN) and 1662 cm^{-1} (CO); MS: *m*/*z* = 196 [M$^+$]; δ_H = 6.72 (d, *j* = 8.57 Hz, 1H, Pyr. H-5), 7.50–7.80 (m, 5H, Ph), 8.20 (d, *j* = 8.57 Hz, 1H, Pyr. H-4), 12.80 (s, 1H, NH).

Anal. Calcd. for $C_{12}H_8N_2O$: (196.20): C, 73.46; H, 4.11; N, 14.28. Found: C, 73.35; H, 4.00; N, 14.20.

6-(Furan-2-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile 9b. Pale brownish crystals, yield (1.67 g, 90%); mp 298–300°C (AcOH) (Lit. 314°C [12]); $\upsilon_{\max}$ = 3215, 3160 (NH), 2225 (CN) and 1659 cm^{-1} (CO); MS: *m*/*z* = 186 [M$^+$]; δ_H = 6.71 (d, *j* = 12.5 Hz, 1H, Pyr. H-5), 6.77 (t, 1H, Fur. H-4), 7.61 (d, 1H, Fur. H-3), 7.85 (d, 1H, Fur. H-5), 8.15 (d, *j* = 12.5 Hz, 1H, Pyr. H-4), 12.80 (s, 1H, NH).

Anal. Calcd. for $C_{10}H_6N_2O_2$: (186.17): C, 64.52; H, 3.25; N, 15.05. Found: C, 64.50; H, 3.15; N, 15.10.

2-Oxo-6-(thiophen-2-yl)-1,2-dihydropyridine-3-carbonitrile 9c. Pale yellowish crystals, yield (1.87 g, 93%); mp 295–296°C (AcOH) (Lit. 288°C [12]); $\upsilon_{\max}$ = 3215, 3145 (NH), 2228 (CN) and 1655 cm^{-1} (CO); MS: *m*/*z* = 202 [M$^+$]; δ_H = 6.65 (d, *j* = 12.55 Hz, 1H, Pyr. H-5), 7.23 (t, 1H, thienyl H), 7.85 (d, 1H, thienyl H), 7.95 (d, 1H, thienyl H), 8.10 (d, *j* = 12.55 Hz, 1H, Pyr. H-4), 12.80 (s, 1H, NH).

Anal. Calcd. for $C_{10}H_6N_2OS$: (202.23): C, 59.39; H, 2.99; N, 13.85; S, 15.86. Found: C, 59.35; H, 3.15; N, 13.90; S, 15.70.

***N*-(5-Cyano-2-methyl-6-oxo-1,6-dihydropyridin-3-yl)-acetamide 16.** To a mixture of **11** (1.7g, 10 mmol; prepared according to the literature method [13]) and malononitrile **2a** (0.66 g, 10 mmol) in ethanol (20 mL) was added a catalytic amount (five drops) of piperidine. The reaction mixture was refluxed for 6 h and then left to cool to room temperature. The contents of the flask were poured into ice-cold water and acidified with few drops of conc. HCl till just neutral (pH paper). The precipitated solid product was filtered off, washed thoroughly with cold water, dried, and recrystallized from ethanol/DMF (4:1) to give **16** as lustrous brown crystals, yield (1.5 g, 78%); mp. 215–217°C (Lit. 200–220°C [13]); υ_{max} = 3340, 3220 (NH), 2195 (CN) and 1655 cm^{-1} (CO); MS: *m*/*z* = 191 [M^+]; δ_H = 1.99 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 7.95 (s, 1H, H-4), 9.3 (br.s., 1H, NH), 12.25 (br.s., 1H, NH). δ_C = 169.5 (s), 159.96 (s), 149.75 (d), 148.5 (s), 116.65 (s), 116.05 (s), 99.56 (s), 23.05 (q), 16.43 (q).

Anal. Calcd. for $C_9H_9N_3O_2$: (191.19): C, 56.54; H, 4.74; N, 21.98. Found: C, 56.35; H, 4.90; N, 21.90.

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A Basic Ionic Liquid Catalyzed Reaction of Benzothiazole, Aldehydes, and 5,5-Dimethyl-1,3-cyclohexanedione: Efficient Synthesis of Tetrahydrobenzo[*b*]pyrans

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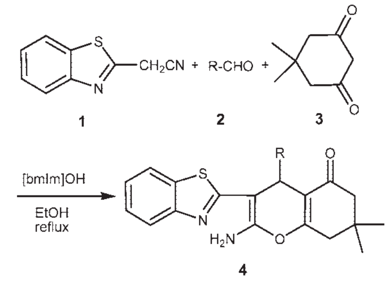

R=3-$NO_2C_6H_4$, 2,5-$Cl_2C_6H_3$, 2-ClC_6H_4, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 2-BrC_6H_4, 4-BrC_6H_4, 2-FC_6H_4, 3-FC_6H_4, 4-FC_6H_4, C_6H_5, 4-$CH_3C_6H_4$, 4-$OMeC_6H_4$, 4-OHC_6H_4, 3,4($CH_3O)_2C_6H_3$, furan, 4-$N(CH_3)_2C_6H_4$

A fast, mild, and quantitative procedure for the preparation of tetrahydrobenzo[*b*]pyran derivatives in the presence of an easily accessible basic ionic liquid—[bmIm]OH(3-butyl-1-methylimidazoliumhydroxide) as the catalyst has been developed. The ionic liquid was stable during the reaction process and could also be reused at least nine times with consistent activity. This procedure may be a practical alternative to the existing procedures to meet the need of academe as well as industries.

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INTRODUCTION

The exploration of privileged structures in drug discovery is a rapidly emerging theme in medicinal chemistry [1]. 4*H*-Benzopyran derivatives constitute a structural unit of a number of natural products [2] and are versatile synthons because of the inherent reactivity of the pyran ring [3]. In addition, 4*H*-benzo[*b*]pyran derivatives are biologically interesting compounds that possess various pharmacological activities [4], such as, anticoagulant, spasmolytic, diuretic, anticancer, and anti-anaphylactin characteristics [5]. These ubiquitous applications of 4*H*-benzo[*b*]pyrans stimulated several groups [6–8] to develop new and efficient synthetic protocols for these two bioactive units.

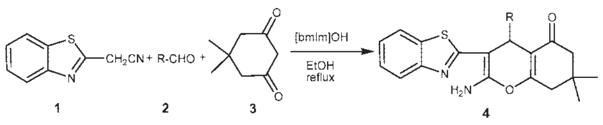
Besides, because of the great pharmacological significance of benzothiazole, which is of particular interest especially within the realm of medicinal chemistry, many useful therapeutic agents also contain the benzothiazole moiety, and these substitution patterns were introduced with efficiency [9].

Because of the vast utility of these kinds of compounds, a number of synthetic routes have been developed for the expedition of these structure frameworks. Some of these reactions were catalyzed by a plethora of reagents including solid or molten state [6], sodium bromide under microwave irradiation [7], [bmIm][BF_4] [8]. However, despite the potential utility of these catalysts, many of these methodologies for the synthesis of 4*H*-benzo[*b*]pyrans are associated with several shortcomings, such as, long reaction time, high temperature, harsh reaction conditions, and using of expensive reagents. Gaps remain in terms of the search for economical and environmentally benign methods.

Multicomponent reactions (MCRs), an important subclass of tandem reaction [10], are one-pot processes in which several easily accessible components react to form a single product. They offer significant advantages over conventional linear step synthesis, by reducing time, saving money, energy, and raw materials, thus resulting in both economical and environmental benefits. At the same time, diversity can be achieved from building up libraries by simply varying each component [11].

Recently, ionic liquids have attracted increasing interest in the context of green synthesis [12]. Choline hydroxide has been used as a basic catalyst for aldol condensation reactions between several ketones and aldehydes [13], whereas the basic ionic liquid

Scheme 1



R=3-$NO_2C_6H_4$, 2,5-$Cl_2C_6H_3$, 2-ClC_6H_4, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 2-BrC_6H_4, 4-BrC_6H_4, 2-FC_6H_4, 3-FC_6H_4, 4-FC_6H_4, C_6H_5, 4-$CH_3C_6H_4$, 4-$OMeC_6H_4$, 4-OHC_6H_4, 3,4($CH_3O)_2C_6H_3$, furan, 4-$N(CH_3)_2C_6H_4$

[bmIm]OH has been successfully applied to catalyze Michael additions of active methylene compounds to conjugated ketones, carboxylic esters, and nitriles [14]. The synthesis of new and important types of heterocyclic compounds using the basic ionic liquid [bmIm]OH continues to attract wide attention among synthetic chemists.

Thus, in view of the advantages of MCRs and Tandem reactions, and promoted by our earlier researches on MCRs [15], herein, we wish to disclose a green protocol for the synthesis of a variety of biologically important 4*H*-Benzo[*b*]pyrans using the catalyst [bmIm]OH under reflux condition (Scheme 1).

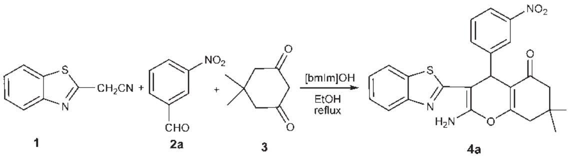
RESULTS AND DISCUSSION

We first studied the effects of a variety of catalysts on the reaction using *m*-nitrobenzaldehyde as the substrate in ethanol to develop the optimal reaction conditions. The results are summarized in Table 1. Although the reaction could take place without any catalyst, the yield of **4a** was relatively low 39.6%, and the reaction time was long (Table 1, entry 1). The yields of **4a** were also unsatisfactory when using Et_3N or piperidine as catalysts (45.2–52.5%; Table 1, entries 2 and 3). To obtain the higher yield, inorganic catalysts were studied; however, the result was disappointing. It turned out that using KF or KF/Al_2O_3 (1:1) as the catalyst, only moderate yields of **4a** were obtained (52.5–55.0%; Table 1, entries 4 and 5). Thus, ionic liquids were tried. Utilizing $[bmIm]BF_4$ and $[bmIm]BF_4$/KOH (1:1), the yields of the products were not obviously improved (50.2–68.0%; Table 1, entries 6 and 7), but when the [bmIm]OH was used as the catalyst, the yield of **4a** was dramatically improved to 83% in 0.5 h. Then, it was observed that when the quantity of [bmIm]OH increased from 20 to 60 mol %, the yield of **4a** improved accordingly to 95% (Table 1, entries 8–10). However, with increasing the amount of the catalyst, the yields of **4a** were not further improved but reduced (Table 1, entries 11 and 12). Therefore, we selected 60 mol % of [bmIm]OH as the catalyst. It was showed that the basic ionic liquid [bmIm]OH plays a significant catalytic role, as well as the acceleration of the reaction rate and improvement of selectivity.

To extend the scope of this new procedure for the synthesis of 4*H*-benzo[*b*]pyrans, a series of reactions were carried out under optimized conditions. We were pleased to find that the reactions proceeded smoothly, and desired products were afforded in excellent yields (77–95%) and in short time (30–50 min) (Table 2). When aromatic aldehydes **2** with more electron-

Table 1

Optimization of reaction conditions for compound **4a**.



Entry	Catalyst (equiv)	EtOH (mL)	Time (h)	Yield (%)[a]
1	–[b]	15	24	39.6
2	Et_3N(0.2)	15	10	52.5
3	Piperidine(0.2)	15	24	45.2
4	KF(0.2)	15	9	52.5
5	KF/Al_2O_3(0.2)	15	8	55.0
6	$[bmIm]BF_4$(0.2)	15	8	50.2
7	$[bmIm]BF_4$/KOH(0.2)	15	8	68.0
8	[bmIm]OH(0.2)	3.0	0.5	83.0
9	[bmIm]OH(0.4)	3.0	0.5	87.3
10	[bmIm]OH(0.6)	3.0	0.5	95.0
11	[bmIm]OH(0.8)	3.0	0.5	86.6
12	[bmIm]OH(1.0)	3.0	0.5	73.0

[a] Isolated.

[b] No catalyst.

Table 2

Synthesis of compounds **4** by [bmIm]**OH** as catalyst.

Entry	Product	R	Time (min)	Yeild (%)[a]
1	**4a**	3-$NO_2C_6H_4$	30	95
2	**4b**	2,5-$Cl_2C_6H_3$	30	90
3	**4c**	2-ClC_6H_4	40	88
4	**4d**	4-ClC_6H_4	30	91
5	**4e**	2,4-$Cl_2C_6H_3$	35	89
6	**4f**	2-BrC_6H_4	30	94
7	**4g**	4-BrC_6H_4	30	94
8	**4h**	2-FC_6H_4	30	90
9	**4i**	3-FC_6H_4	35	89
10	**4j**	4-FC_6H_4	30	92
11	**4k**	C_6H_5	40	87
12	**4l**	4-$CH_3C_6H_4$	50	80
13	**4m**	4-$OMeC_6H_4$	40	83
14	**4n**	4-OHC_6H_4	50	77
15	**4o**	3,4(CH_3O)2C_6H_3	50	79
16	**4p**	Furan	40	82
17	**4r**	4-$N(CH_3)_2C_6H_4$	60	Trace

[a] Isolated.

withdrawing substituents or higher electronegativity were used, the yields of **4** were higher (Table 2, entries 1–10). The heterocyclic aldehyde (furan formaldehyde) was also used to support this reaction (Table 2, entry 16). In a further study, 4-$N(CH_3)_2C_6H_4$ was used in this case, however, though the reactions proceeded smoothly, the 2-(benzo[*d*]thiazol-2-yl)-3-(4-*N*,*N*-dimethyl-phenzyl)-acrylonitrile instead of the desired product **4r** was observed (Table 2, entry17). Presumably, it was arrested at the Knoevenagel condensation product stage, as further aromatization did not occur due to electronic effect.

We also investigated the reusability and the recycling of the basic ionic liquid [bmIm]OH, and found that the catalyst could be easily recovered after completion of the reaction and reused in subsequent reactions. Using the reaction of 2-(benzo[*d*]thiazol-2-yl)acetonitrile **1**, 4-chlorobenzaldehyde **2d** and 5,5-dimethyl-1,3-cyclohexanedione **3** as a model reaction, after completion of the reaction, the mixture was filtrated and the filtrate was evaporated under reduced pressure, then extracted with ethyl acetate:ether (1:1). The ionic liquid left in the reaction vessel was rinsed with ether and dried under vacuum at 90°C for 8 h to remove water leaving behind the ionic liquid. The recovered [bmIm]OH was recycled and reused nine times to carry out the same experiment. The activity of the catalyst did not show any significant decrease after nine runs (Fig. 1).

A plausible mechanism for the reaction is outlined in Scheme 2. The initial event can be considered as a Knoevenagel condensation of aldehydes **2** with benzothiazole **1** to form the intermediate [**A**], followed by the elimination to afford the 2-(benzo[*d*]thiazol-2-yl)-3-(aryl)acrylonitrile under the basic ionic liquid [bmIm]OH. The latter then undergoes Michael addition with 5,5-dimethyl-1,3-cyclohexanedione **3** tautomer to give the intermediate [**B**], followed by a intramolecular O-cyclization to give the products 4*H*-Benzo[*b*]pyrans **4** (Scheme 2).

It may be speculated that the difference in basicity of [bmIm]OH used in this reaction compared with Et_3N and piperidine may play a crucial role in accelerating the reaction and improving the yield.

In conclusion, this procedure using the task-specific basic ionic liquid [bmIm]OH as the catalyst provides a very efficient and convenient methodology for synthesis of 4*H*-benzo[*b*]pyrans through three-component reaction. This method offers remarkable improvements with

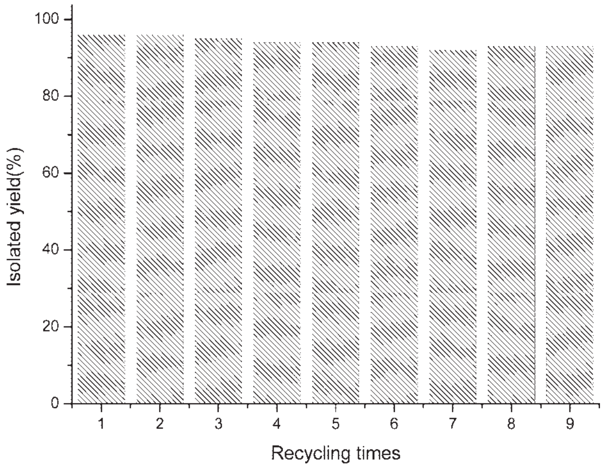
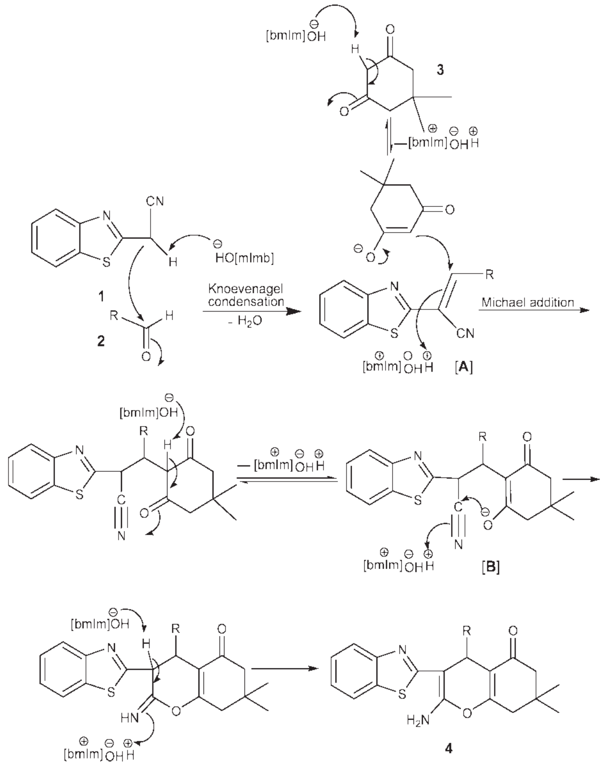


Figure 1. Recycling times of [bmIm]OH and the isolated yields of product **4d**.

Scheme 2



regard to operational simplicity, reaction time, reaction conditions, general applicability, and greenness of procedure, especially high isolated yields of products and the selectivity. Thus, we believe that this simple and green procedure will be a practical alternative to the existing procedures to cater the need of academe as well as industries.

EXPERIMENTAL

General remarks. Melting points were measured by using a RY-1 apparatus and were uncorrected. IR spectra were recorded on a Nicolet 510P FTIR spectrophotometer as KBr pellets. ^{1}H and ^{13}C NMR were recorded in DMSO-d_6 and CDCl$_3$ on a Bruker AC-500 instrument and TMS as internal standard. Mass spectra were performed on a Bruker Esquire Hct spectrometer with an ESI source. Elemental analyses were carried out on a Vario EL III analyzer. All chemicals were purchased and used without further purification.

The synthesis of 2-cyanomethy-1,3-benzothiazloe [16]. mp 101–102°C; IR (KBr) υ: 2250 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.80–8.27 (m, 2H), 7.00–7.80 (m, 2H), 4.72 (s, 2H, CH$_2$). Anal. calcd. for $C_9H_2N_2S$: C, 62.07; H, 3.47; N, 16.09; found: C, 62.16; H, 3.44; N, 16.11.

General procedure for the synthesis of basic ionic liquid. The basic ionic liquid [bmIm]OH was prepared by anion change of [bmIm]Br using 1 mol equivalent KOH. The ionic liquid was dried under vacuum for 24 h and stored in desiccators. The ionic liquid was characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 10.24 (s, 1 H), 7.62 (t, *J* = 1.7 Hz, 1 H), 7.50 (t, *J* = 1.7, 1 H), 4.34 (t, *J* = 7.4 Hz, 2 H), 4.12 (s, 3 H), 3.32–3.25 (br s, 1H), 1.93–1.87 (m, 2 H), 1.40–1.36 (m, 2 H), 0.96 ppm (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 137.2, 123.8, 122.1, 49.7, 36.7, 32.1, 19.4, 13.4 ppm; IR (neat) υ: 3422, 3079, 1571, 1169 cm^{-1}.

General procedure for the synthesis of 2-amino-3-(benzo[*d*]thiazol-2-yl)-4-aryl-7,7-dimethyl–5–carbonyl-5,6,7,8-4*H*-benzo[*b*]pyrans (4). To a mixture of 2-(benzo[*d*]thiazol-2-yl)acetonitrile **1** (1 mmol), aromatic aldehydes **2** (1 mmol), 5,5-dimethyl-1,3-cyclohexanedione **3** (1 mmol) dissolved in a minimum amount (3.0 mL) of ethanol, the basic ionic liquid, [bmIm]OH (60 mol %) was added, and the mixture was refluxed for appropriate time. The progress of reaction was monitored by TLC. After completion of reaction aqueous, the mixture was allowed to cool to room temperature, and filtered to give the crude products, which was further purified by recrystallization (THF/ethanol) to give pure products **4**.

2-Amino-3-(benzo[d]thiazol-2-yl)-4-(3-nitrophenyl)-7,7-dimethyl-5-carbonyl-5,6,7,8-4H-benzo[b]pyran (4a). mp 218–219°C. IR (KBr) υ: 3429, 1679, 1624, 1525, 1473, 822, 696 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.67 (s, 3H, CH$_3$), 0.92 (s, 3H, CH$_3$), 2.07 (d, *J* = 16.5 Hz, 1H), 2.29 (d, *J* = 16.0 Hz, 1H), 2.50 (d, *J* = 17.5 Hz, 1H), 2.59 (d, *J* = 17.5 Hz, 1H), 4.70 (s, 1H) 7.14–8.09 (m, 8H, ArH), 8.52 ppm (s, 2H, NH$_2$); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 25.5, 25.6, 26.6, 29.0, 32.4, 37.4, 50.2, 67.4, 80.5, 114.4, 120.6, 121.9, 122.2, 123.4, 126.6, 130.1, 131.7, 135.3, 147.0, 147.9, 154.6, 162.8, 168.3, 196.3 ppm; ms (ESI) *m/z*: 448.4 [M +H]$^+$. Anal. calcd. for $C_{24}H_{21}N_3O_4S$: C, 64.42; H, 4.73; N, 9.40. Found: C, 64.49; H, 4.75; N, 9.42.

2-Amino-3-(benzo[d]thiazol-2-yl)-4-(2,5-dichlorophenyl)-7,7-dimethyl-5-carbonyl-5,6,7,8-4H-benzo[b]pyran (4b). mp 217–218°C. IR (KBr) υ: 3446, 1679, 1661, 1626, 1477, 820, 669 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ: 1.007 (s, 3H, CH$_3$), 1.09 (s, 3H, CH$_3$), 2.23 (d, *J* = 16.0 Hz, 1H), 2.29 (d, *J* = 16.0 Hz, 1H), 2.50 (d, *J* = 17.5 Hz, 1H), 2.59 (d, *J* = 17.5 Hz, 1H), 5.07 (s, 1H) 7.04–7.30 (m, 7H, ArH), 7.35 ppm (s, 2H, NH$_2$); ^{13}C NMR (125 MHz, CDCl$_3$) δ: 26.6, 29.2, 32.2, 36.8, 50.5, 79.7, 112.7, 120.5, 121.9, 123.4, 126.6, 128.8, 131.3, 132.2, 142.5, 153.0, 154.8, 163.1, 168.4, 196.1 ppm; ms (47 eV) *m/z*: 493.40 (100%, M +Na). Anal. calcd. for $C_{24}H_{21}N_2O_2SCl_2$: C, 61.02; H, 4.48; N, 5.93. Found: C, 60.89; H, 4.47; N, 5.95.

2-Amino-3-(benzo[d]thiazol-2-yl)-4-(2-chlorophenyl)-7,7-dimethyl-5-carbonyl-5,6,7,8-4H-benzo[b]pyran (4c). mp 204–205°C. IR (KBr) υ: 3445, 1678, 1658, 1624, 1475, 748, 666 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.83 (s, 3H, CH$_3$), 0.99 (s, 3H, CH$_3$), 2.01 (d, *J* = 16.0 Hz, 1H), 2.23 (d, *J* = 16.0 Hz, 1H), 2.40 (d, *J* = 17.5 Hz, 1H), 2.57(d, *J* =17.5 Hz, 1H), 4.82 (s, 1H), 7.06–7.83 (m, 8H, ArH), 8.48 ppm (s, 2H, NH$_2$); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 26.6, 29.3, 32.1, 36.4, 39.4, 50.5, 80.4, 113.4, 120.4, 121.7, 123.2, 126.4, 127.0, 128.7, 126.6, 131.9, 133.1, 133.3, 140.5, 153.0, 154.7, 162.6, 168.6, 195.9 ppm; ms (ESI) *m/z*: 437.8 [M +H]$^+$. Anal. calcd. for $C_{24}H_{21}N_2O_2SCl$: C, 65.97; H, 4.84; N, 6.41. Found: C, 66.11; H, 4.85; N, 6.43.

2-Amino-3-(benzo[d]thiazol-2-yl)-4-(4-chlorophenyl)-7,7-dimethyl-5-carbonyl-5,6,7,8-4H-benzo[b]pyran (4d). mp 173–174°. IR (KBr) υ: 3451, 1667, 1618, 1531, 1469, 835, 672 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.85 (s, 3H,

CH_3), 1.12 (s, 3H, CH_3), 2.18 (d, J = 16.5 Hz, 1H), 2.25 (d, J = 16.0 Hz, 1H), 2.41 (d, J = 17.5 Hz, 1H), 2.46 (d, J = 17.5 Hz, 1H), 4.76 (s, 1H), 7.24–7.77 (m, 8H, ArH), 7.79 ppm (s, 2H, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 26.7, 29.2, 32.4, 36.9, 50.4, 81.2, 115.1, 120.6, 121.9, 123.4, 126.6, 128.5, 130.5, 131.5, 131.9, 143.8, 153.3, 154.5, 162.4, 168.7, 196.3 ppm; ms (ESI) m/z: 437.5 $[M+H]^+$. Anal. calcd. for $C_{24}H_{21}N_2O_2SCl$: C, 65.97; H, 4.84; N, 6.41. Found: C, 65.89; H, 4.83; N, 6.39.

2-Amino-3-(benzo[d]thiazol-2-yl)-4-(2,4-dichlorophenyl)-7,7-dimethyl-5-carbonyl-5,6,7,8-4H-benzo[b]pyran (4e). mp 209–210°C. IR (KBr) υ: 3454, 1681, 1618, 1468, 1454, 855, 672 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.85 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.05 (d, J = 16.5 Hz, 1H), 2.29 (d, J = 16.5 Hz, 1H), 2.46 (d, J = 17.5 Hz, 1H), 2.60 (d, J = 17.5 Hz,1H), 4.832 (s, 1H), 7.14–7.85 (m, 7H, ArH), 8.53 ppm (s, 2H, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 26.6, 29.2, 32.2, 36.7, 50.4, 79.9, 113.0, 120.4, 121.7, 123.3, 126.5, 127.3, 129.6, 130.3, 132.3, 134.0, 139.8, 152.9, 154.7, 162.9, 168.4, 196.0 ppm; ms (ESI) m/z: 472.2 $[M+H]^+$. Anal. calcd. for $C_{24}H_{20}N_2O_2SCl_2$: C, 61.15; H, 4.28; N, 5.94. Found: C, 61.45; H, 4.27; N, 5.91.

2-Amino-3-(benzo[d]thiazol-2-yl)-4-(2-bromophenyl)-7,7-dimethyl-5-carbonyl-5,6,7,8-4H-benzo[b]pyran (4f). mp 177–178°C. IR (KBr) υ: 3446, 1677, 1658, 1475, 1454 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.90 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.06 (d, J = 16.0 Hz, 1H), 2.29 (d, J = 16.0 Hz, 1H), 2.45 (d, 1H), 2.60 (d, J = 17.5 Hz, 1H), 4.87 (s, 1H), 7.03–7.88 (m, 8H, ArH), 8.53 ppm (s, 2H, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ:26.8, 29.3, 32.2,38.4, 50.6, 80.6, 80.7, 113.6, 115.7, 120.5, 121.7, 123.3, 126.5, 127.7, 129.0, 132.1, 133.8, 142.1, 147.2, 152.9, 154.8, 162.6, 168.7, 196.0 ppm; ms (ESI) m/z: 483.2 $[M+H]^+$. Anal. calcd. for $C_{24}H_{21}BrN_2O_2S$: C, 59.88; H, 4.40; N, 5.82. Found: C, 59.70; H, 4.39; N, 5.83.

2-Amino-3-(benzo[d]thiazol-2-yl)-4-(4-bromophenyl)-7,7-dimethyl-5-carbonyl-5,6,7,8-4H-benzo[b]pyran (4g). mp 175–176°C. IR (KBr) υ: 3418, 1676, 1652, 1621, 1477, 1456 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.84 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.08 (d, J = 16.0 Hz, 1H), 2.29 (d, J = 16.0 Hz, 1H), 2.46 (d, J = 18.0 Hz, 1H), 2.59 (d, J = 17.5 Hz,1H), 4.56 (s, 1H), 7.17–7.86 (m, 8H, ArH), 8.45 ppm (s, 2H, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 26.7, 29.2, 32.4, 37.1, 50.4, 81.2, 115.0, 120.0, 120.1, 121.9, 123.4, 126.6, 130.9, 131.4, 131.9, 144.2, 153.3, 154.5, 162.4, 168.7, 196.3 ppm; ms (ESI) m/z: 483.2 $[M+H]^+$. Anal. calcd. for $C_{24}H_{21}BrN_2O_2S$: C, 59.88; H, 4.40; N, 5.82. Found: C, 59.64; H, 4.41; N, 5.83.

2-Amino-3-(benzo[d]thiazol-2-yl)-4-(2-fluorophenyl)-7,7-dimethyl-5-carbonyl-5,6,7,8-4H-benzo[b]pyran (4h). mp 173–174°C. IR (KBr) υ: 3429, 1674, 1652, 1614, 1476, 1453 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.88 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.06 (d, J = 15.5 Hz, 1H), 2.30 (d, J = 16.0 Hz, 1H), 2.46 (d, 1H), 2.64 (d, J = 18.0 Hz,1H), 4.75 (s, 1H), 7.02–7.91 (m, 8H, ArH), 8.46 ppm (s, 2H, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 26.5, 29.2, 32.1, 32.3, 50.4, 80.5, 99.9, 113.7, 115.9, 120.4, 121.7, 123.3, 124.4, 126.5, 128.9,129.0, 131.0, 131.1, 131.6, 131.8, 153.2, 154.5, 159.6, 161.6, 168.7, 195.9 ppm; ms (ESI) m/z: 421.2 $[M+H]^+$. Anal. calcd. for $C_{24}H_{21}FN_2O_2S$: C, 68.55; H, 5.03; N, 6.66. Found: C, 68.34; H, 5.02; N, 6.67.

2-Amino-3-(benzo[d]thiazol-2-yl)-4-(3-fluorophenyl)-7,7-dimethyl-5-carbonyl-5,6,7,8-4H-benzo[b]pyran (4i). mp 181–182°C. IR (KBr) υ: 3427, 1679, 1663, 1616, 1480, 1452 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.85 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.10 (d, J = 16.0 Hz, 1H), 2.31 (d, J = 16.5 Hz, 1H), 2.53 (d, 1H), 2.60 (d, J = 17.5 Hz,1H), 4.61 (s, 1H), 6.94–7.89 (m, 8H, ArH), 8.46 ppm (s, 2H, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 26.6, 29.1, 32.4, 37.2, 50.4, 81.0, 99.9, 113.8, 113.9, 114.9, 115.2, 115.4, 120.6, 121.9, 123.4, 124.5, 126.5, 130.4, 130.5, 131.9, 147.7, 147.8, 153.3, 154.6, 161.3, 162.5, 163.3, 168.6, 196.2 ppm; ms (ESI) m/z: 421.2 $[M+H]^+$. Anal. calcd. for $C_{24}H_{21}FN_2O_2S$: C, 68.55; H, 5.03; N, 6.66. Found: C, 68.75; H, 5.04; N, 6.65.

2-Amino-3-(benzo[d]thiazol-2-yl)-4-(4-fluorophenyl)-7,7-dimethyl-5-carbonyl-5,6,7,8-4H-benzo[b]pyran (4j). mp 192–193°C. IR (KBr) υ: 3423, 1664, 1617, 1480, 1453 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.96 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 2.20 (d, J = 16.5 Hz, 1H), 2.27 (d, J = 16.0 Hz, 1H), 2.44(d, J = 17.5 Hz, 1H), 2.52 (d, J = 17.5 Hz, 1H), 4.81 (s, 1H), 6.90–7.81 (m, 8H, ArH), 8.45 ppm (s, 2H, NH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.3, 29.2, 32.3, 36.6, 40.8, 50.8, 83.4, 114.8, 115.0, 116.1, 120.5, 121.2, 123.2, 125.9, 130.1, 130.2, 132.5, 139.6, 152.9, 160.6, 161.2, 162.6, 168.7, 196.4 ppm; ms (ESI) m/z: 421.3 $[M+H]^+$. Anal. calcd. for $C_{24}H_{21}FN_2O_2S$: C, 68.55; H, 5.03; N, 6.66. Found: C, 68.28; H, 5.04; N, 6.67.

2-Amino-3-(benzo[d]thiazol-2-yl)-4-phenyl-7,7-dimethyl-5-carbonyl-5,6,7,8-4H-benzo[b]pyran (4k). mp 185–186°C. IR (KBr) υ: 3428, 1654, 1620, 1532, 1474, 833, 672 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.897 (s, 3H, CH_3), 1.021 (s, 3H, CH_3), 2.055 (d, J = 16.0 Hz, 1H), 2.274 (d, J = 16.0 Hz, 1H), 2.47 (d, J = 17.5 Hz, 1H), 2.58 (d, J = 17.0 Hz, 1H), 4.53 (s, 1H), 7.04–7.85 (m, 9H, ArH), 8.519 ppm (s, 2H, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 26.6, 29.2, 32.3, 37.4, 50.4, 81.7, 115.5, 120.5, 121.8, 123.2, 126.4, 126.9, 128.4, 128.56, 131.9, 144.8, 153.2, 162.1, 168.8, 196.1 ppm; ms (47 eV) m/z: 425.20 (100%, $M+Na$). Anal. calcd. for $C_{24}H_{22}N_2O_2S$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.55; H, 5.49; N, 6.94.

2-Amino-3-(benzo[d]thiazol-2-yl)-4-p-tolyl-7,7-dimethyl-5-carbonyl-5,6,7,8-4H-benzo[b]pyran (4l). mp 189–190°C. IR (KBr) υ: 3430, 1658, 1628, 1542, 1470, 822, 692 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.79 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 2.03 (d, J = 16.0 Hz, 1H), 2.11 (s, 3H) 2.24 (d, J = 16.5 Hz, 1H), 2.42 (d, J = 17.5 Hz, 1H), 2.58(d, J = 17.5 Hz, 1H), 4.46 (s, 1H), 6.95–7.82 (m, 8H, ArH), 8.32 ppm (s, 2H, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 20.9, 26.6, 29.2, 32.3, 36.9, 50.4, 66.8, 81.8, 115.6, 117.6, 121.8, 123.2, 126.4, 128.5, 128.9, 131.9, 135.9, 141.8, 153.2, 154.7, 161.9, 168.9, 196.2 ppm; ms (47 eV) m/z: 439.24 (100%, $M+Na$). Anal. calcd. for $C_{24}H_{24}N_2O_2S$: C, 71.26; H, 5.98; N, 6.92. Found: C, 71.39; H, 5.99; N, 6.94.

2-Amino-3-(benzo[d]thiazol-2-yl)-4-(4-methoxyphenyl)-7,7-dimethyl-5-carbonyl-5,6,7,8-4H-benzo[b]pyran (4m). mp 177–178°C. IR (KBr) υ: 3396, 1675, 1656, 1621, 1474, 754, 665 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.85 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.06 (d, J = 16.0 Hz, 1H), 2.28 (d, J = 16.0 Hz, 1H), 2.48 (d, J = 17.5 Hz, 1H), 2.58(d, J = 17.5 Hz, 1H), 3.63(s 3H), 4.49 (s, 1H), 6.75–7.86 (m, 8H, ArH), 8.35 ppm (s, 2H, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 26.2, 28.7, 31.9, 36.0, 49.9, 54.9, 81.5, 113.3, 115.2, 119.9, 121.9, 123.8, 125.9, 129.1, 131.5, 136.2, 152.7, 153.9, 157.7, 162.5, 168.4, 195.7 ppm; ms (ESI) m/z: 433.4 $[M+H]^+$. Anal.

calcd. for $C_{25}H_{24}N_2O_3S$: C, 69.42; H, 5.59; N, 6.48. Found: C, 69.34; H, 5.61; N, 6.46.

2-Amino-3-(benzo[d]thiazol-2-yl)-4-(4-hydroxyphenyl)-7,7-dimethyl-5-carbonyl-5,6,7,8-4H-benzo[b]pyran (4n). mp 200–201°C. IR (KBr) υ: 3451, 1677, 1652, 1616, 1474, 757, 538 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ: 0.82 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.06 (d, J = 16.0 Hz, 1H), 2.26 (d, J = 16.0 Hz, 1H), 2.44 (d, J = 17.5 Hz, 1H), 2.53 (d, J = 17.0 Hz, 1H), 4.42 (s, 1H), 6.55–7.84 (m, 8H, ArH), 8.30 (s, 2H, NH_2), 9.15 ppm (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 18.9, 26.3, 29.2, 32.3, 36.5, 50.5, 56.5, 81.5, 115.1, 115.9, 120.4, 123.2, 126.4, 129.5, 132.0, 135.0, 153.2, 154.3, 156.2, 169.1, 196.1 ppm; ms (ESI) *m/z*: 419.2 $[M+H]^+$. Anal. calcd. for $C_{24}H_{22}N_2O_3S$: C, 68.88; H, 5.30; N, 6.69. Found: C, 68.75; H, 5.29; N, 6.72.

2-Amino-3-(benzo[d]thiazol-2-yl)-4-(3,4-dimethoxyphenyl)-7,7-dimethyl-5-carbonyl-5,6,7,8-4H-benzo[b]pyran (4o). mp 191–192°C. IR (KBr) υ: 3443, 1662, 1624, 1615, 1560, 838, 669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.20 (s, 3H, CH_3), 1.216 (s, 3H, CH_3), 2.19 (d, J = 16.0 Hz, 1H), 2.24 (d, J = 16.5 Hz, 1H), 2.39 (d, J = 17.5 Hz, 1H), 2.44 (d, J = 17.5 Hz, 1H), 3.75 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.74 (s, 1H), 6.24–7.67 (m, 7H, ArH), 7.67 ppm (s, 2H, NH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 26.7, 29.3, 33.4, 36.9, 32.4, 55.9, 55.9, 81.9, 111.9, 112.7, 115.7, 120.5, 120.7, 121.8, 123.3, 126.5, 132.1, 137.2, 147.9, 148.6, 153.3, 154.5, 161.9, 196.1, 196.3 ppm; ms (ESI) *m/z*: 463.8 $[M+H]^+$. Anal. calcd. for $C_{26}H_{26}N_2O_4S$: C, 67.51; H, 5.67; N, 6.06. Found: C, 67.49; H, 5.68; N, 6.05.

2-Amino-3-(benzo[d]thiazol-2-yl)-4-(furan-2-yl)-7,7-dimethyl-5-carbonyl-5,6,7,8-4H-benzo[b]pyran (4p). mp 201–202°C. IR (KBr) υ: 3458, 1684, 1668, 1621, 1477, 1454 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ: 0.95 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.16 (d, J = 16.0 Hz, 1H), 2.33 (d, J = 16.0 Hz, 1H), 2.48 (d, 1H), 2.59 (d, J = 17.5 Hz,1H), 4.73 (s, 1H), 6.18 (s, 1H), 6.27 (s, 1H), 7.20 (s, 1H), 7.22–7.92 (m, 4H, ArH), 8.39 ppm (s, 2H, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 26.7, 29.2, 32.4, 50.4, 79.2, 107.1, 110.8, 112.6, 120.6, 121.9, 123.4, 126.5, 131.9, 142.1, 153.4, 154.8, 155.5, 163.6, 168.7, 195.9 ppm; ms (ESI) *m/z*: 393.2 $[M+H]^+$. Anal. calcd. for $C_{22}H_{20}N_2O_3S$: C, 67.33; H, 5.14; N, 7.14. Found: C, 67.53; H, 5.13; N, 7.15.

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Palladium-Catalyzed Cross-Coupling Reaction of 2- and/or 5-Substituted 4,6-Dichloropyrimidines with Arylboronic Acids

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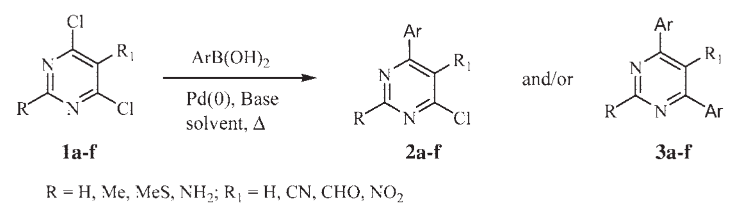

The Suzuki-Miyaura reaction of some 4,6-dichloropyrimidines bearing methylthio-, methyl-, amino-, cyano-, formyl-, and nitro groups in positions 2 and/or 5 of the pyrimidine ring with arylboronic acids has been investigated. Influence of palladium catalyst, ligand, base, and solvent on the reaction outcome was studied. The reaction was found to give the corresponding 4,6-diarylpyrimidines in reasonable yields using Pd(OAc)$_2$/PPh$_3$/K$_3$PO$_4$ or Pd(PPh$_3$)$_2$Cl$_2$/K$_3$PO$_4$ as catalyst systems.

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INTRODUCTION

In the past two decades, the Suzuki-Miyaura cross-coupling reaction has evolved into one of the most widely used carbon-carbon bond forming processes [1,2]. Its impact on organic synthesis is largely attributed to the fact that it provides an applicable method for the preparation of biaryls. Aryl- and heteroarylpyrimidine derivatives have found applications in many contemporary areas of chemistry, such as, ligands for coordination to metal ions [3], components for molecular recognition studies involving hydrogen bonding and π–π interactions [4], compounds with therapeutic and agrochemical properties [5], fluorophores and electron-transporting compounds in organic light-emitting devices [6]. Although the direct arylation of simple chloropyrimidines is well documented [7], arylation of chloropyrimidines containing various reactive groups and application of the Suzuki-Miyaura reaction for the synthesis of densely substituted arylpyrimidines is explored insufficiently. Continuing our studies on the synthesis of pyrimidine derivatives and related heterocycles [8] in this communication, we present the results of investigation of the palladium-catalyzed cross-coupling reaction of some 4,6-dichloropyrimidines (**1a–f**) bearing methylthio-, methyl-, amino-, cyano-, formyl-, and nitro groups in positions 2 and/or 5 of the pyrimidine ring with selected arylboronic acids.

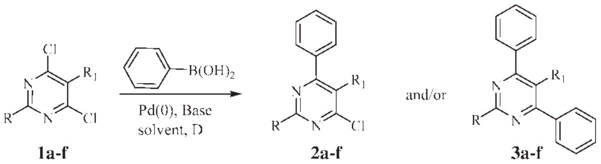
RESULTS AND DISCUSSION

Our investigation started with the cross-coupling of 4,6-dichloropyrimidines **1a–f** with phenylboronic acid (Scheme 1).

Initially, compound **1a** [9] was coupled with a slight excess of phenylboronic acid using Pd(OAc)$_2$/PPh$_3$/Na$_2$CO$_3$ (aqueous 1*M* solution) as a catalyst system in tetrahydrofurane. However, conversion of **1a** was very slow and led to a complex mixture of products from which any product was isolated (Table 1, entry 1). Almost the same result was obtained when Cs$_2$CO$_3$ was used as a base instead Na$_2$CO$_3$. Change of Pd(OAc)$_2$ to Pd$_2$(dba)$_3$ did not give the desirable result again—a mixture of **2a** and **3a** with the latter compound as major product was isolated in negligible amount.

It should be mentioned that in spite of the fact that equivalent amount of phenylboronic acid was used both chlorine groups of compound **1a** took part in the coupling reaction (entries 2 and 3). When 2.16 equiv. of phenylboronic acid was used in the reaction the corresponding 4,6-diphenylpyrimidine **3a** was isolated in 29% low yield (entry 4). We decided that a reason of such poor reaction course can be due to the presence of water in the reaction mixture. Chlorine groups in positions 4 and 6 of the pyrimidine ring are very reactive toward various nucleophiles [11]. Thus, in addition to other possible side reactions, such as, dehalogenation, homocoupling, etc., hydrolysis of chlorine groups under the alkaline reaction conditions could also occur to give several side products. Therefore, for further study, K$_3$PO$_4$/anhydrous dioxane was chosen as a base/solvent system. Using Pd(OAc)$_2$/PPh$_3$/K$_3$PO$_4$ as a catalyst system, the reaction of **1a** with 1.08 equiv. of phenylboronic acid gave a complex mixture of products from which compound **2a** was isolated in 26% yield (entry 5). When the coupling was carried out with 2.16 equiv. of phenylboronic acid in an

Scheme 1



1a-f **2a-f** **3a-f**

a: R = SMe, R_1 = CN; **b**: R = SMe, R_1 = CHO; **c**: R = NH_2, R_1 = CHO;
d: R NH_2, R_1 H; **e**: R Me; R_1 H; **f**: R H, R_1 NO_2

anhydrous dioxane with K_3PO_4 as a base twofold coupling occurred to give compound **3a** in 51% yield (entry 6).

The cross-coupling reaction of 4,6-dichloro-2-methylthiopyrimidine-5-carbaldehyde (**1b**) [9] with 1.08 equiv. phenylboronic acid using $Pd(OAc)_2/PPh_3/K_3PO_4$ in dioxane at 70°C furnished 4-chloro-2-methylthio-6-phenylpyrimidine-5-carbaldehyde (**2b**) in 34% yield (entry 7). A slightly better yield of **2b** (42%) was obtained when $Pd_2(dba)_3$ was used as a catalyst and when the reaction was carried out at room temperature (entry 8). In the reaction of **1b** with 2.16 equiv. of phenylboronic acid at the reflux temperature of dioxane, the corresponding 4,6-diphenylpyrimidine **3b** was obtained in 62% yield (entry 9). Compounds **1c,d** [12,13] bearing strong electron-donating and capable to form complexes with palladium species amino group [14] in the position 2 of the pyrimidine ring reacted with phenylboronic acid only at elevated temperatures. Moreover, possibly due to decreased reactivity of chlorine groups, the cross-coupling reaction with 1.08 equiv. phenylboronic acid did not give monophenyl derivatives **2c,d**. With both substrates **1c,d**, the side reactions competed with the cross-coupling reaction and, at best, formation of both monophenyl and diphenyl derivatives were observed. However, performing the reaction of **1c,d** with double amount of phenylboronic acids using $Pd(OAc)_2/PPh_3/K_3PO_4$ gave **3c,d** in 68% and 59% yields, respectively (entries 10 and 15). To increase the yield of the cross-coupling product **3c** bidentate ligand—1,4-di(triphenylphosphino)butane (dppb) and more electron rich and sterically hindered ligands—tri(*o*-tolyl)phosphane and (2-biphenyl)dicyclohexylphosphine were used in the reaction. However, the side reactions competed again and complex mixtures of products were formed (entries 11 and 12) or no reaction was observed (entry 13). It was found that using $Pd(PPh_3)_2Cl_2$ instead $Pd(OAc)_2$ sometimes gives better results (entries 14 and 16) and there is no necessity to add an additional amount of ligand when $Pd(PPh_3)_2Cl_2$ is used as a catalyst. Under these conditions, 4,6-diphenyl-2-methylpyrimidine (**3e**) was obtained in 73% yield (Table 1, entry 17). The cross-coupling of 4,6-dichloro-5-nitropyrimidine (**1f**) [15] with phenylboronic acid proceeded ambiguously. Nitro group due to its electron-withdrawing nature activates chlorine groups in the positions 4 and 6 of the pyrimidine ring, but this, perhaps, increases chances of side reactions to take place. Thus, after 2 h substrate **1f**

Table 1

Results of the Suzuki-Miyaura reaction of compounds **1a–f** with phenylboronic acid.

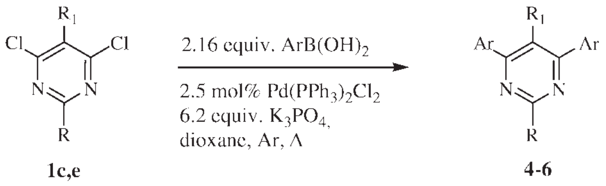
Entry	Compd.	$PhB(OH)_2$ Equiv.	Catalyst/ligand	Base/solvent	Reaction temp. (°C)/duration (h)	Product (yield, %)[a]
1	**1a**	1.08	$Pd(OAc)_2/PPh_3$	$Na_2CO_3/H_2O/THF$	Δ/35	ND
2	**1a**	1.08	$Pd(OAc)_2/PPh_3$	$Cs_2CO_3/H_2O/THF$	Δ/33	**2a** + **3a** (traces)[b]
3	**1a**	1.08	$Pd_2(dba)_3/PPh_3$	$Cs_2CO_3/H_2O/THF$	Δ/28	**2a**:**3a** = 1:3[b]
4	**1a**	2.16	$Pd(OAc)_2/PPh_3$	$Cs_2CO_3/H_2O/THF$	Δ/11	**3a** (29)
5	**1a**	1.08	$Pd(OAc)_2/PPh_3$	K_3PO_4/dioxane	70°C/25	**2a** (26)
6	**1a**	2.16	$Pd(OAc)_2/PPh_3$	K_3PO_4/dioxane	Δ/2.7	**3a** (51)
7	**1b**	1.08	$Pd(OAc)_2/PPh_3$	K_3PO_4/dioxane	70°C/35	**2b** (34)
8	**1b**	1.08	$Pd_2(dba)_3/PPh_3$	K_3PO_4/dioxane	r.t./72	**2b** (42)
9	**1b**	2.16	$Pd(OAc)_2/PPh_3$	K_3PO_4/dioxane	Δ/2.75	**3b** (62)
10	**1c**	2.16	$Pd(OAc)_2/PPh_3$	K_3PO_4/dioxane	Δ/13	**3c** (68)
11	**1c**	2.16	$Pd(OAc)_2$/dppb	K_3PO_4/dioxane	Δ/3	ND
12	**1c**	2.16	$Pd(OAc)_2/P(o\text{-tol})_3$	K_3PO_4/dioxane	Δ/13	ND
13	**1c**	2.16	$Pd(OAc)_2/(2\text{-biPh})PCy_2$	K_3PO_4/dioxane	Δ/5	Recovered **1c**
14	**1c**	2.16	$Pd(PPh_3)_2Cl_2$	K_3PO_4/dioxane	Δ/7	**3c** (85)
15	**1d**	2.16	$Pd(OAc)_2/PPh_3$	K_3PO_4/dioxane	Δ/25	**3d** (59)[c]
16	**1d**	2.16	$Pd(PPh_3)_2Cl_2$	K_3PO_4/dioxane	Δ/3.5	**3d** (51)
17	**1e**	2.16	$Pd(PPh_3)_2Cl_2$	K_3PO_4/dioxane	Δ/3	**3e** (73)[c]
18	**1f**	2.16	$Pd(OAc)_2/PPh_3$	K_3PO_4/dioxane	Δ/2	**3f** (21)

[a] The yields reported are after isolation and purification by the column chromatography.

[b] Determined by ^1H NMR spectra.

[c] Physical properties of compounds **3d,e** corresponded the reported data [10] where they were synthesized from acyclic precursors by cyclocondensation reactions.

Scheme 2



disappeared from the reaction mixture (TLC data), but the desirable 4,6-diphenyl-5-nitropyrimidine (**3f**) was isolated only in 21% yield (Table 1, entry 18).

Taking into account, the results of the cross-coupling reactions of **1a–e** with phenylboronic acid some 4,6-diarylpyrimidines **4–6** using Pd(PPh$_3$)$_2$Cl$_2$/K$_3$PO$_4$ as a catalyst system were synthesized (Scheme 2, Table 2).

In conclusion, the performed investigation showed that the synthesis of 6-aryl-4-chloropyrimidines bearing various substituents in the second and fifth positions of the pyrimidine ring by the Suzuki-Miyaura cross-coupling reaction is problematic. The reaction proceeds with the formation of mixtures of mono- and di-arylpyrimidines. Otherwise, the Suzuki-Miyaura cross-coupling reaction of the corresponding 4,6-dichloropyrimidines with double amount of arylboronic acids using Pd(OAc)$_2$/PPh$_3$/K$_3$PO$_4$ or Pd(PPh$_3$)$_2$Cl$_2$/K$_3$PO$_4$ as catalyst systems in dioxane furnishes the corresponding 2- and/or 5-substituted 4,6-diarylpyrimidines in reasonable yields.

EXPERIMENTAL

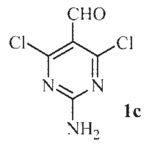
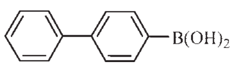
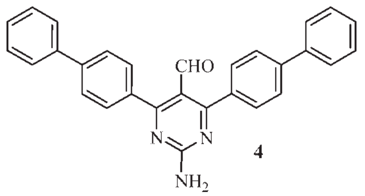
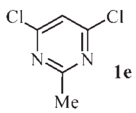
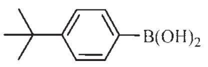
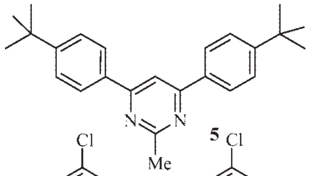
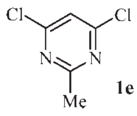
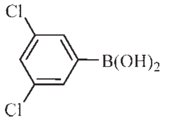
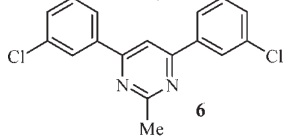
Melting points were determined in open capillaries and are uncorrected. UV spectra were obtained on a PerkinElmer UV-vis spectrophotometer Lambda 20 in ethanol solutions. IR spectra were run on a PerkinElmer FTIR spectrophotometer Spectrum BX II in nujol. ^{1}H and ^{13}C NMR spectra were recorded on a Varian INOVA spectrometer (300 MHz and 75 MHz, respectively). Chemical shifts are reported in ppm relative to tetramethylsilane. Mass spectrum was obtained on a mass spectrometer Kratos 115-30 (70 eV) by direct insertion probe. Elemental analysis (C and H) were found to be in good agreement (±0.4%) with the calculated values. Column chromatography was performed using Silica gel 60 (0.040–0.063 mm) (Merck). All reactions and purity of the synthesized compounds were monitored by TLC using Silica gel 60 F$_{254}$ aluminum plates (Merck). Visualization was accomplished by UV light.

Typical procedure for the synthesis of compounds 2a,b and 3a–d,f using Pd(OAc)$_2$/PPh$_3$/K$_3$PO$_4$. A solution of compound **1a–d,f** (0.45 mmol) in anhydrous dioxane (20 mL) was flushed with argon and K$_3$PO$_4$ (0.61 g, 2.9 mmol), phenylboronic acid (0.118 g, 0.97 mmol) (in case of synthesis **2a,b** 0.3 g, 1.47 mmol K$_3$PO$_4$, and 0.06 g, 0.49 mmol phenylboronic acid was used), 2.5 mol % Pd(OAc)$_2$ and 5 mol % PPh$_3$ were added under stirring and argon flow. The reaction mixture was stirred under argon at a temperature indicated in Table 1. Then dioxane was evaporated under reduced pressure to dryness. To dissolve inorganic salts the residue was treated with water (5 mL) and stirred for 0.5 h. The obtained solution was extracted with chloroform (3 × 25 mL), organic layer was dried with Na$_2$SO$_4$, chloroform removed by distillation under reduced pressure, and the solid was purified by column chromatography to give compounds **2a,b**, and **3a–d,f**.

Typical procedure for the synthesis of compounds 3c–e, 4–6 using Pd(PPh$_3$)$_2$Cl$_2$/K$_3$PO$_4$. A suspension of compounds **1c–e** (0.51 mmol) in dioxane (25 mL) was flushed with argon. Then, K$_3$PO$_4$ (3.16 mmol), arylboronic acid (1.1 mmol), 2.5 mol % Pd(PPh$_3$)$_2$Cl$_2$ were added under stirring and argon flow. The reaction mixture was refluxed under stirring and argon until compounds **1c–e** consumed (TLC control). Then

Table 2

Coupling of compounds **1c,e** with arylboronic acids.

Compound	Arylboronic acid	Duration (h)	Product	Yield (%)
 **1c**		2	 **4**	50
 **1e**		4	 **5**	65
 **1e**		7	 **6**	50

dioxane was evaporated under reduced pressure. To dissolve inorganic salts, the residue was treated with water (5 mL) and stirred for 0.5 h. The solid obtained was filtered off and purified by crystallization or column chromatography.

4-Chloro-2-methylthio-6-phenylpyrimidine-5-carbonitrile (2a). Compound **2a** was purified by column chromatography using benzene, yield 26%, mp 95–96°C. ^{1}H NMR (deuteriochloroform): δ 2.69 (s, 3H, SCH_3), 7.59–7.63 (m, 3H, 3′,4′,5′-H), 8.08–8.11 (m, 2H, 2′, 6′-H). ^{13}C NMR (deuteriochloroform): δ 14.99, 101.0, 114.9, 129.0, 129.6, 131.9, 134.5, 163.8, 168.8, 176.7. Anal. Calcd. for $C_{12}H_8ClN_3S$: C, 55.07; H, 3.08. Found: C, 55.42; H, 3.01.

4-Chloro-2-methylthio-6-phenylpyrimidine-5-carbaldehyde (2b). Compound **2b** was synthesized by the typical procedure using $Pd(OAc)_2$ (yield 34%) or by analogous procedure using 2.5 mol % $Pd_2(dba)_3$ under conditions presented in Table 1 (yield 42%). Compound **2b** was purified by column chromatography using benzene. mp 140–141°C. UV: λ_{max} 266 (ε 17,000), 287 (ε 15,000). IR: 1694 cm^{-1} (CHO). ^{1}H NMR (deuteriochloroform): δ 2.69 (s, 3H, SCH_3), 7.57–7.62 (m, 5H, C_6H_5), 10.09 (s, 1H, CHO). ^{13}C NMR (deuteriochloroform): δ 14.85, 120.7, 129.0, 130.5, 131.6, 135.2, 160.9, 170.1, 176.2, 188.2. Anal. Calcd. for $C_{12}H_9ClN_2OS$: C, 54.44; H, 3.43. Found: C, 54.78; H, 3.64.

2-Methylthio-4,6-diphenylpyrimidine-5-carbonitrile (3a). Compound **3a** was purified by column chromatography using benzene. Yield 29%, mp 220–221°C. UV: λ_{max} 277 (ε 30,000), 339 (ε 2500). IR: 2220 cm^{-1} (CN). ^{1}H NMR (deuteriochloroform): δ, 2.73 (s, 3H, SCH_3), 7.59–7.62 (m, 6H, 2 × 3′,4′,5′-H), 8.07–8.10 (m, 4H, 2 × 2′,6′-H). ^{13}C NMR (deuteriochloroform), δ, ppm: 14.8, 98.4, 117.7, 129.0, 129.6, 131.96, 135.8, 169.4, 175.9. Anal. Calcd. for $C_{18}H_{13}N_3S$: C, 71.26; H, 4.32. Found: C, 71.17; H, 4.55.

2-Methylthio-4,6-diphenylpyrimidine-5-carbaldehyde (3b). Compound **3b** was purified by column chromatography using benzene. Yield 62%, mp 112–113°C. UV: λ_{max} 275 (ε 20,000). IR: 1697 cm^{-1} (CHO). ^{1}H NMR (deuteriochloroform): δ 2.73 (s, 3H, SCH_3), 7.54–7.57 (m, 6H, 3′,4′,5′-H), 7.68–7.71 (m, 4H, 2′,6′-H), 10.05 (s, 1H, CHO). ^{13}C NMR (deuteriochloroform): δ 14.73, 121.8, 128.7, 130.4, 130.9, 136.8, 168.8, 175.1, 190.6. Anal. Calcd. for $C_{18}H_{14}N_2OS$: C, 70.56; H, 4.61. Found: C, 70.79; H, 4.49.

2-Amino-4,6-diphenylpyrimidine-5-carbaldehyde (3c). Yield 85% using $Pd(PPh_3)_2Cl_2$ and 68% using $Pd(OAc)_2/PPh_3$, mp 149–150°C (dec.) (from 2-propanol). UV: λ_{max} 259 (ε 22,000), 276 sh. (ε 21,000), 314 sh. (ε 11,000). IR: 3468, 3380 sh, 3277 (NH_2), 1687 cm^{-1} (C=O). ^{1}H NMR (deuteriochloroform): δ 5.96 (s, 2H, NH_2), 7.50–7.63 (m, 10H, 2× C_6H_5), 9.89 (s, 1H, CHO). ^{13}C NMR (deuteriochloroform): δ 117.9, 128.6, 129.5, 130.4, 137.5, 162.4, 172.5, 189.2. Anal. Calcd. for $C_{17}H_{13}N_3O$: C, 74.17; H, 5.11. Found: C, 74.00; H, 4.95.

5-Nitro-4,6-diphenylpyrimidine (3f). Compound **3f** was purified by column chromatography using benzene. Yield 21%, mp 117°C. UV: λ_{max} 257 sh. (ε 17,000); 271 (ε 18,000). ^{1}H NMR (deuteriochloroform): δ 7.52–7.60 (m, 6H, 2×[3′,4′,5′-H]), 7.73–7.76 (m, 4H, 2×[2′,6′-H]), 9.41 (s, 1H, 2-H). ^{13}C NMR (deuteriochloroform): δ 128.1, 129.3, 131.5, 133.6, 143.99, 158.3, 158.4. ms (ESI): *m/z* (%) 278 (100) (M +1). Anal. Calcd. for $C_{16}H_{11}N_3O_2$: C, 69.31; H, 4.00. Found: C, 69.22; H, 4.08.

2-Amino-4,6-di(4-biphenyl)pyrimidine-5-carbaldehyde (4). Compound **4** was purified by column chromatography using chloroform. Yield 50%, mp 248–251°C (from chloroform). UV: λ_{max} 204 (ε 67,000), 287 (ε 42,000). IR: 3492, 3400 sh., 3290 (NH_2), 1688 cm^{-1} (C=O). ^{1}H NMR (deuteriochloroform): δ 6.10 (s, 2H, NH_2), 7.44–7.46 (m, 2H, 2 × 4″-H), 7.50–7.55 (m, 4H, 2 × 3″,5″-H), 7.68–7.71 (m, 4H, 2 × 2″,6″-H), 7.77 (s, 8H, 2 × 2′,3′,5′,6′-H), 10.01 (s, 1H, CHO). ^{13}C NMR (dimethyl sulfoxide-d_6): δ 116.99, 126.8, 127.6, 128.6, 129.8, 131.1, 137.5, 140.1, 142.0, 163.4, 171.6, 188.9. ms (ESI): *m/z* (%) 428 (100) (M +1). Anal. Calcd. for $C_{29}H_{21}N_3O$: C, 81.48; H, 4.95. Found: C, 81.64; H, 5.04.

4,6-Di(4-tert-butylphenyl)-2-methylpyrimidine (5). Compound **6** was purified by column chromatography using chloroform. Yield 65%, mp 110–111°C. UV: λ_{max} 206 (ε 34,000), 255 (ε 25,000), 283 sh. (ε 21,000), 297 sh. (ε 24,000), 306 (ε 27,000). ^{1}H NMR (deuteriochloroform): δ 1.41 [s, 18H, 2× $C(CH_3)_3$], 2.88 (s, 3H, 2-CH_3), 7.58 (d, *J* = 8.7 Hz, 4H, 2 × 3′,5′-H), 7.88 (s, 1H, 5-H), 8.08 (d, *J* = 8.7 Hz, 4H, 2 × 2′,6′-H). ^{13}C NMR (deuteriochloroform): δ 26.72, 31.50, 35.13, 109.91, 126.17, 127.29, 135.00, 154.33, 164.97, 168.63. Anal. Calcd. for $C_{25}H_{30}N_2$: C, 83.75; H, 8.43. Found: C, 84.06; H, 8.62.

4,6-Bis(3,5-dichlorophenyl)-2-methylpyrimidine (6). Yield 50%, mp 230–231°C (from toluene). UV: λ_{max} 219 (ε 29,000), 247 (ε 12,000), 260 sh. (ε 8100), 295 (ε 12,000), 318 (ε 4600). ^{1}H NMR (deuteriochloroform): δ 2.91 (s, 3H, 2-CH_3), 7.56 (t, ^4J = 1.8 Hz, 2H, 2 × 4′-H), 7.82 (s, 1H, 5-H), 8.07 (d, ^4J = 1.8 Hz, 4H, 2 × 2′,6′-H). ^{13}C NMR (deuteriochloroform): δ 26.6, 110.2, 126.0, 131.0, 136.1, 140.2, 162.9, 169.50. ms (ESI): *m/z* (%) 384 (100) (M^+). Anal. Calcd. for $C_{17}H_{10}Cl_4N_2$: C, 53.16; H. 2,62. Found: C, 53.23; H, 2.57.

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A Facile and Efficient Synthesis of *N*-Substituted Furo[3,4-*b*]indeno[2,1-*e*]pyridine Analogues of Azapodophyllotoxin *via* Microwave-Assisted Multicomponent Reactions

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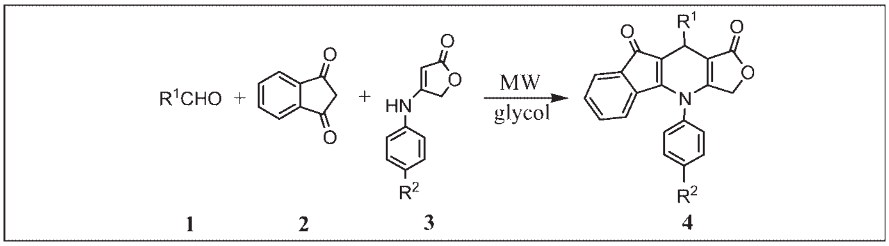

The efficient and facile synthesis of *N*-substituted furo[3,4-*b*]indeno[2,1-*e*]pyridine analogues of azapodophyllotoxin was achieved *via* microwave-assisted multicomponent reactions of aldehyde, 2*H*-indene-1,3-dione and 4-(arylamino)furan-2(5*H*)-one in glycol without catalyst. This method has the obvious advantages over traditional heating ones on short reaction time, high yield, operational simplicity as well as being environmental friendly.

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INTRODUCTION

Tetronic acid derivatives and their metabolites are interesting and intriguing compounds because of their antibiotic [1], anticoagulant [2], antiepileptic [3], antifungal [4], anti-inflammatory [5], and anti-HIV [6] activities. Among them, azapodophyllotoxin (Fig. 1) derivatives are also well-known anticancer agents [7] besides their cardiotonic [8], inotropic [9], pesticidal [10], potassium channel opening [11], and calcium channel agonistic [12] activities. Moreover, more potent and less toxic azapodophyllotoxin derivatives with antitumor activities have also been obtained by extensive structural modifications [13]. However, most modifications were performed on ring B and C (Fig. 1), and the modifications both on ring A and on nitrogen atom were not well documented.

Indenopyridine skeletons, existed in many natural products, such as, onychine and oracin (Fig. 2) as well as lots of synthesized heterocyclic compounds, possess numerous significant bioactivities, namely, anticancer [14], anti-infective [15], anti-inflammatory [16], calcium antagonistic [17], DNA-damaging [18], antimicrobial [19] and anticandidal activities [20]. In addition, not only they are inhibitors against phosphodiesterase [21], cyclic nucleotide synthesis [22], bovine liver glutathione S-transferase (GT) [23], and proliferation of vascular smooth muscle cells [24] but also antagonists of adenosine A2a receptor [25] and human fatty acid synthase thioesterase [26]. It is promising that the modifications on ring A of azapodophyllotoxin, changed into indenole ring, may bring about novel or improved significant bioactivities.

However, survey of the literature reveals only two typical methods on synthesizing *N*-unsubstituted furo[3,4-*b*]indeno[2,1-*e*]pyridine analogues of azapodophyllotoxin. One method is a multistep reaction composed by cyclocondensation of arylideneindandione with 3-aminocrotonic acid ester, both of which should be prepared beforehand, and subsequently intramolecular cyclization treated with NBS to give the target compounds (Scheme 1) [27]. Evidently, this method suffers from the drawbacks of long route, low yields, as well as complicated operation.

Another method is Hantzsch condensation of 1,3-indandione, ammonium acetate, and 3-benzylidenefuran-2,4(3*H*,5*H*)-dione (Scheme 2), which was prepared in advance by condensation of tetronic acid with aromatic aldehyde [21]. However, this method still has some disadvantages such as long reaction time and moderate yields.

In addition, these two methods did not offer the synthesis of *N*-substituted furo[3,4-*b*]indeno[2,1-*e*]pyridine

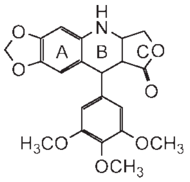


Figure 1. Structure of azapodophyllotoxin.

analogues of azapodophyllotoxin, which may bring about great changes in the bioactivities by the modifications both on nitrogen atom and on ring A of azapodophyllotoxin.

As a result, developing a facile and efficient method on the synthesis of *N*-substituted furo[3,4-*b*]indeno[2,1-*e*]pyridine analogues of azapodophyllotoxin is of great significance.

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry, because the strategies of MCR offer significant advantages over conventional linear-type syntheses [28]. On the other hand, microwave-assisted organic synthesis has been a topic of continued studies as it could lead to higher yields of pure products, easier operation, and shorter reaction time as compared with the traditional heating method [29]. Thus, it goes without saying that the use of atom-economical MCRs, together with the employment of energy-efficient microwave irradiation (MW), must be considered to be facile and efficient synthetic strategy of heterocyclic compounds with important bioactivities in the sense that the combination in itself offers greater potential than the two parts in isolation.

As a continuation of our efforts on structural modifications of azapodophyllotoxin with facile and efficient method [30], herein, we wish to report the synthesis of *N*-substituted furo[3,4-*b*]indeno[2,1-*e*]pyridine analogues of azapodophyllotoxin through three-component reactions of aldehyde **1**, 2*H*-indene-1,3-dione **2** and 4-(arylamino)furan-2(5*H*)-one **3** in glycol under microwave irradiation without catalyst (Scheme 3).

RESULTS AND DISCUSSION

Initially, the three-component reaction of 4-bromobenaldehyde **1c**, 2*H*-indene-1,3-dione **2** and 4-(phenylamino) furan-2(5*H*)-one **3c** was used to optimize the reaction conditions. To find the best suitable solvent, we compared the synthesis of **4c** in different solvents, such as, water, glycol, DMF, glacial acetic acid, and ethanol. The mixture of 4-bromobenaldehyde **1c** (1 mmol), 2*H*-indene-1,3-dione **2** (1 mmol), 4-(phenylamino)furan-2(5*H*)-one **3c** (1 mmol), and corresponding solvent (2 mL) was irradiated under MW at 90°C and 200 W for a given time, then the crude product was purified by recrystallization from EtOH.

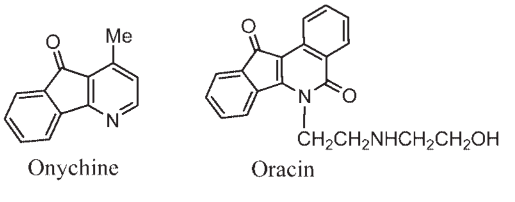
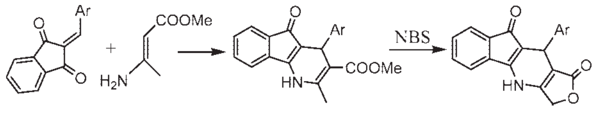


Figure 2. Structures of onychine and oracin.

Scheme 1



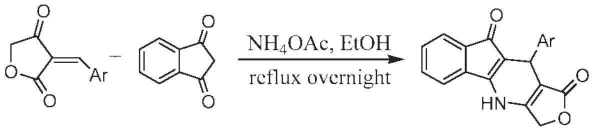
The results (Table 1) reveal that glycol as solvent not only improve the yield but also shorten the time of this reaction. Therefore, glycol was preferred as solvent for all further microwave-assisted reactions.

To optimize the reaction temperature, the reaction of **1c** (1 mmol), **2** (1 mmol), and **3c** (1 mmol) was carried out using glycol (2 mL) as solvent under MW (200 W) at temperatures ranging from 70 to 110°C, with an increment of 10°C each time. Similarly, the crude product was purified by recrystallization from EtOH. The results are shown in Table 2. The yield of product **4c** was increased and the reaction time was shortened when the temperature was increased from 70 to 100°C (Entries 1–4, Table 2), whereas the yield leveled off when the temperature was further increased to 110°C (Entry 5, Table 2). Thus, 100°C is assigned as the most suitable reaction temperature. Furthermore, we found that the yield of this reaction was affected by the volume of glycol. The synthesis of **4c** was tested in different volumes of glycol at 100°C. The outcomes show that 2.0 mL of glycol is optimal as solvent because it generates the highest yield of **4c**.

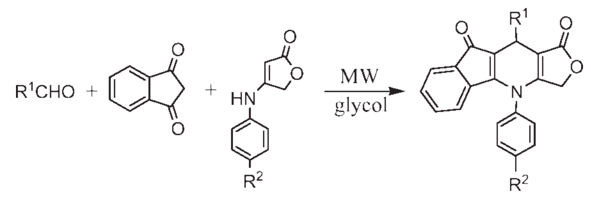
Under these optimized reaction conditions (2.0 mL of glycol, 100°C), a series of novel *N*-substituted furo[3,4-*b*]indeno[2,1-*e*]pyridine analogues of azapodophyllotoxin **4** were synthesized under MW, and the results were summarized in Table 3. As shown in Table 3, this method can be applied to various aromatic aldehydes and enamines of tetronic acid with high yields under the same conditions. Therefore, this synthetic approach has wide scope of applicability.

Moreover, we also performed the synthesis of **4** in glycol at 100°C under standard heating conditions (SC).

Scheme 2



Scheme 3



1 2 3 4

Table 2

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

Entry	*T* (°C)	Time (min)	Yield (%)
1	70	15	77
2	80	12	83
3	90	10	88
4	100	8	92
5	110	8	92

The results (Table 3) reveal that microwave irradiation efficiently promoted the reactions, resulting in dramatic reduction of reaction time, from hours to minutes, and remarkable increase in yields as well.

Although the detailed mechanism of the earlier reaction remains to be fully clarified, the formation of *N*-substituted furo[3,4-*b*]indeno[2,1-*e*]pyridine analogues of azapodophyllotoxin **4** could be explained by a reaction sequence of condensation, addition, cyclization, and dehydration (Scheme 4). First, the condensation of aldehyde **1** and 2*H*-indene-1,3-dione **2** gave the intermediate product **5**. The addition of **3–5** then furnished the intermediate product **6**, which upon intramolecular cyclization and dehydration gave rise to **4**.

All the products were characterized by IR, ^{1}H NMR, and HRMS (ESI). Moreover, the structure of **4g** was also established by X-ray crystallography (Fig. 3) [31].

In conclusion, we have developed an efficient and facile approach to the synthesis of *N*-substituted furo[3,4-*b*]indeno[2,1-*e*]pyridine analogues of azapodophyllotoxin via microwave-assisted MCRs without catalyst. This method has the obvious advantages over traditional heating ones on short reaction time, high yield, operational simplicity as well as being environmental friendly. Besides, this method may provide a shortcut for further investigations on the pharmacological activities of this type of compounds as important and novel azapodophyllotoxin analogues.

EXPERIMENTAL

Microwave irradiation was carried out in a monomodal Emrys^{TM} Creator from Personal Chemistry, Uppsala, Sweden.

Table 1

Solvent optimization for the synthesis of **4c**.

Entry	Solvent	Time (min)	Yield (%)
1	DMF	10	80
2	EtOH	12	69
3	HOAc	12	76
4	Water	12	45
5	Glycol	10	88

Melting points were determined in XT5 apparatus and are uncorrected. IR spectra were recorded on a FTIR-Tensor 27 spectrometer. ^{1}H NMR spectra were measured on a DPX 400 spectrometer operating at 400 MHz, using DMSO-d_6 as solvent and TMS as internal standard. HRMS (ESI) was determined by using micrOTOF-QII HRMS/MS instrument (BRUKER). X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer.

General procedure for the synthesis of compounds 4 with microwave irradiation. Typically, a mixture of aromatic aldehyde **1** (1.0 mmol), 2*H*-indene-1,3-dione **2** (1.0 mmol), 4-(arylamino)furan-2(5*H*)-one **3** (1.0 mmol), and glycol (2.0 mL) was added to the reaction vessel of the monomodal Emrys^{TM} Creator microwave synthesizer and allowed to react under MW at 200 W power (initial power 100 W) and 100°C for several minutes. Upon completion, monitored by TLC, the reaction vessel was cooled to room temperature. The solid compound was collected by filtration and recrystallized from EtOH (95%) to give pure azapodophyllotoxin derivatives **4**.

General procedure for the synthesis of compounds 4 with conventional heating. A mixture containing aromatic aldehyde **1** (1.0 mmol), 2*H*-indene-1,3-dione **2** (1.0 mmol), 4-(arylamino)furan-2(5*H*)-one **3** (1.0 mmol), and glycol (2.0 mL) was introduced into a 10 mL Emrys^{TM} reaction vial, capped, and then stirred at 100°C (oil bath temperature) for a given time. The subsequent work-up procedure was the same as in the microwave irradiation reactions.

10-(4-Fluorophenyl)-4-phenyl-4,10-dihydro-3H-2-oxa-4-aza-cyclopenta[b]fluorene-1,9-dione (4a). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.86–7.85 (m, 1H, ArH), 7.76–7.67 (m, 4H, ArH), 7.52–7.48 (m, 2H, ArH), 7.31–7.25 (m, 2H, ArH), 7.17–7.09 (m, 3H, ArH), 5.53 (d, 1H, J = 7.2 Hz, ArH) 4.79 (s, 1H, CH), 4.76–4.75 (m, 2H, CH_2). IR (KBr, ν, cm^{-1}): 3487, 3068, 2864, 1757, 1689, 1669, 1596, 1553, 1505, 1455, 1407, 1396, 1349, 1319, 1283, 1224, 1185, 1156, 1140, 1113, 1074, 1025, 1013, 899, 861, 836, 803, 787, 775, 764, 730, 707, 620. HRMS (ESI) *m*/*z*: calc. for $C_{26}H_{16}FNO_3$: 432.1007 [M + Na]$^+$, found: 432.0998 [M + Na]$^+$.

10-(4-Chlorophenyl)-4-phenyl-4,10-dihydro-3H-2-oxa-4-aza-cyclopenta[b]fluorene-1,9-dione (4b). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.87–7.85 (m, 1H, ArH), 7.78–7.67 (m, 4H, ArH), 7.50 (d, 2H, J = 8.4 Hz, ArH), 7.39 (d, 2H, J = 8.4 Hz, ArH), 7.32–7.21 (m, 2H, ArH), 7.13–7.09 (m, 1H, ArH), 5.54 (d, 1H, J = 7.6 Hz, ArH), 4.80(s, 1H, CH), 4.76–4.71(m, 2H, CH_2). IR (KBr, ν, cm^{-1}): 3474, 3061, 1754, 1694, 1669, 1595, 1560, 1490, 1454, 1391, 1351, 1283, 1182, 1143, 1114, 1086, 1039, 1025, 1010, 900, 846, 777, 763, 736, 724, 697, 678, 617. HRMS (ESI) *m*/*z*: calc. for $C_{26}H_{16}ClNO_3$: 448.0711 [M + Na]$^+$, found: 448.0703 [M + Na]$^+$.

Table 3

Synthesis of **4** in glycol at 100°C under MW and SC.

Entry	4	R^1	R^2	Time (min)		Yield (%)		Mp (°C)
				MW[a]	SC[b]	MW[a]	SC[b]	
1	**4a**	4-FC_6H_4	H	7	180	89	71	290–291
2	**4b**	4-ClC_6H_4	H	10	240	93	74	280–281
3	**4c**	4-BrC_6H_4	H	8	180	92	73	>300
4	**4d**	C_6H_5	H	10	270	74	61	297–298
5	**4e**	2,4-$Cl_2C_6H_3$	H	7	180	90	76	>300
6	**4f**	4-FC_6H_4	CH_3	8	180	82	68	>300
7	**4g**	4-ClC_6H_4	CH_3	10	210	88	71	>300
8	**4h**	4-BrC_6H_4	CH_3	10	240	85	69	>300
9	**4i**	C_6H_5	CH_3	13	360	71	58	285–286
10	**4j**	2,4-$Cl_2C_6H_3$	CH_3	8	210	91	75	>300
11	**4k**	4-BrC_6H_4	Cl	9	240	86	70	>300
12	**4l**	2,4-$Cl_2C_6H_3$	Cl	8	240	89	73	>300
13	**4m**	4-ClC_6H_4	Cl	10	300	84	72	>300

[a] The time and yields under microwave irradiation conditions.

[b] The time and yields under standard heating conditions.

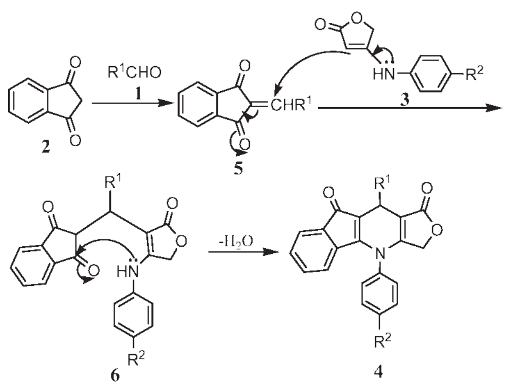
10-(4-Bromophenyl)-4-phenyl-4,10-dihydro-3H-2-oxa-4-aza-cyclopenta[b]fluorene-1,9-dione (4c). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.86–7.84 (m, 1H, ArH), 7.76–7.66 (m, 4H, ArH), 7.52 (d, 2H, J = 8.4 Hz, ArH), 7.43 (d, 2H, J = 8.4 Hz, ArH), 7.31–7.25 (m, 2H, ArH), 7.13–7.09 (m, 1H, ArH), 5.53 (d, 1H, J = 7.6 Hz, ArH), 4.79 (s, 1H, CH), 4.76–4.71 (m, 2H, CH_2). IR (KBr, ν, cm^{-1}): 3446, 3077, 3036, 2926, 2872, 1749, 1690, 1596, 1484, 1454, 1351, 1282, 1182, 1067, 1008, 838, 729, 695. HRMS (ESI) *m/z*: calc. for $C_{26}H_{16}BrNO_3$: 492.0206 [M + Na]$^+$, found: 492.0195 [M + Na]$^+$.

4,10-Diphenyl-4,10-dihydro-3H-2-oxa-4-aza-cyclopenta[b]-fluorene-1,9-dione (4d). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.85–7.84 (m, 1H, ArH), 7.76–7.67 (m, 4H, ArH), 7.45 (d, 2H, J = 7.6 Hz, ArH), 7.35–7.21(m, 5H, ArH), 7.10 (t, 1H, J = 7.6 Hz, ArH), 5.53(d, 1H, J = 7.6 Hz, ArH), 4.77 (s, 1H, CH), 4.76–4.72 (m, 2H, CH_2). IR (KBr, ν, cm^{-1}): 3494, 3063, 3030, 2931, 2862, 1754, 1685, 1595, 1551, 1490, 1451, 1413, 1396, 1349, 1319, 1283, 1182, 1139, 1112, 1074, 1023, 1012, 946, 897, 835, 802, 790, 765, 727, 717, 696, 624. HRMS (ESI) *m/z*: calc. for $C_{26}H_{17}NO_3$: 414.1101 [M + Na]$^+$, found: 414.1108 [M + Na]$^+$.

10-(2,4-Dichlorophenyl)-4-phenyl-4,10-dihydro-3H-2-oxa-4-aza-cyclopenta[b]fluorene-1,9-dione (4e). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.85 (d, J = 7.2 Hz, 1H, ArH), 7.76 (d, J = 7.6 Hz, 1H, ArH), 7.73–7.68 (m, 3H, ArH), 7.65 (d, J = 8.4 Hz, 1H, ArH), 7.58 (d, J = 2.0 Hz, 1H, ArH), 7.40 (dd, J = 8.4, 2.0 Hz, 1H, ArH), 7.29–7.26 (m, 2H, ArH), 7.14–7.08 (m, 1H, ArH), 5.54 (d, J = 7.6 Hz, 1H, ArH), 5.23 (s, 1H, CH), 4.80–4.70 (m, 2H, CH_2); IR (KBr, ν, cm^{-1}): 3060, 1758, 1691, 1668, 1595, 1557, 1497, 1469, 1454, 1407, 1392, 1354, 1283, 1185, 1144, 1038, 1025, 1011, 900, 869, 845, 763, 724, 708, 697. HRMS (ESI) *m/z*: calc. for $C_{26}H_{15}Cl_2NO_3$: 482.0322 [M + Na]$^+$, found: 482.0320 [M + Na]$^+$.

10-(4-Fluorophenyl)-4-p-tolyl-4,10-dihydro-3H-2-oxa-4-aza-cyclopenta[b]fluorene-1,9-dione (4f). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.72 (d, 1H, J = 8.0 Hz, ArH), 7.61 (d, 1H, J = 7.6 Hz, ArH), 7.50–7.45 (m, 4H, ArH), 7.31–7.24 (m, 2H, ArH), 7.17–7.11 (m, 3H, ArH), 5.61 (d, 1H, J = 7.6 Hz, ArH), 4.78 (s, 1H, CH), 4.74–4.73 (m, 2H, CH_2), 2.47 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3483, 3067, 2923, 2871, 1756, 1684, 1604, 1552, 1510, 1455, 1412, 1348, 1319, 1283, 1224, 1185, 1153, 1143, 1112, 1093, 1074, 1038, 1027, 1011, 951, 901, 867, 848, 833, 806, 790, 761, 732, 709, 695, 682,

Scheme 4



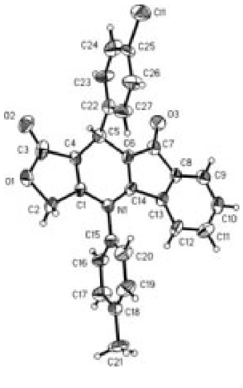


Figure 3. ORTEP diagram of **4g**.

649, 606, 588. HRMS (ESI) *m/z*: calc. for $C_{27}H_{18}FNO_3$: 446.1163 [M + Na]$^+$, found: 446.1160 [M + Na]$^+$.

10-(4-Chlorophenyl)-4-p-tolyl-4,10-dihydro-3H-2-oxa-4-aza-cyclopenta[b]fluorene-1,9-dione (4g). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.72 (d, 1H, *J* = 8.0 Hz, ArH), 7.61 (d, 1H, *J* = 8.0 Hz, ArH), 7.50–7.37 (m, 6H, ArH), 7.31–7.25 (m, 2H, ArH), 7.13 (t, 1H, *J* = 6.8 Hz, ArH), 5.61 (d, 1H, *J* = 7.6 Hz, ArH), 4.78 (s, 1H, CH), 4.74–4.73 (m, 2H, CH_2), 2.47 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3446, 2869, 1751, 1682, 1552, 1486, 1349, 1283, 1141, 1086, 1011, 864, 761, 694, 682. HRMS (ESI) *m/z*: calc. for $C_{27}H_{18}ClNO_3$: 462.0868 [M + Na]$^+$, found: 462.0860 [M + Na]$^+$.

10-(4-Bromophenyl)-4-p-tolyl-4,10-dihydro-3H-2-oxa-4-aza-cyclopenta[b]fluorene-1,9-dione (4h). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.72 (d, 1H, *J* = 8.0 Hz, ArH), 7.61 (d, 1H, *J* = 8.0 Hz, ArH), 7.53–7.41 (m, 6H, ArH), 7.31–7.25 (m, 2H, ArH), 7.15–7.11 (m, 1H, ArH), 5.61 (d, 1H, *J* = 8.0 Hz, ArH), 4.78 (s, 1H, CH), 4.77–4.69 (m, 2H, CH_2), 2.47 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3488, 3065, 2926, 2868, 1752, 1682, 1553, 1483, 1348, 1183, 1071, 835, 761, 695, 679, 647, 583. HRMS (ESI) *m/z*: calc. for $C_{27}H_{18}BrNO_3$: 506.0363 [M + Na]$^+$, found: 506.0345 [M + Na]$^+$.

10-Phenyl-4-p-tolyl-4,10-dihydro-3H-2-oxa-4-aza-cyclopenta[b]fluorene-1,9-dione (4i). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.72–7.70 (m, 1H, ArH), 7.63–7.61 (m, 1H, ArH), 7.49–7.44 (m, 4H, ArH), 7.35–7.21 (m, 5H, ArH), 7.15–7.11 (m, 1H, ArH), 5.62 (d, 1H, *J* = 7.2 Hz, ArH), 4.79 (s, 1H, CH), 4.78–4.72 (m, 2H, CH_2), 2.45 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3378, 3054, 2922, 2858, 1747, 1686, 1543, 1319, 1180, 1045, 826, 798, 682, 669, 634, 576. HRMS (ESI) *m/z*: calc. for $C_{27}H_{19}NO_3$: 428.1258 [M + Na]$^+$, found: 428.1260 [M + Na]$^+$.

10-(2,4-Dichlorophenyl)-4-p-tolyl-4,10-dihydro-3H-2-oxa-4-aza-cyclopenta[b]fluorene-1,9-dione (4j). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.73–7.71 (m, 1H, ArH), 7.64–7.61 (m, 2H, ArH), 7.58–7.57 (m, 1H, ArH), 7.48 (t, 2H, *J* = 8.0 Hz, ArH), 7.40 (dd, 1H, *J* = 8.0, 2.0 Hz, ArH), 7.28–7.27 (m, 2H, ArH), 7.16–7.12 (m, 1H, ArH), 5.63 (d, 1H, *J* = 8.0 Hz, ArH), 5.22 (s, 1H, CH), 4.78–4.69 (m, 2H, CH_2), 2.46 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3071, 1756, 1691, 1666, 1596, 1584, 1557, 1510, 1469, 1394, 1347, 1321, 1282, 1234, 1185, 1144, 1098, 1074, 1038, 1024, 1012, 901, 868, 844, 823, 792, 762, 730, 706, 692. HRMS (ESI) *m/z*: calc. for $C_{27}H_{17}Cl_2NO_3$: 496.0478 [M + Na]$^+$, found: 496.0470 [M + Na]$^+$.

10-(4-Bromophenyl)-4-(4-chlorophenyl)-4,10-dihydro-3H-2-oxa-4-aza-cyclopenta[b]fluorene-1,9-dione (4k). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.73 (d, 1H, *J* = 8.0 Hz, ArH), 7.64 (d, 1H, *J* = 8.0 Hz, ArH), 7.58–7.49 (m, 6H, ArH), 7.39–7.28 (m, 2H, ArH), 7.22–7.17 (m, 1H, ArH), 5.69 (d, 1H, *J* = 8.0 Hz, ArH), 4.80 (s, 1H, CH), 4.78–4.69 (m, 2H, CH_2). IR (KBr, ν, cm^{-1}): 3078, 1762, 1689, 1557, 1473, 1320, 1234, 1177, 1079, 1027, 1016, 838, 765, 698, 679, 643, 586. HRMS (ESI) *m/z*: calc. for $C_{26}H_{15}BrClNO_3$: 525.9817 [M + Na]$^+$, found: 525.9783 [M + Na]$^+$.

10-(2,4-Dichlorophenyl)-4-(4-chlorophenyl)-4,10-dihydro-3H-2-oxa-4-aza-cyclopenta[b]fluorene-1,9-dione (4l). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.77–7.72 (m, 1H, ArH), 7.68–7.63 (m, 2H, ArH), 7.60–7.57 (m, 1H, ArH), 7.50 (t, 2H, *J* = 8.0 Hz, ArH), 7.43 (d, 1H, *J* = 8.0 Hz, ArH), 7.30–7.27 (m, 2H, ArH), 7.20–7.13 (m, 1H, ArH), 5.67 (d, 1H, *J* = 8.0 Hz, ArH), 5.28 (s, 1H, CH), 4.79–4.71 (m, 2H, CH_2). IR (KBr, ν, cm^{-1}): 3085, 1768, 1680, 1579, 1490, 1322, 1236, 1180, 1056, 1026, 1018, 840, 769, 698, 675, 646, 588. HRMS (ESI) *m/z*: calc. for $C_{26}H_{14}Cl_3NO_3$: 515.9932 [M + Na]$^+$, found: 515.9918 [M + Na]$^+$.

4,10-Di-(4-chlorophenyl)-4,10-dihydro-3H-2-oxa-4-aza-cyclopenta[b]fluorene-1,9-dione (4m). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.72 (d, 1H, *J* = 8.0 Hz, ArH), 7.66 (d, 1H, *J* = 8.0 Hz, ArH), 7.59–7.48 (m, 6H, ArH), 7.40–7.32 (m, 2H, ArH), 7.26–7.19 (m, 1H, ArH), 5.72 (d, 1H, *J* = 8.0 Hz, ArH), 4.81 (s, 1H, CH), 4.79–4.69 (m, 2H, CH_2). IR (KBr, ν, cm^{-1}): 3085, 1776, 1687, 1565, 1468, 1328, 1239, 1172, 1085, 1032, 1018, 839, 764, 688, 673, 645, 587. HRMS (ESI) *m/z*: calc. for $C_{26}H_{15}Cl_2NO_3$: 482.0322 [M + Na]$^+$, found: 482.0307 [M + Na]$^+$.

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[31] The single-crystal growth was carried out in ethanol at room temperature. X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer. Crystal data for **4g**: $C_{27}H_{18}ClNO_3$, red brown, crystal dimension 0.09 mm × 0.06 mm × 0.04 mm, monoclinic, space group P2(1)/c, $a = 10.822(5)$ Å, $b = 10.783(6)$ Å, $c = 18.355(9)$ Å, $\alpha = \gamma = 90°$, ß = 94.289(11)°, $V = 2135.8(18)$ Å^3, $M_r = 439.87$, $Z = 4$, Dc = 1.368 mg/m^3, $\lambda = 0.71073$ Å, μ(MoKα) = 0.209 mm^{-1}, $F(000) = 912$, $R_1 = 0.0892$, $wR_2 = 0.1061$.

One-Pot Synthesis of Imidazo[1,2-*c*]quinazoline Derivatives from Nitro-Componds Reduced by Zinc

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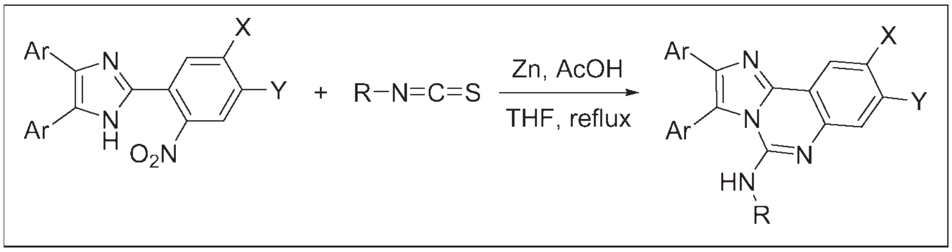

An efficient, convenient, one-pot synthesis of imidazo[1,2-*c*]quinazolines was accomplished in good yields via the novel reductive cyclization of 2-(2-nitrophenyl)-1*H*-imidazole with isothiocyanates mediated by zinc dust.

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INTRODUCTION

The quinazolinone skeleton is a building block for the preparation of natural purine base, alkaloids [1], many biologically active compounds, and intermediates in organic synthesis [2]. The quinazoline moiety present in imidazoquinazolines is responsible for a wide range of biological activities ranging form anticonvulsants and antibacterial to antidiabetic agents [3–9].

As a consequence, much attention has been paid to the development of efficient methods for the preparation of 5-amino derivatives of imidazo[1,2-*c*]quinazoline. The first method involved treatment of 6-mercaptobenzimidazoquinazoline with amines [10] and the second method involved an aza-wittig reaction of iminophosphoranes derived from 2-(*o*-azido)phenylbenzimidazole with isocyanates [11]. Recently, several methods have been developed for synthesizing this heterocyclic system. Sharma et al. [12] developed an efficient strategy for the preparation of imidazoquinazolines, but the use of DBU and multiple steps limited the method. We developed an efficient and one-pot synthesis of imidazoquinazolines from 2-(2-nitrophenyl)-1*H*-imidazole induced by low-valent titanium reagent [13], but this method required anhydrous system. As mentioned in our earlier works, herein, we reported a convenient protocol for the synthesis of imidazo[1,2-*c*]quinazolines in one-pot via the reductive cyclization of 2-(2-nitrophenyl)-1*H*-imidazole and isothiocyanates mediated by zinc dust.

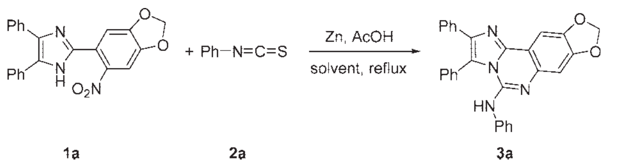
RESULTS AND DISCUSSION

On the basic of our previous experience, we selected 2-(2-nitro-4,5-methylenedioxyphenyl)-4,5-diphenyl-1*H*-imidazole (**1a**) and phenyl isothiocyanate (**2a**) as model substrates to optimize the experimental conditions for the proposed reductive cyclization reaction (Scheme 1). The results are summarized in Table 1.

The results obtained from these experiments indicated that the reaction solvents had a significant influence on the success of this reaction. No product was obtained when the solvent was H_2O or MeOH. When the solvent was AcOH, DMF, CH_3CN or $CHCl_3$, the yield of the product was 40–80%. When THF was used as solvent at refluxing temperature, the products **3a** was obtained in highest yield. To further evaluate the influence of the ratio of **1a**: Zn, this reaction was carried out with different ratio. When the ratio of substrate:Zn was 1:1, 45% yield of the product was obtained in 20 h, it can be seen that increasing the catalyst loading increase the yield. When the ratio of substrate:Zn was 1:5, the yield of the product decrease. From the results, it is obvious that the best ratio is 1:4.

Having established an optimal condition for the protocol, we performed a more detailed examination of the substrates. Thus, the behavior of a variety of substrates, which include different 2-(2-nitrophenyl)-1*H*-imidazole as well as different isothiocyanates was examined (Scheme 2). The results are summarized in Table 2. As

Scheme 1



shown in Table 2, for series of **3**, either the aromatic ring containing electron-withdrawing groups (such as halides) or electron-donating groups (such as alkyl group), reacted well to give the corresponding products **3** in good yields under the same reaction conditions. So, we concluded that no obvious effects from the electronic or nature of the aromatic ring substrates were observed in the above reactions.

We propose the possible following mechanism to account for the reaction. At first step 2-(2-nitrophenyl)-1*H*-imidazole **1** was reduced by Zn/H^+ to 2-(2-aminophenyl)-1*H*-imidazole **4**, the addition reaction of reductive product **4** with isothiocyanates **2** to afford intermediate **5**, intermediate **5** was cyclized by the nucleophilic attack of nitrogen atoms on C=S group and gave the intermediate **6**. Finally the expected products **3** were afforded by losing of H_2S (Scheme 3).

The structures of product **3** were identified by IR, ^{1}H NMR, and HRMS. The structure of product **3a** was further confirmed by X-ray diffraction analysis (Fig. 1).

In conclusion, a series of imidazo[1,2-*c*]quinazolines were synthesized by the reaction of 2-(2-nitrophenyl)-1*H*-imidazoles and isothiocyanates induced by zinc dust. This protocol has advantages of accessible materials, handy manipulation (only one-pot), and isolation of products via simple recrystallization.

Table 1

Optimization for the reductive cyclization reaction.

Entry	Solvent	Ratio[a]	Reaction time (h)	Yield (%)
1	THF	1:2	20	45
2	THF	1:3	12	60
3	THF	1:4	1.5	86
4	THF	1:5	1.5	85
5	MeOH	1:4	12	0
6	H_2O	1:4	12	0
7	AcOH	1:4	2	50
8	CH_3CN	1:4	1.5	80
9	$CHCl_3$	1:4	2	42
10	DMF	1:4	1.5	73

[a] Ratio of **1a** and zinc dust.

EXPERIMENTAL

THF was untreated. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Varian FT-1000 spectrometer in KBr with absorptions in cm^{-1}. ^{1}H NMR was determined on a Varian Inova-400 MHz or a Varian NMR System 300 MHz spectrometer in DMSO-d_6 solution. *J* values are in Hz. Chemical shifts are expressed in ppm downfield from internal standard TMS. HRMS data were obtained using TOF–MS microma GCT-TOF instrument. X-ray diffraction was recorded on a Mercury Bruker Smart-1000 CCD diffractometer.

General procedure for the synthesis of 2-(2-nitrophenyl)-1*H*-imidazole 1. A solution of benzil (5 mmol) in AcOH was treated with 2-nitrobenzaldehyde (5 mmol) and NH_4OAc (40 mmol) [12]. The reaction mixture was refluxed for 4 h, then AcOH was evaporated, and the residue was treated with a 10% aqueous solution of $NaHCO_3$ (pH 8). The mixture was extracted with EtOAc (2 × 25 mL), washed with brine (25 mL), and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give a yellow solid.

General procedure for the synthesis of imidazol[1,2-*c*]quinazolines 3. To a solution of 2-(2-nitrophenyl)-1*H*-imidazole (1 mmol) and isothiocyanates (1 mmol) in THF (15 mL), zinc dust (4 mmol) and AcOH (0.5 mL) was added. The reaction mixture was refluxed for 2 h. After this period, TLC analysis of the mixture showed the reaction to be completed. The reaction mixture was quenched with 5% HCl (15 mL) and extracted with $CHCl_3$ (3 × 20 mL). The combined extracts were washed with water (3 × 20 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product was purified by recrystallization from acetone.

(8,9-Methylenedioxy-2,3-diphenylimidazo[1,2-c]quinazolin-5-yl)phenylamine (3a). This compound was obtained as solid with mp 215–217°C; IR (KBr) ν: 3393, 3059, 2902, 1623, 1598, 1557, 1533, 1466, 1377, 1340, 1271, 1217, 1148, 1036, 941, 864, 824, 750, 706 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): 6.19 (s, 2H, OCH_2O), 6.78 (s, 1H, NH), 7.00 (t, *J* = 8.0 Hz, 1H, ArH), 7.15 (s, 1H, ArH), 7.18 (s, 2H, ArH), 7.25–7.31 (m, 5H, ArH), 7.54 (d, *J* = 7.6 Hz, 2H, ArH), 7.68–7.72 (m, 2H, ArH), 7.76–7.82 (m, 4H, ArH).

HRMS [Found: *m/z* 456.1578 (M^+), Cacld for $C_{29}H_{20}N_4O_2$: M, 456.1586].

(2,3-Diphenylimidazo[1,2-c]quinazolin-5-yl)phenylamine (3b). This compound was obtained as solid with mp 195–197°C (ref. 12, 200–201°C); IR (KBr) ν: 3340, 1625, 1567, 1597, 1537, 1497, 1477, 1444, 1371, 1331, 1232, 1110, 1027, 927, 765, 703 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): 6.89 (s, 1H, NH), 7.02–7.06 (m, 1H, ArH), 7.21–7.23 (m, 2H, ArH), 7.27–7.33 (m, 5H, ArH), 7.47–7.51 (m, 1H, ArH), 7.56–7.58 (m, 2H, ArH), 7.65–7.85 (m, 7H, ArH), 8.43–8.45 (m, 1H, ArH).

Scheme 2

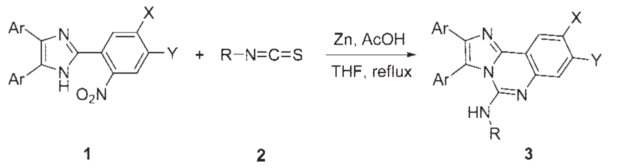


Table 2

Synthesis of imidazo[1,2-*c*]quinazolines.

Entry	Ar	X	Y	R	Time (h)	Yield (%)[a]
3a	C_6H_5	OCH_2O		C_6H_5	1.5	86
3b	C_6H_5	H	H	C_6H_5	2.5	80
3c	4-$CH_3C_6H_4$	H	H	C_6H_5	3	92
3d	4-$CH_3OC_6H_4$	Cl	H	4-$CH_3C_6H_4$	2.5	75
3e	C_6H_5	H	H	4-$CH_3C_6H_4$	1.5	83
3f	C_6H_5	H	H	4-ClC_6H_4	3	65
3g	C_6H_5	Cl	H	C_6H_5	4	63
3h	4-$CH_3C_6H_4$	Cl	H	C_6H_5	3	81
3i	4-$CH_3OC_6H_4$	H	H	3-$CH_3C_6H_4$	1.5	85
3j	C_6H_5	H	H	3-$CH_3C_6H_4$	1.5	72

[a] Isolated yield.

HRMS [Found: *m/z* 412.1688 (M^+), Cacld for $C_{28}H_{20}N_4$: M, 412.1688].

{2,3-Bis(4-methylphenyl)imidazo[1,2-c]quinazolin-5-yl}phenylamine (3c). This compound was obtained as solid with mp 241–243°C; IR (KBr) ν: 3387, 3031, 2915, 2857, 1623, 1599, 1565, 1534, 4550, 1498, 1474, 1461, 1353, 1338, 1282, 1185, 1111, 924, 896, 823, 763, 707, 689, 671 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 2.27 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 6.95 (s, 1H, NH), 7.02–7.05 (m, 1H, ArH), 7.11 (d, J = 8.0 Hz, 2H, ArH),7.21–7.24 (m, 2H, ArH), 7.29–7.33 (m, 2H, ArH), 7.45–7.49 (m, 3H, ArH), 7.53 (d, J = 7.2 Hz, 2H, ArH), 7.62–7.71 (m, 4H, ArH), 8.41–8.43 (m, 1H, ArH).

HRMS [Found: *m/z* 440.2008 (M^+), Cacld for $C_{30}H_{24}N_4$: M, 440.2001].

{9-Chloro-2,3-bis(4-methoxyphenyl)imidazo[1,2-c]quinazolin-5-yl}-p-tolylamine (3d). This compound was obtained as solid with mp 199–200°C; IR (KBr) ν: 3370, 1624, 1610, 1579, 1559, 1533, 1516, 1490, 1473, 1377, 1335, 1289, 1252, 1177, 1073, 1036, 833, 668 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 2.25 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.89 (d, J = 8.4 Hz, 2H, ArH), 6.97 (s, 1H, NH), 7.11–7.16 (m, 4H, ArH), 7.26–7.28 (m, 2H, ArH), 7.49–7.52 (m, 2H, ArH), 7.62–7.65 (m, 2H, ArH), 7.72–7.75 (m, 2H, ArH), 8.32 (s, 1H, ArH).

HRMS [Found: *m/z* 520.1665 (M^+), Cacld for $C_{31}H_{25}{}^{35}ClN_4O_2$: M, 520.1666].

(2,3-Diphenylimidazo[1,2-c]quinazolin-5-yl)-p-tolylamine (3e). This compound was obtained as solid with mp 196–198°C (ref. 13, 192–194°C); IR (KBr) ν: 3400, 3055, 2921, 1630, 1599, 1564, 1543, 1509, 1472, 1378, 1351, 1334, 1240, 1227, 1109, 1026, 924, 831, 814, 778, 760, 712 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 2.24 (s, 3H, CH_3), 6.78 (s, 1H, NH), 7.01 (s, 4H, ArH), 7.26–7.33 (m, 3H, ArH), 7.46–7.48 (m, 1H, ArH), 7.56–7.58 (m, 2H, ArH), 7.64 (d, J = 4.0 Hz, 2H, ArH), 7.70–7.84 (m, 5H, ArH), 8.42–8.44 (m, 1H, ArH).

HRMS [Found: *m/z* 426.1846 (M^+), Cacld for $C_{29}H_{22}N_4$: M, 426.1844].

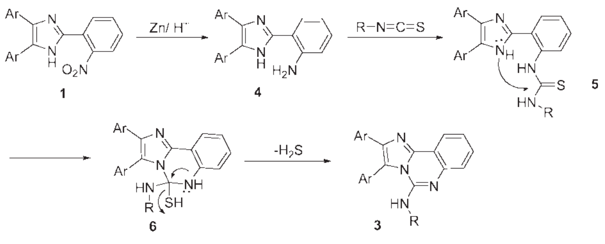
4-Chlorophenyl(2,3-diphenylimidazo[1,2-c]quinazolin-5-yl)amine (3f). This compound was obtained as solid with mp 212–214°C (ref. 13, 208–210°C); IR (KBr) ν: 3400, 3054, 1625, 1596, 1566, 1536, 1490, 1472, 1444, 1404, 1332, 1293, 1088, 830, 802, 757, 709 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 6.92 (s, 1H, NH), 7.21–7.23 (m, 2H, ArH), 7.26–7.52 (m, 5H, ArH), 7.47–7.51 (m, 1H, ArH), 7.56 (d, J = 7.6 Hz, 2H, ArH), 7.66–7.82 (m, 7H, ArH), 8.44 (d, J = 8.0 Hz, 1H, ArH).

HRMS [Found: *m/z* 446.1296 (M^+), Cacld for $C_{28}H_{19}{}^{35}ClN_4$: M, 446.1298].

(9-Chloro-2,3-diphenylimidazo[1,2-c]quinazolin-5-yl)phenylamine (3g). This compound was obtained as solid with mp 190–191°C (ref. 13, 182–184°C); IR (KBr) ν: 3387, 3058, 1627, 1598, 1559, 1532, 1497, 1472, 1446, 1378, 1336, 1234, 1071, 1027, 925, 877, 818, 774, 755, 714, 689 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 6.89 (s, 1H, NH), 7.04 (t, J = 7.6 Hz, 1H, ArH), 7.19 (d, J = 8.4 Hz, 2H, ArH), 7.27–7.31 (m, 5H, ArH), 7.55–7.57 (m, 2H, ArH), 7.61–7.74 (m, 4H, ArH), 7.78 (d, J = 7.2 Hz, 1H, ArH), 7.84 (d, J = 7.2 Hz, 2H, ArH), 8.34 (d, J = 2.4 Hz, 1H, ArH).

HRMS [Found: *m/z* 446.1296 (M^+), Cacld for $C_{28}H_{19}{}^{35}ClN_4$: M, 446.1298].

Scheme 3



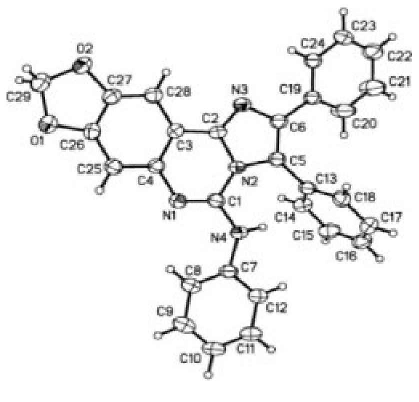


Figure 1. X-ray structure of **3a**.

{9-Chloro-2,3-bis(4-methylphenyl)imidazo[1,2-c]quinazolin-5-yl}phenylamine (3h). This compound was obtained as solid with mp 226–227°C. IR (KBr) ν: 3387, 2916, 2857, 1626, 1597, 1559, 1530, 1497, 1472, 1450, 1374, 1342, 1246, 1185, 1072, 1016, 929, 819, 755, 691 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 2.28 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 6.97 (s, 1H, NH), 7.03–7.08 (m, 1H, ArH), 7.12 (d, $J = 8.0$ Hz, 2H, ArH), 7.21–7.23 (m, 2H, ArH), 7.31 (t, $J = 8.0$ Hz, 2H, ArH), 7.46 (d, $J = 8.4$ Hz, 2H, ArH), 7.54 (d, $J = 7.6$ Hz, 2H, ArH), 7.63–7.72 (m, 4H, ArH), 8.35 (d, $J = 2.4$ Hz, 1H, ArH).

HRMS [Found: *m/z* 474.1609 (M^+), Cacld for $C_{30}H_{23}{}^{35}ClN_4$: M, 474.1611].

{2,3-Bis(4-methoxyphenyl)imidazo[1,2-c]quinazolin-5-yl}-m-tolylamine (3i). This compound was obtained as solid with mp 202–204°C. IR (KBr) ν: 3383, 3064, 2962, 2934, 2834, 1623, 1612, 1567, 1535, 1515, 1493, 1475, 1461, 1411, 1375, 1333, 1286, 1248, 1174, 1109, 1024, 839, 806, 784, 762, 742, 673 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 2.26 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.85–6.87 (m, 2H, ArH), 6.89 (s, 1H, NH), 6.96 (s, 2H, ArH), 7.15–7.21 (m, 2H, ArH), 7.28 (d, $J = 8.4$ Hz, 2H, ArH), 7.43–7.47 (m, 1H, ArH), 7.52 (d, $J = 8.4$ Hz, 2H, ArH), 7.60–7.67 (m, 2H, ArH), 7.74 (d, $J = 8.4$ Hz, 2H, ArH), 8.41 (d, $J = 3.6$ Hz, 1H, ArH).

HRMS [Found: *m/z* 486.2038 (M^+), Cacld for $C_{31}H_{26}N_4O_2$: M, 486.2056].

(2,3-Diphenylimidazo[1,2-c]quinazolin-5-yl)-m-tolylamine (3j). This compound was obtained as solid with mp 168–170°C. IR (KBr) ν: 3399, 3050, 2917, 1624, 1588, 1566, 1533, 1473, 1441, 1374, 1331, 1264, 1194, 1109, 776, 761, 716, 705 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): 2.23 (s, 3H, CH_3), 6.80–6.84 (m, 2H, NH + ArH), 6.98–7.00 (m, 2H, ArH), 7.14 (t, $J = 7.8$ Hz, 1H, ArH), 7.24–7.30 (m, 3H, ArH), 7.42–7.48 (m, 1H, ArH), 7.53–7.56 (m, 2H, ArH), 7.59–7.66 (m, 2H, ArH), 7.69–7.82 (m, 5H, ArH), 8.40 (d, $J = 7.5$ Hz, 1H, ArH).

HRMS [Found: *m/z* 426.1844 (M^+), Cacld for $C_{29}H_{22}N_4$: M, 426.1844].

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Synthesis, Characterization, and Antimicrobial Evaluation of Novel 4-Pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido[4′,3′:4,5] Thieno[2,3-d]pyrimidine Derivatives

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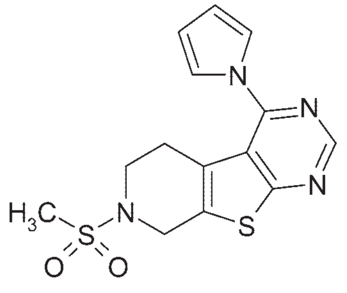
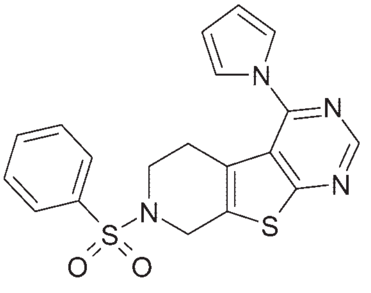


6a



6f

A series of novel 7-alkyl/aryl sulfonyl-4-pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido[4′,3′:4,5]thieno[2,3-d] pyrimidine **6** were synthesized for evaluation of their antibacterial and antifungal activity. The structures were determined by IR, NMR, mass spectroscopy, and elemental analysis. They were screened for activities against bacterial and fungal strains.

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INTRODUCTION

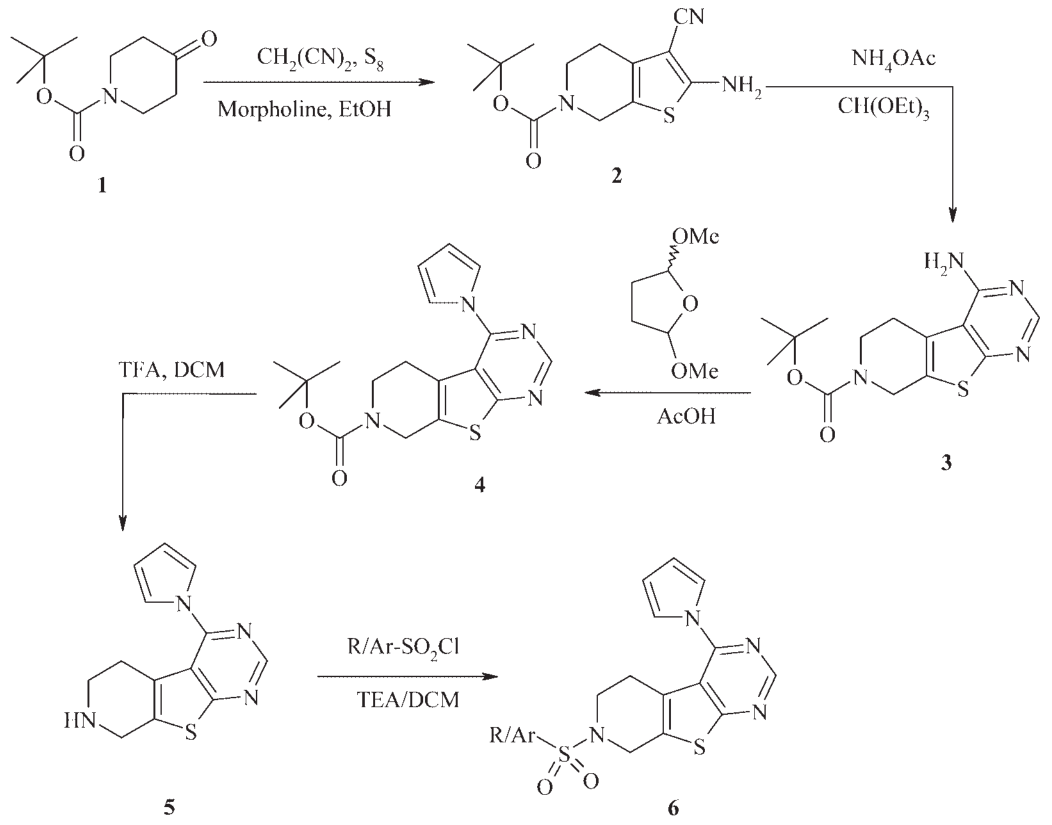
Fused pyrimidines continue to attract considerable attention because of their great practical usefulness, primarily, due to a very wide spectrum of biological activities. This is evident, in particular, from publications of regular reviews on the chemistry of systems where the pyrimidine ring is fused to various heterocycles, such as, purines [1], pteridines [2], quinazolines [3], pyridopyrimidines [4,5], triazolopyrimidines [6], pyrazolopyrimidines [7], pyrimidoazepines [8], furopyrimidines, and pyrrolopyrimidines. Thienopyrimidines occupy a special position among these compounds. Along with some other pyrimidine systems containing an annulated five-membered heteroaromatic ring, thienopyrimidines are structural analogs of biogenic purines and can be considered as potential nucleic acid antimetabolites. Earlier, various aspects of the chemistry and biology of isomeric thienopyrimidines have been reviewed [9,10]. The chemistry of pyrimidines and its derivatives has been studied over a century due to their diverse biological activities [11–14]. Thienopyrimidine possess various physiological and biological properties, and thus, find important use in medicine. According to recent literature survey, thienopyrimidine have been found to have antibacterial [15], antiviral [16], anticancer [17–19], analgesic [20], and antimalarial [21] activities. Though many synthetic strategies have been reported for the preparation of thienopyrimidine derivatives, most of them include use of expensive, commercially nonavailable or hazardous reagents, drastic reaction conditions, longer reaction time and difficult work-up [22–27]. In the view of biological importance of thienopyrimidine, we aimed the synthesis of a series of novel 7-alkyl/aryl sulfonyl-4-pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido[4′,3′:4,5]thieno [2,3-d]pyrimidine **6**.

RESULTS AND DISCUSSION

Chemistry. As shown in synthetic Scheme 1, the synthetic route involves the Gewald reaction [28] of boc-piperidone **1** with malononitrile and sulfur in presence of morpholine in refluxing ethanol to obtain 2-amino thiophene derivative **2**. The formation of 2-amino thiophene **2** was evident from the ^{1}H NMR spectra and mass spectrometry.

The cyclization of 2-amino thiophene **2** with triethyl orthoformate and ammonium acetate at 120°C led to formation of thienopyrimidine derivative **3.** In

Scheme 1



the ^{1}H NMR spectra of **3**, one aromatic proton resonance of pyrimidine ring was observed at 8.85 δδas a singlet, in addition molecular ion peak (M+, 90%) in mass spectrum was also observed. The compound **3** was further reacted with 2,5-dimethoxy-tetrahydrofuran in refluxing acetic acid furnished pyrrole derivative **4**. The identity of pyrrole **4** was established by mass spectrometry and ^{1}H NMR spectra, the aromatic protons resonance of pyrrole ring were observed at 6.32 δ, J = 2.1 and 7.34 δ, J = 2.0 as two doublet. The hydrolysis of carbamate group by TFA furnished secondary amine derivative **5**, which was supported by molecular ion peak in mass spectrum and ^{1}H NMR spectra, where a singlet at 1.38 δ for nine protons of boc group was not present. The target compounds 7-alkyl/aryl sulfonyl-4-pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine **6a–j** were obtained with excellent yield, by reacting secondary amine **5** with various aryl or alkyl sulfonyl chloride in presence of TEA as base.

The structure of all newly synthesized compounds **6a–j** were established on the basis of elemental analysis and spectral (IR, ^{1}H NMR, and mass) data. The physical characterization data are listed in Table 1.

The ^{1}H NMR spectral data of compound **6a** revealed a singlet of CH_3SO_2 group at 2.97 δ, a singlet of pyrimidine ring at 8.95 δ and two doublet of pyrrole ring at 6.36 δ, J = 2.0 Hz and 7.35 δ,J = 2.0 Hz. The IR spectra of **6a** revealed $-SO_2$ absorptions at 1334 cm^{-1} and 1159 cm^{-1}. In addition, the EI-MS spectra of **6a** showed a molecular ion peak (M+, 90%).

In conclusion, we have developed a facile and efficient synthetic method for the preparation of novel 7-alkyl/aryl sulfonyl-4-pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine **6**.

Biological activities.

Antibacterial and antifungal activities. The newly synthesized derivatives were evaluated for their *in vitro* antibacterial activity against Gram-positive *Staphylococcus aureus* and *Streptococcus pyogenes*, Gram-negative *Escherichia coli* and *Pseudomonas aeruginosa*, and antifungal activity against *Candida albicans* and *Aspergillus niger* by micro broth dilution methods [29–31]. The standard strains used for screening antibacterial and antifungal activities were procured from Institute of Microbial Technology (IMTECH), Chandigarh, India. The MIC values are given in Table 2. The standard drugs used for antibacterial activity were ampicillin and ciprofloxacin,

Table 1

Physical characterization data.

Compound	R/Ar	Physical state	Time (h)	Mp (°C)	Yield (%)	Molecular formula/M.W.	Analysis (%) Calcd./found C	H	N
6a	Me	White crystals	3	112–115	93	$C_{14}H_{14}N_4O_2S_2$	50.28	4.22	16.75
						334	50.14	4.31	16.68
6b	Et	White crystals	4	74–75	90	$C_{15}H_{16}N_4O_2S_2$	51.71	4.63	16.08
						348	51.54	4.27	16.21
6c	iso-Pr	Off white crystals	5	77–79	89	$C_{16}H_{18}N_4O_2S_2$	53.02	5.01	15.46
						362	53.23	4.86	15.51
6d	*n*-Pr	White crystals	4	91–93	91	$C_{16}H_{18}N_4O_2S_2$	53.02	5.01	15.46
						362	53.23	5.12	16.31
6e	*n*-Bu	Off white crystals	5	113–115	93	$C_{17}H_{20}N_4O_2S_2$	54.23	5.35	14.88
						376	54.11	5.43	14.72
6f	C_6H_5	White crystals	4	194–196	86	$C_{19}H_{16}N_4O_2S_2$	57.56	4.07	14.13
						396	57.41	4.22	14.01
6g	*p*-$CH_3C_6H_4$	Pale yellow crystals	5	185–187	91	$C_{20}H_{18}N_4O_2S_2$	58.52	4.42	13.65
						410	58.61	4.30	13.71
6h	*p*-F-C_6H_4	Pale yellow crystals	3	269–271	89	$C_{19}H_{15}FN_4O_2S_2$	55.06	3.65	13.52
						414	55.17	3.49	13.64
6i	*p*-CH_3O-C_6H_4	Off white crystals	4	139–141	85	$C_{20}H_{18}N_4O_3S_2$	56.32	4.25	13.14
						426	56.47	4.11	13.34
6j	*p*-NO_2-C_6H_4	Yellow crystals	3	131–133	88	$C_{19}H_{15}N_5O_4S_2$	51.69	3.42	15.86
						441	51.55	3.23	15.98

and nystatin for antifungal activity. Mueller Hinton Broth was used as nutrient medium for bacteria and Sabouraud Dextrose Broth for fungal to grow. Inoculums size for test strain was adjusted to 10^8 CFU/mL by comparing the turbidity. The serial dilutions were prepared in primary and secondary screening. The target compounds and standard drugs were dissolved in DMSO-water at a concentration of 2.0 mg/mL. In primary screening, 500 μg/mL, 250 μg/mL, and 125 μg/mL concentrations of the synthesized drugs were taken. Data were not taken for the initial solution because of the high DMSO concentration (10%). The actively synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms. In secondary screening, the drugs found active in primary screening were similarly diluted to obtain 100 μg/mL, 50 μg/mL, 25 μg/mL, 12.5 μg/mL, and 6.250 μg/mL concentrations. The inoculated wells were incubated overnight at 37°C in a humid atmosphere overnight. The highest dilution showing at least 99% inhibition zone is taken as MIC.

The MIC values revealed that some of the newly synthesized compounds showed moderate to good

Table 2

Antibacterial and antifungal activity of compound **6a–j**.

	Antibacterial MIC (μg/mL)				Antifungal MIC (μg/mL)	
Compounds	*E. coli* MTCC 443	*P. aeruginosa* MTCC 1688	*S. aureus* MTCC 96	*S. pyogenes* MTCC 442	*C. albicans* MTCC 227	*A. niger* MTCC 282
Ampicillin	100	100	250	100	–	–
Ciprofloxacin	25	25	50	50	–	–
Nystatin	–	–	–	–	100	100
6a	62.5	62.5	62.5	62.5	100	500
6b	125	250	25	500	500	500
6c	200	200	125	250	1000	500
6d	25	250	50	100	1000	1000
6e	50	500	62.5	500	1000	500
6f	62.5	500	250	250	500	>1000
6g	100	250	125	500	1000	1000
6h	100	125	100	500	500	1000
6i	200	100	250	500	1000	1000
6j	62.5	62.5	500	250	200	500

inhibition. Compounds **6a**, **6d**, and **6j** exhibited good activity against all the four bacterial strains. Compounds **6d**, **6e**, **6h**, and **6f** showed good activity against *E .coli* and *S. aureus* bacterial strains. The MIC values of antifungal activity revealed that compound **6a** exhibited good activity against *C. albicans* fungal strain. Rest of all compounds did not exhibit comparable activity against both the fungal strains.

EXPERIMENTAL

Melting points were determined with Buchi B-545 melting point apparatus and are uncorrected. IR spectra were recorded on a PerkinElmer PE-1600 FTIR spectrometer in KBr disk. ^{1}H NMR spectra were recorded on a Varian 400 spectrometer in DMSO-d_6 as a solvent and TMS as an internal standard. Peak values are shown in δ ppm. EI-MS spectra were measured on a Waters Mass Spectrometer. All of the solvents and materials were reagent grade and purified as required.

2-Amino-3-cyano-4,7-dihydro-5H-thieno[2,3-c]pyridine-6-carboxylic acid tert-butyl ester (2). To a stirred solution of (10.0 g, 0.050 mol) of 1-Boc-4-piperidone (**1**), malononitrile (3.97 g, 0.060 mol) and sulfur (1.92 g, 0.060 mol) in ethanol (70 mL), morpholine (5.71 mL, 0.065 mol) was added over period of 15 min at room temperature. The reaction mixture was heated at 82°C with stirring for 1 h and cooled at room temperature. Water (200 mL) was charged to a reaction mixture and stirred at room temperature for 30 min. Product was separated by filtration and washed with water (50 mL), hexane (50 mL), and dried. Recrystallization from ethanol gave compound **2** as pale yellow solid, 11.2 g (80%), mp 193–195°C; ^{1}H NMR (DMSO-d_6) δ 1.39 (s, 9H), 2.62 (t, 2H, J = 5.6 Hz), 3.02 (t, 2H, J = 5.7 Hz), 4.21 (s, 2H), 5.84 (bs, 2H); ms: m/z 280 (M + 1). Anal. Calcd. for $C_{13}H_{17}N_3O_2S$: C, 55.89; H, 6.13; N, 15.04. Found: C, 55.92; H, 6.10; N, 15.06.

4-Amino-5,8-dihydro-6H-pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7-carboxylic acid tert-butyl ester (3). A solution of compound **2** (11.0 g, 0.039 mol), ammonium acetate (9.1 g, 0.118 mol) in triethyl orthoformate (50 mL) was heated at 120°C with stirring for 6 h and cooled at room temperature. Water (150 mL) was added to reaction mixture and stirred at room temperature for 15 min. Solid product was filtered, washed with water (50 mL), hexane (50 mL), and dried. Solid was recrystallized from ethanol gave compound **3** as off white solid, 7.6 g (63%), ^{1}H NMR (DMSO-d_6): δ 1.40 (s, 9H), 2.64 (t, 2H, J = 5.7 Hz), 2.99 (t, 2H, J = 5.8 Hz), 4.24 (s, 2H), 5.75 (bs, 2H), 8.85 (s, 1H); ms: m/z 307 (M + 1). Anal. Calcd. for $C_{14}H_{18}N_4O_2S$: C, 54.88; H, 5.92; N, 18.29. Found: C, 54.91; H, 5.89; N, 18.32.

4-Pyrrol-1-yl-5,8-dihydro-6H-pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7-carboxylic acid tert-butyl ester (4). A solution of compound **3** (7.5 g, 0.025 mol), 2,5-dimethoxy-tetrahydrofuran (3.5 mL, 0.027 mol) in acetic acid (50 mL) was heated at 100°C with stirring for 3 h and cooled at room temperature. Reaction mixture was charged in ice water (100 mL) and stirred for 15 min. Product was extracted with ethyl acetate (2 × 100 mL), combined ethyl acetate layer was washed with water (2 × 50 mL), dried on anhydrous sodium sulfate and evaporated to dryness. The residue was purified on a silica gel column, packed in hexane. Elution of the column with hexane: ethyl acetate (80:20 v/v) gave the pure compound **4** as off white solid, 4.88 g (56%), ^{1}H NMR (DMSO-d_6): δ 1.38 (s, 9H), 2.61 (t, 2H, J = 5.6 Hz), 2.98 (t, 2H, 5.6 Hz), 4.19 (s, 2H), 6.32 (d, 2H, J = 2.1 Hz), 7.34 (d, 2H, J = 2.0 Hz), 8.86 (s, 2H); ms: m/z 357 (M + 1). Anal. Calcd. for $C_{18}H_{20}N_4O_2S$: C, 60.65; H, 5.66; N, 15.72. Found: C, 60.68; H, 5.63; N, 15.69.

4-Pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine (5). A solution of compound **4** (4.8 g, 0.013 mol) and TFA (3.2 mL, 0.040 mol) in DCM (20 mL) was stirred at 10°C for 1.5 h. Reaction mixture was charged into saturated $NaHCO_3$ (50 mL) and DCM layer was separated, aqueous layer was washed with DCM (100 mL). Combined DCM layer was washed with water (2 × 50 mL), dried on anhydrous sodium sulfate and evaporated to dryness gave compound **5** as off white solid, 2.05 g (59%), ^{1}H NMR (DMSO-d_6): δ 2.65 (t, 2H, J = 5.7 Hz), 3.01 (t, 2H, J = 5.8 Hz), 4.19 (s, 2H), 5.56–5.58 (m, 1H), 6.33 (d, 2H, J = 2.0 Hz), 7.36 (d, 2H, J = 2.1 Hz), 8.89 (s, 2H); ms: m/z 257 (M + 1). Anal. Calcd. for $C_{13}H_{12}N_4S$: C, 60.92; H, 4.72; N, 21.86. Found: C, 60.90; H, 4.75; N, 21.83.

General procedure for preparation of 7-alkyl/aryl sulfonyl-4-pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine (6). All of these reactions were carried out under a nitrogen atmosphere. To a stirred and cooled (5°C) solution of Compound **5** (0.781 mmol), dimethyl amino pyridine (0.0781 mmol) and triethylamine (1.56 mmol) in dry THF (15 mL), alkyl/aryl sulfonyl chloride (0.859 mmol) was added and the reaction mixture was allowed to warm at room temperature and stirred at room temperature for 3–5 h. Reaction mixture was evaporated under vacuum gave an oily residue. The residue was dissolved in ethyl acetate (50 mL) and washed with 5% aqueous HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and water (50 mL). Ethyl acetate layer was dried and evaporated under vacuum gave solid residue which was washed with hexane (10 mL) and dried, gave **6a–j**. The yield, reaction time, and physical properties are reported in Table 1.

7-Methanesulfonyl-4-pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine (6a). IR: —SO_2 1334, 1159 cm^{-1}; ^{1}H NMR: δ 2.64 (t, 2H, J = 5.4 Hz), 2.97 (s, 3H), 2.98 (t, 2H, J = 6.0 Hz), 4.66 (s, 2H), 6.36 (d, 2H, J = 2.0 Hz), 7.35 (d, 2H, J = 2.0 Hz), 8.95 (s, 1H); ms: m/z 335 (M$^+$).

7-Ethanesulfonyl-4-pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine (6b). IR: —SO_2 1336, 1163 cm^{-1}; ^{1}H NMR: δ 1.31 (t, 3H, J = 6.5), 2.61 (t, 2H, J = 6.0 Hz), 3.01 (t, 2H, J = 6.2 Hz), 3.01 (q, 2H, J = 6.0 Hz), 4.63 (s, 2H), 6.32 (d, 2H, J = 1.9 Hz), 7.32 (d, 2H, J = 2.0 Hz), 8.89 (s, 1H); ms: m/z 349 (M$^+$).

7-(Propane-2-sulfonyl)-4-pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine (6c). IR: —SO_2 1332, 1160 cm^{-1}; ^{1}H NMR: δ 1.13 (d, 6H, J = 6.4 Hz), 2.63 (t, 2H, J = 6.1 Hz), 2.99 (t, 2H, J = 5.9 Hz), 3.32 (m, 1H, J = 6.1 Hz), 4.67 (s, 2H), 6.32 (d, 2H, J = 2.0 Hz), 7.34 (d, 2H, J = 2.0 Hz), 8.91 (s, H); ms: m/z 363 (M$^+$).

7-(Propane-1-sulfonyl)-4-pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine (6d). IR: —SO_2 1330, 1152 cm^{-1}; ^{1}H NMR: δ 1.01 (t, 3H, J = 6.3 Hz), 1.93 (m, 2H, J

$= 5.7$ Hz), 2.67 (t, 2H, $J = 6.1$ Hz), 2.92 (t, 2H, $J = 6.1$ Hz), 3.10 (t, 2H, $J = 6.1$ Hz), 4.68 (s, 2H), 6.38 (d, 2H, $J = 2.1$ Hz), 7.37 (d, 2H, $J = 2.1$ Hz), 8.90 (s, 1H); ms: m/z 363 (M$^+$).

7-(Butane-1-sulfonyl)-4-pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine (6e). IR: —SO$_2$ 1334, 1159 cm^{-1}; ^{1}H NMR: δ 0.97 (t, 3H, $J = 6.2$ Hz), 1.45 (m, 2H, $J = 5.7$ Hz), 2.13 (q, 2H, $J = 6.0$ Hz), 2.64 (t, 2H, $J = 5.8$ Hz), 2.98 (t, 2H, $J = 6.0$ Hz), 3.55 (t, 2H, $J = 6.1$ Hz), 4.66 (s, 2H), 6.35 (d, 2H, $J = 2.1$ Hz), 7.36 (d, 2H, $J = 2.0$ Hz), 8.95 (s, 1H); ms: m/z 377 (M$^+$).

7-Benzenesulfonyl-4-pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine (6f). IR: —SO$_2$ 1342, 1168 cm^{-1}; ^{1}H NMR: δ 2.50 (t, 2H, $J = 5.6$ Hz), 3.29 (t, 2H, $J = 5.1$ Hz), 4.55 (s, 2H), 6.33 (d, 2H, $J = 2.1$ Hz), 7.20 (d, 2H, $J = 2.1$ Hz), 7.60–7.71 (m, 3H), 7.83–7.85 (m, 2H), 8.92 (s, 1H); ms: m/z 397 (M$^+$).

4-Pyrrol-1-yl-7-(toluene-4-sulfonyl)-5,6,7,8-tetrahydro-pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine (6g). IR: —SO$_2$ 1345, 1171 cm^{-1}; ^{1}H NMR: δ 2.35 (s, 3H), 2.60 (t, 2H, $J = 5.4$ Hz), 3.33 (t, 2H, $J = 5.3$ Hz), 4.61 (s, 2H), 6.36 (d, 2H, $J = 2.0$ Hz), 7.25 (d, 2H, $J = 2.0$ Hz), 7.35 (d, 2H, $J = 7.5$ Hz), 7.87 (d, 2H, $J = 7.6$ Hz), 8.89 (s, 1H); ms: m/z 411 (M$^+$).

7-(4-Fluoro-benzenesulfonyl)-4-pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine (6h). IR: —SO$_2$ 1341, 1161 cm^{-1}; ^{1}H NMR: δ 2.62 (t, 2H, $J = 5.4$ Hz), 3.37 (t, 2H, $J = 5.3$ Hz), 4.64 (s, 2H), 6.33 (d, 2H, $J = 2.0$ Hz), 7.31 (d, 2H, $J = 2.0$ Hz), 7.25 (d, 2H, $J = 7.7$ Hz), 7.82 (d, 2H, $J = 7.8$ Hz), 8.91 (s, 1H); ms: m/z 415 (M$^+$).

7-(4-Methoxy-benzenesulfonyl)-4-pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine (6i). IR: —SO$_2$ 1352, 1167 cm^{-1}; ^{1}H NMR: δ 2.63 (t, 2H, $J = 5.2$ Hz), 3.40 (t, 2H, $J = 5.6$ Hz), 3.78 (s, 3H), 4.61 (s, 2H), 6.34 (d, 2H, $J = 2.0$ Hz), 7.23 (d, 2H, $J = 2.1$ Hz), 7.05 (d, 2H, $J = 7.7$ Hz), 7.81 (d, 2H, $J = 7.6$ Hz), 8.90 (s, 1H); ms: m/z 427 (M$^+$).

7-(4-Nitro-benzenesulfonyl)-4-pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine (6j). IR: —SO$_2$ 1345, 1171 cm^{-1}, NO$_2$ 1540, 1361 cm^{-1}; ^{1}H NMR: δ 2.63 (t, 2H, $J = 5.8$ Hz), 3.38 (t, 2H, $J = 5.6$ Hz), 4.64 (s, 2H), 6.38 (d, 2H, $J = 2.0$ Hz), 7.26 (d, 2H, $J = 2.0$ Hz), 8.20 (d, 2H, $J = 7.8$ Hz), 8.46 (d, 2H, $J = 7.7$ Hz), 8.93 (s, 1H); ms: m/z 442 (M$^+$).

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Synthesis, Characterization, and Antimicrobial Activities of Clubbed [1,2,4]-Oxadiazoles with Fluorobenzimidazoles

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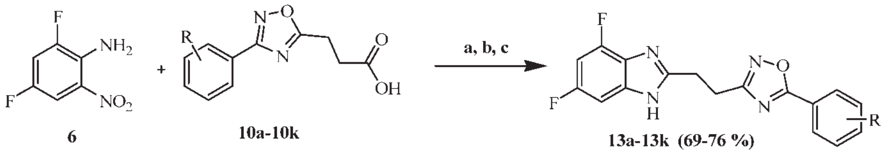

a: 2,4,6 trichlorobenzoyl chloride, Triethylamine, Dimethylaminopyridine, THF:DMF, RT;
b: 10% Pd/C,THF,RT; **c**:2 N HCl, reflux

R= 4-NO_2, 4-Cl., 3-furan, 3-quinoline, 3-Br, 3-F, 3-Cl, napthalene, 3,5 Di-OMe,3-OMe,3-Pyridyl, H

In this study, a novel series of substituted 4,6-difluoro-2-{2-[3-(substituted-phenyl)-[1,2,4]-oxadiazol-5-yl]-ethyl}-1*H*-benzo[d]imidazole derivatives were synthesized by condensation of 2,4-difluoro-6-nitrophenyl amine with 3-(substitutedphenyl-[1,2,4]-oxadiazol-5yl) propionic acid by using 2,4,6-trichlorobenzoyl chloride in the presence of triethyl amine base. The compounds were evaluated for their preliminary *in vitro* antibacterial activity against *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, and *Salmonella typhosa*. The antibacterial data of the tested compounds indicated that most of the synthesized compounds showed moderate activity with reference standard Gentamycin.

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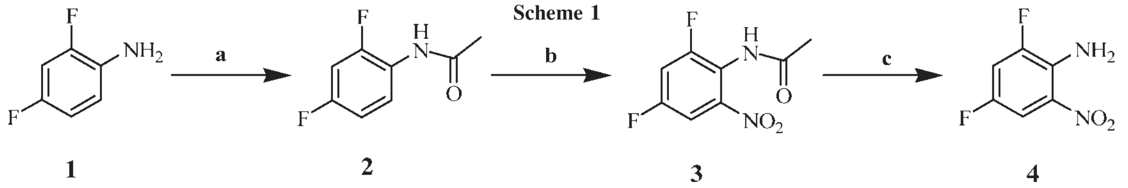
INTRODUCTION

After nitrogen, fluorine occupies the position of second favorite heteroelement in life science-oriented research. Over 10% of newly registered pharmaceutical drugs and some 40% of newly registered agrochemicals contain one or more fluorine atoms [1]. Fluorine containing benzimidazoles, which show promising biological activities, are well documented in the literature. Some of these are like Astemizole (antiallergic, anti-histaminic), Lansoprazole (antiulcerative), Flubendazole (Anthelmintic), and Droperidol (antipsychotic) [2]. So by this idea in view, synthesis of fluorobenzimidazole is the interesting area of research. Interest in benzimidazole containing structure stems not only because of exhibiting broad spectrum of pharmacological activity [3] but also displaying significant activities against several viruses such as casein kinase 2 [4], factor Xa [5], hepatitis C virus [6].

In continuation, heterocyclic species like [1,2,4]-oxadiazole and fluorobenzimidazole derivatives represent a novel emerging major chemical entity as antimicrobial agent. As we know that [1,2,4]-oxadiazoles are an important class of heterocyclic compounds with broad spectrum of pharmacological activity, due to its hydrolytic and metabolic stability of the oxadiazole ring along with improved pharmacokinetics and *in vivo* performance [7]. The biological activities of the compounds containing [1,2,4]-oxadiazoles have been well documented in the literature [8–11]. The oxadiazole moiety is an important structure unit in drugs and chemical materials [12]. Among these oxadiazoles, [1,2,4]-oxadiazoles are gaining interest in the medicinal chemistry [13] and shows numerous biological activities including muscarinic agonists [14], dopamine transporters [15], benzodiazepine receptor partial agonists [16], nematocidal, fungicidal, and microbicides [17], immunosuppressants [18], Fab I inhibitors as antibacterial agents [19], antiplatelet and antithrombotic agents [20], etc. Also, oxadiazoles plays an important role as bioisosteres for amides and esters [21]. Several methods have been reported for the synthesis of [1,2,4]-oxadiazoles in the literature [22–30].

In continuation of our research work [31] and after extensive search, it was observed that enough efforts have not been made till date, to combine these two moieties as a single molecule scaffold. So, we wish to disclose the derivatives of difluorobenzimidazoles clubbed

Scheme 1



a: Acetic anhydride, reflux; **b**: HNO_3, H_2SO_4, RT; **c**: 2N HCl, reflux.

with different substituted [1,2,4]-oxadiazoles and studied their antibacterial activity against different organisms.

RESULTS AND DISCUSSION

Synthesis of 2,4-difluoro-6-nitrophenyl amine [32]. In neat reaction condition, acetic anhydride was added slowly in 2,4-difluorophenyl amine **1** at 0°C, a solid material precipitates. The reaction mixture was quenched in ice water and stirred continuously for 30 min. An off violet colored solid compound separated out, which was filtered and suck dried to obtain 2, 4 difluoro acetanilide **2** as a free solid (Scheme 1).

In the second stage, 2,4-difluoro acetanilide **2** was dissolved in nitric acid and conc. sulfuric acid was added slowly at 5–10°C. The reaction mixture was stirred continuously for 3 h at room temperature. Reaction progress was monitored by TLC system (EA: Hexane 2:8). After completion of reaction, the reaction mixture was quenched in ice water, a pale yellow color solid separated, which was filtered through Büchner funnel and suck dried to obtain 2,4-difluoro-6-nitro acetanilide **3** as a free solid.

In the final stage, to a reaction mixture of **3** in 2*N* HCl, a catalytic amount of sulfuric acid was added slowly. Reaction mixture was heated to reflux for 3–4 h. After completion of reaction, the reaction mixture was cooled slowly at 0–5°C, a yellow color needle type crystal separated, which was filtered and suck dried to obtain as 2,4-difluoro-6-nitro aniline **4.**

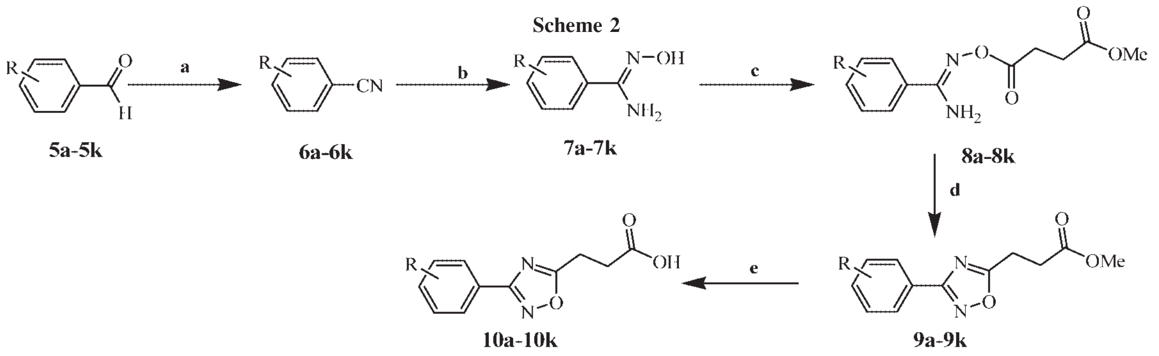
Synthesis of 3-(substitutedphenyl-[1,2,4]-oxadiazol-5-yl)-propionic acid. By using different substituted aromatic aldehydes **5a-5k** in the presence of iodine and aqueous NH_3 in tetrahydrofuran at room temperature, gave substituted benzonitrile **6a-6k.** The compounds were characterized by IR showing cyano functional group at 2210–2245 cm^{-1}. Then followed by amidoxime formation by using hydroxylamine hydrochloride and sodium bicarbonate in methanol at reflux temperature for 8–10 h gives substituted N-hydroxy benzamidine **7a-7k** (Scheme 2).

In the next reaction, condensation of **7a-7k** with monomethyl succinate was carried out by using coupling reagent dicyclohexylcarbodiimide (DCC) and N-hydroxy benzotriazole, and dimethylaminopyridine (DMAP) as a base in dichloromethane at room temperature to obtain **8a-8k**.

In the penultimate step, dehydration followed by cyclization of **8a-8k** was carried out in toluene at reflux temperature in the presence of molecular sieves as a dehydrating agent. It gives 3-(substituted phenyl-[1,2,4]-oxadiazol-5-yl)-propionic acid ethyl ester **9a-9k** as a free solid. In the final step, hydrolysis of **9a-9k** by lithium hydroxide in THF: EtOH: H_2O (7:2:1) at room temperature gives 3-(substituted phenyl-[1,2,4] oxadiazol-5-yl)-propionic acid **10a-10k**.

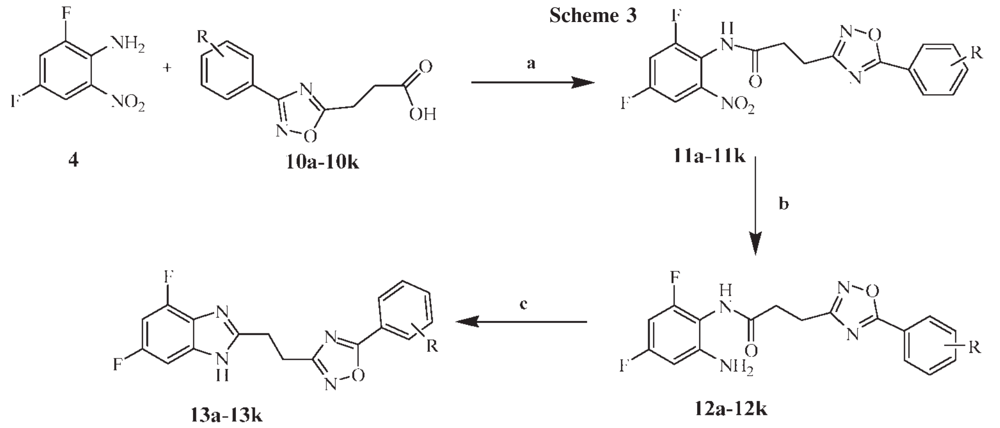
Synthesis of 4,6-difluoro-2-[2-(5-substituted-phenyl-[1,2,4]-oxadiazol-3-yl)-ethyl]-1*H*-benzo[*d*]imidazole. Condensation of 2, 4 difluoro 6-nitro phenyl amine **4** and 3-(substituted phenyl-[1,2,4]oxadiazol-5yl)-propionic acid **10a-10k** in 2,4,6 trichlorobenzoyl chloride [33] as a coupling reagent, in the presence of triethylamine and DMAP in THF: DMF (7:3) solvent at room temperature **11a-11k**. After workup, catalytic reduction of **11a-11k** by using 10% Pd/C in tetrahydrofuran was carried out

Scheme 2



a: I_2, NH_3, THF, RT; **b**: $NH_2OH.HCl$, $NaHCO_3$, methanol, reflux; **c**: monomethyl succinate, dicyclohexylcarbodiimide, dimethylaminopyridine, N-hydroxy benzotriazole, DCM; **d**: toluene, reflux; **e**: LiOH, THF-ETOH-H_2O, RT

Scheme 3



a: 2, 4,6 trichlorobenzoyl chloride, triethylamine, dimethylaminopyridine,THF:DMF, RT; **b**: 10% Pd/C, THF, 25-30 °C; **c**: 2 N HCl , reflux

to obtain **12a-12k**. Then **12a-12k** undergoes cyclization reaction in 2*N* HCl at 100°C to furnish with 4, 6 difluoro-2-{2-[3-(substituted-phenyl)-[1,2,4]-oxadiazol-5-yl]-ethyl}-*1H*-benzo[*d*] imidazole derivatives **13a-13k.** The details of the reaction condition were explained in experimental section (Scheme 3).

ANTIMICROBIAL ACTIVITY

The *in vitro* antibacterial screening of **13a-13k** was assessed against two gram positive and two gram negative bacteria *viz. Staphylococcus aureus* (ATCC 25923), *Pseudomonas aeruginosa* (ATCC 27853), *E. coli* (ATCC 25922), and *Salmonella typhosa* (ATCC 14028). From the antibacterial screening, it was observed that all the compounds exhibited activity against different organisms employed. In this, we studied different electron withdrawing or electron donating moieties. Some of the compounds showed better activity against gram positive organisms compared to gram negative organisms. Looking at the structure-activity relationship, marked inhibition in bacteria was observed in the number of compounds **13a**, **13f**, **13g**, and **13i** have shown moderate activity and others **13b**, **13c**, **13d**, **13e**, **13h**, **13j**, and **13k** showed least activity.

EXPERIMENTAL

The melting points were estimated by Veggo programmable (microprocessor based) melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian 400 MHz spectrometer MHz instrument using CDCl$_3$ as solvent using TMS as internal standard; the chemical shifts (δ) are reported in ppm Signal multiplicities are represented by s (singlet), d (doublet), t (triplet), ds (double singlet), dd (double doublet), m (multiplet), and br s (broad singlet). IR spectra were recorded on (KBr disc) using a FTIR bruker Vector 22 Spectrophotometer. Elemental analyses were determined on Elementor Vario instrument. EIMS spectra recorded on micromass-quatro –II. The purity of the compounds was checked on Merck precoated silica gel 60 F-254.

General experimental procedure for the preparation of 2,4-difluoro-6-nitro phenyl amine (4). In the first stage, under neat reaction condition, acetic anhydride (7.9 g, 77.5 mmol) was added slowly in 2,4-difluoro phenyl amine **1** (10 g, 77.5 mmol) at 0°C, a solid compound precipitates out after 30–45 min. After completion of reaction, the reaction mixture was quenched in ice water with continues stirring for 30 min. The solid was filtered through Büchner funnel and suck dried to obtain 2,4-difluoro acetanilide **2** as a off violet color solid (12.0 g, 92% yield). *m*/*z:* 172 (M$^+$).

In the second stage, to a solution of 2,4-difluoro acetanilide **2** (12 g) in nitric acid (25 mL), Conc. sulfuric acid (25 mL) was added slowly at 5–10°C. The reaction mixture was stirred continuously for 3 h at room temperature. The progress of the reaction was monitored on TLC system (Ethyl acetate: Hexane, 2:8). After completion of reaction, the reaction mass was quenched slowly in ice water and a pale yellow color solid was observed, which was filtered through Büchner funnel and suck dried to obtain 2,4-difluoro-6-nitro acetanilide **3** as a free solid (12.0 g, 80% yield). The compound was characterized by mass and NMR. ^{1}H NMR (CDCl$_3$) δ (ppm): 2.23 (3H, —CH$_3$, s), 7.26 (1H, ArH, m), 7.62 (1H, ArH, m), 8.01 (1H, —NH, s). *m*/*z:* 215 (M$^-$).

In the final stage, to a suspension of 2, 4 difluoro 6-nitro acetanilide **3** (12 g, 69.0 mmol) in 2*N* HCl (25 mL), a catalytic amount of sulfuric acid (1.2 mL) was added slowly and the reaction mixture was heated to reflux for 3–4 h. After completion of reaction, the reaction mixture was cooled gradually at 10°C, a yellow color needle type crystal separated out. The solid compound was filtered and suck dried to obtain 2,4-difluoro-6-nitro aniline **4** as a free solid (7.0 g, 72.9% yield). The compound was characterized by mass and NMR. ^{1}H NMR (CDCl$_3$) δ (ppm): 6.05 (2H, —NH$_2$, s), 7.12 (1H, ArH, m), 7.73 (1H, ArH, s). *m*/*z:* 173 (M$^-$).

General experimental procedure for the preparation of 3-{3-substituted-phenyl-[1,2,4]-oxadiazole-5-yl)-propionic acid (10a). To a solution of 4-nitrobenzaldehyde **5a** (6.0 g, 39.73 mmol) in tetrahydrofuran (30 mL), aqueous NH$_3$ (120 mL) was added and then followed by iodine (10.59 g, 41.69 mmol). The reaction mixture was stirred further for 2 h. After completion of reaction, color of the reaction mixture changed from brownish to colorless. The reaction mixture was extracted with ethyl acetate (50 mL × 2) twice, and the organic layer was dried over sodium sulfate and evaporated under vaccum till dryness. The crude compound was triturated with diethyl ether to obtain a free solid of 4-nitro benzonitrile **6a** (5.1 g, 84% yield). The compound was characterized by IR showing cyano functional group at around 2238 cm^{-1} in this example.

To a solution of **6a** (5.0 g, 33.78 mmol) in methanol (50 mL), hydroxylamine hydrochloride (2.56 g, 37.16 mmol), sodium bicarbonate (4.35 g, 50.67 mmol) were added and the reaction mixture was heated to reflux for 8–10 h. Progress of reaction was monitored on TLC. After completion of reaction, methanol was distilled completely under vaccum. A pale yellow solid compound precipitates after charging water (100 mL), which was filtered through funnel and suck dried to obtain N-hydroxy-4-nitrobenzamidine (4.9 g, 80% yield) **7a** as a free solid.

In the second stage, monomethyl succinate (5.14 g, 38.94 mmol) was dissolved in THF: DMF (7:3 ratio) (25 mL) at 25–30°C. Then DCC (11.15 g, 54.14mmol) a coupling reagent, N-hydroxybenzo triazole (1.09 g, 8.12 mmol) was added at 25–30°C and stirred continuously for 30 min. Mixed anhydride formation, charged 4- nitrobenzamidine, **7a** (4.8 g, 27.07 mmol), and DMAP (0.99 g, 8.12 mmol) with continuous stirring for 60 min. Progress of the reaction was monitored on TLC (ethyl acetate: hexane 3:7). After completion of reaction, the reaction mixture was filtered through Büchner funnel with bed wash of ethyl acetate (25 mL) twice. Water wash given to the organic layer (100 mL × 2) twice separated the organic solution, which was dried over sodium sulphate and distilled out as organic layer under vaccum. The crude compound was triturated with diethyl ether to obtain **8a** (6.2 g, 74% yield) as a free off white solid.

In the penultimate stage, **8a** compound (6.2 g, 20.06 mmol) was dissolved in toluene (60 mL) and molecular sieves were added as dehydrating agent. The reaction mass was stirred at reflux temperature for 2–3 h. After completion of reaction, the reaction mixture was filtered through Büchner funnel with bed wash of toluene (10 mL). The filtrate was concentrated under vaccum and recrystallized with diethyl ether to obtain 3-(3-4-nitrophenyl-[1,2,4]-oxadiazol-5-yl)-propionic acid ethyl ester **9a** (4.5 g, 77% yield) as a pure compound.

In the final stage, 3-(3-4 nitrophenyl-[1,2,4] oxadiazol-5-yl)-propionic acid ethyl ester **9a** (4.5 g, 15.46 mmol) was dissolved in THF: EtOH: H_2O (7:2:1) with 25 mL volume. $LiOH.H_2O$ was added (0.630 g, 18.55 mmol) at room temperature and the reaction mixture was stirred for 2 h at 25–30°C. After completion of reaction, the mixture was acidified by 2*N* HCl, a solid material separated, which was filtered through Büchner funnel and suck dried to obtain 3-(3-4-nitrophenyl-[1,2,4]-oxadiazol-5-yl) propionic acid **10a** (2.9 g) as a pale yellow solid.

All the intermediates **10b-10k** were synthesized by the aforementioned procedure using different substituted aldehydes **5b-5k**, respectively, and were characterized by ^1H NMR and ms. The details of the intermediates were given in Table 1.

General procedure for the preparation of 4,6-difluoro-2-[2-(5-substituted-phenyl-[1,2,4]-oxadiazol-3-yl)-ethyl]-1H-benzimidazole: (13a-13k). In the reaction, 3-(3-4-nitrophenyl-[1,2,4] oxadiazol-5-yl)-propionic acid **10a** (1.5 g, 5.74 mmol) was dissolved in THF: DMF (7:3) 25 mL volume. Then 2,4,6-trichlorobenzoyl chloride (1.47 g, 6.03 mmol) followed by triethyl amine (0.696 g, 6.89 mmol) was added for the mixed anhydride formation. The reaction mass was stirred for 60 min at 25–30°C. DMAP (0.701 g, 5.74mmol) and **4** (1.0 g, 5.74 mmol) were added and stirred continuously for 2 h. Progress of the reaction was monitored on TLC system (ethyl acetate: hexane 3:7). After completion of reaction, the reaction mixture was filtered through Büchner funnel and bed wash of ethyl acetate. Water wash given to the organic solution, dried over sodium sulphate and concentrated under vacuum completely. Finally, the crude compound was triturated with diethyl ether to obtain as a off white color solid **11a** (1.6 g, 66% yield).

Similarly, by using the respective 3-{3-substituted-phenyl-[1,2,4]-oxadiazol-5-yl)-propionic acid **10b-10k,** we have synthesized **11b-11k** for the next stage.

In the second stage. **11a** (1.5 g, 3.58 mmol) was dissolved in THF (50 mL), and 10% Pd/C was added (0.3 g, 20% w/w) at room temperature under nitrogen. Reaction mass was stirred for 2 h at 25–30°C. Progress of the reaction was monitored on TLC system (ethyl acetate: hexane 3:7). After completion of the reaction the mixture was filtered through celite with bed wash of tetrahydrofuran (25 mL). The filtrate was concentrated under vacuum to obtain **12a-12k.** Without isolation of **12a-12k**, next cyclization reaction in 2*N* HCl (15 mL) at reflux temperature for 4–5 h was proceeded. After completion of reaction, aqueous $NaHCO_3$ solution (50 mL) was added to the reaction mixture slowly at 5–10°C. A solid product was separated out, which was filtered through Büchner funnel and suck dried to obtain 4-6-difluoro-2-{2-[3-(4-nitrophenyl)-[1,2,4]-oxadizol-5-yl]-ethyl}-4-6-difluoro-*1H*-benzo[*d*]imidazole **13a** as pale yellow colored solid.

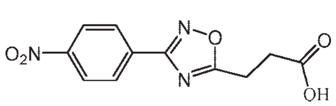
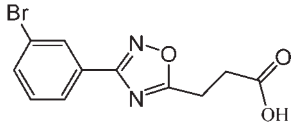
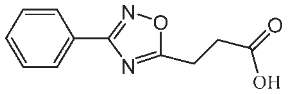
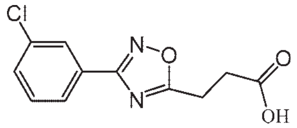
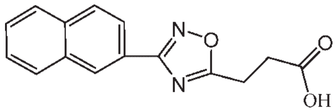
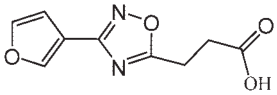
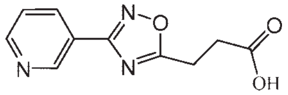
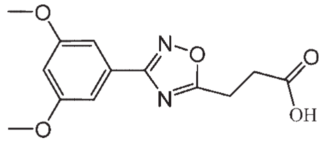
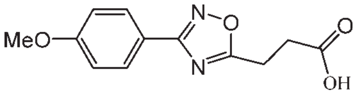
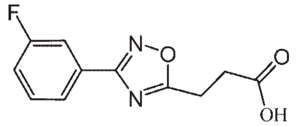
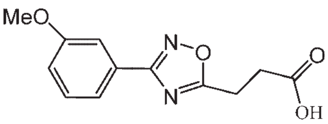
Similarly, by using respective substituted [1,2,4]-oxadiazoles **10a-10k**, we synthesized the respective **13b-13k** by using aforementioned procedure. ^1H NMR, ms, IR, and elemental analysis characterized all the synthesized compounds. The details of the intermediates were given in Table 2.

Synthesis of 4,6-difluoro-2-{2-[3-(4-nitrophenyl)-[1,2,4]-oxadizol-5-yl]-ethyl}-4,6-difluoro-1*H*-benzo[*d*]-imidazole (13a). The compound was obtained using 3-(3-(4-nitrophenyl)-[1,2,4]-oxadiazol-5-yl) propanoic acid as a pale yellow solid (diethyl ether); IR (KBr): 3242, 2768, 2547, 2362, 1719, 1578, 1516, 1438, 1340, 1219, 914, 869, 719 cm^{-1}; ^1H NMR (400 MHz, DMSO d_6): δ 2.87 (2H, t), 3.19 (2H, t), 7.12 (1H, m), 7.29 (1H, d), 8.22 (2H, d), 8.39 (2H, d), 12.4 (1H, s —NH).

Synthesis of 2-(2-(3-(3-bromophenyl)-[1,2,4]-oxadizol-5-yl)-4,6-difluoro-1*H*-benzo[*d*]imidazole (13b). The compound was obtained using 3-[3-(3-bromo-phenyl)-[1,2,4]-oxadiazol-5-yl) propionic acid as a pale yellow solid (diethyl ether); IR (KBr): 3433, 2714, 2608, 2361, 1701, 1566, 1535, 1443, 1358, 846, 744, cm^{-1}; ^1H NMR (400 MHz, DMSO d_6): δ 2.84 (2H, t), 3.19 (2H, t), 7.18(1H, m), 7.52 (2H, m), 7.78–7.81 (1H, m), 7.98 (1H, m), 8.08 (1H, m), 12.14 (1H, s, —NH).

Synthesis of 4,6-difluoro-2-[2-(3-phenyl-[1,2,4]-oxadizol-5-yl)-ethyl]-1*H*-benzo[*d*]imidazole (13c). The compound was obtained using 3-(3-phenyl-[1,2,4]-oxadiazol-5-yl) propionic acid as a off white solid (diethyl ether); IR (KBr): 3133, 2933 2714, 2608, 2361, 1701, 1632, 1590, 1443, 1358, 1231, 912, 846, 718 cm^{-1} ;^1H NMR (400 MHz, DMSO d_6): δ 2.8 (2H, t), 3.15 (2H, t), 7.08(1H, m), 7.12 (1H, d), 7.55 (3H, m), 7.95 (2H, m), 12.21 (1H, s, —NH).

Table 1
Characterization of intermediates **10a–10k**.

No.	Intermediates	ms (*m*/*z*)	^{1}H NMR (δ ppm)
10a		264.0	2.9 (2H, t), 3.3 (2H, t), 8.2 (2H,d), 8.4 (2H,d), 12.0 (1H,s)
10b		298.1	2.85 (2H,t), 3.25 (2H,t), 7.4 (1H,t), 7.8 (1H,d), 8.0 (1H,d) 8.1(1H,s), 12.16 (—COOH, 1H,s)
10c		219.2	2.75 (2H,t), 3.05 (2H,m), 7.4 (2H,t), 7.8 (2H,m), 8.0(1H,dd),12.2 (—COOH,1H,s)
10d		253.2	2.9(2H,t), 3.2 (2H,t), 7.4–7.8 (2H, m), 8.0 (2H, m).12.22 (—COOH,1H,s)
10e		269.3	2.8 (2H,t), 3.2 (2H,t), 7.45–7.55 (2H,m), 8.0–8.3 (2H,m) 8.8 (1H,d) 12.22 (—COOH, 1H, s)
10f		209.0	2.8 (2H, t), 3.3 (2H, t), 6.7(1H, d), 7.2(1H, d), 8.0 (1H, s), 12.2(1H, s)
10g		220.1	2.8 (2H, t), 3.2 (2H, t), 7.6(1H, m) 7.7(1H, m), 8.0 (1H, m), 8.8 (1H, s), 12.2(1H, s).
10h		279.2	2.8 (2H,t),3.2 (2H,t),3.9 (3H,s), 6.7 (1H,t), 7.1 (2H,d), 12.18 (—COOH,1H,s).
10i		249.1	2.8 (2H,t), 3.2(2H,t), 3.85(3H,s), 7.1(2H,d),7.9(2H, d), 12.4 (1H, s)
10j		237.0	2.9 (2H, t), 3.2 (2H, t), 7.4 (1H, t), 7.6 (1H,t), 7.7 (1H, d), 7.8 (1H, d), 12.2(1H, s)
10k		249.2	2.78 (2H, t), 3.25 (2H, t), 7.15 (2H, d), 8.01 (2H, d), 12.29 (1H, s)

Synthesis of 2-{2-[3-(3-chlorophenyl)-[1,2,4]-oxadizol-5-yl]-ethyl}-4,6-difluoro-1*H*-benzo[*d*]-imidazole (13d). The compound was obtained using 3-[3-(3-chloro-phenyl)-[1,2,4]-oxadiazol-5-yl) propionic acid as a brownish solid (diethyl ether); IR (KBr): 3233, 2878, 2731, 2624, 2548, 2362, 1696, 1591, 1432, 1337, 1239, 1168, 898,752 cm^{-1} ;^{1}H NMR (400 MHz, DMSO d_6): δ 2.8–3.08 (4H, s), 7.04 (1H, m), 7.21 (1H, d), 7.62 (2H, m), 7.74 (1H, m), 7.92 (1H, m), 12.1 (1H, s, —NH).

Synthesis of 4,6-difluoro-2-[2-(3-pyridin-3-yl-[1,2,4]-oxadizol-5-yl)-ethyl]-1*H*-benzo[*d*]imidazole (13e). The compound was obtained using 3-(3-pyridin-3-yl)-[1,2,4]-oxadiazol-

Table 2

Characterization of the compounds **13a–13k**.

						Analysis (%)		
						Calcd./Found		
Compound	R	Time (h)	Mp (°C)	Yield %	Molecular Formula	C	H	N
13a	4-NO_2	4	120–122	75	$C_{17}H_{11}F_2N_5O_3$	54.99	2.99	18.86
						55.09	3.01	18.88
13b	3-Br	4	129–131	71	$C_{17}H_{11}BrF_2N_4O$	50.39	2.74	13.83
						50.47	2.79	13.85
13c	H	5	112–114	74	$C_{17}H_{12}F_2N_4O$	62.58	3.71	17.17
						62.71	3.67	17.26
13d	3-Cl	5	118–120	69	$C_{17}H_{11}ClF_2N_4O$	56.60	3.07	15.53
						56.74	3.15	15.74
13e	3-Pyridyl	4	162–164 (dec)	69	$C_{16}H_{11}F_2N_5O$	58.72	3.39	21.40
						58.72	3.46	21.52
13f	3-furan	6	134–136	72	$C_{15}H_{10}F_2N_4O_2$	56.97	3.19	17.71
						56.89	3.30	17.70
13g	Naphthalene	5	123–125	73	$C_{21}H_{14}F_2N_4O$	67.02	3.75	14.89
						67.11	3.78	14.99
13h	3,5-Di-OMe	5	129–131	75	$C_{19}H_{16}F_2N_4O_3$	59.07	4.17	14.50
						59.12	4.23	14.53
13i	4-OMe	5	136–138	70	$C_{18}H_{14}F_2N_4O_2$	60.67	3.96	15.72
						60.62	3.97	15.71
13j	3-F	4	141–143	68	$C_{17}H_{11}ClF_2N_4O$	56.60	3.07	15.53
						56.59	3.16	15.52
13k	3-OMe	4	156–158	76	$C_{18}H_{14}F_2N_4O_2$	60.67	3.96	15.72
						60.80	4.06	15.91

5-yl) propionic acid as a off white solid (diethyl ether); IR (KBr): 3331, 2922, 2731, 2624, 2362, 1695, 1570, 1440, 1358, 1244, 910, 844, 738 cm^{-1}; ^{1}H NMR (400 MHz, DMSO d_6): δ 2.75 (2H, t), 3.18 (2H, t) 7.18 (1H, d), 7.31 (1H, m), 7.89 (2H, m), 8.51 (2H, m), 12.14 (1H, s —NH).

Synthesis of 4,6-difluoro-2-[2-(3-furan-3-yl-[1,2,4]-oxadizol-5-yl)-ethyl]-1*H*-benzo[*d*] imidazole (13f). The compound was obtained using 3-(3-(furan-2-yl)-[1,2,4]-oxadiazol-5-yl) propanoic acid as a off white solid (diethyl ether); IR (KBr): 3327, 2928, 2714, 2604, 2361, 1628, 1580, 1437, 1312, 1275, 1127, 853, 743 cm^{-1}; ^{1}H NMR (400 MHz, DMSO d_6): δ 2.77 (2H, t), 3.12 (2H, t) 7.27 (1H, d), 7.57 (2H, m), 7.69 (2H, m), 12.11(1H, s —NH).

Synthesis of 4,6-difluoro-2-[2-(3-napthalen-2-yl-[1,2,4]-oxadizol-5-yl)-ethyl]-1*H*-benzo[*d*]imidazole (13g). The compound was obtained using 3-(3-naphthalen-2-yl-[1,2,4]-oxadiazol-5-yl)-propionic acid as a buff colored solid (diethyl ether); IR (KBr): 3274, 3054, 2932, 2720, 2362, 1739, 1708, 1584,1499, 1428, 1306, 1157, 898, 749 cm^{-1}; ^{1}H NMR (400 MHz, DMSO d_6): δ 2.96 (2H, t), 3.21 (2H, t), 7.22 (1H, d),

Table 3

Antibacterial activity of compounds **13a–13k**.

		Organisms			
Compound	R	Sa	Pa	Ec	St
13a	4-NO_2	27	25	20	19
13b	3-Br	23	18	16	14
13c	H	21	23	18	19
13d	3-Cl	21	25	18	14
13e	3-Pyridyl	20	22	23	23
13f	3-Furan	25	23	21	24
13g	Naphthalene	27	26	24	20
13h	3,5 Di-OMe	19	20	15	13
13i	4-OMe	29	26	22	19
13j	3-F	20	22	19	18
13k	3-OMe	22	23	21	20
Gentamycin	–	34	35	30	29

Sa: *Staphylococcus aureus*, Ec: *Escherichia coli*, Pa: *Pseudomonas aeruginosa*, St: *Salmonella typhosa*.

7.52– 7.74 (4H, m), 8.05 (1H, d), 8.2 (2H, m), 8.8 (1H, d), 12.36 (1H, s —NH).

Synthesis of 4,6-difluoro-2-{2-[3-(3,5-dimethoxy phenyl)-[1,2,4]-oxadizol-5-yl]-ethyl}-1*H*-benzo[d] imidazole (13h). The compound was obtained using 3-(3-(3,5-dimethoxyphenyl)-[1,2,4]-oxadiazol-5-yl) propanoic acid as a buff colored solid (diethyl ether); IR (KBr): 3101, 2714, 2612, 2361, 1701, 1559, 1535, 1443, 1358, 900, 740 cm^{-1}; ^{1}H NMR (400 MHz, DMSO d_6): δ 2.75–3.1(4H, s), 3.99 (6H, s), 7.11 (2H, m), 7.22 (2H, m), 7.46 (1H, m), 12.14 (1H, s —NH).

Synthesis of 4,6-difluoro-2-{2-[3-(4-methoxy phenyl)–[1,2,4]-oxadizol-5-yl]-ethyl}-1*H*-benzo[*d*]-imidazole (13i). The compound was obtained using 3-(3-(4-methoxyphenyl)-[1,2,4]-oxadiazol-5-yl) propanoic acid as a brownish colored solid (diethyl ether); IR (KBr): 2940, 2608, 2362, 1710, 1596, 1482, 1362, 1255, 1029, 843, 749 cm^{-1}; ^{1}H NMR (400 MHz, DMSO d_6): δ 2.75–3.1(4H, s), 4.02 (3H, s), 7.11 (1H, d), 7.24 (3H, m), 7.46 (2H, m), 12.04 (1H, s —NH).

Synthesis of 4,6-difluoro-2-{2-[3-(3-fluorophenyl)-[1,2,4]-oxadizol-5-yl]-ethyl}-1*H*-benzo[*d*]imidazole (13j). The compound was obtained using 3-(3-(3-fluorophenyl)-[1,2,4]-oxadiazol-5-yl) propanoic acid as a brownish solid (diethyl ether); IR (KBr): 3233, 2878, 2731, 2624, 2548, 2362, 1696, 1591, 1432, 1337, 1239, 1168, 898,752 cm^{-1}; ^{1}H NMR (400 MHz, DMSO d_6): δ 2.8–3.08 (4Hs), 7.04 (1H,m), 7.21 (1H,d), 7.62 (2H,m), 7.74 (1H,m), 7.92 (1H,m), 12.1 (1H,s —NH).

Synthesis of 4,6-difluoro-2-{2-[3-(4-methoxy phenyl)-[1,2,4]-oxadizol-5-yl]-ethyl}-1*H*-benzo[*d*]-imidazole (13k). The compound was obtained using 3-(3-(4-methoxyphenyl)-[1,2,4]-oxadiazol-5-yl) propanoic acid as a brownish colored solid (diethyl ether); IR (KBr): 2940, 2608, 2362, 1710, 1596, 1482, 1362, 1255, 1029, 843, 749 cm^{-1}; ^{1}H NMR (400 MHz, DMSO d_6): δ 2.75–3.1(4H, s), 4.02 (3H, s), 7.11 (1H, d), 7.24 (3H, m), 7.46 (2H, m), 12.04 (1H, s —NH).

PHARMACOLOGICAL ACTIVITY

Antimicrobial activity. The title compounds were screened for the antimicrobial activity against two different gram positive and two gram negative microorganisms *Staphylococcus aureus* (ATCC 25923), *Pseudomonas aeruginosa* (ATCC 27853), *E. coli* (ATCC 25922), and *Salmonella typhosa* (ATCC 14028) under the following conditions. (Table 3).

Method: Well diffusion method [34], Medium: The nutrient agar medium,

Solvent: Chloroform: Concentrations: 50 and 100 μ*M*.

Condition: 24 h at 24–28°C, Standard: The antibiotic Gentamycin.

The nutrient agar medium, 20 mL was poured into the sterile petri dishes. To the solidified plates, wells were made using a sterile cork borer 10 mm in diameter. The 24 h sub cultured bacteria was inoculated in the petri plates, with a sterile cotton swab dipped in the nutrient broth medium. After inoculating, the compounds were dissolved separately with the chloroform solvent and poured into the wells with varying concentrations ranging from 50 and 100 μ*M* using a micropipette. The plates were left over for 24 h at 24–28°C. The antibiotic Gentamycin was used as a standard for comparative study.

The percentage of inhibition was calculated by the formula% Inhibition = Diameter of the inhibition zone × 100.

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Reinvestigation of Alternative Method for the Preparation of Dibenz[*b*,*f*][1,4]oxazepine

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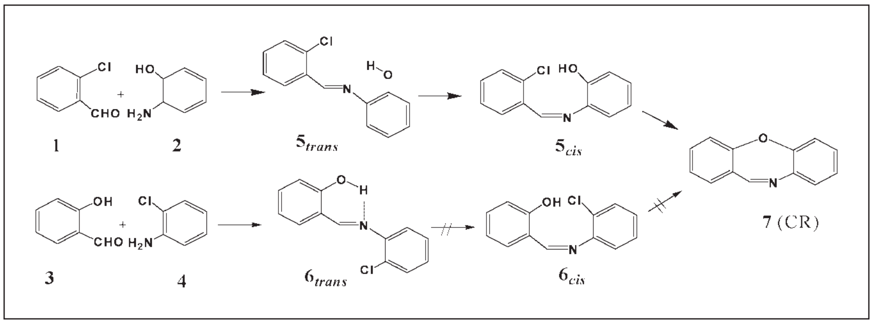

Two distinct alternative methods using different starting materials for the preparation of dibenz[*b*,*f*][1,4]oxazepine (**7**, CR) were reinvestigated. The possibility of *trans-cis* conversion of the Schiff base **5** (produced from **1** and **2**) is considered the favorable orientation that leads to cyclization (production of **7**). Fluoro derivative of **1** afforded excellent and more convenient conditions for the one pot preparation of high yield pure **7**. The presence of only *trans* configuration for the imine **6** (produced from **3** with **4**) and the impossibility of its conversion to *cis*, makes it inadequate for the preparation of **7**.

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INTRODUCTION

Dibenz[*b*,*f*][1,4]oxazepine (**7**, CR) is an incapacitating lachrymatory agent [1–6] and is an intermediate in the synthesis of *loxapine* (antipsychotic), *amoxapine* (antidepressant) [7], and others substituted dibenzoxazepine compounds that are analgesic or useful for the treatment of different diseases [8–11].

Moreover, reduction of the imine group of dibenz[*b*,*f*][1,4]oxazepine and/or the oxidation of the same group to the imid afforded intermediates in the synthesis of several other compounds effective in the prevention and treatment of circulatory disease and osteoporosis [9,11].

There are different methods for the preparation of **7** [12–24]. Two pathways starting from different raw materials can be considered for the preparation of this compound (Schemes 1 and 2).

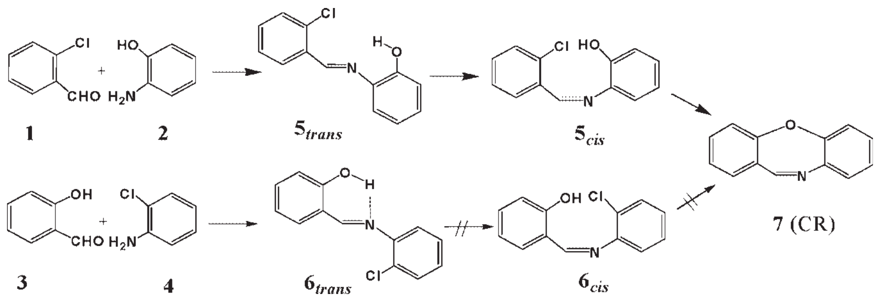
These methods are differentiated in the occurrence of either the imine reaction or etherification in the first step. Thus, in Scheme 1, dibenz[*b*,*f*][1,4]oxazepine is formed by the imine reaction followed by the etherification (cyclization), whereas in Scheme 2, etherification is followed by the imine reaction (cyclization). The two etherification and imine reactions each have limitations that influence the yield of the final product.

Firstly, the method proposed by Tambute [12,13] for the preparation of **7** involves the condensation of salicyl-aldehyde with 2-nitrochlorobenzene (Scheme 2). We have recently reported the effect of temperature and catalyst on the yields and rate of the etherification reaction between sodium salt of salicylaldehyde and 2-nitrochlorobenzene and have emphasized the harsh conditions necessary for the preparation of **7** by this method [22]. We have observed that the etherification reaction of 2-nitrophenol and 2-chlorobenzaldehyde does not occur under the same conditions and requires more difficult circumstances to be performed. This can be rationalized by the electrophilic effect of NO_2 group, which reduces the nucleophilic character of the hydroxy oxygen atom in 2-nitrophenol.

The formation of **7** *via* **1** and **2** (Scheme 1) has been reported recently [19,20], and the kinetic data have been investigated [17,18]. Other attempts to prepare **7** *via* cyclization of 2-[(2-fluorobenzylidene)amino] phenol (fluoro derivative of **5**) in ethanol with excess triethylamine were unsuccessful even after prolonged reflux. In contrast, the preparation of 1,2,3,4-tetrafluorobenzo[*b*,*f*][1,4]oxazepine (**10**) by cyclization of 2-[(2,3,4,5,6-pentaflurobenzylidene)amino] phenol (**8**) (Scheme 3) using the same conditions was successful, whereas the attempts to cyclize **9** into **11** failed [23].

The difference in reactivity between **8** and **9** has been justified by the necessity for the electrophilic arene to be a benzylidene and not a phenyl imine, that is, the

Scheme 1



electron-withdrawing —CH=N substituent enhances the susceptibility of C_6F_5 to nucleophilic attack, whereas the electron-donating —N=CH substituent has the opposite effect [23].

The last report on the synthesis of **7** was consisted in the reaction of 2-fluorobenzaldehyde (fluoro derivative of **1**) with 2-aminophenol using K_2CO_3 in polyethylene glycol (PEG-400) at 100°C, affording 89% of **7** after 8 h [24].

This contribution discussed the feasibility of two distinct pathway methods (Scheme 1) using different starting materials and passing by different intermediates for the preparation of dibenz[*b*,*f*][1,4]oxazepine (**7**, CR).

RESULTS AND DISCUSSION

The preparation of **7** *via* 2-chlorobenzaldehyde (**1**) and 2-aminophenol (**2**) or salicylaldehyde (**3**) and 2-chloro-aniline (**4**) was reinvestigated (Scheme 1). Imine formation following both methods was nearly quantitative, and the water released in the course of the reaction did interfere with imine formation.

We have reported the results of GC, GC-MS, and ^{1}H NMR analysis of the imine products [25], according to which we have presumed the formation of $\mathbf{5}_{cis}$ and $\mathbf{5}_{trans}$ and only $\mathbf{6}_{trans}$ in solution.

The ^{13}C NMR spectrum $\mathbf{5}_{cis}$ and $\mathbf{5}_{trans}$ were similar and their mixture presented 13 resonances for carbon, but the chemical shift of imine proton (in ^{1}H NMR spectrum) was different. However, their MS fragmentation patterns were completely different (see Experimental Section). It is noteworthy that the X-ray crystallography of **5** indicates a unique *trans* configuration [25].

The retention time in GC and GC-MS, and fragmentation pattern of $\mathbf{5}_{trans}$ and $\mathbf{6}_{trans}$ were nearly similar else the more abundant peak (*m*/*z* (100%); 120 for $\mathbf{5}_{trans}$ and 196 for $\mathbf{6}_{trans}$). The occurrence of $\mathbf{5}_{cis}$ increases at high temperature (> 100°C) and with a catalytic amount of acid (H_2SO_4 98%).

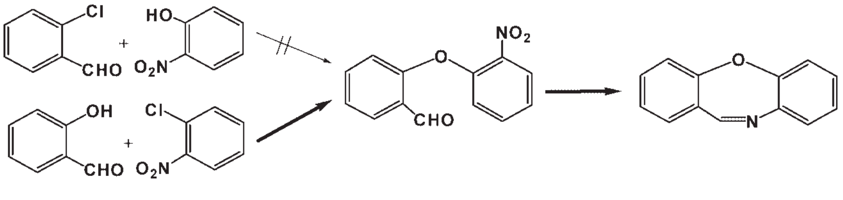
The effect of solvent and UV irradiation in the *trans*-*cis* transformation were also investigated, but complete conversion of $\mathbf{5}_{trans}$ to $\mathbf{5}_{cis}$ was never observed. In contrast, $\mathbf{6}_{trans}$ was not converted to $\mathbf{6}_{cis}$ under any conditions. The target product (**7**) was never obtained by cyclization of imine **6**. Thus, we presumed that apart from electronic parameters, the prevention of *trans-cis* conversion in **6** is another reason that the target product (**7**) was not obtained by cyclization of imine **6**. In fact, *trans-cis* isomerization can occur through the hemiaminal resulting from attack of the phenolic oxygen to the imine carbon, which is much easier in **5** (five-membered ring) than in **6** (four-membered ring).

The preparation of **7** *via* **1** and **2**, performed following several procedures, afforded different yields (Scheme 4).

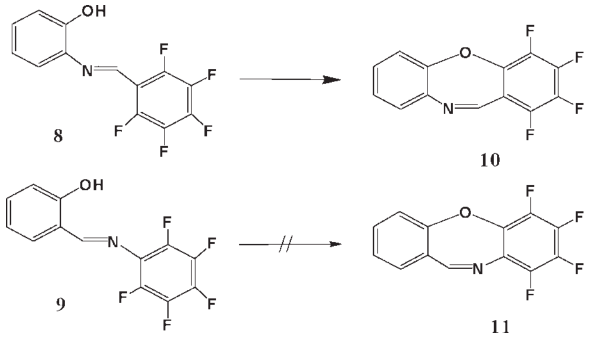
Reaction of **1** with **2** in DMSO at 150°C (the procedure B_1) afforded **7** in 25% yield. Following procedure B_3, the mixture of **1**, **2**, and KOH in CCl_4 are refluxed for 5 h and then after evaporation of solvent, DMSO was added, and the mixture was refluxed for 6 h to afford 50% of **7**.

According to the procedure B_2, when we used xylene as solvent, $\mathbf{5}_{cis}$ and $\mathbf{5}_{trans}$ were formed with proportional amounts of 12 and 88%, respectively. Heating the

Scheme 2



Scheme 3



solution at 120°C for 24 h changed the proportional amount of the two isomers in favor of *cis*, which afforded 75% of **7** after addition of Na and refluxing the reaction mixture. Without heating the solution, the attend product (**7**) was not formed. While when we used DMSO as solvent, prior conversion of *trans* to *cis* was not indispensable and the salt of **5** rearrange for the production of **7**.

Preparation of sodium salt of **2** and its subsequent reaction with **1** in DMSO at 150°C for 6 h (the procedure C) has yielded 47% of **7**.

The reaction conditions following the procedure A are more convenient (the time of reaction and the temperature), and pure products were formed after the first and second steps. In addition to good yield (70%), the formation of **7** following this method can be performed *via* a one-pot procedure (procedure B).

Our last tentative in the preparation of **7** was based on the usage of 2-fluorobenzaldehyde (a fluoro derivative of **1**) in conjunction with polyethylene glycol as was outlined recently [24]. 2-fluorobenzaldehyde is more expensive that **1** (7 fold) but the procedure offered soft conditions to obtain high-yield pure product. Simultaneous mixing of 2-fluorobenzaldehyde, 2-aminophenol (**2**), K_2CO_3 and PEG(300) (as was reported [24]) has not conducted us to the considered results. It seems that simultaneous addition of K_2CO_3 with other reactants causes formation of potassium salt of **2** which alter imine formation and its subsequent cyclization to **7**. In another attempt, 2-amino phenol was first dissolved in PEG(300) at 50°C and after addition of 2-fluorobenzaldehyde, the solution was stirred for 10 h at 50°C to complete imine (schiff base) formation. The production of **7** was accomplished after addition of K_2CO_3 and continuing the reaction for 10 h at 100°C (Scheme 5).

Thus, this procedure is slightly different from which previously proposed [24]. In this manner, the preparation of **7** was performed in one-pot two-step procedure following which preparation of imine in the first step was followed by the potassium salt formation of imine and its cyclization to produce **7** in the second step.

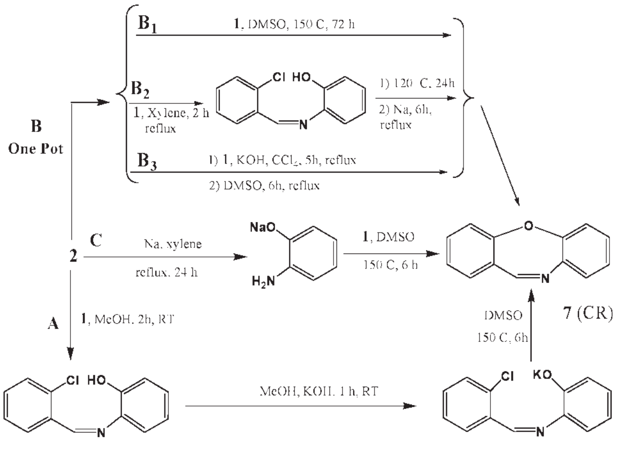
The time of reaction in the second step determined the yield of the final product. In fact, we have found that compound **7** is very temperature sensitive and at temperature higher than 100°C, the target compound decomposed and the yield decreased. Thus the time of reaction and the temperature in the second step should be controlled carefully.

The workup of the reaction mixture to obtain pure **7** was very simplified following this procedure. Effectively, the extraction with ether and several washing of organic phase with water, drying over $CaCl_2$ and stripping of solvent afforded very pure product without need of further purification procedure.

The reaction of **1** with **2** conducted under same conditions with PEG(300) has not afforded **7**. However, the usage of catalytic amount of KF (10 mol%) in the second step (after formation of imine in the first step) favors the formation of **7** (50%) but other experiments should be performed to optimize this method.

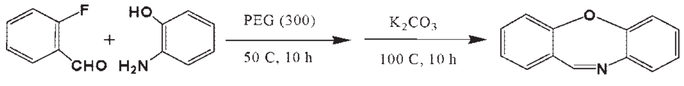
In summary, two distinct alternative methods (Scheme 1) using different starting materials for the preparation of dibenz[*b*,*f*][1,4]oxazepine (**7**) were reinvestigated. The imine reaction, according to these methods, occurs readily and yields of Schiff bases (**5**, its fluoro derivative, and **6**) are nearly quantitative. The possibility of *trans*-*cis* conversion of the Schiff base **5** were considered as favorable conditions that caused its cyclization (production of **7**). This reaction was performed following different procedures and various yields are obtained. The pathway A afforded more convenient and soft conditions for the production of pure **7** and its intermediates. Fluoro derivative of **1** afforded excellent, more convenient and soft conditions for the one-pot preparation of target compound (**7**). The presence of only *trans* configuration for the imine **6** (produced from **3** with **4**)

Scheme 4



Pathway	A	B_1	B_2	B_3	C
Yield (%)	70	25	75	50	47

Scheme 5



7 (CR), 89%

and the impossibility of its conversion to *cis*, makes it inadequate for the preparation of **7**.

EXPERIMENTAL

NMR spectra were obtained on a Bruker DPX-250 instrument (250 MHz for ^{1}H and 62.5 MHz for ^{13}C), and $CDCl_3$ was used as solvent; chemical shifts are reported in δ (ppm) from TMS. Electronic ionization GC-MS spectra were recorded on a Varian (SATURN 4D) spectrometer with capillary column (DB-5MS, 0.1 micron, 30 m × 0.250 mm). Only *m*/*z* values having intensities of more than 10% are given and retention times are reported using temperature programming (100–250°C, 10°C/min) with He flow rate of 10 mL/min. Melting points were obtained on a Mettler FP61 apparatus.

Preparation of 5. 2-Aminophenol (22 g, 0.2 mol) and MeOH (200 mL) were placed in a 300-mL, one-necked flask equipped with a mechanical stirrer. The solution was stirred at 50°C for 30 min. After complete dissolution of 2-aminophenol in MeOH, 2-chlorobenzaldehyde (28 g, 22.5 mL, 0.2 mol) was added, and the mixture was stirred for 2 h at RT. The precipitates formed were filtrated at 0°C and dried to offered 39 g of **5** (84% yield) as an orange solid, mp. 97–99°C.^{1}H NMR ($CDCl_3$): δ 6.89–7.42 (m, 8H, CH), 8.20 (d, $^4J_{H\text{—}H}$ = 2.5 Hz, 1H, CHN_{trans}), 8.23 (m, 1H, CHN_{cis}), 9.15 (s, 1H, OH). ^{13}C NMR ($CDCl_3$): δ 115.2, 116.2, 120.2, 127.2, 128.3, 129.5, 130.2, 132.4, 132.9, 135.4, 136.2, 152.6, 153.4. *Anal.* Calcd for $C_{13}H_{10}NOCl$: C, 67.39; H, 4.32; N, 6.05. Found: C, 68.38; H, 4.19; N, 6.18. GC: retention time: 28 min ($\mathbf{5}_{cis}$) and 38 min ($\mathbf{5}_{trans}$). GC-MS of $\mathbf{5}_{cis}$: retention time: 12.3 min; *m*/*z* (intensity (%)): 50 (11), 63 (51), 64 (25), 75 (11), 92 (13), 166 (19), 201 (25), 229 (100), 230 (20), 231 (38). GC-MS of $\mathbf{5}_{trans}$: retention time: 13.6 min; *m*/*z* (intensity (%)):50 (13), 51 (16), 63 (19), 65 (29), 75 (11), 89 (11), 93 (16), 102 (10), 120 (100), 196 (24), 230 (18), 231 (33), 232 (25), 233 (18), 234 (12).

Preparation of 6. 2-Chloroaniline (12.8 g, 10.6 mL, 0.1 mol) salicylaldehyde (12.2 g, 10.4 mL, 0.1 mol) and xylene (10 mL) were placed in a 100-mL, one-necked flask equipped with a magnetic stir bar. The mixture was stirred at RT for 12 h. Evaporation of solvent and water afforded 21.9 g of $\mathbf{6}_{trans}$ (95% yield) as a yellow-orange solid, mp. 86.5–87°C. ^{1}H NMR ($CDCl_3$): δ 6.9–7.5 (m, 8H, CH), 8.61 (s, 1H, CHN), 13.2 (s, 1H, OH). ^{13}C NMR ($CDCl_3$): δ 117.5, 119.1, 119.2, 127.7, 127.8, 129.6, 130.2, 132.6, 133.7, 144.8, 161.4, 163.2. GC: retention time: 38 min. GC-MS: retention time: 13.5 min; *m*/*z* (intensity (%)): 50 (13), 51 (21), 63 (12), 75 (22), 77 (12), 111 (14), 167 (16), 168 (14), 196 (100), 197 (15), 230 (11), 231 (57), 232 (40), 233 (25), 234 (13).

Preparation of 7 *via* 5. The sodium salt of **5** (25 g, 0.1 mol)—prepared by addition of **5** (23.2 g, 0.1 mol) to a methanolic solution of KOH (5.6 g, 0.1 mol in 70 mL of MeOH) followed by evaporation of solvent and drying the precipitate formed—and DMSO (100 mL) were placed in a 250-mL, glass pressure autoclave equipped with a magnetic stir bar. The mixture was stirred at 150°C for 6 h. Then the mixture was washed with water (2 × 10 mL) and extracted by toluene (3 × 10 mL). Vacuum stripping of solvent and recrystalization from benzene afforded **7** as an orange solid mp. 67–70°C, lit. [14–16] mp. 71–72°C, lit. [12] mp. 68–74°C. ^{1}H NMR ($CDCl_3$): δ 7–7.5 (m, 8H, CH), 8.52 (s, 1H, CHN). ^{13}C NMR ($CDCl_3$): δ 119.6, 120.3, 124, 124.6, 126.3, 127.7, 128.2, 129, 132.3, 139.5, 151.6, 159.4, 159.5, in agreement with literature [26]. *Anal.* Calcd for $C_{13}H_9NO$: C, 80.00; H, 4.61; N, 7.18. Found: C, 79.23; H, 4.42; N, 7.04. GC-MS: retention time: 10.2 min; *m*/*z* (intensity (%)): 50 (11), 51 (16), 63 (16), 139 (27), 140 (13), 166 (29), 167 (55), 195 (100), 196 (24) (lit.[27] 139 (25), 167 (52), 195 (100)).

One-pot preparation of 7 *via* fluoro derivative of 1. 2-aminophenol (5.5 g, 0.05 mol) and PEG(300) (100 mL) were placed in a 200-mL, one-necked flask equipped with a mechanical stirrer. The solution was stirred at 50°C for 30 min. After complete dissolution of 2-aminophenol in PEG(300), 2-fluorobenzaldehyde (6.82 g, 5.77 mL, 0.055 mol) was added and the mixture was stirred for 10 h at 50°C. Finally, K_2CO_3 (6.9 g, 0.05 mol) was added and the mixture was stirred again for 10 h at 100°C. Extraction with ether (4 × 50 mL), several washing of organic phase with water (5 × 200 mL), drying the organic phase over $CaCl_2$ and evaporation of solvent afforded very pure product **7** (7.8 g, 80% yield) as an orange solid.

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Concurrent Formation of Five and Eight-Membered Heterocyclic Methylphosphonates in Cyclization Reactions from Diethyleneglycole

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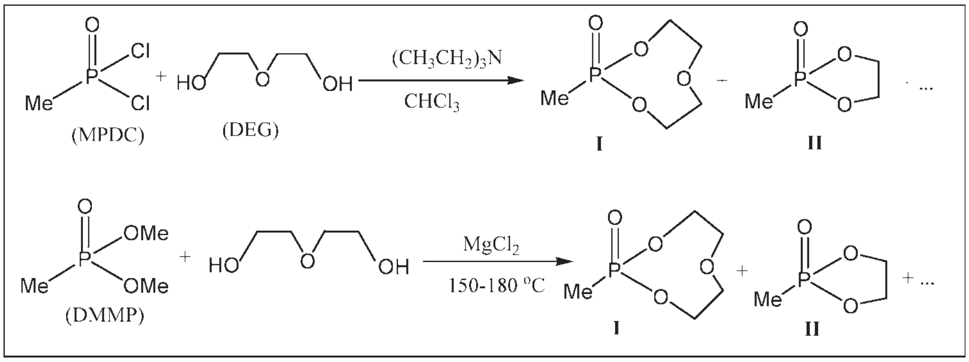

Two methodologies have been investigated for the preparation of heterocyclic methylphosphonate using diethyleneglycole and either MPDC or DMMP as the bifunctional group starting materials needed for cyclization reactions. In addition to the eight-membered ring methylphosphonate **I** the five-membered ring methylphosphonate **II** was unexpectedly found to be formed during the cyclization reactions. This small-size cyclic methylphosphonate may have been generated from an intramolecular cyclization reaction by the nucleophilic attack of the ether oxygen atom of the intermediate Me—P(O)(X)OCH_2CH_2—O—CH_2CH_2OH (X = Cl or OMe). The resulting cyclic phosphonates were purified and characterized by NMR and mass spectroscopy.

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INTRODUCTION

Among the macrocyclic compounds reported to date, little attention has been paid to the phosphorus-containing macrocycles including cyclic phosphonates, hydrogen phosphonates, and alkyl or aryl phosphonates. These compounds are used as flame proofing agents [1,2] and for the recognition and separation of alkali and lanthanide metals [3,4]. Macrocycles containing phosphorus–oxygen bonds may also have special applications both in biological systems and for the recognition of molecules such as alanine [5].

There are two synthetic methods that have been used for the preparation of the few reported macrocyclic methylphosphonates; (i) nucleophilic substitution reaction between $MeP(O)Cl_2$ (MPDC) and diols [3,4,6], (ii) cyclotransesterification methodologies starting with $MeP(O)(OMe)_2$ (DMMP) and diols [7,8].

A search in the literature indicates that although compound **I** was reported in 1957 [9] from ethylene glycol and methylphosphonic dichloride, there also have been some reports, mostly theoretical, for compound **II** [10–13]. Neither of these cyclic phosphonates has been completely spectroscopically identified. Also, to the best of our knowledge, there have been no reports of the formation of the five-membered ring compound **II** by the methodology presented herein. We herein wish to report the concurrent formation of both cyclic phosphonates **I** and **II** during the cyclization reactions between DEG and MPDC and dimethylmethylphosphonate (DMMP).

RESULTS AND DISCUSSION

The cyclization reaction between MPDC and DEG was performed in $CHCl_3$ at room temperature using Et_3N to absorb the HCl. The progress of reaction was followed by measuring the concentration of starting material MPDC in the reaction mixture by $^{31}P\{^1H\}$ NMR. After 5h, no detectable MPDC was found. Therefore, the reaction mixture was filtered off and the filtrate was

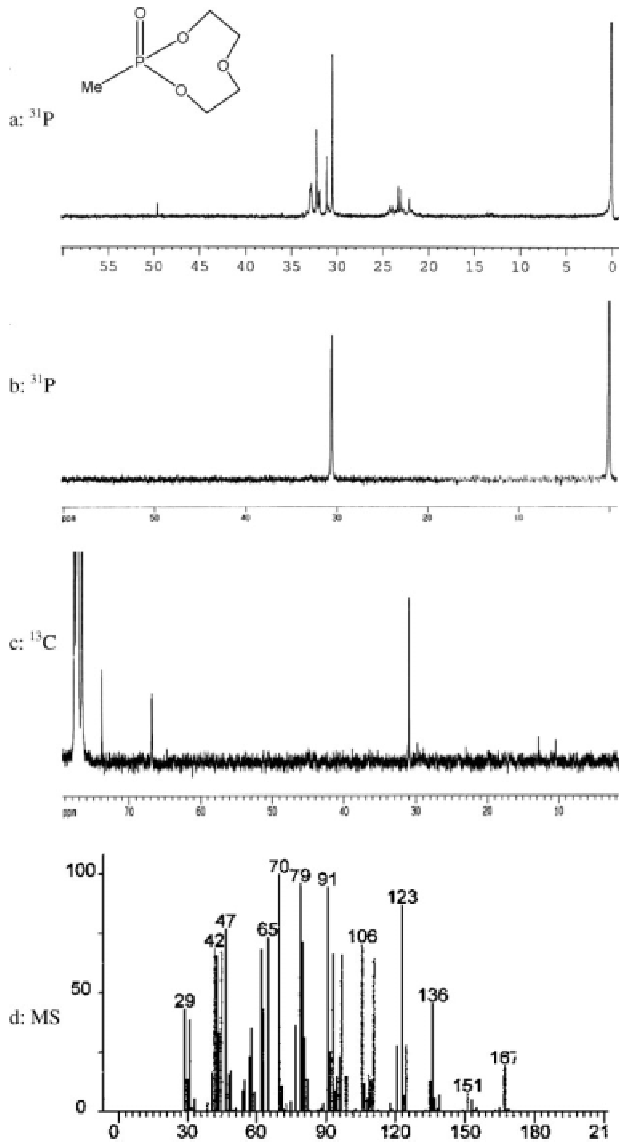

Figure 1. $^{31}P\{^{1}H\}$ NMR spectrum of reaction mixture (a), $^{31}P\{^{1}H\}$ (b) and $^{13}C\{^{1}H\}$ (c) NMR and mass (d) spectra of macrocycle **I** isolated from the reaction mixture obtained by the first cyclization method.

concentrated. The analysis of ^{1}H decoupled ^{31}P NMR spectra of the reaction mixture, shown in Figure 1, indicated the presence of methylphosphonate derivatives and the complete consumption of starting MPDC. The four peaks in the region 30–34 ppm correspond to acyclic methylphos-phonates and cyclic phosphonates with more than eight atoms including **I**. A distinct small ^{31}P peak at 49.36 ppm in Figure 1(a) corresponds to the five membered ring phosphonate **II**. The structure elucidation of **II** will be discussed in more detail.

To identify some of the resulting phosphonates obtained by methodology one, preparative TLC was applied to the concentrated reaction mixture and the macrocyclic phosphonate **I** was isolated. Characterization of the isolated component was performed using ^{31}P and ^{3}C NMR and mass spectroscopy as shown in Figure 1(b–d), respectively. The ^{1}H NMR data of **I** has been given in experimental section. The single peak in the $^{31}P\{^{1}H\}$ NMR spectrum at 30.45 ppm confirmed the presence of a single phosphonate in the isolated component. The chemical structure of **I** was then reconfirmed by $^{13}C\{^{1}H\}$ NMR spectrum [Fig. 1(c)]. Two doublets at 11.75 and 66.78 ppm with $^{1}J_{cp} = 135.5$ and $^{2}J_{cp} = 7.6$ Hz for CH_3P and P—O—CH_2 carbons respectively, and a singlet at 73.80 ppm were in support to the proposed structure for **I**. In the ^{1}H NMR spectrum a doublet at 1.52 ppm for CH_3P and four multipletes at 3.6, 3.8, 4.0, and 4.5 ppm for OCH_2 protons further confirmed the structure.

In mass spectrum of macrocycle **I**, the expected peaks at m/z 167 and 151 for M^+ and M—CH_3 were clearly observed. The possible acyclic structure shown in Figure 3, Me—P(O)$(OCH_2CH_2OCH_2CH_2OH)_2$, as one of the proposed structure for the isolated compound was ruled out not only because of the M^+ peak in the mass spectrum but also because of the four ^{13}C peaks needed for the OCH_2 carbon atoms of this phosphonate. The $^{13}C\{^{1}H\}$ NMR and mass spectral data of this phosphonate was quite different from the data obtained for the isolated phosphonate.

The second methodology applied was based on the high dilution cyclization reaction of DEG and DMMP, in the presence of $MgCl_2$ as catalyst at high temperature. The $^{13}C\{^{1}H\}$ NMR spectrum of the reaction mixture was similar to the products observed from method one. The three doublet peaks in ^{13}C NMR spectrum of the reaction mixture, in the region 10–15 ppm, corresponding to $CH_3P(O)$ carbon atoms, are indicative of the presence of three methylphosphonates as products.

Vacuum fractional distillation was applied to the reaction mixture and one of the resulting fractions with an acceptable purity for further spectral analysis was elected. The NMR and mass spectroscopic data for this fraction were found to be in agreement with the five-membered ring methylphosphonate **II**. A doublet and a singlet at 11.63 and 66.68 ppm in the $^{13}C\{^{1}H\}$ NMR spectrum, a singlet at 49.36 ppm in the $^{31}P\{^{1}H\}$ NMR spectrum, and finally a doublet and two multipletes at 1.5, 4.1, and 4.3 ppm, respectively, in the ^{1}H NMR spectrum clearly support the chemical structure proposed for phosphonate **II**.

The ^{31}P signal observed at 49.36 ppm when using method one is also observed from method two [see Figs. 1(a) and 2(a)]. Therefore, phosphonates **I** and **II** are produced during the cyclization reactions in both methods 1 and 2.

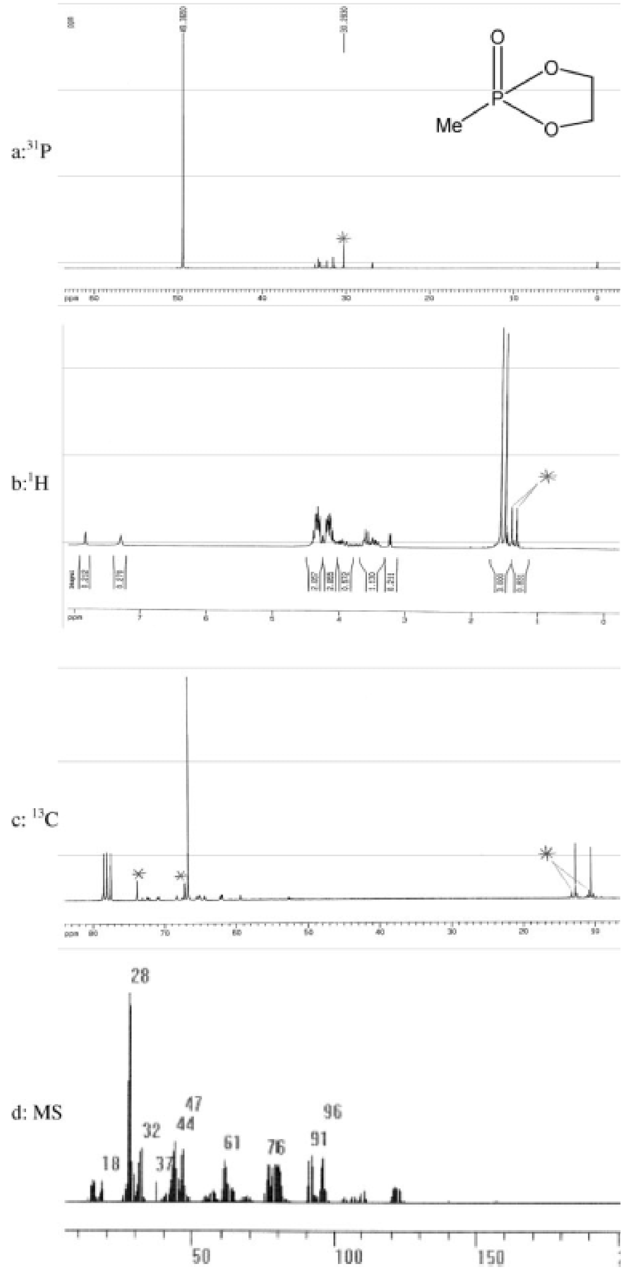

Figure 2. $^{31}P\{^1H\}$ (a), ^1H (b), $^{13}C\{^1H\}$ (c) NMR and mass (d) spectra of heterocycle **II** isolated from the reaction mixture obtained by the second cyclization method. * indicates trace phosphonate **I**.

The mass spectrum of **II** is presented in Figure 2(d). The molecular ion peak at m/z 122, a peak at m/z 28 corresponding to the $CH_2{-}CH_2$ fragment and a peak at m/z 96 for $MeP(O)(OH)_2$ are all supporting data for the proposed structure **II**.

To further confirm the chemical structure II, another cyclization reaction was performed using MPDC and ethylene glycol (EG) instead of DEG under the same conditions. The $^{31}P\{^1H\}$ NMR spectrum of the reaction mixture showed a distinct similar peak at 49 ppm indicating the formation of II. As it is clear from the NMR data presented for I and II, the ^{31}P chemical shift of cyclic methyl phosphonates is strongly dependent on ring size.

The final point to be noticed is the mechanism of the formation of phosphonate II. Though this has not been investigated in detail, an intermolecular nucleophilic attack by the ether oxygen, either from intermediate $Me{-}P(O)(X)OCH_2CH_2OCH_2CH_2OH$ ($X{=}Cl$ or OMe) may result in the formation of five-membered phosphonate ring as an unexpected product.

To estimate the approximate percentages of compounds I and II obtained by each method, the ^{13}P signal intensities were considered. It was determined that I and II have been formed in 15:1 and 10:1 mole ratios by using method one and two, respectively.

It is noted that the reaction mixtures obtained from both cyclization methods contain other products that have not been isolated yet. The possible structures for the other phosphonates produced in the cyclization reaction are given in Figure 3.

EXPERIMENTAL

All chemicals and solvents were purchased from Merck Co. except MPDC that was prepared as procedure reported in literature [14]. The reactions were monitored by TLC (aluminum sheets coated with silica gel no. 5553, Merck) with UV and iodine detection. Some purifications were taken using PLC (glass sheets coated with silica gel no. 5717, Merck). NMR spectra were recorded on a Bruker 250 MHz spectrometer (^1H: 250 MHz, ^{13}C: 62.5 MHz, ^{31}P: 101 MHz) and referenced to 80% phosphoric acid (for $^{31}P\{^1H\}$ spectra) and TMS (for ^1H and $^{13}C\{^1H\}$ spectra) as reference standards. Mass spectra were obtained on a FINNIGAN MAT 8430 instrument using electron impact ionization at 70 eV.

Synthesis of macrocyclic compound I. A total of 0.67 g (5 mmol) of Methylphosphonic acid dichloride dissolved in 50 mL of chloroform in 150 mL flask equipped with a magnetic stirrer. A mixture of 0.48 mL (5 mmol) DEG and 1.52 mL (12 mmol) TEA was then added to the MPDC

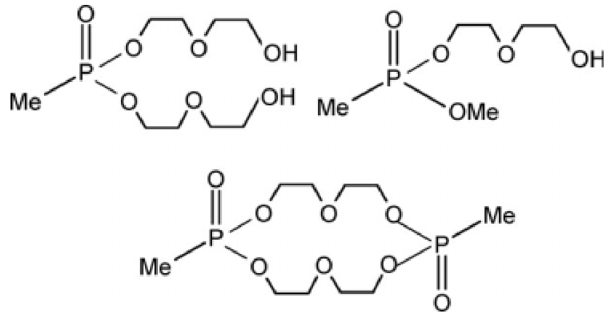

Figure 3. The other possible phosphonates produced during cyclization reaction.

solution over 20 min using a dropping funnel. The reaction mixture was stirred at room temperature for 5 h. The reaction mixture was then filtered with suction and the residue washed with chloroform. The solvent was evaporated and a semi-viscous yellow liquid was obtained. The preparative TLC was applied to the reaction crude product using *n*-heptane/chloroform (1:1) as eluent to obtain 0.15 g liquid pure macrocycle **I** in 25% yield. $^{31}P\ \{^{1}H\}$ NMR ($CDCl_3$): δ 30.54 ppm (P=O); ^{1}H NMR ($CDCl_3$): δ 1.52 (3H, d, $J = 18$ Hz, CH_3P), 3.6 (2H, m, CH_2), 3.8 (2H, m, CH_2), 4.0 (2H, m, CH_2); 4.5 (2H, m, CH_2) ppm; $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 11.75 (d, $^{1}J_{cp} = 135.5$ Hz, CH_3P), 66.78 (d, $^{2}J_{cp} = 7.6$ Hz, CH_2), 73.80 (s, CH_2) ppm; ms: m/z 167 (M^+, 25%), 151 (12), 123 (80), 106 (75), 91 (90), 79 (95), 70 (100), 65 (78), 47 (80), 42 (72), 29 (48).

Synthesis of macrocyclic compound II. A total of 2.75 mL (25 mmol) of DMMP and 0.12 g (1.25 mmol) of magnesium chloride were placed in a 10 mL flask. The mixture was heated at 140–150°C in an oil bath for 9 h, 2.4 mL (25 mmol) of DEG was then added at once and the oil bath temperature increased to 170–180°C. Heating was continued for 19 h and the reaction mixture was then cooled to room temperature to obtain a viscous brown liquid. Three fractions were collected by vacuum fractional distillation of reaction mixture. Fraction 2, 0.2 g, as a pale yellow semi-viscous liquid was compound **II**. $^{31}P\{^{1}H\}$ NMR ($CDCl_3$): δ 49.36; ^{1}H NMR ($CDCl_3$): δ 1.52 (3H, d, $^{1}J_{cp} = 18$ Hz, CH_3P), 4.1 (2H, m, CH_2), 4.3 (2H, m, CH_2) ppm; $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 11.62 (d, $^{1}J_{cp} = 132.9$ Hz CH_3P), 66.68 (s, CH_2) ppm; ms: m/z 122 (M^+, 10%), 91 (25), 76 (20), 47 (25), 28 (100).

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Efficient Synthesis of 14-Substituted-14-H-Dibenzo[*a,j*]xanthenes Using Silica Supported Sodium Hydrogen Sulfate or Amberlyst-15 Catalyst

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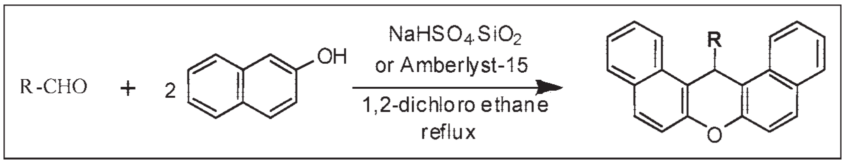

Silica supported sodium hydrogen sulfate ($NaHSO_4{\cdot}SiO_2$) or amberlyst-15 acts as an efficient heterogeneous catalyst for the preparation of 14-alkyl and aryl-14-H-dibenzo[*a,j*]xanthenes with various aldehydes and β-naphthol in dichloroethane solvent in excellent yields. Synthesis of three new compounds are reported using this methodology. Recyclable nature of the amberlyst-15 catalyst was also studied and the catalyst can be reused.

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INTRODUCTION

Xanthenes and Benzoxanthenes are important class of heterocyclic compounds and they possess diverse range of biological properties such as antiviral [1], antibacterial [2], anti-inflammatory [3] activities, as well as in photodynamic therapy [4]. Benzoxanthenes have also been investigated for agricultural bactericide activity for antagonism of the paralyzing action of zoxazolamine [5]. In addition, these compounds have wide applications in dyes [6] and in laser technologies [7] because of their useful spectroscopic properties. These compounds can also be employed as pH sensitive fluorescent materials for visualization of biomolecules [8].

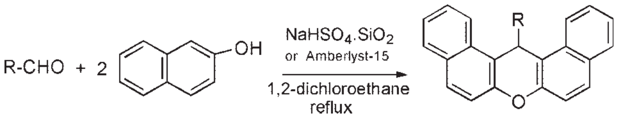
Many synthetic routes have been developed for the synthesis of xanthenes and benzoxanthenes, such as γ-alkylations to the heteroatom [9], trapping of benzynes by phenols [10], cyclocondensation between 2-hydroxy aromatic aldehydes, 2-tetralone [11], intramolecular phenyl carbonyl coupling reactions of benzaldehydes and acetophenones [12], reaction of β-naphthol with formamide [13], carbon monoxide [14], and 2-naphthol-1-methanol [15].

The reaction procedure has been improved by reacting β-naphthol with aldehydes under microwave irradiation [16] and using various acid catalysts [17]. Recently, our group reported using polyaniline based solid acid catalyst for the preparation of dodecahydroxanthenes [18]. In continuation of our research work, in this article we have used silica supported sodium hydrogen sulfate ($NaHSO_4{\cdot}SiO_2$) or amberlyst-15, an efficient heterogeneous acid catalyst for the preparation of 14-Alkyl and Aryl-14-H-dibenzo[*a,j*]xanthenes with various aldehydes and β-naphthol in dichloroethane solvent (Scheme 1). Recyclable nature of the amberlyst-15 catalyst was also studied.

RESULTS AND DISCUSSION

Product was not obtained when benzaldehyde (1 mmol) was reacted with β-naphthol (2 mmol) in 1,2-dichloroethane (5 mL) under reflux conditions for 24 h. However, with the use of Amberlyst-15 (20 wt % with respect to aldehyde) as catalyst yielded dibenzoxanthene in 93% yield in 2 h. Almost same yield (92%) was obtained with the use of silica supported sodium hydrogen sulfate as catalyst. Both catalysts are not soluble in organic solvents and act as heterogeneous catalysts. We have also examined this condensation reaction using different catalysts such as Amberlite IR-120 (H^+ form), Montmorillonite K-10, and Indion-236. However, very low yield (<15%) was obtained even for longer reaction time. This may be because of the acidic nature of these catalysts, *i.e.* these catalysts show less acidic character for this reaction. To evaluate the efficiency of this methodology, the catalytic activity of Amberlyst-15 and silica supported sodium hydrogen sulfate was studied

Scheme 1



for various aldehydes with β-naphthol and the yields are reported in Table 1.The products were obtained within 2 to 4 h in excellent yields and generally, both catalysts provided almost the same yield (Table 1).

We observed that the reactivity of aromatic aldehydes with β-naphthol is higher when compared with the aliphatic aldehydes in terms of yields and reaction time (Table 1). Furfural undergoes condensation smoothly with β-naphthol in 2.5 h with good yield (entry no. 15, Table 1). 4-Dimethylaminobenzaldehyde and pyridine-4-carbaldehyde did not react to give dibenzoxanthenes and it may be due to the presence of basic nitrogen in the system (Table 1). Amberlyst-15 can be recovered by simple filtration and can be reused after activation by treatment with HCl.

In conclusion, we have described a simple, clean, efficient, and environmental friendly method for the synthesis of biologically active heterocyclic compound, dibenzoxanthenes using two different inexpensive and nonhazardous catalysts $NaHSO_4 \cdot SiO_2$ and Amberlyst-15. We feel that this method is a valid contribution to the existing methodologies.

EXPERIMENTAL

All chemicals were of research grade and were used as obtained from Aldrich and Fluka. The reactions were carried out in a round-bottomed flask of 25 mL capacity at reflux temperature in an efficient fume hood. Analytical thin layer chromatography was performed with E. Merck silica gel 60F glass plates and flash chromatography using E. Merck silica gel (60–120 mesh). Melting points were determined on a MEL-TEMP II melting point apparatus and were uncorrected. NMR spectra were recorded of Gemini 200 MHz Varian instrument and Avance 300 MHz Bruker UX 300 FT NMR. All NMR data were obtained in $CDCl_3$ solution and chemical shifts (δ) were given in ppm relative to TMS and are compared with the reported literature values. Mass spectra were recorded on VG Micromass 7070 H (EI), VG Autospec (FAB) using Cs^+ ion gun, MNBA as a matrix, Applied Biosystems QSTAR XL High resolution mass spectrometer, Thermofinnigan ESI ion trap mass spectrometer and GC-MS instruments. Elemental analyses were performed using a Vario-EL elemental analyzer.

Typical procedure for the preparation of dibenzoxanthenes. In a typical procedure, a mixture of aldehyde (1 mmol), β-naphthol (2 mmol), 1,2-dichloroethane (5 mL), and $NaHSO_4.SiO_2$ (100 mg) (Method A) or amberlyst-15 (20 wt % with respect to aldehyde) (method B) was stirred at reflux for the appropriate time according to Table 1. The progress of the reaction was monitored by TLC. After completion of the reaction, the catalyst was filtered off and the organic solvent was evaporated by reduced pressure. The crude products were subjected to column chromatography (silica gel 5% EtOAc in hexane) to afford the pure products. All products were characterized by ^1H NMR, mass spectral data and compared with the reported spectral and physical data for known compounds (entry numbers 1–9, 11–13).

The recovered catalyst (Amberlyst-15) was reused (after treatment with HCl) four more times for the condensation reaction between benzaldehyde and β-naphthol following the above procedure for 2 h in each case the corresponding product furnishes with an yield of 93, 92, 92, and 91%.

Selected analytical data of three new representative dibenzoxanthenes are given below.

14-(3,4-dimethoxyphenyl)-14*H*-ibenzo[*a,j*]xanthene (entry 10). Wheatish solid; mp 186–188°C. IR (KBr): 3065, 1681, 1590, 1269, 1239, 1135, 1019, 815, 746 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.35$ (d, 2H), 7.35–7.81 (m, 10H), 7.08 (dd, 1H), 6.83 (d, 1H), 6.62 (d, 1H), 6.4 (s, 1H), 3.68 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 154.36, 148.95, 148.6,147.45, 137.58, 131.32, 130.98, 128.68, 128.64, 126.64, 126.56, 124.10, 122.6, 122.25, 117.78, 117.30, 111.68, 110.77, 55.85, 55.51, 37.29; HRMS (ESI) Calcd for $C_{29}H_{23}O_3$ $[M+H]^+$ 419.1647, found 419.1633; *Anal.* Calcd for $C_{29}H_{23}O_3$: C, 83.23; H, 5.30; Found: C, 83.17; H, 5.38.

14-Heptyl-14*H*-dibenzo[*a,j*]xanthene (entry 14). Off-white solid; mp 74–76°C. IR (KBr): 2922, 2850, 1589, 1458, 1397, 1241, 810, 741 cm^{-1}. ^1H NMR (300 MHZ, $CDCl_3$): $\delta = 8.25$ (d, 2H), 7.9 (d, 2H), 7.75 (d, 2H), 7.6 (t, 2H), 7.42 (t, 2H), 7.3 (d, 2H), 5.55 (s, 1H), 2.02 (m, 2H), 1.1–0.85 (m, 10 H), 0.7 (t, 3H); ^{13}C NMR (300 MHZ, $CDCl_3$): δ 149.9, 131.4, 131.0, 128.8, 128.1, 126.5, 124.0, 122.4, 117.5, 116.7, 35.9, 31.7, 31.0, 29.7, 29.0, 24.8, 22.4, 14.0. HRMS (ESI) Calcd for $C_{28}H_{29}O$ $[M+H]^+$ 381.2218, found 381.2217; *Anal.* Calcd for $C_{28}H_{29}O$: C, 88.38; H, 7.42; Found: C, 88.41; H, 7.35.

Table 1

Synthesis of dibenzoxanthene derivatives using heterogeneous catalysts.

Entry	R	Time(h)	Yield[a] (%)	
			Method A	Method B
1	C_6H_5	2	92	93
2	$4\text{-}ClC_6H_4$	1.5	91	90
3	$4\text{-}FC_6H_4$	2	96	94
4	$4\text{-}BrC_6H_4$	3	92	94
5	$4\text{-}O_2NC_6H_4$	3	91	90
6	$4\text{-}H_3CC_6H_4$	2	92	93
7	$H_3CCH_2CH_2$	4	81	82
8	$(CH_3)_2CHCH_2$	2	85	83
9	$CH_3(CH_2)_3CH_2$	4	87	88
10	$3,4\text{-}(OCH_3)_2C_6H_2$	4	85	86
11	$3\text{-}O_2NC_6H_4$	2.5	91	90
12	$4\text{-}OHC_6H_4$	4	80	82
13	$4\text{-}H_3COC_6H_4$	3	90	90
14	$H_3C(CH_2)_5CH_2$	4	82	83
15	$2\text{-}C_4H_3O$	2.5	81	84
16	$4\text{-}C_5H_4N$	24	–	–
17	$4\text{-}N(CH_3)_2C_6H_4$	24	–	–

Method A = $NaHSO_4 \cdot SiO_2$; Method B = Amberlyst-15.

[a] Isolated yields.

14-(2-Furyl)-14*H*-dibenzo[*a,j*]xanthene (entry 15). Reddish solid; mp 217–219°C. IR (KBr): 3059, 2923, 1621, 1590, 1245, 1146, 813, 737 cm^{-1}. ^1H NMR (300 MHz, CDCl3): $\delta = 8.33$ (d, 2H), 7.82–7.39 (m, 10H), 7.13 (d, 1H), 6.6 (s, 1H), 6.03 (m, 1H), 5.75 (d, 1H); ^{13}C NMR (300 MHz, CDCl3): δ 156.8, 149.2, 141.2, 129.2, 128.6, 126.8, 126.2, 124.6, 124.4, 122.8, 118.0, 114.2, 110.3, 106.6, 31.6; HRMS: (ESI) Calcd for $C_{25}H_{17}O_2$ $[M+ H]^+$ 349.1228, found 349.1230; *Anal.* Calcd for $C_{25}H_{17}O_2$: C, 86.19; H, 4.63; Found: C, 86.26; H, 4.61.

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A Facile Method for the Synthesis of Thiocoumestan Derivatives

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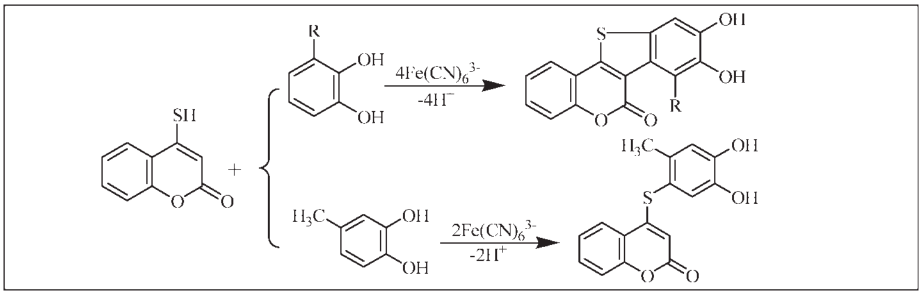

An efficient synthesis of thiocoumestan derivatives, starting from catechols and 4-mercaptocoumarin in the presence of potassium ferricyanide as an oxidizing agent (Decker oxidation) was developed. The results indicate that the 4-mercaptocoumarin participates in Michael addition reactions with *in situ* generated *o*-benzoquinones. The present work has led to the development of a one-pot oxidative method for the synthesis of the 6*H*-benzothieno[3,2-*c*][1]benzopyron-6-one derivatives.

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INTRODUCTION

Coumestans, [1] which are derivatives of 6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one (Fig. 1) have the basic structure of many natural products such as wedelolactone, medicagol, psoralidin, isopsoralidin, erosnin, and estrogenic cumestrol, with interesting physiological activities [2,3]. The importance of these compounds has led us and many workers to synthesize a number of these compounds by chemical [4–10] and electrochemical [11–14] routes. Following our experiences in oxidation of catechols in the presence of nucleophiles [15–23], we envisaged that synthesis of thiocoumestans (6*H*-benzothieno[3,2-*c*][l]benzopyran-6-one) (Fig. 1) might cause an enhancement of physiological activities.

In this direction, some workers synthesize a number of thiocoumestan derivatives [10,24,25]. But, to the best of our knowledge, no reaction of *in situ* generated *o*-benzoquinones (**2**) with 4-mercaptocoumarin (**3**) has been previously reported. Therefore, we now discover a facile and one-pot synthetic route to thiocoumestans involving oxidation of catechols (**1**) in the presence of 4-mercapto-coumarin (**3**), using potassium ferricyanide as an oxidizing agent (Decker oxidation), in high yield and purity.

RESULTS AND DISCUSSION

In our earlier work, comparison of the values of half wave potential ($E_{1/2}$), evaluated from the midpoint potential between anodic and cathodic peaks for catechol (0.165 V *vs.* SCE) and potassium ferricyanide (0.195 V *vs.* SCE), using cyclic voltammetry, revealed that potassium ferricyanide was a suitable agent (Decker agent) for mild oxidation of catechols to their corresponding *o*-benzoquinones without any effect on the nucleophile [8]. Therefore, in this work we used potassium ferricyanide as a stable, easily handled, and commercially available oxidizing agent. This agent has also been used in Decker oxidation. During Decker oxidation, 1,3-disubstituted pyridinium salts converts to isomeric pyridones [26].

The reaction for oxidation of (**1a-c**) in the presence of **3** is presented in Scheme 1. As can be seen, when catechols (**1a-c**) (1 mmol) was treated with potassium ferricyanide (4 mmol) in water/acetonitrile mixture (70/30 v/v) containing 4-mercaptocoumarin (**3**) (1 mmol) and sodium acetate (0.2 *M*), thiocoumestans (**4a-c**) were obtained in good yields (Scheme I). In more basic solutions, the formation of anionic forms of catechols formed by an acid dissociation reaction was enhanced and the coupling of anionic

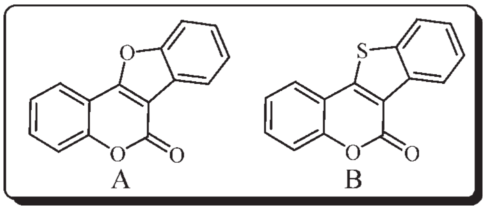


Figure 1. Structures of 6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one (A) and 6*H*-benzothieno[3,2-*c*][l]benzo pyran-6-one (B).

forms with *o*-benzoquinones interfered in the Michael reaction of 4-mercaptocoumarin (**3**) with *o*-benzoquinones (Scheme 2) [23,27,28]. In other words, in an aqueous solution containing 0.2 *M* sodium acetate, any dimerization [27,28] or hydroxylation [29–31] reactions are too slow to interfere in the synthesis of **4a-c**.

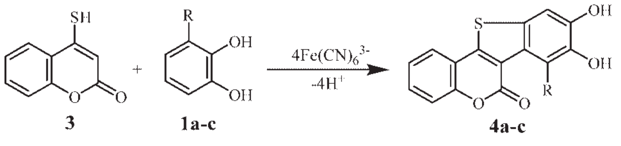
Following our experiences in oxidation of catechols in the presence of nucleophiles [15–23], it seems that in water/acetonitrile mixture (70/30 v/v), the inter and intra Michael addition reactions of anion of 4-mercapto coumarin (**3**) to *o*-benzoquinone (**2a-c**) is faster than other secondary reactions [27–31], leading to the thiocoumestan derivatives (**4a-c**) as final products.

The oxidation of **1b** and **1c** in the presence of **3** proceeded in a similar fashion to that of **1a** (Scheme 2). The existence of a methyl or methoxy group at the C-3 position of these compounds probably causes relevant Michael acceptors (**2b** and **2c**) to be attacked by **3** at the C-4 or C-5 positions to yield two types of product in each case. As in the *o*-benzoquinones **2b** and **2c** C-5 more electropositive, we suggest that *o*-benzoquinones **2b** and **2c** are selectively attacked at C-5 position by **3** leading to the formation of the products **4b** and **4c**, respectively [15–18].

Interestingly, oxidation of 4-methylcatechol (**1d**) in the presence of **3** in aqueous sodium acetate/acetonitrile (70/30) solution, because of the existence of methyl group at C-4 position of it that is a reactive site of cyclization, proceeds in a different manner to that of **1a-c** (Scheme 3).

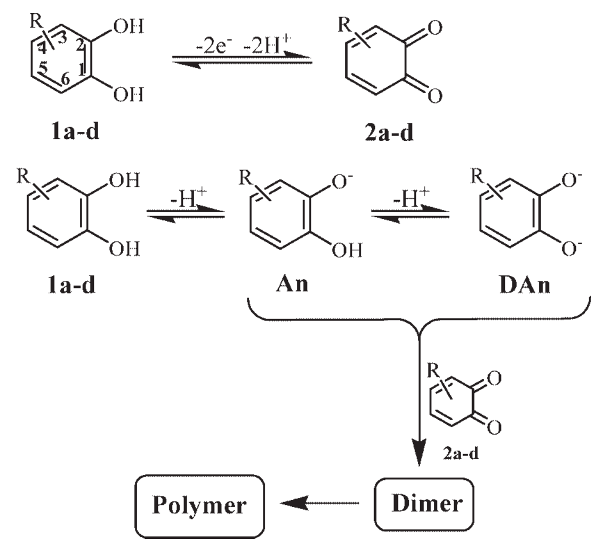
According to Scheme 3, generation of *o*-benzoquinone **2d** is followed by an intermolecular Michael addition of **3** to the *o*-benzoquinone **2d**, producing the catechol derivative (4-(4,5-dihydroxy-2-methylphenylthio)-2*H*-chromen-2-one) **4d** as final product.

Scheme 1



	R	Isolated Yield (%)
4a	H	82
4b	CH_3	75
4c	OCH_3	70

Scheme 2



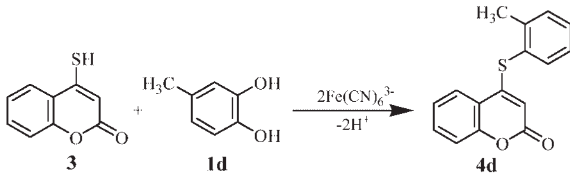
The synthesis of 4-phenylthio-2*H*-chromen-2-ones has been reported previously by us and several groups using different approaches [32–36]. However, to the best of our knowledge, no reaction of *o*-benzoquinone **2d** with 4-mercaptocoumarin (**3**) has been reported and this method described an efficient and one-pot method for the synthesis of 4-(4,5-dihydroxy-2-methylphenylthio)-2*H*-chromen-2-one (**4d**).

EXPERIMENTAL

Reagents. All chemicals were reagent grade materials. Sodium acetate, solvents, and reagents were of proanalysis. These chemicals were used without further purification. 4-mercaptocoumarin was prepared by the procedure reported previously [37].

General procedure for the synthesis of 4a-d. To a stirred solution of aqueous sodium acetate 0.2 *M*/acetonitrile (70/30), 4-mercaptocoumarin (**3**) (1 mmol) was added potassium ferricyanide (4 mmol in the cases of **1a-c** and 2 mmol in the case of **1d**). A solution of catechols (**1a-d**) (1 mmol) in relevant solution was prepared and added dropwise to the stirred solution over a period of 20–30 min. The reaction mixture was kept at r.t., with occasional stirring (1 h for **1a** and 2.5 h for **1b-d**). The solution become dark and formed precipitates. At

Scheme 3



Isolated Yield = 68 %

the end of the reaction, a few drops of acetic acid were added and the mixture was placed in a refrigerator overnight. The solid formed were collected by filtration and washed several times with water. The final products were characterized by IR, ^{1}H NMR, ^{13}C NMR, and MS spectroscopy.

8,9-Dihydroxy-6*H*-benzothieno[3,2-*c*][1]benzopyran-6-one ($C_{15}H_8O_4S$) (4a). mp 265–268° (dec); ir (potassium bromide): 3367, 3253, 1703, 1628, 1474, 1352, 1322, 1274, 1224, 1201, 1086, 1032, 989, 867, 836, 810, 752 cm^{-1}; ^{1}H nmr: δ(300 MHz, acetone-d_6) 7.29 (s, 1H, aromatic), 7.48 (s, 1H, aromatic), 7.52 (t, 2H, aromatic), 7.69 (t, 1H, aromatic), 8.03 (dd, 1H, aromatic), 8.8 (broad, OH, this peak observed in DMSO-d_6); ^{13}C nmr: δ (75.4 MHz, DMSO-d_6) 99.7, 105.7, 106.0, 112.9, 114.6, 117.8, 122.0, 125.9, 132.3, 145.3, 147.1, 150.2, 153.0, 158.6, 158.9; ms: *m*/*z* (relative intensity) 284 [M]$^+$ (95), 266 (73), 233 (60), 177 (45), 144 (10), 140 (35), 121 (30), 89(100), 43 (25).

8,9-Dihydroxy-7-methyl-6*H*-benzothieno[3,2-*c*][1]benzo pyran-6-one ($C_{16}H_{10}O_4S$) (4b). mp 230–232° (dec); ir (potassium bromide): 3374, 3163, 2929, 1708, 1603, 1546, 1448, 1343, 1289, 1124, 1170, 1030, 961, 859, 760, 639 cm^{-1}; ^{1}H nmr: δ(300 MHz, DMSO-d_6) 2.40 (s, 3H, methyl); 7.19 (s, 1H, aromatic); 7.48 (t, 1H, aromatic); 7.57 (d, 1H, aromatic); 7.66 (t, 1H, aromatic); 8.04 (dd, 1H, aromatic), 8.04 (broad, OH) 8.7 (broad, OH); ^{13}C nmr: δ (75.4 MHz, DMSO-d_6) 20.7 (methyl), 104.6, 112.7, 113.0, 122.4, 125.5, 129.2, 129.8, 132.2, 132.8, 136.1, 138.1, 151.0, 152.7, 163.9, 164.3; ms: *m*/*z* (relative intensity) 298 [M]$^+$ (100), 280 (40), 265 (45), 178 (40), 144 (23), 121 (321), 89 (50), 63 (15).

8,9-Dihydroxy-7-methoxy-6*H*-benzothieno[3,2-*c*][1]enzo pyran-6-one ($C_{16}H_{10}O_5S$) (4c). mp 245–248° (dec); ir (potassium bromide): 3641, 3521, 3359, 2923, 2852, 1704, 1628, 1605, 1596, 1466, 1442, 1418, 1396, 1345, 1265, 1204, 1081, 955, 932, 890, 857, 797, 757,746 cm^{-1}; ^{1}H nmr: δ(300 MHz, acetone-d_6) 4.23 (s, 3H, OMe); 7.21 (s, 1H, aromatic); 7.53 (m, 2H, aromatic); 7.70 (t, 1H, aromatic); 8.11 (dd, 1H, aromatic); 8.80 (broad, OH, this peak observed in DMSO-d_6); ^{13}C nmr: δ (75.4 MHz, acetone-d_6) 60.7 (methoxy), 100.1, 106.4, 113.2, 115.8, 117.4, 121.7, 125.1, 131.7, 137.9, 142.4, 142.5, 145.7, 153.5, 157.8, 159.0; ms: *m*/*z* (relative intensity) 314 [M]$^+$ (100), 298(15), 281(60), 271(30), 253 (9), 189 (6), 178 (80), 138 (20), 121 (61), 63 (30), 43 (7).

4-(4,5-Dihydroxy-2-methylphenylthio)-2*H*-chromen-2-one ($C_{16}H_{12}O_4S$) (4d). mp 273–275° (dec); ir (potassium bromide): 3344, 1686, 1600, 1546, 1519, 1445, 1414, 1344, 1320, 1270, 1187, 1158, 950, 869, 841, 824, 767, 743 cm^{-1}; ^{1}H nmr: δ(300 MHz, DMSO-d_6) 2.29 (s, 3H, methyl), 5.41 (s, 1H, aromatic), 7.01 (s, 1H, aromatic), 7.10 (s, 1H, aromatic), 7.44 (m, 2H, aromatic), 7.69 (d, 1H, aromatic), 7.94 (d, 1H, aromatic), 8.5 (broad, 2H,OH); ^{13}C nmr: δ (75.4 MHz, acetone-d_6) 19.2, 107.3, 113.4, 117.2, 118.1, 118.7, 123.5, 124.2, 124.6, 132.9, 135.6, 145.0, 148.9, 152.9, 157.5, 158.5; ms: *m*/*z* (relative intensity) 300 [M]$^+$ (38), 272 (8), 267 (16), 178 (24), 145 (30), 121 (44), 89 (100), 77 (40), 63 (78), 39 (50).

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One-Pot Three-Component Synthesis of Dihydrobenzo- and Naphtho[*e*]-1,3-oxazines in Water

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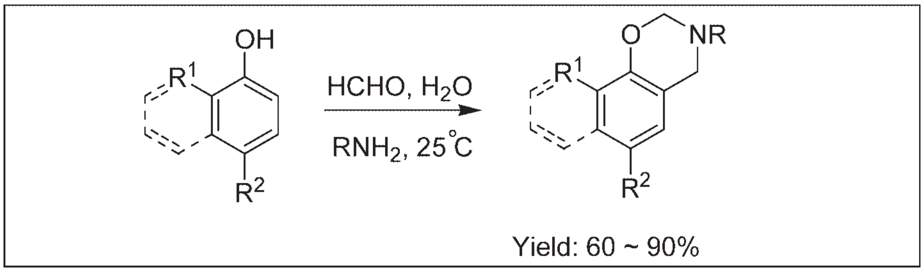

A simple, green and efficient method has been developed for the synthesis of biologically and materially important dihydrobenzo/naphtho[*e*]-1,3-oxazines in good to excellent yields through a Mannich-type condensation cyclization reaction of aromatic alcohols with HCHO and primary amines in aqueous media at ambient temperature.

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INTRODUCTION

Recently, great attention has been focused to develop nonhazardous and environment friendly synthetic strategies for organic reactions by replacing volatile organic solvents with nontoxic and noninflammable media such as water, ionic liquids, supercritical fluids, and even under neat conditions [1]. Among these, water has emerged as a versatile solvent for several organic transformations [2]. Water is not only a desirable solvent for chemical processes because of cost, safety, and environmental concerns but also provides completely new reactivity. The wide range of organic reactions is known in water including Diels-Alder cycloadditions, Knoevenagal condensations, Aldol-condensations, epoxidation, and oxidation–reduction reactions [3–7]. In addition to these, water has also been used as a solvent in reactions involving carbanions, carbocations, radicals, carbenes, and most recently transition metal catalyzed reactions [8]. In many organic reactions, the use of water as a solvent not only accelerates the rate and the yield but also enhances enantioselectivity in chiral synthesis [9].

Dihydrobenzo/naphtho[*e*]-1,3-oxazines are known to exhibit a wide range of valuable pharmacological properties as antitumor [10], antibacterial [11], anti-HIV [12], and antimicrobial agents [13]. In addition, 6-arylbenzoxazines have also been examined as progesterone receptor modulators and reported as potent nonsteroidal progesterone receptor agonists [14]. On the other hand, these molecules are materially very useful for making phenol type polymers such as polybenzoxazines, offers lucrative mechanical, and electrical properties [15]. The diverse applications of this class of heterocyclic systems inspired chemists to develop new and efficient synthetic strategies for the preparation of these bioactive and materially important molecules.

The syntheses of dihydro-1,3-oxazines have been previously reported by several investigators *via* Mannich-type condensation of a phenol or naphthol with formaldehyde and primary amine using highly inflammable organic solvents [16] and alkaline media [17]. Further, researchers have also been successful in developing mild and solvent free protocol for the construction of these molecules [18]. However, many of these processes are associated with several shortcomings such as long duration of reaction, high temperature, use of volatile and hazardous organic solvents, and occurrence of side products. As a part of our research program to develop a simple methodology for the preparation of target compounds of pharmaceutical interests, we wish to report herein a simple one-pot three-component synthesis of 3,4-dihydro-2*H*-benzo[*e*]-1,3-oxazines (Scheme 1) and dihydronaphtho[*e*]-1,3-oxazines (Scheme 2) in neat water at ambient temperature.

RESULTS AND DISCUSSION

Our initial efforts are focused on the search of a green solvent to carry out the synthesis of dihydrobenzo/naphtho[*e*]-1,3-oxazines at ambient temperature. In this connection, water was chosen for the condensation reaction of phenol, HCHO, and butylamine at room temperature. The completion of the reaction was monitored by TLC

Scheme 1

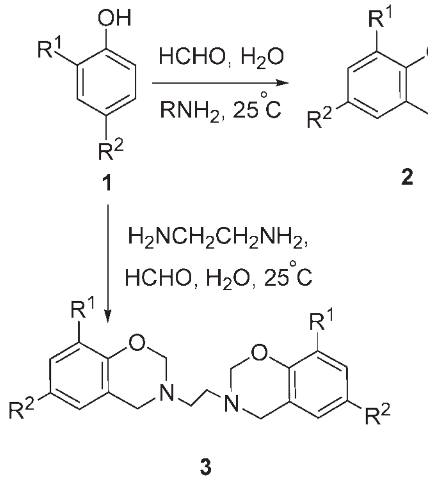

Table 1

Synthesis of 3,4-dihydro-2*H*-benzo[*e*]-1,3-oxazines and 1,2-bis(2*H*-benzo[*e*]-1,3-oxazin-3(4*H*)-yl)ethanes in water.

Entry	Compound	R^1	R^2	R	Yield (%)
1	**2a**	H	H	C_4H_9	64
2	**2b**	H	H	C_6H_5	77
3	**2c**	H	H	C_6H_{11}	80
4	**2d**	Cl	H	4–$CH_3C_6H_4$	90
5	**2e**	H	CH_3	2–ClC_6H_4	82
6	**2f**	H	Cl	2–ClC_6H_4	84
7	**2g**	Cl	H	2–ClC_6H_4	74
8	**3a**	H	H	–	87
9	**3b**	H	Cl	–	75
10	**3c**	Cl	H	–	77
11	**3d**	Cl	Cl	–	70

and the product was extracted with ethyl acetate, and purified by column chromatography on silica gel using ethyl acetate/heptane as eluent to afford 3-butyl-6-chloro-3,4-dihydro-2*H*-benzo[*e*]-1,3-oxazine (**2a**) in 64% yield. To demonstrate the versatility of this methodology, synthesis of a variety of 3,4-dihydro-2*H*-benzo[*e*]-1,3-oxazines (**2b-g**) and 1,2-bis(3,4-dihydro-2*H*-benzo[*e*]-1,3-oxazin-3-yl)ethanes (**3a-d**) has been carried out in good to excellent yields (Table 1).

Under these optimized reaction conditions, the scope of the reaction was then further explored by reacting 1-naphthol (**4a**) and 2-naphthol (**4b**) with aqueous HCHO and primary amines in water at ambient temperature separately to obtain 3,4-dihydro-2*H*-naphtho[*e*]-1,3-oxazines (**5a-d**) and 2,3-dihydro-1*H*-naphtho[*e*]-1,3-oxazines (**6a-g**), respectively in good yields (Table 2).

Our synthetic strategy does not require hazardous and toxic organic solvents, and the products were isolated by extraction with ethyl acetate, a preferred and safer solvent [19]. In fact, the dihydrobenzo/naphtho[*e*]-1,3-oxazines were prepared in a short time (30 min to 1 h) at 25°C in water, whereas in other organic solvents the reaction takes several hours to days for complete consumption of starting materials. All the synthesized dihydro-1,3-oxazine derivatives have been characterized by ^{1}H, ^{13}C NMR, IR, mass, and elemental analyses. The physical data of all the known compounds (**2a-c, 3a, b, d, 5a-c, 6a-e**) are in agreement with those of reported data [11,16,20,21]. The spectral and analytical data of new compounds (**2d-g, 3c, 5d, 6f-g**) are presented in the experimental section.

Furthermore, the polymerization behavior of novel benzoxazine analogues (**2f**; 4.79 mg & **3c**; 6.30 mg) was examined by Differential Scanning Calorimetry (DSC) with a heating rate of 10°C per min. The endothermic peaks at 67.5°C and 167°C are attributed to the melting of both **2f** and **3c**. For 6-chloro-3-(2-chlorophenyl)-3,4-dihydro-2*H*-benzo[*e*]-1,3-oxazine (**2f**), an exotherm was observed due to the ring opening polymerization [16j] with onset at 267°C and maximum at 270°C. The amount of heat of polymerization is 218 J/g. The DSC trace of 1,2-bis(8-chloro-2*H*-benzo[*e*]-1,3-oxazin-3(4*H*)-yl)ethane (**3c**) showed an exotherm with onset

Scheme 2

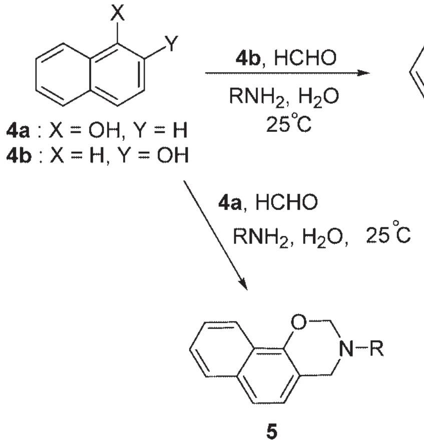

Table 2

Synthesis of 3,4-dihydro-2*H*-naphtho[*e*]-1,3-oxazines and 2,3-dihydro-1H-naphtho[*e*]-1,3-oxazines in water.

Entry	Compound	R	Yield (%)
1	**5a**	C_6H_5	90
2	**5b**	$CH_2C_6H_5$	60
3	**5c**	C_6H_{11}	62
4	**5d**	C_4H_9	85
5	**6a**	C_6H_5	79
6	**6b**	$CH_2C_6H_5$	75
7	**6c**	C_6H_{11}	87
8	**6d**	C_4H_9	80
9	**6e**	4-BrC_6H_4	73
10	**6f**	2,5-$Cl_2C_6H_3$	65
11	**6g**	2,4,6-$Cl_3C_6H_2$	63

at 195°C and maximum at 200°C. The amount of heat of polymerization for **3c** is 289 J/g. The shift of the cure exotherm to a lower temperature in case of **3c** than that of **2f** is possibly due to the flexibilizing effect of the ethylene bridge, which accelerated the ring opening polymerization.

In conclusion, we have developed a rapid, energy efficient, and environmentally conducive one-pot process for the preparation of dihydrobenzo- and naphtho[*e*]-1,3-oxazines in good yields at ambient temperature. In comparison with reported methods for making these molecules, the procedure presented herein avoids the use of hazardous organic media and the reactions are run in pure water, which is the cheapest and most harmless solvent available. Finally, these green advantages make the process more attractive for the synthesis of various biologically important dihydro-1,3-oxazine molecules.

EXPERIMENTAL

All the chemicals were used as received without any further purification. The products were purified by column chromatography using silica gel (60–120 mesh size). ^{1}H and ^{13}C NMR were recorded on Brucker 300 MHz spectrometer in $CDCl_3$ and referenced to the proton or carbon resonances resulting from incomplete deuteration of deuterated solvent. IR spectra were recorded on Perkin Elmer IR spectrometer and mass spectra were recorded on ESI-MS (micromass LCT, Water) mass spectrometer. DSC traces were recorded by using 4–6 mg samples in aluminium pan on Perkin Elmer DSC with a heating rate of 10°C min^{-1} in nitrogen atmosphere. Elemental Analyses were obtained from CHNSO Lab, University Science Instrumentation Centre, University of Delhi, Delhi.

General procedure for the one-pot synthesis of dihydrobenzo/naphtho[*e*]-1,3-oxazines (2a-g, 5a-d, 6a-g). To a mixture of aromatic alcohol (10 mmol) and primary amine (10 mmol) in water (20 ml), formalin (37%, w/v, 20 mmol) was added. The reaction mixture was stirred at 25°C for 30 min to 1 h. After completion of the reaction, the product was extracted with ethyl acetate (20 ml, two times). The organic layers were combined and washed with 10% aqueous NaOH solution (30 ml, two times) followed by water (50 ml). The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using ethyl acetate/heptane as eluent to afford the desired product.

8-Chloro-3-(4-methylphenyl)-3,4-dihydro-2*H*-benzo[*e*]-1,3-oxazine (2d). Brown colored viscous liquid; ν_{max} (film, cm^{-1}): 2922, 2851, 1615, 1574, 1515, 1461, 1378, 1240, 927, 818; ^{1}H nmr ($CDCl_3$): δ 2.26 (s, 3H, CH_3), 4.59 (s, 2H, NCH_2), 5.44 (s, 2H, OCH_2N), 6.79 (dd, *J* = 7.8, 7.6 Hz, 1H, ArH), 6.91 (d, *J* = 7.6 Hz, 1H, ArH), 7.02 (d, *J* = 8.3 Hz, 2H, ArH), 7.07 (d, *J* = 8.3 Hz, 2H, ArH), 7.19 (d, *J* = 7.5 Hz, 1H, ArH), HRMS: exact mass calculated for $C_{15}H_{13}ClNO$ (M^+−H): 258.0686; found: 258.0246.

3-(2-Chlorophenyl)-6-methyl-3,4-dihydro-2*H*-benzo-[*e*]-1,3-oxazine (2e). Viscous liquid; ν_{max} (film, cm^{-1}): 2924, 2856, 1618, 1589, 1502, 1483, 1441, 1226, 1041, 971, 949, 916, 814; ^{1}H nmr ($CDCl_3$): δ 2.24 (s, 3H, CH_3), 4.52 (s, 2H, NCH_2), 5.25 (s, 2H, OCH_2N), 6.72–7.38 (m, 7H, ArH); ^{13}C nmr ($CDCl_3$): δ 152.2, 146.9, 130.9, 130.7, 128.9, 128.1, 127.4, 125.3, 123.3, 120.8, 117.1, 80.8, 51.3, 21.0. HRMS: exact mass calculated for $C_{15}H_{14}ClNO$ (M^+): 259.0764; found: 259.0696.

6-Chloro-3-(2-chlorophenyl)-3,4-dihydro-2*H*-benzo[*e*]-1,3-oxazine (2f). Pale yellow solid; mp 67.5 °C; ν_{max} (film, cm^{-1}): 2921, 2851, 1588, 1481, 1439, 1413, 1248, 1228, 1160, 1040, 942, 878, 815; ^{1}H nmr ($CDCl_3$): δ 4.52 (s, 2H, NCH_2), 5.26 (s, 2H, OCH_2N), 6.77–7.39 (m, 7H, ArH); ^{13}C nmr ($CDCl_3$): δ 153.0, 146.4, 131.0, 128.9, 128.4, 128.1, 126.8, 126.1, 125.6, 123.2, 122.5, 118.7, 81.0, 51.0; HRMS: exact mass calculated for $C_{14}H_{12}Cl_2NO$ (MH^+): 280.0296; found: 280.0770; *Anal*. Calcd. for $C_{14}H_{11}Cl_2NO$: C, 60.02; H, 3.96; N, 5.00. Found: C, 60.07; H, 4.03; N, 5.04.

8-Chloro-3-(2-chlorophenyl)-3,4-dihydro-2*H*-benzo[*e*]-1,3-oxazine (2g). Viscous liquid; ^{1}H nmr ($CDCl_3$): δ 4.58 (s, 2H, NCH_2), 5.41 (s, 2H, OCH_2N), 6.81–6.92 (m, 2H, ArH), 7.03 (t, *J* = 7.6 Hz, 1H, ArH), 7.15 (t, *J* = 8 Hz, 1H, ArH), 7.24 (d, *J* = 8.1 Hz, 1H, ArH), 7.33–7.40 (m, 2H, ArH); HRMS: exact mass calculated for $C_{14}H_{12}Cl_2NO$ (MH^+): 280.0296; found: 280.0972.

3-Butyl-3,4-dihydro-2*H*-naphtho[2,1-*e*]-1,3-oxazine (5d). Dark viscous liquid; ν_{max} (film, cm^{-1}): 2924, 2853, 1578, 1465, 1404, 1070, 913, 801; ^{1}H nmr ($CDCl_3$): δ 0.90 (t, *J* = 7.3 Hz, 3H, CH_3), 1.32–1.39 (m, 2H, CH_2), 1.56–1.61 (m, 2H, CH_2), 2.79 (t, *J* = 7.4 Hz, 2H, CH_2), 4.09 (s, 2H, NCH_2), 5.04 (s, 2H, OCH_2N), 7.05 (d, *J* = 8.3 Hz, 1H, ArH), 7.35 (d, *J* = 8.4 Hz, 1H, ArH), 7.41–7.47 (m, 2H, ArH), 7.73–7.76 (m, 1H, ArH), 8.11–8.14 (m, 1H, ArH); HRMS: exact mass calculated for $C_{16}H_{19}NO$ (M^+): 241.1467; found: 241.5292.

2-(2,5-Dichloro-phenyl)-2,3-dihydro-1*H*-naphtho[1,2-*e*]-1,3-oxazine (6f). Pale yellow solid; mp 139°C; ν_{max} (film, cm^{-1}): 2890, 1625, 1600, 1582, 1559, 1516, 1474, 1435, 1403, 1383, 1267, 1230, 1191, 1159, 1131, 1102, 1059, 1047, 1008, 981, 950, 917, 857, 810; ^{1}H nmr ($CDCl_3$): 4.88 (s, 2H, NCH_2), 5.32 (s, 2H, OCH_2N), 6.97 (dd, *J* = 2.4 Hz, 1H, ArH), 7.10 (d, *J* = 8.9 Hz, 1H, ArH), 7.29 (d, *J* = 8.5 Hz, 1H, ArH), 7.35–7.40 (m, 2H, ArH), 7.47–7.52 (m, 1H, ArH), 7.61–7.69 (m, 2H, ArH), 7.78 (d, *J* = 8.0 Hz, 1H, ArH); *Anal*. Calcd. for $C_{18}H_{13}Cl_2NO$: C, 65.47; H, 3.97, N, 4.24. Found: C, 65.19, H, 4.27, N, 4.16.

2-(2,4,6-Trichloro-phenyl)-2,3-dihydro-1*H*-naphtho[1,2-*e*]-1,3-oxazine (6g). Pale yellow solid; mp 122°C; ν_{max} (film, cm^{-1}): 2891, 1626, 1599, 1516, 1469, 1382, 1334, 1229, 1157, 1138, 1068, 1009, 953, 921, 880, 811; ^{1}H nmr ($CDCl_3$): δ 4.85 (s, 2H, NCH_2), 5.24 (s, 2H, OCH_2N), 7.09 (d, *J* = 8.9 Hz, 1H, ArH), 7.38 (t, *J* = 7.1 Hz, 1H, ArH), 7.46–7.52 (m, 3H, ArH), 7.61 (d, *J* = 8.3 Hz, 1H, ArH), 7.68 (d, *J* = 8.9 Hz, 1H, ArH), 7.78 (d, *J* = 8.0 Hz, 1H, ArH); *Anal*. Calcd. for $C_{18}H_{12}Cl_3NO$: C, 59.29, H, 3.32, N, 3.84. Found: C, 59.22, H, 3.57, N, 3.79.

General procedure for the one-pot synthesis of 1,2-bis(2*H*-benzo[*e*]-1,3-oxazin-3(4*H*)-yl)ethanes (3a-d). To a mixture of aromatic alcohol (20 mmol) and ethylene diamine (10 mmol) in water (20 ml), formalin (37%, w/v, 40 mmol) was added. The reaction mixture was stirred at 25°C for 30 min. After completion of the reaction, the product was extracted with ethyl acetate (20 ml, two times). The organic layers were combined and washed with 10% aqueous NaOH solution (30 ml, two times) followed by water (50 ml). The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The crude solid was washed with ethanol to obtained sufficiently pure product.

1,2-Bis(8-chloro-3,4-dihydro-2*H*-benzo[*e*]-1,3-oxazin-3(4*H*)-yl)ethane (3c). White solid; mp 167°C; ν_{max} (film, cm^{-1}) 2918, 2854, 1572, 1456, 1353, 1321, 1231, 1120, 1071, 1031, 981, 894, 762; ^1H nmr ($CDCl_3$): δ 2.98 (s, 4H, NCH_2CH_2N), 4.04 (s, 4H, $2NCH_2$), 5.02 (s, 4H, $2OCH_2N$), 6.77–6.87 (m, 4H, ArH), 7.21 (d, $J = 6.8$ Hz, 2H, ArH). *Anal.* Calcd. for $C_{18}H_{18}Cl_2N_2O_2$: C, 59.19, H, 4.97, N, 7.67. Found: C, 59.39, H, 5.22, N, 7.91.

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5,5-Diaryl and 5-Alkyl-3-phenyl-4-imidazolidones: A Novel Synthesis

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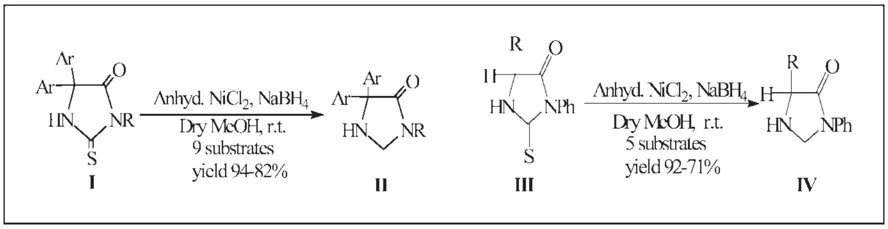

Synthesis of 5,5-diaryl and 5-alkyl-3-phenyl-4-imidazolidones has been reported by reductive desulfurization of 5,5-diaryl and 5-alkyl-3-phenyl-2-thiohydantoins with nickel boride.

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INTRODUCTION

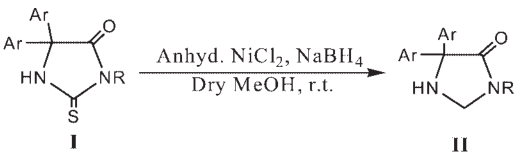
Compounds containing an imidazole ring are well-known in living systems. A number of 4-imidazolidone derivatives display a wide range of biological properties including anti-convulsant [1], anti-depressant [2], anti-inflammatory [3], anti-viral [4], anti-tumor [5], etc. 4-imidazolidones can be prepared by multistep synthesis involving reagents which are difficult to handle [6]. Although sodium and amyl alcohol [7], sodium amalgam [8], H_2 pressure on Pd-charcoal catalyst [9], and Raney nickel [10] have been reported as dethiating agents for 2-thiohydantoins, the yields range from low to moderate. However, the synthesis of 4-imidazolidones by reductive desulfurization of 2-thiohydantoins has not received attention. Reductive desulfurization of 2-thiohydantoins would obviously provide an alternate and convenient method of synthesis of 4-imidazolidones.

Nickel boride [11] has been reported as a convenient and efficient reagent for reductive desulfurization of benzimidazoline-2-thiones, 2-thiobarbituric acids [12], 2-thioxo-4-3*H*-quinazolinones [13], and 2-thioxo-5*H*-pyrano[23-*d*]pyrimidines [14]. In view of its versatility and ease of handling, we decided to explore its application for the desulfurization of 5,5-diaryl, 5-alkyl-3-phenyl and 5-alkyl-2-thiohydantoins.

RESULTS AND DISCUSSION

In this article, we report a convenient synthesis of 5,5-diaryl and 5-alkyl-3-phenyl-4-imidazolidones by reductive desulfurization of 5,5-diaryl-2-thiohydantoins (**Ia–i**) and 5-alkyl-3-phenyl-2-thiohydantoins (**IIIa–e**) with nickel boride in dry methanol at ambient temperature. The nickel boride was prepared *in situ* from anhydrous nickel chloride and sodium borohydride. Reactions were carried out under varying conditions by changing solvents and molar ratio of substrate to nickel boride to optimize conditions for quantitative desulfurization.

The 5,5-diaryl-2-thiohydantoins underwent complete reductive desulfurization to give the corresponding 5,5-diaryl-4-imidazolidones in high yields [Eq. (1)] and were identified by their spectral data. The sulfur by-product of these reactions is hydrogen sulfide gas. A number of new 4-imidazolidones have been synthesized in this manner. All the 4-imidazolidones showed a distinct peak at δ 4.4–4.5 for two protons due to —NH—CH$_2$—NR— group. IR showed a peak at ~1680–1750 cm^{-1} due to —CO—NR group. No 4-imidazolidinones (double bond between 1-2 positions or 2-3 positions) were formed under these conditions. These results are listed in Table 1.



(1)

a: Ar = C_6H_5, R = H
b: Ar = p-MeOC_6H_4, R = H
c: Ar = p-MeC_6H_4, R = H
d: Ar = o-MeC_6H_4, R = H
e: Ar = p-ClC_6H_4, R = H
f: Ar = o-ClC_6H_4, R = H
g: Ar = p-BrC_6H_4, R = H
h: Ar = m-BrC_6H_4, R = H
i: Ar = C_6H_5, R = C_6H_5

The reactions carried out in ethanol, THF, and DMF were sluggish and showed the formation of

Table 1

Reactions of 5,5-diaryl-2-thiohydantoin with nickel boride in dry methanol[a] at ambient temperature.

Run	Substrate (S)	Molar ratio $S:NiCl_2:NaBH_4$	Reaction time (min)	Product (P)	Yield (%)
1.	**Ia**	1:8:8	5	5,5-diphenyl-4-imidazolidone (**IIa**)	94 [15]
2.	**Ib**	1:8:8	15	5,5-di(*p*-anisyl)-4-imidazolidone (**IIb**)	89 [10a]
3.	**Ic**	1:10:10	30	5,5-di(*p*-tolyl)-4-imidazolidone (**IIc**)	89
4.	**Id**	1:5:5	45	5,5-di(*o*-tolyl)-4-imidazolidone (**IId**)	88
5.	**Ie**	1:6:6	120	5,5-di(*p*-chlorophenyl)-4-imidaolidone (**IIe**)	89
6.	**If**	1:6:6	150	5,5-di(*o*-chlorophenyl)-4-imidazolidone (**IIf**)	86
7.	**Ig**	1:10:10	5	5,5-di(*p*-bromophenyl)-4-imidazolidone (**IIg**)	87
8.	**Ih**	1:8:8	10	5,5-di(*m*-bromophenyl)-4-imidazolidone (**IIh**)	84
9.	**Ih**	1:10:10	5	5,5-di(*m*-bromophenyl)-4-imidazolidone (**IIh**)	86
10.	**Ih**	1:15:15	5	5,5-di(*m*-bromophenyl)-4-imidazolidone (**IIh**)	82
11.	**Ii**	1:20:20[b]	6 h	–	–[c]

[a] 5 mL of dry methanol was used for 0.1 g of substrate.

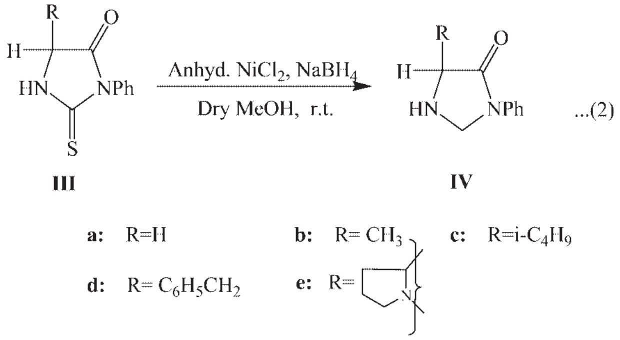
[b] Reaction started with 1:10:10 molar ratio of $S:NiCl_2:NaBH_4$ and another lot of 10:10 $NiCl_2:NaBH_4$ was added after 2 h.

[c] Incomplete reaction.

complex mixture of products, unlike the reactions in dry methanol. Therefore, dry methanol was the solvent of choice in these reactions. Reaction of 5,5-diphenyl-2-thiohydantoin (**Ia**) with sodium borohydride alone in 1:8 molar ratio yielded a mixture of products, whereas starting material was recovered on reaction with nickel chloride alone (molar ratio 1:8) under these conditions. This confirms that the reductive desulfurizations are proceeding due to nickel boride generated *in situ*.

Nickel boride showed high selectivity toward desulfurization because it did not affect the carbonyl group and also no dehalogenated products were obtained in the reactions of **Ie–h**. Reaction of 5,5-di(*m*-bromophenyl)-2-thiohydantoin (**Ih**) in high-molar ratios also did not show any debromination (Table 1) as only 82 and 86% of 5,5-di(*m*-bromophenyl)-4-imidazolidone (IIh) was isolated in runs 9 and 10, respectively. 3,5,5-Triphenyl-2-thiohydantoin (**Ii**) did not undergo any reaction and starting material was recovered unchanged even after using high-molar ratios (run 11). This could be due to steric hindrance of the 3-phenyl groups, which prevents reaction on the surface of catalyst.

Reactions of 5-alkyl-3-phenyl-2-thiohydantoins (**IIIa–d**) also yielded corresponding 5-alkyl-3-phenyl-4-imidazolidones (**IVa–d**) in high yields with nickel boride [Eq. (2)]. Desulfurization of 2-phenyl-1*H*-pyrrolo[1,2-*c*]imidazol-3-thio-1-one (**IIIe**) with nickel boride yielded 2-phenyl-1*H*-pyrrolo[1,2-*c*]imidazol-1-one (**IVe**) with 89% yield. Synthesis of **IVe** has been reported by multistep synthesis [16]. Reactions of 2-thiohydantoin (**Va**), 5-methyl-2-thiohydantoin (**Vb**), and 5-isopropyl-2-thiohydantoin (**Vc**) were not clear and mixtures of products were obtained. All the results are listed in Table 2.



Therefore, we conclude that nickel boride is an efficient reagent for the reductive desulfurization of 5,5-diaryl-2-thiohydantoins (**I**) and 5-alkyl-3-phenyl-2-thiohydantoins (**III**) and provides a convenient route for synthesis of 4-imidazolidones (**II** and **IV**) in high yields.

EXPERIMENTAL

Starting materials. Methanol (S.D. Fine) was used after drying by the reported procedure [17]. Nickel (II) chloride hexahydrate (Thomas Baker Chemicals) was dried by heating in a crucible till golden yellow, it was then allowed to cool at room temperature and stored over calcium chloride in a dessiccator. Sodium borohydride (E. Merck) was used in all the reactions. Thiourea (S.D. Fine) was used as such for the preparation of starting materials. Benzils were prepared from the corresponding hydrobenzoins by oxidation with NBS [18]. Glycine, alanine, isoleucine, phenylalanine, and proline were obtained from commercial sources. 5,5-Diaryl-2-thiohydantoins were prepared by the condensation of thiourea and benzils in the presence of potassium hydroxide [19]. 5-Alkyl-3-phenyl-2-thiohydantoins were prepared by the reaction of corresponding amino acids with aniline, triethyl amine, carbon disulphide, and methyl iodide [20] and 5-alkyl-2-thiohydantoins were

Table 2

Reactions of 5-alkyl-3-phenyl-2-thiohydantoins and 5-alkyl-2-thiohydantoin with nickel boride in dry methanol at ambient temperature.

Run	Substrate (S)	Molar ratio $S:NiCl_2:NaBH_4$	Reaction time (min)	Product (P)	Yield (%)
12.	**IIIa**	1:10:10	5	3-phenyl-4-imidazolidone (**IVa**)	72
13.	**IIIb**	1:10:10	5	5-methyl-3-phenyl-4-imidazolidone (**IVb**)	92
14.	**IIIc**	1:10:10	10	5-isobutyl-3-phenyl-4-imidazolidone (**IVc**)	71
15.	**IIId**	1:5:5	10	5-benzyl-3-phenyl-4-imidazolidone (**IVd**)	85
16.	**IIIe**	1:10:10	15	2-phenyl-1*H*-pyrrolo[1,2-c]imidazol-1-one (**IVe**)	89 [16]
17.	**Va**	1:5:5[a]	150	–	–[b]
18.	**Va**	1:3:9	5	–	–[b]
19.	**Vb**	1:5:5	60	–	–[b]
20.	**Vc**	1:5:5	15	–	–[b]
21.	**Vc**	1:10:10	5	–	–[b]

[a] Reaction started with 1:3:3 molar ratio of $S:NiCl_2:NaBH_4$ and second lot of $NiCl_2:NaBH_4$ was added after 60 min.
[b] Starting material disappeared but number of spots were observed on TLC.

prepared by reaction of amino acids with potassium thiocyanate in acetic anhydride [21].

Reactions of 2-thiohydantoins. In a typical procedure, 5,5-diphenyl-2-thiohydantoin (**Ia**) (0.1 g, 0.37315 mmol), anhydrous nickel chloride (0.3851 g, 2.9851 mmol), and dry methanol (5 mL) were placed in a 50 mL round-bottomed flask fitted with a condenser and a $CaCl_2$ guard tube. The flask was mounted over a magnetic stirrer. Sodium borohydride (0.1135 g, 2.9851 mmol) was added very cautiously while stirring the solution vigorously. The progress of the reaction was monitored by TLC using petroleum ether-ethyl acetate as eluent. After disappearance of the starting material, the reaction mixture was filtered through a celite pad (~1 inch) and washed with methanol (1 × 15 mL). The combined filtrate was diluted with water (~50 mL) and extracted with ethyl acetate (3 × 10 mL). The combined extract was dried over anhydrous $MgSO_4$, filtered, and concentrated on a rotary evaporator to give a new product, which was purified by recrystallization from ethanol and analyzed by mp, IR, NMR, and mass spectra as 5,5-diphenyl-4-imidazolidone (**IIa**) (0.0825 g, 94%) mp 182–183°C (lit. mp 183°C) [15]. All other products were synthesized similarly from the corresponding 2-thiohydantoins. The spectroscopic data of newly synthesized 4-imidazolidones is listed as follows.

IIc: (0.08 g, 89%), mp 170°C; IR: NH 3185, C=O 1699 cm^{-1}; ^1H NMR: δ 2.32–2.35 (2× CH_3, 6H), 4.39 (s, 2H, H-2), 7.12–7.50 (m, 8H, Ar′—H, Ar″—H); MS ES+ for $C_{17}H_{18}N_2O$ (266): 267 (M^+ +1). Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.72; H, 6.82; N, 10.53. Found: C, 76.73; H, 6.82; N, 10.52.

IId: (0.078 g, 88%), mp 150°C; IR: NH 3216, C=O 1710 cm^{-1}; ^1H NMR: δ 1.99 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 4.55 (s, 2H, H-2), 7.11–7.36 (m, 8H, Ar—H); MS ES+ for $C_{17}H_{18}N_2O$ (266): 267 (M^+ +1). Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.72; H, 6.82; N, 10.53. Found: C, 76.72; H, 6.83; N, 10.52.

IIe: (0.082 g, 89%), mp 140°C; IR: NH 3308, C—O 1683 cm^{-1}; ^1H NMR: δ 4.43 (s, 2H, H-2), 7.29–7.36 (m, 4H, 2′, 6′, 2″ and 6″-H), 7.49–7.52 (d, *J* = 8.68 Hz, 2H, 3" and 5"-H), 7.56–7.59 (d, *J* = 8.44 Hz, 2H, 3′ and 5′-H); MS ES+ for $C_{15}H_{12}N_2Cl_2O$ (306): 307 (M^+ +1). Anal. Calcd. for $C_{15}H_{12}N_2Cl_2O$: C, 58.87; H, 3.95; N, 9.15. Found: C, 58.87; H, 3.96; N, 9.15.

IIf: (0.078 g, 86%), mp 142–145°C; IR: NH 3409, C=O 1708 cm^{-1}; ^1H NMR: δ 4.43–4.50 (t, 2H, H-2), 7.26–7.59 (m, 8H, Ar—H); MS ES+ for $C_{15}H_{12}N_2Cl_2O$ (306): 329 (M^+ + Na). Anal. Calcd. for $C_{15}H_{12}N_2Cl_2O$: C, 58.87; H, 3.95; N, 9.15. Found: C, 58.88; H, 3.95; N, 9.14.

IIg: (0.08 g, 87%), mp 176°C; IR: NH 3409, C=O 1708 cm^{-1}; ^1H NMR: δ 4.42 (s, 2H, H-2), 7.26–7.59 (m, 8H, Ar—H); MS ES+ for $C_{15}H_{12}N_2Br_2O$ (394): 395 (M^+ +1). Anal. Calcd. for $C_{15}H_{12}N_2Br_2O$: C, 45.74; H, 3.07; N, 7.11. Found: C, 45.72; H, 3.08; N, 7.10.

IIh: (0.0796 g, 84%), mp 110–112°C; IR: NH 3173, C=O 1686 cm^{-1}; ^1H NMR: δ −4.43 (s, 2H, H-2), 7.18–7.84 (m, 8H, Ar—H); MS ES+ for $C_{15}H_{12}N_2Br_2O$ (394): 395 (M^+ +1). Anal. Calcd. for $C_{15}H_{12}N_2Br_2O$: C, 45.74; H, 3.07; N, 7.11. Found: C, 45.72; H, 3.08; N, 7.11.

IVa: (0.0610 g, 72%), mp 154°C; IR: NH 3155, C=O 1766 cm^{-1}; ^1H NMR: δ 3.60–3.62 (d, 2H, H-4), 4.74 (s, 2H, H-2), 7.16–7.57 (m, 5H, Ar—H); MS ES+ for $C_9H_{10}N_2O$ (162): 162 (M^+). Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.69; H, 6.22; N, 17.26. Found: C, 66.70; H, 6.22; N, 17.25.

IVb: (0.0786 g, 92%); IR: NH 3292, C=O 1714 cm^{-1}; ^1H NMR: δ 1.44–1.46 (d, 3H, 5-CH_3), 3.63–3.70 (q, 1H, H-5), 4.80 (s, 2H, H-2), 7.1644–7.5828 (m, 5H, Ar—H); MS ES+ for $C_{10}H_{12}N_2O$ (176): 177 (M^+ +1). Anal. Calcd. for $C_{10}H_{12}N_2O$: C, 68.21; H, 6.87; N, 15.91. Found: C, 68.21; H, 6.88; N, 15.90.

IVc: (0.0624 g, 71%), mp 113°C; IR: NH 3284, C—O 1689 cm^{-1}; ^1H NMR: δ 0.98–1.02 (t, 6H, H-γ), 1.47–1.50 (m, 1H, H-β), 1.85–1.90 (m, 2H, H-α), 3.60–3.63 (d, 1H, H-4), 4.79 (s, 2H, H-2), 7.35–7.57 (m, 5H, Ar—H); MS ES+ for $C_{13}H_{18}N_2O$ (218): 219 (M^+ +1). Anal. Calcd. for $C_{13}H_{18}N_2O$: C, 71.58; H, 8.32; N, 12.84. Found: C, 71.58; H, 8.33; N, 12.82.

IVd: (0.0750 g, 85%), mp 140°C; IR: NH 3283, C—O 1682 cm^{-1}; ^1H NMR: δ 3.08–3.24 (m, 2H, —CH_2Ph), 3.89 (s, 1H, H-5), 4.53–4.71 (dd, *J* = 7.2 Hz, 2H, H-2), 7.13–7.52 (m, 10H, Ar—H); MS ES+ for $C_{16}H_{16}N_2O$ (252): 253 (M^+ +1). Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.22; H, 6.40; N, 11.11. Found: C, 76.23; H, 6.40; N, 11.10.

IVe: (0.0775 g, 89%), mp 90°C; IR: C=O 1692 cm^{-1}; ^1H NMR: δ 1.82–1.91 (m, 2H, H-6), 2.18–2.25 (q, 2H, H-7), 2.66–2.74 (q, 1H, H-8), 3.24–3.31 (m, 1H, H-8), 3.91–3.95 (t, 1H, H-5), 4.56–4.59 (d, *J* = 8.29 Hz, 1H, H-2), 4.99–5.02 (d,

J = 8.29, 1H, H-2), 7.14–7.59 (m, 5H, Ar—H); MS ES+ for $C_{12}H_{14}N_2O$ (202): 203 (M^+ +1). Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.31; H, 6.98; N, 13.86. Found: C, 71.31; H, 6.98; N, 13.86.

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Synthesis of [2,4-Bis(arylamino)thiazol-5-yl](1-methyl-1*h*-benzimidazol-2-yl)methanones

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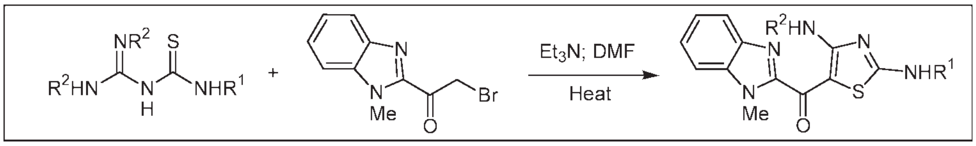

[2,4-Bis(arylamino)thiazol-5-yl]-(1-methyl-1*H*-benzimidazol-2-yl)methanones, as the analogs of the cytotoxic marine alkaloid dendrodoine, are synthesized and characterized by elemental analysis, IR, NMR, and Mass spectral data. The thiourea derivatives provide four ring atoms for the thiazole ring construction and thus act as [C—N—C—S] synthons. The remaining carbon of the thiazole is sourced from 2-(2-bromoacetyl)-1-methyl-1*H*-benzimidazole. This [4+1] heterocyclization reaction is adopted for the synthesis of novel 1-methyl-1*H*-benzimidazole derivatives.

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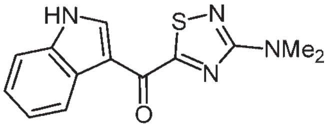
INTRODUCTION

For a natural product, either from terrestrial or from marine sources, dendrodoine **1**, [3-(*N,N*-dimethylamino-1,2,4-thiadiazol-5-yl]-indol-3-yl-methanone, isolated [1] from the ''baked bean ascidian'' or *Dendrodoa grossularia*, is unusual in that it incorporates a 1,2,4-thiadiazole ring. It has been shown to be cytotoxic *in vitro* [1,2] and has been synthesized [3] by a 1,3-dipolar cycloaddition of indoloyl cyanide to a nitrile sulfide obtained by the thermolysis of a 1,3,4-oxathiazol-2-one prepared from *N,N*-dimethylurea and chlorocarbonylsulphenyl chloride. This route is rather inflexible as it is confined solely to the preparation of 3-*N,N*-dialkylamino derivatives. In addition, the hetaroyl cyanides are difficult to access, thereby making the preparation of dendrodoine analogs with a variety of substituents not easy. Moreover, the scope of the substituent manipulation in **1** is restricted due to the availability of only two carbons for substitution or functionalization in the 1,2,4-thiadiazole ring. Therefore, the exchange of a 2-aminothiazole unit for the 3-amino-1,2,4-thiadiazole unit in dendrodoine seemed attractive. Thus, the synthesis of several (2-*N,N*-dimethylaminothiazol-5-yl)-(hetaryl)-methanones as thiazole analogs of dendrodoine and the cancer cell cytotoxicity of the indolyl derivative **2** at submicromolar concentration were reported by us recently [4].

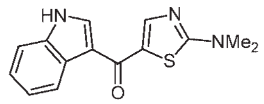


1
Dendrodoine

In this context, the 2-amino-5-ketothiazole synthesis developed by us [5–7] appeared promising. A variety of amino substituents could be placed on C-2 and C-4 carbons of the thiazole ring by choosing the appropriate thiourea synthon and the 5-keto substituent could be accessed through a variety of α-haloketones. As typical examples, [4-amino-2-(4-methoxyphenylamino)-thiazol-5-yl)]-phenylmethanone **3** [8], [4-(4-chlorophenylamino)-2-(4-methoxyphenylamino)thiazol-5-yl)]-*1H*-indol-3-yl-methanone **4**, and 5-[4-amino-2-(4-methoxyphenylamino)-thiazol-5-yl)]-(1-methyl-1*H*-benzimidazol-2-yl)-methan-one **5** [9] were found to be cancer cell cytotoxic at submicromolar levels. To broaden the scope of this study further, we now report the synthesis of [2,4-bis(arylamino)thiazol-5-yl](1-methyl-1*H*-benzoimidazol-2-yl)methanones as further analogs of dendrodoine. Literature survey shows several examples of compounds having a 1*H*-benzimidazole ring which exhibit remarkable bioactivity including anticancer activity [10–14].

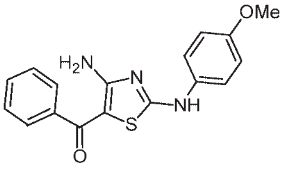
RESULTS AND DISCUSSION

The route adopted for the synthesis of these novel analogs of dendrodoine was based on a retro synthetic analysis as outlined in Scheme 1. The thiourea derivatives [5–7] (**6a–k**) provide four ring atoms for the thiazole ring construction and thus act as [C—N—C—S] synthons. The remaining carbon of the thiazole is sourced from 2-(2-bromoacetyl)-1-methyl-1*H*-benzimidazole. This [4+1] heterocyclization reaction is now selected for the synthesis of novel 1-methyl-1*H*-benzimidazole derivatives (Scheme 2). Thus, the reaction of 1-(*N*,*N*'-diphenylamidino)-3-phenylthiourea (**6a**) in *N*,*N*-dimethylformamide (DMF) with 2-(2-bromoacetyl)-1-methyl-1*H*-benzimidazole (**7**) which was prepared from 2-(1-hydroxyethyl)-1*H*-benzimidazole [15,16], in DMF in the presence of triethylamine afforded an orange, crystalline compound which showed up in the thin layer chromatogram (TLC) as a single fluorescent yellow spot, indicating the formation of only one major product.



2

(2-*N*,*N*-dimethylaminothiazol-5-yl)-(1*H*-indol-3-yl)methanone



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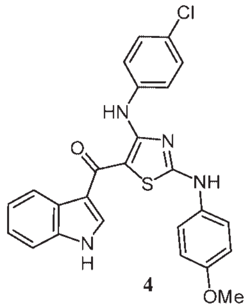

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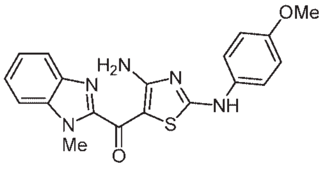


5

The molecular composition of the compound (**8a**) was found to be $C_{24}H_{19}N_5OS$. The IR (KBr) spectrum shows peaks at 3387, 3267, 3200, and 3117 cm^{-1}, which are attributed to the ν_{N-H} vibration. The aromatic ν_{C-H} band appears at 3050 cm^{-1}. The aliphatic ν_{C-H} band is observed at 2928 cm^{-1}and 2861 cm^{-1}. The highly conjugated carbonyl group shows $\nu_{C=O}$ vibration at 1607 cm^{-1}.

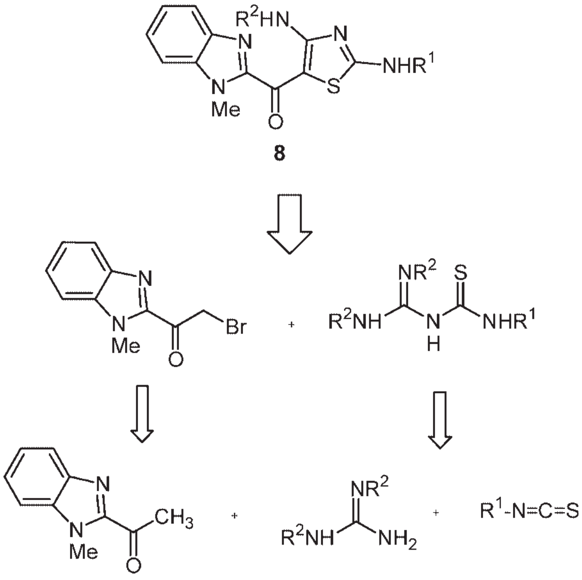
The ^{1}HNMR (300 MHz, DMSO-d_6) spectrum shows a three-hydrogen singlet at δ 4.22, which has been ascribed to the methyl group of 1-methyl-1*H*-benzimidazole ring. The spectrum consists of three multiplets in the aromatic region. The first multiplet at δ 7.06–7.18 is due to two aromatic hydrogens. The H-5 and H-6 of the 1-methyl-1*H*-benzimidazole ring and the four other aromatic hydrogens give rise to the second multiplet at δ 7.25–7.46. The third multiplet at δ 7.64–7.78 arises from H-4 and H-7 of the 1-methyl-1*H*-benzimidazole ring and the remaining four aromatic hydrogens. The two one-hydrogen singlets in the downfield region at δ 11.19 and 11.85 are assignable to NH hydrogen of the two NHAr groups.

The FAB MS confirms the molecular mass of the compound as 425 in accordance with the elemental analysis data. The presence of 24 carbons in the compound is confirmed from the 20 peaks observed in the ^{13}CNMR spectrum. Based on these data, the structure of the compound now obtained was assigned as [2,4-bis(phenylamino)thiazol-5-yl](1-methyl-1*H*-benzim-idazol-2-yl)methanone (**8a**). By following the similar procedure 10 additional [2,4-bis(arylamino)thia-zol-5-yl](1-methyl-1*H*-benzimidazol-2-yl)methanones (**8b–k**) were prepared and characterized.

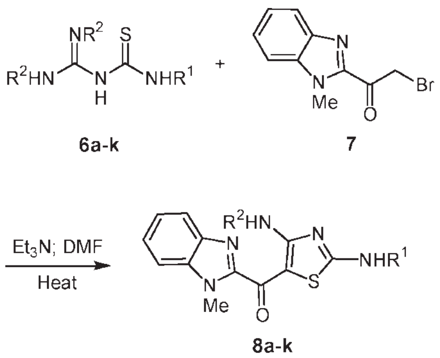
EXPERIMENTAL

Melting points are uncorrected and were determined by open capillary method using an immersion bath of silicon oil. TLC was performed using silica gel-G (E. Merck, India) coated on glass plates. The spots were visualized in iodine vapor or under UV light. The spectra were recorded on: JEOL

Scheme 1



Scheme 2



Physical data of [2,4-bis(arylamino)thiazol-5-yl](1-methyl-*1H*-benzoimidazol-2-yl)methanones (**8a-k**)

	R^1	R^2	Yield % [a]	Yield % [b]
8a	phenyl	phenyl	97	65
8b	4-chlorophenyl	4-chlorophenyl	95	63
8c	4-methylphenyl	4-methylphenyl	96	65
8d	4-chlorophenyl	phenyl	93	63
8e	4-methylphenyl	phenyl	98	65
8f	4-ethoxyphenyl	phenyl	96	61
8g	phenyl	4-chlorophenyl	95	59
8h	4-methoxyphenyl	4-chlorophenyl	97	57
8i	4-methylphenyl	4-chlorophenyl	96	60
8j	4-ethoxyphenyl	4-chlorophenyl	97	58
8k	phenyl	4-methylphenyl	92	62

[a] Crude product [b] Recrystallised product

DRX 300 or DPX 300 NMR spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}CNMR spectra), JEOL SX 102/DA-6000 mass spectrometer (using Argon/Xenon, 6 KV, 10 mA as the FAB gas, and *m*-nitrobenzyl alcohol as the matrix) for FAB mass spectra and Nicolet 400D FTIR spectrometer. All new compounds gave satisfactory C, H, and N analysis (CDRI, Lucknow).

General procedure for the synthesis of [2,4-bis(arylamino)thiazol-5-yl](1-methyl-1*H*-benzoimidazol-2-yl)methanones (8a–k). A solution of 2-(2-bromoacetyl)-1-methyl-1*H*-benzimidazole (**7**) (0.254 g, 1 mmol) which was prepared from 2-(1-hydroxyethyl)-1*H*-benzimidazole [15,16], in DMF (2 mL) was added to a solution of 1-aryl-3-(*N*,*N*'-diarylamidino)thiourea (1 mmol) (**6a–k**) [5] in DMF (2 mL). Triethylamine (0.15 mL, 1 mmol) was added under stirring and the mixture was heated at 80–85°C for 5 min. It was then cooled and poured into ice-cold water with constant stirring. The yellow precipitate thus obtained was filtered, washed with water, and dried. The crude product was purified by crystallization.

[2,4-Bis(phenylamino)thiazol-5-oyl](1-methyl-1H-benzoimidazol-2-yl)methanone (8a). Starting from 1-(*N*,*N*'-diphenylamidino)-3-phenylthiourea (**6a**), 2-(2-bromoacetyl)-1-methyl-1*H*-benzimidazole (**7**), and following the general procedure above, **8a** was obtained as a deep orange solid. It was crystallized from ethanol-water (3:1), m.p. 180–181°C; IR (KBr) ν: 3387, 3267, 3200, 3117, 3050, 2928, 2861, 1607, 1573, 1517, 1483, 1445, 1350, 1217, 950, 900, 733, 690 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 4.22(s, 3H, *N*—CH_3), 7.06–7.18(m, 2H, 2ArH), 7.25–7.46(m, 6H, H-5, H-6, 4ArH), 7.64–7.78(m, 6H, H-4, H-7, 4ArH), 11.19(s, 1H, NH), 11.85(s, 1H, NH); ^{13}CNMR (75 MHz, DMSO-d_6): δ 32.4, 96.4, 111.2, 119.4, 120.0, 120.2, 123.2, 123.4, 124.0, 124.6, 129.2, 129.3, 136.8, 139.1, 139.3, 140.8, 147.2, 162.7, 171.7, 171.8; FABMS: *m*/*z* 426 (MH$^+$), 425 (M$^+$). *Anal.* Calcd for $C_{24}H_{19}N_5OS$: C, 67.74; H, 4.50; N, 16.46%. Found: C, 67.61; H, 4.58; 16.61%.

[2,4-Bis(4-chlorophenylamino)thiazol-5-oyl](1-methyl-1H-benzoimidazol-2-yl)methanone (8b). The reaction of 1-(*N*,*N*'-di(4-chlorophenyl)amidino)-3-(4-chlorophenyl)thiourea (**6b**) with **7** afforded **8b** as a deep orange solid. It was crystallized from ethanol-water (3:1), m.p. 238–239°C; IR (KBr) ν: 3449, 3238, 3189, 3111, 3032, 2933, 2867, 1627, 1576, 1493, 1455, 1411, 1356, 1210, 1093, 1023, 960, 822, 740, 674 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 4.20(s, 3H, *N*—CH_3), 7.27–7.53(m, 6H, H-5, H-6, 4ArH), 7.60–7.78(m, 6H, H-4, H-7, 4ArH), 11.26(s, 1H, NH), 11.79(s, 1H, NH); FABMS: *m*/*z* 494 (MH$^+$), 493 (M$^+$). *Anal.* Calcd for $C_{24}H_{17}Cl_2N_5OS$: C, 58.30; H, 3.47; N, 14.17%. Found: C, 58.53; H, 3.58; N, 14.02%.

[2,4-Bis(4-methylphenylamino)thiazol-5-oyl](1-methyl-1H-benzoimidazol-2-yl)methanone (8c). 1-(*N*,*N*'-di(4-methylphenyl)amidino)-3-(4-methylphenyl)thiourea (**6c**) and **7** on reaction as above gave **8c** a as a deep orange solid. It was crystallized from ethanol-water (3:1), m.p. 208–209°C; IR (KBr) ν: 3312, 3200, 3117, 3050, 2928, 2850, 1607, 1597, 1550, 1519, 1450, 1350, 1216, 1167, 1117, 1017, 879, 825, 733, 683 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 2.29(s, 6H, 2CH_3), 4.23(s, 3H, *N*—CH_3), 7.16–7.26(m, 4H, 4ArH), 7.28–7.43(m, 2H, H-5, H-6), 7.54(d, J = 8.1 Hz, 2H, 2ArH), 7.63(d, J = 8.4 Hz, 2H, 2ArH), 7.69(d, J = 8.1 Hz, 1H, H-7), 7.74(d, J = 7.8 Hz, 1H, H-4), 11.08(s, 1H, NH), 11.87(s, 1H, NH); ^{13}CNMR (75 MHz, DMSO-d_6): δ 20.86, 20.94, 32.27, 95.46, 97.76, 102.35, 110.09, 120.78, 120.92, 121.03, 123.00, 124.47, 129.47, 130.14, 133.20, 135.22, 135.62, 136.82, 141.48, 148.38, 163.25, 172.28; FABMS: *m*/*z* 454 (MH$^+$), 453 (M$^+$). *Anal.* Calcd for $C_{26}H_{23}N_5OS$: C, 68.85; H, 5.11; N, 15.44%. Found: C, 68.58; H, 5.01; N, 15.58%.

[2-(4-Chlorophenylamino)-4-phenylaminothiazol-5-oyl](1-methyl-1H-benzoimidazol-2-yl)methanone (8d). Using 1-(*N*,*N*'-diphenylamidino)-3-(4-chlorophenyl)thiourea (**6d**), and **7**, **8d** was obtained as a deep orange solid. It was crystallized from ethanol-water (3:1), m.p. 171–173°C; IR (KBr) ν: 3367, 3282, 3184, 3117, 2929, 2864, 1621, 1582, 1522, 1494, 1456, 1406, 1355, 1222, 1097, 963, 830, 752, 686 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 4.22(s, 3H, *N*—CH_3), 7.11(t, J = 9 Hz, 1H, 1ArH), 7.26–7.51(m, 6H, H-5, H-6, 4ArH), 7.59–7.79(m, 6H, H-4, H-7, 4ArH), 11.27(s, 1H, NH), 11.80(s, 1H, NH). FABMS: *m*/*z* 460 (MH$^+$). *Anal.* Calcd for $C_{24}H_{18}ClN_5OS$: C, 62.67; H, 3.94; N, 15.23%. Found: C, 62.57; H, 3.81; N, 15.48%.

[2-(4-Methylphenylamino)-4-phenylaminothiazol-5-oyl](1-methyl-1H-benzoimidazol-2-yl)methanone (8e). The reaction of 1-(*N*,*N*'-diphenylamidino)-3-(4-methylphenyl)thiourea (**6e**) with **7** afforded **8e** as a deep orange solid. It was crystallized from ethanol-water (3:1), m.p. 161–164°C; IR (KBr) ν: 3384, 3272, 3200, 3117, 3059, 2931, 2850, 1619, 1580, 1506, 1448, 1418, 1357, 1205, 966, 825, 751 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 2.31(s, 3H, CH_3), 4.25(s, 3H, *N*—CH_3), 7.12(t, *J* = 6.9 Hz, 1H, 1ArH), 7.24(d, *J* = 7.8 Hz, 2H, 2ArH), 7.28–7.49(m, 4H, H-5, H-6, 2ArH), 7.56(d, *J* = 7.5 Hz, 2H, 2ArH), 7.64–7.86(m, 4H, H-4, H-7, 2ArH), 11.10(s, 1H, NH), 11.91(s, 1H, NH); FABMS: *m*/*z* 440 (MH^+), 439 (M^+). *Anal.* Calcd for $C_{25}H_{21}N_5OS$: C, 68.31; H, 4.82; N, 15.94%. Found: C, 68.53; H, 4.95; N, 16.07%.

[2-(4-Ethoxyphenylamino)-4-phenylaminothiazol-5-oyl](1-methyl-1H-benzoimidazol-2-yl)methanone (8f). 1-(*N*,*N*'-diphenylamidino)-3-(4-ethoxyphenyl)thiourea (**6f**) was reacted with **7** to obtain **8f** as a deep orange solid, which was crystallized from ethanol-water (3:1), m.p. 121–124°C; IR (KBr) ν: 3301, 3207, 3124, 3097, 2975, 2925, 2841, 1615, 1600, 1578, 1523, 1457, 1424, 1350, 1237, 1176, 1130, 1059, 949, 834, 747, 690 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 1.32(t, *J* = 6 Hz, 3H, CH_3), 4.03(quartet, *J* = 7 Hz, 2H, CH_2), 4.22(s, 3H, *N*—CH_3), 6.99(d, *J* = 8.7 Hz, 2H, 2ArH), 7.10(t, *J* = 7.35 Hz, 1H, 1ArH), 7.28–7.46(m, 4H, H-5, H-6, 2ArH), 7.53(d, *J* = 8.1 Hz, 2H, 2ArH), 7.68(d, *J* = 8.1 Hz, 1H, H-7), 7.74(d, *J* = 7.8 Hz, 3H, H-4, 2ArH), 11.04(s, 1H, NH), 11.92(s, 1H, NH); FABMS: 470 (MH^+), 469 (M^+). *Anal.* Calcd for $C_{26}H_{23}N_5O_2S$: C, 66.50; H, 4.94; N, 14.92%. Found: C, 66.32; H, 4.85, N, 14.81%.

[4-(4-Chlorophenylamino)-2-phenylaminothiazol-5-oyl](1-methyl-1H-benzoimidazol-2-yl)methanone (8g). Upon reaction of 1-(*N*,*N*'-di(4-chlorophenyl)amidino)-3-phenylthiourea (**6g**) with **7**, **8g** was obtained as a deep orange solid, which was crystallized from ethanol-water (3:1), m.p. 193–198°C; IR (KBr) ν: 3448, 3233, 3187, 3117, 3050, 2925, 2850, 1613, 1575, 1550, 1492, 1445, 1367, 1258, 1217, 1100, 1020, 958, 825, 767, 690 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 4.21(s, 3H, *N*—CH_3), 7.15(t, *J* = 7.2 Hz, 1H, 1ArH), 7.29–7.52(m, 6H, H-5, H-6, 4ArH), 7.59–7.80(m, 6H, H-4, H-7, 4ArH), 11.20(s, 1H, NH), 11.83(s, 1H, NH). *Anal.* Calcd for $C_{24}H_{18}ClN_5OS$: C, 62.67; H, 3.94; N, 15.23%. Found: C, 62.81; H, 4.00; N, 15.39.

[4-(4-Chlorophenylamino)-2-(4-methoxyphenylamino)thiazol-5-oyl](1-methyl-1H-benzoimidazol-2-yl)methanone (8h). Starting from 1-(*N*,*N*'-di(4-chlorophenyl)amidino)-3-(4-methoxyphenyl) thiourea (**6h**), and **7**, **8h** was obtained as a deep orange solid, which was crystallized from ethanol-water (3:1), m.p. 136–138°C; IR (KBr) ν: 3461, 3237, 3190, 3116, 3035, 2931, 2854, 1613, 1580, 1491, 1452, 1402, 1351, 1216, 1094, 1020, 965, 830, 749, 604 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 3.77(s, 3H, OCH_3), 4.22(s, 3H, *N*—CH_3), 7.02(d, *J* = 9 Hz, 2H, 2ArH), 7.23–7.57(m, 6H, H-5, H-6, 4ArH), 7.60–7.83(m, 4H, H-4, H-7, 2ArH), 11.07(s, 1H, NH), 11.91(s, 1H, NH). *Anal.* Calcd for $C_{25}H_{20}ClN_5O_2S$: C, 61.28; H, 4.11; N, 14.29%. Found: C, 61.40; H, 4.25; N, 14.45%.

[4-(4-Chlorophenylamino)-2-(4-methylphenylamino)thiazol-5-oyl](1-methyl-1H-benzoimidazol-2-yl)methanone (8i). The reaction of 1-(*N*,*N*'-di(4-chlorophenyl)amidino)-3-(4-methylphenyl)thiourea (**6i**) with **7** afforded **8i** as a deep orange solid which was crystallized from ethanol-water (3:1), m.p. 218–219°C; IR (KBr) ν: 3464, 3247, 3100, 3034, 2917, 2854, 1617, 1571, 1550, 1514, 1445, 1359, 1217, 1097, 958, 826, 752, 673 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 2.32(s, 3H, CH_3), 4.24(s, 3H, *N*—CH_3), 7.14–7.60(m, 8H, H-5, H-6, 6ArH), 7.61–7.88(m, 4H, H-4, H-7, 2ArH), 11.13(s, 1H, NH), 11.88(s, 1H, NH); FABMS: *m*/*z* 474 (MH^+), 473 (M^+). *Anal.* Calcd for $C_{25}H_{20}ClN_5OS$: C, 63.35; H, 4.25; N, 14.78%. Found: C, 63.50; H, 4.35; N, 14.95%.

[4-(4-Chlorophenylamino)-2-(4-ethoxyphenylamino)thiazol-5-oyl](1-methyl-1H-benzoimidazol-2-yl)methanone (8j). Upon reacting with **7**, 1-(*N*,*N*'-di(4-chlorophenyl)amidino)-3-(4-ethoxyphenyl)thiourea (**6j**) afforded **8j** as a deep orange solid, which was crystallized from ethanol-water (3:1), m.p. 172–173°C; IR (KBr) ν: 3440, 3299, 3200, 3080, 2975, 2917, 2867, 1625, 1600, 1560, 1518, 1490, 1438, 1354, 1249, 1217, 1205, 1181, 1093, 1051, 958, 821, 740, 617 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 1.33(t, *J* = 6.45 Hz, 3H, CH_3), 4.02(quartet, *J* = 6.9 Hz, 2H, CH_2), 4.19(s, 3H, *N*—CH_3), 6.98(d, *J* = 8.4 Hz, 2H, 2ArH), 7.21–7.82(m, 10H, H-4, H-5, H-6, H-7, 6ArH), 11.00(s, 1H, NH), 11.91(s, 1H, NH). *Anal.* Calcd for $C_{26}H_{22}ClN_5O_2S$: C, 61.96; H, 4.40; N, 13.90%. Found: C, 62.08; H, 4.51; N, 13.74%.

[4-(4-Methylphenylamino)-2-phenylaminothiazol-5-oyl](1-methyl-1H-benzoimidazol-2-yl)methanone (8k). The compound **8k** was obtained from 1-(*N*,*N*'-di-(4-methylphenyl)amidino)-3-phenylthiourea (**6k**) and **7** as a deep orange solid. It was crystallized from ethanol-water (3:1), m.p. 225–226°C; IR (KBr) ν: 3306, 3051, 2928, 2859, 1607, 1567, 1538, 1499, 1411, 1364, 1337, 1204, 958, 877, 817, 751 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 2.30(s, 3H, CH_3), 4.23(s, 3H, *N*—CH_3), 7.14(t, *J* = 7.35 Hz, 1H, 1ArH), 7.21(d, *J* = 8.4 Hz, 2H, 2ArH), 7.28–7.49(m, 4H, H-5, H-6, 2ArH), 7.58–7.82(m, 6H, H-4, H-7, 4ArH), 11.16(s, 1H, NH), 11.85(s, 1H, NH); FABMS: *m*/*z* 440 (MH^+), 439 (M^+). *Anal.* Calcd for $C_{25}H_{21}N_5OS$: C, 68.31; H, 4.82; N, 15.94%. Found: C, 68.58; H, 4.92; N, 15.75%.

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Synthesis of Halogenoindirubins

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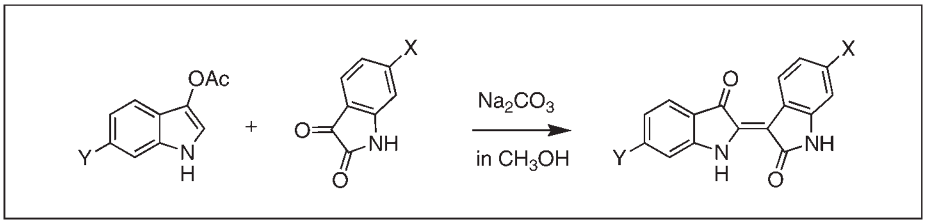

The synthesis of halogenoindirubins was attempted. The reaction of 3-acetoxy-6-bromoindole (**5**) with 6-bromoisation (**10**) in methanol with Na_2CO_3 produced 6-bromo-6′-fluoroindirubin (**11**) in 80% yield. Its structure determination was mainly undertaken using ^1H NMR spectroscopy. A similar reaction gave 6′-bromoindirubin (**12**) and 6-bromoindirubin (**3**) in moderate yields.

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INTRODUCTION

Tyrian purple, royal purple, and ancient purple are all synonyms for a dye of molluscan origin and were used as valuable purple dyes of garments for ancient exalted persons such as princes and nobles in the districts along the Mediterranean [1,2]. The precursors of Tyrian purple are contained in the hypobranchial glands of various species of gastropods from the families Muricidae and Thaidinae, and converted into Tyrian purple by the action of sunlight and purpurase [3,4]. In 1909, Friedländer isolated 1.4 g of the dye from 12,000 specimens of the gastropod *Murex brandaris* and identified it as 6,6′-dibromoindigo (**1**) [5].

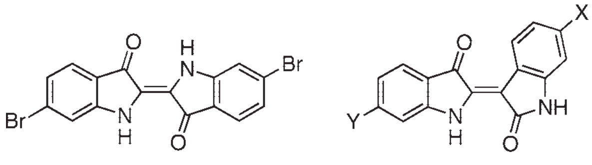
We have already reported that **1** is easily obtained in three steps by the reactions of the commercially available 6-bromoindole [6]. The hypobranchial glands aforementioned contain 6,6′-dibromoindirubin (**2**) and 6-bromo-indiubin (**3**) as minor components [7–10]. Their compounds have become of interest from the standpoint of glycogen synthase kinase (GSK)-3-selective inhibitors [10]. In addition, indirubin (**4**) exhibits strong antitumor [11] and potent aryl hydrocarbon ligand activities [12]. Synthesis of the bromoindirubins has been already reported [13].

The reaction of 3-acetoxy-6-fluoroindole (**5**) with isatin (**6**) produced 6′-fluoroindirubin (**7**). On the basis of this result, we have already revised the synthetic scheme of **2** reported by Cooksey [14]. The revised synthetic scheme is applicable for the syntheses of halogenoindirubins.

The present article describes the syntheses of the halogenoindirubins (Fig. 1).

RESULTS AND DISCUSSION

We have already reported that the 3-acetoxy-halogenoindoles are obtained in two steps by the reactions of the commercially available haloindoles. Iodination of the haloindoles, followed by acetoxylation with silver acetate in acetic acid, afforded 3-acetoxy-6-halogenoindole [15]. The reaction of 3-acetoxy-6-fluoroindole (**5**) with 6-bromoisatin (**10**) was carried out in methanol with Na_2CO_3 at room temperature. The structure of the product (**11**) was based on the ^1H NMR spectral data and MS spectral data. The H-4 signal ($\delta = 8.67$) showed a remarkable downfield shifts relative to the H-4′ signal ($\delta = 7.74$). The absorption of H-4′ is split by H-5′ ($J_{4'\text{-}5'} = 8.5$ Hz) and F-6′ ($J_{4'\text{-F}} = 5.5$ Hz). Unfortunately, the ^{13}C NMR spectra could not be measured, because **11** was

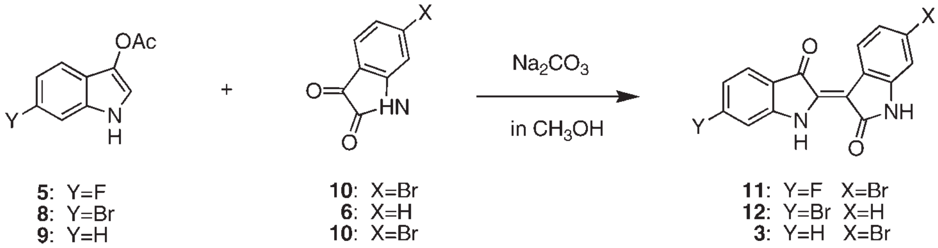


1

2: X=Y=Br
3: X=Br, Y=H
4: X=Y=H

Figure 1. Structures of the indigo and the indirubin families.

Scheme 1. Synthesis of the halogenoindirubins.



only slightly soluble in dimethyl sulfoxide. The mass spectrum of **11** clearly exhibited a molecular ion peak at *m*/*z* 358 (Scheme 1).

The treatment of 3-acetoxy-6-bromoindole (**8**) with **6** gave 6′-bromoindirubin (**12**) in 81% yield. On the other hand, the reaction of 3-acetoxyindole (**9**) [16] with 6-bromoisatin (**10**) afforded 6-bromoindirubin (**3**) in 85% yield.

The ^{1}H NMR spectra of **12** and **3** are shown in Figures 2 and 3 for direct comparison. In general, the signal of the ortho positional proton of Br is observed more downfield than that of the benzene ring proton. The H-5′ (δ = 7.15) and H-7′ (δ = 7.66) signals of **12** showed a downfield shift relative to those of H-5′ (δ = 7.03) and H-7′ (δ = 7.42) of **3**. Similarly, the H-5 (δ = 7.21) and H-7 (δ = 7.04) signals of **3** appeared as a downfield shift compared to those of H-5 (δ = 7.00) and H-7 (δ = 6.89) of **12**.

EXPERIMENTAL

The ^{1}H NMR and ^{13}C NMR spectra were obtained using a JEOL JNM-A500 (500 MHz) spectrometer in dimethyl sulfoxide-d$_6$ at room temperature. The chemical shifts are given in ppm relative to tetramethylsilane as the internal reference standard. The EI mass spectra were performed using a JEOL JMS-SX 102A mass spectrometer. The infrared spectra were recorded using a Shimadzu IR 470 spectrometer in potassium bromide pellets. The melting points were obtained using a Yanaco MS-S3 micro melting point apparatus (hot-plate type). For the preparative column chromatography, Wakogel C-200 silica gel was used. Indole, 6-fluoroindole, 6-bromoisatin, and isatin were purchased from Tokyo Kasei Kogyo (Tokyo, Japan).

General procedure for the synthesis of halogenoindirubins. The reaction of 3-acetoxy-6-fluoroindole (**5**) with 6-bromoisatin (**10**) is described as a typical example. A solution of **5** (65 mg, 0.339 mmol) and **10** (77 mg, 0.339 mmol) in methanol (15 mL) was stirred under a nitrogen atmosphere at room temperature for 10 min. To the mixture was added

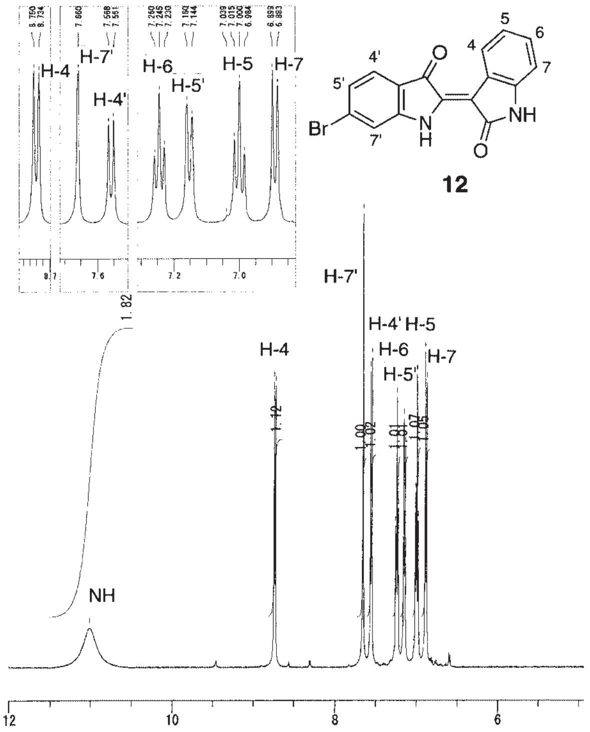


Figure 2. The spectrum of 6′-bromoindirubin (**12**).

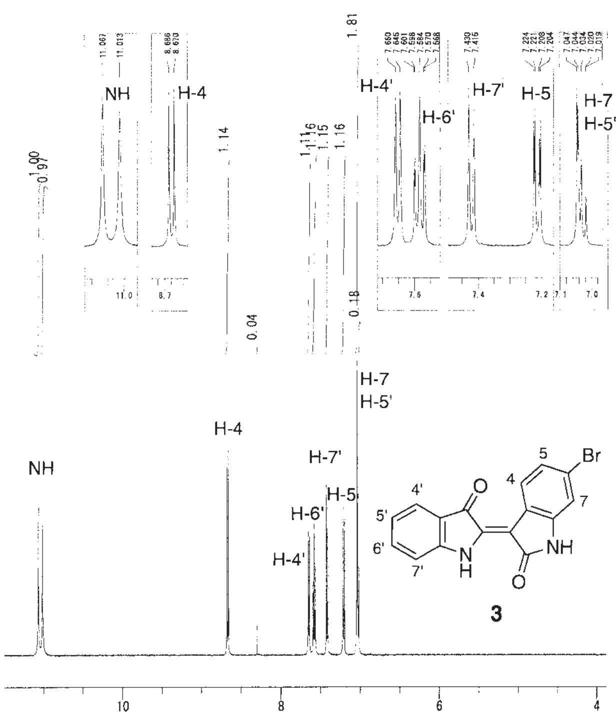


Figure 3. The spectrum of 6-bromoindirubin (**3**).

anhydrous sodium carbonate (86 mg, 0.814 mmol). After the mixture was stirred for 3 h, water was added. The resulting precipitate was collected by filtration, washed with water and aqueous methanol (1:1). The crude product (106 mg) was recrystallized from ethyl acetate to give 6-bromo-6′-fluoroindirubin (**11**) (97 mg, 80% yield) as a red–purple powder, mp $>$ 300°C; ir (potassium bromide): 3300 (NH), 3175 (NH), 1668 (C=O), 1625 (C=O), 1605, 1591, 1451, 1289, 1208, 1129, 1009, 968 cm^{-1}; ^1H NMR (dimethyl sulfoxid-d_6): δ = 6.86 (1H, m, H-5′), 7.11 (1H, d, $J_{7\text{-}5}$ = 2.3 Hz, H-7), 7.20 (1H, dd, $J_{7'\text{-}F}$ = 10, $J_{7'\text{-}5'}$ = 2.5 Hz, H-7′), 7.23 (1H, dd, $J_{5\text{-}4}$ = 8.5, $J_{5\text{-}7}$ = 2.3 Hz, H-5), 7.74 (1H, dd, $J_{4'\text{-}5'}$ = 8.5, $J_{4'\text{-}F}$ = 5.5 Hz, H-4′), 8.67 (1H, d, $J_{4\text{-}5}$ = 8.5 Hz, H-4), 11.05 (1H, s, NH), 11.14 (1H, s, NH); ms (EI): *m*/*z* (relative intensity) 360 (M+2, 99%), 358 (M^+, 100), 332 (21), 330 (21), 223 (62); HRMS(EI) calcd for $C_{16}H_8O_2N_2BrF$, M^+ 357.9753, found 357.9755.

6′-Bromoindirubin (12). This compound was obtained as a brown powder (ethyl acetate), mp $>$ 300°C; ir (potassium bromide): 3330 (NH), 3180 (NH), 1673 (C=O), 1666 (C=O), 1618, 1585, 1444, 1282, 1212, 1008 cm^{-1}; ^1H NMR (dimethyl sulfoxid-d_6): δ = 6.89 (1H, d, $J_{7\text{-}6}$ = 8.0 Hz, H-7), 7.00 (1H, t, J = 7.5 Hz, H-5), 7.15 (1H, d, $J_{5'\text{-}4'}$ = 8.0 Hz, H-5′), 7.25 (1H, t, J = 7.5 Hz, H-6), 7.56 (1H, d, $J_{4'\text{-}5'}$ = 8.5 Hz, H-4′), 7.66 (1H, s, H-7′), 8.74 (1H, d, $J_{4\text{-}5}$ = 8.0 Hz, H-4), 11.01 (2H, broad, NH); ^{13}C NMR (dimethyl sulfoxide-d_6): δ = 108.13, 110.20, 116.51, 118.54, 121.58, 121.87, 124.61, 125.24, 126.33, 130.25, 131.32, 138.40, 141.46, 153.47, 171.18 (C=O), 187.88 (C=O); MS (EI) *m*/*z* (relative intensity) 342 (M+2, 98%), 340 (M^+, 100), 314 (21), 312 (22), 233 (40), 205 (77), 103 (22); HRMS (EI) calcd for $C_{16}H_9O_2N_2Br$, M^+ 339.9848, found 339.9830.

6-Bromoindirubin (3). This compound was obtained as a brown powder (ethyl acetate), mp $>$ 300°C; ir (potassium bromide): 3310 (NH), 3190 (NH), 1664 (C=O), 1605, 1475, 1302, 1209, 1006 cm^{-1}; ^1H NMR (dimethyl sulfoxid-d_6): δ = 7.03 (1H, m, H-5′), 7.04 (1H, d, $J_{7\text{-}5}$ = 1.5 Hz, H-7), 7.21 (1H, dd, $J_{5\text{-}4}$ = 9.0, $J_{5\text{-}7}$ = 1.5 Hz, H-5), 7.42 (1H, d, $J_{7'\text{-}6'}$ = 7.5 Hz, H-7′), 7.58 (1H, m, H-6′), 7.65 (1H, d, $J_{4'\text{-}5'}$ = 7.5 Hz, H-4′), 8.68 (1H, d, $J_{4\text{-}5}$ = 8.0 Hz, H-4), 11.01 (1H, s, NH), 11.07 (1H, s, NH); ^{13}C NMR (dimethyl sulfoxide-d_6): δ = 105.17, 112.23, 113.56, 118.98, 120.70, 121.33, 121.52, 123.81, 124.42, 125.93, 137.21, 138.83, 142.10, 152.48, 170.69 (C=O), 188.71 (C=O); MS (EI) *m*/*z* (relative intensity), 342 (M+2, 100%), 340 (M^+, 100), 314 (24), 312 (24), 233 (27), 205 (59); HRMS (EI) calcd for $C_{16}H_9O_2N_2Br$, M^+ 339.9848, found 339.9832.

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An Efficient One-Pot Synthesis of Naphthoxazinones by a Three-Component Coupling of Naphthol, Aldehydes, and Urea Catalyzed by Zinc Triflate

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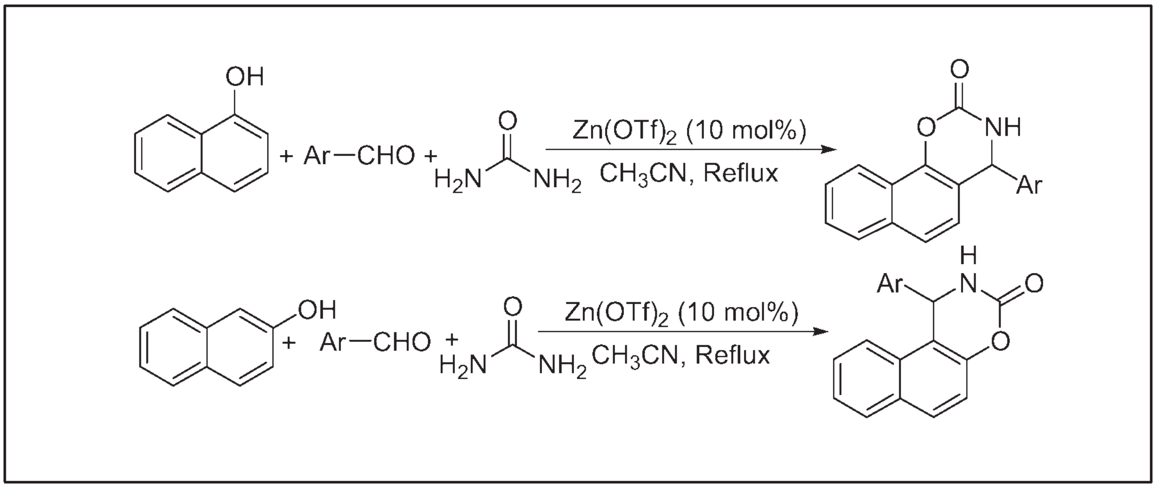

A simple and efficient method has been developed for the synthesis of 4-aryl-3,4-dihydronaphtho[2,1-*e*][1,3]oxazin-2-one and 1-aryl-1,2-dihydronaphtho[1,2-*e*][1,3]oxazin-3-one derivatives through a one-pot three-component coupling of α or β-naphthol, aromatic aldehydes and urea using a catalytic amount of zinc triflate in refluxing acetonitrile.

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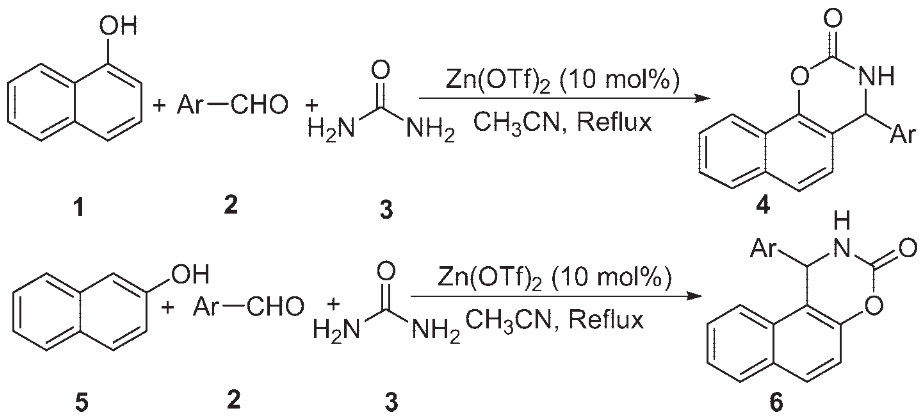
INTRODUCTION

Aromatic-condensed oxazinone derivatives are of significant importance because of their promising biological activities [1]. In addition, these heterocyclic compounds represent an important class of functionalized building blocks. For example, they have been used as valuable precursors in the preparation of phosphinic ligands for asymmetric catalysis and in the synthesis of biologically active heterocyclic derivatives [2]. The general method for the preparation of 2-aminomethyl phenol derivatives is *via* the Mannich-type reaction [3]. To the best of our knowledge, there is only one report for the synthesis of 4-aryl-3,4-dihydronaphtho[2,1-*e*][1,3]oxazin-2-one derivatives in the literature [4]. However, only few methods are available for the preparation of 1-aryl-1,2-dihydronaphtho[1,2-*e*][1,3]oxazin-3-one derivatives [1,4,5]. All of these methods suffer from the same drawbacks, specially in the use of toxic solvents (benzene) or expensive and hazardous reagents (carbamyl chlorides, isocyanates, and phosgene). In addition, they involve multistep synthetic operations which lower the overall yields. Recently, Bazgir *et al.* reported a one-pot synthesis of 1-aryl-1,2-dihydronaphtho[1,2-*e*][1,3]oxaxine-3-one derivatives by three component coupling of β-naphthol, aromatic aldehydes, and urea in moderate to high yields [6]. However, this approach is satisfactory for the condensation with β-naphthol, but α-naphthol produced no product under the reaction conditions. Therefore, it is desirable to develop a more efficient and general method for the synthesis of naphthoxazinone derivatives from both naphthol isomers.

Multicomponent reactions are finding increasing interest in the synthesis of biologically important compounds, as they possess one of the aforementioned qualities namely the possibility of building up complex molecules with simplicity and brevity. The modern synthesis is the one in which the target components are produced in one step, in quantitative yield from readily available and inexpensive starting materials in a resource-effective and environmentally benign process [7]. As a part of our program to synthesize biologically active heterocyclic derivatives using multicomponent coupling reactions [8,9], we wish to report here an efficient zinc triflate catalyzed one-pot synthesis of

Scheme 1



naphthoxazinone derivatives by coupling of α or β-naphthol, an aromatic aldehyde, and urea (Scheme 1).

RESULTS AND DISCUSSION

In our initial investigation, the coupling reaction of β-naphthol (1 mmol), benzaldehyde (1 mmol), and urea (1.5 mmol) was carried out in different solvents in the presence of $Zn(OTf)_2$ (10 mol%) under reflux. Comparing with other organic solvents, CH_3CN was the most effective reaction media (Table 1, entry 1). The coupling reaction was also performed in the presence of different catalysts (10 mol%), such as $La(OTf)_3$, $In(OTf)_3$, $ZnCl_2$, and $Zn(ClO_4)_2$. But, we observed $Zn(OTf)_2$ was the most effective catalyst in the terms of yields (82%).

On the basis of the earlier results, this process was then extended to other aromatic aldehydes to investigate its scope and generality. The results are summarized in Table 2. Aromatic aldehydes with both activating and weekly deactivating groups, such as F, Br, Cl, Me, OMe, and OH, reacted to afford the corresponding products in high yields. Piperonal also afforded high yields without any difficulty.

Table 1

Reaction of β-Naphthol with benzaldehyde and urea under reflux in different reaction conditions.

Entry	Catalyst (10 mol %)	Solvent	Time (h)	Yield (%)[a]
1	$Zn(OTf)_2$	CH_3CN	5	82
2	$Zn(OTf)_2$	$ClCH_2CH_2Cl$	5	70
3	$Zn(OTf)_2$	$HOCH_2CH_2OMe$	5	65
4	$ZnCl_2$	CH_3CN	5	36
5	$Zn(ClO_4)_2$	CH_3CN	5	68
6	$In(OTf)_3$	CH_3CN	5	60
7	$La(OTf)_3$	CH_3CN	5	55

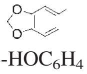
[a] Isolated yields.

Our attention was then turned to the possibility of reaction with α-naphthol. It was found that the replacement of β-naphthol with α-naphthol produced the naphthoxazine-2-one derivatives in good yields under the similar conditions. On the basis of the earlier results, this process was then extended to other substituted aromatic aldehydes. The results are listed in Table 3. It is cleared that under these similar conditions, benzaldehydes containing methyl or methoxy groups easily undergo condensation with α-naphthol and urea to produce 4-aryl-3,4-dihydronaphtho[2,1-*e*][1,3]oxazin-2-ones in good yields. However, under the present reaction conditions aliphatic aldehydes and thiourea did not afford the corresponding naphthoxazinone derivatives, instead leaded to multiple products whose identities are yet to be established.

Based on the experimental results, a plausible mechanism was proposed in Scheme 2. In this hypothesis, $Zn(OTf)_2$ serves as the Lewis-acid catalyst for several stages. The intermediates **7** were isolated in a couple of reactions and properly characterized. These intermediates were subsequently cyclized to naphthoxazinone

Table 2

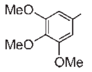
$Zn(OTf)_2$-catalyzed reaction of β-naphthol with aromatic aldehydes and urea.

Product **4**	Ar	Time (h)	Yield (%)[a]	Ref.
a	Ph	5	82	6a
b	$4\text{-}MeC_6H_4$	6	77	6a
c	$4\text{-}MeOC_6H_4$	6	72	6a
d		7	74	
e	$4\text{-}HOC_6H_4$	6	70	6a
f	$4\text{-}FC_6H_4$	7	80	6a
g	$2\text{-}ClC_6H_4$	7	78	6b
h	$4\text{-}ClC_6H_4$	6	84	6a
i	$4\text{-}BrC_6H_4$	6	80	6a

[a] Yields refer to isolated pure product.

Table 3

$Zn(OTf)_2$-catalyzed reaction of α-naphthol with aromatic aldehydes and urea.

Product 6	Ar	Time (h)	Yield (%)[a]	Ref.
a	Ph	5	64	4
b	4-MeC_6H_4	6	67	
c		7	69	

[a] Yields refer to isolated pure product.

derivatives by further heating. It should be pointed out that 4-nitrobenzaldehyde and 3-nitrobenzaldehyde reacted with urea and β-naphthol but the reaction stopped at intermediate stage **7** [10]. The reaction did not proceed further on long time heating.

CONCLUSIONS

In conclusion, the work presented here demonstrates a straightforward and general procedure for the efficient one-pot synthesis of naphthoxazinones by a three-component coupling of naphthols, aromatic aldehydes, and urea. The reaction possesses the following synthetic features: (a) mild conditions, (b) simple operation, (c) good yields, (d) nontoxic and cheap metal catalyst, (e) the compatibility with various functional groups, and (f) applicability for an easy synthesis of 1-aryl-1,2-dihydronaphtho[1,2-*e*][1,3]oxazin-3-ones and 4-aryl-3,4-dihydronaphtho[2,1-*e*][1,3]oxazin-2-ones.We believe that this procedure will provide a better and more practical alternative to the existing methodologies for the synthesis of naphthoxazinone derivatives. Further investigations to broaden the scope of this methodology toward pharmaceuticals and chiral products are in progress.

EXPERIMENTAL

Melting points were determined on a glass disk with an electrical bath and are uncorrected. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were run in DMSO-d_6 solutions. IR spectra were taken as KBr plates. Elemental analyses were done by Perkin-Elmer autoanalyzer. $Zn(OTf)_2$ was purchased from Aldrich. All liquid reagents were distilled before use.

Typical procedure for the synthesis of 1-phenyl-1,2-dihydronaphtho[1,2-*e*][1,3]oxazin-3 one (Table 2, 4a). A solution of benzaldehyde (212 mg, 2 mmol, 203 μL), β-naphthol (288 mg, 2 mmol), and urea (180 mg, 3 mmol) in CH_3CN (4 mL) was heated under reflux (90–95°C) in the presence of zinc triflate (73 mg, 10 mol%) for 5 h (TLC). At completion, the reaction mixture was distilled under vacuum to remove the solvent and then diluted with cold water (10 mL). After extraction with ethyl acetate (20 mL × 3), the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The residue was concentrated and recrystallized from EtOAc-hexane to afford the pure product as a white powder (451 mg, 82%), mp 216–218°C (reported 218–220°C) [6a].

Typical procedure for the synthesis of 4-phenyl-3,4-dihydronaphtho[1,2-*e*][1,3]oxazin-2-one (Table 3, 6a). The procedure reported in the previous experiment was followed using α-naphthol in place of β-naphthol. The corresponding pure product was obtained as a white powder (352 mg, 64%), mp 195–197°C (reported 196–198°C) [4].

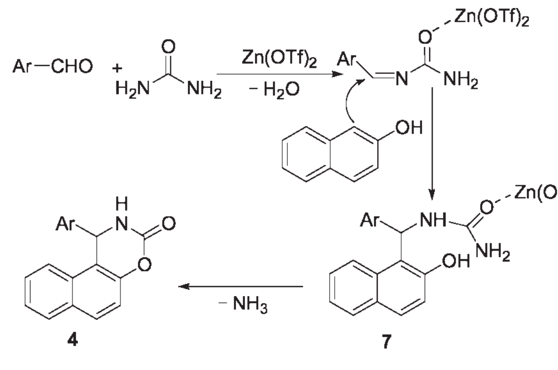
The spectral (IR, ^1H, and ^{13}C NMR) data and elemental analyses of the compounds which are not readily found are provided later.

1-Benzo[1,3]dioxol-5-yl-1,2-dihydronaphtho[1,2-e][1,3]oxazin-3-one (Table 2, 4d). This compound was obtained according to the above procedure as white powder, mp 164–166°C; IR (KBr): 3321, 1701, 1447 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 8.42 (br s, 1H), 7.89–7.84 (m, 2H), 7.64–7.60 (m, 2H), 7.46–7.41 (m, 2H), 7.32–7.27 (m, 1H), 6.83–6.71 (m, 3H), 6.01 (d, J = 4.0 Hz, 1H), 5.91 (d, J = 4.0 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ = 149.5, 147.8, 147.6, 147.1, 137.0, 130.6, 130.4, 129.1, 128.8, 127.6, 125.3, 123.4, 120.6, 117.1, 114.2, 108.6, 107.5, 101.4, 53.6; *Anal.* Calcd for $C_{19}H_{13}NO_4$: C 71.47, H 4.10, N 4.39. Found: C 71.31, H 3.98, N 4.21.

4-p-Tolyl-3,4-dihydronaphtho[2,1-e][1,3]oxazin-2-one (Table 3, 6b). This compound was obtained according to the above procedure as white powder, mp 214–216°C; IR (KBr): 3244, 1723, 1371 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 8.71 (s, 1H), 8.15 (d, J = 7.9 Hz, 1H), 7.90 (d, J = 7.9 Hz, 1H), 7.65–7.55 (m, 3H), 7.16–7.23 (m, 2H), 7.18–7.13 (m, 3H), 5.78 (s, 1H), 2.25 (s, 3H); ^{13}C NMR (DMSO-d_6): δ = 149.2, 143.3, 140.3, 137.3, 133.0, 129.4 (2C), 127.8, 127.0, 126.9, 126.8 (2C), 124.0, 123.7, 122.5, 120.5, 116.3, 56.0, 20.6; *Anal.* Calcd for $C_{19}H_{15}NO_2$: C 78.87, H 5.23, N 4.84. Found: C 78.53, H 5.02, N 4.65.

4-(3,4,5-Trimethoxyphenyl)-3,4-dihydronaphtho[2,1-e][1,3]oxazin-2-one (Table 3, 6c). This compound was obtained according to the above procedure as white powder, mp 228–230°C ; IR (KBr): 2926, 1754, 1592, 1376 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 8.68 (s, 1H), 8.14 (d, J = 7.9 Hz, 1H), 7.93 (d, J = 7.9 Hz, 1H), 7.67–7.57 (m, 3H), 7.23 (d, J = 8.5 Hz, 1H), 6.70 (s, 2H), 5.79 (s, 1H), 3.73 (s, 6H), 3.63 (s, 3H); ^{13}C NMR (DMSO-d_6): δ = 153.1 (2C), 149.1, 143.2, 138.7, 137.1, 133.1, 127.8, 127.0, 126.9, 124.0, 123.6, 122.4, 120.5, 115.8, 104.2 (2C), 60.0, 56.4, 55.9 (2C); *Anal.* Calcd for $C_{21}H_{19}NO_5$: C 69.03, H 5.24, N 3.83. Found: C 68.89, H 5.06, N 3.67.

Scheme 2



[(2-Hydroxynaphthalen-1-yl)-(4-nitrophenyl)-methyl]urea (intermediate 7 from 4-nitrobenzaldehyde). This compound was obtained according as white powder, mp >250°C; IR (KBr): 3480, 3164, 2923, 1714, 1654, 1596, 1347 cm^{-1}; ^{1}H NMR (DMSO-d$_6$): δ = 10.08 (s, 1H), 8.14 (d, J = 8.8 Hz, 2H), 7.84 – 7.77 (m, 3H), 7.39 (d, J = 8.8 Hz, 2H), 7.37 – 7.18 (m, 3H), 6.98 (s, 2H), 5.91 (s, 2H); ^{13}C NMR (DMSO-d$_6$): δ = 158.9, 153.4, 153.3, 146.2, 132.5, 130.0, 129.1, 128.8 (2C), 127.3 (2C), 123.6 (2C), 123.0 (2C), 119.6, 118.8, 48.6; *Anal*. Calcd for $C_{18}H_{15}N_3O_4$: C 64.09, H 4.48, N 12.46. Found: 63.86, H 4.21, N 12.26.

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One-Pot Synthesis of 2*H*-Thiochromenes *via* $TiCl_4$-Promoted Reaction of 2-*tert*-Butylthiobenzaldehydes with Activated Alkenes

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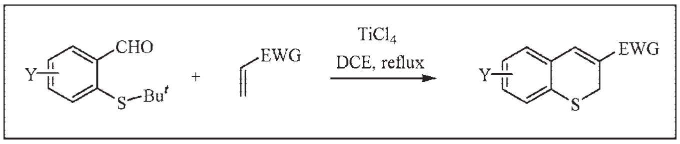

A facile synthesis of 2*H*-thiochromenes through $TiCl_4$-promoted reaction of 2-*tert*-butylthiobenzaldehydes with activated alkenes is described.

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INTRODUCTION

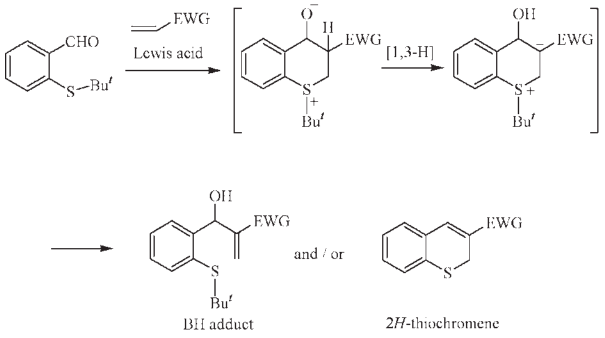
Thiochromenes are of considerable pharmacological and material interest because they display a wide range of biological activities [1] and are occasionally used as scaffolds [2] or synthetic intermediates of functional dyes [3]. In recognition of their importance, several efforts have been made to synthesize this class of molecules so far, but the development of more efficient and general method still remains a continuing challenge. The main synthetic routes involve an initial condensation of thiophenols with acrylic acid derivatives, followed by reduction and dehydration [4], and a magnesium amide-induced sequential conjugate addition-aldol type condensation reaction between 2-mercaptoacetophenone and α,β-unsaturated carboxylic acid derivatives and subsequent dehydration [5]. A similar method to produce chiral 2*H*-thiochromenes through tandem Michael-aldol reactions between 2-mercaptobenzaldehyde and α,β-unsaturated aldehydes has been reported [6]. In addition, several other synthetic methods are available such as the cyclization of 3-(2-*tert*-butylthiophenyl)-prop-2-en-1-ols [7] and the Baylis-Hillman (BH) reaction of 2,2′-dithiodibenzaldehyde with activated alkenes [8]. However, most of these routes suffer from main drawbacks such as multistep processes, the poor availability of starting material, and the limited scope of substrates. Recently, we also reported a tandem S_N2' and S_NAr reaction of BH acetates having an *ortho*-leaving group with sodium sulfide, leading to the formation of 2*H*-thiochromenes, which gave unsatisfactory product yields [9]. In continuation of our ongoing studies on the synthesis of heterocycles, including thiochromenes, using BH methodology [10], we herein describe $TiCl_4$-promoted reaction of 2-*tert*-butylthiobenzaldehydes with activated alkenes, which serves as a facile method for the synthesis of 2*H*-thiochromenes.

RESULTS AND DISCUSSION

The chalcogeno-Baylis-Hillman reaction [11] is well known as a coupling reaction of activated alkenes with electrophiles such as aldehydes [12], activated ketones [13], and acetals [14] catalyzed by a mixture of Lewis acid and base, typically using titanium (IV) chloride ($TiCl_4$)/methyl sulfide [12,13] to give highly functionalized olefins. We envisioned that the reactions of 2-*tert*-butylthiobenzaldehydes with activated alkenes in the presence of $TiCl_4$ could produce the thiochromenes alone or together with the BH adducts, after loss of the *tert*-butyl group under acidic conditions without addition of extra Lewis base such as sulfide, because aldehydes have a chalcogenyl group which might serve as a Lewis base (Scheme 1).

Accordingly, we first synthesized 2-*tert*-butylthiobenzaldehydes **2a–e** as starting materials, following a slightly modified literature procedure [15,16]. The reaction of benzaldehydes **1a–e** with 1.2 equiv of *tert*-butylthiol in the presence of 1 equiv of potassium carbonate in *N*,*N*-dimethylformamide at reflux temperature gave 2-*tert*-butylthiobenzaldehydes **2a–e** in 64–97% yields. Treatment of **2a–e** with 2 equiv of methyl vinyl ketone (MVK) in the presence of 1 equiv of $TiCl_4$ in 1,2-dichloroethane at reflux temperature gave the expected 3-acetyl-2*H*-thiochromenes **4a–e** in low to acceptable yields (8–51%) without the production of BH adducts. The spectral data of **4a** were identical to the reported infrared, ^1H, ^{13}C NMR spectral values [8]. As

Scheme 1



shown in Table 1, the presence of electron-withdrawing chloro- or nitro-substituents in benzene ring of aldehyde **2** demanded a prolonged reaction time to afford the corresponding thiochromenes. For instance, the synthesis of **4b** and **4c** (Entries 7 and 8) having chloro-substituent required longer reaction time than that of **4a** (Entry 6) (2–4 h *vs.* 0.5 h). Nitro-substituted aldehyde **2d** with MVK also gave desired thiochromene **4d** in low yield (8%) after relatively long reaction time (4 h). We consider that the reduced nucleophilicity of the sulfur atom in aldehyde **2** by electron-withdrawing chloro- or nitro-substituent decelerated the reaction. Next, we examined the reaction of **2a–e** with methyl acrylate or acrylonitrile. Using 2 equiv of methyl acrylate, the corresponding thiochromenes **4f–h** and **4j** were produced in 35–70% yields. However, the reaction of **2d** having nitro-substituent with methyl acrylate was unsuccessful, and very complex mixture of unidentified products was observed by thin layer chromatography. The spectral data of **4f–h** and **4j** were identical to the reported infrared, ^{1}H, ^{13}C NMR spectral values [9]. In the cases of acrylonitrile, thiochromenes **4k** and **4l** were produced in relatively low yields (25 and 18%, respectively) and were taken long reaction times (Entries 16 and 17). Because of low yields, additional reactions of **2c–e** with acrylonitrile were not undertaken. A plausible mechanism based on Kataoka's work [12] is shown in Scheme 2. A β-sulfonium-$TiCl_4$-stabilized enolate **3a** is produced by conjugate addition of sulfur atom in aldehyde **2** to $TiCl_4$-activated Michael acceptor, followed by carbon–carbon bond formation through transition state **3b** to give the $TiCl_4$-stabilized alkoxide **3c** and subsequent proton migration to afford **3d**, which gives *2H*-thiochromene **4** by dehydration and loss of the *tert*-butyl group. A similar Michael-aldol process catalyzed by Lewis acid/chalcogenide [11(b)], amine [17], and bifunctional thiourea [18] is well known. It is also known that the *tert*-butyl thioethers are easily cleaved under Lewis [19] or Brønsted [20] acidic conditions.

CONCLUSIONS

In conclusion, a new method for the synthesis of 2*H*-thiochromenes has been developed through $TiCl_4$-promoted reaction of 2-*tert*-butylthiobenzaldehyde derivatives with activated alkenes. Although some products were obtained in low yields, compared with other routes, this synthetic method apparently allows a facile approach to 2*H*-thiochromenes.

EXPERIMENTAL

Silica gel 60 (70–230 mesh ASTM) used for column chromatography was supplied by E. Merck. Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} TLC plates. Melting points were measured by an electrothermal melting point apparatus and were uncorrected. Microanalyses were obtained using a Thermo Electron Corporation Flash EA 1112 element analyzer. Mass spectra were obtained using a ThermoQuest Polaris Q mass spectrometer operating at 70 eV. Infrared spectra were recorded on a Nicolet Magna 550 FTIR spectrometer. The ^{1}H and ^{13}C NMR spectra were measured on a Gemini 300 spectrometer using deuteriochloroform. All chemical shifts are reported in parts per million relative to tetramethylsilane. The coupling constants (*J*) are expressed in Hertz.

Preparation of 2-*tert*-butylthiobenzaldehyde derivatives 2: General procedure. To a stirred solution of aldehyde **1** (40 mmol) and *tert*-butyl thiol (5.40 mL, 48 mmol) in dimethylformamide (40 mL) was added potassium carbonate (5.53 g, 40 mmol) and the mixture was heated to reflux temperature for 1–7 days. After cooling to room temperature, the reaction mixture was diluted with water (300 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated *in vacuo*. The resulting mixture was

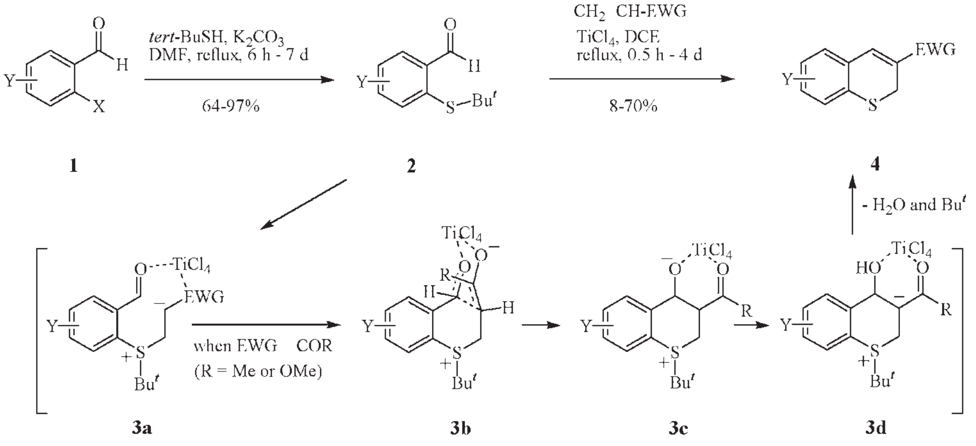
Table 1

Aldehydes **2a–d** and 2*H*-thiochromenes **4a–j.**

Entry	Reactant	Olefin	Reaction time	Product	Yield (%)
1	**1a**	–	1 day	**2a**	84
2	**1b**	–	4 days	**2b**	97
3	**1c**	–	7 days	**2c**	94
4	**1d**	–	6 h	**2d**	64
5	**1e**	–	4 d	**2e**	73
6	**2a**	MVK	0.5 h	**4a**	51
7	**2b**	MVK	2 h	**4b**	22
8	**2c**	MVK	4 h	**4c**	24
9	**2d**	MVK	4 h	**4d**	8
10	**2e**	MVK	0.5 h	**4e**	32
11	**2a**	MA	0.5 h	**4f**	69
12	**2b**	MA	2.5 h	**4g**	70
13	**2c**	MA	4 h	**4h**	42
14	**2d**	MA	3 days	**4i**	–
15	**2e**	MA	1 h	**4j**	35
16	**2a**	AN	4.5 h	**4k**	25
17	**2b**	AN	4 days	**4l**	18

MVK, methyl vinyl ketone; MA, methyl acrylate; AN, acrylonitrile.

Scheme 2



1,2	a	b	c	d	e
X	NO_2	Cl	Cl	Cl	F
Y	H	3-Cl	5-Cl	5-NO_2	5-OMe

4	a	b	c	d	e	f	g	h	i	j	k	l
EWG	COMe	COMe	COMe	COMe	COMe	COOMe	COOMe	COOMe	COOMe	COOMe	CN	CN
Y	H	8-Cl	6-Cl	6-NO_2	6-OMe	H	8-Cl	6-Cl	6-NO_2	6-OMe	H	8-Cl

chromatographed on silica gel eluting with hexane/ethyl acetate (20:1) to produce **2** as an oil or a solid.

The physical and spectral data of **2** prepared by this general method are as follows.

2-tert-Butylthiobenzaldehyde (2a). [15] Yellow oil; yield: 84%; IR (neat): 1692, 1583, 1455, 1363 cm^{-1}; ^1H NMR (deuteriochloroform): δ 1.30 (s, 9H), 7.50–7.65 (m, 3H), 7.98–8.01 (m, 1H), 10.80 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 30.8, 47.5, 128.0, 129.5, 133.5, 136.5, 139.4, 139.9, 193.6; ms: *m/z* (%) 194 (M^+, 100), 138 (14), 137 (6), 109 (12), 104 (8).

2-tert-Butylthio-3-chlorobenzaldehyde (2b). [16] White solid; yield: 97%; mp: 52–54°C; IR (potassium bromide): 1680, 1571, 1458, 1366 cm^{-1}; ^1H NMR (deuteriochloroform): δ 1.32 (s, 9H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.78 (dd, *J* = 7.9 and 1.5 Hz, 1H), 7.91 (dd, *J* = 7.9 and 1.5 Hz, 1H), 10.77 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 31.1, 50.7, 126.7, 130.3, 135.0, 135.5, 142.0, 143.4, 193.5; ms: *m/z* (%) 230 (M^+, 41), 228 (M^+, 100), 173 (5), 172 (7), 171 (6).

2-tert-Butylthio-5-chlorobenzaldehyde (2c). Yellow oil; yield: 94%; IR (neat): 1695, 1570, 1454, 1363 cm^{-1}; ^1H NMR (deuteriochloroform): δ 1.29 (s, 9H), 7.52–7.59 (m, 2H), 7.96 (d, *J* = 2.1 Hz, 1H), 10.71 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 30.8, 47.9, 128.1, 133.5, 134.8, 136.3, 140.4, 141.2, 192.4; ms: *m/z* (%) 230 (M^+, 39), 228 (M^+, 100), 227 (6), 226 (7), 225 (8). Anal. Calcd. for $C_{11}H_{13}ClOS$: C, 57.76; H, 5.73; S, 14.02. Found: C, 57.59; H, 5.55; S, 13.87.

2-tert-Butylthio-5-nitrobenzaldehyde (2d). Yellow oil; yield: 64%; IR (neat): 1696, 1598, 1525, 1458, 1345 cm^{-1}; ^1H NMR (deuteriochloroform): δ 1.38 (s, 9H), 7.85 (d, *J* = 8.5 Hz, 1H), 8.39 (dd, *J* = 8.5 Hz and 2.7 Hz, 1H), 8.78 (d, *J* = 2.7 Hz, 1H), 10.75 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 31.0, 49.5, 123.2, 126.9, 139.9, 140.1, 144.6, 148.2, 191.0; ms: *m/z* (%) 239 (M^+, 8), 210 (9), 183 (100), 182 (14), 136 (43). Anal. Calcd. for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85; S, 13.40. Found: C, 55.32; H, 5.60; N, 5.84; S, 13.26.

2-tert-Butylthio-5-methoxybenzaldehyde (2e). Yellow oil; yield: 73%; IR (neat): 1683, 1589, 1473, 1375 cm^{-1}; ^1H NMR (deuteriochloroform): δ 1.27 (s, 9H), 3.88 (s, 3H), 7.13 (dd, *J* = 8.5 and 3.1 Hz, 1H), 7.49 (d, *J* = 3.1 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 10.73 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 30.7, 47.1, 55.5, 110.9, 121.1, 128.0, 140.3, 141.3, 160.5, 193.7; ms: *m/z* (%) 224 (M^+, 100), 222 (3), 221 (2), 220 (2) 168 (2), 167 (1). Anal. Calcd. for $C_{12}H_{16}O_2S$: C, 64.25; H, 7.19; S, 14.29. Found: C, 64.41; H, 7.22; S, 14.03.

Preparation of 3-substituted 2*H*-thiochromenes 4: General procedure. To a stirred solution of aldehyde **2** (3 mmol) and alkene (6 mmol) in 1,2-dichloroethane (10 mL) was added $TiCl_4$ (0.33 mL, 3 mmol) at room temperature, and then the mixture was heated to reflux temperature for 0.5–96 h. After cooling to room temperature, the reaction mixture was quenched by aqueous saturated $NaHCO_3$ solution (50 mL), diluted with water (150 mL), and extracted with dichloromethane (2 × 150 mL). The combined organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated *in vacuo*. The resulting mixture was chromatographed on silica gel eluting with hexane/ethyl acetate (10:1) to produce **4** as an oil or a solid.

The physical and spectral data of **4** prepared by this general method are as follows.

3-Acetyl-2*H*-thiochromene (4a). [8] Yellow oil; yield: 51%; IR (neat): 1641, 1616, 1439, 1378, 1305, 1281, 1235, 1217 cm^{-1}; ^1H NMR (deuteriochloroform): δ 2.47 (s, 3H), 3.72 (d, *J* = 0.9 Hz, 2H), 7.12–7.31 (m, 4H), 7.40 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 22.8, 25.3, 125.7, 127.3, 130.5, 130.8, 131.4, 131.7, 135.0, 137.8, 196.7; ms: *m/z* (%) 190 (M^{+}, 63), 189 (62), 149 (8), 148 (23), 147 (100).

3-Acetyl-8-chloro-2*H*-thiochromene (4b). Yellow oil; yield: 22%; IR (neat): 1656, 1625, 1412, 1372, 1238, 1214 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.49 (s, 3H), 3.76 (d, $J = 0.9$ Hz, 2H), 7.09 (t, $J = 7.6$ Hz, 1H), 7.20 (dd, $J = 7.6$ and 1.2 Hz, 1H), 7.33 (dd, $J = 7.6$ and 1.2 Hz, 1H), 7.39 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 22.9, 25.4, 125.7, 129.0, 131.2, 131.6, 131.9, 132.9, 134.8, 137.5, 196.5; ms: *m/z* (%) 226 (M^{+}, 23), 225 (20), 224 (M^{+}, 59), 223 (25), 183 (37), 181 (100), 146 (11), 145 (25). Anal. Calcd. for $C_{11}H_9ClOS$: C, 58.80; H, 4.04; S, 14.27. Found: C, 58.71; H, 3.87; S, 14.04.

3-Acetyl-6-chloro-2*H*-thiochromene (4c). Yellow solid; yield: 24%; mp: 85–86°C; IR (potassium bromide): 1662, 1632, 1461, 1369, 1235, 1208 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.48 (s, 3H), 3.71 (d, $J = 0.9$ Hz, 2H), 7.18–7.27 (m, 3H), 7.33 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 22.8, 25.4, 128.3, 130.1, 130.2, 131.2, 132.7, 132.8, 133.3, 136.6, 196.5; ms: *m/z* (%) 226 (M^{+}, 28), 225 (27), 224 (M^{+}, 78), 223 (27), 183 (38), 181 (100), 146 (12), 145 (18). Anal. Calcd. for $C_{11}H_9ClOS$: C, 58.80; H, 4.04; S, 14.27. Found: C, 58.67; H, 3.87; S, 14.03.

3-Acetyl-6-nitro-2*H*-thiochromene (4d). [3(a)] Yellow solid; yield: 8%; mp: 143–144°C; IR (potassium bromide): 1662, 1598, 1558, 1510, 1336, 1226 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.52 (s, 3H), 3.81 (d, $J = 0.9$ Hz, 2H), 7.42 (d, $J = 8.5$ Hz, 1H), 7.45 (s, 1H), 8.06 (dd, $J = 8.5$ Hz and 2.4 Hz, 1H), 8.15 (d, $J = 2.4$ Hz, 1H); ^{13}C NMR (deuteriochloroform): δ 22.8, 25.4, 124.6, 125.0, 127.5, 131.6, 132.6, 135.9, 144.4, 145.5, 196.2; ms: *m/z* (%) 235 (M^{+}, 68), 234 (8), 192 (90), 176 (19), 146 (100).

3-Acetyl-6-methoxy-2*H*-thiochromene (4e). Yellow solid; yield: 32%; mp: 100–102°C; IR (potassium bromide): 1653, 1620, 1485, 1459, 1316, 1247, 1223 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.48 (s, 3H), 3.69 (d, $J = 0.9$ Hz, 2H), 3.81 (s, 3H), 6.82–6.85 (m, 2H), 7.21–7.24 (m, 1H), 7.37 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 23.1, 25.4, 55.5, 115.7, 116.7, 125.5, 128.2, 132.4, 132.7, 137.9, 157.8, 196.8; ms: *m/z* (%) 220 (M^{+}, 87), 219 (33), 177 (100), 162 (8), 134 (33). Anal. Calcd. for $C_{12}H_{12}O_2S$: C, 65.43; H, 5.49; S, 14.56. Found: C, 65.62; H, 5.47; S, 14.31.

3-Carbomethoxy-2*H*-thiochromene (4f). [8,9] Yellow solid; yield: 69%; mp: 34–35°C; IR (potassium bromide): 1704, 1628, 1586, 1552, 1438, 1239 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.73 (d, $J = 0.9$ Hz, 2H), 3.84 (s, 3H), 7.09–7.28 (m, 4H), 7.54 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 24.0, 52.2, 123.0, 125.8, 127.1, 130.2, 130.6, 131.3, 134.0, 137.4, 166.4; ms: *m/z* (%) 206 (M^{+}, 73), 205 (62), 191 (100), 175 (8), 147 (35).

3-Carbomethoxy-8-chloro-2*H*-thiochromene (4g). [9] Yellow solid; yield: 70%; mp: 94–95°C; IR (potassium bromide): 1699, 1641, 1436, 1415, 1247, 1220 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.78 (d, $J = 1.2$ Hz, 2H), 3.86 (s, 3H), 7.06 (t, $J = 7.6$ Hz, 1H), 7.15 (dd, $J = 7.6$ and 1.5 Hz, 1H), 7.29 (dd, $J = 7.6$ and 1.5 Hz, 1H), 7.53 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 24.2, 52.3, 123.2, 125.7, 128.8, 130.9, 131.7, 132.8, 133.9, 137.0, 166.0; ms: *m/z* (%) 242 (M^{+}, 21), 241 (23), 240 (M^{+}, 56), 239 (31), 227 (39), 225 (100), 183 (12), 181 (34).

3-Carbomethoxy-6-chloro-2*H*-thiochromene (4h). [9] Yellow solid; yield: 42%; mp: 75–76°C; IR (potassium bromide): 1705, 1628, 1464, 1433, 1235 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.73 (d, $J = 0.9$ Hz, 2H), 3.85 (s, 3H), 7.16–7.23 (m, 3H), 7.48 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 23.9, 52.3, 124.3, 128.1, 129.8, 129.9, 131.2, 132.3, 132.7, 136.1, 166.0; ms: *m/z* (%) 242 (M^{+}, 25), 241 (20), 240 (M^{+}, 67), 239 (22), 227 (38), 225 (100), 183 (15), 181 (42).

3-Carbomethoxy-6-methoxy-2*H*-thiochromene (4j). [9] Yellow solid; yield: 35%; mp: 38–39°C; IR (potassium bromide): 1704, 1628, 1599, 1561, 1236 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.70 (d, $J = 1.2$ Hz, 2H), 3.80 (s, 3H), 3.85 (s, 3H), 6.75–6.82 (m, 2H), 7.18–7.21 (m, 1H), 7.53 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 24.2, 52.2, 55.4, 115.6, 116.3, 124.0, 124.5, 128.0, 132.3, 137.4, 157.8, 166.3; ms: *m/z* (%) 236 (M^{+}, 86), 235 (25), 221 (100), 205 (4), 177 (20), 134 (12).

3-Cyano-2*H*-thiochromene (4k). [8] Yellow solid; yield: 25%; mp: 87–88°C; IR (potassium bromide): 2208, 1616, 1461, 1436, 1415, 1254 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.58 (d, $J = 0.9$ Hz, 2H), 7.15–7.26 (m, 5H); ^{13}C NMR (deuteriochloroform): δ 25.8, 103.7, 118.3, 126.3, 127.5, 130.06, 130.11, 130.9, 132.7, 142.2; ms: *m/z* (%) 173 (M^{+}, 64), 172 (100), 147 (7), 146 (4), 145 (10).

3-Cyano-8-chloro-2*H*-thiochromene (4l). Yellow solid; yield: 18%; mp: 116–117°C; IR (potassium bromide): 2202, 1620, 1442, 1413, 1282 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.64 (d, $J = 1.2$ Hz, 2H), 7.10–7.18 (m, 3H), 7.32–7.35 (m, 1H); ^{13}C NMR (deuteriochloroform): δ 26.0, 104.1, 117.9, 126.2, 128.4, 131.5, 131.7, 132.1, 132.8, 141.9; ms: *m/z* (%) 209 (M^{+}, 22), 208 (38), 207 (M^{+}, 59), 206 (51), 181 (5), 172 (100). Anal. Calcd. for $C_{10}H_6ClNS$: C, 57.83; H, 2.91; N, 6.74; S, 15.44. Found: C, 57.91; H, 2.70; N, 6.56; S, 15.28.

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Silica Gel-Supported Sulfuric Acid Catalyzed Synthesis of 1,5-Benzodiazepine Derivatives

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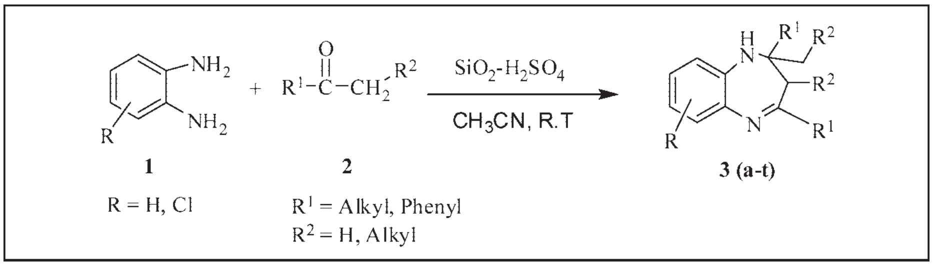

Silica gel-supported sulfuric acid has been found to be an efficient catalyst for the synthesis of 1,5-benzodiazepines from *o*-phenylenediamine and ketones in acetonitrile solvent. This method is simple, effective, and environmentally friendly and gives better yields. Compared to the classical reaction conditions, this new method consistently has the advantage of excellent yields (80–97%) and short reaction time (30–150 min) at room temperature.

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INTRODUCTION

Benzodiazepines are pharmacologically active compounds having anti-inflammatory [1], antianxiety, anticonvulsant, and hypnotic activity [2,3]. Because of the broad biological significance, the syntheses of these compounds have received a great deal of attention. Benzodiazepines have been synthesized by the condensation of *o*-phenylenediamines with β-unsaturated carbonyl compounds, β-haloketones, or ketones. This condensation has been carried out using different reagents, such as BF_3-etherate [4], polyphosphoric acid [5], $NaBH_4$ [6], SiO_2 [5], $MgO/POCl_3$ [7], $Yb(OTf)_3$ [8], $Ga(OTf)_3$ [9], lead nitrate [10], L-proline [11], acetic acid under microwave conditions [12], molecular iodine [13], and in ionic liquids [14]. Recently, this condensation is reported using different acid catalysts [15–22]. Many of these processes suffer from one or more limitations, such as long reaction times, occurrence of several side reactions, drastic reaction conditions, low yields, and tedious workup procedure. Therefore, the search continues for a better catalyst for the synthesis of 1,5-benzodiazepines in terms of mild reaction conditions.

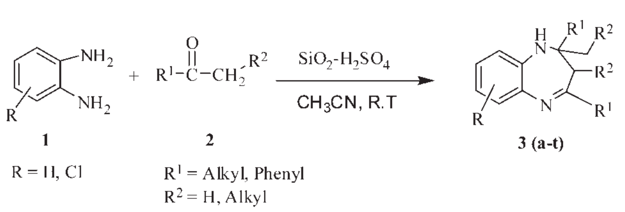
Recently, the use of heterogeneous catalysts [23–26] has received considerable importance in organic synthesis because of their ease of handling, enhanced reaction rates, greater selectivity, simple workup, and recoverability of catalysts. Among the various heterogeneous catalysts, particularly, silica gel-supported sulfuric acid [27] has advantages of low cost, ease of preparation, and catalyst recycling. As the reaction is heterogeneous in nature, the catalyst can conveniently be separated by simple filtration. In view of recent surge in the use of heterogeneous catalysts, we wish to report a simple, convenient, and efficient method for the preparation of 1,5-benzodiazepines under acetonitrile solvent using silica gel-supported sulfuric acid (10 mol %) as a catalyst. This catalyst is easy to handle, thermally robust, nonvolatile, nonexplosive, eco-friendly, and recyclable for a variety of organic transformations.

RESULTS AND DISCUSSION

Initially, we studied the catalytic properties of silica gel-supported sulfuric acid for the synthesis of 1,5-benzodiazepines at room temperature using *o*-phenylenediamine (**1**) and the ketone (**2**) (Scheme 1) and varying the mol % of silica gel-supported sulfuric acid (Table 1). Among the results obtained, use of 10 mol % silica gel-supported sulfuric acid gave better yield (97%) in 30 min for the synthesis of **3a**.We achieved good yield when compared with our earlier report (90% in 30 min) [16].

We investigated the reaction of a series of symmetrical and unsymmetrical ketones with *o*-phenylenediamine to get the corresponding 1,5-benzodiazepinederivatives in 80–97% yield under acetonitrile conditions. All

Scheme 1



synthesized derivatives were characterized using IR, ^{1}H NMR, and mass spectral analysis and also by comparison with authentic samples. The reactions of various ketones with *o*-phenylenediamine in the presence of silica gel-supported sulfuric acid are superior in terms of yields and reaction times (Table 2) than the previously reported methods. Especially, with *p*-chloroacetophenone (Table 2, entry 9), we have obtained 95% yield in 50 min, whereas previously reported was less than 95% in 50 min [17,18].

Chloro-substituted *o*-phenylenediamine and substituted ketones have been used with similar success to provide the corresponding benzodiazepines in high yields, which are also of much interest with regard to biological activity. The efficiency of the recovered catalyst was verified with the reaction of *o*-phenylenediamine and ketone (entry 1). Using the fresh catalyst, the yield of product (**3a**) was 97%, whereas using the recovered catalyst in the three subsequent recyclization, the yields were 94, 92, and 90, respectively.

In summary, we have developed a new methodology for the synthesis of various 1,5-benzodiazepines by using substituted *o*-phenylenediamine and substituted ketones in the presence of catalytic amount of silica gel-supported sulfuric acid catalyst at room temperature. Thus, this method is a simple, high yielding, time saving, and eco-friendly process. The catalyst can be prepared from available inexpensive reagents and can be easily recycled, which is heterogeneous and nonhazardous. Hence, the utility of silica gel-supported sulfuric acid catalyst for the synthesis of 1,5-benzodiazepines would be a valuable addition to available methods.

EXPERIMENTAL

All chemicals were AR grade obtained from Qualigens, India. All the solvents were purified by standard techniques. Column chromatographic separations were carried out on silica gel 100–200 mesh size. IR spectra were scanned on FT/IR-4200 Type A, spectrophotometer with potassium bromide optics. NMR spectra were recorded on a 300 MHz and mass spectra were recorded on a LC-MS.

Preparation of the catalyst. The catalyst was prepared by mixing silica gel (10 g, 200–400 mesh) in dry diethyl ether (50 mL), with sulfuric acid (3 mL). The resulting mixture was stirred for 30 min to absorb sulfuric acid on the surface of silica gel. After the removal of solvent in a rotary evaporator, the solid powder was dried at 120°C for 2–3 h under reduced pressure.

General procedure for the synthesis of 1,5-benzodiazepines. A mixture of *o*-phenylenediamine (**1**) (1 mmol), ketone (**2**) (2.5 mmol), and silica gel-supported sulfuric acid (0.1 mmol) was stirred in acetonitrile at room temperature until thin layer chromatography indicated that the reaction was complete. After the completion of reaction, 20 mL of ethyl acetate was added to the reaction mixture, and the catalyst was recovered by filtration. The organic layer was concentrated, and the crude product was purified by silica gel column chromatography using ethyl acetate–*n*-hexane (1:9) as eluent to afford the desired product (**3**). Entry **1–5** and **11** spectral data [20], entry **7**, **8** spectral data [21], and entry **9**, **10**, and **13** spectral data [22] are in full agreement with the reported literature, and the new compounds spectral data are given later.

Entry 6 (3f). Yellow solid, m.p. 140–142°C, IR(KBr): ν_{max} 3341, 1674, 1589 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.92–0.98 (m, 6H, 2CH$_3$), 1.13 (s, 3H, CH$_3$), 1.18–1.36 (m, 4H, 2CH$_2$), 1.52–1.62 (m,1H, CH^a), 2.10–2.20 (m, 1H, CH^b), 2.51–2.59 (m, 4H, 2CH$_2$), 3.05 (br s,1H, NH), 6.70–6.73 (m, 1H, Ar—H), 6.95–6.98 (m, 2H, Ar—H), 7.12–7.14 (m, 1H, Ar—H). EIMS: *m*/*z* [M$^+$] = 244. *Anal.* Calcd for $C_{16}H_{24}N_2$: C, 78.64; H, 9.90; N, 11.46. Found: C, 78.50; H, 9.85; N, 11.36.

Entry 12 (3l). Yellow solid, m.p. 94–96°C, IR(KBr): ν_{max} 3424, 1595, 1499 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.93 (t, 3H, CH$_3$), 1.24–1.25 (m, 6H, 2CH$_3$), 1.60–1.65 (m, 2H, CH$_2$), 2.22 (m, 2H, CH$_2$), 2.50–2.68 (q, 2H, *J* = 3.23 Hz, CH$_2$), 3.00–3.20 (br s,1H, NH), 6.62–6.71 (m, 1H, Ar—H), 6.88–6.93 (m, 1H, Ar—H), 7.04–7.14 (m, 1H, Ar—H). EIMS: *m*/*z* [M$^+$] = 250, *Anal.* Calcd for $C_{14}H_{19}ClN_2$: C, 67.05; H, 7.64; N, 11.17. Found: C, 67.00; H, 7.54; N, 11.10.

Entry 14 (3n). Light yellow solid, m.p.140–142°C, IR(KBr): ν_{max} 3197, 1623, 1590 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.98–1.02 (m, 12H, 4CH$_3$), 1.25 (m, 2H, 2CH), 1.30 (s, 3H, CH$_3$), 1.70–1.73 (m,2H, 2CH$_2$), 2.15–2.20 (m, 2H, CH$_2$), 2.40 (d, 2H, CH$_2$), 3.50 (br s,1H, NH), 6.60–6.673 (m, 1H, Ar—H), 6.86–6.94 (m, 1H, Ar—H), 7.04–7.13 (m, 1H, Ar—H). EIMS: *m*/*z* [M$^+$] = 306. *Anal.* Calcd for $C_{18}H_{27}ClN_2$: C, 70.45; H, 8.87; N, 9.13. Found: 70.35; H, 8.76; N, 9.09.

Entry 15 (3o). Yellow crystalline solid, m.p.156–158°C, IR(KBr): ν_{max} 3344, 1647, 1603 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.88–2.10 (m, 12H, 6CH$_2$), 2.90–2.95 (d, 1H, CH), 3.90–4.25 (m, 2H, CH$_2$), 3.05 (br s, 1H, NH), 6.63–6.64 (m, 1H, Ar—H), 6.73–6.77 (m, 1H, Ar—H), 7.87–7.90 (m, 1H,

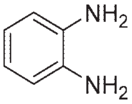
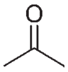
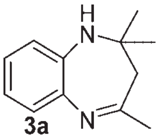
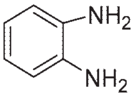
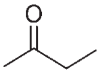
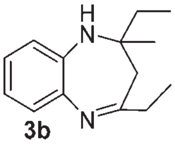
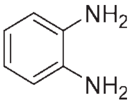
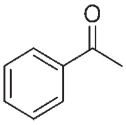
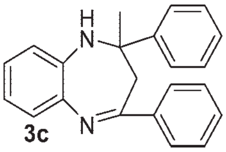
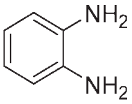
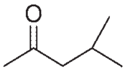
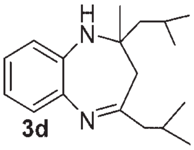
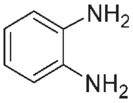
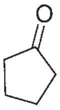
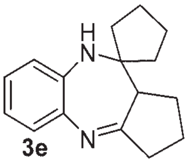
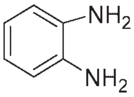
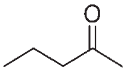
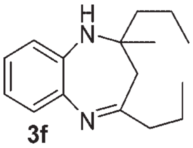
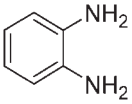
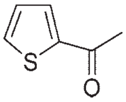
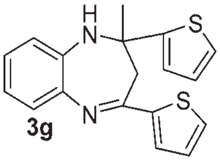
Table 1

Optimization of reaction conditions and the concentration of silica gel-supported sulfuric acid for the synthesis of **3a**.

H_2SO_4/Silica gel (mol %)	Reaction time (min)	Yield (%)
2.5	110	85
5	80	89
10	30	97
15	30	97
20	30	97

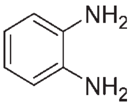
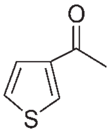
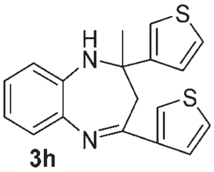
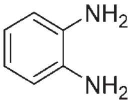
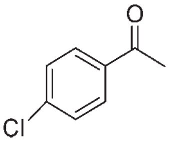
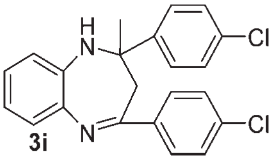
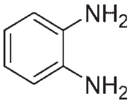
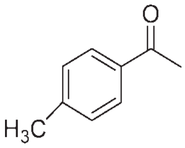
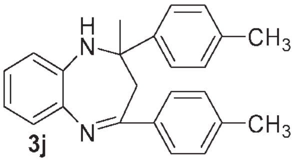
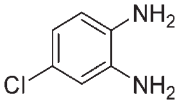
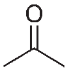
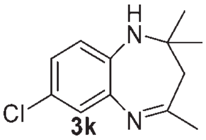
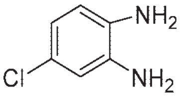
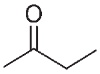
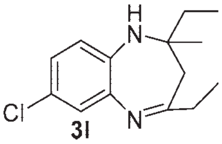
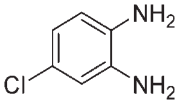
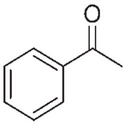
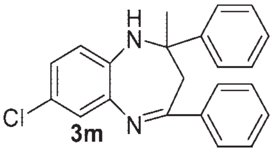
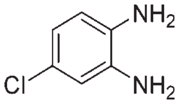
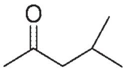
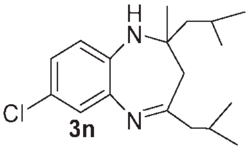
Table 2

Silica gel-supported sulfuric acid catalyzed synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines.

Entry	Diamine	Ketone	Product	Time (min)	Yield (%)
1			 3a	30	97
2			 3b	40	95
3			 3c	40	92
4			 3d	60	94
5			 3e	60	92
6			 3f	50	90
7			 3g	120	86

(*Continued*)

Table 2
(*Continued*)

Entry	Diamine	Ketone	Product	Time (min)	Yield (%)
8			 3h	120	82
9			 3i	50	95
10			 3j	50	96
11			 3k	50	94
12			 3l	60	92
13			 3m	120	90
14			 3n	90	88

(*Continued*)

Table 2
(Continued)

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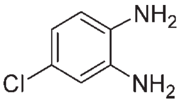
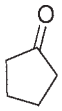
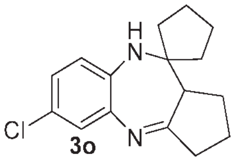
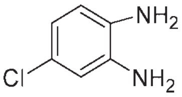
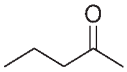
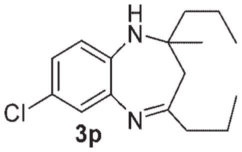
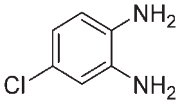
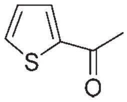
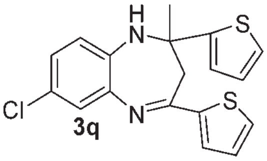
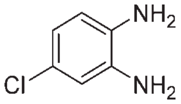
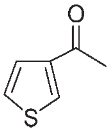
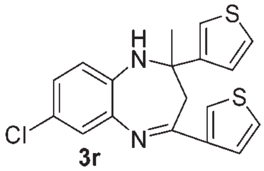
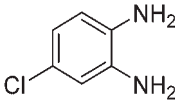
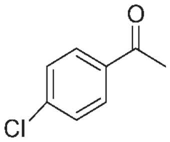
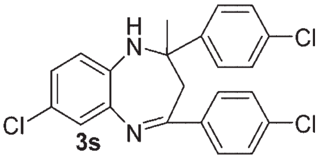
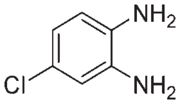
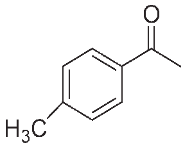
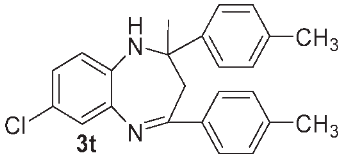
15			 3o	90	86
16			 3p	120	88
17			 3q	140	82
18			 3r	150	80
19			 3s	120	85
20			 3t	120	90

Ar—H). EIMS: m/z [M$^+$] = 274. *Anal.* Calcd for $C_{16}H_{19}ClN_2$: C, 69.93; H, 6.97; N, 10.19. Found: C, 69.83; H, 6.87; N, 10.09.

Entry 16 (3p). Reddish yellow solid, m.p. 160–162°C, IR(KBr): ν_{max} 3338, 1638, 1591 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82–0.92 (m, 6H, $2CH_3$), 1.15 (s, 3H, CH_3), 1.23–1.49 (m, 4H, $2CH_2$), 1.58–1.68 (m, 2H, CH_2), 2.02–2.10 (m, 2H, CH_2), 2.39–2.45 (m, 2H, CH_2), 3.10 (br s, 1H, NH), 6.51–6.60 (m, 1H, Ar—H), 6.77–6.82 (m, 1H, Ar—H), 6.93–7.02 (m, 1H, Ar—H). EIMS: m/z [M$^+$] = 278. *Anal.* Calcd for $C_{16}H_{23}ClN_2$: C, 68.92; H, 8.31; N, 10.05. Found: C, 68.83; H, 8.21; N, 10.00.

Entry 17 (3q). Yellow solid, m.p. 130–132°C, IR(KBr): ν_{max} 3303, 1599, 1471 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.83 (s, 3H, CH_3), 2.99 (d, 1H, J = 13.20 Hz, CH_2), 3.08 (d, 1H, J = 13.20 Hz, CH_2), 3.58 (br s, 1H, NH), 6.79–6.82 (m, 1H, Ar—H), 6.90–6.93 (m, 2H, Ar—H), 7.01–7.10 (m, 4H, Ar—H), 7.30–7.40 (m, 1H, Ar—H), 7.63–7.69 (m, 1H, Ar—H). EIMS: *m/z* [M$^+$] = 358. *Anal.* Calcd for $C_{18}H_{15}ClN_2S_2$: C, 60.24; H, 4.21; N, 7.81. Found: C, 60.14; H, 4.15; N, 7.71.

Entry 18 (3r). Light yellow crystalline solid, m.p.120–122°C, IR(KBr): ν_{max} 3320, 1602, 1490 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.73 (s, 3H, CH_3), 2.86 (d, 1H, *J* = 13.20 Hz, CH_2), 2.93 (d, 1H, *J* = 13.20 Hz, CH_2), 3.43 (br s, 1H, NH), 6.70–6.79 (m, 1H, Ar—H), 6.99–7.01 (m, 2H, Ar—H), 7.10–7.17 (m, 1H, Ar—H), 7.20–7.30 (m, 5H, Ar—H). EIMS: *m/z* [M$^+$] = 358. *Anal.* Calcd for $C_{18}H_{15}ClN_2S_2$: C, 60.24; H, 4.21; N, 7.81. Found: 60.14; H, 4.15; N, 7.71.

Entry 19 (3s). Yellow solid, m.p. 145–147°C, IR(KBr): ν_{max} 3267, 1646, 1562 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.75 (s, 3H, CH_3), 2.86 (d, 1H, *J* = 12.80 Hz, CH_2), 3.14 (d, 1H, *J* = 12.80 Hz, CH_2), 3.50 (br s, 1H, NH), 6.74–6.84 (m, 1H, Ar—H), 6.98–7.06 (m, 1H, Ar—H), 7.19–7.29 (m, 5H, Ar—H), 7.42–7.52 (m, 4H, Ar—H). EIMS: *m/z* [M$^+$] = 415. *Anal.* Calcd for $C_{22}H_{17}Cl_3N_2$: C, 63.56; H, 4.12; N, 6.74. Found: C, 63.46; H, 4.06; N, 6.64.

Entry 20 (3t). Pale yellow solid, m.p. 138–140°C, IR(KBr): ν_{max} 3320, 1602, 1567 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.72 (s, 3H, CH_3), 2.17 (s, 2H, CH_2), 2.33 (s, 6H, $2CH_3$) 3.00 (br s, 1H, NH), 6.80–6.81 (m, 1H, Ar—H), 7.06–7.10 (m, 5H, Ar—H), 7.42–7.53 (m, 5H, Ar—H). EIMS: *m/z* [M$^+$] = 374. *Anal.* Calcd for $C_{24}H_{23}ClN_2$: C, 76.89; H, 6.18; N, 7.47. Found: C, 76.79; H, 6.08; N, 7.37.

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Synthesis of *C*-Pivot Lariat Ethers

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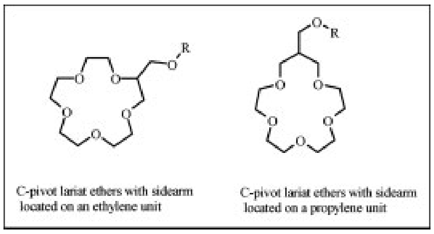

C-pivot lariat ethers with sidearm located on an ethylene unit

C-pivot lariat ethers with sidearm located on a propylene unit

This review covers the main strategies for the synthesis of *C*-pivot lariat ethers as well as their specific syntheses.

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Contents

1. INTRODUCTION

In 1967, Charles Pedersen, who was a chemist working at Du Pont, discovered a simple method for synthesizing a crown ether when he was trying to prepare a complexing agent for divalent cations [1]. Crown ethers are heterocyclic compounds that consist of a ring containing several ether groups. Pedersen realized that the cyclic polyethers presented a new class of complexing agents that were capable of binding alkali metal cations. The fields of organic synthesis, phase transfer catalysis, and other emerging disciplines benefited from the discovery of crown ethers. Pedersen shared the 1987 Nobel Prize in Chemistry for the discovery of the synthetic routes to and binding properties of crown ethers. Since Pedersen's discovery, there has been great interest in the synthesis of crown compounds in an attempt to find molecules with superior properties and proper applications in various areas [2–12].

Lariat ethers are a class of macrocyclic polyether compounds having one or more donor-group-bearing sidearms [13]. Functionalization of macrocyclic polyether compounds with such additional donating centers is a good way to increase their complexing ability and selectivity [14]. Lariat ethers should achieve a somewhat higher level of cation binding than generally observed with simple macrocyclic crown ethers by presenting a cation with a three-dimensional intramolecular array of binding sites as do the cryptands. Moreover, a higher degree of flexibility and dynamics characteristic of ionophores could be achieved. Thus, they combine characteristics of podands, corands, and cryptands [10,15].

The concept of lariat ethers has been extended to include molecules having sidearms that contain ionizable, lipophilic, or chromogenic groups. Functionalization of crown ethers with ionizable sidearms opened access to switchable lariat ethers [16]. Furthermore, lariat ethers with chromogenic sidearms offer distinct advantages in detection of cations when compared with the other available analytical methods. The color changes associated with complexation of different cations could make such sensors more versatile. Changes in potential or other properties could also be useful in sensing, but they would be less apparent. It is noteworthy that Takagi *et al.* pioneered chromogenic lariat ether complexation [17].

Moreover, macrocyclic ligands with one or more fluorine-containing sidearms have potential applications in metal ion separations involving a fluorous phase or supercritical carbon dioxide. Also, macrocycles with a fluoride label on the macrocyclic framework have potential applications as ^{19}F NMR probes [18]. Macrocycles with longer spacers between the macro ring and the perfluoroalkyl group were found to exhibit greater extraction efficiencies than analogues with shorter spacers.

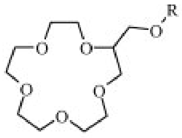
This review casts light on the main strategies for the synthesis of *C*-pivot lariat ethers as well as their specific syntheses. A number of other reviews [10,15,19] that have appeared concerning lariat ethers did not cover the synthesis of these compounds in an organized manner. We have concentrated on the crown compounds containing at least 12-membered rings.

2. NOMENCLATURE

The physical resemblance of CPK molecular models of these compounds to rope lassoes coupled with the concept of ''roping and tying'' a cation suggested the name lariat ethers [13].

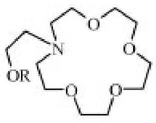
Lariat ethers are divided according to the point at which the sidearm and the macro ring meet (pivot atom), into two main classes:

(i) *C*-pivot lariat ethers **1** [20]: Systems in which sidearms are attached to a carbon of the macro ring.
(ii) *N*-pivot lariat ethers **2** [21]: Systems in which sidearms are attached to a nitrogen of the macro ring.



1

A carbon-pirvot lariat ether

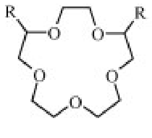


2

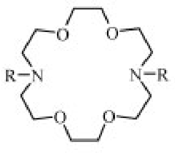
A nitrogen-pivot lariat ether

When more than one sidearm is attached, the number of them is designated using standard prefix and the Latin word brachium which means arm.

Two-armed compounds **3** and **4** are thus bibracchial lariat ether and the name is abbreviated BiBLEs [22,23]. A three-armed compound **5** is tribracchial lariat ether and the name is abbreviated TriBLEs, *etc*.

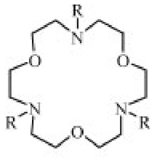


3



4

Bibracchial lariat ether



5

Tribracchial lariat ether

3. LARIAT ETHER COMPLEXATION PROCESS

The lariat ether idea is represented schematically in Figure 1. The sidearm which contains one or more donor groups placed in appropriate position would provide a third dimension of solvation to a ring-bound cation (binding of Type A) [15].

Two armed crown ethers have various kinds of cation binding modes (Fig. 2) [22]

(a) Only one sidearm interacts with guest metal cation (Type B).
(b) Two side arms provide coordination from the same or opposite sides (Type C or Type D).

It is noteworthy to mention that carbon pivot lariat ethers proved to be more chemically stable but less dynamic than the *N*-pivot counterparts. The greater flexibility of the latter is due to the facile inversion of the nitrogen atom, a property not shared by carbon.

In comparison with ordinary crown ethers extractants, a crown ether with a proton-ionizable group has the advantage that metal ion transport into the organic phase does not require concomitant transport of an ion (or ions) from the aqueous phase (Fig. 3). This feature is of immense importance to potential practical applications of crown ether-type extractants in which the hard aqueous phase anions of chloride, nitrate, and sulfate would be involved [24].

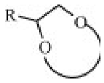
An additional advantage of proton-ionizable crown ethers is that a mechanism for cation release has been incorporated (Fig. 4). Following the extraction step, shaking of the separated organic phase with aqueous hydrochloric acid strips the extracted metal ions into an aqueous phase and regenerates the neutral form of the extractant [24].

The attachment of sufficient lipophilic groups to the proton-ionizable ionophores allows it to remain completely in the organic phase during extraction of alkali-metal cations from alkaline aqueous phases.

4. MAIN CLASSES OF *C*-PIVOT LARIAT ETHERS

C-Pivot lariat ethers are classified into two main classes A and B according to the point of attachment of the sidearm to the macro ring.

4.1. Attachment of the sidearm to an ethylenoxy unit of the macro ring.



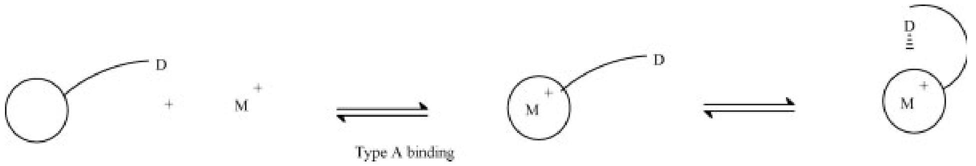


Figure 1. Cation binding by a single sidearmed crown ether.

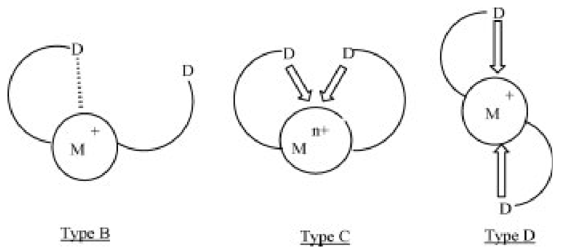
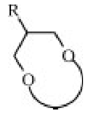


Figure 2. Various modes of cation binding by two armed crown ethers.

4.2. Attachment of the sidearm to the middle carbon of a trimethylene unit of the macro ring.



5. GENERAL AND SPECIFIC SYNTHESIS OF *C*-PIVOT LARIAT ETHERS

5.1. Synthesis of lariat ethers in which the sidearm is attached to an ethylenoxy unit of the macro ring.

5.1.1. Synthesis of C-pivot lariat ethers. There are different methods by which the pivot carbon could be incorporated into the macrocycle.

5.1.1.1. Incorporation of the pivot carbon via a glycerol unit. When the pivot carbon is incorporated *via* a glycerol unit the primary and secondary hydroxyl groups could be used as nucleophiles for formation of the ring. The remaining primary hydroxyl group must be protected by a group which could be removed after cyclization leaving a free hydroxy-methyl group for attachment of the sidearm. In other cases, the sidearm is incorporated into the glycerol unit before cyclization.

Glycerol units needed for the synthesis of *C*-pivot lariat ethers are prepared using one of the following routes:

Route 1: Reactions of alcohols or phenols **6** with epichlorohydrin (**7**). In the case of alcohol precursors, the chlorohydrin was isolated and then treated with 50% NaOH to give the glycidyl ether **8**. In the case of phenolic precursors, the conversion to the glycidyl ether could be accomplished in a single step. Hydrolysis with dilute perchloric acid afforded the corresponding diol **9**, as illustrated in Scheme 1 [25].

Route 2: Reactions of alcohols or phenols **6** with allyl chloride (**10**) to give the corresponding allyl ether **11** followed by bishydroxylation of the ethylene unit to furnish the corresponding diol **9** upon reaction with alkaline OsO_4 and *N*-methylmorpholine *N*-oxide (Scheme 2) [26].

Route 3: Bis(hydroxylation) of acrolein diethyl acetal **12** on treatment with $KMnO_4$ to give 1,2-dihydroxy-3,3-diethoxypropane (**13**) (Scheme 3) [27].

In the above three routes, cyclization of the diol is accomplished in the standard fashion by using NaOH or NaH as the base in concert with the appropriate oligoethylene glycol ditosylate, dimesylate, or dihalide in THF. In some cases, *t*-BuOLi/*t*-BuOH or NaOH/dioxane are used as bases. The reactions were typically heated overnight, although longer reaction times were required in some cases. Purification was usually accomplished by chromatography followed by crystallization in case when the *C*-pivot crown was a solid rather than an oil.

When the protecting group (R) is benzyl or allyl, they can be easily removed after cyclization with the appropriate ditosylates to give the corresponding hydroxymethyl derivative upon treatment with 10% Pd/C and a catalytic amount of *p*-toluenesulfonic acid [28,29] (PTSA) in ethanol under 3.4 atmosphere of H_2 at room temperature.

Yields were not appreciably altered by the presence of an aliphatic rather than an aromatic sidearm [20] (alcohols *vs*. phenol precursors), but the presence of donor group at a distance from the crown's cavity suitable for secondary interaction was important.

It was postulated by Greene [30] that a template effect was responsible for the high yields observed in these ring-formation reactions. Evidence for the template effect has accumulated [31], although there have also been skeptics of this theory [32]. In any event in molecules designed with sidearm capable of secondary binding through donor groups in them, one might anticipate that yields would be high (more organization in the transition state leading to a cycle) when such donor groups are present in contrast to the situation prevailing in their absence.

An example of this is shown in Scheme 4 in which the cyclization of 2-methoxyphenyloxypropanediol (**14**) with

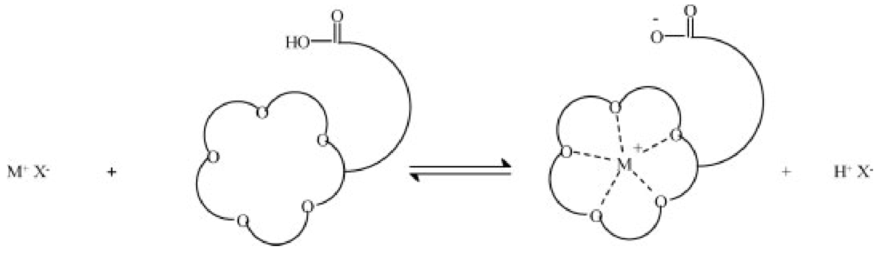


Figure 3. Metal ion extractant by a proton-ionizable crown ether.

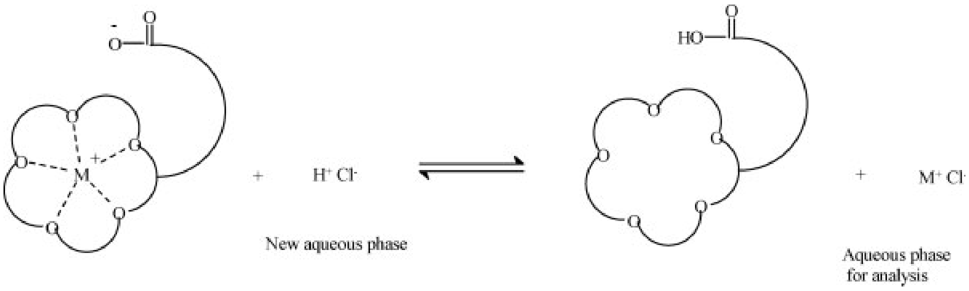
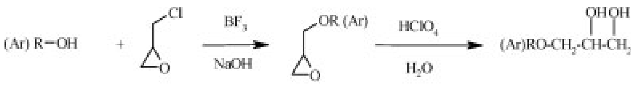


Figure 4. Metal ion stripping from an ionized crown ether-metal ion complex.

tetraethylene glycol ditosylate (**15**) to yield the corresponding 15-crown-5 **16** is illustrated. When the 2-methoxy group is present, the cycle is formed in about 70%, where in its absence the yield of the cyclization decreases to 34%. The yield of cyclization also decreases to 57% and 29%, respectively, when the methoxy group is present in the 3-(*meta*) or 4-(*para*) positions [13,20].

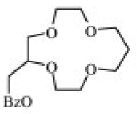
Using route 1 Gokel *et al*. [13] reported the synthesis of a series of 15-crown-5 ether derivatives **18–24** by treatment of the appropriate diols **17** with tetraethylene glycol ditosylates **15a** or dimesylates **15b** in the presence of NaH in THF (Scheme 5).

Scheme 1



6 **7** **8** **9**

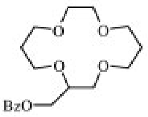
Similarly, a variety of benzyloxymethyl crown ethers of different cavity sizes **25–29** have been prepared.



25

a 13-Crown-4

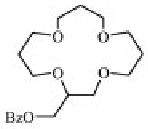
ref. 33, yield = 80%



26

a 14-Crown-4

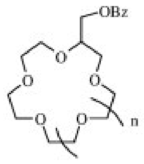
ref. 33, yield = 75%



27

a 15-Crown-4

ref. 33, yield = 49%



28: a 15-Crown-5 (n = 1, ref. 34 (23%), ref. 15 (32%), ref. 35, (67%))

29: a 18-Crown-6 (n = 2, ref. 34, 27 (25%))

The latter compounds can be converted to the corresponding hydroxymethyl derivatives on treatment with H_2 over Pd/C.

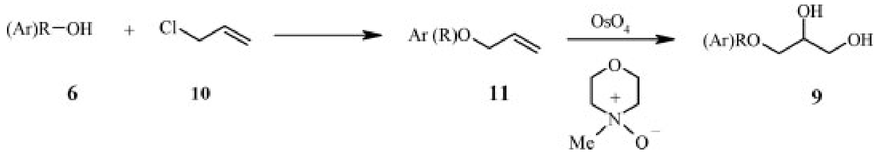
Gokel *et al*. [36] used the same approach for the synthesis of olefinic crown ethers **30**. The latter compounds were used as starting materials for the synthesis of epoxy lariat crown ethers **34** and **35** as outlined in Scheme 6.

Olefinic crown ethers **30** were converted to the corresponding diols **32** by treatment of the olefins with *N*-methylmorpholine *N*-oxide (**31**) in the presence of catalytic osmium tetraoxide. The diols thus obtained were converted to the monotosylates **33** on treatment with *p*-toluenesulfonyl chloride in pyridine. The latter compound underwent ring closure under basic condition to the desired epoxy crown ethers **34** and **35**.

Bradshaw *et al*. [37] reported the synthesis of bis-allyloxymethyl-18-crown-6 **37** by the 2 + 2 cycloaddition reaction of the commercially available allyloxymethyl ethylene glycol **9** and diethylene glycol ditosylate **36** (Scheme 7).

Gokel *et al*. [26] used route 2 for the synthesis of the cholestanyl lariat ether **41** as shown in Scheme 8. Commercially available 3β-cholestanol (**38**) was *O*-allylated under phase transfer catalytic conditions to give the

Scheme 2



6 **10** **11** **9**

Scheme 3

12 13

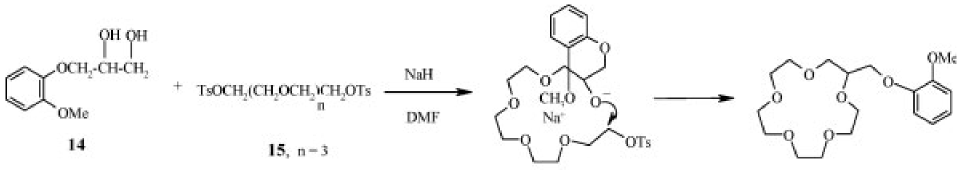
crystalline allyl cholestanyl ether **39**. Catalytic bis-hydroxylation of **39** using OsO$_4$ and *N*-methylmorpholine *N*-oxide afforded the diol **40**. Reaction of dialkoxide derived from diol **40** and NaH in THF with tetraethylene glycol ditosylate **15** gave after chromatography, cholestanyl lariat ether **41**.

Fukunishi *et al*. [27] used route 3 for the synthesis of hydroxylmethyl-18-crown-6 **45**. Thus, cyclization of **13** with pentaethylene glycol ditosylate **42** gave **43**. Hydrolysis of the latter to the aldehde derivative **44** and subsequent reduction produced **45** in 32% yield (Scheme 9).

5.1.1.2. Incorporation of the pivot carbon via a thioglycerol unit. Nabeshima *et al*. [38] used this approach to synthesize thiolariat ethers **50–55** as outlined in Scheme 10. Alkyl halides or benzyl chloride **47** was treated with thioglycerol **46** to give *S*-alkylated diols **48**. Cyclization of diols **48** with the appropriate oligoethylene glycol ditosylates **15**, **36,** and **49** in a THF suspension of NaH afforded thiolariat ethers **50–55**. Subsequent cleavage of the benzyl moiety of **50, 51, 54** gave the corresponding mercaptomethyl crown ethers **56a–c** in moderate yields.

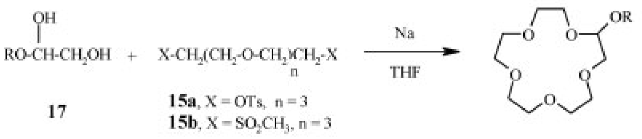
Crown ethers containing a sulfur atom outside the ring have fascinating features for ion and molecular

Scheme 4



14 15, n = 3 16

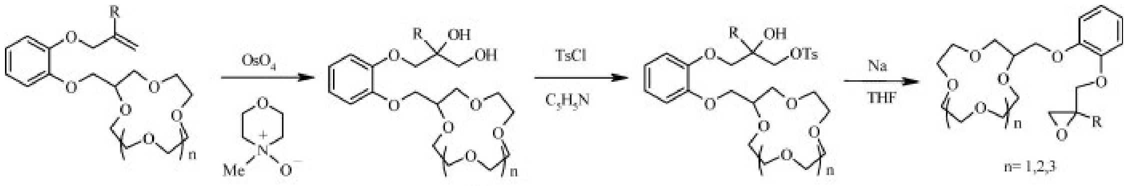
Scheme 5



17 15a, X = OTs, n = 3 15b, X = SO$_2$CH$_3$, n = 3

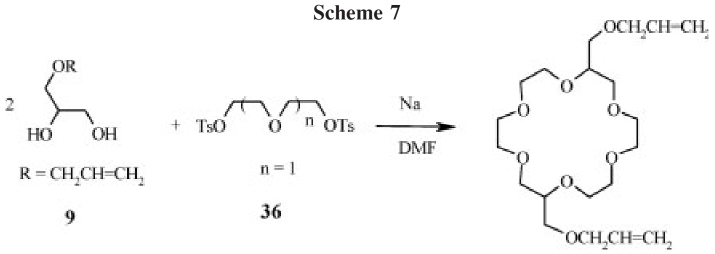
no.	R	yield
18	CH$_2$OCOMe	90%
19	CH$_2$OPh	32%
20	CH$_2$OC$_6$H$_4$OMe-p	29%
21	CH$_2$OCCH$_2$Ph	62%
22	CH$_2$O(CH$_2$)$_2$OMe	61%
23	CH$_2$O(CH$_2$)$_2$O(CH$_2$)$_3$Me	55%
24	CH$_2$O(CH$_2$)$_2$O(CH$_2$)$_2$OMe	48%

Scheme 6



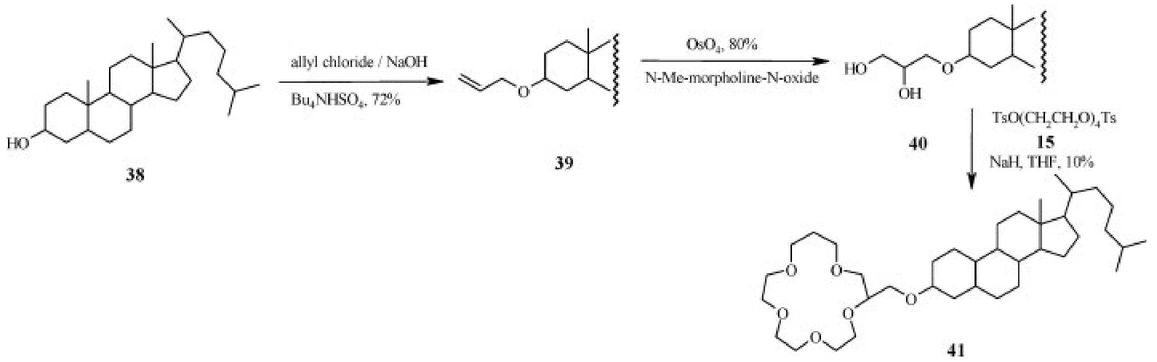
30 31 32 33 n= 1,2,3 34: R = H 35: R = CH$_3$

Scheme 7

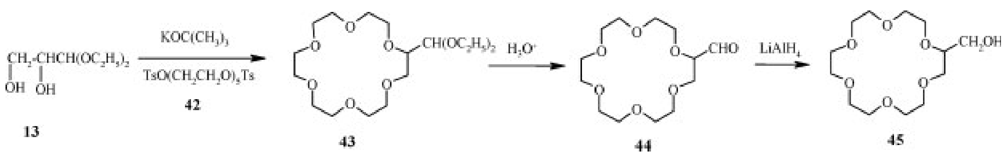


9 R = CH$_2$CH=CH$_2$ 36 n = 1 37 (21%)

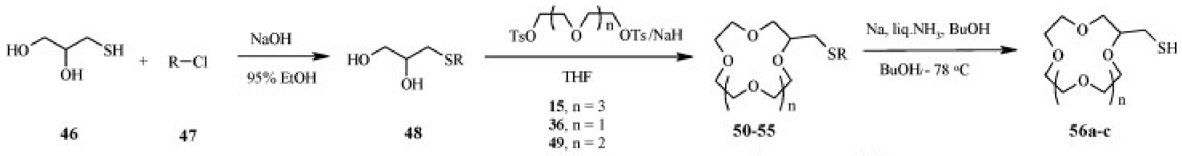
Scheme 8



Scheme 9



Scheme 10



no.	n	R	yield
50	1	Bn	35%
51	2	Bn	58%
52	2	$C_{12}H_{25}$	48%
53	2	Bu	88%
54	3	Bn	52%
55	3	$C_{12}H_{25}$	62%

a, n = 1, 60%
b, n = 2, 65%
c, n = 3, 52%

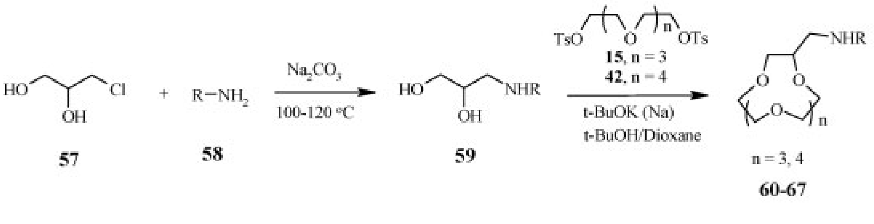
recognition. Crown ethers bearing a mercapto group as a side chain are considered to be key compounds in host–guest chemistry. These mercapto crowns can be used as precursors for various thiolariat ethers whose side chain contain a substituent unstable under basic cyclization reaction conditions. The mercapto crown may also be useful for polymer-support thiolariat ethers and for functionalization of surfaces of electrode and other solid materials [38,39].

5.1.1.3. Incorporation of the pivot carbon via a 3-(N-substituted amino)-1,2-propanediol. Okahara *et al.* [40] reported the synthesis of various *N*-substituted or unsubstituted aminomethyl crown ethers **60–67** from the reaction between 3-amino-1,2-propanediols **59** and the oligoethylene glycol ditosylates **15** and **42** as outlined in Scheme 11.

The starting material, 3-(*N*-substituted amino)-1,2-propanediols (**59**) were prepared from 3-chloro-1,2-propanediol (**57**) and the appropriate primary amine **58**.

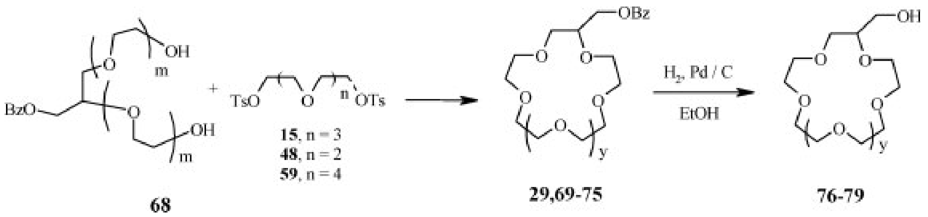
5.1.1.4. Incorporation of the pivot carbon via benzyloxy(alkoxy)methyl oligoethylene glycols or their ditosylates derivatives. Reaction of benzyloxyoligoethylene glycol **68** with the appropriate oligoethylene glycol ditosylate **15**, **48**, and **59** in THF in presence of CsOH, KOH, or *t*-BuOK gave the corresponding benzyloxymethyl 18-crown-6 **29** [35], 21-crown-7 **69** and **71** [41], 24-crown-8 [41] **70** and **72**, 27-crown-9 [41] **74**, and 30-

Scheme 11



no.	R	n = 3 yield	n = 4 yield
60	n-C_6H_{13}	51%	50%
61	Et	61%	51%
62	Ph	43%	48%
63	$PhCH_2$	56%	-
64	n-$C_{10}H_{21}$	48%	-
65	$H_2NCH_2CH_2$	35%	-
66	H	trace	trace
67	t-Bu	56%	51%

Scheme 12

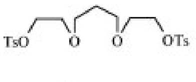


crown-10 **73** and **75** [41]. Debenzylation of **69, 70, 74,** and **75** afforded the hydroxymethyl derivatives **76–79** (Scheme 12) (Table 1) [41,42].

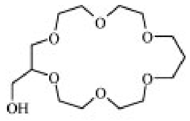
Montanari and Tundo [44] used a similar approach for the synthesis of *t*-butoxymethyl-18-crown-6 in an 38% yield from *t*-butoxymethyldiethylene glycol and triethylene glycol ditosylate followed by conversion into the corresponding hydroxymethyl-18-crown-6 on reaction with HBF_4 in CH_2Cl_2.

The diol **68** ($m = 1$) was obtained by the reaction of (benzyloxymethyl)ethylene glycol with chloroacetic acid followed by reduction. The diols **68** ($m = 2, 3$) were obtained by the reaction of 3-*O*-benzylglycerol with THP-blocked oligoethylene glycol monochloride in the presence of lithium *t*-butoxide in *t*-butyl alcohol followed by deprotection upon treatment with HCl in CH_2Cl_2—MeOH [29,43].

Hydroxymethyl 19-crown-6 **81** was obtained by cyclization of diol **68** ($m = 1$) and ditosylate **80** with potassium *t*-butoxide in THF, followed by debenzylation [45].



80



81

(quantitative yield)

Gandour *et al.* [28] reported the synthesis of alkoxymethyl 18-crown-6 **84–87** by cyclization of 1-(alkoxymethyl)-3,6,9-trioxaundecane-1,11-diol **83** with diethylene glycol ditosylate in the presence of KH. The hydroxymethyl derivative **44** can be easily liberated by removal of the allyl group on treatment of **87** with Pd/C and *p*-toluenesulfonic acid (Scheme 13).

Table 1

Compounds **29**, **60–79**.

Comp. no.	*m*	*n*	*y*	Ref. (yield)
29	1	2	2	35 (73)
69	1	3	3	41 (27)
70	1	4	4	41 (14)
71	1	3	3	43 (44)
72	1	4	4	43 (35)
73	3	2	6	43 (39)
74	2	3	5	42 (38)
75	2	4	6	42 (35)
76	1	3	3	41 (81)
77	1	4	4	41 (72)
78	2	3	5	42 (97)
79	2	4	6	42 (86)

The diol **83** can be obtained by the reaction of (alkoxymethyl) oxirane **8** with excess 3,7-dioxaoctane-1,8-diol **82** in the presence of catalytic amount of NaH.

5.1.1.5. Incorporation of the pivot carbon via bis(aminomethyl) oligoethylene glycols. Okahara *et al.* [46] reported the synthesis of bis(aminomethyl)oligoethylene glycols **89** by treatment oligoethylene glycol diglycidyl ethers **88** with excess amine. Reaction of bis diols **89** with the oligoethylene glycol ditosylates **36** and **48** gave the corresponding bis(aminomethyl) crown ethers **90–98** (Scheme 14).

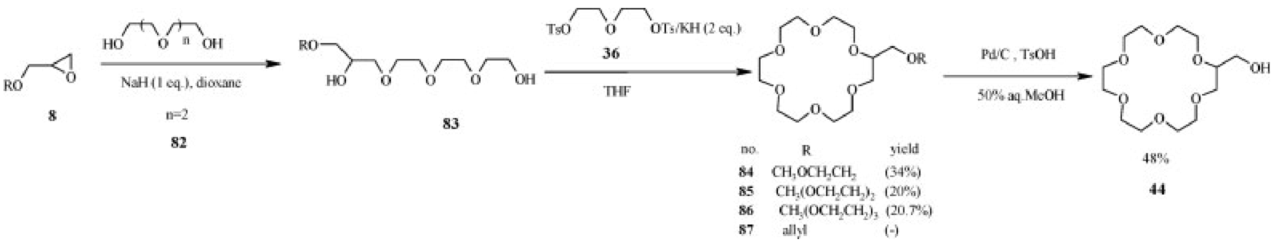
5.1.1.6. Incorporation of the pivot carbon via 2-methylallyl ether derivatives by a one-step or two-step bromination-cyclization sequence. Okahara *et al.* [25,47,48] reported the synthesis of 2-methyl-2-bromomethyl 12-, 13-, 14-, 15-, 16-crown ethers using two methods, A and B.

In method A, the appropriate 2-methylallyl ether **99** (obtained upon treatment of methallyl chloride with excess of the appropriate oligoethylene glycol) undergo intramolecular bromoalkoxylation with *N*-bromosuccinimide (NBS) using $LiBF_4$ as the template in 1,2-dichloroethane. In this instance, NBS acts as a brominating agent toward the double bond rather toward the allylic position. Bromination occurs, as expected from the less substituted side of the alkene with formation of the more stable carbocation [49]. The tertiary carbocation is intercepted intramolecularly by the hydroxyl group. This reaction is probably favored by the templating effect of sodium cation which is also present in this solution as the tetrafluoroborate salt [15,50].

Using this method Okahara *et al.* [25,47] prepared bromomethyl-substituted lariat ethers having a 12-, 14-crown-4 **100** and **101** as well as 15-crown-5 **102** rings (Scheme 15).

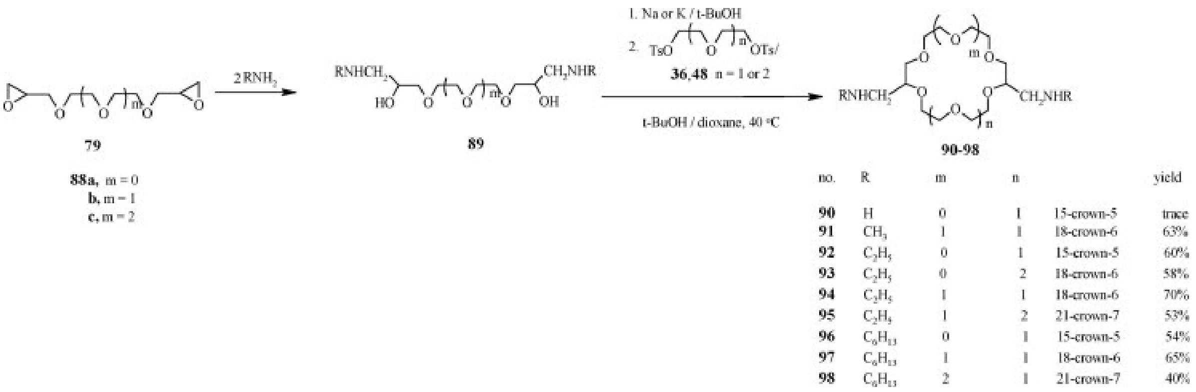
In method B, 2-methylallyl ethers **99** undergo intermolecular bromoalkoxylation with NBS and the appropriate oligoethylene glycol **82** and **103** followed by intramolecular cyclization with benzenesulfonyl chloride using lithium *tert*-butoxide as the base in *tert*-butyl

Scheme 13



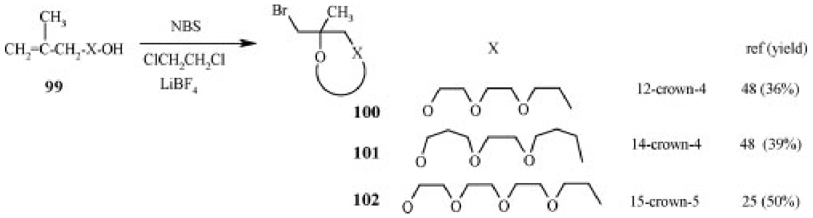
no.	R	yield
84	$CH_3OCH_2CH_2$	(34%)
85	$CH_3(OCH_2CH_2)_2$	(20%)
86	$CH_3(OCH_2CH_2)_3$	(20.7%)
87	allyl	(-)

Scheme 14



no.	R	m	n		yield
90	H	0	1	15-crown-5	trace
91	CH_3	1	1	18-crown-6	63%
92	C_2H_5	0	1	15-crown-5	60%
93	C_2H_5	0	2	18-crown-6	58%
94	C_2H_5	1	1	18-crown-6	70%
95	C_2H_5	1	2	21-crown-7	53%
96	C_6H_{13}	0	1	15-crown-5	54%
97	C_6H_{13}	1	1	18-crown-6	65%
98	C_6H_{13}	2	1	21-crown-7	40%

Scheme 15

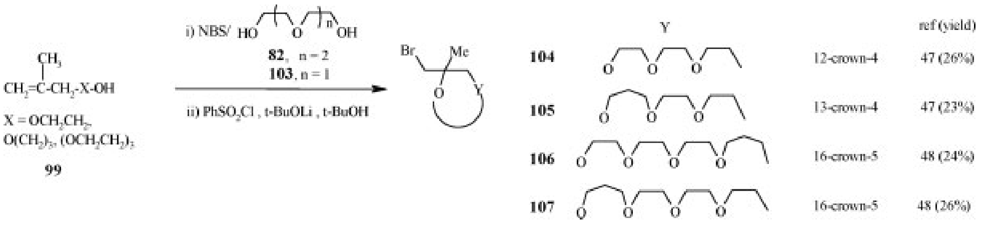


alcohol [47,48]. Using this approach, methyl lariat ether based on 12-crown-4 **104**, 13-crown-4 **105**, and 16-crown-5 **106** and **107** have been prepared as depicted in Scheme 16.

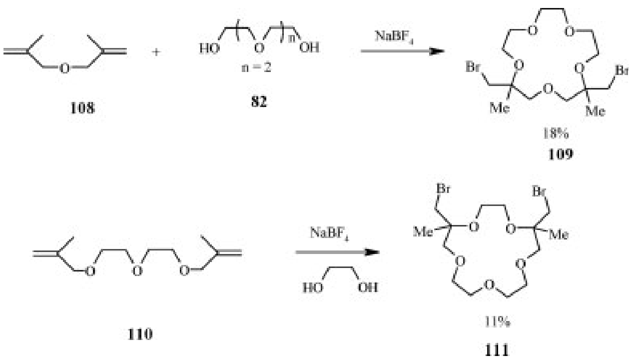
Nakatsuji *et al*. [51] and Okahara *et al*. [52] reported the synthesis of two kinds of positional isomers of the *C*-pivot type of double-armed 15-crown-5 ethers **109** and **111** by bromoalkoxylation reaction of the appropriate bis(2-methylallyl)ethers **108** and **110** with triethylene glycol and ethylene glycol, respectively, in the presence of $NaBF_4$ as the template ion (method A) (Scheme 17).

The same authors [51,52] used (method B) to prepare another positional isomer of double-armed 15-crown-5

Scheme 16



Scheme 17



ether **114** as well as some positional isomers of bis(bromomethyl)dimethyl 18-crown-6 **115** and **116** and 21-crown-7 **117** and **118** by intramolecular cyclization reaction of the diols **113**, which were obtained by bromoalkoxylation reaction of bis(2-methylallyl)ether **112** with the appropriate oligoethylene glycol, by using benzenesulfonyl chloride under basic conditions as depicted in Scheme 18.

5.1.2. Synthesis of C-pivot lariat benzocrown ethers. Bartsch *et al.* [45,53] used route 1 (Incorporation of the pivot carbon *via* a glycerol unit, Section 5.1.1.1) for the synthesis of hydroxymethylbenzo-12-crown-4, 14-crown-4 [45] and hydroxymethylbenzo-18-crown-6 [53] by reaction of the appropriate benzyloxymethy diol with the corresponding ditosylates and subsequent debenzylation.

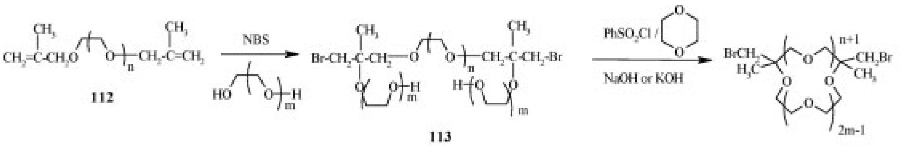
Bartsch *et al.* [53] used the strategy reported in Section 5.1.1.4 (Incorporation of the pivot carbon *via* benzyloxy(alkoxy)methyl oligoethylene glycols or their ditosylate derivatives) for the synthesis of hydroxymethyl benzo-18-crown-6 **120**. Thus, cyclization of the diol **68** ($m = 1$) and ditosylate **119** with KOH in THF/H_2O and subsequent debenzylation gave an 96% yield of **120** (Scheme 19).

The ditosylate **119** was obtained from catechol by initial treatment with 2-chloroethanol to give 1,2-bis(2-hydroxyethoxy)benzene and subsequent reaction with *p*-toluenesulfonyl chloride in pyridine.

The hydroxymethyl benzo-18-crown-6 **120** ($n = 1$) was alternatively obtained in 70% yield by the reaction of catechol **122** with the ditosylate **121** and cesium fluoride in acetonitrile followed by debenzylation (Scheme 20) [43].

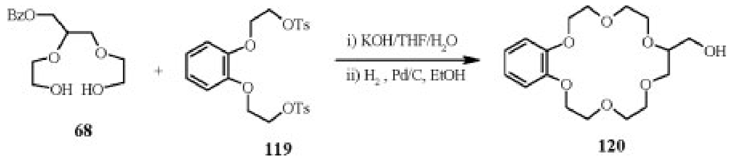
Using a similar approach, Reinhoudt *et al.* [29] reacted benzyloxymethylnonaethylene glycol ditosylate **121** ($n = 3$) with the cesium salt of catechol in acetonitrile followed by debenzylation to furnish 94% of the corresponding hydroxymethylbenzo-30-crown-10 **123**.

Scheme 18

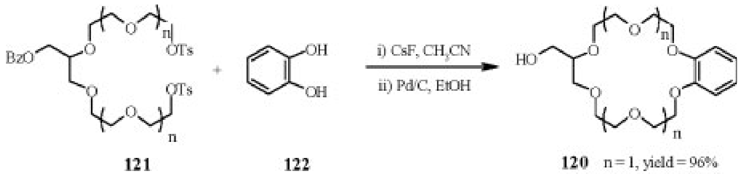


no.	n	m		ref (yield)
114	1	1	15-crown-5	52 (41%)
115	0	2	18-crown-6	52 (31%)
116	2	1	18-crown-6	52 (25%)
117	1	2	21-crown-7	52 (19%)
118	3	1	21-crown-7	52 (20%)

Scheme 19

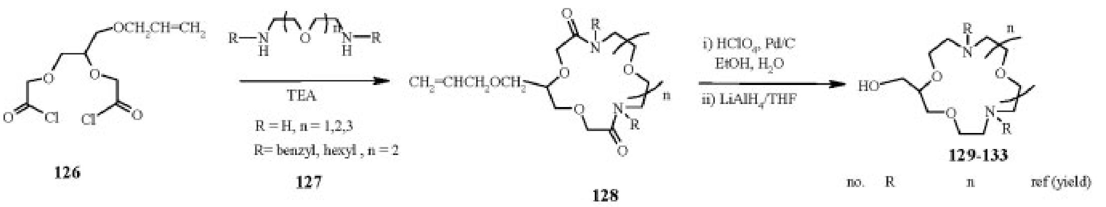


Scheme 20



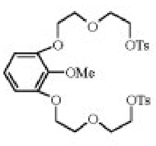
120 n = 1, yield = 96%
123 n = 3, yield = 94%

Scheme 21

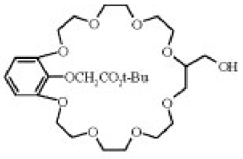


no.	R	n	ref (yield)
129	H	1	55 (78%)
130	H	2	55 (75%)
131	H	3	55 (73%)
132	$PhCH_2$	2	55 (60%)
133	hexyl	2	55 (50%)

Similarly, Bartsch *et al*. [54] reported the synthesis of resorcinol-25-crown-8 **125** with an intraanular oxyacetic acid ester group and a pendant hydroxymethyl function in 99% yield starting from diol **68** ($n = 1$) and ditosylate **124**.



124



125

5.1.3. Synthesis of C-pivot lariat azacrown ethers. Preparation of such systems are classified depending on the starting materials as follows.

5.1.3.1. Action of diacid dichloride on diamines. Bartsch *et al*. [55,56] reported the synthesis of hydroxymethyl-substituted diazacrowns in which the cavity sizes are systematically varied as depicted in Scheme 21.

Thus, reaction of 3,6-dioxa-4-(allyloxymethyl)-1,8-octanedioic acid dichloride **126** with the appropriate diamines **127** under high dilution conditions in the presence of TEA afforded the allyloxymethyl-substituted cyclic diamides **128**. The latter compound underwent deprotection by isomerizatrion of the allyl group with palladium on carbon followed by acid-catalyzed cleavage and subsequent reduction with $LiAlH_4$ to give the hydroxymethyl-substituted diazacrowns **129–133** in good yields (50–78%).

5.1.3.2. Reaction of diamines with diiodide or dimesylate. Bradshaw *et al*. [56] reported the synthesis of [(allyloxy)methyl]-diaza-18-crown-6 **136** and **137** by the reaction of the appropriate diamine **127** with diiodide **135** in CH_3CN containing Na_2CO_3 or dimesylate **134** in hexane containing *n*-butyl lithium (Scheme 22).

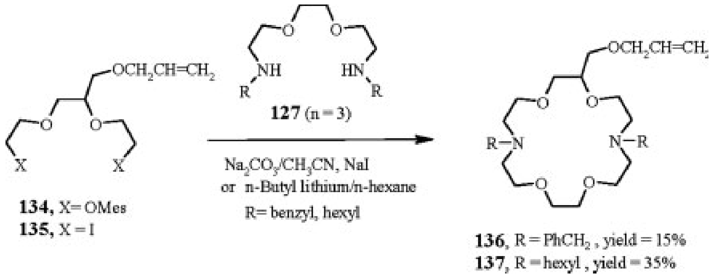
The diacid dichloride **126** as well as the diiodide **135** were prepared as outlined in Scheme 23. Thus, reaction of diol **9** with chloroacetic acid afforded the diacid **138**. The latter underwent chlorination on treatment with oxalyl chloride to give the corresponding diacid dichloride **115**. Reduction of **126** with $LiAlH_4$ afforded the diol **139**. The dimesylate **134** could be obtained from **139** upon treatment with MesCl in pyridine. The diiodide **135** was obtained from **134** by the reaction with NaI in acetone [55].

5.1.3.3. Ring closure of the appropriate diazadiols. The most convenient method to prepare **136** as well as **142** is shown in Scheme 24 [56]. Thus, reaction of diamines **140** with epoxide **8** gave the diazadiol **141**. The Okahara ring closure of **141** using tosyl chloride gave good yields of diaza-18-crown-6 lariat ethers **136** and **142**.

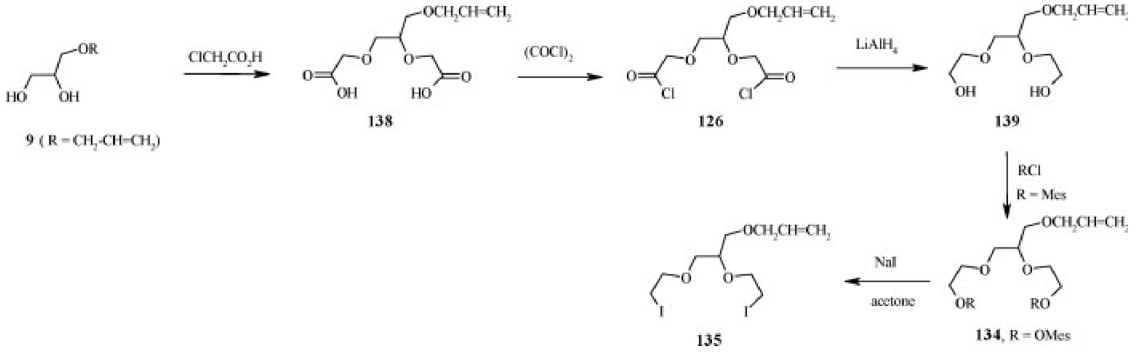
Bradshaw *et al*. [57] prepared *N*,*N*-diethyl- and *N*,*N*-dibenzyldiazapentaethylene glycol **140** in high overall yield from the reaction of *N*-ethyl- or *N*-benzyl-substituted-ethanaolamine **143** with the dihalide **144** (Scheme 25).

Bradshaw [57] reported the synthesis of allyloxymethyl-substituted triaza- and tetraazacrown compounds **146** and **148** by the reaction of the appropriate diamines **145** and **147** with 4-(allyloxymethyl)-1,8-diiodo-3,6-

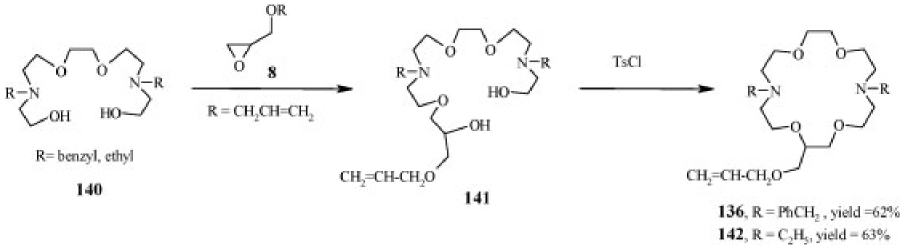
Scheme 22



Scheme 23



Scheme 24



dioxaoctane **135** in refluxing CH_3CN in the presence of anhydrous Na_2CO_3 (Scheme 26).

The starting diamines **145** and **147** were obtained from *N*-[2-(2-chloroethoxy)ethyl]acetamide **149** by initial reaction with each of benzylamine and the appropriate diamines **150** in refluxing toluene in the presence of anhydrous Na_2CO_3 followed by $LiAlH_4$ reduction (Scheme 27).

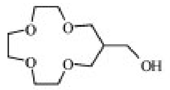
5.2. Synthesis of lariat ethers in which the sidearm is attached to the middle carbon of a trimethylene unit of the macro ring.

5.2.1. Synthesis of C-pivot lariat ethers. There are different methods by which the sidearm can be incorporated into the middle carbon of trimethylene unit of the crown ethers ring.

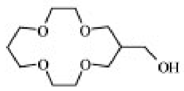
5.2.1.1. Synthesis of methylenecrown ether followed by hydroboration-oxidation. Tomoi [58] reported the synthesis of 15-crown-5 **155**, 19-crown-6 **156**, and 22-crown-7 **157** with vinylidene group by the reaction of 3-chloro-2-chloromethyl-1-propene **151** with the appropriate oligoethylene glycol **152–154**.

The methylene crown ether **155** was transformed into the corresponding hydroxymethyl crown **158** on treatment with borane-dimethyl sulfide complex followed by oxidation with H_2O_2 (Scheme 28).

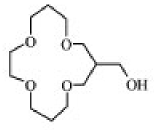
Yoshihisa *et al*. [59] and Bartsch *et al*. [33] used a similar approach for the synthesis of hydroxymethyl-substituted crown ethers **159–162** with four ring oxygens and 13-, 14-, 15-, and 16-membered polyether rings.


96%

159


98%

160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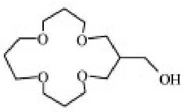
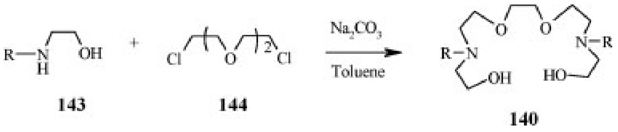
161


55%

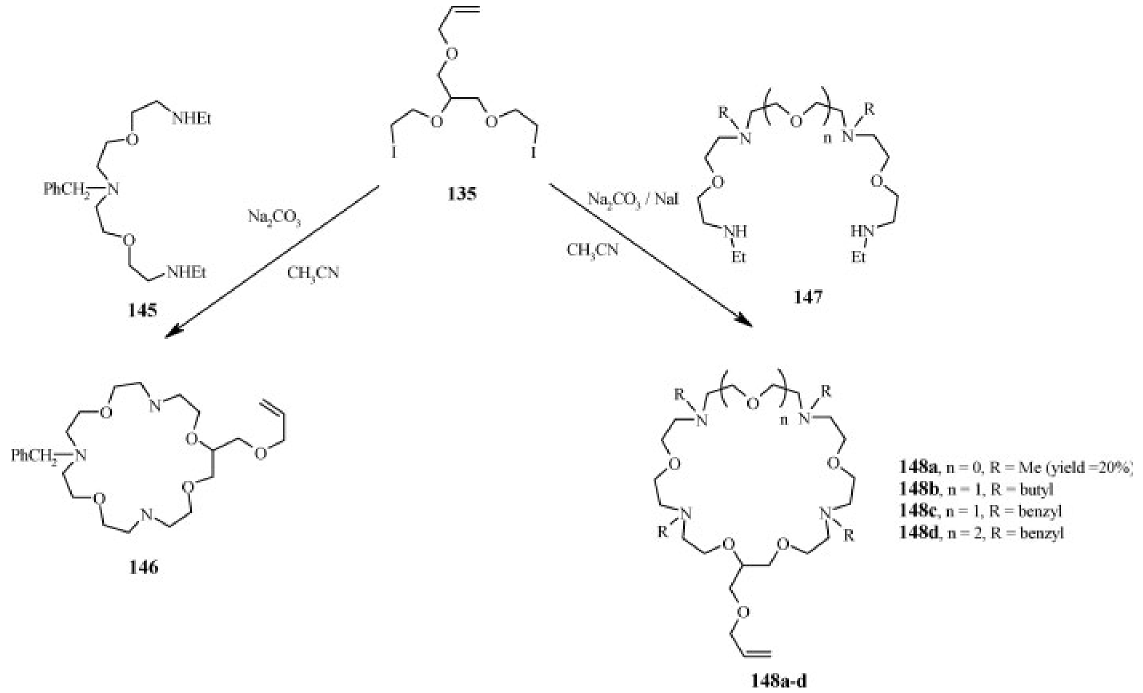
162

5.2.1.2. Photochemical addition of thioacetic acid to a methylene crown ether followed by reduction. Rasteller *et al*. [39] synthesized mercaptomethyl crown ether **164** by photochemical addition of thioacetic acid to **156** to give thioester **163** followed by cleavage of the thioester with $LiAlH_4$ (Scheme 29).

Scheme 25

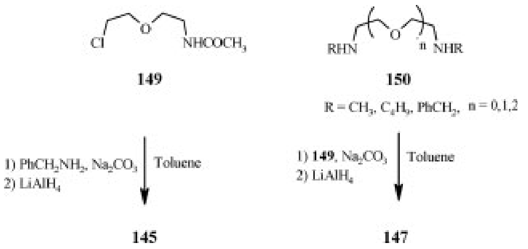


Scheme 26



5.2.1.3. Reaction of diols containing sidearm with the corresponding ditosylate compounds. Yoshihisa *et al.* [59] reported the synthesis of lariat ethers **166–169** having a sidearm attached to the 2-position of propane subunit to which was also attached a methyl group by reaction of the appropriate 1,3-propanediol **165** with the corresponding oligoethylene glycol ditosylates **36** and **48** in the presence of NaH as a base in THF (Scheme 30). The introduction of methyl group to the *C*-pivot remarkable improves the complexation ability toward alkali metal cations. As the methyl group is considered to work in restricting the movement of another substituent, this strategy should be also useful for chiral recognition of ammonium salts [25,60,61].

Scheme 27



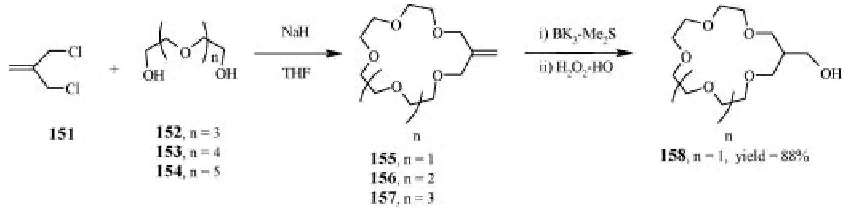
Lariat ethers **166** and **169** (R $= -CH_2-O-CH_2Ph$) underwent debenzylation upon treatment with Pd/C in EtOH to give the corresponding hydroxymethyl derivatives **170** and **171** [59].

Rasteller *et al.* [39] reported the synthesis of mercaptomethyl crown ether **174** by coupling of the diol **172** with triethylene glycol ditosylate followed by reduction and subsequent reaction with methylsulfonyl chloride to give **173**. Reaction of the latter with potassium thioacetate and subsequent reductive cleavage gave **174** (Scheme 31).

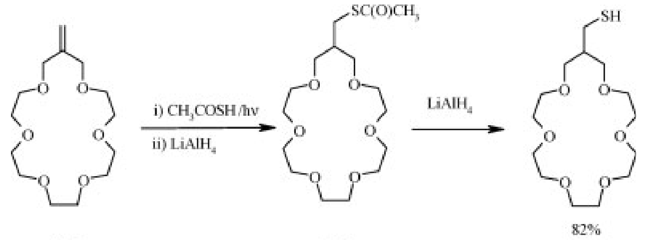
The diol **172** was obtained from multistep reactions starting from diethyl malonate [39].

Weber [62] and Hakushi *et al.* [63] reported the synthesis of lariat ethers with symmetrical double side arms attached through a carbon pivot. They prepared bis(hydroxymethyl) crown ethers **179–183** by reaction of monobenzalpentaerythritol [64] (**175**) with the appropriate oligoethylene glycol ditosylates **15**, **49**, **59**, **176**, and

Scheme 28



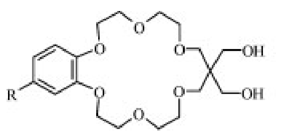
Scheme 29



156 **163** **164**

177 in the presence of NaH, NaOH, or KOH as a base in dioxane or THF, to give the corresponding spirocrown ethers **178** followed by acid hydrolysis (HCl/EtOH) or hydrogenolysis on treatment with H_2, Pd/C (Scheme 32).

Similarly were prepared the bis(hydroxymethyl)benzocrown ethers **184** and **185** from **175** and the appropriate ditosylate followed by acid hydrolysis [62].

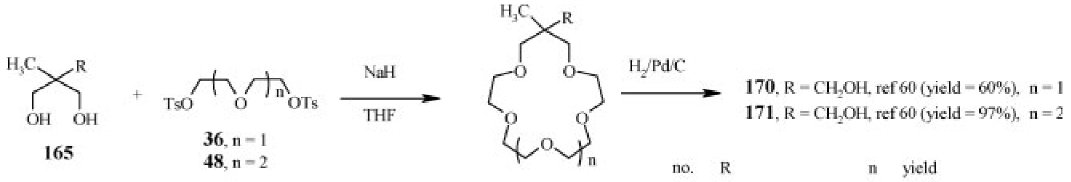


184, R = H, yield = 96%
185, R = CH$_3$, yield = 92%

Reaction of crown ether diols **180** and **181** with the corresponding oligoethylene glycol monoethyl ether tosylate or oligoethylene glycol tetrahydropyranyl ether in the presence of NaH in THF afforded the corresponding crown ether derivatives with double symmetrical oxyethylene side arms of various chain length (cf. Table 16) [59,62,63,65].

Lariat ethers **190–192** with nonsymmetrical double side arms were prepared from the spiro crown ethers **178** by initial reduction with $LiAlH_4/AlCl_3$ in diethyl ether to afford the hydroxymethyl derivatives **186** in 90 and 92% yields. The latter compounds were then reacted with the appropriate chloride **187** in the presence of NaH in THF to give the crown ether derivatives **188**

Scheme 30

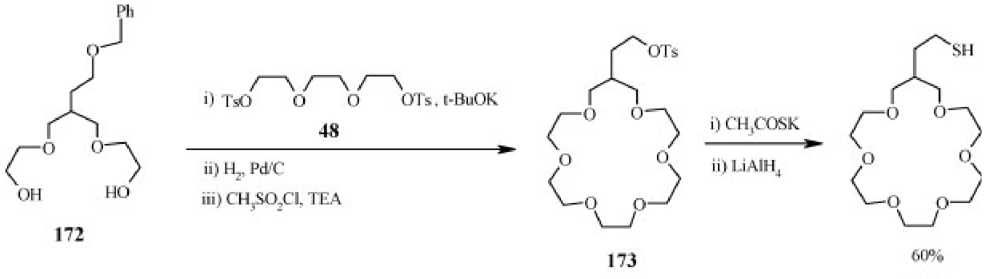


165 **36**, n = 1 **48**, n = 2 **166-169**

170, R = CH$_2$OH, ref 60 (yield = 60%), n = 1
171, R = CH$_2$OH, ref 60 (yield = 97%), n = 2

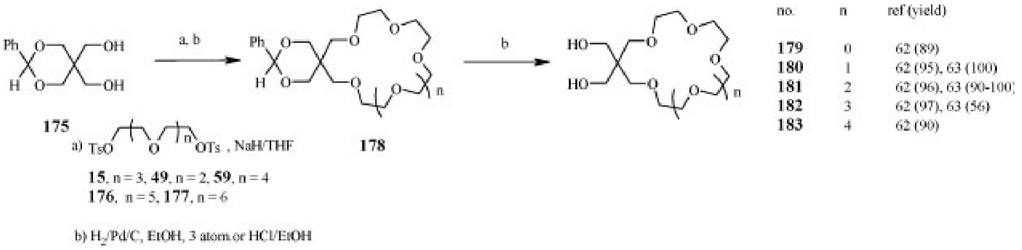
no.	R	n	yield
166	PhCH$_2$OCH$_2$	1	45%
167	CH$_3$O(CH$_2$)$_2$OCH$_2$	1	57%
168	CH$_3$	2	19%
169	PhCH$_2$OCH$_2$	2	48%

Scheme 31



172 **173** **174**

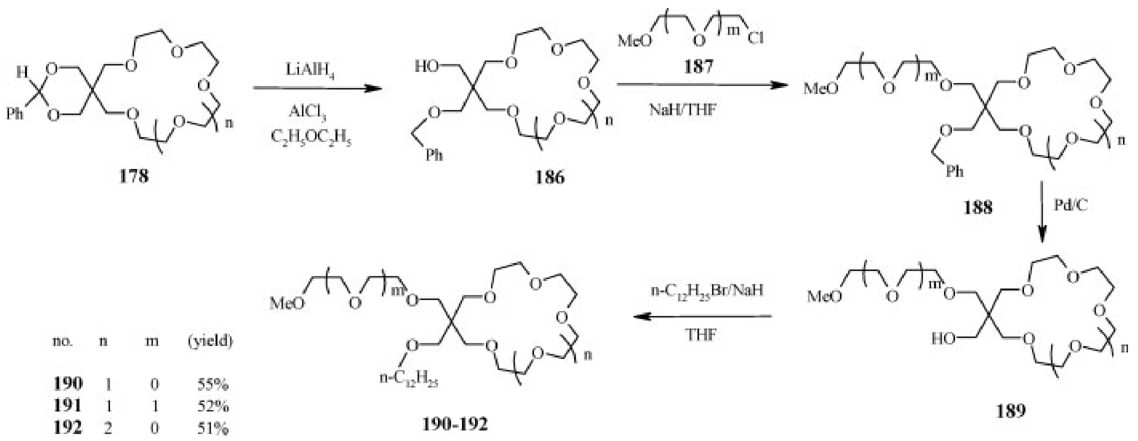
Scheme 32



175 **178**

no.	n	ref (yield)
179	0	62 (89)
180	1	62 (95), 63 (100)
181	2	62 (96), 63 (90-100)
182	3	62 (97), 63 (56)
183	4	62 (90)

Scheme 33



no.	n	m	(yield)
190	1	0	55%
191	1	1	52%
192	2	0	51%

with an oxyethylene chain and a benzyloxymethyl group in 39–47% yields. Hydrogenolysis yielded the corresponding hydroxymethyl crown ethers **189** in 89–95% yields. The latter compounds were then reacted with 1-bromodecane to give **190–192** in 51–55% yield (Scheme 33) [59].

5.2.1.4. Bromoalkoxylation of oligoethylene glycol mono-2-methylallyl ether with NBS and the appropriate alcohol followed by cyclization. Okahara and coworkers [48] prepared lariat crown ethers **195** and **196** having a sidearm in the 2-position to which was also attached a methyl group. Tetraethylene glycol is monosubstituted as its 2-methylpropenyl ether to give **193** and allowed to react with *N*-bromosuccinimide and Me(CH_2CH_2O)$_n$H to give the crown precursor **194** in which Me(CH_2CH_2O)$_n$H was incorporated as the incipient sidearm. The cyclization of **194** to **195** and **196** was accomplished on treatment with sodium *t*-butoxide in *t*-butanol (Scheme 34).

A 13-crown-4 version of these compounds was obtained by using triethylene glycol and lithium *t*-butoxide in *t*-butanol [66]. Other variants in ring size and pivot group were also reported by this group [47].

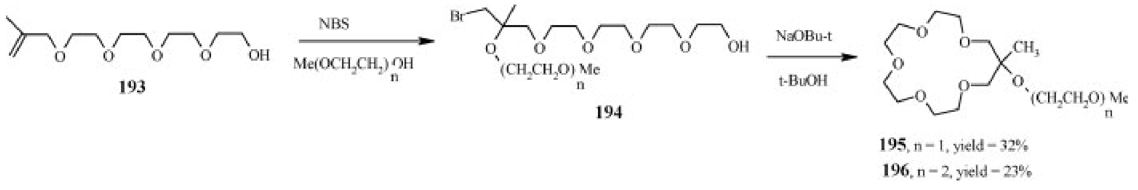
Considerable work has also been done by Inoue and coworkers with (3*n* + 1)-crown systems that incorporate the propene residue [67].

5.2.1.5. Bromoalkoxylation of methylenecrown ethers with NBS and the appropriate alcohol or glycol followed by nucleophilic displacement of the bromide. Ikeda *et al.* [68,69] reported the synthesis of two types of lariat ethers **202–210** and **215** derived from 3*n*-methylene-(3*n* + 1)-crown (*n* = 5, 6, 7) with different lengths of oxyethylene sidearm. These two types of *C*-pivot lariat ethers are different in basic skeleton around the pivot carbon, one type such as **202–210** directly connect the oxygen atom to the pivot carbon. The other type such as **215** contains one carbon atom between the pivot carbon and the oxygen atom.

Ligands **202–210** and **215** are structurally regarded to be derived from glycerol and trimethanol-methane, respectively. The difference in skeletal structure of the pivot position of these lariat ethers was found to remarkably affect their complexation properties. The lariat having a 2-methylglycerol structure around the pivot carbon showed much higher complexing ability than did the trimethylolmethane structure.

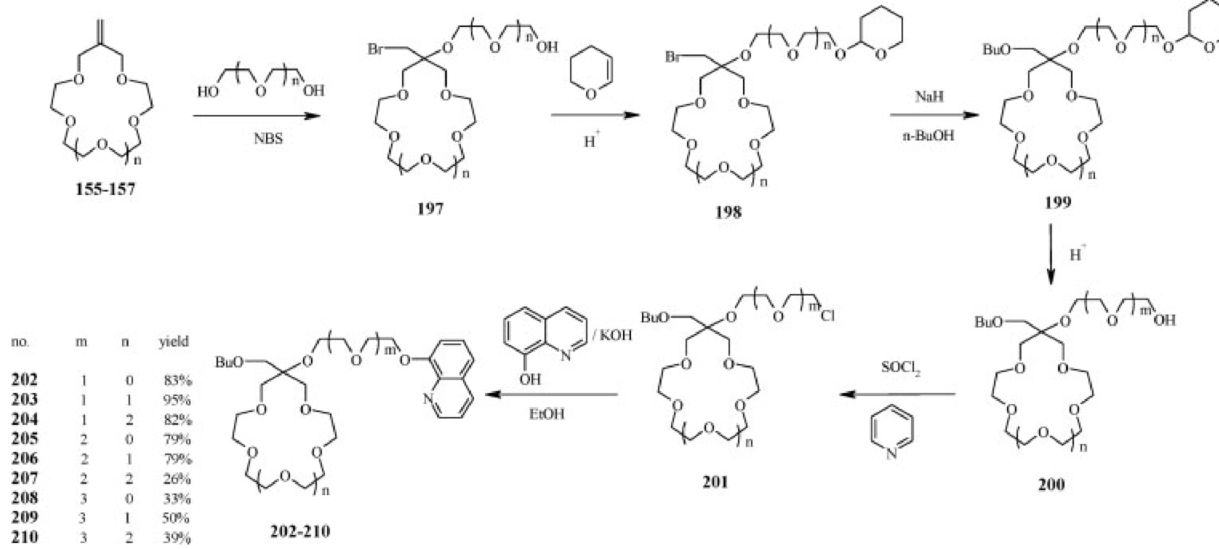
A series of lariat ethers containing a glycerol unit (compounds **202–210**) were designed to afford systematic structural variations of the crown ring size and the length of the oxyethylene sidearm. The 8-oxyquinoline moiety was introduced at the end of the sidearm of these lariat ethers because of its excellent coordination ability toward alkali metal cations [48]. The presence of the methyl group at the pivot position is expected to play an important role in increasing the complexation ability toward alkali metal cations [48,60,70]. The general synthetic procedures for compounds **202–210** are summarized in Scheme 35. Compounds **197** were obtained from the bromoalkoxylation of 3*n*-methylene-(3*n* + 1)-crown-

Scheme 34



195, n = 1, yield = 32%
196, n = 2, yield = 23%

Scheme 35

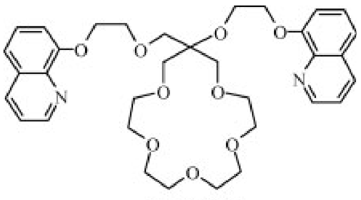


no.	m	n	yield
202	1	0	83%
203	1	1	95%
204	1	2	82%
205	2	0	79%
206	2	1	79%
207	2	2	26%
208	3	0	33%
209	3	1	50%
210	3	2	39%

n (*n* = 5, 6, 7) **155–157** [58] using *N*-bromosuccinimide (NBS) and oligoethylene glycols. The hydroxyl group of compounds **197** was protected by treatment with 3,4-dihydro-2*H*-pyran, according to the conventional method, to give the corresponding tetrahydropyranyl ethers **198**, which were then treated with sodium hydride and *n*-butyl alcohol to give the butoxymethyl derivatives **199**, followed by deprotection under acidic conditions to give butoxymethyl alcohols **200**. The chlorides **201** obtained from the chlorination of alcohols **200** by use of thionyl chloride were further treated with 8-hydroxyquinoline in ethanol in the presence of KOH at reflux temperature for 2 days [71] to give the corresponding lariat ethers **202–210** (Scheme 35).

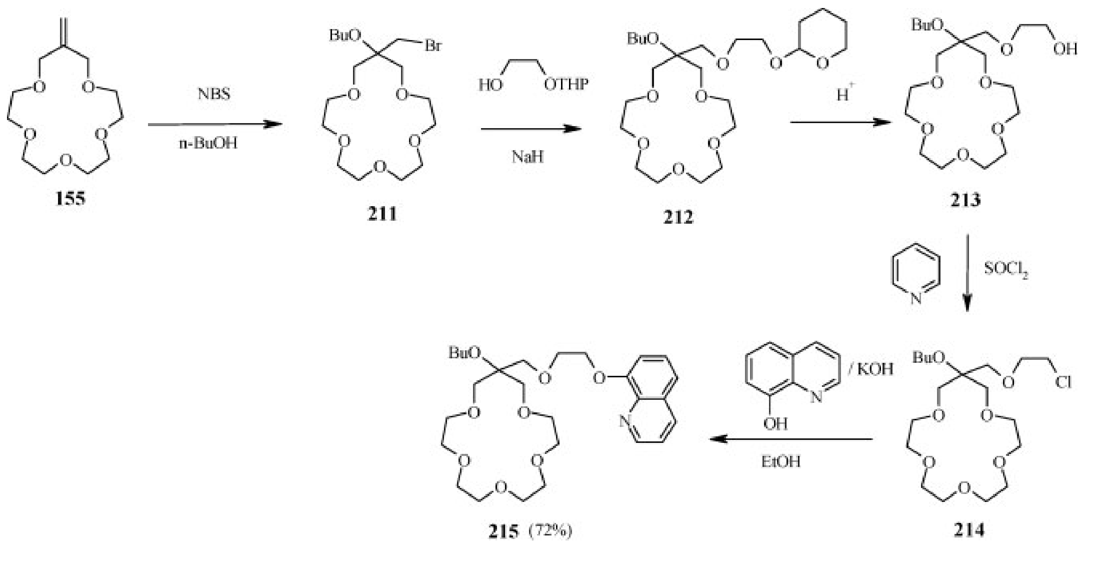
On the other hand, ligand **215** was prepared by changing the reaction sequence used in the case of lariat ethers **202–210**; that is, the bromoalkoxylation of 15-methylene-16-crown-5 (**155**) with NBS and *n*-butyl alcohol was performed as the first step as shown in Scheme 36.

The lariat ether **216**, with two oxyquinoline moieties, was also obtained from substrate **155** in a similar way.

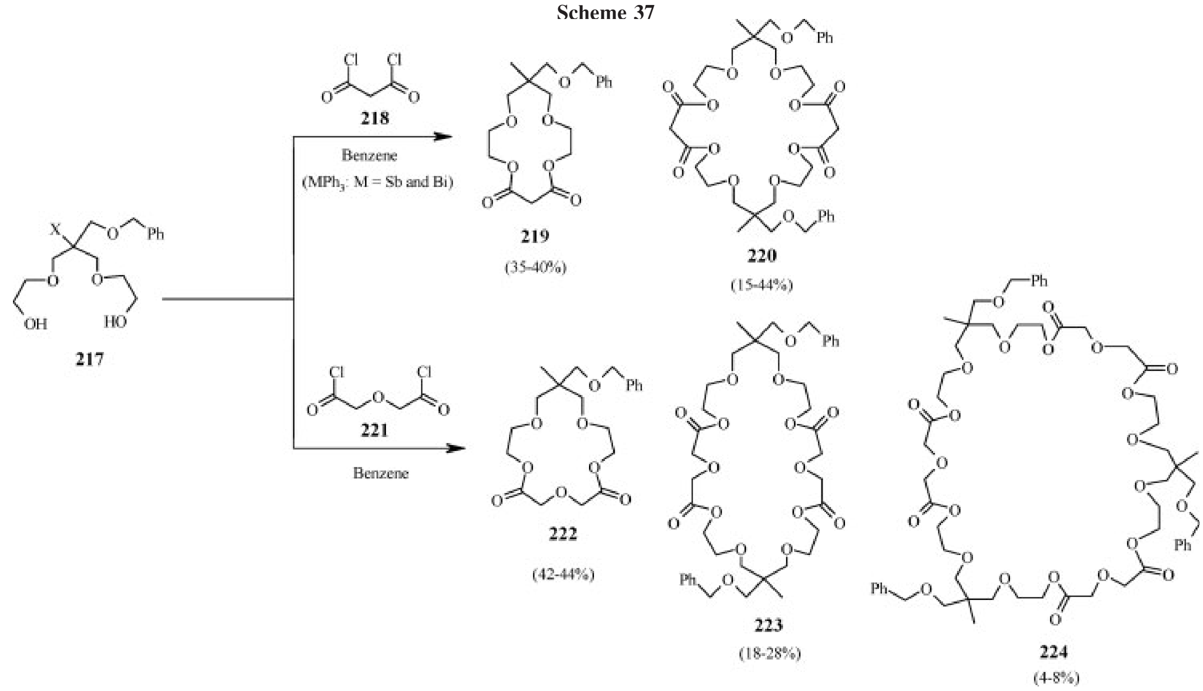


216 (74%)

Scheme 36



Scheme 37



5.2.1.6. Reaction of the appropriate diols with the corresponding diacid dichlorides. Habata *et al.* [72] reported the synthesis of benzyloxymethyl-substituted 14- and 16-membered crown ether ester **219** and **222** by treatment of diols **217** with the corresponding acid chlorides **218** and **221**, respectively, under high dilution condition using $SbPh_3$ and $BiPh_3$ as templates (Scheme 37). It was found that $SbPh_3$ and $BiPh_3$ are effective templates for the synthesis of 14-crown-4 ether ester. When **217** was treated with malonyl chloride, the dimer **220** was obtained together with the monomer **219**.

On the other hand, when diglycolyl chloride **221** was used the dimer **223** and the trimer **224** were obtained as cyclization products together with **222**.

5.2.1.7. Intramolecular cyclization of oligotrimethylene glycol monotosylates. Fredriksen *et al.* [73] reported the synthesis of 12-crown-3 ligands carrying methoxymethyl substituents in either one, two or all three of ring positions 3, 7, and 11.

They prepared 12-crown-3 ether **228** carrying methoxymethyl substituents in position 3 from diol **225** by initial reaction with one equivalent of tosyl chloride in pyridine to give the corresponding monotosylate **226**. Subsequent intramolecular cyclization of **226** in the presence of butyllithium and diisopropylamine **227** in DMF afforded **228** in 48% yield (Scheme 38).

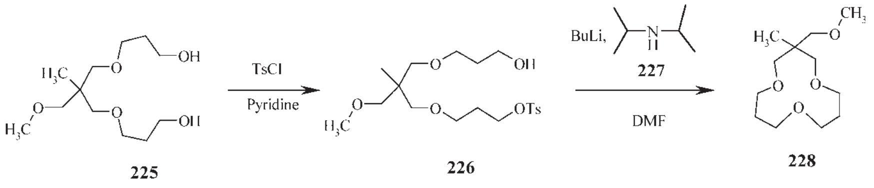
Diol **225** was prepared from the appropriate substituted 1,3-propanediol by double chain extension with acrylonitrile followed by ester formation and $LiAlH_4$ reduction.

The same authors reported the synthesis of **228** from diol **229** by initial reaction with tosyl chloride in pyridine to give the monotosylate **230** followed by intramolecular cyclization using *n*-BuLi in dry DMSO to give the spiro macrocycle **231**. Reduction of **231** with $LiAlH_4$ in dry monoglyme afforded 3-hydroxymethyl derivative **232** which then underwent alkylation with MeI/BuLi to give **228** (Scheme 39).

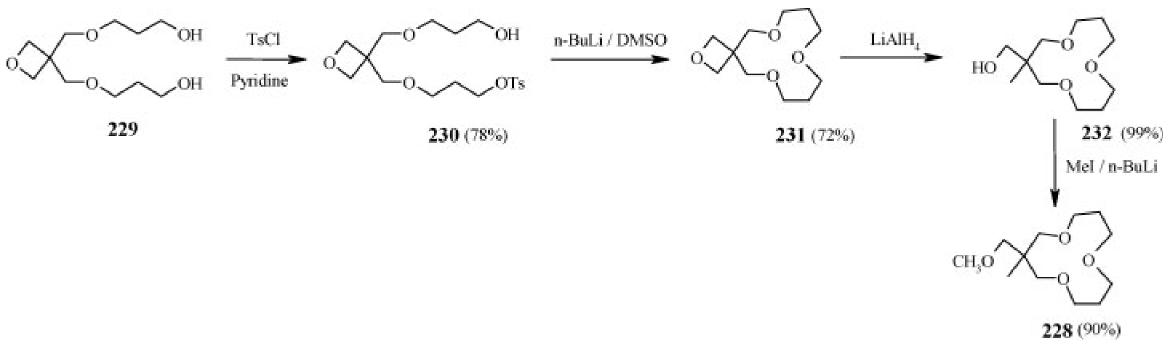
The diol **229** was obtained by the reaction of 3,3-bis(iodomethyl)oxetane with a monobenzyl derivative of 1,3-propanediol followed by removal of the protected-benzyl group using Pd/C in EtOH.

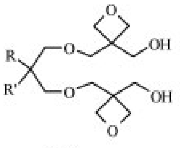
Using the same approach 12-crown-3 ethers carrying methoxymethyl substituent at positions 3, 7 **234a,b** and at positions 3, 7, 11 **234c** were prepared starting from diol **233**.

Scheme 38

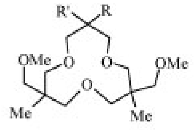


Scheme 39





233



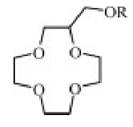
234a-c

234a, R = R' = H (yield = 91%, trans)
234b, R = R' = CH$_3$ (yield = 100%, trans)
234c, R = CH$_3$, R' = CH$_2$OMe (yield = 68%, trans)

5.2.1.8. Alkylation of hydroxymethylcrown ethers with the appropriate electrophiles. Crown ethers with hydroxymethyl sidearms are versatile intermediates in the synthesis of *C*-pivot lariat ethers. They may be used as nucleophiles and alkylated to form alkoxymethyl or phenoxymethylcrown compounds. The alkylation reactions were carried out using suitable basic solutions. The most common bases used are NaH in THF or K_2CO_3 in DMF [74–76].

Alkoxymethyl-substituted crown ethers have attracted considerable attention as synthons for more complex macrocycles and polymer-supported crown ethers. The more tedious problems in syntheses of these lariat ethers

Table 2



12-Crown-4

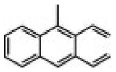
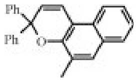
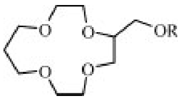
Comp. no.	R	Ref. (yield)
235		77 (73)
236		78 (70)

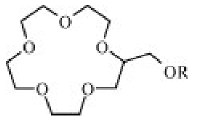
Table 3



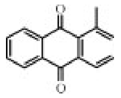
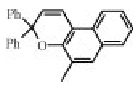
13-Crown-4

Comp. no.	R	Ref. (yield)
237	n-$C_{21}H_{25}$—CH(CO_2H)—	45 (27)

Table 4

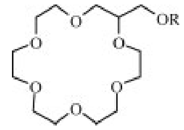


15-Crown-5

Comp. no.	R	Ref. (yield)
238	2-O_2N—C_6H_4-*o*—	79 (55), 80 (55)
239	2-H_2N—C_6H_4-*o*—	80 (90)
240		80 (29)
241[a]		80 (98)
242[b]	$CH_3(CH_2)_2C(O)$—	20 (62)
243[b]	$CH_3(CH_2)_{14}CO$—	20 (32)
244[b]	PhC(O)—	20 (80)
245[b]	4-CH_3O—C_6H_4—C(O)—	20 (74)
246[b]	4-O_2N—C_6H_4—C(O)—	20 (78)
247	$CH_3(CH_2)_3$—	20 (64)
248	$CH_3(CH_2)_{15}$—	20 (84)
249		81 (40)
250	$PhCH_2(OCH_2CH_2)_3$—	82 (68)
251[c]	$CH_3(OCH_2CH_2)_3$—	82 (70)
252		78 (69)
253	n-C_8H_{17}—	25 (64)
254	4-O_2N—C_6H_4—	79 (74)

[a] Compound **241** was obtained by reduction of **240** using H_2/Pd.
[b] Compounds **242–246** were prepared by acylation of the corresponding alcohol in CH_2Cl_2-pyridine.
[c] Compound **251** was obtained by debenzylation of **250** upon treatment with H_2/Pd and subsequent treatment with Me_2SO_4 in the presence of NaH in THF.

Table 5



18-Crown-6 (One side arm)

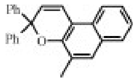
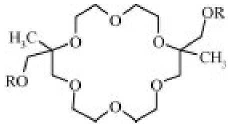
Comp. no.	R	Ref. (yield)
255		78 (83)
256	*n*-$C_{16}H_{33}$—	44 (92)

Table 6



18-Crown-6 (two side arms)

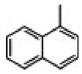
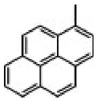
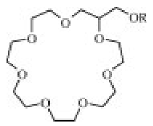
Comp. no.	R	Ref. (yield)
257	$CH_3C(O)$— (*S*,*S*)	61 (30)
258	 (*R*,*R*)	83 (–)
259	 (*R*,*R*)	83 (–)

Table 7

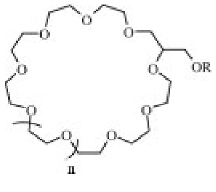


21-Crown-7

Comp. no.	R	Ref. (yield)
260	2-O_2N—C_6H_4-*o*—	80 (40)
261[a]	2-H_2N—C_6H_4-*o*—	80 (98)

[a] Compound **261** was obtained by reduction of **260** using H_2/Pd.

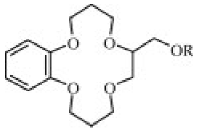
Table 8



27-Crown-9 and 30-Crown-10

Comp. no.	R	*n*	Ref. (yield)
262	*n*-$C_{21}H_{25}$—	1	42 (–)
263	*n*-$C_{21}H_{25}$—	2	42 (–)
264	*n*-$C_{21}H_{25}$—$CH(CO_2H)$—	1	29 (41)

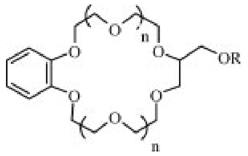
Table 9



Benzo-14-Crown-4

Comp. no.	R	Ref. (yield)
265	*n*-$C_{18}H_{17}$—$CH(CO_2H)$—	45 (47)

Table 10

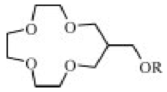


Benzo-12-Crown-4, Benzo-18-Crown-6, and Benzo-30-Crown-10

Comp. no.	R	*n*	Ref. (yield)
266	*n*-C_8H_{17}—$CH(CO_2H)$—	0	45 (63)
267[a]	$HO(O)CC(CH_2)_4$—	1	42 (–), 84 (60)
268[a]	$HO(O)CC(CH_2)_7$—	1	42 (–), 84 (46)
269[a]	$HO(O)CC(CH_2)_{10}$—	1	29 (41), 84 (47)
270	*n*-$C_{18}H_{17}$—$CH(CO_2H)$—	3	29 (56)

[a] Compounds **267–269** were prepared from the corresponding lariat ether alcohol by initial alkylation with the appropriate ester following by basic hydrolysis.

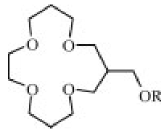
Table 11



13-Crown-4

Comp. no.	R	Ref. (yield)
271	$PhCH_2$—	33 (80)

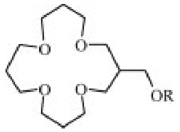
Table 12



15-Crown-4

Comp. no.	R	Ref. (yield)
272	$PhCH_2$—	33 (90)

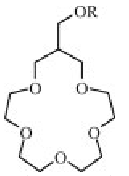
Table 13



16-Crown-4

Comp. no.	R	Ref. (yield)
273	$PhCH_2$—	33 (69)

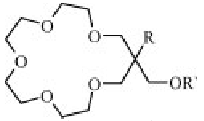
Table 14



16-Crown-5

Comp. no.	R	Ref. (yield)
274	$CH_3OCH_2CH_2$—	59 (85)

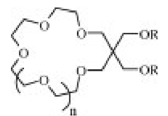
Table 15



16-Crown-5

Comp. no.	R	R′	Ref. (yield)
275	CH_3—	$CH_3(OCH_2CH_2)_2$—	59 (60)
276	CH_3—	n-$C_{21}H_{25}$—	59 (61)
277	$PhCH_2$—OCH_2—	$CH_3OCH_2CH_2$—	59 (44)
278	$PhCH_2$—OCH_2—	$CH_3(OCH_2CH_2)_2$—	59 (39)
279	n-$C_{21}H_{25}$—OCH_2—	$CH_3OCH_2CH_2$—	59 (55)
280	n-$C_{21}H_{25}$—OCH_2—	$CH_3(OCH_2CH_2)_2$—	59 (52)

Table 16

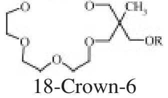


16-Crown-5 (two side arms)

Comp. no.	R	n	Ref. (yield)
281	CH_3—	1	63 (65)
282	n-C_8H_{17}—	1	63 (70)
283	$CH_3OCH_2CH_2$—	1	59 (75), 65 ([a])
284	$CH_3(OCH_2CH_2)_2$—	1	65 ([a]), 59 (75)
285	$CH_3(OCH_2CH_2)_4$—	1	65 ([a]), 59 (78)
286	$CH_3(OCH_2CH_2)_5$—	1	65 ([a]), 59 (75)
287	n-C_4H_9—OCH_2CH_2—	1	59 (72)
288	t-C_4H_9—OCH_2CH_2—	1	59 (60)
289	$HOCH_2CH_2$—	1	62 (87)
290	$H(OCH_2CH_2)_2$—	1	62 (79)
291	$H(OCH_2CH_2)_2$—	2	62 (79)

[a] Yields from 73–78% ref [65].

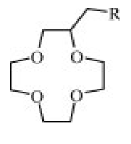
Table 17



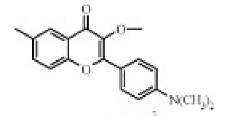
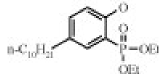
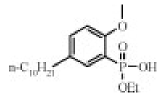
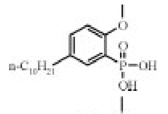
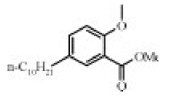
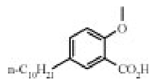
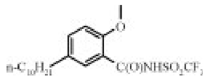
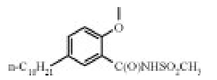
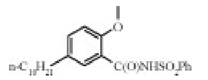
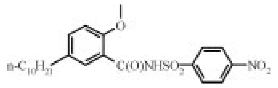
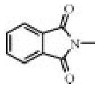
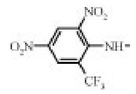
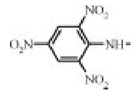
18-Crown-6

Comp. no.	R	Ref. (yield)
292	CH_3O—$(CH_2)_2$—	59 (64)
293	n-$C_{12}H_{25}$—	59 (74)
294	CH_3—$(OCH_2CH_2)_2$—	59 (–)

Table 18



12-Crown-4

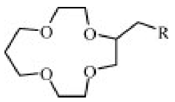
Comp. no.	R	Ref. (yield)
295		85 (0.12)
296		86 (61)
297		86 (93)
298		86 (54)
299		74 (58)
300		74 (83)
301[a]		20 (94)
302[a]		20 (44)
303[a]		20 (95)
304[a]		20 (90)
305		87 (88)
306[b]	H_2N—	87 (60)
307[c]		87 (60)
308[c]		87 (60)

[a] Compounds **301–304** were obtained from **300** by initial treatment with oxalyl chloride followed by reaction with the appropriate sulfonamide.

[b] Compound **306** was obtained from **305** by hydrazinolysis and subsequent acidification.

[c] Compounds **307** and **308** were obtained by the reaction of **306** with the appropriate chlorobenzene.

Table 19



13-Crown-4

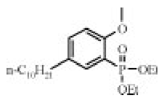
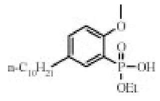
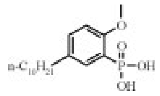
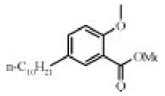
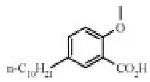
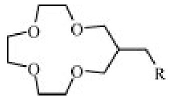
Comp. no.	R	Ref. (yield)
309		86 (40)
310		86 (91)
311		86 (66)
312		45 (–)
313		45 (92)

Table 20



13-Crown-4

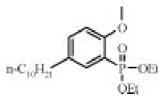
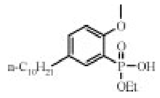
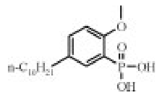
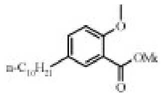
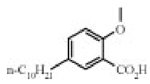
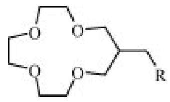
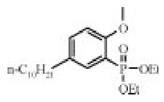
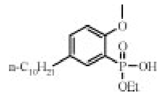
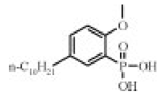
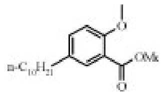
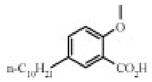
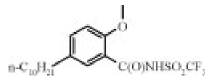
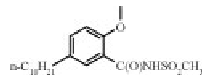
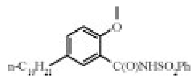
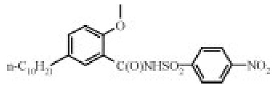
Comp. no.	R	Ref. (yield)
314		86 (40)
315		86 (91)
316		86 (66)
317		45 (–)
318		45 (54)

Table 21



14-Crown-4

Comp. no.	R	Ref. (yield)
319		86 (61)
320		86 (96)
321		86 (71)
322		45 (–)
323		45 (94)
324[a]		35 (84)
325[a]		35 (64)
326[a]		35 (72)
327[a]		35 (89)

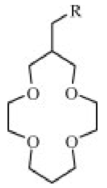
[a] Compounds **324–327** were obtained from **323** by initial treatment with oxalyl chloride followed by reaction with the appropriate sulfonamide.

by cyclization methods are preparation and isolation of the diol precursors [28].

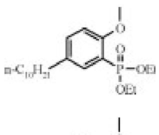
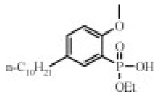
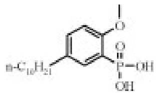
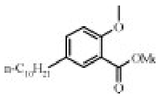
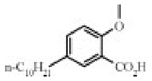
The following *C*-pivot lariat ethers are classified into 16 tables (Tables 2–17) according to the ring size of the macro ring as well as the attachment point of the side-arm. Some lariat ethers were obtained from their precursors by some other reactions as mentioned under the tables.

Compounds **18** and **22** mentioned in Scheme 5 were alternatively obtained in 68% [20] and 58% [59] yields, respectively, from the corresponding lariat ether alcohol on treatment with the appropriate halo compound.

Table 22



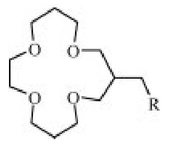
14-Crown-4

Comp. no.	R	Ref. (yield)
328		86 (43)
329		86 (90)
330		86 (49)
331		45 (–)
332		45 (90)

5.2.1.9. Nucleophilic displacement of tosyl groups from tosyloxymethylcrown ethers. Lariat ethers with hydroxymethyl sidearms may be tosylated to afford electrophilic precursors which can be converted into various lariat ethers by nucleophilic displacement of the tosyl group.

The following *C*-pivot lariat ethers are classified into 15 tables (Tables 18–32) according to the ring size of the macro ring as well as the attachment point of the sidearm. Some lariat ethers **297, 300, 310, 313, 315, 318, 320, 323,**

Table 23



15-Crown-4

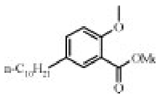
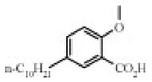
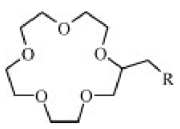
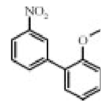
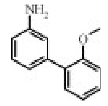
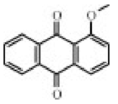
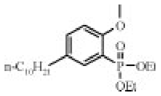
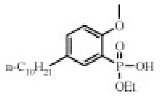
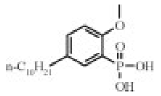
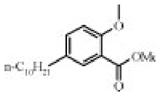
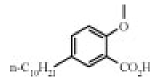
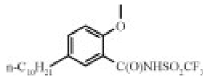
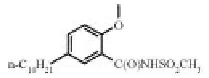
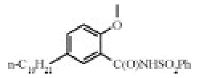
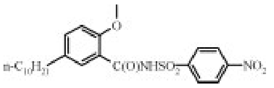
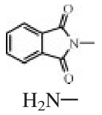
Comp. no.	R	Ref. (yield)
333		45 (–)
334		45 (86)

Table 24



15-Crown-5

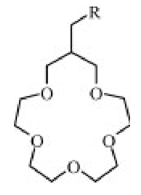
Comp. no.	R	Ref. (yield)
335		80 (61)
336[a]		80 (98)
337		81 (39)
338		86 (59)
339		86 (92)
340		86 (97)
341		74 (61)
342		74 (84)
343[b]		35 (65)
344[b]		35 (61)
345[b]		35 (84)
346[b]		35 (85)
347		87 (90)
348[c]	H_2N—	87 (87)

[a] Compound **336** was obtained by reduction of **335** using H_2/Pd.

[b] Compounds **343–346** were obtained from **342** by initial treatment with oxalyl chloride followed by reaction with the appropriate sulfonamide.

[c] Compound **348** was obtained from **347** by hydrazinolysis and subsequent acidification.

Table 25



16-Crown-5

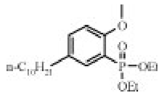
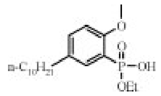
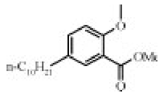
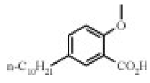
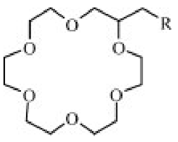
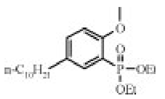
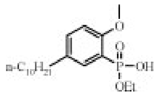
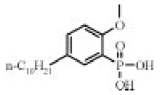
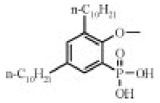
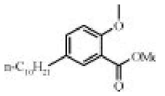
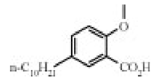
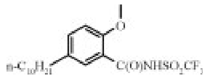
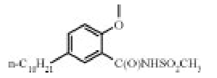
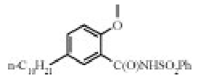
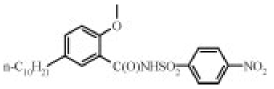
Comp. no.	R	Ref. (yield)
349		86 (35)
350		86 (61)
351		45 (–)
352		45 (91)

Table 26

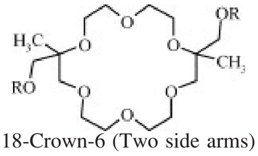


18-Crown-6 (One side arm)

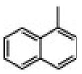
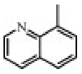
Comp. no.	R	Ref. (yield)
353		86 (71)
354		86 (69)
355		86 (96)
356		86 (90)
357		74 (68)
358		74 (81)
359[a]		74 (29)
360[a]		35 (86)
361[a]		35 (89)
362[a]		35 (92)

[a] Compounds **359–362** were obtained from **358** by initial treatment with oxalyl chloride followed by reaction with the appropriate sulfonamide.

Table 27



18-Crown-6 (Two side arms)

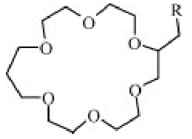
Comp. no.	R	Ref. (yield)
363	 (*S*,*S*)	61 (–)
364	 (*S*,*S*)	83 (–)

334, 339, 342, 350, 352, 354, 358, 366, 375, 377, 379, 381, 383, 386, 388, 390, and **393** in the following tables were obtained from their ester precursors by basic hydrolysis followed by acidification. Some other lariat derivatives **298**, **311**, **316**, **321**, **330**, **340**, **355**, **384,** and **391** were obtained from their ester precursors on treatment with Me_3SiBr at 100°C. Various lariat ethers in the following tables were obtained from their precursors by some other reactions as mentioned under the tables.

5.2.1.10. Nucleophilic displacement of bromide from bromomethylcrown ethers. Lariat ethers with bromomethyl sidearms can also be converted into various lariats by nucleophilic displacement of the bromide. The following *C*-pivot lariat ethers are classified into nine tables (Tables 33–41) according to the ring size of the macro ring as well as the attachment point of the sidearm.

5.2.2. Synthesis of lariat dibenzocrown ethers. Bartsch *et al.* [89] developed an approach to dibenzo lariat ethers in which the sidearm is attached to the C2 position of a propane subunit. They studied some structure variations within these series of lariat ethers with the goal of enhancing their selectivity for alkali metal cations as well as their extraction efficiency. These structure variations include crown ether cavity size, basicity of the oxygen atoms, substituents on the benzene rings, nature of the alkyl group (linear or branched) attached to the central carbon or to the sidearm, and the linkage, which joins the functional group

Table 28



19-Crown-6

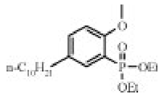
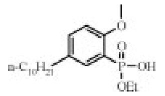
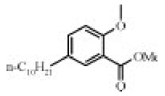
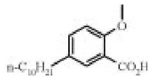
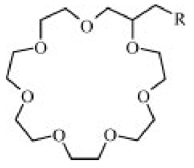
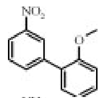
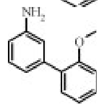
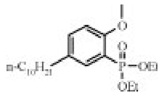
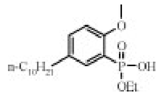
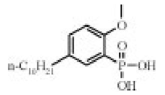
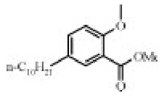
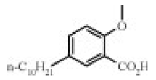
Comp. no.	R	Ref. (yield)
365		86 (73)
366		86 (93)
367		45 (–)
368		45 (94)

Table 29

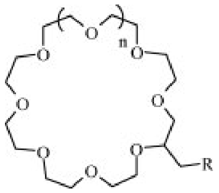


21-Crown-7

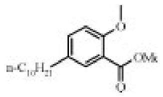
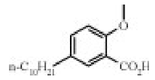
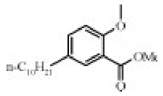
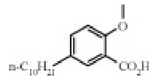
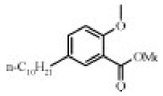
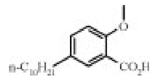
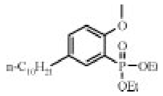
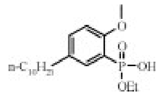
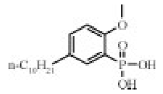
Comp. no.	R	Ref. (yield)
369		80 (53)
370[a]		80 (95)
371		80 (76)
372		86 (91)
373		86 (95)
374		74 (78)
375		74 (79)

[a] Compound **370** was obtained by reduction of **369** using H_2/Pd.

Table 30



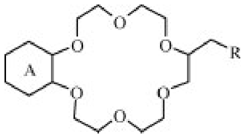
24-Crown-8, 27-Crown-9, and 30-Crown-10

Comp. no.	R	n	Ref. (yield)
376		1	45 (–)
377		1	45 (90)
378		2	45 (–)
379		2	45 (quant.)
380		3	45 (–)
381		3	45 (71)
382		1	86 (69)
383		1	86 (89)
384		1	86 (64)

of the sidearm to a common polyether ring. These series of lariat crown ethers are designed to provide systematic variations of some structural features while keeping the others unvaried. For example, in some cases, the crown ether cavity size is varied while holding the pendant arm constant. In others cases, the attachment site of the lipophilic group is varied while keeping the polyether ring and the linkage which join functional group on the sidearm and polyether portions invariant.

5.2.2.1. Synthesis of dibenzocrown ether alcohols. Bartsch *et al.* [89] reported the synthesis of dibenzocrown ether alcohols and studied their synthetic

Table 31



Cyclohexano-18-Crown-6 and Benzo-18-Crown-6

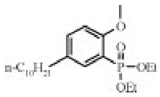
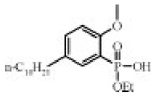
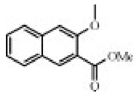
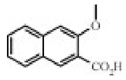
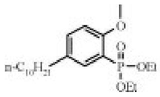
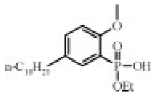
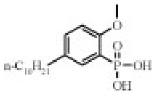
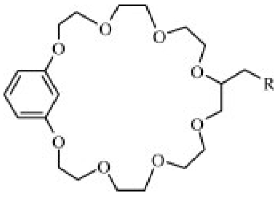
Comp. no.	A	R	Ref. (yield)
385	benzo		86 (50)
386	benzo		86 (98)
387	benzo		53 (–)
388	benzo		53 (58)
389	cyclohexano		86 (45)
390	cyclohexano		86 (96)
391	cyclohexano		86 (90)

Table 32



25-Crown-8

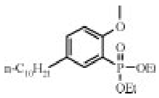
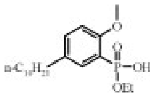
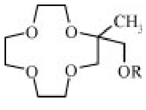
Comp. no.	R	Ref. (yield)
392		54 (74)
393		54 (96)

Table 33



14-Crown-4

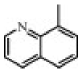
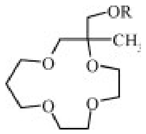
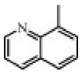
Comp. no.	R	Ref. (yield)
394		47 (56)
395	$CH_3OCH_2CH_2$—	47 (32)
396	$C_{10}H_{21}$—	47 (32)

Table 34



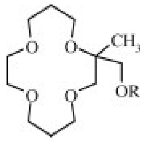
13-Crown-4

Comp. no.	R	Ref. (yield)
397		47 (35)
398	$CH_3OCH_2CH_2$—	47 (68)
399	$C_{10}H_{21}$—	47 (43)

utilities as key intermediates for the preparation of lariat ethers with pendant ether, carboxylic acid, ester, amide, amine, *etc*. groups.

5.2.2.1.1. Dibenzocrown ethers with a hydroxy group on the central carbon of the three carbon bridge. The approach developed by Bartsch *et al*. [89] involves reaction between epichlorohydrin **7** and a diol **456**. In the presence of base the diol presumably opens the epoxide, which recloses in the opposite sense. The remaining hydroxy group then attacks the newly formed epoxide to

Table 35



14-Crown-4

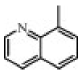
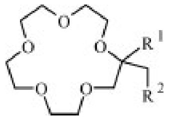
Comp. no.	R	Ref. (yield)
400		47 (31)

Table 36



15-Crown-5

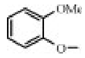
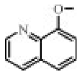
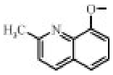
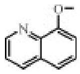
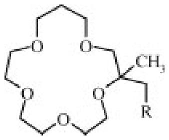
Comp. no.	R^1	R^2	Ref. (yield)
401	CH_3—	n-$C_6H_{13}O$—	60 (–), 25 (68)
402	CH_3—	n-$C_6H_{13}S$—	60 (–), 25 (82)
403	CH_3—	n-$C_6H_{13}NH$—	60 (–), 25 (94)
404	CH_3—	$CH_3OCH_2CH_2O$—	60 (–), 25 (82), 48 (–)
405	CH_3—	$CH_3(OCH_2CH_2)_2O$—	60 (–), 25 (88), 48 (60)
406	CH_3—	$CH_3(OCH_2CH_2)_3O$—	60 (–), 25 (80), 48 (64)
407	CH_3—		48 (74)
408	CH_3—		48 (81)
409	CH_3—		48 (71)
410	CH_3—		48 (63)
411	CH_3—		48 (76)
412	CH_3—	$CH_3OCH_2CH_2CH_2O$—	48 (57)
413	CH_3—	$HOCH_2CH_2O$—	48 (60)
414	CH_3—	$C_8H_{17}O$—	48 (71)
415	CH_3—	$C_8H_{17}OCH_2CH_2O$—	48 (86)
416	CH_3—	$C_8H_{17}O(CH_2CH_2O)_2$—	48 (70)
417	CH_3—	$C_{12}H_{25}O$—	48 (67)
418	CH_3—	$C_{12}H_{25}O(CH_2CH_2O)_2$—	48 (75)
419	C_6H_{13}—	$C_6H_{13}O$—	48 (72)
420	C_6H_{13}—	$CH_3OCH_2CH_2O$—	48 (87)
421	C_6H_{13}—	$CH_3O(CH_2CH_2O)_2$—	48 (78)
422	C_6H_{13}—	$CH_3O(CH_2CH_2O)_3$—	48 (70)
423	C_6H_{13}—	$C_8H_{17}O$—	48 (80)
424	C_6H_{13}—	$C_8H_{17}OCH_2CH_2O$—	48 (71)
425	C_6H_{13}—	$C_8H_{17}O(CH_2CH_2O)_2$—	48 (74)
426	C_6H_{13}—		48 (70)
427	C_8H_{17}—	$CH_3OCH_2CH_2O$—	48 (80)
428	C_8H_{17}—	$CH_3O(CH_2CH_2O)_2$—	48 (64)
429	C_8H_{17}—	$CH_3O(CH_2CH_2O)_3$—	48 (75)

Table 37



16-Crown-5 (3-Substituted isomer)

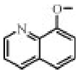
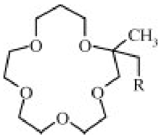
Comp. no.	R	Ref. (yield)
430	$CH_3OCH_2CH_2O$—	48 (68)
431	$CH_3O(CH_2CH_2O)_2$—	48 (83)
432		48 (56)

Table 38



16-Crown-5 (2-Substituted isomer)

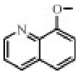
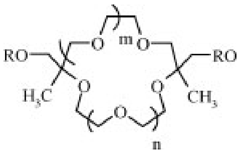
Comp. no.	R	Ref. (yield)
433	$CH_3OCH_2CH_2O$—	48 (70)
434	$CH_3O(CH_2CH_2O)_2$—	48 (83)
435		48 (65)

Table 39



15-Crown-5 (Two sidearms)

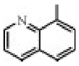
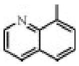
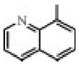
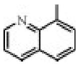
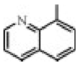
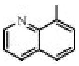
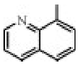
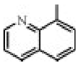
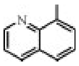
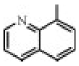
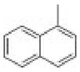
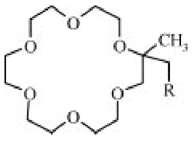
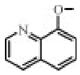
Comp. no.	R	m	n	Ref. (yield)
436	$CH_3OCH_2CH_2$—	0	2	52 (quantitavely)
437	$CH_3OCH_2CH_2$—	1	1	52 (quantitavely)
438		0	2	88 (–) cis
439		0	2	88 (–) trans
440		0	2	51 (43) cis
441		0	2	51 (55) trans
442		1	1	88 (–) cis
443		1	1	88 (–) trans
444		1	1	51 (81) cis
445		1	1	51 (29) trans
446		2	0	51 (38) cis
447		2	0	51 (49) trans
448		1	1	51 (58) cis

Table 40



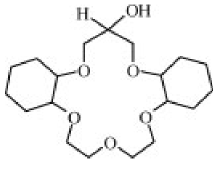
18-Crown-6

Comp. no.	R	Ref. (yield)
449	$C_6H_{13}O—$	48 (60)
450	$C_6H_{13}S—$	48 (61)
451	$C_6H_{13}NH—$	48 (84)
452	$CH_3OCH_2CH_2O—$	48 (88)
453	$CH_3O(CH_2CH_2O)_2—$	48 (78)
454	$CH_3O(CH_2CH_2O)_3—$	48 (72)
455		48 (62)

afford 1,3-disubstituted glycerol derivative **457** in which the 2-hydroxy group is free. An example of this cyclization is shown in Scheme 40.

In this reaction, the alkali hydroxide metal cation was varied to take advantage of the template effect [30,75]. Using this approach, lariat ether alcohols with different cavity sizes and different ring substituents **458–467** (Table 42) have been prepared [75,90–92]. Lariat ether alcohol (R = $C(CH_3)_3$) with *t*-butyl groups attached to the aromatic rings of dibenzocrown ethers was synthesized by reaction of lariat ether alcohol **457** with *tert*-butyl alcohol and 85% phosphoric acid at 100–110°C [92]. Lariat ether alcohol with nitro groups on its benzene rings **466** was obtained by reaction of **457** with nitric acid in acetic acid-chloroform-water. Reduction of **466** to the corresponding diamino derivative **467** was achieved by treatment with hydrazine hydrate over Pd/C as the hydrogen source in ethanol [92].

High-pressure catalytic hydrogenation of *sym*-hydroxydibenzo-16-crown-5 **457** produced the corresponding saturated crown ether alcohol **468** in good yield [75].



468 (50%)

Fuji *et al*. [93] reported the synthesis of binaphthyl crown receptors **470** with pendant hydroxyl group in 30% yield by the reaction of (S)-binaphthol **469** with 2-(2-chloroethoxy)ethanol in the presence of K_2CO_3 and KI, followed by cyclization with epichlorohydrin in the presence of tetrafluoroborate as a template (Scheme 41).

Bartsch *et al*. [92] reported the synthesis of lariat ether **472** with geminal methyl group on the central carbon of the propane subunit by reaction of the

Scheme 40

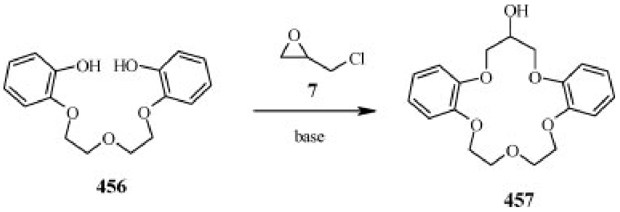
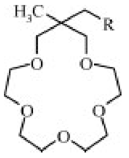


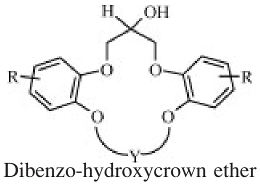
Table 41



16-Crown-5

Comp. no.	R′	Ref. (yield)
167	$CH_3OCH_2CH_2O—$	48 (32)
275	$CH_3O(CH_2CH_2O)_2—$	48 (23)

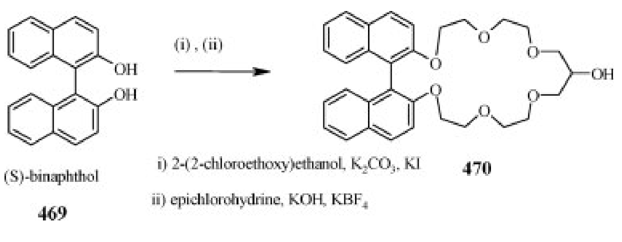
Table 42



Dibenzo-hydroxycrown ether

Comp. no.	R	Y	Ref. (yield)
458	H	$—(CH_2)_2—$	90 (50)
459	H	$—(CH_2)_3—$	75 (51)
460	H	$—CH_2(CH_2OCH_2)_2CH_2—$	75 (39)
461	H	$—CH_2(CH_2OCH_2)_3CH_2—$	75 (35)
462	H	$—CH_2CH(OH)CH_2—$	90 (55)
463	H	$—CH_2C(O)NH(CH_2)_2NHC(O)CH_2—$	90 (–)
464	F	$—(CH_2)_2O(CH_2)_2—$	91 (33)
465	$C(CH_3)_3$	$—(CH_2)_2O(CH_2)_2—$	92 (93)
466	NO_2	$—(CH_2)_2O(CH_2)_2—$	92 (100)
467	NH_2	$—(CH_2)_2O(CH_2)_2—$	92 (50)

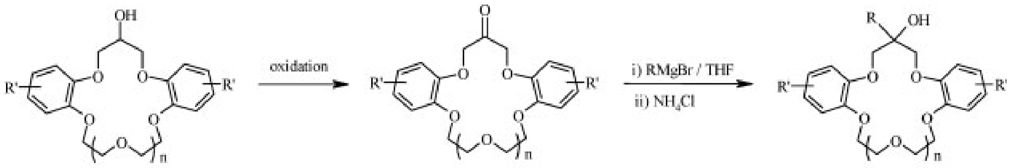
Scheme 41



i) 2-(2-chloroethoxy)ethanol, K_2CO_3, KI

ii) epichlorohydrine, KOH, KBF_4

Scheme 42

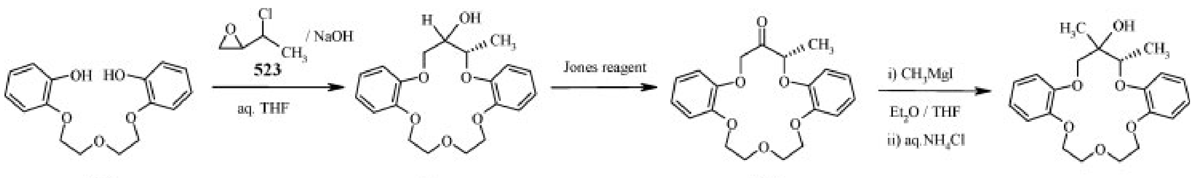


457, R' = H, n = 1
460, R' = H, n = 2
465, R' = $(CH_3)_3C$, n = 1

473

474-522

Scheme 43



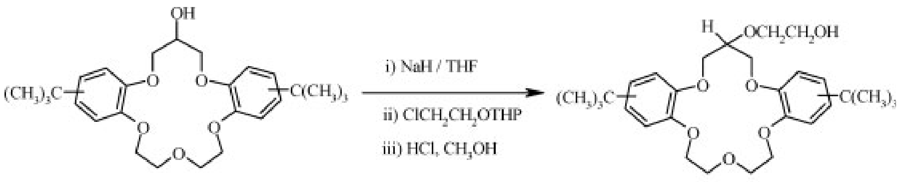
456

524

525

526

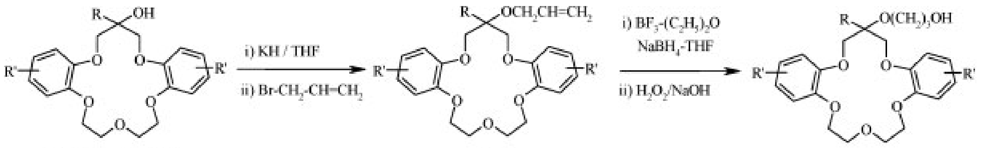
Scheme 44



465

527 (96%)

Scheme 45

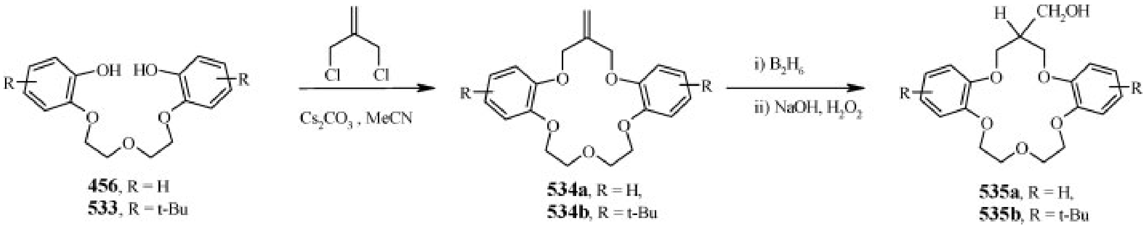


no.	R	R'	yield
529	H	H	26%
530	H	$C(CH_3)_3$	97%
531	CH_3	H	53%
532	$C_{10}H_{21}$	H	91%

457, R = H, R' = H
465, R = H, R' = $(CH_3)_3C$
474, R = CH_3, R' = H
487, R = $C_{10}H_{21}$, R' = H

528

Scheme 46

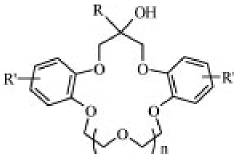


456, R = H
533, R = t-Bu

534a, R = H,
534b, R = t-Bu

535a, R = H,
535b, R = t-Bu

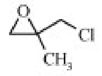
Table 43



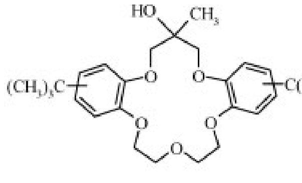
15-Crown-5,18-crown-6

Comp. no.	R′	R	*n*	Ref. (yield)
474	H	CH_3—	1	92 (92)
475	H	C_2H_5—	1	92 (89)
476	H	C_3H_7—	1	92 (84)
477	H	$(CH_3)_2CH$—	1	92 (88)
478	H	C_4H_9—	1	75 (90)
479	H	C_5H_{11}—	1	92 (84)
480	H	$(CH_3)_3CCH_2$—	1	92 (29)
481	H	C_6H_{13}—	1	92 (88)
482	H	c-C_6H_{11}—	1	94 (74)
483	H	C_7H_{15}—	1	92 (89)
484	H	C_8H_{17}—	1	75 (91)
485	H	$C_4H_9CH(C_2H_5)CH_2$—	1	92 (71)
486	H	C_9H_{19}—	1	92 (92)
487	H	$C_{10}H_{21}$—	1	94 (90)
488	H	$C_{11}H_{23}$—	1	92 (97)
489	H	$C_{12}H_{25}$—	1	92 (77)
790	H	$C_{13}H_{27}$—	1	92 (96)
491	H	$C_{14}H_{29}$—	1	75 (79)
492	H	$C_{15}H_{31}$—	1	92 (95)
493	H	$C_{16}H_{33}$—	1	92 (75)
494	H	$C_{18}H_{37}$—	1	94 (89)
495	H	$C_{20}H_{41}$—	1	92 (70)
496	H	Ph—	1	94 (90), 91 (48)
497	H	2-$(CH_3)C_6H_4$—	1	92 (87)
498	H	3-$(CH_3)C_6H_4$—	1	92 (78)
499	H	4-$(CH_3)C_6H_4$—	1	92 (80)
500	H	3,5-$(CH_3)_2C_6H_3$—	1	92 (89)
501	H	4-$(CH_2{=}CH)C_6H_4$—	1	92 (90)
502	H	4-$(CH_2{=}C(CH_3)C_6H_4$—	1	92 (73)
503	H	$PhCH_2CH_2$—	1	92 (92)
504	H	$Ph(CH_2)_3$—	1	92 (95)
505	H	$Ph(CH_2)_4$—	1	92 (81)
506	H	$Ph(CH_2)_5$—	1	92 (97)
507	H	$CH{=}C(CH_3)_2$—	1	92 (86)
508	H	$CH_2{=}CH(CH_2)_8$—	1	92 (56)
509	H	$CH_3(CH_2)_3C{\equiv}C$—	1	92 (96)
510	H	$CH_3(CH_2)_5C{\equiv}C$—	1	92 (94)
511	H	$CH_3(CH_2)_7C{\equiv}C$—	1	92 (94)
512	H	$CH_3(CH_2)_9C{\equiv}C$—	1	92 (96)
513	H	$CH_3(CH_2)_{11}C{\equiv}C$—	1	92 (95)
514	H	C_3F_7—	1	92 (60)
515	H	C_6F_{13}—	1	92 (28)
516	H	C_8F_{17}—	1	92 (33)
517	H	C_6F_5—	1	91 (48)
518	H	2-$(CF_3)C_6H_4$—	1	92 (90)
519	H	3-$(CF_3)C_6H_4$—	1	91 (75)
520	H	3,5-$(CF_3)_2C_6H_3$—	1	91 (68)
521	$(CH_3)_3C$—	C_3H_7—	1	92 (53)
522	H	*n*-C_8H_{17}—	2	75 (74)

appropriate bisphenol with 2-methyl-2-chloromethyloxirane **471** in THF in the presence of NaH.



471



472 (64%)

The preparation of lariat ether tertiary alcohols **474–522** (Table 43) with (R = alkyl, alkenyl, alkynyl, aryl, aralkyl) was alternatively obtained using another strategy as depicted in Scheme 42 [75,91,92,94]. Thus, Jones oxidation or Swern oxidation of the appropriate lariat ether alcohol **457, 460,** and **465** gave the corresponding ketone **473**. Subsequent reaction of **473** with the appropriate Grignard reagent produced the corresponding lariat ether tertiary alcohols.

Kim *et al.* [95] reported the synthesis of lariat ether alcohol **526** with a second methyl group attached to a terminal carbon of the three-carbon bridge by initial cyclization of the bisphenol **456** with epoxide **523** and NaOH in THF-water to give the asymmetric crown ether alcohol **524** in an 31% yield. Oxidation of the latter compound with Jones reagent provided crown ether ketone **525** in 74% yield. Grignard reaction of **525** with methylmagnesium iodide gave the target **526** in an 87% yield (Scheme 43).

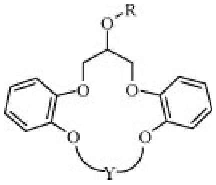
5.2.2.1.2. Dibenzocrown ethers with $O(CH_2)_nOH$ groups on the central carbon of the three carbon bridge. Lariat ether alcohol **527** with a —$O(CH_2)_2$—OH sidearm and a *tert*-butyl group on each benzene ring was prepared by addition of tetrahydropyranyl-protected ethylene chlorohydrin to the sodium alkoxide of lariat ether alcohol **465** followed by removal of the THP group with 10% HCl-methanol (Scheme 44) [92,96].

The synthesis of lariat ether alcohols **529–532** which have a —$O(CH_2)_3$—OH sidearm was accomplished by the addition of allyl bromide to the alkoxide of the appropriate lariat ether alcohol to give the corresponding allyloxycrown ethers **528** followed by hydroboration-oxidation (Scheme 45).

5.2.2.1.3. Dibenzocrown ethers in which one carbon atom mediates between the pivot carbon and the hydroxy group. Hydroxymethyl lariat ethers **535a,b** were synthesized as outlined in Scheme 46 [58,97]. Vinylidene dibenzo-crown ethers **534a,b** were prepared in 72–74% yield by cyclization of bisphenols **456** and **533** with methallyl dichloride and cesium carbonate in acetonitrile. Subsequent hydroboration with borane-THF complex, followed by oxidation with H_2O_2 and basic hydrolysis gave **535a,b** in 60 and 45% yields, respectively.

5.2.2.2. Synthesis of dibenzocrown ethers with a pendant ether groups from the corresponding lariat ethers alcohols. Reaction of lariat ethers alcohols with NaH

Table 44



15-Crown-5

Comp. no.	R	Y	Ref. (yield)
536	$CH_3OCH_2CH_2$—	—$CH_2CH_2OCH_2CH_2$—	99 (85), 98 (85)
537	$CH_2{=}CHCH_2CH_2$—	—$CH_2CH_2OCH_2CH_2$—	99 (35)
538	4-$CH_3OC_6H_4CH_2$—	—$CH_2CH_2OCH_2CH_2$—	100 (81)
539	3-$CH_3OC_6H_4CH_2$—	—$CH_2CH_2OCH_2CH_2$—	100 (80)
540	2-$CH_3OC_6H_4CH_2$—	—$CH_2CH_2OCH_2CH_2$—	100 (80)
541	$PhOCH_2CH_2CH_2$—	—$CH_2CH_2OCH_2CH_2$—	100 (50)
542	3-$CH_3C_6H_4SO_2$—	—$CH_2CH_2OCH_2CH_2$—	100 (80)
543	3,5-$(CH_3O)_2C_6H_3CH_2$—	—$CH_2CH_2OCH_2CH_2$—	100 (80)
544	$HOC(O)CH_2$—	—CH_2CH_2—	89 (76)
545	$HOC(O)CH_2$—	—$CH_2CH_2CH_2$—	89 (80)
546	$HOC(O)CH_2$—	—$CH_2CH_2OCH_2CH_2$—	89 (82)
547	$HOC(O)CH_2$—	—$CH_2(CH_2OCH_2)_2CH_2$—	89 (66)
548	$HOC(O)CH(Et)$—	—$CH_2CH_2OCH_2CH_2$—	89 (40)
549	$HOC(O)CH((CH_2)_3CH_3)$—	—$CH_2CH_2OCH_2CH_2$—	89 (40)
550	$HOC(O)CH((CH_2)_5CH_3)$—	—$CH_2CH_2OCH_2CH_2$—	89 (23)
551	$EtOC(O)(CH_2)_3CH_2$—	—$CH_2CH_2OCH_2CH_2$—	89 (76)
552[a]	$HOC(O)(CH_2)_3CH_2$—	-$CH_2CH_2OCH_2CH_2$—	89 (91)
553	$CH_2{=}CHCH_2$—	—$CH_2CH_2OCH_2CH_2$—	89 (95)
554	$HO(CH_2)_2CH_2$—	—$CH_2CH_2OCH_2CH_2$—	89 (81)
555[b]	$HOC(O)CH_2CH_2$—	—$CH_2CH_2OCH_2CH_2$—	89 (6)

[a] Compound **552** was prepared from **551** by hydrolysis using NaOH/EtOH.

[b] Compound **555** was prepared from **554** by oxidation.

and the appropriate haloalkane in THF gave the corresponding dibenzocrown ethers with pendant ether groups **536–555** (Table 44) [89,98–100].

Lariat ethers **557** was prepared in 18% yield from compound **470** on treatment with the mesylate **556** in the presence of NaH followed by deprotection of the methoxymethyl group under acidic conditions (Scheme 47) [93].

5.2.2.3. Synthesis of dibenzocrown ethers with a pendant carboxylic acid group from the corresponding ethers alcohols. 5.2.2.3.1. Synthesis of dibenzocrown ether oxyacetic acid. Two approaches have been reported for the synthesis of this class of compounds (cf. compounds **558–620**, Table 45). The first approach involves initial formation of methyl ester from the corresponding lariat ether alcohol upon treatment with NaH and methyl bromoacetate in THF followed by basic hydrolysis and subsequent acidification [75,89,101].

In the second approach, the crown ether carboxylic acid were prepared in one step by reaction of the corresponding alcohol with NaH and bromoacetic acid in THF [89].

Using both approaches, Bartsch *et al.* [75,89,94,97,101–104] reported the synthesis of

Scheme 47

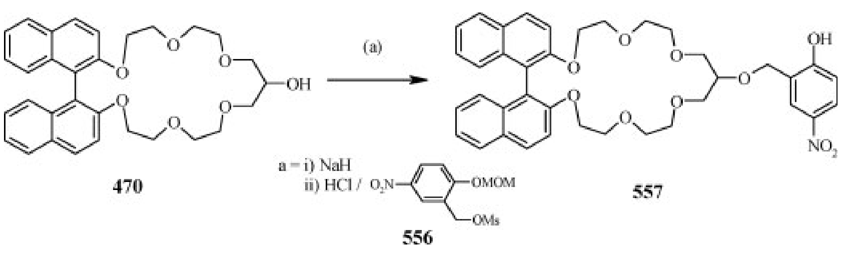
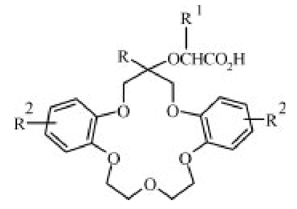


Table 45



Dibenzo-15-crown-5 with pendant oxyacetic acid derivatives

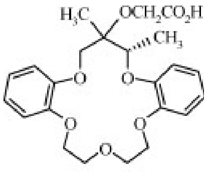
Comp. no.	R	R^1	R^2	Ref. (yield)
558	H	$C_{10}H_{21}$—	H	97 (80)
559	H	$C_{12}H_{25}$—	H	97 (66)
560	H	$C_{14}H_{29}$—	H	97 (70)
561	H	$C_{16}H_{33}$—	H	97 (64)
562	CH_3-	C_8H_{17}—	H	97 (48)
563	Ph—	Ph—	H	97 (97)
564	$C_{10}H_{21}$—	Ph—	H	97 (86)
565	CH_3—	H	H	97 (84)
566	C_2H_5—	H	H	97 (69)
567	C_3H_7—	H	H	97 (62)
568	$(CH_3)_2CH$—	H	H	97 (88)
569	C_3F_7—	H	H	97 (71)
570	C_4H_9—	H	H	97 (55)
571	C_5H_{11}—	H	H	97 (79)
572	$(CH_3)_2CCH_2$—	H	H	97 (76)
573	c-C_6H_{11}—	H	H	97 (26)
574	C_6H_{13}—	H	H	97 (88)
575	C_6F_{13}—	H	H	97 (93)
576	C_7H_{15}—	H	H	97 (79)
577	C_8H_{17}—	H	H	97 (90)
578	C_8H_{17}—	H	H	97 (87)
579	$CH_3(CH_2)_3CH(C_2H_5)CH_2$—	H	H	97 (58)
580	C_9H_{19}—	H	H	97 (98)
581	$C_{10}H_{21}$—	H	H	97 (57)
582	$C_{11}H_{23}$—	H	H	97 (78)
583	$C_{12}H_{25}$—	H	H	97 (92)
584	$C_{13}H_{27}$—	H	H	97 (55)
585	$C_{14}H_{29}$—	H	H	97 (72)
586	$C_{15}H_{31}$—	H	H	97 (81)
587	$C_{16}H_{33}$—	H	H	97 (85)
588	$C_{18}H_{37}$—	H	H	97 (84)
589	$C_{20}H_{41}$—	H	H	97 (92)
590	$PhCH_2CH_2$—	H	H	97 (75)
591	$Ph(CH_2)_3$—	H	H	97 (68)
592	$Ph(CH_2)_4$—	H	H	97 (53)
593	$Ph(CH_2)_5$—	H	H	97 (63)
594	Ph—	H	H	97 (76)
595	2-CH_3—C_6H_4—	H	H	97 (67)
596	3-CH_3—C_6H_4—	H	H	97 (87)
597	4-CH_3—C_6H_4—	H	H	97 (82)
598	3-CF_3—C_6H_4—	H	H	97 (89)
599	4-$(CH_2{=}CH)C_6H_4$—	H	H	97 (90)
600	4-$(CH_2{=}C(CH_3)C_6H_4$—	H	H	97 (80)
601	3,5-$(CH_3)_2C_6H_3$—	H	H	97 (72)
602	3,5-$(CF_3)_2C_6H_3$—	H	H	97 (96)
603	$(CH_3)_2C{=}CH$—	H	H	97 (92)
604	$CH_2{=}CH(CH_2)_6$—	H	H	97 (92)
605	$CH_2{=}CH(CH_2)_8$—	H	H	97 (97)
606	$CH_3(CH_2)_3C\equiv C$—	H	H	97 (94)
607	$CH_3(CH_2)_5C\equiv C$—	H	H	97 (85)
608	$CH_3(CH_2)_7C\equiv C$—	H	H	97 (84)
609	$CH_3(CH_2)_9C\equiv C$—	H	H	97 (88)
610	$CH_3(CH_2)_{11}C\equiv C$—	H	H	97 (86)
611	H	H	F	91 (49)
612	H	H	$(CH_3)_3C$—	97 (86)
613	H	H	NO_2—	97 (99)
614	H	H	NH_2—	97 (89)
615	H	H	HO_3S—	97 (93)
616	CH_3—	H	$(CH_3)_3C$—	97 (74)
617	C_3H_7—	H	NO_2—	97 (99)
618	CH_3—	H	HO_3S—	97 (86)
619	C_4H_9—	H	HO_3S—	97 (82)
620	H	H	F	97 (49)

lipophilic lariat ether carboxylic acids in which the lipophilic group is incorporated either into the sidearm or on the geminal carbon.

Similarly, were prepared lariat carboxylic acids with lipophilic groups at both the geminal position and on the sidearm [97].

Dibenzo lariat ether carboxylic acids with substituents on both benzene rings were prepared by two methods. In the first method, the appropriate lariat ether alcohol containing the ring substituents were reacted with NaH and then bromoacetic acid to give the target lariat ethers [91,97]. In the second method, nitro- and sulfonic acid groups were introduced into the benzene rings of the preformed lariat ether carboxylic acid by nitration and sulfonation, respectively. Reduction of dinitro-derivatives to the corresponding diamines was accomplished with 85% hydrazine hydrate in ethanol in the presence of Pd/C [91,97].

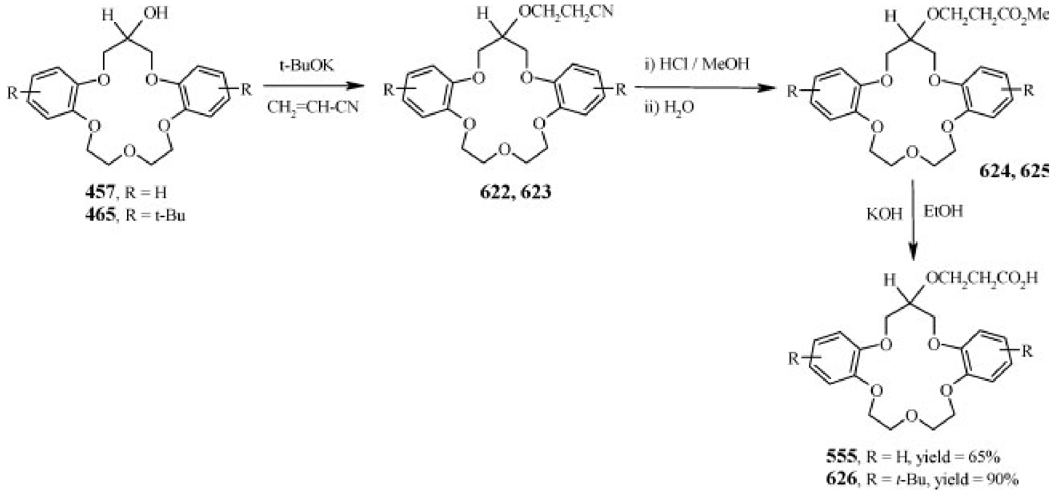
Kim *et al.* [95] used a similar approach for the synthesis of lariat ether carboxylic acid **621** with a second methyl group attached to a terminal carbon of the propane subunit from the corresponding crown ether alcohol.



621 (87%)

5.2.2.3.2. Synthesis of dibenzocrown ether oxypropanoic aicd, oxybutanoic acid and oxypentanoic acid. The length of the spacer that connects the acidic function to the polyether ring is an important structural parameter for proton-ionizable lariat ethers.

Scheme 48



457, R = H
465, R = t-Bu

622, 623

624, 625

555, R = H, yield = 65%
626, R = *t*-Bu, yield = 90%

Three synthetic routes were employed for the synthesis of this class of compounds. In the first route, potassium *tert*-butoxide catalyzed cyanoethylation of the corresponding lariat ether alcohol in neat acrylonitrile or acrylonitrile in THF to give the corresponding lariat ether nitriles **622** and **623**. Hydrolysis of the latter compounds with methanolic solution containing HCl gas afforded the corresponding methyl esters **624** and **625**. Saponification with ethanolic KOH gave **555** and **626**, respectively (Scheme 48) [97].

In the second synthetic route, lariat ether oxypropanoic acid **555** was obtained in 6% yield by Jones oxidation of the corresponding alcohol [89].

In the third synthetic route [97], lariat ether alcohols **529, 531,** and **627** (*n* = 2, 3) were reacted with methanesulfonyl chloride in dichloromethane in the presence of TEA to give lariat ether mesylate **628–630**. Subsequent reaction with NaCN in DMSO gave lariat ether nitriles **631–633**. The latter compounds underwent reaction with anhydrous HCl gas in anhydrous methanol to give the corresponding lariat ether methyl esters **634–636**. Hydrolysis with KOH in 95% ethanol afforded the target molecules **637–639** in 88–97% yields (Scheme 49).

Lariat ether alcohol **627** (*n* = 2, R = Me) was obtained from the corresponding lariat ether acetic acid on estrification with ethanol and *p*-toluenesulfonic acid and subsequent reduction with $LiAlH_4$ [92].

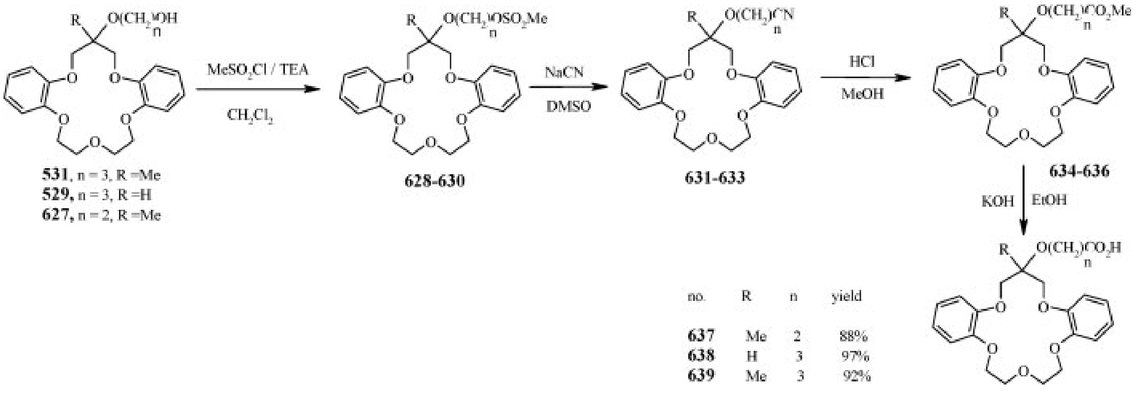
Lariat ether oxypentanoic acid **641** was obtained from lariat ether alcohol **457** by initial reaction with ethyl 5-bromopentanoate in the presence of NaH in THF to give the corresponding ester **640** followed by basic hydrolysis with ethanolic NaOH (Scheme 50) [89].

5.2.2.3.3. Synthesis of dibenzocrown ether acetic acid.

This type of lariat ether contain one or more carbon atom between the pivot carbon and the carboxylic group on the sidearm.

(*sym*-Dibenzo-16-crown-5)acetic acid **645** was synthesized as shown in Scheme 51. Thus, reaction of lariat ether alcohol **535a** with methanesulfonyl chloride in dichloromethane in the presence of triethylamine gave lariat ether mesylate **642** which was treated with sodium

Scheme 49



531, n = 3, R = Me
529, n = 3, R = H
627, n = 2, R = Me

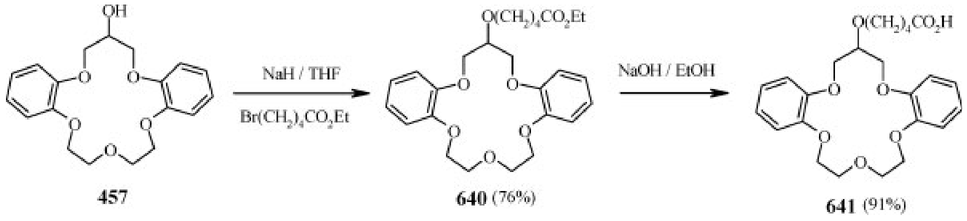
628-630

631-633

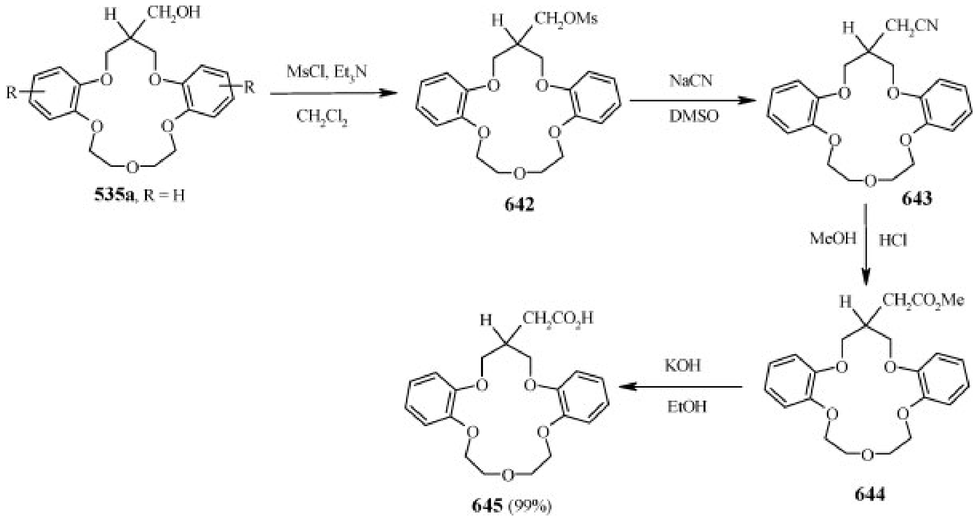
634-636

no.	R	n	yield
637	Me	2	88%
638	H	3	97%
639	Me	3	92%

Scheme 50



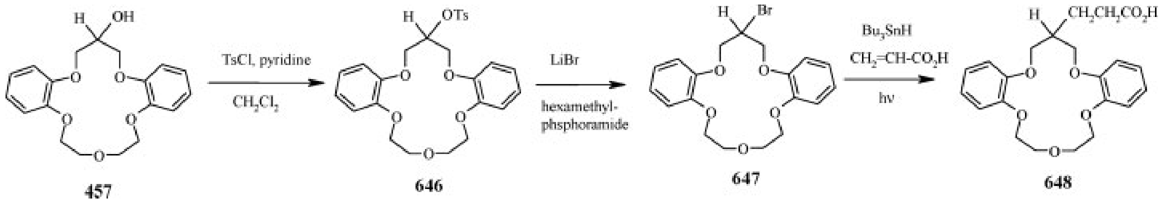
Scheme 51



cyanide in dimethyl sulfoxide at 60°C to provide an 98% yield of lariat ether nitrile **643**. Passing hydrogen chloride gas through a refluxing methanolic solution of the latter compound gave a quantitative yield of lariat ether methyl ester **644**. Hydrolysis with potassium hydroxide in 95% ethanol at room temperature gave a quantitative yield of the target **645** [97].

5.2.2.3.4. Synthesis of dibenzocrown ether propanoic acid. The synthetic route to 3-(sym-dibenzo-16-crown-5)propanoic acid **648** is shown in Scheme 52. Lariat

Scheme 52



Scheme 53

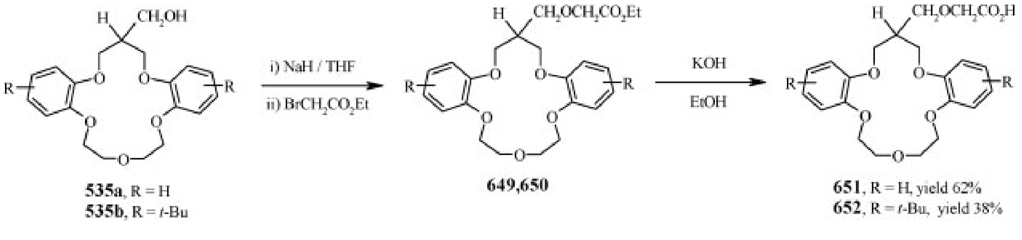
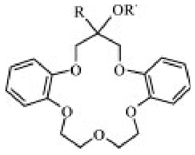
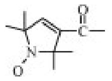


Table 46



Dibenzo-16-crown-5 with a pendant ester group (OCOR')

Comp. no.	R	R′	Method	Ref. (yield)
653	H	$CH_3C(O)$—	d	105 (77)
654	H	$C_5H1_{11}C(O)$—	d	105 (87)
655	H	$(CH_3)_3CC(O)$—	d	105 (66)
656	H	PhC(O)—	d	105 (77)
657	H	4-CH_3O—$C_6H_4C(O)$—	d	105 (59)
658	H	4-O_2N—$C_6H_4C(O)$—	d	105 (70)
659	C_3H_7—	$CH_3C(O)$—	d	105 (46)
660	C_3H_7—	$C_5H1_{11}C(O)$—	d	105 (50)
661	C_3H_7—	$(CH_3)_3CC(O)$—	d	105 (81)
662	C_3H_7—	PhC(O)—	d	105 (99)
663	C_3H_7—	4-CH_3O—$C_6H_4C(O)$—	d	105 (72)
664	C_3H_7—	4-O_2N—$C_6H_4C(O)$—	d	105 (86)
665	C_3H_7—	$(CH_3)_3COC(O)CH_2$—	a	105 (56)
666	4-CH_2=CH—C_6H_4—	$C_2H_5OC(O)CH_2$—	a	105 (72)
667	4-CH_2=$C(CH_3)$—C_6H_4—	$C_2H_5OC(O)CH_2$—	a	105 (80)
668	H	$C_2H_5OC(O)CH_2$—	b	105 (98)
669	C_3H_7—	$C_2H_5OC(O)CH_2$—	b	105 (94)
670	H		c	105 (5)
671	H	$C_2H_5OC(O)CH_2CH_2$—	e	105 (28)

ether alcohol **457** was converted into tosylate **646** in 97% yield. This tosylate was reacted with 10 equivalents of lithium bromide in hexamethylphosphoramide to give an 85% yield of lariat ether bromide **647,** which was photolyzed in the presence of acrylic acid and tributyltin hydride to produce an 30% yield of the desired lariat ether carboxylic acid **648** [97].

5.2.2.3.5. Synthesis of dibenzocrown ether 4-(2-oxabutanoic acid). The preparation of dibenzo-16-crown-5 compounds with 4-(2-oxabutanoic acid) side arms **651** and **652** is summarized in Scheme 53. Reaction of hydroxymethyl lariat ethers **535a,b** with ethyl bromoacetate and sodium hydride in tetrahydrofuran at room temperature gave lariat ether esters **649** and **650** in 36 and 40% yields, respectively. Hydrolysis with potassium hydroxide in 95% ethanol provided lariat ether carboxylic acids **651** and **652** in 94% yields [97].

5.2.2.4. Synthesis of dibenzocrown ethers with a pendant ester group. Bartsch *et al.* [105] reported the synthesis of dibenzo-16-crown-5 with pendant ester groups **653–671** (Table 46) from the corresponding lariat ether alcohols using the following synthetic routes:

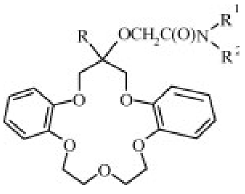
(a) Reaction of the corresponding lariat ether alcohol with NaH and the appropriate alkyl bromoacetate in THF.
(b) Reaction of a lariatether alcohol with ethyl diazoacetate and boron trifluoride in benzene.
(c) Reaction of *sym*-(hydroxy)dibenzo-16-crown-5 and carboxylic acid nitroxide in the presence of *N*,*N*′-dicyclohexylcarbodiimide in THF.
(d) Treatment of a lariat ether alcohol with KH followed by addition of the appropriate acid chloride.
(e) Heating the appropriate lariat ether nitrile under reflux in ethanol-benzene (1:2) through which gaseous HCl was passed.

5.2.2.5. Synthesis of dibenzocrown ethers with a pendant acetamide group. Bartsch *et al.* [106,107] reported the synthesis of *sym*-dibenzo-16-crown-5 oxyacetamides **672–704** (Table 47) by the reaction of *sym*-hydroxydibenzo-16-crown-5 with KH in THF followed by addition of the appropriate 2-chloroacetamide.

5.2.2.6. Synthesis of dibenzocrown ethers with a pendant amine group. Bartsch *et al.* [109] reported a synthetic method for attachment of an amino group to the central carbon atom of a variety of dibenzocrown ethers with subsequent conversion of these lariat ether primary amines into proton-ionizable lariat ether containing picrylamino type side arms.

The synthetic route to *sym*-(amino)dibenzocrown ethers **707** starting from the appropriate lariat ether

Table 47



Dibenzo-16-crown-5 with a pendant oxyacetamide group

Comp. no.	R	R^1	R^2	Ref. (yield)
672	H	C_8H_{17}—	C_8H_{17}—	107 (75)
673	H	$C_{10}H_{21}$—	$C_{10}H_{21}$—	107 (76)
674	C_3H_7—	C_8H_{17}—	C_8H_{17}—	107 (85)
675	C_3H_7—	$C_{10}H_{21}$—	$C_{10}H_{21}$—	107 (70)
676	$(CH_3)_2CH$—	C_5H_{11}—	C_5H_{11}—	107 (76)
677	$(CH_3)_2CH$—	C_6H_{13}—	C_6H_{13}—	107 (76)
678	$(CH_3)_2CH$—	C_8H_{17}—	C_8H_{17}—	107 (77)
679	$(CH_3)_2CH$—	$C_{10}H_{21}$—	$C_{10}H_{21}$—	107 (72)
680	$(CH_3)_3CCH_2$—	C_8H_{17}—	C_8H_{17}—	107 (73)
681	$(CH_3)_3CCH_2$—	$C_{10}H_{21}$—	$C_{10}H_{21}$—	107 (76)
682	H	H	H	106 (93), 108 (65)
683	H	CH_3—	CH_3—	106 (68)
684	H	C_2H_5—	C_2H_5—	106 (96)
685	H	H	C_3H_7—	106 (89)
686	H	C_3H_7—	C_3H_7—	106 (92)
687	H	C_4H_9—	C_4H_9—	106 (98)
688	H	H	C_5H_{11}—	106 (97)
689	H	C_5H_{11}—	C_5H_{11}—	106 (96)
690	H	C_6H_{13}—	C_6H_{13}—	106 (96)
691	H	$CH_3O(CH_2)_2$—	$CH_3O(CH_2)_2$—	106 (100)
692	H	$CH_3O(CH_2)_2O(CH_2)_2$—	$CH_3O(CH_2)_2O(CH_2)_2$—	106 (91)
693	H	—$(CH_2)_5$—		106 (100)
694	H	—$(CH_2)_2O(CH_2)_2$—		106 (100)
695	C_3H_7—	CH_3—	CH_3—	106 (66)
696	C_3H_7—	C_2H_5—	C_2H_5—	106 (100)
697	C_3H_7—	C_3H_7—	C_3H_7—	106 (100)
698	C_3H_7—	C_4H_9—	C_4H_9—	106 (100)
699	C_3H_7—	C_5H_{11}—	C_5H_{11}—	106 (98)
700	C_3H_7—	C_6H_{13}—	C_6H_{13}—	106 (100)
701	C_3H_7—	$CH_3O(CH_2)_2$—	$CH_3O(CH_2)_2$—	106 (97)
702	C_3H_7—	$CH_3O(CH_2)_2O(CH_2)_2$—	$CH_3O(CH_2)_2O(CH_2)_2$—	106 (63)
703	C_3H_7—	—$(CH_2)_5$—		106 (93)
704	C_3H_7—	—$(CH_2)_2O(CH_2)_2$—		106 (95)

Scheme 54

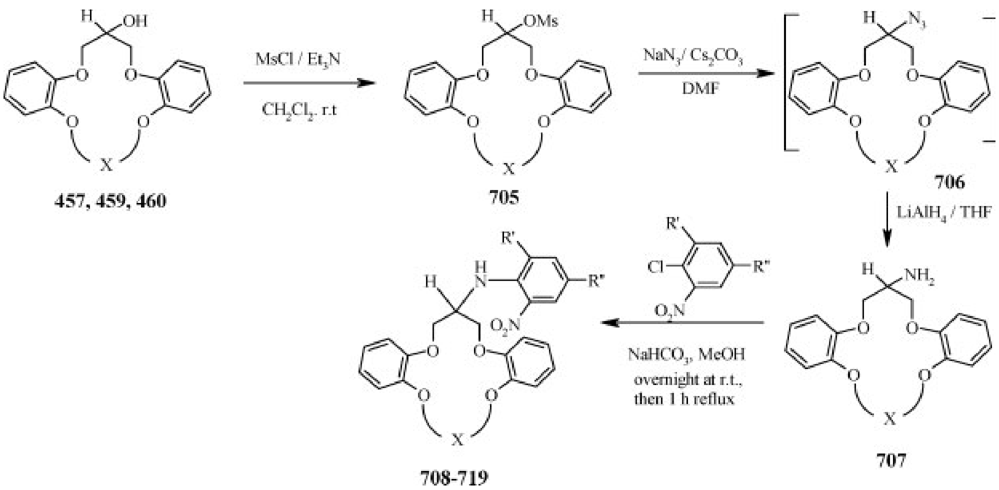
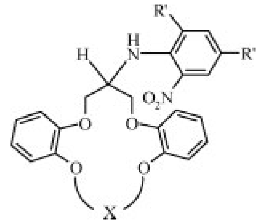


Table 48



Dibenzo-14-crown-4, Dibenzo-16-crown-5, Dibenzo-19-crown-6 with a pendant amine group

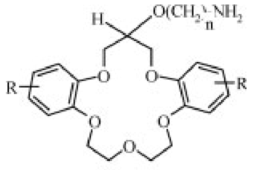
Comp. no.	X	R′	R″	Yield%
708	$—CH_2CH_2CH_2—$	NO_2	NO_2	95
709	$—CH_2CH_2CH_2—$	NO_2	CN	93
710	$—CH_2CH_2CH_2—$	NO_2	CF_3	90
711	$—CH_2CH_2CH_2—$	CF_3	NO_2	68
712	$—CH_2CH_2OCH_2CH_2—$	NO_2	NO_2	91
713	$—CH_2CH_2OCH_2CH_2—$	NO_2	CN	88
714	$—CH_2CH_2OCH_2CH_2—$	NO_2	CF_3	96
715	$—CH_2CH_2OCH_2CH_2—$	CF_3	NO_2	88
716	$—CH_2(CH_2OCH_2)_2CH_2—$	NO_2	NO_2	91
717	$—CH_2(CH_2OCH_2)_2CH_2—$	NO_2	CN	93
718	$—CH_2(CH_2OCH_2)_2CH_2—$	NO_2	CF_3	90
719	$—CH_2(CH_2OCH_2)_2CH_2—$	CF_3	NO_2	88

alcohols is shown in Scheme 54. The latter compounds were converted to lariat ether mesylate **705** in 91–93% yields upon treatment with methylsulfonyl chloride in THF. Reaction of the mesylates **705** with NaN_3 and Na_2CO_3 in DMF produced lariat ether azides **706** which were reduced to the desired lariat ether amines **707** in 75–81% yields. Reaction of the latter with the appropriate chlorobenzenes in methanol containing $NaHCO_3$ afforded the corresponding lariat ethers with picrylamino sidearms **708–719** (Table 48).

Similarly, binaphthyl crown receptor with a pendant amine **722** was prepared from the corresponding alcohol **470** by reaction with tosyl chloride in pyridine to give tosylate **720**. The latter was subjected to azidation of tosyl group to give **721** in 94% yield and then reduced to form the amine **722** in 98% yield. Amine **722** was reacted with a large excess of activated carbamate (which was generated in situ by the reaction of 2,4-dinitroaniline and phenyl chloroforamte) to yield host **723** in 75% yield and an overall yield of 53% (Scheme 55) [110].

Bartsch *et al.* [111] reported also the synthesis of lariat ethers with a pendant amines **724** starting from ketone **473** by initial treatment with the appropriate primary amines and 5*N* HCl-methanol in methanol in the presence of 4 A° molecular sieves as the drying agent followed by reduction with sodium cyanoborohydride. Subsequent reaction of lariat ether amines with *N*,*N*-dipentylchloroacetamide in acetonitrile in the presence of sodium bicarbonate and a catalytic amount of NaI afforded amides **725** and **726**, respectively (Scheme 56).

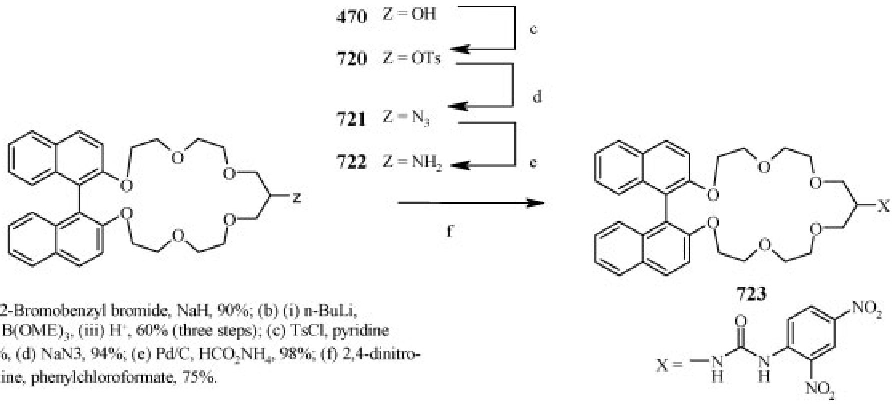
Lariat ether amines **727–729** in which the nitrogen atom is not directly attached to the pivot carbon can be obtained by reduction of the corresponding lariat ether amide [97] or lariat ether nitriles [108] with borane-dimethylsulfide in THF in 68%, 54%, and 40% yields, respectively.



727, R = H, n = 2
728, R = H, n = 3
729, R = *t*-Bu, n = 3

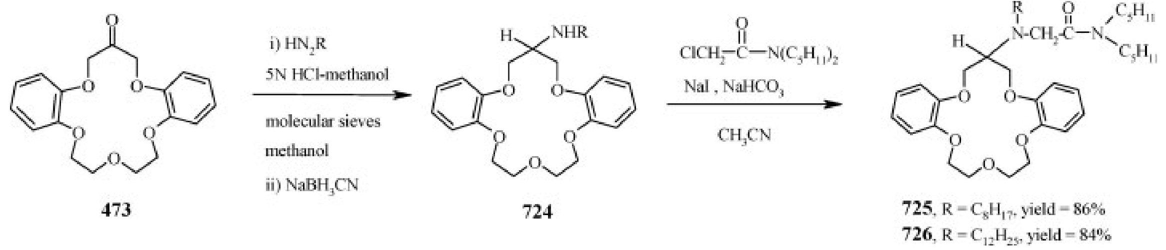
5.2.2.7. Synthesis of dibenzocrown ethers with pendant phosphinic acid and phosphonic acid monoalkyl ester groups. Burns *et al.* [112] reported the synthesis of lariat ether **730** having a phosphinic acid group by condensation of *sym*-hydroxydibenzo-14-crown-4 with

Scheme 55

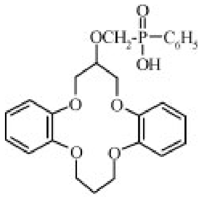


(a) 2-Bromobenzyl bromide, NaH, 90%; (b) (i) n-BuLi, (ii) $B(OME)_3$, (iii) H^+, 60% (three steps); (c) TsCl, pyridine 76%, (d) NaN3, 94%; (e) Pd/C, HCO_2NH_4, 98%; (f) 2,4-dinitroaniline, phenylchloroformate, 75%.

Scheme 56

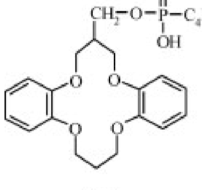


(chloromethyl)phenyl-phosphinic acid in presence of NaH in THF.



730

Habata *et al*. [113–116] reported the synthesis of alkylphosphoric acid armed dibenzo-14-crown-4 **731** by the reaction of hydroxymethyldibenzo-14-crown-4 with dichloroalkylphosphate in benzene or THF followed by hydrolysis.



731

Bartsch *et al*. [96] reported the synthesis of crown ether phosphonic acid monoethyl ester **735** ($n = 1$) by the reaction of the alkoxide from the appropriate lariat ether alcohol with monoethyl iodomethylphosphonic acid. Lariat ether phosphonic acid monoethyl esters **736–738** ($n = 2, 3, 4$) were obtained by the reaction of appropriate lariat ether substituted alkyl bromides **732–734** with triethyl phosphite followed by basic hydrolysis (Scheme 57).

Bromo derivatives **732** and **733** ($n = 2, 3$) were obtained from the corresponding alcohols on treatment with PBr_3 in DMF. Compound **734** ($n = 4$) was obtained from the corresponding alcohol upon treatment with 1,4-dibromobutane in aqueous NaOH in the presence of tetrabutylammonium hydrogen sulfate (Scheme 57).

5.2.2.8. Synthesis of various lariat ethers from dibenzocrown ethers carboxylic acids. Lariat ether carboxylic acids are important starting materials for the synthesis of lariat ethers with pendant ester, amide, hydroxamate, and *N*-(X)-sulfonylcarboxamide groups [97]. The functional groups may provide additional ligating atoms for cation complexation and serve as sites for further structure elaboration or function as attachment points for binding crown ethers to polymers [90].

Scheme 57

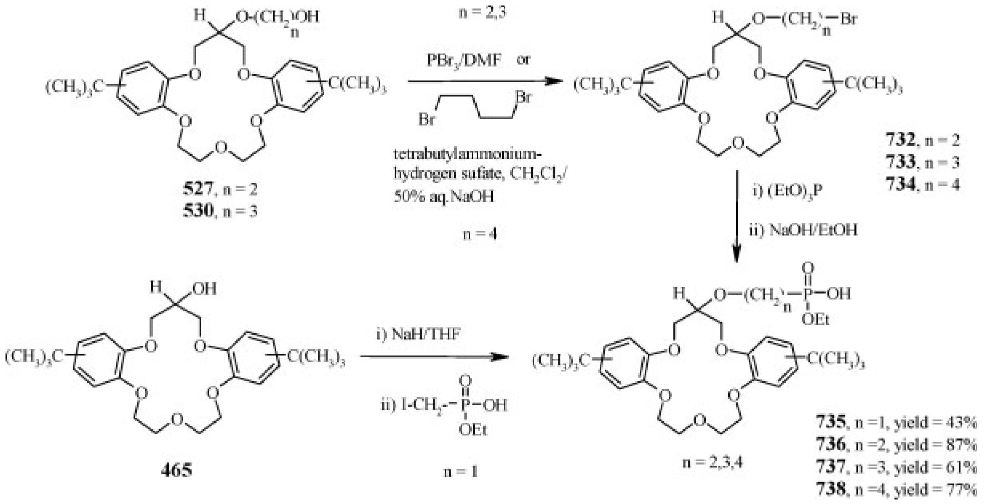
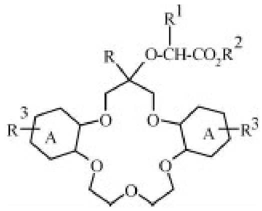


Table 49



Dibenzo(dicyclohexano)-16-crown-5 with a pendant ester group (OCHR^{1}CO$_2$R^2)

Comp. no.	A	R	R^1	R^2	R^3	Ref. (yield)
739	benzo	CH_3—	H	C_2H_5—	H	92 (94)
740	benzo	$C_{10}H_{21}$—	H	C_2H_5—	H	92 (97)
741	benzo	CH_3—	H	C_2H_5—	H	117 (–)
742	benzo	C_2H_5—	H	C_2H_5—	H	117 (–)
743	benzo	C_4H_9—	H	C_2H_5—	H	117 (–)
744	benzo	C_8H_{17}—	H	C_2H_5—	H	117 (–)
745	benzo	$C_{10}H_{21}$—	H	C_2H_5—	H	117 (–)
746	benzo	$(CH_3)_2CH$—	H	C_2H_5—	H	117 (–)
747	benzo	$(CH_3)_3C$—CH_2—	H	C_2H_5—	H	117 (–)
748	benzo	C_6F_{13}—	H	C_2H_5—	H	117 (–)
749	benzo	$(CH_3)_2C{=}CH$—	H	C_2H_5—	H	117 (–)
750	benzo	Ph—	H	C_2H_5—	H	117 (–)
751	benzo	$C_6H_{13}C{\equiv}C$—	H	C_2H_5—	H	117 (–)
752	benzo	H	H	C_6H_{13}—	H	117 (–)
753	benzo	H	H	$C_{10}H_{21}$—	H	117 (–)
754	benzo	H	H	$(CH_3)_2CH$—	H	117 (–)
755	benzo	H	H	$(CH_3)_3C$—	H	117 (–)
756	benzo	C_3H_7—	H	C_6H_{13}—	H	117 (–)
757	benzo	C_3H_7—	H	$C_{10}H_{21}$—	H	117 (–)
758	benzo	C_3H_7—	H	$(CH_3)_2CH$—	H	117 (–)
759	benzo	H	H	CH_3—	H	105 (82)
760	benzo	H	H	C_2H_5—	H	105 (98)
761	benzo	H	H	C_6H_{13}—	H	105 (62)
762	benzo	H	H	C_8H_{17}—	H	105 (86)
763	benzo	H	H	$C_{10}H_{21}$—	H	105 (84)
764	benzo	H	H	$C_{12}H_{25}$—	H	105 (78)
765	benzo	H	H	$(CH_3)_2CH$—	H	105 (94)
766	benzo	H	H	$(CH_3)_3C$—	H	105 (62)
767	benzo	H	Ph—	CH_3—	H	105 (100)
768	benzo	CH_3—	H	C_2H_5—	H	105 (91)
769	benzo	C_2H_5—	H	C_2H_5—	H	105 (93)
770	benzo	C_3H_7—	H	CH_3—	H	105 (94)
771	benzo	C_3H_7—	H	C_2H_5—	H	105 (94)
772	benzo	C_3H_7—	H	C_6H_{13}—	H	105 (85)
773	benzo	$(CH_3)_2C{=}CH$—	H	C_2H_5—	H	105 (53)
774	benzo	$CH_2{=}CH(CH_2)_8$—	H	C_2H_5—	H	105 (90)
775	benzo	$C_6H_{13}C{\equiv}C$—	H	C_2H_5—	H	105 (80)
776	benzo	Ph—	H	C_2H_5—	H	105 (97)
777	benzo	Ph—	H	C_2H_5—	H	105 (84)
778	benzo	Ph—	Ph—	C_2H_5—	H	105 (96)
779	benzo	C_3H_7—	H	C_8H_{17}—	H	105 (80)
780	benzo	C_3H_7—	H	$C_{10}H_{21}$—	H	105 (77)
781	benzo	C_3H_7—	H	$(CH_3)_2CH$—	H	105 (90)
782	benzo	C_3H_7—	H	$(CH_3)_3C$—	H	105 (56)
783	benzo	$(CH_3)_2CH$—	H	C_2H_5—	H	105 (89)
784	benzo	C_3F_7—	H	C_2H_5—	H	105 (90)
785	benzo	C_4H_9—	H	C_2H_5—	H	105 (92)
786	benzo	C_6H_{13}—	H	C_2H_5—	H	105 (94)
787	benzo	C_6F_{13}—	H	C_2H_5—	H	105 (90)
788	benzo	C_8H_{17}—	H	C_2H_5—	H	105 (93)
789	benzo	$C_{10}H_{21}$—	H	CH_3—	H	105 (79)
790	benzo	$C_{10}H_{21}$—	H	C_2H_5—	H	105 (91)

Table 49
(*Continued*)

Comp. no.	A	R	R^1	R^2	R^3	Ref. (yield)
791	benzo	$C_{10}H_{21}$—	Ph—	C_2H_5—	H	105 (99)
792	benzo	$HO(CH_2)_{10}$—	H	C_2H_5—	H	105 (86)
793	benzo	$C_{12}H_{25}$—	H	C_2H_5—	H	105 (95)
794	benzo	$C_{14}H_{29}$—	H	C_2H_5—	H	105 (96)
795	benzo	$C_{16}H_{33}$—	H	C_2H_5—	H	105 (94)
796	benzo	$C_{18}H_{37}$—	H	C_2H_5—	H	105 (97)
797	benzo	$C_{20}H_{41}$—	H	C_2H_5—	H	105 (95)
798	benzo	H	H	C_2H_5—	O_2N—	105 (95)
799	benzo	H	H	CH_3—	H_2N—	105 (92)
800	benzo	H	H	C_2H_5—	H_2N—	105 (93)
801	benzo	C_3H_7—	H	CH_3—	H_2N—	105 (93)
802	benzo	C_3H_7—	H	C_2H_5—	H_2N—	105 (89)
803	cyclohexano	C_3H_7—	H	C_2H_5—	H	105 (93)
804	cyclohexano	C_3H_7—	H	C_2H_5—	H	105 (96)

Compounds no. **665–669** mentioned in Table 46 were prepared in 72—80% yield [117,105] using the above methods.

5.2.2.8.1. Synthesis of dibenzocrown ethers with a pendant ester group. Bartsch *et al*. [105] used two synthetic approaches for the preparation of dibenzo-16-crown-5 with pendant ester group **739–816** (Tables 49 and 50) from the corresponding crown ether carboxylic acid. These synthetic approaches include:

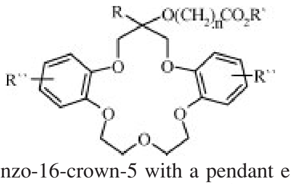
(a) Esterification of a carboxylic acid function in a lariat ether carboxylic acid with ethanol or methanol in the presence of H_2SO_4 or *p*-toluenesulfonic acid as catalyst [92,97,105,117].
(b) Conversion of a lariat ether carboxylic acid into the corresponding lariat ether acid chloride by treatment with oxalyl chloride in benzene and subsequent reaction with the appropriate alcohol in pyridine [95,117].

5.2.2.8.2. Synthesis of dibenzocrown ethers with pendant amide, hydroxamate, hydroxamic acid, and N-(X)sulfonyl carboxamide groups. Lariat ethers with oxyacetamide group were prepared from the corresponding lariat ether carboxylic acids by initial reaction with oxalyl chloride in benzene to give the corresponding acid chloride followed by reaction with ammonia gas or the appropriate alkyl amine [20,106,107,111,118].

Lariat ethers hydroxamates were obtained from the corresponding lariat ether acid chloride upon treatment with *o*-benzylhydroxylamine hydrochloride and pyridine in acetonitrile. Subsequent catalytic hydrogenation of the *o*-benzyl group afforded the lariat ether hydroxamic acid [91,94,111,119]. *N*-(X)sulfonyl carboxamide lariat ethers were prepared by coupling of the corresponding lariat ether acid chloride with the K-salt of the commercially available sulfonamides [18,120]. The following lariat ethers **739–816** (Tables 51 and 52) are prepared using the above strategies.

5.2.3. Synthesis of di-/tetrabenzo lariat azacrown ethers. *5.2.3.1. Synthesis of lariat ether formazan.* Katritzky [122] reported the synthesis of crown formazan **881** with a pendant hydroxyl group by coupling of tetrazotized 1,3-bis(2-aminophenoxy)propan-2-ol **879** with the sodium salt of β-phenylpyruvic acid **880** under phase transfer conditions. Acylation of the hydroxyl group of **881** with 2-chloroacetyl chloride

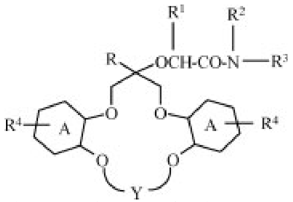
Table 50



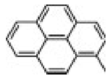
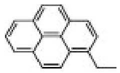
Dibenzo-16-crown-5 with a pendant ester group ($O(CH_2)_nCO_2R'$)

Comp. no.	R	R″	R′	n	Ref. (yield)
805	H	C_2H_5—	H	2	105 (28)
806	H	CH_3—	$(CH_3)_3C$—	2	105 (74)
807	H	CH_3—	H	3	105 (79)
808	CH_3—	CH_3—	H	2	105 (65)
809	CH_3—	C_2H_5—	H	2	105 (92)
810	CH_3—	CH_3—	H	3	105 (94)
811	CH_3—	C_2H_5—	H	3	105 (94)
812	CH_3—	H	CH_3—	2	97 (65)
813	H	H	CH_3—	3	97 (79)
814	CH_3—	H	CH_3—	3	97 (94)
815	H	H	CH_3—	2	97 (94)
816	H	*t*-Bu—	CH_3—	2	97 (74)

Table 51



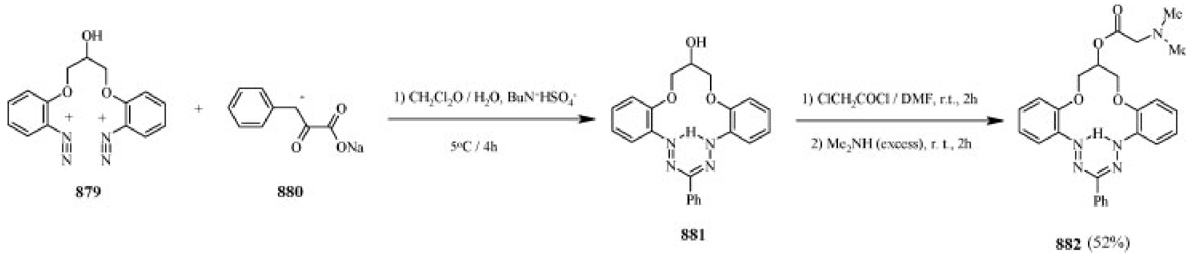
Dibenzo-13-crown-4, Dibenzo-14-crown-4, Dibenzo-16-crown-5, Dibenzo-19-crown-6 with pendant amide, hydroxamate, and hydroxamic acid groups

Comp. no.	Y	R	R^1	R^2	R^3	Ref. (yield)
817	$(CH_2)_2O(CH_2)_2$	$CH_3(CH_2)_2$—	H	H		118 (67)
818	$(CH_2)_2O(CH_2)_2$	$CH_3(CH_2)_2$—	H	H		118 (61)
819	$(CH_2)_2O(CH_2)_2$	CH_3—	H	C_5H_{11}—	C_5H_{11}—	107 (90)
820	$(CH_2)_2O(CH_2)_2$	C_2H_5—	H	C_5H_{11}—	C_5H_{11}—	107 (98)
821	$(CH_2)_2O(CH_2)_2$	C_4H_9—	H	C_5H_{11}—	C_5H_{11}—	107 (97)
822	$(CH_2)_2O(CH_2)_2$	C_6H_{13}—	H	C_5H_{11}—	C_5H_{11}—	107 (99)
823	$(CH_2)_2O(CH_2)_2$	C_8H_{17}—	H	C_5H_{11}—	C_5H_{11}—	107 (89)
824	$(CH_2)_2O(CH_2)_2$	$C_{10}H_{21}$—	H	C_5H_{11}—	C_5H_{11}—	107 (94)
825	$(CH_2)_2O(CH_2)_2$	$C_{12}H_{25}$—	H	C_5H_{11}—	C_5H_{11}—	107 (82)
826	$(CH_2)_2O(CH_2)_2$	$C_{14}H_{29}$—	H	C_5H_{11}—	C_5H_{11}—	107 (97)
827	$(CH_2)_2O(CH_2)_2$	$C_{16}H_{33}$—	H	C_5H_{11}—	C_5H_{11}—	107 (92)
828	$(CH_2)_2O(CH_2)_2$	$C_{18}H_{37}$—	H	C_5H_{11}—	C_5H_{11}—	107 (99)
829	$(CH_2)_2O(CH_2)_2$	$C_{20}H_{41}$—	H	C_5H_{11}—	C_5H_{11}—	107 (88)
830	$(CH_2)_2$	H	H	C_5H_{11}—	C_5H_{11}—	107 (91)
831	$(CH_2)_2$	C_3H_7—	H	C_5H_{11}—	C_5H_{11}—	107 (95)
832	$(CH_2)_3$	H	H	C_5H_{11}—	C_5H_{11}—	107 (93)
833	$(CH_2)_3$	C_3H_7—	H	C_5H_{11}—	C_5H_{11}—	107 (82)
834	$(CH_2)_3$	$(CH_3)_2CH$—	H	C_5H_{11}—	C_5H_{11}—	107 (75)
835	$(CH_2)_3$	$C_{10}H_{21}$—	H	C_5H_{11}—	C_5H_{11}—	107 (88)
836	$(CH_2)_3$	Ph—	H	C_5H_{11}—	C_5H_{11}—	107 (93)
837	$(CH_2)_2O(CH_2)_2$	C_3H_7—	H	H	H	106 (95)
838	$(CH_2)_2O(CH_2)_2$	C_3H_7—	H	H	C_3H_7—	106 (97)
839	$(CH_2)_2O(CH_2)_2$	C_3H_7—	H	H	C_5H_{11}—	106 (97)
840	$(CH_2)_2$	H	H	H	$PhCH_2O$—	94 (80)
841	$(CH_2)_2O(CH_2)_2$	H	H	H	$PhCH_2O$—	94 (83)
842	$CH_2(CH_2OCH_2)_2CH_2$	H	H	H	$PhCH_2O$—	94 (84)
843	$(CH_2)_2O(CH_2)_2$	H	Ph	H	$PhCH_2O$—	94 (74)
844	$(CH_2)_2O(CH_2)_2$	H	$C_{10}H_{21}$—	H	$PhCH_2O$—	94 (69)
845	$(CH_2)_2O(CH_2)_2$	H	$C_{12}H_{25}$—	H	$PhCH_2O$—	94 (73)
846	$(CH_2)_2O(CH_2)_2$	H	$C_{14}H_{29}$—	H	$PhCH_2O$—	94 (79)
847	$(CH_2)_2O(CH_2)_2$	H	$C_{16}H_{33}$—	H	$PhCH_2O$—	94 (76)
848	$(CH_2)_2O(CH_2)_2$	C_3H_7—	H	H	$PhCH_2O$—	94 (66)
849	$(CH_2)_2O(CH_2)_2$	Ph—	H	H	$PhCH_2O$—	94 (79)
850	$(CH_2)_2O(CH_2)_2$	$C_{10}H_{21}$—	H	H	$PhCH_2O$—	94 (92)
851	$(CH_2)_2O(CH_2)_2$	$C_{18}H_{37}$—	H	H	$PhCH_2O$—	94 (88)
852	$(CH_2)_2O(CH_2)_2$	Ph—	$C_{10}H_{21}$—	H	$PhCH_2O$—	94 (93)
853	$(CH_2)_2O(CH_2)_2$	Ph—	Ph	H	$PhCH_2O$—	94 (92)
854	$(CH_2)_2O(CH_2)_2$	3-F_3C—C_6H_4—	H	H	$PhCH_2O$—	91 (46)
855	$(CH_2)_2O(CH_2)_2$	3,5-F_3C—C_6H_3—	H	H	$PhCH_2O$—	91 (46)
856	$(CH_2)_2O(CH_2)_2$	H	C_8H_{17}—	H	$PhCH_2O$—	111 (76)
857[a]	$(CH_2)_2O(CH_2)_2$	H	H	H	$PhCH_2O$—	111 (75)
858	$(CH_2)_2O(CH_2)_2$	2-H_3C—C_6H_4—	H	H	$PhCH_2O$—	111 (68)
859	$(CH_2)_2O(CH_2)_2$	3-H_3C—C_6H_4—	H	H	$PhCH_2O$—	111 (52)
860	$(CH_2)_2O(CH_2)_2$	4-H_3C—C_6H_4—	H	H	$PhCH_2O$—	111 (64)
861	$(CH_2)_2O(CH_2)_2$	c-C_6H_{11}—	H	H	$PhCH_2O$—	111 (62)
862	$(CH_2)_2O(CH_2)_2$	H	H	H	C_6H_{13}—	111 (81)
863	$(CH_2)_2O(CH_2)_2$	H	H	CH_3—	C_6H_{13}—	111 (46)
864	$(CH_2)_2O(CH_2)_2$	H	H	H	$C_{12}H_{25}$—	111 (79)
865	$(CH_2)_2O(CH_2)_2$	H	H	H	Ph—	111 (93)
866	$(CH_2)_2O(CH_2)_2$	$C_{10}H_{21}$—	H	H	H	111 (96)
867	$(CH_2)_2O(CH_2)_2$	$C_{10}H_{21}$—	Ph—	C_5H_{11}—	C_5H_{11}—	111 (96)
868	$(CH_2)_2O(CH_2)_2$	$(CH_3)_3CCH_2$—	H	C_5H_{11}—	C_5H_{11}—	111 (83)
869	$(CH_2)_2O(CH_2)_2$	Ph—	H	H	$PhCH_2$—	111 (70)
870	$(CH_2)_2O(CH_2)_2$	Ph—	Ph—	C_5H_{11}—	Ph—	111 (87)
871[b]	$(CH_2)_2O(CH_2)_2$	H	H	H	C_6H_{13}—	111 (56)
872[b]	$(CH_2)_2O(CH_2)_2$	H	H	H	H	18 (86)

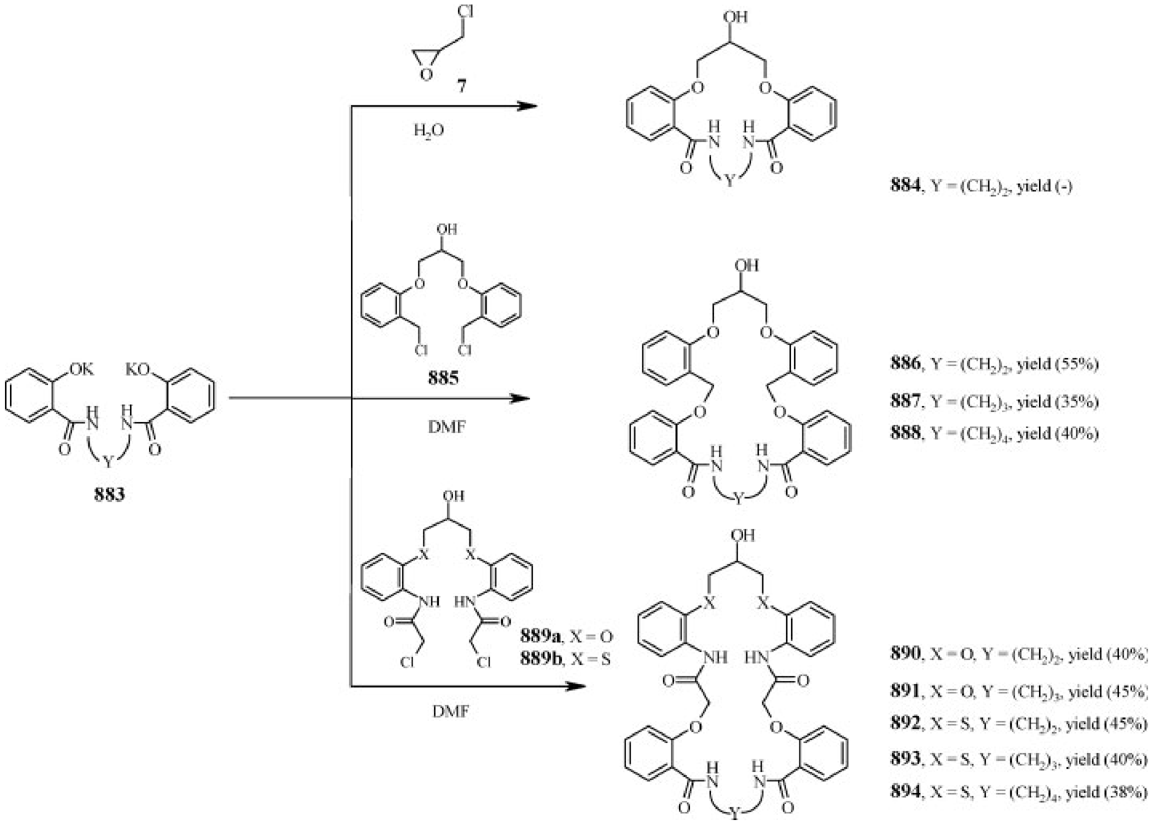
[a] $R^4 = (CH_3)_3C$— but in all other compounds R^4 = H.

[b] A = Cyclohexano but in all other compounds A = benzo.

Scheme 58



Scheme 59



Scheme 60

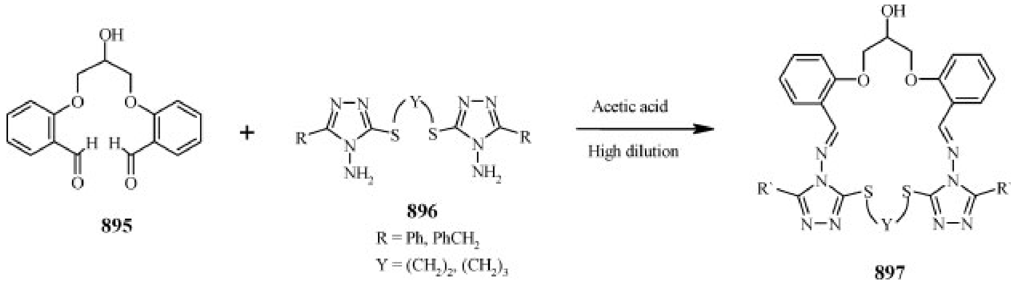
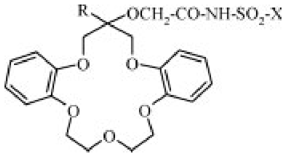
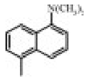
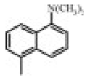


Table 52



Dibenzo-16-crown-5 with a pendant *N*-(X)sulfonyl carboxamide group

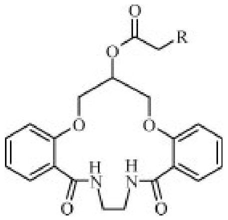
Comp. no.	R	X	Ref. (yield)
873	$C_{10}H_{21}$—	CF_3—	120, 18 (–)
874	$C_{10}H_{21}$—	CH_3—	120, 18 (–)
875	$C_{10}H_{21}$—	Ph	120, 18 (–)
876	$C_{10}H_{21}$—	4-O_2N—C_6H_4—	120, 18 (–)
877	H		121 (76)
878	C_3H_7—		121 (55)

followed by reaction with dimethylamine afforded lariat ether formazans **882** with a pendant aminoacetyloxy group (Scheme 58).

5.2.3.2. Synthesis of lariat azacrown ethers. Abbas *et al.* [123–126] used an approach similar to that described by Katritzky [122] for the synthesis of azacrown ethers with pendant alkylaminoacetyloxy or phenoxy groups **898–917** (Tables 53–56) from the corresponding hydroxyl azacrown ethers **884, 886–888, 890–894,** and **897** by initial acylation of the hydroxyl group in these compounds with 2-choloroacetyl chloride followed by reaction with the appropriate alkyl amine or phenol.

The hydroxyazacrown ethers **884, 886–888,** and **890–894** were obtained by reaction of the appropriate

Table 53



Macrocyclic dibenzodiamides with a pendant ($OCOCH_2NR_2$) group

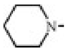
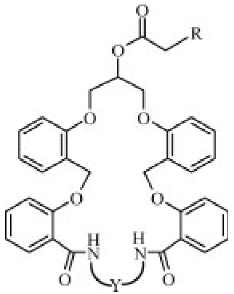
Comp. no.	R	Ref. (yield)
898	$(CH_3CH_2)_2N$—	125 (60)
899		125 (61)
900		125 (65)

Table 54



Macrocyclic tetrabenzodiamides with a pendant $OCOCH_2NR_2$ or $OCOCH_2OAr$ group

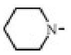
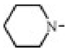
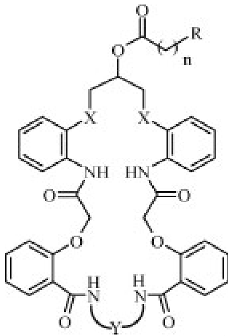
Comp. no.	Y	R	Ref. (yield)
901	$(CH_2)_2$		125 (60)
902	$(CH_2)_4$		125 (63)
903	$(CH_2)_4$		125(60)
904	$(CH_2)_2$	4—H(O)C—C_6H_4—O—	125 (50)
905	$(CH_2)_4$	2-H(O)C—C_6H_4—O—	125 (55)
906	$(CH_2)_2$	2-O_2N—C_6H_4—O—	125 (50)

Table 55



Macrocyclic tetrabenzotetraamides with a pendant $OC(O)CH_2NR_2$ group

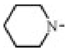
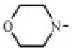
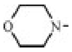
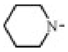
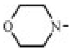
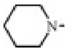
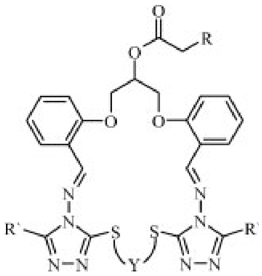
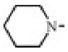
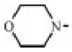
Comp. no.	Y	n	X	R	Ref. (yield)
907	$(CH_2)_2$	1	O	$(CH_3CH_2)_2N$—	124 (60)
908	$(CH_2)_2$	1	O		124 (65)
909	$(CH_2)_3$	1	O		124 (60)
910	$(CH_2)_3$	1	O		124 (65)
911	$(CH_2)_2$	1	S		124 (61)
912	$(CH_2)_3$	2	S		124 (85)
913	$(CH_2)_3$	2	S		124 (92)
914	$(CH_2)_4$	2	S		126 (60)

Table 56



Macrocyclic Schiff bases with a pendant $OC(O)CH_2NR$ group

Comp. no.	X	R′	R	Ref. (yield)
915	$(CH_2)_3$	Ph—		123 (70)
916	$(CH_2)_4$	$PhCH_2$—		123 (65)
917	$(CH_2)_4$	$PhCH_2$—	$(CH_3CH_2)_2N$—	123 (60)

dipotassium salts **883** with epichlorohydrin (**7**) for **884**, 1,3-bis(2-chloromethylphenoxy)propan-2-ol (**885**) for **886–888**, 1,3-bis(2-chloroacetyloxy-aminophenoxy)propan-2-ol (**889a**) and 1,3-bis(2-chloroacetyloxy-aminothiophenoxy)propan-2-ol (**889b**) for **890–894**, respectively [124,125] (Scheme 59).

The hydroxyazacrown ethers **897** were obtained by cyclocondensation of the aldehyde **895** with the corresponding bis(amine)s [123] **896** in refluxing acetic acid under high dilution conditions (Scheme 60).

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Syntheses of Chromenes and Chromanes *via o*-Quinone Methide Intermediates

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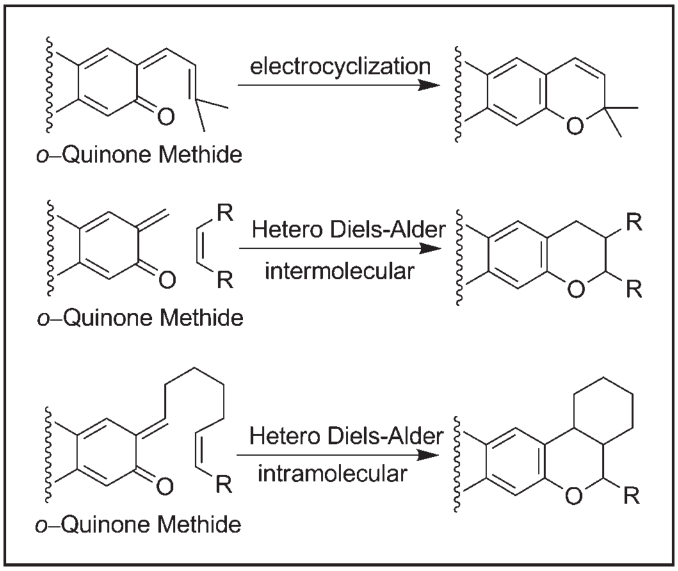

This review intends to explore synthetic methodologies for the preparation of 2*H*-chromenes and their analog chromanes through *ortho*-quinone methide (*o*-QM) intermediates associated with inter and intramolecular hetero-Diels-Alder and electrocyclization reactions.

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INTRODUCTION

Chromane and chromene substructures (Fig. 1) are frequently found in naturally occurring compounds, many of which exhibit useful biological activity [1–3]. Most of the time, the heterocyclic moiety is associated with an aromatic ring, forming 2,3- or 3,4-dihydrobenzopyran systems. From the position of the double bond, the chromene ring can be divided into two classes: 2*H*-chromene and 4*H*-chromene. Chromane is the saturated analog of chromene (Fig. 1).

In general, a number of biologically active chromenes and chromanes have been isolated from several natural sources. These substances have been identified as apoptosis-inducing agents [4], anti-HIV agents [5,6], modulators of the estrogen receptors [7], antibacterials [8], and antifungals [9].

For example, chromenes **1** and **2** (Fig. 2) were isolated from the leaves of *Peperomia serpens* (Sw.) Loudon [10] of genus *Peperomia* (Piperaceae) and presented antifungal activities against *Cladosporium cladosporioides* and *C. sphaerospermum.* Kawahara *et al.* in 1988 [11] isolated 2,2-dialkyl-substituted chromenes **3** and **4**, which exhibited antibacterial activity, from species of the fungi *Crucibulum, Lactarius, Aspergillus silvaticus*, and *Cylindrocarpon* (Fig. 2).

Some other important examples isolated from such diverse natural sources such as fungi, marine organisms, and plants are depicted in Figure 3. Compound **5**, which was isolated from the fungus *Daedalea quercina*, proved to have antioxidant and anti-inflammatory activities [12]. Chromenes with isoprenoid side chains are frequently found in nature [13], being structural analogs of prenylated coumarins, chalcones, and cannabinoids [14,15]. Cordiachromene (**6**) is a chromene with an isoprenoid chain that was isolated from *Cordia alliodora* Ruiz and Pav [16] and marine organisms *Aplidium antillense* [17] and *Aplidium constellatum* [18]. It exhibits antibacterial activity against *Staphylococcus aureus* and anti-inflammatory activity [19].

The most well-known class of naturally occurring 2*H*-chromenes are the precocenes, which are divided in two

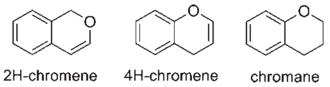


Figure 1. Chemical structures of the systems 2*H*-chromene, 4*H*-chromene, and chromane.

subclasses: precocene I (**7a**) and II (**7b**), also called ageratochromenes. These latter compounds were initially isolated from *Ageratum houstonianum* [2] but later found in several Ageratinae species. They are well known for their insecticidal activity and for inducing precocious metamorphosis [20], meaning they have properties as an antijuvenile hormone by reducing the length of larval life in sensitive species and preventing ovarian development in some adult insects [21].

The chromane moiety is present in other natural products [22–24], such as tocopherols and cannabinoids. α-Tocopherol (**8—**vitamin E) is found in the oil of wheat germ and it is reported that the chromane moiety is responsible for the antiandrogenic properties of vitamin E [25]. 4′-Methoxy-bavachromanol (**9**) was isolated from propolis and was found to be a more powerful antioxidant than lipoxygenases found in soybeans [26]. Among the constituents present in *Cannabis sativa*, tetrahydrocannabinol (**10**) is responsible for the plant's strong hallucinogenic activity (Fig. 4).

Substances that have the chromene or chromane ring fused with *ortho-* or *para*-quinones represent a special class of naturally occurring compounds that are present in many plants, fungi, and insects [27]. Xiloidone, 3,4-dihydro-α-lapachone (**11**) and its isomer, 3,4-dihydro-β-lapachone (**12**), are the most representative substances of the chromene-fused quinone class. These naphthoquinones are minor components in the extract of lapachol (**13**) [28–42]. Rodrigues and coworkers obtained **11** and **12** along with lapachol from *Tabebuia avellanedae* by using supercritical fluid extraction [43]. Gonçalves *et al.* [44,45] reported that xiloidone (**11**) has antibiotic activity against Gram-negative bacteria of the genus *Brucella*. Recently, Kuster *et al.* demonstrated that xiloidone (**11**) has potent antibacterial activity against multiresistant *Staphylococcus aureus* strains [46]. Cho *et al.* isolated xiloidone (**11**) from *Catalpa ovata* stems and demonstrated it had activity against some plant pathogenic fungi [47].

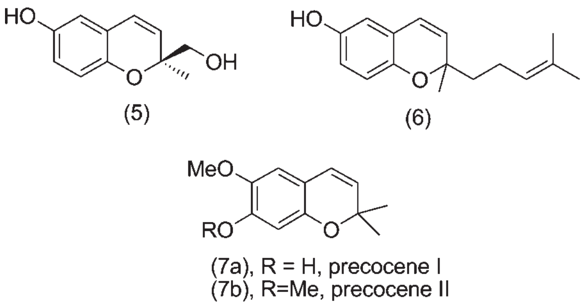


Figure 3. Precocens isolated from different natural sources.

The biogenetic route to naphthoquinone chromenes seems to have originated from lapachol (**13**) which is very abundant in many plants. D'Albuquerque *et al.* in 1972 and later in 2004 Jassbi *et al.* demonstrated that xiloidone can be obtained by $FeCl_3$ oxidation of lapachol in the presence of pyridine and acetic anhydride [48,49]. Indeed, several pathways for the formation of dihydro-α-lapachone from lapachol involving oxidative dehydrogenation [50] and photoirradiation [51] have been suggested. There are other natural and synthetic, biologically active naphthoquinones derived from lapachol (**13**).

The most important substances of the chromane-fused quinone class are α- (**14**) and β- (**15**) lapachones (Fig. 5). These compounds are the 2H hydrogenated analogs of compounds **11** and **12**. Thus, the development of valuable methods for the preparation of naphthoquinone-2*H*-chromene would also provide access to many analogs and derivatives of these substances.

Briefly, quinones have been the subject of much interest for a number of years due to their various biological activities [52–54]. For example, quinones have been studied for antitumor [55,56], molluscicidal [57–59], leischmanicidal [60], anti-inflammatory [61], antifungal [62], and trypanocidal [63,64] activities. It is described in the literature that the biological profiles of these molecules are centered on its *ortho-* or *para*-quinonoid moiety [65]. This group generally accepts one and/or two

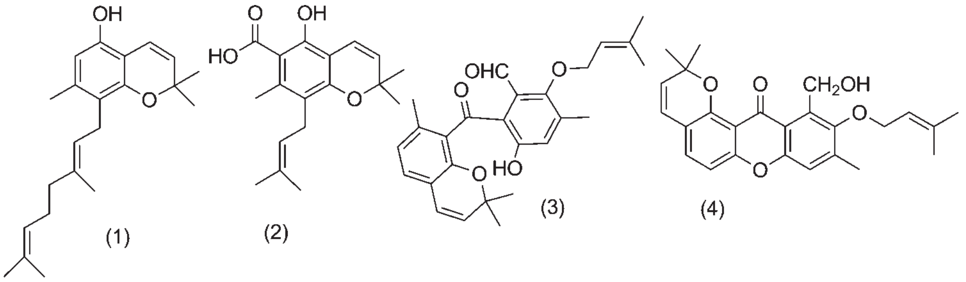
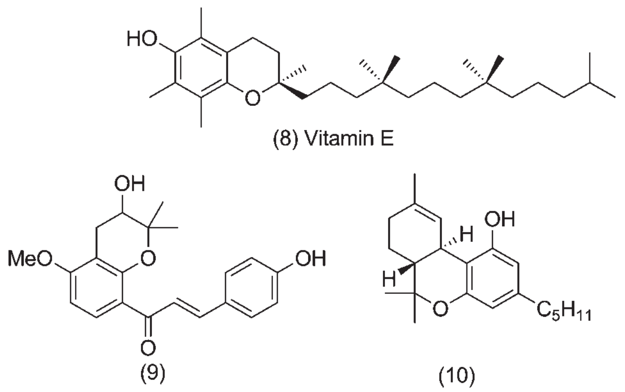


Figure 2. Structures of chromenes isolated from the plant *Peperomia serpens* (**1**–**2**) and from fungi (**3**–**4**).



(8) Vitamin E

(9)

(10)

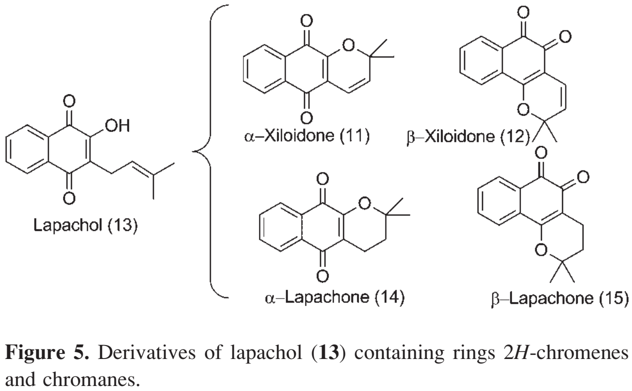
Figure 4. Chromanes isolated from different natural sources.

electrons (redox cycling) [66] to form the corresponding radical anion or dianion species *in situ*. In such way, the semi-quinone radicals accelerate the intracellular hypoxic condition by producing a superoxide anion [67–69]. Because of this mechanism, quinones show cytotoxic activity against cancer cells (and also to normal cells) by interfering with enzymes such as topoisomerases, which are critical for DNA replication [70].

Lapachol (**13**) is a natural naphthoquinone that occurs in the grain of several wooden trees of the Bignoniaceae family and is widely used in American folk medicine for the treatment of several diseases. It was first isolated in 1882 from *Tabebuia Avellanedae* [71], but it occurs in several other species of the genus *Tabebuia* (Tecoma). These trees are commonly known in South America as ''ipês,'' but also as Lapacho, Pau d'Arco, Lapacho roxo, and Taheebo [72,73]. It also occurs in many other families such as Verbenaceae, Proteaceae, Leguminosae, Sapotaceae, Scrophulariaceae, and Malvaceae [68,73]. Since the discovery that lapachol (**13**) [74], a natural naphthoquinone, proved to have antitumor activity against Walker-256 carcinoma, several structural modifications were performed [75,76] in order to find new compounds with other activities [73,77–81].

β-Lapachone (**15**), also known as ARQ501 [82] (Fig. 5), is a natural pyran-*ortho*-naphthoquinone originally obtained from the heartwood of the Lapacho tree, which belongs to the genus *Tabebuia* (Bigoniaceae) and which grows throughout the South America. This compound has been demonstrated to have many different pharmacological effects including promising anticancer activity [70]. Currently, it is undergoing multiple Phase II clinical trials. Several possible mechanisms to explain the cytotoxic effect against cancer cells have been proposed. The most recent proposal suggests that a redox cycle between NAD(P)H and quinone oxireductase 1 (NQO1) enzyme causes the depletion of NAD(P)H and NADH in the cells. This consequently decreases ATP and increases cytochrome C and cytosolic Ca^{+2}, which then affect other pathways in the cell cycle checkpoint resulting in the selective apoptotic cell death of cancer cells. It has also been suggested that the generation of ROS affects the kinases that are involved in cell cycle progression, leading to cell death. β-Lapachone has also been considered as a coadjuvant in killing human cancer cells during radiotherapy treatment. It seems that it inhibits sublethal radiation damage repair. Regarding anticancer activity, it presents significant antineoplasic [83] activity against human cancer cell lines from leukemia [84], prostate [85], malignant glioma [75], hepatoma [86], colon [87], breast [88], ovarian [89], lung [90], and pancreatic [91] tumors, at concentrations in the range of 1–10 μ*M* (IC_{50}). It has also been intensely investigated as a possible drug against the flagellate protozoan *Trypanosoma cruzi*, which is the etiological agent of Chagas disease, in both acute and chronic infections [92–96]. This compound inspired a search for new derivatives with a better therapeutical index. Several heterocyclic derivatives (oxyranes [92(a,b)], oxazoles [64], imidazoles [92(c)], and phenazine [97]) of β-Lapachone (**15**) have been synthesized. Some of them have lower side effects and improved trypanocidal activity.

Because of the multiple uses and variety of biological activities of chromenes, the synthesis of this heterocyclic substructure has been the subject of intense investigations. Several new synthetic methods and improvements in existing and classical methods have been reported recently. In general, phenols and salicylaldehydes have been used in the preparation of chromenes. Table 1 summarizes some methods. The preparation of chromanes can be achieved by simple hydrogenation of the double bond of the chromenes. Nevertheless, there are several procedures that target the chromane ring directly, such as: (a) sequential [3+3] cyclization and Williamson's reaction [98] from salicylaldehydes [99,100], phenols [101], propargylic phenols [102], and 1,2-benzoxazines [103]; (b) iodine-catalyzed cyclocondensation [104]; (c) ring-closing olefin metathesis [105]; (d) *via* Wittig intermediates [106]; and (e) electrochemistry [107].



Lapachol (13)

α–Xiloidone (11)

β–Xiloidone (12)

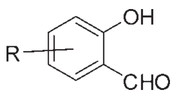
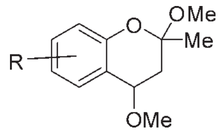
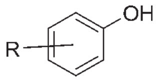
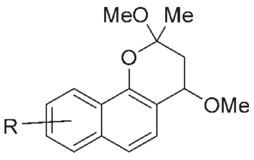
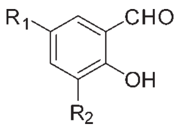
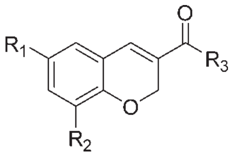
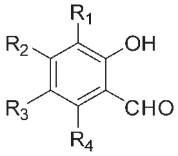
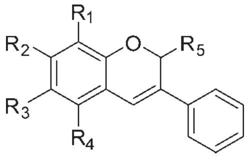
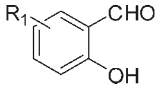
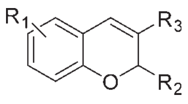
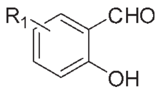
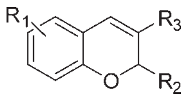
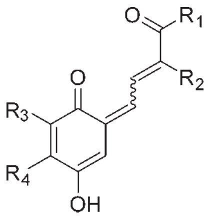
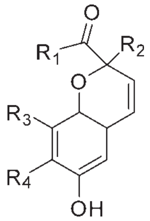
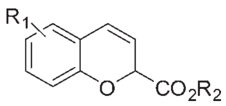
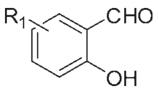
α–Lapachone (14)

β–Lapachone (15)

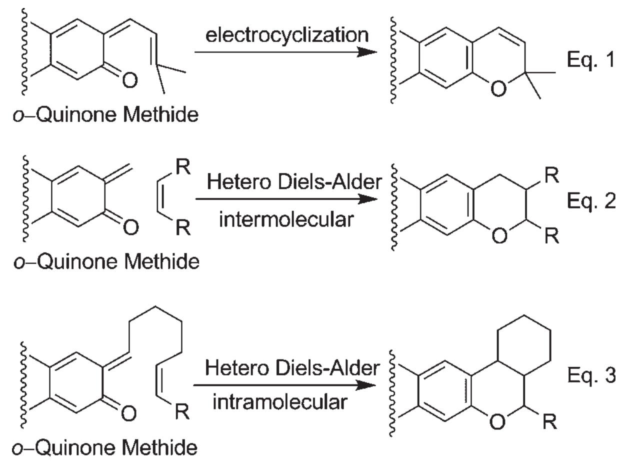
Figure 5. Derivatives of lapachol (**13**) containing rings 2*H*-chromenes and chromanes.

Table 1

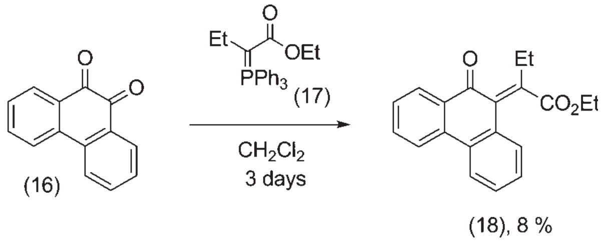
Phenols and salicylaldehydes used in preparation of chromenes.

Phenols and salicylaldehydes	Product	Yield (%)	Ref.
		R = H, 90 R = 8-OMe, 86 R = 8-OEt, 82 R = 6-Me, 88 R = 6-Br, 75 R = 6-NO_2, 78	[108]
		R = 4-OMe, 85 R = 3,4-OCH_2O, 87	[108]
		$R_1 = R_2 = H$; $R_3 = Me$, 81 $R_1 = R_2 = H$; $R_3 = Et$, 83 $R_1 = H$; $R_2 = OMe$; $R_3 = Me$, 79 $R_1 = H$; $R_2 = OEt$; $R_3 = Me$, 84 $R_1 = Br$; $R_2 = H$; $R_3 = Me$, 87 $R_1 = Cl$; $R_2 = H$; $R_3 = Me$, 56	[100]
		$R_1 = R_2 = R_3 = R_4 = H$; R_5 = morpholinyl, 80 $R_1 = OMe$; $R_2 = R_3 = R_4 = H$; R_5 = morpholinyl, 73 $R_1 = R_2 = R_3 = R_4 = H$; R_5 = piperidinyl, 72 $R_1 = R_2 = H$; $R_3 = NO_2$; $R_4 = H$; R_5 = piperidinyl, 85 $R_1 = R_2 = R_3 = R_4 = H$; R_5 = pyrrolidinyl, 71 $R_1 = R_2 = H$; $R_3 = Cl$; $R_4 = H$; R_5 = pyrrolidinyl, 79	[104]
		R_1 = 3-OH; R_2 = butyl; R_3 = H, 88 R_1 = 3-OMe; R_2 = butyl; R_3 = H, 91 R_1 = 5-Br; R_2 = butyl; R_3 = H, 90 R_1 = 3,5-dichloro; R_2 = butyl; R_3 = H, 91 R_1 = 3,5-di-*t*-butyl;R_2 = butyl; R_3 = H, 85	[109]
		$R_1 = R_2 = R_3 = H$, 83 R_1 = 6-Br; $R_2 = R_3 = H$, 92 R_1 = 7-OMe; $R_2 = R_3 = H$, 84 R_1 = 6-NO_2; $R_2 = R_3 = H$, 81 R_1 = 7-$OCH_2CH{=}CH_2$;$R_2 = R_3 = H$, 90	[105a]
		$R_1 = OMe$; $R_2 = R_3 = R_4 = H$, 30 $R_1 = R_4 = OMe$; $R_2 = R_3 = H$, 70 $R_1 = R_4 = OMe$; $R_2 = Me$; $R_3 = H$, 63 R_1 = *i*-Pr; $R_2 = R_3 = H$; $R_4 = OMe$, 75	[110]
		$R_1 = H$; $R_2 = Et$, 85 R_1 = 6-*t*-Bu; $R_2 = Et$, 99 R_1 = 4-Br; $R_2 = Et$, 81 R_1 = 4-Me; $R_2 = Et$, 85 $R_1 = H$; $R_2 = Bn$, 87	[111]

Scheme 1



Scheme 2



o-QUINONE METHIDES: GENERALITY

In general, *ortho*-quinone methides (*o*-QMs) possess a hexadiene ring with a carbonyl group and a methylene unit in the ring. With these two different functional groups, the molecule becomes highly polarized and is very reactive. With both cationic and anionic centers, the molecule can act either as a nucleophile or electrophile. In addition to quinone methides being excellent partners in Diels-Alder reactions, the structures are also present in many molecules with biological activity. A great variety of plants, animals, and fungus use these substances for defense.

o-QMs have been extensively used for the preparation of 2*H*-chromene and chromane substructures. Chromenes are obtained through electrocyclization reactions [eq. (1), Scheme 1] and chromanes by inter or intramolecular hetero-Diels-Alder reactions [eqs. (2) and (3), Scheme 1]. In both cases, quinone methides are the key intermediates (Fig. 6).

o-QMs are involved in a large number of chemical reactions and biological processes such as enzyme inhibition, reactions with phosphodiesters, DNA alkylation [112], and crosslinking [113,114]. Their electrophilicities towards amines, thiols, water, amino acids, and peptides have also been used for interactions with nucleobases of DNA [115]. Several important clinical anticancer drugs (*e.g.*, cisplatin, psoralens, and mitomycin C) are known to induce DNA ISC formation, which can disrupt cell maintenance and replication by a mechanism that involves *o*-QM intermediates. Similarly, *o*-QMs have been detected in daunomycin and have been shown to function as alkylating agents [116]. The formation of *o*-QMs as reactive intermediates in biologically active natural products has been reviewed [117,118]. Apart from their involvement in biological processes, *o*-QMs are also very versatile intermediates in organic synthesis [119–124], but until now they have been less utilized in total syntheses [125]. Since they are ephemeral species [126], they must be generated *in situ* by processes that involve photolysis of *o*-, *m*-, or *p*-hydroxybenzyl alcohols [127], thermal reactions [128,129], thermal extrusion of sulfur dioxide [128] and anionic triggered reactions [130,131]. In this regard, Amouri *et al.* synthesized the first metal-stabilized *o*-QM and found that it is reactive toward alkenes [132,133]. Nevertheless, there are some nonmetal stabilized *o*-QMs that can also be isolated. For example, in 1969, Sullivan *et al.* [134] showed that 9,10-phenanthrenequinone (**16**) reacts with several Wittig reagent (Carbethoxyethylidene) triphenylphosphorane (**17**) reagents to produce *o*-QM derivatives of phenanthrene which were quite stable toward isolation. The authors found that their stabilities were dependent on the electronegativity and bulkiness of the substituents on the *o*-QM moiety. Later on, Nicolaides *et al.* [135] revisited the reaction and prepared other *o*-QMs (*e.g.*, **18**) (Scheme 2).

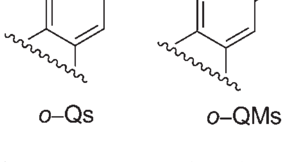
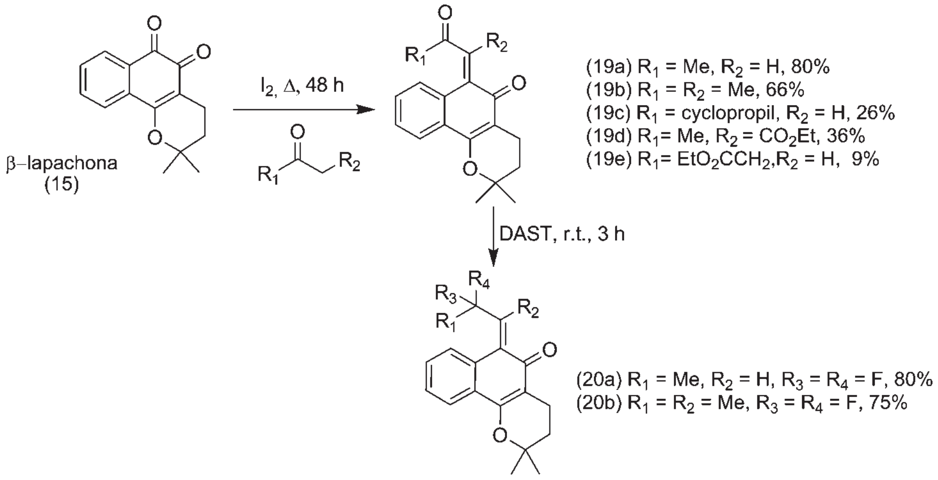


Figure 6. General structure of *o*-quinone methide.

Very recently, Da Silva *et al.* prepared several stable *o*-QMs (**19a–e, 20a–b**) from β-lapachone (**15**) [136] under conditions that allowed for Aldol condensation with one of the carbonyls (Scheme 3).

The *o*-benzoquinone methide moiety (**21**) is a reactive intermediate that has potential synthetic utility as reported in many articles [137]. In 1976, Heldeweg and Hogeveen showed that *o*-benzoquinone methides prepared by pyrolysis of *o*-hydroxybenzyl alcohols (**22**) at 180°C in the presence of 2 equiv of $[Rh(CO)_2Cl]_2$ afforded 2[3H]-benzofuranone (**23**) in 12% yield [138]. Therefore, it is common that *o*-benzoquinone methides cannot be isolated, even though they can be observed *via* low temperature infrared [139], UV [140] or photoelectron spectroscopy [141] (Scheme 4).

Scheme 3



SYNTHETIC METHODOLOGY FOR PREPARING 2*H*-CHROMENES AND CHROMANES

This review will focus specifically on current strategies involving the construction of chromene and chromane rings *via* *o*-QMs that are mainly coupled with a quinone nucleus (Scheme 1).

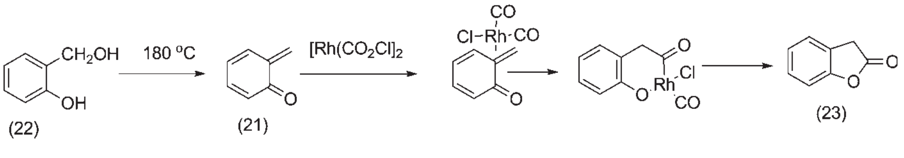
SYNTHESIS OF 2*H*-CHROMENES AND CHROMANES BY TRAPPING OF *o*-QMS *VIA* ELECTROCYCLIZATION

In 1969, Dudley and Chiang [50] reported a one-step synthesis of 2,2-dimethyl-2*H*-chromenes by exposing isolapachol (**24**) to an equimolar quantity of DDQ in benzene, resulting in oxidative cyclization to a mixture of the dehydro-α and -β-lapachones (**11** and **12**, Fig. 5). Consideration of the possible mechanisms by which chromenes **11** and **12** might arise led to the postulate that the isomeric *o*-quinone methide intermediates **25** and **26** might undergo a 6π-electrocyclic reaction. This simple procedure proved to be a facile entry into the lapachone series and was further simplified by the observation that **12** can be converted to **11** by treatment with acid. The authors proposed that the two isomeric *o*-QMs are involved as the key intermediates in the reaction mechanism and that their electrocyclization leads to the formation of the chromene moiety (Scheme 5).

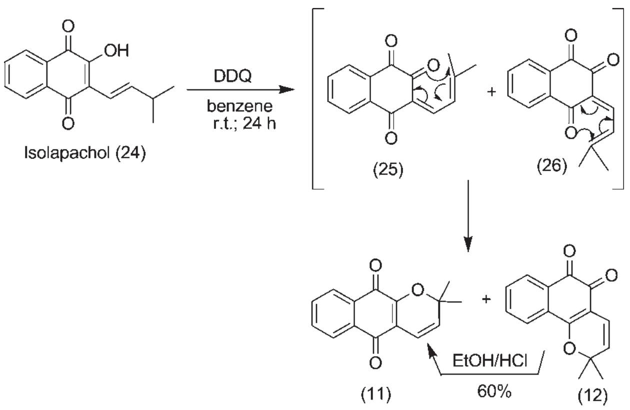
A new route for introducing the chromene moiety, based on the formation of an *o*-QM intermediate (**27**) through a tandem Knoevenagel-electrocyclic reaction, was reported by Ferreira *et al.* in 1980 [142]. The reaction of lawsone (**28**) with α,β-unsaturated aldehydes exclusively produced α-dehydrolapachones (**29–31**) in an average yield of 33%. The same synthetic route and conditions were used by De Oliveira *et al.* [143] for the preparation of the naturally occurring dihydro-α-caryopterone (**32**) and its isomer, 6-hydroxy-dehydro-α-lapachone (**33**) (Scheme 6).

Recently, the reaction of lawsone (**28**) with 3-methyl-2-butenal (**34**) utilizing several bases and Lewis acid catalysts was reinvestigated in order to improve the yield of dehydro-α-lapachone (**11**) [144]. This study found that indium (III) chloride (10 mmol %) and ytterbium (III) triflate (10 mol %) catalysts in acetonitrile produced the desired compound in very low yields. However, by using $Yb(OTf)_3$ in DMF at 100°C, the desired compound was produced in higher yield (55%). By using pyridine as a catalyst and solvent, the product was formed in 54% yield. The best condition found was with ethylenediamine diacetate (10 mol %) as the catalyst in MeOH (75%) or benzene (80%) (Scheme 7) [145]. As previously observed by Ferreira *et al.* in 1980, only the dehydro-α-lapachones were formed under these reaction conditions (Scheme 6).

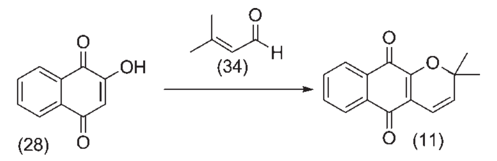
Scheme 4



Scheme 5



Scheme 7



Catalyst	Conditions	Yields (%)
$InCl_3$ (10 mol%)	MeCN, Δ, 5 h	5
$Yb(OTf)_3$ (10 mol%)	MeCN, Δ 5 h	10
$Yb(OTf)_3$ (10 mol%)	DMF, 100 °C, 5 h	55
Pyridine (excess)	$MgSO_4$, Δ, 5 h	54
Ethylenediamine diacetate (10 mol%)	$InCl_3$,(10 mol%)	47
Ethylenediamine diacetate (10 mol%)	MeOH, r.t., 5 h	75
Ethylenediamine diacetate (10 mol%)	Benzeno, Δ, 5 h	80

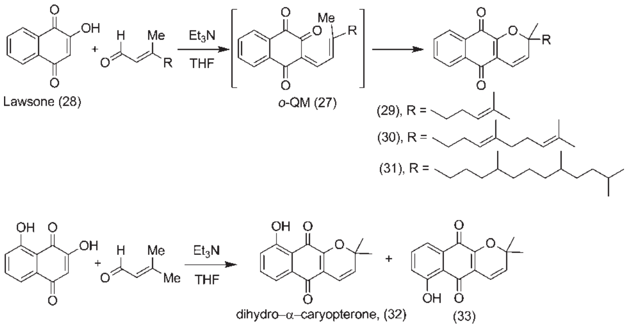
Although the aforementioned tandem-Knoevenagel-electrocyclic reaction with α,β-unsaturated aldehydes exclusively produced dehydro-α-lapachones quite successfully, Hayashi *et al.* found that in sharp contrast, the reaction of lawsone (**28**) with acrolein (**35**) does not even undergo cycloaddition [146]. Instead, two products were formed. The major isolated compound was *o*-QM (**36**), which is very stable. These products arose from two different possible condensations between acrolein and lawsone, a Claisen-Schmidt reaction and a Michael reaction, leading to **36** or **37**, respectively, after acetalization. Tournaire *et al.* [147] revisited this condensation under several acidic conditions and isolated **36** and **37**, as previously reported, along with some other products. When the reaction was performed in the presence of an excess of hydrochloric acid, **39** was isolated in less than 10% yield. Compound **39** is presumably produced *via* the formation of *o*-QM (**38**), followed by chlorination of a double bond (Scheme 8).

Other research groups soon became attracted to the opportunities presented by these tandem Knoevenagel-electrocyclic reactions. For instance, Hua *et al.* reported the condensation of various 6-substituted 4-hydroxypyrones with 1-cyclohexenecarboxaldehydes in the presence of L-proline in ethyl acetate gave high yields of substituted 1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-*b*][1]benzopyrans [148]. And the next advance was disclosed by Snieckus and coworkers. They reported a facile procedure for preparing 2*H*-chromenes (*e.g.*, **40**, Scheme 9) by coupling commercially available phenols (**41**) and naphthols (*e.g.*, **42**) with α,β-unsaturated aldehydes (**43**) under the influence of phenylboronic acid [149]. This reaction protocol was extended to a synthesis of β-lapachone (**15**) [150,151], which illustrates the rapid access to these types of molecules by this method.

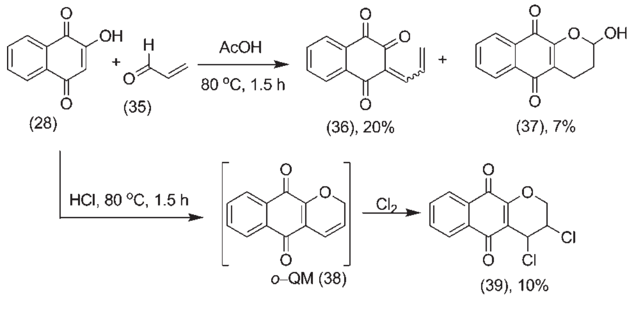
An interesting strategy for the synthesis of epoxynaphthopyranoquinone (**45**), a xiloidone derivative, was reported by Tapia and coworkers [152]. The authors synthesized benzopyran quinone (**46**) using the tandem Knoevenagel-electrocyclic protocol *via* an *o*-QM intermediate (**47**). Their synthetic route started from 2,5-dimethoxyphenol (**48**) that had its phenolic group protected as a tetrahydropyranyl (THP). This intermediate was transformed to *o*-hydroxy-γ,γ-dimethyl allyl alcohol (**49**) by reaction of **50** with 3-methyl-2-butenal (**34**) under basic conditions. The mild hydrolysis of the THP protecting group and dehydration of **50** led to formation of the *o*-QM intermediate, which upon intramolecular electrocyclization, formed benzopyrane (**46**). The latter compound was transformed in three steps to epoxynaphthopyanoquinone (**45**) (Scheme 10).

More recently, Dintzner and coworkers [153] reported for the first time a direct condensation of phenols with α,β-unsaturated aldehydes catalyzed by clays. The reaction between 3-methyl-2-butenal (**34**) and sesamol (**51**)

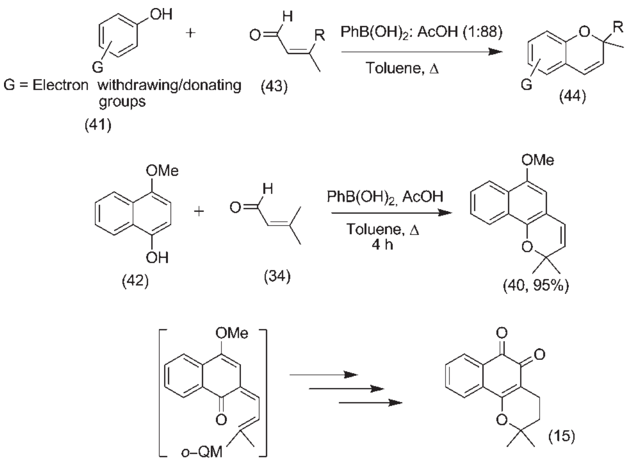
Scheme 6



Scheme 8



Scheme 9

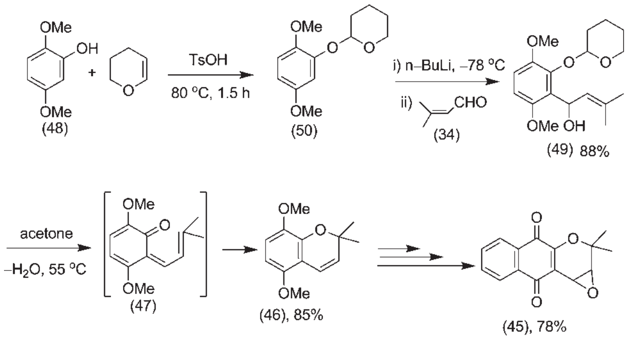


was used as the model reaction in order to prepare methylenedioxyprecocene (**52**), which as mentioned previously, exhibited antijuvenile hormone activity in some insects. Acidic montmorillonite K10 clay promoted the electrophilic aromatic addition yielding the desired 2*H*-chromene (**52**) through an *o*-QM intermediate (**53**). The optimal conditions for this process involved the reaction of the substrate on basic clay (K10–K$^+$) at 110°C, without solvent, under microwave irradiation (Scheme 11).

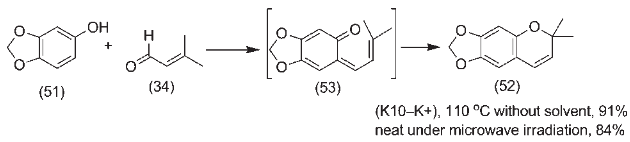
Parker and Mindt developed a very useful one-step procedure for synthesizing chromenes (**54a–c**) by a thermally induced 6π-electrocyclization of the enolizable vinyl quinone (**55**) *via* an intermediate quinone methide (**56**). The enolizable vinyl quinones are the products of Stille coupling. Application of this method led to the total synthesis of an *Ageratum* juvenile hormone (Scheme 12) [110].

Very recently, Da Silva and coworkers [154] developed a new general methodology that involves the reaction of *ortho*-naphthoquinones with allyltriphenylphosphonium salts **58a** and **58b** in the presence of an aqueous solution of NaOH and chloroform. The reaction proceeded *via in situ* formation of an ylide, and subsequent reaction with an *ortho*-naphthoquinone to produce *o*-QM intermediate **59**, which cyclizes to a 2*H*-chromene, as outlined in Scheme 13. With this selective and general one-pot synthesis, several 2*H*-chromene derivatives (**60**, **61,** and **62**) were obtained from the appropriate *ortho*-naphthoquinones and allyltriphenylphosphonium in yields ranging from 47 to 85%. It should be noted that the attack of the phosphorus ylide occurred exclusively at the more reactive 1- or α-position of the carbonyl carbon of the *ortho*-naphthoquinone. No products were detected from attack at the 2- or β-carbonyl.

Scheme 10



Scheme 11



SYNTHESIS OF 2*H*-CHROMENES AND CHROMANES *VIA o*-QMS HETERO-DIELS-ALDER REACTIONS

The unique feature of the Diels-Alder reaction of constructing up to four new stereogenic centers in one step has made this reaction one of the most important tools in the field of organic synthesis. It is not surprising, considering its scope, that Diels-Alder reaction continues to be important for constructing polycyclic ring systems of complex natural product targets [155]. Its broad reaction possibilities have led to an enormous number of variations, both intermolecular and intramolecular [156,157], with high levels of stereocontrol, as summarized in several review articles [158].

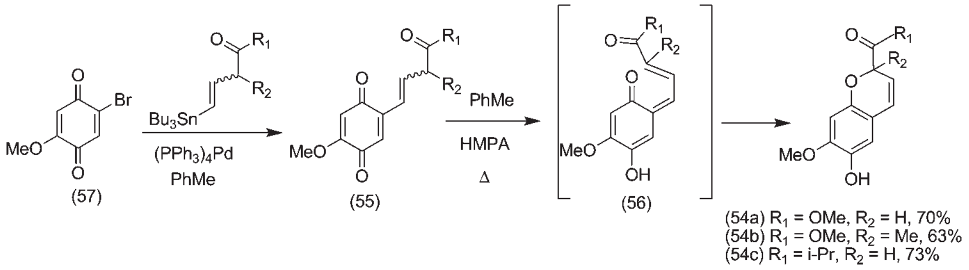
A very important variation of the typical Diels-Alder reaction is the hetero-Diels-Alder reaction. In this variation, heteroatoms, such as a carbonyl group, replace a carbon–carbon double bond in either the diene or dienophile [159–162].

o-QMs are hetero-dienes suitable for [4 + 2] cycloadditions with a wide range of dienophiles in either inter or intramolecular processes (Fig. 7). This reaction would lead directly to the chromane substructures. However, the intermolecular process has two major problems that must be overcome (among others): the fast dimerization of the *o*-QMs to spiro compounds [163,164] and that *o*-QMs generation and trapping must be done *in situ*.

SYNTHESIS OF 2*H*-CHROMENES AND CHROMANES *VIA o*-QMS AND INTERMOLECULAR HETERO-DIELS-ALDER REACTIONS

The first example that generated and made use of an *o*-QM in an intermolecular hetero-Diels-Alder reaction

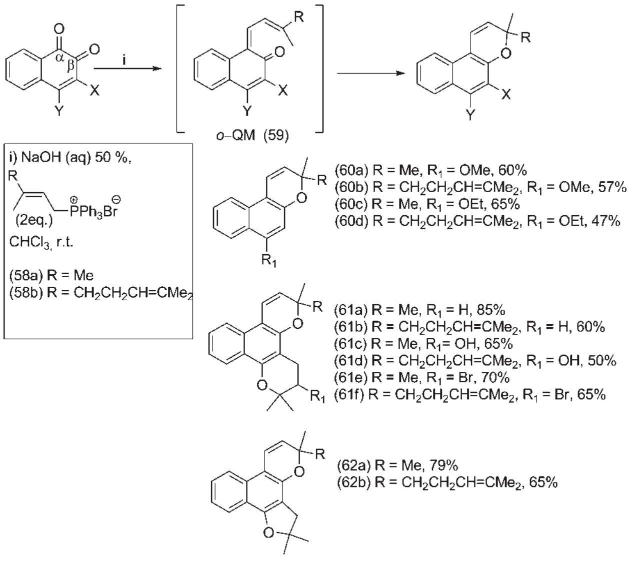
Scheme 12



was reported by Brougidou and Christol [165,166], who reacted *o*-QMs with butadiene (**63**) to obtain 2-vinylchromans (**64**) as the only reaction product. Chapman and Mcintosh in 1971 (Scheme 14) [167] demonstrated that the dimerization of *o*-QMs could be a useful methodology to prepare natural products. In this regard, they produced an *o*-QM by photodecarbonylation of the unsaturated lactone (**65**), which was then efficiently trapped with 1,l-dimethoxyethylene (**66**) producing an *ortho*-lactone (**67**) with high yield (>90%). Very recently, this reaction was reinvestigated, but the generation of *o*-QM (**68**) and subsequent hetero-Diels-Alder reactions was under mild, anionic conditions to prepare benzopyrans (**69a–d**) [168].

Baldwin and coworkers developed a biomimetic synthesis of Lucidene (**71**) based upon the fact that both this compound and humulene (**72**) were isolated from the root bark of *Uvaria lucida ssp. lucida* and **71** could be formed as the products of a double Diels-Alder reaction with two molecules of *o*-benzoquinone methide [169]. In a subsequent work, the same group synthesized pycnidione and epolone B using an *o*-QM derived from benzotropolone (**73**) *via* a hetero-Diels-Alder reaction with humulene [170]. More recently, they reported a biomimetic hetero-Diels-Alder reaction between humulene and a novel tropolone *o*-QM (**74**) to give a deoxy analog of epolone B (**75**) (Scheme 15) [171].

Scheme 13



The search for new *in situ* methods to generate *o*-QM intermediates without side reactions or with long reaction times and at low temperatures continues to be desired. In this regard, Baldwin and coworkers explored reductive transesterification with an aldehyde (**76**) to produce *o*-methyleneacetoxy-phenol (**77**), which under thermal conditions generated an *o*-quinone methide that cyclized (**78**). They applied this methodology to the synthesis of (±)-alboatrin (**79**) [172] and (±)-lucidene (**71**) (Scheme 16) [173].

SYNTHESIS OF 2*H*-CHROMENES AND CHROMANES *VIA* *o*-QMS AND INTRAMOLECULAR HETERO-DIELS-ALDER REACTIONS

Chapman and coworkers demonstrated that palladium chloride induced dimerization of *o*-vinylphenol (**80**) to generate an *o*-QM (**81**), which undergoes intramolecular hetero-Diels-Alder cyclization. They applied this useful methodology to prepare the natural product carpanone (**82**) in one step following a biomimetic pathway (Scheme 17) [174].

Much research has been focused on developing new and better methods for generating *o*-QM intermediates that can be trapped by an intramolecular Diels-Alder reaction. Hug and coworkers [175] reported that thermal dehydration of *o*-hydroxybenzyl alcohol (**83**) led to three products that could only be produced through an intermediate *o*-QM (**84**) generated *in situ*, followed by an intramolecular Diels-Alder cycloaddition. The authors proposed that the formation of the *o*-QM (**84**) occurs by an initial dehydration and concerted [1,5]-hydrogen shift, which is followed by a [4 + 2] cycloaddition to produce the product (**85**, **86**, and **61**) in 69% yield. Later, Boekelheide and Mao [176] performed flash

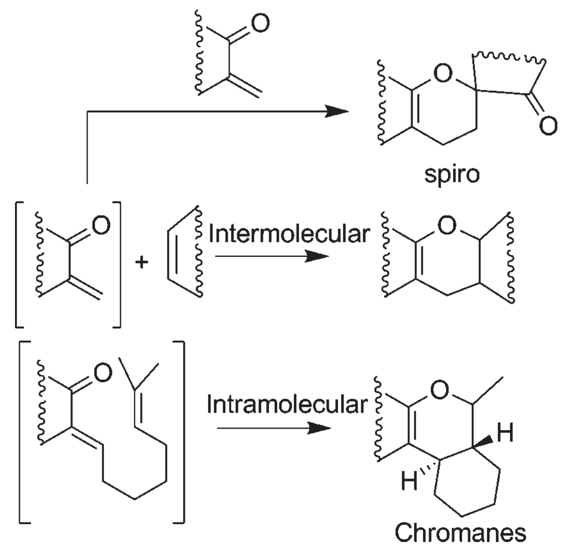


Figure 7. *o*-QMs as hetero-dienes for the construction of chromanes.

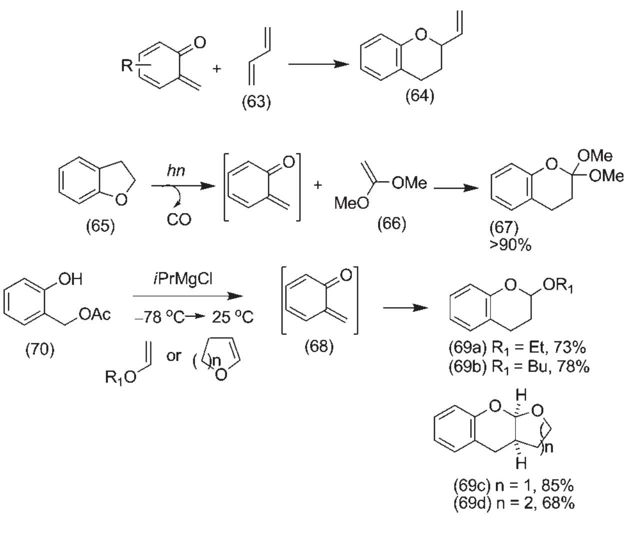
pyrolysis experiments of **84** at 700°C and found only product **85**, but in only 12% yield (Scheme 18).

Tietze and coworkers described the intramolecular Diels-Alder reaction between 1,3-cyclohexadione (**88**) and citronellal (**89**). They obtained tricyclic dihydropyran (**90**) with trans stereochemistry *via* an *exo-E-anti* transition state [177–179]. It is worthy to note that this structure was proved by X-ray structure analysis. The investigation into the conformation of the transition state was extended to benzylidenepyrazolones and benzylideneisoxazolones. The same *exo-E-anti* stereochemistry was also observed for these products (Scheme 19) [180,181].

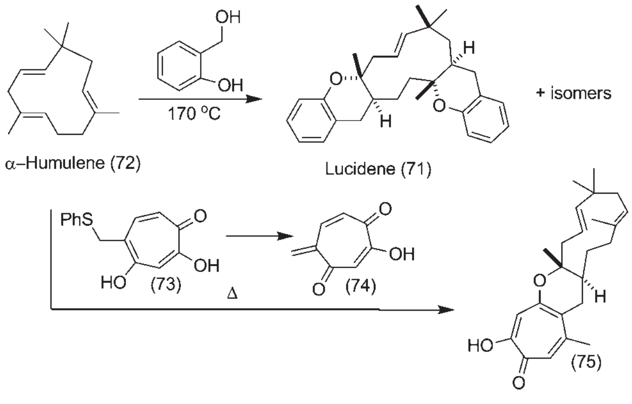
Ferreira and Pinto [182] in 1980 reported a novel preparation of tetracyclic α- and β-pyranaphthoquinones using an *o*-QM intermediate, generated *in situ*, followed by a tandem Knoevenagel/hetero-Diels-Alder reaction. The authors, instead of reacting natural α,β-unsaturated aldehydes with lawsone (**28**) (*e.g.*, citral) [142], reacted lawsone with an aldehyde bearing a remote double bond (*e.g.*, citronellal—**89**). In the later case, the *o*-QMs (**91** and **92**) underwent an intramolecular hetero-Diels-Alder reaction with the double bond to form tetracyclic α- and β-pyranaphthoquinones (**93** and **94**) in 70% yield. In order to obtain β-pyranaphthoquinone (**94**), a tetracyclic derivative of β-lapachone, the mixture was treated with H_2SO_4 (Scheme 20). Recently, Jiménez-Alonso and coworkers performed the asymmetric version of this reaction with (*s*)-(-)-citronellal, producing compounds **93** and **94** in a 1:1 ratio with 94% overall yield [183]. By using Yadav's methodology [184], they extended this reaction to other prenylated aromatic aldehydes with the double bond at an appropriate distance to generate new naphthoquinones. It should be noted that aromatic aldehydes furnished only *cis* adducts due to an *endo-E-syn* transition state. For instance, compounds **95** and **96** were obtained in 72% at a 1:1 ratio (Scheme 20).

Other research groups soon became attracted to the opportunities presented by these aforementioned thermal dehydrations of *o*-hydroxybenzyl alcohols that gave products that could only be produced through an *o*-QM intermediate followed by an intramolecular Diels-Alder cycloaddition. In 1985, Talley [185] studied this reaction both thermally and photochemically, starting with (*R*)-

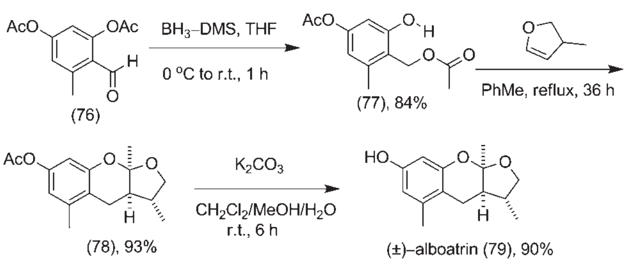
Scheme 14



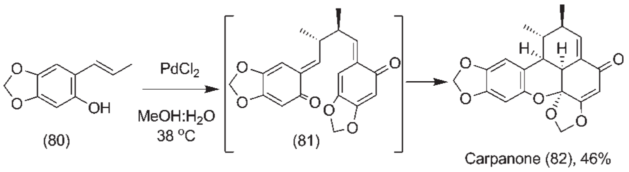
Scheme 15



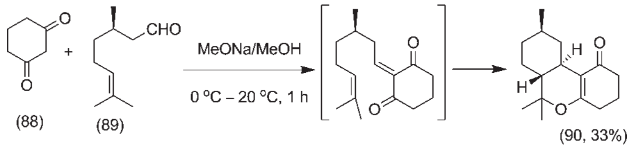
Scheme 16



Scheme 17



Scheme 19

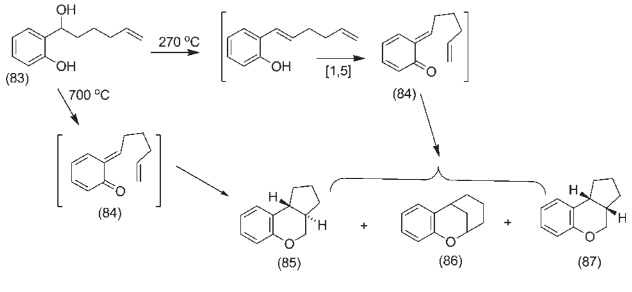


citronellal (**89**), in order to obtain informations about the transition state of the cycloaddition. The reactions were very successful in the generation of substituted *o*-QMs by the thermal dehydration of *o*-hydroxybenzyl alcohol derivatives (**97**) and subsequent intramolecular Diels-Alder reaction. The dehydration of *o*-hydroxybenzyl alcohol followed by intramolecular Diels-Alder reaction proceeded with excellent regio and stereospecificity. The presence of a chiral center on the alkyl side chain resulted in a high degree of stereocontrol during the cycloaddition reaction. The *trans* stereochemistry was the same as observed by Pinto and Ferreira and is thought to proceed *via* a pseudoequatorial conformation adopted by the chair-like exo transition state during the intramolecular Diels-Alder cycloaddition (Scheme 21).

Given the success of the preliminary results [152,186], Tapia's group [187] showed an interesting approach to obtain 2*H*-benzopyrans by using a Tandem Knoevenagel hetero-Diels-Alder reaction with citral (α,β-unsaturated aldehyde) instead of a Tandem Knoevenagel electrocyclization. Their protocol involved the addition of a suitably protected aryl lithium derivative of citral, followed by deprotection and cyclization *via* an *o*-QM to produce the chromane (**100**) [188]. In two more steps, the latter compound was transformed to an α-lapachone derivative (**101**). It is also clear from their results that the cis stereochemistry of **101** is opposite of that found by Hug [175], Ferreira [182] and Talley [185]. This is likely because of the endo transition state is favored due to conjugated double bond with *o*-QM moiety (Scheme 22).

o-Quinone methides (**106**) can also be efficiently produced by photoirradiation of phenolic Mannich bases (**107**) in aqueous solvents at neutral pH, by irradiation with >300 nm light and rapid trapping by ethyl vinyl ether (**108**) *via* an intermolecular hetero-Diels-Alder reaction [189]. This strategy has been used to prepare a series of chromane derivatives such as compounds **109** and **110** in Scheme 23. This procedure was also applied to the formation and trapping of bisquinone methide (**111**), although in low yield (Scheme 23).

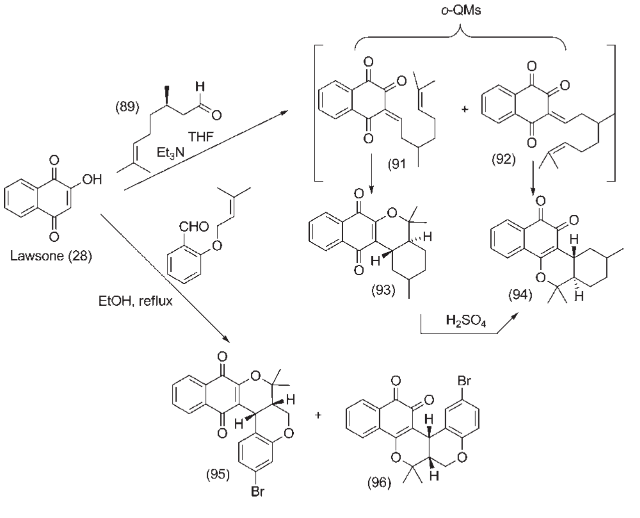
Scheme 18



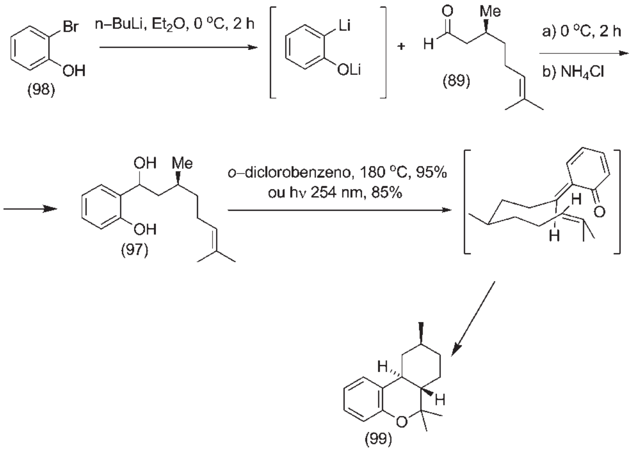
Ye and coworkers conveniently developed an interesting protocol for the synthesis of 5-one heterocyclic systems *via* heterocyclic quinone methides. A wide variety of pyrano[3,2-c]quinolines (**114a–d**) possessing different functional groups have been prepared successfully by the tandem Knoevenagel condensation of 4-Hydroxyquinolin-2(1H)-ones (**115**) with aldehydes (**116**). The formation of the products was rationalized by an initial Aldol condensation, to form the methide intermediate (**117**). This then undergoes a Michael-type-1,4-addition of the enolate anion followed by an intramolecular cyclization (Scheme 24) [190].

Similarly, Nair and coworkers reported a series of articles exploring the reactivity profile of *o*-QMs [191] generated *in situ* from lawsone (**28**), 4-hydroxycoumarin (**118**) and 4-hydroxyquinoline (**119**) and their subsequent intermolecular Diels-Alder reaction. This protocol overcomes the limitation regarding the use of appropriately substituted aldehydes in the tandem Knoevenagel/intramolecular hetero-Diels-Alder cycloaddition methodology.

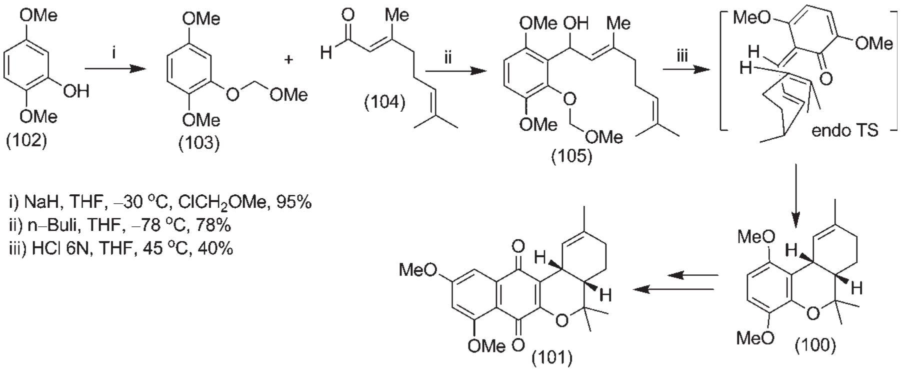
Scheme 20



Scheme 21

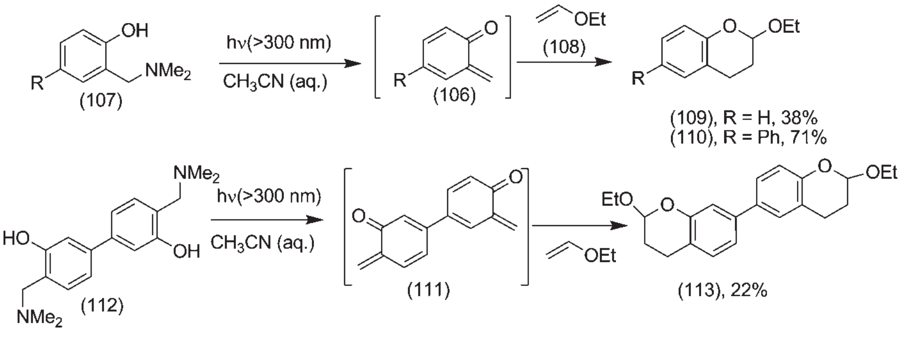


Scheme 22

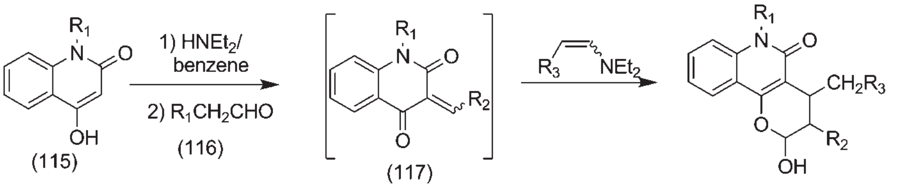


i) NaH, THF, –30 °C, ClCH2OMe, 95%
ii) n–Buli, THF, –78 °C, 78%
iii) HCl 6N, THF, 45 °C, 40%

Scheme 23

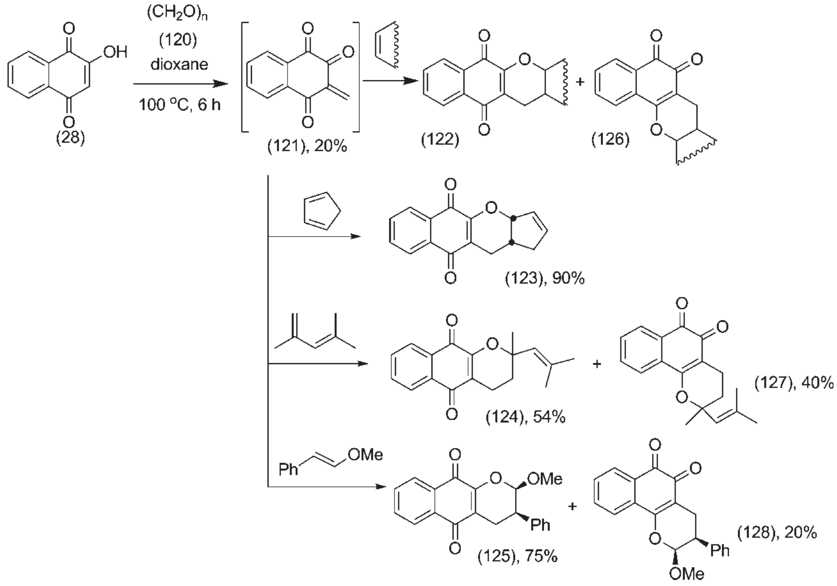


Scheme 24



(114a) $R_1 = R_2 = H$, $R_3 = Me$, 51%
(114b) $R_1 = R_2 = Me$, $R_3 = H$, 60%
(114c) $R_1 = Et$, $R_2 = H$, $R_3 = Me$, 50%
(114d) $R_1 = R_3 = Et$, $R_2 = Me$, 74%

Scheme 25



Scheme 26

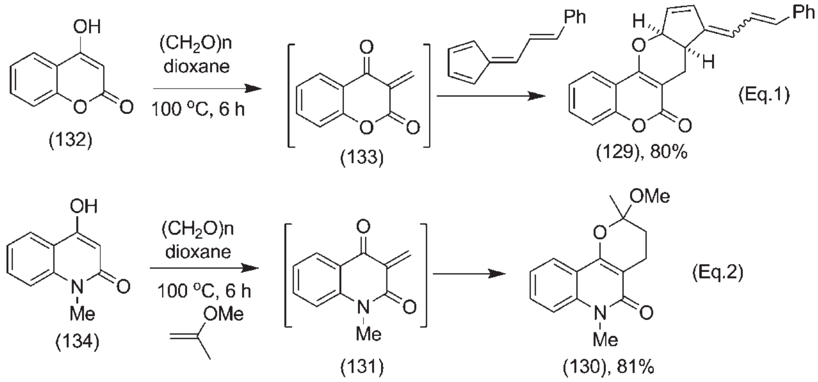
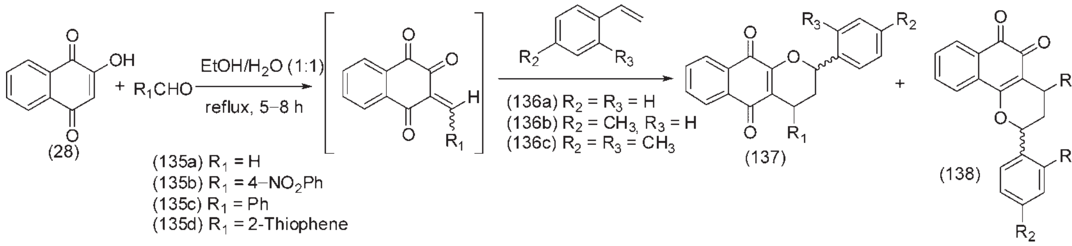


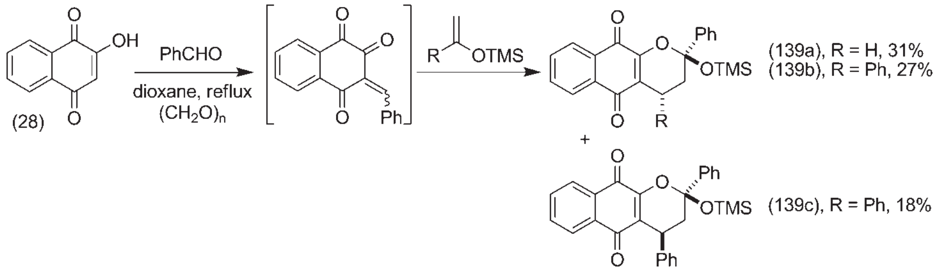
Table 2

Intermolecular hetero Diels-Alder to obtain α- and β-pyranaphthoquinones.



Entry	R_1	R_2	R_3	Conditions	Time (h)	Yield %	Ratio α/β (139:140)	α (cis:trans)	β (cis:trans)
1	H	H	H	$EtOH/H_2O$ (1:1)	6	94	3.1	–	–
2	H	CH_3	H	$EtOH/H_2O$ (1:1)	6	95	3.8	–	–
3	H	CH_3	Me	$EtOH/H_2O$ (1:1)	6	97	4.7	–	–
4	4-NO_2Ph	CH_3	H	$EtOH/H_2O$ (1:1)	5	50	1.4	37:63	18:82
5	2-Thiophene	CH_3	H	$EtOH/H_2O$ (1:1)	8	60	0.8	54:46	0:100
6	Ph	CH_3	H	$EtOH/H_2O$ (1:1)	8	52	0.6	20:80	12:88
7	H	H	H	Dioxane/HOAc	4	96	2.2	–	–
8	4-NO_2Ph	CH_3	H	Dioxane/HOAc	5	55	1.1	35:65	17:83

Scheme 27



In the first approach, Nair and Treesa [192] described a new, general three-component reaction for the synthesis of a wide variety of derivatives of α- and β-lapachone and other heterocyclic compounds. The reaction involved the Knoevenagel condensation between lawsone reagent (**28**) and paraformaldehyde (**120**) leading to the *o*-QM (**121**), which reacts *in situ* with several possible olefins to generate products in moderate to good yields. The latter methodology offers several alternative approaches for the syntheses of α- (**122, 123, 124,** and **125**) and β-lapachone (**126, 127,** and **128**) derivatives as illustrated in the selected examples shown in the Scheme 25.

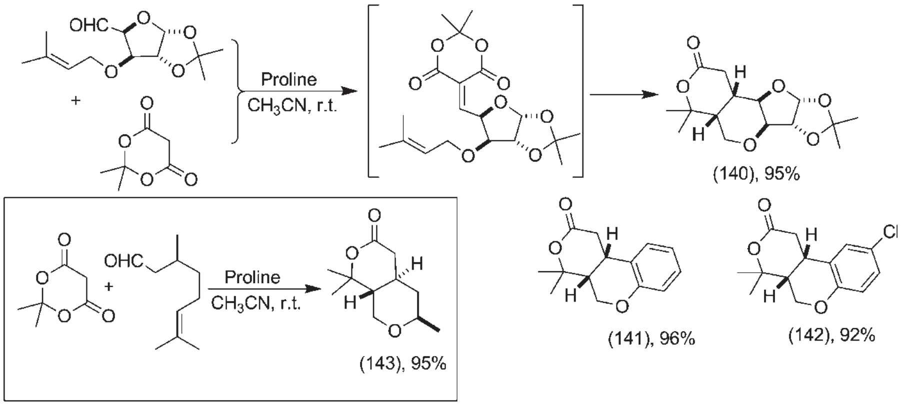
In related studies, the same group extended this three component methodology for the preparation of pyranopyrone derivatives (**129**) [Scheme 26, eq. (1)] [193]. They also demonstrated the potential of this protocol by applying it to the synthesis of pyranquinolines (*e.g.*, **130**) *via* quinoline quinone methide (**131**) as the key intermediate [Scheme 26, eq. (2)] [191].

Despite the good yields achieved in previous reactions with formaldehyde, aromatic aldehydes did not work even at reflux for periods exceeding 48 h. Aiming to improve the scope of this reaction and thus, to obtain various derivatives of lapachones, Ferreira and coworkers investigated the effect of solvents and found that reaction was accelerated in ethanol/water (1:1) at reflux [194]. With this improved methodology, it was possible to obtain β-pyranaphthoquinones more selectively, in better yields and with lower reaction times. Additionally, this methodology allowed the use of other aldehydes, not just formaldehyde (Table 2).

This reaction protocol was extended to the synthesis of silyl enol ethers to give a series of siloxy-containing naphtho[2,3-b]pyran-5,10-dione derivatives (**139a–c**) in moderate to high yields (Scheme 27) [195]. As expected, the reaction regioselectively produced α-lapachone derivatives. The authors rationalized these results by calculating the parameters of the frontier molecular orbital. This indicated that interaction of the *o*-QM with the silyl enol ether is a more energetically favorable pathway.

A very interesting variation of the protocol for *in situ* formation of *o*-QMs followed by Diels-Alder cycloaddition was reported by Sabitha *et al.* [196,197]. In this work, it was shown that the reaction of *O*-prenyl and *N*-prenyl aldehydes with Meldrum's acid led to cis-fused lactones (**140–142**) in excellent yields. Aliphatic aldehydes, such as citral, could also be used in this reaction, but as expected, the product **143** is trans (Scheme 28).

Scheme 28



CONCLUSIONS AND OUTLOOK

This review has given ample evidence that *o*-QM intermediates have developed into a useful synthetic tool for preparing chromene and chromane rings over recent years. Major progress has been made in terms of substrate scope and the development of efficient procedures for their preparation. All these developments have led to extensive use of *o*-QM intermediates in inter and intramolecular hetero-Diels-Alder and electrocyclization reactions in the field of total synthesis. The reaction even turned out to be a key tool for the preparation of pyran naphthoquinones. However, these reactions still have some drawbacks. For example, intermolecular reactions with *o*-QMs are, by far, more difficult to achieve, which is often due to reaction reversibility. Despite the improved methods for generation of *o*-QMs, their use with aldehydes has been difficult. Only very recently has this problem been partly addressed by modifying the conditions in the tandem processes. There is still a need for even more general reaction protocols, especially in the areas of intermolecular reactions and enantioselectivity.

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Synthetic Approaches to 3*H*-Naphtho[2,1-*b*]pyrans and 2,3-Dihydro-1*H*-naphtho[2,1-*b*]pyrans

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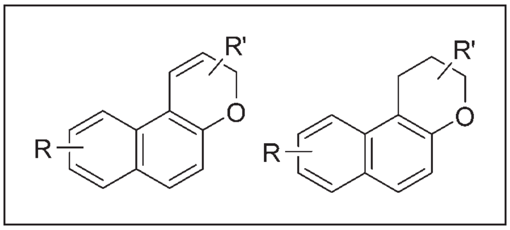

Naphtho[2,1-*b*]pyran nuclei are prevalent in natural products with significant biological and medicinal properties. 3,3-Disubstituted 3*H*-naphtho[2,1-*b*]pyrans are photochromic and find use in electronic display systems, ophthalmic lenses, optical switches, and temporary or permanent memories. Of the various possible structural isomers of naphthopyran framework, this review is an account of reported synthetic procedures to produce 3*H*-naphtho[2,1-*b*]pyrans and their dihydro analogs, 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans. The advantages and disadvantages of each procedure in terms of yields, complexity, formation of side-products, use of uncommon/expensive reagents, *etc*., are also described.

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INTRODUCTION

The pyran ring in the dihydronaphthopyran skeletons can be linearly or angularly fused to a naphthalene nucleus sharing one bond in several orientations. This leads to six different dihydronaphthopyran skeletons as shown in Figure 1. These compounds can also be viewed as dihydrobenzochromenes or dihydrobenzoisochromenes. This review deals with 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans (a.k.a. 2,3-dihydro-1*H*-benzo[*f*]chromenes or 1*H*-benzo[*f*]chromans) and their dehydro analogs 3*H*-naphtho[2,1-*b*]pyrans (a.k.a. 3*H*-benzo[*f*]chromenes).

KNOWN PROPERTIES OF NAPHTHOPYRAN DERIVATIVES

3*H*-Naphtho[2,1-*b*]pyrans, also known as 3*H*-benzo[*f*]chromenes (**1**), are well documented for their photochromic properties [1,2]. Photochromism can be seen as a reversible transformation of a chemical species induced in one or both directions by absorption of electromagnetic radiation. The mechanism involves facile electrocyclic reaction of pyran ring opening to yield a mixture of yellow or purple colored isomers (**2**). These colored species gradually cyclize, returning to the colorless pyran (**1**) ring upon thermal reaction (Scheme 1) [1,2].

This characteristic led to their application in transition lenses, which tinted upon exposure to the sunlight [3]. Photochromic properties of 3*H*-naphtho[2,1-*b*]pyrans also make them valuable to be used for a variety of other applications such as electronic display systems, optical switches, and temporary or permanent memories [4–6]. Furthermore, 3*H*-naphtho[2,1-*b*]pyrans and their oxygenated and/or partially reduced congeners have also been isolated from natural sources [7–9]; several analogs are reported to posses interesting biological activities [8–12]. Molecular structures of several representative examples are shown in Figure 2. A homoprenylated 3*H*-naphtho[2,1-*b*]pyran **3** was isolated from the roots of *Pentas bussei* [7]. In another case, several naphthopyrans including Adenaflorins C (**4**) were isolated from young leaves of *Adenaria floribunda* and bioassays show these compounds have cytotoxic effect against human cancer cells [8]. Bioassay-guided fractionation of extract of *Musa paradisiaca* cultivar using the quinone reductase induction assay led to the isolation of tetrahydro naphtho[2,1-*b*]pyran **5** (stereochemistry relative) [9]. Braccio *et al.* reported potent antiproliferative and cytotoxic properties of 1-*N*,*N*-dialkylamino-3*H*-naphtho[2,1-*b*]pyran-3-ones **6** [10]. Unsubstituted 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran-3-one (**7**), a.k.a. splitomicin, its oxygenated analogs (**8**) and the dehydro-analog **9** were identified as a small molecule inhibitors of Sir2p, an NAD$^+$-dependent histone deacetylase required for chromatin-dependent silencing in yeast [11,12].

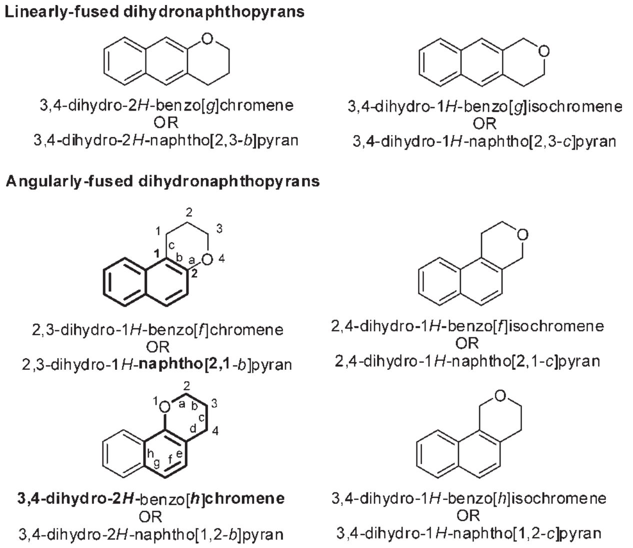


Figure 1. Dihydronaphthopyran skeletons sharing one bond between naphthalene and pyran.

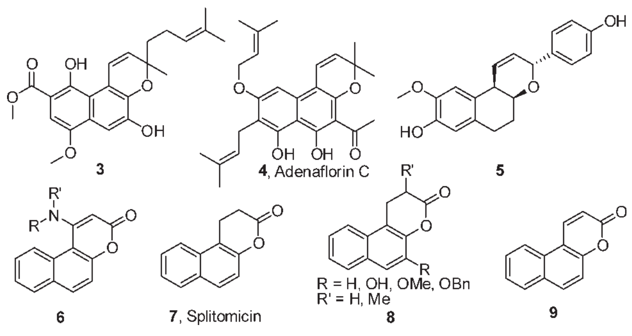


Figure 2. Examples of naturally occurring and biologically active 3*H*-naphtho[2,1-*b*]pyran derivatives.

METHODS OF SYNTHESIS OF 3*H*-NAPHTHO[2,1-*b*]PYRANS

Synthesis and properties of 3*H*-naphtho[2,1-*b*]pyrans have been studied and reported extensively, providing a wide knowledge-base for these molecules. A review on the synthesis and photochromic properties of 3*H*-naphtho[2,1-*b*]pyrans was published in 2005 [13]. Although this review focuses mainly on the synthetic routes to 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans, a brief review of synthetic approaches to its dehydro analogs 3*H*-naphtho[2,1-*b*]pyrans will be presented here providing the update since last review [13] and highlighting the variety in chemical synthesis.

Some methodologies for preparing 3*H*-naphtho[2,1-*b*]pyrans involve multi-step strategies. Hepworth and his colleagues reported a synthesis of 1-bromo-3*H*-naphtho[2,1-*b*]pyrans (**11**) from the corresponding ketones (**10**) and PBr_3. 1-Substituted-3*H*-naphtho[2,1-*b*]pyrans (**12**) can then be further synthesized by reacting **11** with a wide range of electrophiles (Scheme 2) [14].

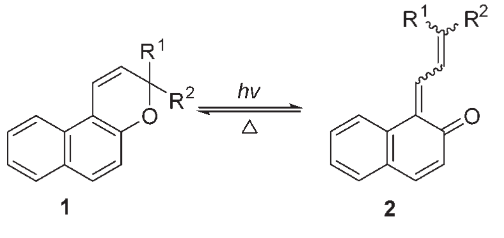
Jacobson and Vander Valde reported the synthesis of enantioenriched 3-methyl-3-(4-methylpent-3-enyl)-3*H*-naphtho[2,1-*b*]pyran-9-yl acetate (**16**) by kinetic resolution of the racemic mixture while attempting to synthesize (+)-teretifolione B (**14**), the monomer component of the potent anti-HIV agent concurvone (**15**, Scheme 3) [15]. Reaction of *E*-citral with 2,7-dihydroxynaphthalene produced racemic compound **16** in good yield [16]. Subsequent acylation followed by kinetic resolution using a manganese complex ((*R,R*)-**17**)-catalyzed asymmetric epoxidation at −78°C resulted in isolation of optically active (+)−**13** in 15% yield and 91% ee (Scheme 3).

While attempting removal of prenyl groups from protein by nucleophilic cleavage, Epstein and coworkers discovered that the 2-naphthoxide nucleophile produces prenylated 3*H*-naptho[2,1-*b*]pyrans [17]. They synthesized the prenylated 3*H*-naptho[2,1-*b*]pyrans **18** and **19** by carrying out an independent synthesis as depicted in Scheme 4. Reaction of sodium 2-naphthoxide with farnesyl bromide and geranylgeranyl chloride yielded 1-alkylated products **20** and **21**, respectively. DDQ-promoted oxidation of **20** and **21** resulted in formation of prenylated 3*H*-naptho[2,1-*b*]pyrans **18** and **19,** respectively [17].

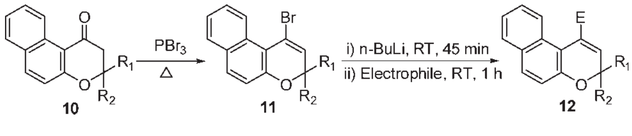
Epstein group then went on to provide more convincing evidence to the observation made during the reaction of prenylated proteins with 2-naphthoxide. They treated 2-naphthoxide with *S*-prenylated cysteine methyl ester with 2-naphthoxide in refluxing dioxane and obtained ~18% of prenylated 3*H*-naphtho[2,1-*b*]pyran **19** (Scheme 5) [17]. The reaction presumably involved C-1 alkylation, aerial oxidation, and [4+2] cycloaddition to yield the product.

Sosnovskikh and coworkers reported an interesting synthesis of a fused oxygen polycycle bearing 3*H*-

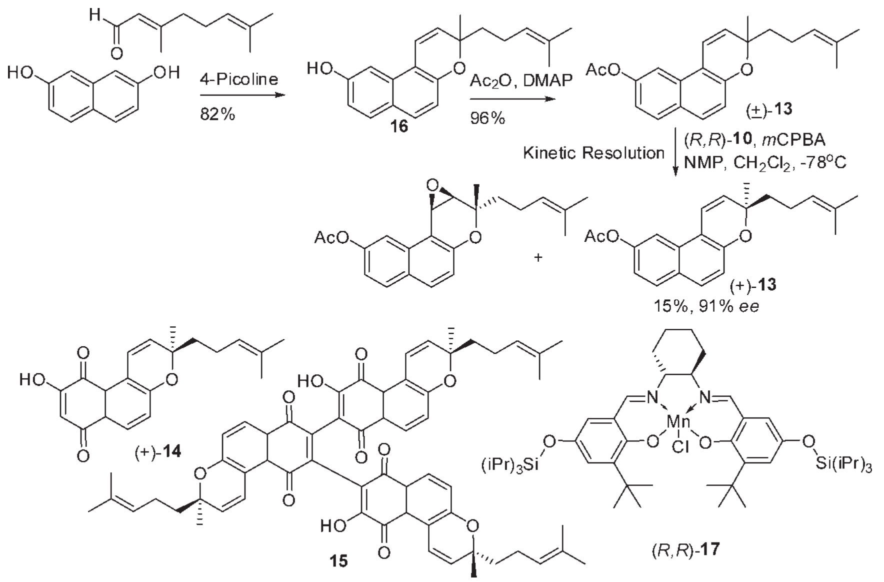
Scheme 1. Pericyclic ring opening/closure in 3*H*-naphtho[2,1-*b*]pyrans.



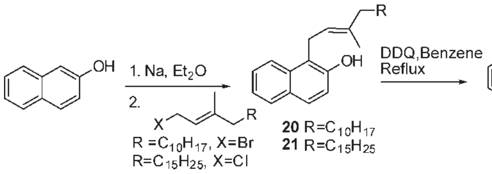
Scheme 2. Synthesis of 1-substituted-3*H*-naphtho[2,1-*b*]pyrans (**12**) from pyranones **10**.



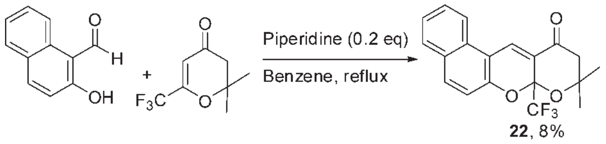
Scheme 3. Synthesis of racemic and enantioenriched 3-methyl-3-(4-methylpent-3-enyl)-3*H*-naphtho[2,1-*b*]pyran-9-yl acetate (**13**).



Scheme 4. Synthesis of prenylated 3*H*-naphtho[2,1-*b*]pyrans (**18** and **19**).



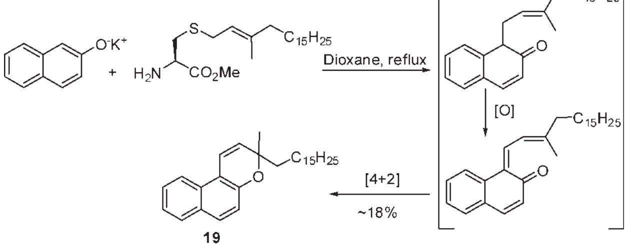
Scheme 6. Synthesis of an oxygen polycycle bearing 3*H*-naphtho[2,1-*b*]pyran nucleus (**22**).



naphtho[2,1-*b*]pyran nucleus (**22**) in 8% yield by reacting polyhaloalkyl-substituted pyrones with 2-hydroxy-1-naphthaldehyde in presence of catalytic piperidine in refluxing benzene (Scheme 6) [18]. Similar reactions with other substituted salicyaldehydes gave higher product yields (12–94%). The authors proposed that a three-component adduct is initially formed either by Michael addition/Schiff's base formation or through Baylis-Hillman protocol, which cyclizes with concomitant elimination of the secondary amine [18].

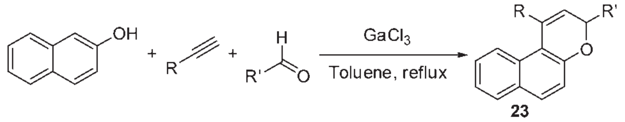
Yadav and coworkers [19] have reported an elegant procedure to produce 1,3-disubstituted 3*H*-naphtho[2,1-*b*]pyrans (**23**) from 2-naphthol, a terminal acetylene and an aldehyde in presence of 10 mol % $GaCl_3$ in refluxing toluene (Scheme 7). The terminal acetylene and the aldehyde can have an aryl or an alkyl substituent. The authors proposed that the reaction proceeds *via* arylation of alkyne to afford vinyl naphthalen-2-ol. This intermediate subsequently undergoes cyclization with an aldehyde to give the desired naphthopyran.

Scheme 5. Synthesis of prenylated 3*H*-naphtho[2,1-*b*]pyran **19** from *S*-prenylated cysteine methyl ester as the prenyl donor.

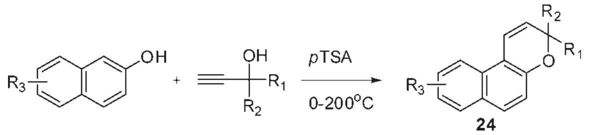


One of the most studied procedures for the preparation of 3*H*-naptho[2.1-*b*]pyrans uses the Claisen rearrangement of propargyl ethers obtained *in situ* from reaction of α,α-disubstituted propargyl alcohols with 2-naphthol under acidic conditions. For instance, 2-naphthol derivatives reacted with disubstituted propargyl alcohol in 1:1 molar ratio with *p*-toluenesulfonic acid (*p*TSA) as a catalyst (Scheme 8) to give naphthopyrans **24** [20]. The starting materials were dissolved in an aprotic organic solvent and reacted at temperatures

Scheme 7. Synthesis of 1,3-disubstituted 3*H*-naphtho[2,1-*b*]pyrans (**23**).



Scheme 8. 3,3-Disubstituted 3*H*-naphtho[2,1-*b*]pyrans (**24**) from 2-naphthols and α,α-disubstituted propargyl alcohols.



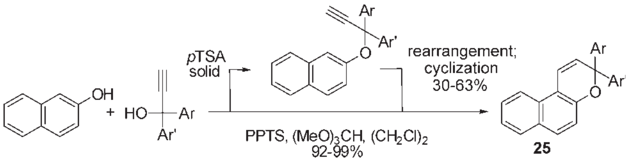
within the range of 0–200°C. However, this procedure did not provide satisfactory yield of the products (4–39%) [20].

In an improvement of this procedure, Tanaka reported a one-pot synthesis of naphthopyrans in the solid state. This reaction involved *p*TSA-catalyzed condensation of disubstituted propargyl alcohol with 2-naphthol in the first step. In the second step, naphthopyran derivatives (**25**) were obtained in moderate yield (30–63%) *via* cyclization of propargyl ether (Scheme 9) [21]. Hence, this solid-state reaction provided a green solvent-free efficient method for the synthesis of naphthopyran derivatives. Catalysts such as pyridinium *p*-toluenesulfonate (PPTS) have been used to improve yields in reactions of this nature. Zhao and Carreira used $(MeO)_3CH$ as a dehydrating agent to improve the synthesis of benzo/naphthapyrans derivatives (92–99%) [22]. In their report, disubstituted propargyl alcohols reacted with naphthol derivatives in the presence of 5 mol % PPTS and 2 equivalents of $(MeO)_3CH$ to yield various types of photochromic pyran systems (**25**, Scheme 9).

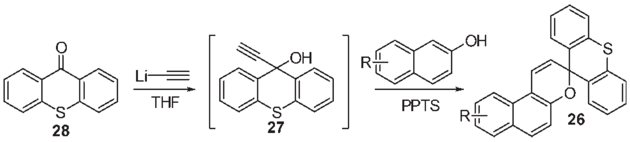
As shown in Scheme 10, Coelho *et al.* prepared spiro[thioxantene-naphthopyrans] **26** through a sequence of reactions. The alcohol intermediate (**27**) was obtained through the reaction of thioxanthone **28** with lithium acetylide in dry THF at 25°C, and reacted with 2-naphthol analogs without isolation to avoid degradation. After work-up, the desired 3*H*-naphtho[2,1-*b*]pyran products were obtained in low to moderate yield (9–61%) [23].

In another variation of this protocol, zeolite was used to condense 2-naphthols with α-alkynols to prepare 3*H*-naphtho[2,1-*b*]pyrans in reasonable yields (65–75%) [24]. Uemura's group used a thiolate-bridged diruthenium complex [Cp*RuCl(μ_2-SMe)$_2$RuCp*Cl] to effect the same transformation with decent yields (64–97%) [25]. While the use of catalysts facilitate the formation of transition state intermediates, *in situ* ether formation, followed by Claisen rearrangement and cycloaddition is generally accepted mechanism for this transformation (Scheme 11) [24].

Scheme 9. Condensation of 2-naphthols and diaryl propargyl alcohols.



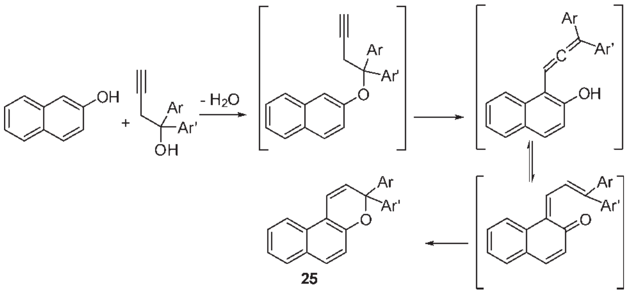
Scheme 10. PPTS-catalyzed synthesis of spiro[thioxantene-naphthopyrans] (**26**).



A large number of decorated 3*H*-naphtho[2,1-*b*]pyrans have been prepared using this protocol or a slightly modified version in the pursuit of photochromic naphthopyrans with interesting/desired properties. A sample of molecular diversity bearing photochromic 3*H*-naphtho[2,1-*b*]pyran core reported in recent literatures in presented in Figure 3. Chamontin *et al.* reported the synthesis of formyl-substituted naphthopyrans (*e.g.*, **29**) either by starting the reaction from formylated 2-naphthol or by conducting formylation on the naphthopyran products [26]. These formylated naphthopyrans can be used to produce an array of derivatives. Navarro and coworkers derivatized compound **29** with 1,4-dithiafulvenes to produce (1,4-dithiafulven-6-yl)substituted 3*H*-naphtho[2,1-*b*]pyrans (*e.g.*, **30**), which dimerized after electrochemical treatment; compound **31** was isolated to confirm this observation [27]. Zhao and Carreira reported the synthesis and photochromic properties of symmetrical phyenylene-linked bisnaphthopyrans (**32, 33**) initiating the synthesis from isoterephthaloyl and terephthaloyl chlorides to make the bisketones, which were converted to bispropargyl alcohols required for the synthesis of the desired naphtho[2,1-*b*]pyrans [28].

Coelho *et al.* also produced a number of symmetrical photochromic di/trinaphtho[2,1-*b*]pyrans (*e.g.*, **34, 35**) by preparing appropriate bis/tris-ketones, followed by propargylation and annulation (with 2-naphthol) sequence [29]. The same research group prepared unsymmetrical photochromic *bis*-naphthopyrans (*e.g.*, **36**) using the same general chemistry where the annulation with naphthol analogs were conducted sequentially

Scheme 11. Generally accepted mechanism of formation of 3*H*-naphtho[2,1-*b*]pyrans (**25**) from 2-naphthols and α-alkynols.



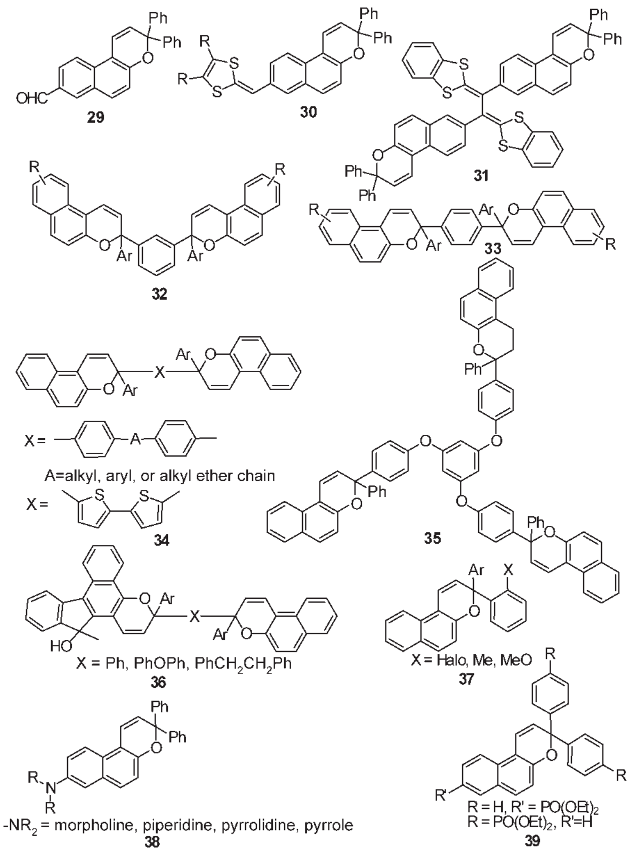
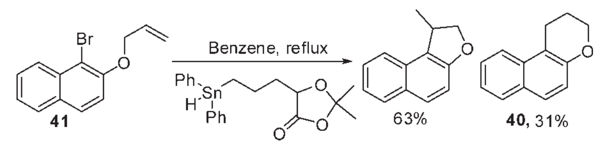


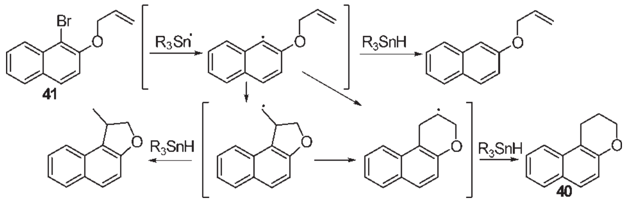
Figure 3. A sample of molecular diversity bearing photochromic 3*H*-naphtho[2,1-*b*]pyran core.

on the bispropargyl alcohol [30]. Effect of *ortho*-substituents on the 3-aryl group of 3,3-diaryl-3*H*-naphtho[2,1-*b*]pyran on photochromism was studied by Gabutt, Heron, and Instone where they synthesized a number of 3,3-diaryl-3*H*-naphtho[2,1-*b*]pyrans bearing substituents on the *ortho*-position of one of the 3-aryl groups (*e.g.*, **37**) [31]. Shilova *et al.* prepared a series of cyclic amine-substituted 3,3-diphenyl-3*H*-naphtho[2,1-*b*]pyrans (**38**) by using the Buchwald C—N coupling protocol on the corresponding bromo-substituted naphthopyrans in an effort to study their effect on photochromism [32]. In a similar endeavor, Campredon and coworkers prepared diethyl phosphonate-substituted 3*H*-naphtho[2,1-*b*]pyrans (**39**) for corresponding bromo-substituted naphthopyrans using Pd-catalyzed diethyl phosphate [33].

Scheme 12. C—C bond formation in 2-allyloxy-1-bromonaphthalene using a modified stannane.



Scheme 13. Proposed mechanism of Sn-mediated C—C bond formation in 2-allyloxy-1-bromonaphthalene (**41**).



METHODS OF SYNTHESIS OF 2,3-DIHYDRO-1*H*-NAPHTHO[2,1-*b*]PYRANS

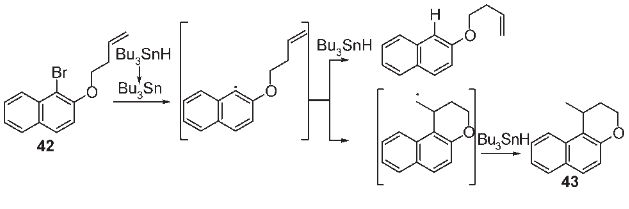
There are numerous procedures related to one another that are known for the synthesis of the 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran analogs with a saturated pyran ring, *i.e.*, 1*H*-benzo[*f*]chromans, which are devoid of photochromic characteristics. In a publication by Clive and Wang, 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran (**40**) was prepared in 31% yield by heating 2-allyloxy-1-bromonaphthalene (**41**) and azobisisobutyronitrile (AIBN) in benzene using a modified stannane reagent (Scheme 12) [34]; the conventional reagent, Bu_3SnH, gave very poor (~17%) yield [35]. Stannanes such as Bu_3SnH and Ph_3SnH are used in standard free radical reactions [35]. In case of modified stannane reagent, the tin-containing byproducts can be easily removed by mild hydrolysis.

The mechanism of stannane-mediated cyclization involves formation of a free radical at the carbon atom bearing the bromine. This intermediate then cyclizes with the alkenyl substituent leading to a 5- or 6-membered ring structure (Scheme 13) [35].

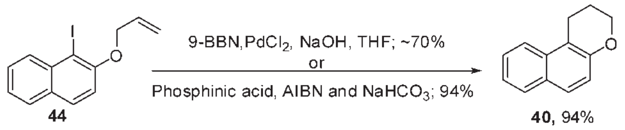
When 1-bromo-2-but-3-enyloxy-naphthalene (**42**) was used as starting material, dihydronaphthopyran **43** was obtained as one of the products (Scheme 14) [36]. The cyclization resulted in formation of a more stable 6-membered ring rather than a 7-membered ring.

According to numerous reports, the cross-coupling reaction of organic electrophiles with organometallic reagents in the presence of transition metals is generally a mild and straightforward method to form a C—C bond. Suzuki and coworkers published a related experiment where they initiated from 2-allyloxy-1-iodonaphthalene (**44**) using 9-borabicyclo[*3.3.1*]nonane (9-BBN) and palladium-catalyzed intramolecular cross-coupling

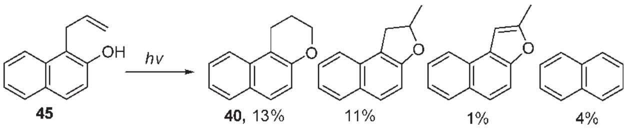
Scheme 14. Synthesis of dihydronaphthopyran **43** from 1-bromo-2-but-3-enyloxynaphthalene (**42**).



Scheme 15. Formation of dihydronaphthopyran **40** *via* intramolecular cross-coupling.



Scheme 16. Dihydronaphthopyran **40** *via* singlet excited-state H-transfer from **45**.



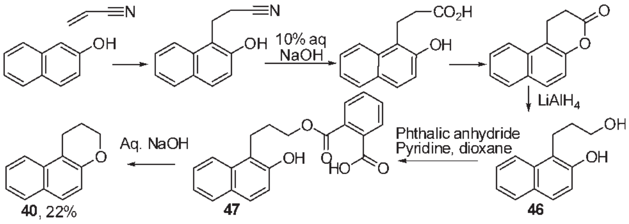
reaction. The desired dihydronaphthopyran **40** was obtained in ~70% yield *via* this reaction (Scheme 15) [37]. Another reaction on 2-allyloxy-1-iodonaphthalene leading to same product in nearly quantitative yield, using phosphinic acid, AIBN, and NaHCO$_3$, is also known (Scheme 15) [38,39].

Chow *et al.* discovered that singlet excited-state proton transfer of 1-allyl-2-naphthol (**45**) causes cyclization and results in formation of **40** in 13% yield. It was noted that secondary photodehydrogenation of the dihydronaphthofuran and formation of naphthalene are competing side reactions (Scheme 16) [40].

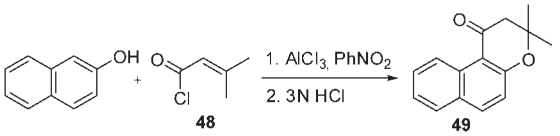
Dihydronaphthopyran **40** was also obtained from 2-naphthol and acrylonitrile by a 6-step reaction sequence in low yield (~22%; Scheme 17) [41]. 1-(3-Hydroxypropyl)naphthalen-2-ol (**46**) was obtained through 2-naphthol and acrylonitrile mixture by Michael addition, hydrolysis, and reduction sequence. It reacted with phthalic anhydride and pyridine to give acid phthalate (**47**), which yielded dihydronaphthopyran **40** upon addition of weak aqueous NaOH solution.

Livingstone has published a one-pot annulation reaction to prepare naphthopyrans [42]. As depicted in Scheme 18, 2-naphthol was mixed with 3-methylbut-2-enoyl chloride (**48**) in nitrobenzene and small amount of anhydrous aluminum chloride was added. The reaction was set aside for 12 days when the desired naphthopyran (**49**) was formed (yield not reported).

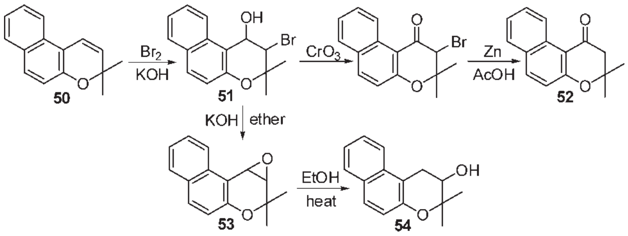
Scheme 17. Dihydronaphthopyran **40** *via* multistep intramolecular cyclization.



Scheme 18. Preparation dihydronaphthopyranone **49** from 2-naphthol *via* Friedel Craft acylation.



Scheme 19. Multiple step synthesis of dihydronaphthopyran derivatives.



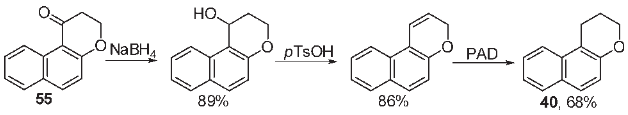
Livingstone subsequently reported a multi-step synthesis of dihydronaphtho[2,1-*b*]pyran derivatives (Scheme 19). 3,3-Dimethyl-3*H*-naphtho[2,1-*b*]pyran (**50**) was first converted to its bromohydrin **51** followed by CrO$_3$ oxidation and subsequent reduction *via* Zn/AcOH to afford 3,3-dimethyl-2,3-dihydronaphtho[2,1-*b*]pyran-1-one (**52**). Application of potassium hydroxide on the bromohydrin **51** resulted in an epoxide intermediate (**53**), which was later converted to 3,3-dimethyl-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran-2-ol (**54**) [43]. Product yields were not reported.

Another multi-step synthesis of dihydronaphthopyran **40** from 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran-1-one (**55**) involves sodium borohydride reduction followed by a dehydration and hydrogenation sequence. Selective reduction of the double bond was achieved by potassium azodicarboxylate (PAD) reduction (Scheme 20) [44].

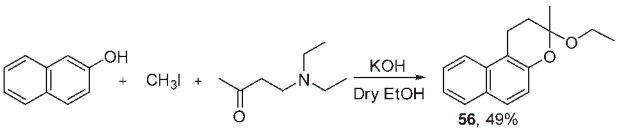
The same research article also reported the synthesis of 3-ethoxy-2,3-dihydro-3-methyl-1*H*-naphtho[2,1-*b*]pyran (**56**) [44]. In this reaction, methyl iodide was added to 1-(*N*,*N*-diethylamino)butan-3-one in dry ethanol. The mixture was then added to a solution of 2-naphthol and potassium hydroxide. The final product **56** was obtained in 49% yield after refluxing for 30 min (Scheme 21).

Scheme 22 depicts an electron transfer reaction where methylene blue-catalyzed photodecarboxylation of 1-allyl-2-naphthoxy acetic acid (**57**) led to formation of 2-

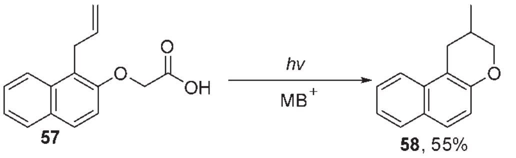
Scheme 20. Dihydronaphthopyran **40** from corresponding 4-pyranone **55**.



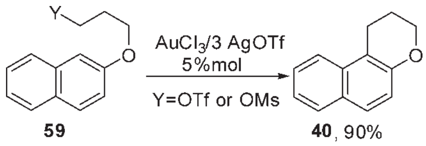
Scheme 21. Formation of 3-ethoxy-2,3-dihydro-3-methyl-1*H*-naphtho[2,1-*b*]pyran (**56**).



Scheme 22. Methylene blue-catalyzed photodecarboxylation and cyclization.



Scheme 23. Au-catalyzed intramolecular cycloalkylation of 2-naphthyloxy-propyl sulfonate **59**.



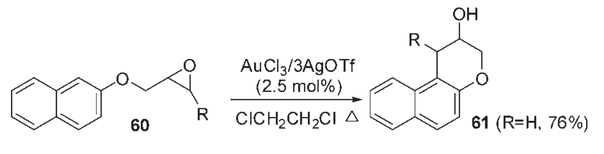
methyl-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran (**58**) in 55% yield [45,46].

Gold-catalyzed organic transformations have been studied quite extensively in recent years. Remarkable results were published by Sih and He who used relatively expensive Au(III) to catalyze carbon—carbon bond formation of 2-naphthyloxy-propyl triflate or methane sulfonate ester (**59**) and obtained 90% yield of 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran (**40**, Scheme 23) [47].

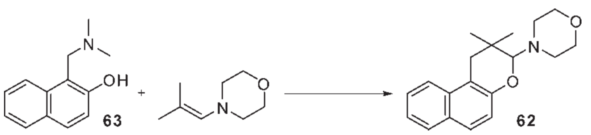
In a related endeavor, the same group reported Au(III)-catalyzed intramolecular cycloalkylation of substituted 2-(2-naphthyloxymethyl)oxiranes (**60**) to substituted 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran-1-ols (**61**) in good yields (Scheme 24) [48].

Strandtmann and his research group reported a new strategy to produce 3-morpholino-2,2-dimethyl-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran (**62**) from 2-naphthol Mannich bases (**63**) and an enamine (Scheme 25; yield not reported) [49,50]. The proposed mechanism involved elimination of the dimethylamine from the Mannich base followed by a Michael-type addition to the enamine. The resulting intermediate then cyclized to give an amine substituted naphthopyran derivative.

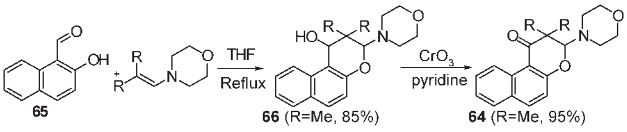
Scheme 24. Au(III)-catalyzed cycloalkylation of 2-(2-naphthyloxymethyl)oxiranes (**60**).



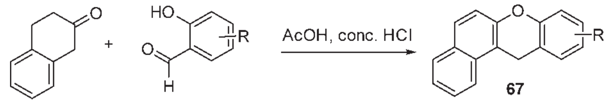
Scheme 25. Morpholino-dihydronaphthopyran **62** from 2-naphthol Mannich base **63**.



Scheme 26. Synthesis of morpholino-dihydronaphthopyranone **64** from 2-hydroxy-1-naphthaldehyde and appropriate enamine.



Scheme 27. 12*H*-benzo[*a*]xanthenes (**67**) from 2-tetralone and substituted salicylaldehydes.

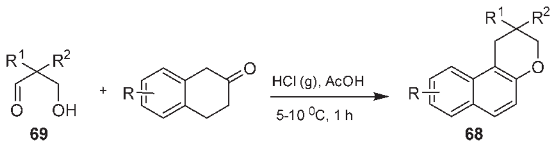


In a similar perspective, Dean *et al.* published a simple method of preparing 3-dialkylamino-2,2-dialkylnaphtho[2,1-*b*]pyran-1-ones (**64**) [51]. The reaction between 2-hydroxy-1-naphthaldehyde (**65**) and enamines gave 3-dialkylamino-2,2-dialkylnaphtho[2,1-*b*]pyran-1-ols (**59**) in high yield. Subsequently, the resulting compounds were oxidized by Sarett's reagent to produce 3-dialkylamino-naphthopyranones **64** in nearly quantitative yeilds (Scheme 26).

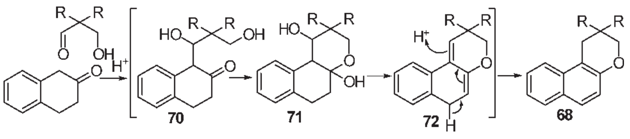
Our research group is also actively engaged in exploitation of 2-naphthol and 2-tetralone analogs to produce novel molecular frameworks [52–58]. Our efforts have also led to synthesis of three kinds of 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans [56–58]. Reaction between 2-tetralone and substituted *ortho*-hydroxy aromatic aldehydes under acidic conditions resulted in formation of benzene-fused 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans or 12*H*-benzo[*a*]xanthenes (**67**, Scheme 27) in moderate to excellent yields (55–94%) [56].

This study was later expanded to expeditiously and conviniently prepare 2,2,-dialkyl-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans (**68**, Scheme 28) in 51–96% yeild range from 2-tetralone analogs and 2,2-dialkyl-3-

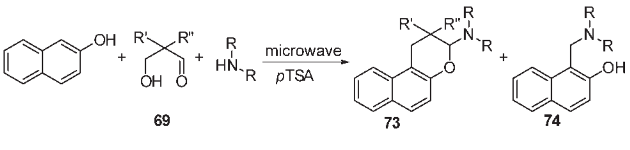
Scheme 28. Synthetic scheme for preparing 2,2,-dialkyl-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans (**68**) for 2-tetralone analogs.



Scheme 29. Most plausible mechanism of formation of 2,2-dialkyl-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans (**68**) from 2-tetralone.



Scheme 30. Formation of dialklamino-dihydronaphthopyrans (**66**) from 2-naphthol.

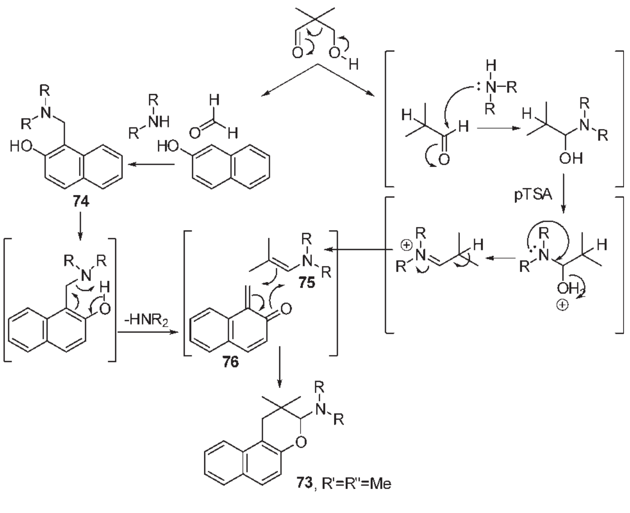


hydroxy propanaldehydes (**69**) under anhydrous acidic conditions [57].

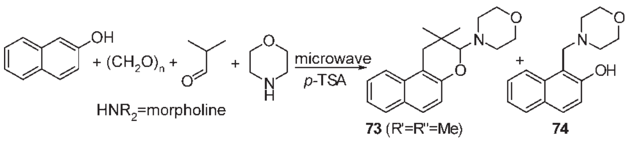
The overall reaction is tendam aldol condensation and hemiacetal formation followed by double dehydration. The most plausible mechanism involves the formation of aldol product (**70**) between the active methylene of 2-tetralone and the corresponding aldehyde. Subsequently, cyclization *via* nucleophilic attack leading to formation of the hemiacetal intermediate (**71**) followed by double dehydration (**72**) and aromatization by proton rearrangement produces stable products (**68**, Scheme 29) [57].

In another endeavor, we developed a microwave-assisted synthesis of 3-(dialklamino)-2,2-dialkyl-1,2-dihydro-naphtho[2,1-*b*]pyrans (**73**) [58]. These series of compounds were formed in moderate to good yields (45–72%) from 2-naphthol, a secondary amine, and 3-hydroxy-2,2-dialkylpropanaldehydes (**69**) in presence of catalytic amount of *p*-toluenesulfonic acid using focused microwave radiation as energy source (Scheme 30).

Scheme 31. Most plausible mechanism of formation of dialkylamino-dihydronaphthopyrans **73** from 2-naphthol, hydroxyl aldehydes **69**, and 2° amines.



Scheme 32. *p*-TSA-catalyzed four-component reaction for the synthesis of 2,2-dimethyl-3-morpholino-1,2-dihydro-naphtho[2,1-*b*]pyran.



The formation of 1-dialkylaminomethyl-2-naphthol byproducts (**74**) gave us a vital clue in discerning the mechanism of this reaction. We elucidated that under applied reaction conditions, 2,2-dialkyl-3-hydroxy-propanaldehydes undergoes retro-aldol condensation to produce formaldehyde and 2,2-dialkylacetaldehydes. These aldehydes meet different fates resulting in facile formation of 1-dialkylaminomethyl-2-naphthols (**74**) and 2,2-dialkylacetaldehyde/secondary amine enamines (**75**). Again, under the used reaction conditions, 1-dialkylaminomethyl-2-naphthols deaminate to naphthoquinone methide (**76**). Pericyclic cycloaddtion between electron deficient **76** and electron rich enamine **75** results in dialkylamino-dihydronaphthopyrans **73** with aromatization being the driving force (Scheme 31) [40].

Subsequently, we substantiated this mechanistic pathway by developing a *p*TSA catalyzed four-component reaction involving 2-naphthol, paraformaldehyde, isobutyraldehyde, and morpholine (1 molar equivalent each) under microwave conditions identical to the original three component reaction [58]. This indeed led to formation of **73** ($R'=R''=Me$, $-NR_2$=morpholine) and **74** ($-NR_2$=morpholine) in 52% and 43% yields, respectively (Scheme 32).

It is abundantly clear from the preceding discussions that 3*H*-naphtho[2,1-*b*]pyran and dihydro-1*H*-naphtho[2,1-*b*]pyran nuclei can be derived from a variety of synthetic routes. Evidently, the majority of these procedures lack simplicity and satisfactory yields; many are accompanied by one or more side-products. Since naphthopyran nuclei are biologically relevant and commercially important, it is paramount to develop expeditious, facile, and convenient synthetic routes to these types of molecular frameworks.

Acknowledgments. Financial support from Natural Sciences and Engineering Research Council (NSERC) of Canada is gratefully acknowledged.

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Oxidative Cyclization of 3-Cinnamoyltropolones with I_2/DMSO/H_2SO_4 System

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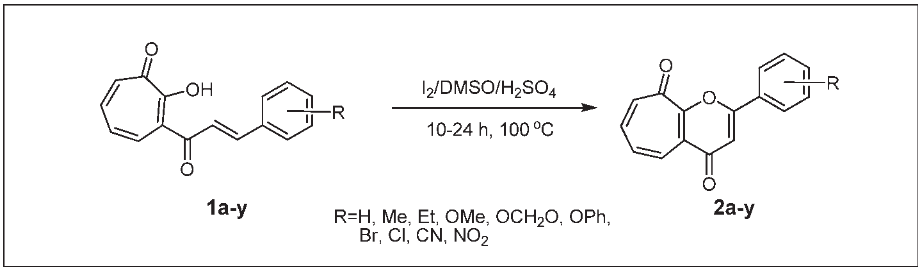

In this study, a facile and general method synthesizing flavone-like 2-aryl-4,9-dihydrocyclohepta[*b*]-pyran-4,9-diones (**2a–y**) from 3-cinnamoyltropolones (**1a–y**) *via* oxidative cyclization reaction by using I_2/DMSO/H_2SO_4 system is described. The method was found to be successfully applicable to a wide range of 3-cinnamoyltropolone derivatives and characterized by generality, compatibility, and easy work-up procedures.

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INTRODUCTION

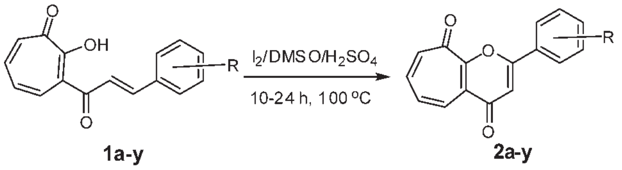
Heterocycle-fused troponoids are a type of compounds with physiological activities such as anticancer [1], germicide, antiphlogistic [2], antihypertension [3], and antidiabetic [4]. They are included in many natural products such as alkaloids and antibiotics. For example, a new antimalarial tropolone, named cordytropolone, was discovered in a culture broth of *Cordyceps* [5]. Heterocycle-fused troponoids can be synthesized in many ways, among which one was to oxidize the side chain of tropolone for cyclization. For instance, it was reported that flavone-like heterocycle-fused troponoid compounds, 2-aryl-4,9-dihydrocyclohepta[*b*]pyran-4,9-diones, were obtained by oxidative cyclization of 3-cinnamoyltropolones using selenium dioxide [6] or 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) [7] as oxidative reagents. We have ever reported that reactions of unsubstituted 3-cinnamoyltropolone or 3-cinnamoyl-5-phenylazo-substituted tropolone with excess bromine can also give heterocycle-fused flavone-like compounds [8]. Although these practical syntheses have been described so far, these methods, however, are limited to unsubstituted or specifically substituted 3-cinnamoyltropolones and lack generality, compatibility, easy work-up procedures, regiochemical control, and high yields. Another approach reported by Wang *et al.* [9] to 2-aryl-4,9-dihydrocyclohepta[*b*]pyran-4,9-diones was based on the reactions of 3-acetyltropolone with methoxyl- and/or hydroxy-substituted benzaldehydes in the presence of triethyl orthoformate and with perchloric acid as the oxidant. However, Wang's procedure is also limited to methoxy- and/or hydroxy-substituted benzaldehyde derivatives and is not applicable to a large number of starting materials. In view of the aforementioned drawbacks, we deemed it desirable to develop a simpler, more efficient, and broadly applicable synthetic approach with a wide range of substrates to overcome the previously mentioned disadvantages. Recently, a method has been reported for the synthesis of flavone compounds from 2′-hydroxychalcone via oxidative cyclization reaction using I_2/DMSO/H_2SO_4 system [10,11]. The reactions were completed in a few hours at 100°C in DMSO, and a catalytic amount of I_2 and concentrated H_2SO_4 to give flavone compounds in good yields. In connection with our studies, we envisioned that the system could also be applied to 3-cinnamoyltropolones, from which flavone-like compounds 2-aryl-4,9-dihydrocyclohepta[*b*]pyran-4,9-diones may be synthesized through oxidative cyclization reaction. Indeed, this was found to be the case and, to the best of our knowledge, it is the first example of the application of the I_2/DMSO/H_2SO_4 system in the oxidative cyclization reaction of 3-cinnamoyltropolones.

RESULTS AND DISCUSSION

Scheme 1 outlines the synthetic sequence used in our laboratories for the preparation of heterocycle-fused flavone-like compounds **2a–y**. The starting materials of our study were readily prepared from 3-acetyltropolone and various benzaldehyde derivatives by aldol condensation [6].

To check the feasibility of this approach using I_2/DMSO/H_2SO_4 system and show a comparable result, we initially chose the representative unsubstituted 3-cinnamoyltropolone (**1a**) and methoxy-substituted 3-cinnamoyltropolones **1d–f** and **1q–t** to perform the initial experiments because their oxidative cyclization reactions have been previously reported by using different oxidative reagents [6–9,12]. As reported earlier, using hydrogen peroxide in the presence of alkali substrates, **1a**, **1d–f**, and **1q–t**, could not be converted into flavone-like compounds [12]. In [6], only **1a** and **1d–f** could be converted to corresponding flavone-like products **2a** and **2d–f** while using SeO_2 as oxidative cyclization reagent. Moreover, this method has some drawbacks, such as the use of toxic reagent, tedious work-up procedures, and narrow scope of the substrates. When under the action of elemental bromine [8], only substrate **1a** could react to give flavone-like products, but the bromination reaction of the aromatic ring of **1a** also occurred at the same time under this condition. In the oxidation cyclization of 3-cinnamoyltropolones with DDQ [7], only unsubstituted and 3-methoxy-substituted 3-cinnamoyltropolones (**1a**, **1e**) gave the flavone-like compounds **2a** and **2e**, while the other methoxy-substituted ones, such as **1d**, **1f**, and **1q–t**, are often limited and gave aurone-like products. However, in our experiment, upon treatment with I_2/DMSO/H_2SO_4 system at 100°C for 10 h, these substrates were all smoothly converted to their corresponding flavone-like compounds (**2a**, **2d–f**, and **2q–t**), which are acceptable to good yields. Thus, I_2/DMSO/H_2SO_4 system offered a general method for the oxidative cyclization reaction of a wide variety of 3-cinnamoyltropolone substrates. The compounds **2a**, **2d–f**, **2q**, and **2t** are known compounds and their structures were unambiguously confirmed by the physical and spectroscopic data, which were in good agreement with the reported values. Through an effort to optimize the reaction conditions, such as the reaction temperature and the amount of the I_2/DMSO/H_2SO_4 system, we found that the best results were achieved when the reactions were conducted at a temperature of 100°C with a ratio of 1 mmol 3-cinnamoyltropolone to 8 mL DMSO, 10 mg I_2, and 3–4 drops of concentrated H_2SO_4. We also found that the addition of increased amounts of I_2 or H_2SO_4 lowered the purity and yield of products.

Scheme 1



1a-y **2a-y**

a: R=H b: R=4-Me c: R=4-Et
d: R=2-OMe e: R=3-OMe f: R=4-OMe
g: R=3-OPh h: R=2-Cl i: R=3-Cl
j: R=4-Cl k: R=2-Br l: R=4-Br
m:R=3-CN n: R=4-CN o: R=3-NO_2
p: R=4-NO_2
q: R=3, 4-(OCH_2O) r: R=2, 3-$(OMe)_2$
s: R=2, 5-$(OMe)_2$ t: R=3, 4-$(OMe)_2$
u: R=2, 3-$(Cl)_2$ v: R=2, 4-$(Cl)_2$
w:R=3, 5-$(Cl)_2$ x: R=3, 4-$(Cl)_2$
y: R=3, 4, 5-$(OMe)_3$

Table 1

Yields and melting points of compounds 2.

Substrate	R	Product	Yield (%)	mp (°C)
1a	H	**2a**	52 ([6]: 70)	202–204 ([6]: 201–202)
1b	4-Me	**2b**	59	190–192
1c	4-Et	**2c**	60	197–199
1d	2-OMe	**2d**	41 ([6]: 56)	216–218 ([6]: 218–220)
1e	3-OMe	**2e**	55 ([6]: 50)	211–213 ([6]: 212–214)
1f	4-OMe	**2f**	70 ([6]: 46)	238–240 ([6]: 231–233)
1g	3-OPh	**2g**	65	198–201
1h	2-Cl	**2h**	58	212–213
1i	3-Cl	**2i**	34	200–202
1j	4-Cl	**2j**	66	288–299
1k	2-Br	**2k**	52	222–223
1l	4-Br	**2l**	61	252–254
1m	3-CN	**2m**	80	296–298
1n	4-CN	**2n**	46	301–302
1o	3-NO_2	**2o**	75	298–300
1p	4-NO_2	**2p**	71	304–305
1q	3,4-(OCH_2O)	**2q**	92 ([9]: 74)	281–283 ([9]: 278–279)
1r	2,3-$(OMe)_2$	**2r**	63	192–194
1s	2,5-$(OMe)_2$	**2s**	33	186–188
1t	3,4-$(OMe)_2$	**2t**	81 ([9]: 64)	268–270 ([9]: 264–265)
1u	2,3-$(Cl)_2$	**2u**	53	218–220
1v	2,4-$(Cl)_2$	**2v**	44	226–227
1w	3,5-$(Cl)_2$	**2w**	53	272–274
1x	3,4-$(Cl)_2$	**2x**	59	260–261
1y	3,4,5-$(OMe)_3$	**2y**	63	249–251

To establish the generality and applicability of this method, a wide variety of 3-cinnamoyltropolones containing electron-donating (such as alkyl or alkoxyl group) and electron-withdrawing (such as cyano, nitro, or halide groups) substituents were subjected to the same set of experiments to furnish the corresponding flavone-like compounds. The results summarized in Table 1 indicated the scope and generality of the oxidation cyclization reaction with respect to various 3-cinnamoyltropolones.

From Table 1, we could see that this method was found to be effective for both electron-donating and electron-withdrawing substituents to afford flavone-like products in moderate to good yields. For example, 3-cinnamoyltropolones, **1c**, **1f**, and **1q**, bearing electron-donating groups on the benzene ring were reacted to give the corresponding products: 2-(4-ethylphenyl)-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (**2c**), 2-(4-methoxyphenyl)-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (**2f**), and 2-(1,3-benzodioxol-5-yl)-4,9-dihydrocyclohepta[*b*]-pyran-4,9-dione (**2q**) in 60%, 70%, and 92% yields, respectively. On the other hand, 3-cinnamoyltropolones, **1m**, **1o,** and **1x**, bearing electron-withdrawing groups gave the following products: 2-(3-cyanophenyl)-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (**2m**), 2-(3-nitrophenyl)-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (**2o**), and 2-(3,4-dichlorophenyl)-4,9-dihydrocyclohepta[*b*]-pyran-4,9-dione (**2x**) in 80%, 75%, and 59% yields, respectively. Thus, we concluded that the electronic nature of the substituents on 3-cinnamoyltropolones has no significant effect on this reaction. Among them, the compounds **2b–c**, **2g–p**, **2r–s,** and **2u–y** have never been reported, and their structures were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and MS. These results showed that our protocol could tolerate a variety of functional groups on the benzene ring. However, we found that when the benzene ring of 3-cinnamoyltropolones was replaced with the pyridine ring, the reaction became complex under the same conditions and a prolonged reaction time of more than 48 h provided only a trace amount of oxidation cyclization products.

The ease of isolation of compounds **2a–y** was notable; after aqueous work-up, flavone-like compounds **2a–y** were isolated as the main products and their structures were analyzed. When the compounds were developed on thin-layer chromatography (TLC; silica gel: GF254, developing agent: ethyl acetate), there was only one main spot with no tailing. The compounds had the negative coloring test with iron (III) chloride in methanol solution. The IR spectrum exhibited an absence of hydroxyl group, which appeared in 3-cinnamoyltropolones, and the presence of two typical carbonyl absorptions for the tropone and pyran moiety at about 1640 and 1600 cm^{-1}, respectively. The ^{1}H NMR spectrum showed the absence of a hydroxy OH signal and the presence of one signal attributable to the proton of the pyran ring in addition to the signals of other groups. In ^{13}C NMR spectra, all the synthesized compounds showed peaks in the 180–183 and 169–172 ppm range for two carbonyl carbons of tropone and pyran (detailed spectral data are given in the ''Experimental'' section). In addition, the structure assigned for this reaction product was fully supported by their mass spectrum as well as their elemental analysis. All these facts show that the hydroxyl group in the tropolone ring had taken part in the reaction.

We believe that this method is the simplest route for the preparation of a wide range of flavone-like compounds, requiring only simple, cheap reagent, and mild conditions.

EXPERIMENTAL

Melting points (uncorrected) were determined using WRS-1B melting points apparatus. The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded with a Varian Inova 400 NMR spectrometer at 400 MHz. The reported chemical shifts were against TMS. The mass spectra were determined using an MSD VL ESI1 spectrometer. Elemental analysis was performed using an Elementar Vario EL-III element analyzer. The progress of reactions was monitored by TLC on silica gel GF254 using ethyl acetate as eluent.

General procedure for the reaction of 3-cinnamoyltropolones 1a–y with I_2/DMSO/H_2SO_4 system. To a solution of 3-cinnamoyltropolones (1 mmol) in 8 mL DMSO, 3–4 drops of concentrated H_2SO_4 were added. The mixture obtained was stirred for 10 min at 100°C, and then I_2 (10 mg) was added to the mixture and continued to stir at the same temperature. After 10–24 h, the completion of reaction was monitored by TLC, the mixture was cooled to room temperature, and the precipitate formed was filtered, washed with water, and dried to yield crude 2-aryl-4,9-dihydrocyclohepta[*b*]pyran-4,9-diones, which was purified by recrystallization to give pure 2-aryl-4,9-dihydrocyclohepta[*b*]pyran-4,9-diones **2a–y** in 33–92% yield.

2-Phenyl-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (2a). This compound was obtained as yellow needles (1,4-dioxane); IR (potassium bromide): ν 3058 (CH), 1660 (tropone CO), 1600 (pyran CO), 1520, 1510, 1390, 1190, 1120, 900, 820, 770, 690 cm^{-1}; ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.13−9.06 ppm (m, 10H, ArH, PhH, C=CH); ^{13}C NMR (CF_3COOD, 100 MHz): δ 182.78, 182.65, 171.54, 163.09, 144.53, 138.70, 135.84, 131.83, 130.72, 129.78, 128.69, 119.91, 117.10, 114.28, 111.47, 109.29; ms: *m*/*z* 251 (M+1)$^+$. Anal. Calcd for $C_{16}H_{10}O_3$: C, 76.79; H, 4.03. Found: C, 76.82; H, 3.99.

2-(4-Methylphenyl)-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (2b). This compound was obtained as yellowish gray needles (1,4-dioxane); IR (potassium bromide): ν 3066 (CH), 2970 (CH), 1640 (tropone CO), 1590 (pyran CO), 1510, 1470, 1420, 1380, 1350, 1300, 1185, 1120, 1040, 890, 820, 710 cm^{-1}; ^{1}H NMR (CF_3COOD, 400 MHz): δ 7.93−8.92 (m, 9H, ArH, PhH, C=CH), 2.97 ppm (s, 3H, CH_3); ^{13}C NMR (CF_3COOD, 100 MHz): δ 182.43, 182.00, 172.43, 162.58, 161.13, 144.39, 144.4, 138.80, 135.28, 131.65, 129.07, 126.71, 119.95, 117.14, 114.32, 111.50, 108.25, 21.39 ppm; ms: *m*/*z* 265 (M+1)$^+$. Anal. Calcd for $C_{17}H_{12}O_3$: C, 77.26; H, 4.58. Found: C, 77.37; H, 4.53.

2-(4-Ethylphenyl)-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (2c). This compound was obtained as yellow needles (ethanol); IR (potassium bromide): ν 3070 (CH), 2985 (CH), 1640 (tropone CO), 1590 (pyran CO), 1520, 1505, 1420, 1375, 1220, 1110, 960, 840, 820, 700 cm^{-1}; ^{1}H NMR (CF_3COOD, 400 MHz): δ 7.29–8.33 (m, 9H, ArH, PhH, C=CH), 2.60–2.67 (q, 2H, CH_2, J = 7.6 Hz, 14.8 Hz), 1.38 ppm (t, 3H, CH_3, J = 6.2 Hz); ^{13}C NMR (CF_3COOD, 100 MHz): δ

182.66, 182.22, 172.31, 162.82, 156.63, 146.73, 144.54, 138.94, 135.35, 133.74, 132.21, 131.59, 129.29, 127.08, 120.09, 117.27, 114.45, 111.64, 108.55, 30.08, 14.72, and 14.54 ppm; ms: *m/z* 279 $(M+1)^+$. Anal. Calcd for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07. Found: C, 77.74; H, 4.99.

2-(2-Methoxyphenyl)-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (2d). This compound was obtained as yellow needles (1,4-dioxane); IR (potassium bromide): ν 3060 (CH), 2920 (CH), 1630 (tropone CO), 1610 (pyran CO), 1590, 1515, 1490, 1450, 1380, 1295, 1250, 1190, 1015, 750 cm^{-1}; ^{1}H NMR (CF_3COOD, 400 MHz): δ 7.51–8.73 (m, 9H, ArH, PhH, C=CH), 4.40 ppm (s, 3H, OCH_3); ^{13}C NMR (CF_3COOD, 100 MHz): δ 182.20, 181.97, 171.10, 162.21, 144.50, 138.89, 135.55, 132.04, 130.65, 127.79, 123.16, 120.07, 117.25, 114.44, 113.69, 113.07, 111.62, 56.53 ppm; ms: *m/z* 281 $(M+1)^+$. Anal. Calcd for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32. Found: C, 72.91; H, 4.28.

2-(3-Methoxyphenyl)-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (2e). This compound was obtained as yellow needles (1,4-dioxane); IR (potassium bromide): ν 3060 (CH), 2960 (CH), 1650 (tropone CO), 1590 (pyran CO), 1520, 1495, 1475, 1440, 1385, 1350, 1290, 1180, 1115, 870, 790, 700 cm^{-1}; ^{1}H NMR (CF_3COOD, 400 MHz): δ 7.86–9.03 (m, 9H, ArH, PhH, C=CH), 4.57 ppm (s, 3H, OCH_3); ^{13}C NMR (CF_3COOD, 100 MHz): δ 182.98, 182.92, 170.35, 162.72, 144.66, 138.81, 135.24, 132.27, 129.76, 122.38, 121.44, 120.03, 117.22, 114.50, 111.58, 109.99, 56.72 ppm; ms: *m/z* 281 $(M+1)^+$. Anal. Calcd for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32. Found: C, 72.81; H, 4.35.

2-(4-Methoxyphenyl)-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (2f). This compound was obtained as golden needles (1,4-dioxane); IR (potassium bromide): ν 3040 (CH), 2920 (CH), 1640 (tropone CO), 1600 (pyran CO), 1510, 1250, 1380, 1270, 1190, 1110, 1020, 830, 810, 690 cm^{-1}; ^{1}H NMR (CF_3COOD, 400 MHz): δ 7.60–8.82 (m, 9H, ArH, PhH, C=CH), 4.47 ppm (s, 3H, OCH_3); ^{13}C NMR (CF_3COOD, 100 MHz): δ 180.44, 178.99, 171.42, 165.85, 161.52, 142.64, 137.39, 133.93, 130.63, 128.84, 126.43, 120.35, 118.34, 116.02, 115.52, 112.70, 109.89, 105.33, 54.84 ppm; ms: *m/z* 281 $(M+1)^+$. Anal. Calcd for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32. Found: C, 72.87; H, 4.29.

2-(3-Phenoxyphenyl)-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (2g). This compound was obtained as yellow needles (1,4-dioxane); IR (potassium bromide): ν 3050 (CH), 1640 (tropone CO), 1605 (pyran CO), 1585, 1520, 1480, 1440, 1380, 1350, 1270, 1230, 1210, 1175, 1110, 870, 700 cm^{-1}; ^{1}H NMR (CF_3COOD, 400 MHz): δ 7.00–8.44 ppm (m, 14H, ArH, PhH, C=CH); ^{13}C NMR (CF_3COOD, 100 MHz): δ 183.23, 170.17, 163.54, 156.92, 144.79, 138.85, 135.25, 132.37, 131.90, 131.40, 130.04, 126.34, 125.04, 123.37, 121.14, 120.13, 117.77, 114.50, 111.68, 110.15 ppm; ms: *m/z* 343 $(M+1)^+$. Anal. Calcd for $C_{22}H_{14}O_4$: C, 77.18; H, 4.12. Found: C, 77.04; H, 4.32.

2-(2-Chlorophenyl)-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (2h). This compound was obtained as pale yellow needles (1,4-dioxane); IR (potassium bromide): ν 3058 (CH), 1655 (tropone CO), 1600 (pyran CO), 1511, 1472, 1430, 1370, 1339, 1170, 1010, 1028, 815, 760, 700 cm^{-1}; ^{1}H NMR (CF_3COOD, 400 MHz): δ 7.78–9.02 ppm (m, 9H, ArH, PhH, C=CH); ^{13}C NMR (CF_3COOD, 100 MHz): δ 183.12, 182.94, 169.31, 163.66, 145.06, 138.72, 135.22, 132.19, 130.10, 128.58, 119.89, 117.57, 115.75, 114.26, 111.44 ppm; ms: *m/z* 285 $(M+1)^+$. Anal. Calcd for $C_{16}H_9ClO_3$: C, 67.50; H, 3.19. Found: C, 67.64; H, 3.10.

2-(3-Chlorophenyl)-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (2i). This compound was obtained as yellow solids (1,4-dioxane); IR (potassium bromide): ν 3060 (CH), 1650 (tropone CO), 1600 (pyran CO), 1520, 1470, 1410, 1365, 1305, 1180, 1110, 880, 700; ^{1}H NMR (CF_3COOD, 400 MHz): δ 7.46–8.54 ppm (m, 9H, ArH, PhH, C=CH); ^{13}C NMR (CF_3COOD, 100 MHz): δ 182.46, 168.34, 162.45, 143.91, 138.14, 136.90, 134.55, 131.57, 129.33, 127.73, 125.90, 119.31, 116.49, 113.68, 110.86, 109.63 ppm; ms: *m/z* 285 $(M+1)^+$. Anal. Calcd for $C_{16}H_9ClO_3$: C, 67.50; H, 3.19. Found: C, 67.47; H, 3.16.

2-(4-Chlorophenyl)-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (2j). This compound was obtained as yellow needles (1,4-dioxane); IR (potassium bromide): ν 3060 (CH), 1650 (tropone CO), 1614 (pyran CO), 1512, 1490, 1410, 1370, 1340, 1286, 1175, 1091, 890, 832, 810, 700 cm^{-1}; ^{1}H NMR (CF_3COOD, 400 MHz): δ 7.83–8.84 ppm (m, 9H, ArH, PhH, C=CH); ^{13}C NMR (CF_3COOD, 400 MHz): δ 182.80, 169.48, 162.63, 144.42, 142.77, 138.70, 135.05, 131.93, 131.07, 129.72, 128.36, 119.91, 117.09, 114.28, 111.46, 109.46 ppm; ms: *m/z* 285 $(M+1)^+$. Anal. Calcd for $C_{16}H_9ClO_3$: C, 67.50; H, 3.19. Found: C, 67.57; H, 3.12.

2-(2-Bromophenyl)-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (2k). This compound was obtained as pale yellow needles (1,4-dioxane); IR (potassium bromide): ν 3040 (CH), 1660 (tropone CO), 1600 (pyran CO), 1520, 1470, 1375, 1350, 1170, 1110, 1020, 820, 770, 700 cm^{-1}; ^{1}H NMR (CF_3COOD, 400 MHz): δ 7.81–9.13 ppm (m, 9H, ArH, PhH, C=CH); ^{13}C NMR (CF_3COOD, 100 MHz): δ 183.07, 182.92, 170.49, 163.51, 145.10, 138.71, 135.33, 134.67, 132.64, 131.91, 130.16, 129.04, 122.52, 119.87, 117.05, 115.74, 114.24, 114.42 ppm; ms: *m/z* 331 $(M+2)^+$. Anal. Calcd for $C_{16}H_9BrO_3$: C, 58.38; H, 2.76. Found: C, 58.45; H, 2.82.

2-(4-Bromophenyl)-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (2l). This compound was obtained as yellow needles (1,4-dioxane); IR (potassium bromide): ν 3050 (CH), 1650 (tropone CO), 1590 (pyran CO), 1510, 1485, 1410, 1370, 1180, 1110, 1075, 1010, 890, 830, 700 cm^{-1}; ^{1}H NMR (CF_3COOD, 400 MHz): δ 7.77–8.77 ppm (m, 9H, ArH, PhH, C=CH); ^{13}C NMR (CF_3COOD, 100 MHz): δ 182.78, 169.47, 163.48, 144.38, 138.67, 135.01, 134.11, 131.91, 130.96, 129.65, 128.78, 119.87, 117.06, 114.24, 111.42, 109.46 ppm; ms: *m/z* 331 $(M+2)^+$. Anal. Calcd for $C_{16}H_9BrO_3$: C, 58.38; H, 2.76. Found: C, 58.28; H, 2.78.

2-(3-Cyanophenyl)-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (2m). This compound was obtained as yellow needles (1,4-dioxane); IR (potassium bromide): ν 3055 (CH), 2220 (CN), 1640 (tropone CO), 1600 (pyran CO), 1511, 1425, 1370, 1300, 1185, 1110, 850, 820, 700 cm^{-1}; ^{1}H NMR (CF_3COOD, 400 MHz): δ 7.00–8.37 ppm (m, 9H, ArH, PhH, C=CH); ^{13}C NMR (CF_3COOD, 100 MHz): δ 182.94, 171.96, 162.83, 155.82, 151.00, 144.74, 138.25, 136.39, 131.65, 129.52, 119.41, 116.59, 113.77, 110.96 ppm; ms: *m/z* 276 $(M+1)^+$. Anal. Calcd for $C_{17}H_9NO_3$: C, 74.18; H, 3.30. Found: C, 74.25; H, 3.28.

2-(4-Cyanophenyl)-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (2n). This compound was obtained as yellow needles (1,4-dioxane); IR (potassium bromide): ν 3060 (CH), 2220 (CN), 1651 (tropone CO), 1590 (pyran CO), 1510, 1420, 1380, 1295, 1160, 1110, 870, 810, 705 cm^{-1}; ^1H NMR (CF_3COOD, 400 MHz): δ 8.13–9.09 ppm (m, 9H, ArH, PhH, C=CH); ^{13}C NMR (CF_3COOD, 100 MHz): δ 183.18, 167.07, 163.59, 144.49, 138.82, 135.58, 135.13, 134.55, 132.03, 130.14, 129.07, 119.95, 117.13, 116.25, 114.31, 111.50 ppm; ms: *m/z* 276 $(M+1)^+$. Anal. Calcd for $C_{17}H_9NO_3$: C, 74.18; H, 3.30. Found: C, 74.04; H, 3.39.

2-(3-Nitrophenyl)-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (2o). This compound was obtained as yellow needles (*N,N*-dimethylformamide); IR (potassium bromide): ν 3090 (CH), 1645 (tropone CO), 1600 (pyran CO), 1540, 1530, 1500, 1390, 1355, 1180, 1110, 915, 820, 750, 710 cm^{-1}; ^1H NMR (CF_3COOD, 400 MHz): δ 8.10–9.50 ppm (m, 9H, ArH, PhH, C=CH); ^{13}C NMR (CF_3COOD, 100 MHz): δ 183.15, 166.86, 163.53, 149.87, 144.64, 138.91, 135.28, 134.62, 132.60, 132.19, 130.20, 128.94, 123.54, 120.03, 117.21, 114.40, 111.58, 111.37 ppm; ms: *m/z* 296 $(M+1)^+$. Anal. Calcd for $C_{16}H_9NO_5$: C, 65.09; H, 3.07. Found: C, 65.12; H, 3.11.

2-(4-Nitrophenyl)-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (2p). This compound was obtained as deep yellow needles (1,4-dioxane); IR (potassium bromide): ν 3060 (CH), 1650 (tropone CO), 1605 (pyran CO), 1515, 1425, 1370, 1350, 1175, 1110, 1040, 850, 810, 755, 695 cm^{-1}; ^1H NMR (CF_3COOD, 400 MHz): δ 7.84–8.73 ppm (m, 9H, ArH, PhH, C=CH); ^{13}C NMR (CF_3COOD, 100 MHz): δ 182.94, 166.49, 162.90, 151.34, 144.32, 138.67, 136.62, 135.01, 131.81, 129.92, 125.48, 119.83, 117.01. 114.19, 111.81, 111.37 ppm; ms: *m/z* 296 $(M+1)^+$. Anal. Calcd for $C_{16}H_9NO_5$: C, 65.09; H, 3.07. Found: C, 65.16; H, 3.13.

2-(1,3-Benzodioxol-5-yl)-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (2q). This compound was obtained as yellow needles (1,4-dioxane); IR (potassium bromide): ν 3055 (CH), 2990 (CH), 1640 (tropone CO), 1595 (pyran CO), 1510, 1460, 1394, 1340, 1260, 1190, 1120, 1030, 920, 860, 850, 816, 700 cm^{-1}; ^1H NMR (CF_3COOD, 400 MHz): δ 7.45–8.85 (m, 8H, ArH, PhH, C=CH), 6.56 ppm (s, 2H, OCH_2O); ^{13}C NMR (CF_3COOD, 100 MHz): δ 182.09, 180.95, 172.2, 163.15, 156.18, 150.74, 144.28, 138.91, 135.46, 130.70, 128.31, 127.17, 123.34, 119.93, 117.11, 114.29, 111.48, 110.82, 108.38, 107.40, 104.13 ppm; ms: *m/z* 295 $(M+1)^+$. Anal. Calcd for $C_{17}H_{10}O_5$: C, 69.39; H, 3.43. Found: C, 69.33; H, 3.36.

2-(2,3-Dimethoxyphenyl)-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (2r). This compound was obtained as yellow needles (1,4-dioxane); IR (potassium bromide): ν 3060 (CH), 2965 (CH), 1644 (tropone CO), 1609 (pyran CO), 1511, 1470, 1428, 1379, 1310, 1010, 910, 850, 760, 710 cm^{-1}; ^1H NMR (CF_3COOD, 400 MHz): δ 7.45–8.65 (m, 8H, ArH, PhH, C=CH), 4.18 (s, 3H, OCH_3), 4.11 ppm (s, 3H, OCH_3); ^{13}C NMR (CF_3COOD, 100 MHz): δ 182.57, 167.99, 162.45, 153.73, 148.37, 144.21, 138.10, 134.61, 131.61, 126.79, 124.29, 122.54, 119.34, 118.75, 116.53, 114.02, 113.71, 110.90, 62.07, 56.06 ppm; ms: *m/z* 311 $(M+1)^+$. Anal. Calcd for $C_{18}H_{14}O_5$: C, 69.67; H, 4.55. Found: C, 69.63; H, 4.57.

2-(2,5-Dimethoxyphenyl)-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (2s). This compound was obtained as orange needles (1,4-dioxane); IR (potassium bromide): ν 3055 (CH), 2930 (CH), 1620 (tropone CO), 1590 (pyran CO), 1510, 1468, 1429, 1370, 1330, 1170, 1140, 1070, 910, 820, 700 cm^{-1}; ^1H NMR (CF_3COOD, 400 MHz): δ 7.26–8.56 (m, 8H, ArH, PhH, C=CH), 4.15 (s, 3H, OCH_3), 4.09 ppm (s, 3H, OCH_3); ^{13}C NMR (CF_3COOD, 100 MHz): δ 182.46, 168.87, 162.93, 157.4, 153.80, 144.43, 138.60, 135.16, 131.12, 128.29, 125.04, 119.82, 118.64, 117.00, 116.32, 114.99, 114.19, 113.69, 111.38, 57.48, 56.66 ppm; ms: *m/z* 311 $(M+1)^+$. Anal. Calcd for $C_{18}H_{14}O_5$: C, 69.67; H, 4.55. Found: C, 69.78; H, 4.61.

2-(3,4-Dimethoxyphenyl)-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (2t). This compound was obtained as yellow needles (1,4-dioxane); IR (potassium bromide): ν 3070 (CH), 2940 (CH), 1635 (tropone CO), 1600 (pyran CO), 1510, 1465, 1430, 1380, 1330, 1265, 1150, 1020, 850, 805, 770, 700 cm^{-1}; ^1H NMR (CF_3COOD, 400 MHz): δ 7.05–8.29 (m, 8H, ArH, PhH, C=CH), 3.95 (s, 3H, OCH_3), 3.92 ppm (s, 3H, OCH_3); ^{13}C NMR (CF_3COOD, 100 MHz): δ 182.55, 181.56, 171.44, 163.26, 156.21, 151.73, 150.24, 144.45, 138.98, 135.37, 131.29, 129.26, 125.48, 122.75, 120.09, 117.27, 116.02, 114.45, 113.13, 112.22, 111.64, 110.37, 107.92, 67.78, 56.78, and 56.71 ppm; ms: *m/z* 311 $(M+1)^+$. Anal. Calcd for $C_{18}H_{14}O_5$: C, 69.67; H, 4.55. Found: C, 69.65; H, 4.57.

2-(2,3-Dichlorophenyl)-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (2u). This compound was obtained as pale yellow solids (1,4-dioxane); IR (potassium bromide): ν 3065 (CH), 1660 (tropone CO), 1600 (pyran CO), 1515, 1410, 1370, 1340, 1170, 1110, 900, 870, 795 cm^{-1}; ^1H NMR (CF_3COOD, 400 MHz): δ 7.67–8.98 ppm (m, 8H, ArH, PhH, C—CH); ^{13}C NMR (CF_3COOD, 100 MHz): δ 183.75, 183.65, 169.13, 163.91, 145.77, 139.56, 137.12, 136.06, 133.23, 130.93, 129.88, 120.69, 117.87, 116.70, 115.06, 112.24 ppm; ms: *m/z* 319 $(M)^+$. Anal. Calcd for $C_{16}H_8Cl_2O_3$: C, 60.22; H, 2.53. Found: C, 60.16; H, 2.63.

2-(2,4-Dichlorophenyl)-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (2v). This compound was obtained as colorless needles (1,4-dioxane); IR (potassium bromide): ν 3050 (CH), 1670 (tropone CO), 1604 (pyran CO), 1550, 1520, 1480, 1380, 1340, 1170, 1110, 890, 870, 820, 700 cm^{-1}; ^1H NMR (CF_3COOD, 400 MHz): δ 7.84–9.06 ppm (m, 8H, ArH, PhH, C=CH); ^{13}C NMR (CF_3COOD, 100 MHz): δ 183.81, 183.60, 168.72, 145.75, 142.19, 139.52, 136.01, 133.45, 130.82, 129.29, 120.66, 117.84, 116.59, 115.03, 112.22 ppm; ms: *m/z* 319 $(M)^+$. Anal. Calcd for $C_{16}H_8Cl_2O_3$: C, 60.22; H, 2.53. Found: C, 60.19; H, 2.66.

2-(3,5-Dichlorophenyl)-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (2w). This compound was obtained as yellow needles (1,4-dioxane); IR (potassium bromide): ν 3040 (CH), 1650 (tropone CO), 1600 (pyran CO), 1560, 1520, 1425, 1375, 1345, 1250, 1115, 860, 800, 700 cm^{-1}; ^1H NMR (CF_3COOD, 400 MHz): δ 7.30–8.37 ppm (m, 8H, ArH, PhH, C=CH); ^{13}C NMR (CF_3COOD, 100 MHz): δ 183.07, 166.99, 163.04, 161.30, 151.73, 144.40, 138.84, 138.20, 135.02, 134.56, 133.17, 132.06, 130.03, 126.53, 119.94, 118.82, 117.12, 115.99, 114.82, 113.17, 111.49, 110.89 ppm; ms: *m/z* 319 $(M)^+$. Anal. Calcd for $C_{16}H_8Cl_2O_3$: C, 60.22; H, 2.53. Found: C, 60.28; H, 2.51.

2-(3,4-Dichlorophenyl)-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (2x). This compound was obtained as yellow needles (1,4-dioxane); IR (potassium bromide): ν 3065 (CH), 1650 (tropone CO), 1600 (pyran CO), 1520, 1468, 1410, 1370, 1340, 1180, 1140, 1110, 1030, 900, 820, 710 cm^{-1}; ^1H NMR (CF_3COOD, 400 MHz): δ 7.27–8.32 ppm (m, 8H, ArH, PhH, C=CH); ^{13}C NMR (CF_3COOD, 100 MHz): δ 183.00, 167.52, 163.40, 161.28, 144.41, 140.39, 138.86, 135.91, 135.06, 132.79, 132.08, 130.06, 127.30, 119.99, 117.17, 114.36, 111.54, 110.25 ppm; ms: *m/z* 319 $(M)^+$. Anal. Calcd for $C_{16}H_8Cl_2O_3$: C, 60.22; H, 2.53. Found: C, 60.19; H, 2.65.

2-(3,4,5-Trimethoxyphenyl)-4,9-dihydrocyclohepta[*b*]-pyran-4,9-dione (2y). This compound was obtained as yellow needles (1,4-dioxane); IR (potassium bromide): ν 3060 (CH), 2935 (CH), 1650 (tropone CO), 1610 (pyran CO), 1520, 1470, 1410, 1370 cm^{-1}; ^1H NMR (CF_3COOD, 400 MHz): δ 7.87–8.91 (m, 7H, ArH, PhH, C=CH), 4.48–4.50 ppm (m, 9H, OCH_3); ^{13}C NMR (CF_3COOD, 100 MHz): δ 182.90, 182.58, 169.80, 162.64, 154.64, 144.59, 142.97, 138.79, 135.19, 131.89, 129.56, 126.77, 119.94, 117.12, 114.31, 111.49, 109.61, 106.75, 62.25, 56.98 ppm; ms: *m/z* 341 $(M+1)^+$. Anal. Calcd for $C_{19}H_{16}O_6$: C, 67.05; H, 4.74. Found: C, 66.98; H, 4.87.

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Efficient Synthesis and Spectroscopy of 3,3-Dimethyl-2,3,4,5,10,11-hexahydro-8-[(*o*-; and *p*-methyl)phenoxy]-11-[(*o*-; and *p*-substituted)phenyl]-1 *H*-dibezo-[*b*,*e*][1,4]diazepin-1-ones

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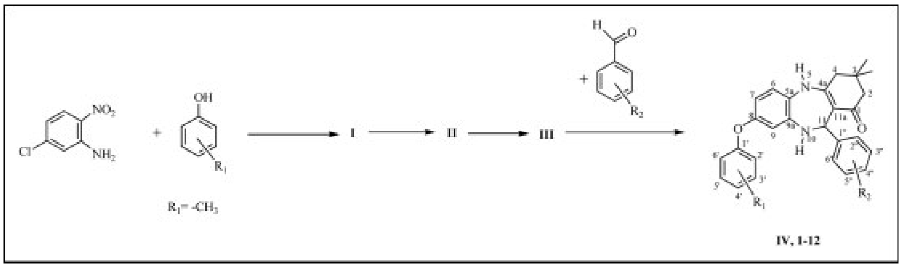

An easy synthesis of four steps to afforded 12 new derivatives of 3,3-dimethyl-2,3,4,5,10,11-hexahydro-8-[(*o*-; and *p*-methyl)phenoxy]-11-[(o-; and *p*-substituted)phenyl]-1H-dibezo-[b,e][1,4]diazep-in-1-ones **IV**, **1-12** with potential biological and pharmacological activity as sedative, hypnotic-muscular relaxing, anticonvulsant, and schizophrenia treatment of the central nervous system (CNS). The final products have been obtained with good yields, by condensation and cyclization between 3-{4-[(*o*-; and *p*-methyl)phenoxy]-1,2-phenylendiamine}-5,5-dimethyl-2-cyclohexanone **III**, with the corresponding (*o*-; and *p*-R)benzaldehyde. The structure of all derivatives was corroborated by spectroscopy of ir, ^{1}H, and ^{13}C NMR, with bi-dimensional experiments and EI-MS in low and high resolution with collision-induced dissociation experiments (CID).

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INTRODUCTION

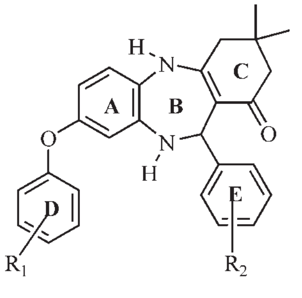
The first 1,4- and 1,5-benzodiazepines appeared in the pharmaceutical industry as tranquilizers in the 1970's, their use and interest in recent years has been broader in areas such as tranquilizer, sedative, hypnotic, muscular relaxant, anticonvulsant, and schizophrenia treatment in the central nervous system. The development of new research projects using benzodiazepines and their application has great importance because these types of compounds have been used as antipsycotic drugs [1,2] and also for their antianaphylactic activity [3].

RESULTS AND DISCUSSION

To continue with our research program on the synthesis and determination of biological activity in different 1,4 and 1,5-benzodiazepines [4–7], we described in this report the synthesis of 12 new derivatives of 3,3-dimethyl-2,3,4,5,10,11-hexahydro-8-[(*o*-; and *p*-methyl)-phenoxy]-11-[(*o*-; and *p*-substituted)phenyl]-1*H*-dibezo-[*b*,*e*][1,4]di-azepin-1-ones **IV**, **1-12** (Fig. 1). The synthesis of the dibenzo[*b*,*e*][1,4]diazepin-1-ones **IV**, **1-12** derivatives was carried out in four steps as shown in the Scheme 1.

The reaction mixture of 5-chloro-2-nitroaniline with the (*o*- and *p*-methyl)phenol in presence of anhydrous potassium carbonate at reflux in anhydrous dimethylformamide was heated for 5 h. After cooling, the reaction mixture was diluted with cold water, the 3-amine-4-nitrophenyl-[(*o*-; and *p*-methyl)phenyl]ether **I** that was precipitated and collected by filtration with suction was obtained in a 90–93% yield [8].

Hydrogenation of the corresponding ether **I** in ethanol in presence of Pd/C 10% under a pressure of 60 pounds/inch^2 at room temperature with magnetic stirring for 22 h, we reduced the nitro group to amine. When the reaction was finished, the catalyst Pd/C 10% was removed



IV, 1-12

	R_1	R_2
1	o-CH_3	o-CH_3
2	o-CH_3	p-CH_3
3	o-CH_3	o-Cl
4	o-CH_3	p-Cl
5	o-CH_3	o-Br
6	o-CH_3	p-Br
7	p-CH_3	o-CH_3
8	p-CH_3	p-CH_3
9	p-CH_3	o-Cl
10	p-CH_3	p-Cl
11	p-CH_3	o-Br
12	p-CH_3	p-Br

Figure 1. Compounds **IV**, **1–12**.

by filtration through celite and ethanol solution was evaporated under reduced pressure. The 3,4-diaminophenyl-[(*o*-; and *p*-methyl)phenyl]ether **II** [9] was obtained in very good yield of 95–98%.

Condensation of the derivatives **II** with 5,5-dimethyl-1,3-cyclohexanedione at reflux in anhydrous benzene with a Dean-Stark trap to eliminate the water produced; afforded after evaporated the ethanol under reduced pressure, the 3-{4-[(*o*-; and *p*-methyl)phenoxy]-1,2-phenylendiamine}-5,5-dimethyl-2-cyclohexenone **III** [10,11], almost pure in 70–75% yield.

Treatment of 1 equiv. of the corresponding 5,5-dimethyl-2-cyclohexenone **III**, with 1 equiv. of the corresponding (*o*-; and *p*-R_2)benzaldehyde in the presence of 0.5 mL of glacial acetic acid at reflux in 10 mL of ethanol with magnetic stirring for 2–4 h afforded the 3,3-dimethyl-2,3,4,5,10,11-hexahydro-8-[(*o*-; and *p*-methyl)phenoxy]-11-[(*o*-; and *p*-substituted)phenyl]-1H-dibezo-[*b*,*e*][1,4]diazepin-1-ones **IV**, **1-12** in 54–75% yields.

The infrared spectra of compounds **IV**, **1-12** displayed absorptions at 3415–3299 cm^{-1} for N—H stretching; at 1700–1600 cm^{-1} for C=O stretching; at 1377–1369 and 1266–1263 cm^{-1} for C—N stretching; at 1187–1171 and 1114–1012 cm^{-1} for C—O stretching and the corresponding absorptions for aromatic and R-substituents.

In the ^1H NMR spectra the presence of two singlet signals (2X3H) at δ 1.01–1.12 and 1.11–1.15 were assigned to the methyl protons joined at C-3. The presence of a doublet at δ 2.18–2.31 and 2.28–2.34 was consistent with the methylene protons at C-2; other doublet signals at δ 2.40–2.57 and 2.54–2.64 was assigned to the methylene protons on C-4. The singlet signal at δ 5.84–6.21 was consistent with methine proton on C-11.

The presence of a broad signal deuterium oxide exchangeable proton a δ 6.45–7.76 was consistent with the N—H. The other signals corresponding at the aromatic protons of the aromatic ring of dibenzodiazepin-1-one appears as a doublet at δ 5.60–6.12 and was consistent with the proton at C-9; the presence of a signal doublet of doublet at δ 6.26–6.40 correspond at the proton on C-7 and the signal doublet at δ 6.66–6.90 was assigned at the proton on C-6.

The other aromatic protons of the rings phenoxy and phenyl substituent on the framework of the dibenzodiazepin-1-one appears as multiplet and as AA′BB′ systems at δ 6.00–7.47. The signals for the methyl substituent in the aromatic rings were also observed as a singlet signal at δ 2.03–2.51.

The ^{13}C NMR spectra data for compounds **IV**, **1-12** are given in Table 1. The signals were confirmed by

Scheme 1

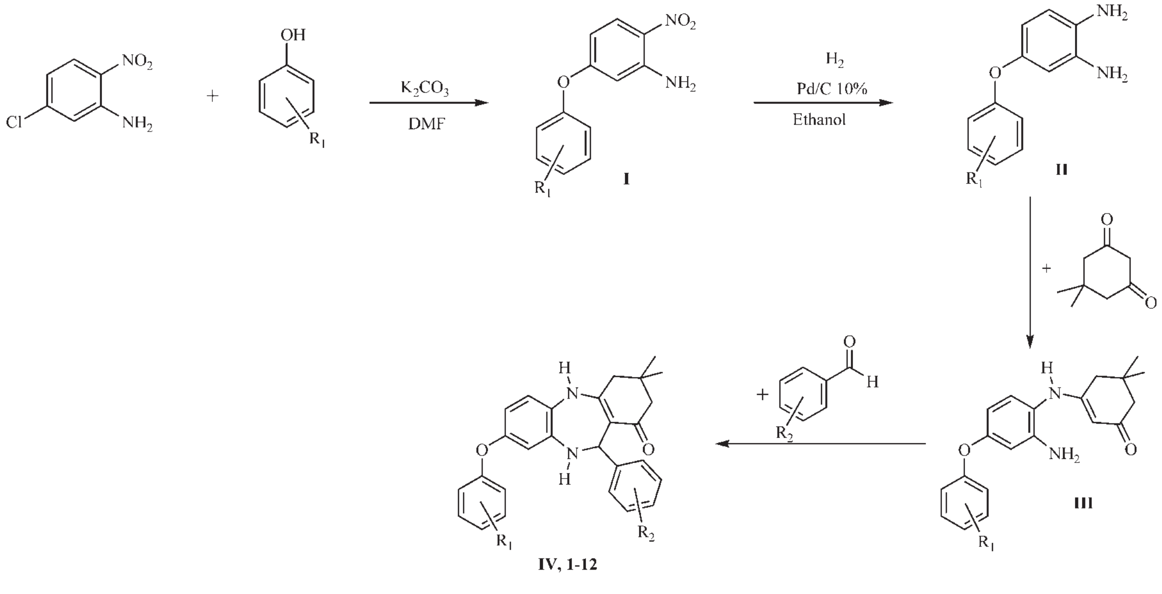
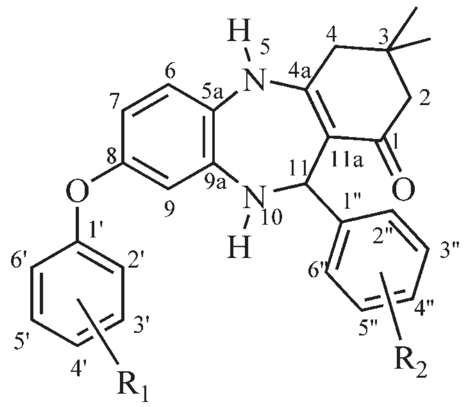


Table 1

^{13}C NMR spectral data for compounds **1–12**.



Compounds	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
R_1	*o*-CH_3	*o*-CH_3	*o*-CH_3	*o*-CH_3	*o*-CH_3	*o*-CH_3	*p*-CH_3	*p*-CH_3	*p*-CH_3	*p*-CH_3	*p*-CH_3	*p*-CH_3
R_2	*o*-CH_3	*p*-CH_3	*o*-Cl	*p*-Cl	*o*-Br	*p*-Br	*o*-CH_3	*p*-CH_3	*o*-Cl	*p*-Cl	*o*-Br	*p*-Br
C-1	193.8	193.6	193.6	193.7	193.2	193.3	193.6	193.7	192.7	193.6	193.6	193.8
C-2	49.8	49.7	49.7	49.7	49.7	49.6	49.6	49.7	49.2	49.7	49.7	49.7
C-3	32.3	32.3	32.3	32.3	32.3	32.0	32.4	32.3	32.3	32.3	32.4	32.3
C-4	46.1	46.4	46.1	46.5	46.2	45.4	46.2	46.3	46.0	46.2	46.3	46.4
C-4a	153.8	153.0	153.8	153.1	154.7	154.8	153.8	153.2	156.0	153.5	153.4	153.3
C-5a	127.3	126.5	127.1	126.4	127.0	127.0	127.8	127.0	126.8	126.9	127.4	126.8
C-6	120.9	120.9	120.9	121.0	121.0	121.6	121.1	121.0	122.0	121.4	120.9	121.1
C-7	111.5	111.0	111.6	111.3	111.6	111.6	111.9	112.2	112.9	112.4	112.7	112.4
C-8	153.6	153.7	154.7	154.2	154.0	153.6	153.3	153.3	153.7	153.7	154.4	153.8
C-9	111.0	110.9	111.0	110.9	111.1	110.9	111.3	111.0	112.0	112.1	112.3	112.1
C-9a	138.5	138.8	138.9	138.4	138.8	137.7	138.6	138.5	139.7	138.3	138.7	138.3
C-11	55.4	57.8	56.1	57.6	58.3	57.6	55.5	57.8	56.1	57.6	58.3	57.7
C-11a	110.9	118.5	109.2	110.5	109.5	109.4	111.9	111.0	109.2	110.3	109.6	110.4
C-1′	155.0	154.9	154.9	154.8	154.9	154.2	155.3	155.3	155.2	155.1	155.2	155.1
C-2′	129.0	140.7	129.1	129.4	129.1	129.1	130.2	130.0	129.9	130.1	130.0	130.1
C-3′	130.5	131.3	131.2	131.4	131.3	131.2	117.7	118.0	117.8	118.1	117.7	118.2
C-4′	123.2	123.5	123.4	123.7	123.5	123.3	129.9	132.3	132.3	132.3	132.6	132.6
C-5′	126.8	126.8	128.1	127.0	126.7	126.9	117.7	118.0	117.8	118.1	117.7	118.2
C-6′	118.2	118.6	118.3	118.9	118.4	118.5	130.2	130.0	129.9	130.1	130.0	130.1
C-1″	141.2	135.9	133.5	132.3	129.1	129.1	130.4	136.0	133.6	132.5	132.6	129.0
C-2″	135.1	128.8	139.9	128.4	141.4	128.9	135.5	127.0	139.7	128.3	142.5	131.2
C-3″	131.2	127.0	129.6	128.3	132.9	130.9	132.2	128.8	129.6	128.2	133.0	128.9
C-4″	126.7	129.2	126.8	142.2	128.4	142.4	126.9	140.5	128.2	142.2	128.4	142.8
C-5″	125.2	127.0	126.1	128.3	126.8	130.9	125.4	128.8	126.2	128.5	126.7	128.9
C-6″	125.7	128.8	127.6	128.4	127.7	128.9	125.8	127.0	127.6	128.3	127.7	131.2
C-3(CH_3)	27.9	27.8	28.2	27.9	28.2	27.6	27.8	27.8	28.1	27.8	28.2	27.9
C-3(CH_3)	28.6	28.7	28.5	28.6	28.4	28.6	28.6	28.8	28.4	28.7	28.5	28.6
$C_{2'}$-CH_3	16.0	16.0	16.0	16.0	16.0	15.9	–	–	–	–	–	–
$C_{4'}$-CH_3						–	20.6	21.0	20.6	20.6	20.6	20.7
$C_{2''}$-CH_3	19.5	–	–	–	–	–	19.6	–	–	–	–	–
$C_{4''}$-CH_3	–	20.9	–	–	–	–	–	20.6	–	–	–	–

The numbering of the phenyl ring is only for the assignment of the chemical shifts of the carbon in ^{13}C NMR spectra.

using HETCOR, FLOCK, COSY, NOESY, and DEPT NMR experiments operating at 300 and 500 MHz. The mass spectra of compounds **IV**, **1-12** exhibit a stable molecular ion with a relative abundance of 24–55%. The base peak is the ion at m/z $[M-(76 + R_2)]^+$. The main fragmentation pathway was consistent with the assigned structures and the mass spectra of the compounds **IV**, **1-12** includes ions of m/z corresponding to molecular ion $[M]^+$; $[M-CH_3]^+$; $[M-CH_4]^+$; $[M-R_2]^+$; $[M-(R_2+ CH_4)]^+$; $[M-28]^+$; $[M-57]^+$; $[M-84]^+$; $[M-85]^+$; $[M-(76 + R_2)]^+$ (the base peak); m/z 363 and 83. The proposed fragmentation pathways leading to the formation of a number of important daughter ions have been confirmed by the corresponding parent ion spectra, using collision-induced dissociation experiments (CID). The elemental composition of the molecular ion and the principal fragment ion were determined by exact mass measurements.

EXPERIMENTAL

The ir spectra were recorded on a Nicolet Magna TR-750 spectrophotometer in chloroform. The ^{1}H NMR spectra were recorded on a Varian Unity 300 spectrometer operating at 300 MHz and the ^{13}C NMR spectra were recorded on a Varian Unity 500 spectrometer operating at 125 MHz in deuterochloroform solution containing tetramethylsilane as the internal standard with chemical shifts δ (ppm) expressed downfield from tetramethylsilane. The mass spectra were measured on a JEOL JMS-AC505 and JEOL MS-SX 102A high-resolution mass spectrometer with accurate mass determination of the molecular ion and the principal fragment ions, using the direct inlet system. The spectra were recorded by electron impact at an ionization chamber temperature of 190°C and ionizing electron energy of 70 eV, using electronic ionization. The compounds **I**, **II**, and **III** were prepared following methods developed by us with modifications [8,9,12].

General procedure for the synthesis of the 3,3-dimethyl-2,3,4,5,10,11-hexahydro-8-[(*o*-; and *p*-methyl)phenoxy]-11-[(*o*-; and *p*-substituted)phenyl]-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-ones IV, 1-12. A mixture of 1 equiv. of the corresponding 3-{4-[(*o*-; and *p*-methyl)phenoxy]-1,2-phenylendiamine}-5,5-dimethyl-2-cyclo-hexenone III; 1 equiv. of the corresponding (*o*-; and *p*-substituted)benzaldehyde, 0.5 mL of acetic acid glacial in 10 mL ethanol was heated at reflux for 2–4 h. The reaction mixture was cooled to room temperature and evaporated *in vacuo* to yield a semisolid. The residual semisolid was purified on a silica gel by choromatography in column and elution with hexane-ethyl acetate (95:5) to yield the compounds **IV**, **1–12**, in 54–75%.

3,3-Dimethyl-8-[(*o*-methyl)phenoxy]-11-[(*o*-methyl)phenyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one (IV, 1). This compound was obtained as an orange solid in 70% yield; mp 135–136°; ir (chloroform): ν N—H 3415, C=O 1619, C—N 1369 and 1264, C—O 1287 and 1113 cm^{-1}; ^{1}H NMR (deuterochloroform): δ 1.05 and 1.11 (s, 6H, C_3—$(CH_3)_2$); 2.05 (s, 3H, $C_{2'}$—CH_3); 2.18 (d, 1H, J = 16.4 Hz, 2-Ha); and 2.28 (d, 1H, J = 16.4 Hz, 2-Hb); 2.43 (d, 1H, J = 15.8 Hz, 4-Ha); and 2.56 (d, 1H, J = 15.8 Hz, 4-Hb); 2.50 (s, 3H, $C_{2''}$—CH_3); 5.88 (d, 1H, J = 2.6 Hz, 9-H); 6.11 (s, 1H, 11-H); 6.27 (dd, 1H, J = 2.6, 8.6 Hz, 7-H); 6.43 (dd, 1H, J = 1.5, 7.8 Hz, 6′-H); 6.64 (dd, 1H, J = 1.1, 7.7 Hz, 6″-H); 6.72 (d, 1H, J = 8.6 Hz, 6-H); 6.81 (dt, 1H, J = 1.0, 7.2 Hz, 5″-H); 6.96 (dt, 1H, J = 1.4, 6.2 Hz, 4′-H); 6.98 (dt, 1H, J = 1.5, 6.2 Hz, 4″-H); 7.0 (bs, 2H, N—H, deuterium oxide exchangeable); 7.05 (dt, 1H, J = 2.1; 6.3 Hz, 5′-H); 7.06 (dd, 1H, J = 1.2, 8.0 Hz, 3′-H); 7.14 (dd, 1H, J = 1.7, 6.6 Hz, 3″-H); ms (IE = 70 eV): m/z (%) 438 (55) $[M^+]$; 423 (24) $[M\text{-}R_1]^+$ $[M\text{-}(CH_3)]^+$; 422 (14); 381 (4); 354 (6); 347 (100) $[M\text{-}(76 + R_1)]^+$; 83 (5). Anal. Calcd. for $C_{29}H_{30}N_2O_2$: (438.55): C, 79.42; H, 6.90; N, 6.40; Found: C, 79.50; H, 6.80; N, 6.49.

3,3-Dimethyl-8-[(*o*-methyl)phenoxy]-11-[(*p*-methyl)phenyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one (IV, 2). This compound was obtained as an orange solid in 70% yield; mp 240°; ir (chloroform): ν N—H 3301, C=O 1600, C—N 1376 and 1263, C—O 1185 and 1114 cm^{-1}; ^{1}H NMR (deuterochloroform): δ 1.08 and 1.13 (s, 6H, C_3—$(CH_3)_2$); 2.08 (s, 3H, $C_{2'}$—CH_3); 2.22 (s, 3H, $C_{4''}$—CH_3); 2.22 (d, 1H, J = 16.5 Hz, 2-Ha); and 2.31 (d, 1H, J = 16.5 Hz, 2-Hb); 2.40 (d, 1H, J = 15.6 Hz, 4-Ha); and 2.57 (d, 1H, J = 15.6 Hz, 4-Hb); 5.86 (s, 1H, 11-H); 5.96 (d, 1H, J = 2.4 Hz, 9-H); 6.32 (dd, 1H, J = 2.7, 8.7 Hz, 7-H); 6.53 (bs, 2H, N—H, deuterium oxide exchangeable); 6.57 (dd, 1H, J = 1.2, 8.1 Hz, 6′-H); 6.66 (d, 1H, J = 8.7 Hz, 6-H); 6.92 (s, 4H, phenyl protons of "E" ring); 6.99 (dt, 1H, J = 1.5, 7.3 Hz, 4′-H); 7.06 (dt, 1H, J = 1.5, 7.4 Hz, 5′-H); 7.16 (dd, 1H, J = 1.2, 6.3 Hz, 3′-H); ms (IE = 70 eV): m/z (%) 438 (49) $[M^+]$; 423 (6) $[M\text{-}R_1]^+$ $[M\text{-}(CH_3)]^+$; 422 (9); 381 (6); 354 (7); 353 (6); 347 (100) $[M\text{-}(76 + R_1)]^+$; 83 (4). Anal. Calcd. for $C_{29}H_{30}N_2O_2$: (438.55): C, 79.42; H, 6.90; N, 6.40; Found: C, 79.55; H, 6.76; N, 6.31.

3,3-Dimethyl-8-[(o-methyl)phenoxy]-11-[(*o*-chloro)phenyl]-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (IV, 3). This compound was obtained as an orange solid in 75% yield; mp 105–107°; ir (chloroform): ν N—H 3299, C=O 1620, C—N 1376 and 1265, C—O 1186 and 1113 cm^{-1}; ^{1}H NMR (deuterochloroform): δ 1.12 and 1.15 (s, 6H, C_3—$(CH_3)_2$); 2.04 (s, 3H, $C_{2'}$—CH_3); 2.23 (d, 1H, J = 16.2 Hz, 2-Ha); and 2.32 (d, 1H, J = 16.2 Hz, 2-Hb); 2.50 (d, 1H, J = 15.9 Hz, 4-Ha); and 2.61 (d, 1H, J = 15.9 Hz, 4-Hb); 6.0 (dt, 1H, J = 1.2; 7.8 Hz, 5″-H); 6.01 (d, 1H, J = 2.4 Hz, 9-H); 6.21 (s, 1H, 11-H); 6.26 (dd, 1H, J = 2.3, 8.8 Hz, 7-H); 6.43 (dd, 1H, J = 1.0, 7.8 Hz, 6′-H); 6.67 (d, 1H, J = 8.7 Hz, 6-H); 6.78 (dd, 1H, J = 1.3, 7.6 Hz, 6″-H); 6.88 (bs, 2H, N—H, deuterium oxide exchangeable); 7.01 (dt, 1H, J = 1.2, 6.6 Hz, 4′-H); 7.02 (dt, 1H, J = 1.2, 7.8 Hz, 5′-H); 7.03 (dt, 1H, J = 1.5, 7.3 Hz, 4″-H); 7.16 (dd, 1H, J = 1.5, 6.5 Hz, 3′-H); 7.27 (dd, 1H, J = 1.2, 6.6 Hz, 3″-H); ms (IE = 70 eV): m/z (%) 460 (15) $[M + 2]^+$; 458 (38) $[M^+]$; 443 (5) $[M\text{-}(CH_3)]^+$; 442 (9); 423 (20) $[M\text{-}R_1]^+$; 401 (4); 374 (5); 373 (4); 347 (100) $[M\text{-}(76+ R_1)]^+$; 83 (3). Anal. Calcd. for $C_{28}H_{27}ClN_2O_2$: (458.97): C, 73.27; H, 5.93; N, 6.10; Found: C, 73.59; H, 5.81; N, 6.25.

3,3-Dimethyl-8-[(*o*-methyl)phenoxy]-11-[(*p*-chloro)phenyl]-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (IV, 4). This compound was obtained as a yellow solid in 70% yield; mp 220–222°; ir (chloroform): ν N—H 3301, C=O 1585, C—N 1377 and 1264, C—O 1185 and 1114 cm^{-1}; ^{1}H NMR (deuterochloroform): δ 1.08 and 1.14 (s, 6H, C_3—$(CH_3)_2$); 2.08 (s, 3H, $C_{2'}$—CH_3); 2.22 (d, 1H, J = 16.5 Hz, 2-Ha); and 2.31 (d, 1H, J = 16.5 Hz, 2-Hb); 2.42 (d, 1H, J = 16.2 Hz, 4-Ha); and 2.58 (d, 1H, J = 16.2 Hz, 4-Hb); 5.85 (s, 1H, 11-H); 5.94 (d, 1H, J = 2.7 Hz, 9-H); 6.36 (dd, 1H, J = 2.4, 8.8 Hz, 7-H); 6.45 (bs, 2H, N—H, deuterium oxide exchangeable); 6.58 (dd, 1H, J = 1.2, 7.8 Hz, 6′-H); 6.68 (d, 1H, J = 8.7 Hz, 6-H); 6.96 and 7.10 (AA′BB′, 4H, J = 8.7 Hz, phenyl protons of "E" ring); 7.0 (dt, 1H, J = 1.2, 6.6 Hz, 4′-H); 7.11 (dt, 1H, J = 1.2, 6.6 Hz, 5′-H); 7.17 (dd, 1H, J = 1.2, 7.5 Hz, 3′-H); ms (IE = 70 eV): m/z (%) 460 (16) $[M+2]^+$; 458 (40) $[M^+]$; 443 (4) $[M\text{-}(CH_3)]^+$; 442 (6); 401 (6); 374 (6); 373 (6); 347 (100) $[M\text{-}(76 + R_1)]^+$; 83 (3). Anal. Calcd. for $C_{28}H_{27}ClN_2O_2$: (458.97): C, 73.27; H, 5.93; N, 6.10; Found: C, 73.15; H, 5.80; N, 6.19.

3,3-Dimethyl-8-[(o-methyl)phenoxy]-11-[(*o*-bromo)phenyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one (IV, 5). This compound was obtained as an orange solid in 60% yield; mp 72–74°; ir (chloroform): ν N—H 3413, C=O 1700, C—N 1371 and 1266, C—O 1285 and 1113 cm^{-1}; ^{1}H NMR (deuterochloroform): δ 1.09 and 1.12 (s, 6H, C_3—$(CH_3)_2$); 2.03 (s, 3H, $C_{2'}$—CH_3); 2.21 (d, 1H, J = 16.5 Hz, 2-Ha); and 2.30 (d, 1H, J = 16.5 Hz, 2-Hb); 2.51 (d, 1H, J = 15.3 Hz, 4-Ha); and 2.62 (d, 1H, J = 15.3 Hz, 4-Hb); 6.01 (d, 1H, J = 2.4 Hz, 9-H); 6.14 (s, 1H, 11-H); 6.26 (dd, 1H, J = 2.3, 8.8 Hz, 7-H); 6.43 (dd, 1H, J = 1.8, 7.8 Hz, 6′-H); 6.72 (d, 1H, J = 8.1 Hz, 6-H); 6.77 (dd, 1H, J = 1.8, 6.8 Hz, 6″-H); 6.78 (bs, 2H, N—H, deuterium oxide exchangeable); 6.91 (dt, 1H, J = 1.8, 6.6 Hz, 4″-H); 6.94 (dt, 1H, J = 1.8; 6.3 Hz, 5″-H); 6.97 (dt, 1H, J = 1.8, 7.2 Hz, 4′-H); 7.03 (dt, 1H, J = 2.1, 7.5 Hz, 5′-H); 7.15 (dd, 1H, J = 1.5, 7.2 Hz, 3′-H); 7.44 (dd, 1H, J = 1.5, 6.6 Hz, 3″-H); ms (IE = 70 eV): m/z (%) 504 (24) $[M + 2]^+$; 502 (24) $[M^+]$; 487 (5) $[M\text{-}(CH_3)]^+$; 486 (8); 423 (36) $[M\text{-}R_1]^+$; 407 (7) $[M\text{-}(R_1 + CH_4)]^+$; 445 (3); 418 (3); 417 (3); 347 (100) $[M\text{-}(76 + R_1)]^+$; 83 (3). Anal. Calcd. for $C_{28}H_{27}BrN_2O_2$: (503.34): C, 66.81; H, 5.41; N, 5.57; Found: C, 66.92; H, 5.33 N, 5.50.

3,3-Dimethyl-8-[(*o*-methyl)phenoxy]-11-[(*p*-bromo)phenyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one (IV, 6). This compound was obtained as a brown solid in 73% yield; mp 208–210°; ir (chloroform): ν N—H 3413, C=O 1618, C—N 1369 and 1266, C—O 1185 and 1112 cm^{-1}; ^{1}H NMR (deuterochloroform): δ 1.07 and 1.13 (s, 6H, C_3—$(CH_3)_2$); 2.08 (s, 3H, $C_{2'}$—CH_3); 2.20 (d, 1H, J = 16.4 Hz, 2-Ha); and 2.29 (d, 1H, J = 16.4 Hz, 2-Hb); 2.49 (d, 1H, J = 16.0 Hz, 4-Ha); and 2.58 (d, 1H, J = 16.0 Hz, 4-Hb); 5.60 (d, 1H, J = 2.4 Hz, 9-H); 5.9 (s, 1H, 11-H); 6.37 (dd, 1H, J = 2.5, 8.7 Hz, 7-H); 6.54 (dd, 1H, J = 1.5, 7.5 Hz, 6′-H); 6.9 (d, 1H, J = 8.4 Hz, 6-H); 6.93 and 7.24 (AA′BB′, 4H, J = 8.4 Hz, phenyl protons of "E" ring); 7.0 (dt, 1H, J = 1.5, 7.4 Hz, 4′-H); 7.14 (dt, 1H, J = 1.6, 7.5 Hz, 5′-H); 7.18 (dd, 1H, J = 1.5, 7.5 Hz, 3′-H); 7.76 (bs, 2H, N—H, deuterium oxide exchangeable);; ms (IE = 70 eV): m/z (%) 504 (31) $[M + 2]^+$; 502 (32) $[M^+]$; 487 (3) $[M\text{-}(CH_3)]^+$; 486 (4); 445 (4); 418 (5); 417 (4); 347 (100) $[M\text{-}(76 + R_1)]^+$; 83 (4). Anal. Calcd. for $C_{28}H_{27}BrN_2O_2$: (503.34): C, 66.81; H, 5.41; N, 5.57; Found: C, 66.70; H, 5.50; N, 5.68.

3,3-Dimethyl-8-[(*p*-methyl)phenoxy]-11-[(*o*-methyl)phenyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one (IV, 7). This compound was obtained as a yellow solid in 51% yield; mp 102–104°; ir (chloroform): ν N—H 3414, C=O 1617, C—N 1369 and 1263, C—O 1171 and 1016 cm^{-1}; ^{1}H NMR (deuterochloroform): δ 1.01 and 1.13 (s, 6H, C_3—$(CH_3)_2$); 2.19 (d, 1H, J = 16.2 Hz, 2-Ha); and 2.31 (d, 1H, J = 16.2 Hz, 2-Hb); 2.28 (s, 3H, $C_{4'}$—CH_3); 2.48 (d, 1H, J = 16.2 Hz, 4-Ha); and 2.54 (d, 1H, J = 16.2 Hz, 4-Hb); 2.51 (s, 3H, $C_{2''}$—CH_3); 6.00 (d, 1H, J = 2.1 Hz, 9-H); 6.14 (s, 1H, 11-H); 6.39 (dd, 1H, J = 2.4, 8.7 Hz, 7-H); 6.55 and 7.01 (AA′BB′, 4H, J = 8.7 Hz, phenyl protons of "D" ring); 6.75 (bs, 2H, N—H, deuterium oxide exchangeable); 6.80 (dd, 1H, J = 1.3, 7.6 Hz, 6″-H); 6.81 (d, 1H, J = 7.8 Hz, 6-H); 6.82 (dt, 1H, J = 1.6, 7.6 Hz, 5″-H);6.99 (dt, 1H, J = 1.5, 6.2 Hz, 4″-H); 7.08 (dd, 1H, J = 1.6, 8.1 Hz, 3″-H); ms (IE = 70 eV): m/z (%) 438 (52) $[M^+]$; 423 (19) $[M\text{-}R_1]^+$ $[M\text{-}(CH_3)]^+$; 422 (12); 381 (3); 354 (5); 353 (4); 347 (100) $[M\text{-}(76 + R_1)]^+$; 83 (5). Anal. Calcd. for $C_{29}H_{30}N_2O_2$: (438.55): C, 79.42; H, 6.90; N, 6.40; Found: C, 79.51; H, 6.79; N, 6.52.

3,3-Dimethyl-8-[(*p*-methyl)phenoxy]-11-[(*p*-methyl)phenyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one (IV, 8). This compound was obtained as a yellow solid in 54% yield; mp 47-49°; ir (chloroform): ν N—H 3415, C=O 1618, C—N 1369 and 1264, C—O 1172 and 1016 cm^{-1}; ^{1}H NMR (deuterochloroform): δ 1.08 and 1.13 (s, 6H, C_3—$(CH_3)_2$); 2.21 (d, 1H, J = 16.2 Hz, 2-Ha); and 2.30 (d, 1H, J = 16.2 Hz, 2-Hb); 2.23 (s, 3H, $C_{4'}$—CH_3); 2.29 (s, 3H, $C_{4''}$—CH_3); 2.42 (d, 1H, J = 15.9 Hz, 4-Ha); and 2.57 (d, 1H, J = 15.9 Hz, 4-Hb); 5.88 (s, 1H, 11-H); 6.08 (d, 1H, J = 2.5 Hz, 9-H); 6.38 (dd, 1H, J = 2.5, 8.6 Hz, 7-H); 6.64 and 7.03 (AA′BB′, 4H, J = 8.8 Hz, phenyl protons of "D" ring); 6.72 (d, 1H, J = 8.8 Hz, 6-H); 6.75 (bs, 2H, N—H, deuterium oxide exchangeable); 6.93 (s, 4H, phenyl protons of "E" ring); ms (IE = 70 eV): m/z (%) 438 (44) $[M^+]$; 423 (8) $[M\text{-}R_1]^+$ $[M\text{-}(CH_3)]^+$; 422 (6); 381 (8); 354 (10); 353 (9); 347 (100) $[M\text{-}(76 + R_1)]^+$; 83 (3). Anal. Calcd. for $C_{29}H_{30}N_2O_2$: (438.55): C, 79.42; H, 6.90; N, 6.40; Found: C, 79.51; H, 6.79; N, 6.52.

3,3-Dimethyl-8-[(p-methyl)phenoxy]-11-[(*o*-chloro)phenyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one (IV, 9). This compound was obtained as a yellow solid in 70% yield; mp 42-44°; ir (chloroform): ν N—H 3413, C=O 1618, C—N 1369 and 1265, C—O 1172 and 1117 cm^{-1}; ^{1}H NMR (deuterochloroform): δ 1.12 and 1.14 (s, 6H, C_3—$(CH_3)_2$); 2.29 (s, 3H, $C_{4'}$—CH_3); 2.22 (d, 1H, J = 16.4 Hz, 2-Ha); and 2.31 (d, 1H, J = 16.4 Hz, 2-Hb); 2.57 (d, 1H, J = 16.2 Hz, 4-Ha); and 2.64 (d, 1H, J = 16.2 Hz, 4-Hb); 6.11 (d, 1H, J = 2.7 Hz, 9-H); 6.20 (s, 1H, 11-H); 6.33 (dd, 1H, J = 2.7, 8.4 Hz, 7-H); 6.56 and 7.02 (AA′BB′, 4H, J = 8.4 Hz, phenyl protons of "D" ring); 6.74 (bs, 2H, N—H, deuterium oxide exchangeable); 6.77 (dd, 1H, J = 1.3, 7.5 Hz, 6″-H); 6.82 (d, 1H, J = 8.7 Hz, 6-H); 6.92 (dt, 1H, J = 1.2; 7.5 Hz, 5″-H); 7.04 (dt, 1H, J = 1.8, 7.7 Hz, 4″-H); 7.28 (dd, 1H, J = 1.5, 7.2 Hz, 3″-H); ms (IE = 70 eV): m/z (%) 460 (16) $[M+2]^+$; 458 (40) $[M^+]$; 443 (3) $[M\text{-}(CH_3)]^+$; 442 (5); 423 (20) $[M\text{-}R_1]^+$; 401 (5); 374 (6); 373 (5); 347 (100) $[M\text{-}(76 + R_1)]^+$; 83 (3). Anal. Calcd. for $C_{28}H_{27}ClN_2O_2$: (458.97): C, 73.27; H, 5.93; N, 6.10; Found: C, 73.33; H, 5.84; N, 6.22.

3,3-Dimethyl-8-[(*p*-methyl)phenoxy]-11-[(*p*-chloro)phenyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one (IV, 10). This compound was obtained as an orange solid in 54% yield; mp 87–88°; ir (chloroform): ν N—H 3413, C=O 1618, C—N 1369 and 1266, C—O 1173 and 1016 cm^{-1}; ^{1}H NMR (deuterochloroform): δ 1.06 and 1.12 (s, 6H, C_3—$(CH_3)_2$); 2.20 (d, 1H, J = 16.1 Hz, 2-Ha); and 2.30 (d, 1H, J = 16.1 Hz, 2-Hb); 2.30 (s, 3H, $C_{4'}$—CH_3); 2.41 (d, 1H, J = 15.8 Hz, 4-Ha); and 2.56 (d, 1H, J = 15.8 Hz, 4-Hb); 5.87 (s, 1H, 11-H); 6.05 (d, 1H, J = 2.6 Hz, 9-H); 6.39 (dd, 1H, J = 2.5, 8.6 Hz, 7-H); 6.5 (bs, 2H, N—H, deuterium oxide exchangeable); 6.63 and 7.06 (AA′BB′, 4H, J = 8.5 Hz, phenyl protons of "D" ring); 6.71 (d, 1H, J = 8.5 Hz, 6-H); 6.96 and 7.10 (AA′BB′, 4H, J = 8.5 Hz, phenyl protons of "E" ring); ms (IE = 70 eV): m/z (%) 460 (12) $[M + 2]^+$; 458 (36) $[M^+]$; 443 (3) $[M\text{-}(CH_3)]^+$; 442 (5); 401 (5); 374 (6); 373 (5); 347 (100) $[M\text{-}(76 + R_1)]^+$; 83 (4). Anal. Calcd. for $C_{28}H_{27}ClN_2O_2$: (458.97): C, 73.27; H, 5.93; N, 6.10; Found: C, 73.39; H, 6.03; N, 6.02.

3,3-Dimethyl-8-[(*p*-methyl)phenoxy]-11-[(*o*-bromo)phenyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one (IV, 11). This compound was obtained as an orange solid in 68% yield; mp 99–101°; ir (chloroform): ν N—H 3413, C=O

1619, C—N 1369 and 1264, C—O 1172 and 1023 cm^{-1}; ^{1}H NMR (deuterochloroform): δ 1.12 and 1.15 (s, 6H, C_3—$(CH_3)_2$); 2.22 (d, 1H, J = 16.5 Hz, 2-Ha); and 2.34 (d, 1H, J = 16.5 Hz, 2-Hb); 2.29 (s, 3H, $C_{4'}$—CH_3); 2.50 (d, 1H, J = 15.9 Hz, 4-Ha); and 2.62 (d, 1H, J = 15.9 Hz, 4-Hb); 6.12 (d, 1H, J = 2.4 Hz, 9-H); 6.16 (s, 1H, 11-H); 6.34 (dd, 1H, J = 2.5, 8.5 Hz, 7-H); 6.55 (dt, 1H, J = 1.2; 6.3 Hz, 5″-H); 6.71 (d, 1H, J = 8.7 Hz, 6-H); 6.78 (dd, 1H, J = 2.1, 7.8 Hz, 6″-H); 6.80 (bs, 2H, N—H, deuterium oxide exchangeable); 6.96 (dt, 1H, J = 1.2, 6.3 Hz, 4″-H); 7.26 (s, 4H, phenyl protons of “D” ring); 7.47 (dd, 1H, J = 2.7, 6.2 Hz, 3″-H); ms (IE = 70 eV): m/z (%) 504 (26) $[M + 2]^+$; 502 (25) $[M^+]$; 487 (8) $[M\text{-}(CH_3)]^+$; 486 (8); 423 (34) $[M\text{-}R_1]^+$; 407 (14) $[M\text{-}(R_1 + CH_4)]^+$; 445 (3); 418 (4); 417 (3); 347 (100) $[M\text{-}(76 + R_1)]^+$; 83 (5). Anal. Calcd. for $C_{28}H_{27}BrN_2O_2$: (503.34): C, 66.81; H, 5.41; N, 5.57; Found: C, 66.73; H, 5.32 N, 5.49.

3,3-Dimethyl-8-[(*p*-methyl)phenoxy]-11-[(*p*-bromo)phenyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one (IV, 12). This compound was obtained as a brown solid in 52% yield; mp 170–172°; ir (chloroform): ν N—H 3413, C=O 1618, C—N 1369 and 1266, C—O 1173 and 1012 cm^{-1}; ^{1}H NMR (deuterochloroform): δ 1.07 and 1.13 (s, 6H, C_3—$(CH_3)_2$); 2.21 (d, 1H, J = 16.5 Hz, 2-Ha); and 2.309 (d, 1H, J = 16.5 Hz, 2-Hb); 2.30 (s, 3H, $C_{4'}$—CH_3); 2.43 (d, 1H, J = 15.9 Hz, 4-Ha); and 2.58 (d, 1H, J = 15.9 Hz, 4-Hb); 5.84 (s, 1H, 11-H); 6.05 (d, 1H, J = 2.4 Hz, 9-H); 6.64 and 7.07 (AA′BB′, 4H, J = 8.4 Hz, phenyl protons of “D” ring); 6.40 (dd, 1H, J = 2.6, 8.8 Hz, 7-H); 6.58 (bs, 2H, N—H, deuterium oxide exchangeable); 6.71 (d, 1H, J = 8.7 Hz, 6-H); 6.91 and 7.25 (AA′BB′, 4H, J = 8.4 Hz, phenyl protons of “E” ring); ms (IE = 70 eV): m/z (%) 504 (23) $[M + 2]^+$; 502 (24) $[M^+]$; 487 (3) $[M\text{-}(CH_3)]^+$; 486 (3); 445 (3); 418 (4); 417 (3); 347 (100) $[M\text{-}(76 + R_1)]^+$; 83 (3). Anal. Calcd. for $C_{28}H_{27}BrN_2O_2$: (503.34): C, 66.81; H, 5.41; N, 5.57; Found: C, 66.95; H, 5.28; N, 5.68.

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New Crown Compounds Containing a 1,3,4-Thiadiazole Moiety: Synthesis and Crystal Structure

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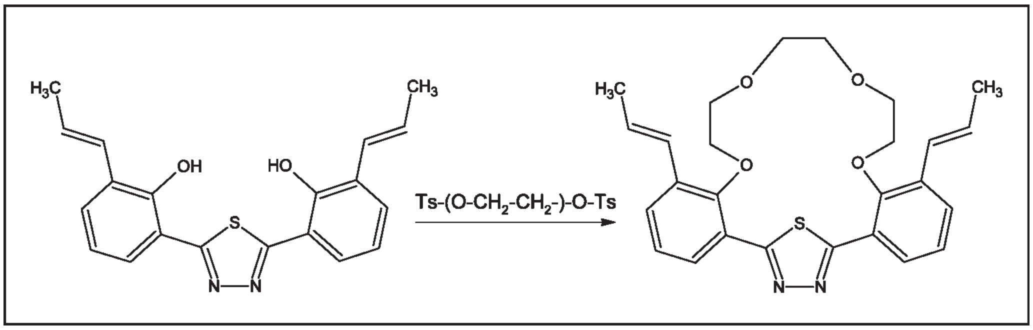

The syntheses of new macrocyclic compounds are described. The 2,5-bis(hydroxyphenyl)-1,3,4-thiadiazole reacts with allyl bromide to give the corresponding allyloxy derivative. The allyl is used to functionalize the ortho position by means of a Claisen rearrangement under microwave irradiation. New 2,5-dihydroxyphenyl-1,3,4-thiadiazoles are obtained, which are converted into macrocyclic polyethers. The structures of the new macrocyclic compounds were confirmed by ^{1}H, ^{13}C NMR, and mass spectroscopy. The crystal structure of 2,5-bis(2-allyloxyphenyl)-1,3,4-thiadiazole has been determined.

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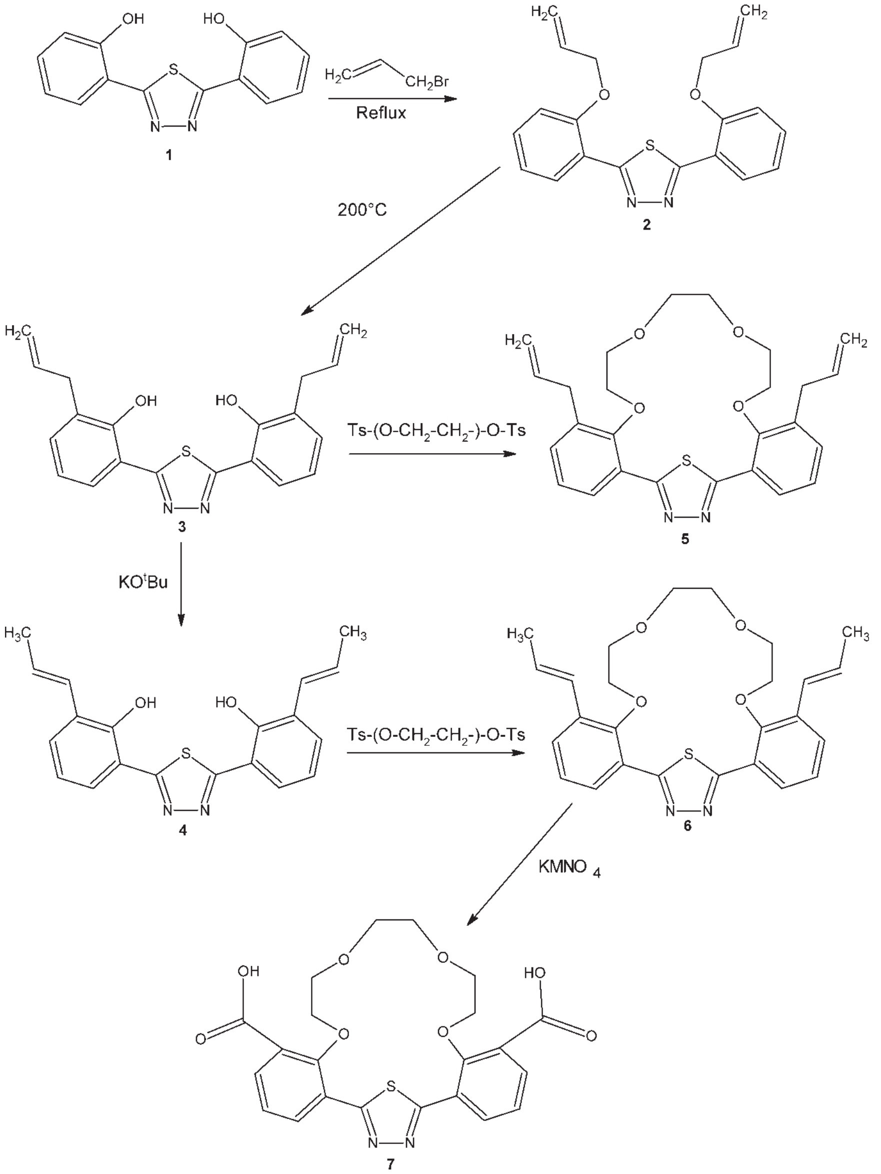
INTRODUCTION

In the field of supramolecular chemistry, crown ethers (CEs) belong to the most popular hosts, because their inclusion complexes have found a vast number of practical applications [1]. Growing interest has focused on the construction of synthetic macrocyclic polyether compounds containing heterocyclic subunits because these compounds have been shown to possess great ability to undergo selective complexation with charged as well as neutral species [2–4]. Cation complexing properties of synthetic macrocyclic polyether ligands containing a heterocyclic subcyclic unit, such as pyridine, have been previously studied by Bradshaw *et al.* using calorimetric technique for the reaction of Na^+, K^+, Ag^+, NH_4^+, and Ba^{2+} [5]. Series of such compounds containing diaryl-1,3,4-oxadiazoles and thiadiazoles have been reported recently [6–8]. In light of the general interest on the construction of synthetic macrocycles containing heterocyclic subunits as well as limited example of 1,3,4-thiadiazole inclusion in a macrocyclic framework, we report in this article the synthesis of new macrocyclic polyethers containing 2,5-diaryl-1,3,4-thiadiazole. These new macrocyclic compounds are expected to show coordinating behaviors toward cations, water, and organic molecules, such as amines or urea. Similar compounds such as crown-annelated oligothiophenes have been previously used as model compounds for molecular actuation [9]. In this work, the cation complexing properties were analyzed by ^{1}H NMR titration experiments with solution of Ba^{2+}, Sr^{2+}, or Pb^{2+}. More recently, the metal cation complexing properties of crown-annelated oligothiophenes containing 3,4-ethylenedioxythiophene have been studied showing that one of these compounds exhibit interesting complexing properties for Pb^{2+} [10]. The problem of recognition and selective binding of ions occupies a prominent place in separation process, especially in radiochemical technologies. For example, the extraction of uranium and of transuranium and rare-earth metals from nitric acid solutions with various functionally substituted CEs has been investigated by Yakshin *et al.* [11]. Recently, some macrocyclic polyether compounds containing a 1,3,4-thiadiazole moiety have been used as corrosion inhibitors for mild steel in acidic media [12]. The existing data show that most organic inhibitors act by adsorption on the metal surface [13], and it was discovered that the corrosion inhibition may be enhanced

Scheme 1



by various chemicals additives such as cation salts. Macrocyclic derivatives with potential complexing properties are expected to be useful for this purpose.

RESULTS AND DISCUSSION

The 2,5-bis (2-hydroxyphenyl)-1,3,4-thiadiazole **1** reacts with allyl bromide in the presence of solid potassium carbonate suspended in acetone. The mixture is heated under reflux during 12 h. The end of the reaction is controlled by TLC (thin layer chromatography) using a 50/50 mixture of ethylacetate and petroleum ether as eluent. Under these experimental conditions, the reaction takes place in basic media to allow the deprotonation of the two OH groups, which implies the rotation of the two oxygen atoms to the sulfur side as previously calculated [8]. After evaporation of the solvent *in vacuo*, the solid residue is treated with a solution of sodium hydroxide. The 2,5-bis-(2-allyloxyphenyl)-1,3,4-thiadiazole **2** was collected by filtration, washed with water, and recrystallized from ethanol. The structure proposed for this new thiadiazole derivative is consistent with the data obtained from their ^{1}H, ^{13}C, MS, and elemental analysis.

Single crystals suitable for X-ray diffraction study were obtained by slow evaporation of ethanol, and the crystal structure of compound **2** was investigated (Scheme 1).

The main features of the crystal structure of **2** are resulting from the quasi planarity of the whole entity:

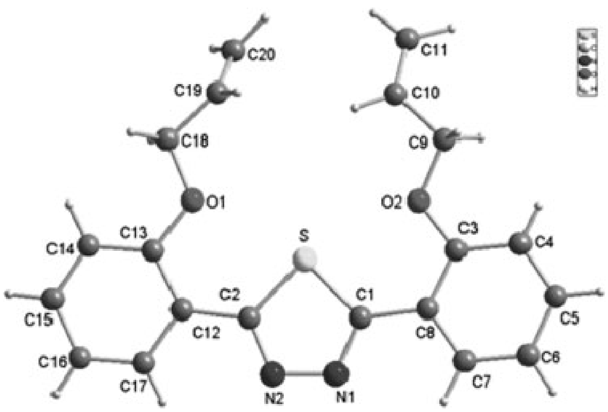


Figure 1. Projection view of compound **2**.

only O2, C10, C11, C18, and C20 are out of the mean plane containing most of the molecule; when using the central thiadiazole ring as planar reference, the phenyl ring on the right (C3 to C8, Fig. 1) is tilted 2° anticlockwise, whereas the other phenyl ring (C12 to C17) is tilted clockwise of 4°. The structure is described by stacking two different layers of such **2** entities along the [001] direction: a first set, located in the (001) basal plane of the unit cell, is seen with molecules of **2** with their central thiadiazole ring pointing upward and downward alternatively, stacked parallel to the [101] direction; a second set with a similar alternating organization of planar entities parallel to the [10-1] axis is seen at about *c*/2. This new ligand with sulfur and two π bonds is offering soft ligation sites and the two oxygen atoms provide hard ligation sites, all five of which are pointed toward a single space and are likely to discriminate between potential metals.

Table 1

Summary of the crystal data and structure refinement for compound **2**.

Formula	C20 H18 N2 O2 S
Formula weight	350.42 g/mol
Crystal system	Monoclinic
Space group	P 21/*n*
a (Å)	$a = 7.6640(2)$
b (Å)	$b = 16.0490(5)$
c (Å)	$c = 14.2818(4)$
α (°)	
β (°)	$\beta = 95.8$
γ (°)	
V (Å^3)	1747.6(4)
Z	4
D_{cal} (mg/m^3)	1.33
T (K)	296
F(000)	736
Crystal size, mm	0.1 × 0.1 × 0.1
μ (mm^{-1})	0.201
Data collection range	
Range of indices	*k*, −12 to 12; *h*, −26 to 26; *l*, −23 to 23
Reflections measured	8482
R_{int}	3.91
(R_{all}; $R_{2\sigma}$)	5.99; 4.24
(wR_{all}; $wR_{2\sigma}$)	11.93; 10.77
Goodness of fit	1.02
Number of parameters	298
Maximum peak in final Δ*F* map (e/Å^3)	0.44
Minimum peak in final Δ*F* map (e/Å^3)	−0.28

The allyl group was used to functionalize the ortho position to the phenol by means of a Claisen rearrangement. The compound **2** was exposed to microwave irradiation in ethylene glycol at an elevated temperature (200°C). This reaction was conducted under microwave heating to improve the yield and the purity of the product. The double bond of the allyl substituent was isomerized into conjugation with the aryl under basic conditions using potassium *tert*-butoxide [14].

EXPERIMENTAL

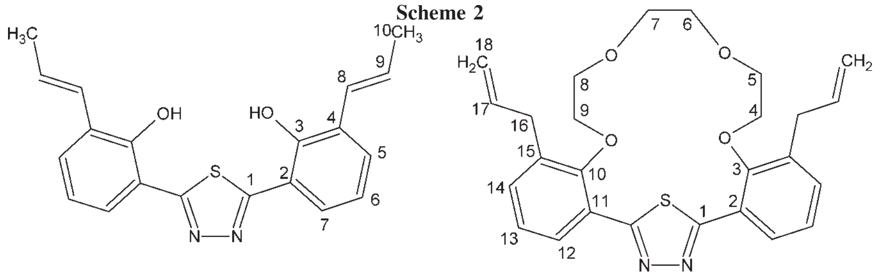
Melting points were determined on an IA 9000 series electrothermal apparatus and are uncorrected. Elemental analyses of C, H, N, and S were performed at the Elemental Analysis service of CNRS, Vernaison, France. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker F.T. AC 300 spectrometer (300

Table 2

Bond distances (Å) and angles (°) for compound **2**.

Bond distances (Å)			
S1—C1	1.727(1)	C9—C10	1.484(2)
S1—C2	1.724(1)	C9—O2	1.432(1)
C1—N1	1.316(1)	C10—C11	1.306(2)
C1—C8	1.470(1)	C12—C17	1.402(1)
N1—N2	1.363(1)	C12—C13	1.407(1)
C2—N2	1.314(1)	C13—O1	1.363(1)
C2—C12	1.471(1)	C13—C14	1.398(1)
C3—O2	1.360(1)	C14—C15	1.381(2)
C3—C4	1.398(1)	C15—C16	1.386(2)
C4—C5	1.385(2)	C17—C16	1.388(2)
C5—C6	1.388(2)	C18—O1	1.441(1)
C7—C6	1.385(2)	C19—C20	1.317(2)
C8—C3	1.402(1)	C19—C18	1.487(2)
C8—C7	1.402(1)		
Angles (°)			
C2—S1—C1	87.82(4)	C3—C8—C1	122.9(1)
C1—N1—N2	113.0(1)	C7—C8—C1	118.9(1)
C2—N2—N1	113.2(1)	O2—C9—C10	108.1(1)
N1—C1—C8	120.2(1)	C17—C12—C13	118.4(1)
N1—C1—S1	113.0(1)	C17—C12—C2	118.7(1)
C8—C1—S1	126.8(1)	C13—C12—C2	122.9(1)
N2—C2—C12	120.3(1)	O1—C13—C14	123.7(1)
N2—C2—S1	113.0(1)	O1—C13—C12	115.9(1)
C12—C2—S1	126.6(1)	C14—C13—C12	120.3(1)
O2—C3—C4	123.7(1)	C15—C14—C13	119.8(1)
O2—C3—C8	115.7(1)	C14—C15—C16	120.9(1)
C4—C3—C8	120.5(1)	C15—C16—C17	119.6(1)
C3—C4—C5	119.7(1)	C16—C17—C12	121.0(1)
C4—C5—C6	120.8(1)	O1—C18—C19	108.0(1)
C6—C7—C8	121.4(1)	C20—C19—C18	123.5(1)
C3—C8—C7	118.2(1)		

Scheme 2



MHz for ^1H NMR and 75 MHz for ^{13}C NMR) using chloroform ($CDCl_3$) solvent. Matrix-assisted laser desorption ionization (MALDI) and time-of-flight mass spectrometry (TOF-MS) are used to record the mass spectra of the correspondent compounds. All starting materials were of reagent grade and used as purchased.

A single crystal of compound **2** was mounted on a Brucker AXS SMART three-circle diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å), equipped with a CCD two-dimensional detector [15]. Data (Table 1) were corrected for Lorentz, polarization, background, and decomposition effects. Atomic positions were determined using SHELXS [16] and refined using full-matrix least-squares [17]. Hydrogen positions were calculated and included in the final cycles of refinement in constrained positions and with fixed isotropic thermal parameters. Absorption corrections were not made because of the small value of the absorption coefficients (Table 1). Extinction was refined for all three structures but was minimal. Table 2 presents the bond angles and distances for compound **2**. The atomic coordinates and the equivalent displacement are given in Table 3. The anisotropic displacement parameters for compound **2** are presented in Table 4.

General procedure for the synthesis of compounds 1–7. The formula of the parent compounds with corresponding numbers to carbons scheme is given later (Scheme 2).

Synthesis of 2,5-Bis(2-hydroxyphenyl)-1,3,4-thiadiazole (1). Experimental method is reported in the literature [18].

Synthesis of 2,5-Bis(2-allyloxyphenyl)-1,3,4-thiadiazole (2). A mixture of 2,5-bis(2-hydroxyphenyl)-1,3,4-thiadiazole **1** (0.02 mol), anhydrous potassium carbonate (10 g), and allyl bromide (0.04 mol) in acetonitrile (100 mL) was heated under reflux for 12 h with vigorous stirring. The solvent was evaporated *in vacuo,* and the solid residue was heated under reflux with 200 mL of a molar potassium hydroxide solution for 1 h. After cooling, the crude product was filtered, washed with water, and recrystallized from ethanol. Pale yellow solids were obtained: mp 130°C; yield 89%; ^1H NMR ($CDCl_3$) δ (ppm) 8.39 (d, $J = 8.9$ Hz, 2H); 7.54 (t, $J = 8.9$ Hz, 2H), 7.30 (d, $J = 7.5$ Hz, 2H); 7.17 (t, $J = 7.5$ Hz, 2H), 6.20 (m, 2H); 5.53 (d, $J_{trans} = 18$ Hz, 2H), 5.36 (d, $J_{cis} = 9.5$ Hz, 2H); 4.84 (d, $J = 6.1$ Hz, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm) C1 162.68; C2 119.17; C3 155.05; C4 119.30; C5 132.63; C6 121.80; C7 128.21; C8 70.21; C9 133.42; C10 113.89. MALDI-TOFMS: m/z 351 ($M + 1$). Anal. Calcd. for $C_{20}H_{18}N_2O_2S$: C, 68.55; H, 5.18; N, 7.99; S, 9.15. Found: C, 68.20; H, 5.20; N, 8.06; S, 9.09.

Synthesis of 2,5-Bis[3-allyl-2-hydroxy)phenyl]-1,3,4-thiadiazole (3). 2,5-Bis(2-allyloxyphenyl)-1,3,4-thiadiazole **2** (0.01 mol) was placed in multimode microwave and irradiated for 1 h (300 W) at 200°C in ethylene glycol (40 mL). Water (100 mL) was added to dilute the solvent. The reaction mixture was filtered. The resulting residue was recrystallized from ethanol: mp 150–152°C; yield 82%; ^1H NMR ($CDCl_3$) δ (ppm) 11.40 (s, 2H, OH); 7.41 (d, $J = 7.8$ Hz, 2H), 7.29 (d,

Table 3

Atomic coordinates and equivalent displacement for compound **2**.

Atom	*x*/*a*	*y*/*b*	*z*/*c*	*U* (Å^2)
S1	0.35157(3)	0.07961(1)	0.54044(1)	0.01935(5)
N1	0.3082(1)	0.1719(1)	0.3948(1)	0.0298(2)
N2	0.2275(1)	0.0984(1)	0.3696(1)	0.0298(2)
C1	0.3798(1)	0.1723(1)	0.4825(1)	0.0217(1)
C2	0.2383(1)	0.0433(1)	0.4381(1)	0.0221(1)
C3	0.5449(1)	0.2526(1)	0.6152(1)	0.0237(2)
C4	0.6399(1)	0.3231(1)	0.6472(1)	0.0307(2)
C5	0.6617(1)	0.3882(1)	0.5857(1)	0.0371(2)
C6	0.5910(2)	0.3840(1)	0.4924(1)	0.0393(2)
C7	0.4993(1)	0.3135(1)	0.4607(1)	0.0317(2)
C8	0.4750(1)	0.2464(1)	0.5209(1)	0.0230(1)
C9	0.5977(1)	0.1867(1)	0.7651(1)	0.0303(2)
C10	0.5423(2)	0.1106(1)	0.8132(1)	0.0472(3)
C11	0.5414(2)	0.1046(1)	0.9043(1)	0.0486(3)
C12	0.1556(1)	−0.0390(1)	0.4234(1)	0.0248(2)
C13	0.1644(1)	−0.1009(1)	0.4935(1)	0.0266(2)
C14	0.0828(1)	−0.1779(1)	0.4755(1)	0.0353(2)
C15	−0.0078(1)	−0.1931(1)	0.3886(1)	0.0405(3)
C16	−0.0198(1)	−0.1328(1)	0.3188(1)	0.0412(3)
C17	0.0620(1)	−0.0564(1)	0.3362(1)	0.0331(2)
C18	0.2491(1)	−0.1369(1)	0.6552(1)	0.0327(2)
C19	0.3599(1)	−0.1018(1)	0.7373(1)	0.0357(2)
C20	0.3049(2)	−0.0918(1)	0.8210(1)	0.0453(3)
O1	0.2557(1)	−0.08041(4)	0.5773(1)	0.0284(1)
O2	0.5126(1)	0.18688(4)	0.6711(0)	0.0275(1)
H1	0.453(2)	0.308(1)	0.395(1)	0.040(4)
H2	0.601(2)	0.429(1)	0.451(1)	0.051(5)
H3	0.728(2)	0.437(1)	0.608(1)	0.046(4)
H4	0.686(2)	0.326(1)	0.708(1)	0.036(4)
H5	0.724(2)	0.187(1)	0.761(1)	0.049(4)
H6	0.562(2)	0.237(1)	0.797(1)	0.041(4)
H7	0.519(3)	0.065(1)	0.771(2)	0.090(7)
H8	0.568(3)	0.1556(1)	0.944(1)	0.079(6)
H9	0.502(3)	0.055(1)	0.929(1)	0.072(6)
H10	0.052(2)	−0.014(1)	0.291(1)	0.038(4)
H11	−0.085(2)	−0.142(1)	0.261(1)	0.050(4)
H12	−0.065(2)	−0.246(1)	0.379(1)	0.050(4)
H13	0.097(2)	−0.222(1)	0.523(1)	0.051(4)
H14	0.293(2)	−0.193(1)	0.635(1)	0.041(4)
H15	0.125(2)	−0.142(1)	0.667(1)	0.040(4)
H16	0.480(2)	−0.091(1)	0.728(1)	0.047(4)
H17	0.383(3)	−0.072(1)	0.875(1)	0.068(6)
H18	0.184(2)	−0.104(1)	0.833(1)	0.047(4)

Table 4

Anisotropic displacement parameters for compound **2**.

	U11	U22	U33	U12	U13	U23
S1	0.0197(1)	0.0198(1)	0.0184(1)	0.0020(1)	0.0016(1)	0.0013(1)
N1	0.0307(4)	0.0340(4)	0.0237(3)	−0.0045(3)	−0.0028(3)	0.0078(3)
N2	0.0299(4)	0.0368(4)	0.0219(3)	−0.0052(3)	−0.0018(3)	0.0034(3)
C1	0.0202(3)	0.0239(4)	0.0209(3)	0.0018(3)	0.0021(3)	0.0044(3)
C2	0.0184(3)	0.0274(4)	0.0209(3)	0.0009(3)	0.0029(3)	−0.0016(3)
C3	0.0219(3)	0.0228(4)	0.0269(4)	0.0007(3)	0.0053(3)	−0.0016(3)
C4	0.0285(4)	0.0278(4)	0.0367(5)	−0.0042(3)	0.0080(4)	−0.0081(4)
C5	0.0351(5)	0.0262(5)	0.0514(7)	−0.0074(4)	0.0117(5)	−0.0050(4)
C6	0.0395(5)	0.0268(5)	0.0525(7)	−0.0048(4)	0.0095(5)	0.0090(5)
C7	0.0310(4)	0.0278(5)	0.0366(5)	−0.0011(4)	0.0039(4)	0.0096(4)
C8	0.0212(3)	0.0213(4)	0.0267(4)	0.0015(3)	0.0037(3)	0.0030(3)
C9	0.0308(4)	0.0388(5)	0.0209(4)	−0.0037(4)	0.0014(3)	−0.0036(4)
C10	0.0710(9)	0.0432(7)	0.0249(5)	−0.0145(6)	−0.0069(5)	0.0030(5)
C11	0.0705(9)	0.0474(7)	0.0277(5)	0.0009(7)	0.0047(5)	0.0061(5)
C12	0.0190(3)	0.0282(4)	0.0279(4)	0.0005(3)	0.0055(3)	−0.0078(3)
C13	0.0185(3)	0.0231(4)	0.0388(5)	0.0017(3)	0.0055(3)	−0.0049(4)
C14	0.0238(4)	0.0246(4)	0.0587(7)	−0.0008(3)	0.0090(4)	−0.0083(4)
C15	0.0276(4)	0.0353(6)	0.0604(8)	−0.0052(4)	0.0138(5)	−0.0237(5)
C16	0.0303(5)	0.0528(7)	0.0419(6)	−0.0086(5)	0.0105(4)	−0.0272(5)
C17	0.0271(4)	0.0447(6)	0.0284(4)	−0.0033(4)	0.0069(3)	−0.0135(4)
C18	0.0281(4)	0.0253(4)	0.0450(6)	0.0003(3)	0.0058(4)	0.0119(4)
C19	0.0274(4)	0.0366(5)	0.0426(6)	−0.0006(4)	0.0014(4)	0.0177(5)
C20	0.0462(6)	0.0464(7)	0.0432(7)	−0.0087(5)	0.0047(5)	0.0154(5)
O1	0.0249(3)	0.0239(3)	0.0358(4)	−0.0026(2)	−0.0003(3)	0.0062(3)
O2	0.0329(3)	0.0274(3)	0.0215(3)	−0.0054(3)	−0.0016(2)	−0.0001(2)

J = 7.8 Hz, 2H); 6.94 (t, J = 7.8 Hz, 2H), 6.07 (m, 2H); 5.17 (d, J_{trans} = 17 Hz, 2H), 5.12 (d, J_{cis} = 9.8 Hz, 2H); 3.54 (d, J = 6.8 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm) C1 165.90; C2 120.92; C3 153.52; C4 127.20; C5 133.28; C6 116.60; C7 128.84; C8 34.05; C9 136.72; C10 116.60. MALDI-TOFMS: *m/z* 351 (M + 1). Anal. Calcd. for $C_{20}H_{18}N_2O_2S$: C, 68.55; H, 5.18; N, 7.99; S, 9.15. Found: C, 68.33; H, 5.14; N, 8.02; S, 9.14.

Synthesis of 2,5-Bis[2-hydroxy-3-trans-1-propenyl)phenyl]-1,3,4-thiadiazole (4). A suspension of potassium *tert*-butoxide (8.40 g, 75 mmol) in acetonitrile (40 mL) was heated at 120°C under stirring until it was completely dissolved. 2,5-Bis[3-allyl-2-hydroxy)phenyl]-1,3,4-thiadiazole **3** (7.5 mmol) was added and stirring was continued for 10 min. The solvent was evaporated. The residue was treated and recrystallized from ethanol: mp 172°C; yield 61%; ^{1}H NMR ($CDCl_3$) δ (ppm) 11.36 (s, 2H, OH); 7.87 (d, J = 7.6 Hz, 2H), 7.52 (d, J = 7.6 Hz, 2H); 6.95 (t, J = 7.6 Hz, 2H), 6.82 (d, J = 16 Hz, 2H), 6.35 (m, 2H); 1.81 (d, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm) C1 169.98; C2 118.42; C3 157.35; C4 130.27; C5 135.53; C6 121.20; C7 133.92; C8 132.15; C9 125.79; C10 18.95. MALDI-TOFMS: *m/z* 351 (M + 1). Anal. Calcd. for $C_{20}H_{18}N_2O_2S$: C, 68.55; H, 5.18; N, 7.99; S, 9.15. Found: C, 68.30; H, 5.27; N, 7.83; S, 9.11.

General procedure for the synthesis of macrocycles (5) and (6). A mixture of 2,5-bis[3-allyl-2-hydroxy)phenyl]-1,3,4-thiadiazole **3** or 3,5-bis[2-hydroxy-3-trans-1-propenyl)phenyl]-1,3,4-thiadiazole **4** (5 mmol), anhydrous potassium carbonate (24 mmol), and ethylene or polyethylene glycol ditosylate (5 mmol) in 150 mL of nonprotic polar solvent (acetone, acetonitrile, *etc.*) was irradiated in multimode microwave for 9 h. The solvent was evaporated *in vacuo* and the solid residue was heated under reflux with 200 mL of a potassium hydroxide solution for 1 h. After cooling, the crude product was filtered, washed with water, and recrystallized from ethanol.

Macrocycle 5. mp 85°C; yield 31%; 8.28 (d, J = 7.8 Hz, 2H), 7.42 (t, J = 7.8 Hz, 2H), 7.32 (d, J = 7.8 Hz, 2H), 6.04 (m, 2H), 5.14 (t, J = 17 Hz, 4H); 4.02 (m, 4H), 3.88 (m, 4H), 3.52 (s, 4H); 3.33 (d, J = 6.0 Hz, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm) C1 163.72; C2 116.24; C3 154.43; C4 73.98; C5 69.77; C6 71.48; C12 130.74; C13 126.12; C14 131.18; C15 125.93; C16 34.23; C17 135.42.51; C18 117.79. MALDI-TOFMS: *m/z* 465 (M + 1). Anal. Calcd. for $C_{26}H_{28}N_2O_4S$: C, 67.24; H, 6.07; N, 6.03; S, 6.90. Found: C, 67.11; H, 6.08; N, 5.94; S, 6.88.

Macrocycle 6. mp 128°C; yield 27%; 8.44 (d, J = 7.8 Hz, 2H), 7.85 (t, J = 7.8 Hz, 2H), 7.28 (d, J = 7.8 Hz, 2H), 6.85 (d, J = 16 Hz, 2H), 6.04 (m, 2H); 4.10 (m, 4H), 3.93 (m, 4H), 3.56 (s, 4H); 1.78 (d, J = 6.8 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ (ppm) C1 167.41; C2 117.27; C3 156.43; C4 74.84; C5 69.30; C6 71.33; C12 133.81; C13 125.35; C14 134.18; C15 126.63; C16 137.11; C17 124.51; C18 18.83. MALDI-TOFMS: *m/z* 465 (M + 1). Anal. Calcd. for $C_{26}H_{28}N_2O_4S$: C, 67.24; H, 6.07; N, 6.03; S, 6.90. Found: C, 67.09; H, 6.03; N, 5.98; S, 6.82.

Synthesis of macrocycle (7). A suspension of macrocyclic compound **6** (1 g, 2.15 mmol) in boiling water (100 mL) was prepared, to which sodium carbonate crystals (0.5 g) were added, and 4 g of finely powdered potassium permanganate (4 g) was slowly introduced. The mixture was heated under reflux until the purple color of the permanganate disappeared (1–4 h). After cooling, the mixture was filtered to remove any excess of manganese dioxide and carefully acidified with hydrochloride acid. The crude product was filtered, washed with water, and recrystallized from ethanol. mp 258°C; yield 47%; 11.31 (s, OH, 2H), 7.57 (d, $J = 7.8$ Hz, 2H), 7.11 (d, $J = 7.8$ Hz, 2H), 6.98 (t, $J = 16$ Hz, 2H); 4.15 (m, 4H), 3.58 (s, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm) C1 167.77; C2 117.27; C3 157.11; C4 72.52; C5 69.43; C6 72.01; C12 134.6; C13 127.16; C14 135.75; C15 127.12; C16 163.67. MALDI-TOFMS: m/z 473 ($M + 1$). Anal. Calcd. for $C_{22}H_{20}N_2O_8S$: C, 55.93; H, 4.27; N, 5.93; S, 6.79. Found: C, 56.10; H, 4.30; N, 6.06; S, 6.74.

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A Single-Step Preparation of Thiazolo[5,4-*b*]pyridine- and Thiazolo[5,4-*c*]pyridine Derivatives from Chloronitropyridines and Thioamides, or Thioureas

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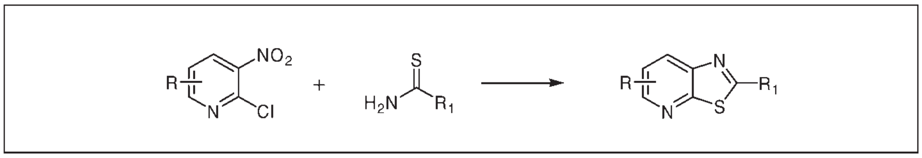

A one-step synthesis of thiazolo[5,4-*b*]pyridines from an appropriately substituted chloronitropyridine and thioamide, or thiourea, is presented. In particular, the reaction was used to prepare a large number of 6-nitrothiazolo[5,4-*b*]pyridine derivatives, bearing hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, and amine substituents at the 2-position. The reaction could also be extended to produce a thiazolo[4,5-*c*]pyridine derivative and thiazolo[5,4-*b*]pyridines with alternative substituents on the pyridinoid ring.

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INTRODUCTION

The thiazolo[5,4-*b*]pyridine nucleus is of interest to those working in the agrochemical, pharmaceutical, and materials industries [1]. For instance, compounds containing a thiazolo[5,4-*b*]pyridine substructure have been described as ligands, or modulators, of leukotriene A_4 [2], VEGFR-2 [3], p38 MAP kinase [4], CCR3 [5], IAP [6], PPAR [7], D_4 [8], ubiquitin ligase [9], glucokinase [10], JAK3 [11], and sirtuin [12] amongst others [13]. A number of methods to prepare thiazolo[5,4-*b*]pyridines have been documented in the literature [1]. For example, methods that construct the bicycle by formation of a thiazole ring, include condensations of 3-amino-2-halopyridine, or 3-amino-2-pyridone derivatives, with thiocyanates, thioamides, or thioesters [14], the oxidative ring-closure of 3-aminopyridine thioamides or thioureas [15], condensations with 3-aminopyridin-2-thiones [16], and reactions of *N*-(2-pyridone-3-yl)acetamides with phosphorous pentasulfide [17]. Recently, a cross-coupling/cyclization sequence starting from *N*-(2-bromopyridin-3-yl)acetamide was also detailed [18]. In this article, we would like to disclose a new, single-step synthesis of the thiazolo[5,4-*b*]pyridine and thiazolo[4,5-*c*]pyridine nuclei. The approach is based upon the reaction of a thioamide, or thiourea, with an appropriately substituted chloronitropyridine to give a number of interesting thiazolopyridines in up to 60% yield (Fig. 1) [19]. In contrast to many literature methods of thiazolopyridine synthesis, our method does not use reagents such as tin(II) chloride, thiocyanate salts, thiophosgene, organometallics, or bromine [14–18].

RESULTS AND DISCUSSION

Our initial interest in compounds based around thiazolo[5,4-*b*]pyridines was stimulated by an examination of their potential use as modulators of ion-channel activity [20]. Toward this end, we required access to a number of 2-substituted-6-nitrothiazolo[5,4-*b*]pyridines. Our first attempts targeted the preparation of ethyl 6-nitrothiazolo[5,4-*b*]pyridine-2-carboxylate (**3a**). Fusing 2-chloro-3,5-dinitropyridine (**1**) with ethyl 2-amino-2-thioxoacetate (**2a**) in a 1:2 ratio at 70°C, then diluting with xylene and heating at 140°C gave the desired product (**3a**) in a moderate yield after column chromatography (Scheme 1). Subsequently, we found that the reaction could be performed using sulfolane as a solvent without any loss in efficiency (20% isolated yield). Sulfolane was chosen as similar reactions have used this solvent to give benzothiazole derivatives [21].

To investigate the scope of this ring-forming process, a diverse set of thioamides was reacted with 2-chloro-3,5-dinitropyridine to provide a range of thiazolo[5,4-*b*]pyridines that would be of interest to the medicinal chemist (Table 1). For example, it was found that this method could give compounds with substituted alkyl groups at the 2-position. The reaction was tolerant of a number of functional groups in the alkyl side chain,

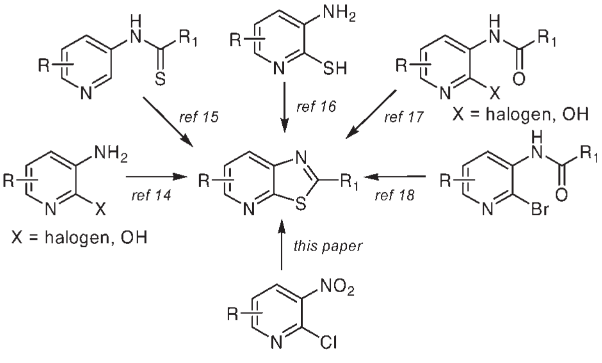


Figure 1. Some approaches to thiazolo[5,4-*b*]pyridines.

such as ester, ether, thioether, nitrile, and sulfone (entries 1–7). Branching on the alkyl chain was also tolerated as demonstrated by the successful reaction to produce compounds (**3i**)–(**3k**) (entries 8–10). 2-Aryl and heteroaryl derivatives were also accessible (entries 11–13), as was the 2-amino thiazolopyridine (entry 14). The parent hydrido compound (**3o**) was also produced (entry 15), although in this instance the final compound was synthesized by reacting 2-chloro-3,5-dinitropyridine with neat *N*,*N*-dimethylthioformamide at 60°C, then diluting with xylenes and refluxing overnight [22]. Yields for the synthesis of 2-substituted-6-nitrothiazolo[5,4-*b*]pyridines ranged from the moderate (*ca*. 40%) to the modest (10–20%). Although the reactions seemed to progress smoothly when followed by analytical techniques such as LC/MS, obtaining material with acceptable purity proved to be problematic in a number of cases. As such, at least part of the lower isolated yield may be attributable to difficulties with purification for many compounds, since preparative high-performance liquid chromatography, or repeated trituration, had to be used. Nevertheless, the above one-step process could be used to make compounds on a gram-scale, without any reduction in yield, for a number of final compounds (*e.g*., **3b** and **3c**).

Attempts to optimize a model transformation, (**2**–**3k**), by variation in solvent, or additives, did not result in any improvement in conversion as measured by high-performance liquid chromatography (Table 2). For example, changing from sulfolane to a similarly polar solvent such as DMF, DMSO, or NMP resulted in a marked retardation in the formation of desired product (entries 3–5) [23]. The use of diphenylether, ethanol, or 1,4-dioxane (entries 6–8) resulted in a moderate amount of thiazolo[5,4-*b*]pyridine formation, although efficiencies were lower than for sulfolane. We next investigated the influence of a small selection of additives on the amount of product formation (entries 9–14), finding that only the inclusion of scandium(III) triflate (entry 11) resulted in a comparable conversion compared with the reference transformation (entry 1). Significantly, other model transformations noticed that the use of heating under microwave irradiation resulted in a reduced reaction time, with no loss in isolated yield (Table 3, entry 1). Indeed, the use of 4 equivalents of thioamide starting material, together with microwave irradiation resulted in an enhanced conversion compared to the thermal conditions used previously (Table 3, entries 2–5 *cf*. Table 1 entries 3, 6, 7, and 15, respectively). This improvement in yield was most likely due to a combination of factors, including a rapid initial reaction under microwave conditions, resulting in a transient overshoot in temperature, particularly when reactions were run at high concentrations (*ca*. 1*M*; entry 5). In general, the microwave reactions also gave cleaner mixtures, with fewer by-products, which facilitated the purification process of final compounds.

Scheme 1. Synthesis of ethyl 6-nitrothiazolo[5,4-*b*]pyridine-2-carboxylate. *i*. Fuse 70°C, then dilute with xylene and heat to 140°C (20%).

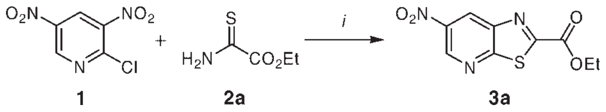
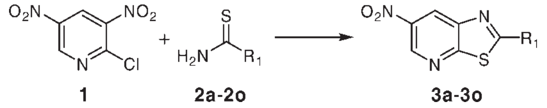


Table 1

Synthesis of 6-nitrothiazolo[5,4-*b*]pyridines.



Entry	Product	R_1	% Yield[a]
1	**3a**	CO_2Et	20
2	**3b**	Me	43[b]
3	**3c**	$CH_2OC(O)C(Me)_3$	36
4	**3d**	$CH_2OC_6H_4OMe$ (4-methoxy isomer)	16
5	**3e**	CH_2SPh	14
6	**3f**	CH_2CN	7
7	**3g**	$CH_2SO_2C(Me)_3$	9
8	**3h**	$CH(Me)OC(O)C(Me)_3$	35
9	**3i**	$CH(Ph)_2$	7
10	**3j**	Cyclopropyl	4
11	**3k**	Ph	20
12	**3l**	2-Thienyl	20
13	**3m**	3-Pyridyl	6
14	**3n**	NH_2	15
15	**3o**	H	11[c]

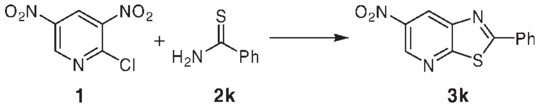
[a] Performed using 1 equiv of compound (**1**) and 2 equiv of thioamide (or thiourea) (**2a**)–(**2n**) in sulfolane at 100–110°C.

[b] Performed using 1 equiv of compound (**1**) and 4 equiv of thioamide (**2b**) in sulfolane at 100°C.

[c] Performed using 1 equiv of compound (**1**) and 4.6 equiv of *N*,*N*-dimethylthioformamide at 60°C and then diluted with xylene and refluxed.

Table 2

Effect of solvent/additives on conversion for a model transformation.



Entry	Solvent	Additive	% Conversion[a]
1	Sulfolane	None	44
2	Sulfolane	None	20[b]
3	DMF	None	10
4	DMSO	None	0
5	NMP	None	4
6	Ph_2O	None	12
7	EtOH	None	12
8	1,4-Dioxane	None	24
9	Sulfolane	^{i}PrNEt	0
10	Sulfolane	DDQ	4
11	Sulfolane	$Sc(OTf)_3$	39
12	Sulfolane	NaOAc	0
13	Sulfolane	K_2CO_3	0
14	Sulfolane	KI	21

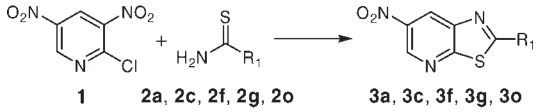
[a] Reaction performed using 2 equiv of (**2k**). Conversion to (**3k**) was based upon integration of peak area in LC/MS trace after 4 h at 100°C.

[b] Reaction performed using 1 equiv of (**2k**).

Reactions with 2-chloro-3-nitropyridine. To explore the potential of our method in providing thiazolo[5,4-*b*]pyridines with only hydrogen substituents on the pyridinoid ring, 2-chloro-3-nitropyridine (**4**) was reacted with a representative selection of thioamides (**2b**, **2k**, **2o**) and with thiourea (**2n**) to provide cyclized products (Table 4). Either thermal or microwave conditions could be used to give thiazolo[5,4-*b*]pyridines (**5a**)–(**5d**) in up to 49% yield. As can be seen when comparing the entries in Table 4 to their counterparts in Table 1, the absence of a nitro-group in the pyridinoid ring seemed to be slightly beneficial in terms of isolated yield.

Table 3

Microwave-assisted synthesis of 6-nitrothiazolo[5,4-*b*]pyridines.



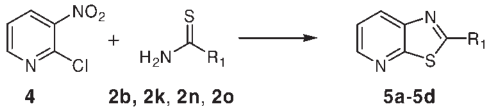
Entry	Product	R_1	% Yield[a]
1	**3a**	CO_2Et	26
2	**3c**	$CH_2OC(O)C(Me)_3$	36[b]
3	**3f**	CH_2CN	16
4	**3g**	$CH_2SO_2C(Me)_3$	18
5	**3o**	H	50

[a] Reaction of (**1**) using 4 equiv of appropriate thioamide at 110–130°C under microwave irradiation.

[b] Reaction performed using 2 equiv of thioamide (**2c**) at 110–130°C under microwave irradiation (4 equiv of (**2c**) not performed).

Table 4

Synthesis of thiazolo[5,4-*b*]pyridines.



Entry	Thioamide	Product	R_1	% Yield[a]
1	**2b**	**5a**	Me	49
2	**2k**	**5b**	Ph	26
3	**2n**	**5c**	NH_2	46/10[b]
4	**2o**	**5d**	H	26

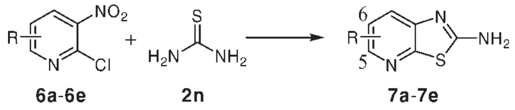
[a] Reaction of (**4**) using 4 equiv of appropriate thioamide at 135°C under microwave irradiation.

[b] Reaction performed using 2 equiv of thioamide (**2n**) at 130°C (no microwave irradiation).

Reactions with substituted 2-chloro-3-nitropyridines. As a further extension of the reaction, we sought to investigate the use of pyridine starting materials in which a substituent other than nitro, or hydrogen, was present. As can be seen from Table 5, a number of interesting derivatives were prepared. The mildness of the technique was illustrated in the preparation of thiazolo[5,4-*b*]pyridines incorporating a halogen (**7a**)–(**7c**) (entries 1–3). The synthesis of such compounds is somewhat sparse in the chemical literature, and our approach to the bromo- and iodo-analogues (entries 2 and 3) is significant, as some thiazolopyridine syntheses may not be able to provide such compounds (*e.g.*, methods involving metal-mediated approaches). Our methodology is therefore attractive, as halogenated thiazolopyridines are potentially useful building blocks for medicinal chemistry libraries. For instance, compounds (**7b**) and (**7c**) possess a halo- and amine handle for derivatization (*e.g.*, palladium-mediated reactions for halo-substituent;

Table 5

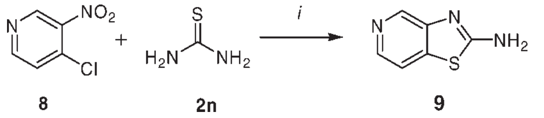
Synthesis of 2-aminothiazolo[5,4-*b*]pyridines.



Entry	Nitropyridine	Product	R_1	% Yield[a]
1	**6a**	**7a**	6-Cl	48
2	**6b**	**7b**	6-Br	62
3	**6c**	**7c**	6-I	39
4	**6d**	**7d**	6-Me	19
5	**6e**	**7e**	5-OMe	8

[a] Reaction of (**6a**)–(**6e**) using 4 equiv of appropriate thioamide at 135°C under microwave irradiation for 45 min.

Scheme 2. Preparation of 2-amainothiazolo[4,5-*c*]pyridine. *i*. Sulfolane, 135°C, microwave, 75 min (22%).



amide, urea, and reductive alkylation reactions for the amine group). Thus, chemical libraries with two points of diversity could be envisaged around these scaffolds. Compounds with alternative substituents on the pyridinoid ring, such as the 6-methyl and 5-methoxy derivatives (**7d**) and (**7e**) (entries 4–5), were also prepared. However, the reaction to give (**7e**) was particularly low yielding (8%), which may be as a result of the methoxy-group also being activated toward nucleophilic substitution by the thiourea starting material.

Reaction with 4-chloro-3-nitropyridine. As demonstrated, thiazolo[5,4-*b*]pyridines can be synthesized with diverse substituents on both the thiazole and pyridine rings. To probe the utility of the reaction in providing other isomeric thiazolopyridines, a synthesis of 2-aminothiazolo[4,5-*c*]pyridine (**9**) from 4-chloro-3-nitropyridine (**8**) and thiourea (**2n**) was devised (Scheme 2). Heating at 135°C under microwave irradiation gave the desired product (**9**) in 22% yield after column chromatography. Thus, we believe that the reaction may have the potential to access other thiazolo[4,5-*c*]pyridine derivatives, such as those with an alkyl- or aryl-group at the 2-position, or those with substituents other than hydrogen on the pyridinoid ring. However, investigations toward such molecules were beyond the scope of our studies and will await further experimentation. In addition, it would also be desirable to explore the potential of forming thiazolo[5,4-*c*]pyridines from 3-chloro-4-nitropyridine precursors.

The reaction pathway. Currently, we believe that the reaction proceeds by an initial displacement of the chloro-group followed by nitro-group reduction and concomitant cyclization. For example, with 2-chloro-3,5-dinitropyridine (**1**), displacement with an appropriate thioamide gives intermediates (**10a**)–(**10o**) (Fig. 2). Reductive cyclization of (**10a**)–(**10o**), on exposure to excess thioamide in the reaction mixture, provides the desired thiazolopyridines (**3a**)–(**3o**). Although nitro-group reductions with thioamides, or thiourea, have not been detailed extensively in the chemical literature, related reductions with sulfur reagents, such as sulfides (Zinin reduction), sodium dithionite, elemental sulfur, and thiourea *S*,*S*-dioxide, have been used frequently [24–27]. Of note in the reduction step is an apparent selectivity in nitro-reduction for the postulated intermediates (**10a**)–(**10o**). Although some low yields encountered in our synthesis meant that we cannot exclude the possibility that both nitro groups in (**10a**)–(**10o**) are reduced, the observed selectivity in reduction of (**10a**)–(**10o**) is consistent with that seen for other 2-substituted-3,5-dinitropyridines, such as the reduction of 2-amino-3,5-dinitropyridine with sodium sulfide [28,29]. Evidence for the type of reaction described earlier, as opposed to one involving displacement of the nitro group from intermediate (**10a**)–(**10o**), is provided in the preparation of parent hydrido derivative (**3o**) using *N*,*N*-dimethylthioformamide (Table 1, entry 15), and the formation of both (**12**) and (**3n**) when 2-chloro-3,5-dinitropyridine (**1**) is reacted with piperidine-1-carbothioamide (**11**) (Scheme 3).

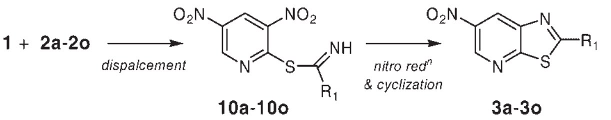
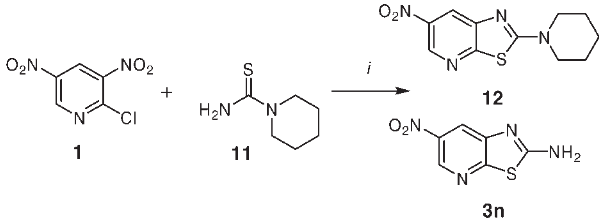


Figure 2. Proposed reaction pathway.

Scheme 3. Reaction with piperidine-1-carbothioamide. *i*. Sulfolane, 100°C (9% **12** and 6% **3n**).



CONCLUSIONS

In conclusion, we have developed an expeditious new single-step synthesis of the thiazolo[5,4-*b*]pyridine and thiazolo[4,5-*c*]pyridine nuclei by condensing an appropriately substituted chloronitropyridine with a thioamide or thiourea. The use of such conditions is complementary to existing techniques to thiazolopyridines and may offer advantages in terms of scope, speed of synthesis, and availability of starting materials. The single-step nature of the reaction is particularly noteworthy, as many established thiazolopyridine syntheses use multistep routes, and frequently resort to toxic reactants, or reagents requiring special handling conditions, to prepare suitable starting materials or final products. Additionally, our method tolerates sensitive functionality in the coupling partners, may be accelerated by the use of microwave irradiation and is operationally simple to perform, giving final products in moderate yield. The synthesis outlined in this article will be of particular interest to those in the medicinal, agrochemical, materials, and heterocyclic fields, where thiazolo[5,4-*b*]- and thiazolo[4,5-*c*]pyridines have found many uses.

EXPERIMENTAL

All reagents except 1-amino-1-thiooxopropan-2-yl pivalate and cyclopropanecarbothioamide were purchased from commercial sources and used without further purification. 1-Amino-1-thiooxopropan-2-yl pivalate (example **3h**) and cyclopropanecarbothioamide (example **3j**) were synthesized by GVK Biosciences Private (Hyderabad, India). All microwave-assisted reactions were performed with a CEM Discover S-Class microwave with 48-position autosampler. Temperature during microwave reactions was monitored by a vertically sensored infrared temperature sensor, which comes as a standard feature of the CEM Discover S-Class system. All NMR spectra are quoted in ppm relative to a tetramethylsilane internal standard, or by referencing on the chemical shift of the deuterated solvent.

General procedure for preparation of thiazolo[5,4-*b*]pyridines under thermal conditions.

Preparation of (6-nitrothiazolo[5,4-b]pyridin-2-yl)methyl pivalate (3c). A mixture of 2-chloro-3,5-dinitropyridine (1) (5.1 g, 25 mmol) and 2-amino-2-thioxoethylpivalate (2c) (8.8 g, 50 mmol) in sulfolane (50 mL) was heated to 100–110°C under a nitrogen atmosphere and stirred for 2 h. After allowing to cool to room temperature, the mixture was poured into EtOAc (150 mL), and the organic layer was washed with H_2O (3 × 200 mL) and brine (1 × 100 mL). The organic layer was dried ($MgSO_4$), filtered, and the solvent removed under vacuum to leave a crude oil. The oil was purified by filtration through a plug of silica eluting with EtOAc/hexanes (1:9–1:4) to give a solid (*ca.* 6–7g). The solid was then triturated with MeOH (*ca.* 20 mL) and filtered to give the desired product (2.17g). Further product was obtained by concentrating the filtrate under vacuum and purifying by column chromatography on silica gel using EtOAc/hexanes (0:1–1:4) as eluent to give a solid (1.1 g). The solid was triturated with MeOH to give further product (0.5g). Total yield 2.67 g (36%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.46 (d, J = 2.4 Hz, 1H), 9.00 (d, J = 2.4 Hz, 1H), 5.54 (s, 2H), 1.32 (s, 9H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 177.4, 172.6, 163.6, 145.2, 143.1, 142.3, 125.1, 63.4, 38.9, 27.1; m/z = 296.5 (M + 1).

Ethyl 6-nitrothiazolo[5,4-b]pyridine-2-carboxylate (3a). ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.59 (d, J = 2.4 Hz, 1H), 9.23 (d, J = 2.4 Hz, 1H), 4.62 (q, J = 7.0 Hz, 2H), 1.53 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 164.0, 163.2, 159.4, 145.5, 144.6, 143.5, 127.7, 64.1, 14.2.

2-Methyl-6-nitrothiazolo[5,4-b]pyridine (3b). ^{1}H NMR (400 MHz; d_6-DMSO) δ 9.38 (d, J = 2.3 Hz, 1H), 9.25 (d, J = 2.3 Hz, 1H), 2.91 (s, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 172.4, 164.5, 145.7, 142.9, 141.5, 124.0, 21.4; m/z = 196.2 (M + 1).

2-(4-Methoxyphenoxymethyl)-6-nitrothiazolo[5,4-b]pyridine (3d). ^{1}H NMR (400 MHz; d_6-DMSO) δ 9.45 (d, J = 2.4 Hz, 1H), 9.21 (d, J = 2.4 Hz, 1H), 7.07–7.09 (m, 2H), 6.90–6.92 (m, 2H), 5.64 (s, 2H), 3.71 (s, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 174.9, 163.7, 154.9, 151.4, 145.2, 142.9, 142.1, 124.9, 116.0, 114.8, 68.8, 55.6.

6-Nitro-2-(phenylthiomethyl)thiazolo[5,4-b]pyridine (3e). ^{1}H NMR (400 MHz; d_6-DMSO) δ 9.38 (d, J = 2.0 Hz, 1H), 9.09 (d, J = 2.0 Hz, 1H), 7.42–7.45 (m, 2H), 7.29–7.33 (m, 2H), 7.21–7.23 (m, 1H), 4.89 (s, 2H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 175.7, 163.3, 144.8, 143.3, 142.2, 133.7, 129.3, 129.0, 127.0, 125.0, 35.6; m/z = 302.2 (M – 1).

2-(6-Nitrothiazolo[5,4-b]pyridin-2-yl)acetonitrile (3f). ^{1}H NMR (400 MHz; d_6-DMSO) δ 9.46 (d, J = 2.4 Hz, 1H), 9.27 (d, J = 2.4 Hz, 1H), 4.94 (s, 2H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 165.9, 163.2, 144.4, 143.5, 142.7, 125.5, 115.9, 23.7; m/z = 219.0 (M – 1).

2-(tert-Butylsulfonylmethyl)-6-nitrothiazolo[5,4-b]pyridine (3g). ^{1}H NMR (400 MHz; d_6-DMSO) δ 9.41 (d, J = 2.4 Hz, 1H), 9.28 (d, J = 2.4 Hz, 1H), 5.35 (s, 2H), 1.42 (s, 9H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 163.5, 163.3, 144.1, 143.4, 142.8, 125.8, 60.8, 51.7, 22.8; m/z = 316.3 (M + 1).

1-(6-Nitrothiazolo[5,4-b]pyridin-2-yl)ethyl pivalate (3h). ^{1}H NMR (400 MHz; d_6-DMSO) δ 9.45 (d, J = 2.4 Hz, 1H), 9.21 (d, J = 2.4 Hz, 1H), 6.16–6.21 (q, J = 6.6 Hz, 1H), 1.70 (d, J = 6.6 Hz, 3H), 1.24 (s, 9H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 176.6, 176.3, 162.5, 144.6, 143.4, 142.5, 125.6, 70.0, 38.3, 26.7, 19.9; m/z = 310.4 (M + 1).

2-Benzhydryl-6-nitrothiazolo[5,4-b]pyridine (3i). ^{1}H NMR (400 MHz; d_6-DMSO) δ 9.40 (d, J = 2.0 Hz, 1H), 9.17 (d, J = 2.0 Hz, 1H), 7.37–7.43 (m, 11H), 7.31–7.33 (m, 2H), 6.29 (s, 1H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 179.7, 164.0, 146.1, 144.2, 143.0, 141.6, 129.9, 129.8, 129.0, 128.5, 128.4, 126.2, 56.0; m/z = 348.2 (M + 1).

2-Cyclopropyl-6-nitrothiazolo[5,4-b]pyridine (3j). ^{1}H NMR (400 MHz; d_6-DMSO) δ 9.34 (d, J = 2.4 Hz, 1H), 8.97 (d, J = 2.4 Hz, 1H), 2.66–2.72 (m, 1H), 1.34–1.39 (m, 2H), 1.25–1.29 (m, 2H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 179.2, 162.6, 145.2, 143.2, 141.1, 123.6, 15.8, 12.9; m/z = 222.1 (M + 1).

6-Nitro-2-phenylthiazolo[5,4-b]pyridine (3k). ^{1}H NMR (400 MHz; d_6-DMSO) δ 9.44 (d, J = 2.0 Hz, 1H), 9.22 (d, J = 2.0 Hz, 1H), 8.18–8.21 (m, 2H), 7.65–7.68 (m, 3H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 158.3, 147.9, 142.0, 141.9, 141.5, 132.6, 129.4, 129.4, 127.5, 124.8; m/z = 259.0 (M + 1).

6-Nitro-2-(thiophen-2-yl)thiazolo[5,4-b]pyridine (3l). ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.37 (d, J = 2.0 Hz, 1H), 8.95 (d, J = 2.0 Hz, 1H), 7.78–7.79 (m, 1H), 7.66–7.67 (m, 1H), 7.22–7.23 (m, 1H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 146.4, 141.7, 136.1, 132.0, 131.0, 128.7, 124.0; m/z = 263.0 (M – 1).

6-Nitro-2-(pyridin-3-yl)thiazolo[5,4-b]pyridine (3m). ^{1}H NMR (400 MHz; d_6-DMSO) δ 9.47 (d, J = 2.4 Hz, 1H), 9.36 (dd, J = 2.0 and 0.8 Hz, 1H), 9.27 (d, J = 2.4 Hz, 1H), 8.85 (dd, J = 4.8 and 1.5 Hz, 1H), 8.55 (ddd, J = 8.0, 2.0 and 1.5 Hz, 1H), 7.69 (ddd, J = 8.0, 4.8 and 0.8 Hz, 1H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 154.1, 149.2, 143.6, 136.2, 129.1, 126.4, 125.6, 100.5; m/z = 259.2 (M + 1).

6-Nitrothiazolo[5,4-b]pyridine-2-amine (3n). ^{1}H NMR (400 MHz; d_6-DMSO) δ 8.93 (d, J = 2.5 Hz, 1H), 8.34 (br. s, 2H), 8.26 (d, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 168.0, 161.8, 147.0, 143.3, 136.5, 116.7; m/z = 195.1 (M – 1).

6-Nitrothiazolo[5,4-b]pyridine (3o) [22]. A mixture of 2-chloro-3,5-dinitropyridine (**1**) (8.0 g, 39 mmol) and *N*,*N*-dimethylthioformamide (14.5 mL, 178 mmol) was heated at 60°C for 3 h (a yellow precipitate was formed). Xylene (20 mL) was added, and the mixture was heated to reflux for 4 h, then stirred at room temperature for 18 h. The mixture was diluted with EtOH (12 mL), filtered, and the solid recrystallized from EtOH to give the product (800 mg, 11%) as a solid. ^{1}H NMR (400 MHz; d_6-DMSO) δ 9.82 (s, 1H), 9.49 (d, J = 2.4 Hz, 1H), 9.27 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 162.4, 161.8, 144.7, 143.1, 142.6, 125.8; m/z = 182.2 (M + 1).

6-Nitro-2-piperidin-1-yl-thiazolo[5,4-b]pyridine (12). ^{1}H NMR (400 MHz; d_6-DMSO) δ 8.94 (d, J = 2.3 Hz, 1H), 8.34 (d, J = 2.3 Hz, 1H), 3.66–3.70 (m, 4H), 1.61–1.66 (m, 6H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 166.7, 159.5, 145.3, 141.9, 134.8, 115.7, 23.3, 21.9; m/z = 264.8 (M + 1). Separately, 6-nitrothiazolo[5,4-*b*]pyridin-2-amine (**3n**) (13 mg, 6%) was also isolated.

General procedure for reactions using microwave-assisted synthesis.

Preparation of 6-nitrothiazolo[5,4-b]pyridine (3o). A 5-mL microwave vial was charged with 2-chloro-3,5-dinitropyridine (**1**) (0.41 g, 2.0 mmol), *N*,*N*-dimethylthioformamide (0.69 mL, 8.0 mmol), and sulfolane (2 mL). The mixture was heated under microwave irradiation with a target temperature of 110°C (CARE: the reaction displayed a significant exotherm on heating and reached 130°C within 25 s). After 2 min the mixture had cooled to 110°C, and heating was continued at this temperature for 40 min. After cooling to room temperature, the mixture was diluted with MeOH (5 mL) and EtOAc (60 mL) and then washed with brine (50 mL, 3 × 20 mL) and saturated $NaHCO_3$ (20 mL). The organic layer was dried (Na_2SO_4), filtered, and the solvent removed under vacuum to leave a crude solid (1.08 g). Purification by column chromatography on silica gel (dry-loaded on 4.5 g of silica) using EtOAc/hexanes (1:9–3:2) as eluent gave the product (183 mg, 50%) as a solid.

2-Methylthiazolo[5,4-b]pyridine (5a). ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.54 (d, J = 4.6 Hz, 1H), 8.19 (d, J = 8.2 Hz, 1H), 7.42 (dd, J = 8.2, 4.6 Hz, 1H), 2.87 (s, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 162.3, 159.2, 146.7, 146.6, 129.4, 121.2, 21.1; m/z = 151.2 (M + 1).

2-Phenylthiazolo[5,4-b]pyridine (5b). ^{1}H NMR (400 MHz; d_6-DMSO) δ 8.64 (dd, J = 4.5, 1.5 Hz, 1H), 8.46 (dd, J = 8.2, 1.5 Hz, 1H), 8.15–8.12 (m, 2H), 7.64–7.61 (m, 4H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 167.5, 157.5, 147.6, 146.5, 135.5, 132.0, 130.2, 129.4, 127.3, 122.2; m/z = 213.4 (M + 1).

2-Aminothiazolo[5,4-b]pyridine (5c). ^{1}H NMR (400 MHz; d_6-DMSO) δ 8.09 (dd, J = 1.6, 4.6 Hz, 1H), 7.79 (br. s, 2H), 7.62 (dd, J = 1.6, 7.9 Hz, 1H), 7.24 (dd, J = 4.6, 7.9 Hz, 1H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 165.5, 155.4, 146.8, 141.6, 123.4, 121.1; m/z = 152.2 (M + 1).

Thiazolo[5,4-b]pyridine (5d). ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.18 (s, 1H), 8.66 (m, H), 8.37 (m, 1H), 7.48 (dd, J = 8.3, 4.6 Hz, 1H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 157.4, 155.4, 147.9, 145.8, 131.0, 121.3; m/z = 137.2 (M + 1).

6-Chlorothiazolo[5,4-b]pyridin-2-amine (7a). ^{1}H NMR (400 MHz; d_6-DMSO) δ 8.12 (d, J = 2.2 Hz, 1H), 8.06 (br. s, 2H), 7.74 (d, J = 2.2 Hz, 1H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 167.4, 153.8, 147.9, 139.4, 128.6, 122.8; m/z = 186.2 (M + 1 for ^{35}Cl).

6-Bromothiazolo[5,4-b]pyridin-2-amine (7b). ^{1}H NMR (400 MHz; d_6-DMSO) δ 8.19 (d, J = 2.1 Hz, 1H), 8.06 (br. s, 2H), 7.86 (d, J = 2.1 Hz, 1H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 167.1, 154.1, 148.3, 141.5, 125.4, 117.1; m/z = 230.1/232.1 (M + 1).

6-Iodothiazolo[5,4-b]pyridin-2-amine (7c). ^{1}H NMR (400 MHz; d_6-DMSO) δ 8.27 (d, J = 1.9 Hz, 1H), 8.01 (br. s, 2H), 7.97 (d, J = 1.9 Hz, 1H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 166.5, 154.5, 148.6, 146.4, 130.8, 90.1; m/z = 277.9 (M + 1).

6-Methylthiazolo[5,4-b]pyridin-2-amine (7d). ^{1}H NMR (400 MHz; d_6-DMSO) δ 7.94 (d, J = 1.2 Hz, 1H), 7.74 (br. s, 2H), 7.45 (d, J = 1.2 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 165.8, 152.4, 146.7, 142.0, 130.4, 124.0, 17.8; m/z = 166.3 (M + 1).

5-Methoxythiazolo[5,4-b]pyridin-2-amine (7e). ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.69 (d, J = 8.6 Hz, 1H), 6.72 (d, J = 8.6 Hz, 1H), 5.52 (br. s, 1H), 5.39 (br. s, 1H), 3.94 (s, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 163.3, 160.6, 151.4, 140.2, 128.7, 108.8, 54.0; m/z = 182.2 (M + 1).

2-Aminothiazolo[4,5-c]pyridine (9). ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.55 (d, J = 0.9 Hz, 1H), 8.13 (d, J = 5.4 Hz, 1H), 7.79 (br. s, 2H), 7.75 (dd, J = 0.9, 5.4 Hz, 1H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 167.0, 149.8, 140.4, 139.5, 138.4, 116.3; m/z = 152.0 (M + 1).

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Synthesis of 9-Amino-5,6,7,8-tetrahydrothieno[3,2-*b*]quinoline and 9-Amino-5,6,7,8-tetrahydrothieno[3,2-*b*]quinolin-8-ol Derivatives

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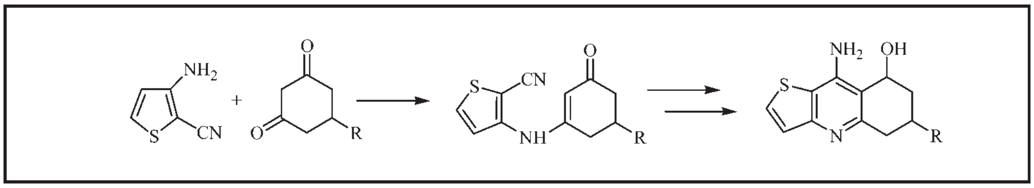

The synthesis of 9-amino-5,6,7,8-tetrahydrothieno[3,2-*b*]quinoline (**3**) and 9-amino-5,6,7,8-tetrahydrothieno[3,2-*b*]quinolin-5-ol derivatives (**4a–g**) in good yield by three-step procedures starting from 3-aminothiophene-2-carbonitrile and 5-substituted cyclohexane-1,3-dione is described.

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INTRODUCTION

Alzheimer's disease (AD) is characterized by the deficits in the cholinergic system [1,2] and presence of neurofibrillary tangles and amyloid plaques [3,4]. Since the deficiency in cholinergic neurotransmission is believed to be one of the major causes of the decline in cognitive and mental functions associated with AD, cholinergic system became a target for the design of anti-Alzheimer drugs.

Acetylcholinesterase (AChE) inhibitors such as tacrine (**1a**) and donepezil by "cholinergic hypothesis" have been a useful and practical treatment for AD [5,6]. Moreover, the interest for AChE inhibitors has been greatly renewed due to the recent evidences that AChE might function to accelerate β-amyloid peptide (Aβ) formation and could play a role during amyloid deposition in AD brain [7,8].

We have recently reported the synthesis of new 4-amino-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline (**2a**) and 4-amino-5,6,7,8-tetrahydrothieno[2,3-*b*]quinolin-5-ol derivatives (**2b**) as potential AChE inhibitors as shown in Figure 1 [9]. Similar analogues based on the substituted thieno[3,2-*b*]quinoline and the thieno[2,3-*b*]quinoline moiety were also reported [10]. As a continuation of our previous works on thienopyridine and thienopyrimidine [9,11,12], we now report the synthesis of 9-amino-5,6,7,8-tetrahydrothieno[3,2-*b*]quinoline (**3**) and 9-amino-5,6,7,8-tetrahydrothieno[3,2-*b*]quinolin-8-ol (**4a–g**) derivatives, which have hitherto not reported.

For the synthesis of **3** and **4**, 3-aminothiophene-2-carbonitrile (**9**) as starting material was needed. However, the only synthetic method for **9** is associated with several drawbacks, such as use of toxic H_2S, low yield, and poor selectivity [13]. The reaction, in addition, was capricious, and further scale-up led reaction that would occasionally fail. Gronowitz et al. has prepared 3-bromothiophene-2-carbaldeyde (**6**) in low yield from 2,3-dibromothiophene through its successive treatment butyllithium and DMF [14]. As shown in Scheme 1, the aldehyde **6** could be obtained in high yield more conveniently and on a large scale by selective deprotonation at position-2 of 3-bromothiophene (**5**) with LDA followed by *N*-formylpiperidine quench [15]. The nucleophilic substitution of Br in **6** by sodium azide in DMPU afforded 3-azidothiophene-2-carbaldehyde (**7**) in good yield [16].

The conversion of aldehyde in **7** into nitrile was obtained in high yield by heating **7** with hydroxylamine-*O*-sulfonic acid in water. The use of hydroxylamine-*O*-sulfonic acid in water instead of hydroxylamine in dry alumina [17] could lead to a more efficient and clear route to 3-azidothiophene-2-carbonitrile (**8**). Finally, the reduction of azide in **8** to amine without affecting nitrile group could be achieved by hydrogenation over 10% Pd-carbon, not using toxic H_2S gas, to give **5** in high yield. Compounds **10a–g**, 5-substituted cyclohexane-1,3-dione, were prepared by previously known procedures [18,19] or purchased.

The synthetic routes to **3** and **4a–g** are shown in Scheme 1. The condensation of **9** with **10** in the presence of catalytic amounts of *p*-toluenesulfonic acid gave the corresponding enamines **11a–g**, 3-(3-oxo-cyclohex-1-enylamino)thiophene-2-carbonitrile derivatives in good yield. These enamins were then cyclized in refluxing THF in the presence of cuprous chloride and potassium carbonate to give thienoquinolinones **12a–g**, 9-amino-6,7-dihydro-5*H*-thieno[3,2-*b*]quinolin-8-one derivatives. It was noteworthy that a stoichiometric cuprous chloride has to be used to run the reaction effectively and to

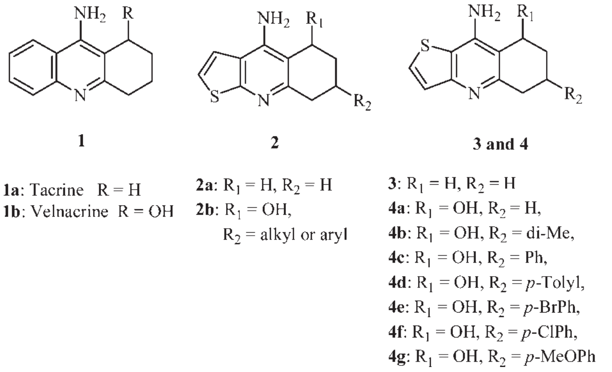


Figure 1. Tacrine and biosteric analogs.

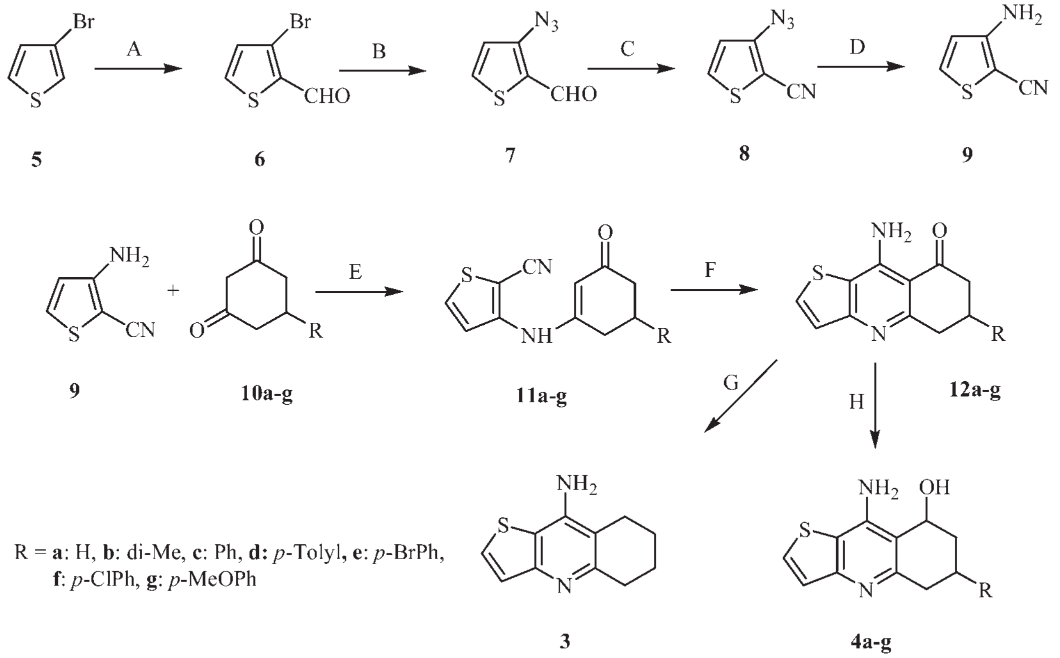
obtain a higher yield. The carbonyl of **12a** was transformed into methylene group by modified Wolff-Kishner reduction (hydrazine hydrate and KOH under hot ethylene glycol) [20] to give a new 9-amino-5,6,7,8-tetrahydrothieno[3,2-*b*]quinoline (**3**) in 57% yield. In another way, the reduction reaction of compounds **12a–g** with lithium aluminum hydride in dry THF, followed by work up of aqueous acidification, and by washing with 30% NaOH solution in order to remove the aluminum salt from the product and to get free amine, provided the expected compounds **4a–g**, 9-amino-5,6,7,8-tetrahydrothieno[3,2-*b*]quinolin-8-ol derivatives in quantitative yields. The compounds **4c–g** were formed with two diastereomers, and major products were *cis* compounds. Because the hydrogens on the alicyclic rings of **4c–g** were resolved at 300 MHz, it is possible to determine all the coupling constants by first-order analysis and to assign the relative stereochemistry of two diastereomers [21]. The product compounds **4a–g** were assayed on AChE inhibitory activity by the modified Ellman method [22]. None of these compounds showed an improved AChE inhibition ($IC_{50} \geq 100\ \mu M$) as compared with tacrine ($IC_{50} = 0.40\ \mu M$), with compound **4a** ($IC_{50} = 3.36\ \mu M$) being the most active. It showed that the introduction of alkyl or aryl group at the C-6 of cyclohexane ring resulted in marked decline in activity.

In conclusion, 9-amino-5,6,7,8-tetrahydrothieno[3,2-*b*]quinoline and 9-amino-5,6,7,8-tetrahydrothieno[3,2-*b*]quinolin-8-ol derivatives have been synthesized in good yield by three-step procedures.

EXPERIMENTAL

Melting points were determined in capillary tubes on Büchi apparatus and are uncorrected. Each compound of the reactions was checked on thin layer chromatography of Merck Kieselgel $60F_{254}$ and purified by column chromatography Merck silica gel (70–230 mesh). The ^1H NMR spectra were recorded on Bruker DRX-300 FT-NMR spectrometer (300 MHz) with Me_4Si as internal standard and chemical shifts are given in ppm (δ). Electron ionization mass spectra were recorded on a HP 59580 B spectrometer. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer.

Scheme 1. A: LDA/THF, *N*-formylpiperidne, 0°C; B: NaN_3/DMPU, 35°C; C: hydroxylamine-*O*-sulfonic acid/H_2O, 40–50°C; D: H_2, Pd-C/ EtOH, rt; E: *p*-TsOH/toluene, reflux; F: K_2CO_3, CuCl/THF, reflux; G: NH_2NH_2, KOH/ethylene glycol, reflux; H: $LiLH_4$/THF, H^+, 30% NaOH, rt.



Preparation of 3-aminothiophene-2-carbonitrile (9). 3-Bromothiophene (**5**) (0.3 mol) was added to a stirred solution of lithium diisopropylamide (0.3 mol) in dry THF (300 mL) at 0°C under nitrogen. After addition of *N*-formylpiperidine (0.3 mol), the reaction solution was stirred for 5 h. Then, it was poured into 30% aqueous ammonium chloride solution and extracted with ether. The combined extracts were dried over magnesium sulfate and evaporated to dryness to afford 3-bromothiophene-2-carbaldeyde (**6**) in 86% yield, bp 115–117°C at 10 mmHg (ref. 13, 113–115°C at 10 mmHg).

A suspension of **6** (0.2 mol) and sodium azide (0.8 mol) in DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidinone, 100 mL) was stirred at 50°C for 24 h. Then, it was poured into water and extracted with ether. The combined extracts were dried over magnesium sulfate and evaporated to dryness to give 3-azidothiophene-2-carbaldehyde **(7)** in 83% yield, mp 57–58°C (ref. 12, 56.6–57.2°C; ref. 15, 56–58°C).

A suspension of **7** (0.1 mol) and hydroxylamine-*O*-sulfonic acid (0.12 mol) in water (100 mL) was stirred at 50°C for 24 h. After cooling, the precipitate was filtered off and washed with water, giving 3-azidothiophene-2-carbonitrile (**8**) in 90% yield, mp 78–79°C (ref. 12, 77.5–79°C).

A suspension of **8** (0.05 mol) and 10% Pd-carbon (0.3 g) in ethanol (50 mL) was stirred under hydrogen at room temperature for 4 h. After completion of the reaction, the reaction mixture was filtered and evaporated to dryness to give 3-aminothiophene-2-carbonitrile (**9**) in 95% yield, mp 49–50°C (ref. 12, 47.5–50°C). ^{1}H NMR (deuteriochloroform): δ 7.28 (d, $J_{4,5}$ = 5.8 Hz, 1H, H-5), 6.54 (d, $J_{4,5}$ = 5.8 Hz, 1H, H-4), 4.48 (s, 2H, NH_2); ms: (*m/z*) 124 (M^+), 110. Anal. Calcd. for $C_5H_4N_2S$: C, 48.37; H, 3.25; N, 22.56. Found: C, 48.50; H, 3.40; N, 22.41.

General procedure for the preparation of 3-(3-oxocyclohex-1-enylamino)thiophene-2-carbonitrile derivatives (11a–g). A suspension of 3-aminothiophene-2-carbonitrile (0.03 mol), the appropriate 1,3-cyclohexanedione (0.03 mol) and *p*-toluene sulfonic acid monohydrate (0.10 g) in dry toluene (20 mL) was refluxed for 7–8 h, and the water was collected in a Dean-Stark trap. After cooling, the reaction mixture was filtered off. The filtrate was evaporated to dryness, and the residue was chromatographed on a silica gel column by eluting with a 20:80 v/v ethyl acetate/chloroform mixture.

3-(3-Oxocyclohex-1-enylamino)thiophene-3-carbonitrile (11a). This compound was obtained from 1,3-cyclohexanedione in 70% yield, mp 142–143°C; ^{1}H NMR (deuteriochloroform): δ 7.54 (d, $J_{4,5}$ = 5.8 Hz, 1H, thiophene proton), 7.21 (d, $J_{4,5}$ = 5.8 Hz, 1H, thiophene proton), 6.88 (s, 2H, NH_2), 5.61 (s, 1H, vinyl proton, H-2), 2.56 (t, 2H, H-6), 2.40 (t, 2H, H-4), 2.07 (quintet, 2H, H-5); ms: (*m/z*) 218 (M^+), 190, 162, 123, 68. Anal. Calcd. for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.83. Found: C, 60.72; H, 4.49; N, 12.70.

3-(5,5-Dimethyl-3-oxocyclohex-1-enylamino)thiophene-2-carbonitrile (11b). This compound was obtained from 5,5-dimethylcyclohexane-1,3-dione in 68% yield, mp 152–153°C; ^{1}H NMR (deuteriochloroform): δ 7.54 (d, $J_{4,5}$ = 5.8 Hz, 1H, thiophene proton), 7.22 (d, $J_{4,5}$ = 5.8 Hz, 1H, thiophene proton), 6.23 (s, 2H, NH_2), 5.64 (s, 1H, vinyl proton, H-2), 2.40 (s, 1H, H-6), 2.26 (s, 1H, H-4), 1.13 [s, 6H, $(CH_3)_2$]; ms: (*m/z*) 246 (M^+), 190, 123, 67. Anal. Calcd. for $C_{13}H_{14}N_2OS$: C, 63.39; H, 5.73; N, 11.37. Found: C, 63.50; H, 5.50; N, 11.44.

3-(3-Oxo-5-phenylcyclohex-1-enylamino)thiophene-2-carbonitrile (11c). This compound was obtained from 5-phenylcyclohexane-1,3-dione in 70% yield, mp 189–190°C; ^{1}H NMR (deuteriochloroform): δ 7.56 (d, $J_{4,5}$ = 5.8 Hz, 1H, thiophene proton), 7.36–7.20 (m, 6H, thiophene and phenyl protons), 6.43 (s, 2H, NH_2), 5.70 (s, 1H, vinyl proton, H-2), 3.45 (m, 1H, H-5), 2.95(dd, 1H, H-6a), 2.68–2.58 (m, 3H, H-4 and H-6b); ms: (*m/z*) 294 (M^+), 265, 190, 159, 123. Anal. Calcd. for $C_{17}H_{14}N_2OS$: C, 69.36; H, 4.79; N, 9.52. Found: C, 69.47; H, 4.92; N, 9.38.

3-(3-Oxo-5-p-tolylcyclohex-1-enylamino)thiophene-2-carbonitrile (11d). This compound was obtained from 5-*p*-tolylcyclohexane-1,3-dione in 76% yield, mp 238–239°C; ^{1}H NMR (deuteriochloroform): δ 7.56 (d, $J_{4,5}$ = 5.8 Hz, 1H, thiophene proton), 7.22 (d, $J_{4,5}$ = 5.8 Hz, 1H, thiophene proton), 7.20 (s, 4H, phenyl protons), 6.60 (s, 2H, NH_2), 5.87 (s, 1H, vinyl proton, H-2), 3.42 (m, 1H, H-5), 2.89 (dd, 1H, H-6a), 2.66–2.59 (m, 3H, H-4 and H-6b), 2.35(s, 3H, CH_3); ms: (*m/z*) 308 (M^+), 279, 190, 162, 123, 67. Anal. Calcd. for $C_{18}H_{16}N_2OS$: C, 70.10; H, 5.23; N, 9.80. Found: C, 69.92; H, 5.10; N, 9.69.

3-(5-(4-Bromophenyl)-3-oxocyclohex-1-enylamino)thiophene-2-carbonitrile (11e). This compound was obtained from 5-(4-bromophenyl)-cyclohexane-1,3-dione in 70% yield, mp 238–239°C; ^{1}H NMR (deuteriochloroform): δ 7.60 (d, $J_{4,5}$ = 5.8 Hz, 1H, thiophene proton), 7.36 (d, $J_{2',3'}$ = 7.5 Hz, 2H, phenyl protons), 7.22 (d, $J_{4,5}$ = 5.8 Hz, 1H, thiophene proton), 7.18 (d, 2H, phenyl protons), 6.80 (s, 2H, NH_2), 5.71 (s, 1H, vinyl proton, H-2), 3.42 (m, 1H, H-5), 2.84 (dd, 1H, H-6a), 2.69–2.59 (m, 3H, H-4 and H-6b); ms: (*m/z*) 372 (M^+), 190, 123. Anal. Calcd. for $C_{17}H_{13}BrN_2OS$: C, 54.70; H, 3.51; N, 7.50. Found: C, 54.88; H, 3.70; N, 7.44.

3-(5-(4-Chlorophenyl)-3-oxocyclohex-1-enylamino)thiophene-2-carbonitrile (11f). This compound was obtained from 5-(4-chlorophenyl)cyclohexane-1,3-dione in 75% yield, mp 216–217°C; ^{1}H NMR (deuteriochloroform): δ 7.59 (d, $J_{4,5}$ = 5.8 Hz, 1H, thiophene proton), 7.37–7.24 (dd, $J_{2',3'}$ = 7.5 Hz, 4H, phenyl protons), 7.22 (d, $J_{4,5}$ = 5.8 Hz, 1H, thiophene proton), 6.32 (s, 2H, NH_2), 5.70 (s, 1H, vinyl proton, H-2), 3.43 (m, 1H, H-5), 2.83 (dd, 1H, H-6a), 2.70–2.60 (m, 3H, H-4 and H-6b); ms: (*m/z*) 328 (M^+), 190, 123. Anal. Calcd. for $C_{17}H_{13}ClN_2OS$: C, 62.10; H, 3.98; N, 8.52. Found: C, 61.92; H, 3.88; N, 8.63.

3-(5-(4-Methoxyphenyl)-3-oxocyclohex-1-enylamino)thiophene-2-carbonitrile (11g). This compound was obtained from 5-(4-methoxyphenyl) cyclohexane-1,3-dione in 75% yield, mp 147–148°C; ^{1}H NMR (deuteriochloroform): δ 7.56 (d, $J_{4,5}$ = 5.8 Hz, 1H, thiophene proton), 7.36 (d, $J_{2',3'}$ = 7.5 Hz, 2H, phenyl protons), 7.21 (d, $J_{4,5}$ = 5.8 Hz, 1H, thiophene proton), 6.92 (d, 2H, phenyl protons), 6.40 (s, 2H, NH_2), 5.70 (s, 1H, vinyl proton, H-2), 3.46 (m, 1H, H-5), 2.84 (dd, 1H, H-6a), 2.70–2.63 (m, 3H, H-4 and H-6b); ms: (*m/z*) 324 (M^+), 190, 123, 67. Anal. Calcd. for $C_{18}H_{16}ClN_2OS$: C, 66.64; H, 4.97; N, 8.64. Found: C, 66.75; H, 5.13; N, 8.48.

General procedure for the preparation of 9-amino-6,7-dihydro-5*H*-thieno[3,2-*b*]quinolin-8-one derivatives (12a–g). A suspension of the appropriate 3-(3-oxocyclohex-1-enylamino)thiophene-2-carbonitrile (0.01 mol), K_2CO_3 (0.01 mol) and CuCl (0.01 mol) in dry THF (10 mL) was refluxed for 10 h. After completion of reaction, the warm reaction solution was filtered off. The filtrate was evaporated to dryness, and the residue was chromatographed on a silica gel column by eluting with a 30:70 v/v ethyl acetate/chloroform mixture.

9-Amino-6,7-dihydro-5H-thieno[3,2-b]quinolin-8-one (12a). This compound was obtained from 3-(3-oxocyclohex-1-enyl-amino)-thiophene-2-carbonitrile in 55% yield, mp 199–200°C; ^{1}H NMR (deuteriochloroform): δ 7.70 and 7.40 (d and d, $J_{2,\,3}$ = 5.7 Hz, 2H, thiophene protons), 3.13 (t, 2H, H-5), 2.72 (t, 2H, H-7), 2.16 (quintet, 2H, H-6); ms: (*m*/*z*) 218 (M$^+$), 190, 71, 57. Anal. Calcd. for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.83. Found: C, 60.66; H, 4.50; N, 12.94.

9-Amino-6,6-dimethyl-6,7-dihydro-5H-thieno[3,2-b]quinolin-8-one (12b). This compound was obtained from 3-(5,5-dimethyl-3-oxocyclohex-1-enylamino)thiophene-2-carbonitrile in 67% yield, mp 255–256°C; ^{1}H NMR (deuteriochloroform): δ 7.72 and 7.40 (d and d, $J_{2,\,3}$ = 5.7 Hz, 2H, thiophene protons), 3.01 (s, 2H, H-5), 2.57 (s, 2H, H-7), 1.01 [s, 6H, $(CH_3)_2$]; ms: (*m*/*z*) 246 (M$^+$), 230, 216. Anal. Calcd. for $C_{13}H_{14}N_2OS$: C, 63.39; H, 5.73; N, 11.37. Found: C, 63.23; H, 5.89; N, 11.48.

9-Amino-6-phenyl-6,7-dihydro-5H-thieno[3,2-b]quinolin-8-one (12c). This compound was obtained from 3-(3-oxo-5-phenylcyclohex-1-enylamino)thiophene-2-carbonitrile in 65% yield, mp 189–190°C; ^{1}H NMR (deuteriochloroform): δ 7.74 and 7.40 (d and d, $J_{2,\,3}$ = 5.7 Hz, 2H, thiophene protons), 7.38–7.25 (m, 5H, phenyl), 3.53 (m, 1H, H-6), 3.34–3.28 (m, 2H, H-5), 2.95–2.91 (m, 2H, H-7); ms: (*m*/*z*) 294 (M$^+$), 265, 238, 203, 190. Anal. Calcd. for $C_{17}H_{14}N_2OS$: C, 69.36; H, 4.79; N, 9.52. Found: C, 69.48; H, 4.63; N, 9.65.

9-Amino-6-p-tolyl-6,7-dihydro-5H-thieno[3,2-b]quinolin-8-one (12d). This compound was obtained from 3-(3-oxo-5-*p*-tolylcyclohex-1-enylamino)thiophene-2-carbonitrile in 62% yield, mp 262–263°C; ^{1}H NMR (deuteriochloroform): δ 7.74 and 7.41 (d and d, $J_{2,\,3}$ = 5.7 Hz, 2H, thiophene protons), 7.26–7.18 (m, 4H, phenyl), 3.55 (m, 1H, H-6), 3.33–3.29 (m, 2H, H-5), 2.95–2.92 (m, 2H, H-7), 2.35 (s, 3H, CH_3); ms: (*m*/*z*) 308 (M$^+$), 292, 201, 135. Anal. Calcd. for $C_{18}H_{16}N_2OS$: C, 70.10; H, 5.23; N, 9.08. Found: C, 70.28; H, 5.33; N, 9.19.

9-Amino-6-(4-bromophenyl)-6,7-dihydro-5H-thieno[3,2-b]quinolin-8-one (12e). This compound was obtained from 3-(5-(4-bromophenyl)-3-oxocyclohex-1-enylamino)thiophene-2-carbonitrile in 67% yield, mp 197–198°C; ^{1}H NMR (deuteriochloroform): δ 7.74 and 7.42 (d and d, $J_{2,\,3}$ = 5.7 Hz, 2H, thiophene protons), 7.45 and 7.19 (d and d, $J_{2',\,3'}$ = 7.5 Hz, 4H, phenyl H-3′and H-2′), 3.55 (m, 1H, H-6), 3.40–3.29 (m, 2H, H-5), 2.96–2.89 (m, 2H, H-7); ms: (*m*/*z*) 308 (M$^+$), 292, 203, 161. Anal. Calcd. for $C_{18}H_{16}N_2OS$: C, 70.10; H, 5.23; N, 9.08. Found: C, 70.21; H, 5.40; N, 9.22.

9-Amino-6-(4-chlorophenyl)-6,7-dihydro-5H-thieno[3,2-b]quinolin-8-one (12f). This compound was obtained from 3-(5-(4-chlorophenyl)-3-oxocyclohex-1-enylamino)thiophene-2-carbonitrile in 68% yield, mp 204–205°C; ^{1}H NMR (deuteriochloroform): δ 7.77 and 7.52 (d and d, $J_{2,\,3}$ = 5.7 Hz, 2H, thiophene protons), 7.35 and 7.24 (d and d, $J_{2',\,3'}$ = 7.5 Hz, 4H, phenyl), 3.57 (m, 1H, H-6), 3.38–3.30 (m, 2H, H-5), 2.97–2.90 (m, 2H, H-7); ms: (*m*/*z*) 328 (M$^+$), 312, 201. Anal. Calcd. for $C_{17}H_{13}ClN_2OS$: C, 62.10; H, 3.98; N, 8.52. Found: C, 62.27; H, 4.14; N, 8.40.

9-Amino-6-(4-methoxyphenyl)-6,7-dihydro-5H-thieno[3,2-b]quinolin-8-one (12g). This compound was obtained from 3-(5-(4-methoxyphenyl)-3-oxocyclohex-1-enylamino)thiophene-2-carbonitrile in 70% yield, mp 244–245°C; ^{1}H NMR (deuteriochloroform): δ 7.74 and 7.29 (d and d, $J_{2,\,3}$ = 5.7 Hz, 2H, thiophene protons), 7.24 and 6.90 (d and d, $J_{2',\,3'}$ = 7.5 Hz, 4H, phenyl), 3.78 (s, 3H, OCH_3), 3.55 (m, 1H, H-6), 3.39–3.31 (m, 2H, H-5), 2.98–2.89 (m, 2H, H-7); ms: (*m*/*z*) 324 (M$^+$), 308, 201, 190. Anal. Calcd. for $C_{18}H_{16}N_2O_2S$: C, 66.64; H, 4.97; N, 8.64. Found: C, 66.79; H, 5.08; N, 8.53.

Preparation of 9-amino-5,6,7,8-tetrahydrothieno[3,2-*b*] quinoline (3). A mixture of 0.65 g (3.0 mmol) of 9-amino-6,7-dihydro-5*H*-thieno[3,2-*b*]quinolin-8-one (12a), 0.60 g (12.0 mmol) of hydrazine hydrate, and 0.67 g (12.0 mmol) of potassium hydroxide in 30 mL of ethylene glycol was refluxed for 8 h. After the starting material was disappeared, the reaction mixture was concentrated by distillating off water and ethylene glycol. The concentrate was allowed to reach room temperature and extracted repeatedly with chloroform. The organic extract was dried with magnesium sulfate and evaporated. The residue was purified with silica gel column chromatography eluting with a 30:70 v/v ethyl acetate/chloroform mixture to give 0.35 g (57%) of **3**, mp 137–138°C; ^{1}H NMR (deuteriochloroform): δ 7.21 and 7.10 (d and d, 2H, thiophene protons), 4.47 (s, 2H, NH_2), 2.99 (m, 2H, H-5), 2.54 (m, 2H, H-8), 1.99–1.84 (m, 4H, H-6 and H-7); ms: (*m*/*z*) 204 (M$^+$), 190, 161, 135. Anal. Calcd. for $C_{11}H_{12}N_2S$: C, 64.67; H, 5.92; N, 13.71. Found: C, 64.88; H, 6.09; N, 13.60.

General procedure for the preparation of 9-amino-5,6,7,8-tetrahydrothieno[3,2-*b*]quinolin-8-ol derivatives (4a–g). A solution of $LiAlH_4$ in Et_2O (2.0 mL of 1.0*M*, 2.0 mmol) was added dropwise to a solution of the appropriate 9-amino-6,7-dihydro-5*H*-thieno[3,2-*b*]quinolin-8-one (2.0 mmol) in dry THF (10 mL) maintained at 0°C under nitrogen. After stirring at room temperature for 5 h, the reaction solution was quenched by adding 10% HCl, followed by washing with 30% NaOH to make free base and extracted with chloroform. The combined organic layers were evaporated to dryness, and the residue was purified by silica gel column chromatography eluting with a 50:50 v/v ethyl acetate/chloroform mixture.

9-Amino-5,6,7,8-tetrahydrothieno[3,2-b]quinolin-8-ol (4a). This compound was obtained from 9-amino-6,7-dihydro-5*H*-thieno[3,2-*b*]quinolin-8-one in 80% yield, mp 218–219°C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 7.78 and 7.22 (d and d, $J_{2,\,3}$ = 5.8 Hz, 2H, thiophene protons), 6.16 (s, 2H, NH_2), 5.06 (m, 1H, H-8), 2.78–2.66 (m, 2H, H-5), 1.93–1.70 (m, 4H, H-6 and H-7); ms: (*m*/*z*) 220 (M$^+$), 202, 201, 187, 175, 164. Anal. Calcd. for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72. Found: C, 60.18; H, 5.33; N, 12.88.

9-Amino-6,6-dimethyl-5,6,7,8-tetrahydrothieno[3,2-b]quinolin-8-ol (4b). This compound was obtained from 9-amino-6,6-dimethyl-6,7-dihydro-5*H*-thieno[3,2-b]quinolin-8-one in 84% yield, mp 176–177°C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 7.74 and 7.24 (d and d, $J_{2,\,3}$ = 5.8 Hz, 2H, thiophene protons), 5.06 (m, 1H, H-8), 2.80 and 2.58 (d and d, $J_{5a,\,5b}$ = 13 Hz, 2H, H-5), 2.10 (dd, *J* = 5.5 and 13 Hz, 1H, H-7a), 1.74 (dd, *J* = 6.0 and 13 Hz, 1H, H-7b), 1.13 (s, 3H, CH_3), 0.99 (s, 3H, CH_3); ms: (*m*/*z*) 248 (M$^+$), 230, 215, 203, 188. Anal. Calcd. for $C_{13}H_{16}N_2OS$: C, 62.87; H, 6.49; N, 11.28. Found: C, 62.94; H, 6.40; N, 11.39.

9-Amino-6-phenyl-5,6,7,8-tetrahydrothieno[3,2-b]quinolin 8-ol (4c). This compound was obtained from 9-amino-6-phenyl-6,7-dihydro-5*H*-thieno[3,2-b]quinolin-8-one in 89% yield, mp 193–194°C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 7.57 (d, $J_{2,\,3}$ = 5.8 Hz, 1H, thiophene proton), 7.41–7.29 (m, 6H, thiophene and phenyl protons), 5.20 (m, 1H, H-8), 3.19–3.09 (m, 3H, H-5 and H-6), 2.68–2.62 (m, 1H, H-7a), 2.06–2.02 (m, 1H, H-7b); ms: (*m*/*z*) 296 (M$^+$), 278, 263, 251, 201, 187.

Anal. Calcd. for $C_{17}H_{16}N_2OS$: C, 68.89; H, 5.44; N, 9.45. Found: C, 69.98; H, 5.53; N, 9.57.

9-Amino-6-p-tolyl-5,6,7,8-tetrahydrothieno[3,2-b]quinolin-8-ol (4d). This compound was obtained from 9-amino-6-*p*-tolyl-6,7-dihydro-5*H*-thieno[3,2-b]quinolin-8-one in 78% yield, mp 131–132°C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 7.84 and 7.25 (d and d, $J_{2,3}$ = 5.7 Hz, 2H, thiophene protons), 7.22 (d, $J_{2',3'}$ = 7.5 Hz, 2H, phenyl H-2′), 7.16 (d, 2H, phenyl H-3′), 5.18 (m, 1H, H-5), 3.15–2.98 (m, 3H, H-5 and H-6), 2.60–2.52 (m, 1H, H-7a), 2.32 (s, 3H, CH_3), 2.06–2.00 (m, 1H, H-7b); ms: (*m*/*z*) 310 (M^+), 292, 277, 265, 201. Anal. Calcd. for $C_{18}H_{18}N_2OS$: C, 69.65; H, 5.84; N, 9.02. Found: C, 69.77; H, 5.70; N, 9.10.

9-Amino-6-(4-bromophenyl)-5,6,7,8-tetrahydrothieno[3,2-b]quinolin-8-ol (4e). This compound was obtained from 9-amino-6-(4-bromo-phenyl)-6,7-dihydro-5*H*-thieno[3,2-b]quinolin-8-one in 85% yield, mp 116.5–117.5°C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 7.75 (d, $J_{2,3}$ = 5.7 Hz, 1H, thiophene proton), 7.50 (d, $J_{2',3'}$ = 7.5 Hz, 2H, phenyl H-3′), 7.34 (d, 1H, thiophene proton), 7.25 (d, 2H, phenyl H-2′), 5.13 (m, 1H, H-5), 3.14–3.02 (m, 3H, H-5 and H-6), 2.54–2.49 (m, 1H, H-7a), 2.10–2.03 (m, 1H, H-7b); ms: (*m*/*z*) 374 (M^+), 356, 277, 201. Anal. Calcd. for $C_{17}H_{15}BrN_2OS$: C, 54.41; H, 4.03; N, 7.46. Found: C, 54.57; H, 4.13; N, 7.34.

9-Amino-6-(4-chlorophenyl)-5,6,7,8-tetrahydrothieno[3,2-b]quinolin-8-ol (4f). This compound was obtained from 9-amino-6-(4-chloro-phenyl)-6,7-dihydro-5*H*-thieno[3,2-b]quinolin-8-one in 88% yield, mp 117–118°C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 7.75 (d, $J_{2,3}$ = 5.7 Hz, 1H, thiophene proton), 7.35 (s, 4H, phenyl protons), 7.24 (d, 1H, thiophene proton), 5.16 (m, 1H, H-5), 3.13–3.03 (m, 3H, H-5 and H-6), 2.53–2.48 (m, 1H, H-7a), 2.10–2.03 (m, 1H, H-7b); ms: (*m*/*z*) 330 (M^+), 312, 277, 187, 201, 126. Anal. Calcd. for $C_{17}H_{15}ClN_2OS$: C, 61.72; H, 4.57; N, 8.47. Found: C, 61.83; H, 4.64; N, 8.58.

9-Amino-6-(4-methoxyphenyl)-5,6,7,8-tetrahydrothieno[3,2-b]quinolin-8-ol (4g). This compound was obtained from 9-amino-6-(4-methoxy-phenyl)-6,7-dihydro-5*H*-thieno[3,2-b]quinolin-8-one in 86% yield, mp 170–171°C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 7.74 (d, $J_{2,3}$ = 6.0 Hz, 1H, thiophene H-2), 7.28–7.23 (m, 3H, thiophene H-3 proton and phenyl H-3′), 6.90 (d, $J_{2',3'}$ = 7.5 Hz, 2H, phenyl H-2′), 5.12 (m, 1H, H-5), 3.77 (s, 3H, OCH_3), 3.07–2.99 (m, 3H, H-5 and H-6), 2.53–2.48 (m, 1H, H-7a), 2.09–2.00 (m, 1H, H-7b); ms: (*m*/*z*) 326 (M^+), 308, 293, 201. Anal. Calcd. for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58. Found: C, 66.34; H, 5.64; N, 8.47.

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Synthesis and Molecular Recognition of Novel Multiimidazole Cyclophanes

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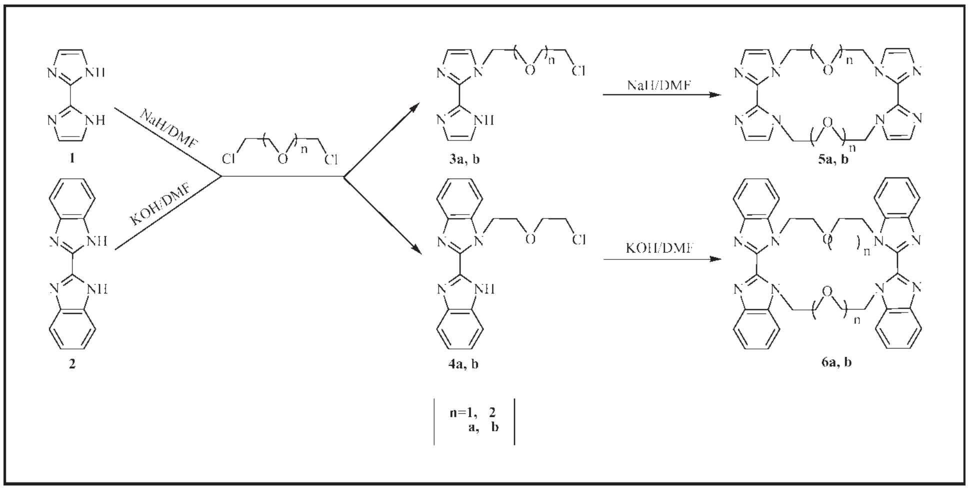

Cyclophanes based on 2,2′-biimidazole and 2,2′-bibenzimidazole were synthesized as receptors. UV spectroscopic titration in chloroform at 25°C showed 1:1 complexes between the cyclophanes and the guests, and the binding constants (K) and Gibbs free energy changes ($-\Delta G_0$) were calculated according to the modified Benesi-Hildebrand equation.

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INTRODUCTION

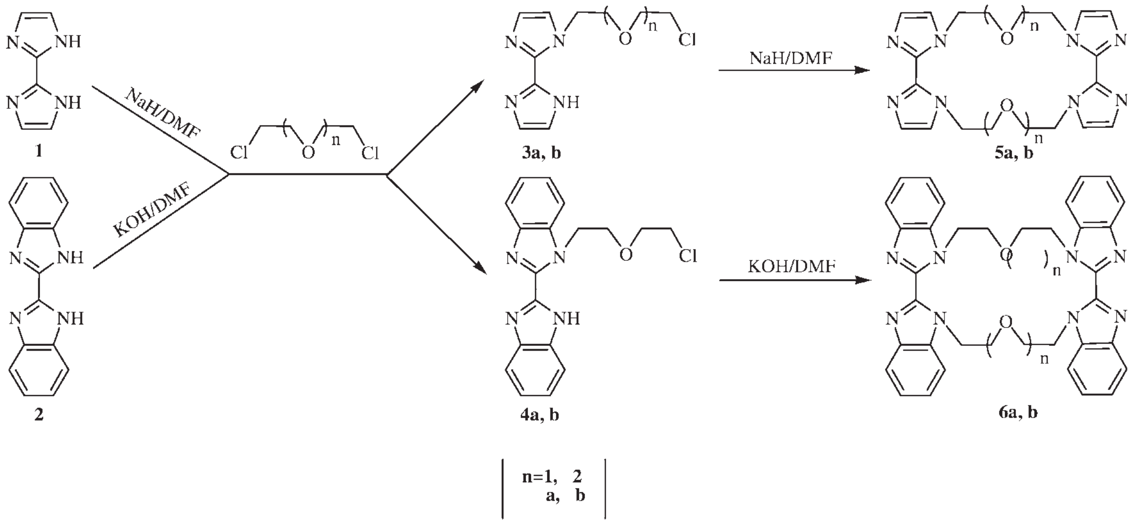
It is known that molecular recognition is a fundamental characteristic of biochemical system. The design and synthesis of receptors is of prime importance in supramolecular chemistry, due to its biological, medical, and environmental relevances [1,2]. During the last two decades, considerable attention have been addressed to develop systems capable of recognizing, self-assembling, catalyzing, and sensing, but the design of effective hosts for guests are still particularly challenging because of the characteristics of guests [3].

In biochemical host-guest processes, noncovalent interactions, such as, hydrogen bonding and coordination bonding play a central role in the creation of a variety of molecular architectures for molecular recognition, molecular self-assembly, and supramolecular catalysis. Imidazole can serve as proton donor-acceptor, general acid-base, nucleophile, and selective binding group [4]. Compounds with imidazole ring systems have many pharmaceutical activities and play important roles in biochemical processes [5]. Imidazole-based cyclophanes have received increasing attention in host-guest chemistry and biomimetic chemistry. Pioneering work has been carried out by Shi and Thummel [6]. Although much progress has been achieved [7], the construction of cyclophanes are of only one or two imidazole rings and has not yet overtaken the natural high efficiency and selectivity. We recently synthesized novel multiimidazole cyclophanes linked by alkyl groups [8]. However, these receptors only show poor recognition ability for amino acid esters. Noncovalent interactions, especially, hydrogen bonding and π-π stacking interaction may contribute to the attractive forces between hosts and guests. Because of the greater chemical stability and bidentate chelating sites [9], 2,2′-biimidazole (**Biim**) and 2,2′-bibenzimidazole (**BiBim**) are chosen as the component. We report, herein, the facile synthesis and characterization of novel multiimidazole cyclophanes which are comprised of four imidazole rings linked by ether chains (Scheme 1), and found that these artificial receptors exhibit excellent recognition ability toward amino acid esters.

RESULTS AND DISCUSSION

Design and synthesis of cyclophanes 5a,b and 6a,b. Cyclophanes **5a,b** and **6a,b** with different cavity and structure were designed and synthesized.

Scheme 1



Cyclophane **5a** contains four imidazole rings that could function as binding sites and two oxygen atoms on the macrocyclic skeleton that might serve as two hydrogen bonding recognition sites. Cyclophane **5b** also has four imidazole rings but with bigger cavity. For comparison, cyclophanes **6a**,**b** with more aromatic **BiBim** subunits linked to polyether dichlorides were also synthesized.

The multiimidazole compounds are generally considered to be difficult to prepare because of low solubility and several reactive sites. The reaction conditions have a significant influence on the selectivity. The *N*-alkylation of **Biim** and **BiBim** may have many possible substitutions at different sites, such as, quaternization or *N*,*N*′-bridged cyclization, 1,1′-disubstitution. By optimizing conditions, these competitive reactions can be minimized. Temperature and basicity are important in obtaining products. The temperature of the reaction affects on the yields of [1 + 1] and [2 + 2] cyclization. Excessive heating may lead [1 + 1] condensation. If excessive base are used, the mixture of quaternization, *N*,*N*′-bridged cyclization and 1,1′-disubstitution are formed. Under equivalent basicity to **Biim** and **BiBim**, 1-substitution of **Biim** and **BiBim** are produced. The bridged **Biim** and **BiBim** intermediates were synthesized by the *N*-alkylation of **Biim** and **BiBim**, respectively, with the corresponding polyether dichlorides in the presence of a slight excess of NaH or KOH in dry DMF at 70°C. The cyclization reactions of the bridged

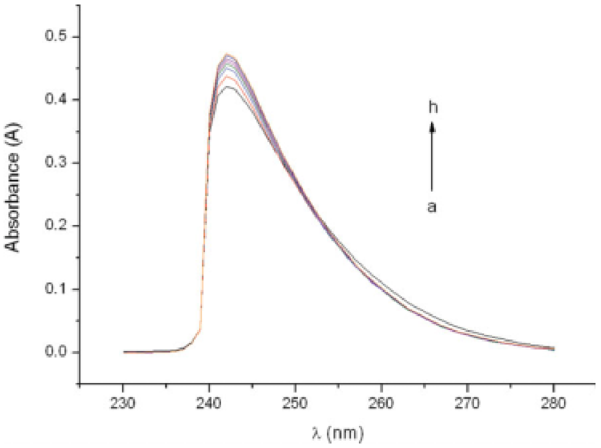


Figure 1. Spectrum of **5a** with varying Val-OMe concentration at 25°C ± 0.1°C. The concentration of **5a** is 6.8×10^{-5} mol dm^{-3}. The concentration of Val-OMe (mol dm^{-3}) are 0, 10×10^{-5}, 20×10^{-5}, 30×10^{-5}, 40×10^{-5}, 50×10^{-5}, 60×10^{-5}, and 70×10^{-5} reading from a to h. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

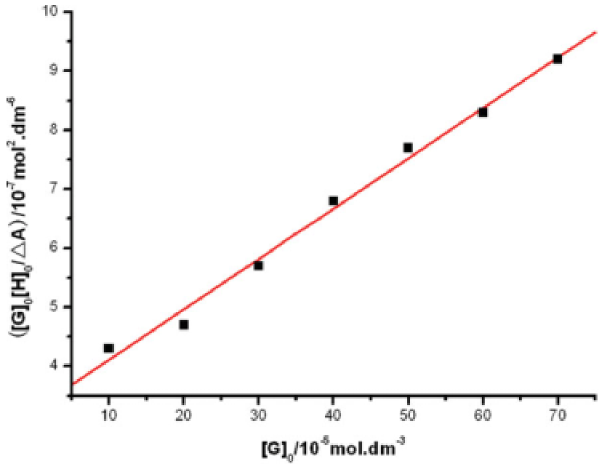


Figure 2. Typical plots of $[G]_0[H]_0/\Delta A$ versus $[G]_0$ for the host-guest complexation of Val-OMe and **5a** at 25°C ± 0.1°C. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Table 1

Binding constants (*K*) and Gibbs free energy of complexation ($-\Delta G_0$) for the 1:1 complexes between cylcophanes and guests in $CHCl_3$ at 25°C.

Entry	Host	Guest[a]	K ($dm^3\ mol^{-1}$)	$-\Delta G_0$ ($kJ\ mol^{-1}$)
1	**5a**	Ala-OMe	377	14.71
2	**5a**	Val-OMe	2656	19.55
3	**5a**	Leu-OMe	707	16.27
4	**5a**	Pro-OMe	1330	17.83
5	**5a**	Gly-OMe	160	12.58
6	**5b**	Ala-OMe	429	15.03
7	**5b**	Val-OMe	960	17.02
8	**5b**	Leu-OMe	480	15.31
9	**5b**	Pro-OMe	2750	19.64
10	**5b**	Gly-OMe	687	16.20
11	**6a**	Ala-OMe	913	16.90
12	**6a**	Val-OMe	3295	20.08
13	**6a**	Leu-OMe	1502	18.13
14	**6a**	Pro-OMe	544	15.61
15	**6a**	Gly-OMe	734	16.36
16	**6b**	Ala-OMe	980	17.08
17	**6b**	Val-OMe	960	17.02
18	**6b**	Leu-OMe	725	16.33
19	**6b**	Pro-OMe	723	16.32
20	**6b**	Gly-OMe	1358	17.89

[a] Ala-OMe, alanine methyl ester; Leu-OMe, leucine methyl ester; Pro-OMe, proline methyl ester; Val-OMe, valine methyl ester; Gly-OMe, glycine methyl ester.

intermediates were carried out in DMF at 95°C. The slow addition of the intermediates made the cyclization facile and efficient. The structures proposed for these novel multiimidazole cyclophanes were confirmed by elemental analysis, MS, and ^1H NMR.

Molecular recognition of hosts in UV spectroscopic titration. Among the various methods to characterize host-guest interactions, the UV-vis titration method is widely used for its high sensitivity to host-guest binding [1,10]. In this article, the binding constants (*K*) of inclusion complexes of aforementioned receptors with amino acid esters were determined on the basis of the differential UV spectrometry in chloroform. In UV spectroscopic titration experiments, addition of varying concentration of amino acid derivatives resulted in a gradual increase of the characteristic absorptions of the host molecules. Typical UV spectral changes upon the addition of valine methyl ester (**Val-OMe**) to host **5a** are shown in Figure 1.

With the assumption of a 1:1 stoichiometry, the complexation of amino acid derivatives (*G*) with cyclophane (*H*) is expressed by eq. (1):

$$H + G \rightleftharpoons GH \tag{1}$$

Under the conditions used, the concentration of the receptors (6.8×10^{-5} mol dm^{-3}) is much lower than that of amino acid derivatives, that is, $[H]_0 << [G]_0$. Therefore, the stability constant of supramolecular system formed can be calculated according to the modified Hildebrand-Benesi equation [11], eq. (2).

$$[G]_0[H]_0/\Delta A = 1/K\Delta\varepsilon + [G]_0/\Delta\varepsilon \tag{2}$$

where $[H]_0$ represents the total concentration of host, $[G]_0$ denotes the total concentration of guest amino acid derivatives, $\Delta\varepsilon$ is the difference between the molar extinction coefficient for the free and complexing cyclophane, ΔA denotes the changes in the absorption of the host on adding amino acid derivatives. For all guest molecules examined, plots of calculated $[G]_0[H]_0/\Delta A$ values as a function of porting the 1:1 complex formation. Typical plots are shown for the complexation of compound **5a** with Val-OMe in Figure 2.

The association constants (*K*) and the free-energy change ($-\Delta G_0$) calculated from the slope and the intercept are shown in Table 1. Inspection of Table 1 shows that these receptors can recognize the differences between the cyclophane size and shape of amino acid derivatives. Our study clearly demonstrates that the different cavity size strongly influences the recognition ability of the cyclophane receptor. The multiimidazole cyclophane **5a** shows selective binding to amino acid derivatives in chloroform. For example, the association constants (*K*) of **5a** and **5b** for Val-OMe are 2656 and 960, respectively. The similar structure of **5a** and **6a** gives us the similar association constants (*K*) for Val-OMe, which are 2656 and 3295, respectively. Thus, the cavity size, steric effects, and structural rigidity of the receptors may play an important role in the selective recognition.

Figure 3 and Table 1 show the selective recognition ability of the receptor **6a** with α-animo acid esters, affording the *K* of 544–3295 and the ΔG_0 of 15.61–20.08 KJ mol^{-1}. The selectivity is highly sensitive to the chain length and shape of the substituted group in amino acids. Indeed, the receptor **6a** exhibits stronger binding for amino acid esters containing an acyclic group, inferring the hydrogen bonding interaction between the receptor and the amino acid is the principal attractive interaction involved. The acyclic Val-OMe is included most effectively by **6a**, giving the highest and the strongest binding. According to CPK model, when Val-OMe is embedded into the cavity, the supramolecular complex should be formed (Fig. 4). It has been proposed that the dimension of the cavity of cyclophane **6a** is more suitable for Val-OMe than other amino acid esters.

Different structure strongly influences the recognition ability of the receptor for amino acid esters. The similar structures **5b** and **6b** give us the association constants (*K*) for Gly-OMe, which are 687 and 1358, respectively. From this result, we think that the π-π stacking interaction between the receptor and the aromatic side chain of amino acid play an important role in recognition. Because **5b** and **6b** have bigger cavity, they cannot be propitious to the formation of stable supramolecular system. They give us low selective ability.

CONCLUSION

In conclusion, a facile synthesis led to cyclophanes based on biimidazole and bibenzimidazole units as molecular recognition motifs for amino acid esters. These receptors exhibit excellent recognition ability toward amino acid derivatives. The cavity size, steric effects, and structural rigidity, hydrogen bond, and π-π stacking interaction between the aromatic groups may be responsible for the recognition of amino acid derivatives.

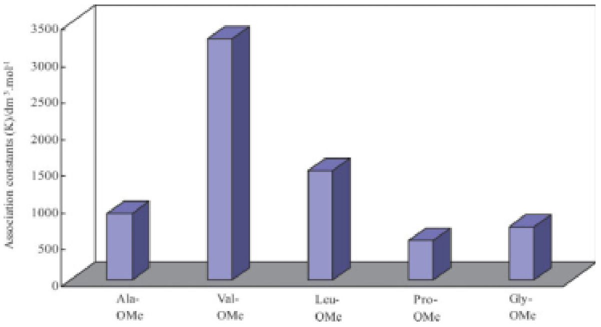


Figure 3. Recognition ability of the cyclophane **6a** for α-animo acid esters. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

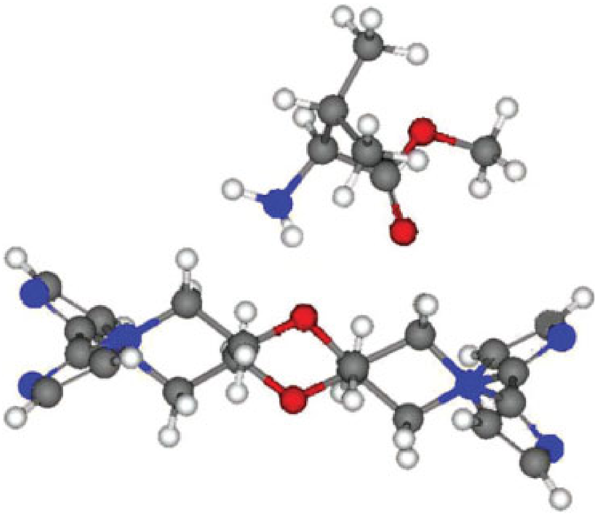


Figure 4. Proposed recognition mechanism of Val-OMe by host **5a**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

EXPERIMENTAL

Physical measurements. Melting points were taken on a X-6 micro-melting point apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Bruker AVANCE/400 MHz instrument, and chemical shifts in ppm were reported with TMS as the internal standard. Mass spectra (ms) were measured on a VG Autospec 3000 mass spectrometer. Elemental analyses were performed on a Carlo Erba 1106 instrument. UV-vis spectra were obtained with TU-1810 spectrophotometer.

Reagents and general techniques. Anhydrous DMF was purified according to the standard method. **Biim** [12], **BiBim** [13], and polyether dichlorides [14] were prepared according to literature procedure. Amino acid methyl ester hydrochloride used was prepared by adding dropwise $SOCl_2$ into a suspension of the free amino acid in absolute methanol at 0°C. Free amino acid esters were obtained by neutralization with $NH_3 \cdot nH_2O$ before use. All other chemicals and reagents were obtained commercially and used without further purification.

General procedure for preparation of 3a, b and 4a, b. In a 25-mL flask, **Biim** or **BiBim** (5 mmol), DMF (10 mL) and NaH or KOH (6 mmol) were stirred at room temperature. Polyether dichlorides (5 mmol) was added quickly. The mixture was stirred for 12 h at 70°C. The solid was filtered and washed with a less absolute ethanol. The combined solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (dichloromethane/ethanol 19:1 or petroleum ether/ethyl acetate 4:1) to give the pure products **3a,b** and **4a,b**.

1-(5-Chloro-3-oxa-pentyl)-2,2′-biimidazole, 3a. Red viscous liquid, yield 63.1% ^{1}H NMR ($CDCl_3$) δ: 3.539–3.564 (t, 2H, CH_2Cl), 3.681–3.709 (t, 2H, $ClCH_2—CH_2O$), 3.912–3.937 (t, 2H, $NCH_2—CH_2O$), 4.875–4.900 (t, 2H, NCH_2), 7.114 (d, 2H, BiIm 5,5′-H), 7.144 (d, 2H, BiIm 4,4′-H) ppm; ms (*m*/*z*): 241.08 (M+H$^+$). Anal. Calcd for $C_{10}H_{13}ClN_4O$: C 49.90, H 5.44, N 23.28, Cl 14.73; found: C 50.08, H 5.47, N 23.48, Cl 14.85.

1-(8-Chloro-3,6-dioxa-octyl)-2,2′-biimidazole, 3b. Red viscous liquid, yield 42.1% ^{1}H NMR ($CDCl_3$) δ: 3.575–3.590 (t, 2H, CH_2Cl), 3.598–3.612 (t, 2H, $ClCH_2$—CH_2O), 3.678–3.850 (m, 4H, OCH_2—CH_2O), 3.869–3.914 (t, 2H, NCH_2—CH_2O), 4.876–4.900 (t, 2H, NCH_2), 7.114 (d, 2H, BiIm 5,5′-H), 7.154 (d, 2H, BiIm 4,4′-H) ppm; ms (*m/z*): 285.10 ($M+H^+$). Anal. Calcd for $C_{12}H_{17}ClN_4O_2$: C 50.62, H 6.02, N 19.68, Cl 12.45; found: C 50.83, H 6.15, N 19.80, Cl 12.54.

1-(5-Chloro-3-oxa-pentyl)-2,2′-bibenzimidazole, 4a. Pale yellow solid, yield 61.6% ^{1}H NMR ($CDCl_3$) δ: 3.498–3.508 (t, 2H, CH_2Cl), 3.724–3.733 (t, 2H, $ClCH_2$—CH_2O), 4.149–4.158 (t, 2H, NCH_2—CH_2O), 5.294–5.302 (t, 2H, NCH_2), 7.261–7.850 (m,8H, Ar—H) ppm; ms (*m/z*): 343.12 ($M+H^+$). Anal. Calcd for $C_{18}H_{19}ClN_4O$: C 63.06, H 5.59, N 16.34, Cl 10.34; found: C 63.16, H 5.61, N 16.56, Cl 10.50.

1-(8-Chloro-3,6-dioxa-octyl)-2,2′-bibenzimidazole, 4b. Pale yellow solid, yield 40.9% ^{1}H NMR ($CDCl_3$) δ: 3.534–3.586 (t, 2H, CH_2Cl), 3.641–3.669 (t, 2H, $ClCH_2$—CH_2O), 3.925–3.950 (m, 4H, OCH_2—CH_2O),4.116–4.125 (t, 2H, NCH_2—CH_2O), 5.186–5.194 (t, 2H, NCH_2), 7.186–7.781 (m,8H, Ar—H) ppm; ms (*m/z*): 285.10 ($M+H^+$). Anal. Calcd for $C_{12}H_{17}ClN_4O_2$: C 50.62, H 6.02, N 19.68, Cl 12.45; found: C 50.83, H 6.15, N 19.80, Cl 12.54.

General procedure for the synthesis of cyclophanes 5a, b and 6a, b. To a stirred and warmed (95°C) solution of NaH or KOH (2.5 mmol) and DMF (5 mL), compounds **3a, b** and **4a, b** (2.1 mmol) in DMF was added dropwise over 5 h. The mixture was stirred at this temperature for 20 h. The solid was filtered and washed with a less absolute ethanol. The combined solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (dichloromethane/ethanol 14:1 or petroleum ether/ethyl acetate 1:1) to give the pure products **5a, b** and **6a, b**.

Cyclophane 5a. Off-white solid, yield 45.6%, mp 186–188°C. ^{1}H NMR ($CDCl_3$) δ: 3.770–3.794 (t, 8H, OCH_2), 3.950–3.971 (t, 8H, NCH_2), 7.192 (s, 4H, BiIm 5,5′-H), 7.323 (s, 4H, BiIm 4,4′-H) ppm; ms (*m/z*): 409.5 ($M+H^+$). Anal. Calcd for $C_{20}H_{24}N_8O_2$: C 58.81, H 5.92, N 27.43; found: C 58.63, H 5.95, N 27.23.

Cyclophane 5b. Off-white solid, yield 24.1%, mp 172–174°C. ^{1}H NMR ($CDCl_3$) δ 3.610–3.632 (t, 8H, OCH_2—-CH_2O), 3.683 (s, 8H, NCH_2—CH_2O), 3.735–3.757 (t, 8H, NCH_2), 7.030 (s, 4H, BiIm 5,5′-H), 7.149 (s, 4H, BiIm 4,4′-H) ppm; ms (*m/z*): 497.2 ($M+H^+$). Anal. Calcd for $C_{24}H_{32}N_8O_4$: C 58.05, H 6.50, N 22.57; found: C 57.87, 6.46, 22.28.

Cyclophane 6a. Off-white solid, yield 42.3%, mp 161–163°C. ^{1}H NMR ($CDCl_3$) δ: 3.797–3.821 (t, 8H, OCH_2), 4.189–4.212 (t, 8H, NCH_2), 7.405–7.948 (m, 16H, Ar—H) ppm; ms (*m/z*): 609.1 ($M+H^+$). Anal. Calcd for $C_{36}H_{32}N_8O_2$: C 71.04, H 5.30, N 18.41; found: C 70.87, H 5.28, N 18.23.

Cyclophane 6b. Off-white solid, yield 22.3%, mp 124–126°C. ^{1}H NMR ($CDCl_3$) δ: 3.424–3.474 (m, 8H, OCH_2—-CH_2O), 3.559–3.644 (m, 8H, NCH_2—CH_2O), 4.053–4.080 (t, 8H, NCH_2), 7.259–7.717 (m, 16H, Ar—H) ppm; ms (*m/z*): 697.0 ($M+H^+$). Anal. Calcd for $C_{40}H_{40}N_8O_2$: C 68.95, H 5.79, N 16.08; found: C 70.13, H 5.77, N 15.96.

UV titration. UV spectra were recorded on a TU-1810 UV-vis spectrophotometer at 25°C ± 0.1°C with a 1-cm quartz cell. A 3.0 mL of chloroform solution of host was put into the cell. After the cell temperature had become constant at 25°C with a thermostatic cell compartment, the solution of amino acid esters in chloroform was added in portions via microsyringe to the cell. The concentration of guest increased along with each addition, as far as the concentration of guest reached about 15-fold of the concentration of host. Different absorption spectra were obtained directly using the instrument according to its normal procedure. The absorption of the guest was cancelled by using the guest solutions of $[G]_0$ concentration for each titration as the reference solution. The whole volume of guest solution added to the cell did not exceed 100 μL to dispel the effect of volume change. For example, when the concentration of host **5a** was 6.8×10^{-5} mol dm^{-3}, its maximum absorption wavelength was at 242 nm, and the absorbance A_0 was 0.422. When the guest Val-OMe was portion-wise added to the cell to make its concentration of 10×10^{-5}, 20×10^{-5}, 30×10^{-5}, 40×10^{-5}, 50×10^{-5}, 60×10^{-5}, 70×10^{-5} mol dm^{-3}, respectively, the maximal absorption increased orderly and gave the corresponding ΔA ($A-A_0$) values 0.016, 0.029, 0.036, 0.040, 0.044, 0.049, 0.052. According to eq. (2), plots of calculated $[G]_0[H]_0/\Delta A$ values as a function of $[G]_0$ values gave an excellent linear relationship (Fig. 2). From Figure 2, we can obtain the association constant $K = 2655$ dm^3 mol^{-1}.

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Dual Behavior of 2-Tetralone: A New Approach for the Synthesis of 5-Aryl-7,8,13,14-tetrahydrodibenzo[*a*,*i*]phenanthridine

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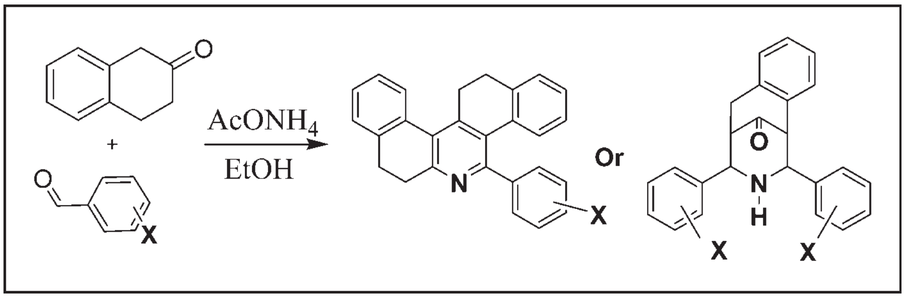

The one-pot reaction of 2-tetralone with ammonium acetate and substituted benzaldehydes affords in a good yield of 5-aryl-7,8,13,14-tetrahydrodibenzo[*a*,*i*]phenanthridine or 2,4-diaryl-6,7-benzo-3-azabicyclo[3.3.1]nonan-9-one. The course of the reaction seems to be dictated by the position of the substituents present on the benzaldehyde ring.

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INTRODUCTION

Phenanthridines, an important class of heterocyclic compounds in medicinal chemistry, are attractive synthetic targets due to their widespread occurrence in nature and broad range of biological activities, including anti-tumor and anti-viral activities [1–7]. Phenanthridine derivatives exhibit interesting pharmacological properties related to the planarity of the system. Benzophenanthridines are reported as compounds with topoisomerase I-targeting activity and cytotoxicity [8].

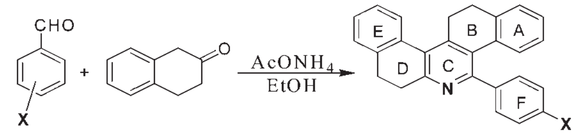
In addition, the high charge mobility of this heterocyclic system provides pronounced photoconducting, optoelectrical switching, and photovoltaic properties [9–11], which are key features in the field of dye lasers and electroluminescence [12,13]. Therefore, during the last few years, phenanthridines have gained much attention because of their promising applications in the development of optical materials, information recordings, such as, holography, lithographic plates for printing, and electric equipment [14].

The literature preparations of the phenanthridine ring system have disadvantages, such as, lengthy syntheses, low yields, and structurally complicated precursors [8,15–20]. Even a synthesis involving a few steps from simple precursors such as formaldehyde and 2-methylbenzonitrile affords benzo[c]phenanthridine in a 6% overall yield [15]. In this study, we found that one-step reaction of benzaldehyde or 4-substituted benzaldehydes, ammonium acetate, and 2-tetralone gave 5-aryl-7,8,13,14-tetrahydrodibenzo[*a*,*i*]phenanthridine (Scheme 1). On the other hand, the one-step reaction of 2-substituted benzaldehydes, ammonium acetate, and 2-tetralone gave 2,4-diaryl-6,7-benzo-3-azabicyclo[3.3.1]nonan-9-ones (Scheme 2).

In spite of their importance, only very few of them involve less than a few steps [16,20–22]. On the contrary, this study involves single step. Hence, the authors wish to explore a new and more versatile synthetic route for 5-aryl-7,8,13,14-tetrahydrodibenzo [*a*,*i*]phenanthridine.

The preparation of 5-phenyltetrahydrodibenzo[*a*,*i*]phenanthridine (4) and 2,4-diaryl-6,7-benzo-3-azabicyclo[3.3.1]nonan-9-one (5) was accomplished by the procedure reported by Noller and Baliah [23] through a simple three-compound reaction involving ammonium acetate (2), benzaldehyde (1), and 2-tetralone (3). We tried to carry out the Mannich reaction as reported in the article. However, we ended up with 5-aryl-7,8,13,14-tetrahydrodibenzo[*a*,*i*]phenanthridine in the case of parent benzaldehyde and para-substituted benzaldehydes. However, ortho-substituted benzaldehydes yielded 2,4-diaryl-6,7-benzo-3-azabicyclo[3.3.1]nonan-9-ones. The two reactions are not competing with each

Scheme 1

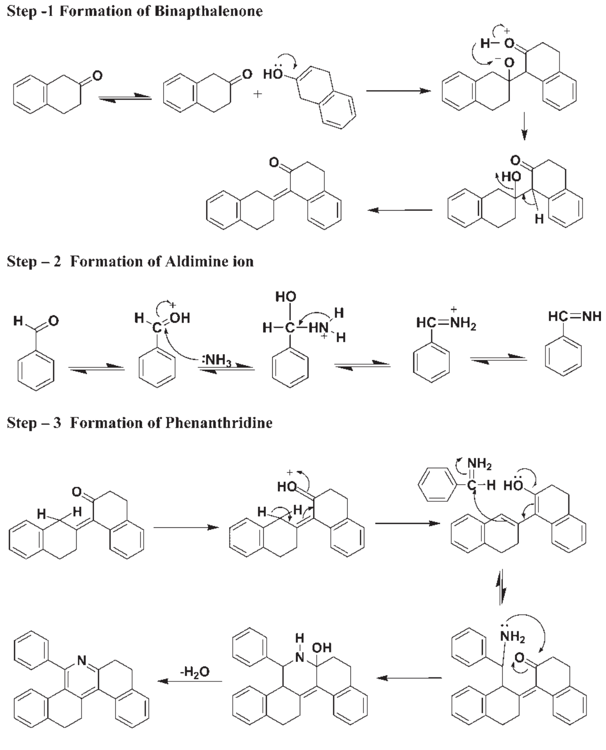


X = 1a, 1b, 1c
X = H, 4-Cl, 4-MeO

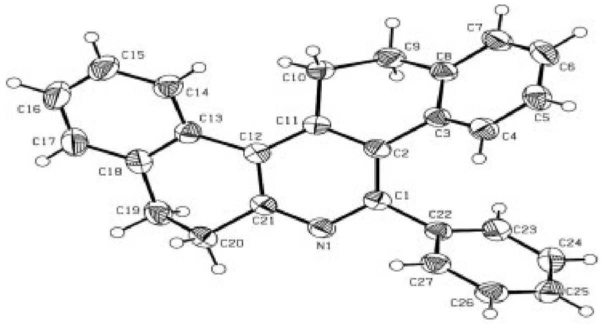
Compound - 4a, 4b, 4c
X = H, 4-Cl, 4-MeO

other. We are getting either phenanthridine or azabicyclo[3.3.1]nonan-9-one only. The product formation is exclusive. We are not getting the mixture of products. In Mannich reaction, the active methylene group in the 2-tetralone took part, whereas in the other reaction the enol form of 2-tetralone occurred. This reaction was found to be very easy and useful for synthesizing phenanthridine because other methods now being used are cumbersome and involve more steps (Table 1).

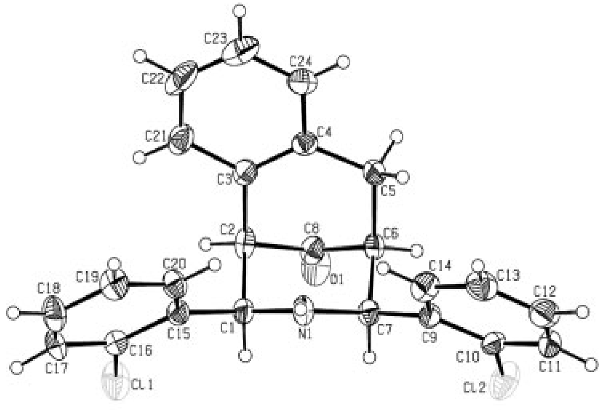
The mechanism for the formation of 2,4-diaryl-6,7-benzo-3-azabicyclo[3.3.1]nonan-9-one is already well documented [23]. We are proposing the following mechanism for the formation of phenanthridine derivative. The mechanism proposed is similar to the one reported for the reaction between tetralone and nitrile [20]. All the structures were confirmed by single crystal X-ray analysis.



The parent and para-substituted benzaldehydes give phenanthridine, and ortho-substituted benzaldehydes give azabicyclo[3.3.1]nonan-9-one. This is due to the steric hindrance in the ortho-substituted benzaldehydes and it is clearly shown in the mechanism. The aldimine formation in ortho-substituted benzaldehydes is impossible. Once it is able to form the aldimine then only the formation of phenanthridine is possible otherwise keto form will react with benzaldehyde and ammonium acetate to form azabicyclo[3.3.1]nonan-9-one.



Ortep diagram of compound 4a

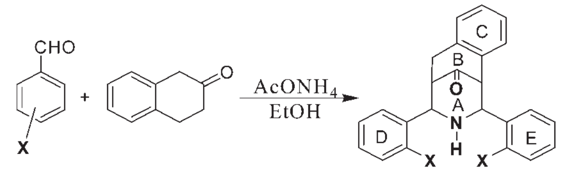


Ortep diagram of compound 5d

Even the structures are also confirmed by single crystal X-ray analysis.

In conclusion, the authors developed two short, distinct, and complementary methods for the synthesis of various 5-aryl-7,8,13,14-tetrahydrodibenzo[*a*,*i*]phenanthridine and 2,4-diaryl-6,7-benzo-3-azabicyclo[3.3.1]-nonan-9-one with excellent yield. We believe that the

Scheme 2



X = 1d, 1e
X = 2-Cl, 2-MeO

Compound -5d,5e
X = 2-Cl, 2-MeO

Table 1

Reaction of 2-tetralone with benzaldehydes.

Aldehyde	Product	Yield
Benzaldehyde (1a)	**4a**	86%
p-Chlorobenzaldehyde (1b)	**4b**	74%
p-Methoxybenzaldehyde (1c)	**4c**	76%
o-Chlorobenzaldehyde (1d)	**5d**	68%
o-Methoxybenzaldehyde (1e)	**5e**	65%

reported method provides a potential utility of chemistry in organic synthesis.

EXPERIMENTAL

General procedure. 0.2*M* of respective benzaldehyde was treated with 0.1*M* of 2-tetralone and 0.1*M* of ammonium acetate in 15 mL of ethanol. The mixture was gently warmed in a water bath until the color changed to orange and kept aside for overnight at room temperature. The completion of the reaction was identified with TLC. The solid obtained was separated and the crude compound was purified by silica gel column chromatography using hexane and ethyl acetate as elutant.

Spectral data

5-Phenyl-7,8,13,14-tetrahydrodibenzo[a,i]phenanthridine (4a). Crystal; mp 170°C; IR (KBr): 3057, 2833, 1606, 1549, 1425, 1396, 1245 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.76–3.20 (m, 8H), 7.00–7.53 (m, 13H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.79, 27.41, 29.53, 31.38,124.68, 125.60, 126.30, 126.92, 127.25, 127.64, 127.75, 128.33, 128.68, 129.62, 129.80, 130.58, 132.77, 133.04, 136.99, 138.68, 139.43, 139.67, 140.29, 142.06, 145.65, 153.95, 158.08.

5-(p-Chlorophenyl)-7,8,13,14-tetrahydrodibenzo[a,i]phenanthridine (4b). Crystal; mp 178°C; IR (KBr): 3032, 2833, 1605, 1549, 1425, 1358, 1245, 763 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.54 (m, 2H), 2.74–3.26 (m, 6H), 7.12–7.61 (m, 12H); MS (LC-MS): $m/z = 394$ (M^+).

5-(p-Methoxyphenyl)-7,8,13,14-tetrahydrodibenzo[a,i]phenanthridine (4c). Crystal; mp 174°C; IR (KBr) 3032, 2833, 1606, 1549, 1425, 1358, 1245 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.50–3.08 (m, 8H), 3.78 (s, 3H), 6.86–6.91 (m, 4H), 7.29–7.32 (m, 8H); MS (LGC-MS): $m/z = 390$ (M^+).

2,4-Di(o-chlorophenyl)-6,7-benzo-3-azabicyclo[3.3.1]nonan-9-one (5d). Crystal; mp 230°C; IR (KBr): 3309, 2846, 1711, 1423, 1243, 751 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.92–3.15 (m, 4H), 3.56 (s, 1H, NH), 4.59–4.62 (d, 1H), 5.73–5.76 (d, 1H), 6.74–7.78 (m, 12H).

2,4-Di(o-methoxyphenyl)-6,7-benzo-3-azabicyclo[3.3.1]nonan-9-one (5e). Crystal; mp 220°C; IR (KBr) 3313, 2832, 1715, 1491, 1243 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.48–2.97 (m, 4H), 3.48 (s, 1H, NH), 3.81–4.01 (s, 6H), 4.52–4.55 (d, 1H), 5.75 (d, 1H), 6.66–7.60 (m, 12H).

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One-Pot Synthesis of Polyfunctionalized Pyrans Catalyzed by Basic Ionic Liquid in Aqueous Media

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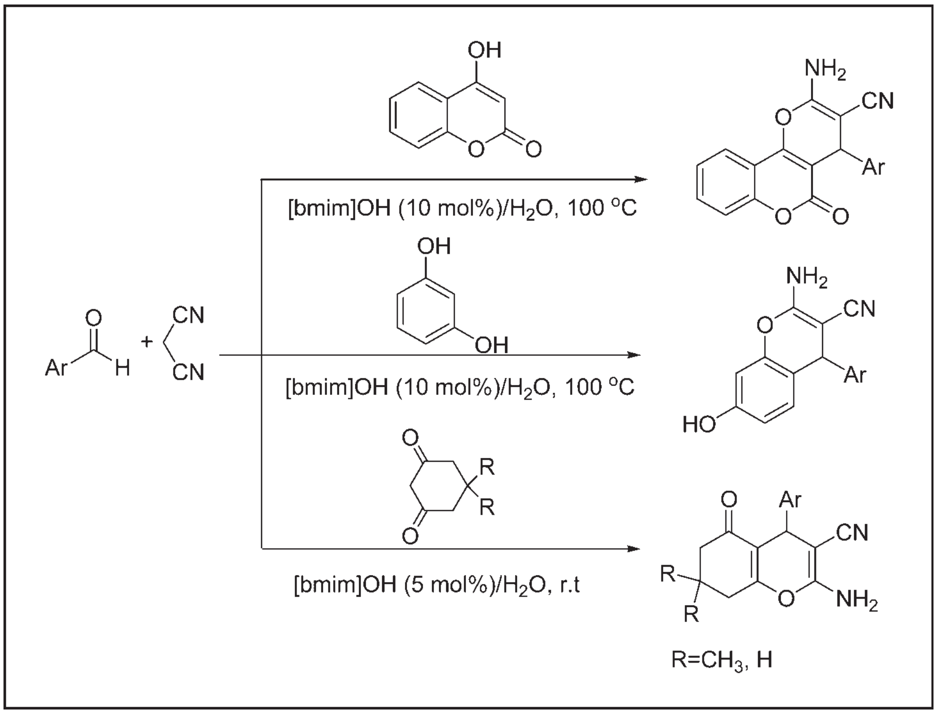

An efficient and convenient method for the synthesis of polyfunctionalized 4*H*-pyrans has been achieved through the one-pot condensation of aromatic aldehydes, malononitrile, and 4-hydroxycoumarin, phenols or active methylene carbonyl compounds such as 1, 3-cyclohexanedione and dimedone in the presence of 1-butyl-3-methyl imidazolium hydroxide ([bmim]OH) as catalyst in aqueous media. This method offers several advantages short reaction time, high yields, and simple procedure.

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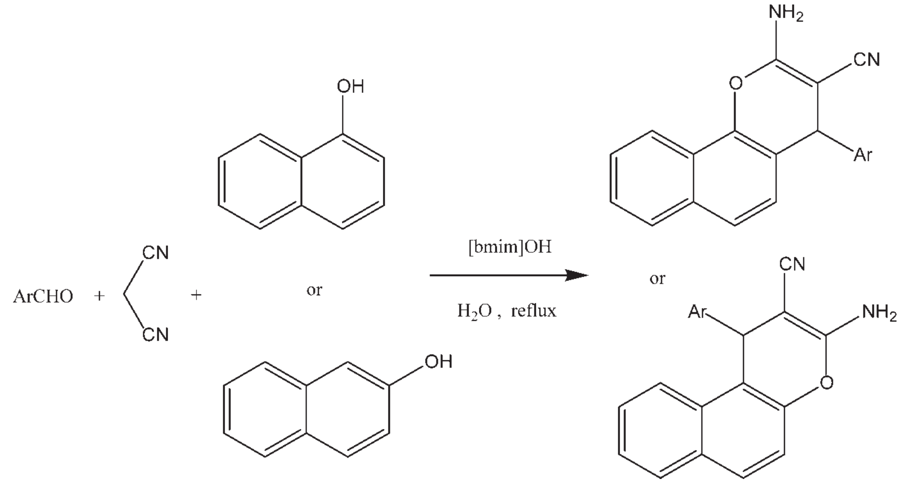
INTRODUCTION

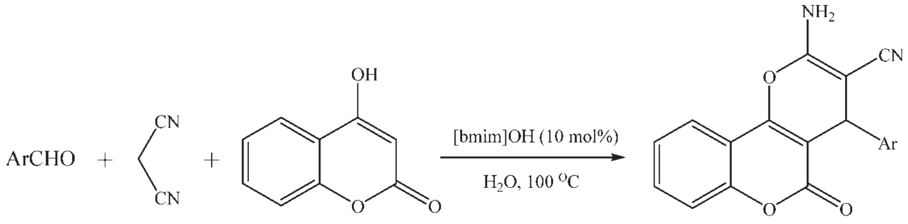
The 4*H*-pyrans and their derivatives have attracted considerable attention from organic and medicinal chemists due to their useful biological and pharmacological properties [1], such as spasmolytic, diuretic, anticoagulant, anticancer, and antianaphylactic activity [2]. Furthermore, those compounds can be used as pigments [3], as photoactive materials [4], and as potential biodegradable agrochemicals [5]. Thus, the synthesis of 4*H*-pyran derivatives currently is of much importance. Various methods have been reported for the synthesis of 4*H*-pyrans, including the reaction of aromatic aldehydes, malononitrile with naphthol for the synthesis 2-amino-2-chromenes [6], the condensation of aromatic aldehydes, malononitrile with 4-hydroxycoumarin [7], and the condensation of aromatic aldehydes, malononitrile with active methylene carbonyl compounds [8]. Those reactions have been reported in the presence of a catalyst, such as piperidine [9], KF-Alumina [10], phase-transfer catalyst [11], and $(NH_4)HPO_4$ [12]. Pyrans have also been synthesized under microwave and ultrasound irradiations [13]. These methods also suffer from some disadvantages such as long reaction times, low yields, the use of organic solvent, special apparatus, and tedious workup procedures. Thus, the need for the development of an efficient and facile method for the synthesis of 4*H*-pyran derivatives is in high demand.

Our recent interest has been in the development of new synthetic methods on using ionic liquids as reaction media and catalyst [14]. Herein, we would like to report a highly efficient, convenient, and facile method for the synthesis of 4*H*-pyrans in the presence of basic ionic liquid [bmim]OH as catalyst in aqueous medium.

Scheme 1. Synthesis of 2-amino-2-chromenes.



Scheme 2. Synthesis of 2-amino-4-aryl-3-cyano-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromenes (**4a-4l**).



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

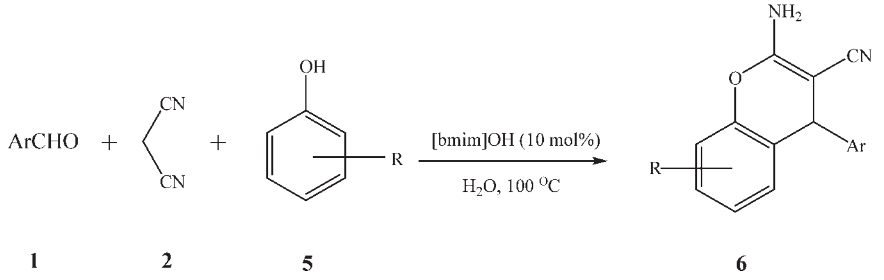
Table 1

Synthesis of **4a–4l** using [bmim]OH as catalyst in aqueous medium.[a]

Entry	Ar	Time (min)	Product	Yield (%)[b]	MP (°C)	
					Found	Reported
1	C_6H_5	8	**4a**	92	257–258	256–258[12a]
2	$2\text{-Cl-}C_6H_4$	15	**4b**	91	265–266	266–268[11b]
3	$4\text{-Cl-}C_6H_4$	5	**4c**	97	264–266	265–265[12a]
4	$2,4\text{-}Cl_2\text{-}C_6H_3$	15	**4d**	95	253–255	257–259[12a]
5	$4\text{-F-}C_6H_4$	5	**4e**	96	261–263	260–262[11b]
6	$4\text{-Br-}C_6H_4$	5	**4f**	93	255–257	256–258[10b]
7	$2\text{-}NO_2\text{-}C_6H_4$	6	**4g**	94	254–256	255–256[10b]
8	$3\text{-}NO_2\text{-}C_6H_4$	5	**4h**	93	258–260	262–264[12a]
9	$4\text{-}NO_2\text{-}C_6H_4$	5	**4i**	96	259–260	258–260[12a]
10	$4\text{-}CH_3\text{-}C_6H_4$	8	**4j**	90	258–260	259–261[10b]
11	$4\text{-}CH_3O\text{-}C_6H_4$	10	**4k**	89	240–242	240–244[12a]
12	$4\text{-OH-}C_6H_4$	30	**4l**	90	260–261	261–262[10b]

[a] Reaction conditions: aldehyde (5 mmol), malononitrile (5 mmol), 4-hydroxycoumarin (5 mmol), [bmim]OH (0.5 mmol), H_2O (2 mL), 100°C.
[b] Isolated yield.

Scheme 3. Synthesis of 2-amino-4-aryl-3-cyano-4*H*-chromenes (**6a-6e**).



RESULTS AND DISCUSSION

Very recently, we reported a simple and convenient method for the synthesis of 2-amino-2-chromenes by condensation of aromatic aldehydes, malononitrile with α- or β-naphthol using [bmim]OH as catalyst in aqueous medium (Scheme 1) [15]. This versatility of this ionic liquid encourages us to study its use in other organic reactions. We have now extended the use of this functionalized ionic liquid to catalyze the reaction of aromatic aldehydes, malononitrile with 4-hydroxycoumarin (Scheme 2). The synthesis of 2-amino-4-aryl-5-oxo-4*H*,5*H*-pyrano-[3,2-*c*]chromence-3-carbonitrile was achieved by the three-component condensation of an aromatic aldehyde, malononitrile with 4-hydroxycoumarin in the presence of 10 mol% [bmim]OH at 100°C. The results are summarized in Table 1. In all cases, the corresponding dihydropyrano[*c*]chromenes were obtained in good to excellent yields. However, when aldehydes with electron-withdrawing groups (such as nitro group and halide) are reactants, the reaction time is shorter than that with electron-donating groups (such as methoxy group and hydroxyl group).

Encouraged by these results, we replaced the substituted phenols **5** instead of 4-hydroxycoumarin **3** in the same conditions (Scheme 3). The results are summarized in Table 2. No significant formation of product (**6a**) was observed, when the reaction of benzaldehyde, malononitrile, and phenol was preceded in the same conditions, even prolonged reaction time to 24 hours. However, resorcinol is an activated phenol, when used in the reaction instead of phenol, the yields were promoted greatly with shorter reaction time, which indicated that resorcinol can be successfully used in this reaction.

The versatility of this ionic liquid encourages us to study its utility for one-pot synthesis of other heterocyclic compounds. The reaction of aromatic aldehyde, malononitrile, and active methylene carbonyl compounds for synthesis of 4*H*-benzo[*b*]pyrans has been reported. We then investigated the three-component condesation of aromatic aldehydes, malononitrile, and active methylene carbonyl compounds using [bmim]OH as a catalyst (Scheme 4). When 5 mol% [bmim]OH was used, the corresponding 4*H*-benzo[*b*]pyrans were obtained in good to excellent yields at room temperature, and the results are summarized in Table 3.

As shown in Table 3, the substituents of aromatic aldehydes affect the reaction times, and the yields of 4*H*-benzo[*b*]pyrans to a large extent. When aromatic aldehydes with electron-withdrawing groups (such as nitro group and halide) are reactants, the reaction time is shorter than that with electron-donating groups (such as methoxy group and hydroxyl group).

CONCLUSION

In summary, we have developed an efficient and general method for the synthesis of polyfunctionalized 4*H*-

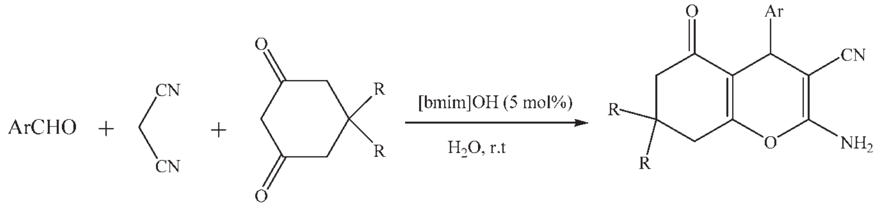
Table 2

Synthesis of **6a–6e** using [bmim]OH as catalyst in aqueous medium.[a]

Entry	Ar	R	Time (hr)	Product	Yield (%)[b]	Mp (°C)	
						Found	Reported
1	C_6H_5	H	2	**6a**	–		
2	C_6H_5	3-OH	2	**6b**	90	230–232	232–234[13a]
3	2-Cl-C_6H_4	3-OH	2	**6c**	88	95–96	94–95[13c]
4	4-Cl-C_6H_4	3-OH	2	**6d**	94	162–163	161–162[13c]
5	4-CH_3O-C_6H_4	3-OH	2	**6e**	90	112–113	112–114[13c]

[a] Reaction conditions: aldehyde (5 mmol), malononitrile (5 mmol), phenol (5 mmol), [bmim]OH (0.5 mmol), H_2O (2 mL), 100°C.
[b] Isolated yield.

Scheme 4. Synthesis of 4*H*-benzo[*b*]pyrans (**8a-8z**).



R=CH_3, H

1 **2** **7** **8**

pyrans via [bmim]OH-catalyzed the one-pot, three-component reaction of aromatic aldehyde, malononitrile, and 4-hydroxycoumarin or active methylene carbonyl compounds. The attractive features of this protocol are simple procedure, short reaction time, excellent yields, mild conditions, and the easy workup procedure. In addition, water was chosen as a green solvent.

EXPERIMENTAL

General. Melting points were determined on an X6-data microscopic melting points apparatus and were uncorrected. Infrared (IR) spectra were recorded on a BRUKER VECTER 22. ^{1}H NMR spectra were obtained from solution $CDCl_3$ or DMSO-d_6 with TMS as internal standard using a BRUKER DRX-500 (500 MHz) spectrometer. Mass spectra were obtained with an automated Finnigan Trace Ultra-Trace DSQ GC/MS spectrometer.

The synthesis of this task-specific ionic liquid has been carried out from a similar method in the literature [16]. The ionic liquid was formed quantitatively and in high purity as assessed by ^{1}H NMR. All other chemicals (AR grade) were commercially available and used without further purification.

General procedure for the synthesis of 4a–4l and 6a–6e. The mixture of the aromatic aldehyde **1** (5 mmol), malononitrile **2** (5 mmol), phenol **3** or **5** (5 mmol), [bmim]OH (0.5

Table 3

Synthesis of 4*H*-benzo[*b*]pyrans catalyzed by [bmim]OH in aqueous media.[a]

Entry	Ar	R	Time (min)	Product	Yield (%)[b]	Mp (°C) Found	Mp (°C) Reported
1	C_6H_5	CH_3	10	**8a**	92	223–224	224[8b]
2	2-Cl-C_6H_4	CH_3	12	**8b**	90	211–212	214–215[8e]
3	4-Cl-C_6H_4	CH_3	5	**8c**	94	208–209	207–209[8b]
4	2,4-Cl_2-C_6H_3	CH_3	10	**8d**	90	192–193	192–194[8d]
5	4-F-C_6H_4	CH_3	5	**8e**	93	190–191	192–194[8a]
6	2-NO_2-C_6H_4	CH_3	15	**8f**	91	223–224	222–223[8d]
7	3-NO_2-C_6H_4	CH_3	10	**8g**	92	208–209	208–210[8b]
8	4-NO_2-C_6H_4	CH_3	5	**8h**	96	179–180	179[8b]
9	4-CH_3-C_6H_4	CH_3	20	**8i**	93	217–218	218[8c]
10	4-CH_3O-C_6H_4	CH_3	20	**8j**	87	198–200	201[8b]
11	4-OH-C_6H_4	CH_3	60	**4k**	85	204–205	205–206[8e]
12	4-NMe_2-C_6H_4	CH_3	20	**8l**	86	201–202	198–200[8b]
13	2-furyl	CH_3	20	**8m**	91	215–216	218–220[8c]
14	C_6H_5	H	15	**8n**	90	218–220	
15	2-Cl-C_6H_4	H	15	**8o**	91	212–214	213–215[8a]
16	4-Cl-C_6H_4	H	6	**8p**	93	227–228	226–228[8e]
17	2,4-Cl_2-C_6H_4	H	10	**8q**	90	224–225	225–227[8a]
18	4-F-C_6H_4	H	8	**8r**	92	213–215	
19	2-NO_2-C_6H_4	H	10	**8s**	91	196–198	
20	3-NO_2-C_6H_4	H	8	**8t**	92	201–202	198–200[13b]
21	4-NO_2-C_6H_4	H	6	**8u**	95	235–236	235–236[8b]
22	4-CH_3-C_6H_4	H	10	**8v**	90	214–216	
23	4-CH_3O-C_6H_4	H	30	**8w**	90	192–193	193–195[8a]
24	4-OH-C_6H_4	H	60	**8x**	91	234–236	
25	4-NMe_2-C_6H_4	H	40	**8y**	85	168–170	
26	2-furyl	H	20	**8z**	92	222–224	

[a] Reaction conditions: aldehyde (5 mmol), malononitrile (5 mmol), 5, 5-dimethyl-1, 3-cyclohexanedione or 1, 3-cyclohexanedione (5 mmol), [bmim]OH (0.25 mmol), H_2O (2 mL), room temperature.

[b] Isolated yield.

mmol) in H_2O (2 mL) was stirred at 100°C for the appropriate time (monitored by thin-layer chromatography [TLC]). After completion of the reaction, the solid compound obtained was filtered off and washed with H_2O (10 mL). The crude products were purified by recrystallization from EtOH (95%).

Data of selected compounds are given below:

Compound **4a**: IR (KBr): ν_{max} = 3379, 3290, 3179, 2196, 1712, 1671, 1603 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 4.67 (1 H, s, H-4), 4.80 (2 H, s, NH_2), 7.35–7.49 (6 H, m, ArH), 7.61–7.64 (1 H, t, ArH), 7.82–7.84 (1 H, d, ArH) ppm. ESI^+-MS: *m/z* (%) 316.2 (M^+, 23), 239.1 (100).

Compound **4c**: IR (KBr): ν_{max} = 3382, 3315, 3189, 2194, 1715, 1673, 1606 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 4.52 (1 H, s, H-4), 7.32 (2 H, d, *J* = 8.2 Hz, ArH), 7.36 (2 H, s, NH_2), 7.38 (2 H, brs, ArH), 7.42 (1 H, d, *J* = 8.2 Hz, ArH), 7.50 (1 H, t, *J* = 7.6 Hz, ArH), 7.70 (1 H, t, *J* = 7.8 Hz, ArH), 7.93 (1 H, t, *J* = 7.6 Hz, ArH) ppm.

Compound **6b**: IR (KBr): ν_{max} = 3429, 3211, 2191, 1651, 1506, 1458 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 4.62 (1 H, s, H-4), 6.41 (1 H, s, ArH), 6.48 (1 H, d, *J* = 8.3 Hz, ArH), 6.80 (1 H, d, *J* = 9.2 Hz, ArH), 6.85 (2 H, s, NH_2), 7.16–7.22 (3 H, m, ArH), 7.31 (2 H, t, *J* = 7.1 Hz, ArH), 9.68 (1 H, s, ArOH) ppm. ESI^--MS: *m/z* (%) 263.1 (M^-, 20), 218.0 (85), 197.0 (100).

General procedure for the synthesis of 4H-benzo[b] pyrans (8a–8z). The mixture of the aromatic aldehyde **1** (5 mmol), malononitrile **2** (5 mmol), 5, 5-dimethyl-1, 3-cyclohexanedione, or 1, 3-cyclohexanedione **7** (5 mmol), [bmim]OH (0.25 mmol) in H_2O (2 mL) was stirred at room temperature for the appropriate time (monitored by TLC). After completion of the reaction, the solid compound obtained was filtered off and washed with H_2O (10 mL). The crude products were purified by recrystalization from EtOH (95%).

Data of selected compounds are given below:

Compound **8a**: IR (KBr): ν_{max} = 3394, 3251, 2965, 2197, 1670, 1603 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.04 (3 H, s, CH_3), 1.11 (3 H, s, CH_3), 2.18–2.26 (2H, q, CH_2), 2.42–2.49 (2 H, m, CH_2), 4.40 (1 H, s, H-4), 4.52 (2 H, s, NH_2), 7.18–7.30 (5 H, m, ArH) ppm. ESI^--MS: *m/z* (%) 293.2 (M^+, 38), 65.1 (100).

Compound **8h**: IR (KBr): ν_{max} = 3451, 3321, 3209, 2193, 1655, 1599 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.05 (3 H, s, CH_3), 1.14 (3 H, s, CH_3), 2.12–2.26 (2 H, q, CH_2), 2.50 (2 H, s, CH_2), 4.53 (1 H, s, H-4), 4.68 (2 H, s, NH_2), 7.43 (2 H, d, *J* = 8.5 Hz, ArH), 8.18 (2 H, d, *J* = 8.5 Hz, ArH) ppm.

Compound **8i**: IR (KBr): ν_{max} = 3424, 3324, 2958, 2921, 2191, 1676, 1511 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.04 (3 H, s, CH_3), 1.11 (3 H, s, CH_3), 2.18–2.26 (2 H, q, CH_2), 2.29 (3 H, s, CH_3), 2.45 (2 H, s, CH_2), 4.36 (1 H, s, H-4), 4.50 (2 H, s, NH_2), 7.08–7.12 (4 H, m, ArH) ppm.

Compound **8n**: IR (KBr): ν_{max} = 3326, 3172, 2926, 2193, 1685, 1650 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.99–2.08 (2 H, m, CH_2), 2.34–2.39 (2 H, m, CH_2), 2.57–2.65 (2H, m, CH_2), 4.43(1 H, s, H-4), 4.52 (2 H, s, NH_2), 7.20–7.31 (5 H, m, ArH) ppm. ESI^--MS: *m/z* (%) 265.1 (M^+, 10), 65.1 (100).

Compound **8r**: IR (KBr): ν_{max} = 3412, 3334, 3257, 2928, 2192, 1651, 1603, 1503 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.02–2.08 (2 H, m, CH_2), 2.36–2.41 (2 H, m, CH_2), 2.59–2.64 (2H, m, CH_2), 4.44 (1 H, s, H-4), 4.66 (2 H, s, NH_2), 6.98–7.01 (2 H, m, ArH), 7.22–7.25 (2 H, m, ArH) ppm. ESI^--MS: *m/z* (%) 283.1 (M^+, 10), 65.1 (100).

Compound **8s**: IR (KBr): ν_{max} = 3415, 3337, 3250, 3139, 2954, 2189, 1669, 1597 cm^{-1}. ^1H NMR($CDCl_3$): δ = 1.94–2.06 (2 H, m, CH_2), 2.29–2.32 (2 H, m, CH_2), 2.57–2.61 (2H, m, CH_2), 4.68 (1 H, s, H-4), 5.17 (2 H, s, NH_2), 7.32–7.35 (2 H, t, ArH), 7.51–7.54 (1 H, t, ArH), 7.77 (1 H, d, *J* = 8.0 Hz, ArH) ppm.

Compound **8v**: IR (KBr): ν_{max} = 3406, 3330, 3257, 3210, 2921, 2196, 1655, 1607 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.01–2.08 (2 H, m, CH_2), 2.32 (3 H, s, CH_3), 2.36–2.40 (2 H, m, CH_2), 2.58–2.66 (2H, m, CH_2), 4.42 (1 H, s, H-4), 4.52 (2 H, s, NH_2), 7.11 (2 H, d, *J* = 7.7 Hz, ArH), 7.15 (2 H, d, *J* = 7.7 Hz, ArH) ppm. ESI^--MS: *m/z* (%) 279.0 (M^+, 10), 65.1 (100).

Compound **8x**: IR (KBr): ν_{max} = 3740, 3518, 3378, 3317, 3199, 2893, 2817, 2199, 1672, 1643, 1600 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 1.87–1.97 (2 H, m, CH_2), 2.22–2.33 (2 H, m, CH_2), 2.51–2.63 (2H, m, CH_2), 4.09 (1 H, s, H-4), 6.65–6.67 (2 H, d, ArH), 6.89 (2 H, s, NH_2),6.94–6.95 (2 H, d, ArH), 9.22 (1 H, s, OH) ppm.

Compound **8y**: IR (KBr): ν_{max} = 3741, 3440, 3446, 3317, 3178, 2894, 2201, 1683, 1649, 1611, 1560 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.01–2.07 (2 H, m, CH_2), 2.35–2.40 (2 H, m, CH_2), 2.57–2.62 (2H, m, CH_2), 3.16 (6 H, s, $N(CH_3)_2$), 4.38 (1 H, s, H-4), 4.51 (2 H, s, NH_2), 6.70–6.72 (2 H, d, ArH), 7.80–7.82 (2 H, d, ArH) ppm.

Compound **8z**: IR (KBr): ν_{max} = 3397, 3322, 3254, 2961, 2188, 1651, 1507 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.05–2.10 (2 H, m, CH_2), 2.39–2.48 (2 H, m, CH_2), 2.57–2.66 (2H, m, CH_2), 4.57 (2 H, s, NH_2), 4.62 (1 H, s, H-4), 6.21 (1 H, m, ArH), 6.30 (1 H, m, ArH), 7.23 (1 H, m, ArH) ppm.

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Synthesis of 2-Amino-4-hydroxyl-6-hydroxymethyl-5,6,7,8-tetrahydropyrido[3,2-*d*]pyrimidine from 2-Amino-4-hydroxyl-6-methylpyrimidine

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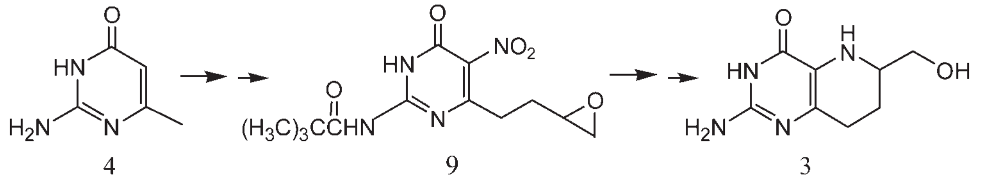

The synthesis of 2-amino-4-hydroxyl-6-hydroxymethyl-5,6,7,8-tetrahydropyrido[3,2-d]pyrimidine **3** is described from 2-amino-6-methyluracil **4** through the crucial step of 2-pivaloyl protecting and cyclization. The assignment of the structure of **3** was performed by its spectral data, the ^{1}H NMR, ^{13}C NMR, gHMQC, and HRMS spectra.

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INTRODUCTION

The requirement for folic acid in the metabolism of one carbon units is well established [1]. The coenzyme forms are actually their reduced products, mostly 5,6,7,8-tetrahydro derivatives, whose nitrogen atom at position 5 is reactive site of those molecules in C_1-unit metabolism [2]. The inhibitors of these enzymes will cause a deficiency of tetrahydrofolate (Fig. 1) cofactors, which will result in blocks in the synthesis of pyrimidine, purines, and protein. Consequently, these blocks will affect both DNA synthesis and cell division. Thus, the enzymes in folate cycle have been recognized as an attractive target for cancer chemotherapy [3,4].

RESULTS AND DISCUSSION

As part of a program focused on the design and synthesis of inhibitors of methionine synthase [5], access to 2-amino-4-hydroxyl-6-hydroxymethyl-5,6,7,8-tetrahydropyrido[3,2-d]pyrimidine (**3**) was required as the intermediate of the preparation of 8-deaza 5,6,7,8-tetrahydrofolic acid (**2**) and their derivatives. Although the structure of **3** is not complicated, the direct synthesis of the 8-deaza-5,6,7,8-tetrahydropterdine and derivatives has not been reported. Limited reports describe the synthesis of N^5-substituted derivatives of **2** from a hydrogenation of 8-deazafolic acid (**1**) [6–8]; however, the yields are quite low. In this article, we report a successful synthesis of the 6-substituted 8-deazatetrahydropteridine starting from commercially available 2-amino-6-methyluracil.

Initial attempts to get access to the target compound **3** using 2-acetamide-5-nitro-6-methyluracil (**6**) were investigated. 2-Amino-5-nitro-6-methylpyrimidin-4-one (**5**) was prepared in 91% yield by reaction of 2-amino-6-methyluracil (**4**) with HNO_3-P_2O_5 under 0°C (Scheme 1) [9]. Compound **5** was reacted with Ac_2O to give the corresponding 2-acetamide (**6**). Attempted the transformation of 2-acetamide-5-nitro-6-methyluracil (**6**) into **7** expecting the successive cyclization of the resulting adduct by nucleophilic attack of the 5-amino group obtained from 5-nitro group. However, the reactions of **6** with 3-chloro-1,2-epoxypropane or 3-bromo-1,2-epoxypropane in different base conditions failed to yield any product **7**, a large percent of starting material (**5**) being recovered. The failure reason could be less stable acetyl group, and the pivaloyl group was selected to improve the stability of the protect group at 2-position.

The successful synthesis route of **3** using the more stable pivaloyl group was shown in Scheme 2. The 2-amino-5-nitro-6-methyluracil (**5**) was pivaloylated by pivaloyl chloride in acetonitrile or pyridine to give the corresponding 2-pivaloylamide (**8**) [10], which was then successfully epoxyalkylated in 6 position with 3-chloro-

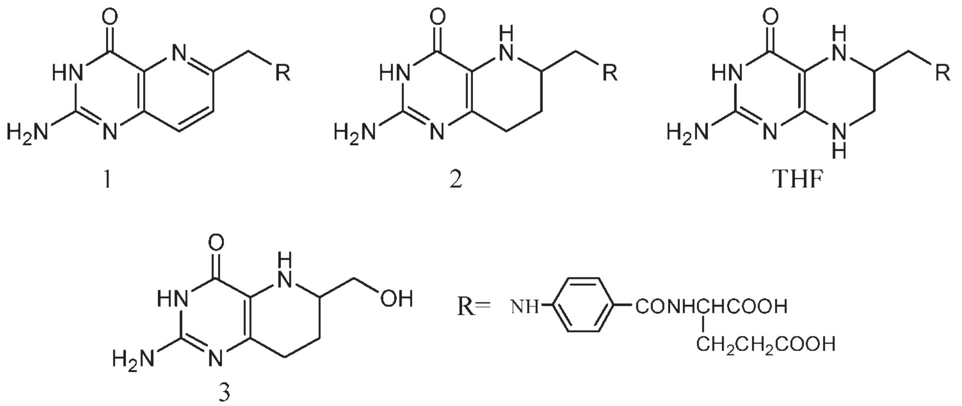


Figure 1. Structures of tetrahydrofolate (THF), compounds **1**, **2**, and **3**.

1,2-epoxypropane and KI in ethanolic sodium ethoxide to form the key intermediate **9** [11]. 2-Pivaloylamino-5-nitro-6-(3,4-epoxybutyl)uracil (**9**) was reduced by sodium dithionite under refluxing for 7 h to afford 2,5-diamino-6-(3,4-epoxybutyl)uracil (**10**). The next crucial step was the cyclization of **10** to give compound **3**. This was carried out by treatment of **10** with BF_3-etherate in dichloromethane to give ca. 1:1(high performance liquid chromatography) mixture R and S isomer of 2-amino-4-hydroxyl-6-hydroxymethyl-5,6,7,8-tetrahydropyrido[3,2-*d*] pyrimidine (**3**) in 37% yield. The structure of product was confirmed by its spectral data, the ^1H NMR, ^{13}C NMR, gHMQC, and HRMS spectra.

CONCLUSION

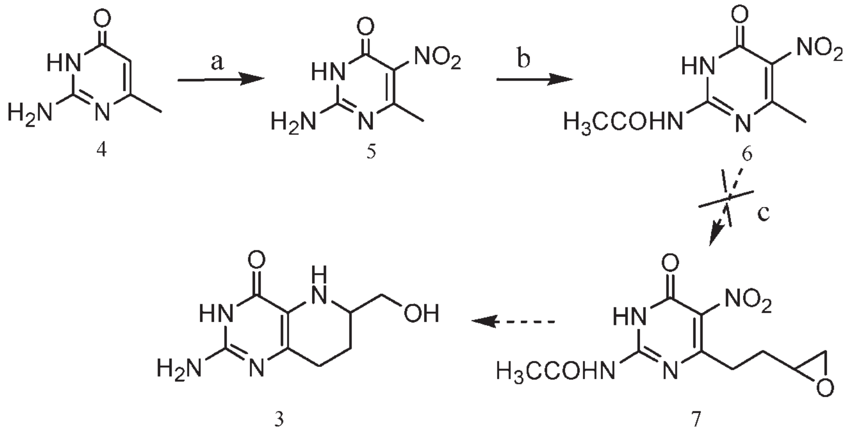
In conclusion, we have developed a new and general approach to the synthesis of 2-amino-4-hydroxyl-6-hydroxymethyl-5,6,7,8-tetrahydropyrido[3,2-*d*]pyrimidine, which is an interesting biological model and synthetic precursor used in synthesis of the modified tetrahydrofolic acid derivatives. The procedure described in this article should be a convenient means for the preparation of such analogues due to its simplicity.

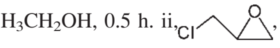
EXPERIMENTAL

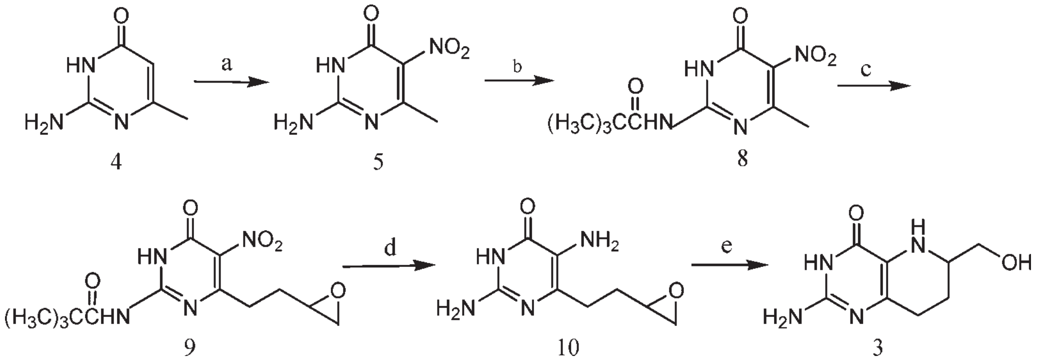
Melting points (uncorrected) were determined with an X_4-type apparatus. ^1H and ^{13}C NMR spectra were recorded on JNM-AL-300 or a varian INOVA-500 spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a VG-ZAB-HS spectrometry. Infrared spectra were recorded with Avatar 360 FT-IR and reported in cm^{-1}. Silica gel (0.40–0.64 mm) was used for column chromatography.

2-Amino-5-nitro-6-methylpyrimidin-4-one (5). To a suspension of fuming nitric acid (6.5 mL, 15.5 mmoles) and P_2O_5 (2.2 g, 15.5 mmoles) 2-amino-6-methylpyrimidin-4-one (1.25g, 10 mmoles) was added at −5 to 0°C. The reaction mixture was stirred for 4 h and poured into ice water (10 mL). The resulting solid was filtered and recrystallized from ethanol to give 2-amino-5-nitro-6-methylpyrimidin-4-one as light yellow crystal (1.55 g, 91%), mp 250°C (dec). ^1H nmr (300 MHz, DMSO-d_6): δ 2.29 (s, 3H), 11.78 (s, 2H), 11.81 (s, 1H); ^{13}C nmr (75 MHz, DMSO-d_6): $\delta = 16.7$, 127.2, 149.1, 154.2, 156.4; ms: m/z 170.

Scheme 1. Reagents and conditions: a, HNO_3, P_2O_5, −5 to 0°C, 4 h; b, Ac_2O, 80 to 90°C, 5 h; c: i, NaOEt, EtOH. ii, 3-bromo-1,2-epoxypropane.



Scheme 2. Reagents and conditions: a, HNO_3, P_2O_5, −5 to 0°C, 4 h; b, $(CH_3)_3COCl$, acetonitrile/pyridine, 80 to 90°C, 4 h; c: i, CH_3CH_2ONa, CH_3CH_2OH, 0.5 h. ii, , KI, DMF, 80 to 90°C, 3 h; d, $Na_2S_2O_4$, CH_3CH_2OH, 80°C, 7 h; e, BF_3-etherate, CH_2Cl_2, room temperature, 10 h.



2-Acetamide-5-nitro-6-methylpyrimidin-4-one (6). 2-Amino-5-nitro-6-methyl pyrimidin-4-one (2.0 g, 11.8 mmoles) was added to acetic anhydride (15 mL) and refluxed for 5 h. The reaction mixture was cooled to 0°C. The resulting solid was filtered and washed with ethyl acetate and petrol to give the product **6** as a light yellow (2.0 g, 80%), mp > 250°C (dec). ^{1}H nmr (500 MHz, DMSO-d_6): δ 2.19 (s, 3H), 2.33 (s, 3H), 12.10–12.30 (m, 2H); ^{13}C nmr (125 MHz, DMSO-d_6): δ 20.9, 23.9, 133.4, 150.5, 153.1, 161.5, 174.2; ms: m/z 213.0292.

2-Pivaloylamino-5-nitro-6-methyluracil (8). A mixture of 1.5 g (8.8 mmoles) of **5** and 3.8 mL (30.8 mmoles) of pivaloyl chloride in acetonitrile or pyrimidine (20 mL, v/v: 5/2) was stirred and refluxed for 4 h. The solution was evaporated to dryness, and the residue was recrystallized in 10% ammonia in water to give 1.4 g (63%) of **8**. mp 211–214°C. ^{1}H nmr (300 MHz, DMSO-d_6): δ 1.22 (s, 9H), 2.29 (s, 3H), 10.0 (br, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.7, 26.1, 27.0, 133.4, 151.9, 167.4, 181.5; esi-ms: $[M+H]^+$ *m/z* 254.9.

2-Pivaloylamino-5-nitro-6-(3,4-epoxybutyl)uracil (9). To a solution of 0.83 g (3.27 mmoles) of **8** in 7 mL of dry ethanol, 3.5 mL of ethanolic sodium ethoxide was added (1 N), and the mixture was reluxed for 0.5 h. The solvent was removed in vacuo, and the residue was added to 6 mL of dry *N*,*N*-dimethyformamide (DMF). To the solution, 0.35 ml (4.48 mmoles) of 3-chloro-1,2-epoxypropane and 0.22 g (1.33 mmoles) of KI was added. The resulting solution was refluxed for 3 h. Then the solvent was removed in vacuo, and the residue was suspended in water and extracted with ethyl acetate. The organic layers were pooled, dried over anhydrous sodium sulfate, and concentrated to a small volume. The residue was purified by preparative thin layer chromatograph (silica gel). Elution with $CHCl_3$—CH_3OH (9:1) gave pure **9** (0.25 g, 25%) as yellow oil. ^{1}H nmr (300 MHz, $CDCl_3$): δ 1.26 (s, 9H), 2.27–2.44 (m, 4H), 3.41–3.53, 3.66–3.81 (m, 1H), 4.10–4.26 (m, 1H), 4.49–4.56 (m, 1H); esi-tof-ms: $[M+H]^+$ *m/z* 311.0.

2,5-Diamino-6-(3,4-epoxybutyl)uracil (10). To the solution of 0.6 g (1.94 mmoles) of **9** in 30 ml of 95% ethanol, 3.36 g (19.3 mmoles) of sodium dithionite was added. The mixture was heated at 80°C for 7 h and filtered after cooling to room temperature. The filtrate was evaporated to dryness under reduced pressure, and the residue was purified by preparative thin layer chromatograph (silica gel). Elution with $CHCl_3$—CH_3OH (20:1) gave pure **10** (0.17 g, 45%) as oil. ^{1}H nmr (300 MHz, $CDCl_3$): δ 2.17–2.34 (m, 2H), 3.17, 3.21 (d, 2H), 3.37, 3.40 (d, 1H), 3.49, 3.53 (d,1 H), 4.09–4.17 (m, 1H), 4.25 (s, 2H), 5.45 (s, 2H), 8.88 (s, 1H); esi-tof-ms: $[M+H]^+$ *m/z* 197.1.

2-Amino-4-hydroxyl-6-hydroxymethyl-5,6,7,8-tetrahydropyrido[3,2-*d*]pyrimidine (3). To a solution of 0.24 g (0.86 mmoles) of **10** in 20 mL of dry dichloromethane in a dry and nitrogen flushed flask, the BF_3-etherate (0.11 mL, 0.86 mmoles) was added dropwise. The mixture was stirred for 10 h at room temperature in the dark, quenched by adding water, and extracted with dichloromethane. The extracts were pooled and dried over anhydrous $MgSO_4$. After the evaporation of solvent to a small volume, the residue was purified by column chromatography (silica gel) to give pure **3** (0.089 g, 37%) as yellow oil. ^{1}H nmr (300 MHz, DMSO): δ 1.09–1.13 (m, 2H), 3.07–3.29 (m, 2H), 3.52, 3.56 (d, 1H, J = 14 Hz), 4.00, 4.04 (d, 1H, J = 14 Hz), 4.12 (br, 1H); ^{13}C nmr (75 MHz, DMSO): δ 22.4, 44.7, 45.1, 57.2, 126.9, 152.1, 155.0, 162.2; esi-hrms: $[M+H]^+$ *m/z* 197.10251 (error (ppm): −4.02).

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Access to Indoles *via* Diels-Alder Reactions of 2-Vinylpyrroles with Maleimides

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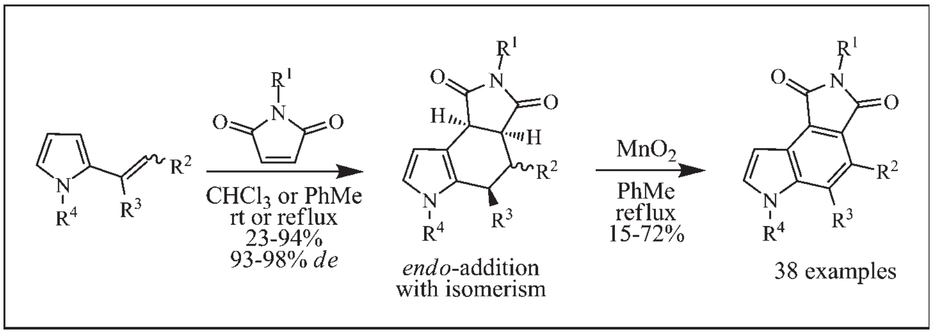

Variously substituted 2-vinylpyrroles underwent an *endo*-addition [4+2] cycloaddition reaction with maleimides followed by a spontaneous highly diastereoselective (93–98% *de*) isomerization to give tetrahydroindoles in moderate to excellent yield. Treatment with activated MnO_2 in refluxing toluene provided the corresponding indoles in moderate to good yield. This highly convergent methodology for formation of indoles is versatile and the starting materials are conveniently prepared.

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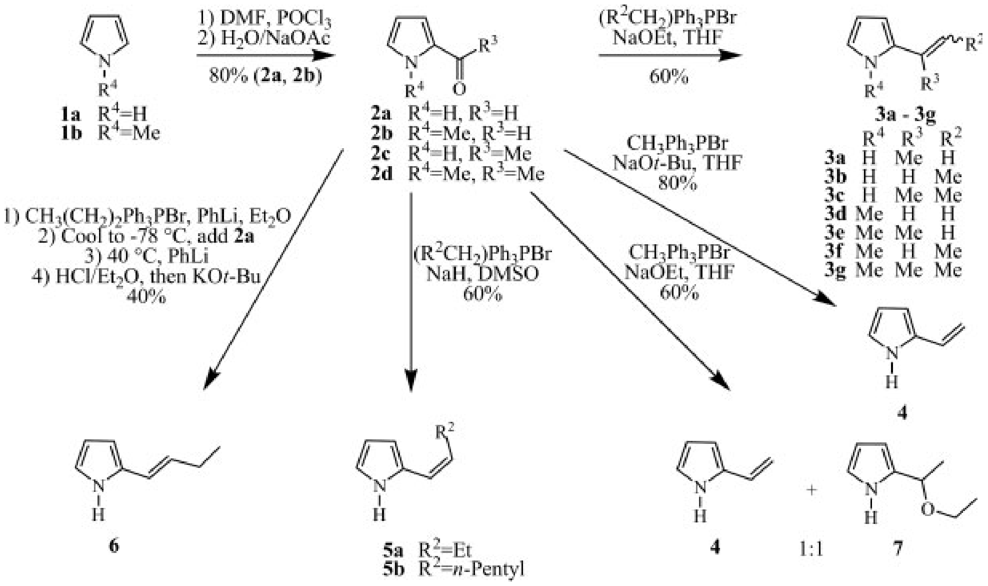
INTRODUCTION

The formation of indole continues to attract much study [1] because of its frequent occurrence in nature and its biological activity in both natural [2] and synthetic [3] products. We have reported that 3-vinylindoles are generated from condensation of indole and ketones, which then undergo an *in situ* Diels-Alder reaction with maleimides to form tetrahydrocarbazoles [4]. We recently reported the analogous work in which pyrroles are condensed with cyclic ketones to give 2-vinylpyrroles that also undergo *in situ* Diels-Alder reactions with maleimides to give the corresponding tetrahydroindoles, many of which exhibited high levels of *in vitro* activity against a variety of human cancer cell lines [5]. Although the *in situ* Diels-Alder approach toward indoles is advantageous with its one-pot method, it is somewhat limited in that acidic conditions are required to catalyze the condensation, and pyrroles are well known to form polymers under acidic conditions [6]. Indeed, we battled with the formation of polymeric material when using vinylpyrroles for *in situ* Diels-Alder reactions and found that to circumvent the problem, the use of 5-alkyl-substituted pyrroles was essential.

These results inspired us to explore the Diels-Alder chemistry of separately prepared 2-vinylpyrroles. Preparing the vinylpyrrole in a separate step *via* methods not using acidic conditions has the advantage of allowing the use of 5-unsubstituted 2-vinylpyrroles in Diels-Alder reactions. In addition, we were interested in effecting aromatization of the resulting tetrahydroindoles to give indoles. Some studies have been conducted on this route toward indoles using as the dienophiles carboxyl-substituted acetylenes [7,8], several acyclic electron-deficient alkenes [8,9], maleic anhydride and/or *N*-phenylmaleimide with *N*-benzenesulfonyl-2-vinylpyrrole [9,10] and methyl 3-nitroacrylate with *N*-*p*-toluenesulfonyl-2-vinylpyrroles [11] (neither of which was taken through to the aromatic indole), tetrachloro- or tetrabromocyclopropene with *N*-*p*-toluenesulfonyl-2-vinylpyrrole [12], *N*-phenylmaleimide with *N*-methyl- and *N*-propanoyloxy-2-vinylpyrrole [9], *N*-H-maleimide with 3-(*N*-alkyl-2-pyrrolyl) acrylates [13] and *N*-alkyl-2-styrylpyrroles [13,14], and one report using various maleimides with both *N*-H and *N*-alkyl-2-vinylpyrroles [15]. Several of these studies report biological activity from this class of compounds, particularly anticancer activity [13–15]. To our knowledge, no prior broad study of the efficacy of the synthesis of indoles *via* Diels-Alder reactions of 5-unsubstituted 2-vinylpyrroles with *N*-substituted maleimides has been reported. In most of the earlier studies, only *N*-alkyl-substituted pyrroles were studied, presumably due to both the higher reactivity of *N*-H pyrroles and the formation of Michael-addition products between the adduct

Scheme 1. Synthesis of 2-vinylpyrroles.



and dienophile when certain *N*-H-2-vinylpyrroles are used in Diels-Alder reactions, reported here for the first time. None of the earlier studies has characterized the diastereoselective isomerism of the adduct, potentially valuable for synthetic applications. We report here the first demonstration of the use of chiral maleimides in Diels-Alder reactions with 2-vinylpyrroles.

Herein, we report 38 examples where indoles are conveniently available from oxidation of the corresponding tetrahydroindoles, formed *via* Diels-Alder reactions of both *N*-H and *N*-alkyl-2-vinylpyrroles with a wide range of *N*-substituted maleimides. We also report a highly diastereoselective isomerism of the Diels-Alder adduct, and isolation of Michael-addition products between the adduct and the dienophile with the major product being the more sterically congested diastereomer. Additionally, we report an improved synthesis of *N*-H-2-vinylpyrrole.

RESULTS AND DISCUSSION

Synthesis of starting materials. A Vilsmeier-Haack formylation [16] was performed on the appropriate pyrrole (**1a** and **1b**, Scheme 1) to give pyrrole-2-carboxaldehydes **2a** and **2b**. Next, a Wittig reaction was conducted on **2a** and **2b** or on commercially available **2c** and **2d** to form the appropriate vinylpyrrole **3–6** [7a,8,17,18]. Various procedures for the Wittig reaction were used to synthesize the vinylpyrroles. The common procedure for the synthesis of 2-vinylpyrroles [18,19] using sodium ethoxide as the base for formation of the ylide was used to make methyl-substituted vinylpyrroles **3a–3g**. For vinylpyrroles **3b**, **3c**, **3f**, and **3g**, this procedure gave ~1:3.9, 2.8:1, 1:1.8, and 1:1.5 *E*:*Z* molar mixtures, respectively, as determined by ^{1}H NMR, which were used without further purification for formation of the Diels-Alder adducts. Vinylpyrrole **3a** decomposed or polymerized [20] rapidly at room temperature (rt) to a dark viscous liquid before it could be used in any Diels-Alder reaction.

Although the sodium ethoxide procedure produced the desired *N*-H-2-vinylpyrrole **4**, it also consistently gave a 1:1 molar ratio of the unwanted and not easily separated byproduct 2-(1-ethoxyethyl)-pyrrole **7**. X-ray crystallography proved the structure of **7** (Fig. 1). The isolation of **7** was surprising, considering the lack of mention of this compound in any literature procedure for synthesis of **4**. Although the mixture of **4** and **7** was used as is for

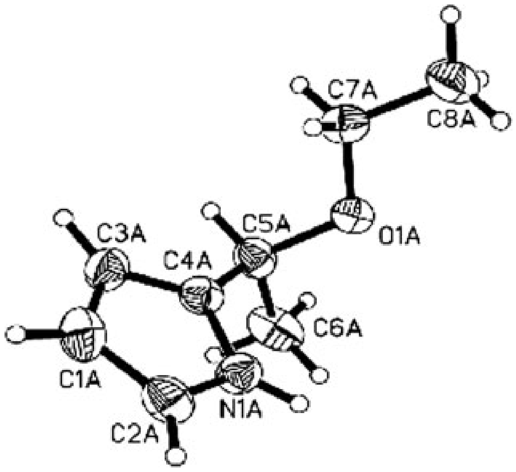
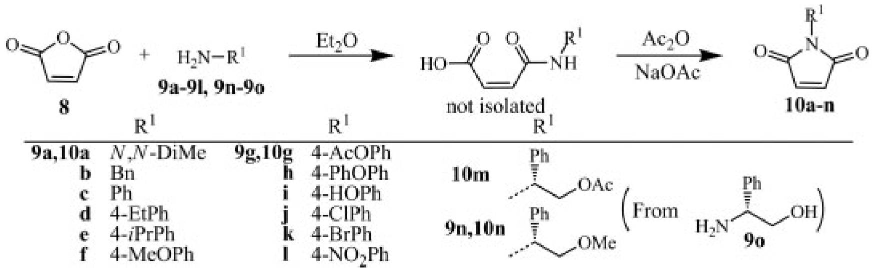


Figure 1. ORTEP representation of the X-ray structure of 2-(1-ethoxyethyl)pyrrole (**7**).

Scheme 2. Synthesis of maleimides.



formation of the Diels-Alder adducts, a search for a way to avoid contamination with this impurity was sought, which probably comes from an acid-catalyzed addition of ethoxide to the vinyl group in the expected Markovnikov orientation. Eliminating the acidic aqueous sodium bisulfite wash from the workup had no effect on the proportion of **7** formed. Heating the mixture of **4** and **7** in DMSO was attempted with the hope of effecting deethanolysis, which did occur, but with the destruction of a large amount of the desired **4**, probably from polymerization. It was found that using sodium *t*-butoxide in place of sodium ethoxide completely eliminated the byproduct and gave a higher efficiency than the sodium ethoxide procedure, with a consistent yield of ~80%, and less need for excess methyltriphenylphosphonium bromide and base (1.25 equiv) than was required for complete conversion using the sodium ethoxide procedure (2 equiv).

To determine whether the Diels-Alder reactions of 2-vinylpyroles with maleimides took place with the predicted *endo*-addition, vinylpyrroles with predominantly *E* or *Z* stereochemistry were desired. Ethyl- and pentyl-substituted vinylpyrroles **5a** and **5b** were made from aldehyde **2a** with the Corey procedure for the Wittig reaction [21], using methylsulfinyl carbanion as the base, formed from the reaction of DMSO with sodium hydride. ^{1}H NMR analysis showed that this procedure gave **5a** [18a] exclusively as the *Z* isomer and **5b** in a 1:9 *E*:*Z* mixture. For comparison of the stereochemistry in the resulting Diels-Alder adducts, (*E*)-2-(2-ethylvinyl)pyrrole **6** [18a] was synthesized using the Schlosser modification of the Wittig reaction [22], giving a 40% yield of an ~12:1 *E*:*Z* molar mixture.

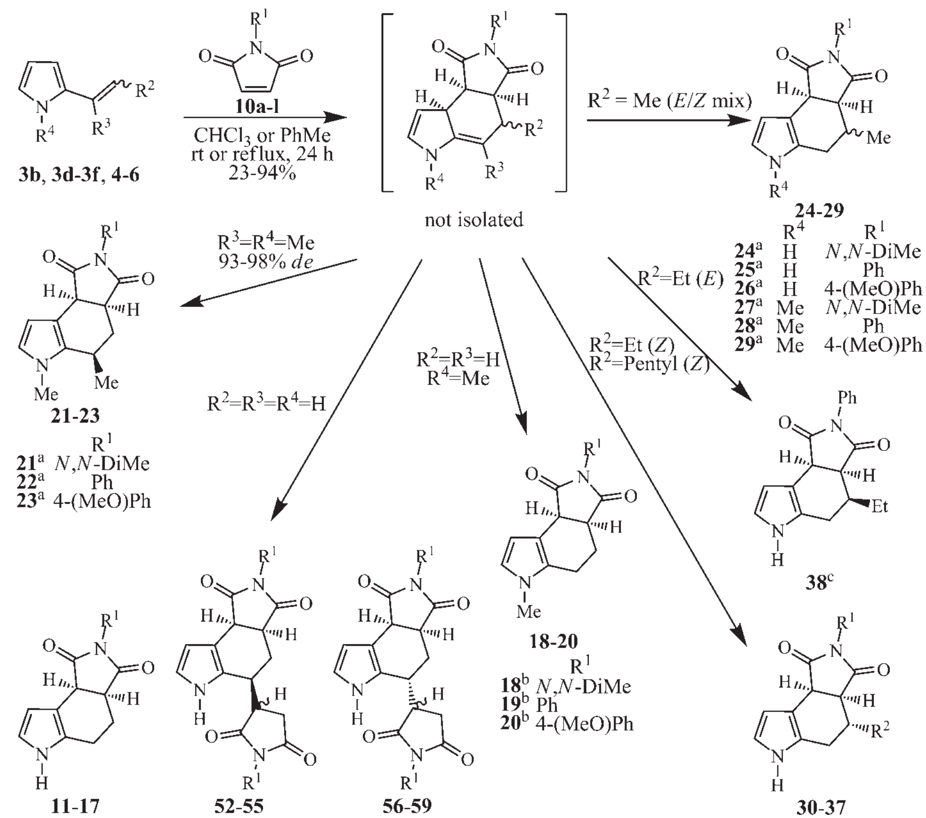
Maleimides were synthesized by the typical procedure [23], by reaction of maleic anhydride **8** with the appropriate primary amine **9a–9l** and **9n–9o**, and then heating the resulting amide-acid in an excess of acetic anhydride (10 equiv) with sodium acetate (0.5 equiv), giving the corresponding *N*-substituted maleimide (**10a–10n**, Scheme 2). When the acid from reaction of **8** with (*R*)-(−)-phenylglycinol (**9o**) was cyclized, the primary alcohol group was acetylated, giving acetate **10m**. To make the chiral methyl ether **10n**, (*R*)-2-methoxy-1-phenylethanamine (**9n**) was synthesized by methylation of **9o** by reaction of sodium hydride followed by addition of methyl iodide [24].

Diels-Alder reactions. Diels-Alder reactions of 2-vinylpyrroles **3b–3g**, **4**, and **5a** with maleimides **10a–10f**, **10h**, **10m**, and **10n** in chloroform gave adducts **11–29**, **31**, and **39–51** (Scheme 3, Table 1). The chiral adducts **39–51** were not isolated but were taken directly through to the aromatic indoles **85–97** (Scheme 4). The reaction solution was refluxed, if necessary, and stopped when complete, as indicated by TLC. Alternatively, the Diels-Alder reactions of 2-vinylpyrroles **5** and **6** with maleimides **10c**, **10d**, **10g**, and **10i–10l** were run in refluxing toluene, giving adducts **30–38**. In both procedures, vinylpyrroles **3–6** were used in slight excess (1.1 equiv) to simplify the required chromatographic purification procedure, because, while the vinylpyrroles were always eluted first, unreacted maleimides generally were eluted very near to the adducts. The unrearranged adducts were not isolated in any case; instead, the rearomatized form of the adducts was obtained. Although an extensive case-by-case comparison of the efficiency of the two procedures was not undertaken, adduct **31** was produced in both chloroform (70% yield) and toluene (41%). Further, comparing the average yield of the toluene-procedure-derived products **30–38** (38%) to the average yield of the chloroform-procedure-derived products **12**, **14**, **15**, **17–29**, and **31** (73%), the chloroform procedure gave better yields.

To determine whether *endo*- or *exo*-addition was predominant, the orientation of a terminal substituent on the vinyl group of the pyrrole was studied in the resulting isomerized adducts using nuclear Overhauser effect (NOE) experiments (Fig. 2). For description of the orientation, the diastereomer with the *syn* 3a-H and 8b-H protons (Fig. 3) protruding from the α-face and the fused maleimide protruding from the β-face will always be used, corresponding to the structures at the top of Figure 2, this convention is also used throughout the Experimental.

2-(2-Methylvinyl)-pyrroles **3b** and **3f** gave the expected mixture of 4α-Me and 4β-Me in rearranged adducts **24–29**, expected for either *endo*- or *exo*-

Scheme 3. Diels-Alder reactions of 2-vinylpyrroles.



24-29

	R^4	R^1
24[a]	H	*N*,*N*-DiMe
25[a]	H	Ph
26[a]	H	4-(MeO)Ph
27[a]	Me	*N*,*N*-DiMe
28[a]	Me	Ph
29[a]	Me	4-(MeO)Ph

21-23

	R^1
21[a]	*N*,*N*-DiMe
22[a]	Ph
23[a]	4-(MeO)Ph

18-20

	R^1
18[b]	*N*,*N*-DiMe
19[b]	Ph
20[b]	4-(MeO)Ph

	R^1		Yield(%)		Yield(%)	Molar Ratio
11[b]	*N*,*N*-DiMe	*	-	*	-	-
12[a]	Bn	**52**	45	**56**	18	**52**:**56** = 3:1
13[b]	Ph	*	-	*	-	-
14[a]	4-EtPh	**53**	23	**57**	5	**53**:**57** = 5:1
15[a]	4-*i*PrPh	**54**	29	**58**	8	**54**:**58** = 4:1
16[b]	4-(MeO)Ph	*	-	*	-	-
17[a]	4-(PhO)Ph	**55**	38	**59**	8	**55**:**59** = 5:1

* Detected by TLC but not isolated.

	R^2	R^1
30[c]	Et	Ph
31[b,c]	Et	4-EtPh
32[c]	Et	4-(AcO)Ph
33[c]	Et	4-(HO)Ph
34[c]	Et	4-ClPh
35[c]	Et	4-BrPh
36[c]	Et	4-NO_2Ph
37[c]	*n*-Pentyl	Ph

Reaction conditions: [a] $CHCl_3$, rt, 24 h [b] $CHCl_3$, reflux, 24 h [c] PhMe, reflux, 24 h

addition. (*Z*)-2-Vinylpyrroles **5a** and **5b** gave adducts **30–37** with exclusively 4α-Et and 4α-*n*-pentyl substituents, as shown by ^{1}H NMR analysis. Correspondingly, adduct **38** from the *E*-vinylpyrrole **6** had mainly 4β-Me with ~12:1 ratio of 4β-Et to 4α-Et product. To the extent of ^{1}H NMR sensitivity, this is strong evidence of predominantly *endo*-addition Diels-Alder reactions.

The spontaneous rearrangement of Diels-Alder adducts to their aromatic counterparts was also observed in our previous work with *in situ* Diels-Alder reactions of 2-vinylpyrrole with maleimides [5]. As noted in that work, because orbital symmetry considerations forbid suprafacial 1,3-hydride shifts and antarafacial 1,3-hydride shifts are geometrically difficult [25], the isomerism probably takes place *via* acid catalysis, a "formal 1,3-hydride shift" [26]. A proton should approach from the least sterically hindered face of the adduct, the opposite face from which the maleimide protrudes and the same face from which the 8b-H and 3a-H protons protrude (the α-face); thus, the 5-H proton of the rearranged adduct would have the predominant orientation of α. The predominance of a particular diastereomer was observed in our earlier work [4,5], and to verify it occurred here as well, NOE experiments were performed on the rearranged adducts **22** and **23**, which had a methyl substituent at the 5-postion; compound **21** had overlapping ^{1}H NMR peaks which prevented accurate measurement of NOE interactions. The assignment of the two peaks corresponding to the 4α-H and 4β-H protons was confirmed by a weak NOE interaction between the 8bα-H and 4α-H protons, whereas no interaction between the 8bα-H and 4β-H protons was observed. Additionally, a much stronger interaction was observed between the 3aα-H and 4α-H protons than between the 3aα-H and 4β-H protons. A strong NOE interaction between the 4α-H and 5-H protons occurred, with no

Table 1

Diels-Alder reactions of 2-vinylpyrroles.

Vinylpyrrole	Maleimide	R^1	R^2	R^3	R^4	Conditions	Adduct	Yield %	PhMe reflux t	Indole	Yield %[a]
4	**10a**	*N,N*-DiMe	H	H	H	$CHCl_3$, reflux 24 h	**11**	–[b]	24 h	**60**	64
4	**10b**	Bn	H	H	H	$CHCl_3$, rt 24 h	**12**	23	3 h	**61**	45
4	**10c**	Ph	H	H	H	$CHCl_3$, reflux 24 h	**13**	–[b]	24 h	**62**	67
4	**10d**	4-EtPh	H	H	H	$CHCl_3$, rt 24 h	**14**	49	3 h	**63**	47
4	**10e**	4-*i*PrPh	H	H	H	$CHCl_3$, rt 24 h	**15**	32	3 h	**64**	61
4	**10f**	4-(MeO)Ph	H	H	H	$CHCl_3$, reflux 24 h	**16**	–[b]	24 h	**65**	64
4	**10h**	4-(PhO)Ph	H	H	H	$CHCl_3$, rt 24 h	**17**	33	3 h	**66**	38
3d	**10a**	*N,N*-DiMe	H	H	Me	$CHCl_3$, reflux 24 h	**18**	89	24 h	**67**	66
3d	**10c**	Ph	H	H	Me	$CHCl_3$, reflux 24 h	**19**	94	24 h	**68**	71
3d	**10f**	4-(MeO)Ph	H	H	Me	$CHCl_3$, reflux 24 h	**20**	93	24 h	**69**	66
3e	**10a**	*N,N*-DiMe	H	Me	Me	$CHCl_3$, rt 24 h	**21**	86	24 h	**70**	70
3e	**10c**	Ph	H	Me	Me	$CHCl_3$, rt 24 h	**22**	91	24 h	**71**	72
3e	**10f**	4-(MeO)Ph	H	Me	Me	$CHCl_3$, rt 24 h	**23**	93	24 h	**72**	66
3b	**10a**	*N,N*-DiMe	Me	H	H	$CHCl_3$, rt 24 h	**24**	57	24 h	**73**	57
3b	**10c**	Ph	Me	H	H	$CHCl_3$, rt 24 h	**25**	93	24 h	**74**	61
3b	**10f**	4-(MeO)Ph	Me	H	H	$CHCl_3$, rt 24 h	**26**	90	24 h	**75**	59
3f	**10a**	*N,N*-DiMe	Me	H	Me	$CHCl_3$, rt 24 h	**27**	67	24 h	**76**	56
3f	**10c**	Ph	Me	H	Me	$CHCl_3$, rt 24 h	**28**	89	24 h	**77**	62
3f	**10f**	4-(MeO)Ph	Me	H	Me	$CHCl_3$, rt 24 h	**29**	84	24 h	**78**	61
5a	**10c**	Ph	Et	H	H	PhMe, reflux 24 h	**30**	36	24 h	**79**	44
5a	**10d**	4-EtPh	Et	H	H	PhMe, reflux 24 h	**31**	41	3 h	**80**	53
5a	**10d**	4-EtPh	Et	H	H	$CHCl_3$, reflux 24 h	**31**	70	–	–	–
5a	**10g**	4-(AcO)Ph	Et	H	H	PhMe, reflux 24 h	**32**[c]	31	24 h	**81**[c]	15
5a	**10i**	4-(HO)Ph	Et	H	H	PhMe, reflux 24 h	**33**	54	–	–[d]	–[d]
5a	**10j**	4-ClPh	Et	H	H	PhMe, reflux 24 h	**34**	32	24 h	**82**	33
5a	**10k**	4-BrPh	Et	H	H	PhMe, reflux 24 h	**35**	35	24 h	**83**	36
5a	**10l**	4-NO_2Ph	Et	H	H	PhMe, reflux 24 h	**36**	45	24 h	**84**	28
5b	**10c**	Ph	Pentyl	H	H	PhMe, reflux 24 h	**37**	30	–	–	–
6	**10c**	Ph	Et	H	H	PhMe, reflux 24 h	**38**	41	–	–	–
4	**10m**	$AcOCH_2CHPh$	H	H	H	$CHCl_3$, reflux 24 h	**39**	–	24 h	**85**	46
3b	**10m**	$AcOCH_2CHPh$	Me	H	H	$CHCl_3$, reflux 24 h	**40**	–	24 h	**86**	27
3d	**10m**	$AcOCH_2CHPh$	H	H	Me	$CHCl_3$, reflux 24 h	**41**	–	24 h	**87**	44
3c	**10m**	$AcOCH_2CHPh$	Me	Me	H	$CHCl_3$, reflux 24 h	**42**	–	24 h	**88**	29
3f	**10m**	$AcOCH_2CHPh$	Me	H	Me	$CHCl_3$, reflux 24 h	**43**	–	24 h	**89**	26
3g	**10m**	$AcOCH_2CHPh$	Me	Me	Me	$CHCl_3$, reflux 24 h	**44**	–	24 h	**90**	21
4	**10n**	$MeOCH_2CHPh$	H	H	H	$CHCl_3$, reflux 24 h	**45**	–	24 h	**91**	39
3b	**10n**	$MeOCH_2CHPh$	Me	H	H	$CHCl_3$, reflux 24 h	**46**	–	24 h	**92**	30
3e	**10n**	$MeOCH_2CHPh$	H	Me	Me	$CHCl_3$, reflux 24 h	**47**	–	24 h	**93**	26
3d	**10n**	$MeOCH_2CHPh$	H	H	Me	$CHCl_3$, reflux 24 h	**48**	–	24 h	**94**	40
3c	**10n**	$MeOCH_2CHPh$	Me	Me	H	$CHCl_3$, reflux 24 h	**49**	–	24 h	**95**	32
3f	**10n**	$MeOCH_2CHPh$	Me	H	Me	$CHCl_3$, reflux 24 h	**50**	–	24 h	**96**	29
3g	**10n**	$MeOCH_2CHPh$	Me	Me	Me	$CHCl_3$, reflux 24 h	**51**	–	24 h	**97**	23

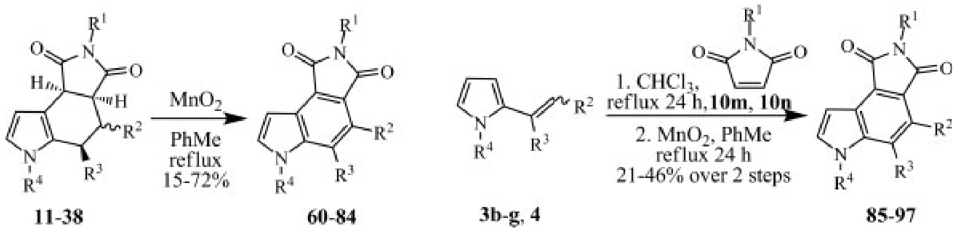
[a] Yields for chiral indoles are over two steps.

[b] Crude yields for adducts **11** (64%), **13** (92%), and **16** (90%) include double-addition type products detected by TLC but not isolated.

[c] Product was deacetylated to **81** during the reaction or workup.

[d] Only starting material **33** was recovered, but see note c above.

Scheme 4. Aromatization of Diels-Alder adducts.



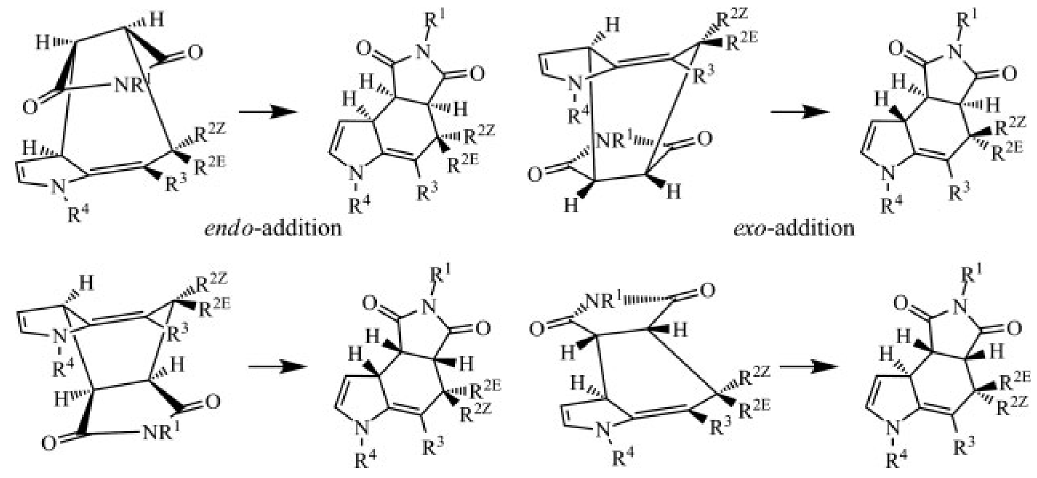


Figure 2. Effect of *endo*- or *exo*-addition on the stereochemistry of Diels-Alder adducts.

detectable interaction between the 4α-H proton and the 5-methyl group. Correspondingly, a strong NOE interaction was seen between the 4β-H proton and the 5-methyl group, whereas no detectable response was observed between the 4β-H and 5-H protons, showing the 5-methyl group to be in the β-orientation. The ^{1}H NMR integrations of **21–23** showed between a 13:1 and 54:1 molar ratio of major to minor product, a 93–98% diastereomeric excess. The predominant diastereomers had the sterically more congested configuration, with the 5-methyl group protruding from the same face as the maleimide.

The high diastereoselectivity of the formal 1,3-hydride shift is further evidenced from products **52–59**. These types of products were detected whenever unsubstituted vinylpyrrole **4** was used in Diels-Alder reactions with maleimides, where they were isolated and characterized in four reactions. Compound **56** was not completely separated from **52**, although sufficient purity was obtained to accurately report ^{1}H NMR data. In several cases, these products were detected by TLC but not isolated, although their masses were included in determining the percent yield; hence, yields for products **11**, **13**, and **16** do not reflect the actual isolated yield. NOE studies of **55** and **59** verified the structure of products **52–59**, giving evidence of the same kind of stereochemistry as described earlier for the 5β-Me adducts **22** and **23** (Fig. 4).

For minor product **59**, an NOE interaction was observed between the 8bα-H proton and a geminal proton of the succinimide substituent, an interaction absent in major product **55**. In **55**, an interaction between the 8bα-H and 4α-H protons showed a *syn*-relationship. Multiple strong interactions were observed in compound **55** between the 4β-H proton and the succinimide protons, whereas no such interactions were observed with the 4α-H proton, giving evidence that the succinimide is attached to the β-face in the major product. In compounds **52–59**, the stereochemistry of the succinimidyl proton at the point of attachment was not determined. However, coupling constants and NOE interactions between the geminal protons of the succinimide and the succinimidyl proton at the point of attachment did allow determination of a probable *syn*- or *anti*-relationship. In compound **55**, the ^{1}H NMR peaks of the 5α-H proton

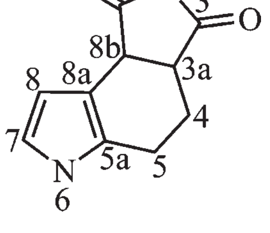
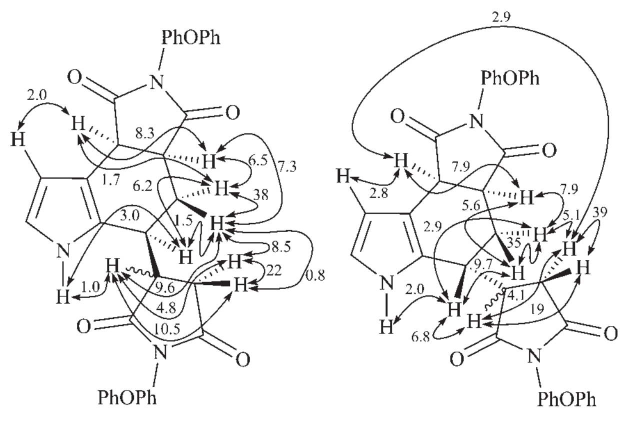


Figure 3. Numbering scheme.



55

59

Figure 4. NOE experiments. *Numbers indicate % enhancement.

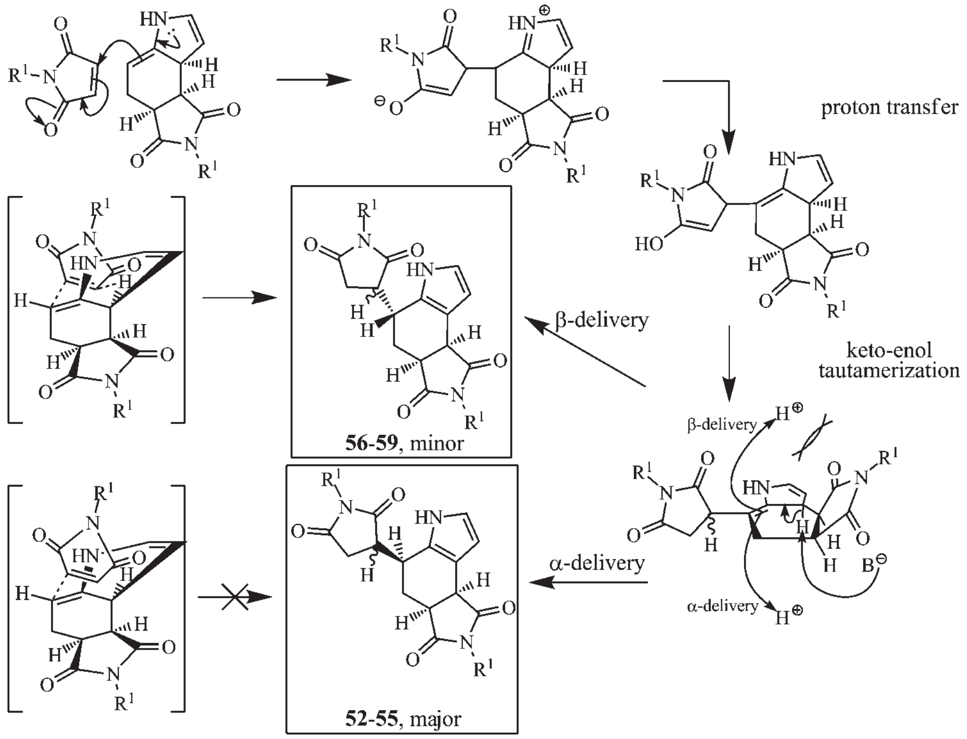


Figure 5. Proposed mechanism for the formation of **52–59**.

and the proton at the point of succinimide attachment overlapped too greatly to allow accurate measurement of NOE interactions.

When first detected, products **52–59** were assumed to be the result of ene-reactions between the Diels-Alder adduct and the maleimide, as there are several reports of ene-products formed between Diels-Alder adducts and their corresponding dienophiles [27]. However, after determining the stereochemistry at C5, it was realized that an ene reaction could not adequately explain the formation of both epimers. Although an ene reaction could justify the formation of minor products **56–59**, the tight transition state required [28] makes the ene reaction an impossible route toward major products **52–55** (Fig. 5). Because the more sterically congested epimers **52–55** were the predominant products, thermodynamic equilibration of the feasibly ene-reaction-formed **56–59** is also highly unlikely.

In light of the diastereoselective rearrangement at C5 noted in this work and in our earlier *in situ* Diels-Alder reaction work [4,5], it was realized that our mechanistic explanation for formation of the rearranged adducts could also explain the formation of **52–59**. A Michael-addition of the unrearranged adduct to the maleimide would result in 5-succinimide-substituted adducts. When a proton approaches the molecule to cause the formal 1,3-hydride shift, an addition from the least sterically congested face (the α-face in the Figures) would predominate and would result in products **52–55**, with a smaller amount of hydrogen delivery occurring from the more sterically occluded face to give minor products **56–59**. The presence of the succinimide substituent at C5 may cause the steric environment of the α-face to be more similar to the β-face than does a 5-methyl group; this would explain the 3:1–5:1 ratios of products **52–59** (75–83% *de*) as contrasted with the higher diastereomeric excess observed in 5-methyl products **21–23** (93–98% *de*).

Aromatization of Diels-Alder adducts. Diels-Alder adducts **11–32**, **34–36**, and **39–51** were dehydrogenated using activated MnO_2, giving the corresponding indoles **60–84** in 15–72% yield and giving chiral indoles **85–97** with 21–46% yield over two steps (Scheme 4, Table 1). Using manganese sulfate with potassium permanganate [29] to make the activated MnO_2 gave consistent and moderate-yielding aromatizations. Some restrictions to this technique apply, as when aromatization of hydroxyl-adduct **33** was attempted, only starting material was obtained. Competition for adsorption on the oxide surface of the activated MnO_2 from the phenol group of **33** may have partially deactivated the reagent. When MnO_2 treatment of acetoxy-adduct **32** was conducted, the hydroxy-indole **81** was the exclusive product isolated. When oxidation occurs, water can be produced, but deacetylation appears to be unprecedented under these oxidative conditions; therefore, the aromatized product was more likely deacetylated on silica gel during chromatography, giving **81**. Aromatization and purification of chiral adducts **39–44** gave indoles **85–90** with no deacetylation.

Biological activity. While participating in the Developmental Therapeutics Program at the National Cancer Institute (NCI), we submitted 11 compounds to the NCI for a one-dose 60 human tumor cell line prescreen: compounds **12**, **14**, **17**, **30**, **32**, **33**, **61**, **63**, **66**, and **79**. Of these, two compounds, **63** and **66**, were judged by the NCI to have sufficient activity to justify screening with 60 human tumor cell lines at five concentrations with 10-fold dilutions, from 1×10^{-4} to 1×10^{-8} M. Both of these compounds were found to have high levels of activity against many of the 60 different cell lines tested. Compound **63** was most active against non–small-cell lung cancer HOP-92 and melanoma cell lines SK-MEL-5 and LOX IMVI with an IC_{50} of 322, 412, and 462 ng/mL, respectively. Compound **66** was most active against breast cancer HS 578T, melanoma UACC-257, and leukemia RPMI-8226, with an IC_{50} of 3.5, 34, and 230 ng/mL, respectively.

CONCLUSIONS

Variously substituted 2-vinylpyrroles undergo *endo*-addition Diels-Alder additions with maleimides, followed by a highly diastereoselective (93–98% *de*) rearrangement to tetrahydroindoles in moderate to excellent yield. Treatment with activated MnO_2 in refluxing toluene gives the corresponding indole aromatized products in moderate to good yield. This highly convergent methodology for formation of indoles is flexible and the starting materials are conveniently prepared.

EXPERIMENTAL

General. Solvents and reagents were purchased and used as received. Flash chromatography was performed using 230–450 mesh silica gel. TLC analyses were performed on plastic-backed plates precoated with 0.2-mm silica with F_{254} indicator. Infrared spectra were recorded on a 4000 FTIR spectrometer; only the most intense and/or diagnostic peaks are reported. High-resolution mass spectra were recorded with a time-of-flight instrument using electrospray ionization with PEG as an internal calibrant. For NMR spectra, chemical shifts (δ) were referenced to the solvent. ^{13}C NMR spectra were proton decoupled. Melting points are uncalibrated. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. Petroleum ether refers to the fraction boiling at 35–60°C.

^{1}H NMR analysis. In the ^{1}H NMR spectra of adducts **11–38**, the 8bα-H proton often appears as a doublet of doublet of doublets in 5-unsubstituted adducts; COSY experiments indicate that the 8bα-H proton is coupled not only to the 3aα-H proton but also to the 5-bond-distant 5-H protons with a coupling constant of about 1.5 Hz [10,30]. In 5-methyl adducts, the 3aα-H proton was sometimes observed to couple to the 5α-H proton at 0.6–0.9 Hz. Additionally, in 4-alkyl adducts, the 3aα-H proton was coupled to the 5α-H proton at ~1.0 Hz. For indoles **60–97**, the 8-H proton and the 5-H proton were consistently coupled at about 1.0 Hz [31].

General methods for the preparation of vinylpyrroles. ***Method I.*** Sodium ethoxide (0.125 mol, 2.5 equiv, made freshly from sodium (2.87 g, 0.125 mol, 2.5 equiv) and EtOH followed by evaporation using a rotating evaporator) was suspended with the appropriate alkyltriphenylphosphonium bromide (0.1 mol, 2 equiv) in THF (50 mL) [18,19]. The mixture was stirred at rt under nitrogen for 3 h. Then, a solution of the appropriate pyrrole-2-carboxaldehyde **2a** or **2b** or 2-acetylpyrrole **2c** or **2d** (0.05 mol) in THF (20 mL) was added over 1 min, and the mixture was stirred under reflux for 15 h. The solvent was removed using a rotating evaporator, the residue was suspended in dichloromethane and filtered, and the filter cake was washed with dichloromethane (3 × 50 mL). The filtrate was washed with saturated $NaHSO_3$ (50 mL), saturated Na_2CO_3 (50 mL), and brine (50 mL), and dried over Na_2SO_4. The solvent was removed using a rotating evaporator and the crude product was vacuum-distilled, giving the appropriate pure 2-vinylpyrrole (with the exception of **4**, see later) at comparable 60% yield [18,19]. When method I was used to generate vinylpyrrole **4**, **7** was found to be an unwanted byproduct in an ~1:1 molar ratio to the desired product. This mixture was used without further purification in subsequent Diels-Alder reactions.

Method II. Potassium *t*-butoxide (14.76 g, 0.132 mol, 1.25 equiv) was added slowly to methyltriphenylphosphonium bromide (46.98 g, 0.132 mol, 1.25 equiv) in THF (100 mL) at 0°C. Formation of the bright yellow color characteristic of the ylide was observed immediately. The mixture was stirred at rt under nitrogen for 30 min and then cooled to 0°C. A solution of the pyrrole **2a** (10.00 g, 0.105 mmol) in THF (20 mL) was added over 5 min, with stirring, and refluxed for 30 min until TLC analysis indicated the reaction was complete. The mixture was allowed to cool to rt and filtered. The filter cake was washed with diethyl ether (4 × 25 mL). The filtrate was washed with saturated $NaHSO_3$ (50 mL), saturated Na_2CO_3 (50 mL), and brine (50 mL), and dried over anhydrous Na_2SO_4. The solvents were removed using a rotating evaporator and the residue was vacuum-distilled, giving **4** as a colorless liquid (7.66 g, 78%). The ^{1}H and ^{13}C NMR data matched the values in the literature [18,19].

For Diels-Alder reactions, vinylpyrroles **5a** and **5b** were synthesized using Corey's procedure for the Wittig reaction [21], and method I was used to synthesize vinylpyrroles **3a–g**. However, for purposes of characterization **3a–c**, **3e–f**, and **5b** were synthesized using method II.

2-(2-Propenyl)-1H-pyrrole (3a). Method II with **2c** (3.16 g, 0.029 mol) and distillation at 37°C/0.04 mm Hg gave **3a** (436 mg, 14%) as a white waxy solid [17a]: mp 71–73°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.32 (bs, 1H, 1-H), 6.82 (ddd, *J* = 2.8, 2.8, 1.4 Hz, 1H, 5-H), 6.37 (dddd, *J* = 3.1, 3.1, 1.7, 1.3 Hz, 1H, 3-H), 6.32 (dddd, *J* = 3.3, 2.6, 2.6, 0.9 Hz, 1H, 4-H), 5.09–5.11 (m, 1H, 1′-H *cis* to pyrrole), 4.91–4.93 (m, 1H, 1′-H *trans* to pyrrole), 2.17 (ddd, *J* = 1.6, 0.8, 0.8 Hz, 3H, 3′-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 135.1, 133.2, 118.8, 109.5, 107.0, 105.7, 20.8; IR (thin film, cm^{-1}) 3450(bs), 3400(s), 2969(s), 2925(m), 2840(w), 1634(m), 1597(m), 1557(w), 1499(w), 1470(m), 1403(m), 1235(m), 1110(w), 1035(m); HRMS *m*/*z* (M + H$^+$) calcd. for C_7H_9N: 108.0808, found 108.0815.

2-(1-Propenyl)-1H-pyrrole (3b). Method II with **2a** (2.66 g, 0.028 mol) and distillation at 35.5°C/0.05 mm Hg gave **3b** (2.32 g, 77%) as a white solid [17b,18a]: 1.0:3.9 *E*:*Z*; mp 27–28°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.10 (bs, 1H, 1-H), 6.82 (ddd, *J* = 2.6, 2.6, 1.4 Hz, 1H, 5maj-H), 6.74 (ddd, *J* = 2.7, 2.7, 1.4 Hz, 1H, 5min-H), 6.22–6.42 (m, 3H, 3-H, 4-H, 1′-H), 5.80–5.93 (m, 1H, 2′min-H), 5.61–5.74 (m, 1H, 2′maj-H), 2.03–2.07 (m, 3H, 3′maj-H), 1.93–1.97 (m, 3H, 3′min-H); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 130.4, 122.2, 121.8, 120.9, 120.4, 118.0, 117.8, 109.6, 109.4, 109.0, 106.6, 18.5, 15.2; IR (thin film, cm^{-1}) 3469(s), 3396(bs), 3107(w), 3024(m), 2963(m), 2950(m), 2935(m), 2857(w), 1642(m), 1603(w), 1546(w), 1459(m), 1409(w), 1366(m), 1294(w), 1278(w), 1216(w), 1118(m), 1098(m), 1032(m), 957(w), 800(s); HRMS *m*/*z* (M + H$^+$) calcd. 108.0808, found 108.0802. Anal. Calcd. for C_7H_9N: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.28; H, 8.66; N, 12.94.

2-(2-But-2-enyl)-1H-pyrrole (3c). Method II with **2c** (3.16 g, 0.029 mol) and distillation at 43°C/0.04 mm Hg gave **3c** (922 mg, 26%) as a colorless liquid: 2.8:1.0 *E*:*Z*; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.32 (bs, 1H, 1-H), 6.87 (ddd, *J* = 2.4, 2.4, 2.4 Hz, 1H, 5maj-H), 6.77 (ddd, *J* = 2.2, 2.2, 2.2 Hz, 1H, 5min-H), 6.36–6.40 (m, 2H, 3maj-H, 4maj-H), 6.27–6.31 (m, 2H, 3min-H, 4min-H), 5.67–5.76 (m, 1H, 3′min-H), 5.50–5.59 (m, 1H, 3′maj-H), 2.12–2.15 (m, 3H, 1′maj-H), 2.05–2.07 (m, 3H, 1′min-H), 1.97–2.01 (m, 3H, 4′maj-H), 1.86–1.90 (m, 3H, 4′min-H); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 134.9, 132.4, 127.6, 126.9, 119.5, 117.8, 117.5, 116.0, 109.1, 109.0, 108.4, 105.2, 23.1, 15.4, 14.4, 13.7; IR (thin film, cm^{-1}) 3481(s), 3419(bm), 2973(m), 2922(m), 2862(m), 1643(w), 1551(w), 1452(m), 1403(m), 1378(m), 1353(w), 1119(m), 1090(m), 1068(w), 1036(m), 806(m), 791(m); HRMS *m*/*z* (M + H$^+$) calcd. 122.0964, found 122.0965. Anal. Calcd. for $C_8H_{11}N$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.22; H, 8.96; N, 11.33.

N-Methyl-2-(2-propenyl)-1H-pyrrole (3e). Method II with **2d** (3.57 g, 0.029 mol) and distillation at 31.5°C/0.04 mm Hg gave **3e** (1.62 g, 46%) as a colorless liquid [7a,17c,17e,17f]: ^{1}H NMR (300 MHz, CDCl$_3$, δ) 6.77 (ddd, *J* = 2.7, 1.4, 1.4 Hz, 1H, 5-H), 6.37 (ddd, *J* = 3.7, 1.9, 1.9 Hz, 1H, 3-H), 6.30 (ddd, *J* = 3.8, 2.7, 1.8 Hz, 1H, 4-H), 5.26 (dq, *J* = 3.0, 1.5 Hz, 1H, 1′-H *cis* to pyrrole), 5.17 (dq, *J* = 3.0, 1.5 Hz, 1H, 1′-H *trans* to pyrrole), 3.85 (d, *J* = 1.2 Hz, 3H, 1-CH$_3$), 2.28 (dddd, *J* = 1.7, 1.7, 1.0, 0.9 Hz, 3H, 3′-H); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 135.9, 134.7, 124.7, 111.6, 108.8, 107.3, 36.3, 24.1; IR (thin film, cm^{-1}) 3104(m), 2974(s), 2952(s), 2921(s), 2881(m), 2806(w), 2726(w), 1794(w), 1701(w), 1626(s), 1478(s), 1449(m), 1434(s), 1413(m), 1374(m), 1363(m), 1313(s), 1260(m), 1224(w), 1094(m), 1062(w), 997(w), 789(m), 605(m); HRMS *m*/*z* (M + H$^+$) calcd. 122.0964, found 122.0959. Anal. Calcd. for $C_8H_{11}N$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.54; H, 8.92; N, 11.54.

N-Methyl-2-(1-propenyl)-1H-pyrrole (3f). Method II with **2b** (3.50 g, 0.032 mol) and distillation at 32.5°C/0.04 mm Hg gave **3f** (2.66 g, 68%) as a colorless liquid [17d,17g,17i]: 1.0:1.8 *E*:*Z*; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 6.72 (ddd, *J* = 2.9, 1.5, 1.5 Hz, 1H, 5maj-H), 6.66 (ddd, *J* = 2.4, 2.0, 2.0 Hz, 1H, 5min-H), 6.36–6.44 (m, 2H, 3-H, 4-H), 6.29–6.32 (m, 1H, 1′maj-H), 6.20–6.23 (m, 1H, 5′min-H), 6.06–6.19 (m, 1H, 2′min-H), 5.76–5.88 (m, 1H, 2′maj-H), 3.69 (s, 3H, 1min-CH$_3$), 3.69 (s, 3H, 1maj-CH$_3$), 2.04–2.08 (m, 3H, 3′maj-H), 1.98–2.02 (m, 3H, 2′maj-H); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 132.4, 130.4, 124.3, 124.1, 122.24, 122.16, 120.1, 118.6, 109.6, 107.8, 107.6, 105.3, 34.1, 18.9, 15.3; IR (thin film, cm^{-1}) 3103(m), 3018(m), 2967(s), 2937(s), 2917(s), 2860(m), 1698(w), 1640(w), 1479(s), 1450(m), 1412(m), 1376(m), 1356(w), 1342(w), 1302(m), 1292(s), 1241(w), 1228(w), 1089(m), 1064(w), 1033(w), 998(w), 832(w), 781(m), 649(s), 608(s); HRMS *m*/*z* (M + H$^+$) calcd. 122.0964, found 122.0956. Anal. Calcd. for $C_8H_{11}N$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.50; H, 8.93; N, 11.80.

2-(2-But-2-enyl)-N-methyl-1H-pyrrole (3g). Method II with **2d** (3.50 g, 0.032 mol) and distillation at 31.5°C/0.04 mm Hg gave **3g** (1.01 g, 23%) as a colorless liquid: 1.0:1.5 *E*:*Z*; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 6.70 (ddd, *J* = 2.7, 1.8, 1.8 Hz, 1H, 5maj-H), 6.64 (ddd, *J* = 2.7, 2.0, 2.0 Hz, 1H, 5min-H), 6.24 (ddd, *J* = 3.5, 2.4, 2.4 Hz, 1H, 3maj-H), 6.18 (ddd, *J* = 3.6, 2.4, 2.4 Hz, 1H, 3min-H), 6.10 (dddd, *J* = 3.9, 3.9, 2.0, 2.0 Hz, 1H, 4min-H), 6.02 (dddd, *J* = 3.8, 3.8, 2.0, 2.0 Hz, 1H, 4maj-H), 5.74–5.84 (m, 1H, 3′maj-H), 5.60–5.69 (m, 1H, 3′min-H), 3.68 (d, *J* = 2.1 Hz, 3H, 1min-CH$_3$), 3.57 (d, *J* = 1.8 Hz, 3H, 1maj-CH$_3$), 2.04–2.06 (m, 3H, 1′-H), 1.85–1.90 (m, 3H, 4′min-H), 1.59–1.64 (m, 3H, 4′maj-H); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 137.7, 133.6, 129.1, 128.1, 126.3, 124.1, 122.7, 121.4, 107.4, 107.1, 106.8, 33.3, 34.0, 25.5, 17.3, 15.5, 14.2; IR (thin film, cm^{-1}) 3106(m), 3026(m), 2943(m), 2918(m), 2884(m), 2857(w), 2810(w), 1703(w), 1638(m), 1484(s), 1451(m), 1367(w), 1305(s), 1261(w), 1228(w), 1091(m), 1058(w), 1009(w), 954(m), 789(m), 648(s), 605(m); HRMS *m*/*z* (M + H$^+$) calcd. for $C_9H_{13}N$: 136.1121, found 136.1124.

2-Ethenyl-1H-pyrrole (4). Method II with **2a** (10.00 g, 0.105 mol) and distillation at 30°C/0.04 mm Hg gave **4** (7.66 g, 78%) as a colorless liquid [18,19]; the ^{1}H and ^{13}C NMR data matched the literature values [18,19]. Anal. Calcd. for C_6H_7N: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.17; H, 7.67; N, 14.83.

2-(1-Heptenyl)-1H-pyrrole (5b). Method II with **2a** (2.91 g, 0.031 mol) and distillation at 68°C/0.04 mm Hg gave **5b** (4.40 g, 81%) as a colorless liquid: 1.0:9.0 *E*:*Z*; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.10 (bs, 1H, 1-H), 6.81 (ddd, *J* = 2.3, 2.3, 1.7 Hz, 1H, 5maj-H), 6.74 (ddd, *J* = 2.6, 2.6, 1.4 Hz, 1H, 5min-H), 6.21–6.37 (m, 3H, 3-H, 4-H, 1′-H), 5.85 (ddd, *J* = 16.1, 7.0, 7.0 Hz, 1H, 2′min-H), 5.53 (ddd, *J* = 12.8, 6.8, 5.8 Hz, 1H, 2′maj-H), 2.45 (ddt, *J* = 7.3, 7.2, 1.8 Hz, 2H, 3′maj-H), 2.25 (dt, *J* = 7.2, 7.1, 1.5 Hz, 2H, 3′min-H), 1.34–1.65 (m, 6H, 4′-H, 5′-H, 6′-H), 1.01 (t, *J* = 7.2 Hz, 3H, 7′-H); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 134.0, 133.7, 130.3, 128.9, 128.8, 128.7, 128.6, 126.3, 120.5, 119.0, 117.8, 117.7, 109.6, 109.4, 108.9, 106.7, 32.9, 31.8, 31.5, 29.4, 29.4, 22.7, 14.2; IR (thin film, cm^{-1}) 3469(s), 3392(bs), 3105(m), 3014(m), 2957(s), 2926(s), 2857(s), 1712(w), 1639(m), 1545(w), 1460(m), 1434(m), 1412(m), 1379(m), 1293(w), 1280(w), 1212(w), 1182(w), 1118(m), 1095(m), 1033(m), 955(m), 799(m), 949(m); HRMS *m*/*z* (M + H$^+$) calcd. 164.1434, found 164.1434. Anal. Calcd. for $C_{11}H_{17}N$: C, 80.93; H, 10.50; N, 8.58. Found: C, 81.07; H, 10.32; N, 8.74.

2-(1-Ethoxyethyl)-N-methyl-1H-pyrrole (7). A 1:1 molar mixture of **4** and **7**, prepared using method I, was left in a refrigerator for 6 months, giving large colorless crystals of **7**. The crystals were removed and the liquid **4** was washed off using ice-cold petroleum ether, giving colorless crystals: mp 26.5–28.5°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.39 (bs, 1H, 1-H), 6.78 (ddd, J = 2.6, 2.6, 1.6 Hz, 1H, 5-H), 6.16 (ddd, J = 3.3, 2.7, 2.5 Hz, 1H, 4-H), 6.08 (ddd, J = 3.5, 2.6, 1.5 Hz, 1H, 3-H), 4.55 (q, J = 6.6 Hz, 1H, 1′-H), 3.44 (dq, J = 12.0, 7.0 Hz, 1H, OCH_2CH_3), 3.40 (dq, overlapped, J = 11.7, 7.0 Hz, 1H, OCH_2CH_3), 1.51 (d, J = 6.6 Hz, 3H, 2′-H), 1.19 (dd, J = 6.9, 7.2 Hz, 3H, OCH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 133.7 (C2), 117.5 (C5), 107.9 (C4), 106.0 (C3), 71.1 (C1′), 63.4 (OCH_2CH_3), 21.7 (C2′), 15.5 (OCH_2CH_3); IR (film, cm^{-1}) 3464(m), 3322(w), 3054(m), 2980(m), 2933(w), 2873(w), 1446(w), 1422(w), 1373(w), 1325(w), 1266(s), 1151(w), 1086(m), 1028(w), 1006(w), 896(w), 796(w), 739(s), 707(s). X-ray data for **7** in CIF format are available in the Supporting Information.

General method for the synthesis of chiral maleimides. The primary amine (0.070 mol) dissolved in a large excess of diethyl ether (100 mL) was added over 20 min using a dropping funnel to a 2-L flask containing maleic anhydride (6.85 g, 0.070 mol, 1 equiv) dissolved in diethyl ether (500 mL) [23]. Throughout the addition, the mixture turned into a thick off-white suspension. The suspension was concentrated to half-volume, cooled in the freezer, and vacuum-filtered, giving the crude acid as a thick paste. Acetic anhydride (300 mL) and sodium acetate (2.87 g, 0.035 mol, 0.5 equiv) were added to the crude acid and the mixture was heated to 100°C in a boiling water bath for 2 h. The mixture was then cooled to rt, diluted with water (200 mL), and portions of $NaHCO_3$ were added slowly with vigorous stirring until the acetic acid was nearly neutralized. The solution was extracted with ether (3 × 200 mL), and the organic extracts were washed with saturated $NaHCO_3$ until neutral, then washed with water (100 mL) and brine (100 mL), and dried over anhydrous Na_2SO_4. The solvent was removed using a rotating evaporator and the product was purified using flash chromatography on silica gel using ethyl acetate/hexanes to give the pure chiral maleimide in moderate yield (~50%).

(+)-(R)-2-(2,5-Dioxo-1H-pyrrol-1-yl)-2-phenylethyl acetate (10m). The general method gave **10m** (8.167 g, 45%) as a light-red oil: $[\alpha]^{23}{}_D$ +1.7 (c 10.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.43–7.46 (m, 2H, Ph), 7.33–7.40 (m, 3H, Ph), 6.71 (s, 2H, vinyl-H), 5.43 (dd, J = 10.5, 5.4 Hz, 1H, 2′-H), 4.99 (dd, J = 11.1, 10.5 Hz, 1H, 1′-H), 4.71 (dd, J = 11.1, 5.4 Hz, 1H, 1′-H), 2.04 (s, 3H, OAc); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 170.7, 170.6, 135.9, 134.3, 128.9, 128.6, 128.0, 62.4, 53.6, 20.8; IR (film, cm^{-1}) 3465(m), 3101(m), 2950(w), 1743(s), 1713(s), 1399(s), 1370(s), 1232(s), 1163(m), 1043(m), 828(m), 696(s); HRMS m/z (M + Na^+) calcd. for $C_{14}H_{13}NO_4$: 282.0738, found 282.0740.

(+)-(R)-1-(2-Methoxy-1-phenylethyl)-1H-pyrrole-2,5-dione (10n). The general method gave **10n** (7.608 g, 47%) as white crystals: mp 55–56°C; $[\alpha]^{23}{}_D$ +22.5 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.41–7.45 (m, 2H, Ph), 7.30–7.38 (m, 3H, Ph), 6.68 (s, 2H, vinyl-H), 5.38 (dd, J = 10.5, 5.4 Hz, 1H, 1′-H), 4.46 (dd, J = 11.2, 11.2 Hz, 1H, 2′-H), 3.82 (dd, J = 10.9, 5.4 Hz, 1H, 2′-H), 3.39 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 171.0, 137.0, 134.2, 128.8, 128.3, 128.0, 70.8, 58.8, 54.3; IR (film, cm^{-1}) 3460(bm), 3095(m), 2915(m), 2810(w), 1706(s), 1400(m), 1368(m), 1154(w), 1110(m), 826(m), 696(s); HRMS m/z (M + Na^+) calcd. for $C_{13}H_{13}NO_3$: 254.0783, found 254.0783.

General method for Diels-Alder reactions. A mixture of the vinylpyrrole (0.0050 mol, 1.1 equiv) and the maleimide (0.0045 mol) (1) in chloroform (20 mL) was stirred at rt for 24 h and, if TLC analysis indicated maleimide remaining, the mixture was also refluxed for 24 h (method A) or (2) in toluene (20 mL) was refluxed for 24 h (method B). The solvent was removed using a rotating evaporator. The crude adduct was purified with flash chromatography or MPLC with ethyl acetate/hexanes as eluent, except in the case of chiral adducts, which were used without further purification in the next step.

General method for the dehydrogenation of Diels-Alder adducts. A mixture of the adduct (3.76 mmol) and activated MnO_2 [29] (18.8 mmol, 5 equiv) in toluene (30 mL) was refluxed for 2–3 h until the reaction was complete, as indicated by TLC (method C), or refluxed for 24 h (method D). For dehydrogenation of chiral adducts, the crude Diels-Alder reaction product was placed in toluene (30 mL) along with activated MnO_2 (5 equiv) and refluxed for 24 h (method E). The mixture was cooled to rt and filtered through a fine glass frit. The insoluble manganese salts were washed with several portions of dichloromethane until the washings ran clear (5 × 20 mL), and the combined organic filtrate and washings were evaporated to dryness using a rotating evaporator. Flash chromatography or MPLC with ethyl acetate/hexanes as eluent provided the desired product in good yields.

2-Dimethylamino-3aα,4,5,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (11). Method A with vinylpyrrole **4** and maleimide **10a** gave **11** (597 mg, 64% crude yield, including contamination from double-addition type products, detected by TLC; the crude adduct was recrystallized from methylene chloride/petroleum ether, giving the pure compound, but the isolated yield is not available) as a light-brown powder: mp 56–57°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.02 (bs, 1H, 6-H), 6.68 (dd, J = 2.7, 2.7 Hz, 1H, 7-H), 6.37 (dd, J = 2.9, 2.9 Hz, 1H, 8-H), 3.89 (ddd, J = 8.1, 1.4, 1.4 Hz, 1H, 8bα-H), 3.18 (ddd, J = 7.8, 5.4, 5.4 Hz, 1H, 3aα-H), 2.84 (s, 6H, $N(CH_3)_2$), 2.57–2.65 (m, 2H, 5α-H and 5β-H), 2.34 (dddd, J = 13.6, 5.1, 5.1, 5.1 Hz, 1H, 4β-H), 2.00 (dddd, J = 13.7, 8.6, 6.3, 5.1 Hz, 1H, 4α-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 177.6, 176.7, 127.1, 117.2, 109.9, 107.7, 44.0, 38.8, 38.7, 22.2, 19.5; IR (film, cm^{-1}) 3361(bs), 2930(m), 1777(w), 1711(s), 1448(w), 1369(m), 1200(m), 1147(m), 719(w); HRMS m/z (M + Na^+) calcd. 256.1057, found 256.1057. Anal. Calcd. for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.59; H, 6.32; N, 17.90.

2-Benzyl-3aα,4,5,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (12). Method A with vinylpyrrole **4** and maleimide **10b** gave **12** (258 mg, 23%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.98 (bs, 1H, 6-H), 7.24–7.29 (m, 5H, Ph), 6.68 (dd, J = 2.7, 2.7 Hz, 1H, 7-H), 6.37 (dd, J = 2.7, 2.7 Hz, 1H, 8-H), 4.64 (AA′ d, J = 14.4 Hz, 1H, Bn), 4.58 (AA′ d, J = 14.1 Hz, 1H, Bn), 3.98 (ddd, J = 8.1, 1.2, 1.2 Hz, 1H, 8bα-H), 3.24 (ddd, J = 7.8, 5.1, 5.1 Hz, 1H, 3aα-H), 2.61 (dddd, J = 16.0, 5.3, 5.3, 0.9 Hz, 1H, 5β-H), 2.51 (dddd, J = 15.4, 9.9, 5.4, 0.9 Hz, 1H, 5α-H), 2.37 (dddd, J = 13.5, 4.8, 4.8, 4.8, 1H, 4β-H), 1.99 (dddd, J = 13.7, 9.8, 5.5, 5.3 Hz, 1H, 4α-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 179.0, 178.0, 136.0, 128.7, 128.4, 127.8, 127.2, 117.2, 110.4, 107.6, 42.3, 40.4, 40.1, 22.2, 19.6; IR (KBr, cm^{-1}) 3450s, 3100w, 2924m, 2980w, 1701s; HRMS *m/z* (M + Na$^+$) calcd. 303.1105, found 303.1093. Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.92; H, 5.75; N, 9.43.

2-Phenyl-3aα,4,5,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (13). Method A with vinylpyrrole **4** and maleimide **10c** gave **13** (980 mg, 92% crude yield, including contamination from double-addition type products, detected by TLC; the crude adduct was recrystallized from methylene chloride/petroleum ether, giving the pure compound, but the isolated yield is not available) as a light-brown powder: mp 155–156°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.95 (bs, 1H, 6-H), 7.41–7.47 (m, 2H, Ph), 7.33–7.39 (m, 1H, Ph), 7.23–7.28 (m, 2H, Ph), 6.70 (dd, *J* = 2.9, 2.9 Hz, 1H, 7-H), 6.41 (dd, *J* = 2.6, 2.6 Hz, 1H, 8-H), 4.15 (ddd, *J* = 8.1, 1.4, 1.4 Hz, 1H, 8bα-H), 3.45 (ddd, *J* = 8.1, 5.0, 5.0 Hz, 1H, 3aα-H), 2.63–2.67 (m, 2H, 5α-H and 5β-H), 2.53 (dddd, *J* = 13.6, 4.5, 4.5, 4.5 Hz, 1H, 4β-H), 2.06 (dddd, *J* = 13.4, 8.3, 7.6, 5.2 Hz, 1H, 4α-H); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 178.3, 177.3, 132.1, 129.1, 128.4, 127.3, 126.4, 117.3, 110.2, 107.7, 40.5, 40.4, 22.0, 19.4; IR (film, cm^{-1}) 3374(bs), 2857(m), 1775(w), 1707(s), 1596(w), 1498(m), 1383(m), 1177(m), 1064(m), 793(m), 723(m); HRMS *m/z* (M + Na$^+$) calcd. 289.0948, found 289.0947. Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 71.96; H, 5.43; N, 10.57.

2-(4-Ethylphenyl)-3aα,4,5,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (14). Method A with vinylpyrrole **4** and maleimide **10d** gave **14** (577 mg, 49%) as a white powder: mp 144–146°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.93 (bs, 1H, 6-H), 7.26 (d, *J* = 8.9, 2H, Ph), 7.15 (d, *J* = 8.4 Hz, 2H, Ph), 6.70 (dd, *J* = 2.6, 2.6 Hz, 1H, 7-H), 6.41 (dd, *J* = 2.7, 2.7 Hz, 1H, 8-H), 4.13 (ddd, *J* = 7.8, 1.4, 1.4 Hz, 1H, 8bα-H), 3.43 (ddd, *J* = 8.1, 5.0, 5.0 Hz, 1H, 3aα-H), 2.63–2.71 (m, 2H, 5α-H and 5β-H), 2.66 (q, overlapped, *J* = 7.6 Hz, 2H, CH_2CH$_3$), 2.52 (dddd, *J* = 13.7, 4.6, 4.6, 4.6 Hz, 1H, 4β-H), 2.06 (dddd, *J* = 13.4, 8.4, 7.3, 5.1 Hz, 1H, 4α-H), 1.23 (t, *J* = 7.7 Hz, 3H, CH$_2$CH_3); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 178.7, 177.7, 144.7, 129.6, 128.6, 127.3, 126.4, 117.3, 110.1, 107.4, 40.6, 40.4, 28.7, 22.1, 19.4, 15.6; IR (KBr, cm^{-1}) 3340(bs), 3030(w), 2970(m), 2940(m), 2860(w), 1780(m), 1700(s), 1600(w), 1510(m), 1445(w), 1395(s), 1360(w), 1310(w), 1295(w), 1205(m), 1195(m), 1170(m), 850(w), 815(w), 785(m), 720(m), 695(m); HRMS *m/z* (M + Na$^+$) calcd. 317.1261, found 317.1262. Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.60; H, 6.26; N, 9.36.

2-(4-Isopropylphenyl)-3aα,4,5,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (15). Method A with vinylpyrrole **4** and maleimide **10e** gave **15** (395 mg, 32%) as a light-orange powder: mp 188–190°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.93 (bs, 1H, 6-H), 7.29 (d, *J* = 8.4 Hz, 2H, Ph), 7.16 (d, *J* = 8.7 Hz, 2H, Ph), 6.70 (dd, *J* = 2.6, 2.6 Hz, 1H, 7-H), 6.41 (dd, *J* = 2.6, 2.6 Hz, 1H, 8-H), 4.13 (ddd, *J* = 8.1, 1.4, 1.4 Hz, 1H, 8bα-H), 3.44 (ddd, *J* = 8.1, 5.0, 5.0 Hz, 1H, 3aα-H), 2.92 (septet, *J* = 6.9 Hz, 1H, C*H*(CH$_3$)$_2$), 2.65 (m, 2H, 5α-H and 5β-H), 2.52 (dddd, *J* = 13.7, 4.6, 4.6, 4.6 Hz, 1H, 4β-H), 2.06 (dddd, *J* = 13.5, 8.3, 7.4, 5.1 Hz, 1H, 4α-H), 1.24 (d, *J* = 6.9 Hz, 6H, CH(CH_3)$_2$); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 178.6, 177.5, 149.2, 129.6, 127.2 (two peaks overlapped), 117.2, 110.2, 107.6, 40.5, 40.4, 34.0, 24.0, 22.0, 19.4; ^{13}C NMR (75 MHz, DMSO-d_6, δ) 179.0, 177.8, 148.9, 130.7, 127.2 (three peaks overlapped), 117.1, 110.0, 106.8, ~40 (two peaks obscured by DMSO), 33.7, 24.3, 22.5, 19.5; IR (KBr, cm^{-1}) 3444(m), 3353(bs), 3105(w), 2959(m), 2931(m), 2863(w), 1773(w), 1704(s), 1513(m), 1463(w), 1428(w), 1381(m), 1347(w), 1280(w), 1194(m), 1177(m), 1152(m), 1093(w), 1067(w), 1051(w), 721(m); HRMS *m/z* (M + Na$^+$) calcd. 331.1418, found 331.1410. Anal. Calcd. for $C_{19}H_{20}N_2O_3$: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.00; H, 6.51; N, 9.16.

2-(4-Methoxyphenyl)-3aα,4,5,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (16). Method A with vinylpyrrole **4** and maleimide **10f** gave **16** (1.067 g, 90% crude yield, including contamination from double-addition type products, detected by TLC; the crude adduct was recrystallized from methylene chloride/petroleum ether, giving the pure compound, but the isolated yield is not available) as a white powder: mp 187–188°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.94 (bs, 1H, 6-H), 7.17 (d, *J* = 9.0 Hz, 2H, Ph), 6.94 (d, *J* = 9.0 Hz, 2H, Ph), 6.70 (dd, *J* = 2.7, 2.7 Hz, 1H, 7-H), 6.41 (dd, *J* = 2.9, 2.9 Hz, 1H, 8-H), 4.15 (ddd, *J* = 8.1, 1.4, 1.4 Hz, 1H, 8bα-H), 3.82 (s, 3H, OCH$_3$), 3.45 (ddd, *J* = 7.8, 5.0, 5.0 Hz, 1H, 3aα-H), 2.63–2.67 (m, 2H, 5α-H and 5β-H), 2.53 (dddd, *J* = 13.5, 4.5, 4.5, 4.5 Hz, 1H, 4β-H), 2.06 (dddd, *J* = 13.7, 8.0, 7.7, 5.2 Hz, 1H, 4α-H); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 178.5, 177.5, 159.3, 127.7, 127.2, 124.8, 117.2, 114.4, 110.4, 107.7, 55.6, 40.5, 40.3, 22.0, 19.4; IR (film, cm^{-1}) 3378(bm), 2931(w), 2842(w), 1776(w), 1704(s), 1608(w), 1513(s), 1466(w), 1441(w), 1389(m), 1300(w), 1251(m), 1168(m), 1030(w), 729(w); HRMS *m/z* (M + Na$^+$) calcd. 319.1054, found 319.1056. Anal. Calcd. for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.86; H, 5.61; N, 9.28.

2-(4-Phenoxyphenyl)-3aα,4,5,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (17). Method A with vinylpyrrole **4** and maleimide **10h** gave **17** (473 mg, 33%) as a light-yellow powder: mp 200–202°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.93 (bs, 1H, 6-H), 7.33–7.39 (m, 2H, Ph), 7.21 (d, *J* = 9.0 Hz, 2H, Ph), 7.12–7.17 (m, 1H, Ph), 7.01–7.06 (m, 2H, Ph), 7.03 (d, overlapped, *J* = 9.0 Hz, 2H, Ph), 6.70 (dd, *J* = 2.7, 2.7 Hz, 1H, 7-H), 6.41 (dd, *J* = 2.7, 2.7 Hz, 1H, 8-H), 4.14 (ddd, *J* = 8.1, 1.4, 1.4 Hz, 1H, 8bα-H), 3.44 (ddd, *J* = 7.8, 4.9, 4.9 Hz, 1H, 3aα-H), 2.63–2.67 (m, 2H, 5α-H and 5β-H), 2.53 (dddd, *J* = 13.4, 4.6, 4.6, 4.6 Hz, 1H, 4β-H), 2.06 (dddd, *J* = 13.6, 8.5, 7.3, 5.1 Hz, 1H, 4α-H); ^{1}H NMR (300 MHz, DMSO-d_6) 10.60 (bs, 1H, 6-H), 7.39–7.44 (m, 2H, Ph), 7.15–7.20 (m, 1H, Ph), 7.19 (d, overlapped, *J* = 8.7 Hz, 2H, Ph), 7.03–7.07 (m, 2H, Ph), 7.05 (d, overlapped, *J* = 8.7 Hz, 2H, Ph), 6.59 (dd, *J* = 2.6, 2.6 Hz, 1H, 7-H), 6.04 (dd, *J* = 2.4, 2.4 Hz, 1H, 8-H), 4.02 (d, *J* = 8.1 Hz, 1H, 8bα-H), 3.51 (ddd, *J* = 8.1, 5.2, 5.2 Hz, 1H, 3aα-H), 2.58 (ddd, *J* = 15.5, 4.7, 4.7 Hz, 1H, 5β-H), 2.43 (ddd, 15.2, 10.0, 4.9 Hz, 1H, 5α-H), 2.23 (dddd, *J* = 13.5, 4.8, 4.8, 4.8 Hz, 1H, 4β-H), 1.88 (dddd, *J* = 13.6, 10.1, 5.2, 5.2 Hz, 1H, 4α-H); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.9, 177.8, 156.9, 156.6, 130.8, 129.1, 127.9, 127.3, 124.5, 119.7, 118.9, 117.1, 110.0, 106.8, 22.5, 21.3, 19.5, 18.2; IR (KBr, cm^{-1}) 3387(bs), 3104(w), 2960(w), 2934(w), 2854(w), 1771(w), 1702(s), 1588(m), 1506(m), 1487(m), 1430(w), 1390(m), 1352(w), 1285(w), 1244(s), 1199(m), 1179(m), 1155(m), 1093(w), 1069(w), 876(w), 723(m); HRMS *m/z* (M + Na$^+$) calcd. 381.1210, found 381.1202. Anal. Calcd. for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.95; H, 5.03; N, 7.71.

2-Dimethylamino-6-methyl-3aα,4,5,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (18). Method A with vinylpyrrole **3d** and maleimide **10a** gave **18** (880 mg, 89%) as a dark-brown oil: ^{1}H NMR (300 MHz, CDCl$_3$, δ) 6.54 (d, J = 2.7 Hz, 1H, 7-H), 6.28 (d, J = 2.7 Hz, 1H, 8-H), 3.87 (ddd, J = 8.1, 1.4, 1.4 Hz, 1H, 8bα-H), 3.50 (s, 3H, 6-CH$_3$), 3.15 (ddd, J = 8.1, 5.3, 5.3 Hz, 1H, 3aα-H), 2.85 (s, 6H, N(CH$_3$)$_2$), 2.58 (dddd, J = 16.1, 5.6, 5.6, 1.2 Hz, 1H, 5β-H), 2.48 (dddd, J = 15.5, 9.5, 5.6, 1.2 Hz, 1H, 5α-H), 2.34 (dddd, J = 13.4, 5.3, 5.3, 5.3 Hz, 1H, 4β-H), 1.99 (dddd, J = 13.5, 9.1, 5.5, 5.5 Hz, 1H, 4α-H); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 177.5, 176.6, 128.1, 121.5, 110.1, 106.5, 44.0, 38.9, 38.6, 33.2, 22.1, 18.2; IR (film, cm^{-1}) 3105(w), 3054(w), 2931(m), 2891(m), 1777(m), 1716(s), 1497(m), 1446(m), 1364(s), 1270(w), 1248(w), 1181(m), 1145(m), 1053(w), 714(m); HRMS *m/z* (M + Na$^+$) calcd. 270.1214, found 270.1221. Anal. Calcd. for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 62.94; H, 7.07; N, 16.76.

6-Methyl-2-phenyl-3aα,4,5,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (19). Method A with vinylpyrrole **3d** and maleimide **10c** gave **19** (1.054 g, 94%) as a light-brown powder: mp 169–170°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.38–7.47 (m, 2H, Ph), 7.32–7.38 (m, 1H, Ph), 7.24–7.29 (m, 2H, Ph), 6.57 (d, J = 2.7, 2.7 Hz, 1H, 7-H), 6.33 (d, J = 2.7, 2.7 Hz, 1H, 8-H), 4.13 (ddd, J = 8.4, 1.4, 1.4 Hz, 1H, 8bα-H), 3.52 (s, 3H, 6-CH$_3$), 3.43 (ddd, J = 8.1, 4.5, 4.4 Hz, 1H, 3aα-H), 2.50–2.68 (m, 3H, 4β-H, 5α-H and 5β-H), 2.05 (dddd, J = 15.4, 12.5, 6.2, 5.0 Hz, 1H, 4α-H); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 178.2, 177.2, 132.2, 129.0, 128.3, 128.2, 126.4, 121.6, 110.6, 106.5, 40.6, 40.4, 33.2, 21.7, 18.2; IR (film, cm^{-1}) 3060(w), 2931(m), 2849(w), 1777(w), 1711(s), 1596(w), 1498(m), 1455(w), 1380(m), 1290(w), 1269(w), 1173(m), 1150(m), 718(m), 692(m); HRMS *m/z* (M + Na$^+$) calcd. 303.1105, found 303.1109. Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.60; H, 5.67; N, 9.81.

2-(4-Methoxyphenyl)-6-methyl-3aα,4,5,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (20). Method A with vinylpyrrole **3d** and maleimide **10f** gave **20** (1.154 g, 93%) as a cream-colored powder: mp 161–162°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.17 (d, J = 9.0 Hz, 2H, Ph), 6.94 (d, J = 9.0 Hz, 2H, Ph), 6.57 (d, J = 2.7 Hz, 1H, 7-H), 6.33 (d, J = 2.7 Hz, 1H, 8-H), 4.11 (ddd, J = 8.4, 2.0, 2.0 Hz, 1H, 8bα-H), 3.82 (s, 3H, OCH$_3$), 3.52 (s, 3H, 6-CH$_3$), 3.40 (ddd, J = 7.8, 4.7, 4.7 Hz, 1H, 3aα-H), 2.49–2.68 (m, 3H, 4β-H, 5α-H and 5β-H), 2.05 (dddd, J = 16.5, 7.6, 6.0, 4.5 Hz, 1H, 4α-H); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 178.5, 177.5, 159.3, 128.2, 127.6, 124.9, 121.5, 114.3, 110.6, 106.5, 55.6, 40.5, 40.4, 33.2, 21.8, 18.2; IR (film, cm^{-1}) 2934(w), 2841(w), 1776(w), 1709(s), 1609(w), 1513(s), 1442(w), 1386(m), 1300(w), 1250(m), 1171(m), 1151(w), 1030(w); HRMS *m/z* (M + Na$^+$) calcd. 333.1210, found 333.1222. Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.89; H, 6.00; N, 8.90.

2-Dimethylamino-5β,6-dimethyl-3aα,4,5α,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (21). Method A with vinylpyrrole **3e** and maleimide **10a** with reflux gave **21** (899 mg, 86%) as a light-orange powder: mp 100–101°C; maj/min = 13:1; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 6.55 (d, J = 2.7 Hz, 1H, 7-H), 6.28 (d, J = 2.7 Hz, 1H, 8-H), 3.92 (dd, J = 9.0, 0.6 Hz, 1H, 8bα-H), 3.53 (s, 3H, 6-CH$_3$), 3.14 (ddd, J = 8.9, 7.0, 2.3 Hz, 1H, 3aα-H), 3.02 (dddq, J = 7.2, 5.7, 2.1, 0.6 Hz, 1H, 5α-H), 2.87 (s, 6H, N(CH$_3$)$_2$), 2.50 (ddd, J = 14.1, 2.1, 2.1 Hz, 1H, 4β-H), 2.04 (ddd, J = 14.1, 7.2, 5.7 Hz, 1H, 4α-H), 1.11 (d, J = 7.2 Hz, 3H, 5β-CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 178.7, 176.6, 132.5, 121.9, 109.2, 106.5, 43.7, 38.3, 36.8, 33.0, 28.8, 25.3, 22.0; IR (film, cm^{-1}) 2962(s), 1777(m), 1711(s), 1500(w), 1446(w), 1369(m), 1293(w), 1189(m), 1149(m), 1046(w); HRMS *m/z* (M + Na$^+$) calcd. 284.1370, found 284.1373. Anal. Calcd. for $C_{14}H_{19}N_3O_2$: C, 64.35; H, 7.33; N, 16.08. Found: C, 64.15; H, 7.12; N, 16.18.

5β,6-Dimethyl-2-phenyl-3aα,4,5α,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (22). Method A with vinylpyrrole **3e** and maleimide **10c** with reflux gave **22** (1.071 g, 91%) as a light-yellow cream-colored powder: mp 239–240°C; maj/min = 54:1; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.42–7.48 (m, 2H, Ph), 7.33–7.39 (m, 1H, Ph), 7.25–7.29 (m, 2H, Ph), 6.58 (d, J = 3.0 Hz, 1H, 7-H), 6.32 (d, J = 2.7 Hz, 1H, 8-H), 4.16 (d, J = 8.7 Hz, 1H, 8bα-H), 3.55 (s, 3H, 6-CH$_3$), 3.39 (ddd, J = 8.8, 6.7, 2.2 Hz, 1H, 3aα-H), 3.08 (ddq, J = 6.6, 6.6, 2.4 Hz, 1H, 5α-H), 2.62 (ddd, J = 14.1, 2.1, 2.1 Hz, 1H, 4β-H), 2.16 (ddd, J = 14.0, 6.3, 6.3 Hz, 1H, 4α-H), 1.19 (d, J = 6.9 Hz, 3H, 5β-CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 179.5, 177.3, 132.6, 132.3, 129.1, 128.4, 126.4, 122.0, 109.5, 106.5, 40.0, 38.6, 33.1, 29.0, 25.4, 22.2; IR (film, cm^{-1}) 2960(m), 2956(m), 1775(w), 1711(s), 1595(w), 1499(m), 1453(w), 1380(m), 1348(m), 1293(w), 1270(w), 1175(m), 1157(m), 1062(w), 741(w), 728(w), 717(w), 691(m); HRMS *m/z* (M + Na$^+$) calcd. 317.1261, found 317.1253. Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.55; H, 6.31; N, 9.51.

2-(4-Methoxyphenyl)-5β,6-dimethyl-3aα,4,5α,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (23). Method A with vinylpyrrole **3e** and maleimide **10f** with reflux gave **23** (1.207 g, 93%) as a white powder: mp 190–191°C; maj/min = 37:1; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.18 (d, J = 9.3 Hz, 2H, Ph), 6.95 (d, J = 9.3 Hz, 2H, Ph), 6.57 (d, J = 3.0 Hz, 1H, 7-H), 6.32 (d, J = 2.7 Hz, 1H, 8-H), 4.15 (dd, J = 8.7, 0.6 Hz, 1H, 8bα-H), 3.82 (s, 3H, OCH$_3$), 3.55 (s, 3H, 6-CH$_3$), 3.37 (ddd, J = 8.9, 6.8, 2.3 Hz, 1H, 3aα-H), 3.07 (dddq, J = 6.9, 5.7, 2.1, 0.6 Hz, 1H, 5α-H), 2.61 (ddd, J = 14.1, 2.1, 2.1 Hz, 1H, 4β-H), 2.15 (ddd, J = 14.1, 6.9, 5.7 Hz, 1H, 4α-H), 1.17 (d, J = 6.9 Hz, 3H, 5β-CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 179.7, 177.5, 159.4, 132.6, 127.7, 125.0, 122.0, 114.5, 109.6, 106.5, 55.6, 39.9, 38.5, 33.1, 29.0, 25.4, 22.2; IR (film, cm^{-1}) 2964(m), 1777(w), 1709(s), 1610(w), 1513(s), 1386(m), 1299(w), 1250(m), 1196(m), 1030(w); HRMS *m/z* (M + Na$^+$) calcd. 347.1367, found 347.1367. Anal. Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.20; H, 6.37; N, 8.44.

2-Dimethylamino-4-methyl-3aα,4,5,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (24). Method A with vinylpyrrole **3b** and maleimide **10a** with reflux gave **24** (564 mg, 57%) as a brown powder: mp 117–118°C; maj/min = 1.4:1.0; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.94 (bs, 1H, 6-H), 6.66–6.69 (m, 1H, 7-H), 6.35–6.66 (m, 1H, 8-H), 3.83–3.87 (m, 1H, 8bα-H), 3.12 (ddd, J = 7.8, 4.4, 0.9 Hz, 1H, 3aαmin-H), 2.83–2.88 (m, 1H, 3aαmaj-H), 2.85 (s, overlapped by 3aαmaj-H, 6H, N(CH$_3$)$_2$maj), 2.84 (s, overlapped by 3aαmaj-H, 6H, N(CH$_3$)$_2$min), 2.32–2.78 (m, 3H, 4-H and 5-H × 2), 1.34 (d, J = 6.9 Hz, 3H, 4βmin-CH$_3$), 1.56 (d, J = 6.9 Hz, 3H, 4αmaj-CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 177.2, 176.6, 125.7, 117.2, 109.0, 107.5, 45.1, 44.0, 37.9, 28.2, 27.4, 19.5; IR (film, cm^{-1}) 3321(bm), 2960(m), 1776(w), 1710(s), 1448(w), 1367(m), 1199(m), 1145(m), 1063(w), 719(w); HRMS *m/z* (M + Na$^+$) calcd. 270.1214, found 270.1217. Anal. Calcd. for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 63.40; H, 7.10; N, 16.88.

4-Methyl-2-phenyl-3aα,4,5,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (25). Method A with vinylpyrrole **3b** and maleimide **10c** with reflux gave **25** (1.043 g, 93%) as a cream-colored powder: mp 208–209°C; maj/min = 2.0:1.0; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.90 (bs, 1H, 6-H), 7.21–7.46 (m, 5H, Ph), 6.68–6.71 (m, 1H, 7-H), 6.39–6.41 (m, 1H, 8-H), 4.11 (d, *J* = 7.8 Hz, 1H, 8bαmin-H), 4.10 (d, overlapped by 8bαmin-H, *J* = 7.5 Hz, 1H, 8bαmaj-H), 3.38 (dd, *J* = 7.7, 4.1 Hz, 1H, 3aαmin-H), 3.14 (ddd, *J* = 8.0, 5.0, 0.9 Hz, 1H, 3aαmaj-H), 2.39–2.86 (m, 3H, 4-H and 5-H × 2), 1.47 (d, *J* = 6.9 Hz, 3H, 4βmin-CH_3), 1.21 (d, *J* = 6.9 Hz, 3H, 4αmaj-CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.3, 177.5, 133.0, 129.4, 128.6, 127.4, 125.8, 117.2, 109.0, 106.8, 46.7, 41.3, 28.6, 27.5, 19.9; IR (film, cm^{-1}) 3367(bs), 3050(m), 2990(m), 2900(m), 1776(w), 1693(s), 1591(w), 1495(w), 1453(w), 1386(m), 1177(m), 1164(m), 1065(w), 786(w), 769(w), 741(w); HRMS *m/z* (M + Na^+) calcd. 303.1105, found 303.1103. Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.61; H, 5.59; N, 9.96.

2-(4-Methoxyphenyl)-4-methyl-3aα,4,5,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (26). Method A with vinylpyrrole **3b** and maleimide **10f** with reflux gave **26** (1.117 g, 90%) as a cream-colored powder: mp 163–164°C; maj/min = 1.3:1.0; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.91 (bs, 1H, 6-H), 7.10–7.19 (m, 4H, Ph), 6.68–6.71 (m, 1H, 7-H), 6.38–6.41 (m, 1H, 8-H), 4.05–4.11 (m, 1H, 8bα-H), 3.82 (s, 3H, OCH_3), 3.36 (ddd, *J* = 7.5, 4.2, 0.6 Hz, 1H, 3aαmin-H), 3.11 (ddd, *J* = 8.0, 4.5, 0.9 Hz, 1H, 3aαmaj-H), 2.37–2.86 (m, 3H, 4-H and 5-H × 2), 1.45 (d, *J* = 6.9 Hz, 1H, 4βmin-CH_3), 1.21 (d, *J* = 7.2 Hz, 1H, 4αmaj-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 178.1, 177.5, 159.3, 127.7, 125.7, 124.7, 117.3, 114.4, 109.3, 107.5, 55.6, 46.8, 39.4, 28.0, 27.2, 19.6; IR (film, cm^{-1}) 3370(bs), 2930(m), 2870(m), 1767(w), 1703(s), 1609(w), 1513(s), 1442(w), 1389(m), 1300(w), 1251(m), 1192(m), 1166(m), 1028(w), 721(w); HRMS *m/z* (M + Na^+) calcd. 333.1210, found 333.1216. Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.45; H, 6.00; N, 8.83.

2-Dimethylamino-4,6-dimethyl-3aα,4,5,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (27). Method A with vinylpyrrole **3f** and maleimide **10a** with reflux gave **27** (700 mg, 67%) as a cream-colored powder: mp 85–86°C; maj/min = 1.2:1.0; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 6.55 (d, *J* = 2.7 Hz, 1H, 7min-H), 6.52 (d, *J* = 2.7 Hz, 1H, 7maj-H), 6.28 (d, *J* = 2.7 Hz, 1H, 8min-H), 6.26 (d, *J* = 2.7 Hz, 1H, 8maj-H), 3.85 (ddd, *J* = 7.5, 1.4, 1.4 Hz, 1H, 8bαmaj-H), 3.80–3.84 (m, overlapped by 8bαmaj-H, 1H, 8bαmin-H), 3.09 (ddd, *J* = 7.6, 4.1, 0.6 Hz, 1H, 3aαmaj-H), 2.81–2.86 (m, 1H, 3aαmin-H), 2.85 (s, overlapped by 3aαmin-H, 6H, $N(CH_3)_2$min), 2.83 (s, overlapped by 3aαmin-H, 6H, $N(CH_3)_2$maj), 2.27–2.70 (m, 3H, 4-H and 5-H × 2), 1.40 (d, *J* = 6.6 Hz, 3H, 4βmaj-CH_3), 1.18 (d, *J* = 6.6 Hz, 4αmaj-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 176.8, 176.5, 128.0, 121.4, 110.2, 106.3, 44.0, 43.5, 39.9, 33.1, 29.9, 26.5, 18.2; IR (film, cm^{-1}) 2956(m), 2893(m), 1776(m), 1713(s), 1500(w), 1448(m), 1365(m), 1196(m), 1181(m), 1144(m), 706(w), 662(w); HRMS *m/z* (M + Na^+) calcd. 284.1370, found 284.1370. Anal. Calcd. for $C_{14}H_{19}N_3O_2$: C, 64.35; H, 7.33; N, 16.08. Found: C, 64.30; H, 7.51; N, 16.11.

4,6-Dimethyl-2-phenyl-3aα,4,5,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (28). Method A with vinylpyrrole **3f** and maleimide **10c** with reflux gave **28** (1.048 g, 89%) as a light-brown powder: mp 178–179°C; maj/min = 2.4:1.0; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.20–7.46 (m, 5H, Ph), 6.57 (d, *J* = 2.7 Hz, 1H, 7min-H), 6.55 (d, *J* = 2.7 Hz, 1H, 7maj-H), 6.32 (d, *J* = 2.7 Hz, 1H, 8min-H), 6.30 (d, *J* = 2.7 Hz, 1H, 8maj-H), 4.07–4.13 (m, 1H, 8bα-H), 3.51 (s, 3H, 6-CH_3), 3.36 (ddd, *J* = 7.4, 3.8, 1.0 Hz, 1H, 3αmaj-H), 3.12 (ddd, *J* = 8.0, 4.8, 0.9 Hz, 1H, 3αmin-H), 2.32–2.83 (m, 3H, 4-H and 5-H × 2), 1.52 (d, *J* = 6.9 Hz, 3H, 4αmaj-CH_3), 1.23 (d, *J* = 6.9 Hz, 3H, 4βmin-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 177.3, 177.0, 132.1, 129.0, 128.4, 128.2, 126.4, 121.6, 110.7, 106.4, 45.5, 42.0, 33.2, 30.0, 26.4, 18.7; IR (film, cm^{-1}) 3060(m), 3030(m), 2929(m), 1775(w), 1710(s), 1597(w), 1498(m), 1453(w), 1377(m), 1174(m), 1142(m), 691(w); HRMS *m/z* (M + Na^+) calcd. 317.1261, found 317.1268. Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.51; H, 5.98; N, 9.54.

2-(4-Methoxyphenyl)-4,6-dimethyl-3aα,4,5,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (29). Method A with vinylpyrrole **3f** and maleimide **10f** with reflux gave **29** (1.090 g, 84%) as a light-brown powder: mp 126–127°C; maj/min = 2.4:1.0; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.10–7.19 (m, 2H, Ph), 6.90–7.00 (m, 2H, Ph), 6.57 (d, *J* = 2.7 Hz, 1H, 7min-H), 6.55 (d, *J* = 3.0, 1H, 7maj-H), 6.32 (d, *J* = 3.0 Hz, 1H, 8min-H), 6.30 (d, *J* = 3.0 Hz, 1H, 8maj-H), 4.05–4.10 (m, 1H, 8bα-H), 3.82 (s, 3H, OCH_3), 3.51 (s, 3H 6-CH_3), 3.33 (ddd, *J* = 7.6, 3.8, 1.1 Hz, 1H, 3αmaj-H), 3.09 (ddd, *J* = 7.9, 4.6, 0.8, 1H, 3aαmin-H), 2.32–2.81 (m, 3H, 4-H and 5-H × 2), 1.51 (d, *J* = 6.9 Hz, 3H, 4αmaj-CH_3), 1.22 (d, *J* = 7.2 Hz, 1H, 4βmin-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 177.6, 177.3, 159.2, 128.4, 127.7, 124.8, 121.5, 114.3, 110.8, 106.4, 55.6, 45.4, 41.8, 33.2, 30.0, 26.5, 18.6; IR (film, cm^{-1}) 2950(m), 2931(m), 2839(m), 1770(w), 1708(s), 1610(w), 1513(s), 1442(w), 1384(m), 1300(w), 1250(m), 1168(m), 1143(w), 1031(w), 704(w); HRMS *m/z* (M + Na^+) calcd. 347.1367, found 347.1362. Anal. Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.51; H, 6.40; N, 8.79.

4α-Ethyl-2-phenyl-3aα,4β,5,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (30). Method B with vinylpyrrole **5a** and maleimide **10c** gave **30** (424 mg, 36%) as a white powder: mp 203–204°C; ^{1}H NMR (500 MHz, $CDCl_3$, δ) 7.93 (bs, 1H, 6-H), 7.40–7.44 (m, 2H, Ph), 7.32–7.36 (m, 1H, Ph), 7.22–7.27 (m, 2H, Ph), 6.66 (dd, *J* = 2.8, 2.8 Hz, 1H, 7-H), 6.35 (dd, *J* = 2.5, 2.5 Hz, 1H, 8-H), 4.05 (ddd, *J* = 7.5, 1.4, 1.4 Hz, 1H, 8bα-H), 3.28 (ddd, *J* = 7.5, 4.0, 0.9 Hz, 1H, 3aα-H), 2.77 (ddd, *J* = 15.8, 5.3, 1.7 Hz, 1H, 5β-H), 2.61 (m, 1H, 4β-H), 2.51 (dd, *J* = 15.8, 2.5 Hz, 1H, 5α-H, see 3aα-H and 8bα-H), 1.56 (ddq, *J* = 14.1, 8.0, 7.3 Hz, 1H, 4α-$C\mathit{H}_2CH_3$), 1.44 (ddq, *J* = 14.4, 7.5, 7.3 Hz, 1H, 4α-$C\mathit{H}_2CH_3$), 1.00 (dd, *J* = 7.3, 7.3 Hz, 3H, 4α-$CH_2C\mathit{H}_3$); ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.57 (bs, 1H, 6-H), 7.35–7.48 (m, 3H, Ph), 7.17–7.18 (m, 2H, Ph), 6.59 (dd, *J* = 2.6, 2.6 Hz, 1H, 7-H), 6.02 (dd, *J* = 2.6, 2.6 Hz, 1H, 8-H), 3.98 (d, *J* = 7.8 Hz, 1H, 8bα-H), 3.41 (ddd, *J* = 8.1, 4.2, 0.9 Hz, 1H, 3aα-H), 2.60 (dd, *J* = 15.9, 5.1 Hz, 1H, 5β-H), 2.45 (dd, *J* = 15.6, 3.6 Hz, 1H, 5α-H), 2.32–2.40 (m, 1H, 4β-H), 1.47 (ddq, *J* = 14.2, 7.5, 6.8 Hz, 1H, 4α-$C\mathit{H}_2CH_3$), 1.32 (ddq, *J* = 14.3, 7.7, 7.5 Hz, 1H, 4α-$C\mathit{H}_2CH_3$), 0.93 (dd, *J* = 7.5, 7.5 Hz, 3H, 4α-$CH_2C\mathit{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 178.1, 177.3, 132.1, 129.0, 128.3, 126.4, 125.6, 117.2, 109.6, 107.6, 45.2, 39.3, 33.9, 25.6, 23.8, 12.1; ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.6, 177.7, 132.9, 129.4, 128.6, 127.3, 125.5, 117.2, 109.2, 106.7, 44.8, ~40 (obscured by DMSO), 34.4, 25.6, 24.1, 12.3; IR (KBr, cm^{-1}) 3346(bs), 3064(w), 2962(m), 2962(m), 2925(m), 2875(m), 2859(m), 1771(m), 1699(s), 1599(w), 1499(m), 1459(w), 1390(m), 1308(w), 1287(w), 1187(s), 1150(m), 1083(w), 1065(w), 743(m), 731(m), 689(m); HRMS *m*/*z* (M + Na$^+$) calcd. 317.1261, found 317.1263. Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.60; H, 6.08; N, 9.71.

4α-Ethyl-2-(4-ethylphenyl)-3aα,4β,5,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (31). Method A with vinylpyrrole **5a** and maleimide **10d** gave **31** (903 mg, 70%), method B with vinylpyrrole **5a** and maleimide **10d** gave **31** (529 mg, 41%), as a light-orange powder: mp 247–248°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.93 (bs, 1H, 6-H), 7.25 (d, J = 8.1 Hz, 2H, Ph), 7.14 (d, J = 8.4 Hz, 2H, Ph), 6.67 (dd, J = 2.6, 2.6 Hz, 1H, 7-H), 6.36 (dd, J = 2.7, 2.7, 1H, 8-H), 4.05 (ddd, J = 7.8, 1.2, 1.2 Hz, 1H, 8bα-H), 3.28 (ddd, J = 7.8, 3.9, 0.9 Hz, 1H, 3aα-H), 2.78 (ddd, J = 15.3, 5.4, 0.9 Hz, 1H, 5β-H), 2.66 (q, J = 7.6 Hz, 2H, PhCH_2CH$_3$), 2.58–2.64 (m, overlapped by PhCH_2CH$_3$, 1H, 4β-H), 2.52 (dd, J = 15.6, 3.0 Hz, 1H, 5α-H, see 3aα-H and 8bα-H), 1.56 (ddq, J = 13.8, 7.5, 6.9 Hz, 1H, 4α-CH_2CH$_3$), 1.44 (ddq, J = 14.3, 7.4, 7.2 Hz, 1H, 4α-CH_2CH$_3$), 1.23 (t, J = 7.7 Hz, 3H, PhCH$_2$CH_3), 1.00 (dd, J = 7.7 Hz, 3H, 4α-CH$_2$CH_3); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 178.3, 177.5, 144.6, 129.6, 128.5, 126.3, 125.6, 117.1, 109.7, 107.6, 45.2, 39.3, 34.0, 28.6, 25.6, 23.8, 15.5, 12.1; IR (KBr, cm^{-1}) 3342(bs), 2960(m), 2929(w), 2872(w), 1768(m), 1697(s), 1514(m), 1461(w), 1444(w), 1392(m), 1306(w), 1289(w), 1190(s), 1151(m), 834(w), 772(m), 723(m), 702(m); HRMS *m*/*z* (M + Na$^+$) calcd. 345.1574, found 345.1575. Anal. Calcd. for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.48; H, 6.96; N, 8.68.

4-(4α-Ethyl-1,3-dioxo-3aα,4β,5,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indol-2-yl)phenyl acetate (32). Method B with vinylpyrrole **5a** and maleimide **10g** gave **32** (437 mg, 31%) as a cream-colored powder: mp 218–219°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.93 (bs, 1H, 6-H), 7.29 (d, J = 9.3 Hz, 2H, Ph), 7.16 (d, J = 9.0 Hz, 2H, Ph), 6.67 (dd, J = 2.7, 2.7 Hz, 1H, 7-H), 6.35 (dd, J = 2.7, 2.7 Hz, 1H, 8-H), 4.06 (ddd, J = 7.8, 1.4, 1.4 Hz, 1H, 8bα-H), 3.29 (ddd, J = 7.7, 3.9, 0.9 Hz, 1H, 3aα-H), 2.78 (ddd, J = 14.4, 5.4, 1.2 Hz, 1H, 5β-H), 2.58–2.65 (m, 1H, 4β-H), 2.52 (dd, J = 15.8, 3.2 Hz, 1H, 5α-H, see 3aα-H and 8bα-H), 2.29 (s, 3H, Ac), 1.56 (ddq, J = 14.4, 7.5, 7.4 Hz, 1H, 4α-CH_2CH$_3$), 1.47 (ddq, J = 14.7, 7.4, 7.2 Hz, 1H, 4α-CH_2CH$_3$), 1.01 (dd, J = 7.4, 7.4 Hz, 3H, 4α-CH$_2$CH_3); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 177.9, 177.1, 169.2, 150.1, 129.5, 127.4, 125.6, 122.2, 117.2, 109.5, 107.5, 45.1, 39.3, 33.9, 25.6, 23.8, 21.2, 12.1; IR (KBr, cm^{-1}) 3359(bs), 3114(w), 3081(w), 2964(m), 2926(m), 2876(m), 2855(w), 1767(m), 1699(s), 1601(w), 1510(m), 1464(w), 1441(w), 1392(s), 1372(m), 1199(s), 1150(m), 1105(w), 1084(w), 1016(w), 938(w), 911(w), 849(w), 773(m), 719(m), 706(m); HRMS *m*/*z* (M + Na$^+$) calcd. 375.1316, found 375.1317. Anal. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 67.89; H, 5.53; N, 7.90.

4α-Ethyl-2-(4-hydroxyphenyl)-3aα,4β,5,8bα-tetrahydro-2H, 6H-pyrrolo[3,4-e]indole-1,3-dione (33). Method B with vinylpyrrole **5a** and maleimide **10i** gave **33** (670 mg, 54%) as a cream-colored powder: mp 238–239°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 10.54 (bs, 1H, 6-H), 9.70 (s, 1H, OH), 6.92 (d, J = 9.0 Hz, 2H, Ph), 6.78 (d, J = 8.7 Hz, 2H, Ph), 6.57 (dd, J = 2.6, 2.6 Hz, 1H, 7-H), 6.01 (dd, J = 2.4, 2.4 Hz, 1H, 8-H), 3.93 (d, J = 7.8 Hz, 1H, 8bα-H), 3.35 (dd, overlapped by H$_2$O, J = 4.2, 7.8 Hz, 1H, 3aα-H), 2.57 (dd, J = 16.2, 4.8 Hz, 1H, 5β-H), 2.44 (dd, J = 15.6, 3.3 Hz, 1H, 5α-H), 2.33–2.39 (m, 1H, 4β-H), 1.45 (ddq, J = 13.8, 7.5, 7.2 Hz, 1H, 4α-CH_2CH$_3$), 1.27 (ddq, J = 14.1, 7.7, 7.5 Hz, 1H, 4α-CH_2CH$_3$), 0.91 (dd, J = 7.5, 7.5 Hz, 3H, 4α-CH$_2$CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.9, 178.0, 157.6, 128.6, 125.5, 124.0, 117.1, 115.8, 109.4, 106.7, 44.6, ~40 (obscured by DMSO), 34.4, 25.6, 24.1, 12.3; IR (KBr, cm^{-1}) 3467(m), 3374(bm), 2965(w), 2927(w), 2877(w), 1767(w), 1696(s), 1601(w), 1518(m), 1447(w), 1398(m), 1274(w), 1198(m), 1165(m), 1105(w), 1065(w), 1021(w), 837(w), 776(w), 725(m), 708(m); HRMS *m*/*z* (M + Na$^+$) calcd. 333.1210, found 333.1205. Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.49; H, 6.05; N, 9.20.

2-(4-Chlorophenyl)-4α-ethyl-3aα,4β,5,8bα-tetrahydro-2H, 6H-pyrrolo[3,4-e]indole-1,3-dione (34). Method B with vinylpyrrole **5a** and maleimide **10j** gave **34** (421 mg, 32%) as a white powder: mp 197–198°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.88 (bs, 1H, 6-H), 7.40 (d, J = 9.0 Hz, 2H, Ph), 7.22 (d, J = 9.0 Hz, 2H, Ph), 6.69 (dd, J = 2.9, 2.9 Hz, 1H, 7-H), 6.36 (d, J = 2.7, 2.7 Hz, 1H, 8-H), 4.06 (ddd, J = 8.1, 1.4, 1.4 Hz, 1H, 8bα-H), 3.29 (ddd, J = 7.8, 3.6, 1.0 Hz, 1H, 3aα-H), 2.78 (ddd, J = 15.3, 5.4, 1.5 Hz, 1H, 5β-H), 2.58–2.65 (m, 1H, 4β-H), 2.53 (dd, J = 16.0, 2.6 Hz, 1H, 5α-H, see 3aα-H and 8bα-H), 1.54 (ddq, overlapped by H$_2$O, J = 14.5, 1.2, 7.2 Hz, 1H, 4α-CH_2CH$_3$), 1.44 (ddq, J = 14.5, 7.2, 7.2 Hz, 1H, 4α-CH_2CH$_3$), 1.28 (dd, J = 7.2, 7.2 Hz, 3H, 4α-CH$_2$CH_3); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 177.8, 177.0, 134.0, 130.6, 129.2, 127.6, 125.6, 117.3, 109.4, 107.6, 45.1, 39.3, 33.9, 25.6, 23.8, 12.1; IR (KBr, cm^{-1}) 3370(s), 3342(s), 3095(w), 2969(m), 2925(m), 2877(m), 2856(m), 1769(m), 1698(s), 1600(w), 1495(m), 1463(w), 1445(w), 1390(m), 1358(m), 1308(w), 1274(w), 1183(s), 1149(m), 1090(m), 1066(w), 1017(w), 768(m), 715(m); HRMS *m*/*z* (M + Na$^+$) calcd. 351.0872, found 351.0871. Anal. Calcd. for $C_{18}H_{17}ClN_2O_2$: C, 65.75; H, 5.21; N, 8.52. Found: C, 65.58; H, 5.09; N, 8.69.

2-(4-Bromophenyl)-4α-ethyl-3aα,4β,5,8bα-tetrahydro-2H, 6H-pyrrolo[3,4-e]indole-1,3-dione (35). Method B with vinylpyrrole **5a** and maleimide **10k** gave **35** (523 mg, 35%) as a cream-colored powder: mp 193–194°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.88 (bs, 1H, 6-H), 7.55 (d, J = 8.7 Hz, 2H, Ph), 7.16 (d, J = 8.7 Hz, 2H, Ph), 6.69 (dd, J = 2.6, 2.6 Hz, 1H, 7-H), 6.35 (dd, J = 2.7, 2.7 Hz, 1H, 8-H), 4.06 (ddd, J = 7.5, 1.2, 1.2 Hz, 1H, 8bα-H), 3.29 (ddd, J = 7.8, 3.6, 0.9 Hz, 1H, 3aα-H), 2.78 (ddd, J = 15.6, 5.4, 1.8 Hz, 1H, 5β-H), 2.59–2.65 (m, 1H, 4β-H), 2.53 (dd, J = 16.5, 2.1 Hz, 1H, 5α-H, see 3aα-H and 8bα-H), 1.53 (ddq, overlapped by H$_2$O, J = 14.0, 7.5, 7.5 Hz, 1H, 4α-CH_2CH$_3$), 1.44 (ddq, J = 14.0, 7.5, 7.5 Hz, 1H, 4α-CH_2CH$_3$), 1.01 (dd, J = 7.4, 7.4 Hz, 3H, 4α-CH$_2$CH_3); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 177.8, 176.9, 132.2, 131.1, 127.9, 125.6, 122.0, 117.3, 109.4, 107.6, 45.2, 39.3, 33.9, 25.6, 23.8, 12.1; IR (KBr, cm^{-1}) 3364(s), 3341(s), 3092(w), 2963(m), 2924(m), 2875(m), 2860(m), 1771(w), 1699(s), 1599(w), 1492(m), 1463(w), 1444(w), 1389(m), 1358(w), 1307(w), 1274(w), 1184(s), 1148(m), 1069(m), 1015(m), 935(w), 829(w), 783(w), 767(m), 714(m); HRMS *m*/*z* (M + Na$^+$) calcd. 395.0366, found 395.0363. Anal. Calcd. for $C_{18}H_{17}BrN_2O_2$: C, 57.92; H, 4.59; N, 7.51. Found: C, 57.71; H, 4.54; N, 7.59.

4α-Ethyl-2-(4-nitrophenyl)-3aα,4β,5,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (36). Method B with vinylpyrrole

5a and maleimide **10l** gave **36** (611 mg, 45%) as a cream-colored powder: mp 145–146°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.29 (d, *J* = 9.0 Hz, 2H, Ph), 7.92 (bs, 1H, 6-H), 7.57 (d, *J* = 9.3 Hz, 2H, Ph), 6.71 (dd, *J* = 2.9, 2.9 Hz, 1H, 7-H), 6.35 (dd, *J* = 2.7, 2.7 Hz, 1H, 8-H), 4.11 (ddd, *J* = 7.9, 1.4, 1.4 Hz, 1H, 8bα-H), 3.34 (ddd, *J* = 7.7, 3.8, 0.9 Hz, 1H, 3aα-H), 2.80 (ddd, *J* = 15.6, 5.3, 1.7 Hz, 1H, 5β-H), 2.61–2.70 (m, 1H, 4β-H), 2.56 (dd, *J* = 15.8, 2.9 Hz, 1H, 5α-H, see 3aα-H and 8bα-H), 1.39–1.63 (m, 2H, 4-C*H*$_2$CH$_3$), 1.02 (dd, *J* = 7.2, 7.2 Hz, 3H, 4-CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 177.3, 176.4, 146.7, 137.8, 126.7, 125.6, 124.3, 117.5, 109.1, 107.5, 45.2, 39.3, 33.8, 25.5, 23.8, 12.1; IR (KBr, cm^{-1}) 3375(bm), 3115(w), 2960(m), 2929(w), 2873(w), 1771(w), 1704(s), 1611(w), 1598(w), 1519(m), 1499(m), 1460(w), 1384(m), 1348(m), 1297(w), 1193(m), 1170(m), 1147(m), 1105(w), 1067(w), 1019(w), 851(w), 782(w), 743(m), 717(m); HRMS *m/z* (M + Na$^+$) calcd. for C$_{18}$H$_{17}$N$_3$O$_4$: 362.1112, found 362.1114.

4α-n-Pentyl-2-phenyl-3aα,4β,5,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (37). Method B with vinylpyrrole **5b** and maleimide **10c** gave **37** (404 mg, 30%) as a light-brown powder: mp 208–209°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.90 (bs, 1H, 6-H), 7.40–7.46 (m, 2H, Ph), 7.32–7.37 (m, 1H, Ph), 7.22–7.27 (m, 2H, Ph), 6.68 (dd, *J* = 2.7, 2.7 Hz, 1H, 7-H), 6.37 (dd, *J* = 2.7, 2.7 Hz, 1H, 8-H), 4.07 (d, *J* = 7.8 Hz, 1H, 8bα-H), 3.28 (ddd, *J* = 8.0, 3.0, 0.9 Hz, 1H, 3aα-H), 2.79 (ddd, *J* = 15.5, 5.2, 1.1 Hz, 1H, 5β-H), 2.67–2.75 (m, 1H, 4β-H), 2.50 (dd, *J* = 15.3, 2.0 Hz, 1H, 5α-H, see 3aα-H), 1.25–1.52 (m, 8H, 4α-(C*H*$_2$)$_4$CH$_3$), 0.90 (t, *J* = 6.9 Hz, 3H, 4α-(CH$_2$)$_4$C*H*$_3$); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 178.0, 177.3, 132.1, 129.0, 128.3, 126.4, 125.6, 117.2, 109.6, 107.6, 45.4, 39.3, 32.7, 32.2, 31.8, 27.3, 24.3, 22.7, 14.1; IR (KBr, cm^{-1}) 3361(bs), 3066(w), 2953(m), 2926(s), 2855(m), 1766(w), 1708(s), 1598(w), 1497(m), 1457(w), 1380(s), 1291(w), 1187(m), 1150(w), 1090(w), 1072(w), 742(w); HRMS *m/z* (M + Na$^+$) calcd. 359.1731, found 359.1734. Anal. Calcd. for C$_{21}$H$_{24}$N$_2$O$_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.72; H, 6.93; N, 8.22.

4β-Ethyl-2-phenyl-3aα,4α,5,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (38). Method B with vinylpyrrole **6** and maleimide **10c** gave **38** (483 mg, 41%) as a cream-colored powder: mp 182–183°C; maj/min = 12:1; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.89 (bs, 1H, 6-H), 7.41 (dd, *J* = 7.8, 7.8 Hz, 2H, Ph), 7.32–7.38 (m, 1H, Ph), 7.20 (d, *J* = 7.5 Hz, 2H, Ph), 6.67 (dd, *J* = 2.5, 2.5 Hz, 1H, 7-H), 6.36 (dd, *J* = 2.8, 2.8 Hz, 1H, 8-H), 4.11 (ddd, *J* = 7.5, 1.3, 1.3 Hz, 1H, 8bα-H), 3.46 (ddd, *J* = 7.3, 3.8, 0.9 Hz, 1H, 3aα-H), 2.74 (dd, *J* = 15.8, 4.3 Hz, 1H, 5α-H, see 3aα-H and 8bα-H), 2.51 (ddd, *J* = 15.0, 11.0, 1.5 Hz, 1H, 5β-H), 2.08–2.15 (m, 1H, 4α-H), 2.05 (ddq, overlapped by 4α-H, *J* = 13.1, 7.5, 7.5 Hz, 1H, 4β-C*H*$_2$CH$_3$), 1.95 (ddq, *J* = 13.1, 7.5, 7.5 Hz, 1H, 4β-C*H*$_2$CH$_3$), 1.07 (dd, *J* = 7.5, 7.5 Hz, 3H, 4β-CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 177.25, 177.20, 132.0, 129.0, 128.3, 127.5, 126.5, 117.4, 111.0, 107.4, 44.1, 42.0, 37.3, 25.5, 25.2, 12.6; IR (KBr, cm^{-1}) 3369(bs), 3112(w), 3053(m), 2958(m), 2925(m), 2895(m), 2871(m), 2840(w), 1768(m), 1706(w), 1595(m), 1553(w), 1497(m), 1455(m), 1384(s), 1316(w), 1294(m), 1268(w), 1194(s), 1153(m), 1137(m), 1089(w), 1059(m), 1026(w), 994(w), 910(w), 817(w), 719(s); HRMS *m/z* (M + Na$^+$) calcd. 317.1261, found 317.1262. Anal. Calcd. for C$_{18}$H$_{18}$N$_2$O$_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.21; H, 6.13; N, 9.72.

2-Benzyl-5β-(1-benzyl-2,5-dioxopyrrolidin-3-yl)-3aα,4,5α,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (52). Method A with vinylpyrrole **4** and maleimide **10b** gave **52** (421 mg, 45%) as a light-brown powder: mp 212–213°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 10.58 (bs, 1H, 6-H), 7.32–7.42 (m, 5H, Ph), 7.18–7.26 (m, 5H, Ph), 6.76 (dd, *J* = 2.6, 2.6 Hz, 1H, 7-H), 6.34 (dd, *J* = 2.7, 2.7 Hz, 1H, 8-H), 4.74 (AA′ d, *J* = 14.1 Hz, 1H, Bn), 4.69 (AA′ d, *J* = 13.8 Hz, 1H, Bn), 4.59 (AA′ d, *J* = 14.4 Hz, 1H, Bn), 4.52 (AA′ d, *J* = 14.4 Hz, 1H, Bn), 4.02 (dd, *J* = 7.8, 1.2 Hz, 1H, 8bα-H), 3.32 (ddd, *J* = 7.9, 4.7, 3.5 Hz, 1H, 3aα-H), 3.01 (ddd, *J* = 9.4, 9.4, 6.1 Hz, 1H, 1′-H), 2.93 (dd, overlapped by 1′-H, *J* = 17.3, 9.6 Hz, 1H, 2′-H), 2.83–2.95 (m, overlapped by 2′-H, 1H, 5α-H), 2.77 (dd, overlapped by 5α-H, *J* = 17.0, 5.6 Hz, 1H, 2′-H), 2.54 (ddd, *J* = 13.3, 3.8, 3.8 Hz, 1H, 4β-H), 1.58 (ddd, *J* = 13.3, 11.5, 4.9 Hz, 1H, 4α-H); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 180.0, 178.2, 177.7, 174.7, 135.8, 135.3, 129.0, 128.9, 128.7, 128.4, 128.3, 127.9, 127.3, 118.3, 111.8, 107.2, 44.6, 42.9, 42.3, 40.1, 40.0, 33.0, 31.5, 26.6; IR (KBr, cm^{-1}) 3446(w), 3329(bs), 3062(w), 3033(w), 2924(m), 2854(w), 1772(m), 1702(s), 1586(w), 1495(w), 1453(w), 1433(m), 1398(s), 1341(m), 1314(m), 1292(w), 1167(s), 1119(w), 1083(w), 714(m), 696(m); HRMS *m/z* (M + Na$^+$) calcd. 490.1738, found 490.1745. Anal. Calcd. for C$_{28}$H$_{25}$N$_3$O$_4$: C, 71.93; H, 5.39; N, 8.99. Found: C, 71.97; H, 5.44; N, 8.70.

2-(4-Ethylphenyl)-5β-(1-(4-ethylphenyl)-2,5-dioxopyrrolidin-3-yl)-3aα,4,5α,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (53). Method A with vinylpyrrole **4** and maleimide **10d** gave **53** (228 mg, 23%) as a light-brown powder: mp 173–174°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 10.52 (bs, 1H, 6-H), 7.35 (d, *J* = 8.4 Hz, 2H, Ph), 7.25 (d, *J* = 8.4 Hz, 2H, Ph), 7.20 (d, *J* = 8.4 Hz, 2H, Ph), 7.12 (d, *J* = 8.4 Hz, 2H, Ph), 6.75 (dd, *J* = 2.9, 2.9 Hz, 1H, 7-H), 6.39 (dd, *J* = 2.7, 2.7 Hz, 1H, 8-H), 4.19 (dd, *J* = 8.1, 1.2 Hz, 1H, 8bα-H), 3.57 (ddd, *J* = 8.0, 4.7, 3.4 Hz, 1H, 3aα-H), 3.24 (ddd, *J* = 9.1, 9.1, 6.2 Hz, 1H, 1′-H), 3.13–3.23 (m, overlapped by 1′-H, 1H, 5α-H), 3.11 (dd, overlapped by 5α-H, *J* = 17.7, 8.7 Hz, 1H, 2′-H), 2.98 (dd, *J* = 17.7, 6.6 Hz, 1H, 2′-H), 2.73 (ddd, *J* = 12.9, 3.6, 3.6 Hz, 1H, 4β-H), 2.72 (q, overlapped by 4β-H, *J* =7.6 Hz, 2H, C*H*$_2$CH$_3$), 2.66 (q, overlapped by C*H*$_2$CH$_3$, *J* = 7.7 Hz, 2H, C*H*$_2$CH$_3$), 1.75 (ddd, *J* = 13.2, 10.8, 4.8 Hz, 1H, 4α-H), 1.28 (t, *J* = 7.1 Hz, 3H, CH$_2$C*H*$_3$), 1.23 (t, *J* = 7.2 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 179.7, 177.7, 177.1, 174.2, 145.6, 144.8, 129.4, 129.0, 128.9, 128.6, 127.3, 126.4, 126.2, 118.4, 111.8, 107.3, 44.8, 40.4, 40.2, 33.2, 31.6, 28.7, 28.6, 26.6, 15.5, 15.4; IR (KBr, cm^{-1}) 3353(bs), 3122(w), 3103(w), 3038(w), 2964(m), 2930(m), 2872(w), 1777(m), 1711(s), 1580(w), 1514(m), 1485(w), 1459(w), 1440(w), 1390(s), 1294(w), 1282(w), 1179(s), 1117(m), 1064(w), 832(m), 797(w), 768(w), 731(m); HRMS *m/z* (M + Na$^+$) calcd. 518.2051, found 518.2069. Anal. Calcd. for C$_{30}$H$_{29}$N$_3$O$_4$: C, 72.71; H, 5.90; N, 8.48. Found: C, 73.00; H, 6.19; N, 8.34.

2-(4-Isopropylphenyl)-5β-(1-(4-isopropylphenyl)-2,5-dioxopyrrolidin-3-yl)-3aα,4,5α,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (54). Method A with vinylpyrrole **4** and maleimide **10e** gave **54** (304 mg, 29%) as a light-brown powder: mp 148–150°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 10.45 (bs, 1H, 6-H), 7.37 (d, *J* = 8.4 Hz, 2H, Ph), 7.27 (d, *J* = 8.7 Hz, 2H, Ph), 7.20 (d, *J* = 8.4 Hz, 2H, Ph), 7.13 (d, *J* = 8.4 Hz, 2H, Ph), 6.70 (dd, *J* = 2.4, 2.4 Hz, 1H, 7-H), 6.38 (dd, *J* = 2.7, 2.7 Hz, 1H, 8-H), 4.17 (d, *J* = 7.8 Hz, 1H, 8bα), 3.56 (ddd, *J* = 7.7, 4.0, 4.0 Hz, 1H, 3aα), 3.24 (ddd, *J* = 8.8, 8.8, 6.1 Hz, 1H, 1′-H), 2.85–3.25 (m, overlapped by 1′-H, 5H, 2′-H × 2 and 5α-H and C*H*(CH$_3$)$_2$ × 2), 2.69 (ddd, *J* = 13.4, 3.8, 3.8 Hz, 1H, 4β-H), 1.72 (ddd, *J* = 13.0, 10.7, 4.3 Hz, 1H, 4α-H), 1.29 (d, *J* = 6.9 Hz, 6H, CH(C*H*$_3$)$_2$), 1.24 (d, *J* = 6.9 Hz, 6H, CH(C*H*$_3$)$_2$); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 179.7, 177.8, 177.2, 174.4, 150.1, 149.3, 129.4, 129.0, 127.6, 127.3, 127.2, 126.4, 126.1, 118.4, 111.8, 107.3, 44.6, 40.4, 40.2, 35.04, 34.97, 33.1, 31.5, 26.4, 24.0; IR (KBr, cm^{-1}) 3354(bs), 3039(w), 2960(s), 2928(m), 2871(m), 1779(m), 1708(s), 1574(w), 1514(m), 1461(m), 1385(s), 1281(w), 1168(s), 1114(m), 1059(m), 831(m), 732(m), 693(m), 659(m); HRMS *m/z* (M + Na$^+$) calcd. 546.2364, found 546.2377. Anal. Calcd. for $C_{32}H_{33}N_3O_4$: C, 73.40; H, 6.35; N, 8.02. Found: C, 73.18; H, 6.52; N, 8.04.

2-(4-Phenoxyphenyl)-5β-(1-(4-phenoxyphenyl)-2,5-dioxopyrrolidin-3-yl)-3aα,4,5α,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (55). Method A with vinylpyrrole **4** and maleimide **10h** gave **55** (474 mg, 38%) as a cream-colored powder: mp 133–135°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 10.51 (bs, 1H, 6-H), 7.33–7.42 (m, 4H, Ph), 7.01–7.26 (m, 14H, Ph), 6.76 (dd, *J* = 2.6, 2.6 Hz, 1H, 7-H), 6.39 (dd, *J* = 2.6, 2.6 Hz, 1H, 8-H), 4.20 (dd, *J* = 7.8, 1.4 Hz, 1H, 8bα-H), 3.58 (ddd, *J* = 8.0, 4.7, 3.3 Hz, 1H, 3aα-H), 3.13–3.26 (m, 1H, 5α-H), 3.25 (ddd, overlapped by 5α-H, *J* = 9.2, 9.2, 6.2 Hz, 1H, 1′-H), 3.14 (dd, overlapped by 5α-H, *J* = 17.7, 8.7 Hz, 1H, 2′-H), 3.00 (dd, *J* = 17.9, 6.5 Hz, 1H, 2′-H), 2.74 (ddd, *J* = 13.3, 4.3, 3.5 Hz, 1H, 4β-H), 1.76 (ddd, *J* = 13.1, 11.0, 4.9 Hz, 1H, 4α-H); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 179.7, 177.7, 177.1, 174.2, 158.2, 157.3, 156.5, 156.2, 130.1, 130.0, 128.0, 127.8, 127.3, 126.6, 125.9, 124.3, 124.0, 119.9, 119.5, 118.8, 118.5, 111.8, 107.4, 44.7, 40.4, 40.2, 33.2, 31.6, 26.5; IR (KBr, cm^{-1}) 3346(bs), 3061(m), 2922(m), 1778(m), 1718(s), 1588(m), 1506(s), 1487(s), 1388(m), 1286(m), 1244(s), 1196(m), 1113(m), 1067(m), 1017(w), 875(m), 845(m), 770(m), 695(m); HRMS *m/z* (M + Na$^+$) calcd. 646.1949, found 646.1951. Anal. Calcd. for $C_{38}H_{29}N_3O_6$: C, 73.18; H, 4.69; N, 6.74. Found: C, 73.40; H, 4.87; N, 6.61.

2-Benzyl-5α-(1-benzyl-2,5-dioxopyrrolidin-3-yl)-3aα,4,5β,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (56) and 2-benzyl-5β-(1-benzyl-2,5-dioxopyrrolidin-3-yl)-3aα,4,5α,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (52). Method A with vinylpyrrole **4** and maleimide **10b** followed by fractional recrystallizations from CH$_2$Cl$_2$/petroleum ether gave **56** (168 mg, 18%) as a light-brown powder, with a maximum purity of **56**:**52** in a 5:1 molar ratio, mass calculated from ^{1}H NMR, spectroscopic data for **56** only reported: mp 86–91°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.36–7.41 (m, 4H, Ph), 7.27–7.28 (m, 6H, Ph), 7.02 (bs, 1H, 6-H), 6.24 (dd, *J* = 2.6, 2.6 Hz, 1H, 7-H), 6.15 (dd, *J* = 2.7, 2.7 Hz, 1H, 8-H), 4.79 (AA′ d, *J* = 13.8 Hz, 1H, Bn), 4.62 (AA′ d, *J* = 13.8 Hz, 1H, Bn), 4.61 (AA′ d, overlapped, *J* = 14.1 Hz, 1H, Bn), 4.54 (AA′ d, *J* = 14.1 Hz, 1H, Bn), 3.89 (dd, *J* = 7.8, 0.6 Hz, 1H, 8bα-H), 3.63 (dddd, *J* = 7.5, 5.4, 3.3, 0.8 Hz, 1H, 5β-H), 3.17 (ddd, *J* = 8.0, 8.0, 5.6 Hz, 1H, 3aα-H), 3.13 (ddd, overlapped by 5β-H, *J* = 8.9, 5.8, 3.1 Hz, 1H, 1′-H), 2.74 (dd, *J* = 18.0, 9.3 Hz, 1H, 2′-H *syn* to 1′-H), 2.26 (ddd, *J* = 13.5, 7.8, 5.7 Hz, 1H, 4β-H), 2.22 (dd, overlapped by 4β-H, *J* = 18.0, 5.7 Hz, 1H, 2′-H *anti* to 1′-H), 1.88 (ddd, *J* = 13.6, 7.7, 5.8 Hz, 1H, 4α-H); IR (KBr, cm^{-1}) 3382(bm), 3063(w), 3033(m), 2922(s), 2853(m), 1773(m), 1702(s), 1585(w), 1495(w), 1455(w), 1432(m), 1397(m), 1341(m), 1314(w), 1166(m), 1083(w), 1065(w), 723(w), 699(m); HRMS *m/z* (M + Na$^+$) calcd. 490.1738, found 490.1739. Anal. Calcd. for $C_{28}H_{25}N_3O_4$: C, 71.93; H, 5.39; N, 8.99. Found: C, 71.87; H, 5.52; N, 8.73.

2-(4-Ethylphenyl)-5α-(1-(4-ethylphenyl)-2,5-dioxopyrrolidin-3-yl)-3aα,4,5β,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (57). Method A with vinylpyrrole **4** and maleimide **10d** gave **57** (50 mg, 5%) as a cream-colored powder: mp 252–254°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.96 (bs, 1H, 6-H), 7.34 (d, *J* = 8.4 Hz, 2H, Ph), 7.29 (d, *J* = 8.7 Hz, 2H, Ph), 7.16 (d, *J* = 8.4 Hz, 2H, Ph), 7.15 (d, overlapped, *J* = 8.4 Hz, 2H, Ph), 6.71 (dd, *J* = 2.7, 2.7 Hz, 1H, 7-H), 6.48 (dd, *J* = 2.7, 2.7 Hz, 1H, 8-H), 4.14 (d, *J* = 8.1 Hz, 1H, 8bα-H), 3.92 (ddd, *J* = 5.9, 5.9, 3.3 Hz, 1H, 5β-H), 3.40 (ddd, *J* = 9.2, 6.8, 3.3 Hz, 1H, 1′-H), 3.39 (ddd, overlapped by 1′-H, *J* = 9.6, 7.9, 5.3 Hz, 1H, 3aα-H), 2.95 (dd, *J* = 17.6, 9.2 Hz, 1H, 2′-H *syn* to 1′-H), 2.71 (q, *J* = 7.7 Hz, 2H, C*H*$_2$CH$_3$), 2.68 (q, overlapped by C*H*$_2$CH$_3$, *J* = 7.5 Hz, 2H, C*H*$_2$CH$_3$), 2.52 (dd, *J* = 17.6, 6.8 Hz, 1H, 2′-H *anti* to 1′-H), 2.42 (ddd, *J* = 13.9, 9.2, 5.9 Hz, 1H, 4β-H), 2.21 (ddd, *J* = 13.7, 5.7, 5.7 Hz, 1H, 4α-H), 1.27 (t, *J* = 7.6 Hz, 3H, CH$_2$C*H*$_3$), 1.25 (t, overlapped by CH$_2$C*H*$_3$, *J* = 7.6 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 179.1, 177.9, 176.1, 174.9, 145.5, 144.9, 129.3, 129.1, 129.0, 128.7, 126.23, 126.18, 124.6, 119.4, 113.5, 108.4, 45.4, 39.8, 38.9, 31.3, 30.3, 28.7, 28.4, 15.5; IR (KBr, cm^{-1}) 3462(w), 3364(bs), 3037(w), 2965(m), 2929(m), 2871(w), 1776(m), 1705(s), 1514(m), 1488(w), 1458(w), 1386(s), 1354(m), 1313(w), 1301(w), 1223(w), 1163(s), 1190(s), 1110(w), 1100(w), 1083(w), 770(m), 720(m); HRMS *m/z* (M + Na$^+$) calcd. 518.2051, found 518.2059. Anal. Calcd. for $C_{30}H_{29}N_3O_4$: C, 72.71; H, 5.90; N, 8.48. Found: C, 72.99; H, 5.93; N, 8.70.

2-(4-Isopropylphenyl)-5α-(1-(4-isopropylphenyl)-2,5-dioxopyrrolidin-3-yl)-3aα,4,5β,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (58). Method A with vinylpyrrole **4** and maleimide **10e** gave **58** (84 mg, 8%) as a cream-colored powder: mp 280–282°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.94 (bs, 1H, 6-H), 7.37 (d, *J* = 8.1 Hz, 2H, Ph), 7.31 (d, *J* = 8.4 Hz, 2H, Ph), 7.17 (d, *J* = 8.7 Hz, 2H, Ph), 7.16 (d, *J* = 8.4 Hz, 2H, Ph), 6.71 (dd, *J* = 2.9, 2.9 Hz, 1H, 7-H), 6.48 (dd, *J* = 2.6, 2.6 Hz, 1H, 8-H), 4.14 (d, *J* = 8.4 Hz, 1H, 8bα-H), 3.93 (ddd, *J* = 5.6, 5.6, 3.2 Hz, 1H, 5β-H), 3.40 (ddd, *J* = 9.2, 6.6, 3.3 Hz, 1H, 1′-H), 3.40 (ddd, overlapped, *J* = 9.3, 8.0, 5.6 Hz, 1H, 3α-H), 2.97 (septet, *J* = 7.0 Hz, 1H, C*H*(CH$_3$)$_2$), 2.95 (dd, overlapped by C*H*(CH$_3$)$_2$ × 2, *J* = 17.6, 9.2 Hz, 1H, 2′-H *syn* to 1′-H), 2.94 (dd, overlapped by C*H*(CH$_3$)$_2$ and 2′-H, *J* = 6.9 Hz, 1H, C*H*(CH$_3$)$_2$), 2.53 (dd, *J* = 17.9, 6.8 Hz, 1H, 2′-H *anti* to 1′-H), 2.43 (ddd, *J* = 14.0, 9.0, 5.9 Hz, 1H, 4β-H), 2.21 (ddd, *J* = 14.0, 5.8, 5.8 Hz, 1H, 4α-H), 1.28 (d, *J* = 7.2 Hz, 6H, CH(C*H*$_3$)$_2$), 1.26 (d, overlapped by CH(C*H*$_3$)$_2$, *J* = 7.2 Hz, 6H, CH(C*H*$_3$)$_2$); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 179.1, 177.9, 176.1, 175.0, 150.0, 149.5, 129.3, 129.1, 127.6, 127.3, 126.2, 126.1, 124.6, 119.4, 113.5, 108.4, 45.4, 39.8, 38.9, 34.0, 31.3, 30.3, 28.4, 24.0; IR (KBr, cm^{-1}) 3365(bs), 3038(w), 2961(s), 2927(m), 2899(m), 1776(m), 1708(s), 1514(m), 1460(w), 1387(s), 1355(m), 1306(w), 1187(s), 1160(s), 1105(m), 1085(w), 1055(m), 832(m), 727(m); HRMS *m/z* (M + Na$^+$) calcd. 546.2364, found 546.2373. Anal. Calcd. for $C_{32}H_{33}N_3O_4$: C, 73.40; H, 6.35; N, 8.02. Found: C, 73.22; H, 6.51; N, 7.96.

2-(4-Phenoxyphenyl)-5α-(1-(4-phenoxyphenyl)-2,5-dioxopyrrolidin-3-yl)-3aα,4,5β,8bα-tetrahydro-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (59). Method A with vinylpyrrole **4** and maleimide **10h** gave **59** (100 mg, 8%) as a white powder: mp 267–268°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.94 (bs, 1H, 6-H), 7.34–7.43 (m, 4H, Ph), 7.03–7.24 (m, 14H, Ph), 6.72 (dd, J = 2.9, 2.9 Hz, 1H, 7-H), 6.48 (dd, J = 2.7, 2.7 Hz, 1H, 8-H), 4.15 (d, J = 8.1 Hz, 1H, 8bα-H), 3.93 (ddd, J = 5.6, 5.6, 3.4 Hz, 1H, 5β-H), 3.41 (ddd, J = 9.0, 6.6, 3.3 Hz, 1H, 1′-H), 3.41 (ddd, overlapped by 1′-H, J = 9.1, 7.8, 5.9 Hz, 1H, 3aα-H), 2.96 (dd, J = 17.7, 9.0 Hz, 1H, 2′-H *syn* to 1′-H), 2.53 (dd, 17.7, 6.6 Hz, 1H, 2′-H *anti* to 1′-H), 2.43 (ddd, J = 14.2, 8.6, 5.6 Hz, 1H, 4β-H), 2.21 (ddd, J = 14.0, 5.9, 5.9 Hz, 1H, 4α-H); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 179.0, 178.2, 177.2, 176.1, 157.1, 156.60, 156.59, 130.8, 129.4, 128.0, 127.9, 127.2, 124.6, 119.75, 119.69, 118.9, 118.4, 111.5, 107.2, 43.4, ∼40 (obscured by DMSO), 38.4, 33.2, 32.7, 28.5; ^{13}C NMR (75 MHz, CDCl$_3$, δ) 179.01, 178.95, 177.8, 174.8, 157.6, 154.6, 152.8, 130.1, 130.0, 127.82, 127.78, 126.2, 126.0, 124.6, 124.3, 124.0, 119.8, 119.6, 119.4, 118.8, 113.5, 108.4, 45.4, 39.7, 38.9, 31.3, 30.3, 28.3; IR (KBr, cm^{-1}) 3358(bs), 3053(w), 2994(W), 2950(w), 2915(m), 2856(w), 1770(m), 1711(s), 1589(m), 1506(m), 1489(m), 1456(w), 1386(m), 1350(w), 1294(w), 1244(s), 1193(m), 1155(m), 1102(m), 1072(m), 1019(w), 880(w), 800(w), 760(m), 730(m), 699(m); HRMS *m*/*z* (M + Na$^+$) calcd. 646.1949, found 646.1958. Anal. Calcd. for C$_{38}$H$_{29}$N$_3$O$_6$: C, 73.18; H, 4.69; N, 6.74. Found: C, 72.96; H, 4.80; N, 6.58.

2-Dimethylamino-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (60). Method D with adduct **11** gave **60** (55 mg, 64%) as orange crystals: mp 237–238°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 11.89 (bs, 1H, 6-H), 7.79 (m, 2H, 4-H and 5-H), 7.49 (dd, J = 8.1, 1.2 Hz, 1H, 7-H), 6.79 (ddd, J = 2.1, 2.1, 0.9 Hz, 1H, 8-H), 2.89 (s, 6H, N(CH$_3$)$_2$); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 168.6, 168.4, 141.3, 132.5, 122.8, 122.5, 121.3, 117.3, 115.4, 100.2, 45.0; IR (film, cm^{-1}) 3251(bs), 2940(m), 2870(m), 1756(m), 1704(s), 1448(m), 1440(w), 1357(m), 1274(w), 1142(w), 1104(m), 740(m); HRMS *m*/*z* (M + Na$^+$) calcd. 252.0744, found 252.0748. Anal. Calcd. for C$_{12}$H$_{11}$N$_3$O$_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.68; H, 4.81; N, 18.17.

2-Benzyl-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (61). Method C with adduct **12** gave **61** (47 mg, 45%) as a yellow powder: mp 195–196°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 11.99 (bs, 1H, 6-H), 7.81 (dd, J = 8.1, 1.1 Hz, 1H, 5-H), 7.79–7.81 (m, overlapped by 4-H, 1H, 7-H), 7.56 (d, J = 8.1 Hz, 1H, 4-H), 7.23–7.37 (m, 5H, Ph), 6.81 (ddd, J = 3.0, 2.0, 0.9 Hz, 1H, 8-H), 4.76 (s, 2H, Bn); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 169.7, 169.4, 140.4, 137.2, 129.7, 128.7, 128.6, 127.7, 125.2, 124.0, 123.2, 116.4, 115.8, 102.1, 41.4; ^{13}C NMR (75 MHz, DMSO-d_6, δ) 169.7, 169.4, 141.3, 137.8, 132.6, 129.1, 127.8 (two peaks overlapped), 124.3, 123.0, 115.2, 113.8, 100.3, ∼40 (obscured by DMSO); IR (KBr, cm^{-1}) 3275(bs), 3108(w), 3057(w), 3035(w), 2941(w), 1756(m), 1687(s), 1590(w), 1508(w), 1492(w), 1455(w), 1433(m), 1398(m), 1368(m), 1340(m), 1272(w), 1062(m), 764(w), 745(m), 675(m); HRMS *m*/*z* (M + Na$^+$) calcd. 299.0792, found 299.0794. Anal. Calcd. for C$_{17}$H$_{12}$N$_2$O$_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.63; H, 4.28; N, 9.90.

2-Phenyl-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (62). Method D with adduct **13** gave **62** (66 mg, 67%) as bright-yellow crystals: mp 265–266°C; ^{1}H NMR (300 MHz, acetone-d_6, δ) 11.16 (bs, 1H, 6-H), 7.94 (dd, J = 8.4, 0.9 Hz, 1H, 5-H), 7.82 (dd, J = 2.9, 2.9 Hz, 1H, 7-H), 7.68 (d, J = 8.4 Hz, 1H, 4-H), 7.55–7.60 (m, 4H, Ph), 7.40–7.44 (m, 1H, Ph), 7.01 (ddd, J = 3.2, 2.1, 0.9 Hz, 1H, 8-H); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 168.9, 168.6, 141.3, 132.9, 132.5, 129.3, 128.1, 127.8, 124.1, 123.1, 123.0, 117.5, 115.8, 100.5; IR (film, cm^{-1}) 3288(bs), 2953(m), 2870(m), 1753(m), 1696(s), 1620(w), 1590(w), 1495(w), 1490(w), 1365(m), 1265(w), 1227(w), 1153(w), 1061(w), 753(m); HRMS *m*/*z* (M + Na$^+$) calcd. 285.0635, found 285.0641. Anal. Calcd. for C$_{16}$H$_{10}$N$_2$O$_2$: C, 73.27; H, 3.84; N, 10.68. Found: C, 73.00; H, 3.73; N, 10.82.

2-(4-Ethylphenyl)-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (63). Method C with adduct **14** gave **63** (51 mg, 47%) as a yellow powder: mp 172–173°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.82 (bs, 1H, 6-H), 7.76 (d, J = 8.4 Hz, 1H, 4-H), 7.71 (dd, J = 8.1, 0.9 Hz, 1H, 5-H), 7.52 (dd, J = 3.3, 2.4 Hz, 1H, 7-H), 7.40 (d, J = 8.7 Hz, 2H, Ph), 7.34 (d, J = 8.7 Hz, 2H, Ph), 7.13 (ddd, J = 3.1, 2.0, 0.8 Hz, 1H, 8-H), 2.72 (q, J = 7.7 Hz, 2H, CH_2CH$_3$), 1.29 (t, J = 7.7 Hz, 3H, CH$_2$CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 169.1, 168.7, 143.9, 141.3, 132.6, 130.4, 128.7, 127.8, 124.2, 123.1, 123.0, 117.5, 115.8, 100.4, 28.4, 16.2; IR (KBr, cm^{-1}) 3417(bs), 3319(w), 2963(w), 2929(w), 1760(m), 1706(s), 1629(w), 1592(w), 1517(m), 1460(w), 1426(w), 1380(s), 1366(s), 1274(w), 1228(w), 1088(m), 1068(w), 823(w), 800(w), 759(m), 745(m); HRMS *m*/*z* (M + Na$^+$) calcd. 313.0948, found 313.0942. Anal. Calcd. for C$_{18}$H$_{14}$N$_2$O$_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.35; H, 4.94; N, 9.51.

2-(4-Isopropylphenyl)-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (64). Method C with adduct **15** gave **64** (70 mg, 61%) as yellow needle-like crystals: mp 178–179°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.68 (bs, 1H, 6-H), 7.78 (d, J = 8.4 Hz, 1H, 4-H), 7.73 (dd, J = 8.1, 0.9 Hz, 1H, 5-H), 7.55 (dd, J = 2.4, 0.9 Hz, 1H, 7-H), 7.41 (d, J = 8.4 Hz, 2H, Ph), 7.37 (d, J = 8.4 Hz, 2H, Ph), 7.15 (ddd, J = 3.1, 2.0, 1.0 Hz, 1H, 8-H), 2.98 (septet, J = 6.9 Hz, 1H, CH(CH$_3$)$_2$), 1.30 (d, J = 6.9 Hz, 6H, CH(CH_3)$_2$); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 169.1, 168.7, 148.4, 141.3, 132.6, 130.5, 127.8, 127.2, 124.2, 123.1, 123.0, 117.6, 115.8, 108.5, 100.5, 39.2, 24.4; IR (KBr, cm^{-1}) 3419(s), 2960(m), 2925(s), 2855(m), 1758(m), 1711(s), 1516(w), 1457(w), 1427(w), 1378(m), 1367(m), 1315(w), 1274(m), 1227(w), 1155(w), 1120(m), 1070(w), 714(w); HRMS *m*/*z* (M + Na$^+$) calcd. 327.1105, found 327.1113. Anal. Calcd. for C$_{19}$H$_{16}$N$_2$O$_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 74.71; H, 5.12; N, 9.07.

2-(4-Methoxyphenyl)-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (65). Method D with adduct **16** gave **65** (70 mg, 64%) as brown crystals: mp 220–221°C; ^{1}H NMR (300 MHz, acetone-d_6, δ) 11.12 (bs, 1H, 6-H), 7.93 (dd, J = 8.1, 0.9 Hz, 1H, 5-H), 7.81 (dd, J = 2.9, 2.9 Hz, 1H, 7-H), 7.66 (d, J = 8.1 Hz, 1H, 4-H), 7.44 (d, J = 9.0 Hz, 2H, Ph), 7.09 (d, J = 9.0 Hz, 2H, Ph), 6.98–7.02 (m, 1H, 8-H), 3.89 (s, 3H, OCH$_3$); ^{13}C NMR (75 MHz, acetone-d_6, δ) 168.7, 168.4, 159.0, 141.2, 131.2, 128.5, 125.6, 124.6, 123.4, 123.2, 116.8, 115.4, 114.0, 100.7, 55.0; IR (film, cm^{-1}) 3300(bs), 2920(m), 2810(m), 1758(w), 1706(s), 1517(m), 1441(w), 1369(m), 1250(m), 1155(w), 1117(w), 743(m); HRMS *m*/*z* (M + Na$^+$) calcd. 315.0741, found 315.0743. Anal. Calcd. for C$_{17}$H$_{12}$N$_2$O$_3$: C, 69.86; H, 4.14; N, 9.58. Found: C, 69.67; H, 4.10; N, 9.39.

2-(4-Phenoxyphenyl)-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (66). Method C with adduct **17** gave **66** (51 mg, 38%) as bright yellow crystals: mp 193–194°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.72 (bs, 1H, 6-H), 7.78 (d, J = 8.4 Hz, 1H, 4-H), 7.73 (dd, J = 8.4, 0.8 Hz, 1H, 5-H), 7.56 (dd, J = 3.2, 2.6 Hz, 1H, 7-H), 7.36–7.48 (m, 4H, Ph), 7.08–7.19 (m, 6H, 8-H, Ph); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 169.0, 168.7, 156.8, 156.6, 141.3, 132.6, 130.7, 129.6, 127.9, 124.4, 124.2, 123.1, 123.0, 119.6, 119.0, 117.6, 115.8, 100.5; IR (KBr, cm^{-1}) 3316(bm), 3065(w), 1764(m), 1703(s), 1629(w), 1588(w), 1506(m), 1487(m), 1460(w), 1433(w), 1383(m), 1370(m), 1241(s), 1151(m), 1105(m), 1089(m), 1070(m), 1005(w), 870(w), 822(w), 744(m), 691(m); HRMS m/z (M + Na$^+$) calcd. 377.0897, found 377.0883. Anal. Calcd. for $C_{22}H_{14}N_2O_3$: C, 74.57; H, 3.98; N, 7.91. Found: C, 74.44; H, 3.93; N, 7.54.

2-Dimethylamino-6-methyl-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (67). Method D with adduct **18** gave **67** (60 mg, 66%) as yellow crystals: mp 201–202°C; ^{1}H NMR (300 MHz, acetone-d_6, δ) 7.84 (d, J = 8.4 Hz, 1H, 4-H), 7.67 (d, J = 3.3 Hz, 1H, 7-H), 7.57 (dd, J = 8.1, 0.6 Hz, 1H, 5-H), 6.88 (dd, J = 3.0, 0.6 Hz, 1H, 8-H), 3.99 (s, 3H, 6-CH_3), 2.99 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 168.8, 168.5, 141.2, 134.6, 123.5, 122.7, 122.0, 115.8, 114.2, 100.7, 45.2, 33.4; IR (film, cm^{-1}) 3102(m), 2969(m), 2877(m), 2854(w), 1763(m), 1706(s), 1509(w), 1498(w), 1375(w), 1357(m), 1296(w), 1168(w), 1092(w), 1023(w); HRMS m/z (M + Na$^+$) calcd. 266.0901, found 266.0892. Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 64.46; H, 5.30; N, 17.27.

6-Methyl-2-phenyl-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (68). Method D with adduct **19** gave **68** (74 mg, 71%) as bright orange-yellow crystals: mp 214–215°C; ^{1}H NMR (300 MHz, CD_2Cl_2, δ) 7.76 (d, J = 8.4 Hz, 1H, 4-H), 7.71 (dd, J = 8.4, 0.6 Hz, 1H, 5-H), 7.41–7.58 (m, 6H, 7-H and Ph), 7.03 (dd, J = 3.9, 0.7 Hz, 1H, 8-H), 3.93 (s, 3H, 6-CH_3); ^{13}C NMR (75 MHz, CD_2Cl_2, δ) 168.8, 168.3, 141.3, 134.9, 132.6, 129.0, 127.8, 127.6, 126.9, 124.3, 123.6, 115.7, 114.6, 100.4, 33.5; IR (film, cm^{-1}) 3125(m), 2900(w), 1759(m), 1710(s), 1595(m), 1512(m), 1490(m), 1453(w), 1377(s), 1361(s), 1294(m), 1223(w), 1171(w), 1094(w), 1063(w), 744(m); HRMS m/z (M + Na$^+$) calcd. 299.0792, found 299.0792. Anal. Calcd. for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.71; H, 4.28; N, 10.14.

2-(4-Methoxyphenyl)-6-methyl-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (69). Method D with adduct **20** gave **69** (76 mg, 66%) as bright-yellow crystals: mp 236–237°C; ^{1}H NMR (300 MHz, CD_2Cl_2, δ) 7.75 (d, J = 8.4 Hz, 1H, 4-H), 7.70 (dd, J = 8.4, 0.6 Hz, 1H, 5-H), 7.44 (d, J = 3.3 Hz, 1H, 7-H), 7.38 (d, J = 9.0 Hz, 2H, Ph), 7.06 (d, J = 9.0 Hz, 2H, Ph), 7.01 (dd, J = 3.3, 0.7 Hz, 1H, 8-H), 3.93 (s, 3H, OCH_3), 3.89 (s, 3H, 6-CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 169.1, 168.7, 159.1, 141.4, 136.6, 129.2, 125.4, 124.2, 123.3, 123.2, 115.9, 115.6, 114.6, 99.8, 55.9, 33.6; IR (film, cm^{-1}) 3125(w), 2988(m), 2870(w), 1753(m), 1709(s), 1509(s), 1388(m), 1366(w), 1352(w), 1299(m), 1249(s), 1170(w), 1092(w), 806(w), 704(m); HRMS m/z (M + Na$^+$) calcd. 329.0897, found 329.0908. Anal. Calcd. for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.40; H, 4.59; N, 9.01.

2-Dimethylamino-5,6-dimethyl-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (70). Method D with adduct **21** gave **70** (68 mg, 70%) as bright-yellow crystals: mp 226–227°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.33 (s, 1H, 4-H), 7.21 (d, J = 3.3 Hz, 1H, 7-H), 6.95 (d, J = 3.0 Hz, 1H, 8-H), 4.13 (s, 3H, 6-CH_3), 3.05 (s, 6H, $N(CH_3)_2$), 2.87 (s, 3H, 5-CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 168.5, 168.3, 139.6, 137.8, 129.0, 124.1, 122.8, 119.6, 117.4, 99.2, 45.0, 37.3, 20.1; IR (film, cm^{-1}) 3120(m), 2998(m), 2963(m), 2875(m), 2815(m), 1757(s), 1709(s), 1596(w), 1517(m), 1477(w), 1448(m), 1348(s), 1321(m), 1188(w), 1172(m), 1105(w), 1015(w), 760(m), 740(m); HRMS m/z (M + Na$^+$) calcd. 280.1057, found 280.1055. Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.55; H, 5.99; N, 16.50.

5,6-Dimethyl-2-phenyl-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (71). Method D with adduct **22** gave **71** (79 mg, 72%) as bright orange-yellow crystals: mp 225–226°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.48–7.53 (m, 4H, Ph), 7.45 (s, 1H, 4-H), 7.38–7.41 (m, 1H, Ph), 7.24 (d, J = 3.0 Hz, 1H, 7-H), 7.01 (d, J = 3.0 Hz, 1H, 8-H), 4.16 (s, 3H, 6-CH_3), 2.91 (s, 3H, 5-CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 168.8, 168.4, 139.7, 138.0, 132.9, 129.4, 129.3, 128.0, 127.7, 124.6, 124.4, 121.3, 117.9, 99.5, 37.3, 20.1; IR (film, cm^{-1}) 3120(m), 2940(m), 1752(m), 1706(s), 1596(w), 1517(w), 1501(m), 1453(w), 1405(w), 1376(m), 1356(m), 1321(w), 1226(w), 1102(w), 753(m); HRMS m/z (M + Na$^+$) calcd. 313.0948, found 313.0945. Anal. Calcd. for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.70; H, 4.63; N, 9.80.

2-(4-Methoxyphenyl)-5,6-dimethyl-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (72). Method D with adduct **23** gave **72** (79 mg, 66%) as bright-red crystals: mp 229-230°C; ^{1}H NMR (300 MHz, CD_2Cl_2, δ) 7.43 (s, 1H, 4-H), 7.36 (d, J = 9.0 Hz, 2H, Ph), 7.31 (d, J = 3.0 Hz, 1H, 7-H), 7.05 (d, J = 9.0 Hz, 2H, Ph), 6.97 (d, J = 3.0 Hz, 1H, 8-H), 4.17 (s, 3H, 6-CH_3), 3.88 (s, 3H, OCH_3), 2.94 (s, 3H, 5-CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 169.1, 168.7, 159.0, 139.6, 137.92, 137.87, 129.2, 125.4, 124.6, 124.4, 121.1, 117.8, 114.6, 99.5, 55.9, 37.3, 20.1; IR (film, cm^{-1}) 3104(m), 2938(m), 2844(m), 1751(m), 1698(s), 1512(s), 1461(m), 1384(m), 1356(m), 1327(w), 1299(w), 1249(m), 1171(m), 1090(w), 1074(w), 1031(w), 802(w); HRMS m/z (M + Na$^+$) calcd. 343.1054, found 343.1069. Anal. Calcd. for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.62; H, 5.10; N, 8.55.

2-Dimethylamino-4-methyl-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (73). Method D with adduct **24** gave **73** (52 mg, 57%) as yellow crystals: mp 255–256°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.70 (bs, 1H, 6-H), 7.41–7.45 (m, 2H, 5-H and 7-H), 7.03 (ddd, J = 3.2, 2.0, 1.1 Hz, 1H, 8-H), 3.07 (s, 6H, $N(CH_3)_2$), 2.77 (d, J = 0.9 Hz, 3H, 4-CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 169.2, 168.1, 141.3, 131.8, 129.3, 121.6, 121.5, 119.5, 118.3, 100.0, 44.9, 18.2; IR (film, cm^{-1}) 3250(bs), 2995(m), 2880(m), 2871(m), 1748(m), 1697(s), 1446(m), 1402(w), 1390(w), 1350(m), 1101(w), 762(m); HRMS m/z (M + Na$^+$) calcd. 266.0901, found 266.0907. Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 63.96; H, 5.34; N, 17.08.

4-Methyl-2-phenyl-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (74). Method D with adduct **25** gave **74** (63 mg, 61%) as yellow crystals: mp 305-306°C; ^{1}H NMR (300 MHz, acetone-d_6, δ) 10.93 (bs, 1H, 6-H), 7.72 (dd, J = 2.9, 2.9 Hz, 1H, 7-H), 7.67 (dq, J = 0.9, 0.9 Hz, 1H, 5-H), 7.50–7.60 (m, 4H, Ph), 7.40–7.50 (m, 1H, Ph), 6.94 (ddd, J = 3.6, 2.1, 0.9 Hz, 1H, 8-H), 2.77 (d, J = 0.6 Hz, 3H, 4-CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 169.0, 168.4, 141.4, 132.9, 131.9, 129.7, 129.3, 128.0, 127.9, 123.2, 121.9, 121.2, 118.5, 100.3, 18.4; IR (film, cm^{-1}) 3288(bs), 2900(m), 2880(m), 1764(w), 1752(m), 1693(s), 1640(w), 1496(m), 1392(m), 1368(m), 1167(w), 763(m);

HRMS *m/z* (M + Na$^+$) calcd. 299.0792, found 299.0785. Anal. Calcd. for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.71; H, 4.54; N, 9.86.

2-(4-Methoxyphenyl)-4-methyl-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (75). Method D with adduct **26** gave **75** (68 mg, 59%) as yellow crystals: mp 207–208°C; ^{1}H NMR (300 MHz, acetone-d_6, δ) 10.91 (bs, 1H, 6-H), 7.71 (dd, *J* = 3.0, 2.6 Hz, 1H, 7-H), 7.66 (dq, *J* = 0.9, 0.9 Hz, 1H, 5-H), 7.43 (d, *J* = 9.3 Hz, 2H, Ph), 7.08 (d, *J* = 9.0 Hz, 2H, Ph), 6.94 (ddd, *J* = 3.2, 2.0, 0.9 Hz, 1H, 8-H), 3.89 (s, 3H, OCH_3), 2.76 (d, *J* = 0.9 Hz, 3H, 4-CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 169.6, 168.6, 159.0, 141.4, 131.7, 129.6, 129.3, 125.5, 123.2, 121.9, 121.2, 118.4, 114.5, 100.3, 55.8, 18.4; IR (film, cm^{-1}) 3331(bs), 2989(m), 2810(m), 1756(m), 1702(s), 1518(m), 1400(m), 1301(w), 1256(m), 1168(w), 1117(w), 760(m); HRMS *m/z* (M + Na$^+$) calcd. 329.0897, found 329.0905. Anal. Calcd. for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.86; N, 8.98. Found: C, 70.77; H, 4.86; N, 8.98.

2-Dimethylamino-4,6-dimethyl-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (76). Method D with adduct **27** gave **76** (54 mg, 56%) as light-yellow crystals: mp 179–180°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.31 (dq, *J* = 1.0, 0.9 Hz, 1H, 5-H), 7.25 (d, *J* = 3.3 Hz, 1H, 7-H), 6.95 (dd, *J* = 3.3, 0.9 Hz, 1H, 8-H), 3.84 (s, 3H, 6-CH_3), 3.07 (s, 6H, $N(CH_3)_2$), 2.78 (d, *J* = 0.9 Hz, 3H, 4-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 169.4, 168.3, 141.3, 134.0, 130.3, 122.3, 122.2, 119.8, 115.6, 100.5, 45.1, 33.3, 18.5; IR (film, cm^{-1}) 3125(m), 3100(m), 2945(m), 3877(m), 3851(m), 1759(m), 1704(s), 1632(w), 1513(m), 1470(w), 1446(w), 1403(w), 1375(m), 1353(m), 1294(w), 1099(m), 758(w); HRMS *m/z* (M + Na$^+$) calcd. 280.1057, found 280.1057. Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.11; H, 5.71; N, 16.38.

4,6-Dimethyl-2-phenyl-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (77). Method D with adduct **28** gave **77** (68 mg, 62%) as bright orange-yellow crystals: mp 181–182°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.45–7.55 (m, 4H, Ph), 7.35–7.41 (m, 2H, 5-H and Ph), 7.28 (d, *J* = 3.0 Hz, 1H, 7-H), 6.99 (d, *J* = 2.7, 0.9 Hz, 1H, 8-H), 3.85 (s, 3H, 6-CH_3), 2.84 (d, *J* = 0.9 Hz, 3H, 4-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 169.3, 168.3, 141.4, 134.1, 132.4, 130.6, 129.0, 127.5, 126.7, 123.9, 122.5, 121.4, 115.8, 100.7, 33.3, 18.6; IR (film, cm^{-1}) 3120(m), 2900(m), 2860(m), 1754(m), 1710(S), 1595(w), 1492(m), 1375(s), 1357(s), 1294(w), 1168(w); HRMS *m/z* (M + Na$^+$) calcd. 313.0948, found 313.0951. Anal. Calcd. for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.28; H, 4.61; N, 9.60.

2-(4-Methoxyphenyl)-4,6-dimethyl-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (78). Method D with adduct **29** gave **78** (73 mg, 61%) as bright-yellow crystals: mp 243–244°C; ^{1}H NMR (300 MHz, CD_2Cl_2, δ) 7.43 (dq, *J* = 0.9, 0.9 Hz, 1H, 5-H), 7.37–7.40 (m, 3H, 7-H and Ph), 7.06 (d, *J* = 9.0 Hz, 2H, Ph), 6.95 (dd, *J* = 3.0, 0.9 Hz, 1H, 8-H), 3.89 (s, 3H, 6-CH_3 or OCH_3), 3.87 (s, 3H, 6-CH_3 or OCH_3), 2.83 (d, *J* = 0.9 Hz, 3H, 4-CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 169.6, 168.5, 159.1, 141.5, 136.0, 129.6, 129.3, 125.4, 123.5, 122.1, 121.3, 117.0, 114.6, 99.6, 55.9, 33.5, 18.5; IR (film, cm^{-1}) 3120(m), 2999(m), 2940(w), 2860(w), 1751(m), 1706(s), 1632(w), 1612(w), 1510(s), 1480(w), 1438(w), 1402(m), 1382(m), 1362(w), 1345(m), 1290(m), 1244(s), 1167(m), 1113(w), 1089(w), 1028(w); HRMS *m/z* (M + Na$^+$) calcd. 343.1054, found 343.1064. Anal. Calcd. for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.41; H, 4.87; N, 8.54.

4-Ethyl-2-phenyl-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (79). Method D with adduct **30** gave **79** (48 mg, 44%) as light-brown crystals: mp 261–262°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 11.85 (bs, 1H, 6-H), 7.81 (ddd, *J* = 2.0, 1.0, 1.0 Hz, 1H, 8-H), 7.75 (dd, *J* = 3.0, 3.0 Hz, 1H, 7-H), 7.64 (d, *J* = 0.9 Hz, 1H, 5-H), 7.39–7.55 (m, 5H, Ph), 3.15 (q, *J* = 7.5 Hz, 2H, 4-$C\mathit{H}_2CH_3$), 1.28 (t, *J* = 7.4 Hz, 3H, 4-$CH_2C\mathit{H}_3$); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 169.1, 168.4, 141.6, 136.5, 132.9, 132.1, 129.3, 128.1, 128.0, 123.5, 122.0, 120.7, 117.2, 100.3, 24.9, 16.1; IR (KBr, cm^{-1}) 3300(bs), 2970(m), 1763(m), 1683(s), 1637(m), 1592(w), 1496(m), 1456(w), 1368(s), 1163(w), 1101(w), 1062(w), 848(w), 760(m); HRMS *m/z* (M + Na$^+$) calcd. 313.0948, found 313.0945. Anal. Calcd. for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.61; H, 4.88; N, 9.48.

4-Ethyl-2-(4-ethylphenyl)-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (80). Method C with adduct **31** gave **80** (63 mg, 53%) as orange crystals: mp 238–239°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 11.83 (bs, 1H, 6-H), 7.73 (dd, *J* = 2.4, 0.9 Hz, 1H, 7-H), 7.63 (d, *J* = 0.6 Hz, 1H, 5-H), 7.36–7.39 (m, 4H, Ph), 6.80 (ddd, *J* = 2.9, 1.7, 1.0 Hz, 1H, 8-H), 3.14 (q, *J* = 7.4 Hz, 2H, 4-$C\mathit{H}_2CH_3$), 2.67 (q, *J* = 7.6 Hz, 2H, $PhC\mathit{H}_2CH_3$), 1.27 (t, *J* = 7.5 Hz, 3H, 4-$CH_2C\mathit{H}_3$), 1.23 (t, *J* = 7.7, 3H, $PhCH_2C\mathit{H}_3$); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 169.3, 168.5, 143.7, 141.5, 136.4, 132.1, 130.4, 128.6, 127.9, 123.5, 121.9, 120.7, 117.1, 100.3, 28.4, 24.9, 16.2, 16.1; IR (KBr, cm^{-1}) 3307(bs), 2964(m), 2929(w), 2871(w), 1757(m), 1696(s), 1633(w), 1514(m), 1458(m), 1368(s), 1294(m), 1167(m), 1117(w), 1095(m), 1066(w), 832(w), 764(m), 726(w); HRMS *m/z* (M + Na$^+$) calcd. 341.1261, found 341.1260. Anal. Calcd. for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.70; H, 5.58; N, 8.20.

4-Ethyl-2-(4-hydroxyphenyl)-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (81). Method D with adduct **32** gave **81** (17 mg, 15%) as yellow crystals: mp 265–267°C; ^{1}H NMR (500 MHz, DMSO-d_6, δ) 11.80 (bs, 1H, 6-H), 9.69 (bs, 1H, Ph-O*H*), 7.69–7.74 (m, 1H, 5-H), 7.58–7.62 (m, 1H, 7-H), 7.18 (d, *J* = 7.5 Hz, 2H, Ph), 6.85 (d, *J* = 8.0 Hz, 2H, Ph), 6.75–6.79 (m, 1H, 8-H), 3.11 (q, *J* = 7.3 Hz, 2H, 4-$C\mathit{H}_2CH_3$), 1.25 (t, *J* = 7.3 Hz, 3H, 4-$CH_2C\mathit{H}_3$); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 169.6, 168.8, 157.4, 141.5, 136.3, 132.0, 129.5, 123.8, 123.5, 121.9, 120.7, 117.0, 115.8, 100.2, 24.9, 16.1; IR (KBr, cm^{-1}) 3464(m), 3311(bs), 3115(w), 2966(m), 2926(m), 1751(m), 1683(s), 1636(w), 1597(w), 1515(s), 1455(w), 1379(s), 1295(w), 1269(m), 1206(m), 1162(m), 1114(m), 1087(w), 834(w), 765(w); HRMS *m/z* (M + Na$^+$) calcd. for $C_{18}H_{14}N_2O_3$: 329.0897, found 329.0906.

2-(4-Chlorophenyl)-4-ethyl-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (82). Method D with adduct **34** gave **82** (40 mg, 33%) as yellow crystals: mp 219–220°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.56 (bs, 1H, 6-H), 7.53 (app. s, 1H, 5-H), 7.47–7.49 (m, 5H, 7-H and Ph), 7.09 (app. dd, *J* = 2.3, 2.3 Hz, 1H, 8-H), 3.25 (q, *J* = 7.6 Hz, 2H, 4-$C\mathit{H}_2CH_3$), 1.36 (t, *J* = 7.7 Hz, 3H, 4-$CH_2C\mathit{H}_3$); ^{1}H NMR (300 MHz, DMSO-d_6, δ) 11.86 (bs, 1H, 6-H), 7.64 (d, *J* = 0.9 Hz, 1H, 5-H), 7.59 (d, *J* = 9.0 Hz, 2H, Ph), 7.50 (d, *J* = 9.0 Hz, 2H, Ph), 7.49 (dd, *J* = 3.1, 2.6 Hz, 1H, 7-H), 6.80 (ddd, *J* = 3.0, 1.8, 1.1 Hz, 1H, 8-H), 3.14 (q, *J* = 7.4 Hz, 2H, 4-$C\mathit{H}_2CH_3$), 1.27 (t, *J* = 7.5 Hz, 3H, 4-$CH_2C\mathit{H}_3$); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 168.9, 168.1, 141.6, 136.5, 132.4, 132.2, 131.8, 129.6, 129.3, 123.4, 122.0, 120.7, 117.2, 100.3, 24.9, 16.0; IR (KBr, cm^{-1}) 3308(bs), 3105(w), 2968(m), 2933(w), 2880(w), 1762(m), 1707(s), 1635(w), 1495(m), 1459(w), 1409(m), 1376(s), 1313(w), 1295(m), 1241(w), 1209(w), 1167(w), 1109(w), 1092(m), 1066(w), 1016(w), 852(w), 830(m), 807(m), 781(m), 753(m), 717(w); HRMS m/z (M + Na$^+$) calcd. for $C_{18}H_{13}ClN_2O_2$: 347.0559, found 347.0557.

2-(4-Bromophenyl)-4-ethyl-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (83). Method D with adduct **35** gave **83** (50 mg, 36%) as yellow crystals: mp 246–247°C; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.53 (bs, 1H, 6-H), 7.63 (d, J = 9.0 Hz, 2H, Ph), 7.53 (d, J = 0.9 Hz, 1H, 5-H), 7.48 (dd, J = 3.3, 2.4 Hz, 1H, 7-H), 7.42 (d, J = 9.0 Hz, 2H, Ph), 7.10 (ddd, J = 3.2, 2.2, 0.9 Hz, 1H, 8-H), 3.25 (q, J = 7.4 Hz, 2H, 4-CH_2CH$_3$), 1.37 (t, J = 7.7 Hz, 3H, 4-CH$_2$CH_3); ^{1}H NMR (300 MHz, DMSO-d_6, δ) 11.86 (bs, 1H, 6-H), 7.75 (dd, J = 2.7 Hz, 1H, 7-H), 7.72 (d, J = 8.7 Hz, 2H, Ph), 7.65 (d, J = 0.9 Hz, 1H, 5-H), 7.44 (d, J = 8.7 Hz, 2H, Ph), 6.80 (ddd, J = 3.0, 2.0, 0.9 Hz, 1H, 8-H), 3.14 (q, J = 7.5 Hz, 2H, 4-CH_2CH$_3$), 1.27 (t, J = 7.5 Hz, 3H, 4-CH$_2$CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 168.8, 168.1, 141.6, 136.5, 132.2, 129.9, 123.4, 122.0, 120.9, 120.69, 120.65, 117.2, 105.0, 100.3, 24.9, 16.1; IR (KBr, cm^{-1}) 3307(bs), 3100(w), 3082(w), 2966(m), 2878(w), 1763(m), 1707(s), 1637(m), 1493(m), 1460(w), 1367(s), 1314(w), 1298(w), 1243(w), 1209(w), 1167(w), 1122(w), 1108(w), 1090(w), 1074(m), 1012(w), 980(w), 820(m), 790(m), 740(m); HRMS m/z (M + Na$^+$) calcd. 391.0053, found 391.0044. Anal. Calcd. for $C_{18}H_{13}BrN_2O_2$: C, 58.56; H, 3.55; N, 7.59. Found: C, 58.59; H, 3.41; N, 7.46.

4-Ethyl-2-(4-nitrophenyl)-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (84). Method D with adduct **36** gave **84** (35 mg, 28%) as light-orange crystals: mp 296–297°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 11.90 (bs, 1H, 6-H), 8.39 (d, J = 9.3 Hz, 1H, Ph), 7.83 (d, J = 9.3 Hz, 2H, Ph), 7.77 (dd, J = 2.9, 2.9 Hz, 1H, 7-H), 7.68 (d, J = 0.6 Hz, 1H, 5-H), 6.84 (ddd, J = 3.2, 2.0, 1.1 Hz, 1H, 8-H), 3.16 (q, J = 7.4 Hz, 2H, 4-CH_2CH$_3$), 1.29 (t, J = 7.5 Hz, 3H, 4-CH$_2$CH_3); ^{13}C NMR (75 MHz, DMSO-$d6$, δ) 168.4, 167.7, 146.1, 141.7, 138.9, 136.7, 132.4, 127.9, 124.6, 123.4, 122.1, 120.6, 117.6, 100.4, 25.0, 16.1; IR (KBr, cm^{-1}) 3378(bs), 3120(w), 2970(w), 2933(w), 2879(w), 1765(m), 1718(s), 1631(w), 1591(m), 1516(m), 1498(m), 1471(w), 1411(w), 1376(m), 1318(s), 1213(m), 1185(m), 1165(w), 1718(s), 1631(w), 1591(m), 1516(m), 1498(m), 1471(m), 1411(w), 1376(m), 1318(s), 1213(m), 1185(m), 1165(m), 1110(m), 1086(m), 1051(m), 851(m), 781(m), 750(m); HRMS m/z (M + Na$^+$) calcd. 358.0799, found 358.0800. Anal. Calcd. for $C_{18}H_{13}N_3O_4$: C, 64.47; H, 3.91; N, 12.53. Found: C, 64.10; H, 4.25; N, 12.16.

(+)-(R)-2-(1,3-Dioxo-2H,6H-pyrrolo[3,4-e]indol-2-yl)-2-phenylethyl acetate (85). Method A with vinylpyrrole **4** and maleimide **10m** gave adduct **39**, which with method E gave **85** (641 mg, 46%) as dark-yellow crystals: mp 62–63°C; $[\alpha]^{23}_D$ +2.1 (c 1.0, CHCl$_3$); ^{1}H NMR (300 MHz, CD$_2$Cl$_2$, δ) 8.88 (bs, 1H, 6-H), 7.74 (dd, J = 8.1, 0.9 Hz, 1H, 5-H), 7.64 (d, J = 8.1 Hz, 1H, 4-H), 7.56–7.61 (m, 3H, 7-H and Ph), 7.31–7.42 (m, 3H, Ph), 7.04 (ddd, J = 3.2, 2.0, 1.1 Hz, 1H, 8-H), 5.63 (dd, J = 9.9, 5.7 Hz, 1H, 2′-H), 5.13 (dd, J = 11.1, 9.9 Hz, 1H, 1′-H), 4.83 (dd, J = 11.1, 5.7 Hz, 1H, 1′-H), 2.02 (s, 3H, Ac); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 171.2, 170.2, 169.8, 140.9, 136.7, 130.5, 128.9, 128.5, 128.1, 124.5, 123.4, 123.2, 116.4, 116.1, 101.5, 63.0, 53.2, 21.0; IR (film, cm^{-1}) 3360(bs), 1749(m), 1698(s), 1629(w), 1458(w), 1350(s), 1236(m), 1041(w), 750(m), 699(m); HRMS m/z (M + Na$^+$) calcd. 371.1003, found 371.1009. Anal. Calcd. for $C_{20}H_{16}N_2O_4$: C, 68.96; H, 4.63; N, 8.04. Found: C, 68.80; H, 4.62; N, 8.00.

(R)-2-(4-Methyl-1,3-dioxo-2H,6H-pyrrolo[3,4-e]indol-2-yl)-2-phenylethyl acetate (86). Method A with vinylpyrrole **3b** and maleimide **10m** gave adduct **40**, which with method E gave **86** (391 mg, 27%) as light-yellow crystals: mp 158–159°C; ^{1}H NMR (300 MHz, CD$_2$Cl$_2$, δ) 8.85 (bs, 1H, 6-H), 7.55–7.59 (m, 2H, Ph), 7.33–7.46 (m, 5H, 5-H, 7-H and Ph), 6.95 (ddd, J = 3.1, 2.1, 1.0 Hz, 1H, 8-H), 5.65 (dd, J = 9.6, 6.0 Hz, 1H, 2′-H), 5.16 (dd, J = 11.1, 9.6 Hz, 1H, 1′-H), 4.86 (dd, J = 6.0, 11.1 Hz, 1H, 1′-H), 2.73 (d, J = 0.9 Hz, 3H, 4-CH$_3$), 2.01 (s, 3H, Ac); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 171.2, 170.4, 169.6, 140.8, 137.0, 130.7, 129.7, 128.9, 128.4, 128.2, 123.6, 121.9, 121.7, 117.6, 101.5, 63.1, 53.0, 21.0, 18.3; IR (film, cm^{-1}) 3370(bs), 1747(m), 1696(s), 1637(m), 1457(w), 1391(m), 1350(m), 1238(m), 1043(w), 767(m), 738(w), 700(m); HRMS m/z (M + Na$^+$) calcd. 385.1160, found 385.1161. Anal. Calcd. for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73. Found: C, 69.51; H, 4.98; N, 7.52.

(+)-(R)-2-(6-Methyl-1,3-dioxo-2H,6H-pyrrolo[3,4-e]indol-2-yl)-2-phenylethyl acetate (87). Method A with vinylpyrrole **3d** and maleimide **10m** gave adduct **41**, which with method E gave **87** (638 mg, 44%) as light-brown crystals: mp 52–53°C; $[\alpha]^{23}_D$ +3.6 (c 2.0, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.66 (dd, J = 8.4, 0.6 Hz, 1H, 5-H), 7.57–7.61 (m, 2H, Ph), 7.58 (d, overlapped, J = 8.4 Hz, 1H, 4-H), 7.28–7.40 (m, 4H, 7-H, Ph), 6.98 (d, J = 3.0 Hz, 1H, 8-H), 5.65 (dd, J = 10.2, 5.7 Hz, 1H, 2′-H), 5.16 (dd, J = 10.5, 10.5 Hz, 1H, 1′-H), 4.87 (dd, J = 10.7, 5.7 Hz, 1H, 1′-H), 3.89 (s, 3H, 6-CH$_3$), 2.01 (s, 3H, Ac); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 170.8, 169.9, 169.5, 141.1, 136.8, 134.6, 128.8, 128.4, 128.2, 124.2, 123.6, 123.5, 115.7, 114.1, 100.1, 62.8, 53.3, 33.4, 20.9; IR (film, cm^{-1}) 3447(bs), 3108(w), 3063(w), 2950(w), 1741(s), 1703(s), 1626(w), 1511(m), 1457(m), 1352(s), 1295(m), 1232(s), 1042(m), 749(s), 701(s); HRMS m/z (M + Na$^+$) calcd. 385.1160, found 385.1166. Anal. Calcd. for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.93. Found: C, 69.75; H, 4.89; N, 7.93.

(+)-(R)-2-(5,6-Dimethyl-1,3-dioxo-2H,6H-pyrrolo[3,4-e]indol-2-yl)-2-phenylethyl acetate (88). Method A with vinylpyrrole **3c** and maleimide **10m** gave adduct **42**, which with method E gave **88** (437 mg, 29%) as yellow crystals: mp 125–126°C; $[\alpha]^{23}_D$ +3.9 (c 2.0, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.56–7.59 (m, 2H, Ph), 7.27–7.41 (m, 4H, 4-H and Ph), 7.20 (d, J = 3.3 Hz, 1H, 7-H), 6.94 (d, J = 3.0 Hz, 1H, 8-H), 5.60 (dd, J = 9.9, 5.4 Hz, 1H, 2′-H), 5.14 (dd, J = 11.1, 10.2 Hz, 1H, 1′-H), 4.85 (dd, J = 11.1, 5.4 Hz, 1H, 1′-H), 4.13 (s, 3H, 6-CH$_3$), 2.87 (s, 3H, 5-CH$_3$), 2.00 (s, 3H, Ac); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 170.8, 169.9, 169.6, 139.6, 136.9, 136.0, 128.8, 128.3, 128.2, 127.6, 124.8, 124.7, 121.9, 118.2, 100.5, 62.9, 53.2, 37.3, 20.9, 20.4; IR (film, cm^{-1}) 3440(bs), 1742(m), 1701(s), 1518(w), 1496(w), 1367(m), 1347(s), 1232(m), 1089(w), 762(w), 750(w), 731(w), 701(w); HRMS m/z (M + Na$^+$) calcd. 399.1316, found 399.1328. Anal. Calcd. for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44. Found: C, 70.08; H, 5.39; N, 7.29.

(+)-(R)-2-(4,6-Dimethyl-1,3-dioxo-2H,6H-pyrrolo[3,4-e]indol-2-yl)-2-phenylethyl acetate (89). Method A with vinylpyrrole **3f** and maleimide **10m** gave adduct **43**, which with method E gave **89** (391 mg, 26%) as brownish-orange crystals: mp 163–164°C; $[\alpha]^{23}_D$ +5.9 (c 5.0, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.57–7.60 (m, 2H, Ph), 7.27–7.40 (m, 4H, 5-H and Ph), 7.25 (d, J = 3.0 Hz, 1H, 7-H), 6.98 (d, J = 3.0 Hz, 1H, 8-H), 5.63 (dd, J = 10.2, 5.7 Hz, 1H, 2′-H), 5.15 (dd, J = 11.1, 10.2 Hz, 1H, 1′-H), 4.88 (dd, J = 11.1, 5.7 Hz, 1H, 1′-H), 3.81 (s, 3H, 6-CH$_3$), 2.77 (s, 3H, 4-CH$_3$), 2.02 (s, 3H, Ac); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 170.8, 170.4, 169.4, 141.2, 137.0, 134.0, 130.2, 128.8, 128.6, 128.3, 123.8, 122.2, 121.4, 115.5, 100.3, 62.9, 53.0, 33.2, 21.0, 18.4; IR (film, cm^{-1}) 3440(bm), 2925(w), 1746(s), 1698(s), 1510(w), 1381(m), 1350(s), 1291(w), 1233(m), 1041(w), 763(w), 701(w); HRMS m/z (M + Na$^+$) calcd. 399.1316, found 399.1301. Anal. Calcd. for C$_{22}$H$_{20}$N$_2$O$_4$: C, 70.20; H, 5.36; N, 7.44. Found: C, 70.31; H, 5.49; N, 7.36.

(+)-(R)-2-(4,5,6-Trimethyl-1,3-dioxo-2H,6H-pyrrolo[3,4-e]indol-2-yl)-2-phenylethyl acetate (90). Method A with vinylpyrrole **3g** and maleimide **10m** gave adduct **44**, which with method E gave **90** (328 mg, 21%) as yellow crystals: mp 197–198°C; $[\alpha]^{23}_{D}$ +4.1 (c 2.5, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.55–7.59 (m, 2H, Ph), 7.28–7.40 (m, 3H, Ph), 7.14 (d, J = 2.7 Hz, 1H, 7-H), 6.92 (d, J = 3.0 Hz, 1H, 8-H), 5.62 (dd, J = 9.9, 5.7 Hz, 1H, 2′-H), 5.14 (dd, J = 10.7, 9.9 Hz, 1H, 1′-H), 4.88 (dd, J = 11.1, 5.7 Hz, 1H, 1′-H), 4.12 (s, 3H, 6-CH$_3$), 2.75 (s, 3H, 4-CH$_3$ or 5-CH$_3$), 2.74 (s, 3H, 4-CH$_3$ or 5-CH$_3$), 2.01 (s, 3H, Ac); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 170.8, 169.3, 140.0, 137.1, 136.4, 129.4, 128.8, 128.3, 128.2, 126.8, 123.4, 122.0, 121.3, 116.5, 100.0, 62.9, 53.2, 38.0, 25.8, 14.5, 13.8; IR (film, cm^{-1}) 3451(bs), 1746(m), 1697(s), 1498(w), 1455(w), 1387(m), 1344(m), 1309(w), 1231(m), 1039(w), 806(w), 766(m), 730(w); HRMS m/z (M + Na$^+$) calcd. 413.1473, found 413.1456. Anal. Calcd. for C$_{23}$H$_{22}$N$_2$O$_4$: C, 70.75; H, 5.68; N, 7.17. Found: C, 70.82; H, 5.65; N, 6.96.

(+)-(R)-2-(2-Methoxy-1-phenylethyl)-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (91). Method A with vinylpyrrole **4** and maleimide **10n** gave adduct **45**, which with method E gave **91** (500 mg, 39%) as light-yellow crystals: mp 63–64°C; $[\alpha]^{23}_{D}$ +27.0 (c 5.0, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.75 (bs, 1H, 6-H), 7.55–7.60 (m, 4H, 4-H and 5-H and Ph), 7.28–7.43 (m, 4H, 7-H and Ph), 6.98 (dd, J = 3.3, 1.8 Hz, 1H, 8-H), 5.63 (dd, J = 10.2, 5.7 Hz, 1H, 1′-H), 4.69 (dd, J = 10.2, 10.2 Hz, 1H, 2′-H), 4.01 (dd, J = 10.2, 5.7 Hz, 1H, 2′-H), 3.47 (s, 3H, OCH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 170.4, 169.9, 140.6, 137.5, 130.3, 128.9, 128.4, 128.2, 124.0, 123.1, 122.8, 115.9, 115.8, 101.5, 71.4, 58.9, 53.8; IR (film, cm^{-1}) 3402(bs), 1754(m), 1699(s), 1610(m), 1458(w), 1393(w), 1353(s), 1109(w), 750(m), 700(m); HRMS m/z (M + Na$^+$) calcd. 343.1054, found 343.1045. Anal. Calcd. for C$_{19}$H$_{16}$N$_2$O$_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.46; H, 5.14; N, 8.82.

(+)-(R)-2-(2-Methoxy-1-phenylethyl)-4-methyl-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (92). Method A with vinylpyrrole **3b** and maleimide **10n** gave adduct **46**, which with method E gave **92** (401 mg, 30%) as dark-yellow crystals: mp 139–140°C; $[\alpha]^{23}_{D}$ +14.9 (c 2.3, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.68 (bs, 1H, 6-H), 7.57–7.60 (m, 2H, Ph), 7.28–7.40 (m, 5H, 5-H and 7-H and Ph), 6.79–6.81 (m, 1H, 8-H), 5.62 (dd, J = 10.2, 5.7 Hz, 1H, 1′-H), 4.77 (dd, J = 10.2, 10.2 Hz, 1H, 2′-H), 4.00 (dd, J = 10.2, 5.4 Hz, 1H, 2′-H), 3.52 (s, 3H, OCH$_3$), 2.65 (d, J = 0.9 Hz, 3H, 4-CH$_3$); ^{13}C NMR (75 MHz, CD$_2$Cl$_2$, δ) 170.4, 169.6, 140.5, 137.9, 130.3, 129.5, 128.7, 128.6, 128.2, 128.1, 123.3, 121.3, 117.2, 101.1, 71.4, 58.7, 53.3, 18.0; IR (film, cm^{-1}) 3413(bs), 1749(w), 1694(s), 1636(m), 1456(w), 1394(w), 1350(m), 766(w), 699(w); HRMS m/z (M + Na$^+$) calcd. for C$_{20}$H$_{18}$N$_2$O$_3$: 357.1210, found 357.1211.

(+)-(R)-2-(2-Methoxy-1-phenylethyl)-4,5-dimethyl-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (93). Method A with vinylpyrrole **3e** and maleimide **10n** gave adduct **47**, which with method E gave **93** (362 mg, 26%) as light-yellow crystals: mp 177–178°C; $[\alpha]^{23}_{D}$ +17.6 (c 0.8, CHCl$_3$); ^{1}H NMR (300 MHz, CD$_2$Cl$_2$ δ) 8.67 (bs, 1H, 6-H), 7.53–7.60 (m, 2H, Ph), 7.28–7.41 (m, 4H, 7-H, Ph), 6.87 (d, J = 3.0, 1.8 Hz, 1H, 8-H), 5.59 (dd, J = 9.9, 5.7 Hz, 1H, 1′-H), 4.60 (dd, J = 9.9, 9.9 Hz, 1H, 2′-H), 4.02 (dd, 9.9, 5.5 Hz, 1H, 2′-H), 3.47 (s, 3H, OCH$_3$), 2.67 (s, 3H, 4-CH$_3$), 2.45 (s, 3H, 5-CH$_3$); ^{13}C NMR (75 MHz, CD$_2$Cl$_2$, δ) 170.9, 169.3, 139.9, 138.0, 129.0, 128.6, 128.1, 128.0, 127.9, 125.4, 121.9, 120.9, 120.5, 101.6, 71.5, 58.8, 53.9, 13.2, 13.1; IR (film, cm^{-1}) 3430(bs), 2900(w), 1747(m), 1693(s), 1650(m), 1394(m), 1352(m), 1092(w), 767(m), 732(m), 699(m); HRMS m/z (M + Na$^+$) calcd. 371.1367, found 371.1351. Anal. Calcd. for C$_{21}$H$_{20}$N$_2$O$_3$: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.22; H, 5.74; N, 7.88.

(+)-(R)-2-(2-Methoxy-1-phenylethyl)-6-methyl-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (94). Method A with vinylpyrrole **3d** and maleimide **10n** gave adduct **48**, which with method E gave **94** (535 mg, 40%) as light-yellow crystals: mp 123–124°C; $[\alpha]^{23}_{D}$ +30.4 (c 5.0, CHCl$_3$); ^{1}H NMR (300 MHz, CD$_2$Cl$_2$, δ) 7.59–7.62 (m, 2H, 4-H, 5-H), 7.54–7.58 (m, 2H, Ph), 7.28–7.52 (m, 4H, 7-H and Ph), 6.94 (dd, J = 3.3, 0.9 Hz, 1H, 8-H), 5.58 (dd, J = 9.9, 6.3 Hz, 1H, 1′-H), 4.52 (dd, J = 9.6, 9.6 Hz, 1H, 2′-H), 4.02 (dd, J = 9.9, 6.0 Hz, 1H, 2′-H), 3.89 (s, 3H, 6-CH$_3$), 3.41 (s, 3H, OCH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$, δ) 170.2, 169.8, 141.0, 137.7, 134.4, 128.7, 128.3, 128.1, 124.5, 123.9, 123.5, 115.7, 113.9, 100.6, 71.4, 58.9, 53.9, 33.4; IR (film, cm^{-1}) 3443(bs), 2905(m), 2800(w), 1755(m), 1702(s), 1511(m), 1458(w), 1385(m), 1353(s), 1295(w), 1114(m), 1090(w), 748(s), 700(m); HRMS m/z (M + Na$^+$) calcd. 357.1210, found 357.1200. Anal. Calcd. for C$_{20}$H$_{18}$N$_2$O$_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.61; H, 5.32; N, 8.41.

(+)-(R)-2-(2-Methoxy-1-phenylethyl)-5,6-dimethyl-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (95). Method A with vinylpyrrole **3c** and maleimide **10n** gave adduct **49**, which with method E gave **95** (446 mg, 32%) as orangish-yellow crystals: mp 157–158°C; $[\alpha]^{23}_{D}$ +30.2 (c 5.0, CHCl$_3$); ^{1}H NMR (300 MHz, CD$_2$Cl$_2$, δ) 7.53–7.58 (m, 2H, Ph), 7.27–7.39 (m, 4H, 4-H, Ph), 7.25 (d, J = 3.3 Hz, 1H, 7-H), 6.89 (d, J = 3.3 Hz, 1H, 8-H), 5.54 (dd, J = 9.6, 5.7 Hz, 1H, 1′-H), 4.49 (dd, J = 9.6, 9.6 Hz, 1H, 2′-H), 4.12 (s, 3H, 6-CH$_3$), 4.02 (dd, J = 9.6, 6.0 Hz, 1H, 2′-H), 3.40 (s, 3H, OCH$_3$), 2.88 (s, 3H, 5-CH$_3$); ^{13}C NMR (75 MHz, CD$_2$Cl$_2$, δ) 170.0, 169.6, 139.4, 138.1, 136.0, 128.6, 128.2, 127.9, 127.7, 124.8, 124.4, 121.8, 117.6, 99.9, 71.3, 58.6, 53.6, 37.1, 20.0; IR (film, cm^{-1}) 3440(bs), 2999(w), 2933(w), 2805(w), 1750(m), 1696(s), 1518(w), 1495(w), 1404(w), 1347(s), 1116(m), 1092(w), 760(w), 750(w), 730(w), 701(m), 661(m); HRMS m/z (M + Na$^+$) calcd. 371.1367, found 371.1372. Anal. Calcd. for C$_{21}$H$_{20}$N$_2$O$_3$: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.56; H, 5.93; N, 7.96.

(+)-(R)-2-(2-Methoxy-1-phenylethyl)-4,6-dimethyl-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (96). Method A with vinylpyrrole **3f** and maleimide **10n** gave adduct **50**, which with method

E gave **96** (404 mg, 29%) as yellow crystals: mp 132–133°C; $[\alpha]^{23}_{D}$ +30.2 (*c* 5.0, $CHCl_3$); ^1H NMR (300 MHz, CD_2Cl_2, δ) 7.54–7.58 (m, 2H, Ph), 7.30–7.40 (m, 5H, 5-H and 7-H and Ph), 6.88 (dd, $J = 3.0$, 0.9 Hz, 1H, 8-H), 5.57 (dd, $J = 9.3$, 6.0 Hz, 1H, 1′-H), 4.53 (dd, $J = 9.9$, 9.9 Hz, 1H, 2′-H), 4.04 (dd, $J = 9.9$, 6.3 Hz, 1H, 2′-H), 3.82 (s, 3H, 6-CH_3), 3.42 (s, 3H, OCH_3), 2.77 (d, $J = 0.9$ Hz, 3H, 4-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 170.6, 169.6, 141.0, 138.0, 133.7, 129.8, 128.8, 128.4, 128.1, 123.7, 122.0, 121.3, 115.2, 100.1, 71.4, 58.9, 53.7, 33.0, 18.3; IR (film, cm^{-1}) 3442(bs), 2915(w), 2790(w), 1749(m), 1697(s), 1636(m), 1508(w), 1350(m), 1291(w), 1104(w), 762(m), 700(m); HRMS *m*/*z* (M + Na^+) calcd. 371.1367, found 371.1381. Anal. Calcd. for $C_{21}H_{20}N_2O_3$: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.30; H, 5.81; N, 7.84.

(+)-(R)-2-(2-Methoxy-1-phenylethyl)-4,5,6-trimethyl-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (97). Method A with vinylpyrrole **3g** and maleimide **10n** gave adduct **51**, which with method E gave **97** (333 mg, 23%) as dark-orange crystals: mp 164–165°C; $[\alpha]^{23}_{D}$ +26.5 (*c* 0.4, $CHCl_3$); ^1H NMR (300 MHz, CD_2Cl_2, δ) 7.52–7.58 (m, 2H, Ph), 7.28–7.40 (m, 3H, Ph), 7.17 (d, $J = 3.0$ Hz, 1H, 7-H), 6.86 (d, $J = 3.3$ Hz, 1H, 8-H), 5.56 (dd, $J = 9.6$, 6.0 Hz, 1H, 1′-H), 4.50 (dd, $J = 9.6$, 9.6 Hz, 1H, 2′-H), 4.10 (s, 3H, 6-CH_3), 4.04 (dd, $J = 9.9$, 6.0 Hz, 1H, 2′-H), 3.42 (s, 3H, OCH_3), 2.73 (s, 3H, 4-CH_3 or 5-CH_3), 2.72 (s, 3H, 4-CH_3 or 5-CH_3); ^{13}C NMR (75 MHz, CD_2Cl_2, δ) 170.9, 169.4, 139.9, 138.2, 136.4, 129.2, 128.5, 128.1, 127.8, 126.9, 123.2, 122.0, 121.3, 99.5, 71.4, 58.6, 53.3, 37.9, 14.3, 13.4; IR (film, cm^{-1}) 3450(bs), 2932(w), 1748(m), 1695(s), 1519(w), 1496(w), 1395(m), 1345(m), 1309(w), 1112(w), 765(m), 731(m), 700(m); HRMS *m*/*z* (M + Na^+) calcd. for $C_{22}H_{22}N_2O_3$: 385.1523, found 385.1518.

^1H and ^{13}C NMR spectra for compounds **3a-3c**, **3e-3g**, **5b**, **7**, **10m**, **10n**, **11-38**, **53-97**, the ^1H NMR spectrum for compound **52**, biological activity data for compounds **63** and **66**, and X-ray data for 7 in CIF format. This material is available online free of charge (see Supporting Information).

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Synthesis of New Compounds Containing the Pyrazolo[3,4-*b*]pyridine-3-one Subunit

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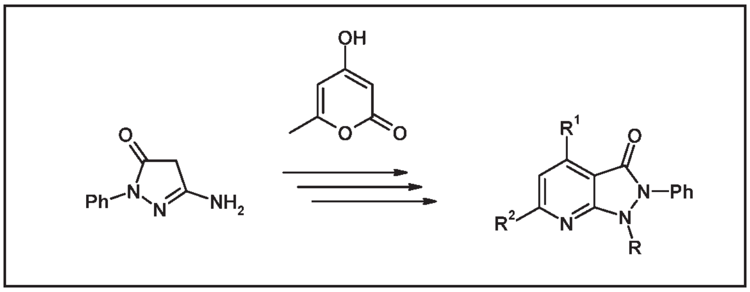

A convenient route for the synthesis of pyrazolo[3,4-*b*]pyridine-3-ones *via* condensation of 3-amino-1-phenylpyrazolin-5-one with 4-hydroxy-6-methylpyran-2-one is described. The pyrazolo[3,4-*b*]pyridine-3-one isomers obtained were functionalized at 1-, 4-, or 6- position by different pharmacophore entities allowing the synthesis of new compounds with promising biological activities.

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INTRODUCTION

The pyrazolo[3,4-*b*]pyridines are important compounds, particularly in pharmaceutical research because of their significant and versatile biological activities such as antimicrobial, antimalarial, antiviral, antiproliferative, anticoagulative, hypotensive, and antiarrythmic [1–5].

Because of the potential of pyrazolo[3,4-*b*]pyridines, much work has been done over the years. The most important synthetic method used to reach these derivatives the condensation of aminopyrazole with α,β-unsaturated compounds reported by Quiroga et al. [6,7].

We were interested in the synthesis of pyridine analogues of these systems involving the condensation of the aminopyrazolone **1** with 2-pyrone **2** [8]. The latter skeleton was proven to be valuable scaffold to obtain new heterocyclic compounds [9,10]. The pyrazolo[3,4-*b*]pyridines prepared will be functionalized at 1-, 4-, and 6-positions.

RESULTS AND DISCUSSION

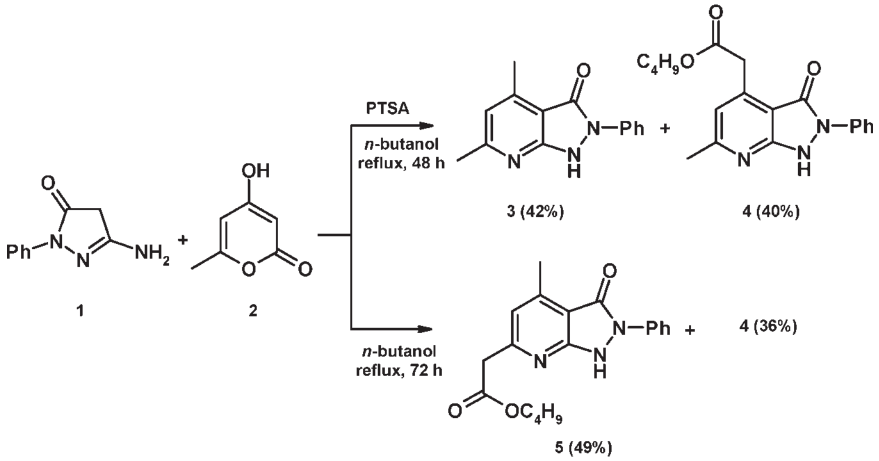
Synthesis of pyrazolo[3,4-*b*]pyridine-3-ones. The reaction of 3-amino-1-phenylpyrazolin-5-one **1** with 4-hydroxy-6-methylpyran-2-one **2** was carried out in butanol at reflux with or without PTSA as catalyst. Pyrazolo[3,4-*b*]pyridine-3-one **4** was isolated in both cases with moderate yields (36–40%). Depending on the reaction conditions used (presence or not of the catalyst), the product **4** was accompanied with pyrazolo[3,4-*b*]pyridine-3-ones **3** or **5** in comparable yields of 42 and 49%, respectively (Scheme 1) [8].

This sequence is of particular interest since it allows a rapid and easy functionalization of 1-, 4-, and 6-positions of the pyrazolo[3,4-*b*]pyridine-3-one scaffold. Thus, the development of synthesis of new molecules with potential biological and/or pharmacological properties appears attractive.

Synthesis of pyrazolo[3,4-*b*]pyridine-3-ones functionalized at 1- position. To widen the substitution of 1-position of pyrazolo[3,4-*b*]pyridine-3-ones, we decided to introduce a bromoethane linker in order to incorporate a bicyclic compound such as a saturated pyridodiazepine known to interact with 5-HT_7/5-HT_{1A} receptors [11].

For this purpose, Deprotonation of pyrazolo[3,4-b]pyridine-3-one 3 with sodium hydride and further nucleophilic substitution with dibromoethane allows the alkylation of position 1 and compound 7 was isolated in 60% yield (Scheme 2) [12].

Scheme 1



We then carried out the preparation of the decahydropyrido[1,2-*a*][1,4]diazepine **6**. This cyclic diamine was prepared in four steps from the piperidine-2-carboxylic acid ethyl ester according to the literature [13].

The final step of this synthetic route was the substitution of the bromine of derivative **7** with the saturated pyridodiazepine **6** in acetonitrile, in the presence of potassium carbonate and a catalytic amount of potassium iodide. The desired compound **8** was obtained in a good yield (78%) (Scheme 3).

Synthesis of pyrazolo[3,4-*b*]pyridine-3-ones functionalized at 4- or 6-position with an amine chain. In a second approach, we focused on the reactivity of the alkyl acetate group present at 4- or 6-position on pyrazolo[3,4-*b*]pyridine-3-ones. Functionalizations with amines and notably with aryl piperazines, often present in serotoninergic ligands, have been especially chosen.

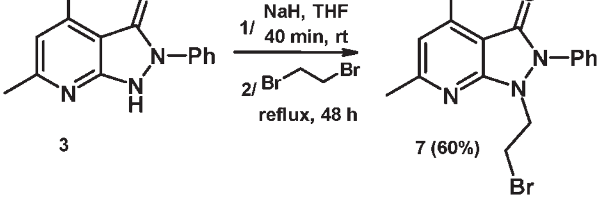
First, the protection of the amine present in compound **5** was necessary. To carry out this step, we choose the *para*-methoxybenzyl chloride (PMBCl) like protective agent. In a basic medium, reaction of pyrazolo[3,4-*b*]pyridine-3-one **5** with the PMBCl led to the amino protected derivative **9** in an excellent yield (97%). Reduction of the ester group with $LiAlH_4$ in THF at reflux led to the desired alcohol **10** in 40% yield. It is worth mentioning that a further reduction of the amide function occurred under these conditions to yield additional product **11** (29%).

To increase the chemioselectivity of the reduction reaction, we performed the reaction in diethyl ether at 0°C. These conditions lead only to the reduction of the function ester making it possible to obtain compound **10** with an average yield (53%). Activation of the alcohol function with methylsulfonyl chloride in the presence of pyridine led to the mesylate derivative **12** in good yield. Substitution of the leaving group with *N*,*N*-dibutylamine and phenylpiperazine provided compounds **13** and **14** in 92 and 93% yields, respectively. The deprotection of the pyrazolic amine group of **13** and **14** was carried out in TFA at reflux leading to compounds **15** and **16** in very good yields (Scheme 4).

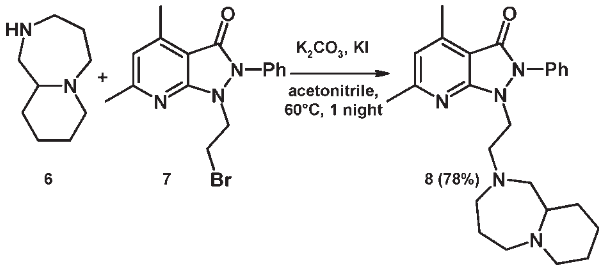
According to the procedure quoted earlier, we then prepared 4-aminoethylpyrazolo[3,4-*b*]pyridin-3-ones **22** and **23** from ester **4** with good yields (Scheme 5). The protection of the amine group of the pyrazoline ring with PMBCl was also realized in a quantitative yield.

The ester group of the resulting protected amine **17** was reduced by $LiAlH_4$ leading to alcohol **18** in 55% yield. The mesylation of the alcohol was carried out leading to the pyrazolo[3,4-*b*]pyridine-3-one **19** in 89% yield. Reaction of *N*,*N*-dibutylamine and phenylpiperazine provided

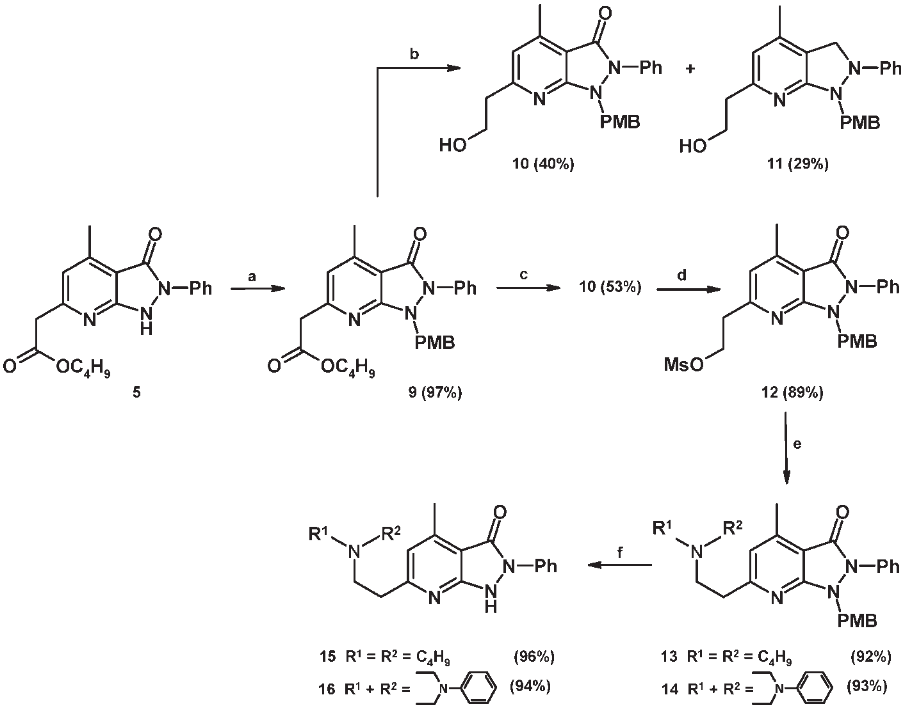
Scheme 2



Scheme 3



Scheme 4. (a) PMBCl, K_2CO_3, CH_2Cl_2, rt, 48 h; (b) $LiAlH_4$, THF, reflux, 3 h; (c) $LiAlH_4$, diethyl ether, 0°C, 24 h; (d) CH_3SO_2Cl, pyridine, 0°C to rt, 48 h; (e) *N*,*N*-dibutylamine or phenylpiperazine, DMF, 70°C, 1 night ; (f) TFA, reflux, 5 h.

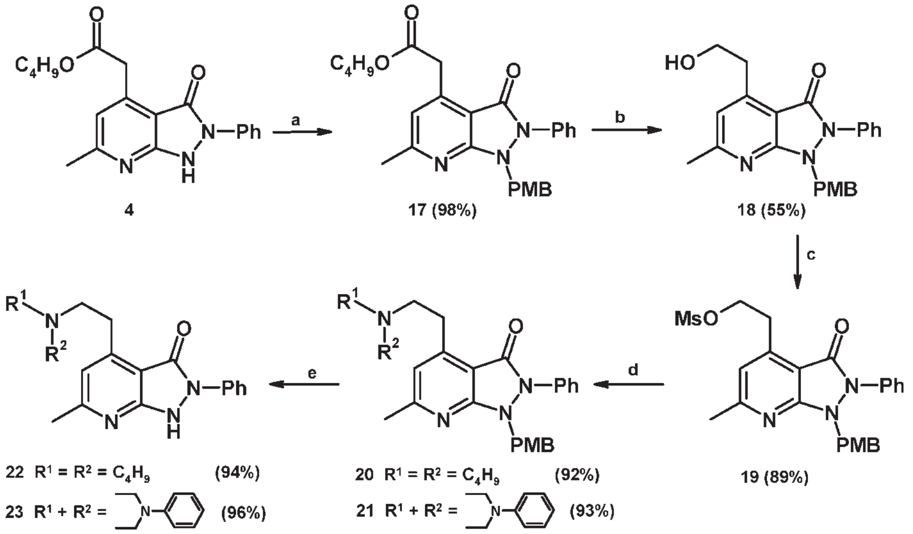


amino compounds **20** and **21** in 92 and 93% yields, respectively.

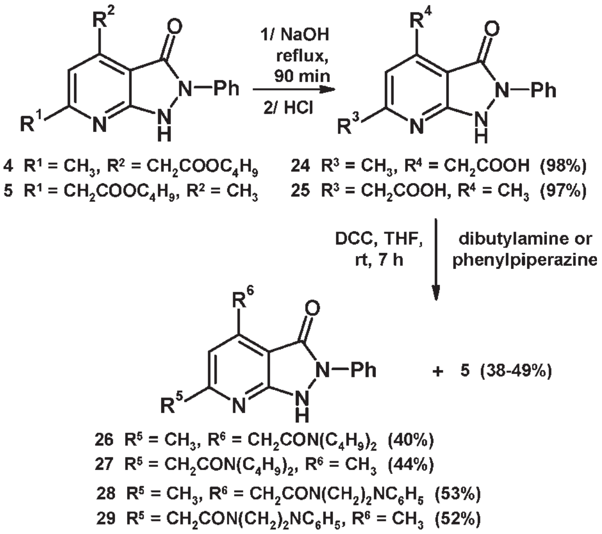
The final deprotection of the pyrazole amine systems was unrolled, like previously, in TFA at reflux affording 4-(2-(dibutylamino)ethyl)-6-methyl-2-phenyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one **22** in a 94% yield and 6-methyl-2-phenyl-4-(2-(4-phenylpiperazin-1-yl)ethyl)-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one **23** in a 96% yield.

Synthesis of pyrazolo[3,4-*b*]pyridine-3-ones functionalized at 4- or 6-position with an amide chain. At last, we showed that the ester function at 4- or 6-position could be converted into amide. The preparation of

Scheme 5. (a) PMBCl, K_2CO_3, CH_2Cl_2, rt, 48 h; (b) $LiAlH_4$, diethyl ether, 0°C, 24 h; (c) CH_3SO_2Cl, pyridine, 0°C to rt, 48 h; (d) *N*,*N*-dibutylamine or phenylpiperazine, DMF, 70°C, 1 night ; (e) TFA, reflux, 5 h.



Scheme 6



amido-pyrazolopyridinones **26–29** was accomplished easily in two-step sequence by saponification of ester **4** and **5** followed by peptidic coupling with *N*,*N*-dibutylamine and phenylpiperazine using DCC as coupling agent (Scheme 6).

CONCLUSION

In summary, we have developed an efficient method for the synthesis of novel pyrazolo[3,4-*b*]pyridine-3-one derivatives. Thereafter, we have shown that 1-, 4-, and 6-positions of the pyrazolopyridine skeleton can be easily and rapidly functionalized in order to introduce new pharmacophore entities allowing the synthesis of potential biological molecules. One of the new molecules tested, is compound **26**, has shown pharmacological activities toward the serotoninergic receptors 5-HT_{1A} (Ki = 220 n*M*) and 5-HT_7 (Ki = 870 n*M*).

EXPERIMENTAL

All reagents were purchased either from Acros Organics or Aldrich. Thin layer chromatography was performed on 0.5 mm × 20 cm × 20 cm E. Merck silica gel plates (60 F-254). Infrared (IR) spectra were obtained on Perkin–Elmer Paragon 1000 PC FTIR. Infrared spectra were recorded using NaCl films or KBr pellets. ^{13}C and ^{1}H NMR spectra were recorded at room temperature using a Bruker Advance DXP250 at 62.9 and 250 MHz, respectively. Chemical shifts (δ) are given in parts per million downfield from tetramethylsilane as internal standard. Mass spectra were determined with a Perkin-Elmer SCIEX AOI 300 spectrometer. All chemicals were of reagent grade and used without further purification. THF was freshly distilled from Na/benzophenone, while CH_2Cl_2 was distilled over CaH_2. The biological characterization of the compounds was based on the screening protocol described by Zajdel et al. [14,15].

1-(2-Bromoethyl)-4,6-dimethyl-2-phenyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one.(7). Sixty milligrams (1.51 mmol; 1.8 eq) of sodium hydride 60% were suspended in 8 mL of THF then 200 mg (0.84 mmol; 1 eq) of 4,6-dimethyl-2-phenyl-1,2-dihydro-pyrazolo[3,4-*b*]pyridin-3-one **3** were dissolved in 10 mL of THF and added slowly. The mixture was stirred for 40 min at room temperature. Then 0.216 mL (2.51 mmol; 5 eq) of dibromoethane in 3 mL of THF were added dropwise. The resulting mixture was heated at reflux for 30 h. The solution was hydrolyzed and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 6.5:3.5). Yield 60% (maroon solid); mp 84–86°C; IR (KBr) cm^{-1}: 1656 (CO); ^{1}H NMR ($CDCl_3$): δ (ppm) 2.59 (s, 3H), 2.68 (s, 3H), 3.25 (t, 2H, $J = 7.3$ Hz), 4.25 (t, 2H, $J = 7.3$ Hz), 6.81 (s, 1H), 7.28–7.35 (m, 1H), 7.45–7.53 (m, 4H); ^{13}C NMR ($CDCl_3$): δ (ppm) 17.3 (CH_3), 25.1 (CH_3), 25.9 (CH_2), 49.2 (NCH_2), 107.7 (C), 120.6 (CH), 124.0 (2CH), 126.0 (CH), 129.4 (2CH), 135.0 (C), 149.6 (C), 160.7 (C), 162.3 (C), 163.8 (C); MS (m/z, %): 347 (M+1, 65), 348 (M+2, 82), 106 (100).

1-(2-(Hexanhydropyrido[1,2-*a*][1,4]diazepin-2(1*H*,3*H*,7*H*)-yl)ethyl)-4,6-dimethyl-2-phenyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (8). Under inert atmosphere, 45 mg (0.29 mmol; 1 eq) of decahydropyrido[1,2-*a*][1,4]diazepine **6** were put in 8 mL of acetonitrile then 120 mg (0.87 mmol; 3 eq) of potassium carbonate, 7 mg (0.43 mmol; 0.15 eq) of potassium iodide and 100 mg (0.29 mmol;1 eq) of bromoethylpyrazolo[3,4-*b*]pyridin-3-one **7** were added. The resulting mixture was stirred overnight at 60°C. The solvent was evaporated and the residue was taken again with water and extracted with CH_2Cl_2. The organic phases were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2/MeOH/NH_4OH, 9:1:0.5). Yield 78% (maroon solid); mp 94–96°C; IR (KBr) cm^{-1}: 1683 (CO); ^{1}H NMR ($CDCl_3$): δ (ppm) 1.02–1.32 (m, 4H), 1.48–1.68 (m, 5H), 1.81–1.94 (m, 2H), 2.04–2.10 (m, 1H), 2.23–2.32 (m, 1H), 2.35–2.40 (m, 4H), 2.57 (s, 3H), 2.60–2.71 (m, 5H), 4.02 (t, 2H, $J = 6.0$ Hz,), 6.75 (s, 1H), 7.24–7.30 (m, 1H), 7.44–7.58 (m, 4H); ^{13}C NMR (*$CDCl_3$*): δ (ppm) 17.3 (CH_3), 24.3 (CH_2), 25.1 (CH_3), 26.0 (CH_2), 27.4 (CH_2), 31.2 (CH_2), 46.0 (CH_2), 54.0 (CH_2), 55.6 (CH_2), 55.7 (CH_2), 57.3 (CH_2), 61.1 (CH_2), 65.6 (CH), 107.3 (C), 119.5 (CH), 123.4 (2CH), 126.2 (CH), 129.2 (2CH), 135.5 (C), 149.1 (C), 161.9 (C), 162.2 (C), 162.8 (C); MS (m/z, %): 420 (M+1, 100), 119 (25).

Butyl.2-(1-(4-methoxybenzyl)-4-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl)acetate (9). Ninety milligrams (0.65 mmol; 1.1 eq) of potassium carbonate were put in 8 mL of CH_2Cl_2 and 200 mg (0.59 mmol; 1 eq) of pyrazolo[3,4-*b*]pyridine-3-one **5** were added. After 20 min of stirring, 0.09 mL (0.65 mmol; 1.1 eq) of *para*-methoxybenzyl chloride in 4 mL of CH_2Cl_2 were added. The mixture was stirred for three days at room temperature. The solution was hydrolyzed and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$ then evaporated in vacuo. The residue was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 7.5:2.5). Yield 97% (maroon clearly oil); IR (NaCl) cm^{-1}: 1650, 1723 (CO); ^{1}H NMR (*$CDCl_3$*): δ (ppm) 0.86 (t, 3H, $J = 7.2$ Hz), 1.19–1.36 (m, 2H), 1.48–1.59 (m, 2H), 2.67 (s, 3H), 3.68 (s, 3H), 4.04–4.12 (m, 4H), 5.01 (s, 2H), 6.62

(AB, 4H, $J_{AB} = 8.8$ Hz, $\Delta\nu = 24.1$ Hz), 6.90 (s, 1H), 7.25–7.33 (m, 1H), 7.53 (d, 4H, $J = 3.1$ Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 13.6 (CH_3), 19.0 (CH_2), 25.1 (CH_3), 30.4 (CH_2), 35.4 (CH_2), 51.3 (NCH_2), 55.0 (OCH_3), 65.0 (OCH_2), 108.1 (C), 113.4 (2CH), 119.7 (CH), 123.9 (2CH), 125.5 (C), 126.3 (CH), 129.1 (2CH), 130.3 (2CH), 135.0 (C), 143.9 (C), 159.3 (C), 160.7 (C), 161.2 (C), 163.6 (C), 169.9 (C); MS (m/z, %): 460 (M+1, 90), 119 (100).

1-(4-Methoxybenzyl)-6-(2-hydroxyethyl)-4-methyl-2-phenyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (10). Under inert atmosphere, 440 mg (0.96 mmol; 1 eq) of compound **9** weredissolved in 8 mL of Et_2O and this mixture was added at 0°C to suspension of 36 mg (0.96 mmol; 1 eq) of $LiAlH_4$ in 10 mL of Et_2O. The resulting mixture was maintained at 0°C for 24 h. The medium was hydrolyzed and the salt was filtered off. The solution was extracted with CH_2Cl_2 and the organic phases were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 4.5:6.5). Yield 53% (white foam); IR (KBr) cm^{-1}: 1681 (CO), 3419 (OH); ^{1}H NMR ($CDCl_3$): δ (ppm) 2.67 (s, 3H), 3.21 (t, 2H, $J = 6.0$ Hz), 3.70 (s, 3H), 3.91 (t, 2H, $J = 6.0$ Hz), 5.03 (s, 2H), 6.62 (AB, 4H, $J_{AB} = 8.8$ Hz, $\Delta\nu = 19.6$ Hz), 6.83 (s, 1H), 7.29–7.35 (m, 1H), 7.44–7.49 (m, 4H); ^{13}C NMR ($CDCl_3$): δ (ppm) 25.3 (CH_3), 35.2 (CH_2), 51.4 (NCH_2), 55.2 (OCH_3), 63.0 (CH_2), 108.6 (C), 113.6 (2CH), 120.1 (CH), 124.4 (2CH), 125.6 (C), 126.8 (CH), 129.3 (2CH), 130.4 (2CH), 134.9 (C), 150.2 (C), 159.5 (C), 160.6 (C), 162.3 (C), 163.8 (C); MS (m/z, %): 390 (M+1, 60), 119 (100).

2-(1-(4-Methoxybenzyl)-4-methyl-2-phenyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6yl)ethanol (11). This compound was obtained from **10** (eluent: petroleum ether/ethyl acetate, 6:4). Yield 29% (white foam); IR (KBr) cm^{-1}: 3416 (OH); ^{1}H NMR ($CDCl_3$): δ (ppm) 2.46 (s, 3H), 2.56 (t, 2H, $J = 6.6$ Hz), 3.68–3.77 (m, 5H), 4.48 (s, 2H), 4.56 (s, 2H), 6.47 (s, 1H), 6.66 (d, 2H, $J = 8.7$ Hz), 6.90 (t, 1H, $J = 7.3$ Hz), 6.99 (d, 2H, $J = 8.7$ Hz), 7.07 (d, 2H, $J = 8.5$ Hz), 7.25–7.34 (m, 2H); ^{13}C NMR ($CDCl_3$): δ (ppm) 24.1 (CH_3), 36.3 (CH_2), 55.3 (OCH_3), 57.4 (CH_2), 57.5 (CH_2), 62.1 (CH_2), 115.2 (2CH), 118.9 (C), 120.1 (CH), 127.2 (CH), 127.8 (2CH), 129.2 (2CH), 129.3 (C), 130.1 (2CH), 136.7 (C), 143.1 (C), 152.2 (C), 157.2 (C), 162.2 (C); 376 (M+1, 100), 119 (23).

2-(1-(4-Methoxybenzyl)-4-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl)ethyl methanesulfonate (12). 0.63 mL (7.71 mmol; 5 eq) of pyridine were added to 600 mg (1.54 mmol; 1 eq) of alcohol **10** in 15 mL of CH_2Cl_2 at 0°C. The solution was stirred 45 min at 0°C then 0.30 mL (3.86 mmol; 2.5 eq) of mesyl chloride in 2 mL of CH_2Cl_2 are run. The mixture was stirred for 48 h at room temperature. The medium was hydrolyzed then the solution was extracted with CH_2Cl_2. The organic phases were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 5:5). Yield 89% (yellow oil); IR (NaCl) cm^{-1}: (1678 (CO); ^{1}H NMR ($CDCl_3$): δ (ppm) 2.67 (s, 3H), 2.80 (s, 3H), 3.36 (t, 2H, $J = 6.6$ Hz), 3.68 (s, 3H), 4.54 (t, 2H, $J = 6.6$ Hz), 5.01 (s, 2H), 6.62 (AB, 4H, $J_{AB} = 8.8$ Hz, $\Delta\nu = 23.1$ Hz), 6.85 (s, 1H), 7.30–7.36 (m, 1H), 7.46–7.54 (m, 4H); ^{13}C NMR ($CDCl_3$): δ (ppm) 25.1 (CH_3), 31.4 (CH_2), 36.8 (CH_3), 51.3 (CH_2), 55.0 (CH_3), 68.9 (CH_2), 107.7 (C), 113.4 (2CH), 120.1 (CH), 124.0 (2CH), 125.3 (C), 126.6 (CH), 129.2 (2CH), 130.3 (2CH), 134.7 (C), 146.5 (C), 159.3 (C), 160.8 (C), 161.0 (C), 163.9 (C); MS (m/z, %): 468 (M+1, 70), 119 (100).

1-(4-Methoxybenzyl)-6-(2-(dibutylamino)ethyl)-4-methyl-2-phenyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (13). Two hundred milligrams (0.43 mmol; 1 eq) of sulphonate **12** were introduced into a sealed tube containing 2 mL of DMF then 1 mL (5.95 mmol; 13.9 eq) of *N*,*N*-dibutylamine. The mixture was heated with stirring at 70°C overnight. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 5:5). Yield 92% (yellow oil); IR (NaCl) cm^{-1}: 1672 (CO); ^{1}H NMR ($CDCl_3$): δ (ppm) 0.86 (t, 6H, $J = 7.2$ Hz), 1.19–1.30 (m, 4H), 1.33–1.40 (m, 4H), 2.44 (t, 4H, $J = 7.5$ Hz), 2.65 (s, 3H), 2.75 (t, 2H, $J = 7.5$ Hz), 3.11 (t, 2H, $J = 7.5$ Hz), 3.68 (s, 3H), 4.99 (s, 2H), 6.62 (AB, 4H, $J_{AB} = 8.8$ Hz, $\Delta\nu = 23.7$ Hz), 6.81 (s, 1H), 7.28–7.34 (m, 1H), 7.50 (d, 4H, $J = 4.1$ Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 14.2 ($2CH_3$), 20.7 ($2CH_2$), 25.2 (CH_3), 28.5 (CH_2), 29.7 ($2CH_2$), 51.6 (CH_2), 53.7 ($2CH_2$), 54.3 (CH_2), 55.2 (CH_3), 108.3 (C), 113.5 (2CH), 119.7 (CH), 124.1 (2CH), 125.8 (C), 126.3 (CH), 129.3 (2CH), 130.5 (2CH), 135.4 (C), 152.3 (C), 159.4 (C); 161.1 (C); 161.6 (C), 163.1 (C); MS (m/z, %): 501 (M+1, 100), 102 (10).

1-(4-Methoxybenzyl)-4-methyl-2-phenyl-6-(2-(4-phenylpiperazin-1-yl)ethyl)-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (14). This product was obtained using same procedure as for **13** (eluent: petroleum ether/ethyl acetate, 6:4). Yield 93% (yellow oil); IR (NaCl) cm^{-1}: 1686 (CO); ^{1}H NMR ($CDCl_3$): δ (ppm) 2.66–2.76 (m, 9H), 3.14–3.25 (m, 6H), 3.68 (s, 3H), 5.00 (s, 2H), 6.63 (AB, 4H, $J_{AB} = 8.8$ Hz, $\Delta\nu = 24.8$ Hz), 6.80–6.86 (m, 2H), 6.90 (d, 2H, $J = 7.8$ Hz), 7.21–7.33 (m, 3H), 7.51 (d, 4H, $J = 4.4$ Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 25.3 (CH_3), 28.5 (CH_2), 49.2 ($2CH_2$), 51.6 (CH_2), 52.9 ($2CH_2$), 55.2 (CH_3), 58.4 (CH_2), 108.3 (C), 113.5 (2CH), 116.1 (2CH), 119.6 (CH), 119.7 (CH), 124.2 (2CH), 125.7 (C), 126.5 (CH), 129.2 (2CH), 129.3 (2CH), 130.5 (2CH), 135.3 (C), 151.5 (2C), 159.5 (C), 161.1 (C), 161.5 (C), 163.4 (C); MS (m/z, %): 534 (M+1, 80), 102 (100).

6-(2-(Dibutylamino)ethyl)-4-methyl-2-phenyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (15). One hundred and sixty milligrams (0.32 mmol; 1 eq) of compound **13** were dissolved in 5 mL of TFA then the solution was heated at reflux during 5 h. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel (eluent: methanol/ethyl acetate, 1:9). Yield 96% (red solid); mp 114–116°C; IR (KBr) cm^{-1}: 1667 (CO), 3445 (NH); ^{1}H NMR ($CDCl_3$): δ (ppm) 0.85 (t, 6H, $J = 7.2$ Hz), 1.24–1.34 (m, 4H), 1.38–1.46 (m, 4H), 2.47 (s, 3H), 2.91–3.00 (m, 6H), 3.19 (t, 2H, $J = 6.8$ Hz), 6.61 (s, 1H), 7.16–7.23 (m, 1H), 7.41 (t, 2H, $J = 7.8$ Hz), 7.88 (d, 2H, $J = 7.8$ Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 14.2 ($2CH_3$), 20.5 ($2CH_2$), 25.2 (CH_3), 29.2 (CH_2), 29.9 ($2CH_2$), 53.6 ($2CH_2$), 54.2 (CH_2), 108.9 (C), 118.5 (CH), 119.7 (2CH), 125.3 (CH), 129.2 (2CH), 137.3 (C), 151.8 (C), 156.4 (C), 159.6 (C), 159.9 (C); MS (m/z, %): 381 (M+1, 100), 102 (40).

4-Methyl-2-phenyl-6-(2-(4-phenylpiperazin-1-yl)ethyl)-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (16). This product was obtained in 94% yield from the pyrazolopyridine **14** (130 mg, 0.24 mmol) following the procedure described earlier for compound **15** as a red solid; mp 116–118°C; IR (KBr) cm^{-1}: 1674 (CO), 3419 (NH); ^{1}H NMR ($CDCl_3$): δ (ppm) 2.35 (s, 3H), 3.03–3.18 (m, 6H), 3.32–3.45 (m, 6H), 6.70 (s, 1H), 6.92 (d, 3H, J = 8.2 Hz), 7.20–7.30 (m, 3H), 7.45 (t, 2H, J = 7.8 Hz), 7.87 (d, 2H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 23.0 (CH_3), 27.9 (CH_2), 48.5 ($2CH_2$), 52.6 ($2CH_2$), 57.5 (CH_2), 108.7 (C), 116.4 (C), 116.5 (2CH), 120.5 (CH), 120.6 (2CH), 125.8 (CH), 129.3 (4CH), 137.8 (C), 150.8 (C), 154.9 (C), 159.2 (C), 159.3 (C); MS (m/z, %): 414 (M+1, 100), 102 (30).

Butyl.2-(1-(4-methoybenzyl)-6-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl)acetate (17). This product was obtained in 98% yield from the pyrazolopyridine **4** (300 mg, 0.89 mmol) following the procedure described earlier for compound **9** as a maroon clearly oil; IR (NaCl) cm^{-1}: 1683, 1724 (CO); ^{1}H NMR ($CDCl_3$): δ (ppm) 0.93 (t, 3H, J = 7.2 Hz), 1.35–1.45 (m, 2H), 1.65–1.70 (m, 2H), 2.63 (s, 3H), 3.69 (s, 3H), 3.91 (s, 2H), 4.20 (t, 2H, J = 6.6 Hz), 4.99 (s, 2H), 6.63 (AB, 4H, J_{AB} = 8.8 Hz, $\Delta\nu$ = 26.9 Hz), 6.68 (s, 1H), 7.32 (t, 1H, J = 4.4 Hz), 7.50 (d, 4H, J = 4.4 Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 13.8 (CH_3), 17.3 (CH_3), 19.2 (CH_2), 30.8 (CH_2), 44.4 (CH_2), 51.6 (CH_2), 55.2 (CH_3), 65.2 (CH_2), 109.8 (C), 113.5 (2CH), 120.5 (CH), 124.1 (2CH), 125.5 (C), 126.5 (CH), 129.3 (2CH), 130.6 (2CH), 135.2 (C), 150.0 (C), 158.5 (C), 159.5 (C), 160.8 (C), 161.7 (C), 170.3 (C); MS (m/z, %): 460 (M+1, 100), 106 (26).

1-(4-Methoxybenzyl)-4-(2-hydroxyethyl)-6-methyl-2-phenyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (18). This product was obtained in 55% yield from the pyrazolopyridine **17** (440 mg, 0.87 mmol) following the procedure described earlier for compound **10** as a white foam; IR (KBr) cm^{-1}: 1660 (CO), 3412 (OH); ^{1}H NMR ($CDCl_3$): δ (ppm) 2.61 (s, 3H), 3.10 (t, 2H, J = 5.7 Hz), 3.69 (s, 3H), 4.12 (dd, 2H, J = 11.3 Hz, J' = 5.3 Hz), 4.96 (s, 2H), 6.66 (AB, 4H, J_{AB} = 8.8 Hz, $\Delta\nu$ = 31.4 Hz), 6.76 (s, 1H), 7.29–7.35 (m, 1H), 7.52 (d, 4H, J = 4.1 Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 17.3 (CH_3), 39.8 (CH_2), 51.6 (CH_2), 55.2 (CH_3), 61.7 (CH_2), 109.3 (C), 113.6 (2CH), 120.2 (CH), 124.1 (2CH), 125.5 (C), 126.6 (CH), 129.3 (2CH), 130.4 (2CH), 135.1 (C), 149.7 (C), 159.5 (C), 160.4 (C), 161.8 (C), 164.7 (C); MS (m/z, %): 390 (M+1, 17), 102 (100).

2-(1-(4-Methoxybenzyl)-6-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl)ethyl methanesulfonate (19). This product was obtained in 89% yield from the pyrazolopyridine **18** (500 mg, 1.29 mmol) and mesyl chloride (0.25 mL, 3.21mmol) following the procedure described earlier for compound **12** as a yellow oil; IR (NaCl) cm^{-1}: 1692 (CO); ^{1}H NMR ($CDCl_3$): δ (ppm) 2.61 (s, 3H), 2.94 (s, 3H), 3.29 (t, 2H, J = 6.6 Hz), 3.68 (s, 3H), 4.77 (t, 2H, J = 6.6 Hz), 4.99 (s, 2H), 6.64 (AB, 4H, J_{AB} = 8.8 Hz, $\Delta\nu$ = 23.9), 6.79 (s, 1H), 7.29–7.35 (m, 1H), 7.50 (d, 4H, J = 4.1 Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 17.2 (CH_3), 37.5 (CH_3), 37.7 (CH_2), 51.5 (CH_2), 55.2 (CH_3), 68.3 (CH_2), 109.7 (C), 113.6 (2CH), 120.4 (CH), 124.1 (2CH), 125.5 (C), 126.6 (CH), 129.3 (2CH), 130.4 (2CH), 135.1 (C), 149.9 (C), 159.5 (C), 160.7 (C), 160.8 (C), 161.6 (C); MS (m/z, %): 468 (M+1, 15), 97 (100).

1-(4-Methoxybenzyl)-4-(2-(dibutylamino)ethyl)-6-methyl-2-phenyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (20). This product was obtained in 92% yield from the pyrazolopyridine **19** (200 mg, 0.43 mmol) and *N*,*N*-dibutylamine 1 mL (0.53 mL, 5.95 mmol) following the procedure described earlier for compound **13** as a yellow oil; IR (NaCl) cm^{-1}: 1697 (CO); ^{1}H NMR ($CDCl_3$): δ (ppm) 0.92 (t, 6H, J = 7.2 Hz), 1.24–1.42 (m, 4H), 1.44–1.54 (m, 4H), 2.53 (t, 4H, J = 7.5 Hz), 2.59 (s, 3H), 2.97 (s, 4H), 3.67 (s, 3H), 4.99 (s, 2H), 6.63 (AB, 4H, J_{AB} = 8.8 Hz, $\Delta\nu$ = 32.9 Hz), 6.76 (s, 1H), 7.28–7.32 (m, 1H), 7.47–7.53 (m, 4H); ^{13}C NMR ($CDCl_3$): δ (ppm) 14.2 ($2CH_3$), 17.2 (CH_3), 20.8 ($2CH_2$), 29.5 ($2CH_2$), 35.9 (CH_2), 51.5 (CH_2), 53.8 ($2CH_2$), 53.9 (CH_2), 55.1 (CH_3), 108.8 (C), 113.4 (2CH), 120.2 (CH), 123.9 (2CH), 125.7 (C), 126.2 (CH), 129.2 (2CH), 130.5 (2CH), 135.3 (C), 149.0 (C), 159.4 (C), 161.1 (C), 162.0 (C), 165.7 (C); MS (m/z, %): 501 (M+1, 41), 119 (100).

1-(4-Methoxybenzyl)-6-methyl-2-phenyl-4-(2-(4-phenylpiperazin-1-yl)ethyl)-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (21). This product was obtained in 93% yield from the pyrazolopyridine **19** (150 mg, 0.24 mmol) and phenylpiperazine (0.53 mL, 4.50 mmol) following the procedure described earlier for compound **14** as a yellow oil; IR (NaCl) cm^{-1}: 1683 (CO); ^{1}H NMR ($CDCl_3$): δ (ppm) 2.62 (s, 3H), 2.77 (t, 4H, J = 5.0 Hz), 2.97 (dd, 2H, J = 8.1 Hz, J' = 6.3 Hz), 3.12 (dd, 2H, J = 8.1 Hz, J' = 6.3 Hz), 3.27 (t, 4H, J = 5.0 Hz), 3.68 (s, 3H), 5.02 (s, 2H), 6.65 (AB, 4H, J_{AB} = 8.8 Hz, $\Delta\nu$ = 32.0 Hz), 6.80 (s, 1H), 6.87 (t, 1H, J = 7.8 Hz), 6.96 (d, 2H, J = 7.8 Hz), 7.25–7.32 (m, 3H), 7.50–7.54 (m, 4H); ^{13}C NMR ($CDCl_3$): δ (ppm) 17.2 (CH_3), 36.1 (CH_2), 49.3 ($2CH_2$), 51.6 (CH_2), 53.3 ($2CH_2$), 55.2 (CH_3), 60.5 (CH_2), 109.1 (C), 113.5 (2CH), 116.2 (2CH), 119.8 (CH), 120.1 (CH), 124.0 (2CH), 125.7 (C), 126.3 (CH), 129.2 (4CH), 130.5 (2CH), 135.3 (C), 149.3 (C), 151.4 (C), 159.4 (C), 161.0 (C), 162.0 (C), 164.9 (C); MS (m/z, %): 534 (M+1, 42), 102 (100).

4-(2-(Dibutylamino)ethyl)-6-methyl-2-phenyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (22). This product was obtained in 94% yield from the pyrazolopyridine **20** (150 mg, 0.30 mmol) following the procedure described earlier for compound **15** as a red solid; mp 118–120°C; IR (KBr) cm^{-1}: 1697 (CO), 3440 (NH); ^{1}H NMR ($CDCl_3$): δ (ppm) 0.94 (t, 6H, J = 7.2 Hz), 1.30–1.40 (m, 4H), 1.61–1.68 (m, 4H), 2.66 (s, 3H), 3.03–3.08 (m, 6H), 3.40 (t, 2H, J = 6.6 Hz), 6.60 (s, 1H), 7.14–7.21 (m, 1H), 7.40 (t, 2H, J = 7.8 Hz), 7.91 (d, 2H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 13.7 ($2CH_3$), 17.3 (CH_3), 20.1 ($2CH_2$), 25.1 ($2CH_2$), 30.6 (CH_2), 50.5 (CH_2), 52.7 ($2CH_2$), 109.1 (C), 118.3 (CH), 119.7 (2CH), 125.4 (CH), 129.1 (2CH), 137.4 (C), 150.8 (C), 156.8 (C), 159.5 (C), 159.8 (C); MS (m/z, %): 381 (M+1, 100), 102 (44).

6-Methyl-2-phenyl-4-(2-(4-phenylpiperazin-1-yl)ethyl)-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (23). This product was obtained in 96% yield from the pyrazolopyridine **21** (120 mg, 0.23 mmol) following the procedure described earlier for compound **15** as a red solid; mp 122–124°C; IR (KBr) cm^{-1}: 1669 (CO), 3422 (NH); ^{1}H NMR ($CDCl_3$): δ (ppm) 2.63 (s, 3H), 3.10–3.42 (m, 12H), 6.59 (s, 1H), 6.86–6.98 (m, 3H), 7.17 (t, 1H, J = 7.6 Hz), 7.25–7.32 (m, 2H), 7.39 (t, 2H, J = 7.8 Hz), 7.90 (d, 2H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 17.1 (CH_3), 31.1 (CH_2), 47.0 ($2CH_2$), 52.0 ($2CH_2$), 55.3 (CH_2), 109.7 (C), 117.0 (2CH), 119.5 (2CH), 121.6 (CH), 125.4 (CH), 129.1 (2CH), 129.4 (2CH), 137.4 (C), 149.4 (C), 151.0 (C), 159.2 (C), 159.8 (C); MS (m/z, %): 414 (M+1, 100), 102 (32).

2-(6-Methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl) acetic acid (24). Three hundred milligrams (0.88 mmol; 1 eq) of pyrazolo[3,4-*b*]pyridine **4** were introduced under magnetic agitation into 15 mL of NaOH solution 10%. The solution was heated at reflux during 90 min. After cooling, the solution was neutralized until pH = 2 with concentrated HCl. The precipitate thus formed was filtered and washed with water and then with diethyl ether (no purification was necessary). Yield 98% (yellow solid); mp 122–124°C; IR (KBr) cm^{-1}: 1706 (CO), 3070 (OH); ^1H NMR (CD_3OD): δ (ppm) 2.73 (s, 3H), 3.85 (s, 2H), 6.83 (s, 1H), 7.29 (m, 1H), 7.49 (t, 2H, $J = 7.9$ Hz), 7.91 (d, 2H, $J = 7.9$ Hz); ^{13}C NMR (CD_3OD): δ (ppm) 17.2 (CH_3), 42.3 (CH_2), 111.9 (C), 119.8 (2CH), 122.6 (CH), 125.2 (CH), 129.9 (2CH), 140.5 (C), 151.9 (C), 155.5 (C), 157.2 (C), 160.5 (C), 178.0 (C); MS (m/z, %): 284 (M+1, 100), 181 (65).

2-(4-Methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl)-acetic acid (25). Three hundred milligrams (0.88 mmol; 1 eq) of pyrazolo[3,4-*b*]pyridine **5** were introduced under magnetic agitation into 15 mL of NaOH solution 10%. The solution was heated at reflux during 90 min. After cooling, the solution was neutralized until pH = 2 with concentrated HCl. The precipitate thus formed was filtered and washed with water and then with diethyl ether (no purification was necessary). Yield 97% (yellow solid); mp 172–174°C; IR (KBr) cm^{-1}: 1700 (CO), 3061 (OH); ^1H NMR (CD_3OD): δ (ppm) 2.50 (s, 3H), 4.04 (s, 2H), 6.93 (s, 1H), 7.26 (m, 1H), 7.46 (t, 2H, $J = 7.9$ Hz), 7.85 (d, 2H, $J = 7.9$ Hz); ^{13}C NMR (CD_3OD): δ (ppm) 15.7 (CH_3), 48.4 (CH_2), 111.3 (C), 120.1 (2CH), 122.5 (CH), 126.2 (CH), 130.8 (2CH), 141.2 (C), 151.5 (C), 155.3 (C), 157.1 (C), 160.9 (C), 178.3 (C); MS (m/z, %): 284 (M+1, 53), 181 (100).

***N*,*N*-Dibutyl-2-(6-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl)acetamide (26).** One hundred and nine milligrams (0.53 mmol; 1.5 eq) of DCC were put in 10 mL of THF then 100 mg (0.35 mmol; 1 eq) of acid **24** were added. After stirring at room temperature for 20 min, 65 µL (0.39 mmol; 1.1 eq) of *N*,*N*-dibutylamine in 2 ml of THF were cast. The mixture was stirred for 7 h at room temperature. The solution was hydrolyzed with a saturated solution of NH_4Cl and extracted with AcOEt. The organic phases were dried over $MgSO_4$ and evaporated in vacuo. The crude reaction was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 5:5). Yield 40% (yellow clearly solid); mp 134–136°C; IR (KBr) cm^{-1}: 1591, 1637 (CO), 3414 (NH); ^1H NMR ($CDCl_3$): δ (ppm) 0.87–0.94 (m, 6H), 1.25–1.32 (m, 4H), 1.43–1.49 (m, 4H), 2.69 (s, 3H), 3.16 (t, 2H, $J = 7.6$ Hz), 3.29 (t, 2H, $J = 7.6$ Hz), 3.70 (s, 2H), 6.67 (s, 1H), 7.18 (t, 1H, $J = 7.9$ Hz), 7.41 (t, 2H, $J = 7.9$ Hz), 7.93 (d, 2H, $J = 7.9$ Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 13.6 ($2CH_3$), 17.2 (CH_3), 19.9 (CH_2), 20.0 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 41.9 (CH_2), 45.9 (CH_2), 47.9 (CH_2), 109.6 (C), 118.6 (CH), 118.7 (2CH), 125.1 (CH), 129.0 (2CH), 137.6 (C), 150.8 (C), 156.2 (C), 157.7 (C), 159.9 (C), 168.6 (C); MS (m/z, %): 395 (M+1, 26), 119 (100).

***N*,*N*-Dibutyl-2-(4-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl)acetamide (27).** This product was obtained in 44% yield from acid **25** (100 mg, 0.35 mmol) and *N*,*N*-dibutylamine (65 µL, 0.39 mmol) following the procedure described earlier for compound **29** as a orange solid; mp 128–130°C; IR (KBr) cm^{-1}: 1612, 1683 (CO), 3424 (NH); ^1H NMR ($CDCl_3$): δ (ppm) 0.82–0.91 (m, 6H), 1.21–1.29 (m, 4H), 1.40–1.48 (m, 4H), 2.36 (s, 3H), 3.04 (t, 2H, $J = 7.6$ Hz), 3.23 (t, 2H, $J = 7.6$ Hz), 3.77 (s, 2H), 6.69 (s, 1H), 7.21 (t, 1H, $J = 7.7$ Hz), 7.41 (t, 2H, $J = 7.7$ Hz), 7.89 (d, 2H, $J = 7.7$ Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 13.9 ($2CH_3$), 20.0 (CH_2), 20.1 (CH_2), 23.2 (CH_3), 29.7 (CH_2), 29.8 (CH_2), 42.1 (CH_2), 46.2 (CH_2), 48.0 (CH_2), 109.1 (C), 118.1 (CH), 119.0 (2CH), 125.4 (CH), 129.1 (2CH), 137.5 (C), 148.8 (C), 155.6 (C), 158.7 (C), 159.8 (C), 168.7 (C); MS (m/z, %): 395 (M+1, 44), 119 (100).

6-Methyl-4-(2-oxo-2-(4-phenylpiperazin-1-yl)ethyl)-2-phenyl-1,2-dihydropyrazolo[3,4-*b*]pyridine-3-one (28). This product was obtained in 56% yield from acid **24** (100 mg, 0.35 mmol) and phenylpiperazine (46 µL, 0.39 mmol) following the procedure described earlier for compound **26** as a yellow clearly solid; mp 142–144°C; IR (KBr) cm^{-1}: 1591, 1651 (CO), 3440 (NH); ^1H NMR ($CDCl_3$): δ (ppm) 2.69 (s, 3H), 3.03–3.12 (m, 4H), 3.53 (t, 2H, $J = 4.9$ Hz), 3.69–3.74 (m, 4H), 6.78 (s, 1H), 6.86–6.93 (m, 3H), 7.19–7.30 (m, 3H), 7.41 (t, 2H, $J = 8.0$ Hz), 7.90 (d, 2H, $J = 8.0$ Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 17.4 (CH_3), 41.9 (CH_2), 42.6 (CH_2), 45.9 (CH_2), 49.2 (CH_2), 49.6 (CH_2), 109.5 (C), 116.7 (2CH), 119.4 (2CH), 119.7(CH), 120.7 (CH), 125.3 (CH), 129.2 (2CH), 129.3 (2CH), 137.5 (C), 150.7 (C), 150.8 (C), 157.4 (C), 158.4 (C), 160.0 (C), 167.8 (C); MS (m/z, %): 428 (M+1, 60), 119 (100).

4-Methyl-6-(2-oxo-2-(4-phenylpiperazin-1-yl)ethyl)-2-phenyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (29). This product was obtained in 52% yield from acid **25** (130 mg, 0.46 mmol) and phenylpiperazine (60 µL, 0.51 mmol) following the procedure described earlier for compound **26** as a orange solid; mp 136–138°C; IR (KBr) cm^{-1}: 1618, 1690 (CO), 3454 (NH); ^1H NMR ($CDCl_3$): δ (ppm) 2.35 (s, 3H), 3.01–3.11 (m, 4H), 3.51 (t, 2H, $J = 4.9$ Hz), 3.64–3.70 (m, 2H), 4.19 (s, 2H), 6.75 (s, 1H), 6.84–6.92 (m, 3H), 7.18–7.28 (m, 3H), 7.40 (t, 2H, $J = 8.2$ Hz), 7.88 (d, 2H, $J = 8.2$ Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 19.4 (CH_3), 40.7 (CH_2), 43.6 (CH_2), 46.0 (CH_2), 49.2 (CH_2), 49.7 (CH_2), 110.5 (C), 115.9 (2CH), 118.8 (2CH), 119.0 (CH), 120.1 (CH), 125.1 (CH), 129.2 (2CH), 129.5 (2CH), 137.7 (C), 149.4 (C), 150.1 (C), 156.8 (C), 159.1 (C), 160.1 (C), 168.8 (C); MS (m/z, %): 428 (M+1, 65), 119 (100).

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Regioselective Synthesis of 2-Methyl-2,5,6,11,12,13-hexahydro 4H indazolo[5,4-a]pyrrolo[3,4-c]carbazole-4-ones

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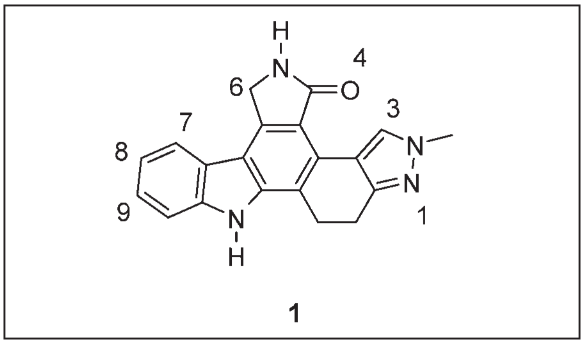

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2-Methyl-2,5,6,11,12,13-hexahydro 4H indazolo[5,4-a]pyrrolo[3,4-c]carbazole-4-one was synthesized utilizing a regioselective Diels-Alder reaction with 5-(1H-indol-2-yl)-2-methyl-6,7-dihydro-2H-indazole and ethyl *cis*-β-cyanoacrylate. Acetic acid and $YtBr_3$ were the best solvent and catalyst for the regioselective Diels-Alder reaction. The chemistry was used to synthesize novel 8-pyrimidinyloxy-2,5,6,11,12,13-hexahydro 4H indazolo[5,4-a]pyrrolo[3,4-c]carbazole-4-ones that were screened and found to be potent inhibitors of DLK.

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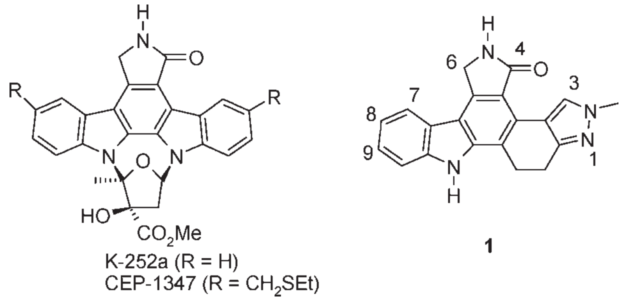
INTRODUCTION

Indolocarbazole alkaloids have emerged as an attractive scaffold in the search for kinase inhibitors. Minor structural variations can dramatically change their biological profiles [1]. CEP-1347 is a semi-synthetic derivative of the indolocarbazole K-252a [1], and a potent MLK/DLK inhibitor with a broad neuroprotective profile (Figure 1) [1]. Recently, we reported a series dihydronaphthyl[2,1-a]pyrrolo[3,4-c]carbazoles (DHN) as selective MLK inhibitors [2]. As part of the continued chemistry effort to design inhibitors with potent DLK activity, we required an approach to synthesize hexahydroindazolo[5,4-a]pyrrolo[3,4-c]carbazoles (DHI) and the corresponding 8-pyrimidinyloxy analogs. Our approach to the synthesis was envisioned via a Diels-Alder reaction using 5-(1H-indol-2-yl)-2-methyl-6,7-dihydro-2H-indazole and ethyl *cis*-β-cyanoacrylate. Previously, we reported the synthesis of indeno[2,1-a]pyrrolo[3,4-c]carbazole-5-one and-7-one via a Diels-Alder reaction with 2-indenylindole and ethyl *cis*-β-cyanoacrylate as the dienophile [3a]. There are few references concerning the synthesis of heterocyclic vinyl indoles as dienes due to their accessibility and stability [4]. Reported here is the synthesis of hexahydroindazolo[5,4-a]pyrrolo[3,4-c]carbazole-4-one core **1**. The synthesis and characterization of the 8-hydroxy, 8-pyrimidin-2-yloxy analogs, and their DLK activity are also described.

RESULTS AND DISCUSSION

2-Methyl-2,4,6,7-tetrahydroindazol-5-one **2** was prepared in three steps from commercially available 1,4-cyclohexanedione monoethylene acetal using our recently described regioselective procedure (Scheme 1) [5]. The assignment of the *N*-methyl regiochemistry was confirmed with X-ray crystallography. The 1-carboxy dilithio indole species was generated *in situ* by treatment of indole with *n*-butyllithium followed by carbon dioxide and subsequent 2-metalation with *tert*-butyllithium [6]. Addition of the ketone **2** to the *in situ* generated dilithio species provided the 2-substituted indole-alcohol **3** [5]. Elimination of the alcohol **3** using D,L-camphorsulfonic acid as catalyst in chloroform containing anhydrous magnesium sulfate produced 5-(1H-indol-2-yl)-2-methyl-6,7-dihydro-2H-indazole **3a** in low to moderate yield. The Diels-Alder reaction using dihydro-1H-indazole diene and ethyl *cis*-β-cyanoacrylate was surveyed with different catalysts and solvents. The use of benzene, toluene, xylene, and dichlorobenzene gave either low yields of the cycloadduct or no reaction at room



K-252a (R = H)
CEP-1347 (R = CH_2SEt)

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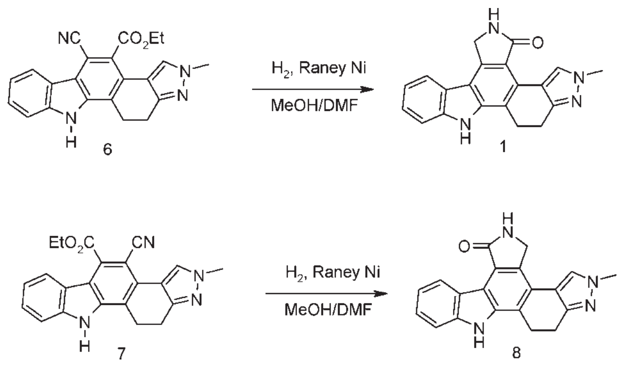
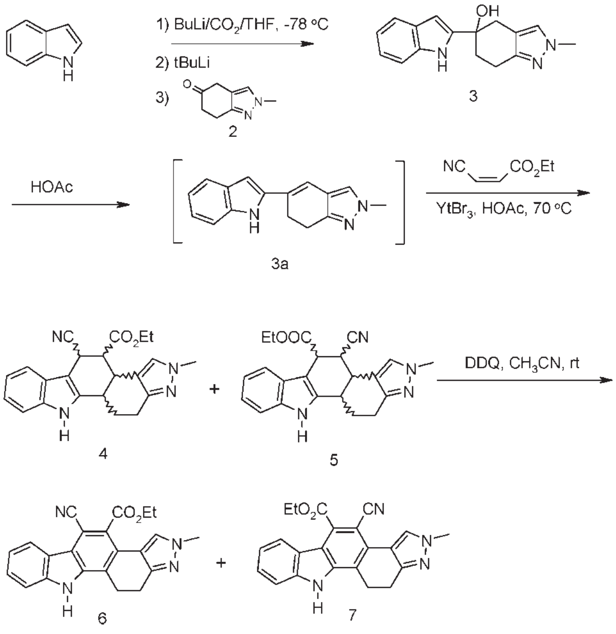
Figure 1. K-252a, CEP-1347, and hexahydroindazolo[5,4-a]pyrrolo[3,4-c]carbazole-4-one core **1**.

Scheme 2



temperature or under refluxing conditions. After screening a number of solvents, we found that the favored solvent was acetic acid. We also found that the problematic diene **3a** from dihydro-1H-indazo-5-ol **3** elimination could be generated *in situ* with HOAc as solvent. Lewis acid catalysts ($MgBr_2$, $YtBr_3$, and $ZnCl_2$) all improved the regioselectivity favoring the 4-CN isomer. The best conditions were using 0.1 mol % $YtBr_3$ in acetic acid at 70°C to give about 55% yield as 3:1 mixtures of the 4-CN-tetrahydrocarbazole isomer (**4**) and 5-CN-tetrahydrocarbazole isomer (**5**). The mixtures of isomers **4** and **5** were dehydrogenated using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in acetonitrile at room temperature or in methanol at 50°C to give a mixture of carbazoles **6** and **7**. Fractional crystallization isolated **6** in 39% yield for the two steps in >95% purity. Lactam **1** was produced by reductive cyclization of the cyano-ester **6** (RaNi, H_2, DMF/MeOH) in good yield (85%). The minor isomer the 6-lactam isomer **8** was formed by reductive cyclization of cyano-ester **7** (Scheme 2).

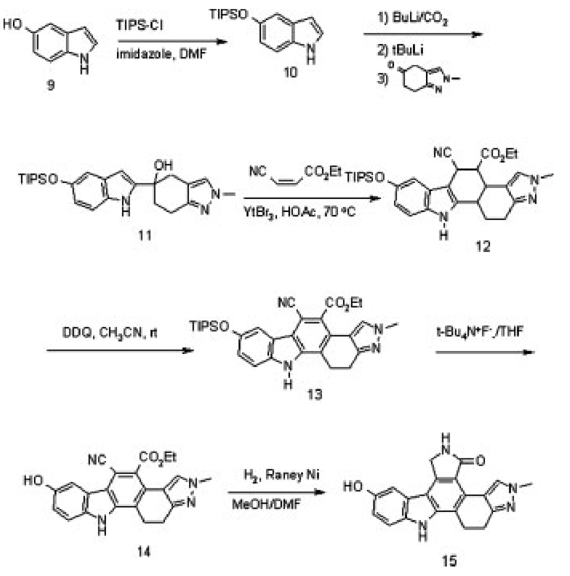
Scheme 1



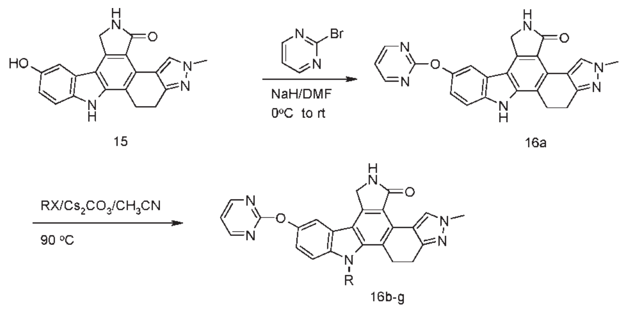
Several differences were observed in the proton ^1H NMR spectral data of lactams **1** and **8**. The regioisomers could be distinguished from ^1H NMR chemical shifts of the C-3 and C-7 protons. The C-7 aryl proton lactam **1** appeared at δ 7.90 and for lactam **8** appeared at δ 9.00 due to the deshielding effect of the lactam carbonyl. The chemical shifts of H-3 on **1** and **8** are found at δ 8.90 ppm and δ 8.00 ppm, respectively. The regioselectivity of the Diels-Alder reaction based on Frontier Molecular Orbital theory should favor of the formation of lactam **1** [3a]. The NMR assignment is in accord with our previously described structure assignment of indeno[2,1-a]pyrrolo[3,4-c]carbazoles, which was confirmed with X-ray crystallography [3a].

The synthesis of the 8-hydroxy analog is shown in Scheme 3. The dihydro-1H-indazo-5-ol **11** was prepared from TIPS-protected hydroxyindole **10** using the same

Scheme 3



Scheme 4



procedure to synthesize **3**. Diels-Alder reaction of **11** and ethyl *cis*-β-cyanoacrylate with 0.1 mol % of $YtBr_3$ in acetic acid at 70°C gave predominately the 4-CN-tetrahydrocarbazole isomer **12** as the major product. The high regioselectivity may be controlled by the steric effect of the triisopropylsilyloxy. Tetrahydrocarbazole **12** was dehydrogenated using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in acetonitrile at 60°C to give the aromatized product **13**. Deprotection of the TIPS group with tetrabutylammonium fluoride, followed by reductive cyclization of **14** afforded the 8-hydroxy lactam **15**. Lactam **15** could be easily assigned from the ^1H NMR chemical shifts of the C-3 (8.90 ppm), C-6 (4.75 ppm), and C-7 (7.20 ppm) protons, consistent with the structure of indeno[2,1-a]pyrrolo[3,4-c]carbazoles [3a].

8-Hydroxy-2,5,6,11,12,13-hexahydroindazolo[5,4-a] pyrrolo[3,4-c]carbazoles **15** was used as an intermediate to produce 8-pyrimidyloxydihydroindazoles **16a**. The reaction of **15** with 2-bromopyrimidine in the presence of sodium hydride in DMF gave **16a**. N11 alkylation of **16a** with various alkyl halides and Cs_2CO_3 as the base in CH_3CN resulted in N-substituted analogs **16b–g** (Scheme 4).

The analogs **1**, **15**, and **16a–g** were screened for DLK inhibitory activity [7]. The 4-oxo-lactam **1** displayed an IC_{50} value of 156 n*M*, whereas the 8-OH **15** was two-fold more potent. The 8-pyrimidin-2-oxy analog **16a** improved DLK potency greater than 30-fold compared with **15**. The N-11 ethyl **16c** and iPr **16d** were optimum with potent IC_{50} values of 1 and 2 n*M*. DLK activities decreased further with increasing alkyl size (Table 1).

In summary, we have developed the regioselective synthesis of 2,5,6,11,12,13-hexahydroindazolo[5,4-a] pyrrolo[3,4-c]carbazole-4-one utilizing a Diels-Alder reaction with dihydroindazoles and ethyl *cis*-β-cyanoacrylate. The acetic acid/$YtBr_3$ system was found to be superior in the Diels-Alder reaction to all other conditions evaluated. The 8-hydroxydihydroindazole provided a versatile intermediate to further functionalize and explore new kinase inhibitors. Further SAR evaluation and lead optimization on the scaffold leading to the progression of a clinical candidate compound will be disclosed in due course.

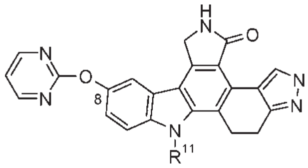
EXPERIMENTAL

All reagents were purchased from commercial sources and used as received. The NMR spectra were recorded at 400 MHz instrument in the solvent indicated with tetramethylsilane as an internal standard. Column chromatography was performed on silica gel 60 (230–400 mesh).

5-(1H-Indol-2-yl)-2-methyl-6,7-dihydro-1H-indazo-5-ol (3). A solution of indole (77 g, 0.66 mol) was dissolved in 3 L of anhydrous THF at −78°C under argon as *n*-butyllithium (330 mL, 0.83 mol, 2.5*M* solution in hexane) was added dropwise over 20 min. After 30 min stirring at −78°C, carbon dioxide was bubbled into the solution for 15 min. The solvent was removed under vacuum at 10–15°C to about 500 mL in volume. The reaction was diluted with 3 L of dry THF and recooled to −78°C and *tert*-butyllithium (570 mL, 0.86 mol, 1.5*M* solution in pentane) was slowly added. After 1 h at −78°C, the α-ketone **2** (100 g, 0.67 mol) in 1 L of anhydrous THF was added to the reaction dropwise over 40 min and stirred for 2 h. The reaction was quenched with brine and extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The brown solid was then triturated with cold methanol to form a white solid. The white solid was dissolved in 1 L of hot THF and the insoluble material was removed by filtration. The filtrate was concentrated and dried to give 102 g (58%) of **3**, mp 200–201°C; ^1H NMR (DMSO-d_6): δ 2.13 (m, 2H), 2.40 (m, 1H), 2.75 (m, 1H), 2.83 (d, 1H), 3.04 (d, 1H), 3.73 (s, 3H), 5.25 (s, 1H), 6.18 (s, 1H), 6.91 (t, 1H), 7.00 (t, 1H), 7.32 (d, 1H), 7.36 (s,1H), 7.41 (d, 1H), 10.96 (s,1H); ms: *m*/*z* = 268 (M +1).

Table 1

DLK activity of DHI analogs



Compound	R^{11}	DLK (IC_{50} n*M*)[a]
1[b]	H	118
15[c]	H	71
16a	H	2
16b	Me	5
16c	Et	2
16d	i-Pr	1
16e	*n*-Bu	7
16f	cyclopentyl	4.5
16g	cyclopropylmethyl	5
	CEP-1347	104

[a] IC_{50} values reported as the average of at least two separated determinations.

[b] R_8 = H.

[c] R_8 = OH.

5-Cyano-4-ethoxycarbonyl-2,10,11,12-tetrahydro-2-methyl-indazolo[5,4-a]carbazole (6). A mixture of **3** (16.0 g, 60.0 mmol), ethyl *cis*-β-cyanoacrylate (50.0 mL, 600 mmol), and $YbBr_3$ (1.66 g, 4.0 mmol) in 70 mL of acetic acid was stirred at 70°C for 40 h. HPLC indicated the completion of the reaction. The mixture was allowed to cool at room temperature and the solvent was evaporated. The thick oil (~100 mL) was triturated with 400 mL of ether overnight and the resulting solid was filtered, washed with water, ether, and dried to give 10.0 g of product. The trituration with ether was repeated to afford mixture of **4** and **5** (8.77 g) with HPLC ratios, 69%:25%.

The mixture of **4** and **5** (8.65 g, 23.1 mmol) and 2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone (10.5 g, 46.2 mmol) in 450 mL of acetonitrile was stirred at room temperature for 16 h. The resulting solid was filtered, and washed with cold MeOH to give tan solid (11.2 g) with HPLC ratio of two isomers, 77%:22% and with other impurities. Fractional crystallization with hot MeOH twice gave pure isomer **6** (6.6 g, 95.5% HPLC purity), mp: >250°C (dec.); ^{1}H NMR (DMSO-d_6): δ 1.41 (t,3H), 2.85 (t, 2H), 3.25 (t, 2H), 3.92 (s, 3H), 4.52 (q, 2H), 7.25 (t, 1H), 7.50 (t, 1H), 7.60 (m, 2H), 8.35 (d, 1H), 11.90 (s, 1H); ms: m/z = 343 (M +1).

4-Cyano-5-ethoxycarbonyl-2,10,11,12-tetrahydro-2-methyl-indazolo[5,4-a]carbazole (7). The mother liquid of **6** from fractional crystallization was combined and some solid appeared after a week at room temperature to give isomer **7**, mp: >250°C (dec.);^{1}H NMR (DMSO-d_6): δ 1.43 (t, 3H), 2.95 (t, 2H), 3.35 (t, 2H), 3.96 (s, 3H), 4.60 (q, 2H), 7.20 (t, 1H), 7.51 (t, 1H), 7.65 (m, 2H), 7.90 (d, 1H), 8.40 (s, 1H), 12.01 (s, 1H); ms: m/z = 343 (M +1).

2-Methyl-2,5,6,11,12,13-hexahydroindazolo-[5,4-a]pyrrolo [3,4-c]carbazole-4-one (1). A mixture of **6** (6.6 g, 17.83 mmol) and Raney Nickel catalyst (ca. 20 g) in DMF-methanol (150 mL:15 mL) was hydrogenated on a Parr Apparatus, until HPLC analysis indicated completion of the reaction. The solution was filtered through celite under N_2, washed with hot DMF, and the solvent was concentrated. The solid was recrystallized and triturated with methanol to give 3.72 g (65%) of **1** as colorless crystals with >97% purity by HPLC, mp: 250°C (dec.); ^{1}H NMR (DMSO-d_6): δ 2.80 (t, 2H), 3.20 (t, 2H), 3.80 (s, 3H), 4.75 (s, 2H), 7.20 (t, 1H), 7.90 (t, 1H), 7.51 (d, 1H), 7.91 (d,1H), 8.30 (s, 1H), 8.90 (s, 1H), 11.50 (s, 1H); ms: m/z = 329 (M +1). Anal. Calcd. For $C_{20}H_{16}N_4O\cdot1.0H_2O$: C, 69.35; H, 5.23; N, 16.17. Found: C, 69.85; H, 4.88; N, 16.28.

2-Methyl-2,5,6,11,12,13-dihydroindazolo-[5,4-a]pyrrolo [3,4-c]carbazole-6-one (8). A mixture of **7** (500 mg, 1.34 mmol, contains ~5% of **6**) and Raney Nickel catalyst (ca. 1 g) in DMF-methanol (30 mL:3 mL) was hydrogenated on a Parr Apparatus, until HPLC analysis indicated completion of the reaction. The solution was filtered through celite under N_2, washed with hot DMF, and the solvent was concentrated. The solid was recrystallized and triturated with methanol to give 110 mg (25%) of **8** as colorless crystals with ~9% of isomer **1**, mp 310–312°C; ^{1}H NMR (DMSO-d_6): δ 2.90 (t, 2H), 3.25 (t, 2H), 3.85 (s, 3H), 4.50 (s, 2H), 7.10 (t, 1H), 7.40 (t, 1H), 8.00 (s, 1H), 8.65 (s, 1H), 9.05 (d, 1H), 11.35 (s, 1H); ms: m/z = 329 (M +1).

5-[[Tris(1-methylethyl)silyl]oxy]-1H-indole (10). A solution of 5-hydroxyindole (5.0 g, 40.3 mmol) in 40 mL of DMF under N_2 was stirred as triisopropyl silyl chloride (12.0 mL, 60.45 mmol) was added dropwise, followed by imidazole (10.3 g, 161.2 mmol). After stirring overnight at room temperature, the reaction mixture was poured into water:hexane (1:1) and stirred for 1 h. The organic layer was separated, washed with brine, and dried over $MgSO_4$. Compound **10** (4.51 g) was used directly in the next step without purification. ^{1}H NMR (DMSO-d_6): δ 1.01 (d, 18H), 1.25 (m, 3H), 6.27 (s, 1H), 6.60 (d, 1H), 6.90 (s, 1H), 7.25 (m, 2H), 10.89 (s, 1H).

2-Methyl-5-(5-tris(1-methylethyl)silyloxy-1H-indol-2-yl)-4, 5,6,7-tetrahydro-2H-indazol-5-ol (11). A solution of indole **10** (3.47 g, 12 mmol) in 25 mL of anhydrous THF at −78°C under argon as *n*-butyllithium (7.1 mL, 12.1 mmol, 2.5*M* solution in hexane) was added dropwise over 20 min. After 30 min stirring at −78°C, carbon dioxide was bubbled into the solution for 15 min. The solvent was removed under vacuum at 10–15°C to about 10 mL in volume. The reaction was diluted with 15 mL of dry THF and recooled to −78°C and *tert*-butyllithium (8 mL, 12 mmol, 1.5*M* solution in pentane) was slowly added. After 1 h at −78°C, the α-ketone **2** (1.8 g, 12 mmol) in 15 mL of anhydrous THF was added to the reaction dropwise over 10 min and stirred for 2 h. The reaction was quenched with brine and the solvent was evaporated. The residue was stirred in 8.0 mL of water and 12.0 mL of ether for 30 min. The resulting solid was filtered and dried to give 2.5 g (47%) of **11**: ^{1}H NMR (DMSO-d_6): δ 1.01 (d, 18H), 1.25 (m, 3H), 2.10 (m, 2H), 2.45 (m, 1H), 2. 65 (m, 1H), 2.90 (dd, 2H), 3.65 (s, 3H), 5.20 (s, 1H), 6.08 (s, 1H), 6.60 (d, 1H), 6.80 (s, 1H), 7.20 (d, 1H), 7.39 (s, 1H), 10.85 (s, 1H); ms: m/z = 440 (M +1).

5-Cyano-4-ethoxycarbonyl-2,10,11,12-tetrahydro-2-methyl-(7-tris(1-methylethyl)silyloxy)indazolo[5,4-a]carbazole (12). A mixture of **11** (3.11 g, 7.05 mmol) and *cis*-β-cyanoacrylate (8.85 g, 70 mmol) and $YbBr_3$ (0.61 g, 1.41 mmol) in 50 mL of acetic acid was stirred at 70°C for 48 h. HPLC indicated the completion of the reaction (one major peak and with small peaks). The mixture was allowed to cool at room temperature and the solvent was evaporated. The thick oil (~50 mL) was triturated with 50 mL of ether for overnight and the resulting solid was filtered, washed with water (3 × 20 mL), ether (20 mL), and dried to give 0.91 g of the product of two isomers **12** with HPLC ratios: 84%:14%. The crude product was triturated with ether to give the pure **12** as a single isomer. ^{1}H NMR (DMSO-d_6): δ 1.01 (d, 18H), 1.25 (m, 3H), 1.28 (q, 3H), 1.95 (m, 1H), 2.15 (m, 1H), 2.58 (m, 1H), 3.50 (m, 2H), 3.55 (S, 3H), 3.85 (m, 1H), 4.15 (m, 1H), 4.45 (t, 2H), 4.48 (d, 1H), 6.68 (d, 1H), 6.80 (s, 1H), 7.39 (m, 2H), 10.85 (s, 1H); ms: m/z = 543 (M +1).

5-Cyano-4-ethoxycarbonyl-2,10,11,12-tetrahydro-2-methyl-(7-tris(1-methylethyl)silyloxy) indazolo[5,4-a]carbazole (13). A mixture of **12** (1.86 g, 3.40 mmol) and 2, 3-dichloro-5,6-dicyano-1,4-benzoquinone (1.55 g, 6.80 mmol) in 60 mL of methanol was stirred at 50°C for 1 h. HPLC indicated the completion of the reaction. The reaction mixture was then cooled to 0°C, stirred for 30 min, and the resulting solid was filtered and washed with cold MeOH to give colorless crystals **13** (1.09 g, 59%) with >95% purity by HPLC. ^{1}H NMR (DMSO-d_6): δ 1.01 (d, 18H), 1.25 (q, 3H), 1.28 (m, 3H), 2.88 (m, 2H), 3.50 (m, 2H), 3.80 (S, 3H), 4.50 (t, 2H), 7.15 (d, 1H), 7.50 (d, 1H), 7.62 (s, 1H), 7.90 (s, 1H), 11.75 (s, 1H); ms: m/z = 539 (M +1).

5-Cyano-2-methyl-4-ethoxycarbonyl-7-hydroxy-2,10,11,12-tetrahydro-4H-indazol[5,4-a]carbazole (14). A solution of **13** (1.08 g, 2.0 mmol) in 10.0 mL of THF was stirred at 0°C as 1*M* of $n\mathrm{Bu}_4N^+F^-$ in THF (2.0 mL, 2.0 mmol) was added dropwise. After addition, the ice-bath was removed and the reaction was stirred at room temperature for 2 h. HPLC indicated the completion of the reaction. The solvent was evaporated, and the residue was stirred in 1 mL of EtOAc and 5 mL of hot water. The resulting solid was filtered, washed with more hot water, and dried under vacuum to give 0.55 g (71%) of colorless crystals **14**. ^{1}H NMR (DMSO-d_6): δ 1.40 (q, 3H), 2.88 (m, 2H), 3.50 (m, 2H), 3.90 (S, 3H), 4.50 (t, 2H), 7.05 (d, 1H), 7.90 (d, 1H), 7.62(s,1H), 7.75 (s, 1H), 9.30 (s,1H), 11.65 (s, 1H); ms: *m/z* = 387 (M +1).

2-Methyl-8-hydroxy-2,5,6,11,12,13-hexahydo-4H-indazolo[5,4-a]pyrrolo[3,4-c]carbazol-4-one (15). A mixture of **14** (0.52 g, 1.36 mmol) and excess Raney Nickel catalyst (ca. 1 g) in DMF-methanol (20 mL:2 mL) was hydrogenated on a Parr Apparatus, until HPLC analysis indicated completion of the reaction. The solution was filtered through celite under N_2, washed with hot DMF, and the solvent was concentrated. The solid was washed and triturated with ether to give 0.4 g (85%) of **15** as colorless crystals with >97% purity by HPLC. ^{1}H NMR (DMSO-d_6): δ 2.75 (m, 2H), 3.15 (m, 2H), 3.80 (S, 3H), 4.65 (s, 2H), 6.90 (d, 1H), 7.20 (s, 1H), 7.35 (d, 1H), 8.30 (s, 1H), 8.90 (s,1H), 9.00 (s, 1H), 11.20 (s, 1H); ms: *m/z* = 345 (M +1). Anal. Calcd. For $C_{20}H_{16}N_4O_2 \cdot 1.5\ H_2O$: C, 64.67; H, 5.15; N, 15.08. Found: C, 64.86; H, 4.80; N, 14.52.

2-Methyl-8-(pyrimidin-2-yloxy)-2,5,6,11,12,13-hexahydro-4H-indazolo[5,4-a]pyrrolo[3,4-c]carbazol-4-one (16a). A mixture of sodium hydride (48 mg, 1.2 mmol, 60% in mineral oil) in 8.0 mL of DMF was stirred at 0°C under N_2 as 15 (137.6 mg, 0.4 mmol) in 4.0 mL of DMF was added dropwise. After stirred at 0°C for 15 min, 2-bromopyrimidine (127.2 mg, 0.8 mmol) in 2.0 mL of DMF was added dropwise. The reaction was stirred at 60°C for 20 h and HPLC indicated the completion of the reaction. After the reaction was cooled to room temperature, the solvent was evaporated and the residue was purified by preparation TLC with 10% MeOH in CH_2Cl_2 to give **16a** (90 mg, 53%): ^{1}H NMR (DMSO-d_6): δ 2.75 (m, 2H), 3.15 (m, 2H), 3.80 (S, 3H), 4.75 (s, 2H), 7.20 (d, 1H), 7.60 (d, 1H), 7.75 (s, 1H), 8.15 (s, 1H), 8.30 (s, 2H), 8.51 (s, 1H), 8.88 (s, 1H), 11.55 (s, 1H); ms: *m/z* = 423 (M +1).

2,11-Dimethyl-8-(-pyrimidin-2-yloxy)-2,5,6,11,12,13-hexahydro-4H-indazolo[5,4-a]pyrrolo[3,4-c]carbazol-4-one (16b). A mixture of **16a** (22.2 mg, 9.05 mmol) and Cs_2CO_3 (81.0 mg, 0.5 mmol) in 5.0 mL of CH_3CN was stirred as CH_3I (32 μL, 0.5 mmol) was added dropwise. After 14 h stirring at 80°C, the reaction mixture was cooled to room temperature, filtered through celite, washed with dichloromethane, and concentrated. The crude was purified by preparative TLC with 10% MeOH in CH_2Cl_2 to give **16b** (6.0 mg, 26%): ^{1}H NMR (DMSO-d_6): δ 2.75 (m, 2H), 3.65 (m, 2H), 3.80 (S, 3H), 4.15 (s, 3H), 4.65 (s, 2H), 7.20 (m, 1H), 7.30 (m, 2H), 7.65 (m, 2H), 8.35 (s, 1H), 8.55 (d, 1H), 8.88 (d, 1H); ms: *m/z* = 459 (M +23).

16 c–g were synthesized were carried out with different alkyl halides. The representative procedure given above for **16b** was used. Compounds **16 c–g** are all colorless crystals with melting point >250°C.

2-Methyl-8-(-pyrimidin-2-yloxy)-11-ethyl-2,5,6,11,12,13-hexahydro-4H-indazolo[5,4-a]pyrrolo[3,4-c]carbazol-4-one (16c). ^{1}H NMR (DMSO-d_6): δ 1.47 (t, 3H), 2.88 (m, 2H), 3.50 (m, 2H), 3.87 (S, 3H), 4.65 (q, 2H), 4.74 (s, 2H), 7.27 (m, 1H), 7.33 (m, 1H), 7.72 (d, 1H), 7.75 (s, 1H), 8.40 (s, 1H), 8.64 (d, 2H), 8.85 (s, 1H); ms: *m/z* = 451(M +1).

2-Methyl-11-(1-methylethyl)-8-(pyrimidin-2-yloxy)-2,5,6,11,12,13-hexahydro-4H-indazolo[5,4-a]pyrrolo[3,4-c]carbazol-4-one (16d). ^{1}H NMR (DMSO-d_6): δ 1.64 (d, 6H), 2.88 (m, 2H), 3.43 (m, 2H), 3.87 (S, 3H), 4.72 (s, 2H), 5.29 (m, 1H), 7.23 (m, 2H), 7.72 (d, 1H), 7.84 (d, 1H), 8.41 (s, 1H), 8.65 (d, 2H), 8.78 (s, 1H); ms: *m/z* = 465 (M +1).

2-Methyl-11-butyl-8-(pyrimidin-2-yloxy)-2,5,6,11,12,13-hexahydro-4H-indazolo[5,4-a]pyrrolo[3,4-c]carbazol-4-one (16e). ^{1}H NMR (DMSO-d_6): δ 0.99 (t, 3H), 1.38 (m, 2H), 1.80 (m, 2H), 2.86 (m, 2H), 3.49 (m, 2H), 3.87 (S, 3H), 4.62 (t, 2H), 4.74 (s, 2H), 7.26 (m, 1H), 7.32 (d, 1H), 7.72 (d, 1H), 7.73 (s, 1H), 8.41 (s, 1H), 8.65 (d, 2H), 8.87 (s, 1H); ms: *m/z* = 479 (M +1).

2-Methyl-11-cyclopentyl-8-(pyrimidin-2-yloxy)-2,5,6,11,12,13-hexahydro-4H-indazolo[5,4-a]pyrrolo[3,4-c]carbazol-4-one (16f). ^{1}H NMR (DMSO-d_6): δ 1.76 (m, 2H), 1.90 (m, 2H), 2.25 (m, 4H), 2.86 (m, 2H), 3.49 (m, 2H), 3.87 (S, 3H), 4.74 (s, 2H), 4.80 (m, 1H), 7.26 (m, 1H), 7.32 (d, 1H), 7.72 (d, 1H), 7.73 (s, 1H), 8.20 (d, 1H), 8.41 (s, 1H), 8.55 (d, 2h), 8.87 (s, 1H); ms: *m/z* = 513 (M +23).

2-Methyl-11-cyclopropylmethyl-8-(pyrimidin-2-yloxy)-2,5,6,11,12,13-hexahydro-4H-indazolo[5,4-a]pyrrolo[3,4-c]carbazol-4-one (16g). ^{1}H NMR (DMSO-d_6): δ 0.50 (m, 2H), 0.98 (m, 2H), 1.76 (m, 1H), 2.86 (m, 2H), 3.44 (m, 2H), 3.87 (S, 3H), 4.74 (s, 2H), 4.80 (d, 2H), 7.26 (m, 2H), 7.72 (d, 1H), 7.73 (m, 2H), 8.41 (s, 1H), 8.65 (d, 2H), 8.87 (s, 1H); ms: *m/z* = 477 (M +1).

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Facile Synthesis of 10-*tert*-Butyl[1]benzoxepino[3,4-*b*][1,3]-dioxolo[4,5-*g*]quinolin-12(6*H*)-ones

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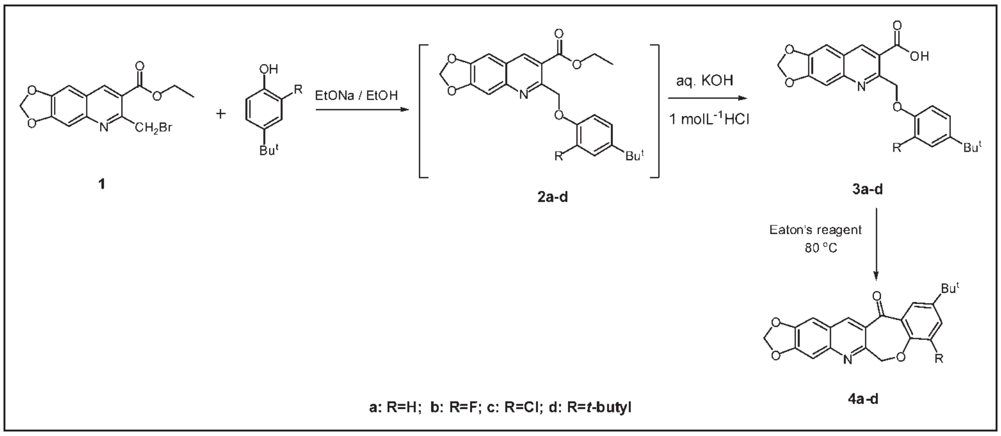

In this study a facile synthesis of novel 10-*tert*-butyl[1]benzoxepino[3,4-*b*][1,3]dioxolo[4, 5-*g*]quinolin-12(6*H*)-ones is described, featuring the one-pot synthesis of 6-[(*tert*-butylphenoxy)methyl][1,3]dioxolo[4,5-*g*]quinoline-7-carboxylic acids from ethyl 6-(bromomethyl)[1,3]dioxolo[4,5-*g*]quinoline-7-carboxylate and their intramolecular Friedel-Crafts acylation reaction by the use of Eaton's reagent (P_2O_5–CH_3 SO_3H) under mild conditions.

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INTRODUCTION

Quinoline-fused ring systems are a backbone of many natural products and pharmacologically significant compounds and display a broad range of biological activities [1–3]. Particularly, five-, six- and seven-membered heterocyclic compounds containing one or two heteroatoms fused to a quinoline ring are found in many natural products as well as in synthetic compounds, which are known to exhibit anticancer [4,5], antiallergenic [6], antibacterial [7], and antiviral properties [8]. The quinoline-fused compounds have been popular targets of synthesis, and a wide variety of protocols have been used. For instance, syntheses have included Friedländer condensation reactions [9], radical cyclization reactions [10], and intramolecular Friedel-Crafts acylation reactions [11,12]. The intramolecular Friedel-Crafts acylation of arylcarboxylic acids is an important route to construct fused ring compounds. Conventionally, intramolecular Friedel-Crafts acylation reaction can be achieved by treating aryl acids with a variety of condensing agents including liquid HF, H_2SO_4, $TiCl_4$, $AlCl_3$, and $AlCl_3$/NaCl [13]. However, using these reagents, not only does the harsh reaction conditions make synthesis and product isolation difficult but also a quantity of acidic waste is inevitably produced, which leads to pollution problems after the reaction. Hence, the development of new synthetic methods would be of considerable importance to the chemistry community.

On the other hand, the introduction of *tert*-butyl group to some compounds can enhance greatly their biological activity. Recently Huy et al. [14] reported that the placement of a metabolically stable *tert*-butyl group at C-2 position of a quinoline ring in primaquine results in a tremendous improvement in blood schizontocidal antimalarial activity (Fig. 1).

In light of these foundings and in view of structural diversity playing a prominent role in medicinal and combinatorial chemistry for a faster and efficient lead generation toward the new drug discovery [15], the synthesis of novel *tert*-butyl substituted quinoline-fused compounds would be much more attractive if a facile and mild broadly applicable synthetic approach could be used. Therefore, we reported herein the simple and effective synthesis of 10-*tert*-butyl[1]benzoxepino[3,4-*b*][1,3]dioxolo[4,5-*g*] quinolin-12(6*H*)-one derivatives by the intramolecular Friedel-Crafts acylation of the arylcarboxylic acids 6-[(*tert*-butyphenoxy)methyl][1,3]dioxolo-[4,5-*g*]quinoline-7-carboxylic acids using Eaton's reagent (P_2O_5–CH_3 SO_3H) as catalyst and solvent as shown in Scheme 1.

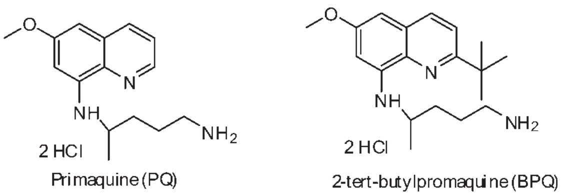


Figure 1. Structures of PQ and BPQ.

RESULT AND DISCUSSION

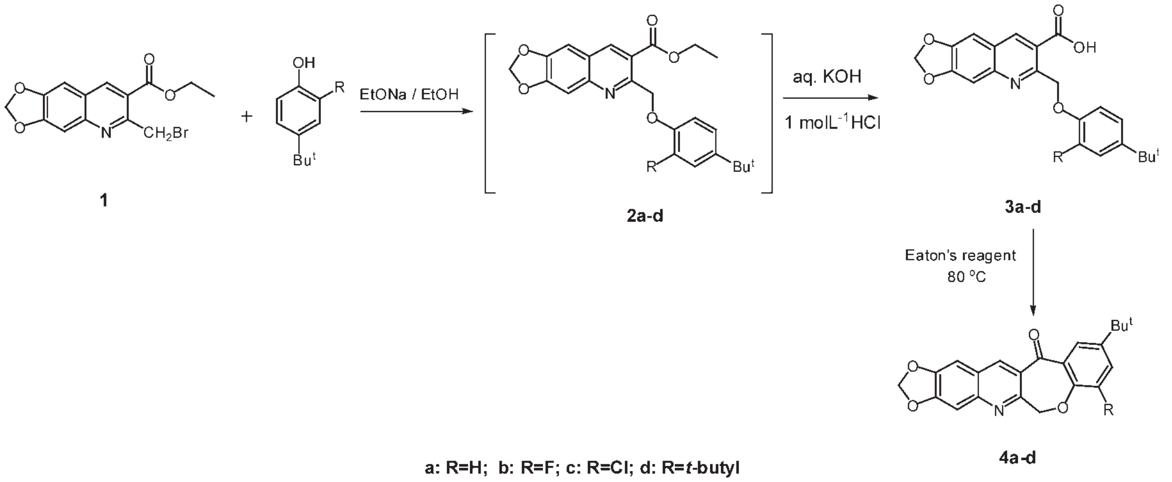
One-pot synthesis 6-[(*tert*-Butyphenoxy)methyl][1,3] dioxolo-[4,5-g]quinoline-7-carboxylic acids. The synthesis starts from readily available ethyl 6-(bromomethyl)[1,3]dioxolo[4,5-*g*]quinoline-7-carboxylate (**1**), which was prepared according to the literature method [11]. The ester ethers ethyl 6-[(*tert*-butylphenoxy)methyl][1,3]dioxolo[4,5-*g*]quinoline-7-carboxylates (**2a–d**) were formed by the Willamson reaction of starting compound **1** and *tert*-butyl substituted phenols. However, the resulting products were difficult to purify from the reaction mixture. Addition some water to the reaction mixture did not have the compounds **2a–d** precipitated out, but instead produced oils. We also tried to chromatograph the reaction mixture on a column to isolate the intermediates but in low yields. Therefore, we developed an efficient one-pot synthesis of the key intermediates 6-[(*tert*-butyphenoxy)methyl][1,3]dioxolo-[4,5-*g*]quinoline-7-carboxylic acids (**3a–d**), which involved the *in situ* formation of compounds **2a–d** followed by hydrolysis with aqueous ethanolic potassium hydroxide solution. Thus, the two reactions, Williamson reaction and hydrolysis reaction proceeded in one pot, avoiding the tedious isolation of **2a–d**. The value of the one-pot procedure is very obvious: high yields, simple manipulation, and easy purification.

The facile synthesis of the title compounds. Our initial efforts at cyclizing **3a** used polyphosphoric acid as catalyst and solvent. The cyclization reaction could be achieved at 150°C; however, only 37% yield of the cyclized product was isolated. The cyclized product in the obtained mixture was purified by recrystallization from ethanol and was identified as [1]benzoxepino[3,4-*b*][1,3]dioxolo[4,5-*g*]quinolin-12(6*H*)-one (**5**) by spectroscopic methods (Scheme 2). The IR spectrum of **5** exhibited an absence of carboxyl group, which appeared in the substrate **3a** at 3393 cm^{-1}, and the presence of one typical carbonyl absorption for cyclic ketone moiety at 1641 cm^{-1}. Its structure was unequivocal proven by the ^1H NMR spectrum. Particularly, characteristic was the absence of *tert*-butyl protons' resonance at the range of 1.3 to 1.4 ppm, and the presence of seven-proton multiplet in the aromatic region at 7.13 to 8.60 ppm, besides the signals for two methylene protons at 5.41 and 6.16 ppm, respectively. Moreover, the obtained elemental analysis values are also in agreement with theoretical data.

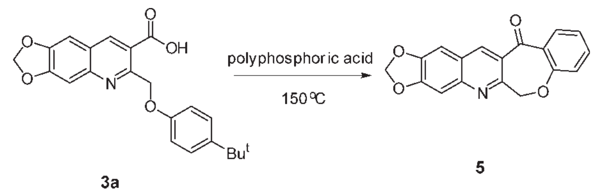
This process involves problem discussed below, which is accompanied by debutylation subsequent to the intramolecular Friedel-Crafts acylation reaction, and it is known that the debutylation reaction is usually carried out in a high-boiling solvent at a high temperature, and the *tert*-butyl substituent is easily removed from aromatic nuclei by Friedel-Crafts reaction using an acid catalyst [16–19]. Hence, we presumed that the high-reaction temperature might lead to the occurrence of debutylation reaction during the cyclization course.

A plausible intramolecular Friedel-Crafts acylation and debutylation mechanism is proposed as shown in Scheme 3. The substrate **3a** was treated with polyphosphoric acid to form the mixed phosphoric-carboxylic anhydride A [20], which further underwent the

Scheme 1



Scheme 2



intramolecular Friedel-Crafts acylation to afford cyclic ketone **4a.** Subsequently, nucleophilic attack of the resulting **4a** to H_3PO_4 under high temperature, followed by loss of isobutene, led to the formation of **5**. The mechanism is analogous to the de-*tert*-butylation of *p-tert*-butylcalix[n]arene in literature [21].

To verify the proposed mechanism, HPLC/MS analysis was selected as a simple and powerful tool, and the reaction was tested as a typical process. Thus, the reaction was monitored with HPLC/MS analysis as follows: portions of the reaction mixture were sampled and were worked up; the qualitative analysis was performed by HPLC/MS. The results revealed that compound **5** existed during the reaction process, and there were no compound **4a** observed during the course of the reaction according to mass spectroscopic detection.

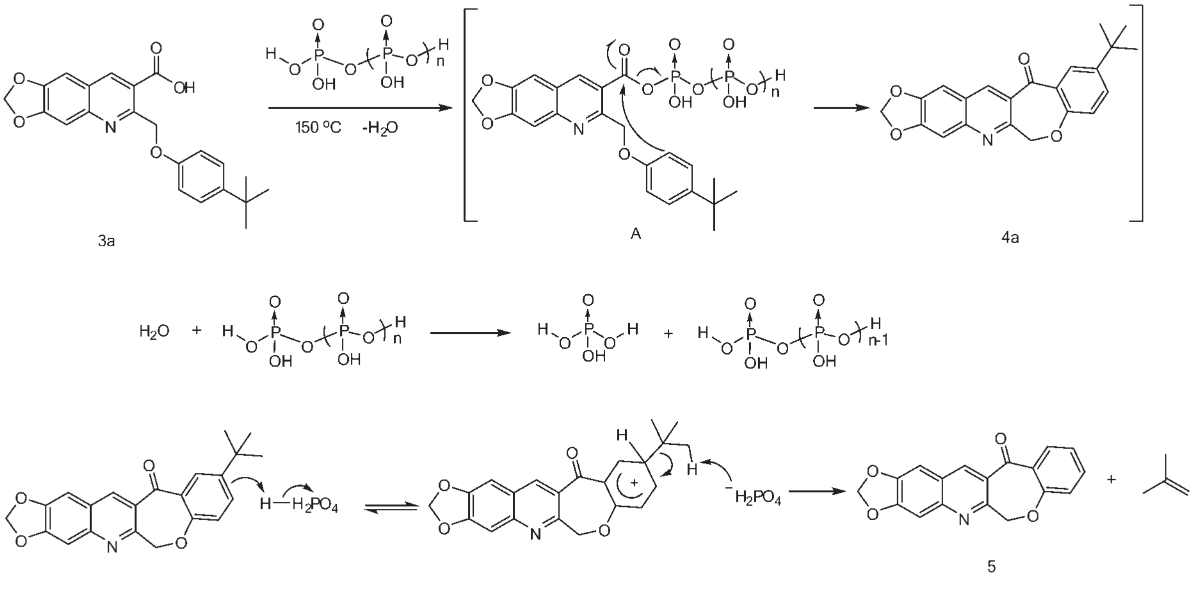
Recently, the inexpensive and commercially available Eaton's reagent, a mixture of P_2O_5 and $MeSO_3H$ [22], has been widely used for effecting intramolecular cyclizations under mild conditions. A number of interesting examples of intramolecular Friedel-Crafts acylation using Eaton's reagent have been published, including the syntheses of quinolone heterocycles [23], 4-hydroxycoumarins [24], and aromatic poly(ether ketone)s [25]. In connection with our studies, we envisioned that the reagent could also be applied to 6-[(*tert*-butylphenoxy)-methyl][1,3]dioxolo[4,5-*g*]quinoline-7-carboxylic acids, from which the desired quinoline-fused ring systems may be synthesized through intramolecular Friedel-Crafts acylation reaction. We were pleased to discover that simply dissolving **3a** in Eaton's reagent and heating to only 80°C resulted in conversion into **4a** in 65% yield within 3 hours. The ease of isolation of **4a** was notable: a simple quench into a basic solution precipitated the product in acceptable purity (94%). The role of P_2O_5 in the reagent mixture $P_2O_5/MeSO_3H$ is as a drying agent. Addition of P_2O_5 decreases the strength of the sulfonic acid. A small amount of water resulting from the cyclization reaction produced a decrease in acidity of $MeSO_3H$ but had little effect on the acid strength of $MeSO_3H$-P_2O_5 acid mixture. Phosphorus pentoxide is, thus, able to delay the deactivation by the water from the cyclization. In neat $MeSO_3H$ substrate **3a** does not give cyclized product after heating at 80°C over 10 hours.

Encouraged by the successful synthesis of compound **4a,** we tested this protocol for the intramolecular cyclization of other substrates **3b–d**. It was found that the method was effective, and all the *tert*-butyl substituted substrates were smoothly converted to the corresponding cyclized products without any evidence for the formation of de-*tert*-butyl products. Thus, the corresponding *tert*-butyl substituted cyclized products **4b–d** were afforded in 49%, 52%, and 58% yield, respectively.

EXPERIMENTAL

General. The melting points were determined by using WRS-1B melting points apparatus. The ^1H NMR was

Scheme 3



measured with a Varian Inova 400 NMR spectrometer at 400 MHz. The reported chemical shifts were against TMS. Elemental analysis was performed using an Elementar Vario EL-III element analyzer. HPLC/MS analysis was performed on a HP 1100 system HPLC/MS spectrometer.

General Procedure for the Preparation of 6-[(*tert*-Butyl phenoxy)methyl][1,3]dioxolo[4,5-*g*]quinoline-7-carboxylic acids (3a–d). To 0.046 g metal sodium (2 mmol) dissolved in 8 mL CH_3CH_2OH *tert*-butyl phenol (2 mmol) and 0.676 g ethyl 6-(bromomethyl)[1,3]dioxolo[4,5-*g*]quinoline-7-carboxylate (**1**) (2 mmol) were added. The mixture was refluxed for 2 hours. Then 60% (v/v) ethanolic potassium hydroxide solution 15 mL was added to the reaction mixture and continued to reflux for 2 hours, cooled, and acidified with 1 M HCl solution. The resulting crude product was recrystalized from 95% ethanol to afford compounds **3a–d**.

6-[(4-*tert*-Butylphenoxy)methyl][1,3]dioxolo[4,5-*g*]quinoline-7-carboxylic acid (3a). Yield 86%; mp 204 to 205°C. IR (KBr): 3393 (COOH), 3058, 2937, 2786, 1712 (C=O), 1610, 1502, 1426, 1245, 1047 (COC), 947 (OCH_2O). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.30$ (s, 9H, *t*-butyl), 5.51 (s, 2H, O-CH_2-Ar), 6.10 (s, 2H, OCH_2O), 6.76 to 6.82 (m, 2H, ArH), 6.91 (m, 2H, ArH), 7.38 to 7.41 (m, 2H, ArH), 8.44 (s, 1H, ArH). Anal. Calcd. For $C_{22}H_{21}NO_5$: C, 69.64; H, 5.58; N, 3.69 Found: C, 69.72; H, 5.63; N, 3.65%.

6-[(4-*tert*-Butyl-2-fluorophenoxy)methyl][1,3]dioxolo[4,5-*g*] quinoline-7-carboxylic acid (3b). Yield 79%, mp 185 to 187°C. IR (KBr): 3410 (COOH), 3064, 2930, 2853, 1698 (C=O), 1599, 1497, 1410, 1237, 1041 (COC), 948 (OCH_2O). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.36$ (s, 9H, *t*-butyl), 5.59 (s, 2H, O-CH_2-Ar), 6.21 (s, 2H, OCH_2O), 6.89 to 7.17 (m, 3H, ArH), 7.31 (s, 1H, ArH), 7.48 (s, 1H, ArH), 8.65 (s, 1H, ArH). Anal. Calcd. For $C_{22}H_{20}FNO_5$: C, 66.49; H 5.07; N 3.52 Found: C 66.53; H 5.12; N 3.59%.

6-[(4-*tert*-Butyl-2-chlorophenoxy)methyl][1,3]dioxolo[4,5-*g*] quinoline-7-carboxylic acid (3c). Yield 77%, mp 216 to 217°C. IR (KBr): 3421 (COOH), 3048, 2936, 2855, 1701 (C=O), 1579, 1514, 1428, 1240, 1035 (COC), 947 (OCH_2O). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.33$ s (9H, *t*-butyl), 5.58 s (2H, O-CH_2-Ar), 6.20 s (2H, OCH_2O), 7.12 to 7.18 m (2H, ArH), 7.32 to 7.35 m (1H, ArH), 7.41 to 7.55 m (2H, ArH), 8.54 s (1H, ArH). Anal. Calcd. For $C_{22}H_{20}ClNO_5$: C, 63.85; H, 4.87; N, 3.38 Found: C, 63.92; H, 4.85; N, 3.48%.

6-[(2,4-Di-*tert*-Butylphenoxy)methyl][1,3]dioxolo[4,5-*g*]quinoline-7-carboxylic acid (3d). Yield 68%, mp 178 to 180°C. IR spectrum (KBr), v, cm^{-1}: 3432 (COOH), 3044, 2939, 2851, 1707 (C=O), 1580, 1507, 1449, 1422, 1243, 1046 (COC), 950 (OCH_2O). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.31$ (s, 9H, *t*-butyl), 1.37 (s, 9H, *t*-butyl), 5.55 (s, 2H, O-CH_2-Ar), 6.19 (s, 2H, OCH_2O), 7.08 to 7.21 (m, 3H, ArH), 7.35 to 7.41 (m, 2H, ArH), 8.61 (s, 1H, ArH). Anal. Calcd. For $C_{26}H_{29}NO_5$: C, 71.70; H, 6.71; N, 3.22 Found: C, 71.82; H, 6.69; N, 3.28%.

Synthesis of [1]benzoxepino[3,4-b][1,3]dioxolo[4,5-*g*]quinolin-12(6*H*)-one (5). The 6-[(4-*tert*-butylphenoxy)methyl][1,3]-dioxolo[4,5-*g*]quinoline-7-carboxylic acid (**3a**) (0.38 g, 1 mmol) and polyphosphoric acid (12 g) were added to round flask (25 mL) and stirred at 150°C for 2.5 hours. Then, the reaction mixture was poured into icy water and neutralized with an icy saturated sodium carbonate solution. The crude products were obtained after filtration and washed with water. The pure product **5** was obtained by recrystalization from THF-H_2O. Yield 37%, mp 196 to 197°C. IR (KBr): 3019, 1641 (C=O), 1598, 1559, 1505, 1457, 1400, 1365, 1297,1222, 1168, 1109, 929. ^{1}H NMR (400 MHz, $CDCl_3$): 5.41 (s, 2H, Oxepan-H), 6.16 (s, 2H, OCH_2O), 7.13 to 7.20 (m, 2H, ArH), 7.26 (s, 1H, ArH), 7.40 (s, 1H, ArH), 7.51 to 7.54 (m, 2H, ArH), 8.29 to 8.31 (m, 1H, ArH), 8.60 (s, 1H, ArH). Anal. Calcd. For $C_{18}H_{11}$NO4: C, 70.82; H, 3.63; N, 4.59 Found: C, 70.63; H, 3.78; N, 4.57%.

General Procedure for the Preparation of Title Compounds (4a–d). 6-[(*tert*-Butylphenoxy)methyl][1,3]dioxolo[4,5-*g*]quinolin-7-carboxylic acids **(3a–d)** (1 mmol) and Eaton's reagent (8 mL) were added to round flask (25 mL) and stirred at 80°C for 3 hours. Then, the reaction mixture was poured slowly with stirring into an icy saturated sodium carbonate solution. The crude products were obtained after filtration and washed with water. The pure product **4a–d** was obtained by recrystalization from ethanol.

10-*tert*-Butyl[1]benzoxepino[3,4-b][1,3]dioxolo[4,5-*g*]quinolin-12(6*H*)-one (4a). Yield 65%, mp 201 to 203°C. IR (KBr): 3033, 2925, 2779, 1647 (C=O), 1604, 1586, 1457, 1400, 1249, 1029, 949 (OCH_2O). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.34$ (s, 9H, 3-*t*-butyl), 5.43 (s, 2H, Oxepan-H), 6.25 (s, 2H, OCH_2O), 7.24 to 7.27 (m, 1H, ArH), 7.47 (s, 1H, ArH), 7.61 (s, 1H, ArH), 7.83 (s, 1H, ArH), 8.12 to 8.14 (m, 1H, ArH), 8.74 (s, 1H, ArH). Anal. Calcd. For $C_{22}H_{19}NO_4$: C, 73.12; H, 5.30; N, 3.88 Found: C, 73.37; H, 5.18; N, 3.92%.

10-*tert*-Butyl-8-fluoro[1]benzoxepino[3,4-b][1,3]dioxolo[4,5-*g*]quinolin-12(6*H*)-one (4b). Yield 49%, mp 215 to 217°C. IR (KBr): 3031, 2927, 2791, 1637 (C=O), 1616, 1471, 1242, 1073, 1028 (COC), 951 (OCH_2O). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.39$ (s, 9H, *t*-butyl), 5.58 (s, 2H, Oxepan-H), 6.27 (s, 2H, OCH_2O), 7.29 to 7.31 (m, 1H, ArH), 7.52 (s, 1H, ArH), 7.85 (s, 1H, ArH), 8.13 to 8.16 (m, 1H, ArH), 8.78 (s, 1H, ArH). Anal. Calcd. For $C_{22}H_{18}FNO_4$: C, 69.65; H, 4.78; N, 3.69 Found: C, 69.89; H, 4.61; N, 3.70%.

10-*tert*-Butyl-8-chloro[1]benzoxepino[3,4-b][1,3]dioxolo[4,5-*g*]quinolin-12(6*H*)-one (4c). Yield 52%, mp 226 to 227°C. IR (KBr): 3011, 2920, 2815, 1647 (C=O), 1591, 1461, 1400, 1245, 1038 (COC), 948 (OCH_2O). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.32$ (s, 9H, *t*-butyl), 5.57 (s, 2H, Oxepan-H), 6.26 (s, 2H, OCH_2O), 7.19 to 7.23 (m, 1H, ArH), 7.47 (s, 1H, ArH), 7.81 to 7.84 (m, 1H, ArH), 8.11 to 8.13 (m, 1H, ArH), 8.66 (s, 1H, ArH). Anal. Calcd. For $C_{22}H_{18}ClNO_4$: C, 66.75; H, 4.85; N, 3.54 Found: C, 66.46; H, 4.91; N, 3.60%.

8,10-Di-*tert*-Butyl[1]benzoxepino[3,4-b][1,3]dioxolo[4,5-*g*] quinolin-12(6*H*)-one (4d). Yield 58%, mp 241 to 243°C. IR (KBr): 3015, 2923, 2810, 1636 (C=O), 1596, 1462, 1400, 1237, 1036 (COC), 949 (OCH_2O). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.35$ (s, 9H, *t*-butyl), 1.34 (s, 9H, *t*-butyl), 5.40 (s, 2H, Oxepan-H), 6.23 (s, 2H, OCH_2O), 7.07 to 7.10 (m, 1H, ArH), 7.43 (s, 1H, ArH), 8.01 to 8.03 (m, 1H, ArH), 8.12 (s, 1H, ArH), 8.67 (s, 1H, ArH). Anal. Calcd. For $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35 Found: C, 74.68; H, 6.59; N, 3.29%.

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A New Reaction of 1,2-Di- and 1,2,3-Trialkyldiaziridines: Ring Expansion under the Action of Diethyl Acetylenedicarboxylate in Ionic Liquids

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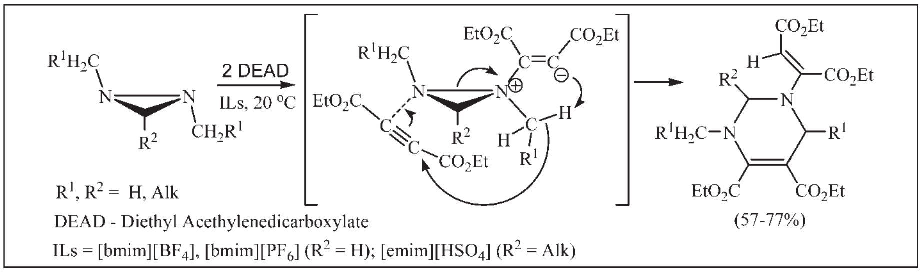

New reaction of diaziridine ring expansion resulting in diethyl 1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate derivatives was discovered under the action of diethyl acetylenedicarboxylate on 1,2-di- and 1,2,3-trialkyldiaziridines in ionic liquids.

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INTRODUCTION

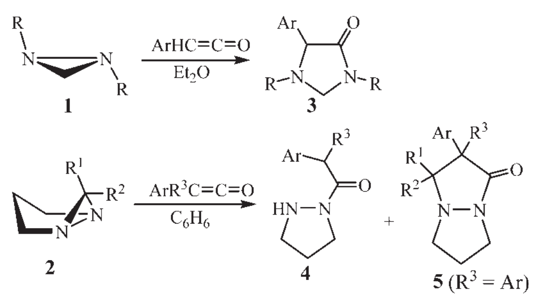
Over a few last years, new simple approaches to the construction of different nitrogen-containing heterocyclic systems have been developed in our laboratory. These are based on the strained diaziridine ring transformation in readily available [1,2] 1,2-dialkyldiaziridines **1** and 1,5-diazabicyclo[3.1.0]hexanes **2** under the action of electrophilic reagents, in particular, dipolarophiles. Herein, the diaziridine ring is capable of opening on the C—N or N—N bonds to generate dipolar intermediates prone to cycloaddition reactions (so-called ring expansion reactions) resulting in other heterocyclic structures [3–10].

Arylketenes [3–6], aroyliso- and aroylisothiocyanates [7,8], carbon disulfide [9,10], and activated nitriles [10,11] were investigated as dipolarophiles. Thus, the reaction of arylketenes with 1,2-dialkyldiaziridines **1** resulted in 5-aryl-1,3-dialkylimidazolidin-4-ones **3** and with 1,5-diazabicyclo[3.1.0]hexanes **2**—in heterocyclic compounds of two kinds—1-(arylacetyl)pyrazolidines **4** and 1,5-diazabicyclo[3.3.0]octan-2-ones **5** (Scheme 1).

However, these researches showed that new heterocyclic systems in common organic solvents could only be achieved in reactions with highly reactive reagents—arylketenes [3–6] and aroylisocyanates [7]. A reaction between diaziridines **1** and **2** and the other foresaid reagents was also performed successfully though only with ionic liquids (ILs) used as a reaction medium [8–11]. Moreover, absolutely unexpected heterocyclic structures were built in those solvents in some cases. For example, derivatives of earlier unknown infused 1,2,4,6-tetrazepan-5-thione were obtained in one preparative step by an interaction of 1,2-dialkyldiaziridines **1** with benzoylisothiocyanate in 1-butyl-3-methylimidazilium tetrafluoroborate ([bmim][BF$_4$]) or hexafluorophosphate ([bmim][PF$_6$]) [8].

We continued examining ring expansion reactions of monocyclic 1,2-dialkyldiaziridines **1** with dipolarophiles in ionic liquids within this research effort. As a dipolarophile dialkyl esters of acetylenedicarboxylic acid were selected. The reaction between 1,2-dialkyldiaziridine derivatives and dimethyl acetylenedicarboxylate in benzene had been described in literature [12]. The authors of this study have found out that the interaction of these compounds resulted in only linear products **7** and **8** and the diaziridine ring opening occurred on the N—N bond. The research on this reaction mechanism was assisted by labeled atoms (D). On the basis of the obtained compounds structure authors of the work [12] assumed that the first reaction step was the formation of dipolar intermediates **9**. Where one of the substituents at nitrogen atoms of initial diaziridine **1a** was benzyl, intermediate **9a** was stabilized by a proton split-off from the CH$_2$ group of the benzyl fragment followed by the generation of enamine **7**. If one of the substituents at nitrogen atoms was Ph (**1b**), intermediate **9b** was stabilized by proton breaking from the C(3)-carbon atom of the

Scheme 1



diaziridine ring with further generation of product **8** (Scheme 2) [12].

Originating from the data obtained in [8–11] we hoped that ILs as a reaction medium would change the stabilization pathways of intermediates **9** and result in heterocyclic structures **10** or **11** depending on C—N- or N—N-positioned opening of the diaziridine ring in the interaction of 1,2-dialkyldiaziridines **1** with dialkyl esters of acetylenedicarboxylic acid (Scheme 3).

Ionic liquids have been widely used over the past years as a potential replacement of conventional solvents for a variety of chemical processes [13,14]. ILs have considerable advantages over available organic solvents—they are fire-resistant and have limited vapor pressure thus allowing efficient recovery of organic products. In addition, they are recyclable and can be used several times in the same reactions. Moreover, many reactions gain acceleration in ILs due to stabilization of charged intermediates or ions [15–17]. The realization of different reactions in ILs pertains to a new prospective field of organic chemistry—''green chemistry.''

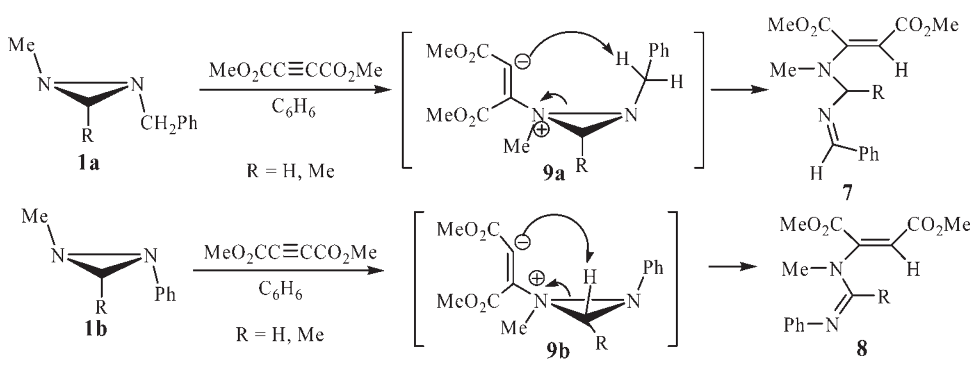
RESULTS AND DISCUSSION

1,2-Dibutyl-(**1c**), 1,2-dipropyl-(**1d**), 1,2-diethyl-(**1e**), 1,2-dimethyl-(**1f**), 1,2,3-triethyl-(**1g**), 1,2-diethyl-3-methyl-(**1h**), 1,2-dipropyl-3-ethyl-(**1i**), and 3-benzyl-1,2-di(2-phenylethyl)- (**1j**) diaziridines were examined as initial dialkyldiaziridines **1** and diethyl acetylenedicarboxylate **12** as a dipolarophyle. From a large number of ILs we picked 1-butyl-3-methylimidazolium tetrafluoroborate or hexafluorophosphate ([bmim][BF$_4$] or [bmim][PF$_6$]). These ionic liquids relate to room temperature ionic liquids group (RTIL) and are one of the most accessible ones. Note that during the reaction the reaction mixture is colored orange at first and then red at reaction end.

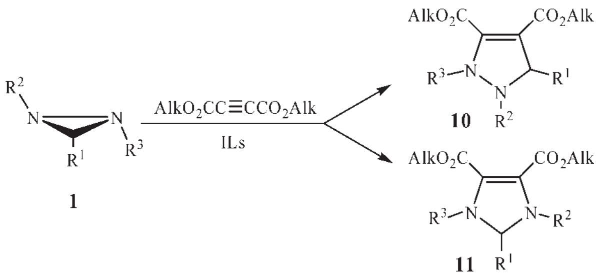
The investigations were started with 1,2-dibutyldiaziridine **1c** in [bmim][BF$_4$]. At first, the equimolar quantity of the reagents was added to the reaction. In about 30 min at 20°C, the reaction was completed (as shown by TLC) and a new compound, diethyl 1-[3-ethoxy-1-(ethoxycarbonyl)-3-oxoprop-1-enyl]-3-buthyl-6-propyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate **13c,** was obtained in 37% yield. According to mass spectra this contained one molecule of diaziridine **1c** and two molecules of diethyl acetylenedicarboxylate **12**. After adding one mole of diaziridine **1c** and two moles of dipolarophile **12** to the reaction, the yield of **13c** became higher −69%. This reaction was found to have a general character—compounds **13d–f** were synthesized from diaziridines **1d–f** and dipolarophile **12** in close yields. The reaction ran in ionic liquid [bmim][PF$_6$] as well as in [bmim][BF$_4$]. Reaction rate depended on solubility of initial diaziridines **1c–f** in Ils—the shorter alkyl substituents at nitrogen atoms the higher their solubility and rate of reaction.

Further on, it was found that, apart from 1,2-dialkyldiaziridines **1c–f**, 1,2,3-trialkyldiaziridines **1g–i** were also capable of entering the reaction with diethyl acetylenedicarboxylate **12** to produce corresponding tetrahydropyrimidine derivatives **13g–i**. However, the latter are formed only at the replacement of ionic liquids [bmim][BF$_4$] or [bmim][PF$_6$] with [emim][HSO$_4$] being herein both a reaction medium and an acidic catalyst. Yields of compounds **13g–i** were also increased as affected by lengthening of the alkyl substituents both at N and at C(3) atoms of initial diaziridines **1g–i**.

Scheme 2



Scheme 3



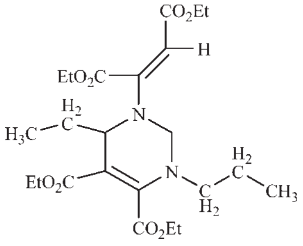


Figure 1. The molecule **13d** structure.

The structures of compounds **13c–i** were established by aggregating elemental analysis data and spectral characteristics (mass-spectra, IR-, NMR ^{1}H, ^{13}C, ^{15}N-spectra with use of COSY, NOESY, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC, and ^{1}H-^{15}N HMBC methods). The proof of compounds **13** structure was demonstrated on example of compound **13d**. ^{13}C APT spectrum revealed 6 CH_3 groups, 8 CH_2 groups, 2 CH groups, and 7 quaternary carbon atoms, four of them were in the region of carboxylic carbon resonance. ^{1}H spectrum was assigned with COSY, NOESY, and HSQC 2D spectra. The investigation of these spectra showed that molecule contained four carboethoxy, one *N*-propyl-, one 1-substituted *N*-propyl group, one CH_2 group which had no interactions with other protons, and one sp^{2}-CH group. ^{1}H-^{13}C HMBC 2D spectral correlations allowed us to approve the structure of these fragments and interconnections between them, as well as positions of quaternary carbon atoms. The proposed molecular structure was tetrahydropyrimidine ring with substituents (Fig. 1)

The ^{1}H-^{13}C HMBC correlations of the compound **13d** are shown in Figure 2.

The ^{1}H-^{15}N HMBC spectrum revealed two sp^{3} N-atoms with chemical shifts of −295.1 and −291.9 ppm (with an external reference CH_3NO_2, $\delta = 0.0$ ppm) and connectivity between both N-atoms and protons, which is shown in Figure 3.

The most important NOE interactions in the molecule **13d** revealed in NOESY experiment (Fig. 4)

Cis-configuration of two carboethoxy groups near double bond at N-1 was proved by NOE interactions H-8/H-2 and H-6/H-12 in NOESY spectrum. Another important NOE correlation was between H-2 and H-9 also proved the structure of this molecule.

Initial 1,2-dialkyldiaziridines **1c–i** are chiral compounds but they were introduced to the reaction with diethyl acetylenedicarboxylate **12** in a racemic form.

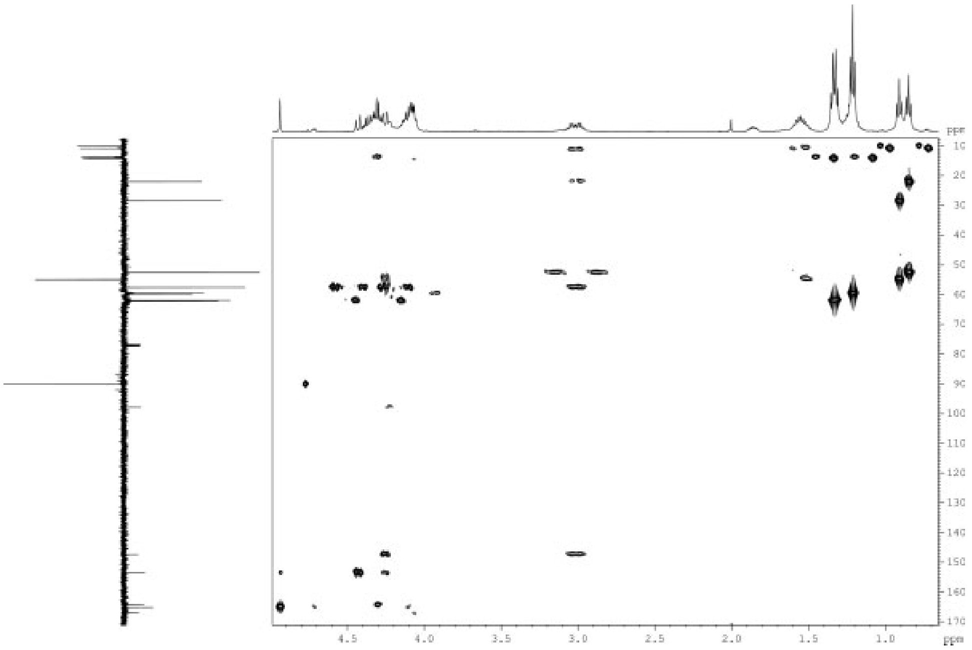


Figure 2. ^{1}H-^{13}C HMBC correlations of the compound **13d**.

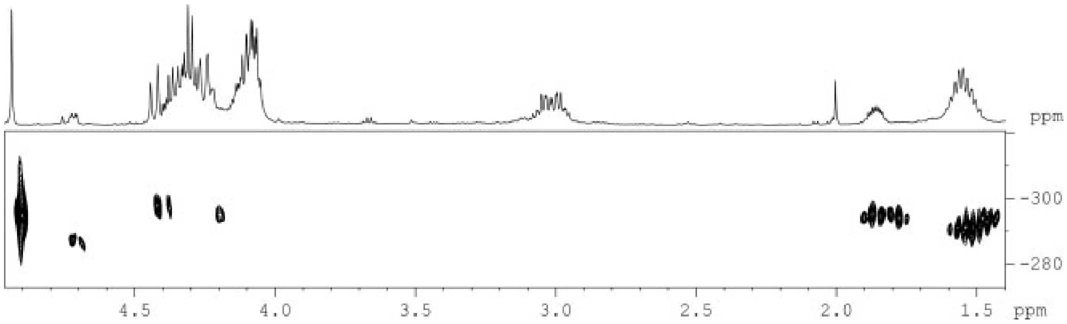


Figure 3. ^{1}H-^{15}N HMBC correlations of the compound **13d**.

And the reaction evidently proceeds not stereoselectively. The synthesized compounds (**13c–i**) contain chiral carbon atoms (C(6) in **13c–f** and C(2) and C(6) in **13g–i**), however, **13c–f** are racemates and, as seen from the spectral characteristics, no diastereomers were fixed in **13g–i** prepared from 1,2,3-trialkyldiaziridines **1g–i**.

The chemical shifts of signals NMR ^{1}H, ^{13}C, ^{15}N spectra by the example of compounds **13c**, **13d**, **13h** are presented in Table 1. The atom numeration is shown on Figure 5.

This result is in agreement with the assumed mechanism of the reaction. The first step (as in ref. [12]) is the formation of dipolar intermediate **9**, however, its life time evidently increases in ionic liquids able to solvate both positively and negatively charged particles or molecule moieties [15–17]. Therefore, the second molecule of diethyl acetylenedicarboxylate **12** has time to enter a reaction with intermediate **9,** generating the second intermediate **14,** which is transformed to final compound **13**. Generally, the formation of compounds **13** can be presented as two-step condensation of one molecule of initial diaziridine **1** and two molecules of compound **12** according to Scheme 4. Unlike the transformation of intermediate **9** in benzene (Scheme 2), the anion of intermediate **9** in ILs evidently attacks the proton of the CH_2 group bound to same nitrogen atom to generate a new anion, which in turn attacks the second molecule of diethyl acetylenedicarboxylate **12** (Scheme 4).

The expected five-member heterocyclic compound, *i.e.*, diethyl 5-benzyl-1,2-bis(2-phenylethyl)-2,5-dihydro-1*H*-pyrazole-3,4-dicarboxylate **15**, was obtained only in one case by the interaction of 1,2-di(2-phenylethyl)-3-phenylmethyldiaziridine **1j** with diethyl acetylenedicarboxylate **12** in ionic liquid [emim][HSO_4] (Scheme 5). Evidently, here, the attack of the second molecule of dipolarophile **12** on intermediate **9j** was sterically hindered.

Thus a new unexpected transformation of 1,2-dialkyldiaziridines **1** under the action of diethyl acetylenedicarboxylate **12** in ionic liquids resulting in tetrahydropyrimidine derivatives **13** was discovered. The reaction is a new method for preparing tetrahydropyrimidine derivatives and is a valuable supplement to the known synthetic methods for such kind of compounds. Pyrimidines and their analogs represent an important class of nitrogen heterocycles, which are components both of various biologically active natural compounds and of diverse drugs [18(a)]. They display antiviral [18(b)], antibacterial [18(b,c)], anti-inflammatory [18(a,b)], and anti-HIV (HIV Integrase inhibitors) activities [18(d)] and are useful as inflammatory mediators in Parkinson's disease therapy [18(e)].

EXPERIMENTAL

Elemental analysis was performed by the CHN Analyzer Perkin–Elmer 2400. The IR spectra (ν, cm^{-1}) were measured using a SPECORD-M82 spectrometer. Mass spectra were measured using a Finnigan MAT INCOS-50 instrument. The NMR spectra of compound **15** were recorded using a Bruker AM-300 spectrometer at 300 MHz for ^{1}H and 75.47 MHz for ^{13}C Spectra in $CDCl_3$. The NMR spectra of all compounds **13c–i** were measured on Bruker AV-600 instrument with the frequencies 600.13, 150.90, and 60.81 MHz for ^{1}H, ^{13}C, and ^{15}N, correspondingly. The chemical shifts of the signals of $CDCl_3$ residual proton (7.27 ppm) and carbon (77.0 ppm) were used as the internal standard. The ^{15}N spectra were measured with CH_3NO_2 ($\delta_{^{15}N} = 0.0$ ppm) as the external standard. All 2D-spectra were recorded using standard Bruker methods with Z-gradient. The spectra were measured at 30°C. Analytical thin-layer chromatography (TLC) was conducted on silica gel plates (Silufol UV-254). New compounds were purified by flash-chromatography (column chromatography for **15**) on

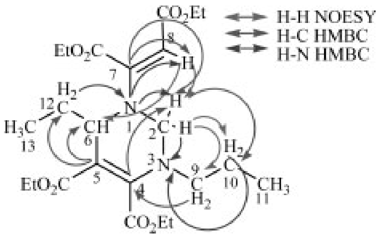


Figure 4. The most important NOE interactions in the molecule revealed in NOESY experiment.

Table 1

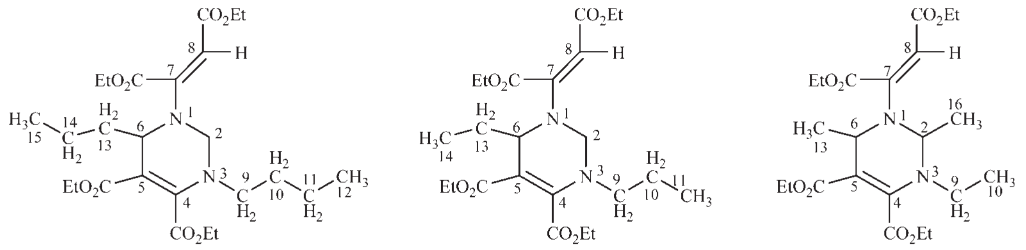
Chemical shifts of **13c**, **13d**, **13h** NMR ^{1}H, ^{13}C, ^{15}N spectra.

Atom numbers (Fig. 5)	Compounds					
	13c		**13d**		**13h**	
	^{1}H	^{13}C/^{15}N	^{1}H	^{13}C/^{15}N	^{1}H	^{13}C/^{15}N
1	–	−292.2	–	−291.9	–	–
2	4.24; 4.45	59.1	4.25; 4.43	57.6	4.48	67.5
3	–	−293.8	–	−295.2	–	–
4	–	148.8	–	147.5	–	146.0
5	–	99.3	–	97.9	–	106.3
6	4.33	53.4	4.22	55.0	4.22	47.1
7	–	154.9	–	153.6	–	150.1
8	4.94	91.8	4.94	90.2	4.99	91.0
9	3.03; 3.07	52.3	2.98; 3.04	52.7	3.03; 3.19	45.6
10	1.52	32.4	1.55	22.1	1.18	14.4
11	1.26	21.3	0.85	10.9	–	–
12	0.89	15.2	–	–	–	–
13	1.51; 1.76	39.3	1.51; 1.85	28.6	1.42	20.0
14	1.34; 1.41	20.2	0.91	10.1	–	–
15	0.89	15.2	–	–	–	–
16	–	–	–	–	1.36	16.9
4-COOEt	–	168.5	–	167.0	–	167.2
	4.06	61.1	4.07	59.5	4.09	59.6
	1.23	15.3	1.22	13.7	1.25	14.2
5-COOEt	–	165.7	–	164.2	–	164.5
	4.31	63.4	4.30	61.9	4.32	61.9
	1.35	15.3	1.32	13.7	1.33	14.3
7-COOEt	–	166.6	–	165.1	–	164.7
	4.14	61.3	4.12	59.8	4.17	60.2
	1.22	15.7	1.22	14.2	1.27	14.4
8-COOEt	–	166.6	–	165.1	–	165.5
	4.36	63.7	4.36	62.2	4.43	62.1
	1.33	15.7	1.35	14.2	1.39	14.2

Silicagel, 0.060–0.200 mm, 60 A (ACROS). R_f of all compounds **13** and **15** was measured with the usage of eluent [*n*-hexane-ethyl acetate, 2:1 (v/v)].

General procedure for the synthesis of substituted 1,2,3,6-tetrahydropyrimidines by the reaction of 1,2-di- and 1,2,3-trialkyldiaziridines 1c-i with diethyl acetylenedicarboxylate 12 in ionic liquid. To a stirred mixture (20°C) of diaziridine **1c–i** (1.0 mmol) and ionic liquid ([bmim][BF$_4$] or [bmim][PF$_6$] for 1,2-dialkyldiaziridines **1c–f** and [emim][HSO$_4$] for 1,2,3-trialkyldiaziridines **1g–i**) (0.4 g), diethyl acetylenedicarboxylate **12** (2.0 mmol) was added dropwise for about 1 min and the reaction mixture was stirred for an additional 30 min to the full conversion of initial compounds (TLC-control), the reaction mixture color was changed through the time from orange to red. After that the resulting substituted 1,2,3,6-tetrahydropyrimidine **13** was extracted from ionic liquid by mixture of solvents hexane and ethyl acetate (5:1, 4–5 times by 7 mL), then the solvent was evaporated. Final substituted 1,2,3,6-tetrahydropyrimidine **13** was purified by the method of flash-chromatography on Silicagel with the solvent of *n*-hexane and ethyl acetate (2:1).

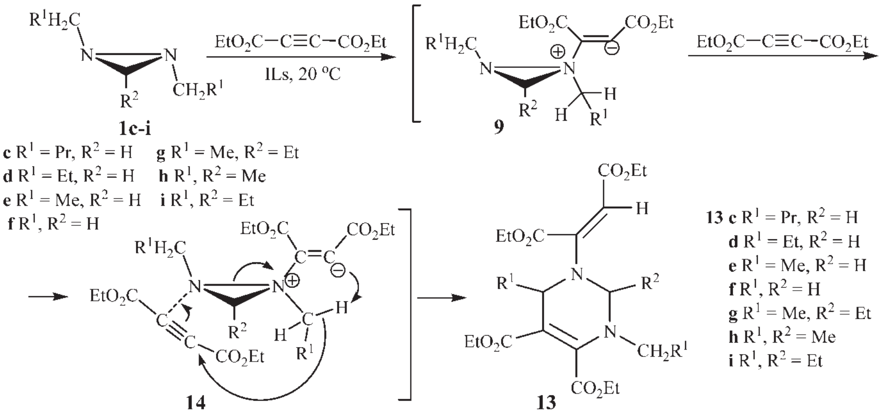
Synthesis of diethyl 5-benzyl-1,2-bis(2-phenylethyl)-2,5-dihydro-1*H*-pyrazole-3,4-dicarboxylate (15). To a stirred mixture (20°C) of diaziridine **1j** (1.0 mmol) and ionic liquid ([bmim][BF$_4$] or [bmim][PF$_6$]) (0.4 g), diethyl acetylenedicarboxylate **12** (1.0 mmol) was added dropwise for about 1 min



13c **13d** **13h**

Figure 5. Atom numeration of compounds **13c**, **13d**, and **13h**.

Scheme 4



ILs = [bmim][BF$_4$], [bmim][PF$_6$] (R^2 = H); [emim][HSO$_4$] (R^2 = Alk)

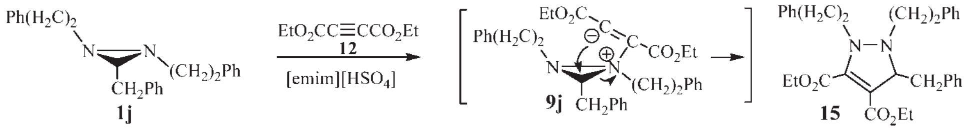
and the reaction mixture was stirred for an additional 48 h to the full conversion of initial compounds (TLC-control), the reaction mixture color was changed through the time from orange to red. After that the resulting compound **15** was extracted from ionic liquid by mixture of solvents hexane and ethyl acetate (5:1, 6 times by 7 mL), then the solvent was evaporated. Final compound **15** was purified by the method of column chromatography on Silicagel with the solvent of *n*-hexane and ethyl acetate (3:1).

The physical and spectral data of compounds **13c–i** and **15** are as follows.

Diethyl 1-[3-ethoxy-1-(ethoxycarbonyl)-3-oxoprop-1-enyl]-3-buthyl-6-propyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (13c). This compound was obtained as yellow nondistilled oil, 69% yield, R_f 0.37; IR: 668, 772, 864, 924, 1024, 1044, 1096, 1152, 1172, 1220, 1248, 1372, 1444, 1456, 1580, 1652, 1700, 1740, 2876, 2936, 2960, 2970 cm^{-1}; ^{1}H NMR: δ 0.89 (t, 6H, $\mathrm{C}H_3\mathrm{(CH_2)_3N}$ + $\mathrm{C}H_3\mathrm{(CH_2)_2N}$, ^3J = 7.1 Hz), 1.22 (t, 3H, $\mathrm{C}H_3\mathrm{CH_2OOCC_{chain}N}$, ^3J = 7.2 Hz), 1.23 (t, 3H, $\mathrm{C}H_3\mathrm{CH_2OOCC^4_{ring}}$, ^3J = 7.2 Hz), 1.26 (m, 2H, $\mathrm{CH_3C}H_2\mathrm{(CH_2)_2N}$, ^3J = 7.2), 1.33 (t, 3H, $\mathrm{C}H_3\mathrm{CH_2OOCC_{chain}H}$, ^3J = 7.2 Hz), 1.34, 1.41 (2m, 2H, $\mathrm{CH_3C}H_2\mathrm{CH_2C^6_{ring}}$), 1.35 (t, 3H, $\mathrm{C}H_3\mathrm{CH_2OOCC^5_{ring}}$, ^3J = 7.2 Hz), 1.51, 1.76 (2m, 2H, $\mathrm{CH_3CH_2C}H_2\mathrm{C^6_{ring}}$), 1.52 (m, 2H, $\mathrm{CH_3CH_2C}H_2\mathrm{CH_2N}$), 3.03, 3.07 (2m, 2H, $\mathrm{CH_3(CH_2)_2C}H_2\mathrm{N}$), 4.06 (m, 2H, $\mathrm{CH_3C}H_2\mathrm{OOCC^4_{ring}}$, ^3J = 7.2 Hz), 4.14 (m, 2H, $\mathrm{CH_3C}H_2\mathrm{OOCC_{chain}N}$, ^3J = 7.2 Hz), 4.24, 4.45 (dd, 2H, $\mathrm{C^2_{ring}}H_2$), 4.31 (m, 2H, $\mathrm{CH_3C}H_2\mathrm{OOCC^5_{ring}}$, ^3J = 7.2 Hz), 4.33 (m, 2H, $\mathrm{C^6_{ring}}H$), 4.36 (m, 2H, $\mathrm{CH_3C}H_2\mathrm{OOCC_{chain}H}$, ^3J = 7.2 Hz), 4.94 ppm (s, 1H, $\mathrm{EtOOCC_{chain}}H$); ^{13}C NMR: 15.25 ($C\mathrm{H_3(CH_2)_3N}$ and $C\mathrm{H_3(CH_2)_2C^6_{ring}}$), 15.26 ($C\mathrm{H_3CH_2OOCC^4_{ring}}$), 15.29 ($C\mathrm{H_3CH_2OOCC^5_{ring}}$), 15.68 ($C\mathrm{H_3CH_2OOCC_{chain}N}$), 15.74 ($C\mathrm{H_3CH_2OOCC_{chain}H}$), 20.24 ($\mathrm{CH_3}C\mathrm{H_2CH_2C^6_{ring}}$), 21.27 ($\mathrm{CH_3}C\mathrm{H_2CH_2CH_2N}$), 32.39 ($\mathrm{CH_3CH_2}C\mathrm{H_2CH_2N}$), 39.32 ($\mathrm{C^6_{ring}}C\mathrm{H_2}$), 52.27 ($\mathrm{CH_3CH_2CH_2}C\mathrm{H_2N}$), 53.36 ($C^6_{\mathrm{ring}}\mathrm{H}$), 59.11 ($C^2_{\mathrm{ring}}\mathrm{H_2}$), 61.08 ($\mathrm{CH_3}C\mathrm{H_2OOCC^4_{ring}}$), 61.28 ($\mathrm{CH_3}C\mathrm{H_2OOCC_{chain}N}$), 63.44 ($\mathrm{CH_3}C\mathrm{H_2OOCC^5_{ring}}$), 63.73 ($\mathrm{CH_3}C\mathrm{H_2OOCC_{chain}H}$), 91.79 ($\mathrm{EtOOC}C_{\mathrm{chain}}\mathrm{H}$), 99.26 ($\mathrm{EtOOC}C^5_{\mathrm{ring}}$), 148.85 ($\mathrm{EtOOC}C^4_{\mathrm{ring}}$), 154.90 ($\mathrm{EtOOC}C_{\mathrm{chain}}\mathrm{N}$), 165.72 ($\mathrm{EtOO}C\mathrm{C^5_{ring}}$), 166.58 ($\mathrm{EtOO}C\mathrm{C_{chain}H}$), 166.61 ($\mathrm{EtOO}C\mathrm{C_{chain}N}$), 168.51 ppm ($\mathrm{EtOO}C\mathrm{C^4_{ring}}$); ^{15}N NMR: δ −292.2 ppm (N^1), −293.8 (N^3); ms: *m*/*z* (I, %) 496 (3, M), 467 (23, M – $\mathrm{C_2H_5}$), 451 (5, M – $\mathrm{C_3H_7}$ – 2H), 438 (4, M – $\mathrm{2C_2H_5}$), 323 (13, M – $\mathrm{CO_2C_2H_5}$), 350 (6, M – $\mathrm{2CO_2C_2H_5}$), 168 (15, diethyl acetilenedicarboxylate – 2H), 155 (71, 1,2-dibutyl diaziridine – H), 43 (100, $\mathrm{C_3H_7}$). Anal. Calcd for $\mathrm{C_{25}H_{40}N_2O_8}$ (496.59): C, 60.47; H, 8.12; N, 5.64. Found: C, 60.44; H, 8.15; N, 5.63.

Diethyl 1-[3-ethoxy-1-(ethoxycarbonyl)-3-oxoprop-1-enyl]-3-propyl-6-ethyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (13d). This compound was obtained as yellow nondistilled oil, 77% yield, R_f 0.37; IR: 666, 748, 774, 864, 1024, 1046, 1098, 1154, 1222, 1246, 1372, 1446, 1462, 1580, 1700, 1738, 2876, 2922, 2950, 2984 cm^{-1}; ^{1}H NMR: δ 0.85 (t, 3H, $\mathrm{C}H_3\mathrm{(CH_2)_2N}$, ^3J = 7.2 Hz), 0.91 (t, 3H, $\mathrm{C}H_3\mathrm{CH_2C^6_{ring}H}$, ^3J = 7.3 Hz), 1.22 (t, 6H, $\mathrm{C}H_3\mathrm{CH_2OOCC^4_{ring}}$ + $\mathrm{C}H_3\mathrm{CH_2OOCC_{chain}N}$, ^3J = 7.2 Hz), 1.32 (t, 3H, $\mathrm{C}H_3\mathrm{CH_2OOCC^5_{ring}}$, ^3J = 7.2 Hz), 1.35 (t, 3H, $\mathrm{C}H_3\mathrm{CH_2OOCC_{chain}H}$, ^3J = 7.2 Hz), 1.51, 1.85 (2m, 2H, $\mathrm{CH_3C}H_2\mathrm{C^6_{ring}}$), 1.55 (m, 2H, $\mathrm{CH_3C}H_2\mathrm{CH_2N}$), 2.98, 3.04 (2m, 2H, $\mathrm{CH_3CH_2C}H_2\mathrm{N}$), 4.07 (m, 2H, $\mathrm{CH_3C}H_2\mathrm{OOCC^4_{ring}}$, ^3J = 7.2 Hz), 4.12 (m, 2H, $\mathrm{CH_3C}H_2\mathrm{OOCC_{chain}N}$, ^3J = 7.2 Hz), 4.22 (m, 2H, $\mathrm{C^6_{ring}}H$), 4.25, 4.43 (dd, 2H, $\mathrm{C^2_{ring}}H_2$), 4.30 (m, 2H, $\mathrm{CH_3C}H_2\mathrm{OOCC^6_{ring}}$, ^3J = 7.2 Hz), 4.36 (m, 2H, $\mathrm{CH_3C}H_2\mathrm{OOCC_{chain}H}$, ^3J = 7.2 Hz), 4.94 ppm (s, 1H, $\mathrm{EtOOCC_{chain}}H$); ^{13}C NMR: δ 10.12 ($C\mathrm{H_3CH_2C^6_{ring}}$), 10.86 ($C\mathrm{H_3CH_2CH_2N}$), 13.72 ($C\mathrm{H_3CH_2OOCC^4_{ring}}$), 13.76 ($C\mathrm{H_3CH_2OOCC^5_{ring}}$), 14.18 ($C\mathrm{H_3CH_2OOCC_{chain}N}$), 14.23 ($C\mathrm{H_3CH_2OOCC_{chain}H}$), 22.09 ($\mathrm{CH_3}C\mathrm{H_2CH_2N}$), 28.56 ($\mathrm{C^6_{ring}}C\mathrm{H_2CH_3}$), 52.67 ($\mathrm{CH_3CH_2}C\mathrm{H_2N}$), 55.02 ($C^6_{\mathrm{ring}}\mathrm{H}$), 57.55 ($C^2_{\mathrm{ring}}\mathrm{H_2}$), 59.51 ($\mathrm{CH_3}C\mathrm{H_2OOCC^4_{ring}}$), 59.77 ($\mathrm{CH_3}C\mathrm{H_2OOCC_{chain}N}$), 61.93 ($\mathrm{CH_3}C\mathrm{H_2OOCC^5_{ring}}$),

Scheme 5



62.16 ($\mathrm{CH_3\mathit{C}H_2OOCC_{chain}H}$), 90.23 ($\mathrm{EtOOC\mathit{C}_{chain}H}$), 97.90 ($\mathrm{EtOOC\mathit{C}^5_{ring}}$), 147.46 ($\mathrm{EtOOC\mathit{C}^4_{ring}}$), 153.60 ($\mathrm{EtOOC\mathit{C}_{chain}N}$), 164.17 ($\mathrm{EtOO\mathit{C}C^5_{ring}}$), 165.10 ($\mathrm{EtOO\mathit{C}C_{chain}N}$ and $\mathrm{EtOO\mathit{C}C_{chain}H}$), 167.01 ppm ($\mathrm{EtOO\mathit{C}C^4_{ring}N}$); ^{15}N NMR: δ −291.9 ppm (N^1), −295.2 (N^3); ms: *m*/*z* (I, %) 468 (5, M), 439 (30, M – C_2H_5), 423 (4, M – C_3H_7 – 2H), 410 (3, M – $2C_2H_5$), 395 (7, M – $CO_2C_2H_5$), 322 (3, M – $2CO_2C_2H_5$), 168 (17, diethyl acetilenedicarboxylate – 2H), 126 (60, 1,2-dipropyl diaziridine – 2H), 43 (100, C_3H_7). Anal. Calcd for $C_{23}H_{36}N_2O_8$ (468.54): C, 58.96; H, 7.74; N, 5.98. Found: C, 59.00; H, 8.11; N, 5.96.

Diethyl 1-[3-ethoxy-1-(ethoxycarbonyl)-3-oxoprop-1-enyl]-3-ethyl-6-methyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (13e). This compound was obtained as yellow nondistilled oil, 65% yield, R_f 0.36; IR: 664, 752, 776, 804, 864, 1024, 1048, 1100, 1156, 1224, 1244, 1300, 1372, 1384, 1448, 1468, 1580, 1700, 1736, 2876, 2908, 2940, 2984 cm^{-1}; ^{1}H NMR: δ 1.06 (t, 3H, $\mathrm{C\mathit{H}_3CH_2N}$, ^3J = 7.3 Hz), 1.13 (t, 3H, $\mathrm{C\mathit{H}_3C^6_{ring}}$, ^3J = 7.5 Hz), 1.21 (t, 6H, $\mathrm{C\mathit{H}_3CH_2OOCC_{chain}H}$ + $\mathrm{C\mathit{H}_3CH_2OOCC^4_{ring}}$, ^3J = 7.3 Hz), 1.34 (t, 6H, $\mathrm{C\mathit{H}_3CH_2OOCC^5_{ring}}$ + $\mathrm{C\mathit{H}_3CH_2OOCC_{chain}N}$, ^3J = 7.3 Hz), 3.15, 3.25 (2m, 2H, $\mathrm{CH_3C\mathit{H}_2N}$), 4.06 (m, 2H, $\mathrm{CH_3C\mathit{H}_2OOCC^4_{ring}}$, ^3J = 7.3 Hz), 4.11 (m, 2H, $\mathrm{CH_3C\mathit{H}_2OOCC_{chain}H}$, ^3J = 7.3 Hz), 4.28 (m, 2H, $\mathrm{CH_3C\mathit{H}_2OOCC^5_{ring}}$, ^3J = 7.3 Hz), 4.35, 4.46 (dd, 2H, $\mathrm{C^2_{ring}\mathit{H}_2}$), 4.36 (m, 2H, $\mathrm{CH_3C\mathit{H}_2OOCC_{chain}N}$, ^3J = 7.3 Hz), 4.82 (m, 2H, $\mathrm{C^6_{ring}\mathit{H}Me}$), 4.83 ppm (s, 1H, $\mathrm{EtOOCC_{chain}\mathit{H}}$); ^{13}C NMR: 10.33 ($\mathrm{\mathit{C}H_3CH_2N}$), 13.65 ($\mathrm{\mathit{C}H_3CH_2OOCC^5_{ring}}$ and $\mathrm{\mathit{C}H_3CH_2OOCC_{chain}N}$), 13.92 ($\mathrm{\mathit{C}H_3CH_2OOCC_{chain}H}$ and $\mathrm{\mathit{C}H_3CH_2OOCC^4_{ring}}$), 16.02 ($\mathrm{C^6_{ring}\mathit{C}H_3}$), 41.22 ($\mathrm{CH_3\mathit{C}H_2N}$), 48.97 ($\mathrm{\mathit{C}^6_{ring}H}$), 59.41 ($\mathrm{CH_3\mathit{C}H_2OOCC^4_{ring}}$), 59.55 ($\mathrm{CH_3\mathit{C}H_2OOCC_{chain}H}$), 61.32 ($\mathrm{CH_3\mathit{C}H_2OOCC^5_{ring}}$), 62.31 ($\mathrm{CH_3\mathit{C}H_2OOCC_{chain}N}$), 63.98 ($\mathrm{\mathit{C}^2_{ring}H_2}$), 88.45 ($\mathrm{EtOOC\mathit{C}_{chain}H}$), 112.33 ($\mathrm{EtOOC\mathit{C}^5_{ring}}$), 149.43 ($\mathrm{EtOOC\mathit{C}^4_{ring}N}$), 151.95 ($\mathrm{EtOOC\mathit{C}_{chain}N}$), 163.65 ($\mathrm{EtOO\mathit{C}C_{chain}H}$), 165.16 ($\mathrm{EtOO\mathit{C}C_{chain}N}$), 166.78 ($\mathrm{EtOOC\mathit{C}^4_{ring}N}$), 167.01 ppm ($\mathrm{EtOO\mathit{C}C^5_{ring}}$); ^{15}N NMR: δ −280.3 (N^1), −288.0 ppm (N^3). Anal. Calcd for $C_{21}H_{32}N_2O_8$ (440.49): C, 57.26; H, 7.32; N, 6.36. Found: C, 57.30; H, 7.29; N, 6.33.

Diethyl 1-[3-ethoxy-1-(ethoxycarbonyl)-3-oxoprop-1-enyl]-3-methyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (13f). This compound was obtained as yellow nondistilled oil, 34% yield, R_f 0.36; IR: 664, 756, 860, 1028, 1096, 1144, 1252, 1372, 1448, 1560, 1696, 1736, 2872, 2940, 2984 cm^{-1}; ^{1}H NMR: δ 1.06 (t, 3H, $\mathrm{C\mathit{H}_3CH_2N}$, ^3J = 7.34 Hz), 1.13 (t, 3H, $\mathrm{C\mathit{H}_3C_{ring}HN}$, ^3J = 6.61 Hz), 1.21 (t, 6H, $\mathrm{C\mathit{H}_3CH_2OOCC_{chain}H}$, $\mathrm{C\mathit{H}_3CH_2OOCC_{ring}NEt}$, ^3J = 5.14 Hz), 1.34 (t, 6H, $\mathrm{C\mathit{H}_3CH_2OOCC_{ring}CHMe}$, $\mathrm{C\mathit{H}_3CH_2OOCC_{chain}N}$, ^3J = 5.87 Hz), 3.15, 3.25 (2m, 2H, $\mathrm{CH_3C\mathit{H}_2N}$), 4.06 (m, 2H, $\mathrm{CH_3C\mathit{H}_2OOCC_{ring}NEt}$), 4.11 (m, 2H, $\mathrm{CH_3C\mathit{H}_2OOCC_{chain}H}$), 4.28 (m, 2H, $\mathrm{CH_3C\mathit{H}_2OOCC_{ring}CHMe}$), 4.35, 4.46 (dd, 2H, $\mathrm{C^2_{ring}\mathit{H}_2}$, ^2J = 5.87 Hz), 4.36 (m, 2H, $\mathrm{CH_3C\mathit{H}_2OOCC_{chain}N}$), 4.82 (m, 1H, $\mathrm{C\mathit{H}Me}$), 4.83 ppm (s, 1H, $\mathrm{CH_3CH_2OOCC_{chain}\mathit{H}}$); ^{13}C NMR: 13.77 ($\mathrm{\mathit{C}H_3}$ in $\mathrm{EtOOCC_{ring}CHMe}$ and $\mathrm{EtOOCC_{chain}N}$), 14.23 ($\mathrm{\mathit{C}H_3}$ in $\mathrm{EtOOCC_{chain}H}$ and $\mathrm{EtOOCC_{ring}N}$), 16.02 ($\mathrm{NC_{ring}H\mathit{C}H_3}$), 41.22 ($\mathrm{CH_3\mathit{C}H_2N}$), 48.97 ($\mathrm{N\mathit{C}_{ring}HMe}$), 59.41 ($\mathrm{\mathit{C}H_2}$ in $\mathrm{EtOOCC_{ring}N}$), 59.55 ($\mathrm{\mathit{C}H_2}$ in $\mathrm{EtOOCC_{chain}H}$), 61.32 ($\mathrm{\mathit{C}H_2}$ in $\mathrm{EtOOCC_{ring}CHN}$), 62.31 ($\mathrm{\mathit{C}H_2}$ in $\mathrm{EtOOCC_{chain}N}$), 63.98 ($\mathrm{N\mathit{C}H_2N}$), 88.45 ($\mathrm{EtOOC\mathit{C}_{chain}H}$), 112.33 ($\mathrm{EtOOC\mathit{C}_{ring}CHN}$), 149.43 ($\mathrm{EtOOC\mathit{C}_{ring}N}$), 151.95 ($\mathrm{EtOOC\mathit{C}_{chain}N}$), 163.65 ($\mathrm{EtOO\mathit{C}C_{chain}H}$), 165.16 ($\mathrm{EtOO\mathit{C}C_{chain}N}$), 166.78 ($\mathrm{EtOOC\mathit{C}_{ring}N}$), 167.01 ppm ($\mathrm{EtOO\mathit{C}C_{ring}CHN}$). Anal. Calcd for $C_{19}H_{28}N_2O_8$ (412.43): C, 55.33; H, 6.84; N, 6.79. Found: C, 55.35; H, 6.84; N, 6.76.

Diethyl 1-[3-ethoxy-1-(ethoxycarbonyl)-3-oxoprop-1-enyl]-2,3-diethyl-6-methyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (13g). This compound was obtained as yellow nondistilled oil, 57% yield, R_f 0.38; IR: 664, 748, 782, 810, 866, 974, 1042, 1110, 1160, 1234, 1282, 1366, 1442, 1588, 1710, 1738, 2868, 2910, 2940, 2974, 2986 cm^{-1}; ^{1}H NMR: δ 0.82 (t, 3H, $\mathrm{C\mathit{H}_3CH_2C^2_{ring}}$, ^3J = 6.35 Hz), 1.20, 1.28 (2t, 12H, $\mathrm{C\mathit{H}_3CH_2COO}$, ^3J = 7.33 Hz), 1.49 (m, 3H, $\mathrm{NCH_2C\mathit{H}_3}$, ^3J = 6.84 Hz), 1.59, 1.97 (2m, 3H, $\mathrm{C\mathit{H}_3C^6_{ring}}$, ^3J = 5.86 Hz), 1.86, 2.22 (2m, 2H, $\mathrm{CH_3C\mathit{H}_2C^2_{ring}}$, ^3J = 5.37 Hz), 3.01, 3.22 (2m, 2H, $\mathrm{NC\mathit{H}_2CH_3}$, ^3J = 6.83 Hz), 4.11, 4.26 (2m, 10H, $\mathrm{C^6_{ring}\mathit{H}}$, $\mathrm{C^2_{ring}\mathit{H}}$, 4 $\mathrm{CH_3C\mathit{H}_2OOC}$), 4.79 ppm (s, 1H, $\mathrm{EtOOCC_{chain}\mathit{H}}$); ^{13}C NMR: δ 10.36 ($\mathrm{\mathit{C}H_3CH_2C^2_{ring}}$), 13.91, 14.27 ($\mathrm{\mathit{C}H_3CH_2COO}$), 14.73 ($\mathrm{NCH_2\mathit{C}H_3}$), 20.24 ($\mathrm{C^6_{ring}\mathit{C}H_3}$), 24.63 ($\mathrm{CH_3\mathit{C}H_2C^2_{ring}}$), 47.34 ($\mathrm{N\mathit{C}H_2CH_3}$), 63.03 ($\mathrm{\mathit{C}^2_{ring}H}$), 59.70, 60.36, 61.99, 62.22 ($\mathrm{CH_3\mathit{C}H_2COO}$), 73.57 ($\mathrm{\mathit{C}^6_{ring}H}$), 91.10 ($\mathrm{EtOOC\mathit{C}_{chain}H}$), 108.28 ($\mathrm{EtOOC\mathit{C}_{chain}N}$), 145.55 ($\mathrm{EtOOC\mathit{C}^4_{ring}}$), 150.67 ($\mathrm{EtOOC\mathit{C}^5_{ring}}$), 164.78, 164.86, 165.61, 167.15 ppm ($\mathrm{\mathit{C}OOEt}$). Anal. Calcd for $C_{23}H_{36}N_2O_8$ (468.54): C, 58.96; H, 7.74; N, 5.98. Found: C, 58.96; H, 7.77; N, 5.98.

Diethyl 1-[3-ethoxy-1-(ethoxycarbonyl)-3-oxoprop-1-enyl]-3-ethyl-2,6-dimethyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (13h). This compound was obtained as yellow nondistilled oil, 35% yield, R_f 0.39; IR: 668, 756, 864, 1032, 1040, 1040, 1152, 1296, 1368, 1444, 1464, 1588, 1736, 2880, 2940, 2984 cm^{-1}; ^{1}H NMR: δ 1.18 (t, 3H, $\mathrm{C\mathit{H}_3CH_2N}$, ^3J = 5.37 Hz), 1.25 (t, 3H, $\mathrm{C\mathit{H}_3CH_2OOCC^4_{ring}}$, ^3J = 6.35 Hz), 1.27 (t, 3H, $\mathrm{C\mathit{H}_3CH_2OOCC_{chain}N}$, ^3J = 6.35 Hz), 1.33 (t, 3H, $\mathrm{C\mathit{H}_3CH_2OOCC^5_{ring}}$, ^3J = 6.35 Hz), 1.36 (t, 3H, $\mathrm{C\mathit{H}_3C^2_{ring}}$, ^3J = 5.86 Hz), 1.39 (t, 3H, $\mathrm{C\mathit{H}_3CH_2OOCC_{chain}H}$, ^3J = 6.35 Hz), 1.42 (d, 3H, $\mathrm{C\mathit{H}_3C^6_{ring}}$, ^3J = 4.88 Hz), 3.03, 3.19 (2m, 2H, $\mathrm{CH_3C\mathit{H}_2N}$, ^3J = 6.84 Hz), 4.09 (qv, 2H, $\mathrm{CH_3C\mathit{H}_2OOCC^4_{ring}}$, ^3J = 6.35 Hz), 4.17 (qv, 2H, $\mathrm{CH_3C\mathit{H}_2OOCC_{chain}N}$, ^3J = 6.35 Hz), 4.22 (qv, 1H, $\mathrm{C^6_{ring}\mathit{H}}$, ^3J = 4.88 Hz), 4.32 (m, 2H, $\mathrm{CH_3C\mathit{H}_2OOCC^5_{ring}}$, ^3J = 6.35 Hz), 4.43 (m, 2H, $\mathrm{CH_3C\mathit{H}_2OOCC_{chain}H}$, ^3J = 6.35 Hz), 4.48 (qv, 1H, $\mathrm{C^2_{ring}\mathit{H}}$, ^3J = 5.86 Hz), 4.99 ppm (s, 1H, $\mathrm{EtOOCC_{chain}\mathit{H}}$); ^{13}C NMR: δ 14.18 ($\mathrm{\mathit{C}H_3CH_2OOCC^4_{ring}}$), 14.22 ($\mathrm{\mathit{C}H_3CH_2OOCC_{chain}H}$), 14.30 ($\mathrm{\mathit{C}H_3CH_2OOCC^5_{ring}}$), 14.38 ($\mathrm{\mathit{C}H_3CH_2OOCC_{chain}N}$), 14.39 ($\mathrm{\mathit{C}H_3CH_2N}$), 16.94 ($\mathrm{\mathit{C}H_3C^2}$), 19.98 ($\mathrm{\mathit{C}H_3C^6_{ring}}$), 45.64 ($\mathrm{N\mathit{C}H_2CH_3}$), 47.10 ($\mathrm{\mathit{C}^6_{ring}H}$), 59.57 ($\mathrm{CH_3\mathit{C}H_2OOCC^4_{ring}}$), 60.16 ($\mathrm{CH_3\mathit{C}H_2OOCC_{chain}N}$), 61.91 ($\mathrm{CH_3\mathit{C}H_2OOCC^5_{ring}}$), 62.13 ($\mathrm{CH_3\mathit{C}H_2OOCC_{chain}H}$), 67.50 ($\mathrm{\mathit{C}^2_{ring}H}$), 91.03 ($\mathrm{EtOOC\mathit{C}_{chain}H}$), 106.32 ($\mathrm{EtOOC\mathit{C}^5_{ring}}$), 145.99 ($\mathrm{EtOOC\mathit{C}^4_{ring}}$), 150.11 ($\mathrm{EtOOC\mathit{C}_{chain}N}$), 164.52 ($\mathrm{EtOO\mathit{C}C^5_{ring}}$), 164.75 ($\mathrm{EtOO\mathit{C}C_{chain}N}$), 165.53 ($\mathrm{EtOO\mathit{C}C_{chain}H}$), 167.17 ppm ($\mathrm{EtOO\mathit{C}C^4_{ring}}$); ms: *m*/*z* (I, %) 423 (3, M – OC_2H_5 – 2H), 381 (7, M – $CO_2C_2H_5$), 366 (3, M – OC_2H_5 – C_2H_5 – 2 CH_3), 243 (36, M – 2 $CO_2C_2H_5$ – 2 C – CH – CH_3), 168 (100, pyrimidine + 2 CO_2), 138 (23, pyrimidine + 2 H +2 CH_3) + C_2H_5), 94 (37, pyrimidine + H + CH_3), 45 (46, C_2H_5). Anal. Calcd for $C_{22}H_{34}N_2O_8$ (454.51): C, 58.14; H, 7.54; N, 6.16. Found: C, 58.17; H, 7.53; N, 6.16.

Diethyl 1-[3-ethoxy-1-(ethoxycarbonyl)-3-oxoprop-1-enyl]-3-propyl-2,6-diethyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (13i). This compound was obtained as yellow nondistilled oil, 62% yield, R_f 0.38; IR: 668, 748, 780, 808, 864, 976, 1048, 1100, 1156, 1232, 1280, 1368, 1448, 1584, 1700, 1736, 2876, 2908, 2936, 2980 cm^{-1}; ^{1}H NMR: δ 0.64 (t, 3H, $\mathrm{C\mathit{H}_3CH_2C^2_{ring}}$, ^3J = 6.84 Hz), 0.77 (t, 3H, $\mathrm{C\mathit{H}_3CH_2CH_2N}$), 0.79 (t, 3H, $\mathrm{C\mathit{H}_3CH_2C^6_{ring}H}$), 1.16, 1.28 (2t, 12H, $\mathrm{C\mathit{H}_3CH_2COO}$, ^3J = 6.35 Hz), 1.44 (m, 2H, $\mathrm{NCH_2C\mathit{H}_2CH_3}$, ^3J = 6.84 Hz), 1.51, 1.86 (2m, 2H, $CH_3\mathit{CH}_2C^6_{ring}H$, $^3J = 7.32$ Hz), 1.62, 2.09 (2m, 2H, $CH_3\mathit{CH}_2C^2_{ring}$, $^3J = 7.33$ Hz), 2.81, 3.07 (2m, 2H, $N\mathit{CH}_2CH_2$, $^3J = 6.35$ Hz), 4.11 (m, 1H, $C^6_{ring}\mathit{H}$), 4.24, 4.32 (2m, 8H, $CH_3\mathit{CH}_2OOC$, $^3J = 6.35$ Hz), 4.27 (m, 1H, $C^2_{ring}\mathit{H}$), 4.82 ppm (s, 1H, $EtOOCC_{chain}\mathit{H}$); ^{13}C NMR: δ 7.45 ($\mathit{C}H_3CH_2C^2_{ring}$), 10.38 ($\mathit{C}H_3CH_2C^6_{ring}$), 11.46 ($\mathit{C}H_3CH_2CH_2N$), 14.18, 14.63 ($\mathit{C}H_3CH_2COO$), 22.18 ($CH_3\mathit{C}H_2C^2_{ring}$), 23.12 ($NCH_2\mathit{C}H_2CH_3$), 24.22 ($CH_3\mathit{C}H_2C^6_{ring}$), 51.44 ($\mathit{C}^2_{ring}H$), 54.46 ($N\mathit{C}H_2CH_2CH_3$), 59.32, 59.78, 61.94, 62.36 ($CH_3\mathit{C}H_2COO$), 73.94 ($\mathit{C}^6_{ring}H$), 92.16 ($EtOOC\mathit{C}_{chain}H$), 102.96 ($EtOOC\mathit{C}_{chain}N$), 147.94 ($EtOOC\mathit{C}^4_{ring}$), 150.08 ($EtOOC\mathit{C}^5_{ring}$), 164.56, 167.22 ($EtOO\mathit{C}C^4_{ring}$, $EtOO\mathit{C}C^5_{ring}$, $EtOO\mathit{C}C_{chain}N$), 165.28 ppm ($EtOO\mathit{C}C_{chain}H$). Anal. Calcd for $C_{25}H_{40}N_2O_8$ (496.59): C, 60.47; H, 8.12; N, 5.64. Found: C, 60.46; H, 8.14; N, 5.62.

Diethyl 5-benzyl-1,2-bis(2-phenylethyl)-2,5-dihydro-1*H*-pyrazole-3,4-dicarboxylate (15). This compound was obtained as yellow nondistilled oil, 47% yield, R_f 0.41; IR: 700, 752, 860, 1028, 1096, 1180, 1240, 1372, 1456, 1500, 1604, 1740, 2876, 2940, 2984, 3028, 3064 cm^{-1}; ^1H NMR: δ 1.31 (t, 6H, 2 CH_3CH_2OOC, $^3J = 6.33$ Hz), 2.92 (m, 6H, 3 $C_6H_5\mathit{CH}_2$, $^3J = 7.34$ Hz), 4.24 (m, 5H, $C^5_{ring}\mathit{H}$, 2 $N\mathit{CH}_2$, $^3J = 6.61$ Hz), 4.30 (qv, 4H, 2 $CH_3\mathit{CH}_2OOC$, $^3J = 6.35$ Hz), 7.27 ppm (m, 15H, H in C_6H_5); ^{13}C NMR: δ 14.06 ($\mathit{C}H_3CH_2OOC$), 33.17, 35.13, 36.04 ($C_6H_5\mathit{C}H_2$), 54.44, 63.02 ($N\mathit{C}H_2$), 60.44, 61.84 (CH_3CH_2OOC), 66.30 ($\mathit{C}^5_{ring}H$), 126.62, 127.74, 128.02, 128.13, 128.39, 128.48, 128.66, 128.83 (*o*-, *m*-, *p-C* in C_6H_5), 137.56, 139.65, 139.82 ppm (*ipso- C* in C_6H_5); ms: *m*/*z* 481 (5, M – CH_2CH_3 – 2H), 445 (6, M – CH_3CH_2OO – 2H), 346 (8, M – $2C_6H_5$ – CH_2), 329 (10, M – $2C_6H_5CH_2$), 301 (16, M – $2C_6H_5CH_2CH_2$), 226 (14, M – $3C_6H_5$ – $2CH_2CH_2$), 105 (100, $C_6H_5CH_2CH_2$), 91 (88, $C_6H_5CH_2$), 77 (64, C_6H_5), 65 (35, pyrazole), 43 (36, NCH_2CH_2 + H). Anal. Calcd for $C_{19}H_{28}N_2O_8$ (512.43): C, 74.97; H, 7.08; N, 5.46. Found: C, 74.95; H, 7.10; N, 5.48.

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Efficient Synthesis of Pyrrolo[2,1-*a*]isoquinoline and Pyrrolo[1,2-*a*]quinoline Derivatives in Aqueous Media

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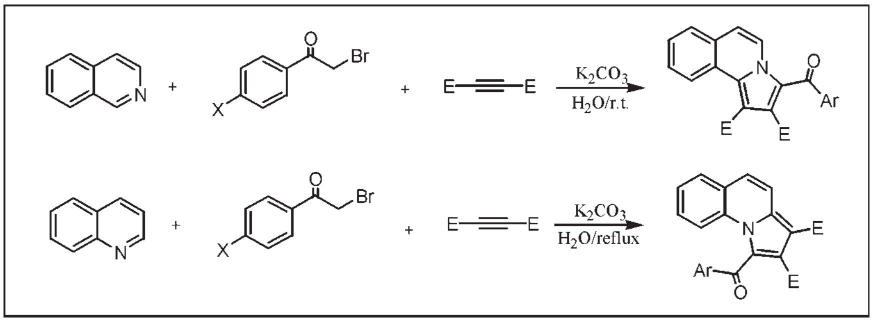

A one-pot procedure for the synthesis of pyrrolo[2,1-*a*]isoquinolines and pyrrolo[1,2-*a*]quinolines in good to excellent yields has been reported, using quinoline or isoquinoline, phenacylbromide derivatives and activated alkynes in aqueous medium.

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INTRODUCTION

The synthesis of indolizines, and their derivatives with additional rings fused like pyrrolo[2,1-*a*]isoquinolines and pyrrolo[1,2-*a*]quinolines, has puzzled scientists for decades. The interest in these compounds is largely owing to their properties. Synthetic indolizines are used as potential central nervous system depressants [1], calcium entry blockers [2], testosterone 5α-reductase inhibitors [3], cardiovascular agents [4], spectral sensitizers [5], and novel dyes [6]. Pyrrolo[2,1-*a*]isoquinoline derivatives [7] have attracted considerable interest, because they possess antidepressant [8], muscarinic agonist [9], antiplatelet [10], and anticancer activity [11]. Moreover, they can be used as Positron emission tomography (PET) radiotracers for imaging serotinine uptake sites [12]. The importance of these nitrogen heterocycles is further enhanced by their utility as advanced intermediates for the synthesis of alkaloids [13]. Acetoxy substituted 5,6-dihydro[2,1-*a*]isoquinolines (**1** in Fig. 1) exhibit strong binding affinities for the estrogen receptor of MDA-MB 231 and MCF-7 mammary tumor cell lines [14].

The parent framework of **1** (**2** in Fig. 1) is an α_2-adrenoreceptor antagonist[15] and its 5-phenyl derivatives exhibit antidepressant-like activity.[16] 1-benzoyl-3-cyano-pyrrolo[1,2-a]quinolines (**3** in Fig. 1) have been shown to be activators of caspases and inducers of apoptosis and also are used as therapeutically effective anticancer agents [17]. As a result, development of new methods to synthesize these classes of compounds is of considerable importance, and a number of general synthetic methods for their preparation have been reported [7,18].

The increasing environmental consciousness of the chemical community has led to the search for more efficient and environmentally friendly methods for chemical syntheses [19]. Because of the environmental acceptability, abundance, and low cost of water, organic reactions in water have received increased attention [20]. Many reactions that are traditionally carried out in organic solvent can be carried out in water with additional interesting features [21]. Thus, the development of efficient procedures for useful chemical transformations in water is highly appreciated.

RESULTS AND DISCUSSION

As part of our current studies on the development of ylide reactions in aqueous media [22], we report herein an efficient synthesis of pyrrolo[2,1-*a*]isoquinolines and pyrrolo[1,2-*a*]quinolines via a one-pot three component reaction of isoquinoline or quinoline with phenacylbromide derivatives and activated alkynes.

We began our study by investigating the reactivity of preformed salts, such as **4** or **5** as nitrogen ylide precursors (Scheme 1).

Treatment of salt **4** or **5** with activated acetylenes in water, in the presence of a base, formed compounds **6**, **7**, respectively, in good to excellent yields. The temperature was of crucial importance. No reaction was observed at room temperature with quinoline ylides and

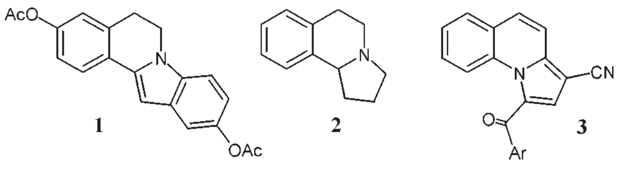


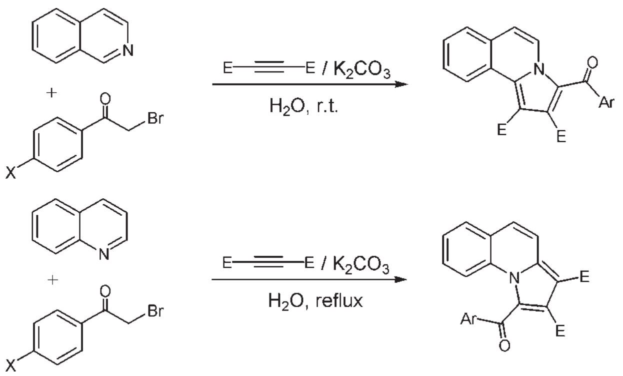
Figure 1. Chemical structures of **1**, **2**, and **3**.

all of the reactions were carried out at reflux. However, isoquinoline ylides produced the corresponding products in good to excellent yields at room temperature. To increase the efficiency of this process, we investigated the development of a one-pot reaction in which the salt and the ylide could be generated *in situ*, in water, from readily available starting materials. Accordingly, phenacylbromide derivative was added to isoquioline or quinoline in water, and after a while, activated alkyne and base were added to the reaction mixture, and the reaction continued at room temperature or at reflux (Scheme 2).

The use of optimal conditions to the reaction of quinoline and isoquinoline with different phenacylbromide derivatives and activated acetylenes afforded good to excellent yields of pyrrolo[2,1-*a*]isoquinolines and pyrrolo[1,2-*a*]quinolines. The results of this study are summarized in Tables 1 and 2.

The structures of all the synthesized compounds were established on the basis of their spectroscopic data. The ^{1}H NMR spectrum of **6d** exhibited two coupled pairs of triplet and quarted signals for ethoxy groups, centered at δ = 1.02, 1.43 ppm and δ = 3.83, 4.48 ppm, respectively. Methoxy group resonated at δ = 3.91 ppm as a single sharp line. The peaks corresponding to aromatic protons of methoxyphenyl moiety and protons of nitrogen containing ring of isoquinoline were seen as two coupled pairs of doublet signals at δ = 6.98, 7.86 ppm (J = 8.7 Hz) and δ = 7.12, 8.66 ppm (J = 7.5 Hz), respectively. Other aromatic protons gave rise to characteristic signals in the aromatic region of the spectrum. The proton decoupled ^{13}C NMR spectrum of **6d** showed 24 distinct resonances in agreement with the proposed structure. ^{1}H NMR spectrum of **7c** exhibited three sharp singlet signals readily recognized as arising from methoxy protons. (δ = 3.55, 3.90 and 3.93 ppm) Signals due to aromatic protons of methoxyphenyl moiety and protons of nitrogen containing ring of quinoline were discernible as two coupled pairs of doublet signals at δ = 6.98, 7.98 ppm (J = 8.7 Hz) and δ = 7.55, 8.22 ppm (J = 9.4 Hz). Other aromatic protons gave rise to characteristic signals in the aromatic region of the spectrum. The proton decoupled ^{13}C NMR spectrum of **7c** showed 22 distinct resonances in agreement with the proposed structure.

Scheme 2



Mechanistically, it is conceivable that the reaction involves the initial formation of ylide A by the reaction of isoquinoline (or quinoline) and phenacylbromide derivative followed by deprotonation in the presence of K_2CO_3 as the base. This ylide intermediate then undergoes reaction with activated alkynes to produce B, which leads to C by oxidation (Scheme 3).

In summary, a one-pot procedure for the synthesis of pyrrolo[2,1-*a*]isoquinolines and pyrrolo[1,2-*a*]quinolines via *in situ* formation of quinoline or isoquinoline ylides and reaction of with activated alkynes in aqueous media has been reported. The notable advantages offered by this method are simple operation, mild and environment friendly reaction conditions, high yields of products, and costeffectiveness. Most significantly, this demonstrates

Scheme 1

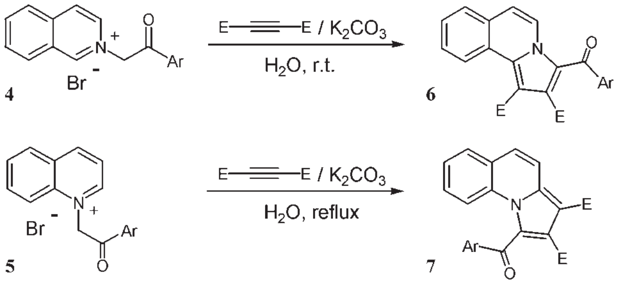


Table 1

Reaction of isoquinoline with phenacylbromide derivatives and activated alkynes in H_2O.

6	X	E	Time (h)	Yield (%)
a	H	CO_2Me	6	90
b	H	CO_2Et	6	85
c	4-OMe	CO_2Me	6	94
d	4-OMe	CO_2Et	6	93
e	4-Br	CO_2Me	6	87
f	4-Br	CO_2Et	7	83
g	4-Ph	CO_2Me	7	80
h	4-Ph	CO_2Et	7	80

Table 2

Reaction of quinoline with phenacylbromide derivatives and activated alkynes in H$_2$O.

7	X	E	Time (h)	Yield (%)
a	H	CO$_2$Me	14	77
b	H	CO$_2$Et	15	78
c	4-OMe	CO$_2$Me	12	82
d	4-OMe	CO$_2$Et	12	85
e	4-Br	CO$_2$Me	14	69
f	4-Br	CO$_2$Et	13	71
g	4-Ph	CO$_2$Me	14	86
h	4-Ph	CO$_2$Et	11	84

the potential of water as an efficient promoter and provides much promise for the use of water in other chemical transformations.

EXPERIMENTAL

^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Bruker DRX-500 NMR spectrometer using TMS as an internal standard. Mass spectrometry (MS) spectra were carried out on HP 5973 GC-MS instrument. Infrared (IR) spectra were measured using a Shimadzu FTIR-4300. Chemicals were purchased from Merck and were used as received. Column chromatography was performed on silica gel (0.063-0.200 mm; Merck).

General procedure for the preparation of compound 6a. Isoquinoline (0.19 g, 1.5 mmol) and phenacylbromide (0.3 g, 1.5 mmol) were taken in water (10 mL), and the mixture was stirred at room temperature for 2 h. To this mixture, dimethyl acetylenedicarboxylate (0.14 g, 1.0 mmol) and K$_2$CO$_3$ (0.28 g, 2.0 mmol) were added, and it was allowed to stir at room temperature for 4 h. The reaction mixture was filtered and purified by column chromatography on silica gel with eluent 10%EtOAc in hexane to afford **6a** as yellow solid.

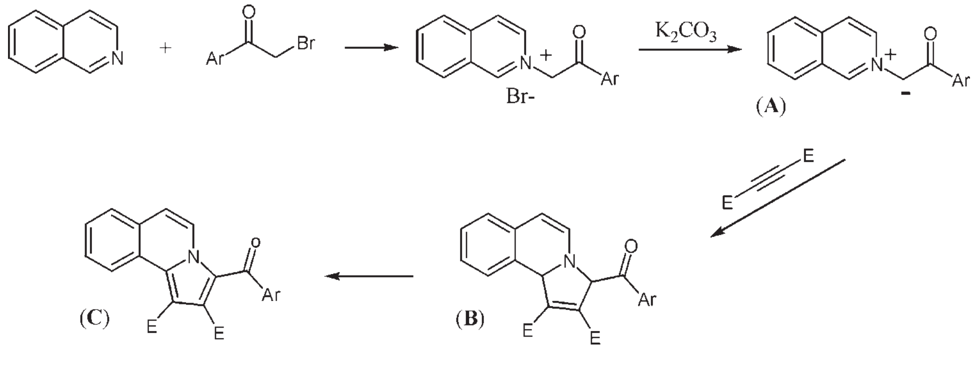
Compound (6a). Yellow solid; mp 154–155°C. IR (KBr) υ/cm^{-1}: 2951, 1749, 1709, 1624, 1518, 1492, 1475, 1398, 1363, 1269, 1225, 1201, 1101, 897, 866, 787 cm^{-1}. ^{1}H NMR: δ (ppm) 3.29 (s, 3H), 4.0 (s, 3H), 7.22 (d, J = 7.5 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.62 (m, 1H), 7.65 (m, 2H), 7.77 (m, 1H), 7.82 (dd, J = 7.1Hz, J = 1.3Hz, 2H), 8.91 (m, 1H), 8.94 (d, J = 7.5 Hz, 1H). ^{13}C NMR: δ (ppm) 52.3, 52.9, 110.0, 116.3, 123.4, 124.1, 124.7, 126.1, 127.6, 128.7, 128.8, 129.3, 129.5, 130.0, 132.8, 133.1, 140.2, 165.1, 166.4, 187.7. MS (EI, 70 eV) *m/z* (%) 387 (M^{+}, 100), 356 (57), 324 (58), 310 (20), 298 (11), 284 (22), 269 (16), 252 (10), 240 (21), 193 (10), 164 (14), 139 (10), 105 (19).

Compound (6b). Yellow solid; mp 115–117°C. IR (KBr) υ/cm^{-1}: 2991, 2876, 1728, 1622, 1527, 1500, 1404, 1354, 1227, 1198, 1101, 1020, 966, 919, 800 cm^{-1}. ^{1}H NMR: δ (ppm) 1.0 (t, J = 7.2 Hz, 3H), 1.39 (t, J = 7.2 Hz, 3H), 3.67 (q, J = 7.2 Hz, 2H), 4.46 (q, J = 7.2 Hz, 2H), 7.19 (d, J = 7.5 Hz, 1H), 7.49 (t, J = 7.53,2H), 7.59 (m, 1H), 7.63 (m, 2H), 7.74 (m, 1H), 7.84 (dd, J = 8.4Hz, J = 1.3Hz, 2H), 8.89 (d, J = 7.5 Hz, 1H), 8.90 (m, 1H). ^{13}C NMR: δ (ppm) 14.0, 14.4, 61.8, 62.0, 110.4, 116.2, 123.2, 124.1,124.8, 126.1, 127.6, 127.7, 128.7, 128.8, 129.4, 129.6, 130.0, 132.7, 133.2, 140.1, 164.7, 166.0, 187.6. MS (EI, 70 eV) *m/z* (%) 415 (M^{+}, 100), 387 (9), 370 (20), 343 (25), 324 (17), 298 (44), 279, 279 (10), 270 (19), 241 (21), 220 (12), 167 (23), 149 (53), 105 (23).

Compound (6c). Yellow solid; mp 137–138°C. IR (KBr) υ/cm^{-1}: 2953, 2841, 1734, 1708, 1620, 1600, 1572, 1504, 1396, 1362, 1313, 1259, 1222, 1201, 1101, 1026, 903, 839, 785 cm^{-1}. ^{1}H NMR: δ (ppm) 3.42 (s, 3H), 3.92 (s, 3H), 4.01 (s, 3H), 7.0 (d, J = 8.77 Hz, 2H), 7.15 (d, J = 7.5 Hz, 1H), 7.64 (m, 2H), 7.74 (m, 1H), 7.84 (d, J = 8.77 Hz, 2H), 8.7 (d, J = 7.5 Hz, 1H), 8.8 (m, 1H). ^{13}C NMR: δ (ppm) 52.4, 53.0, 56.0, 109.8, 114.2, 116.0, 123.9, 124.2, 124.9, 125.9, 127.6, 128.7, 129.3, 129.7, 131.9, 132.1, 132.7, 164.0, 165.1, 166.6, 186.4. MS (EI, 70 eV) *m/z* (%) 417 (M^{+}, 6), 387 (100), 356 (69), 324 (76), 310 (29), 298 (16), 284 (29), 269 (20), 252 (31), 240 (26), 167 (20), 149 (39), 105 (22).

Compound (6d). Yellow solid; mp 112–114°C. IR (KBr) υ/cm^{-1}: 2997, 1738, 1705, 1626, 1599, 1504, 1464, 1360, 1309, 1257, 1217, 1202, 1169, 1097, 1022,846, 796 cm^{-1}. ^{1}H NMR: δ (ppm) 1.02 (t, J = 7.16 Hz, 3H), 1.43 (t, J = 7.14 Hz, 3H), 3.84 (q, J = 7.15 Hz, 2H), 3.91 (s, 3H), 4.49 (q, J = 7.1 Hz 2H), 7.0 (d, J = 8.75 Hz,2H), 7.12 (d, J = 7.5 Hz, 1H)7.6 (m, 2H), 7.7 (m, 1H), 7.9 (d, J = 8.7 Hz, 2H), 8.66 (d, J = 7.53 Hz, 1H), 8.9 (dd, J = 7Hz, J=1.9 Hz, 1H). ^{13}C NMR: δ (ppm) 14.0, 14.4, 56.0, 61.7, 62.0, 110.2, 114.1, 115.8, 123.9, 124.0, 125.0, 125.9, 126.0, 127.6, 128.6, 129.1, 129.7, 132.0, 132.1, 132.7, 164.1, 164.7, 166.2, 186.4. MS (EI, 70 eV) *m/z* (%) 445 (M^{+}, 31), 415 (2), 400 (3), 328 (12), 311 (100), 266 (43), 238 (92), 211 (15), 194 (25), 167 (41), 149 (16), 139 (27), 128 (15).

Scheme 3



Compound (6e). Yellow solid; mp 142–144°C. IR (KBr) υ/cm^{-1}: 3004, 2842, 1740, 1732, 1624, 1585, 1504, 1398, 1360, 1263, 1225, 1201, 1176, 1097, 895, 831, 797 cm^{-1}. ^{1}H NMR: δ (ppm) 3.39 (s, 3H), 4.0 (s, 3H), 7.23 (d, J = .5 Hz, 1H), 7.67 (m, 6H), 7.77 (m, 1H), 8.90 (m, 1H), 8.91 (d, J = 7.5 Hz, 1H). ^{13}C NMR: δ (ppm) 52.5, 53.0, 110.3, 116.5, 122.9, 124.0, 124.7, 126.2, 127.7, 128.0, 128.9, 129.6, 130.1, 130.9, 132.1, 133.0, 139.0, 164.9, 166.2, 186.4. MS (EI, 70 eV) *m/z* (%) 467 (M^{+}, ^{81}Br, 100), 465 (M^{+}, ^{79}Br, 99), 436 (27), 434 (27), 404 (22), 402 (18), 324 (33), 310 (26), 297 (13), 240 (21), 213 (21), 185 (39), 183 (39), 155 (24).

Compound (6f). Yellow solid; mp 125–126°C. IR (KBr) υ/cm^{-1}: 2363, 1722, 1628, 1585, 1516, 1473, 1450, 1400, 1354, 1263, 1196, 1097, 1068, 1030, 960, 916, 833, 796 cm $^{-1}$. ^{1}H NMR: δ (ppm) 1.10 (t, J = 7.1 Hz, 3H), 1.42 (t, J = 7.1 Hz, 3H), 3.80 (q, J = 7.1 Hz, 2H), 4.49 (q, J = 7.1 Hz, 2H), 7.22 (d, J = 7.5 Hz, 1H), 7.66 (m, 4H), 7.72 (d, J = 8.5 Hz, 2H), 7.77 (m, 1H), 8.89 (d, J = 7.5 Hz, 1H), 8.92 (m, 1H). ^{13}C NMR: δ (ppm) 14.0, 14.4, 62.0, 62.1, 110.7, 116.4, 122.8, 124.0, 124.8, 126.2, 127.6, 127.7, 128.1, 128.8, 129.5, 130.0, 131.1, 132.1, 132.8, 139.0, 164.6, 165.9, 186.4. MS (EI, 70 eV) *m/z* (%) 495 (M^{+}, ^{81}Br, 100), 493 (M^{+}, ^{79}Br, 99), 450 (13), 448 (14), 421 (27), 376 (28), 348 (17), 297 (29), 264 (19), 238 (36), 220 (24), 199 (18), 183 (24), 164 (17), 149 (21), 139 (16), 128 (14).

Compound (6g). Yellow solid; mp 174–176°C. IR (KBr) υ/cm^{-1}: 2945, 1727, 1720, 1637, 1603, 1502, 1479, 1358, 1273, 1230, 1201, 1176, 1101, 897, 869, 820 cm^{-1}. ^{1}H NMR: δ (ppm) 3.35 (s, 3H), 4.01 (s, 3H), 7.22 (d, J = 7.5 Hz, 1H), 7.46 (m, 1H), 7.53 (t, J = 7.3 Hz, 2H), 7.66 (m, 2H), 7.69 (d, J = 7.3Hz,2H), 7.76 (m, 3H), 7.91 (d, J = 8.2 Hz, 2H), 8.8 (m, 1H), 8.90 (m, 1H), 8.91 (d, J = 7.5 Hz, 1H). ^{13}C NMR: δ (ppm) 52.4, 53.0, 110.1, 116.3, 123.6, 124.1, 124.8, 126.1, 127.3, 127.4, 127.6, 127.7, 128.7,128.8, 129.4, 129.5, 130.0, 130.1, 132.7, 138.9, 140.2, 145.9, 165.1, 166.4, 187.2. MS (EI, 70 eV) *m/z* (%) 463(M^{+}, 100), 432 (22), 400 (45), 387 (13.4), 374 (7.1), 360 (13), 345 (8), 310 (18), 252 (7), 218 (8), 194 (10), 181 (18), 152 (35).

Compound (6h). Yellow solid; mp 149–150°C. IR (KBr) υ/cm^{-1}: 2956, 2854, 1736, 1711, 1624, 1604, 1524, 1501, 1470, 1371, 1352, 1221, 1097, 1020, 920, 800 cm $^{-1}$. ^{1}H NMR: δ (ppm) 1.01 (t, J = 7.1 Hz, 3H), 1.43 (t, J = 7.1 Hz, 3H), 3.77 (q, J = 7.1 Hz, 2H), 4.49 (q, J = 7.1 Hz, 2H), 7.21 (d, J = 7.5 Hz, 1H), 7.46 (m, 1H), 7.53 (m, 2H), 7.67 (m, 4H), 7.74 (d, J = 8.2 Hz, 2H), 7.77 (m, 1H), 7.95 (d, J = 8.2 Hz, 2H), 8.89 (d, J = 7.5 Hz, 1H), 8.91 (m, 1H) ppm. ^{13}C NMR: δ (ppm) 14.0, 14.4, 61.9, 62.0, 110.6, 116.2, 123.4, 124.1, 124.9, 126.1, 127.3, 127.4, 127.6, 127.7, 128.71, 128.73, 129.36, 129.44, 129.9, 130.3, 132.5, 138.9, 140.2, 146.0, 164.7, 166.1, 187.2 ppm. MS (EI, 70 eV) *m/z* (%) 491 (M^{+}, 52), 463 (9), 400 (13), 374 (16), 279 (11), 198 (17), 181 (46), 167 (29), 149 (60), 125 (28), 111 (44), 97 (61), 83 (59), 71 (76).

Compound (7a). Yellow solid; mp 158–160°C. IR (KBr) υ/cm^{-1}: 2993, 2360, 1730, 1697, 1633, 1612, 1550, 1491, 1450, 1418, 1362, 1323, 1259, 1219, 1171, 1093, 877, cm^{-1}. ^{1}H NMR: δ (ppm) 3.48 (s, 3H), 3.95 (s, 3H), 7.47 (m, 2H), 7.54 (t, J = 7.59 Hz, 2H), 7.68 (m, 3H), 7.83 (m, 1H), 8.01 (d, J = 7.6 Hz, 2H), 8.30 (d, J = 9.43 Hz, 1H) ppm. ^{13}C NMR: δ (ppm) 52.1, 52.6, 106.0, 118.4, 119.5, 125.7, 126.1, 126.9, 128.4, 129.1, 129.4, 129.5, 129.6, 130.3, 132.9, 134.3, 137.6, 138.1, 164.1, 165.5, 188.2. MS (EI, 70 eV) *m/z* (%) 387 (M^{+}, 34), 356 (10), 330 (75), 298 (61), 283 (96), 252 (100), 241 (17), 222 (34), 194 (18), 166 (35), 139 (14), 128 (13), 105 (60), 77 (41).

Compound (7b). Yellow solid; mp 154–156°C. IR (KBr) υ/cm^{-1}: 2975, 1730, 1697, 1634, 1612, 1556, 1494, 1437, 1392, 1323, 1237, 1213, 1167, 1095, 874 cm^{-1}. ^{1}H NMR: δ (ppm) 1.11 (t, J = 7.2 Hz, 3H), 1.41 (t, J = 7.2 Hz, 3H), 3.90 (q, J = 7.2 Hz, 2H), 4.41 (q, J = 7.2 Hz, 2H), 7.4 (m, 2H), 7.46 (t, J = 7.7 Hz, 2H), 7.62 (d, J = 9.4 Hz, 1H),7.67 (m, 2H), 7.8 (m, 1H), 8.03 (d, J = 7.3 Hz, 2H), 8.30 (d, J = 9.4 Hz, 1H). ^{13}C NMR: δ (ppm) 14.1, 14.7, 60.9, 62.0, 106.2, 118.3, 119.4, 125.7, 126.0, 128.3, 128.6, 129.1, 129.3, 129.6, 130.5, 132.9, 134.3, 137.6, 138.1, 163.7, 165.2, 188.1. MS (EI, 70 eV) *m/z* (%) 415 (M^{+}, 100), 387 (5), 370 (30), 343 (19), 324 (14), 312 (16), 298 (59), 270 (35), 241 (35), 220 (26), 194 (12), 164 (15), 128 (113), 105 (50), 77 (50).

Compound (7c). Yellow solid; mp 169–172°C. IR (KBr) υ/cm^{-1}: 2949, 1724, 1710, 1649, 1597, 1573, 1508, 1448, 1421, 1323, 1259, 1213, 1174, 1091, 889cm^{-1}. ^{1}H NMR: δ (ppm) 3.55 (s, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 6.98 (d, J = 8.8 Hz, 2H), 7.41 (m, 2H), 7.55 (d, J = 9.4 Hz, 1H), 7.68 (m, 1H), 7.75 (m,1H), 7.98 (d, J = 8.7 Hz, 2H), 8.22 (d, J = 9.4 Hz, 1H) ppm. ^{13}C NMR: δ (ppm) 52.1, 52.7, 56.0, 105.8, 114.4, 118.3, 119.2, 125.6, 126.0, 126.9, 127.1, 127.8, 129.3, 129.6, 130.9, 132.8, 132.9, 137.0, 164.2, 164.8, 165.6, 187.2. MS (EI, 70 eV) *m/z* (%) 417 (M^{+}, 65), 386 (11), 354 (25), 328 (18), 298 (13), 287 (24), 179 (14), 252 (18), 228 (13), 167 (36), 149 (92), 135 (85), 111 (27),97 (40), 83 (48).

Compound (7d). Yellow solid; mp 166–168°C. IR (KBr) υ/cm^{-1}: 2980, 1716, 1702, 1643, 1597, 1577, 1508, 1441, 1257, 1217, 1173, 1093, 877 cm^{-1}. ^{1}H NMR: δ (ppm)1.13 (t, J = 7.2Hz, 3H), 1.4 (t, J = 7.2 Hz, 3H), 3.99 (q, J = 7.2 Hz, 2H), 4.41 (q, J = 7.2 Hz, 2H), 7.0 (d, J = 8.8 Hz, 2H), 7.44 (m, 2H), 7.58 (d, J = 9.4 Hz, 1H), 7.70 (m, 1H), 7.79 (m, 1H), 8.0 (d, J = 8.7 Hz, 2H), 8.29 (d, J = 9.4 Hz, 2H). ^{13}C NMR: δ (ppm) 14.1, 14.7, 56.0, 60.9, 62.0, 106.0, 114.4, 118.4, 119.2, 125.7, 125.9, 126.8, 127.2, 127.7, 129.3, 129.6, 131.0, 132.9, 137.1, 163.8, 164.8, 165.2, 187.2. MS (EI, 70 eV) *m/z* (%) 445 (M^{+}, 100), 400 (19), 354 (13), 328 (21), 300 (17), 266 (15), 238 (16), 220 (14), 167 (16), 149 (37), 135 (62), 107 (12), 97 (12),77 (17).

Compound (7e). Yellow solid; mp 194–195°C. IR (KBr) υ/cm^{-1}: 2852, 1742, 1693, 1651, 1583, 1543, 1477, 1446, 1392, 1267, 1207, 1102, 1095, 885, 810 cm $^{-1}$. ^{1}H NMR: δ (ppm) 3.55 (s, 3H), 3.95 (s, 3H), 7.48 (m, 2H), 7.64 (m, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.82 (m, 1H), 7.87 (d, J = 8.4 Hz, 2H), 8.28 (d, J = 9.4 Hz, 1H). ^{13}C NMR: δ (ppm) 52.2, 52.8, 106.1, 118.3, 119.3, 125.7, 126.2, 126.3, 128.60, 128.62, 129.5, 129.6, 129.7, 131.7, 132.4, 132.8, 136.9, 137.7, 164.0, 165.5, 187.0. MS (EI, 70 eV) *m/z* (%) 467 (M^{+}, ^{81}Br, 100), 465 (M^{+}, ^{79}Br, 99), 434 (21), 406 (18), 347 (8), 324 (18), 310 (47), 252 (22), 239 (19), 193 (14), 183 (20), 167 (21), 149 (42), 97 (21), 83 (23), 71 (34).

Compound (7f). Yellow solid; mp 150–152°C. IR (KBr) υ/cm^{-1}: 2937, 1716, 1695, 1645, 1581, 1544, 1483, 1434, 1400, 1342, 1300, 1257, 1225, 1093, 889cm^{-1}. ^{1}H NMR: δ (ppm) 1.15 (t, J = 7.2 Hz, 3H), 1.4 (t, J = 7.2Hz, 3H), 3.97 (q, J = 7.2 Hz, 2H), 4.42 (q, J = 7.2 Hz, 2H), 7.49 (m,2H), 7.63 (m, 2H), 7.68 (d, J = 8.5 Hz, 2H), 7.84 (m, 1H), 7.90 (d, J = 8.5 Hz, 2H), 8.32 (d, J = 9.4 Hz, 1H). ^{13}C NMR: δ (ppm) 14.1, 14.7, 61.0, 62.1, 106.3, 118.3, 119.3, 125.7, 126.0, 126.2, 128.5, 128.9, 129.4, 129.6, 129.7, 131.8, 132.4, 132.8, 136.9, 137.7, 163.5, 165.1, 186.9. MS (EI, 70 eV) *m*/*z* (%) 495 (M^+, ^{81}Br, 100), 493 (M^+, ^{79}Br, 96), 450 (13), 422 (13), 376 (22), 348 (16), 297 (17), 266 (28), 238 (44), 220 (25), 183 (25), 166 (14), 155 (18), 128 (16), 97 (15).

Compound (7g). Yellow solid; mp 164–165°C. IR (KBr) υ/ cm^{-1}: 2954, 1745, 1707, 1637, 1604, 1554, 1477, 1444, 1361, 1325, 1259, 1213, 1095, 883, 744 cm $^{-1}$. ^{1}H NMR: δ (ppm) 3.53 (s, 3H), 3.97 (s, 3H), 7.47 (m, 3H), 7.53 (m, 2H), 7.65 (d, $J = 9.4$ Hz, 1H), 7.70 (d, $J = 7.4$ Hz, 2H), 7.75 (m, 1H), 7.77 (d, $J = 8.3$ Hz, 2H), 7.83 (m, 1H), 8.10 (d, $J = 8.3$ Hz, 2H), 8.30 (d, $J = 9.4$ Hz, 1H). ^{13}C NMR: δ (ppm) 52.2, 52.7, 106.0, 118.4, 119.5, 125.7, 126.1, 127.0, 127.70, 127.74, 128.1, 128.3, 128.9, 129.5, 129.7, 131.0, 133.0, 136.8, 137.5, 140.0, 147.0, 164.1, 165.6, 187.8. MS (EI, 70 eV) *m*/*z* (%) 463 (M^+, 53), 432 (6), 400 (8), 283 (86), 252 (92), 222 (27), 181 (17), 167 (30), 149 (69), 135 (46), 125 (24), 111 (39), 97 (59), 83 (58), 71 (72), 57 (100).

Compound (7h). Yellow solid; mp 139–142°C. IR (KBr) υ/ cm^{-1}: 2902, 1725, 1703, 1639, 1600, 1547, 1483, 1435, 1301, 1342, 1255, 1220, 1184, 1110, 1056, 976,891, 852cm^{-1}. ^{1}H NMR: δ (ppm)1.12 (t, $J = 7.2$ Hz, 3H), 1.4 (t, $J = 7.2$Hz, 3H), 4.0 (q, $J = 7.2$ Hz, 2H), 4.4 (q, $J = 7.2$ Hz, 2H), 7.46 (m, 3H), 7.53 (t, $J = 7.5$Hz, 2H), 7.64 (d, $J = 9.4$ Hz, 1H), 7.68 (d, $J = 7.4$ Hz, 2H), 7.73 (m, 1H), 7.76 (d, $J = 8.2$ Hz, 2H), 7.83 (m, 2H), 8.11 (d, $J = 8.2$ Hz, 2H), 8.33 (d, $J = 9.4$ Hz, 1H). ^{13}C NMR: δ (ppm) 14.1, 14.7, 60.9, 62.0, 106.2, 118.4, 119.4, 125.7, 126.0, 126.7, 127.68, 127.72, 128.1, 128.3, 128.9, 129.4, 129.5,129.6, 131, 133.0, 136.9, 137.5, 140.1, 147.0,163.7, 165.2, 187.8. MS (EI, 70 eV) *m*/*z* (%) 491 (M^+, 100), 463 (2), 446 (15), 400 (13), 374 (20), 346 (17), 311 (31), 259 (28), 238 (42), 220 (17), 181 (34), 166 (16), 152 (49), 139 (113), 97 (17), 83 (20).

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An Efficient Procedure for the Synthesis of Substituted Pyridines Using KF·Al_2O_3

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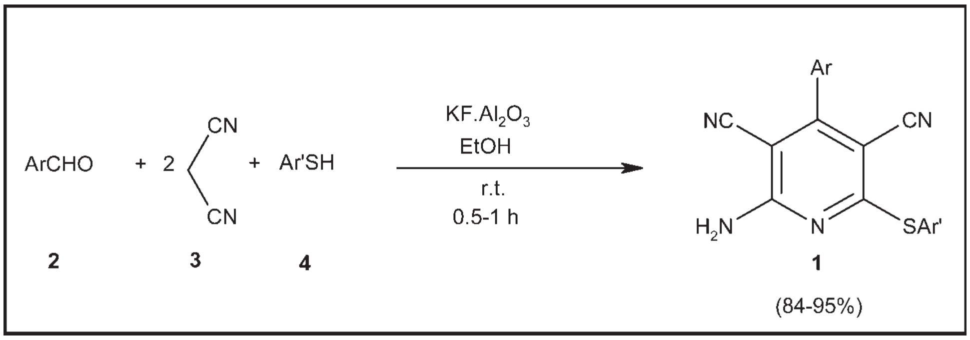

Three-component coupling of aldehydes, malononitrile, and thiophenols has efficiently been carried out at room temperature using potassium fluoride on alumina (KF·Al_2O_3) as a catalyst to furnish highly substituted pyridines in high yields.

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INTRODUCTION

Pyridine moiety in highly substituted form is frequently observed in various bioactive compounds [1–3]. This ring exists in both naturally occurring and synthetic drugs. The substituted pyridines of the common structure **1** possess significant antibacterial and anti-infective properties [4] and are useful for the development of other bioactive agents [5]. Thus, a number of methods for the synthesis of substituted pyridines have been reported [6–14]. One of the convenient methods involving three-component coupling of aldehydes, malononitrile, and thiols using bases, such as 1,4-diaza bicyclo [2,2,2,] octane and Et_3N, in ethanol under reflux led to the direct formation of **1** [8]. However, the yields of the products are unsatisfactory (20–48%), and the reactions are conducted at high temperature. The yields were improved by performing the reaction in the presence of an oxidizing agent [9]. Very recently, the similar method using ionic liquid has also been reported [12].

RESULTS AND DISCUSSION

In continuation of our work [15–17] on the development of useful synthetic methodologies, we have observed that the condensation of aldehydes, malononitrile, and thiols can efficiently be accomplished using potassium fluoride on alumina (KF·Al_2O_3) to produce the substituted pyridines at room temperature. (Scheme 1).

A series of 2-amino-4-aryl-3,5-dicyano-6-sulfanyl pyridines have been prepared from various aromatic aldehydes following the aforementioned procedure (Table 1). The aldehydes containing both electron-donating and electron-withdrawing groups underwent the conversion smoothly. Different functionalities, such as hydroxyl, ether, halogen, and nitro, remained unchanged. The conversion was complete within 0.5–1 h and the substituted pyridines were formed in high yields (84–95%). However, with aliphatic aldehydes and thiols, the reaction was not successful. The structures of the products were established from their spectral (^{1}H NMR, IR, and MS) data.

KF·Al_2O_3 has recently emerged as a valuable solid-phase catalyst for various organic transformations [18,19]. It possesses interesting catalytic activity. It can easily be handled and removed from the reaction mixture. It has been used here for the first time for the

Scheme 1

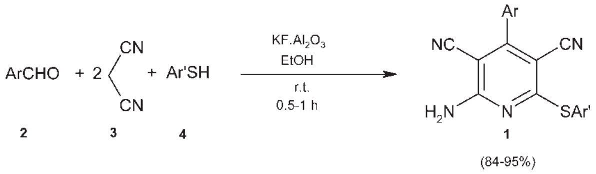


Table 1

Synthesis of substituted pyridines using KF·Al_2O_3.[a]

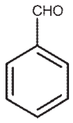
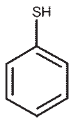
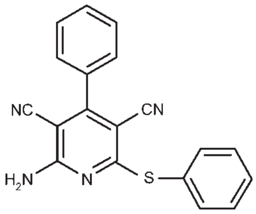
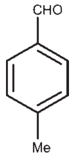
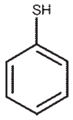
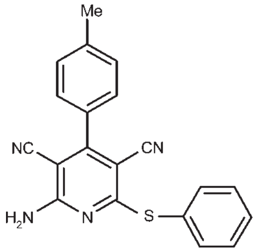
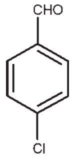
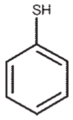
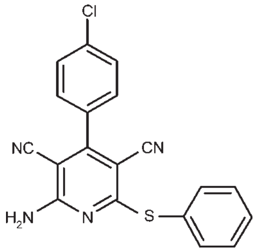
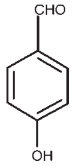
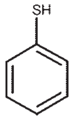
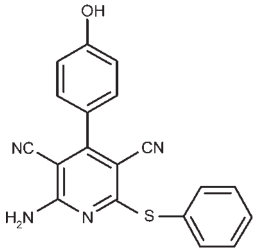
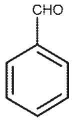
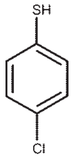
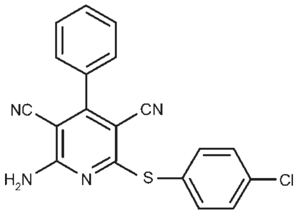
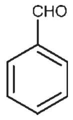
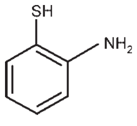
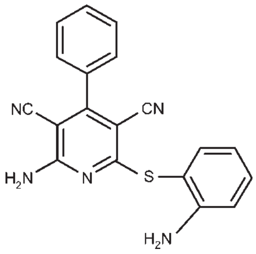
Entry	Aldehyde (**2**)	Thiol (**3**)	Product (**1**)	Time (min)	Isolated yield (%)	Mp (°C) [reference]
a				30	87	216–218 [11]
b				40	90	208–211 [11]
c				35	92	222–224 [11]
d				40	88	315–316 [11]
e				30	90	228–230 [11]
f				35	85	224–225 [11]

Table 1
(*Continued*)

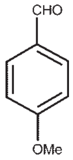
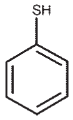
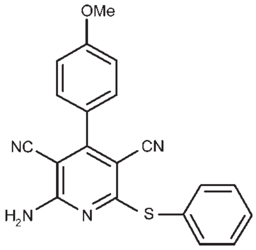
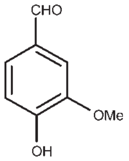
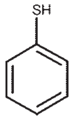
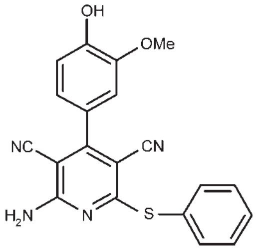
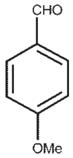
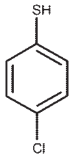
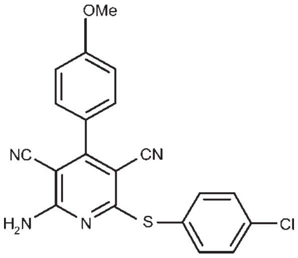
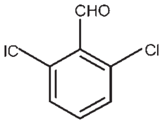
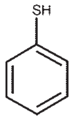
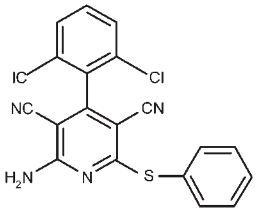
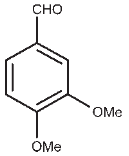
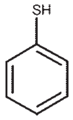
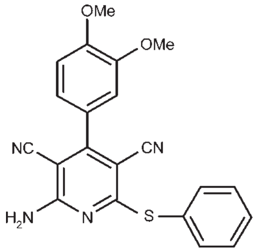
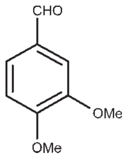
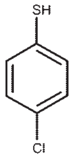
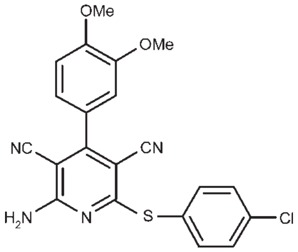
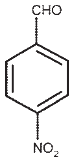
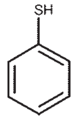
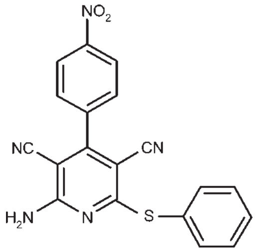
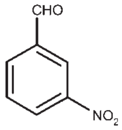
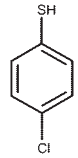
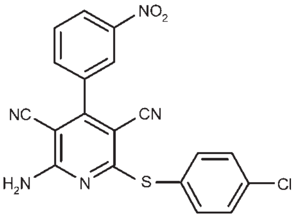
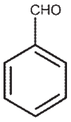
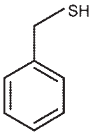
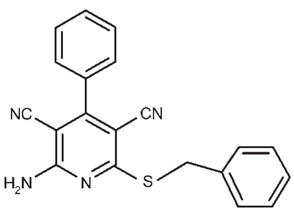
Entry	Aldehyde (**2**)	Thiol (**3**)	Product (**1**)	Time (min)	Isolated yield (%)	Mp (°C) [reference]
g				50	89	238–240 [11]
h				30	92	218–220 [11]
i				40	87	252–254
j				30	95	319–320 [11]
k				35	91	261–263 [10]
l				40	95	273–275

Table 1
(*Continued*)

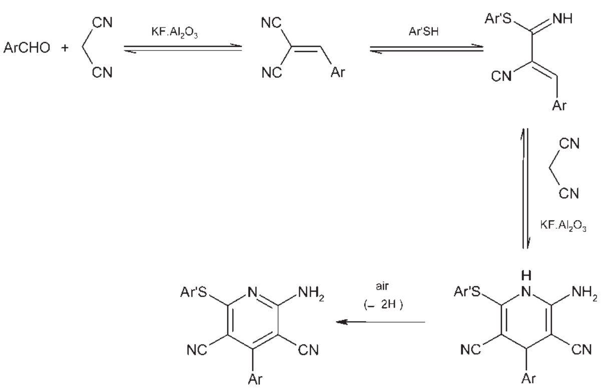
Entry	Aldehyde (**2**)	Thiol (**3**)	Product (**1**)	Time (min)	Isolated yield (%)	Mp (°C) [reference]
m				55	84	287–289 [11]
n				60	85	279–281
o				45	90	193–195 [11]

[a] The structures of the products were settled from their spectral (^1H NMR, IR, and MS) values.

preparation of substituted pyridines. In the absence of this catalyst, the reaction did not proceed.

The formation of substituted pyridines in impressive yields in the present reaction can be explained by a mechanism (Scheme 2) related to that described by Ranu *et al.* [12] for their high-yielding synthesis of pyridines through a similar reaction in the presence of a basic ionic liquid. In both the cases, air played the role of an oxidant under the reaction conditions, and no additional oxidant was required [9,11,12].

Scheme 2



In conclusion, we have improved the process of synthesis of the substituted pyridines from aldehydes, malononitrile, and thiols using KF·Al_2O_3 at room temperature. The use of (i) inexpensive solid-phase catalyst, (ii) mild reaction conditions, (iii) impressive yields, and (iv) operational simplicity are the notable advantages of the present procedure.

General Procedure for the Synthesis of Substituted Pyridines. To a mixture of an aldehyde (0.5 mmol), malononitrile (1 mmol) and thiophenol (0.5 mmol) dissolved in EtOH (5 mL) KF·Al_2O_3 (prepared by reported method [15]) (10 mol%) was added, and the mixture was stirred at room temperature. The reaction was monitored by thin layer chromatography. After completion, the mixture was filtered, and the filtrate was concentrated. The residue was purified by column chromatography (silica gel, hexane-EtOAc) to obtain pure pyridine derivative.

The spectral (IR, ^1H NMR, and MS) data of the unknown products are given.

1i: IR (KBr): 3427, 2209, 1614, 1543 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$$^+$ DMSO-d$_6$): δ 7.60–7.41 (6H, m), 7.04 (2H, d, J = 8.0 Hz), 6.89 (2H, brs), 3.90 (3H, s); FABMS: *m/z* 415, 417 [M+Na]$^+$. Anal. Calcd. for $C_{20}H_{13}ClN_4OS$: C 61.14, H 3.31, N 14.26; Found: C 61.82, H 3.43, N 14.38.

1l: IR (KBr): 3425, 2212, 1621, 1546 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$$^+$ DMSO-d$_6$): δ 7.56 (2H, d, J = 8.0 Hz), 7.42 (2H, d, J = 8.0 Hz), 7.15 (1H, dd, J = 8.0, 2.0 Hz), 7.06 (1H, d, J = 2.0 Hz), 7.02 (1H, d, J = 8.0 Hz), 6.79 (2H, brs), 3.96 (3H, s); 3.92 (3H, s); FABMS: *m/z* 445, 447 [M+Na]$^+$. Anal. Calcd. for $C_{21}H_{15}ClN_4O_2S$: C 59.64, H 3.55, N 13.25; Found: C 59.84, H 3.67, N 13.13.

1n: IR (KBr): 3417, 2214, 1638, 1551 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$$^+$ DMSO-d$_6$): δ 8.50–8.36 (2H, m), 7.95–7.80 (2H, m), 7.54 (2H, d, J = 8.0 Hz), 7.45 (2H, d, J = 8.0 Hz), 7.28 (2H, brs); FABMS: *m/z* 430, 432 [M+Na.]$^+$. Anal. Calcd. for $C_{19}H_{10}ClN_5O_2S$: C 55.95, H 2.45, N 17.17; Found: C 56.32, H 2.57, N 17.28.

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Synthesis of Imidacloprid Analogues from Novel Chloronicotinaldehydes

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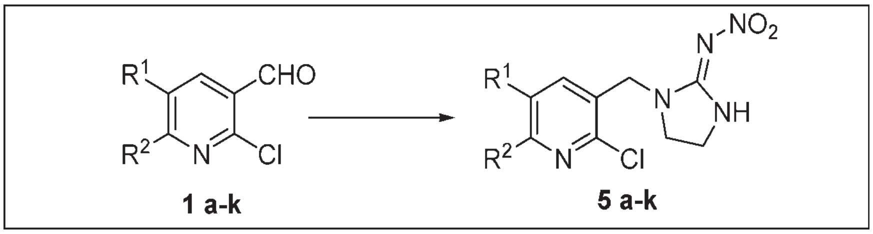

A serious of imidacloprid analogues have been synthesized from novel chloronicotinaldehydes. The chloronicotinaldehydes are the important synthons obtained from Vilsmeier reaction of various enamides. Thus synthesized imidacloprid analogues are new heterocyclic compounds obtained in very good yields.

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INTRODUCTION

Neonicotinoids [1] are used worldwide for controlling insects because of their low mammalian toxicity, potency, and broad insecticidal and systemic properties. Imidacloprid (Fig. 1) is a new systemic insecticide for crop protection [2], and it is the first chloronicotinyl nonnatural insecticide, which consists of 2-(*N*-nitroimino)imidazolidine coupled with (6-chloropyridin-3-yl)methyl (CPM) residue [3]. It belongs to chloronicotinyl subclass of nicotinoids, which are a novel and distinct chemical class of insecticides with remarkable chemical and biological properties. It has a novel mode of action—binding to the nicotinergic acetylcholine receptor in the postsynaptic region of the insect nerve. Because of the importance of neonicotinoids, several imidacloprid analogues has been synthesized and reported in the literature [4].

Synthesis of large number of new heterocyclic molecules and their bioevaluation in agrochemical and pharmaceutical areas is the worldwide current interest. Discovery of new insecticides is an ongoing process and challenging area for organic chemists. Because of our continuous interest on synthesis of bioactive heterocyclic molecules [5a–g], we report the synthesis of novel imidacloprid derivatives from the substituted chloronicotinaldehydes in very good yields.

RESULTS AND DISCUSSION

The imidacloprid analogues reported in this article are synthesized from substituted chloronicotinaldehydes by Vilsmeier reaction of various enamide substrates according to our earlier reported method [5a]. Thus, prepared chloronicotinaldehydes were an important synthons used for various organic transformations such as synthesis of 2-chloro-5-methylpyridine-3-carbaldehydeimines (Schiff bases) [5b], Baylis-Hillman adducts [5e], reactions with cyclic enones [5c], and conversion of Baylis-Hillman adducts to synthesis of biologically important quinolines [5d]. As mentioned in the Scheme 1, the carboxaldehydes (**1a–k**) were subjected for reduction using sodium borohydride in methanol to give corresponding alcohols (**2a–k**). Under these reaction conditions, all the aldehydes (**1a–k**) were smoothly converted to alcohols (**2a–k**) without disturbing other functional groups present in the compounds. These alcohols (**2a–k**) were then converted to corresponding chlorides (**3a–k**) by using thionyl chloride, with catalytic amounts of dimethylformamide (DMF) as chlorinating agent in heptane solvent. The DMF used in catalytic amounts enhances the rate of reaction, subsequently, the reaction proceeds efficiently because of the formation of a complex between thionyl chloride and DMF, which actually acts as chlorinating agent.

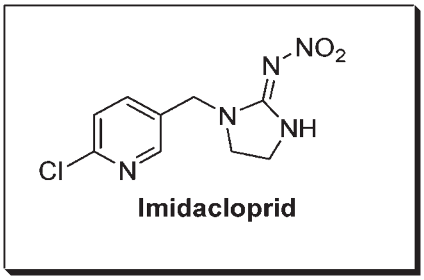


Figure 1. Imidacloprid.

The formed chlorides (**3a–k**) were allowed to react with nitroimino imidazole moiety (**4**) in acetonitrile using potassium carbonate and CsCl (5 mol%) under reflux conditions to give corresponding imidacloprid analogues (**5a–k**, Scheme 2) in very good yields. Thus prepared imidacloprid analogues (**5a–k**) are new compounds and are characterized by spectral data.

The 2-nitroiminoimidazole (**4**) is synthesized from ethylenediamine and nitroguanidine in the presence of hydrochloric acid as per our reported procedure [6]. In conclusion, the imidacloprid analogues have been synthesized from chloronicotinaldehydes in very good yields. Thus prepared new heterocyclic compounds are well characterized by spectral data. To achieve these target molecules, the important synthons such as chloronicotinaldehydes and nitraminoimidazolidine were used to complete the imidacloprid analogues.

EXPERIMENTAL

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian, Gemini 200 and Avance 300 MHz spectrometer in $CDCl_3$ with TMS as internal standard. Infrared (IR) spectra were recorded on Nicollet 740 FT spectrometer. EI-MS obtained on 7070H spectrometer operating at 70 eV using a direct inlet system. Melting points were determined in open glass capillary tubes on a Metler FP 51 melting point apparatus and are uncorrected. The CHN analyses were recorded on Vario EL analyzer. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F_{254} (mesh); spots were visualized under UV light. Merck silica gel (60–120; 100–200 mesh) was used for chromatography.

General procedure for the synthesis of 2-chloro-5/6-substituted pyridyl methanol (2a–k). Methyl 6-chloro-5-formyl-2-pyridinecarboxylate (**1j**; 200 mg, 0.0012 mol) was dissolved in methanol solvent, and sodium borohydride (15 mg, 0.00039 moles) was added slowly at 0°C over a period of 15 min. The reaction was monitored by TLC, and after completion of the reaction, the reaction mixture was quenched with saturated ammonium chloride solution, solvent was removed under reduced pressure, and the residue was extracted with dichloromethane and obtained methyl-6-chloro-5-(hydroxymethyl)-2-pyridinecarboxylate (**2j**) on column chromatography. All the alcohols were synthesized by using the similar procedure.

(2-Chloro-5-methyl-3-pyridyl)methanol (2a). Yield: 92%, solid; mp: 59–61°C. ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H, CH_3), 4.73 (s, 2H, -CH_2OH), 7.66 (s, 1H, heteroaromatic), 8.07 (s, 1H, heteroaromatic). EI-MS (*m/z*): 157 (90) (M^+), 142 (23), 130 (9), 122 (100), 106 (20), 99 (4), 92 (57), 78 (10), 65 (25), 51 (8), 39 (14), 31 (3). UV: $\lambda_{max} = 268$ nm in acetonitrile. IR (KBr): ν = 3325, 2969, 2932, 2874, 1568, 1432, 1399, 1355, 1164, 1083, 1044, 904, 731 cm^{-1}. Anal. Calcd for C_7H_8ClNO: C, 53.35; H, 5.12; N, 8.89. Found: C, 53.39; H, 5.19; N, 8.72.

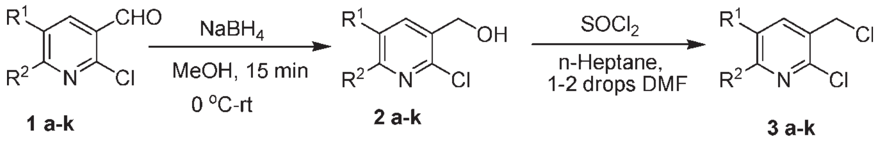
(2-Chloro-5-ethyl-3-pyridyl)methanol (2b). Yield: 91%, solid; mp: 62–64°C. ^{1}H NMR ($CDCl_3$): δ 1.31 (t, 3H, CH_3), 2.65 (q, 2H, CH_2), 4.75 (s, 2H, CH_2OH), 7.73 (s, 1H, heteroaromatic), 8.09 (s, 1H, heteroaromatic). EI-MS (*m/z*): 171 (50) (M^+), 174 (40), 154 (100), 140 (5), 91 (20), 77 (15). UV: $\lambda_{max} = 272$ nm in acetonitrile. IR (KBr): ν = 3330, 2960, 2935, 2870, 1575, 1340, 1160, 1090, 1040, 906, 735 cm^{-1}. Anal. Calcd for $C_8H_{10}ClNO$: C, 55.99; H, 5.87; N, 8.18. Found: C, 56.02; H, 5.84; N, 8.21.

(2-Chloro-5-propyl-3-pyridyl)methanol (2c). Yield: 90%, solid; mp: 64–65°C. ^{1}H NMR ($CDCl_3$): δ 0.9 (t, 3H, CH_3), 1.7 (m, 2H, CH_2), 2.64 (t, 2H, CH_2), 4.75 (s, 2H, CH_2OH), 7.73 (s, 1H, heteroaromatic), 8.09 (s, 1H, heteroaromatic). EI-MS (*m/z*): 185.

(2-Chloro-5-isopropyl-3-pyridyl)methanol (2d). Yield: 90%, solid; mp: 70–72°C. ^{1}H NMR ($CDCl_3$): δ 1.2–1.4 (m, 6H, 2CH_3), 3.20 (m, 1H, CH), 4.75 (s, 2H, CH_2OH), 7.73 (s, 1H, heteroaromatic), 8.09 (s, 1H, heteroaromatic). EI-MS (*m/z*): 185.

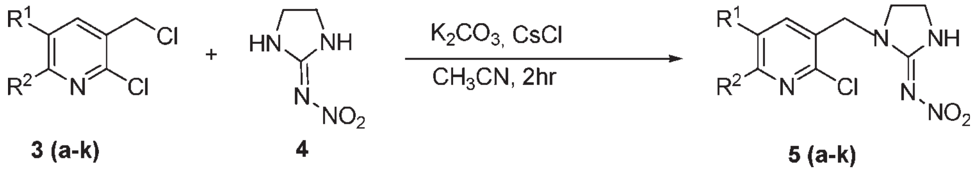
(2-Chloro-5-pentyl-3-pyridyl)methanol (2e). Yield: 87%, solid; mp: 58–60°C. ^{1}H NMR ($CDCl_3$): δ 0.9 (t, 3H, CH_3),

Scheme 1



1a = **2a** = **3a**: R^1 = Me; R^2 = H
1b = **2b** = **3b**: R^1 = Et; R^2 = H
1c = **2c** = **3c** : R^1 = n-Pr; R^2 = H
1d = 2d = 3d: R^1 = i-Pr; R^2 = H
1e = **2e** = **3e**: R^1 = n-Pent; R^2 = H
1f = **2f** = **3f**: R^1 = Ph; R^2 =H
1g = **2g** = **3g**: R^1 = *p*-(OCH_3)Ph; R^2 = H
1h = **2h** = **3h**: R^1 = Me; R^2 = Ph
1i = **2i** = **3i:** R^1 = CO_2Et; R^2 = Ph
1j = **2j** = **3j**: R^1 = H; R^2 = CO_2Me
1k = **2k** = **3k:** R^1 = CH_3; R^2 = CO_2Me

Scheme 2



3a = 5a: R^1 = Me; R^2 = H
3b = 5b: R^1 = Et; R^2 = H
3c = 5c: R^1 = n-Pr; R^2 = H
3d = 5d: R^1 = i-Pr; R^2 = H
3e = 5e: R^1 = n-Pentyl; R^2 = H
3f = 5f: R^1 =Ph; R^2 = H
3g = 5g: R^1 = *p*-(OCH_3)Ph; R^2 = H
3h = 5h: R^1 = Me; R^2 = Ph
3i = 5i: R^1 = COOEt; R^2 = Ph
3j = 5j: R^1 = H; R^2 = COOMe
3k = 5k: R^1 = Me; R^2 = COOMe

1.38 (m, 4H, $2CH_2$), 1.70 (q, 2H, CH_2), 2.7 (t, 2H, CH_2), 4.75 (s, 2H, CH_2OH), 7.73 (s, 1H, heteroaromatic), 8.09 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 213.

(2-Chloro-5-phenyl-3-pyridyl)methanol (2f). Yield: 90%, solid; mp: 89–91°C. ^1H NMR ($CDCl_3$): δ 4.85 (s, 2H, -CH_2OH), 7.46 (m, 3H, aromatic), 7.59 (m, 2H, aromatic), 8.08 (m, 1H, heteroaromatic), 8.55 (m, 1H, heteroaromatic). EI-MS (*m*/*z*): 219 (100) (M^+), 184 (45), 166 (5), 154 (38), 140 (5), 127 (24), 115 (9), 102 (8), 77 (10). UV: λ_{max} = 254 nm in acetonitrile. IR (KBr): ν = 3420, 2240, 1665, 1520, 1370, 1037, 1030, 760 cm^{-1}. Anal. Calcd for $C_{12}H_{10}ClNO$: C, 65.75; H, 4.56; N, 6.39. Found: C, 65.66; H, 4.62; N, 6.36.

[2-Chloro-5-(4-methoxyphenyl)-3-pyridyl]methanol (2g). Yield: 94%, solid; mp: 63–64°C. ^1H NMR ($CDCl_3$): δ 3.76 (s, 3H, OCH_3), 4.62 (s, 2H, CH_2OH), 6.93 (d, 2H, aromatic), 7.49 (d, 2H, aromatic), 8.07 (s, 1H, heteroaromatic), 8.34 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 249 (M^+) (100), 206 (13), 179 (25), 162 (60), 137 (70), 105(55), 66 (100), 43 (80). UV: λ_{max} = 272 nm in acetonitrile. IR (KBr): ν = 3423, 2253, 2127, 1653, 1516, 1433, 1378, 1027, 764 cm^{-1}. Anal. Calcd for $C_{13}H_{12}ClNO_2$: C, 62.65; H, 4.82; N, 5.62. Found: C, 62.61; H, 4.84; N, 5.71.

(2-Chloro-5-methyl-6-phenyl-3-pyridyl)methanol (2h). Yield: 96%, solid; mp: 78–80°C, ^1H NMR ($CDCl_3$): δ 2.34 (s, 3H, CH_3), 4.71 (s, 2H, CH_2OH), 7.35–7.45 (m, 5H), 7.69 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 233 (42) (M^+), 232 (100), 196 (5), 167 (10), 115 (6), 77 (4). UV: λ_{max} = 284 nm acetonitrile. IR (KBr): ν = 3384, 3059, 2924, 2856, 1591, 1550, 1415, 1054, 701 cm^{-1}. Anal. Calcd for $C_{13}H_{12}ClNO$: C, 66.95; H, 5.18; N, 5.99. Found: C, 66.91; H, 5.22; N, 6.01.

Ethyl-6-chloro-5-(hydroxymethyl)-2-phenylnicotinate (2i). Yield: 90%, light yellow liquid. ^1H NMR ($CDCl_3$): δ 1.12 (t, 3H, CH_3), 4.20 (q, 2H, CH_2), 4.80 (s, 2H, CH_2OH), 7.42 (m, 3H), 7.60 (m, 2H), 8.76 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 291 (15) (M^+), 262 (100), 246 (37), 218 (6), 190 (6), 127 (7). UV: λ_{max} = 252 nm acetonitrile. IR (KBr): ν = 3443, 3269, 2985, 2922, 2853, 1732, 1540, 1431, 1305, 1221, 1134, 1016, 701 cm^{-1}. Anal. Calcd for $C_{15}H_{14}ClNO_3$: C, 61.85; H, 4.84; N, 4.80. Found: C, 61.80; H, 4.89; N, 4.82.

Methyl-6-chloro-5-(hydroxymethyl)-2-pyridinecarboxylate (2j). Yield: 92%, solid; mp: 68–70°C. ^1H NMR ($CDCl_3$): δ 3.99 (s, 3H, OCH_3), 4.84 (s, 2H, CH_2OH), 8.07 (s, 2H, heteroaromatic). EI-MS (*m*/*z*): 201 (3) (M^+), 171 (20), 143 (100), 112 (19), 78 (11), 51 (4). UV: λ_{max} = 276 nm. IR (KBr): ν = 3416, 2923, 2853, 1730, 1310, 1258, 1046, 778 cm^{-1}. Anal. Calcd for $C_8H_8ClNO_3$: C, 47.76; H, 4.00; N, 6.95. Found: C, 47.69; H, 4.11; N, 6.99.

Methyl-6-chloro-5-(hydroxymethyl)-3-methyl-2-pyridinecarboxylate (2k). Yield: 91%, Solid; mp: 86–88°C. ^1H NMR ($CDCl_3$): δ 2.57 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 4.78 (s, 2H, CH_2OH), 7.78 (s, 2H, heteroaromatic). EI-MS (*m*/*z*): 215 (M^+) (55), 200 (5), 183 (100), 157 (70), 137 (11), 126 (20), 92 (17), 65 (11), 51 (3), 39 (6). UV: λ_{max} = 282 nm. IR (KBr): ν = 3468, 1705, 1440, 1406, 1327, 1243, 1120, 1063, 722 cm^{-1}. Anal. Calcd for $C_9H_{10}ClNO_3$: C, 50.23; H, 4.67; N, 6.50. Found: C, 50.14; H, 4.68; N, 6.46.

General procedure for the synthesis of 2-chloro-3-chloromethyl-5/6-substituted pyridines (3a–k). Methyl-6-chloro-5-(hydroxymethyl)-2-pyridinecarboxylate (**2j**) (200 mg, 0.0009 moles) was dissolved in heptane (50 mL) and added one drop of DMF. The reaction mixture was heated to 60–65°C. Thionyl chloride (150 mg; 0.00135 mol) was added dropwise to the hot reaction mixture. After completion of the addition, the temperature was raised to 80°C and maintained for 2 h. Progress of the reaction was monitored by TLC. The organic solvent was removed under reduced pressure, and obtained crude methyl-6-chloro-5-(chloromethyl)-2-pyridinecarboxylate (**3j**) was recrystallized in hexane.

2-Chloro-3-(chloromethyl)-5-methylpyridine (3a). Yield: 88%, solid; mp: 55–58°C. ^1H NMR ($CDCl_3$): δ 2.37 (s, 3H, CH_3), 4.62 (s, 2H, -CH_2Cl), 7.65 (s, 1H, heteroaromatic), 8.17 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 175 (40) (M^+), 140 (100), 104 (12), 77 (23), 51 (9), 39 (5). UV: λ_{max} = 258 nm in acetonitrile. IR (KBr): ν = 2971, 2934, 2874, 1563, 1429, 1407, 1076, 908, 758 cm^{-1}. Anal. Calcd for C_7H_7 Cl_2N: C, 48.02; H, 4.01; N, 8.00. Found: C, 48.09; H, 4.08; N, 7.99.

2-Chloro-3-(chloromethyl)-5-ethylpyridine (3b). Yield: 94%, solid; mp: 63–64°C. ^1H NMR ($CDCl_3$): δ 1.32 (t, 3H, CH_3), 2.70 (q, 2H, CH_2), 4.75 (s, 2H, CH_2Cl), 7.65 (s, 1H, heteroaromatic), 8.18 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 189 (23) (M^+), 174 (13), 154 (100), 91 (5), 77 (4), 51 (3). UV: λ_{max} = 266 nm in acetonitrile. IR (KBr): ν = 2990, 2960, 1560, 1420, 1417, 1070, 900, 750 cm^{-1}. Anal. Calcd for C_8H_9 Cl_2 N: C, 50.79; H, 4.77; N, 7.40. Found: C, 50.71; H, 4.82; N, 7.38.

2-Chloro-3-(chloromethyl)-5-propylpyridine (3c). Yield: 88%, solid; mp: 65–66°C. ^1H NMR ($CDCl_3$): δ 0.9 (t, 3H, CH_3), 1.7 (m, 2H, CH_2), 2.64 (t, 2H, CH_2), 4.75 (s, 2H, CH_2-Cl), 7.65 (s, 1H, heteroaromatic), 8.18 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 217.

2-Chloro-3-(chloromethyl)-5-isopropylpyridine (3d). Yield: 89%, solid; mp: 66–68°C. ^{1}H NMR ($CDCl_3$): δ 1.2–1.4 (m, 6H, $2CH_3$), 3.20 (m, 1H, CH), 4.75 (s, 2H, CH_2-Cl), 7.65 (s, 1H, heteroaromatic), 8.18 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 217.

2-Chloro-3-(chloromethyl)-5-pentylpyridine (3e). Yield: 88%, solid; mp: 70–72°C. ^{1}H NMR ($CDCl_3$): δ 0.9 (t, 3H, CH_3), 1.38 (m, 4H, $2CH_2$), 1.70 (q, 2H, CH_2), 2.7 (t, 2H, CH_2), 4.75 (s, 2H, CH_2-Cl), 7.65 (s, 1H, heteroaromatic), 8.18 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 231.

2-Chloro-3-(chloromethyl)-5-phenylpyridine (3f). Yield: 91%, solid; mp: 78–80°C. ^{1}H NMR ($CDCl_3$): δ 4.77 (s, 2H, CH_2), 7.44–7.58 (m, 5H), 8.06 (s, 1H, heteroaromatic), 8.58 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 237 (82) (M^+), 202 (100), 166 (18), 139 (17), 115 (11), 101 (6), 69 (5). UV: λ_{max} = 256 nm in acetonitrile. IR (KBr): ν = 2970, 2910, 2880, 1420, 1240, 1170, 1060, 1020 cm^{-1}. Anal. Calcd for $C_{12}H_9$ Cl_2 N: C, 60.75; H, 3.79; N, 5.90. Found: C, 60.77; H, 3.72; N, 5.88.

2-Chloro-3-(chloromethyl)-5-(4-methoxyphenyl)pyridine (3g). Yield: 91%, solid; mp: 79–80°C. ^{1}H NMR ($CDCl_3$): δ 3.84 (s, 3H, OCH_3), 4.77 (s, 2H, -CH_2Cl), 6.97 (d, 2H, aromatic), 7.49 (d, 2H, aromatic), 7.98 (s, 1H, heteroaromatic), 8.50 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 267 (100) (M^+), 252 (15), 232 (45), 189 (6), 154 (6), 127 (12), UV: λ_{max} = 276 nm in acetonitrile. IR (KBr): ν = 2957, 2925, 2854, 1735, 1606, 1426, 1249, 1182, 1082, 1027, 832, 753 cm^{-1}. Anal. Calcd for $C_{13}H_{11}$ Cl_2 NO: C, 58.43; H, 4.13; N, 5.24. Found: C, 58.33; H, 4.22; N, 5.21.

2-Chloro-3-(chloromethyl)-5-methyl-6-phenylpyridine (3h). Yield: 88%, solid; mp: 78–82°C. ^{1}H NMR ($CDCl_3$): δ 2.43 (s, 3H, CH_3), 4.70 (s, 2H, -CH_2Cl), 7.28–7.38 (m, 5H), 7.73 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 251 (44) (M^+), 250 (100), 216 (39), 180 (11), 153 (13), 140 (4), 128 (5), 115 (5), 89 (5), 76 (10), 63 (4), 51 (5). UV: λ_{max} = 288 nm in acetonitrile. IR (KBr): ν = 2967, 2927, 1588, 1543, 1443, 1412, 1383, 1185, 1067, 984, 735, 702 cm^{-1}. Anal. Calcd for $C_{13}H_{11}$ Cl_2N: C, 62.16; H, 4.40; N, 5.57. Found: C, 60.81; H, 4.42; N, 5.61.

Ethyl-6-chloro-5-(chloromethyl)-2-phenylnicotinate (3i). Yield: 91%, light yellow liquid. ^{1}H NMR ($CDCl_3$): δ 1.13 (t, 3H, CH_3), 4.24 (q, 2H, CH_2), 4.74 (s, 2H, -CH_2Cl), 7.46 (m, 3H, aromatic), 8.76 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 309 (18) (M^+), 280 (100), 264(34), 245 (11), 229 (7), 202 (6), 166 (14), 139 (17), 105 (7). UV: λ_{max} = 256 nm in acetonitrile. IR (KBr): ν = 2925, 2853, 1724, 1573, 1531, 1440, 1237, 1129, 757 cm^{-1}. Anal. Calcd for $C_{15}H_{13}Cl_2NO_2$: C, 58.28; H, 4.22; N, 4.52. Found: C, 58.21; H, 4.28; N, 4.61.

Methyl-6-chloro-5-(chloromethyl)-2-pyridinecarboxylate (3j). Yield: 93% solid; mp: 78–80°C. ^{1}H NMR ($CDCl_3$): δ 4.04 (s, 3H, OCH_3), 4.76 (s, 2H, -CH_2Cl), 8.08 (q, 2H). EI-MS (*m*/*z*): 219 (4) (M^+), 189 (20), 161 (100), 124 (15), 90 (11), 63 (10). UV: λ_{max} = 258 nm in acetonitrile. IR (KBr): ν = 2925, 2854, 1728, 1562, 1450, 1369, 1137, 744 cm^{-1}. Anal. Calcd for C_8H_7 Cl_2NO_2: C, 43.84; H, 3.20; N, 6.39. Found: C, 37.21; H, 2.69; N, 7.21.

Methyl-6-chloro-5-(chloromethyl)-3-methyl-2-pyridinecar-boxylate (3k). Yield: 90%, solid; mp: 75–77°C. ^{1}H NMR ($CDCl_3$): δ 2.60 (s, 3H, CH_3), 3.99 (s, 3H, OCH_3), 4.69 (s, 2H, CH_2Cl), 7.80 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 234 (43) (M^+), 218 (5), 201(100), 175 (64), 138 (46), 102 (20), 77 (15), 51 (9). UV: λ_{max} = 286 nm in acetonitrile. IR (KBr): ν = 2915, 2850, 1729, 1560, 1455, 1360, 1130, 740 cm^{-1}. Anal. Calcd for $C_9H_9Cl_2NO_2$: C, 46.18; H, 3.84; N, 5.98. Found: C, 46.18; H, 3.92; N, 5.92.

General procedure for the synthesis of (substituted pyridyl)-methyl]tetrahydro-1*H*-2-imidazolyliden}-1-oxo-1-hydraziniumolate (5a–k). A mixture of pyridine substituted methyl chloride (**3**; 0.5 g, 0.002 moles), 2-nitraimino imidazole (0.67 g, 0.005 mol), K_2CO_3 (0.33 g, 0.002 mol), and CsCl (5 mol %) in CH_3CN (10 mL) was refluxed for 2.5 h. After completion of the reaction, acetonitrile was removed. The solid crude was washed with water. The solid when recrystallized by methanol gave the title compounds in good yield.

2-{1-[(2-Chloro-5-methyl-3-pyridyl)methyl]-tetrahydro-1H-2-imidazolyliden}-1-oxo-1-hydraziniumolate (5a). Yield: 82%, solid; mp: 193–195°C. ^{1}H NMR (DMSO-d_6): δ 2.36 (s, 3H, CH_3), 3.5–3.8 (m, 4H, -CH_2-CH_2-), 4.62 (s, 2H, -CH_2N-), 7.62 (s, 1H, heteroaromatic), 8.20 (s, 1H, heteroaromatic), 9.05 (s, NH, 1H). UV: λ_{max} = 272 nm in acetonitrile. EI-MS (*m*/*z*): 269; IR (KBr): ν = 3792, 3307, 2922, 2861, 1584, 1546, 1439, 1286, 1240, 1148, 1053, 724, 679, 642 cm^{-1}. Anal. Calcd for $C_{10}H_{12}$Cl N_5O_2: C, 44.61; H, 4.48; N, 26.06. Found: C, 44.64; H, 4.51; N, 26.12.

2-{1-[(2-Chloro-5-ethyl-3-pyridyl)methyl]-tetrahydro-1H-2-imidazolyliden}-1-oxo-1-hydraziniumolate (5b). Yield: 81%, solid; mp: 197–199°C. ^{1}H NMR (DMSO-d_6): δ 1.32 (t, 3H, CH_3), 2.70 (q, 2H, CH_2), 3.5–3.8 (m, 4H, -CH_2-CH_2-), 4.60 (s, 2H, -CH_2N-), 7.62 (s, 1H, heteroaromatic), 8.20 (s, 1H, heteroaromatic), 9.05 (s, NH, 1H). EI-MS (*m*/*z*): 283; IR (KBr): ν = 3790, 3300, 2855, 1580, 1540, 1280, 1240, 1050, 724, cm^{-1}. Anal. Calcd for $C_{11}H_{14}ClN_5O_2$: C, 46.56; H, 4.97; N, 24.68. Found: C, 46.59; H, 4.99; N, 24.70.

2-{1-[(2-Chloro-5-propyl-3-pyridyl)methyl]-tetrahydro-1H-2-imidazolyliden}-1-oxo-1-hydraziniumolate (5c). Yield: 82%, solid; mp: 196–198°C. ^{1}H NMR (DMSO-d_6): δ 0.9 (t, 3H, CH_3), 1.7 (m, 2H, CH_2), 2.64 (t, 2H, CH_2), 3.5–3.8 (m, 4H, -CH_2-CH_2-), 4.60 (s, 2H, -CH_2N-), 7.64 (s, 1H, heteroaromatic), 8.22 (s, 1H, heteroaromatic), 9.05 (s, 1H, NH). EI-MS (*m*/*z*): 297.

2-{1-[(2-Chloro-5-isopropyl-3-pyridyl)methyl]-tetrahydro-1H-2-imidazolyliden}-1-oxo-1-hydraziniumolate (5d). Yield: 84%, solid; mp: 190–192°C. ^{1}H NMR (DMSO-d_6): δ 1.2–1.4 (m, 6H, $2CH_3$), 3.20 (m, 1H, CH), 3.5–3.8 (m, 4H, -CH_2-CH_2-), 4.64 (s, 2H, -CH_2N-), 7.60 (s, 1H, heteroaromatic), 8.21 (s, 1H, heteroaromatic), 9.05 (s, 1H, NH). EI-MS (*m*/*z*): 297.

2-{1-[(2-Chloro-5-pentyl-3-pyridyl)methyl]-tetrahydro-1H-2-imidazolyliden}-1-oxo-1-hydraziniumolate (5e). Yield: 86%, solid; mp: 198–201°C. ^{1}H NMR (DMSO-d_6): δ 0.9 (t, 3H, CH_3), 1.38 (m, 4H, $2CH_2$), 1.70 (q, 2H, CH_2), 2.7 (t, 2H, CH_2), 3.5–3.8 (m, 4H, -CH_2-CH_2-), 4.60 (s, 2H, -CH_2N-), 7.62 (s, 1H, heteroaromatic), 8.20 (s, 1H, heteroaromatic), 9.05 (s, 1H, NH). EI-MS (*m*/*z*): 325.

2-{1-[(2-Chloro-5-phenyl-3-pyridyl)methyl]-tetrahydro-1H-2-imidazolyliden}-1-oxo-1-hydraziniumolate (5f). Yield: 80%, solid; mp: 248–250°C. ^{1}H NMR (DMSO-d_6): δ 3.60–3.80 (m, 4H, -CH_2-CH_2-), 4.62 (s, 2H, -CH_2N-), 7.50 (m, 3H, aromatic), 7.75 (d, 2H, aromatic), 8.05 (s, 1H, heteroaromatic), 8.68 (s, 1H, heteroaromatic), 9.05 (s, 1H, NH). EI-MS (*m*/*z*): 331; UV: λ_{max} = 262 nm in acetonitrile. IR (KBr): ν = 3253, 3065, 2879, 1580, 1542, 1438, 1284, 1240, 1145, 1050, 953, 759, 687 cm$-^1$. Anal. Calcd for $C_{15}H_{14}ClN_5O_2$: C, 54.30; H, 4.25; N, 21.11. Found: C, 55.41; H, 4.32; N, 21.21.

2-(1-{[2-Chloro-5-(4-methoxyphenyl)-3-pyridyl]methyl}-tetrahydro-1H-2-imidazolyliden)-1-oxo-1-hydraziniumolate (5g). Yield: 81%, solid; mp: 159–160°C. ^{1}H NMR (DMSO-d$_6$): δ 3.60–3.80 (m, 4H, -CH_2-CH_2-), 3.84 (s, 3H, OCH_3), 4.62 (s, 2H, -CH_2N-), 6.97 (d, 2H, aromatic), 7.49 (d, 2H, aromatic), 8.05 (s, 1H, heteroaromatic), 8.68 (s, 1H, heteroaromatic), 9.05 (s, 1H, NH). IR (KBr): ν = 3416, 2923, 2853, 1572, 1540, 1436, 1282, 1237 cm^{-1}. EI-MS (*m*/*z*): 361; Anal. Calcd for $C_{16}H_{16}Cl\ N_5O_3$: C, 53.11; H, 4.45; N, 19.39. Found: C, 53.21; H, 4.29; N, 19.35.

2-{1-[(2-Chloro-5-methyl-6-phenyl-3-pyridyl)methyl]-tetrahydro-1H-2-imidazolyliden)-1-oxo-1-hydraziniumolate (5h). Yield: 89%, solid; mp: 168–170°C. ^{1}H NMR (DMSO-d$_6$): δ 2.38 (s, 3H, CH_3), 3.60–3.78 (m, 4H, -CH_2-CH_2-), 4.58 (s, 2H, -CH_2N-), 7.40–7.60 (m, 5H, aromatic), 7.78 (s, 1H, heteroaromatic), 9.05 (s, 1H, NH). UV: λ_{max} = 272 nm in acetonitrile. IR (KBr): ν = 3331, 2925, 2854, 1554, 1433, 1292, 1261, 1228, 1126, 1044, 982, 701 cm^{-1}. EI-MS (*m*/*z*): 345; Anal. Calcd for $C_{16}H_{16}Cl\ N_5O_2$: C, 55.57; H, 4.66; N, 20.25. Found: C, 55.61; H, 4.77; N, 20.21.

2-(1-{[2-Chloro-5-(ethoxycarbonyl)-6-phenyl-3-pyridyl]-methyl}tetrahydro-1H-2-imidazolyliden)-1-oxo-1-hydraziniumolate (5i). Yield: 88%, solid; mp: 133–135°C. ^{1}H NMR ($CDCl_3$): δ 1.13 (t, 3H, CH_3), 3.62 (m, 2H,CH_2), 3.80 (m, 2H, CH_2), 4.22 (q, 2H, CH_2), 4.78 (s, 2H, -CH_2N-), 7.42 (m, 3H, aromatic), 7.60 (m, 2H, aromatic), 8.28 (s, 1H, NH), 8.72 (s, 1H, heteroaromatic). UV: λ_{max} = 270 nm in acetonitrile. EI-MS (*m*/*z*): 403; IR (KBr): ν = 3255, 2899, 1734, 1570, 1525, 1441, 1402, 1259, 1230, 1114, 1049, 1008, 951, 777, 695, 622 cm^{-1}. Anal. Calcd for $C_{18}H_{18}ClN_5O_4$: C, 53.53; H, 4.49; N, 17.34. Found: C, 53.61; H, 4.52; N, 17.41.

2-(1-{[2-Chloro-6-(methoxycarbonyl)-3-pyridyl]methyl}-tetrahydro-1H-2-imidazolyliden)-1-oxo-1-hydraziniumolate (5j). Yield: 86%, solid; mp: 169–170°C. ^{1}H NMR ($CDCl_3$ + DMSO-d$_6$): δ 3.69 (q, 2H, CH_2), 3.82 (q, 2H, CH_2), 3.94 (s, 3H, OCH_3), 4.66 (s, 2H, -CH_2N-), 7.88 (d, 1H, heteroaromatic), 8.03 (d, 1H, heteroaromatic), 8.16 (s, 1H, NH). ^{13}C NMR (DMSO-d$_6$): δ 41.63, 44.62, 45.32, 52.10, 115.53, 124.80, 136.27, 149.57, 151.48, 161.55, 168.28. EI-MS (*m*/*z*): (M^+ + 23) 336. UV: λ_{max} = 272 nm. IR (KBr): ν = 3341, 2924, 1713, 1574, 1445, 1322, 1264, 1055, 786 cm^{-1}. Anal. Calcd for $C_{11}H_{12}ClN_5O_4$: C, 42.11; H, 3.85; N, 22.32. Found: C, 42.18; H, 3.98; N, 22.33.

2-(1-{[2-Chloro-6-(methoxycarbonyl)-5-methyl-3-pyridyl]-methyl}-tetrahydro-1H-2-imidazolyliden)-1-oxo-1-hydraziniumolate (5k). Yield: 80%, solid; mp: 175–177°C. ^{1}H NMR ($CDCl_3$): δ 2.58 (s, 3H, CH_3), 3.6–3.7 (q, 2H, CH_2), 3.8–3.9 (q, 2H, CH_2), 3.98 (s, 3H, OCH_3), 4.72 (s, 2H, -CH_2N), 7.72 (s, 1H, heteroaromatic), 8.24 (s, 1H, NH). EI-MS (*m*/*z*): (M^++ 23) 350. UV: λ_{max} = 272 nm in acetonitrile. IR (KBr): ν = 3412, 2921, 2852, 1712, 1579, 1441, 1320, 1293, 1240, 1120, 1045 cm^{-1}. Anal. Calcd for $C_{12}H_{14}ClN_5O_4$: C, 43.97; H, 4.30; N, 21.36. Found: C, 43.99; H, 4.32; N, 21.41.

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Synthesis and Biological Activities of *O-(E)*-(Arylmethyl) 1-[1-(arylmethyl)-5-methyl-1*H*-1,2,3-triazol-4-yl] Ethanone Oxime Ethers

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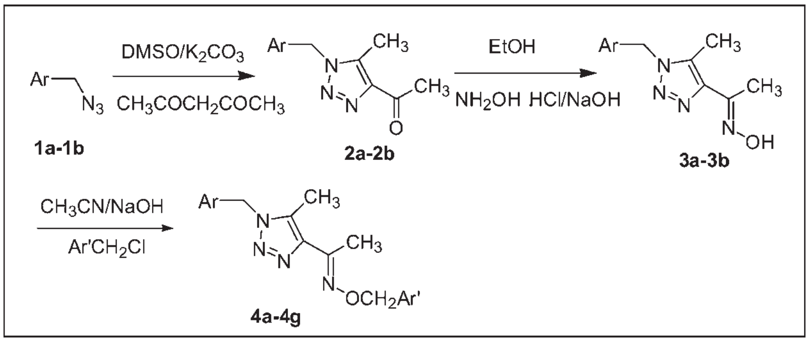

A series of novel *O*-(*E*)-(arylmethyl) 1-[1-(arylmethyl)-5-methyl-1*H*-1,2,3-triazol-4-yl] ethanone oxime ethers were synthesized by the *O*-alkylation of 1-[1-(arylmethyl)-5-methyl-1*H*-1,2,3-triazol-4-yl] ethanone oximes with various arylmethyl chlorides in the basic condition. Their structures were confirmed by IR, ^{1}H NMR, mass spectroscopy, and elemental analyses. The preliminary bioassay indicated that some of the target compounds (**4a–f**) displayed good insecticidal and moderate fungicidal activity. For example, compounds **4c** and **4g** showed 100% and 90.6% death rates against aphides at the concentration of 250 mg/L, respectively, and compounds **4f** and **4g** displayed 67% and 78.4% inhibitory rates against *Rhizoctonia solani* at the dosage of 100 mg/L, respectively.

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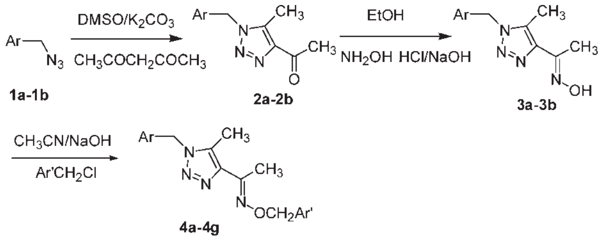
INTRODUCTION

Oxime ether derivatives are very important agrochemicals and are receiving more and more attention because of their widespread biological activities—some of them can be used as insecticides, acaricides [1,2], fungicides [3,4], and herbicides and its safener [5,6]—which are widely used in the worldwide plant protection. The 1,2,3-triazole ring has been known for more than 100 years. However, it was only in recent decades that the 1,2,3-triazole chemistry developed very fast due to the discovery of the diverse biologically active triazole derivatives. Many of them have been used as insecticides, nematocides, acaricides, and plant growth regulators [7–13]. Recently, heterocyclic compounds containing nitrogen play more and more important role in pesticide science and industry; moreover, the introduction of a pyridyl or a thiazole ring into a parent compound may improve its properties and biological activities in the looking for novel pharmaceutical and agrochemical lead compounds, and many pyridyl and thiazole containing compounds are also known to possess a wide range of biological and pharmacological activities, as well as low toxicity toward mammals, and the widely development of neonicotinic insecticides in the world are very successful examples [14–17]. As a continuation of our ongoing project aimed at investigating novel biologically nitrogen-containing heterocyclic compounds [18,19], we designed and synthesized a series of novel *O-(E)*-(arylmethyl) 1-[1-(arylmethyl)-5-methyl-1*H*-1,2,3-triazol-4-yl] ethanone oxime ethers. We would like to report the synthesis and biological activities of the title compounds **4a–g** in this article (Scheme 1).

RESULTS AND DISCUSSION

2-Chloro-5-(chloromethyl)-pyridine (or thiazole) was treated with sodium azide in dry ethanol under refluxing condition to obtain 5-(azidomethyl)-2-chloro-pyridine (or thiazole) (**1**) in high yields, which was annulated with acetylacetone in DMSO in the presence of anhydrous potassium carbonate to generate compound **2**. Treatment of **2** with hydroxylamine hydrochloride

Scheme 1



4a: Ar = 6-chloropyridin-3-yl, Ar' = 6-chloropyridin-3-yl; **4b**: Ar = 6-chloropyridin-3-yl, Ar' = 2-chlorothiazol-5-yl; **4c**: Ar = 6-chloropyridin-3-yl, Ar' = phenyl; **4d**: Ar = 6-chloropyridin-3-yl, Ar' = pyridin-3-yl; **4e**: Ar = 2-chlorothiazol-5-yl, Ar' = 6-chloropyridin-3-yl; **4f**: Ar = 2-chlorothiazol-5-yl, Ar' = 2-chlorothiazol-5-yl; **4g**: Ar = 2-chlorothiazol-5-yl, Ar' = phenyl

afforded oxime **3**, which reacted with various arylmethyl chlorides in the basic condition to get the title compounds **4** in moderate yields.

To optimize the reaction condition of *O*-alkylation, we attempted to react 1-[1-(arylmethyl)-5-methyl-1*H*-1,2,3-triazol-4-yl]ethanone oxime **3** with various alkyl chlorides in different base-solvent systems (e.g., Et_3N-CH_2Cl_2, Et_3N-CH_3CN, Et_3N-toluene, NaOH-CH_3CN, NaOH-DMF, and NaOH-toluene). Finally, we found that the *O*-alkylation can take place smoothly in sodium hydroxide and acetonitrile system to give the target products **4** in moderate yield (58–85%), and no other by-product was detected by TLC. In the *O*-alkylation, 2-chloro-5-(chloromethyl)-pyridine and 2-chloro-(5-chloromethyl)-thiazole are more active than 3-(chloromethyl)-pyridine and benzyl chloride. For example, when 2-chloro-5-(chloromethyl)-pyridine and 2-chloro-(5-chloromethyl)-thiazole are used as the alkylation reagents, the reaction can complete at room temperature for 4 to 5 h, however, for 3-(chloromethyl)-pyridine and benzyl chloride, the reactions underwent very slow and needed more high temperature and prolonged reation time.

Their structures of compounds **4** were confirmed by IR, ^{1}H NMR, EI-MS, and elemental analyses, which were listed in the experimental part. Because of C=N bond, it probably existed as Z and E-isomers in compounds **3** and **4a–g**. In ^{1}H NMR spectra, the CH_3 protons of the E isomer is shifted downfield relative to that of Z isomer, owing to its shorter distance between the oxygen atom in C=N—O— moiety and stronger unshielded effect [1]. In this article, both of compounds **3** and **4** are in E configurations, which were deduced by NMR analysis and further by compared with one of its phosphorothioate analog determined by X-ray diffraction analysis [20].

Biological activity

Insecticidal activity. Compounds **4** were tested for insecticidal activities against aphides at the concentration of 250 mg/L according to a previously reported method [21]. The results of preliminary bioassays indicated that some of the target compounds displayed good insecticidal activity against aphides (Table 1). For example, compounds **4c** and **4g** exhibited 100% and 90.6% inhibitory rates against aphides at the concentration of 250 mg/L, respectively.

Fungicidal activity. The preliminary fungicidal activity of the target compounds **4** was evaluated by the classic plate method at a dosage of 100 mg/L, which was described in the experimental part. The six fungi used—*Fusarium oxysporium, Rhizoctonia solani, Botrytis cinereapers, Gibberella zeae, Dothiorella gregaria,* and *Colletotrichum gossypi*—belong to the group of field fungi and were isolated from corresponding crops. The activities data were also listed in Table 1. The results indicated that most of compounds **4** exhibit moderate to weak inhibitory activities against the above six fungi. For example, compounds **4f** and **4g** displayed 67% and 78.4% inhibitory rates against *Rhizoctonia solani* at the dosage of 100 mg/L, respectively. Further structure-activity relationships are under investigation.

In conclusion, a series of novel *O*-(*E*)-(arylmethyl) 1-[1-(arylmethyl)-5-methyl-1*H*-1,2,3-triazol-4-yl] ethanone oxime ethers were synthesized by the *O*-alkylation reactions of 1-[1-(arylmethyl)-5-methyl-1*H*-1,2,3-triazol-4-yl] ethanone oximes with various arylmethyl chlorides in the basic condition. The preliminary bioassay indicated that some of the target compounds (**4a–f**) displayed good insecticidal and moderate fungicidal activity. For example, compounds **4c** and **4g** showed 100% and 90.6% death rates against aphides at the concentration of 250 mg/L, compounds **4f** and **4g** displayed 67% and 78.4% inhibitory rates against *Rhizoctonia solani* at the dosage of 100 mg/L, respectively.

EXPERIMENTAL

Melting points were determined with a WRS-1B digital melting point apparatus and are uncorrected. ^{1}H NMR spectra was recorded with a Varian Mercury PLUS400 spectrometer with TMS as the internal reference and $CDCl_3$ as the solvent, while mass spectra were obtained with a Finnigan TRACEMS2000 spectrometer using the EI method. Infrared (IR) spectra were measured by a Nicolet NEXUS470 spectrometer. Elemental analyses were performed with an Elementar Vario ELIII CHNSO elemental analyzer. All the solvents and materials were reagent grade and purified as required. 5-(Azidomethyl)-2-chloro-pyridine (or thiazole) (**1a–b**) was prepared according to the literature procedure [22].

General procedure for the synthesis of 1-[1-(arylmethyl)-5-methyl-1H-1,2,3-triazol-4-yl] ethanone 2 [23]. 5-(Azidomethyl)-2-chloro-pyridine (or thiazole) **1** (0.05 mol) and acetylacetone (5.0 g, 0.05 mol) were added to a suspension of milled potassium carbonate (20.7 g, 0.15 mol) in DMSO (50 mL). The mixture was stirred at room temperature for 6–8 h

Table 1

The insecticidal and fungicidal activities of **4a–4g** (inhibitory rate (%).

Compd.	Insecticidal activity (250 mg/L) against aphides	Fungicidal activity (100 mg/L)					
		Fusarium oxysporium	*Rhizoctonia solani*	*Botrytis cinereapers*	*Gibberella zeae*	*Dothiorella gregaria*	*Colletotrichum gossypii*
4a	50.9	23.1	44.3	22.2	61.1	65.4	66.7
4b	45.8	30.4	52.5	33.3	54.6	52.4	45.5
4c	100	34.6	63.9	40.7	58.3	50.0	48.2
4d	23.3	26.9	52.6	25.9	55.6	53.9	55.7
4e	16.0	23.1	38.1	55.6	50.0	30.8	48.2
4f	44.8	15.4	67.0	48.2	38.9	15.4	29.6
4g	90.6	26.9	78.4	51.9	63.9	69.2	51.9

(monitored by TLC); the mixture was poured to water (500 mL). The solid was collected by filtration, washed with water and diethyl ether, and dried to give **2** as a white solid.

1-{1-[(6-Chloropyridin-3-yl) methyl]-5-methyl-1H-1,2,3-triazol-4-yl} ethanone (2a) [19]. White solid, yield: 81%, mp 121–122°C; ^{1}H NMR ($CDCl_3$): δ 2.55 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 5.52 (s, 2H, CH_2), 7.36 (d, J = 8.4 Hz, 1H, PyH), 7.52 (d, J = 11.2 Hz, 1H, PyH), 8.36 (s, 1H, PyH).

1-{1-[(2-Chlorothiazol-5-yl) methyl]-5-methyl-1H-1,2,3-triazol-4-yl} ethanone (2b). White solid, yield: 78%, mp 97–98°C; ^{1}H NMR ($CDCl_3$): δ 2.42 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 5.60 (s, 2H, CH_2), 7.51 (s, 1H, thiazole-H).

General procedure for the synthesis of 1-[1-(arylmethyl)-5-methyl-1*H*-1,2,3-triazol-4-yl] ethanone oxime (3a–b). To the stirred mixture of hydroxylamine hydrochloride (2.2 g, 32 mmol), **2** (20.0 mmol), ethanol (40 mL), and H_2O (4 mL), sodium hydroxide (2 g, 50 mmol) was added slowly. After the addition completed, the solution was stirred at room temperature (for **3b**) or under reflux (for **3a**) for 5–6 h, the mixture was poured to water (200 mL). The solid was collected by filtration and recrystallized from toluene to get **3** as a white solid.

1-{1-[(6-Chloropyridin-3-yl) methyl]-5-methyl-1H-1,2,3-triazol-4-yl} ethanone oxime (3a). White solid, yield: 51%, mp 172–174°C; IR: OH 3421, CH_3 1419, 1385 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.54 (s, 1H, OH), 2.42 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 5.49 (s, 2H, CH_2), 7.34 (d, J = 8.0 Hz, 1H, PyH), 7.50 (d, J = 10.8 Hz, 1H, PyH), 8.35 (s, 1H, PyH); ms: *m*/*z* 265 (M^+, 10.5), 236 (37.1), 126 (100), 90 (22.3), 77 (8.3), 73 (32.9), 63 (15.8). Anal. Calcd. for $C_{11}H_{12}ClN_5O$: C, 49.72; H, 4.55; N, 26.36. Found: C, 49.57; H, 4.75; N, 26.18.

1-{1-[(2-Chlorothiazol-5-yl) methyl]-5-methyl-1H-1,2,3-triazol-4-yl} ethanone oxime (3b). White solid, yield: 43%, mp 139–141°C; ^{1}H NMR ($CDCl_3$): δ 1.62 (s, 1H, OH), 2.60 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 5.62 (s, 2H, CH_2), 7.53 (s, 1H, thiazole-H). Anal. Calcd. for $C_9H_{10}ClN_5OS$: C, 39.78; H, 3.71; N, 25.77. Found: C, 39.94; H, 3.53; N, 25.89.

General procedure for the synthesis of *O-(E)*-(arylmethyl) 1-[1-(arylmethyl)-5-methyl-1*H*-1,2,3-triazol-4-yl] ethanone oxime ethers 4a–g. A solution of **3** (2 mmol) in anhydrous CH_3CN (10 mL) and NaOH powder (2 mmol) was added to a three-necked flask. After vigorously stirring for 5–10 min, a solution of arylmethyl chloride (2 mmol) in anhydrous CH_3CN (5 mL) was added dropwise. After the addition completed, the mixture was stirred at room temperature or under reflux till the reaction was complete (monitored by TLC). The solid was filtered off, and the filtrate was concentrated under vacuum. The residue was purified by column chromatography on silica gel using petroleum ether and ethyl acetate (1:1 v/v) as the eluent, giving the corresponding **4a–g** in 58–85% yields.

O-(E)-[(6-chloropyridin-3-yl)methy] 1-{1-[(6-chloropyridin-3-yl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl} ethanone oxime ether (4a). White crystal, yield: 85%, mp 125–127°C; IR: C=N 1589, 1566, Ar 1460, 1436, 1388, 1349, N-O-C 1019; ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 5.13 (s, 2H, CH_2), 5.47 (s, 2H, CH_2), 7.27–8.40 (m, 6H, PyH); ms: *m*/*z* 388 (M^+, 94.1), 264 (9.2), 248(4.50), 126 (100). Anal. Calcd. for $C_{17}H_{16}Cl_2N_6O$: C, 52.19; H, 4.12; N, 21.48. Found: C, 52.33; H, 4.34; N, 21.32.

O-(E)-[(2-chlorothiazol-5-yl)methyl] 1-{1-[(6-chloropyridin-3-yl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}ethanone oxime ether (4b). White crystal, yield: 82%, mp 90–91°C; IR: C=N 1590, 1566, Ar 1461, 1412, 1396, 1366, N-O-C 1017; ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 5.22 (s, 2H, CH_2), 5.50 (s, 2H, CH_2), 7.26–8.35 (m, 4H, thiazole-H, PyH); ms: *m*/*z* 396 (M^+, 12.5), 131 (100), 126 (94.3), 89 (47.7), 70 (69.4). Anal. Calcd. for $C_{15}H_{14}Cl_2N_6OS$: C, 45.35; H, 3.55; N, 21.15. Found: C, 45.03; H, 3.62; N, 20.97.

O-(E)-benzyl 1-{1-[(6-chloropyridin-3-yl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}ethanone oxime ether (4c). White crystal, yield: 80%, mp 75–77°C; ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 5.16 (s, 2H, CH_2), 5.47 (s, 2H, CH_2), 7.26–8.33 (m, 8H, PhH, PyH); Anal. Calcd. for $C_{18}H_{18}ClN_5O$: C, 60.76; H, 5.10; N, 19.68. Found: C, 60.85; H, 5.23; N, 19.84.

O-(E)-[(pyridin-3-yl)methyl] 1-{1-[(6-chloropyridin-3-yl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}ethanone oxime ether (4d). White crystal, yield: 68%, mp 80–82°C; IR: CH=N 1586, Ar-H, Py-H 1565, 1484, 1460, 1392, 1334, N-O-C 1033; ^{1}H NMR ($CDCl_3$): δ 2.39 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 5.18 (s, 2H, CH_2), 5.47 (s, 2H, CH_2), 7.26–8.62 (m, 7H, PyH); Anal. Calcd. for $C_{17}H_{17}ClN_6O$: C, 57.22; H, 4.80; N, 23.55. Found: C, 57.48; H, 4.74; N, 23.27.

O-(E)-[(6-chloropyridin-3-yl)methyl] 1-{1-[(2-chlorothiazol-5-yl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}ethanone oxime ether (4e). Yellow oil, yield: 61%; IR: CH=N 1592, Ar-H, Py-H 1567, 1491, 1448, 1392, 1327, N-O-C 1039; ^{1}H NMR ($CDCl_3$): δ 2.60 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 5.14 (s, 2H, CH_2), 5.58 (s, 2H, CH_2), 7.27–8.40 (m, 4H, thiazole-H, PyH). Anal. Calcd. for $C_{15}H_{14}Cl_2N_6OS$: C, 45.35; H, 3.55; N, 21.15. Found: C, 45.46; H, 3.78; N, 21.36.

O-(E)-[(2-chlorothiazol-5-yl)methyl] 1-{1-[(2-chlorothiazol-5-yl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}ethanone oxime ether (4f). Yellow oil, yield: 74%; ^{1}H NMR ($CDCl_3$): δ 2.38 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 5.22 (s, 2H, CH_2), 5.61 (s, 2H, CH_2), 7.49 (s, 1H, thiazloe-H), 7.52 (s, 1H, thiazole-H). Anal. Calcd. for $C_{13}H_{12}Cl_2N_6OS_2$: C, 38.71; H, 3.00; N, 20.84. Found: C, 38.96; H, 3.21; N, 20.93.

O-(E)-benzyl 1-{1-[(2-chlorothiazol-5-yl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}ethanone oxime ether (4g). Yellow oil, yield: 58%; ^{1}H NMR ($CDCl_3$): δ 2.36 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 5.17 (s, 2H, CH_2), 5.57 (s, 2H, CH_2), 7.27–7.52 (m, 6H, thiazole-H, PhH); ms: *m/z* 361 (M^+, 10.9), 131 (34.8), 90 (100), 76 (60.7), 62 (25.7). Anal. Calcd. for $C_{16}H_{16}ClN_5OS$: C, 53.11; H, 4.46; N, 19.35. Found: C, 53.28; H, 4.70; N, 19.61.

Fungicidal activity testing. The fungicidal activity measurement method was adapted from the one described by Molina-Torres et al. [24]. The synthesized target compounds were dissolved in 0.5–1.0 mL of DMF to the concentration of 1000 mg/L. The solutions (1 mL) were mixed rapidly with thawed potato glucose agar culture medium (9 mL) under 50°C. The mixtures were poured into petridishes. After the dished were cooled, the solidified plates were incubated with 4-mm mycelium disk, inverted, and incubated at 28°C for 48 h. Distilled water was used as the blank control. Three replicates of each test were carried out. The mycelial elongation radius (mm) of fungi settlements was measured after 48 h of culture. The growth inhibitory rates were calculated with the following equation: $I = [(C-T)/C] \times 100\%$. Here, I is the growth inhibitory rate (%), T is the treatment group fungi settlement radius (mm), and C is the radius of the blank control. The results are listed in Table 1.

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An Efficient Synthesis of 1,3-Diarylbenzo[*f*]quinolines from 2-Halogenated Acetophenone, Aromatic Aldehyde, and Naphthalen-2-Amine Catalyzed by Iodine

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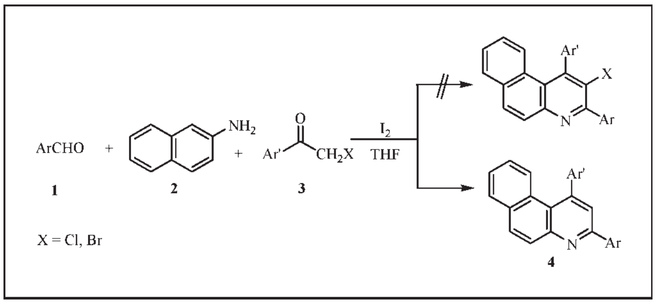

The three-component reaction of aromatic aldehyde, naphthalen-2-amine and 2-halogenated acetophenone in THF catalyzed by 5 mol % iodine at reflux unexpectedly gave 1,3-diarylbenzo[*f*]quinolines, with halogen losing in the formation of the products. The formation of unexpected 1,3-diarylbenzo[*f*]-quinolines was tentatively explained by Cram's rule to one of the steps in the mechanism.

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INTRODUCTION

There has been tremendous interest in developing highly efficient transformations for the preparation of organic compounds, as well as, biologically active materials. There is also a need for synthetic chemists to find new, efficient, and strategically important processes, which are environmentally benign and lead to greater structural variation in short period of times with high yields and simple work-up procedures. Multicomponent reactions are useful and efficient methods in organic synthesis. The major advantages of these reactions are a single purification step, higher yields than stepwise assembly, the use of simple and diverse precursors to construct complex molecules, and the use of only a single promoter or catalyst. Thus, the development of new multicomponent reactions is a popular area of research in current organic chemistry and is also acceptable from a ''Green Chemistry" point of view [1]. They provide a powerful tool toward the one-pot synthesis of diverse and complex compounds as well as small and drug-like heterocycles [2]. Such as benzo[*f*]quinoline and its derivatives, are very useful compounds in the various fields of chemistry including biological and pharmacological viewpoints. Some of which exhibit antibacterial activity [3], UDP (Uridine diphosphate)-glucuronosyl transferase activity [4], antimicrobial activity [5], antimalarial activity [6], agonistic activity [7], and antipsychotic activity [8].

In view of the importance of the benzoquinoline and its derivatives, several methods for the synthesis of benzo[*f*]quinoline and its derivatives were developed by Kozlov [9] and other groups [10]. However, many of these reported methods suffer from drawbacks such as harsh reaction conditions, unsatisfactory yields, prolonged reaction time or cumbersome product isolation procedure. In our previous paper, we have reported the 1,3-substituented benzoquinolines *via* three component reaction of aromatic aldehyde, naphthalen-2-amine and ketones [11]. Our interest in synthesis of heterocyclic compounds [12] by multicomponent reaction stimulates us to find some new and more substituented benzoquinolines, such as 1,3-diaryl-2-halogenated benzoquinoline derivatives, so we perform the 2-halogenated acetophenone in the aforementioned reaction instead of acetophenone. To our surprised, the desired products 1,3-diaryl-2-halogenated benzoquinolines were not observed, with 1,3-diarylbenzoquinoline derivatives being obtained. It should be noted that the halogen lose in these I_2-catalyzed three-component reactions.

RESULTS AND DISCUSSION

Initially, the reaction of 4-chlorobenzaldehyde **1a**, naphthalen-2-amine **2** and 2-bromo-1-(4-nitrophenyl) ethanone **3a** was used as a model reaction to optimize the

Table 1

Synthesis of **4a** under different reaction conditions.[a]

Entry	Temperature(°C)	I_2 (mol %)	Solvent	Yields[b](%)
1	RT	0	THF	0
2	Reflux	0	THF	0
3	RT	5	THF	Trace
4	50	5	THF	76
5	Reflux	5	THF	90
6	Reflux	10	THF	86
7	Reflux	20	THF	89
8	Reflux	5	CH_3CN	82
9	Reflux	5	Benzene	78
10	80	5	DMF	84
11	Reflux	5	$ClCH_2CH_2Cl$	79

[a] Reagents and conditions: **1a** (2 mmol, 0.281 g), **2** (2 mmol, 0.286 g), **3a** (2 mmol, 0.488 g), solvent (10 mL), 12 h.

[b] Isolated yields.

conditions. The reaction was first carried out in THF in the absence of I_2. No reaction occurred at room temperature and reflux condition (Table 1, entries 1 and 2). We also evaluated the amount of catalyst required for this transformation. It was found that 5 mol % of I_2 at reflux in THF was sufficient to push the reaction forward. More amounts of the catalyst did not improve yields. To find the optimum reaction temperature, the reaction was carried out with 5 mol % of I_2 at room temperature, 50 and refluxing temperature, resulting in the isolation of **4a** in trace amount, 76% and 90% yields (Table 1, entries 3, 4, and 5), respectively. Thus, 5 mol % of I_2 and a reaction temperature at reflux were optimal conditions. In addition, we also looked into the solvent effect at reflux condition for this reaction. As showed in Table 1, THF gave the most satisfactory result in comparison with other solvents. (Table 1, entries 8–11).

In our initial study, we think it was an unexpected product. Subsequently, we repeated the reactions under the same reaction conditions with various kinds of benzaldehydes bearing either electron-withdrawing groups (such as halide, nitro) or electron-donating groups (such as alkyl group, or alkoxyl group) or α-halogenated acetophenones (Scheme 1). However, the designed reactions all gave the products of 1,3-diarylbenzoquinoline derivatives rather than 1,3-diaryl-2-halogenated benzoquinolines in good to high yields (Table 2). Furthermore, in order to confirm the structure of product, the X-ray diffraction of **4a** was carried out [13]. The crystal structure of **4a** was shown in Figure 1, which made further confirmation of structure **4**. This raises an interesting question: why do the halogens lose in the formation of the benzoquinolines?

According to the literatures [14], in these I_2-catalyzed reactions, the subsequent reactions including condensation, addition, Friedel–Crafts, dehydration and aromatization were proposed to form the quinoline or benzoquinoline derivatives (Scheme 2). However, no stereoselectivity was put forward in the Friedel–Crafts cyclization of the addition product. It is a Friedel–Crafts cyclization as well as an intra-molecular nucleophilic addition reaction with benzene as nucleophilic reagent attacking carboxyl group, with a chiral centre being connected with this carboxyl group. The stereochemistry of the Friedel–Crafts cyclization should be in agreement with Cram's rule, so the hydroxyl group and the hydrogen atom lie on syn periplanar geometry with halogen on the anti periplanar geometry. Subsequent elimination reaction of HX for their anti periplanar rather than H_2O results in oxirenoquinoline. The oxirane ring is opened to give 2-hydroxybenzoquinoline induced by iodine, which is further dehydrated to afford final 1,3-diaryl benzoquinoline (Scheme 2). The reason why the halogens lose is perhaps best explained by Cram's rule in the formation of the benzoquinolines.

In conclusion, we found an efficient method for the synthesis of benzo[*f*]quinoline derivatives via three-component reaction of aromatic aldehyde, naphthalen-2-amine and 2-halogenated acetophenone using 5 mol % of iodine as catalyst, with halogen losing in the formation of the products. A Cram's rule in the I_2-catalyzed Friedel–Crafts reaction was proposed to occur in the formation of the products.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a TENSOR 27 spectrometer in KBr pellet. ^1H NMR spectra were obtained from solution in DMSO-d_6 with Me_4Si as internal standard using a Bruker-400 spectrometer. HRMS analyses were carried out using a Bruker-micro-TOF-Q-MS analyzer.

Typical procedure for 1,3-diarylbenzo[f]quinoline derivatives 4. A dry 50 mL flask was charged with aromatic aldehyde (2.0 mmol), naphthalen-2-amine (2.0 mmol, 0.286 g), 2-halogenated acetophenone (2.0 mmol), I_2 (0.1 mmol, 0.026 g) and THF (10 mL). The reaction mixture was stirred at reflux for 11–15 h. After completion of the reaction as indicated by TLC, a little DMF was added to the mixture until the all yellow solid was dissolved. The generated crystals were collected by filtration to give 4 when the mixture was cooled to room temperature.

Scheme 1

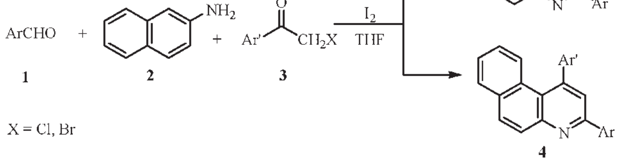


Table 2

I_2-catalyzed reactions of benzaldehyde, naphthalen-2-amine, and α-halogenated acetophenones in THF.[a]

Entry	Ar	Ar′	X	Products	Time (h)	Yields[b] (%)
1	4-ClC_6H_4	4-$NO_2C_6H_4$	Br	**4a**	12	90
2	2,3-$(CH_3O)_2C_6H_3$	4-$NO_2C_6H_4$	Br	**4b**	14	86
3	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	Br	**4c**	11	91
4	2,3-$Cl_2C_6H_3$	4-$NO_2C_6H_4$	Br	**4d**	12	82
5	2,4-$Cl_2C_6H_3$	4-$NO_2C_6H_4$	Br	**4e**	13	81
6	3,4-$(CH_3)_2C_6H_3$	4-$NO_2C_6H_4$	Br	**4f**	14	84
7	2,4-$Cl_2C_6H_3$	4-FC_6H_4	Br	**4g**	15	88
8	3-BrC_6H_4	4-FC_6H_4	Br	**4h**	12	79
9	4-ClC_6H_4	4-FC_6H_4	Br	**4i**	13	80
10	3,5-$(CH_3O)_2C_6H_3$	4-FC_6H_4	Br	**4j**	15	82
11	4-BrC_6H_4	4-FC_6H_4	Br	**4k**	13	89
12	3-$NO_2C_6H_4$	4-FC_6H_4	Br	**4l**	13	84
13	3-BrC_6H_4	4-ClC_6H_4	Br	**4m**	15	78
14	2,4-$Cl_2C_6H_3$	4-ClC_6H_4	Br	**4n**	12	83
15	2-Thiophenyl	3-ClC_6H_4	Br	**4o**	13	82
16	3-BrC_6H_4	3-ClC_6H_4	Br	**4p**	15	78
17	4-BrC_6H_4	3-ClC_6H_4	Br	**4q**	14	80
18	3-$NO_2C_6H_4$	3-ClC_6H_4	Br	**4r**	15	81
19	3,4-$(CH_3)_2C_6H_3$	3-ClC_6H_4	Br	**4s**	15	86
20	4-$NO_2C_6H_4$	C_6H_5	Cl	**4t**	12	82
21	4-ClC_6H_4	C_6H_5	Cl	**4u**	12	79
22	4-BrC_6H_4	C_6H_5	Cl	**4v**	14	87
23	3-BrC_6H_4	C_6H_5	Cl	**4w**	15	84
24	2-Thiophenyl	3-$NO_2C_6H_4$	Br	**4x**	15	89
25	4-ClC_6H_4	3-$NO_2C_6H_4$	Br	**4y**	13	86
26	4-BrC_6H_4	3-$NO_2C_6H_4$	Br	**4z**	15	86

[a] Reagents and conditions: **1** (2 mmol), **2** (2 mmol, 0.286g), **3** (2 mmol), I_2 (0.1 mmol, 0.026 g), and THF (10 mL).
[b] Isolated yields.

3-(4-Chlorophenyl)-1-(4-nitrophenyl)benzo[*f*] quinoline (4a). This compound was obtained as pale yellow crystals, mp 286–288°C; ir (KBr): ν_{max} 3101, 3074, 3048, 1596, 1580, 1544, 1514, 1493, 1476, 1449, 1408, 1388, 1344, 1305, 1282, 1177, 1152, 1107, 1091, 1010, 851, 832, 797, 758, 744, 717, 704, 692; ^{1}H NMR (DMSO-d_6): δ 7.28–7.32 (m, 1H, ArH), 7.48–7.50 (m, 1H, ArH), 7.57–7.64 (m, 3H, ArH), 7.85 (d, J = 8.4 Hz, 2H, ArH), 8.08 (d, J = 8.4 Hz, 2H, ArH), 8.09 (s, 1H, ArH), 8.21–8.23 (m, 1H, ArH), 8.41–8.47 (m, 4H, ArH). HRMS (ESI, *m*/*z*): calcd. for $C_{25}H_{16}N_2O_2$ (M+H$^+$) 411.0900, found 411.0915.

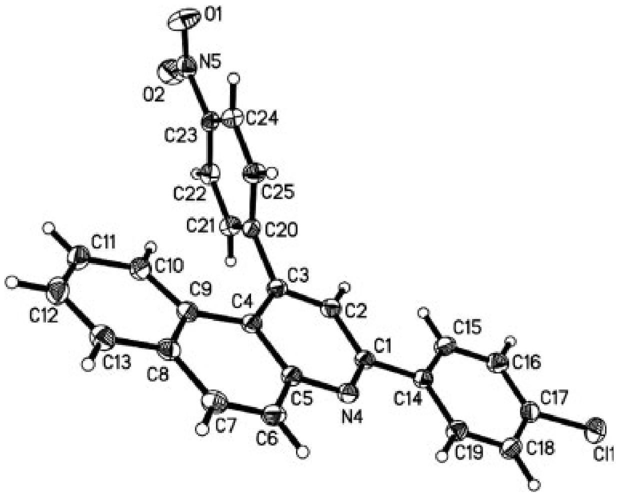


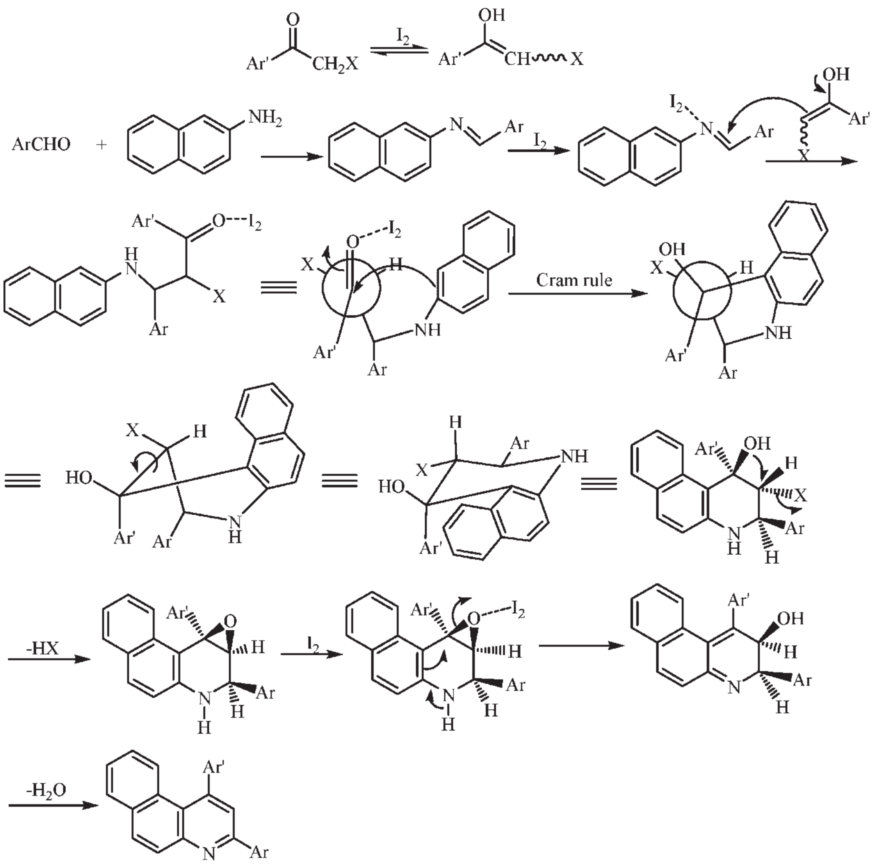
Figure 1. The crystal structure of product **4a.**

3-(2,3-Dimethoxyphenyl)-1-(4-nitrophenyl)benzo[*f*] quinoline (4b). This compound was obtained as pale yellow crystals, mp 140–141°C; ir (KBr): ν_{max} 3073, 3006, 2970, 2937, 2838, 1598, 1578, 1519, 1465, 1430, 1302, 1263, 1227, 1167, 1179, 1167, 1107, 1085, 1040, 1001, 856, 837, 805, 781, 746, 703; ^{1}H NMR (DMSO-d_6): δ 3.75 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 7.05 (dd, J = 8.0 Hz, J' = 1.2 Hz, 1H, ArH), 7.19–7.26 (m, 2H, ArH), 7.51–7.61 (m, 3H, ArH), 7.68 (d, J = 8.8 Hz, 2H, ArH), 7.91–7.93 (m, 2H, ArH), 8.03 (d, J = 8.8 Hz, 1H, ArH), 8.14 (d, J = 8.8 Hz, 1H, ArH), 8.39 (d, J = 8.8 Hz, 2H, ArH). HRMS (ESI, *m*/*z*): calcd. for $C_{27}H_{21}N_2O_4$ (M+H$^+$) 437.1501, found 437.1498.

3-(4-Nitrophenyl)-1-(4-nitrophenyl)benzo[*f*]quinoline (4c). This compound was obtained as pale yellow crystals, mp 235–237°C, Lit.[15] 231–232 °C; ir (KBr): ν_{max} 3083, 1598, 1578, 1545, 1514, 1450, 1343, 1257, 1163, 1106, 1084, 1041, 1015, 993, 850, 816, 750, 694; ^{1}H NMR (DMSO-d_6): δ 7.22–7.24 (m, 1H, ArH), 7.54–7.59 (m, 2H, ArH), 7.70 (d, J = 8.4 Hz, 2H, ArH), 7.82 (s, 1H, ArH), 7.95 (d, J = 7.6 Hz, 1H, ArH), 8.09 (d, J = 9.2 Hz, 1H, ArH), 8.15 (d, J = 8.8 Hz, 1H, ArH), 8.38–8.46 (m, 6H, ArH). HRMS (ESI, *m*/*z*): calcd. for $C_{25}H_{16}N_3O_4$ (M+H$^+$) 422.1141, found 422.1145.

3-(2,3-Dichlorophenyl)-1-(4-nitrophenyl)benzo[*f*]quinoline (4d). This compound was obtained as pale yellow crystals, mp 196–197°C; ir (KBr): ν_{max} 3099, 3056, 1597, 1575, 1545,

Scheme 2



1515, 1478, 1446, 1412, 1341, 1286, 1251, 1192, 1156, 1124, 1104, 1049, 875, 859, 844, 789, 767, 723, 705; ^{1}H NMR (DMSO-d_6): δ 7.21–7.25 (m, 1H, ArH), 7.36–7.40 (m, 1H, ArH), 7.53–7.59 (m, 3H, ArH), 7.65–7.71 (m, 4H, ArH), 7.94 (d, J = 7.6 Hz, 1H, ArH), 8.06 (d, J = 9.2 Hz, 1H, ArH), 8.11 (d, J = 9.2 Hz, 1H, ArH), 8.40 (d, J = 8.8 Hz, 2H, ArH). HRMS (ESI, *m/z*): calcd. for $C_{25}H_{15}N_2Cl_2O_2$ (M+H$^+$) 445.0511, found 445.0508.

3-(2,4-Dichlorophenyl)-1-(4-nitrophenyl)benzo[*f*]quinoline (4e). This compound was obtained as pale yellow crystals, mp 202–203°C. ir (KBr): ν_{max} 3104, 3077, 1589, 1579, 1556, 1545, 1516, 1473, 1448, 1381, 1348, 1249, 1162, 1142, 1102, 1048, 1038, 991, 860, 838, 824, 803, 789, 758, 707; ^{1}H NMR (DMSO-d_6): δ 7.30–7.34 (m, 1H, ArH), 7.54 (d, J = 8.4 Hz, 1H, ArH), 7.60–7.66 (m, 2H, ArH), 7.78 (s, 1H, ArH), 7.82–7.89 (m, 4H, ArH), 8.06 (d, J = 8.8 Hz, 1H, ArH), 8.11 (d, J = 8.0 Hz, 1H, ArH), 8.25 (d, J = 9.2 Hz, 1H, ArH), 8.44 (d, J = 8.8 Hz, 2H, ArH). HRMS (ESI, *m/z*): calcd. for $C_{25}H_{15}N_2Cl_2O_2$ (M+H$^+$) 445.0511, found 445.0493.

3-(3,4-Dimethylphenyl)-1-(4-nitrophenyl)benzo[*f*]quinoline (4f). This compound was obtained as pale yellow crystals, mp 234–236°C; ir (KBr): ν_{max} 3068, 2974, 2917, 2858, 1595, 1579, 1544, 1452, 1477, 1451, 1339, 1283, 1260, 1126, 1103, 1015, 1005, 885, 860, 851, 831, 802, 759, 742, 714, 705; ^{1}H NMR (DMSO-d_6): δ 2.31 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 7.29–7.34 (m, 2H, ArH), 7.48 (d, J = 8.8 Hz, 1H, ArH), 7.55–7.59 (m, 1H, ArH), 7.85 (d, J = 8.4 Hz, 2H, ArH), 8.02 (s, 1H, ArH), 8.06–8.12 (m, 3H, ArH), 8.17–8.21 (m, 2H, ArH), 8.45 (d, J = 8.4 Hz, 2H, ArH). HRMS (ESI, *m/z*): calcd. for $C_{27}H_{21}N_2O_2$ (M+H$^+$) 405.1603, found 405.1593.

3-(2,4-Dichlorophenyl)-1-(4-fluorophenyl)benzo[*f*]quinoline (4g). This compound was obtained as pale yellow crystals, mp 172–174°C; ir (KBr): ν_{max} 3069, 1601, 1586, 1555, 1507, 1475, 1448, 1378, 1347, 1332, 1246, 1217, 1158, 1139, 1100, 1048, 1038, 1016, 952, 896, 873, 859, 849, 825, 805, 775, 752; ^{1}H NMR (DMSO-d_6): δ 7.28–7.30 (m, 1H, ArH), 7.32–7.45 (m, 2H, ArH), 7.53–7.63 (m, 5H, ArH), 7.71 (s, 1H, ArH), 7.81 (d, J = 2.0 Hz, 1H, ArH), 7.85 (d, J = 8.4 Hz, 1H, ArH), 8.02 (d, J = 8.8 Hz, 1H, ArH), 8.07 (d, J = 7.6 Hz, 1H, ArH), 8.20 (d, J = 8.8 Hz, 1H, ArH). HRMS (ESI, *m/z*): calcd. for $C_{25}H_{15}Cl_2NF$ (M+H$^+$) 418.0566, found 418.0550.

3-(3-Bromophenyl)-1-(4-fluorophenyl)benzo[*f*]quinoline (4h). This compound was obtained as pale yellow crystals, mp 221–222°C; ir (KBr): ν_{max} 3058, 1601, 157 2, 1542, 1506, 1477, 1446, 1386, 1344, 1328, 1252, 1230, 1154, 1088, 1069, 994, 873, 834, 796, 782, 756, 709, 689; ^{1}H NMR (DMSO-d_6): δ 7.26–7.30 (m, 1H, ArH), 7.42–7.46 (m, 2H, ArH), 7.50–7.59 (m, 5H, ArH), 7.69–7.72 (m, 1H, ArH), 8.03–8.07 (m, 3H, ArH, 8.17 (d, J = 9.2 Hz, 1H, ArH), 8.36 (d, J = 8.0 Hz, 1H, ArH), 8.56–8.57 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd. for $C_{25}H_{16}BrFN$ (M+H$^+$) 428.0450, found 428.0468.

3-(4-Chlorophenyl)-1-(4-fluorophenyl)benzo[*f*]quinoline (4i). This compound was obtained as pale yellow crystals, mp 173–174°C; ir (KBr): ν_{max} 3054, 1602, 1579, 1544, 1505, 1 478, 1449, 1406, 1385, 1356, 1330, 1215, 1155, 1090, 1010, 866, 830, 799, 745, 714; ^{1}H NMR (DMSO-d_6): δ 7.25–7.30

(m, 1H, ArH), 7.42–7.46 (m, 2H, ArH), 7.54–7.63 (m, 6H, ArH), 8.01 (s, 1H, ArH), 8.04 (d, J = 8.8 Hz, 2H, ArH), 8.16 (d, J = 9.2 Hz, 1H, ArH), 8.36 (d, J = 8.4 Hz, 1H, ArH), 8.39 (d, J = 8.8 Hz, 2H, ArH). HRMS (ESI, *m/z*): calcd. for $C_{25}H_{16}ClFN$ (M+H$^+$) 384.0955, found 384.0966.

3-(3,5-Dimethoxyphenyl)-1-(4-fluorophenyl)benzo[*f*]quinoline (4j). This compound was obtained as pale yellow crystals, mp 119–120°C; ir (KBr): ν_{max} 3051, 2984, 2952, 2935, 2830, 1592, 1549, 1528, 1508, 1488, 1451, 1357, 1301, 1216, 1201, 1157, 1061, 1047, 941, 862, 833, 807, 752, 698; ^{1}H NMR (DMSO-d_6): δ 3.87 (s, 6H, 2CH$_3$O), 6.64–6.66 (m, 1H, ArH), 7.27–7.29 (m, 1H, ArH), 7.42–7.46 (m, 2H, ArH), 7.50 (d, J = 2.4 Hz, 2H, ArH), 7.54–7.59 (m, 4H, ArH), 8.01–8.05 (m, 3H, ArH), 8.16 (d, J = 9.2 Hz, 1H, ArH). HRMS (ESI, *m/z*): calcd. for $C_{27}H_{21}FNO_2$ (M+H$^+$) 410.1556, found 410.1558.

3-(4-Bromophenyl)-1-(4-fluorophenyl)benzo[*f*]quinoline (4k). This compound was obtained as white powder, mp 167–169°C, ir (KBr): ν_{max} 3050, 1603, 1579, 1544, 1505, 1475, 1448, 1354, 1227, 1153, 1089, 1073, 1007, 865, 830, 756; ^{1}H NMR (DMSO-d_6): δ 7.26–7.30 (m, 1H, ArH), 7.42–7.47 (m, 2H, ArH), 7.55–7.59 (m, 4H, ArH), 7.25 (d, J = 8.8 Hz, 2H, ArH), 8.02 (s, 1H, ArH), 8.04 (d, J = 8.8 Hz, 2H, ArH), 8.17 (d, J = 8.8 Hz, 1H, ArH), 8.33 (d, J = 8.4 Hz, 2H, ArH). HRMS (ESI, *m/z*): calcd. for $C_{25}H_{16}FBrN$ (M+H$^+$) 428.0450, found 428.0435.

1-(4-Fluorophenyl)-3-(3-nitrophenyl)benzo[*f*]quinoline (4l). This compound was obtained as pale yellow crystals, mp 222–224°C; ir (KBr): ν_{max} 3055, 1605, 1580, 1527, 1481, 1450, 1434, 1345, 1256, 1225, 1163, 1109, 1072, 896, 873, 849, 834, 801, 791, 746, 712; ^{1}H NMR (DMSO-d_6): δ 7.21–7.29 (m, 3H, ArH), 7.45–7.55 (m, 3H, ArH), 7.67–7.73 (m, 2H, ArH), 7.82 (s, 1H, ArH), 7.91 (d, J = 7.6 Hz, 1H, ArH), 8.04 (d, J = 8.8 Hz, 2H, ArH), 8.13 (d, J = 8.8 Hz, 1H, ArH), 8.30–8.33 (m, 1H, ArH), 8.61–8.63 (m, 1H, ArH), 9.08–9.09 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd. for $C_{25}H_{16}FN_2O_2$ (M+H$^+$) 395.1196, found 395.1196.

3-(3-Bromophenyl)-1-(4-chlorophenyl)benzo[*f*]quinoline (4m). This compound was obtained as white powder, mp 218–220°C; ir (KBr): ν_{max} 3049, 1595, 1577, 1564, 1547, 1524, 1491, 1477, 1449, 1394, 1350, 1330, 1255, 1236, 1084, 1067, 1015, 993, 890, 870, 837, 804, 755, 710, 699; ^{1}H NMR (DMSO-d_6): δ 7.29–7.32 (m, 1H, ArH), 7.50–7.72 (m, 8H, ArH), 8.04–8.08 (m, 3H, ArH), 8.18 (d, J = 9.2 Hz, 1H, ArH), 8.37 (d, J = 8.0 Hz, 1H, ArH), 8.51–8.58 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd. for $C_{25}H_{16}BrClN$ (M+H$^+$) 444.0155, found 444.0155.

3-(2,4-Dichlorophenyl)-1-(4-chlorophenyl)benzo[*f*]quinoline (4n). This compound was obtained as pale yellow crystals, mp 172–174°C; ir (KBr): ν_{max} 3086, 3049, 1585, 1552, 1524, 1490, 1474, 1448, 1392, 1378, 1347, 1332, 1247, 1138, 1100, 1090, 1047, 1037, 1013, 952, 871, 861, 834, 822, 802, 791, 751, 716; ^{1}H NMR (DMSO-d_6): δ 7.30–7.35 (m, 1H, ArH), 7.54 (d, J = 8.4 Hz, 1H, ArH), 7.59–7.66 (m, 5H, ArH), 7.71 (m, 1H, ArH), 7.82 (d, J = 2.4 Hz, 1H, ArH), 7.86 (d, J = 8.4 Hz, 1H, ArH), 8.03 (d, J = 9.2 Hz, 1H, ArH), 8.08 (d, J = 7.6 Hz, 1H, ArH), 8.21 (d, J = 9.2 Hz, 1H, ArH). HRMS (ESI, *m/z*): calcd. for $C_{25}H_{15}Cl_3N$ (M+H$^+$) 434.0270, found 434.0264.

1-(3-Chlorophenyl)-3-(2-thiophenyl)benzo[*f*]quinoline (4o). This compound was obtained as pale yellow crystals, mp 211–213°C; ir (KBr): ν_{max} 3097, 3067, 1580, 1562, 1469, 1453, 1421, 1352, 1321, 1255, 1242, 1166, 1154, 1098, 1068, 1027, 860, 851, 829, 794, 779, 744, 716; ^{1}H NMR (DMSO-d_6): δ 7.21–7.23 (m, 1H, ArH), 7.24–7.28 (m, 1H, ArH), 7.43–7.67 (m, 6H, ArH), 7.76 (dd, J = 8.0 Hz, J' = 1.2 Hz, 1H, ArH), 7.95 (d, J = 8.8 Hz, 1H, ArH), 8.02 (s, 1H, ArH), 8.03 (d, J = 8.8 Hz, 1H, ArH), 8.09 (dd, J = 8.0 Hz, J' = 1.2 Hz, 1H, ArH), 8.15 (d, J = 8.8 Hz, 1H, ArH). HRMS (ESI, *m/z*): calcd. for $C_{23}H_{15}ClNS$ (M+H$^+$) 372.0614, found 372.0625.

3-(3-Bromophenyl)-1-(3-chlorophenyl)benzo[*f*]quinoline (4p). This compound was obtained as pale yellow crystals, mp 195–196°C; ir (KBr): ν_{max} 3052, 1592, 1578, 1544, 1529, 1467, 1451, 1407, 1382, 1358, 1327, 1262, 1239, 1161, 1098, 1078, 1066, 951, 881, 872, 834, 793, 770, 745, 718, 702, 692; ^{1}H NMR (DMSO-d_6): δ 7.27–7.32 (m, 1H, ArH), 7.46 (dd, J = 7.6 Hz, J' = 1.2 Hz, 1H, ArH), 7.51–7.73 (m, 7H, ArH), 8.05–8.11 (m, 3H, ArH), 8.20 (d, J = 8.8 Hz, 1H, ArH), 8.39 (d, J = 8.0 Hz, 1H, ArH), 8.59–8.60 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd. for $C_{25}H_{16}BrClN$(M+H$^+$) 444.0155, found 444.0163.

3-(4-Bromophenyl)-1-(3-chlorophenyl)benzo[*f*]quinoline (4q). This compound was obtained as pale yellow crystals, mp 216–218°C; ir (KBr): ν_{max} 3047, 1578, 1562, 1543, 1527, 1472, 1451, 1417, 1384, 1355, 1329, 1101, 1074, 1008, 871, 862, 834, 825, 806, 784, 745, 718, 706; ^{1}H NMR (DMSO-d_6): δ 7.28–7.32 (m, 1H, ArH), 7.47 (d, J = 7.2 Hz, 1H, ArH), 7.56–7.69 (m, 5H, ArH), 7.76 (d, J = 8.4 Hz, 2H, ArH), 8.05–8.08 (m, 3H, ArH), 8.19 (d, J = 9.2 Hz, 1H, ArH), 8.35 (d, J = 8.4 Hz, 2H, ArH). HRMS (ESI, *m/z*): calcd. for $C_{25}H_{16}BrClN$ (M+H$^+$) 444.0155, found 444.0157.

1-(3-Chlorophenyl)-3-(3-nitrophenyl)benzo[*f*]quinoline (4r). This compound was obtained as pale yellow crystals, mp 221–222°C; ir (KBr): ν_{max} 3052, 1580, 1563, 1531, 1484, 1472, 1450, 1408, 1347, 1297, 1278, 1256, 1237, 1164, 1113, 1098, 1074, 909, 871, 833, 801, 745, 717, 704; ^{1}H NMR (DMSO-d_6): δ 7.28–7.32 (m, 1H, ArH), 7.47 (d, J = 7.2 Hz, 1H, ArH), 7.56–7.70 (m, 5H, ArH), 7.82–7.86 (m, 1H, ArH), 8.06–8.11 (m, 2H, ArH), 8.20– 8.22 (m, 2H, ArH), 8.35 (d, J = 7.6 Hz, 1H, ArH), 8.81 (d, J = 7.6 Hz, 1H, ArH), 9.17 (s, 1H, ArH). HRMS (ESI, *m/z*): calcd. for $C_{25}H_{16}N_2O_2$ (M+H$^+$) 411.0900, found 411.0899.

1-(3-Chlorophenyl)-3-(3,4-dimethylphenyl)benzo[*f*]quinoline (4s). This compound was obtained as yellow crystals, mp 182–184°C; ir (KBr): ν_{max} 3053, 2963, 2939, 2916, 1580, 1561, 1544, 1505, 1471, 1451, 1416, 1390, 1345, 1327, 1258, 1246, 1163, 1133, 1097, 1073, 998, 890, 873, 832, 812, 790, 745, 716, 705; ^{1}H NMR (DMSO-d_6): δ 2.31 (s, 3H, CH$_3$), 2.35 (s, 3H, CH$_3$), 7.25–7.32 (m, 2H, ArH), 7.44–7.47 (m, 1H, ArH), 7.53–7.67 (m, 5H, ArH), 7.98 (s, 1H, ArH), 8.03–8.10 (m, 3H, ArH), 8.15– 8.17 (m, 2H, ArH). HRMS (ESI, *m/z*): calcd. for $C_{27}H_{21}NCl$ (M+H$^+$) 394.1363, found 394.1366.

3-(4-Nitrophenyl)-1-phenylbenzo[*f*]quinoline (4t). This compound was obtained as yellow crystals, mp 200-201 °C, Lit.[15] 192 °C; ir (KBr): ν_{max} 3053, 1599, 1578, 1547, 1509, 1475, 1397, 1340, 1259, 1153, 1106, 1078, 1008, 860, 849, 832, 774, 755, 699; ^{1}H NMR (DMSO-d_6): δ 7.22–7.25 (m, 1H, ArH), 7.55–7.63 (m, 7H, ArH), 8.07 (d, J = 7.0 Hz, 1H, ArH), 8.11 (d, J = 9.2 Hz, 1H, ArH), 8.17 (s, 1H, ArH), 8.22 (d, J = 8.8 Hz, 1H, ArH), 8.40 (d, J = 8.8 Hz, 2H, ArH), 8.67 (d, J = 8.8 Hz, 2H, ArH). HRMS (ESI, *m/z*): calcd. for $C_{25}H_{17}N_2O_2$ (M+H$^+$) 377.1290, found 377.1274.

3-(4-Chlorophenyl)-1-phenylbenzo[*f*]quinoline (4u). This compound was obtained as yellow crystals, mp 164–165°C; ir (KBr): ν_{max} 3051, 1576, 1545, 1527, 1491, 1474, 1449, 1354, 1279, 1255.1167, 1088, 1009, 834, 722, 753, 700; ^{1}H NMR (DMSO-d_6): δ 7.19–7.23 (m, 1H, ArH), 7.51–7.62 (m, 9H, ArH), 8.01–8.07 (m, 3H, ArH), 8.17 (d, *J* = 8.8 Hz, 1H, ArH), 8.41 (d, *J* = 8.4 Hz, 2H, ArH). HRMS (ESI, *m/z*): calcd. for $C_{25}H_{17}ClN$ (M+H$^{+)}$ 366.1050, found 366.1057.

3-(4-Bromophenyl)-1-phenylbenzo[*f*]quinoline (4v). This compound was obtained as yellow crystals, mp 171–172°C; ir (KBr): ν_{max} 3051, 3028, 1575, 1544, 1527, 1474, 1448, 1353, 1329, 1278, 1256, 1073, 1006, 833, 814, 771, 753, 700; ^{1}H NMR (DMSO-d_6): δ 7.19–7.23 (m, 1H, ArH), 7.51–7.61 (m, 7H, ArH), 7.75 (d, *J* = 8.4 Hz, 2H, ArH). 8.01–8.07 (m, 3H, ArH), 8.17 (d, *J* = 8.8 Hz, 1H, ArH), 8.33 (d, *J* = 8.4 Hz, 2H, ArH). HRMS (ESI, *m/z*): calcd. for $C_{25}H_{17}BrN$ (M+H^{+}) 410.0544, found 410.0544.

3-(3-Bromophenyl)-1-phenylbenzo[*f*]quinoline (4w). This compound was obtained as yellow crystals, mp 207–209°C; ir (KBr): ν_{max} 3054, 1576, 1542, 1522, 1476, 1447, 1388, 1345, 1328, 1252, 1231, 1083, 1069, 995, 943, 869, 838, 781, 756, 702, 689; ^{1}H NMR (DMSO-d_6): δ 7.15–7.19 (m, 1H, ArH), 7.37–7.41 (m, 1H, ArH), 7.47–7.59 (m, 7H, ArH), 7.67 (d, *J* = 8.4 Hz, 1H, ArH), 7.77 (s, 1H, ArH), 7.89 (d, *J* = 8.0 Hz, 1H, ArH), 8.02 (d, *J* = 9.2 Hz, 1H, ArH), 8.10–8.16 (m, 2H, ArH), 8.41 (s, 1H, ArH). HRMS (ESI, *m/z*): calcd. for $C_{25}H_{17}BrN$ (M+H^{+}) 410.0544, found 410.0556.

1-(3-Nitrophenyl)-3-(2-thiophenyl) benzo[*f*]quinoline (4x). This compound was obtained as yellow crystals, mp 278–280°C; ir (KBr): ν_{max} 3050, 1584, 1845, 1525, 1484, 1454, 1420, 1347, 1259, 1042, 1092, 1083, 883, 870, 835, 799, 753, 743, 696; ^{1}H NMR (DMSO-d_6): δ 7.23–7.27 (m, 2H, ArH), 7.46 (d, *J* = 8.4 Hz, 1H, ArH), 7.54–7.58(m, 1H, ArH), 7.78 (dd, *J* = 5.2 Hz;*J*′ = 1.2 Hz, 1H, ArH), 7.85–7.90 (m, 1H, ArH), 7.94–7.97 (m, 2H, ArH), 8.05 (d, *J* = 8.8 Hz, 1H, ArH), 8.09–8.10 (m, 2H, ArH), 8.18 (d, *J* = 8. 8 Hz, 1H, ArH), 8.45–8.47 (m, 2H, ArH). HRMS (ESI, *m/z*): calcd. for $C_{23}H_{15}N_2O_2S$ (M+H^{+}) 383.0854, found 383.0841.

3-(4-Chlorophenyl)-1-(3-nitrophenyl)benzo[*f*] quinoline (4y). This compound was obtained as yellow crystals, mp 258–259°C; ir (KBr): ν_{max} 3083, 3058, 1582, 1527, 1489, 1451, 1407, 1351, 1303, 1258, 1209, 1164, 1092, 1047, 1009, 892, 862, 832, 813, 745, 715; ^{1}H NMR (DMSO-d_6): δ 7.24–7.28 (m, 1H, ArH), 7.51 (d, *J* = 8.4 Hz, 1H, ArH), 7.56–7.60 (m, 1H, ArH), 7.62 (d, *J* = 8.4 Hz, 2H, ArH), 7.85–7.88 (m, 1H, ArH), 7.95 (d, *J* = 7.6 Hz, 1H, ArH), 8.06–8.08 (m, 2H, ArH), 8.13 (s, 1H, ArH), 8.20 (d, *J* = 9.2 Hz, 1H, ArH), 8.42 (d, *J* = 8.4 Hz, 2H, ArH), 8.45–8.47 (m, 2H, ArH). HRMS (ESI, *m/z*): calcd. for $C_{25}H_{16}ClN_2O_2$ (M+H^{+}) 411.0900, found 411.0894.

3-(4-Bromophenyl)-1-(3-nitrophenyl)benzo[*f*] quinoline (4z). This compound was obtained as yellow crystals, mp 263–264°C; ir (KBr): ν_{max} 3056, 1581, 1527, 1486, 1451, 1384, 1351, 1304, 1258, 1210, 1179, 1163, 1075, 1006, 891, 861, 831, 814, 744, 705; ^{1}H NMR (DMSO-d_6): δ 7.25–7.29 (m, 1H, ArH), 7.52 (d, *J* = 8.4 Hz, 1H, ArH), 7.57–7.61(m, 1H, ArH), 7.77 (d, *J* = 8.4 Hz, 2H, ArH), 7.88 (d, *J* = 8.0 Hz, 1H, ArH), 7.95–7.97 (m, 1H, ArH), 8.04–8.10 (m, 2H, ArH), 8.15 (m, 1H, ArH), 8.27 (d, *J* = 9.2 Hz, 1H, ArH), 8.37 (d, *J* = 8.4 Hz, 2H, ArH), 8.45–8.48 (m, 2H, ArH). HRMS (ESI, *m/z*): calcd. for $C_{25}H_{16}BrN_2O_2$ (M+H^{+}) 455.0395, found 455.0399.

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[13] Crystal data for **4a**: $C_{25}H_{15}ClN_2O_2$; *M* = 410.84, colorless block crystals, 0.34 × 0.32 × 0.22 mm^{3}, Triclinic, space group P-1, *a* = 9.1390 (12), *b* = 9.5350 (11), *c* = 11.9668 (17) Å, α = 108.182 (4), β = 105.366 (4), γ = 92.739 (3)°, *V* = 945.6 (2) ^{3}, *Z* = 2, D_c = 1.443 g cm^{-3}. *F*(000) = 424, μ(Mo*K*α) = 0.228 mm^{-1}. Intensity data were collected on Rigaku Mercury diffractometer with graphite monochromated Mo*K*α radiation (λ = 0.71070 Å) using ω scan mode with 2.27 ° < θ < 27.87 °. 4467

unique reflections were measured and 3779 reflections with $I > 2\sigma(I)$ were used in the refinement. Structure solved by direct methods and expanded using Fourier techniques. The final cycle of full-matrix least squares technique to $R = 0.0493$ and $wR = 0.1209$.

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A Novel and Efficient Method for the Synthesis of 5-Arylnaphtho[2,1-*c*][2,7]naphthyridine Derivatives Catalyzed by Iodine

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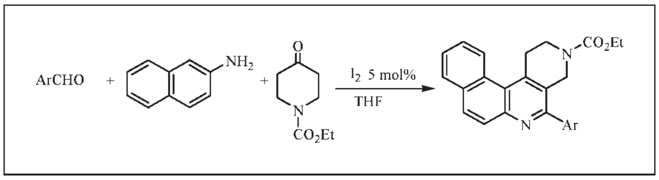

A novel method for the synthesis of 1,2-dihydro-5-arylnaphtho[2,1-*c*][2,7]naphthyridine derivatives via a three-component reaction of aromatic aldehyde, naphthalen-2-amine, and *N*-substituted piperidin-4-one derivatives is described using 5 mol % iodine as catalyst. The features of this new procedure are mild reaction condition, high yield, operational simplicity, and uses available reactants.

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INTRODUCTION

Multicomponent reactions (MCRs) can be distinguished from classical, sequential two-component chemistry synthesis processes in that they use three or more chemical starting materials as the input for product formation. Up to seven starting components have been used, and MCRs have often been shown to produce higher product yields than classical chemistry [1]. They provide a powerful tool toward the one-pot synthesis of diverse and complex compounds, as well as small and drug-like heterocycles [2].

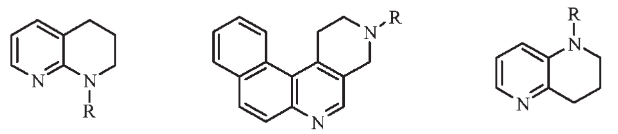
The naphtho[2,1-*c*][2,7]naphthyridine **1** ring system (Fig. 1) is a rare heterocycle compared with [1,8]naphthyridine **2** and [1,5]naphthyridine **3** substructures. Naphthyridines, which encompass two pyridine rings, are known to display a wide range of biological activities, including antibacterial activity [3], antimalarial activity [4], antimicrobial activity [5], anticancer activity [6], and antiinflammatory activity [7]. Moreover, it is envisioned that naphtho[2,1-*c*][2,7]naphthyridines **1**, which contained both naphthalene ring and naphthyridine moieties, may afford unique biological activities, such as Barta-Szalai et al. [8] revealed in 2003 that spiro[naphto[2,1-*c*][2,7]naphtiridine-5,4'-piperidine] derivatives were potent inhibitors of lipid peroxidation.

Previously, it has been demonstrated that naphthonaphthyridines can be obtained from 2-aminobenzo[*f*]-quinoline with glycerol in the presence of H_2SO_4 [9], or by the Skraup reaction of 3-aminobenzo[*h*]quinoline with ketone [10], or by any other methods [11]. However, despite their potential utility, many of these reported methods suffer from drawbacks such as harsh reaction conditions, unsatisfactory yields, prolonged reaction time, multistep reactions, and cumbersome product isolation procedure. This work is in connection with our previous research on the MCRs to the intriguing heterocycles [12] and successfully realized a three-component reaction of aromatic aldehyde, naphthalen-2-amine, and *N*-substituted piperidin-4-one catalyzed by iodine in THF without isolating and purifying the intermediates to afford naphtho[2,1-*c*][2,7]naphthyridine moiety.

RESULTS AND DISCUSSION

The treatment of aromatic aldehyde **4**, naphthalen-2-amine **5**, and ethyl 4-piperidinone-1-carboxylate **6** in THF in the presence of 5 mol % iodine at reflux afforded the corresponding ethyl 1,2-dihydro-5-arylnaphtho[2,1-*c*][2,7]naphthyridine-3(4*H*)-carboxylate derivatives **1** in high yields (Scheme 1).

In an initial endeavor, 3,4-dichlorobenzaldehyde **4a**, naphthalen-2-amine **5**, and ethyl 4-piperidinone-1-carboxylate **6** were stirred in THF in the absence of I_2. No reaction occurred at room temperature and reflux condition (Table 1, entries 1 and 2). Similar reactions were then attempted in the presence of 5, 10, and 20 mol % of I_2. The results from Table 1 (entries 5–7) showed



2 1 3

[1,8]naphthyridine naphtho[2,1-c][2,7]naphthyridine [1,5]naphthyridine

Figure 1.

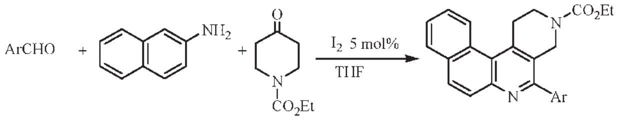
that 5 mol % I_2 at reflux in THF was sufficient to push the reaction forward. Based on these observations, we have also conducted the reaction with 5 mol % of I_2 at room temperature, and 50 mol % at reflux temperature, resulting in the isolation of **1a** in trace amount, 62 and 91% yields (Table 1, entries 3–5), respectively. In addition, CH_3CN, benzene, DMF, and $CHCl_3$ (Table 1, entries 8–11) were also tested as the solvents. In these cases, product **1a** was formed in slightly lower yield (Table 1, entries 8–11).

To evaluate the efficiency of iodine as a catalyst, a range of benzaldehydes **4b–p** were subjected to react with **5** and **6** in the presence of 5 mol % I_2 to generate **1**, and the results are summarized in Table 2. It can be observed that the process tolerates both electron-donating and electron-withdrawing substituents in the benzaldehydes. In all cases, the reactions proceeded efficiently at reflux under mild conditions to afford the corresponding naphtho[2,1-*c*][2,7]naphthyridines in high yields (Table 2).

The structure of **1** was characterized by ^{1}H NMR, IR, and HRMS. The analyses were in agreement with their structures. For example, in the ^{1}H NMR of **1a**, the protons on the ethyl group appear at 1.31 (triplet, $J = 6.8$ Hz) and 4.22 ppm (quartet, $J = 6.8$ Hz), respectively. The adjacent methylene groups exhibit two triplets at 3.66 ($J = 5.6$ Hz) and 3.76 ($J = 5.6$ Hz), respectively. The singlet at 4.73 ppm is assigned as another methylene group in the pyridine moiety. Totally, nine corresponding protons detected make further confirmation of structure **1a**. The IR spectra for **1a** exhibit strong bands at 1715 cm^{-1} for the carboxyl group in the structure. The HRMS of **1a** is in good agreement with its structure (Calcd for $C_{25}H_{20}Cl_2N_2NaO_2$ (M+Na$^+$) 473.0800, found 473.0791) with a deviation of 1.9 ppm.

As expected, the substrate of ethyl 4-piperidinone-1-carboxylate could be extended to other 4-piperidinones.

Scheme 1



4 5 6 1

Table 1

Synthesis of **1a** in THF under different reaction conditions.[a]

Entry	Temperature (°C)	I_2 (mol %)	Solvent	Yields[b] (%)
1	RT	0	THF	0
2	Reflux	0	THF	0
3	RT	5	THF	Trace
4	50	5	THF	62
5	Reflux	5	THF	91
6	Reflux	10	THF	88
7	Reflux	20	THF	89
8	Reflux	5	CH_3CN	82
9	Reflux	5	Benzene	86
10	80	5	DMF	78
11	Reflux	5	$CHCl_3$	83

[a] Reagents and conditions: **4** (0.350 g, 2 mmol), **5** (0.286 g, 2 mmol), **6** (0.343 g, 2 mmol), solvent (10 mL).

[b] Isolated yields.

The 1-(3-chlorobenzoyl)-4-piperidinone was also chosen as reactant to react with benzaldehyde, naphthalen-2-amine (Scheme 2), and were found to generate the corresponding naphtho[2,1-*c*][2,7]naphthyridines (**8a-8d**, Table 3). However, to our surprise, we failed to get the expected products when 4-piperidinone, *N*-methyl-4-piperidinone, and *N*-benzyl-4-piperidinone were used as reactants. Perhaps the stabilities of these above-mentioned 4-piperidinones restrained their reactions.

It was interesting that the 1,4-di(1,2,3,4-tetrahydro-3-ethoxycarbonyl-naphtho[2,1-*c*][2,7]naphthyridine-5-yl) benzene **9** was obtained in 87% yield when

Table 2

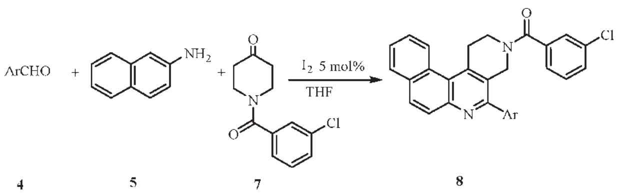
I_2 catalyzed reaction of benzaldehydes, naphthalen-2-amine, and ethyl 4-piperidinone-1-carboxylate in THF.[a]

Entry	Ar	Products	Time (h)	Yields[b] (%)
1	3,4-$Cl_2C_6H_3$	**1a**	14	91
2	3-$NO_2C_6H_4$	**1b**	12	92
3	2-Thiophenyl	**1c**	16	81
4	2,4-$Cl_2C_6H_3$	**1d**	14	83
5	4-BrC_6H_4	**1e**	12	86
6	4-ClC_6H_4	**1f**	12	88
7	2,3-$Cl_2C_6H_3$	**1g**	10	90
8	4-$NO_2C_6H_4$	**1h**	10	87
9	4-FC_6H_4	**1i**	14	87
10	2-$NO_2C_6H_4$	**1j**	10	90
11	3-ClC_6H_4	**1k**	16	83
12	4-$CH_3OC_6H_4$	**1l**	18	82
13	4-Cl-2-$NO_2C_6H_3$	**1m**	10	84
14	C_6H_5	**1n**	16	83
15	2-FC_6H_4	**1o**	12	88
16	3,5-$(CH_3O)_2C_6H_3$	**1p**	16	86

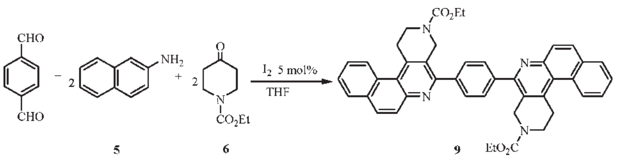
[a] Reagents and conditions: **4** (2 mmol), **5** (2 mmol, 0.286 g), **6** (2 mmol, 0.342 g), I_2 (0.1 mmol, 0.026 g), THF (10 mL).

[b] Isolated yields.

Scheme 2



Scheme 3



terephthalaldehyde was chosen as aromatic aldehyde to react with two equivalent of naphthalen-2-amine and ethyl 4-piperidinone-1-carboxylate (Scheme 3).

According to the literatures [13], we think that iodine catalyzes the reaction as a mild Lewis acid. The mechanism was proposed as shown in Scheme 4. In the presence of iodine, cyclophentone is in equilibrium with the enol form **I**. The enol immediately attack iodine-activated Schiff base to form intermediate **II**, followed by an intramolecular Friedel–Crafts cyclization to give **III**. The subsequent dehydration of **III** results in tetrahydronaphtho[2,1-*c*][2,7]naphthyridine **IV**, which is further oxidized by air to afford an aromatized naphtho[2,1-*c*][2,7]naphthyridine **1**.

To verify the mechanism, we individually performed each separate step. The Schiff base, *N*-(3,4-dichlorophenylidene) naphthalen-2-amine, was obtained in 92% yield, when the 3,4-dichlorobenzaldehyde (**1**, Ar = 3,4-$Cl_2C_6H_3$) was treated with naphthalen-2-amine in THF at ambient temperature (Scheme 5). As expected, Schiff base smoothly reacted with **6** to give the corresponding ethyl 1,2-dihydro-5-(3,4-dichlorophenyl) naphtha [2,1-*c*][2,7]naphthyridine-3(4*H*)-carboxylate **1a**. This result suggests that a formation of Schiff base took place during the reaction. It should be noted that the overall yield was low (76%) in the above separate reaction.

In conclusion, we found an efficient method for the synthesis of naphtho[2,1-*c*][2,7]naphthyridine derivatives by three-component reaction of aromatic aldehyde, naphthalen-2-amine, and ethyl 4-piperidinone-1-carboxylate or (3-chlorobenzoyl)-4-piperidinone using 5 mol % I_2 as catalyst. The features of this procedure are mild reaction conditions, high yields, operational simplicity, and environmentally friendly procedure.

Table 3

I_2 catalyzed reaction of benzaldehyde, naphthalen-2-amine and 1-(3-chlorobenzoyl)-4-piperidinone in THF.[a]

Entry	Ar	Products	Time (h)	Yields[b] (%)
1	4-ClC_6H_4	**8a**	15	82
2	4-BrC_6H_4	**8b**	16	86
3	2,4-$Cl_2C_6H_3$	**8c**	14	78
4	4-$NO_2C_6H_4$	**8d**	12	83

[a] Reagents and conditions: **4** (2 mmol), **5** (2 mmol, 0.286 g), **7** (2 mmol, 0.474 g), I_2 (0.1 mmol, 0.026 g), THF (10 mL).

[b] Isolated yields.

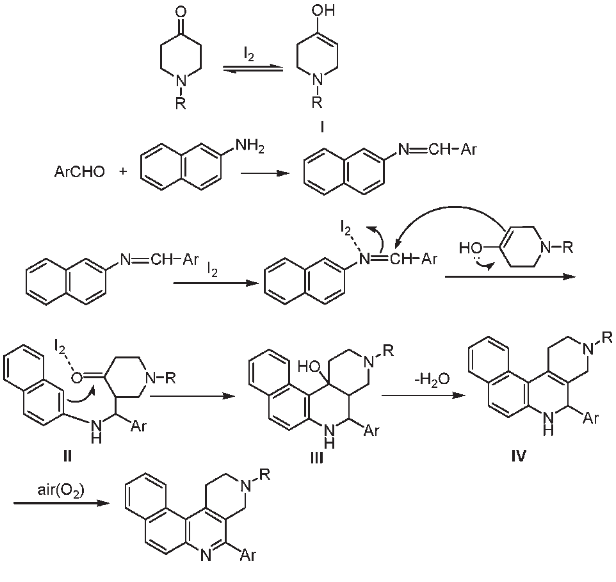
EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. Infrared (IR) spectra were recorded on a TENSOR 27 spectrometer in KBr pellet. ^1H NMR spectra were obtained from solution in DMSO-d_6 with Me_4Si as internal standard using a Bruker-400 spectrometer. HRMS analyses were carried out using a Bruker-micro-TOF-Q-MS analyzer.

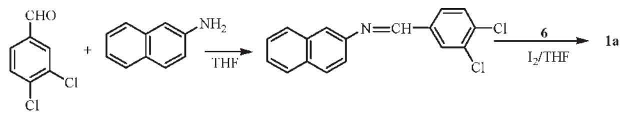
General procedure for the syntheses of 1,2-dihydro-5-arylnaphtho [2,1-*c*] [2,7]naphthyridine derivatives 1 and 8. A dry 50-mL flask was charged with aromatic aldehyde (2.0 mmol), naphthalen-2-amine (2.0 mmol, 0.286 g), ethyl 4-piperidinone-1-carboxylate or (3-chlorobenzoyl)-4-piperidinone (2.0 mmol), I_2 (0.1 mmol, 0.026 g), and THF (10 mL). The reaction mixture was stirred at reflux for 10–18 h. After completion of the reaction, as indicated by TLC, a little DMF was added to the mixture until the all yellow solid was dissolved. The generated crystals were collected by filtration to give 1 or 8 when the mixture was cooled to room temperature.

Ethyl 1,2-dihydro-5-(3,4-dichlorophenyl)naphtho[2,1-c][2,7] naphthyridine-3(4H)-carboxylate (1a). This compound was obtained as pale yellow crystals (0.819 g, 91%), mp 192–194°C. IR (KBr): ν_{max} 3057, 2983, 2957, 2869, 1715, 1564, 1549, 1473, 1451, 1381, 1338, 1282, 1255, 1203, 1169, 1138, 1110, 1087, 1059, 1029, 966, 954, 894, 838, 808, 788, 779, 755 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.31 (t, J = 6.8 Hz, 3H,

Scheme 4



Scheme 5



CH$_3$), 3.66 (t, J = 5.6 Hz, 2H, CH$_2$), 3.76 (t, J = 5.6 Hz, 2H, CH$_2$), 4.22 (q, J = 6.8 Hz, 2H, CH$_2$O), 4.73 (s, 2H, CH$_2$), 7.42 (dd, J = 8.0 Hz, J' = 2.0 Hz, 1H, ArH), 7.60 (d, J = 8.0 Hz, 1H, ArH), 7.66–7.70 (m, 2H, ArH), 7.74 (d, J = 2.0 Hz, 1H, ArH), 7.96–8.00 (m, 3H, ArH), 8.00–8.63 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{25}H_{20}Cl_2N_2NaO_2$ (M+Na$^+$) 473.0800, found 473.0791.

Ethyl 1,2-dihydro-5-(3-nitrophenyl)naphtho[2,1-c][2,7]naphthyridine-3(4H)-carboxylate (1b). This compound was obtained as pale yellow crystals (0.785 g, 92%), mp 156−157°C. IR (KBr): ν_{max} 3090, 2960, 1694, 1534, 1466, 1447, 1382, 1348, 1303, 1260, 1204, 1095, 1081, 1001, 832, 807, 771, 759, 738, 708 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.20 (b, 3H, CH$_3$), 3.58–3.60 (m, 2H, CH$_2$), 3.74–3.76 (m, 2H, CH$_2$), 4.08 (q, J = 6.4 Hz, 2H, CH$_2$), 4.69 (s, 2H, CH$_2$), 7.75 (dd, J = 6.0 Hz, J' = 3.2 Hz, 2H, ArH), 7.86–7.91 (m, 2H, ArH), 8.11–8.13 (m, 3H, ArH), 8.40 (dd, J = 8.0 Hz, J' = 1.6 Hz, 1H, ArH), 8.49 (s, 1H, ArH), 8.74–8.76 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{25}H_{22}N_3O_4$ (M+H$^+$) 428.1610, found 428.1611.

Ethyl 1,2-dihydro-5-(2-thiophenyl)naphtho[2,1-c][2,7]naphthyridine-3(4H)-carboxylate (1c). This compound was obtained as pale yellow crystals (0.629 g, 81%), mp 111−112°C. IR (KBr): ν_{max} 3057, 2981, 1697, 1606, 1551, 1478, 1436, 1379, 1359, 1332, 1304, 1258, 1227, 1199, 1169, 1134, 1117, 1074, 1028, 969, 827, 817, 767, 749, 712 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.26 (t, J = 7.2 Hz, 3H, CH$_3$), 3.62–3.63 (m, 2H, CH$_2$), 3.73–3.74 (m, 2H, CH$_2$), 4.16 (q, J = 7.2 Hz, 2H, CH$_2$), 5.01 (s, 2H, CH$_2$), 7.29–7.31 (m, 1H, ArH), 7.62 (d, J = 3.6 Hz, 1H, ArH), 7.72–7.74 (m, 2H, ArH), 7.81–7.85 (m, 2H, ArH), 8.08–8.11 (m, 2H, ArH), 8.71–8.73 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{23}H_{20}N_2NaO_2S$ (M+Na$^+$) 411.1143, found 411.1130.

Ethyl 1,2-dihydro-5-(2,4-dichlorophenyl)naphtho[2,1-c][2,7]naphthyridine-3(4H)-carboxylate (1d). This compound was obtained as pale yellow crystals (0.729 g, 83%), mp 168−169°C. IR (KBr): ν_{max} 3083, 2975, 1708, 1587, 1557, 1474, 1426, 1379, 1360, 1341, 1303, 1281, 1247, 1201, 1170, 1139, 1116, 1098, 1064, 1051, 947, 863, 837, 800, 767, 746 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.22 (b, 3H, CH$_3$), 3.42–3.45 (m, 1H, CH), 3.68–3.70 (m, 1H, CH), 3.78–3.84 (m, 2H, CH$_2$), 4.08–4.13 (m, 2H, CH$_2$), 4.34–4.38 (m, 1H, CH), 4.48–4.51 (m, 1H, CH), 7.59 (d, J = 8.4 Hz, 1H, ArH), 7.66 (dd, J = 8.4 Hz, J' = 2.0 Hz, 1H, ArH), 7.74–7.77 (m, 2H, ArH), 7.86–7.88 (m, 2H, ArH), 8.11–8.14 (m, 2H, ArH), 8.77–8.80 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{25}H_{21}Cl_2N_2O_2$ (M+H$^+$) 451.0980, found 451.0983.

Ethyl 1,2-dihydro-5-(4-bromophenyl)naphtho[2,1-c][2,7]naphthyridine-3(4H)-carboxylate (1e). This compound was obtained as pale yellow crystals (0.790 g, 86%), mp 188−190°C. IR (KBr): ν_{max} 3050, 2980, 1687, 1590, 1564, 1516, 1429, 1380, 1321, 1300, 1248, 1204, 1169, 1136, 1115, 1084, 1010, 953, 911, 886, 832, 765 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.20 (b, 3H, CH$_3$), 3.54–3.57 (m, 2H, CH$_2$), 3.70–3.73 (m, 2H, CH$_2$), 4.09 (q, J = 7.2 Hz, 2H, CH$_2$), 4.65 (s, 2H, CH$_2$), 7.59 (d, J = 8.4 Hz, 2H, ArH), 7.72–7.75 (m, 4H, ArH), 7.86 (d, J = 8.8 Hz, 1H, ArH), 8.07–8.11 (m, 2H, ArH), 8.70–8.72 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{25}H_{22}BrN_2O_2$ (M+H$^+$) 461.0865, found 461.0831.

Ethyl 1,2-dihydro-5-(4-chlorophenyl)naphtho[2,1-c][2,7]naphthyridine-3(4H)-carboxylate (1f). This compound was obtained as pale yellow crystals (0.730 g, 88%), mp 210−212°C. IR (KBr): ν_{max} 3055, 2979, 1695, 1595, 1559, 1481, 1460, 1432, 1382, 1362, 1337, 1321, 1302, 1284, 1246, 1203, 1169, 1138, 1114, 1087, 1046, 1014, 979, 945, 870, 837, 757 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.20 (b, 3H, CH$_3$), 3.58 (t, J = 5.6 Hz, 2H, CH$_2$), 3.75 (t, J = 5.6 Hz, 2H, CH$_2$), 4.09 (q, J = 6.8 Hz, 2H, CH$_2$O), 4.66 (s, 2H, CH$_2$), 7.63–7.74 (m, 4H, ArH), 7.75–7.76 (m, 2H, ArH), 7.87 (d, J = 8.8 Hz, 1H, ArH), 8.09–8.13 (m, 2H, ArH), 8.73–8.75 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{25}H_{22}ClN_2O_2$ (M+H$^+$) 417.1370, found 417.1387.

Ethyl 1,2-dihydro-5-(2,3-dichlorophenyl)naphtho[2,1-c][2,7]naphthyri-dine-3(4H)-carboxylate (1g). This compound was obtained as pale yellow crystals (0.810 g, 90%), mp 165−167°C. IR (KBr): ν_{max} 3057, 2979, 2905, 1694, 1604, 1561, 1482, 1430, 1379, 1362, 1343, 1253, 1207, 1170, 1142, 1117, 1048, 1028, 870, 833, 788, 770, 753, 717, 701 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.29 (b, 3H, CH$_3$), 3.67–3.76 (m, 4H, 2CH$_2$), 4.16–4.23 (m, 2H, CH$_2$O), 4.57 (s, 2H, CH$_2$), 7.33–7.40 (m, 2H, ArH), 7.60 (d, J = 8.8 Hz, 1H, ArH), 7.67–7.70 (m, 2H, ArH), 7.97–8.00 (m, 3H, ArH), 8.67–8.69 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{25}H_{21}Cl_2N_2O_2$ (M+H$^+$) 451.0980, found 451.0956.

Ethyl 1,2-dihydro-5-(4-nitrophenyl)naphtho[2,1-c][2,7]naphthyridine-3(4H)-carboxylate (1h). This compound was obtained as pale yellow crystals (0.743 g, 87%), mp 209−211°C. IR (KBr): ν_{max} 3063, 2999, 2982, 2960, 2941, 2902, 1684, 1600, 1581, 1515, 1468, 1451, 1385, 1347, 1261, 1228, 1170, 1140, 1098, 1083, 1017, 968, 952, 886, 858, 837, 770, 751, 700 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.20 (b, 3H, CH$_3$), 3.58–3.59 (m, 2H, CH$_2$), 3.74–3.75 (m, 2H, CH$_2$), 4.07 (q, J = 7.2 Hz, 2H, CH$_2$), 4.65 (m, 2H, CH$_2$), 7.76 (dd, J = 6.0 Hz, J' = 3.2 Hz, 2H, ArH), 7.87–7.92 (m, 3H, ArH), 8.11–8.13 (m, 2H, ArH), 8.41 (d, J = 8.8 Hz, 2H, ArH), 8.73–8.76 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{25}H_{22}N_3O_4$ (M+H$^+$) 428.1610, found 428.1605.

Ethyl 1,2-dihydro-5-(4-fluorophenyl)naphtho[2,1-c][2,7]naphthyridine-3(4H)-carboxylate (1i). This compound was obtained as pale yellow crystals (0.695 g, 87%), mp 207−209°C. IR (KBr): ν_{max} 3060, 2982, 2943, 2906, 1697, 1602, 1561, 1509, 1482, 1461, 1433, 1384, 1361, 1337, 1321, 1285, 1248, 1159, 1113, 1046, 1030, 979, 944, 869, 837, 808, 758 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.20 (b, 3H, CH$_3$), 3.54–3.57 (m, 2H, CH$_2$), 3.71–3.74 (m, 2H, CH$_2$), 4.07 (q, J = 6.8 Hz, 2H, CH$_2$O), 4.64 (s, 2H, CH$_2$), 7.37–7.42 (m, 2H, ArH), 7.66–7.76 (m, 4H, ArH), 7.86 (d, J = 9.2 Hz, 1H, ArH), 8.07–8.11 (m, 2H, ArH), 8.70–8.73 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{25}H_{22}FN_2O_2$ (M+H$^+$) 401.1665, found 401.1661.

Ethyl 1,2-dihydro-5-(2-nitrophenyl)naphtho[2,1-c][2,7]naphthyridine-3(4H)-carboxylate (1j). This compound was obtained as pale yellow crystals (0.769 g, 90%), mp 218−220°C. IR (KBr): ν_{max} 3057, 2978, 2924, 2905, 2851, 2684, 1608, 1560, 1529, 1468, 1442, 1383, 1350, 1302, 1266, 1224, 1140, 1118, 1092, 1028, 979, 954, 895, 860, 840, 790, 758, 740, 705, 693 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.13–1.22 (m, 3H, CH$_3$), 3.64 (b, 2H, CH$_2$), 3.75 (b, 2H, CH$_2$), 4.08 (b, 2H, CH$_2$), 4.51 (s, 2H, CH_2), 7.74–7.85 (m, 5H, ArH), 7.92–7.96 (m, 1H, ArH), 8.08–8.12 (m, 2H, ArH), 8.27 (d, *J* = 8.0 Hz, 1H, ArH), 8.78–8.80 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{25}H_{22}N_3O_4$ ($M+H^+$) 428.1610, found 428.1610.

Ethyl 1,2-dihydro-5-(3-chlorophenyl)naphtho[2,1-c][2,7]naphthyridine-3(4H)-carboxylate (1k). This compound was obtained as pale yellow crystals (0.691 g, 83%), mp 131−132°C. IR (KBr): ν_{max} 3053, 2969, 2869, 1700, 1568, 1479, 1466, 1417, 1363, 1346, 1280, 1255, 1202, 1170, 1137, 1111, 1060, 1027, 997, 957, 875, 837, 794, 768, 752, 722, 696 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.22 (b, 3H, CH_3), 3.57–3.58 (m, 2H, CH_2), 3.71–3.72 (m, 2H, CH_2), 4.09 (q, *J* = 6.4 Hz, 2H, CH_2), 4.66 (s, 2H, CH_2), 7.59–7.60 (m, 3H, ArH), 7.73–7.76 (m, 3H, ArH), 7.87 (d, *J* = 8.8 Hz, 1H, ArH), 8.09–8.13 (m, 2H, ArH), 8.71–8.74 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{25}H_{22}ClN_2O_2$ ($M+H^+$) 417.1370, found 417.1350.

Ethyl 1,2-dihydro-5-(4-methoxyphenyl)naphtho[2,1-c][2,7] naphthyridine-3(4H)-carboxylate (1l). This compound was obtained as pale yellow crystals (0.674 g, 82%), mp 193−194°C. IR (KBr): ν_{max} 3018, 2978, 2958, 2934, 2903, 2871, 2841, 1702, 1610, 1556, 1518, 1418, 1367, 1292, 1204, 1135, 1109, 1087, 1060, 964, 952, 858, 836, 795, 759 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.20 (b, 3H, CH_3), 3.55 (t, *J* = 5.2 Hz, 2H, CH_2), 3.72 (s, 2H, CH_2), 3.86 (s, 3H, CH_3O), 4.08 (q, *J* = 7.2 Hz, 2H, CH_2), 4.69 (s, 2H, CH_2), 7.11 (d, *J* = 8.4 Hz, 2H, ArH), 7.59 (d, *J* = 8.4 Hz, 2H, ArH), 7.73 (t, *J* = 4.4 Hz, 2H, ArH), 7.86 (d, *J* = 8.8 Hz, 1H, ArH), 8.06–8.11 (m, 2H, ArH), 8.69–8.71 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{26}H_{25}N_2O_2$ ($M+H^+$) 413.1865, found 413.1865.

Ethyl 1,2-dihydro-5-(4-chloro-2-nitrophenyl)naphtha [2,1-c][2,7] naphthyridine-3(4H)-carboxylate (1m). This compound was obtained as pale yellow crystals (0.774 g, 84%), mp 185−186°C. IR (KBr): ν_{max} 3061, 2986, 2906, 1698, 1683, 1605, 1567, 1537, 1484, 1470, 1435, 1383, 1339, 1297, 1246, 1224, 1204, 1144, 1117, 1026, 980, 960, 894, 868, 834, 756 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.31 (b, 3H, CH_3), 3.75 (b, 4H, $2CH_2$), 4.20 (b, 2H, CH_2), 4.54 (b, 2H, CH_2), 7.51 (s, 1H, ArH), 7.62–7.69 (m, 3H, ArH), 7.86 (d, *J* = 9.2 Hz, 1H, ArH), 7.94–8.01 (m, 2H, ArH), 8.22 (d, *J* = 8.8 Hz, 1H, ArH), 8.65–8.67 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{25}H_{21}ClN_3O_4$ ($M+H^+$) 462.1221, found 462.1201.

Ethyl 1,2-dihydro-5-phenylnaphtho[2,1-c][2,7]naphthyridine-3(4H)-carboxylate (1n). This compound was obtained as pale yellow crystals (0.634 g, 83%), mp 175−177°C. IR (KBr): ν_{max} 3056, 2975, 2931, 2869, 1703, 1565, 1478, 1446, 1419, 1376, 1364, 1344, 1278, 1261, 1231, 1200, 1169, 1135, 1110, 1088, 1060, 1029, 954, 880, 853, 838, 782, 757, 737, 700 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.29 (b, 3H, CH_3), 3.65–3.66 (m, 2H, CH_2), 3.73–3.75 (m, 2H, CH_2), 4.20 (q, *J* = 6.8 Hz, 2H, CH_2), 4.74 (s, 2H, CH_2), 7.47–7.60 (m, 5H, ArH), 7.64–7.68 (m, 2H, ArH), 7.93–8.00 (m, 3H, ArH), 8.60–8.63 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{25}H_{22}N_2NaO_2$ ($M+Na^+$) 405.1579, found 405.1579.

Ethyl 1,2-dihydro-5-(2-fluorophenyl)naphtho[2,1-c][2,7]naphthyridine-3(4H)-carboxylate (1o). This compound was obtained as pale yellow crystals (0.704 g, 88%), mp 95−97°C. IR (KBr): ν_{max} 3059, 2990, 2964, 2902, 2851, 1701, 1616, 1579, 1561, 1528, 1489, 1438, 1385, 1365, 1247, 1216, 1141, 1046, 1024, 978, 951, 896, 858, 842, 814, 755 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.22 (b, 3H, CH_3), 3.60–3.74 (m, 4H, $2CH_2$), 4.08 (b, 2H, CH_2O), 4.52 (b, 2H, CH_2), 7.41–7.45 (m, 2H, ArH), 7.57–7.65 (m, 2H, ArH), 7.74–7.76 (m, 2H, ArH), 7.88 (d, *J* = 8.8 Hz, 1H, ArH), 8.10–8.13 (m, 2H, ArH), 8.75–8.77 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{25}H_{21}FN_2NaO_2$ ($M+Na^+$) 423.1485, found 423.1467.

Ethyl 1,2-dihydro-5-(3,5-dimethoxyphenyl)naphtha [2,1-c][2,7] naphthyridine-3(4H)-carboxylate (1p). This compound was obtained as pale yellow crystals (0.760 g, 86%), mp 157−159°C. IR (KBr): ν_{max} 3052, 2985, 2936, 2843, 1694, 1599, 1454, 1423, 1372, 1321, 1301, 1247, 1204, 1193, 1112, 1088, 1058, 969, 897, 852, 836, 802, 770, 752, 729 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.30 (b, 3H, CH_3), 3.66–3.69 (m, 2H, CH_2), 3.74–3.76 (m, 2H, CH_2), 3.85 (s, 6H, $2CH_3O$), 4.21 (q, *J* = 6.8Hz, 2H, CH_2O), 4.77 (s, 2H, CH_2), 6.57 (s, 1H, ArH), 6.70 (d, *J* = 2.0 Hz, 2H, ArH), 7.65–7.68 (m, 2H, ArH), 7.94–8.01 (m, 3H, ArH), 8.61–8.64 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{27}H_{27}N_2O_4$ ($M+H^+$) 443.1971, found 443.1948.

1,2,3,4-Tetrahydro-3-(3-chlorobenzoyl)-5-(4-chlorophenyl)-naphtho[2,1-c][2,7]naphthyridine (8a). This compound was obtained as pale yellow crystals (0.789 g, 82%), mp 184−185°C. IR (KBr): ν_{max} 3062, 3014, 2977, 2899, 2853, 1623, 1560, 1479, 1430, 1361, 1322, 1259, 1211, 1165, 1126, 1085, 1055, 1045, 1012, 965, 946, 900, 838, 805, 744, 699 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.54–3.80 (m, 4H, $2CH_2$), 4.67–4.85 (m, 2H, CH_2), 7.43–7.75 (m, 10H, ArH), 7.89 (d, *J* = 8.8 Hz, 1H, ArH), 8.10–8.13 (m, 2H, ArH), 8.14 (s, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{29}H_{20}Cl_2N_2NaO$ ($M+Na^+$) 505.0850, found 505.0857.

1,2,3,4-Tetrahydro-3-(3-chlorobenzoyl)-5-(4-bromophenyl)-naphtho[2,1-c][2,7]naphthyridine (8b). This compound was obtained as pale yellow crystals (0.902 g, 86%), mp 171−172°C. IR (KBr): ν_{max} 3060, 3016, 2980, 2946, 2898, 2852, 1634, 1563, 1518, 1479, 1430, 1362, 1321, 1259, 1227, 1211, 1165, 1125, 1083, 1068, 1009, 966, 900, 833, 805, 745, 703, 683 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.79–3.85 (m, 4H, $2CH_2$), 4.67–4.85 (m, 2H, CH_2), 7.32–7.80 (m, 10H, ArH), 7.89 (d, *J* = 8.8 Hz, 1H, ArH), 8.09–8.12 (m, 2H, ArH), 8.74 (s, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{29}H_{21}BrClN_2O$ ($M+H^+$) 527.0526, found 527.0525.

1,2,3,4-Tetrahydro-3-(3-chlorobenzoyl)-5-(2,4-dichlorophenyl)naphtho[2,1-c][2,7]naphthyridine (8c). This compound was obtained as pale yellow crystals (0.805 g, 78%), mp 217−218°C. IR (KBr): ν_{max} 3058, 3022, 2944, 1641, 1588, 1562, 1518, 1477, 1460, 1439, 1380, 1360, 1343, 1321, 1263, 1228, 1170, 1131, 1099, 1049, 971, 906, 870, 834, 798, 781, 759, 745, 698 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.49–3.95 (m, 4H, $2CH_2$), 4.44–4.74 (m, 2H, CH_2), 7.43–7.78 (m, 9H, ArH), 7.89 (d, *J* = 8.8 Hz, 1H, ArH), 8.12–8.14 (m, 2H, ArH), 8.80 (s, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{29}H_{19}Cl_3N_2NaO$ ($M+Na^+$) 539.0461, found 539.0456.

1,2,3,4-Tetrahydro-3-(3-chlorobenzoyl)-5-(4-nitrophenyl)-naphtho[2,1-c][2,7]naphthyridine (8d). This compound was obtained as pale yellow crystals (0.818 g, 83%), mp 133−134°C. IR (KBr): ν_{max} 3055, 2944, 2887, 2855, 1658, 1629, 1564, 1515, 1478, 1430, 1349, 1322, 1258, 1211, 1098, 1045, 859, 837, 807, 757, 737, 701 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.57–3.87 (m, 4H, $2CH_2$), 4.67–4.86 (m, 2H, CH_2), 7.36–7.58 (m, 4H, ArH), 7.76–7.78(m, 2H, ArH), 7.91 (d, *J* = 8.8 Hz, 1H, ArH), 7.96–7.99 (m, 2H, ArH), 8.13 (d, *J* = 9.2 Hz, 2H, ArH), 8.26–8.45 (m, 2H, ArH), 8.76–8.78 (m, 1H, ArH). HRMS (ESI, *m/z*): calcd for $C_{29}H_{20}ClN_3NaO_3$ ($M+Na^+$) 516.1091, found 516.1099.

General procedure for the syntheses of binaphtho[2,1-*c*][2,7]naphthyridine 9. A dry 50-mL flask was charged with terephthalaldehyde (1.0 mmol, 0.134 g), naphthalen-2-amine (2.0 mmol, 0.286 g), ethyl 4-piperidinone-1-carboxylate (2.0 mmol, 0.342 g), I_2 (0.05 mmol, 0.013 g), and THF (10 mL). The reaction mixture was stirred at reflux for 10 h. After completion of the reaction, as indicated by TLC, a little DMF was added to the mixture until the all yellow solid was dissolved. The generated crystals were collected by filtration to give **9** when the mixture was cooled to room temperature.

1,4-di(1,2,3,4-tetrahydro-3-ethoxycarbonyl-naphtho[2,1-c][2,7]naphthyri-dine-5-yl)benzene (9). This compound was obtained as pale yellow crystals (0.597 g, 87%), mp 249−250°C. IR (KBr): ν_{max} 3054, 2987, 2872, 1708, 1564, 1479, 1449, 1419, 1379, 1362, 1259, 1205, 1137, 1112, 1086, 853, 837, 752cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.21–1.23 (b, 6H, 2CH_3), 3.61–3.64 (m, 4H, 2CH_2), 3.78–3.80 (m, 4H, 2CH_2), 4.12 (q, $J = 6.8$ Hz, 4H, 2CH_2O), 4.80 (s, 4H, 2CH_2), 7.75–7.77 (m, 4H, ArH), 7.83 (s, 4H, ArH), 7.95 (d, $J = 9.2$ Hz, 2H, ArH), 8.12–8.15 (m, 4H, ArH), 8.76–8.78 (m, 2H, ArH). HRMS (ESI, *m/z*): calcd for $C_{44}H_{39}N_4O_4$ (M+H$^+$) 687.2971, found 687.2936.

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Novel and Convenient to Substituted Imidazoles

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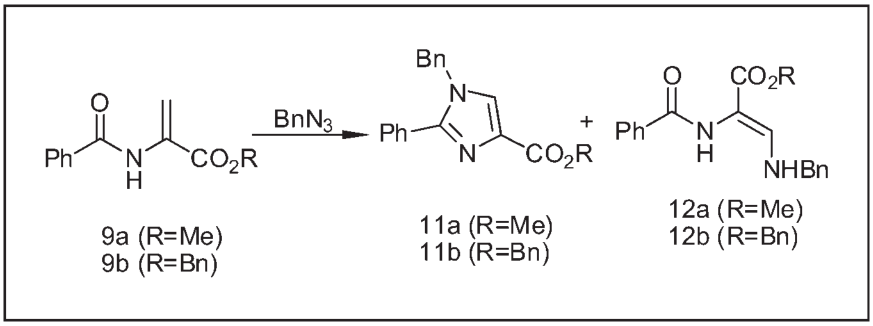


A one-pot synthesis of imidazoles has been established from the addition of azides to 2-amidoacrylates, and this synthetic method demonstrates an efficient synthesis of imidazole-4-carboxylates.

J. Heterocyclic Chem., **46**, 1235 (2009).

INTRODUCTION

Over the century, the chemical and biochemical properties of imidazoles in the biological system have been attracting much interest. Even today, research in imidazole chemistry continues unabated. Compounds with imidazole ring systems have many pharmacological properties and play important roles in biochemical processes [1]. Many substituted imidazoles are known as key pharmacophore in modern drugs [2]. Therefore, the preparation of imidazoles has gained considerable attention in recent years [3].

In 1998, Hadjiantou-Maroulis et al. [4] found the pyrolysis of 1-aroylamino-4,5-diphenyl-1,2,3-triazoles (**I**) yields 2,3-diphenyl-2H-azirine (**II**) and 2-aryl-4,5-diphenylimidazoles (**III**) as the major products (Scheme 1).

More recently, great attention has been given to dipolar cycloaddition chemistry using azides, especially azide cycloadditions to alkynes to generate triazoles [5] (Scheme 2). Addition of azides to α,β-unsaturated carbonyl compounds **IV** has been reported in the literature [6–10] (Scheme 3). Particularly interesting were the transformations of 2-amido-3-arylaminoacrylates **V** and **VII** to imidazoles **VI** and **VIII,** respectively [11] (Scheme 4).

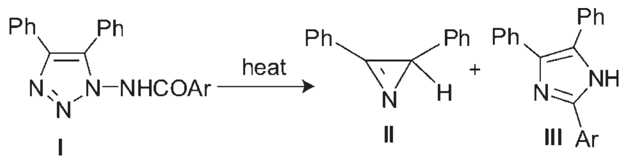
According to Hadjiantou-Maroulis et al. [4], we found a novel synthesis of imidazoles **XI** from 2-aminoacrylates **IX** and azides **X**. To our knowledge, no report has described such a one-pot procedure to synthesize imidazoles **XI** from 2-amidoacrylates **IX** (Scheme 5). In this article, we have systematically investigated each possible reaction of various 2-aminoacrylates and presented the results as follows.

RESULTS AND DISCUSSION

When 2-amidoacrylates **9** were heated with benzyl azide at reflux in toluene, imidazoles **11** were obtained as the main product in the reaction mixture. The effects of temperature, azide equivalents, and reaction time on the yield of imidazoles and byproducts **12** were investigated (Table 1). It is clear that temperature has a pivotal role in the reaction, since only trace amounts of imidazoles were observed under 100°C, and the yield of imidazoles increased with regard to reaction temperature. Likewise, we found that required reaction time could be shortened from 2–4 d to 15 h if reaction temperature increased from reflexing toluene to 190°C in a sealed tube (Table 1, entries 4, 6, and 7). Increased equivalents of benzyl azide appeared to be slightly detrimental to the yield of imidazoles, and more byproducts were yielded (Table 1, entries 6 and 7). Optimal yield of imidazoles was achieved when the reactants were heated in toluene in a sealed tube at 190°C for 15 h (Table 1, entries 4 and 6).

Based on similar imidazole synthesis previously reported [12] and the chemical properties of organic azides, we proposed a mechanism (Scheme 6) that can possibly explain the formation of 2-amido-

Scheme 1



3aminoacrylate byproduct **12** as an intermediate in the synthesis of imidazole **11**. Dipolar cycloaddition of benzyl azide to 2-amidoacrylate **9** should offer the regioisomeric triazolines A and B, even previous studies reported [13] that the formation of triazoline A would be greatly favored over the regioisomeric triazoline B. Thermal decomposition of triazolines A and B would provide compounds C and D, on extrusion of nitrogen, which would yield either aziridine E or imine F. Tautomerization of imine F would provide E-enamine G or the observed Z-enamine **12**, which on intramolecular cyclization would provide imidazole **11** after dehydration of tetrahedral intermediate H.

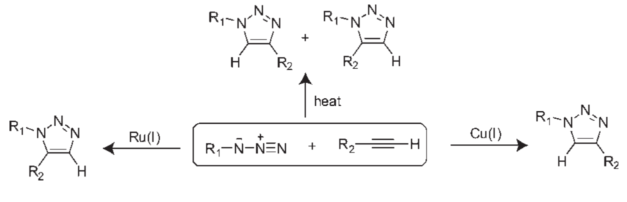
On the basis of proposed mechanism, we suggest that byproduct **12** appeared to be an intermediate contributing to the production of imidazole **11**. We found that enamine **12** was accumulated exclusively only in the sealed reaction conditions where water was confined in reaction system, otherwise imidazole **11** was observed (Table 2) [14].

A one-pot synthesis of imidazoles **11** has been developed from adding azides to 2-amidoacrylates **9**, and this synthetic method represents an efficient synthesis for imidazole-4-carboxylates **11**.

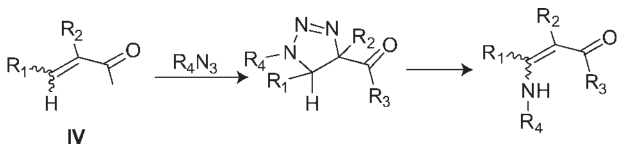
EXPERIMENTAL

All reactions were performed under an atmosphere of dry nitrogen unless noted otherwise. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 300 MHz or 500 MHz spectrometer using $CDCl_3$ as solvent under ambient temperatures unless otherwise noted. Infrared spectra were recorded using an FT-IR spectrometer and are reported in cm^{-1}. Mass spectra were obtained as specified. Low-resolution mass and high-resolution mass spectra were measured with a Hitachi M-52-Instrument or Bruker APEX II mass spectrometer. Melting points were uncorrected and were determined either using recrystallized samples or samples, which crystallized during concentration of the chromatography eluents.

Scheme 2



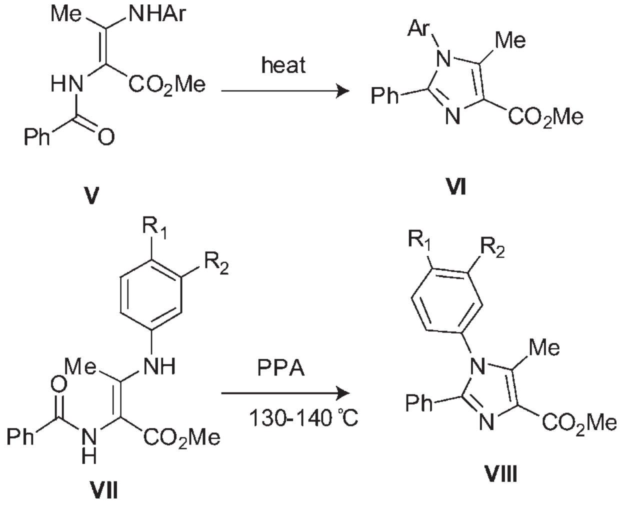
Scheme 3



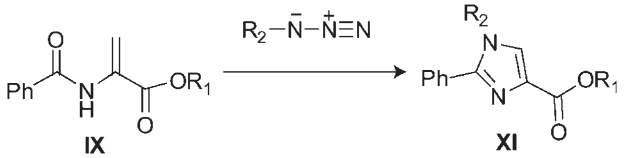
Methyl 2-benzamidoacrylate (9a). The (*S*)-Methyl 2-benzamido-3-hydroxypropanoate compound (1.21 g, 5.40 mmol) was dissolved in 50 mL of dry CH_2Cl_2 in a flame-dried 100-mL round-bottomed flask under Ar. EDC HCl (1.24 g, 6.46 mmol) was added to the solution in one portion followed by CuCl (160.7 mg, 1.62 mmol). The reaction was wrapped in foil and stirred under Ar at room temperature. After 2 h, TLC of the reaction (1:1 hexanes/EtOAc) indicated starting material had been completely consumed, and a new, less polar compound was observed. After 3 h, H_2O (100 mL) was added to the reaction, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the combined CH_2Cl_2 layers were washed with H_2O (100 mL), dried over $MgSO_4$, filtered, and concentrated to yield a yellow oil. The oil was purified through a plug (30 g) of silica gel using CH_2Cl_2 and yielded **9a** as a colorless, cloudy liquid (1.06 g, 96% yield). IR: 3300, 3150, 3075, 1740, 1640, 1210, 830, 750 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 8.49 (br-s, 1H), 7.75 (dd, *J* = 7.1, 1.9 Hz, 2H), 7.43 (m, 1H), 7.37 (m, 2H), 6.71 (d, *J* = 1.6 Hz, 1H), 5.90 (d, *J* = 1.6 Hz, 1H), 3.76 (s, 3H). ^{13}C NMR: δ 165.3, 164.3, 133.9, 131.7, 130.8, 128.4, 126.6, 108.5, 52.7. HRMS (FAB): m/z $[M+H]^+$ calcd for $C_{11}H_{12}NO_3^+$, 206.0817; found, 206.0818.

Benzyl 2-benzamidoacrylate (9b). Compound **9b** was prepared following a similar procedure for **9a**. The (*S*)-Benzyl 2-benzamido-3-hydroxypropanoate compound (1.51 g, 5.03 mmol), EDC HCl (1.17 g, 6.12 mmol), and CuCl (0.15 g, 1.51 mmol) provided an oil. Chromatography through silica gel using CH_2Cl_2 yielded **9b** as a white solid (1.45 g, 99% yield); mp 51–52°C. IR (KBr): 3310, 3140, 3010, 1735, 1630, 1210, 840, 730 cm^{-1}; ^{1}H NMR: δ 8.56 (br-s, 1H), 7.84 (dd, *J* = 7.0, 1.5 Hz, 2H), 7.55 (m, 1H), 7.47 (m, 2H), 7.41–7.36 (m, 5H),

Scheme 4



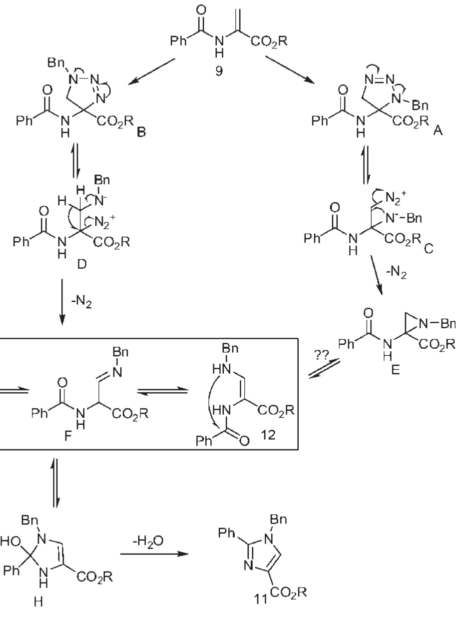
Scheme 5



6.82 (d, $J = 2.0$ Hz, 1H), 6.06 (d, $J = 2.0$ Hz, 1H), 5.32 (s, 2H). ^{13}C NMR: δ 165.7, 164.2, 135.0, 134.2, 132.0, 131.0, 128.8, 128.7, 128.6, 128.2, 126.9, 109.1, 67.9. HRMS (FAB): m/z $[M+H]^+$ calcd for $C_{17}H_{16}NO_3^+$, 282.1130; found, 282.1140.

General procedure for the preparation of imidazoles from 2-amidoacrylates and azides. Methyl 1-benzyl-2-phenyl-1H-imidazole-4-carboxylate (11a). Compound **9a** (116.2 mg, 0.57 mmol) and benzyl azide (0.11 mL, 0.87 mmol) were dissolved in 5 mL of toluene in a sealed pyrex tube fitted with a stir bar. The tube was heated in an oil bath maintained at 190°C. After 1 h, the colorless solution turned yellow in color, and gradually, the color became brown. After 15 h, the reaction was cooled to RT and concentrated. The crude brown oil was purified through 25 g of silica gel using a solvent gradient from CH_2Cl_2 to 80% CH_2Cl_2/EtOAc and yielded pure **12a** (26.5 mg, 15.1% yield), pure **11a** as an amber oil (84.1 mg, 50.8% yield), and a mixture of **12a** and **11a** (26.1 mg). Total yield of **11a** isolated as amber oil was 90.1 mg (54%). **11a** was recrystallized from EtOAc/hexanes to produce light yellow crystals. Rf = 0.14 (1:1 hexanes/EtOAc). IR (KBr): 3010, 1735, 1590, 1320, 1210, 840, 730 cm^{-1}; ^{1}H NMR: δ 7.69 (s, 1H), 7.60 (m, 2H), 7.44–7.40 (m, 3H), 7.37–7.32 (m, 3H), 7.09 (m, 2H), 5.23 (s, 2H), 3.90 (s, 3H). ^{13}C NMR: δ 163.0, 148.8, 135.4, 132.5, 129.2, 129.0, 128.8, 128.7, 128.2, 127.9, 126.9, 126.5, 51.3, 50.5. HRMS (FAB): m/z $[M+H]^+$ calcd for $C_{18}H_{17}N_2O_2^+$, 293.1290; found, 293.1293.

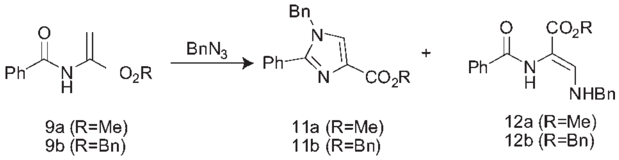
Scheme 6. Proposed formation mechanism of imidazole.



(Z)-Methyl 2-benzamido-3-(benzylamino)acrylate (12a). Compound **12a** was isolated as amber oil. Total yield isolated was 46.6 mg (27%). Compound **12a** was recrystallized from 70% EtOH/H_2O to yield colorless crystals. Rf = 0.26 (1:1 hexanes/EtOAc). IR (KBr): 3270, 3140, 3010, 2400, 1750, 1630, 840, 730 cm^{-1}; ^{1}H NMR: δ 8.00 (br, 1H), 7.84 (m, 2H), 7.51 (m, 1H), 7.44 (m, 2H), 7.37–7.26 (m, 6H), 6.50 (br, 1H), 4.42 (d, $J = 6.0$ Hz, 2H), 3.73 (s, 3H). ^{13}C NMR: δ 166.5, 164.8, 140.1, 138.5, 134.0, 131.6, 131.3, 128.73, 128.69, 128.6, 128.51, 128.46, 127.2, 127.1, 127.0, 126.9, 52.5, 51.6. HRMS

Table 1

Investigation of reaction conditions for the addition of benzyl azide to 2-amidoacrylates.

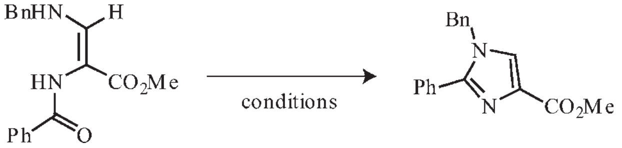


Entry	R	BnN_3 (equiv)	Solvent	Temp (°C)	Time	Result/yield (%) 11a/11b	 12a/12b
1	Me	1.5	Toluene	110	2 d	29	7
2	Me	1.5	Toluene	110	4 d	33	4
3	Me	1.3	Xylene	150	26 h	52	13
4	Me	1.5	Toluene	190[a]	15 h	54	27
5	Bn	1.5	Toluene	110	4 d	39	10
6	Bn	1.5	Toluene	190[a]	15 h	63	18
7	Bn	3.0	Toluene	190[a]	15 h	54	25

[a] Reaction was performed in a sealed pyrex tube and heated in an oil bath.

Table 2

Thermal cyclization of methyl 2-benzamido-3-(benzylamino) acrylate (12a).



Entry	Solvent	Temp (°C)	Time	Result/yield (%) 11a
1	Anisole	154[a]	15 h	40
2	Toluene	190[b]	15 h	No reaction
3	Toluene	110	15 h	35

[a] According to Stanovik et al. [11].

[b] Reaction was performed in a sealed pyrex tube and heated in an oil bath.

(FAB): m/z $[M]^+$ calcd for $C_{18}H_{18}N_2O_3^+$, 310.1317; found, 310.1297.

Benzyl 1-benzyl-2-phenyl-1H-imidazole-4-carboxylate (11b). Compound **11b** was prepared following the general procedure for the synthesis of imidazoles from acrylates and azides. Acrylate **9b** (0.14 g, 0.51 mmol) and benzyl azide (0.10 mL, 0.79 mmol) were heated in toluene (5 mL) in a sealed pyrex tube for 15 h in a 190°C oil bath. Chromatography through 25 g of silica gel using a solvent gradient from CH_2Cl_2 to 90% CH_2Cl_2/EtOAc yielded pure **12b**, **11b**, and a mixture of **11b** and **12b** as amber oils. Total yield of **11b** was 120 mg (63%). IR (KBr): 3010, 1735, 1667, 1590, 1310, 1160, 820, 730 cm^{-1}; ^1H NMR: δ 7.65 (s, 1H), 7.56 (m, 2H), 7.44 (m, 2H), 7.42–7.29 (m, 9H), 7.05 (d, $J = 7.0$ Hz, 2H), 5.36 (s, 2H), 5.18 (s, 2H). ^{13}C NMR: δ 162.6, 149.2, 136.1, 135.6, 132.8, 129.4, 129.3, 129.1, 129.0, 128.44, 128.36, 128.3, 128.2, 128.0, 127.2, 126.7, 66.0, 50.7. HRMS (FAB): m/z $[M+H]^+$ calcd for $C_{24}H_{21}N_2O_2^+$, 369.1603; found, 369.1602.

(Z)-Benzyl 2-benzamido-3-(benzylamino)acrylate (12b). Compound **12b** was isolated as amber oil (35 mg, 18%). IR : 3270, 3140, 3010, 2400, 1735, 1630, 1210, 840, 730 cm^{-1}; ^1H NMR: δ 9.04 (br, 1H), 7.84 (d, $J = 7.5$ Hz, 2H), 7.79 (d, $J = 7.5$ Hz, 2H, isomer), 7.51 (m, 1H), 7.45–7.26 (m, 13H), 6.59 (br, 1H), 5.21 (s, 2H), 4.44 (d, $J = 6.0$ Hz, 2H). ^{13}C NMR: δ 164.9, 138.4, 136.5, 134.0, 131.6, 128.8, 128.7, 128.6, 128.53, 128.47, 128.02, 127.98, 127.5, 127.2, 127.1, 126.9, 66.1, 52.6. HRMS (FAB): m/z $[M]^+$ calcd for $C_{24}H_{22}N_2O_3^+$, 386.1630; found, 386.1628.

General procedure for thermal cyclization of methyl 2-benzamido-3-(benzylamino)acrylate (12a). A mixture of **12a** (0.01 mol) and toluene (6 mL) were heated under reflux for 1.5–15 h, volatile components were evaporated *in vacuo*, the residue was triturated with toluene–hexane or with Et_2O, and the precipitate was collected by filtration to give **11a**.

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[14] The thermal cyclization of enamine compound is reversible reaction, so no reaction was observed in the sealed pyrex tube.

Ethyl-3,4-diaroyl-2-cyanobutyrate: A Synthon for Novel Heterocycles

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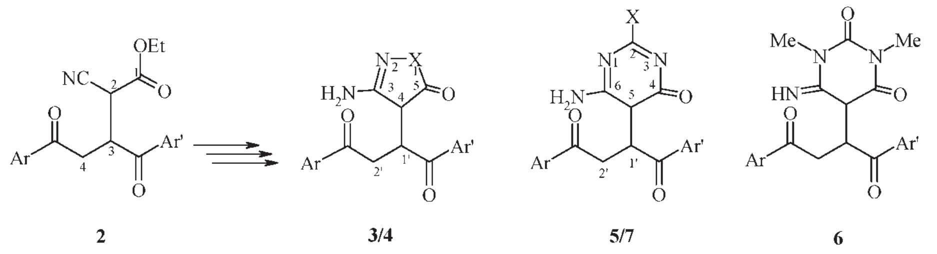

3, 4 X = NH, O; 5, 7 X = OH, SH

A new class of aminopyrazolones, aminoisoxazolones, aminopyrimidinones, and thioxopyrimidinones were synthesized from Michael adduct, ethyl-3,4-diaroyl-2-cyanobutyrate, on reaction with different nucleophiles, hydrazine hydrate, hydroxylamine hydrochloride, and urea derivatives.

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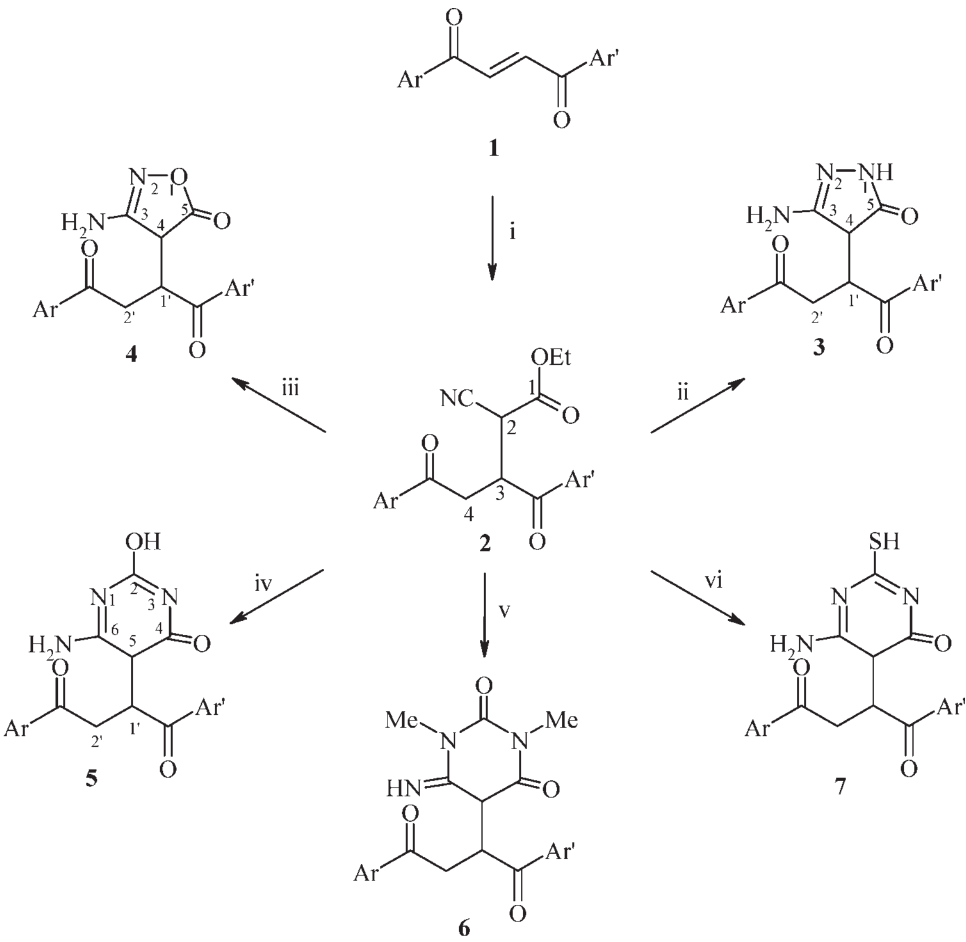
INTRODUCTION

A large number of heterocyclic compounds play a vital role as drugs and pharmaceutical agents. A number of barbiturate and thiobarbiturate derivatives exhibit anticonvulsant, anaesthetic, sedative, and hypnotic properties [1–5]. In fact, phenobarbital and mephobarbital are used for clinical treatment of epilepsy [6]. Besides, methohexital is still used worldwide in hospitals as injection narcotics [7]. Increasing evidence suggests that pyrazole and isoxazole derivatives possess a broad spectrum of biological activity such as bacteriostatic, antidiabetic, analgesic, antiarrhythmic, anti-inflammatory, antifungal, and antiviral properties [8–13]. Celecoxib, a pyrazole derivative, valdecoxib, an isoxazole derivative are now being used as anti-inflammatory drugs [14]. Thus, the development of practical and convenient method for the construction of nitrogen containing heterocycles is an important goal. Michael adducts afford a rich and diverse array of options for the synthesis of variety of five and six membered heterocycles. In fact, we have exploited a variety of Michael adducts to develop different heterocycles [15–19]. In a continuing quest for further ways of utilizing Michael adducts, the present work has been taken up.

RESULTS AND DISCUSSION

The synthetic scheme involves the Michael addition of ethyl cyanoacetate to (*E*)-1,4-diaroylbut-2-ene-1,4-dione (**1**) in the presence of K_2CO_3 in MEK to get ethyl-3,4-diaroyl-2-cyanobutyrate (**2**) (Scheme 1 and Table 1). The IR spectra of **2** displayed absorption bands at 2241–2250 (CN), 1698–1715 (ArCO), 1731–1748 cm^{-1} (CO_2Et) (Table 2). The ^{1}H NMR spectrum of **2a** showed a doublet at 4.53 (C_2—H), a multiplet at 4.02–4.07 (C_3—H), and two double doublets at 3.27 and 3.35 ppm (C_4—H). Apart from these, a quartet and a triplet are observed at 3.54, 1.25 ppm due to carboethoxy group (Table 3). The *gem*-cyanoester functionality in **2** is exploited to get the desired heterocycles. The cyclocondensation of **2** with hydrazine hydrate in the presence of piperidine in ethanol produced 3-amino-4(1′,2′-diaroylethyl)-1*H*-pyrazol-5(4*H*)-one (**3**). Likewise, the reaction of **2** with hydroxylamine hydrochloride gave 3-amino-4-(1′,2′-diaroylethyl)isoxazolo-5(4*H*)-one (**4**) (Scheme 1 and Table 1). The IR spectra of **3** and **4** displayed absorption bands at 3342–3375, 3438–3479 (NH_2), 1604–1624 (C=N), 1624–1636 (*C*ONH), 1692–1711 (Ar-CO), and at 1738–1749 cm^{-1} (*C*O—O) (Table 2). The ^{1}H NMR spectra of **3a** and **4a** exhibited a doublet at 4.37, 4.34 for C_4—H, a multiplet at 4.17–4.22, 4.15–4.24 for C_1'—H and two double doublets at 3.14 and 3.82 and 3.11 and 3.72 ppm for C_2'—H. Further, a broad singlet is observed at 5.87, 5.90 ppm due to NH_2 which disappeared on deuteration (Table 3). Similar reaction of **2** with urea, *N*,*N*′-dimethylurea, and thiourea produced 6-amino-5-(1′,2′-diaroylethyl)-2-hydroxypyrimidine-4(5*H*)-one (**5**), 6-imino-5-(1′,2′-diaroylethyl)-1,3-

Scheme 1



(i) $CNCH_2CO_2Et$ / K_2CO_3 / MEK
(ii) $NH_2NH_2.H_2O$ / Piperidine / EtOH
(iii) $NH_2OH.HCl$ / Piperidine / EtOH
(iv) NH_2CONH_2 / Piperidine / EtOH
(v) MeNHCONHMe / Piperidine / EtOH
(vi) NH_2CSNH_2 / Piperidine / EtOH

	Ar	Ar'
a	C_6H_5,	C_6H_5
b	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$
c	*p*-ClC_6H_4	*p*-ClC_6H_4
d	C_6H_5	*p*-$CH_3C_6H_4$
e	C_6H_5	*p*-ClC_6H_4
f	*p*-$CH_3C_6H_4$	*p*-ClC_6H_4

dimethyl-pyrimidine-2,4(5*H*)-dione (**6**), and 6-amino-5-(1′,2′-diaroylethyl)-2-mercapto-pyrimidine-4(5*H*)-one (**7**), respectively (Scheme 1 and Table 1). The IR spectra of **5**–**7** showed absorption bands in the regions 3345–3460 (NH_2), 1625–1645 (*CO*—N), and 1695–1715 cm^{-1} (Ar-CO). In addition to these, the compound **5** displayed a band at 3315–3321 (OH), **6** at 1629–1642 (C=O of pyrimidine ring), and 3311–3238 cm^{-1} (NH), while **7** at 2543–2564 cm^{-1} (SH). The compounds **5** and **7** also showed an absorption band at 1603–1617 cm^{-1} (C=N) (Table 2). The ^1H NMR spectra of **5a, 6a,** and **7a** displayed a doublet at 4.37, 4.39, 4.33 for C_5—H, a multiplet at 4.18–4.24, 4.15–4.21, 4.13–4.25 for C'_1—H and two doublet of doublets at 3.08 and 3.82, 307 and 3.76, 3.04 and 3.77 ppm for C'_2—H. Besides these, **6a** showed two singlets at 2.73 and 2.75 for *N*-methyl protons and a broad singlet at 9.24 ppm for =NH. The compounds **5a** and **7a** also displayed a broad singlet at 5.87 and 5.73 ppm for NH_2. Another singlet is observed at 6.90 in **5a** due to OH and at 1.33 ppm in **7a** due to SH. The signals of NH, NH_2, OH, and SH are disappeared on deuteration. The structures of all the new compounds are further confirmed by ^{13}C NMR spectra (Table 3).

Table 1

Physical and analytical data of compounds **2–10.**

						Analysis % Calcd./Found		
Compound	Mp (°C)	Yield (%)	Ar	Ar′	Molecular formula	C	H	N
2a	116–118	72	C_6H_5	C_6H_5	$C_{21}H_{19}NO_4$ (349.38)	72.19	5.48	4.01
						72.29	5.46	4.14
2b	130–132	70	*P*-$CH_3C_6H_4$	*P*-$CH_3C_6H_4$	$C_{23}H_{23}NO_4$ (377.43)	73.19	6.14	3.71
						73.22	6.12	3.75
2c	144–146	78	*P*-ClC_6H_4	*P*-ClC_6H_4	$C_{21}H_{17}Cl_2NO_4$ (418.27)	60.30	4.10	3.35
						60.24	4.06	3.37
2d	138–140	74	C_6H_5	*P*-$CH_3C_6H_4$	$C_{22}H_{21}NO_4$ (363.41)	72.71	5.82	3.85
						72.67	5.85	3.80
2e	152–154	76	C_6H_5	*P*-ClC_6H_4	$C_{21}H_{18}ClNO_4$ (383.82)	65.71	4.73	3.65
						65.79	4.71	3.67
2f	126–128	73	*P*-$CH_3C_6H_4$	*P*-ClC_6H_4	$C_{22}H_{20}ClNO_4$ (397.85)	66.42	5.07	3.52
						66.51	5.02	3.50
3a	156–158	85	C_6H_5	C_6H_5	$C_{19}H_{17}N_3O_3$ (335.36)	68.05	5.11	12.53
						68.00	5.15	12.59
3b	165–167	82	*P*-$CH_3C_6H_4$	*P*-$CH_3C_6H_4$	$C_{21}H_{21}N_3O_3$ (363.41)	69.41	5.82	11.56
						69.50	5.80	11.66
3c	172–174	87	*P*-ClC_6H_4	*P*-ClC_6H_4	$C_{19}H_{15}Cl_2N_3O_3$ (404.25)	56.45	3.74	10.39
						56.38	3.71	10.45
3d	175–177	80	C_6H_5	*P*-$CH_3C_6H_4$	$C_{20}H_{19}N_3O_3$ (349.38)	68.75	5.48	12.03
						68.81	5.50	12.09
3e	180–182	78	C_6H_5	*P*-ClC_6H_4	$C_{19}H_{16}ClN_3O_3$ (369.8)	61.71	4.36	11.36
						61.76	4.40	11.30
3f	166–168	84	*P*-$CH_3C_6H_4$	*P*-ClC_6H_4	$C_{20}H_{18}ClN_3O_3$ (383.83)	62.58	4.73	10.95
						62.52	4.70	11.02
4a	151–153	75	C_6H_5	C_6H_5	$C_{19}H_{16}N_2O_4$ (336.34)	67.85	4.79	8.33
						67.89	4.84	8.37
4b	164–166	77	*P*-$CH_3C_6H_4$	*P*-$CH_3C_6H_4$	$C_{21}H_{20}N_2O_4$ (364.39)	69.22	5.53	7.69
						69.18	5.51	7.66
4c	170–172	72	*P*-ClC_6H_4	*P*-ClC_6H_4	$C_{19}H_{14}Cl_2N_2O_4$ (405.23)	56.31	3.48	6.91
						56.35	3.49	6.94
4d	176–178	74	C_6H_5	*P*-$CH_3C_6H_4$	$C_{20}H_{18}N_2O_4$ (350.37)	68.56	5.18	8.00
						68.60	5.17	8.08
4e	161–163	70	C_6H_5	*P*-ClC_6H_4	$C_{19}H_{15}ClN_2O_4$ (370.79)	61.55	4.08	7.56
						61.58	4.06	7.52
4f	154–156	67	*P*-$CH_3C_6H_4$	*P*-ClC_6H_4	$C_{20}H_{17}ClN_2O_4$ (384.81)	62.42	4.45	7.28
						62.38	4.48	7.24
5a	182–184	65	C_6H_5	C_6H_5	$C_{20}H_{17}N_3O_4$ (363.37)	66.11	4.72	11.56
						66.08	4.71	11.66
5b	201–203	68	*P*-$CH_3C_6H_4$	*P*-$CH_3C_6H_4$	$C_{22}H_{21}N_3O_4$ (391.42)	67.51	5.41	10.74
						67.57	5.45	10.80
5c	215–217	70	*P*-ClC_6H_4	*P*-ClC_6H_4	$C_{20}H_{15}Cl_2N_3O_4$ (432.26)	55.57	3.50	9.72
						55.61	3.51	9.80
5d	188–190	73	C_6H_5	*P*-$CH_3C_6H_4$	$C_{21}H_{19}N_3O_4$ (377.39)	66.83	5.07	11.13
						66.89	5.10	11.20
5e	194–196	76	C_6H_5	*P*-ClC_6H_4	$C_{20}H_{16}ClN_3O_4$ (397.81)	60.38	4.05	10.56
						60.35	4.04	10.60
5f	207–209	69	*P*-$CH_3C_6H_4$	*P*-ClC_6H_4	$C_{21}H_{18}ClN_3O_4$ (411.84)	61.24	4.41	10.20
						61.28	4.44	10.15
6a	186–188	64	C_6H_5	C_6H_5	$C_{22}H_{21}N_3O_4$ (391.42)	67.51	5.41	10.74
						67.45	5.42	10.71
6b	204–206	66	*P*-$CH_3C_6H_4$	*P*-$CH_3C_6H_4$	$C_{24}H_{25}N_3O_4$ (419.47)	68.72	6.01	10.02
						68.80	6.00	10.08
6c	219–221	62	*P*-ClC_6H_4	*P*-ClC_6H_4	$C_{22}H_{19}Cl_2N_3O_4$ (460.31)	57.40	4.16	9.13
						57.45	4.14	9.08
6d	193–195	65	C_6H_5	*P*-$CH_3C_6H_4$	$C_{23}H_{23}N_3O_4$ (405.45)	68.13	5.72	10.36
						68.19	5.75	10.42
6e	198–200	68	C_6H_5	*P*-ClC_6H_4	$C_{22}H_{20}ClN_3O_4$ (425.86)	62.05	4.73	9.87
						62.09	4.71	9.82
6f	211–213	63	*P*-$CH_3C_6H_4$	*P*-ClC_6H_4	$C_{23}H_{22}ClN_3O_4$ (439.89)	62.80	5.04	9.55
						62.87	5.02	9.59

(*Continued*)

Table 1
(*Continued*)

						Analysis % Calcd./Found		
Compound	Mp (°C)	Yield (%)	Ar	Ar′	Molecular formula	C	H	N
7a	195–197	74	C_6H_5	C_6H_5	$C_{20}H_{17}N_3O_3S$ (379.43)	63.31	4.52	11.07
						63.28	4.51	11.14
7b	214–216	72	*P*-$CH_3C_6H_4$	*P*-$CH_3C_6H_4$	$C_{22}H_{21}N_3O_3S$ (407.49)	64.85	5.19	10.31
						64.89	5.22	10.36
7c	220–222	66	*P*-ClC_6H_4	*P*-ClC_6H_4	$C_{20}H_{15}Cl_2N_3O_3S$ (448.32)	53.58	3.37	9.37
						53.57	3.40	9.32
7d	218–220	77	C_6H_5	*P*-$CH_3C_6H_4$	$C_{21}H_{19}N_3O_3S$ (393.46)	64.10	4.87	10.68
						64.13	4.86	10.74
7e	205–207	71	C_6H_5	*P*-ClC_6H_4	$C_{20}H_{16}ClN_3O_3S$ (413.88)	58.04	3.90	10.15
						58.00	3.88	10.17
7f	225–227	69	*P*-$CH_3C_6H_4$	*P*-ClC_6H_4	$C_{21}H_{18}ClN_3O_3S$ (427.9)	58.94	4.24	9.82
						58.97	4.27	9.88

Table 2
IR data of compounds **2–10**.

	IR (KBr) cm^{-1}							
Compound	C≡N/C=N	C=O	Ar-C=O	CO_2Et	OH/SH	NH	NH_2	
2a	2243	–	1710	1733	–	–	–	–
2b	2250	–	1702	1735	–	–	–	–
2c	2246	–	1698	1731	–	–	–	–
2d	2241	–	1704	1736	–	–	–	–
2e	2245	–	1715	1742	–	–	–	–
2f	2244	–	1701	1748	–	–	–	–
3a	1608	1634	1695	–	–	3210	3361	3472
3b	1613	1628	1702	–	–	3204	3357	3479
3c	1606	1631	1707	–	–	3209	3361	3474
3d	1624	1636	1698	–	–	3201	3358	3444
3e	1619	1630	1690	–	–	3206	3342	3438
3f	1621	1624	1696	–	–	3200	3350	3442
4a	1605	1741	1703	–	–	–	3352	3449
4b	1609	1749	1700	–	–	–	3349	3451
4c	1613	1746	1692	–	–	–	3364	3448
4d	1610	1738	1695	–	–	–	3375	3452
4e	1604	1744	1704	–	–	–	3357	3445
4f	1610	1742	1711	–	–	–	3338	3443
5a	1603	1644	1707	–	3328	–	3351	3457
5b	1610	1634	1713	–	3315	–	3347	3449
5c	1612	1640	1699	–	3331	–	3361	3452
5d	1618	1636	1711	–	3324	–	3359	3445
5e	1616	1638	1702	–	3322	–	3361	3448
5f	1609	1645	1709	–	3319	–	3352	3454
6a	–	1634	1715	–	–	3211	–	–
6b	–	1642	1712	–	–	3216	–	–
6c	–	1632	1697	–	–	3234	–	–
6d	–	1629	1692	–	–	3222	–	–
6e	–	1634	1701	–	–	3227	–	–
6f	–	1631	1694	–	–	3238	–	–
7a	1610	1633	1702	–	2564	–	3350	3451
7b	1612	1639	1709	–	2557	–	3346	3446
7c	1601	1643	1705	–	2545	–	3362	3454
7d	1609	1637	1699	–	2543	–	3351	3444
7e	1604	1635	1711	–	2559	–	3362	3446
7f	1617	1640	1702	–	2561	–	3353	3453

Table 3

^{1}H and ^{13}C NMR data of compounds **2–7**.

Compound	^{1}H NMR (CDCl$_3$/DMSO-*d*$_6$) δ, ppm	^{13}C NMR (CDCl$_3$/DMSO-*d*$_6$) δ, ppm
2a	1.25 (t, 3H, OCH$_2$*CH*$_3$), 3.27 (dd, 1H, C$_4$—H, *J* = 8.6, 14.4 Hz), 3.35 (dd, 1H, C$_4$—H, *J* = 4.2, 14.6 Hz), 3.54 (q, 2H, O*CH*$_2$CH$_3$), 4.02–4.07 (m, 1H, C$_3$—H), 4.53 (d, 1H, C$_2$—H, *J* = 8.6 Hz), 7.16–7.48 (m, 10H, Ar-H)	13.9 (OCH$_2$CH$_3$), 36.1 (C-3), 41.6 (C-2), 52.9 (C-4), 61.1 (O*C*H$_2$CH$_3$), 116.2 (CN), 166.8 (*C*O$_2$Et), 205.8 (Ar-CO), 206.2 (Ar′-CO), 125.7, 127.7, 128.5, 129.1, 131.4, 134.2, 134.7, 135.9 (aromatic carbons)
2b	1.28 (t, 3H, OCH$_2$*CH*$_3$), 2.26 (s, 6H, Ar-CH$_3$ and Ar′-CH$_3$), 3.24 (dd, 1H, C$_4$—H, *J* = 9.0, 14.3 Hz), 3.29 (dd, 1H, C$_4$—H, *J* = 4.5, 14.8 Hz), 3.51 (q, 2H, O*CH*$_2$CH$_3$), 3.97–3.99 (m, 1H, C$_3$—H), 4.48 (d, 1H, C$_2$—H, *J* = 8.5 Hz), 7.21–7.46 (m, 8H, Ar-H)	22.7 (Ar-CH$_3$ and Ar′-CH$_3$), 13.4 (OCH$_2$*C*H$_3$), 36.8 (C-3), 42.1 (C-2), 51.6 (C-4), 62.0 (O*C*H$_2$CH$_3$), 114.9 (CN), 167.6 (*C*O$_2$Et), 205.1 (Ar-CO), 206.6 (Ar′-CO), 126.1, 128.4, 128.9, 129.7, 132.5, 134.3, 134.7, 135.1 (aromatic carbons)
2c	1.31 (t, 3H, OCH$_2$*CH*$_3$), 3.28 (dd, 1H, C$_4$—H, *J* = 8.8, 14.5 Hz), 3.31 (dd, 1H, C$_4$—H, *J* = 4.4, 14.6 Hz), 3.57 (q, 2H, O*CH*$_2$CH$_3$), 3.92–4.01 (m, 1H, C$_3$—H), 4.51 (d, 1H, C$_2$—H, *J* = 8.7 Hz), 7.26–7.58 (m, 8H, Ar-H)	13.7 (OCH$_2$CH$_3$), 37.4 (C-3), 42.9 (C-2), 52.1 (C-4), 62.6 (O*C*H$_2$CH$_3$), 114.2 (CN), 167.9 (*C*O$_2$Et), 205.9 (Ar-CO), 206.0 (Ar′-CO), 126.8, 128.9, 129.9, 132.2, 134.5, 134.2, 136.9 (aromatic carbons)
2d	1.27 (t, 3H, OCH$_2$*CH*$_3$), 2.25 (s, 3H, Ar′-CH$_3$), 3.25 (dd, 1H, C$_4$—H, *J* = 8.5, 14.2 Hz), 3.34 (dd, 1H, C$_4$—H, *J* = 4.6, 14.4 Hz), 3.55 (q, 2H, O*CH*$_2$CH$_3$), 3.91–4.03 (m, 1H, C$_3$—H), 4.54 (d, 1H, C$_2$—H, *J* = 8.6 Hz), 7.21–7.51 (m, 9H, Ar-H)	13.0 (OCH$_2$CH$_3$), 22.4 (Ar′-CH$_3$), 37.1 (C-3), 42.4 (C-2), 52.3 (C-4), 62.2 (O*C*H$_2$CH$_3$), 114.8 (CN), 167.2 (*C*O$_2$Et), 205.6 (Ar-CO), 206.8 (Ar′-CO), 126.2, 128.4, 129.3, 132.0, 134.1, 134.8, 135.1 (aromatic carbons)
2e	1.34 (t, 3H, OCH$_2$*CH*$_3$), 3.21 (dd, 1H, C$_4$—H, *J* = 8.3, 14.5 Hz), 3.31 (dd, 1H, C$_4$—H, *J* = 4.5, 14.3 Hz), 3.58 (q, 2H, O*CH*$_2$CH$_3$), 3.94–4.01 (m, 1H, C$_3$—H), 4.52 (d, 1H, C$_2$—H, *J* = 8.6 Hz), 7.28–7.67 (m, 9H, Ar-H)	13.2 (OCH$_2$CH$_3$), 37.6 (C-3), 42.7 (C-2), 52.6 (C-4), 62.8 (O*C*H$_2$CH$_3$), 114.3 (CN), 167.1 (*C*O$_2$Et), 205.7 (Ar-CO), 206.4 (Ar′-CO), 126.8, 127.9, 129.2, 132.8, 134.7, 135.9, 135.1 (aromatic carbons)
2f	1.26 (t, 3H, OCH$_2$*CH*$_3$), 2.27 (s, 3H, Ar-CH$_3$), 3.25 (dd, 1H, C$_4$—H, *J* = 8.2, 14.2 Hz), 3.34 (dd, 1H, C$_4$—H, *J* = 4.6, 14.4 Hz), 3.50 (q, 2H, O*CH*$_2$CH$_3$), 3.93–4.04 (m, 1H, C$_3$—H), 4.50 (d, 1H, C$_2$—H, *J* = 8.8 Hz), 7.31–7.74 (m, 9H, Ar-H)	13.8 (OCH$_2$CH$_3$), 21.9 (Ar-CH$_3$), 37.3 (C-3), 42.9 (C-2), 52.3 (C-4), 62.0 (O*C*H$_2$CH$_3$), 114.1 (CN), 167.1 (*C*O$_2$Et), 205.2 (Ar-CO), 206.9 (Ar′-CO), 126.1, 127.6, 129.0, 132.2, 133.4, 134.9, 136.4 (aromatic carbons)
3a	3.14 (dd, 1H, C$_2'$—H, *J* = 4.3, 14.1 Hz), 3.82 (dd, 1H, C$_2'$—H, *J* = 9.1, 14.3 Hz), 4.17–4.22 (m, 1H, C$_1'$—H), 4.37 (d, 1H, C$_4$—H, *J* = 5.6 Hz), 5.87 (bs, 2H, NH$_2$), 7.10–7.85 (m, 10H, Ar-H), 9.11 (bs, 1H, NH)	53.1 (C-2′), 55.8 (C-1′), 62.9 (C-4), 156.6 (C-5), 171.5 (C-3), 205.5 (Ar-CO), 206.2 (Ar′-CO), 129.6, 130.2, 131.8, 132.9, 133.6, 134.9, 135.4, 136.2 (aromatic carbons)
3b	2.24 (s, 6H, Ar-CH$_3$ and Ar′-CH$_3$), 3.10 (dd, 1H, C$_2'$—H, *J* = 4.1, 14.0 Hz), 3.79 (dd, 1H, C$_2'$—H, *J* = 9.2, 14.1 Hz), 4.12–4.25 (m, 1H, C$_1'$—H), 4.35 (d, 1H, C$_4$—H, *J* = 5.4 Hz), 5.82 (bs, 2H, NH$_2$), 7.12–7.81 (m, 8H, Ar-H), 9.19 (bs, 1H, NH)	22.4 (Ar-CH$_3$ and Ar′-CH$_3$), 53.8 (C-2′), 56.1 (C-1′), 63.3 (C-4), 156.9 (C-5), 169.5 (C-3), 205.6 (Ar-CO), 206.6 (Ar′-CO), 128.5, 129.1, 130.6, 131.5, 132.2, 133.5, 134.1, 135.4 (aromatic carbons)
3c	3.08 (dd, 1H, C$_2'$—H, *J* = 4.0, 14.2 Hz), 3.74 (dd, 1H, C$_2'$—H, *J* = 9.1, 14.3 Hz), 4.15–4.21 (m, 1H, C$_1'$—H), 4.34 (d, 1H, C$_4$—H, *J* = 5.4 Hz), 5.84 (bs, 2H, NH$_2$), 7.14–7.86 (m, 8H, Ar-H), 9.78 (bs, 1H, NH)	53.3 (C-2′), 56.5 (C-1′), 63.9 (C-4), 157.1 (C-5), 169.9 (C-3), 205.2 (Ar-CO), 206.9 (Ar′-CO), 128.9, 129.7, 130.2, 131.2, 132.9, 133.9, 134.9, 136.4 (aromatic carbons)
3d	2.28 (s, 3H, Ar′-CH$_3$), 3.12 (dd, 1H, C$_2'$—H, *J* = 4.3, 14.4 Hz), 3.78 (dd, 1H, C$_2'$—H, *J* = 9.2, 14.4 Hz), 4.11–4.24 (m, 1H, C$_1'$—H), 4.38 (d, 1H, C$_4$—H, *J* = 5.7 Hz), 5.89 (bs, 2H, NH$_2$), 7.10–7.82 (m, 9H, Ar-H), 9.86 (bs, 1H, NH)	21.5 (Ar′-CH$_3$), 53.5 (C-2′), 56.3 (C-1′), 63.6 (C-4), 156.7 (C-5), 169.1 (C-3), 205.0 (Ar-CO), 206.2 (Ar′-CO), 128.1, 129.4, 130.8, 131.9, 132.1, 133.7, 134.2, 135.9 (aromatic carbons)
3e	3.07 (dd, 1H, C$_2'$—H, *J* = 4.1, 14.2 Hz), 3.74 (dd, 1H, C$_2'$—H, *J* = 9.0, 14.3 Hz), 4.16–4.27 (m, 1H, C$_1'$—H), 4.36 (d, 1H, C$_4$—H, *J* = 5.4 Hz), 5.86 (bs, 2H, NH$_2$), 7.19–7.69 (m, 9H, Ar-H), 9.71 (bs, 1H, NH)	52.6 (C-2′), 56.0 (C-1′), 63.2 (C-4), 157.2 (C-5), 169.6 (C-3), 205.4 (Ar-CO), 206.8 (Ar′-CO), 128.5, 129.9, 130.2, 131.2, 132.2, 133.3, 134.8, 135.2 (aromatic carbons)
3f	2.25 (s, 3H, Ar-CH$_3$), 3.16 (dd, 1H, C$_2'$—H, *J* = 4.4, 14.4 Hz), 3.77 (dd, 1H, C$_2'$—H, *J* = 9.2, 14.5 Hz), 4.18–4.28 (m, 1H, C$_1'$—H), 4.42 (d, 1H, C$_4$—H, *J* = 5.7 Hz), 5.89 (bs, 2H, NH$_2$), 7.16–7.85 (m, 8H, Ar-H), 9.77 (bs, 1H, NH)	22.1 (Ar-CH$_3$), 52.8 (C-2′), 55.6 (C-1′), 62.7 (C-4), 156.6 (C-5), 169.4 (C-3), 205.9 (Ar-CO), 206.4 (Ar′-CO), 128.7, 129.2, 130.9, 131.7, 132.1, 133.9, 134.7, 136.9 (aromatic carbons)
4a	3.11 (dd, 1H, C$_2'$—H, *J* = 4.6, 14.7 Hz), 3.72 (dd, 1H, C$_2'$—H, *J* = 9.1, 14.6 Hz), 4.15–4.24 (m, 1H, C$_1'$—H), 4.34 (d, 1H, C$_4$—H, *J* = 5.4 Hz), 5.90 (bs, 2H, NH$_2$), 7.22–7.74 (m, 10H, Ar-H)	53.1 (C-2′), 57.2 (C-1′), 63.0 (C-4), 159.3 (C-3), 174.1 (C-5), 205.1 (Ar-CO), 206.8 (Ar′-CO), 128.1, 129.5, 130.1, 131.2, 132.6, 133.2, 134.0, 135.2 (aromatic carbons)
4b	2.22 (s, 6H, Ar-CH$_3$ and Ar′-CH$_3$), 3.04 (dd, 1H, C$_2'$—H, *J* = 4.5, 14.5 Hz), 3.69 (dd, 1H, C$_2'$—H, *J* = 9.0, 14.7 Hz), 4.19–4.27 (m, 1H, C$_1'$—H), 4.36 (d, 1H, C$_4$—H, *J* = 5.4 Hz), 5.92 (bs, 2H, NH$_2$), 7.08–7.65 (m, 8H, Ar-H)	22.9 (Ar-CH$_3$ and Ar′-CH$_3$), 53.8 (C-2′), 57.7 (C-1′), 62.8 (C-4), 158.8 (C-3), 174.6 (C-5), 205.9 (Ar-CO), 206.1 (Ar′-CO), 128.7, 129.3, 130.9, 131.9, 132.2, 133.9, 134.8, 135.1 (aromatic carbons)

(*Continued*)

Table 3
(*Continued*)

Compound	^1H NMR ($CDCl_3$/DMSO-d_6) δ, ppm	^{13}C NMR ($CDCl_3$/DMSO-d_6) δ, ppm
4c	3.09 (dd, 1H, C_2'—H, J = 4.7, 14.4 Hz), 3.71 (dd, 1H, C_2'—H, J = 9.1, 14.6 Hz), 4.13–4.24 (m, 1H, C_1'—H), 4.32 (d, 1H, C_4—H, J = 5.5 Hz), 5.84 (bs, 2H, NH_2), 7.12–7.77 (m, 8H, Ar-H)	53.4 (C-2′), 57.6 (C-1′), 61.7 (C-4), 158.0 (C-3), 173.7 (C-5), 204.9 (Ar-CO), 206.7 (Ar′-CO), 128.1, 129.8, 131.4, 132.3, 133.7, 134.8, 135.2, 136.9 (aromatic carbons)
4d	2.24 (s, 3H, Ar′-CH_3), 3.12 (dd, 1H, C_2'—H, J = 4.6, 14.6 Hz), 3.76 (dd, 1H, C_2'—H, J = 9.0, 14.4 Hz), 4.17–4.27 (m, 1H, C_1'—H), 4.35 (d, 1H, C_4—H, J = 5.7 Hz), 5.86 (bs, 2H, NH_2), 7.08–7.71 (m, 9H, Ar-H)	22.3 (Ar′-CH_3), 52.6 (C-2′), 58.7 (C-1′), 61.5 (C-4), 158.9 (C-3), 173.9 (C-5), 205.2 (Ar-CO), 206.3 (Ar′-CO), 128.7, 129.4, 131.7, 132.5, 133.1, 134.2, 135.1, 136.2 (aromatic carbons)
4e	3.07 (dd, 1H, C_2'—H, J = 4.5, 14.5 Hz), 3.78 (dd, 1H, C_2'—H, J = 8.9, 14.6 Hz), 4.12–4.23 (m, 1H, C_1'—H), 4.30 (d, 1H, C_4—H, J = 5.5 Hz), 5.94 (bs, 2H, NH_2), 7.10–7.75 (m, 9H, Ar-H)	52.1 (C-2′), 58.2 (C-1′), 61.8 (C-4), 158.1 (C-3), 173.6 (C-5), 205.7 (Ar-CO), 206.2 (Ar′-CO), 127.9, 128.6, 130.4, 131.5, 132.9, 134.2, 135.6, 136.9 (aromatic carbons)
4f	2.22 (s, 3H, Ar-CH_3), 3.10 (dd, 1H, C_2'—H, J = 4.7, 14.7 Hz), 3.72 (dd, 1H, C_2'—H, J = 8.3, 14.4 Hz), 4.14–4.27 (m, 1H, C_1'—H), 4.31 (d, 1H, C_4—H, J = 5.3 Hz), 5.89 (bs, 2H, NH_2), 7.15–7.79 (m, 8H, Ar-H),	21.9 (Ar-CH_3), 53.7 (C-2′), 57.9 (C-1′), 62.4 (C-4), 157.8 (C-3), 174.4 (C-5), 204.6 (Ar-CO), 206.1 (Ar′-CO), 127.2, 128.9, 130.7, 131.1, 132.2, 134.9, 135.2, 136.1 (aromatic carbons)
5a	3.08 (dd, 1H, C_2'—H, J = 4.4, 14.5 Hz), 3.82 (dd, 1H, C_2'—H, J = 9.0, 14.4 Hz), 4.18–4.24 (m, 1H, C_1'—H), 4.37 (d, 1H, C_5—H, J = 5.3 Hz), 5.87 (bs, 2H, NH_2), 6.90 (bs, 1H, OH), 7.20–7.71 (m, 10H, Ar-H)	52.9 (C-2′), 57.7 (C-1′), 64.2 (C-5), 158.6 (C-6), 164.3 (C-2), 174.2 (C-4), 205.9 (Ar-CO), 206.8 (Ar′-CO), 127.9, 129.9, 130.9, 131.8, 132.1, 133.6, 134.9, 135.4 (aromatic carbons)
5b	2.23 (s, 6H, Ar-CH_3 and Ar′-CH_3), 3.09 (dd, 1H, C_2'—H, J = 4.5, 14.3 Hz), 3.76 (dd, 1H, C_2'—H, J = 9.1, 14.1 Hz), 4.12–4.21 (m, 1H, C_1'—H), 4.34 (d, 1H, C_5—H, J = 5.0 Hz), 5.80 (bs, 2H, NH_2), 6.86 (bs, 1H, OH), 7.20–7.62 (m, 8H, Ar-H)	22.7 (Ar-CH_3 and Ar′-CH_3), 51.8 (C-2′), 55.1 (C-1′), 64.9 (C-5), 157.8 (C-6), 164.9 (C-2), 170.6 (C-4), 205.1 (Ar-CO), 206.2 (Ar′-CO), 127.1, 129.3, 130.2, 131.4, 132.9, 133.4, 134.4, 136.9 (aromatic carbons)
5c	3.11 (dd, 1H, C_2'—H, J = 4.6, 14.6 Hz), 3.83 (dd, 1H, C_2'—H, J = 9.0, 14.4 Hz), 4.11–4.23 (m, 1H, C_1'—H), 4.36 (d, 1H, C_5—H, J = 5.3 Hz), 5.84 (bs, 2H, NH_2), 6.87 (bs, 1H, OH), 7.25–7.81 (m, 8H, Ar-H)	52.4 (C-2′), 55.8 (C-1′), 64.0 (C-5), 158.3 (C-6), 163.7 (C-2), 170.9 (C-4), 205.6 (Ar-CO), 206.7 (Ar′-CO), 127.8, 129.4, 130.8, 131.6, 132.3, 133.9, 135.8, 136.9 (aromatic carbons)
5d	2.26 (s, 3H, Ar′-CH_3), 3.07 (dd, 1H, C_2'—H, J = 4.4, 14.2 Hz), 3.79 (dd, 1H, C_2'—H, J = 8.9, 14.3 Hz), 4.13–4.21 (m, 1H, C_1'—H), 4.32 (d, 1H, C_5—H, J = 5.1 Hz), 5.82 (bs, 2H, NH_2), 6.89 (bs, 1H, OH), 7.16–7.61 (m, 9H, Ar-H)	21.8 (Ar′-CH_3), 52.3 (C-2′), 55.2 (C-1′), 64.7 (C-5), 159.1 (C-6), 164.2 (C-2), 170.2 (C-4), 205.3 (Ar-CO), 206.8 (Ar′-CO), 127.2, 129.5, 130.4, 131.7, 132.0, 134.6, 135.1, 136.7 (aromatic carbons)
5e	3.10 (dd, 1H, C_2'—H, J = 4.6, 14.5 Hz), 3.84 (dd, 1H, C_2'—H, J = 8.6, 14.4 Hz), 4.18–4.23 (m, 1H, C_1'—H), 4.35 (d, 1H, C_5—H, J = 5.5 Hz), 5.86 (bs, 2H, NH_2), 6.82 (bs, 1H, OH), 7.21–7.78 (m, 9H, Ar-H)	52.8 (C-2′), 56.0 (C-1′), 64.1 (C-5), 159.8 (C-6), 164.7 (C-2), 169.9 (C-4), 205.7 (Ar-CO), 207.2 (Ar′-CO), 127.9, 128.7, 130.9, 131.6, 132.9, 134.1, 135.8, 136.4 (aromatic carbons)
5f	2.21 (s, 3H, Ar-CH_3), 3.14 (dd, 1H, C_2'—H, J = 4.7, 14.4 Hz), 3.81 (dd, 1H, C_2'—H, J = 8.3, 14.1 Hz), 4.16–4.25 (m, 1H, C_1'—H), 4.30 (d, 1H, C_5—H, J = 5.3 Hz), 5.89 (bs, 2H, NH_2), 6.87 (bs, 1H, OH), 7.20–7.72 (m, 8H, Ar-H)	22.4 (Ar-CH_3), 52.5 (C-2′), 55.6 (C-1′), 63.7 (C-5), 159.2 (C-6), 164.1 (C-2), 169.6 (C-4), 206.0 (Ar-CO), 207.4 (Ar′-CO), 127.0, 128.5, 130.6, 131.9, 132.3, 134.8, 135.2, 136.8 (aromatic carbons)
6a	2.73 and 2.75 (s, 6H, N—CH_3), 3.07 (dd, 1H, C_2'—H, J = 4.0, 14.1 Hz), 3.76 (dd, 1H, C_2'—H, J = 8.1, 14.0 Hz), 4.15–4.21 (m, 1H, C_1'—H), 4.39 (d, 1H, C_5—H, J = 5.1 Hz), 7.01–7.48 (m, 10H, Ar-H), 9.24 (bs, 1H, NH)	26.8 (N—CH_3), 27.4 (N—CH_3), 52.4 (C-2′), 54.8 (C-1′), 64.0 (C-5), 159.9 (C-2), 163.7 (C-6), 174.2 (C-4), 205.1 (Ar-CO), 207.0 (Ar′-CO), 126.4, 127.2, 128.2, 130.1, 131.5, 132.0, 134.5, 135.7 (aromatic carbons)
6b	2.26 (s, 6H, Ar-CH_3 and Ar′-CH_3), 2.74 and 2.79 (s, 6H, N—CH_3), 3.11 (dd, 1H, C_2'—H, J = 4.2, 14.3 Hz), 3.68 (dd, 1H, C_2'—H, J = 8.0, 14.1 Hz), 4.12–4.24 (m, 1H, C_1'—H), 4.31 (d, 1H, C_5—H, J = 5.3 Hz), 7.12–7.71 (m, 8H, Ar-H), 9.12 (bs, 1H, NH)	22.1 (Ar-CH_3 and Ar′-CH_3), 26.2 (N—CH_3), 27.9 (N—CH_3), 51.9 (C-2′), 54.1 (C-1′), 64.7 (C-5), 158.8 (C-2), 164.1 (C-6), 173.9 (C-4), 204.8 (Ar-CO), 207.6 (Ar′-CO), 126.9, 128.4, 128.9, 130.4, 131.4, 132.7, 133.8, 134.1, 135.4 (aromatic carbons)
6c	2.71 and 2.76 (s, 6H, N—CH_3), 3.06 (dd, 1H, C_2'—H, J = 4.0, 14.2 Hz), 3.71 (dd, 1H, C_2'—H, J = 8.0, 14.0 Hz), 4.16–4.23 (m, 1H, C_1'—H), 4.36 (d, 1H, C_5—H, J = 5.1 Hz), 7.04–7.88 (m, 8H, Ar-H), 8.99 (bs, 1H, NH)	27.9 (N—CH_3), 28.4 (N—CH_3), 51.1 (C-2′), 54.7 (C-1′), 64.2 (C-5), 158.2 (C-2), 164.9 (C-6), 173.4 (C-4), 205.3 (Ar-CO), 207.9 (Ar′-CO), 126.1, 128.9, 129.4, 130.9, 131.7, 132.3, 133.6, 135.8, 139.4 (aromatic carbons)
6d	2.25 (s, 3H, Ar′-CH_3), 2.74 and 2.79 (s, 6H, N—CH_3), 3.10 (dd, 1H, C_2'—H, J = 4.1, 14.3 Hz), 3.74 (dd, 1H, C_2'—H, J = 8.2, 14.2 Hz), 4.13–4.24 (m, 1H, C_1'—H), 4.30 (d, 1H, C_5—H, J = 5.1 Hz), 7.08–7.68 (m, 9H, Ar-H), 9.17 (bs, 1H, NH)	22.1 (Ar′-CH_3), 28.3 (N—CH_3), 29.7 (N—CH_3), 52.8 (C-2′), 54.1 (C-1′), 65.4 (C-5), 158.7 (C-2), 164.2 (C-6), 173.8 (C-4), 205.9 (Ar-CO), 207.1(Ar′-CO), 125.6, 127.8, 128.6, 130.1, 131.2, 132.6, 133.9, 134.4 (aromatic carbons)

(*Continued*)

Table 3
(*Continued*)

Compound	^{1}H NMR (CDCl$_3$/DMSO-d_6) δ, ppm	^{13}C NMR (CDCl$_3$/DMSO-d_6) δ, ppm
6e	2.78 and 2.81 (s, 6H, N—CH$_3$), 3.16 (dd, 1H, C_2'—H, J = 4.3, 14.4 Hz), 3.78 (dd, 1H, C_2'—H, J = 8.3, 14.3 Hz), 4.18–4.27 (m, 1H, C_1'—H), 4.37 (d, 1H, C$_5$—H, J = 5.3 Hz), 7.11–7.77 (m, 9H, Ar-H), 9.06 (bs, 1H, NH)	28.0 (N—CH$_3$), 29.9 (N—CH$_3$), 52.3 (C-2′), 54.8 (C-1′), 65.0 (C-5), 158.1 (C-2), 164.9 (C-6), 174.3 (C-4), 205.2 (Ar-CO), 207.4 (Ar′-CO), 125.2, 128.4, 130.9, 131.8, 132.2, 133.2, 134.7, 136.4 (aromatic carbons)
6f	2.24 (s, 3H, Ar-CH$_3$), 2.71 and 2.79 (s, 6H, N—CH$_3$), 3.12 (dd, 1H, C_2'—H, J = 4.0, 14.2 Hz), 3.72 (dd, 1H, C_2'—H, J = 8.0, 14.1 Hz), 4.11–4.23 (m, 1H, C_1'—H), 4.32 (d, 1H, C$_5$—H, J = 5.2 Hz), 7.21–7.89 (m, 8H, Ar-H), 9.09 (bs, 1H, NH)	21.9 (Ar-CH$_3$), 28.5 (N—CH$_3$), 28.7 (N—CH$_3$), 52.9 (C-2′), 54.0 (C-1′), 65.5 (C-5), 158.9 (C-2), 164.2 (C-6), 173.9 (C-4), 205.4 (Ar-CO), 208.1 (Ar′-CO), 125.9, 128.1, 130.1, 131.2, 132.9, 133.6, 134.1, 136.9 (aromatic carbons)
7a	1.33 (bs, 1H, SH), 3.04 (dd, 1H, C_2'—H, J = 4.1, 14.2 Hz), 3.77 (dd, 1H, C_2'—H, J = 9.1, 14.1 Hz), 4.13–4.25 (m, 1H, C_1'—H), 4.33 (d, 1H, C$_5$—H, J = 5.3 Hz), 5.73 (bs, 2H, NH$_2$), 7.11–7.79 (m, 10H, Ar-H)	52.1 (C-2′), 55.0 (C-1′), 63.8 (C-5), 161.6 (C-6), 174.3 (C-4), 184.2 (C-2), 205.1 (Ar-CO), 206.4 (Ar′-CO), 127.2, 129.4, 130.2, 131.6, 132.4, 133.1, 134.9, 135.6 (aromatic carbons)
7b	2.21 (s, 6H, Ar-CH$_3$ and Ar′-CH$_3$), 1.39 (bs, 1H, SH), 3.01 (dd, 1H, C_2'—H, J = 4.0, 14.1 Hz), 3.73 (dd, 1H, C_2'—H, J = 9.0, 14.2 Hz), 4.12–4.23 (m, 1H, C_1'—H), 4.36 (d, 1H, C$_5$—H, J = 5.4 Hz), 5.78 (bs, 2H, NH$_2$), 7.10–7.69 (m, 8H, Ar-H)	22.6 (Ar-CH$_3$ and Ar′-CH$_3$), 52.6 (C-2′), 55.4 (C-1′), 63.1 (C-5), 161.9 (C-6), 174.0 (C-4), 184.6 (C-2), 205.7 (Ar-CO), 206.9 (Ar′-CO), 127.8, 129.2, 130.6, 131.3, 132.9, 133.5, 134.6, 135.1 (aromatic carbons)
7c	1.32 (bs, 1H, SH), 3.08 (dd, 1H, C_2'—H, J = 4.1, 14.3 Hz), 3.77 (dd, 1H, C_2'—H, J = 9.2, 14.4 Hz), 4.18–4.27 (m, 1H, C_1'—H), 4.32 (d, 1H, C$_5$—H, J = 5.3 Hz), 5.72 (bs, 2H, NH$_2$), 7.14–7.89 (m, 8H, Ar-H)	52.9 (C-2′), 54.7 (C-1′), 63.7 (C-5), 161.3 (C-6), 174.7 (C-4), 184.9 (C-2), 206.4 (Ar-CO), 207.7 (Ar′-CO), 127.2, 129.9, 130.1, 131.8, 132.2, 133.9, 135.9, 136.3 (aromatic carbons)
7d	2.26 (s, 3H, Ar′-CH$_3$), 1.37 (bs, 1H, SH), 3.02 (dd, 1H, C_2'—H, J = 4.0, 14.2 Hz), 3.73 (dd, 1H, C_2'—H, J = 9.1, 14.3 Hz), 4.11–4.25 (m, 1H, C_1'—H), 4.33 (d, 1H, C$_5$—H, J = 5.4 Hz), 5.79 (bs, 2H, NH$_2$), 7.12–7.77 (m, 9H, Ar-H)	22.4 (Ar′-CH$_3$), 52.2 (C-2′), 53.9 (C-1′), 63.1 (C-5), 161.8 (C-6), 174.1 (C-4), 184.4 (C-2), 205.5 (Ar-CO), 206.1 (Ar′-CO), 127.6, 129.2, 130.6, 131.4, 132.6, 133.2, 134.2, 135.4 (aromatic carbons)
7e	1.35 (bs, 1H, SH), 3.06 (dd, 1H, C_2'—H, J = 4.1, 14.4 Hz), 3.70 (dd, 1H, C_2'—H, J = 9.0, 14.2 Hz), 4.13–4.23 (m, 1H, C_1'—H), 4.37 (d, 1H, C$_5$—H, J = 5.6 Hz), 5.84 (bs, 2H, NH$_2$), 7.16–7.79 (m, 9H, Ar-H)	52.9 (C-2′), 54.5 (C-1′), 62.8 (C-5), 162.4 (C-6), 174.7 (C-4), 184.1 (C-2), 205.0 (Ar-CO), 207.0 (Ar′-CO), 127.1, 129.8, 130.9, 131.1, 132.3, 133.5, 134.8, 136.2 (aromatic carbons)
7f	2.27 (s, 3H, Ar-CH$_3$), 1.31 (bs, 1H, SH), 3.09 (dd, 1H, C_2'—H, J = 4.2, 14.5 Hz), 3.74 (dd, 1H, C_2'—H, J = 9.1, 14.3 Hz), 4.16–4.27 (m, 1H, C_1'—H), 4.35 (d, 1H, C$_5$—H, J = 5.5 Hz), 5.76 (bs, 2H, NH$_2$), 7.18–7.83 (m, 9H, Ar-H)	22.9 (Ar-CH$_3$), 52.2 (C-2′), 54.0 (C-1′), 62.3 (C-5), 163.1 (C-6), 173.4 (C-4), 183.7 (C-2), 205.3 (Ar-CO), 207.4 (Ar′-CO), 127.8, 129.2, 130.1, 131.8, 132.4, 133.9, 134.1, 136.8 (aromatic carbons)

EXPERIMENTAL

General. Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The purity of the compounds was checked by TLC (silica gel H, BDH, ethyl acetate/hexane, 1:3). The IR spectra were recorded on a Thermo Nicolet IR 200 FT-IR spectrometer as KBr pellets and the wave numbers were given in cm^{-1}. The ^{1}H NMR spectra were recorded in CDCl$_3$/DMSO-d_6 on a Varian EM-360 spectrometer (300 MHz). The ^{13}C NMR spectra were recorded in CDCl$_3$/DMSO-d_6 on a Varian VXR spectrometer operating at 75.5 MHz. All chemical shifts are reported in δ (ppm) using TMS as an internal standard. The microanalyses were performed on a Perkin-Elmer 240C elemental analyzer. The starting compounds (*E*)-1,4-diaroylbut-2-ene-1,4-dione (**1**) was prepared by the literature procedure [20].

Ethyl-3,4-diaroyl-2-cyanobutyrate (2): General procedure. A mixture of ethyl cyanoacetate (15 mmol), methyl ethyl ketone (5 mL), and potassium carbonate (10 mmol) was cooled to 5–10°C. To this, compound **1** (10 mmol) was added and stirred for 3–5 h maintaining the same temperature. The contents of the flask were diluted with water and extracted with dichloromethane. The organic layer was washed with water, brine and dried (anhyd. Na$_2$SO$_4$). The solvent was removed *in vacuo*. The resultant solid was recrystallized from 2-propanol.

3-Amino-4(1′,2′-diaroylethyl)-1H-pyrazol-5(4H)-one (3): General procedure. The compound **2** (10 mmol), hydrazine hydrate (15 mmol), ethanol (20 mL), and piperidine (5 mL) was refluxed for 6–8 h. It was cooled and poured onto crushed ice containing conc. HCl. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na$_2$SO$_4$, and the solvent was removed under reduced pressure. The resultant solid was recrystallized from methanol.

3-Amino-4-(1′,2′-diaroylethyl)isoxazolo-5(4H)-one (4): General procedure. To a solution of **2** (10 mmol) in ethanol (20 mL), hydroxylamine hydrochloride (10 mmol) and piperidine (5 mL) were added and refluxed for 4–6 h. It was cooled and poured onto crushed ice containing conc. HCl. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum gave crude product which was purified by recrystallization from methanol.

6-Amino-5-(1′,2′-diaroylethyl)-2-hydroxy-pyrimidine-4(5H)-one (5): General procedure. The compound **2** (10 mmol) was dissolved in ethanol (10 mL). To this, urea (10 mmol) in ethanol (10 mL) and piperidine (5 mL) were added and refluxed for 6–10 h. The contents were cooled, poured onto crushed ice containing conc. HCl, and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent *in vacuo* gave crude product which was recrystallized from methanol.

6-Imino-5-(1′,2′-diaroylethyl)-1,3-dimethyl-pyrimidine-2,4(5H)-dione (6): General procedure. A mixture of **2** (10 mmol), 1,3-dimethylurea (10 mmol), ethanol (15 mL), and piperidine (5 mL) was refluxed for 8–12 h. The contents were diluted with ice-cold water, acidified with conc. HCl, and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent with rotary evaporator afforded crude product which was purified by recrystallization from methanol.

6-Amino-5-(1′,2′-diaroylethyl)-2-mercapto-pyrimidine-4(5H)-one (7): General procedure. To an equimolar mixture (10 mmol) of **2** and thiourea, ethanol (20 mL) and piperidine (5 mL) were added and refluxed for 10–15 h. The reaction mixture was cooled, poured onto crushed ice containing conc. HCl, and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The resultant solid was recrystallized from methanol.

CONCLUSION

The *gem*-cyanoester functionality in ethyl-3,4-diaroyl-2-cyanobutyrate is conveniently exploited to get a new class of aminopyrazolones, isoxazolones, pyrimidinediones, and thioxopyrimidinones adopting facile, simple, and well-versed synthetic methodologies.

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Solvent-free Route to β-Enamino Dichloromethyl Ketones and Application in the Synthesis of Novel 5-Dichloromethyl-1*H*-pyrazoles

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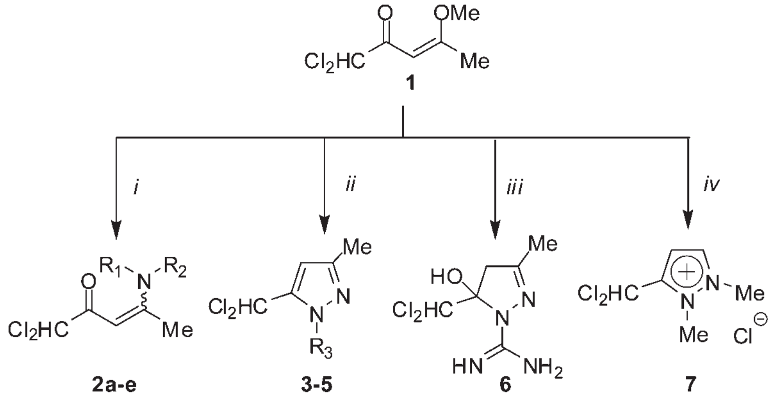

R^1, R^2 = H/Ph, H/Bn; H/CH_2CH_2OH; -$(CH_2)_4$-; -$CH_2CH_2OCH_2CH_2$-
R^3 = H, Ph, C(O)NH_2
i: NHR^1R^2, 0-25°C, 5 min (yield 60-85%)
ii: R^3NHNH_2 HCl, EtOH, 75°C, 24h (yield 56-83%)
iii: $NH_2C(NH)NH_2$ HCl, EtOH, 75°C, 24h (yield 58%)
iv: MeNHNHMe 2HCl, EtOH/HCl, 75°C, 24h (yield 60%)

An efficient procedure to prepare a series of five 4-amino-1,1-dichloro-3-penten-2-ones [$CHCl_2C(O)CH{=}C(Me)NR^1R^2$, where R^1/R^2 = H/Ph, H/Bn, H/CH_2CH_2OH, —$(CH_2)_4$—, —$(CH_2)_2O(CH_2)_2$] from the solvent-free reaction of 1,1-dichloro-4-methoxy-3-penten-2-one with primary and secondary amines is reported. 1,1-Dichloro-4-methoxy-3-penten-2-one was reacted with hydrazine hydrochloride, phenylhydrazine hydrochloride and semicarbazide hydrochloride to obtain 5-dichloromethyl-3-methylpyrazoles. Aminoguanidine hydrochloride and 1,2-dimethylhydrazine dihydrochloride were also reacted with 1,1-dichloro-4-methoxy-3-penten-2-one to obtain 5-dichloromethyl-3-methylpyrazoline and 5-dichloromethyl-1,2,3-trimethyl pyrazolium chloride, respectively. All cyclocondensation reactions were performed in one-pot procedures.

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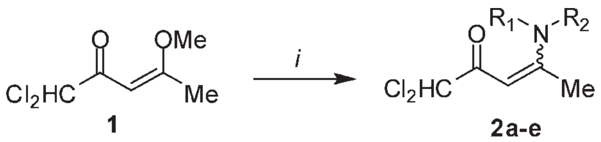
INTRODUCTION

Substituted pyrazoles are important synthetic targets in the pharmaceutical industry because the pyrazole motif makes up the core structure of numerous biologically active compounds, including blockbuster drugs such as Celecoxib [1] and Sildenafil [2]. Specifically, 5-hydroxy-4,5-dihydro-1*H*-pyrazoles are known to possess anti-inflammatory and analgesic activity [3,4]. Although numerous methods have been developed, regioselective synthesis of the pyrazole ring remains a significant challenge for organic chemists. For example, the prevalent method of reacting hydrazines with 1,3-dicarbonyl compounds often results in a mixture of regioisomers when the reactivity of the two carbonyl groups is not drastically different. A modification of this method, replacing 1,3-dicarbonyl compounds with α,β-unsaturated ketones

Scheme 1. *i*: NHR^1R^2, 0–25°C, 5 min.



Product	R^1	R^2	Yield[a] (%)
2a	H	Ph	83
2b	H	Bn	68
2c	H	$-CH_2CH_2OH$	78
2d	$-(CH_2)_4-$		60
2e	$-(CH_2)_2O(CH_2)_2-$		85

[a]Yields of isolated products

or esters affords products with higher regioselectivity [5]. Over the last twenty years, our research group has developed a general procedure for preparing β-alkoxyvinyl halomethyl ketones from the β-haloacetylation of enol ethers using functionalized acyl groups RCO (with R = CF_3, CCl_3 and $CHCl_2$) [6,7], and demonstrated their importance in the construction of halomethyl-heterocyclic rings [6–11]. Our results have shown that the reaction of β-alkoxyvinyl trihalomethyl ketones and hydrazines generally produces highly regioselective 5-hydroxy-4,5-dihydro-1*H*-pyrazoles. Although trihalomethyl pyrazolium chlorides have been synthesized by the cyclocondensation reaction of 4-alkoxy-1,1,1-trichloro-3-alken-2-ones with 1,2-dimethylhydrazine [12], they remain rare in the literature. The reactivity of β-alkoxyvinyl dichloromethyl ketones with amines to obtain enaminones and reactions with different hydrazines in an attempt to obtain the respective 5-dichloromethylpyrazoles and 5-dichloromethylpyrazolium has not yet been studied. There is only one report in the literature concerning the reactivity of these compounds with hydroxylamine, and scarce reports on their reaction with amines [13].

In the last few years, our research group has been interested in developing environmental alternatives to obtain heterocyclic building blocks and heterocycles. More recently, we have employed ionic liquids for this objective [13–17]. We have also developed synthetic methods under solvent-free conditions to obtain enaminones [13,18] and 5-hydroxy-4,5-dihydro-1*H*-pyrazoles [19]. Considering our interest in new and green routes in organic synthesis, we have investigated the synthesis of β-enamino dichloromethyl ketones by the solvent-free reaction of 1,1,1-trihalo-4-alkoxy-3-alken-2-ones with primary and secondary amines. In addition, we have studied the cyclocondensation reaction of dichloromethyl substituted α,β-unsaturated ketone with hydrazines in environmentally favorable conditions.

RESULTS AND DISCUSSION

The starting material, 1,1-dichloro-4-methoxy-3-penten-2-one **1**, was synthesized from the reaction of 2-methoxypropene with dichloroacetyl chloride, by methodologies developed in our laboratories [6,20,21]. The synthetic method used to obtain β-enamino dichloromethyl ketones presented in this article was based on the solvent-free reaction of 1,1-dihalo-4-methoxy-3-penten-2-one with amines. The typical experiment was carried out through the addition of the appropriate amine to 1,1-dichloro-4-methoxy-3-penten-2-one **1** at 0°C, followed by stirring the reaction mixture at room temperature for 5 min (Scheme 1). The structures of the synthesized compounds were analyzed by ^1H, and ^{13}C NMR spectroscopy and GC-MS spectrometry. Data are reported in the Experimental Section. In every case, the stereochemistry of the 1,1-dichloro-4-methyl-aminopent-3-en-2-ones **2a–e** (Scheme 1) was determined based on ^1H NMR spectroscopy. The chemical shift of the enamino hydrogen (NH) was observed at 10–12 ppm, which further confirms the *Z*-configuration for the enaminones **2a–c**. This configuration is stabilized by the intramolecular hydrogen bond between the NH and the carbonyl oxygen [13,18]. The *E*-configuration of enaminones **2d–e** was determined by X-ray diffraction. The proposed structure of enaminone **2e** is illustrated in Figure 1.

When the results were compared with those obtained from the same reaction carried out in ionic liquid, the yields (81–88%) and reaction times were similar [13]. For compounds with a trichloromethyl substituent synthesized by this method, the yields were slightly better [18]. Consequently, it was demonstrated that 1,1-dichloro-4-methoxy-3-penten-2-one reacted in good yields with primary and secondary amines in solvent-free conditions.

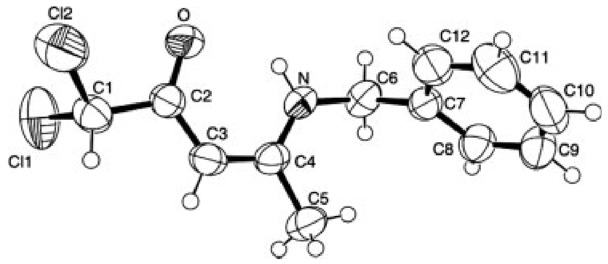
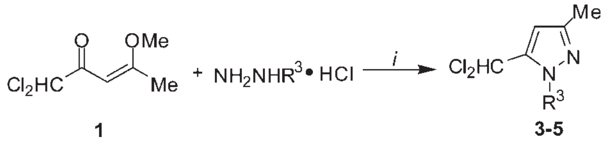


Figure 1. ORTEP of (*E*)-1,1-dichloro-4-morpholin-4-yl-3-penten-2-one (**2e**).

Scheme 2. R = H (83%), Ph (68%), C(O)NH_2 (56%), *i*: EtOH, 75°C, 24 h.

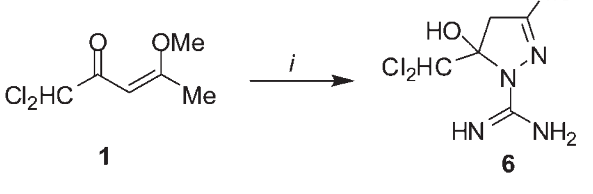


The second part of this study involved the reactivity of 1,1-dichloro-4-methoxy-3-penten-2-one with hydrazines. When 1,1-dichloro-4-methoxy-3-penten-2-one reacted with hydrazine hydrochoride, phenylhydrazine hydrochloride and semicarbazide hydrochloride, the 5-dichloromethyl-3-methylpyrazoles **3–5** (Scheme 2) were obtained. In accordance with previous results published by us, the formation of compound **5** was expected under the conditions used in the present study (refluxing ethanol for 24 h) [22]. On the other hand, the formation of compound **4** with high regioselectivity was unexpected, considering that the reaction of 1,1,1-trihalo-4-methoxy-3-penten-2-ones with phenyl hydrazine resulted in a mixture of isomers when the reaction was carried out in a microwave oven [23]. More surprising was the dehydrated product obtained from the reaction of 1,1-dichloro-4-methoxy-3-penten-2-one with semicarbazide hydrochloride. This result is especially surprising considering the reaction conditions employed in this study because, for the reaction of trihalomethyl precursors the dehydrated product is only obtained after heating 5-trihalomethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole with concentrated sulphuric acid [24]. The yields and reaction conditions are summarized in Scheme 2.

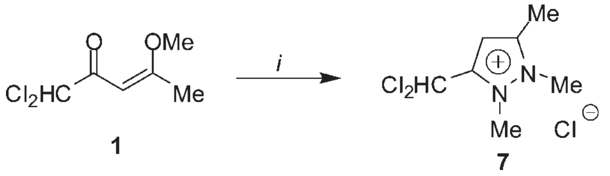
Another dinucleophile evaluated was aminoguanidine hydrochloride, which led to 5-dicloromethyl-5-hydroxy-4,5-dihydropyrazoles **6** (Scheme 3), the expected product under the reaction conditions used [25]. The pair of doublets (H4) for geminal protons observed in ^1H NMR spectra appeared at 3.4 and 3.6 ppm, with $J = 19.5$ Hz, which is typical spectroscopic data for 4,5-dihydropyrazoles [17,19,25]. Compound **6** is stable and was not converted to the corresponding pyrazole derivative.

In the same context, 5-dichloromethyl-1,2,3-trimethyl pyrazolium chloride **7** (Scheme 4) was formed from the reaction of 1,1-dichloro-4-methoxy-3-penten-2-one **1** with 1,2-dimethylhydrazine dihydrochloride in the presence of hydrochloric acid as a catalyst and ethanol as solvent. The reaction mixture was stirred at reflux temperature for 24 h. There is little information on the synthesis of these compounds using cyclocondensation methods such as the reaction of a β-diketone derivative with 1,2-dialkylhydrazines [26]. In addition, the most important route to synthesis of 1,2-dialkylpyrazolium salts is the *N*-alkylation of pyrazoles [27].

Scheme 3. *i*: $NH_2C(NH)NH_2$ • 2HCl, EtOH, 75°C, 24h, 58%.



Scheme 4. *i*: MeNHNHMe • 2HCl, EtOH/HCl 1:1, 75°C, 24h, 60%.



In conclusion, this article has demonstrated that 1,1-dichloro-4-methoxy-3-penten-2-one reacted with amines in solvent-free conditions to result in enaminones in good yields. In addition, they were reacted with hydrazines under mild reaction conditions furnishing products with high regioselectivity and in some cases led to unexpected products. Thus, we have demonstrated that the presence of the dichloromethyl group is a determining factor in the regiochemistry of the reaction because it provides a good deal of stability for the intermediate 5-dicloromethyl-5-hydroxy-4,5-dihydropyrazole, which contributes for high regioselectivity.

EXPERIMENTAL

General procedures. Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer (^1H at 400.13 MHz and ^{13}C at 100.61 MHz) 298 K, digital resolution of ±0.01 ppm, with 0.1 mol L^{-1} solution in $CDCl_3$, DMSO-$d_6$or H_2D/C_6D_6 as solvent. All spectra were registered in a 5 mm tube, at a natural abundance. Mass spectra were registered in a HP 5973 MSD connected to a HP 6890 GC and interfaced by a Pentium PC. The CG was equipped with a split–splitless, injector, auto sampler, cross-linked HP-5 capillary column (30 m, 0.32 mm of internal diameter), and helium was used as the carrier gas.

Synthesis of 4-amino-1,1-dichloro-3-penten-2-ones (2a–e). The appropriate amine (2 mmol) was added to 1,1-dichloro-4-methoxy-3-penten-2-one **1** (2 mmol) at 0°C. The reaction mixture was stirred at room temperature for 5 min. The residue was extracted with dichloromethane, dried over anhydrous ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The crude product **2e** was obtained with good purity, and the solids' products **2a–d** were recrystallized from hexane/ethyl acetate 9:1 as solvent.

Synthesis of 5-dichloromethyl-3-methylpyrazoles (3–5) and 5-dichloromethyl-3-methylpyrazoline (6). The appropriate hydrazine (2 mmol) was added to a solution of 1,1-

dichloro-4-methoxy-3-penten-2-one **1** (2 mmol) in ethanol (2 mL) at room temperature. The reaction mixture was stirred at reflux temperature for 24 h. The residue was extracted with dichloromethane, dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The crude product **4** was obtained with good purity, and the solids products **3** and **5–6** were recrystallized from ethanol as solvent.

Synthesis of 5-dichloromethyl-1,2,3-trimethyl pyrazolium chloride (7). 1,2-dimethylhydrazine dihydrochloride (2 mmol) and 36% hydrochloric acid (2 mL) were added to a solution of 1,1-dichloro-4-methoxypent-3-en-2-one **1** (2 mmol) in ethanol (2 mL) at room temperature. The reaction mixture was stirred at reflux temperature for 24 and the byproducts were extracted with dichloromethane. The product **7** was obtained in good purity from the aqueous phase after evaporation of water under vacuum.

(*Z*) 1,1-Dichloro-4-phenylaminopent-3-en-2-one (2a). $C_{11}H_{11}Cl_2NO$ Mol. Wt.: 244.12 (83%); mp 63–65°C; ^1H NMR (200 MHz, $CDCl_3$) δ 2.08 (s, 3H, H5), 5.56 (s, 1H, H3), 5.90 (s, 1H, H1), 7.20–7.40 (m, 5H, Ph), 12.32 (s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.1 (C5), 70.3 (C3), 91.0 (C1), 124.9, 126.7, 129.2, 137.3, 165.9 (C4), 184.6 (C2); *m*/*z* 243 (M^+, 31%), 160 (100), 144 (43), 77 (64).

(*Z*) 4-Benzylamino-1,1-dichloropent-3-en-2-one (2b). $C_{12}H_{13}Cl_2NO$ Mol. Wt.: 258.15 (68%); mp 72–74°C; ^1H NMR (200 MHz, $CDCl_3$) δ 2.07 (s, 3H, H5), 4.50 (d, *J* = 5.9 Hz, 2H, CH_2), 5.41 (s, 1H, H3), 5.85 (s, 1H, H1), 7.30–7.40 (m, 5H, Ph), 11.11 (br s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.3 (C5), 47.2 (CH_2), 70.4 (C3), 80.7 (C1), 126.8, 127.7, 128.8, 136.3, 168.0 (C4), 183.8 (C2); *m*/*z* 257 (M^+, 24%), 174 (98), 91 (100), 65 (49).

(*Z*) 1,1-Dichloro-4-(2-hydroxyethylamino)-pent-3-en-2-one (2c). $C_7H_{11}Cl_2NO_2$ Mol. Wt.: 212.07 (78%); mp 70–72°C; ^1H NMR (200 MHz, $CDCl_3$) δ 2.09 (s, 3H, H5), 3.50 (t, *J* = 5.6 Hz, 2H, CH_2), 3.80 (t, *J* = 5.2 Hz, 2H, CH_2), 5.36 (s, 1H, H3), 5.84 (s, 1H, H1), 10.96 (s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.6 (C5), 45.7 (CH_2), 60.9 (CH_2), 70.6 (C3), 89.8 (C1), 168.9 (C4), 183.3 (C2); *m*/*z* 211 (M^+, 15%), 128 (100), 82 (24).

(*E*) 1,1-Dichloro-4-(pyrrolidin-1-yl)-pent-3-en-2-one (2d). $C_9H_{13}Cl_2NO$ Mol. Wt.: 222.11 (60%); mp 112–113°C; ^1H NMR (200 MHz, $CDCl_3$) δ 1.94–2.12 (m, 4H, 2 × CH_2), 2.57 (s, 3H, H5), 3.39 (t, *J* = 6.1 Hz, 2H, CH_2), 3.52 (t, *J* = 5.9 Hz, 2H, CH_2), 5.25 (s, 1H, H3), 5.80 (s, 1H, H1); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.9 (C5), 24.6 (CH_2), 24.9 (CH_2), 48.5 (CH_2), 48.7 (CH_2), 72.5 (C3), 87.8 (C1), 164.6 (C4), 182.6 (C2); *m*/*z* 221 (M^+, 25%), 138 (100), 70 (37).

(*E*) 1,1-Dichloro-4-(morpholin-4-yl)-pent-3-en-2-one (2e). $C_7H_{11}Cl_2NO$ Mol. Wt.: 238.11 (85%) Mp 96–98°C; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.56 (s, CH_3), 3.51 (qua, 2 × CH_2), 3.76 (qua, 2 × CH_2), 5.53 (s, CH), 5.79 (s, CH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.1 (CH3), 46.5 (CH_2), 66.1 (CH_2), 72.4 (C), 88.7 (CH), 165.9 (CH), 184.4 (C=O); *m*/*z* 237 (M^+, 6%), 154 (100), 55 (33), 96 (22), 174 (12), 126 (7), 202 (5). Crystallographic data for **2e** were deposited at the Cambridge Crystallographic Data Center (CCDC 649396). Copies of the data can be obtained, free of charge, on application to CCDC 12 Union Road, Cambridge CB2 1EZ, UK (Fax: ±44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

5-Dichloromethyl-3-methyl-1*H*-pyrazole (3). $C_5H_6Cl_2N_2$ Mol. Wt.: 165.02 (83%); mp 89–90°C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H, CH_3), 6.28 (s, 1H, CH), 6.74 (s, 1H, $CHCl_2$), 8.15 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.8 (CH_3), 69.0 ($CHCl_2$), 105.6 (C4), 142.9 (C5), 143.0 (C3); *m*/*z* 164.1 (M^+, 13%), 149.1 (100), 109.1 (22).

5-Dichloromethyl-3-methyl-1-phenyl-1*H*-pyrazole (4). $C_{11}H_{10}Cl_2N_2$ Mol. Wt.: 241.12 (68%); oil; ^1H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H, CH_3), 6.57 (s, 1H, CH), 6.65 (s, 1H, $CHCl_2$), 7.43–7.52 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4 (CH_3), 61.1 ($CHCl_2$), 107.5 (C4), 125.9, 128.9, 129.4, 138.3, 142.3 (C5), 149.5 (C3); *m*/*z* 240 (M^+, 36%), 205.1 (73), 169.1 (100).

1-Carboxamide-5-dichloromethyl-3-methyl-1*H*-pyrazole (5). $C_6H_7Cl_2N_3O$ Mol. Wt.: 208.05 (46%); mp 110–111°C; ^1H NMR (400 MHz, DMSO-*d_6*) δ 2.22 (s, 3H, CH_3), 6.41 (s, 1H, CH), 7.76 (s, 1H, $CHCl_2$); ^{13}C NMR (100 MHz, DMSO-*d_6*) δ 14.2 (CH_3), 64.3 ($CHCl_2$), 107.3 (C4), 145.2 (C5), 151.7 (C3), 152.6 [C(O)NH_2]; *m*/*z* 207 (M^+, 84%), 191 (38), 161 (62), 133 (100), 115 (85).

1-Carboximidamide-5-dichloromethyl-5-hydroxy-3-methyl-4,5-dihydro-1*H*-pyrazole (6). $C_6H_{10}Cl_2N_4O$ Mol. Wt.: 225.08 (58%); mp 68–70°C; ^1H NMR (200 MHz, DMSO-*d_6*) δ 2.08 (m, 3H, CH_3), 3.61 (d, *J* = 19.6 Hz, 1H, H4a), 3.38 (d, *J* = 19.4 Hz, 1H, H4b), 7.89 (s, 1H, $CHCl_2$), 9.01 (br s, 3H, 3 × NH); ^{13}C NMR (50 MHz, DMSO-*d_6*) δ 15.7 (CH_3), 47.2 (C4), 73.0 ($CHCl_2$), 96.7 (C5), 152.5 (C3), 158.7 [C(NH)NH_2].

5-Dichloromethyl-1,2,3-trimethyl pyrazolium chloride (7). $C_7H_{11}Cl_3N_2$ Mol. Wt.: 229.54 (60%); mp 112–113°C; ^1H NMR (200 MHz, H_2O/C_6D_6) δ 2.73 (s, 3H, CH_3), 4.22 (s, 3H, CH_3), 4.34 (s, 3H, CH_3), 7.19 (s, 1H, CH), 7.58 (s, 1H, $CHCl_2$); ^{13}C NMR (50 MHz, H_2O/C_6D_6) δ 11.9 (CH_3), 34.2 (CH_3), 35.4 (CH_3), 59.9 ($CHCl_2$), 107.5 (C4), 145.4 (C5), 147.6 (C3); *m*/*z* 193 (M–Cl, 59%), 156 (100), 129 (39).

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A New and Efficient Approach to the Synthesis of Nicotine and Anabasine Analogues

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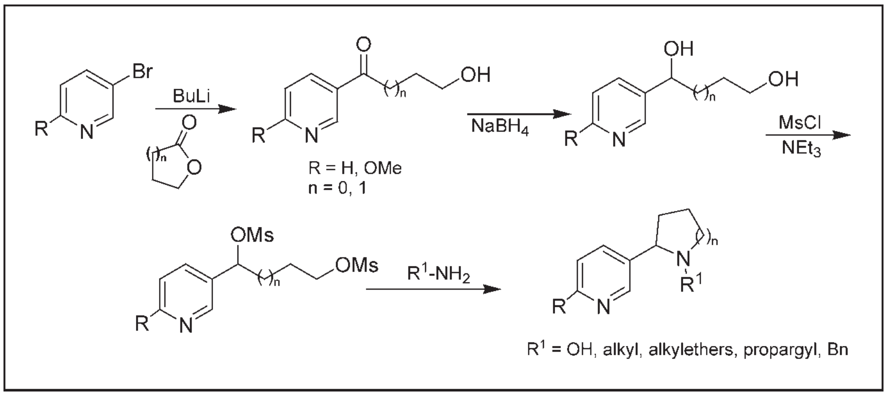

A straightforward and practical approach was established for the synthesis of nicotine and anabasine analogues by the cyclization of mesylated 1-(3-pyridinyl)-1,4, and 1,5-diol derivatives to form the pyrrolidino or piperidino fragments. Nicotine analogue (*S*)-**15** was prepared with good enantioselectivity using the developed azacyclization procedure of nonracemic (*R*)-1-pyridin-3-yl-butane-1,4-diol, which was obtained by the borane-mediated reduction of ketone **12** in the presence of the spiroborate ester derived from diphenyl prolinol and ethylene glycol.

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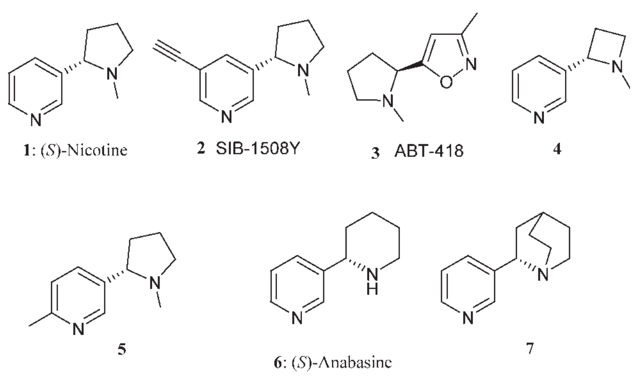
INTRODUCTION

As a group of ligand-gated ion channels, neuronal nicotinic acetylcholine receptors (nAChRs) hold significant promise as therapeutic targets for the treatment of the central nervous system (CNS) and peripheral nervous disorders [1]. Recent studies have shown that nicotine **1** (Fig. 1) displays beneficial effects on patients suffering from Parkinson's disease, anxiety, schizophrenia, Alzheimer's disease, ulcerative colitis, and other CNS disorders [2]. Furthermore, nicotine has been used on a large scale as an insecticide [3].

In the past decade, much attention has been concentrated on the discovery of novel nicotine analogues (Fig. 1) that would display higher selectivity to particular AChRs subtypes, targeting the beneficial actions of nicotine whereas reducing the toxicity effects [2–8]. SIB-1508Y (**2**) was designed as a memory enhancer and anti-Parkinson's agent [4]. The nAChR agonist ABT-418 (**3**), containing an isoxazole bioisostere of pyridine, was promising for the treatment of Alzheimer's patients because this analogue not only have binding potencies comparable with nicotine but also produce enhanced cognitive activity with less adverse effects [5]. The four-member ring analogue, *N*-methyl-(3-pyridyl)azetidine (**4**), produced a 10-fold increase in binding affinity compared with nicotine [6]. Wang et al. demonstrated that 6-methylnicotine (**5**) possess higher affinity in competition studies for [3H]nicotine in rat brain membranes [7]. Anabasine **6** has been established to be a selective α7-nAChR agonist in an animal model and with low toxicity for the potential treatment of schizophrenia [1e]. Recently, Bhatti et al. [8] evaluated the activity of bicyclic analogue **7**, which displayed high affinity for the α4β2 receptor.

Consequently, considerable efforts had been focused on the development of new syntheses of nicotine and anabasine analogues, which have been recently reviewed [9a]. Although various methods have been reported, including asymmetric induction using chiral auxiliaries [9b,c] and enantioselective stoichiometric allylboration of the 3-pyridyl carboxaldehyde [9d], surprisingly, there is a lack of a suitable direct synthetic routes for the pyrrolidine and piperidine ring construction of nicotine and anabasine analogues, respectively. Furthermore, our research program for the synthesis of potential biological active amino derivatives as nicotinic receptor


1: (*S*)-Nicotine 2 SIB-1508Y 3 ABT-418 4

5 6: (*S*)-Anabasine 7

Figure 1. Nicotinic acetylcholine receptor agonists.

agonists, a practical synthesis of racemic and nonracemic nicotine and anabasine analogues was required. Herein, we report a new and efficient approach to prepare these compounds in racemic form from inexpensive commercial sources in good to excellent yields. In addition, an asymmetric synthesis of a representative nicotine derivative using our recently developed chiral spiroborate ester, as an environmentally friendly catalyst, is also described.

RESULTS AND DISCUSSION

As shown in Scheme 1, lithiation of 3-bromopyridine with *n*-butyl lithium at −78°C, followed by treatment with γ-butyrolactone at the same temperature, furnished ketone [8] in good yield (81%) [10]. Diol **9** was readily available from **8** by reduction with NaBH$_4$ in excellent yield (96%). Treatment of **9** with methanesulfonyl chloride in the presence of Et$_3$N afforded dimesylate **10**. Attempts to purify this product by column chromatography on silica gel failed because it decomposed during the process. Accordingly, after a simple work-up and solvents removal under reduced pressure, compound **10** was used directly for the next step. After stirring overnight the crude dimesylated diol with neat benzylamine, the benzyl substituted nornicotine (**11**) was obtained. Purification of this compound by flash column chromatography provided the desired pure product in 83% overall yield from **9**. This facile and effective azacyclization reaction opens a new way for the direct access to *N*-substituted nornicotine derivatives.

With an interest in developing compounds with potential biological activity and to demonstrate the synthetic potential of our new methodology, we prepared nicotine and a variety of analogues with N-substitution on the pyrrolidine ring (Table 1). The corresponding primary amines were allowed to react with dimesylate **10** under the previous established reaction conditions. By TLC and GC-MS analysis of the reaction mixture, only the azacyclization product was observed. As a result, the desired nicotine and its derivatives were easily purified and obtained in high yield (entries 1–7).

To further develop our methodology, the aza-annulation of the 1,5- and 1,6-dimesylated 1-(6-methoxypyridyl)diol to form six and seven member rings were investigated (Scheme 2). In general, the 1,5-dimesylated diol was readily annulated to yield the desired anabasine derivatives in moderate to good yield (Table 1, entries 8–11). On the other hand, as observed by GC-MS analysis, the 1,6-dimesylate was found to be unsuitable for the formation of azepanes under the previous conditions due to the less favored seven membered ring closure.

Enantiomers of a given racemate often display difference on the basis of potency, selectivity, or efficacy at biologic targets. (*S*)-Nicotine is more bioactive than the (*R*)-enantiomer, as it is also observed for related analogues [11]. The high yield and excellent enantionselectivity achieved in the borane reduction of heterocyclic ketones catalyzed by our spiroborate ester **13** derived from diphenyl prolinol (Scheme 3) [12a], prompted us to investigate the asymmetric synthesis of the nicotine derivative (*S*)-**15**.

Considering that borane can react with the hydroxyl group of ketone **8**, and that an intramolecular uncatalyzed reaction can take place, the hydroxyl group was initially protected with an acetyl group. The acetylated ketone was then reduced with borane employing 10% and 30% mol of catalyst **13** obtaining 81% ee and 85.5% ee of the diacetylated product, respectively. When the temperature was decreased at −10°C using 30% of catalyst, the enantioselectivity decreased to 78% ee. Therefore, the hydroxyl group was protected with TIPSCl affording **12** in 95% yield. High yield and excellent enantioselectivity (94% ee) was then achieved by the borane-mediated reduction of **12** employing 50% of catalyst **13**. The absolute *R* configuration of the product was assigned according to the catalyst **13** predicted stereoselectivity. After deprotection of silylated ether (***R***)-**14** with Bu$_4$F to yield the diol (***R***)-**9**, followed by dimesylation according to our previous procedure, the

Scheme 1. Synthesis of *N*-1′-benzyl nornicotine as a model method for the preparation of nicotine analogues.

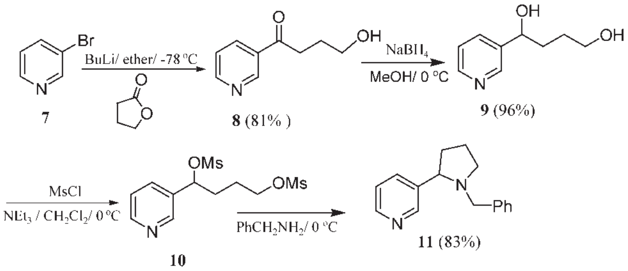
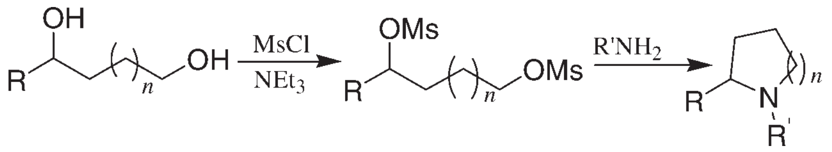
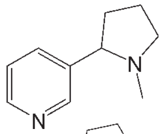
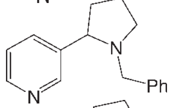
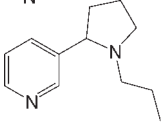
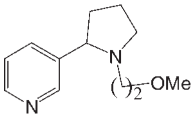
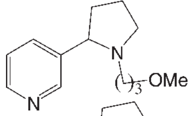
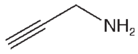
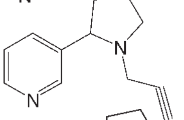
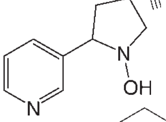
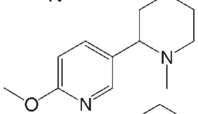
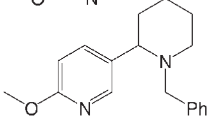
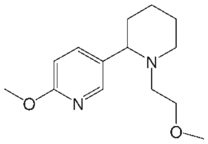
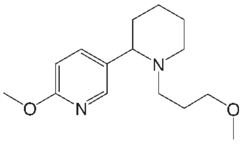


Table 1

Aza-cyclization of dimesylated diols with representative primary amine.



Entry	*n*	*R*	*R*′	Product[a]	Yield (%)[b]
1	1	Py	CH_3NH_2[c]		86
2	1	Py	$PhCH_2NH_2$		83
3	1	Py	$CH_3(CH_2)_2NH_2$		88
4	1	Py	$CH_3O(CH_2)_2NH_2$		81
5	1	Py	$CH_3O(CH_2)_3NH_2$		83
6	1	Py			82
7	1	Py	$NH_2OH{\cdot}HCl$[d]		82
8	2	6-MeOPy	CH_3NH_2[c]		78
9	2	6-MeOPy	$PhCH_2NH_2$		76
10	2	6-MeOPy	$CH_3O(CH_2)_2NH_2$		78
11	2	6-MeOPy	$CH_3O(CH_2)_3NH_2$		81

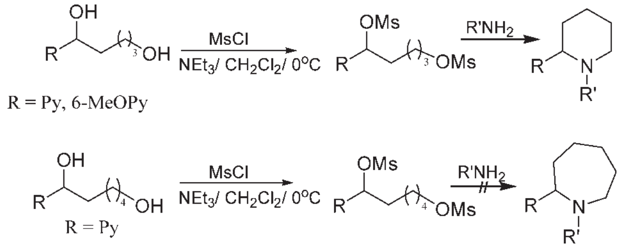
[a] The mixture of the corresponding dimesylate diol and the neat primary amine was stirred at 0°C overnight.

[b] Purified by flash column chromatography.

[c] Methylamine solution (33 wt %) in absolute ethanol was employed and the reaction was conducted at room temperature.

[d] $NH_2OH.HCl$ and Et_3N was used in ethanol and dichloromethane at room temperature.

Scheme 2. Pyperidine and azepane rings formation of pyridyl analogues.



azacyclization of (***R***)-**10** was successfully achieved, providing the desired nicotine derivative (***S***)-**15**.

Although some racemization took place at the benzylic position during the cyclization step, even at −10°C, the desired nicotine derivative (*S*)-15 was obtained in good enantiomeric excess (82% ee) and in good overall yield (76%).

CONCLUSION

In summary, a direct, mild, and efficient methodology for the synthesis of a variety of nicotine and anabasine analogues from commercially available sources has been described. Moreover, a catalytic asymmetric synthesis of the nicotine derivative (***S***)-**15** in good enantiomeric purity was established by the enantioselective reduction of the TIPS protected ketone **12**. Considering the readily available starting materials, facile synthetic procedures, easy purification and high yields, the present work constitutes an excellent methodology for the rapid access to important nicotinic receptor agonists, and will find applications in academic research and in the pharmaceutical industry.

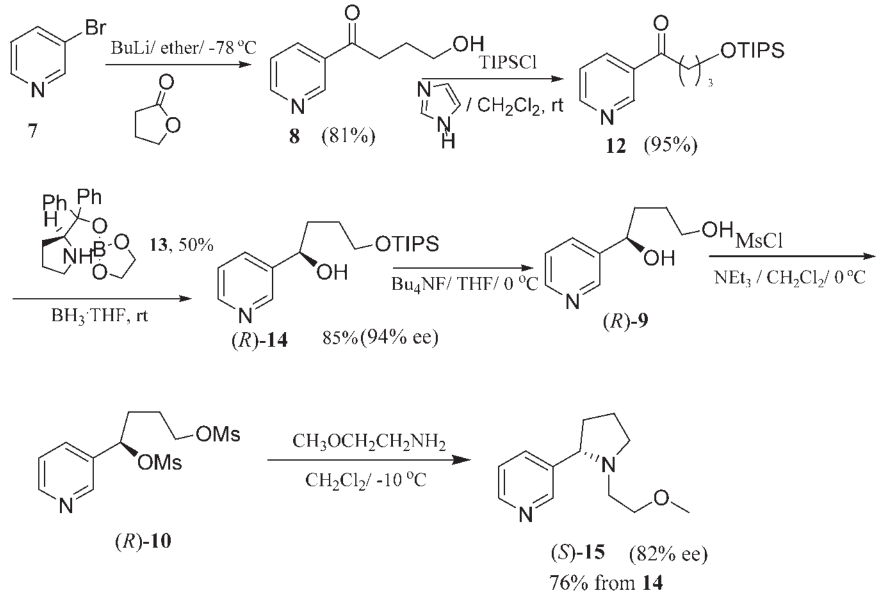
EXPERIMENTAL

Air- and moisture-sensitive reactions were performed under N_2 atmosphere in flame-dried glassware. Common solvents were dried and distilled by standard procedures. All reagents were obtained commercially unless otherwise noted. Chromatographic purification of products was accomplished using flash chromatography on a Merck silica gel® Si 60 Å (70–230 mesh). ^1H and ^{13}C spectra were recorded on a Bruker Avance 400 MHz spectrometer with standard pulse sequences operating at 400.152 MHz and 100.627 MHz for ^1H and ^{13}C, respectively. Chiral GC analysis was processed with a Crompack Chirasil-Dex-CB column (30 m × 0.25 mm × 0.25 μm). High-resolution mass spectral analyses (HRMS) were performed at the University of Florida.

General procedure for the synthesis of hydroxy ketones [10]. To a stirred solution of 3-bromopyridine (10 g, 63.3 mmol) in anhydrous ether (100 mL) was added *n*-BuLi (40 mL, 1.6 *M* in hexane, 64 mmol) dropwise at −78°C. The mixture was stirred for 15 min and a solution of γ-butyrolactone, δ-valerolactone, or ε-caprolactone (63.6 mmol) in ether (20 mL) was added dropwise. The solution was stirred 1 h and then it was left overnight at room temperature. The mixture was diluted with brine (100 mL). The product was extracted with *n*-BuOH (3 × 150 mL) and the combined extracts were washed with brine (100 mL) and dried over anhydrous $MgSO_4$. The solvents were evaporated under reduced pressure and the residue was purified by column chromatography, eluted by CH_2Cl_2/MeOH (10/1).

4-Hydroxy-1-(pyridin-3-yl)butan-1-one. Yellow oil, Lit [10] mp 36–37°C; yield 81% (6.45 g); ^1H NMR (400 MHz, $CDCl_3$): δ 2.06 (m, 2H, CH_2), 2.22 (br s, 1H, OH), 3.19 (m, 2H, CH_2), 3.80 (m, 2H, CH_2), 7.46 (m, 1H, Py), 8.28 (m, 1H,

Scheme 3. Asymmetric synthesis of nicotine analogue (*S*)-**15**.



Py), 8.81 (m, 1H, Py), 9.22 (m, 1H, Py); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.6, 35.5, 61.9, 123.7, 132.2, 135.4, 149.6, 153.5, 199.2.

5-Hydroxy-1-(6-methoxypyridin-3-yl)pentan-1-one. Colorless oil, yield 85% (5.68 g); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.66 (m, 2H, CH_2), 1.87 (m, 2H, CH_2), 2.05 (br s, 1H, OH), 2.99 (t, J = 7.0 Hz, 2H, CH_2), 3.70 (t, J = 6.2 Hz 2H, CH_2), 4.03 (s, 3H, OCH_3), 6.80, d, J = 9 Hz, 1H, Py), 8.18 (dd, J_1 = 2,4 Hz, J_2 = 8.7 Hz, 1H, Py), 8.83 (d, J = 2.0 Hz, 1H, Py); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203, 32.2, 38.0, 54.1, 62.3, 111.2, 126.7, 138.2, 149.0, 166.8, 198.1. EIS TOF HRMS calcd. for $[M + H]^+$ $C_{11}H_{16}NO_3$: 210.1125; found 210.1124.

6-Hydroxy-1-(pyridin-3-yl)hexan-1-one [10]. Light yellow crystals, mp 27–29°C; yield 68% (8.26 g); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47 (m, 2H, CH_2), 1.67 (m, 2H, CH_2), 1.85 (m, 2H, CH_2), 2.18 (br s, 1H, OH), 3.03 (m, 2H, CH_2), 3.70 (m, 2H, CH_2), 7.44 (m, 1H, Py), 8.26 (m, 1H, Py), 8.78 (m, 1H, Py), 9.22 (m, 1H, Py); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.6, 25.5, 32.5, 38.8, 62.5, 123.7, 132.2, 135.4, 149.6, 153.3, 199.1.

General procedure for the synthesis of diols. To a flask was added the ketone (20 mmol) and MeOH (40 mL) at room temperature. Then, neat $NaBH_4$ (1.52 g, 40 mmol) was added portion-wise to the solution at 0°C. The resulting mixture was stirred for 1 h and the solvent was evaporated under reduced pressure. Distilled water was added (50 mL) and the mixture was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic phases were removed under reduced pressure. The residue was directly submitted to the next step or recrystallized.

1-(Pyridin-3-yl)butane-1,4-diol (9) [13]. Light yellow oil; yield 96% (4.38 g); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.88 (m, 2H, CH_2), 1.93 (m, 2H, CH_2), 3.51 (br s, 1H, OH), 3.72 (m, 2H, CH_2), 4.63 (br s, 1H, OH), 4.80 (m, 1H, OCH), 7.30 (m, 1H, Py), 7.76 (m, 1H, Py), 8.46 (m, 1H, Py), 8.54 (m, 1H, Py); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.0, 36.6, 62.5, 123.5, 133.9, 140.5, 147.5, 148.3.

1-(6-Methoxypyridin-3-yl)pentane-1,5-diol. Light yellow oil; yield 93% (1.88 g); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (m, 1H, CH_2), 1.45 (m, 1H, CH_2), 1.62 (m, 2H, CH_2), 1.75 (m, 1H, CH_2), 1.85 (m, 1H, CH_2), 1.95 (br s, 1H, OH), 2.63 (br s, 1H, OH), 3.66 (t, J = 6.3 Hz, 2H, CH_2), 3.96 (s, 3H, CH_3), 4.68 (t, J = 6.6 Hz, 1H, OCH), 6.78 (d, J = 8.6 Hz, 1H, Py), 7.63 (dd, J_1 = 2.4 Hz, J_2 = 8.6 Hz, 1H, Py), 8.01 (d, J = 2.2 Hz, 1H, Py); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 32.3, 38.4, 53.5, 62.5, 71.8, 110.9, 132.8, 136.7, 144.6, 163.8. EIS TOF HRMS calcd. for $[M + H]^+$ $C_{11}H_{18}NO_3$: 212.1281; found 212.1288.

1-(Pyridin-3-yl)hexane-1,6-diol. Colorless oil; yield 96% (1.88 g); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34–1.59 (m, 4H, CH_2), 1.55–1.62 (m, 2H, CH_2), 1.71–1.87 (m, 2H, CH_2), 2.39 (br s, 1H, OH), 3.66 (t J = 6.4 Hz, over s, 3H, CH_2 and OH), 4.76 (m, 1H, OCH), 7.30 (t, J = 3.8 Hz,, 1H, Py), 7.75 (dt, J_1 = 1.8 Hz, J_2 = 7.8 Hz, 1H, Py), 8.47 (dd, J_1 = 1.6 Hz, J_2 = 4.8 Hz, 1H, Py), 8.52 (d, J_1 = 2.0 Hz, 1H, Py); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.4, 25.6, 32.5, 39.0, 62.5, 71.9, 123.6, 133.8, 140.5, 147.6, 148.5. EIS TOF HRMS calcd. for $[M + H]^+$ $C_{11}H_{18}NO_2$: 196.1332; found 196.1344.

Typical procedure: Synthesis of *rac*-nicotine derivative 11 from diol 9. To a two-neck round bottom flask was added a solution of diol **9** (1.67 mg, 10 mmol) in anhydrous CH_2Cl_2 (100 mL) and Et_3N (7 mL, 50 mmol) under nitrogen. The mixture was cooled to 0°C and MsCl (2.3 mL, 30 mmol) was added dropwise for 1 h by a syringe pump. The resulting solution was stirred until TLC indicated that the starting material was consumed. Water (100 mL) was added to quench the reaction and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with brine, dried over $MgSO_{4,}$ and concentrated under reduced pressure at 25°C to obtain the crude dimesylate **10:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.90 (m, 2H), 2.10 (m, 1H), 2.19 (m, 1H), 2.96 (s, 3H, CH_3SO_2), 3.09 (s, 3H, CH_3SO_2), 4.35 (t, J = 6.3 Hz 2H, OCH_2), 5.80 (m, 1H, OCH), 7.59 (m, 1H, Py), 8.01 (dt, J_1 = 1.8 Hz, J_2 = 7.9 Hz, 1H, Py), 8.74 (m, 1H, Py), 8.82 (m, 1H, Py); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.1, 33.1, 37.5, 39.0, 52.6, 68.7, 124.9, 135.7, 136.9, 145.8, 148.0.

3-(1-Benzylpyrrolidin-2-yl)pyridine (11) [9c]. To the crude dimesylate **10** (323 mg, 1 mmol), neat benzylamine (3 mL, 27 mmol) at 0°C was added. The resulting mixture was stirred overnight at the same temperature. The remaining benzylamine was removed in a Kugelrohr at 80°C under high vacuum and the residue was mixed with 10 mL water. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic phases were washed with brine (2 × 5 mL) solution and dried over Na_2SO_4. The pure product was obtained after flash column chromatography on silica gel eluted with hexane/EtOAc (1:1): Colorless oil, yield 83% (197 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.76–1.95 (m, 3H), 2.29 (m, 2H), 3.17 (m, 2H), 3.48 (m, 1H), 3.85 (m, 1H), 7.25–7.35 (m, 6H, Ar), 7.85 (m, 1H, Py), 8.54 (m, 1H, Py), 8.70 (m, 1H, Py; ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 35.3, 53.5, 58.1, 67.0, 123.6, 126.9, 128.2, 128.6, 135.0, 139.3, 139.5, 148.6, 149.7; GC-MS m/z 238.1 (M^+).

3-(1-Methylpyrrolidin-2-yl)pyridine (or 1-methyl-2-(3-pyridyl)pyrrolidine) (*rac*-nicotine) [9c]. Colorless oil, yield 86% (139 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.74–1.84 (m, 2H, CH_2), 1.96 (m, 1H, CH_2), 2.18 (m, 4H, CH_2), 2.34 (m, 1H, CH_2), 3.12 (t, J = 8.5 Hz, 1H, CH), 3.28 (t, J = 8.5 Hz, 1H, CH), 7.26 (m, 1H, Py), 7.70 (m, 1H, Py), 8.51 (s, 1H, Py), 8.55 (m, 1H, Py); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 35.2, 40.4, 57.0, 68.9, 123.6, 134.8, 138.8, 148.6, 149.6; GC-MS m/z 162.0 (M^+).

3-(1-Propylpyrrolidin-2-yl)pyridine [14]. Colorless oil, yield 88% (167 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (t, 3H, J = 7.2 Hz, CH_3), 1.43–1.51 (m, 2H, CH_2), 1.72 (m, 1H, CH), 1.86 (m, 1H, CH), 1.98 (m, 1H, CH), 2.07 (m, 1H, CH), 2.21 (m, 2H, CH), 2.46 (m, 1H, CH), 3.36 (t, J = 8.2 Hz, 1H, CH), 3.40 (td, J_1 = 2.4 Hz, J_2 = 8.5 Hz, 1H, CH), 7.26 (dd, J_1 = 4.8 Hz, J_2 = 7.8 Hz, 1H, Py), 7.75 (d, J = 7.8 Hz, 1H, Py), 8.52 (dd, J_1 = 0.8 Hz, J_2 = 4.7 Hz, 1H, Py), 8.59 (d, J = 1.9 Hz, 1H, Py); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.9, 22.0, 22.7, 35.2, 53.6, 56.4, 67.6, 123.5, 134.9, 139.8, 148.4, 149.6; GC-MS m/z 190.1 (M^+).

3-[1-(2-Methoxyethyl)pyrrolidin-2-yl]pyridine [9c]. Colorless oil, yield 81% (167 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.73 (m, 1H, CH), 1.86 (m, 1H, CH), 2.01 (m, 1H, CH), 2.20 (m, 1H, CH), 2.36 (m, 2H, CH), 2.79 (m, 1H, CH), 3.29 (s, 3H, OCH_3), 3.34–3.47 (m, 4H, CH), 7.26 (dd, J_1 = 4.8 Hz, J_2 = 7.8 Hz, 1H, Py), 7.75 (d, J = 7.8 Hz, 1H, Py), 8.52 (dd, J_1 = 1.5 Hz, J_2 = 4.7 Hz, 1H, Py), 8.59 (d, J = 2.0 Hz, 1H, Py); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.8, 35.0, 53.7, 54.5, 58.7, 67.8, 71.5, 123.5, 134.9, 139.4, 148.5, 149.6; GC-MS m/z 206.0 (M^+).

3-[1-(3-Methoxypropyl)pyrrolidin-2-yl]pyridine. Colorless oil, yield 83% (183 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.68–1.74 (m, 3H, CH), 1.81–2.01 (m, 2H, CH), 2.17–2.27 (m, 3H, CH), 2.59 (m, 1H, CH), 3.28 (s, 3H, OCH_3), 3.29–3.43 (m, 4H, CH), 7.26 (dd, J_1 = 4.8 Hz, J_2 = 7.8 Hz, 1H, Py), 7.77 (dt, J_1 = 1.9 Hz, J_2 = 7.8 Hz, 1H, Py), 8.51 (dd, J_1 = 1.7 Hz, J_2 = 4.8 Hz, 1H, Py), 8.57 (d, J = 2.0 Hz, 1H, Py); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.7, 28.9, 35.3, 51.2, 53.6, 58.5, 67.6, 70.9, 123.4, 134.9, 139.7, 148.5, 149.5; GC-MS *m*/*z* 220.1 (M^+). EIS TOF HRMS calcd. for $[M + H]^+$ $C_{14}H_{21}N_2O$: 221.1654; found 221.1626.

3-[1-(Prop-2-ynyl)pyrrolidin-2-yl]pyridine [14]. Colorless oil, yield 82% (152 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ δ1.77 (m, 1H, CH), 1.85 (m, 1H, CH), 2.03 (m, 1H, CH), 2.24 (m, 2H, CH), 2.78 (q, J = 8.8 Hz, 1H, CH), 3.22 (m, 2H, CH), 3.47 (m, 1H, CH), 3.61 (t, J = 8.2 Hz, 1H, CH), 7.26 (dd, J_1 = 4.8 Hz, J_2 = 7.7 Hz, 1H, Py), 7.71 (d, J = 7.8 Hz, 1H, Py), 8.52 (d, J = 3.5 Hz, 1H, Py), 8.59 (d, J = 1.4 Hz, Py); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 34.9, 40.1, 52.2, 63.7, 72.9, 78.5, 123.6, 135.0, 138.2, 148.8, 149.7; GC-MS *m*/*z* 186.1 (M^+).

2-(Pyridin-3-yl)pyrrolidin-1-ol [15]. Colorless oil, yield 82% (134 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.76 (m, 1H, CH), 1.92 (m, 2H, CH), 2.26 (m, 1H, CH), 2.87 (q, J = 9.5 Hz, 1H, CH), 3.38 (m, 1H, CH), 3.76 (m, 1H, CH), 7.18 (dd, J_1 = 4.8 Hz, J_2 = 7.8 Hz, 1H, Py), 7.65 (dt, J_1 = 1.6 Hz, J_2 = 7.8 Hz 1H, Py), 8.35 (dd, J_1 = 1.4 Hz, J_2 = 4.8 Hz, 1H, Py), 8.54 (d, J = 1.8 Hz, 1H, Py); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.9, 30.3, 57.5, 70.2, 123.2, 135.6, 137.5, 148.1, 149.3.

6-Methoxy-3-(1-methylpiperidin-2-yl)pyridine. Colorless oil, yield 78% (161 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (m, 1H, CH), 1.48 (m, 1H, CH), 1.61 (m, 3H, OH), 1.73 (m, 1H, CH), 1.90 (s, 3H, CH_3), 2.02 (m, 1H, CH), 2.65 (dd, J_1 = 2.9 Hz, J_2 = 11 Hz, 1H, CH), 2.95 (m, 1H, CH), 3.85 (s, 3H, OCH_3), 6.63 (d, J = 8.6 Hz, 1H, Py), 7.50 (dd, J_1 = 2.4 Hz, J_2 = 8.5 Hz, 1H, Py), 7.93 (d, J = 2.3 Hz, 1H, Py); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.9, 26.1, 35.8, 44.5, 53.4, 57.5, 67.5, 110.9, 132.9, 137.7, 145.7, 163.6; GC-MS *m*/*z* 206.1 (M^+). EIS TOF HRMS calcd. for $[M + H]^+$ $C_{12}H_{19}N_2O$: 207.1492; found 207.1500.

6-Methoxy-3-(1-benzylpiperidin-2-yl)pyridine. Colorless oil, yield 76% (214 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (m, 1H, CH), 1.63 (m, 3H, CH), 1.82 (m, 2H, CH), 1.99 (td, J_1 = 3.5 Hz, J_2 = 11.5 Hz, 1H, CH), 2.86 (d, J = 13.6 Hz, 1H, CH), 3.00 (m, 1H, CH), 3.17 (dd, J_1 = 2.8 Hz, J_2 = 11 Hz 1H, CH), 3.80 (d, J = 13.5 Hz, 1H, CH), 3.98 (s, 3H, OCH_3), 6.78 (d, J = 8.5 Hz, 1H, Py), 7.24–7.33 (m, 5H, Ph), 7.78 (dd, J_1 = 2.3 Hz, J_2 = 8.5 Hz, 1H, Py), 8.19 (d, J = 2.2 Hz, 1H, Py); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.1, 26.0, 36.9, 53.37, 53.4, 59.6, 65.7, 111.1, 126.6, 128.1, 128.6, 133.7, 137.8, 139.6, 145.8, 163.5; GC-MS *m*/*z* 282.1 (M^+). EIS TOF HRMS calcd. for $[M + H]^+$ $C_{18}H_{23}N_2O$: 283.1805; found 283.1817.

6-Methoxy-3-[1-(2-methoxyethyl)piperidin-2-yl]pyridine. Colorless oil, yield 78% (195 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (m, 1H, CH), 1.48 (m, 1H, CH), 1.58 (m, 3H, CH), 1.70 (m, 1H, CH), 2.01 (m, 2H, CH), 2.60 (m, 1H, CH), 2.97 (dd, J_1 = 2.7 Hz, J_2 = 11 Hz, 1H, CH), 3.11 (s, 3H, OCH_3), 3.30 (m, 2H, CH), 3.85 (s, 3H, CH_3), 6.62 (d, J = 8.5 Hz, 1H, Py), 7.52 (dd, J_1 = 2.2 Hz, J_2 = 8.5 Hz, 1H, Py), 7.94 (d, J = 2.3 Hz, 1H, Py); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.9, 26.0, 36.6, 53.4, 54.3, 54.4, 58.7, 65.7, 70.6, 110.9, 133.2, 137.9, 145.8, 163.5. EIS TOF HRMS calcd. for $[M + H]^+$ $C_{14}H_{23}N_2O_2$: 251.1754; found 251.1762.

6′-Methoxy-1-(3-methoxypropyl)-1,2,3,4,5,6-hexahydro-[2,3′]bipyridinyl. Colorless oil, yield 81% (206 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (m, 1H, CH), 1.43 (m, 1H, CH), 1.52–1.71 (m, 6H, CH), 1.86 (m, 1H, CH), 1.94 (m, 1H, CH), 2.39 (m, 1H, CH), 2.91 (dd, J_1 = 2.7 Hz, J_2 = 11 Hz, 1H, CH), 3.05–3.21 (m, 6H, CH), 3.85 (s, 3H, OCH_3), 3.34–3.47 (m, 4H, CH), 6.62 (d, J = 8.5 Hz, 1H, Py), 7.50 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H, Py), 7.93 (d, J = 2.3 Hz, 1H, Py); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.0, 26.1, 26.4, 36.7, 51.8, 53.2, 53.3, 58.4, 65.6, 71.1, 110.8, 133.4, 137.9, 145.7, 163.4. EIS TOF HRMS calcd. for $[M + H]^+$ $C_{15}H_{25}N_2O_2$: 265.1911; found 265.1929.

Asymmetric synthesis of (*S*)-3-[1-(2-methoxyethyl)pyrrolidin-2-yl]pyridine (*S*)-15 [9c]

Borane reduction of ketone 12. To a 25 mL round flask, equipped with a septa and nitrogen flow, was added catalyst **13** (244 mg, 0.75 mmol). Then, dry THF (4 mL) and BH_3.THF (2.6 mL, 1 *M*, 2.6 mmol) were added to the flask and the resulting mixture was stirred about 1 h at room temperature. A solution of ketone **12** (482 mg, 1.5 mmol) in dry THF (3 mL) was added dropwise by a syringe pump for 1 h. After addition, the mixture was stirred for 1 h and then cooled by an ice bath. MeOH (5 mL) was added slowly to quench the excess of borane and the mixture was refluxed overnight. The solvents were removed under reduced pressure and the residue was purified by column chromatography on silica gel, eluted with CH_2Cl_2/MeOH (20/1).

(*R*)-1-(Pyridin-3-yl)-4-triisopropylsilyloxybutan-1-ol (*R*)-14. This was obtained as a colorless oil; yield 85% (411 mg); 94% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08–1.19 (m, 21H, TIPS), 1.60–1.70 (m, 2H, CH_2), 1.77 (m, 2H, CH_2), 3.84 (m, 2H, CH_2), 3.98 (br s, 1H, OH), 4.84 (m, 1H, CH), 7.32 (m, 1H, Py), 7.79 (m, 1H, Py), 8.53 (m, 1H, Py), 8.63 (s, 1H, Py); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.9, 18.0, 29.4, 37.3, 63.7, 71.9, 123.4, 133.5, 140.4, 147.9, 148.6. Chiral-GC analysis of acetyl derivate gave t_R = 121.479 min for major enantiomer, t_R = 124.10 min for minor enantiomer under the following gradient conditions: 80°C, 1°C/min up to 120°C, maintained for 40 min; then, 2°C/min up to 150°C, maintained for 30 min; 2°C/min up to 160°C and maintained for 15 min.

Azacyclization of (*R*)-14. To a solution of (*R*)-**14** (323 mg, 1 mmol) in 15 mL THF was added Bu_4NF (1.5 mL, 1.0 *M* in THF) dropwise at 0°C. The mixture was stirred until TLC indicated that the starting material was consumed (about 1 h). The solvents were removed under reduced pressure and the residue was directly submitted to the cyclization at −10°C following the general procedure given above. Compound (***S***)-**15** was obtained as a colorless oil after purification by column chromatography on silica gel, eluted with CH_2Cl_2/MeOH (30:1); yield 76% (156 mg, three steps); 82% ee; $[\alpha]_D^{20} = -82$ (*c* 1.7, $CHCl_3$); Chiral-GC analysis gave t_R = 110.67 min for major enantiomer, t_R = 118.38 min for minor enantiomer under the following gradient condition: 80°C, 1°C/min up to 110°C, and maintained for 20 min; then 1°C/min up to 120°C, then, maintained for 50 min; then, 1°C/min up to 130°C, and maintained for 30 min.

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Synthesis of 4-Substituted 2-(4-Methylpiperazino)pyrimidines and Quinazoline Analogs as Serotonin 5-HT_{2A} Receptor Ligands

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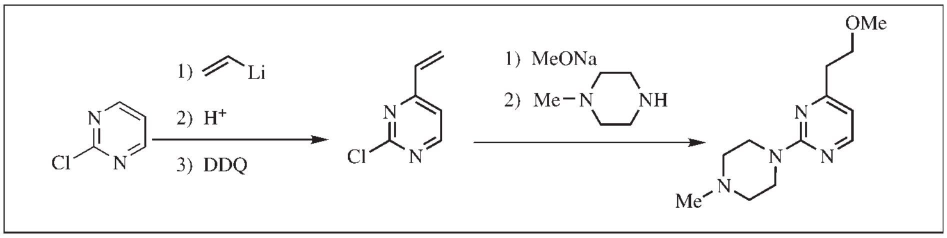


The addition reaction of lithium reagents to the 4 position of 2-chloropyrimidine or 2-chloroquinazoline followed by oxidation of the resultant dihydro intermediate product is a powerful tool for the synthesis of 4-substituted 2-chloropyrimidines or 2-chloroquinazolines. 4-Vinyl derivatives undergo a conjugate nucleophilic addition across the vinyl group. A nucleophilic displacement of chloride in 4-substituted 2-chloropyrimidines or 2-chloroquinazolines by treatment with 4-methylpiperazine provides compounds that are antagonists of the serotonin 5-HT_{2A} receptor.

J. Heterocyclic Chem., **46**, 1259 (2009).

INTRODUCTION

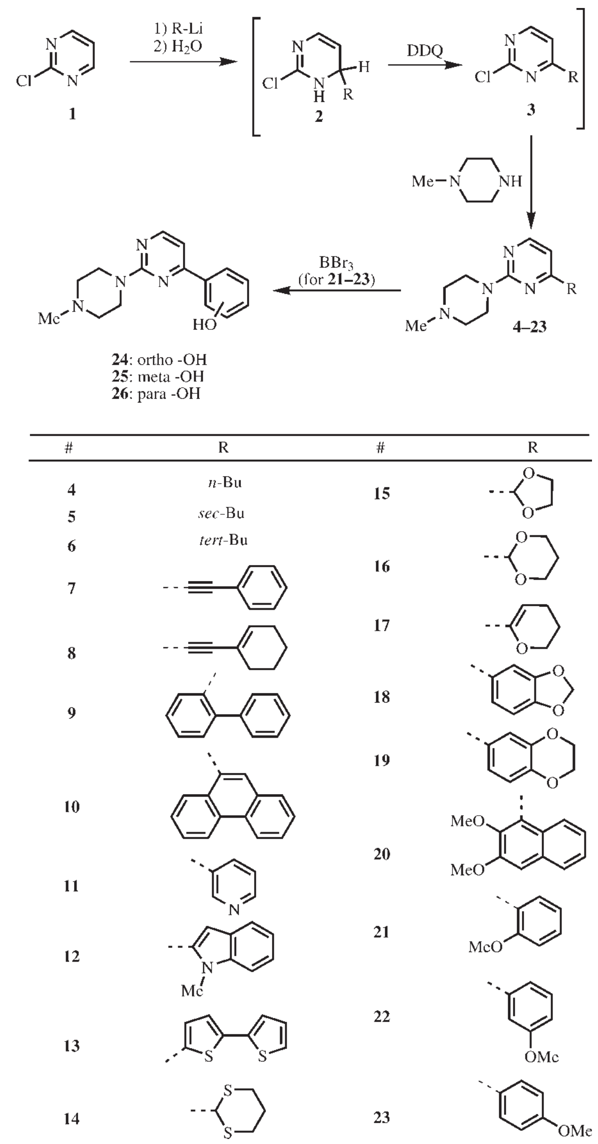
The addition reaction of organolithium reagents to the formal C=N bond in electron-deficient heteroaromatic compounds is known as the Ziegler reaction [3]. In particular, the addition reaction of organolithium reagents across the formal N3=C4 double bond in 2-chloropyrimidine followed by oxidation (aromatization) of the resultant adduct 2 (Scheme 1) is a powerful tool for the synthesis of 4-substituted 2-chloropyrimidines 3 [4,5]. The synthetic utility of this methodology is further enhanced by the facile nucleophilic displacement of chloride in 3 with common nucleophiles. In particular, 2-(4-methylpiperazino)pyrimidines obtained by this approach have been shown to interact with the central nervous system (CNS) (Chart 1) [6–9].

Related compounds bind with nucleic acids [10–15], enhance activity of the antitumor antibiotic bleomycin [16,17], and are anti-HIV-1 agents [18,19]. Surprisingly, relatively few potential CNS agents have been obtained, that is, only a limited number of simple 4-substituted pyrimidines have been synthesized by using this methodology. Herewith, we report that the synthetic sequence of Scheme 1 provides an easy access to pyrimidines containing structurally diverse groups at position 4. Because some of the previously reported 4-substituted 2-(4-methylpiperazino)pyrimidines are potent 5-HT_{2A} ligands (Chart 1, Table 1), the majority of new derivatives, obtained as part of this work, were tested for binding to the 5-HT_{2A} sites. This serotonin receptor is of immense interest because of its role in normal brain function. In particular, the powerful hallucinogens, such as LSD, presumably have the 5-HT_{2A} receptor as their primary target [20,21].

RESULTS AND DISCUSSION

The original synthetic route to 4-substituted 2-chloropyrimidines 3 (Scheme 1) was developed in our laboratories using a limited number of organolithium reagents R-Li [4,5]. The current study of the scope of this chemistry revealed that a large number of diverse compounds 3 can easily be synthesized. The 2-chloropyrimidines 3 are precursors to biologically active 2-aminopyrimidine derivatives [7–10]. As part of this work, it was found that the 2-aminopyrimidine derivatives, such as 4-23 in Scheme 1, can be prepared by using crude intermediate products 2 and 3. Thus, the methodology was greatly simplified. The yields of selected products 4–23 obtained using analytically pure and crude intermediate products 3 were similar. Purification of products 4–23 involved chromatography. Because most of these compounds are oils, they were transformed into hydrobromides, and the

Scheme 1



salts were additionally purified by crystallization. Conversely, demethylation of methoxyphenyl derivatives 21–23 by treatment with boron tribromide gave the corresponding hydrobromide salts 24–26 directly.

Chart 1

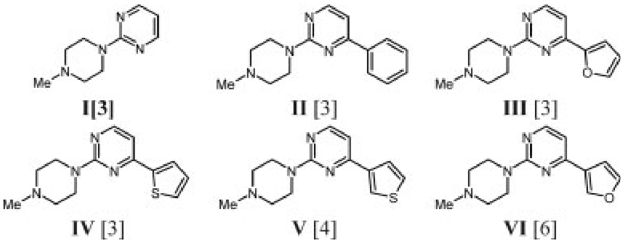

I[3] II [3] III [3]
IV [3] V [4] VI [6]

Table 1

5-HT$_{2A}$ affinity data of compounds **I–VI**, **4–26**, **29**, **31**, **35** and **37**.

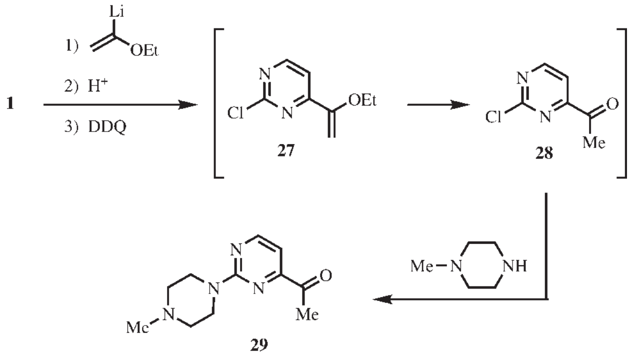
#	K_i 5-HT$_{2A}$ [nM][a]	#	K_i 5-HT$_{2A}$ [nM][a]
I[b]	19 700	**15**	5280
II[b]	2 095	**16**	>10 000
III[b]	745	**17**	2 142
IV[b]	208	**18**	3 815
V[c]	192	**19**	2 670
VI[d]	10	**20**	>10 000
4	410	**21**	1 209
5	254	**22**	544
6	206	**23**	875
7	3 427	**24**	1 936
8	1 142	**25**	>10 000
9	31	**26**	1 243
10	3 910	**29**	547
11	>10 000	**31**	656
12	854	**35**	388
13	>10 000	**37**	>10 000
14	5 257		

[a] The estimated K_i values (see ref. 24 for the protocol).
[b] Ref. 6.
[c] Ref. 7.
[d] Ref. 9.

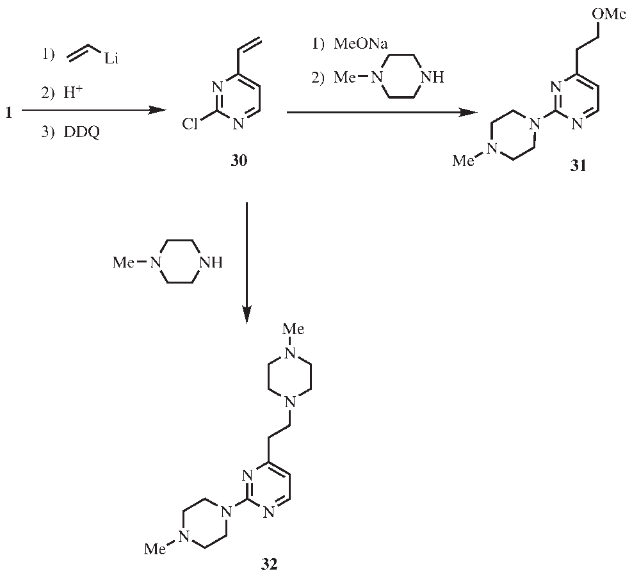
The introduction of the acetyl group at position 4 of the pyrimidine was achieved by using the umpolung approach [22]. Thus, a nucleophilic reagent derived from ethyl vinyl ether was allowed to react with 2-chloropyrimidine (1) followed by aromatization of the resultant adduct by treatment with 2,3-dichloro-5,6-dicyanoquinone (DDQ) to give the intermediate product 27 (Scheme 2). Then the ethoxyvinyl function in 27 was hydrolyzed under acidic conditions to give the acetyl-substituted pyrimidine 28. Nucleophilic displacement of chloride in 28 by treatment with *N*-methylpiperazine furnished the desired compound 29 in an overall yield of 70%. It should be noted that this preparation was achieved using crude intermediate products 27 and 28.

A vinyl function is easily introduced at position 4 of 2-chloropyrimidine (1, Scheme 3) or 2-chloroquinazoline (33, Scheme 4) by using the discussed chemistry.

Scheme 2



Scheme 3



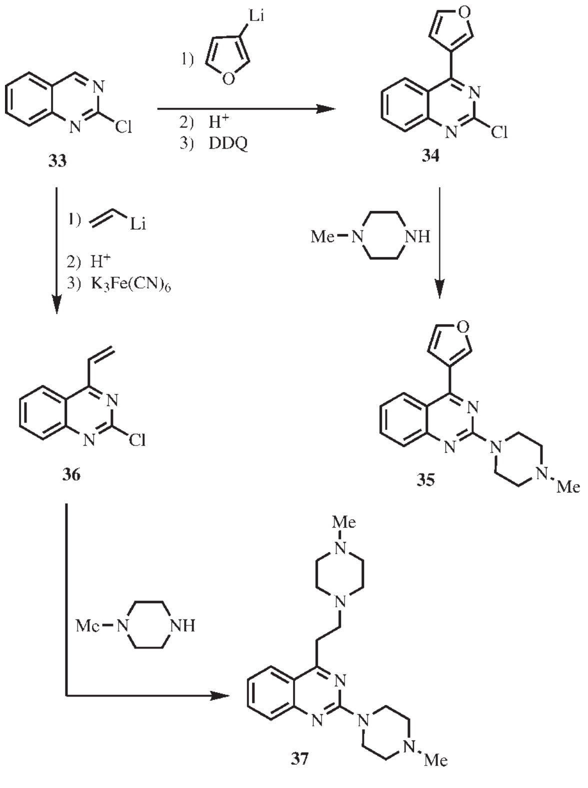
While 2-chloro-4-vinylpyrimidine (30) has been obtained previously using cumbersome chemistry [23], its quinazoline analog 36 is a new compound. In the synthesis of 36, the general protocol was modified in that the intermediate 2-chloro-4-vinyl-3,4-dihydroquinazoline (data not shown) was aromatized by the reaction with potassium ferricyanide, which has previously been used for the oxidation of 4-vinyl-3,4-dihydroquinazoline [24]. The standard treatment of the adduct with DDQ resulted in opening of the pyrimidine subunit, which was previously demonstrated [4]. The vinyl derivatives 30 and 36 are unusual substrates for the reaction with nucleophiles in that they undergo conjugate addition across the vinyl group. Thus, treatment of 30 with 1 equivalent of sodium methoxide and then with *N*-methylpiperazine furnished product 31 in an overall yield of 58%. This result shows that the methoxy anion undergoes selective conjugate addition reaction with the involvement of the vinyl group, and then chloride in the intermediate product (not shown) is displaced by the reaction with the amine. Conversely, the reaction of 30 with 1 equivalent of *N*-methylpiperazine gave a mixture of products that was difficult to separate, suggesting no selectivity between the conjugate addition and chloride displacement reactions. The treatment of 30 with excess amine gave the expected compound 32 as the sole product. In a similar way, the reaction of 2-chloro-4-vinylquinazoline (36, Scheme 4) with *N*-methylpiperazine furnished the displacement/addition product 37. It should be noted that the conjugate addition reactions with vinyl-substituted heterocyclic compounds are extremely rare, and we are aware of only single report on the conjugate addition to a vinylpyrimidine substrate [25].

In addition to the introduction of the vinyl group at position 4 of 2-chloroquinazoline as discussed earlier, a number of other 4-substituted quinazolines was synthesized using the discussed approach. This is illustrated in Scheme 4 by the preparation of 4-(3-furyl)-2-(4-methylpiperazino)quinazoline through the intermediary of 2-chloro analog 34. Again, the simplified methodology was used in that the intermediate product 34 was not purified before the treatment with the amine.

New compounds were evaluated for their affinity to serotonin 5-HT$_{2A}$ receptors according to the previously validated and published procedure [26]. The results of binding experiments are summarized in Table 1. The majority of new 4-substituted 2-(4-methylpiperazino)-pyrimidines show greater 5-HT$_{2A}$ affinity than the unsubstituted compound I. The highest affinity was found for biphenyl derivative 9, which is somewhat surprising, because the phenyl analog II displays only moderate activity (K_i = 2095 nM).

Because the 3-furyl derivative VI was earlier characterized as a potent 5-HT$_{2A}$ ligand [10], compounds 15–26, 29 and 31 were designed to have an oxygen atom in the substituent of the pyrimidine. Unfortunately, all these compounds are less active than the previously reported ligand VI. Quinazoline ligand 35 is also less active than its pyrimidine analog VI.

Scheme 4



In conclusion it seems that the ligand binding pocket in 5-HT_{2A} receptor has very discriminating structural requirements. The finding of the highly active biphenyl derivative 9 suggests possible direction of further structural modifications of 2-(4-methylpiperazino)-pyrimidines.

EXPERIMENTAL

General. All organometallic reactions were conducted under a nitrogen atmosphere in tetrahydrofuran distilled from sodium benzophenone ketyl immediately before use. Final products were purified on a chromatotron using silica gel-coated rotors (2 mm). Hydrobromide or hydrochloride salts of the piperazine products were obtained by using a general procedure [7], and the salts were crystallized from 95% ethanol. In several cases, it was necessary to dilute the ethanolic solution with ether to induce crystallization. Melting points (Pyrex capillary) are not corrected. ^{1}H NMR spectra were recorded at 400 MHz. Unless stated otherwise, the spectra were obtained for free bases in deuteriochloroform.

Lithium reagents. *n*-Butyllithium (2.0*M* in cyclohexane), *sec*-butyllithium (1.4*M* in cyclohexane), and *tert*-butyllithium (1.7*M* in pentane) were commercial reagents. The following lithium reagents (required for the preparation of compounds given in parentheses) were generated by bromine-lithium exchange reaction: 2-lithiobiphenyl (**9**), 9-lithiophenanthrene (**10**), 3-lithiopyridine (**11**), 5-lithio-2,2′-bithiophene (**13**), 4-lithio-1,2-(methylenedioxy)benzene (**18**), 6-lithio-1,4-benzodioxane (**19**), 1-lithio-2,3-dimethoxynaphthalene (**20**), 2-lithioanisole (**21**), 3-lithioanisole (**22**), 4-lithioanisole (**23**), and 3-lithiofuran (**35**). Briefly, a solution of the corresponding bromo derivative (12.5 mmol) in anhydrous tetrahydrofuran (15 mL) was cooled to −70°C and treated dropwise with *n*-butyllithium (6.3 mL, 12.6 mmol) for 5 min. Then the mixture was kept at −70°C for 2 h before treatment with 2-chloropyrimidine. The following lithium reagents (required for the preparation of compounds given in parentheses) were generated by lithiation (hydrogen-lithium exchange): 1-lithio-2-phenylacetylene (**7**), 1-lithio-2-(cyclohexen-1-yl)acetylene (**8**), 6-lithio-3,4-dihydro-2*H*-pyran (**17**), and 1-lithio-1-ethoxyethylene (**29**). Briefly, a solution of the corresponding substrate (12.5 mmol) in anhydrous tetrahydrofuran (15 mL) was treated at −10°C with *tert*-butyllithium (7.4 mL, 12.6 mmol), and the mixture was allowed to stand at this temperature for 10 min before cooling to −70°C. To generate 2-lithio-1,3-dithiane (for the preparation of **14**), a mixture of 1,3-dithiane (12.5 mmol) and *n*-butyllithium (6.3 mL, 12.6 mmol) in anhydrous tetrahydrofuran (10 mL) was allowed to react at −25°C for 3 h before cooling to −70°C. 2-Lithio-1,3-dioxolane (for **15**) and 2-lithio-1,3-dioxane (for **16**) were generated from the corresponding stannyl derivatives, as reported in the literature [27,28]. This is a multistep synthesis, and the final step was adjusted to generate 12.5 mmol of the lithium reagent in 15 mL of tetrahydrofuran. Vinyllithium (for **31**, **32**, and **37**) was generated by the reaction of tetravinyltin with *tert*-butyllithium as previously described [28,29]. Briefly, a solution of tetravinyltin (0.7 mL, 3.2 mmol) in tetrahydrofuran (15 mL) was treated dropwise at −70°C for 5 min with *tert*-butyllithium (7.4 mL, 12.6 mmol), and the mixture was stirred for an additional 15 min at −70°C before use.

General procedure for the synthesis of 4-substituted 2-(4-methylpiperazino)pyrimidines 4–23. A solution of the corresponding lithium reagent (12.5 mmol) was treated dropwise at −70°C with a solution of 2-chloropyrimidine (1.35 g, 12 mmol) in tetrahydrofuran (15 mL). The mixture was stirred and allowed to reach gradually 0°C within 2 h, then quenched with a solution of water (1 mL) in tetrahydrofuran (5 mL). After treatment with a solution of DDQ (2.8 g, 12.5 mmol) in tetrahydrofuran (15 mL), the mixture was stirred at 23°C for 5 min, then cooled to 0°C, treated with a cold solution of sodium hydroxide (4*M*, 5 mL, 20 mmol), and extracted at 0°C with cold hexanes (20 mL). The residue was additionally extracted with a mixture of ether or hexanes (1:1, 2 × 15 mL), and the organic extracts were combined, dried over sodium sulfate, and passed through silica gel (5 g) to remove tar. Concentration on a rotary evaporator gave crude 4-substituted 2-chloropyrimidine **3** that, without further purification, was used for the reaction with *N*-methylpiperazine. Thus, a solution of crude compound **3** and *N*-methylpiperazine (5.5 mL, 50 mmol) in toluene (20 mL) was heated to 70°C until a thin layer chromatography analysis on silica gel eluting with ethyl acetate or triethylamine (95:5) showed the absence of **1** (several hours). Filtration of the mixture was followed by concentration on a rotary evaporator and chromatography of the residue eluting with ethyl acetate or triethylamine/hexanes (90:5:5). All products **4–23** were transformed into salts as mentioned earlier (see General Section). Selected intermediate products **3** (R = *n*-Bu, 9-phenanthryl, 2,2′-bithiophen-5-yl) were purified by chromatography as described earlier before the treatment with *N*-methylpiperazine. The yields of the corresponding products **4**, **10**, and **13** and the yields of the same respective products obtained using crude compounds **3** were similar (±1%).

4-Butyl-2-(4-methylpiperazino)pyrimidine (4). This compound was obtained as an oil in 68% yield; ^{1}H NMR: δ 0.94 (t, *J* = 7 Hz, 3H), 1.38 (m, 2H), 1.67 (m, 2H), 2.34 (s, 3H), 2.47 (m, 4H), 2.56 (t, *J* = 7 Hz, 2H), 3.85 (m, 4H), 6.37 (d, *J* = 5 Hz, 1H), 8.18 ppm (d, *J* = 5 Hz, 1H). The hydrobromide salt had mp 100–101°C. Anal. Calcd. for $2C_{13}H_{22}N_4\cdot 4HBr\cdot H_2O$: C, 38.53; H, 6.22; N, 13.83. Found: C, 38.34; H, 6.23; N, 13.77.

4-(sec-Butyl)-2-(4-methylpiperazino)pyrimidine (5). This compound was obtained as an oil in 42% yield; ^{1}H NMR: δ 0.84–0.88 (m, 3H), 1.20–1.22 (m, 3H), 1.63 (m, 2H), 2.34 (s, 3H), 2.47 (m, 4H), 2.53 (m, 1H), 3.85 (m, 4H), 6.35 (d, *J* = 5 Hz, 1H), 8.19 ppm (d, *J* = 5 Hz, 1H). The hydrobromide salt had mp 177–178°C. Anal. Calcd. for $C_{13}H_{22}N_4\cdot HBr$: C, 49.53; H, 7.35; N, 17.77. Found: C, 49.41; H, 7.47; N, 17.47.

4-(tert-Butyl)-2-(4-methylpiperazino)pyrimidine (6). This compound was obtained as an oil in 53% yield; ^{1}H NMR: δ 1.27 (s, 9H), 2.47 (m, 4H), 3.85 (m, 4H), 6.51 (d, *J* = 5 Hz, 1H), 8.21 ppm (d, *J* = 5 Hz, 1H). The hydrobromide salt had mp 224–226°C. Anal. Calcd. for $4C_{13}H_{22}N_4\cdot 4HBr\cdot H_2O$: C, 48.15; H, 7.46; N, 17.28. Found: C, 47.82; H, 7.16; N, 16.93.

2-(4-Methylpiperazino)-4-(phenylethynyl)pyrimidine (7). This compound was obtained as an oil in 60% yield; ^{1}H NMR: δ 2.24 (s, 3H), 2.48 (t, *J* = 5 Hz, 4H), 3.89 (t, *J* = 5 Hz, 4H), 6.68 (d, *J* = 5 Hz, 1H), 7.39 (m, 3H), 7.61 (m, 2H), 8.30 ppm (d, *J* = 5 Hz, 1H). The hydrobromide salt had mp 193–195°C. Anal. Calcd. for $C_{17}H_{18}N_4\cdot 2HBr\cdot H_2O$: C, 44.56; H, 4.84; N, 12.23. Found: C, 44.18; H, 4.82; N, 11.94.

4-[(Cyclohexen-1-yl)ethynyl)]-2-(4-methylpiperazino)- pyrimidine (8). This compound was obtained as an oil in 59% yield; ^{1}H NMR: δ 1.66 (???m, 4H), 2.20 (m, 4H), 2.34 (s, 3H), 2.46 (m,4H), 3.85 (m, 4H), 6.37 (m, 1H), 6.55 (d, J = 5 Hz, 1H), 8.24 ppm (d, J = 5 Hz, 1H). The hydrobromide salt had mp 242°C (decomp). Anal. Calcd. for $C_{17}H_{22}N_4{\cdot}HBr$: C, 56.20; H, 6.38; N, 15.42. Found: C, 56.08; H, 6.47; N, 15.34.

2-(4-Methylpiperazino)-4-(2-biphenyl)pyrimidine (9). This compound had mp 8587°C and was obtained in 86% yield; ^{1}H NMR: δ 2.04 (s, 3H), 2.37 (m, 4H), 3.67–3.69 (m, 4H), 6.29 (d, J = 5 Hz, 1H), 7.25 (m, 3H), 7.44 (m, 3H), 7.70 (m, 3H), 8.09 ppm (d, J = 5 Hz, 1H). Anal. Calcd. for $C_{21}H_{22}N_4{\cdot}2HBr{\cdot}H_2O$: C, 49.43; H, 5.14; N, 10.98. Found: C, 49.32; H, 5.00; N, 10.57.

2-(4-Methylpiperazino)-4-(9-phenanthryl)pyrimidine (10). This compound was obtained as an oil in 78% yield; ^{1}H NMR: δ 2.32 (s, 3H), 2.48 (m, 4H), 3.93–3.97 (m, 4H), 6.81 (d, J = 5 Hz, 1H), 7.58 (m, 2H), 7.63–7.67 (m, 2H), 7.89 (m, 2H), 8.28 (d, J = 8 Hz, 1H), 8.44 (d, J = 5 Hz, 1H), 8.70 ppm (m, 2H). The hydrobromide salt had mp 195–198°C. Anal. Calcd. for $2C_{23}H_{22}N_4{\cdot}3HBr{\cdot}4H_2O$: C, 53.97; H, 5.42; N, 10.95. Found: C, 54.35; H, 5.04; N, 10.96.

2-(4-Methylpiperazino)-4-(3-pyridyl)pyrimidine (11). This compound was obtained as an oil in 84% yield. The hydrobromide salt had mp 163–165°C; ^{1}H NMR (salt, deuterated dimethyl sulfoxide): δ 2.87(s, 3H), 3.13 (m, 2H), 3.37 (m, 2H), 3.55 (m, 2H), 4.91 (m, 2H), 7.55 (d, J = 5 Hz, 1H), 7.91 (m, 1H), 8.66 (d, J = 5 Hz, 1H), 8.92 (m, 2H), 9.53 (s, 1H), 9.93 ppm (br s, 2H).Anal. Calcd. for $22C_{14}H_{17}N_5{\cdot}4HBr{\cdot}3H_2O$: C, 37.86; H, 4.99; N, 15.77. Found: C, 38.02; H, 4.66; N, 15.58.

4-(1-Methylindol-2-yl)-2-(4-methylpiperazino)pyrimidine (12). This compound was obtained as an oil in 78%; ^{1}H NMR: δ 240 (s, 3H), 2.55 (m, 4H), 3.94 (m, 4H), 4.18 (s, 3H), 6.97 (d, J = 5 Hz, 1H), 7.06 (s, 3H), 7.19 (t, J = 8 Hz, 1H), 7.36 (t, J = 8 Hz, 1H), 7.45 (d, J = 8 Hz, 1H), 7.70 (d, J = 8 Hz, 1H), 8.38 ppm (d, J = 5 Hz, 1H). The hydrobromide salt had mp 302–303°C. Anal. Calcd. for $2C_{18}H_{23}N_5{\cdot}4HBr{\cdot}H_2O$: C, 45.02; H, 5.46; N, 14.58. Found: C, 45.10; H, 5.26; N, 14.47.

4-(2,2′-Bithiophen-5-yl)-2-(4-methylpiperazino)-pyrimidine (13). This compound was obtained as an oil in 76% yield; ^{1}H NMR: δ 2.36 (s, 3H), 2.50 (m, 4H), 3.92 (m, 4H), 6.79 (d, J = 5 Hz, 1H), 7.05 (t, J = 4 Hz, 1H), 7.18 (d, J = 4 Hz, 1H), 7.27 (m, 2H), 7.55 (d, J = 4 Hz, 1H), 8.29 ppm (d, J = 5 Hz, 1H). The hydrobromide salt had mp 187–190°C. Anal. Calcd. for $2C_{17}H_{18}N_4S_2{\cdot}3HBr{\cdot}4H_2O$: C, 40.85; H, 4.74; N, 11.21. Found: C, 40.54; H, 4.41; N, 11.04.

4-(1,3-Dithiane-2-yl)-2-(4-methylpiperazino)pyrimidine (14). This compound was obtained as an oil in 69% yield; ^{1}H NMR: δ 204 (m, 2H), 2.17 (m, 1H), 2.35 (s, 3H), 2.47 (m, 4H), 3.03 (m, 4H), 3.88 (m, 4H), 8.30 (d, J = 5 Hz, 1H), 8.65 ppm (d, J = 5 Hz, 1H). The hydrobromide salt had mp 175–176°C. Anal. Calcd. for $C_{13}H_{20}N_4S_2{\cdot}2HBr$: C, 34.07; H, 4.84; N, 12.23. Found: C, 34.30; H, 5.13; N, 12.02.

4-(1,3-Dioxolane-2-yl)-2-(4-methylpiperazino)pyrimidine (15). This compound was obtained as an oil in 69% yield; ^{1}H NMR: δ 233 (s, 3H), 2.46 (t, J = 5 Hz, 4H), 3.87 (t, J = 5 Hz, 4H), 4.10 (m, 4H), 5.60 (s, 1H), 6.66 (d, J = 5 Hz, 1H), 8.34 ppm (d, J = 5 Hz, 1H). The hydrobromide had mp 166–170°C. Anal. Calcd. for $C_{12}H_{18}N_4O_2{\cdot}HBr$: C, 43.53; H, 5.78; N, 16.92. Found: C, 43.87; H, 5.87; N, 17.00.

4-(1,3-Dioxane-2-yl)-2-(4-methylpiperazino)pyrimidine (16). This compound was obtained as an oil in 71% yield The hydrobromide salt had mp 179–180°C; ^{1}H NMR (salt, deuteriochloroform): δ 1.49 (m, 1H),2.26(m, 1H), 2.82 (s, 3H), 2.85 (m, 2H), 3.59 (m, 2H), 3.94 (m, 4H), 4.28 (m, 2H), 4.98 (m, 2H), 5.32 (s, 1H), 6.97 (d, J = 5 Hz, 1H), 8.42 ppm (d, J = 5 Hz, 1H). Anal. Calcd. for $2C_{13}H_{20}N_4O_2{\cdot}2HBr{\cdot}H_2O$: C, 44.08; H, 6.26; N, 15.82. Found: C, 43.93; H, 6.01; N, 15.64.

4-(3,4-Dihydro-2H-pyran-6-yl)-2-(4-methylpiperazino)-pyrimidine (17). This compound was obtained as an oil in 80% yield; ^{1}H NMR: δ 1.91 (m, 2H), 2.25 (m, 2H), 2.33 (s, 3H), 2.47 (m, 4H), 3.86 (m, 4H), 4.15 (m, 2H), 6.21 (m, 1H), 6.74 (d, J = 5 Hz, 1H), 8.32 ppm (d, J = 5 Hz, 1H). The hydrobromide had mp 192–194°C. Anal. Calcd. for $4C_{14}H_{20}N_4O{\cdot}5HBr{\cdot}2H_2O$: C, 45.39; H, 6.05; N, 15.12. Found: C, 45.71; H, 6.08; N, 15.27.

4-(3,4-Methylenedioxyphenyl)-2-(4-methylpiperazino)-pyrimidine (18). This compound was obtained in 77% yield; mp (free base) 115–116°C; mp (hydrobromide salt) 287–288°C; ^{1}H NMR: δ 2.39 (s, 3H), 2.57 (m, 4H), 3.96 (m, 4H), 6.06 (s, 2H), 6.88 (d, J = 5 Hz, 1H), 6.92 (d, J = 8 Hz, 1H), 7.61 (m, 2H), 8.36 ppm (d, J = 5 Hz, 1H). Anal. Calcd. for $C_{16}H_{18}N_4O_2{\cdot}2HBr$: C, 41.76; H, 4.38; N, 12.18. Found: C, 41.58; H, 4.43; N, 12.12.

4-(1,4-Benzodioxane-4-yl)-2-(4-methylpiperazino)-pyrimidine (19). This compound was obtained as an oil in 81% yield; ^{1}H NMR: δ 2.38 (s, 3H), 2.57 (m, 4H), 3.96 (m, 4H), 4.33 (s, 4H), 6.89 (d, J = 5 Hz, 1H), 6.97 (d, J = 8 Hz, 1H), 7.57 (m, 1H), 7.68 (m, 1H), 8.35 ppm (d, J = 5 Hz, 1H). The hydrobromide salt had mp 297–298°C. Anal. Calcd. for $2C_{17}H_{20}N_4O_2{\cdot}4HBr{\cdot}H_2O$: C, 42.26; H, 4.80; N, 11.60. Found: C, 42.29; H, 4.65; N, 11.55.

4-(2,3-Dimethoxy-1-naphthyl)-2-(4-methylpiperazino)-pyrimidine (20). This compound was obtained as an oil in 70% yield; ^{1}H NMR: δ 2.37 (s, 3H), 2.51 (m, 4H), 3.85 (s, 3H), 3.93 (m, 4H), 4.05 (s, 3H), 6.69 (d, J = 5 Hz, 1H), 7.27 (s, 1H), 7.32 (m, 1H), 7.42 (m, 1H), 7.59 (d, J = 8 Hz, 1H), 7.78 (d, J = 8 Hz, 1H), 8.47 ppm (d, J = 5 Hz, 1H). The hydrobromide salt had mp 240–241°C. Anal. Calcd. for $4C_{21}H_{23}N_4O_2{\cdot}4HBr{\cdot}H_2O$: C, 56.19; H, 5.50; N, 12.48. Found: C, 56.01; H, 5.68; N, 12.48.

4-(2-Methoxyphenyl)-2-(4-methylpiperazino)pyrimidine (21). This compound was obtained in 88% yield; mp (free base) 79–80°C; mp (hydrobromide salt) 191–192°C; ^{1}H NMR: δ 238 (s, 3H), 3.51 (m, 4H), 3.91 (s, 3H), 3.93 (m, 4H), 7.03 (d, J = 8Hz, 1H), 7.18 (t, J = 8 Hz, 1H), 7.21 (d, J = 5 Hz, 1H), 7.43 (m, 1H), 8.01 (d, J = 8 Hz, 1H), 8.36 ppm (d, J = 5 Hz, 1H). Anal. Calcd. for $2C_{16}H_{20}N_4O{\cdot}4HBr{\cdot}H_2O$: C, 42.22; H, 5.09; N, 12.31. Found: C, 42.25; H, 5.06; N, 12.33.

4-(3-Methoxyphenyl)-2-(4-methylpiperazino)pyrimidine (22). This compound was obtained as an oil in 80% yield; ^{1}H NMR: δ 237 (s, 3H), 2.57 (m, 4H), 3.90 (s, 3H), 3.97 (m, 4H), 6.95 (d, J = 5 Hz, 1H), 7.42 (t, J = 8 Hz, 1H), 7.63 (m, 3H), 8.39 ppm (d, J = 5 Hz, 1H). The hydrobromide had mp 244–245°C. Anal. Calcd. for $2C_{16}H_{20}N_4O{\cdot}4HBr{\cdot}H_2O$: C, 42.20; H, 5.09; N, 12.31. Found: C, 42.18; H, 5.08; N, 12.35.

4-(4-Methoxyphenyl)-2-(4-methylpiperazino)pyrimidine (23). This compound was obtained in 89% yield; mp (free base) 66–67°C; mp (hydrobromide salt) 278–279°C; ^{1}H NMR: δ 237 (s, 3H), 2.52 (m, 4H), 3.89 (s, 3H), 3.96 (m, 4H), 6.90 (d, J = 5 Hz, 1H), 6.98 (m, 2H), 8.04 (m, 2H), 8.34 ppm (d, J = 5

Hz, 1H). Anal. Calcd. for $C_{16}H_{20}N_4O{\cdot}2HBr{\cdot}H_2O$: C, 41.40; H, 5.21; N, 12.07. Found: C, 41.74; H, 5.15; N, 12.03.

General procedure for demethylation of 21–23 to 24–26. A solution of **21–23** (free bases, 0.29 g, 1 mmol) in dichloromethane (10 mL) was treated at 23°C with boron tribromide in dichloromethane (1*M*, 4 mL, 4 mmol). The mixture was stirred at 23°C for 12 h and then quenched with a saturated solution of sodium bisulfate (5 mL). The resultant precipitate of the hydrobromide salt of **24–26** was filtered and crystallized from ethyl acetate or ether.

4-(2-Hydroxyphenyl)-2-(4-methylpiperazino)pyrimidine dihydrobromide (24·2HBr). This salt was obtained in 56% yield; mp 284–285°C; ^1H NMR (deuteriochloroform): δ 2.39(s, 3H), 2.55 (m, 4H), 3.86 (m, 4H), 6.97 (t, *J* = 8 Hz, 1H), 7.03 (d, *J* = 8 Hz, 1H), 7.06 (d, *J* = 5 Hz, 1H), 7.41 (t, *J* = 8 Hz, 1H), 7.79 (d, *J* = 8 Hz, 1H), 8.46 ppm (d, *J* = 5 Hz, 1H). Anal. Calcd. for $4C_{15}H_{18}N_4O{\cdot}8HBr{\cdot}H_2O$: C, 41.26; H, 4.73; N, 12.83. Found: C, 41.07; H, 4.61; N, 12.61.

4-(3-Hydroxyphenyl)-2(4-methylpiperazino)pyrimidine dihydrobromide (25·2HBr). This salt was obtained in 60% yield; mp >300°C; ^1H NMR (deuterated dimethyl sulfoxide): δ 3.21 (s, 3H), 3.56 (m, 4H), 4.76 (m, 4H), 6.96 (d, *J* = 5 Hz, 1H), 7.32 (t, *J* = 8 Hz, 1H), 7.63 (m, 3H), 8.51 ppm (d, *J* = 5 Hz, 1H). Anal. Calcd. for $4C_{15}H_{18}N_4O{\cdot}8HBr{\cdot}H_2O$: C, 41.26; H, 4.73; N, 12.83. Found: C, 41.11; H, 4.67; N, 12.70.

4-(4-Hydroxyphenyl)-2(4-methylpiperazino)pyrimidine dihydrobromide (26·2HBr). This salt was obtained in 60% yield; mp >300°C; ^1H NMR (deuterated dimethyl sulfoxide): δ 3.21 (s, 3H), 3.58 (m, 4H), 4.76 (m, 4H), 6.92 (d, *J* = 8 Hz, 2H), 7.32 (d, *J* = 5 Hz, 1H), 8.11 (d, *J* = 8 Hz, 2H), 8.45 ppm (d, *J* = 5 Hz, 1H). Anal. Calcd. for $2C_{15}H_{18}N_4O{\cdot}4HBr{\cdot}H_2O$: C, 40.84; H, 4.78; N, 12.70. Found: C, 40.84; H, 4.63; N, 12.58.

4-Acetyl-2-(4-methylpiperazino)pyrimidine (29). The reaction of 1-ethoxyvinyllithium (12.5 mmol) with 2-chloro-pyrimidine (1.35 g, 12 mmol) followed by aromatization of the resultant dihydropyrimidine intermediate by treatment with DDQ to give **27** was conducted as described earlier for other addition reactions. Crude product **27** was hydrolyzed to 4-acetyl-2-chloropyrimidine (**28**) by stirring the mixture of **27**, ethanol (25 mL), and hydrochloric acid (35%, 5 mL) at 23°C for 12 h. The acidic mixture was neutralized by addition of a saturated solution of sodium carbonate and then extracted with ether or hexanes (2:1, 3 × 50 mL). The extract was decolorized on a short column packed with silica gel (5 g), dried over magnesium sulfate and concentrated on a rotary evaporator. Crude product **28** gave the following ^1H NMR spectrum (deuteriochloroform): δ 2.27 (s, 3H), 7.84 (d, *J* = 5 Hz, 1H), 8.86 ppm (d, *J* = 5 Hz, 1H). Crude compound **28** was subjected to the reaction with *N*-methylpiperazine, and product **29** was purified by using the general procedure described earlier. Compound **29** (yield 70%) is an oil; ^1H NMR: δ 2.36 (s, 3H), 2.49 (m, 4H), 2.62 (s, 3H), 3.90 (m, 4H), 7.03 (d, *J* = 5 Hz, 1H), 8.50 ppm (d, *J* = 5 Hz, 1H). On heating, the hydrobromide salt **29**·1.5HBr undergoes melting with decomposition at 234°C. Anal. Calcd. for $2C_{11}H_{16}N_4O{\cdot}3HBr$: C, 38.67; H, 5.16; N, 16.40. Found: C, 38.82; H, 5.05; N, 16.41.

2-Chloro-4-vinylpyrimidine (30). The addition reaction of vinyllithium (25 mmol) with 2-chloropyrimidine (**1**, 24 mmol) followed by oxidation of the intermediate dihydropyrimidine was conducted by using a general procedure described earlier. After purification on a chromatotron eluting with hexanes or dichloromethane (2:1), compound **30** was obtained as an oil in 46% yield (1.5 g). The ^1H NMR spectrum of **30** [deuteriochloroform, δ 5.80 (m, 1H), 6.52 (m, 1H), 6.70 (m, 1H), 7.22 (d, *J* = 5 Hz, 1H), 8.57 ppm (d, *J* = 5 Hz, 1H)] was virtually identical with that reported in the literature for the compound obtained by an independent route [23].

4-(2-Methoxyethyl)-2-(4-methylpiperazino)pyrimidine (31). A solution of compound **30** (91 mg, 0.64 mmol) in anhydrous methanol (2 mL) was treated with a solution of sodium methoxide (0.5*M* in methanol, 0.65 mL, 0.65 mmol). The mixture was stirred at 23°C for 12 h, quenched with a saturated solution of sodium chloride (1 mL), and extracted with toluene (3 × 3 mL). The extract containing 2-chloro-4-(2-methoxyethyl)-pyrimidine was concentrated on a rotary evaporator to 3 mL and treated with *N*-methylpiperazine (0.25 mL, 2.0 mmol). The mixture was heated under reflux for 3 h, cooled, treated with a saturated solution of sodium carbonate (1 mL), and extracted with ether (2 × 5 mL), and the extract was concentrated on a rotary evaporator. Chromatography of the residue eluting with hexanes or triethylamine or methanol (4:1:1) gave 88 mg (58%) of **31** as an oil; ^1H NMR: δ 2.36 (s, 3H), 2.48 (m, 4H), 2.85 (t, *J* = 7 Hz, 2H), 3.37 (s, 3H), 3.77 (t, *J* = 7 Hz, 2H), 3.87 (m, 4H), 6.44 (d, *J* = 5 Hz, 1H), 8.22 ppm (d, *J* = 5 Hz, 1H). Anal. Calcd. for $C_{12}H_{21}N_4O{\cdot}HBr$: C, 30.09; H, 4.84; N, 11.70. Found: C, 29.86; H, 4.64; N, 12.02.

2-(4-Methylpiperazino)-4-[2-(4-methylpiperazino)ethyl]-pyrimidine (32). A mixture of 30 (0.33 g, 2.3 mmol) and *N*-methylpiperazine (0.55 mL, 5 mmol), and toluene (6 mL) was heated under reflux for 3 h. Workup and chromatography, as described for **31**, furnished 0.16 g (22%) of product **32** as an oil; ^1H NMR: δ 1.92 (m, 2H), 2.89 (s, 3H), 2.33 (s, 3H), 2.47 (m, 10H), 2.75 (m, 4H), 3.84 (m, 4H), 6.39 (d, *J* = 5 Hz, 1H), 8.17 ppm (d, *J* = 5 Hz, 1H). The hydrochloride has mp 202–206°C. Anal. Calcd. for $2C_{16}H_{28}N_4O{\cdot}8HCl{\cdot}H_2O$: C, 41.84; H, 7.24; N, 18.30. Found: C, 41.76; H, 7.10; N, 18.06.

4-(3-Furyl)-2-(4-methylpiperazino)quinazoline (35). The reaction of 2-chloroquinazoline [30] (**33**, 2.0 g, 12 mmol) with 3-furyllithium (12.5 mmol) and aromatization of the intermediate dihydroquinazoline by treatment with DDQ was conducted by using the general procedure described earlier. A mixture of the resultant crude product **34**, *N*-methylpiperazine 3 mL, 3 mmol, and toluene 15 mL was heated under reflux for 3 h, and the final product **35** was isolated and purified as described earlier. Product **35** was obtained in 18% yield (0.6 g); mp 67–69°C; ^1H NMR: δ 2.38 (s, 3H), 2.55(m, 4H), 4.05 (m, 4H), 7.02 (s, 1H), 7.22 (m, 1H), 7.60 (m, 1H), 7.66 (m, 2H), 8.08 ppm (m, 2H). Anal. Calcd. for $C_{17}H_{18}N_4O$: C, 69.37; H, 6.16; N, 19.03. Found: C, 69.21; H, 6.16; N, 18.83.

2-Chloro-4-vinylquinazoline (36). 2-Chloroquinazoline [30] (2.75 g, 12 mmol) in tetrahydrofuran (30 mL) was allowed to react with vinyllithium (12.5 mmol), and then the mixture was quenched by using the general procedure described earlier. A mixture of crude 2-chloro-4-vinyl-3,4-dihydroquinazoline thus obtained, potassium hydroxide (40 mg, 0.7 mmol), potassium ferricyanide (0.18 g, 0.55 mmol), water (0.3 mL), and benzene (1.5 mL) were stirred at 23°C for 5 h, and then treated with benzene (15 ml) and water (15 ml). The benzene layer was dried over magnesium sulfate, concentrated on a rotary evaporator, and the solid residue was crystallized from hexanes to give 29 mg (68%) of compound **36**; mp 65–67°C; ^1H NMR: δ 6.02 (m, 1H), 6.97 (m, 1H), 7.55 (m, 1H), 7.68 (m, 1H), 7.94

(m, 1H), 8.01 (m, 1H), 8.21 ppm (m, 1H). High resolution ms (esi, positive ion mode): Calcd. for $C_{10}H_7ClN_2$, *m/z* 190.0379 ($M^+ + 1$), found *m/z* 190.0376.

4-[2-(4-Methylpiperazino)ethyl]-2-(4-methylpiperazino)-quinazoline (37). A mixture of 36 (25 mg, 0.15 mmol), *N*-methylpiperazine (0.05 mL, 0.45 mmol), and toluene (2 mL) was heated to 70°C for 3 h. After cooling, the mixture was treated with a saturated solution of sodium carbonate (0.5 mL), extracted with ether (3 × 10 mL), and the extract was dried over magnesium sulfate and concentrated to give a solid residue. Chromatography eluting with hexanes or triethylamine or methanol (4:1:1, 100 mL; then 1:1:1, 400 mL) followed by crystallization from hexanes gave compound 37 in 40% yield (21 mg); mp 72–74°C; ^{1}H NMR: δ 2.33 (s, 3H), 2.37 (s, 3H), 2.52 (m, 8H), 2.66 (m, 4H), 2.96 (m, 2H), 3.35 (m, 2H), 4.00 (m, 4H), 7.20 (m, 1H), 7.60 (m, 2H), 7.88 ppm (d, $J = 8$ Hz, 1H). Anal. Calcd. for $C_{20}H_{30}N_6$: C, 67.76; H, 8.53; N, 23.71. Found: C, 67.93; H, 8.84; N, 23.96.

Radioligand Binding Studies. The *in vitro* affinity for native serotonin 5-HT_{2A} receptors was determined by inhibiting [^{3}H]-ketanserin (88 Ci/mmol; NEN Chemicals) binding to rat cortical membranes. Membrane preparation and a general assay procedure were carried out according to the previously published protocols [31]. Two compound concentrations were tested: 0.1 and 1 μM, each run in triplicate. The Cheng and Prusoff equation was used for calculations of estimated K_i values [32].

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An Efficient, Three-Component Synthesis of Spiro[benzo[*g*]chromene-4,3′-indoline]-3-carbonitrile and Spiro[indoline-3,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitrile Derivatives

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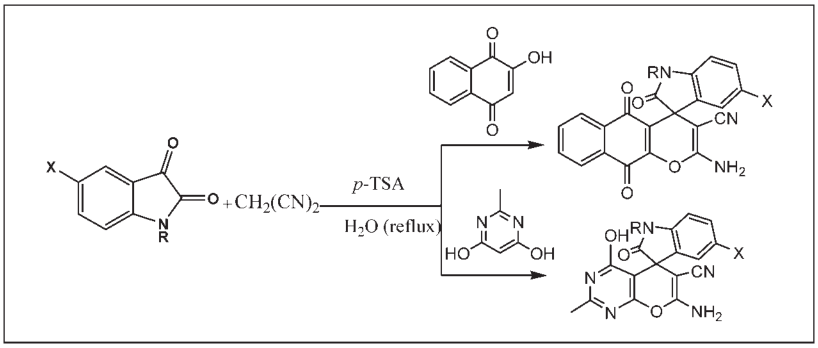

Spiro[benzo[g]chromene-4,3′-indoline]-3-carbonitriles and spiro[indoline-3,5′-pyrano[2,3-d]pyrimidine]-6′-carbonitriles were synthesized *via* a three-component reaction of isatins, 2-hydroxynaphthalene-1,4-dione or 2-methylpyrimidine-4,6-diol, and malononitrile in aqueous media.

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INTRODUCTION

With the emphasis on the search for atom-efficient transformations of easily available starting materials into complex organic molecules [1], reactions that provide maximum diversity are especially desirable. Here, expeditious domino [2] and multicomponent reactions [3] (MCRs) have emerged as powerful strategies. MCRs are economically and environmentally very advantageous, because multistep syntheses produce considerable amounts of waste mainly due to complex isolation procedures often involving expensive, toxic, and hazardous solvents after each step.

The indole moiety is probably the most well-known heterocycle, a common and important feature of a variety of natural products and medicinal agents [4]. Furthermore, it has been reported that sharing of the indole 3-carbon atom in the formation of spiroindoline derivatives highly enhance biological activity [5–7]. The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids [8–11].

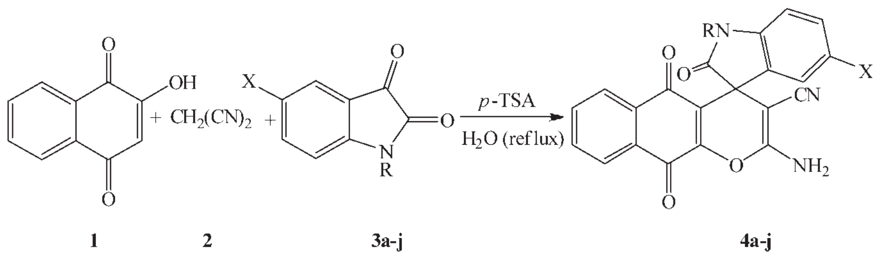
The quinone moiety is involved in a wide variety of biochemical processes including electron transport and oxidative phosphorylation [12]. Various biological properties, including enzyme inhibition, antibacterial, antifungal, and anticancer activities, have been reported for quinones and quinone derivatives [13–15]. Quinone-annulated heterocycles are found in nature, and most of them exhibit interesting biological activities. The chemistry of quinone annulated heterocycles is dependent largely on the substituent being either on the quinone or on adjacent rings [16,17]. These activities, combined with the diverse chemical behavior make quinones attractive targets in organic synthesis.

MCRs of isatins, malononitrile, and enol-neuclophilic compounds have recently attracted the interest of the synthetic community, because the formation of different condensation products can be expected depending on the specific conditions and structure of the building blocks [18–20]. 2-Hydroxynaphthalene-1,4-dione by containing enol group is a very interesting compound. As part of our program aimed at developing new selective and environmentally friendly methodologies for the preparation of heterocyclic compounds [21–28], we took advantage of enol group in 2-hydroxynaphthalene-1,4-dione for the preparation of spirooxindoles with fused chromene moiety. Fused chromenes have been found to have a wide spectrum of activities such as antimicrobial [29], antiviral [30], antiproliferative [31], sex pheromone [32], antitumor [33], and central nervous system activities [34].

RESULTS AND DISCUSSION

To achieve suitable conditions for the synthesis of spiro [benzo[*g*]chromene-4,3′-indoline]-3-carbonitriles, we first

Scheme 1



tested the reaction of 2-hydroxynaphthalene-1,4-dione 1, malononitrile 2 and isatin 3a, and as a simple model substrate in different solvents in the presence of *p*-toluenesulfonic acid (*p*-TSA) as an inexpensive and available catalyst at different conditions (Scheme 1). The results are shown in Table 1. It was found that water was a solvent of choice for the reaction, and the desired product was obtained in excellent yield in water (Entry 2).

Encouraged by this success, we extended the reaction of 2-hydroxynaphthalene-1,4-dione **1** and malononitrile **2** with a range of other isatin derivatives **3b-j** under similar conditions (Water/*p*-TSA) for 3–10 h, furnishing the respective 2-amino-2′,5,10-trioxo-5,10-dihydrospiro[benzo[*g*]chromene-4,3′-indoline]-3-carbonitrile derivatives **4b-j** in high yields. The optimized results are summarized in Table 2. The results were excellent in terms of yields and product purity using isatin derivatives in the presence of *p*-TSA, whereas without it for long period of time (24 h), the yields of products were low (< 30%). However, when this reaction was carried out with ethyl cyanoacetate, the thin layer chromatography (TLC) and ^{1}H NMR spectra of the reaction mixture showed a combination of starting materials and numerous products; the expected product was obtained in only trace amount.

A possible mechanism for the formation of **4** is proposed in Scheme 2. It is reasonable to assume that **4** results from initial formation of a intermediate **5** by standard Knoevenagel condensation of the malonitrile **2** and isatin **3**. Subsequently, Michael-type addition of the 2-hydroxynaphthalene-1,4-dione **1** to the intermediate **5**, followed by cyclization and tautomerization leads to the final products **4** (Scheme 2).

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

As expected, when the 2-hydroxynaphthalene-1,4-dione **1** was replaced by 2-methylpyrimidine-4,6-diol **6**, another series of spiro[indoline-3,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitriles **7a–d** were obtained under the same reaction conditions (Scheme 3).

In conclusion, we have developed an efficient, clean, and three-component synthesis of new spiro[benzo[*g*]-chromene-4,3′-indoline] and spiro[indoline-3,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitrile derivatives *via* cyclocondensation reaction of isatins, 2-malononitrile, and hydroxynaphthalene-1,4-dione or 2-methylpyrimidine-4,6-diol in aqueous media.

EXPERIMENTAL

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

Table 1

Conditions effect on the reaction.[a]

Entry	Conditions	Cat.	Yield (%)
1	Water/80°C	*p*-TSA	65
2	Water (reflux)	*p*-TSA	90
3	Water (reflux)	–	<30
4	CH_3CN (reflux)	*p*-TSA	45
5	EtOH (reflux)	*p*-TSA	63
6	DMF/100°C	*p*-TSA	50

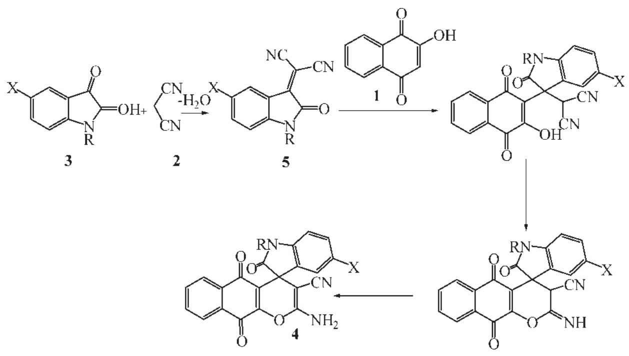
[a] Malononitrile (**2**) (1 mmol), 2-hydroxynaphthalene-1,4-dione (**1**) (1 mmol), isatin (**3a**) (1 mmol) and *p*-TSA (0.1 g), time = 7 h.

Table 2

Synthesis of spiro[benzo[*g*]chromene 4,3′-indoline] derivatives **4**.

Products **4**	R	X	Time (h)	Yield (%)
a	H	H	7	90
b	Me	H	10	98
c	Et	H	10	85
d	H	NO_2	6	85
e	Me	NO_2	4.5	94
f	Et	NO_2	3	97
g	H	Br	6	86
h	Me	Br	3	93
i	Et	Br	3	80
j	H	Me	3	96

Scheme 2

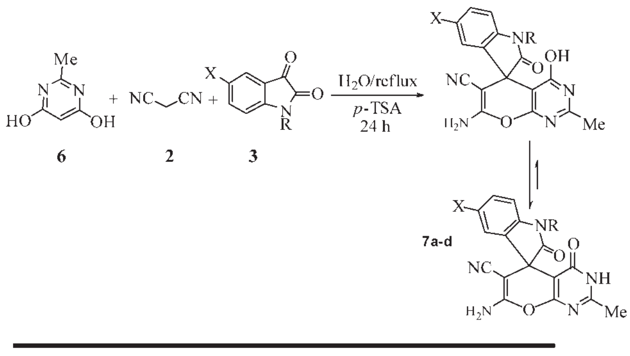


using an Shimadzu IR-470 apparatus. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

Typical procedure for the preparation of 2-amino-2′,5,10-trioxo-5,10-dihydrospiro[benzo[*g*]chromene-4,3′-indoline]-3-carbonitrile (4a). A mixture of malononitrile **2** (0.07 g, 1mmol), isatin **3** (0.15 g, 1mmol), 2-hydroxynaphthalene-1,4-dione **1** (0.17 g, 1 mmol), and *p*-TSA (0.1 g) was refluxed in water (5 mL) for 7 h (TLC). After cooling to room temperature, the resulting solid product was filtered, and the precipitate was washed with ethanol to afford the pure product **4a.** Light brown powder (90%); mp 295°C (dec.); ir (KBr) (ν_{max}/cm^{-1}): 3346 (NH_2), 3214 (NH), 2206 (CN), 1732, 1667, and 1633 (CO). MS(EI, 70 eV) *m*/*z* (%): 369 (M^+, 56), 325 (45), 105 (50), 76 (100). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 6.87–6.93 (m, 2H, H—Ar), 7.18–7.24 (m, 2H, H—Ar), 7.57 (s, 2H, NH_2), 7.82–7.88 (m, 3H, H—Ar), 8.05–8.07 (m, 1H, H—Ar), 10.68 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 48.49, 57.38, 110.04, 117.42, 119.93, 122.39, 124.69, 126.45, 126.68, 129.32, 130.75, 131.01, 134.94, 135.27, 124.17, 150.89, 159.08, 176.83, 178, 182.25. Anal. Calcd for $C_{21}H_{11}N_3O_4$: C, 68.29; H, 3.00; N, 11.38%. Found: C, 68.23; H, 2.95; N, 11.31%.

2-Amino-1′-methyl-2′,5,10-trioxo-5,10-dihydrospiro[benzo[*g*]chromene-4,3′-indoline]-3-carbonitrile (4b). Brown powder (98%); mp 265°C (dec.); ir (KBr) (ν_{max} /cm^{-1}): 3347 (NH_2), 2197 (CN), 1721, 1669, and 1627 (CO). MS (EI, 70 eV) *m*/*z* (%): 383 (M^+, 95), 338 (100), 105 (40), 76 (40). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.24 (s, 3H, CH_3), 6.99 (t, *J* = 5.7 Hz, 1H, H—Ar), 7.09 (d, *J* = 5.8 Hz, 1H, H—Ar), 7.31 (d, *J* = 6.1 Hz, 2H, H—Ar), 7.63 (s, 2H, NH_2), 7.76–7.88 (m, 3H, H—Ar), 8.05–8.07 (m, 1H, H—Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 27.0, 48.0, 56.9, 109.0, 117.3, 119.7, 123.1, 124.5, 126.5, 126.7, 129.5, 130.8, 131.0, 134.0, 134.9, 135.3, 142.6, 150.9, 159.1, 176.5, 176.7, 182.3. Anal. Calcd for $C_{21}H_{11}N_3O_4$: C, 68.29; H, 3.00; N, 11.38%. Found: C, 68.21; H, 3.06; N, 11.31%.

Scheme 3



Product **7**	R	X	Yield (%)
a	H	H	80
b	H	NO_2	82
c	Me	NO_2	65
d	Et	NO_2	63

2-Amino-1′-ethyl-2′,5,10-trioxo-5,10-dihydrospiro[benzo[*g*]chromene-4,3′-indoline]-3-carbonitrile (4c). Light brown powder (85%); mp 211°C (dec.); ir (KBr) (ν_{max} /cm^{-1}): 3349 (NH_2), 2196 (CN), 1717, 1668 and 1626 (CO). MS (EI, 70 eV) *m*/*z* (%): 397 (M^+, 100), 353 (100), 312 (58), 105 (40), 76 (45). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.25 (3H, t, *J* = 3.5 Hz, CH_3), 3.72–3.88 (2H, m, CH_2), 6.97 (t, *J* = 6.1 Hz, 1H, H—Ar), 7.12 (d, *J* = 6.0 Hz, 1H, H—Ar), 7.28–7.32 (m, 2H, H—Ar), 7.62 (s, 2H, NH_2), 7.78–7.88 (m, 3H, H—Ar), 8.06 (d, *J* = 6.2 Hz, 1H, H—Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.6, 47.9, 57.15, 109.1, 117.1, 119.7, 122.9, 124.6, 126.5, 126.7, 129.5, 130.7, 130.9, 134.2, 134.9, 135.2, 142.5, 150.9, 159.1, 175.9, 176.7, 182.2. Anal. Calcd for $C_{23}H_{15}N_3O_4$: C, 69.52; H, 3.80; N, 10.57%. Found: C, 69.47; H, 3.86; N, 10.51%.

2-Amino-5′-nitro-2′,5,10-trioxo-5,10-dihydrospiro[benzo[*g*]chromene-4,3′-indoline]-3-carbonitrile (4d). Light brown powder (85%); mp 290°C (dec.); ir (KBr) (ν_{max}/cm^{-1}): 3354 (NH_2), 3203 (NH), 2216 (CN), 1749, 1673, and 1629 (CO). MS (EI, 70 eV) *m*/*z* (%): 414 (M^+, 28), 371 (87), 324 (58), 297 (37), 174 (28), 105 (65), 43 (100). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 7.12 (d, *J* = 6.1 Hz, 1H, H—Ar), 7.80–7.89 (m, 5H, NH_2, 3H—Ar), 8.08 (d, *J* = 6.4 Hz, 1H, H—Ar), 8.19–8.22 (m, 1H, H—Ar), 8.33 (brs, 1H, H—Ar), 11.45 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 48.5, 56.0, 110.2, 117.1, 118.4, 120.8, 126.5, 126.7, 130.8, 135.0, 135.2, 135.6, 143.0, 148.6, 151.4, 159.3, 176.7, 178.5, 182.5. Anal. Calcd for $C_{21}H_{10}N_4O_6$: C, 60.88; H, 2.43; N, 13.52%. Found: C, 60.93; H, 2.47; N, 13.58%.

2-Amino-1′-methyl-5′-nitro-2′,5,10-trioxo-5,10-dihydrospiro[benzo[*g*]chromene-4,3′-indoline]-3-carbonitrile (4e). Light brown powder (94%); mp 320°C (dec.); ir (KBr) (ν_{max}/cm^{-1}): 3335 (NH_2), 2197 (CN), 1728, 1668, and 1632 (CO). MS (EI, 70 eV) *m*/*z* (%): 428 (M^+, 83), 384 (55), 364 (35), 254 (55), 224 (55), 174 (53), 76 (100). ^{1}H NMR (300 MH$_Z$, DMSO-d_6): δ_H 3.34 (s, 3H, CH_3), 7.38 (d, *J* = 8.8 Hz, 1H, H—Ar), 7.08–7.89 (m, 5H, NH_2, 3H—Ar), 8.07 (d, *J* = 8.9 Hz, 1H, H—Ar), 8.29–8.33 (m, 1H, H—Ar), 8.38–8.39 (m, 1H, H—Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 29.7, 111.6, 119.2, 122.7, 128.7, 128.9, 129.0, 133.0, 133.1, 136.9, 137.2, 137.4, 145.8, 151.7, 161.6, 178.8, 179.3, 184.7. Anal. Calcd for $C_{22}H_{12}N_4O_6$: C, 61.69; H, 2.82; N, 13.08%. Found: C, 61.75; H, 2.77; N, 13.00%.

2-Amino-1′-ethyl-5′-nitro-2′,5,10-trioxo-5,10-dihydrospiro[benzo[*g*]chromene-4,3′-indoline]-3-carbonitrile (4f). Light brown powder (97%); mp 287°C (dec.); ir (KBr) (ν_{max}/cm^{-1}): 3350 (NH_2), 2200 (CN), 1727, 1669, and 1630 (CO). MS (EI, 70 eV) *m*/*z* (%): 442 (M^+, 100), 398 (73), 367 (30), 297 (25), 105 (73), 76 (87). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.26 (t, 3H, *J* = 6.78 Hz, CH_3), 3.86–3.96 (m, 2H, CH_2), 7.43 (d, *J* =

8.7 Hz, 1H, H—Ar), 7.80–7.89 (m, 5H, NH_2, 3H—Ar), 8.08 (d, *J* = 8.8 Hz, 1H, H—Ar), 8.27–8.30 (m, 1H, H—Ar), 8.38 (brs, 1H, H—Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.6, 35.6, 47.8, 55.8, 109.3, 116.9, 118.2, 120.7, 126.5, 127.7, 130.8, 130.9, 135.1, 135.2, 143.4, 148.6, 151.6, 159.3, 176.6, 176.7, 182.5. Anal. Calcd for $C_{23}H_{14}N_4O_6$: C, 62.45; H, 3.19; N, 12.66%. Found: C, 62.39; H, 3.15; N, 12.61%.

2-Amino-5′-bromo-2′,5,10-trioxo-5,10-dihydrospiro[benzo[*g*]chromene-4,3′-indoline]-3-carbonitrile (4g). Light brown powder (86%); mp 275°C (dec.); ir (KBr) (ν_{max}/cm^{-1}): 3378 (NH_2), 3305 (NH), 2200 (CN), 1741, 1672, and 1651 (CO). MS (EI, 70 eV) *m*/*z* (%): 449 (M^++2, 40), 447 (M^+, 40), 405 (70), 76 (100). ^1H NMR (300 MHz, DMSO-d_6): δ_H 6.85 (d, *J* = 8.9 Hz, 1H, H—Ar), 7.37–8.05 (m, 6H, H—Ar), 7.83 (brs, 2H, NH_2), 10.83 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 48.6, 56.7, 111.9, 114.1, 117.3, 119.1, 126.5, 127.6, 130.8, 130.9, 132.0, 134.9, 135.2, 137.2, 141.5, 151.1, 159.1, 176.7, 177.6, 182.4. Anal. Calcd for $C_{21}H_{10}BrN_3O_4$: C, 56.27; H, 2.25; N, 9.37%. Found: C, 56.33; H, 2.20; N, 9.44%.

2-Amino-5′-bromo-1′-methyl-2′,5,10-trioxo-5,10-dihydrospiro[benzo[*g*]chromene-4,3′-indoline]-3-carbonitrile (4h). Light brown powder (93%); mp 282°C (dec.); ir (KBr) (ν_{max}/cm^{-1}): 3357 (NH_2), 2196 (CN), 1712, 1664, 1629 (CO). MS (EI, 70 eV) *m*/*z* (%): 464 (M^+ +2, 18), 462 (22), 419 (50), 391 (38), 105 (67), 76 (100). ^1H NMR (300 MHz, DMSO-d_6): δ_H 3.23 (s, 3H, CH_3), 7.09 (d, *J* = 6.3 Hz, 1H, H—Ar), 7.49–7.59 (m, 2H, H—Ar), 7.73 (s, 2H, NH_2), 7.82–7.87 (m, 3H, H—Ar), 8.06–8.09 (m, 1H, H—Ar).^{13}C NMR (75 MHz, DMSO-d_6): δ_C 27.1, 48.1, 56.4, 111.0, 114.9, 117.1, 118.9, 126.5, 126.7, 127.5, 130.8, 130.9, 132.1, 134.9, 135.2, 136.1, 142.9, 151.2, 159.2, 176.1, 176.7, 182.3. Anal. Calcd for $C_{22}H_{12}BrN_3O_4$: C, 57.16; H, 2.62; N, 9.09%. Found: C, 57.10; H, 2.67; N, 9.16%.

2-Amino-5′-bromo-1′-ethyl-2′,5,10-trioxo-5,10-dihydrospiro[benzo[*g*]chromene-4,3′-indoline]-3-carbonitrile (4i). Brown powder (80%); mp 288°C (dec.); ir (KBr) (ν_{max}/cm^{-1}): 3336 (NH_2), 2205 (CN), 1721, 1677, and 1632 (CO). MS (EI, 70 eV) *m*/*z* (%): 477 (M^++2, 55), 475 (M^+, 55), 433 (85), 105 (38), 76 (100). ^1H NMR (300 MHz, DMSO-d_6): δ_H 1.21 (t, 3H, *J* = 6.79 Hz, CH_3), 3.71–3.87 (m, 2H, CH_2), 7.12 (d, *J* = 9.1 Hz, 1H, H—Ar), 7.49 (d, *J* = 7.9 Hz, 1H, H—Ar), 7.59 (brs, 1H, H—Ar), 7.71 (s, 2H, NH_2), 7.81–8.08 (m, 4H, H—Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.5, 35.1, 47.9, 56.5, 111.1, 114.7, 117.0, 118.9, 126.5, 126.7, 127.6, 130.8, 130.9, 132.1, 134.9, 135.2, 136.4, 141.9, 151.2, 159.2, 175.6, 176.7, 182.3. Anal. Calcd for $C_{23}H_{14}BrN_3O_4$: C, 58.00; H, 2.96; N, 8.82%. Found: C, 57.93; H, 2.90; N, 8.89%.

2-Amino-5′-methyl-2′,5,10-trioxo-5,10-dihydrospiro[benzo[*g*]chromene-4,3′-indoline]-3-carbonitrile (4j). Light brown powder (98%); mp 310°C (dec.); ir (KBr) (ν_{max}/cm^{-1}): 3349 (NH_2), 3224 (NH), 2186 (CN), 1724, 1663, and 1631 (CO). MS (EI, 70 eV) *m*/*z* (%): 383 (M^+, 100), 339 (100), 311 (33), 282 (50), 104 (30), 76 (80). ^1H NMR (300 MHz, DMSO-d_6): δ_H 3.03 (3H, s, CH_3), 6.75–6.79 (m, 1H, H—Ar), 6.99–7.01 (m, 1H, H—Ar), 7.06 (brs, 1H, H—Ar), 7.57 (s, 2H, NH_2), 7.81–7.89 (m, 3H, H—Ar), 8.05–8.077 (m, 1H, H—Ar) 10.59 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 21.0, 48.5, 57.5, 109.7, 117.4, 120.0, 122.2, 126.4, 126.6, 129.5, 130.7, 131.0, 131.2, 134.8, 135.0, 135.2, 139.6, 150.8, 159.0, 176.8, 177.9, 182.2. Anal. Calcd for $C_{22}H_{13}N_3O_4$: C, 68.93; H, 3.42; N, 10.96%. Found: C, 68.99; H, 3.37; N, 11.04%.

Typical procedure for the preparation of 7′-amino-2′-methyl-2,4′-dioxo-3′,4′-dihydrospiro[indoline-3,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitrile (7a). A mixture of malononitrile **2** (0.07 g, 1mmol), isatin **3** (0.15 g, 1mmol), 2-methylpyrimidine-4,6-diol **6** (0.13 g, 1 mmol), *p*-TSA (0.1 g) was refluxed in water (5 mL) for 24 h (TLC). After cooling to room temperature, the resulting solid product was filtered, and the precipitate was washed with ethanol to afford the pure product **7a.** Cream powder (80%); mp 287°C (dec.); ir (KBr) (ν_{max}/cm^{-1}): 3378 (NH_2), 3306 (NH), 3142 (NH), 2207 (CN), 1716 and 1676 (CO). MS (EI, 70 eV) *m*/*z* (%): 321 (M^+). ^1H NMR (300 MHz, DMSO-d_6): δ_H 2.27 (s, 3H, CH_3), 6.78–7.18 (m, 4H, ArH), 7.31 (s, 2H, NH_2), 10.49 (s, 1H, NH), 12.61 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 21.4, 47.9, 57.1, 98.3, 109.7, 117.9, 122.2, 124.0, 128.8, 134.0, 142.6, 160.0, 160.3, 160.8, 161.0, 177.9. Anal. Calcd for $C_{16}H_{11}N_5O_3$: C, 59.81; H, 3.45; N, 21.80. Found: C, 59.76; H, 3.41; N, 21.86.

7′-Amino-2′-methyl-5-nitro2,4′-dioxo-3′,4′-dihydrospiro [indoline-3,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitrile (7b). Cream powder (82%); mp 270°C (dec.); ir (KBr) (ν_{max}/cm^{-1}): 3471 (NH_2), 3363 (NH), 2202 (CN), 1704, and 1658 (CO). MS (EI, 70 eV) *m*/*z* (%): 366 (M^+). ^1H NMR (300 MHz, DMSO-d_6): δ_H 2.28 (s, 3H, CH_3), 7.02 (d, *J* = 8.8 Hz, 1H, ArH), 7.50 (s, 2H, NH_2), 8.04 (s, 1H, ArH), 8.16 (d, *J* = 8.6 Hz, 1H, ArH), 11.24 (s, 1H, NH), 12.68 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 21.5, 48.1, 55.4, 97.2, 109.9, 117.7, 120.0, 126.4, 134.9, 142.9, 149.1, 160.4, 160.8, 161.1, 161.2, 178.7. Anal. Calcd for $C_{16}H_{10}N_6O_5$: C, 52.46; H, 2.75; N, 22.94. Found: C, 52.50; H, 2.80; N, 22.88.

7′-Amino-1,2′-dimethyl-5-nitro2,4′-dioxo-3′,4′-dihydrospiro [indoline-3,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitrile (7c). Cream powder (65%); mp 180°C (dec.); ir (KBr) (ν_{max}/cm^{-1}): 3429 (NH_2), 3322 (NH), 2202 (CN), 1730, and 1667 (CO). MS (EI, 70 eV) *m*/*z*(%): 380 (M^+). ^1H NMR (300 MHz, DMSO-d_6): δ_H 2.29 (s, 3H, CH_3), 3.25 (s, 3H, CH_3), 7.30 (d, *J* = 9.0 Hz, 1H, ArH), 7.57 (s, 2H, NH_2), 8.11 (s, 1H, ArH), 8.27 (d, *J* = 8.9 Hz, 1H, ArH), 12.66 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C. 21.5, 27.3, 47.7, 55.1, 97.1, 108.9, 117.6, 119.6, 126.4, 134.2, 143.4, 150.1, 160.6, 160.9, 161.0, 161.1, 177.3. Anal. Calcd for $C_{17}H_{12}N_6O_5$: C, 53.69; H, 3.18; N, 22.10. Found: C, 53.64; H, 3.22; N, 22.18.

7′-Amino-1-ethyl-2′-methyl-5-nitro2,4′-dioxo-3′,4′-dihydrospiro[indoline-3,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitrile (7d). Cream powder (63%); mp 233°C (dec.); ir (KBr) (ν_{max}/cm^{-1}): 3481 (NH_2), 3325 (NH), 2197 (CN), 1755, 1668, and 1647 (CO). MS (EI, 70 eV) *m*/*z* (%): 394 (M^+). ^1H NMR (300 MHz, DMSO-d_6): δ_H 1.17 (t, *J* = 8.4 Hz, 3H, CH_3), 2.22 (s, 3H, CH_3), 3.74 (m, 2H, CH_2), 7.10 (d, *J* = 8.9 Hz, 1H, ArH), 7.59 (s, 2H, NH_2), 8.14 (d, *J* = 8.9 Hz, 1H, ArH), 8.14 (s, 1H, ArH), 12.16 (brs, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 11.9, 18.0, 34.9, 39.07, 48.5, 95.3, 107.5, 118.4, 125.3, 135.3, 141.8, 150.6, 158.2, 161.4, 171.8, 178.6. Anal. Calcd for $C_{18}H_{14}N_6O_5$: C, 54.82; H, 3.58; N, 21.31. Found: C, 54.86; H, 3.63; N, 21.36.

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Synthesis and Antibacterial Activity of Novel Pyridine and Pyrazine Derivatives Obtained from Amidoximes

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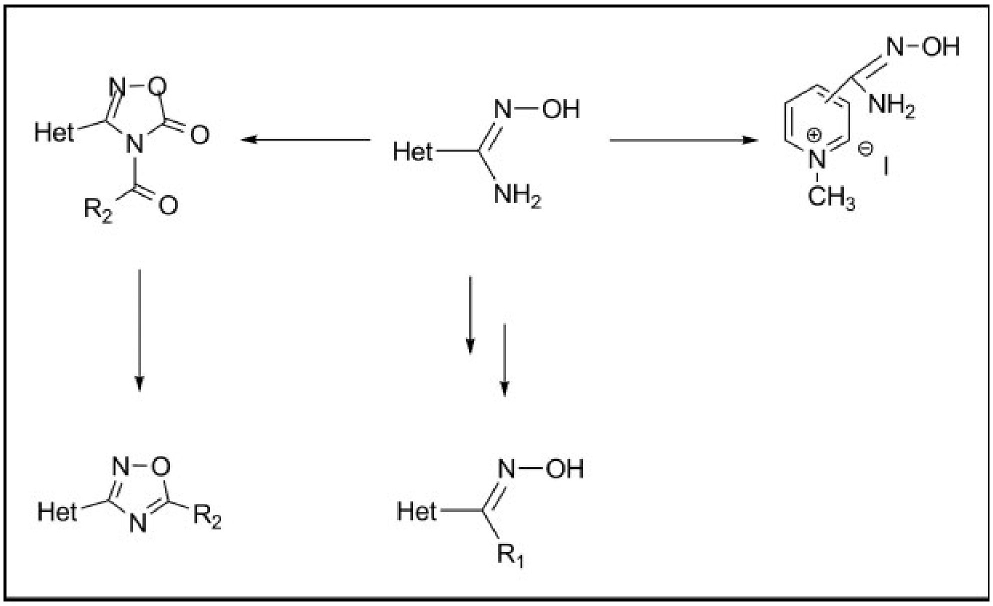

The new pyridine, 4-pyridine *N*-oxide and pyrazine derivatives exhibiting an antibacterial activity have been synthesized. Amidoximes were transformed into *N*-hydroxyimidoyl chlorides and then into appropriate oximes. Upon treatment of pyridinecaboxamidoximes with methyl iodide 1-methylpyridynium iodides were formed. Reaction of amidoximes with various carbamoyl chlorides led to corresponding 5-aminocarbonyl-1,2,4-oxadiazoles. Some of carboxamides have undergone thermal decarboxylation to tertiary amines. The newly synthesized compounds were tested *in vitro* for their tuberculostatic activity. MIC of the most active compound **9** was 12.5 μg/mL for $H_{37}Rv$ strain. Their activity towards 25 strains of anaerobic and 25 strains of aerobic bacteria was also studied. Derivative **18** was active against both aerobic and anaerobic types of the bacteria.

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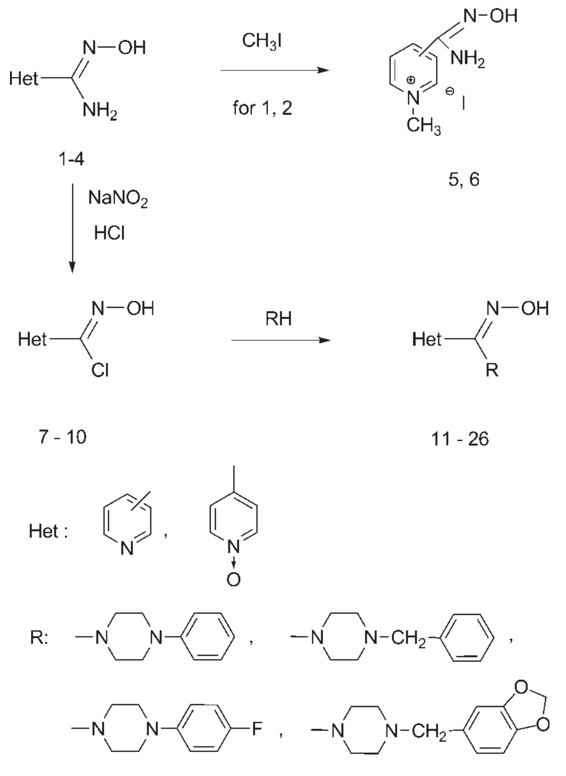
INTRODUCTION

Infections caused by *Mycobacteria* (*M. tuberculosis*, *M. avium*, *M. kansasaii*, *M. bovis*) are known to express multidrug-resistance toward most chemicals, disinfectants and number of antibiotics and chemotherapeutics as a consequence of single point mutations [1]. This phenomenon is very dangerous especially for HIV-infected individuals because of significantly increased risk of the infection progress to active disease. Other pathogenic strains, e.g. *Streptococcus pneumonia*, *Staphylococcus aureus*, *Enterococcus faecium*, also exhibit multidrug-resistance but mediated by other gene changes [2]. Thus antimicrobial therapy with a combination of different drugs is required and new active compounds for first-line therapy are needed.

In the last few years, many isoniazide and pyrazinamide derivatives have been synthesized. Few groups demonstrate high activity against *M. tuberculosis*: 2′-monosubstituted isonicotinohydrazides [3], isonicotinoylhydrazones [4], pyridine-2-carboxamidrazones [5,6] and 2-pyrazine or 3-pyridine-1,2,4-oxadiazole-5-ones [7]. Various pyridinium halides also exhibit antibacterial activity [8–10]. In our previous papers, we reported tuberculostatic activity of 4-mono- and 4-disubstituted pyridoyl thiosemicarbazides [11] and some derivatives

Scheme 1



of 5-substituted 3-pyrazine-1,2,4-oxadiazoles [12]. Further studies on antituberculosis agents active against multidrug- resistant strains prompted us to synthesize a series of new pyridine, pyridine-4-*N*-oxide and pyrazine derivatives possessing substituted amidoxime group or 1,2,4-oxadiazole ring substituted with amide in 4-position or amine group in 5-position. Both types of compounds could be synthesized from the same substrates, derivatives possessing carboxamidoxime functional group [13]. We now report on the synthesis and *in vitro* evaluation of their antibacterial and antituberculostatic activities *in vitro*.

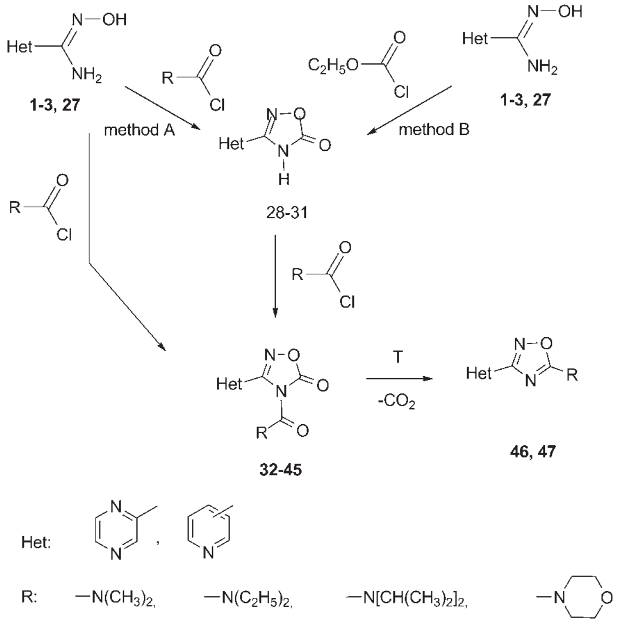
RESULTS AND DISCUSSION

Carboxamidoximes **1–4** and **27** were obtained in reaction of appropriate carbonitriles with hydroxylamine. Methylation of 3- and 4-pyridinecarboxamidoximes **2**, **3** on pyridine nitrogen atom was performed with methyl iodide in anhydrous dioxane and resulted in 1-methylpyridynium iodides **5**, **6** formation (Scheme 1).

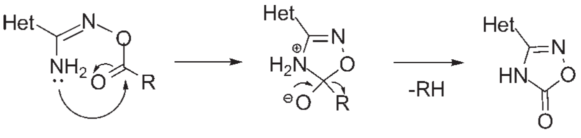
Compounds **2** and **3** also reacted with methyl iodide in alkaline solution but both pyridine nitrogen and amidoxime oxygen underwent methylation. *N*-hydroxycarboximidoylchlorides **7–10** were prepared from corresponding carboxamidoximes on treatment with sodium nitrite in hydrochloric acid solution at 0°C. Syntheses performed for pyridine derivatives required an use of sodium hydrogen carbonate to isolate products from reaction mixtures at pH 3. The obtained chlorides were used for the synthesis of appropriate oximes **11–26**. The reactions with secondary amines were performed in mole ratio 1:2 to neutralize hydrochloride generated during the reactions. Anhydrous dioxane was used as the solvent and reactions took about 15 min. In the case of oximes synthesized as pyridine *N*-oxide derivatives **23–26** refluxing time was prolonged to 1.5 h.

Amidoximes **1–4** and **27** were also treated with triple excess of appropriate carbamoyl chlorides in pyridine environment giving expected 3,4-disubstituted 5-oxo-[1,2,4]oxadiazoles **32–45** (Scheme 2) as a result of intramolecular nucleophilic attack of NH nitrogen electron pair for carbonyl carbon of carbamoyl moiety bound to OH oxygen instead proton. That attack followed substitution of OH proton and one of NH_2 protons by two carbamoyl moieties agreeably to mechanism proposed earlier by Marquez and DiPersia [14]. In two cases, the rate of that reaction was different resulting in formation of 3-monosubstituted 1,2,4-oxadiazole-5(4*H*)-ones **30** and **31** (method A). Those products forms probably as result of fast attack of NH_2 nitrogen electron pair for carbonyl carbon before NH_2 proton was substituted by carbamoyl (Scheme 3). Similar result was reached in control reactions between corresponding amidoximes and ethyl chloroformate (method B). Obtained compounds **28** and **29** were next transformed to 3,4-disubstituted derivatives by substitution in N4 position. Two amides **34** and **37** were undergone thermal decarboxylation at 215°C to tertiary amines **46** and **47**.

Scheme 2



Scheme 3



R: $N(CH_3)_2$, OC_2H_5

Characteristics of newly synthesized compounds have been presented in Table 1.

The investigations of aerobic and anaerobic bacteria susceptibility to the synthesized pyridine derivatives are summarized in Table 2. The results have been compared with that obtained while testing the susceptibility of the same bacteria to metronidazole (for anaerobes) and amikacin (for aerobes).

Low metronidazole concentrations in range ≤0.1–3.1 µg/mL inhibited the growth of Gram-negative bacteria except single strains of *Bacteroides fragilis*, *B. forsythus* and *Fusobacerium necrophorum*. These results were coincided with those obtained by other authors [15,16]. The lowest susceptibility to metronidazole exhibited Gram-positive rods from *Propionibacterium acnes* species (MIC > 12.5 µg/mL). Among 26 tested derivatives 24 (92%) exhibited differential activity against anaerobic bacteria (8–52% of the tested strains). The anaerobes were the most susceptible at concentrations in ranges from ≤6.2 to 100 µg/mL to derivatives **24** and **26** (52% were susceptible) and to compound **9** (40% of susceptible strains). The aerobic bacteria were generally not susceptible to compounds **13** and **15** in mentioned range of concentrations. Among 24 derivatives active towards anaerobic bacteria, 21 were more effective to Gram-positive strains. Compounds **30** (MIC 25–100 µg/mL, 100% of susceptible strains), **9** and **24** (MIC ≤6.2–100 µg/mL, 89%) exhibited the highest activity. Derivatives **26**, **27**, and **29** were more active against Gram-negative anaerobic rods. Compound **27** was the most active one (MIC ≤6.2–100 µg/mL, 38%).

Only one from 30 (3%) tested compounds was active towards aerobic bacteria. Derivative **18** was active in concentration 50–100 µg/mL and inhibited the growth of 16% of the tested aerobic bacteria. Other compounds did not inhibit the growth of aerobic bacteria in the range of tested concentration (≤6.2–200 µg/mL). Derivative **18** was active against both aerobic and anaerobic types of bacteria.

The standard strains of both types of bacteria exhibited rather high resistance towards tested compounds (MIC ≥ 200 µg/mL). In the case of anaerobic *Fusobacterium nucleatum*, ATCC 25586 compounds **21** (MIC 100 µg/mL), **23** (MIC 100 µg/mL) and **15** (MIC 100 µg/mL) were active. Derivative **18** induced the growth inhibition of *Bacteroides vulgatus* ATCC 8482 in concentration of 100 µg/mL. That compound also inhibited the growth of two aerobic standard strains: *Klebsiella pneumoniae* ATCC 13883 and *Staphylococcus aureus* ATCC 25923 and MIC value for that derivative was 100 µg/mL in both casas.

The determined minimum concentrations inhibiting the growth of tuberculous strains (MIC) for most of the tested compounds were within the limits 12–100 µg/mL. MIC of the most active compound **9** was 12.5 µg/mL for $H_{37}Rv$ strain and 25 µg/mL for other strains.

In conclusion, the present research showed that reaction between carboxamidoximes and carbamoyl chlorides can occur according to two different rates. One derivative (**18**) exhibited wide spectrum of antibacterial activity but it did not performe better that metronidazole against anaerobes and amikacin against aerobes. Other compound (**9**) exhibited interesting tuberculostatic activity and it can be good lead structure for further modifications.

EXPERIMENTAL

All materials and solvents were of analytical reagent grade. Thin-layer chromatography was performed on Merck silica gel $60F_{254}$ plates and visualized with UV. The results of elemental analyses (%C, H, N) for all of obtained compounds were in agreement with calculated values within ± 0.3 % range. ^1H NMR spectra in $CDCl_3$ or DMSO-d_6 were recorded on Varian Unity Plus (500 MHz) and Varian Gemini (200 MHz) instruments. IR Spectra (KBr) were determined as KBr pellets of the solids on a Satellite FT-IR spectrophotometer. Mass spectra for compounds **28**, **29**, and **46** were taken on Finingan MAT 95 by a chemical ionization method with isobutane. Melting points were determined on BOETIUS apparatus and were uncorrected.

Pyridinecarboxamidoximes (1–3). To a stirred solution of hydroxylamine hydrochloride (7 g, 0.1 mol) in methanol (50 mL) a solution of potassium hydroxide (6 g, 0.1 mol) in methanol was added. The precipitated potassium chloride was filtered off and appropriate pyridinecabonitrile (7 g, 60 mmol) was added to the clear filtrate. Reaction mixture was refluxed for 1 h and after cooling the final solid of **3** was filtered off, washed with water and dried at room temperature. The crude product was recrystallized to afford of bright leaflets (7.5 g). To isolate two other isomers final reaction mixtures were evaporated and 20 mL of water was added to the residue. The crude products were filtered off after cooling and purified by crystallization yielding 8 g of **1** and 6.7 g of **2**.

2-Pyridinecarboxamidoxime (1). This compound was obtained as colorless short needles. Yield 87%; m.p. 117–118°C. (ref. [17], m.p. 117°C).

3-Pyridinecarboxamidoxime (2). This compound was obtained as colorless small needles. Yield 73%; m.p. 131–133°C. (ref. [17], m.p. 131°C).

4-Pyridinecarboxamidoxime (3). This compound was obtained as colorless small needles. Yield 82%; m.p. 197–199°C. (ref. [17], m.p. 207°C).

Table 1

Characteristics of the newly synthesized derivatives.

No	Het	R	Mp [°C] Solvent	Yield [%]	Molecular formula	MW	Calcd/found					
							C		H		N	
4	1-oxide-pyridin-4-yl	NH_2	258-260 water	75	$C_6H_7N_3O_2$	153.14	47.05	47.11	4.61	4.65	27.44	27.49
5	3-(1-methyl)-pyridinium iodide	NH_2	165-167 methanol	90	$C_7H_{10}IN_3O$	279.07	30.13	30.10	3.61	3.56	15.06	15.12
6	4-(1-methy)-pyridinium iodide	NH_2	199-201 methanol	42	$C_7H_{10}IN_3O$	279.07	30.13	30.18	3.61	3.66	15.06	15.01
10	1-oxide-pyridin-4-yl	Cl	147-149 methanol	97	$C_6H_5ClN_2O_2$	172.57	41.76	41.73	2.92	2.81	16.24	16.28
11	pyridin-2-yl	4-phenyl-piperazin-1-yl	190-192 toluene	78	$C_{16}H_{18}N_4O$	282.33	68.06	68.12	6.43	6.29	19.85	19.88
12	pyridin-2-yl	4-benzyl-piperazin-1-yl	152-154 toluene	67	$C_{17}H_{20}N_4O$	296.36	68.89	68.84	6.80	6.83	18.91	18.96
13	pyridin-2-yl	4-(4-fluorophenyl-piperazin-1-yl	154-156 toluene	88	$C_{16}H_{17}FN_4O$	300.34	63.98	64.17	5.71	5.67	18.66	18.70
14	pyridin-2-yl	4-piperonyl-piperazin-1-yl	167-169 toluene	56	$C_{18}H_{20}N_4O_3$	340.37	63.51	63.48	5.92	6.09	16.46	16.54
15	pyridin-3-yl	4-phenyl-piperazin-1-yl	130-132 toluene	89	$C_{16}H_{18}N_4O$	282.33	68.06	67.81	6.43	6.51	19.85	19.99
16	pyridin-3-yl	4-benzyl-piperazin-1-yl	159-161 toluene	74	$C_{17}H_{20}N_4O$	296.36	68.89	68.93	6.80	6.73	18.91	18.86
17	pyridin-3-yl	4-(4-fluorophenyl-piperazin-1-yl	143-145 toluene	83	$C_{16}H_{17}FN_4O$	300.34	63.98	63.79	5.71	5.86	18.66	18.52
18	pyridin-3-yl	4-piperonyl-piperazin-1-yl	156-158 toluene	65	$C_{18}H_{20}N_4O_3$	340.37	63.51	63.45	5.92	6.08	16.46	16.42
19	pyridin-4-yl	4-phenyl-piperazin-1-yl	78-80 toluene	76	$C_{16}H_{18}N_4O$	282.33	68.06	68.31	6.43	6.41	19.85	19.88
20	pyridin-4-yl	4-benzyl-piperazin-1-yl	83-85 acetonitrile	86	$C_{17}H_{20}N_4O$	296.33	68.89	68.84	6.80	6.92	18.91	19.07
21	pyridin-4-yl	4-(4-fluorophenyl-piperazin-1-yl	167-169 acetonitrile	71	$C_{16}H_{17}FN_4O$	300.34	63.98	64.31	5.71	5.83	18.66	18.62
22	pyridin-4-yl	4-piperonyl-piperazin-1-yl	150-152 toluene	60	$C_{18}H_{20}N_4O_3$	340.37	63.51	63.33	5.92	5.87	16.46	16.59
23	1-oxide-pyridin-4-yl	4-phenyl-piperazin-1-yl	195-197 DMF/water	49	$C_{16}H_{18}N_4O_2$	298.33	64.41	64.57	6.08	6.05	18.78	18.51
24	1-oxide-pyridin-4-yl	4-benzyl-piperazin-1-yl	194-196 DMF/water	33	$C_{17}H_{20}N_4O_2$	312.36	65.36	65.42	6.45	6.31	17.94	18.06
25	1-oxide-pyridin-4-yl	4-(4-fluorophenyl-piperazin-1-yl	232-234 methanol	36	$C_{16}H_{17}FN_4O_2$	316.34	60.74	60.78	5.42	5.56	17.71	17.60
26	1-oxide-pyridin-4-yl	4-piperonyl-piperazin-1-yl	165-167 toluene	33	$C_{18}H_{20}N_4O_4$	356.37	60.66	60.29	5.66	5.78	15.72	15.48
28	pyridin-3-yl	–	229-231 water	A: 28 B: 52	$C_7H_5N_3O_2$	163.13	51.54	51.46	3.09	3.11	25.76	25.83
29	pyridin-4-yl	–	240-245 water	A: 26 B: 55	$C_7H_5N_3O_2$	163.13	51.54	51.47	3.09	3.17	25.76	25.88
31	pyridin-2-yl	–	185-190 water	97	$C_7H_5N_3O_2$	163.13	51.54	51.43	3.09	3.08	25.76	25.79
32	pyrazin-2-yl	$(C_2H_5)_2N$	133-134 toluene	50	$C_{11}H_{13}N_5O_3$	263.25	50.19	50.11	4.98	4.79	26.60	26.52
33	pyridin-2-yl	$(C_2H_5)_2N$	111-112 ethanol/water	73	$C_{12}H_{14}N_4O_3$	262.26	54.96	54.98	5.38	5.27	21.36	21.38
34	pyridin-3-yl	$(C_2H_5)_2N$	117-118 ethanol/water	52	$C_{12}H_{14}N_4O_3$	262.26	54.96	54.85	5.38	5.39	21.36	21.25
35	pyridin-4-yl	$(C_2H_5)_2N$	88-89 ethanol/water	52	$C_{12}H_{14}N_4O_3$	262.26	54.96	54.87	5.38	5.26	21.36	21.17
36	pyrazin-2-yl	$[(CH_3)_2CH]_2N$	105-107 ethanol/water	32	$C_{13}H_{17}N_5O_3$	291.31	53.60	53.69	5.88	5.97	24.04	24.06
37	pyridin-2-yl	$[(CH_3)_2CH]_2N$	145-148 ethanol/water	77	$C_{14}H_{18}N_4O_3$	290.32	57.92	57.90	6.25	6.32	19.30	19.35
38	pyridin-3-yl	$[(CH_3)_2CH]_2N$	66-69 *CCh*	62	$C_{14}H_{18}N_4O_3$	290.32	57.92	57.97	6.25	6.36	19.30	19.42
39	pyridin-4-yl	$[(CH_3)_2CH]_2N$	110-112 *CCh*	9	$C_{14}H_{18}N_4O_3$	290.32	57.92	57.83	6.25	6.14	19.30	19.32
40	pyrazin-2-yl	$(CH_3)_2N$	182-184 water	21	$C_9H_9N_5O_3$	235.20	45.96	45.89	3.86	3.77	29.78	29.69
42	pyridin-3-yl	$(CH_3)_2N$	101-103 water	5	$C_{10}H_{10}N_4O_3$	234.21	51.28	51.47	4.30	4.35	23.92	23.71
43	pyridin-4-yl	$(CH_3)_2N$	129-131 water	13	$C_{10}H_{10}N_4O_3$	234.21	51.28	51.39	4.30	4.21	23.92	23.80
44	pyrazin-2-yl	morpholin-4-yl	170-171 A: water B: *CCh*	A: 6 B: 57	$C_{11}H_{11}N_5O_4$	277.24	47.66	47.54	4.00	3.98	25.26	25.37
45	pyridin-2-yl	morpholin-4-yl	143-145 *CCh*	54	$C_{12}H_{12}N_4O_4$	276.25	52.17	52.29	4.38	4.53	20.28	20.20
46	pyridin-3-yl	$(C_2H_5)_2N$	30-31 *CCh*	39	$C_{11}H_{14}N_4O$	218.26	60.53	60.55	6.47	6.54	25.67	25.78
47	pyridin-2-yl	$[(CH_3)_2CH]_2N$	80-83 *CCh*	51	$C_{13}H_{18}N_4O$	246.31	63.39	63.24	7.37	7.24	22.75	22.56

Table 2

In vitro antibacterial activity of newly synthesized compounds

	MIC [μg/mL]													
	G+					G−								
No	1	2	3	4	5	6	7	8	9	10	11	12	13	14
A														
5	12.5	≤6.2	≥200	100	50	100	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200
6	≤6.2	≤6.2	≥200	50	≥200	25	50	≥200	≥200	≥200	≥200	≥200	≥200	≥200
7	25	≤6.2	≥200	≥200	≥200	100	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200
8	25	≤6.2	≥200	≥200	25	25	≥200	≥200	≥200	≥200	≥200	≥200	≥200	100
9	50	≤6.2	≥200	12.5	12.5	≤6.2	≤6.2	≥200	≥200	≥200	≥200	≥200	≥200	≥200
10	50	≤6.2	25	25	≥200	12.5	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200
11	≤6.2	12.5	≥200	12.5	≥200	12.5	100	≥200	≥200	≥200	≥200	100	≥200	≥200
12	≥200	≤6.2	≥200	25	100	100	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200
14	25	25	≤6.2	12.5	12.5	12.5	25	≥200	≥200	≥200	≥200	≥200	≥200	≥200
16	≥200	≤6.2	100	100	≥200	25	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200
17	≥200	12.5	≥200	≤6.2	≥200	25	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200
18	≥200	25	≥200	≥200	≥200	25	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200
19	≥200	50	≥200	25	≥200	25	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200
20	≥200	50	≥200	25	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200
21	≥200	≤6.2	12.5	≤6.2	≥200	12.5	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200
22	12.5	≤6.2	≥200	100	≥200	100	≥200	50	≥200	≥200	≥200	≥200	≥200	≥200
23	≥200	50	25	25	≥200	≤6.2	≤6.2	≥200	12.5	≤6.2	≥200	≥200	≥200	100
24	100	≤6.2	≤6.2	25	25	≤6.2	≤6.2	≥200	≤6.2	≤6.2	≥200	≥200	≥200	100
25	≤6.2	≤6.2	≥200	≤6.2	≤6.2	≤6.2	≤6.2	≥200	≤6.2	≤6.2	≥200	≥200	≥200	≥200
26	≥200	≤6.2	–	25	≥200	≤6.2	≤6.2	≥200	≤6.2	≤6.2	≥200	≥200	50	50
27	≥200	≤6.2	≤6.2	≥200	≥200	≤6.2	12.5	≥200	50	12.5	≥200	≥200	100	100
28	≥200	25	50	100	100	12.5	25	≥200	≥200	25	≥200	≥200	100	50
29	≥200	12.5	12.5	≥200	≥200	≤6.2	≤6.2	≥200	≥200	50	≥200	≥200	≥200	100
30	50	50	25	100	100	≤6.2	50	≥200	≥200	100	≥200	≥200	≥200	100
Metronidazole[a]	0.8	0.4	1.6	6.2	12.5	≤0.4	≤0.4	≤0.4	≤0.4	≤0.4	≤0.4	≤0.4	≤0.4	≤0.4
	1	2				3	4	5	6	7				
B														
18	100	100				≥200	50	≥200	≥200	≥200				
Amikacin[b]	≤6.2	50				≤6.2	≤6.2	≤6.2	≤6.2	12.5				

A: (1) *Peptostreptococcus magnus*, (2) *Peptostreptococcus micros*, (3) *Actinomyces israelii*, (4) *Actinomyces naeslundii*, (5) *Propionibacterium acnes*, (6) *Prevotella bivia*, (7) *Prevotella buccalis*, (8) *Prevotella intermedia*, (9) *Prevotella loescii*, (10) *Porhyromonas asacharolytica*, (11) *Fusobacterium nucleatum*, (12) *Fusobacterium necrophorum*, (13) *Bacteroides forsythus*, (14) *Bacteroides fragilis*.

B: (1) *Staphylococcus aureus*, (2) *Corynebacterium spp*., (3) *Klebsiella pneumonia*, (4) *Acinetobacter baumanii*, (5) *Acinetobacter baumanii*, (6) *Pseudomonas aeruginosa*, (7) *Pseudomonas stutzeri*.

[a] Metronidazole (Sigma).

[b] Amikacin sulfate salt (Sigma).

1-Oxy-isonicotincarboxamidoxime (4). A 7.2 g (60 mmol) quantity of 4-cyanopyridine N-oxide was dissolved in 50 mL of hot water and then water solution of hydroxylamine was added in small portions with stirring. Hot reaction mixture was left at room temperature for 1 h then cooled and precipitate was filtered and recrystallized giving 6.85 g of small colorless needles. Hydroxylamine solution was prepared by mixing 7 g (0.1 mol) of hydroxylamine hydrochloride in 10 mL of water with 6 g (0.1 mol) of potassium hydroxide in 10 mL of water. IR: 3416, 3296, 3180, 2834, 1644, 1608, 1500, 1439, 1379, 1226, 1189, 1099, 1036, 946, 863 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.03 (s; 2H, NH_2), 7.65 (m; 2H, 4-pyridyl), 8.20 (m; 2H, 4-pyridyl), 10.07 (s; 1H, OH) ppm.

***N*-hydroxycarbamimidoyl-1-methyl-pyridynium iodides (5, 6).** 1.3 g (10 mmol) of **2** or **3** was dissolved in hot anhydrous dioxane. After cooling to room temperature 2.5 mL (40 mmol) of methyl iodide was added. Reaction mixture was refluxed for 1 h then left at room temperature for next 1 h. After cooling precipitate was filtered and recrystallized to afford 2.6 g (**5**) and 2.7 g (**6**) of the product.

N-hydroxycarbamimidoyl-1-methyl-3-pyridynium iodide (5). This compound was obtained as light yellow prisms. IR: 3389, 3286, 1639, 1592, 1506, 1462, 1416, 1361, 1299, 1206, 953, 898, 876, 669 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 4.37 (s; 3H, N^+CH_3), 6.33 (s; 2H, NH_2), 8.14 (q; 1H, 3-pyridyl, J_1 8.3 Hz, J_2 6 Hz), 8.70 (d; 1H, 3-pyridyl, J 8.3 Hz), 8.96 (d; 1H, 3-pyridyl, J 6 Hz), 9.19 (s; 1H, 3-pyridyl), 10.39 (s; 1H,OH) ppm.

N-hydroxycarbamimidoyl-1-methyl-3-pyridynium iodide (6). This compound was obtained as light yellow prisms. IR: 3462, 3342, 1649, 1624, 1557, 1525, 1410, 1360, 1289, 1225, 1196, 1081, 952, 839, 824 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 4.31 (s; 3H, N^+CH_3), 6.42 (s; 2H, NH_2), 8.26 (d; 2H, 4-pyridyl, J 6.4 Hz), 8.94 (d; 2H, 4-pyridyl, J 6.4 Hz), 10.92 (s; 1H, OH) ppm.

***N*-Hydroxy-pyridinecarboximidoyl chlorides (7–9).** Appropriate pyridinecarboxamidoxime **1–3** (2.8 g, 20 mmol) was dissolved in a mixture of concentrated hydrochloric acid (20 mL) and water (100 mL) at 0°C. Sodium nitrite (1.6 g, 23 mmol) in 10 mL of water was added dropwise and reaction mixture was stirred for 1 h at 0°C. Next saturated solution of sodium hydrogen carbonate was slowly added to the reaction mixture until pH 3 was reached. The precipitate was filtered, washed with ice-cold water and purified by crystallization giving 2.8 g (**7**), 1.6 g (**8**), and 2.5 g (**9**) of the product.

N-Hydroxy-2-pyridinecarboximidoyl chloride (7). This compound was obtained as white small crystals. Yield: 80%; m.p. 120–122°C (ref. [18], m.p. 126–128°C.

N-Hydroxy-2-pyridinecarboximidoyl chloride (8). This compound was obtained as white small crystals. Yield: 80%; m.p. 129–131°C (ref. [18], m.p. 142–145°C).

N-Hydroxy-2-pyridinecarboximidoyl chloride (9). This compound was obtained as white small crystals 138–139°C (ref. [18], m.p. 148–150°C).

1-Oxide-*N*-hydoxy-4-pyridinecarboximidoyl chloride (10). 5.6 g of **4** (10 mmol) was dissolved in 40 mL of concentrated hydrochloric acid. The reaction mixture was cooled to temperature 0°C. Next sodium nitrite (5.5 g, 80 mmol) in water (10 mL) was added dropwise and mixture was stirred for 0.5 h. The precipitate was filtered and washed with ice-cold water. The crude product was recrystallized yielding bright needles (4.2 g). IR: 3098, 2520, 1603, 1550, 1476, 1444, 1232, 1213, 1183,1029, 959, 838, 623 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 7.73 (d; 2H, 4-pyridyl, J 7.5 Hz) 8.26 (d;2H, 4-pyridyl, J 20 Hz), 12.85 (s;1H, OH) ppm.

General procedure for the synthesis of pyridylmethanone oximes (11–26). A 0.78 g (5mmol) quantity of carboximidoyl chlorides **7–10** was dissolved in 10 mL of anhydrous dioxane. Next 10 mmol of appropriate secondary amine was added dropwise. Solid amines, 1-(4-flourophenyl)piperazine and 1-piperonylpiperazine, were dissolved in a small volume of the solvent (5 mL). The reaction mixture was heated under reflux for 15 min. In the case of 1-oxy-isonicitin derivatives, **23–26** refluxing time was prolonged for 1.5 h. The solvent was evaporated and 40 mL of ice-cold water was added to the residue. The precipitate was filtered, washed with water and recrystallized from suitable solvent yielding the solid.

4-Phenylpiperazin-1-yl-pyridin-2-yl-methanone oxime (11). This compound was obtained as white powder. IR: 3457, 2844, 1615, 1595, 1502, 1448, 1382, 1340, 1276, 1236, 1167, 1153, 951, 789, 754, 685 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.27 (s; 8H, NCH_2), 6.89–7.00 (m; 3H, ArH), 7.28 (m; 3H, 2H ArH and 1H 2-pyridyl), 7.38 (M; 1H, 2-pyridyl), 7.61 (m; 1H, 2-pyridyl), 7.85 (m; 1H, 2-pyridyl), 8.72 (s; 1H, OH) ppm.

4-Benzylpiperazin-1-yl-pyridin-2-yl-methanone oxime (12). This compound was obtained as white powder. IR: 3168, 3053, 2826, 1621, 1588, 1566, 1447, 1432, 1385, 1275, 1172, 1140, 966, 943, 791, 754, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.53 (s; 4H, NCH_2), 3.09 (s; 4H, NCH_2), 3.57 (s; 2H, NCH_2Ar), 7.31 (s; 6H, 5H ArH and 1H 2-pyridyl), 7.53 (s; 1H, 2-pyridyl), 7.79 (s; 1H, 2-pyridyl), 8.69 (s; 1H, 2-pyridyl), 9.18 (s;1H,OH) ppm.

4-(4-Fluorophenyl)piperazin-1-yl-pyridin-2-yl-methanone oxime (13). This compound was obtained as white powder. IR: 3207, 2828, 1631, 1512, 1455, 1434, 1390, 1236, 1170, 988, 953, 818, 789 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 3.15–3.23 (dd; 8H, NCH_2, J_1 38 Hz, J_2 5 Hz), 6.90 (m; 4H, ArH), 7.50 (d; 3H, 2-pyridyl, J 7.8 Hz), 7.84 (m; 1H, 2-pyridyl), 8.72 (s; 1H, OH) ppm.

4-Piperonylpiperazin-1-yl-pyridin-2-yl-methanone oxime (14). This compound was obtained as white powder. IR: 3179, 2831, 1608, 1590, 1487, 1439, 1370, 1244, 1169, 1141, 1039, 975, 799 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.49 (s; 4H, NCH_2), 3.08 (s; 4H, NCH_2), 3.47 (s;2H, NCH_2Ar), 5.93 (s; 2H, OCH_2O), 6.73 (s; 2H, ArH), 6.87 (s; 1H, ArH), 7.33–7.53 (m; 2H, 2-pyridyl), 7.80 (s;1H, 2-pyridyl), 8,69 (s;1H, 2-pyridyl), 9.07 (s; 1H, OH) ppm.

4-Phenylpiperazin-1-yl-pyridin-3-yl-methanone oxime (15). This compound was obtained as white powder. IR: 3151, 3037, 2843, 1599, 1497, 1446, 1337, 1242, 1153, 1014, 923, 899, 765, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.21, (s; 4H, NCH_2), 3.57 (s; 4H, NCH_2), 6.89–6.95 (m; 3H, ArH), 7.28–7.41 (m;4H, 2H ArH and 2H 3-pyridyl), 7.86 (s; 1H, OH), 8.75 (m; 2H, 3-pyridyl) ppm.

4-Benzylpiperazin-1-yl-pyridin-3-yl-methanone oxime (16). This compound was obtained as white powder. IR: 3173, 2820, 1615, 1593, 1454, 1416, 1380, 1266, 1157, 1142, 1031, 1010, 965, 742, 714, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.47 (s; 4H, NCH_2), 3.05 (s; 4H, NCH_2), 3.54 (s; 2H, NCH_2ArH), 7.25–7.37 (m; 6H, 5H ArH and 1H 3-pyridyl), 7.80 (m; 1H, 3-pyridyl), 8.37 (s; 1H, OH), 8.65 (m; 2H, 3-pyridyl) ppm.

4-(4-Fluorophenyl)piperazin-1-yl-pyridin-3-yl-methanone oxime (17). This compound was obtained as white powder. IR: 3176, 3056, 2839, 1624, 1592, 1510, 1417, 1382, 1267, 1235, 1152, 1025, 982, 957, 815, 713 cm^{-1}; ^{1}H NMR 500 MHz, CDCl$_3$: 3.15 (d; 8H, NCH$_2$, *J* 48 Hz), 6.87–6.90 (m; 4H, ArH), 7.42 (m; 1H, 3-pyridyl), 7.88 (d; 1H, 3-pyridyl, *J* 7 Hz), 8.22 (brs;1H,OH) 8.70 (d; 2H, 3-pyridyl, *J* 45 Hz).

4-Piperonylpiperazin-1-yl-pyridin-3-yl-methanone oxime (18). This compound was obtained as white powder. IR: 3162, 2827, 1600, 1592, 1487, 1440, 1368, 1265, 1246, 1159, 1142, 1033, 969, 921, 869, 809, 714 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ 2.45 (s; 4H, NCH$_2$), 3.04 (s; 4H, NCH$_2$), 3.42 (s; 2H, NCH$_2$Ar), 5.92 (s; 2H, OCH$_2$O), 6.72 (s; 2H, ArH), 6.84 (s; 1H, ArH), 7.37 (s; 1H, 3-pyridyl), 7.81 (s; 1H, 3-pyridyl), 8.18 (brs; 1H, OH), 8.62–8.69 (d; 2H, 3-pyridyl, *J* 33 Hz) ppm.

4-Phenylpiperazin-1-yl-pyridin-4-yl-methanone oxime (19). This compound was obtained as light beige powder. IR: 3063, 2889, 2851, 1633, 1600, 1496, 1410, 1383, 1243, 1150, 1023, 962, 927, 830, 760, 692 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ 3.18 (s; 8H, NCH$_2$), 6.89 (m; 3H, ArH), 7.25 (t; 2H, ArH, *J* 7.5 Hz), 7.42 (d; 2H, 4-pyridyl, *J* 4.5 Hz), 8.03 (s; 1H, OH), 8.74 (d; 2H, 4-pyridyl, *J* 4.5 Hz) ppm.

4-Benzylpiperazin-1-yl-pyridin-4-yl-methanone oxime (20). This compound was obtained as small white crystals. IR: 3054, 2920, 2820, 1623, 1597, 1457, 1402, 1300, 1154, 1002, 967, 833, 743 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ 2.50 (s; 2H, NCH$_2$), 2.60 (s; 2H, NCH$_2$), 3.06 (s; 2H, NCH$_2$), 3.45 (s; 2H, NCH$_2$), 3.57 (s; 1H, NCH$_2$Ar), 3.64 (s; 1H, NCH$_2$Ar), 7.26–7.39 (m; 7H, 5H ArH and 2H 4-pyridyl), 8.10 (brs; 1H, OH), 8.59 (d; 1H, 4-pyridyl, *J* 6 Hz), 8,68 (d; 1H, 4-pyridyl, *J* 5.5 Hz) ppm.

4-(4-Fluorophenyl)piperazin-1-yl-pyridin-4-yl-methanone oxime (21). This compound was obtained as white powder. IR: 3193, 3070, 2837, 1640, 1598, 1508, 1449, 1386, 1285, 1267, 1231, 1147, 1023, 959, 927, 825 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ 3.15 (d; 8H, NCH$_2$, *J* 43 Hz), 6.83–7.14 (m; 4H, ArH), 7.26–7.51 (m; 3H, 2H 4-pyridyl and 1H OH), 8.15 (brs; 1H, OH) 8.75 (m; 2H, 4-pyridyl) ppm.

4-Piperonylpiperazin-1-yl-pyridin-4-yl-methanone oxime (22). This compound was obtained as white powder. IR: 3180, 3024, 2815, 1599, 1488, 1441, 1369, 1248, 1159, 1142, 1037, 973, 826 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ 2.43 (s; 4H, NCH$_2$), 3.01 (s; 4H, NCH$_2$), 3.43 (s; 2H, NCH$_2$Ar), 5.92 (s; 2H, OCH$_2$O), 6.72 (s; 2H, ArH), 6.83 (s; 1H, ArH), 7.35 (s; 2H,4-pyridyl), 8.25 (s; 1H, OH), 8,69 (s; 2H, 4-pyridyl) ppm.

4-Phenylpiperazin-1-yl-1-oxide-pyridin-4-yl-methanone oxime (23). This compound was obtained as white powder. IR: 3141, 3027, 2832, 1597, 1481, 1453, 1383, 1235, 1173, 1157, 1012, 971, 860, 735 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 2.49 (s; 4H, NCH$_2$), 3.16 (s; 4H, NCH$_2$), 6.78 (t; 1H, ArH, *J* 7 Hz), 6.94 (d; 2H, ArH, *J* 8.5 Hz), 7.21 (t; 2H, ArH, J_1 8.5 Hz, J_2 7 Hz), 7.50 (d; 2H, 4-pyridine-N-oxide, *J* 6.5 Hz), 8.17 (d; 2H, 4-pyridine-N-oxide, *J* 6.5 Hz), 10.49 (s; 1H, OH) ppm.

4-Benzylpiperazin-1-yl-1-oxide-pyridin-4-yl-methanone oxime (24). This compound was obtained as white powder. IR: 3139, 3078, 2845, 1623, 1596, 1481, 1453, 1408, 1336, 1226, 1177, 1156, 1012, 928, 763, 632 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 3.05 (s; 4H, NCH$_2$), 3.17 (s; 4H, NCH$_2$), 3.33 (s; 2H, NCH$_2$Ar), 6.94–7.23 (m; 5H, ArH), 7.47 (d; 2H, 4-pyridine-N-oxide, *J* 6.5 Hz), 8.26 (d; 2H, 4-pyridine-N-oxide, *J* 6 Hz), 9.99 (s; 1H, OH) ppm.

4-(4-Fluorophenyl)piperazin-1-yl-1-oxide-pyridin-4-yl-methanone oxime (25). This compound was obtained as white powder. IR: 3174, 3059, 2848, 1637, 1614, 1442, 1375, 1361, 1221, 1186, 1147, 1037, 989, 965, 854, 834, 819 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 3.07 (dd; 8H, NCH$_2$, J_1 28 Hz, J_2 8 Hz), 6.94–7.06 (m; 4H, ArH), 7.45 (m; 2H, 4-pyridine-N-oxide), 8.25 (m; 2H, 4-pyridine-N-oxide), 9.98 (s;1H,OH) ppm.

4-Piperonylpiperazin-1-yl-1-oxide-pyridin-4-yl-methanone oxime (26). This compound was obtained as white powder. IR: 3055, 2901, 2839, 1612, 1488, 1439, 1369, 1230, 1179, 1156, 1035, 970, 854 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ 2.44 (m; 4H, NCH$_2$), 2.89 (s; 2H, NCH$_2$Ar), 3.42 (m; 4H, NCH$_2$), 5.97 (s; 2H, OCH$_2$O), 6.73–6.87 (m;3H, ArH), 7.42 (dd; 2H, 4-pyridine-N-oxide, J_1 25 Hz, J_2 7 Hz), 8.20 (dd; 2H, 4-pyridine-N-oxide, J_1 27 Hz, J_2 7 Hz), 9.89 (s; 1H,OH) ppm.

Pyrazinecarboxamidoxime (27). This compound was obtained as light beige needles according to method described earlier [19]. Yield: 96%; m.p. 186–187°C (lit. ref. [19], m.p. 186–187°C).

1,2,4-Oxadiazol-5-ones (28, 29). *Method A*. In 10 mL of dry pyridine 0.01 mol of appropriate carboxamidoxime was dissolved and 0.03 mol of carbamoyl chloride was added. The mixture was refluxed for 3 h. Then pyridine was evaporated and residue was cooled. Precipitate was filtered, washed with cold water and recrystallized. *Method B*. In 10 mL of dry pyridine 5 mmol of appropriate carboxamidoxime was dissolved and 0.956 mL (10 mmol) of ethyl chloroformate was added. The mixture was refluxed for 6 h. Then pyridine was evaporated and residue was cooled. Precipitate was filtered, washed with cold water and recrystallized with addition of active carbon.

3-Pyridin-3-yl-4H-[1,2,4]oxadiazol-5-one (28). This compound was obtained as small beige needles. IR: 3060, 2936, 1772, 1604, 1558, 1511, 1477, 1416, 1359, 1223, 1141, 1124, 1051, 1029, 915, 892, 761 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d$_6$): δ 7.63 (t; 1H, 3-pyridyl, J_1 3.0 Hz, J_2 5.0 Hz), 8.17 (q; 1H, 3-pyridyl, J_1 4.7 Hz, J_2 1.8 Hz), 8.79 (d; 1H, 3-pyridyl, *J* 4.9 Hz), 8.97 (s; 1H, 3-pyridyl), 12.8–13.4 (brs; 1H, NH) ppm. MS: m/z 164 (100 MH$^+$), 120 (32.4).

3-Pyridin-4-yl-4H-[1,2,4]oxadiazol-5-one (29). This compound was obtained as small white needles. IR: 3104, 3057, 1636, 1547, 1471, 1409, 1308, 1259, 1223, 1151, 1099, 1000, 933, 884, 846, 778 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d$_6$): δ 7.75 (q; 2H, 4-pyridyl, J_1 1.8 Hz, J_2 2.7 Hz), 8.82 (q; 2H, 4-pyridyl, J_1 1.7 Hz, J_2 2.8 Hz), 12.40–13.40 (brs; 1H, NH) ppm. MS: m/z 164 (62.6 MH$^+$), 120 (100).

1,2,4-Oxadiazole-5-ones (30, 31). Synthesis was performed according to procedure described above for compounds **28**, **29** *method B*.

3-Pyrazin-2-yl-4H-[1,2,4]oxadiazol-5-one (30). This compound was obtained as small beige crystals. Yield: 63%; m.p. 259–261°C (ref. [12], m.p. 260–262°C).

3-Pyridin-2-yl-4H-[1,2,4]oxadiazol-5-one (31). This compound was obtained as small beige needles. IR: 3061, 1788, 1585, 1567, 1496, 1460, 1419, 1301, 1114, 1096, 990, 953, 893, 798 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d$_6$): δ 7.62–7.86 (m; 1H, 2-pyridyl), 7.95–8.09 (m; 2H, 2-pyridyl), 8.75 (m; 1H, 2-pyridyl), 12.85–13.40 (brs; 1H, NH) ppm.

4-Aminocarbonyl-[1,2,4]oxadiazol-5-ones (32–41). Synthesis was performed according to procedure described for compounds **28**, **29** *method A*.

4-Diethylaminocarbonyl-3-pyrazin-2-yl-4H-[1,2,4]oxadiazol-5-one (32). This compound was obtained as small colorless crystals. IR: 2981, 1790, 1733, 1584, 1568, 1474, 1453, 1425, 1378, 1268, 1181, 1166, 1147, 1018, 905, 857, 759 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ 1.31–1.39 (m; 6H, $2CH_2C\underline{H}_3$), 3.47–3.63 (m; 4H, $2NC\underline{H}_2CH_3$), 8.63 (t; 1H, pyrazinyl, J 1.8 Hz) 8,79 (d, 1H, pyrazinyl, J 2.5 Hz), 9.28 (d; 1H, pirazyna, J 1.5 Hz) ppm.

4-Diethylaminocarbonyl-3-pyridin-2-yl-4H-[1,2,4]oxadiazol-5-one (33). This compound was obtained as small colorless crystals. IR 2977; 1780; 1724; 1565, 1476; 1454; 1426; 1400; 1272; 1212; 1177; 1059; 903; 859; 756 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): 1.31–1.39 (m; 6H, $2CH_2C\underline{H}_3$), 3.44–3.55 (m; 4H, $2NC\underline{H}_2CH_3$), 7.46–7.53 (m; 1H, 2-pirydyl), 7.86–7.94 (m; 1H, 2-pyridyl), 8.62 (m; 1H, 2-pyridyl) ppm.

4-Diethylaminocarbonyl-3-pyridin-3-yl-4H-[1,2,4]oxadiazol-5-one (34). This compound was obtained as small beige crystals. IR: 2976, 1786, 1722, 1589, 1550, 1426, 1383, 1273, 1255, 1211, 1140, 1056, 1023, 901, 857, 814, 796, 758 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ 1.23–1.34 (m, 6H, $2CH_2C\underline{H}_3$), 3.46–3.52 (m; 4H, $2NC\underline{H}_2CH_3$), 7,46–7,53 (q; 1H, 3-pyridyl, J_1 5.1 Hz, J_2 3.0 Hz), 8.01–8.07 (m; 1H, 3-pyridyl), 8.81 (q; 2H, 3-pyridyl, J_1 1.8 Hz, J_2 3.3 Hz) ppm.

4-Diethylaminocarbonyl-3-pyridin-3-yl-4H-[1,2,4]oxadiazol-5-one (35). This compound was obtained as small beige crystals. IR: 2978, 1792, 1725, 1659, 1637, 1600, 1583, 1408, 1270, 1251, 1212, 1064, 991, 909, 859, 827, 780, 759 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ 1.25–1.35 (q; 6H, $2CH_2C\underline{H}_3$, J_1 7.1 Hz, J_2 6.3 Hz), 3.45 (m; 4H, $2NC\underline{H}_2CH_3$), 7.57 (d; 2H, 4-pyridyl, J 5.0 Hz), 8.83 (d; 2H, 4-pyridyl, J 6.2 Hz) ppm.

4-Diisopropylaminocarbonyl-3-pyrazin-2-yl-4H-[1,2,4]oxadiazol-5-one (36). This compound was obtained as beige powder. IR: 2995, 1801, 1721, 1581, 1434, 1375, 1312, 1245, 1206, 1176, 1029, 1016, 900, 866, 825, 763 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ 1.27–1.49 (m; 12H, $2CH(C\underline{H}_3)_2$), 3,57–3,71 (m; 1H, $NC\underline{H}(CH_3)_2$), 4,05–4,19 (m; 1H, $NC\underline{H}(CH)_3$), 8,57 (q; 1H, pyrazinyl, J_1 1.5 Hz, J_2 1.0 Hz), 8.76 (d; 1H, pyrazinyl, J 2.5 Hz); 9,23 (d; 1H, pyrazinyl, J 1.5 Hz) ppm.

4-Diisopropylaminocarbonyl-3-pyridin-2-yl-4H-[1,2,4]oxadiazol-5-one (37). This compound was obtained as beige powder. IR: 3004, 2986, 2969, 1792, 1717, 1565, 1480, 1436, 1400, 1375, 1317, 1251, 1209, 1171, 1137, 1034, 897, 827, 789, 755 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ 1.28–1.38 (q; 6H, $CH(C\underline{H}_3)_2$ J_1 6.6 Hz, J_2 7.2 Hz), 1,5 (t; 6H, $CH(C\underline{H}_3)_2$ J 5.6 Hz), 3.49–3.71 (m; 1H; $NC\underline{H}(CH_3)_2$), 4.06–4.19 (m; 1H; $NC\underline{H}(CH_3)_2$); 7.45 (m; 1H, 2-pyridyl), 7.82–7.91 (m; 1H, 2-pyridyl); 7.99 (d; 1H, 2-pyridyl, J 7.9 Hz), 8.60 (q; 1H, 2-pyridyl, J_1 1.1 Hz, J_2 3.7 Hz) ppm.

4-Diisopropylaminocarbonyl-3-pyridin-3-yl-4H-[1,2,4]oxadiazol-5-one (38). This compound was obtained as beige powder. IR: 2994, 2973, 2938, 1797, 1716, 1588, 1433, 1378, 1309, 1247, 1152, 1029, 898, 852, 793, 755 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ 1.38 (d; 12H, $2CH(C\underline{H}_3)_2$, J 6.7 Hz), 4.11–4.25 (m; 2H, $2NC\underline{H}(CH_3)_2$), 7.43–7.50 (q; 1H, 3-pyridyl, J_1 5.1 Hz, J_2 2.6 Hz), 8.38 (d; 1H, 3-pyridyl, J 8.0 Hz), 8.71 (d; 1H, 3-pyridyl, J 4.0 Hz), 9.26 (s; 1H, 3-pirydyl).

4-Diisopropylaminocarbonyl-3-pyridin-4-yl-4H-[1,2,4]oxadiazol-5-one (39). This compound was obtained as beige powder. IR: 2983, 1798, 1716, 1534, 1419, 1375, 1308, 1246, 1200, 1027, 995, 901, 827, 794, 755 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ 1.26(d; 3H, $C\underline{H}_3CH$, J 6.8 Hz), 1.40 (d; 3H, $C\underline{H}_3CH$, J 6.8 Hz), 1.47 (d; 6H, $CH(C\underline{H}_3)_2$, J 6.8 Hz), 3.63–3.82 (m; 1H, $NC\underline{H}(CH_3)_2$), 4.07–4.12 (m; 1H, $NC\underline{H}(CH_3)_2$), 7.56 (d; 2H, 4-pyridyl, J 5.4 Hz), 8.82 (d; 2H, 4-pyridyl, J 5.4 Hz) ppm.

4-Dimethylaminocarbonyl-3-pyrazin-2-yl-4H-[1,2,4]oxadiazol-5-one (40). This compound was obtained as small white needles. IR: 2931, 1784, 1725, 1587, 1484, 1450, 1384, 1274, 1193, 1144, 1059, 1019, 910, 868, 794, 765 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ 3.17 (s; 3H, NCH_3), 3.21 (s; 3H, NCH_3), 8.64 (m; 1H, pyrazinyl), 8.77 (d; 1H, pyrazinyl, J 2.5 Hz), 9.22 (d; 1H, pyrazinyl, J 1.5 Hz) ppm.

4-Dimethylaminocarbonyl-3-pyridin-2-yl-4H-[1,2,4]oxadiazol-5-one (41). Yield: 35%; m.p. 139–141°C (ref. [13], m.p. 142–143°C).

4-Aminocarbonyl-[1,2,4]oxadiazol-5-ones (42–45). In 5 mL of dry pyridine 2.5 mmole of appropriate 1,2,4-oxadiazole-5-one **28–31** was dissolved and 7.5 mmol of carbamoyl chloride was added. The mixture was refluxed for 12–30 h. Reaction progress was monitored by TLC analysis. Pyridine was evaporated. Residue was cooled, filtered, washed, dried and recrystallized.

4-Dimethylaminocarbonyl-3-pyridin-3-yl-4H-[1,2,4]oxadiazol-5-one (42). This compound was obtained as beige powder. IR: 3060, 1772, 1728, 1604 1559, 1512, 1477, 1359, 1260, 1223, 1140, 1124, 1053, 1028, 910, 893, 829, 761 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d$_6$): δ 3.01 (s; 3H, NCH_3), 3.20 (s; 3H, NCH_3), 7.59–7.66 (q; 1H, 3-pyridyl, J_1 4.9 Hz, J_2 3.1 Hz), 8.04 (d; 1H, 3-pyridyl, J 8.0 Hz), 8.81 (m; 2H, 3-pyridyl) ppm.

4-Dimethylaminocarbonyl-3-pyridin-4-yl-4H-[1,2,4]oxadiazol-5-one (43). This compound was obtained as beige powder. IR: 2943, 1785, 1718, 1586, 1548, 1492, 1417, 1382, 1269, 1140, 1060, 1000, 903, 835, 759 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ 3.18 (s; 3H, CH_3), 3.25 (s; 3H, CH_3), 7.56 (d, 2H, 4-pyridyl, J 6.2 Hz), 8.83 (d; 2H, 4-pyridyl, J 6.1 Hz) ppm.

4-(Morpholine-4-carbonyl)-3-pyrazin-2-yl-4H-[1,2,4]oxadiazol-5-one (44). This compound was obtained as white powder. IR: 2922, 2867, 1808, 1735, 1584, 1421, 1377, 1263, 1233, 1178, 1114, 1017, 905, 840, 760 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d$_6$): δ 3.64–3.74 (m; 8H, morpholine), 8.88–8.95 (m; 2H, pyrazinyl), 9.26 (d; 1H, pyrazinyl, J 1.4 Hz) ppm.

4-(Morpholine-4-carbonyl)-3-pyrazin-2-yl-4H-[1,2,4]oxadiazol-5-one (45). This compound was obtained as white powder. IR: 2965, 2928, 1799, 1774, 1711, 1591, 1564, 1432, 1406, 1392, 1292, 1262, 1109, 1020, 1000, 900, 797, 755 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ 3.61 (t, 2H, NCH_2, J 4.4 Hz), 3.76 (d; 2H, NCH_2, J 4.9 Hz), 3.85 (d; 4H, 2 OCH_2, J 3.3 Hz), 7.50 (t; 1H, 2-pyridyl, J 4.9 Hz); 7.85–8.02 (m; 2H, 2-pyridyl), 8.65 (d; 1H, 2-pyridyl, J 4.7 Hz) ppm.

5-Alkylamino-[1,2,4]oxadiazoles (46, 47). 3 mmole of compound **34** or **37** was heated in pressure vessel in silicon bath gradually to 215°C. Then vessel was cooled slowly. Decarboxylation product was separated from substrate and purified by column chromatography on silica gel using chloroform–ethyl acetate as liquid phase.

5-Diethylamino-3-pyridin-3-yl-[1,2,4]oxadiazole (46). This compound was obtained as beige powder. IR: 2972, 1636, 1594, 1579, 1519, 1439, 1355, 1261, 1214, 1137, 1083, 1022, 963, 883, 821, 759 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d$_6$): δ 1.20 (t; 6H, $2CH_2C\underline{H}_3$, *J* 7.0 Hz), 3.48–3.59 (q; 4H, $2NC\underline{H}_2CH_3$, J_1 7.3 Hz, J_2 7.0 Hz), 7.51–7.58 (q; 1H, 3-pyridyl, J_1 4,84 Hz, J_2 3,14 Hz,), 8.23 (d; 1H, 3-pyridyl, *J* 7.9 Hz); 8.72 (d; 1H, 3-pyridyl, *J* 4.8 Hz), 9.05 (s; 1H, 3-pyridyl) ppm. MS: m/z 219 (100MH$^+$).

5-Diisopropylamino-3-pyridin-2-yl-[1,2,4]oxadiazole (47). This compound was obtained as beige powder. IR: 2976, 1610, 1523, 1410, 1391, 1368, 1298, 1197, 1160, 1123, 1024, 990, 925, 807, 757 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ 1.37 (d; 12H, $2CH(C\underline{H}_3)_2$, *J* 6.8 Hz), 4.26 (t; 2H, $2NC\underline{H}(CH_3)_2$, *J* 6.5 Hz); 7.39 (q; 1H, 2-pyridyl, J_1 5.4 Hz, J_2 1.5 Hz), 7.82 (t; 1H, 2-pyridyl, *J* 7.1 Hz), 8.07 (d; 1H, 2-pyridyl, *J* 7.8 Hz), 8.80 (d; 1H, 2-pyridyl, *J* 4.4 Hz) ppm.

Antibacterial activity. The investigations included 25 strains of anaerobic bacteria and 25 strains of aerobic bacteria isolated from the oral cavity, respiratory system and abdominal cavity as well as 12 standard strains. The anaerobes belonged to the following genera: *Peptostreptococcus* (5 strains), *Actinomyces* (2), *Propionibacterium* (2), *Prevotella* (6), *Porphyromonas* (2), *Fusobacterium* (3), *Bacteroides* (5), and standard strains: *Bacteroides fragilis* ATCC 25285, *Bacteroides vulgatus* ATCC 8482, *Bacteroides ovatus* ATCC 8483, *Fusobacterium nucleatum* ATCC 25586, *Peptostreptococcus anaerobius* ATCC 27337 and *Propionibacterium acnes* ATCC 11827. There were also the following aerobes: Staphylococcus aureus (4 strains), *Corynebacterium spp*. (2), *Klebsiella pneumoniae* (3), *Acinetobacter baumannii* (2), *Escherichia coli* (6), *Pseudomonas aeruginosa* (6), *Pseudomonas stutzeri* (2) and 6 standard strains: *Staphylococcus aureus* ATCC 25923, *Enterococcus faecalis* ATCC 29212, *Klebsiella pneumoniae* ATCC 13883, *Acinetobacter baumannii* ATCC 19606, *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853.

The susceptibility of the anaerobic bacteria was determined by means of the plate dilution technique in Brucella agar, supplemented with 5% sheep's blood [20,21]. For aerobic bacteria experiments agar dilution technique with Miller-Hinton agar was used. The derivatives were dissolved in 1mL of DMSO immediately before the experiment. Sterile distilled water was used for further dilutions. The following concentrations of derivatives were used: 200, 100, 50, 25, 12.5, and 6.2 μg/mL. The inoculum containing 10^6 CFU/spot applied to the agar plates with Steers replicator. For aerobes the inoculated agar plates and agar plates without derivatives were incubated for 24 h at 37°C. For anaerobes agar plates were incubated in anaerobic jars for 48 h at 37°C in 10% CO$_2$, 10% H$_2$ and 80% N$_2$ with palladium catalyst and indicator for anaerobiosis. The minimal inhibitory concentration (MIC) was defined as the lowest concentration of the derivative that inhibited growth of the anaerobes.

Mycobacterium tuberculosis. The compounds were examined for their tuberculostatic activity towards *Mycobacterium tuberculosis* H$_{37}$Rv strain and two ''wild'' strains isolated from tuberculotic patients: one (Spec. 210) resistant to p-aminosalicic acid (PAS), isonicotinic acid hydrazide (INH), etambutol (ETB) and rifampicine (RFP), another (Spec. 192) fully sensitive to the administrated drugs. *In vitro* investigations were performed by a classical test tube method of successive dilution with Youman's liquid medium containing 10% of bovine serum [22].

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The Arylimines of 2,4-Dioxo-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde: Synthesis and Their Application in 1,3-Dipolar Cycloaddition Reaction

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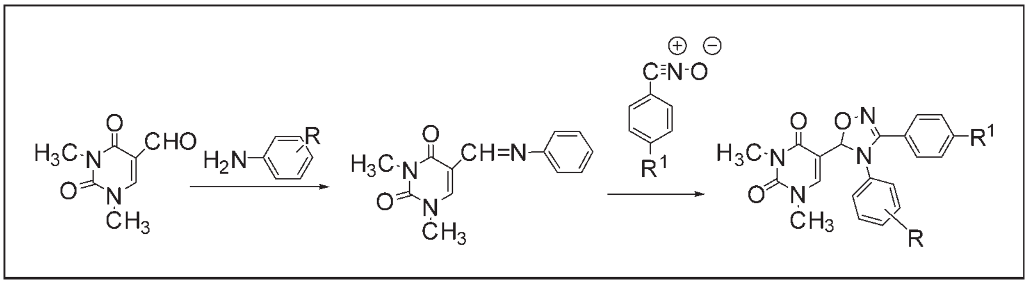

A number of aldimines have been obtained in very good yield in reaction of 5-formyl-1,3-dimethyluracil with various substituted anilines in boiling methanol. Selected aldimines were treated with nitrile oxides generated from 4-chlorobenzaldoxime or 4-methylbenzaldoxime forming the appropriate 1,3-cycloadducts in moderate yields.

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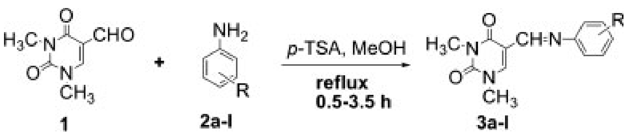
INTRODUCTION

The uracil derivatives are broadly known due to their application in bioorganic and medicinal chemistry. The 5-substituted uracils, mostly in the form of N1-glycosyl derivatives, possess biological activity, especially against viruses and neoplastic cells. 5-Fluorouracil and (*E*)-5-(2-bromovinyl)-2′-deoxyuridine belong to the best described uracil derivatives [1–3]. Similar to 5-halouridines, their analogues substituted with another heterocyclic system at C5 carbon of uracil ring, exhibit interesting biological activities. They form stable complexes with RNA [4] and inhibit thymidine kinase of HIV-1 virus [5,6]. The introduction of heteroaryl group into uracil ring can be performed using various methods. The UV irradiation of persilylated 5-iodo-2′-deoxycytidine in the presence of thiophene leads to appropriate 5-(2-thienyl)-2′-deoxycytidine in moderate yield [7]. The opposite variant of this reaction, when a mixture of 2-iodothiophene and 2-deoxycytidine was irradiated is also known [7]. Several 5-heteroaryl-2′-deoxyuridines have been obtained in palladium complexes catalyzed reaction of 5-iodo-2′-deoxyuridine with heteroaryltrialkyltin derivatives [8,9]. Other approaches based on traditional synthesis of heterocyclic rings involving 5-aminouracil as a building block in the construction of heterocyclic system have also been reported [10,11].

As a part of our research interest in the reactivity of uracil derivatives containing electron-withdrawing substituents, we have considered the molecule of 5-formyluracil (2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde) as a suitable reagent for the preparation of Schiff bases, which could be used further as dipolarophiles in 1,3-cycloaddition reaction. The chemical properties of 5-formyluracil are reported in the literature mainly in the context of its cytotoxic effect. The 5-formyl-2′-deoxyuridine formed by the oxidation of thymidine induces the damage of DNA [12–16]. Surprisingly, the syntheses involving 5-formyluracil as a reagent are rarely reported. 5-Formyl-1,3-dimethyluracil reacts with enamines giving 5-(acylvinyl)uracil derivatives. When enamines derived from 1,3-cyclohexanedione or ethyl acetate were applied, 5-(9-xanthenyl)uracil and 5-(6-cyclohexadienyl)uracil were obtained [17]. Recently, 5-formyluracil was used for the formation of nitrones, which treated with allyl alcohol as dipolarophile under harsh conditions to form isoxazolines in moderate yields [18]. Similarly, several isoxazoles, isoxazolines, and isoxazolidines have been synthesized by 1,3-dipolar cycloaddition reactions of nitrile oxides and nitrones derived from mono- and di-substituted uracil-5-carbaldehydes and 2,4-dimethoxypyrimidine-5-carbaldehyde [19].

The nickel, cobalt, and copper complexes of 5-formyluracil thiosemicarbazones were synthesized and their activity against model leukemia cells was examined [20]. Schiff bases of 5-formyluracil and chiral amino

Scheme 1. Synthesis of aldimines.



alcohols undergo highly diastereoselective 1,2- and 1,3-allylations to form homoallylic amino alcohol appended uracils [21].

RESULTS AND DISCUSSION

In our trials, which we report herein, 5-formyl-1,3-dimethyluracil (**1**) has been used as a carbonyl component in the synthesis of imines. For the preparation of **1** uracil was methylated by dimethyl sulfate followed by the Vilsmeier-Haack formylation using DMF and phosphorous trichloride [22]. Overall yield exceeded 60%. The condensation of **1** with substituted anilines **2a–l** occurs smoothly under mild condition (Scheme 1, Table 1). The desired aldimines **3a–l** were obtained by refluxing the equimolar amounts of reagents in methanol. The reaction time did not exceed 4 h in the case of less active anilines. The products **3a–l** are well soluble in hot methanol and, after cooling down to room temperature, they precipitate from the post-reaction solution in the form of crystalline solids in satisfactory yields (Table 1). The purity of the obtained imines **3a–d** was sufficient for the further synthesis as it was concluded from the NMR spectra. Other imines **3e–l** were recrystallized from methanol.

The structure of the products was assigned on the bases of NMR data and elemental analysis. The configuration of the double bond in the obtained imines was assumed as (*E*), which was confirmed by X-ray analysis of **3j** (Fig. 1) [23]. Because the synthesis of **3a–l** was performed under similar conditions (excluding time of reaction), we anticipated the same *E* configuration for all the obtained products.

For the primary trials of 1,3-dipolar cycloaddition reaction four imines **3a–d** possessing the substituent on C4 carbon of benzene ring were selected. The 1,3-dipole **4a** was generated *in situ* from 4-chlobenzaldehyde oxime using *N*-chlorosuccinimide and triethylamine as a base in chloroform solution according to the modified procedure [24]. The cycloaddition reaction of appropriate aldimine **3a–d** with 4-chlorobenzonitrile oxide **4** proceeded in refluxed $CHCl_3$ (Scheme 2). The products of reactions: 5-[3-(4-chlorophenyl)-4-(4-aryl)-4,5-dihydro-1,2,4-oxadiazole-5-yl]-1,3-dimethyl-1H-pyrimidine-2,4-dione **5a–d** were separated by column chromatography in satisfactory yields (Table 2). A same procedure was applied when 4-methylbenzonitrile oxide **4b** was used as the 1,3-dipole and cycloaddition reactions were occurred in 49–51% yields. The structure for all new compounds **5a–h** was confirmed by NMR spectroscopy and elemental analysis. As it was mentioned, the obtained aldimines have *E* configuration. The presence of single bond between C(5) of uracil ring and imine carbon atom allows for free rotation around this bond. The 1,3-cycloaddition reaction of nitrile oxide with double bond is the suprafacially concerted reaction [25]. However, when the free rotation is possible, the attack of dipole can occurs from both sides of imines and results in the formation of racemic mixture.

CONCLUSION

In summary, we have successfully carried out the condensation reaction of 1,3-dimethyl-5-formyluracil with substituted anilines. Reactions proceed under mild conditions and purity of aldimines in most of the cases was sufficient for the next step. It should be noticed that

Table 1

Synthesis of imines **3a–l** derived from 1,3-dimethyl-5-formyluracil and substituted anilines.

Product 3	R	Yield[a] (%)	Reaction time (h)	Mp (°C)
a	H	81	1.0	147–148
b	4-CH_3	91	1.5	155–156
c	4-Cl	93	0.5	183–185
d	4-Br	93	0.5	204–206
e	4-NO_2	84	1.0	282–284
f	3-CH_3	61	3.0	88–90
g	3-Cl	77	3.0	140–141
h	3-Br	75	3.5	143–144
i	3-I	79	3.0	148–149
j	2-CH_3	93	2.0	166–167
k	2-Cl	81	2.5	197–198
l	2-Br	75	2.5	195–197

[a] Isolated yield.

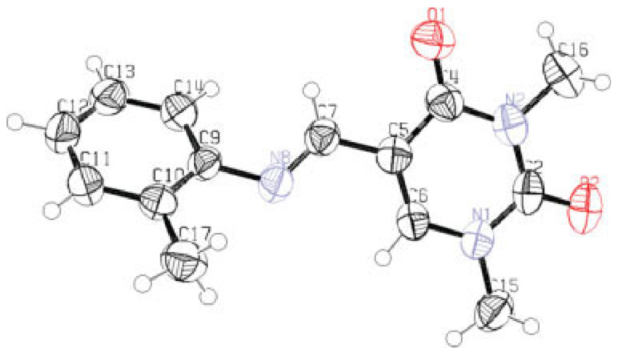


Figure 1. Crystal structure of **3j**. Displacement ellipsoids are drawn at the 50% probability level. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

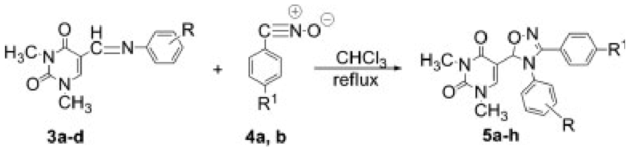
the presence of neighboring carbonyl group has not influence on reactivity of 5-formyl group in uracil ring rather toward weak nucleophiles like aromatic amines. The obtained Schiff bases were applied as dipolarophiles in the 1,3-dipolar cycloaddition reactions of 4-chlorobenzonitrile oxide or 4-methylbenzonitrile oxide to produce the racemic 5-(4,5-dihydro-1,2,4-oxadiazole-5-yl)uracil derivatives in satisfactory yields. The attack of 1,3-dipole on C(5)—C(6)—double bond of uracil ring was not observed [26].

EXPERIMENTAL

NMR spectra were recorded at 300 MHz for ^{1}H NMR and 75.5 MHz for ^{13}C NMR on a Varian Inova 300 MHz in $CDCl_3$ solution; δ values are in parts per million relative to tetramethylsilane as an internal standard. Elemental analyses were obtained using a PerkinElmer 240C apparatus. 4-Chlorobenzaldoxime (mp 107–108°C, lit. mp 107–109°C) and 4-methylbenzaldoxime (mp 71–73°C, lit. mp 76–78°C) were prepared according to known procedures [27]. The other used reagents were purchased from Lancaster. TLC $60F_{254}$ plates and silica gel 60 (0.040–0.063 mm) were purchased from Merck.

General procedure for synthesis of imines (3a–l). To the solution of 1,3-dimethyl-5-formyluracil **1** (0.34 g, 2 mmol) in MeOH (4 mL) containing 10 mg of *p*-TSA, appropriate aniline **2a–l** (2 mmol) was added and the reaction mixture was refluxed until the decay of substrates (0.5–3.5 h, Table 1), then cooled down to 0°C. The precipitate was filtered off, rinsed with cold methanol (2 mL), and dried in vacuum dessicator over P_2O_5. The products were sufficiently pure for the next step. If necessary the crystallization from methanol was applied and the pure compounds were obtained as light yellow crystals.

Scheme 2. Synthesis of 1,3-cycloadducts.



1,3-Dimethyl-5-(phenyliminomethyl)-1H,3H-pyrimidine-2,4-dione (3a). ^{1}H NMR ($CDCl_3$): δ 3.41 (s, 3H, CH_3), 3.51 (s, 3H, CH_3), 7.15 (d, 2H, J = 7.5 Hz, arom.), 7.22 (t, 1H, J = 7.5 Hz, arom.), 7.37 (t, 2H, J = 7.5 Hz, arom.), 8.24 (s, 1H, H-6), 8.58 (s, 1H, imine). ^{13}C NMR ($CDCl_3$): δ 28.1., 37.7, 100.2, 109.8, 121.1 (2C), 126.3, 129.3 (2C), 142.9, 151.3, 153.1, 162.5. Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 63.89; H, 5.01; N, 16.91.

1,3-Dimethyl-5-[(4-methylphenylimino)-methyl]-1H,3H-pyrimidine-2,4-dione (3b). ^{1}H NMR ($CDCl_3$): δ 2.36 (s, 3H, CH_3, *p*-tol), 3.41 (s, 3H, CH_3), 3.55 (s, 3H, CH_3), 7.10 (d, 2H, J = 8.1 Hz, arom.), 7.17 (d, 2H, J = 8.1 Hz, arom.), 8.23 (s, 1H, H-6), 8.58 (s, 1H, imine). ^{13}C NMR ($CDCl_3$): δ 21.1, 28.2, 37.7, 110.0, 121.0 (2C), 129.9 (2C), 136.2, 142.7, 148.7, 151.4, 152.1, 162.5. Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.36; H, 5.88; N, 16.33. Found: C, 65.63; H, 5.47; N, 15.98.

5-[(4-chloro-phenylimino)-methyl]-1,3-dimethyl-1H,3H-pyrimidine-2,4-dione (3c). ^{1}H NMR ($CDCl_3$): δ 3.41 (s, 3H, CH_3), 3.53 (s, 3H, CH_3), 7.10 (d, 2H, J = 8.7 Hz, arom.), 7.33 (d, 2H, J = 8.7 Hz, arom.), 8.24 (s, 1H, H-6), 8.55 (s, 1H, imine). ^{13}C NMR ($CDCl_3$): δ 28.2, 37.8, 109.7, 122.4 (2C), 129.4 (2C), 131.9, 143.2, 149.8, 151.3, 153.5, 162.5. Anal. Calcd. for $C_{13}H_{12}ClN_3O_2$: C, 56.23; H, 4.36; N, 15.13. Found: C, 55. 96; H, 4.02; N, 14.89.

5-[(4-Bromo-phenylimino)-methyl]-1,3-dimethyl-1H,3H-pyrimidine-2,4-dione (3d). ^{1}H NMR ($CDCl_3$): δ 3.41 (s, 3H, CH_3), 3.53 (s, 3H, CH_3), 7.04 (dt, 2H, J = 9.3 Hz, 2.4 Hz, arom.), 7.48 (dt, 2H, J = 9.3 Hz, 2.4 Hz, arom.), 8.24 (s, 1H, H-6), 8.55 (s, 1H, imine). ^{13}C NMR ($CDCl_3$): δ 28.2, 37.8, 109.7, 119.7, 122.8 (2C), 132.4 (2C), 143.2, 150.3, 151.3, 153.5,

Table 2

The products of 1,3-dipolar cycloaddition **5a–h**.

Product 5	R	R^{1}	Reaction time (h)	Yield[a] (%)	Mp (°C)
a	H	Cl	1	50	114–115
b	4-CH_3	Cl	2	51	179–180
c	4-Cl	Cl	1	44	185–187
d	4-Br	Cl	1	47	212–214
e	H	CH_3	2.5	49	202–203
f	4-CH_3	CH_3	2.5	51	181–182
g	4-Cl	CH_3	2.5	44	180–181
h	4-Br	CH_3	2.5	51	184–185

[a] Isolated yield.

162.5. Anal. Calcd. for $C_{13}H_{12}BrN_3O_2$: C, 48.47; H, 3.75; N, 13.04. Found C, 48.85; H, 3.68; N, 12.75.

5-[(4-Nitro-phenylimino)-methyl]-1,3-dimethyl-1H,3H-pyrimidine-2,4-dione (3e). ^{1}H NMR ($CDCl_3$): δ 3.40 (s, 3H, CH_3), 3.54 (s, 3H, CH_3), 6.63 (dt, 2H, J = 9.0 Hz, 2.6 Hz, arom.), 8.07 (m, 3H, H-6, arom.), 10.04 (s, 1H, imine). ^{13}C NMR ($CDCl_3$): δ 28.0, 38.2, 69.3, 110.4, 113.5 (2C), 126.5 (2C), 147.7, 151.1, 152.7, 162.1. Anal. Calcd. for $C_{13}H_{12}N_4O_4$: C, 54.17; H, 4.20; N, 19.44. Found: C, 53.88; H, 3.87; N, 19.06.

1,3-Dimethyl-5-[(3-methylphenyimino)-methyl]-1H,3H-pyrimidine-2,4-dione (3f). ^{1}H NMR ($CDCl_3$): δ 2.37 (s, 3H, CH_3, *m*-tol), 3.41 (s, 3H, CH_3), 3.53 (s, 3H, CH_3), 6.97–7.06 (m, 3H, arom.), 7.26 (t, 1H, J = 8.0 Hz, arom.), 8.32 (s, 1H, H-6), 8.61 (s, 1H, imine). ^{13}C NMR ($CDCl_3$): δ 21.5, 28.2, 37.8, 109.8, 118.2, 121.7, 127.3, 129.2, 139.2, 142.6, 147.6, 151.3, 153.0, 162.5. Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.36; H, 5.88; N, 16.33. Found: C, 64.98; H, 5.55; N, 15.98.

5-[(3-chloro-phenylimino)-methyl]-1,3-dimethyl-1H,3H-pyrimidine-2,4-dione (3g). ^{1}H NMR ($CDCl_3$): δ 3.41 (s, 3H, CH_3), 3.53 (s, 3H, CH_3), 7.02 (d, 1H, J = 8.0 Hz, arom.), 7.14 (m, 1H, arom.), 7.18 (d, 1H, J = 8.0 Hz, arom.), 7.29 (t, 1H, J = 8.0 Hz, arom.), 8.24 (s, 1H, H-6), 8.54 (s, 1H, imine). ^{13}C NMR ($CDCl_3$): δ 28.2, 37.8, 109.5, 119.4, 121.4, 126.2, 130.3, 134.9, 143.4, 151.3, 152.7, 154.2, 162.4. Anal. Calcd. for $C_{13}H_{12}ClN_3O_2$: C, 56.23; H, 4.36; N, 15.13. Found: C, 55.92; H, 3.98; N, 14.87.

5-[(3-Bromo-phenylimino)-methyl]-1,3-dimethyl-1H,3H-pyrimidine-2,4-dione (3h). ^{1}H NMR ($CDCl_3$): δ 3.41 (s, 3H, CH_3), 3.54 (s, 3H, CH_3), 7.07 (dq, 1H, J = 7.5 Hz, 1.3 Hz, arom.), 7.23 (t, 1H, J = 7.5 Hz, arom.), 7.33 (dt, 2H, J = 7.5 Hz, 1.3 Hz, arom.), 8.24 (s, 1H, H-6), 8.54 (s, 1H, imine). ^{13}C NMR ($CDCl_3$): δ 28.2, 37.8, 109.5, 120.0, 123.0, 124.2, 129.1, 130.6, 143.4, 151.3, 152.8, 154.2, 162.4. Anal. Calcd. for $C_{13}H_{12}BrN_3O_2$: C, 48.47; H, 3.75; N, 13.04. Found: C, 48.09; H, 3.46; N, 12.88.

5-[(3-Iodo-phenylimino)-methyl]-1,3-dimethyl-1H,3H-pyrimidine-2,4-dione (3i). ^{1}H NMR ($CDCl_3$): δ 3.41 (s, 3H, CH_3), 3.54 (s, 3H, CH_3), 7.03–7.15 (m, 2H, arom.), 7.51–7.56 (m, 2H, arom.), 8.30 (s, 1H, H-6), 8.55 (s, 1H, imine). ^{13}C NMR ($CDCl_3$): δ 28.2, 37.9, 94.6, 109.2, 120.6, 129.9, 130.7, 135.7, 143.7, 151.2, 154.2, 162.3. Anal. Calcd. for $C_{13}H_{12}IN_3O_2$: C, 42.30; H, 3.28; N, 11.38. Found: C, 42.05; H, 2.96; N, 11.03.

1,3-Dimethyl-5-[(2-methylphenylmino)-methyl]-1H,3H-pyrimidine-2,4-dione (3j). ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H, CH_3, *o*-tol), 3.41 (s, 3H, CH_3), 3.53 (s, 3H, CH_3), 6.89 (d, 1H, J = 6.9 Hz, arom.), 7.09–7.21 (m, 3H, arom.), 8.23 (s, 1H, H-6), 8.46 (s, 1H, imine). ^{13}C NMR ($CDCl_3$): δ 18.0, 28.1, 37.8, 110.0, 118.1, 126.0, 126.9, 130.4, 131.8, 142.8, 150.6, 151.4, 152.4, 162.6. Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.36; H, 5.88; N, 16.33. Found: C, 64.97; H, 5.52; N, 15.98.

5-[(2-chloro-phenylimino)-methyl]-1,3-dimethyl-1H,3H-pyrimidine-2,4-dione (3k). ^{1}H NMR ($CDCl_3$): δ 3.41 (s, 3H, CH_3), 3.54 (s, 3H, CH_3), 7.00 (dd, 1H, J = 7.7 Hz, 1.6 Hz, arom.), 7.13 (dt, 1H, J = 7.7 Hz, 1.6 Hz, arom.), 7.24 (dq, 1H, J = 7.7 Hz, 1.6 Hz, arom.), 7.41 (dd, 1H, J = 7.7 Hz, 1.6 Hz, arom.), 8.32 (s, 1H, H-6), 8.50 (s, 1H, imine). ^{13}C NMR ($CDCl_3$): δ 28.2, 37.8, 109.6, 120.2, 126.8, 127.8, 128.2, 130.0, 143.7, 149.0, 151.4, 155.0, 162.4. Anal. Calcd. for $C_{13}H_{12}ClN_3O_2$: C, 56.23; H, 4.36; N, 15.13. Found: C, 56.56; H, 4.32; N, 14.91.

5-[(2-Bromo-phenylimino)-methyl]-1,3-dimethyl-1H,3H-pyrimidine-2,4-dione (3l). ^{1}H NMR ($CDCl_3$): δ 3.13 (s, 3H, CH_3), 3.26 (s, 3H, CH_3), 6.61 (dd, 1H, J = 7.9 Hz, 1.2 Hz, arom.), 6.77 (dt, 1H, J = 7.9 Hz, 1.2 Hz, arom.), 7.02 (dt, 1H, J = 7.9 Hz, 1.2 Hz, arom.), 7.31 (dd, 1H, J = 7.9 Hz, 1.2 Hz, arom.), 8.03 (s, 1H, H-6), 8.18 (s, 1H, imine). ^{13}C NMR ($CDCl_3$): δ 28.2, 37.9, 109.5, 118.5, 120.0, 127.0, 128.6, 133.1, 143.7, 150.2, 151.4, 154.7, 162.4. Anal. Calcd. for $C_{13}H_{12}BrN_3O_2$: C, 48.47; H, 3.75; N, 13.04. Found: C, 48.23; H, 3.54; N, 12.85.

General procedure for synthesis of 5-[3-(4-chlorophenyl)-(4-substituted-phenyl)-4,5-dihydro-1,2,4-oxadiazol-5-yl]-1,3-dimethyl-1*H*,3*H*-pyrimidine-2,4-dione (5a–d). To a solution of 4-chlorobenzaldoxime (0.12 g, 0.77 mmol) in $CHCl_3$ (4 mL) NCS (0.11 g, 0.85 mmol) was added at room temperature while stirring. The reaction mixture changed the color from light yellow, through blue to green. Completion of the reaction was indicated by the turn the color of reaction mixture to yellow (40 min). The solution of 4-chlorobenzohydroximinoyl chloride was washed with small amounts of cold water (2 mL), dried over anhydrous $MgSO_4$, and immediately used for the next step. To the solution of 4-chlorobenzohydroximinoyl chloride the imine **3a–d** (0.7 mmol) was added followed by addition of triethylamine (0.11 mL, 0.77 mmol). The reaction mixture was refluxed for the time indicated in Table 2, concentrated under diminished pressure, and purified on silica gel packed column using AcOEt:*n*-hexane (1:1) as an eluent. The products **5a–d** were obtained as solid colorless materials, crystallized if necessarily from methanol.

The same procedure starting from the same molar amounts of substrates was applied for preparation of 4-methylbenzonitrile oxide **4b**. The 1,3-dipolar cycloaddition of **4b** to aldimines **3a–d** was carried out under conditions described earlier. The products **5e–h** were purified by silica gel packed column using a (1:1) mixture of *n*-hexane-ethyl acetate as eluent, in the form of colorless solids.

5-[3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1,2,4-oxadiazol-5-yl]-1,3-dimethyl-1H,3H-pyrimidine-2,4-dione (5a). ^{1}H NMR ($CDCl_3$): δ 3.39 (s, 3H, CH_3), 3.42 (s, 3H, CH_3), 6.64 (s, 1H, oxadiaz.), 7.09 (d, 2H, J = 7.7 Hz, arom.), 7.15 (t, 1H, J = 7.7 Hz, arom.), 7.25 (d, 2H, J = 7.7 Hz, arom.), 7.30 (dt, 2H, J = 8.6 Hz, 1.9 Hz, arom.), 7.52 (s, 1H, H-6), 7.57 (dt, 2H, J = 8.6, 1.9 Hz, arom.). ^{13}C NMR ($CDCl_3$): δ 27.9, 37.4, 94.6, 110.5, 123.8, 124.3 (2C), 126.0, 129.1 (2C), 129.3 (2C), 129.3 (2C), 137.0, 142.0, 142.1, 151.4, 154.8, 161.9. Anal. Calcd. for $C_{20}H_{17}ClN_4O_3$: C, 60.53; H, 4.32; N, 14.12. Found: C, 60.14; H, 3.98; N, 13.88.

5-[3-(4-chlorophenyl)-4-(4-methylphenyl)-4,5-dihydro-1,2,4-oxadiazol-5-yl]-1,3-dimethyl-1H,3H-pyrimidine-2,4-dione (5b). ^{1}H NMR ($CDCl_3$): δ 2.28 (s, 3H, CH_3, *p*-tol), 3.38 (s, 3H, CH_3), 3.42 (s, 3H, CH_3), 6.59 (s, 1H, oxadiaz.), 6.97 (d, 2H, J = 8.4 Hz, arom.), 7.05 (d, 2H, J = 8.4 Hz, arom.), 7.29 (d, 2H, J = 8.6 Hz, arom.), 7.51 (s, 1H, H-6), 7.56 (d, 2H, J = 8.6 Hz, arom.). ^{13}C NMR ($CDCl_3$) δ: 21.0, 28.0, 37.6, 94.8, 110.8, 124.0, 124.9 (2C), 129.1 (2C), 129.5 (2C), 130.1 (2C), 136.3, 137.0, 139.4, 142.3, 151.6, 155.1, 162.0. Anal. Calcd. for $C_{21}H_{19}ClN_4O_3$: C, 61.39; H, 4.66; N, 13.64. Found: C, 61.62; H, 4.65; N, 13.29.

5-[3-(3,4-bis-(4-chlorophenyl)-4,5-dihydro-1,2,4-oxadiazol-5-yl]-1,3-dimethyl-1H,3H-pyrimidine-2,4-dione (5c). ^{1}H NMR ($CDCl_3$): δ 3.39 (s, 3H, CH_3), 3.42 (s, 3H, CH_3), 6.59

(s, 1H, oxadiaz.), 7.10 (dt, 2H, J = 8.9 Hz, 2.4 Hz, arom.), 7.22 (dt, 2H, J = 8.9 Hz, 2.4 Hz, arom.), 7.32 (dt, 2H, J = 8.6 Hz, 2.2 Hz, arom.), 7.51 (s, 1H, H-6), 7.55 (dt, 2H, J = 8.6 Hz, 2.2 Hz, arom.). ^{13}C NMR ($CDCl_3$): δ 28.1, 37.6, 94.8, 110.3, 123.6, 126.0 (2C), 129.4 (2C), 129.5 (2C), 129.6 (2C), 131.9, 137.4, 140.9, 142.3, 151.5, 154.9, 162.1. Anal. Calcd. for $C_{20}H_{16}Cl_2N_4O_3$: C, 55.70; H, 3.74; N, 12.99. Found: C, 55.31; H, 3.39; N, 12.67.

5-[3-(4-chlorophenyl)-4-(4-bromo-phenyl)-4,5-dihydro-1,2,4-oxadiazol-5-yl]-1,3-dimethyl-1H,3H-pyrimidine-2,4-dione (5d). ^{1}H NMR ($CDCl_3$): δ 3.39 (s, 3H, CH_3), 3.42 (s, 3H, CH_3), 6.59 (s, 1H, oxadiaz.), 7.04 (d, 2H, J = 8.6 Hz, arom.), 7.32 (d, 2H, J = 8.7 Hz, arom.), 7.37 (d, 2H, J = 8.6 Hz, arom.), 7.50 (s, 1H, H-6), 7.55 (d, 2H, J = 8.7 Hz, arom.). ^{13}C NMR ($CDCl_3$): δ 28.1, 37.6, 94.7, 110.3, 119.6, 123.6, 126.2 (2C), 129.4 (2C), 129.5 (2C), 132.6 (2C), 137.4, 141.4, 142.4, 151.5, 154.8, 162.1. Anal. Calcd. for $C_{20}H_{16}BrClN_4O_3$: C, 50.50; H, 3.39; N, 11.78. Found: C, 50.09; H, 2.98; N, 11.39.

1,3-Dimethyl-5-[4-phenyl-3-(4-methylphenyl)-4,5-dihydro-1,2,4-oxadiazol-5-yl]-1H,3H-pyrimidine-2,4-dione (5e). ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H, CH_3, *p*-tol), 3.39 (s, 3H, CH_3), 3.41 (s, 3H, CH_3), 6.66 (s, 1H, oxadiaz.), 7.08–7.15 (m, 5H, arom.), 7.21–7.26 (m, 2H, arom.), 7.53 (m, 3H, H-6, arom.). ^{13}C NMR ($CDCl_3$): δ 21.6, 28.0, 37.6, 94.2, 110.9, 122.5, 124.2 (2C), 125.7, 128.1 (2C), 129.3 (2C), 129.6 (2C), 141.5, 142.3, 142.5, 151.6, 155.6, 162.2. Anal. Calcd. for $C_{21}H_{20}N_4O_3$: C, 67.01; H, 5.36; N, 14.88. Found: C, 66.87; H, 4.98; N, 14.49.

1,3-Dimethyl-5-[3,4-di-(4-methylphenyl)-4,5-dihydro-1,2,4-oxadiazol-5-yl)-1H,3H-pyrimidine-2,4-dione (5f). ^{1}H NMR ($CDCl_3$): 2.27 (s, 3H, CH_3, *p*-tol), 2.33 (s, 3H, CH_3, *p*-tol), 3.38 (s, 3H, CH_3), δ 3.41 (s, 3H, CH_3), 6.61 (s, 1H, oxadiaz.), 6.98 (d, 2H, J = 8.6 Hz, arom.), 7.03 (d, 2H, J = 8.6 Hz, arom.), 7.12 (d, 2H, J = 8.0 Hz, arom.), 7.52 (d, 2H, J = 8.0 Hz, arom.) 7.54 (s, 1H, H-6). ^{13}C NMR ($CDCl_3$): δ 21.0, 21.60, 28.0, 37.6, 94.2, 111.1, 122.5, 124.5 (2C), 128.2 (2C), 129.5 (2C), 129.9 (2C), 135.8, 139.8, 141.3, 142.2, 151.6, 155.8, 162.2. Anal. Calcd. for $C_{22}H_{22}N_4O_3$: C, 67.68; H, 5.68; N, 14.35. Found: C, 67.28; H, 5.33; N, 14.01.

5-[4-(4-chlorophenyl)-3-(4-methylphenyl)-4,5-dihydro-1,2,4-oxadiazol-5-yl]-1,3-dimethyl-1H,3H-pyrimidine-2,4-dione (5g). ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H, CH_3, *p*-tol), 3.39 (s, 3H, CH_3), 3.41 (s, 3H, CH_3), 6.60 (s, 1H, oxadiaz.), 7.10 (d, 2H, J = 8.9 Hz, arom.), 7.15 (d, 2H, J = 8.1 Hz, arom.), 7.20 (d, 2H, J = 8.9 Hz, arom.), 7.51 (d, 2H, J = 8.1 Hz, arom.) 7.54 (s, 1H, H-6). ^{13}C NMR ($CDCl_3$): δ 21.6, 28.1, 37.6, 94.2, 110.5, 122.1, 125.6 (2C), 128.2 (2C), 129.4 (2C), 129.7 (2C), 131.3, 141.3, 141.8, 142.3, 151.6, 155.5, 162.2. Anal. Calcd. for $C_{21}H_{19}ClN_4O_3$: C, 61.39; H, 4.66; N, 13.64. Found: C, 61.02; H, 4.34; N, 13.35.

5-[4-(4-Bromophenyl)-3-(4-methylphenyl)-4,5-dihydro-1,2,4-oxadiazol-5-yl]-1,3-dimethyl-1H,3H-pyrimidine-2,4-dione (5h). ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H, CH_3, *p*-tol), 3.39 (s, 3H, CH_3), 3.41 (s, 3H, CH_3), 6.60 (s, 1H, oxadiaz.), 7.04 (d, 2H, J = 8.9 Hz, arom.), 7.15 (d, 2H, J = 8.1 Hz, arom.), 7.35 (d, 2H, J = 8.9 Hz, arom.), 7.51 (d, 2H, J = 8.1 Hz, arom.) 7.53 (s, 1H, H-6). ^{13}C NMR ($CDCl_3$): δ 21.6, 28.1, 37.6, 94.1, 110.5, 119.1, 122.1, 125.9 (2C), 128.1 (2C), 129.8 (2C), 132.3 (2C), 141.8, 142.3, 151.6, 155.5, 162.2. Anal. Calcd. for $C_{21}H_{19}BrN_4O_3$: C, 55.40; H, 4.21; N, 12.31. Found: C, 54.99; H, 3.85; N, 11.98.

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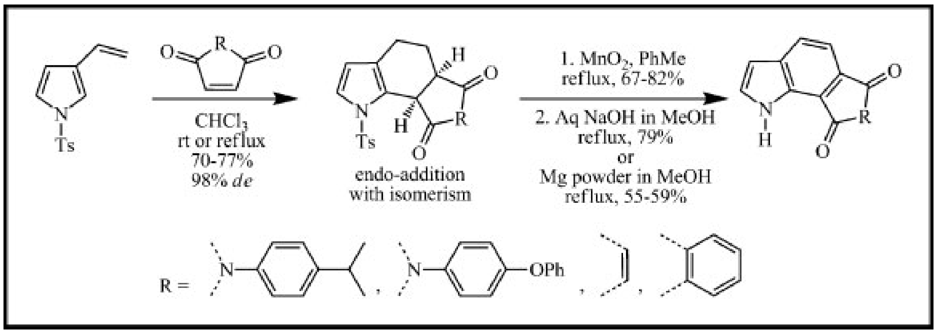

N-*p*-Toluenesulfonyl-3-vinylpyrrole underwent *endo*-addition [4 + 2] cycloaddition reactions with maleimides and benzoquinones, followed by isomerization to give tetrahydroindoles in good yields. Dehydrogenation with activated MnO$_2$ in refluxing toluene gave the corresponding indoles in fair to good yields. Detosylation *via* saponification or with magnesium in refluxing methanol gave the *N*-H indoles in moderate to good yields. This method for formation of indoles is both convergent and versatile and uses starting materials that are conveniently prepared.

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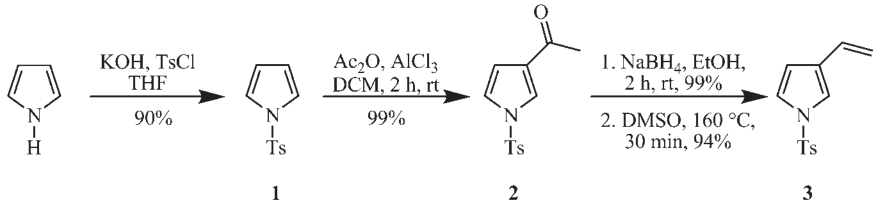
INTRODUCTION

Synthesis of the indole nucleus continues to receive much attention [1] due to its common occurrence in the molecules of living systems and also the biological activity exhibited in both natural [2] and synthetic [3] indole-containing products. We have reported that tetrahydroindoles are available *via* 2-vinylpyrroles derived from an acid-catalyzed condensation of pyrrole with cyclic ketones, followed by *in situ* trapping by various maleimides in a Diels-Alder reaction [4,5]. We recently reported that indoles are available from oxidation of tetrahydroindoles synthesized by Diels-Alder reactions of both *N*-H and *N*-alkyl-2-vinylpyrroles with a wide range of *N*-substituted maleimides [6]. To expand upon this general methodology, in a desire to find improved synthetic methods towards indole and to generate novel indoles for biological testing, we chose to study the use of 3-vinylpyrroles as the diene in Diels-Alder reactions.

Pyrrole preferentially undergoes electrophilic attack at its 2-position as the most stable resonance structure of the reactive species has its greatest electron density α to the iminium nitrogen. Therefore, 2-vinylpyrroles are the most obviously accessible vinylated pyrroles, and there are numerous examples of 2-vinylpyrroles being used as dienes in Diels-Alder reactions [4,7–10]. Several of these studies report biological activity from the resulting class of compounds and the corresponding aromatized indoles, particularly anti-cancer activity [4,10].

To the best of our knowledge, only four reports of 3-vinylpyrroles being used in Diels-Alder reactions exist [8,9,11,12]. Jones *et al*. reported the Diels-Alder reaction of *N*-*t*-butyl-3-vinylpyrrole with DMAD and oxidation with DDQ to give the corresponding indoles [8]. Murase *et al*. reported Diels-Alder reactions of sulfur-substituted *N*-methyl-3-vinylpyrrole generated *in situ* from the corresponding 3-thioacetylpyrrole, using as the dienophile DMAD, maleic anhydride, *N*-methylmaleimide, 1,4-naphthoquinone, and several unsymmetrical alkenes, followed by DDQ aromatization of the indoles [11]. The Diels-Alder adducts were not isolated, but were oxidized directly to the indoles in a maximum of 31% yield over three steps. Xiao and Ketcha reported Diels-Alder reactions of *N*-benzenesulfonyl-3-vinylpyrrole and ethyl 3-(1-(benzenesulfonyl)-1*H*-2-pyrrolyl)acrylate with *N*-phenylmaleimide and maleic anhydride, without taking the adducts through to the indoles [9]. Most recently, Hodges *et al*. reported Diels-Alder reactions of osmium-complexed *N*-methyl-3-vinylpyrroles with *N*-phenylmaleimide to give tetrahydroindoles, which were then oxidized with DDQ to give the corresponding indoles, but difficulties with oxidation and pyrrole polymerization were experienced [12]. In most of the prior examples of Diels-Alder reactions of 3-vinylpyrroles, the isolated tetrahydroindole had isomerized from the originally formed adducts, with a double bond having moved into the five-membered ring to form the aromatic pyrrole. In the one exception, the work by Hodges *et al*. [12], the

Scheme 1. Synthesis of *N*-*p*-toluenesulfonyl-3-vinylpyrrole **3**.



unrearranged adduct was complexed with osmium when isolated.

The synthesis of 3-vinylpyrrole was first reported, to the best of our knowledge, in 1979 by Jones *et al*., by the photoaddition of acetaldehyde and *N*-methylpyrrole followed by dehydration of the resulting alcohol to *N*-methyl-3-vinylpyrrole in 32% overall yield [13]. A more efficient method uses 3-(*N*-*t*-butylpyrrole)carboxaldehyde in a Wittig methylenation in 55% overall yield [14]. The *t*-butyl group, due to its steric bulk, directs selective Vilsmeier-Haack formylation to the 3-position. The most efficient method to 3-vinylate pyrrole is likely *via* *N*-benzenesulfonylation followed by 3-acetylation under Friedel-Crafts acylation conditions using AlCl$_3$ as the Lewis acid, which selectively acetylates the 3-position [15–17]. The resulting acetylpyrrole is then reduced and dehydrated to the 3-vinylpyrrole [9,17]. An extensive study by Huffman *et al*. indicates that subjecting *N*-*p*-toluenesulfonylpyrrole to Friedel-Crafts acylation conditions using AlCl$_3$ does not result in a Friedel-Crafts-type acylation, but instead causes reversible formation of 2- and 3-dichloroaluminum intermediates, the latter being sterically favored, and the former possibly experiencing a stabilizing electronic interaction between the electrophilic aluminum and an oxygen of the *N*-sulfonyl group [18]. The predominant and more reactive 3-substituted organoaluminum intermediate then reacts with the acylating agent to give mainly 3-acylpyrroles.

While altering the side to which the dienophile-component is fused in the resulting tetrahydroindole, using 3-vinylpyrroles in Diels-Alder reactions is significantly advantageous over the use of 2-vinylpyrroles. 2-Vinylpyrroles are generally volatile liquids which polymerize or decompose on exposure to air and light, but *N*-*p*-toluenesulfonyl-3-vinylpyrroles are robust crystalline solids which are easy to store and handle. 2-Vinylpyrroles are most efficiently made from pyrrole-2-carboxaldehyde or from the 2-acylpyrrole *via* a Wittig reaction in ~50% yield over two steps from *N*-H-pyrrole [6,19]. In comparison, *N*-*p*-toluenesulfonyl-3-vinylpyrrole is generated using the Lewis Acid-catalyzed process outlined above in 83% yield from *N*-H-pyrrole over four steps, a sizable increase in efficiency. In most of the prior examples, the 2-vinylpyrroles are *N*-alkylated due to the high reactivity and tendency towards polymerization and decomposition of *N*-H-2-vinylpyrroles, whereas an *N*-*p*-toluenesulfonyl group decreases reactivity, increases stability, and may be removed later to give the *N*-H-indole derivative, or the H can then be replaced with another group of choice.

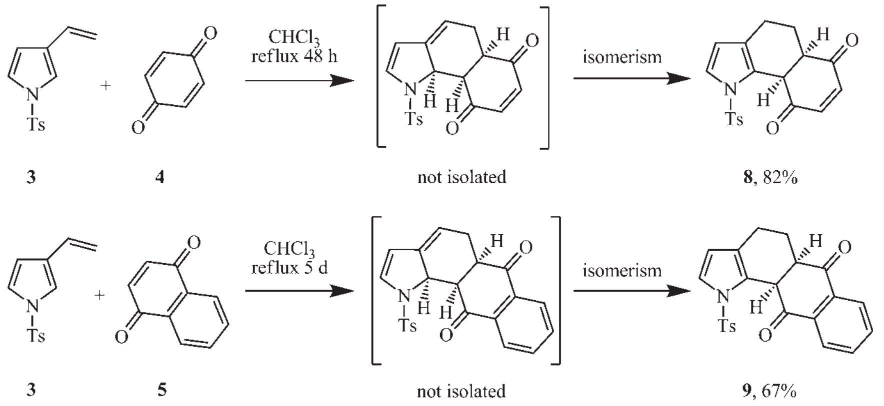
RESULTS AND DISCUSSION

Synthesis of starting materials. Vinylpyrrole **3** was prepared in 83% overall yield in four steps from pyrrole by literature methods (Scheme 1) [9,15,17,20].

Commercial *p*-benzoquinone **4** and 1,4-naphthoquinone **5** were used. *N*-(4-Isopropylphenyl)maleimide **6** and *N*-(4-phenoxyphenyl)maleimide **7** were synthesized by reported procedures [6,21]. Flash chromatography on silica gel, followed by recrystallization, was used to purify the maleimides.

Diels-Alder reactions. Diels-Alder reactions of *N*-*p*-toluenesulfonyl-3-vinylpyrrole **3** with *p*-benzoquinone **4**, 1,4-naphthoquinone **5**, *N*-(4-isopropylphenyl)maleimide **6**, and *N*-(4-phenoxyphenyl)maleimide **7** in chloroform gave compounds **8**, **9**, **10**, and **11**, respectively (Schemes 2 and 3). The reactions were monitored by TLC. While the maleimide-containing reactions which gave adducts **10** and **11** went to completion at rt over 5 days, the Diels-Alder reactions giving **8** and **9** required, for completion, refluxing for 48 h and 5 days, respectively. In each reaction, the vinylpyrrole was used in slight excess (1.1 equiv.) to simplify the required chromatographic purification procedure, because the vinylpyrroles were always eluted first, unreacted maleimides or quinones were eluted very close to the adducts. Chromatography on silica gel, followed by recrystallization, was used to purify the adducts. Conditions for the Diels-Alder reactions were not optimized, except that chloroform was used as the solvent, which is based on the considerably higher yields obtained in our earlier work in Diels-Alder reactions with 2-vinylpyrroles in chloroform *versus* toluene [6].

In Diels-Alder reactions with *p*-benzoquinone and 1,4-naphthoquinone, unisomerized adducts were not isolated or detected; instead compounds **8** and **9** were isolated, in which a double-bond had moved into the five-membered ring, giving the more stable aromatic

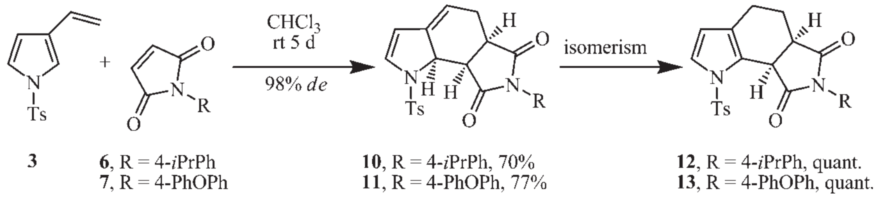


Scheme 2. Diels-Alder reactions of *N-p*-toluenesulfonyl-2-vinylpyrrole **3** with quinones **4** and **5**.

pyrrole. In Diels-Alder reactions with maleimides, however, the unisomerized adducts **10** and **11** were isolated first, and quantitative isomerization of these compounds into the aromatic **12** and **13** occured in chloroform at rt over a month, or over several days at reflux (Scheme 3). Although unisomerized adducts were not isolated in our 2-vinylpyrrole work, evidence of them as intermediates was provided by the isolation of products likely resulting from a Michael addition of an unisomerized adduct with a maleimide [6]. NOE experiments were used to confirm the stereochemistry of **10** and **11**. This seems to be the first report of the isolation of unisomerized Diels-Alder adducts being formed from vinylpyrroles. The average yield of the Diels-Alder products **8**, **9**, **10**, and **11** was 74%, nearly identical with the 73% average for Diels-Alder products from 2-vinylpyrrole obtained in chloroform in our prior work [6], although a greater number of Diels-Alder reactions of 3-vinylpyrroles would be needed for an accurate comparison of the relative efficiency of the two procedures.

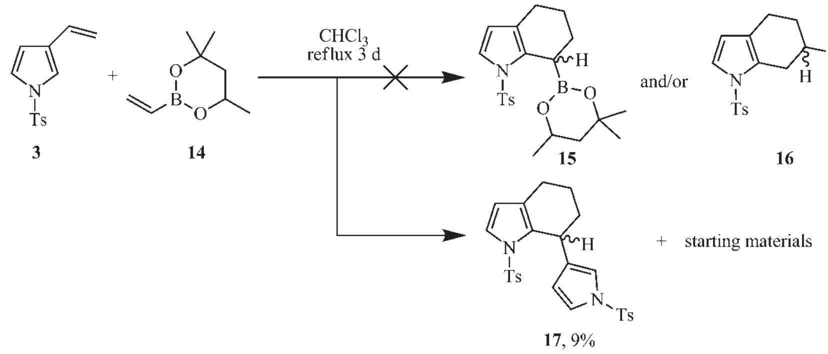
For descriptions of orientation, the diastereomer with the *cis*-protons at the points of diene fusion protruding from the α-face and the fused-dienophile protruding from the β-face will always be used; this convention is also used throughout the Experimental. In the ^{1}H NMR spectra of unisomerized adducts **10** and **11**, the 5α-H proton appears as a doublet of doublet of doublet of doublets; COSY experiments indicate that the 5α-H proton is coupled not only to the 5β-H, 4-H, and 5aα-H protons, but also to the 8bα-H proton, with a coupling constant of about 3.0 Hz [9,22]. For isomerized adduct **8**, the 7-H proton is coupled not only to the 8-H proton but also to the 5aα-H proton, with a coupling constant of about 1.2 Hz [23].

Diels-Alder dimerization. In an effort to extend our method to allow for a highly convergent synthetic step after indole formation *via* a potential Suzuki coupling [24], a Diels-Alder reaction between *N-p*-toluenesulfonyl-3-vinylpyrrole **3** and commercially available vinylboronic acid 2-methyl-2,4-pentanediol ester **14** was attempted (Scheme 4) [25]. Although Diels-Alder reactions of vinylboranes [26], vinylboronates [27], and of **14** [28] are known, to the best of our knowledge they are not reported to have occurred with vinylpyrroles. No reaction was observed to occur in chloroform at room temperature over 5 days, so the solution was refluxed. After 3 days, a new TLC spot had appeared, and no further consumption of the vinylpyrrole **3** seemed to be occurring. Isolation of the single new product from the remaining starting materials and purification revealed *via* ^{1}H NMR that the new product was in fact not the expected Diels-Alder adduct **15** and/or **16**, as it lacked any of the characteristic aliphatic methyl groups from vinyl boronate **14**. Characterization of this product using HRMS, COSY, and NOE studies showed it to be the result of a formal Diels-Alder reaction between two molecules of *N-p*-toluenesulfonyl-3-vinylpyrrole **3**, giving the dimer **17** (Fig. 1). In the ^{1}H NMR, the 4α-H and 4β-H protons were overlapped, which prevented distinguishing between them in the NOE study.



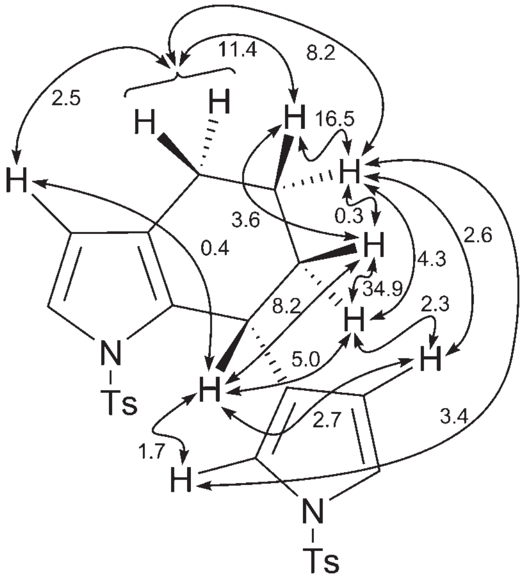
Scheme 3. Diels-Alder reactions of *N-p*-toluenesulfonyl-2-vinylpyrrole **3** with maleimides **6** and **7**.

Scheme 4. Attempted Diels-Alder reaction of *N*-*p*-toluenesulfonyl-3-vinylpyrrole **3** with vinylboronate **14**.



Formation of dimer **17** would occur when two vinylpyrroles approach each other with the terminal ends of their vinyl groups nearest to one another, but would seem to maximize proximity of repulsive like partial-charges and to violate the *ortho*/*para* rule [29] of adduct substitution in Diels-Alder reactions. Refluxing *N*-*p*-toluenesulfonyl-3-vinylpyrrole **3** in toluene or chloroform without vinylboronate **14** for 2 weeks produced no sign of dimer **17** by ^{1}H NMR and HRMS analysis; only starting materials were shown to be present by ^{1}H NMR. Refluxing 100 mg of *N*-*p*-toluenesulfonyl-3-vinylpyrrole **3** in 10 mL of chloroform with one drop of concentrated hydrochloric acid for several days produced no sign of dimer **17** by TLC analysis; only starting materials were present. It is likely that the vinylboronate acted as a Lewis acid and activated a vinylpyrrole to form the dimer **17**.

Considering the electron-rich nature of vinylpyrrole systems, the reaction reported above seems unexpected. Examples of compounds undergoing Diels-Alder-dimerization include butadiene [30], natural products [31], 2-styrylindolizine [32], 2-vinylindoles [33,34], 3-vinylindoles [35,36], and 2-vinylpyrroles [37]. Several of these dimeric products violate the '*ortho*/*para*' rule [34,36,37], and in each case the diene and the dienophile is connected to an electron-donating substituent, the nitrogen atom of the pyrrole ring, as in the present case, but no Lewis acid was present. This type of '*meta*' regioselectivity in Diels-Alder reactions having electron-donating substituents on the diene and dienophile was predicted by Houk in 1972 using frontier molecular orbital theory [38,39], and it has been experimentally observed in nondimerization Diels-Alder reactions not involving pyrrole as well (between the diene generated from benzocyclobutenes with the dienophiles propyne and ethoxyethene) [40]. As in some of the examples of *ortho*/*para* rule violation [34,36,37,40], a steric argument may also be made to help explain the formation of the dimer **17**, especially considering that in the present case dimer formation did not occur without the Lewis acid. This can be rationalized if one molecule of **3** complexes with the boronate **14** acting as a Lewis acid present at the more basic, terminal end of **3**. This may cause the terminal end of the vinylpyrrole to be so sterically bulky as to prohibit approach by either a free vinylpyrrole in the normal *ortho*/*para* regiochemistry or another Lewis acid-complexed vinylpyrrole (statistically unlikely), allowing only the approach of a free vinylpyrrole with the pyrrole ring farthest from the complexing-Lewis acid. The electrons of the nitrogen of the noncomplexed vinylpyrrole may then drive an attack from the α-carbon of that pyrrole to the α-carbon of the vinyl group of the complexed pyrrole, the positive charge of which is induced by complexation with the Lewis acid (Fig. 2). This is followed by dissociation of the catalyst and concomitant formation of a bond between the terminal carbons of each



*Numbers indicate percent enhancement

Figure 1. Relevant NOE interactions for Diels-Alder dimer **17***.

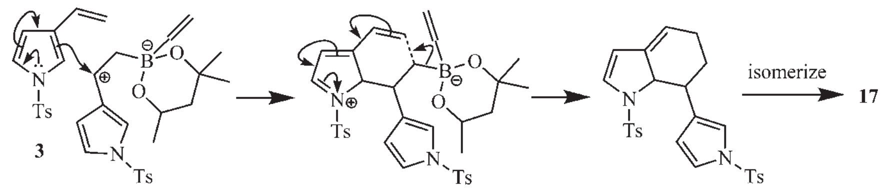


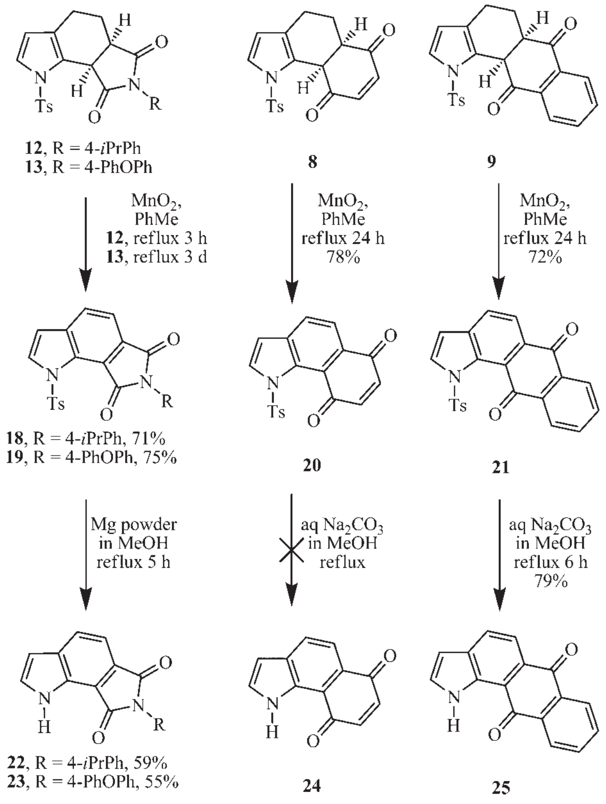
Figure 2. Formation of the 3-vinylpyrrole dimer **17**.

vinylpyrrole. Then, isomerization of the double bond in the adduct gives the observed 7-pyrrolyl-substituted tetrahydroindole **17**. In this proposed mechanism, nucleophilic attack by the free pyrrole in the first step effectively allows reversal of the normal polarity of the terminus of its vinyl group, allowing the second carbon-carbon bond formation, an example of umpolung [41]. Further studies are currently underway in our labs to determine the scope of such a dimerization approach towards indoles.

Aromatization of Diels-Alder adducts. Tetrahydroindoles **12**, **13**, **8**, and **9** were aromatized using MnO_2 in refluxing toluene for 3–72 h, giving **18**, **19**, **20**, and **21** in 71, 75, 78, and 72% yields, respectively (Scheme 5). The most consistent and high-yielding results were achieved using MnO_2 generated from manganese(II) sulfate and potassium permanganate [42], which was also used in our 2-vinylpyrrole work [6]. The average yield from dehydrogenations was 74%, higher than the 54% average achieved in aromatizing the adducts resulting from 2-vinylpyrrole, indicating that the tosyl group may help to facilitate the reaction or provide some degree of stability to the tetrahydroindoles during the aromatization process [6].

Detosylation of *N*-*p*-toluenesulfonylindoles. Detosylation of maleimide-derived indoles **18** and **19** was accomplished by magnesium in refluxing methanol for 5 h, giving **22** and **23** in 59 and 55% yield, respectively (Scheme 5) [43]. Detosylation of 1,4-naphthoquinone-derived indole **21** [44] was effected by saponification with aqueous sodium carbonate in methanol under reflux for 6 h. With saponification of **18** and **19**, competition between removal of the *p*-toluenesulfonyl group and hydrolysis of the imide was observed. When these two methods were applied to the *p*-benzoquinone-derived indole **20**, decomposition occurred with no recovery of starting materials. Various other methods were attempted, such as TBAF in refluxing THF/MeOH [45], 5% sodium-mercury amalgam in THF/MeOH [46], the dilithium salt of thioglycolate in DMF [47], and concentrated sulfuric acid [48], but none of these methods gave the desired *N*-H indole **24**. The failure to achieve compound **24** is likely due to the α,β-unsaturated dione portion of indole **20**, which is acting as a strong Michael acceptor. An example exists of saponification failing to detosylate an *N*-tosyl compound containing such a dione portion [49], an *N*-*p*-toluenesulfonyl-1*H*-indole-4,7-dione, but some precedent exists for detosylation of such compounds using TBAF in THF [50]. However, 1*H*-indole-4,7-diones may be distinguished from **20** because the carbonyls of these compounds are in more direct conjugation with the electron-releasing nitrogen, causing deactivation. If the conjugated dione of compound **20** indeed prevented its detosylation by the means attempted, then a masking technique could be used, such as reduction of **20** and formation of the *bis*-silyl ether [51], detosylation *via* conventional means, then desilylation followed by tautomerization to the quinone [52] to give *N*-H indole **24**. Such a route toward **24** is currently under investigation in our labs.

Scheme 5. Aromatization and detosylation of tetrahydroindoles **8**, **9**, **12**, and **13**.



Biological activity. While participating in the Developmental Therapeutics Program at the National Cancer Institute (NCI), we submitted eight compounds to the NCI for a one-dose 60-human tumor cell line prescreen: compounds **8**, **9**, **12**, **13**, **18**, **19**, **20**, and **21**. Of these, four compounds, **8**, **9**, **20**, and **21**, were judged by the NCI to have sufficient activity to justify screening with 60 human-tumor cell lines at five concentrations with 10-fold dilutions, from 1×10^{-4} M to 1×10^{-8} M. All four of these compounds were found to have high levels of activity against many of the 60 different cell lines tested. Compound **8** was most active against colon cancer HCT-116, melanoma M14, and nonsmall cell lung cancer, with IC_{50}'s of 67, 63, and 37 ng/mL, respectively. Compound **9** was most active against melanoma M14, and leukemia cell lines CCRF-CEM and HL-60(TB), with IC_{50}'s of 11, 13, and 11 ng/mL, respectively. Compound **20** was most active against melanoma UACC-257, and leukemia cell lines MOLT-4 and SR, with IC_{50}'s of 21, 56, and 50 ng/mL, respectively. Compound **21** was most active against CNS cancer SF-295, ovarian cancer OVCAR-3, and melanoma MDA-MB-435, with IC_{50}'s of 10, 9.6, and 9.1 ng/mL, respectively. Compounds **8** and **20** were selected by the NCI for toxicity testing and subsequent hollow fiber testing. Compound **8** had a maximum tolerated dose of 100 mg/Kg body wt in athymic nude mice, with death resulting in 3 days at 200 mg/Kg body wt and 2 days at 400 mg/Kg body wt. Hollow fiber testing of compound **8** against breast cancer MDA-MB-231, nonsmall cell lung cancer NCI-H23 and NCI-H522, colon cancer SW-620 and COLO 205, melanoma LOX IMVI, UACC-62, and MDA-MB-435, ovarian cancer OVCAR-3, CNS cancer U251 and SF-295 gave a score of 4/96 with no cell kill, below the 20/96 minimum score required for selection for xenograft testing. Toxicity and hollow fiber testing data for compound **20** were pending at the time of submission of this article.

CONCLUSION

N-*p*-Toluenesulfonyl-3-vinylpyrrole underwent *endo*-addition [4 + 2] cycloaddition reactions with *p*-benzoquinone, 1,4-naphthoquinone, and maleimides giving isomerized aromatic tetrahydroindoles with *p*-benzoquinone and 1,4-naphthoquinone, and unisomerized tetrahydroindoles with maleimides. In the presence of vinylboronic acid 2-methyl-2,4-pentanediol ester, *N*-tosyl-3-vinylpyrrole underwent a Diels-Alder dimerization. Dehydrogenation of the tetrahydroindoles with activated MnO_2 in refluxing toluene gave the corresponding indoles. The maleimide-fused indoles were detosylated *via* saponification, and the 1,4-naphthoquinone-fused indole was detosylated with magnesium in refluxing methanol, giving the *N*-H indoles in moderate to good yields. This efficient method for formation of indoles offers high convergency and easily accessible starting materials.

EXPERIMENTAL

General. Solvents and reagents were purchased and used as received. Flash chromatography was performed using 230–450 mesh silica gel. MPLC refers to medium pressure liquid chromatography was performed using 325–635 mesh silica gel. Ethyl acetate/hexanes were used as eluent unless otherwise specified. TLC analyses were performed on plastic-backed plates pre-coated with 0.2 mm silica with F_{254} indicator. Infrared spectra were recorded on a 4000 FT IR spectrometer; only the most intense and/or diagnostic peaks are reported. High-resolution mass spectra were recorded with a time-of-flight instrument using electrospray ionization with PEG as an internal calibrant. For NMR spectra, chemical shifts (δ) were compared to the solvent. ^{13}C NMR spectra were proton-decoupled. Melting points are uncalibrated. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. Petroleum ether refers to the 35–60°C boiling point fraction.

General method for Diels-Alder reactions. A mixture of *N*-*p*-toluenesulfonyl-3-vinylpyrrole **3** (1.237 g, 0.005 mol) and the dienophile (0.0045 mol, 1.1 equiv.) in chloroform (20 mL) was stirred at rt for 24 h and, if TLC analysis indicated insignificant consumption of the dienophile, was refluxed until the reaction was complete. The solvent was removed using a rotating evaporator. The crude adduct was purified by MPLC using ethyl acetate/hexanes as eluent, followed by recrystallization from dichloromethane/petroleum ether, giving the desired product in good yields.

General method for dehydrogenation of Diels-Alder adducts. A mixture of the adduct (0.003 mol) and activated MnO_2 [42] (0.015 mol, 5 equiv.) in toluene (30 mL) was stirred under reflux until the reaction was complete, as indicated by TLC analysis. The mixture was cooled to rt and vacuum-filtered through a fine glass fritted funnel. The insoluble manganese salts were washed using several portions of dichloromethane until the washings ran clear (5 × 20 mL). The combined organic filtrate and washings were evaporated to dryness using a rotating evaporator. MPLC with ethyl acetate/hexanes as eluant, followed by recrystallization from dichloromethane/petroleum ether, gave the desired product in fair to good yields.

1-p-Toluenesulfonyl-4,5,5aα,9aα-tetrahydro-1H-benzo[g]indole-6,9-dione (8). The general method with quinone **4** and reflux for 48 h gave **8** (1.325 g, 82%) as light-yellow crystals: mp 172–174°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.74 (d, J = 8.4 Hz, 2H, Ts), 7.33 (d, J = 8.1 Hz, 2H, Ts), 7.20 (d, J = 3.5 Hz, 1H, 2-H), 6.88 (d, J = 10.2 Hz, 1H, 8-H), 6.70 (dd, J = 10.4, 1.4 Hz, 1H, 7-H), 6.17 (d, J = 3.6 Hz, 1H, 3-H), 4.84 (d, J = 5.7 Hz, 1H, 9aα-H), 3.06 (ddddd, J = 13.2, 5.5, 2.7, 1.4, 0.9 Hz, 1H, 5aα-H), 2.54–2.70 (m, 2H, 4α-H, 4β-H), 2.43 (s, 3H, Ts-CH_3), 2.07 (dddd, J = 13.6, 5.0, 2.5, 2.5 Hz, 1H, 5β-H), 1.68 (dddd, J = 13.2, 13.2, 10.4, 7.4 Hz, 1H, 5aα-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 200.6, 196.5, 145.0, 141.5, 138.9, 136.5, 129.9, 127.2, 124.2, 123.9, 123.3, 112.6, 49.8, 47.3, 26.3, 22.8, 21.8; IR (KBr, cm^{-1}) 3382(w), 3137(w), 3101(w), 3051(m), 2946(m), 2853(m), 1702(s), 1673(s), 1595(m), 1486(w), 1433(w), 1379(s), 1276(m), 1260(m), 1228(m), 1209(w), 1173(s), 1137(m), 1121(s), 1089(s), 1061(m), 1033(m), 986(m), 923(w), 902(w), 850(m), 813(m), 775(w), 734(w), 704(m), 673(s); HRMS m/z (M + Na$^+$) calcd 378.0771, found 378.0782. Anal. Calcd for $C_{19}H_{17}NO_4S$: C, 64.21; H, 4.82; N, 3.94. Found: C, 64.35; H, 4.73; N, 3.88.

1-p-Toluenesulfonyl-4,5,5aα,11aα-tetrahydro-1H-naphtho[2,3-g]indole-6,11-dione (9). The general method with naphthoquinone **5** and reflux for 5 d gave **9** (1.235 g, 67%) as a dark-orange powder: mp 114–116°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.11–8.17 (m, 1H, 10-H), 7.97–8.03 (m, 1H, 7-H), 7.74–7.83 (m, 4H, 8-H, 9-H, Ts), 7.34 (d, *J* = 8.4 Hz, 2H, Ts), 7.40 (d, *J* = 3.3 Hz, 1H, 2-H), 6.20 (d, *J* = 3.3 Hz, 1H, 3-H), 4.99 (d, *J* = 5.4 Hz, 1H, 11aα-H), 3.25 (ddd, *J* = 13.4, 5.3, 2.7 Hz, 1H, 5aα-H), 2.64–2.69 (m, 2H, 4α-H, 4β-H), 2.46 (s, 3H, Ts-CH_3), 2.13 (dddd, *J* = 12.7, 4.1, 2.6, 1.4 Hz, 1H, 5β-H), 1.71 (dddd, *J* = 12.7, 12.7, 8.8, 7.4 Hz, 1H, 5α-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 198.5, 195.5, 144.9, 136.6, 135.9, 134.8, 134.4, 133.3, 129.9, 127.3, 127.2, 127.0, 124.9, 123.8, 123.1, 112.6, 50.1, 47.4, 26.0, 23.0, 21.8; IR (KBr, cm^{-1}) 3140(w), 3067(w), 2920(m), 2853(w), 1702(s), 1687(s), 1594(m), 1485(w), 1434(w), 1400(w), 1364(s), 1291(m), 1272(m), 1243(m), 1208(m), 1175(s), 1142(m), 1127(s), 1106(m), 1089(m), 1058(w), 1043(w), 1027(w), 986(w), 903(w), 812(w), 759(w), 716(m), 703(m), 669(s), 611(w); HRMS m/z (M + Na$^+$) calcd 428.0928, found 428.0943. Anal. Calcd for $C_{23}H_{19}NO_4S$: C, 68.13; H, 4.72; N, 3.45. Found: C, 67.86; H, 4.71; N, 3.36.

7-(4-Isopropylphenyl)-1-p-toluenesulfonyl-5,5aα,8aα,8bα-tetrahydropyrrolo-1H,7H-benzo[g]indole-6,8-dione (10). The general method with maleimide **6** and rt for 5 d gave **10** (1.472 g, 70%) as light-orange crystals: mp 96–98°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.81 (d, *J* = 8.4 Hz, 2H, Ts), 7.35 (d, *J* = 8.4 Hz, 2H, Ts), 7.27 (d, *J* = 8.4 Hz, 2H, *i*PrPh), 7.08 (d, *J* = 8.4 Hz, 2H, *i*PrPh), 6.83 (d, *J* = 4.2 Hz, 1H, 2-H), 5.69 (d, *J* = 3.9 Hz, 1H, 3-H), 5.56 (ddd, *J* = 7.4, 3.8, 3.8 Hz, 1H, 4-H), 4.23 (ddd, *J* = 6.9, 3.3, 3.4 Hz, 1H, 8bα-H), 3.97 (dd, *J* = 9.0, 7.2 Hz, 1H, 8aα-H), 3.23 (ddd, *J* = 9.0, 7.2, 1.8 Hz, 1H, 5aα-H), 3.01 (ddd, *J* = 15.5, 7.4, 1.9 Hz, 1H, 5β-H), 2.91 (septet, *J* = 6.9 Hz, 1H, —$CH(CH_3)_2$), 2.45 (s, 3H, Ts-CH_3), 2.05 (dddd, *J* = 15.3, 7.2, 4.1, 3.0 Hz, 1H, 5α-H), 1.23 (d, *J* = 7.2 Hz, 6H, —$CH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 178.1, 173.1, 149.4, 144.5, 142.5, 137.7, 133.8, 130.1, 129.3, 127.7, 127.2, 126.2, 110.8, 110.6, 59.5, 42.3, 36.3, 34.0, 26.1, 24.0, 21.7; IR (KBr, cm^{-1}) 3472(w), 3138(w), 3104(w), 3049(w), 2960(m), 2929(m), 2870(m), 1781(w), 1714(s), 1596(m), 1565(w), 1514(m), 1491(w), 1449(m), 1371(s), 1306(m), 1294(m), 1170(s), 1123(s), 1091(m), 1056(m), 1018(m), 991(m), 900(w), 874(w), 832(m), 812(m), 767(w), 704(m), 669(s); HRMS m/z (M + Na$^+$) calcd 485.1506, found 485.1523. Anal. Calcd for $C_{26}H_{26}N_2O_4S$: C, 67.51; H, 5.67; N, 6.06. Found: C, 67.46; H, 5.61; N, 6.17.

7-(4-Phenoxyphenyl)-1-p-toluenesulfonyl-5,5aα,8aα,8bα-tetrahydropyrrolo-1H,7H-benzo[g]indole-6,8-dione (11). The general method with maleimide **7** and rt for 5 d gave **11** (1.794 g, 77%) as white crystals: mp 217–218°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.80 (d, *J* = 8.1 Hz, 2H, Ts), 7.32–7.40 (m, 4H, Ts, PhOPh), 7.14–7.17 (m, 3H, PhOPh), 6.99–7.05 (m, 4H, PhOPh), 6.85 (d, *J* = 3.9 Hz, 1H, 2-H), 5.69 (d, *J* = 3.9 Hz, 1H, 3-H), 5.56 (ddd, *J* = 7.3, 3.7, 3.6 Hz, 1H, 4-H), 4.23 (ddd, *J* = 6.8, 3.2, 3.2 Hz, 1H, 8bα-H), 3.99 (dd, *J* = 9.0, 7.2 Hz, 1H, 8aα-H), 3.24 (ddd, *J* = 8.9, 7.1, 1.7 Hz, 1H, 5aα-H), 3.02 (ddd, *J* = 15.5, 7.4, 1.4 Hz, 1H, 5β-H), 2.45 (s, 3H, Ts-CH_3), 2.06 (dddd, *J* = 15.9, 6.9, 4.0, 2.7 Hz, 1H, 5α-H); ^{1}H NMR (300 MHz, DMSO-d_6, δ) 7.80 (d, *J* = 8.1 Hz, 2H, Ts), 7.38–7.46 (m, 4H, PhOPh), 7.15–7.21 (m, 1H, PhOPh), 7.03–7.07 (m, 6H, PhOPh), 6.76 (d, *J* = 3.9 Hz, 1H, 2-H), 5.80 (d, *J* = 4.2 Hz, 1H, 3-H), 5.53 (ddd, *J* = 7.1, 3.7, 3.7 Hz, 1H, 4-H), 4.29 (ddd, *J* = 7.1, 3.3, 3.3 Hz, 1H, 8bα-H), 3.89 (dd, *J* = 8.7, 7.2 Hz, 1H, 8aα-H), 3.28 (ddd, *J* = 8.9, 7.1, 1.4 Hz, 1H, 5aα-H), 2.66 (ddd, *J* = 15.2, 7.1, 1.7 Hz, 1H, 5β-H), 2.40 (s, 3H, Ts-CH_3), 2.12 (dddd, *J* = 15.2, 7.1, 3.7, 3.3 Hz, 1H, 5α-H); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 178.9, 174.1, 157.0, 156.6, 144.8, 142.3, 138.0, 133.5, 130.7, 130.5, 129.0, 127.9, 127.8, 124.5, 119.6, 119.1, 111.9, 111.4, 59.8, 43.3, 36.9, 25.7, 21.6; IR (KBr, cm^{-1}) 3458(w), 3103(m), 3064(m), 2929(w), 2903(w), 2853(w), 1772(w), 1702(s), 1651(w), 1586(m), 1564(w), 1504(m), 1483(m), 1360(m), 1342(m), 1294(w), 1235(s), 1195(s), 1165(s), 1107(m), 1094(m), 1063(m), 1018(w), 991(w), 963(w), 912(w), 874(w), 845(m), 801(m), 730(m), 615(m); HRMS m/z (M + Na$^+$) calcd 535.1299, found 535.1311. Anal. Calcd for $C_{29}H_{24}N_2O_5S$: C, 67.95; H, 4.72; N, 5.47. Found: C, 68.13; H, 4.59; N, 5.16.

7-(4-Isopropylphenyl)-1-p-toluenesulfonyl-4,5,5aα,8aα-tetrahydropyrrolo-1H,7H-benzo[g]indole-6,8-dione (12). Diels-Alder adduct **10** (1.000 g, 2.162 mmol) was dissolved in chloroform (30 mL) and refluxed for 4 d. The solvent was removed with a rotating evaporator, giving **12** (1.000 g, quant.) as a white powder: mp 96–98°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.99 (d, *J* = 8.4 Hz, 2H, Ts), 7.28–7.34 (m, 4H, Ts, *i*PrPh), 7.18 (d, *J* = 8.7 Hz, 2H, *i*PrPh), 7.12 (d, *J* = 3.6 Hz, 1H, 2-H), 6.16 (d, *J* = 3.3 Hz, 1H, 3-H), 5.02 (d, *J* = 8.4 Hz, 1H, 8aα-H), 3.42 (ddd, *J* = 8.6, 5.9, 5.9 Hz, 1H, 5aα-H), 2.94 (septet, *J* = 7.1 Hz, 1H, —$CH(CH_3)_2$), 2.59 (ddd, *J* = 16.0, 5.5, 5.5 Hz, 1H, 4α-H), 2.43 (ddd, *J* = 16.3, 8.6, 4.6 Hz, 1H, 4β-H), 2.42 (s, 3H, Ts-CH_3), 2.29 (dddd, *J* = 13.3, 6.1, 6.1, 4.4 Hz, 1H, 5β-H), 1.99 (dddd, *J* = 14.0, 8.3, 5.2, 4.8 Hz, 1H, 5α-H), 1.26 (d, *J* = 6.9 Hz, 6H, —$CH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 178.1, 173.8, 149.4, 145.0, 136.5, 129.8, 129.5, 127.8, 127.3, 126.4, 125.6, 123.6, 123.0, 112.6, 41.2, 39.5, 34.0, 25.1, 24.0, 21.8, 21.2; IR (KBr, cm^{-1}) 3478(w), 3137(w), 3103(w), 3037(w), 2959(s), 2929(m), 2868(m), 1783(m), 1718(s), 1595(m), 1514(m), 1484(m), 1451(m), 1370(s), 1306(w), 1295(w), 1226(m), 1171(s), 1123(s), 1090(m), 1017(w), 990(m), 898(w), 873(w), 835(w), 812(m), 766(w), 702(m), 668(s); HRMS m/z (M + Na$^+$) calcd 485.1506, found 485.1527. Anal. Calcd for $C_{26}H_{26}N_2O_4S$: C, 67.51; H, 5.67; N, 6.06. Found: C, 67.24; H, 5.68; N, 6.16.

7-(4-Phenoxyphenyl)-1-p-toluenesulfonyl-4,5,5aα,8aα-tetrahydropyrrolo-1H,7H-benzo[g]indole-6,8-dione (13). Diels-Alder adduct **11** (1.000 g, 1.951 mmol) was dissolved in chloroform (30 mL) and refluxed for 4 d. The solvent was removed with a rotating evaporator, giving **13** (1.000 g, quant.) as an orange powder: mp 217–218°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.97 (d, *J* = 8.4 Hz, 2H, Ts), 7.30–7.41 (m, 4H, Ts, PhOPh), 7.13–7.25 (m, 4H, PhOPh), 7.02–7.08 (m, 4H, PhOPh, 2-H), 6.16 (d, *J* = 3.3 Hz, 1H, 3-H), 5.02 (d, *J* = 8.4 Hz, 1H, 8aα-H), 3.43 (ddd, *J* = 8.6, 5.9, 5.9 Hz, 1H, 5aα-H), 2.59 (ddd, *J* = 16.1, 5.4, 5.4 Hz, 1H, 4α-H), 2.43 (ddd, *J* =

16.2, 8.6, 4.7 Hz, 1H, 4β-H), 2.42 (s, 3H, Ts-CH_3), 2.29 (dddd, J = 13.4, 6.0, 6.0, 4.3 Hz, 1H, 5β-H), 1.99 (dddd, J = 13.6, 8.5, 5.4, 4.7 Hz, 1H, 5α-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 178.0, 173.8, 157.6, 156.5, 145.0, 136.5, 130.0, 129.9, 128.0, 127.7, 126.6, 125.7, 124.0, 123.7, 122.8, 119.6, 118.8, 112.6, 41.2, 39.5, 25.0, 21.8, 21.2; IR (KBr, cm^{-1}) 3464(w), 3146(w), 3111(m), 3065(m), 2943(m), 2850(w), 1773(w), 1707(s), 1586(m), 1505(m), 1484(m), 1445(w), 1397(m), 1372(m), 1335(m), 1293(w), 1232(s), 1203(m), 1187(s), 1167(s), 1120(m), 1091(m), 1017(w), 989(w), 916(w), 901(w), 885(m), 811(m), 782(m), 743(w), 703(m), 646(m); HRMS m/z (M + Na^{+}) calcd 535.1299, found 535.1318. Anal. Calcd for $C_{29}H_{24}N_2O_5S$: C, 67.95; H, 4.72; N, 5.47. Found: C, 67.93; H, 4.64; N, 5.26.

1-p-Toluenesulfonyl-7α-(1-p-toluenesulfonyl-1H-pyrrol-3-yl)-4,5,6,7β-tetrahydro-1H-indole (17). A mixture of *N*-*p*-toluenesulfonyl-3-vinylpyrrole **3** (1.237 g, 0.005 mol) and vinylboronic acid 2-methyl-2,4-pentanediol ester **14** (693 mg, 0.0045 mol, 1.1 equiv.) in chloroform (20 mL) was stirred under reflux for 3 d, at which point TLC analysis indicated that a new spot had formed and no starting materials were being consumed. The solvent was removed using a rotating evaporator. The crude mixture was purified by MPLC with ethyl acetate/hexanes as eluant, followed by recrystallization from dichloromethane/petroleum ether, giving **17** (210 mg, 9%) as a white powder: mp 157–158°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.61 (d, J = 8.4 Hz, 2H, 1′-Ts), 7.31 (d, J = 8.4 Hz, 2H, 1-Ts), 7.26 (d, J = 8.4 Hz, 2H, 1′-Ts), 7.26 (d, J = 3.3 Hz, 1H, 2-H), 7.12 (d, J = 8.1 Hz, 2H, 1-Ts), 6.87 (dd, J = 3.3, 2.4 Hz, 1H, 5′-H), 6.20 (dd, J = 2.4, 2.1 Hz, 1H, 2′-H), 6.12 (d, J = 3.3 Hz, 1H, 3-H), 6.02 (dd, J = 3.2, 1.7 Hz, 1H, 4′-H), 4.41 (dd, J = 5.1, 2.4 Hz, 1H, 7β-H), 2.31–2.54 (m, 2H, 4-H), 2.41 (s, 3H, Ts-CH_3), 2.39 (s, 3H, Ts-CH_3), 1.84 (dddd, J = 13.1, 13.1, 5.2, 3.1 Hz, 1H, 6β-H), 1.69 (dddd, J = 12.8, 3.8, 2.8, 2.8 Hz, 1H, 6α-H), 1.44–1.60 (m, 1H, 5β-H), 1.24–1.48 (m, 1H, 5α-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 144.8, 144.6, 136.4, 135.8, 132.8, 130.1, 130.0, 129.6, 126.6, 124.0, 121.9, 120.3, 118.9, 114.4, 111.9, 31.1, 31.0, 22.9, 21.72, 21.69, 17.0; IR (KBr, cm^{-1}) 3144(m), 3113(m), 3065(w), 3031(w), 2944(s), 2925(s), 2856(m), 1596(m), 1490(m), 1473(w), 1442(w), 1424(w), 1401(w), 1365(s), 1243(m), 1232(m), 1175(s), 1146(m), 1124(s), 1094(s), 1056(s), 1019(w), 996(m), 953(w), 905(w), 874(w), 855(w), 799(m), 780(m), 775(m), 748(m), 722(m), 673(s), 630(w); HRMS m/z (M + Na^{+}) calcd 517.1227, found 517.1241. Anal. Calcd for $C_{26}H_{26}N_2O_4S_2$: C, 63.13; H, 5.30; N, 5.66. Found: C, 62.91; H, 5.25; N, 5.71.

7-(4-Isopropylphenyl)-1-p-toluenesulfonyl-1H,7H-benzo[g]indole-6,8-dione (18). The general method with tetrahydroindole **12** and reflux for 3 h gave **18** (977 mg, 71%) as a white powder: mp 106–108°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.10 (d, J = 3.9 Hz, 1H, 2-H), 8.00 (d, J = 8.1 Hz, 1H, 4-H), 7.94 (d, J = 8.4 Hz, 2H, Ts), 7.88 (d, J = 7.8 Hz, 1H, 5-H), 7.35 (d, J = 8.4 Hz, 2H, *i*PrPh), 7.29 (d, J = 8.7 Hz, 4H, *i*PrPh, Ts), 6.91 (d, J = 3.9 Hz, 1H, 3-H), 2.97 (septet, J = 6.9 Hz, 1H, $-CH(CH_3)_2$), 2.43 (s, 3H, Ts-CH_3), 1.29 (d, J = 6.9 Hz, 6H, $-CH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 167.5, 164.6, 148.7, 144.8, 138.4, 136.5, 133.6, 129.73, 129.68, 129.5, 128.2, 127.7, 127.6, 127.1, 126.7, 118.4, 117.3, 108.0, 34.0, 24.0, 21.8; IR (KBr, cm^{-1}) 3648(w), 3475(w), 3154(w), 3123(w), 3070(w), 2959(s), 2901(m), 2871(m), 1776(m), 1722(s), 1619(w), 1595(m), 1537(w), 1515(m), 1453(w), 1424(m), 1402(s), 1374(s), 1309(w), 1266(m), 1247(m), 1226(w), 1190(m), 1173(s), 1150(s), 1124(m), 1093(s), 1056(w), 1016(m), 991(m), 880(w), 839(m), 811(m), 750(m), 739(m), 711(m), 666(s), 608(m); HRMS m/z (M + Na^{+}) calcd 481.1193, found 481.1206. Anal. Calcd for $C_{26}H_{22}N_2O_4S$: C, 68.10; H, 4.84; N, 6.11. Found: C, 68.02; H, 5.03; N, 6.19.

7-(4-Phenoxyphenyl)-1-p-toluenesulfonyl-1H,7H-benzo[g]indole-6,8-dione (19). The general method with tetrahydroindole **13** and reflux for 3 d gave **19** (1.144 g, 75%) as yellow crystals: mp 216–217°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.12 (d, J = 3.6 Hz, 1H, 2-H), 8.00 (d, J = 7.8 Hz, 1H, 4-H), 7.94 (d, J = 8.1 Hz, 2H, Ts), 7.88 (d, J = 7.8 Hz, 1H, 5-H), 7.31–7.45 (m, 6H, Ts, PhOPh), 7.06–7.20 (m, 5H, PhOPh), 6.91 (d, J = 3.9 Hz, 1H, 3-H), 2.43 (s, 3H, Ts-CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 167.4, 164.7, 157.1, 156.6, 145.3, 138.6, 136.5, 134.7, 130.8, 130.3, 130.0, 129.9, 128.8, 128.1, 127.6, 127.4, 124.6, 119.8, 118.9, 118.8, 117.4, 109.4, 21.6; IR (KBr, cm^{-1}) 3159(m), 3114(m), 1773(w), 1716(s), 1587(w), 1536(w), 1506(s), 1487(m), 1454(w), 1428(m), 1398(m), 1365(s), 1320(w), 1266(m), 1233(s), 1178(m), 1147(m), 1121(m), 1093(m), 1017(m), 990(m), 938(w), 909(w), 864(w), 830(m), 806(m), 777(w), 740(m), 665(m); HRMS m/z (M + Na^{+}) calcd 531.0986, found 531.1006. Anal. Calcd for $C_{29}H_{20}N_2O_5S$: C, 68.49; H, 3.96; N, 5.51. Found: C, 68.57; H, 4.03; N, 5.33.

1-p-Toluenesulfonyl-1H-benzo[g]indole-6,9-dione (20). The general method with tetrahydroindole **8** and reflux for 24 h gave **20** (822 mg, 78%) as light-orange crystals: mp 186–187°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.08 (d, J = 8.08 Hz, 1H, 4-H), 7.91 (d, J = 3.9 Hz, 1H, 2-H), 7.89 (d, J = 8.4 Hz, 1H, 5-H), 7.89 (J = 8.7 Hz, 2H, Ts), 7.41 (d, J = 8.4 Hz, 2H, Ts), 6.97 (d, J = 10.2 Hz, 1H, 8-H), 6.90 (d, J = 10.2 Hz, 1H, 7-H), 6.83 (d, J = 3.9 Hz, 1H, 3-H), 2.49 (s, 3H, Ts-CH_3); ^{1}H NMR (300 MHz, acetone-d_6, δ) 8.11 (d, J = 3.9 Hz, 1H, 2-H), 8.08 (d, J = 8.4 Hz, 1H, 4-H), 8.04 (d, J = 8.1 Hz, 1H, 5-H), 7.94 (d, J = 8.4 Hz, 2H, Ts), 7.50 (d, J = 8.1 Hz, 2H, Ts), 7.09 (d, J = 10.2 Hz, 1H, 8-H), 7.04 (d, J = 3.6 Hz, 1H, 3-H), 7.01 (d, J = 10.5 Hz, 1H, 7-H), 2.45 (s, 3H, Ts-CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 185.3, 184.8, 145.3, 139.4, 138.0, 137.8, 136.9, 136.7, 131.6, 130.1, 129.5, 127.4, 127.3, 123.2, 122.5, 110.8, 21.6; IR (KBr, cm^{-1}) 3311(m), 3153(m), 3116(w), 3065(m), 1718(w), 1660(s), 1609(m), 1594(m), 1533(m), 1494(w), 1459(w), 1415(w), 1380(m), 1354(s), 1301(s), 1282(m), 1252(m), 1241(w), 1189(m), 1163(s), 1119(m), 1088(m), 1070(s), 997(m), 967(w), 956(w), 882(w), 860(w), 831(m), 810(m), 756(w), 720(m), 666(s), 622(w); HRMS m/z (M + Na^{+}) calcd 374.0458, found 374.0464. Anal. Calcd for $C_{19}H_{13}NO_4S$: C, 64.95; H, 3.73; N, 3.99. Found: C, 64.82; H, 4.10; N, 4.10.

1-p-Toluenesulfonyl-1H-naphtho[2,3-g]indole-6,11-dione (21). The general method with tetrahydroindole **9** and reflux for 24 h gave **21** (867 mg, 72%) as light-orange crystals: mp 139–140°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 831 (d, J = 8.1 Hz, 1H, 4-H), 8.26–8.28 (m, 1H, 8-H), 8.14–8.17 (m, 1H, 9-H), 7.91–7.95 (m, 4H, Ts, 2-H, 5-H), 7.77–7.81 (m, 2H, 7-H, 10-H), 7.43 (d, J = 7.8 Hz, 2H, Ts), 6.84 (d, J = 3.6 Hz, 1H, 3-H), 2.51 (s, 3H, Ts-CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 184.1, 182.6, 145.4, 137.8, 136.8, 135.1, 134.8, 134.7, 133.0, 132.1, 130.7, 130.1, 127.7, 127.6, 127.4, 127.0, 126.9, 125.2, 123.1, 110.8, 21.7; IR (KBr, cm^{-1}) 3180(m), 3066(m), 2915(w), 1668(s), 1593(m), 1529(w), 1458(w), 1412(w), 1379(w), 1352(m), 1324(m), 1286(s), 1258(m), 1195(w), 1172(m), 1130(w), 1095(m), 1044(w), 1014(m), 955(w), 884(w), 851(w), 811(w), 737(w), 715(m), 705(w), 669(m), 636(w); HRMS m/z (M + Na$^+$) calcd 424.0615, found 424.0622. Anal. Calcd for $C_{23}H_{15}NO_4S$: C, 68.81; H, 3.77; N, 3.49. Found: C, 68.70; H, 3.79; N, 3.51.

7-(4-Isopropylphenyl)-1H,7H-benzo[g]indole-6,8-dione (22). Forty mesh magnesium metal powder (245 mg, 101 mmol, 20 equiv.) was ground with a mortar and pestle by hand for 1 min, and then placed immediately in anhydrous methanol (20 mL, ≤0.100% water). The indole **18** (231 mg, 0.504 mmol) was added, and the mixture was stirred under reflux for 5 h, at which time TLC analysis indicated that the starting materials were completely converted. The mixture was cooled to rt, vacuum-filtered on a fritted-glass funnel, and the remaining solids were washed several times with dichloromethane (3 × 20 mL). The filtrate and washings were diluted with water (100 mL), and extracted with dichloromethane (3 × 20 mL). The dichloromethane was washed with saturated aqueous sodium bicarbonate (20 mL), water (20 mL), and brine (20 mL), and dried over anhydrous sodium sulfate. The solvent was removed using a rotating evaporator. The crude product was purified using MPLC with ethyl acetate/hexanes as eluent, and recrystallized from dichloromethane/petroleum ether, giving **22** (90 mg, 59%) as bright-yellow crystals: mp 185–186°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 9.48 (s, 1H, 1-H), 7.99 (d, *J* = 8.1 Hz, 1H, 4-H), 7.69 (d, *J* = 8.1 Hz, 1H, 5-H), 7.49 (dd, *J* = 3.0, 2.4 Hz, 1H, 2-H), 7.41 (d, *J* = 8.1 Hz, 2H, *i*PrPh), 7.38 (d, *J* = 8.1 Hz, 2H, *i*PrPh), 6.74 (dd, *J* = 3.3, 1.8 Hz, 1H, 3-H), 2.99 (septet, *J* = 7.1 Hz, 1H, —C*H*(CH$_3$)$_2$), 1.31 (d, *J* = 7.2 Hz, 6H, —CH(C*H*$_3$)$_2$); ^{1}H NMR (300 MHz, DMSO-d_6, δ) 2.19 (s, 1H, 1-H), 8.04 (d, *J* = 7.8 Hz, 1H, 4-H), 7.69 (dd, *J* = 2.9, 2.9 Hz, 1H, 2-H), 7.54 (d, *J* = 7.8 Hz, 1H, 5-H), 7.40 (d, *J* = 9.0 Hz, 2H, *i*PrPh), 7.37 (d, *J* = 9.0 Hz, 2H, *i*PrPh), 6.75 (dd *J* = 3.2, 1.7 Hz, 1H, 3-H), 2.96 (septet, *J* = 6.9 Hz, 1H, —C*H*(CH$_3$)$_2$), 1.25 (d, *J* = 6.9 Hz, 6H, —CH(C*H*$_3$)$_2$); ^{1}H NMR (300 MHz, acetone-d_6, δ) 11.22 (s, 1H, 1-H), 8.10 (d, *J* = 7.8 Hz, 1H, 4-H), 7.77 (d, *J* = 2.7, 2.7 Hz, 1H, 2-H), 7.60 (d, *J* = 7.8 Hz, 1H, 5-H), 7.46 (d, *J* = 9.0 Hz, 2H, *i*PrPh), 7.42 (d, *J* = 8.7 Hz, 2H, *i*PrPh), 6.82 (dd, *J* = 3.2, 2.0 Hz, 1H, 3-H), 3.02 (septet, *J* = 7.1 Hz, 1H, —C*H*(CH$_3$)$_2$), 1.31 (d, *J* = 6.9 Hz, 6H, —CH(C*H*$_3$)$_2$); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 169.0, 168.0, 148.5, 135.5, 132.3, 130.4, 129.3, 127.9, 127.3, 126.8, 125.6, 115.0, 114.0, 103.7, 33.8, 24.4; IR (KBr, cm^{-1}) 3392(bs), 3115(w), 3041(w), 2965(m), 2873(m), 1764(m), 1702(s), 1603(w), 1579(w), 1511(s), 1481(m), 1447(m), 1414(m), 1390(s), 1366(s), 1330(m), 1294(m), 1241(m), 1229(m), 1160(w), 1128(w), 1098(s), 1082(m), 971(w), 944(w), 888(w), 851(m), 825(m), 796(w), 762(m), 730(m), 670(m); HRMS m/z (M + Na$^+$) calcd 327.1105, found 327.1102. Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 74.78; H, 5.16; N, 9.21.

7-(4-Phenoxyphenyl)-1H,7H-benzo[g]indole-6,8-dione (23). Forty mesh magnesium metal powder (96 mg, 93 mmol, 20 equiv.) was ground with a mortar and pestle by hand for 1 min, and then placed immediately in anhydrous methanol (10 mL, ≤0.100% water). The indole **19** (100 mg, 0.196 mmol) was added, and the mixture was stirred under reflux for 5 h, at which time TLC analysis indicated complete conversion of the starting materials. The mixture was cooled to rt, vacuum-filtered on a fritted-glass funnel, and the remaining solids were washed with dichloromethane (3 × 10 mL). The filtrate and washings were diluted with water (50 mL), and extracted with dichloromethane (3 × 10 mL). The dichloromethane was washed with saturated aqueous sodium bicarbonate (10 mL), water (10 mL), and brine (10 mL), and dried over anhydrous sodium sulfate. The solvent was removed using a rotating evaporator. The crude product was purified by MPLC with ethyl acetate/hexanes as eluent, and recrystallized from dichloromethane/petroleum ether, giving **23** (38 mg, 55%) as yellow crystals: mp 206–207°C; ^{1}H NMR (300 MHz, DMSO-d_6, δ) 12.19 (s, 1H, 1-H), 8.05 (d, *J* = 7.8 Hz, 1H, 4-H), 7.70 (dd, *J* = 2.9, 2.9 Hz, 1H, 2-H), 7.56 (d, *J* = 8.1 Hz, 1H, 5-H), 7.42–7.51 (m, 4H, PhOPh), 7.09–7.23 (m, 5H, PhOPh), 6.76 (dd, *J* = 3.0, 1.8 Hz, 1H, 3-H); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 169.0, 167.9, 156.7, 135.5, 132.3, 130.8, 129.7, 129.4, 127.8, 126.8, 125.6, 124.5, 119.7, 119.0, 114.0, 105.0, 104.3, 103.7; IR (KBr, cm^{-1}) 3346(bs), 2960(m), 2922(s), 2853(m), 1761(m), 1698(s), 1590(w), 1509(m), 1486(m), 1447(m), 1392(m), 1368(m), 1332(w), 1291(w), 1245(m), 1159(w), 1109(m), 1074(m), 1009(w), 871(w), 828(w), 803(w), 756(w), 722(w); HRMS m/z (M + Na$^+$) calcd for $C_{22}H_{14}N_2O_3$: 377.0897, found 377.0891.

1H-Naphtho[2,3-g]indole-6,11-dione (25) [44]. A mixture of indole **21** (105 mg, 0.262 mmol), saturated aqueous sodium carbonate (10 mL), and methanol (10 mL) were stirred under reflux for 6 h, at which time TLC analysis indicated complete conversion of the starting materials. The mixture was cooled to rt, diluted with water (100 mL), and extracted with dichloromethane (3 × 20 mL). The dichloromethane was washed with saturated aqueous ammonium chloride (20 mL), and brine (20 mL), and dried over anhydrous sodium sulfate. The solvent was removed using a rotating evaporator, and the product was recrystallized from dichloromethane/petroleum ether, giving **25** (51 mg, 79%) as light-orange crystals: mp 205–206°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 10.66 (s, 1H, 1-H), 8.07 (d, *J* = 8.4 Hz, 1H, 4-H), 8.00 (d, *J* = 8.1 Hz, 1H, 5-H), 8.23–8.34 (m, 2H, 8-H, 9-H), 7.75–7.81 (m, 2H, 7-H, 10-H), 7.57 (dd, *J* = 3.0, 2.4 Hz, 1H, 2-H), 6.68 (dd, *J* = 3.3, 1.8 Hz, 1H, 3-H); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 185.0, 183.5, 135.0, 134.8, 134.70, 134.65, 133.8, 133.3, 132.8, 128.0, 127.6, 127.2, 126.7, 118.0, 117.8, 103.2; IR (KBr, cm^{-1}) 3095(w), 2960(m), 2923(m), 2852(w), 1719(w), 1668(s), 1660(m), 1590(m), 1572(w), 1545(w), 1487(m), 1445(w), 1405(w), 1329(m), 1289(s), 1235(w), 1199(w), 1158(m), 1090(s), 1048(m), 1008(m), 898(w), 844(w), 816(m), 724(s), 716(s), 638(w); HRMS m/z (M + Na$^+$) calcd 270.0526, found 270.0538. Anal. Calcd for $C_{16}H_9NO_2$: C, 77.72; H, 3.67; N, 5.67. Found: C, 77.74; H, 3.80; N, 5.49.

^{1}H and ^{13}C NMR spectra for **8**, **9**, **10**, **11**, **12**, **13**, **17**, **18**, **19**, **20**, **21**, **22**, **23**, and **25**. This material is available online free of charge (see Supporting Information).

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Novel Synthetic Route for 5-Substituted 6-Arylmethylluracils from 2,4,6-Trichloropyrimidines

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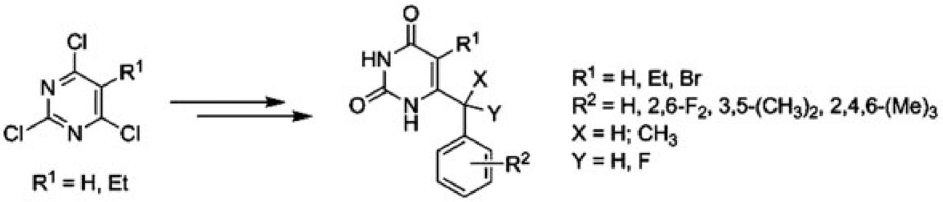

Treatment of 2,4,6-trichloropyrimidines (**1a,b**) with the sodium salt of benzyl cyanide derivatives (**2a,b**) afforded 5-substituted 4-aryl(cyanomethyl)-2,6-dichloropyrimidines (**3a–f**). Compounds **3a,b** were alkylated with methyl iodide to furnish 4-(1-aryl-1-cyanoethyl)-2,6-dichloropyrimidines (**4a,b**). Compounds **3a–f** and **4a,b** were hydrolyzed with concentrated hydrochloric acid to afford 5-substituted 6-arylalkyluracils **5a–h**. 5-Bromo-6-arymethylluracils (**6a–d**) were synthesized by bromination of 6-arylmethylluracils (**5a–d**) with *N*-bromosuccinimide (NBS). Refluxing 2-(2,6-dichloro-5-ethylpyrimidin-4-yl)-2-(3,5-dimethylphenyl)acetonitrile (**3f**) with sodium methoxide followed by oxidation afforded (3,5-dimethylphenyl)(5-ethyl-2,6-dimethoxypyrimidin-4-yl)methanone (**7**). Addition of methylmagnesium bromide to compound **7** gave the tertiary alcohol derivative **8** which was fluorinated by diethylaminosulfurtrifluoride and deprotected by trimethylsilyl iodide to furnish 6-(1-(3,5-dimethylphenyl)-1-fluoroethyl)-5-ethylpyrimidine-2,4(1*H*,3*H*)-dione (**12**).

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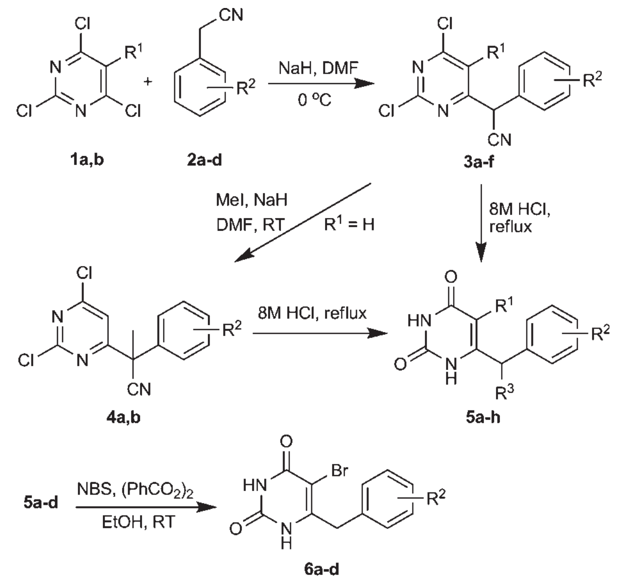
INTRODUCTION

5-Substituted 6-arylmethyluracils are important intermediates for the synthesis of many biologically active compounds. 5-Alkyl-6-arylmethyluracils are used for the synthesis of 6-benzyl-1-ethoxymethyl-5-isopropyluracil (MKC-442) [1–3] analogs as human immunodeficiency virus type 1 (HIV-1) nonnucleoside reverse transcriptase inhibitors (NNRTIs) [4–10]. 5-Bromo-6-arylmethyluracils were used as inhibitors of thymidine phosphorylase [11–13]. Uracil derivatives are known to be synthesized by refluxing the corresponding thiouracils with 10% aqueous chloroacetic acid [14–21]. Thiouracils are synthesized by the condensation of the appropriate β-ketoester with thiourea in strong basic medium [14–21]. Lee and Kim [22] have reported the synthesis of 5-alkyl-6-benzyluracil derivatives by the reaction of 5-alkyl-2,4,6-trichloropyrimidines with various arylmethyl magnesium halides to afford the regioselectively 6-arylmethyl-2,4-dichloropyrimidines as the major products. The dichloropyrimidine derivatives were refluxed with sodium methoxide to afford the dimethoxy derivatives which were refluxed with 37% hydrochloric acid to give 5-alkyl-6-benzyluracil derivatives [22]. El-Brollosy *et al*. [23] have synthesized some of 6-arylmethyluracils by the treatment of Grignard reagents of the corresponding benzyl halides with 4-chloro-5-ethyl-2,6-dimethoxypyrimidine. Hydrolysis of the Grignard products with 4 *M* hydrochloric acid afforded 6-benzyluracil derivatives [23]. In the present work, a novel synthetic route for 5-substituted 6-arylmethyluracils is reported.

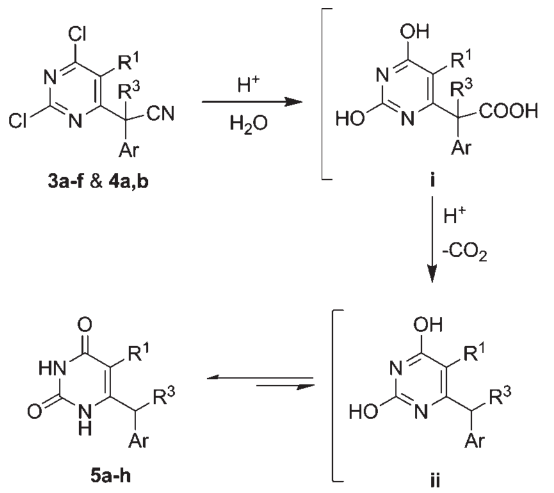
RESULTS AND DISCUSSION

Treatment of the sodium salt of arylacetonitriles (**2a–d**) with 2,4,6-trichloropyrimidine (**1a**) and/or 2,4,6-trichloro-5-ethylpyrimidine (**1b**) afforded 2-aryl-2-(2,6-dichloropyrimidin-4-yl)acetonitrile (**3a–d**) and 2-aryl-2-(2,6-dichloro-5-ethylpyrimidin-4-yl)acetonitriles (**3a,f**), respectively as sole products. No coupling at the 2-position of the pyrimidine ring was observed. As reported,

Scheme 1



Scheme 2



the 4- or 6-position (4-position is equivalent to 6-position in **1a,b**) in chloropyrimidines is more reactive than the 2-position in the nucleophilic substitution reaction [22,24,25]. Coupling at the 4-position of the pyrimidine ring was confirmed by nuclear Overhauser effect (NOE). On irradiation of CH—CN of compound **3c**, 1.29 NOE was detected with H5 which showed 2.0 NOE with CH—CN when irradiated. Compounds **3a,b** were methylated by stirring their sodium salts with methyl iodide in dry dimethylformamide to furnish 2-(2,6-dichloropyrimidin-4-yl)-2-arylacetonitriles **4a,b**. 6-Arylalkyluracils **5a–h** were obtained by refluxing of each compound of **3a–f** and **4a,b** with concentrated hydrochloric acid (Scheme 1). The mechanism for the synthesis of **5a–h** from **3a–f** and **4ab** is postulated as described by Smith and March [26]. The mechanism proceeds through acid hydrolysis of compounds **3a–f** and **4a,b** to their corresponding 2-(2,4-dihydroxypyrimidin-6-yl)-ethanoic acid derivatives **i** as intermediates. The intermediates **i** were decarboxylated in strong acidic medium to afford 6-arylpyrimidine-2,4-diols **ii** which are the enol forms of compounds **5a–h** (Scheme 2). Compounds **5a,b,f** have previously been prepared through desulfurization of the corresponding 2-thiouracil derivatives [14–16]. Compounds **5a–d** were brominated with *N*-bromosuccinimide in absolute ethanol in the presence of benzoyl peroxide at room temperature to give the 5-bromouracil derivatives **6a–d** (Scheme 1). Previously, Johnson and Ambelang [14] has synthesized compound **6a** through attacking compound **5a** with bromine in glacial acetic acid at 40–50°C.

2-(2,6-Dichloro-5-ethylpyrimidin-4-yl)-2-(3,5-dimethylphenyl)acetonitrile (**3f**) was refluxed with sodium methoxide in methanol followed by oxidation with a stream of oxygen at room temperature to furnish (3,5-dimethylphenyl)(5-ethyl-2,6-dimethoxypyrimidin-4-yl)methanone (**7**). Grignard reaction was applied on compound **7** by the treatment with methylmagnesium bromide to give 1-(3,5-dimethylphenyl)-1-(5-ethyl-2,6-dimethoxypyrimidin-4-yl)ethanol (**8**). Treatment of compound **8** with diethylaminosulfurtrifluoride (DAST) furnished two different compounds. One of them is dehydrated compound **9** in 28% yield and the other one is the fluoro derivative **10** in 37% yield. Compound **10** was deprotected by refluxing with trimethylsilyl iodide (TMSI) in dry chloroform to afford 6-[1-(3,5-dimethylphenyl)-1-fluoroethyl]-5-ethylpyrimidine-2,4(1*H*,3*H*)-dione (**11**) (Scheme 3; Table 1).

Scheme 3

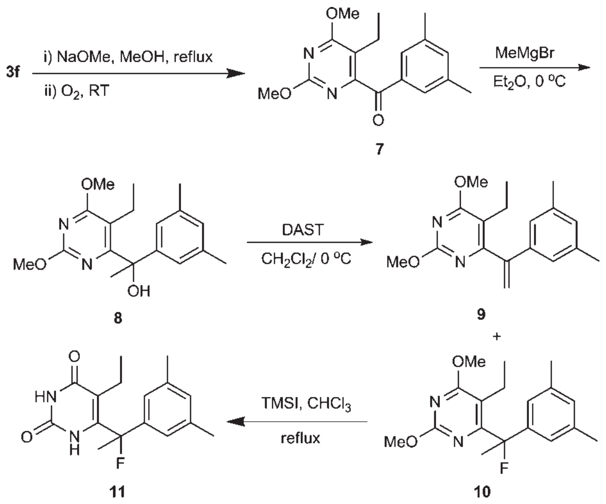


Table 1

Yields and physical data for compounds **3a-f**, **4a,b**, **5a–h,** and **6a–d**.

Compound	R^1	R^2	R^3	Yield (%)	mp (°C)
3a	H	H		71	66–68
3b	H	2,6-(F_2)		72	115–117
3c	H	3,5-$(Me)_2$		79	150–151
3d	H	2,4,6-$(Me)_3$		56	148–150
3e	Et	2,6-(F_2)		84	91–93
3f	Et	3,5-$(Me)_2$		81	108–110
4a		H		72	76–78
4b		3,5-$(Me)_2$		75	84–86
5a	H	H	H	82	261–262[a]
5b	H	2,6-(F_2)	H	83	283–284[b]
5c	H	3,5-$(Me)_2$	H	87	280–282
5d	H	2,4,6-$(Me)_3$	H	78	>300
5e	Et	2,6-(F_2)	H	87	220–221
5f	Et	3,5-$(Me)_2$	H	80	218–220[c]
5g	H	H	Me	74	182–184
5h	H	3,5-$(Me)_2$	Me	72	219–220
6a		H		77	232–233[d]
6b		2,6-(F_2)		79	259–260
6c		3,5-$(Me)_2$		81	263–264
6d		2,4,6-$(Me)_3$		72	251–252

[a] mp 260–262°C [14].
[b] mp > 300°C (AcOH) [15].
[c] mp 216–218°C [16].
[d] mp 230–232°C [14].

Novel and facile synthetic route for uracil derivatives starting with the commercially available 2,4,6-trichloropyrimidines and arylmethyl cyanides was achieved. One pot reaction was carried out by the hydrolysis of compounds **3a–f** and **4a,b** followed by decarboxylation of the resultant intermediates in strong acidic medium. The novel synthesized uracil derivatives can be used for the synthesis of NNRTIs and also N1-nucleosides.

EXPERIMENTAL

NMR spectra were recorded on Varian Gemini 2000 spectrometer (300 MHz for ^1H and 75 MHz for ^{13}C) and a Bruker AVANCE III 400 spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C) with TMS as an internal standard. Electron impact mass spectra were recorded on a Finnigan MAT SSQ 710. MALDI spectra were recorded on a 4.7 T Ultima Fourier transform Mass spectrometer (IonSpec, Irvine, CA). Melting points were determined in a Büchi melting point apparatus. The silica gel (0.040–0.063 mm) used for column chromatography was purchased from Merck. Microanalyses were carried out at Chemical Laboratory II, University of Copenhagen, Denmark.

General procedure for the synthesis of 2-aryl-2-(2,6-dichloropyrimidin-4-yl)acetonitriles (3a–f). Sodium hydride (1.1 g, 25 mmol, and 55% suspension in paraffin oil) was added portionwise to a stirred solution of **1a,b** (10 mmol) and the appropriate benzyl cyanide (**2a–d**) (11 mmol) in dry dimethylformamide (20 mL) at 0°C. The mixture was allowed to reach room temperature gradually and left to be stirred for 3 h. The mixture was poured on the ice-cold water and stirred for 1 h. The solid product formed was filtered off and washed with cold water. The solid was purified by stirring with methanol (15 mL), filtered off, washed with methanol, and dried to afford the pure compounds **3b–f**. Only compound **3a** was extracted with ether (3 × 20 mL) from the aqueous mixture. The ether phase was dried and evaporated under reduced pressure. The residual material was purified by silica gel column chromatography using petroleum ether:ether (1:1, v/v) as eluent.

2-(2,6-Dichloropyrimidin-4-yl)-2-phenylacetonitrile (3a). This compound was obtained as white crystals; ^1H nmr ($CDCl_3$, 400 MHz): δ 5.22 (s, 1H, CH—CN), 7.41 (s, 1H, H5), 7.42–7.47 ppm (m, 5H, H_{arom}); ^{13}C nmr ($CDCl_3$, 100 MHz): δ 44.36 (*C*H—CN), 116.67 (CN), 117.81 (C5), 127.81, 129.47, 129.74, 131.65 (C_{arom}), 161.10 (C6), 163.91 (C2), 167.61 ppm (C4); ms: (70 eV, electron impact) *m/z* 51 (100%), 263, (39%, $C_{12}H_7{}^{35}Cl_2N_3$, M^+), 265 (20%, $C_{12}H_7{}^{35}Cl^{37}ClN_3$, M^++2), 267 (4%, $C_{12}H_7{}^{37}Cl^{37}ClN_3$, M^++4). Anal. Calcd. for $C_{12}H_7Cl_2N_3$ (264.11): C,54.57; H, 2.67; N, 15.91. Found: C, 55.02; H, 2.59; N, 15.74.

2-(2,6-Dichloropyrimidin-4-yl)-2-(2,6-difluorophenyl)acetonitrile (3b). This compound was obtained as white crystals; ^1H nmr ($CDCl_3$, 400 MHz): δ 5.60 (s, 1H, CH—CN), 7.03 (t, 2H, J = 8.4 Hz, H_{arom}), 7.43–7.47 (m, 1H, H_{arom}), 7.66 ppm (s, 1H, H5); ^{13}C nmr ($CDCl_3$, 100 MHz): δ 32.70 (t, J = 3.3 Hz, *C*H—CN), 108.95 (t, J = 17.2 Hz, C_{arom}), 112.34 (dd, J = 2.8, 22 Hz, C_{arom}), 114.60 (CN), 117.73 (C5), 132.11 (t, J = 10.1 Hz, C_{arom}), 160.38 (dd, J = 6.0, 252.4 Hz, C_{arom}), 161.17 (C6), 164.08 (C2), 165.50 ppm (C4); ms: (70 eV, electron impact) *m/z* 125 (100%), 299 (56%, $C_{12}H_5{}^{35}Cl_2F_2N_3$, M^+), 301 (27%, $C_{12}H_5{}^{35}Cl^{37}ClF_2N_3$, M^++2), 303 (6%, $C_{12}H_5{}^{37}$

$Cl_2F_2N_3$, M^++4). Anal. Calcd. for $C_{12}H_5Cl_2F_2N_3$ (300.09): C, 48.03; H, 1.68; N, 14.00. Found: C, 48.15; H, 1.58; N, 13.93.

2-(2,6-Dichloropyrimidin-4-yl)-2-(3,5-dimethylphenyl)acetonitrile (3c). This compound was obtained as white crystals; ^{1}H nmr ($CDCl_3$, 400 MHz) δ: 2.33 (s, 6H, $(CH_3)_2$N), 5.12 (s, 1H, CH—CN), 7.03 (s, 3H, H_{arom}), 7.39 ppm (s, 1H, H5); ^{13}C nmr ($CDCl_3$, 100 MHz) δ: 21.21 [$(CH_3)_2$N], 44.31 (*C*H—CN), 116.87 (C5), 117.87 (CN), 125.46, 131.10, 131.41, 139.64 (C_{arom}), 161.02 (C4), 163.78 (C2), 167.91 (C4) ppm; ms: (70 eV, electron impact) *m/z* 144 (100%), 291 (86%, $C_{14}H_{11}{}^{35}Cl_2N_3$, M^+), 293 (51%, $C_{14}H_{11}{}^{35}Cl^{37}ClN_3$, M^++2), 295 (6%, $C_{14}H_{11}{}^{37}Cl_2N_3$, M^++4). *Anal.* Calcd. for $C_{14}H_{11}Cl_2N_3$ (292.16): C, 57.55; H, 3.79; N, 14.38. Found: C, 58.11; H, 3.85; N, 14.14.

(2,6-Dichloropyrimidin-4-yl)(mesityl)acetonitrile (3d). This compound was obtained as yellow crystals ^{1}H nmr ($CDCl_3$, 300 MHz): δ 2.30 (s, 6H, $3CH_3$), 5.62 (CH—CN), 6.95 (s, 2H, H_{arom}), 7.14 ppm (s, 1H, H5); ^{13}C nmr ($CDCl_3$, 75 MHz): δ 20.67 [$(CH_3)_2$Ar], 20.90 (*C*H_3Ar), 38.52 (*C*H—CN), 115.96 (CN), 117.20 (C5), 125.74, 130.57, 136.92, 139.53 (C_{arom}), 161.19 (C4), 163.60 (C2), 167.86 ppm (C6); ms: (70 eV, electron impact) *m/z* 32 (100%), 305 (78%, $C_{15}H_{13}{}^{35}Cl_2N_3$, M^+), 307 (55%, $C_{15}H_{13}{}^{35}Cl^{37}ClN_3$, M^++2), 309 (9%, $C_{15}H_{13}{}^{37}Cl_2N_3$, M^++4). Anal. Calcd. for $C_{15}H_{13}Cl_2N_3$ (306.19): C, 58.84; H, 4.28; N, 13.72. Found: C, 58.96; H, 4.05; N, 13.75.

2-(2,6-Dichloro-5-ethylpyrimidin-4-yl)-2-(2,6-difluorophenyl) acetonitrile (3e). This compound was obtained as yellow crystals; ^{1}H nmr ($CDCl_3$, 300 MHz): δ 1.09 (t, 3H, *J* = 7.2 Hz, *CH₃*CH_2), 2.81 (q, 2H, *J* = 7.2 Hz, CH_3*CH₂*), 5.72 (s, 1H, CH—CN), 7.03 (t, 2H, *J* = 8.4 Hz, H_{arom}), 7.26–7.44 ppm (m, 1H, H_{arom}); ^{13}C nmr ($CDCl_3$, 75 MHz): δ 11.76 (*C*H_3CH_2), 21.54 (CH_3*C*H_2), 31.66 (t, *J* = 2.6 Hz, CH—CN), 105.87 (C5), 108.81 (t, *J* = 16.9 Hz, C_{arom}), 112.27 (dd, *J* = 3.2, 22.3 Hz, C_{arom}), 114.69 (CN), 131.96 (t, *J* = 10.4 Hz, C_{arom}), 157.54 (C2), 158.84 (d, *J* = 6.1 Hz, C_{arom}), 161.95 (C4), 162.19 (d, *J* = 6.2 Hz, C_{arom}), 163.72 ppm (C6); ms: (70 eV, electron impact) *m/z* 308 (100%), 327 (69%, $C_{14}H_9{}^{35}Cl_2F_2N_3$, M^+), 329 (36%, $C_{14}H_9{}^{35}Cl^{37}ClF_2N_3$, M^++2), 331 (7%, $C_{14}H_9{}^{37}Cl_2F_2N_3$, M^++4). Anal. Calcd. for $C_{14}H_9Cl_2F_2N_3$ (328.14): C, 51.24; H, 2.76; N, 12.81. Found: C, 51.31; H, 2.26; N, 12.71.

2-(2,6-Dichloro-5-ethylpyrimidin-4-yl)-2-(3,5-dimethylphenyl) acetonitrile (3f). This compound was obtained as white crystals; ^{1}H nmr ($CDCl_3$, 300 MHz): δ 1.01 (t, 3H, *J* = 7.6 Hz, *CH₃*CH_2), 2.31 [s, 6H, (*CH₃*)$_2$Ar], 2.75 (q, 2H, *J* = 7.6 Hz, CH_3*CH₂*), 5.35 (s, 1H, CH—CN), 6.98 ppm (s, 3H, H_{arom}); ^{13}C nmr ($CDCl_3$, 75 MHz): δ 11.91 (*C*H_3CH_2), 21.21 (CH_3*C*H_2), 21.67 [(*C*H_3)$_2$Ar], 116.94 (CN), 125.43, 130.87, 131.67, 139.45 (C_{arom}), 132.04 (C5), 157.57 (C2), 163.98 (C4), 164.58 ppm (C6); hrms: (maldi) *m/z* calcd. for $C_{16}H_{16}Cl_2N_3$ (MH^+) 320.0716, found 320.0719.

Synthesis of 2-aryl-2-(2,6-dichloropyrimidin-4-yl)propanenitriles (4a,b). To a solution of **3a,b** (2 mmol) in dry dimethylformamide (10 mL) sodium hydride (131 mg, 3 mmol, 55% suspension in paraffin oil) was added portionwise at 0°C. The mixture was stirred for 1 h and then methyl iodide (0.19 mL, 3 mmol) was added at 0°C. The reaction mixture was stirred for 6 h at room temperature then poured on ice-cold water (100 mL). The mixture was extracted with ether (2 × 20 mL) and the combined ether phases were dried ($MgSO_4$) and evaporated under reduced pressure. The residual material was purified by a silica gel column chromatography using petroleum ether:ether (1:1, v/v) as eluent to afford compounds **4a,b**.

2-(2,6-Dichloropyrimidin-4-yl)-2-phenylpropanenitrile (4a). This compound was obtained as colorless prisms; ^{1}H nmr ($CDCl_3$, 400 MHz): δ 2.18 (s, 3H, CH_3), 7.36–7.45 (m, 3H, H_{arom}), 7.47 (s, 1H, H5), 7.49–7.51 ppm (m, 2H, H_{arom}); ^{13}C nmr ($CDCl_3$, 100 MHz): δ 25.80 (CH_3), 48.30 (*C*—CN), 117.63 (CN), 120.61 (C5), 126.19, 129.01, 129.41, 137.11 (C_{arom}), 160.93 (C4), 163.68 (C2), 171.49 ppm (C6); ms: (70 eV, electron impact) *m/z* 77 (100%), 277 (52%, $C_{13}H_9{}^{35}Cl_2N_3$, M^+), 279 (30%, $C_{13}H_9{}^{35}Cl^{37}ClN_3$, M^++2), 281 (6%, $C_{13}H_9{}^{37}Cl_2N_3$, M^++4). Anal. Calcd. for $C_{13}H_9Cl_2N_3$ (278.14): C, 56.14; H, 3.26; N, 15.11. Found: C, 56.70; H, 3.22; N, 15.11.

2-(2,6-Dichloropyrimidin-4-yl)-2-(3,5-dimethylphenyl)propanenitrile (4b). This compound was obtained as colorless prisms; ^{1}H nmr ($CDCl_3$, 400 MHz): δ 2.14 (s, 3H, CH_3), 2.33 [s, 6H, (C*H₃*)$_2$Ar], 6.99 (s, 1H, H_{arom}), 7.06 (s, 2H, H_{arom}), 7.43 ppm (s, 1H, H5); ^{13}C nmr ($CDCl_3$, 100 MHz): δ 21.36 [(*C*H_3)$_2$Ar], 25.65 (CH_3), 48.16 (*C*—CN), 117.77 (CN), 120.85 (C5), 123.87, 130.64, 136.99, 139.21 (C_{arom}), 160.85 (C4), 163.53 (C2), 171.80 ppm (C6); ms: (70 eV, electron impact) *m/z* 158 (100%), 305 (47%, $C_{15}H_{13}{}^{35}Cl_2N_3$, M^+), 307 (47%, $C_{15}H_{13}{}^{35}Cl^{37}ClN_3$, M^++2), 309 (9%, $C_{15}H_{13}{}^{37}Cl_2N_3$, M^++4). Anal. Calcd. for $C_{15}H_{13}Cl_2N_3$ (306.19): C, 58.84; H, 4.28; N, 13.72. Found: C, 58.71; H, 4.23; N, 13.57.

General procedure for synthesis of 6-arylalkylpyrimidine-2,4(*1H*,*3H*)-dione derivatives 5a–h. Each compound of **3a–f** and **4a,b** (5 mmol) was refluxed in a mixture of concentrated hydrochloric acid (30 mL) and acetic acid (5 mL) for 50 h. The reaction mixture was cooled to room temperature and the solid product formed was filtered off, washed with water, and dried to furnish compounds **5a–h**.

6-(2,6-Difluorobenzyl)pyrimidine-2,4(1*H*,3*H*)-dione (5b). This compound was obtained as a white solid; ^{1}H nmr (DMSO-*d₆*, 400 MHz): δ 3.75 (s, 2H, CH_2), 4.78 (s, 1H, H5), 7.18 (t, *J* = 8.0 Hz, 2H, H_{arom}), 7.44–7.51 (m, 1H, H_{arom}), 11.09 ppm (bs, 2H, 2NH) ; ^{13}C nmr (DMSO-*d₆*, 100 MHz): δ 24.42 (CH_2), 97.41 (C5), 110.80 (t, *J* = 20.2 Hz, C_{arom}), 111.69 (dd, *J* = 18.7, 6.2 Hz, C_{arom}), 130.21 (t, *J* = 10.3Hz, C_{arom}), 151.31 (C6), 153.54 (C2), 160.76 (dd, *J* = 246.8, 7.7 Hz, C_{arom}), 163.79 ppm (C4); ms: (70 eV, electron impact) *m/z* 68 (100%), 238 (79%, M^+). Anal. Calcd. for $C_{11}H_8F_2N_2O_2.0.4H_2O$ (245): C, 53.93; H, 3.46; N, 11.43. Found: C, 53.82; H, 3.15; N, 11.33.

6-(3,5-Dimethylbenzyl)pyrimidine-2,4(1*H*,3*H*)-dione (5c). This compound was obtained as a white solid; ^{1}H nmr (DMSO-*d₆*, 400 MHz): δ 2.25 (s, 6H, (C*H₃*)$_2$Ar)), 3.54 (s, 2H, CH_2), 5.23 (s, 1H, H5), 6.90 (s, 1H, H_{arom}), 6.93 (s, 2H, H_{arom}), 10.93 ppm (s, 2H, 2NH); ^{13}C nmr (DMSO-*d₆*, 100 MHz): δ 20.75 [$(CH_3)_2$Ar], 37.30 (CH_2), 98.70 (C5), 126.65, 128.29, 135.82, 137.44 (C_{arom}), 151.53 (C6), 155.61 (C2), 164.02 ppm (C4); ms: (70 eV, electron impact) *m/z* 187 (100%), 230 (49%, M^+). Anal. Calcd. for $C_{13}H_{14}N_2O_2{\cdot}0.25\ H_2O$ (232.07): C, 67.28; H, 6.17; N, 12.07. Found: C, 67.15; H, 6.13; N, 12.08

6-(Mesitylmethyl)pyrimidine-2,4(1*H*,3*H*)-dione (5d). This compound was obtained as a white solid; ^{1}H nmr (DMSO-*d₆*, 300 MHz): δ 2.15 (s, 6H, $2CH_3$), 2.23 (s, 3H, CH_3), 3.62 (s, 2H, CH_2), 4.40 (s, 1H, H5), 6.89 (s, 2H, H_{arom}), 10.98 ppm (bs, 2H, 2NH); ^{13}C nmr (DMSO-*d₆*, 75 MHz): δ 19.32 ($2CH_3$), 20.47 (CH_3), 30.94 (CH_2), 96.55 (C5), 128.68, 128.76, 136.00, 136.61 (C_{arom}), 151.47 (C4), 155.18 (C2), 163.97 ppm

(C6); hrms: (maldi) *m/z* Calcd. for $C_{14}H_{17}N_2O_2$ (MH^+) 245.1285, found 245.1294.

6-(2,6-Difluorobenzyl)-5-ethylpyrimidine-2,4(1H,3H)-dione (5e). This compound was obtained as a white solid; ^1H nmr (DMSO-d_6, 300 MHz): δ 0.60 (t, 3H, J = 7.4 Hz, CH_3CH_2), 2.12 (q, 2H, J = 7.4 Hz, CH_3CH_2), 3.82 (s, 2H, CH_2Ar), 7.11 (t, 2H, J = 8.3 Hz, H_{arom}), 7.37–7.43 (m, 1H, H_{arom}), 10.78 (s, 1H, NH), 11.04 ppm (s, 1H, NH); ^{13}C nmr (DMSO-d_6, 75 MHz): δ 12.54 (CH_3CH_2), 17.30 (CH_3CH_2), 23.72 (CH_2Ar), 111.23 (C5), 111.67 (dd, J = 7.5, 17.7 Hz, C_{arom}), 129.54 (t, J = 10.5 Hz, C_{arom}), 147.50 (C2), 150.73 (C6), 159.09 (d, J = 8.5 Hz, C_{arom}), 162.36 (d, J = 8.1 Hz, C_{arom}), 164.27 ppm (C4); ms: (70 eV, electron impact) *m/z* 266 (100%, M^+). Anal. Calcd. for $C_{13}H_{12}F_2N_2O_2$ (266.24): C, 58.65; H, 4.54; N, 10.52. Found: C, 58.68; H, 4.23; N, 10.38.

6-(1-Phenylethyl)pyrimidine-2,4(1H,3H)-dione (5g). This compound was obtained as a white solid; ^1H nmr (DMSO-d_6, 400 MHz): δ 1.48 (d, 3H, J = 7.3 Hz, CH_3CH), 3.80 (q, 1H, J = 7.3 Hz, CH_3CH), 5.41 (s, 1H, H5), 7.25–7.50 (m, 5H, H_{arom}), 10.83 (s, 1H, NH), 10.96 ppm (s, 1H, NH); ^{13}C nmr (DMSO-d_6, 100 MHz): δ 180.60 (CH_3), 41.27 (CH), 97.18 (C5), 126.98, 127.42, 128.44, 141.54 (C_{arom}), 151.55 (C6), 159.45 (C2), 164.15 ppm (C4); ms: (70 eV, electron impact) *m/z* 216 (100%, M^+). Anal. Calcd. for $C_{12}H_{12}N_2O_2.0.6H_2O$ (227.05): C, 63.48; H, 5.86; N, 12.34. Found: C, 63.46; H, 5.24; N, 12.57.

6-[1-(3,5-Dimethylphenyl)ethyl]pyrimidine-2,4(1H,3H)-dione (5h). This compound was obtained as a white solid; ^1H nmr (DMSO-d_6, 400 MHz): δ 1.44 (d, 3H, J = 7.3 Hz, CH_3CH), 2.25 [s, 6H, $(CH_3)_2Ar$], 3.70 (q, 1H, J = 7.3 Hz, CH_3CH), 5.39 (s, 1H, H5), 6.89 (s, 1H, H_{arom}), 6.95 (s, 2H, H_{arom}), 10.77 (s, 1H, NH), 10.94 ppm (s, 1H, NH); ^{13}C nmr (DMSO-d_6, 100 MHz): δ 18.59 (CH_3CH), 20.85 [$(CH_3)_2Ar$], 41.18 (CH_3CH), 97.06 (C5), 125.13, 128.38, 137.36, 141.35 (C_{arom}), 151.53 (C6), 159.59 (C2), 164.17 ppm (C4); ms: (70 eV, electron impact) *m/z* 158 (100%), 244 (86%, M^+). Anal. Calcd. for $C_{14}H_{16}N_2O_2$ (244.3): C, 68.83; H, 6.60; N, 11.47. Found: C, 68.35; H, 6.54; N, 11.62.

Synthesis of 6-arylmethyl-5-bromopyrimidine-2,4(1*H*, 3*H*)-diones (6a–d). A suspension of **5a–d** (2 mmol), *N*-bromosuccinimide (0.4 g, 2.25 mmol) and benzoyl peroxide (10 mg) in absolute ethanol (15 mL) was stirred for 5 h at room temperature. The solid product was filtered off, washed with ethanol (5 mL) and dried to afford compounds **6a–d**.

6-Benzyl-5-bromopyrimidine-2,4(1H,3H)-dione (6a). This compound was obtained as a white solid; ^1H nmr (DMSO-d_6, 400 MHz): δ 3.90 (s, 2H, CH_2), 7.25–7.37 (m, 5H, H_{arom}), 11.50 (s, 1H, NH), 11.53 ppm (s, 1H, NH); ^{13}C nmr (DMSO-d_6, 400 MHz): δ 37.96 (CH_2), 96.01 (C5), 126.95, 128.30, 128.58, 135.13 (C_{arom}), 150.31 (C6), 152.41 (C2), 160.15 ppm (C4); ms: (70 eV, electron impact) *m/z* 201 (100%), 280 (13%, $C_{11}H_9{}^{79}BrN_2O_2$, M^+), 282 (19%, $C_{11}H_9{}^{81}BrN_2O_2$, M^++2). Anal. Calcd. for $C_{11}H_9BrN_2O_2$ (281): C, 47.00; H, 3.23; N, 9.97. Found: C, 46.99; H, 3.12; N, 9.86.

5-Bromo-6-(2,6-difluorobenzyl)pyrimidine-2,4(1H,3H)-dione (6b). This compound was obtained as a white solid; ^1H nmr (DMSO-d_6, 400 MHz): δ 3.93 (s, 2H, CH_2); 7.11 (t, 2H, J = 8.3 Hz, H_{arom}), 7.37–7.44 (m, 1H, H_{arom}), 11.58 ppm (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 400 MHz): δ 26.98 (CH_2), 95.72 (C5), 110.96 (t, J = 19.1 Hz, C_{arom}), 111.55 (dd, J = 18.8, 6.2 Hz, C_{arom}), 129.67 (t, J =10.6 Hz, C_{arom}), 150.20 (C6), 151.28 (C2), 159.97 (C4), 160.41 ppm (dd, J =247.2, 8.1 Hz, C_{arom}); ms: (70 eV, electron impact) *m/z* 127 (100%), 316 (28%, $C_{11}H_7{}^{79}BrF_2N_2O_2$, M^+), 318 (23%, $C_{11}H_7{}^{81}BrF_2N_2O_2$, M^++2). Anal. Calcd. for $C_{11}H_7BrF_2N_2O_2$ (318.09): C, 41.67; H, 2.23; N, 8.83. Found: C, 41.46; H, 2.03; N, 8.64.

5-Bromo-6-(3,5-dimethylbenzyl)pyrimidine-2,4(1H,3H)-dione (6c). This compound was obtained as a white solid; ^1H nmr (DMSO-d_6, 400 MHz): δ 2.24 (s, 6H, $2CH_3$), 3.82 (s, 2H, CH_2), 6.89 (s, 1H, H_{arom}), 6.93 (s, 2H, H_{arom}), 11.42 (s, 1H, NH), 11.51 ppm (s, 1H, NH); ^{13}C nmr (DMSO-d_6, 100 MHz): δ 20.82 ($2CH_3$), 37.81 (CH_2), 95.95 (C5), 125.96, 128.33, 134.90, 137.51 (C_{arom}), 150.28 (C6), 152.45 (C2), 160.13 ppm (C4); ms: (70 eV, electron impact) *m/z* 158 (100%) 308 (22%, $C_{13}H_{13}{}^{79}BrN_2O_2$, M^+), 310 (20%, $C_{13}H_{13}{}^{81}BrN_2O_2$, M^++2). Anal. Calcd. for $C_{13}H_{13}BrN_2O_2$ (309.2): C, 50.50; H, 4.24; N, 9.06. Found: C, 50.78; H, 4.12; N, 8.97.

5-Bromo-6-(2,4,6-trimethylbenzyl)pyrimidine-2,4(1H,3H)-dione (6d). This compound was obtained as a white solid; ^1H nmr (DMSO-d_6, 400 MHz): δ 2.19 (s, 6H, $2CH_3$), 2.21 (s, 3H, CH_3), 3.90 (s, 2H, CH_2), 6.83 (s, 2H, H_{arom}), 10.60 (s, 1H, NH), 11.51 ppm (s, 1H, NH); ^{13}C nmr (DMSO-d_6, 100 MHz): δ 20.26 ($2CH_3$), 20.38 (CH_3), 95.65 (C5), 128.46, 128.88, 135.77, 137.20 (C_{arom}), 150.14 (C6), 152.61 (C2), 159.87 ppm (C4); ms: (70 eV, electron impact) *m/z* 243 (100%), 322 (21%, $C_{14}H_{15}{}^{79}BrN_2O_2$, M^+), 324 (19%, $C_{14}H_{15}{}^{81}BrN_2O_2$, M^++2). Anal. Calcd. for $C_{14}H_{15}BrN_2O_2$ (323.19): C, 52.03; H, 4.68; N, 8.67. Found: C, 51.93; H, 4.63; N, 8.49.

(3,5-Dimethylphenyl)(5-ethyl-2,6-dimethoxypyrimidin-4-yl) methanone (7). Sodium (0.3 g, 13 mmol) was dissolved in anhydrous methanol (15 mL) at 0°C. Compound **3f** (1 g, 3.1 mmol) was added and the mixture was refluxed for 20 h. Stream of oxygen was pumped through the solution at room temperature for 2 h, the solvent was concentrated to 5 mL under reduced pressure. Water (30 mL) was added to the mixture and the solid product formed was filtered off and dried to give 0.85 g (91%) of **7** as a white solid; mp 99–100°C, 97–99°C [27].

Synthesis of 1-(3,5-dimethylphenyl)-1-(5-ethyl-2,6-dimethoxypyrimidin-4-yl)ethanol (8). Under stream of nitrogen, a solution of MeMgBr (4 mL, 12 mmol, and 3 *M* in Et_2O) was added dropwise to a stirred solution of compound **7** (3.0 g, 10 mmol) in diethyl ether (20 mL) at –20°C, the reaction was left to reach room temperature with stirring for 2 h. The reaction was quenched by a saturated solution of ammonium chloride (10 mL). Water (10 mL) was added to the mixture and was extracted with ether (2 × 15 mL). The combined ether phases were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column using ether:petroleum ether (1:10, v/v) as eluent to afford 2.9 g of **8** as a colorless prisms; yield 92%; mp 73–75°C; ^1H nmr ($CDCl_3$, 300 MHz): δ 0.59 (t, 3H, J = 7.0 Hz, CH_3CH_2), 1.89 (s, 3H, CH_3—C—OH), 2.24 (q, 2H, J = 7.0 Hz, CH_3CH_2), 2.27 (s, 6H, $(CH_3)_2Ar$) 3.99 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 6.29 (s, 1H, OH), 6.88 (s, 1H, H_{arom}), 6.94 ppm (s, 2H, H_{arom}); ^{13}C nmr ($CDCl_3$, 75 MHz): δ 11.87 (CH_3CH_2), 18.56 (CH_3CH_2), 21.32 [$(CH_3)_2Ar$], 27.29 (CH_3—C—OH), 54.27, 54.67 (2 OCH_3), 74.41 (C—OH), 113.21 (C5), 124.17, 128.93, 137.58, 145.17 (C_{arom}), 161.08 (C6), 169.89 (C2), 171.33 ppm (C4); ms: (70 eV, electron impact) *m/z* 316 (100%, M^+).

Fluorination of 8: Synthesis of compounds 9 and 10. A solution of DAST (0.5 mL, 3.8 mmol) in 1 mL dichloromethane was added dropwise at –5°C to a solution of compound

8 (0.7 g, 2.5 mmol) in dichloromethane (10 mL) under argon at –5°C. The solution was stirred and left to reach room temperature for 4 h. The reaction was quenched by addition of 1 mL saturated solution of sodium carbonate with stirring. Water (10 mL) was added to the mixture and extracted with dichloromethane (2 × 10 mL). The combined dichloromethane phases were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed by a silica gel column using petroleum ether:ether (2:1, v/v) as eluent to give compounds **9** and **10**.

4-[1-(3,5-Dimethylphenyl)vinyl]-5-ethyl-2,6-dimethoxypyrimidine (9). This compound was obtained as a white solid; yield 37%; mp 112–114°C; ^{1}H nmr ($CDCl_3$, 300 MHz): δ 0.93 (t, 3H, J = 7.4 Hz, CH_3CH_2), 2.27 [s, 6H, $(CH_3)_2Ar$], 2.38 (q, 2H, J = 7.4 Hz, CH_3CH_2), 3.96 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 5.27, 5.81 (2s, 2H, $CH_2{=}C$), 6.92 ppm (s, 3H, H_{arom}); ^{13}C nmr ($CDCl_3$, 75 MHz): δ 13.59 (CH_3CH_2), 18.88 (CH_3CH_2), 21.26 [$(CH_3)_2Ar$], 53.90, 54.53 (2 OCH_3), 114.78 (C5), 115.54 ($CH_2{=}C$), 124.16, 129.65, 137.72, 146.43 (C_{arom}), 138.46 ($CH_2{=}C$), 162.83 (C2), 166.92 (C6), 171.12 ppm (C4); ms: (70 eV, electron impact) m/z 298 (100%, M^+). Anal Calcd. for $C_{18}H_{22}N_2O_2$ (298.38): Calcd: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.42; H, 7.53; N, 9.38.

4-[1-(3,5-Dimethylphenyl)-1-fluoroethyl]-5-ethyl-2,6-dimethoxypyrimidine (10). This compound was obtained as an oil; yield 28%; ^{1}H nmr ($CDCl_3$, 300 MHz): δ 0.86 (t, 3H, J = 7.3 Hz, CH_3CH_2), 2.00 (d, 3H, $J_{H,F}$ = 24.0 Hz, CH_3—C—F), 2.27 [s, 6H, $(CH_3)_2Ar$], 2-39–2.47 (m, 2H, CH_3CH_2), 3.97 (s, 1H, OCH_3), 4.02 (s, 3H, OCH_3), 6.88 (s, 1H, H_{arom}), 6.93 ppm (s, 2H, H_{arom}); ^{13}C nmr ($CDCl_3$, 75 MHz): δ 13.31 (d, J = 1.9 Hz, CH_3CH_2), 18.24 (d, J = 6.7 Hz, CH_3CH_2), 21.36 [$(CH_3)_2Ar$], 29.22 (d, J = 25.4 Hz, CH_3—C—F), 54.08 (OCH_3), 54.48 (OCH_3), 99.52 (d, J = 174.8 Hz, C—F), 115.68 (C5), 121.79 (d, J = 7.2 Hz, C_{arom}), 129.05 (C_{arom}), 137.66 (d, J = 1.3 Hz, C_{arom}), 143.99 (d, J = 23.7 Hz, C_{arom}), 161.88 (C2), 166.28 (d, J = 23.7 Hz, C4), 171.26 ppm (C6); hrms: (MALDI) m/z Calcd. for $C_{18}H_{24}FN_2O_2$ (MH^+) 319.1816, found 319.1808.

6-[1-(3,5-Dimethylphenyl)-1-fluoroethyl]-5-ethylpyrimidine-2,4(1*H*,3*H*)-dione (11). Under stream of nitrogen, a mixture of TMSI (0.16 mL, 1.1 mmol) and compound **10** (160 mg, 0.5 mmol) in dry chloroform (15 mL) was refluxed for 2 h and the mixture was left to reach room temperature. The reaction was quenched with 5% aqueous sodium bicarbonate solution (2 mL), water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with chloroform (2 × 10 mL). The chloroform phases were dried using sodium sulfate and evaporated under reduced pressure. The residual material was chromatographed on a silica gel column using ether as eluent to give 60 mg of **11** as a white solid; yield 63%; mp 200–202°C; ^{1}H nmr ($CDCl_3$, 300 MHz): δ 0.69 (t, 3H, J = 7.2 Hz, CH_3CH_2), 2.07 (q, 2H, J = 7.2 Hz, CH_3CH_2), 2.08 (d, 3H, $J_{H,F}$ = 24 Hz, CH_3—C—F), 2.34 [s, 6H, $(CH_3)_2Ar$], 7.04 (s, 3H, H_{arom}), 8.61 (s, 1H, NH), 9.72 ppm (s, 1H, NH); ^{13}C nmr ($CDCl_3$, 75 MHz): δ 12.29 (CH_3CH_2), 18.62 (CH_3CH_2), 21.30 [$(CH_3)_2Ar$], 24.30 (d, J = 26.5 Hz, CH_3—C—F), 95.29 (d, J = 174.5 Hz, C—F), 111.63 (C5), 123.97 (d, J = 5.1 Hz, C_{arom}), 131.50 (d, J = 3.3 Hz, C_{arom}), 138.59 (d, J = 2.1 Hz, C_{arom}), 138.18 (d, J = 20.8 Hz, C_{arom}), 149.93 (d, J = 43.5 Hz, C6), 150.29 (C2), 164.79 ppm (C4); hrms: (maldi) m/z Calcd. for $C_{16}H_{19}FNaN_2O_2$ (MNa^+) 313.1323, found 313.1323. Anal. Calcd. for $C_{16}H_{19}FN_2O_2 \cdot 0.7H_2O$ (302.95): C, 63.44; H, 6.79; N, 9.25. Found: C, 63.26; H, 6.51; N, 8.82.

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Syntheses and Reactions of Halo- and Arylazo-Substituted 3-(3-(2-Naphthyl)acryloyl)tropolones: Formation of (Naphthalen-2-yl)Vinyl)-Substituted Heterocycle-Fused Troponoid Compounds

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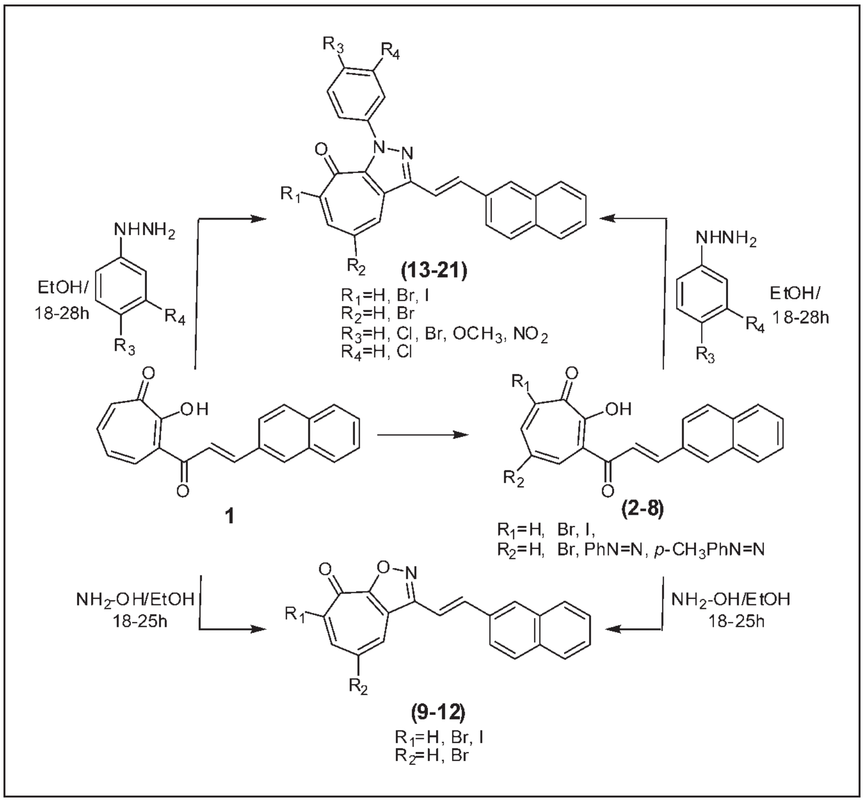

The starting substrate 3-(3-(2-naphthyl)acryloyl)tropolone (**1**) was achieved by the aldol condensation reaction of 3-acetyltropolone with 2-naphthaldehyde. Compound (**1**) reacted with bromine to give 7-bromo-(**2**) and 5,7-dibromo-3-(3-(2-naphthyl)acryloyl)tropolone (**3**) according to the amount of the brominated reagent. Iodination of **1** gave 7-iodo-3-(3-(2-naphthyl)acryloyl)tropolone (**4**). Azo-coupling reactions of **1**, **2**, and **4** gave 5-arylazo-3-(3-(2-naphthyl)acryloyl) tropolones (**5–8**). Compounds **1–4** reacted with hydroxyamine to give 3-[2-(2-naphthyl)vinyl]-8*H*-cyclohepta[*d*]isoxazol-8-ones (**9–12**). The reactions of **1–4** with phenylhydrazine and substituted phenylhydrazines gave 3-[2-(2-naphthyl)vinyl]-1-phenylcyclohepta[*c*]pyrazol-8(1*H*)-ones (**13–21**).

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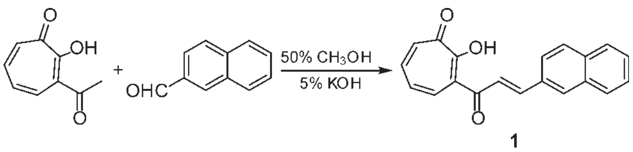
INTRODUCTION

Tropolone is an aromatic compound with a seven-membered ring, a metabolite of *Pseudomonas* sp.; the tropolone ring system represents the key structural element in a wide range of natural products, many of which are isolated from fungi [1] and higher plants [2]. Troponoids display various biological activities, such as pesticides [3], metals protease inhibition [4], and antifungal plant genetic disease genes [5]. Therefore, natural and synthetic tropolone derivatives have attracted considerable interest to organic chemists. The synthesis of substituted troponoids continues to be a considerable synthetic challenge. We have reported the electrophilic reactions of 3-acetyltropolone [6], 3-acetamidotropolone

Scheme 1



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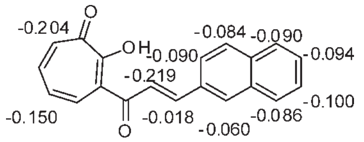


Figure 1. The calculated electronegativity of compound 1.

[7], 3-cinnamoyltropolone [8], 3-isopropenyltropolone [9], and 3-(2-quinolyl)tropolone [10], meanwhile various fused-heterocyclic troponoids have been prepared. In continuation of our interests in these compounds, we report the synthesis of 3-(3-(2-naphthyl)acryloyl)tropolone by the condensation of 3-acetyltropolone with 2-naphthaldehyde. 3-(3-(2-Naphthyl)acryloyl)tropolone possesses similar structure to 3-cinnamonytropolone and has three reactive parts for electrophilic reagents, two of which are seven-membered tropolone ring and a naphthalene ring and the third is a propenyl part between the two rings. Therefore, the reactions of 3-(3-(2-naphthyl)acryloyl)tropolone with electrophilic reagents are also expected to be interesting. On the other hand, the reactions with nucleophilic reagents are also of interest for participation of the tropolone ring, because chalcones reacted with hydroxylamine [11–14] and hydrazine [15–19] at the propenyl moiety to give diaryl-substituted isoxazolines and pyrazolines, respectively.

This article deals with the preparation of 3-(3-(2-naphthyl)acryloyl)tropolone as well as its electrophilic substitution reactions with halo and diazonium salts and the condensation reactions with hydroxylamine, phenylhydrazine, and substituted phenylhydrazines.

RESULTS AND DISCUSSION

The aldol condensation reactions of 3-acetyltropolone with substituted benzaldehydes [20] and heterocyclic aldehydes [21–23] have been reported. However, to our knowledge, the research of 3-acetyltropolone with 2-naphthaldehyde has never been performed, despite their important potential biological activities. Thus, we tried for the first time to study the preparation of 3-(3-(2-naphthyl)acryloyl)tropolone (**1**) from 3-acetyltropolone and 2-naphthaldehyde.

Scheme 1 outlines the aldol condensation reaction of 3-acetyltropolone with 2-naphthaldehyde using aqueous KOH (5%) as a catalyst and 50% methanol as solvent to furnish 3-(3-(2-naphthyl)acryloyl)tropolone (**1**) in 85.3% yield, mp 166–167°C. Its structure was established from the elemental analysis ($C_{20}H_{14}O_3$) and spectral data.

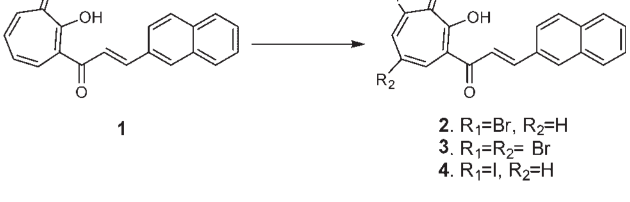
In its IR spectrum, an absorption band for the hydroxyl group was observed at 3190 cm^{-1}, and the two typical carbonyl absorption bands were observed at 1658 and 1613 cm^{-1}, respectively. The ^{1}H NMR spectrum showed a proton singlet at 7.98 (s, 1H) assignable to naphthalene H-1 and unresolved complex peaks at δ 7.14–7.86 for the protons of the aromatic ring and the exocyclic double bond. Moreover, the structure assigned for this reaction product was fully supported by its mass spectrum, which showed a molecular ion peak at 302 (M$^+$).

By theoretical calculation, the 5- and 7-position of the tropolone ring and the propenyl part have higher reactive activities than the naphthalene ring for electrophilic reagents, and their electronegativities are −0.150, −0.204, and −0.219, respectively, as shown in Figure 1.

To verify the calculated results, compound **1** was treated with some electrophilic reagents such as bromine, iodine, and diazonium salts. Thus, compound **1** was first subjected to react with bromine. When 3-(3-(2-naphthyl)acryloyl)tropolone (**1**) was reacted with bromine in acetic acid in a mole ratio of 1:1 or 1:2, the corresponding monosubstituted 7-bromo-3-(3-(2-naphthyl)acryloyl)tropolone (**2**) and disubstituted 5,7-dibromo-3-(3-(2-naphthyl)acryloyl)tropolone (**3**) were obtained in 67.7% and 73.2% yield, respectively (Scheme 2).

The structure of **2** was determined by the elemental analysis and spectral data. In the IR spectrum, an absorption band for the hydroxyl group was at 3180 cm^{-1}, and the two typical carbonyl absorption bands were observed at 1641 and 1601 cm^{-1}, respectively. The ^{1}H NMR spectrum showed a doublet at δ 8.50 (d, 1H, J = 8.5 Hz) assignable to tropolone H-4, a quartet at 7.76 (q, 1H, J = 10.0 Hz) attributable to tropolone H-5, a doublet at 8.18 (d, 1H, J = 10.0 Hz) for naphthalene H-6, a doublet at 7.99 (d, 1H, J = 6.3 Hz) for naphthalene H-1, and a triplet at 7.16 (t, 1H, J = 11.0 Hz) and a doublet at 7.26 (d, 1H, J = 15.6 Hz) for the proton of the carbon–carbon double bond, besides multiplet peaks at δ 7.50–7.56 and 7.83–7.87 for the

Scheme 2



1

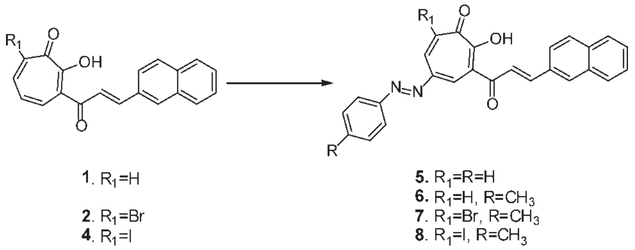
2. R_1=Br, R_2=H
3. R_1=R_2= Br
4. R_1=I, R_2=H

aromatic ring protons. It is worth mentioning that when compound **1** was treated with three equivalents of bromine, neither oxidative cyclization nor electrophilic addition reaction on carbon–carbon double bond occurred. Therefore, we concluded that the electrophilic reactivity of the 5- and 7-position of the tropolone ring were indeed higher than that of the naphthalene ring and of the propenyl part. The reaction of 3-(3-(2-naphthyl)acryloyl)tropolone (**1**) with excess iodine in the presence of potassium carbonate afforded only the monosubstituted compound 7-iodo-3-(3-(2-naphthyl)acryloyl)tropolone (**6**) in 51.9% yield. The reaction indicated that the 7-position of tropolone ring had the highest electrophilic activity, which is in agreement with the theoretically calculated results. In a similar method to compound **2**, the structures of **3** and **4** were also established from elemental analysis and spectral data. In addition, although the nitration of 3-acetyl, 3-acetamido, 3-cinnamoyl [6–8], and 3-(2-quinolyl)tropolone [10] gave 5-nitro- and/or 5,7-dinitro-substituted products, when 3-(3-(2-naphthyl)acryloyl)tropolone (**1**) was treated with concentrated or fuming nitric acid, any expected product was not observed. The reaction may proceed with an unknown mechanism that needs further investigation.

The azo-coupling reaction of tropolone took place exclusively at the 5-position to give crystalline dyes. The reactions of 3-(3-(2-naphthyl)acryloyl)tropolone (**1**) with diazonium salts gave 5-arylazo-substituted 3-(3-(2-naphthyl)acryloyl)tropolones (**5** and **6**) in 47.8% and 76.2% yield, respectively. The compounds (**2**) and (**4**) were also reacted with *p*-toluidine diazonium salt to afford 7-bromo-3-(3-(2-naphthyl)acryloyl)-5-(*p*-tolyldiazenyl)tropolone (**7**) and 7-iodo-3-(3-(2-naphthyl)acryloyl)-5-(*p*-tolyldiazenyl)tropolone (**8**) in 28.5% and 20.9% yield, respectively. These structures were confirmed from the elemental analysis and spectral data (see Experimental section). For example, in the IR spectrum of compound **5**, an absorption band for the hydroxyl group was at 3185 cm^{-1}, for the tropolone carbonyl group was at 1648 cm^{-1}, and for the propenyl carbonyl group was at 1608 cm^{-1}. Its ^1H NMR spectrum showed peaks at δ 8.53 (d, 1H, $J = 2.1$ Hz) for tropolone H-4, at 8.31 (q, 1H, $J = 2.2$ Hz) for tropolone H-6, at 7.99 (s, 1H) for naphthalene H-1, at 7.74 (dd, 1H, $J = 16.0$, 2.2 Hz) for tropolone H-7, and an unresolved complex peaks at δ 7.73–7.93 and 7.34–7.59 for the protons of the aromatic ring and carbon–carbon double bond (Scheme 3).

As attacking site of nucleophilic reagents, chalcones have an enone moiety that connects two benzene rings. Thus, it has been reported that the chalcones reacted with hydroxylamine [11–14] and hydrazine [15–19] to afford diphenyl-substituted isoxazolines and pyrazolines, respectively. On the other hand, we found that 3-acetyl [6] and 3-cinnamoyltropolone [8] reacted with various nucleophilic reagents bearing two reactive sides to give a wide variety of heterocycle-fused troponoid compounds [24].

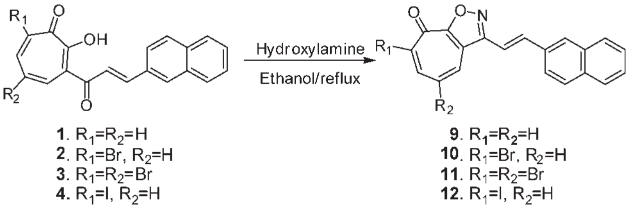
Scheme 3



The reactions of 3-(3-(2-naphthyl)acryloyl)tropolone (**1**) with hydroxylamine in refluxing ethanol gave 3-[2-(2-naphthyl)vinyl]-8*H*-cyclohepta[*d*]isoxazol-8-one (**9**) in 47.7% yield. In the IR spectrum of **9**, the disappearance of characteristic hydroxyl and carbonyl absorption for tropolone and the carbonyl group in the side chain and the appearance of tropone carbonyl absorption at 1629 cm^{-1} were clear evidence for the formation of a new compound. Its ^1H NMR spectrum showed the absence of the hydroxy OH signal in addition to 7.12 (q, 1H, $J = 8.5$ Hz), 7.23 (d, 1H, $J = 16.0$ Hz) for carbon–carbon double bond protons, 7.29 (d, 1H, $J = 12.6$ Hz) for tropolone H-7, 7.44 (dd, 1H, $J = 4.0$, 8.2 Hz) for tropolone H-5, 7.77 (q, 1H, $J = 16.5$ Hz) for tropolone H-6, 7.98 (s, 1H) for naphthalene H-1, 8.21 (d, 1H, $J = 4.5$ Hz) for tropolone H-4, besides an unresolved complex peaks in the aromatic region at δ 7.51–7.54 and 7.85–7.90. The mass spectrum exhibited a molecular ion 299 (M^+), which matched the expected molecular weight for the corresponding compound **9**. The elemental analysis further supported the assigned structure. The vital characteristic structure of compound **9** could be authenticated by a simple method: when the compound was developed on thin layer chromatography (TLC) (silica gel: GF254, developing agent: ethyl acetate), there was only one main spot with no tailing, as well as giving a negative coloring test with iron (β) chloride in ethanol solution. In a similar way, the reactions of compounds **2**, **3**, and **4** with hydroxylamine also afforded the corresponding 5-substituted or 5,7-substituted 3-[2-(2-naphthyl)vinyl]-8*H*-cyclohepta[*d*]isoxazol-8-ones (**10–12**), and their structures were determined on the basis of a negative coloring test with iron (III) chloride and the elemental analysis as well as on spectral data (Scheme 4).

When a solution of 3-(3-(2-naphthyl)acryloyl)tropolone (**1**) and phenylhydrazine in ethanol was refluxed for 18 h, the 3-[2-(2-naphthyl)vinyl]-1-phenylcyclohepta[*c*]pyrazol-8(1*H*)-one (**13**) was isolated in 19.3% yield.

Scheme 4



1. $R_1=R_2=H$
2. $R_1=Br$, $R_2=H$
3. $R_1=R_2=Br$
4. $R_1=I$, $R_2=H$

9. $R_1=R_2=H$
10. $R_1=Br$, $R_2=H$
11. $R_1=R_2=Br$
12. $R_1=I$, $R_2=H$

Its structure was confirmed from the elemental analysis ($C_{26}H_{18}N_2O$) and spectral data. The IR spectrum showed the absorption for tropone carbonyl group at 1630 cm^{-1}. Its ^1H NMR spectrum showed the absence of the hydroxy OH signal, and all the protons were observed at δ 6.86 (q, 1H, $J = 8.4$ Hz) for tropolone H-5, 7.94 (s, 1H) for naphthalene H-1, 6.99 (d, 1H, $J = 12.5$ Hz) for one proton of carbon–carbon double bond, 7.25–7.30 (m, 1H) for tropolone H-7, 7.44–7.52 (m, 8H), 7.77–7.87 (m, 6H) for the aromatic region and the other protons of carbon–carbon double bond. The compound (**1**) reacted with 4-nitro, 4-bromo, 4-chloro, 4-methoxy, and 3-chlorophenylhydrazines to give 3-(2-(2-naphthyl)vinyl)-1-(4-nitrophenyl)cyclohepta[*c*]pyrazol-8 (1*H*)-one (**14**), 1-(4-bromophenyl)-3-(2-(2-naphthyl)vinyl)cyclohepta[*c*]pyrazol-8(1*H*)-one (**15**), 1-(4-chlorophenyl)-3-(2-(2-naphthyl)vinyl)cyclohepta[*c*]pyrazol-8(1*H*) -one (**16**), 1-(4-methoxyphenyl)-3-(2-(2-naphthyl)vinyl)cyclohepta[*c*]pyrazol-8(1*H*)-one (**17**), and 1-(3-chlorophenyl)-3-(2-(2-naphthyl)vinyl)cyclohepta[*c*]-pyrazol-8(1*H*) -one (**18**) in 57.6%, 53.8%, 43.3%, 26.2%, and 41.2% yield, respectively. The electrophilic substitution products (**2–4**) reacted with phenylhydrazine and also gave the corresponding 1,8-dihydrocycloheptapyrazol-8-one derivatives (**19–21**). In conclusion, this investigation has demonstrated the synthesis of naphthalene-substituted tropolones and troponoids compounds (Scheme 5).

EXPERIMENTAL

The melting points were determined by using WRS-1B melting points apparatus. ^1H NMR was measured with a Varian Inova 500 NMR spectrometer at 500 MHz or a Varian Inova 400 NMR spectrometer at 400 MHz. The reported chemical shifts were against TMS. Mass spectra were determined using a MSD VL ESII spectrometer. Elemental analysis was performed using an Elementar Vario EL-III element analyzer.

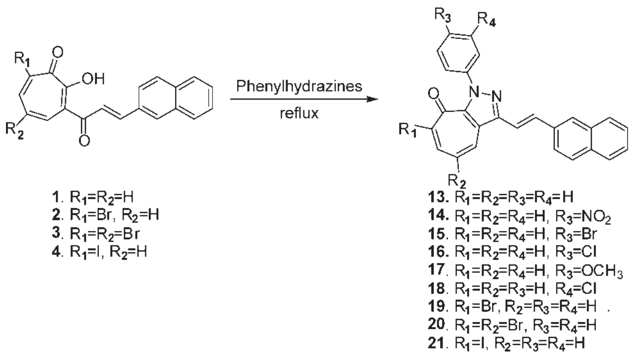
3-(3-(2-Naphthyl)acryloyl)tropolone (1). To a stirred solution of 3-acetyltropolone and 2-naphthaldehyde in 50% methanol, a solution of 5% KOH aqueous was added dropwise at room temperature. Having monitored by TLC, and after the reaction was completed, the mixture was acidified with 6*M* hydrochloric acid to precipitate yellow crystals. The crystals were collected and recrystallized from ethanol to give 3-(3-(2-naphthyl)acryloyl)tropolone (**1**) as yellow crystals, yield 85.3%; mp 166–167°C; IR (KBr): 3190 (OH), 1658 (C=O), 1613 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.14–7.86 (m, 12H, Ar-H and HC=CH), 7.98 (s, 1H, 2-NaphthH-1); ms: *m*/*z* 303 $(M+1)^+$. Anal. Calcd. for $C_{20}H_{14}O_3$: C, 79.46; H, 4.67. Found: C, 79.30; H, 4.52.

7-Bromo-3-(3-(2-naphthyl)acryloyl)tropolone (2). To a stirred solution of 3-(3-(2-naphthyl) acryloyl)tropolone (0.302 g, 1 mmol) and sodium acetate (0.125 g) in acetic acid (50 mL), a solution of bromine (0.160 g, 1 mmol) in acetic acid (2 mL) was added dropwise at room temperature. After the reaction was completed, water (100 mL) was added. The precipitate was collected and recrystallized from ethyl acetate to give 7-bromo-3-(3-(2-naphthyl)acryloyl)tropolone as yellow crystals, yield 70.6%; mp 182–184°C; IR (KBr): 3180 (OH), 1641 (C=O), 1601 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.16 (t, 1H, —C=CH, $J = 11.0$ Hz), 7.26 (d, 1H, CH=C—, $J = 15.6$ Hz), 7.50–7.56 (m, 2H, Ar-H), 7.76 (q, 1H, tropolone H-5, $J = 10.0$ Hz), 7.83–7.87 (m, 4H, Ar-H), 7.99 (d, 1H, 2-NaphthH-1, $J = 6.3$ Hz), 8.18 (d, 1H, tropolone H-6, $J = 10.0$ Hz), 8.50 (d, 1H, tropolone H-4, $J = 8.5$ Hz); ms: *m*/*z* 381 $(M+1)^+$. Anal. Calcd. for $C_{20}H_{13}BrO_3$: C, 63.01; H, 3.44. Found: C, 62.97; H, 3.20.

5,7-Dibromo-3-(3-(2-naphthyl)acryloyl)tropolone (3). To a stirred solution of sodium acetate and 3-(3-(2-naphthyl)acryloyl)tropolone (0.302 g,1 mmol) in acetic acid, a solution of bromine (0.320 g, 2 mmol) in acetic acid (2 mL) was added dropwise at room temperature. After completion, the mixture was poured into water (150 mL), and then the precipitate was collected and recrystallized from ethyl acetate to give 5,7-dibromo-3-(3-(2-naphthyl)acryloyl)tropolone as yellowish blue powder, yield 72.3%; mp 212–213°C; IR (KBr): 3185 (OH), 1647 (C=O), 1592 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.25 (d, 1H, —C=CH, $J = 15.9$ Hz), 7.50–7.56 (m, 2H, Ar-H), 7.71 (q, 1H, —C=CH, $J = 1.6$ Hz), 7.83–7.87 (m, 4H, Ar-H), 7.78 (d, 1H, tropolone H-6, $J = 15.9$ Hz), 7.99 (s, 1H, 2-NaphthH-1), 8.50 (d, 1H, tropolone H-4, $J = 2.0$ Hz); ms: *m*/*z* 461 $(M+1)^+$. Anal. Calcd. for $C_{20}H_{12}Br_2O_3$: C, 52.21; H, 2.63. Found: C, 52.01; H, 2.45.

7-Iodo-3-(3-(2-naphthyl)acryloyl)tropolone (4). To a stirred mixture of 3-(3-(2-naphthyl)acryloyl)tropolone (0.302 g,1 mmol) and potassium carbonate (0.305 g) in water (0.85 mL), a solution of iodine (0.325 g) and potassium iodide (0.325 g) in water (1.85 mL) was added in an ice water bath. After being stirred for 11.5 h, excess iodine was reduced with

Scheme 5



1. $R_1=R_2=H$
2. $R_1=Br$, $R_2=H$
3. $R_1=R_2=Br$
4. $R_1=I$, $R_2=H$

13. $R_1=R_2=R_3=R_4=H$
14. $R_1=R_2=R_4=H$, $R_3=NO_2$
15. $R_1=R_2=R_4=H$, $R_3=Br$
16. $R_1=R_2=R_4=H$, $R_3=Cl$
17. $R_1=R_2=R_4=H$, $R_3=OCH_3$
18. $R_1=R_2=R_3=H$, $R_4=Cl$
19. $R_1=Br$, $R_2=R_3=R_4=H$
20. $R_1=R_2=Br$, $R_3=R_4=H$
21. $R_1=I$, $R_2=R_3=R_4=H$

sodium hydrogen sulfite. The mixture was acidified with 6*M* hydrochloric acid (80 mL) to precipitate pale greenish crystals. The crystals were collected and recrystallized from ethyl acetate to give 7-iodo-3-(3-(2-naphthyl)acryloyl)tropolone as pale greenish crystals, yield 52.0%; mp 197–198°C; IR (KBr): 3179 (OH), 1670 (C=O), 1585 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.78 (t, 1H, CH=C—, *J* = 10.25 Hz), 7.29 (d, 1H, —C=CH, *J* = 15.9 Hz), 7.49–7.54 (m, 2H, Ar-H), 7.82–7.86 (m, 4H, Ar-H), 7.57 (dd, 1H, tropolone H-5, *J* = 7.5, 4.0 Hz), 7.75 (d, 1H, tropolone H-6, *J* = 10.2 Hz), 7.98 (s, 1H, 2-NaphthH-1), 8.49 (d, 1H, *J* = 10.0 Hz, tropolone H-4); ms: *m*/*z* 429 $(M+1)^+$. Anal. Calcd. for $C_{20}H_{13}IO_3$: C, 56.10; H, 3.06. Found: C, 56.14; H, 2.85.

3-(3-(2-Naphthyl)acryloyl)-5-(phenyldiazenyl)tropolone (5). To an ice-cooled stirred solution of compound **1** (0.302 g, 1 mmol) in pyridine (4 mL), arenediazonium chloride solution (2 mmol, 2 mL), prepared from aniline or *p*-toluidine, was added dropwise. After additional stirring for 2–3 h, the precipitate was collected and recrystallized from benzene or ethyl acetate to give product (**5**) as pale yellow crystals, yield 47.8%; mp 190–191°C; IR (KBr): 3185 (OH), 1648 (C=O), 1608 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.34–7.59 (m, 6H, Ar-H and CH=CH), 7.74 (dd, 1H, tropolone H-7, *J* = 16.0, 2.2 Hz), 7.73–7.93 (m, 7H, Ar-H), 7.99 (s, 1H, 2-NaphthH-1), 8.31 (q, 1H, tropolone H-6, *J* = 2.2 Hz), 8.53 (d, 1H, tropolone H-4, *J* = 2.1 Hz); ms: *m*/*z* 407 $(M+1)^+$. Anal. Calcd. for $C_{26}H_{18}N_2O_3$: C, 76.83; H, 4.46; N, 6.89. Found: C, 76.79; H, 4.29; N, 6.87.

3-(3-(2-Naphthyl)acryloyl)-5-(*p*-tolyldiazenyl)tropolone (6). The same experimental method as compound (**5**) was followed. This compound was obtained as deep red powder, yield 76.2%; mp 173–174°C; IR (KBr): 3203 (OH), 1673 (C=O), 1610 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.44 (s, 3H, CH_3), 7.30–7.58 (m, 6H, Ar-H and CH=CH), 7.73 (q, 1H, tropolone H-7, *J* = 1.5 Hz), 7.82–7.86 (m, 6H, Ar-H), 7.99 (s, 1H, 2-NaphthH-1), 8.28 (q, 1H, tropolone H-6, *J* = 2.1 Hz), 8.50 (d, 1H, tropolone H-4, *J* = 2.0 Hz); ms: *m*/*z* 421 $(M+1)^+$. Anal. Calcd. for $C_{27}H_{20}N_2O_3$: C, 77.13; H, 4.79; N, 6.66. Found: C, 77.11; H, 4.58; N, 6.53.

7-Bromo-3-(3-(2-naphthyl)acryloyl)-5-(*p*-tolyldiazenyl)tropolone (7). The same experimental method as compound (**5**) was followed. The compound was obtained as orange crystals, yield 38.5%; mp > 290°C; IR (KBr): 3210 (OH), 1673 (C=O), 1608 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.45 (s, 3H, —CH_3), 7.31–7.80 (m, 6H, Ar-H and CH=CH), 7.84–7.87 (m, 6H, Ar-H), 8.00 (s, 1H, 2-NaphthH-1), 8.38 (d, 1H, tropolone H-6, *J* = 2.0 Hz), 9.02 (d, 1H, tropolone H-4, *J* = 1.6 Hz); ms: *m*/*z* 499 $(M+1)^+$. Anal. Calcd. for $C_{27}H_{19}BrN_2O_3$: C, 64.94; H, 3.84; N, 5.61. Found: C, 64.89; H, 3.50; N, 5.65.

7-Iodo-3-(3-(2-naphthyl)acryloyl)-5-(*p*-tolyldiazenyl)tropolone (8). The same experimental method of compound (**7**) was followed. This compound was obtained as deep red crystals, yield 20.9%; mp > 290°C; IR (KBr): 3304 (OH), 1682 (C=O), 1617 (C=O) cm^{-1}; δ 2.45 (s, 3H, —CH_3), 7.30–7.55 (m, 3H, Ar-H and CH=C—), 7.75–7.87 (m, 9H, Ar-H and —C=CH), 8.00 (s, 1H, 2-NaphthH-1), 8.36 (d, 1H, tropolone H-6, *J* = 2.0 Hz), 9.26 (d, 1H, tropolone H-4, *J* = 1.6 Hz); ms: *m*/*z* 547 $(M+1)^+$. Anal. Calcd. for $C_{27}H_{19}IN_2O_3$: C, 59.35; H, 3.51; N, 5.13. Found: C, 59.38; H, 3.1 6; N, 5.10.

3-[2-(2-Naphthyl)vinyl]-8*H*-cyclohepta[*d*]isoxazol-8-one (9). A solution of 3-(3-(2-naphthyl)acryloyl)tropolone (0.151 g, 0.5 mmol) and hydroxylamine hydrochloride (0.071 g, 1 mmol) in ethanol (5 mL) was refluxed for 12 h. The precipitate was collected and recrystallized from acetic acid to give 3-[2-(2-naphthyl)vinyl]-8*H*-cyclohepta[*d*]isoxazol-8-one as pale brown powder, yield 47.7%; mp 252–253°C; IR (KBr): 1629 (C=O), 1573 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.12 (q, 1H, CH=C—, *J* = 8.5 Hz), 7.23 (d, 1H, —C=CH, *J* = 16.0 Hz), 7.51–7.54 (m, 2H, Ar-H), 7.29 (d, 1H, tropolone H-7, *J* = 12.6 Hz), 7.44 (dd, 1H, tropolone H-5, *J* = 4.0, 8.2 Hz), 7.77 (q, 1H, tropolone H-6, *J* = 16.5 Hz), 7.85–7.90 (m, 4H, Ar-H), 7.98 (s, 1H, 2-NaphthH-1), 8.21 (d, 1H, tropolone H-4, *J* = 4.5 Hz); ms: *m*/*z* 300 $(M+1)^+$. Anal. Calcd. for $C_{20}H_{13}NO_2$: C, 80.25; H, 4.38; N, 4.68. Found: C, 80.17; H, 4.01; N, 4.82.

7-Bromo-3-[2-(2-naphthyl)vinyl]-8*H*-cyclohepta[*d*]isoxazol-8-one (10). A solution of 7-bromo-3-(3-(2-naphthyl)acryloyl)tropolone (0.100 g) and hydroxylamine hydrochloride (0.036 g) in ethanol (5 mL) was refluxed for 20 h. The precipitate was collected and recrystallized from acetic acid to give 7-bromo-3-[2-(2-naphthyl)vinyl]-8*H*-cyclohepta[*d*]isoxazol-8-one as golden powder, yield 41.4%; mp 243–244°C; IR (KBr): 1670 (C=O), 1549 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.30–7.79 (m, 8H, Ar-H and CH=CH), 7.53 (q, 1H, tropolone H-5, *J* = 3.2 Hz), 7.88 (d, 1H, tropolone H-6, *J* = 6.8 Hz), 7.94 (s, 1H, 2-NaphthH-1), 8.41(d, 1H, tropolone H-4, *J* = 10.0 Hz); ms: *m*/*z* 378 $(M+1)^+$. Anal. Calcd. for $C_{20}H_{12}BrNO_2$: C, 63.51; H, 3.20; N, 3.70. Found: C, 63.33; H, 3.50; N, 3.59.

5,7-Dibromo-3-[2-(2-naphthyl)vinyl]-8*H*-cyclohepta[*d*]isoxazol-8-one (11). A solution of 5,7-dibromo-3-(3-(2-naphthyl)acryloyl)tropolone (0.100 g) and hydroxylamine hydrochloride (0.030 g) in ethanol (5 mL) was refluxed for 28 h. The precipitate was collected and recrystallized from ethyl acetate to give 5,7-dibromo-3-[2-(2-naphthyl)vinyl]-8*H*-cyclohepta[*d*]isoxazol-8-one as brown crystals, yield 60.7%; mp 196–197°C; IR (KBr): 1679 (C=O), 1560 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.89–7.24 (m, 8H, Ar-H and CH=CH), 7.78 (d, 1H, tropolone H-6, *J* = 12.7 Hz), 7.99 (s, 1H, 2-NaphthH-1), 8.51 (d, 1H, tropolone H-4, *J* = 1.5 Hz); ms: *m*/*z* 458 $(M+1)^+$. Anal. Calcd. for $C_{20}H_{11}Br_2NO_2$: C, 52.55; H, 2.43; N, 3.06. Found: C, 52.41; H, 3.39; N, 3.18.

7-Iodo-3-[2-(2-naphthyl)vinyl]-8*H*-cyclohepta[*d*]isoxazol-8-one (12). A solution of 7-iodo-3-(3-(2-naphthyl)acryloyl)tropolone (0.100 g) and hydroxylamine hydrochloride (0.032 g) in ethanol (5 mL) was refluxed for 24 h. The precipitate was collected and recrystallized from tetrahydrofuran to give 7-iodo-3-[2-(2-naphthyl)vinyl]-8*H*-cyclohepta[*d*]isoxazol-8-one as pale brown powder, yield 41.0%; mp 275°C decomposition; IR (KBr): 1692 (C=O), 1602 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.81–7.24 (m, 2H, CH=CH), 7.85–7.90 (m, 6H, Ar-H), 7.53 (q, 1H, tropolone H-5, *J* = 3.6 Hz), 7.78 (d, 1H, tropolone H-6, *J* = 8.4 Hz), 7.99 (s, 1H, 2-NaphthH-1), 8.76 (d, 1H, tropolone H-4, *J* = 9.2 Hz); ms: *m*/*z* 426 $(M+1)^+$. Anal. Calcd. for $C_{20}H_{12}INO_2$: C, 56.49; H, 2.84; N, 3.29. Found: C, 56.42; H, 2.61; N, 3.34.

Synthesis of 2-vinyl naphthalene heterocycle-fused troponoid compounds (13–18). A mixture of 3-(3-(2-naphthyl)acryloyl)tropolone (0.151 g, 0.5 mmol) and substituted phenylhydrazines (1 mmol) in ethanol (10 mL) was refluxed for 18–28 h. The precipitates were collected and recrystallized to give the products.

3-[2-(2-Naphthyl)vinyl]-1-phenylcyclohepta[c]pyrazol-8(1H)-one (13). This compound was obtained as golden needles, yield 19.3%; mp 193–194°C; IR (KBr): 1630 (C=O), 1600 (C=N)

cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.86 (q, 1H, tropolone H-5, J = 8.4 Hz), 6.99 (d, 1H, CH=C—, J = 12.5 Hz), 7.25–7.30 (m, 1H, tropolone H-7), 7.44–7.52 (m, 8H, Ar-H and CH=C—), 7.77–7.87 (m, 6H, Ar-H), 7.94 (s, 1H, 2-NaphthH-1); ms: m/z 375 $(M+1)^+$. Anal. Calcd. for $C_{26}H_{18}N_2O$: C, 83.40; H, 4.85; N, 7.48. Found: C, 83.17; H, 5.30; N, 7.45.

3-(2-(2-Naphthyl)vinyl)-1-(4-nitrophenyl)cyclohepta[c]pyrazol-8(1H)-one (14). This compound was obtained as brown powder, yield 57.6%; mp 280°C decomposition; IR (KBr): 1630 (C=O), 1604 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.95–7.10 (m, 2H, Ar-H and CH=C—), 7.43–7.51 (m, 4H, Ar-H and —C=CH), 7.66 (d, 2H, Ar-H, J = 9.2 Hz), 7.80–7.89 (m, 6H, Ar-H), 7.96 (s, 1H, 2-NaphthH-1), 8.37 (d, 2H, Ar-H, J = 9.2 Hz); ms: m/z 420 $(M+1)^+$. Anal. Calcd. for $C_{26}H_{17}N_3O_3$: C, 74.45; H, 4.09; N, 10.02. Found: C, 74.51; H, 4.38; N, 9.99.

1-(4-Bromophenyl)-3-(2-(2-naphthyl)vinyl)cyclohepta[c]-pyrazol-8(1H)-one (15). This compound was obtained as yellow crystals, yield 53.8%; mp 284–285°C; IR (KBr): 1625 (C=O), 1576 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.91 (t, 1H, tropolone H-5, J = 5.6 Hz), 7.01 (d, 1H, CH=C—, J = 8.0 Hz), 7.26–7.64 (m, 8H, Ar-H and CH=C—), 7.77–7.86 (m, 6H, Ar-H), 7.95 (s, 1H, 2-NaphthH-1); ms: m/z 453 $(M+1)^+$. Anal. Calcd. for $C_{26}H_{17}BrN_2O$: C, 68.89; H, 3.78; N, 6.18. Found: C, 68.80; H, 3.87; N, 6.07.

1-(4-Chlorophenyl)-3-(2-(2-naphthyl)vinyl)cyclohepta[c]-pyrazol-8(1H)-one (16). This compound was obtained as pale yellow crystals, yield 26.2%; mp 212–213°C; IR (KBr): 1652 (C=O), 1590 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.90–7.02 (m, 2H, Ar-H and —C=CH), 7.27 (d, 1H, tropolone H-7, J = 11.2 Hz), 7.39–7.50 (m, 7H, Ar-H and CH=C—), 7.77–7.88 (m, 6H, Ar-H), 7.94 (s, 1H, 2-NaphthH-1); ms: m/z 409 $(M+1)^+$. Anal. Calcd. for $C_{26}H_{17}ClN_2O$: C, 76.37; H, 4.19; N, 6.85. Found: C, 76.30; H, 3.95; N, 6.80.

1-(4-Methoxyphenyl)-3-(2-(2-naphthyl)vinyl)cyclohepta[c]-pyrazol-8(1H)-one (17). This compound was obtained as golden powder, yield 43.3%; mp 277–278°C; IR (KBr): 1660 (C=O), 1587 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.89 (s, 3H, —OCH_3), 6.86 (q, 1H, tropolone H-5, J = 10.0 Hz), 7.01 (d, 1H, tropolone H-7, J = 4.8 Hz), 7.37–7.50 (m, 7H, Ar-H and CH=CH), 7.77–7.85 (m, 7H, Ar-H), 7.94 (s, 1H, 2-NaphthH-1); ms: m/z 405 $(M+1)^+$. Anal. Calcd. for $C_{27}H_{20}N_2O_2$: C, 80.18; H, 4.98; N, 6.93. Found: C, 80.11; H, 4.73; N, 6.94.

1-(3-Chlorophenyl)-3-(2-(2-naphthyl)vinyl)cyclohepta[c]-pyrazol-8(1H)-one (18). This compound was obtained as golden crystals, yield 41.2%; mp 247°C decomposition; IR (KBr): 1639 (C=O), 1574 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.91 (q, 1H, tropolone H-5, J = 10.0 Hz), 7.02 (d, 1H, —C=CH, J = 12.8 Hz), 7.35–7.52 (m, 8H, Ar-H and CH=C—), 7.77–7.84 (m, 6H, Ar-H), 7.95 (s, 1H, 2-NaphthH-1); ms: m/z 409 $(M+1)^+$. Anal. Calcd. for $C_{26}H_{17}ClN_2O$: C, 76.37; H, 4.19; N, 6.85. Found: C, 76.25; H, 4.50; N, 6.90.

7-Bromo-3-[2-(2-naphthyl)vinyl]-1-phenylcyclohepta[c]pyrazol-8(1H)-one (19). A mixture of 7-bromo-3-(3-(2-naphthyl)acryloyl)tropolone (0.100 g) and phenylhydrazine hydrochloride (0.056 g) in absolute ethanol (5 mL) was refluxed for 19 h. The precipitate was collected and recrystallized from ethyl acetate to give 7-bromo-3-[2-(2-naphthyl)vinyl]-1-phenylcyclohepta[*c*]pyrazol-8(1*H*)-one as yellow crystals, yield 29.0%; mp 288–289°C; IR (KBr): 1644 (C=O), 1589 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.75 (q, 1H, tropolone H-5, J = 9.6 Hz), 7.47–7.52 (m, 6H, Ar-H and CH=CH), 7.81–7.90 (m, 7H, Ar-H), 7.94 (s, 1H, 2-NaphthH-1), 8.28 (d, 1H, tropolone H-6, J = 6.8 Hz), 8.51 (d, 1H, tropolone H-4, J = 8.0 Hz); ms: m/z 453 $(M+1)^+$. Anal. Calcd. for $C_{26}H_{17}BrN_2O$: C, 68.89; H, 3.78; N, 6.18. Found: C, 68.70; H, 3.47; N, 6.07.

5,7-Dibromo-3-[2-(2-naphthyl)vinyl]-1-phenylcyclohepta[c]-pyrazol-8(1H)-one (20). A mixture of 5,7-dibromo-3-(3-(2-naphthyl)acryloyl)tropolone (0.100 g) and phenylhydrazine hydrochloride (0.048 g) in absolute ethanol (5 mL) was refluxed for 22 h. The precipitate was collected and recrystallized from ethyl acetate to give 5,7-dibromo-3-[2-(2-naphthyl)-vinyl]-1-phenylcyclohepta[*c*] pyrazol-8(1*H*)-one as orange crystals, yield 35.0%; mp > 290°C; IR (KBr): 1656 (C=O), 1591 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.26–7.53 (m, 5H, Ar-H and CH=CH), 7.80–7.87 (m, 8H, Ar-H), 7.95 (s, 1H, 2-NaphthH-1), 8.16 (d, 1H, tropolone H-6, J = 1.6 Hz), 8.52 (d, 1H, tropolone H-4, J = 1.6 Hz); ms: m/z 533 $(M+1)^+$. Anal. Calcd. for $C_{26}H_{16}Br_2N_2O$: C, 58.67; H, 3.03; N, 5.26. Found: C, 58.63; H, 3.29; N, 5.33.

7-Iodo-3-[2-(2-naphthyl)vinyl]-1-phenylcyclohepta[c]pyrazol-8(1H)-one (21). A mixture of 7-iodo-3-(3-(2-naphthyl)acryloyl)tropolone (0.100 g) and phenylhydrazine hydrochloride (0.051 g) in absolute ethanol (5 mL) was refluxed for 47 h. The precipitate was collected and recrystallized from ethyl acetate to give 7-iodo-3-[2-(2-naphthyl)vinyl]-1-phenylcyclohepta[*c*]pyrazol-8(1*H*)-one as yellowish blue powder, yield 24.0%; mp >290°C; IR (KBr): 1635 (C=O), 1581 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.60 (t, 1H, tropolone-5, J = 10.0 Hz), 7.41–7.43 (m, 2H, CH=CH), 7.43–7.52 (m, 5H, Ar-H), 7.79–7.88 (m, 6H, Ar-H), 7.87 (d, 1H, tropolone H-6, J = 2.4 Hz), 7.94 (s, 1H, 2-NaphthH-1), 8.63 (d, 1H, tropolone-4, J = 9.6 Hz); ms: m/z 501 $(M+1)^+$. Anal. Calcd. for $C_{26}H_{17}IN_2O$: C, 62.41; H, 3.42; N, 5.60. Found: C, 62.32; H, 3.64; N, 5.71.

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Microwave-Assisted Cadogan Reaction for the Synthesis of 2-Aryl-2*H*-indazoles, 2-Aryl-1*H*-benzimidazoles, 2-Carbonylindoles, Carbazole, and Phenazine

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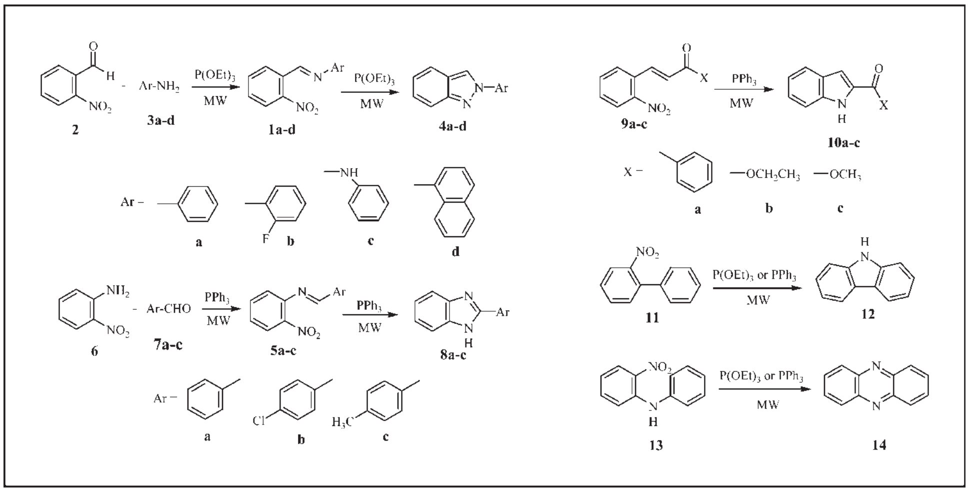

The Cadogan reaction, a widely accepted route for the synthesis of nitrogen containing heterocycles, is modified by using microwave radiation as the source of heat instead of the conventional heating by reflux in a nitrogen atmosphere for several hours. Appropriate starting materials were mixed with triethyl phosphite or triphenylphosphine and irradiated with microwaves for several minutes at a specific power to give the desired products. The indazoles were prepared by irradiating *N*-(2-nitrobenzylidene) anilines with triethyl phosphite at 200 W for 12–14 min to give 85–92% product yields. Irradiation of the mixture of *N*-benzylidene-2-nitroanilines and triphenylphosphine at 200 W for 3–5 min yielded 93–96% of the benzimidazoles. The carbonylindoles were obtained in 61–68% yields by irradiating 2-nitrochalcone or alkyl 2-nitrocinnamates and triphenylphosphine with microwaves at 80–200 W for 8–11 min. The mixture of 2-nitrobiphenyl and triphenylphosphine yielded 96% of carbazole when irradiated with microwaves at 200 W for 2 min while 75% of phenazine was obtained by irradiating the mixture of 2-nitrodiphenylamine and triphenylphosphine with microwaves at 200 W for 3.5 min. These results show that microwave-assisted Cadogan reactions gave better product yields at shorter reaction times.

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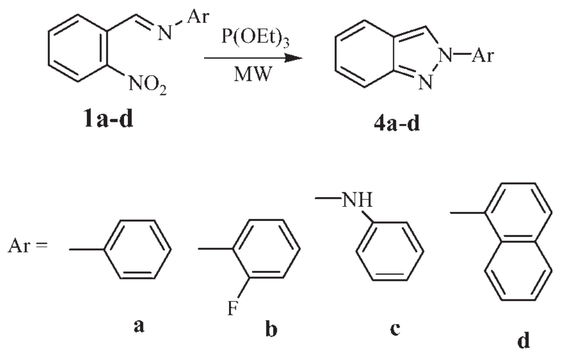
INTRODUCTION

The search for better methods for the syntheses of *N*-containing heterocyclic compounds has never ended as evidenced by the increasing number of articles devoted to this topic. This has led some researchers to look into the possibility of improving the reaction by heating the reaction mixture with microwave radiation instead of the usual conventional heating procedure. The microwave ovens have been with us for some time now but it was not until 1986 when researchers started to utilize the microwave oven for chemical syntheses [1]. Since then, many researchers have been using the technique for organic syntheses, thus contributing to the enormous volume of literatures we now see in print. Microwave-assisted heating under controlled conditions is a valuable technology for chemical syntheses as it can increase the rate of reaction, improve the product yield, and reduce the formation of side products [2].

Several methods for the syntheses of indazoles, indoles and benzimidazoles have been modified by carrying out the reactions under microwave irradiation [3].

Scheme 1



Dubey and Moorthy did a comparative study on conventional and microwave assisted synthesis of benzimidazoles and their derivatives and concluded that the microwave assisted reactions have reduced the reaction times by 96–98% and increased the yields by about 10 to 50% [3(d)]. Yu *et al.* and Navarrete-Vazquez *et al.* have developed a simple and rapid synthesis of substituted benzimidazoles under solvent-free condition using readily available reagents and the microwave oven [3(l,m)]. Sridar as well as Abramovitch and Bulman have reported that rate enhancement in the Fischer indole synthesis was observed when assisted by microwave radiations, that the reaction goes to completion in a short time furnishing good yields [3(n,o)]. Furthermore, Varma described the microwave-enhanced solvent-free synthetic approach to a variety of heterocyclic compounds and observed that the method was simple, easy to manipulate, uses minimal amounts of solvents, and give good product yields [3(p)]. Thus, the prospect of using microwave radiation for organic synthesis seems to be limitless, offering routes of shorter reaction times, minimal side products, and better product yields. It is this idea that led our laboratory to venture into microwave-assisted organic synthesis.

The reduction or deoxygenation of aromatic nitrocompounds by triethyl phosphite and related reagents is referred to as the Cadogan reaction [4]. The reaction is carried out at high temperature under nitrogen atmosphere for several hours. This reaction has been widely investigated as a synthetic route for *N*-containing heterocycles [5] and since the discovery of the reaction in 1962 [4], the reduction of aromatic nitro-compounds by triethyl phosphite and related reagents has been exploited as a route to a wide variety of nitrogen

Table 1

Microwave-assisted Cadogan reaction for the synthesis of 2-aryl-2*H*-indazoles.

Entry	Starting material[a,b]	P(OEt)$_3$ (mmol)	Power (W)	Time (minutes)	Power (W)	Time (minutes)	Product	Yield[c] (%)
1	**1a**	4.0	600	4	–	–	**4a**	33
2	**1a**	4.0, 4.0[d]	600	4, 4	–	–	**4a**	67
3	**1a**	4.0	200	14	–	–	**4a**	77
4	**1a**	8.0	200	14	–	–	**4a**	76
5	**1a**	4.0, 4.0[e]	200	14, 14	–	–	**4a**	86
6	**1a**	4.0, 4.0, 4.0[f]	200	14, 14, 14	–	–	**4a**	89
7	**1b**	4.0	200	13	–	–	**4b**	92
8	**1c**	4.0	200	12	–	–	**4c**	85
9	**1d**	4.0	200	14	–	–	**4d**	89
10[g]	**2 + 3a**	4.0	200	9	–	–	**4a**	17
11[g]	**2 + 3b**	4.0	200	10	–	–	**4b**	16
12[g]	**2 + 3c**	4.0	200	12	–	–	**4c**	47
13[g]	**2 + 3d**	4.0	200	12	–	–	**4d**	32
14[h]	**2 + 3a**	4.0	80	2	200	8	**4a**	45
15[h]	**2 + 3b**	4.0	80	2	200	12	**4b**	38
16[h]	**2 + 3c**	4.0	80	1	200	12	**4c**	63
17[h]	**2 + 3d**	4.0	80	2	200	11	**4d**	55

[a] Starting material: 1.0 mmol.

[b] Reaction vessel: test tube.

[c] Isolated yield.

[d] The starting material was added with 4.0 mmol P(OEt)$_3$ and irradiated for 4 min followed by the addition of another 4 mmol P(OEt)$_3$ and irradiated for 4 min more.

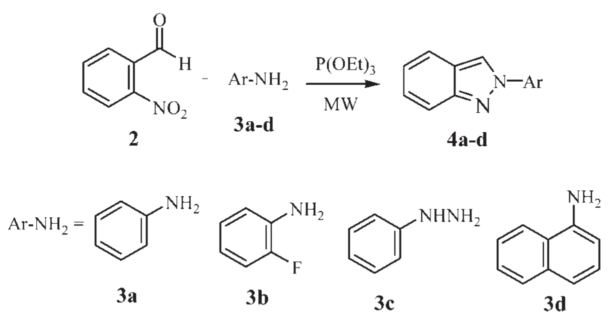
[e] The starting material was added with 4.0 mmol P(OEt)$_3$ and irradiated for 14 min followed by the addition of another 4 mmol P(OEt)$_3$ and irradiated for 14 min more.

[f] Same as [e], after which another 4 mmol of P(OEt)$_3$ was added and the mixture irradiated for 14 min more.

[g] One-pot-one-step reaction.

[h] One-pot-two-steps reaction.

Scheme 2



containing heterocyclic compounds, including carbazoles [4,6], indoles [4,7], indazoles [6], and other related compounds [5(b),6,8].

Because of the versatility of Cadogan reaction, a number of researchers have tried to modify the method to shorten the reaction time and improve the yield by using microwave radiations as the source of heat and were successful [9].

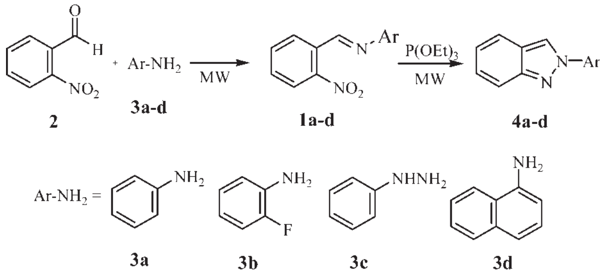
In this article, we report the microwave-assisted Cadogan reaction for the synthesis of indazoles, benzimidazoles, indoles, carbazole and phenazine.

RESULTS AND DISCUSSION

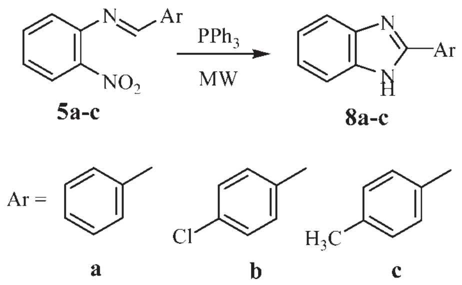
The starting materials used were either synthesized according to literature or purchased from the manufacturer and used as received. The Cadogan reaction was done by irradiating the starting materials with microwaves from a domestic microwave oven. For the synthesis of indazoles, the imines **1a–d** were mixed with triethyl phosphite and irradiated with microwaves to give the corresponding indazoles **4a–d** (Scheme 1). The results are tabulated in Table 1. Initially, 1.0 mmol of *N*-(2-nitrobenzylidene)aniline **1a** was added with 4.0 mmol triethyl phosphite in a Pyrex test tube and irradiated for 4 min at 600 W. The reaction afforded 2-phenyl-2*H*-indazole **4a** in 33% yield (Table 1, Entry 1). The procedure was repeated but this time after 4 min of irradiation, another 4.0 mmol of triethyl phosphite was added and the mixture irradiated for 4 min more. This resulted to an increase in the yield (67%) of 2-phenyl-2*H*-indazole **4a** (Table 1, Entry 2). However, the reaction mixture showed signs of decomposition, so the reaction was further investigated by using lower power rating. A mixture of 1.0 mmol of *N*-(2-nitrobenzylidene)aniline **1a** and 4.0 mmol of triethyl phosphite was irradiated for 14 min at 200 W. The reaction afforded 2-phenyl-2*H*-indazole **4a** in 77% yield (Table 1, Entry 3). Increasing the amount of triethyl phosphite to 8.0 mmol and irradiating the mixture for 14 minutes at 200 W did not give any significant change in the yield (76%, Table 1, Entry 4). The procedure was repeated using 4.0 mmol of triethyl phosphite. After irradiation for 14 min, the mixture was added with another 4.0 mmol of triethyl phosphite and irradiated for another 14 min at 200 W. The reaction afforded 2-phenyl-2*H*-indazole **4a** in 86% yield (Table 1, Entry 5). A third addition of 4.0 mmol of triethyl phosphite and 14 min more of irradiation gave only a slight increase in the yield of 2-phenyl-2*H*-indazole **4a** (89%, Table 1, Entry 6). These results show that irradiation of the mixture of *N*-(2-nitrobenzylidene)aniline **1a** and triethyl phosphite at 200 W gave better results than irradiation of the mixture at 600 W, and a second addition of the triethyl phosphite can increase the yield further. This method gave a better yield of 2-phenyl-2*H*-indazole **4a** (89%) compared to that reported by Song and Yee in the palladium-catalyzed intramolecular amination of *N*-phenyl-*N*-(*o*-bromobenzyl)hydrazine which yielded only 58% of 2-phenyl-2*H*-indazole **4a** after 15 h [10]. On the other hand, Varughese *et al.* reported a 60–65% yields of 2-phenyl-2*H*-indazole **4a** by the microwave-assisted Cadogan reaction of 2-nitrobenzaldehyde and aniline [9(b)] while the classical Cadogan method yielded 60% of 2-phenyl-2*H*-indazole **4a** after 6 h [6,11].

For the other three imines, **1b-d**, the reaction was carried out at 200W and various reaction times. When 1.0 mmol of *N*-(2-nitrobenzylidene)-2-fluoroaniline **1b** and 4.0 mmol triethyl phosphite were mixed and irradiated for 13 min at 200 W, 92% of 2-(2-fluorophenyl)-2*H*-indazole **4b** was obtained (Table 1, Entry 7). Irradiation of 1-(2-nitrobenzylidene)-2-phenylhydrazine **1c** at 200 W for 12 min gave 85% of 2-phenylamino-2*H*-indazole **4c** (Table 1, Entry 8). Dyablo *et al.* obtained 16% of 2-phenylamino-2*H*-indazole **4c** by mixing the corresponding amine with cupric acetate, phenylboric acid and triethylamine and stirring the mixture at 20°C for 17 h [12]. Irradiation of *N*-(2-nitrobenzylidene)-1-naphthylamine **1d** at 200 W for 14 min gave 89% of 2-(1-naphthyl)-2*H*-indazole **4d** (Table 1, Entry 9). The classical Cadogan reaction produced 51% of 2-α-naphthylamine after 6 h [6]. Sequential addition of triethyl phosphite

Scheme 3



Scheme 4

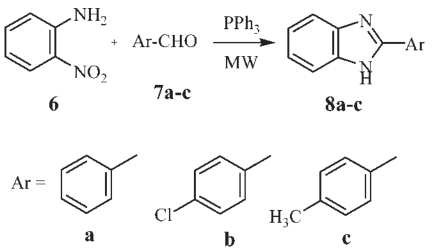


was no longer done because yields of the products were already good.

In the interest of saving time, a one-pot-one-step and one-pot-two-steps reaction procedures for the synthesis of indazoles were developed. For the one-pot-one-step procedure, 2-nitrobenzaldehyde **2** and aryl amines **3a-d** were mixed together in a test tube and added with triethyl phosphite. This mixture was then irradiated at 200 W for several minutes (Scheme 2). The results in Table 1 show that the procedure gave a fair yield of 2-phenylamino-2*H*-indazole **4c** when the mixture was irradiated for 12 min at 200 W (47%, Table 1, Entry 12). For the one-pot-two-steps procedure, 2-nitrobenzaldehyde **2** and aryl amines **3a–d** were mixed in a test tube and irradiated at 80 W for 1–2 min. After this, triethyl phosphite was added and the mixture irradiated again at 200 W for several minutes (Scheme 3). The results show that this method gave higher yields compared to the one-pot-one-step procedure (Table 1, Entries 14–17). However, the synthesis of indazoles from the starting imines is a better method as it gave better yield. These imply that the formation of the imine is an important step in the synthesis of indazoles.

For the synthesis of benzimidazoles, the imines **5a–c** were added with triethyl phosphite and irradiated with microwaves for several minutes at a specific power. However, the reactions gave poor product yields.

Scheme 5



Triethyl phosphite was replaced with triphenylphosphine as this reagent can also deoxygenate aromatic nitro-compounds and is easily handled, inexpensive and a stable solid (Scheme 4) [6,13]. One millimole of *N*-benzylidene-2-nitroaniline **5a** was mixed with 4.0 mmol of triphenylphosphine and irradiated with microwaves for 5 min at 200 W. The reaction gave 96% of 2-phenyl-1*H*-benzimidazole **8a** (Table 2, Entry 1). 2-(4-Chlorophenyl)-1*H*-benzimidazole **8b** and 2-(4-methylphenyl)-1*H*-benzimidazole **8c** were also synthesized from the corresponding imines, *N*-(4-chlorobenzylidene)-2-nitroaniline **5b** and *N*-(4-methylbenzylidene)-2-nitroaniline **5c**, respectively, by irradiating the mixture with microwaves for 3 min at 200 W. The reactions gave 94% of 2-(4-chlorophenyl)-1*H*-benzimidazole **8b** and 93% of 2-(4-methylphenyl)-1*H*-benzimidazole **8c** (Table 2, Entries 2, 3). The group of Sharghi reported the synthesis of benzimidazoles by the reaction of phenylenediamine and benzaldehyde in the presence of phorphyrinatoiron(III) complex as catalyst. They were able to synthesize 2-phenyl-1*H*-benzimidazole **8a** at 97% by carrying out the reaction for 30 min, 2-(4-chlorophenyl)-1*H*-benzimidazole **8b** at 94% by carrying out the reaction for 55 min and 2-(4-methylphenyl)-1*H*-benzimidazole **8c** at 95% by carrying out the reaction for 55 min [14]. The results of the two methods are comparable but the microwave-assisted Cadogan reaction does not require a metal-complex catalyst and was complete in 3 to 5 min only. Other researchers also reported the synthesis of 2-

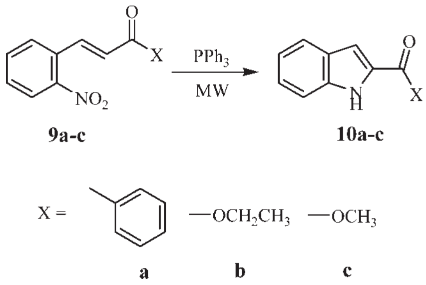
Table 2

Microwave-assisted Cadogan reaction for the synthesis of 2-aryl-1*H*-benzimidazoles.

Entry	Starting material[a,b]	PPh_3 (mmol)	Power (W)	Time (minutes)	Product	Yield[c] (%)
1	**5a**	4.0	200	5	**8a**	96
2	**5b**	4.0	200	3	**8b**	94
3	**5c**	4.0	200	3	**8c**	93
4[d]	**6 + 7a**	4.0	200	4	**8a**	82
5[d]	**6 + 7b**	4.0	200	2.5	**8b**	78
6[d]	**6 + 7c**	4.0	200	4	**8c**	81

[a] Starting material: 1.0 mmol.
[b] Reaction vessel: test tube.
[c] Isolated yield.
[d] One-pot-one-step reaction.

Scheme 6

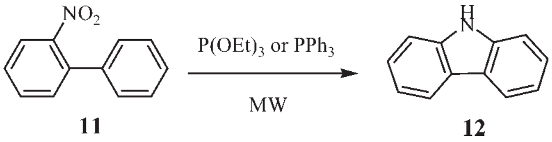


phenylbenzimidazole by other methods but the yields were relatively low and reaction times longer [15].

The one-pot-one-step synthesis of the benzimidazoles (Scheme 5) gave relatively lower yields compared to the synthesis from the corresponding imines (Table 2, Entries 4, 5, 6). However, the one-pot-one-step synthesis is a simple and convenient procedure.

The carbonylindoles were synthesized using 2-nitrochalcone **9a** and alkyl 2-nitrocinnamates **9b-c**. The reaction with triethyl phosphite gave low product yields so triphenylphosphine was used instead (Scheme 6). The reaction of 2-nitrochalcone **9a** with triphenylphosphine at 200 W and 8 min gave 68% of 2-benzoylindole **10a** (Table 3, Entry 1). Mahboobi *et al.* obtained 73% 2-benzoylindole **10a** from a reaction which required heating the reagents under reflux for 12 h [16]. On the other hand, the reaction with ethyl 2-nitrocinnamate **9b** yielded 64% of 2-ethoxycarbonylindole **10b** while reaction with methyl 2-nitrocinnamate **9c** yielded 61% of 2-methoxycarbonylindole **10c**, with the reactions being carried out at 80 W for 10 min and 11 min, respectively (Table 3, Entries 2, 3). At higher power, decomposition products are formed. Csomos *et al.* obtained 83% of 2-ethoxycarbonylindole **10b** by reacting indole-2-carboxylic acid, thionyl chloride and dry ethanol, and carrying out the reaction at different temperatures, requiring a total of 4.5 h for the reaction to complete [17]. Cadogan *et al.* reacted *o*-nitrocinnamic acid with triethyl phosphite for 24 h to give 7.5% of 2-ethoxycarbonylindole **10b** [6]. Sechi *et al.*, on the other hand, heated azidocinnamates in xylene under reflux for 15 min to yield 67% of 2-methoxycarbonylindole **10c** [18].

Scheme 7



Deoxygenation of 2-nitrobiphenyl **11** to give carbazole **12** was done with triethyl phosphite and triphenylphosphine (Scheme 7). The results show that 64% of carbazole **12** was obtained when 2-nitrobiphenyl **11** and triethyl phosphite were irradiated with microwaves for 7.5 min at 600 W while 96% of carbazole **12** was obtained when triphenylphosphine was used instead and irradiating the mixture for 2 min at 200 W (Table 4, Entries 2, 3). With the classical Cadogan reaction, 82.5% of carbazole **12** was obtained by refluxing 2-nitrobiphenyl **11** and triethyl phosphite, under nitrogen atmosphere, for 9 hours, and 43% of carbazole **12** was obtained when triphenylphosphine was used and the mixture placed in a sealed tube and heated at 130°C for 9 h [6]. On the other hand, Freeman *et al.* obtained 91% of carbazole **12** by refluxing 2-nitrobiphenyl **11** in triphenylphosphine for 21 h [13(a)]. When 2-nitrodiphenylamine **13** was mixed with triethyl phosphite and irradiated with microwaves for 5 min at 600 W, 43% of phenazine **14** was obtained (Table 4, Entry 4) (Scheme 8). When triphenylphosphine was used and the mixture irradiated at 200 W for 3.5 min, 75% of phenazine **14** was obtained (Table 4, Entry 5).

The results in this article indicate that the use of microwave radiation greatly enhances the yield of the products and reduces the reaction time from hours to minutes. When decomposition is observed, triphenylphosphine is a better alternative because the reaction can be carried out at lower power and still gives good yields. The procedure can be used to synthesize a variety of *N*-containing heterocyclic compounds once the appropriate starting materials have been prepared.

Table 3

Microwave-assisted Cadogan reaction for the synthesis of 2-carbonylindoles from chalcone and alkyl 2-nitrocinnamates.

Entry	Starting material[a]	PPh_3 (mmol)	Power (W)	Time (minutes)	Product	Yield[b] (%)
1[c]	**9a**	4.0	200	8	**10a**	68
2[d]	**9b**	3.0	80	10	**10b**	64
3[d]	**9c**	3.0	80	11	**10c**	61

[a] Starting material: 1.0 mmol.
[b] Isolated yield.
[c] reaction vessel: test tube.
[d] reaction vessel: 50-mL round bottom flask.

Table 4

Microwave-assisted Cadogan reaction for the synthesis of carbazole and phenazine.

Entry	Starting material	(POEt)$_3$ (mmol)	PPh$_3$ (mmol)	Power (W)	Time (minutes)	Product	Yield[a] (%)
1[b]	**11**[c]	4.0	–	600	15	**12**	63
2[d]	**11**[e]	3.0	–	600	7.5	**12**	64
3[d]	**11**[c]	–	3.0	200	2	**12**	96
4[d]	**13**[e]	2.0	–	600	5	**14**	43
5[d]	**13**[c]	–	3.0	200	3.5	**14**	75

[a] Isolated yield.

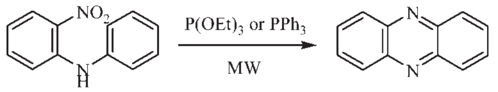
[b] Reaction vessel: 50-mL Erlenmeyer flask.

[c] Starting material: 1.0 mmol.

[d] Reaction vessel: test tube.

[c] Starting material: 0.5 mmol.

Scheme 8



13 **14**

EXPERIMENTAL

The microwave oven used for the reactions was Model YD-17 (W), Yoshii Electric Co., Ltd. The reaction vessel was either a Pyrex test tube (15 mm i.d. × 19 mm o.d. × 129 mm h.) placed in a 50-mL Erlenmeyer flask for support, a 50-mL round bottom flask placed in a beaker for support, or a 50-mL Erlenmeyer flask. The melting points are uncorrected. Column chromatography was performed on silica gel (Wakogel C-200). Unless otherwise stated, anhydrous sodium sulfate was used as the drying agent. The IR spectra were measured on a Hitachi Model 270-30 IR spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were measured at 500 MHz and 125 MHz, respectively, on a Varian Unity plus-500W NMR spectrometer, using tetramethylsilane as the internal standard. The starting materials were synthesized according to literature while those which were available commercially were used as received.

***N*-(2-nitrobenzylidene)aniline (1a).** Compounds **1a–d** were prepared according to the procedure in literature [9(b)]. *o*-Nitrobenzaldehyde (3.022 g, 20 mmol) and aniline (2.235 g, 24 mmol) were placed into a 100 mL round bottom flask. The mixture was heated in a water bath at 70°C for 15 min with continuous stirring. The resulting product was separated from the mixture and recrystallized from ethanol to give yellow plates of *N*-(2-nitrobenzylidene)aniline **1a** (4.203 g, 93%), mp 63–64°C (ref. [9(b)] mp 64–65°C); IR (KBr): 1518 cm^{-1} and 1346 cm^{-1} (NO$_2$); ^{1}H NMR (CDCl$_3$): δ 7.26–7.31 (m, 3H, 3 Ar-H), 7.43 (dd, *J* = 7.5 Hz and 7.5 Hz, 2H, 2 Ar-H), 7.63 (dd, *J* = 7.5 Hz and 7.5 Hz, 1H, Ar-H), 7.75 (dd, *J* = 7.5Hz and 7.5Hz, 1H, Ar-H), 8.08 (d, *J* = 7.5Hz, 1H, Ar-H), 8.32 (d, *J* = 7.5Hz, 1H, Ar-H), 8.95 (s, 1H, N=CH); ^{13}C NMR (CDCl$_3$): δ 121.2 (d), 124.5 (d), 126.9 (d), 129.2 (d), 129.7 (s), 131.1 (d), 131.2 (d), 133.5 (d), 149.3 (s), 151.0 (s), 155.8 (d).

***N*-(2-nitrobenzylidene)-2-fluoroaniline (1b).** *o*-Nitrobenzaldehyde (3.022 g, 20 mmol) and 2-fluoroaniline (2.667 g, 24 mmol) were placed into a 100-mL round bottom flask. The mixture was heated in a water bath at 70°C for 15 min with continuous stirring. The resulting product was separated from the mixture and recystallized from ethanol to give yellow needles of *N*-(2-nitrobenzylidene)-2-fluoroaniline **1b** (4.099 g, 84%), mp 76–78°C (ref. [19] mp 72–73°C); IR (KBr): 1520 cm^{-1} and 1348 cm^{-1} (NO$_2$); ^{1}H NMR (CDCl$_3$): δ 7.15–7.26 (m, 4H, 4 Ar-H), 7.65 (dd, *J* = 8.0 Hz and 8.0 Hz, 1H, Ar-H), 7.76 (dd, *J* = 8.0 Hz and 8.0 Hz, 1H, Ar-H), 8.10 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.35 (d, *J* = 8.0 Hz, 1H, Ar-H), 9.02 (s, 1H, N=CH); ^{13}C NMR (CDCl$_3$): δ 116.3 (d), 121.8 (s), 124.5 (d), 124.6 (d), 127.7 (d), 129.9 (d), 130.9 (s), 131.5 (d), 133.7(d), 139.4 (d), 149.2 (s), 155.4 (s), 158.2 (d).

1-(2-nitrobenzylidene)-2-phenylhydrazine (1c) [20]. *o*-Nitrobenzaldehyde (3.022 g, 20 mmol) and phenylhydrazine (2.595 g, 24 mmol) were placed into a 100-mL round bottom flask. The mixture was heated in a water bath at 70°C for 5 min with continuous stirring. The product was separated from the mixture and recrystallized from ethanol to give red crystals of 1-(2-nitrobenzylidene)-2-phenylhydrazine **1c** (4.627 g, 96%), mp 118–119°C (ref. [20] mp 117°C); IR (KBr): 3292 cm^{-1} (NH), 1532 cm^{-1}, and 1334 cm^{-1} (NO$_2$); ^{1}H NMR (CDCl$_3$): δ 6.93 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.14 (d, *J* = 8.0 Hz, 2H, 2 Ar-H), 7.31 (dd, *J* = 8.0 Hz and 8.0 Hz, 2H, 2 Ar-H), 7.40 (dd, *J* = 8.0 Hz and 8.0 Hz, 1H, Ar-H), 7.61 (dd, *J* = 8.0 Hz and 8.0 Hz, 1H, Ar-H), 7.99 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.06 (br s, 1H, Ph-NH), 8.27 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.32 (s, 1H, N=CH); ^{13}C NMR (CDCl$_3$): δ 113.1 (d), 121.0 (d), 124.8 (d), 127.7 (s), 128.1 (d), 129.4 (d), 130.4 (d), 131.6 (d), 133.1 (d), 143.8 (s), 146.9 (s).

***N*-(2-nitrobenzylidene)-1-naphthylamine (1d) [21].** *o*-Nitrobenzaldehyde (3.022 g, 20 mmol) and 1-naphthylamine (3.437 g, 24 mmol) were placed into a 100-mL round bottom flask. The mixture was heated in a water bath at 70°C for 15 min with continuous stirring. The product was separated from the mixture and recrystallized from ethanol to give yellow plates of *N*-(2-nitrobenzylidene)-1-naphthylamine **1d** (6.536 g, 95%), mp 110–111°C; IR (KBr): 1514 cm^{-1} and 1336 cm^{-1} (NO$_2$); ^{1}H NMR (CDCl$_3$): δ 7.17 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.50 (dd, *J* = 8.0 Hz and 8.0 Hz, 1H, Ar-H), 7.52–7.55 (m, 2H, 2 Ar-H), 7.66 (dd, *J* = 8.0 Hz and 8.0 Hz, 1H, Ar-H), 7.81 (d, *J* = 8.0 Hz, 2H, 2 Ar-H), 7.87–7.88 (m, 1H, Ar-H), 8.10 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.34-8.36 (m, 1H, Ar-H), 8.50 (d, *J* = 8.0 Hz, 1H, Ar-H), 9.04 (s, 1H, N=CH); ^{13}C NMR (CDCl$_3$): δ 113.2 (d), 123.6 (s), 124.5 (s), 126.0 (d), 126.0 (d), 126.5 (d), 126.8 (d), 127.7 (d), 128.8 (d), 130.0 (s), 131.1 (d), 131.2 (d), 133.5 (d), 133.9 (d), 148.2 (s), 155.7 (s), 155.8 (d).

***N*-benzylidene-2-nitroaniline (5a).** Imine compounds **5a-c** were prepared according to literature [22]. *o*-Nitroaniline (2.486g, 18 mmol), benzaldehyde (1.592 g, 15 mmol), sulfuric acid (5 drops), and molecular sieves (15 g) were added to benzene (30 mL) in a 100-mL round bottom flask. The mixture was heated under reflux for 8.5 h using Soxhlet extractor packed with molecular sieves. The resulting mixture was extracted with benzene, filtered to remove the molecular sieves, and the solvent evaporated under reduced pressure. The extract was then chromatographed on a silica gel column and eluted with hexane:EtOAc (85:15, 2% triethylamine) to give *N*-benzylidene-2-nitroaniline **5a** (2.787g, 82%). The structure of *N*-benzylidene-2-nitroaniline **5a** was determined by comparison of mp and ^{1}H NMR spectrum with those of literature [22]. Recrystallization from hexane gave yellow crystals, mp 70–71°C (ref. [22] mp 71–72°C); IR (KBr): 1594 cm^{-1} and 1334 cm^{-1} (NO_2); ^{1}H NMR ($CDCl_3$): δ 7.06 (d, *J* = 7.5 Hz, 1H, Ar-H), 7.30 (dd, *J* = 7.5 Hz and 7.5 Hz, 1H, Ar-H), 7.47–7.55 (m, 3H, 3 Ar-H), 7.59 (dd, *J* = 7.5 Hz and 7.5 Hz, 1H, Ar-H), 7.91 (d, *J* = 7.5 Hz, 2H, 2 Ar-H), 7.96 (d, *J* = 7.5 Hz, 1H, Ar-H), 8.41 (s, 1H, CH=N); ^{13}C NMR ($CDCl_3$): δ 121.0 (d), 124.6 (d), 125.3 (d), 128.8 (d), 129.2 (d), 132.1 (d), 133.8 (d), 135.4 (s), 142.9 (s), 146.8 (s), 161.8 (d).

***N*-(4-chlorobenzylidene)-2-nitroaniline (5b).** *o*-Nitroaniline (2.486 g, 18 mmol), *p*-chlorobenzaldehyde (2.109 g, 15 mmol), sulfuric acid (5 drops), and molecular sieves (10 g) were added to benzene (30 mL) in a 100-mL round bottom flask. The mixture was heated under reflux for 10 h using Soxhlet extractor packed with molecular sieves. The resulting mixture was extracted with benzene, filtered to remove the molecular sieves, and the solvent was evaporated under reduced pressure. The extract was then chromatographed on a silica gel column and eluted with hexane:EtOAc (85:15, 2% triethylamine) to give *N*-(4-chlorobenzylidene)-2-nitroaniline **5b** (2.226 g, 57%). Recrystallization from hexane gave yellow crystals, mp 78–79°C (ref. [23] mp 79–80°C); IR (KBr): 1586 cm^{-1} and 1348 cm^{-1} (NO_2); ^{1}H NMR ($CDCl_3$): δ 7.05 (d, *J* = 7.5 Hz, 1H, Ar-H), 7.32 (dd, *J* = 7.5 Hz and 7.5 Hz, 1H, Ar-H), 7.47 (d, *J* = 7.5 Hz, 2H, 2 Ar-H), 7.60 (dd, *J* = 7.5 Hz and 7.5 Hz, 1H, Ar-H), 7.85 (d, *J* = 7.5 Hz, 2H, 2 Ar-H), 7.97 (d, *J* = 7.5 Hz, 1H, Ar-H), 8.37 (s, 1H, CH=N); ^{13}C NMR ($CDCl_3$): δ 120.9 (d), 124.6 (d), 125.5 (d), 129.2 (d), 130.4 (d), 133.9 (d), 133.9 (s), 138.3 (s), 142.9 (s), 146.5 (s), 160.4 (d).

***N*-(4-methylbenzylidene)-2-nitroaniline (5c).** *o*-Nitroaniline (2.486 g, 18 mmol), *p*-methylbenzaldehyde (1.802 g, 15 mmol), sulfuric acid (5 drops), and molecular sieves (7.5 g) were added to benzene (30 mL) in a 100-mL round bottom flask. The mixture was heated under reflux for 9 h using Soxhlet extractor packed with molecular sieves. The resulting mixture was extracted with benzene, filtered to remove the molecular sieves, and the solvent evaporated under reduced pressure. The extract was then chromatographed on a silica gel column and eluted with hexane:EtOAc (85:15, 2% triethylamine) to give *N*-(4-methylbenzylidene)-2-nitroaniline **5c** (1.783 g, 49%). Recrystallization from hexane gave yellow crystals, mp 71–72°C (ref. [23] mp 72–74°C); IR (KBr): 1592 cm^{-1} and 1348 cm^{-1} (NO_2); ^{1}H NMR ($CDCl_3$): δ 2.43 (s, 3H, CH_3), 7.05 (d, *J* = 7.5 Hz, 1H, Ar-H), 7.27–7.30 (m, 3H, 3 Ar-H), 7.58 (dd, *J* = 7.5 Hz and 7.5 Hz, 1H, Ar-H), 7.80 (d, *J* = 7.5 Hz, 2H, 2 Ar-H), 7.95 (d, *J* = 7.5 Hz, 1H, Ar-H), 8.36 (s, 1H, CH=N); ^{13}C NMR ($CDCl_3$): δ 21.6 (q), 121.1 (d), 124.5 (d), 125.0 (d), 129.2 (d), 132.1 (d), 133.8 (s), 135.4 (d), 142.9 (s), 142.9 (s), 146.8 (s), 161.8 (d).

Ethyl 2-nitrocinnamate (9b). 2-Nitrobenzaldehyde (1.09 g, 7 mmol), triphenylphosphine (2.56 g, 9.8 mmol), ethyl bromoacetate (1.87 g, 11.2 mmol) and saturated aqueous solution of $NaHCO_3$ (15 mL) were placed in an Erlenmeyer flask and stirred for 1.5 hours at 20°C. The resulting mixture was extracted with benzene, dried over anhydrous sodium sulfate, and the solvent evaporated under reduced pressure. The extract was chromatographed on a silica gel column and eluted with hexane:EtOAc (3:1) to give ethyl 2-nitrocinnamate **9b** (1.09 g, 68%) as colorless liquid. The structure of ethyl2-nitrocinnamate **9b** was determined by comparison of IR, ^{1}H NMR and ^{13}C NMR spectra with those of literature [24]. IR (neat): 1700 cm^{-1} (CO_2), 1510 cm^{-1}, and 1272 cm^{-1} (NO_2); ^{1}H NMR ($CDCl_3$): δ 1.36 (t, *J* = 7.5 Hz, 3H, CH_3); 4.30 (q, *J* = 7.5 Hz, 2H, CH_2), 6.37 (d, *J* = 17 Hz, 1H, C=CH), 7.55 (dd, *J* = 7.5 Hz and 7.5 Hz, 1H, Ar-H), 7.64–7.65 (m, 2H, 2 Ar-H), 8.04 (d, *J* = 7.5 Hz, 1H, Ar-H), 8.11 (d, *J* = 17 Hz, 1H, Ph-CH=C); ^{13}C NMR ($CDCl_3$): δ 14.7 (q), 60.9 (t), 123.9 (d), 125.5 (d), 129.8 (d), 130.9 (s), 132.8 (d), 134.1 (d), 139.1 (d), 140.4 (s), 165.7 (s).

Methyl 2-nitrocinnamate (9c). 2-Nitrobenzaldehyde (1.09 g, 7 mmol), triphenylphosphine (2.56 g, 9.8 mmol), methyl bromoacetate (1.71 g, 11.2 mmol) and saturated aqueous solution of $NaHCO_3$ (15 mL) were placed in an Erlenmeyer and stirred for 1.5 h at 20°C. The resulting mixture was extracted with benzene, dried over anhydrous sodium sulfate, and the solvent evaporated under reduced pressure. The extract was chromatographed on a silica gel column and eluted with hexane:EtOAc (3:1) to give methyl 2-nitrocinnamate **9c** (0.98 g, 66%). The structure of methyl 2-nitrocinnamate **9c** was determined by comparison of mp, ^{1}H NMR and ^{13}C NMR spectra with those of literature [25]. Recrystallization from hexane gave colorless plates, mp 70–73°C (ref. [25(a)] mp 71–73°C); IR (KBr): 1712 cm^{-1} (CO_2), 1504 cm^{-1}, and 1332 cm^{-1} (NO_2); ^{1}H NMR ($CDCl_3$): δ 3.84 (s, 3H, CH_3), 6.37 (d, *J* = 17 Hz, 1H, C=CH), 7.56 (dd, *J* = 7.5 Hz and 7.5 Hz, 1H, Ar-H), 7.64–7.66 (m, 2H, 2 Ar-H), 8.05 (d, *J* = 7.5 Hz, 1H, Ar-H), 8.12 (d, *J* = 17 Hz, 1H, Ph-CH=C); ^{13}C NMR ($CDCl_3$): δ 52.5 (q), 123.5 (d), 125.5 (d), 129.7 (d), 131.0 (s), 132.9 (d), 134.2 (d), 139.4 (d), 140.7 (s), 166.2 (s).

General procedure of the microwave-assisted Cadogan reaction for the synthesis of indazoles, benzimidazoles, indoles, carbazole, and phenazine. Microwave-assisted Cadogan reaction for the synthesis of the various *N*-containing heterocyclic compounds was performed using the appropriate starting materials. Thus, for indazoles, the following starting materials were used: *N*-(2-nitrobenzylidene)aniline, *N*-(2-nitrobenzylidene)-2-fluoroaniline, 1-(2-nitrobenzylidene)-2-phenylhydrazine and *N*-(2-nitrobenzylidene)-1-naphthylamine; for benzimidazoles: *N*-benzylidene-2-nitroaniline, *N*-(4-chlorobenzylidene)-2-nitroaniline and *N*-(4-methylbenzylidene)-2-nitroaniline; for indoles: chalcone, ethyl 2-nitrocinnamate and methyl 2-nitrocinnamate; for carbazole: 2-nitrobiphenyl; and for phenazine: 2-nitrodiphenylamine. One millimole of the starting material was placed in the reaction vessel and added with 4 mmol of triethyl phosphite or triphenylphosphine. The reaction vessel containing the mixture was plugged with quartz wool and then placed inside the cavity of the microwave oven (Model YD-17 (W), Yoshii Electric Co., Ltd.). The mixture was irradiated at various power ratings and different reaction times to get the best result. The resulting mixture was then extracted with acetone, filtered, and the solvent evaporated under reduced pressure. The extract was chromatographed on a silica gel column and eluted with benzene, benzene:EtOAc, hexane:EtOAc, or hexane:acetone to yield the different products.

In the one-pot-one-step procedure, 2-nitrobenzaldehyde and aryl amine or 2-nitroaniline and aryl aldehyde were mixed with triethyl phosphite or triphenylphosphine in the reaction vessel and irradiated with microwaves at different power ratings and reaction times to get the best results. In the one-pot-two-steps procedure, 2-nitrobenzaldehyde and aryl amine were placed in the reaction vessel and irradiated with microwaves at certain power rating and reaction time, after which, triethyl phosphite was added and the mixture irradiated again. The products were isolated in the same manner as described above.

2-Phenyl-2H-indazole (4a) [6]. Compound **4a** was obtained as white plates from hexane, mp 80–82°C (ref. [26] mp 80–82°C); ^{1}H NMR ($CDCl_3$): δ 7.12 (dd, J = 7.5 Hz and 7.5 Hz, 1H, Ar-H), 7.32 (dd, J = 7.5 Hz and 7.5 Hz, 1H, Ar-H), 7.40 (t, J = 7.5 Hz, 1H, Ar-H), 7.53, (dd, J = 7.5 Hz and 7.5 Hz, 2H, 2 Ar-H), 7.71 (d, J = 7.5 Hz, 1H, Ar-H), 7.80 (d, J = 7.5 Hz, 1H, Ar-H), 7.91 (d, J = 7.5 Hz, 2H, 2 Ar-H), 8.41 (s, 1H, N—CH=C); ^{13}C NMR ($CDCl_3$): δ 117.9 (d), 120.4 (d), 120.4 (d), 121.0 (d), 122.1 (d), 122.7 (s), 126.8 (d), 127.9 (d), 129.5 (d), 140.5 (s), 149.8 (s).

2-(2-Fluorophenyl)-2H-indazole (4b) [27]. Compound **4b** was obtained as yellow liquid, IR (neat): 1222 cm^{-1} (Ar-F); ^{1}H NMR ($CDCl_3$): δ 7.12 (dd, J = 8.0 Hz and 8.0 Hz, 1H, Ar-H), 7.28–7.40 (m, 4H, 4 Ar-H), 7.73 (d, J = 8.0 Hz, 1H, Ar-H), 7.79 (d, J = 8.0 Hz, 1H, Ar-H), 8.09 (dd, J = 8.0 Hz and 8.0 Hz, 1H, Ar-H), 8.51 (s, 1H, N—CH=C); ^{13}C NMR ($CDCl_3$): δ 116.9 (d), 117.7 (d), 120.5 (d), 122.4 (d), 122.5 (s), 124.5 (d), 124.6 (d), 125.0 (d), 125.8 (d), 127.1 (d), 129.0 (s), 149.1 (s), 154.1 (s).

2-Phenylamino-2H-indazole (4c). Compound **4c** was obtained as white needles from benzene-hexane, mp 138–139°C (ref. [12] mp 140–142°C); IR (KBr): 3168 cm^{-1} (NH); ^{1}H NMR ($CDCl_3$): δ 6.54 (d, J = 7.5 Hz, 2H, 2 Ar-H), 6.97 (t, J = 7.5 Hz, 1H, Ar-H), 7.15 (dd, J = 7.5 Hz and 7.5 Hz, 1H, Ar-H), 7.21 (dd, J = 7.5 Hz and 7.5 Hz, 2H, 2 Ar-H), 7.34 (dd. J = 7.5 Hz and 7.5 Hz, 1H, Ar-H), 7.65 (br s, 1H, NH), 7.70 (d, J = 7.5 Hz, 2H, 2 Ar-H), 8.14 (s, 1H, N—CH=); ^{13}C NMR ($CDCl_3$): δ 114.1 (d), 117.6 (d), 120.4 (d), 122.3 (d), 122.5 (d), 124.1 (s), 126.7 (d), 128.3 (d), 129.2 (d), 146.8 (s), 147.3 (s).

2-(1-Naphthyl)-2H-indazole (4d) [6]. Compound **4d** was obtained as yellow liquid, ^{1}H NMR ($CDCl_3$):δ 7.18 (dd, J = 8.0 Hz and 8.0 Hz, 1H, Ar-H), 7.38 (dd, J = 8.0 Hz and 8.0 Hz, 1H, Ar-H), 7.48 (dd, J = 8.0 Hz and 8.0 Hz, 1H, Ar-H), 7.54 (dd, J = 8.0 Hz and 8.0 Hz, 1H, Ar-H), 7.56 (dd, J = 8.0 Hz and 8.0 Hz, 1H, Ar-H), 7.64 (d, J = 8.0 Hz, 1H, Ar-H), 7.74 (d, J = 8.0 Hz, 1H, Ar-H), 7.77 (d, J = 8.0 Hz, 1H, Ar-H), 7.86 (d, J = 8.0 Hz, 1H, Ar-H), 7.94 (d, J = 8.0 Hz, 1H, Ar-H), 7.98 (d, J = 8.0 Hz, 1H, Ar-H), 8.28 (s, 1H, N—CH=); ^{13}C NMR ($CDCl_3$): δ 117.8 (d), 120.2 (d), 121.9 (d), 122.2 (d), 122.9 (d), 123.7 (d), 124.8 (d), 125.3 (s), 126.5 (d), 126.6 (d), 127.4 (d), 127.9 (d), 128.8 (s), 129.5 (d), 134.0 (s), 137.5 (s), 149.5 (s).

2-Phenyl-1H-benzimidazole (8a). The structure of 2-phenyl-1*H*-benzimidazole **8a** was determined by comparison of mp, IR, ^{1}H NMR and ^{13}C NMR spectra with those of literature [14]. Colorless crystals from hexane-EtOAc, mp (hexane: EtOAc) 289–290°C (ref. [14] mp 290–292°C); IR (KBr): 3436 cm^{-1} (NH); ^{1}H NMR ($(CD_3)_2CO$): δ 7.21 (dd, J = 7.5 Hz and 7.5 Hz, 2H, 2 Ar-H), 7.47–7.68 (m, 5H, 5 Ar-H), 8.24 (d, J = 7.5 Hz, 2H, 2 Ar-H), 11.97 (br s, 1H, NH); ^{13}C NMR (CD_3OD): δ 123.9 (d), 123.9 (d), 127.7 (d), 130.1 (d), 130.9 (d), 131.3 (s), 153.3 (s).

2-(4-Chlorophenyl)-1H-benzimidazole (8b). The structure of 2-(4-chlorophenyl)-1*H*-benzimidazole **8b** was determined by comparison of mp, IR and ^{1}H NMR spectra with those of literature [14]. Colorless crystals from acetone, mp 291–292°C (ref. [14] mp 292–293°C); IR (KBr): 3405 cm^{-1} (NH); ^{1}H NMR ($(CD_3)_2CO$): δ 7.22–7.24 (m, 2H, 2 Ar-H), 7.51–7.70 (m, 4H, 4 Ar-H), 8.23 (d, J = 7.5 Hz, 2H, 2 Ar-H), 11.98 (br s, 1H, NH). No data for ^{13}C NMR, not determined due to low solubility.

2-(4-Methylphenyl)-1H-benzimidazole (8c). The structure of 2-(4-methylphenyl)-1*H*-benzimidazole **8c** was determined by comparison of mp, IR and ^{1}H NMR spectra with those of literature [14]. Colorless crystals from acetone, mp (acetone) 270–271°C (ref. [14] mp 270–272°C); IR (KBr): 3476 cm^{-1} (NH); ^{1}H NMR ($(CD_3)_2CO$): δ 2.40 (s, 3H, CH_3), 7.17–7.21 (m, 2H, 2 Ar-H), 7.35 (d, J = 7.5 Hz, 2H, 2 Ar-H), 7.49–7.66 (m, 2H, 2 Ar-H), 8.11 (d, J = 7.5 Hz, 2H. 2 Ar-H), 11.82 (br s, 1H, NH). No data for ^{13}C NMR, not determined due to low solubility.

2-Benzoylindole (10a). The structure of 2-benzoylindole **10a** was determined by comparison of mp, IR and ^{1}H NMR spectra with those of literature [16]. Pale yellow needles from hexane, mp 147–148°C (ref. [16] mp 145–147°C); IR (KBr): 3300 cm^{-1} (NH), 1610 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ 7.17 (s, 1H, indole CH), 7.17 (dd, J = 7.5 Hz and 7.5 Hz, 1H, Ar-H), 7.38 (dd, J = 7.5 Hz and 7.5 Hz, 1H, Ar-H), 7.48 (d, J = 7.5 Hz, 1H, Ar-H), 7.54 (dd, J = 7.5 Hz and 7.5 Hz, 2H, 2 Ar-H), 7.62 (t, J = 7.5 Hz, 1H, Ar-H), 7.72 (d, J = 7.5 Hz, 1H, ArH), 8.00 (d, J = 7.5 Hz, 2H, 2 Ar-H), 9.31 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 112.3 (d), 113.0 (d), 120.9 (d), 123.1 (d), 126.5 (d), 127.6 (s), 128.4 (d), 129.3 (d), 132.3 (d), 134.3 (s), 137.7 (s), 138.0 (s), 187.3 (s).

2-Ethoxycarbonylindole (10b). The structure of 2-ethoxycarbonylindole **10b** was determined by comparison of mp, IR, ^{1}H NMR and ^{13}C NMR spectra with those of literature [17]. Colorless needles from hexane, mp 121–123°C (ref. [17] mp 124–125°C); IR (KBr): 3300 cm^{-1} (NH), 1680 cm^{-1} (CO_2); ^{1}H NMR ($CDCl_3$): δ 1.42 (t, J = 7.5 Hz, 3H, CH_3), 4.41 (q, J = 7.5 Hz, 2H, CH_2), 7.15 (dd, J = 7.5 Hz and 7.5 Hz, 1H, Ar-H), 7.23 (s, 1H, indole CH), 7.32 (dd, J = 7.5 Hz and 7.5 Hz, 1H, Ar-H), 7.42 (d, J = 7.5 Hz, 1 H, Ar-H), 7.69 (d, J = 7.5 Hz, 1H, Ar-H), 8.91 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 14.4 (q), 61.0 (t), 108.6 (d), 111.9 (d), 120.7 (d), 122.5 (d), 125.3 (d), 127.4 (s), 127.4 (s), 136.9 (s), 162.2 (s).

2-Methoxycarbonylindole (10c). The structure of 2-methoxycarbonylindole **10c** was determined by comparison of mp, IR and ^{1}H NMR spectra with those of literature [18]. Colorless crystal from hexane, mp 144–147°C (ref. [18] mp 145–147°C); IR (KBr): 3308 cm^{-1} (NH), 1680 cm^{-1} (CO_2); ^{1}H

NMR ($CDCl_3$): δ 3.95 (s, 3H, CH_3), 7.16 (dd, J = 7.5 Hz and 7.5 Hz, 1H, Ar-H), 7.23 (s, 1H, indole CH), 7.33 (dd, J = 7.5 Hz and 7.5 Hz, 1H, Ar-H), 7.42 (d, J = 7.5 Hz, 1H, Ar-H), 7.69 (d, J = 7.5 Hz, 1H, Ar-H), 8.90 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 51.0 (q), 108.8 (d), 111.9 (d), 120.8 (d), 122.6 (d), 125.4 (d), 127.0 (s), 127.4 (s), 137.0 (s), 162.6 (s).

Carbazole (12). The mp, IR, ^{1}H NMR and ^{13}C NMR spectra of the compound were identical with those of commercially available sample. Colorless plates from ethanol, mp 245-250°C (ref. [6] mp 246–248°C); IR (KBr): 3420 cm^{-1} (NH); ^{1}H NMR ($CDCl_3$): δ 7.24 (dd, J = 7.5 Hz and 7.5 Hz, 2H, 2 Ar-H), 7.42 (dd, J = 7.5 Hz and 7.5 Hz, 2H, 2 Ar-H), 7.42 (d, J = 7.5 Hz, 2H, 2 Ar-H), 8.04 (br s, 1H, NH), 8.09 (d, J = 7.5 Hz, 2H, 2 Ar-H); ^{13}C NMR ($CDCl_3$): δ 110.5 (d), 119.4 (d), 120.3 (d), 123.3 (s), 125.8 (d), 139.4 (s).

Phenazine (14). The mp, IR, ^{1}H NMR and ^{13}C NMR spectra of the compound were identical with those of commercially available sample. Pale yellow needles from ethanol, mp 169–171°C; ^{1}H NMR ($CDCl_3$): δ 7.80 (ddd, J = 7.5 Hz, 7.5 Hz and 1.5 Hz, 4H, 4 Ar-H), 8.26 (dd, J = 7.5 Hz and 1.5 Hz, 4H, 4 Ar-H); ^{13}C NMR ($CDCl_3$): δ 129.6 (d), 130.3 (d), 143.3 (s).

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Regioselectivity of a 1,3-Dipolar Cycloaddition to Phenyl Vinyl Sulfoxide

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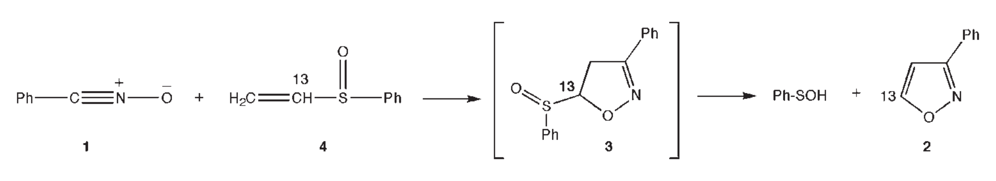

The regioselectivity of the 1,3-dipolar cycloaddition of benzonitrile *N*-oxide to phenyl vinyl sulfoxide is established by isotopic labeling and ^{13}C NMR analysis, and by DFT calculations.

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INTRODUCTION

The synthesis of 3-phenylisoxazoles is an active area because that structural unit is the core of many compounds with biological or agricultural activity [1]. One of the prominent routes to these molecules is the reaction of a benzonitrile *N*-oxide **1** with a substituted alkyne or alkene, a pathway first recognized as a 1,3-dipolar cycloaddition by Huisgen [2]. Several hundred examples of this process have been documented [3].

The parent compound **2** can be prepared by this procedure with acetylene as the dipolarophile [4], but more often a two-step sequence is used whereby a monosubstituted alkene serves as the dipolarophile, followed by an elimination process on the intermediate isoxazoline **3** (Scheme 1). In the latter case, two distinct isomeric intermediates are possible depending on whether the oxygen terminal of **1** adds to the substituted or the unsubstituted carbon of the alkene (paths **a** and **b**, respectively in Scheme 1). This reaction is known to be generally regioselective for the 5-substituted cycloadduct **3a** [5]. However, yields for the process are not quantitative, and rigorous analyses for the isomeric 4-substituted cycloadduct are seldom reported [6].

Phenyl vinyl sulfoxide **4** and its 2-substituted analogs (R—CH═CH—S(O)—Ph) are among the useful dipolarophiles in the synthesis of isoxazoles *via* 1,3-dipolar cycloaddition, particularly, because subsequent elimination of phenylsulfenous acid occurs spontaneously [7]. Maiorana and coworkers investigated the regioselectivity of the addition step in the 2-substituted systems based on the distribution of the final isomeric oxazole products using ^{1}H NMR spectroscopy and found that the regioselectivity ratio is dramatically altered (90:10 to 10:90) depending on R [7b]. Clearly, direct analysis of the product ratio cannot be used to determine the regioselectivity when R = H, as the two intermediates (**3a/3b**) yield the same product (**2a/2b**), although this case may easily be the most relevant to understanding the influence of the S(O)Ph group. Herein, we report the results for a simple isotope labeling experiment that solve this problem.

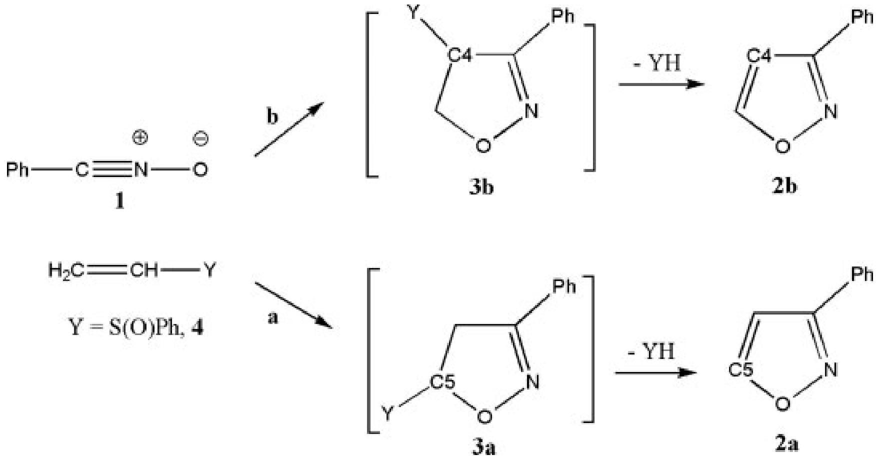
Our approach, summarized in Scheme 2, was to analyze product **2** by ^{13}C NMR spectroscopy following reaction of **1** with a sample of **4** selectively enriched with ^{13}C in the 1-position (C1). The results show that the ^{13}C label is incorporated largely at the 5-position of the isoxazole ring. We estimate a regioselectivity of 110:1 based on the integrated ^{13}C peak areas in the final product. These conclusions were then supported with DFT calculations.

RESULTS AND DISCUSSION

Synthesis. Standard procedures were used to convert 1-^{13}C-ethyl iodide to phenyl 1-^{13}C-vinyl sulfoxide **4*** (see Experimental Section). A mixture consisting of ~80% unlabeled **4** and 20 % labeled **4** (*i.e.* **4***) was then reacted with benzonitrile *N*-oxide **1** under conditions [7] that directly produced 3-phenyl-5-isoxazole **2** (Scheme 2). The crude product of this reaction was contaminated only with by-products resulting from the phenylsulfenous acid elimination (*i.e.* Ph_2S_2); purification by flash column chromatography produced pure **2**.

^{13}C NMR analysis. Initial chemical shift assignment of the isoxazole carbons in the ^{13}C NMR spectrum of **2** was straightforward (see Experimental Section). In

Scheme 1



earlier work, we definitively assigned the signal at δ 161.48 to C3 by preparing **2** selectively ^{13}C-lableled at this position [8]. This was accomplished by using the synthetic approach summarized in Scheme 2 beginning with benzaldehyde oxime ^{13}C-labeled at the oxime carbon. C4 and C5 (δ 102.42 and 158.85, respectively) were assigned by comparison with data from the NMR literature [9].

The first row in Table 1 gives the integrated peak areas observed in a natural abundance sample of **2**. In this case, the areas of C4 and C5 are roughly equal (C5/C4 = 1.12), and each is about three times the C3 peak area. The second row gives ^{13}C data observed when **2** is prepared from a mixture that was ~20% ^{13}C1-enriched phenyl 1-vinyl sulfoxide (**4***) and 80% natural abundance **4**. As expected, the enrichment causes significant

Scheme 2

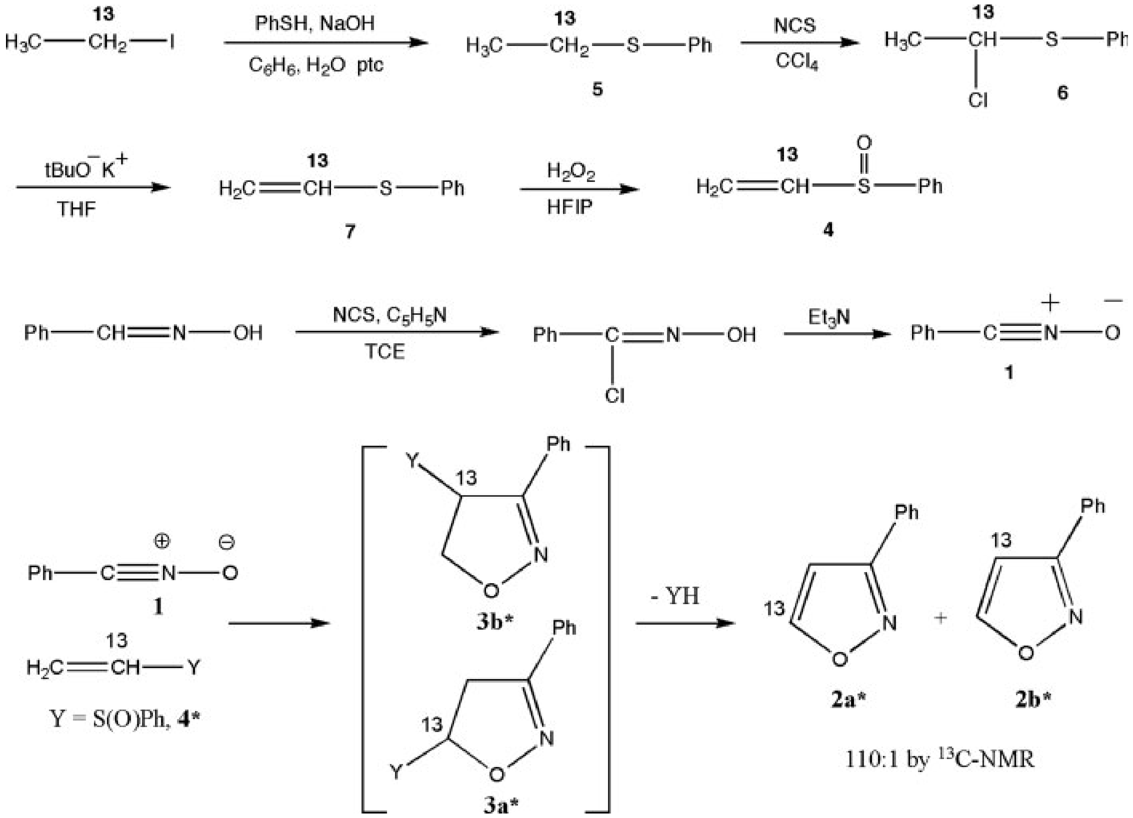


Table 1

Data from ^{13}C NMR analysis of **2**.

	Integrated peak area ratio		
	C5/C3	C4/C3	C5/C4
Natural abundance	3.53	3.15	1.12
^{13}C-Enriched[a]	53.59	3.56	15.05
^{13}C 1st adjustment[b]	50.66	0.95	
^{13}C 2nd adjustment[c]	50.66	0.41	
^{13}C Final adjustment[d]	50.66	0.46	

[a] Observed areas when 2 is prepared from 4* with 17% ^{13}C label at the 1-position.

[b] Adjusted peak areas in the ^{13}C-enriched experiment; obtained by subtracting the contribution from natural abundance component (83% of the area in row 1) from the observed area (row 2).

[c] Estimated distribution of the ^{13}C label originating from 4* onto C5 and C4 before scaling (see Discussion).

[d] Scaled for C5/C4 relative sensitivity (1.12).

increase in the C5 and C4 peak areas relative to C3. From the total amount of this increase, we can, in fact, determine that a total of 17% of the product obtained in the enriched experiment comes from labeled **4***. The distribution of ^{13}C from C1 of this component onto the C5 and C4 positions in **2** (**2a***/**2b*** in Scheme 2) provides the measure of regioselectivity in our reaction. When the natural abundance ^{13}C contributions from the C1 and C2 carbons of the **4**(83%)/**4***(17%) mixture are subtracted from the areas in row 2, the resulting data (third row in Table 1) clearly show that in the reaction of **4*** with **1**, the ^{13}C label at C1 has been deposited largely at the 5-position of the isoxazole ring. This implies that C4 in **2** originates mostly from the C2 carbon of **4***, which is not labeled. If the reaction were 100% regioselective, the natural ^{13}C abundance at C2 in **4*** (1.108%) should produce a net peak area of 0.54 for C4 in row 3 (*i.e.* 17% of the respective C4 value in row 1). As the observed area, 0.95, is larger by 0.41, this excess area must have come from a small fraction of the ^{13}C label at C1 in **4***, and this can now be used to make a quantitative estimate of the regioselectivity. To do this, we first scale the excess area by 1.12 to account for the inherently greater sensitivity of C5 toward integration (*i.e.* C5/C4 = 1.12 in row 1). Thus, our analysis, based on the final, adjusted integrated ^{13}C data (row 5), affords an overall regioselectivity of 50.66:0.46, or 110:1, for the reaction between **1** and **4** (in dichloroethane at 50°C).

It should be noted that, because of differences in relaxation times (T1) and NOE effects between protonated (*i.e.* C4, C5) and non-protonated carbons (*i.e.* C3), integrated peak areas from Fourier-Transform ^{13}C NMR spectra acquired with standard pulse sequences cannot be used to obtain accurate values for relative numbers of carbons in the same molecule (in contrast to the common integration practice in ^{1}H NMR spectroscopy). In this study, however, as we are comparing relative peak areas for the same carbon atoms in isotopically-distinct isomers, this limitation does not apply.

DFT calculations and analysis. 1,3-Dipolar addition reactions have been the subject of numerous electronic structure investigations [10]. Among the earlier studies in this area is work by Houk [11], which analyzed the frontier MO interactions in cycloaddition reactions. Subsequent studies used increasingly more sophisticated theoretical tools to obtain more accurate activation and reactions energies. However, elucidation and interpretation of the factors that control reactivity and regioselectivity in 1,3-dipolar addition reactions remains debatable and an active topic of research. For instance, Although Schleyer searched for a role for the in plane aromaticity in the cyclic transition states of 1,3-dipolar addition reactions [12], Ponti and Molteni advocated a possible role for the reactivity indices of the separate reactants in driving the reactions in the context of hard-soft acid-base theory [13]. More recently, Ess and Houk showed that the reactivities of different 1,3-dipoles correlate with the energy needed to distort the dipole and the dipolarophile to the transition state geometries ($E_{\mathrm{d}}^{\ddagger}$) [14]. Because none of the prior theoretical studies had considered any dipolar reactions of a vinyl sulfoxide, we became interested in investigating the reaction we studied experimentally (**1** + **4**) using density functional theory. For this purpose, we used the B3LYP and B3P86/6-31+G(d,p) levels of theory to study the transition states (TS), and products of the actual molecules used in the experiments. To present the results in perspective, we also calculated the reactions between **1** and each of ethylene and propene. Relevant geometrical parameters and energies of the reaction of **4** are presented in Figure 1, and Table 2 compares the results for the three alkenes considered.

Figure 1 shows that the TS in which the oxygen atom adds to the substituted carbon of **4** (**TS3a**) is 2.8 kcal/mol lower in energy than the alternative TS where oxygen adds to the terminal carbon (**TS3b**) ($\Delta\Delta G^{\circ\ddagger}$, at 298 K and 1 atm). A nearly identical $\Delta\Delta G^{\circ\ddagger}$ is obtained at the B3P86 level, and this value remains largely unchanged when the energies are calculated in a dichloroethane solvent continuum. The computed regioselectivity agrees well with the estimated experimental regioselectivity of 110:1, which affords and experimental $\Delta\Delta G^{\ddagger} = 2.6$ kcal/mol at 323 K. The calculations reveal that the kinetic product (**3a**) is also the thermodynamic product in the given reaction, with $\Delta\Delta G^{\circ} = 5.5$ kcal/mol in favor of the isomer in which the S(O)Ph substituent is attached at the 5-position before loss of phenylsulfenous acid to give the isoxazole ring (Fig. 1).

In light of the recent studies by Ess and Houk [14], we analyzed the calculated regioselectivity in reactions

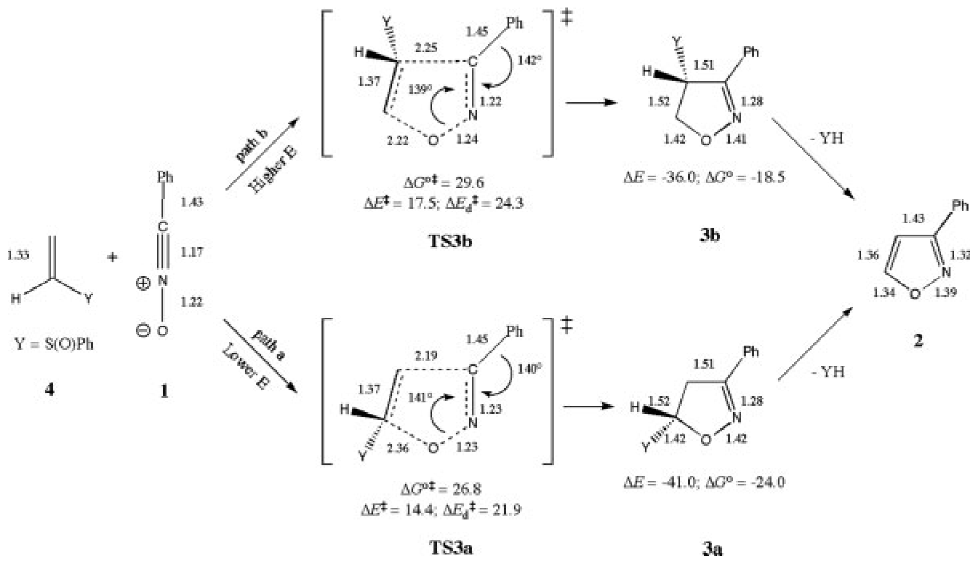


Figure 1. Selected B3LYP geometric parameters and energies of the transition states and products in the reaction between 4 and 1 (in Å and kcal/mol).

of **4** using the activation strain model. This model is built on a thermodynamic cycle that gives the activation energy ($\Delta E^{\ddagger}$) as the sum of a distortion energy ($\Delta E^{\ddagger}_{\mathrm{d}}$; defined as the energy needed to distort the equilibrium geometry of the reactants to the respective geometries in the TS) and an electronic interaction term ($\Delta E^{\ddagger}_{\mathrm{int}}$, for the energy change that takes place when the distorted reactants are brought to the TS). In our system, $\Delta E^{\ddagger}_{\mathrm{d}}$ has a term from the dipole ($\Delta E^{\ddagger}_{\mathrm{d1}}$) and another from the alkene ($\Delta E^{\ddagger}_{\mathrm{d2}}$, Table 2). Each of these terms is larger for the higher energy TS (**TS3b**). The net difference between the total $\Delta E^{\ddagger}_{\mathrm{d}}$ in the two TSs ($\Delta\Delta E^{\ddagger}_{\mathrm{d}} = 2.9$ kcal/mol) is very close to the difference between the actual activation energies ($\Delta\Delta E^{\ddagger} = 2.4$ kcal/mol). This behavior is in line with the general conclusions reached by Ess and Houk [14] on the reactivities of 1,3-dipole addition reactions.

Finally, to examine if S(O)Ph imparts any special substituent effects on the dipolarophilicity of ethylene, we calculated the reactions of ethylene and propene with **1**. The results are included in Table 2. In spite of the large electronic difference among the given three alkenes when the lower energy **TS3a** is considered, the activation energy appears to be rather invariant: $\Delta G^{\circ\ddagger} =$ 26.8, 27.2, and 25.8 kcal/mol, for Y = H, CH_3 or S(O)Ph, respectively. The same holds for the reaction energies: $\Delta G^{\circ}_{\mathrm{rxn}} = -23.3$ (H), -22.7 (CH_3), and -24.0 (S(O)Ph). Similarly, the calculated regioselectivity is comparable for Y = CH_3 ($\Delta\Delta G^{\circ\ddagger} = 3.3$ kcal/mol) and S(O)Ph ($\Delta\Delta G^{\circ\ddagger} = 2.8$ kcal/mol). Noticeably, the small variations in the activation energies among the three substituents correlate with the variation in the respective distortion energies.

Table 2

B3LYP activation and reaction energies of addition of PhCNO (**1**) to substituted ethylene (CH_2=CHY).[a]

Y	O adds to	$\Delta E^{\ddagger}$	$\Delta G^{\circ\ddagger}$	$\Delta E^{\ddagger}_{\mathrm{d1}}$	$\Delta E^{\ddagger}_{\mathrm{d2}}$	$\Delta G^{\circ}_{\mathrm{rxn}}$
S(O)Ph	C1	14.4	26.8	17.6	4.3	−24.0
S(O)Ph	C2	17.5	29.6	18.7	5.6	−18.9
CH_3	C1	14.9	27.2	17.6	3.7	−22.7
CH_3	C2	17.9	30.5	19.3	4.9	−18.3
H	C1 = C2	14.1	25.8	17.1	3.0	−23.3

$\Delta E^{\ddagger}$ is the raw electronic activation energy without ZPE correction. $\Delta G^{\circ\ddagger}$ and $\Delta G^{\circ}_{\mathrm{rxn}}$ are the standard state activation and reaction free energies, respectively, obtained at 298 K and 1 atm using unscaled harmonic vibrational frequencies. $\Delta E^{\ddagger}_{\mathrm{d1}}$ and $\Delta E^{\ddagger}_{\mathrm{d2}}$ are the energies needed to distort the geometries of **1** and the alkene, respectively, to their corresponding parameters in the transition state. When Y = S(O)Ph, the results are for the lowest energy conformer.

[a] Units are in kcal/mol, relative to the separated reactants.

Overall, the DFT calculations support the experimental quantification of the regioselectivity in the reaction between **1** and **4** made from the integrated ^{13}C areas of the final product (**2**). The calculations confirm that the observed regioselectivity is not the result of any special effects provided by the S(O)Ph group.

EXPERIMENTAL

Melting points were determined on a MelTemp apparatus. Extracts were dried over Na_2SO_4, and solvents were removed by rotary evaporation at reduced pressure. Product purities were determined by gas chromatography-mass spectrometry analysis on a Hewlett Packard HP 6890 system equipped with a HP-5MS crosslinked diphenyl (5%) dimethyl (95%) polysiloxane capillary column (30 m × 0.25 mm × 0.25 μm film), a 5973 mass selective detector, and a HP Kayak XA computer. NMR spectra were measured at 298 K with a Brüker Avance DRX 500 MHz NMR spectrometer operating at frequencies of 500.630 (^{1}H) and 125.884 (^{13}C) using a standard 5 mm broadband multinuclear (PABBO) probehead (90° pulse widths: ^{1}H, 11.5 μs; ^{13}C, 6.0 μs). Chemical shifts (ppm) were measured relative to internal Me_4Si (^{1}H) or internal $CDCl_3$ (^{13}C). ^{13}C chemical shifts were measured using a standard power gated decoupling pulse sequence (zgpg30) from the Brüker pulse sequence library. Spectral windows for ^{13}C acquisitions were set at 240 ppm, and a total of *ca*. 300 scans of 32 k data points were collected and then zero-filled to 64 k points before Fourier transformation. The recycle delay (D1) was set at 2 s.

Phenyl 1-^{13}C-vinyl sulfoxide (4). The synthesis of phenyl vinyl sulfoxide selectively ^{13}C-labeled in the 1-position began with a sample of *ca*. 20% ^{13}C-enriched 1-^{13}C-ethyl iodide that was prepared by mixing 4 volumes of unlabeled ethyl iodide (Sigma–Aldrich, 17780) with 1 volume of 99% atom purity 1-^{13}C-ethyl iodide (Cambridge Isotope Laboratories, CLM-1025). As shown in Scheme 2, preparation of phenyl 1-^{13}C-vinyl sulfoxide **4** proceeded from labeled ethyl iodide *via* the sequence: 1-^{13}C-ethyl phenyl sulfide **5** [15] to 1-^{13}C-chloroethyl phenyl sulfide **6** [16] to phenyl 1-^{13}C-vinyl sulfide **7** [17] to **4** [18], following methods that have been reported previously. The crude product was used for the subsequent synthesis of **2**; GC-MS analysis of crude **4** showed that it was at least 94% pure.

3-Phenyl-5-^{13}C isoxazole (2). We have reported a general synthesis of unlabeled 3-phenyl-5-isoxazole beginning from benzaldehyde oxime previously [7a]. Adaptation of this method using phenyl 1-^{13}C-vinyl sulfoxide **4** afforded 3-phenyl-5-^{13}C isoxazole **2**, as follows. To a solution of *N*-chlorosuccinimide (0.119 g, 0.8913 mmol) and pyridine (4 μL, 0.124 mmol) in 1,1,2-trichloroethane (TCE) (1.0 mL) was added benzaldehyde oxime (0.098 g, 0.809 mmol; Aldrich 245674) and the solution was stirred at 50°C for 30 min. A solution of phenyl 1-^{13}C-vinyl sulfoxide **4** (0.138 g, 0.905 mmol) and triethylamine (0.12 mL, 0.86 mmol) in TCE (98 μL) was added dropwise *via* Pasteur pipet over 3 min. The solution was stirred at 50°C for 20 min and then heated to reflux for an additional 60 min. The reaction mixture was cooled to room temperature and evaporated to dryness, and the residue was treated with 2*M* NaOH (5 mL). The mixture was heated at reflux for 35 min, cooled to room temperature, neutralized with saturated NH_4Cl solution (3 mL), and extracted with CH_2Cl_2. The extract was washed with water (2 × 10 mL), dried (anhydrous Na_2SO_4), and evaporated to give 0.092 g of crude product **2**. Purification by flash liquid chromatography (4:1 hexane:ethyl acetate on flash silica gel) removed the Ph_2S_2 by-product and afforded **2** as a pale yellow oil in *ca*. 94% purity by GC-MS analysis. ^{13}C NMR (deuteriochloroform) δ 102.42 (C4), 126.86 (C2′/3′; assignments may be interchanged), 128.76 (C1′), 128.91 (C2′/3′; assignments may be interchanged), 130.00 (C4′), 158.85 (C5), 161.48 (C3).

Computational methods. All computations were carried out using Gaussian 03. [19]. The B3LYP [20] and B3P89 [21] levels of theory and the standard 6-31+G(d,p) basis set [22] were used to optimize the reactants, transition states, and products for normal mode vibrational analysis. Several conformers defined by rotation of the S(O)Ph group were considered for the transition state and products, but we report only the results for the lowest energy conformer. Solvent effects were calculated *via* single point calculations on the gas phase optimized geometries using the polarizable continuum model (PCM) [23].

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C—C Bond Formation by Radical Cyclization: Facile Syntheses of [6,6]Pyranothiopyrans and [6,6]Pyridothiopyrans

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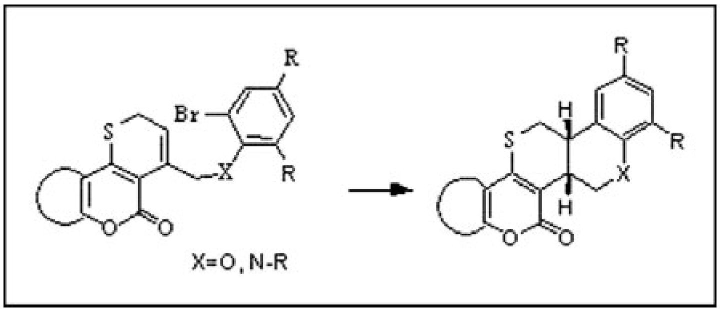

4-Chloromethylthiopyrano[3,2-*c*][1]benzopyran-5-(2*H*)-ones were refluxed with *o*-bromophenols in acetone in the presence of anhydrous potassium carbonate and sodium iodide to afford a number of 4-aryloxymethylthiopyrano[3,2-*c*][1]benzopyran-5-(2*H*)-ones in 72–79% yields. These compounds were refluxed with tri-*n*-butyltin hydride and azobisisobutyronitrile in dry benzene for 7–8 h to give [6,6]pyranothiopyrans in 76–84% yields with good diastereoselectivity. Similarly, [6,6]pyridothiopyrans were also synthesized in 70–75% yields with excellent diastereoselectivity.

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INTRODUCTION

In recent years, radical cyclization has emerged as a valuable tool for the construction of carbo- and heterocyclic compounds, including natural products [1]. An understanding of the kinetic and the structural information of these reactive intermediates paved the way for the development of modern synthetic radical chemistry [2]. There has been continuing enhanced interest in recent years in the synthesis of coumarin derivatives largely on account of their occurrence in nature [3,4] and biological activity [5] *viz*., anthelmintic, hypnotic, insecticidal, antifungal activities, anticoagulant effect on blood, and diuretic properties. During our work on the synthesis of heterocycles by the application of sigmatropic rearrangements [6], we recently observed the unusual formation of [6,6]pyranopyrans in case of substrates containing 5-hydroxypyrimidines [7] and 3-hydroxycoumarin [8], in the second Claisen rearrangement step. The generation and subsequent reactions of radicals formed from aryl halides using tri-*n*-butyltin hydride and azobisisobutyronitrile (AIBN) are now well established [9]. However, literature reveals only a few examples of heteroaryl radicals [10–13]. Aryl radical cyclization normally has a high 5-*exo*:6-*endo* ratio indicating stronger preference for *exo* cyclization compared to the alkyl radicals. However, this preference is found to be reversed in cyclizations involving stabilized radicals [14]. Recently, we have reported [15] the synthesis of [6,6]pyranothiopyrans by the application of sequential Claisen rearrangement followed by pyridine hydrotribromide-mediated regioselective 6-endo cyclization. We have also reported some successful 6-*endo* aryl radical cyclizations by tri-*n*-butyltin hydride-mediated radical reaction [16]. In continuation of our studies, we became interested to examine the viability of synthesizing the [6,6]pyranothiopyran ring system by tri-*n*-butyltin hydride-induced radical cyclization of appropriate substrates (**3a–f**).

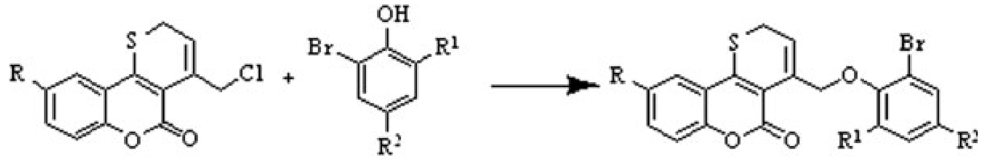
RESULTS AND DISCUSSION

4-Chloromethylthiopyrano[3,2-*c*][1]benzopyran-5-(2*H*)-ones (**1a–b**) were refluxed with *o*-bromophenol in acetone in the presence of anhydrous potassium carbonate and sodium iodide to afford a number of 4-aryloxymethylthiopyrano[3,2-*c*][1]benzopyran-5-(2*H*)-ones (**3a–f**) (Scheme 1).

Compounds (**3a–f**) were characterized from their elemental analyses and spectral data. IR spectrum of compound **3a** showed carbonyl absorption at 1690 cm^{-1}. The high-field (300 MHz) ^1H NMR spectrum of compound **3a** exhibited two proton doublet at δ 3.48 for —SCH_2, two proton doublet at δ 5.18 for —OCH_2, one proton triplet at δ 6.35 for the vinylic proton among other signals for aromatic protons.

The substrate **3a** was refluxed in dry benzene under nitrogen atmosphere with tri-*n*-butyl tin hydride and

Scheme 1. Reagents and condition: K_2CO_3, NaI, dry acetone, reflux 3–5 h.



1a-b

1a. R=H
1b. R=Me

2a-c

2a. R^1=R^2=H
2b. R^1=H, R^2=Me
2c. R^1=R^2=Me

3a-f

3a. R=R^1=R^2=H
3b. R=H, R^1=R^2=Me
3c. R=Me, R^1=R^2=H
3d. R=R^1=H, R^2=Me
3e. R=R^1=Me, R^2=H
3f. R=R^1=R^2=Me

AIBN for 7 h to afford cyclic product **4a** in 80% yield as an inseparable diastereoisomeric mixture (3:1), which was determined by ^{1}H, ^{13}C, COSY, and NOESY experiments. ^{1}H NMR spectrum of the product **4a** displayed peaks for two —SC**H**$_2$ protons at δ 3.23 and 3.33, two —OC**H**$_2$ protons at δ 3.88 and 4.70, and two ring juncture protons at δ 3.25 and 3.75 along with eight aromatic protons (δ 6.91–7.76) for the major diastereoisomer, whereas minor diastereoisomer displayed peaks at δ 3.05 and 3.74 for two —SC**H**$_2$ protons, δ 3.93 and 5.67 for two —OC**H**$_2$ protons, and δ 3.17 and 3.42 for two ring juncture protons. IR spectrum of compound **4a** also showed carbonyl absorption at 1700 cm^{-1}. The generality of the reaction was tested by subjecting five other substrates **3b–f** under the same reaction condition to give products **4b–f** in 76–84% yields (Scheme 2).

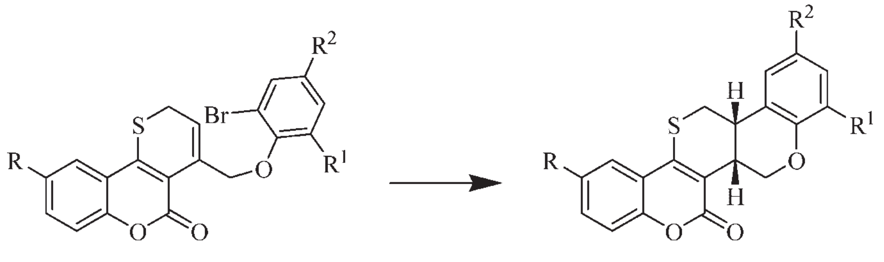
In the course of our studies on the application of sigmatropic rearrangements for the synthesis of heterocyclic compounds, we have already noted the formation of several [6,6]pyranopyran and [6,6]pyranothiopyran ring systems [17] using sequential Claisen rearrangements. However, we failed to synthesize [6,6]pyridothiopyran ring system using the Claisen rearrangement. The aforesaid results motivated us to investigate the synthesis of [6,6]pyridothiopyran ring system by tributyl tin hydride-mediated aryl radical cyclization.

The starting materials for our study 4-arylaminomethyl-7-methyl thioyrano[3,2-*c*]pyran-5-ones **7a–e** were synthesized from 4-chloromethyl-7-methyl-thiopyrano[3,2-*c*]pyran-5-ones **5** and various substituted *o*-bromoanilines **6a–e** in refluxing acetone in the presence of anhydrous K_2CO_3 and catalytic amount of NaI (Scheme 3).

Substrate **7a** was refluxed in benzene with tributyl tin (IV) hydride in the presence of azoisobutyronitrile (AIBN) for 5 h to give compound **8a** (70%), which was characterized from its elemental analysis and spectroscopic data. The IR spectrum of the compound **8a** showed peaks at 3387 and 1682 cm^{-1} for secondary N—H group and carbonyl group, respectively. The high-field ^{1}H NMR (500 MHz) spectrum of the product **8a** displayed peaks for two —SC**H**$_2$ protons at δ 2.90 and δ 3.02, two ring juncture protons at δ 3.09 and δ 3.65, and two —NC**H**$_2$ protons at δ 3.19 and 3.33. The mass spectrum of the compound **8a** also displayed a molecular ion peak at *m*/*z* 286 (M^+ + 1). Encouraged by this result, other substrates **7b–e** were also similarly treated to give tetracyclic heterocycles **8b–e** in 70–75% yields (Scheme 4).

Substrates **3b** and **3c** also gave diastereomeric mixtures [18] (2.5:1 and 2:1, respectively) under similar reaction conditions, whereas substrates **3d–f** and **7a–e** with Bu_3SnH and AIBN in refluxing benzene gave the

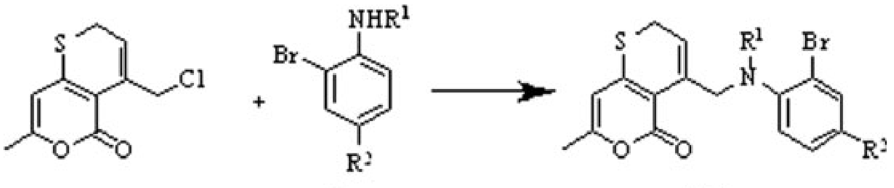
Scheme 2. Reagents and condition: Bu_3SnH, AIBN, dry benzene, under N_2, reflux 7–8 h.



3a-f

4a-f

Scheme 3. Reagents and reaction condition: K_2CO_3, NaI, dry acetone, reflux 4–5 h.



5 **6a-e** **7a-f**

6a. $R^1 = R^2 = H$
6b. $R^1 = H$, $R^2 = Me$
6c. $R^1 = H$, $R^2 = Et$
6d. $R^1 = R^2 = Me$
6e. $R^1 = Me$, $R^2 = Et$

7a. $R^1 = R^2 = H$
7b. $R^1 = H$, $R^2 = Me$
7c. $R^1 = H$, $R^2 = Et$
7d. $R^1 = R^2 = Me$
7e. $R^1 = Me$, $R^2 = Et$

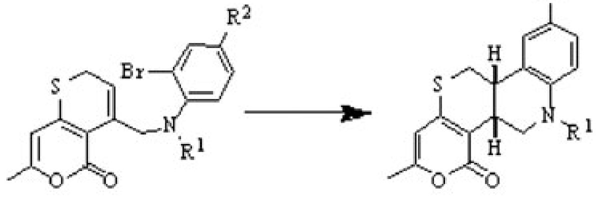
cyclized products **4d–f** and **8a–e**, respectively, with 100% diastereoselectivity. The high-field ^1H NMR (500 MHz) of the compound **8a** showed the two ring juncture protons at δ 3.09–3.12 (dt, 1H, $J = 12.1$, 3.5 Hz) and δ 3.65–3.69 (dt, 1H, $J = 11.5$, 3.6 Hz). The low coupling constants ($J = 3.5$ and 3.6 Hz) for the ring juncture protons indicate *cis*-stereochemistry of the ring juncture. The *cis*-stereochemistry of the ring juncture is also supported by the comparison of the ^1H NMR data of similar compounds published earlier [17]. The stereochemistry at the ring juncture can also be surmised from the molecular models (Dreiding model), which shows a strain free *cis*-arrangement.

It was already established [19] that very high level of diastereoselectivity (>50:1) could be obtained when the concentration of the reactants is reduced from 0.1 to 0.01 M. This observation has been attributed to the reversibility of the cyclization and decreased availability of the Bu_3SnH. However, no significant change in diastereoselectivity was observed when the substrates **3a–c** were treated with $^nBu_3SnH$ and AIBN in refluxing benzene under a very dilute condition. Therefore, the reason behind the reduced diastereoselectivity in case of **3a–c** over the other is not clear.

The formation of products **4a–f** and **8a–e** from the substrates **3a–f** and **7a–e**, respectively, may easily be explained by the generation of an aryl radical **9** in the tri-*n*-butyltin hydride and azobisisobutyronitrile-mediated reaction. The aryl radical **9** may undergo cyclization by two different modes, a 6-*endo* trig cyclization to afford the heterocyclic radical **11** (pathway a) or a 5-*exo* trig cyclization to give the spiroheterocyclic radical [20] **10** (not isolated, pathway b). The possibility of the formation of heterocyclic radical **11** *via* spirocyclic radical **10** by a neophyl rearrangement [21] cannot be ruled out (Scheme 5).

It is known that radical cyclizations leading to six-membered rings are usually less general than cyclization leading to five-membered rings. The six-membered ring forming reactions are also slower than five-membered ring forming reactions and are subject to competitive formation of reduced uncyclized by-products. However, appropriately substituted 5-hexenyl radicals are known to undergo 6-*endo* cyclization to give six-membered rings. Our noteworthy observation is that the usual oxidation [13] does not occur at the present instance, and the dihydro compounds are isolated in excellent yield with good diastereoselectivity. It is also interesting to note that six-membered heterocyclic rings are regioselectively formed in all the cases. This is an attractive and simple methodology for the synthesis of [6,6]pyranothiopyran and [6,6]pyridothiopyran ring systems.

Scheme 4. Reagents and reaction condition: Bu_3SnH, AIBN, dry acetone, under N_2, reflux 5–8 h.

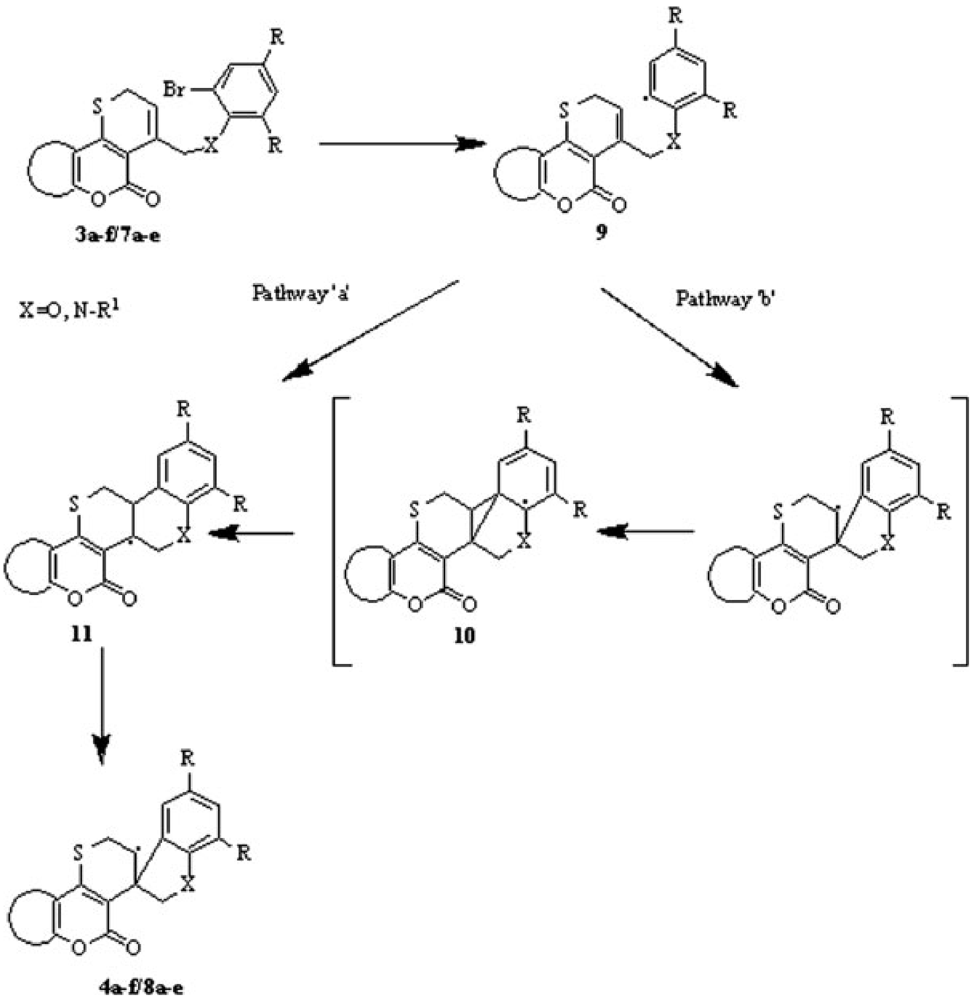


7a-e **8a-e**

EXPERIMENTAL

Melting points were determined in an open capillary and are uncorrected. IR spectra were recorded on a Perkin-Elmer L120-000A spectrometer (ν_{max} in cm^{-1}) on KBr disks. UV absorption spectra were recorded in EtOH on a Shimadzu UV-2401PC spectrophotometer (λ_{max} in nm). ^1H NMR (300 MHz, 500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Bruker DPX-300 and Bruker DPX-500 spectrometer in $CDCl_3$ (chemical shift in δ) with TMS as an internal standard. ^1H NMR and ^{13}C NMR spectra were recorded at the Indian Institute of Chemical Biology, Kolkata and Bose Institute,

Scheme 5



Kolkata. Silica gel [(60–120 mesh), Spectrochem, India] was used for chromatographic separation. Silica gel G [E-Merck (India)] was used for TLC. Petroleum ether refers to the fraction boiling between 60 and 80°C.

The starting materials (**1a**,**b**) and **5** for this study were prepared according to our earlier published procedure [22,23].

General procedure for the preparation of compound 3a–f. Compound (**1a, b**) (1 mmol) was refluxed with several *o*-bromophenols (**2a–c**) (1 mmol) in acetone (100 mL) in the presence of anhydrous potassium carbonate (1g) and catalytic amount of NaI for 3–5 h. The reaction mixture was then cooled, filtered, and the solvent was removed. The residual mass was subjected to column chromatography over silica gel using petroleum ether–ethylacetate (19:1) as eluant to give compounds **3a**–**f**, which were then recrystallized from chloroform.

Compound 3a. Yield 75%; yellow solid; m.p. 90°C; UV(EtOH)λ_{max}: 214, 243, 371 nm; IR(KBr) ν_{max}: 1690, 1600, 1260 cm^{-1}; ^{1}H NMR (500 MHz): δ 3.48 (d, 2H, J = 6 Hz, —SCH$_2$), 4.99 (d, 2H, J = 1 Hz, —OCH$_2$), 6.38–6.42 (tt, 1H, J = 1, 6 Hz, =CH), 7.17–7.23 (m, 3H, ArH), 7.29–7.37 (m, 4H, ArH), 7.50–7.61 (m, 1H, ArH); Anal. Calcd. for $C_{19}H_{13}BrO_3S$: C, 56.85%; H, 3.24%; Found C, 56.91%; H, 3.57%.

Compound 3b. Yield 79%; yellow solid; m.p. 138°C; UV(EtOH) λ_{max}: 209, 246, 355 nm; IR(KBr) ν_{max}: 1690, 1600, 1270 cm^{-1}; ^{1}H NMR (500 MHz): δ 2.34 (s, 3H, —CH$_3$), 2.38 (s, 3H, —CH$_3$), 3.49 (d, 2H, J = 6 Hz, —SCH$_2$), 4.97 (d, 2H, J = 1 Hz, —OCH$_2$), 6.39–6.41 (tt, 1H, J = 1, 6 Hz, =CH), 7.29–7.32 (m, 4H, ArH), 7.51–7.55 (m, 1H, ArH), 7.83–7.85 (m, 1H, ArH); Anal. Calcd. for $C_{21}H_{17}BrO_3S$: C, 58.74%; H, 3.96%; Found C, 59.05%; H, 3.61%.

Compound 3c. Yield 74%; yellow solid; m.p. 136°C; UV(EtOH)λ_{max}: 218, 240, 336 nm; IR(KBr) ν_{max}: 1700, 1600, 1240 cm^{-1}; ^{1}H NMR (500 MH$_Z$): δ 2.43 (s, 3H, —CH$_3$), 3.46 (d, 2H, J = 6 Hz, —SCH$_2$), 5.20 (d, 2H, J = 1 Hz, —OCH$_2$), 6.34–6.35 (tt, 1H, J = 1,6 Hz, =CH), 6.83–7.61 (m, 7H, ArH); Anal. Calcd. for $C_{20}H_{15}BrO_3S$: C, 57.83%; H, 3.61%; Found C, 58.04%; H, 3.73%.

Compound 3d. Yield 72%; yellow solid; m.p. 94°C; UV(EtOH)λ_{max}: 221, 243, 375 nm; IR(KBr) ν_{max}: 1700, 1590, 1290 cm^{-1}; ^{1}H NMR (300 MHz): δ 2.26 (s, 3H, —CH$_3$), 3.46 (d, 2H, J = 6 Hz, —SCH$_2$), 5.16 (d, 2H, J = 1 Hz, —OCH$_2$), 6.31–6.35 (tt, 1H, J = 1, 6 Hz, =CH), 6.84–6.87 (m, 1H, ArH), 7.02–7.05 (m, 1H, ArH), 7.29–7.35 (m, 3H, ArH), 7.51–7.57 (m, 1H, ArH), 7.82–7.85 (m, 1H, ArH); Anal. Calcd. for $C_{20}H_{15}BrO_3S$: C, 57.83%; H, 3.61%; Found C, 57.98%; H, 3.47%.

Compound 3e. Yield 75%; yellow solid; m.p. 122°C; UV(EtOH)λ_{max}: 216, 245, 359 nm; IR(KBr) ν_{max}: 3300, 1680, 1590, 1250 cm^{-1}; ^{1}H NMR (500 MHz): δ 2.26 (s, 3H, —C**H**$_3$), 2.43 (s, 3H, —C**H**$_3$), 3.45 (d, 2H, J = 6 Hz, —SC**H**$_2$), 5.16 (d, 2H, J = 1 Hz, —OC**H**$_2$), 6.30–6.33 (tt, 1H, J = 1, 6 Hz, =C**H**), 6.84–6.86 (d, J = 9 Hz, 1H, Ar**H**), 7.01–7.03 (dd, 1H, J = 2.5, 9 Hz, Ar**H**), 7.21–7.26 (m, 1H, Ar**H**), 7.32–7.34 (m, 2H, Ar**H**), 7.60 (s, 1H, Ar**H**); Anal. Calcd. for $C_{21}H_{17}BrO_3S$: C, 58.74%; H, 3.96%; Found C, 58.60%; H, 4.19%.

Compound 3f. Yield 73%; yellow solid; m.p. 168°C; UV(EtOH)λ_{max}: 212, 240, 326 nm; IR(KBr) ν_{max}: 1720, 1700, 1230 cm^{-1}; ^{1}H NMR (500 MHz): δ 2.24 (s, 3H, —C**H**$_3$), 2.26 (s, 3H, —C**H**$_3$), 2.43 (s, 3H, —C**H**$_3$), 3.48 (d, 2H, J = 6 Hz, —SC**H**$_2$), 5.00 (d, 2H, J = 1 Hz, —OC**H**$_2$), 6.38–6.42 (t, 1H, J = 6 Hz, =C**H**), 7.19–7.61 (m, 5H, Ar**H**); Anal. Calcd. for $C_{22}H_{19}BrO_3S$: C, 59.59%; H, 4.29%; Found C, 59.70%; H, 4.06%.

General procedure for the synthesis of compounds 7a–e. Compound 5 (1 mmol) was refluxed with several *o*-bromoanilines (**6a**–**e**) (1 mmol) in dry acetone (100 mL) in the presence of anhydrous potassium carbonate (1 g) and catalytic amount of NaI for 4–5 h. The reaction mixture was cooled, filtered, and the solvent was removed. The residual mass was subjected to column chromatography over silica gel using petroleum ether–ethylacetate (19:1) as eluant to give compounds **7a**–**e**.

Compound 7a. Yield: 80%; Solid, m.p. 170°C; IR (KBr)ν_{max}: 3410, 1698, 1596, 1497 cm^{-11} H NMR (CDCl$_3$, 400 MHz) δ_H 2.21 (s, 3H), 3.27–3.28 (d, 2H, J = 5.8 Hz), 4.38 (s, 2H), 5.76–5.79 (t, 1H, J = 5.8 Hz), 5.99 (s, 1H), 6.49–6.53 (t, 1H, J = 7.42 Hz), 6.59–6.61 (d, 1H, J = 8 Hz), 7.09–7.12 (t, 1H, J = 7.5 Hz), 7.35–7.37 (d, 1H, J = 8.04 Hz). UV (EtOH) λ_{max}= 361, 302, 245, 209 nm. Anal. Calcd. for $C_{16}H_{14}NO_2SBr$: C, 52.75%; H, 3.85%; N, 3.85%; Found C, 52.45%; H, 3.55%; N, 3.65%.

Compound 7b. Yield: 80%; Gummy mass. IR (KBr)ν_{max}: 3399, 1698, 1492 cm^{-1} ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 2.18 (s, 3H), 2.21 (s, 1H), 3.26–3.28 (d, 2H, J = 5.8 Hz), 4.36 (s, 2H), 5.75–5.78 (t, 1H, J = 5.86 Hz), 5.99 (s, 1H), 6.50–6.52 (d, 1H, J = 8.2 Hz), 6.90–6.92 (dd, 1H, J = 8.24, 1.32 Hz), 7.20–7.21 (d, 1H, J = 1.16 Hz). UV (EtOH) λ_{max}= 302, 243, 208 nm. Anal. Calcd. for $C_{17}H_{16}NO_2SBr$: C, 53.96%; H, 4.23%; N, 3.70%; Found C, 53.66%; H, 4.53%; N, 3.40%.

Compound 7c. Yield: 75%; Solid, m.p. 125–130°C; IR (KBr)ν_{max}: 3391, 1699, 1594 cm^{-1} ^{1}H NMR (CDCl$_3$, 500 MHz) δ_H 1.15–1.18 (t, 3H, J = 7.58 Hz), 2.22 (s, 3H), 2.47–2.52 (q, 2H, J = 7.58 Hz), 3.28–3.29 (d, 2H, J = 5.88 Hz), 4.36–4.37 (d, 2H, J = 1.09 Hz), 5.77–5.79 (t, 1H, J = 5.87 Hz), 5.99 (s, 1H), 6.56–6.58 (d, 1H, J = 8.26 Hz), 6.94–6.96 (dd, 1H, J = 8.26, 1.98 Hz), 7.23–7.24 (d, 1H, J = 1.99 Hz). UV (EtOH) λ_{max}= 303, 246, 209 nm. Anal. Calcd. for $C_{18}H_{18}NO_2SBr$: C, 55.10%; H, 4.59%; N, 3.57%; Found C, 55.40%; H, 4.49%; N, 3.27%.

Compound 7d. Yield: 80%; Solid, m.p. 120°C; IR (KBr)ν_{max}: 1711, 1493 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 2.17 (s, 3H), 2.24 (s, 3H), 2.61 (s, 3H, —NMe), 3.23–3.25 (d, 2H, J = 6.04 Hz), 4.15 (s, 2H), 5.92–5.95 (m, 2H), 6.89–6.91 (d, 1H, J = 8.12 Hz), 6.96–6.98 (dd, 1H, J = 8, 1.68 Hz), 7.33 (d, 1H, J = 1.68 Hz). UV (EtOH) λ_{max} = 356, 248, 205 nm. Anal. Calcd. for $C_{18}H_{18}NO_2SBr$: C, 55.10%; H, 4.59%; N, 3.57%; Found C, 54.80%; H, 4.89%; N, 3.28%.

Compound 7e. Yield: 75%; Solid, m.p. 110°C; IR (KBr)ν_{max}: 1711, 1495 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ_H 1.17–1.20 (t, 3H, J = 7.59 Hz), 2.18 (s, 3H), 2.52–2.57 (q, 2H, J = 7.57 Hz), 2.62 (s, 3H, —NMe), 3.25–3.26 (d, 2H, J = 5.99 Hz), 4.16 (s, 2H), 5.96–5.99 (m, 2H), 6.94–6.96 (d, 1H, J = 8.12 Hz), 7.0–7.02 (dd, 1H, J = 8.15, 1.9 Hz), 7.35 (d, 1H, J = 1.9 Hz). UV (EtOH) λ_{max}= 359, 299, 249, 215 nm. Anal. Calcd. for $C_{19}H_{20}NO_2SBr$: C, 56.16%; H, 4.93%; N, 3.45%; Found C, 56.36%; H, 4.63%; N, 3.15%.

General procedure for the preparation of compounds 4a–f and 8a–e by radical cyclization. A suspension of the compound 3a (0.5 mmol), ^{n}Bu$_3$SnH (0.075 mL), and AIBN (0.5–0.6 mol equiv) in dry benzene (7–10 mL) were refluxed for 7–8 h under N$_2$ atmosphere. The solvent was evaporated under reduced pressure. The residue was dissolved in 10 mL of ether and stirred with 10 mL of 10% aqueous potassium fluoride for 45 min. The white precipitate separated by filtration and the aqueous phase was extracted with CHCl$_3$ (3 × 10 mL). The combined organic extract was washed with brine and dried (Na$_2$SO$_4$). The residual mass after removal of the solvent was subjected to column chromatography over silica gel using pet-ether–ethyl acetate (19:1) as eluant to give cyclized products **4a**, which were then recrystallized from chloroform–petroleum ether. Similarly, other compounds **4b**–**f** and **8a**–**e** were also synthesized.

Compound 4a. Yield 80%; white solid; m.p. 140°C; UV (EtOH) λ_{max}: 219, 279 nm; IR (KBr) ν_{max}: 2900, 1700, 1195 cm^{-1}, ^{1}H NMR (CDCl$_3$, 500 MHz): Major diastereomer: δ 3.23 (t, 1H, J = 11.4 Hz, —SC**H**$_2$), 3.25 (dt, 1H, J = 3.6, 10.5 Hz, ring juncture), 3.33 (dd, 1H, J = 2.4 Hz, 12.6 Hz, SC**H**$_2$), 3.75 (dt, 1H, J = 3.1, 11.4 Hz, ring juncture), 3.88 (t, 1H, J = 10.5 Hz, OC**H**$_2$), 4.70 (dd, 1H, J = 3.08, 10.8 Hz, OC**H**$_2$), 6.88–6.97 (m, 2H, Ar**H**), 7.28–7.35 (m, 2H, Ar**H**), 7.51–7.57 (m, 3H, Ar**H**), 7.74–7.76 (m, 1H, Ar**H**); ^{13}C NMR (125 MHz, CDCl$_3$): at 29.6, 31.7, 32.4, 64.5, 114.9, 117.7, 120.7, 121.2, 124.0, 124.5, 129.3, 130.1, 130.2, 130.6, 132.2, 149.9, 151.3, 154.7, and 159.5; MS m/z 322 (M$^+$); Anal. Calcd. for $C_{19}H_{14}O_3S$: C, 70.81%; H, 4.35%; Found C, 71.02%; H, 4.43%. Minor diastereomer: ^{1}H NMR (CDCl$_3$, 500 MHz): δ 3.05–3.07 (m, 1H), 3.17–3.20 (m, 1H), 3.42–3.45 (m, 1H), 3.74–3.76 (m, 1H), 3.93–3.96 (m, 1H), 5.66 (dd, 1H, J = 3.4 Hz, 10.46 Hz); ^{13}C NMR (125 MHz, CDCl$_3$): δ 28.7, 37.5, 38.8, and 69.

Compound 4b. Yield 76%; white solid; m.p. 198°C; UV (EtOH) λ_{max}: 215, 279 nm; IR (KBr) ν_{max}: 2910, 1700, 1190 cm^{-1}, ^{1}H NMR (CDCl$_3$, 500 MHz): Major diastereomer: δ 2.19 (s, 3H, —C**H**$_3$), 2.28 (s, 3H, —C**H**$_3$), 3.20 (t, 1H, J = 11.2 Hz, —SC**H**$_2$), 3.24 (dt, 1H, J = 3.4, 10.8 Hz, ring juncture proton), 3.34 (dd, 1H, J = 2.6, 12.4 Hz, —SC**H**$_2$), 3.72 (dt, 1H, J = 3.2, 11.2 Hz, ring juncture proton), 3.90 (t, 1H, J = 10.8 Hz, —OC**H**$_2$), 4.68 (dd, 1H, J = 2.6, 11.8 Hz, —OC**H**$_2$), 6.84–6.89(s, 2H, Ar**H**), 7.32–7.61 (m, 2H, Ar**H**), 7.73–7.76 (m, 2H, Ar**H**); MS m/z 350 (M$^+$); Anal. Calcd. for $C_{21}H_{18}O_3S$: C, 72.0%; H, 5.14%; Found C, 72.25%; H, 5.43%. *Minor diastereomer:* ^{1}H NMR (CDCl$_3$, 500 MHz): δ 2.99–3.22 (m, 3H), 3.73–3.87 (m, 2H), 5.64 (dd, 1H, J = 3.5, 10.7 Hz).

Compound 4c. Yield 82%; white solid; m.p. 182°C; UV (EtOH) λ_{max}: 219, 280 nm; IR (KBr) ν_{max} : 2915, 1710, 1190 cm^{-1}, ^{1}H NMR (CDCl$_3$, 300 MHz): Major diastereomer: δ 2.43

(s, 3H, —C**H**$_3$), 3.26 (t, 1H, $J = 11.4$ Hz, —SC**H**$_2$), 3.27 (dt, 1H, $J = 3.4$, 10.7 Hz, ring juncture proton), 3.35 (dd, 1H, $J = 2.5$, 12.2 Hz, —SC**H**$_2$), 3.74 (dt, 1H, $J = 3.5$, 11.4 Hz, ring juncture proton), 3.87 (t, 1H, $J = 10.7$ Hz, —OC**H**$_2$), 4.64 (dd, 1H, $J =$ 2.6, 10.2 Hz, —OC**H**$_2$), 6.88–6.97 (m, 3H, Ar**H**), 7.14–7.35 (m, 3H, Ar**H**), 7.51(s, 1H, Ar**H**); MS *m*/*z* 336 (M$^+$); Anal. Calcd. for $C_{20}H_{16}O_3S$: C, 71.43%; H, 4.76%; Found C, 71.62%; H, 4.83%. Minor diastereomer: ^{1}H NMR (CDCl$_3$, 300 MHz): δ 3.00–3.22 (m, 3H), 3.88–3.93 (m, 2H), 5.62 (dd, 1H, $J = 3.4$, 10.4 Hz).

Compound 4d. Yield 82%; white solid; m.p. 182°C; UV (EtOH) λ_{max}: 220, 279 nm; IR (KBr) ν_{max} : 2900, 1700, 1196 cm^{-1}, ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.29 (s, 3H, —C**H**$_3$), 3.19 (dd, 1H, $J = 2.4$, 11.2 Hz, —SC**H**$_2$), 3.26–3.34 (m, 2H), 3.69 (dt, 1H, $J = 3.5$, 11.0 Hz, ring juncture proton), 3.78 (t, 1H, $J = 10.5$ Hz, —OC**H**$_2$), 4.61 (dd, 1H, $J = 2.1$, 10.0 Hz, —OC**H**$_2$), 6.78–7.00 (m, 3H, Ar**H**), 7.27–7.34 (m, 2H, Ar**H**), 7.51–7.56 (m, 1H, Ar**H**), 7.73 (d, $J = 7.8$ Hz, 1H, Ar**H**); MS *m*/*z* 336 (M$^+$); Anal. Calcd. for $C_{20}H_{16}O_3S$: C, 71.43%; H, 4.76%; Found C, 71.59%; H, 4.62%.

Compound 4e. Yield 84%; white solid; m.p. 208°C; UV (EtOH) λ_{max}: 219, 280 nm; IR (KBr) ν_{max}: 2900, 1690, 1220 cm^{-1}, ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.29 (s, 3H, —C**H**$_3$), 2.43 (s, 3H, —C**H**$_3$), 3.18–3.29 (m, 3H), 3.72 (dt, 1H, $J = 3.4$, 10.7 Hz, ring juncture proton), 3.77 (t, 1H, $J = 10.5$ Hz, —OC**H**$_2$), 4.60 (dd, 1H, $J = 3.2$, 10.4 Hz, —OC**H**$_2$), 6.77–7.01 (m, 3H, Ar**H**), 7.20–7.24 (m, 1H, Ar**H**), 7.32 (dd, 1H, $J = 1.6$, 8.3 Hz, Ar**H**), 7.51 (s, 1H, Ar**H**); MS *m*/*z* 350 (M$^+$); Anal. Calcd. for $C_{21}H_{18}O_3S$: C, 72.0%; H, 5.14%; Found C, 72.17%; H, 5.25%.

Compound 4f. Yield 77%; white solid; m.p. 214°C; UV (EtOH) λ_{max}: 219, 278 nm; IR (KBr) ν_{max} : 2910, 1690, 1210 cm^{-1}, ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.18 (s, 3H, —CH$_3$), 2.26 (s, 3H, —CH$_3$), 2.43 (s, 3H, —CH$_3$), 3.13–3.30 (m, 3H), 3.66–3.71 (dt, 2H, $J = 3.6$, 10.7 Hz, ring juncture proton), 3.76 (t, 1H, $J = 10.6$ Hz, —OCH$_2$), 4.66 (dd, 1H, $J = 2.1$, 10.3 Hz, —OCH$_2$), 6.84–6.87 (d, 2H, $J = 9$ Hz, ArH), 7.20–7.23 (m, 1H, ArH), 7.32–7.34 (m, 1H, ArH), 7.52 (s, 1H, ArH); MS *m*/*z* 364 (M$^+$); Anal. Calcd. for $C_{22}H_{20}O_3S$: C, 72.53%; H, 5.49%; Found C, 72.71%; H, 5.25%.

Compound 8a. Yield: 70%; Solid, m.p. 218°C; IR (KBr)ν_{max}: 3387, 1682, 1539 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ_H 2.18 (s, 3H), 2.90–2.94 (ddd, 1H, $J = 12.9$, 3.2, 2.1 Hz), 3.02–3.06 (t, 1H, $J = 11.4$ Hz), 3.09–3.12 (dt, 1H, $J =$ 12.1, 3.5 Hz), 3.19–3.24 (t, 1H, $J = 12.6$ Hz), 3.33–3.37 (dt, 1H, $J = 11.02$, 4.1 Hz), 3.65–3.69 (dt, 1H, $J = 11.5$, 3.6 Hz), 4.02 (brs, 1H, N—H), 5.81 (s, 1H), 6.51–6.53 (dd, 1H, $J = 8.04$, 0.76 Hz), 6.64–6.67 (dt, 1H, $J = 7.32$, 1.12 Hz), 7.02–7.06 (m, 2H). MS: *m*/*z* = 286 (M + 1); UV (EtOH) λ_{max}= 306, 255, 232, 209 nm. Anal. Calcd. for $C_{16}H_{15}NO_2S$: C, 67.37%; H, 5.26%; N, 4.91%; Found C, 67.67%; H, 4.96%; N, 5.21%.

Compound 8b. Yield: 75%; Solid, m.p. 210°C; IR (KBr)ν_{max}: 3392, 1684, 1539 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ_H 2.18 (s, 3H), 2.23 (s, 3H), 2.90–2.97 (m, 1H), 3.00–3.08 (m, 2H), 3.17–3.25 (t, 1H, $J = 12.35$ Hz), 3.30–3.34 (m, 1H), 3.62–3.66 (d, 1H, $J = 11.17$ Hz), 3.90 (brs, 1H, N—H), 5.81 (s, 1H), 6.45–6.47 (d, 1H, $J = 7.77$ Hz), 6.85–6.87 (d, 1H, $J = 7.63$ Hz), 6.87 (s, 1H). ^{13}C NMR (125 MHz, CDCl$_3$): 19.8, 20.7, 30.8, 31.0, 35.2, 42.0, 104.3, 112.9, 115.0, 121.9, 126.8, 129.3, 130.5, 141.7, 151.7, 158.0, 161.7. MS: *m*/*z* = 300 (M + 1); UV (EtOH) λ_{max} = 308, 257, 232, 208 nm. Anal. Calcd. for $C_{17}H_{17}NO_2S$: C, 68.23%; H, 5.69%; N, 4.68%; Found C, 68.53%; H, 5.39%; N, 4.98%.

Compound 8c. Yield: 75%; Solid, m.p. 200°C; IR (KBr)ν_{max}: 3386, 1693, 1545 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ_H 1.17–1.20 (t, 3H, $J = 7.58$ Hz), 2.19 (s, 3H), 2.50–2.55 (q, 2H, $J = 7.57$ Hz), 2.92–2.95 (dd, 1H, $J = 13.11$, 2.49 Hz), 2.99–3.03 (t, 1H, $J = 11.4$ Hz), 3.06–3.09 (dt, 1H, $J =$ 12.14, 3.5 Hz), 3.19–3.24 (t, 1H, $J = 12.63$ Hz), 3.31–3.34 (dt, 1H, $J = 10.98$, 4.0 Hz), 3.64–3.66 (dt, 1H, $J = 11.44$, 3.68 Hz), 3.91 (brs, 1H, N—H), 5.80 (s, 1H), 6.47–6.49 (d, 1H, $J = 8.63$ Hz), 6.88–6.89 (m, 2H). MS: *m*/*z* = 314 (M + 1); UV (EtOH) λ_{max}= 309, 257, 232, 210 nm. Anal. Calcd. For $C_{18}H_{19}NO_2S$: C, 69.01%; H, 6.07%; N, 4.47%; Found C, 69.31%; H, 5.87%; N, 4.19%.

Compound 8d. Yield: 70%; Solid, m.p. 162°C; IR (KBr)ν_{max}: 1694, 1463 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ_H 2.19 (s, 3H), 2.23 (s, 3H), 2.97–3.01 (t, 1H, $J = 11.09$ Hz), 3.03–3.07 (m, 1H), 3.14–3.19 (t, 1H, $J = 12.54$ Hz), 3.43–3.47 (dt, 1H, $J = 10.83$, 4.19 Hz), 3.48–3.51 (ddd, 1H, $J = 11.25$, 3.9, 1.3 Hz), 5.80 (s, 1H), 6.53–6.55 (d, 1H, $J = 8.37$ Hz), 6.88–6.89 (d, 1H, $J = 1.78$ Hz), 6.95–6.97 (dd, 1H, $J = 8.31$, 1.84 Hz). ^{13}C NMR (125 MHz, CDCl$_3$): 19.8, 20.6, 30.9, 31.0, 35.8, 39.3, 50.7, 104.3, 111.8, 112.9, 123.2, 125.9, 129.5, 130.4, 143.8, 151.9, 158.0, 161.7. MS: *m*/*z* = 314 (M + 1); UV (EtOH) λ_{max} = 309, 260, 208 nm. Anal, Calcd. for $C_{18}H_{19}NO_2S$: C, 69.01%; H, 6.07%; N, 4.47%; Found C, 69.29%; H, 6.28%; N, 4.25%.

Compound 8e. Yield: 70%; Solid, m.p. 140°C; IR (KBr)ν_{max}: 1700, 1463 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ_H 1.18–1.21 (t, 3H, $J = 7.59$ Hz), 2.19 (s, 3H), 2.51–2.56 (q, 2H, $J = 7.59$ Hz), 2.88–2.90 (ddd, 1H, $J = 12.8$, 3.16, 2.0 Hz), 2.91 (s, 3H), 2.98–3.02 (t, 1H, $J = 11.08$ Hz), 3.05–3.08 (dt, 1H, $J = 12.08$, 3.4 Hz), 3.15–3.20 (t, 1H, $J = 12.53$ Hz), 3.43–3.47 (dt, 1H, $J = 10.87$, 4.2 Hz), 3.49–3.52 (ddd, 1H, J = 11.2, 2.76, 1.2 Hz), 5.81 (s, 1H), 6.56–6.58 (d, 1H, $J =$ 8.34 Hz), 6.90–6.91 (d, 1H, $J = 1.87$ Hz), 6.98–7.00 (dd, 1H, $J = 8.4$, 1.99 Hz). MS: *m*/*z* = 328 (M + 1); UV (EtOH) λ_{max} = 308, 262, 231, 208 nm. Anal. Calcd. For $C_{19}H_{21}NO_2S$: C, 69.72%; H, 6.42%; N, 4.28%; Found C, 69.45%; H, 6.22%; N, 4.50%.

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An Efficient and Clean Synthesis of Pyrido[2,3-*d*]pyrimidine-4,7-dione Derivatives in Aqueous Media

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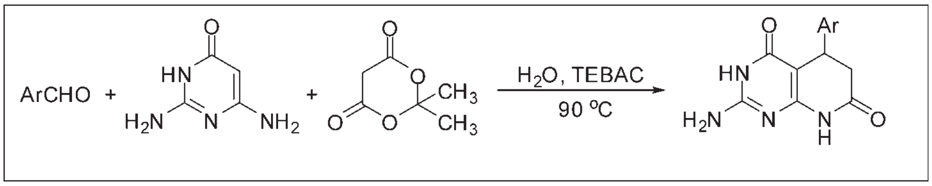

A series of 2-amino-5-aryl-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione derivatives were synthesized via the three-component reaction of aromatic aldehyde, 2,6-diaminopyrimidine- 4(3*H*)-one, and Meldrum's acid in water in the presence of triethylbenzylammonium chloride (TEBAC). This protocol has the advantages of easier work-up, milder reaction conditions, and environmentally benign procedure.

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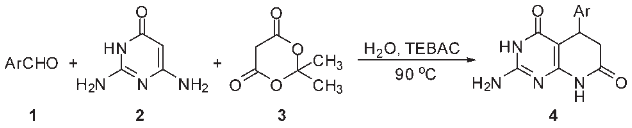
INTRODUCTION

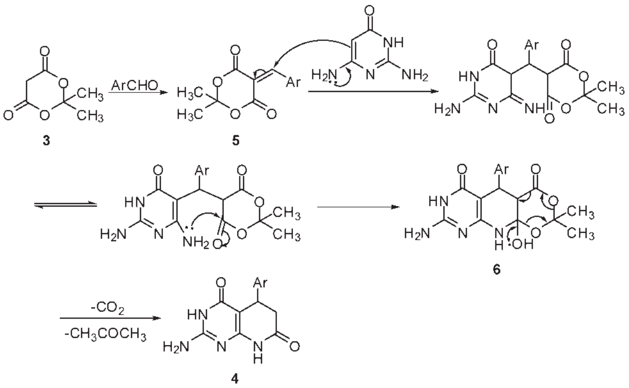
Multicomponent reactions (MCRs), in which multiple reactions are combined into one synthetic operation, have been extensively used in synthetic chemistry for the formation of carbon-carbon and carbon–heteroatom bonds [1]. Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step, thus avoiding complication operations and allowing saving both of solvent and of reagents. In the past decade there have been tremendous developments in three- and four-component reactions and great efforts continue to be made to develop new MCRs [2]. The need to reduce the amount of toxic waste and by-product arising from chemical processes requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods. One of the most promising approaches is using water as the reaction medium. Breslow rediscovered the use of water as a solvent in organic synthesis in the 1980s [3]. There has been growing recognition that water is an attractive medium for many organic reactions [4] and many MCRs in aqueous media have been reported [5].

The importance of uracil and its annulated derivatives is well recognized by synthetic [6] as well as biological [7] chemists. With the development of clinically useful anticancer and antiviral drugs [8], there has recently been remarkable interest in the synthetic manipulations of uracils [9]. Pyrido[2,3-*d*]pyrimidines have received considerable attention over the past years because of their wide range of biological activities, which include antitumor [10], antibacterial [11], anti-inflammatory [12], antifungal [13], and antileishmaniasis [14] properties, and also act as cyclin-dependent kinase 4 inhibitors [15]. Therefore, for the preparation of these complex molecules large efforts have been directed toward the synthetic manipulation of uracils. Broom *et al.* [16] synthesized pyrido[2,3-*d*]pyrimidines from the reaction of DMAD and 6-aminouracile in protic solvent but obtained uncyclized condensed acetylenic adduct when the reaction was carried in DMF [17]. Bhuyan *et al.* [18] reported the synthesis of pyrido[2,3-*d*]pyrimidines from the reaction of arylidenemalononitrile with 6-aminouracil in refluxing 1-propanol, but in this reaction, benzylmalononitrile was obtained as by-product and the amount of arylidenemalononitrile needed was in excess. Rodríguez *et al.* [19] reported the synthesis of 9-aryl substituted 2-amino-4,7-dioxopyrido[2,3-*d*]pyrimidines by refluxing equimolar amounts of 5-arylidene substituted Meldrum's acid and 2,6-diamino-4-oxopyrimidine in acetic acid. Recently, Devi *et al.* [20] reported a novel three-component one-pot synthesis of pyrido[2,3-*d*]pyrimidines using microwave heating. These methods usually require forcing conditions, using organic solvents, long reaction times and complex synthetic pathways. As part of our current studies on the development of new routes to heterocyclic systems [21], recently we have reported the synthesis of pyrido[2,3-*d*]pyrimidine derivatives by the three-component reaction of aldehyde,

Scheme 1



Scheme 2



alkyl nitriles, and aminopyrimidines in water [22]. In this article, we would report an efficient and clean synthetic route to 2-amino-5-aryl-5,6-dihydropyrido[2,3-*d*] pyrimidine-4,7(3*H*,8*H*)-dione derivatives in aqueous media catalyzed by TEBAC.

RESULTS AND DISCUSSION

When the three-components of aromatic aldehyde **1**, 2,6-diaminopyrimidine-4(3*H*)-one **2**, and Meldrum's acid **3** were treated in water in the presence of TEBAC at 90°C for a few hours (Scheme 1), the desired 2-amino-5-aryl-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*, 8*H*)-dione **4** were obtained in high yields (Table 1).

As shown in Table 1, this protocol could be applied not only to the aromatic aldehydes with electron-withdrawing groups (such as halide and nitro groups), but also to aromatic aldehydes with electron-donating groups (such as alkyl and alkoxyl groups). Therefore, we concluded that the electronic nature of the substituents of aldehydes has no significant effect on this reaction. However, because some aldehydes were remaining in the mixture, so some aldehydes gave low yields.

The structures of the compounds **4** were identified by their spectroscopy analysis. Thus, the IR spectra of compounds **4** measured in potassium bromide pellets show two bands of the elongation vibrations of the C=O group at 1703–1646 cm^{-1}, NH$_2$, and NH groups at 3467–3157 cm^{-1}. In the ^{1}H NMR spectra of compounds **4** measured in dimethyl-d_6 sulfoxide were observed the CH$_2$ proton signals at 2.41–2.57 and 2.91–3.17 ppm, the CH proton signals at 4.05–4.46 ppm, the NH$_2$ proton signals at 6.53–6.66 ppm, the aromatic proton signals at 6.82–8.16 ppm, and the NH proton signals at 10.10–10.33 and 10.60–10.90 ppm, respectively.

Table 1

Synthesis of 2-amino-5-aryl-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione **4** in aqueous media.

Entry	Ar	Time (h)	Yield (%)
4a	4-FC$_6$H$_4$	5	76
4b	4-CH$_3$OC$_6$H$_4$	3	74
4c	4-BrC$_6$H$_4$	9	69
4d	4-ClC$_6$H$_4$	4	67
4e	2-NO$_2$C$_6$H$_4$	6	75
4f	4-CH$_3$C$_6$H$_4$	9	65
4g	3-NO$_2$C$_6$H$_4$	5	95
4h	3-ClC$_6$H$_4$	4	72
4i	2-ClC$_6$H$_4$	4	69
4j	3,4-OCH$_2$OC$_6$H$_3$	8	80
4k	4-NO$_2$C$_6$H$_4$	6	82

Although the detailed mechanism of earlier reaction remains not to be fully clarified, the formation of compounds **4** could be explained by a reaction sequence presented in Scheme 2. According to the literature [23], we proposed that the reaction proceeded via a reaction sequence of condensation, addition, cyclization, and elimination. First, the condensation of aldehyde **1** and Meldrum's acid **3** gave the intermediate product **5**. The addition of **5** to 2,6-diaminopyrimidine-4(3*H*)-one **2**, then cyclized to give intermediate product **6**. The carbon dioxide and acetone were losing from the intermediate product **6** to give the products **4**.

In conclusion, we have developed a simple three-component reaction consisting of an aldehyde, 2,6-diaminopyrimidine-4(3*H*)-one, and Meldrum's acid for the synthesis of 2-amino-5-aryl-5,6-dihydropyrido[2,3-*d*] pyrimidine-4,7(3*H*,8*H*)-dione derivatives in aqueous media. This method has the advantages of easier work-up, milder reaction conditions, and environmentally benign procedure.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded on a Tensor 27 spectrometer in KBr with absorption in cm^{-1}. ^{1}H NMR spectra were recorded on a Bruker DPX 400-MHz spectrometer as DMSO-d_6 solution. *J* values are in Hz. Chemical shifts are expressed in δ downfield from internal tetramethylsilane.

General procedure for the synthesis of 2-amino-5-aryl-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione derivatives 4 in aqueous media. A suspension of a mixture of aromatic aldehyde **1** (2 mmol), 2,6-diaminopyrimidine-4(3*H*)-one 2 (2 mmol), Meldrum's acid 3 (2 mmol) and TEBAC (0.15 g) was stirred in water (10 mL) at 90°C for several hours. After completion monitored by TLC, the reaction mixture was allowed to cool to room temperature. The crystalline powder formed recrystallized from DMF and water to give pure **4**.

2-Amino-5-(4-fluorophenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*, 8*H*)-dione (4a). This compound was obtained as solid with mp > 300°C (Lit. [24] > 300°C); IR (potassium bromide): 3325, 3167, 1691, 1652, 1591, 1537, 1508, 1485, 1361, 1305, 1264, 1211, 1158, 1099, 1015, 973, 906, 838, 794 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.48 (d, J = 16 Hz, 1H, CH), 2.96 (dd, J_1 = 7.6 Hz, J_2 = 16 Hz, 1H, CH), 4.13 (d, J = 7.6 Hz, 1H, CH), 6.59 (br., s, 2H, NH$_2$), 7.07–7.12 (m, 2H, ArH), 7.16–7.20 (m, 2H, ArH), 10.16 (s, 1H, NH), 10.64 (s, 1H, NH).

2-Amino-5-(4-methoxylphenyl)-5,6-dihydropyrido[2,3-*d*] pyrimidine-4,7(3*H*,8*H*)-dione (4b). This compound was obtained as solid with mp > 300°C (Lit. [24] > 300°C); IR (potassium bromide): 3464, 3315, 3159, 1691, 1652, 1596, 1559, 1539, 1511, 1488, 1457, 1396, 1361, 1310, 1251, 1220, 1178, 1033, 907, 831, 793, 699 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.45 (d, J = 16 Hz, 1H, CH), 2.91 (dd, J_1 = 7.6 Hz, J_2 = 16 Hz, 1H, CH), 3.70 (s, 3H, CH$_3$O), 4.06 (d, J = 7.6 Hz, 1H, CH), 6.53 (br., s, 2H, NH$_2$), 6.82 (d, J = 8.4 Hz, 2H, ArH), 7.06 (d, J = 8.4 Hz, 2H, ArH), 10.08 (s, 1H, NH), 10.80 (s, 1H, NH).

2-Amino-5-(4-bromophenyl)-5,6-dihydro[2,3-*d*] pyrimidine-4,7(3*H*,8*H*)-dione (4c). This compound was obtained as solid with mp > 300°C (Lit. [24] > 300°C); IR (potassium bromide): 3325, 3159, 1688, 1646, 1588, 1539, 1486, 1398, 1362, 1307, 1262, 1212, 1158, 1074, 1010, 972, 907, 817, 793 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.47 (d, J = 16.4 Hz, 1H, CH), 2.97 (dd, J_1 = 8.0 Hz, J_2 = 16.4 Hz, 1H, CH), 4.11 (d, J = 8.0 Hz, 1H, CH), 6.60 (br., s, 2H, NH$_2$), 7.11 (d, J = 8.4 Hz, 2H, ArH), 7.47 (d, J = 8.4 Hz, 2H, ArH), 10.18 (s, 1H, NH), 10.66 (s, 1H, NH).

2-Amino-5-(4-chlorophenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (4d). This compound was obtained as solid with mp > 300°C (Lit. [24] > 300 °C); IR (potassium bromide): 3460, 3319, 3158, 1698, 1650, 1591, 1539, 1487, 1398, 1361, 1307, 1261, 1211, 1159, 1091, 1014, 973, 907, 819, 793 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.47 (d, J = 16 Hz, 1H, CH), 2.97 (dd, J_1 = 8.0 Hz, J_2 = 16 Hz, 1H, CH), 4.12 (d, J = 8.0 Hz, 1H, CH), 6.59 (br., s, 2H, NH$_2$), 7.17 (d, J = 8.4 Hz, 2H, ArH), 7.34 (d, J = 8.4 Hz, 2H, ArH), 10.16 (s, 1H, NH), 10.65 (s, 1H, NH).

2-Amino-5-(2-nitrophenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (4e). This compound was obtained as solid with mp > 300°C (Lit. [19] > 300°C); IR (potassium bromide): 3433, 3319, 3167, 1698, 1652, 1588, 1536, 1519, 1477, 1408, 1340, 1281, 1259, 1233, 1213, 1165, 1018, 967, 930, 904, 862, 824, 794, 744, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.41 (d, J = 16.4 Hz, 1H, CH), 3.17 (dd, J_1 = 8.8 Hz, J_2 = 16.4 Hz, 1H, CH), 4.49 (d, J = 8.8 Hz, 1H, CH), 6.65 (br., s, 2H, NH$_2$), 7.16 (d, J = 7.6 Hz, 1H, ArH), 7.49 (t, J = 7.6 Hz, 1H, ArH), 7.63 (t, J = 7.6 Hz, 1H, ArH), 7.93 (d, J = 8.0 Hz, 1H, ArH), 10.33 (s, 1H, NH), 10.67 (s, 1H, NH).

2-Amino-5-(4-methylphenyl)-5,6-dihydro-pyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (4f). This compound was obtained as solid with mp > 300°C (Lit. [24] > 300°C); IR (potassium bromide): 3315, 3157, 1698, 1653, 1636, 1600, 1559, 1540, 1487, 1457, 1395, 1362, 1309, 1264, 948, 904, 835, 809 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.23 (s, 3H, CH$_3$), 2.45 (d, J = 16 Hz, 1H, CH), 2.93 (dd, J_1 = 7.6 Hz, J_2 = 16 Hz, 1H, CH), 4.07 (d, J = 7.6 Hz, 1H, CH), 6.55 (br., s, 2H, NH$_2$), 7.02 (d, J = 8.0 Hz, 2H, ArH), 7.15 (d, J = 8.0 Hz, 2H, ArH), 10.10 (s, 1H, NH), 10.60 (s, 1H, NH).

2-Amino-5-(3-nitrophenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (4g). This compound was obtained as solid with mp > 300°C (Lit. [24] > 300°C); IR (potassium bromide): 3450, 3317, 3163, 1691, 1652, 1588, 1530, 1470, 1405, 1353, 1301, 1266, 1020, 977, 929, 894, 826, 807, 790, 737 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.57 (d, J = 16.4 Hz, 1H, CH), 3.05 (dd, J_1 =8.0 Hz, J_2 = 16.4 Hz, 1H, CH), 4.30 (d, J = 8.0 Hz, 1H, CH), 6.66 (br, s, 2H, NH$_2$), 7.58∼7.67 (m, 2H, ArH), 8.01 (s, 1H, ArH), 8.06–8.11 (m,1H, ArH), 10.28 (s, 1H, NH), 10.71 (s, 1H, NH).

2-Amino-5-(3-chlorophenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (4h). This compound was obtained as solid with mp > 300°C (Lit. [24] > 300 °C); IR (potassium bromide): 3325, 3169, 1683, 1652, 1585, 1539, 1477, 1391, 1264, 1212, 953, 907, 840, 786, 781 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.49 (d, J = 16 Hz, 1H, CH), 2.97(dd, J_1 = 7.6 Hz, J_2 = 16 Hz, 1H, CH), 4.14(d, J = 7.6 Hz, 1H, CH), 6.62 (br., s, 2H, NH$_2$), 7.12 (d, J = 7.6 Hz, 1H, ArH), 7.17 (s, 1H, ArH), 7.25–7.34 (m, 2H, ArH), 10.17 (s, 1H, NH), 10.67 (s, 1H, NH).

2-Amino-5-(2-chlorophenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (4i). This compound was obtained as solid with mp > 300°C (Lit. [24] > 300°C); IR (potassium bromide): 3327, 3174, 1703, 1670, 1621, 1540, 1487, 1440, 1395, 1359, 1325, 1098, 1048, 1035, 1005, 975, 909, 813, 753 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.37 (d, J = 16.4 Hz, 1H, CH), 3.04 (dd, J_1 = 8.4 Hz, J_2 = 16.4 Hz, 1H, CH), 4.46 (d, J = 8.4 Hz, 1H, CH), 6.61 (br, s, 2H, NH$_2$), 6.89–6.93 (m, 1H, ArH), 7.21–7.28 (m, 2H, ArH), 7.45–7.49 (m, 1H, ArH), 10.20 (s, 1H, NH), 10.68 (s, 1H, NH).

2-Amino-5-(benzo[d][1,3]dioxol-6-yl)-5,6-dihydropyrido [2,3-*d*]pyrimidine-4,7-(3*H*,8*H*)-dione (4j). This compound was obtained as solid with mp > 300°C (Lit. [24] > 300°C); IR (potassium bromide): 3467, 3320, 3164, 1694, 1639, 1591, 1540, 1502, 1486, 1438, 1405, 1356, 1311, 1242, 1212, 1121, 967, 934, 811, 807, 790 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.45 (d, J = 16 Hz, 1H, CH), 2.91 (dd, J_1 = 7.6 Hz, J_2 = 16 Hz, 1H, CH), 4.05 (d, J = 7.6 Hz, 1H, CH), 5.95 (s, 2H, OCH$_2$O), 6.50–6.62 (m, 3H, NH$_2$+ArH), 6.73 (s, 1H, ArH), 6.79 (d, J = 8.0 Hz, 1H, ArH), 10.12 (s, 1H, NH), 10.62 (s, 1H, NH).

2-Amino-5,6-dihydro-5-(4-nitrophenyl)pyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (4k). This compound was obtained as solid with mp > 300°C (Lit. [24] > 300°C); IR (potassium bromide): 3360, 3308, 3186, 1693, 1675, 1588, 1513, 1482, 1412, 1347, 1305, 1262, 1180, 1058, 1022, 966, 905, 826, 791, 701 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.53 (d, J = 16.4 Hz, 1H, CH), 3.06 (dd, J_1 = 8.0 Hz, J_2 = 16.4 Hz, 1H, CH), 4.27 (d, J = 8.0 Hz, 1H, CH), 6.64 (br., s, 2H, NH$_2$), 7.44 (d, J = 8.4 Hz, 2H, ArH), 8.16 (d, J = 8.4 Hz, 2H, ArH), 10.27 (s, 1H, NH), 10.70 (s, 1H, NH).

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Clean Synthesis of Furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one Derivatives in Aqueous Media

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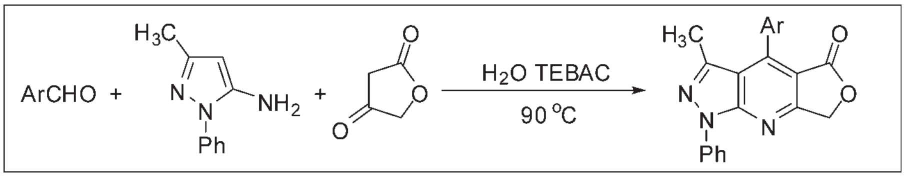

A series of 4-aryl-3-methyl-1-phenyl-7*H*-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-ones were synthesized *via* the three-component reaction of an aldehyde, 5-amino-3-methyl-1-phenyl-1*H*-pyrazole and tetronic acid in aqueous media in the presence of triethylbenzylammonium chloride (TEBAC). This method has the advantages of easier work-up, mild reaction conditions, high yields, and an environmentally benign procedure.

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INTRODUCTION

The need to reduce the amount of toxic waste and byproducts arising from chemical processes requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods [1]. One of the most promising approaches uses water as the reaction medium [2]. Breslow [3], who showed that hydrophobic effects could strongly enhance the rate of several organic reactions, rediscovered the use of water as a solvent in organic reactions in 1980s. In recent years, there has been increasing recognition that water is an attractive medium for many organic reactions [4]. The aqueous medium with respect to organic solvent is less expensive, less dangerous, and environment-friendly. Many important types of heterocyclic compounds, such as triazines, acridines, quinolines, pyridines, indoles, pyrazines, furans, and pyrimidines [5], have been synthesized in aqueous media. The synthesis of new and important type of heterocyclic compounds in water continues to attract wide attention among synthetic chemists.

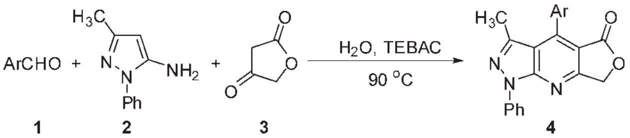
Pyrazole derivatives have been reported in the literature to be versatile building blocks for the synthesis of a wide range of the heterocyclic motifs, such as pyrazolopyridines [6], pyrazolequinolines [7], and pyrazolopyrazoles [8]. The pyrazolo[3,4-*b*]pyridine system has interesting biological and pharmacological properties [9]. Furopyridines is one of the ''privileged medical scaffolds,'' which are used for the development of pharmaceutical agents of various applications. Compounds with this motif show a wide range of pharmacological activities [10] and used as calcium influx promoters, HIV-1 non-nucleoside reverse transcriptase inhibitors and acetylcholinesterase inhibitors [11]. As part of our current studies on the development of new routes to heterocyclic systems in aqueous media [12], we now report an efficient and clean synthetic route to furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one derivatives (**4**) via the three-component reaction of arylaldehyde **1**, 5-amino-3-methyl-1-phenyl-1*H*-pyrazole **2** and tetronic acid **3** in aqueous media (Scheme 1).

RESULTS AND DISCUSSION

Choosing an appropriate solvent is of crucial importance for the successful organic synthesis. To search for the optimal solvent, the three-component reaction of 3,4-dimethoxybenzaldehyde **1a**, 5-amino-3-methyl-1-phenyl-1*H*-pyrazole **2** and tetronic acid **3** was examined using water, acetonitrile, acetone, ethanol, DMF and 1,2-dichloroethane as solvent, respectively, at different temperature for the synthesis of **4a**. The results are summarized in Table 1.

It can be seen from the Table 1 that the reactions using water as the solvent resulted in higher yields and shorter reaction times than those using organic solvents. On the basis of the obtained results, H_2O/TEBAC was found to be superior in terms of yield. Under these optimized reaction conditions, a series of furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one derivatives **4** were synthesized. The products

Scheme 1



were different from those in ethanol in the presences of *L*-proline [13]. The results are summarized in Table 2.

Apart from the mild conditions of the process and its excellent results, the simplicity of product isolation and the possibility to recycle the reaction solution offer a significant advantage. Because TEBAC is soluble in water and the desired product is less soluble in water, the products can be directly separated by cooling to room temperature and filtering after the reaction is completed. The remaining reaction solution can be recycled. Studies using **1a**, **2**, and **3** as model substrates showed that the recovered reaction solution could be successively recycled in subsequent reaction without any decrease of yield (Table 3).

All the products **4** were characterized by mp, IR, and ^{1}H NMR spectra as well as HRMS.

Although the detailed mechanism of the aforementioned reaction remains to be fully clarified the formation of furo[3,4-*4*]pyrazolo[3,4-*b*]pyridine-5-ones **4** could be explained by a reaction sequence presented in Scheme 2. We proposed that the reaction proceeded via a reaction sequence of condensation, addition, cyclization, dehydration, and aromatization. First, the condensation of aldehyde **1** and tetronic acid **3** gave the intermediate product **5**. The addition of **2** to **5** then furnished the intermediate product **7**, which upon intramolecular cyclization and dehydration gave rise to **9**. In the last step, the intermediate product **9** aromatized to product **4**.

In conclusion, we have developed a simple and clean three-component reaction of an aldehyde, 5-amino-3-methyl-1-phenyl-1*H*-pyrazole and tetronic acid for the synthesis of furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one derivatives in the presence of TEBAC in aqueous media. This method has the advantages of good yields, convenient procedure and environmentally friendly reaction conditions.

Table 1

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

Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	H_2O/SDS	90	15	90
2	H_2O/TEBAC	90	9	98
3	CH_3CN	Reflux	20	41
4	CH_3COCH_3	Reflux	20	0
5	EtOH	Reflux	20	56
6	DMF	100	22	46
7	$ClCH_2CH_2Cl$	Reflux	15	0

Table 2

The synthesis of **4** in aqueous media in the presence of TEBAC.[a]

Entry	Compound	Ar	Time (h)	Yield (%)
1	**4a**	3,4-$(CH_3O)_2C_6H_3$	9	98
2	**4b**	4-BrC_6H_4	20	97
3	**4c**	4-FC_6H_4	24	95
4	**4d**	4-$NO_2C_6H_4$	30	80
5	**4e**	4-$CH_3OC_6H_4$	23	97
6	**4f**	2,4-$Cl_2C_6H_3$	20	83
7	**4g**	3,4-$(CH_3)_2C_6H_3$	10	97
8	**4h**	4-ClC_6H_4	25	98
9	**4i**	Pyridin-2-yl	22	95
10	**4j**	Thiophen-2-yl	15	87
11	**4k**	3-ClC_6H_4	35	89
12	**4l**	2-ClC_6H_4	30	85
13	**4m**	3,4-$Cl_2C_6H_3$	30	93

[a] In all entries 90°C temperature was used.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded on a Tensor 27 spectrometer in KBr with absorption in cm^{-1}. ^{1}H NMR spectra were recorded on a Bruker DPX 400-MHz spectrometer as DMSO-d_6 solution, *J* values are in Hz. Chemical shifts are expressed in δ downfield from internal tetramethylsilane. HRMS were obtained using TOF-MS or Bruker-micro TOF-Q-MS instrument.

General procedure for the synthesis of furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one derivatives 4 in aqueous media. Aldehyde **1** (2 mmol), 5-amino-3-methyl-1-phenyl-1*H*-pyrazole **2** (2 mmol), tetronic acid **3** (2 mmol) and TEBAC (0.1 g) were added to a 50-mL round-bottom flask containing 10 mL water. The mixture was then stirred at 90°C for given times. After completion of the reaction, the reaction mixture was cooled to room temperature. The precipitate was collected by suction and purified by recrystallization from EtOH to give products **4**.

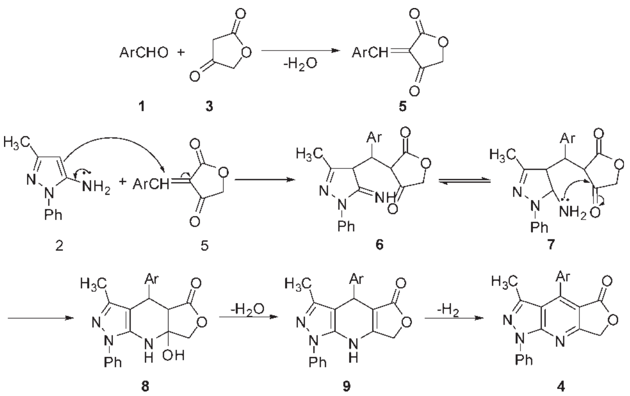
3-Methyl-1-phenyl-4-(3,4-dimethoxyphenyl)-7*H*-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one (4a). This compound was obtained as solid with mp 200–202°C (lit. [14] 203–205°C); IR (potassium bromide): 3059, 3018, 1768, 1590, 1570, 1512, 1460, 1438, 1412, 1355, 1325, 1309, 1259, 1234, 1203, 1174, 1130, 1070, 1045, 1027, 843, 795, 761, 701 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.18 (s, 3H, CH_3), 3.79 (s, 3H, CH_3O), 3.88 (s, 3H, CH_3O), 5.46 (s, 2H, CH_2), 7.13 (d, $J = 7.6$ Hz, 2H, ArH), 7.19 (s, 1H, ArH), 7.40 (t, $J = 7.6$ Hz, 1H, ArH), 7.60 (t, $J = 7.6$ Hz, 2H, ArH), 8.19 (d, $J = 8.0$ Hz, 2H, ArH). HRMS

Table 3

Studies on the reuse of reaction solution in the preparation of **4a**.

Round	1	2	3	4	5	6
Yield (%)	98	97	92	94	95	92

Scheme 2



[Found: *m*/*z* 402.1450 (M + H$^+$); calcd for $C_{23}H_{20}N_3O_4$: 402.1452].

3-Methyl-1-phenyl-4-(4-bromophenyl)-7*H*-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one (4b). This compound was obtained as solid with mp 226–228°C (lit. [14] 226–227°C); IR (potassium bromide): 3058, 1765, 1579, 1558, 1507, 1489, 1440, 1387, 1356, 1314, 1210, 1140, 1070, 1047, 1029, 1012, 847, 821, 798, 758, 720 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.11 (s, 3H, CH$_3$), 5.48 (s, 2H, CH$_2$), 7.40 (t, *J* = 7.2 Hz, 1H, ArH), 7.54 (d, *J* = 8.0 Hz, 2H, ArH), 7.60 (t, *J* = 7.6 Hz, 2H, ArH), 7.79 (d, *J* = 8.0 Hz, 2H, ArH), 8.18 (d, *J* = 8.0 Hz, 2H, ArH). HRMS [Found: *m*/*z* 442.0161 (M + Na$^+$); calcd for $C_{21}H_{14}{}^{79}BrN_3O_2Na$: 442.0167].

3-Methyl-1-phenyl-4-(4-fluorophenyl)-7*H*-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one (4c). This compound was obtained as solid with mp 235–237°C (lit. [14] 235–237°C); IR (potassium bromide): 3070, 1756, 1597, 1578, 1512, 1490, 1449, 1437, 1423, 1319, 1360, 1315, 1222, 1210, 1167, 1137, 1069, 1043, 1029, 830, 798, 757 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.12 (s, 3H, CH$_3$), 5.49 (s, 2H, CH$_2$), 7.39–7.45 (m, 3H, ArH), 7.59–7.67 (m, 4H, ArH), 8.19 (d, *J* = 8.0 Hz, 2H, ArH). HRMS [Found: *m*/*z* 382.0945 (M + Na$^+$); calcd for $C_{21}H_{14}FN_3O_2Na$: 382.0968].

3-Methyl-1-phenyl-4-(4-nitrophenyl)-7*H*-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one (4d). This compound was obtained as solid with mp 283–285°C (lit. [14] 288–289°C); IR (potassium bromide): 3067, 1763, 1580, 1517, 1438, 1388, 1349, 1314, 1294, 1213, 1142, 1109, 1073, 1050, 1021, 838, 802, 754, 709 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.10 (s, 3H, CH$_3$), 5.54 (s, 2H, CH$_2$), 7.42 (t, *J* = 7.6 Hz, 1H, ArH), 7.62 (d, *J* = 8.0 Hz, 2H, ArH), 7.90 (d, *J* = 8.4 Hz, 2H, ArH), 8.19 (d, *J* = 8.0 Hz, 2H, ArH), 8.43 (d, *J* = 8.4 Hz, 2H, ArH). HRMS [Found: *m*/*z* 409.0891 (M + Na$^+$); calcd for $C_{21}H_{14}N_4O_4Na$: 409.0913].

3-Methyl-1-phenyl-4-(4-methoxyphenyl)-7*H*-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one (4e). This compound was obtained as solid with mp 192–194°C (lit. [14] 190–192°C); IR (potassium bromide): 3047, 1765, 1608, 1580, 1516, 1509, 1458, 1445, 1420, 1384, 1358, 1309, 1294, 1259, 1208, 1176, 1140, 1072, 1048, 1036, 1019, 824, 798, 758 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.15 (s, 3H, CH$_3$), 3.88 (s, 3H, CH$_3$O), 5.45 (s, 2H, CH$_2$), 7.13 (d, *J* = 8.4 Hz, 2H, ArH), 7.40 (t, *J* = 7.2 Hz, 1H, ArH), 7.52 (d, *J* = 8.4 Hz, 2H, ArH), 7.59 (d, *J* = 7.6 Hz, 2H, ArH), 8.19 (d, *J* = 7.6 Hz, 2H, ArH). HRMS [Found: *m*/*z* 394.1164 (M + Na$^+$); calcd for $C_{22}H_{17}N_3O_2Na$: 394.1168].

3-Methyl-1-phenyl-4-(2,4-dichlorophenyl)-7*H*-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one (4f). This compound was obtained as solid with mp 206–208°C (lit. [14] 206–208°C); IR (potassium bromide): 3065, 1763, 1585, 1507, 1475, 1442, 1420, 1389, 1376, 1361, 1316, 1211, 1150, 1127, 1101, 1078, 1050, 1025, 853, 821, 801, 787, 758 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.10 (s, 3H, CH$_3$), 5.54 (d, *J* = 16.0 Hz, 1H, CH), 5.61 (d, *J* = 16.0 Hz, 1H, CH), 7.43 (t, *J* = 7.2 Hz, 1H, ArH), 7.60-7.65 (m, 3H, ArH), 7.68 (d, *J* = 8.4 Hz, 1H, ArH), 7.95 (s, 1H, ArH), 8.19 (d, *J* = 8.0 Hz, 2H, ArH). HRMS [Found: *m*/*z* 409.0385 (M$^+$); Calcd for $C_{21}H_{13}{}^{35}Cl_2N_3O_2$: M 409.0385].

3-Methyl-1-phenyl-4-(3,4-dimethylphenyl)-7*H*-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one (4g). This compound was obtained as solid with mp 232–233°C (lit. [14] 231–233°C); IR (potassium bromide): 1768, 1513, 1500, 1459, 1433, 1385, 1355, 1310, 1268, 1227, 1210, 1182, 1070, 1041, 1026, 852, 818, 798, 758, 719 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.11 (s, 3H, CH$_3$), 2.33 (s, 3H, CH$_3$), 2.36 (s, 3H, CH$_3$), 5.47 (s, 2H, CH$_2$), 7.28 (d, *J* = 8.0 Hz, 1H, ArH), 7.32-7.35 (m, 2H, ArH), 7.41 (t, *J* = 7.6 Hz, 1H, ArH), 7.61 (t, *J* = 8.0 Hz, 2H, ArH),, 8.19 (d, *J* = 8.0 Hz, 2H, ArH). HRMS [Found: *m*/*z* 392.1355 (M + Na$^+$); calcd for $C_{23}H_{19}N_3O_2Na$: 392.1375].

3-Methyl-1-phenyl-4-(4-chlorophenyl)-7*H*-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one (4h). This compound was obtained as solid with mp 220–222°C (lit. [14] 223–225°C); IR (potassium bromide): 3063, 1764, 1598, 1581, 1562, 1506, 1489, 1459, 1442, 1421, 1386, 1358, 1314, 1211, 1141, 1125, 1089, 1072, 1048, 1028, 1015, 915, 848, 799, 760, 723 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.12 (s, 3H, CH$_3$), 5.49 (s, 2H, CH$_2$), 7.39–7.43 (m, 1H, ArH), 7.59–7.67 (m, 6H, ArH), 8.19 (d, *J* = 8.0 Hz, 2H, ArH). HRMS [Found: *m*/*z* 398.0670 (M + Na$^+$); calcd for $C_{21}H_{14}N_3O_2Na$: 398.0672].

3-Methyl-1-phenyl-4-(pyridine-2-yl)-7*H*-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one (4i). This compound was obtained as solid with mp 245–246°C; IR (potassium bromide): 3032, 1760, 1578, 1515, 1490, 1437, 1383, 1359, 1340, 1311, 1266, 1225, 1201, 1130, 1115, 1076, 1050, 1027, 851, 817, 794, 762 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.11 (s, 3H, CH$_3$), 5.53 (s, 2H, CH$_2$), 7.42 (t, *J* = 7.6 Hz, 1H, ArH), 7.60–7.65 (m, 4H, ArH), 8.18 (d, *J* = 8.0 Hz, 2H, ArH), 8.80 (d, *J* = 5.2 Hz, 2H, ArH). HRMS [Found: *m*/*z* 342.1119 (M$^+$); Calcd for $C_{20}H_{14}N_4O_2$: M 342.1117].

3-Methyl-1-phenyl-4-(thiophen-2-yl)-7*H*-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one (4j). This compound was obtained as solid with mp 246–248°C (lit. [14] 248–250°C); IR (potassium bromide): 3098, 1767, 1583, 1544, 1509, 1491, 1440, 1421, 1388, 1363, 1313, 1244, 1149, 1073, 1051, 1022, 796, 756 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.22 (s, 3H, CH$_3$), 5.47 (s, 2H, CH$_2$), 7.30–7.33 (m, 1H, ArH), 7.39–7.46 (m, 2H, ArH), 7.61 (t, *J* = 8.0 Hz, 2H, ArH), 7.97 (d, *J* = 5.2 Hz, 1H, ArH), 8.17 (d, *J* = 7.6 Hz, 2H, ArH). HRMS [Found: *m*/*z* 370.0621 (M + Na$^+$); calcd for $C_{19}H_{13}N_3O_2SNa$: 370.0626].

3-Methyl-1-phenyl-4-(3-chlorophenyl)-7*H*-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one (4k). This compound was obtained as solid with mp 201–203°C; IR (potassium bromide): 1776, 1583, 1562, 1515, 1437, 1387, 1357, 1313, 1210, 1146, 1073, 1047, 1031, 939, 784, 752, 725, 707 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.12 (s, 3H, CH$_3$), 5.50 (s, 2H, CH$_2$), 7.41 (t, *J* = 7.2 Hz, 1H, ArH), 7.55 (d, *J* = 7.2 Hz, 1H, ArH), 7.61 (t, *J* =

7.6 Hz, 3H, ArH), 7.67 (d, J = 8.4 Hz, 1H, ArH), 7.71 (s, 1H, ArH), 8.19 (d, J = 8.0 Hz, 2H, ArH). HRMS [Found: m/z 375.0754 (M^+); Calcd for $C_{21}H_{14}{}^{35}ClN_3O_2$: M 375.0775].

3-Methyl-1-phenyl-4-(2-chlorophenyl)-7*H*-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one (4l). This compound was obtained as solid with mp 227–228°C; IR (potassium bromide): 1774, 1600, 1585, 1510, 1492, 1474, 1438, 1387, 1359, 1313, 1210, 1148, 1127, 1074, 1058, 1046, 1027, 872, 846, 757, 726, 710 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.05 (s, 3H, CH_3), 5.53 (d, J = 16.0 Hz, 1H, CH), 5.60 (d, J = 16.0 Hz, 1H, CH), 7.42 (t, J = 7.6 Hz, 1H, ArH), 7.55–7.64 (m, 5H, ArH), 772 (d, J = 8.0 Hz, 1H, ArH), 8.20 (d, J = 7.6 Hz, 2H, ArH). HRMS [Found: m/z 375.0783 (M^+); Calcd for $C_{21}H_{14}{}^{35}ClN_3O_2$: M 375.0775].

3-Methyl-1-phenyl-4-(3,4-dichlorophenyl)-7*H*-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one (4m). This compound was obtained as solid with mp 218–220°C; IR (potassium bromide): 3036, 1771, 1582, 1551, 1506, 1473, 1439, 1382, 1359, 1315, 1212, 1141, 1072, 1050, 1032, 944, 911, 820, 800, 756, 714 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.16 (s, 3H, CH_3), 5.51 (s, 2H, CH_2), 7.41 (t, J = 7.2 Hz, 1H, ArH), 7.58–7.64 (m, 3H, ArH), 7.87 (d, J = 8.0 Hz, 1H, ArH), 7.95 (s, 1H, ArH), 8.18 (d, J = 7.6 Hz, 2H, ArH). HRMS [Found: m/z 409.0377 (M^+); Calcd for $C_{21}H_{13}{}^{35}Cl_2N_3O_2$: M 409.0385].

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Synthesis of Novel Annelated Systems Based on the Interaction and Reactivity Estimation of Amino-1,5-benzodiazepin-2-ones with Dimethyl-2-oxoglutaconate

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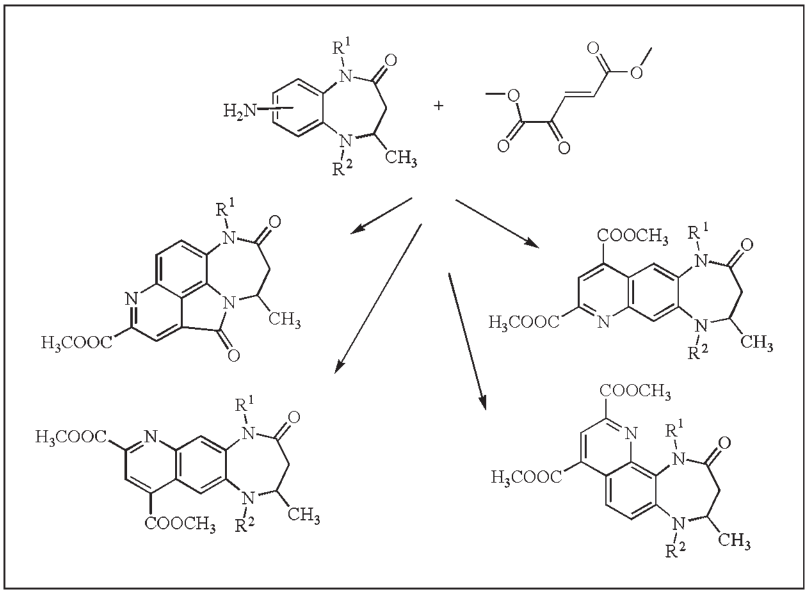

A number of substituted tetracyclic 4*H*-[1,4]diazepino[3,2,1-*hi*]pyrido[4,3,2-*cd*]indole and tricyclic 1*H*-[1,4]diazepino[2,3-*g*] or [2,3-*h*]quinoline derivatives were prepared from 7- (or 8, or 9)amino-1,5-benzodiazepin-2-ones by the Doebner–von Miller quinoline synthesis. The structure of the cyclized products depends on the position of the primary amino group and on the substituents of the diazepine ring of the starting compounds. The regiochemical outcome of the reaction was estimated by calculating average local ionization energies on the molecular surface at the Density Functional Theory (DFT) level of theory.

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INTRODUCTION

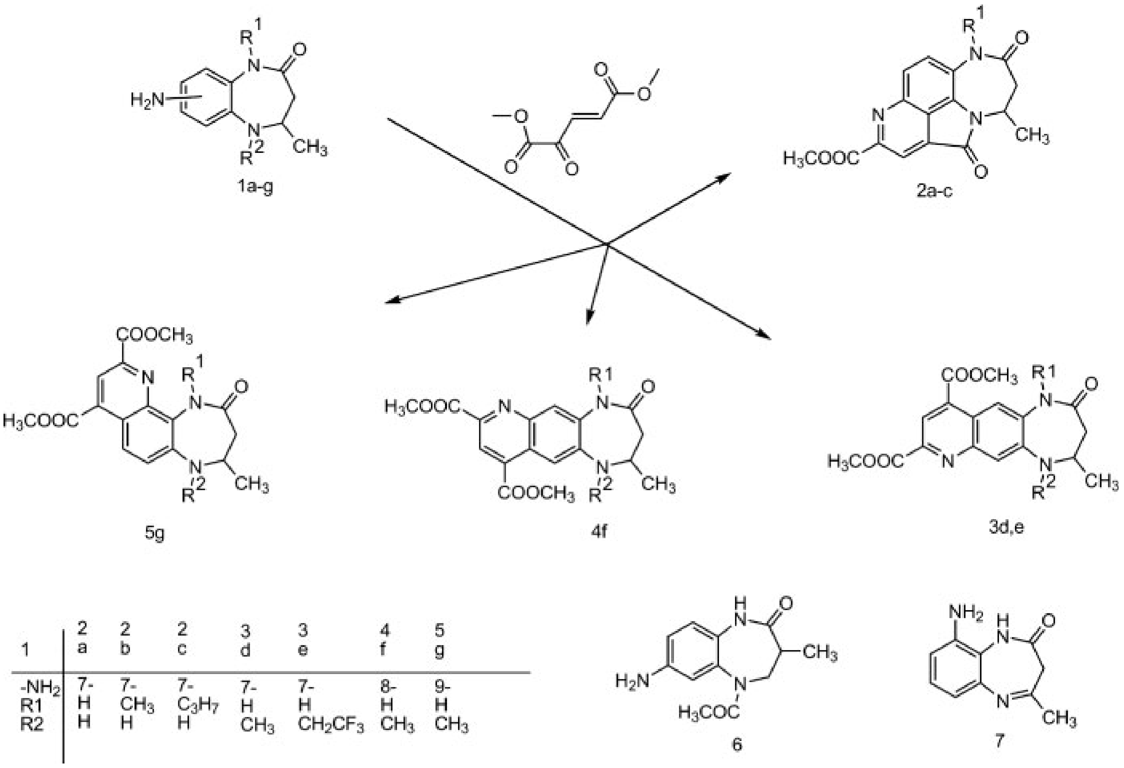
Benzodiazepines and their polycyclic derivatives are known as medically active synthetic substances [1]. Quinoline ring system derivatives are important as antimalarial agents. In addition, quinolines are present as structural subunits of naturally occurring products, such as quinonoid alcohol dehydrogenase coenzyme [2,3]. Numerous papers have described the synthesis of polycyclic 1,5-benzodiazepine derivatives with a pyridine ring annelated to the heptatomic diazepine nucleus [4]. It is known that some of such derivatives exhibit widespread biological activities. As a continuation of our interest in polycyclic 1,5-benzodiazepines we investigated the combination of the diazepine and quinoline heterocycles in the common polyheterocyclic system where the pyridine ring is annelated to the aromatic ring of bicyclic benzodiazepine.

The classical Skraup-Doebner-von Miller synthesis is among the most general approaches to the quinoline ring system [2,3]. The key substrates for this condensation reaction are aromatic amines and α,β-unsaturated ketones [2]. In this article, we report our results on the preparation of tetracyclic diazepinopyridoindoles and tricyclic diazepinoquinolines.

RESULTS AND DISCUSSION

In this study, 7-(or 8, or 9)amino-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-ones **1a–g** were used as starting amine components to prepare annelated derivatives

Scheme 1



1	2 a	2 b	2 c	3 d	3 e	4 f	5 g
-NH$_2$	7-	7-	7-	7-	7-	8-	9-
R1	H	CH$_3$	C$_3$H$_7$	H	H	H	H
R2	H	H	H	CH$_3$	CH$_2$CF$_3$	CH$_3$	CH$_3$

(Scheme 1). Cyclocondensation was accomplished by the reaction of amines with dimethyl-2-oxoglutaconate [5] (modified Doebner-von Miller sequence) in a single step. Thus, the treatment of amines **1a–g** with 1.5 equiv of dimethyl-2-oxoglutaconate in dichloromethane at room temperature for 24 h and then for additional 24 h after the addition of 3*M* hydrogen chloride solution in glacial acetic acid gave cyclic derivatives **2a–c, 3d,e, 4f,** and **5g**. The yields of compounds ranged from poor to moderate (16–51%).

For the application of this cyclization methodology, first we employed amines **1a–c,** which did not possess an alkyl group on the N_5 atom of the heterocyclic diazepine ring. The reaction of **1a–c** with dimethyl-2-oxoglutaconate afforded tetracyclic tetrahydro-4*H*-[1,4]diazepino[3,2,1-*hi*]pyrido[4,3,2-*cd*]indole derivatives **2a–c**. During the first stage of this reaction, the amino group added to the carbon atom of unsaturated ketone at β-position with respect to the ketonic function and cyclization occurred to give the cyclized piperidinol [3]. The addition of the acid catalyst effected the dehydration and aromatization of the latter together with intramolecular acylation of the diazepine ring N_5 atom by the cyclic ester group and an indole ring was formed [6]. The pyridine ring closure in 7-aminoderivatives **1a–c** took place at the 6-position of the benzodiazepine moiety.

When 7-amino-5-alkylsubstituted benzodiazepinones **1d,e** were treated with oxoglutaconate, the cyclocondensation proceeded at the 8-position of the bicyclic heterocycle and linear tricyclic diazepinoquinolines **3d,e** were obtained. The TLC analysis did not indicate the formation of isomeric products. On the other hand, the reaction of amine **6** with oxoglutaconate under parallel reaction conditions did not take place, and about 30% of the starting N_5-acetylsubstituted amine **6** was recovered.

Analogically, the cyclocondensation of 8-amino **1f** and 9-aminoderivative **1g** with oxoglutaconate under the same conditions gave linear [1,4]diazepino[2,3-*g*]quinoline **4f** and angular [1,4]diazepino[2,3-*h*]quinoline **5g**, respectively (in low yields). The isolation of the reaction products was rather complicated because the formation of polymeric products of unknown structure was observed. The attempts to prepare a new tricyclic derivative from 9-amino-2,3-dihydro-1,5-benzodiazepin-2-one **7** were not straightforward. In the reaction of **7** with oxoglutaconate, the isolated product was not identified. In the ^{1}H NMR spectrum, the observed signals at 8.79 (pyridine ring), doublets at 8.73 and 7.91 (benzene ring), and singlets at 4.09 and 4.10 ppm (COOCH$_3$ groups) confirmed the presence of the 2,4-substituted quinoline structure fragment (compare with **5g**), but there were no signals dependant on diazepine unit protons. Our early studies showed that in acidic medium the split of the N_5—C_4 bond of dihydro-1,5-benzodiazepinones or their transformation to a five-membered cycle could occur [7].

The synthesis of the starting materials **1a** [8] and **1d,f** [9] was described in our previous studies. Derivatives **1b,c,e,g, 6** and **7** were then easily obtained from the corresponding nitroderivatives **8b,c,e,g,** 5-acetyl-3-methyl-7-nitro-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (**9**) and 2,3-dihydro-4-methyl-9-nitro-1*H*-1,5-benzodiazepin-2-one (**10**) [10] by catalytic hydrogenation. 1,4-Dimethyl-7-nitro-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (**8b**) and 4-methyl-7-nitro-5-(2,2,2-trifluorethyl)-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (**8e**) were prepared according to the procedure described in our previous work [11]. Compound **8c** was synthesized by alkylation of 4-methyl-7-nitro-1,3,4,5,-tetrahydro-2*H*-1,5-benzodiazepin-2-one [12] with 1-bromopropane under phase-transfer catalysis conditions. 4,5-Dimethyl-9-nitroderivative **8g** was prepared by reductive alkylation of dihydronitroderivative **10** with sodium borohydride and formic acid. Compound **9** was synthesized by nitration of 5-acetyl-3-methyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one [13]. The starting aminobenzodiazepinones carrying various alkyl groups at the N_1 and N_5 atoms of the diazepine heterocycle ring were chosen for their acute solubility in organic solvents.

The structures attributed to the compounds described in this article are consistent with the results of elemental analysis, IR, ^{1}H and ^{13}C NMR spectral data. In this connection, the ^{1}H NMR spectra of linear and angular condensed regioisomeric systems are particularly significant. The signals of two benzene ring protons form two doublets or two singlets for compounds **2a–c, 5g** and **3d,e, 4f**, respectively. These assignments are unambiguously confirmed when NOE is observed between amide group (N—H) or methyl group (N—CH_3) protons and the nearest benzene ring proton (16–25% and 11–24%, respectively). Furthermore, we can point out that the ^{1}H NMR spectra of **2a–c** confirm the structure attributed to these tetracyclic systems because no signals for heterocyclic amine (N—H) group and for one of OCH_3 group protons were detected. Moreover, the diazepine CH proton signals were shifted downfield by about 0.9 ppm with respect to those of the starting compounds **1a–c**. It is interesting to note that the vicinal spin-spin coupling constants of seven-membered ring protons for **2a–c** were very low (2.1–2.4 and 5.3–5.4 Hz) in comparison with those of precursors **1b,c** (7.5–7.7 and 5.2 Hz) or 5-acetyl-4-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (13.0 Hz) [14]. This observation suggests that the conformation of the seven-membered ring in tetracyclic derivatives **2a–c** is exchanged. ^{13}C NMR spectral data agree with the proposed structures.

The quinoline derivatives are highly colored compounds and ethanolic solutions of **3d,e** and **4f** exhibit deep colors accompanied with fluorescence.

Generally, we have described the synthesis of novel heterocyclic systems from various N_1- and N_5-substituted amino-1,5-benzodiazepinones employing the Doebner-von Miller quinoline synthesis. It is confirmed that the formation of a new pyridine ring takes place at the adjacent position with respect to the primary amine group of the starting compound. However, the regiochemical outcome of cyclization reaction for asymmetrically substituted aromatic amines is unpredictable [3,15]. To get more insight into the nature of the studied cyclization process, the theoretical investigation of the electronic structure of the starting compounds was carried out.

Considering the reaction mechanism of the Doebner-von Miller quinoline synthesis, it was shown [2,3,15] that cyclization reaction involves a stepwise mechanism. The cyclocondensation step is based on the electrophilic addition to the carbon atom of the aromatic ring [2,15]. This step determinates the regiochemical features of the reaction. Hence, our goal was to estimate the most reactive aromatic sites for electrophilic attack. One of the best indicators of electrophilic attraction is provided by local ionization energy map calculations based on molecular electron density surfaces [16–22].

In this study, we computed local ionization energy maps for a series of N_1- and N_5-substituted amino-1,5-benzodiazepinones **1a,b,d,f,g** and **6**. First, a conformational search was performed using Molecular Mechanics Force Field to identify the lowest energy conformer for each structure [23]. The lowest energy conformer structures were further optimized using quantum mechanics at the DFT level of theory with B3LYP functional and 6-31G* basis set [24]. This basis set then was used to calculate the local ionization energy map on three dimension surfaces corresponding to the contour of constant electronic density equal to 0.025 electron/bohr^3 [17,23–25]. The surface of value 0.025 electron/bohr^3 displays the surface that indicates electron density on the π-electron surface of aromatic compounds. The literature [17,25] suggests that this contour gives physically reasonable molecular dimensions and reflects molecular features such as bond formation, electron lone pairs, *etc*.

We present two distinct and typical local ionization energy maps, which are most important for the interpretation of the observed regiochemistry. Figure 1 demonstrates the optimized geometry structures of **1a** and **6** heterocycles and shows the computed local ionization energy maps onto the molecular surfaces of these heterocycles. The dark gray regions on the surface area around the aromatic ring represent localizations on the

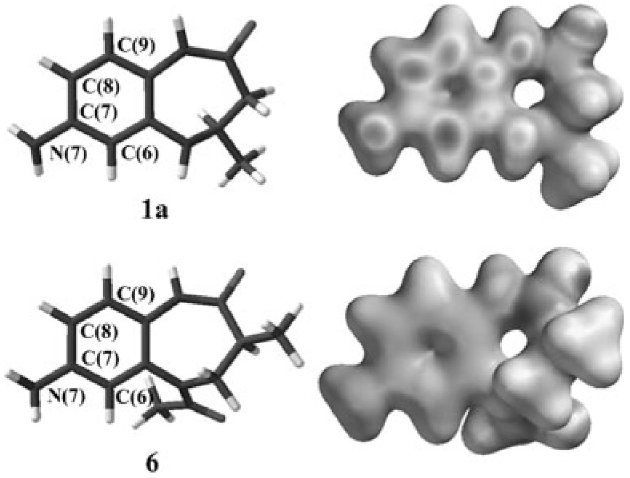


Figure 1. Optimized geometry structures and local ionization energy surface maps on the molecular surfaces defined by the contour of constant electron density equal 0.025 electron/bohr^3 for compounds **1a** and **6**. Color ranges in kcal/mol: from dark gray 259.43 to bright gray 593.62.

molecular surface where electron removal occurs easily (with minimal energy). For **1a** the lowest average localization of local ionization energies are found at adjacent positions with respect to the aromatic primary amino group. The results indicate the affinity to electrophiles at the adjacent positions of the aromatic carbon atoms. Analogical tendencies in localization of the lowest average local ionization energies are observed for heterocycles **1b,d,f,g** (not shown in Fig. 1). Otherwise, the pictured evenly gray molecular surface above the aromatic ring area for **6** shows that the aromatic ring is deactivated toward the electrophilic attack. Experimentally, the reaction of amine **6** with oxoglutaconate does not lead to the cyclized product. These findings reveal the deactivating tendency of the acetyl group in **6** for the pending reaction. In Table 1, the smallest local ionization energy values (I_{min}) and total energy values for optimized geometry structures **1a,b,d,f,g** and **6** are presented. I_{min} values are the points at which the smallest amount of energy is required to remove the electron from the surface and show the most reactive sites toward electrophiles. The lowest average local ionization energy localizations (Fig. 1) for 7-amino substituted **1a** are found on the molecular surface over the aromatic C_6 and C_8 atoms. Furthermore, as shown in Table 1, the I_{min} values for **1a,b** are lower for C_6 position than for C_8. This suggests a higher electrophilic affinity and propensity of ring cyclization at C_6 position. In the experiments with 7-aminoderivatives **1a–c**, the pyridine ring closure is observed at C_6 position. The lowest I_{min} values for 7-amino-5-methylsubstituted **1d** located above the C_8 atom show the C_8-directing ring closure tendency. Accordingly, the experimental cyclocondensation of compound **1d** proceeds at C_8 position. In the case of 7-amino-5-acetylsubstituted derivative **6**, I_{min} values are higher than those for compounds **1a,b,d,f,g**. The calculated I_{min} values for 8-aminosubstituted **1f** show that the lowest value is located above the C_7 carbon atom and is consistent with the tendency of the ring closure at the C_7 position. The same consequence of calculated and experimental results is in accordance with 9-aminoderivative **1g** where I_{min} values are located at C_8 position of the aromatic ring. Thus, in general, the obtained results are in agreement with experimental data.

In conclusion, quantum-chemical calculations show that cyclization reaction behavior is governed by the easiness of electron removal (ionization) from definite π-electron density surface regions of molecules. Local ionization energy maps and I_{min} values are indicative tools for the calculation of the relative activating and deactivating tendencies of the aromatic ring in the studied compounds.

EXPERIMENTAL

Melting points were determined in open capillaries method on a MEL-TEMP 1202D apparatus and are uncorrected. The IR spectra (potassium bromide) were taken on a Perkin Elmer Spectrum GX FTIR spectrometer. The electronic absorption spectra were obtained on Nicolet evoliution 300

Table 1

Calculated total energies (a.u.) of optimized geometries and smallest local ionization energy values I_{min} (kcal/mol) on the molecular surfaces defined by the contour of constant electron density equal 0.025 electron/bohr^3 on carbon atoms of the aromatic ring and the nitrogen atom of the primary amino group for compounds **1a,b,d,f,g** and **6**.

	Compounds					
	1a	**1b**	**1d**	**1f**	**1g**	**6**
Total energy, a.u.	−628.5704	−667.6857	−667.6856	−667.6741	−667.6892	−781.0432
I_{min}, kcal/mol	358.58(N_7)	287.79(N_7)	368.50(N_7)	287.79(N_8)	293.09(N_9)	436.99(N_7)
	358.28(C_6)	301.39(C_6)	379.90(C_6)	329.76(C_6)	315.23(C_6)	431.22(C_6)
	399.40(C_7)	353.28(C_7)	399.40(C_7)	313.62(C_7)	328.84(C_7)	441.37(C_7)
	380.49(C_8)	320.30(C_8)	368.96(C_8)	352.82(C_8)	314.77(C_8)	436.61(C_8)
	381.64(C_9)	328.61(C_9)	375.88(C_9)	320.30(C_9)	360.89(C_9)	439.52(C_9)

spectrophotometer, and the fluorescence emission spectra were recorded on Hitachi MPF-4 Fluorescence spectrophotometer in ethanol. Except where noted otherwise, ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded in deuteriochloroform on a Varian Unity Inova 300 spectrometer at 302 K. The chemical shifts are referenced to tetramethylsilane (δ (^{1}H) = 0) and the solvent signal deuteriochloroform (δ (^{13}C) = 77.0 ppm), deuteriodimethylsulfoxide (δ (^{13}C) = 49.5 ppm). The values of chemical shifts are expressed in ppm and coupling constants (*J*) in Hz. The CH$_3$, CH$_2$, CH and C$_{\text{quart}}$ groups in ^{13}C NMR were differentiated by means of the APT method. The reactions were controlled by the TLC method and performed on a Merck precoated silica gel aluminum roll (60F$_{254}$) with chloroform-ethyl acetate-methanol (v/v, 14:7:1) as the eluent and was visualized with UV light. Dry column vacuum chromatography [26] was performed with silica gel Chemapol L 5/40 mesh.

General Procedure for the Synthesis of 2a–c, 3d,e, 4f and 5g. To a stirred solution of the appropriate aminobenzodiazepinone **1a–g** (5.0 mmol) in 100–300 mL of dry dichloromethane, 1.28 g (7.5 mmol) of dimethyl-2-oxoglutaconate was added. The mixture was stirred at room temperature for 24 h. Then 4 mL (12.0 mmol) of 3*M* hydrogen chloride solution in glacial acetic acid was added and the intensively colored mixture was stirred at room temperature for additional 24 h. In some occasions, the precipitate was formed. The mixture was treated with a saturated aqueous sodium hydrogencarbonate solution until the aqueous phase became alkaline (pH 7–8), then the organic phase was washed with water. After drying over magnesium sulfate and the removal of the solvent in vacuum, the dark semisolid residue was subjected to purification. Recrystallization from a proper solvent gave pure compounds **3d** and **3e**. Dark oily residues were subjected to dry column vacuum chromatography (silicagel) using the dichloroethane-ethyl acetate system for gradient elution. Organic fractions with R$_f$ ~ 0.35 were collected and after removal of the solvent gave compounds **2a–c** and fractions collected with R$_f$ ~ 0.50 gave compounds **4f** and **5g**. Pure compounds were obtained by recrystallization from a proper solvent.

Methyl 6-methyl-4,8-dioxo-6,7,8,9-tetrahydro-4*H*-[1,4]diazepino[3,2,1-*hi*]pyrido[4,3,2-*cd*]indole-2-carboxylate (2a). Brightly yellow crystals (chloroform, 30% yield), mp 299–302°C [6]; ^{1}H NMR: δ 1.52 (d, *J* = 6.6 Hz, 3H, CH$_3$), 3.07 (dd, *J* = 2.3, 14.8 Hz, 1H, CH$_2$), 3.18 (ddd, *J* = 1.3, 5.3, 14.8 Hz, 1H, CH$_2$), 4.13 (s, 3H, OCH$_3$), 4.99 (m, 1H, CH), 7.33 (d, *J* = 9.1 Hz, 1H, 10-H), 7.97 (d, *J* = 9.1 Hz, 1H, 11-H), 8.47 (br s, 1H, NH), 8.74 (s, 1H, 3-H); ^{13}C NMR (dimethylsulfoxide-*d$_6$*): δ 19.12 (6-CH$_3$), 42.53 (7-C), 44.06 (6-C), 52.81 (OCH$_3$), 117.82 (3-C), 120.72, 120.98, 123.17, 123.81 (11-C), 127.79 (10-C), 133.31, 141.47, 148.49, 163.08 (CO), 164.92 (CO), 171.04 ppm (8-CO).

Methyl 6,9-dimethyl-4,8-dioxo-6,7,8,9-tetrahydro-4*H*-[1,4]-diazepino[3,2,1-*hi*]pyrido[4,3,2-*cd*]indole-2-carboxylate (2b). Orange crystals (chloroform, 29% yield), mp 231–233°C [6]; ^{1}H NMR: δ 1.49 (d, *J* = 6.7 Hz, 3H, CH$_3$), 3.00 (dd, *J* = 2.1, 14.2 Hz, 1H, CH$_2$), 3.18 (dd, *J* = 5.4, 14.3 Hz, 1H, CH$_2$), 3.59 (s, 3H, 9-OCH$_3$), 4.13 (s, 3H, OCH$_3$), 4.90 (m, 1H, CH), 7.65 (d, *J* = 9.3 Hz, 1H, 10-H), 8.01 (d, *J* = 9.3 Hz, 1H, 11-H), 8.72 (s, 1H, 3-H); ^{13}C NMR: δ 19.29 (6-CH$_3$), 34.31 (9-CH$_3$), 42.60 (C-7), 46.30 (C-6), 53.52 (OCH$_3$), 119.29 (d, *J* = 173.0 Hz, 3-C), 121.57, 124.44, 124.87 (d, *J* = 166.7 Hz, 11-C), 126.83, 127.17 (d, *J* = 160.6 Hz, 10-C), 134.31, 142.31, 150.19, 164.48 (CO), 165.19 (CO), 169.92 ppm (8-CO).

Methyl 6-methyl-4,8-dioxo-9-propyl-6,7,8,9-tetrahydro-4*H*-[1,4]diazepino[3,2,1-*hi*]pyrido[4,3,2-*cd*]indole-2-carboxylate (2c). Orange crystals (mixture of diethyl ether and ethyl acetate, yield 25%), mp 163–165°C; IR: 1725, 1702, 1660 cm^{-1}; ^{1}H NMR: δ 1.00 (t, *J* = 7.4 Hz, 3H, CH$_3$), 1.49 (d, *J* = 6.7 Hz, 3H, CH$_3$), 1.65–1.89 (m, 2H, CH$_2$), 2.99 (dd, *J* = 2.4, 14.0 Hz, 1H, CH$_2$), 3.13 (dd, *J* = 5.4, 13.9 Hz, 1H, CH$_2$), 3.96–4.12 (m, 2H, CH$_2$), 4.13 (s, 3H, OCH$_3$), 4.89 (m, 1H, CH), 7.64 (d, *J* = 9.4 Hz, 1H, 10-H), 8.00 (d, *J* = 9.4 Hz, 1H, 11-H), 8.72 (s, 1H, 3-H); ^{13}C NMR: δ 11.29 (9-CH$_3$), 19.26 (6-CH$_3$), 21.72 (9$''$-CH$_2$), 42.60 (7-C), 46.56 (6-C), 48.34 (9$'$-CH$_2$), 53.56 (OCH$_3$), 119.22 (3-C), 121.90, 123.75, 124.91 (11-C), 127.28 (10-C), 127.38, 134.21, 142.37, 150.04, 164.67 (CO), 165.23 (CO), 169.65 ppm (8-CO). *Anal.* Calcd. for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89. Found: C, 64.30; H, 5.31; N, 11.64.

Dimethyl 4,5-dimethyl-2-oxo-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[2,3-*g*]quinoline-8,10-dicarboxylate (3d). Yellow crystals (ethyl acetate, 46% yield), mp 203–205°C; IR: 3319, 3196, 1723, 1670 cm^{-1}; UV-vis: λ$_{\max}$ (ε × 10^{-3}) 245 (30.5), 290 (21.2), 355 (6.2) nm (M^{-1}cm^{-1}); ^{1}H NMR: δ 1.31 (d, *J* = 6.1 Hz, 3H, CH$_3$), 2.44 (dd, *J* = 8.9, 13.4 Hz, 1H, CH$_2$), 2.72 (dd, *J* = 4.8, 13.4 Hz, 1H, CH$_2$), 3.02 (s, 3H, CH$_3$), 3.94 (m, 1H, CH), 4.06 (s, 3H, OCH$_3$), 4.11 (s, 3H, OCH$_3$), 7.83 (s, 1H, 6-H), 8.49 (s, 1H, 11-H), 8.59 (s, 1H, 9-H), 8.67 (br s, 1H, NH); ^{13}C NMR: δ 17.26 (4-CH$_3$), 39.33 (5-CH$_3$), 40.89 (3-C), 52.84 (OCH$_3$), 53.32 (OCH$_3$), 60.62 (4-C), 116.04 (d, *J* = 165.2 Hz, 11-C), 120.01 (d, *J* = 162.3 Hz, 6-C), 121.06 (d, *J* = 171.2 Hz, 9-C), 122.48, 133.99, 136.70, 145.02, 146.59, 147.87, 165.35 (CO), 165.97 (CO), 172.41 ppm (2-CO). *Anal.* Calcd. for $C_{18}H_{19}N_3O_5$: C, 60.50; H, 5.36; N, 11.76. Found: C, 60.64; H, 5.30; N, 11.90.

Dimethyl 4-methyl-2-oxo-5-(2,2,2-trifluorethyl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[2,3-*g*]quinoline-8,10-dicarboxylate (3e). Yellow crystals (ethyl acetate, 51% yield), mp 236–238°C; IR: 3320, 1745, 1727, 1693 cm^{-1}; UV-vis: λ$_{\max}$ (ε × 10^{-3}) 245 (18.2), 284 (12.5), 365 (4.7) nm (M^{-1}cm^{-1}); ^{1}H NMR: δ 1.21 (d, *J* = 6.1 Hz, 3H, CH$_3$), 2.36 (dd, *J* = 11.3, 13.4 Hz, 1H, CH$_2$), 2.61 (ddd, *J* = 1.4, 5.4, 13.4 Hz, 1H, CH$_2$), 3.78 (m, 1H, CH), 4.06 (s, 3H, OCH$_3$), 4.06–4.20 (m, 2H, 5-CH$_2$), 4.10 (s, 3H, OCH$_3$), 8.06 (s, 1H, 6-H), 8.44 (br s, 1H, NH), 8.60 (s, 1H, 11-H), 8.67 (s, 1H, 9-H); ^{13}C NMR: δ 16.45 (4-CH$_3$), 41.05 (3-C), 52.50 (q, *J* = 32.9 Hz, 5-CH$_2$), 52.98 (OCH$_3$), 53.41 (OCH$_3$), 60.12 (4-C), 116.89 (11-C), 122.27 (9-C), 124.08, 124.47 (q, *J* = 280.2 Hz, CF$_3$), 125.11 (6-C), 134.43, 138.63, 142.49, 147.01, 147.37, 165.09 (CO), 165.76 (CO), 172.15 ppm (2-CO). *Anal.* Calcd. for $C_{19}H_{18}F_3N_3O_5$: C, 53.65; H, 4.27; N, 9.88. Found: C, 53.48; H, 4.36; N, 10.01.

Dimethyl 1,2-dimethyl-4-oxo-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[2,3-*g*]quinoline-8,10-dicarboxylate (4f). Yellow crystals (isopropanol, 16% yield), mp 255–258°C; IR: 3198, 3122, 1715, 1683 cm^{-1}; UV-vis: λ$_{\max}$ (ε × 10^{-3}) 245 (31.1), 295 (14.7), 410 (9.0) nm (M^{-1}cm^{-1}); fluorescence: λ$_{\text{ex}}$ 300 and 410, λ$_{\text{em}}$ 550 nm; ^{1}H NMR: δ 1.37 (d, *J* = 6.2 Hz, 3H, CH$_3$), 2.47 (dd, *J* = 8.3, 13.5 Hz, 1H, CH$_2$), 2.75 (dd, *J* = 4.4, 13.4 Hz, 1H, CH$_2$), 3.09 (s, 3H, CH$_3$), 3.94 (m, 1H, CH), 4.07 (s, 3H, OCH$_3$), 4.10 (s, 3H, OCH$_3$), 7.85 (s, 1H, 6-H), 8.30 (br s, 1H, NH), 8.45 (s, 1H, 11-H), 8.66 (s, 1H, 9-H); ^{13}C NMR: δ 17.90 (2-CH$_3$), 39.47 (1-CH$_3$), 40.74 (3-C), 52.70 (OCH$_3$), 53.19 (OCH$_3$), 60.66 (2-C), 113.58 (11-C), 121.31 (6-

C), 122.47 (9-C), 125.65, 132.23, 136.38, 145.13, 145.20 (2-C), 165.44 (CO), 166.19 (CO), 172.21 ppm (4-CO). *Anal.* Calcd. for $C_{18}H_{19}N_3O_5$: C, 60.50; H, 5.36; N, 11.76. Found: C, 60.63; H, 5.29; N, 11.65.

Dimethyl 4,5-dimethyl-2-oxo-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[2,3-*h*]quinoline-8,10-dicarboxylate (5g). Dark red crystals (tert-butylmetyl ether, 20% yield), mp 161–163°C; IR: 3273, 1730, 1708, 1672 cm^{-1}; ^{1}H NMR: δ 1.38 (d, *J* = 6.4 Hz, 3H, CH_3), 2.56 (ddd, *J* = 1.0, 7.6, 13.8 Hz, 1H, CH_2), 2.84 (dd, *J* = 4.4, 13.9 Hz, 1H, CH_2), 3.07 (s, 3H, CH_3), 4.02 (m, 1H, CH), 4.05 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 7.54 (d, *J* = 9.4 Hz, 1H, 6-H), 8.52 (s, 1H, 9-H), 8.53 (d, *J* = 9.4 Hz, 1H, 7-H), 9.24 (br s, 1H, NH); ^{13}C NMR: δ 18.37 (4-CH_3), 39.39 (5-CH_3), 42.04 (3-C), 52.88 (OCH_3), 53.06 (OCH_3), 61.07 (4-C), 120.32 (d, *J* = 171.6 Hz, 9-C), 120.99 (d, *J* = 168.5 Hz, 7-C), 121.06, 124.35, 124.98 (d, *J* = 159.6 Hz, 6-C), 135.61, 139.74, 140.55, 146.31, 165.27 (CO), 166.01 (CO), 171.72 ppm (2-CO). *Anal.* Calcd. for $C_{18}H_{19}N_3O_5$: C, 60.50; H, 5.36; N, 11.76. Found: C, 60.79; H, 5.40; N, 11.93.

General procedure for the synthesis of 1b,c,e,g, 6 and 7. In a hydrogenation apparatus, equipped with a magnetic stirrer, the catalyst 10% palladium on carbon (10% of the weight of the starting nitroderivative) was added to a solution of suitable nitrobenzodiazepinone **8b,c,e,g, 9** and **10** (20.0 mmol) in 150–200 mL of methanol and the mixture was hydrogenated at room temperature and atmospheric pressure. After the consumption of 1.34 L (60 mmol) of hydrogen the catalyst was filtered off. The filtrate was concentrated to dryness in vacuum and the resultant solid residue was crystallized from a proper solvent.

7-Amino-1,4-dimethyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (1b). Synthesized from **8b** [11]. Yellowish crystals (ethyl acetate, 77% yield), mp 149–151°C; ^{1}H NMR: δ 1.24 (d, *J* = 6.2 Hz, 3H, CH_3), 2.28 (dd, *J* = 7.7, 12.7 Hz, 1H, 3-CH_2), 2.51 (dd, *J* = 5.2, 12.6 Hz, 1H, 3-CH_2), 3.13 (br s, 1H, NH), 3.28 (s, 3H, 1-CH_3), 3.66 (br s, 2H, NH_2), 4.00 (m, 1H, CH), 6.18 (d, *J* = 2.5 Hz, 1H, 6-H), 6.36 (dd, *J* = 2.5, 8.4 Hz, 1H, 8-H), 6.91 (d, *J* = 8.4 Hz, 1H, 9-H); ^{13}C NMR: δ 23.19 (4-CH_3), 35.45 (1-CH_3), 40.24 (3-C), 56.80 (4-C), 108.31, 109.43, 123.62, 127.90, 140.15, 144.72, 171.37 ppm (CO). *Anal.* Calcd. for $C_{11}H_{15}N_3O$: C, 64.34; H, 7.37; N, 20.47. Found: C, 64.38; H, 7.30; N, 20.66.

7-Amino-4-methyl-1-propyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (1c). Synthesized from **8c**. Beige colored crystals (mixture of methanol and diethyl ether, 71% yield), mp 143-145°C; IR: 3407, 3345, 3330, 3233, 1666–1609 cm^{-1}; ^{1}H NMR: δ 0.84 (t, *J* = 7.4 Hz, 3H, CH_3), 1.23 (d, *J* = 6.2 Hz, 3H, CH_3), 1.50 (m, 2H, CH_2), 2.23 (dd, *J* = 7.5, 12.6 Hz, 1H, 3-CH_2), 2.48 (dd, *J* = 5.2, 12.6 Hz, 1H, 3-CH_2), 3.05 (br s, 1H, NH), 3.64 (br s, 2H, NH_2), 3.73 (m, 2H, CH_2), 3.98 (m, 1H, CH), 6.18 (d, *J* = 2.5 Hz, 1H, 6-H), 6.35 (dd, *J* = 2.5, 8.4 Hz, 1H, 8-H), 6.93 (d, *J* = 8.4 Hz, 1H, 9-H); ^{13}C NMR: δ 11.22 (CH_3), 21.13 (CH_2), 23.11 (4-CH_3), 40.38 (3-C), 49.26 (CH_2), 56.89 (4-C), 108.52, 109.51, 124.08, 126.60, 141.20, 144.74, 171.20 ppm (CO). *Anal.* Calcd. for $C_{13}H_{19}N_3O$: C, 66.92; H, 8.21; N, 18.01. Found: C, 67.23; H, 8.32; N, 17.89.

7-Amino-4-methyl-5(2,2,2-trifluoroethyl)-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (1e). Synthesized from **8e** [11]. Yellowish crystals (mixture of diethyl ether and hexane, 95% yield), mp 156–158°C; IR: 3454, 3371, 3174, 1677 cm^{-1}; ^{1}H NMR: δ 1.08 (d, *J* = 6.1 Hz, 3H, CH_3), 2.22–2.40 (m, 2H, CH_2), 3.3–3.7 (br s, 2H, NH_2), 3.53 (dq, *J* = 8.9, 15.4 Hz, 1H, 5-CH_2), 3.83 (dq, *J* = 8.6, 15.4 Hz, 1H, 5-CH_2), 4.02 (m, 1H, CH), 6.42–6.46 (m, 2H, 6-H, 8-H), 6.81 (m, 1H, 9-H), 7.83 (br s, 1H, NH); ^{13}C NMR: δ 17.05 (4-CH_3), 41.07 (3-C), 52.80 (q, *J* = 32.4 Hz, 5-CH_2), 61.37 (4-C), 111.82, 112.00, 123.68, 124.49, 126.69, 140.05, 144.93, 173.44 ppm (CO). *Anal.* Calcd. for $C_{12}H_{14}F_3N_3O$: C, 52.75; H, 5.16; N, 15.38. Found: C, 52.87; H, 5.24; N, 15.30.

9-Amino-4,5-dimethyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (1g). Synthesized from **8g**. Cream crystals (methanol, 70% yield), mp 213–215°C; IR: 3453, 3367, 3198, 1678 cm^{-1}; ^{1}H NMR: δ 1.09 (d, *J* = 6.1 Hz, 3H, CH_3), 2.24 (dd, *J* = 10.0, 12.6 Hz, 1H, CH_2), 2.42 (ddd, *J* = 1.2, 5.4, 12.6 Hz, 1H, CH_2), 2.77 (s, 3H, CH_3), 3.86 (m, 1H, CH), 3.95 (br s, 2H, NH_2), 6.45–6.51 (m, 2H, 6-H, 8-H), 6.98 (dd, *J* = 8.0, 8.0 Hz, 1H, 7-H), 8.34 (br s, 1H, NH); ^{13}C NMR: δ 15.78 (4-CH_3), 38.65 (5-CH_3), 41.52 (3-C), 62.83 (4-C), 110.53, 111.84, 119.72, 126.29, 139.59, 142.66, 174.76 ppm (CO). *Anal.* Calcd. for $C_{11}H_{15}N_3O$: C, 64.34; H, 7.37; N, 20.47. Found: C, 64.47; H, 7.29; N, 20.59.

5-Acetyl-7-amino-3-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (6). Synthesized from **9**. Yellow crystals (acetonitrile, 89% yield), mp 191–193°C; IR: 3438, 3348, 3233, 1673, 1653 cm^{-1}; ^{1}H NMR: δ 1.11 (d, *J* = 6.7 Hz, 3H, CH_3), 1.86 (br s, 3H, CH_3), 2.75 (m, 1H, CH), 3.46 (dd, *J* = 6.9, 13.5 Hz, 1H, CH_2), 3.83 (br s, 2H, NH_2), 4.56 (dd, *J* = 12.3, 13.1 Hz, 1H, CH_2), 6.51 (d, *J* = 2.5 Hz, 1H, 6-H), 6.67 (dd, *J* = 2.5, 8.4 Hz, 1H, 8-H), 6.94 (d, *J* = 8.5 Hz, 1H, 9-H), 7.90 (br s, 1H, NH); ^{13}C NMR: δ 12.51 (4-CH_3), 22.66 (5-CH_3), 34.88(3-C), 54.74 (4-C), 115.06, 115.39, 124.35, 126.05, 135.66, 145.29, 170.38, 175.20 ppm. *Anal.* Calcd. for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.62; H, 6.41; N, 18.13.

9-Amino-2,3-dihydro-1*H*-1,5-benzodiazepin-2-one (7). Synthesized from 10 [10] Yellowish crystals (methanol, 90% yield), mp 170–172°C; ^{1}H NMR: δ 2.39 (s, 3H, CH_3), 3.16 (s, 2H, CH_2), 3.81 (br s, 2H, NH_2), 6.66 (dd, *J* = 1.4, 7.8 Hz, 1H, 8-H or 6-H), 6.83 (dd, *J* = 1.3, 8.1 Hz, 1H, 6-H or 8-H), 7.05 (t, *J* = 7.9 Hz, 1H, 7-H), 8.00 (m, 1H, NH); ^{13}C NMR: δ 28.00, 43.80, 113.38, 117.81, 125.54, 138.41, 141.09, 163.09, 166.45 ppm. *Anal.* Calcd. for $C_{10}H_{11}N_3O$: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.57; H, 5.79; N, 22.37.

4-Methyl-7-nitro-1-propyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (8c). To a solution of 2.2 g (10.0 mmol) of 4-methyl-7-nitro-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one [12] in 150 mL of benzene, 0.5 g (1.50 mmol) of tetrabutylammonium bromide, 15 mL 50% aqueous sodium hydroxide and 1.8 mL (20.0 mmol) of 1-bromopropane were added. The reaction was performed according to the procedure method A previously described by us [11]. The working-up of the reaction mixture gave 1.6 g (61%) of **8c**. Yellowish crystals (ethyl acetate), mp 116–118°C; IR: 3296, 1651, 1517, 1344 cm^{-1}; ^{1}H NMR: δ 0.85 (t, *J* = 7.4 Hz, 3H, CH_3), 1.32 (d, *J* = 6.3 Hz, 3H, CH_3), 1.54 (m, 2H, CH_2), 2.28 (dd, *J* = 7.4, 12.9 Hz, 1H, 3-CH_2), 2.57 (dd, *J* = 5.2, 12.9 Hz, 1H, 3-CH_2), 3.55 (br s, 1H, NH), 3.86 (m, 2H, CH_2), 4.12 (m, 1H, CH), 7.29 (d, *J* = 8.8 Hz, 1H, 9-H), 7.76 (d, *J* = 2.6 Hz, 1H, 6-H), 7.89 (dd, *J* = 2.5, 8.8 Hz, 1H, 8-H); ^{13}C NMR: δ 11.08 (CH_3), 21.13(CH_2), 23.01(4-CH_3), 40.29 (3-C), 49.67 (CH_2), 57.32 (4-C), 117.23, 117.84, 123.27, 140.29, 140.78, 145.10, 170.57 ppm (CO). *Anal.* Calcd. for $C_{13}H_{17}N_3O_3$: C, 59.30; H, 6.51; N, 15.96. Found: C, 59.61; H, 6.63; N, 16.12.

4,5-Dimethyl-9-nitro-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (8g). To a solution of 2.2 g (10.0 mmol) of dihydro-9-nitroderivative **10** [10] in 50 mL of formic acid, 3.25 g

(70.0 mmol) of sodium borohydride was added. The reaction was performed following the procedure previously described by us [11]. The working-up of the reaction mixture gave 1.3 g (57%) of **8g**. Yellow crystals (ethyl acetate), mp 184–186°C; IR: 3192, 3122, 1686, 1636, 1529, 1345 cm^{-1}; ^1H NMR: δ 1.19 (d, J = 6.1 Hz, 3H, CH_3), 2.25 (dd, J = 9.8, 13.0 Hz, 1H, CH_2), 2.55 (ddd, J = 1.4, 5.7, 13.0 Hz, 1H, CH_2), 2.88 (s, 3H, 5-CH_3), 3.95 (m, 1H, CH), 7.24 (dd, J = 8.1, 8.1 Hz, 1H, 7-H), 7.37 (dd, J = 1.4, 8.1 Hz, 1H, 6-H), 7.77 (dd, J = 1.5, 8.2 Hz, 1H, 8-H), 8.80 (br s, 1H, NH); ^{13}C NMR: δ 15.93 (4-CH_3), 39.41 (5-CH_3), 41.37 (3-C), 62.77 (4-C), 119.42, 124.36, 127.95, 130.04, 140.28, 143.11, 171.89 ppm (CO). *Anal.* Calcd. for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.35; H, 5.65; N, 17.71.

5-Acetyl-3-methyl-7-nitro-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (9). A solution of 2.2 g (10.0 mmol) of 5-acetyl-3-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one [13] in 30 mL of conc. sulfuric acid, and a solution of 2.2 g (20.0 mmol) of potassium nitrate in 25 mL of conc. sulfuric acid were precooled to −18°C and were combined. The reaction mixture was kept at −18°C for 1 h, then at 4°C for 5 h and at room temperature for 24 h. After that the reaction mixture was poured on ice and extracted with ethyl acetate (3 × 70 mL). The organic phase was washed successively with water and a saturated aqueous sodium hydrogencarbonate solution (3 × 40 mL), dried over magnesium sulfate and concentrated in vacuum to dryness. Recrystallization of the solid residue from ethyl acetate gave 1.3 g (50%) of yellowish crystals of **9**, mp 212–214°C; IR: 3208, 3156, 1697, 1650, 1523, 1347 cm^{-1}; ^1H NMR: δ 1.22 (br d, 3H, CH_3), 1.88 (br s, 3H, CH_3), 2.82 (br m, 1H, CH), 3.63 (br m, 1H, CH_2), 4.67 (br m, 1H, CH_2), 7.34 (d, J = 8.7 Hz, 1H, 9-H), 8.17 (br d, 1H, 6-H), 8.29 (br dd, 1H, 9-H), 9.05 ppm (br s, 1H, NH). *Anal.* Calcd. for $C_{12}H_{13}N_3O_4$: C, 54.75; H, 4.98; N, 15.96. Found: C, 54.93; H, 4.79; N, 16.17.

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A Simple and Practical Method for the Synthesis of 2-Amino-5,6-dihydro-5,7-diarylquinazolin-4-ols

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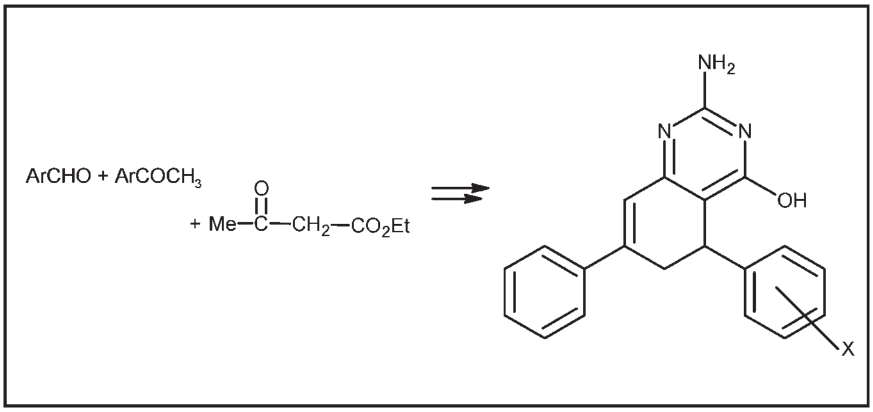

We report an efficient and new method of synthesis of 2-amino-5,6-dihydro-5,7-diarylquinazolin-4-ols by the reaction of substituted cyclohexenones with guanidine hydrochloride in presence of NaOEt. The reactions are with 50–72% yield. All the synthesized compounds are characterized using IR, NMR and CHN analysis.

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INTRODUCTION

Quinazoline skeleton is an important pharmacophore that occurs frequently in medicinal chemistry literature [1]. Quinazolines are recently been the subject of deep investigation due to their diverse pharmacological properties such as analgesic, narcotic, antimalarial, sedative, hypoglycemic [2], anti-cancer [3] and anti-tubercular activities[4]. It has been reported that quinazolines act as potent [5] and highly selective inhibitors of epidermal growth factor receptor tyrosine kinase and have been employed as DNA binder [6]. Alkaloids with quinazoline ring system are known for natural compounds having a wide spectrum of biological effects. The biological activity of quinazolines strongly depends on the nature and the position of the substituents in the quinazoline ring. The 2-amino substituted quinazolines are reported as potential histamine antagonists [7]. This large interest in medicinal chemistry stimulated the development of new and more efficient synthesis of amino substituted heterocycles recently we have reported the synthesis and antibacterial activity of naphthyl and thienyl substituted 2-aminopyrimidines [8]. In continuation of synthesis of the biologically active heterocyclic compounds here we report a simple synthesis for 2-amino-5,6-dihydro-5,7-diarylquinazolin-4-ols.

RESULTS AND DISCUSSION

Quinazolin-4-ols are synthesized in three steps (Scheme 1) starting from easily available acetophenone and benzaldehyde. Initialy, chalcones **1** were synthesized by Claisen-Schmidt condensation between benzaldehyde and acetophenone.

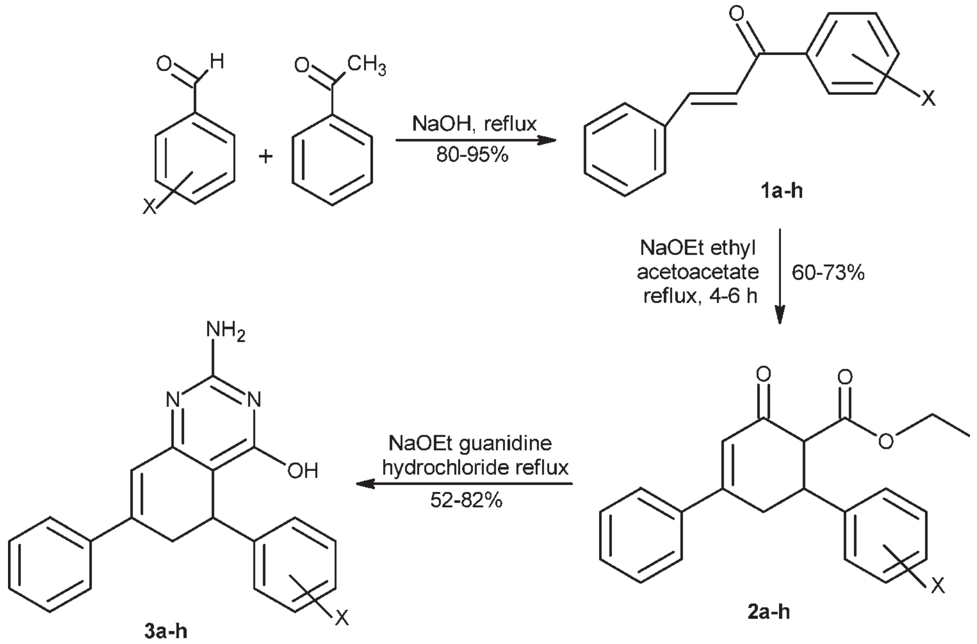
The chalcones on treatment with ethyl acetoacetate in the presence of sodium ethoxide gave carbethoxycyclohex-2-en-one derivatives **2.** The structure of the carbethoxycyclohex-2-en-one derivatives were conformed by comparing with their reported IR and melting points.

Carbethoxycyclohex-2-en-one derivatives **2** on treatment with guanidine hydrochloride in the presence of sodium ethoxide under go condensation reaction and gave 2-amino-5,6-dihydro-5,7-diarylquinazolin-4-ols (**3a–h**).

The structures of **3a–h** were elucidated by ^{1}H and ^{13}C NMR, mass spectral analysis and elemental analysis. In the ^{1}H NMR spectra, the characteristic chemical shift of the hydroxy protons of **3a–h** were found at $\delta = 10.76$–10.81 ppm as a broad singlet. The two amino protons were observed as a singlet at $\delta = 6.20$–6.42 ppm. The alkenic proton signal was observed at around 6.40 ppm.

To conclude, we have proposed an efficient method for the preparation of 2-amino-5,6-dihydro-5,7-diarylquinazoline-4-ols by reaction of guanidine hydrochloride

Scheme 1. Synthesis of 2-amino-5,6-dihydro-5,7-diarylquinazoline-4-ols.



Entry	X
a	-H
b	4-F
c	4-Cl
d	3-Br
e	4-Br
f	4-Me
g	4-OMe
h	$3\text{-}NO_2$

with carbethoxycyclohex-2-enone derivatives. These compounds are known pharmacophores in several structure based drug design approaches.

EXPERIMENTAL

Melting points are determined in open capillaries and are uncorrected. The NMR spectra were recorded on 300 MHz spectrometer in DMSO-d_6. Chemical shifts are expressed in parts per million using residual solvent proton and carbon as internal standards. The FT-IR spectra were recorded on NICOLET AVATAR 360-FTIR instrument by using KBr pellets. Elemental analyses were done on Vario EL. CHN elemental analyzer.

Preparation of chalcone (1a–h). About 0.5 g of sodium hydroxide was dissolved in 50 mL of water. A mixture of acetophenone (0.01 mole) and aromatic aldehyde (0.01 mole) in 50 mL of absolute ethanol was added. The mixture was stirred at room temperature for 3 h and allow to stand for overnight. The preceipitated solid was separated, washed with distilled water and recrystallized from hot ethanol. The products were confirmed from their reported IR spectra and melting points.

Ethyl-2-oxo-4,6-diarylcyclohex-2-en-carboxylate (2a-h). A mixture of chalcone (0.01 mole) (**1a-h**) and ethyl acetoacetate (0.01 mole) was dissolved in absolute ethanol (30 mL). Sodium ethoxide (2 g sodium in 60 mL ethanol) was added to the mixture and refluxed for the 5 h. The reaction mixture was kept aside for more than 1 h and the solid mass obtained was collected and recrystallized from ethanol. The products were confirmed from their reported IR spectra and melting points.

2-Amino-5,6-dihydro-5,7-diarylquinazolin-4-ols (3a–h). Appropriate diarylcyclohexenone (**2a–h**, 0.01 mole), guanidine hydrochloride (0.01 mole) and sodium ethoxide (2 g in 30 mL ethanol) were refluxed for 28–32 h. The reaction mixture was cooled to room temperature, poured into crushed ice and stirred. The separated product was purified using column chromatography (silica gel, 100–200 mesh, $CHCl_3$-EtOAc, 6:4). All the compounds were characterized using IR, ^1H and ^{13}C NMR and elemental analysis.

2-Amino-5,6-dihydro-5,7-diphenylquinazolin-4-ol (3a). This compound was obtained as a yellow solid. mp 134–136°C; yield 72.5%; IR (KBr) ν cm^{-1} 3415 (N—H stretching), 2836 (C—H stretching), 1649 (C=C stretching) ^1H NMR (DMSO-d_6, 300 MHz), δ ppm 2.94 (d, 1H, $J = 17.1$ Hz), 3.12–3.22 (m, 1H), 4.21 (d, 1H, $J = 7.5$ Hz), 6.42 (s, NH_2), 6.46 (s, H-8), 7.09–7.49 (Ar-H), 10.76 (s, —OH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm 34.3, 41.7, 110.1, 125.4, 125.9, 126.3, 126.9, 127.3, 127.8, 128.3, 128.5, 128.9, 129.1, 140.1, 145.2, 155.4, 161.5. Calc. for $C_{20}H_{17}N_3O$: C 76.17; H, 5.43; N, 13.32%. Observed were C, 76.12; H, 5.48; N, 13.48%.

2-Amino-5,6-dihydro-5-(4-flurophenyl)-7-phenylquinazolin-4-ol (3b). This compound was obtained as white solid. mp 217–219°C; yield 60.4%; IR (KBr) ν cm^{-1} 3336 (N—H stretching), 2852 (C—H stretching), 1648 (C=C stretching) ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm 2.92 (d, 1H, J = 17.4 Hz), 3.21–3.11 (m, 1H), 4.21 (d, 1H, J = 8.1 Hz), 6.38 (s, NH$_2$), 6.44 (s, 1H), 7.00–7.50 (Ar-H), 10.76 (s, —OH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm 34.2, C-6 (merged with DMSO), 115.3, 125.3, 125.5,125.9, 127.8, 128.9, 129.0, 129.1, 129.2, 129.3, 130.0, 130.2, 132.0, 132.1, 132.5, 139.5, 143.9, 155.3, 169.7. Calc. for $C_{20}H_{16}N_3O$ C, 72.06; H, 4.84; N, 12.61%; Observed were C, 72.02; H, 4.86; N, 12.59%.

2-Amino-5-(4-chlorophenyl)-5,6-dihydro-7-phenylquinazolin-4-ol (3c). This compound was obtained as white amorphous solid. mp 196–198°C; yield 70.1%; IR (KBr) ν cm^{-1} 3437 (N—H stretching), 2858 (C—H stretching), 1647 (C=C stretching) ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm 2.93 (d, 1H, J = 17.6 Hz), 3.75–3.14 (m, 1H), 4.29 (d, 1H, J = 8.4 Hz), 6.47 (s, NH$_2$), 6.54 (s. H-8), 7.13–7.51 (Ar-H), 10.78 (s, —OH). ^{13}C NMR (DMSO-d_6, 300 MHz) δ ppm 34.9, 43.1, 113.8, 120.1, 122.8, 125.2, 125.6, 126.4, 128.8, 129.9, 130.4, 130.5, 131.2, 137.2, 140.9, 159.1, 169.1. Calc. for $C_{20}H_{19}N_3ClO$ C, 68.67; H, 4.61; N, 12.01%; observed were C, 68.62; H, 4.64; N, 12.03%.

2-Amino-5-(3-bromophenyl)-5,6-dihydro-7-phenylquinazolin-4-ol (3d). This compound is obtained as brown solid. mp 226–229°C; yield 50.2%; IR (KBr) ν cm^{-1} 3464 (N—H stretching), 2920 (C—H stretching), 1638 (C=C stretching) ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm 2.97 (d, 1H, J = 17.2 Hz), 3.32–3.12 (m, 1H), 4.21 (d, 1H, J = 8.4 Hz), 6.41 (s, NH$_2$), 6.47 (s, H-8), 7.18–7.51 (Ar-H), 10.77 (s, —OH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm 34.1, 41.5, 115.9, 121.0, 121.8, 123.9, 125.5, 125.9, 126.4, 127.8, 128.0, 129.2, 130.1, 139.4, 143.9, 147.9, 155.4, 170.9. Calc. for $C_{20}H_{16}N_3BrO$ C, 60.93; H, 4.09; N, 10.66%. Observed were C, 60.90; H, 4.05; N, 10.62%.

2-Amino-5-(4-bromophenyl)-5-dihydro-7-phenylquinazolin-4-ol (3e). This compound was obtained as a yellowish brown colour solid. mp 184–186°C; yield 55.1%; IR (KBr) ν cm^{-1} 3377 (N—H stretching), 2853 (C—H stretching), 1630 (C=C stretching) ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm 2.89 (d, 1H, J = 17.7 Hz), 3.21–3.11 (m, 1H), 4.19 (d, 1H, J = 8.4 Hz), 6.42 (s, NH$_2$), 6.47 (s, H—), 7.13–7.49 (Ar-H), 10.83 (s, —OH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm 34.4, C-6 (merged with DMSO), 113.9, 125.4, 125.9, 126.0, 127.1, 127.7, 128.3, 128.4, 128.9, 129.0, 129.3, 129.4, 129.5, 139.7, 144.0, 155.2, 170.0. Calc. for $C_{20}H_{16}N_3BrO$ C, 50.93; H, 4.09; N, 10.66%, observed were C, 50.89; H, 4.10; N, 10.59%.

2-Amino-5,6-dihydro-5-(4-methylphenyl)-7-phenylquinazolin-4-ol (3f). This compound was obtained as brownish red colour solid. mp 174–178°C; yield 45.7%; IR (KBr) ν cm^{-1} 3331 (N—H stretching), 2852 (C—H stretching), 1644 (C=C stretching) ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm 1.23 (s, 3H, —CH$_3$), 2.91 (d, 1H, J = 17.4 Hz), 3.19–3.09 (m, 1H), 4.16 (d, 1H, J = 8.1 Hz), 6.35 (s, —NH$_2$), 6.41 (s, 1H), 6.99–7.49 (Ar-H), 10.71, (s, —OH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm 15.1, 32.8, 40.8, 116.1, 125.0, 125.3, 125.4, 125.9, 126.0, 127.1, 127.3, 127.7, 128.9, 129.0, 129.1, 129.2, 129.5, 131.5, 135.2, 136.2, 139.5, 140.2, 142.2, 155.2, 168.4. Calc. for $C_{21}H_{19}N_3O$ C, 76.57; H, 5.81; N, 12.76%; observed were C, 76.52; H, 5.79; N, 12.69%.

2-Amino-5,6-dihydro-5-(4-methoxyphenyl)-7-phenylquinazolin-4-ol (3g). This compound was obtained as yellow crystalline solid. mp 204–206°C; yield 65.3%; IR (KBr) ν cm^{-1} 3371 (N—H stretching), 2852 (C—H stretching), 1645 (C=C stretching) ^{1}H NMR (DMSO-d_6 300 MHz) 2.08 (s, 3H, —OCH$_3$), 2.90 (d, 1H, J = 17.1 Hz), 3.34–3.08 (m, 1H), 4.16 (d, 1H, J = 8.1 Hz), 6.44 (s, NH$_2$), 6.53 (s, H-8), 7.08–7.49 (Ar-H), 10.79 (s, OH). ^{13}C NMR (DMSO-d_6 75 MHz) 35.5, 40.8, 60.5, 110.8, 123.3, 126.8, 126.9, 128.8, 129.3, 130.1, 131.0, 132.1, 159.7, 169.6. Calc. for $C_{21}H_{19}N_3O_2$ C, 73.03; H, 5.54; N, 12.17%; observed were C, 73.10; H, 5.61; N, 12.15%.

2-Amino-5,6-dihydro-5-(3-nitrophenyl)-7-phenylquinazolin-4-ol (3h). This compound was obtained as brownish yellow solid. mp 262–265°C; yield 65.3%; IR (KBr) ν cm^{-1} 3448 (N—H stretching), 2923 C—H stretching, 1653 (C=C stretching) ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm 3.01 (d. 1H, J = 17.4 Hz), 3.18–3.32 (m, 1H), 4.37 (d, 1H, J = 8.1 Hz), 6.45 (s, NH$_2$), 6.51 (s, 1H), 7.35–7.54 (Ar-H), 10.85 (s, —OH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm 34.4, C-6 (merged with DMSO), 113.5, 125.4, 125.9, 128.8, 129.2, 129.7, 131.4, 131.6, 139.5, 143.9, 144.0, 144.5, 155.5, 166.6. Calc. for $C_{20}H_{16}N_4O_3$ C, 66.66; H, 4.48; N, 15.55%; observed were C, 66.62; H, 4.45; N, 15.50%.

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A Simple and Expedient Method for the Synthesis of Ethyl 3-amino-4,6-diarylthieno[2,3-*b*]pyridine-2-carboxylate

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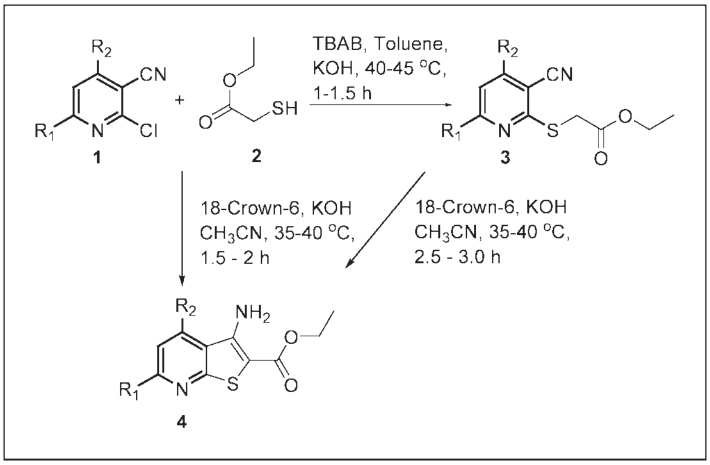
Dedicated to the memory of Dr. Chaitanya G. Dave.



2-Chloro-4,6-diarylnicotinonitrile **1** was reacted with ethyl 2-mercaptoacetate **2** to furnish ethyl 2-(3-cyano-4,6-diarylpyridin-2-ylthio)acetate **3** as intermediates. These intermediates were cyclized by Thorpe–Zeigler cyclization using solid–liquid phase-transfer catalysis conditions to give ethyl 3-amino-4,6-diarylthieno[2,3-*b*]pyridine-2-carboxylate **4**. One-pot heterocyclization without isolating the intermediates was also achieved using solid–liquid phase transfer conditions.

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INTRODUCTION

Many thienopyridines have been evaluated pharmacologically and in particular thieno[2,3-*b*]pyridines are of special importance due to the reported biological activities, including antibacterial [1], anti-inflammatory [2], antiparasitic [3], and antidiabetic [4] agents. Moreover, thieno[2,3-*b*]pyridine-5-carbonitrile were synthesizes as kinase inhibitors [5–7], were as thieno[2,3-*b*]pyridin-4-one derivatives were prepared as orally active, nonpeptide luteinizing hormone-releasing hormone (LHRH) receptor antagonists [8].

Despite the recent emergence of the thieno[2,3-*b*]pyridines moiety as a useful pharmacophore, methodology for preparation of this interesting heterocyclic ring system remains severely limited. Traditionally, the alkylation of substituted 3-cyano-2(1*H*)-pyridinethiones [9a–c] or 2-chloro-4,6-diarylnicotinonitrile [10] and Thorpe–Ziegler cyclization of the latter in alkali medium to give 3-aminothieno[2,3-*b*]pyridines have been extensively studied. Hard base like sodium or potassium alkoxide, which are relatively difficult to handle are used in such multistep synthesis.

The Thorpe–Zeigler cyclizations [11] are one of the most promising lines in the chemistry of amino heterocycles. They are base catalyzed and sodium or potassium alkoxide [12a–f], sodium hydride [12g,h], potassium hydroxide [12i], and lithium hydroxide [12j] were used frequently. Radical alternatives [13a], solvent free [13b] strategies as well as iridium hydride complexes [13c] also have been applied to Thorpe–Ziegler cyclizations. However, a little to our surprise, no attempt has been made to use comprehensive strategies for Thorpe–Zeigler cyclization involving phase-transfer conditions. In light of these considerations, we decided to set an improved protocol by introducing phase-transfer catalysis conditions for the Thorpe–Ziegler cyclization.

RESULTS AND DISCUSSION

2-Chloro-4,6-diarylnicotinonitrile **1** was reacted with ethyl 2-mercaptoacetate **2** in powdered KOH at 40–45°C using triethylbenzylammonium chloride (TEBA) as phase transfer catalyst and toluene as solvent to furnish ethyl 2-(3-cyano-4,6-diarylpyridin-2-ylthio)acetate **3** as

Table 1

Synthesis of 2-(3-cyano-4,6-diarylpyridin-2-ylthio)acetate **3a–k**.

Entry	R^1	R^2	Yield[a] (%)	Mp (°C) Found/Lit. [10]
3a	C_6H_5	C_6H_5	90	183–184/181–182
3b	C_6H_5	4-$OCH_3C_6H_4$	93	178–179/177–178
3c	C_6H_5	4-FC_6H_4	89	188–189
3d	C_6H_5	3-Cl-4-FC_6H_3	91	202–203
3e	C_6H_5	4-$CH_3C_6H_4$	80	238–239/238–239
3f	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	90	183–184/182–184
3g	4-$CH_3C_6H_4$	4-ClC_6H_4	89	191–192
3h	4-$CH_3C_6H_4$	4-FC_6H_4	88	195–196
3i	4-$CH_3OC_6H_4$	C_6H_5	94	202–203/202–203
3j	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	91	200–201/198–199
3k	4-FC_6H_4	C_6H_5	93	169–170

[a] Isolated yields.

intermediates (Table 1). The reaction was optimized using different reaction conditions and catalysts, for liquid–liquid phase-transfer conditions CH_2Cl_2/KOH (aq. 40% w/v), the most lipophilic *quats*, the Aliquat, and the tetrabutylammonium cation (TBA) were ineffective phase transfer catalyst were as more hydrophilic cation, TEBA gave poor yields. However in solid–liquid phase-transfer conditions Toluene/powdered KOH TEBA was the preferred choice. These intermediates were cyclized by Thorpe–Zeigler cyclization using 18-crown-6 and potassium hydroxide complex dissolved in acetonitrile, the heterocyclization allowed efficient access to various ethyl 3-amino-4,6-diarylthieno[2,3-*b*]pyridine-2-carboxylate **4** in excellent yields. One-pot heterocyclization without isolating the intermediates **3** was also achieved using solid–liquid phase-transfer catalysis (SL-PTC) conditions (Table 2; Scheme 1).

Given the frequent appearance of thieno[2,3-*b*]pyridine fragments in pharmaceutical compounds, we sought to expand the scope of this potentially useful phase-transfer method and optimize its efficiency. To optimize the synthesis of **4**, different catalysts and reaction conditions were examined. For liquid–liquid phase-transfer conditions CH_2Cl_2/KOH (aq. 40% w/v), lack of reactivity was observed in the presence of catalysts such as tetrabutylammonium iodide (TBAI) and tricaprylmethylammonium chloride (Aliquat® 336) even after prolonged heating (24 h, 40°C). Thus, the most lipophilic *quats*, the Aliquat, and the TBA are ineffective as phase-transfer catalysts. Changing the counter ion in the TBA *quat* [iodide (TBAI) or chloride (TBACl)] was also unsuccessful thus discarding the possibility that the lack of reactivity in the presence of the catalyst could be due to the effect of the iodide counter ion (‘‘catalyst poisoning’’ by association with the quat in the organic phase [14a–d]) the results also showed that swapping anions such as BF_4^-, ClO_4^-, and HSO_4^- have no catalytic activity. On the other hand, smaller and more

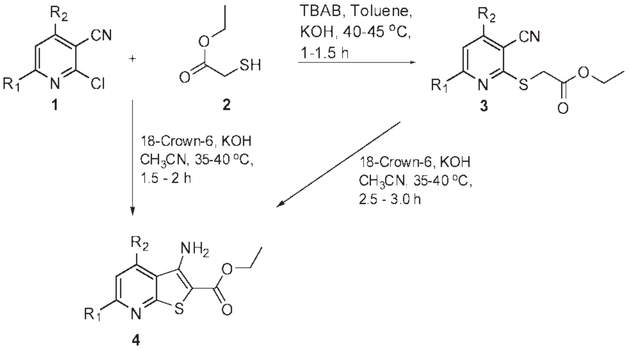
Table 2

Synthesis ethyl 3-amino-4,6-diarylthieno[2,3-*b*]pyridine-2-carboxylate **4a–k**.

			Yield (%)		
Entry	R^1	R^2	Method I	Method II[a]	Mp (°C) Found/Lit. [10]
4a	C_6H_5	C_6H_5	90	80	172–173/171–172
4b	C_6H_5	4-$OCH_3C_6H_4$	93	78	184–185/183–184
4c	C_6H_5	4-FC_6H_4	89	75	175–176
4d	C_6H_5	3-Cl-4-FC_6H_3	91	79	183–184
4e	C_6H_5	4-$CH_3C_6H_4$	80	69	175–176/174–175
4f	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	90	78	181–182/181–182
4g	4-$CH_3C_6H_4$	4-ClC_6H_4	89	75	176–177
4h	4-$CH_3C_6H_4$	4-FC_6H_4	88	70	181–182
4i	4-$CH_3OC_6H_4$	C_6H_5	94	84	188–189
4j	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	91	82	175–176/173–174
4k	4-FC_6H_4	C_6H_5	93	80	161–162

[a] Overall yields for method II from compound **1**.

Scheme 1. Synthesis of ethyl 3-amino-4,6-diarylthieno[2,3-*b*]pyridine-2-carboxylate **4**.



hydrophilic cations such as tributylmethylammonium and TEBA were unsuccessful to facilitate the reaction. These results indicate that the structure of the quaternary ammonium cation (*quat*) does not seem to be crucial for the success of the reaction. Catalyst loading, changing the solvent, or change in temperature resulted the same. The heterocyclization in SL-PTC conditions using 18-crown-6, KOH along with acetonitrile as solvent furnished products **4** in excellent yields. One-pot synthesis of thieno[2,3-*b*]pyridine-2-carboxylate **4** without isolation of intermediates **3** from 2-chloro-4,6-diarylnicotinonitrile **1** using same conditions was successful. Solvents like toluene, benzene, chlorobenzene, diethyl ether, methanol, and hexane were used, however, acetonitrile was the best choice for such heterocyclization.

The structure of compound ethyl 3-amino-4-tolyl-6-phenylthieno[2,3-*b*]pyridine-2-carboxylate **4e** was confirmed using X-ray crystallography [15] (Fig. 1).

A plausible mechanism for the Thorpe–Zeigler cyclization is proposed in Figure 2. The initial complex formation between crown ether and potassium hydroxide extracts proton from ethyl 2-(3-cyano-4,6-diarylpyridin-2-ylthio)acetate **3**, resulting into the intermediate, followed by intramolecular nucleophilic addition of —CH— onto an imine that could yield an enamine and also aromatic system for the formation of ethyl 3-amino-4,6-diarylthieno[2,3-*b*]pyridine-2-carboxylate **4**.

CONCLUSIONS

In conclusion, we have described a simple, cleaner, and convenient synthesis of ethyl 3-amino-4,6-diarylthieno[2,3-b]pyridine-2-carboxylate **3**, which are important building blocks for the construction of various fused heterocycles. SL-PTC conditions using 18-crown-6 is the method of choice with excellent yields even for one-pot heterocyclization. The ease with which phase-transfer catalyst reacts, presents new opportunities for expanding Thorpe–Zeigler cyclization for the synthesis of numerous heterocycles.

EXPERIMENTAL

Melting points were determined by electro thermal method in open capillary tube and are uncorrected. The IR spectra were recorded in cm^{-1} for KBr pellets on a Buck-500 spectrophotometer. The ^{1}H NMR spectra were recorded on a Varian 300 MHz spectrophotometer in DMSO-d_6 using TMS as internal standard and the chemical shifts are expressed in δ ppm. MS spectra were recorded on a JEOL/ SX-102 mass spectrophotometer under electron-impact (EI) ionization. Elemental analyses were performed on a Carlo Erba 1108 microanalyzer or Elementar's Vario EL III microanalyzer. The completion of the reaction was checked by TLC using silica gel G and spots were exposed to iodine vapor. 2-Chloro-4,6-diarylnicotinonitrile **1** were synthesized by refluxing 2-oxo-4,6-diaryl-1,2-dihydropyridine-3-carbonitrile [16] in phosphoryl trichloride.

General procedure for the synthesis of ethyl 2-(3-cyano-4,6-diarylpyridin-2-ylthio)acetate (3a-k). To a well stirred mixture of powdered potassium hydroxide (0.7 g, 12.5 mmol), triethylbenzylammoniumchloride (0.113 g, 0.5 mmol) and 2-chloro-4,6-diarylnicotinonitrile **1** (5 mmol) in toluene (25 mL), was added drop wise ethyl 2-mercaptoacetate **2** (6 mmol). The reaction mixture was heated up to 40–45°C. After the completion of reaction 1–1.5 h (TLC), water (25 mL) was added to the reaction mixture and stirring was continued for 5 min. Organic layer was separated and aqueous layer was washed with toluene (15 mL). The combined organic layer was dried over anhydrous magnesium sulfate, the solvent was removed *in vacuo*, and the solid **3a–k** thus obtained was crystallized from EtOH-DMF mixture.

Ethyl 2-(3-cyano-4,6-diphenylpyridin-2-ylthio)acetate (3a). IR (KBr): ν = 3020, 2940, 2228, 1748, 1584 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.47 (t, *J* = 7.2 Hz, 3H, —CH$_2$CH$_3$), 4.35 (s, 2H, —CH$_2$—), 4.56 (q, *J* = 7.0 Hz, 2H, —CH$_2$CH$_3$), 7.60–8.30 (m, 11H, Ar—H); MS: m/z = 374 (M$^+$). *Anal.* Calcd for $C_{22}H_{18}N_2O_2S$ (374.46): C, 70.57; H, 4.85; N, 7.48; Found: C, 70.63; H, 4.90; N, 7.61%.

Ethyl 2-(3-cyano-4-(4-methoxyphenyl)-6-phenylpyridin-2-ylthio)acetate (3b). IR (KBr): ν = 3030, 2994, 2232, 1756, 1590 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.35 (t, *J* =

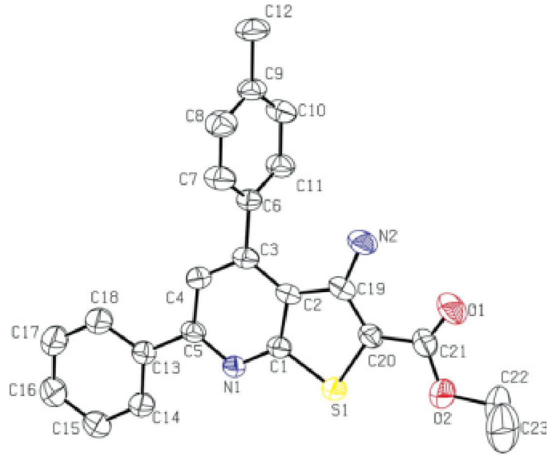


Figure 1. Ethyl 2-amino-6-phenyl-4-p-tolylthieno[2,3-*b*]pyridine-3-carboxylate [15] (**4e**). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

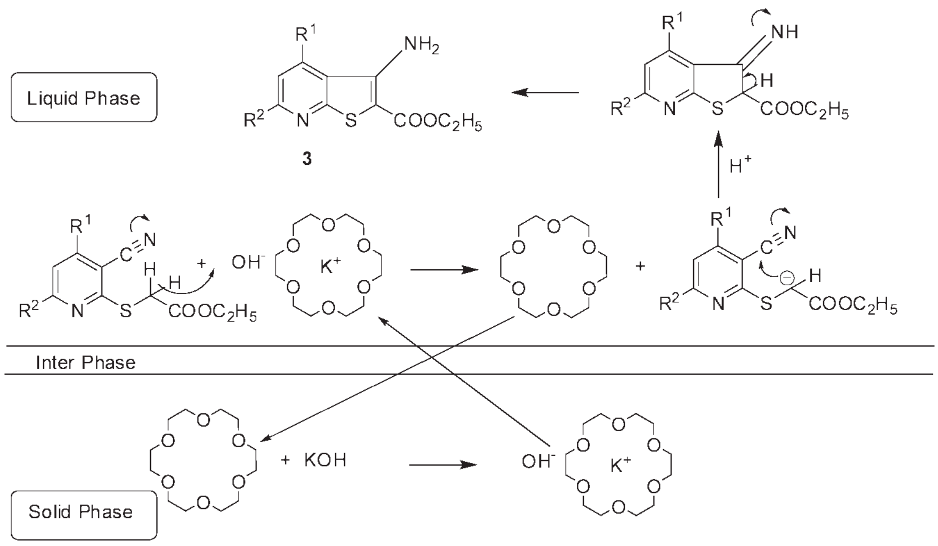


Figure 2. A plausible mechanism for the Thorpe–Zeigler cyclization in solid–liquid phase-transfer catalysis conditions.

7.2 Hz, 3H, —CH_2CH_3), 3.98 (s, 3H, OCH_3), 4.25 (s, 2H, —CH_2) 4.52 (q, J = 7.0 Hz, 2H, —CH_2CH_3), 7.12–8.15 (m, 10H, Ar—H); MS: m/z = 404 (M^+). *Anal.* Calcd for $C_{23}H_{20}N_2O_3S$ (404.48): C, 68.30; H, 4.98; N, 6.93; Found: C, 68.35; H, 5.12; N, 7.06%.

Ethyl 2-(3-cyano-4-(4-fluorophenyl)-6-phenylpyridin-2-ylthio)acetate (3c). IR (KBr): ν = 3004, 2980, 2216, 1758, 1600 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.32 (t, 3H, J = 7.2 Hz, —CH_2CH_3), 4.35 (s, 2H, —CH_2), 4.60 (q, J = 7.0 Hz, 2H, —CH_2CH_3), 7.50–8.31 (m, 10H, Ar—H); MS: m/z = 392 (M^+). *Anal.* Calcd for $C_{22}H_{17}FN_2O_2S$ (392.45): C, 67.33; H, 4.37; N, 7.14; Found: C, 67.44; H, 4.26; N, 7.26%.

Ethyl 2-(4-(3-chloro-4-fluorophenyl)-3-cyano-6-phenylpyridin-2-ylthio)acetate (3d). IR (KBr): ν = 3020, 2940, 2224, 17408, 1580 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.38 (t, J = 7.2 Hz, 3H, —CH_2CH_3), 4.32 (s, 2H, —CH_2), 4.59 (q, J = 7.0 Hz, 2H, —CH_2CH_3), 7.45–8.60 (m, 9H, Ar—H); MS: m/z = 426 (M^+). *Anal.* Calcd for $C_{22}H_{16}ClFN_2O_2S$ (426.89): C, 61.90; H, 3.78; N, 6.56; Found: C, 61.83; H, 3.66; N, 6.60%.

Ethyl 2-(3-cyano-6-phenyl-4-p-tolylpyridin-2-ylthio)acetate (3e). IR (KBr): ν = 3020, 2980, 2208, 1736, 1600 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.43 (t, J = 7.2 Hz, 3H, —CH_2CH_3), 2.40 (s, 3H, CH_3), 4.44 (s, 2H, —CH_2), 4.70 (q, J = 7.0 Hz, 2H, —CH_2CH_3), 7.12–8.55 (m, 10H, Ar—H); MS: m/z = 388 (M^+). *Anal.* Calcd for $C_{23}H_{20}N_2O_2S$ (388.48): C, 71.11; H, 5.19; N, 7.21; Found: C, 71.14; H, 5.02; N, 7.14%.

Ethyl 2-(3-cyano-4,6-dip-tolylpyridin-2-ylthio)acetate (3f). IR (KBr): ν = 3010, 2940, 2236, 1748, 1612 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.35 (t, J =7.2 Hz, 3H, —CH_2CH_3), 2.53 (s, 6H, CH_3), 4.33 (s, 2H, —CH_2), 4.62 (q, J = 7.0 Hz, 2H, —CH_2CH_3), 7.58–8.56 (m, 9H, Ar—H); MS: m/z = 402 (M^+). *Anal.* Calcd for $C_{24}H_{22}N_2O_2S$ (402.51): C, 71.62; H, 5.51; N, 6.96; Found: C, 71.70; H, 5.46; N, 6.86%.

Ethyl 2-(4-(4-chlorophenyl)-3-cyano-6-p-tolylpyridin-2-ylthio)acetate (3g). IR (KBr): ν = 3020, 2970, 2228, 1742, 1584 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.34 (t, J = 7.2 Hz, 3H, —CH_2CH_3), 2.49 (s, 3H, CH_3), 4.38 (s, 2H, —CH_2), 4.66 (q, J =7.0 Hz, 2H, —CH_2CH_3), 7.30–8.25 (m, 9H, Ar—H); MS: m/z = 422 (M^+). *Anal.* Calcd for $C_{23}H_{19}ClN_2O_2S$ (422.93): C, 65.32; H, 4.53; N, 6.62; Found: C, 65.43; H, 4.56; N, 6.76%.

Ethyl 2-(3-cyano-4-(4-fluorophenyl)-6-p-tolylpyridin-2-ylthio)acetate (3h). IR (KBr): ν = 3010, 2992, 2232, 1744, 1596 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.39 (t, J = 7.2 Hz, 3H, —CH_2CH_3), 2.47 (s, 3H, CH_3), 4.37 (s, 2H, —CH_2), 4.67 (q, J = 7.0 Hz, 2H, —CH_2CH_3), 7.23–8.55 (m, 9H, Ar—H); MS: m/z = 406 (M^+). *Anal.* Calcd for $C_{23}H_{19}FN_2O_2S$ (406.47): C, 67.96; H, 4.71 N, 6.89; Found: C, 67.83; H, 4.86; N, 6.96%.

Ethyl 2-(3-cyano-6-(4-methoxyphenyl)-4-phenylpyridin-2-ylthio)acetate (3i). IR (KBr): ν = 3000, 2988, 2212, 1756, 1584 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.43 (t, J = 7.2 Hz, 3H, —CH_2CH_3), 4.05 (s, 3H, OCH_3), 4.30 (s, 2H, —CH_2), 4.66 (q, J = 7.0 Hz, 2H, —CH_2CH_3), 7.20–8.37 (m, 10H, Ar—H); MS: m/z = 404 (M^+). *Anal.* Calcd for $C_{23}H_{20}N_2O_3S$ (404.48): C, 68.30; H, 4.98; N, 6.93; Found: C, 68.33; H, 5.06; N, 7.12%.

Ethyl 2-(3-cyano-4,6-bis(4-methoxyphenyl)pyridin-2-ylthio)acetate (3j). IR (KBr): ν = 3010, 2960, 2236, 1756, 1600 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.33 (t, J = 7.2 Hz, 3H, —CH_2CH_3), 3.64 (s, 2H, —CH_2), 4.12 (s, 6H, OCH_3), 4.50 (q, J = 7.0 Hz, 2H, —CH_2CH_3), 6.99–8.19 (m, 9H, Ar—H); MS: m/z = 434 (M^+). *Anal.* Calcd for $C_{24}H_{22}N_2O_4S$ (434.51): C, 66.34; H, 5.10; N, 6.45; Found: C, 66.37; H, 5.16; N, 6.55%.

Ethyl 2-(3-cyano-6-(4-fluorophenyl)-4-phenylpyridin-2-ylthio)acetate (3k). IR (KBr): ν = 3000, 2980, 2224, 1752, 1604 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.38 (t, J = 7.2 Hz, 3H, —CH_2CH_3), 4.35 (s, 2H, —CH_2), 4.62 (q, J = 7.0 Hz, 2H, —CH_2CH_3), 7.55–8.48 (m, 10H, Ar—H); MS: m/z = 392 (M^+). *Anal.* Calcd for $C_{22}H_{17}FN_2O_2S$ (392.45): C, 67.33; H, 4.37; N, 7.14; Found: C, 67.46; H, 4.26; N, 7.20%.

General procedure for the synthesis of ethyl 3-amino-4,6-diarylthieno[2,3-b]pyridine-2-carboxylate 4a–k. ***Method I.*** To the well stirred solution of MeCN (20 mL), powdered KOH (0.700 g, 12.5 mmol), and 18-crown-6 (0.132 g, 0.5 mmol) was added ethyl 2-(3-cyano-4,6-diarylpyridin-2-ylthio)acetate **3** (5 mmol). The reaction mixture was further stirred at 35–40°C for 1.5–2 h (TLC). The solvent was distilled under reduced pressure and the reaction mixture was poured onto crushed ice (20 g) and neutralized with acetic acid (50% v/v). The products thus obtained were filtered, washed with water, dried, and crystallized from glacial acetic acid.

Method II. Ethyl 2-mercaptoacetate **2** (6 mmol) was added drop wise to a stirred mixture of powdered potassium hydroxide (15 mmol, 0.84 g) and 18-crown-6 (1 mmol, 0.264 g) in acetonitrile (20 mL). 2-Chloro-4,6-diarylnicotinonitrile **1** (5 mmol) was added portion wise to the reaction mixture with stirring. The reaction was further stirred at 35–40°C for 2.5–3.0 h (TLC). The solvent was distilled under reduced pressure and the reaction mixture was poured onto crushed ice (20 g) and neutralized with acetic acid (50% v/v). The products thus obtained were filtered, washed with water, dried, and crystallized from glacial acetic acid.

Ethyl 3-amino-4,6-diphenylthieno[2,3-b]pyridine-2-carboxylate (4a). IR (KBr): ν = 3510, 3380, 3020, 2900, 1686, 1600 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.42 (t, J = 7.2 Hz, 3H, —CH_2CH_3), 4.42 (q, J = 6.9 Hz, 2H, —CH_2CH_3), 5.70 (s, 2H, —NH_2), 7.23–8.16 (m, 11H, Ar—H); MS: m/z = 374 (M^+). *Anal.* Calcd for $C_{22}H_{18}N_2O_2S$ (374.46): C, 70.57; H, 4.85; N, 7.48; Found: C, 70.51; H, 4.89; N, 7.42%.

Ethyl 3-amino-4-(4-methoxyphenyl)-6-phenylthieno[2,3-b]pyridine-2-carboxylate (4b). IR (KBr): ν = 3480, 3380, 3030, 2990, 1664, 1604 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.41 (t, J = 7.2 Hz, 3H, —CH_2CH_3), 3.95 (s, 3H, —OCH_3), 4.49 (q, J = 6.9 Hz, 2H, —CH_2CH_3), 5.85 (s, 2H, —NH_2), 7.18–8.10 (m, 10H, Ar—H); MS: m/z = 404 (M^+). *Anal.* Calcd for $C_{23}H_{20}N_2O_3S$ (404.48): C, 68.30; H, 4.98; N, 6.93; Found: C, 68.35; H, 4.88; N, 6.88%.

Ethyl 3-amino-4-(4-fluorophenyl)-6-phenylthieno[2,3-b]pyridine-2-carboxylate (4c). IR (KBr): ν = 3480, 3380, 3030, 2990, 1664, 1604 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.43 (t, J = 7.2 Hz, 3H, —CH_2CH_3), 4.40 (q, J = 6.9 Hz, 2H, —CH_2CH_3), 5.65 (s, 2H, —NH_2), 7.45–8.15 (m, 10H, Ar—H); MS: m/z = 392 (M^+). *Anal.* Calcd for $C_{22}H_{17}FN_2O_2S$ (392.45): C, 67.33; H, 4.37; N, 7.14; Found: C, 67.41; H, 4.45; N, 7.10%.

Ethyl 3-amino-4-(3-chloro-4-fluorophenyl)-6-phenylthieno-[2,3-b]pyridine-2-carboxylate (4d). IR (KBr): ν = 3455, 3300, 3010, 2980, 2204, 1624, 1596 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.35 (t, J = 7.2 Hz, 3H, —CH_2CH_3), 4.24 (q, J = 6.9 Hz, 2H, —CH_2CH_3), δ = 5.34 (s, 2H, NH_2), 7.67–8.14 (m, 9H, Ar—H); MS: m/z = 426 (M^+). *Anal.* Calcd for $C_{22}H_{16}ClFN_2O_2S$ (426.89): C, 61.90; H, 3.78; N, 6.56; Found: C, 61.81; H, 3.88; N, 6.60%.

Ethyl 2-amino-6-phenyl-4-p-tolylthieno[2,3-b]pyridine-2-carboxylate (4e). IR (KBr): ν = 3520, 3400, 3000, 2980, 1674, 1608 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.30 (t, J = 7.2 Hz, 3H, —CH_2CH_3), 2.45 (s, 3H, CH_3), 4.42 (q, J = 6.9 Hz, 2H, —CH_2CH_3), 5.75 (s, 2H, —NH_2), 7.04–8.25 (m, 10H, Ar—H); MS: m/z = 388 (M^+). *Anal.* Calcd for $C_{23}H_{20}N_2O_2S$ (388.48): C, 71.11; H, 5.19; N, 7.21; Found: C, 71.22; H, 5.05; N, 7.15%.

Ethyl 3-amino-4,6-dip-tolylthieno[2,3-b]pyridine-2-carboxylate (4f). IR (KBr): ν = 3480, 3380, 3030, 2990, 1664, 1604 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.39 (t, J = 7.2 Hz, 3H, —CH_2CH_3), 2.47 (s, 6H, CH_3), 4.43 (q, J = 6.9 Hz, 2H, —CH_2CH_3), 5.63 (s, 2H, —NH_2), 7.38–8.11 (m, 9H, Ar—H); MS: m/z = 402 (M^+). *Anal.* Calcd for $C_{24}H_{22}N_2O_2S$ (402.51): C, 71.62; H, 5.51; N, 6.96; Found: C, 71.68; H, 5.45; N, 6.89%.

Ethyl 3-amino-4-(4-chlorophenyl)-6-p-tolylthieno[2,3-b]pyridine-2-carboxylate (4g). IR (KBr): ν = 3510, 3380, 3000, 2940, 1676, 1616 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.35 (t, J =7.2 Hz, 3H, —CH_2CH_3), 2.40 (s, 3H, CH_3), 4.36 (q, J = 6.9 Hz, 2H, —CH_2CH_3), 5.60 (s, 2H, —NH_2), 7.18–8.21 (m, 9H, Ar—H); MS: m/z = 422 (M^+). *Anal.* Calcd for $C_{23}H_{19}ClN_2O_2S$ (422.93): C, 65.32; H, 4.53; N, 6.62; Found: C, 65.23; H, 4.44; N, 6.55%.

Ethyl 3-amino-4-(4-fluorophenyl)-6-p-tolylthieno[2,3-b]pyridine-2-carboxylate (4h). IR (KBr): ν = 3500, 3390, 3010, 2940, 1682, 1600 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.33 (t, J = 7.2 Hz, 3H, —CH_2CH_3), 2.39 (s, 3H, CH_3), 4.35 (q, J = 6.9 Hz, 2H, —CH_2CH_3), 5.62 (s, 2H, —NH_2), 7.13–8.19 (m, 9H, Ar—H); MS: m/z = 406 (M^+). *Anal.* Calcd for $C_{23}H_{19}FN_2O_2S$ (406.47): C, 67.96; H, 4.71; N, 6.89; Found: C, 67.99; H, 4.80; N, 6.86%.

Ethyl 3-amino-6-(4-methoxyphenyl)-4-phenylthieno[2,3-b]-pyridine-2-carboxylate (4i). IR (KBr): ν = 3520, 3400, 3000, 2980, 1676, 1608 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.39 (t, J = 7.2 Hz, 3H, —CH_2CH_3), 3.98 (s, 3H, OCH_3), 4.36 (q, J = 6.9 Hz, 2H, —CH_2CH_3), 5.96 (s, 2H, —NH_2), 7.27–8.24 (m, 10H, Ar—H); MS: m/z = 404 (M^+). *Anal.* Calcd for $C_{23}H_{20}N_2O_3S$ (404.48): C, 68.30; H, 4.98; N, 6.93; Found: C, 68.38; H, 4.88; N, 6.87%.

Ethyl 3-amino-4,6-bis(4-methoxyphenyl)thieno[2,3-b]pyridine-2-carboxylate (4j). IR (KBr): ν = 3510, 3300, 3020, 2970, 1672, 1596 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.42 (t, J = 7.2 Hz, 3H, —CH_2CH_3), 4.02 (s, 6H, OCH_3), 4.39 (q, J = 6.9 Hz, 2H, —CH_2CH_3), 5.99 (s, 2H, —NH_2), 7.26–8.20 (m, 9H, Ar—H); MS: m/z = 434 (M^+). *Anal.* Calcd for $C_{24}H_{22}N_2O_4S$ (434.51): C, 66.34; H, 5.10; N, 6.45; Found: C, 66.30; H, 5.12; N, 6.39.

Ethyl 3-amino-6-(4-fluorophenyl)-4-phenylthieno[2,3-b]pyridine-2-carboxylate (4k). IR (KBr): ν = 3500, 3390, 3010, 2980, 1668, 1600 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.45 (t, J = 7.2 Hz, 3H, —CH_2CH_3), 4.46 (q, J = 6.9 Hz, 2H, —CH_2CH_3), 5.55 (s, 2H, —NH_2), 7.21–8.24 (m, 10H, Ar—H); MS: m/z = 392 (M^+). *Anal.* Calcd for $C_{22}H_{17}FN_2O_2S$ (392.45): C, 67.33; H, 4.37; N, 7.14; Found: C, 67.22; H, 4.25; N, 7.26.

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A Novel and Green Method for the Synthesis of Highly Substituted Isoquinoline Derivatives in Ionic Liquid

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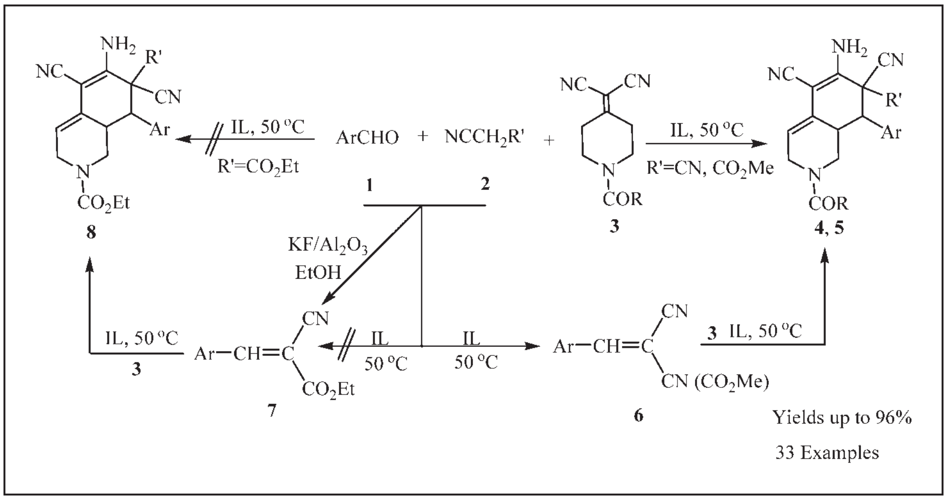

A series of new highly substituted isoquinoline derivatives was obtained from the reaction of 2-(1-substituted piperidin-4-ylidene)malononitrile, benzaldehyde and malononitrile or cyanoacetate in ionic liquid at 50°C. This novel procedure was different from the previous method in the synthesis of isoquinoline using pyridine fragment as reactant to construct benzene ring, and as well as had the advantages of one-pot, mild and environmentally benign. A possible mechanism was proposed based on the further experimental results.

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INTRODUCTION

Multi-component reactions (MCRs) are economically and environmentally very advantageous because multi-step syntheses produce considerable amounts of waste mainly due to complex isolation procedures often involving expensive, toxic, and hazardous solvents after each step. MCRs are perfectly suited for combinatorial library synthesis, and thus find increasing use in the discovery process for new drugs and agrochemicals [1]. In addition, ionic liquids have attracted increasing interest in the context of green synthesis in recent years. They were initially introduced as alternative green reaction media because of their unique chemical and physical properties of nonvolatility, nonflammability, thermal stability, and controlled miscibility. The possibility of recycling them and the low vapor pressure also ensure their utility in environmentally friendly technologies. They have been used as solvents for a large number of organic transformations [2].

Molecules with heterocyclic substructures are attractive targets for synthesis as they often exhibit diverse and important biological properties, such as isoquinoline derivatives. They have been reported to possess antifungal activity [3], antitumor activity [4], anticoagulant activity [5], anti-inflammatory, and analgesic activity [6]. 3-Cyanoisoquinoline **I** (Fig. 1), was reported as a Kv1.5 antagonist, and evaluated *in vitro* and *in vivo* assays for inhibition of the Kv1.5 potassium channel and its associated cardiac potassium current. Its derivatives afforded with excellent potency, selectivity, and oral bioavailability [7].

Accordingly, novel strategies for the synthesis of isoquinolines continue to receive considerable attention in the field of synthetic organic chemistry [8], except for the known classical isquinoline synthetic methods [9(a)–(f)], *e.g.* Bischler-Napieralski reaction, Pictet-Gams isoquinoline synthesis, Pomeranz-Fritsch reaction, Gabriel-Colman rearrangement, and Pictet-Spengler isoquinoline synthesis. Commonly, amines containing benzene ring

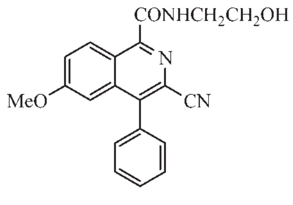


Figure 1. 3-Cyanoisoquinoline.

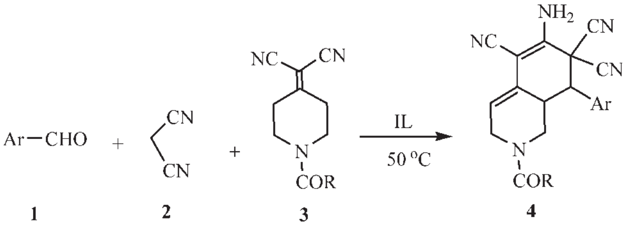
were used as reactants to construct the pyridine nucleus to gain the isoquinolines. On the contrary, our interest was focused on the synthesis of isoquinoline derivatives using a fragment containing pyridine ring as starting material to form benzene moiety. Inspired this novel idea and as part of a continuing effort in our laboratory toward the new methods for the e biologically relevant heterocyclic compounds in ionic liquids [10], herein, we would like to report a novel reaction of 2-(1-substituted-piperidin-4-ylidene)malononitrile, benzaldehyde, and malononitrile or cyanoacetate in the synthesis of highly substituted isoquinoline derivatives.

RESULTS AND DISCUSSION

The three-component reaction of benzaldehyde **1**, malononitrile **2**, and ethyl 4-(dicyanomethylene) piperidine-1-carboxylate **3** (*R*=OEt) was treated in ionic liquid at 50°C, with ethyl 6-amino-5,7,7-tricyano-3,4,7,8-tetrahydro-8-arylisoquinoline-2(1*H*)-carboxylate derivatives **4** being obtained in high yields (Scheme 1).

Firstly, optimizations of the reaction conditions, including reaction temperature and solvents, were investigated using 2-chlorobenzaldehyde, malononitrile and ethyl 4-(dicyanomethylene)piperidine-1-carboxylate as model reactants. As summarized in Table 1, the results showed that at room temperature, only trace products were observed by TLC. (Table 1, entry 1). To our delight, the reaction proceeded smoothly in high yield at 50°C, higher temperature 90°C gave a complicated system, only 52% yield of **4a** was isolated by silica gel column chromatography. Moreover, different ionic liquids were further tested as reaction medium and it was observed that [bmim$^+$] [BF$_4^-$] was the best ionic liquid for the reaction (Table 1, entries 4–8). In addition, we also looked into the water and other organic solvent effect at 50°C for this reaction. As showed in Table 1, ionic liquid of [bmim$^+$] [BF$_4^-$] gave the most satisfactory result in comparison with other solvents (Table 1, entries 9–12).

Scheme 1



After the reaction was completed, the reaction mixtures were cooled to room temperature. Water (5 mL) was then added to the mixture and the solid was isolated by filtration. The water in the filtrate was removed by evaporation at reduced pressure, and the ionic liquid in the filtrate could be recycled easily at 80°C *in vacuum* for 4 h. The recovered ionic liquid could be directly used for the same reactions. Alternatively, if the ionic liquid was used for other reactions with different substrates, it was washed with ethyl acetate, followed by evaporation at 80°C *in vacuum* for 3 h. Investigations by using 2-chlorobenzaldehyde, ethyl 4-(dicyanomethylene) piperidine-1-carboxylate, and malononitrile as model substrates proved the successive reuse of ionic liquid. Even in the fourth cycle the yield (87%) of product **4a** is fairly high.

According to the optimized conditions, we next examined the utility of this process (Scheme 1) to synthesize a range of isoquinoline **4**. Various arylaldehydes **1**, bearing either electron-withdrawing groups (such as halide, nitro) or electron-donating groups (such as alkyl group or alkoxyl group), were subjected to react with **3** to give the corresponding isoquinoline derivatives **4** in high yields (Table 2, entries 1–16). Replacing the ethyl 4-(dicyanomethylene)piperidine-1-carboxylate to 2-(1-(3-chlorobenzoyl)piperidin-4-ylidene)malononitrile

Table 1

Synthesis of **4a** at different reaction conditions.[a]

Entry	T/°C	Solvents[b]	Yields[c]/%
1	r.t.	[bmim$^+$][BF$_4^-$]	Trace
2	50	[bmim$^+$][BF$_4^-$]	93
3	90	[bmim$^+$][BF$_4^-$]	52
4	50	[emim$^+$] Br$^-$	82
5	50	[pmim$^+$] Br$^-$	85
6	50	[bmim$^+$]Br$^-$	85
7	50	[emim$^+$][BF$_4^-$]	86
8	50	[pmim$^+$][BF$_4^-$]	84
9	50	H_2O	72
10	50	EtOH	78
11	50	THF	67
12	50	DMF	83

[a] Reaction conditions: ionic liquid (2 mL), 2-chlorobenzaldehyde (0.281 g, 2 mmol), ethyl 4-(dicyanomethylene)piperidine-1-carboxylate (0.438 g, 2 mmol), malononitrile (0.132 g, 2 mmol) and other solvents 10 mL.

[b] bmim = 1-butyl-3-methylimidazolium; emim = 1-ethyl-3-methylimidazolium; pmim=1-methyl-3-propylimidazolium.

[c] Isolated yields.

Table 2

The reactions of 2-(1-substitutedpiperidin-4-ylidene) malononitrile, benzaldehyde, and malononitrile in ionic liquid.[a]

Entry	Ar	R	Products	Time /h	Yields[b]/%
1	2-ClC_6H_4	OEt	**4a**	8	93
2	3,4-$Cl_2C_6H_4$	OEt	**4b**	10	92
3	2,4-$Cl_2C_6H_4$	OEt	**4c**	8	94
4	4-$NO_2C_6H_4$	OEt	**4d**	7	89
5	4-$CH_3C_6H_4$	OEt	**4e**	11	90
6	2-$NO_2C_6H_4$	OEt	**4f**	6	95
7	4-BrC_6H_4	OEt	**4g**	10	90
8	3-ClC_6H_4	OEt	**4h**	9	87
9	3-BrC_6H_4	OEt	**4i**	9	93
10	2-FC_6H_4	OEt	**4j**	7	95
11	2,3-$Cl_2C_6H_4$	OEt	**4k**	8	87
12	2-CNC_6H_4	OEt	**4l**	9	83
13	4-FC_6H_4	OEt	**4m**	8	90
14	2-BrC_6H_4	OEt	**4n**	7	95
15	4-ClC_6H_4	OEt	**4o**	8	93
16	2,3-$OMe_2C_6H_3$	OEt	**4p**	10	87
17	3-ClC_6H_4	3-ClC_6H_4	**4q**	10	84
18	2-FC_6H_4	3-ClC_6H_4	**4r**	9	86
19	2-BrC_6H_4	3-ClC_6H_4	**4s**	9	85
20	2-ClC_6H_4	3-ClC_6H_4	**4t**	9	85

[a] Reaction conditions: ionic liquid (2 mL), benzaldehyde (2 mmol), ethyl 4-(dicyanomethylene)piperidine-1-carboxylate (0.438 g, 2 mmol), malononitrile (0.132 g, 2 mmol).

[b] Isolated yields.

also gave the satisfactory results (Table 2, entries 17–20). As expected, the substrate of malononitrile could be extended to other active methylene compound. Methyl cyanoacetate was also chosen as reactant to treat with benzaldehyde, 4-(dicyanomethylene) piperidine-1-carboxylate (Scheme 2), and was found to generate the corresponding 2-ethyl 7-methyl 6-amino-5,7-dicyano-3,4,7,8-tetrahydro-8-arylisoquinoline-2,7(1*H*)-dicarboxylate derivatives (**5a–5f**) (Scheme 2) in high yields (Table 3).

However, to our surprise, we failed to get the expected products when ethyl cyanoacetate was used (Scheme 2). This raised an interesting question: why could the methyl cyanoacetate give good results, while ethyl cyanoacetate could not? This also stimulated us to carry out new experiments to find the reason as well as explore the reaction mechanism.

In our continued study, we find the reaction of benzaldehyde and methyl cyanoacetate could be proceeded smoothly to give corresponding methyl 2-cyano-3-(2-chlorophenyl)acrylate **6** in ionic liquid, while other cyanoacetates, such as ethyl or propyl cyanoacetate could not react with benzaldehyde. Perhaps, the reaction activity of ethyl cyanoacetate is less than that of methyl cyanoacetate or malononitrile. The results were agreed to those of the same reactions in water [11] or ethanol [12] without catalyst. Subsequently, we also tested the reaction of **6** and ethyl 4-(dicyanomethylene)piperidine-1-

Scheme 2

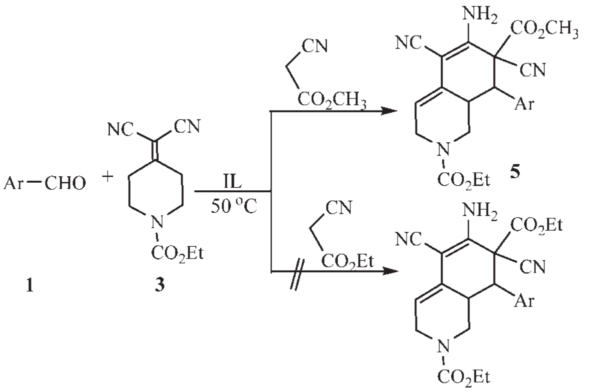


Table 3

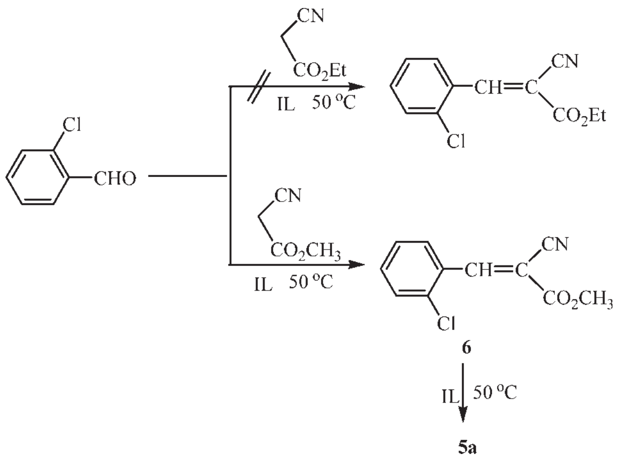
The reactions of ethyl 4-(dicyanomethylene)piperidine-1-carboxylate, benzaldehyde, and methyl cyanoacetate in ionic liquid.[a]

Entry	Ar	Products	Time /h	Yields[b] %
1	2-ClC_6H_4	**5a**	12	86
2	2,3-$OMe_2C_6H_3$	**5b**	15	83
3	2,3-$Cl_2C_6H_3$	**5c**	11	87
4	4-BrC_6H_4	**5d**	15	85
5	3,4-$Cl_2C_6H_3$	**5e**	14	87
6	4-ClC_6H_4	**5f**	15	90

[a] Reaction conditions: ionic liquid (2 mL), benzaldehyde (2 mmol), ethyl 4-(dicyanomethylene)piperidine-1-carboxylate (0.438 g, 2 mmol), methyl cyanoacetate (0.198 g, 2 mmol).

[b] Isolated yields.

Scheme 3

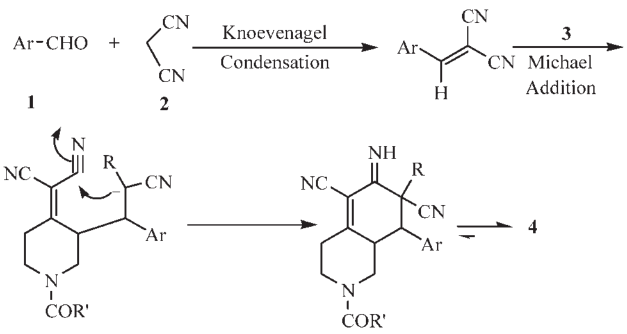


carboxylate **3** in ionic liquid at the same temperature, the desired 2-ethyl 7-methyl 6-amino-5,7-dicyano-3,4,7,8-tetrahydro-8-(2-chlorophenyl)isoquinoline-2,7(1*H*)-dicarboxylate **5a** was obtained successfully in high yield of (total yield 78%) (Scheme 3).

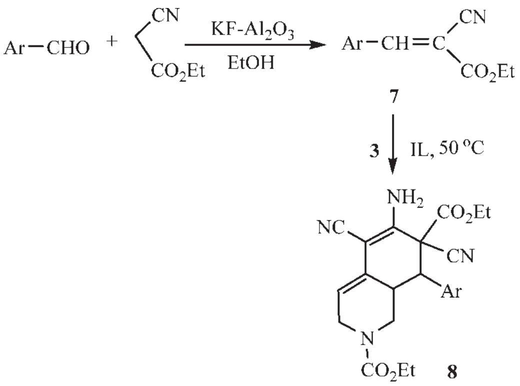
According to the above results, a sequential reaction of the Knoevenagel condensation, Michael addition reaction cyclization and isomerization may take place to give the final products **4**. A tentative mechanism was outlined in Scheme 4.

Encouraged by this result and to obtain the desired diethyl isoquinoline-2,7-dicarboxylate derivatives, a number of ethyl 2-cyano-3-arylacrylate **7** were synthesized by the known Knoevenagel condensation [13] of benzaldehydes and ethyl cyanoacetate in EtOH firstly, and then applied to react with **3** in ionic liquid (Scheme 5). Similarly, **7** smoothly reacted in ionic liquid at 50 °C to give the corresponding diethyl-6-amino-5,7-dicyano-3,4,7,8-tetrahydro-8-arylisoquinoline-2,7(1*H*)-dicarboxy late derivatives **8** in high yields (Table 4) as expected. The results were listed in Table 4.

Scheme 4



Scheme 5



CONCLUSION

In conclusion, we have disclosed a green and novel method to synthesize of new highly substituted isoquinoline derivatives was obtained from the reaction of 2-(1-substituted piperidin-4-ylidene)malononitrile, benzaldehyde and malononitrile or cyanoacetate in ionic liquid at 50°C. The note-worthy features of this procedure are different from the previous method in the synthesis of isoquinoline using pyridine fragment as reactant to construct benzene ring, mild reaction conditions, one-pot, high yield, operational simplicity and the environmentally friendly procedure. Meanwhile, [bmim$^+$] [BF$_4^-$] could be reused for several rounds without significant loss of activity.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a TENSOR 27 spectrometer in KBr pellet. ^{1}H NMR spectra were obtained from solution in DMSO-*d*$_6$ or CDCl$_3$ with Me$_4$Si as internal standard using a Bruker-400 spectrometer. HRMS analyses were carried out using Bruker-micro TOF-Q-MS analyzer.

Table 4

The reactions of ethyl 2-cyano-3-arylacrylate and ethyl 4-(dicyanomethylene) piperidine-1-carboxylate in ionic liquid.[a]

Entry	Ar	Products	Time /h	Yields[b]%
1	2-NO$_2$C$_6$H$_4$	**8a**	6	94
2	4-MeC$_6$H$_4$	**8b**	8	96
3	2-ClC$_6$H$_4$	**8c**	7	92
4	2,4-Cl$_2$C$_6$H$_3$	**8d**	7	94
5	3,4-Me$_2$C$_6$H$_3$	**8e**	10	90
6	3-ClC$_6$H$_4$	**8f**	9	95
7	4-OMeC$_6$H$_4$	**8g**	10	92

[a] Reaction conditions: ionic liquid (2 mL), ethyl 2-cyano-3-arylacrylate (2mmol), ethyl 4-(dicyanomethylene)piperidine-1-carboxylate (0.438 g, 2 mmol).

[b] Isolated yields.

General procedure for the syntheses of 6-amino-8-arylisoquinoline derivatives 4. A dry 50 mL flask was charged with arylaldehyde (2.0 mmol), malononitrile (0.132 g, 2.0 mmol), 2-(1-substitutedpiperidin-4-ylidene)malononitrile (2.0 mmol), and ionic liquid of [bmim$^+$][BF$_4^-$] (2 mL). The reaction mixture was stirred at 50°C for 7–11 h, and then cooled to room temperature. The generated yellow solid was filtered off, and the ionic liquid in filtrate was then recovered for reuse by evaporating at 80°C several h at *vacuum*. The crude yellow products were washed with water and purified by recrystallization from DMF and water, followed by being dried at 50°C several h at *vacuum* to give **4**.

Ethyl 6-amino-8-(2-chlorophenyl)-5,7,7-tricyano-3,4,7,8-tetrahydroisoquinoline-2(1H)-carboxylate 4a. Mp 230–232°C. IR (KBr)/cm^{-1} 3346, 3207, 3028, 2992, 2937, 2845, 2211, 1655, 1603, 1574, 1486, 1467, 1440, 1396, 1378, 1339, 1299, 1242, 1135, 1028, 1007, 941, 883, 818, 775, 750, 704. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.12–1.15 (m, 3H, CH_3), 2.37–2.40 (m, 1H, CH), 3.04–3.06 (m, 1H, CH), 3.57–3.81 (m, 2H, 2CH) 3.92–4.05 (m, 3H, CH_2O+CH), 4.27–4.37 (m, 1H, CH), 5.72 (s, 1H, CH), 7.55–7.61 (m, 2H, ArH), 7.67–7.69 (m, 3H, ArH+NH_2), 7.81–7.83 (m, 1H, ArH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 14.4, 33.8, 40.0, 40.2, 41.2, 43.4, 61.0, 80.1, 111.1, 111.6, 112.7, 115.5, 128.0, 129.99, 130.02, 130.6, 135.1, 136.1, 144.2, 164.1. HRMS-ESI. calcd for $C_{21}H_{18}ClN_5NaO_2$, M + Na$^+$: 430.1047, found: 430.1018.

Ethyl 6-amino-8-(3,4-dichlorophenyl)-5,7,7-tricyano-3,4,7,8-tetrahydroisoquinoline-2(1H)-carboxylate 4b. Mp 264–265°C. IR (KBr)/cm^{-1} 3343, 3159, 3063, 2994, 2980, 2209, 1656, 1605, 1488, 1468, 1444, 1396, 1343, 1298, 1248, 1207, 1189, 1136, 1115, 1032, 1007, 896, 814, 981, 761, 728. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.15–1.18 (m, 3H, CH_3), 2.35–2.40 (m, 1H, CH), 2.97–3.05 (m, 1H, CH), 3.66–3.78 (m, 2H, 2CH), 3.88–4.03 (m, 3H, CH_2O + CH), 4.28–4.41 (m, 1H, CH), 5.69 (s, 1H, CH), 7.46–7.66 (m, 1H, ArH), 7.67 (s, 2H, NH_2), 7.77–7.92 (m, 2H, ArH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 14.4, 32.7, 40.0, 40.2, 42.4, 43.4, 61.0, 80.1, 111.7, 111.8, 112.7, 115.6, 127.3, 131.1, 131.3, 131.4, 132.5, 134.7, 144.1, 167.0. HRMS-ESI. calcd for $C_{21}H_{18}Cl_2N_5O_2$, M + H$^+$: 442.0838, found: 442.0835.

Ethyl 6-amino-8-(2,4-dichlorophenyl)-5,7,7-tricyano-3,4,7,8-tetrahydroisoquinoline-2(1H)-carboxylate 4c. Mp 241–243°C. IR (KBr)/cm^{-1} 3340, 3194, 3029, 2984, 2933, 2895, 2847, 2212, 1692, 1653, 1604, 1559, 1478, 1439, 1395, 1341, 1299, 1242, 1110, 1052, 1025, 1005, 884, 864, 821, 783, 771. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.14–1.15 (m, 3H, CH_3), 2.35–2.42 (m, 1H, CH), 3.02–3.08 (m, 1H, CH), 3.52–3.80 (m, 2H, 2CH), 4.02–4.06 (m, 3H, CH_2O + CH), 4.27–4.40 (m, 1H, CH), 5.71 (s, 1H, CH), 7.67 (s, 2H, NH_2), 7.75 (dd, J = 8.4 Hz, 2.0, 1H, ArH), 7.84 (d, J = 8.4 Hz, 1H, ArH), 7.89 (d, J = 2.4 Hz, 1H, ArH). HRMS-ESI. calcd for $C_{21}H_{17}Cl_2N_5NaO_2$, M + Na$^+$: 464.0657, found: 464.0658.

Ethyl 6-amino-5,7,7-tricyano-3,4,7,8-tetrahydro-8-(4-nitrophenyl)isoquinoline-2(1H)-carboxylate 4d. Mp 243–244°C. IR (KBr)/cm^{-1} 3430, 3331, 3222, 3079, 2984, 2213, 1679, 1645, 1603, 1526, 1476, 1420, 1386, 1353, 1297, 1277, 1229, 1127, 1111, 1022, 867, 841, 822, 783, 725. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.15 (s, 3H, CH_3), 2.37–2.43 (m, 1H, CH), 3.04–3.10 (m, 1H, CH), 3.66–3.79 (m, 2H, 2CH), 4.01–4.10 (m, 3H, CH_2O + CH), 4.29–4.39 (m, 1H, CH), 5.71 (s, 1H, CH), 7.69 (s, 2H, NH_2), 7.76 (d, J = 8.0 Hz, 1H, ArH), 7.95 (s, 1H, ArH), 8.37–8.49 (m, 2H, ArH). HRMS-ESI. calcd for $C_{21}H_{18}N_6NaO_4$, M + Na$^+$: 441.1287, found: 441.1272.

Ethyl 6-amino-5,7,7-tricyano-3,4,7,8-tetrahydro-8-p-tolylisoquinoline-2(1H)-carboxylate 4e. Mp. 244–246°C. IR (KBr)/cm^{-1} 3345, 3164, 3061, 3032, 2982, 2929, 2851, 2211, 1670, 1635, 1517, 1487, 1395, 1344, 1299, 1279, 1190, 1050, 1026, 882, 524, 813, 783, 773, 751. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.14–1.17 (m, 3H, CH_3), 2.36–2.40 (s, 4H, $CH_{3+}CH$), 2.94 (b, 1H, CH), 3.68–3.74 (m, 3H, 3CH), 4.00–4.03 (m, 2H, CH_2O), 4.29–4.37 (m, 1H, CH), 5.67 (s, 1H, CH), 7.29–7.38 (m, 3H, ArH), 7.50–7.51 (m, 1H, ArH), 7.61 (s, 2H, NH_2). HRMS-ESI. calcd for $C_{22}H_{21}N_5NaO_2$, M + Na$^+$: 410.1593, found: 410.1587.

Ethyl 6-amino-5,7,7-tricyano-3,4,7,8-tetrahydro-8-(2-nitrophenyl)isoquinoline-2(1H)-carboxylate 4f. Mp. 227–228°C. IR (KBr)/cm^{-1} 3345, 3217, 3022, 2989, 2860, 2212, 1675, 1603, 1535, 1485, 1466, 1435, 1399, 1357, 1299, 1236, 1192, 1132, 1026, 941, 883, 862, 820, 763, 731, 696. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.08–1.15 (m, 3H, CH_3), 2.59–2.67 (m, 1H, CH), 3.19–3.22 (m, 1H, CH), 3.68–3.84 (m, 2H, 2CH), 3.94–4.03 (m, 2H, CH_2O), 4.22–4.40 (m, 2H, 2CH), 5.73 (s, 1H, CH), 7.66 (s, 2H, NH_2), 7.80–7.84 (m, 1H, ArH), 7.95–8.02 (m, 1H, ArH), 8.06 (d, J = 7.6 Hz, 1H, ArH), 8.14 (d, J = 8.0 Hz, 1H, ArH). HRMS-ESI. calcd for $C_{21}H_{18}N_6NaO_4$, M + Na$^+$: 441.1287, found: 441.1263.

Ethyl 6-amino-8-(4-bromophenyl)-5,7,7-tricyano-3,4,7,8-tetrahydroisoquinoline-2(1H)carboxylate 4g. Mp. 247–248°C. IR (KBr)/cm^{-1} 3344, 3166, 2983, 2210, 1687, 1660, 1605, 1491, 1468, 1443, 1413, 1394, 1342, 1299, 1273, 1246, 1190, 1133, 1077, 1051, 1024, 1012, 883, 833, 814, 778, 767, 754. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.15 (s, 3H, CH_3), 2.34–2.41 (m, 1H, CH), 2.95–2.99 (m, 1H, CH), 3.65–3.85 (m, 3H, 3CH), 3.99–4.05 (m, 2H, CH_2O), 4.28–4.39 (m, 1H, CH), 5.68 (s, 1H, CH), 7.40–7.42 (m, 1H, ArH), 7.59–7.62 (m, 1H, ArH), 7.64 (s, 2H, NH_2), 7.72–7.81 (m, 2H, ArH). HRMS-ESI. calcd for $C_{21}H_{18}BrN_5NaO_2$, M + Na$^+$: 474.0542, found: 474.0542.

Ethyl 6-amino-8-(3-chlorophenyl)-5,7,7-tricyano-3,4,7,8-tetrahydroisoquinoline-2(1H)-carboxylate 4h. Mp. 241–243°C. IR (KBr)/cm^{-1} 3342, 3171, 2994, 2849, 2210, 1668, 1602, 1575, 1488, 1469, 1442, 1393, 1377, 1344, 1298, 1247, 1203, 1189, 1132, 1049, 1025, 1008, 888, 814, 798, 781, 750, 711. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 4.15–4.18 (m, 3H, CH_3), 2.34–2.41 (m, 1H, CH), 2.97–3.03 (m, 1H, CH), 3.65–3.78 (m, 2H, 2CH), 3.83–3.89 (m, 1H, CH), 4.02–4.03 (m, 2H, CH_2O), 4.28–4.41 (m, 1H, CH_3), 5.69 (s, 1H, CH), 7.43–7.62 (m, 4H, ArH), 7.66 (s, 2H, NH_2). HRMS-ESI. calcd for $C_{21}H_{18}ClN_5NaO_2$, M + Na$^+$: 430.1047, found: 430.1046.

Ethyl 6-amino-8-(3-bromophenyl)-5,7,7-tricyano-3,4,7,8-tetrahydroisoquinoline-2(1H)-carboxylate 4i. Mp. 265–267°C. IR (KBr)/ cm^{-1} 3343, 3169, 2995, 2980, 2851, 2208, 1662, 1602, 1571, 1487, 1466, 1441, 1391, 1344, 1297, 1248, 1188, 1122, 1077, 1044, 1024, 1008, 882, 812, 793, 782, 748, 694. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.16–1.17 (m, 3H, CH_3), 2.34–2.41 (m, 1H, CH), 2.96–3.01 (m, 1H, CH), 3.65–3.78 (m, 2H, 2CH), 3.82–3.87 (m, 1H, CH), 3.95–4.03 (m, 2H, CH_2O), 4.29–4.41 (m, 1H, CH), 5.69 (s, 1H, CH), 7.48–7.58 (m, 2H, ArH), 7.66 (s, 2H, NH_2), 7.70–7.79 (m, 2H, ArH). HRMS-ESI. calcd for $C_{21}H_{18}BrN_5NaO_2$, M + Na$^+$: 474.0542, found: 474.0542.

Ethyl 6-amino-5,7,7-tricyano-8-(2-fluorophenyl)-3,4,7,8-tetrahydroisoquinoline-2(1H)-carboxylate 4j. Mp. 252–254°C. IR (KBr)/ cm^{-1} 3337, 3182, 3032, 2993, 2937, 2844, 2212, 1650, 1602, 1491, 1444, 1397, 1341, 1299, 1247, 1198, 1181, 1136, 1053, 1028, 1007, 884, 864, 818, 773, 759. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.14–1.15 (m, 3H, CH_3), 2.43–2.46 (m, 1H, CH), 3.03–3.18 (m, 1H, CH), 3.64–3.78 (m, 2H, 2CH), 3.90–4.04 (m, 3H, CH_2O+CH), 4.28–4.39 (m, 1H, CH), 5.70 (s, 1H, CH), 7.33–7.47 (m, 2H, ArH), 7.54–7.64 (m, 3H, ArH+NH_2), 7.72–7.76 (m, 1H, ArH). RMS-ESI. calcd for $C_{21}H_{18}FN_5NaO_2$, M + Na$^+$: 414.1342, found: 414.1342.

Ethyl 6-amino-8-(2,3-dichlorophenyl)-5,7,7-tricyano-3,4,7,8-tetrahydroisoquinoline-2(1H)-carboxylate 4k. Mp. 234–235°C. IR (KBr)/ cm^{-1} 3336, 3174, 2993, 2978, 2933, 2844, 2209, 1653, 1487, 1467, 1444, 1391, 1340, 1298, 1274, 1246, 1185, 1164, 1048, 1028, 1008, 889, 817, 800, 780, 757, 741, 697. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.10–1.15 (m, 3H, CH_3), 2.39–2.43 (m, 1H, CH), 3.07 (s, 1H, CH), 3.61–3.80 (m, 2H, 2CH), 3.93–4.02 (m, 2H, CH_2O), 4.16 (d, J = 12.8 Hz, 1H, CH). 4.28–4.38 (m, 1H, CH), 5.72 (s, 1H, CH), 7.64–7.68 (m, 3H, ArH+NH_2), 7.81–7.86 (m, 2H, ArH). HRMS-ESI. calcd for $C_{21}H_{17}Cl_2N_5NaO_2$, M + Na$^+$: 464.0557, found: 464.0552.

Ethyl 6-amino-5,7,7-tricyano-8-(2-cyanophenyl)-3,4,7,8-tetrahydroisoquinoline-2(1H)-carboxylate 4l. Mp. 220–222°C. IR (KBr)/ cm^{-1} 3406, 3340, 3222, 3017, 2987, 2225, 2210, 1693, 1634, 1609, 1481, 1435, 1390, 1339, 1301, 1278, 1237, 1130, 1049, 1026, 1007, 888, 822, 776, 759. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.11–1.15 (m, 3H, CH_3), 2.58–2.62 (m, 1H, CH), 3.18 (s, 1H, CH), 3.53–3.77 (m, 3H, 3CH), 3.90–4.02 (m, 2H, CH_2O), 4.29–4.39 (m, 1H, CH), 5.76 (s, 1H, CH), 7.24–7.79 (m, 3H, ArH), 7.99 (s, 2H, NH_2), 8.08 (d, J = 7.6 Hz, 1H, ArH). HRMS-ESI. calcd for $C_{22}H_{18}N_6NaO_2$, M + Na$^+$: 421.1389, found: 421.1367.

Ethyl 6-amino-5,7,7-tricyano-8-(4-fluorophenyl)-3,4,7,8-tetrahydroisoquinoline-2(1H)-carboxylate 4m. Mp. 240–242°C. IR (KBr)/ cm^{-1} 3342, 3172, 2984, 2934, 2851, 2211, 1668, 1602, 1515, 1487, 1468, 1443, 1396, 1233, 1299, 1280, 1164, 1134, 1024, 882, 841, 811, 786, 777, 760. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.15 (s, 3H, CH_3), 2.34–2.44 (m, 1H, CH), 2.94–2.98 (m, 1H, CH), 3.65–3.78 (m, 2H, 2CH), 3.83 (d, J = 12.8 Hz, 1H, CH), 3.99–4.02 (m, 2H, CH_2O), 4.29–4.39 (m, 1H, CH), 5.68 (s, 1H, CH), 7.35–7.46 (m, 3H, ArH), 7.51 (s, 2H, NH_2), 7.63–7.68 (m, 1H, ArH). HRMS-ESI. calcd for $C_{21}H_{18}FN_5NaO_2$, M + Na$^+$: 414.1342, found: 414.1325.

Ethyl 6-amino-8-(2-bromophenyl)-5,7,7-tricyano-3,4,7,8-tetrahydroisoquinoline-2(1H)-carboxylate 4n. Mp. 222–224°C. IR (KBr)/ cm^{-1} 3346, 3202, 2991, 2933, 2861, 2212, 1662, 1648, 1602, 1486, 1473, 1398, 1339, 1298, 1242, 1130, 1050, 1026, 941, 884, 819, 775, 747. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.08–1.15 (m, 3H, CH_3), 2.35–2.41 (m, 1H, CH), 3.07 (s, 1H, CH), 3.54–3.82 (m, 2H, 2CH), 3.90–4.01 (m, 3H, CH_2O+CH), 4.27–4.37 (m, 1H, CH), 5.72 (s, 1H, CH), 7.45–7.49 (m, 1H, ArH), 7.63–7.67 (m, 1H, ArH), 7.70 (s, 2H, NH_2), 7.80–7.86 (m, 2H, ArH). HRMS-ESI. calcd for $C_{21}H_{18}BrN_5NaO_2$, M + Na$^+$: 474.0542, found: 474.0523.

Ethyl 6-amino-8-(4-chlorophenyl)-5,7,7-tricyano-3,4,7,8-tetrahydroisoquinoline-2(1H)-carboxylate 4o. Mp. 238–240°C. IR (KBr)/ cm^{-1} 3342, 3169, 2987, 2850, 2211, 1687, 1661′ 1604, 1494, 1442, 1395, 1342, 1299, 1275, 1239, 1132, 1096, 1016, 941, 883, 835, 815, 778, 757. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.15 (s, 3H, CH_3), 2.34–2.44 (m, 1H, CH), 2.98 (s, 1H, CH), 3.65–3.78 (m, 2H, CH_2), 3.85 (d, J = 12.8 Hz, 1H, CH), 3.99–4.05 (m, 2H, CH_2O), 4.26–4.42 (m, 1H, CH), 5.69 (s, 1H, CH), 7.47–7.60 (m, 2H, ArH), 7.64–7.67 (m, 4H, ArH+NH_2). HRMS-ESI. calcd for $C_{21}H_{18}ClN_5NaO_2$, M + Na$^+$: 430.1047, found: 430.1025.

Ethyl 6-amino-5,7,7-tricyano-3,4,7,8-tetrahydro-8-(2,3-dimethoxyphenyl)isoquinoline-2(1H)-carboxylate 4p. Mp. 229–231°C. IR (KBr)/ cm^{-1} 3377, 3334, 3191, 2971, 2946, 2837, 2210, 1661, 1605, 1482, 1445, 1393, 1340, 1296, 1271, 1240, 1171, 1137, 1097, 1073, 1044, 1003, 819, 794, 766, 724. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.14 (b, 3H, CH_3), 2.35–2.41 (m, 1H, CH), 2.85–2.88 (m, 1H, CH), 3.59–3.69 (m, 2H, 2CH), 3.78 (s, 3H, CH_3O), 3.87 (s, 3H, CH_3O), 3.91–4.03 (m, 3H, CH_2O + CH), 4.28–4.39 (m, 1H, CH), 5.69 (s, 1H, CH), 7.19–7.20 (m, 2H, ArH), 7.25–7.28 (m, 1H, ArH), 7.60 (s, 2H, NH_2). HRMS-ESI. calcd for $C_{23}H_{24}N_5O_4$, M + H$^+$: 434.1828, found: 434.1806.

Ethyl 6-amino-2-(3-chlorobenzoyl)-8-(3-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline-5,7,7(8H)-tricarbonitrile 4q. Mp. 263–265°C. IR (KBr)/ cm^{-1} 3333, 3192, 2843, 2211, 1642, 1595, 1568, 1481, 1462, 1442, 1397, 1372, 1347, 1300, 1258, 1114, 1085, 1025, 1000, 884, 800, 786, 742, 711, 693. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 2.67–2.72 (m, 1H, CH), 3.11–3.19 (m, 1H, CH), 3.72–4.18 (m, 3H, 3CH), 4.65–4.70 (m, 1H, CH), 5.78 (s, 1H, CH), 7.30–7.61 (m, 8H, ArH), 7.68 (s, 2H, NH_2). HRMS-ESI. calcd for $C_{25}H_{17}Cl_2N_5NaO$, M + Na$^+$: 496.0708, found: 496.0708.

Ethyl 6-amino-2-(3-chlorobenzoyl)-8-(2-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline-5,7,7(8H)-tricarbonitrile 4r. Mp. 248–250°C. IR (KBr)/ cm^{-1} 3448, 3342, 3191, 2215, 1647, 1602, 1564, 1492, 1451, 396, 1345, 1306, 1285, 1250, 1235, 1127, 1089, 1039, 836, 812, 798, 759, 742, 718, 690. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 2.76–2.79 (m, 1H, CH), 3.10–3.13 (m, 1H, CH), 3.72–4.20 (m, 3H, 3CH), 4.64–4.69 (m, 1H, CH), 5.78 (s, 1H, CH), 7.21–7.54 (m, 8H, ArH), 7.66 (s, 2H, NH_2). HRMS-ESI. calcd for $C_{25}H_{17}ClFN_5NaO$, M + Na$^+$: 480.1003, found: 480.1003.

Ethyl 6-amino-2-(3-chlorobenzoyl)-8-(2-bromophenyl)-1,2,3,4-tetrahydroisoquinoline-5,7,7(8H)-tricarbonitrile 4s. Mp. 170–172°C. IR (KBr)/ cm^{-1} 3381, 3168, 2966, 2882, 2213, 1630, 1598, 1440, 1375, 1342, 1281, 1246, 1196, 1160, 1117, 1081, 1049, 1025, 922, 835, 799, 752, 714, 694. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 2.65–2.71 (m, 1H, CH), 2.99–3.03 (m, 1H, CH), 3.75–4.09 (m, 3H, 3CH), 4.64–4.68 (m, 1H, CH), 5.80 (s, 1H, CH), 7.30–7.50 (m, 6H, ArH), 7.64–7.69 (m, 2H, ArH), 7.71 (s, 2H, NH_2). HRMS-ESI. calcd for $C_{25}H_{17}ClBrN_5NaO$, M + Na$^+$: 540.0203, found: 540.0215.

Ethyl 6-amino-2-(3-chlorobenzoyl)-8-(2-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline-5,7,7(8H)-tricarbonitrile 4t. Mp. 235–237°C. IR (KBr)/ cm^{-1} 3326, 3192, 3069 2941, 2881, 2842, 2212, 1641, 1605, 1568, 1478, 1440, 1398, 1374, 1341, 1301, 1288, 1255, 1120, 1080, 1058, 1039, 813, 799, 774, 748, 707. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 2.67–2.70 (m, 1H, CH), 3.01–3.16 (m, 1H, CH), 3.77 (d, J = 19.6 Hz, 1H, CH), 3.96–4.14 (m, 2H, 2CH), 4.67 (d, J = 19.6 Hz, 1H, CH), 5.79 (s, 1H, CH), 7.32–7.52 (m, 7H, ArH), 7.65–7.70 (m, 3H, ArH + NH_2). HRMS-ESI. calcd for $C_{25}H_{18}Cl_2N_5O$, M + H$^+$: 474.0888, found: 474.0881.

General procedure for the syntheses of 2-ethyl 7-methyl 6-amino-5,7-dicyano-3,4,7,8-tetrahydro-8-arylisoquinoline-2,7(1*H*)-dicarboxylate derivatives 5. A dry 50 mL flask was charged with arylaldehyde (2.0 mmol), methyl cyanoacetate (0.198 g, 2.0 mmol), ethyl 4-(dicyanomethylene)piperidine-1-carboxylate (0.438 g, 2.0 mmol), and ionic liquid of [bmim$^+$][BF$_4^-$] (2 mL). The reaction mixture was stirred at 50°C for 11–15 h, and then cooled to room temperature. The generated yellow solid was filtered off, and the ionic liquid in filtrate was then recovered for reuse by evaporating at 80°C several hours at *vacuum*. The crude yellow products were washed with water and purified by recrystallization from DMF and water, followed by being dried at 50°C several hours at *vacuum* to give **5**.

2-Ethyl 7-methyl 6-amino-8-(2-chlorophenyl)-5,7-dicyano-3,4,7,8-tetrahydroisoquinoline-2,7(1H)-dicarboxylate 5a. Mp. 249–251°C. IR (KBr)/ cm^{-1} 3342, 3206, 2986, 2842, 2204, 1758, 1651, 1593, 1483, 1434, 1396, 1328, 1299, 1287, 1248, 1185, 1127, 1018, 926, 881, 816, 781, 749, 705. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.09–1.14 (m, 3H, CH$_3$), 2.31–2.37 (m, 1H, CH), 2.93–3.07 (m, 1H, CH), 3.61 (s, 3H, CH$_3$O), 3.73–3.77 (m, 2H, 2CH), 3.91–4.05 (m, 3H, CH$_2$O+CH), 4.26–4.3 (m, 1H, CH), 5.64 (s, 1H, CH), 7.26 (s, 2H, NH$_2$), 7.41–7.47 (m, 1H, ArH), 7.54–7.56 (m, 2H, ArH), 7.77–7.79 (m, 1H, ArH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 14.3, 33.8, 40.2, 41.4, 43.1, 53.2, 54.2, 60.9, 79.5, 115.4, 116.4, 128.5, 128.9, 129.8, 130.4, 130.8, 131.8, 133.1, 134.1, 148.9, 164.1, 197.2. 1HRMS-ESI. calcd for $C_{27}H_{21}ClN_4NaO_4$, M + Na$^+$: 463.1149, found: 463.1123.

2-Ethyl 7-methyl 6-amino-5,7-dicyano-3,4,7,8-tetrahydro-8-(2,3-dimethoxyphenyl)isoquinoline-2,7(1H)-dicarboxylate 5b. Mp. 260–263°c. IR (KBr)/ cm^{-1} 3347, 3203, 2982, 2957, 2935, 2838, 2204. 1758, 1650, 1595, 1481, 1434, 1397, 1335, 1249, 1189, 1168, 1128, 1096, 1065, 1009, 809, 777, 754. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.14 (b, 3H, CH$_3$), 2.32–2.42 (m, 1H, CH), 2.77–2.83 (m, 1H, CH), 3.60–3.72 (m, 8H, 2CH$_{3+}$2CH), 3.78–4.02 (m, 6H, CH$_3$O + 2CH$_2$O + CH), 4.72–4.38 (m, 1H, CH), 5.61 (s, 1H, CH),7.08–7.10 (m, 1H, ArH), 7.15 (s, 2H, NH$_2$), 7.16–7.20 (m, 2H, ArH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 14.4, 33.8, 40.2, 42.1, 43.4, 54.0, 54.1, 55.7, 60.5, 60.9, 79.5, 112.7, 113.0, 115.6, 116.5, 119.0, 124.0, 127.3, 130.7, 147.5, 149.5, 152.2, 164.4, 197.3. HRMS-ESI. calcd for $C_{24}H_{26}N_4NaO_6$, M + Na$^+$: 489.1750, found: 489.1747.

2-Ethyl 7-methyl 6-amino-8-(2,3-dichlorophenyl)-5,7-dicyano-3,4,7,8-tetrahydroisoquinoline-2,7(1H)-dicarboxylate 5c. Mp. 253–255°C. IR (KBr)/ cm^{-1} 3340, 3286, 3200, 2986, 2958, 2844, 2203, 1758, 1652, 1591, 1483, 1456, 1433, 1397, 1339, 1300, 1250, 1182, 1163, 1128, 1106, 1045, 1015, 887, 814, 785, 750, 722. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.07–1016 (m, 3H, CH$_3$), 2.34–2.41 (m, 1H, CH), 2.92–2.98 (m, 1H, CH), 3.48–3.75 (m, 5H, CH$_3$O+2CH), 3.71–4.00 (m, 3H, CH$_2$O+CH), 4.27–4.34 (m, H, CH$_3$), 5.65 (s, 1H, CH$_3$), 7.28 (s, 2H, NH$_2$),7.57–7.61 (m, 1H, ArH). 7.74–7.79 (m, 2H, ArH). HRMS-ESI. calcd for $C_{22}H_{20}Cl_2N_4NaO_4$, M + Na$^+$: 497.0759, found: 497.0727.

2-Ethyl 7-methyl 6-amino-8-(4-bromophenyl)-5,7-dicyano-3,4,7,8-tetrahydroisoquinoline-2,7(1H)-dicarboxylate 5d. Mp. 257–258°C. IR (KBr)/ cm^{-1} 3194, 2981, 1846, 2207, 1759, 1681, 1595, 1505, 1487, 1455, 1435, 1394, 1337, 1299, 1250, 1189, 1132, 1078, 1012, 889, 840, 771. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.15 (b, 3H, CH$_3$), 2.40–2.46 (m, 1H, CH), 2.87–2.92 (m, 1H, CH), 3.58 (s, 3H, CH$_3$O), 3.63–3.75 (m, 3H, 3CH), 4.00–4.05 (m, 2H, CH$_2$O), 4.29–4.38 (m, 1H, CH), 5.62 (s, 1H, CH), 6.98 (d, J = 8.0 Hz, 1H, ArH), 7.15 (s, 2H, NH$_2$), 7.53–7.59 (m, 2H, ArH), 7.76 (d, J = 8.0 Hz, 1H, ArH). HRMS-ESI. calcd for $C_{22}H_{21}BrN_4NaO_4$, M + Na$^+$: 507.0644, found: 507.0643.

2-Ethyl 7-methyl 6-amino-8-(3,4-dichlorophenyl)-5,7-dicyano-3,4,7,8-tetrahydroisoquinoline-2,7(1H)-dicarboxylate 5e. Mp. 270–271°C. IR (KBr)/ cm^{-1} 3350, 3205, 3025, 2994, 2853, 2205, 1759, 1651, 1598, 1487, 1470, 1455, 1435, 1401. 1298, 1250, 1186, 1133, 1033, 1014, 882, 818, 772. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.15–1.18 (m, 3H, CH$_3$), 2.50–2.54 (m, 1H, CH), 2.90–2.96 (m, 1H, CH), 3.44 (d, J = 12.8 Hz, 1H, CH), 3.60 (s, 3H, CH$_3$O), 3.62–3.78 (m, 1H, CH), 4.01–4.05 (m, 3H, CH$_2$O + CH), 4.29–4.39 (m, 1H, CH), 5.63 (s, 1H, CH$_3$), 7.04–7.35 (m, 3H, ArH+NH$_2$), 7.59–7.68 (m, 1H, ArH), 7.79–7.86 (m, 1H, ArH). HRMS-ESI. calcd for $C_{22}H_{20}Cl_2N_4NaO_4$, M + Na$^+$: 497.0759, found: 497.0760.

2-Ethyl 7-methyl 6-amino-8-(4-chlorophenyl)-5,7-dicyano-3,4,7,8-tetrahydroisoquinoline-2,7(1H)-dicarboxylate 5f. Mp. 250–252°C. IR (KBr)/ cm^{-1} 3352, 3207, 2980, 2850, 2206, 1759, 1656, 1597, 1489, 1468, 1437, 1397, 1339, 1300, 1249, 1188, 1130, 1096, 1048, 1016, 923, 883, 840, 814, 771, 751, 722. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.15 (b, 3H, CH$_3$), 2.39–2.47 (m, 1H, CH), 2.86–2.92 (m, 1H, CH), 3.64–3.76 (m, 6H, CH$_3$O+3CH), 3.99–4.05 (m, 2H, CH$_2$O), 4.26–4.41 (m, 1H, CH), 5.62 (s, 1H, CH), 7.05 (d, J = 8.0 Hz, 1H, CH), 7.16 (s, 2H, NH$_2$), 7.45 (d, J = 8.0 Hz, 1H, ArH), 7.62–7.64 (m, 2H, ArH). HRMS-ESI. calcd for $C_{22}H_{21}ClN_4NaO_4$, M + Na$^+$: 463.1149, found: 463.1129.

General procedure for the syntheses of diethyl-6-amino-5,7-dicyano-3,4,7,8-tetrahydro-8-arylisoquinoline-2,7(1*H*)-dicarboxylate derivatives 8. A dry 50 mL flask was charged with ethyl 2-cyano-3-arylacrylate (2.0 mmol), ethyl 4-(dicyanomethylene)piperidine-1-carboxylate (0.438 g, 2.0 mmol), and ionic liquid of [bmim$^+$][BF$_4^-$] (2 mL). The reaction mixture was stirred at 50°C for 6–10 h, and then cooled to room temperature. The generated yellow solid was filtered off, and the ionic liquid in filtrate was then recovered for reuse by evaporating at 80°C several h at *vacuum*. The crude yellow products were washed with water and purified by recrystallization from DMF and water, followed by being dried at 50°C several h at *vacuum* to give **8**.

Diethyl 6-amino-5,7-dicyano-3,4,7,8-tetrahydro-8-(2-nitrophenyl) isoquinoline-2,7(1H)-dicarboxylate 8a. Mp. 235–236°C. IR (KBr)/ cm^{-1} 3404, 3348, 3303, 3237, 2993, 2880, 2844, 2205, 1752, 1662, 1590, 1536, 1479, 1428, 1391, 1352, 1299, 1247, 1194, 1126, 1022, 973, 881, 863, 845, 821, 788, 773, 765, 718. ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 1.14–1.26 (m, 6H, 2CH$_3$), 2.75–2.79 (m, 1H, CH), 3.08–3.15 (m, 1H, CH), 3.72–4.06 (m, 7H, 2CH$_2$O+3CH), 4.46–4.51 (m, 1H, CH), 4.73 (s, 2H, ArH), 5.92 (s, 1H, CH), 7.54–7.57 (m, 1H, ArH), 7.74–7.81 (m, 2H, ArH), 8.06–8.08 (m, 1H, ArH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 12.8, 14.4, 34.3, 40.2, 41.4, 43.4, 54.1, 60.9, 64.0, 79.4, 114.8, 115.2, 116.2, 125.1, 127.4, 128.2, 128.7, 130.4, 133.5, 148.8, 150.8, 163.8, 198.3. HRMS-ESI. calcd for $C_{23}H_{23}N_5NaO_6$, M + Na$^+$: 488.1546, found: 488.1536.

Diethyl 6-amino-5,7-dicyano-3,4,7,8-tetrahydro-8-p-tolylisoquinoline-2,7(1H)-dicarboxylate 8b. Mp. 223–224°C. IR (KBr)/ cm^{-1} 3354, 3214, 3026, 2983, 2931, 2855, 2205, 1754, 1664, 1597, 1518, 1487, 1468, 1441, 1399, 1345, 1298, 1241, 1130, 1020, 885, 857, 817, 771, 748. ^1H NMR ($CDCl_3$, 400 MHz) δ_H 1.14–1.26 (m, 6H, $2CH_3$), 2.35–2.41 (m, 4H, $CH_{3+}CH$), 3.04–3.07 (m, 1H, CH), 3.27 (d, J = 12.8 Hz, 1H, CH), 3.71–3.76 (m, 1H, CH), 3.92–4.19 (m, 5H, $2CH_2O$ + CH), 4.43–4.54 (m, 1H, CH), 4.65 (s, 2H, NH_2), 5.87 (s, 1H, CH), 6.89–7.35 (m, 3H, ArH), 7.58–7.63 (m, 1H, ArH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 13.3, 14.4, 20.7, 32.8, 40.2, 42.7, 43.4, 54.8, 60.8, 63.3, 79.5, 112.0, 115.6, 116.4, 125.9, 129.0, 129.4, 131.1, 138.1, 149.1, 164.1, 196.7. HRMS-ESI. calcd for $C_{24}H_{26}N_4NaO_4$, M + Na^+: 457.1852, found: 457.1844.

Diethyl 6-amino-8-(2-chlorophenyl)-5,7-dicyano-3,4,7,8-tetrahydroisoquinoline-2,7(1H)-dicarboxylate 8c. Mp. 251–252°C. IR (KBr)/ cm^{-1} 3350, 3222, 3072, 2988, 2940, 2843, 2204, 1751, 1648, 1593, 1487, 1440, 1396, 1340, 1297, 1244, 1201, 1127, 1081, 1023, 883, 855, 816, 773, 751, 704. ^1H NMR ($CDCl_3$, 400 MHz) δ_H 1.06–1.24 (m, 6H, $2CH_3$), 2.43–2.47 (m, 1H, CH), 2.99–3.04 (m, 1H, CH), 3.74–3.86 (m, 2H, 2CH), 4.03–4.22 (m, 5H, $2CH_2O$+1CH), 4.43–4.54 (m, 1H, CH), 4.69 (s, 2H, NH_2), 5.90 (s, 1H, CH), 7.31–7.34 (m, 1H, ArH), 7.41–7.46 (m, 2H, ArH), 7.91 (d, J = 7.6 Hz, 1H, ArH). HRMS-ESI. calcd for $C_{23}H_{23}ClN_4NaO_4$, M + Na^+: 477.1306, found: 477.1288.

Diethyl 6-amino-8-(2,4-dichlorophenyl)-5,7-dicyano-3,4,7,8-tetrahydroisoquinoline-2,7(1H)-dicarboxylate 8d. Mp. 215–216°C. IR (KBr)/ cm^{-1} 3353, 3173, 3033, 2983, 2204, 1758, 1673, 1601,1560, 1482, 1437, 1391, 1338, 1296, 1237, 1112, 1046, 1023, 888, 875, 862, 832, 815, 768. ^1H NMR ($CDCl_3$, 400 MHz) δ_H 1.13–1.26 (m, 6H, $2CH_3$), 2.40–2.45 (m, 1H, CH), 2.96–3.00 (m, 1H, CH), 3.73–3.81 (m, 2H, 2CH), 3.98–4.25 (m, 5H, $2CH_2O$+CH), 4.44–4.56 (m, 1H, CH), 4.79 (s, 2H, NH_2), 5.89 (s, 1H, CH), 7.41–7.44 (m, 2H, ArH), 7.84 (d, J = 8.4 Hz, 1H, ArH). HRMS-ESI. calcd for $C_{23}H_{23}Cl_2N_4O_4$, M + H^+: 489.1096 found: 489.1077.

Diethyl 6-amino-5,7-dicyano-3,4,7,8-tetrahydro-8-(3,4-dimethylphenyl)isoquinoline-2,7(1H)-dicarboxylate 8e. Mp. 201–203°C. IR (KBr)/ cm^{-1} 3349, 3210, 2983, 2923, 2209, 1758, 1652, 1593, 1505, 1486, 1467, 1436, 1394, 1375, 1343, 1298, 1244, 1165, 1129, 1105, 1023, 881, 856, 831, 811, 771, 744. ^1H NMR (DMSO-d_6, 400 MHz) δ_H 0.93–0.97 (m, 3H, CH_3), 1.14–1.15 (m, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.34–2.44 (m, 1H, CH), 2.83–2.87 (m, 1H, CH), 3.14–3.20 (m, 1H, CH), 3.62–4.05 (m, 6H, $2CH_2O$+2CH), 4.28–4.40 (m, 1H, CH), 5.60 (s, 1H, CH), 6.72–6.77 (m, 1H, ArH), 7.09 (s, 2H, NH_2), 7.28–7.35 (m, 2H, ArH). HRMS-ESI. calcd for $C_{25}H_{28}N_4NaO_4$, M + Na^+: 471.2008, found: 471.1993.

Diethyl 6-amino-8-(3-chlorophenyl)-5,7-dicyano-3,4,7,8-tetrahydroisoquinoline-2,7(1H)-dicarboxylate 8f. Mp. 235–236°C. IR (KBr)/ cm^{-1} 3351, 3212, 2984, 2933, 2207, 1751, 1659, 1596, 1487, 1439, 1396, 1340, 1297, 1245, 1130, 1020, 890, 856, 809, 770, 710. ^1H NMR (DMSO-d_6, 400 MHz) δ_H 0.94–0.97 (m, 3H, CH_3), 1.15–1.23 (m, 3H, CH_3), 2.43–2.47 (m, 1H, CH), 2.86–2.92 (m, 1H, CH), 3.58–3.75 (m, 2H, 2CH), 3.99–4.09 (m, 5H, $2CH_2O$+CH), 4.28–4.40 (m, 1H, CH), 5.61 (s, 1H, CH), 7.03–7.12 (m, 3H, NH_2+ArH), 7.38–7.61 (m, 3H, ArH). HRMS-ESI. calcd for $C_{23}H_{23}ClN_4NaO_4$, M + Na^+: 477.1306, found: 477.1292.

Diethyl 6-amino-5,7-dicyano-3,4,7,8-tetrahydro-8-(4-methoxyphenyl)isoquinoline-2,7(1H)-dicarboxylate 8g. Mp. 185–186°C. IR (KBr)/ cm^{-1} 3354, 3214, 2982, 2934, 2839, 2205, 1752, 1655, 1518, 1487, 1468, 1441, 1398, 1345, 1241, 1183, 1129, 1035, 941, 884, 856, 842, 817, 771. ^1H NMR (DMSO-d_6, 400 MHz) δ_H 0.95–0.99 (m, 3H, CH_3), 1.15 (b, 3H, CH_3), 2.33–2.43 (m, 1H, CH), 2.81–2.92 (m, 1H, CH), 2.23 (d, J = 12.8 Hz, 1H, CH), 3.60–3.82 (m, 5H, CH_3O+2CH), 3.98–4.07 (m, 4H, $2CH_2O$), 4.32–4.38 (m, 1H, CH), 5.60 (m, 1H, CH), 6.88–7.10 (m, 4H, NH_2+ArH), 7.36–7.59 (m, 2H, ArH). HRMS-ESI. calcd for $C_{24}H_{26}N_4NaO_5$, M + Na^+: 473.1801, found: 473.1774.

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One-Pot Synthesis of Iimidazo[1,2-*c*]quinazoline-5(6*H*)-thione and Imidazo[1,2-*c*]quinazolin-5(6*H*)-one with the Aid of Tin(II) Chloride

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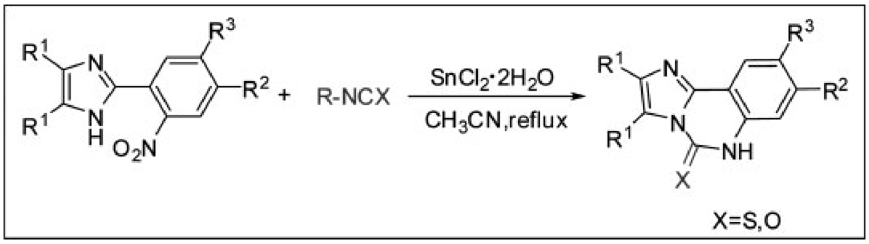

An efficient, convenient, one-pot synthesis of imidazo[1,2-*c*]quinazoline-5(6*H*)-thione and imidazo[1,2-*c*]quinazolin-5(6*H*)-one was accomplished in good yields via the novel reductive cyclization of 2-(2-nitrophenyl)-1*H*-imidazoles with isothiocyanates or isocyanates mediated by $SnCl_2{\cdot}2H_2O$ system.

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INTRODUCTION

A literature survey revealed that quinazolinones show antihypertonic, antirheumatic, antianaphylactic, antiasthmatic, tranquilizing, neurostimulating, and benzodiazepine binding activity [1,2]. For example, 3-substituted quinazolinones, such as SGB-1534 (**1**) [3] and ketanserin (**2**) have been found to have antihypertensive activities mediated via α-adrenoceptor and serotonic receptor anatgonism, respectively. Addition of a (2-methoxyphenyl)piperazine side chain at the 2- or 3-position of the angular tricyclic 2,3-dihydroimidazo[1,2-*c*]quinazoline ring system of SGB-1534 resulted in the formation of potent antihypertensive agents, such as 2-[[4-(2-methoxyphenyl)- piperazin-1-yl]methyl]-2,3-dihydroimidazo[1,2-*c*]-quinazolin-5(6*H*)-one (**3**) and 3-[[4-(2-methoxy phenyl)piperazin-1-yl]methyl]-2,3-dihydroimidazo[1,2-*c*]-quinazolin-5(6*H*)-one (**4**) that selectively antagonized the α_1-adrenoceptor [4]. (Fig. 1)

Imidazo[1,2-*c*]quinazolinone derivatives also are of considerable interest because of their biological and pharmacological activities, including antimicrobial, antihypertension, diuresis, and muscle relaxation [5,6].

The imidazo[1,2-*c*]quinazolinone ring system can generally be prepared by the reaction of α-aminoketones with 2-isocyanatobenzonitrile [7], α-aminocarboxylic esters with 2-isocyanatobenzonitrile [8], and 2-(2-nitrophenyl)-1*H*-imidazoles with triphosgene [9]. Chern et al. also have reported the synthesis of imidazo[1,2-*c*]quinazolinone derivatives based on cyclocondensations of NBS [10]. However, these methods suffer from some disadvantages, such as drastic conditions, unsatisfactory yields, long reaction time, high temperature, complex manipulation, and inaccessible starting materials. Therefore, we became interested in developing a convenient synthetic methods for the preparation of imidazo[1,2-*c*]quinazolinone derivatives.

In recent years, our interest has been focused on the usage of $SnCl_2$ reagent. We have previously reported the synthesis of 2-aryl-2*H*-indazoles [11], 1-hydroxy quinazolinones [12], respectively mediated by $SnCl_2$ reagent. As our earlier works goes, herein, we will describe a new approach to synthesize imidazo[1,2-*c*]quinazolinone derivatives by treating 2-(2-nitrophenyl)-1*H*-imidazoles with isothiocyanates or isocyanates mediated by $SnCl_2$ reagent.

RESULTS AND DISCUSSION

On the basis of our previous experience, we selected 2-(2-nitrophenyl)-4,5-diphenyl-1*H*-imidazole **1a** and the 4-methylphenyl isothiocyanate **2a** as model substrates to optimize the experimental conditions for the proposed reductive cyclization reaction (Scheme 1). The results are summarized in Table 1.

As shown in Table 1, we briefly examined the effect of different temperatures, different solvents and ratio of **1a**:$SnCl_2{\cdot}2H_2O$. The results showed that at reflux the reaction proceeded smoothly in high yield. To further

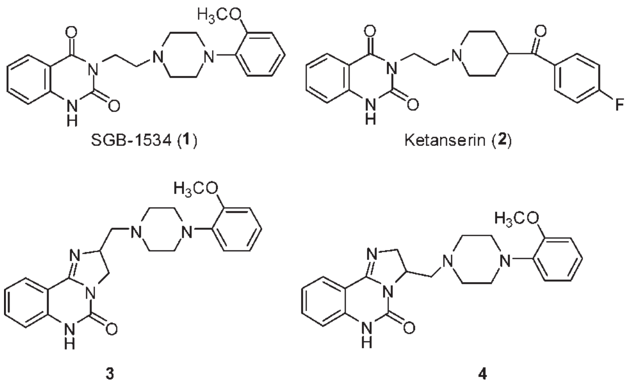


Figure 1. Some biologically active quinazolinones.

evaluate the influence of the ratio of **1a**:$SnCl_2 \cdot 2H_2O$, the reaction was carried out in acetonitrile using a 1:3–1:8 ratio of **1a**:$SnCl_2 \cdot 2H_2O$ (Table 1, entries 5, 6, 7, 8, 4, 9), leading to **3a** in 37%, 67%, 70%, 75%, 81%, and 82% yields, respectively. We concluded the best ratio of **1a**:$SnCl_2 \cdot 2H_2O$ was 1:7. Moreover, different organic solvents were further investigated as shown in Table 1; we concluded that acetonitrile was the best solvent for this reaction.

Having established an optimal condition for the protocol, we performed a more detailed examination of the substrates. Thus, the behavior of a variety of substrates, which include different 2-(2-nitrophenyl)-1*H*-imidazoles as well as different isothiocyanates or isocyanates was examined.

First of all, we performed the reaction of a variety of 2-(2-nitrophenyl)-1*H*-imidazoles **1** and isothiocyanates **2** via $SnCl_2 \cdot 2H_2O$ system (Scheme 2, Table 2).

As shown in Table 2, it can be seen that this protocol can be applied to isothiocyanates with either electron-withdrawing groups (such as halide groups) or electron-donating groups (such as alkyl groups) under the same conditions. Furthermore, it was particularly noteworthy that the effects of substituted 2-(2-nitrophenyl)-1*H*-imidazoles were also investigated. 4-fluorophenyl and 4-methoxyphenyl substitution can also give moderate to good yields.

A second part of the research was designed to synthesize imidazo[1,2-*c*]quinazolin-5(6*H*)-ones *via* the novel reductive cyclization of 2-(2-nitrophenyl)-1*H*-imidazoles with isocyanates under the same reaction conditions (Scheme 3, Table 3).

Table 1

Optimization for the reductive cyclization reaction.

Entry	Temperature (°C)	Solvent	Ratio[a]	Isolated yield (%)
1	rt	CH_3CN	1:7	0
2	40	CH_3CN	1:7	0
3	60	CH_3CN	1:7	60
4	Reflux	CH_3CN	1:7	81
5	Reflux	CH_3CN	1:3	37
6	Reflux	CH_3CN	1:4	67
7	Reflux	CH_3CN	1:5	70
8	Reflux	CH_3CN	1:6	75
9	Reflux	CH_3CN	1:8	82
10	Reflux	THF	1:7	42
11	Reflux	$CHCl_3$	1:7	0

[a] Ratio of **1** and $SnCl_2 \cdot 2H_2O$ system.

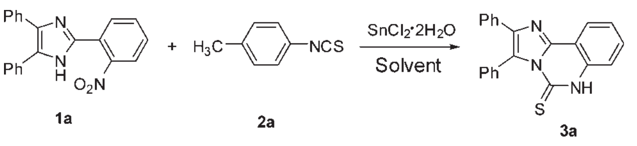
Similarly, aryl isocyanates containing electron-donating and electron-withdrawing substituents were reacted well with 2-(2-nitrophenyl)-1*H*-imidazoles, therefore, we can conclude that the electronic nature of the substituents has no significant effect on this reaction. Meanwhile, it was found that isocyanates showed better reactivity trends than isothiocyanates.

A plausible mechanistic pathway to products **3** and **5** is illustrated in Scheme 4, although the details are still unclear. In the initial step, 2-(2-nitrophenyl)-1*H*-imidazoles **1** are reduced by tin(II) chloride to **A**. The amine compounds **A** then reacted with isothiocyanates or isocyanates to give intermediate **B**. Intermediate **C** was formed by attack of the amino group onto the the central carbon atom of the urea or thiourea. Finally, products **3** and **5** were obtained by eliminating a amine molecule.

The structures of products **3** and **5** were confirmed by IR, ^{1}H NMR, and HRMS.

In summary, a series of imidazo[1,2-*c*]quinazoline-5(6*H*)-thiones and imidazo[1,2-*c*]quinazolin-5(6*H*)-ones were synthesized *via* $SnCl_2 \cdot 2H_2O$ induced reductive cyclization of isothiocyanates and isocyanates with 2-(2-nitrophenyl)-1*H*-imidazoles, respectively. The new method has advantages, such as easily accessible starting materials, convenient manipulation, and moderate to high yields.

Scheme 1



Scheme 2

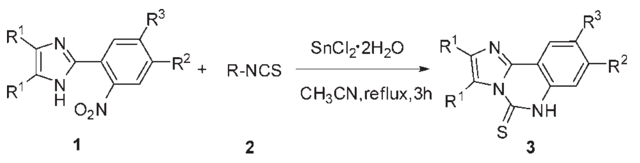


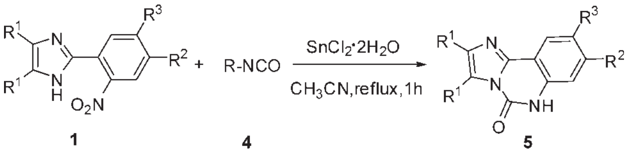
Table 2

Synthesis of imidazo[1,2-*c*]quinazoline-5(6*H*)-thiones.

Compound	R^1	R^2	R^3	R	Yield[a] (%)
3a	4-$CH_3OC_6H_4$	H	Cl	4-$CH_3C_6H_4$	78
3b	C_6H_5	H	Cl	C_6H_5	90
3c	C_6H_5	H	H	4-$CH_3C_6H_4$	81
3d	4-$CH_3C_6H_4$	H	H	4-$CH_3C_6H_4$	88
3e	4-FC_6H_4	H	H	4-ClC_6H_4	81
3f	4-$CH_3OC_6H_4$	H	H	3-$CH_3C_6H_4$	84

aIsolated yield.

Scheme 3



EXPERIMENTAL

Commercial solvents and reagents were used as received. Melting points were uncorrected. IR spectra were recorded on Varian F-1000 spectrometer in KBr with absorptions in cm^{-1}. ^{1}H NMR was determined on Varian-400 MHz spectrometer in DMSO-d_6 solution. *J* values are in Hz. Chemical shifts are expressed in ppm downfield from internal standard TMS. HRMS data were obtained using microma GCT-TOF instrument.

General procedure for synthesis of imidazo[1,2-*c*]quinazoline-5(6*H*)-thione 3. A solution of 2-(2-nitrophenyl)-1H-imidazoles (0.5 mmol), isothiocyanates (0.5 mmol), and $SnCl_2{\cdot}2H_2O$ (3.5 mmol) in CH_3CN (5 mL) was stirred at reflux for 3 h. After this period, the TLC analysis of the mixture showed the reaction to be completed. The mixture was quenched with 3% HCl (10 mL) and filtered to yield a crude product, which was purified *via* silica gel column chromatography using acetone/petroleum ether (1:9, v/v) as eluent to furnish pure products in 78–90% yield.

9-Chloro-2,3-bis(4-methoxyphenyl)imidazo[1,2-c] quinazoline-5(6H)-thione (3a). This compound was obtained as solid with mp 284–286°C; IR(KBr):ν: 3172, 3109, 3006, 2960, 1616, 1533, 1520, 1490, 1472, 1389, 1369, 1312, 1291, 1245, 1171, 1134, 1083, 1034, 984, 875, 840, 816, 743, 696 cm^{-1}. ^{1}H NMR (DMSO-d_6): 3.73(s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.85 (d, J = 8.4 Hz, 2H, ArH),6.97 (d, J = 7.6 Hz, 2H, ArH), 7.30 (d, J = 8.0 Hz, 2H, ArH), 7.46 (d, J = 8.4 Hz, 2H, ArH), 7.56 (d, J = 8.4 Hz, 1H, ArH), 7.67 (d, J = 8.8 Hz, 1H, ArH), 8.26 (s, 1H, ArH), 13.38 (s, 1H, NH).

HRMS [Found: *m*/*z* 447.0806 (M^+), calcd for $C_{24}H_{18}N_3O_2S^{35}Cl$: M, 447.0808].

9-Chloro-2,3-diphenylimidazo[1,2-c]quinazoline-5(6H)-thione (3b). This compound was obtained as solid with mp 284–287°C; IR (KBr) ν: 3156, 3081, 3001, 2938, 1601, 1526, 1473, 1443, 1367, 1303, 1265, 1172, 1136, 1088, 875, 819, 777, 759, 694 cm^{-1}. ^{1}H NMR (DMSO-d_6): 7.25–7.27 (m, 3H, ArH), 7.40–7.44 (m, 4H, ArH), 7.47–7.50 (m, 3H, ArH), 7.57 (d, J = 8.8 Hz, 1H, ArH), 7.69 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H, ArH), 8.28 (d, J = 2.0, 1H, ArH), 13.45 (s, 1H, NH).

HRMS [Found: *m*/*z* 387.0594 (M^+), calcd for $C_{22}H_{14}N_3S^{35}Cl$: M, 387.0597].

2,3-Diphenylimidazo[1,2-c]quinazoline-5(6H)-thione (3c). This compound was obtained as solid with mp 278–280°C (ref. 7; 283–288°C); IR (KBr) ν: 3160, 3093, 3012, 2957, 1626, 1530, 1481, 1443, 1398, 1375, 1324, 1287, 1174, 1132, 1065, 753, 695 cm^{-1}. ^{1}H NMR (DMSO-d_6): 7.25–7.26 (m, 3H, ArH), 7.40–7.43 (m, 5H, ArH), 7.48–7.49 (m, 3H, ArH), 7.58 (d, J = 8.0 Hz, 1H, ArH), 7.65 (t, J = 7.2 Hz, 1H, ArH), 8.35 (d, J = 7.6 Hz, 1H, ArH), 13.36 (s, 1H, NH).

HRMS [Found: *m*/*z* 353.0985 (M^+), calcd for $C_{22}H_{15}N_3S$: M, 353.0987].

2,3-Dip-tolylimidazo[1,2-c]quinazoline-5(6H)-thione (3d). This compound was obtained as solid with mp 281–282°C; IR (KBr) ν: 3169, 3102, 3018, 2959, 1653, 1635, 1559, 1530, 1490, 1477, 1395, 1374, 1322, 1283, 1172, 1131, 825, 751, 696 cm^{-1}. ^{1}H NMR (DMSO-d_6): 2.25 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 7.07 (d, J = 8.0 Hz, 2H, ArH), 7.19 (d, J = 7.6 Hz, 2H, ArH), 7.27 (d, J = 8.0 Hz, 2H, ArH), 7.38 (d, J = 8.0 Hz, 2H, ArH), 7.46 (t, J = 7.2 Hz, 1H, ArH), 7.56 (d, J =

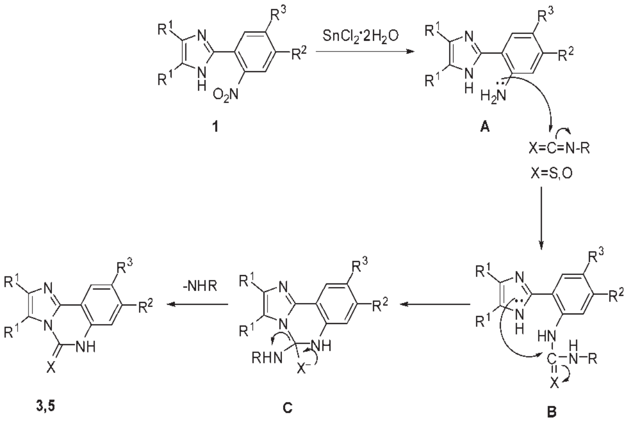
Table 3

Synthesis of imidazo[1,2-*c*]quinazolin-5(6*H*)-ones.

Compound	R^1	R^2	R^3	R	Yield[a] (%)
5a	C_6H_5	H	H	4-$CH_3C_6H_4$	89
5b	C_6H_5	H	H	4-ClC_6H_4	82
5c	4-$CH_3C_6H_4$	H	H	3-ClC_6H_4	73
5d	4-$CH_3OC_6H_4$	H	Cl	C_6H_{11}	85
5e	C_6H_5	3,4-OCH_2O		3-$CH_3C_6H_4$	85

aIsolated yield.

Scheme 4



8.0 Hz, 1H, ArH), 7.63 (t, *J* = 7.2 Hz, 1H, ArH), 8.33 (d, *J* = 8.0 Hz, 1H, ArH), 13.31 (s, 1H, NH).

HRMS [Found: *m*/*z* 381.1301 (M^+), calcd for $C_{24}H_{19}N_3S$: M, 381.1300].

2,3-Bis(4-fluorophenyl)imidazo[1,2-c]quinazoline-5(6H)-thione (3e). This compound was obtained as solid with mp 288–290°C; IR (KBr): ν: 3169, 3105, 3014, 2960, 1629, 1533, 1515, 1492, 1396, 1374, 1322, 1271, 1222, 1163, 1130, 844, 818, 782, 747, 698 cm^{-1}. ^1H NMR (DMSO-d_6): 7.15 (t, *J* = 8.8 Hz, 2H, ArH), 7.24 (t, *J* = 8.8 Hz, 2H, ArH), 7.45–7.53 (m, 5H, ArH), 7.58 (d, *J* = 8.4, 1H, ArH), 7.66 (t, *J* = 7.6 Hz, 1H, ArH), 8.34 (d, *J* = 8.0 Hz, 1H, ArH), 13.39 (s, 1H, NH).

HRMS [Found: *m*/*z* 389.0794 (M^+), calcd for $C_{22}H_{13}N_3F_2S$: M, 389.0798].

2,3-Bis(4-methoxyphenyl)imidazo[1,2-c]quinazoline-5(6H)-thione (3f). This compound was obtained as solid with mp 258–260°C; IR (KBr) ν: 3170, 3104, 3008, 2957, 2834, 1614, 1536, 1496, 1476, 1377, 1326, 1283, 1249, 1176, 1035, 834, 754, 697 cm^{-1}. ^1H NMR (DMSO-d_6): 3.73 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.85 (d, *J* = 8.8 Hz, 2H, ArH), 6.96 (d, *J* = 8.4 Hz, 2H, ArH), 7.30 (d, *J* = 8.0 Hz, 2H, ArH), 7.44–7.47 (m, 3H, ArH), 7.56 (d, *J* = 8.4 Hz, 1H, ArH), 7.63 (t, *J* = 7.6 Hz, 1H, ArH), 8.33 (d, *J* = 7.6 Hz, 1H, ArH), 13.28 (s, 1H, NH).

HRMS [Found: *m*/*z* 413.1196 (M^+), calcd for $C_{24}H_{19}N_3O_2S$: M, 413.1198].

General procedure for synthesis of imidazo[1,2-*c*]quinazolin-5(6*H*)-one 5. A solution of 2-(2-nitrophenyl)-1*H*-imidazoles (0.5 mmol), isocyanates (0.5 mmol), and $SnCl_2·2H_2O$ (3.5 mmol) in CH_3CN (5 mL) was stirred at reflux for 1 h. After this period, the TLC analysis of the mixture showed the reaction to be completed. The mixture was quenched with 3% HCl (10 mL) and filtered and the crude product was purified by recrystallization from 95% ethanol and DMF.

2,3-Diphenylimidazo[1,2-c]quinazolin-5(6H)-one (5a). This compound was obtained as solid with mp > 300°C (ref. 9; >300°C); IR (KBr): ν: 3215, 3164, 3103, 3053, 2926, 1706, 1597, 1555, 1481, 1443, 1379, 1336, 1216, 1109, 803, 780, 749, 696 cm^{-1}. ^1H NMR (DMSO-d_6): 7.21–7.26 (m, 4H, ArH), 7.30–7.35 (m, 2H, ArH), 7.42–7.44 (m, 6H, ArH), 7.54 (t, *J* = 7.2 Hz, 1H, ArH), 8.23 (d, *J* = 7.6 Hz, 1H, ArH), 11.72 (s, 1H, NH).

2,3-Diphenylimidazo[1,2-c]quinazolin-5(6H)-one (5b). This compound was obtained as solid with mp > 300°C (ref. 9; >300°C); IR (KBr): ν: 3215, 3164, 3103, 3053, 2926, 1706, 1597, 1555, 1481, 1443, 1379, 1336, 1263, 1216, 1110, 803, 780, 749, 696 cm^{-1}. ^1H NMR (DMSO-d_6): 7.19–7.25 (m, 3H, ArH), 7.29–7.35 (m, 2H, ArH), 7.41–7.44 (m, 7H, ArH), 7.53 (t, *J* = 7.2 Hz, 1H, ArH), 8.23 (t, *J* = 6.8 Hz, 1H, ArH), 11.71 (s, 1H, NH).

2,3-Dip-tolylimidazo[1,2-c]quinazolin-5(6H)-one (5c). This compound was obtained as solid with mp > 300°C (ref. 9; > 300°C); IR (KBr): ν: 3224, 3167, 2933, 2875, 1706, 1596, 1551, 1491, 1399, 1344, 1207, 961, 819, 745, 693 cm^{-1}. ^1H NMR (DMSO-d_6): 2.26 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 7.08 (d, *J* = 8.0 Hz, 2H, ArH), 7.23 (d, *J* = 8.4 Hz, 2H, ArH), 7.31 (d, *J* = 8.0 Hz, 2H, ArH), 7.33–7.37 (m, 4H, ArH), 7.55 (t, *J* = 7.6 Hz, 1H, ArH), 8.24 (d, *J* = 7.6 Hz, 1H, ArH), 11.71 (s, 1H, NH).

9-Chloro-2,3-bis(4-methoxyphenyl)imidazo[1,2-c] quinazolin-5(6H)-one (5d). This compound was obtained as solid with mp > 300°C (ref. 9; > 300°C); IR (KBr): ν: 3210, 3092, 2906, 2835, 1701, 1614, 1555, 1521, 1491, 1367, 1331, 1288, 1247, 1171, 1038, 829 cm^{-1}. ^1H NMR (DMSO-d_6): 3.73 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.85 (d, *J* = 8.8 Hz, 2H, ArH), 6.99 (d, *J* = 8.8 Hz, 2H, ArH), 7.35 (d, *J* = 8.8 Hz, 3H, ArH), 7.42 (d, *J* = 8.8 Hz, 2H, ArH), 7.58 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H, ArH), 8.16 (d, *J* = 2.4 Hz, 1H, ArH), 11.81 (s, 1H, NH).

2,3-Diphenyl-[1,3]dioxolo[4,5-g]imidazo[1,2-c] quinazolin-5(6H)-one (5e). This compound was obtained as solid with mp > 300°C; IR (KBr): ν: 3251, 3196, 3088, 3017, 2858, 1719, 1659, 1565, 1473, 1354, 1310, 1270, 1200, 1039, 936, 862, 801, 748, 706, 667 cm^{-1}. ^1H NMR (DMSO-d_6): 6.16 (s, 2H, OCH_2O), 6.87 (s, 1H, ArH), 7.22–7.27 (m, 3H, ArH), 7.43–7.45 (m, 7H, ArH), 7.62 (s, 1H, ArH), 11.62 (s, 1H, NH).

HRMS [Found: *m*/*z* 381.1124 (M^+), calcd for $C_{23}H_{15}N_3O_3$: M, 381.1113].

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Synthesis of Some Heterocyclic Imides and Azomethine Derivatives Under Solvent Free Condition and Their Anti-Inflammatory Activity Evaluation

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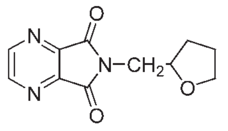

8e

31.0 % Anti-inflammatory activity at 50 mg/kg p.o.

Condensation of various mono amines with various diacids gave heterocyclic imide derivatives and condensation of amines with various aldehydes gave azomethine derivatives in good yields under solvent free condition. Structures assigned to imide and azomethine derivatives are fully supported by spectral data. All these compounds were screened for anti-inflammatory activity at a dose of 50 mg/kg p.o. Compound **8a** (6-((tetrahydrofuran-2-yl)methyl)-6H-pyrrolo[3,4]pyrazine-5,7-dione) exhibited anti-inflammatory activity comparable to standard drug phenyl butazone which showed 37% activity at 50 mg/kg p.o.

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INTRODUCTION

Increasing interest to synthesize small molecules as the structural building block is driving the development of new technologies under green chemistry research that can produce highly pure compounds at very high rate in very less time. Imides and azomethine derivatives are well known compounds as the productive component in various reactions [1]. Imides form structural part of various important natural and synthetic molecules such as fumaramidmycin [2], coniothyromycin [3], and SB-253514 [4], thalidomide [5], granulatimide [6], and isogranulatimide [7]. Wide range of biological activities, *i.e.*, anti-inflammatory [8], anticancer [9], and insecticidal [10] are shown by imide derivatives. Azomethine derivatives also possess anti-inflammatory [11], anticancer [12], antibacterial [13], and antimicrobial [14] activities.

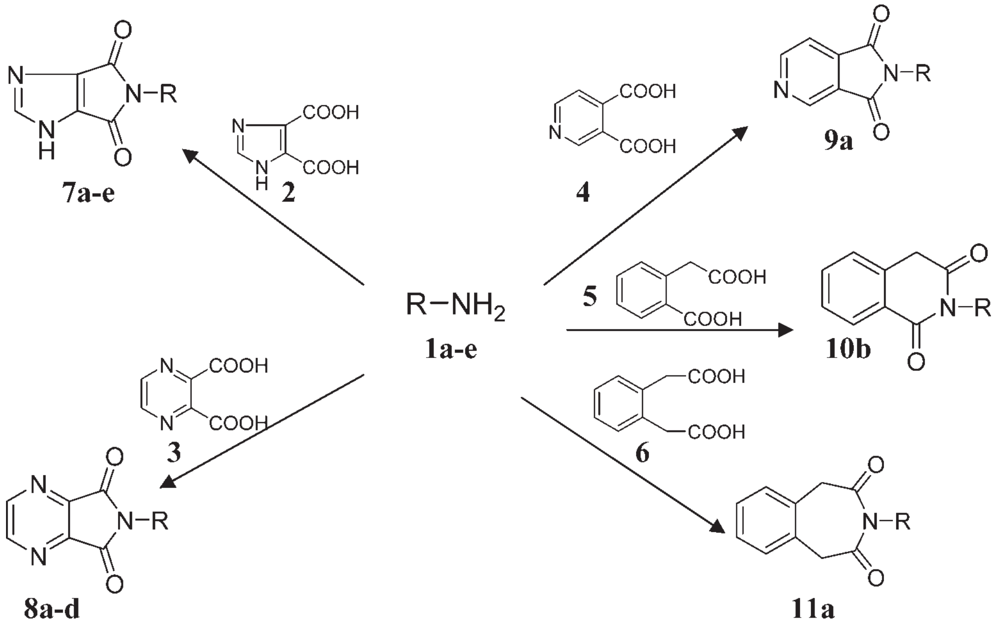
Microwave chemistry is relatively new technology that has been reported to significantly improve productivity in generation of complex target molecules. Some important features of microwave irradiation, *i.e.*, solvent free reactions, low waste, energy efficiency, high yield, and short reaction time make this technique an important tool for organic synthetic chemistry. Use of microwave chemistry and solvent free reaction conditions allow us to synthesize a large number of compounds in a very short period of time. With this hypothesis and in continuation of our work [15] in search of potent molecules exhibiting the anti-inflammatory activity, we have synthesized a number of heterocyclic imide and azomethine derivatives and screened them for anti-inflammatory activity, which we wish to report in this article.

RESULTS AND DISCUSSION

Chemistry. A number of heterocyclic imide derivatives **7a–e**, **8a–d**, **9a, 10b** and **11a** (Scheme 1) have been synthesized *via* the condensation of various amines (**1a–e**; Scheme 1) with various diacids (**2–6;** Scheme 1) under microwave irradiation conditions (power 600 Watt). Microwave irradiation of a mixture of tetrahydrofurfuryl amine (**1a**) and 4,5-imidazoledicarboxlic acid (1:1 molar ratio) at 600W for 4 min gave product **7a**. For compound **7a**, IR absorption band at 1728 cm^{-1} indicates the presence of —CO—N—CO— group. Spectral data of **7a** reported in experimental section fully support the structure assigned to it. Irradiation time and percentage yield of **7b–e**, **8a–d**, **9a**, **10b**, and **11a** synthesized by following above method is reported in Table 1.

A number of heterocyclic azomethine derivatives **15a–c** and **16a–c** have been synthesized *via* the condensation of **12**, **1c** and **1d** amines with aromatic aldehydes **13** and **14** by following reaction Scheme 2.

Scheme 1. Synthesis of heterocyclic imide derivatives.



Condensation of thiophen-2-ylmethanamine (**12**) with 2-hydroxy-1-naphthaldehyde (**13**) by irradiating at 600W for 1 min gave product **15a** in 99% yield.

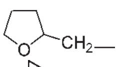
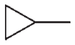
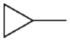
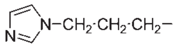
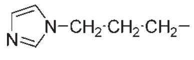
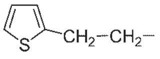
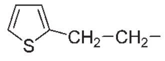
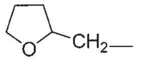
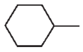
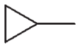
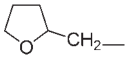
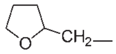
Spectral data of **15a** reported in experimental section of this article fully support the structure assigned to it. By following above method other azomethine derivatives, *i.e.*, **15b–c** and **16a–c** have been synthesized. Power level, Irradiation time and percentage yield of all the azomethine derivatives synthesized is reported in Table 2.

Conventional methods for the synthesis of imide derivatives involve refluxing of reactants in pyridine [16a], or toluene [16b], or use of PCl_3/CH_3CN [16c] etc. whereas synthesis of schiffs bases involve use of P_2O_5/Al_2O_3 [17a] as a catalyst, refluxing of reactants in toluene [17b] or ethanol [17c] or chloroform [17d] for long hours and still yields are not very good. Microwave irradiation technique [18] is reported to be an efficient way of energy transfer as compared to conventional heating and thus reduces reaction time which leads to a few side products and hence high yield of required products. In the synthesis of imide and azomethine, we used microwave irradiation technique and got desired products in high yields but in a very short period of reaction time.

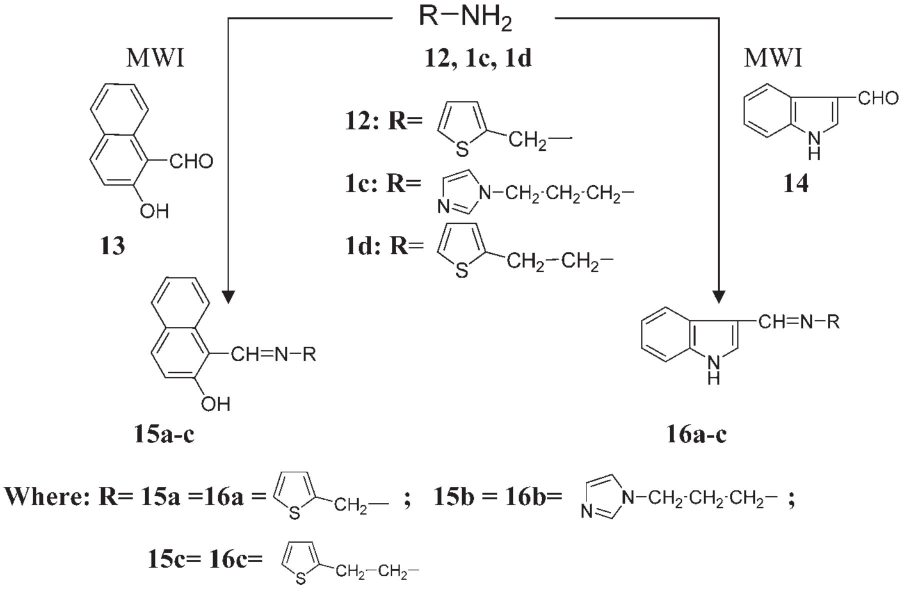
Crystal structure of compound 15a. To get the structure of compound **15a**, single crystal of compound **15a** was grown by slow evaporation of methanol solution. The quality of data for the crystal of **15a** was not very good but it was enough to predict the structure of

Table 1

Irradiation time, and percentage yield of compounds **7a–e**, **8a–d**, **9a**, **10b**, and **11a**.

Compds	R	Time (min)	% Yield	Compds	R	Time (min)	% Yield
7a		4	95	**8b**		2	90
7b		4	93	**8c**		3	86
7c		4	89	**8d**		3	85
7d		2	92	**9a**		2	98
7e		4	96	**10b**		2	96
8a		3	92	**11a**		1.5	95

Scheme 2. Synthesis of heterocyclic azomethine derivatives.



compound **15a** (Fig. 1). The crystal data of **15a** is summarized in Table 3. The crystal structure give rise to C=N bond distance of 1.301 A° which is comparable to reported value 1.282(3) A° [19].

Biological activity. Anti-inflammatory [20] activity evaluation of **7a–e**, **8a–d**, **9a, 10b**, **11a, 15a–c** and **16a–c** was carried out using carrageenan-induced paw oedema model and results are summarized in Table 4. Compound **8a** exhibited 31% (50 mg/kg p.o.) where as standard drug phenyl butazone exhibited 37% (50 mg/kg p.o.) anti-inflammatory activity. Anti inflammatory activity of **8a** is comparable to phenyl butazone.

CONCLUSION

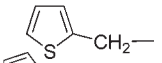
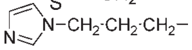
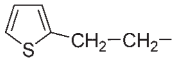
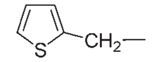
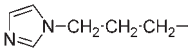
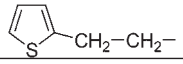
A number of heterocyclic- imide and azomethine derivatives have been synthesized in high yields in a very short time period using microwave irradiation technique. These imide and azomethine derivatives were screened for anti-inflammatory activity and compound **8a** exhibited good anti-inflammatory activity. Microwave technique is an important tool for synthetic organic chemistry.

EXPERIMENTAL

General. Microwave oven model M197DL (Samsung) was used for microwave irradiation. Compounds **7a**, **8d**, and **11a** were purified by crystallization from methanol/ ethyl acetate (8:2) whereas all other compounds reported in this article were purified by crystallization from methanol. Melting points (mp) were determined on a JSGW apparatus and are uncorrected. IR spectra were recorded using a Perkin Elmer 1600 FT spectrometer ^{1}H NMR spectra were recorded on a Bruker WH-500 spectrometer at a ca 5–15% (w/v) solution in DMSO-d_6 (TMS

Table 2

Power (Watt), irradiation time, and percentage yield of **15a–c** and **16a–c**.

Compd.	R	Watt	Time (min)	% yield
15a		600W	1.5	99
15b		600W	2	98
15c		600W	2	95
16a		450W	2	98
16b		450W	3	94
16c		450W	2	90

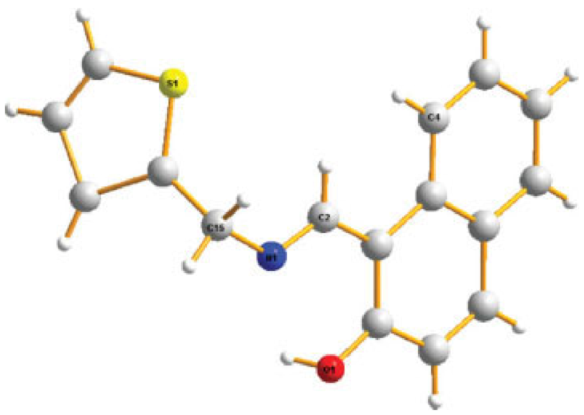


Figure 1. Crystal structure of **15a**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Table 3

Crystal data and X-ray experimental parameters for compound **15a**.

Formula	$C_{16}H_{13}NOS$	α(deg)	90.00
Colour	White	β(deg)	108.695(2)
Crystal system	*P21/c*	γ(deg)	90.00
Space group	Monoclinic	$V(A^{\circ 3})$	1293.60(7)
T(K)	273(2)	$\rho_{calcd}(g\ cm^{-3})$	2.506
a(A°)	9.8722(3)	$\mu(mm^{-1})$	1.198
b(A°)	9.8664(3)	R1[a]	0.1899
c(A°)	14.0206(4)	wR2[b]	0.5181
Z	26	GOF[c]	4.216

[a] $R1 = \Sigma|F_o| - |F_c|/\Sigma F_o|$.

[b] $wR2 = [\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]]^{1/2}$.

[c] $GOF = [\Sigma[w(F_o^2 - F_c^2)^2]/M\text{-}N)]^{1/2}$ (M = number of reflections, N = number of parameters refined).

as internal standard) FAB-MS was recorded on JEOL SX-120 (FAB) spectrometer. GC-MS was recorded on Perkin Elmer Clarus 500 gas chromatograph where built in MS detector was used. Elemental analysis was carried out on a Vario EL III elementor. Thin layer chromatography (TLC) was performed on silica gel G for TLC (Merck) and spots were visualized by iodine vapour or by irradiation with ultraviolet light (254 nm). The X-ray data collection and processing were performed on Bruker Kappa Apex-II CCD diffractometer by using graphite monochromated Mo-Kα radiation (λ = 0.71070 Å) at 100 K. Crystal structures were solved by direct methods. Structure solution, refinement and data output were carried out with the SHELXTL program [21,22]. All nonhydrogen atoms were refined anisotropically. Hydrogen atoms were placed in geometrically calculated positions and refined using a riding model. Images were created with the DIAMOND program [23].

Reaction procedure for synthesis of 7a. 4,5-Imidazoledicarboxlic acid (0.200 g, 1.28 mmol) and tetrahydrofurfuryl amine (0.20 mL, 1.98 mmol) were mixed together thoroughly in a petri dish to form a paste. This paste was subjected to microwave irradiation for 4 min at a power level of 600 Watt. Completion of reaction was checked by TLC. Crude reaction product was washed with ether. The product so obtained was further purified by crystallization from ethylacetate:methanol (8:2). Yield 210mg (95%) m.p. 212°C.

Similarly were prepared compounds **7a–e**, **8a–d**, **9a, 10b** and **11a**.

Physical constant and spectral data of heterocyclic imidie derivatives **7a–e**, **8a–d**, **9a, 10b**, **11a**.

5-((Tetrahydrofuran-2-yl)methyl)pyrrolo[3,4-d]imidazole-4,6(1H,5H)-dione (7a). Mp 212–214°C; IR (KBr) ν_{max}: 1728 (—CO—N—CO—), 1636, 1585, and 1462 (Ar) cm^{-1} ^1H NMR δ 1.20 (s, 1H, aliphatic), 1.66–1.69(d, 2H, aliphatic), 1.95–1.96 (d, 1H, aliphatic), 2.73–2.77 (t, 1H, aliphatic), 2.91–2.93 (d, 1H, aliphatic), 3.64–3.68 (q, 1H, aliphatic), 3.75–3.78 (t, 1H, CH_2), 3.98 (s, 1H, CH_2), 7.65 (s, 1H, imidazole), NH (not observed). **GC-MS** m/z 221 (M^+, 32%). Anal. Calcd. For $C_{10}H_{11}N_3O_3$ C, 54.29; H, 4.97; N, 19.00. Found C, 54.30; H, 4.93; N, 18.89.

5-Cyclopropylpyrrolo[3,4-d]imidazole-4,6(1H,5H)-dione (7b). Mp 235–236°C; IR (KBr) ν_{max}: 1709 (—CO—N—CO—), 1601, 1556, and 1489 (Ar) cm^{-1} ^1H NMR δ 0.66–0.71 (t, 4H, —CH_2—CH_2—), one H of cyclopropyl ring merged with DMSO-d_6 signal, 7.63(s, 1H, Ar), NH (not observed). **GC-MS** m/z 177 (M^+, 20%). Anal. Calcd. For $C_8H_7N_3O_2$ C, 54.23; H, 3.95; N, 23.72. Found C, 54.23; H, 3.93; N, 23.69.

5-(3-(1H-imidazol-1-yl)propyl)pyrrolo[3,4-d]imidazole-4,6(1H,5H)-dione (7c). Mp 220–221°C; IR (KBr) ν_{max}: 3399 (NH), 1670 (—CO—N—CO—), 1601 and 1556 (Ar) cm^{-1} ^1H NMR δ 1.94–1.99 (s, 2H, CH_2), 2.75 (s, 2H, CH_2), 4.07 (s, 2H, CH_2), 6.95 (s, 1H, Ar), 7.27 (s, 1H, Ar), 7.72 (s, 1H, Ar), 7.77 (s, 1H, Ar), 7.99 (bs, 1H, NH, exch.) **GC-MS** m/z 245 (M^+, 10%), Anal. Calcd. For $C_{11}H_{11}N_5O_2$ C, 53.87; H, 4.48; N, 28.57. Found C, 53.85; H, 4.46; N, 28.53.

5-(2-(Thiophen-2-yl)ethyl)pyrrolo[3,4-d]imidazole-4,6(1H,5H)-dione (7d). Mp 250–252°C; IR (KBr) ν_{max}: 1698 (—CO—N—CO—), 1584, 1504, and 1431 (Ar) cm^{-1} ^1H NMR δ 3.07–3.16 (s, 4H, 2 × CH_2), 6.97–6.99 (q, 2H, Ar), 7.41 (d, 1H, Ar), 7.56 (s, 1H, Ar), 7.84 (s, 1H, NH exch.). **GC-MS** Does not show M^+ ion peak but gave fragments at *m/z* 151($C_6H_5N_3O_2\rceil^{+\bullet}$, 9%), 150($C_6H_4N_3O_2^{\oplus}$, 7%), 137 ($C_5H_3N_3O_2\rceil^{+\bullet}$, 12%), 110 ($C_6H_6S\rceil^{+\bullet}$, 98%), 97 ($C_5H_5S^{\oplus}$, 100%). Anal. Calcd. For $C_{11}H_9N_3O_2S$ C, 53.44; H, 3.64; N, 17.00; S, 12.95. Found C, 53.40; H, 3.63; N, 17.00; S, 12.94.

5-Cyclohexylpyrrolo[3,4]imidazole-4,6-(1H,5H)-dione (7e). Mp 205–206°C; IR (KBr) ν_{max}: 1723 (—CO—N—CO—), 1589, and 1458 (Ar) cm^{-1} ^1H NMR δ 1.14–1.15 (m, 1H, aliphatic), 1.18–1.27 (m, 4H, aliphatic), 1.55–1.58 (m, 1H, aliphatic), 1.69 (s, 2H, aliphatic), 1.87 (s, 2H, aliphatic), 2.94 (s, 1H, aliphatic), 7.87 (s, 1H, Ar). **GC-MS** Does not show M^+ ion peak but gave fragmentation ions at *m/z* 191 ($C_{10}H_{13}N_3O\rceil^{+\bullet}$, 12%), 83 ($C_6H_{11}^{\oplus}$, 12%). Anal. Calcd. For $C_{11}H_{13}N_3O_2$ C, 60.27; H,5.93; N, 19.17. Found C, 60.25; H, 5.92; N, 19.15.

6-((Tetrahydrofuran-2-yl)methyl)-6H-pyrrolo[3,4]pyrazine-5,7-dione (8a). Mp 128–129°C; IR (KBr) ν_{max}: 1719 (—CO—N—CO—), 1585 and 1445 (Ar) cm^{-1} ^1H NMR δ 1.49–1.56 (m, 1H, aliphatic), 1.77–1.88 (m, 2H, aliphatic), 1.91–1.98 (m, 1H, aliphatic), 2.71–2.75 (q, 1H, aliphatic), 2.89–2.93 (dd, 1H, aliphatic), 3.64–3.68 (m, 1H, aliphatic), 3.74–3.79 (m, 1H, aliphatic), 3.95–4.00 (m, 1H, aliphatic), 8.73 (s, 2H, pyrazine). **GC-MS** m/z 233 (M^+, 20%). Anal. Calcd. For $C_{11}H_{11}N_3O_3$ C, 56.65; H, 4.72; N, 18.02. Found C, 56.64; H, 4.73; N, 18.00.

6-Cyclopropyl-6H-pyrrolo[3,4-b]pyrazine-5,7-dione (8b). Mp 195–196°C; IR (KBr) ν_{max}: 1718 (—CO—N—CO—), 1605 and

Table 4

Anti-inflammatory activity evaluation of compounds **7a–e**, **8a–d**, **9a**, **10b**, **1 1a**, **15a–c** and **16a–c** at 50 mg /kg p.o.

Compds	Anti-inflammatory activity (%)	Compds	Anti-inflammatory activity (%)
7a	25.4	**9a**	26.1
7b	1.4	**10b**	16.0
7c	15.5	**11a**	18.3
7d	24.2	**15a**	19.7
7e	26.8	**15b**	15.6
8a	**31.0**	**15c**	0.0
8b	16.9	**16a**	27.2
8c	29.6	**16b**	10.8
8d	14.1	**16c**	0.0
		***PB**	37

* PB denote for phenyl butzone.

1421 (Ar) cm^{-1} ^{1}H NMR δ 0.48–0.71 (m, 4H, —CH_2—CH_2—), one H of cyclopropyl ring merged with DMSO-d_6 signal, 8.73 (s, 2H, pyrazine). **GC-MS** m/z 189 (M$^+$, 13%). Anal. Calcd. For $C_9H_7N_3O_2$ C,57.14; H, 3.70; N, 22.22. Found C, 57.12; H, 3.71; N, 22.20.

6-(3-(1H-imidazole-1-yl)propyl)-6H-pyrrolo-[3,4-b]pyrazine-5,7-dione (8c). Mp 189–191°C; IR (KBr) ν_{max}: 1698 (—CO—N—CO—), 1627, 1586, and 1564 (Ar) cm^{-1} ^{1}H NMR δ 1.98 (bs, 2H, CH_2), 2.64 (bs, 2H, CH_2), 4.06 (bs, 2H, CH_2), 6.92 (s, 1H, imidazole), 7.19 (s, 1H, imidazole), 7.66 (s, 1H, imidazole), 8.71 (s, 2H, pyrazine). **GC-MS** m/z 257 (M$^+$, 13%), Anal. Calcd. For $C_{12}H_{11}N_5O_2$ C, 54.30; H, 3.02; N, 12.67; S, 9.65. Found C, 54.37; H, 3.02; N, 12.65; S, 9.88.

6-(2-(Thiophene-2yl)ethyl)-6H-pyrrolo[3,4-b]pyrazine-5,7-dione (8d). Mp 136–137°C; IR (KBr) ν_{max}: 1717 (—CO—N—CO—), 1635 and 1495 (Ar) cm^{-1} ^{1}H NMR δ 3.03–3.09 (m, 4H, 2 × CH_2), 6.95–6.98 (q, 2H, thiophene), 7.35–7.36 (m, 1H, thiophene), 8.71 (s, 2H, pyrazine). **GC-MS** m/z 259 (M$^+$, 12%). Anal. Calcd. For $C_{12}H_9N_3O_2S$ C, 55.59; H, 3.47; N, 16.21; S, 12.35. Found C, 55.59; H, 3.47; N, 16.21; S, 12.35.

2-((-Tetrahydrofuran-2-yl) methyl)-2H-pyrrolo[3,4-c]pyridine-1,3dione (9a). Mp 107–108°C; IR (KBr) ν_{max}: 1715 (—CO—N—CO—), 1593, 1489, and1400 (Ar) cm^{-1} ^{1}H NMR δ 1.51–1.55 (q, 1H, aliphatic), 1.80–1.87 (m, 2H, aliphatic), 1.94–1.99 (m, 1H, aliphatic), 2.72–2.76 (m, 1H, aliphatic), 2.90–2.93 (m, 1H, aliphatic), 3.66–3.70 (m, 1H, aliphatic), 3.95–4.00 (m, 2H, CH_2), 7.97–7.98 (d, 1H, py), 8.73–8.74 (d, 1H, py), 9.24 (s, 1H, py). **GC-MS** m/z 232 (M$^+$, 21%). Anal. Calcd. For $C_{12}H_{12}N_2O_3$ C, 62.06; H, 5.17; N, 12.06. Found C, 62.05; H, 5.17; N, 12.03.

2-Cyclopropylisoquinoline-1,3-(2H,4H)-dione (10b). Mp 40–41°C; IR (KBr) ν_{max}: 1715 (—CO—N—CO—), 1629 and 1590 (Ar) cm^{-1}. ^{1}H NMR δ 0.63–0.68 (m, 4H, CH_2—CH_2—), one H of cyclopropyl ring merged with DMSO-d_6 signal, 3.58 (s, 2H, CH_2), 7.17–7.19 (d, 1H, Ar), 7.23–7.26 (t, 1H, Ar), 7.30–7.33 (m, 1H, Ar), 7.63–7.65 (d, 1H, Ar). **GC-MS** m/z 201 (M$^+$, 35%). Anal. Calcd. For $C_{12}H_{11}NO_2$ C, 71.64; H, 5.47; N, 6.96. Found C, 71.62; H, 5.44; N, 6.96.

3-(Tetrahydrofran-2-yl)methyl)-1H-benzo[d]azepine-2,4(3H,5H)-dione (11a). Mp150–151°C; IR (KBr) ν_{max}: 1711 (—CO—N—CO—), 1634, 1582, and 1491 (Ar) cm^{-1}. ^{1}H NMR δ 1.51–1.56 (m, 1H, aliphatic), 1.81–1.86(m, 2H, aliphatic), 1.93–1.96 (q, 1H, aliphatic), 2.68–2.73 (q, 1H, aliphatic), 2.84–2.87 (dd, 1H, aliphatic), 2.30 (s, 4H, 2 × CH_2,) 3.76–3.80 (m, 2H, aliphatic), 3.94–3.97 (q, 1H, aliphatic), 7.14–7.19 (m, 4H, Ar). **GC-MS** m/z 259 (M$^+$, 2%), Anal. Calcd. For $C_{15}H_{17}NO_3$ C, 69.49; H, 6.56; N, 5.40. Found C, 69.47; H, 5.56; N, 5.38.

Reaction procedure for synthesis of 15a. 2-Hydroxy-1-naphthaldehyde (0.200 g, 1.16 mmol) and thiophen-2-ylmethanamine (0.20 mL, 1.76 mmol) were mixed together thoroughly in a petri dish to form a paste. This paste was subjected to microwave irradiation for 1.5 min at power level of 600 Watt.. Completion of reaction was checked by TLC. Crude reaction product was washed with chilled ethyl acetate. The product so obtained was further purified by crystallization from Methanol. Yield 265mg (99%) m.p. 135°C.

Similarly compounds **15a–c, 16a,b** and **16c** were prepared. Physical constants and spectral data is reported as below.

1-((Thiophen-2-ylmethylimino)methyl)naphthalen-2-ol (15a). Mp 135–137°C; IR (KBr) ν_{max}: 3439 (OH), 1628 (C=N), 1544 and 1493 (Ar) cm^{-1}. ^{1}H NMR δ 5.08 (s, 2H, CH_2), 6.78–6.79 (d, 1H, Ar), 7.05–7.07 (q, 1H, Ar), 7.17–7.18 (q, 1H, Ar), 7.23–7.26 (m, 1H, Ar), 7.46–7.49 (m, 1H, Ar), 7.52–7.53 (q, 1H, Ar), 7.68–7.69 (q, 1H, Ar), 7.773–7.792 (d, 1H, Ar), 8.12–8.13 (d, 1H, Ar), 9.33–9.35 (d, 1H, Ar), 14.34 (s, 1H, OH exch.). **GC-MS** m/z 267 (M$^+$, 58%), Anal. Calcd. For $C_{16}H_{13}NSO$ C, 71.91; H, 4.87; N, 5.24; S, 11.98. Found C, 71.89; H, 4.86; N, 5.24; S, 11.96.

1-((3-(1H-imidazol-1-yl)propylimino)methyl)naphthalen-2-ol (15b). Mp 95–96°C; IR (KBr) ν_{max}: 3428 (OH), 1631 (C=N), 1542, 1523, and 1445 (Ar) cm^{-1}. ^{1}H NMR δ 2.14–2.19 (m, 2H, CH_2), 3.60–3.64 (t, 2H, CH_2), 4.06–4.09 (t, 2H, CH_2), 6.75–6.77 (d, 1H, Ar), 6.93 (s, 1H, Ar), 7.19–7.25 (m, 2H, Ar), 7.42–7.45 (m, 1H, Ar), 7.64–7.69 (m, 2H, Ar), 7.74–7.76 (d, 1H, Ar), 8.07–8.09 (d, 1H, Ar), 9.10–9.12 (d, 1H, Ar), 14.21 (s, 1H, OH exch). **GC-MS** m/z 279 (M$^+$, 20%). Anal. Calcd. For $C_{17}H_{17}N_3O$ C, 73.11; H, 6.09; N, 15.05. Found C, 73.10; H, 6.02; N, 15.05.

1-((Thiophen-2-yl)ethylimino)methyl)naphthalen-2-ol (15c). Mp 115–116°C; IR (KBr) ν_{max}: 3442 (OH), 1638 (C=N), 1598 and 1543 (Ar) cm^{-1}. ^{1}H NMR δ 3.22–3.25 (t, 2H, CH_2), 3.90–3.92 (t, 2H, CH_2), 6.71–6.73 (d, 1H, Ar), 6.97–6.99 (q, 2H, Ar), 7.17–7.21 (m, 1H, Ar), 7.36–7.38 (dd, 1H, Ar), 7.40–7.43 (m, 1H, Ar), 7.62–7.64 (dd, 1H, Ar), 7.72–7.73 (d, 1H, Ar), 8.00–8.02 (d, 1H, Ar), 9.05–9.07 (d, 1H, Ar), 14.0 (s, 1H, OH exch.). **GC-MS** m/z 281 (M$^+$, 49%), Anal. Calcd. For $C_{17}H_{15}NSO$ C, 72.59; H, 5.33; N, 4.98; S, 11.38. Found C, 72.59; H, 5.34; N, 4.95; S, 11.39.

N-(1H-Indol-3-yl)methylene)(thiophen-2-yl)methanamine (16a). Semisolid; IR (KBr) ν_{max}: 3395 (NH), 1637 (C=N), 1578, 1533, and 1453 (Ar) cm^{-1}. ^{1}H NMR δ 4.89 (s, 2H, CH_2), 7.00–7.03 (m, 2H, Ar), 7.12–7.15 (m, 1H, Ar), 7.19–7.22 (m, 1H, Ar), 7.396–7.399 (dd, 1H, Ar), 7.41–7.47 (d, 1H, Ar), 7.83 (s, 1H, Ar), 8.29–8.30 (t, 1H, Ar), 8.58 (s, 1H, Ar), 11.60 (s, 1H, NH exch.). **GC-MS** m/z 240 (M$^+$, 100%). Anal. Calcd. For $C_{14}H_{12}N_2S$ C, 70.00; H, 5.00; N, 11.66; S, 13.33. Found C, 69.98; H, 5.00; N, 11.65; S, 13.30.

N-((1H-indol-3-yl)methylene)-3-(1H-imidazol-1-yl)propan-1-amine (16b). Semisolid; IR (KBr) ν_{max}: 3434 (NH), 1635 (C=N), 1601, 1512, and 1499 (Ar) cm^{-1}. ^{1}H NMR δ 2.04–2.09 (m, 2H, CH_2), 3.44–3.47 (t, 2H, CH_2), 4.08–4.11 (t, 2H, CH_2), 6.911–6.912 (d, 1H, CH), 7.05–7.13 (m, 1H, Ar), 7.17–7.19 (m, 1H, Ar), 7.23–7.24 (m, 1H, Ar), 7.42–7.43 (d, 1H, Ar), 7.65 (s, 1H, Ar), 7.77–7.79 (d, 1H, Ar), 8.21–8.29 (t, 1H, Ar), 8.44 (s, 1H, Ar), 11.54 (s, 1H, NH exch.). **GC-MS** m/z 252 (M$^+$, 39%). Anal. Calcd. For $C_{15}H_{16}N_4$ C, 71.43; H, 6.35; N, 22.22. Found C, 71.42; H, 6.34; N, 22.22.

N-(1H-Indol-3-yl)methylene)(thiophen-2-yl)ethanamine (16c). Mp 98–100°C; IR (KBr) ν_{max}: 3431(NH), 1627 (C=N), 1543 and 1443 (Ar) cm^{-1}. ^{1}H NMR δ 3.15–3.18 (t, 2H, CH_2), 3.75–3.77 (t, 2H, CH_2), 6.92–6.95 (m, 2H, Ar), 7.10–7.13 (m, 1H, Ar), 7.17–7.20 (m, 1H, Ar), 7.29–7.30 (m, 1H, Ar), 7.426–7.432 (d, 1H, Ar), 7.74–7.77 (d, 1H, Ar), 8.27–8.28 (d, 1H, Ar), 8.42–8.44 (d, 1H, Ar), 11.52 (s, 1H, NHexch.). **GC-MS** m/z 254 (M$^+$, 12%). Anal. Calcd. For $C_{15}H_{14}N_2S$ C, 70.86; H, 5.51; N, 11.02; S, 12.59. Found C, 70.85; H, 5.52; N, 11.00; S, 12.58.

Preparation of single crystal for X-ray analysis. All the crystallographic parameters are tabulated in Table 3 and selected bond distance is reported in Text. Crystals of compound **15a** were obtained from slow evaporation of methanol solution of compound **15a**. Compound **15a** crystallized in monoclinic space group *P21/c*.

Anti-inflammatory activity [20]. Paw oedema inhibition test was used on albino rats of Charles Foster by adopting the method of Winter et al [20]. Groups of five animals of both sexes (body weight 120–160 g), excluding pregnant females, were given a dose of test compound. Thirty minute later, 0.20 mL of 1% freshly prepared carrageenan suspension in 0.9% NaCl solution was injected subcutaneously into the planter aponeurosis of the hind paw and the volume was measured by a water plethysmometer apparatus and then measured again 1–3 h later. The mean increase of paw volume at each interval was compared with that of control group (five rats treated with carrageenan but not with test compound) at the same intervals and percent inhibition value calculated by the formula given below.

$$\%\ \text{anti-inflammatory activity} = [1 - D_t/D_c] \times 100$$

D_t and D_c are paw volumes of oedema in tested and control groups, respectively. Compounds **7a–e**, **8a–d**, **9a**, **10**b, **1 1a**, **15a–**c, and **16a–c** were screened for anti-inflammatory activity and results are summarized in Table 4.

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Synthesis and Antimicrobial Activity of New Tetrahydro-Naphthalene-Thiazolidinedione and Thiohydantoine Derivatives

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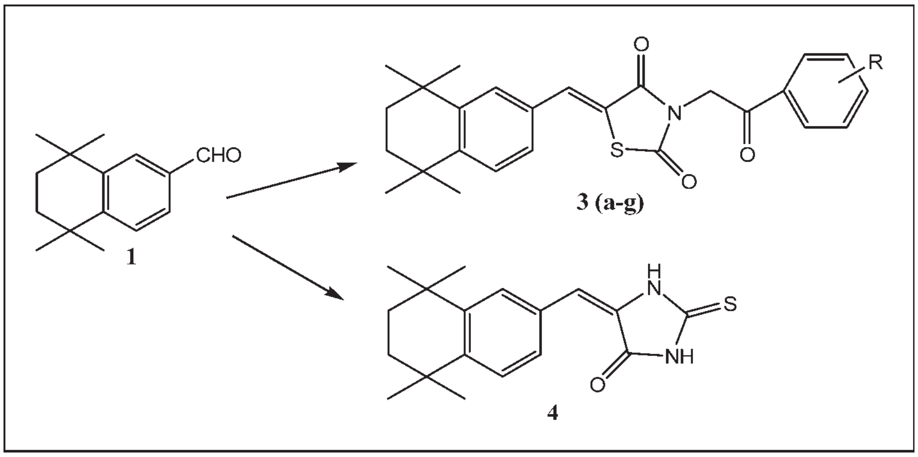

As part of an ongoing program aimed at recognizing novel antioxidant, antimicrobial, and anticancer molecules, herein we report the synthesis and biological evaluation of imidazolidin-4-one and thiazolidine-2,4-dione derivatives as antimicrobial agents. These compounds were prepared from 5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-carboxaldehyde and 3-substituted phenacyl-2,4-thiazolidinediones using Knoevenagel reaction. The structures of compounds were confirmed by ^{1}H NMR, mass spectral data, and elemental analyses. The molecules were evaluated for *in vitro* antimicrobial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) (standard), methicillin-resistant *Staphylococcus aureus* (isolated), *Staphylococcus aureus* (SA), *Escherichia coli* (EC), *Bacillus subtilis* (BS), and *Candida albicans* (CA). Compounds **3(a–g)** and compound **4** showed equal and/or greater antimicrobial activity against MRSA and EC than ampicillin and sultamicillin.

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INTRODUCTION

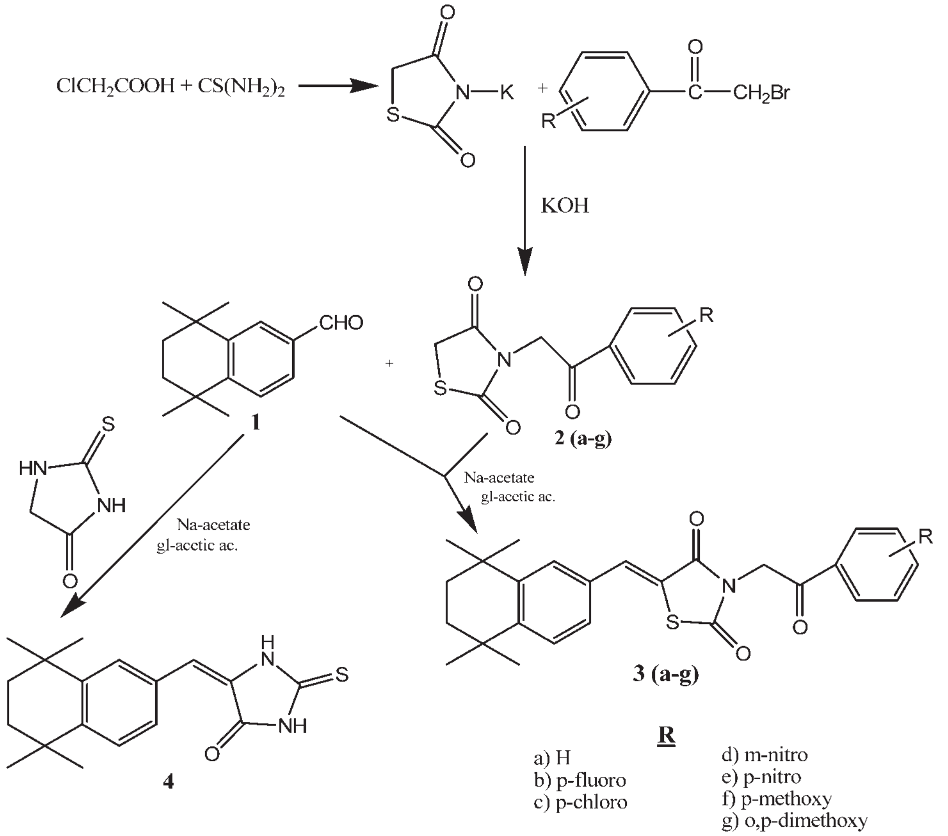
Previously, we reported that the synthesis and antimicrobial evaluation of tetrahydro-tetramethyl-naphthalene benzimidazoles, and tetrahydro-tetramethyl-naphthalene benzimidazole-amidines showed an activity comparable with that of fluconazole and sultamicillin against methicillin-resistant *Staphylococcus aureus*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Candida krusei*, and *Candida albicans* [1,2].

Recent investigations have used retinoids both in chemotherapeutic and chemopreventive modes either as single agents or in combination with other agents such as growth factors and biological response modifiers [3]. The presence of a thiazolidine ring in penicillins and related derivatives was the first recognition of its occurence in nature [4]. The thiazolidinone nucleus is present in many compounds that have antibacterial and antifungal activity [5–9] This started the detailed structure-activity studies on thiazoline-2,4-diones and analogues related to them [10].

To provide more effective therapeutic agents with the benefical effects of all *trans*-retinoic acid (ATRA) but with reduced side effects, we developed conformationally constrained retinoids consisting of tetrahydro-tetramethyl-naphthalene moiety, which is integrated with thiazolidinedion and hydantoin ring systems and studied on their biological activity in terms of antimicrobial prospect.

In this article, synthesis and antimicrobial activity of a new series of 3-[2-(2,3,4-substitue-phenyl)-2-oxo-ethyl]-5-[1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-meth-(*Z*)-ylidene]-thiazolidine-2,4-dione and 1-substitue-5-[1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-

Scheme 1. General synthesis of **3**(**a-g**) and **4**.



naphthalen-2-yl)-meth-(*E*)-ylidene]-2-thioxo-imidazolidine-4-one are described.

RESULTS AND DISCUSSION

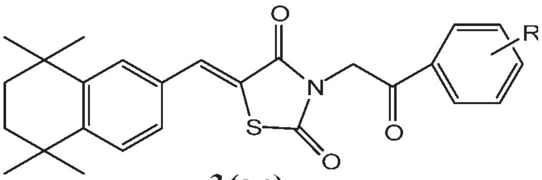
The synthetic procedure of the retinoidal thiazolidinedione derivatives is shown in Scheme 1. Because of the labile hydrogen atom at the 3-position, the thiazolidine-2,4-dione was *N*-alkylated with appropriate phenacyl halides in alkaline medium. The condensation of *N*-phenacylintermediates **2**(**a–g**) with retinoidal carboxaldehyde in glacial acetic acid and in the presence of sodium acetate by Knoevenagel reaction, led to 3-[2-(2,3,4-substitue-phenyl)-2-oxo-ethyl]-5-[1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-meth-(*Z*)-ylidene]-thiazolidine-2,4-dione derivatives **3**(**a–g**).

The appearance of pathogens resistant to known antibiotic therapy is becoming an important healthcare problem including the increase in the isolation and treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) strains [11]. Besides resistance to beta-lactam antibiotics, MRSA strains are also found to possess resistance to several antibiotics (macrolides, tetracyclines, and aminoglycosides) other than beta-lactams. Although MRSA are resistant to many drugs, most remain susceptible to the antibiotics vancomycin, teicoplanin (belongs to a group of antibiotics called glycopeptides), and linezolid [12,13]. Linezolid is a new antibiotic that is found active against MRSA and has good safety, tolerability even for newborns and children [14]. The chemical structure of linezolid is related to oxazolidine moiety, which is quite similar to those we have synthesized thiazolidinedione retinoids. The oxazolidinones, including linezolid and eperezolid, denote a unique class of synthetic antimicrobial agents with good activity against MRSA and vancomycin-resistant enterococci. Because of their unique mode of action, they do not display cross-resistance with other classes of antimicrobial agents [15].

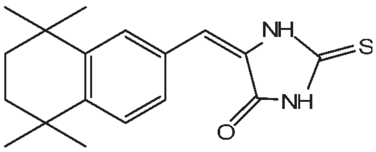
In our study, the prepared compounds [novel compounds **3**(**a–g**) and **4**] were screened *in vitro* against *Staphylococcus aureus* (ATCC 25923), methicillin-resistant *Staphylococcus aureus* (standard) (ATCC 43300), methicillin-resistant *Staphylococcus aureus* (isolated), *Escherichia coli* (ATCC 23556), *Bacillus subtilis* (ATCC 6633), and *Candida albicans* (ATCC10145) by dilution method and ciprofloxacin, ampicilline, sultamicillin, and fluconazole were used as standard drugs whose minimum inhibitory concentration (MIC) values

Table 1

The structures and *in vitro* antimicrobial activities of compounds **3a–g** and **4**.



3 (a-g)



4

Compounds	R	MRSA (Standard)	MRSA (Isolated)	*S. aureus*	*E. coli*	*B. subtilis*	*C. albicans*
3a	H	25	25	50	50	25	25
3b	*p*-fluoro	50	50	50	50	25	12.5
3c	*p*-chloro	50	50	50	50	50	6.25
3d	*m*-nitro	25	25	50	50	25	12.5
3e	*p*-nitro	25	25	50	25	50	6.25
3f	*p*-methoxy	25	25	25	25	50	25
3g	*o,p*-dimethoxy	50	50	50	25	50	3.125
4		50	50	50	25	3.125	6.25
Cipro		6.25	12.5	0.78	0.19		
Ampicillin		50	50	0.78	50	50	
Sultamicilin		50	50	1.56	25	0.78	
Fluconazole							1.56

MIC, minimum inhibitory concentration μg/mL.

are provided (Table 1). The results of the antimicrobial screening showed that the thiazolidinedione derivatives integrated to partial retinoic acid moiety exhibited varying degrees of moderate activity against bacteria comparable with ampicilline and sultamiclline on MRSA. Moreover, compounds **3c**, **3e**, **3g**, and **4** were active toward *C. albicans*. The MICs ranging between 3.125 and 25 μg/mL were reported for these compounds.

EXPERIMENTAL

Chemistry. Melting points were determined with a Buchi SMP-20 and Buchi 9100 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 MHz spectrometer in DMSO-d_6, chemical shifts are expressed as δ (ppm) values with tetramethylsilane (TMS) as an internal standard and coupling constants (J) are reported in Hertz (in NMR description, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad peak). The mass spectra were recorded with a Waters ZQ micromass LC-MS spectrometer by the method of ES$^+$ and elemental analyses were performed on LECO 932 CHNS instrument and were within ±0.5% of the theoretical values (analyses performed at Scientific and Technical Research Council of Turkey, Instrumental Analysis Center, Ankara, Turkey). Analytical thin-layer chromatography (TLC) was run on Merck silica gel plates (Kieselgel 60F-254). Column chromatographies were accomplished on silica gel 60 (40-63 μm particle size) (Merck). All starting materials and reagents were high-grade commercial products purchased from Aldrich, Merck or Fluka. Compound **2a**, **2c**, **2e** [16], **2b** [17], **2d** [18], **2f–g** [19], and retinoidal-carboxaldehyde **1** [20] were prepared according to the literature.

General synthesis of compounds 3a-g and 4. 3-(Substituted phenacyl)-2,4-thiazolidinedione 2a–g or thiohydantoine (1 mmol) and CH_3COONa (0.25 g) were added to a solution of retinoidal carboxaldehyde 1 (1.2 mmol) in glacial CH_3COOH (3 mL). The reaction mixture was heated to 140–150°C for a period of 4-6 h. The resulting precipitate was filtered, washed with H_2O, and then with acetone. The residue was purified by column chromatography silica gel 60 (230–400 mesh ASTM) using *n*-hexane: $CHCl_3$ (2:1) mL or *n*-hexane: EtOAc (3:1) mL as eluant [18].

3-[2-(Phenyl)-2-oxo-ethyl]-5-[1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-meth-(Z)-ylidene]-thiazolidine-2,4-dione (3a). Yield: 42%, mp: 197°C, ^{1}H NMR (DMSO): 1.5 (d,12 H, J = 9.2), 1.65 (s, 4H), 5.34 (s, 2 H, CH_2), 7.4 (dd, 1H, J = 6.8, J = 1.6), 7.52 (d, 1H, J = 8), 7.6 (t, 1H), 7.65 (d, 1H, J = 1.6), 7.74 (t, 1H), 7.98 (s, 1H, =CH) 8.09 (d, 2H, J = 6.8). MS (ESI+) *m/z*: 434 (M+1, 100) Anal. for $C_{26}H_{27}NO_3S$ Calcd. C: 72.03 H: 6.28 N: 3.23 S: 7.40 found C: 71.87 H: 6.24 N: 3.26 S: 7.39.

3-[2-(4-Flouro-phenyl)-2-oxo-ethyl]-5-[1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-meth-(Z)-ylidene]-thiazolidine-2,4-dione (3b). Yield: 44%, mp: 199°C, ^{1}H NMR (DMSO): 1.3 (d, 12 H, J = 9.2), 1.67 (s, 4H), 5.35 (s, 2 H, CH_2), 7.39–7.56 (m, 4H), 7.67 (d, 1H, J = 1.6), 7.99 (s, 1H, =CH), 8.19 (m, 2H). MS (ESI+) *m/z*: 452 (M+1, 100) Anal. for $C_{26}H_{26}FNO_3S.0.2\ H_2O$ Calcd. C: 68.60 H: 5.84 N: 3.07 S: 7.05 found C: 68.39 H: 5.68 N: 3.10 S: 6.98.

3-[2-(4-Chloro-phenyl)-2-oxo-ethyl]-5-[1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-meth-(Z)-ylidene]-thiazolidine-2,4-dione (3c). Yield: 45%, mp: 195°C, ^{1}H NMR (DMSO): 1.3 (d, 12 H, J = 8.8), 1.65 (s, 4H), 5.35 (s, 2 H, CH$_2$), 7.42 (dd, 1H, J = 6.8, J = 2), 7.54 (d, 1H, J = 8.8), 7.68 (m, 3H), 7.99 (s, 1H, =CH) 8.12 (d, 2H, J = 8.4). MS (ESI+) *m*/*z*: 468 (M+1, 75) Anal. for $C_{26}H_{26}ClNO_3S.0.1\ CHCl_3 0.2\ H_2O$ Calcd. C: 64.90 H: 5.53 N: 2.90 S: 6.62 found C: 64.80 H: 5.08 N: 2.90 S: 6.12.

3-[2-(3-Nitro-phenyl)-2-oxo-ethyl]-5-[1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-meth-(Z)-ylidene]-thiazolidine-2,4-dione (3d). Yield: 38%, mp: 139°C, ^{1}H NMR (DMSO): 1.28 (d, 12 H, J = 9.2), 1.67 (s, 4H), 5.48 (s, 2 H, CH$_2$), 7.42 (dd, 1H, J = 6.8, J = 1.6), 7.54 (d, 1H, J = 8.4), 7.67 (d, 1H, J = 1.2), 7.92 (t, 1H), 8.01 (s, 1H, =CH) 8.57 (m, 2H), 8.78 (s, 1H). MS (ESI+) *m*/*z*: 479 (M+1, 100) Anal. for $C_{26}H_{26}N_2O_5S.0.1\ C_6H_6$ Calcd. C: 65.69 H: 5.51 N: 5.75 S: 6.59 found C: 66.05 H: 5.14 N: 5.75 S: 6.23.

3-[2-(4-Nitro-phenyl)-2-oxo-ethyl]-5-[1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-meth-(Z)-ylidene]-thiazolidine-2,4-dione (3e). Yield: 42%, mp: 181°C, ^{1}H NMR (DMSO): 1.28 (d, 12 H, J = 9.2), 1.67 (s, 4H), 5.35 (s, 2 H, CH$_2$), 7.42 (d,1H, J = 8.4), 7.54 (d, 1H, J = 8.4), 7.67 (s, 1H), 8.01 (s, 1H, =CH), 8.31–8.44 (m, 4H). MS (ESI+) *m*/*z*: 479 (M+1, 100) Anal. for $C_{26}H_{26}N_2O_5S.0.1\ C_6H_6$ Calcd. C: 65.25 H: 5.48 N: 5.85 S: 6.70 found C: 65.31 H: 5.44 N: 5.83 S: 6.61.

3-[2-(4-Dimethoxy-phenyl)-2-oxo-ethyl]-5-[1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-meth-(Z)-ylidene]-thiazolidine-2,4-dione (3f). Yield: 47%, mp: 146°C, ^{1}H NMR (DMSO): 1.28 (d, 12 H, J = 8.8), 1,67 (s, 4H), 3,88 (s, 3H), 5.26 (s, 2 H, CH$_2$), 7.12 (d, 2H, J = 8.8), 7.41 (dd, 1H, J = 6.4, J = 2), 7.53 (d, 1H, J = 8.4), 7.66 (d, 1H, J = 2), 7.99 (s, 1H, =CH) 8.07 (d, 2H, J = 8.8). MS (ESI+) *m*/*z*: 464 (M+1, 100) Anal. for $C_{27}H_{29}NO_4S$ Calcd. C: 69.95 H: 6.31 N: 3.02 S: 6.92 found C: 69.79 H: 6.25 N: 3.09 S: 6.90.

3-[2-(2,5-Dimethoxy-phenyl)-2-oxo-ethyl]-5-[1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-meth-(Z)-ylidene]-thiazolidine-2,4-dione (3g). Yield: 43%, mp: 151°C, ^{1}H NMR (DMSO): 1.46 (d, 12 H, J = 9.2), 1,53 (s, 4H), 3,55 (s, 3H), 3,59 (s, 3H),5.1 (s, 2 H, CH$_2$), 7.27 (m, 3H), 7.42 (d, 1H, J = 8.4), 7.54 (d, 1H, J = 8.4), 7.66 (d, 1H, J = 1.6), 7.98 (s, 1H, =CH). ^{13}C NMR (DMSO) δ 191.46, 167.80, 165.97, 154.84, 153.80, 148.71, 146.31, 134.85, 130.93, 129.95, 128.34, 127.58, 124.35, 122.96, 120.28, 115.18, 113.98, 57.18, 56.29, 52.16, 34.97, 34.94, 34.70, 32.15, 31.92. MS (ESI+) *m*/*z*: 494 (M+1, 50) Anal. for $C_{28}H_{31}NO_5S$ Calcd. C: 68.13 H: 6.33 N: 2.84 S: 6.50 found C: 67.80 H: 5.89 N: 2.85 S: 6.37.

5-[1-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-methl-(E/Z)-ylidene]-2-thioxo-imidazolidine-4-one (4). Yield: 32%, mp: 207°C, ^{1}H NMR (DMSO): 1.26 (d, 12 H, J = 13.2), 1,64 (s, 4H), 6.47 (s, 1H, =CH), 7.37–7.6 (m, 3H, Ar—H), 12.14 (s, 1H), 12.36 (s, 1H). MS (ESI+) *m*/*z*: 315 (M+1, 100) Anal. for $C_{18}H_{21}N_2OS.0.1\ CHCl_3$ Calcd. C: 66.84 H: 6.54 N: 8.61 S: 9.83 found C: 66.77 H: 6.56 N: 8.46 S: 9.51. According to the literatures, the thiazolidinedione compounds usually possess the *Z* configuration [21–23]. On the other hand, 5-arylidene-4-thio-imidazolidine-2-ones are theoretically able to exist both in the *Z* and *E* configurations. To explain configurations of our thio-imidazolidine compound. The NOESY and ROESY spectra of the compound 4 showed the compound is a mixture of *E* (more in amount) and *Z* configurations.

Microbiology. Determination of the minimal inhibitory concentrations (MIC) of the compounds by dilution method.

Sample preparation. Each of the test compounds and standards (ampicillin, floconazole, cipro, and sultamicilin) were dissolved in 12.5% DMSO, at concentrations of 200 μg/mL. Further dilutions of the compounds and standards in the test medium were prepared at the required quantities of 100, 50, 25, 12.5, 6.25, 3.125, 1.56, and 0.78 μg/mL.

Culture of microorganims. All the compounds were tested for their *in vitro* growth inhibitory activity against different bacteria and the yeasts *Candida albicans*. The bacterial strains and *Candida albicans* used in this study were obtained from the culture collection of Refik Saydam Health Institution of Health Ministry, Ankara, and maintained at the Microbiology Department of Faculty of Pharmacy of Ankara University. The bacterial strains were maintained on MHA (Mueller-Hinton Agar) medium for 24 h at 37°C and fungi were maintained on SDA (Sabouraud Dextrose Agar) for 2–5 days at 25°C ± 1°C. The bacteria and fungi inocula were prepared by suspension in 9 mL of sterile water for colonies from culture on MHA and SDA medium.

Assay for in vitro antimicrobial activity. The *in vitro* antimicrobial activity of compounds was tested by the tube dilution technique [24,25]. The tube dilution technique was followed to determine the MIC of all the synthesized compounds. MHB (Mueller-Hinton Broth) was used for bacteria, and SDB (Sabouraud Dextrose Broth) was used for *Candida spp*. The cell density of each inoculum was adjusted in sterile water of a 0.5 Mc Farland standard. A final concentration of $\sim 10^5$ CFU/mL and 10^4 CFU/ mL for the bacteria and fungi, respectively. Microbial inocula were added to the twofold diluted samples. After incubation for bacteria 18–24 h at 37°C ± 1°C and for fungi 2–5 days 25°C ± 1°C, the last tube with no growth of microorganism was recorded to represent MIC expressed in μg/mL.

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A Novel Synthesis of Some 1,4-Phenylene-bis-heterocyclic Carboxamide Derivatives

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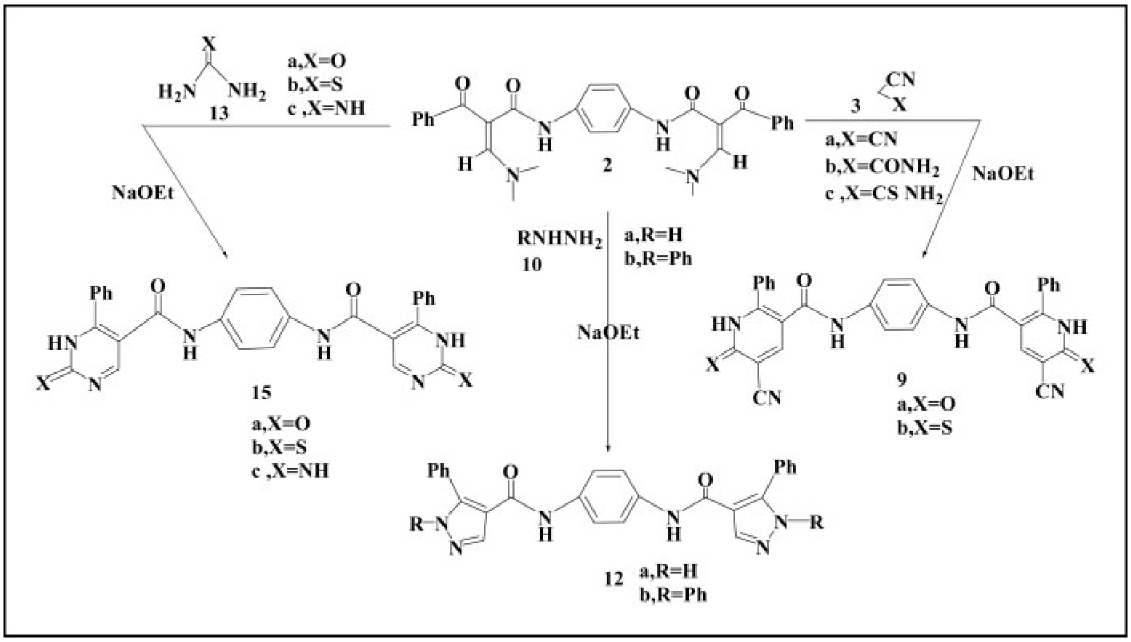

N,N′-(1,4-phenylene)bis(3-oxo-3-phenylpropanamide) **1** reacts with DMFDMA in refluxing toluene to afford *N,N′*-(1,4-phenylene)bis(2-benzoyl-3-(dimethylamino)acrylamide) **2**. Compound **2** reacts with a twofold excess of the active methylene reagents **3a-c** to afford the pent-2-enediamide derivatives **7** and **8a,b**, respectively. Compounds **7** and **8a** could be cyclized to afford the same compound *N,N′*-(1,4-phenylene)bis(5-cyano-6-oxo-2-phenyl-1,6-dihydropyridine-3-carboxamide) **9a** while **8b** was cyclized to afford the 6-thioxo analogue **9b**. Compound **2** reacts with hydrazine derivatives **10a,b** in refluxing ethanol/piperidine to afford the hydrazinylacrylamide derivatives **11a,b**, which have been cyclized to the corresponding *N,N′*-(1,4-phenylene)bis(1*H*-pyrazole-4-carboxamide) derivatives **12a,b**, respectively. Compound **2** reacts also with urea derivatives **13a-c** in refluxing ethanol/piperidine to afford the *N,N′*-(1,4-phenylene)bis(2-benzoyl-3-substituted-acrylamide) derivatives **14a-c**, which could be cyclized into *N,N′*-(1,4-phenylene)bis(6-phenyl-1,2-dihydropyrimidine-5-carboxamide)-2-oxo; 2-thioxo or 2-imino derivatives **15a-c**, respectively.

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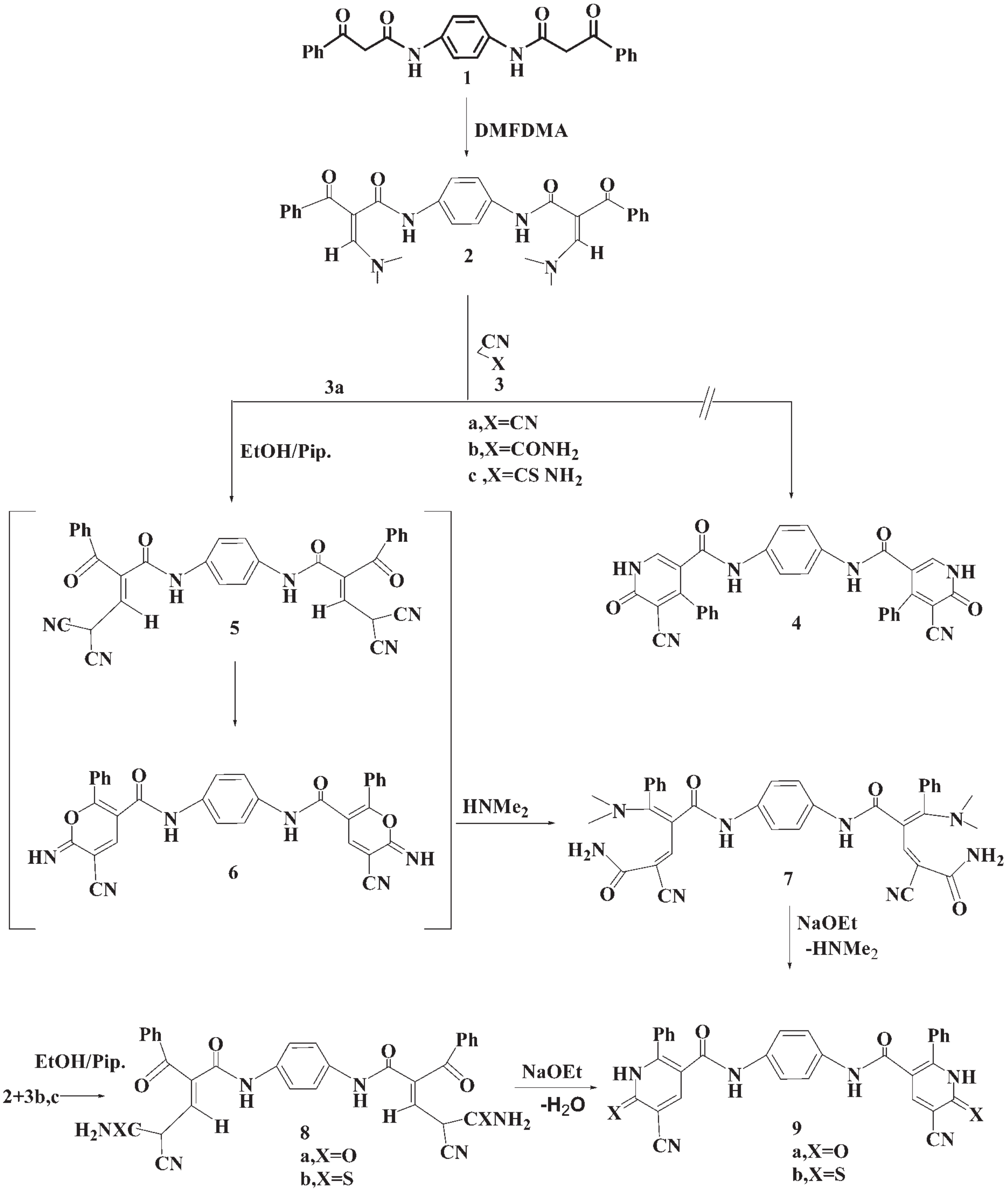
INTRODUCTION

Pyridines and pyridones represent an important class of organic compounds due to their pharmaceutical applications [2–4]. Furthermore functionalized pyrazoles have received much attention due to their diverse biological activities as immunosuppressant agents, selective COX-2 inhibitors, and antitumor agents [5]. Pyrimidine derivatives also exhibit HMG-CoA reductase inhibitory effect and antitumor activity [6]. The majority of attention has been so far paid to the development of syntheses of only one functionally substituted unit of these nuclei [7,8]. To our knowledge there is only one report describing the synthesis of compounds containing two 4*H*-benzopyran units [9], but those containing two pyridone units, two pyrazole units or two pyrimidine units, are hitherto not investigated. The reaction of enaminones with active methylene reagents [10], amines [11], or hydrazines [12] represents one of the strategies for the preparation of 2-1*H*-pyridones, pyrroles, and pyridazines, respectively. In the last two decades, we have been involved in a program aiming at the synthesis of functionally substituted heterocyclic compounds from

Scheme 1. Preparation of compounds **2**, **7**, **8**, and **9**.

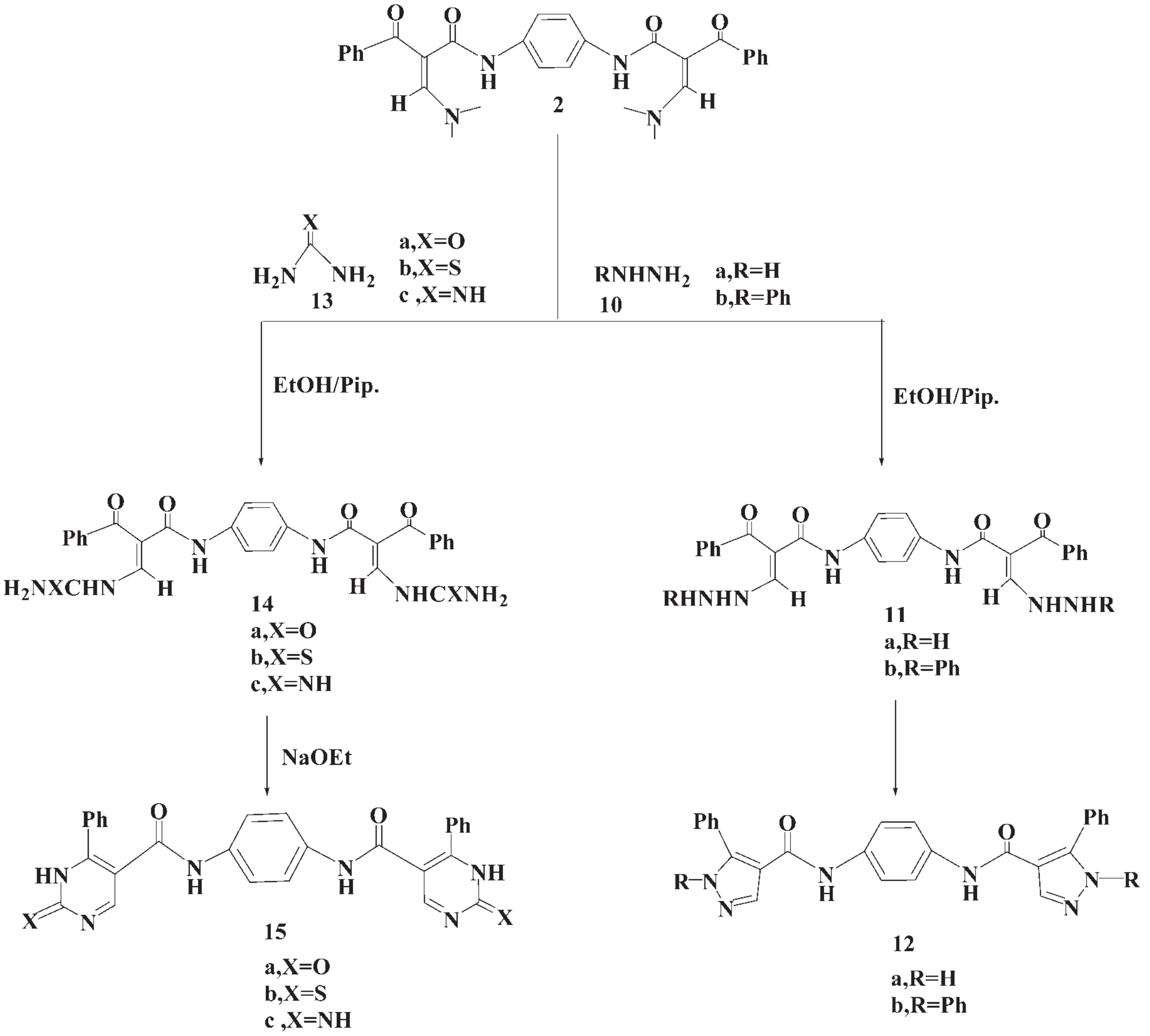


cheap laboratory available starting materials to be tested as biodegradable agrochemicals [13–15]. Some functional compounds bearing two or more of the aforementioned units are required for biological activity studies. 1,4-Phenylenediamine seemed a suitable candidate to fulfill this objective.

RESULTS AND DISCUSSION

1,4-Phenylenediamine smoothly undergoes the condensation reaction with twofold excess of ethyl benzoylacetate in refluxing dimethylformamide (DMF) to afford quantitatively *N*,*N*′-(1,4-phenylene)bis(3-oxo-3-phenylpropanamide) **1**.

Scheme 2. Preparation of compounds **11**, **12**, **14**, **15**.



Compound **1** reacts with dimethylformamide dimethylacetal (DMFDMA) in refluxing toluene to afford *N,N′*-(1,4-phenylene)bis(2-benzoyl-3-(dimethylamino)acrylamide) **2** in quantitative yield (*cf.* Scheme 1).

Compound **2** reacts with a twofold excess of malononitrile **3a** to afford a product of molecular mass m/z = 642. This molecular mass is applicable to the molecular formula $C_{36}H_{34}N_8O_4$. *N,N′*-(1,4-phenylene)bis(2-cyano-4-((dimethylamino)(phenyl)methylene)pent-2-enediamide) **7** (Scheme 1) was assigned to this product based on analytical and spectral data (*cf.* Experimental part). In this reaction it is apparent that malononitrile moieties readily substitute the dimethylamino groups in **2** with elimination of dimethylamine to give the intermediate **5** rather than the initial condensation of **3a** with the carbonyl groups of **2** and cyclization after the claimed hydrolysis of two cyano groups (one on each side) to amide groups to give **4** [16,17]. The intermediate **5** undergoes cyclization to the bis-iminopyran derivative **6**, which is re attacked by dimethylamine to afford the isolable product **7**. Recently, we could prove via an X-ray crystallographic study that **3a** substitutes NMe_2 followed by cyclization into iminopyran and ring opening by the attack of dimethylamine [10].

Refluxing compound **7** in ethanol/sodium ethoxide furnished its cyclization to the desired *N,N′*-(1,4-phenylene)bis(5-cyano-6-oxo-2-phenyl-1,6-dihydropyridine-3-carboxamide) **9a** via re-elimination of dimethylamine. The IR spectrum of this product showed absorption bands at υ_{max} at 3451–3141 cm^{-1} for the NH protons, 2213 cm^{-1} for the CN groups, 1687 and 1659 cm^{-1} for the carbonyl groups. The mass spectrum showed the molecular ion peak at m/z = 552 [M^+]. ^1H NMR spectrum showed signals at δ_H = 7.15–7.68 (m, 14H, Ar-Hs), 7.70 (s, 2H, 2NH), 7.99 (s, 2H, Pyridone 4-Hs), 10.07 (s, 2H, 2NH). Thus structure **9a** was established for this product on the basis of the spectral and element analysis data, which are in complete agreement with this structure.

Compound **2** also reacts with cyanoacetamide **3b** in refluxing ethanol with few drops of piperidine as catalyst to afford the product **8a** via substitution of NMe_2 in **2** by cyanoacetamide. Refluxing compound **8a** in ethanol/sodium ethoxide furnished its cyclization to afford the same product **9a** via loss of water. This finding is in complete agreement with our reported behavior of **3b** with enaminones that had been rationalized in our previous article [10].

Following the same mechanistic pathway during its reaction with **3b**, compound **2** reacts with cyanothioacetamide **3c** in refluxing ethanol/piperidine to afford a yellow crystalline product, which showed the presence of sulfur in the element test. The IR spectrum showed carbonyl absorption bands at $\upsilon_{max} = 1658$ & $1680\ cm^{-1}$ and the mass spectrum showed the molecular ion peak at $m/z = 620$ [M^+]. Based on these data as well as the ^1H NMR and elemental analytical data structure **8b** was assigned to this product. Refluxing compound **8b** in ethanol/sodium ethoxide led to its cyclization via loss of water to afford the *N*,*N*′-(1,4-phenylene)bis(5-cyano-2-phenyl-6-thioxo-1,6-dihydropyridine-3-carboxamide) compound **9b** (*cf.* Scheme 1 and Experimental part).

Compound **2** reacts also with hydrazine hydrate **10a** and with phenyl hydrazine **10b** in refluxing ethanol/piperidine to afford the hydrazinylacrylamide derivatives **11a** and **11b**, respectively (Scheme 2), in which the hydrazino moiety (—NHNHR) of **10a** or **10b** substitutes the -NMe_2 of **2** on both sides. These could be readily cyclized in refluxing ethanol/sodium ethoxide to give *N*,*N*′-(1,4-phenylene)bis(5-phenyl-1*H*-pyrazole-4-carboxamide) **12a** and *N*,*N*′-(1,4-phenylene)bis(1,5-diphenyl-1*H*-pyrazole-4-carboxamide) **12b**. Analytical and spectral data are in complete agreement with structures **11a,b** and **12a,b** (*cf.* experimental).

Similarly, compound **2** reacts with urea **13a**, thiourea **13b**, and guanidine **13c** in refluxing ethanol/piperidine to afford yellow products with molecular masses 540, 672, and 538, respectively. It is apparent also in this case that the dimethylamino groups of **2** were substituted by the —$NHCXNH_2$ of the respective urea derivative with elimination of dimethylamine to afford compounds **14a**, **14b**, and **14c**, respectively.

Compounds **14a-c** could also be cyclized upon their reflux in ethanol/sodium ethoxide solution to afford the desired *N*,*N*′-(1,4-phenylene)bis(2-oxo-6-phenyl-1,2-dihydropyrimidine-5-carboxamide) **15a** *N*,*N*′-(1,4-phenylene)bis(6-phenyl-2-thioxo-1,2-dihydropyrimidine-5-carboxamide) **15b** and *N*,*N*′-(1,4-phenylene)bis (2-imino-6-phenyl-1,2-dihydropyrimidine-5-carboxamide) **15c**, respectively.

CONCLUSION

We could obtain some novel *p*-phenylene-bis-heterocyclic carboxamides from readily available cheap starting materials that could be useful for biological evaluation studies.

EXPERIMENTAL

Melting points were measured on an Electrothermal (9100) apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin Elmer 1430 spectrophotometer. The ^1H NMR and ^{13}C NMR spectra were taken on a Varian Gemini 300 MHz spectrometer in DMSO-d_6 using TMS as internal standard and chemical shifts are expressed in δ ppm values. Mass spectra were taken on a Shimadzu GCMS-GB 1000 PX (70 ev). Elemental analyses were carried out at the Micro-analytical Center at Cairo University.

***N*,*N*′-(1,4-phenylene)bis(3-oxo-3-phenylpropanamide) 1.** A mixture of *p*-phenylenediamine (10 mmol) and ethyl benzoylacetate (20 mmol) in DMF (15 mL) was refluxed for 3 h and then left to cool to room temperature. The reaction mixture was then poured onto ice-cold water and the precipitated solid was filtered off and recrystallized from ethanol to afford **1** as yellow crystalline solid; yield (3.84 g; 96%); mp 237–238°C (EtOH/DMF). $\upsilon_{max} = 3470, 3377, 3271$ (NH), 1687(CO), 1641 (amide CO); δ_H. MS: $m/z = 400$ (M^+). $\delta_H = 3.54$ (s, 4H, $2CH_2$), 7.29–7.85 (m, 14H, arom. H), 9.95 (s, 2H, 2NH).

Anal. Calcd for $C_{24}H_{20}N_2O_4$ (400.43): C, 71.99; H, 5.03; N, 7.00. Found: C, 72.08; H, 5.13; N, 7.28.

***N*,*N*′-(1,4-phenylene)bis(2-benzoyl-3-(dimethylamino)acrylamide) 2.** To compound **1** (4 g; 10 mmol) in 20 mL of dry toluene was added (2.4 g; 20 mmol) of DMFDMA and the reaction mixture was refluxed for 4 h, whereby the reactants dissolve completely to a clear solution and then a precipitate reappeared. The flask was left to cool to room temperature and the solid product was collected by filtration and recrystallized from ethanol to give compound **2** as yellow crystalline solid; yield (4.85 g; 95%); mp 209–210°C (EtOH/DMF). $\upsilon_{max} = 3400, 3265, 3131$ (NH), 1655(CO), 1642 (amide CO); $\delta_H = 3.33$ (s, 12H, $4CH_3$), 7.14–8.00 (m, 14H, arom.), 7.44 (s, 2H, olefinic protons), 10.07 (s, 2H D_2O exch., 2NH). MS: $m/z = 510$ (M^+).

Anal. Calcd for $C_{30}H_{30}N_4O_4$ (510.58): C, 70.57; H, 5.92; N, 10.97. Found: C, 70.62; H, 5.98; N, 11.17.

***N*,*N*′-(1,4-phenylene)bis(2-cyano-4-((dimethylamino)(phenyl)methylene)pent-2-enediamide)7.** To a mixture of the enaminone **2** (5.1 g; 10 mmol) and malononitrile **3a** (1.32 g; 20 mmol) in ethanol (25 mL) was added few drops of piperidine as catalyst. The reaction mixture was refluxed for 2 h and then left to cool to room temperature. The solid product thus precipitated that was collected by filtration and crystallized from acetic acid to afford compound **7** as yellow crystalline product: yield (5 g, 78%); mp 246–247°C (AcOH); $\upsilon_{max} = 3451, 3333, 3141$ (NH & NH_2), 2213 (CN), 1687 (CO), and 1659 (CO) cm^{-1}; MS: $m/z = 642$ [M^+]; $\delta_H = 2.85$ (s, 12H, $4 \times CH_3$), 7.15–7.68 (m, 14H, Ar-Hs), , 6.78 (s, 4H, $2NH_2$), 7.70 (s, 2H, 2NH), 7.98 (s, 2H, 3-Hs).

Anal. Calcd *for* $C_{36}H_{34}N_8O_4$: (642.71): C, 67.28; H, 5.33; N, 17.43. Found: C, 67.35; H, 5.38; N, 17.35.

The reaction of the enaminone 2 with the acetamides 3b,c. To a mixture of the enaminone **2** (5.1 g; 10 mmol) and cyanoacetamide **3b** (1.64 g; 20 mmol) or cyanothioacetamide **3c** (2.0 g, 20 mmol) in ethanol (25 mL) was added few drops of piperidine as catalyst. The reaction mixture was refluxed in each case for 2 h and then left to cool at room temperature. The solid products thus precipitated were collected by filtration and crystallized from acetic acid to afford compound **8a** and **8b**.

***N,N*′-(1,4-phenylene)bis(2-benzoyl-4-cyanopent-2-enediamide) 8a.** Yellow crystalline product: yield (4.47 g, 76%); mp 234–235°C (AcOH); υ_{max} = 3452, 3330, 3142 (NH & NH_2), 2215 (CN), 1686 (CO), and 1656 (CO), 1640 (CO) cm^{-1}; MS: *m/z* = 588 [M^+]; δ_H = 3.34 (d, 2H, 2Hs; *j* = 12.62 Hz), 7.15–7.68 (m, 14H, Ar-Hs), 7.72 (s, 2H, 2NH), 7.98 (d, 2H, 3-Hs; *j* = 12.62 Hz), 10.05 (s, 4H, $2NH_2$).

Anal. Calcd *for* $C_{32}H_{24}N_6O_6$: (588.57): C, 65.30; H, 4.11; N, 14.28. Found: C, 65.32; H, 4.15; N, 14.38.

***N,N*′-(1,4-phenylene)bis(5-amino-2-benzoyl-4-cyano-5-thioxopent-2-enamide) 8b.** Yellow crystalline product: yield (4.28 g, 69%); mp 213–215°C (AcOH); υ_{max} = 3454, 3332, 3140 (NH & NH_2), 2219 (CN), 1679 (CO), and 1656 (CO) cm^{-1}; MS: *m/z* = 621 [$M^+ + 1$]; δ_H = 3.32 (d, 2H, 2Hs; *j* = 12.6 Hz), 7.14–7.67 (m, 14H, Ar-Hs), 7.73 (s, 2H, 2NH), 7.92 (d, 2H, 3-Hs; *j* = 12.6 Hz), 10.04 (s, 4H, $2NH_2$).

Anal. Calcd for $C_{32}H_{24}N_6O_4S_2$: (620.70): C, 61.92; H, 3.90; N, 13.54; S, 10.33. Found: C, 61.98; H, 3.85; N, 13.74; S, 10.50.

Cyclization of 7 and 8a,b. To the solution of each compounds **7**, **8a**, and **8b** (10 mmol) in 20 mL of ethanol was added few drops of sodium ethoxide (freshly prepared by dissolving 0.1 g of sodium metal in 10 mL of absolute ethanol). The reaction mixture was refluxed for 1 h in each case then left to cool overnight. The contents of the flask was poured on ice cold water and acidified with few drops of HCl till just neutral. The precipitated solids were collected by filtration and recrystallized to give.

***N,N*′-(1,4-phenylene)bis(5-cyano-6-oxo-2-phenyl-1,6-dihydropyridine-3-carboxamide) 9a.** Pale yellow crystals, yield (3.7 g, 67 % from **7**; mp 282–283°C (AcOH) and 3.86 g; 70% from **8a**; mp 284–285°C (AcOH); υ_{max} = 3451, 3333, 3141 (NH), 2213 (CN), 1687 (CO), and 1659 (CO) cm^{-1}; MS: *m/z* = 552 [M^+]; δ_H = 7.15–7.68 (m, 14H, Ar-Hs), 7.70 (s, 2H, 2NH), 7.99 (s, 2H, Pyridone 4-Hs), 10.07 (s, 2H, 2NH).

Anal. Calcd for $C_{32}H_{20}N_6O_4$: (552.54): C, 69.56; H, 3.65; N, 15.21. Found: C, 69.55; H, 3.68; N, 15.28.

***N,N*′-(1,4-phenylene)bis(5-cyano-2-phenyl-6-thioxo-1,6-dihydropyridine-3-carboxamide) 9b.** Yellow crystalline product, yield (4.2 g; 72 %), mp. 291–292°C (AcOH); υ_{max} = 3345, 3228 (NH), 2215 (CN), and 1658 cm^{-1} (CO); MS: *m/z* = 585 [$M^+ + 1$]; δ_H = 7.15–7.68 (m, 16H, Ar.), 8.25 (br.s., 2H, 2NH), 10.12 (br.s., 2H, 2NH). δ_C = 104.9 (s), 116.2 (s), 118.05 (s), 119.58 (d), 127.34 (d), 127.67 (d), 128.34 (d), 133.14 (s), 136.85 (s), 154.39 (s), 160.17 (d), 166.5 (s), 175, 52 (s).

Anal. Calcd for $C_{32}H_{20}N_6O_2S_2$: (584.67): C, 65.74; H, 3.45; N, 14.37; S, 10.97. Found: C, 65.78; H, 3.55; N, 14.45; S, 10.58.

The reaction of the enaminone 2 with hydrazine hydrate and phenyl hydrazine 10a,b. To a mixture of the enaminone **2** (5.1 g; 10 mmol) and hydrazine hydrate **10a** or phenyl hydrazine **10b** (20 mmol) in ethanol (25 mL) was added few drops of piperidine as catalyst. The reaction mixture was refluxed for 3 h, where a solid precipitate was formed during the reflux. The flask was left to cool to room temperature and the product was collected by filtration in each case and washed thoroughly with cold ethanol and recrystallized from DMF/ethanol to afford **11a,b**, respectively.

***N,N*′-(1,4-phenylene)bis(2-benzoyl-3-hydrazinylacrylamide) 11a.** Pale yellow crystals, Yield (2.7 g; 56%), mp. 235–236°C (EtOH/DMF); υ_{max} = 3343, 3235, 2156 (NH & NH_2), 1687 and 1655 cm^{-1} (2CO); MS: *m/z* = 484 [M^+]; δ_H = 4.45 (br. s, 4H, $2NH_2$), 7.04–7.68 (m, 14H, Ar.Hs), 7.76 (s, 2H, olefin Hs), 8.15 (s, 2H, 2NH), 9.55 (br.s., 2H, 2NH).

Anal. Calcd for $C_{26}H_{24}N_6O_4$: (484.51): C, 64.45; H, 4.99; N, 17.35. Found: C, 64.48; H, 5.09; N, 17.47.

***N,N*′-(1,4-phenylene)bis(2-benzoyl-3-(2-phenylhydrazinyl)acrylamide) 11b.** Yellow crystals, Yield (3.8 g; 60%), mp. 243–245°C (EtOH/DMF); υ_{max} = 3344, 3226 (NH), 1685, and 1654 (2CO) cm^{-1}; MS: *m/z* = 636 [M^+]; δ_H = 5.56 (s, 2H, 2NH), 7.14–7.72 (m, 24H, Ar. Hs), 7.74 (s, 2H, olefin Hs), 8.25 (s, 2H, 2NH), 9.77 (br.s., 2H, NH).

Anal. Calcd for $C_{38}H_{32}N_6O_4$: (636.70): C, 71.68; H, 5.07; N, 13.20. Found: C, 71.75; H, 5.27; N, 13.38.

Cyclization of 11a,b. To a solution of each of compounds **11a** and **11b** (10 mmol) in 20 mL of ethanol was added few drops of sodium ethoxide (freshly prepared by dissolving 0.1 g of sodium metal in 10 mL of absolute ethanol). The reaction mixture was refluxed for 1 h in each case then left to cool overnight. The reaction mixture was poured on ice cold water and neutralized with few drops of HCl. The precipitated solids were collected by filtration and recrystallized to give **12a,b**, respectively.

***N,N*′-(1,4-phenylene)bis(5-phenyl-1H-pyrazole-4-carboxamide) 12a.** Pale yellow crystals, Yield (2.6 g; 58%), mp. 295–296°C (EtOH/DMF); υ_{max} = 3343, 3235 (NH), and 1655 cm^{-1} (CO); MS: *m/z* = 448 [M^+]; δ_H = 7.06–7.65 (m, 16H, Ar.Hs), 8.15 (s, 2H, 2NH), 9.25 (br.s., 2H, 2NH).

Anal. Calcd for $C_{26}H_{20}N_6O_2$: (448.48): C, 69.63; H, 4.49; N, 18.74. Found: C, 69.52; H, 4.58; N, 18.96.

***N,N*′-(1,4-phenylene)bis(1,5-diphenyl-1H-pyrazole-4-carboxamide) 12b.** Yellow crystals, Yield (3.78 g; 63%), mp. 300–302°C (EtOH/DMF); υ_{max} = 3344, 3226 (NH), and 1657 (CO) cm^{-1}; MS: *m/z* = 600 [M^+]; δ_H = 7.21–8.34 (m, 26H, Ar. Hs), 9.77 (br.s., 2H, NH). δ_C = 118.81 (s), 119.55 (d), 120.67 (d), 127.75 (d), 127.3 (d), 128.55 (d), 129.05 (d), 129.22 (d), 133.08 (s), 136.53 (s), 138.94 (s), 139.52 (d), 140.01 (s), 193.19 (s).

Anal. Calcd for $C_{38}H_{28}N_6O_2$: (600.67): C, 75.98; H, 4.70; N, 13.99. Found: C, 76.08; H, 4.76; N, 13.85.

The reaction of the enaminone 2 with urea derivatives 13a-c. To a mixture of the enaminone **2** (5.1 g; 10 mmol) and urea **13a**, thiourea **13b**, or guanidine hydrochloride **13c** (20 mmol) in ethanol (25 mL) was added few drops of triethylamine as catalyst in case of **13a,b** and two mole equivalents in case of **13c**. The reaction mixture was refluxed in each case for 3 h and then left to cool overnight. The contents of the flask was poured on ice-cold water and neutralized by HCl. The precipitated products were collected by filtration in each case and recrystallized from DMF/ethanol to afford **14a**, **14b**, and **14c**, respectively.

***N,N*′-(1,4-phenylene)bis(2-benzoyl-3-ureidoacrylamide) 14a.** Yellow crystals, Yield (3.51 g; 65%), mp. 213–215°C (EtOH/DMF); υ_{max} = 3342, 3226, 3167 (NH & NH_2), 1678, 1662, and 1658 (3CO) cm^{-1}; MS: *m/z* = 540 [M^+]; δ_H = 5.51 (s, 4H, $2NH_2$), 7.08–7.65 (m, 14H, Ar. Hs), 7.92 (s, 2H, 2NH), 8.45 (s, 2H, olefin Hs), 10.17 (s, 2H, 2NH).

Anal. Calcd. for $C_{28}H_{24}N_6O_6$: (540.53): C, 62.22; H, 4.48; N, 15.55. Found: C, 62.28; H, 4.56; N, 15.75.

***N,N*′-(1,4-phenylene)bis(2-benzoyl-3-thioureidoacrylamide) 14b.** Yellow crystalline product, Yield (3.8 g; 67%), mp. 219–220°C (EtOH/DMF); υ_{max} = 3340, 3225, 3165 (NH & NH_2), 1676, 1660, and 1655 (3CO) cm^{-1}; MS: *m/z* = 572 [M^+]; δ_H = 5.52 (s, 4H, $2NH_2$), 7.08–7.66 (m, 14H, Ar. Hs), 7.75 (s, 2H, olefin Hs), 7.93 (s, 2H, 2NH), 10.15 (s, 2H, 2NH).

Anal. Calcd. for $C_{28}H_{24}N_6O_4S_2$: (572.66): C, 58.73; H, 4.22; N, 14.68; S, 11.20. Found: C, 58.78; H, 4.26; N, 14.78; S, 11.00.

***N,N*′-(1,4-phenylene)bis(2-benzoyl-3-guanidinoacrylamide) 14c.** Yellow powder, Yield (3.6 g; 68%), mp. 222–224°C (EtOH/DMF); υ_{max} = 3338, 3222, 3170 (NH & NH_2), 1678, and 1658 (2CO) cm^{-1}; MS: *m/z* = 538 [M^+]; δ_H = 5.51 (s, 4H, $2NH_2$), 7.05–7.68 (m, 16H, Ar. + olefin Hs), 7.92 (s, 2H, 2NH), 8.15 (s, 2H, 2NH), 10.17 (s, 2H, 2NH).

Anal. Calcd. for $C_{28}H_{26}N_8O_4$: (538.56): C, 62.44; H, 4.87; N, 20.81. Found: C, 62.32; H, 4.58; N, 20.70.

Cyclization of compounds 14a-c. To a solution of each of compounds **14a, 14b**, or **14c** (10 mmol) in 20 mL of ethanol was added few drops of sodium ethoxide and the reaction mixture was refluxed for 1 h in each case then left to stand overnight. The reaction mixture was poured on ice cold water and neutralized with few drops of HCl. The precipitated solids were collected by filtration and recrystallized to give **15a-c**, respectively.

***N,N*′-(1,4-phenylene)bis(2-oxo-6-phenyl-1,2-dihydropyrimidine-5-carboxamide) 15a.** Yellow crystals, Yield (3.27 g; 65%), mp. 286–287°C (EtOH/DMF); υ_{max} = 3342, 3226 (NH), 1662, and 1658 (2CO) cm^{-1}; MS: *m/z* = 504 [M^+]; δ_H = 7.12–7.85 (m, 16H, Ar. Hs), 7.92 (s, 2H, 2NH), 10.17 (s, 2H, 2NH).

Anal. Calcd. for $C_{28}H_{20}N_6O_4$: (504.50): C, 66.66; H, 4.00; N, 16.66. Found: C, 66.70; H, 4.05; N, 16.48.

***N,N*′-(1,4-phenylene)bis(6-phenyl-2-thioxo-1,2-dihydropyrimidine-5-carboxamide) 15b.** Yellow crystals, Yield (3.59 g; 67%), mp. 290–291°C (EtOH/DMF); υ_{max} = 3345, 3228 (NH), and 1655 (CO) cm^{-1}; MS: *m/z* = 535 [$M^+ - 1$]; δ_H = 7.14–7.88 (m, 16H, Ar. Hs), 7.90 (s, 2H, 2NH), 10.17 (s, 2H, 2NH).

Anal. Calcd. for $C_{28}H_{20}N_6O_2S_2$: (536.63): C, 62.67; H, 3.76; N, 15.66; S, 11.95. Found: C, 62.80; H, 3.72; N, 15.45; S, 12.25.

***N,N*′-(1,4-phenylene)bis(2-imino-6-phenyl-1,2-dihydropyrimidine-5-carboxamide) 15c.** Yellowish orange crystals, Yield (3.16 g; 63%), mp. 280–282°C (EtOH/DMF); υ_{max} = 3343, 3232 (NH), and 1656 (CO) cm^{-1}; MS: *m/z* = 502 [M^+]; δ_H = 6.45 (s, 2H, 2NH), 7.14–7.88 (m, 16H, Ar), 7.94 (s, 2H, 2NH), 10.17 (s, 2H, 2NH).

Anal. Calcd. for $C_{28}H_{22}N_8O_2$: (502.53): C, 66.92; H, 4.41; N, 22.30. Found: C, 67.12; H, 4.47; N, 22.50.

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(4,4-Difluoro-4-bora-3a,4a,-diaza-s-indacen-3-yl)acetaldehyde: Synthesis and Chemical Properties

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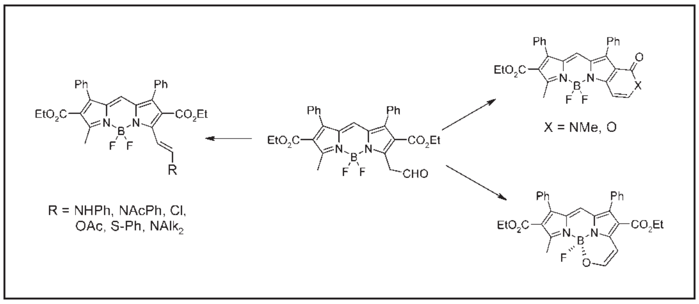

A reaction of 3,5-dimethylborondipyrromethene **3** with the DMF dimethylacetal gives rise to monoenamine **4**. The latter is converted to the corresponding aldehyde **5**. A considerable contribution of the enolic form of the aldehyde allows preparing numerous 3-vinyl substituted borondipyrromethenes and some heterocyclic derivatives. A reaction of the aldehyde **5** with tertiary aliphatic amines and the consecutive Hofmann-type decomposition of the intermediary quaternary salt give rise to the corresponding dialkylaminovinyl derivatives.

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INTRODUCTION

The 4,4-difluoro-4-boron-3a,4a-diazo-s-indacene (so-called borondipyrromethene (BODIPY))-derived dyes have both very intensive absorption bands in their ultraviolet-visible (UV-Vis) spectra and intensive fluorescence [1,2]. A low sensitivity of these properties of the BODIPY dyes toward both solvent polarity and the pH led to their numerous applications, such as labeling of proteins [3–5] and DNA [6]. To widen the range of the biochemical applications requiring deeply colored dyes, the extension of the chromophoric system of the BODIPY dyes by means of their peripheral functionalization is usually carried out. For example, the Knoevenagel reaction of the BODIPY involving methyl groups in 3- and 5-positions with aromatic aldehydes led to the corresponding monostyryl or distyryl derivatives [7–9]. The latter compounds exhibit absorption maxima at considerably longer wavelengths compared with the parent BODIPY. In this contribution, we report an efficient synthetic approach to the 3-vinyl substituted BODIPY dyes using the reactivity of the α-methyl groups. The obtained compounds are useful scaffolds that could be used in further structural and functional modifications of the dipyrromethene dyes.

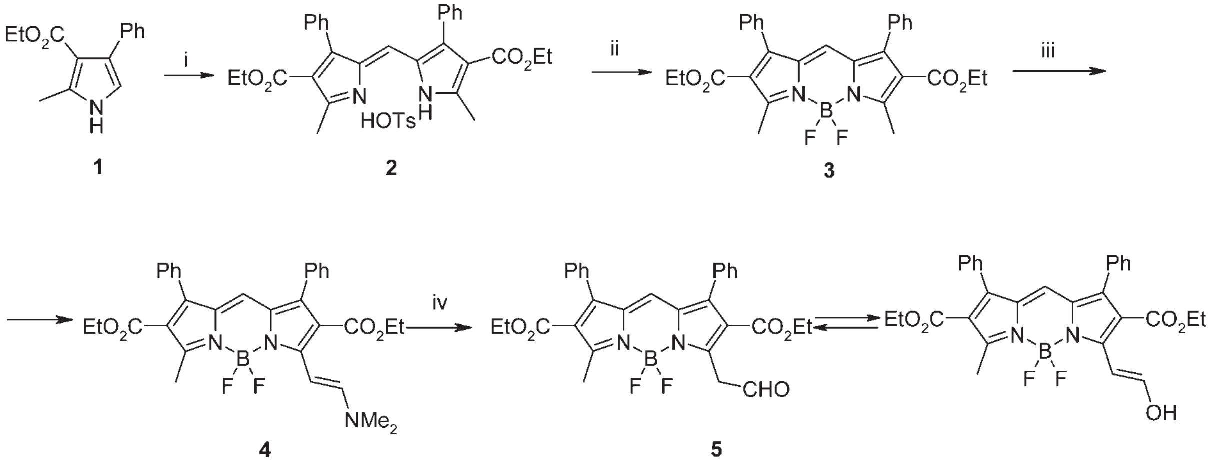
RESULTS AND DISCUSSION

As shown in Scheme 1, the condensation of the pyrrole **1** with trimethylorthoformate in the presence of *p*-toluenesulfonic acid leads to the dipyrromethene tosylate **2** in a 95% yield. Noteworthy, the preparation of hydrobromide of the dipyrromethene **2** from the pyrrole and triethyl orthoformate dissolved in the 50% HBr in acetic acid was reported in the literature [10], but no yield was given. Finally, the treatment of the tosylate **2** with $BF_3{\cdot}Et_2O$ and the Hünig's base gives rise to 84% of the BODIPY **3** that is used as the starting compound in our study.

A reaction of **3** with the DMF dimethylacetal in the presence of acetic anhydride in hot xylene results in 89% enamine **4** (Scheme 1). The fact that only one methyl group of **3** reacts even if a large excess of the DMF dimethylacetal is used reflects a decreased reactivity of the remaining methyl group of **4** on introduction of the electron donor enamine fragment.

Treatment of the enamine **4** with TFA in water gives rise to the corresponding aldehyde **5**. The latter compound exists in a medium dependent equilibrium of two tautomeric forms. Thus, ^{1}H NMR spectrum of **5** recorded in $CDCl_3$ reveals characteristic peaks of CH_2 and aldehyde protons at 4.52 ppm and 9.82 ppm, respectively. The presence of the enolic form of **5** in $CDCl_3$ is, therefore, negligible and cannot be detected by means ^{1}H NMR. On the contrary, the DMSO-d$_6$ ^{1}H NMR spectrum of **5** shows both tautomeric forms in a 1:1 ratio. The latter manifests itself in two peaks of the CH_3 group at 2.76 and 2.81 ppm, one peak of the CH_2 group

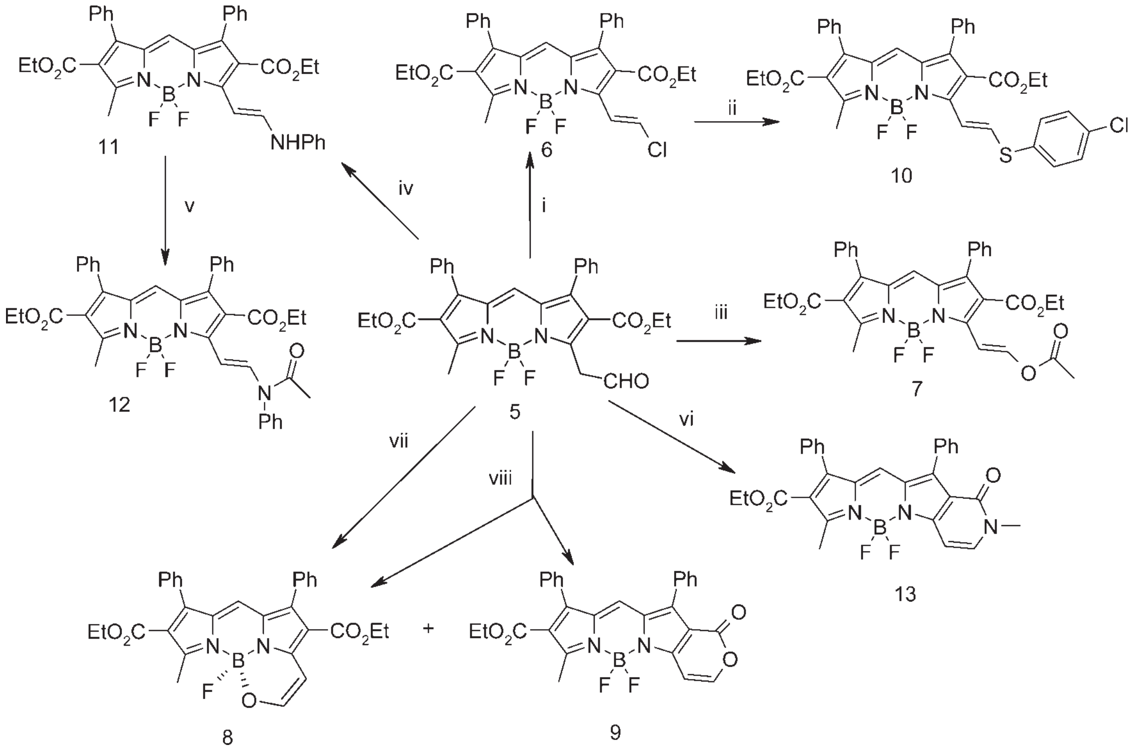
Scheme 1. Reagents and conditions. i, $CH(OCH_3)_3$, HOTs, room temperature; ii, $BF_3{*}Et_2O$, $EtN(i\text{-}Pr)_2$, room temperature; iii, $(CH_3O)_2CHN(CH_3)_2$, Ac_2O, o-xylene, reflux 1 min; iv, 30% TFA in water, reflux 1 min.



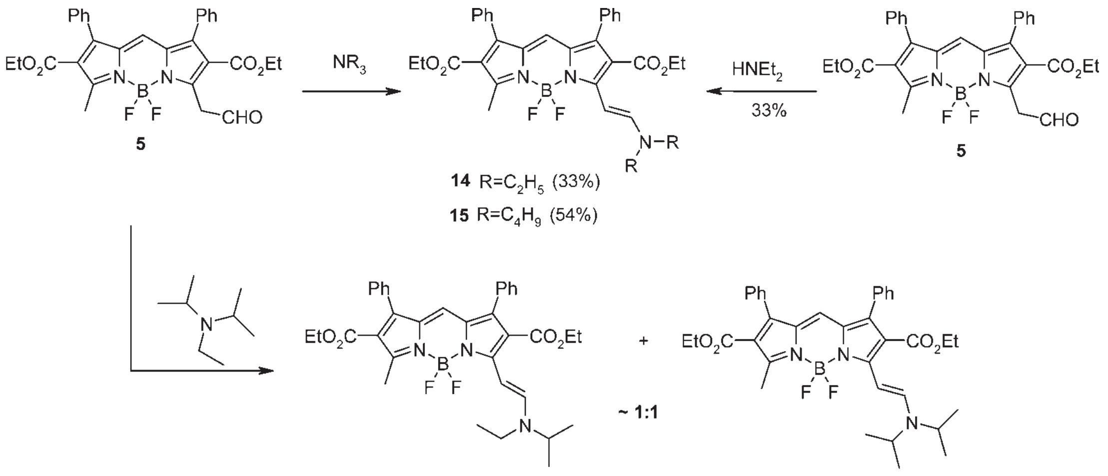
at 4.45 ppm, broad peaks of CH=CH at 6.46 and 8.09 ppm, two peaks of meso-protons at 6.7 and 6.98 ppm, and the aldehyde proton peak at 9.76 ppm.

Scheme 2 shows reactions of aldehyde **5** leading to a variety of vinyl derivatives. For example, heating of **5** in $POCl_3$ in the presence of *N,N*-diethylaniline results in the chlorovinyl compound **6**, whereas heating of **5** in acetic anhydride in the presence of catalytic amount of DMF gives rise to the enole acetate **7**. Interestingly, treatment of **5** with $BF_3{\cdot}Et_2O$ in toluene at room temperature leads to the intramolecular displacement of the fluorine with the enolic unit producing the cyclic structure **8**. ^1H NMR data show that the coupling constant of the ethylene protons in **8** is equal to 5.1 Hz, which is typical for the *cis*-configuration of the bond. This observation is in stark contrast with those for the noncyclic vynil

Scheme 2. Reagents and conditions. i, $POCl_3$, $PhN(Et)_2$, 90°C;ii, $4\text{-}ClC_6H_4SNa$, DMF, room temperature; iii, Ac_2O, DMF, reflux 4 min; iv, $PhNH_2$, HOAc; v, Ac_2O, $N(Et)_3$; vi, $MeNH_2$, HOAc, toluene, reflux 2 min; vii, $BF_3{*}Et_2O$, toluene, room temperature; viii, HOAc, H_2SO_4, 100°C.



Scheme 3



derivatives shown in Scheme 2 in which the corresponding coupling constants are in the range of 12–16 Hz and characteristic of the *trans*-configuration of the double bond. ^{19}F NMR spectrum of **8** shows that the peak corresponding to its fluorine atom is shifted to the low field (−137.2 ppm) compared with that of **5** (−141.6 ppm). Mass spectrum of **8** (mw 524) recorded in the positive mode reveals cationic peak with *m*/*z* of 505 that corresponds to the loss of the remaining fluorine anion. The intermolecular displacement of the fluorine in BODIPYs with alkoxy and phenoxy groups in the presence of $AlCl_3$ has already been reported in the literature [11]. There are also reports on an intramolecular *O*-chelation of the boron atom in BODIPYs [12]. The described here compound **8** is the representative of unsymmetrically chelated BODIPYs recently reported in [13].

A mixture of cyclic structures **8** (28%) and **9** (22%) is obtained from the aldehyde **5** in hot acetic acid in the presence of sulfuric acid. The formation of the both cycles is also observed (TLC) while heating aldehyde **5** over 200°C.

The chlorine atom of the compound **6** is considerably reactive. Addition of bases, such as pyridine, triethylamine, carbonates etc., to **6** leads to the formation of tars. This observation can possibly be explained by the formation of the corresponding acetylene derivative and its polymerization. Similar tar formation is observed when a phenolate anion reacts with **6**. However, a reaction of **6** with a thiophenolate anion that is less basic but more nucleophilic gives rise to the sulfide **10**.

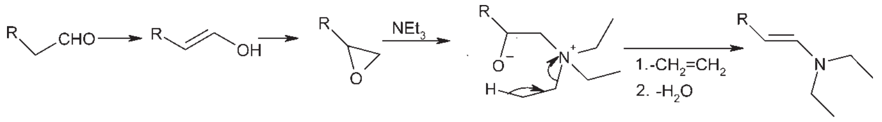
The aldehyde **5** reacts easily with aromatic amines. For example, a reaction of **5** with aniline gives rise to the anilinovinyl derivative **11** in a yield of 80%. The acylation of the latter compound leads to the corresponding acetanilide **12**. The derivatives of type **11** can also be obtained by the reaction of aniline with the enamine **4** and enole acetate **7**. However, reactions of **5** with primary aliphatic amines cannot be used for the preparation of the corresponding aminovinyl derivatives because of their follow-up cyclization to pyridones of type **13**. The pyridone **13** is easily obtained by the reaction of **5** with a methanol solution of methylamine in hot toluene in the presence of acetic acid (Scheme 2).

Attempting to carry out the reaction of **5** with different CH-acids in the presence of triethylamine led to a dye product. The structure of this dye does not depend on the structure of the CH-acid used as TLC and UV-Vis absorption spectra reveal. Further, analytical characterization of this new product confirms the structure of a diethylaminovinyl derivative **14** that is the result of a direct coupling of **5** and the triethylamine (Scheme 3). This reaction takes place after either 10–15 min of heating or 24 h of standing at room temperature of the reaction mixture in pyridine or dioxane. The enamine **14** can also be obtained by a reaction of **5** with diethylamine (Scheme 3).

A reaction of **5** with tributylamine proceeds in a similar way, giving rise to the dibutylamino-derivative **15**. The reaction results a chromatographically nonseparable mixture of two products if ethyldiisopropylamine is used. According to the ^{1}H NMR data, the mixture consists of equal amounts of diisopropylamino and ethylisopropylamino derivatives.

A possible mechanism of the reaction of **5** with trialkylamines is depicted in Scheme 4. The enolic form of the aldehyde **5** undergoes cyclization to an oxirane intermediate, which reacts with the amine producing betaine. The following Hoffman-type decomposition of the quaternary salt leads to the consecutive elimination of the alkene and the water. To our knowledge, the reactions of acetaldehyde derivatives with trialkylamines leading

Scheme 4



to enamines or similar transformations have not been reported in the literature.

Optical properties. The cyclization of dipyrromethene **2** to boron dipyrromethene **3** leads to a bathochromic shift of the UV-Vis absorption maximum of **3** compared with **2** by 35 nm. Compound **3** has also a more intense UV-Vis absorption band when compared with **2** (Table 1). All vinyl derivatives prepared from **3** have their UV-Vis absorption maxima at longer wavelengths compared with the precursor. However, their absorption bands become broader than that of **3**. The smallest bathochromic shifts of the UV-Vis absorption maxima are observed for the chlorovinyl derivative **6** (29 nm) and enole acetates **7** (33 nm) and **9** (34 nm). Aminovinyl derivatives **4**, **11**, **14**, and **15** show significantly larger bathochromic shifts of their UV-Vis absorption maxima when compared with that of **3** ranging from 102 to 107 nm. However, the absorption intensities of the UV-Vis spectra of the aminovinyl derivatives show a twofold decrease while their absorption bands broaden.

The synthesized vinyl-substituted BODIPYs with the exception of the amino-derivatives exhibit high fluorescence quantum yields (φ = 0.73-1). The fluorescence quenching in enamines **4**, **14**, and **15** takes place seemingly *via* photoinduced electron transfer (PET) as it is described for some other amino-substituted BODIPYs [14,15]. In the case of aniline derivative **11**, the PET is much less pronounced (φ = 0.17). The PET quenching can be avoided by, e.g., acylation or cyclization into pyridone **13**. These structural modifications lead to the fluorescence increase. The largest Stokes shifts are observed for sulfide **10** and enamine **11** (1150 and 1400 cm^{-1}, respectively). The remaining vinyl derivatives show the Stokes shifts comparable with that of the starting BODIPY (500–700 cm^{-1}).

Table 1

Optical properties of the synthesized dyes (in CH_2Cl_2).

	λ_{abs}, nm ($\varepsilon \cdot 10^{-4}$, M^{-1} cm^{-1})	fwhm, cm^{-1}	λ_{em}, nm (φ)	$\Delta\upsilon$, cm^{-1}
2	484 (10.9)	1200		
3	519 (12.2)	782	535 (0.98)	577
4	621 (6.0)	2385	659 (<0.001)	929
5	518 (12.4)	823	533 (0.97)	544
6	547 (10.3)	1013	566 (1)	516
7	552 (11.3)	791	569 (0.94)	541
8	579 (8.4)	901	598 (0.80)	549
9	553 (10.8)	921	574 (0.98)	662
10	584 (8.4)	1460	626 (0.84)	1149
11	626 (8.5)	1905	686 (0.17)	1397
12	580 (10.3)	1135	602 (0.83)	630
13	586 (9.5)	1146	614 (0.73)	778
14	622 (6.0)	2481	668 (<0.001)	1107

To sum up, the reported here BODIPY-3-acetaldehyde is a useful scaffold for the synthesis of 3-vinyl-substituted BODIPYs and some heterocycles having the BODIPYs core as the cycle component. The synthesized 3-vinyl-substituted BODIPYs can, in turn, be used for the further modification of BODIPYs.

EXPERIMENTAL

Electronic absorption spectra were recorded on Shimadzu UV-3100 spectrophotometer. ^{1}H (300 MHz, 25°C, $Si(CH_3)_4$ as an internal standard) and ^{19}F NMR (188 MHz, $CFCl_3$ as internal standard) spectra were obtained with Varian VXR-300 instrument. LC/MS spectra were recorded using chromatography/mass spectrometric system that consists of high-performance liquid chromatograph ''Agilent 1100 Series'' equipped with diode-matrix and mass-selective detector ''Agilent LC\MSD SL.'' Purification by column chromatography was carried out with neutral silica gel 100 (70–230). Fluorescence spectra were recorded on a Solar CM 2203 fluorescence spectrophotometer. The relative fluorescent quantum yields (φ) were determined using Rhodamine 6G (φ = 0.95, EtOH) and indodicarbocyanine iodide (φ = 0.25, EtOH) as the references.

2-[3-Phenyl-4-carbethoxy-5-methylpyrrol-2-yl]methyliden-3-phenyl-4-carbethoxy-5-methylpyrrolium tosylate (2). Toluene-4-sulfonic acid (3.6 g, 21 mmol) was added to a stirred solution of pyrrole **1** (9.16 g, 40 mmol) in 20 mL trimethyl orthoformate at room temperature, and stirring was continued for 15 min. Then the mixture was diluted with benzene (50 mL), and the solid product was filtered. Yield 12.1 g (95%). mp 138–140°C. ^{1}H NMR ($CDCl_3$): δ 1.07(t, $^3J_{H,H}$ = 7.2 Hz, 6H, CH_2CH_3), 2.40 (s, 3H, CH_3), 2.85 (s, 6H, CH_3), 4.12 (q, $^3J_{H,H}$ = 7.2 Hz, 4H, CH_2CH_3), 6.82 (s, 1H, meso-CH), 7.09 (m, 4H, ArH), 7.27 (m, 8H, ArH), 7.91 (d, $^3J_{H,H}$ = 8.1 Hz, 2H, ArH), 13.82 (s, 2H, NH). Anal. calcd. for $C_{36}H_{36}N_2O_7S$: C,67.5; H, 5.62; N, 4.37. Found: C, 67.2; H, 5.65; N, 4.65.

1,7-Diphenyl-2,6-dicarbethoxy-3,5-dimethyl-4,4-difluoro-4-bora-3a,4a,-diaza-s-indacene (3). Diisopropylethylamine (14 mL, 80 mmol) was added dropwise to a stirred solution of compound **2** (12.8 g, 20 mmol) in $BF_3 \cdot Et_2O$ (50 mL) at room temperature The mixture was stirred for additional 20 min, followed by pouring into ice water (250 mL), and then was left for 2 h. The precipitate was filtered, air-dried, and recrystallized from hexane-toluene. Yield 8.7 g (84%). M.p. 217–218°C. ^{1}H NMR (DMSO-d_6): δ 1.03 (t, $^3J_{H,H}$ = 7.2 Hz, 6H, CH_2CH_3), 2.81 (s, 6H, CH_3), 4.08 (q, $^3J_{H,H}$ = 7.2 Hz, 4H, CH_2CH_3), 6.91 (s, 1H, meso-CH), 7.42 (s, 10H, ArH). Anal.

calcd. for $C_{29}H_{27}BF_2N_2O_4$: C, 67.4; H, 5.23; N, 5.43. Found: C, 67.5; H, 5.5; N, 5.5.

3-(2-Dimethylaminoethen-1-yl)-5-methyl-1,7-diphenyl-2,6-dicarbethoxy-4,4-difluoro-4-bora-3a,4a,-diaza-s-indacene (4). DMF dimethylacetal (3 g, 25 mmol) was added to a solution of compound **3** (2.58 g, 5 mmol), Ac_2O (6 mL) in o-xylene (15 mL), and the mixture was refluxed for 1 min. After cooling to room temperature, hexane (20 mL) was added, and the mixture was left overnight. The precipitate was filtered and washed with hexane. Yield 2.46 g (89%). M.p. 204–205°C. ^{1}H NMR (DMSO-d_6): δ 0.94 (t, 3H, CH_2CH_3), 1.01 (t, 3H, CH_2CH_3), 2.71 (s, 3H, CH_3), 3.08 (s, 3H, NCH_3), 3.29 (s, 3H, NCH_3), 4.06 (m, 4H, CH_2CH_3), 6.02 (d, $^3J_{H,H}$ = 12.9 Hz, 1H, CH), 6.30 (s, 1H, meso-CH), 7.25–7.44 (m, 10H, ArH), 8.19 (d, $^3J_{H,H}$ = 12.9 Hz, 1H, CH). Anal. calcd. for $C_{32}H_{32}BF_2N_3O_4$: C, 67.2; H, 5.6; N, 7.35. Found: C, 67.4; H, 5.4; N, 7.5.

(5-Methyl-1,7-diphenyl-2,6-dicarbethoxy-4,4-difluoro-4-bora-3a,4a,-diaza-s-indacen-3-yl)acetaldehyde (5). A mixture of enamine **4** (2.28 g, 4 mmol), water (12 mL), and trifluoroacetic acid (5 mL) was refluxed for 1 min. After cooling to room temperature, the product was filtered and recrystallized from acetonitrile. Yield 1.4 g (73%). M.p. 194–196°C. ^{1}H NMR ($CDCl_3$): δ 1.09 (m, 6H, CH_2CH_3), 2.92 (s, 3H, CH_3), 4.13 (m, 4H, CH_2CH_3), 4.52 (s, 2H, CH_2CHO), 6.98 (s, 1H, meso-CH), 7.28–7.39 (m, 10H, ArH), 9.82 (s, 1H, CHO). ^{19}F NMR ($CDCl_3$): δ −141.6 (m).

^{1}H NMR (DMSO-d_6) a mixture of tautomers: δ 1.01 (m, CH_2CH_3), 2.76 (s, CH_3), 2.81 (s, CH_3), 4.08 (m, CH_2CH_3), 4.45 (s, CH_2CHO), 6.46 (br.s, CH), 6.70 (s, meso-CH), 6.98 (s, meso-CH), 7.75 (m, ArH), 8.09 (br.s, CH), 9.76 (s, CHO). Anal. calcd. for $C_{30}H_{27}BF_2N_2O_5$: C, 66.2; H, 4.96 N, 5.15. Found: C, 66.4; H, 4.8; N, 5.1.

3-(2-Chloroethen-1-yl)-5-methyl-1,7-diphenyl-2,6-dicarbethoxy-4,4-difluoro-4-bora-3a,4a,-diaza-s-indacene (6). A mixture of aldehyde **5** (270 mg, 0.5 mmol), $POCl_3$ (1 mL, 11 mmol), and *N,N*-diethylaniline (150 mg, 1 mmol) was heated at 90–95°C for 45 min. After cooling to room temperature, the mixture was poured into ice water, the precipitate was filtered and washed with hot ethanol. Yield 200 mg (71%). M.p. 186–187°C. ^{1}H NMR ($CDCl_3$): δ 0.99 (t, 3H, CH_2CH_3), 1.01 (t, 3H, CH_2CH_3), 2.93 (s, 3H, CH_3), 4.14 (m, 4H, CH_2CH_3), 6.93 (s, 1H, meso-CH), 7.25–7.40 (m, 10H, ArH), 7.53 (d, $^3J_{H,H}$ = 13.5 Hz,1H, CH), 7.68 (d, $^3J_{H,H}$ = 13.5 Hz, 1H, CH). ^{19}F NMR ($CDCl_3$): δ −141.4 (m). Anal. calcd. for $C_{30}H_{26}BClF_2N_2O_4$: C, 64.0; H, 4.62; N, 4.98. Found: C, 63.7; H, 4.4; N, 5.1.

3-(2-Acetoxyethen-1-yl)-5-methyl-1,7-diphenyl-2,6-dicarbethoxy-4,4-difluoro-4-bora-3a,4a,-diaza-s-indacene (7). A mixture of aldehyde **5** (270 mg, 0.5 mmol), Ac_2O (1.3 mL), and DMF (35 mg, 0.5 mmol) was heated at reflux for 4 min. After cooling to room temperature, the mixture was diluted with i-PrOH (3 mL), and the precipitate was filtered. Yield 240 mg (82%). M.p. 209–210°C. ^{1}H NMR ($CDCl_3$): δ 1.04 (m, 6H, CH_2CH_3), 2.25 (s, 3H, $COCH_3$), 2.93 (s, 3H, CH_3), 4.13 (m, 4H, CH_2CH_3), 6.90 (s, 1H, meso-CH), 7.11 (d, $^3J_{H,H}$ = 13.5 Hz,1H, CH), 7.26–7.39 (m, 10H, ArH), 8.68 (d, $^3J_{H,H}$ = 13.5 Hz, 1H, CH). ^{19}F NMR ($CDCl_3$): δ −142.5 (m). Anal. calcd. for $C_{32}H_{29}BF_2N_2O_6$: C, 65.5; H, 4.95; N, 4.78. Found: C, 65.7; H, 4.8; N, 5.0.

9b-Fluoro-9-methyl-5,7-diphenyl-4,8-dicarbethoxy-1-oxa-9a,9c-diaza-9b-bora-cyclopenta[e]acenaphtylene (8). $BF_3{\cdot}Et_2O$ (500 mg, 3.5 mmol) was added to a solution of aldehyde **5** (270 mg, 0.5 mmol) in toluene (5 mL) at room temperature. The mixture was allowed for stand for 45 min, followed by addition of water (5 mL). The organic layer was separated, washed with water, dried over Na_2SO_4, and then evaporated to dryness. The residue was purified by column chromatography on silica gel (eluent hexane:EtOAc, 4:1). Yield 150 mg (58%). M.p. 167–168°C. ^{1}H NMR(DMSO-d_6): δ 1.01 (t, 3H, CH_2CH_3), 1.15 (t, 3H, CH_2CH_3), 2.87 (s, 3H, CH_3), 4.06 (q, 2H, CH_2CH_3), 4.17 (q, 2H, CH_2CH_3), 6.69 (d, $^3J_{H,H}$ = 5.1 Hz, 1H, CH), 6.88 (s, 1H, meso-CH), 7.40–7.52 (m, 10H, ArH), 7.72 (d, $^3J_{H,H}$ = 5.1 Hz, 1H, CH). ^{19}F NMR ($CDCl_3$): δ −137.2 (m). LS-MS: *m/z* 505 $[M-19(F)]^+$. Anal. calcd. for $C_{30}H_{26}BFN_2O_5$: C, 68.7; H, 4.94; N, 5.34. Found: C, 68.5; H, 4.9; N, 5.1.

2-Carbethoxy-3,7-dimetyl-1,9-diphenyl-4,4-difluoro-7-oxa-3a,4a-diaza-4-bora-cyclopenta[b]fluoren-8-on (9). A solution of aldehyde **5** (300 mg, 0.55 mmol), H_2SO_4 (98 mg, 1 mmol) in AcOH (3 mL) was heated at 100°C for 30 min. After cooling to room temperature, the mixture was poured into water. The precipitate was filtered and air dried. The crude product was purified by column chromatography on silica gel (eluent hexane-EtOAc, 4:1) to give **8** (80 mg), and **9** (60 mg) in 28% and 22% yield, respectively. mp 234–235°C. ^{1}H NMR ($CDCl_3$): δ 1.11 (t, 3H, CH_2CH_3), 2.99 (s, 3H, CH_3), 4.18 (q, 2H, CH_2CH_3), 6.96 (d, $^3J_{H,H}$ = 5.7 Hz, 1H, CH), 7.23 (s, 1H, meso-CH), 7.33–7.55 (m, 11H, ArH, CH), ^{19}F NMR ($CDCl_3$): δ −143.6 (m). Anal. calcd. for $C_{28}H_{21}BF_2N_2O_4$: C, 67.5; H, 4.21; N, 5.62. Found: C, 67.4; H, 4.4; N, 5.76.

3-[2-(4-Chlorophenylsulfanyl)ethen-1-yl)-5-methyl-1,7-diphenyl-2,6-dicarbethoxy-4,4-difluoro-4-bora-3a,4a,-diaza-s-indacene (10). An ethanol solution of sodium *p*-chlorotiophenolate (consisted of *p*-chlorotiophenole (54 mg, 0.37 mmol), NaOH (15 mg, 0.37 mmol) and EtOH (1 mL)) was added to a solution of compound **6** (160 mg, 0.28 mmol) in DMF (2 mL). The mixture was left for 30 min at room temperature followed by pouring into 10% aqueous NH_4Cl, and then the precipitate was filtered. The wet product was dissolved in EtOAc, dried over Na_2SO_4, and evaporated to dryness. The residue was recrystallized from cyclohexane. Yield 140 mg (74%). M.p.125–126°C. ^{1}H NMR (DMSO-d_6): δ 0.90 (t, 3H, CH_2CH_3), 1.03 (t, 3H, CH_2CH_3), 2.79 (s, 3H, CH_3), 4.08 (m, 4H, CH_2CH_3), 6.89 (s, 1H, meso-CH), 7.05 (d, $^3J_{H,H}$ = 15.9 Hz, 1H, CH), 7.42 (m, 10H, ArH), 7.59 (s, 4H, ArH), 8.08 (d, $^3J_{H,H}$ = 15.9 Hz, 1H, CH). Anal. calcd. for $C_{36}H_{30}BClF_2N_2O_4S$: C, 64.5; H, 4.48; N, 4.18. Found: C, 64.7; H, 4.6; N, 4.1.

3-(2-Phenylaminoethen-1-yl)-5-methyl-1,7-diphenyl-2,6-dicarbethoxy-4,4-difluoro-4-bora-3a,4a,-diaza-s-indacene (11). a. A mixture of aldehyde **5** (130 mg, 0.24 mmol), aniline (35 mg, 0.38 mmol), and acetic acid (2 mL) was heated to 80°C. After cooling to room temperature, the precipitate was filtered. Yield 120 mg (81%).

b. A mixture of enamine **4** (570 mg, 1 mmol), aniline (130 mg, 1.4 mmol), and acetic acid (3 mL) was refluxed for 20 min. After cooling to room temperature, the precipitate was filtered. Yield 360 mg (58%).

M.p.217–218°C. ^{1}H NMR (DMSO-d_6): δ 0.88 (t, 3H, CH_2CH_3), 1.01 (t, 3H, CH_2CH_3), 2.76 (s, 3H, CH_3), 4.06 (m, 4H, CH_2CH_3), 6.46 (s, 1H, meso-CH), 6.68 (d, $^3J_{H,H}$ = 13.2 Hz, 1H, CH), 7.15 (m, 3H, ArH), 7.34–7.44 (m, 12H, ArH), 8.81 (dd, $^3J_{H,H}$ = 13.5 Hz, $^3J_{H,H}$=13.2 Hz,1H, CH), 10.96 (d, $^3J_{H,H}$ = 13.5 Hz, 1H, NH). ^{19}F NMR (DMSO-d_6): δ −140.8

(m). Anal. calcd. for $C_{36}H_{32}BF_2N_3O_4$: C, 69.8; H, 5.16; N, 6.78. Found: C, 69.7; H, 5.4; N, 7.1.

3-(2-Acetanilidoethen-1-yl)-5-methyl-1,7-diphenyl-2,6-dicarbethoxy-4,4-difluoro-4-bora-3a,4a,-diaza-s-indacene (12). A solution of compound **10** (200 mg, 0.32 mmol), Ac_2O (0.5 g, 4.9 mmol), and triethylamine (15 mg, 0.15 mmol) in acetonitrile (2 mL) was refluxed for 1 min. After cooling to room temperature, the mixture was poured into water and allowed to stand for 30 min. The product was filtered and recrystallized from EtOH. Yield 120 mg (56%). M.p. 145–146°C. ^{1}H NMR (DMSO-d_6): δ 1.01 (m, 6H, CH_2CH_3), 1.99 (s, 3H, $COCH_3$), 2.69 (s, 3H, CH_3), 4.08 (m, 4H, CH_2CH_3), 5.93 (d, $^{3}J_{H,H}$ = 14.7 Hz, 1H, CH), 6.78 (s, 1H, meso-CH), 7.38–7.48 (m, 12H, ArH), 7.64 (m, 3H, ArH), 8.93 (d, $^{3}J_{H,H}$ = 14.7 Hz, 1H, CH). Anal. calcd. for $C_{38}H_{34}BF_2N_3O_5$: C, 70.0; H, 5.14; N, 6.35. Found: C, 69.9; H, 5.1; N, 6.1.

2-Carbethoxy-3,7-dimetyl-1,9-diphenyl-4,4-difluoro-3a,4a,7-triaza-4-bora-cyclopenta[b]fluoren-8-on (13). A mixture of aldehyde **5** (200 mg, 0.37 mmol), acetic acid (22 mg, 0.37 mmol), 27% methanol solution of methylamine (100 mg), and toluene (3 mL) was refluxed for 2 min. After cooling to room temperature, the precipitate was filtered. Yield 80 mg (42%). M.p. 273–274°C. ^{1}H NMR (DMSO-d_6): δ 1.04 (t, 3H, CH_2CH_3), 2.85 (s, 3H, CH_3), 3.43 (s, 3H, NCH_3), 4.10 (q, 2H, CH_2CH_3), 6.58 (d, $^{3}J_{H,H}$ = 6.9 Hz, 1H, CH), 7.11 (s, 1H,meso-CH), 7.47 (m, 8H, ArH), 7.64 (m, 2H, ArH), 7.84 (d, $^{3}J_{H,H}$ = 6.9 Hz, 1H, CH).^{19}F NMR (DMSO-d_6): δ −141.6 (m). LS-MS: m/z 511 $[M]^+$. Anal. calcd. for $C_{29}H_{24}BF_2N_3O_3$: C, 68.1; H, 4.69; N, 8.22. Found: C, 68.4; H, 4.6; N, 7.96.

3-(2-Diethylaminoethen-1-yl)-5-methyl-1,7-diphenyl-2,6-dicarbethoxy-4,4-difluoro-4-bora-3a,4a,-diaza-s-indacene (14). a. A solution of aldehyde **5** (270 mg, 0.5 mmol) and triethylamine (150 mg, 1.5 mmol) in dioxane (3 mL) was allowed to stand for 24 h at room temperature. The reaction mixture was purified by column chromatography on silica gel (eluent CH_2Cl_2) to give the pure product. Yield 100 mg (33%).

b. A solution of aldehyde **5** (136 mg, 0.25 mmol), diethylamine (91 mg, 1.25 mmol), and acetic acid (60 mg, 1 mmol) in methanol (2 mL) was heated at reflux for 5 min. After cooling to room temperature, the product was filtered and purified by column chromatography (eluent hexane-EtOAc, 3:2). Yield 50 mg (33%).

M.p. 188–189°C. ^{1}H NMR (DMSO-d_6): δ 0.92 (t, 3H, CH_2CH_3), 0.99 (t, 3H, CH_2CH_3), 1.25 (t, 6H, NCH_2CH_3), 2.71 (s, 3H, CH_3), 3.49 (q, 4H, NCH_2CH_3), 4.03 (m, 4H, CH_2CH_3), 6.10 (d, $^{3}J_{H,H}$ = 12.9 Hz, 1H, CH), 6.28 (s, 1H, meso-CH), 7.30–7.44 (m, 10H, ArH), 8.25 (d, $^{3}J_{H,H}$ = 12.9 Hz, 1H, CH). ^{19}F NMR (DMSO-d_6): δ −141.1 (m). Anal. calcd. for $C_{34}H_{36}BF_2N_3O_4$: C, 68.1; H, 6.0; N, 7.01. Found: C, 67.9; H, 5.9; N, 7.1.

3-(2-Dibuthylaminoethen-1-yl)-5-methyl-1,7-diphenyl-2,6-dicarbethoxy-4,4-difluoro-4-bora-3a,4a,-diaza-s-indacene (15). The product was prepared using tributylamine analogously to **14**. Yield 180 mg (54 %). M.p. 179–180°C. ^{1}H NMR (DMSO-d_6): δ 0.97 (m, 12H, $CH_2CH_3+N(CH_2)_3CH_3$), 1.39 (m, 4H, CH_2), 1.65 (m, 4H, CH_2), 2.7 (s, 3H, CH_3), 3.44 (q, 4H, NCH_2), 4.04 (m, 4H, CH_2CH_3), 6.11 (d, $^{3}J_{H,H}$ = 13.2 Hz, 1H, CH), 6.27 (s, 1H, meso-CH), 7.30–7.42 (m, 10H, ArH), 8.23 (d, $^{3}J_{H,H}$ = 13.2 Hz, 1H, CH). Anal. calcd. for $C_{38}H_{45}BF_2N_3O_4$: C, 69.6; H, 6.87; N, 6.41. Found: C, 69.9; H, 6.9; N, 6.2.

Reaction of aldehyde 5 with ethyldiisopropylamine. A solution of aldehyde **5** (270 mg, 0.5 mmol), ethyldiisopropylamine (130 mg, 1 mmol) in dioxane (3 mL) was allowed to stand for 24 h at room temperature. The reaction mixture was purified by column chromatography on silica gel (eluent CH_2Cl_2) to give 110 mg of the mixture of two dyes. ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 6H, CH_2CH_3), 1.07 (t, 6H, CH_2CH_3), 1.36 (m, 21H, $CH(CH_3)_2$ + NCH_2CH_3), 2.86 (s, 6H, CH_3), 3.47 (q, 2H, NCH_2CH_3), 3.75 (m, 2H, $CH(CH_3)_2$), 4.01–4.11 (m, 8H, CH_2CH_3), 4.28 (m, 1H, $CH(CH_3)_2$), 6.31 (d, $^{3}J_{H,H}$ = 13.5 Hz, 1H, CH), 6.43 (m, 3H, meso-CH + CH), 7.25–7.44 (m, 20H, ArH), 8.57 (d, $^{3}J_{H,H}$ = 13.5 Hz, 1H, CH), 8.69 (d, $^{3}J_{H,H}$ = 13.5 Hz, 1H, CH).

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Facile, Efficient, and Eco-Friendly Synthesis of Benzo[b]pyran-2-imines over MgO and Transformation to the Coumarin Derivatives

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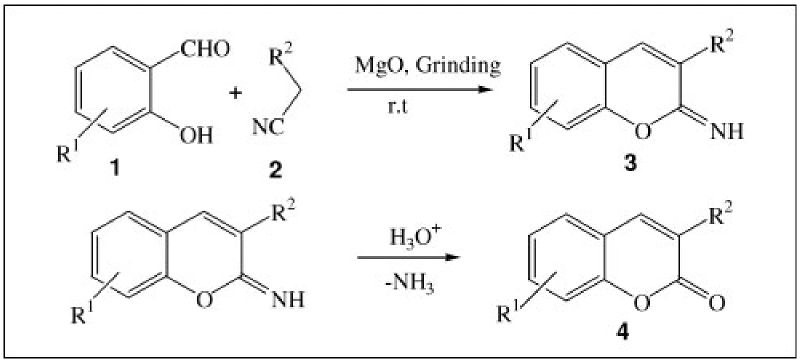

Room temperature synthesis of benzo[b]pyran-2-imine derivatives *via* the Knoevenagel condensation of malononitrile and cyanoacetates with salicylaldehyde derivatives over MgO and their transformation to the known coumarins is described. The satisfactory results were obtained with good yields, short reaction time, and simplicity in the experimental procedure.

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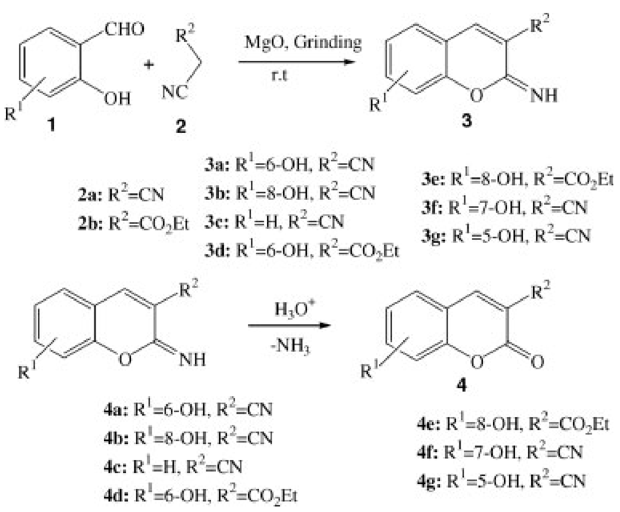
INTRODUCTION

Organic reactions under solvent-free [1] and aqueous [2] conditions have increasingly attracted chemists' interests, particularly from the viewpoint of green chemistry [3]. As an important carbon-carbon bond forming reaction, Knoevenagel condensation has been extensively studied. Generally, this type of reaction is catalyzed by base or Lewis acid in the liquid-phase system. In recent years, chemists paid more and more attention to the clean synthesis of alkenes by Knoevenagel condensations. Alkali metal hydroxides (e.g., NaOH and KOH), pyridine, and piperidine are the traditional catalysts used in these reactions. However, basic zeolites, such as Cs-exchanged NaX (CsNaX) and GeX, as well as cesium and cesium-lanthanum impregnated mesoporous MCM-41 are also able to catalyze the Knoevenagel condensation under mild reaction conditions [4]. The Knoevenagel condensations between aldehydes and malononitrile in dry media catalyzed by silica gel [5], ammonium acetate (NH_4OAc)-basic alumina [6], and zinc dichloride [7] have been reported. We described the same reactions, which could proceed efficiently in NH_4Cl aqueous solution [8]. Recently, we reported a convenient method for the preparation of coumarins *via* the Knoevenagel reaction in ionic liquids [ILs] [9].

Magnesium oxide has been used for benzylation of aromatic compounds [10], transesterification [11], Michael addition of sulfonamides to α,β-unsaturated esters [12], synthesis of chiral epoxy ketones, chiral nitro alcohols, and Michael adducts [13], etc. More recently, we reported the efficient synthesis of nitrones over MgO under solvent-free conditions [14]. In continuation of our recent interest to use solid supports, ILs, water, or solventless systems as a green reaction medium and microwave (MW)-mediated reactions [15], we wish to report here the synthesis of several benzopyran-2-imines over MgO in solventless system followed by their transformation to the coumarin derivatives without using MW and conventional heating technique in solventless system over MgO solid support (Scheme 1).

The use of ILs has received more attention as eco-friendly, reusable, and alternative reaction media in organic synthesis because of their unique properties [16–21]. A number of organic reactions, including hydrogenation, oxidation, and C—C bond forming reactions, have already been demonstrated in ILs [22–25]. We first examined the reaction of 2,5-dihydroxysalicylaldehyde with active methylene compounds **2a–b** over a variety of solid supports at room temperature (Table 1). As shown in Table 1, we found that the

Scheme 1



reaction using MgO as a solid support was accelerated to produce the related 3-cyano-2H-1-benzopyran-2-imines **3a** and **3d** in 93% and 91% yields, respectively, at room temperature for 25 min by grinding.

In another experiment, for the same reaction, several butylmethylimidazolium-based ILs, [bmim]X, with varying anions, such as Cl^-, BF_4^-, and PF_6^-, were examined in the presence of $KHCO_3$ at room temperature. The observation shows that the reaction in ILs was carried out slower with lower yields in comparison with the reaction by hand grinding of reactants over MgO and all ILs examined gave similar results (entries 5–7). The reactions in ILs were conducted at higher temperatures for optimizing the conditions and no significant improvements were observed in yields or reaction times. There is no significance difference in the results using different bases such as Na_2CO_3, K_2CO_3, $NaHCO_3$, NH_4OAc, NaOH, NH_4Cl, and piperidine as the catalyst in this procedure. It should be noted that in the absence of any catalyst, the condensation reaction failed to give the desired 2H-1-benzopyran-2-imines.

From the results obtained as shown in Table 1, it is clear that the reaction over MgO should be the method of choice for synthesizing 2H-1-benzopyran-2-imines, because a comparatively higher yield was achieved in a shorter reaction time. Under identical conditions, a variety of salicylaldehydes were reacted with active methylene compounds to afford the related benzo[b]pyran-2-imine derivatives in good to high yield, which hydrolyzed in acidic conditions to afford the related coumarins (Table 2). A plausible mechanism for the Knoevenagel condensation reaction catalyzed by MgO is outlined in Scheme 2.

In summary, we have successfully applied MgO as efficient support and catalyst for the synthesis of benzo[b]pyran-2-imine derivatives in solventless system. This methodology is highly profitable in terms of convenient, fast, and safe synthesis of benzo[b]pyran-2-imines in pure form and good yields. The products were purified by column chromatography using hexane/ethylacetate mixtures as eluent and were characterized by ^1H NMR, ^{13}C NMR, IR, and elemental analysis.

EXPERIMENTAL

General information. All reagents were purchased from Merck Company (Germany) and used without further purification. ^1H NMR spectra were obtained in $CDCl_3$ solution from Bruker Avance AC-400MHz or 300MHz and ^{13}C NMR spectra at 100MHz or 75MHz on the aforementioned instrument using TMS as internal standard. Elemental analyses were carried out on a Perkin–Elmer 240C elemental analyzer and are reported in percent atomic abundance.

Preparation of benzo[b]pyran-2-imine in ILs, general procedure. The selected arylaldehyde (10 mmol), the active methylene compound (11 mmol), $KHCO_3$ (10 mmol), and IL

Table 1

Effect of different solid supports and ionic liquids on synthesis of 2H-1-benzopyran-2-imines **3a** and **3d**.[a]

				Yield[d](%)	
Entry	Solid support[b]/base	Ionic liquid[c]	Time (min)	**3a**	**3d**
1	MgO	–	25	93	91
2	Alumina/$KHCO_3$	–	30	62	58
3	Molecular sieves 3A°/$KHCO_3$	–	35	59	60
4	Silica gel/$KHCO_3$	–	45	50	54
5	–	[bmim]Cl/$KHCO_3$	120	58	55
6	–	[bmim]PF_6/$KHCO_3$	120	55	58
7	–	[bmim]BF_4/$KHCO_3$	120	61	64

[a] Reaction conditions: 10 mmole of salicylaldehyde, 11 mmole of active methylene compound, and 10 mmole of base.
[b] Reactants were carried out by Hand-Grinding over solid support at room temperature.
[c] Reactants were carried out by stirring of the mixture of reactants in ionic liquids (2 mL) at room temperature.
[d] Isolated yields after column chromatography.

Table 2

Synthesis of benzo[b]pyran-2-imine derivatives by hand-grinding over MgO and their transformation to coumarins.[a]

			Product **3**		Product **4**
Entry	R^1	R^2	Time (min)	Yield[b] (%)	Yield[b] (%)
1	6-OH	CN	25	93	92
2	8-OH	CN	25	91	89
3	H	CN	30	93	90
4	6-OH	CO_2Et	28	91	90
5	8-OH	CO_2Et	28	89	88
6	7-OH	CN	22	94	92
7	5-OH	CN	22	95	94

[a] Reaction conditions: 10 mmole of salicylaldehyde, 11 mmole of active methylene compound, and 10 mmole of base.

[b] Isolated yields after column chromatography.

(2 ml) were stirred at room temperature for appropriate time (Table 1). The completion of reaction was monitored by thin layer chromatography (TLC) using (ethylacetate/n-hexane:1/5) as eluent. After completion of the reaction, the mixture was extracted with ethylacetate. The extracts were concentrated on a rotary evaporator, and the crude mixture was purified by silica gel (Merck 230–240 mesh) column chromatography using (ethylacetate/n-hexane:1/5) mixtures as eluent.

Preparation of benzo[b]pyran-2-imine over solid supports, general procedure. The selected aldehyde (10 mmol), the active methylene compound (11 mmol), $KHCO_3$ (10 mmol), and solid support (1 g) were co-grinded in a mortar at room temperature for appropriate time (Table 2). The completion of reaction was monitored by TLC using (ethylacetate/petroleum:1/5) as eluent. After completion of the reaction, the mixture was extracted with ethylacetate. The extracts were concentrated on a rotary evaporator, and the crude mixture was purified by silica gel (Merck 230–240 mesh) column chromatography using (ethylacetate/n-hexane:1/5) mixtures as eluent.

3-Cyano-6-hydroxy-benzo[b]pyran-2-imine (3a). IR (KBr, λ_{max} = cm^{-1}: 3411 (broad, OH), 3302 (NH), 2222 (CN), 1660 (C=NH), 1612 (C=C); ^{1}H NMR: δ 8.40 (s, 1H), 7.51 (dd, 1H, *J* = 8.12, 1.43 Hz), 7.39 (d, 1H, *J* = 1.43 Hz), 7.36 (d, 1H, *J* = 8.12 Hz); ^{13}C NMR: δ 161.1, 151.2, 132.3, 125.7, 124.5, 117.8, 116.4, 115.1, 114.1, 104.4; Anal. Calcd. for $C_{10}H_6N_2O_2$: C,64.52; H,2.25; N,15.05. Found: C,64.55; H,2.22; N,15.12.

3-Cyano-8-hydroxy-benzo[b]pyran-2-imine (3b). IR (KBr, λ_{max} = cm^{-1}: 3383 (broad, OH), 3310 (NH), 2219 (CN), 1658 (C=NH), 1608 (C=C); ^{1}H NMR: δ 8.15 (s, 1H), 7.57 (dd, 1H, *J* = 8.12, 8.08 Hz), 7.49 (dd, 1H, *J* = 8.12, 1.67 Hz), 7.41 (dd, 1H, *J* = 8.08, 1.67 Hz); ^{13}C NMR: δ 160.5, 150.9, 140.1, 131.08, 123.6, 120.2, 116.1, 115.8, 112.7, 105.5; Anal. Calcd. for $C_{10}H_6N_2O_2$: C,64.52; H,2.25; N,15.05. Found: C,64.59; H,2.20; N,15.09.

3-Cyano benzo[b]pyran-2-imine (3c). IR (KBr, λ_{max} = cm^{-1}: 3308 (NH), 2218 (CN), 1658 (C=NH), 1610 (C=C); ^{1}H NMR: δ 8.12 (s, 1H), 7.61 (dd, 1H, *J* = 8.10, 1.42 Hz), 7.43 (m, 2H), 7.40 (dd, 1H, *J* = 8.12, 1.45 Hz); ^{13}C NMR: δ 161.0, 150.4, 138.4, 131.5, 128.5, 119.5, 118.8, 117.0, 116.9, 105.1; Anal. Calcd. for $C_{10}H_6N_2O$: C, 70.58; H, 3.55; N, 16.46. Found: C, 71.01; H, 3.51; N, 16.50.

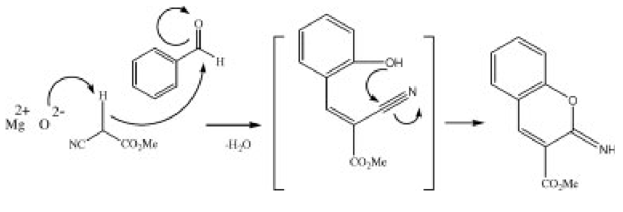
3-Carb-ethoxy-6-hydroxy-benzo[b]pyran-2-imine (3d). IR λ_{max} = cm^{-1}: 3370 (broad, OH), 3315 (NH), 2225 (CN), 1712 (C=O), 1652 (C=NH), 1613 (C=C); ^{1}H NMR δ 8.64 (s, 1H), 7.79 (d, 1H, *J* = 1.51 Hz), 6.84 (dd, 1H, *J* = 8.19, 1.51 Hz), 6.73 (d, 1H, *J* = 8.19 Hz), 4.23 (q, 2H, *J* = 7.23 Hz), 1.29 (t, 3H, *J* = 7.23 Hz); ^{13}C NMR δ 166.1, 153.4, 145.4, 141.0, 138.2, 121.3, 120.4, 119.8, 117.5, 116.1, 62.0, 17.2; Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.95; H, 4.61; N, 6.08.

3-Carbethoxy-8-hydroxy-benzo[b]pyran-2-imine (3e): IR λ_{max} ***cm***^{1}**.** 3365 (broad, OH), 3311 (NH), 2221 (CN), 1710 (C=O), 1660 (C=NH), 1609 (C=C); ^{1}H NMR δ 8.67 (s, 1H), 7.57 (dd, 1H, *J* = 8.10, 7.98 Hz), 7.49 (dd, 1H, *J* = 8.10, 1.50 Hz), 7.41 (dd, 1H, *J* = 7.98, 1.53 Hz), 4.19 (q, 2H, *J* = 7.20 Hz), 1.26 (t, 3H, *J* = 7.20 Hz); ^{13}C NMR δ 168.6, 154.0, 147.0, 143.1, 140.1, 123.2, 120.0, 121.1, 116.6, 118.3, 63.1, 16.1; Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 62.02; H, 4.63; N, 6.09.

3-Cyano-7-hydroxy-benzo[b]pyran-2-imine (3f). IR (KBr, λ_{max} = cm^{-1}: 3357 (broad, OH), 3310 (NH), 2216 (CN), 1659 (C=NH), 1616 (C=C); ^{1}H NMR: δ 8.24 (s, 1H), 7.61 (dd, 1H, *J* = 7.88, 1.28 Hz), 7.31 (d, 1H, *J* = 7.88 Hz), 7.29 (d, 1H, *J* = 1.28 Hz); ^{13}C NMR: δ 159.1, 154.3, 141.7, 135.4, 128.8, 122.0, 119.8, 118.4, 118.02, 105.5; Anal. Calcd. for $C_{10}H_6N_2O_2$: C, 64.52; H, 2.25; N, 15.05. Found: C, 64.60; H, 2.21; N, 15.07.

3-Cyano-5-hydroxy-benzo[b]pyran-2-imine (3g). IR (KBr, λ_{max} = cm^{-1}: 3360 (broad, OH), 3300 (NH), 2219 (CN), 1706 (C=O), 1612 (C=C); ^{1}H NMR: δ 8.18 (s, 1H), 7.59 (dd, 1H, *J* = 7.80, 1.32 Hz), 7.30 (d, 1H, *J* = 7.80 Hz), 7.26 (d, 1H, *J* = 1.32 Hz); ^{13}C NMR: δ 157.9, 153.2, 140.0, 136.4, 127.7, 123.4, 119.8, 117.7, 116.5, 106.8; Anal. Calcd. for

Scheme 2



$C_{10}H_6N_2O_2$: C, 64.52; H, 2.25; N, 15.05. Found: C, 64.58; H, 2.19; N, 15.11.

Hydrolysis of the freshly prepared benzo[b]pyran-2-imines under acidic conditions afforded to related coumarins.

6-Hydroxy-2-oxo-2H-chromene-3-carbonitrile (4a). IR (KBr, λ_{max} = cm^{-1}: 3415 (broad, OH), 2229 (CN), 1712 (C=O), 1604 (C=C); ^{1}H NMR: δ 8.28 (s, 1H), 7.70 (dd, 1H, *J* = 7.88, 1.28 Hz), 7.39 (d, 1H, *J* = 7.85 Hz), 7.32 (d, 1H, *J* = 1.28 Hz); ^{13}C NMR: δ 159.5, 154.0, 136.5, 130.8, 126.5, 118.5, 118.3, 117.9, 115.2, 103.8; Anal. Calcd. for $C_{10}H_6NO_3$: C, 64.18; H, 2.69; N, 7.48. Found: C, 64.28; H, 2.66; N, 7.39.

8-Hydroxy-2-oxo-2H-chromene-3-carbonitrile (4b). IR (KBr, λ_{max} = cm^{-1}: 3371 (broad, OH), 2223 (CN), 1708 (C=O), 1610 (C=C); ^{1}H NMR: δ 8.24 (s, 1H), 7.68 (dd, 1H, *J* = 8.15, 8.10 Hz), 7.49 (dd, 1H, *J* = 8.15, 1.75 Hz), 7.41 (dd, 1H, *J* = 8.10, 1.70 Hz); ^{13}C NMR: δ 160.1, 151.4, 139.7, 132.1, 125.1, 119.0, 117.2, 115.4, 114.02, 101.1; Anal. Calcd. for $C_{10}H_6NO_3$: C, 64.18; H, 2.69; N, 7.48. Found: C, 64.28; H, 2.66; N, 7.39.

2-Oxo-2H-chromene-3-carbonitrile (4c). IR (KBr, λ_{max} = cm^{-1}: 2229 (CN), 1711 (C=O), 1608 (C=C); ^{1}H NMR: δ 8.19 (s, 1H), 7.65 (dd, 1H, *J* = 7.89, 1.22 Hz), 7.49 (m, 2H), 7.44 (dd, 1H, *J* = 8.10, 1.34 Hz); ^{13}C NMR: δ 162.5, 154.0, 136.5, 130.8, 126.5, 118.5, 118.3, 117.9, 115.2, 103.8; Anal. Calcd. for $C_{10}H_5NO_2$: C, 70.18; H, 2.94; N, 8.18. Found: C, 70.23; H, 2.91; N, 8.21.

Ethyl 6-Hydroxy-2-oxo-2H-chromene-3-carboxylate (4d). IR λ_{max} = cm^{-1}: 3313 (broad, OH), 3030, 2989, 1739 (C=O), 1672 (C=O), 1612 (C=C); ^{1}H NMR (300 MHz, DMSO-d6) δ 8.52 (s, 1H), 7.61 (dd, 1H, *J* = 8.13, 1.30 Hz), 7.30 (d, 1H, *J* = 1.32 Hz), 7.32 (d, 1H, *J* = 8.09 Hz), 4.20 (q, 2H, *J* = 7.21 Hz), 1.29 (t, 3H, *J* = 7.21 Hz); ^{13}C NMR (75MHz, DMSO-d6) δ 164.3, 152.2, 146.0, 142.6, 137.8, 119.53, 118.6, 116.1, 115.5, 115.1, 63.0, 18.6.

Ethyl 8-Hydroxy-2-oxo-2H-chromene-3-carboxylate (4e). IR λ_{max} = cm^{-1}: 3313 (broad, OH), 3030, 2989, 1739 (C=O), 1672 (C=O), 1672 (C=O); ^{1}H NMR (300 MHz, DMSO-d6) δ 8.01 (s, 1H), 7.60 (t, 1H, *J* = 7.91 Hz), 7.38 (dd, 1H, *J* = 7.91, 1.95 Hz), 7.32 (dd, 1H, *J* = 7.91, 1.95Hz), 4.15 (q, 2H, *J* = 7.18 Hz), 1.21 (t, 3H, *J* = 7.18 Hz); ^{13}C NMR (75MHz, DMSO-d6) δ 165.9, 156.4, 148.4, 145.9, 141.2, 123.4, 121.1, 121.0, 118.5, 117.3, 61.9, 18.4.

7-Hydroxy-2-oxo-2H-chromene-3-carbonitrile (4f). IR (KBr, λ_{max} = cm^{-1}: 3370 (broad, OH), 2220 (CN), 1709 (C=O), 1613 (C=C); ^{1}H NMR(300 MHz, DMSO-d6): δ 8.19 (s, 1H), 8.07 (s, 1H), 7.69 (dd, 1H, *J* = 7.81, 1.29 Hz), 7.43 (d, 1H, *J* = 7.81 Hz), 7.29 (d, 1H, *J* = 1.29 Hz); ^{13}C NMR: δ 160.1, 156.5, 143.8, 136.6, 129.1, 123.1, 120.5, 119.8, 118.3, 108.8; Anal. Calcd. for $C_{10}H_6NO_3$: C, 64.18; H, 2.69; N, 7.48. Found: C, 64.30; H, 2.61; N, 7.50.

5-Hydroxy-2-oxo-2H-chromene-3-carbonitrile (4g). IR (KBr, λ_{max} = cm^{-1}: 3383 (broad, OH), 2223 (CN), 1719 (C=O), 1611 (C=C); ^{1}H NMR(300 MHz, DMSO-d6): δ 8.14 (s, 1H), 7.61 (dd, 1H, *J* = 8.11, 1.31 Hz), 7.31 (dd, 1H, *J* = 7.98, 1.31 Hz), 7.29 (dd, 1H, *J* = 7.98, 8.11 Hz); ^{13}C NMR: δ 165.0, 156.7, 143.2, 136.8, 130.8, 124.4, 120.2, 119.4, 118.5, 109.1; Anal. Calcd. for $C_{10}H_6NO_3$: C, 64.18; H, 2.69; N, 7.48. Found: C, 64.27; H, 2.64; N, 7.52.

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Application of 3-Methylthiopyrido[4,3-*e*]-1,4,2-dithiazine 1,1-Dioxide to the Synthesis of Novel Series of 4*H*-Pyrido[4,3-*e*]-1,2,4-thiadiazine Derivatives with Potential Biological Activity

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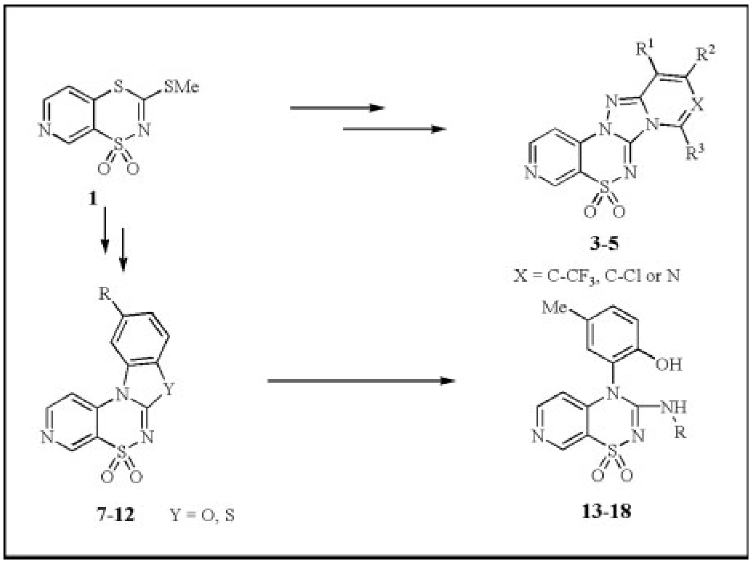

Two series of 4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine derivatives **3–5** and **7–12** were synthesized by the reactions of 3-methylthiopyrido[4,3-*e*]-1,4,2-dithiazine 1,1-dioxide **1** with 2-or 6-hydrazinoazines and 2-aminophenols or 2-aminothiophenol, respectively. Aminolysis of **8** (R = Me, Y = O) afforded the corresponding 3-(R-amino)-4-(2-hydroxy-5-methylphenyl)-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides **13–18**. The structures of these compounds were confirmed on the basis of elemental analysis, spectral data, and X-ray crystallography. Compounds **3–5**, **7–10**, **12–15**, and **17–18** were screened *in vitro* for antibacterial activity. Moreover, preliminary *in vitro* anticancer assay was performed for compounds **3**, **7**, **10**, **11–13**, and **17–18** at the National Cancer Institute (Bethesda, MD) at a single dose (10 μ*M*) in the full NCI 60 cell panel.

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INTRODUCTION

The aryl/heteroaryl sulfonamides constitute an important class of compounds with several types of biological activities and well-established safety profile [1]. Previously, as part of an extensive research program on the synthesis of compound containing 2-thiobenzenesulfonamide scaffold, several series of novel sulfonamides with remarkable antitumor activity [2–22], anti-HIV activity [2–6,16,22–28], or carbonic anhydrase inhibitors [29–31] were discovered in our laboratories. In the course of study on the synthesis of heterocyclic compounds bearing sulfonamide moiety, we developed a new synthetic method for preparation of 4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (**I–III**, Fig. 1) which involves reaction of the previously described [32] 3-methylthiopyrido[4,3-*e*]-1,4,2-thiadiazine 1,1-dioxide (**1**) with 2- or 6-hydrazinoazines, 2-aminophenols or 2-aminothiophenols as a key step. The previously described 4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides (**IV** and **V**, Fig. 1) as the potassium channel openers, were obtained starting from 4-(hydroxy-, amino-, or alkylamino) pyridine-3-sulfonamide [33,34].

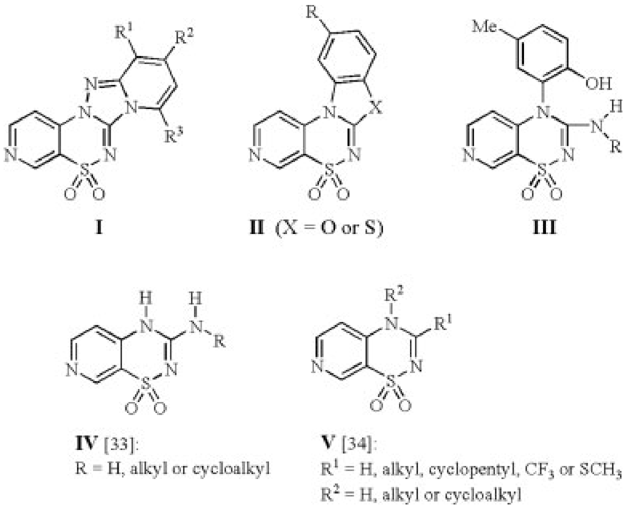


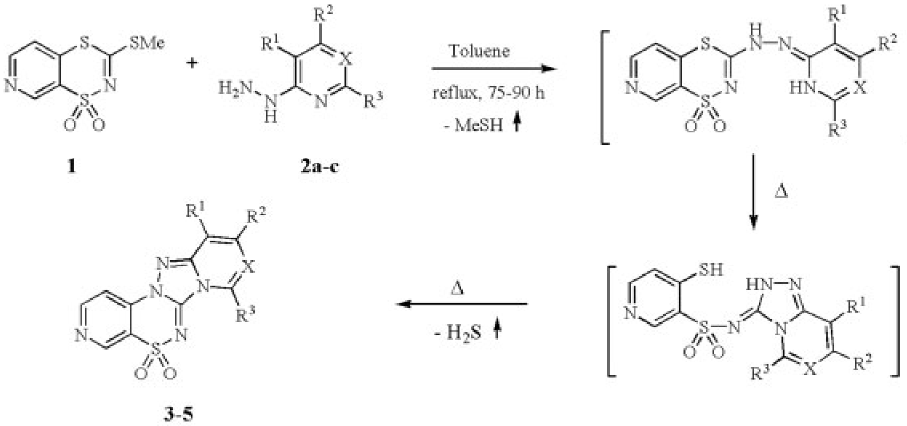
Figure 1. General structures of novel 4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides **I–III** and structures of known potassium channel openers **IV** and **V**.

RESULTS AND DISCUSSION

Synthesis of the target compounds **3–5** and **7–12** was achieved by a convenient one-pot procedure starting from methylthiopyridodithiazine **1** as shown in Schemes 1 and 2. Thus, the reaction of **1** with appropriate 2-hydrazinopyridine **2a–b** or 2,4-dimethyl-6-hydrazinopyrimidine **2c** carried out in boiling toluene led to the pyridothiadiazine derivatives **3–5**. An analogous reaction of 2-aminophenols **6a–e** or 2-aminothiophenol **6f** with **1** furnished 5-thia-3,6,11b-triaza-benzo[*c*]fluorene 5,5-dioxides **7–12**. We propose a reaction sequence for the transformations as shown in Scheme 2. The initial step is believed to be formation of 3-arylaminopyridodithiazine intermediate **A**, which may arise by nucleophilic displacement of the thiomethyl group, and subsequent transformation resulting in the formation of 4-mercaptopyridine intermediate **B**. In the final stage of the reaction, the nonisolable intermediate **B** undergoes an intramolecular ring closure *via* two-step addition–elimination (S_NAr) process leading to the formation of benzo[*c*]fluorene derivatives **7–12** in 46–58% yields. The structures of the newly obtained compounds **3–5** and **7–12** were confirmed by elemental analyses (C, H, N) and spectroscopic data presented in the experimental section.

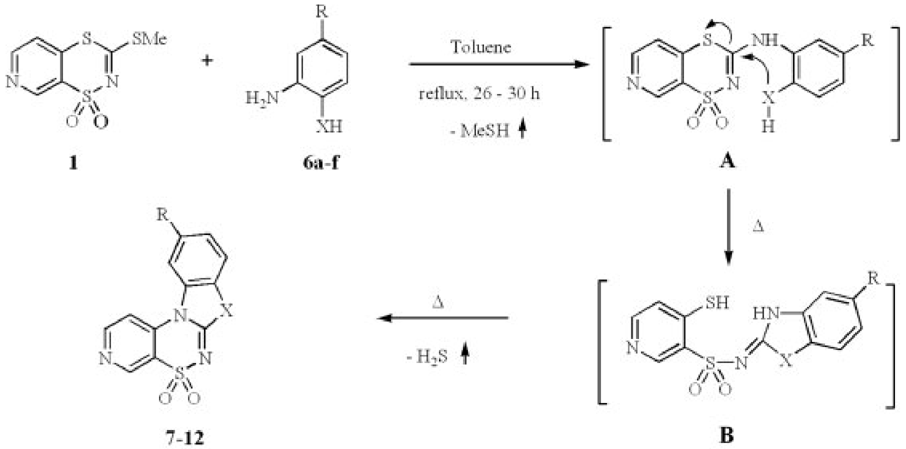
Further reactions of **8** with methylhydrazine or amines in boiling THF led to the formation of desired 3-(R-amino)-4-(2-hydroxy-5-methylphenyl)-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides **13–18** in good yields (78–92%). The proposed mechanism leading to the compounds **13–18** is outlined in Scheme 3. Nucleophilic attack of amine at the carbon C-6b atom of benzo[*c*]fluorene ring results in C—O bond cleavage, and formation of the 4-substituted-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine products **13–18** (structure **C**). It is worth noticing, however, that the spectroscopic data for the latter

Scheme 1. Synthesis and proposed mechanism of the formation of pyridothiadiazine derivatives **3–5**.



Compd	R¹	R²	X	R³	% yield
2a, 3	Cl	H	C-CF$_3$	H	68
2b, 4	CF$_3$	H	C-Cl	H	63
2c, 5	H	Me	N	Me	51

Scheme 2. Syntheses and proposed mechanism of the formation of 5-thia-3,6,11b-triaza-benzo[c]fluorene 5,5-dioxide derivatives **7–12**.



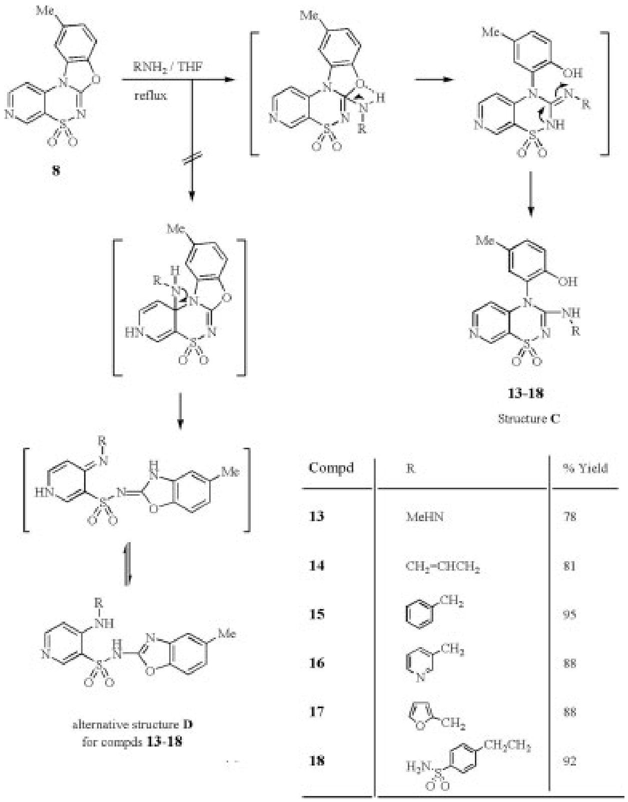
Compd	X	R	% yield
6a, 7	O	H	50
6b, 8	O	Me	57
6c, 9	O	Cl	49
6d, 10	O	NO_2	46
6e, 11	O	$EtSO_2$	58
6f, 12	S	H	49

compounds (Experimental section) did not allow straightforward discrimination between the actual pyrido[4,3-*e*]-1,2,4-thiadiazines **13–18** (structure **C**) and the alternative 4-aminopyridine-3-sulfonamides (structure **D**, Scheme 3). Therefore, X-ray crystallography was undertaken to confirm the proposed structure **C** on representative compounds **14** and **17**. Molecular structures of compounds **14** and **17** are shown in Figures 2 and 3, respectively. These compounds crystallize as pyridothiadiazine derivatives, *i.e.*, the 2-hydroxy-5-methylphenyl moiety is bound to the N-4 nitrogen atom of 1,2,4-thiadiazine ring.

Biological assay. Compounds **3–5**, **7–10**, **12–15**, and **17–18** were tested *in vitro* for antibacterial activity. The investigation was carried out on 26 strains of anaerobic bacteria isolated from the oral cavity, respiratory tract, and intestinal tract, as well as 11 standard strains. The anaerobes belonged to the following genera: *Finegoldia* (2 strains), *Micromonas* (3), *Actinomyces* (2), *Propionibacterium* (2), *Prevotella* (6), *Porphyromonas* (2), *Fusobacterium* (3), *Bacterioides* (6), and standard strains: *Bacteroides fragilis* ATCC 25285, *Fusobacterium nucleatum* ATCC 25586, *Peptostreptococcus anaerobius* ATCC 27337, *Peptostreptococcus magnus* ATCC 29328, and *Propionibacterium acnes* ATCC 11827. The susceptibility of the anaerobic bacteria was determined by means of the plate dilution technique in Brucella agar supplemented with 5% sheep blood [35–37]. The derivatives were dissolved in 1 mL of DMSO immediately before the experiment. Further dilutions were performed in sterile distilled water. The following concentrations of the compounds were used: 200, 100, 50, 25, 12.5, and 6.2 μg/mL. Metronidazole was used as a reference compound. The inoculum containing 10^6 CFU/spot was applied to the agar plates with Steers replicator. The inoculated agar plates and compound-free ones were incubated in anaerobic jars for 48 h at 37°C in 10% CO_2, 10% H_2 and 80% N_2 atmosphere with palladium catalyst and indicator of anaerobiosis.

Furthermore, 25 strains of aerobic bacteria isolated from the oral cavity, respiratory tract, and intestinal tract as well as six standard strains were tested. The aerobes were as follows: *Staphylococcus* (four strains), *Corynebacterium* (2), *Klebsiella* (3), *Acinetobacter* (2), *Escherichia* (6), *Pseudomonas* (8), as well as standard strains: *Staphylococcus aureus* ATCC 25923, *Enterococcus faecalis* ATCC 29212, *Klebsiella pneumoniae* ATCC 13883, *Acinetobacter baumannii* ATCC 19606, *Escherichia coli* ATCC 25922, *and Pseudomonas aeruginosa* ATCC 27853. Amikacin was used as a reference compound. The susceptibility of the aerobic bacteria was determined by means of agar dilution technique with Mueller-Hinton agar [35–37]. Further dilutions were performed in sterile distilled water. The following concentrations of the compounds were used: 200, 100, 50, 25, 12.5, and 6.2 μg/mL. The inoculum containing 10^6

Scheme 3. Syntheses and proposed mechanism of the formation of 3-(R-amino)-4-(2-hydroxy-5-methylphenyl)-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxides **13–18**.



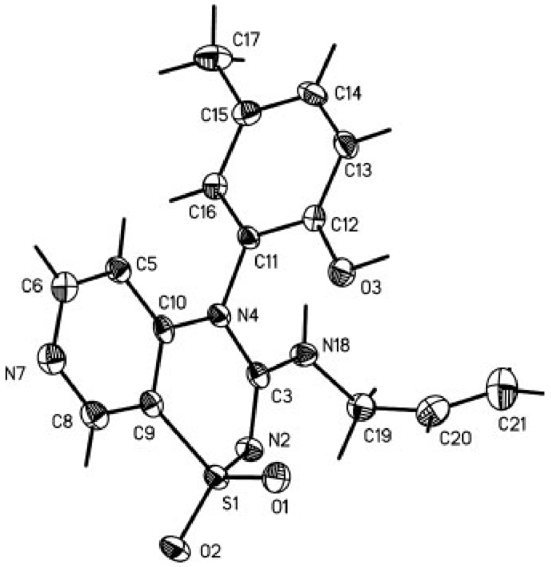


Figure 2. ORTEP drawing of compound **14** with the atom labeling scheme. Displacement ellipsoids are drawn at the 50% probability level.

CFU/spot was applied to the agar plates with Steers replicator. The inoculated agar plates and the compound-free ones were incubated for 24 h at 37°C in aerobic conditions. The minimal inhibitory concentration (MIC) was defined as the lowest compound concentration, which inhibited growth of bacteria.

The susceptibility of anaerobic and aerobic bacteria toward compounds **3–5**, **7–10**, **12–15**, and **17–18** was shown in Table 1. The results have been compared with those obtained either for metronidazole (anaerobes) or amikacin (aerobes). Activity toward anaerobic bacteria exhibited 3 of 13 tested compounds (**3**, **4**, and **18**). The anaerobes were the most susceptible for compounds **4** and **18** which inhibited 7–8 (27–31%) strains at concentrations in the range from 25 to 100 μg/mL, whereas compound **3** inhibited growth of 2 (8%) strains in lower concentrations within limits 6.2–25 μg/mL) and other 3 (12%) strains at concentration of 100 μg/mL (Table 1). The compounds active toward anaerobic bacteria (**3**, **4**, and **18**) were effective to both Gram-positive and Gram-negative strains.

In general, aerobic bacteria were less susceptible to the tested compounds **3–5**, **7–10**, **12–15**, and **17–18**. Activity toward aerobes was shown only for compound **13** which acted against 6 (24%) strains at concentrations ranged from 50 to 100 μg/mL and was more effective to Gram-negative strains. It is worthy of notice, however, that **13** was able to inhibit growth of four among six standard strains tested, such as *Staphylococcus aureus* ATCC 25923, *Enterococcus faecalis* ATCC 29212, *Klebsiella pneumoniae* ATCC 13883, and *Escherichia*

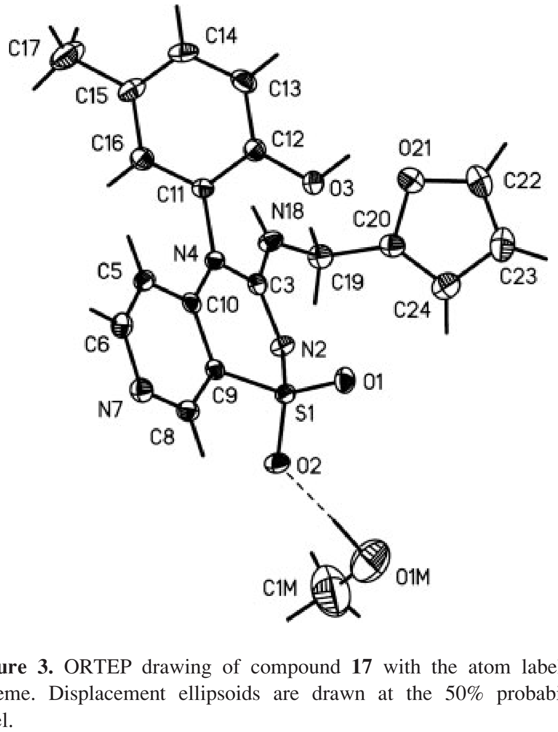


Figure 3. ORTEP drawing of compound **17** with the atom labeling scheme. Displacement ellipsoids are drawn at the 50% probability level.

Table 1

Antibacterial activity of compounds **3–5**, **7–10**, **12–15**, and **17–18**.

	MIC (μg/mL)													
Anaerobic bacteria	Metronidazole[a]	3	4	5	7	8	9	10	12	13	14	15	17	18
Gram-positive														
Finegoldia magna	≤0.4	–	50	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	50
Micromonas micros	≤0.4	≤6.2	50	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	25
Actinomyces israelii	1.0	≥200	25	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	50
Propionibacterium acnes	≥100	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200
Gram-negative														
Prevotella bivia	≤0.4	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200
Prevotella buccalis	≤0.4	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200
Prevotella intermedia	≤0.4	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200
Prevotella loescheii	≤0.4	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200
Porphyromonas asaccharolytica	≤0.4	100	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	50
Fusobacterium nucleatum	≤0.4	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	100
Fusobacterium necrophorum	1.6	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200
Bacteroides fragilis	≤0.4	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200
Bacteroides ureolyticus	12.5	25	100	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200
Aerobic bacteria	Amikacin[b]													
Gram-positive														
Staphylococcus aureus	≤6.2	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	100	≥200	≥200	≥200	≥200
Corynebacterium spp.	25	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	100	≥200	≥200	≥200	≥200
Gram-negative														
Klebsiella pneumoniae	≤6.2	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200
Acinetobacter baumannii	≤6.2	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200
Escherichia coli	≤6.2	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	100	≥200	≥200	≥200	≥200
Pseudomonas aeruginosa	≤6.2	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200
Pseudomonas stutzeri	12.5	≥200	≥200	≥200	≥200	≥200	≥200	≥200	≥200	50	≥200	≥200	≥200	≥200

[a] Metronidazole (Sigma).

[b] Amikacin sulfate salt (Sigma).

coli ATCC 25922 (MIC 100 μg/mL). The remaining compounds were active toward aerobic bacteria at the concentration equal or higher then 200 μg/mL.

The compounds **3**, **7**, **10**, **11–13**, and **17–18** were tested *in vitro* at the National Cancer Institute (Bethesda, MD) at a single dose (10 μ*M*) in the full NCI 60 cell panel. All tested compounds acted selectively and exhibited structure depended reasonable or high activity against one to two cell lines of leukemia, lung and CNS cancers, or renal cancer cells as shown in Table 2. Compounds **7** and **17** were the most potent of all derivatives tested. Relatively highest sensitivity to the compounds described here was found for cell lines of CNS cancer (SF-295), leukemia (SR, MOLT-4), and lung cancer (HOP-92) (Table 2). It is pertinent to note that further evaluations concerning biological activity of pyridosulfonamides of type **II** and **III** (Fig. 1) are still in progress.

EXPERIMENTAL

The following instruments and parameters were used: melting points Büchi 535 apparatus; ir spectra: KBr pellets, 400–4000 cm^{-1} Perkin Elmer 1600 FTIR spectrometer; ^{1}H and ^{13}C NMR: Varian Gemini 200 apparatus at 200 and 50 MHz, respectively; chemical shifts are expressed as δ values relative to Me_4Si as standard. The starting 3-methylthiopyrido[4,3-*e*]-1,4,2-dithiazine 1,1-dioxide **1** was prepared according to method described previously [32].

General procedure for the preparation of pyridothiadiazine derivatives (3–5). A mixture of 3-methylthiopyrido[4,3-*e*]-1,4,2-dithiazine 1,1-dioxide **1** (1.48 g, 6 mmol) and the corresponding 2-hydrazinopyridine **2a–b** or 2,4-dimethyl-6-hydrazinopyrimidine **2c** (6 mmol) in dry toluene (20 mL) was refluxed with stirring until the evolution of MeSH and H_2S had ceased (75–90 h). (CAUTION: because of high toxicity, MeSH and H_2S should be trapped in an aqueous NaOH solution). After cooling to room temperature, the precipitate was collected by filtration, washed successively with toluene (4 × 3 mL) and methanol (3 × 1 mL), dried and purified by crystallization from DMF. In this manner, the following compounds were obtained.

10-Chloro-8-trifluoromethyl-5-thia-3,6,6b,11,11a-pentaazabenzo[a]fluorene 5,5-dioxide (3). Starting from 3-chloro-5-trifluoromethyl-2-hydrazinopyridine **2a** (1.27 g) the title compound **3** was obtained (1.55 g, 68%): mp 347–348°C dec.; ir (KBr): 1645, 1580 (C=N, C=C) 1310, 1185, 1160 (SO_2) cm^{-1}; ^{1}H NMR (dimethyl sulfoxide-d$_6$): δ 8.05 (d, J = 5.6 Hz, 1H, H-1), 8.30 (s, 1H, H-9), 8.99 (s, 1H, H-7), 9.03 (d, J = 5.6 Hz, 1H, H-2), 9.26 (s, 1H, H-4) ppm; ^{13}C NMR (dimethyl sulfoxide-d$_6$): δ 109.95 (CF_3), 115.95, 116.65, 119.17,

Table 2

In vitro tumor growth inhibition data for compounds **3, 7, 10, 11–13**, and **17–18**.[a]

Compound	Tumor cell line	Growth inhibition %
3	Leukemia	
	MOLT-4	67.7
7	Leukemia	
	SR	89.8
	MOLT-4	82.2
10	CNS cancer	
	SF-295	61.1
11	Nonsmall cell lung cancer	
	HOP-92	80.7
12	Leukemia	
	CRF-CEM	65.6
	Nonsmall cell lung cancer	
	HOP-92	63.1
13	Renal cancer	
	RXF 393	60.1
	UO-31	51.5
17	CNS cancer	
	SF-295	99.1
	Nonsmall cell lung cancer	
	HOP-92	72.3
18	CNS cancer	
	SF-295	81.4

[a] Data obtained from the National Cancer Institute (Bethesda MD). Compounds were tested at a single dose (10 μ*M*) in the full NCI 60 cell panel.

121.15, 124.80, 128.56, 138.05, 143.33, 143.55, 146.56, 154.15 ppm. *Anal*. Calcd. for $C_{12}H_5ClF_3N_5O_2S$ (375.71): C, 38.36; H, 1.34; N, 18.64. Found: C, 38.38, H, 1.42, N, 18.76.

8-Chloro-10-trifluoromethyl-5-thia-3,6,6b,11,11a-pentaaza-benzo[a]fluorene 5,5-dioxide (4). Starting from 5-chloro-3-trifluoromethyl-2-hydrazinopyridine **2b** (1.27 g) the title **4** was obtained (1.43 g, 63%): mp 392–394°C dec.; ir (KBr): 1635, 1585, (C=N, C=C), 1335, 1310, 1170, 1145 (SO_2) cm^{-1}; ^{1}H NMR (dimethyl sulfoxide-d$_6$): δ 7.97 (d, *J* = 5.5 Hz, 1H, H-1), 8.31 (s, 1H, H-9), 8.96 (d, *J* = 5.5 Hz, 1H, H-2), 9.05 (s, 1H, H-7), 9.20 (s, 1H, H-4), ppm. *Anal*. Calcd. for $C_{12}H_5ClF_3N_5O_2S$ (375.71): C, 38.36; H, 1.34; N, 18.64. Found: C, 38.42, H, 1.39, N, 18.68.

7,9-Dimethyl-5-thia-3,6,6b,11,11a-heksaaza-benzo[a]fluorene 5,5-dioxide (5). Starting from 2,4-dimethyl-6-hydrazinopyrimidine **2c** (0.83 g) the title **5** was obtained (0.93 g, 51%): mp 406–408°C dec.; ir (KBr): 1640, 1595, 1570 (C=N, C=C), 1300, 1295, 1150 (SO_2) cm^{-1}; ^{1}H NMR (dimethyl sulfoxide-d$_6$): δ 2.72 (s, 3H, CH_3-9), 2.90 (s, 3H, CH_3-7), 8.26 (d, *J* = 5.8 Hz, 1H, H-1), 8.60 (s, 1H, H-10), 8.98 (d, *J* = 5.8 Hz, 1H, H-2), 9.14 (s, 1H, H-4) ppm. *Anal*. Calcd. for $C_{12}H_{10}N_6O_2S$ (302.21): C, 47.67; H, 3.33; N, 27.79. Found: C, 47.61, H, 3.50, N, 27.78.

General procedure for the preparation of 5-thia-3,6,11b-triaza-benzo[*c*]fluorene 5,5-dioxide derivatives (7–12). A solution of 3-methylthiopyrido[4,3-*e*]-1,4,2-dithiazine 1,1-dioxide **1** (1.73 g, 7 mmol) and appropriate 2-aminophenol **6a–e** or 2-aminothiophenol **6f** (7.2 mmol) in dry 1,4-dioxane (7 mL) was refluxed with stirring until the evolution of MeSH and H_2S had ceased (26–30 h). (CAUTION: because of high toxicity, MeSH and H_2S should be trapped in an aqueous NaOH solution). After cooling to room temperature, the reaction mixture was left overnight. The precipitate was collected by filtration, washed with 1,4-dioxane (2 × 0.5 mL), dried, and purified by crystallization from DMF. In this manner, the following products were obtained.

7-Oxa-5-thia-3,6,11b-triaza-benzo[c]fluorene 5,5-dioxide (7). Starting from 2-aminophenol **6a** (0.78 g) the title compound **7** was obtained (0.97 g, 50%): mp 352–353°C dec.; ir (KBr): 1635, 1580, 1560 (C=N, C=C), 1360, 1305, 1175, 1135 (SO_2) cm^{-1}; ^{1}H NMR (dimethyl sulfoxide-d$_6$): δ 7.47–7.58 (m, 2H, H-9, and H-10), 7.35–7.80 (m, 1H, H-11), 8.30–8.33 (m, 1H, H-8), 8.35 (d, *J* = 5.9 Hz, 1H, H-1), 8.96 (d, *J* = 5.9 Hz, 1H, H-2), 9.22 (s, 1H, H-4) ppm. *Anal*. Calcd. for $C_{12}H_7N_3O_3S$ (273.27): C, 52.74; H, 2.58; N, 15.37. Found: C, 52.72, H, 2.69, N, 15.49.

10-Methyl-7-oxa-5-thia-3,6,11b-triaza-benzo[c]fluorene 5,5-dioxide (8). Starting from 2-amino-4-methylphenol **6b** (0.89 g) the title compound **8** was obtained (1.15 g, 57%): mp 346–347°C; ir (KBr): 1660, 1625, 1575 (C=N, C=C), 1335, 1305, 1170 (SO_2) cm^{-1}; ^{1}H NMR (dimethyl sulfoxide-d$_6$): δ 3.30 (s, 3H, CH_3), 7.31 (d, *J* = 8.4 Hz, 1H, H-9), 7.63 (d, *J* = 8.4 Hz, 1H, H-8), 8.17 (s, 1H, H-11), 8.37 (d, *J* = 5.9 Hz, 1H, H-1), 8.96 (d, *J* = 5.9 Hz, 1H, H-2), 9.21 (s, 1H, H-4) ppm; ^{13}C NMR (dimethyl sulfoxide-d$_6$): δ 21.28, 110.91, 111.31, 118.91, 126.64, 126.89, 127.27, 135.91, 138.44, 141.94, 146.59, 154.00 ppm. *Anal*. Calcd. for $C_{13}H_9N_3O_3S$ (287.29): C, 54.35; H, 3.15; N, 14.62. Found: C, 54.39, H, 3.27, N, 14.64.

10-Chloro-7-oxa-5-thia-3,6,11b-triaza-benzo[c]fluorene 5,5-dioxide (9). Starting from 2-amino-4-chlorophenol **6c** (1.03 g) the title compound **9** was obtained (1.06 g, 49%): mp 357–358°C; ir (KBr): 1670, 1620, 1575 (C=N, C=C), 1385, 1315, 1170 (SO_2) cm^{-1}; ^{1}H NMR (dimethyl sulfoxide-d$_6$): δ 7.57 (d, *J* = 8.8 Hz, 1H, H-9), 7.97 (d, *J* = 8.8 Hz, 1H, H-8), 8.38 (d, *J* = 5.8 Hz, 1H, H-1), 8.46 (s, 1H, H-11), 8.94 (d, *J* = 5.8 Hz, 1H, H-2), 9.21 (s, 1H, H-4) ppm; ^{13}C NMR (dimethyl sulfoxide-d$_6$): δ 111.12, 113.04, 114.69, 118.81, 126.45, 128.44, 130.19, 137.97, 142.76, 146.63, 153.09, 154.15 ppm. *Anal*. Calcd. for $C_{12}H_6ClN_3O_3S$ (307.71): C, 46.84; H, 1.96; N, 13.65. Found: C, 46.81, H, 2.02, N, 13.67.

10-Nitro-7-oxa-5-thia-3,6,11b-triaza-benzo[c]fluorene 5,5-dioxide (10). Starting from 2-amino-4-nitrophenol **6d** (1.11 g) the title compound **10** was obtained (1.04 g, 46%): mp 393–396°C dec.; ir (KBr): 1680, 1630, 1570 (C=N, C=C), 1385, 1340, 1170, 1155 (SO_2) cm^{-1}; ^{1}H NMR (dimethyl sulfoxide-d$_6$): δ 8.03 (d, *J* = 8.7 Hz, 1H, H-8), 8.45 (d, *J* = 6.0 Hz, 2H, H-1, and H-2), 8.99 (s, 2H, H-10, and H-11), 9.27 (s, 1H, H-4) ppm. *Anal*. Calcd. for $C_{12}H_6N_4O_5S$ (318.27): C, 45.28; H, 1.90; N, 17.60. Found: C, 45.34, H, 2.00, N, 17.59.

10-(Ethylsulfonyl)-7-oxa-5-thia-3,6,11b-triaza-benzo[c]fluorene 5,5-dioxide (11). Starting from 2-amino-4-(ethylsulfonyl)phenol **6e** (1.45 g) the title compound **11** was obtained (1.49 g, 58%): mp 283–284°C; ir (KBr): 1665, 1620, 1580 (C=N, C=C), 1350, 1325, 1165, 1135 (SO_2) cm^{-1}; ^{1}H NMR (dimethyl sulfoxide-d$_6$): δ 1.15 (t, *J* = 5.2 Hz, 3H, CH_3), 3.52 (q, 2H, CH2), 8.03 (s, 2H, H-8, and H-9), 8.40 (d, *J* = 5.5 Hz, 1H, H-1), 8.62 (s, 1H, H-11), 9.04 (d, *J* = 5.5 Hz, 1H, H-2), 9.26 (s, 1H, H-4) ppm. *Anal*. Calcd. for $C_{14}H_{11}N_3O_5S_2$ (365.40): C, 46.02; H, 3.03; N, 11.49. Found: C, 46.11, H, 3.19, N, 11.52.

5,7-Dithia-3,6,11b-triaza-benzo[c]fluorene 5,5-dioxide (12). Starting from 2-aminothiophenol **6f** (0.9 g) the title compound **12** was obtained (1.0 g, 49%): mp 318–319°C; ir (KBr): 1685, 1580, 1565 (C=N, C=C), 1345, 1320, 1160 (SO_2) cm^{-1}; ^1H NMR (dimethyl sulfoxide-d_6): δ 7.56 (t, J = 7.6 Hz, 1H, H-9), 7.63 (t, J = 7.6 Hz, 1H, H-10), 8.09 (d, J = 7.6 Hz, 1H, H-8), 8.25 (d, J = 7.6 Hz, 1H, H-11), 8.27 (d, J = 5.9 Hz, 1H, H-1), 8.97 (d, J = 5.9 Hz, 1H, H-2), 9.21 (s, 1H, H-4) ppm; ^{13}C NMR (dimethyl sulfoxide-d_6): δ 112.52, 117.76, 119.69, 123.50, 124.94, 127.56, 128.26, 135.51, 141.32, 146.83, 154.25, 167.59 ppm. *Anal.* Calcd. for $C_{12}H_7N_3O_2S_2$ (289.34): C, 49.81; H, 2.44; N, 14.52. Found: C, 49.85, H, 2.52, N, 14.61.

General procedure for the preparation of 3-(R-amino)-4-(2-hydroxy-5-methylphenyl)-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides (13–17). A solution of dioxide **8** (0.58 g, 2 mmol) and the appropriate amine RNH_2 (2.2 mmol) in tetrahydrofuran (8 mL) was stirred at reflux for 3 h. The solvent was evaporated under lowered pressure, and then dry residue was dissolved in hot methanol (5–10 mL). After cooling to room temperature and standing overnight, the precipitate of the adequate product was filtered off, washed with methanol, and dried at temperatures gradually increasing to 105°C.

4-(2-Hydroxy-5-methylphenyl)-3-(2-methylhydrazino)-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide (13). Starting from methylhydrazine (0.1 g), the title compound **13** was obtained (0.52 g, 78%): mp 187–189°C dec.; ir (KBr): 3425, 3315, 3195 (OH, NH), 1595, 1545 (C=N, C=C), 1345, 1175 (SO_2) cm^{-1}; ^1H NMR (dimethyl sulfoxide-d_6) δ 2.22 (s, 3H, CH_3 Ph), 3.38 (s, 3H, CH_3N), 6.19 (d, J = 5.6 Hz, 1H, H-5, pyridothiadiazine), 6.90–6.94 (m, 2H, arom.), 7.09–7.14 (m, 1H, arom.) 8.83 (d, J = 5.6 Hz, 1H, H-6, pyridothiadiazine), 8.69 (s, 1H, H-8, pyridothiadiazine), 9.30–9.80 (br.s, 3H, OH and 2 × NH) ppm. *Anal.* Calcd. for $C_{14}H_{15}N_5O_3S$ (333.37): C, 50.44; H, 4.53; N, 21.00. Found: C, 50.47; H, 4.62; N, 21.02.

3-Allylamino-4-(2-hydroxy-5-methylphenyl)-4H-pyrido [4,3-e]-1,2,4-thiadiazine 1,1-dioxide (14). Starting from allylamine (0.13 g), the title compound **14** was obtained (0.56 g, 81%): mp 247–248°C; ir (KBr): 3500, 3380 (OH), 3335 (NH), 1600, 1555 (C=N, C=C), 1345, 1175, 1160 (SO_2) cm^{-1}; ^1H NMR (dimethyl sulfoxide-d_6) δ 2.27 (s, 3H, CH_3), 3.81 (d, J = 4.2 Hz, 2H, CH_2), 5.04 (dd, J_{cis} = 10.3 Hz, J_{gem} = 1 Hz, 1H, NCH_2 $CH_C{=}CH_A$), 5.09 (dd, J_{trans} = 17.2 Hz, I_{gem} = 1.0 Hz, 1H, NCH_2 $CH_C{=}CH_B$), 5.75–5.86 (m, 1H, $NCH_2CH_C{=}CH_2$), 6.23 (d, J = 5.9 Hz, 1H, H-5, pyridothiadiazine), 7.03–7.08 (m, 1H, arom.), 7.13 (br.s, 1H, OH), 7.21–7.32 (m, 2H, arom.), 8.47 (d, J = 5.9 Hz, 1H, H-6, pyridothiadiazine), 8.84 (s, 1H, H-8, pyridothiadiazine), 10.20 (s, 1H, NH) ppm; ^{13}C NMR (dimethyl sulfoxide-d_6) δ 20.22, 43.71, 110.61, 115.44, 118.17, 119.92, 120.20, 130.45, 130.56, 133,22, 134.42, 144.48, 145.11, 150.40, 152.02, 152.67 ppm. *Anal.* Calcd for $C_{16}H_{16}N_4O_3$ S (344.40): C, 55.80; H, 4.68; N, 16.27, Found: C, 55.84; H, 4.77; N, 16.39.

3-Benzylamino-4-(2-hydroxy-5-methylphenyl)-4H-pyrido[4,3-e]-1, 2,4-thiadiazine 1,1-dioxide (15). Starting from benzylamine (0.24 g), the title compound **15** was obtained (0.75 g, 95%): mp 256–257°C; ir (KBr): 3660, 3485, 3410 (OH), 3290 (NH), 1600, 1560 (C=N, C=C), 1340, 1180, 1150 (SO_2)cm^{-1}; ^1H NMR (dimethyl sulfoxide-d_6) δ 2.27 (s, 3H, CH_3), 4.43 (d, J = 4.1 Hz, 2H, CH_2), 6.28 (d, J = 5.9 Hz, 1H, pyridothiadiazine), 7.06–7.3 (m, 8H, arom.), 7.64 (br.s, 1H, OH), 8.49 (d, J = 5.9 Hz, 1H, H-6, pyridothiadiazine), 8.58 (s, 1H, H-8, pyridothiadiazine), 10.30 (br.s, 1H, NH) ppm; ^{13}C NMR (dimethyl sulfoxide-d_6) δ 20.23, 44.76, 110.67, 118.19, 119.93, 120.24, 126.96, 128.44, 130.43, 130.59, 133.26, 138.81, 144.52, 145.12, 150.73, 152.12, 152.74 ppm. *Anal.* Calcd. for $C_{20}H_{18}N_4O_3S$ (394.45): C, 60.89; H, 4.59; N, 14.20. Found: C, 60.92; H, 4.67; N, 14.19.

4-(2-Hydroxy-5-methylphenyl)-3-(2-pyridylmethylamino)-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide (16). Starting from 2-pyridylmethylamine (0.24 g) the title compound **16** was obtained (0.7 g, 88%): mp 168–169°C dec.; ir (KBr): 3470 (OH), 3275 (NH), 1600, 1590, 1575 (C=N, C=C), 1345, 1150 (SO_2)cm^{-1}; ^1H NMR (dimethyl sulfoxide-d_6) δ 2.27 (s, 3H, CH_3), 3.14 (d, J = 5.1 Hz, 2H, CH_2), 6.27 (d, J = 5.9 Hz, 1H, H-5, pyridothiadiazine), 7.07 (d, J = 8.3 Hz, 1H, arom.), 7.20 (s, 1H, OH), 7.29–7.36 (m, 2H, arom.), 7.66–7.70 (m, 2H, arom.), 8.42–8.47 (m, 2H, arom.), 8.50 (d, J = 5.9 Hz, 1H, H-6, pyridothiadiazine), 8.85 (s, 1H, H-8, pyridothiadiazine), 10.27 (s, 1H, NH) ppm. *Anal.* Calcd. for $C_{19}H_{17}N_5O_3S$ (395.43): C, 57.71; H, 4.33; N, 17.71. Found: C, 57.78; H, 4.41; N, 17.89.

3-(Furfurylamino)-4-(2-hydroxy-5-methylphenyl)-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide (17). Starting from furfurylamine (0.22 g), the title compound **17** was obtained (0.68 g, 88%): mp 240–241°C dec.; ir (KBr): 3505 (OH), 3375 (NH), 1605, 1590, 1555 (C=N, C=C), 1340, 1175, 1150 (SO_2) cm^{-1}; ^1H NMR (dimethyl sulfoxide-d_6) δ 2.27 (s, 3H, CH_3), 4.37 (s, 2H, CH_2), 6.26 (d, J = 5.6 Hz, 2H, arom.), 6.38 (s, 1H, arom.), 7.05 (d, J = 8.3 Hz, 1H, arom.), 7.14 (s, 1H, OH), 7.30 (d, J = 8.3 Hz, 1H arom.), 7.45–7.60 (m, 2H, arom.), 8.48 (d, J = 5.9 Hz, 1H, H-6, pyridothiadiazine), 8.86 (s, 1H, H-8, pyridothiadiazine), 10.22 (s, 1H, NH) ppm. *Anal.* Calcd. for $C_{18}H_{16}N_4O_4S$ (384.42): C, 56.24; H, 4.19; N, 14.57. Found: C, 56.30; H, 4.27; N, 14.58.

Synthesis of 4-(2-hydroxy-5-methylphenyl)-3-[2-(4-sulfamoylphenyl)ethylamino]-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (18). A solution of dioxide **8** (0.58 g, 2 mmol) and 4-(2-aminoethyl)benzenesulfonamide (0.44 g, 2.2 mmol) in tetrahydrofuran (25 mL) was refluxed with stirring for 5 h. After cooling to room temperature, the suspension was left overnight. The precipitate was collected by filtration, washed successively with tetrahydrofuran (2 × 1.5 mL) and methanol (5 × 2 mL), and dried initially at room temperature and then at 105°C. Yield 0.9 g (92%): mp 276–277°C; ir (KBr): 3500 (OH), 3360, 3305, 3280 (NH and SO_2NH_2), 1600, 1555 (C=N, C=C), 1335, 1160, 1150 (SO_2)cm^{-1}; ^1H NMR (dimethyl sulfoxide-d_6) δ 2.24 (s, 3H, CH_3), 2.86 (t, J = 5.0 Hz, 2H, $NCH_2\mathit{CH_2}PhSO_2$), 3.39 (t, J = 5.0 Hz, 2H, $N\mathit{CH_2}CH_2PhSO_2$), 6.25 (d, J = 5.2 Hz, 1H, H-5, pyridothiadiazine), 6.95–7.19 (m, 3H, arom.), 7.27 (br.s, 3H, SO_2NH_2, and OH), 7.35 (d, J = 7.4 Hz, 2H, H-3 and H-5, Ph SO_2), 7.74 (d, J = 7.4 Hz, 2H, H-2 and H-6, Ph SO_2), 8.47 (d, J = 5.2 Hz, 1H, H-6, pyridothiadiazine), 8.88 (s, 1H, H-8, pyridothiadiazine), 10.08 (s, 1H, NH) ppm. *Anal.* Calcd. for $C_{21}H_{21}N_5O_5S_2$ (487.56): C, 51.73; H, 4.34; N, 14.36. Found: C, 51.70; H, 4.41; N, 14.45.

X-ray structure analysis. The diffraction data were collected with a KumaCCD diffractometer using graphite monochromated Mo K_α radiation. The intensity data were collected and processed using Oxford Diffraction CrysAlis Software [38]. The crystal structures were solved by direct methods with the program SHELXS-97 [39] and refined by full-matrix least-squares method on F^2 with SHELXL-97 [40].

Crystal data for **14**: $C_{16}H_{16}N_4O_3S$, monoclinic, space group $P2_1/c$, $a = 9.2385(9)$, $b = 11.6851(10)$, $c = 15.0960(14)$ Å, $\beta = 95.274(8)°$, $V = 1622.8(3)$ Å^3, $Z = 4$, $d_x = 1.410$ g cm^{-3}, $T = 130$ K. Data were collected for a crystal with dimensions $0.4 \times 0.4 \times 0.1$ mm. Final R indices for 2570 reflections with $I > 2\sigma(I)$ and 227 refined parameters are: $R_1 = 0.0367$, $wR_2 = 0.0942$ ($R_1 = 0.0502$, $wR_2 = 0.1009$ for all 3309 data).

Crystal data for **17**: $C_{18}H_{16}N_4O_4S{\cdot}CH_3OH$, monoclinic, space group $P2_1/c$, $a = 10.9766(10)$, $b = 11.4912(11)$, $c = 15.6294(15)$ Å, $\beta = 102.592(8)°$, $V = 1924.0(3)$ Å^3, $Z = 4$, $d_x = 1.438$ g cm^{-3}, $T = 130$ K. Data were collected for a crystal with dimensions $0.4 \times 0.4 \times 0.1$ mm. Final R indices for 2798 reflections with $I > 2\sigma(I)$ and 271 refined parameters are as follows: $R_1 = 0.0435$, $wR_2 = 0.1131$ ($R_1 = 0.0640$, $wR_2 = 0.1235$ for all 3903 data).

Crystallographic data for compounds **14** and **17** have been deposited with Cambridge Crystallographic Data Centre (CCDC deposition numbers CCDC 684581 and 684582, respectively). Copies of the data can be obtained upon request from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, quoting the deposition numbers.

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7,8-Dihydro-4*H*-cyclohepta[*b*]furan (thiophene) Skeleton from Furyl (thiophene)-Derived Tertiary Allylic Alcohols

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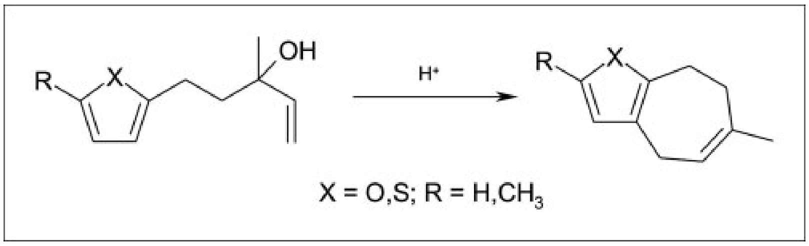

2,6-Dimethyl-7,8-dihydro-4*H*-cyclohepta[*b*]furan and 2,6-dimethyl-7,8-dihydro-4*H*-cyclohepta[*b*]thiophene were prepared by direct cyclization of 3-methyl-5-(5-methylfuran-2-yl)-pent-1-en-3-ol and 3-methyl-5-(5-methyltiophen-2-yl)-pent-1-en-3-ol, respectively.

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INTRODUCTION

Cyclic furan and thiophene derivatives have attracted increased attention due to their potential use as basic synthetic building blocks. Especially, in pharmaceutical drug design, a variety of heterocycles are used as pharmacophores [1,2].

Although many methods have been devised for the synthesis of furan (thiophene) core and cycloheptane ring, the formation of both condensed rings has rarely been reported. 5,6,7,8-Tetrahydro-4*H*-cyclohepta[*b*]furan has been prepared by Herz and Juo [3] through the conversion of 3,6-dihydro-1,2-dioxin derivative obtained in a 1,3-diene photo-oxygenation process. The same fused furan has been synthesized from 2-(2-phenylsulfanyl-allyl)-cycloheptanon via its cyclization under acidic conditions [4] and its 2-methyl derivative by mercuric triftalete-catalyzed cyclization of 2-prop-2-ynyl-cycloheptanone [5]. The corresponding thiophene analogues are reported to be available in a multistep transformation of 5-thiophene pentanoyl chloride [6]. We have found only one report on the preparation of 7,8-dihydro-4*H*-cyclohepta[*b*]furan (thiophene) in the 1-furyl (thienyl)-2-vinylcyclopropane Cope rearrangement [7].

RESULTS AND DISCUSSION

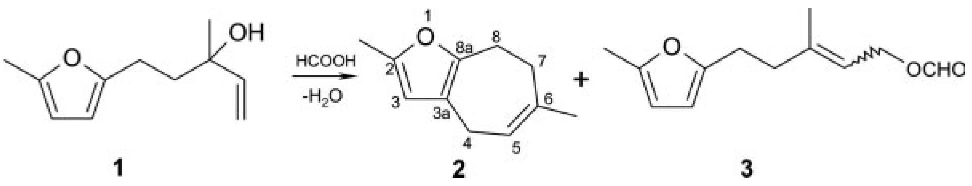
Working on the synthesis of furyl analogues of acyclic monoterpenes [8], we could observe that the formic acid catalyzed allylic rearrangement of furyl-derived tertiary allylic alcohol **1** did not yield primary alcohols and/or their formates as main components of the product mixture. The main compound composed 60% of the reaction mixture (gc) was isolated by flash chromatography in a yield of 45%. Its ^{1}H and ^{13}C NMR analyses revealed the presence of six *sp*^{2} carbon atoms in the molecule indicating thereby a bicyclic structure of **2** (Scheme 1).

The double bond position in the seven-membered ring was unambiguously confirmed by heteronuclear multiple bond correlation (HMBC) experiment. Heteronuclear long–range correlations ($^2J_{C\text{—}H}$ and $^3J_{C\text{—}H}$) between ^{13}C-3a (117.37 ppm) and protons 3, 4, 5, 8, and between ^{13}C-8a (149.19 ppm) and protons 3, 4, 7, 8 were used to distinguish correctly between structure **2** and presumable structure of its 5,8-dihydro-isomer that would have very similar one-dimensional ^{1}H and ^{13}C NMR spectra. Table 1 includes complete ^{1}H and ^{13}C assignments of compound **2**.

The second major product (ca. 35% of a crude material) was an E/Z-mixture (5:1) of formate **3**, the structure of which was proved by MS and NMR. No substrate alcohol was detectable in the gc trace of the crude reaction product. This reflects the ease of tertiary allylic carbocation formation from the alcohol. So, the reaction in the presence of formic acid likely proceeds through a cation and the formation of the bicyclic compound can be clarify by the participation of the allylic carbocation in a two-pathway mechanism (Scheme 2).

Although, in general the 2-positions at furan ring are more reactive than the 3-ones, the first intramolecular electrophilic attack on C-3 carbon atom seems to come into consideration (Path A) assuming the charge distribution as the kinetic criterion. Similarly, an intramolecular carbocationic attack on C-3 position in a 2,5-disubstituted furan moiety of 2-furyl benzo[b]furan derivatives leading

Scheme 1. Transformation of furyl-derived tertiary allylic alcohol **1** to 2,6-dimethyl-7,8-dihydro-4*H*-cyclohepta[*b*]furan (**2**) and formate **3**.



to benzofuro-oxaazulene derivatives had been reported by Russian team [9]. Worth mentioning is that the gas-phase alkylation of 2-methylfuran occurs preferentially at β-position with high charge densities [10]. In our work, the charge distribution has been determined by theory calculations at B3LYP/6-31G(d) (Gaussian 03W ver. 6.1) for allylic carbocation. The charge densities are −0.18 and −0.19 for C3 and C4, respectively, and −0.46 for the oxygen. However, the rearrangement of 5/6 spiro-intermediate to 7,8-dihydro-4*H*-cyclohepta[*b*]furan skeleton is also a considerable reaction path (Path B).

Based on these observations, an attempt to apply the method for the preparation of some other 7,8-dihydro-4*H*-cyclohepta[*b*]furan and 7,8-dihydro-4*H*-cyclohepta[*b*]thiophene derivatives was made (Scheme 3).

However, under similar reaction conditions, the yield of the isolated compounds not containing methyl substituent in the aromatic ring (**5a**, **5b**) was much poorer (13%). Presumably, it is a consequence of competitive intermolecular reactions which resulted in formation of much polymeric material. Alcohols **4a** and **4b** reacted rapidly and the process was difficult to control under changing conditions studied (e.g., dilution, temperature 0°C).

It should be pointed out that the substrate alcohols are easily obtainable from the corresponding furyl and thienyl butanones and their acid catalyzed cyclization can also be of some value for the access to furan and thiophene derivatives with seven-membered ring. To the best of our knowledge, there are no reports on the direct use of tertiary allylic alcohol derivatives for annulation of any hetero- or carbo-cycles.

EXPERIMENTAL

The courses of all reactions, composition products and their purity were checked by means of thin layer chromatography (TLC) and capillary gas chromatography (gc). A THF 1*M* solution of vinyl magnesium bromide was purchased from Aldrich®. The final products were isolated by flash chromatography (silica gel:hexane/ethyl acetate in ratio 100:2.5). gc-ms (mass spectra) were obtained with a Carlo Erba gc coupled to MD 800 Fisons Instruments at 70 eV. ^{1}H NMR (250 MHz) and ^{13}C NMR (62.90 MHz) were recorded in $CDCl_3$ on a Bruker instrument.

2,6-Dimethyl-7,8-dihydro-4*H*-cyclohepta[*b*]furan (2). 1 g (5.5 mmol) of allylic alcohol **1** [6] in hexane (5 mL) was added dropwise to a stirred mixture of hexane (20 mL) and concentrated formic acid (20 mL) at room temperature. The stirring was continued for another 3 h and then 10 cm^3 of water was added. The crude product was extracted with hexane (2 × 20 mL), washed neutral with water and dried over anhydrous sodium sulphate. Furan derivative **2** was isolated by flash chromatography in a yield of 405 mg (45%). Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.19; H, 8.68.

^{1}H NMR, ^{13}C NMR data: see Table 1. ms: *m*/*z* 162 (M^+, 100), 147 (90), 129 (40), 119 (85), 105 (50), 91 (50), 79 (20), 77 (25), 65 (10), 43 (30).

Formic acid 3-methyl-5-(5-methyl-furan-2-yl)-pent-2-enyl ester (3). E-isomer, ^{1}H NMR: δ 8.06 (s, 1H), 5.84 (m, 2H), 5.40 (t, *J* = 7.5 Hz, 1H), 4.69 (d, *J* = 7.5 Hz, 2H), 2.69 (m, 2H), 2.35 (m, 2H), 2.24 (s, 3H), 1.74 (s, 3H). ^{13}C NMR: δ 160.89 (d), 153.37 (s), 150.21 (s), 142.03 (s), 118.27 (d), 105.72 (d), 105.46 (d), 60.50 (t), 37.82 (t), 26.41 (t), 16.29 (q), 13. 37 (q). ms: *m*/*z* 208 (M^+, 7), 162 (3), 96 (6), 95 (100), 94 (3), 67 (3), 65 (2), 53 (2), 43 (6), 41 (4). Z-isomer, ^{1}H NMR: δ 8.03 (s, 1H), 5.84 (m, 2H), 5.39 (t, *J* = 7.5 Hz, 1H), 4.56 (t, *J* = 7.5 Hz, 2H), 2.68 (m, 2H), 2.37 (m, 2H), 2.24 (s, 3H), 1.77 (s, 3H). ^{13}C NMR: δ 160.89 (d), 152.91 (s), 150.43 (s), 141.79 (s), 119.37 (d), 105.88 (d), 105.78 (d), 60.20 (t), 30.75 (t), 26.43 (t), 23.12 (q), 13.37 (q). ms: *m*/*z* 208 (M^+, 7), 162 (3), 96 (6), 95 (100), 94 (3), 67 (3), 65 (2), 53 (2), 43 (6), 41 (4).

6-Methyl-7,8-dihydro-4*H*-cyclohepta[*b*]furan (5a). To a stirred mixture of hexane (40 mL) and concentrated formic acid (10 mL) 1 g (6 mmol) of allylic alcohol **4a** [5] was dropped in hexane (5 mL) at room temperature. The stirring was continued for 20 min and then 10 mL of water was added. The crude product was extracted with hexane (2 × 20 mL), washed neutral with water, and dried over anhydrous sodium sulphate. Furan derivative **5a** was isolated by flash chromatography in a yield of 117 mg (13%). Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.93; H, 12.11.

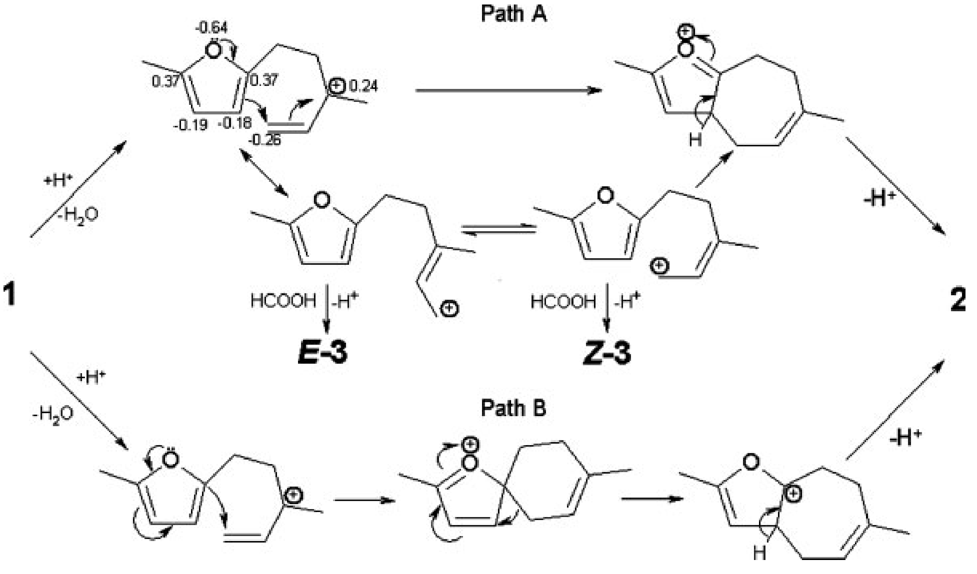
^{1}H NMR: δ 7.15 (d, *J* = 1.68 Hz, 1H), 6.10 (d, *J* = 1.75 Hz, 1H)), 5.74 (tq, *J* = 5.92, 1.52 Hz, 1H), 3,05 (d, *J* = 4.8 Hz, 2H), 2.73 (m, 2H), 2.36–2.41 (m, 2H), 1.81 ppm (d, *J* = 1 Hz, 3H).

Table 1

^{1}H- and ^{13}C-NMR data of **2** (Bruker 700 MHz, 176 MHz, $CDCl_3$).

	700 MHz (ppm) ^{1}H	176 MHz (ppm) ^{13}C
2	–	147.99
3	5.69 (s)	108.01
3a	–	117.37
4	3.00 (d, *J* = 5.2 Hz)	23.59
5	5.73 (td, *J* = 5.9, 1.3 Hz)	124.57
6	–	138.52
7	2.38 (m)	29.72
8	2.69 (m)	24.83
8a	–	149.19
2-Me	2.20 (s)	13.22
6-Me	1.81 (s)	25.03

Scheme 2. Plausible mechanisms of 2,6-dimethyl-7,8-dihydro-4*H*-cyclohepta[*b*]furan (**2**) formation from **1**.

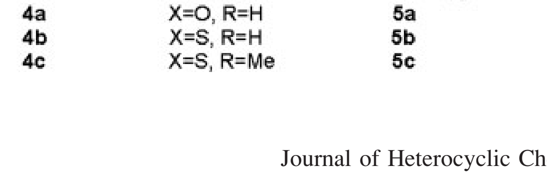


^{13}C NMR: δ 151.19 (s), 138.63 (d), 138.62 (s), 125.47 (d), 116.62 (s), 112.06 (d), 29.56 (t), 24.48 (t), 23.87 (q), 23.54 (t). ms: *m/z* 148 (M^{+}, 100), 133 (60), 119 (25), 115 (30), 105 (65), 91 (45), 77 (15), 65 (15), 55 (20), 39 (20).

3-Methyl-5-thiophen-2-yl-pent-1-en-3-ol (4b). To a 1*M* solution of vinyl magnesium bromide in THF (33 mL, 0.035 mol), 5 g (0.032 mol) of 4-thiophen-2-yl-butan-2-one [11] was added dropwise for 20 min. The reagents were stirred for 2 h at room temperature and thereafter the mixture was poured into ice-water (6 g), and a 30% solution of ammonium chloride (30 mL) was added. The crude product was extracted with toluene (3× 50 mL), washed neutral with water and dried over anhydrous sodium sulfate. Toluene was vacuum removed and the residue was distilled to give alcohol **4b** in 74% yield; b.p., 92°C/0.4 mmHg. ^{1}H NMR: δ 7.10 (m, 1H), 6.90 (m, 1H), 6.78 (m, 1H), 5.93 (dd, *J* = 17.3, 10.7 Hz, 1H), 5.26 (dd, *J* = 10.7, 0.7 Hz, 1H), 5.10 (dd, *J* = 10.7, 0.7 Hz, 1H), 2.86 (m, 2H), 1.93 (m, 2H), 1.33 ppm (s, 3H). ^{13}C NMR: δ 145.07 (s), 144.45 (d), 126.48 (d), 124.13 (d), 123.87 (d), 112.21 (t), 73.00 (s), 43.92 (t), 28.01 (q), 24.47 (t). ms: *m/z* 182 (M^{+}, 21), 164 (48), 149 (72), 135 (18), 115 (17), 111 (23), 97 (100), 80 (15), 71 (65), 43 (20).

6-Methyl-7,8-dihydro-4*H*-cyclohepta[*b*]thiophene (5b). The compound was prepared from alcohol **4b** in the same manner like furan derivative **5a** (yield 13%). Anal. Calcd for $C_{10}H_{12}S$: C, 73.11; H, 7.37. Found: C, 73.41; H, 7.37. ^{1}H NMR: δ 6.92 (d, *J* = 5 Hz, 1H), 6.70 (d, *J* = 5 Hz, 1H), 5.62 (t, *J* = 5 Hz, 1H), 3.34 (d, *J* = 5 Hz, 2H), 2.96 (m, 2H), 2.37 (m, 2H), 1.75 ppm (s, 3H). ^{13}C NMR: δ 137.73 (s), 137.52 (s), 136.36 (s), 129.52 (d), 121.85 (d), 119.94 (d), 31.91 (t), 28.01 (t), 25.87 (q), 25.76 (t). ms: *m/z* 164 (M^{+}, 100), 149 (85), 135 (55), 115 (50), 97 (10), 91 (22), 77 (15), 69 (10), 65 (8), 45 (7).

Scheme 3. Transformation of allylic alcohols into 7,8-dihydro-4*H*-cyclohepta[*b*]furan and 7,8-dihydro-4*H*-cyclohepta[*b*]thiophene derivatives.



3-Methyl-5-(5-methylthiophen-2-yl)-pent-1-en-3-ol (4c). The alcohol was prepared from 4-(5-methylthiophen-2-yl)-butan-2-one (6) in the same fashion like **4b** in a yield of 75%; b.p., 97°C/1.5 mmHg. ^{1}H NMR: δ 6.54 (m, 2H), 5.93 (dd, *J* = 10.75, 17.25 Hz, 1H), 5.21 (d, *J* = 17.25 Hz, 1H), 5.12 (d, *J* = 10.75 Hz, 1H), 2.81 (m, 2H), 2.42 (s, 3H), 1.88 (br.m, 2H), 1.33 ppm (s, 3H). ^{13}C NMR: δ 144.50 (d), 142.98 (s), 137.22 (s), 124.57 (d), 123.81 (d), 112.10 (t), 73.01 (s), 43.88 (t), 27.25 (q), 24.20 (t), 15.18 (q). ms: *m/z* 196 (M^{+}, 22), 178 (30), 163 (45), 149 (17), 129 (18), 125 (23), 111 (100), 97 (15), 80 (20), 71 (27).

2,6-Dimethyl-7,8-dihydro-4*H*-cyclohepta[*b*]thiophene (5c). Starting from alcohol **4c** the thiophene derivative **5c** was obtained by the same procedure as given earlier for compound **2** (yield 46%). Anal. Calcd for $C_{11}H_{14}S$: C, 74.10; H, 7.91. Found: C, 74.48; H, 7.89. ^{1}H NMR: δ 6.36 (s, 1H), 5.60 (t, *J* = 5.1 Hz, 1H), 3.24 (d, *J* = 5 Hz, 2H), 2.86 (t, *J* = 6.25 Hz, 2H), 2.27–2.44 (m, s; 5H), 1.74 ppm (s, 3H). ^{13}C NMR: δ 137.67 (s), 135.81 (s), 134.94 (s), 133.93 (s), 127.74 (d), 121.99 (d), 31.91 (t), 27.93 (t), 25.93 (t), 25.67 (q), 14.76 (q). ms: *m/z* 178 (M^{+}, 100), 163 (95), 148 (35), 135 (20), 129 (40), 115 (15), 105 (12), 91 (20), 77 (18), 59 (15).

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Synthesis, Reactivity, and NMR Spectroscopy of 4,6- and 6,7-Difluoro-3-Methyl-1*H*-Indazoles

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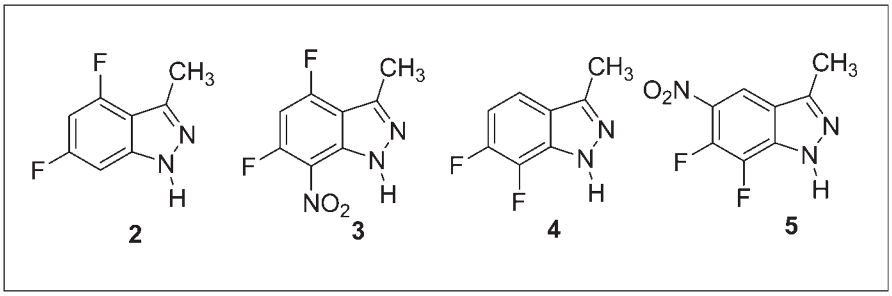
Dedicated to the memory of Professor Robert Jacquier, Université de Montpellier (France).



Four 1*H*-indazoles, two of them doubly substituted by fluorine atoms and the other two obtained by nitration of the foregoing derivatives, were prepared and fully characterized by multinuclear NMR in solution and in solid state in view of their potential nitric oxide synthase inhibition properties.

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INTRODUCTION

We have been interested in 1*H*-indazoles for many years [1–4], some of them being potent inhibitors of the nitric oxide synthase (NOS) family of isozymes [5–8]. Amongst indazoles, 3-bromo-7-nitro-1*H*-indazole **1** (NIBr) is one of those that show highest affinity for type I NOS [9]. This work is concerned with four new 1*H*-indazole derivatives bearing two fluorine substituents **2–5** (Scheme 1). We have already reported studies on fluorinated indazoles [10] as well as indazoles with NOS inhibitory properties [11,12].

RESULTS AND DISCUSSION

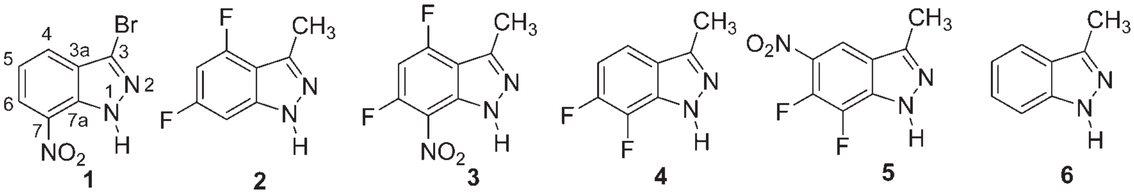
Synthesis. Compounds **2–5** were prepared using one of the classical methods of synthesis of this family of heterocycles [13,14]: the reaction of hydrazine with *ortho*-fluoro carbonyl derivatives (Scheme 2). Thus, starting from appropriately fluorinated acetophenones **7** and **8**, 4,6-difluoro-3-methyl-1*H*-indazole **2** and 6,7-difluoro-3-methyl-1*H*-indazole **4** were obtained with yields in pure compound of 98% and 50%, respectively. In the latter case, formation of hydrazine and azine compete, lowering the yield [15,16].

Reactivity. The nitration of 1*H*-indazole itself **9** in strongly acidic conditions affords 5-nitro-1*H*-indazole **10** as the main product together with 5,7-dinitro-1*H*-indazole **11** in minor proportion [2,17–20]. Further nitration of **10** leads to **11** [21]. Thus, formation of 6,7-difluoro-3-methyl-5-nitro-1*H*-indazole **5** from **4** is the expected reaction. However, nitration of **2** occurs at position 7 yielding 4,6-difluoro-3-methyl-7-nitro-1*H*-indazole **3**, due to the deactivating effect of both fluorine atoms at positions 4 and 6 [13,14].

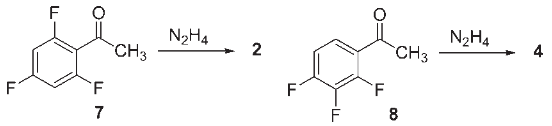
NMR results. We have gathered the solution NMR data for indazoles **2–5** in Tables 1 (^{1}H), 2 (^{19}F), 3 (^{13}C), and 4 (^{15}N). We have already reported the data relating to 3-methyl-1*H*-indazole **6** in $CDCl_3$ [10], but now we have recorded ^{13}C NMR and ^{15}N NMR in DMSO-d_6 for comparative purposes. Moreover, Table 5 contains the ^{13}C and ^{15}N CPMAS NMR chemical shifts for all of them. The spin-spin systems of 1,2- and 1,3-difluorobenzenes have been analyzed and the signs of the SSCC were determined [22]: we have given a negative sign to those couplings in Tables 2 and 3 that have a negative sign in difluorobenzenes.

Couplings with ^{19}F (Tables 1–3) are very sensitive to the positions of both nuclei and, consequently, they are useful for structure determination. Chemical shifts in Table 3 can be analyzed to determine the contribution of the different substituents or pairs of substituents (the F atoms are always associated two by two). The methyl group is almost insensitive (largest shift: -1.6 ppm for

Scheme 1. Indazoles.



Scheme 2. Synthesis of indazoles **2** and **4**.



the 6,7-difluoro) and C3 is only a little more sensitive (between 3.3 ppm for the 5-nitro and −1.7 ppm for the 4,6-difluoro). The substituent chemical shifts (SCS) on the six-membered ring have been averaged and are shown in Scheme 3 together with literature data on benzenes [23].

We have analyzed the ^{15}N chemical shifts in Table 4 using a presence–absence matrix (also called a Free-Wilson matrix) [24]. The effects are: on N1 −0.4 (5-NO_2), −5.4 (7-NO_2), 4.5 (4,6-diF), −3.2 (6.7-diF), and on N2 4.3 (5-NO_2), −0.4 (7-NO_2), 1.9 (4,6-diF), 4.4 (6.7-diF).

In Scheme 4, some representative coupling constants are reported, to show the analogies and differences between difluorobenzenes and difluoroindazoles.

The data in the solid state and in solution are very similar as can be seen in Figure 1. When signals (C4 and C5 of **4**) are split in the solid state, their averaged value has been used. This consistency reflects the fact that all these compounds are 1*H*-tautomers, just like most indazoles [10,18,25].

Table 1

^{1}H NMR chemical shifts (ppm) and coupling constants (Hz) in DMSO-d_6.

	2	3	4	5
3-CH_3	2.52	2.57	2.47	2.56
H4	–	–	7.52 $^{3}J_{H5} = 8.8$ $^{4}J_{F6} = 4.0$ $^{5}J_{F7} = 0.7$	8.61 $^{4}J_{F6} = 6.1$ $^{5}J_{F7} = 1.3$
H5	6.83 $^{3}J_{F4} = {}^{3}J_{F6}$ $= 10.3$ $^{4}J_{H7} = 1.9$	7.31 $^{3}J_{F4} = 10.0$ $^{3}J_{F6} = 12.6$	7.10 $^{3}J_{F6} = 10.9$ $^{3}J_{H4} = 8.8$ $^{4}J_{F7} = 6.5$	–
H7	7.09 $^{3}J_{F6} = 9.0$ $^{4}J_{H5} = 1.9$	–	–	–
N1H[a]	13.0	13.8	13.3	14.0

[a] Broad signal.

EXPERIMENTAL

Melting points were determined by DSC (Seiko 220C with a scanning rate of 5.0°C min^{-1}. Column chromatography: Merck silica (70–230 mesh). Microanalyses were determined at the Centro de Análisis Elemental-UCM, Madrid [Perkin Elmer 240 (CHN)].

Solution NMR spectra were recorded on a Bruker DRX 400 (9.4 Tesla, 400.13 MHz for ^{1}H, 100.62 MHz for ^{13}C, 376.50 MHz for ^{19}F, and 40.56 MHz for ^{15}N) spectrometer with a 5-mm inverse-detection H-X probe equipped with a z-gradient coil, at 300 K. Chemical shifts (δ in ppm) are given from internal solvent, DMSO-d_6 2.49 for ^{1}H and 39.5 for ^{13}C, external reference $CFCl_3$ for ^{19}F and for ^{15}N NMR nitromethane (0.00) was used as external standard. Digital resolution: 1.25 Hz for ^{13}C and 0.80 Hz for ^{19}F. 2D (^{1}H-^{13}C) gs-HMQC, gs-HMBC and (^{1}H-^{15}N) gs-HMQC, gs-HMBC, were acquired and processed using standard Bruker NMR software and in nonphase-sensitive mode [26]. Variable temperature experiments were recorded on the same spectrometer. A Bruker BVT3000 temperature unit was used to control the temperature of the cooling gas stream and an exchanger to achieve low temperatures.

Solid state ^{13}C (100.73 MHz) and ^{15}N (40.60 MHz) CPMAS NMR spectra have been obtained on a Bruker WB 400 spectrometer at 300 K using a 4 mm DVT probehead. Samples were carefully packed in a 4-mm diameter cylindrical zirconia rotor with Kel-F end-caps. Operating conditions involved 3.2 μs 90° ^{1}H pulses and decoupling field strength of 78.1 kHz by TPPM sequence. ^{13}C spectra were originally referenced to a

Table 2

^{19}F NMR chemical shifts (ppm) and coupling constants (Hz) in DMSO-d_6.

	2	3	4	5
F4	−117.7 $^{3}J_{H5} = 10.3$ $^{4}J_{F6} = 7.7$	−103.0 $^{3}J_{H5} = 10.0$ $^{4}J_{F6} = 16.3$	–	–
F6	−112.7 $^{3}J_{H5} = 10.3$ $^{3}J_{H7} = 9.0$ $^{4}J_{F4} = 7.7$	−111.3 $^{3}J_{H5} = 12.6$ $^{4}J_{F4} = 16.3$	−143.8[a]	−150.7[a]
F7	–	–	−160.5 $^{4}J_{H5} = 6.5$ $^{3}J_{F6} = -20.5$	−154.8 $^{3}J_{F6} = 19.5$

[a] Complex multiplet.

Table 3

^{13}C NMR chemical shifts (ppm) and ^{13}C-^{19}F coupling constants (Hz) in DMSO-d_6.

	2	3	4	5	6
CH_3	13.2	13.1	11.4	11.1	13.0
C3	139.2	141.6	142.3	145.6	140.9
C3a	109.0	111.3	122.5	118.6	122.1
	$^2J = 21.4$	$^2J = 21.5$	[a]	[a]	
C4	155.7	159.1	116.5	116.0	119.8
	$^1J = -251.4$	$^1J = -263.7$	$^3J = 2.7$		
	$^3J = 16.2$	$^3J = 16.4$	$^4J = 7.5$		
C5	95.4	97.6	110.2	132.1	119.3
	$^2J = 30.5$	$^2J = 28.9$	$^2J = 21.4$	$^2J = 8.8$	
	$^2J = 23.5$	$^2J = 25.7$			
C6	161.1	157.6	147.4	141.6	125.8
	$^1J = -242.5$	$^1J = -265.7$	$^1J = -240.5$	$^1J = -256.2$	
	$^3J = 11.6$	$^3J = 14.4$	$^2J = 8.7$	$^2J = 12.6$	
C7	92.2	119.1	134.9	135.8	109.9
	$^2J = 26.1$	$^2J = 8.2$	$^1J = -248.8$	$^1J = -253.7$	
	$^4J = 3.9$	$^4J = 4.4$	$^2J = 16.5$		
C7a	142.7	136.5	130.6	132.1	140.8
	$^3J = 14.4$	$^3J = 12.6$	[b]	$^2J = 8.8$	
	$^3J = 12.0$	$^3J = 2.5$			

[a] No coupling constants could be measured.
[b] Complex multiplet.

Table 4

^{15}N NMR chemical shifts (ppm) and ^1H-^{15}N coupling constants (Hz).

	2	3	4	5		6
Solvent	DMSO-d_6[a]	$CDCl_3$[a]	DMSO-d_6[a]	THF-d_8[b]	DMSO-d_6[a]	
N1	−197.8	−203.2	−205.5	−205.9	−202.3	
				$^1J_{NH} = 109$	$^1J_{NH} = 105$	
N2	−69.3	−69.7	−66.8	−62.5	−71.2	
NO_2	–	[c]	–	−16.6		–

[a] At 300K.
[b] At 207 K.
[c] Not detected.

glycine sample and then the chemical shifts were recalculated to the Me_4Si [for the carbonyl atom δ (glycine) = 176.1 ppm] and ^{15}N spectra to $^{15}NH_4Cl$ and then converted to nitromethane scale using the relationship: $\delta\ ^{15}N\ (MeNO_2) = \delta\ ^{15}N(NH_4Cl) - 338.1$ ppm. Typical acquisition parameters for ^{13}C CPMAS were: spectral width, 40 kHz; recycle delay, 40 s; acquisition time, 30 ms; contact time, 2 ms; and spin rate, 12 kHz. To distinguish protonated and nonprotonated carbon atoms, the NQS (Non-quaternary suppression) experiment by conventional cross-polarization was recorded [26]. Typical acquisition parameters for ^{15}N CPMAS were: spectral width, 40 kHz; recycle delay, 40 s; acquisition time, 35 ms; contact time, 6 ms; and spin rate, 6 kHz.

4,6-Difluoro-3-methyl-1*H*-indazole (2). A solution of 2,4,6-trifluoroacetophenone (**7**) (0.20 g, 1.1 mmol, in 15 mL of tetrahydrofurane) was placed in a three-neck round-bottom flask equipped with a reflux condenser and 98% hydrazine monohydrate (0.09 g, 1.7 mmol) was added dropwise. Then, the

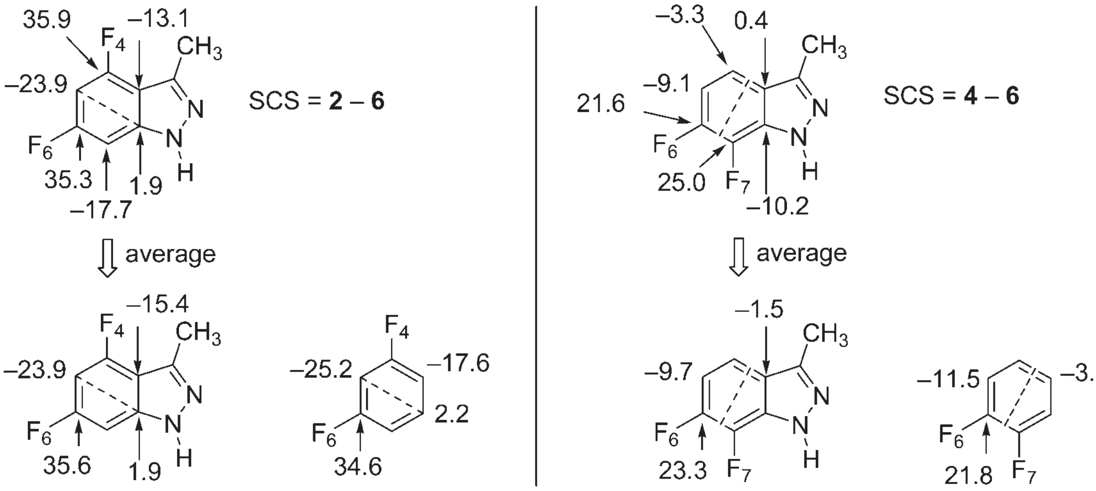
Table 5

^{13}C and ^{15}N CPMAS NMR chemical shifts (ppm).

	2	3	4	5	6 [10]**
CH_3	13.5	12.2	11.2	10.2	10.5
C3	138.7	143.9	142.2	147.2	144.5
C3a	107.9	111.5	121.1	117.6	123.6
C4	154.9	159[a]	115.2 113.8	117.6	121.2
C5	95.8	99.1	112.3 109.8	132.0	121.2
C6	160.9	159[a]	146.8	143[a]	127.9
C7	90.2	118.0	136[a]	138[a]	111.5
C7a	141.5	136.7	129.9	131.1	140.8
N1	−196.3	−196.2	−203.0	−201.5	−205.1
N2	−85.1	−73.8	−82.9	−82.1	−80.6
NO_2	–	−15.7	–	−17.0	–

[a] Broad signal.

Scheme 3. ^{13}C SCS (Substituent chemical shifts, ppm).

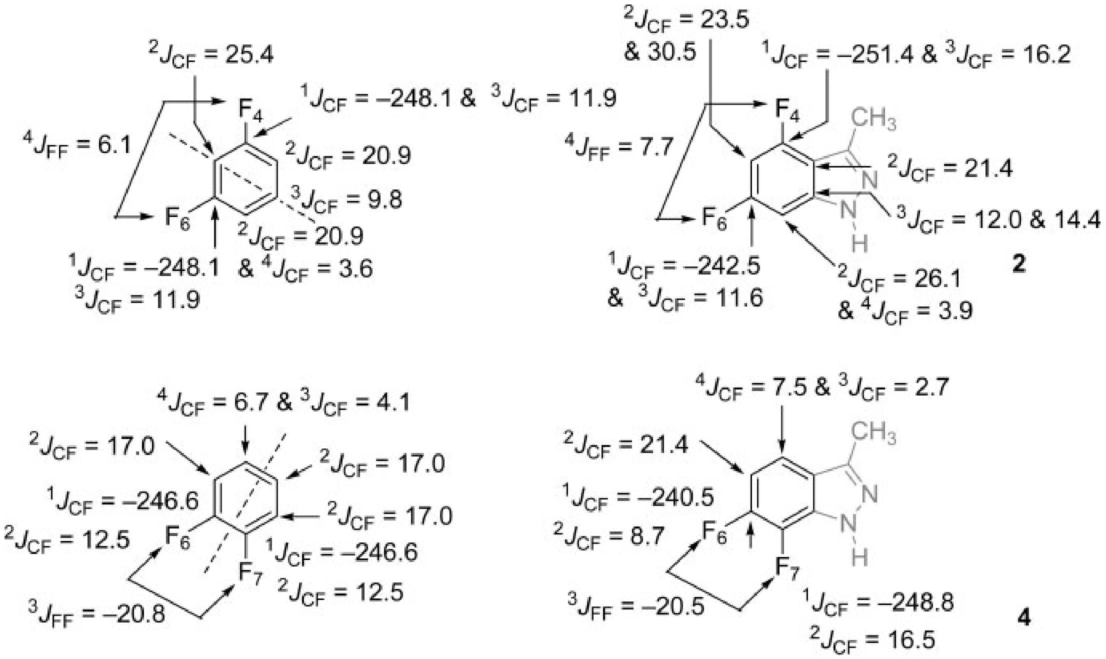


mixture was heated at 80°C during 15 h. After cooling at room temperature, the solution was decanted and the organic solvent evaporated under vacuum. The solid residue is pure **2**, mp 163.2°C (by DSC). Yield: 0.185 g, 98%. Anal. Calcd. for $C_8H_6F_2N_2$: C, 57.15; H, 3.60; N, 16.66. Found: C, 57.09; H, 3.68; N, 16.36.

4,6-Difluoro-3-methyl-7-nitro-1*H*-indazole (3). To a round-bottom flask cooled in an ice-water bath, 0.10 g of **2** (0.60 mmol) were introduced, and 0.07 g of potassium nitrate (0.7 mmol) dissolved in 1 mL of sulfuric acid 95–98% conc. (d = 1.84 g/mL) was then added dropwise. The mixture was stirred at room temperature during 24 h and poured into 5 mL of ice-water afterward, resulting in the formation of a yellowish precipitate. This mixture was maintained at 4°C for 6 h and then filtered. The solid is washed with water, filtered, and dried to obtain pure **3**, mp 213.6°C (by DSC). Yield: 0.11 g, 86%. Anal. Calcd. for $C_8H_5F_2N_3O_2$: C, 45.08; H, 2.36; N, 19.71. Found: C, 45.24; H, 2.53; N, 19.62.

6,7-Difluoro-3-methyl-1*H*-indazole (4). A solution of 2,3,4-trifluoroacetophenone (**8**) (0.20 g, 1.1 mmol, in 15 mL of tetrahydrofurane) was placed in a three-neck round-bottom flask equipped with a reflux condenser, and 98% hydrazine monohydrate (0.11 g, 2.2 mmol) was added dropwise keeping the temperature around 0°C. Then, the mixture was heated at 70°C during 24 h. After cooling at room temperature, the solution was decanted and the organic solvent evaporated under vacuum. The solid residue was chromatographed over silica using hexane/diethyl ether 7:1 as eluent, obtaining **2**, mp 182.2°C (by DSC). Yield: 0.10 g, 50%. Anal. Calcd. for $C_8H_6F_2N_2$: C, 57.15; H, 3.60; N, 16.66. Found: C, 57.15; H, 3.66; N, 16.38.

Scheme 4. ^{19}F-^{19}F and ^{13}C-^{19}F coupling constants of difluorobenzenes together with compounds **2** and **4**.



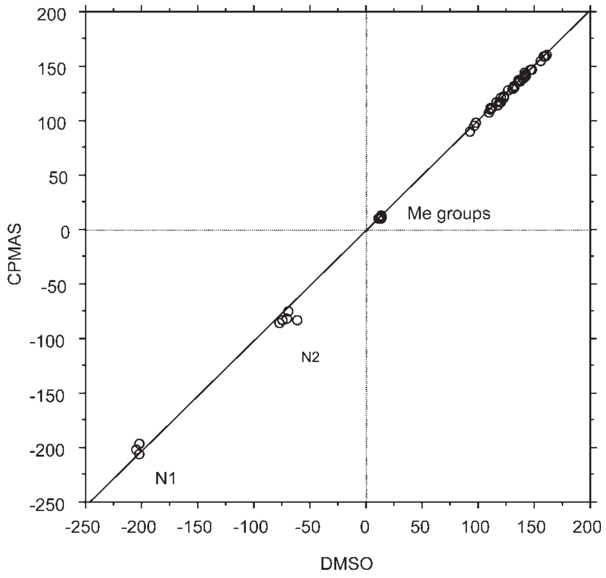


Figure 1. Comparison of ^{13}C and ^{15}N chemical shifts (ppm) in the solid-state (CPMAS) and in DMSO-d_6 solution. The straight line corresponds to CPMAS = (1.004 ± 0.005)* DMSO, $n = 48$, $R^2 = 0.999$.

6,7-Difluoro-3-methyl-5-nitro-1*H*-indazole (5). To a round-bottom flask cooled in an ice-water bath 0.11 g of **4** (0.65 mmol) were introduced, and 0.08 g of potassium nitrate (0.8 mmol) dissolved in 1 mL of sulfuric acid 95–98% conc. (d = 1.84 g/mL) was then added dropwise. The mixture was stirred at room temperature during 24 h and then poured into 5 mL of ice-water mixture resulting in the formation of a yellowish precipitate. The mixture was maintained at 4°C for 6 h and then filtered. The solid is washed with water, filtered, dried, and chromatographed over silica using hexane/diethyl ether 8:1 as eluent to obtain **5**, mp 167.5°C (by DSC). Yield: 0.10 g, 72%. Anal. Calcd. for $C_8H_5F_2N_3O_2$: C, 45.08; H, 2.36; N, 19.71. Found: C, 45.82; H, 2.74; N, 19.04.

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Addition of Hydrazine to 4,7-Dihydro[1,2,4]triazolo[1,5-*a*]pyrimidines: Hydrazine Derivatives of 4,5,6,7-Tetrahydro[1,2,4]triazolo[1,5-*a*]pyrimidine

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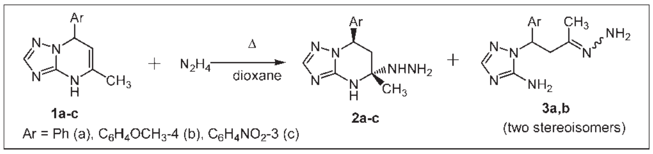

The 7-aryl-4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidines **1a-c** can undergo addition of hydrazine to the enamine double bond leading to hydrazine derivatives of tetrahydrotriazolopyrimidines **2a-c**; the process is usually accompanied by partial opening of pyrimidine ring leading to **3a,b**.

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INTRODUCTION

1,4-Dihydroazines are compounds which are very important in biological processes. According to the available data about the structure–activity relationship for 1,4-dihydropyridines [1], the phenyl substituent at position 4 of dihydropyrimidine ring is the most suitable for showing physiological activity. However, the stereochemistry of addition processes for 4-aryl-1,4-dihydroazines was not widely investigated, in spite of their simplicity and their similarity to chemical processes in nature [2]. It is also known that dihydroazines fused with azole ring possess a relatively stable dihydro structure (in comparison with nonfused 1,4-dihydroazines, such as 1,4-dihydropyridine and 1,6-dihydropyrimidine). This makes them convenient models for studying many theoretical problems of organic chemistry, e.g. tautomerization, stereochemistry, and chemical reactivity [3]. In addition, there are many compounds with various types of physiological activity exactly among dihydroazolopyrimidines [4].

Only several adducts of dihydroazolopyrimidines (namely hydrates) are described; they were formed either by attempt of preparation of corresponding dihydroazolopyrimidine [5], or directly from previously prepared dihydroazolopyrimidine in attempts of its salt formation with HCl (as side product without isolation) [6].

The aim of this work was to investigate the ability of the enamine fragment of the 7-aryl-5-methyl-4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine to react with nucleophile and to study the stereochemistry of nucleophilic addition to dihydroazine ring which should be influenced by aryl ring. The investigated dihydroazolopyrimidine contains supposedly only one reaction center for nucleophile attack, namely the C-5 carbon. The most appropriate nucleophilic reagent for this case, in our opinion, could be hydrazine. The earlier described reactions of analogous acetyl derivatives with hydrazine or hydroxylamine [2] (Scheme 1) were accompanied by heterocyclizations leading to only one stereoisomer (a pair of enantiomers) in both cases; the stereochemistry of heterocyclization products was consistent with nucleophilic attack of the enamine double bond from the sterically less hindered side of the dihydroazolopyrimidine system.

RESULTS AND DISCUSSION

We studied the reaction of dihydroazolopyrimidines **1a-c** with hydrazine by heating in dioxane. The products obtained from **1a,b** were showed in the NMR ^{1}H spectrum in the presence of two groups of signals (compounds **2a,b** and **3a,b**, respectively). In case of 3-nitrophenyl derivative (**1c**), the presence of only one compound was observed (**2c**). Pure compound **3b** was isolated by fractional crystallisation of the obtained mixture **2b** and **3b**; the attempts to isolate either **2a** or **3a** in analogous way were fully unsuccessful.

The elemental analysis for pure **3b** and **2c** and for obtained mixtures showed that compounds **2** and **3** are isomers, and their composition corresponded to addition of one molecule of hydrazine to azolopyrimidine **1**.

The ^{1}H NMR spectra of **2a–c**, **3a,b** in DMSO-d_6 (Table 1) were similar and showed signals of ABX systems

Table 1

The ^1H NMR data for **2a-c, 3a,b** (δ/ ppm).

				Aliphatic protons				Coupling constants / Hz		
Compound	Substituent	NH	ArH	H_X (7-H)	H_B (2-H)	H_A (2-H)	CH_3	$^3J_{BX}$	$^3J_{AX}$	$^2J_{AB}$
2a (in mixture with **3a**)	Ph	–	7.14–7.57	5.25	2.43	1.85	1.30	4.6	11.3	15.0
2b (in mixture with **3b**)	4-$CH_3OC_6H_4$	–	6.80–7.35	5.14	2.36	1.83	1.28	4.9	11.6	13.8
2c	3- $O_2NC_6H_4$	7.37 (1H, s)	8.16 (1H, m), 8.09 (1H, s), 7.60–7.72 (2H, m), 7.42 (1H, m)	5.40	2.49	1.87	1.30	5.0	11.6	11.8
3a (in mixture with **2a**)	Ph	6.10, 5.53	7.14–7.57	5.55	3.11	2.84	1.50	8.8	5.8	15.0
3b	4-$CH_3OC_6H_4$	6.10, 5.51	7.29–7.31 (2H, m), 7.29 (1H, s), 6.81–6.85 (2H, m)	5.51	3.03	2.79	1.55	8.6	6.1	14.7

(the signals of **3** were shifted downfield in comparison with **2**), singlets of CH_3 groups, and multiplets of aromatic rings. Compound **3b** also showed broad signals of two NH_2 groups, but in the spectrum of **2c** only one signal of NH protons was observed in the aromatic region.

The ^{13}C NMR spectra of **2c** and **3b** were allowed to make the structure assignment. Both compounds showed signals of aliphatic CH and CH_2 carbons, but compound **2c** showed signal of quaternary carbon in the aliphatic region, at 69.2 ppm, which was consistent with the proposed structure of cyclic adduct. In contrast, the spectrum of **3b** contained an additional signal downfields, at ~159.0 ppm, which was assigned to imine carbon. Thus, compound **3b** has the opened, noncyclic structure, as shown in Scheme 2. Two series of signals were observed in the spectrum of **3b**. The minor signals had low intensity and probably represented the stereoisomers of **3b** which had different configuration of the $C{=}N{-}NH_2$ fragment. The assignment of signals in ^{13}C NMR spectrum of **3b** was based on HSQC experiment.

The reaction can be described by Scheme 2:

Two stereoisomers are possible for compounds **2**, but in their NMR spectra the signals of only one stereoisomer were observed. The stereochemistry of **2** was investigated by NOE measurements. The irradiation of CH_3 showed enhancement for *ortho* protons of aromatic ring which proved proximity of the protons and showed that methyl group and aryl substituent are both oriented in the same direction from the plane of the azolopyrimidine system. Thus, compounds **2** have the stereochemistry as shown in Scheme 2.

The ^3J values between H_X and H_A in **2a–c** were 11.3–11.6 Hz (Table 1) indicating that H_X and H_A are both axial. Such contradiction between coupling data and NOE results could be explained by equilibrium between conformers of **2a–c** (Scheme 3).

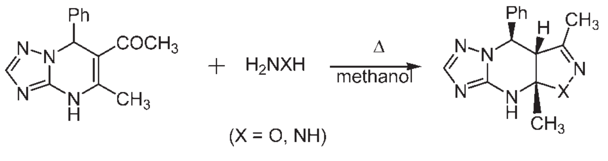
Thus, 7-aryl derivatives of 4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidines can add nucleophiles directly, and their nucleophilic attack occurs from the side opposite to the orientation of aryl substituent. Compounds **2a–c**, **3a, b** were quite unstable in DMSO-d_6 solutions undergoing partial elimination of hydrazine (for **2**), partially full decomposition in about 0.5–1.0 h at room temperature.

EXPERIMENTAL

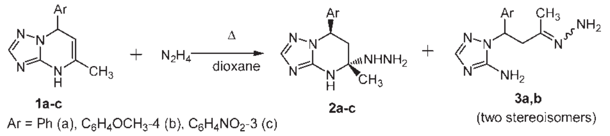
The melting points, determined on a Kofler apparatus, are uncorrected. The ^1H and ^{13}C NMR spectra were obtained on a Varian Mercury VX-200 or Bruker DMX 600 in DMSO-d_6 with TMS as a internal standard. The EI mass spectra were measured on a Varian 1200L at 70 eV.

4,7-Dihydro-5-methyl-7-aryl[1,2,4]triazolo[1,5-*a*]pyrimidines (1b,c). General procedure. Compounds 1b,c were prepared by the procedure described in ref. 7 for 1a. A mixture of commercially available 3-amino-1,2,4-triazole (0.84 g, 10 mmol) and the corresponding substituted benzylideneacetone (10.0 mmol)

Scheme 1



Scheme 2



1a-c

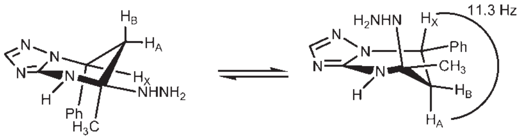
Ar = Ph (a), $C_6H_4OCH_3$-4 (b), $C_6H_4NO_2$-3 (c)

2a-c

3a,b

(two stereoisomers)

Scheme 3



2a

in DMF (1 mL) was refluxed for 30 min. The reaction mixture was cooled to 20°C, mixed with benzene (20 mL) and the precipitate formed was collected by filtration and crystallized from DMF-methanol mixture.

4,7-Dihydro-5-methyl-7-(4-methoxyphenyl)[1,2,4]triazolo [1,5-*a*]pyrimidine (1b). 4,7-Dihydro-5-methyl-7-(4-methoxyphenyl)[1,2,4]triazolo[1,5-*a*]pyrimidine (1b) was isolated with yield 58% and melted at 215–216°C (from mixture of DMF and methanol). The ^{1}H NMR signals were found in DMSO-d$_6$ at 1.85 s, 3H (4-CH$_3$), 3.70 s, 3H (OCH$_3$), 4.50 d, 1H (6-H), 5.09 d, 1H, $^{3}J = 2.0$ (7-H), 6.86 m, 2H (*m*-ArH), 7.11 m, 2H (*o*-ArH), 7.51 s, 1H (2-H), 9.52 br.s, 1H (NH). The ^{13}C NMR signals were measured in DMSO-d$_6$ at δ, ppm: 18.9 (5-CH$_3$), 55.8 (OCH$_3$), 59.6 (C-7), 96.1 (C-6), 114.5 (*m*-C$_{Ar}$), 128.8 (o-C$_{Ar}$), 132.4 (*i*- C$_{Ar}$), 135.3 (C-5), 149.6 (C-3*a*), 149.8 (C-2), 159.5 (*p*-C$_{Ar}$). The ei ms spectrum showed peaks at *m*/*z* (%)242 (87) [M^{+}], 227 (57) [M^{+}-15], 214 (34) [M^{+}-28], 200 (40) [M^{+}-42], 135 (100) [M^{+}-107]. Anal. Calcd. for $C_{13}H_{14}N_4O$ (242.3): 64.45% C, 5.82% H, 23.13% N. Found: 64.39% C, 5.71% H, 23.05% N.

4,7-Dihydro-5-methyl-7-(3-nitrophenyl)[1,2,4]triazolo[1,5-*a*] pyrimidine (1c). Yield 52%; m.p. 249–250°C (ethanol). ^{1}H NMR (DMSO-d$_6$): 1.88 s, 3H (CH$_3$), 4.61 m, 1H (6-H), 6.23 m, 1H (7-H), 7.60 s, 1H (2-H), 7.62–7.67 m, 2H (5,6-ArH), 8.03 m, 1H (2-ArH), 8.12–8.18 m, 1H (4-ArH), 9.73 br.s, 1H (NH). ^{13}C NMR (DMSO-d$_6$): 19.0 (5-CH$_3$), 59.3 (C-7), 94.9 (C-6), 121.9 (2-C$_{Ar}$), 123.5 (4-C$_{Ar}$), 131.0 (5-C$_{Ar}$), 133.5 (6-C$_{Ar}$), 134.1 (C-5), 145.2 (1-C$_{Ar}$), 148.6 (3-C$_{Ar}$), 149.9 (C-3*a*), 150.4 (C-2). MS [EI, *m*/*z* (rel. %)]: 257 (78) [M^{+}], 242 (25) [M^{+}-15], 210 (14) [M^{+}-47], 135 (100) [M^{+}-122], 128 (13) [M^{+}-129]. Anal. Calcd. for $C_{12}H_{11}N_5O_2$ (257.3): 56.03% C, 4.31% H, 27.22% N. Found: 55.92% C, 4.24% H, 27.18% N.

5-Methyl-7-phenyl-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-*a*] pyrimidin-5-yl)hydrazine (2a) and 2-(3-hydrazono-1-phenyl-butyl)[1,2,4]triazol-3-amine (3a). A solution of 1a [7] (1.40 g, 6.6 mmol) and 85% hydrazine hydrate (1.66 g, 30 mmol) in dioxane (7 mL) was heated for 60 min and the solvent was evaporated under reduced pressure. The residue was triturated with diethyl ether (10 mL) and allowed to stand for 2 days. The formed precipitate (1.51 g) was filtered off. It contained, according to the ^{1}H NMR data (Table 1) about 60% of 2a and 40% of 3a. Anal. Calcd. for $C_{12}H_{16}N_6$ (244.3): 59.00% C, 6.60% H, 34.40% N. Found: 58.87% C, 6.54% H, 34.35% N.

Compounds **2b,c** and **3b** were prepared in analogous way from **1b** and **1c**, respectively. In case of **1c**, the precipitate formed contained only pure **2c**.

A mixture of **2b** and **3b** was isolated in 96% yield and contained, according to the ^{1}H NMR data, 65% of **2b** and 35% of **3b**.

Pure compound **3b** was isolated by careful crystallization of the obtained mixture from dioxane-diethyl ether; m.p. 175–177°C. ^{13}C NMR (DMSO-d$_6$), for major stereoisomer: 14.5 (CH$_3$), 44.1 (CH$_2$), 55.6 (OCH$_3$), 56.4 (CH), 114.1, 129.0 (*m*- and *o*-C$_{Ar}$), 133.2 (*i*-C$_{Ar}$), 144.2 (C-5 of triazole), 148.6 (CH of triazole), 155.1 (—C=N—), 159.0 (*p*-C$_{Ar}$); for minor stereoisomer: 22.8 (CH$_3$), 34.8 (CH$_2$), 54.8 (OCH$_3$), 55.6 (CH), 114.2, 128.6 (*m*- and *o*-C$_{Ar}$), 133.1 (*i*-C$_{Ar}$), 145.3 (C-5 of triazole), 148.9 (CH of triazole), 155.4 (—C=N—), 159.2 (*p*-C$_{Ar}$). Anal. Calcd. for $C_{13}H_{18}N_6O$ (274.3): 56.92% C, 6.61% H, 30.64% N. Found: 56.83% C, 6.55% H, 30.71% N.

Compound **2c**, m.p. 153–154°C, was isolated in yield 73%. ^{13}C NMR (DMSO-d$_6$) δ, ppm: 24.2 (CH$_3$), 41.2 (C-6), 55.7 (C-7), 69.2 (C-5), 122.6 (*p*-C$_{Ar}$), 123.1 (*o*-C$_{Ar}$), 130.5 (*m*′-C$_{Ar}$), 134.6 (o′-C$_{Ar}$), 143.3 (*i*-C$_{Ar}$), 148.3 (*m*-C$_{Ar}$), 149.3 (C-2), 154.7 (C-3*a*). Anal. Calcd. for $C_{12}H_{15}N_7O_2$ (289.3): 49.82% C, 5.23% H, 33.89% N. Found: 49.69% C, 5.14% H, 33.97% N.

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Studies on the Synthesis of 4-Oxo-2,3,4,9-tetrahydrocarbazole Derivatives

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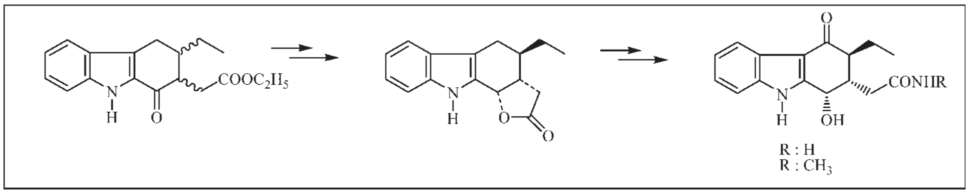

In this study, a new synthetic route for the synthesis of 1-hydroxy-4-oxo-1,2,3,4-tetrahydrocarbazole derivatives **12** and **13** from lactone **11** is described. Unfortunately, cyclization of compounds **12** and **13** to their respective azocino[4,3-*b*]indole derivatives **14** and **15** was unsuccessful.

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INTRODUCTION

Recently we reported the total synthesis of (±)-epidasycarpidone [1] based on the acid catalyzed D-ring cyclization of the appropriate 4-oxo-1,2,3,4-tetrahydrocarbazol derivative. 4-Oxotetrahydrocarbazole with a functionalized ethyl side chain plays an important role in the synthesis of the hexahydroazocino[4,3-*b*]indole frame work [2–5]. In the present work, the synthesis of 2-ethyl-substituted 4-oxo-tetrahydrocarbazole derivatives is described. These intermediates, such as **12** and **13**, could be useful starting materials for the synthesis of uleine alkaloids.

RESULTS AND DISCUSSION

For the synthesis of 4-oxotetrahyrocarbazole derivatives, we started from the diastereomers **1**, which were reported previously [1]. Diastereomers like 1-oxo-2-substituted-2,3,4,9-tetrahydrocarbazole were converted into the racemic trans form by treatment with sodium methoxide [6,7]. However, the diastereomer of **1** was transformed into the racemic trans keto acid **2** by using 15% potassium hydroxide in methanol-water (3:1) at room temperature (Scheme 1). Synthesis of racemic trans ester **3** was achieved under mild conditions by stirring compound **2** for 4 h in DMSO using K_2CO_3 and ethyl iodide. The GC-MS analysis of the isolated ester shows only a single isomer, whose spectral data were identical to those of the trans ester **3** reported in the literature [8]. Treatment of trans ketoester **3** or ketoacid **2** with $NaBH_4$ in THF-CH_3OH (1:1) at room temperature yielded the corresponding alcohols **4** and **5**, which underwent acid-catalyzed ring closure to produce lactone **10** (Scheme 2).

Compound **10** was oxidized to the corresponding 4-oxo-lactone **11** by treatment with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone at 0°C [9].

Subsequent opening of lactone **11** with ammonia and methylamine at room temperature in THF-MeOH afforded amides **12** and **13**.

Unfortunately, cyclization of compounds **12** and **13** under a variety of conditions failed. Compounds **14** and **15** were never detected [2–5] (Scheme 3).

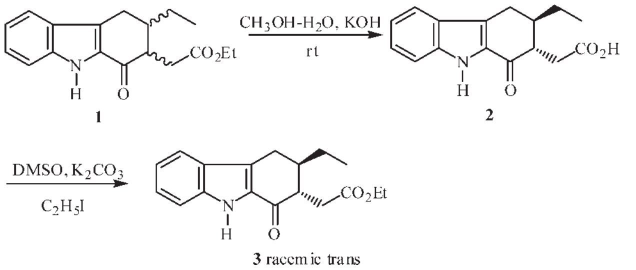
At this point, we decided to reduce alcohol **12** to compound **16**. Treatment of **12** with Et_3SiH and $TiCl_4$ in CH_2Cl_2, however, afforded compound **17** [10] (Scheme 4).

In conclusion, starting from compound **1** and using common intermediates **11**, we obtained the racemic trans amides **12** and **13**. Unfortunately, all attempts to convert amides **12** and **13** to the corresponding tetracyclic lactams **14** and **15** were unsuccessful and reduction of alcohol **12** into compound **16** also failed.

EXPERIMENTAL

^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded with a Bruker instrument DPX-400, 400-MHz High-Performance Digital FT-NMR Spectrometer using $CDCl_3$

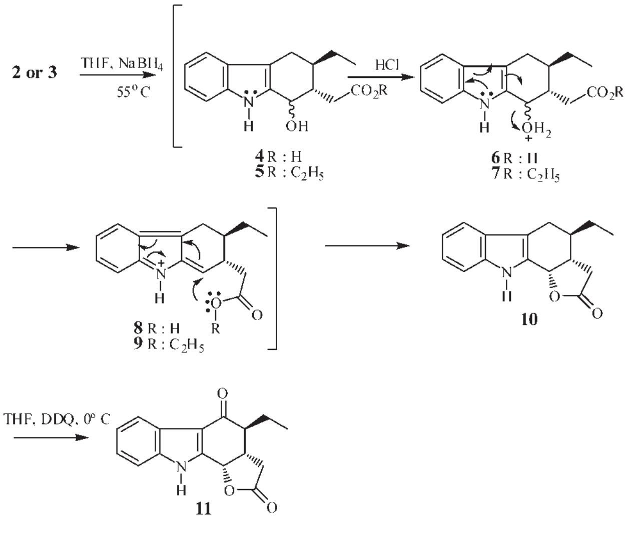
Scheme 1



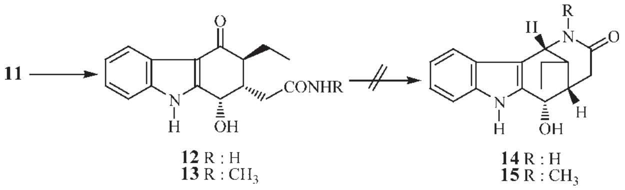
and DMSO as solvents and tetramethylsilane (TMS) as an internal standard at 25°C. Chemical shifts are expressed in terms of parts per million (δ) and the coupling constants are given in Hz. IR spectra were recorded using a Mattson 1000 FTIR spectrometer. Melting points were determined in a capillary tube on a Gallenkamp apparatus and are uncorrected. Reactions were monitored by thin layer chromatography (silica gel 60 F254). Purification of solvents was performed according to standard methods.

2-(3-Ethyl-1-oxo-1,2,3,4,9-tetrahydrocarbazole-2-yl)-2-acetic acid (2). A solution of 5.00 g (16.72 mmol) of compound 1 in 20 mL tetrahydrofurane and 100 mL 15% potassium hydroxide solution (methanol-water (1:1) was stirred for 4 h. The organic solvent was evaporated under vacuum. The residue was acidified slowly with 100 mL of 10% hydrochloric acid. The mixture was cooled to 0°C and the precipitate was filtered. The product was washed with water and ether and recrystallized from ethyl acetate to yield 4.38 g (96%) of compound 2; m.p. 229–231°C. R_f = 0.69 (EtOAc/methanol, 20:1); IR (potassium bromide): ν 3283, 2959, 2912, 1706, 1639 cm^{-1}; ^{1}H NMR (dimethyl sulfoxide-d$_6$): δ 0.96–0.99 (t, 3H, CH_2CH_3, J = 7.37 Hz), 1.40–1.49 (m, 1H), 1.60–1.66 (m, 1H), 2.22–2.35 (m, 1H), 2.65–2.71 (m, 3H), 2.73–2.80 (m, 1H), 3.18 (dd, 1H, J = 4.46 and 16.48 Hz), 7.07–7.10 (m, 1H, aromatic proton), 7.25–7.32 (m, 1H, arom. H), 7.39–7.42 (d, 1H, arom. H, J = 8.30 Hz), 7.69–7.71 (d, 1H, arom H, J = 7.80 Hz), 11.72 (s, 1H, N—H), 12.13 (bs, 1H, OH); APT NMR (dimethyl sulfoxide-d6): δ 11.0 (CH$_3$), 25.2 (CH$_2$), 25.4 (CH$_2$), 31.8 (CH$_2$), 41.8 (CH), 49.0 (CH), 113.2 (CH), 120.1 (CH), 121.6 (CH), 125.8 (C), 126.6 (CH), 126.7 (C), 130.8 (C), 137.6 (C), 173.8 (C=O, acid), 191.1 (C=O, ketone); MS: m/z 271 (M$^+$), 253 (M$^+$-H$_2$O), 225 (M$^+$-CO$_2$H), 78 (M$^+$-C$_{10}$H$_{11}$NO$_3$); *Anal.* Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.78; H, 6.36; N, 5.17.

Scheme 2

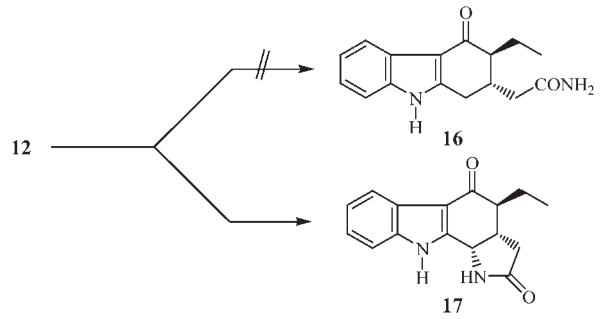


Scheme 3



Ethyl(3-ethyl-1-oxo-1,2,3,4,9-tetrahydro-1*H*-carbazole-2-yl)-2-acetate (3). A solution of 2.00 g (7.37 mmol) of compound 2 in 20 mL of DMSO, 2.00 g potassium carbonate (14.47 mmol) and 5.00 g iodoethane (32.05 mmol) was stirred for 3 h at room temperature. The residue was poured into water and extracted with dichloromethane. The organic layer was dried with anhydrous magnesium sulfate and the solvent was removed. The residue was purified by chromatography using silica gel and dichloromethane/ethyl acetate (15:1). The product was recrystallized from ether to yield 2.07 g (94%) of compound 3; mp 158°C.R_f = 0.47 (dichloromethane/EtOAc, 15:1); IR (potassium bromide): ν 3283, 2964, 1705, 1641, 1545, 1431, 1334, 810, 750 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 1.10 (t, 3H, J = 7.43 Hz), 1.34 (t, 3H, J = 7.13 Hz), 1.55–1.61 (m, 1H), 1.74–1.80 (m,1H), 2.34-2.36 (m, 1H), 2.77–2.94 (m, 3H), 3.03–3.07 (m, 1H), 3.29 (dd, 1H, J = 16.62 and 4.60 Hz), 4.22–4.28 (q, 2H), 7.19–7.23 (m, 1H), 7.41–7.45 (m, 1H), 7.52 (d, 1H, J = 8.36 Hz), 7.72 (d, 1H, J = 8.03 Hz), 9.41 (s, 1H); APT NMR (deuteriochloroform): δ 10.8 (CH$_3$), 14.2 (CH$_3$), 25.5 (CH$_2$), 26.1 (CH$_2$), 32.3 (CH$_2$), 42.4 (CH), 48.9 (CH), 60.6 (CH$_2$), 112.6 (CH), 120.4 (CH), 121.2 (CH), 125.8 (C), 127.0 (CH), 127.7 (C), 130.3 (C), 138.33 (C), 172.6 (C=O, ester), 191.4 (C=O, ketone); MS: m/z 299 (M$^+$), 270 (M$^+$-C$_2$H$_5$), 254 (M$^+$-OC$_2$H$_5$), 225 (M$^+$—CO$_2$C$_2$H$_5$). Anal. Calcd for $C_{16}H_{17}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.25; H, 7.10; N, 4.70.

Scheme 4



4-Ethyl-3,3a,4,5-tetrahydro-10*H*-furo[2,3-α]carbazol -2(10bH)-one (10). A solution of 1.00 g (31.75 mmol) of compound **2** in 20 mL tetrahydrofuran was treated with 2.00 g of sodium borohydride and the mixture was refluxed for 2 h. The reaction mixture was poured into a solution of 50 mL of 10% hydrochloric acid and cooled to 0°C. Then, the precipitate was filtered and the product was recrystallized from ether to yield 0.85 g (90%) of compound **10**; m.p. 202°C. $R_f = 0.57$ (EtOAc); IR (potassium bromide): ν 3371, 2959, 2857, 1762 cm^{-1}; ^{1}H NMR (dimethyl sulfoxide-d$_6$): δ 1.04–1.08 (t, 3H, $\mathrm{CH_2}\mathit{CH_3}$, J = 7.46), 1.32–1.44 (m, 1H), 1.62–1.73 (m, 1H), 1.77–1.86 (m, 1H), 2.46–2.52 (dd, 1H, J = 7.79 and 16.20 Hz), 2.61–2.66 (dd, 1H, J = 4.10 and 16.47 Hz), 2.69–2.82 (m, 2H), 3.04–3.09 (dd, 1H, J = 4.94 and 16.18 Hz), 5.55–5.56 (d, 1H, J = 5.95 Hz), 7.14–7.17 (m, 1H, aromatic proton), 7.24–7.28 (m, 1H, aromatic proton), 7.38-7.40 (d, 1H, aromatic proton, J = 8.73 Hz), 7.58–7.60 (d, 1H, aromatic proton, J = 7.88 Hz), 8.28 (s, 1H, N—H); APT NMR (dimethyl sulfoxide-d$_6$): δ 11.6 (CH_3), 23.4 (CH_2), 25.8 (CH_2), 33.4 (CH_2), 36.5 (CH), 40.2 (CH), 73.8 (CH), 111.4 (CH), 113.5 (C), 119.2 (CH), 119.8 (CH), 123.4 (CH), 126.22 (C), 128.0 (C), 137.2 (C), 176.5 (C=O, lactone); MS: m/z 255 (M^+), 196 (M^+-CH_3CO_2H), 140 (M^+—- CH_3CO_2H—C_4H_8), 78 (M^+—$C_{10}H_{11}NO_2$); Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 7.33; H, 6.76; N, 5.53.

4-Ethyl-3,3a,4,10-tetrahydro-3*H*-furo[2,3-α]carbazol-2,5 (10*H*,10b*H*)-dione (11). To a solution of 1.00 g (3.92 mmol) of compound **10** in 20 mL tetrahydrofuran (10% water) was added dropwise 1.78 g (7.84 mmol) of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone in 5 mL tetrahydrofuran at 0°C. The reaction mixture was stirred for 12 h at room temperature. Then, the solution was poured into 5% potassium carbonate solution and extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate and the solvent was removed. The residue was purified by chromatography using silica gel and ethyl acetate. The product was recrystallized from ether to yield 0.95 g (90%); of compound **11**. m.p. 237°C. $R_f = 0.79$ (EtOAc); IR (potassium bromide): ν 3195, 2964, 2888, 1781, 1644 cm^{-1}; ^{1}H NMR (dimethyl sulfoxide-d$_6$): δ :0.92–0.95 (t, 3H, $\mathrm{CH_2}\mathit{CH_3}$, J = 7.30 Hz), 1.58–1.65 (m, 1H), 1.74–1.80 (m, 1H), 2.41–2.51 (m, 3H), 2.83–2.89 (dd, 1H, J = 8.21 and 16.43 Hz), 6.05 (d, 1H, J = 6.75 Hz), 7.21–7.31 (m, 2H, aromatic proton), 7.50 (d, 1H, aromatic proton, J = 7.95 Hz), 8.06 (d, 1H, aromatic proton, J = 7.61 Hz), 12.39 (s, 1H, N-H); APT NMR (dimethyl sulfoxide-d$_6$): δ 12.0 (CH_3), 24.1 (CH_2), 34.0 (CH_2), 39.4 (CH), 49.9 (CH), 71.9 (CH), 111.9 (C), 112.8 (CH), 122.6 (CH), 122.8 (CH), 123.9 (C), 124.4 (CH), 137.6 (C), 142.7 (C), 175.9 (C=O, lactone), 193.6 (C=O, ketone); MS: m/z 269 (M^+), 223 (M^+—CO_2H), 167 (M^+—CO_2H—C_4H_8), 78 (M^+—$C_{10}H_9NO_3$); *Anal.* Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.33; H, 5.58; N 5.23.

2-(3-Ethyl-1-hydroxy-4-oxo-1,2,3,4,9-tetrahydro-1*H*-carbazol-2-yl)-acetamide (12). A solution of 1.00 g (37.17 mmol) of compound 11 in 30 mL of methanol and 30 mL of 25% ammonia solution was stirred for 4 h at room temperature. The residue was poured into water and cooled to 0°C. The precipitate was filtered. The product was washed with water and ether and recrystallized from methanol to yield 0.85 g (80%) of compound 12; m.p. 160–161°C. $R_f = 0.27$ (EtOAc/methanol, 20:1); IR (potassium bromide): ν 3379, 2953–2868, 1624 cm^{-1}; ^{1}H NMR (dimethyl sulfoxide-d$_6$): δ 0.91–0.95 (t, 3H, $\mathrm{CH_2}\mathit{CH_3}$, J = 7.17 Hz), 1.56–1.64 (m, 1H), 1.75–1.83 (m, 1H), 1.94–2.09 (m, 1H), 2.31–2.34 (m, 2H), 2.79–2.83 (dd, 1H, J = 4.50 and 4.19 Hz), 5.26-5.27 (d, 1H,J = 4,43 Hz), 5,95 (s,1H, OH), 6.83 (s, 1H, NH), 7.13–7.20 (m, 2H, aromatic proton), 7.32 (s, 1H, NH), 7.42–7.44(d, 1H, aromatic proton, J = 8.01 Hz), 7.95–7.97 (d, 1H, aromatic proton, J = 7.50 Hz), 11.97 (s, 1H, N—H); APT NMR (dimethyl sulfoxide-d$_6$): δ 12.2 (CH_3), 22.5 (CH_2), 33.9 (CH_2), 42.4 (CH), 52.3 (CH), 62.8 (CH), 109.7 (C), 112.6 (CH), 120.9 (CH), 120.1 (CH), 123.1 (CH), 125.1 (C), 136.9 (C), 151.5 (C), 174.1 (C=O, amid), 194.7 (C=O, ketone); MS: m/z 285 (M^+), 268 (M^+—OH), 251 (M^+—OH—NH_3), 223 (M^+—OH—NH_3—CO), 78 (M^+—$C_{10}H_{11}N_2O_3$); *Anal.* Calcd for $C_{16}H_{17}N_2O_3$: C, 67.35; H, 6.01; N, 9.82. Found: C, 67.38; H, 5.96; N, 9.87.

***N*-Methyl-2-(3-Ethyl-1-hydroxy-4-oxo-1,2,3,4,9-tetrahydro-1*H*-carbazol-2-yl)-acetamide (13).** A solution of 1.00 g (37.17 mmol) of compound **11** in 30 mL of methanol and 30 mL of 40% methylamine was stirred for 4 h at room temperature. The residue was poured into the water and cooled to 0°C. The precipitate was filtered. The product was washed with water and ether and recrystallized from methanol to yield 0.69 g (62%) of compound **13**; m.p. 161°C $R_f = 0.24$ (EtOAc/methanol, 20:1); IR (potassium bromide): ν 3254, 2965, 2932, 1655, 1630 cm^{-1}; ^{1}H NMR (dimethyl sulfoxide-d6): δ 0.91–0.94 (t, 3H, $\mathrm{CH_2}\mathit{CH_3}$, J = 7.30 Hz), 1.55–1.62 (m, 1H), 1.73–1.82 (m, 1H), 1.93–2.01 (m, 1H), 2.29–2.33 (m, 1H), 2.50 (d, NCH_3, J = 6.80 Hz), 2.82–2.85 (m, 1H,), 5.24–5.26 (t, 1H, J = 5,28 Hz), 5.90 (d, 1H, OH, J = 5,79 Hz), 7.13–7.21 (m, 2H, aromatic proton), 7.43 (d, 1H, aromatic proton, J = 7.78 Hz), 7,77 (s, 1H, NH), 7.96 (d, 1H, aromatic proton, J = 7.10 Hz), 11.89 (s, 1H, N—H); APT NMR (dimethyl sulfoxide-d$_6$): δ 12.2 (CH_3), 22.49 (CH_2), 26.0 (CH_3), 34.3 (CH_2), 42.5 (CH), 52.2 (CH), 62.9 (CH), 109.7 (C), 112.6 (CH), 120.9 (CH), 122.1 (CH), 123.1 (CH), 125.0 (C), 136.9 (C), 151.4 (C), 172.3 (C=O, amid), 194.69 (C=O, ketone); MS: *m/z* 269 (M^+—NH_2CH_3), 241 (M^+—CO—NH_2CH_3), 224 (M^+—OH—CO—NH_2CH_3); *Anal.* Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.95; H, 6.73; N, 9.30.

4-Ethyl-1,3a,4,10b-tetrahydropyrrolo[2,3-α]carbazole-2,5 (3*H*,10*H*)-dione (17). A solution of 1.00 *g* (3.50mmol) of compound **12** in 20 mL tetrahydrofuran was cooled to -78°C. After addition of 0.45 mL (6.48 mmol) $TiCl_4$ and 2.2 mL (14.25 mmol) triethylsilane, the resulting mixture was stirred for 2 h and poured into water. Then, the precipitate was filtered and the product was recrystallized from ether to yield 0.48 g (54%) of compound **17**; m.p. 183°C (dec.). $R_f = 0.19$ (EtOAc/methanol, 20:1); IR (potassium bromide): ν 3239, 2965, 2931, 1655, 1630 cm^{-1}; ^{1}H NMR (dimethyl sulfoxide-d$_6$): δ :0.92–0.96 (t, 3H, $\mathrm{CH_2}\mathit{CH_3}$, J = 7.28 Hz), 1.55–1.60 (m, 1H), 1.70–1.76 (m, 1H), 1.92–2.07 (m, 2H), 2.30–233 (m, 1H), 2.80–2.83 (m, 1H), 5.24 (d, 1H, J = 4.92 Hz), 6.74 (s, 1H, N—H), 7.10–7.17 (m, 2H, aromatic proton), 7.28 (s, 1H, N—H), 7.40 (d, 1H, aromatic proton, J = 7.60 Hz), 7.94 (d, 1H, aromatic proton, J = 7.96 Hz); APT NMR (dimethyl sulfoxide-d$_6$): δ 12.4 (CH_3), 23.0 (CH_2), 33.9 (CH_2), 42.2 (CH), 52.2 (CH), 62.7 (CH), 110.0 (C), 112.6 (CH), 120.9 (CH), 121.9 (CH), 122.9 (C), 125.1 (CH), 137.2 (C), 142.5 (C), 174.1 (C=O, lactam), 195.1 (C=O, ketone); MS: *m/z* 211 (M^+—CH_2CON), 182 (M^+—C_2H_5—CH_2CON), 167

(M^+—$C_3H_6CO_2N$); *Anal*. Calcd for $C_{16}H_{16}NO_2$: C, 75.57; H, 6.34; N, 5.51. Found: C, 75.62; H, 6.36; N 5.48.

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Synthesis of New Pyridazine Derivatives as Potential Anti-HIV-1 Agents

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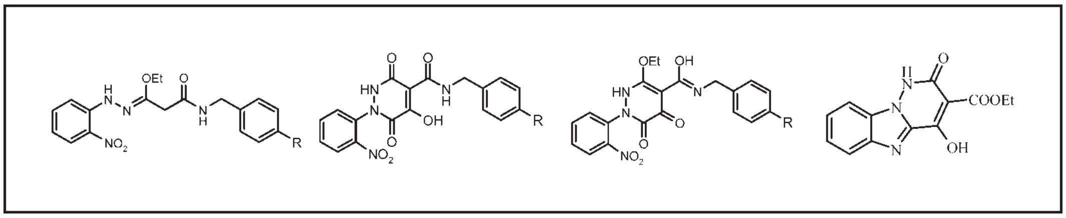

We herein report conventional and microwave-assisted methods for the synthesis of a series of compounds containing some bivalent ion chelating requirements useful to exert potential HIV-1 integrase (IN) enzyme inhibition activity. The biological screening highlighted that only derivative **5** proved to be a strand-transfer step inhibitor of the virus integration process at micromolar concentration.

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INTRODUCTION

Human immunodeficiency virus (HIV), the etiological agent of acquired immunodeficiency syndrome (AIDS) continues to be a major health threat worldwide. The main steps in the viral life cycle include viral entry, replication of the viral genome, and proteolytic processing of viral polyproteins. In addition, HIV replication depends on the integration of the proviral DNA into the genome of infected cells, which is catalyzed by HIV integrase (IN). All these steps are potential targets for antiviral drugs.

The IN-catalyzed insertion of viral DNA into the host cell chromosome is a multistep process that includes two catalytic reactions: 3′-Processing (3′P) and strand-transfer (ST) [1]. Moreover, it has been suggested that the integration mechanism involves bivalent metal ions (Mg^{2+} or Mn^{2+}) in the enzyme catalytic site [2,3].

After many years of research, several molecules were identified as IN inhibitors and among them β-diketo acids (DKAs) [4] and their analogs [5] represent one of the major leads in the identification of new antiviral agents. In particular, it has been reported that the DKA pharmacophoric motif could be able to sequester one or both metal ions necessary for IN-enzymatic activity [2].

In fact, the only one integrase strand-transfer inhibitor (INSTI) (Raltegravir) (Fig. 1) [6] so far approved by Food and Drug Administration (FDA), belongs to the DKAs analogs class, in which the diketo acid moiety, as ‘‘ketoenole,’’ has been included in a rigid system.

Taking into account these findings and considering the results of our previously reported studies [7–10], we planned the synthesis of new derivatives containing a pyridazine core as well as the chemical features able to inhibit IN activity as chelating agents for bivalent metal ions. The obtained compounds were characterized and tested to evaluate their antiviral activity and enzymatic inhibition.

RESULTS AND DISCUSSION

The synthesis of the first designed compound **4** was carried out, as reported in Scheme 1, starting from the commercially available nitrophenylhydrazine **1**.

At first it was converted into 3-ethoxy-3-[(2-nitrophenyl)hydrazono]propanoic acid ethyl ester (**2**) by reaction with 3-amino-3-ethoxy-acrylic acid ethyl ester. This is a novel synthetic approach with respect to a previously reported procedure [11] thus improving the yields and reducing reaction time. The obtained mixture of Z- and E-isomers (**2**), without further separation, was successively used for the cyclocondensation with oxalyl chloride to give the ethyl 5-hydroxy-1-(2-nitrophenyl)-3,6-dioxo-1,2,3,6-tetrahydropyridazine-4-carboxylate (**3**). The pyridazine

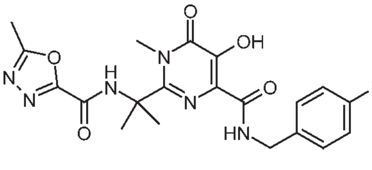


Figure 1. Chemical structure of Raltegravir.

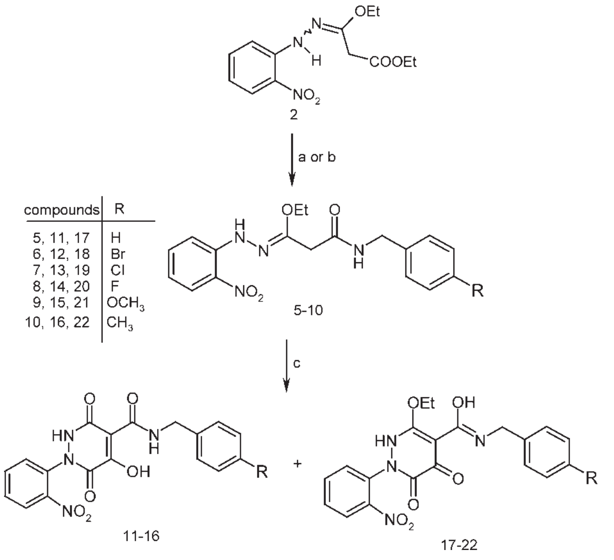
derivative **3** was finally treated with platinum dioxide under hydrogen atmosphere to give the ethyl 4-hydroxy-2-oxo-1,2-dihydropyridazino[1,6-a]benzimidazole-3-carboxylate (**4**) resulting from the nitro-group reduction and the consequent ring closure.

With the aim to prepare the amide derivatives **5–22**, we used the synthetic route described in Scheme 2. The (Z) isomer of intermediate **2**, obtained as red crystals from ethanol, was used as starting material, and was converted into the corresponding (*Z*)*N*-benzyl-3-ethoxy-3-[(2-nitrophenyl)hydrazono]propanamides **5–10**, by reaction with appropriate benzylamine. With the aim to optimize the synthetic procedure, we performed this step both at room temperature and under reflux (50°C). We found that even elevating the reaction temperature no significant reduction in reaction time occurred. Alternatively, when we used the microwave-assisted organic synthesis (MAOS) approach we observed a remarkable reduction of reaction time (1 h rather than 15 h). Moreover, this approach was used in free-solvent conditions (see experimental section). Then, the condensation with oxalyl chloride gave a mixture of two different series (**11–16** and **17–22** in a ratio of 2:1) of pyridazine derivatives depending on the tautomeric form of the amide precursors **5–10** as well as the hydrolytic processes occurred on their ethoxy functionality.

The *N*-benzyl-5-hydroxy-1-(2-nitrophenyl)-3,6-dioxo-1,2,3,6-tetrahydropyridazine-4-carboxamides **11–16** were directly recovered as crude precipitate from reaction mixture, while the evaporation of the resulting solution furnished the *N*-benzyl-3-ethoxy-1-(2-nitrophenyl)-5,6-dioxo-1,2,5,6-tetrahydropyridazine-4-carboximidic acids **17–22**.

All the synthesized compounds were tested for their IN enzymatic inhibitory effect both against the overall integration reaction and more specifically against the strand-transfer step. The biological results showed that compound **5** was able to inhibit the enzymatic activity at micromolar concentration (Table 1).

Scheme 2. Reagents and conditions: a) $ArCH_2NH_2$, CH_2Cl_2, r.t. 15 h; b) $ArCH_2NH_2$, two steps in the same conditions: 280 W, 50°C, 30 min; and c) oxalyl chloride, toluene, 0°C, 2 h.



compounds	R
5, 11, 17	H
6, 12, 18	Br
7, 13, 19	Cl
8, 14, 20	F
9, 15, 21	OCH_3
10, 16, 22	CH_3

Moreover, the HIV-induced cytopathic effect (CPE) in human lymphocyte MT-4 cell culture was determined by the MT-4/MTT-assay. The screening data put in evidence that only the *N*-benzyl-3-ethoxy-3-[(2-nitrophenyl)hydrazono]propanamides (**5–10**) showed antiviral activity in cells test, but also toxicity at same concentration.

EXPERIMENTAL

Chemistry. All microwave-assisted reactions were carried out in a CEM Focused Microwave Synthesis System, Model Discover working at the potency necessary for refluxing under atmospheric conditions. Melting points were determined on a BUCHI Melting Point B-545 apparatus and are uncorrected. Elemental analyses (C, H, N) were carried out on a Carlo Erba Model 1106 Elemental Analyzer and the results are within ±0.4% of the theoretical values. Merck silica gel 60 F_{254} plates were used for analytical tlc. ^1H NMR spectra were recorded in DMSO-d_6 on a Varian Gemini-300 spectrometer. Chemical shifts were expressed in δ (ppm).

Scheme 1. Reagents and conditions: a) 3-amino-3-ethoxy-acrylic acid ethyl ester, dry EtOH, N_2, rt, 2h; b) oxalyl chloride, toluene, 0°C, 5 h; and c) PtO_2, H_2, EtOH, rt, 5 h.

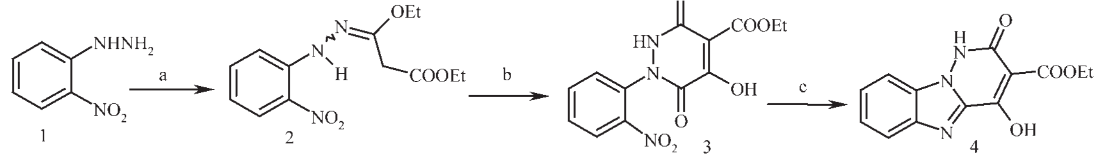


Table 1

Inhibition of HIV-1 integrase enzymatic activity, replication of HIV-1 (IIIB), and cytotoxicity in MT-4 cells.

	IN enzymatic activity		Activity in MT-4 cells		
Compound	Over-all[a] IC_{50} (μM)	ST[b] IC_{50} (μM)	HIV-1[c] EC_{50} (μM)	Cytotoxicity[d] CC_{50} (μM)	SI[e]
5	15.32	37.39	0.82	0.82	1
6	>250	>250	53.28	53.28	1
7	>250	>250	15.91	15.91	1
8	>250	>250	5.17	5.17	1
9	>250	>250	>30.68	>30.68	1
10	>250	>250	18.16	18.16	1
CHI 1043[9]	0.08	0.14	0.59	41.1	70

[a] Concentration required to inhibit the *in vitro* overall integrase activity by 50%.

[b] Concentration required to inhibit the *in vitro* strand transfer step by 50%.

[c] Effective concentration required to reduce HIV-1-induced cytopathic effect by 50% in MT-4 cells.

[d] Cytotoxic concentration to reduce MT-4 cell viability by 50%.

[e] Selectivity index: ratio CC_{50} /EC_{50}.

Synthesis of (*Z-E*)3-ethoxy-3-[(2-nitrophenyl)hydrazono]-propanoic acid ethyl ester (2). 2-Nitrophenylhydrazine (0.001 mol, 137.14 mg) (**1**) and 3-amino-3-ethoxy-acrylic acid ethyl ester hydrochloride (0.001 mol, 195.65 mg) were suspended in ethanol (3 mL), under N_2 atmosphere, and stirred at room temperature for 2 h. The precipitate was filtered off and the solution concentrated *in vacuo*. Yield 69%. Spectral measurements (^1H NMR) and experimental data were in accordance with reported data in the literature [11].

Synthesis of ethyl 5-hydroxy-1-(2-nitrophenyl)-3,6-dioxo-1,2,3,6-tetrahydropyridazine-4-carboxylate (3). Oxalyl chloride (0.001 mol, 126.93 mg) was added dropwise at 0°C to a solution of (*Z-E*)3-ethoxy-3-[(2-nitrophenyl)hydrazono]propanoic acid ethyl ester (**2**) (0.001 mol, 295.30 mg) in toluene (6 mL). The mixture was stirred for 5 h and allowed to reach room temperature. Yellow crystals were formed, the precipitate was filtered off, and crystallized from diethyl ether. Mp 260–262°C yield 81%; ^1H NMR: δ 1.15 (t, 3H, J = 7.1, CH_3), 3.40 (q, 2H, J = 7.1, CH_2), 6.78–8.12 (m, 4H, ArH), 9.40 (bs, 1H, NH). Anal. Calcd. for $C_{13}H_{11}N_3O_7$: C, 48.61; H, 3.45; N, 13.08. Found: C, 48.54; H, 3.38; N, 13.24.

Synthesis of ethyl 4-hydroxy-2-oxo-1,2-dihydropyridazino[1,6-a]benzimidazole-3-carboxylate (4). Compound **3** (0.001 mol, 321.25 mg) was dissolved in dry ethanol (50 mL) in a flask suitable for a normal pressure hydrogenation. Platinum dioxide (0.002 mol, 32 mg) was added and the compound **3** was hydrogenated under ambient pressure. The mixture was stirred for 5 h. The catalyst was filtered off on diatomaceous earth and the solvent removed under reduced pressure. The residue was powdered by treatment with diethyl ether and crystallized from ethanol. Mp 230–232°C, yield 26%; ^1H NMR: δ 1.22 (t, 3H, J = 7.1, CH_3), 4.16 (q, 2H, J = 7.1, CH_2), 6.55–7.97 (m, 4H, ArH), 10.43 (bs, 1H, NH). Anal. Calcd. for $C_{13}H_{11}N_3O_4$: C, 57.14; H, 4.06; N, 15.38. Found: C, 57.20; H, 4.12; N, 15.30.

General procedure for the synthesis of (*Z*)*N*-benzyl-3-ethoxy-3-[(2-nitrophenyl)hydrazono]propanamides (5–10)

Conventional method. (*Z*)3-Ethoxy-3-[(2-nitrophenyl)hydrazono]propanoic acid ethyl ester (**2**) (0.001 mol, 295.30 mg) was dissolved in methylene chloride (2 mL), under N_2 atmosphere, and the solution stirred at room temperature for 10 min. The appropriate benzylamine (0.010 mol) was added and the resulting solution was stirred for 15 h. Precipitate was filtered and crystallized from ethanol.

Microwave-assisted synthesis. The appropriate benzylamine (0.010 mol) was added to the (*Z*)3-ethoxy-3-[(2-nitrophenyl)-hydrazono]propanoic acid ethyl ester (**2**) (0.001 mol, 295.30 mg), under N_2 atmosphere, and the resulting mixture was placed in a cylindrical quartz tube (Ø 2 cm). The reaction mixture was then stirred and irradiated in a microwave oven for two subsequent periods in the same conditions: 280 W, 30 min, and 50°C. After cooling the work-up was carried out as described for the conventional method.

(Z)N-Benzyl-3-ethoxy-3-[(2-nitrophenyl)hydrazono]propanamide (5). Mp 172–174°C, yield 100%; ^1H NMR: δ 1.30 (t, 3H, J = 7.1, CH_3), 3.55 (s, 2H, CH_2), 4.23 (q, 2H, J = 7.1, CH_2), 4.31 (d, 2H, J = 5.99, CH_2), 6.76–8.08 (m, 9H, ArH), 8.68 (t, 1H, J = 5.99, NH), 10.93 (bs, 1H, NH). Anal. Calcd. for $C_{18}H_{20}N_4O_4$: C, 60.67; H, 5.66; N, 15.72. Found: C, 60.60; H, 5.59; N, 15.78.

(Z)N-(4-Bromobenzyl)-3-ethoxy-3-[(2-nitrophenyl)hydrazono]propanamide (6). Mp 175–177° C, yield 99%; ^1H NMR: δ 1.30 (t, 3H, J = 6.9, CH_3), 3.54 (s, 2H, CH_2), 4.22 (q, 2H, J = 6.9, CH_2), 4.27 (d, 2H, J = 5.8, CH_2), 6.76–8.08 (m, 8H, ArH), 8.71 (t, 1H, J = 5.8, NH), 10.92 (bs, 1H, NH). Anal. Calcd. for $C_{18}H_{19}BrN_4O_4$: C, 49.67; H, 4.40; N, 12.87. Found: C, 49.62; H, 4.43; N, 12.83.

(Z)N-(4-Chlorobenzyl)-3-ethoxy-3-[(2-nitrophenyl)hydrazono]propanamide (7). Mp 171–173°C, yield 100%; ^1H NMR: δ 1.30 (t, 3H, J = 6.9, CH_3), 3.69 (s, 2H, CH_2), 4.22 (q, 2H, J = 6.9, CH_2), 4.29 (d, 2H, J = 5.8, CH_2), 6.76–8.08 (m, 8H, ArH), 8.72 (t, 1H, J = 5.8, NH), 10.93 (bs, 1H, NH). $C_{12}H_{12}O_4$: C, 65.45; H, 5.49; C, 65.31; H, 5.63. Anal. Calcd. for $C_{18}H_{19}ClN_4O_4$: C, 55.32; H, 4.90; N, 14.34. Found: C, 55.28; H, 4.95; N, 14.31.

(Z)N-(4-Fluorobenzyl)-3-ethoxy-3-[(2-nitrophenyl)hydrazono]propanamide (8). Mp 180–182°C, yield 93%; ^1H NMR: δ 1.30 (t, 3H, J = 7.1, CH_3), 3.69 (s, 2H, CH_2), 4.22 (q, 2H, J = 7.1, CH_2), 4.29 (d, 2H, J = 5.8, CH_2), 6.78–8.08 (m, 8H, ArH), 8.68 (t, 1H, J = 5.8, NH), 10.93 (bs, 1H, NH). Anal. Calcd. for $C_{18}H_{19}FN_4O_4$: C, 57.75; H, 5.12; N, 14.97. Found: C, 57.71; H, 5.08; N, 14.93.

(Z)N-(4-Methoxybenzyl)-3-ethoxy-3-[(2-nitrophenyl)hydrazono]propanamide (9). Mp 171–173°C, yield 84%; ^1H NMR:

δ 1.30 (t, 3H, $J = 7.3$, CH_3), 3.52 (s, 2H, CH_2), 3.72 (s, 3H, CH_3O), 4.21 (q, 2H, $J = 7.3$, CH_2), 4.23 (d, 2H, $J = 5.7$, CH_2), 6.75–8.07 (m, 8H, ArH), 8.58 (t, 1H, $J = 5.7$, NH), 10.92 (bs, 1H, NH). Anal. Calcd. for $C_{19}H_{22}N_4O_5$: C, 59.06; H, 5.74; N, 14.50. Found: C, 59.02; H, 5.69; N, 14.55.

(Z)N-(4-Methylbenzyl)-3-ethoxy-3-[(2-nitrophenyl)hydrazono]propanamide (10). Mp 179–181°C, yield 90%; ^{1}H NMR: δ 1.30 (t, 3H, $J = 7.1$, CH_3), 2.27 (s, 3H, CH_3), 3.53 (s, 2H, CH_2), 4.22 (q, 2H, $J = 7.1$, CH_2), 4.26 (d, 2H, $J = 5.7$, CH_2), 6.76–8.08 (m, 8H, ArH), 8.63 (t, 1H, $J = 5.7$, NH), 10.93 (bs, 1H, NH). Anal. Calcd. for $C_{19}H_{22}N_4O_4$: C, 61.61; H, 5.99; N, 15.13. Found: C, 61.58; H, 5.95; N, 15.16.

General procedures for the synthesis of N-benzyl-5-hydroxy-1-(2-nitrophenyl)-3,6-dioxo-1,2,3,6-tetrahydropyridazine-4-carboxamides (11–16) and N-benzyl-3-ethoxy-1-(2-nitrophenyl)-5,6-dioxo-1,2,5,6-tetrahydropyridazine-4-carboximidic acids (17–22). The appropriate (*Z*)*N*-benzyl-3-ethoxy-3-[(2-nitrophenyl)hydrazono]propanamide (**5–10**) (0.001 mol) was dissolved in dry toluene (6.5 mL). Oxalyl chloride (0.001 mol, 126.93 mg) was added dropwise at 0°C and the reaction mixture stirred for 2 h. The obtained precipitate was filtered and crystallized from ethanol/methanol (1:1, v/v) to give derivatives **11–16**. The solution was concentrated under reduced pressure and the residue treated with diethyl ether to afford derivatives **17–22**.

N-Benzyl-5-hydroxy-1-(2-nitrophenyl)-3,6-dioxo-1,2,3,6-tetrahydropyridazine-4-carboxamide (11). Mp 164–166°C, yield 56%; ^{1}H NMR: δ 4.41 (s, 2H, CH_2), 6.87–8.12 (m, 9H, ArH), 9.44 (bs, 1H, NH). Anal. Calcd. for $C_{18}H_{14}N_4O_6$: C, 56.55; H, 3.69; N, 14.65. Found: C, 56.49; H, 3.65; N, 14.68.

N-(4-Bromobenzyl)-5-hydroxy-1-(2-nitrophenyl)-3,6-dioxo-1,2,3,6-tetrahydropyridazine-4-carboxamide (12). Mp 171–173°C, yield 64%; ^{1}H NMR: δ 4.36 (s, 2H, CH_2), 6.84–8.11 (m, 8H, ArH), 9.41 (bs, 1H, NH). Anal. Calcd. for $C_{18}H_{13}BrN_4O_6$: C, 46.87; H, 2.84; N, 12.15. Found: C, 46.61; H, 2.55; N, 12.82.

N-(4-Chlorobenzyl)-5-hydroxy-1-(2-nitrophenyl)-3,6-dioxo-1,2,3,6-tetrahydropyridazine-4-carboxamide (13). Mp 182–184°C, yield 48%; ^{1}H NMR: δ 4.36 (s, 2H, CH_2), 6.82–8.09 (m, 8H, ArH), 9.41 (bs, 1H, NH). Anal. Calcd. for $C_{18}H_{13}ClN_4O_6$: C, 51.87; H, 3.14; N, 13.44. Found: C, 51.63; H, 3.38; N, 13.21.

N-(4-Fluorobenzyl)-1-(2-nitrophenyl)-3,6-dioxo-1,2,3,6-tetrahydropyridazine-4-carboxamide (14). Mp 172–174°C, yield 59%; ^{1}H NMR: δ 4.37 (s, 2H, CH_2), 6.86–8.09 (m, 8H, ArH), 9.42 (bs, 1H, NH). Anal. Calcd. for $C_{18}H_{13}FN_4O_6$: C, 54.01; H, 3.27; N, 14.00. Found: C, 54.06; H, 3.31; N, 14.05.

N-(4-Methoxylbenzyl)-5-hydroxy-1-(2-nitrophenyl)-3,6-dioxo-1,2,3,6-tetrahydropyridazine-4-carboxamide (15). Mp 184–186°C, yield 37%; ^{1}H NMR: δ 3.72 (s, 3H, CH_3O), 4.33 (s, 2H, CH_2), 6.87–8.13 (m, 8H, ArH), 9.43 (bs, 1H, NH). Anal. Calcd. for $C_{19}H_{16}N_4O_7$: C, 55.34; H, 3.91; N, 13.59%. Found: C, 55.31; H, 3.96; N, 13.52%.

N-(4-Methylbenzyl)-5-hydroxy-1-(2-nitrophenyl)-3,6-dioxo-1,2,3,6-tetrahydropyridazine-4-carboxamide (16). Mp 180–182°C, yield 44%; ^{1}H NMR: δ 2.27 (s, 3H, CH_3), 4.36 (s, 2H, CH_2), 6.87–8.12 (m, 8H, ArH), 9.43 (bs, 1H, NH). Anal. Calcd. for $C_{19}H_{16}N_4O_6$: C, 57.58; H, 4.07; N, 14.14. Found: C, 57.53; H, 4.02; N, 14.19.

N-Benzyl-3-ethoxy-1-(2-nitrophenyl)-5,6-dioxo-1,2,5,6-tetrahydropyridazine-4-carboximidic acid (17). Mp 190–192°C, yield 21%; ^{1}H NMR: δ 1.33 (t, 3H, $J = 6.8$, CH_3), 4.20 (q, 2H, $J = 6.8$, CH_2), 4.54 (s, 2H, CH_2), 6.90–8.16 (m, 9H, ArH), 11.19 (bs, 1H, NH). Anal. Calcd. for $C_{20}H_{18}N_4O_6$: C, 58.54; H, 4.42; N, 13.65. Found: C, 58.51; H, 4.47; N, 13.61.

N-(4-Bromobenzyl)-3-ethoxy-1-(2-nitrophenyl)-5,6-dioxo-1,2,5,6-tetrahydropyridazine-4-carboximidic acid (18). Mp 184–186°C, yield 23%; ^{1}H NMR: δ 1.35 (t, 3H, $J = 6.8$, CH_3), 4.24 (q, 2H, $J = 6.8$, CH_2), 4.52 (s, 2H, CH_2), 6.96–8.19 (m, 8H, ArH), 11.23 (bs, 1H, NH). Anal. Calcd. for $C_{20}H_{17}BrN_4O_6$: C, 49.10; H, 3.50; N, 11.45. Found: C, 49.16; H, 3.57; N, 11.50.

N-(4-Chlorobenzyl)-3-ethoxy-1-(2-nitrophenyl)-5,6-dioxo-1,2,5,6-tetrahydropyridazine-4-carboximidic acid (19). Mp 184–186°C, yield 25%; ^{1}H NMR: δ 1.34 (t, 3H, $J = 6.8$, CH_3), 4.19 (q, 2H, $J = 6.8$, CH_2), 4.19 (s, 2H, CH_2), 6.99–8.16 (m, 8H, ArH), 11.26 (bs, 1H, NH). Anal. Calcd. for $C_{20}H_{17}ClN_4O_6$: C, 54.00; H, 3.85; N, 12.59. Found: C, 54.05; H, 3.89; N, 12.53.

N-(4-Fluorobenzyl)-3-ethoxy-1-(2-nitrophenyl)-5,6-dioxo-1,2,5,6-tetrahydropyridazine-4-carboximidic acid (20). Mp 186–188°C, yield 23%; ^{1}H NMR: δ 1.34 (t, 3H, $J = 6.8$, CH_3), 4.19 (q, 2H, $J = 6.8$, CH_2), 4.67 (s, 2H, CH_2), 6.97–8.17 (m, 8H, ArH), 11.27 (bs, 1H, NH). Anal. Calcd. for $C_{20}H_{17}FN_4O_6$: C, 56.08; H, 4.00; N, 13.08. Found: C, 56.03; H, 4.05; N, 13.03.

N-(4-Methoxylbenzyl)-3-ethoxy-1-(2-nitrophenyl)-5,6-dioxo-1,2,5,6-tetrahydropyridazine-4-carboximidic acid (21). Mp 184–186°C, yield 18%; ^{1}H NMR: δ 1.33 (t, 3H, $J = 6.8$, CH_3), 3.72 (s, 3H, CH_3O), 4.19 (q, 2H, $J = 6.8$, CH_2), 4.61 (s, 2H, CH_2), 6.88–8.16 (m, 8H, ArH), 11.26 (bs, 1H, NH). Anal. Calcd. for $C_{21}H_{20}N_4O_7$: C, 57.27; H, 4.58; N, 12.72. Found: C, 57.22; H, 4.53; N, 12.66.

N-(4-Methylbenzyl)-3-ethoxy-1-(2-nitrophenyl)-5,6-dioxo-1,2,5,6-tetrahydropyridazine-4-carboximidic acid (22). Mp 185–187°C, yield 17%; ^{1}H NMR: δ 1.33 (t, 3H, $J = 6.8$, CH_3), 2.27 (s, 3H, CH_3), 4.19 (q, 2H, $J = 6.8$, CH_2), 4.63 (s, 2H, CH_2), 6.97–8.16 (m, 8H, ArH), 11.26 (bs, 1H, NH). Anal. Calcd. for $C_{21}H_{20}N_4O_6$: C, 59.43; H, 4.75; N, 13.20. Found: C, 59.47; H, 4.71; N, 13.25.

Bioassays ***Overall integrase assay using an enzyme-linked immunosorbent assay and strand-transfer inhibition.*** We used enzyme-linked immunosorbent assays to determine the susceptibility of the HIV-1 integrase enzyme towards different compounds. These assays use an oligonucleotide substrate of which one oligonucleotide (5′-ACTGCTAGAGATTTTCCA-CACT GACTAAAAGGGTC-3′) is labeled with biotin at the 3′ end and the other oligonucleotide is labeled with digoxigenin at the 5′ end. For the overall integration assay the second 5′-digoxigenin labeled oligonucleotide is (5′-GACCCTTT-TAGT CAGTGTGGAAAATCTCTAGCAGT-3′). For the strand transfer assay the second oligonucleotide lacks GT at the 3′ end. The integrase enzyme was diluted in 750 m*M* NaCl, 10 m*M* Tris pH 7.6, 10% glycerol, and 1 m*M* β-mercapto ethanol. To perform the reaction 4 μL diluted integrase (corresponding to a concentration of 1.6 μ*M*) and 4 μL of annealed oligonucleotides (7 n*M*) were added in a final reaction volume of 40 μL containing 10 m*M* $MgCl_2$, 5 m*M* DTT, 20 m*M* HEPES pH 7.5, 5% PEG and 15% DMSO. The reaction was carried out at 37°C for 1 h. Reaction products were denatured with 30 m*M* NaOH and detected by an immunosorbent assay on avidin-coated plates [12].

In vitro anti-HIV and drug susceptibility assays. The inhibitory effect of antiviral drugs on the HIV-induced cytopathic effect (CPE) in human lymphocyte MT-4 cell culture was determined by the MT-4/MTT-assay [13]. This assay is based on the reduction of the yellow colored 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) by mitochondrial dehydrogenase of metabolically active cells to a blue formazan derivative, which can be measured spectrophotometrically. The 50% cell culture infective dose (CCID50) of the HIV(IIIB) strain was determined by titration of the virus stock using MT-4 cells. For the drug-susceptibility assays MT-4 cells were infected with 100–300 CCID50 of the virus stock in the presence of fivefold serial dilutions of the antiviral drugs. The concentration of various compounds achieving 50% protection against the CPE of the different HIV strains, which is defined as the EC_{50}, was determined. In parallel the 50% cytotoxic concentration (CC_{50}) was determined.

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An Efficient Method to Prepare 4-Aminoquinazolines: Potential Application to Conformation-Restricted Bleomycin Analogs

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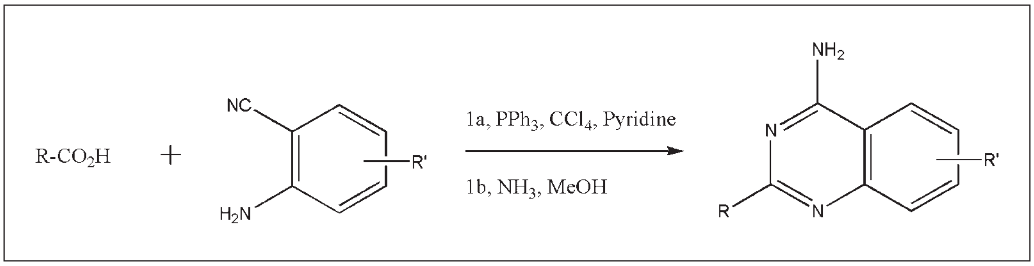

To enhance the iron-chelating ability of P-3A, 4-aminoquinazolines were designed as conformation-restricted bleomycin analogs. An efficient method was developed to prepare the 4-aminoquinazoline heterocyclic nucleus, which entails a two-step one-pot procedure leading to 4-aminoquinazolines in good yields. The application of this method to synthesis 4-aminoquinazoline bleomycin analogs is envisioned.

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INTRODUCTION

Bleomycins are a family of glycopeptide natural products and have been used clinically to treat various cancers for decades. However, dose-dependent undesired side effects, such as pulmonary toxicity are limiting the therapeutic efficacy of bleomycins. Thus, it has been suggested that improved bleomycin analogs may have enhanced therapeutic index between anticancer activity and undesired toxicity [1]. The seminal studies by Hecht [2–4], and Boger [5] groups not only established synthetic methodologies to access bleomycin analogs but also contributed to the understanding of mechanism of action for this important class of compounds.

Bleomycins exert their antitumor activities through sequence-specific cleavages of DNA, which requires the activation of oxygen *via* the formation of a complex consisting of the metal-binding domain of bleomycins, a transition metal such as Fe(II) or Cu(I) and molecular oxygen [6]. In medicinal chemistry, conformational restriction is commonly used to improve potency [7]. We envision that the application of such a strategy to the metal-binding domain of bleomycin could lead to analogs that promote more efficient formation of the oxygen-Fe(II)-bleomycin complex. To test this concept, P-3A, the smallest member of the bleomycin family but still retaining DNA cleavage properties was selected (Figure 1). The four atoms of **P-3A** responsible for metal-coordination are highlighted in bold (Figure 1), and it is evident that the —NH— of the amide group participates in the metal binding, but the carbonyl group does not. Therefore, the cyclization of the carbonyl group onto the 6-position of the pyrimidine nucleus *via* a benzene ring, leading to compounds **1**. The quinazoline ring system in compounds **1** should fix the —NH— group in a position that has higher propensity for metal binding compared with the relatively flexible amide group in **P-3A** and other bleomycins.

Syntheses of quinazolines are widely reported as a result of efforts towards natural product total synthesis and medicinal chemistry programs [8]. For example, the quinazoline scaffold is common to numerous kinase inhibitors including Iressa [9]. 4-Aminoquinazolines were prepared from 2-aminobenzonitrile with either a nitrile [10] or an orthoester [11] under microwave conditions. Recently, 2-aminonitrile was cyclized with formic acid at the elevated temperature of 200°C leading to 5,6-dihydro-quinazolines [12]; 2-aminobenzamide was cyclized with anilines and orthoesters to give 4-arylaminoquinazolines [13]. We envisioned that 2-aminobenzonitrile (**2**) also could react with a carboxylic acid in an one-pot two-step procedure to produce the key intermediate (**4**) required for our conformation-restricted P-3A analogs (Scheme 1).

RESULTS AND DISCUSSION

Imidoyl chlorides were readily prepared from carboxylic acids and amines under the mild conditions of PPh_3-CCl_4 [14], and this method has been applied to the synthesis of various heterocycles [15]. Our strategy is to generate the imidoyl chloride **3** *in situ* and then

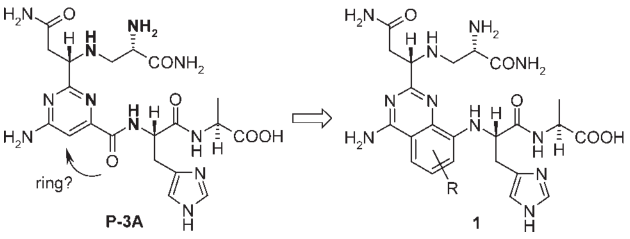
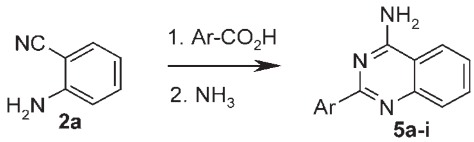


Figure 1. Design of conformationally restricted P-3A analogs.

Table 1

Cyclization of 2-aminobenzonitrile and Ar-CO_2H.[a]



Entry	Ar	T_1/T_2[b]	Pdt	Yield (%)
1	Ph-	8h/6h	**5a**	75
2	4-Me-Ph-	8h/6h	**5b**	74
3	4-F-Ph-	8h/6h	**5c**	81
4	4-NO_2-Ph-	8h/6h	**5d**	60
5	4-Br-Ph-	8h/6h	**5e**	72
6	4-MeO-Ph-	48h/6h	**5f**	30
7	3-pyridyl	12h/6h	**5g**	58
8	Quinoline-2-yl	12h/6h	**5h**	40
9	Furan-2-yl	8h/6h	**5i**	46

[a] Reaction conditions: 3.3 equiv Ph_3P, 3.3 equiv pyridine, 24 equiv CCl_4/CH_3CN, reflux, then NH_3-MeOH, 100°C.

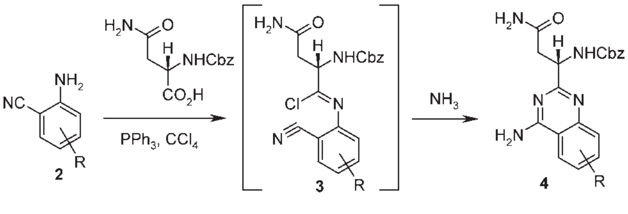
[b] T_1 and T_2, reaction times for step 1 and 2, respectively.

substitute it with ammonia; the resulting amidine should readily be cyclized onto the neighboring nitrile group leading to the desired 4-aminoquinazolines (**4**). To test this one-pot procedure, 2-aminobenzonitrile **2a** was reacted with various aromatic carboxylic acids, and the results are summarized in Table 1.

Most benzoic acid studies gave the desired quinazolines in good-to-high yields (entries 1–5, Table 1). However, para-methoxybenzoic gave lower yield compared to other benzoic acids (entry 6, Table 1), and it is possible that the strong electron-donating property of the MeO group reduces the reactivity of the benzoic acid. Heterocyclic aromatic acids were also suitable substrates for this reaction leading to desired quinazolines in moderate yields (entries 7–9). Encouraged by the success with aromatic acids, aliphatic acids including *N*-Cbz-L-asparagine (*N*-Cbz-Asn) required for the synthesis of bleomycin analogs were studied and the results are summarized in Table 2.

As evident from Table 2, aliphatic carboxylic acids are also suitable for this one-pot two-step reaction leading to 4-aminoquinazolines in good yields (entries 1–4, Table 2). To compare this new one-pot procedure against the conventional stepwise approach, phenylacetic acid was coupled with 2-aminobenzonitrile *via* its acyl chloride to give 2-*N*-(phenylacetyl) aminobenzonitrile in 72% yield; the resulting amide was subjected to the new one-pot two-step procedure and give compound **6d** in 54% yield (entry 5, Table 2). This indicates that preformation of the amide bond did not lead to higher yield of the desired 4-aminoquinazoline. More importantly, *N*-Cbz-Asn reacted with 2-aminobenzonitrile to give 4-aminoquinazoline **6f** in good yield (entry 7, Table 2), suggesting that our planned syntheses of conformation-restricted bleomycin analogs **1** are likely feasible. To gain confidence of our planned synthesis of bleomycin analog **1**, substituted 2-aminobenzonitriles were studied to expand the scope of this new one-pot procedure (Table 3).

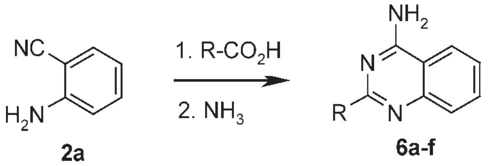
Scheme 1. Synthesis of 4-aminoquinazolines (**4**) from carboxylic acids.



2-Aminobenzonitriles with halo groups reacted with either *N*-Cbz-L-asparagine or phenylacetic acid to give the desired products **7a–d** in moderate yields (entries 1–

Table 2

Cyclization of 2-aminobenzonitrile and R-CO_2H.[a]



Entry	R	T_1/T_2[b]	Pdt	Yield (%)
1	Me-	12 h/6 h	**6a**	73
2	*i*-Pr	12 h/6 h	**6b**	58
3	Cyclohexyl	12 h/6 h	**6c**	81
4	Ph-CH_2-	12 h/6 h	**6d**	62
5	Ph-CH_2-	12 h/6 h	**6d**	54[c]
6	Ph-CH(OH)-	14 h/6 h	**6e**	54
7	Asn[d]	16 h/6 h[e]	**6f**	69
8	Gly[f]	14 h/6 h[e]	**6g**	40

[a] Reaction conditions: 3.3 equiv Ph_3P, 3.3 equiv pyridine, 24 equiv CCl_4/CH_3CN, reflux, then NH_3-MeOH, 100°C.

[b] T_1 and T_2, reaction times for step 1 and step 2, respectively.

[c] A stepwise procedure was used (see text).

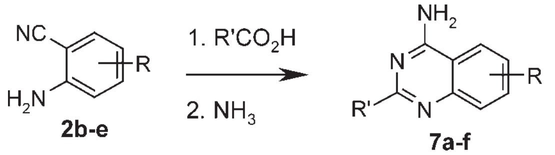
[d] Asn, *N*-Cbz-L-asparagine.

[e] Reaction temperature 50°C.

[f] Gly, *N*-Cbz-glycine.

Table 3

Cyclization of substituted 2-aminobenzonitriles.[a]



Entry	R	R′	T_1/T_2[b]	Pdt	Yield (%)
1	5-Cl (**2b**)	Asn[c]	16 h/6 h[d]	**7a**	32
2	5-Cl (**2b**)	Bn	12 h/6 h	**7b**	35
3	4-Cl (**2c**)	Asn[c]	16 h/6 h[d]	**7c**	29
4	4-Cl (**2c**)	Bn	12 h/6 h	**7d**	32

[a] Reaction conditions: 3.3 equiv Ph_3P, 3.3 equiv pyridine, 24 equiv CCl_4/CH_3CN, reflux, then NH_3-MeOH, 100°C.

[b] T_1 and T_2, reaction times for step 1 and step 2, respectively.

[c] Asn, *N*-Cbz-L-asparagine.

[d] Reaction temperature 50°C.

4, Table 3). The electron-withdrawing effects of the halo groups likely decreased the nucleophilicity of the aniline group, which may account for the observed lower yields compared to reactions with compound **2a**.

In summary, a series of 4-aminoquinazolines were designed as conformationally restricted bleomycin analogs, which may have improved metal-binding efficiency. A new one-pot two-step procedure was developed to prepare 4-aminoquinazolines from carboxylic acids and 2-aminobenzonitriles. Various carboxylic acids, including aromatic, aliphatic, and amino acids, are suitable substrates for this new method. Given there are numerous carboxylic acids available, this method should complement existing methods to access broad range of quinazolines. The application of this new method to 4-aminoquinazoline bleomycin analogs are in progress and will be reported in due course.

EXPERIMENTAL

Melting points are uncorrected. Mass spectra and HPLC (ELSD) data were recorded on an 1100 LC/MS system (Agilent Technology) with Alltech ELSD 2000, using a 4.6 × 50 mm Column (CenturySIL C-18 AQ$^+$, 5 μm) with a linear gradient 30–90% (v/v) acetonitrile–water with 0.035% trifluoroacetic acid over 5 min with a flow rate of 3.5 mL/min. Analytical TLC was performed using 2 × 5 cm plates coated with a 0.25-mm thickness of silica gel 60 F_{254}. Column chromatography was performed using silica gel G (200–300 mesh). All ^1H NMR spectra (300 MHz) and ^{13}C NMR spectra (75 MHz) were measured on a Varian 300 MHz spectrometer using TMS as an internal standard and $CDCl_3$ or DMSO-d_6 as solvent. The ammonia methanol solution was prepared by the saturation of anhydrous methanol with ammonia gas at 0°C.

General procedure for the one-pot two-step synthesis of compounds 5a. A solution of benzoic acid (1.0 mmol, 122 mg), 2-aminobenzonitrile **2a** (1.1 mmol, 130 mg), and pyridine (3.3 mmol, 260 mg, and 0.26 mL) in 4 mL CCl_4 and 6 mL acetonitrile was stirred at room temperature for 10 min, and triphenylphosphine (3.3 mmol, 866 mg) was added. The mixture was refluxed at 80°C for 8 h and then the mixture and a 10 mL ammonia methanol solution (2 *M*) were added into a sealed steel reactor. The reactor was heated at 100°C for 6 h and then concentrated. The residue was purified by column chromatography (hexanes/EtOAc, 6/1) affording 2-phenyl-4-aminoquinazoline **5a** (166 mg, 75%) as a white solid. white solid, mp 144–145°C; 1H NMR (300 MHz, DMSO-d6) δ = 8.48–8.44 (m, 2H), 8.25 (d, J = 7.8 Hz, 1H), 7.84 (br., 2H), 7.81–7.76 (m, 2H), 7.51–7.44 (m, 4H). 13C NMR (75 MHz, DMSO-d_6): δ = 161.7, 159.3, 149.9, 138.1, 132.5, 129.4, 127.7, 127.4, 127.2, 124.6, 123.1, and 112.8. ES-MS: *m*/*z* 222 [M+H$^+$].

4-Amino-2-phenylquinazoline (5a). White solid, mp 144–145°C; ^1H NMR (300 MHz, DMSO-d_6): δ = 8.48–8.44 (m, 2H), 8.25 (d, *J* = 7.8 Hz, 1H), 7.84 (br., 2H), 7.81–7.76 (m, 2H), 7.51–7.44 (m, 4H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 161.7, 159.3, 149.9, 138.1, 132.5, 129.4, 127.7, 127.4, 127.2, 124.6, 123.1, and 112.8. ES-MS: *m*/*z* 222 [M + H$^+$].

4-Amino-2-(*p*-tolyl)quinazoline (5b). White solid, mp 139–140°C; ^1H NMR (300 MHz, DMSO-d_6): δ = 8.36 (d, *J* = 6.6 Hz, 2H), 8.23 (d, *J* = 8.1 Hz, 1H), 7.79–7.74 (m, 4H), 7.47–7.43 (m, 1H), 7.29 (d, *J* = 7.2 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 161.6, 159.3, 150.0, 139.0, 135.4, 132.4, 128.3, 127.4, 127.1, 124.4, 123.1, 112.8, and 20.5. ES-MS: *m*/*z* 236 [M + H$^+$].

4-Amino-2-(4-fluorophenyl)quinazoline (5c). White solid, mp 156–158°C; ^1H NMR (300 MHz, DMSO-d_6): δ = 8.52–8.47 (m, 2H), 8.24 (d, *J* = 8.1 Hz, 1H), 7.86 (br., 2H), 7.81–7.73 (m, 2H), 7.47 (t, *J* = 6.9 Hz, 1H), 7.31 (t, *J* = 8.7 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 163.5 (d, *J* = 245.2 Hz), 162.2, 158.9, 150.3, 135.1, 133.0, and 130.1 (d, *J* = 8.6 Hz), 127.6, 125.1, 123.6, and 115.0 (d, *J* = 21.1 Hz), 113.2. ES-MS: *m*/*z* 240 [M + H$^+$].

4-Amino-2-(4-nitrophenyl)quinazoline (5d). Yellow solid, mp 218–220°C; ^1H NMR (300 MHz, DMSO-d_6): δ = 8.68 (d, *J* = 9.3 Hz, 2H), 8.38 (d, *J* = 8.7 Hz, 2H), 8.29 (d, *J* = 7.8 Hz, 1H), 8.03 (br, 2H), 7.83–7.82 (m, 2H), 7.57–7.52 (m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 162.3, 157.8, 150.1, 148.3, 144.7, 133.3, 128.8, 127.9, 126.1, 123.7, 123.5, and 113.4. ES-MS: *m*/*z* 267 [M + H$^+$].

4-Amino-2-(4-bromophenyl)quinazoline (5e). White solid, mp 167–168°C; ^1H NMR (300 MHz, DMSO-d_6): δ = 8.38 (d, *J* = 7.5 Hz, 2H), 8.24 (d, *J*=8.1 Hz, 1H), 7.89 (br., 2H), 7.81–7.68 (m, 4H), 7.51–7.46 (m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 162.2, 158.8, 150.3, 137.8, 133.0, 131.2, 129.8, 127.7, 125.3, 123.7, 123.6, and 113.3. ES-MS: *m*/*z* 300, 302 [M + H$^+$].

4-Amino-2-(4-methoxyphenyl)quinazoline (5f). White solid, mp 177–179°C; ^1H NMR (300 MHz, DMSO-d_6): δ = 8.41 (d, *J* = 8.7 Hz, 2H), 8.21 (d, *J* = 8.1 Hz, 1H), 7.77–7.70 (m, 4H), 7.45–7.40 (m, 1H), 7.04 (d, *J* = 9.0 Hz, 2H), 3.84 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 162.0, 161.0, 159.7, 150.6, 132.9, 131.2, 129.5, 127.5, 124.7, 123.6, 113.5, 113.1, and 55.2. ES-MS: *m*/*z* 252 [M + H$^+$].

4-Amino-2-(pyridin-3-yl)quinazoline (5g). White solid, mp 226–227°C; ^1H NMR (300 MHz, DMSO-d_6): δ = 9.56 (s, 1H), 8.71–8.66 (m, 2H), 8.27 (d, *J* = 8.1 Hz, 1H), 7.96 (br., 2H), 7.84–7.77 (m, 2H), 7.55–7.48 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 162.2, 158.2, 150.6, 150.2, 149.2, 135.0, 133.8, 133.1, 127.7, 125.6, 123.7, 123.4, and 113.4. ES-MS: *m*/*z* 223 [M + H$^+$].

4-Amino-2-(quinolin-2-yl)quinazoline (5h). White solid, mp 261–262°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.59 (d, *J* = 9.0 Hz, 1H), 8.49 (d, *J* = 8.1 Hz, 1H), 8.31 (d, *J* = 8.1 Hz, 1H), 8.16 (d, *J* = 9.0 Hz, 1H), 8.07 (br. 2H), 8.04 (s, 1H), 7.90–7.80 (m, 3H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.56 (t, *J* = 7.2 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 162.6, 160.0, 156.2, 150.2, 147.4, 136.3, 133.1, 129.7, 129.5, 128.0, 127.9, 127.8, 127.1, 126.0, 123.6, 121.1, and 113.6. ES-MS: *m*/*z* 273 [M + H$^+$].

4-Amino-2-(furan-2-yl)quinazoline (5i). White solid, mp 221°C (decomp.); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.21 (d, *J* = 8.1 Hz, 1H), 7.86–7.68 (m, 5H), 7.47–7.42 (m, 1H), 7.18 (d, *J* = 2.7 Hz, 1H), 6.65 (t, *J* = 1.5 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ= 162.1, 153.7, 153.1, 150.2, 144.7, 133.2, 127.4, 125.1, 123.7, 113.4, 112.2, and 112.1. ES-MS: *m*/*z* 212 [M + H$^+$].

4-Amino-2-methylquinazoline (6a). White solid, mp 226°C (decomp.); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.47 (br., 2H), 8.27 (d, *J* = 8.7 Hz, 1H), 7.83 (t, *J* = 7.5 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 1.76 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 171.7, 162.8, 162.4, 134.1, 125.8, 124.2, 123.4, 111.9, and 24.2. ES-MS: *m*/*z* 160 [M + H$^+$].

4-Amino-2-isopropylquinazoline (6b). White solid, mp 117–119°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.17 (d, *J* = 8.1 Hz, 1H), 7.74–7.68 (m, 3H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.43–7.38 (m ,1H), 2.95–2.90 (m, 1H), 1.26 (d, *J* = 8.7 Hz, 6H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 170.8, 162.0, 150.1, 132.6, 127.0, 124.5, 123.4, 113.0, 37.1, and 21.7. ES-MS: *m*/*z* 188 [M + H$^+$].

4-Amino-2-cyclohexylquinazoline (6c). White solid, mp 210–213°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.16 (d, *J* = 8.7 Hz, 1H), 7.72–7.55 (m, 4H), 3.39 (t, *J* = 7.8 Hz, 1H), 2.64–2.56 (m, 1H), 1.92–1.55 (m, 7H), 1.41–1.21 (m, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 170.0, 162.0, 150.3, 132.4, 127.1, 124.4, 123.4, 113.0, 47.1, 31.4, and 25.9. ES-MS: *m*/*z* 228 [M + H$^+$].

4-Amino-2-benzylquinazoline (6d). White solid, mp 240–242°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.16 (d, *J* = 8.7 Hz, 1H), 7.75–7.69 (m, 3H), 7.65–7.62 (m, 1H), 7.44–7.39 (m, 1H), 7.34–7.24 (m, 4H), 7.20–7.15 (m, 1H), 3.99 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 165.4, 162.1, 150.1, 139.3, 132.7, 128.9, 128.1, 127.0, 125.9, 124.7, 123.4, 112.7, and 45.6. ES-MS: *m*/*z* 236 [M + H$^+$].

4-Amino-2-(hydroxy(phenyl)methyl)quinazoline (6e). Yellow oil; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.89 (d, *J* = 8.1 Hz, 1H), 7.79 (td, *J* = 1.5, 6.6 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.54–7.44 (m, 4H), 7.36–7.28 (m, 2H), 5.68 (br., 2H), 5.42 (br., 1H). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 165.3, 161.8, 148.9, 142.7, 133.4, 128.4, 127.9, 127.8, 127.7, 126.0, 121.8, 113.3, and 75.1. ES-MS: *m*/*z* 252 [M + H$^+$].

Benzyl 3-amino-1-(4-aminoquinazolin-2-yl)-3-oxopropylcarbamate (6f). White solid, mp 244–246°C; $[\alpha]_D^{15}$= −77.2 (*c* = 1, MeOH:TFA = 10:1); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.18 (d, *J* = 8.1 Hz, 1H), 7.73 (t, *J* = 6.9 Hz, 3H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.45–7.43 (m, 2H), 7.26 (s, 5H), 7.05 (s, 1H), 5.04–4.93 (m, 2H), 4.63–4.62 (m, 1H), 3.16–3.09 (m, 1H), 2.98–2.90 (m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 170.0, 161.9, 150.2, 132.4, 131.5, 128.8, 128.6, 127.1, 124.3, 123.4, 113.0, 47.0, 31.4, and 25.9. ES-MS: *m*/*z* 366 [M + H$^+$].

Benzyl (4-aminoquinazolin-2-yl)methylcarbamate (6g). White solid, mp 209°C (decomp.); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.19 (d, *J* = 8.4 Hz, 1H), 7.77–7.72 (m, 3H), 7.63 (d, *J* = 8.1 Hz, 1H), 7.50–7.35 (m, 6H), 5.07 (s, 2H), 4.22 (d, *J* = 6.0 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 163.1, 162.0, 156.3, 149.8, 137.3, 132.8, 128.3, 127.7, 127.6, 127.0, 124.9, 123.6, 113.3, 65.2, and 46.5. ES-MS: *m*/*z* 309 [M + H$^+$].

Benzyl 3-amino-1-(4-amino-6-chloroquinazolin-2-yl)-3-oxopropylcarbamate (7a). Yellow solid, mp 252–254°C; $[\alpha]_D^{15}$= −92.2 (*c* = 1, MeOH:TFA = 10:1); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.34 (d, *J* = 2.4 Hz, 1H), 7.82 (br., 2H), 7.74 (dd, *J* = 2.1 Hz, 8.7 Hz, 1H), 7.60 (d, *J* = 9.0 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.27 (s, 5H), 7.24 (s, 1H), 7.03 (br, 1H), 5.03–4.96 (t, 2H), 4.62–4.60 (t, 1H), 3.32–3.09 (t, 1H), 3.97–3.92 (t, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 173.4, 164.2, 161.0, 155.7, 148.6, 137.0, 133.0, 129.2, 128.7, 128.2, 127.6, 127.4, 122.7, 113.7, 65.2, 53.4, and 40.9; ES-MS: *m*/*z* 400 [M + H$^+$].

4-amino-6-chloro-2-benzylquinazoline (7b). White solid, mp 239–242°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.36 (d, *J* = 2.1 Hz, 1H), 8.19 (d, *J* = 2.4 Hz, 1H), 8.03 (br., 2H), 7.35–7.25 (m, 5H), 7.21–7.18 (m, 1H), 4.02 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 166.9, 161.7, 146.6, 138.7, 135.7, 128.9, 128.6, 128.2, 126.1, 123.6, 122.6, 114.2, and 45.6. ES-MS: *m*/*z* 270 [M + H$^+$].

Benzyl 3-amino-1-(4-amino-7-chloroquinazolin-2-yl)-3-oxopropylcarbamate (7c). Yellow solid, mp 259–261°C; $[\alpha]_D^{15}$= −57.6 (*c* = 1, MeOH:TFA = 10:1); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.22 (d, *J* = 8.7 Hz, 1H), 7.88 (br., 2H), 7.62 (d, *J* = 1.8 Hz, 1H), 7.48 (dd, *J* = 1.8 Hz, 8.7 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.27 (s, 6H), 7.05 (s, 1H), 5.05–4.93 (m, 2H), 4.65–4.60 (m, 1H), 3.16–3.09 (m, 1H), 2.97–2.90 (m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 173.5, 165.7, 165.0, 161.6, 155.7, 150.9, 137.3, 128.2, 127.6, 127.4, 125.7, 125.1, 111.5, 65.2, 53.6, and 40.9.; ES-MS: *m*/*z* 400 [M + H$^+$].

4-Amino-7-chloro-2-benzylquinazoline (7d). White solid, mp 210–212°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.20 (d, *J* = 8.7 Hz, 1H), 7.90 (br., 2H), 7.68 (d, *J* = 2.1 Hz, 1H), 7.49–7.46 (m, 1H), 7.36–7.16 (m, 5H), 3.98 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 166.9, 162.0, 151.3, 139.0, 137.4, 128.9, 128.2, 127.7, 126.1, 125.7, 125.2, 111.4, and 45.5. ES-MS: *m*/*z* 270 [M + H$^+$].

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Three-Component One-Pot Synthesis of Pyrimidinone Derivatives in Fluorous Media: Ytterbium Bis(perfluorooctanesulfonyl)imide Complex Catalyzed Biginelli-Type Reaction

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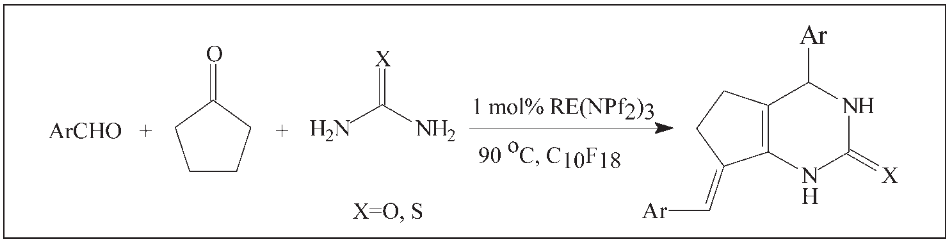

The condensation of aromatic aldehyde, cyclopentanone, and urea or thiourea in the presence of Ytterbium bis(perfluorooctanesulfonyl)imide complex in perfluorodecalin was used to synthesize a variety of benzylidene heterobicyclic pyrimidinones in excellent yields.

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INTRODUCTION

Multicomponent reactions (MCRs) are powerful tools in modern medicinal chemistry, enabling straightforward access to large libraries of structurally related, drug-like compounds and thereby facilitating the generation of precursor candidates compounds. Hence, combined with the use of combinatorial chemistry and high throughput parallel synthesis, such reactions have constituted an increasingly valuable approach to drug discovery efforts in recent years [1,2].

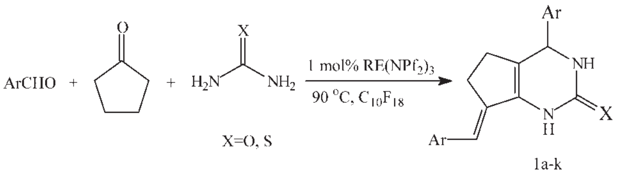
Over the past decade, pyrimidinone derivatives have attracted strong interest because of their useful biological activities, pharmaceutical, and therapeutic properties, such as antiviral, antitumor, antibacterial, and anti-inflammatory activities [3–6]. Classical Biginelli reactions involve one-pot condensations of an aldehyde, α,β-ketoester, and urea under strongly acidic conditions. In recent decades, the Biginelli reaction was extended the scope [7]. Especially, some fused pyrimidinones carrying an arylidene moiety exit not only the broad-spectrum antitumor activity but also a distinctive pattern of selectivity toward individual cell line such as that of leukemia. Thus, synthesis of these heterocycles is of much current importance for both organic synthesis and medicinal chemistry. Conventional methods for synthesis of this type of pyrimidinones involve condensation of α, α′-bis(substituted benzylidene)cycloalkanones with urea or thiourea using strong Bronsted acid [8] or base [9] as catalysts. Recently Pan and coworkers [7b] and Xu and coworkers [10] described efficiently alternative synthesis of these fused pyrimidinones by a three-component condensation with aromatic aldehyde, cyclopentanone, and urea or thiourea as starting materials. Each of the aforementioned methods has its own merits, while some of these methods are plagued with the limitation of poor yields, difficult workup, effluent pollution, and unrecyclability of catalysts.

Metal complexes with bis(perfluorooctanesulfonyl)-imide ligands are active and recyclable catalysts in the fluorous immobilized phase for Baeyer-Villiger oxidation [11], Diels-Alder reaction [12], esterification [13], and Friedel-Crafts acylation [14]. A key factor to accomplish the catalytic processes was ascribed to the use of long-enough perfluorinated—N(SO$_2$C$_8$F$_{17}$)$_2$, whose structural characteristic can coordinate with a variety of metal cations to obtain the desired Lewis acid catalysts with appropriate catalytic activity, and the selective immobilization in the fluorous. Herein, this letter attempts to describe the catalytic activity of rare earth (III) bis-(perfluorooctanesulfonyl)imide complexes RE[N(SO$_2$—C$_8$F$_{17}$)$_2$]$_3$, (RE(NPf$_2$)$_3$) in the one-pot synthesis of pyri-midinone from aromatic aldehyde, cyclopentanone, and urea or thiourea (Scheme 1), the so-called Biginelli-type three-component reaction.

RESULTS AND DISCUSSION

At first, we began to study the catalytic activities of a series of rare earth bis(perfluorooctanesulfonyl)imide complexes to optimize the reaction condition of benzaldehyde, cyclopentanone, and urea (Scheme 2), which was chosen as a model reaction. The results are

Scheme 1



summarized in Table 1. It was obviously that rare earth bis(perfluorooctanesulfonyl)imide complexes catalyzed the Bigineli-type reaction efficiently and $Yb(NPf_2)_3$ showed the best catalytic activity among these complexes.

By using $Yb(NPf_2)_3$ as catalyst, we examined the effect of the amount of the catalyst on the model reaction mentioned earlier. When the amount of $Yb(NPf_2)_3$ was increased from 0.4 to 1.2 mol%, the yield was increased until to a maximum and then gradually decreased, and the highest yield was obtained at 1 mol% catalyst loading (Table 2, Entries 1–5).

Based on the earlier optimized results, with 1 mol% $Yb(NPf_2)_3$ as catalyst, we also investigated the effect of the reaction temperature ranging from 80 to 100°C, and the best results were obtained at 90°C (Table 2, Entries 4, 6 and 7). Meanwhile, further studies showed that the molar ratio of benzaldehyde, cyclopentanone, and urea at 1:1:1.2 was preferred.

Under the optimized conditions, the reactions of different aldehydes with cyclopentanone and urea or thiourea were examined. As listed in Table 3, aromatic aldehydes carrying different functional groups, such as methyl, methoxy, chloro, bromo, and nitro, were subjected to the reactions, and in all cases, the desired products were obtained in high yields (81–93%). All reactions were clean and free from any by-products. It is important to note that aldehydes with electron-withdrawing group were more reactive, and the reactions with cyclopentanone and urea were faster. The reason may be that the carbonyl carbon in aldehydes containing electron-withdrawing group are more electrophilic. Thiourea exhibited behavior similar to that urea.

The possibility of recycling $Yb(NPf_2)_3$ catalyst for the synthesis of 1a was also investigated. When the reaction was finished, the reaction mixture was cooled to room temperature. The fluorous phase containing catalysts was separated from reaction mixture by decantation and reused for the next cycle. The condensations of benzaldehyde, cyclopentanone, and urea under the conditions as mentioned earlier were run for five consecutive cycles, respectively, furnishing the corresponding pyrimidinones with 91%, 89%, 88%, 87%, and 87% isolated yields.

The mechanism for formation of benzylidene heterobicyclic pyrimidinones products is assumed to take place *via* coordination of $Yb(NPf_2)_3$ with an aldehyde, which then activates the attack of keto compound in its enol form and subsequent removal of OH group gives enone. Similar reaction further proceeds on this enone to give bis-benzylidene derivatives. The next are the Michael addition of urea, elimination of water, and cyclization to form pyrimidione.

In conclusion, we report a one-pot synthesis of fused pyrimidinone by $Yb(NPf_2)_3$-catalyzed Biginelli-type reaction of aromatic aldehyde, cyclopentanone, and urea or thiourea in fluorous media. The easy workup procedure, recyclable catalyst, short reaction times, and very good yields are the main advantages of this method.

Scheme 2

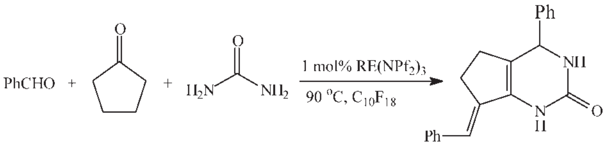


Table 1

$RE(NPf_2)_3$-catalyzed one-pot synthesis of benzylidene heterobicyclic pyrimidinones.[a]

Entry	Catalyst	Yield[b] (%)
1	$Y(NPf_2)_3$	73
2	$La(NPf_2)_3$	64
3	$Ce(NPf_2)_3$	83
4	$Nd(NPf_2)_3$	68
5	$Sm(NPf_2)_3$	71
6	$Eu(NPf_2)_3$	72
7	$Tb(NPf_2)_3$	77
8	$Dy(NPf_2)_3$	79
9	$Er(NPf_2)_3$	85
10	$Yb(NPf_2)_3$	91

[a] Reaction conditions: benzaldehyde (0.212 g, 2 mmol), cyclopentanone (0.168 g, 2 mmol), urea (0.146 g, 2.4 mmol), $C_{10}F_{18}$ (2 mL), $RE(NPf_2)_3$ (0.02 mmol), 90°C, 2.5 h.

[b] Isolated yield.

Table 2

Reaction of benzaldehyde, cyclopentanone, and urea in the presence of $Yb(Npf_2)_3$ under different reaction conditions.[a]

Entry	Amount of $Yb(NPf_2)_3$ (mol%)	Temperature (°C)	Yield[b] (%)
1	0.4	90	42
2	0.6	90	67
3	0.8	90	83
4	1.0	90	91
5	1.2	90	89
6	1.0	80	68
7	1.0	100	85

[a] Reaction conditions: benzaldehyde (0.212 g, 2 mmol), cyclopentanone (0.168 g, 2 mmol), urea (0.146 g, 2.4 mmol), $C_{10}F_{18}$ (2 mL), 2.5 h.

[b] Isolated yield.

Table 3

Synthesis of benzylidene heterobicyclic pyrimidinones in the presence of $Yb(Npf_2)_3$ in $C_{10}F_{18}$.[a]

Entry	Ar	X	Time (h)	Product	Yield[b] (%)
1	Ph	O	2	1a	91
2	4-$CH_3C_6H_4$	O	3	1b	93
3	2-$CH_3C_6H_4$	O	3	1c	81
4	4-$OCH_3C_6H_4$	O	3	1d	85
5	4-ClC_6H_4	O	2	1e	89
6	2-ClC_6H_4	O	2	1f	84
7	4-BrC_6H_4	O	2	1g	83
8	4-$NO_2C_6H_4$	O	2	1h	92
9	Ph	S	6	1i	94
10	4-$CH_3C_6H_4$	S	6	1j	86
11	4-ClC_6H_4	S	5	1k	92

[a] Reaction conditions: aldehyde (2 mmol), cyclopentanone (2 mmol), thiourea or urea (2.4 mmol), $C_{10}F_{18}$(2 mL), 90°C.

[b] Isolated yield.

EXPERIMENTAL

Chemicals used were obtained from commercial suppliers and used without further purifications. ^1H NMR, ^{13}C, and ^{19}F NMR spectra were recorded with a Bruker Advance RX500 spectrometer. Mass spectra were recorded on a Saturn 2000GC/MS instrument. Inductively coupled plasma (ICP) spectra were measured on an Ultima2C apparatus. Elemental analyses were performed on a Yanagimoto MT3CHN recorder.

Typical procedure for preparation of $(C_8F_{17}SO_2)_2NH$. $(C_8F_{17}SO_2)_2NH$ was prepared according to the literature [15,16]. Ammonia (300 mmol) was transferred with stirring perfluorooctanesulfonyl fluoride (50 g, 99.6 mmol) at −20°C for about 1 h, it was then continued at room temperature for 1 h. The solid product was acidified with HCl followed by addition of Et_2O. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, dried in vacuum at 80°C for 16 h to give $C_8F_{17}SO_2NH_2$ (87% yield). Then the mixture of perfluorooctanesulfonyl fluoride (45.4 g, 91 mmol), perfluorooctanesulfonamide (43.4 g, 87 mmol), and Et_3N (76 mL) was heated at reflux for 23 h. The lower brown fluorous layer was washed with 10% HCl and dried in vacuum at 70°C for 6 h to afford $(C_8F_{17}SO_2)_2N\ HNEt_3$. Finally, through acidic ion exchange resin column, $(C_8F_{17}SO_2)_2N\ HNEt_3$ changed to afford $(C_8F_{17}SO_2)_2NH$ in 50% yield. Anal. Calcd. for $(C_8F_{17}SO_2)_2NH$: C,19.57; N: 1.43 H: 0.10. Found: C, 19.61; N: 1.45, H, 0.16. ^{19}F NMR: δ-126.2, -121.8, -114.0, -81.2.

Typical procedure for preparation of $Yb(NPf_2)_3$. Ytterbium bis(perfluorooctanesulfonyl)imide complex, $Yb(NPf_2)_3$ was prepared according to the reported procedure [17]. The mixture of Yb_2O_3 (0.118 g, 0.3 mmol) and bis (perfluorooctanesulfonyl)imide (0.883 g, 0.9 mmol) in H_2O (10 mL) at 110°C for 1 h. The resulting mixture was filtered through a membrane filter. The remaining water was removed under reduced pressure at 80°C for 16 h. The Ytterbium bis (perfluorooctanesulfonyl)imide complex was obtained in 98% yield. ICP: Calcd for $C_{48}O_{12}N_3F_{102}S_6Yb$: Yb, 5.56. Found: 5.60 Anal. Calcd. For $Yb[N(SO_2C_8F_{17})_2]_3$: C, 18.50; N, 1.35. Found: C: 18.45; N, 1.41. ^{19}F NMR: δ −126.1, −121.2, −114.2, −81.4.

Typical procedure for the preparation of 7-benzylidene-4-phenyl-3,4,6,7-tetrahydro-1*H*- cyclopenta[d] pyrimidin-2(5H)-one. A mixture of benzaldehyde (0.212 g, 2 mmol), cyclopentanone (0.168 g, 2 mmol), urea (0.146 g, 2.4 mmol), and $Yb(NPf_2)_3$ (0.062 g, 0.02mmol) in perfluo-rodecalin ($C_{10}F_{18}$, cis and trans-mixture, 2mL) was well stirred at 90°C for appropriate time. After the reaction was completed, the system was cooled to room temperature. Then, the perfluorodecalin on the bottom was separated for the next cycle. Water was added to the reaction mixture, and the pure product was obtained by filtration followed by washing with acetone, ethyl acetate, and alcohol. Selected data: 7-benzylidene-4-phenyl-3,4,6,7-tetrahydro-1*H*-cyclopenta[d]pyrimidin-2(5*H*)-one, pale yellow solid; mp 236–239°C; ^1H NMR (500 MHz, DMSO): δ = 1.97–2.01 (m, 1H), 2.49 (m, 1H), 2.71–2.82 (m, 2H), 5.15 (s, 1H), 6.63 (s, 1H), 7.21–7.38 (m, 11H), 8.78 (s, 1H). ^{13}C NMR: δ = 29.5, 29.8, 58.7, 117.8, 119.6, 127.2, 127.4, 128.6, 129.0, 129.5, 129.6, 137.1, 138.8, 140.3, 144.3, 154.4 ppm. MS (EI) *m/z* 303 $[M+H]^+$.

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