

Synthesis of Benzoxazole Derivatives to Develop Molecular Agonists for Biogenesis of Utrophin

5.1 INTRODUCTION

Benzoxazole is a dual heteroatom-bearing important building block in organic synthesis and is widely used in the pharmaceutical industry.¹⁶⁸ Both the heteroatom in their motif can form hydrogen bonds with biological targets, leading to specific interactions and enhanced the activity.¹⁶⁸ Besides, the benzene ring provides hydrophobicity and lipophilicity, enabling the compounds to penetrate cell membranes and reach their targets.¹⁶⁹ They exhibit various biological activities,²³³ including antiviral, antibacterial, anticancer, antifungal, and anticonvulsant activities and are found in a variety of bioactive compounds, including antibiotics, antifungal agents, and anticancer drugs (Figure 5.1).²³⁴ These compounds have also been reported to have insecticidal, herbicidal, and fungicidal activities, making them useful in agricultural applications.²³⁵ The pharmacological activities of benzoxazoles are believed to be related to their ability to bind to specific biological targets, such as enzymes, receptors, and ion channels, and to modulate their functions.²³⁶ Benzoxazole derivatives also have applications as fluorescent dyes, photochromic materials, and liquid crystals.²³⁷ The development of new benzoxazole derivatives with enhanced biological activities, with the ultimate objective of developing new drugs for the treatment of a broad range of diseases, is an attractive field of research. There are numerous methods to synthesize benzoxazoles, such as by cyclizing *o*-aminophenols with diacyl chlorides, reacting *o*-nitrophenols with carbonyl compounds, and condensation of *o*-aminophenols with variants of carboxylic acids.²³⁸ Several additional methods were also developed to construct benzoxazole motifs, including the condensation of *ortho*-hydroxy anilines with isocyanates, the oxidative coupling of *ortho*-aminophenol, the Pd-catalyzed reaction of aryl halides with amides, and the reaction of aryl halides with amides.²³⁹ Many benzoxazole derivatives were also synthesized without altering the fundamental benzoxazole structure just by adding different functional groups or substituting benzene or oxazole rings.²⁴⁰ These modifications can lead to the synthesis of a wide range of benzoxazole derivatives with different physical and chemical properties and biological activities.

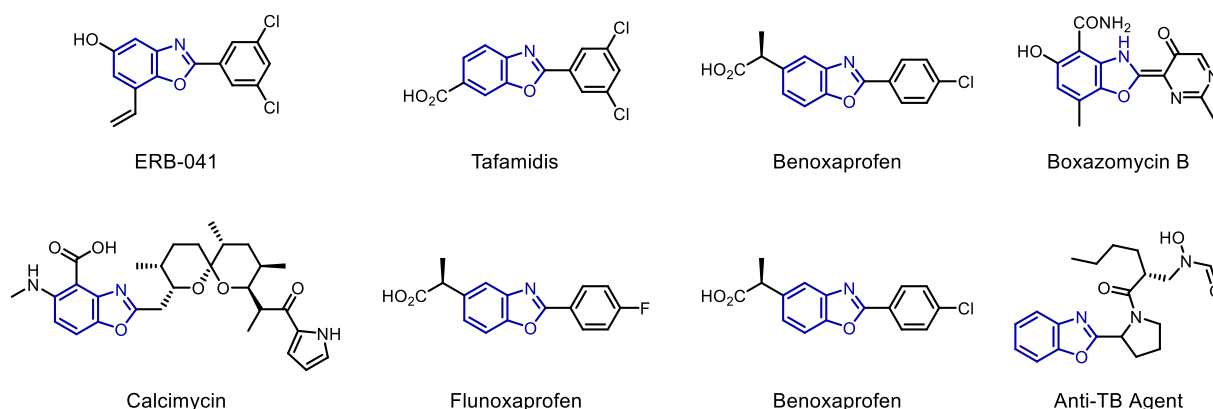


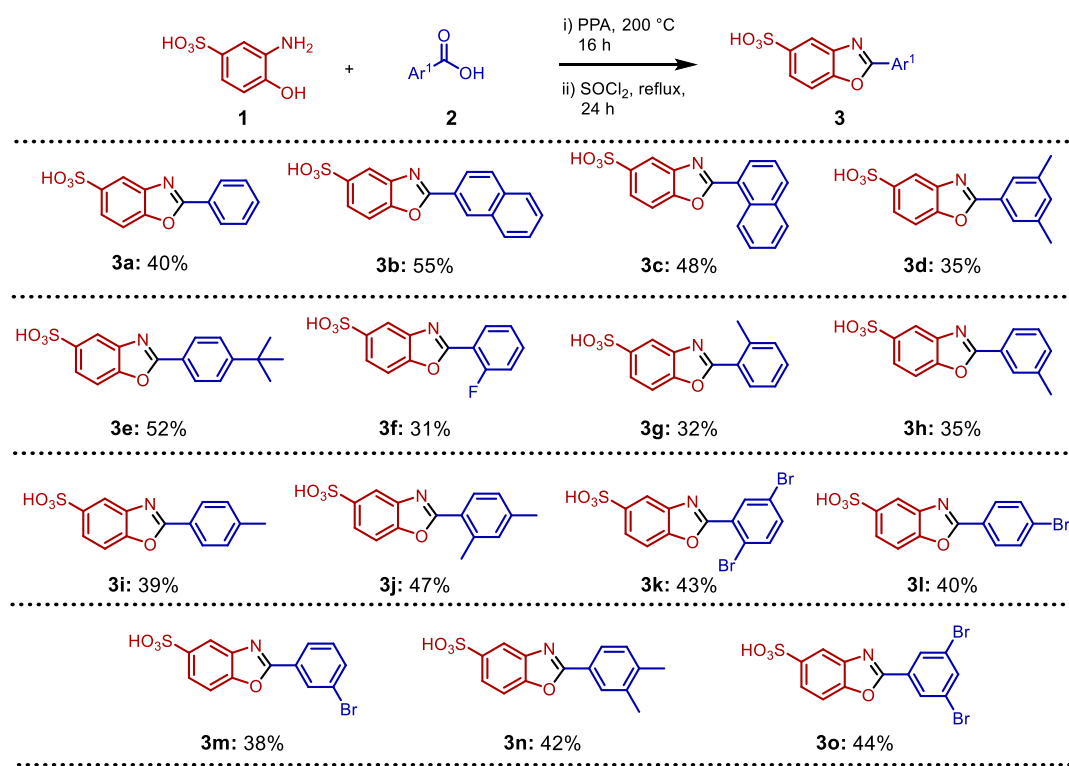
Figure 5.1: Selective bio-active compounds having benzoxazole core

On the other hand, benzoxazole derivatives have demonstrated promise as a treatment for Duchenne muscular dystrophy (DMD).²⁴¹ It is a severe X-linked genetic disease that causes

progressive disability and early death by causing muscle weakness and degeneration. DMD currently has no known permanent treatment of choice and no known cure. Recent studies have revealed that benzoxazole derivatives can modulate the activity of the utrophin protein, which is a potential therapeutic target for DMD.²⁴² Utrophin is a structural and functional homolog of dystrophin, the protein that is mutated in DMD patients.²⁴³ Muscle performance can be improved in DMD patients by increasing the expression and activity of utrophin, which can compensate for the absence of dystrophin in these patients. In animal models of Duchenne muscular dystrophy, benzoxazole derivatives have been shown to increase utrophin expression and activity, resulting in enhanced muscle strength and function.²⁴⁴ In addition, it has been demonstrated that benzoxazole derivatives have anti-inflammatory and antioxidant properties, which can reduce muscle damage and inflammation in DMD patients.²⁴⁵ While additional research is required to make a definitive determination regarding the therapeutic potential of benzoxazole derivatives in the treatment of DMD. Therefore, we have planned and targeted a synthesis of 2-aryl substituted benzoxazole derivative having sulphate and sulphonic acid groups at 5-position.

5.2 RESULT AND DISCUSSION

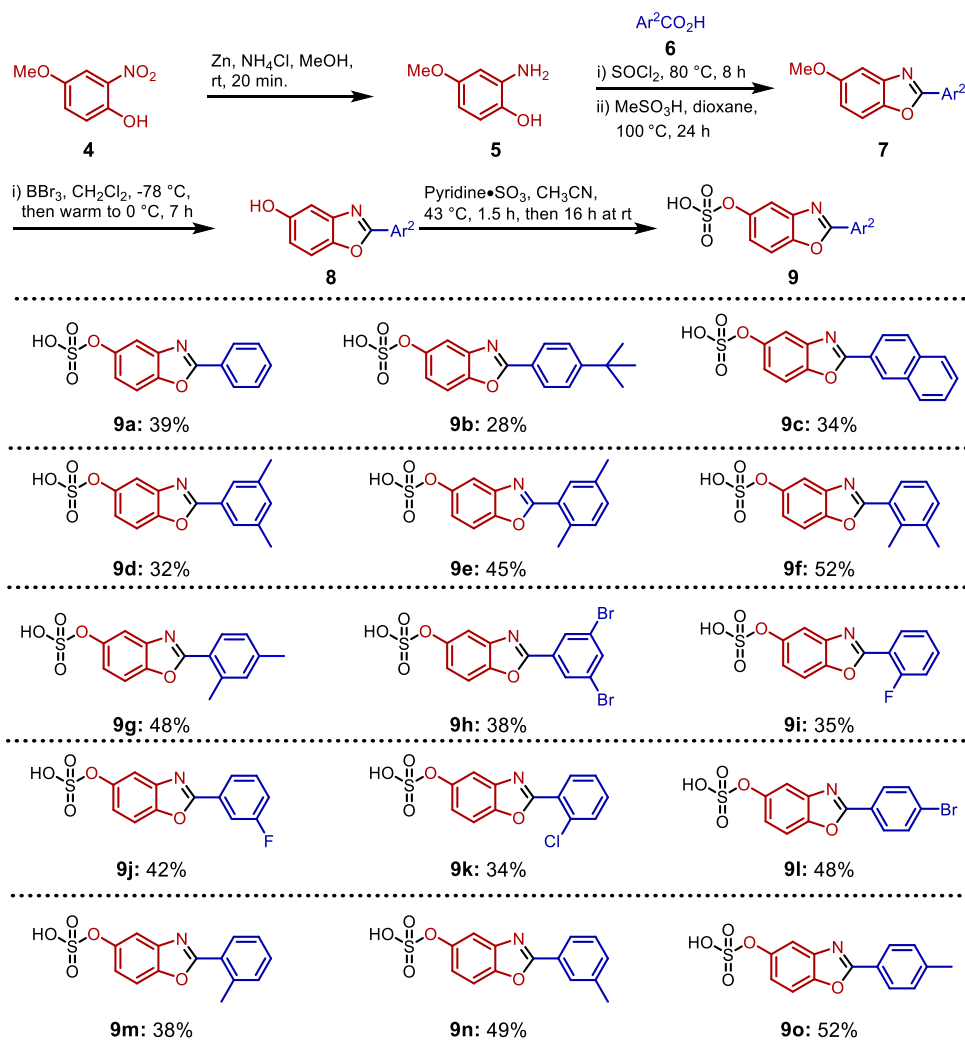
We have developed a cascade condensation/cyclization reaction of 3-amino-4-hydroxy benzenesulfonic acid with benzoic acid derivatives for the synthesis of 2-aryl substituted benzoxazoles having at 5-position (Scheme 5.1). A library of 5-sulfonic acid-bearing benzoxazole derivatives were synthesized in moderate yields.



Scheme 5.1: Synthesis of 2-aryl benzoxazole-5-sulfonic acid derivatives

Next, we have developed a method for the synthesis of 5-sulphate-2-aryl-substituted benzoxazole derivatives. Initially, 4-methoxy-2-aminophenol **5** was prepared via the reduction of 4-methoxy-2-nitrophenol in the presence of zinc and ammonium chloride. The synthesized aniline derivative was used for the cascade synthesis of benzoxazole derivatives. The reaction has relied on one-pot condensation/cyclization of aniline **5** with various substituted aryl acids **6**. Next, the methoxy group of benzoxazole derivatives **7** was deprotected in the presence of borontribromide at -78 °C. Further, the hydroxy group of **8** was reacted with pyridine sulfur trioxide complex to afford 5-sulphate-2-aryl-substituted benzoxazole derivatives. A library of

hydrogen sulphate group containing benzoxazole derivatives **9** were synthesized in moderated yield with this developed method.



Scheme 5.2: Synthesis of 2-aryl benzoxazole-5-hydrogen sulfate derivatives

5.3 EXPERIMENTAL

5.3.1 General Information

Unless otherwise noted, all reactions were carried out in closed vial. ^1H NMR spectra was recorded on a 500 MHz or 400 MHz spectrometer (125 MHz or 100 MHz for ^{13}C NMR). The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. TLC was performed with silica gel GF₂₅₄ precoated on aluminium plates and spots were visualized with UV. Flash column chromatography was performed on silica gel. HPLC analysis was performed on an HPLC instrument equipped with a UV-Vis detector. High-resolution mass spectra (HRMS) were obtained by the ESI-TOF method. All the other reagents were purchased from commercial sources and used as received, unless specified.

5.3.2 Synthetic procedure for the synthesis of 2-aryl benzoxazole-5-sulfonic acids and their characterization

5.3.2.1 Synthetic Procedure

A stirred mixture of 3-amino-4-hydroxy benzene sulfonic acid (5.00 gm, 26.4 mmol 1 equiv.), benzoic acid derivatives (1.2 equiv.) and PPA (15 ml) was heated to 200 °C for 16 hours.

After cooling to room temperature, the reaction mixture was poured onto water and neutralized by the addition of sodium bicarbonate and sodium carbonate, giving a grey solid. This precipitate was washed with dichloromethane and then suspended in chloroform (25 ml). Thionyl chloride (4 equiv.) was added dropwise and the mixture was heated to reflux overnight. After cooling, the grey precipitate was removed by filtration and the filtrate was concentrated and crystallized in a mixture of ethanol and water to give the title compound.

5.3.2.2 Characterization Data

2-phenylbenzo[d]oxazole-5-sulfonic acid (3a): 40% yield, ^1H NMR (500 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 8.31 – 8.24 (m, 2H), 7.79 (dd, J = 5.9, 3.2 Hz, 1H), 7.63 – 7.57 (m, 1H), 7.56 – 7.50 (m, 3H), 7.39 – 7.33 (m, 2H); ^{13}C NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 163.17, 150.88, 142.22, 131.66, 129.04, 127.75, 127.28, 125.24, 124.71, 120.14, 110.73; HRMS (ES+) calc. for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{NH}_4]^+$: 293.0591, found : 293.0612.

2-(naphthalen-2-yl)benzo[d]oxazole-5-sulfonic acid (3b): 55% yield, ^1H NMR (500 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 8.78 (s, 1H), 8.32 (d, J = 7.8 Hz, 1H), 7.95 (m, 2H), 7.89 (s, 1H), 7.82 (s, 1H), 7.60 (m, 3H), 7.38 (s, 2H); ^{13}C NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 163.36, 151.00, 142.30, 134.91, 133.12, 129.10, 128.94, 128.32, 128.05, 127.96, 127.05, 125.35, 124.81, 124.50, 124.10, 120.16, 110.75; HRMS (ES+) calc. for $\text{C}_{17}\text{H}_{11}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 326.0482, found: 326.0472.

2-(naphthalen-1-yl)benzo[d]oxazole-5-sulfonic acid (3c): 48% yield, ^1H NMR (500 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 9.47 (d, J = 8.7 Hz, 1H), 8.44 (dd, J = 7.3, 1.0 Hz, 1H), 8.05 (d, J = 8.2 Hz, 1H), 7.95 (d, J = 8.1 Hz, 1H), 7.91 – 7.86 (m, 1H), 7.72 (t, J = 7.7 Hz, 1H), 7.67 – 7.58 (m, 3H), 7.42 – 7.39 (m, 2H); ^{13}C NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 162.93, 150.30, 142.44, 134.08, 132.44, 130.81, 129.45, 128.80, 128.05, 126.58, 126.41, 125.41, 125.07, 124.63, 123.73, 120.40, 110.64; HRMS (ES+) calc. for $\text{C}_{17}\text{H}_{11}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 326.0482, found: 326.0504.

2-(3,5-dimethylphenyl)benzo[d]oxazole-5-sulfonic acid (3d): 35% yield, ^1H NMR (500 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 7.96 (s, 2H), 7.83 (s, 1H), 7.62 (s, 1H), 7.40 – 7.39 (m, 2H), 7.29 (s, 1H), 2.46 (s, 6H); ^{13}C NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 163.61, 150.87, 142.25, 138.77, 133.47, 127.03, 125.54, 125.10, 124.65, 120.05, 110.66, 21.38; HRMS (ES+) calc. for $\text{C}_{15}\text{H}_{14}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 304.0638, found : 304.0640.

2-(4-(tert-butyl)phenyl)benzo[d]oxazole-5-sulfonic acid (3e): 52% yield, ^1H NMR (500 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 8.21 – 8.18 (m, 2H), 7.79 – 7.75 (m, 1H), 7.60 – 7.57 (m, 1H), 7.57 – 7.53 (m, 2H), 7.37 – 7.32 (m, 2H), 1.38 (s, 9H); ^{13}C NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 163.14, 155.04, 150.62, 142.11, 127.37, 125.81, 124.76, 124.37, 124.25, 119.77, 110.41, 34.97, 31.05; HRMS (ES+) calc. for $\text{C}_{17}\text{H}_{18}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 332.0951, found: 332.041.

2-(2-fluorophenyl)benzo[d]oxazole-5-sulfonic acid (3f): 31% yield, ^1H NMR (500 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 8.26 – 8.25 (m, 1H), 7.84 (dd, J = 5.2, 3.9 Hz, 1H), 7.63 (dd, J = 5.2, 3.9 Hz, 1H), 7.55 – 7.51 (m, 1H), 7.41 – 7.35 (m, 2H), 7.35 – 7.27 (m, 2H); ^{13}C NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 162.01, 159.95, 159.62, 159.58, 150.63, 141.89, 133.31, 133.24, 130.70, 130.69, 125.65, 124.85, 124.67, 124.64, 120.52, 117.34, 117.17, 115.71, 115.63, 110.86; HRMS (ES+) calc. for $\text{C}_{13}\text{H}_8\text{FKNO}_4\text{S}$ $[\text{M}+\text{K}]^+$: 331.9790, found: 331.9809.

2-(o-tolyl)benzo[d]oxazole-5-sulfonic acid (3g): 32% yield, ^1H NMR (500 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 8.20 – 8.16 (m, 1H), 7.82 – 7.78 (m, 1H), 7.61 – 7.57 (m, 1H), 7.43 – 7.39 (m, 1H), 7.38 – 7.33 (m, 4H), 2.82 (s, 3H); ^{13}C NMR (126 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 163.55, 150.43, 142.26, 138.99, 131.93, 131.04, 130.08, 126.37, 126.20, 125.15, 124.50, 120.28, 110.62, 22.36; HRMS (ES+) calc. for $\text{C}_{14}\text{H}_{10}\text{NO}_4\text{S}$ $[\text{M}-\text{H}]^-$: 288.0336, found: 288.0304.

3-(*m*-tolyl)benzo[d]oxazole-5-sulfonic acid (3h): 35% Yield, ^1H NMR (500 MHz, $\text{CDCl}_3/\text{DMSO}-D_6$) δ 8.10 (s, 1H), 8.06 (d, $J = 7.7$ Hz, 1H), 7.80 – 7.75 (m, 1H), 7.61 – 7.55 (m, 1H), 7.41 (t, $J = 7.6$ Hz, 1H), 7.38 – 7.32 (m, 3H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-D_6$) δ 163.40, 150.87, 142.23, 138.89, 132.51, 128.97, 128.33, 127.14, 125.17, 124.89, 124.68, 120.09, 110.70, 21.50; HRMS (ES+) calc. for $\text{C}_{14}\text{H}_{10}\text{NO}_4\text{S}$ $[\text{M}-\text{H}]^-$: 288.0336, found : 288.0304.

4-(*p*-tolyl)benzo[d]oxazole-5-sulfonic acid (3i): 39% Yield, ^1H NMR (500 MHz, $\text{CDCl}_3/\text{DMSO}-D_6$) δ 8.16 (d, $J = 8.2$ Hz, 2H), 7.81 – 7.71 (m, 1H), 7.64 – 7.49 (m, 1H), 7.38 – 7.30 (m, 4H), 2.45 (s, 3H); ^{13}C NMR (126 MHz, $\text{CDCl}_3/\text{DMSO}-D_6$) δ 163.45, 150.82, 142.25, 141.98, 129.81, 127.75, 125.03, 124.64, 124.50, 119.97, 110.65, 21.81; HRMS (ES+) calc. for $\text{C}_{14}\text{H}_{10}\text{NO}_4\text{S}$ $[\text{M}-\text{H}]^-$: 288.0336, found : 288.0359.

2-(2,4-dimethylphenyl)benzo[d]oxazole-5-sulfonic acid (3j): 47% Yield, ^1H NMR (500 MHz, $\text{CDCl}_3/\text{DMSO}-D_6$) δ 8.09 (d, $J = 8.0$ Hz, 1H), 7.82 – 7.75 (m, 1H), 7.64 – 7.54 (m, 1H), 7.37 – 7.32 (m, 2H), 7.16 (d, $J = 7.7$ Hz, 2H), 2.79 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-D_6$) δ 163.81, 150.34, 142.10, 141.53, 138.90, 132.74, 130.15, 127.05, 124.98, 124.48, 123.44, 120.06, 110.55, 22.27, 21.54; HRMS (ES+) calc. for $\text{C}_{15}\text{H}_{14}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 304.0638, found : 304.0640.

2-(2,5-dibromophenyl)benzo[d]oxazole-5-sulfonic acid (3k): 43% Yield, ^1H NMR (500 MHz, $\text{CDCl}_3/\text{DMSO}-D_6$) δ 8.26 (d, $J = 2.4$ Hz, 1H), 7.88 – 7.82 (m, 1H), 7.65 – 7.60 (m, 2H), 7.51 – 7.39 (m, 3H); ^{13}C NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-D_6$) δ 160.23, 150.78, 141.61, 136.25, 135.02, 134.87, 130.05, 126.13, 125.05, 121.48, 120.86, 120.62, 111.03; HRMS (ES+) calc. for $\text{C}_{13}\text{H}_7\text{Br}_2\text{NO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 453.8355 & 455.8335, found : 453.8346 & 455.8337.

2-(4-bromophenyl)benzo[d]oxazole-5-sulfonic acid (3l): 40% Yield, ^1H NMR (500 MHz, $\text{CDCl}_3/\text{DMSO}-D_6$) δ 8.14 (d, $J = 8.5$ Hz, 2H), 7.79 (dd, $J = 6.1, 3.0$ Hz, 1H), 7.68 (d, $J = 8.4$ Hz, 2H), 7.59 (dd, $J = 6.2, 3.0$ Hz, 1H), 7.44 – 7.34 (m, 2H); ^{13}C NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-D_6$) δ 162.27, 150.86, 142.04, 132.39, 129.16, 126.42, 126.17, 125.56, 124.93, 120.24, 110.80, ; HRMS (ES+) calc. for $\text{C}_{13}\text{H}_8\text{BrNO}_4\text{S}$ $[\text{M}]^+$: 352.9357 & 354.9337, found : 352.9351 & 354.9302.

2-(3-bromophenyl)benzo[d]oxazole-5-sulfonic acid (3m): 38% Yield, ^1H NMR (500 MHz, $\text{CDCl}_3/\text{DMSO}-D_6$) δ 8.43 (d, $J = 1.6$ Hz, 1H), 8.21 (d, $J = 7.8$ Hz, 1H), 7.80 (dd, $J = 6.0, 3.0$ Hz, 1H), 7.67 (d, $J = 8.0$ Hz, 1H), 7.65 – 7.55 (m, 1H), 7.48 – 7.30 (m, 3H); ^{13}C NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-D_6$) δ 161.63, 150.82, 141.51, 134.76, 130.71, 130.67, 128.89, 126.36, 125.86, 125.14, 123.20, 120.25, 110.92; HRMS (ES+) calc. for $\text{C}_{13}\text{H}_{12}\text{BrN}_2\text{O}_4\text{S}$ $[\text{M}+\text{NH}_4]^+$: 370.9696 & 372.9676, found : 370.9709 & 372.9658

2-(3,4-dimethylphenyl)benzo[d]oxazole-5-sulfonic acid (3n): 42% Yield, ^1H NMR (500 MHz, $\text{CDCl}_3/\text{DMSO}-D_6$) δ 8.04 (s, 1H), 7.96 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.75 – 7.73 (m, 1H), 7.60 – 7.51 (m, 1H), 7.35 – 7.30 (m, 2H), 7.28 – 7.24 (m, 1H), 2.35 (s, 3H), 2.33 (s, 3H).; ^{13}C NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-D_6$) δ 163.60, 150.81, 142.31, 140.99, 137.51, 130.33, 128.80, 125.26, 124.93, 124.77, 124.58, 119.92, 110.60, 20.13, 19.88; HRMS (ES+) calc. for $\text{C}_{15}\text{H}_{14}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 304.0638, found : 304.0656.

2-(3,5-dibromophenyl)benzo[d]oxazole-5-sulfonic acid (3o): 44% Yield, ^1H NMR (500 MHz, $\text{CDCl}_3/\text{DMSO}-D_6$) δ 8.40 – 8.27 (m, 2H), 7.81 – 7.77 (m, 2H), 7.62 – 7.55 (m, 1H), 7.45 – 7.34 (m, 2H); ^{13}C NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-D_6$) δ 160.23, 150.91, 141.66, 136.92, 130.35, 129.29, 126.18, 125.27, 123.69, 120.52, 110.99; HRMS (ES+) calc. for $\text{C}_{13}\text{H}_7\text{Br}_2\text{NO}_4\text{S}$ $[\text{M}]^+$: 433.8515 & 435.8495, found : 433.8533 & 435.8470.

5.3.3 General procedure for the synthesis of 2-aryl benzoxazole-5-hydrogen sulfate derivatives and their characterization

5.3.3.1 Synthetic Procedure

To a vigorously stirred solution of 4-methoxy-2-nitrophenol (1 equiv., 10 mmol) in MeOH (60 ml), saturated aqueous solution of NH_4Cl (5 ml) and Zn dust (15 equiv.) were added. (Pressure equalizing funnel) After completion of the reaction, the mixture was filtered through the celite and washed with ethyl acetate. The filtrate was dried over the sodium sulphate and evaporated under reduced pressure to give the corresponding amine 2-hydroxy-5-methoxy aniline.

Substituted benzoic acid (2.5 mmol) was treated with SOCl_2 (3.0 mmol, 1.2 equiv.) at 80 °C until quenching of an aliquot with a few drops of MeOH revealed the complete consumption of acid and appearance of a new spot (methyl benzoate) by TLC. The excess SOCl_2 was distilled off and the residue was dissolved in dioxane. 2-hydroxy-5-methoxy aniline (2.5 mmol) was added in the reaction mixture followed by the addition of $\text{CH}_3\text{SO}_3\text{H}$ (0.5 mL). The resultant mixture was stirred at 100 °C. After complete consumption of 2-hydroxy-5-methoxy aniline (TLC), the dioxane was removed by rotary evaporation and the residue was diluted with EtOAc (10 mL) followed by saturated aq. NaHCO_3 (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined EtOAc extracts were washed with H_2O (3 × 5 mL), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure to afford 5-methoxy-2'-arylbenzoxazole derivatives.

To a stirred solution of 5-methoxy-2'-arylbenzoxazole (1.0 mmol) in CH_2Cl_2 (10 ml) was added BBr_3 (1.0 M solution in CH_2Cl_2 , 3.5 ml, 3.5 mmol) at -78 °C under N_2 . The reaction mixture was gradually warmed to 0 °C and stirred for 7 h. After that, the reaction mixture was poured into ice water and extracted with EtOAc. The extract organic layer was washed with brine and dried over MgSO_4 and evaporated under reduced pressure to give 5-hydroxy-2'-arylbenzoxazole. 5-hydroxy-2'-arylbenzoxazole derivative (5.2 mmol) was dissolved in 60 mL of acetonitrile at 43 °C. Pyridine- SO_3 (1:1) (8 mmol) was added in 5 portions over 1.5 hours. The reaction mixture was stirred overnight at room temperature. The liquor was removed and the residue was crystallized in a mixture of water and ethanol to give the 2-aryl benzoxazole-5-hydrogen sulphate derivatives.

5.3.3.2 Characterization Data

2-phenylbenzo[d]oxazol-5-yl hydrogen sulphate (9a): 39% yield, ^1H NMR (500 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 8.25 – 8.19 (m, 2H), 7.56 – 7.49 (m, 3H), 7.43 (d, J = 8.7 Hz, 1H), 7.22 (d, J = 1.6 Hz, 1H), 6.91 – 6.86 (m, 1H), 5.27 (s, 1H); ^{13}C NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 164.20, 153.57, 145.55, 142.82, 131.75, 129.10, 127.70, 127.14, 113.95, 110.97, 105.63; HRMS (ES+) calc. for $\text{C}_{13}\text{H}_9\text{NO}_5\text{S}$ $[\text{M}]^+$: 291.0196, found : 291.0213.

2-(4-(tert-butyl)phenyl)benzo[d]oxazol-5-yl hydrogen sulphate (9b): 28% yield, ^1H NMR (500 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 8.14 (d, J = 4.9 Hz, 2H), 7.51 (d, J = 4.9 Hz, 2H), 7.36 (d, J = 6.2 Hz, 1H), 7.26 (s, 1H), 6.90 (d, J = 7.5 Hz, 1H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 164.12, 155.65, 155.10, 145.05, 142.41, 127.77, 126.30, 124.33, 114.31, 110.85, 105.50, 35.42, 31.47 HRMS (ES+) calc. for $\text{C}_{17}\text{H}_{17}\text{NO}_5\text{S}$ $[\text{M}]^+$: 347.0822, found : 347.0807.

2-(naphthalen-2-yl)benzo[d]oxazol-5-yl hydrogen sulphate (9c): 34% yield, ^1H NMR (500 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 8.82 (s, 1H), 8.31 (d, J = 7.8 Hz, 1H), 7.99 – 7.97 (m, 2H), 7.89 (d, J = 7.5 Hz, 1H), 7.65 – 7.53 (m, 2H), 7.48 (d, J = 8.8 Hz, 1H), 7.41 (d, J = 1.7 Hz, 1H), 6.97 (dd, J = 8.7, 2.1 Hz, 1H); ^{13}C NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 163.30, 154.68, 144.58, 142.65, 134.29, 132.63, 128.59, 128.46, 127.61, 127.50, 127.48, 126.65, 124.24, 123.54, 113.81, 110.21, 105.10; HRMS (ES+) calc. for $\text{C}_{17}\text{H}_{11}\text{NO}_5\text{S}$ $[\text{M}]^+$: 341.0352, found : 341.0357.

2-(3,5-dimethylphenyl)benzo[d]oxazol-5-yl hydrogen sulphate (9d): 32% yield, ^1H NMR (500 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 7.91 (s, 2H), 7.44 (d, J = 8.8 Hz, 1H), 7.34 (d, J = 2.4 Hz, 1H), 7.21 (s,

1H), 6.95 – 6.93 (m, 1H), 2.43 (s, 6H); ¹³C NMR (125 MHz, CDCl₃/DMSO-D₆) δ 164.47, 154.05, 145.19, 138.97, 134.08, 126.13, 125.68, 114.31, 111.03, 105.17, 21.38; HRMS (ES+) calc. for C₁₅H₁₇N₂O₅S [M+NH₄]⁺: 337.0853, found: 337.0834.

2-(2,5-dimethylphenyl)benzo[d]oxazol-5-yl hydrogen sulphate (9e): 45% yield, ¹H NMR (500 MHz, CDCl₃/DMSO-D₆) δ 8.00 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 8.7 Hz, 1H), 7.22 (d, *J* = 2.4 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.86 (dd, *J* = 8.7, 2.4 Hz, 1H), 2.72 (s, 3H), 2.36 (s, 3H); ¹³C NMR (100 MHz, CDCl₃/DMSO-D₆) δ 164.25, 154.49, 144.34, 142.78, 141.04, 138.37, 132.48, 129.79, 126.80, 123.56, 113.59, 110.19, 105.39, 22.00, 21.30; HRMS (ES+) calc. for C₁₅H₁₄NO₅S [M+H]⁺: 320.0587, found: 320.0594.

2-(2,3-dimethylphenyl)benzo[d]oxazol-5-yl hydrogen sulphate (9f): 52% yield, ¹H NMR (500 MHz, CDCl₃/DMSO-D₆) δ 7.86 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 8.7 Hz, 1H), 7.32 (d, *J* = 7.4 Hz, 1H), 7.25 – 7.22 (m, 2H), 6.88 (dd, *J* = 8.7, 2.5 Hz, 1H), 2.64 (s, 3H), 2.38 (s, 3H); ¹³C NMR (100 MHz, CDCl₃/DMSO-D₆) δ 164.59, 154.51, 144.52, 142.66, 138.15, 137.00, 132.38, 128.05, 126.98, 125.56, 113.82, 110.36, 105.47, 20.73, 17.14; HRMS (ES+) calc. for C₁₅H₁₃NO₅SK [M+K]⁺: 358.0146, found: 358.0124.

2-(2,4-dimethylphenyl)benzo[d]oxazol-5-yl hydrogen sulphate (9g): 48% yield, ¹H NMR (500 MHz, CDCl₃/DMSO-D₆) δ 7.90 (s, 1H), 7.32 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.21 (d, *J* = 2.2 Hz, 1H), 7.15 (d, *J* = 1.6 Hz, 2H), 6.86 (dd, *J* = 8.7, 2.3 Hz, 1H), 2.67 (s, 3H), 2.33 (s, 3H); ¹³C NMR (125 MHz, CDCl₃/DMSO-D₆) δ 164.28, 154.60, 144.43, 142.54, 135.55, 135.42, 131.69, 131.66, 130.28, 126.00, 113.81, 110.30, 105.39, 21.60, 20.80; HRMS (ES+) calc. for C₁₅H₁₃NO₅SNa [M+Na]⁺: 342.0407, found: 342.0398.

2-(3,5-dibromophenyl)benzo[d]oxazol-5-yl hydrogen sulphate (9h): 38% yield, ¹H NMR (500 MHz, CDCl₃/DMSO-D₆) δ 8.20 (d, *J* = 1.7 Hz, 2H), 7.70 (t, *J* = 1.7 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 1H), 7.14 (d, *J* = 2.3 Hz, 1H), 6.86 (dd, *J* = 8.8, 2.4 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃/DMSO-D₆) δ 160.37, 155.14, 144.82, 142.46, 136.27, 130.54, 128.82, 123.36, 114.93, 110.58, 105.51; HRMS (ES+) calc. for C₁₃H₁₁Br₂N₂O₅S [M+NH₄]⁺: 466.8730 & 464.8750, found: 466.8734 & 464.8759.

2-(2-fluorophenyl)benzo[d]oxazol-5-yl hydrogen sulphate (9i): 35% yield, ¹H NMR (500 MHz, CDCl₃/DMSO-D₆) δ 8.22 – 8.18 (m, 1H), 7.54 – 7.47 (m, 1H), 7.42 (d, *J* = 8.7 Hz, 1H), 7.33 – 7.22 (m, 3H), 6.94 (dd, *J* = 8.8, 2.4 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃/DMSO-D₆) δ 161.66, 159.86, 159.82, 159.60, 154.91, 144.53, 142.34, 133.00, 132.93, 130.38, 124.51, 124.48, 117.11, 116.94, 115.59, 115.51, 114.56, 110.55, 105.55, 77.41, 77.16, 76.91; HRMS (ES+) calc. for C₁₃H₉FNO₅S [M+H]⁺: 310.0180, found: 310.0174.

2-(3-fluorophenyl)benzo[d]oxazol-5-yl hydrogen sulphate (9j): 42% yield, ¹H NMR (400 MHz, CDCl₃/DMSO-D₆) δ 7.8 (d, *J* = 7.7 Hz, 1H), 7.74 (d, *J* = 9.4 Hz, 1H), 7.40 – 7.30 (m, 1H), 7.29 – 7.23 (m, 1H), 7.08 – 7.07 (m, 2H), 6.82 – 6.73 (m, 1H); ¹³C NMR (100 MHz, CDCl₃/DMSO-D₆) δ 163.81, 161.92 (*J*_{C-F} = 4 Hz), 161.36, 154.82, 144.53, 142.45, 130.43 (*J*_{C-F} = 8 Hz), 129.15 (*J*_{C-F} = 8 Hz), 122.89 (*J*_{C-F} = 3 Hz), 118.01 (*J*_{C-F} = 21 Hz), 114.17 (*J*_{C-F} = 11 Hz), 110.32, 105.22; HRMS (ES+) calc. for C₁₃H₉FNO₅S [M+H]⁺: 310.0180, found: 310.0181.

2-(2-chlorophenyl)benzo[d]oxazol-5-yl hydrogen sulphate (9k): 34% yield, ¹H NMR (400 MHz, CDCl₃/DMSO-D₆) δ 8.03 – 7.96 (m, 1H), 7.44 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.36 – 7.27 (m, 3H), 7.18 (d, *J* = 2.3 Hz, 1H), 6.83 (dd, *J* = 8.8, 2.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃/DMSO-D₆) δ 161.24, 154.78, 144.53, 142.32, 133.03, 131.63, 131.57, 131.17, 126.81, 126.29, 114.47, 110.44, 105.55, 77.48, 77.16, 76.84; HRMS (ES+) calc. for C₁₃H₉ClNO₅S [M+H]⁺: 325.9884, found: 325.9881.

2-(4-bromophenyl)benzo[d]oxazol-5-yl hydrogen sulphate (9l): 48% yield, ¹H NMR (500 MHz, CDCl₃/DMSO-D₆) δ 8.04 – 8.02 (m, 2H), 7.60 – 7.58 (m, 2H), 7.32 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.17 (d, *J* = 2.2 Hz, 1H), 6.86 (dt, *J* = 8.7, 2.1 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃/DMSO-D₆) δ 162.53, 155.05,

144.74, 142.40, 132.19, 128.88, 126.11, 126.05, 114.40, 110.51, 105.33; HRMS (ES+) calc. for $C_{13}H_9BrNO_5S$ $[M+H]^+$: 369.9380 & 371.9359, found: 369.9381 & 371.9358.

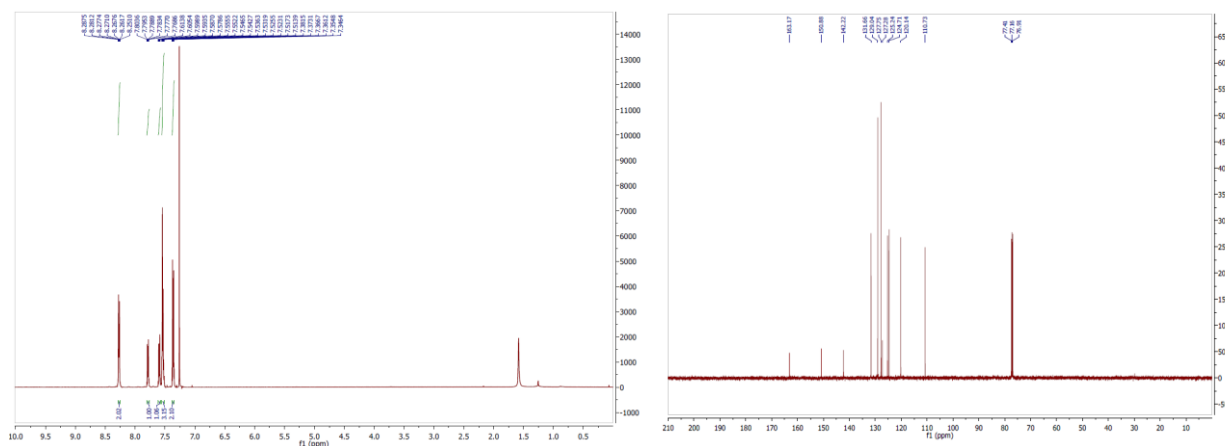
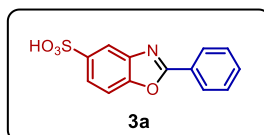
2-(2-methylphenyl)benzo[d]oxazol-5-yl hydrogen sulphate (9m): 38% yield, ^1H NMR (400 MHz, $CDCl_3/DMSO-D_6$) δ 8.15 – 8.00 (m, 1H), 7.41 – 7.26 (m, 4H), 7.22 (dd, J = 7.8, 2.3 Hz, 1H), 6.94 – 6.82 (m, 1H), 2.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3/DMSO-D_6$) δ 164.03, 154.59, 144.47, 142.82, 138.58, 131.76, 130.75, 129.84, 126.46, 126.04, 113.86, 110.33, 105.54, 77.48, 77.16, 76.84, 22.17; HRMS (ES+) calc. for $C_{14}H_{15}N_2O_5S$ $[M+NH_4]^+$: 323.0697, found: 323.0691.

2-(3-methylphenyl)benzo[d]oxazol-5-yl hydrogen sulphate (9n): 49% yield, ^1H NMR (400 MHz, $CDCl_3/DMSO-D_6$) δ 8.06 – 7.90 (m, 2H), 7.36 – 7.25 (m, 3H), 7.18 – 7.16 (m, 1H), 6.86 – 6.82 (m, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3/DMSO-D_6$) δ 163.63, 154.73, 144.71, 142.74, 138.57, 132.07, 128.70, 127.90, 127.10, 124.47, 113.82, 110.30, 105.32, 21.24; HRMS (ES+) calc. for $C_{14}H_{12}NO_5S$ $[M+H]^+$: 306.0431, found: 306.0432

2-(4-methylphenyl)benzo[d]oxazol-5-yl hydrogen sulphate (9o): 52% yield, ^1H NMR (400 MHz, $CDCl_3/DMSO-D_6$) δ 8.07 – 7.92 (m, 2H), 7.30 – 7.10 (m, 4H), 6.87 – 6.74 (m, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3/DMSO-D_6$) δ 163.64, 154.67, 144.57, 142.69, 141.71, 129.47, 127.24, 124.37, 113.59, 110.21, 105.16, 21.45; HRMS (ES+) calc. for $C_{14}H_{12}NO_5S$ $[M+H]^+$: 306.0431, found: 306.0432

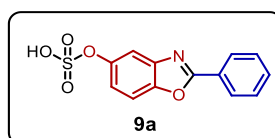
5.4 SPECTRAL DATA

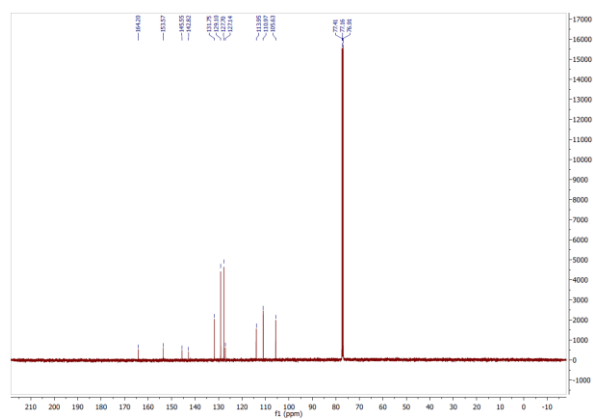
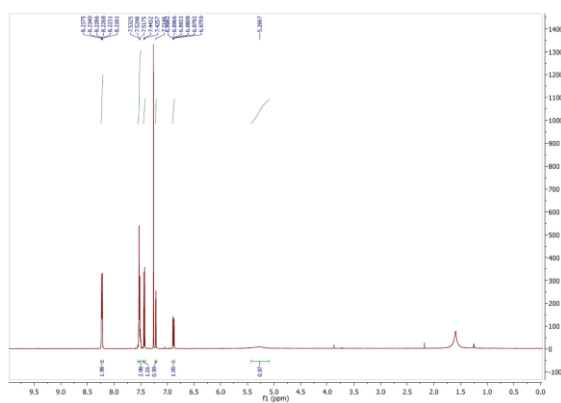
5.4.1 ^1H and ^{13}C NMR Spectra of 2-aryl benzoxazole-5-sulfonic acid derivatives



500 MHz ^1H NMR and 125 MHz ^{13}C NMR Spectra of **3a**

5.4.2 ^1H and ^{13}C NMR Spectra of 2-aryl benzoxazole-5-hydrogen sulfate derivatives





500 MHz ^1H NMR and 125 MHz ^{13}C NMR Spectra of **9a**

