

## Synthesis of new *N*-[3-(Benzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene] substituted benzamides

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**Abstract:** A series of novel *N*-[3-(2-benzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene] substituted benzamides (**2a–k**) were efficiently synthesized by heterocyclization of the corresponding 1-(benzo[d]thiazol-2-yl)-3-arylothioureas (**1a–k**). The cyclization was achieved by the reaction of  $\alpha$ -bromoacetone produced in situ using bromine in dry acetone in the presence of triethylamine.

**Key words:** *N*-[3-(2-Benzothiazolyl)-4-methylthiazol-2(3H)-ylidene] substituted benzamides, 1-(benzo[d] thiazol-2-yl)-3-arylothioureas, 2-aminobenzothiazoles

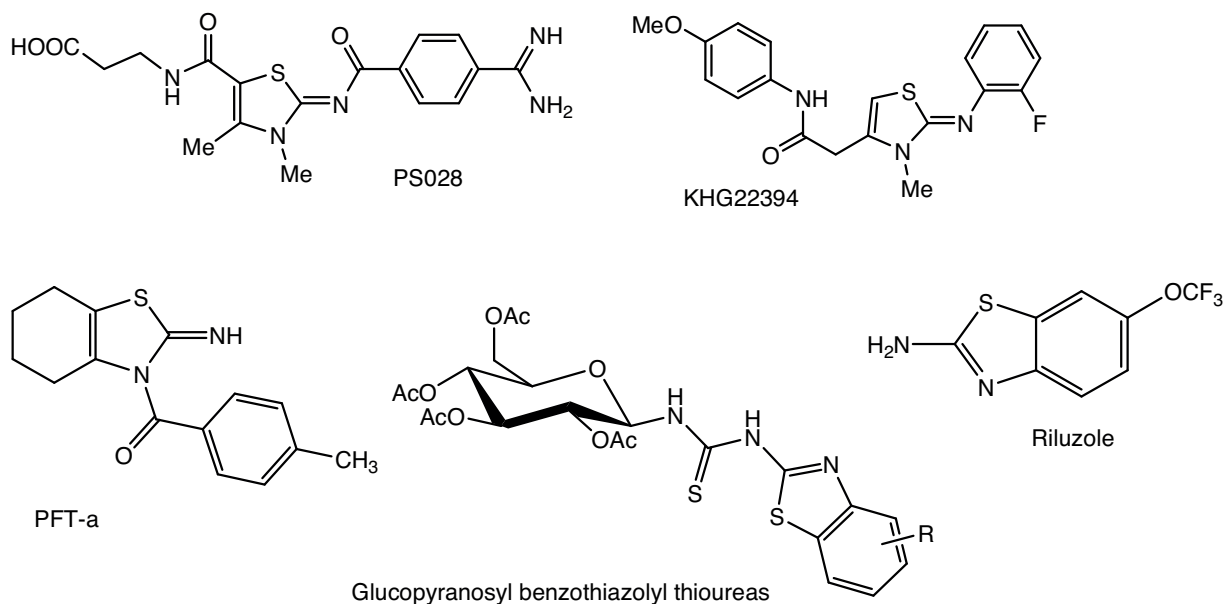
### 1. Introduction

The 2-iminothiazoline scaffold is found in many bioactive heterocycles, which have a wide variety of pharmaceutical applications such as analgesic, antipyretic, antirheumatic,<sup>1</sup> anti-*Schistosomiasis*,<sup>2</sup> and anti-HIV activities.<sup>3–5</sup> Bis-thiazoline derivatives are potent antitumor,<sup>6,7</sup> antihistaminic,<sup>8</sup> antihypertensive,<sup>9</sup> hypnotic,<sup>10</sup> and antimycobacterial and potent antibacterial agents.<sup>11,12</sup> Coumarin derivatives of thiazolines display significant anticonvulsant activities against PTZ-induced seizures.<sup>13,14</sup> Thiazoline analogues also inhibit the enzyme indoleamine-*N*-methyltransferase and are useful for the treatment of schizophrenia.<sup>15</sup> Pifithrin- $\alpha$  (PFT- $\alpha$ ), a reversible inhibitor of p53-mediated apoptosis and p53-dependent gene transcription, is another well-known iminothiazoline derivative.<sup>16</sup> *N*'-[3,4-disubstituted-1,3-thiazol-2(3H)-ylidene]-2-(pyrazin-2-yl)oxy)aceto-hydrazide derivatives exhibit remarkable activity against the (H37 Rv) strain of *Mycobacterium tuberculosis*.<sup>17</sup>

Similarly, 2-aminobenzothiazole is a privileged structure and different derivatives have been used for the treatment of diabetes,<sup>18</sup> epilepsy,<sup>19</sup> inflammation,<sup>20</sup> amyotrophic lateral sclerosis,<sup>21</sup> analgesia,<sup>22</sup> tuberculosis,<sup>23</sup> and viral infections,<sup>24</sup> and as central muscle relaxants.<sup>25</sup> 6-(Trifluoromethoxy)-2-benzothiazolamine (Riluzole) possesses potent anticonvulsant and neuroprotective effects (Figure).<sup>26,27</sup>

In view of the above observations, in this study, we report an efficient synthesis of some new *N*-(4-methyl-3-tolylthiazol-2(3H)-ylidene) substituted benzamides containing these 2 important heterocycles in a single molecule. We envisioned 2 points of structural diversity in our target molecule (R and R' on aromatic rings) for systematic evaluation of biological activities and establishment of the structure–activity relationship (SAR) in depth.

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**Figure.** Structures of some pharmacologically important iminothiazolines and aminothiazoles reported in the literature.

## 2. Experimental

Melting points were recorded using a digital Gallenkamp (SANYO) model MPD.BM 3.5 apparatus and are uncorrected.  $^1\text{H}$  NMR (300 MHz) and  $^{13}\text{C}$  NMR (75 MHz) spectra were recorded using a Bruker AM-300 spectrophotometer. FTIR spectra were recorded on an FTS 3000 MX spectrophotometer. Mass spectra (EI, 70 eV) were recorded on a GC-MS instrument (Agilent Technologies) and elemental analyses were conducted using a LECO-183 CHNS analyzer. Thin layer chromatography (TLC) was conducted on 0.25-mm silica gel plates (60 F254, Merck). Visualization of chromatograms was performed with UV at 365 and 254 nm.

1-(Benzo[d]thiazol-2-yl)-3-aryl thioureas were prepared according to a method reported earlier.<sup>28</sup>

### 2.1. General procedures for the synthesis of N-[3-(benzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene] substituted benzamides (2a–k)

A solution of 1-(benzo[d]thiazol-2-yl)-3-aryl thioureas (**1a–k**) (3 mmol) in 20 mL of dry acetone was stirred under inert atmosphere. Triethylamine (3 mmol) was added dropwise through the rubber septum using a syringe (3 mL), and then a solution of bromine (3 mmol) in dry acetone (10 mL) was added slowly. The reaction mixture was allowed to stir for 3–4 h. After completion (monitored by TLC), the reaction mixture was filtered and the filtrate was concentrated to get crude N-[3-(benzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene] substituted benzamides (**2a–k**), which were then recrystallized from ethanol to afford pure products.

#### N-[3-(Benzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene] benzamide (**2a**)

(Yield: 70%).  $R_f$  0.4 (ethyl acetate/hexane, 2:8). mp 97–98 °C. IR (KBr)  $\nu_{max}$ : 2926 (C=C-H), 2832 (-CH<sub>3</sub>), 1678 (amide C=O), 1582 (C=N), 1558 (C=C), 1461 (C-N), 1168 (C-S)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) $\delta$  (ppm): 8.12 (1H, d,  $J = 7.6$  Hz, H-4'), 8.06 (1H, d,  $J = 7.6$  Hz, H-7'), 7.61–7.94 (5H, m, Ar), 7.57 (1H, dd,  $J = 7.2, 7.4$  Hz, H-5'), 7.34 (1H, dd,  $J = 7.1, 7.4$  Hz, H-6'), 6.44 (1H, s, C=C-H, ring H-5), 2.23 (-CH<sub>3</sub>).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) $\delta$  (ppm): 166.5 (C-2'), 165.3 (amide C=O), 162.4 (C-2), 151.3 (C-4),

146.3 (C-9'), 136.7 (C-1''), 134.5 (C-2'', C-6''), 133.4 (C-3'', C-5''), 128.2 (C-4''), 127.4 (C-6'), 125.6 (C-5'), 124.3 (C-8'), 123.7 (C-4'), 122.5 (C-7'), 101.6 (C-5), 15.4 (-CH<sub>3</sub>). Anal. calcd. for C<sub>18</sub>H<sub>13</sub>N<sub>3</sub>OS<sub>2</sub> (351.45); C, 61.53; H, 3.70; N, 11.96; S, 18.23. Found: C, 61.47; H, 3.51; N, 11.83; S, 18.14. MS (70 eV): *m/z* (%), 351 (M<sup>+</sup> 54), 274 (30), 140 (100), 134 (36), 112 (25), 96 (13), 77 (19).

**N-[3-(Benzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene]-2-methoxybenzamide (2b)**

(Yield: 74%). *R<sub>f</sub>*. 0.45 (ethyl acetate/hexane, 2:8). mp 76–77 °C. IR (KBr)  $\nu_{max}$ : 2931 (C=C-H), 2834 (-CH<sub>3</sub>), 1674 (amide C=O), 1586 (C=N), 1553 (C=C), 1466 (C-N), 1171 (C-S) cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) $\delta$  (ppm): 8.14 (1H, d, *J* = 7.6 Hz, H-4'), 8.08 (1H, d, *J* = 7.6 Hz, H-7'), 7.91 (1H, d, *J* = 7.1 Hz, H-6''), 7.84 (1H, dd, *J* = 7.4, 7.6, Hz, H-5'), 7.76 (1H, dd, *J* = 7.6, 7.4, Hz, H-6'), 7.61 (1H, dd, *J* = 7.1, 7.2 Hz, H-5''), 7.47 (1H, dd, *J* = 7.3, 7.2, Hz, H-4''), 7.38 (1H, d, *J* = 7.3 Hz, H-3''), 6.45 (1H, s, C=C-H, ring H-5), 3.76 (3H, s, -OCH<sub>3</sub>), 2.24 (3H, s, -CH<sub>3</sub>). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 166.7 (C-2'), 165.5 (amide C=O), 162.7 (C-2), 151.6 (C-4), 146.4 (C-9'), 137.5 (C-1''), 136.4 (C-2''), 135.7 (C-6''), 134.6 (C-3''), 133.2 (C-5''), 128.6 (C-4''), 127.4 (C-6'), 126.3 (C-5'), 125.7 (C-8'), 124.6 (C-4'), 123.4 (C-7'), 101.5 (C-5), 54.3 (-OCH<sub>3</sub>), 15.8 (-CH<sub>3</sub>). MS (70 eV): *m/z* (%), 381 (M<sup>+</sup> 67), 274 (36), 140 (100), 134 (29), 112 (20), 107 (41), 96 (21), 77 (14). Anal. calcd. for C<sub>19</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>S<sub>2</sub> (381.46); C, 59.84; H, 3.94; N, 11.02; S, 16.78. Found: C, 59.77; H, 3.82; N, 10.93; S, 16.67.

**N-[3-(Benzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene]-4-methylbenzamide (2c)**

(Yield: 71%) *R<sub>f</sub>*. 0.5 (ethyl acetate/hexane, 2:8). mp 84–85 °C. IR (KBr)  $\nu_{max}$ : 2935 (C=C-H), 2826 (-CH<sub>3</sub>), 1676 (amide C=O), 1588 (C=N), 1555 (C=C), 1464 (C-N), 1173 (C-S) cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) $\delta$  (ppm): 8.11 (1H, d, *J* = 7.6 Hz, H-4'), 8.05 (1H, d, *J* = 7.6 Hz, H-6'), 7.84 (1H, d, *J* = 7.2 Hz, H-2'', H-6''), 7.73 (1H, d, *J* = 7.2 Hz, H-3'', H-5''), 7.66 (1H, dd, *J* = 7.2, 7.4 Hz, H-7'), 7.57 (1H, dd, *J* = 7.2, 7.4 Hz, H-5'), 6.43 (1H, s, C=C-H, ring H-5), 2.56 (3H, s, Ar-CH<sub>3</sub>), 2.22 (3H, s, -CH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) $\delta$  (ppm): 166.6 (C-2'), 165.4 (amide C=O), 162.6 (C-2), 151.3 (C-4), 146.8 (C-9'), 134.4 (C-1''), 132.7 (C-2'', C-6''), 131.5 (C-3'', C-5''), 127.4 (C-4''), 126.3 (C-6'), 125.5 (C-5'), 124.7 (C-8'), 123.6 (C-4'), 122.4 (C-7'), 101.6 (C-2), 21.3 (Ar-CH<sub>3</sub>), 15.6 (-CH<sub>3</sub>). Anal. calcd. for C<sub>19</sub>H<sub>15</sub>N<sub>3</sub>OS<sub>2</sub> (365.47); C, 62.47; H, 4.11; N, 11.51; S, 17.53. Found: C, 62.34; H, 3.97; N, 11.38; S, 17.42. MS (70 eV): *m/z* (%), 365 (M<sup>+</sup> 49), 274 (71), 140 (100), 134 (50), 112 (30), 107 (38), 96 (24), 91 (45), 77 (20).

**N-[3-(6-Bromobenzo[d]thiazol-2-yl)-3-methylthiazol-2(3H)-ylidene]-3-chlorobenzamide (2d)**

(Yield: 73%). *R<sub>f</sub>*. 0.5 (ethyl acetate/hexane, 2:8). mp 89–90 °C. IR (KBr)  $\nu_{max}$ : 2955 (C=C-H), 2841 (-CH<sub>3</sub>), 1685 (amide C=O), 1576 (C=N), 1563 (C=C), 1462 (C-N), 1172 (C-S) cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) $\delta$  (ppm): 8.26 (1H, d, *J* = 7.4 Hz, H-7'), 8.14 (1H, d, *J* = 2.3 Hz, H-4'), 7.83 (1H, d, *J* = 2.4 Hz, H-2''), 7.75 (1H, d, *J* = 7.4 Hz, H-5'), 7.71 (1H, d, *J* = 7.2 Hz, H-6''), 7.54 (1H, dd, *J* = 7.2, 2.2 Hz, H-4''), 7.42 (1H, d, *J* = 7.2, 7.1 Hz, H-5'), 6.44 (1H, s, C=C-H, ring H-5), 2.26 (3H, s, -CH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 166.4 (C-2'), 165.2 (amide C=O), 162.5 (C-2), 152.3 (C-4), 146.5 (C-9'), 136.7 (C-1''), 135.6 (C-3''), 134.5 (C-4''), 130.6 (C-5''), 130.3 (C-2''), 128.3 (C-6''), 128.5 (C-5'), 126.7 (C-8'), 124.5 (C-7'), 124.2 (C-4'), 117.4 (C-6'), 101.6 (C-5), 16.4 (-CH<sub>3</sub>). Anal. calcd. for C<sub>18</sub>H<sub>11</sub>N<sub>3</sub>OBrS<sub>2</sub>Cl (363.78); C, 46.52; H, 2.38; N, 9.05; S, 13.78. Found: C, 46.36; H, 2.26; N, 8.93; S, 13.64. MS (70 eV): *m/z* (%), 463.5 (M<sup>+</sup> 45), 352 (64), 212 (56), 140 (100), 134 (24), 112 (10), 111.5 (22), 96 (19), 77 (28).

**N-[3-(6-Bromobenzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene]-2-fluorobenzamide (2e)**

(Yield: 68%). *R<sub>f</sub>*. 0.55 (ethyl acetate/hexane, 2:8). mp 78–79 °C. IR (KBr)  $\nu_{max}$ : 3021 (C=C-H), 2863 (-CH<sub>3</sub>), 1684 (amide C=O), 1585 (C=N), 1568 (C=C), 1485 (C-N), 1187 (C-S) cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) $\delta$  (ppm): 8.17 (1H, d, *J* = 7.6 Hz, H-7'), 8.11 (1H, d, *J* = 2.3 Hz, H-4'), 7.81 (1H, d, *J* = 7.4 Hz, H-5'), 7.73 (1H, d, *J* = 7.1 Hz, H-3''), 7.64 (1H, dd, *J* = 7.1, 7.3 Hz, H-5''), 7.52 (1H, dd, *J* = 7.4, 7.1 Hz, H-4''), 7.32 (1H, d, *J* = 7.4 Hz, H-6''), 6.46 (1H, s, C=C-H, ring H-5), 2.27 (3H, s, -CH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 166.7 (C-2'), 165.8 (amide C=O), 162.7 (C-2), 151.6 (C-4), 146.8 (C-9'), 141.6 (C-2''), 137.3 (C-1''), 136.4 (C-6''), 134.6 (C-4''), 132.5 (C-5'), 128.7 (C-5''), 127.5 (C-3''), 126.4 (C-8'), 125.6 (C-4'), 124.7 (C-7'), 121.6 (C-6'), 101.7 (C-5), 15.6 (-CH<sub>3</sub>). Anal. calcd. for C<sub>18</sub>H<sub>11</sub>N<sub>3</sub>OS<sub>2</sub>BrF (448.33); C, 48.21; H, 2.46; N, 9.37; S, 14.28. Found: C, 48.13; H, 2.35; N, 9.23; S, 14.17. MS (70 eV): *m/z*(%), 448 (M<sup>+</sup> 37), 351 (61), 211 (48), 140 (100), 112 (26), 95 (31), 77 (22).

**N-[3-(6-Methylbenzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene]-3-chlorobenzamide (2f)**

(Yield: 72%). *R<sub>f</sub>*. 0.45 (ethyl acetate/hexane, 2:8). mp 86–87 °C. IR (KBr)  $\nu_{max}$ : 2965 (C=C-H), 2839 (-CH<sub>3</sub>), 1683 (amide C=O), 1576 (C=N), 1561 (C=C), 1463 (C-N), 1165 (C-S) cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) $\delta$  (ppm): 8.12 (1H, d, *J* = 7.4 Hz, H-4'), 8.07 (1H, d, *J* = 2.3 Hz, H-7'), 7.76 (1H, d, *J* = 7.4 Hz, H-5'), 7.65 (1H, d, *J* = 7.2 Hz, H-6''), 7.56 (1H, d, *J* = 2.2 Hz, H-2''), 7.34 (1H, dd, *J* = 7.2, 2.2 Hz, H-5''), 7.28 (1H, d, *J* = 7.2, 7.1 Hz, H-4''), 6.45 (1H, s, C=C-H, ring H-5), 2.55 (3H, s, Ar-CH<sub>3</sub>), 2.25 (3H, s, -CH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) $\delta$  (ppm): 166.5 (C-2'), 165.7 (amide C=O), 162.6 (C-2), 151.7 (C-4), 146.8 (C-9'), 138.7 (C-1''), 137.6 (C-3''), 136.5 (C-6''), 135.4 (C-4''), 134.2 (C-6'), 133.6 (C-5''), 128.3 (C-2''), 126.5 (C-5'), 124.4 (C-8'), 122.5 (C-4'), 121.6 (C-7'), 101.8 (C-5), 22.7 (Ar-CH<sub>3</sub>), 15.5 (-CH<sub>3</sub>). Anal. calcd. for C<sub>19</sub>H<sub>14</sub>N<sub>3</sub>OS<sub>2</sub>Cl (399.92); C, 57.07; H, 3.50; N, 10.51; S, 16.02. Found: C, 56.96; H, 3.31; N, 10.43; S, 15.84. MS (70 eV): *m/z*(%), 399.5 (M<sup>+</sup> 45), 288 (64), 148 (53), 140 (100), 134 (26), 112 (30), 111.5 (32), 96 (29) 77 (18).

**2-Bromo-N-[4-methyl-3-(6-methylbenzo[d]thiazol-2-yl)thiazol-2(3H)-ylidene]benzamide (2g)**

(Yield: 77%). *R<sub>f</sub>*. 0.35 (ethyl acetate/hexane, 2:8). mp 90–91 °C. IR (KBr)  $\nu_{max}$ : 2956 (C=C-H), 2835 (-CH<sub>3</sub>), 1677 (amide C=O), 1570 (C=N), 1554 (C=C), 1454 (C-N), 1157 (C-S) cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) $\delta$  (ppm): 8.13 (1H, d, *J* = 7.6 Hz, H-4'), 8.09 (1H, d, *J* = 2.4 Hz, H-7'), 7.74 (1H, d, *J* = 7.6 Hz, H-5'), 7.65 (1H, d, *J* = 7.1 Hz, H-6''), 7.52 (1H, dd, *J* = 7.1, 7.2 Hz, H-5''), 7.43 (1H, dd, *J* = 7.4, 7.1 Hz, H-4''), 7.23 (1H, d, *J* = 7.4 Hz, H-3''), 6.42 (1H, s, C=C-H, ring H-5), 2.57 (3H, s, Ar-CH<sub>3</sub>), 2.26 (3H, s, -CH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) $\delta$  (ppm): 166.3 (C-2'), 165.4 (amide C=O), 162.5 (C-2), 151.5 (C-4), 146.4 (C-9'), 138.3 (C-1''), 137.4 (C-6''), 136.5 (C-4''), 135.4 (C-3''), 134.6 (C-5''), 133.5 (C-6'), 128.7 (C-2''), 127.5 (C-5'), 125.4 (C-8'), 123.6 (C-4'), 122.7 (C-7'), 101.6 (C-5), 22.4 (Ar-CH<sub>3</sub>), 15.2 (-CH<sub>3</sub>). Anal. calcd. for C<sub>19</sub>H<sub>14</sub>N<sub>3</sub>OS<sub>2</sub>Br (444.37); C, 51.35; H, 3.15; N, 9.46; S, 14.41. Found: C, 51.24; H, 3.09; N, 9.32; S, 14.27. MS (70 eV): *m/z*(%), 444 (M<sup>+</sup> 57), 288 (49), 154 (63), 140 (100), 134 (38), 112 (20), 96 (21) 77 (25).

**N-[3-(6-Methoxybenzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene]benzamide (2h)**

(Yield: 71%). *R<sub>f</sub>*. 0.35 (ethyl acetate/hexane, 2:8). mp 82–83 °C. IR (KBr)  $\nu_{max}$ : 2943 (C=C-H), 2843 (-CH<sub>3</sub>), 1675 (amide C=O), 1572 (C=N), 1556 (C=C), 1453 (C-N), 1162 (C-S) cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) $\delta$  (ppm): 8.11 (1H, d, *J* = 7.6 Hz, H-4'), 8.06 (1H, d, *J* = 2.4 Hz, H-7'), 7.82 (1H, d, *J* = 7.6 Hz, H-5'), 7.38–7.78 (5H, m, Ar), 6.43 (1H, s, C=C-H, ring H-5), 3.78 (3H, s, -OCH<sub>3</sub>), 2.24 (3H, s, -CH<sub>3</sub>).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) $\delta$  (ppm): 166.5 (C-2'), 165.3 (amide C=O), 162.4 (C-2), 151.3 (C-4), 146.3 (C-9'), 127.4 (C-6'), 135.6 (C-1''), 134.3 (C-2''), C-6''), 132.8 (C-3''), C-5''), 128.5 (C-4''), 127.6 (C-8''), 126.3 (C-4'), 124.2 (C-5'), 122.4 (C-7'), 101.7 (C-5), 54.7 (-OCH<sub>3</sub>), 15.6 (-CH<sub>3</sub>). Anal. calcd. for C<sub>19</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>S<sub>2</sub> (381.47); C, 59.84; H, 3.94; N, 11.02; S, 16.78. Found: C, 59.75; H, 3.81; N, 10.93; S, 16.64. MS (70 eV):  $m/z$  (%), 381 (M<sup>+</sup> 68), 217 (41), 164 (53), 140 (100), 134 (28), 112 (40), 96 (19) 77 (35).

**2,4-Dichloro-N-[3-(6-methoxybenzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene]beza-mide (2i)**

(Yield: 76%).  $R_f$ . 0.4 (ethyl acetate/hexane, 2:8). mp 79–80 °C. IR (KBr)  $\nu_{max}$ : 3027 (C=C-H), 2857 (-CH<sub>3</sub>), 1687 (amide C=O), 1584 (C=N), 1564 (C=C), 1471 (C-N), 1181 (C-S)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) $\delta$  (ppm): 8.16 (1H, d,  $J = 7.6$  Hz, H-4'), 8.08 (1H, d,  $J = 2.4$  Hz, H-7'), 7.84 (1H, d,  $J = 7.6$  Hz, H-5'), 7.73 (1H, d,  $J = 7.4$  Hz, H-6''), 7.64 (1H, d,  $J = 2.4$  Hz, H-3''), 7.48 (1H, d,  $J = 7.4$  Hz, H-5''), 6.46 (1H, s, C=C-H, ring H-5), 3.83 (3H, s, -OCH<sub>3</sub>), 2.27 (3H, s, -CH<sub>3</sub>).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) $\delta$  (ppm): 167.2 (C-2'), 166.2 (amide C=O), 162.8 (C-2), 152.3 (C-4), 147.5 (C-9'), 138.6 (C-6'), 137.5 (C-1''), 136.3 (C-2''), 134.7 (C-4''), 133.6 (C-6''), 132.5 (C-3''), 131.8 (C-5''), 128.4 (C-8''), 126.4 (C-4'), 124.6 (C-5'), 121.8 (C-7''), 102.6 (C-5), 54.6 (-OCH<sub>3</sub>), 15.4 (-CH<sub>3</sub>). Anal. calcd. for C<sub>19</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>S<sub>2</sub>Cl<sub>2</sub> (450.36); C, 50.67; H, 2.88; N, 9.33; S, 14.22. Found: C, 50.44; H, 2.73; N, 9.18; S, 14.13. MS (70 eV):  $m/z$  (%), 450 (M<sup>+</sup> 58), 284 (34), 164 (73), 144 (35), 140 (100), 112 (20), 96 (23) 77 (13).

**2,4-Dichloro-N-[3-(4,6-dichlorobenzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene] benzamide (2j)**

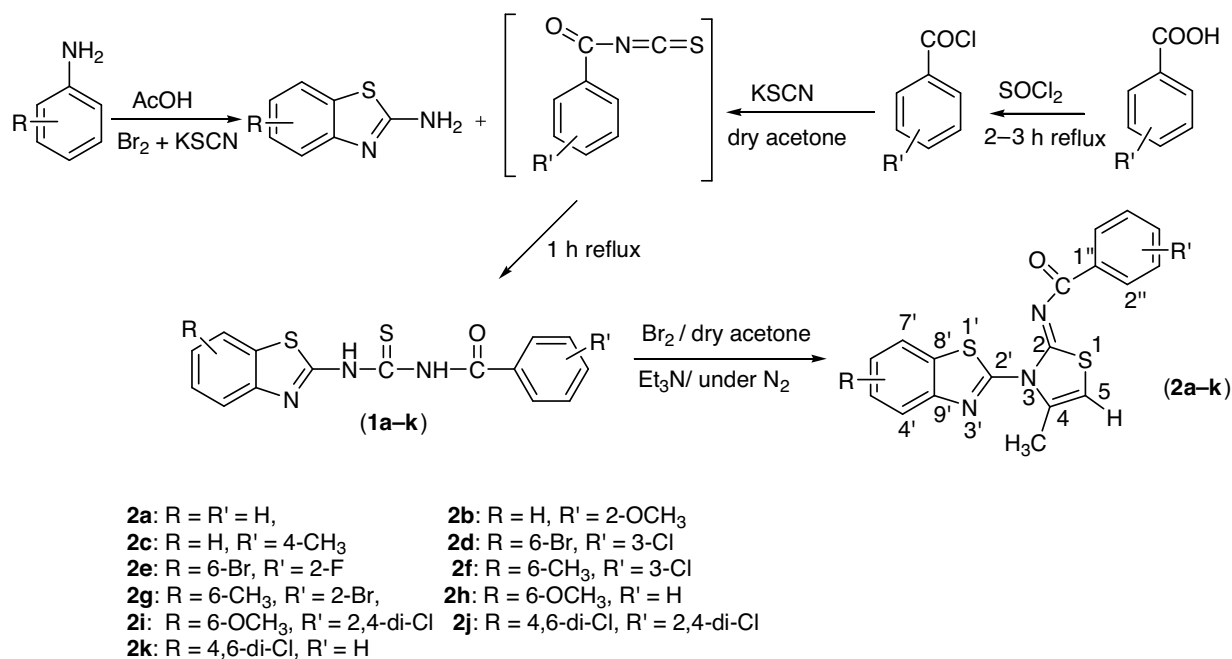
(Yield: 75%).  $R_f$ . 0.6 (ethyl acetate/hexane, 2:8). mp 74–76 °C. IR (KBr)  $\nu_{max}$ : 2963 (C=C-H), 2846 (-CH<sub>3</sub>), 1691 (amide C=O), 1587 (C=N), 1568 (C=C), 1477 (C-N), 1186 (C-S)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) $\delta$  (ppm): 8.24 (1H, d,  $J = 2.2$  Hz, H-7'), 8.17 (1H, d,  $J = 2.2$  Hz, H-5'), 7.96 (1H, d,  $J = 7.6$  Hz, H-6''), 7.87 (1H, d,  $J = 2.3$  Hz, H-3''), 7.78 (1H, d,  $J = 7.6$  Hz, H-5''), 6.48 (1H, s, C=C-H, ring H-5), 2.31 (3H, s, -CH<sub>3</sub>).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 167.4 (C-2'), 166.5 (amide C=O), 163.1 (C-2), 152.5 (C-4), 147.7 (C-9'), 138.4 (C-1''), 137.6 (C-2''), 136.5 (C-4''), 134.8 (C-6''), 133.4 (C-6'), 132.3 (C-4'), 131.8 (C-3''), 128.2 (C-5''), 125.1 (C-8'), 124.6 (C-5'), 123.7 (C-7'), 102.8 (C-5), 15.7 (-CH<sub>3</sub>). Anal. calcd. for C<sub>18</sub>H<sub>9</sub>N<sub>3</sub>OS<sub>2</sub>Cl<sub>4</sub> (489.23); C, 44.17; H, 1.84; N, 8.58; S, 13.08. Found: C, 44.09; H, 1.61; N, 8.43; S, 13.01. MS (70 eV):  $m/z$  (%), 489 (M<sup>+</sup> 58), 284 (65), 201 (52), 167 (46), 144 (65), 140 (100), 134 (42), 112 (31), 111.5 (34), 96 (26), 77 (18).

**N-[3-(4,6-Dichlorobenzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene]benzamide (2k)**

(Yield: 78%).  $R_f$ . 0.4 (ethyl acetate/hexane, 2:8). mp 70–71 °C. IR (KBr)  $\nu_{max}$ : 3031 (C=C-H), 2855 (-CH<sub>3</sub>), 1686 (amide C=O), 1583 (C=N), 1565 (C=C), 1474 (C-N), 1183 (C-S)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) $\delta$  (ppm): 8.21 (1H, d,  $J = 2.3$  Hz, H-7'), 8.16 (1H, d,  $J = 2.3$  Hz, H-5'), 7.63–7.91 (5H, m, Ar), 6.47 (1H, s, C=C-H, ring H-5), 2.28 (3H, s, -CH<sub>3</sub>).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) $\delta$  (ppm): 167.3 (C-2'), 166.1 (amide C=O), 162.6 (C-2), 152.3 (C-4), 147.3 (C-9'), 136.5 (C-1''), 134.7 (C-6'), 133.8 (C-4'), 132.6 (C-2''), C-6''), 131.5 (C-3''), C-5''), 127.4 (C-4''), 124.6 (C-8''), 123.8 (C-5'), 122.7 (C-7'), 102.3 (C-5), 15.3 (ring -CH<sub>3</sub>). Anal. calcd. for C<sub>18</sub>H<sub>11</sub>N<sub>3</sub>OS<sub>2</sub>Cl<sub>2</sub> (420.34); C, 51.42; H, 2.62; N, 10.01; S, 15.24. Found: C, 51.37; H, 2.43; N, 9.92; S, 15.14. MS (70 eV):  $m/z$  (%), 420 (M<sup>+</sup> 46), 274 (52), 201 (36), 167 (40), 144 (65), 140 (100), 134 (33), 112 (23), 96 (16), 77 (24).

### 3. Results and discussion

The synthesis of the title compounds (**2a–k**) was carried out according to the synthetic route sketched in the Scheme. Thus suitably substituted anilines were converted into the requisite benzo[d]thiazol-2-amines by reaction with thiocyanogen generated in situ from bromine and potassium thiocyanate in acidic medium. The 2-aminobenzothiazoles showed characteristic peaks at 3390–3460 (NH), 1630–1650 (C=N), 2723–2734 (C–S), and 1527–1542  $\text{cm}^{-1}$  for (C–N) in the FTIR spectral data. The  $^1\text{H}$  NMR shows a broad singlet at 5.4 ppm due to  $-\text{NH}_2$  protons besides those for aromatic protons in the region 6.92–7.47 ppm.



**Scheme.** Synthetic route to *N*-[3-(2-benzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene] substituted benzamides (**2a–k**).

1-(Benzo[d]thiazol-2-yl)-3-(substituted) thioureas (**1a–k**) were synthesized by treating suitably substituted acid chlorides with potassium thiocyanate, followed by their reaction with benzo[d]thiazol-2-amines prepared above.<sup>28</sup> The FTIR spectra of thioureas showed peaks at 3150–3382 (N–H) and 1627–1720 and 1230–1250  $\text{cm}^{-1}$  for carbonyl and thiocarbonyl groups, respectively, in addition to those at 1235–1278, (C–N), 1211–1173 (C=N), and 1517–1558 (C=C)  $\text{cm}^{-1}$ . The  $^1\text{H}$  NMR spectral data show 2 characteristic singlets of NH protons at  $\delta$  11.38 and 10.09 ppm for HN(1) and HN(3) in the  $^1\text{H}$  NMR spectra, respectively.

Base-catalyzed cyclization of benzothiazolyl thioureas with 2-bromoacetone produced in situ by the reaction of bromine with dry acetone afforded the title *N*-[3-(benzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene] substituted benzamides (**2a–k**) in good yields (Scheme).

TLC analysis was carried out to authenticate the purity of the compounds. Iminothiazoline derivatives have  $R_f$  values lower than those of the corresponding benzothiazolyl thioureas.<sup>29</sup> Analytical and spectral data (IR and  $^1\text{H}$  NMR) of all the newly synthesized compounds were found in full conformity with the proposed structures. In the  $^1\text{H}$  NMR spectra the signals of the particular proton of the compounds were established on the basis of their chemical shifts and multiplicities. The FTIR spectra of compounds revealed the disappearance

of N-H peaks around 3200–3400  $\text{cm}^{-1}$  and the appearance of characteristic strong absorption peaks of C=N in the range of 1660–1680  $\text{cm}^{-1}$  for the iminothiazoline moiety besides C-S absorptions at 1250–1275  $\text{cm}^{-1}$ , C-N at 1420–1465  $\text{cm}^{-1}$ , and the aromatic C=C at 1565–1600  $\text{cm}^{-1}$ . In  $^1\text{H}$  NMR the characteristic singlet was observed at  $\delta$  6.42–6.48 for thiazoline proton and the singlet for  $-\text{CH}_3$  protons of the thiazoline moiety appeared in  $\text{CDCl}_3$  at  $\delta$  2.22–2.31 ppm. In  $^{13}\text{C}$  NMR the characteristic signals for olefinic carbon appeared at  $\delta$  101.5–102.8, for methyl carbon at  $\delta$  15.2–16.4, and for imino carbon at  $\delta$  166.3–167.4 ppm. In the EIMS, in addition to the molecular ions, the base peaks were observed at  $m/z$  140, corresponding to fragment  $[\text{C}_5\text{H}_4\text{N}_2\text{SO}]^+$ .

#### 4. Conclusion

Synthesis of a number of iminothiazol–benzothiazole hybrid molecules has been carried out; they can potentially be used as new lead compounds in drug discovery.

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