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Microwave-assisted one-pot synthesis of benzothiazole and benzoxazole libraries as analgesic agents

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Abstract. Microwave-assisted synthesis of benzothiazole and benzoxazole libraries via PIFA promoted cyclocondensation of 2-aminothiophenols/2-aminophenols with aldehydes under one-pot condition in good to excellent yields was achieved. Twenty compounds have been investigated for their analgesic activity and showed moderate to good activity.

Keywords. Microwave; one-pot synthesis; benzothiazoles; benzoxazoles; analgesic activity.

1. Introduction

The biaryl pharmacophore of benzothiazole and benzoxazole exhibits a wide range of biological properties and has led to continued interest in medicinal chemistry.[1] The benzothiazolyl moiety is a component in various antagonists like Ca^{2+} channel,[2] LTD_4 [3] and orexin receptor.[4] Benzothiazoles are known to inhibit several enzymes such as acetyl cholinesterase,[5] monamine oxidase,[6–9] lipoxygenase,[10] lysophosphatidic acid acyltransferase-β,[11] aldose reductase,[12] cyclooxygenase,[13] carbonic anhydrase,[14] H^+-K^+ATPase,[15] HCV helicase,[16] protease[17] and stearoyl-coA δ-9 desaturase.[18] Other recognized pharmacological activities of benzothiazoles include antitumour,[19] antimicrobial,[20] antioxidant[21] and antiglutamate.[22] On the other hand, benzoxazole moiety is found in various pharmaceuticals displaying a broad spectrum of biological activity including antiinflammatory, antitumour, antirheumatic, antimicrobial and antiviral effects.[23] Other significant physiological activities associated with benzoxazoles are H37Rv inhibitory,[24] elastase inhibitory,[25] $5HT_3$ receptor agonist[26] and cytotoxicity towards P338 cells.[27]

The most useful synthesis of benzothiazoles include condensation of 2-aminobenzenethiol with carboxyl derivatives,[28] cyclization of *ortho*-haloanilides,[29] the radical cyclization of thioacylbenzanilides,[30] DMP mediated intramolecular cyclization of thioformanilides.[31] Apart from these general methods, there have been many methodologies disclosed in the literature for the construction of benzothiazoles.[32–40] On the other hand, the classical approach for the synthesis of benzoxazoles involves (i) coupling of carboxylic acids with 2-aminophenols by dehydration catalysed by strong acid;[41] and (ii) the oxidative cyclization of phenolic Schiff's bases derived from the condensation of 2-aminophenols and aldehydes, using various oxidants such as $PhI(OAc)_2$,[42] $Mn(OAc)_3$,[43] $ThClO_4$,[44] $Ba(MnO_4)_2$,[45] NiO_2,[46] $Pb(OAc)_4$,[47] DDQ,[48] NIS,[49] Cu-np,[50] aerial oxidation in the presence of activated carbon (Darco KB),[51] CuCl[52] and Pd/Pt-C.[53] Other synthetic routes for benzoxazole include microwave-assisted reaction of *N*-acyl-aminophenol,[54] iron catalysed intramolecular *O*-arylation of 2-haloacetanilides[55] and cyclization of phenolic Schiff base under UV irradiation.[56] Apart from these methodologies, there have been many precedents for the synthesis of 2-aryl benzothiazoles and benzoxazoles via palladium catalysed cross-coupling reactions have been disclosed in the literature.[57]

The synthetic scope of the aforesaid protocols is limited by two factors: (i) lack of general procedure that supports the synthesis of both benzothiazoles and benzoxazoles, (ii) lack of practical synthesis supporting structurally diverse spacers and substitution patterns in the target library. Thus, it is clear that an efficient protocol is needed. In the context of heterocycle

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synthesis,[58] we have already addressed this problem by employing PCC as an effective oxidant for the synthesis of both benzothiazoles and benzoxazoles via oxidative cyclization of thiophenolic and phenolic Schiff's bases, respectively.[58a] Although the substrate scope was modestly explored, this procedure is limited by the powerful oxidizing ability of PCC and the potential carcinogenicity of Cr^{6+}. In order to circumvent this limitation, we envisaged an alternate oxidant for the synthesis of benz(oxa)thiazoles. In this paper, we report PIFA [phenyliodonium bis(trifluoroacetate)] as an effective oxidant for the one-pot synthesis of benz(oxa)thiazoles via cyclocondensation of 2-aminothiophenols/2-aminophenols with aldehydes under microwave irradiation. Representative compounds were screened for their *in vivo* analgesic activity and the results were presented.

2. Experimental

2.1 *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 (δ) 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 nH. 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 ±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 (λ = 254 and 365 nm).

2.2 *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°C) for 15 min. 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 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated and purified by column chromatography on silica gel using petroleum ether/EtOAc to afford the pure product.

2.2a *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, -OCH_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%.

2.2b *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, $J = 0.8, 0.8, 8.4$ 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 ($J_{C\text{-}F} = 268.0$ Hz), 125.5, 126.0 ($J_{C\text{-}F} = 3.6$ Hz), 126.7, 132.4 ($J_{C\text{-}F} = 32.9$ Hz), 135.0, 136.7, 154.2, 159.9. MS (EI): $m/z = 280$ [M+H]$^+$. Anal. Calcd for $C_{14}H_8F_3NS$: C, 60.21; H, 2.89; N, 5.02%. Found: C, 59.99; H, 2.94; N, 5.11%.

2.2c *4-(Benzo[d]thiazol-2-yl)-N,N-dimethylbvenzenamine (**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, $CDCl_3$) δ_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,

$CDCl_3$) δ_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 $C_{15}H_{14}N_2S$: C, 70.83; H, 5.55; N, 11.01%. Found: C, 71.01; H, 5.51; N, 10.92%.

2.2d *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}. ^1H NMR (500 MHz, $CDCl_3$) δ_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, $CDCl_3$) δ_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 $[M^{+2}]$. Anal. Calcd for $C_{13}H_8ClNS$: C, 63.54; H, 3.28; N, 5.70%. Found: C, 63.75; H, 3.24; N, 5.63%.

2.2e *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}. ^1H NMR (500 MHz, $CDCl_3$) δ_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, $CDCl_3$) δ_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%.

2.2f *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}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 3.99 (s, 3H, -COOCH_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, $CDCl_3$) δ_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 $C_{15}H_{11}NO_2S$: C, 66.89; H, 4.12; N, 5.20%. Found: C, 67.10; H, 4.06; N, 5.11%.

2.2g *5-Methoxy-2-phenylbenzo[d]thiazole (**2g**)*: Colourless 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}. ^1H NMR (500 MHz, $CDCl_3$) δ_H 3.86 (s, 3H, -OCH_3); 7.05 (dd, 1H, J_1 = 2.6 Hz, J_2 = 9.1 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, $CDCl_3$) δ_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 $C_{14}H_{11}NOS$: C, 69.68; H, 4.59; N, 5.80%. Found: C, 69.48; H, 4.61; N, 5.87%.

2.2h *2-(3-Nitrophenyl)benzo[d]thiazole (**2h**)*: Colourless 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}. ^1H NMR (500 MHz, $CDCl_3$) δ_H 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, $CDCl_3$) δ_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 $C_{13}H_8N_2SO_2$: C, 60.92; H, 3.15; N, 10.93%. Found: C, 60.75; H, 3.22; N, 10.89%.

2.2i *2-(2-Methoxyphenyl)benzo[d]thiazole (**2i**)*: Colourless solid; mp 123–125°C; R_f = 0.55 (AcOEt/petroleum ether 10%). IR (KBr): 3024, 2999, 2900, 2837, 1604, 1521, 1485, 1260, 831 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_H 3.99 (s, 3H, -OCH_3); 7.10–7.55 (m, 4H, Ar-H); 7.92–8.49 (m, 4H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_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 $C_{14}H_{11}NOS$: C, 69.68; H, 4.59; N, 5.80%. Found: C, 69.91; H, 4.53; N, 5.70%.

2.2j *2-(2-Chlorophenyl)benzo[d]thiazole (**2j**)*: Colourless solid; mp 71–73°C; R_f = 0.39 (AcOEt/petroleum ether 10%). IR (KBr): 3053, 2359, 1559, 1454, 1429, 1316, 1270, 1059, 965, 749, 726 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_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). ^{13}C NMR (125 MHz, $CDCl_3$) δ_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 $C_{13}H_8ClNS$: C, 63.54; H, 3.28; N, 5.70%. Found: C, 63.44; H, 3.33; N, 5.67%.

2.2k *2-(3,4-Dimethoxyphenyl)benzo[d]thiazole (**2k**)*: Colourless solid; mp 133–135°C; R_f = 0.54 (AcOEt/petroleum ether 20%). IR (KBr): 2955, 2940, 2840, 1600, 1521, 1483, 1431, 1336, 1312, 1260, 1167, 1145, 1075 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_H 3.96

(s, 3H, -OCH_3); 4.03 (s, 3H, -OCH_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). ^{13}C NMR (125 MHz, $CDCl_3$) δ_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 $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16%. Found: C, 66.61; H, 4.79; N, 5.04%.

2.2l *2-[4-(Benzyloxy)-3-methoxyphenyl]benzo[d] thiazole (**2l**)*: Colourless 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, $CDCl_3$) δ_H 3.94 (s, 3H, -OCH_3); 5.22 (s, 2H, -OC$H_2C_6H_5$); 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, $CDCl_3$) δ_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 (EI): 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%.

2.2m *4-(Benzo[d]thiazol-2-yl)-2,6-methoxyphenol (**2m**)*: Colourless 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, $CDCl_3$) δ_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, $CDCl_3$) δ_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 (EI): m/z = 287 [M^+]. Anal. Calcd for $C_{15}H_{13}NO_3S$: C, 62.70; H, 4.56; N, 4.87%. Found: C, 62.88; H, 4.51; N, 4.81%.

2.2n *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, $CDCl_3$) δ_H 3.93 (s, 6H, -OCH_3); 5.09 (s, 2H, -OC$H_2C_6H_5$); 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, $CDCl_3$) δ_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%.

2.2o *4-(1,3-Benzo[d]thiazol-2-yl)-2-bromo-6-methoxyphenol (**2o**)*: Colourless 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) δ_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) δ_C 56.9, 109.7, 110.2, 122.8, 123.1, 124.1, 125.5, 125.8, 127.2, 134.9, 147.4, 149.2, 153.9, 166.5. MS (EI): m/z = 335 [M^+], 337 [M^{+2}]. Anal. Calcd for $C_{14}H_{10}BrNO_2S$: C, 50.01; H, 3.00; N, 4.17%. Found: C, 49.89; H, 3.09; N, 4.10%.

2.2p *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, $CDCl_3$) δ_H 6.07 (s, 2H, -OCH_2O-); 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, $CDCl_3$) δ_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 $C_{14}H_9NO_2S$: C, 65.87; H, 3.55; N, 5.49%. Found: C, 66.01; H, 3.51; N, 5.42%.

2.2q *2-(Phenylbenzo[d]thiazole (**2q**)*: Colourless solid; mp 114–116°C; R_f = 0.60 (AcOEt/petroleum ether 10%). IR (KBr): 3064, 1588, 1555, 1509, 1478, 1433, 1244, 962, 766 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ_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). ^{13}C NMR (125 MHz, $CDCl_3$) δ_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^+]. Anal. Calcd for $C_{13}H_9NS$: C, 73.90; H, 4.29; N, 6.63%. Found: C, 74.05; H, 4.24; N, 6.55%.

2.2r *2-(Pyridin-2-yl)benzo[d]thiazole (**2r**)*: Yellow solid; mp 130–131°C; R_f = 0.15 (AcOEt/petroleum ether 40%). IR (KBr): 3322, 3079, 2901, 1655, 989, 874 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ_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). ^{13}C NMR (125 MHz, $CDCl_3$) δ_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 $[M+H]^+$. Anal. Calcd for $C_{12}H_8N_2S$: C, 67.90; H, 3.80; N, 13.20%. Found: C, 68.10; H, 3.76; N, 13.11%.

2.2s *2-(Thiophen-2-yl)benzo[d]thiazole (**2s**)*: Colourless solid; mp 98–100°C; R_f = 0.65 (AcOEt/petroleum ether 15%). IR (KBr): 3083, 3043, 1628, 1064, 829 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ_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). ^{13}C NMR (125 MHz, $CDCl_3$) δ_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 $[M^+]$. Anal. Calcd for $C_{11}H_7NS_2$: C, 60.80; H, 3.25; N, 6.45%. Found: C, 60.99; H, 3.21; N, 6.39%.

2.2t *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, $CDCl_3$) δ_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). ^{13}C NMR (125 MHz, $CDCl_3$) δ_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 $C_{11}H_7NOS$: C, 65.65; H, 3.51; N, 6.96%. Found: C, 65.41; H, 3.56; N, 7.02%.

2.2u *2-(1-Methyl-1H-indol-2-yl)benzo[d]thiazole (**2u**)*: Colourless 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, $CDCl_3$) δ_H 4.31 (s, 3H, -NCH_3); 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, $CDCl_3$) δ_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 $C_{16}H_{12}N_2S$: C, 72.70; H, 4.58; N, 10.60%. Found: C, 72.81; H, 4.62; N, 10.53%.

2.2v *2-[3-(4-Bromophenyl)-1-phenyl-1H-pyrazol-4-yl]benzo[d]thiazole (**2v**)*: Colourless 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}. 1H NMR (500 MHz, $CDCl_3$) δ_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, $CDCl_3$) δ_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 $C_{22}H_{13}N_3SBr$: C, 61.12; H, 3.26; N, 9.72%. Found: C, 61.00; H, 3.33; N, 9.77%.

2.2w *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, $CDCl_3$) δ_H 1.46 (t, 3H J = 7.5 Hz, -OCH_2CH_3); 4.10 (q, 2H J = 6.8 Hz, -OCH_2CH$_3$); 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, $CDCl_3$) δ_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 $C_{24}H_{19}N_3OS$: C, 72.52; H, 4.82; N, 10.57%. Found: C, 72.67; H, 4.75; N, 10.22%.

2.2x *2-[3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]benzo[d]thiazole (**2x**)*: Colourless 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, $CDCl_3$) δ_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, $CDCl_3$) δ_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 $C_{22}H_{14}ClN_3S$: C, 68.12; H, 3.64; N, 10.83%. Found: C, 67.99; H, 3.76; N, 10.90%.

2.2y *2-[3-(4-Methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl]benzo[d]thiazole (**2y**)*: Colourless 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}. ^1H NMR (500 MHz, $CDCl_3$) δ_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, $CDCl_3$) δ_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 $C_{23}H_{17}N_3SO$: C, 72.02; H, 4.47; N, 10.96%. Found: C, 71.89; H, 4.45; N, 11.01%.

2.2z *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}. ^1H NMR (500 MHz, $CDCl_3$) δ_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, $CDCl_3$) δ_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 $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16%. Found: C, 66.19; H, 4.85; N, 6.20%.

2.3 *General procedure for the synthesis of benzoxazoles **2a′–2z′***

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 min. 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 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated and purified by column chromatography on silica gel using petroleum ether/EtOAc to afford the pure product.

2.3a *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}. ^1H NMR (500 MHz, $CDCl_3$) δ_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, $CDCl_3$) δ_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 $C_{14}H_{10}N_2O_3$: C, 66.14; H, 3.96; N, 11.02%. Found: C, 66.00; H, 4.02; N, 10.89%.

2.3b *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}. ^1H NMR (500 MHz, $CDCl_3$) δ_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, $CDCl_3$) δ_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 $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53%. Found: C, 70.36; H, 4.33; N, 5.44%.

2.3c *2-(2-Chlorophenyl)-5-methylbenzo[d]oxazole (**2c′**)*: Colourless 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}. ^1H NMR (500 MHz, $CDCl_3$) δ_H 2.49 (s, 3H, -CH_3); 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, $CDCl_3$) δ_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 $C_{14}H_{10}ClNO$: C, 69.00; H, 4.14; N, 5.75%. Found: C, 69.22; H, 4.25; N, 5.88%.

2.3d *2-(4-Chlorophenyl)benzo[d]oxazole (**2d′**)*: Colourless solid; mp: 143–145°C; R_f = 0.50 (AcOEt/petroleum ether 10%). IR (KBr): 2961, 1621, 1439, 1245, 1092, 740 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_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, $CDCl_3$) δ_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 $C_{13}H_6ClNO$: C, 67.99; H, 3.51; N, 6.10%. Found: C, 67.81; H, 3.56; N, 6.18%.

2.3e *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}. ^1H NMR (500 MHz, $CDCl_3$) δ_H 2.41 (s, 3H, -CH_3); 6.83–7.16 (4H, m, Ar-H); 7.35–7.81 (m, 4H, Ar-H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_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%.

2.3f *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, $CDCl_3$) δ_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, $CDCl_3$) δ_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%.

2.3g *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, $CDCl_3$) δ_H 3.96 (s, 3H, -COOCH_3); 7.40–7.43 (m, 2H, Ar-H); 7.60–7.65 (m, 2H, Ar-H); 7.80–7.83 (m, 1H, Ar-H); 8.25 (d, 1H, $J = 7.6$ Hz, Ar-H); 8.48 (d, 1H, $J = 7.6$ Hz, Ar-H); 8.95 (s, 1H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_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 $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53%. Found: C, 70.99; H, 4.41; N, 5.60%.

2.3h *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, $CDCl_3$) δ_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, $CDCl_3$) δ_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 $C_{14}H_{10}N_2O_3$: C, 66.14; H, 3.96; N, 11.02%. Found: C, 66.32; H, 4.10; N, 10.92%.

2.3i *5-Nitro-2-phenylbenzo[d]oxazole (**2i′**)*: Yellow solid; mp: 241–243°C; $R_f = 0.20$ (AcOEt/petroleum ether 30%). IR (KBr): 1641, 1525, 1350, 1247, 1051 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 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). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 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 $C_{13}H_8N_2O_3$: C, 65.00; H, 3.36; N, 11.66%. Found: C, 64.81; H, 3.41; N, 11.75%.

2.3j *2-(4-Bromophenyl)benzo[d]oxazole (**2j′**)*: Pale yellow solid; mp: 142–144°C; $R_f = 0.40$ (AcOEt/petroleum ether 25%). IR (KBr): 1581, 1501, 1269, 1052, 944, 830, 799 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 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). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 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 $C_{13}H_8BrNO$: C, 56.96; H, 2.94; N, 5.11%. Found: C, 57.16; H, 2.90; N, 5.05%.

2.3k *2-(4-Nitrophenyl)benzo[d]oxazole (**2k′**)*: Yellow solid; mp: 262–264°C; $R_f = 0.25$ (AcOEt/petroleum ether 50%). IR (KBr): 1640, 1524, 1346, 1242, 1058 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.75–8.11 (m, 4H, Ar-H); 8.22–8.5 (4H, m, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 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 $C_{13}H_8N_2O_3$: C, 65.00; H, 3.36; N, 11.66%. Found: C, 65.13; H, 3.31; N, 11.58%.

2.3l *2-(Benzo[d][1,3]dioxol-5-yl)benzo[d]oxazole (**2l′**)*: Yellow solid; mp 147–149°C; $R_f = 0.30$ (AcOEt/petroleum ether 20%). IR (KBr): 2931, 1639, 1245, 1042, 1115, 761 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 4.39 (s, 2H, -OCH_2O-); 6.86–7.02 (m, 3H, Ar-H); 7.37–7.78 (m, 4H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 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 $C_{14}H_9NO_3$: C, 70.29; H, 3.79; N, 5.86%. Found: C, 70.51; H, 3.66; N, 5.79%.

2.3m *2-(4-Methoxyphenyl)benzo[d]oxazole (**2m′**)*: Colourless solid; mp: 97–99°C; $R_f = 0.55$ (AcOEt/petroleum ether 10%). IR (KBr): 3052, 1618, 1255, 1248, 1037, 1025, 802 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.88 (s, 3H, -OCH_3); 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). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 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 $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22%. Found: C, 74.81; H, 4.89; N, 6.15%.

2.3n *2-(3,4-Dichlorophenyl)benzo[d]oxazole (**2n′**)*: Colourless solid; mp: 139–141°C; R_f = 0.50 (AcOEt/petroleum ether 30%). IR (KBr): 2963, 1620, 1440, 1241, 1099, 747 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 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). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 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^{+4}]. Anal. Calcd for $C_{13}H_7Cl_2NO$: C, 59.12; H, 2.67; N, 5.30%. Found: C, 58.96; H, 2.71; N, 5.37%.

2.3o *2-(3-Methoxyphenyl)benzo[d]oxazole (**2o′**)*: Yellow solid; mp: 107–109°C; R_f = 0.50 (AcOEt/petroleum ether 10%). IR (KBr): 3055, 1620, 1250, 1241, 1030, 1021 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.95 (s, 3H, -OCH_3); 7.10–7.15 (m, 1H, Ar-H); 7.35–7.41 (m, 2H, Ar-H); 7.47 (dd, 1H, J = 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). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 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): m/z = 225 [M$^+$]. Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22%. Found: C, 74.52; H, 4.95; N, 6.29%.

2.3p *5-Chloro-2-(3-nitrophenyl)benzo[d]oxazole (**2p′**)*: Colourless solid; mp 184–186°C; R_f = 0.52 (AcOEt/petroleum ether 30%). IR (KBr): 3424, 2361, 1526, 1449, 1351, 1100, 821 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.38 (q, 1H, J = 8.4 Hz, Ar-H); 7.54 (d, 1H, J = 9.1 Hz, Ar-H); 7.72 (d, 1H, J = 8.4 Hz, Ar-H); 7.78 (s, 1H, Ar-H); 8.39 (d, 1H, J = 8.8 Hz, Ar-H); 8.55 (d, 1H, J = 7.6 Hz, Ar-H); 9.07 (s, 1H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 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): m/z = 274 [M$^+$], 276 [M^{+2}]. Anal. Calcd for $C_{13}H_7ClN_2O_3$: C, 56.85; H, 2.57; N, 10.20%. Found: C, 56.75; H, 2.49; N, 10.15%.

2.3q *2-Phenylbenzo[d]oxazole (**2q′**)*: Colourless solid; mp: 100–102°C; R_f = 0.60 (AcOEt/petroleum ether 10%). IR (KBr): 2975, 1614, 1248, 1040, 803 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 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). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 110.5, 120.0, 124.5, 125.0, 127.0, 127.8, 129.0, 131.6, 142.0, 150.8, 162.9. MS (EI): m/z = 195 [M$^+$]. Anal. Calcd for $C_{13}H_9NO$: C, 79.98; H, 4.65; N, 7.17%. Found: C, 80.11; H, 4.61; N, 7.08%.

2.3r *2-(2-Chlorophenyl)benzo[d]oxazole (**2r′**)*: Colourless 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, $CDCl_3$) δ_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, $CDCl_3$) δ_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 $C_{13}H_6ClNO$: C, 67.99; H, 3.51; N, 6.10%. Found: C, 68.11; H, 3.62; N, 5.99%.

2.3s *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, $CDCl_3$) δ_H 6.51–6.98 (m, 3H, Ar-H); 7.02–7.56 (m, 4H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_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 $C_{11}H_7NO_2$: C, 71.35; H, 3.81; N, 7.56%. Found: C, 71.05; H, 3.86; N, 7.65%.

2.3t *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, $CDCl_3$) δ_H 6.66–6.98 (m, 3H, Ar-H); 7.52–7.72 (m, 4H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_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 $C_{11}H_7NOS$: C, 65.65; H, 3.51; N, 6.96%. Found: C, 65.83; H, 3.46; N, 6.88%.

2.3u *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, $CDCl_3$) δ_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, $CDCl_3$) δ_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 $C_{11}H_8N_2O$:

C, 71.73; H, 4.38; N, 15.21%. Found: C, 71.81; H, 4.25; N, 15.25%.

2.3v *2-(1-Methyl-1H-indol-2-yl)benzo[d]oxazole (**2v′**)*: Colourless solid; mp 161–163°C; R_f = 0.55 (AcOEt/petroleum ether 25%). IR (KBr): 2332, 1579, 1450, 1340, 1240, 1141, 753 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_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, $CDCl_3$) δ_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 $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28%. Found: C, 77.55; H, 4.75; N, 11.39%.

2.3w *2-[3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]benzo[d]oxazole (**2w′**)*: Colourless 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}. ^1H NMR (500 MHz, $CDCl_3$) δ_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); 8.71 (s, 1H, pyrazolyl-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_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 $C_{22}H_{14}ClN_3O$: C, 71.07; H, 3.80; N, 11.30%. Found: C, 71.25; H, 3.75; N, 11.25%.

2.3x *2-[3-(4-Bromophenyl)-1-phenyl-1H-pyrazol-4-yl]-5-methylbenzo[d]oxazole (**2x′**)*: Colourless solid; mp 210–214°C; R_f = 0.52 (AcOEt/petroleum ether 30%). IR (KBr): 2920, 1589, 1500, 1262, 1223, 1057, 944, 830, 799 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_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, $CDCl_3$) δ_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 $C_{23}H_{15}BrN_3O$: C, 64.20; H, 3.75; N, 9.77%. Found: C, 64.25; H, 3.69; N, 10.02%.

2.3y *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/petroleumether 50%). IR (KBr): 3430, 2930, 1631, 1583, 1450, 1240, 1045, 750 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_H 1.43 (t, 3H, J = 6.9 Hz, -OCH_2CH_3); 4.09 (q, 2H, J = 6.9 Hz, -OCH_2CH$_3$); 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, $CDCl_3$) δ_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 $C_{24}H_{19}N_3O_2$: C, 75.57; H, 5.02; N, 11.02%. Found: C, 75.44; H, 5.11; N, 11.09%.

2.3z *5-Chloro-2-phenylethylbenzo[d]oxazole (**2z′**)*: Yellow solid; mp 114–116°C; R_f = 0.50 (AcOEt/petroleumether 40%). IR (KBr): 3402, 1621, 1585, 1488, 1391, 1239, 1088, 985 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_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, $CDCl_3$) δ_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 $C_{24}H_{19}N_3O_2$: C, 69.91; H, 4.69; N, 5.43%. Found: C, 70.07; H, 4.65; N, 5.47%.

2.4 *Animals and drug dosage*

2.4a *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 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).[59]

2.4b *Dose and administration of compounds*: The synthesized compounds (50 mg/kg), pentazocine as a reference opiod analgesic drug (50 mg/kg) and 2% gum acacia as control were administered orally by intragastric tube.

2.5 *Statistical analysis*

The obtained data were analysed 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, USA). The results are presented as mean ± Standard error of means (SEM). Differences between data sets were considered as significant when $P < 0.001$.

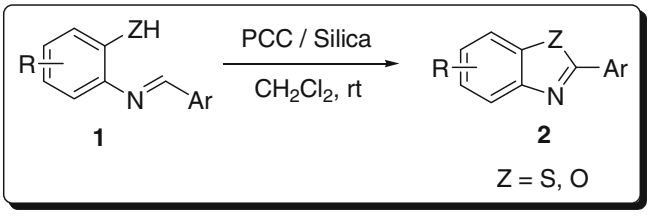
3. Results and discussion

3.1 *Chemistry*

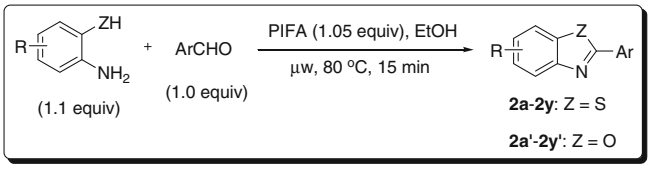
It is pertinent to note that in our earlier study, a two-step approach for the synthesis of a series of benzoxazoles and benzothiazoles have been described via PCC promoted oxidative cyclization of phenolic and thiophenolic imines, respectively (scheme 1).[58a]

Given 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 alternate 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.[42] 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.[60]

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[61] 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 the increase in product yield. Attempts to decrease the reaction temperature were unsuccessful. Starting 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) (see supporting information). 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 1). As shown in figure 1, 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.[28e]



Scheme 1. PCC promoted synthesis of benz(oxa)thiazoles.



Scheme 2. PIFA promoted synthesis of benz(oxa)thiazoles under microwave irradiation.

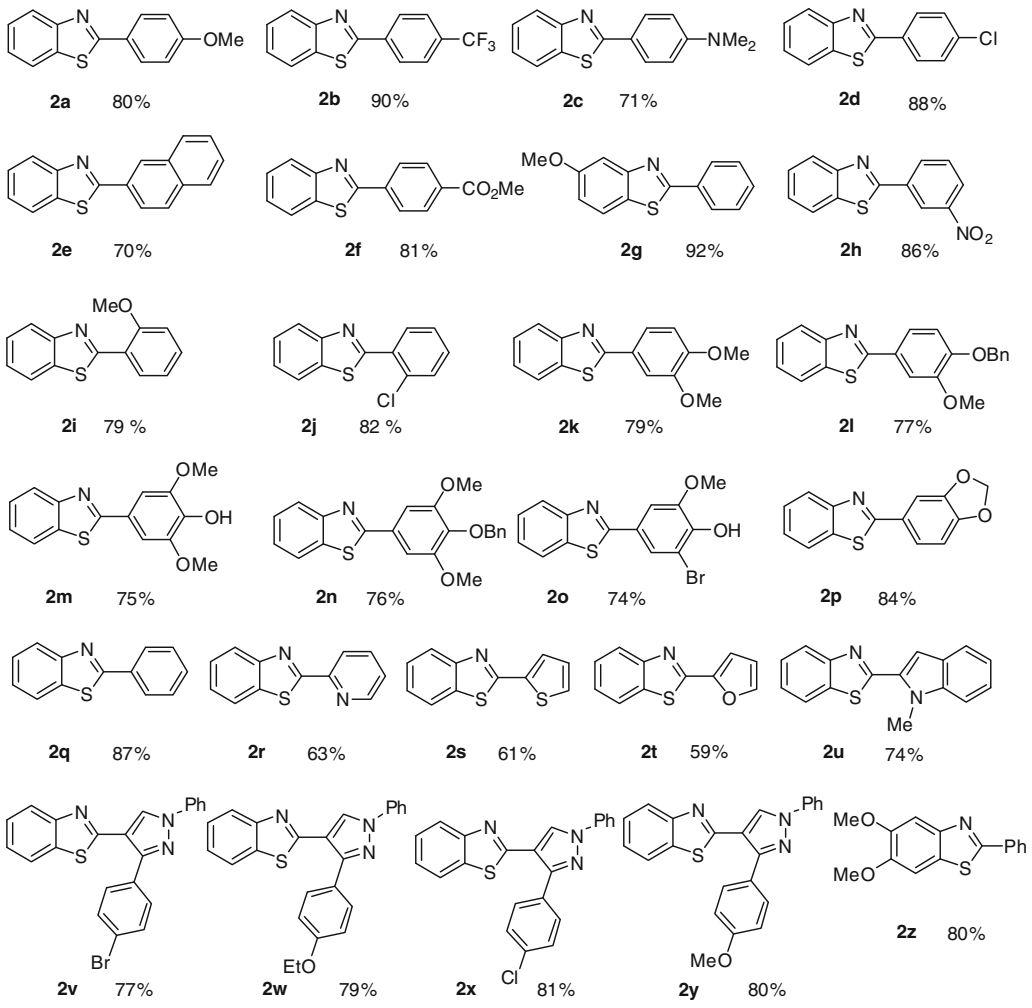


Figure 1. Library of benzothiazoles **2a**–**2z** and their isolated yield (%).

To 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. As shown in figure 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′** (see supporting information). 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 (see supplementary information).

The formation of benzoxa(thia)zole derivatives can be explained by scheme 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 makes 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.

4. Pharmacology

4.1 *Evaluation of in vivo analgesic activity*

Ten compounds of benzothiazoles (**2h**, **2j**, **2l**, **2n**, **2o** and **2u**–**2y**) and benzoxazoles (**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.[59] The selected adult albino rats were used to determine the dose. The animals were

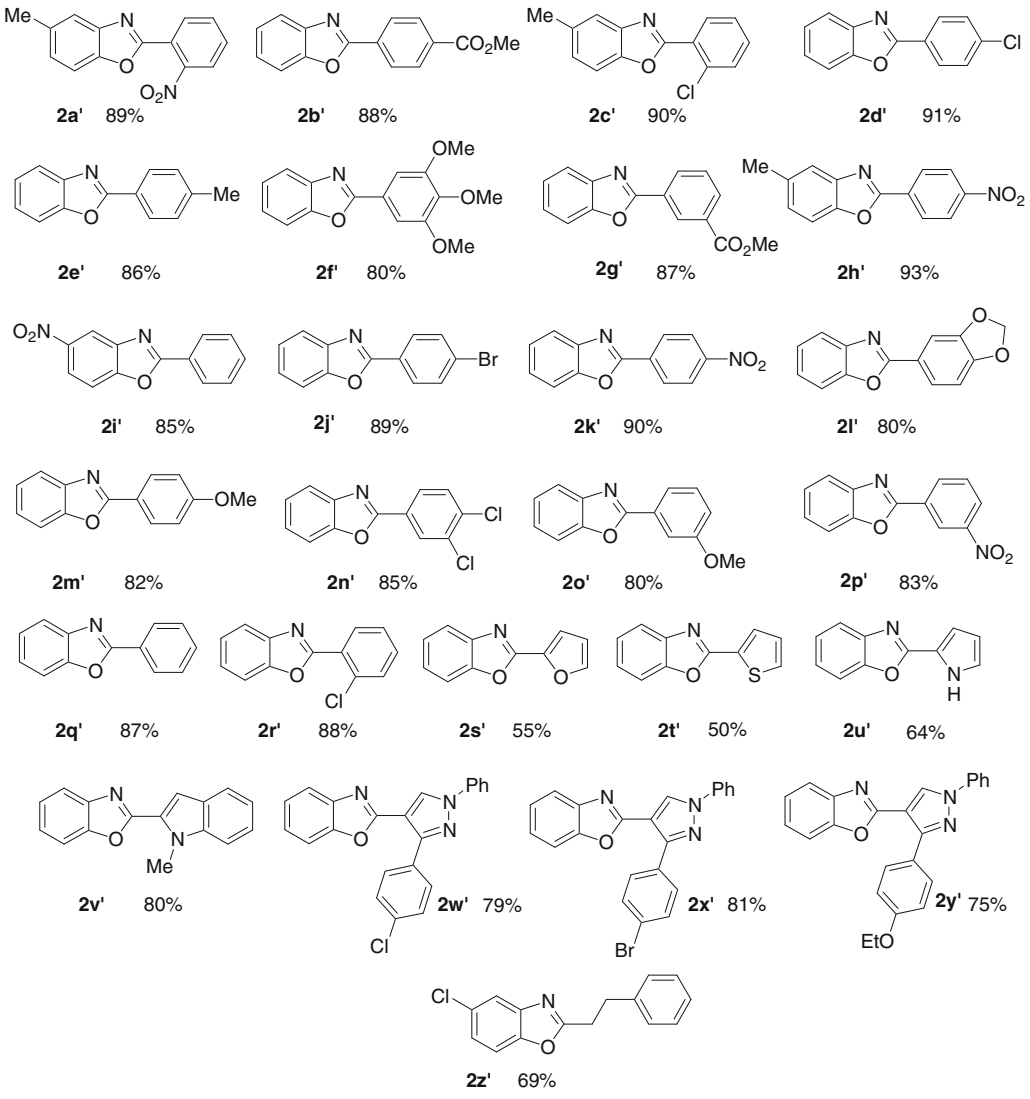
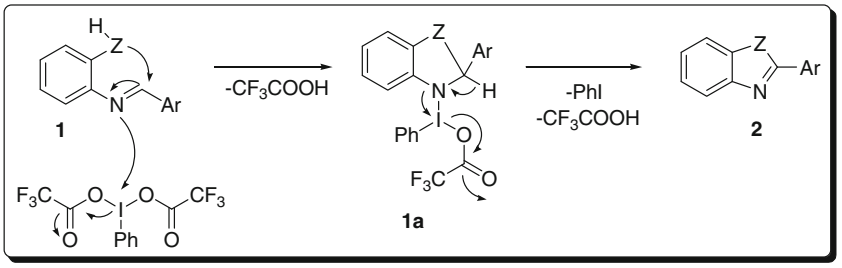


Figure 2. Library of benzoxazoles **2a′**–**2z′** and their isolated yield (%).

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 continuosly for the first 30 min for behavioural 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 LD_{50} 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 LD_{50} cut-off values > 50 mg/kg body weight.



Scheme 3. Plausible mechanism for the formation of benz(oxa)thiazoles **2**.

Table 1. Analgesic activity of selected compounds by tail immersion test.

Entry	Treatments	Dose levels	Tail immersion response in seconds (mean ± SEM)					
			0 min	15 min	30 min	60 min	90 min	% potency
1	**2h**	50 mg/kg	1.31 ± 0.01	2.46 ± 0.02	2.52 ± 0.02	2.56 ± 0.02	2.61 ± 0.01*	50.0
2	**2j**	50 mg/kg	1.30 ± 0.01	2.46 ± 0.02	2.50 ± 0.02	2.55 ± 0.02	2.61 ± 0.02*	50.0
3	**2l**	50 mg/kg	1.30 ± 0.01	2.50 ± 0.01	2.54 ± 0.04	2.60 ± 0.02	2.67 ± 0.01*	51.3
4	**2n**	50 mg/kg	1.32 ± 0.01	2.66 ± 0.02	2.69 ± 0.02	2.73 ± 0.03	2.78 ± 0.03*	52.5
5	**2o**	50 mg/kg	1.31 ± 0.01	2.33 ± 0.02	2.38 ± 0.01	2.62 ± 0.09	2.78 ± 0.08*	52.8
6	**2u**	50 mg/kg	1.30 ± 0.01	2.63 ± 0.01	2.66 ± 0.03	2.83 ± 0.01	3.09 ± 0.08*	58.0
7	**2v**	50 mg/kg	1.30 ± 0.01	2.68 ± 0.02	3.52 ± 0.01	4.10 ± 0.03	4.98 ± 0.02*	73.9
8	**2w**	50 mg/kg	1.31 ± 0.01	2.69 ± 0.01	3.62 ± 0.01	4.37 ± 0.04	5.00 ± 0.01*	73.8
9	**2x**	50 mg/kg	1.30 ± 0.01	2.55 ± 0.02	3.49 ± 0.01	3.99 ± 0.03	4.70 ± 0.02*	72.3
10	**2y**	50 mg/kg	1.31 ± 0.01	2.59 ± 0.02	3.59 ± 0.02	4.00 ± 0.02	4.64 ± 0.03*	71.7
11	**2a′**	50 mg/kg	1.30 ± 0.01	2.45 ± 0.02	2.56 ± 0.03	2.60 ± 0.02	2.63 ± 0.01*	50.6
12	**2c′**	50 mg/kg	1.30 ± 0.01	2.46 ± 0.01	2.50 ± 0.02	2.59 ± 0.01	2.65 ± 0.01*	50.9
13	**2h′**	50 mg/kg	1.30 ± 0.01	2.47 ± 0.01	2.60 ± 0.01	2.64 ± 0.01	2.67 ± 0.01*	51.3
14	**2p′**	50 mg/kg	1.31 ± 0.01	2.49 ± 0.03	2.59 ± 0.2	2.64 ± 0.01	2.69 ± 0.02*	51.3
15	**2r′**	50 mg/kg	1.30 ± 0.01	2.38 ± 0.02	2.44 ± 0.01	2.51 ± 0.01	2.60 ± 0.01*	50.0
16	**2u′**	50 mg/kg	1.30 ± 0.01	2.37 ± 0.02	2.43 ± 0.03	2.70 ± 0.09	2.86 ± 0.08*	54.5
17	**2v′**	50 mg/kg	1.30 ± 0.01	2.69 ± 0.01	3.01 ± 0.01	3.13 ± 0.01	3.22 ± 0.08*	59.6
18	**2w′**	50 mg/kg	1.32 ± 0.01	2.60 ± 0.02	3.37 ± 0.03	4.12 ± 0.01	4.99 ± 0.01*	73.5
19	**2x′**	50 mg/kg	1.31 ± 0.01	2.78 ± 0.01	3.57 ± 0.03	4.31 ± 0.01	5.02 ± 0.01*	76.4
20	**2y′**	50 mg/kg	1.30 ± 0.01	2.67 ± 0.02	3.45 ± 0.01	4.25 ± 0.03	5.00 ± 0.02*	74.0
21	Gum acacia[a]	2 mL/kg	1.30 ± 0.01	1.24 ± 0.01	1.12 ± 0.01	1.15 ± 0.01	1.30 ± 0.01*	-
22	Pentazocine	50 mg/kg	1.30 ± 0.01	6.31 ± 0.03	6.39 ± 0.04	6.54 ± 0.03	6.72 ± 0.02*	80.6

Data were analysed by one way ANOVA followed by Dunnet's test; *indicates $p < 0.001$; SEM: Standard error of means.
[a]2% (w/v) of gum acacia was used as control.

Analgesic activity of the synthesized compounds was determined using tail immersion method.[62] Healthy Swiss mice ($n = 6$) of either sex was selected 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 min 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 reacted 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 s. 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:

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

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

The results of analgesic activity are presented in table 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 pyrollyl motifs (**2u′**) showed moderate potency with activities greater than 2-aryl analogues but lesser than 2-pyrazolyl analogues.

5. Conclusion

In summary, we have explored a useful and practical approach to benzoxazoles 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.

Supplementary information

For supplementary information see www.ias.ac.in/chemsci.

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