Microwave assisted synthesis of some novel pyrimidinones/thiones

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A novel series of 1-substituted-4-aryl-5-ethoxycarbonyl-6-methylpyrimidine-2-ones/thiones are prepared in the one pot condensation of appropriate aldehyde, ethylacetoacetate and substituted urea in ethanol medium under microwave irradiation. The new compounds are well characterized by IR, 1H NMR, mass spectra, C,H,N-analysis and in a typical example the structure was further confirmed by X-ray crystallographic data.

Keywords: Microwave synthesis, pyrimidinones, thiones, biological activity

Dihydropyrimidinones are an important class of compounds and gaining increasingly importance due to their therapeutic and pharmacological properties. They have emerged as the integral backbones of several calcium channel blockers, anti-hypertensive agents and alpha-1α-antagonists. Recently several isolated marine alkaloids with interesting biological activities were also found to contain the dihydropyrimidinone-5-carboxylate core. Most notable among them are the batzelladine alkaloids, which have been found to be potent human immunodeficiency virus (HIV) gp-120-CD4 inhibitors. In modern laboratories organic transformations must be rapidly executed and products readily purified. Clearly there will be a continuing need for the definition of novel reaction routes to both multifunctional scaffolds for lead generation and to unique drug like heterocyclic structures. In this field controlled microwave irradiation has proved to be a powerful tool for both speeding up chemical optimizations and for efficient preparation of new target compounds. The recent development in highly chemoselective metal catalyzed coupling reactions has further enabled direct incorporation of wide variety of chemical functionalities that previously were difficult to accomplish.

Results and Discussion

The reaction between substituted aldehyde 1, substituted urea 2 and ethylacetoacetate 3 in ethanol medium in the presence of an acid catalyst under microwave irradiation resulted in the formation of 1-substituted-4-aryl-5-ethoxycarbonyl-6-methyl-pyrimidine-2-one/thiones 4a-i (Scheme I). The generality of this method with respect to various precursors is summarized in Table I. The starting materials except phenyl thiourea obtained commercially and were used after purification. Phenylthiourea was prepared by refluxing aniline and ammonium thiocyanate in presence of hydrochloric acid. The structure of the newly synthesized compounds was established on the basis of analytical data IR, 1H NMR and mass spectra. Further in a representative example for compound 4c the structure was confirmed by recording its single crystal X-ray Figure 1.

Biological activities

The newly synthesized compounds 4a-i were screened for their antibacterial and antifungal activity. The bacteria employed were Staphylococcus aureus, Bacillus subtilis, Escherichia coli and Pseudomonas aeruginosa and the antifungal activity was tested against the fungus Candida albicans. The screening results indicated that among the compounds tested 4a-c showed significant activity against all the microorganisms tested and were active at a very low concentration compared to the standards employed Furacin and Flucanazole (Table II).

Experimental Section

General

Melting points were determined by open capillary method and are uncorrected. All compounds were analyzed satisfactorily for C, H, and N. 1H NMR spectra were recorded on a Bruker AC 300F (400 MHz) NMR spectrometer using CDCl3 as
solvent and TMS as internal standard. Mass spectra were recorded either on a Jeol JMS-D 300 mass spectrometer or API 3000 LCMS instrument operating at 70 eV.

**Procedure for the preparation of phenylthiourea**

Aniline (0.1 mole) was dissolved in minimum amount of dilute hydrochloric acid in a round bottomed flask. Ammonium thiocyanate (0.2 mole)
was then added and the mixture was refluxed for 5-6 hr. After cooling, the product separated was filtered and washed several times with cold water and recrystallized from ethanol.

General procedure for the synthesis of 1-substituted-4-aryl-5-carboxyethyl-6-methyl-pyrimidine-2-one/thiones 4a-i

A mixture of substituted aldehyde (0.01 mole), ethylacetocetate (0.015 mole), urea/thiourea/phenylthiourea (0.01 mole) and Conc.H2SO4 (1-2 drops) in absolute ethanol (10mL) were taken in a borosil beaker (100 mL) was zapped inside the microwave oven for a period of 3-4 minutes (at 160 W i.e. 25% microwave power). The reaction-mixture was then allowed to stand at RT and the product formed was filtered, washed with ethanol, water, dried and recrystallized from ethanol to afford 4a-i in 52-68% yield (microwave oven: LG-Little Chef MS-192W). The characterization data of the compounds 4a-i is given in Table I.

Spectral data for compounds 4a-i

4a: Ethyl 4-(4,5-dimethoxy-2-nitrophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate 1H NMR (400 MHz), Solvent CDCl3: δ 1.01 (t, 3H, CH3 of ethyl group), 2.49 (s, 3H, Me), 3.95 (s, 3H, OCH3) and 3.98 (s, 3H, OCH3), 4.04 (q, 2H, CH2 of ethyl group), 5.99 (s, 1H, CH), 6.78 (s, 1H, NH), 7.27 (s, 1H, Ar-H), 7.63 (s, 1H, ArH), 8.40 (s, 1H, NH); MS: m/z 365 for C16H19N3O7.

4b: Ethyl 4-(4,5-dimethoxy-2-nitrophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate 1H NMR (400 MHz), CDCl3: δ 1.02 (t, 3H, CH3 of ethyl group), 2.50 (s, 3H, Me), 3.96 (s, 3H, OCH3) and 3.98 (s, 3H, OCH3), 4.02 (q, 2H, CH2 of ethyl group), 5.99 (s, 1H, CH), 6.78 (s, 1H, NH), 7.27 (s, 1H, Ar-H), 7.61(s, 1H, ArH), 8.09(s, 1H, NH); MS: m/z 381 for C16H19N3O6S.

4c: Ethyl-4-(4,5-dimethoxy-2-nitrophenyl)-6-methyl-1-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate 1H NMR (400 MHz), CDCl3: δ 1.03 (t, 3H, CH3 of ethyl group), 2.28 (s, 3H, Me), 4.01(s, 6H, 2xOMe), 4.04 (q, 2H, CH2 of ethyl group), 6.05 (s, 1H, CH), 6.98(s, 1H, NH) 7.27 -7.61(m, 7H, ArH); MS: m/z 457 for C22H23N3O6S.

4d: Ethyl-4-[4-(methylthio)phenyl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate 1H NMR (400 MHz), CDCl3: δ 1.16 (t, 3H, CH3 of ethyl group), 2.35 (s, 3H, Me), 2.45 (s, 3H, SMe), 4.08 (q, 2H, CH2 of ethyl group), 4.94 (s, 2H, CH2 of ethyl group), 6.05 (s, 1H, CH), 6.98(s, 1H, NH) 7.27 -7.61(m, 7H, ArH); MS: m/z 457 for C22H23N3O6S.

Table II — Antibacterial and antifungal activity data of compounds 4a-i

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Antibacterial activity (MIC in μg/mL)</th>
<th>Antifungal activity (MIC in μg/mL)</th>
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<tr>
<td></td>
<td>S. aureus</td>
<td>E. coli</td>
</tr>
<tr>
<td>4a</td>
<td>0.125</td>
<td>0.125</td>
</tr>
<tr>
<td>4b</td>
<td>0.125</td>
<td>0.125</td>
</tr>
<tr>
<td>4c</td>
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<td>0.125</td>
</tr>
<tr>
<td>4d</td>
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<td>0.25</td>
</tr>
<tr>
<td>4e</td>
<td>0.25</td>
<td>0.25</td>
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<tr>
<td>4f</td>
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<td>0.25</td>
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<tr>
<td>4g</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>4h</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>4i</td>
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<td>0.25</td>
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<tr>
<td>Standard:Furacin</td>
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<td>0.5</td>
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<tr>
<td>Standard:Fucanazol</td>
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<td>DMF</td>
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</tbody>
</table>
2H, CH₂ of ethyl group), 5.34 (s, 1H, CH), 7.16-7.27 (m, 4H, ArH), 7.94 (s, 1H, NH) 8.51 (s, 1H, NH).

4e: Ethyl-4-[4-(methylthio)phenyl]-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate ¹H NMR (400 MHz), CDCl₃: δ 1.18 (t, 3H, CH₃ of ethyl group), 2.36 (s, 3H, Me), 2.46 (s, 3H, SMe), 4.09 (q, 2H, CH₂ of ethyl group), 5.35 (s, 1H, CH), 7.16-7.27 (m, 4H, ArH) 7.94 (s, 1H, NH) 8.51 (s, 1H, NH); MS: m/z 322 for C₁₅H₁₈N₂O₂S₂.

4f: Ethyl-4-[4-(methylthio)phenyl]-6-methyl-1-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate ¹H NMR (400 MHz), CDCl₃: δ 1.22 (t, 3H, CH₃ of ethyl group), 2.15 (s, 3H, Me), 2.53 (s, 3H, SMe), 4.14 (q, 2H, CH₂ of ethyl group), 5.43 (s, 1H, CH), 7.23-7.48 (m, 9H, ArH) 8.08 (s, 1H, NH); MS: m/z 398 for C₂₁H₂₂N₂O₂S₂.

4h: Ethyl 4-[4-(dimethylamino) phenyl]-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate. MS: m/z 347 for C₁₉H₂₅N₃O₂S.

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References
1 Beginelli P, Gazz Chim Ital, 23, 1893, 360.