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Synthesis and Antimicrobial Activity of Some New Isoxazolines and 1,5-Benzothiazepines

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New six isoxazolines and five 1,5-benzothiazepines are synthesised from 1-(substituted phenyl)-3-(2-methoxy-1-naphthyd-2-propen-1-ones. Their structural assignments are based on spectral data (IR and PMR) and elemental analysis. All these compounds have been screened for antimicrobial activity. The compounds with a methyl or chloro and methyl as well as chloro group on the aromatic ring showed good antimicrobial activity.

Nitrogen containing heterocyclic compounds like isoxazolines, nitrogen and sulphur containing heterocyclic compounds like benzothiazepines have received considerable attention in recent years due to their wide range of physiological activities. A number of isoxazole derivatives have been found to possess potential antibacterial, anti-tubercular, antifungal and antidiabetic activity. Anilidoisoxazolines synthesised by Zari and Yammi were found to possess remarkable bactericidal activity against some gram positive and gram negative bacteria. Mittal and Singhal have reported antibacterial and antifungal activity in 3-methyl-4-(4'-bromo-2'-methyl benzene azo)-5-isoazoline. Benzothiazepines such as diltiazen or thiazesim are constantly used as antidepressant, coronary vasodilator and antiangiota agents. Levitiz has reviewed the syntheses of four known groups of optically active 1,5-benzothiazepines. The references included show the most important biological activities like CNS, cardiotonic, histamine H1 antagonist and antiulcer. Bioassay screening of some substituted 1,5-benzothiazepines show mild analgesic and anticonvulsant activity. These reports prompted us to synthesize new isoxazoline and benzothiazepine derivatives and evaluate their antimicrobial activity.

Melting points were determined in open capillaries and are uncorrected. The structures of the compounds were sup-

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ported by elemental analysis and spectral data. The IR spectra (nujol) were recorded on a Beckman spectrophotometer (υ max in cm⁻¹) and PMR spectra obtained on a Gemini 200 spectrometer using CDCl₃ as solvent and TMS as an internal standard (δ in ppm). Elemental analysis (C, H, N and S) was carried out on a Carlo Ebra Strum DP 200.

1-(substituted phenyl)-3-(2-methoxy-1-naphthyl)-2-propen-1-ones, i.e., chalcones, on treatment with hydroxylamine hydrochloride in alcoholic sodium acetate under reflux yielded the respective isoxazolines ¹ 1a-f (yield 52-65%). Similarly some of the above chalcones were converted to the corresponding 1,5-benzothiazepines ² 2a-e (yield 66-72%) by treatment with o-aminophenol in alcoholic piperidine.

The compound if was synthesised by refluxing a mixture of 1-(3′,5′-dichloro-2′-hydroxyphenyl)-3-(2-methoxy-1-naphthyl)-2-propen-1-one (3.73 g, 0.01 mol), and hydroxylamine hydrochloride (1.03 g, 0.015 mol) and sodium acetate (1.64 g, 0.02 mol) in ethanol (25 ml) for 5-6 h. The reaction mixture was cooled and poured into ice cold water. The solid product obtained was filtered, washed, dried and

### TABLE 1: PHYSICAL DATA* AND ANTIMICROBIAL ACTIVITY OF ISOXAZOLINES (1a-f) AND 1,5-BENZOTHIAZEPINES (2a-e).

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R</th>
<th>m.p. (°)</th>
<th>% yield</th>
<th>Antibacterial inhibition zone (mm)</th>
<th>Antifungal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>E. coli</td>
<td>S. aureus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>germ-</td>
<td>germ</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>% tube</td>
<td>tube length (µ)</td>
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<tr>
<td>1a</td>
<td>2′-OH</td>
<td>165</td>
<td>52</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>1b</td>
<td>2′-OH-5′-CH₃</td>
<td>198</td>
<td>52</td>
<td>42</td>
<td>28</td>
</tr>
<tr>
<td>1c</td>
<td>2′-OH-5′-C₁</td>
<td>187</td>
<td>55</td>
<td>14</td>
<td>22</td>
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<tr>
<td>1d</td>
<td>2′-OH-5′-Br</td>
<td>188</td>
<td>55</td>
<td>10</td>
<td>22</td>
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<tr>
<td>1e</td>
<td>2′-OH-4′-CH₃ 5′-C₁</td>
<td>202</td>
<td>58</td>
<td>39</td>
<td>24</td>
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<td>1f</td>
<td>2′-OH-3′,5′-di Cl</td>
<td>171</td>
<td>65</td>
<td>19</td>
<td>14</td>
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<tr>
<td>2a</td>
<td>2′-OH</td>
<td>214</td>
<td>70</td>
<td>Nil</td>
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<tr>
<td>2b</td>
<td>2′-OH, 5′-Cl</td>
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<td>68</td>
<td>40</td>
<td>26</td>
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<tr>
<td>2c</td>
<td>2′-OH-5′-Br</td>
<td>194</td>
<td>66</td>
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<tr>
<td>2d</td>
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<td>178</td>
<td>17</td>
<td>46</td>
<td>26</td>
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<tr>
<td>2e</td>
<td>2′-OH-3′,5′-di Cl</td>
<td>216</td>
<td>72</td>
<td>42</td>
<td>24</td>
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<tr>
<td>Tetracycline</td>
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<tr>
<td>Water-ethanol (90:10, v/v)</td>
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</tr>
</tbody>
</table>

* All compounds gave satisfactory elemental analysis within ± 0.05% of theoretical values.
crystallised from ethanol yield: 3.09 g (65%); m.p: 171°.

Anal of If: IR (nujol) cm⁻¹: 1605 (C = N); 1470, 1260 (N-O-C); 3370 (OH). PMR (CDCl₃) δ: 3.42-3.54 (dd, 2H, CH₂); 3.86 (s, 3H, OCH₃); 5.8-6.2 (t, 1H, CH); 7.0-8.2 (m, 8H, Ar-H); 10.82 (s, 1H, OH). The compounds 1a-f were prepared using a similar procedure as mentioned above.

The compound 2a was synthesised by refluxing a mixture of 1-(2'-hydroxyphenyl)-3-methoxy-1-naphthyl-2-propen-1-one (3.04 g, 0.01 mol) and α-aminothiophenol (1.25 g, 0.01 mol), few drops of piperidine in ethanol (50 ml) for 4 h. Thereafter glacial acetic acid (10 ml) was added to the reaction mixture and further refluxed for 2 h. The reaction mixture was left overnight at room temperature and the resultant solid obtained was filtered and crystallised from ethanol-acetic acid: 3.0 g (70%); m.p: 214°. Anal of 2a: IR (nujol) cm⁻¹: 1610 (C=N); 3190 (OH). PMR (CDCl₃) δ: 3.73 (s, 3H, OCH₃); 3.24-3.32 (dd, 2H, CH₂); 6.31 (m, 1H, CH); 6.89-9.05 (m, 14H, Ar-H) and 14.6 (s, 1H, OH). Similarly other members of the series were prepared.

All the compounds have been screened for antibacterial activity against *Escherichia coli*, *Staphylococcus aureus* and antifungal activity against *Curvularia lunata*, *Helminthosporium oryzae* by the disc diffusion¹³ and hanging drop¹⁴ methods with slight modification. For antibacterial activity, the concentration of the compounds screened was 200 μg/0.1 ml. The zone of inhibition of bacterial growth was measured after 24 h, after incubating at 37°. The results are tabulated in Table 1. The compounds with a methyl or chloro and methyl as well as chloro group (1b, 2c, 1e, 2b, 2d and 2e) on the aromatic ring showed potent antibacterial activity and all other compounds showed mild to moderate activity.

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