Synthesis of new biologically active arylfuranylmethyltriazinones and their antibacterial activity studies

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In view of the pharmacological activities of 1,2,4-triazinones, a series of 4-amino-6-arylfuranylmethyl-3-mercapto-1,2,4-triazin-5(4H)-ones 7 have been synthesized by refluxing pyruvic acids 5 in ethanol with thiocarbohydrazide 6 on a steam-bath. The structures of 7 are confirmed by elemental analysis, IR, NMR and mass spectral data. Also, these compounds 7 have been screened for antibacterial activities against E. coli, S. aureus, P. aeruginosa and G. baillus. Their MIC values are determined. The results indicate that among the compounds tested, compounds 7a and 7c carrying p-chloro and p-bromo substituents show excellent antibacterial activity against all the bacteria tested. It is concluded that compounds 7a, 7c, 7d and 7f may prove to be promising antibacterial agents.

In continuation of our work on the synthesis of biologically active triazinones derivatives, it was thought worthwhile to undertake the synthesis of a novel series of arylfuranylmethyltriazinones and to explore their potency as chemotherapeutic agents in medicine.

Results and Discussion

4-Amino-6-arylfuranylmethyl-3-mercapto-1,2,4-triazin-5(4H)-ones 7 were synthesized according to the procedure of Dornow and co-workers, by refluxing corresponding substituted arylfuranylpyruvic acids 5 in ethanol with a solution of thiocarbohydrazide 6 on a steam-bath (Scheme I). The structures of the newly synthesized arylfuranylmethyltriazinones 7 were confirmed by elemental analysis, IR, NMR and mass spectral data. Their characterization data are given in Table I. The results of elemental analysis agree with the theoretical values within the limits of experimental error.

The 300 MHz ¹H NMR spectrum of 7a showed a singlet at δ 4.16 which corresponded to CH₂ protons attached to p-chlorophenylfuryl group. The sharp singlet observed at δ 6.16 integrating for two protons was ascribed to the 4-amino group of triazinone 7a. The furan 3H proton signal appeared as a closely spaced doublet at δ 6.31-6.32 (J=3.4 Hz), while the signals due to 4H proton of the furan ring appeared at δ 6.56-6.58 (J=3.4 Hz). The aromatic protons signals

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Table I—Characterization data and antibacterial activity of 4-amino-6-(5-aryl-2-furanyl)methyl-3-mercapto-1,2,4-triazin-5(4H)-ones 7a-f

<table>
<thead>
<tr>
<th>Compd*</th>
<th>R</th>
<th>m.p. °C</th>
<th>MIC values</th>
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<tbody>
<tr>
<td>7a</td>
<td>p-Cl</td>
<td>200-02</td>
<td>3</td>
<td>6</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>7b</td>
<td>p-NO₂</td>
<td>223-24</td>
<td>6</td>
<td>12.5</td>
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<td>6</td>
</tr>
<tr>
<td>7c</td>
<td>p-Br</td>
<td>193-95</td>
<td>3</td>
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<tr>
<td>7d</td>
<td>o-NO₂</td>
<td>178-79</td>
<td>6</td>
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</tr>
<tr>
<td>7e</td>
<td>m-NO₂</td>
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<tr>
<td>7f</td>
<td>o-Cl</td>
<td>153-55</td>
<td>6</td>
<td>12.5</td>
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<td>12.5</td>
</tr>
</tbody>
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*Mass: 7a; m/z 334/336 (M⁺/M+2, 100%/30,3%), 318/320(M⁺-NH₂, 9.8%/13,3%), 217(p-chlorophenylfuranyl-acetonitrile, 89.5%), 111/113(p-chlorophenyl cation, 13%/13,3%); 7b; m/z 345 (M⁺/M+2,100%), 228(p-nitrophenylfuranylacetanitride,73%); 7c; m/z 378/380 (M⁺/M+2, 66%/63%), 261/263(p-romophenylfuranyl-acetonitrile, 84%/67%).

of p-chlorophenylfuryl group were seen as two distinct doublets at δ 7.31-7.34 (J=8.4 Hz) and 7.52-7.55 (J=8.7 Hz), respectively integrating for four protons. The mercapto group signal appeared as a broad singlet at δ 10.56.

The mass spectrum of 7a showed a fairly intense molecular ion peak at m/z 334 corresponding to the molecular formula C₁₄H₁₁CIN₄O₂S. The peak observed at m/z 217/219 corresponded to the molecular ion of p-chlorophenylfuranylacetonitrile. An intense peak at m/z 59 was observed corresponding to the formation of HN=C=S radical ion in both the triazinones 7a and 7b.

Antibacterial activity

All the newly synthesized arylfuranyl methyltriazinones 7 were screened for their in vitro antibacterial activities⁴ against E. coli, S. aureus, P. aeruginosa and G. bacillus. Their minimal inhibitory concentrations (MIC) were determined. Furacin was used as a standard drug for comparison. The screening data indicated that among the compounds tested, compounds 7a and 7c carrying p-chloro and p-bromo substituents showed excellent antibacterial activity against all the bacteria. Also, compounds 7d and 7f carrying o-nitro and o-chloro moieties showed greater degree of antibacterial activities against S. aureus, P. aeruginosa and G. bacillus compared to the furacin. However, the antibacterial activities of compounds 7b and 7e were found to be greater than the standard drug especially against P. aeruginosa, G. bacillus and S. aureus, respectively. Thus, it was concluded that compounds 7a, 7c, 7d and 7f are promising antibacterial agents and hence deserve further in-depth pharmacological investigations.

Experimental Section

General procedure for the preparation of arylfuranylpyruvic acids 5. A suspension of α-acetamido-β-(5-aryl-2-furanyl)acrylic acid (4, 0.05 mole) in hydrochloric acid (1N, 200 mL) was placed in a round bottomed flask and boiled under reflux for 3 hr. A few droplets of oil separated from the boiling solution. These were removed by filtration. The crystals which separated from the filtrate were transferred to a Buchner funnel and washed with small quantity of ice-cold water. The product was dried in a vacuum desiccator over anhydrous calcium chloride and potassium hydroxide pellets.

General procedure for the synthesis of 4-amino-6-(5-aryl-2-furanyl)methyl-3-mercapto-1,2,4-triazin-5(4H)-ones 7. To thiocarboxylic acid (6; 1.06 g, 0.01 M), dissolved in water (30 mL) was added arylfuranylpyruvic acid (5; 0.01 M) dissolved in ethanol, dropwise with stirring. The reaction mixture was then refluxed on a steam-bath for 1 hr. The solid product that separated out was collected by filtration and recrystallized from a mixture of DMF-EtOH in 68-73% yield. The characterization data of the compounds prepared according to this procedure are given in Table I.

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