Synthesis and Antimicrobial Activity of Some Novel 4-(1H-Benz[d]imidazol-2-yl)-1,3-thiazol-2-amines

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A new series of novel 4-(1H-benz[d]imidazol-2-yl)-1,3-thiazol-2-amines 5a—d and 4-(1H-benz[d]imidazol-2-yl)-3-alkyl-2,3-dihydro-1,3-thiazol-2-amine 8a—d has been synthesized by the cyclocondensation of 2-acetyl benzimidazoles 4a—d and 2-bromo-1-(1-alkyl-1H-benz[d]imidazol-2-yl)-1-ethanone 7a—d with thiourea respectively, and evaluated for their antibacterial and antifungal activity against clinical isolates of Gram-positive and Gram-negative bacteria. Some of these hybrids in this series exhibited antibacterial activity comparable to standard Streptomycin and Benzyl penicillin and antifungal activity against Fluconazole. All the newly synthesized compounds were characterized by their spectral data and further used to estimate their ability towards antimicrobial activity.

Key words  thiazol-2-amine; benzimidazole; antimicrobial activity

Benzimidazoles show significant activity against several viruses such as human cytomegalovirus (HCMV), human immunodeficiency virus (HIV), herpes (HSV-1), RNA and influenza. In view of the tremendous activities of benzimidazoles, their preparation has gained considerable attention. While many strategies are available for benzimidazole synthesis, almost all benzimidazoles with their two ring systems bear different functional substituents and this leads to essential modification of the physico-chemical, metabolic and pharmacokinetic properties of drugs.

Thiazoles are an important group of heterocyclic compounds contains sulfur and nitrogen in a five member ring. A lot of research work on thiazoles has been done in the past. The nucleus is also known as wonder nucleus because it gives out different derivatives with all different types of biological activities. Various methods are available in the literature for synthesis of thiazoles by using various agents. Heterocycles based on thiazole ring systems are biologically active. Hence, thiazole ring systems containing molecules are known in pharmaceuticals such as Meloxicam, Nitazoxamide, Thiabendazole, Cefdinir, Nizatidine, Alagebrum, Sulfathiazole, Amthamine, Pramipexole.

Inspired with the biological profile of benzimidazoles and thiazoles and their increasing importance in pharmaceutical and biological fields, and in connection with our research on the design and synthesis of biologically active and pharmaceutically important new heterocycles, it was thought worthwhile to synthesize the title compounds with a view to obtain certain new chemical entities with two active pharmacophores in a single molecular framework in order to prepare molecules having with potentially enhanced biological activities and to have them evaluated for their antimicrobial activity. On the other hand, to the best of my knowledge previously there is no report, on the synthesis of 4-(1H-benz[d]imidazol-2-yl)-1,3-thiazol-2-amine 5 and 4-(1H-benz[d]imidazol-2-yl)-3-alkyl-2,3-dihydro-1,3-thiazol-2-amine 8 skeleton system represented as in Chart 1.

Chart 1 outlines the synthetic strategy developed to obtain the 4-(1H-benz[d]imidazol-2-yl)-1,3-thiazol-2-amine 5 from 2-acetyl benzimidazole 4 with thiourea. For the synthesis of target compounds, 2-(α-hydroxy) ethyl benzimidazole 3 was prepared by the reaction of substituted o-phenylenediamine 1 with α-hydroxy propionic acid 2 in presence of hydrochloric acid under reflux, followed by oxidation of compound 3 in presence of potassium dichromate and sulfuric acid at room temperature yields 2-acetyl benzimidazoles, 4 which on cyclo condensation reaction with thiourea under reflux in presence of iodine and isopropanol gave 4-(1H-benz[d]imidazol-2-yl)-1,3-thiazol-2-amine 5. Similarly, the synthesis of 4-(1H-benz[d]imidazol-2-yl)-3-alkyl-2,3-dihy-

![Chem. Pharm. Bull.](https://example.com/figure.png)
Table 1. Antibacterial and Antifungal Activity of 4-(1H-Benz[d]imidazol-2-yl)-1,3-thiazol-2-amines 5a—d and 4-(1H-Benz[d]imidazol-2-yl)-3-alkyl-2,3-dihydro-1,3-thiazol-2-amine 8a—d

<table>
<thead>
<tr>
<th>Compound</th>
<th>B. subtilis (mm)</th>
<th>S. aureus (mm)</th>
<th>E. coli (mm)</th>
<th>K. pneumoniae (mm)</th>
<th>F. oxysporum (mm)</th>
<th>A. niger (mm)</th>
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<tbody>
<tr>
<td>5a</td>
<td>05/05</td>
<td>07/06</td>
<td>04/04</td>
<td>06/05</td>
<td>03/02</td>
<td>02/02</td>
</tr>
<tr>
<td>5b</td>
<td>12/11</td>
<td>13/12</td>
<td>10/08</td>
<td>11/09</td>
<td>04/03</td>
<td>04/03</td>
</tr>
<tr>
<td>5c</td>
<td>14/13</td>
<td>13/11</td>
<td>12/11</td>
<td>14/12</td>
<td>05/04</td>
<td>04/03</td>
</tr>
<tr>
<td>5d</td>
<td>15/14</td>
<td>13/12</td>
<td>14/12</td>
<td>13/12</td>
<td>05/04</td>
<td>04/03</td>
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<tr>
<td>8a</td>
<td>09/08</td>
<td>08/07</td>
<td>09/07</td>
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<tr>
<td>8b</td>
<td>13/12</td>
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</tr>
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<td>Streptomycin(a)</td>
<td>—</td>
<td>16</td>
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<tr>
<td>Benzylic penicillin(b)</td>
<td>—</td>
<td>16</td>
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<td>Fluconazole(c)</td>
<td>—</td>
<td>—</td>
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<td>—</td>
<td>06</td>
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</tr>
</tbody>
</table>

(a) Zone of inhibition in mm at 500 μg/ml concentration. (b) Zone of inhibition in mm at 250 μg/ml concentration. (c) Zone of inhibition in mm at 40 μg/ml concentration.

dro-1,3-thiazol-2-amine 8 was obtained by the cyclocondensation of 2-bromo-1-(1-alkyl-1H-benzo[d]imidazol-2-yl)-1-ethanone 7 with thiourea in N,N-dimethylformamide (DMF) solvent under reflux. The compound 7 was achieved through α-bromination of acetyl group of 1-(1-alkyl-1H-benzo[d]imidazol-2-yl)-1-ethanone 6 with the mixture of molecular bromine and acetic acid. The intermediate 6 was resulted through N-methylation/benzylation of 2-acetyl benzimidazoles 4 with dimethyl sulphate/benzyl chloride in presence of triethyl benzyl ammonium chloride (TEBAC) at room temperature. The chemical structures of all the newly synthesized compounds were confirmed by their IR, 1H-NMR and mass spectral analysis and further used to estimate their ability towards antimicrobial activity.

**Antibacterial Activity** In an approach, we have synthesized a new class of compounds and evaluated them for their in vitro antimicrobial activities against clinical isolates two Gram-positive bacteria namely *Bacillus subtilis* and *Staphylococcus aureus* and two Gram-negative bacteria viz., *Escherichia coli* and *Klebsiella pneumoniae* by Cup-plate method(11) using Streptomycin and Benzylic penicillin as control drugs. The Minimum Inhibitory Concentration (MIC) was determined according to the protocols of National Committee for Clinical Laboratory Standards (NCCLS). In general the compounds showed improved antibacterial activity to their antifungal activity. It is observed from the results as illustrated in Table 1 that almost all the compounds exhibited good to moderate antibacterial activity towards all the organisms employed. Compounds 5d and 8c exhibited almost equipotent inhibitory activity as compared to the control against *B. subtilis*, whereas compounds 8b and 8d have shown high activity and none of the compounds showed better activity than the control against the same organism. Compounds 5c, 5d, 8b and 8d are the most effective against *S. aureus*. Similarly only compound 8b against *E. coli* and 5c against *K. pneumoniae* showed effective activity.

**Antifungal Activity** The synthesized compounds have also been evaluated for their antifungal activity against two representative fungi viz., *Fusarium oxysporum* and *Aspergillus niger* by Cup-plate method(11) using Fluconazole as standard drug at 40 μg/ml concentration. Compounds 5c, 5d, 8b and 8c are most active which possessed higher activity against *F. oxysporum* in comparison to standard drug. For activity against *A. niger* compounds 5b, 5d, 8c and 8d yielded better activity in comparison to other compounds synthesized. However almost all synthesized benzimidazolyl-1,3-thiazol-2-amines have shown moderate to significant antifungal activity against the two organisms employed. From the above discussion it is evident that compounds 5d and 8c have emerged as the most effective antibacterial agents whereas compounds 8c and 8d were the most active ones towards antifungal activity.

**Experimental**

**General** All reagents and solvents were used as purchased without further purification. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Crude products were purified by column chromatography on silica gel of 60—120 mesh. IR spectra were obtained on a Perkin Elmer BX series FTIR 5000 spectrometer using KBr pellet. NMR spectra were recorded on a Varian 300 MHz spectrometer for 1H-NMR. The chemical shifts were reported as ppm down field using TMS as an internal standard. Mass spectra were recorded on a VG-Micromass 7070H spectrometer operating at 70 eV.

**Typical Procedure 2-(α-Hydroxyethyl Benzimidazoles (3)** α-Phenylene-diamine (0.01 mol) was treated with lactic acid (0.01 mol) in presence of 4N-hydrochloric acid (5 ml) and refluxed on water both for 24 h. After completion of the reaction (monitored by TLC) the reaction mixture was cooled and neutralized with NH₄ solution. The solid was separated through filter and recrystallized from absolute ethanol.

**2-Acetyl Benzimidazoles (4)** To a solution of 2-(α-hydroxyethyl) benzimidazoles 3 (0.01 mol) in diH₂SO₄ (5%, 40 ml) was drop wise added the solution of K₂Cr₂O₇ (0.15 mol) and aqueous H₂SO₄ (25%, 80 ml) with constant stirring at room temperature over a period of 20 min. Further the reaction mixture was stirred at room temperature for 2 h. After completion of the reaction, (monitored by TLC), the reaction mixture was neutralized with NH₄ solution (1:1) and formed orange solid was filtered, washed with water and dried, recrystallized from ethyl acetate.

**4-(1H-Benz[d]imidazol-2-yl)-1,3-thiazol-2-amines (5)** A solution of 2-acetyl benzimidazoles (4) (0.01 mol) in isopropanol (20 ml) was added to the mixture of thiourea (0.01 mol) and sodium (0.12 mol) in isopropanol (20 ml). Then the reaction mixture was heated under reflux for 3 h. After completion of the reaction, (monitored by TLC) the solvent was removed in vacuo. The solid separated was washed with acq. sodium bicarbonate solution, dried and recrystallized from ethanol to give product 5 in pure state.

**1-(1-Alkyl-1H-benzo[d]imidazol-2-yl)-1-ethanones (6)** To a suspension of potassium carbonate (0.01 mol) in acetonitrile (20 ml) was added tri-ethyl benzyl ammonium chloride and the reaction was stirred for 10 min. To this mixture, added 2-acetyl benzimidazole 4 was added and continued stirring for 30 min followed by the addition of dimethyl sulphate/benzyl chloride (0.01 mol) in acetonitrile. After completion of the reaction, the solvent was removed in vacuo. The solid separated was dissolved in chloroform (15 ml). The chloroform layer was washed with water (2×250 ml), dried and recrystallized from ethyl acetate to give product 6 in pure form.
2-Bromo-1-(1-alyl-1H-benzof[1,3]imidazol-2-yl)-1-ethanone (7) To a solution of 1-(1-alkyl-1H-benzof[1,3]imidazol-2-yl)-1-ethanones (0.01 mol) in acetic acid (15 ml) at reflux, drop wise added a solution of bromine (0.01 mol) in acetic acid. Then the reaction mixture was maintained under similar conditions for 3 h with constant stirring. After completion of the reaction, the mixture was cooled into room temperature, poured into ice cold water and washed with aq. Sodium bicarbonate solution, dried and recrystallized from ethanol.

4-(1H-Benzof[1,3]imidazol-2-yl)-2,3-dihydro-1,3-thiazol-2-amine (8) To a solution of 2-bromo-1-(1-alkyl-1H-benzof[1,3]imidazol-2-yl)-1-ethanone (7) (0.01 mol) in dimethylformamide (DMF) (20 ml) was added the solution of thiourea (0.01 mol) in DMF (15 ml). The reaction mixture was then stirred at room temperature for 2 h. When the reaction was completed (monitored by TLC), the reaction mixture was poured into ice cold water to separate the product in solid form, dried and recrystallized from ethanol.

1-(1H-Benzof[1,3]imidazol-2-yl)-1-ethanone (3a): Yellow solid, yield 90%, mp 180—182 °C. IR (KBr) cm

1-(1-Benzyl-5-methyl-1H-benzof[1,3]imidazol-2-yl)-1-ethanone (4a): Yellow solid, yield 65%, mp 78—80 °C. IR (KBr) cm

1-(1-Benzyl-5-chloro-1H-benzof[1,3]imidazol-2-yl)-1-ethanone (4d): Colorless solid, yield 62%, mp 78—80 °C. IR (KBr) cm

1-(1-Benzyl-5-methyl-1H-benzof[1,3]imidazol-2-yl)-2-bromo-1-ethanone (5b): Yellow solid, yield 68%, mp 148—150 °C. IR (KBr) cm

1-(1-Benzyl-5-chloro-1H-benzof[1,3]imidazol-2-yl)-2-bromo-1-ethanone (5d): Orange solid, yield 71%, mp 124—126 °C. IR (KBr) cm

1-(1-Benzyl-5-methyl-1H-benzof[1,3]imidazol-2-yl)-1-thio-1,3-thiazol-2-amine (9a): Colorless solid, yield 62%, mp 113—115 °C. IR (KBr) cm

1-(1-Benzyl-5-methyl-1H-benzof[1,3]imidazol-2-yl)-2-thio-1,3-thiazol-2-amine (5c): Yellow solid, yield 62%, mp 115—117 °C. IR (KBr) cm

1-(1-Benzyl-5-methyl-1H-benzof[1,3]imidazol-2-yl)-2-thio-1,3-thiazol-2-amine (5e): Brown solid, yield 80%, mp 116—118 °C. IR (KBr) cm

References