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Note

Reaction and antimicrobial activity of 1-arylethylene benzofuranyl ketone derivatives

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Interaction of benzalvisnaginone or khellinone derivatives with thiourea gives the tetrahydropyrimidin-2-thione derivatives which are condensed with chloroacetic acid in acetic anhydride to form thiazolo[3,2-*a*]pytimidin-3-one. Its behaviour towards benzaldehyde, and aromatic amine is discussed. While the reaction of the benzalvisnaginone derivative with quanidine yields 2-amino-pyrimidine and its reaction with 2,3-dichloro-1,4,- naphthaquinone and 2-aminothiazole chloroacetamide, is investigated. The compounds are tested for their antibacterial activity.

Keywords: Benzalvisnaginone, naphthaquinone, 2-aminothiazole chloroacetamide, antibacterial activity

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The interesting biological activity[1] of pyrimidine derivatives led us to synthesize some pyrimidine derivatives containing benzofuranyl moiety in their structures. Thus, interaction of benzalvisnaginone or khellinone derivatives **1a-e** with thiourea in alcoholic KOH solution gave the tetrahydropyrimidin-2-thiones **2a-e** or the possible isomers. The reaction proceeds *via* Michael addition of the anion derived from thiourea followed by cyclization.

Condensation of **2a,c,d** with chloroacetic acid in acetic anhydride produced derivatives of 7-aryl-5-benzofuranyl-2,3-dihydro-6*H*-thiazolo[3,2-*a*]pyrimidin-3-ones **3a-c** and this was in the agreement with previous work[2].

Compound **3b** was condensed with benzaldehyde to yield 2-(phenylmethylene)-7-phenyl-5-(4,6-dimethyoxybenzofuran-5-yl)2,3-dihydro-6*H*-thiazolo-[3,2-*a*]pyrimidin-3-one **4**, which could also be conveniently prepared through reaction of **2c** with chloroacetic acid and benzaldehyde in acetic anahydride in the presence of sodium acetate. Treatment of **3b** with 2-chloroaniline led to break the thioazolidione ring to afford the corresponding N-(2-chlorophenyl)-6-aryl-4-(4,6-dimethoxybenzofuran-5-yl)-3,4-dihydro-pyrimidine-2-ylthio)acetanilide **5**. It was also obtained through reaction of **2c** with N-(2-chlorphenyl)-2-chloroacetamide (**Scheme I**).

On the other hand, when the arylmethylene benzofuranyl methyl ketones **1a,b,e** were allowed to react with guanidine in alcoholic KOH solution, 2-amino-4-aryl-6-(benzofuran-5-yl)pyrimidines **6a-c** were obtained. The reaction mechanism proceeds *via* Michael reaction followed by cyclization through elimination of H_2O and H_2.

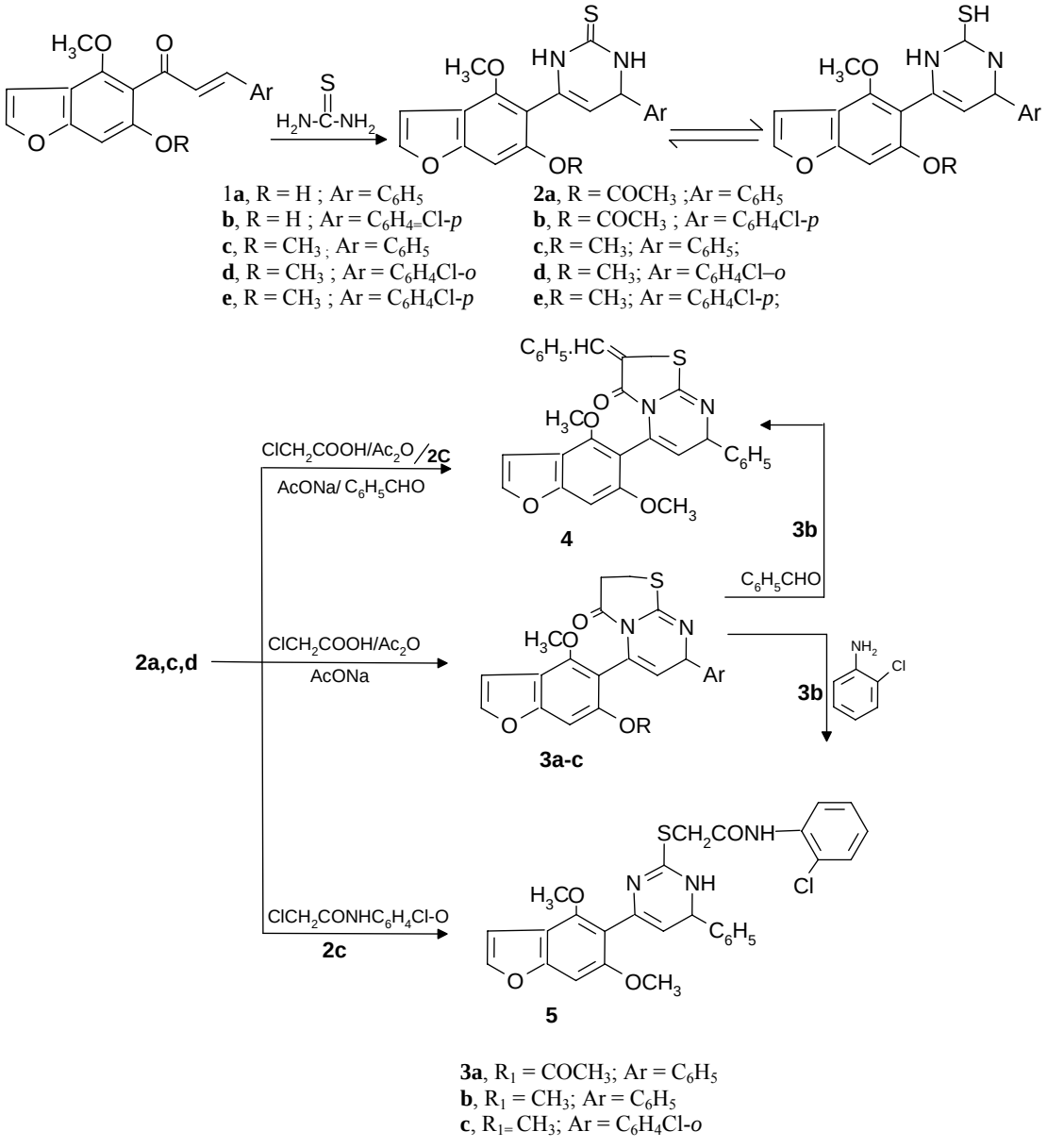
Compound **6** was proved to be a versatile starting material for the synthesis of some novel pyrimidine ring. Thus, condensation of **6b** with 2,3-dichloronaphthaquinone produced 3-(3-chloro-1,4-dioxonaphthyl-amino-4-(chlorophenyl)-6-(4,6-dimethoxybenzofuran-5-yl)pyrimidin-2-imine **7** accompanied by the loss of a molecule of HCl.

Compound **6b** on treatment with 2-aminothiazole chloroacetaimide furnished 3,4,6-trisubstituted pyrimidin-2-imine **8**. The structures of **7** and **8** were elucidated by analytical and spectral data, which were in agreement with the proposed structures (**Scheme II**).

In the present investigation, the Michael condensation of acetylacetone with chalcone had also been investigated. Thus, when chalcone **1d** was allowed to react with acetylacetone in the presence of sodium methoxide; 6-acetyl-5-(2-chlorophenyl)-3-(4,6-dimethoxybenzo-furan-5-yl)-cyclohex 2-enone **9** was formed.

Moreover, the reaction of hydroxychalcones **1a,b** with sulphur in boiling DMF caused cyclization through Michael reaction followed by oxidation to furnish 5-methoxy-2-aryl-furo[3,2-*g*] benzopyran-4-one **10a,b**. This is in accordance with results reported by Yukio *et al.*[3]

On the other hand, when chalcone **1a** was refluxed with 20% H_2SO_4, cyclization occurred to yield 5-methoxy-2-phenyl-2,3-dihydrofuro[3,2-*g*]benzo-pyran-4-one **11** which was oxidized when boiled with sulphur in DMF to form **10a**. Finally, when **1e** was treated with 2-arylidine aminothiophenol, adduct compound **12** was obtained (**Scheme III**).



Scheme I

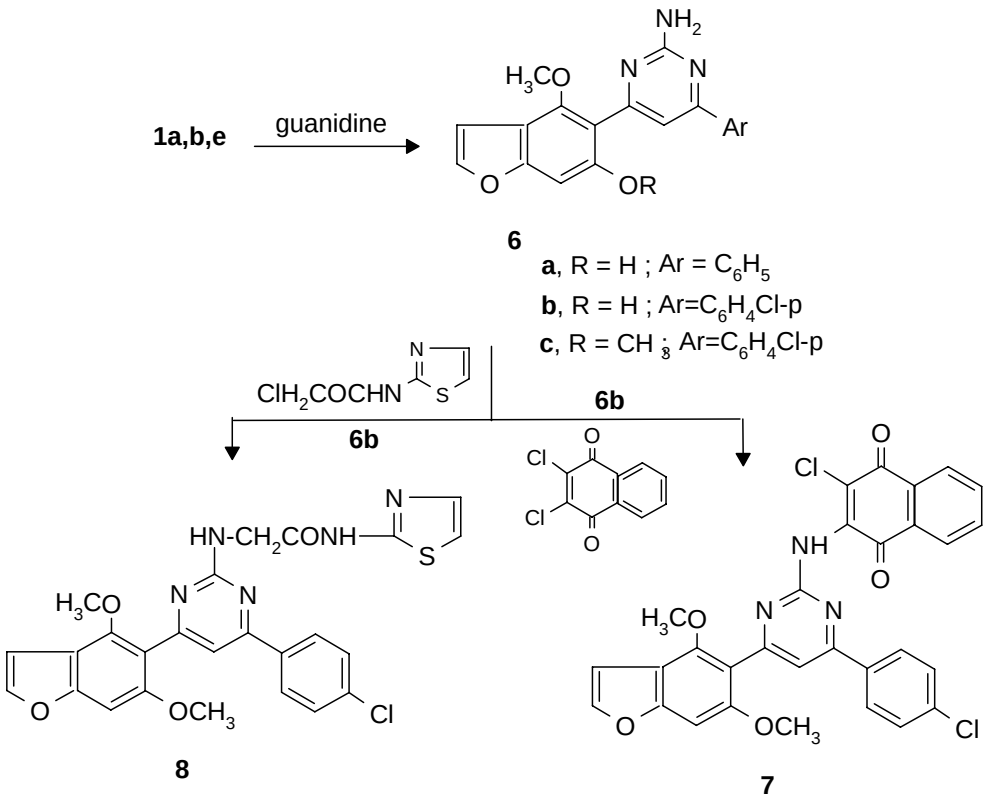
Biological activity

Seven compounds were screened *in vitro* for their antimicrobial activity against two strains of bacteria *Bacillus cerens* (gram positive) and *Escherichia coli* (gram negative) by the agar diffusion technique[4]. A 1 mg mL^{-1} solution in DMF was used. The bacteria was maintained on nutrient agar, DMF showed no inhibition zone. The agar media were inoculated with different microorganisms culture tested. After 24h of incubation at 30°C, the diameter of inhibition zone (mm) was measured. Ampicillin in a concentration 25 μg mL^{-1} was used as a reference. The minimal inhibitory concentration (MIC) of some of the tested compounds was measured by a two fold serial dilution method[5].

It was found that compounds **2a** and **2c** had moderate activity due to presence of pyrimidine-2-thione moiety. While introduction of thiazolo[3,2-*a*]pyrimidine-3-one moiety caused big activity as in case of compounds **3a-c** and **4**.

Experimental Section

Melting points are uncorrected. IR spectra were recorded on a Pye-Unicam SP/1100 spectrophoto-



Scheme II

meter, ^{1}H NMR spectra ($CDCl_3$ or DMSO-d_6) on a Varian 90 (200MHz) spectrometer, and mass spectra on a Varian Mat. CH-4B spectrometer.

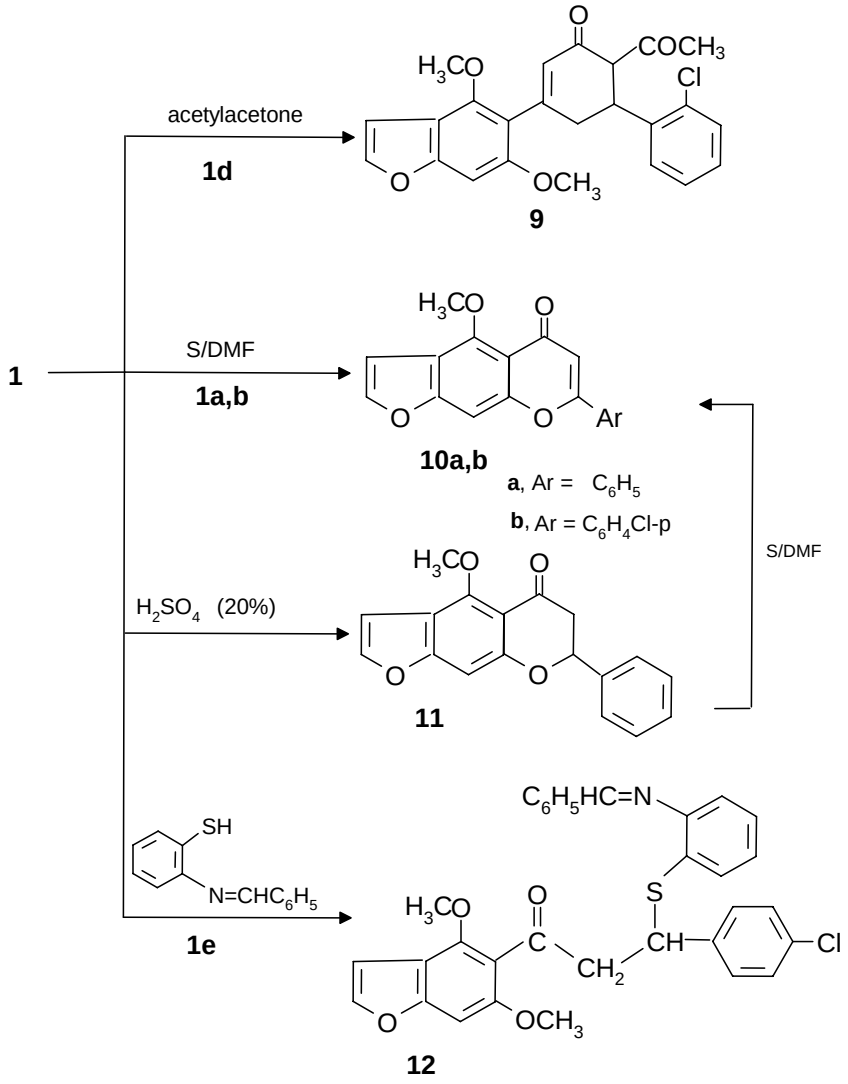
Tetrahydropyrimidine-2-thione derivatives 2a-e.

To a solution of **1a-g** (0.1 mole) in ethanol (30 mL) was added thiourea (0.01 mole) and 0.01 mL of KOH (1g) and the mixture was refluxed for 3h. The solvent was then removed and the resulting solid was recrystallized to obtain the desired product. **2a**: Yield 90%; m.p. 147°C (ethanol); ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.38 (3H,s,OCH_3), 4.92 (1H,d) (J = 7.01 Hz), H_4 pyrimidne moiety), 5.10 (1H,d, J = 7.12Hz, H_5), of pyrimidine moiety), 6.52 (1H, s, H_7 of benzofuran moiety), 6.67 (1H,d, J = 2Hz, H_3 furan), 7.18-7.36 (5H,m, ArH), 7.59 (1H,d (J = 2.01 Hz), H_2 furan), 7.72 (1H, s,NH), 12.5 (1H,sNH). **2b**: Yield 70%; m.p. 153°C (*n*-hexane); IR 3443, 3162, 3126 (HO/NH), 114 cm^{-1} (C=S). **2c**: Yield 80%; m.p. 118°C (*n*-hexane). **2d**: Yield 80%; m.p. 138°C (ethanol). 2e: Yield 72%; m.p. 153°C (ethanol).

7-Aryl-5-(4,6-dimethoxybenzofuran-5-yl)-2,3-dihydro-6*H*[1,3] thiazole [3,2-*a*] pyrimidin-3-one 3a-c.

To a mixture of **2a,c,d** (0.01 mole), chloroacetic acid (0.01 mole) and anhyd. sodium acetate (0.025 mole), a mixture of acetic anhydride and acetic acid (20 mL) was added and then refluxed for 20 h. It was then poured into ice water, with stirring for 10 min. The resulting solid was recrystallized from suitable solvents to obtain the desired product. **3a**: Yield 65%; m.p. 160°C (ethanol); ^{1}H NMR(DMSO-d_6): δ 2.75 (3H, s, $OCOCH_3$), 3.9 (3H,s,OCH_3), 5.15 (2H,s,CH_2), 4.55 and 6.01 [2H,d-d-(1H each) pyrimidine moiety], 6.74 (1H,s,benzofuran), 7.0-7.9 (6H,m, ArH + furan protons). **3b**: Yield (65%); m.p. 146°C (ethanol). **3c**: Yield 66%; m.p. 151°C (ethanol); IR: 1701 (C=O), 1620 cm^{-1} (C=N).

2-(Phenylmethylene)-5-Phenyl-7 (4,6-dimethoxybenzofuran-5-yl)-2,3-dihydro-6*H*-thiazolo [3,2-*a*] pyrimidin-3-one 4. A solution of **3b** (0.01 mole) and benzaldehyde (0.01 mole) in a mixture of AcOH/Ac_2O (20 mL) was refluxed for 2h, then poured into cold water. The resulting solid was recrystallized to obtain the desired product. **4**: Yield 65%; m.p. 160°C (ethanol); ^{1}H NMR ($CDCl_3$): 4.19-4.22 (6H, 2s, $2OCH_3$), 5.41, 6.21 (2H, d-d, pyrimidine moiety), 6.73 (1H,s,HH–7), 6.90 (1H,d, (J = 2Hz, H-3), 6.99 (1H,s,=CH), 7.26-7.47 (11H, m, ArH + H-2).



Scheme III

Compound **4** was also obtained by refluxing a solution of **2c** (0.01 mole), chloroacetic acid (0.01 mole), benzaldehyde and anhyd. sodium acetate (0.025 mole) in a mixture of AcOH-Ac_2O 20 mL for 2h.

N-(2-Chlorophenyl)-6-phenyl-4-(4,6-dimethoxybenzofuran-5-yl)-3,4-dilydro-pyrimidin-2-yl thio] acetamide 5.

A solution of **3b** (0.01 mole) and 2-chloroaniline (0.02 mole) in ethanol (30 mL) was refluxed for 3h. The resulting solid was recrystallized to obtain the desired product. **5**: Yield 70%; m.p. 140°C (ethanol); MS: m/z 532 [M^+, 1%], 411(2%), 308 (3%), 205 (100%).

Compound **5** could also be conveniently prepared by refluxing **2c** (0.01 mole) with N-(-2-chlorophenyl)-2-chloroacetamide (0.01 mole) for 3h.

2-Amino-4-aryl-6-(4,6-dimethoxy benzofuran-5-yl) pyrimidine 6a-c.

A solution of **1a,b,d** (0.01 mole), guanidine (0.01 mole) and KOH (0.01 mole) in ethanol (30 mL) was refluxed for 4h. Then, the solvent was evaporated and the resulting solid was recrystallized to obtain the desired product. **6a**: Yield 70%; m.p. 167°C (ethanol); IR 3388, 3275, 3121cm^{-1} (OH/NH_2). **6b**: Yield 67%; m.p. 142°C (ethanol). **6c**: Yield 72%; m.p. 150°C (ethanol).

2-Amino-3-(3chloro-1,4-dioxonaphthylamino)-4-(4-chlorophenyl)-6-(4,6-dimethoxy-benzofuran-5-yl) pyrimidine 7.

A mixture of **6c**, 2,3-dichloro-1,4-naphthaquinone (0.01 mole) and TEA (0.5 mL) in DMF (20 mL) was

refluxed for 4h. The reaction mixture was cooled and acidified by HCl to obtain the desired product. **7**: Yield 52%; m.p. 131°C (*n*-hexane); MS: m/z 573 [M^+, 1%], 368 (1%), 342 (13%), 205 (100%), 191 (79%), 57 (21%).

3,4,6-Trisubtituted pyrimidin-2-amino 8.

A solution of **6c** (0.01 mole) and 2-aminothiazole chloroacetamide (0.02 mole) in ethanol (30 mL) was refluxed for 3h to obtain the desired product. **8**: Yield 72%; m.p. 142°C (ethanol); MS: m/z 522 [M^+, 1%], 368 (2%), 342 (51), 190 (100%).

6-Acetyl-5-[2-chlorophenyl-3-(4,6-dimethoxy-benzofuran-5-yl]-cyclohex-2-enone 9.

A solution of **1d** (0.01 mole), acetylacetone (0.01 mole) and sodium methoxide (0.01 mole) in methanol (20 mL) was refluxed in a water bath for 3h. The resulting yellow semi-solid was recrystallized to obtain the desired product. **9**: Yield 40%; m.p. 115°C (per-ether 80-110°C); MS: m/z 421 [M^+, 1%], 393 (3%), 381,(1%) 342 (4%), 307 (17%), 146 (100%).°

4-Methoxy-7-arylfuro [3,2-g] benzopyran-5-one 10a,b.

A mixture of **1a**,**b** (0.01 mole) and sulphur powder (0.01 mole) in DMF (20 mL) was refluxed for 3h. The resulting solid was recrystallized to obtain the desired product. **10a**: Yield 40%; m.p. 215°C (ethanol); IR: 1681, 1670 cm^{-1} (C=O); ^{1}H NMR (DMSO-d_6): δ 3.44 (3H,s,OCH_3), 7.23 (1H,s,H–9), 7.29, 8.13 (2H,d-d) (J = 2.01 Hz, furan protons, 7.83 (1H,s,H–3), 7.62-7.93 (5H,m,ArH). **10b**: yield 40%; m.p. 172°C (ethanol).

4-Methoxy-7-phenylfuro[3,2-g] benzopyrolidin-5-one 11.

A solution of **1a** (0.01 mole in ethanol (20 mL) and conc. H_2SO_4 (2mL) was refluxed for 4h. The resulting solid was recrystallized to obtain the desired product. **11**: Yield 70%; m.p. 110°C (*n*-hexane); IR 1629 cm^{-1} (C=O).

When **10a** was reacted with sulphur and DMF compound **11** was obtained.

2-Arylidene aminthiophenol derivatives 12.

A mixture of (0.01 mole) and 2-arylidene aminothiophenol (0.01 mole) in benzene (50 mL) in the presence of piperidine (0.2 mL) was refluxed for 2h. The resulting solid was recrystallized to obtain the desired product. **12**: Yield 60%; m.p. 125°C (*n*-hexane); IR: 1622 (C=O), 760 cm^{-1} (C=S); MS: m/z 590 [M^+,3%], 536 (4%), 488 (7%), 344 (4%), 345 (100%).

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