CHAPTER 2

MICROWAVE ASSISTED ONE-POT SYNTHESIS
OF BENZOXAZOLE AND BENZOTHIAZOLE
LIBRARIES AS ANALGESIC AGENTS

2.1 INTRODUCTION

2.1.1 Benzoxazole Derivatives

2-Arylbenzoxazoles possess the important biaryl pharmacophore and have exhibited a variety of biological activities, including antimicrobial and antitumor properties. For example, a 2-arylbenzoxazole, AJI9561 was recently isolated as a cytotoxic metabolite from the extract of *Streptomyces* sp. The two most popular methods for synthesizing 2-substituted benzoxazoles are: (1) coupling of carboxylic acids with 2-aminophenols by dehydration catalyzed by a strong acid and (2) the oxidative cyclization of phenolic Schiff bases, derived from the condensation of 2-aminophenols and aldehydes, using various oxidants such as PhI(OAc)$_2$ (Varma et al 1997), Mn(OAc)$_3$, ThClO$_4$, Ba(MnO$_4$)$_2$, NiO$_2$ and Pb(OAc)$_4$ (Park et al 1996). The First method has been used for making large quantities of pharmaceutical intermediates but typically requires activation of carboxylic acids under strongly acidic conditions at high temperature. The second method usually involves the use of transition metals that require purification by filtration or aqueous treatments to remove the metal by products.
2.1.2 Biological Properties of Benzoxazole

The benzoxazole ring system is a feature of several drug molecules e.g. Benoxaprofen (antiinflammatory) and oxazolamine (antirheumatic). Pseudopteroxazole (1) is a potent growth inhibitor of mycobacterium tuberculosis H37Rv, while seco- pseudopteroxazole (2) shows moderate to strong inhibitorial activity.

UK-1 (3), an antitumor metabolite produced by streptomyces sp.517-02, was first isolated and characterised by Taniguchi and co-workers. UK-1 is a structurally unique bis(benzoxazole) in which the 2-position of one benzoxazole is joined to the 4-position of a second benzoxazole ring. UK-1 shows moderate cytotoxic activity against B16, HeLa and P338 cells, but does not inhibit the growth of Gram-negative or Gram-positive bacteria, yeast or fungi (Mark et al 1997).
2.1.3 Benzothiazole Derivatives

Benzothiazole is a privileged bicyclic ring system (Horton et al 2003). Due to their potent antitumor activity (Khasiyama et al 1999) and other important pharmaceutical utilities (Hutchinson et al 2002), the synthesis of these compounds are of considerable interest (Hutchinson et al 2000). In general benzothiazoles are synthesized by condensing 2-aminobenzenethiol with carboxylic acid derivatives (Ben et al 1997), the base induced cyclisation of the corresponding 2-haloanilides, or the radical cyclisation of thioacylbenzanilides.

2.1.4 Biological Properties of Benzothiazole Derivatives

The benzothiazolyl-moiety is a structural element of compounds with potent and selective antitumor activity (Khasiyama et al 1999), of wide spectrum Ca$^{2+}$ channel antagonists (4) and inhibitors of several enzymes such as monamine oxidase (MAO) lipoxygenase, acetylcholinesterase (Nagel et al 1995), thrombin, collagenase and neutral proteases, aldose reductase (Mylari et al 1991), HKATPase and carbonic anhydrase.
2.1.5 General Methods of Preparation Of Benzoxazoles and Benzothiazoles

Varma et al 1997 reported the use of hypervalent iodine in the synthesis of 2-arylbenzoxazoles.

Chang et al 2002 had reported DDQ as an efficient oxidant for library synthesis of 2-arylbenzoxazoles.

Pottorf et al 2003 had reported the parallel synthesis of benzoxazoles via microwave assisted dielectric heating.

Yi Chen et al 2004 reported the preparation of benzoxazoles under basic condition.
Huxley et al 2006 reported microwave-assisted synthesis of benzoxazole-7-carboxylate esters using trifluoroacetic acid and acetic acid.

Om Prakash et al 2006 had reported the synthesis of some new 2-(3-Aryl-1-phenyl-4-pyrazolyl)-benzoxazoles using hypervalent iodine mediated oxidative cyclisation of Schiff’s Bases.

Mu et al 2005 had reported the synthesis of 2-substituted benzothiazoles by Mn(III) promoted cyclisation of substituted “thioformanilildes” under microwave irradiation.

Carolina Benedi et al 2003 had reported the synthesis of 2-substituted benzothiazoles by palladium catalysed intramolecular cyclization of O-bromophenylthioureas and O-bromophenylthioamides.
Bose et al 2006 had described the hypervalent iodine mediated intramolecular cyclization of thioformanilides for the synthesis of 2-aryl benzothiazoles.

Ranu et al 2004 had reported an efficient and green synthesis of 2-arylbenzothiazoles in an ionic liquid, [pmIm]Br under microwave conditions.

Mourtas et al 2001 had reported the solid phase synthesis of benzothiazoyl compounds.
2.2 RESULTS AND DISCUSSION

2.2.1 Chemistry

It is pertinent to note that in our earlier studies, a two-step approach for the synthesis of a series of benzoxazoles and benzothiazoles have been described via PCC promoted oxidative cyclization of phenolic and thiophenolic imines respectively (Scheme 2.2.1).

![Scheme 2.2.1 PCC promoted synthesis of benz(oxa)thiazoles]

The significance of this methodology, we were interested in a one-pot process by combining the reactions such as condensation and oxidation with particular emphasis on performing this transformation under microwave condition using an alternant oxidant. The choice of the oxidant plays a crucial role, since we wished a particular oxidant to be capable of promoting the oxidative cyclization of both thiophenolic and phenolic Schiff bases. The IBD (iodobenzene diacetate) promoted synthesis of substituted benzoxazoles through oxidative intramolecular cyclization of the corresponding phenolic imines was particularly attractive, since this reaction utilizes a mild oxidant(Pottorf et al 2003). However this protocol was amenable to the synthesis of only benzoxazoles and no synthesis of benzothiazoles was reported. It was anticipated that similar oxidant, PIFA (Phenyliodonium bis(trifluoroacetate)) could promote the oxidative cyclization of phenolic and thiophenolic imines. The oxidizing capability of PIFA in organic synthesis is well documented but recent developments have seen a host of further applications.
Scheme 2.2.2  PIFA promoted synthesis of benz(oxa)thiazoles under microwave irradiation

To begin our studies, we proceeded to explore the PIFA (1.05 mmoL) promoted oxidative cyclization reaction of 2-aminothiophenol (1.1 mmoL) with \( p \)-anisaldehyde (1.0 mmoL) in ethanol at 80 °C under microwave irradiation. To our delight the reaction was complete after 5 min and showed a good conversion towards benzothiazole 2a, which was isolated in 60% yield after aqueous work-up followed by column chromatography. This positive initial result prompted us to further investigate the conditions suitable for this reaction under microwave irradiation. Extension of the irradiation time from to 15 min resulted in the complete conversion and 2a was isolated in 80% yield. Further irradiation up to 30 min did not lead to further increase in product yield. Attempts to decrease the reaction temperature were unsuccessful. From these observations, we chose microwave irradiation of the substrates with PIFA (1.05 mmoL) in ethanol at 80 °C for 15 min as the standard reaction conditions for the synthesis of a wide range of benzothiazoles (Scheme 2.2.2).

The versatility of this methodology was demonstrated with respect to variation in the aldehyde and amine by synthesis of a small family of benzothiazoles 2a-2z (Figure 2.1). As shown in Figure 2.2, our microwave assisted oxidative cyclization worked well for a variety of aldehydes and 2-aminothiophenols, giving good to excellent yields of the corresponding benzothiazoles 2a-2z. However, compounds (2r, 2s and 2t) containing
heterocyclic cores like pyridine, thiophene and furan, respectively were obtained only in moderate yields. These results can be attributed to the cleavage of these heterocycles under microwave condition. However, other microwave assisted protocols resulted in excellent yield of similar products (Quideau et al 2002).

To further study the scope of this reaction, a range of 2-aminophenols and aldehydes carrying different functional groups were subjected under the same reaction condition. The results obtained are summarized in Figure 2.2. As shown in Figure 2.2, the substrates possessing both electron releasing and electron donating groups were compatible with this microwave assisted protocol giving good to excellent yields of the corresponding benzoxazole derivatives 2a'-2z'. Similar to the benzothiazole series, benzoxazoles possessing furan, thiophene and pyrrolle (2s', 2t' and 2u') were obtained in moderate yields. The structure of all the synthesized compounds was confirmed by spectral data (IR, \(^1\)H NMR, \(^13\)C NMR and EI-MS) and elemental analyses.

![Figure 2.1 Library of benzothiazoles 2a-2z and their isolated yield (%)](image)
The formation of benzoxa(thia)zole derivatives can be explained by Scheme 2.2.3. Reaction of aldehyde with 2-aminothiophenol/2-aminophenol produces the imine intermediate 1. The attack of the imino nitrogen of intermediate 1 on the Lewis acidic trivalent iodine makes the adjacent carbon more electrophilic, thus it make way for the facile attack of nucleophilic Z (S or O) atom leading to the benzoxa(thia)zoline intermediate 1a. Subsequent dehydrogenation affords the benzoxa(thia)zole product 2 along with iodobenzene and trifluoroacetic acid as by-product. From the mechanism it was evident that PIFA serves both as a Lewis acid as well as an oxidant.

Scheme 2.2.3 Plausible mechanism for the formation of benz(oxa)thiazoles 2.
2.2.2 Evaluation of in Vivo Analgesic Activity

The results of analgesic activity are presented in Table 2.1, which demonstrate that 2-aryl benz(oxa)thiazole analogues (2h-2o) were generally found to be less potent than their corresponding heteroaryl analogues (2u-2y and 2u'-2y'). Among the heteroaryl analogues, pyrazolyl groups (2v-2y and 2w'-2y') exhibited good analgesic activity and their values are comparable to the standard pentazocine. Compounds adjoined with indolyl (2u and 2v') and pyrrollyl motifs (2u') showed moderate potency with activities greater than 2-aryl analogues but lesser than 2-pyrazolyl analogues.

Table 2.1 Analgesic activity of selected compounds by tail immersion test

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cond</th>
<th>Dose levels</th>
<th>Tail immersion response in seconds (mean ± SEM)</th>
<th>% potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2h</td>
<td>50 mg/kg</td>
<td>1.31±0.01 2.46±0.02 2.52±0.02 2.56±0.02 2.61±0.01*</td>
<td>50.0</td>
</tr>
<tr>
<td>2</td>
<td>2j</td>
<td>50 mg/kg</td>
<td>1.30±0.01 2.46±0.02 2.50±0.02 2.55±0.02 2.61±0.02*</td>
<td>50.0</td>
</tr>
<tr>
<td>3</td>
<td>2l</td>
<td>50 mg/kg</td>
<td>1.30±0.01 2.50±0.01 2.54±0.04 2.60±0.02 2.67±0.01*</td>
<td>51.3</td>
</tr>
<tr>
<td>4</td>
<td>2n</td>
<td>50 mg/kg</td>
<td>1.32±0.01 2.66±0.02 2.69±0.02 2.73±0.03 2.78±0.03*</td>
<td>52.5</td>
</tr>
<tr>
<td>5</td>
<td>2o</td>
<td>50 mg/kg</td>
<td>1.31±0.01 2.33±0.02 2.38±0.01 2.62±0.09 2.78±0.08*</td>
<td>52.8</td>
</tr>
<tr>
<td>6</td>
<td>2u</td>
<td>50 mg/kg</td>
<td>1.30±0.01 2.63±0.01 2.66±0.03 2.83±0.01 3.09±0.08*</td>
<td>58.0</td>
</tr>
<tr>
<td>7</td>
<td>2v</td>
<td>50 mg/kg</td>
<td>1.30±0.01 2.68±0.02 3.52±0.01 4.10±0.03 4.98±0.02*</td>
<td>73.9</td>
</tr>
<tr>
<td>8</td>
<td>2w</td>
<td>50 mg/kg</td>
<td>1.31±0.01 2.69±0.01 3.62±0.01 4.37±0.04 5.00±0.01*</td>
<td>73.8</td>
</tr>
<tr>
<td>9</td>
<td>2x</td>
<td>50 mg/kg</td>
<td>1.30±0.01 2.55±0.02 3.49±0.01 3.99±0.03 4.70±0.02*</td>
<td>72.3</td>
</tr>
<tr>
<td>10</td>
<td>2y</td>
<td>50 mg/kg</td>
<td>1.31±0.01 2.59±0.02 3.59±0.02 4.00±0.02 4.64±0.03*</td>
<td>71.7</td>
</tr>
<tr>
<td>11</td>
<td>2a'</td>
<td>50 mg/kg</td>
<td>1.30±0.01 2.45±0.02 2.56±0.03 2.60±0.02 2.63±0.01*</td>
<td>50.6</td>
</tr>
<tr>
<td>12</td>
<td>2c'</td>
<td>50 mg/kg</td>
<td>1.30±0.01 2.46±0.01 2.50±0.02 2.59±0.01 2.65±0.01*</td>
<td>50.9</td>
</tr>
<tr>
<td>13</td>
<td>2h'</td>
<td>50 mg/kg</td>
<td>1.30±0.01 2.47±0.01 2.60±0.01 2.64±0.01 2.67±0.01*</td>
<td>51.3</td>
</tr>
<tr>
<td>14</td>
<td>2p'</td>
<td>50 mg/kg</td>
<td>1.30±0.01 2.49±0.03 2.59±0.02 2.64±0.01 2.69±0.02*</td>
<td>51.3</td>
</tr>
<tr>
<td>15</td>
<td>2r'</td>
<td>50 mg/kg</td>
<td>1.30±0.01 2.38±0.02 2.44±0.01 2.51±0.01 2.60±0.01*</td>
<td>50.0</td>
</tr>
<tr>
<td>16</td>
<td>2u'</td>
<td>50 mg/kg</td>
<td>1.30±0.01 2.37±0.02 2.43±0.03 2.70±0.09 2.86±0.08*</td>
<td>54.5</td>
</tr>
<tr>
<td>17</td>
<td>2v'</td>
<td>50 mg/kg</td>
<td>1.30±0.01 2.69±0.01 3.01±0.01 3.13±0.01 3.22±0.08*</td>
<td>59.6</td>
</tr>
<tr>
<td>18</td>
<td>2w'</td>
<td>50 mg/kg</td>
<td>1.32±0.01 2.60±0.02 3.37±0.03 4.12±0.01 4.99±0.01*</td>
<td>73.5</td>
</tr>
<tr>
<td>19</td>
<td>2x'</td>
<td>50 mg/kg</td>
<td>1.31±0.01 2.78±0.01 3.57±0.03 4.31±0.01 5.02±0.01*</td>
<td>76.4</td>
</tr>
<tr>
<td>20</td>
<td>2y'</td>
<td>50 mg/kg</td>
<td>1.30±0.01 2.67±0.02 3.45±0.01 4.25±0.03 5.00±0.02*</td>
<td>74.0</td>
</tr>
<tr>
<td>21</td>
<td>X</td>
<td>2 mL/kg</td>
<td>1.30±0.01 1.24±0.01 1.12±0.01 1.15±0.01 1.30±0.01*</td>
<td>-</td>
</tr>
<tr>
<td>22</td>
<td>Y</td>
<td>50 mg/kg</td>
<td>1.30±0.01 6.31±0.03 6.39±0.04 6.54±0.03 6.72±0.02*</td>
<td>80.6</td>
</tr>
</tbody>
</table>

X = Gum acacia, Y = Pentazocine; Data were analysed by one way ANOVA followed by Dunnet’s test, *indicates p < 0.001, SEM: Standard error of means.

2% (w/v) of gum acacia was used as control.
Figure 2.3 IR Spectrum of compound 2j

Figure 2.4 Mass spectrum of compound 2j
Figure 2.5 $^1$H NMR spectrum of compound 2j

Figure 2.6 $^{13}$C NMR spectrum of compound 2j
2.3 EXPERIMENTAL METHODS

2.3.1 Materials, Methods and Instruments

Melting points were determined on Gallenkamp melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer FTIR spectrophotometer as KBr pellets. $^1$H and $^{13}$C NMR spectra were obtained in CDCl$_3$ and DMSO-$d_6$ on a JEOL spectrometer at 500 and 125 MHz, respectively. Proton chemical shifts ($\delta$) are relative to tetramethylsilane (TMS, $\delta = 0.00$) as internal standard and expressed in parts per million. The number of protons ($n$) for a given resonance was indicated as $n$H. Coupling constants ($J$) are given in hertz. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet). Mass spectra were recorded on a Thermo Finnigan LCQ Advantage MAX 6000 ESI mass spectrometer and Perkin-Elmer GC-MS. Elemental analyses were recorded using a Thermo Finnigan FLASH EA 1112CHN analyzer. All the compounds gave C, H and N analysis within $\pm 0.5\%$ of the theoretical values. All microwave experiments were performed using an Emrys Optimizer in 2–5 mL pyrex reaction vessels. Each vessel contained a Teflon stir bar and Teflon-coated reaction vessel cap. Column chromatography was performed using a mixture of petroleum ether and ethyl acetate on silica gel (100-200 mesh, SRL, India). Analytical TLC was performed on precoated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness (Macherey-Nagel, Germany) using analytical grade solvents and visualizing with iodine spray (10% (w/w) I$_2$ in silica gel) or UV light ($\lambda = 254$ and 365 nm).

2.3.2 General procedure for the synthesis of benzothiazoles 2a-2z

To a pyrex reaction vessel were added 2-aminothiophenol (1.1 mmoL), aldehyde (1.0 mmoL) and PIFA (1.05 mmoL) in ethanol (3 mL). The reaction vessel was then placed in the Emrys Optimizer and exposed to microwave irradiation (80 $^\circ$C) for 15 minutes. The reaction mixture was then allowed to cool at room temperature and quenched with 15 mL of water. The crude reaction mixture was extracted with EtOAc (3 X 15 mL). The combined
organic layers were dried over anhydrous Na$_2$SO$_4$, filtered, concentrated and purified by column chromatography on silica gel using petroleum ether/EtOAc to afford the pure product.

2-(4-Methoxyphenyl)benzo[d]thiazole (2a)

Yellow solid; mp 122–124 °C; $R_f$=0.59 (AcOEt/petroleum ether 10%). IR (KBr): 3023, 2996, 2900, 2836, 1605, 1521, 1485, 1260, 832 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) δ$_H$ 3.91 (s, 3H, -OC$_3$H$_3$); 7.00-7.05 (m, 2H, Ar-H); 7.35 (d, 1H, $J$ = 7.6 Hz, Ar-H); 7.50 (d, 1H, $J$ = 7.6 Hz, Ar-H); 7.91-8.04 (m, 4H, Ar-H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ$_C$ 55.5, 114.4, 121.6, 122.9, 124.9, 126.3, 126.5, 129.2, 135.0, 154.3, 162.0, 167.9. MS (EI): $m/z$=241 [M$^+$]. Anal. Calcd for C$_{14}$H$_{11}$NOS: C, 69.68; H, 4.59; N, 5.80%. Found: C, 69.89; H, 4.54; N, 5.72%.

2-(4-(Trifluoromethyl)phenyl)benzo[d]thiazole (2b)

Colourless solid; mp 158-160 °C; $R_f$=0.35 (AcOEt/petroleum ether 40%). IR (KBr): 3058, 2898, 1658, 1154, 1071, 798 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) δ$_H$ 7.40-7.45 (m, 1H, Ar-H); 7.50-7.54 (m, 1H, Ar-H); 7.77 (d, 2H, $J$ = 8.4 Hz, Ar-H); 7.93 (ddd, 1H, $J$ = 0.8, 0.78, 8.4 Hz, Ar-H); 8.11 (ddd, 1H, $J$ = 1.1, 1.1, 7.1 Hz, Ar-H); 8.20 (dd, 2H, $J$ = 0.7, 8.8 Hz, Ar-H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ$_C$ 121.8, 123.4, 124.5 ($J_{C,F}$ = 268.0 Hz), 125.5, 126.0 ($J_{C,F}$ = 3.6 Hz), 126.7, 132.4 ($J_{C,F}$ = 32.9 Hz), 135.0, 136.7, 154.2, 159.9. MS (EI): $m/z$=280 [M+H]$^+$. Anal. Calcd for C$_{14}$H$_8$F$_3$NS: C, 60.21; H, 2.89; N, 5.02%. Found: C, 59.99; H, 2.94; N, 5.11%.
4-(Benzo[d]thiazol-2-yl)-N,N-dimethylbenzenamine (2c)

Brown solid; mp 175-177 °C; $R_f=0.30$ (AcOEt/petroleum ether 20%). IR (KBr): 3398, 1598, 1478, 1201, 1012, 981 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 3.07 (s, 6H, -N(CH$_3$_)$_2$); 6.75 (dd, 2H, $J = 7.2$, 1.8 Hz, Ar-H); 7.31-7.35 (m, 1H, Ar-H); 7.43-7.46 (m, 1H, Ar-H); 7.85-7.88 (m, 1H, Ar-H); 8.01 (dd, 3H, $J = 7.2$, 1.8 Hz, Ar-H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$C 39.9, 111.5, 121.2, 122.3, 124.0, 126.0, 128.9, 134.6, 152.0, 154.5, 168.9. MS (EI): $m/z=255$ [M+H$^+$]. Anal. Calcd for C$_{15}$H$_{14}$N$_2$S: C, 70.83; H, 5.55; N, 11.01%. Found: C, 71.01; H, 5.51; N, 10.92%.

2-(4-Chlorophenyl)benzo[d]thiazole (2d)

Yellow solid; mp 114-116 °C; $R_f=0.50$ (AcOEt/petroleum ether 10%). IR (KBr): 3055, 2360, 1560, 1455, 1430, 1317, 1275, 1060, 966, 750, 725 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 7.39-7.43 (m, 2H, Ar-H); 7.45-7.52 (m, 2H, Ar-H); 7.85-8.01 (m, 4H, Ar-H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$C 121.9, 123.6, 125.5, 126.8, 129.0, 129.6, 132.4, 135.4, 137.1, 154.4, 166.9. MS (EI): $m/z=245$ [M$^+$], 247 [M$^{12}$]. Anal. Calcd for C$_{13}$H$_8$ClNS: C, 63.54; H, 3.28; N, 5.70%. Found: C, 63.75; H, 3.24; N, 5.63%.

2-(Naphthalen-2-yl)benzo[d]thiazole (2e)

Brown solid; mp 123-125 °C; $R_f=0.64$ (AcOEt/petroleum ether 20%). IR (KBr): 3049, 2920, 2855, 1597, 1499, 1452, 1430, 1362, 1306, 1270, 1174, 1123, 982, 937, 880 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 7.30–7.37 (m, 1H, Ar-H); 7.44–7.50 (m, 3H, Ar-H); 7.80–7.91 (m, 4H, Ar-H); 8.09 (d, 1H, $J = 8.0$ Hz, Ar-H); 8.15 (d, 1H, $J = 8.4$ Hz); 8.50 (s, 1H, Ar-H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$C 121.6, 123.2, 124.4, 125.2, 126.7, 127.4, 127.5, 127.9, 128.8, 130.9, 133.1, 134.6, 135.1, 154.2, 168.1. MS (EI): $m/z=261$ [M$^+$]. Anal. Calcd for C$_{17}$H$_{11}$NS: C, 78.13; H, 4.24; N, 5.36%. Found: C, 78.30; H, 4.17; N, 5.29%.
Methyl 4-(benzo[d]thiazol-2-yl)benzoate (2f)

Colourless solid; mp 148-151 °C; \( R_f = 0.25 \) (AcOEt/petroleum ether 30%). IR (KBr): 3360, 3270, 2933, 2853, 1724, 1679, 751, 724 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 3.99 (s, 3H, -COOC\(_3\)H\(_3\)); 6.94-6.99 (td, 1H, \( J = 7.6, 1.3 \) Hz, Ar-H); 7.26-7.29 (m, 1H, Ar-H); 7.45-7.49 (dd, 1H, \( J = 7.6, 1.3 \) Hz, Ar-H); 7.70-7.73 (d, 2H, \( J = 8.3 \) Hz, Ar-H); 8.09-8.12 (d, 2H, \( J = 8.3 \) Hz, Ar-H); 8.42-8.46 (d, 1H, \( J = 8.3 \) Hz, 1H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \)C 52.5, 120.7, 124.0, 124.7, 127.1, 130.0, 132.4, 133.2, 136.7, 138.0, 139.7, 164.0, 166.2. MS (EI): \( m/z = 270 \) [M+H]. Anal. Calcd for C\(_{15}\)H\(_{11}\)NO\(_2\)S: C, 66.89; H, 4.12; N, 5.20%. Found: C, 67.10; H, 4.06; N, 5.11%.

5-Methoxy-2-phenylbenzo[d]thiazole (2g)

Colorless solid; mp 74–76 °C; \( R_f = 0.62 \) (AcOEt/petroleum ether 15%). IR (KBr): 2955, 2940, 2840, 1597, 1462, 1429, 1256, 1167, 1150, 1077 cm\(^{-1}\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 3.86 (s, 3H, -OC\(_3\)H\(_3\)); 7.05 (dd, 1H, \( J_1 = 9.1 \) Hz, \( J_2 = 2.6 \) Hz, Ar-H); 7.39-7.47 (m, 3H, Ar-H); 7.56 (d, 1H, \( J = 2.6 \) Hz, Ar-H); 7.70 (d, 1H, \( J = 9.1 \) Hz, Ar-H); 8.01-8.10 (m, 2H, Ar-H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \)C 55.9, 106.0, 115.4, 122.1, 127.3, 127.7, 129.3, 131.1, 134.1, 156.0, 159.5, 169.4. MS (EI): \( m/z = 241 \) [M\(^+\)]. Anal. Calcd for C\(_{14}\)H\(_{11}\)NO\(_2\): C, 69.68; H, 4.59; N, 5.80%. Found: C, 69.48; H, 4.61; N, 5.87%.

2-(3-Nitrophenyl)benzo[d]thiazole (2h)

Colorless solid; mp 181-183 °C; \( R_f = 0.50 \) (AcOEt/petroleum ether 30%). IR (KBr): 3402, 2937, 1529, 1461, 1347, 1107, 1048, 731 cm\(^{-1}\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.42 (t, 1H, \( J = 7.6 \) Hz, Ar-H); 7.51 (t, 1H, \( J = 7.6 \) Hz, Ar-H); 7.65 (t, 1H, \( J = 7.6 \) Hz, Ar-H); 7.92 (d, 1H, \( J = 7.6 \) Hz, Ar-H); 8.09 (d, 1H, \( J = 7.6 \) Hz, Ar-H); 8.30 (dd, 1H, \( J = 6.9, 9.2 \) Hz, Ar-H); 8.38 (d, 1H, \( J = 7.6 \) Hz, Ar-H); 8.90 (s, 1H, Ar-H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \)C 121.9, 122.4, 123.8, 125.2, 126.1, 126.9, 130.2, 133.1, 135.3, 135.4, 148.8,
154.0, 164.9. MS (EI): m/z=256 [M+]. Anal. Calcd for C\textsubscript{13}H\textsubscript{8}N\textsubscript{2}SO\textsubscript{2}: C, 60.92; H, 3.15; N, 10.93%. Found: C, 60.75; H, 3.22; N, 10.89%.

2-(2-Methoxyphenyl)benzo[d]thiazole (2i)

Colourless solid; mp 123-125 °C; R\textsubscript{f}=0.55 (AcOEt/petroleum ether 10%). IR (KBr): 3024, 2999, 2900, 2837, 1604, 1521, 1485, 1260, 831 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \textit{d}H 3.99 (s, 3H, -OC\textsubscript{3}H\textsubscript{3}); 7.10-7.55 (m, 4H, Ar-H); 7.92-8.49 (m, 4H, Ar-H). \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \textit{d}C 55.5, 111.5, 120.9, 121.0, 122.6, 124.4, 125.7, 129.3, 131.5, 135.9, 152.0, 157.0, 162.9. MS (EI): m/z=242 [M+H]+. Anal. Calcd for C\textsubscript{14}H\textsubscript{11}NOS: C, 69.68; H, 4.59; N, 5.80%. Found: C, 69.91; H, 4.53; N, 5.70%.

2-(2-Chlorophenyl)benzo[d]thiazole (2j)

Colorless solid; mp 71-73 °C; R\textsubscript{f}=0.39 (AcOEt/petroleum ether 10%). IR (KBr): 3053, 2359, 1559, 1454, 1429, 1316, 1270, 1059, 965, 749, 726 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \textit{d}H 7.38-7.44 (m, 3H, Ar-H); 7.51-7.54 (m, 2H, Ar-H); 7.93 (d, 1H, J = 7.6 Hz, Ar-H); 8.13 (d, 1H, J = 8.4 Hz, Ar-H); 8.20-8.21 (m, 1H, Ar-H). \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \textit{d}C 121.5, 123.6, 125.6, 126.4, 127.2, 130.9, 131.3, 131.9, 132.4, 132.8, 136.2, 152.6, 164.3. MS (EI): m/z=245 [M+], 247 [M+2]. Anal. Calcd for C\textsubscript{14}H\textsubscript{11}ClNS: C, 63.54; H, 3.28; N, 5.70%. Found: C, 63.44; H, 3.33; N, 5.67%.

2-(3,4-Dimethoxyphenyl)benzo[d]thiazole (2k)

Colorless solid; mp 133–135 °C; R\textsubscript{f}=0.54 (AcOEt/petroleum ether 20%). IR (KBr): 2955, 2940, 2840, 1600, 1521, 1483, 1431, 1336, 1312, 1260, 1167, 1145, 1075 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \textit{d}H 3.96 (s, 3H, -OC\textsubscript{3}H\textsubscript{3}); 4.03 (s, 3H, -OC\textsubscript{3}H\textsubscript{3}); 6.97 (d, 1H, J = 8.4 Hz, Ar-H); 7.35 (t, 1H, J = 7.6 Hz, Ar-H); 7.49 (t, 1H, J = 7.4 Hz, Ar-H); 7.65 (d, 1H J = 8.4 Hz, Ar-H); 7.76 (s, 1 H, Ar-H); 7.89 (d, 1H J = 7.6 Hz, Ar-H); 8.00 (d, 1H, J = 8.0 Hz, Ar-H). \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \textit{d}C 55.9, 109.7, 111.0, 121.1, 121.5, 122.8, 124.9, 126.2, 126.6, 134.9, 149.2, 151.5, 154.0, 168.1. MS (EI):
$m/z=271$ [M$^+$]. Anal. Calcd for C$_{15}$H$_{13}$NO$_2$S: C, 66.40; H, 4.83; N, 5.16%. Found: C, 66.61; H, 4.79; N, 5.04%.

2-[4-(Benzyloxy)-3-methoxyphenyl]benzo[d]thiazole (2l)

Colorless solid; mp 97-99 °C; $R_f=0.63$ (AcOEt/petroleum ether 30%). IR (KBr): 3468, 2937, 1630, 1264, 1141, 997 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta_H$ 3.94 (s, 3H, -OC$_3$H$_3$); 5.22 (s, 2H, -OCH$_2$C$_6$H$_5$); 6.93 (d, 1H, $J = 8.4$ Hz, Ar-H); 7.31-7.39 (m, 4H, Ar-H); 7.42-7.48 (m, 3H, Ar-H); 7.51 (dd, 1H, $J = 2.3, 8.4$ Hz, Ar-H); 7.72 (d, 1H, $J = 2.3$ Hz, Ar-H); 7.85 (d, 1H, $J = 7.6$ Hz, Ar-H); 8.01 (d, 1H, $J = 8.4$ Hz, Ar-H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta_C$ 56.3, 71.0, 110.3, 113.5, 121.1, 121.6, 122.9, 124.9, 126.3, 127.1, 127.3, 128.1, 128.8, 134.9, 136.6, 149.9, 150.7, 154.2, 168.1. MS (El): $m/z=349$ [M$^+$]. Anal. Calcd for C$_{20}$H$_{17}$NSO: C, 72.60; H, 4.93; N, 4.03%. Found: C, 72.49; H, 4.82; N, 3.99%.

4-(Benzo[d]thiazol-2-yl)-2,6-methoxyphenol (2m)

Colorless solid; mp 140-142 °C; $R_f=0.59$ (AcOEt/petroleum ether 25%). IR (KBr): 3480, 2939, 1615, 1530, 1480, 1450, 1427, 1366, 1334, 1284, 1211, 1200 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta_H$ 3.99 (s, 6H, -OCH$_3$); 5.98 (s, 1H, -OH); 7.33-7.39 (m, 3H, Ar-H); 7.50 (t, 1H $J = 7.6$ Hz, Ar-H); 7.89 (d, 1H, $J = 7.6$ Hz, Ar-H); 8.03 (d, 1H, $J = 8.1$ Hz, Ar-H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta_C$ 56.6, 106.6, 121.5 (2C), 122.8, 124.9, 125.1, 126.2, 134.8, 137.7, 147.3, 154.0, 168.1. MS (El): $m/z=287$ [M$^+$]. Anal. Calcd for C$_{15}$H$_{13}$NO$_3$S: C, 62.70; H, 4.56; N, 4.87%. Found: C, 62.88; H, 4.51; N, 4.81%. 
2-[4-(Benzyloxy)-3,5-dimethoxyphenyl]benzo[d]thiazole (2n)

Brown solid; mp 77-79 °C; $R_f$=0.58 (AcOEt/petroleum ether 30%). IR (KBr): 3432, 2915, 2369, 1623, 1590, 1406, 1329, 1240, 1118, 1019 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 3.93 (s, 6H, -OCH$_3$); 5.09 (s, 2H, -OCH$_2$C$_6$H$_5$); 7.29-7.38 (m, 6H, Ar-H); 7.46-7.50 (m, 3H, Ar-H); 7.86 (d, 1H, $J = 7.6$ Hz, Ar-H); 8.04 (d, 1H, $J = 8.4$ Hz, Ar-H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$C 56.2, 76.9, 104.9, 121.7, 123.1, 125.2, 126.4, 128.1, 128.3, 128.6, 129.3, 135.1, 137.6, 139.5. MS (EI): m/z=377 [M$^+$]. Anal. Calcd for C$_{22}$H$_{19}$NSO$_3$: C, 70.00; H, 5.07; N, 3.71%. Found: C, 69.89; H, 4.99; N, 3.82%.

4-(1,3-Benzodthiazol-2-yl)-2-bromo-6-methoxyphenol (2o)

Colorless solid; mp 184-186 °C; $R_f$=0.46 (AcOEt/petroleum ether 30%). IR (KBr): 3447, 2922, 1510, 1416, 1292, 1183, 1022, 831, 722 cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-d$_6$) $\delta$H 3.93 (s, 3H, -OCH$_3$); 7.39 (d, 1H, $J = 7.6$ Hz, Ar-H); 7.49-7.50 (m, 1H, Ar-H); 7.57 (s, 1H, Ar-H); 7.72 (s, 1H, Ar-H); 7.97-8.07 (m, 2H, Ar-H); 10.32 (s, 1H, -OH). $^{13}$C NMR (125 MHz, DMSO-d$_6$) $\delta$C 56.9, 109.7, 110.2, 122.8, 123.1, 124.1, 125.5, 125.8, 127.2, 134.9, 144.7, 149.2, 153.9, 166.5. MS (EI): m/z=335 [M$^+$], 337 [M$^{+2}$]. Anal. Calcd for C$_{14}$H$_{10}$BrNO$_2$: C, 50.01; H, 3.00; N, 4.17%. Found: C, 49.89; H, 3.09; N, 4.10%.

2-(Benzo[d][1,3]dioxol-5-yl)benzo[d]thiazole (2p)

Yellow solid; mp 128-130 °C; $R_f$=0.60 (AcOEt/petroleum ether 15%). IR (KBr): 1602, 1492, 1454, 1377, 1305, 1274, 1149, 744, 699 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 6.07 (s, 2H, -OCH$_2$O-); 6.99 (d, 1H, $J = 7.6$ Hz, Ar-H); 7.35-7.40 (m, 1H, Ar-H); 7.45-7.50 (m, 1H, Ar-H); 7.61-7.65 (m, 2H, Ar-H); 7.91 (d, 1H, $J = 8.4$ Hz, Ar-H); 8.05 (d, 1H, $J = 8.4$ Hz, Ar-H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$C 101.5, 107.4, 108.5, 121.4, 122.4, 123.0, 125.0, 126.3, 128.0, 135.0, 148.5, 150.2, 154.2, 167.5. MS (EI): m/z=256 [M+H$^+$].
Anal. Calcd for C\textsubscript{14}H\textsubscript{9}NO\textsubscript{2}S: C, 65.87; H, 3.55; N, 5.49%. Found: C, 66.01; H, 3.51; N, 5.42%.

2-(Phenylbenzo[d]thiazole (2q)

Colourless solid; mp 114-116 °C; R\textsubscript{f}=0.60 (AcOEt/petroleum ether 10%). IR (KBr): 3064, 1588, 1555, 1509, 1478, 1433, 1244, 962, 766 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \text{H} \) 7.38 (d, 2H, \( J = 7.6 \) Hz, Ar-H); 7.50-755 (m, 4H, Ar-H); 7.92 (d, 1H, \( J = 7.6 \) Hz, Ar-H); 8.07-8.15 (m, 3H, Ar-H). \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \( \delta \text{C} \) 121.5, 123.1, 125.1, 126.2, 127.5, 129.0, 130.8, 133.6, 135.1, 154.2, 167.9. MS (EI): \( m/z=211 \) [M\textsuperscript{+}]. Anal. Calcd for C\textsubscript{13}H\textsubscript{9}NS: C, 73.90; H, 4.29; N, 6.63%. Found: C, 74.05; H, 4.24; N, 6.55%.

2-(Pyridin-2-yl)benzo[d]thiazole (2r)

Yellow solid; mp 130-131 °C; R\textsubscript{f}=0.15 (AcOEt/petroleum ether 40%). IR (KBr): 3322, 3079, 2901, 1655, 989, 874 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \text{H} \) 7.35-7.41 (m, 2H, Ar-H); 7.50-7.54 (m, 1H, Ar-H); 7.81 (ddd, 1H, \( J = 1.6, 7.6, 7.6 \) Hz, Ar-H); 7.95 (dd, 1H, \( J = 0.8, 8.4 \) Hz, Ar-H); 8.10 (dd, 1H, \( J = 0.8, 8.4 \) Hz, Ar-H); 8.35-8.38 (m, 1H, Ar-H); 8.69 (d, 1H, \( J = 4.7 \) Hz, Ar-H). \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \( \delta \text{C} \) 120.6, 121.9, 123.5, 125.2, 125.5, 126.4, 137.1, 149.5, 151.3, 154.1, 159.0, 169.1. MS (EI): \( m/z=213 \) [M+H\textsuperscript{+}]. Anal. Calcd for C\textsubscript{12}H\textsubscript{8}N\textsubscript{2}S: C, 67.90; H, 3.80; N, 13.20%. Found: C, 68.10; H, 3.76; N, 13.11%.

2-(Thiophen-2-yl)benzo[d]thiazole (2s)

Colorless solid; mp 98–100 °C; R\textsubscript{f}=0.65 (AcOEt/petroleum ether 15%). IR (KBr): 3083, 3043, 1628, 1064, 829 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \text{H} \) 7.30 (t, 1H, \( J = 3.9 \) Hz, Ar-H); 7.52-7.63 (m, 2H, Ar-H); 7.65 (d, 1H, \( J = 3.9 \) Hz, Ar-H); 7.72 (d, 1H, \( J = 3.9 \) Hz); 8.10 (d, 1H, \( J = 7.6 \) Hz, Ar-H); 8.20 (d, 1H, \( J = 7.6 \) Hz, Ar-H). \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \( \delta \text{C} \) 121.3, 123.0, 125.1, 126.3, 127.9, 128.5, 129.2, 134.5, 137.2, 153.5, 161.2. MS (EI): \( m/z=217 \) [M\textsuperscript{+}]. Anal. Calcd for C\textsubscript{11}H\textsubscript{7}NS\textsubscript{2}: C, 60.80; H, 3.25; N, 6.45%. Found: C, 60.99; H, 3.21; N, 6.39%. 
2-(Furan-2-yl)benzo[d]thiazole (2t)

Yellow solid; mp 100-102 °C; \( R_f \)=0.25 (AcOEt/petroleum ether 30%). IR (KBr): 2929, 1602, 1475, 1103, 885 cm\(^{-1}\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \)H 6.60-6.62 (m, 1H); 7.20-7.22 (m, 1H, Ar-H); 7.36-7.42 (m, 1H, Ar-H); 7.45-7.50 (m, 1H, Ar-H); 7.61 (s, 1H, Ar-H); 7.93 (d, 1H, \( J \)= 8.3 Hz, Ar-H); 8.06 (d, 1H, \( J \)= 8.3 Hz, Ar-H). \(^13\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \)C 111.5, 112.8, 121.8, 123.5, 125.4, 126.7, 134.6, 141.0, 154.0, 157.8. MS (EI): \( m/z \)=202 [M+H]. Anal. Calcd for C\(_{11}\)H\(_7\)NOS: C, 65.65; H, 3.51; N, 6.96%. Found: C, 65.41; H, 3.56; N, 7.02%.

2-(1-Methyl-1H-indol-2-yl)benzo[d]thiazole (2u)

Colorless solid; mp 147-149 °C; \( R_f \)=0.66 (AcOEt/petroleum ether 30%). IR (KBr): 3419, 3051, 1542, 1450, 1345, 1310, 1191, 1150, 975, 787, 751 cm\(^{-1}\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \)H 4.31 (s, 3H, -NC\(_3\)H); 7.17-7.20 (m, 2H, Ar-H); 7.33-7.44 (m, 3H, Ar-H); 7.48-7.51 (m, 1H, Ar-H); 7.67 (d, 1H, \( J \)= 8.4 Hz, Ar-H); 7.88 (d, 1H, \( J \)= 7.6 Hz, Ar-H); 8.06 (d, 1H, \( J \)= 8.4 Hz, Ar-H). \(^13\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \)C 32.4, 107.3, 110.2, 120.6, 121.4, 121.6, 123.3, 124.2, 125.4, 126.4, 127.3, 132.3, 134.5, 139.8, 154.3, 160.7. MS (EI): \( m/z \)=264 [M\(^+\)]. Anal. Calcd for C\(_{16}\)H\(_{12}\)N\(_2\)S: C, 72.70; H, 4.58; N, 10.60%. Found: C, 72.81; H, 4.62; N, 10.53%.

2-[3-(4-Bromophenyl)-1-phenyl-1H-pyrazol-4-yl]benzo[d]thiazole (2v)

Colorless solid; mp 200-202 °C; \( R_f \)=0.47 (AcOEt/petroleum ether 25%). IR (KBr): 3359, 1637, 1554, 1506, 1406, 1222, 1085, 829, 754, 684 cm\(^{-1}\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \)H 7.35-7.37 (m, 2H, Ar-H); 7.46-7.51 (m, 3H, Ar-H); 7.58 (d, 2H, \( J \)= 8.4 Hz, Ar-H); 7.66 (d, 2H, \( J \)= 8.4 Hz, Ar-H); 7.80 (d, 3H, \( J \)= 8.4 Hz, Ar-H); 8.00 (d, 1H, \( J \)= 8.4 Hz, Ar-H); 8.59 (s, 1H, pyrazolyl-H). \(^13\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \)C 117.2, 119.5, 121.5, 122.8, 123.6, 125.1, 126.4, 127.5, 128.7, 129.7, 131.0, 131.2, 131.28, 131.7, 139.3, 151.0, 153.4, 154.2, 154.9. MS (EI): \( m/z \)=431 [M\(^+\)], 433 [M\(^{+2}\)]. Anal. Calcd
for \( \text{C}_{22}\text{H}_{13}\text{N}_{3}\text{SBr} \): C, 61.12; H, 3.26; N, 9.72%. Found: C, 61.00; H, 3.33; N, 9.77%.

**2-[3-(4-Ethoxyphenyl)-1-phenyl-1H-pyrazole-4-yl]benzo[d]thiazole (2w)**

Pale yellow solid; mp 152-154 °C; \( R_f \)=0.50 (AcOEt/petroleum ether 30%). IR (KBr): 3434, 2965, 1613, 1558, 1503, 1247, 1106, 1043, 812 cm\(^{-1}\). \( ^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta_H \) 1.46 (t, 3H, \( J = 7.5 \) Hz, -OCH\(_2\)\( \text{C}_3\)); 4.10 (q, 2H \( J = 6.8 \) Hz, -OCH\(_2\)\( \text{C}_3\)); 6.98 (d, 2H, \( J = 8.6 \) Hz, Ar-H); 7.31 (q, 2H, \( J = 8.0 \) Hz, Ar-H); 7.44-7.50 (m, 3H, Ar-H); 7.62-7.66 (m, 2H, Ar-H); 7.76 (d, 1H, \( J = 8.0 \) Hz, Ar-H); 7.81 (d, 2H, \( J = 8.6 \) Hz, Ar-H); 7.99 (d, 1H, \( J = 8.0 \) Hz, Ar-H); 8.64 (s, 1H, pyrazolyl-H). \( ^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta_C \) 14.9, 63.6, 114.5, 117.4, 119.4, 121.5, 122.6, 124.1, 124.9, 126.2, 127.3, 128.1, 129.7, 131.1, 135.1, 139.5, 152.2, 153.2, 159.9, 163.2. MS (EI): \( m/z=397 \) [M\(^+\)]. Anal. Calcd for \( \text{C}_{24}\text{H}_{19}\text{N}_{3}\text{OS} \): C, 72.52; H, 4.82; N, 10.57%. Found: C, 72.67; H, 4.75; N, 10.22%.

**2-[3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]benzo[d]thiazole (2x)**

Colorless solid; mp 173-175 °C; \( R_f \)=0.45 (AcOEt/petroleum ether 25%). IR (KBr): 3421, 1599, 1502, 1388, 1203, 1067, 932, 823 cm\(^{-1}\). \( ^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta_H \) 7.33-7.37 (m, 2H, Ar-H); 7.43-7.51 (m, 5H, Ar-H); 7.72 (d, 2H, \( J = 8.4 \) Hz, Ar-H); 7.79 = 7.82 (m, 3H, Ar-H); 8.00 (d, 1H, \( J = 8.4 \) Hz, Ar-H); 8.59 (s, 1H, pyrazolyl-H). \( ^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta_C \) 117.3, 119.4, 121.5, 122.8, 125.1, 126.4, 127.5, 128.7, 128.8, 129.7, 130.6, 131.0, 135.0, 135.2, 139.3, 150.9, 153.4, 159.8. MS (EI): \( m/z=388 \) [M\(^+\)], 390 [M\(^{+2}\)]. Anal. Calcd for \( \text{C}_{22}\text{H}_{13}\text{ClN}_{3}\text{S} \): C, 68.12; H, 3.64; N, 10.83%. Found: C, 67.99; H, 3.76; N, 10.90%. 

2-[3-(4-Methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl]benzo[d]thiazole (2y)

Colorless solid; mp 167-169 °C; $R_f$=0.44 (AcOEt/petroleum ether 30%). IR (KBr): 3402, 2346, 1609, 1558, 1505, 1406, 1248, 1034, 833, 755 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 3.87 (s, 3H, -OCH$_3$); 6.99 (d, 2H, $J$ = 8.4 Hz, Ar-H); 7.32 (q, 2H, $J$ = 7.6 Hz, Ar-H); 7.44-7.48 (m, 3H, Ar-H); 7.66 (d, 2H, $J$ = 8.4 Hz, Ar-H); 7.76 (d, 1H, $J$ = 7.6 Hz, Ar-H); 7.81 (d, 2H, $J$ = 7.6 Hz, Ar-H); 7.99 (d, 1H, $J$ = 8.4 Hz, Ar-H); 8.63 (s, 1H, pyrazolyl-H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$C 55.4, 114.0, 117.4, 119.4, 121.5, 122.6, 124.3, 124.9, 126.2, 127.3, 128.2, 129.7, 131.1, 135.1, 139.5, 152.1, 153.2, 160.4, 160.5. MS (EI): $m/z$=383 [M$^+$]. Anal. Calcd for C$_{23}$H$_{17}$N$_3$SO: C, 72.02; H, 4.47; N, 10.96%. Found: C, 71.89; H, 4.45; N, 11.01%.

5,6-Dimethoxy-2-phenylbenzo[d]thiazole (2z)

Colourless solid; mp 143-145 °C; $R_f$ = 0.45 (AcOEt/petroleum ether 10%). IR (KBr): 3025, 2997, 2837, 1606, 1525, 1491, 1260, 840 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 3.91 (s, 3H, -OCH$_3$); 3.93 (s, 3H, -OCH$_3$); 7.55-7.59 (m, 3H, Ar-H); 7.65 (s, 1H, Ar-H); 7.72 (s, 1H, Ar-H); 8.06-8.09 (m, 2H, Ar-H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$C 56.1, 56.3, 103.6, 105.9, 126.6, 127.0, 129.8, 131.1, 133.5, 148.1, 149.0, 165.1. MS (EI): $m/z$=271 [M$^+$]. Anal. Calcd for C$_{15}$H$_{13}$NO$_2$S: C, 66.40; H, 4.83; N, 5.16%. Found: C, 66.19; H, 4.85; N, 6.20%.
2.3.3 General procedure for the synthesis of benzoxazoles 2.3.3a'-2.3.3z'

To a pyrex reaction vessel were added 2-aminophenol (1.1 mmol), aldehyde (1.0 mmol), PIFA (1.05 mmol) in ethanol (3 mL). The reaction vessel was then placed in the Emrys Optimizer and exposed to microwave irradiation (80 °C) for 15 minutes. The reaction mixture was then allowed to cool at room temperature and quenched with 15 mL of water. The crude reaction mixture was extracted with EtOAc (3 X 15 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered, concentrated and purified by column chromatography on silica gel using petroleum ether/EtOAc to afford the pure product.

5-Methyl-2-(2-nitrophenyl)benzo[d]oxazole (2a')

Pink solid; mp 134-136 °C; $R_f = 0.49$ (AcOEt/petroleum ether 30%). IR (KBr): 3431, 2915, 1542, 1480, 1374, 1196, 1044, 800, 772 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 2.48 (s, 3H, -CH$_3$); 7.19 (d, 1H, $J = 8.4$ Hz, Ar-H); 7.42 (d, 1H, $J = 8.4$ Hz, Ar-H); 7.58 (s, 1H, Ar-H); 7.65 (t, 1H, $J = 7.6$ Hz, Ar-H); 7.71 (t, 1H, $J = 7.6$ Hz, Ar-H); 7.86 (d, 1H, $J = 7.6$ Hz, Ar-H); 8.11 (d, 1H, $J = 7.6$ Hz, Ar-H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$C 21.6, 110.4, 120.5, 121.6, 124.2, 127.3, 131.8, 132.4, 134.9, 141.7, 149.2, 149.3, 158.9. MS (EI): $m/z$=254 [M$^+$]. Anal. Calcd for C$_{14}$H$_{10}$N$_2$O$_3$: C, 66.14; H, 3.96; N, 11.02%. Found: C, 66.00; H, 4.02; N, 10.89%.

Methyl 4-(benzo[d]oxazol-2-yl)benzoate (2b')

Colourless solid; mp: 194-196 °C; $R_f=0.25$ (AcOEt/petroleum ether 50%). IR (KBr): 3091, 2925, 2852, 1725, 1606, 740, 707 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 3.97 (s, 3H, -COOCH$_3$); 7.35-7.43 (m, 2H, Ar-H); 7.60-7.63 (m, 1H, Ar-H); 7.79-7.81 (m, 1H, Ar-H); 8.20 (d, 2H, $J = 8.4$ Hz, Ar-H); 8.35 (d, 2H, $J = 8.4$ Hz, Ar-H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$C 52.4, 120.3, 124.9, 125.7, 127.5, 129.5, 130.1, 131.0, 132.6, 141.9, 150.8, 161.9,
166.3. MS (EI): \( m/z = 253 \) [M⁺]. Anal. Calcd for C₁₅H₁₁NO₃: C, 71.14; H, 4.38; N, 5.53%. Found: C, 70.36; H, 4.33; N, 5.44%.

2-(2-Chlorophenyl)-5-methylbenzo[d]oxazole (2c')

Colorless solid; mp 74-76 °C; \( R_f = 0.59 \) (AcOEt/petroleum ether 25%). IR (KBr): 2921, 1734, 1590, 1548, 1468, 1423, 1325, 1263, 1194, 1019, 774, 730 cm⁻¹. \(^1\)H NMR (500 MHz, CDCl₃) \( \delta_H \) 2.49 (s, 3H, -CH₃); 7.18 (d, 1H, \( J = 8.4 \) Hz, Ar-H); 7.38 (m, 2H, Ar-H); 7.47 (d, 1H, \( J = 8.4 \) Hz, Ar-H); 7.54 (d, 1H, \( J = 9.2 \) Hz, Ar-H); 7.62 (s, 1H, Ar-H); 8.11 (d, 1H, \( J = 8.4 \) Hz, Ar-H). \(^{13}\)C NMR (125 MHz, CDCl₃) \( \delta_C \) 21.6, 110.2, 120.4, 123.5, 126.5, 126.8, 126.9, 131.4, 131.9, 133.5, 134.6, 141.9, 148.9, 161.1. MS (EI): \( m/z = 245 \) [M⁺], 247 [M⁺²]. Anal. Calcd for C₁₄H₁₀ClNO: C, 69.00; H, 4.14; N, 5.75%. Found: C, 69.22; H, 4.25; N, 5.88%.

2-(4-Chlorophenyl)benzo[d]oxazole (2d')

Colourless solid; mp: 143-145 °C; \( R_f = 0.50 \) (AcOEt/petroleum ether 10%). IR (KBr): 2921, 1621, 1439, 1245, 1092, 740 cm⁻¹. \(^1\)H NMR (500 MHz, CDCl₃) \( \delta_H \) 7.28-7.32 (m, 2H, Ar-H); 7.40-7.45 (m, 2H, Ar-H); 7.49-7.53 (m, 1H, Ar-H); 7.66-7.70 (m, 1H, Ar-H); 8.10-8.13 (m, 2H, Ar-H). \(^{13}\)C NMR (125 MHz, CDCl₃) \( \delta_C \) 110.5, 120.0, 124.9, 125.1, 125.8, 128.6, 130.0, 129.1, 129.2, 137.9, 141.9, 150.9, 161.8. MS (EI): \( m/z = 229 \) [M⁺], 231 [M⁺²]. Anal. Calcd for C₁₃H₆ClNO: C, 67.99; H, 3.51; N, 6.10%. Found: C, 67.81; H, 3.56; N, 6.18%.

2-p-Tolylbenzo[d]oxazole (2e')

Colourless solid; mp: 115-117 °C; \( R_f = 0.50 \) (AcOEt/petroleum ether 10%). IR (KBr): 3088, 1628, 1244, 1055 cm⁻¹. \(^1\)H NMR (500 MHz, CDCl₃) \( \delta_H \) 2.41 (s, 3H, -CH₃); 6.83-7.16 (4H, m, Ar-H); 7.35-7.81 (m, 4H, Ar-H). \(^{13}\)C NMR (125 MHz, CDCl₃) \( \delta_C \) 22.4, 110.6, 120.8, 123.5, 125.5, 126.8, 127.9,
131.1, 142.2, 150.9, 164.7. MS (EI): $m/z=209$ [M$^+$]. Anal. Calcd for 
C$_{14}$H$_{11}$NO: C, 80.36; H, 5.30; N, 6.69%. Found: C, 80.12; H, 5.35; N, 6.77%.

2-(3,4,5-Trimethoxyphenyl)benzo[d]oxazole (2f')

Colourless solid; mp 111-113 °C; $R_f=0.25$ (AcOEt/petroleum ether 10%). IR (KBr): 2935, 1632, 1246, 1145, 1058 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta_H$ 3.89 (s, 3H, -OCH$_3$); 3.91 (s, 3H, -OCH$_3$); 3.96 (s, 3H, -OCH$_3$); 7.35-7.69 (m, 4H, Ar-H) 7.99-8.18 (m, 2H, Ar-H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta_C$ 57.0, 57.5, 58.7, 112.8, 122.7, 124.4, 127.5, 131.0, 132.5, 143.4, 149.5, 150.1, 151.1. MS (EI): $m/z=285$ [M$^+$]. Anal. Calcd for C$_{16}$H$_{15}$NO$_4$: C, 67.36; H, 5.30; N, 4.91%. Found: C, 67.51; H, 5.26; N, 4.85%.

Methyl 3-(benzo[d]oxazol-2-yl)benzoate (2g')

Yellow solid; mp: 128-130 °C; $R_f=0.30$ (AcOEt/petroleum ether 50%). IR (KBr): 3083, 2950, 2922, 1720, 1606, 745 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta_H$ 3.96 (s, 3H, -COOC$_2$H$_3$); 7.22 (d, 1H, $J=8.4$ Hz, Ar-H); 7.48 (d, 1H, $J=8.4$ Hz Ar-H); 8.35-8.41 (m, 4H, Ar-H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta_C$ 110.7, 120.1, 124.9, 125.5, 127.4, 128.7, 129.2, 131.1, 131.7, 132.5, 141.7, 150.7, 162.0, 166.2. MS (EI): $m/z=253$ [M$^+$]. Anal. Calcd for C$_{15}$H$_{13}$NO$_5$: C, 71.14; H, 4.38; N, 5.53%. Found: C, 70.99; H, 4.41; N, 5.60%.

5-Methyl-2-(4-nitrophenyl)benzo[d]oxazole (2h')

Pale yellow solid; mp 218-250 °C; $R_f=0.44$ (AcOEt/petroleum ether 30%). IR (KBr): 3402, 1556, 1521, 1342, 854, 706 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta_H$ 2.50 (s, 3H, -CH$_3$); 7.22 (d, 1H, $J=8.4$ Hz, Ar-H); 7.48 (d, 1H, $J=8.4$ Hz Ar-H); 7.59 (s, 1H, Ar-H); 8.35-8.41 (m, 4H, Ar-H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta_C$ 21.6, 110.4, 120.5, 124.3, 127.6, 128.4, 133.0, 135.3, 142.2, 149.4, 160.8, 162.7. MS (EI): $m/z=254$ [M$^+$]. Anal. Calcd for C$_{14}$H$_{10}$N$_2$O$_3$: C, 66.14; H, 3.96; N, 11.02%. Found: C, 66.32; H, 4.10; N, 10.92%.
5-Nitro-2-phenylbenzo[d]oxazole (2i')

Yellow solid; mp: 241-243 °C; Rf=0.20 (AcOEt/petroleum ether 30%). IR (KBr): 1641, 1525, 1350, 1247, 1051 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δH 7.51-7.58 (m, 3H, Ar-H); 7.70 (d, 1H, J = 9.2 Hz, Ar-H); 8.22-8.27 (m, 2H, Ar-H); 8.29 (dd, 1H, J = 9.2, 2.1 Hz, Ar-H); 8.65 (d, 2H, J = 2.1 Hz, Ar-H). ¹³C NMR (125 MHz, CDCl₃) δC 110.8, 116.1, 121.0, 125.8, 127.9, 129.0, 132.5, 142.5, 154.0. MS (EI): m/z = 240 [M⁺]. Anal. Calcd for C₁₃H₈N₂O₃: C, 65.00; H, 3.36; N, 11.66%. Found: C, 64.81; H, 3.41; N, 11.75%.

2-(4-Bromophenyl)benzo[d]oxazole (2j')

Pale yellow solid; mp: 142-144 °C; Rf=0.40 (AcOEt/petroleum ether 25%). IR (KBr): 1581, 1501, 1269, 1052, 944, 830, 799 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δH 7.30-7.37 (m, 2H, Ar-H); 7.50-7.55 (m, 1H, Ar-H); 7.60-7.65 (m, 2H, Ar-H); 7.70-7.75 (m, 1H, Ar-H); 8.05-8.10 (m, 2H, Ar-H). ¹³C NMR (125 MHz, CDCl₃) δC 110.5, 120.0, 124.6, 125.5, 126.1, 126.3, 128.9, 132.3, 142.0, 150.5, 161.9. MS (EI): m/z = 273 [M⁺], 275 [M⁺²]. Anal. Calcd for C₁₃H₈BrNO: C, 56.96; H, 2.94; N, 5.11%. Found: C, 57.16; H, 2.90; N, 5.05%.

2-(4-Nitrophenyl)benzo[d]oxazole (2k')

Yellow solid; mp: 262-264 °C; Rf=0.25 (AcOEt/petroleum ether 50%). IR (KBr): 1640, 1524, 1346, 1242, 1058 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δH 7.75-8.11 (m, 4H, Ar-H); 8.22-8.5 (4H, m, Ar-H). ¹³C NMR (125 MHz, CDCl₃) δC 112.4, 120.8, 124.8, 126.0, 127.0, 129.1, 130.7, 141.0, 148.9, 150.5, 161.0. MS (EI): m/z = 240 [M⁺]. Anal. Calcd for C₁₃H₈N₃O₃: C, 65.00; H, 3.36; N, 11.66%. Found: C, 65.13; H, 3.31; N, 11.58%.
2-(Benzod[d][1,3]dioxol-5-yl)benzo[d]oxazole (2l')

Yellow solid; mp 147-149 °C; Rf=0.30 (AcOEt/petroleum ether 20%). IR (KBr): 2931, 1639, 1245, 1042, 1115, 761 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δH 4.39 (s, 2H, -OCH₂O-); 6.86-7.02 (m, 3H, Ar-H); 7.37-7.78 (m, 4H, Ar-H). ¹³C NMR (125 MHz, CDCl₃) δC 91.1, 113.0, 114.5, 119.0, 124.8, 125.5, 131.0, 138.4, 145.2, 146.7. MS (EI): m/z=239 [M⁺]. Anal. Calcd for C₁₄H₉NO₃: C, 70.29; H, 3.79; N, 5.86%. Found: C, 70.51; H, 3.66; N, 5.79%.

2-(4-Methoxyphenyl)benzo[d]oxazole (2m')

Colourless solid; mp: 97-99 °C; Rf=0.55 (AcOEt/petroleum ether 10%). IR (KBr): 3052, 1618, 1255, 1248, 1037, 1025, 802 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δH 3.88 (s, 3H, -OCH₃); 7.00 (d, 2H, J = 8.4 Hz, Ar-H); 7.29-7.36 (m, 2H, Ar-H); 7.48-7.52 (m, 1H, Ar-H); 7.65-7.73 (m, 1H, Ar-H); 8.21 (d, 2H, J = 8.7 Hz, Ar-H). ¹³C NMR (125 MHz, CDCl₃) δC 55.5, 110.5, 114.5, 119.5, 119.9, 124.5, 124.8, 129.4, 142.3, 150.8, 162.3, 162.8. MS (EI): m/z=225 [M⁺]. Anal. Calcd for C₁₄H₁₁NO₂: C, 74.65; H, 4.92; N, 6.22%. Found: C, 74.81; H, 4.89; N, 6.15%.

2-(3,4-Dichlorophenyl)benzo[d]oxazole (2n')

Colourless solid; mp: 139-141 °C; Rf=0.50 (AcOEt/petroleum ether 30%). IR (KBr): 2963, 1620, 1440, 1241, 1099, 747 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δH 7.20-7.24 (m, 2H, Ar-H); 7.31-7.39 (m, 2H, Ar-H); 7.55-7.63 (m, 1H, Ar-H); 7.75-7.80 (m, 1H, Ar-H); 8.05 (dt, 1H, J = 8.1, 2.1 Hz, Ar-H); 8.34 (t, 1H, J = 2.1 Hz, Ar-H). ¹³C NMR (125 MHz, CDCl₃) δC 110.5, 120.0, 125.0, 125.6, 126.3, 127.0, 129.2, 131.0, 133.3, 141.6, 150.5, 160.9. MS (EI): m/z=263 [M⁺], 265 [M⁺²], 267 [M⁺³]. Anal. Calcd for C₁₃H₇Cl₂NO: C, 59.12; H, 2.67; N, 5.30%. Found: C, 58.96; H, 2.71; N, 5.37%.
2-(3-Methoxyphenyl)benzol[d]oxazole (2o')

Yellow solid; mp: 107-109 °C; R<sub>f</sub>=0.50 (AcOEt/petroleum ether 10%). IR (KBr): 3055, 1620, 1250, 1241, 1030, 1021 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 3.95 (s, 3H, -OC<sub>3</sub>H<sub>3</sub>); 7.10-7.15 (m, 1H, Ar-H); 7.35-7.41 (m, 2H, Ar-H); 7.47 (dd, 1H, <i>J</i> = 8.1, 8.1 Hz, Ar-H); 7.60-7.65 (m, 1H, Ar-H); 7.75-7.82 (m, 2H, Ar-H); 7.85-7.90 (m, 1H, Ar-H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) 55.5, 110.7, 112.1, 118.5, 119.9, 124.4, 125.0, 128.2, 128.9, 141.9, 151.0, 159.9, 162.8. MS (EI): <i>m/z</i>=225 [M<sup>+</sup>]. Anal. Calcd for C<sub>14</sub>H<sub>11</sub>NO<sub>2</sub>: C, 74.65; H, 4.92; N, 6.22%. Found: C, 74.52; H, 4.95; N, 6.29%.

5-Chloro-2-(3-nitrophenyl)benzol[d]oxazole (2p')

Colorless solid; mp 184-186 °C; R<sub>f</sub>=0.52 (AcOEt/petroleum ether 30%). IR (KBr): 3424, 2361, 1526, 1449, 1351, 1100, 821 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 7.38 (q, 1H, <i>J</i> = 8.4 Hz, Ar-H); 7.54 (d, 1H, <i>J</i> = 9.1 Hz, Ar-H); 7.72 (d, 1H, <i>J</i> = 8.4 Hz, Ar-H); 7.78 (s, 1H, Ar-H); 8.39 (d, 1H, <i>J</i> = 8.8 Hz, Ar-H); 8.55 (d, 1H, <i>J</i> = 7.6 Hz, Ar-H); 9.07 (s, 1H, Ar-H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) 111.8, 120.5, 122.7, 126.3, 126.5, 130.4, 130.7, 133.3, 142.9, 149.5, 157.5, 161.9. MS (EI): <i>m/z</i>=274 [M<sup>+</sup>], 276 [M<sup>+</sup>+2]. Anal. Calcd for C<sub>13</sub>H<sub>7</sub>ClN<sub>2</sub>O<sub>3</sub>: C, 56.85; H, 2.57; N, 10.20%. Found: C, 56.75; H, 2.49; N, 10.15%.

2-Phenylbenzol[d]oxazole (2q')

Colourless solid; mp: 100-102 °C; R<sub>f</sub>=0.60 (AcOEt/petroleum ether 10%). IR (KBr): 2975, 1614, 1248, 1040, 803 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 7.35-7.40 (m, 2H, Ar-H); 7.50-7.55 (m, 2H, Ar-H); 7.60-7.63 (m, 1H, Ar-H); 7.75-7.85 (m, 1H, Ar-H); 8.25-8.31 (m, 2H, Ar-H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) 110.5, 120.0, 124.5, 125.0, 127.0, 127.8, 129.0, 131.6, 142.0, 150.8, 162.9. MS (EI): <i>m/z</i>=195 [M<sup>+</sup>]. Anal. Calcd for C<sub>13</sub>H<sub>9</sub>NO: C, 79.98; H, 4.65; N, 7.17%. Found: C, 80.11; H, 4.61; N, 7.08%. 
2-(2-Chlorophenyl)benzo[d]oxazole (2r')

Colorless solid; mp 61-64 °C; $R_f$=0.53 (AcOEt/petroleum ether 30%). IR (KBr): 2953, 1537, 1430, 1253, 1194, 1022, 806, 738 cm⁻¹. $^1$H NMR (500 MHz, CDCl₃) $\delta_H$ 7.36-7.46 (m, 4H, Ar-H); 7.56-7.57 (m, 1H, Ar-H); 7.61-7.62 (m, 1H, Ar-H); 7.84-7.86 (m, 1H, Ar-H); 8.13 (dd, 1H, $J = 7.6, 2.3$ Hz, Ar-H). $^{13}$C NMR (125 MHz, CDCl₃) $\delta_C$ 110.9, 120.6, 124.8, 125.7, 126.2, 127.1, 131.5, 131.9, 132.0, 133.6, 141.8, 150.6, 161.1. MS (EI): $m/z$=229 [M⁺], 231 [M⁺²]. Anal. Calcd for C₁₃H₈ClNO: C, 67.99; H, 3.51; N, 6.10%. Found: C, 68.11; H, 3.62; N, 5.99%.

2-(Furan-2-yl)benzo[d]oxazole (2s')

Colourless solid; mp 90-92 °C; $R_f$=0.45 (AcOEt/petroleum ether 15%). IR (KBr): 2926, 1620, 1245, 1141, 1046, 751 cm⁻¹. $^1$H NMR (500 MHz, CDCl₃) $\delta_H$ 6.51-6.98 (m, 3H, Ar-H); 7.02-7.56 (m, 4H, Ar-H). $^{13}$C NMR (125 MHz, CDCl₃) $\delta_C$ 103.9, 115.0, 116.2, 124.5, 125.6, 126.2, 145.0, 146.3, 150.5, 153.1, 156.5. MS (EI): $m/z$=185 [M⁺]. Anal. Calcd for C₁₁H₇NO₂: C, 71.35; H, 3.81; N, 7.56%. Found: C, 71.05; H, 3.86; N, 7.65%.

2-(Thiophen-2-yl)benzo[d]oxazole (2t')

Yellow solid; mp 104-106 °C; $R_f$=0.50 (AcOEt/petroleum ether 10%). IR (KBr): 2930, 1638, 1252, 1135, 1043, 749 cm⁻¹. $^1$H NMR (500 MHz, CDCl₃) $\delta_H$ 6.66-6.98 (m, 3H, Ar-H); 7.52-7.72 (m, 4H, Ar-H). $^{13}$C NMR (125 MHz, CDCl₃) $\delta_C$ 112.5, 120.8, 124.5, 125.0, 126.5, 127.0, 127.2, 138.0, 140.6, 149.1, 154.6. MS (EI): $m/z$=201 [M⁺]. Anal. Calcd for C₁₁H₇NOS: C, 65.65; H, 3.51; N, 6.96%. Found: C, 65.83; H, 3.46; N, 6.88%.
2-(1H-Pyrrol-2-yl)benzo[d]oxazole (2u')

Pink solid; mp 144-146 °C; \( R_f = 0.51 \) (AcOEt/petroleum ether 30%). IR (KBr): 3401, 1629, 1585, 1455, 1403, 1243, 1117, 741 cm\(^{-1}\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta_H \) 6.36-6.38 (m, 1H, Ar-H); 7.04-7.05 (m, 1H, Ar-H); 7.28-7.33 (m, 2H, Ar-H); 7.52 (d, 1H, \( J = 7.6 \) Hz, Ar-H); 7.64 (d, 1H, \( J = 7.6 \) Hz, Ar-H); 10.25 (s, 1H, -NH). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta_C \) 110.5, 110.9, 113.3, 118.9, 119.9, 123.1, 124.4, 124.7, 150.2, 158.2, 163.7. MS (EI): \( m/z = 184 \) [M\(^+\)]. Anal. Calcd for C\(_{11}\)H\(_8\)N\(_2\)O: C, 71.73; H, 4.38; N, 15.21%. Found: C, 71.81; H, 4.25; N, 15.25%.

2-(1-Methyl-1H-indol-2-yl)benzo[d]oxazole (2v')

Colorless solid; mp 161-163 °C; \( R_f = 0.55 \) (AcOEt/petroleum ether 25%). IR (KBr): 2332, 1579, 1450, 1340, 1240, 1141, 753 cm\(^{-1}\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta_H \) 4.31 (s, 3H, -NCH\(_3\)); 7.18 (t, 1H, \( J = 7.6 \) Hz, Ar-H); 7.35-7.38 (m, 3H, Ar-H); 7.42 (d, 2H, \( J = 10.7 \) Hz, Ar-H); 7.57 (d, 1H, \( J = 7.6 \) Hz, Ar-H); 7.72 (d, 1H, \( J = 7.6 \) Hz, Ar-H); 7.80 - 780 (m, 1H, Ar-H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta_C \) 32.2, 107.6, 110.2, 110.5, 119.9, 120.7, 122.1, 124.5, 124.6, 125.2, 126.3, 126.9, 139.9, 142.2, 149.9, 157.8. MS (EI): \( m/z = 248 \) [M\(^+\)]. Anal. Calcd for C\(_{16}\)H\(_{12}\)N\(_2\)O: C, 77.40; H, 4.87; N, 11.28%. Found: C, 77.55; H, 4.75; N, 11.39%.
2-[3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]benzo[d]oxazole (2w')

Colorless solid; mp 205-207 °C; $R_f=0.44$ (AcOEt/petroleum ether 25%). IR (KBr): 3411, 1627, 1590, 1502, 1454, 1391, 1244, 1093, 989 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta_H$ 7.32-7.33 (m, 2H, Ar-H); 7.37-7.39 (m, 1H, Ar-H); 7.45-7.53 (m, 5H, Ar-H); 7.71 (d, 1H, $J = 9.1$ Hz, Ar-H); 7.81 (d, 2H, $J = 8.4$ Hz, Ar-H); 7.99 (d, 2H, $J = 8.4$ Hz, Ar-H); 8.1 (s, 1H, pyrazolyl-H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta_C$ 110.3, 110.4, 119.5, 124.6, 124.9, 127.7, 128.5, 129.8, 130.3, 130.6, 134.9, 139.3, 141.9, 150.2, 151.1, 158.1. MS (EI): $m/z=372$ [M$^+$], 374 [M$^+2$]. Anal. Calcd for C$_{22}$H$_{14}$ClN$_3$O: C, 71.07; H, 3.80; N, 11.30%. Found: C, 71.25; H, 3.75; N, 11.25%.

2-[3-(4-Bromophenyl)-1-phenyl-1H-pyrazol-4-yl]-5-methylbenzo[d]oxazole (2x')

Colorless solid; mp 210-214 oC; $R_f=0.52$ (AcOEt/petroleum ether 30%). IR (KBr): 2920, 1589, 1500, 1262, 1223, 1057, 944, 830, 799 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta_H$ 2.46 (s, 3H, -CH$_3$); 7.11 (d, 1H, $J = 8.4$ Hz, Ar-H); 7.34-7.39 (m, 2H, Ar-H); 7.49-7.52 (m, 3H, Ar-H); 7.60 (d, 2H, $J = 8.4$ Hz, Ar-H); 7.80 (d, 2H, $J = 7.6$ Hz, Ar-H); 7.91 (d, 2H, $J = 8.4$ Hz, Ar-H); 8.68 (s, 1H, pyrazolyl-H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta_C$ 21.6, 109.7, 110.4, 119.8, 123.3, 126.1, 127.7, 129.7, 130.9, 131.1, 131.4. MS (EI): $m/z=430$ [M$^+$], 432 [M$^+2$]. Anal. Calcd for C$_{23}$H$_{15}$BrN$_3$O: C, 64.20; H, 3.75; N, 9.77%. Found: C, 64.25; H, 3.69; N, 10.02%.

2-[3-(4-Ethoxyphenyl)-1-phenyl-1H-pyrazole-4-yl]benzo[d]oxazole (2y')

Orange solid; mp 189-191 °C; $R_f=0.44$ (AcOEt/petroleum ether 50%). IR (KBr): 3430, 2930, 1631, 1583, 1450, 1240, 1045, 750 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta_H$ 1.43 (t, 3H, $J = 6.9$ Hz, -OCH$_2$CH$_3$); 4.09 (q, 2H, $J = 6.9$ Hz, -OCH$_2$CH$_3$); 6.98 (d, 2H, $J = 9.1$ Hz, Ar-H); 7.26-7.29 (m, 2H, Ar-H); 7.34 (t, 1H, $J = 7.6$ Hz, Ar-H); 7.46-7.54 (m, 3H, Ar-H); 7.69 (d, 1H, $J = 6.9$ Hz, Ar-H); 7.80 (d, 2H, $J = 7.6$ Hz, Ar-H); 7.94 (d, 2H, $J = 8.4$ Hz, Ar-
H); 8.68 (s, 1H, pyrazolyl-H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$C 14.9, 63.6, 109.9, 110.4, 114.3, 119.4, 119.8, 124.5, 124.7, 127.4, 129.7, 130.2, 130.6, 139.4, 142.0, 147.0, 150.2, 152.1, 158.6, 159.7. MS (EI): $m/z=381$ [M$^+$].

Anal. Calcd for C$_{24}$H$_{19}$N$_3$O$_2$: C, 75.57; H, 5.02; N, 11.02%. Found: C, 75.44; H, 5.11; N, 11.09%.

5-Chloro-2-phenylethylbenzo[d]oxazole (2z')

Yellow solid; mp 114-116 °C; $R_f=0.50$ (AcOEt/petroleum ether 40%). IR (KBr): 3402, 1621, 1585, 1488, 1391, 1239, 1088, 985 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 3.14 (t, 2H, $J = 7.6$ Hz); 3.29 (t, 2H, $J = 7.6$ Hz); 7.15-7.20 (m, 1H, Ar-H); 7.24-7.28 (m, 4H, Ar-H); 7.38 (dd, 1H, $J = 2.1, 8.6$ Hz, Ar-H); 7.71 (d, 1H, $J = 8.6$ Hz, Ar-H); 7.75-7.77 (m, 1H, Ar-H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$C 29.4, 31.6, 111.7, 119.0, 124.6, 126.2, 128.2, 128.3, 128.4, 140.0, 142.1, 148.9, 167.9. MS (EI): $m/z=257$ [M$^+$], 259 [M$^{+2}$].

Anal. Calcd for C$_{24}$H$_{19}$N$_3$O$_2$: C, 69.91; H, 4.69; N, 5.43%. Found: C, 70.07; H, 4.65; N, 5.47%.
2.3.4 Evaluation of in Vivo Analgesic Activity

Ten compounds of benzothiazoles (2h, 2j, 2l, 2n, 2o and 2u-2y) and benoxazoles (2a', 2c', 2h', 2p', 2r' and 2u'-2y') respectively were selected to evaluate the analgesic activity. To begin with the oral toxicity of the synthesized compounds was performed by acute toxic class method (Mehta et al 2009). The selected adult albino rats were used to determine the dose. The animals were fasted overnight prior to the acute experimental procedure. Following the period of fasting, the animals were weighed and the synthesized compounds were orally administered at a dose of 50 mg/kg body weight. Immediately after dosing, the animals were observed continuously for the first 30 min for behavioral changes and for mortality at the end of 24 h, 48 h, 72 h and 96 h respectively. As no mortality was observed with the above dose even after 96 h, the LD50 value of the compounds expected to exceed 50 mg/kg body weight. Toxicity assays showed that all the compounds proved to be non toxic at tested dose levels and well tolerated by the experimental animals as their LD50 cut – off values > 50 mg/kg body weight.

Analgesic activity of the synthesized compounds was determined using tail immersion method. Healthy Swiss mice (n=6) of either sex was elected by random sampling technique and placed into individual restraining cages leaving the tail hanging out freely. The animals were then allowed to adapt in the cages for 30 minutes before testing. The lower 5 cm portion of the tail was marked and immersed in a beaker of freshly filled warm water of at 55 ± 5°C. Within a few seconds the rat reacts by withdrawing the tail. The reaction time was recorded by a stop watch. After each determination the tail was carefully dried. This reaction was determined before oral feeding of the drug and synthesized compounds which were recorded as zero minutes reading. The test compounds, control (2% gum acacia) and standard
(pentazocine) at a dose level of 50 mg/kg body weight were administered orally by intragastric tube. The time (in seconds) to withdraw the tail clearly out of water was taken as the reaction time. The first reading (0 min) was taken immediately after the administration of the test compound and subsequent reaction time was recorded at 15, 30, 60 and 90 min respectively. The cut-off time of the immersion is 15 seconds. The mean reaction time was recorded for each group and compared with the value of the standard drug pentazocine. The percentage analgesic activity was calculated using the formula:

\[
\% \text{ potency} = \left( \frac{T_2 - T_1}{T_2} \right) \times 100
\]

Where, \( T_1 \) is the reaction time (in sec) before treatment and \( T_2 \) is the reaction time (in sec) after treatment.

2.3.5 Animals and Drug Dosage

2.3.5.1 Animals

The selection of animals, caring and handling was done as per the guidelines set by the Indian National Science Academy, New Delhi, India. Inbred albino mice (Swiss strain) of adult gender weighing 120-150 g were used for the study. The mice were housed individually in clean polypropylene cages containing sterile paddy husk (procured locally) as bedding throughout the experiment. All animals were fed with sterile commercial pelleted rat chow supplied by Hindustan Lever Ltd (Mumbai, India) with free access to water (ad libitum) under standardized housing conditions (natural light-dark cycle, temperature 23 ± 1 °C, relative humidity 55 ± 5%). After 7 days of adaptation to laboratory conditions, the animals were randomly assigned to 12 experimental groups of 5 mice each. Each mouse was used only once. All tests were performed between 08:00 and 16:00 h. All efforts were made to minimize animal suffering and to use only the minimum number of animals.
necessary to produce reliable scientific data. The experimental protocols and procedures listed below conformed to the Guide for the Care and Use of Laboratory Animals and approved by the Institutional Ethics Committee. Mice equivalent doses in mg/kg body weight of clinical doses were calculated as mg/kg body weight with the help of standard tables (Karber’s method).

2.3.5.2 Dose and administration of compounds

The synthesized compounds (50 mg/kg), pentazocine as a reference opioid analgesic drug (50 mg/kg) and 2% gum acacia as control were administered orally by intragastric tube.

2.3.5.3 Statistical analysis

The obtained data were analyzed using one-way analysis of variance (ANOVA) followed by Dunnet’s multiple comparison test using computerized Graph Pad Instat version 3.05 (Graph Pad software, U.S.A.). The results are presented as mean ± Standard Error of Means (SEM). Differences between data sets were considered as significant when $P < 0.001$. 
2.4 CONCLUSION

In summary, we have explored a useful and practical approach to benzoazoles and benzothiazoles by PIFA promoted cyclocondensation of 2-aminothiophenol/2-aminophenol with aldehydes. The current protocol is noteworthy, since it has advantages like wide substrate scope, short reaction time, microwave condition and satisfactory yields. Evaluation of analgesic activity of twenty compounds was performed by tail immersion test. All the tested compounds displayed varying degrees of analgesic activity. Benz(oxa)thiazole derivatives bearing pyrazolyl system exhibited comparable to or slightly less potent activity than the standard pentazocine.