SYNTHESIS, CHARACTERIZATION, AND ANTHELMINTIC ACTIVITY OF NOVEL BENZOTHIAZOLE DERIVATIVES CONTAINING INDOLE MOIETIES

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INTRODUCTION

Heterocyclic compounds are those which have a cyclic structure with two, or more, different kinds of atom in the ring. This two kinds of atoms are like carbon and the other elements (heteroatoms), most often N, O and S. Although the parent compound, benzothiazole is not widely used, many of its derivatives are found in commercial products or in nature[1-3]. Benzothiazole ring found to be possessing pharmacological activities such as antitumor, antitubercular, antimalarial, anticonvulsant, anthelmintic, analgesic, anti inflammatory and antifungal. Isatin or 1H-indole-2, 3-dione is an indole derivative. Indole derivatives have acquired conspicuous significance due to their wide spectrum of biological activities.

In view of the high degree of bioactivity shown by the benzothiazole derivatives mentioned above facts, we aimed to construct a system combining both these vital moieties such as benzothiazole and indole in a single molecular framework, together with an exploration of the additive effects of their biological activities. Hence, we describe here in the synthesis, characterization, and anthelmintic activity (AA) of novel benzothiazole derivatives containing indole moieties (BDIM).

METHODS

The synthesized compounds were screened for anthelmintic activities [4-7]. The IR spectra were recorded on a Shimadzu 8700 spectrometer using the ATR technique (Attenuated Total Reflectance) in the range of 400–4000 cm⁻¹. and values are reported in cm⁻¹ and the spectra were interpreted. "H-nuclear magnetic resonance (NMR) spectra were recorded on DPX-200 MHz NMR spectrometer using dimethyl sulfoxide (DMSO)-d₆, and chemical shifts (δ) are reported in parts per million downfield from internal reference tetramethylsilane ,and the spectra were interpreted. Mass spectra were recorded on mass spectrophotometer (model Shimadzu) by Liquid chromatography–mass spectrometry (LC-MS) and the spectra were interpreted. Precoated silica gel G plates were used to monitor the progress of reaction as well as to check the purity of the compounds: n-Hexane:ethyl acetate (8:2).

General procedures for the preparation of 2-aminobenzothiazole (2-ABT)

Aniline (4.6 g, 0.05 mol) and potassium thiocyanate (3.8 g, 0.05 mol) were dissolved in absolute ethanol containing 4 ml of concentrated hydrochloric acid (HCl). To this mixture, bromine in glacial acetic acid (6.75 ml, 0.125 mol) was added and the reaction mixture was refluxed for 1 h. Then, it was cooled in ice bath. The precipitate obtained was filtered, washed with cold water, and dried. The crude product was recrystallized from ethanol [8].

Synthesis of substituted isatin from aniline

In a round-bottomed flask are placed 9gm of chloral hydrate and 120ml of water. To this solution are then added, in order: 13gm of crystallized sodium sulphate, a solution of 4.5 gm of aniline in 30ml of water to which 5.12 gm of concentrated hydrochloric acid has been added to dissolve the amine and finally, a solution of 1gm of 5 hydrochlorid in 50ml of water. Flask was then heated vigorously until the reaction was completed. After it, the solution containing beaker was cooled in running water followed by the filtration of reminder crystallized product with suction pump and air dried. 18.4 g of dry isonitrosoacetanilide was added in such a rate so as to keep the temperature between 60°C and 70°C but not higher. External cooling was applied at this stage so that the reaction could be carried out more rapidly after the addition of isonitroso compound was finished. The solution was heated to 80°C and kept at this temperature for about 10 min to complete the reaction. Then, the reaction mixture was cooled to room temperature and poured it into 10 times its volume of cracked ice. After standing for 90 min, the final product was filtered with suction pump followed by washing with cold water to remove sulfuric acid and dried in air.
Synthesis of isatin Schiff bases (ISB) (3a-3i)
A mixture of equimolar quantity of substituted aromatic aniline (0.01 mol) and compound 2a-2d was dissolved in 20 ml of ethanol and refluxed for 2–3 h in the presence of few drops of 2 ml glacial acetic acid. The progress of the reaction was monitored by thin-layer chromatography (TLC) (n-Hexane:EtoAc 7:3). The reaction mixture was cooled to room temperature and kept in the refrigerator for overnight to get precipitate. A solid was obtained, which was filtered off and recrystallized from methanol or ethanol to give crystalline solid.\(^9\)

Synthesis of 1-acetyl-3-(phenylimino) indolin-2-one derivatives
A mixture of equimolar (0.01) quantity of compound (3a-3i, ISB) and 5.1 ml of acetic anhydride was taken into a 250 ml round bottom flask. Then, whole of the content was refluxed for about 4 h, and then, the solution was poured into a beaker containing crushed ice followed by the filtration and drying of the product.

General procedure for the synthesis of novel 1-((E)-1-(benzo[d]thiazol-2-yl) imino) ethyl)-3-(phenylimino) indolin-2-one (5a-5o)
A mixture of equimolar quantity of substituted N-acetyl isatin derivatives (0.01 mol) and compound 1a-1b was dissolved in 20 ml of ethanol and refluxed for 2–3 h in the presence of few drops of 2 ml glacial acetic acid. The progress of the reaction was monitored by TLC (n-Hexane:EtoAc 8:2). The reaction mixture was cooled to room temperature and kept in the refrigerator for overnight to get precipitate. A solid was obtained, which was filtered off and recrystallized from methanol or ethanol to give crystalline solid (Fig 1)

5a: (E)-1-((E)-1-(benzo[d]thiazol-2-yl) imino) ethyl)-3-(phenylimino) indolin-2-one
M.P. 219–221°C; Mol. formula: C\(_{23}\)H\(_{16}\)N\(_4\)O\(_5\), yield 78%, IR (\(\nu\) cm\(^{-1}\)): 3143, 3054 (C-H Str, Ar), 2930, 2891, 2793 (C–H Str, Aliphatic), 2311 (C-S-C Str), 1684 (C=O Str, Indole), 1588 (C=N Str), 1515 (C=CH Str), 1431 (C=C Str, Ar), \(^{1}H\)-NMR (DMSO) \(\delta\) ppm: 8.39–8.27 (d, 2H, Ar-H), 8.11–7.88 (d, 2H, Ar-H), 7.84–7.77 (t, 3H, Ar-H), 7.69–7.67 (d, 2H, Ar-H), 7.55–7.54 (d, 2H, Ar-H), 7.51–7.41 (t, 3H, Ar-H). 3.33 (s, 3H, -CH\(_3\)). Mass (ESI-MS): m/z 396 (M), 397 (M+1, 100%).

5b: (E)-5-chloro-1-((E)-1-(benzo[d]thiazol-2-yl) imino) ethyl)-3-(phenylimino) indolin-2-one
M.P. 213-215°C; Mol. formula: C\(_{23}\)H\(_{15}\)N\(_4\)O\(_5\)Cl, yield 82%, IR (\(\nu\) cm\(^{-1}\)): 3037, 2932 (C-H Str, Ar), 2872 (C–H Str, Aliphatic), 2346 (C-S-C Str), 1721 (C=O Str; Indole), 1555 (C=N Str), 1520 (C=CH Str), 1432 (C=C Str, Ar).771 (C=Cl Str, Ar). \(^{1}H\)-NMR (DMSO) \(\delta\) ppm: 8.37–8.28 (t, 3H, Ar-H), 7.86–7.84 (t, 3H, Ar-H), 8.10 (s, 1H, Ar-H), 7.83–7.68 (d, 4H, Ar-H), 7.58–7.57 (d, 2H, Ar-H), 7.55–7.51 (d, 2H, Ar-H). 3.39 (s, 3H, -CH\(_3\)). Mass (ESI-MS): m/z 430 (M), 431 (M+1, 100%), 432 (M+2, 30%).

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Fig. 1: Synthetic scheme
Table 1: Antihelmintic activity of BDIM

<table>
<thead>
<tr>
<th>S. No</th>
<th>Name</th>
<th>Concentration</th>
<th>Time (min)</th>
<th>For paralysis % concentration</th>
<th>For death % concentration</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.1</td>
<td>0.2</td>
<td>0.5</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control</td>
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<td></td>
<td>15±0.121</td>
<td>12±0.053</td>
<td>8±0.043</td>
</tr>
<tr>
<td>1</td>
<td>AB</td>
<td></td>
<td>19±0.23</td>
<td>15±0.092</td>
<td>18±0.120</td>
</tr>
<tr>
<td>2</td>
<td>5a</td>
<td></td>
<td>31±0.129</td>
<td>23±0.120</td>
<td>19±0.124</td>
</tr>
<tr>
<td>3</td>
<td>5b</td>
<td></td>
<td>26±0.031</td>
<td>24±0.135</td>
<td>20±0.132</td>
</tr>
<tr>
<td>4</td>
<td>5d</td>
<td></td>
<td>23±0.051</td>
<td>21±0.171</td>
<td>18±0.141</td>
</tr>
<tr>
<td>5</td>
<td>5e</td>
<td></td>
<td>22±0.021</td>
<td>19±0.093</td>
<td>18±0.021</td>
</tr>
<tr>
<td>6</td>
<td>5f</td>
<td></td>
<td>25±0.134</td>
<td>16±0.122</td>
<td>15±0.031*</td>
</tr>
<tr>
<td>7</td>
<td>5g</td>
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<td>23±0.028</td>
<td>21±0.128</td>
<td>20±0.154</td>
</tr>
<tr>
<td>8</td>
<td>5h</td>
<td></td>
<td>18±0.132</td>
<td>18±0.053</td>
<td>16±0.120</td>
</tr>
<tr>
<td>9</td>
<td>5i</td>
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<td>25±0.032</td>
<td>20±0.120</td>
<td>19±0.032</td>
</tr>
<tr>
<td>10</td>
<td>5j</td>
<td></td>
<td>24±0.053</td>
<td>20±0.120</td>
<td>17±0.120</td>
</tr>
<tr>
<td>11</td>
<td>5k</td>
<td></td>
<td>20±0.125</td>
<td>21±0.065</td>
<td>14±0.054</td>
</tr>
<tr>
<td>12</td>
<td>5l</td>
<td></td>
<td>23±0.043</td>
<td>23±0.125</td>
<td>15±0.132</td>
</tr>
<tr>
<td>13</td>
<td>5m</td>
<td></td>
<td>19±0.063</td>
<td>19±0.122</td>
<td>15±0.120</td>
</tr>
<tr>
<td>14</td>
<td>5n</td>
<td></td>
<td>18±0.063</td>
<td>15±0.043*</td>
<td>10±0.131*</td>
</tr>
<tr>
<td>15</td>
<td>5o</td>
<td></td>
<td>17±0.415</td>
<td>14±0.043*</td>
<td>11±0.132</td>
</tr>
</tbody>
</table>

All the results were shown in table and expressed as a mean±SEM of six worms in each group, BDIM: Benzothiazole derivatives containing indole moiety.

SEM: Standard error of mean, AB: Albendazole

Table 2: Physical data of compounds 4a-4i

<table>
<thead>
<tr>
<th>S. Code</th>
<th>M. for.</th>
<th>R</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>M. Wt.</th>
<th>M. P (°C)</th>
<th>% Yield</th>
<th>R&lt;sub&gt;1&lt;/sub&gt; value</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>C₆H₅N₂O₂</td>
<td>H</td>
<td>H</td>
<td>264.09</td>
<td>137–139</td>
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<tr>
<td>4b</td>
<td>C₆H₅N₂O₂</td>
<td>Cl</td>
<td>H</td>
<td>298</td>
<td>181–183</td>
<td>72</td>
<td>0.82</td>
</tr>
<tr>
<td>4c</td>
<td>C₆H₅N₂O₂</td>
<td>CH₃</td>
<td>H</td>
<td>278</td>
<td>193–195</td>
<td>68</td>
<td>0.63</td>
</tr>
<tr>
<td>4d</td>
<td>C₆H₅N₂O₂Cl</td>
<td>Cl</td>
<td>H</td>
<td>312</td>
<td>153–155</td>
<td>75</td>
<td>0.59</td>
</tr>
<tr>
<td>4e</td>
<td>C₆H₅N₂O₂</td>
<td>CH₃</td>
<td>H</td>
<td>278</td>
<td>186–188</td>
<td>82</td>
<td>0.73</td>
</tr>
<tr>
<td>4f</td>
<td>C₆H₅N₂O₂</td>
<td>CH₂</td>
<td>H</td>
<td>292</td>
<td>187–189</td>
<td>80</td>
<td>0.72</td>
</tr>
<tr>
<td>4g</td>
<td>C₆H₅N₂O₂</td>
<td>4-N₂H</td>
<td>H</td>
<td>309</td>
<td>225–227</td>
<td>76</td>
<td>0.57</td>
</tr>
<tr>
<td>4h</td>
<td>C₆H₅N₂O₂</td>
<td>3-N₂H</td>
<td>CH₃</td>
<td>323</td>
<td>183–185</td>
<td>74</td>
<td>0.63</td>
</tr>
<tr>
<td>4i</td>
<td>C₆H₅N₂O₂Cl</td>
<td>Cl</td>
<td>H</td>
<td>298</td>
<td>167–169</td>
<td>69</td>
<td>0.57</td>
</tr>
</tbody>
</table>

S. Code: Sample code, M. for.: Molecular formula, M. wt.: Molecular weight, M. P: Melting point
The synthesized compounds (5a-5o) were evaluated for AA on Indian earthworms (Pheretima posthuma). All compounds showed that AA is shown in Table 1. A closer inspiration of data from this table indicated that the synthesized compounds 5f, 5n, and 5o showed good AA, whereas others showed significant activities. After all, the synthesized compounds in overall estimation confirm the better activity against P. posthuma. The results are shown in Figs. 2 and 3.

The statistical analyses were carried out using one-way analysis of variance (Dunnett’s test) at a 95% confidence interval, and all the activity data on comparison with vehicle control reach statistical significance with p<0.05 (Fig. 4).

### Table 3: Physical data of compounds 5a-5o

<table>
<thead>
<tr>
<th>S. Code</th>
<th>M. for.</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>M. Wt.</th>
<th>M. P</th>
<th>% Yield</th>
<th>Rf</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>C₄H₂N₂O₂S</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>396</td>
<td>219–221</td>
<td>78</td>
<td>0.63</td>
</tr>
<tr>
<td>5b</td>
<td>C₄H₂N₂O₂S</td>
<td>H</td>
<td>H</td>
<td>Cl</td>
<td>H</td>
<td>430</td>
<td>213–215</td>
<td>82</td>
<td>0.76</td>
</tr>
<tr>
<td>5c</td>
<td>C₄H₂N₂O₂S</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>CH₃</td>
<td>410</td>
<td>203–205</td>
<td>77</td>
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</tr>
<tr>
<td>5d</td>
<td>C₄H₂N₂O₂S</td>
<td>H</td>
<td>H</td>
<td>Cl</td>
<td>CH₃</td>
<td>444</td>
<td>231–233</td>
<td>66</td>
<td>0.61</td>
</tr>
<tr>
<td>5e</td>
<td>C₄H₂N₂O₂S</td>
<td>H</td>
<td>H</td>
<td>CH₂</td>
<td>H</td>
<td>410</td>
<td>191–193</td>
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<tr>
<td>5f</td>
<td>C₄H₂N₂O₂S</td>
<td>H</td>
<td>H</td>
<td>CH₃</td>
<td>CH₃</td>
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<td>217–219</td>
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<tr>
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<td>H</td>
<td>H</td>
<td>NO₂</td>
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</tr>
<tr>
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<td>H</td>
<td>H</td>
<td>H</td>
<td>Cl</td>
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<td>231–233</td>
<td>81</td>
<td>0.51</td>
</tr>
<tr>
<td>5i</td>
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<td>Cl</td>
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<td>H</td>
<td>H</td>
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<td>231–233</td>
<td>80</td>
<td>0.59</td>
</tr>
<tr>
<td>5j</td>
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<td>CH₃</td>
<td>H</td>
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<td>F</td>
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<td>CH₃</td>
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S. Code: Sample code, M. for.: Molecular formula, M. wt.: Molecular weight, M. P: Melting point, Rf: Rf value

benzothiazole (2-ABT). The substituted ISBs undergo acetylation and react with 2-ABT to give novel BDIM. The physical data results are shown in Tables 2 and 3. The synthesized compounds were screened for AA. The structures of all the newly synthesized compounds were characterized as 5a-5o on the basis of satisfactory analytical and spectral data including IR, LC-Mass, and 1H NMR data.

AA

The synthesized compounds (5a-5o) were evaluated for AA on Indian earthworms (Pheretima posthuma). All compounds showed that...
CONCLUSION

The present study highlights the importance of benzothiazole derivatives having various heterocyclic moiety features responsible for the AA and may serve as a lead molecule for further modification to obtain clinically useful novel entities. The AA of all the synthesized compounds showed moderate activity.

AUTHORS’ CONTRIBUTIONS

The corresponding author has done all the work, interpreted the data, and written the manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES


Fig. 4: Photographs of various benzothiazole derivatives - Anthelmintic activities