Synthesis of symmetrically / unsymmetrically substituted bisbenzimidazolesulphides of potential pharmacological interest

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Results and Discussion

2-(1-Chloroethyl)-1H-benzimidazole 1a (i.e., 1, R=H) on condensation with 2-mercaptobenzimidazole 2a in methanol using triethylamine (TEA) as a base under reflux for 3 hr gave the previously reported7 2-((1-(1H-benzimidazol-2-yl)ethyl)thio)-1H-benzimidazole 3a. Compound 3a on methylation using two equivalents of dimethylsulphate with dimethylformamide (DMF) as solvent and K2CO3 as a base using tetrabutylammonium bromide (TBAB) as PTC at RT for 3 hr gave N,N′-dimethylbisbenzimidazole sulphide 3b. Using this strategy, the reactions of 3a was also performed with two equivalents each of diethyl sulphate, benzyl chloride and n-butyl bromide to obtain N,N′-diethylbisbenzimidazolesulphide 3c, N,N′-dibenzylbisbenzimidazolesulphide 3d and N,N′-dibutylbisbenzimidazolesulphide 3e respectively. The structures of 3b-e have been assigned on the basis of their spectral and analytical data (please see Experimental Section for details).

Compound 3b (i.e., 3, R=R′=methyl) was also synthesized by condensing N-methyl-2-chloromethylbenzimidazole 1b (i.e., 1, R=CH3) with 2-(1-chloroethyl)-1-methylbenzimidazole 2b in methanol using TEA as a base under refluxing conditions for 3 hr (Scheme I). Similarly, 3c, 3d and 3e were also synthesized by the condensation of N-ethyl-2-mercaptobenzimidazole 2c, N-benzyl-2-mercaptobenzimidazole 2d and N-n-butyl-2-mercapto benzimidazole 2e with the corresponding 2-(1-chloroethyl)-1-ethylbenzimidazole 1c, 2-(1-chloroethyl)-1-benzylbenzimidazole 1d and 2-(1-chloroethyl)-1-n-butylbenzimidazole 1e respectively. The products obtained above have been found to be identical with reported sample with respect to m.p. and TLC (Table I).

Using this protocol, N,N′-unsymmetrically disubstituted derivatives 3f-q were prepared as follows: Condensation of 2-(1-chloroethyl)-1-methylbenzimidazole 1b with 2-mercaptobenzimidazole 2a gave 3r. Compound 3r when subjected to ethylation under PTC conditions gave 3f. Similarly, 3g was synthesized by condensing 2-(1-chloroethyl)-1-methylbenzimidazole 1b with 2-mercaptobenzimidazole 2a to
of IR, of other compounds could also be prepared. The structures of 3a-e were characterized by their physical data, such as melting points and IR spectra.

**Experimental Section**

Melting points were determined in open capillaries in sulfuric acid bath and are uncorrected. Thin-layer chromatography (TLC) were performed on pre-coated silica gel glass plates GF-254. IR spectra were recorded on a Jasco FT-IR 5300 spectrometer. 

**Preparation of 3b-e from 3a**

A mixture of 3a (0.14 g, 5 mM), K$_2$CO$_3$ (1.3 g, 10 mM), TBAB (10 mg), DMF (20 mL) and two equivalents of appropriate alkylating agent were stirred at RT for 3 hr. At the end of this period, the reaction mixture was poured into ice-cold water. The separated solid was filtered, washed with water (2×10 mL) and dried to obtain crude 3b-e which on recrystallization from a suitable solvent gave pure 3b-e.

**Table I — Physical characterization data of the synthesized compounds 3a-e**

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Substrate</th>
<th>Alkylating agent</th>
<th>Product</th>
<th>Yield (%)</th>
<th>m.p. (°C)</th>
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<tr>
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<td>–</td>
<td>3a</td>
<td>86</td>
<td>294</td>
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<td>2</td>
<td>3</td>
<td>DMS</td>
<td>3b</td>
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<td>3</td>
<td>PhCH$_3$-Cl</td>
<td>3e</td>
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<tr>
<td>5</td>
<td>3</td>
<td>n-BuBr</td>
<td>3e</td>
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**Preparation of 3f-q from 3a** (R=R'=H)

A mixture of 3a (0.14 g, 5 mM), K$_2$CO$_3$ (1.3 g, 10 mM), TBAB (10 mg), DMF (20 mL) and two equivalents of appropriate alkylating agent were stirred at RT for 3 hr. At the end of this period, the reaction mixture was poured into ice-cold water. The separated solid was filtered, washed with water (2×10 mL) and dried to obtain crude 3f-q which on recrystallization from a suitable solvent gave pure 3f-q.

**Table II — Physical characterization data of the synthesized compounds 3f-q**

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Starting materials used</th>
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<th>Yield (%)</th>
<th>m.p. (°C)</th>
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<tr>
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<td>1b</td>
<td>2d</td>
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<td>3</td>
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<td>2e</td>
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<td>286</td>
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<tr>
<td>4</td>
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<td>2b</td>
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<td>5</td>
<td>1c</td>
<td>2d</td>
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<td>6</td>
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<td>2e</td>
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<td>2d</td>
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<td>12</td>
<td>2e</td>
<td>2d</td>
<td>68</td>
<td>269</td>
</tr>
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Thus, 3d, 3e, 3f-q (Table II) have been established on the basis of IR, 1H NMR and LC-MS (Q+1) spectral data.
1-Benzyl-2-((1-(1-benzyl-1H-benzimidazol-2-yl)-ethyl)thio)-1H-benzimidazole, 3d: IR (KBr): No diagnostic peak in IR region 3500 – 3000 cm⁻¹, indicating absence of-NH group; ¹H NMR (400 MHz, DMSO-d₆ / TMS): δ 1.72 (d, 3H,-CH(CH₃)₂), 3.89 (m, 1H,-CH(CH₃)₂), 4.69 (s, 2H,-NCH₂ of benzyl of –CH₂CH₃Bz), 5.25 (s, 2H, NCH₂ of benzyl of-SBz), 7.27-8.36 (complex, m, 18H, 10 aromatic benzyl + 8H aryl protons); MS (Cl): m/z 475 [M⁺+1].

1-(n-Butyl)-2-((1-(n-butyl)-1H-benzimidazol-2-yl)ethyl)thio)-1H-benzimidazole, 3e: IR (KBr): No diagnostic peak in IR region 3500 – 3000 cm⁻¹, indicating absence of-NH group; ¹H NMR (400 MHz, DMSO-d₆ / TMS): δ 1.26 (t, 2H,-NCH₂ of butyl of –CH₂CH₃Bz), 1.65 (m, 2H,-NCH₂CH₂CH₃ of butyl of –CH₂CH₃Bz), 1.70 (d, 3H,-CH(CH₃)₂), 2.54 (m, 2H,-NCH₂CH₂CH₃ of butyl of –CH₂CH₃Bz), 3.72 (t, 3H,-NCH₂CH₂CH₃ of butyl of –CH₂CH₃Bz), 1.45 (t, 2H,-NCH₂ of butyl of SBz), 1.79 (m, 2H,-NCH₂CH₂CH₃ of butyl of –SBz), 2.68 (m, 2H,-NCH₂CH₂CH₃ of butyl of –SBz), 3.85 (t, 3H,-NCH₂CH₂CH₃ of butyl of –SBz), 6.68-7.68 (complex, m, 8H, aryl protons), 3.92 (m, 1H,-CH(CH₃)₂); MS (Cl): m/z 407 [M⁺+1].

Alternative procedure for preparation of 3b-e
A mixture of 1 (R=alkyl) (0.87 g, 5 mM), 2 (R²=alkyl) (0.95 g, 5 mM), methanol (20 mL) and TEA (0.46 mL) was refluxed for 3 hr. At the end of this period, the reaction mixture was poured into iced-cold water. The separated solid was filtered, washed and dried to obtain crude 3b-e which on recrystallization from a suitable solvent gave pure 3b-e.

General Procedure for the preparation of 3f-q from 3 (R=H, R¹=alkyl) / 3 (R=alkyl, R²=H)
A mixture of 3 (R=H, R¹=alkyl) / 3 (R=alkyl, R²=H) (0.14 g, 5 mM), KO₂CO₃ (1.6 g, 10 mM), TBAB (10 mg), DMF (20 mL) and alkylating agent (5 mM) was stirred at RT for 3 hr. At the end of this period, the reaction mixture was poured into iced-cold water. The separated solid was filtered, washed with water and dried to obtain crude 3f-q which on recrystallization from ethyl acetate gave pure 3f-q.

1-Ethyl-2-((1-(1-methyl-1H-benzimidazol-2-yl)-ethyl)thio)-1H-benzimidazole, 3f: IR (KBr): No diagnostic peak in IR region 3500 – 3000 cm⁻¹, indicating absence of-NH group; ¹H NMR (400 MHz, DMSO-d₆ / TMS): δ 3.65 (s, 3H,-NCH₃ of-CH₂CH₃Bz), 1.68 (m, 2H,-NCH₂ of ethyl of –SBz), 3.94 (t, 3H,-CH₃ of ethyl of –SBz), 6.65-7.64 (complex, m, 8H, aryl protons), 1.74 (d, 3H,-CH(CH₃)₂), 3.91 (m, 1H,-CH(CH₃)₂); MS (Cl): m/z 337 [M⁺+1].

1-Benzyl-2-((1-(1-methyl-1H-benzimidazol-2-yl)-ethyl)thio)-1H-benzimidazole 3g: IR (KBr): No diagnostic peak in IR region 3500 – 3000 cm⁻¹, indicating absence of-NH group; ¹H NMR (400 MHz, DMSO-d₆ / TMS): δ 3.70 (s, 3H,-NCH₃ of-CH₂CH₃Bz), 4.62 (s, 2H,-NCH₂ of benzyl of SBz), 7.22-8.58 (complex, m, 13H, 5H aromatic benzyl + 8H aryl protons), 1.65 (d, 3H,-CH(CH₃)₂), 3.85 (m, 1H,-CH(CH₃)₂); MS (Cl): m/z 399 [M⁺+H⁺].

1-Butyl-2-((1-(1-methyl-1H-benzimidazol-2-yl)-ethyl)thio)-1H-benzimidazole 3h: IR (KBr): No diagnostic peak in IR region 3500 – 3000 cm⁻¹, indicating absence of-NH group; ¹H NMR (400 MHz, DMSO-d₆ / TMS): δ 3.56 (s, 3H,-NCH₃ of-CH₂CH₃Bz), 1.32 (t, 2H,-NCH₂ of butyl of –SBz), 1.65 (m, 2H,-NCH₂ of butyl of –SBz), 2.54 (m, 2H,-NCH₂CH₂CH₃ of butyl of –SBz), 3.68 (t, 3H,-NCH₂CH₂CH₃ of butyl of –SBz), 6.69-7.68 (complex, m, 8H, aryl protons), 1.70 (d, 3H,-CH(CH₃)₂), 3.88 (q, 1H,-CH(CH₃)₂); MS (Cl): m/z 365 [M⁺+1].

1-Ethyl-2-((1-(1-methyl-1H-benzimidazol-2-yl)-ethyl)thio)-1H-benzimidazole 3i: No diagnostic peak in IR region 3500 – 3000 cm⁻¹, indicating absence of-NH group; ¹H NMR (400 MHz, DMSO-d₆ / TMS): δ 1.54 (m, 2H,-NCH₂ of ethyl of-CH₂CH₃Bz), 3.76 (t, 3H,-CH₃ of ethyl of-CH₂CH₃Bz), 3.53 (s, 3H,-NCH₃ of-SBz), 6.65-7.58 (complex, m, 8H, aryl protons), 1.69 (d, 3H,-CH(CH₃)₂), 3.78 (q, 1H,-CH(CH₃)₂); MS (Cl): m/z 413 [M⁺+1].

1-Benzyl-2-((1-(1-ethyl-1H-benzimidazol-2-yl)-ethyl)thio)-1H-benzimidazole 3j: No diagnostic peak in IR region 3500 – 3000 cm⁻¹, indicating absence of-NH group; ¹H NMR (400 MHz, DMSO-d₆ / TMS): δ 1.50 (m, 2H,-NCH₂ of ethyl of-CH₂CH₃Bz), 3.80 (t, 3H,-CH₃ of ethyl of-CH₂CH₃Bz), 4.65 (s, 2H,-NCH₂ of benzyl of SBz), 7.22-8.19 (complex, m, 13H, 5H aromatic benzyl + 8H aryl protons), 1.79 (d, 3H,-CH(CH₃)₂), 3.85 (q, 1H,-CH(CH₃)₂); MS (Cl): m/z 413 [M⁺+1].

1-Butyl-2-((1-(1-ethyl-1H-benzimidazol-2-yl)-ethyl)thio)-1H-benzimidazole 3k: No diagnostic peak in IR region 3500 – 3000 cm⁻¹, indicating absence of-NH group; ¹H NMR (400 MHz, DMSO-d₆ / TMS): δ 1.55 (m, 2H,-NCH₂ of ethyl of-CH₂CH₃Bz), 3.80 (t, 3H,-CH₃ of ethyl of-CH₂CH₃Bz), 1.38 (t, 2H,-NCH₂ of butyl of –SBz), 1.68 (m, 2H,-NCH₂CH₂ of butyl of –SBz), 2.59 (m, 2H,-NCH₂CH₂CH₃ of butyl of –SBz), 3.72 (t, 3H,-NCH₂CH₂CH₂CH₃ of butyl of –SBz), 6.65-7.62 (complex, m, 8H, aryl protons), 1.82 (d, 3H,-CH(CH₃)₂), 3.96 (m, 1H,-CH(CH₃)₂); MS (Cl): m/z 379 [M⁺+1].
1-Benzyl-2-((1-(1-methyl-1'H-benzimidazol-2-yl)-thio)ethyl)-1'H-benzimidazole 3f: No diagnostic peak in IR region 3500 – 3000 cm\(^{-1}\), indicating absence of -NH group; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)/TMS): \(\delta\) 4.88 (s, 2H, -NCH\(_2\) benzyl of -CHCH\(_3\)), 1.67 (m, 2H, -CHCH\(_3\) of ethyl of -SBz), 7.30-8.26 (complex, m, 13H, 5H aromatic benzyl + 8H aryl protons), 1.79 (d, 3H, -CHCH\(_3\)), 3.76 (m, 1H, -CHCH\(_3\)); MS (Cl): \(m/z\) 441 [M\(^+\)+1].

1-Benzyl-2-(1-((1-ethyl-1'H-benzimidazol-2-yl)-thio)ethyl)-1'H-benzimidazole 3m: No diagnostic peak in IR region 3500 – 3000 cm\(^{-1}\), indicating absence of -NH group; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)/TMS): \(\delta\) 4.82 (s, 2H, -NCH\(_2\) benzyl of -CHCH\(_3\)), 1.65 (m, 2H, -NCH\(_2\) of ethyl of -SBz), 3.90 (t, 3H, -CHCH\(_3\) of ethyl of -SBz) 7.30-8.34 (complex, m, 13H, 5H aromatic benzyl + 8H aryl protons), 1.65 (d, 3H, -CHCH\(_3\)), 3.98 (m, 1H, -CHCH\(_3\)); MS (Cl): \(m/z\) 413 [M\(^+\)+1].

1-Benzyl-2-(1-(1-butyl-1'H-benzimidazol-2-yl)-thio)ethyl)-1'H-benzimidazole 3n: No diagnostic peak in IR region 3500 – 3000 cm\(^{-1}\), indicating absence of -NH group; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)/TMS): \(\delta\) 1.35 (t, 2H, -NCH\(_2\) of butyl of -CHCH\(_3\)), 1.67 (m, 2H, -NCH\(_2\)CH\(_2\) of butyl of -SBz), 2.56 (m, 2H, -NCH\(_2\)CH\(_2\)H of butyl of -SBz), 3.70 (t, 3H, -NCH\(_2\)CH\(_2\)CH\(_3\) of butyl of -SBz), 6.62-7.62 (complex, m, 8H, aryl protons), 1.48 (d, 3H, -CHCH\(_3\)), 3.32 (m, 1H, -CHCH\(_3\)); MS (Cl): \(m/z\) 441 [M\(^+\)+1].

1-Butyl-2-(1-(1-methyl-1'H-benzimidazol-2-yl-thio)ethyl)-1'H-benzimidazole 3o: No diagnostic peak in IR region 3500 – 3000 cm\(^{-1}\), indicating absence of -NH group; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)/TMS): \(\delta\) 1.41 (s, 2H, -NCH\(_2\) benzyl of -CHCH\(_3\)), 1.65 (m, 2H, -NCH\(_2\)CH\(_2\) of butyl of -CHCH\(_3\)), 2.56 (m, 2H, -NCH\(_2\)CH\(_2\)H of butyl of -SBz), 3.70 (t, 3H, -NCH\(_2\)CH\(_2\)CH\(_3\) of butyl of -SBz), 6.62-7.62 (complex, m, 8H, aryl protons), 1.58 (d, 3H, -CHCH\(_3\)), 3.49 (m, 1H, -CHCH\(_3\)); MS (Cl): \(m/z\) 365 [M\(^+\)+1].

1-Butyl-2-(1-(1-ethyl-1'H-benzimidazol-2-yl-thio)-ethyl)-1'H-benzimidazole 3p: No diagnostic peak in IR region 3500 – 3000 cm\(^{-1}\), indicating absence of -NH group; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)/TMS): \(\delta\) 1.35 (t, 2H, -NCH\(_2\) of butyl of -CHCH\(_3\)), 1.67 (m, 2H, -NCH\(_2\)CH\(_2\) of butyl of -CHCH\(_3\)), 2.56 (m, 2H, -NCH\(_2\)CH\(_2\)H of butyl of -SBz), 3.70 (t, 3H, -NCH\(_2\)CH\(_2\)CH\(_3\) of butyl of -SBz), 6.62-7.62 (complex, m, 8H, aryl protons), 1.66 (d, 3H, -CHCH\(_3\)), 3.87 (m, 1H, -CHCH\(_3\)); MS (Cl): \(m/z\) 379 [M\(^+\)+1].

1-Benzyl-2-((1-(1-butyl-1'H-benzimidazol-2-yl)-thio)ethyl)-1'H-benzimidazole 3q: No diagnostic peak in IR region 3500 – 3000 cm\(^{-1}\), indicating absence of -NH group; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)/TMS): \(\delta\) 1.35 (t, 2H, -NCH\(_2\) benzyl of -CHCH\(_3\)), 1.67 (m, 2H, -NCH\(_2\)CH\(_2\) of butyl of -CHCH\(_3\)), 2.56 (m, 2H, -NCH\(_2\)CH\(_2\)H of butyl of -CHCH\(_3\)), 3.70 (t, 3H, -NCH\(_2\)CH\(_2\)CH\(_3\) of butyl of -CHCH\(_3\)), 4.82 (s, 2H, -NCH\(_2\) benzyl of -SBz)), 7.30-8.26 (complex, m, 13H, 5H aromatic benzyl + 8H aryl protons), 1.79 (d, 3H, -CHCH\(_3\)), 3.76 (m, 1H, -CHCH\(_3\)); MS (Cl): \(m/z\) 441 [M\(^+\)+1].

Alternative route for preparation of 3f-q
A mixture of N-alkyl-2-chloromethylbenzimidazolide (1, R=alkyl) (0.95g, 5 mmole), N-alkyl-2-mercaptobenzimidazole 2 (R'=alkyl) (5 mM), in methanol using TEA as a base under reflux for 3 hr gave 3f-q. Compound 3f-q was found to be identical in m.p., m.m.p. and TLC with the corresponding derivatives prepared earlier in the route 3 (R=H, R'=alkyl) / 3 (R=alkyl, R'=H) to 3f-q.

Conclusion
A mild and simple method for the synthesis of a variety of symmetrical/unsymmetrical substituted bisbenzimidazole sulphides has been developed. The synthesized compounds have been found to have significant biological activity.

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References


