SYNTHESIS, CHARACTERIZATION AND PHARMACOLOGICAL ACTIVITIES OF 2-ARYL-3-[4'-PHENYL THIAZOLIDINYL]-4-OXO-THIAZOLIDINES

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ABSTRACT
A novel series of 2-amino-4-substituted phenyl thiazole (1a-i), 2-imine substituted phenyl-4-substituted phenyl thiazole (2a-i) 2-(4-oxo-2 substituted aryl-Thiazolidinyl)-4/substituted phenyl thiazole. (3a-i) were prepared by the reaction of thiourea with different acetophene with excellent yield. Elemental analysis, IR, H1NMR, C13NMR & Mass spectral data established identification of the compounds (3a-i) was evaluated for their antimicrobial and antifungal activity.

KEYWORDS: 4-oxo-thiazolidines, thioglycolic acid, spectral data, antibacterial activity, etc.

INTRODUCTION
Heterocyclic compounds have played an important role in the evolution of life, as dyes, drugs and are also used in many commercially important species and their analogs in which one or more ring carbons have been replaced by a heteroatom, such as nitrogen, oxygen, sulfur, phosphorus, silicon, a metal and so on. The most-common heterocyclic systems contain nitrogen or oxygen or both. 4-Thiazolidinones are derivatives or Thiazolidine with a carbonyl group at the 4-position substitution is possible at 2,3 and 5-position.[1-2] The nucleus is also known as wonder nucleus because it gives out different derivatives with all different types of biological activities and therefore thiazolidinone with varied substituent are being synthesized and as better medicinal agent in recent years 4-oxo-thiazolidine are the most extensively investigated class of compounds, which exhibit various biological activities antimicrobial, anti-inflammatory, anti HIV, antitubercular, antioxidant
and analgesic.\textsuperscript{[3-8]} 4-Thiazolidinones nucleus has occupied unique place in the field of pharmaceutical activities like antibacterial, anticancer, antiviral, cardiovascular, antitumor, CNS depressant.

**RESULT AND DISCUSSION**

In view of these observations, it was thought worthwhile to synthesize several compounds in which 2-amino, 4-substituted phenyl thiazole, 2-substituted phenyl imine 4-substituted phenyl thiazole, 2-substituted aryl, 3-substituted phenyl thiazole, 4-thiazolidinones have been linked with moiety.

The reaction sequence leading to the formation of desired heterocyclic compounds are outlined in scheme-1. The starting material 2-amino, 4-substituted phenyl thiazole (1a-i) was prepared by the reaction of substituted acetophenone with thiazole in presence of Br\textsubscript{2} –H\textsubscript{2}O and ethanol. Synthesis of 2-amine substituted phenyl 4-substituted phenyl thiazole (2a-i) the substituted 2-[4-oxo-2-substituted aryl-Thiazolidinyl] 4-substituted phenyl thiazole (3a-i) by the reaction of 2-amine substituted phenyl, 4-substituted phenyl thiazole with thioglycolic acid and zinc chloride in presence of benzene the IR, H\textsuperscript{1} NMR,C\textsuperscript{13} NMR, Mass spectra of the 2-substituted aryl-3-substituted phenyl thiazole 4-thiazolidinones.

**Biological Studies**

Biological Study of thiourea with different acetophenones and (3a-i) has been observed by using Norfloxacine and Griseofulvaline as standards. The enhancement in biological activity of compound (1) as compared with the newly synthesized (3a-i) has been observed. The synthesized compounds were tested at 100ml concentration against staphylococcus aureus, E-coli, P. vulgaris, A. niger, B. substillis, C. albicans for its antibacterial and antifungal screening as shown in Table-I.

**Table-I Antibacterial and Antifungal activities of compounds 3a-i.**

<table>
<thead>
<tr>
<th>compounds</th>
<th>Antibacterial activity</th>
<th>antifungal activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S. aureus</td>
<td>B. subtilis</td>
</tr>
<tr>
<td>3a</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>3b</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>3c</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>3d</td>
<td>_</td>
<td>+++</td>
</tr>
<tr>
<td>3e</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>3f</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>3g</td>
<td>+++</td>
<td>_</td>
</tr>
<tr>
<td>3h</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>
SM (streptomycin) and GF (Griseofulvin). The inhibition diameter in Mm (-) < 6, (+) 7-9, (+++) 10-15, (++++) 16-22, (++++) 23-28.

**EXPERIMENTAL**

Melting points were taken in open capillary tubes and are uncorrected. IR spectra were run in KBr pellets on a Perkin-Elmer 157 spectrometer. H NMR spectra were recorded in a CDCl3 on a Bruker-Variah 300MHz FT NMR spectrometer using TMS as internal standard. Purity or the compounds was checked by TLC on silica gel G plates and the spots were located by exposure to iodine vapors’. The characterization data of the compounds is given in Table-II.

<table>
<thead>
<tr>
<th>comp</th>
<th>R′</th>
<th>Mol. Formula</th>
<th>M. Pt (°C)</th>
<th>RF Value</th>
<th>% Yield</th>
<th>Analysis found(Cal)</th>
<th>% C</th>
<th>% H</th>
<th>% N</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>H</td>
<td>C_{18}H_{10}N_{2}S_{2}O</td>
<td>165</td>
<td>0.91</td>
<td>83</td>
<td>74.1 (74.0)</td>
<td>4.46 (4.45)</td>
<td>7.84</td>
<td>7.83</td>
</tr>
<tr>
<td>3b</td>
<td>2-OH</td>
<td>C_{18}H_{12}N_{2}S_{2}O_{2}</td>
<td>172</td>
<td>0.72</td>
<td>79</td>
<td>70.5</td>
<td>70.4</td>
<td>7.75</td>
<td>7.74</td>
</tr>
<tr>
<td>3c</td>
<td>3-OH</td>
<td>C_{18}H_{12}N_{2}S_{2}O_{2}</td>
<td>181</td>
<td>0.75</td>
<td>75</td>
<td>70.8</td>
<td>70.4</td>
<td>7.75</td>
<td>7.74</td>
</tr>
<tr>
<td>3d</td>
<td>4-OH</td>
<td>C_{18}H_{12}N_{2}S_{2}O_{2}</td>
<td>188</td>
<td>0.82</td>
<td>58</td>
<td>70.5</td>
<td>70.4</td>
<td>7.75</td>
<td>7.74</td>
</tr>
<tr>
<td>3e</td>
<td>2-NO₂</td>
<td>C_{18}H_{12}N_{2}S_{2}O_{3}</td>
<td>191</td>
<td>0.77</td>
<td>54</td>
<td>72.70</td>
<td>72.69</td>
<td>4.22</td>
<td>4.21</td>
</tr>
<tr>
<td>3f</td>
<td>3-NO₂</td>
<td>C_{18}H_{12}N_{2}S_{2}O_{3}</td>
<td>192</td>
<td>0.54</td>
<td>62</td>
<td>72.70</td>
<td>72.69</td>
<td>4.22</td>
<td>4.21</td>
</tr>
<tr>
<td>3g</td>
<td>4-NO₂</td>
<td>C_{18}H_{12}N_{2}S_{2}O_{3}</td>
<td>189</td>
<td>0.86</td>
<td>65</td>
<td>72.70</td>
<td>72.69</td>
<td>4.22</td>
<td>4.21</td>
</tr>
<tr>
<td>3h</td>
<td>2-CL</td>
<td>C_{18}H_{10}N_{2}S_{2}OCl_{1}</td>
<td>157</td>
<td>0.75</td>
<td>49</td>
<td>73.4</td>
<td>73.3</td>
<td>4.21</td>
<td>4.20</td>
</tr>
<tr>
<td>3i</td>
<td>4-CL</td>
<td>C_{18}H_{10}N_{2}S_{2}OCl_{1}</td>
<td>143</td>
<td>0.78</td>
<td>58</td>
<td>73.4</td>
<td>73.3</td>
<td>4.21</td>
<td>4.20</td>
</tr>
</tbody>
</table>

* Eluents for TLC: Benzene-acetone (6:4) for 3a-i.

* Solvent for crystallization; aq. ethanol for 3a-i.

**EXPERIMENTAL**

Melting points were taken in open capillary tubes and are uncorrected. IR spectra were run in KBr pellets on a Perkin-Elmer 157 spectrometer. H NMR spectra were recorded in CDCl3 on a Bruker-Variah 300MHz FT NMR spectrometer using TMS as internal standard. Purity of
the compounds was checked by TLC on silica gel G plates and the spots were located by exposure to iodine vapors. The characterization data of the compounds is given in Table.

**Method of synthesis**

1. **Synthesis of 2-amino, 4-substituted phenyl thiazole**

A mixture of substituted acetophenone (0.1 mole) thiourea (0.2 mole) in 100 ml of ethanol addition of Br₂ –H₂O was refluxed for overnight. A resulting solid material reported which was crystallized from DMF similarly other compounds were also prepared.

2. **Synthesis of 2-imine substituted phenyl 4-substituted phenyl thiazole**

A mixture of compound I (0.01 mole) and substituted benzaldehyde (0.01 mole) on discovery in ethanol in presence of Glacial acetic acid. The reaction mixture was refluxed for 12-14 hr and resulting solid was washed with ether and crystallized from DMF similarly other compound were also prepared.

3. **Synthesis of 2-[4 oxo-2-substituted-aryl Thiazolidinyl] substituted phenyl thiazole**

A mixture of compound 2(0.01 mole) and anhydrous ZnCl₂ (one pinch) in dry benzene, thioglycolic acid (0.02 mole) were added drop wise with stirring and mixture were kept from 3 days at room temperature refluxed for 12 hr. the react mixture was filtered and poured on to ice the resulting solid was washed and recrystallized from DMF.

**3a:** (M.P. 165 yield 83), IR(KBr); 2945 (C-H Aromatic stretch) 1791.8, 1713, 1641, 1520, 779 (C=S); H¹NMR (300MHz DMSO) δ 9.53 (S1H NH), C¹³NMR (300MHz, DMSO-d₆), 14.2, 13.1, 13.6, 23.0, 37.9, 38.2, 34.5, 39.4, 40.0, 58.5, 76.8, 7.3, 111.8, 159.1, 126.2, 137.3, 160.2, 162.1.

**3b:** (M.P. 172 yield 79), IR(KBr); 2945 (C-H Aromatic stretch), 3275(OH of phenyl ring) 1639 & 1655 cyclic carbonyl ring, 690 (C-S-C linkage of thiazolidinone ring), 1152 (c-ost) δ 3209 (N-H Stretch) 1791.8, 1713, 1641, 1520, 779(C-S); H¹NMR(300MHz DMSO) δ 2.24, 4.23, 3.56 6.8-7.8 (M.8H Aromatic proton) 3.5 (s,2H,CH₂ Thiazolidine ring) C¹³NMR (300MHz, DMSO-d₆), 14.1, 13.0, 13.62, 23.1, 37.9, 38.0, 34.1, 39.2, 40.1, 58.3, 72.3, 7.3, 111.5, 159.1, 126.0, 137.1, 160.2, 162.1.

**3c:** (M.P. 181 yield 75), IR(KBr); 2945 (C-H Aromatic stretch), 3272(OH of phenyl ring) 1637 & 1653 cyclic carbonyl ring, 693(C-S-C linkage of thiazolidinone ring), 1151 (c-ost) δ 3208 (N-H Stretch) 1791.8, 1713, 1641, 1520, 779(C-S); H¹NMR(300MHz DMSO) δ
2.24, 4.21, 3.54  6.8-7.8 (M.8H Aromatic proton) 3.4 (s, 2H, CH₂ Thiazolidine ring) C¹³NMR (300MHz, DMSO_d₆), 14.2, 13.1, 13.2, 23.0, 37.8, 38.1, 34.2, 39.4, 40.0, 58.5, 76.5, 7.3, 111.8, 159.1, 126.1, 137.3, 160.2, 162.2.

3d: (M. P. 188 yield 58), IR (KBr); 2945 (C-H Aromatic stretch) 3274 (OH of phenyl ring) 1638 & 1650 cyclic carbonyl ring, 691 (C-S-C linkage of thiazolidinone ring), 1150 (c-o str) 3207 (N-H Stretch) 1791.8, 1713, 1641, 1520, 779 (C-S); H¹NMR (300MHz DMSO) δ 2.25, 4.20, 3.52 6.8-7.8 (M.8H Aromatic proton) 3.3 (s, 2H, CH₂ Thiazolidine ring) C¹³NMR (300MHz, DMSO_d₆), 14.2, 13.1, 13.6, 23.0, 37.9, 38.2, 34.5, 39.4, 40.0, 58.5, 76.8, 7.3, 111.8, 159.1, 126.2, 137.3, 160.2, 162.1.

3e: (M. P. 191 yield 54), IR (KBr); 2945 (C-H Aromatic stretch) 1791.8, 1713, 1641, 1520, 779 (C-S); H¹NMR (300MHz DMSO) δ 2.22, 4.20, 3.51 6.8-7.8 (M.8H Aromatic proton) 3.3 (s, 2H, CH₂ Thiazolidine ring) (300MHz, DMSO-d₆), 14.2, 13.1, 13.2, 23.1, 37.9, 38.1, 34.2, 39.4, 40.0, 58.2, 76.8, 7.3, 111.2, 159.0, 126.1, 137.3, 160.1, 162.1.

3f: (M. P. 192 yield 62), IR (KBr); 2945 (C-H Aromatic stretch) 1791.8, 1713, 1641, 1520, 779 (C-S); H¹NMR (300MHz DMSO) δ 2.20, 4.21, 3.54m, 6.8-7.8 (M.8H Aromatic proton) 3.3 (s, 2H, CH₂ Thiazolidine ring) C¹³NMR (300MHz, DMSO_d₆), 14.1, 13.2, 13.0, 23.0, 37.9, 38.1, 34.5, 39.2, 40.0, 58.2, 76.8, 7.3, 111.2, 159.1, 126.2, 137.3, 160.2, 162.1.

3g: (M. P. 189 yield 65), IR (KBr); 2942 (C-H Aromatic stretch) 1791.8, 1713, 1641, 1520, 779 (C-S); H¹NMR (300 MHz DMSO) δ 2.24, 4.23, 3.56 6.8-7.8 (M.8H Aromatic proton) 3.4 (s, 2H, CH₂ Thiazolidine ring) C¹³NMR (300MHz, DMSO-d₆), 14.0, 13.1, 13.6, 23.1, 37.9, 38.0, 34.5, 39.4, 40.0, 58.2, 76.2, 7.3, 111.3, 159.1, 126.1, 137.2, 160.2, 162.1.

3h: (M. P. 157 yield 49), IR (KBr); 2944 (C-H Aromatic stretch) 1791.8, 1713, 1641, 1520, 779 (C-S); 1689 (C= O) of thiazolidinone ring H¹NMR (300 MHz DMSO) δ 2.24, 4.23, 3.56 6.5-7.8 (M.8H Aromatic proton) 3.3 (s, 2H, CH₂ Thiazolidine ring) C¹³NMR (300MHz, DMSO_d₆), 14.0, 13.213.6, 23.0, 37.9, 38.2, 34.2, 39.1, 40.0, 58.5, 76.2, 7.3, 111.3, 159.1, 126.2, 137.3, 160.2, 162.1.

3i: (M. P. 143 yield 58), IR (KBr); 2941 (C-H Aromatic stretch) 1791.8, 1713, 1641, 1520, 779 (C-S); H¹NMR (300MHz DMSO) δ 2.24, 4.23, 3.56, 6.7-7.8 (M.8H Aromatic proton) 3.3 (s, 2H, CH₂ Thiazolidine ring) C¹³NMR (300 MHz, DMSO-d₆), 14.2, 13.1, 13.5, 23.1, 37.9, 38.2, 34.5, 39.4, 40.1, 58.5, 76.8, 7.3, 111.8, 159.1, 126.2, 137.3, 160.2, 162.1.
CONCLUSION

Efficient methods for synthesis of (3a-i) with excellent yield have been developed. The results of this study indicate that present synthetic method is a simple and efficient in expensive and easy synthesis of biologically active compound (3a-i) these compound showing good result tested at 100 mg Conc. against E-coli, S-aureus, P-Vulgaris, A-niger, C-albicans.

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