Supporting Information

2-(2-Arylphenyl)benzoxazole as a Novel Anti-Inflammatory Scaffold: Synthesis and Biological Evaluation

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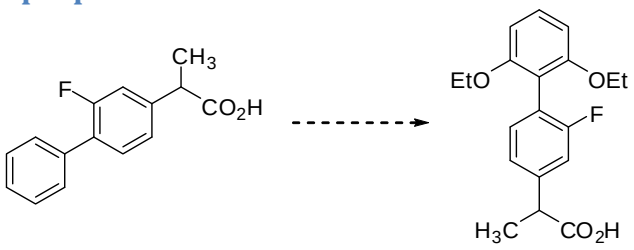
Evolution of selective COX-2 inhibitors from non-selective COX-2 inhibitors:

Figure A. Transformation of nonselective cyclooxygenase inhibitor to COX-2 selective agnets in the phenyl propionic acid class.

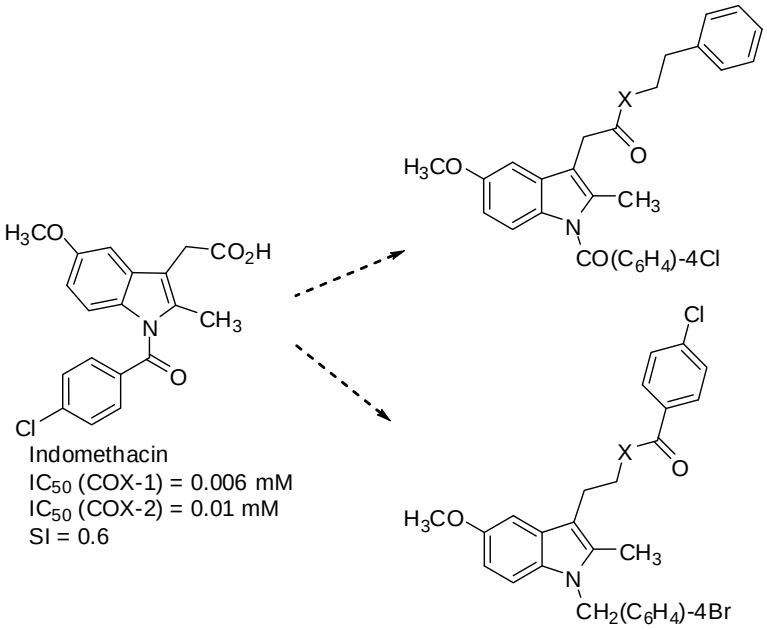


Flurbiprofen
IC_{50} (COX-1) = 0.01 mM
IC_{50} (COX-2) = 0.01 mM
SI = 1

Diethoxy modification
IC_{50} (COX-1) = 7.70 mM
IC_{50} (COX-2) = 0.10 mM
SI = 77

Bioorg. Med. Chem. Lett. (1999) 9:307-312

Figure B. Transformation of nonselective cyclooxygenase inhibitor to COX-2 selective agnets in the indole-3-acetic acid class.



Indomethacin
IC_{50} (COX-1) = 0.006 mM
IC_{50} (COX-2) = 0.01 mM
SI = 0.6

Indomethacin Ester: X = O
IC_{50} (COX-1) > 66 mM
IC_{50} (COX-2) = 0.05 mM
SI = > 1320

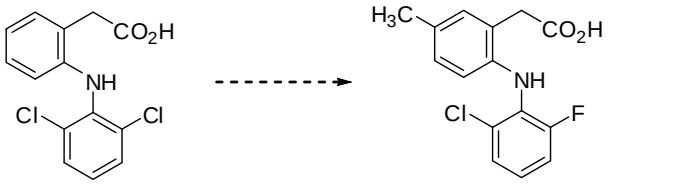
Indomethacin Amide: X = NH
IC_{50} (COX-1) > 66 mM
IC_{50} (COX-2) = 0.06 mM
SI = > 1100

Indomethacin Reverse Ester: X = O
IC_{50} (COX-1) > 66 mM
IC_{50} (COX-2) = 0.05 mM
SI = > 1320

Indomethacin Reverse Amide: X = NH
IC_{50} (COX-1) > 66 mM
IC_{50} (COX-2) = 0.05 mM
SI = >1320

Bioorg. Med. Chem. Lett. (2002) 12:1315-1318.
J. Med. Chem. (2000) 43:2860-2870.
Bioorg. Med. Chem. Lett. (2005) 13:6810-6822.

Figure C. Transformation of nonselective cyclooxygenase inhibitor diclofenac to COX-2 selective analogue as the most selective COX-2 inhibitor.

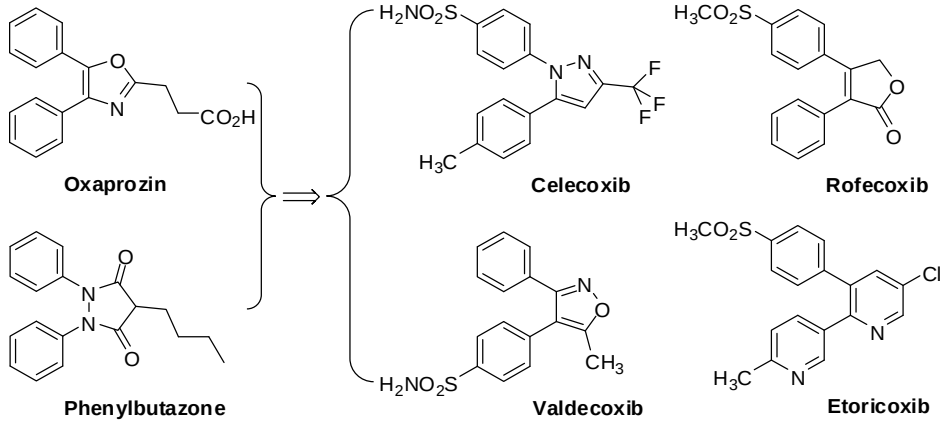


Diclofenac
IC_{50} (COX-1) = 0.07 mM
IC_{50} (COX-2) = 0.02 mM
SI = 3.5

Lumiracoxib
IC_{50} (COX-1) > 10 mM
IC_{50} (COX-2) = 0.007 mM
SI = > 1428.57

J. Med. Chem. (1990) 33:2358-2368

Figure D. Evolution of the 1,2-diarylheterocycle class (coxibs) selective COX-2 inhibitors from non-selective COX-2 inhibitors.



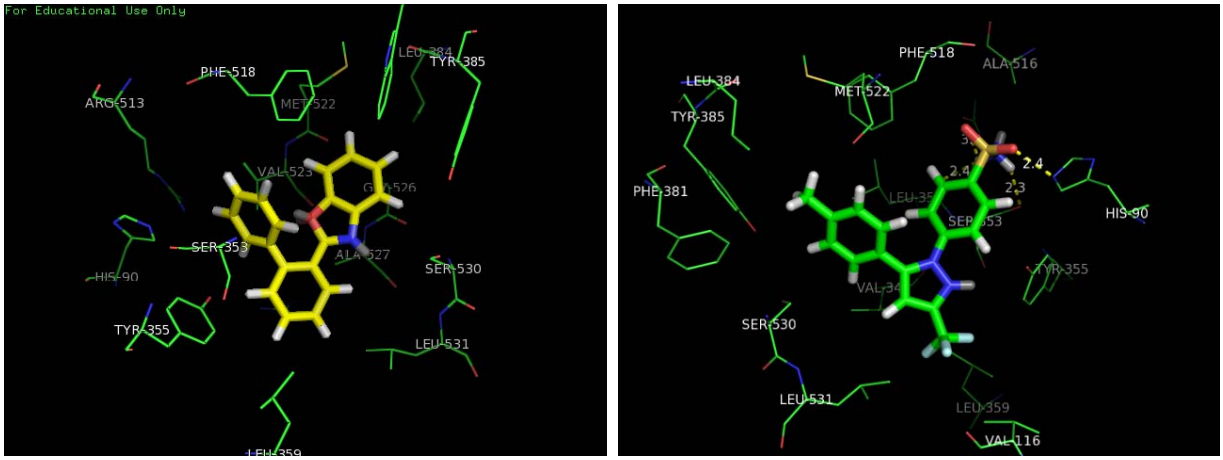
Determination of Interaction of the Newly Designed Scaffold II in the COX-2 Active Site:

To ascertain whether the newly designed scaffold **II** would be a ligand for COX-2 it was planned to identify the various possible interaction of the representative compound **3a** (belonging to the scaffold **II**) in the COX-2 active site. Therefore, the computational studies (3D QSAR) was performed individually on the COX-1 (3KK6.pdb)[1] and COX-2 (6COX.pdb)[2] active sites using the 'GOLD 4.1.2' software.[3-5]

The X-ray crystal structures of CYCLOOXYGENASE-2 with compound SC-558 was used. 'PyMOL 1.3' was used to optimize the enzyme by removing water molecules, residues and fragments of enzyme. The file was saved in pdb file format. After protein optimization a standard mode of 'GOLD 4.1.2' software was used for the docking purpose. 'GOLD' gives the best poses by a Genetic algorithm search strategy. In 'GOLD' software 'hermes 1.3.1' was used as the visualizer. Validation of process was done by calculating root-mean-square deviation (RMSD), which was 0.21. For docking of the molecules, optimized protein was loaded in the 'GOLD' software, followed by addition of hydrogen and deletion of ligand. The atom and residue were selected in 10 Å range. Then celecoxib and **3a** were separately added to the active

site. The analysis of the interactions was done in 'PyMOL' software. The specific interactions are provided in the docking pose in Fig. E. The satisfactory docking score was obtained with the simplest molecular structure **3a** representing the newly designed scaffold **II**. This encouraged us to generate structural analogues of **3a** through modification/functionalisation of the aryl 2 moiety (Fig. F).

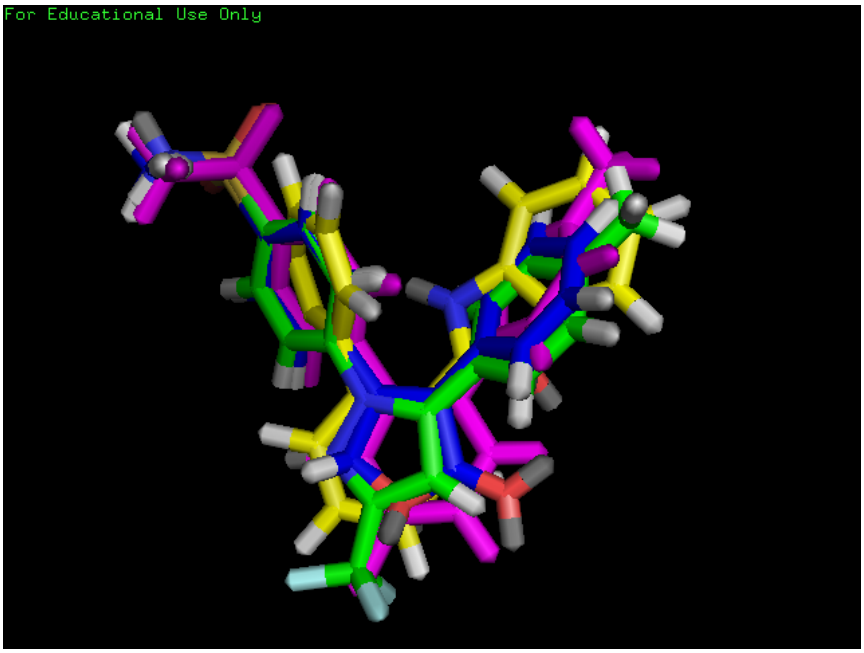
Figure E. Docking pose of 3a representing the new pharmacophoric feature (II) and of Celecoxib on the active site of COX-2 (6COX).



Docking pose of **3a** with score 54.3682 Docking pose of **Celecoxib** with score 70.5354

Comparison of docking pose of **3a** with marketed COX-2 selective drugs celecoxib, etoricoxib and rofecoxib was performed (Fig. F) and it is observed that **3a** has similar 'V shape' docking pose like celecoxib, etoricoxib and rofecoxib.

Figure F: Comparison of poses of different coxibs with 3a inside the active site of COX-2.

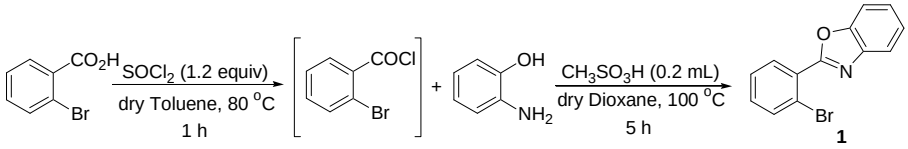


(Celecoxib is in green color, Rofecoxib is in blue color, Etoricoxib is in light pink color and compound **3a** is in yellow color).

General consideration

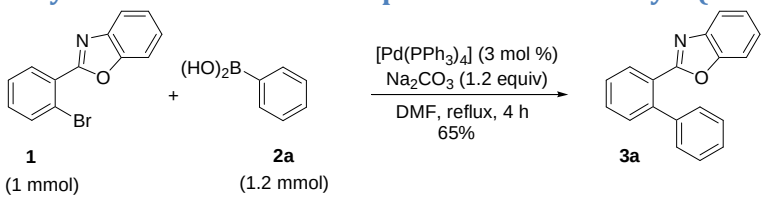
The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance 400 MHz NMR spectrometer in $CDCl_3$ with residual undeuterated solvent ($CDCl_3$: 7.26/77.0) using Me_4Si as an internal standard. Chemical shifts (δ) are given in ppm and *J* values are given in Hz. The IR spectra were recorded either on KBr pellets (for solids) or neat (for liquids) on a Nicolet Impact 410 FTIR spectrometer. The HRMS spectra were recorded on Bruker Maxis instrument. Melting points were measured with Gupta scientific, India melting point apparatus. Open column chromatography, thin layer chromatography (TLC) was performed on Silica gel [CDH silica gel 60-120 mesh, F254 and Merck® silica gel respectively]. Evaporation of solvents was performed at reduced pressure, using a Bűchi rotary evaporator. The HPLC was performed in Shimadzu CLASS-VP V6.12 SP3 instrument. All chemicals were purchased from Aldrich, Lancaster and Fluka Chemicals and used as received.

Typical procedure for the preparation of 2-(2-bromo-phenyl)-benzoxazole 1 (Ref 6):-



2-Bromobenzoic acid (2.01 g, 10 mmol) was treated with $SOCl_2$ (1.427 g, 12 mmol, 0.88 mL, 1.2 equiv) in dry toluene (20 mL) at 80 °C until quenching of an aliquot with few drops of MeOH revealed the complete consumption of acid and appearance of new spot in TLC (1 h). The excess $SOCl_2$ was distilled off and the reaction mixture was treated with 2-aminophenol (1.09 g, 10 mmol) in dry 1,4-dioxane (20 mL) followed by addition of CH_3SO_3H (2 mL) and the mixture was stirred magnetically at 100 °C. After complete consumption of 2-aminophenol (checked through TLC, 5 h), dioxane was distilled off in rotary evaporator and the residue was diluted with EtOAc (20 mL) followed by saturated aq. $NaHCO_3$ (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined EtOAc extracts were washed with H_2O (3 × 10 mL), dried (anh Na_2SO_4) and purified by column chromatography (60-120 mesh silica-gel) using hexane/EtOAc solvent system to afford the **1** as yellow solid, (2.056 g, 75%), mp: 51-53 °C; TLC (Hexane:EtOAc, 95:5 v/v): $R_f \approx 0.5$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.46-7.38 (m, 3H), 7.50 (dd, J = 7.6 Hz, 1.2 Hz, 1H), 7.66–7.63 (m, 1H), 7.81 (dd, J = 8.0 Hz, 1.2 Hz, 1H), 7.90-7.87 (m, 1H), 8.11 (dd, J = 7.8 Hz, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 110.8, 120.6, 121.9, 124.7, 125.6, 127.5, 128.4, 132.0, 132.2, 134.7, 141.6, 150.7, 161.6; IR (KBr) ν_{max}: 2927, 1277, 1267, 1057, 1039 cm^{-1}; HRMS (ESI) $(M + Na)^+$ calcd. for $C_{13}H_8NOBrNa$, 295.9687; found, 295.9684.

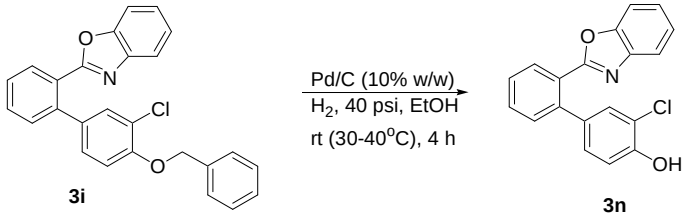
Typical procedure for the conventional Suzuki coupling of 1 with phenylboronic acid 2a to form 2-biphenyl-2-yl-benzoxazole 3a in the presence of Pd catalyst (Scheme 1):-



1 (1 mmol) **2a** (1.2 mmol) **3a**

To a magnetically stirred solution of $[Pd(PPh_3)_4]$ (3.5 mg, 0.03 mmol, 3 mol%) in DMF (2 mL) were added **1** (0.274 g, 1 mmol), phenylboronic acid **2a** (0.146 g, 1.2 mmol, 1.2 equiv) and Na_2CO_3 (0.127 g, 1.2 mmol, 1.2 equiv) at reflux (the oil-bath temperature was 165 ^oC). Upon completion of the reaction (4 h, TLC), the reaction mixture was cooled to room temperature; diluted with H_2O (10 mL) and extracted with DCM (2 × 5 mL) followed by washing with brine (5 mL). The DCM layer was separated from the aqueous layer and then dried (anh Na_2SO_4); filtered off and evaporated to dryness under vacuum (30 mm Hg). The residue was passed through chromatography column (silica-gel; 60-120 mesh) and eluted with hexane-EtOAc to afford the **3a** as off white semi-solid, (0.176 g, 65%); TLC (Hexane:EtOAc, 95:5 v/v): $R_f \approx 0.5$; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.32 – 7.37 (m, 8H), 7.52 – 7.56 (m, 2H), 7.60 – 7.64 (m, 1H), 7.74 – 7.76 (m, 1H), 8.14 – 8.16 (m, 1H); IR (KBr) ν_{max}: 1616, 1455, 1247, 1027 cm^{-1}; MS (ESI) $(M + H)^+ = 272.6$.

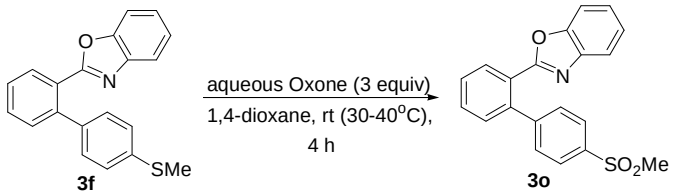
Typical procedure for the synthesis of 2'-benzoxazol-2-yl-3-chloro-biphenyl-4-ol 3n (Scheme 2):-



3i **3n**

To a solution of 2-(4'-benzyloxy-3'-chloro-biphenyl-2-yl)-benzoxazole **3i** (0.412 g, 1 mmol, 1 equiv) in EtOH (10 mL) was added catalytic Pd/C (10% w/w, 100 mg) at room temperature (30-40 ^oC). The reaction mixture was charged with H_2 (40 psi pressure) and shaken on parr hydrogenator. After the completion of the reaction (4 h, TLC), the reaction mixture was filtered through a pad of celite and was concentrated under reduced pressure in rotary vacuum evaporator to afford the crude product which was purified by column chromatography (60-120 mesh silica-gel) using hexane/EtOAc solvent system to afford the **3n** as off white semi-solid, (0.257 g, 80%); TLC (Hexane:EtOAc, 85:15 v/v): $R_f \approx 0.5$; ^1H NMR (CD_3OD, 400 MHz) δ (ppm): 6.84 (d, J = 8.0 Hz, 1H), 6.94 (d, J = 8.4 Hz, 1H), 7.26 (s, 1H), 7.38–7.32 (m, 2H), 7.42–7.40 (m, 1H), 7.55–7.48 (m, 2H), 7.65–7.61 (m, 1H), 7.70–7.68 (m, 1H), 8.00 (d, J = 8.0 Hz, 1H); ^{13}C NMR (CD_3OD + $CDCl_3$, 100 MHz) δ (ppm): 110.5, 116.0, 119.4, 120.2, 124.6, 125.3, 125.7, 127.4, 128.1, 129.9, 130.7, 130.9, 131.3, 133.0, 140.9, 141.1, 150.6, 152.4, 164.0; IR (KBr) ν_{max}: 3549, 2987, 1612, 1501, 1476, 1455, 1281, 1259, 1243, 1103 cm^{-1}; HRMS (ESI) $(M + Na)^+$ calcd. for $C_{19}H_{12}NO_2ClNa$, 344.0454; found, 344.0459.

Typical procedure for the synthesis of 2-(4'-methanesulfonyl-biphenyl-2-yl)-benzoxazole 3o (Scheme 2):-



An aqueous solution of oxone (50% w/v, 3 mmol, 3 equiv) was added dropwise to a stirred solution of 2-(4'-methylsulfanyl-biphenyl-2-yl)-benzoxazole **3f** (0.317 g, 1 mmol) in 1,4-dioxane (5 mL) at 0 °C. The reaction was allowed to proceed with stirring at room temperature (30-40 °C) for 4 h (TLC). The reaction mixture was diluted with H_2O (5 mL), extracted with EtOAc (2 × 5 mL), the EtOAc layer was washed successively with brine solution and water (5 mL each), the organic phase was separated, dried (anh Na_2SO_4) and concentrated under reduced pressure in rotary vacuum evaporator to afford the crude product which was purified by column chromatography (60-120 mesh silica-gel) using hexane/EtOAc solvent system to afford the **3o** as off white semi-solid, (0.279 g, 80%); TLC (Hexane:EtOAc, 80:20 v/v): $R_f \approx 0.5$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 3.10 (s, 3H), 7.34–7.31 (m, 3H), 7.46 (dd, J = 7.2 Hz, 1.6 Hz, 1H), 7.52–7.50 (m, 2H), 7.62–7.57 (m, 2H), 7.69–7.63 (m, 1H), 7.94–7.92 (m, 2H), 8.20 (dd, J = 7.2 Hz, 1.6 Hz, 1H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 44.6, 110.5, 120.2, 124.6, 125.4, 126.2, 127.2, 128.7, 129.9, 131.0, 131.2, 139.3, 140.3, 141.5, 146.9, 150.6, 162.7; IR (KBr) ν_{max}: 2953, 2853, 1667, 1594, 1452, 1311, 1150 cm^{-1}; HRMS (ESI) $(M + Na)^+$ calcd. for $C_{20}H_{15}NO_3SNa$, 372.0670; found, 372.0666.

Characterization of compounds

2-Biphenyl-2-yl-benzoxazole[7] 3a (Scheme 1):- Off white semi-solid; TLC (Hexane:EtOAc, 95:5 v/v): $R_f \approx 0.5$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.32 – 7.37 (m, 8H), 7.52 – 7.56 (m, 2H), 7.60 – 7.64 (m, 1H), 7.74 – 7.76 (m, 1H), 8.14 – 8.16 (m, 1H); IR (KBr) ν_{max}: 1616, 1455, 1247, 1027 cm^{-1}; MS (ESI) $(M + H)^+$ = 272.6.

2-(4'-Methoxy-biphenyl-2-yl)-benzoxazole 3b (Scheme 1):- Off white solid; mp: 109-111 °C; TLC (Hexane:EtOAc, 80:20 v/v): $R_f \approx 0.5$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 3.78 (s, 3H), 6.83 – 6.85 (m, 2H), 7.18 – 7.22 (m, 2H), 7.23 – 7.31 (m, 3H), 7.42 – 7.44 (m, 2H), 7.51 – 7.55 (m, 1H), 7.71 – 7.73 (m, 1H), 8.05 – 8.08 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 55.3, 110.6, 113.7, 120.1, 124.3, 124.9, 126.2, 127.2, 130.0, 131.0, 131.1, 131.2, 133.3, 141.8, 142.1, 150.8, 159.0, 164.1; IR (KBr) ν_{max}: 2952, 2929, 1615, 1457, 1249, 1184, 1030 cm^{-1}; HRMS $(M + Na)^+$ calcd. for $C_{20}H_{15}NO_2Na$, 324.1000; found, 324.1021.

2-(3',4'-Dimethoxy-biphenyl-2-yl)-benzoxazole 3c (Scheme 1):- Off white semi-solid; TLC (Hexane:EtOAc, 75:25 v/v): $R_f \approx 0.5$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 3.46 (s, 3H), 3.88 (s, 3H), 6.88 (dd, J = 7.6 Hz, 1.5 Hz, 1H), 6.98 (dd, J = 8.2 Hz, 1.5 Hz, 1H), 7.08 – 7.12 (m, 1H), 7.26 – 7.30 (m, 3H), 7.49 – 7.51 (m, 1H), 7.54 – 7.60 (m, 2H), 7.68 – 7.71 (m, 1H), 8.24 –

8.26 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 56.1, 60.4, 110.4, 112.3, 120.1, 122.7, 123.8, 124.2, 124.7, 127.0, 127.6, 130.2, 130.6, 131.7, 135.6, 138.3, 141.8, 146.6, 150.7, 152.5, 163.8; IR (KBr) ν_{max}: 2933, 1609, 1521, 1457, 1249, 1027 cm^{-1}; HRMS $(M + Na)^+$ calcd. for $C_{21}H_{17}NO_3Na$, 354.1106; found, 354.1107.

2-(2',3'-Dimethoxy-biphenyl-2-yl)-benzoxazole 3d (Scheme 1):- Off white semi-solid; TLC (Hexane:EtOAc, 75:25 v/v): $R_f \approx 0.5$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 3.64 (s, 3H), 3.92 (s, 3H), 6.79 (d, J = 1.9 Hz, 1H), 6.86 – 6.91 (m, 2H), 7.30 – 7.35 (m, 3H), 7.51 – 7.56 (m, 2H), 7.59 – 7.61 (m, 1H), 7.75 – 7.77 (m, 1H), 8.05 – 8.08 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 55.7, 55.9, 110.6, 110.9, 112.1, 120.0, 121.1, 124.4, 125.0, 126.4, 127.3, 130.9, 131.0, 131.1, 133.5, 141.6, 142.1, 148.4, 148.5, 150.7, 164.1; IR (KBr) ν_{max}: 2933, 1575, 1471, 1453, 1263, 1022 cm^{-1}; HRMS $(M + Na)^+$ calcd. for $C_{21}H_{17}NO_3Na$, 354.1106; found, 354.1104.

2-(3'-Cyclopentyloxy-4'-methoxy-biphenyl-2-yl)-benzoxazole 3e (Scheme 1):- Off white semi-solid; TLC (Hexane:EtOAc, 90:10 v/v): $R_f \approx 0.5$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.61 – 1.67 (m, 8H), 3.88 (s, 3H), 4.42 – 4.44 (m, 1H), 6.72 (d, J = 2.0 Hz, 1H), 6.89 – 6.96 (m, 2H), 7.27 – 7.37 (m, 3H), 7.48 – 7.54 (m, 2H), 7.58 – 7.62 (m, 1H), 7.74 – 7.76 (m, 1H), 8.04 (dd, J = 7.8 Hz, 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 24.0, 32.6, 56.0, 80.2, 110.7, 111.6, 115.7, 120.0, 120.8, 124.3, 124.9, 126.4, 127.2, 130.9, 131.0, 131.1, 133.4, 141.8, 142.3, 147.1, 149.4, 150.9, 164.2; IR (KBr) ν_{max}: 2929, 2657, 1522, 1473, 1457, 1249, 1022 cm^{-1}; HRMS $(M + Na)^+$ calcd. for $C_{25}H_{23}NO_3Na$, 408.1576; found, 408.1575.

2-(4'-Methylsulfanyl-biphenyl-2-yl)-benzoxazole 3f (Scheme 1):- Off white solid; mp: 89-91 °C; TLC (Hexane:EtOAc, 95:5 v/v): $R_f \approx 0.5$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.51 (s, 3H), 7.23 (s, 4H), 7.29 – 7.36 (m, 3H), 7.48 – 7.53 (m, 2H), 7.58 – 7.61 (m, 1H), 7.73 – 7.75 (m, 1H), 8.11 (dd, J = 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 15.7, 110.6, 120.1, 124.3, 125.0, 126.1, 127.5, 129.2, 131.0, 131.1, 131.1, 137.7, 141.7, 141.8, 150.7, 163.8; IR (KBr) ν_{max}: 2927, 2657, 1599, 1473, 1451, 1249, 1020 cm^{-1}; HRMS $(M + Na)^+$ calcd. for $C_{20}H_{15}NOSNa$, 340.0772; found, 340.0770.

2-(3'-Chloro-4'-methoxy-biphenyl-2-yl)-benzoxazole 3g (Scheme 1):- Light yellow solid; mp: 103-105 °C; TLC (Hexane:EtOAc, 90:10 v/v): $R_f \approx 0.5$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 3.94 (s, 3H), 6.88 (d, J = 8.5 Hz, 1H), 7.10 (dd, J = 8.5 Hz, 2.2 Hz, 1H), 7.31 – 7.38 (m, 3H), 7.44 (dd, J = 2.2 Hz, 1H), 7.46 – 7.48 (m, 1H), 7.53 (dt, J = 8.6 Hz, 1.4 Hz, 1H), 7.58 – 7.60 (m, 1H), 7.74 – 7.76 (m, 1H), 8.13 (dd, J = 7.8 Hz, 1.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 56.2, 110.6, 111.5, 120.2, 122.1, 124.4, 125.1, 126.2, 127.7, 128.3, 130.6, 131.1, 131.2, 134.2, 140.7, 141.6, 150.7, 154.3, 163.5; IR (KBr) ν_{max}: 2983, 1611, 1500, 1476, 1453, 1282, 1260, 1243, 1106, 1059 cm^{-1}; HRMS $(M + Na)^+$ calcd. for $C_{20}H_{14}NO_2ClNa$, 358.0611; found, 358.0611.

2-(3'-Chloro-4'-isopropoxy-biphenyl-2-yl)-benzoxazole 3h (Scheme 1):- Off white semi-solid; TLC (Hexane:EtOAc, 95:5 v/v): $R_f \approx 0.5$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.41 (d, J = 6.1 Hz, 6H), 4.55 – 4.60 (m, 1H), 6.88 (d, J = 8.5 Hz, 1H), 7.04 (dd, J = 8.4, 2.2 Hz, 1H), 7.30 – 7.37 (m, 3H), 7.43 (d, J = 2.2 Hz, 1H), 7.47 – 7.49 (m, 1H), 7.52 – 7.54 (m, 1H), 7.57 – 7.60 (m, 1H), 7.74 – 7.76 (m, 1H), 8.14 (dd, J = 7.7 Hz, 1.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100

MHz) δ (ppm): 22.0, 72.2, 110.5, 116.0, 120.1, 124.0, 124.4, 125.0, 126.2, 127.6, 128.2, 130.7, 131.0, 131.1, 134.4, 140.8, 141.7, 150.7, 153.0, 163.6; IR (KBr) ν_{max}: 2977, 1613, 1509, 1478, 1452, 1281, 1260, 1241, 1111, 1062 cm^{-1}; HRMS $(M + Na)^+$ calcd. for $C_{22}H_{18}NO_2ClNa$, 386.0924; found, 386.0927.

2-(4'-Benzyloxy-3'-chloro-biphenyl-2-yl)-benzoxazole 3i (Scheme 1):- Off white semi-solid; TLC (Hexane:EtOAc, 93:7 v/v): $R_f \approx 0.5$; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 5.18 (s, 2H), 6.90 (d, J = 8.5 Hz, 1H), 7.06 (dd, J = 8.4, 2.1 Hz, 1H), 7.31 – 7.38 (m, 4H), 7.40 – 7.45 (m, 2H), 7.47 – 7.54 (m, 5H), 7.56 – 7.60 (m, 1H), 7.76 – 7.78 (m, 1H), 8.16 (d, J = 7.7Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 70.9, 110.6, 113.5, 120.2, 122.9, 124.5, 125.1, 126.2, 127.1, 127.7, 128.0, 128.3, 128.6, 130.7, 131.1, 131.1, 131.2, 134.6, 136.5, 140.7, 141.6, 150.7, 153.5, 163.5; IR (KBr) ν_{max}: 1607, 1500, 1453, 1293, 1260, 1241, 1057 cm^{-1}; HRMS $(M + Na)^+$ calcd. for $C_{26}H_{18}NO_2ClNa$, 434.0924; found, 434.0922.

2-(4'-Fluoro-biphenyl-2-yl)-benzoxazole 3j (Scheme 1):- Off white semi-solid; TLC (Hexane:EtOAc, 95:5 v/v): $R_f \approx 0.5$; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.31 – 7.34 (m, 3H), 7.43 - 7.45 (m, 2H), 7.48 – 7.50 (m, 1H), 7.59 – 7.65 (m, 4H), 7.72 – 7.74 (m, 1H), 8.19 – 8.22 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 110.5, 120.2, 124.5, 125.0, 125.1, 125.2, 125.6, 126.2, 128.3, 129.2, 129.6, 131.0, 131.1, 131.2, 140.9, 141.6, 144.7, 150.6, 163.1; IR (KBr) ν_{max}: 2927, 1749, 1609, 1459, 1278, 1261, 1091 cm^{-1}; HRMS $(M + Na)^+$ calcd. for $C_{19}H_{12}NOFNa$, 312.0801; found, 312.0806.

2-(4'-Trifluoromethyl-biphenyl-2-yl)-benzoxazole 3k (Scheme 1):- Off white semi-solid; TLC (Hexane:EtOAc, 95:5 v/v): $R_f \approx 0.5$; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.28 – 7.33 (m, 3H), 7.40 – 7.42 (m, 2H), 7.46 (dd, J = 7.4, 1.4 Hz, 1H), 7.54 – 7.63 (m, 4H), 7.69 – 7.71 (m, 1H), 8.18 (dd, J = 7.7, 1.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 110.5, 120.2, 124.5, 125.0, 125.0, 125.1, 125.1, 125.2, 126.2, 128.3, 128.9, 129.3, 129.6, 131.0, 131.1, 131.1, 140.9, 141.6, 144.8, 150.6, 163.1; IR (KBr) ν_{max}: 3001, 1737, 1698, 1677, 1540, 1522, 1457, 1326, 1277, 1261, 1122 cm^{-1}; HRMS $(M + Na)^+$ calcd. for $C_{20}H_{12}NOF_3Na$, 362.0769; found, 362.0774.

2'-Benzoxazol-2-yl-biphenyl-4-carbaldehyde 3l (Scheme 1):- Off white semi-solid; TLC (Hexane:EtOAc, 90:10 v/v): $R_f \approx 0.5$; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.30 – 7.35 (m, 3H), 7.48 – 7.53 (m, 3H), 7.59 – 7.66 (m, 2H), 7.71 – 7.73 (m, 1H), 7.88 – 7.90 (m, 2H), 8.19 – 8.22 (m, 1H), 10.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 110.6, 120.2, 124.5, 125.2, 126.2, 128.5, 129.6, 129.6, 131.0, 131.0, 131.2, 135.2, 141.0, 141.6, 147.4, 150.6, 163.0, 192.1; IR (KBr) ν_{max}: 1708, 1600, 1241, 1211, 1030 cm^{-1}; HRMS $(M + Na)^+$ calcd. for $C_{20}H_{13}NO_2Na$, 322.0844; found, 322.0849.

2'-Benzoxazol-2-yl-biphenyl-4-carbonitrile 3m (Scheme 1):- Off white semi-solid; TLC (Hexane:EtOAc, 85:15 v/v): $R_f \approx 0.5$; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.34 – 7.36 (m, 3H), 7.42 – 7.44 (m, 2H), 7.46 – 7.48 (m, 1H), 7.61 – 7.64 (m, 2H), 7.65 – 7.68 (m, 2H), 7.70 – 7.72 (m, 1H), 8.20 – 8.24 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 110.5, 111.1, 120.3, 124.6, 125.4, 126.1, 128.7, 129.7, 130.9, 131.0, 131.2, 131.9, 140.4, 141.5, 145.9, 150.6; IR (KBr) ν_{max}:

2921, 2859, 2223, 1611, 1457, 1244, 1032 cm^{-1}; HRMS $(M + Na)^+$ calcd. for $C_{20}H_{12}N_2ONa$, 319.0847; found, 319.0844.

Biology Data

Cyclooxygenase Inhibition Studies

In vitro COX-1 and COX-2 inhibitory activities (μM) were determined using COX inhibitor screening assay kit (ovine COX-1 and human recombinant COX-2) with 96-well plates as per the manufacturer's protocol through direct measurement of $PGF_{2\alpha}$ produced by $SnCl_2$ reduction of COX-derived PGH_2.[8] The samples for determination of initial activity of COX-1, COX-2 and inhibitor screening were prepared by adding 950 μL reaction buffer, 10 μL heme, 10 μL of COX-1/COX-2 enzyme and 20 μL of DMSO (inhibitor dissolved in DMSO in case of inhibitor screening) in separate test tubes. The COX-1/COX-2 background samples were prepared by adding 970 μL reaction buffer, 10 μL heme and 10 μL of inactivated COX-1/COX-2 enzyme (inactivated by incubating in boiling water for 3 min) in the test tube. Reactions were initiated by adding 10 μL of arachidonic acid (AA) to each test tube and incubated at 37 ºC for 2 minutes. The enzyme catalysis was quenched by adding 50 μL of 1 M HCl. PGH_2 thus formed was reduced to $PGF_{2\alpha}$ by adding 100 μL of $SnCl_2$ solution to each test tube. The quantification of prostaglandin formed in each well was done using specific prostaglandin antiserum and reading the 96-well plate at 405 nm using ELISA plate reader. The results of this assay have been represented in terms of the percent inhibition of COX-1 and COX-2 enzymes at 10 μM of inhibitor/standard concentration. The IC_{50} values of the selected test compounds and standard drug was calculated from concentration-inhibition response curve.

Carrageenan-Induced Paw Edema Method

The acute anti-inflammatory effect was evaluated by the carrageenan-induced paw edema assay in Wistar albino rats following the reported protocol[9] in compliance with the relevant laws on approval with IAEC (Institutional Animal Ethics Committee). The rats were divided into the following groups: carrageenan control, test compounds, celecoxib and diclofenac as standards, each comprising six animals. Acute edema was induced by subplantar administration of 0.1 mL of carrageenan (1%). The test compounds were suspended in 1% Tween-80 suspension and administrated intraperitoneally 10 min after the administration of Carrageenan. Paw volume was measured prior to injection of carrageenan (0 h) and then at an interval of 1 h up to 3 h using a plethysmograph. The results are reported as paw volume expressed in mL. The change in paw volume was measured using the formula:

$$\% \text{ reduction of inflammation} = [1 - (V_t/V_c) \times 100]$$

Where, V_t is the change in paw volume in the test compound treated group, and V_c, is the change in paw volume in the control group.

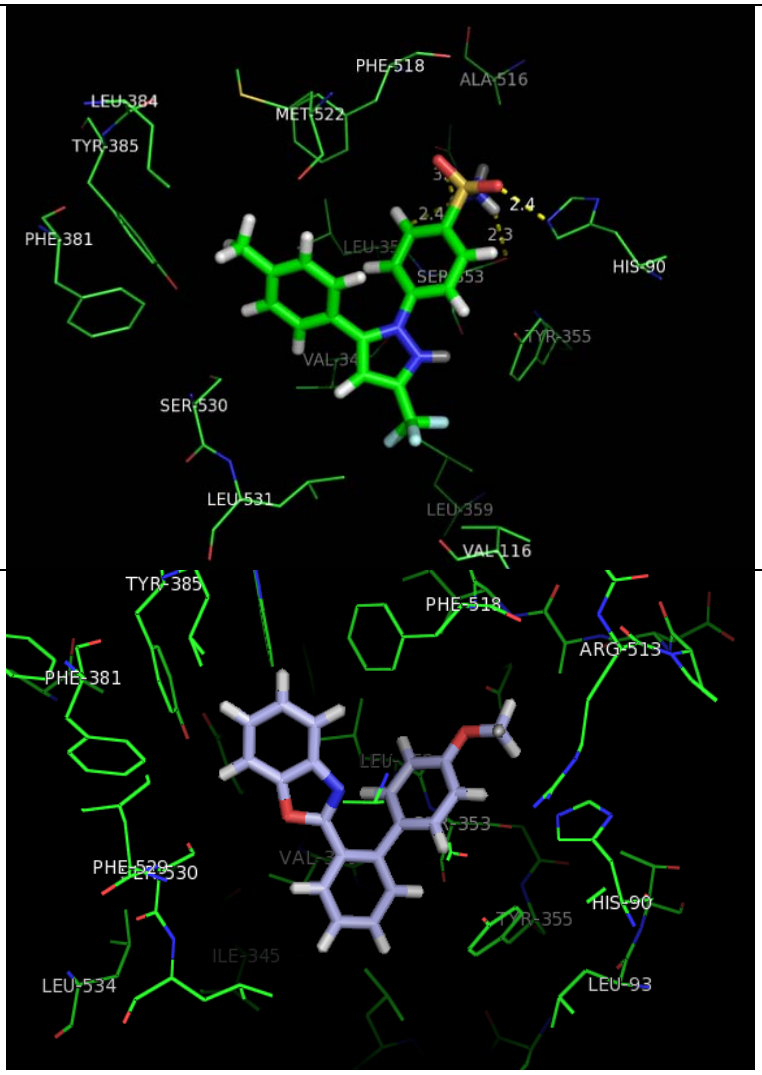
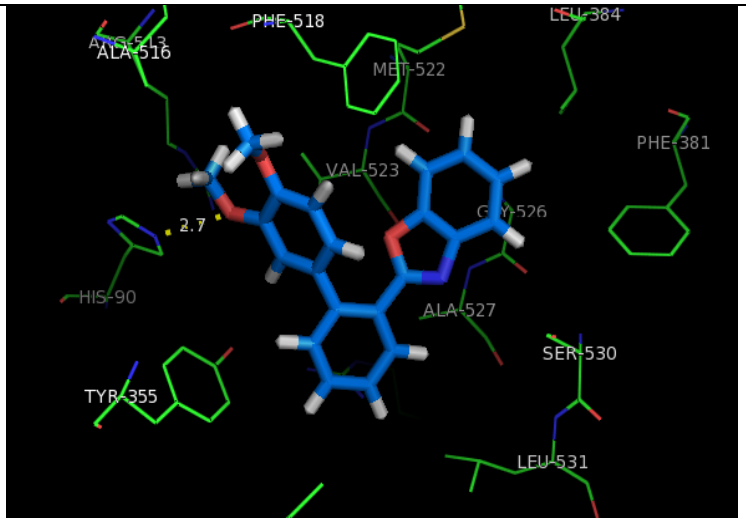
Rationalisation of COX-2 selectivity of the novel inhibitors 3g, 3n, and 3o through Computational Studies (3D QSAR) and correlation with the coxibs (Celecoxib, Rofecoxib, and Etoricoxib).

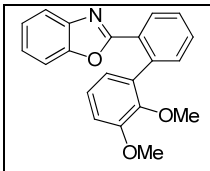
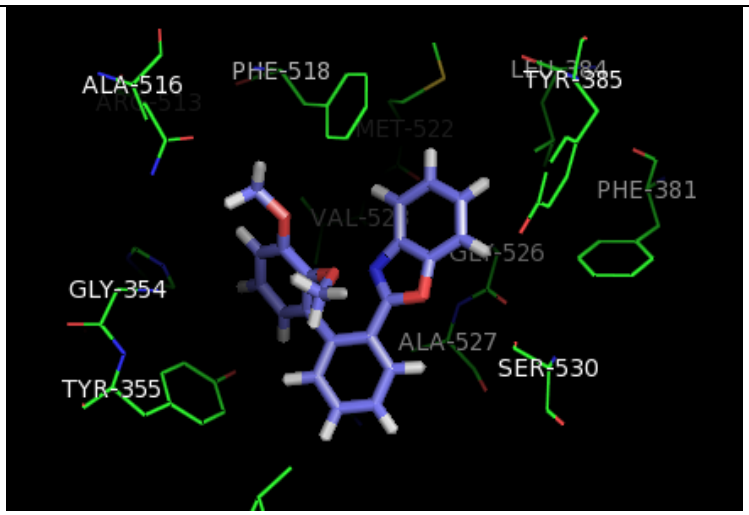
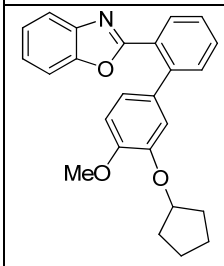
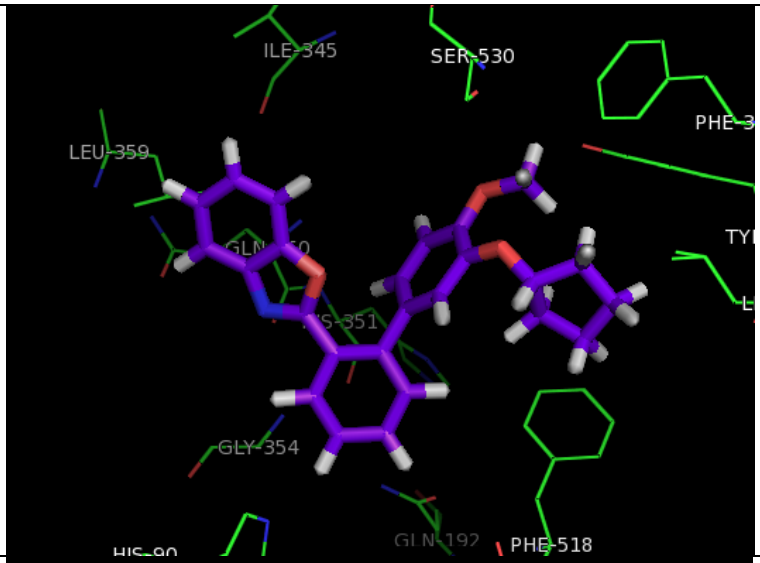
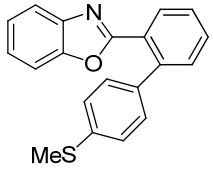
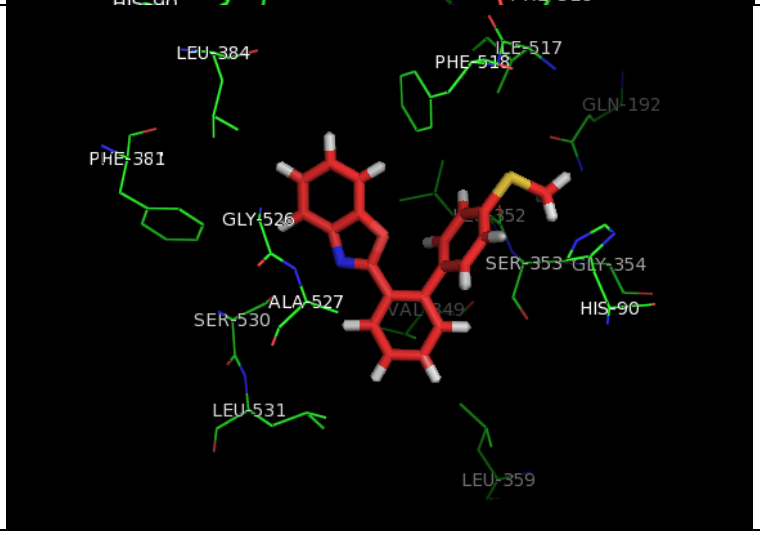
For the COX-2 docking studies celecoxib was used as the standard. Celecoxib gave more or less same results as SC-558. Celecoxib maintained four major interactions with Gln192, His90, Ser353 and Leu352 in the COX-2 active site.[10] The hydrogen atom attached to the N atom of the sulfonamide moiety of celecoxib forms hydrogen bonding interaction with the carbonyl oxygen of Gln192 (N-*H*···*O*=C-Gln192, 3.0 Å), Leu352 (N-*H*···*O*=C-Leu352, 2.4 Å) and Ser353 ((N-*H*···*O*=C-Ser353, 2.3 Å). The oxygen atom of sulfonamide moiety of celecoxib forms hydrogen bonding interaction with the imidazole NH of His90 (S=*O*···*H*-N-His90, 2.4 Å).

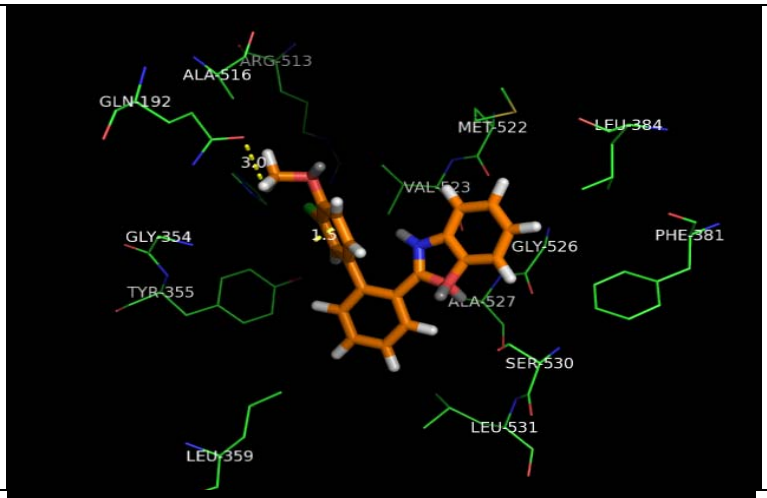
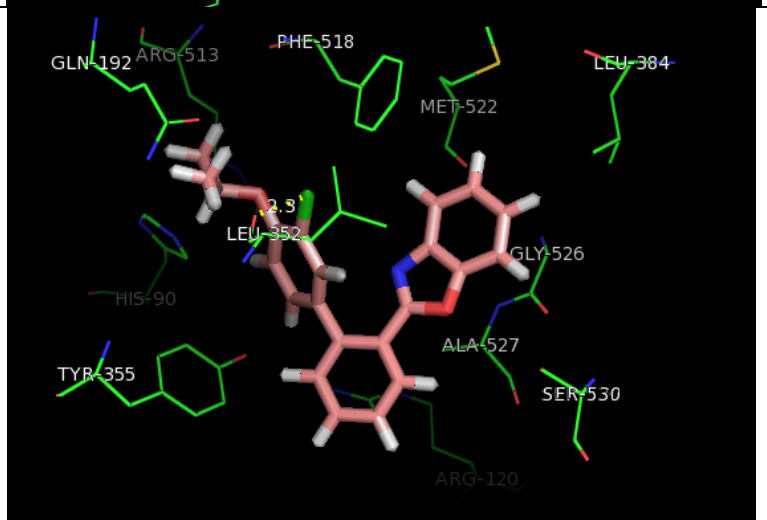
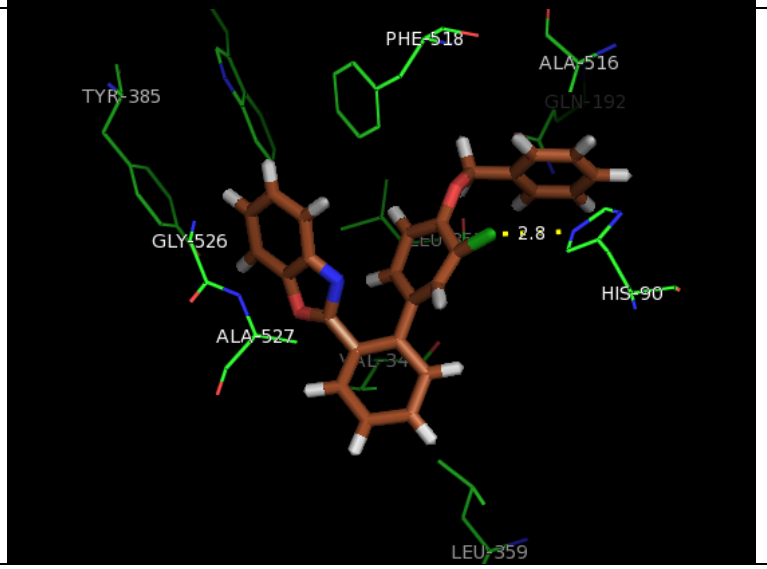
The compounds **3g**, **3n** and **3o** were docked individually. The **3g** showed weak interaction of the hydrogen atom of the methoxy group with the carbonyl (C = O) oxygen atom of Gln192. The docking score was 66.9734. The compound **3n** showed hydrogen bonding interaction through the hydrogen atom of the hydroxyl group with the carbonyl (C = O) oxygen atom of Gln192 (O-*H*···*O*=C-Gln192, 3.0 Å). The docking score was 63.1820. The **3o** showed strong hydrogen bonding interaction through the oxygen atom of SO_2Me group with the hydrogen atom of the C = NH of the guanidine moiety of Arg513 (S=*O*···*H*-N-Arg512, 2.8 Å). The docking score was 63.2420. The marketed COX-2 selective drugs, having methyl sulfonyl moieties e.g. rofecoxib and etoricoxib were docked into the active site of COX-2 and similar type of interactions were observed. The devoid of the amino acid Arg513 in COX-1 provides the advantage for COX-2 selectivity.

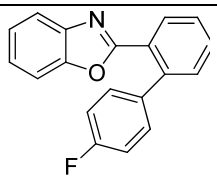
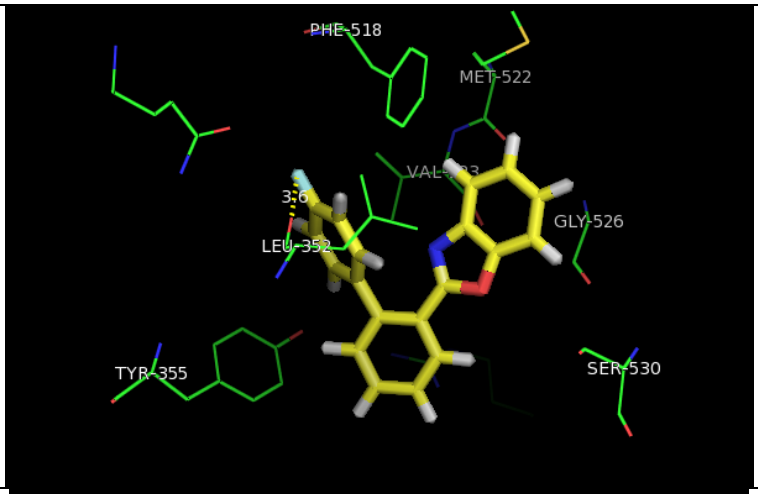
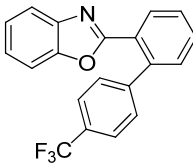
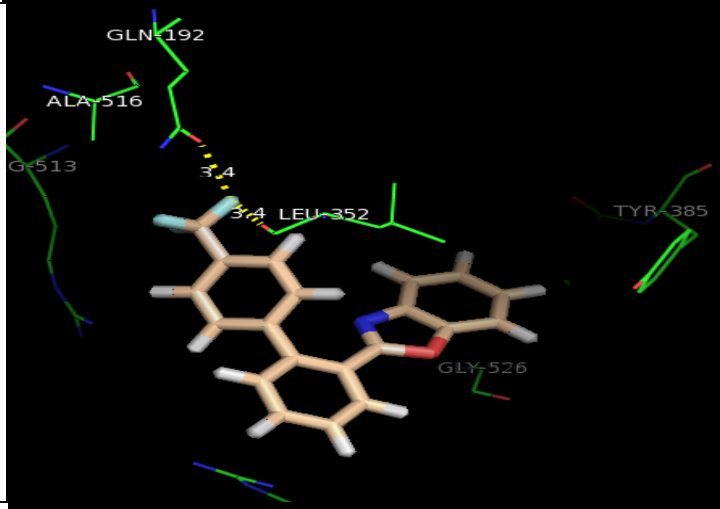
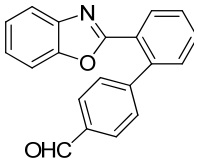
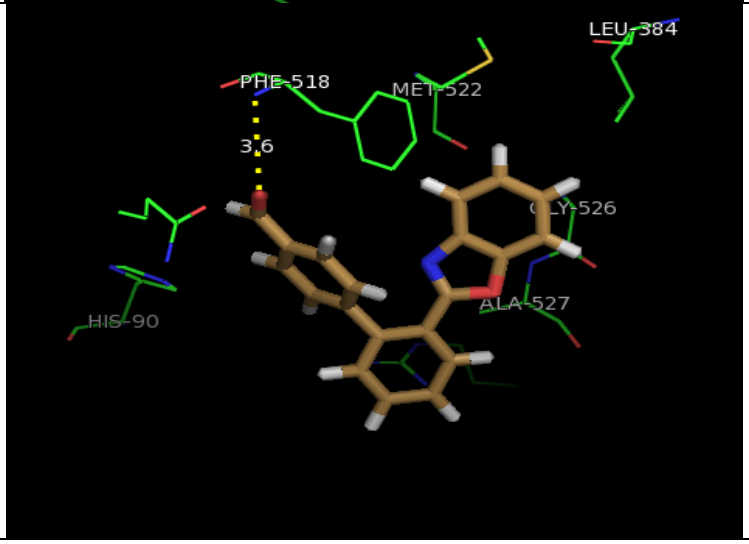
Celecoxib, **3a**, **3g**, **3n** and **3o** were docked individually into the active site of COX-1 (3KK6). However, none of these showed any significant interaction in the COX-1 active site that account for the COX-2 selectivity of these compounds.

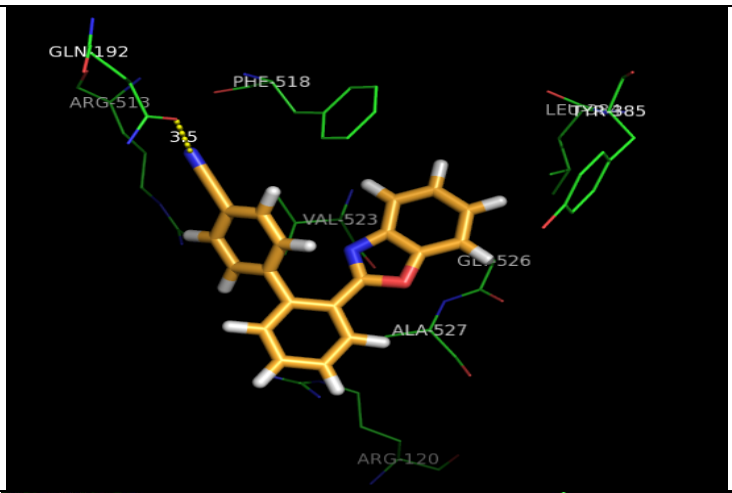
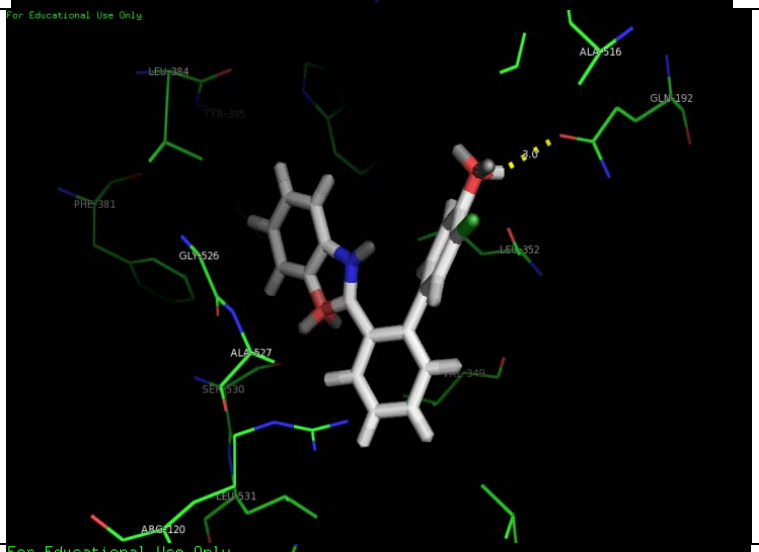
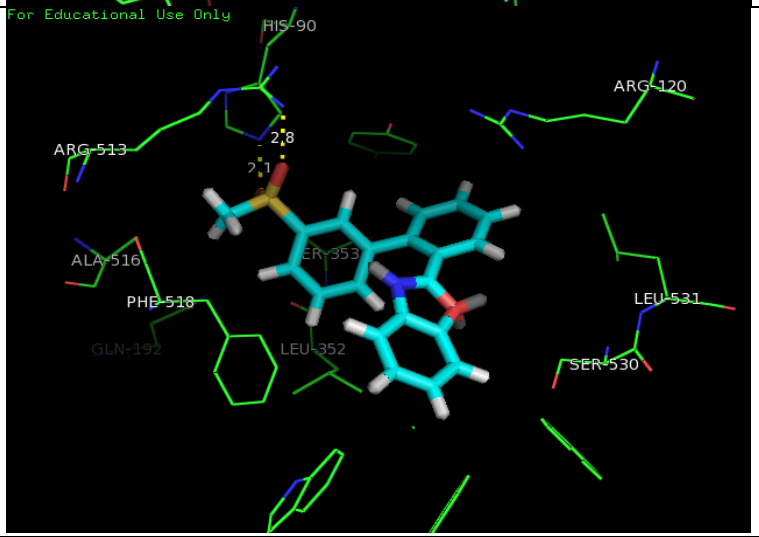
Table C: Comparison of benzoxazole derivatives with celecoxib in COX-2 (6COX)

COMPOUND	DOCKING POSE	INTERACTION	GOLD SCORE
(Celecoxib)		Gln192, His90, Ser353, Leu352.	70.5354
(Compound 3b)		No interaction	56.2468
(Compound 3c)		Oxygen of OMe is interacting with His 90.	58.3078

 **(Compound 3d)**		No interaction	52.5738
 **(Compound 3e)**		No interaction	39.0231
 **(Compound 3f)**		No interaction	58.1373

(Compound 3g)		Weak interaction of hydrogen of methoxy group with Gln192	66.9734
(Compound 3h)		Lone pair of Cl is weakly interacting with carbonyl of Leu 352.	58.1217
(Compound 3i)		Lone pair of Cl is weakly interacting with NH of His 90.	52.3478

 **(Compound 3j)**		Lone pair of F is very weakly interacting with carbonyl of Leu 352.	51.5463
 **(Compound 3k)**		Lone pair of F is very weakly interacting with carbonyl of Leu 352 and Gln 192.	58.3421
 **(Compound 3l)**		Oxygen of C= O is interacting with N-H of PHE 518.	55.4321

(Compound 3m)		Nitrogen of cyano group is weakly interacting of C= O of Gln 192.	56.3256
(Compound 3n)		Hydroxy is interacting with Gln192	63.1820
(Compound 3o)		Oxygen of SO_2Me is interacting with Arg 513	63.2420

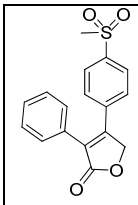
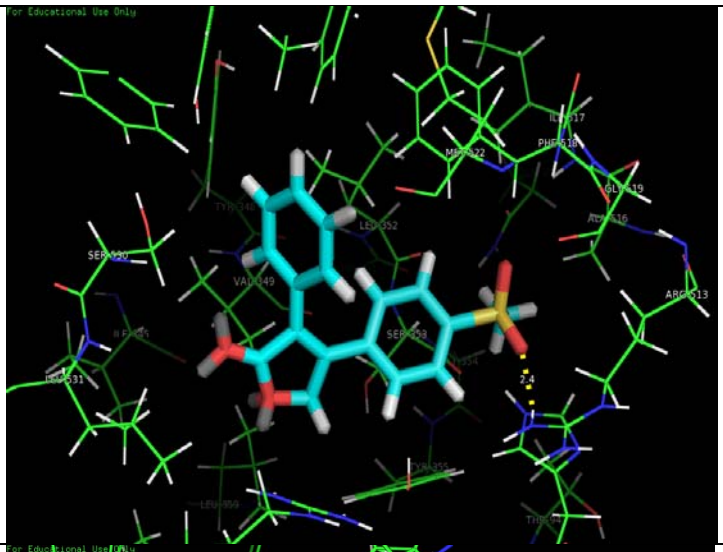
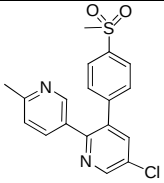
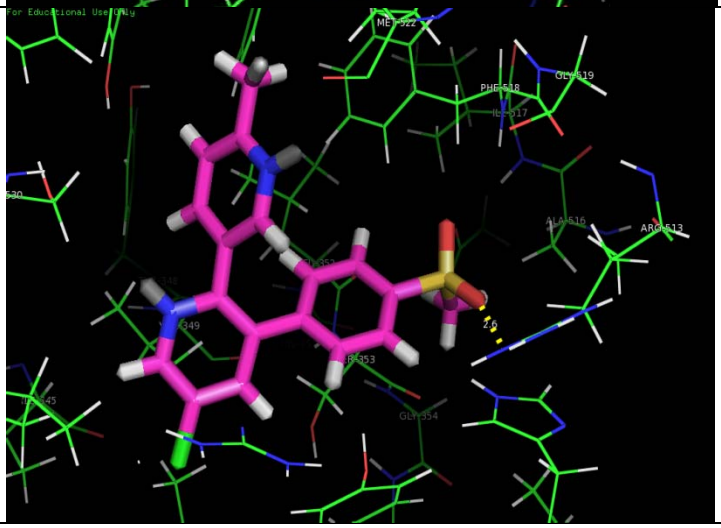
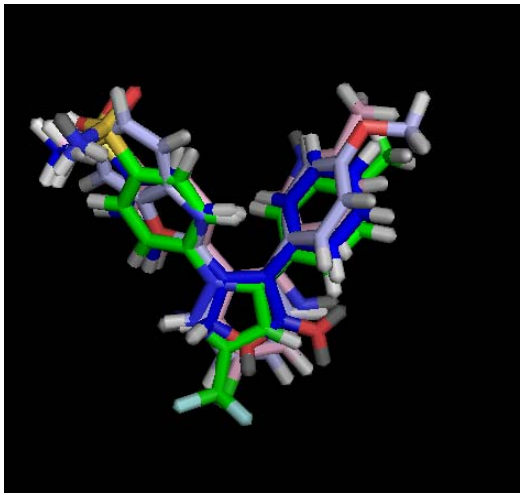
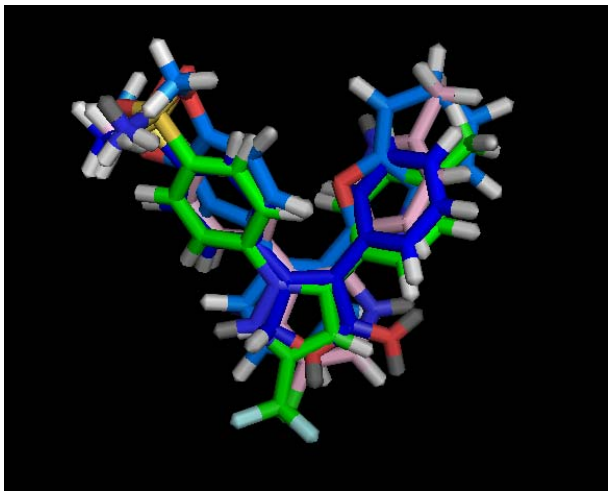
 (**Rofecoxib)**			Oxygen of SO_2Me is interacting with Arg513	64.2373
 (**Etoricoxib**)			Oxygen of SO_2Me is interacting with Arg513	71.1039

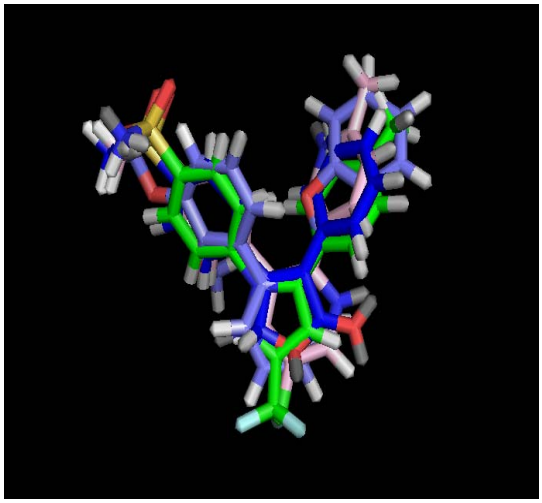
Figure G: Comparison of poses of different coxibs (celecoxib, etoricoxib, rofecoxib) with 3b-3f and 3h-3m inside the active site of COX-2.



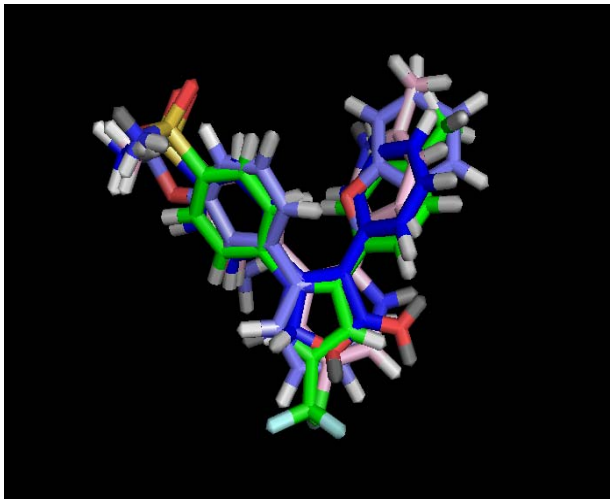
Celecoxib is in green color, Etoricoxib is in pink color, Rofecoxib is in blue color and **compound 3b** is in light blue.



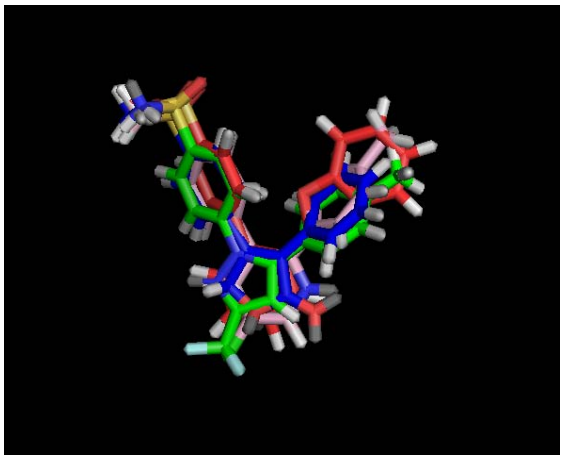
Celecoxib is in green color, Etoricoxib is in pink color, Rofecoxib is in blue color and **compound 3c** is in marine blue.



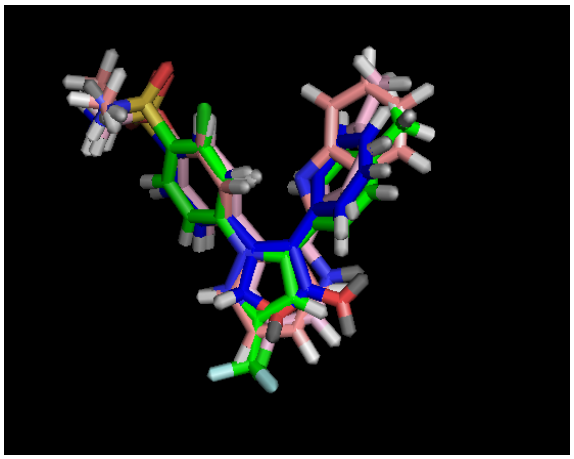
Celecoxib is in green color, Etoricoxib is in pink color, Rofecoxib is in blue color and **compound 3d** is in slate blue.



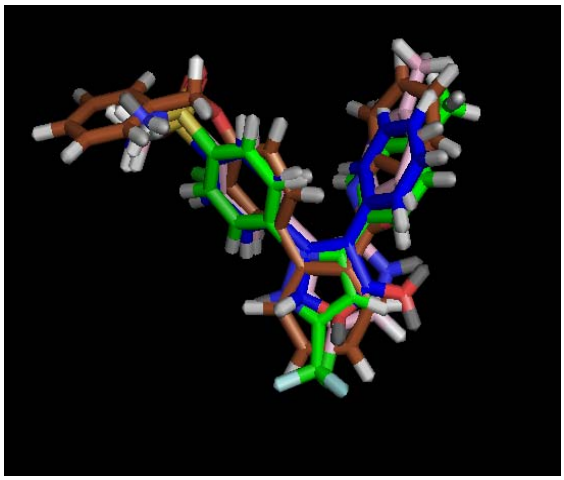
Celecoxib is in green color, Etoricoxib is in pink color, Rofecoxib is in blue color and **compound 3e** is in purple blue.



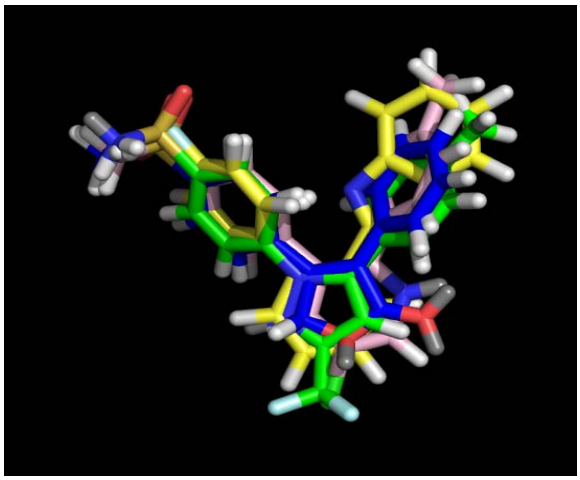
Celecoxib is in green color, Etoricoxib is in pink color, Rofecoxib is in blue color and **compound 3f** is in tv red.



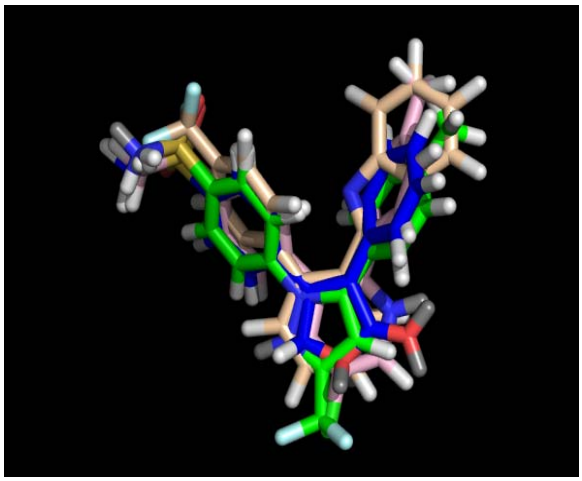
Celecoxib is in green color, Etoricoxib is in pink color, Rofecoxib is in blue color and **compound 3h** is in red selmon.



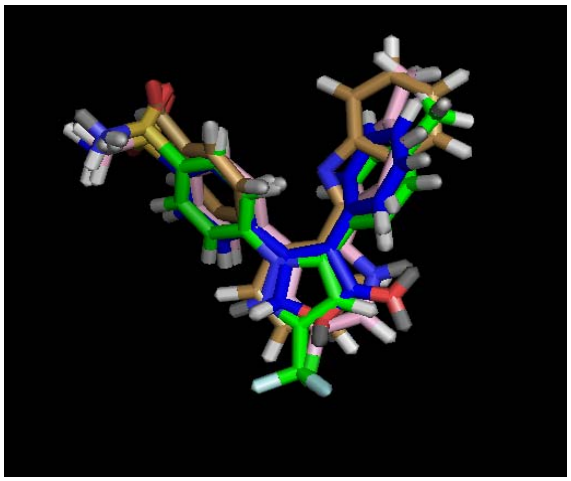
Celecoxib is in green color, Etoricoxib is in pink color, Rofecoxib is in blue color and **compound 3i** is in red brown color.



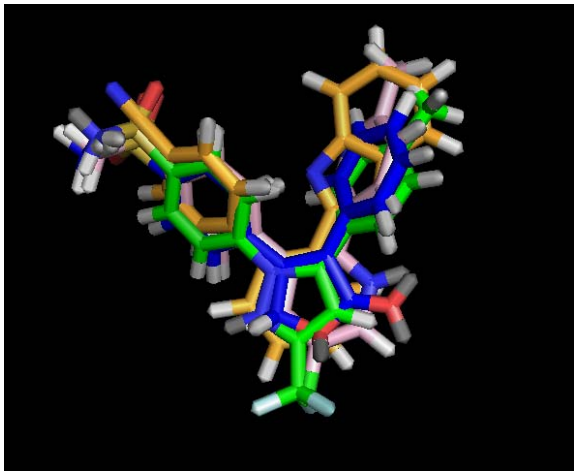
Celecoxib is in green color, Etoricoxib is in pink color, Rofecoxib is in blue color and **compound 3j** is in tv yellow color.



Celecoxib is in green color, Etoricoxib is in pink color, Rofecoxib is in blue color and **compound 3k** is in yellow wheat color.



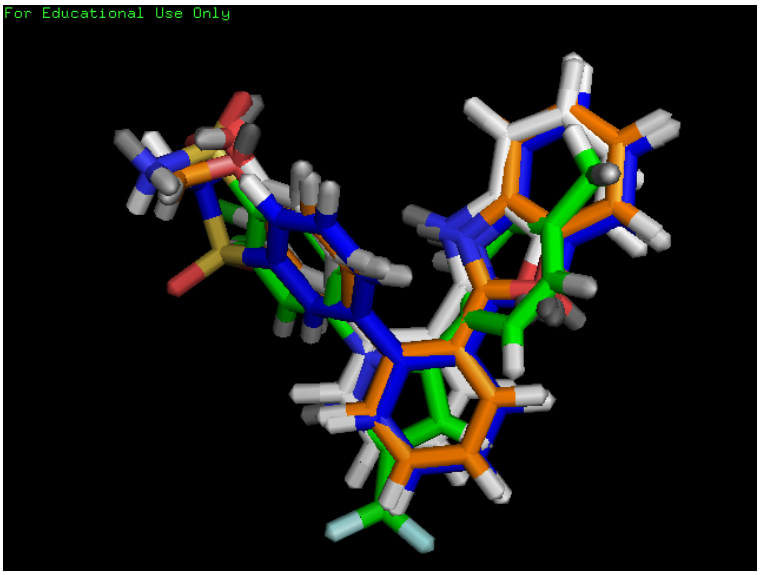
Celecoxib is in green color, Etoricoxib is in pink color, Rofecoxib is in blue color and **compound 3l** is in yellow sand color.



Celecoxib is in green color, Etoricoxib is in pink color, Rofecoxib is in blue color and **compound 3m** is in bright orange color.

Comparison of docking poses of **3g**, **3n** and **3o** with celecoxib was performed (Fig. H) and it was observed that all of these compounds have 'V shape' docking pose similar to that with celecoxib.

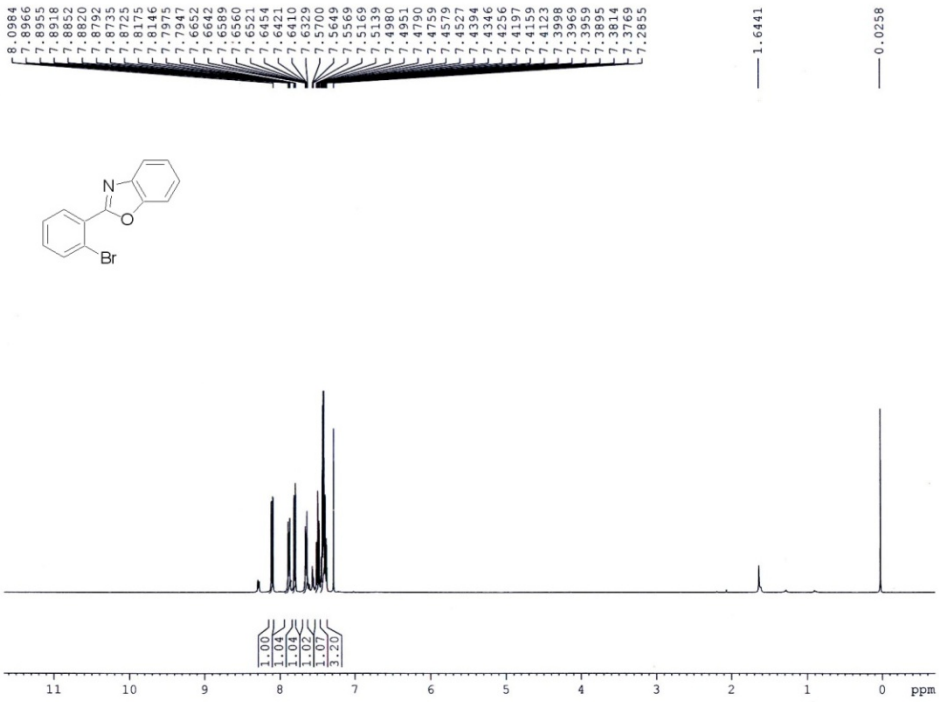
Figure H: Comparison of interaction poses of 3g, 3n and 3o with celecoxib inside the active site of COX-2.



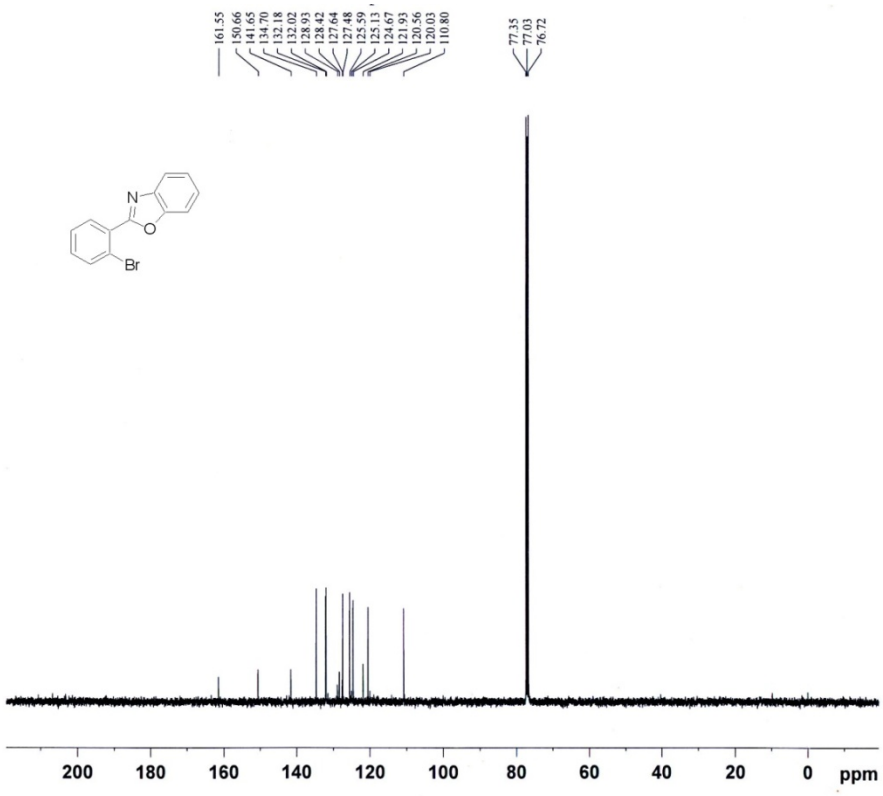
(Celecoxib is in green color, **3g** is in orange color, **3n** is in gray white color and **3o** is in blue color).

Scanned NMR Spectra

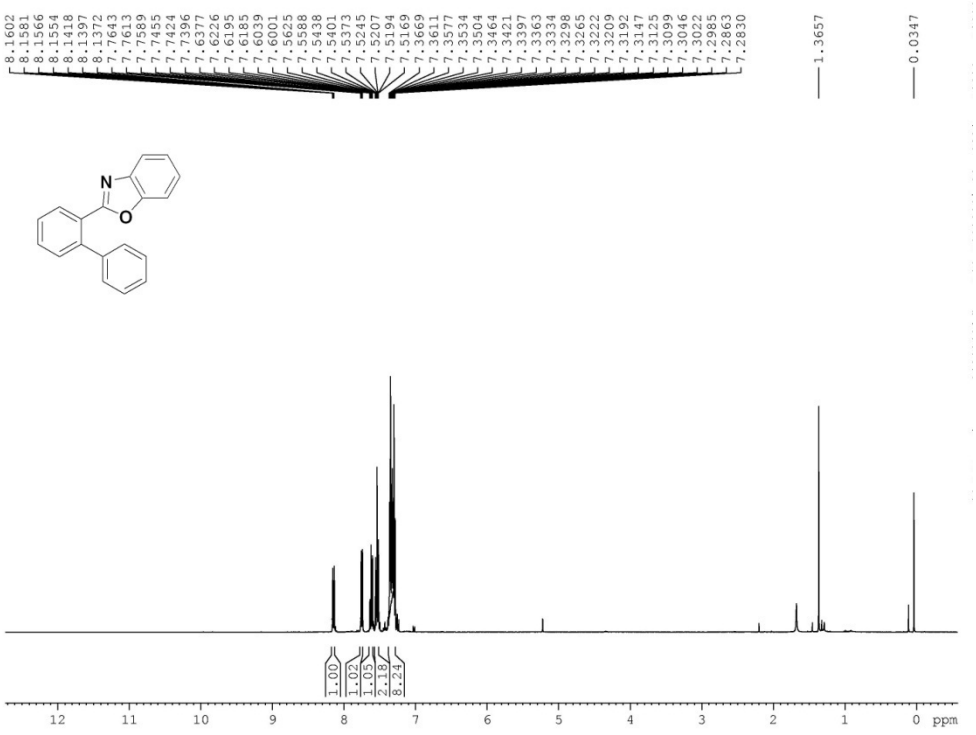
^{1}H NMR of 2-(2-Bromophenyl)-benzoxazole 1:-



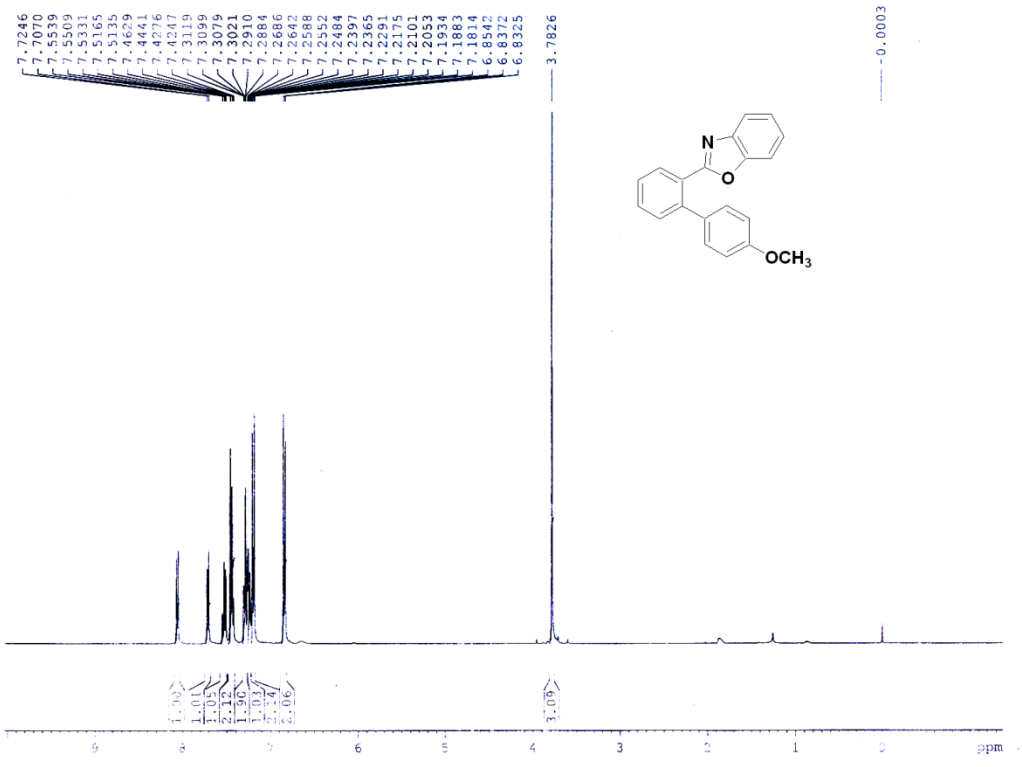
^{13}C NMR of 2-(2-Bromophenyl)-benzoxazole 1:-



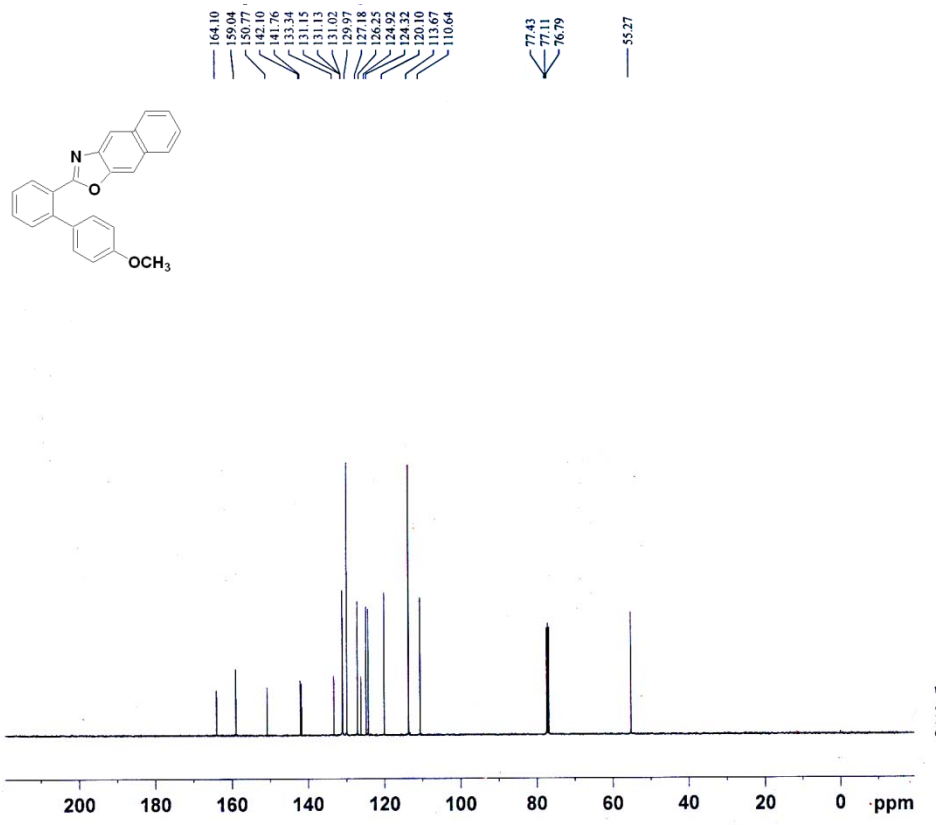
^{1}H NMR of 2-Biphenyl-2-yl-benzoxazole 3a (Scheme 1):-



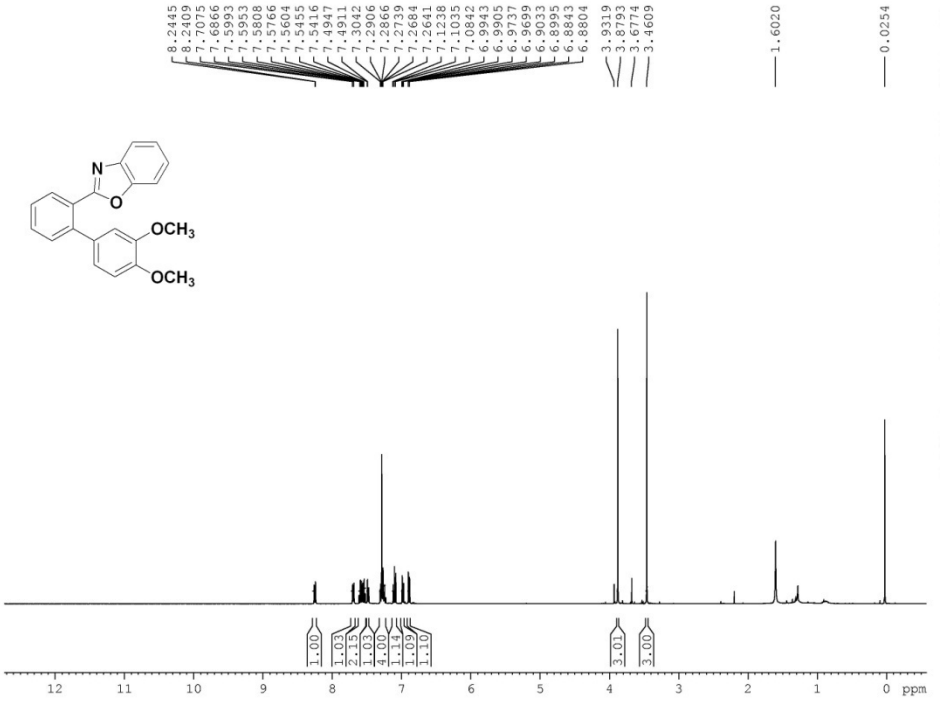
^{1}H NMR of 2-(4'-Methoxy-biphenyl-2-yl)-benzoxazole 3b (Scheme 1):-



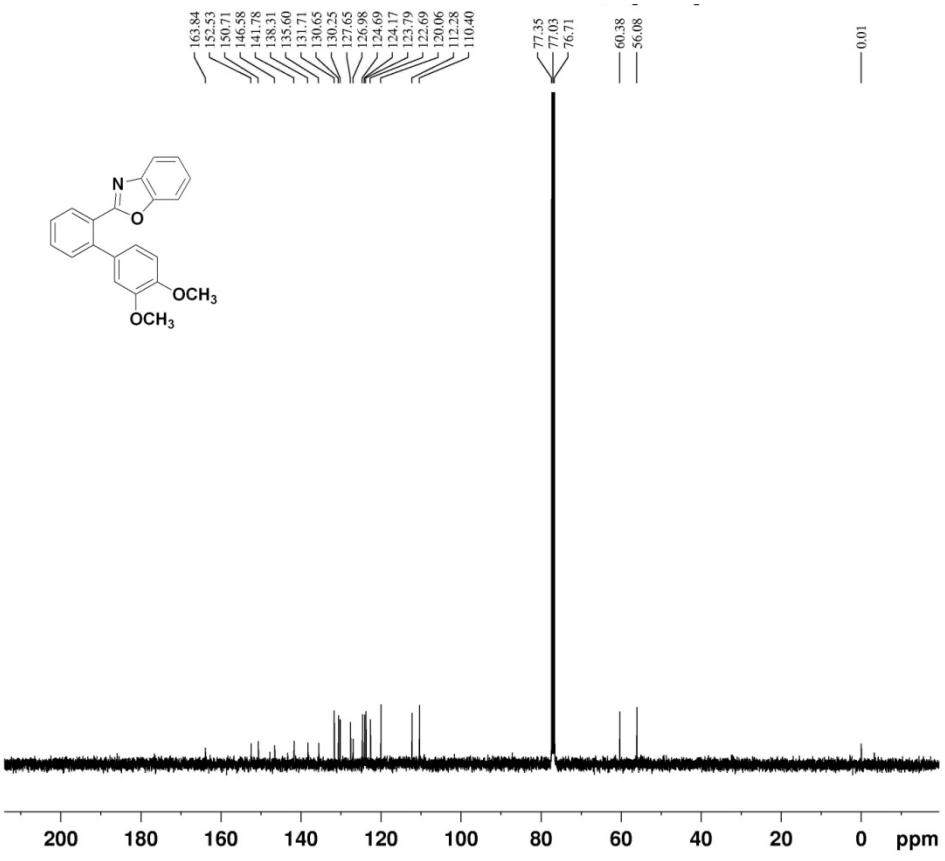
^{13}C NMR of 2-(4'-Methoxy-biphenyl-2-yl)-benzoxazole 3b (Scheme 1):-



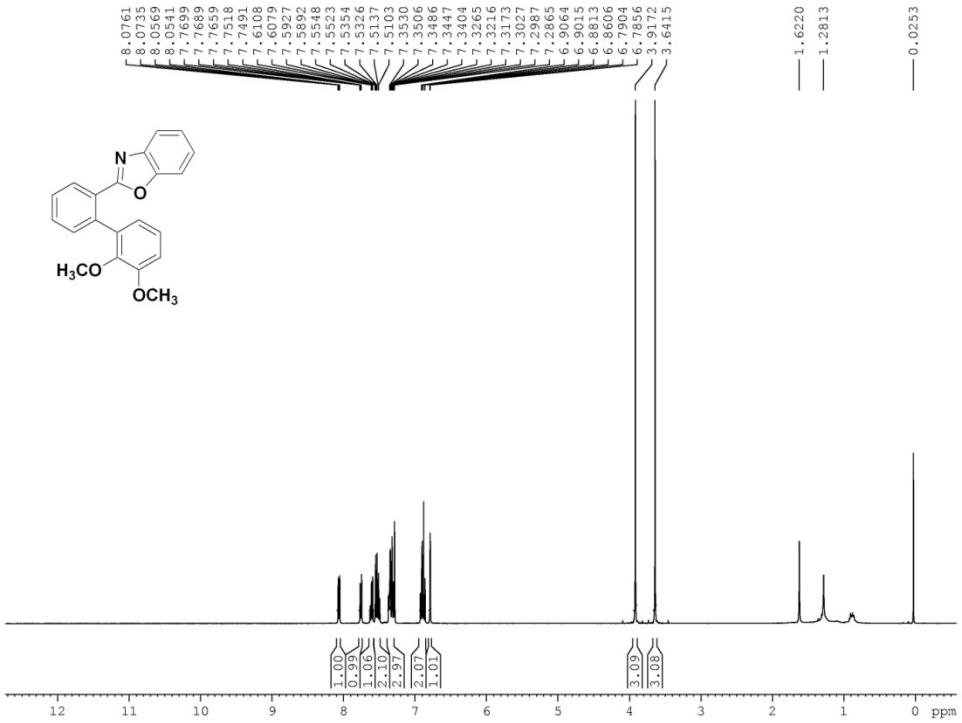
^{1}H NMR of 2-(3',4'-Dimethoxy-biphenyl-2-yl)-benzoxazole 3c (Scheme 1):-



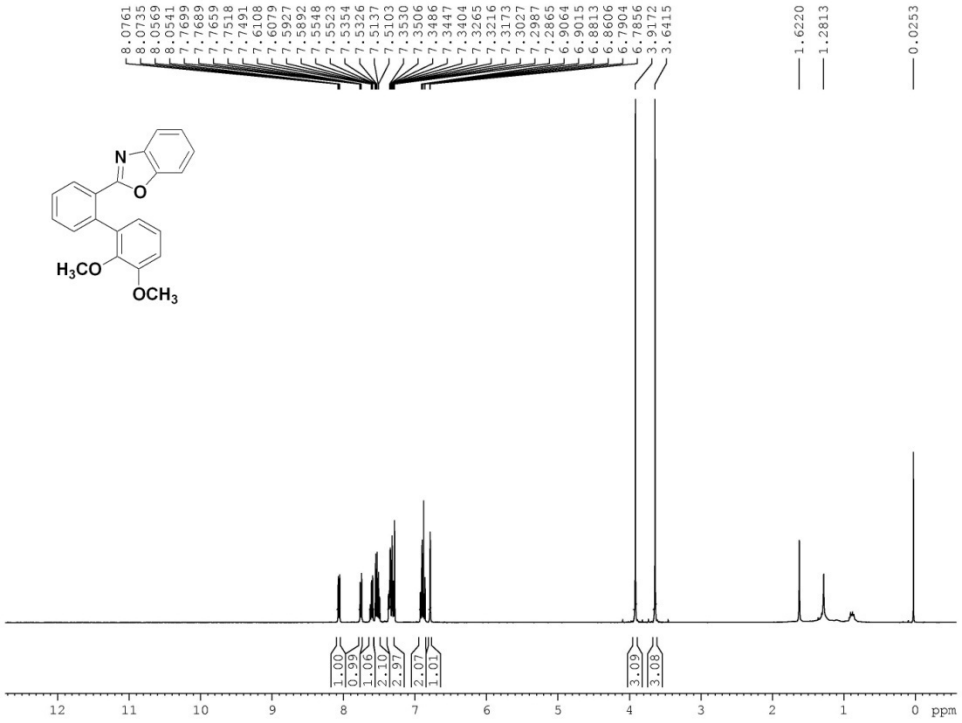
^{13}C NMR of 2-(3',4'-Dimethoxy-biphenyl-2-yl)-benzoxazole 3c (Scheme 1):-



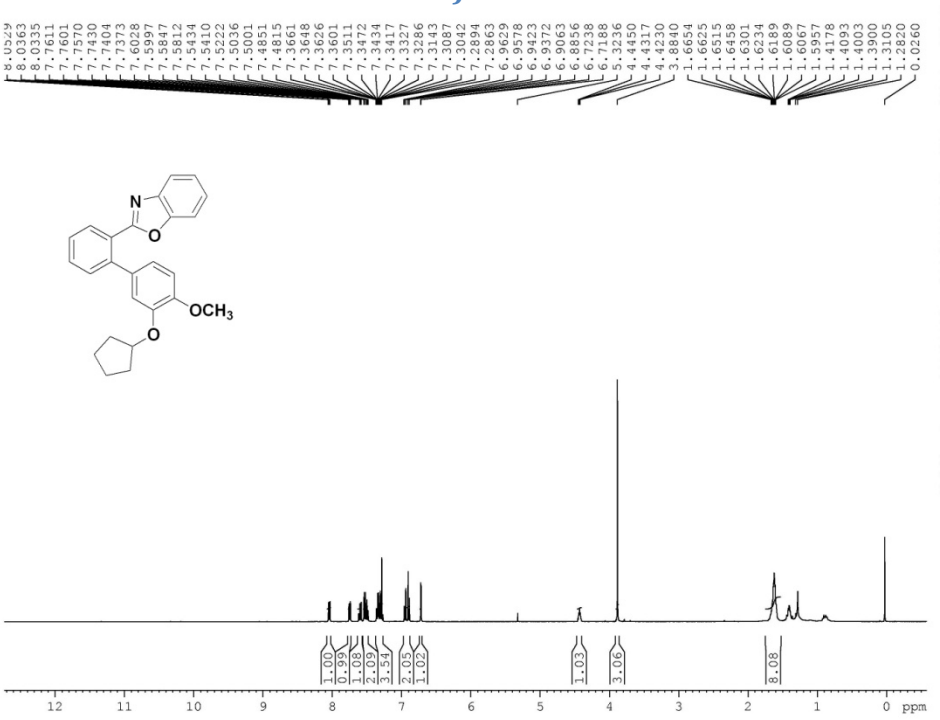
^{1}H NMR of 2-(2',3'-Dimethoxy-biphenyl-2-yl)-benzoxazole 3d (Scheme 1):-



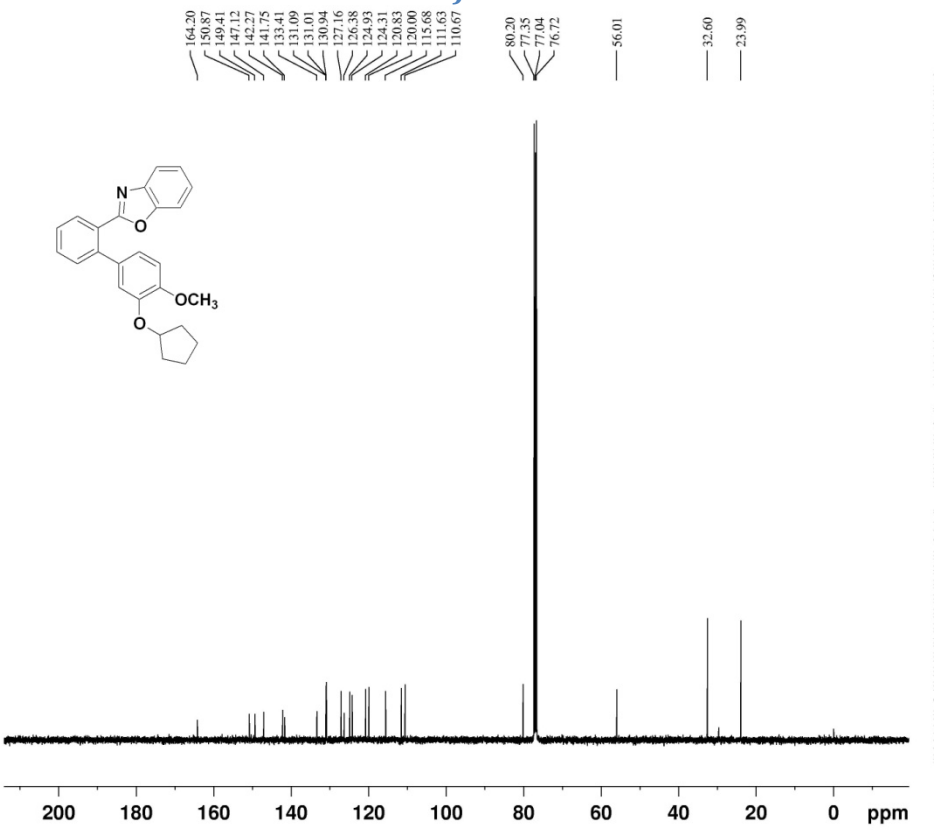
^{13}C NMR of 2-(2',3'-Dimethoxy-biphenyl-2-yl)-benzoxazole 3d (Scheme 1):-



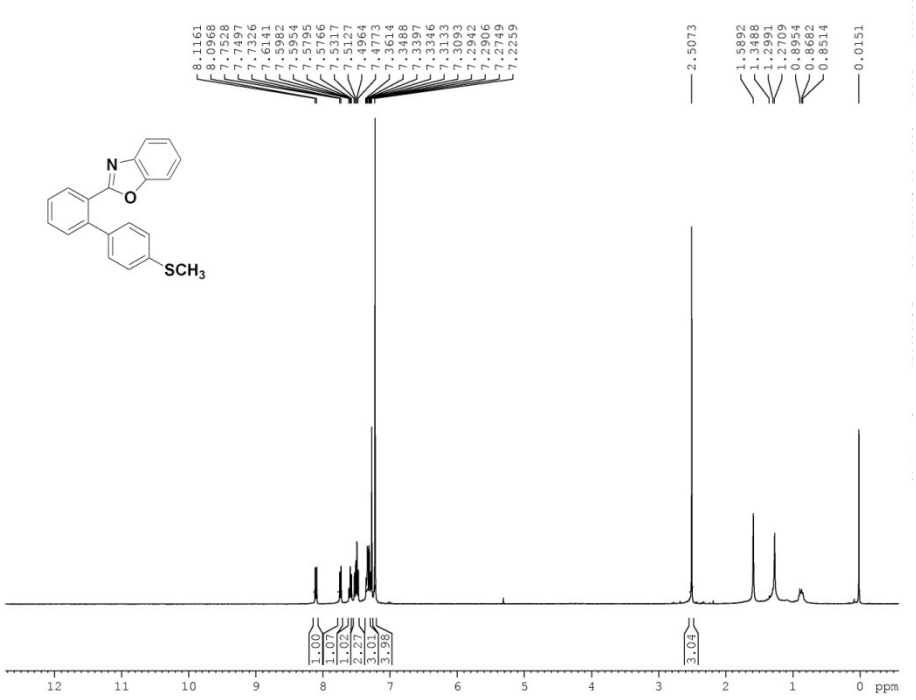
^{1}H NMR of 2-(3'-Cyclopentyloxy-4'-methoxy-biphenyl-2-yl)-benzoxazole 3e (Scheme 1):-



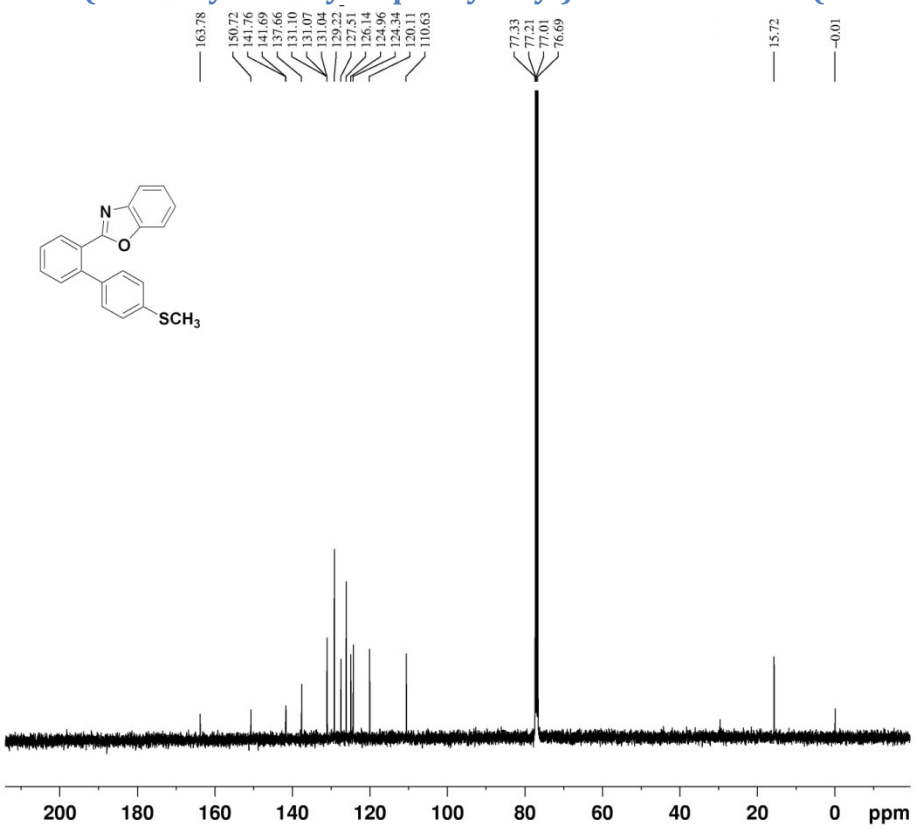
^{13}C NMR of 2-(3'-Cyclopentyloxy-4'-methoxy-biphenyl-2-yl)-benzoxazole 3e (Scheme 1):-



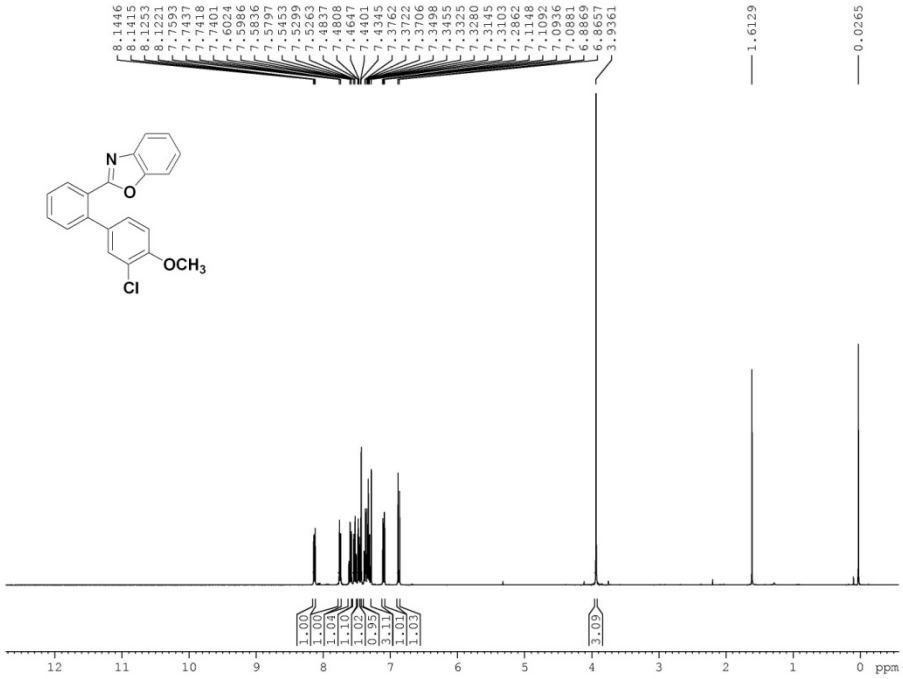
^{1}H NMR of 2-(4'-Methylsulfanyl-biphenyl-2-yl)-benzoxazole 3f (Scheme 1):-



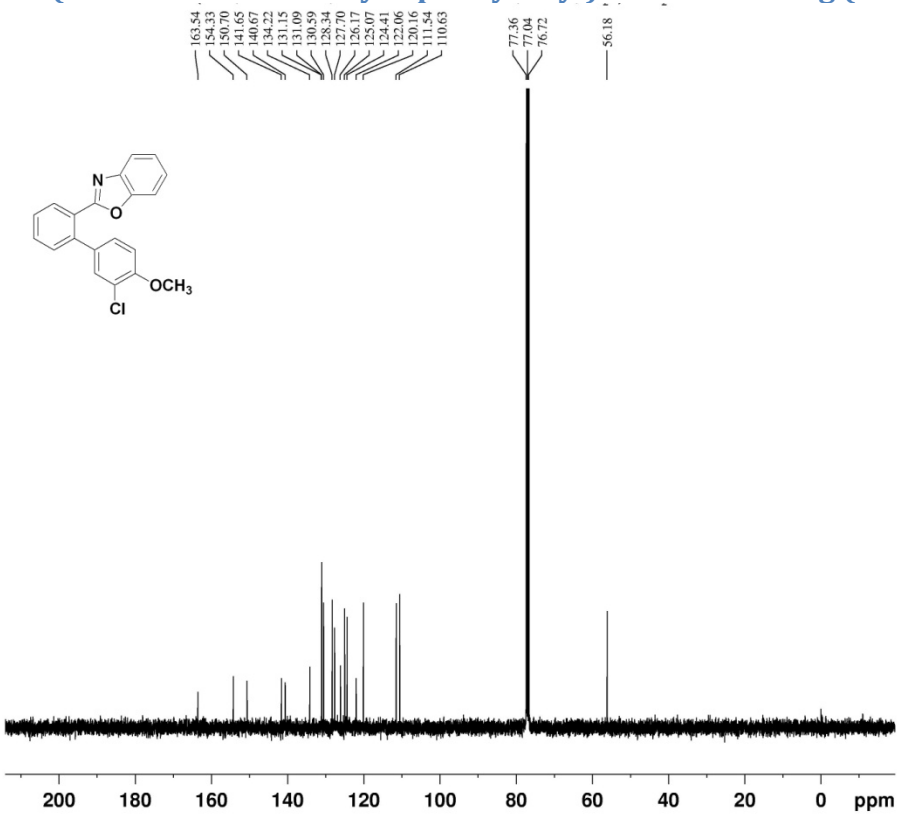
^{13}C NMR of 2-(4'-Methylsulfanyl-biphenyl-2-yl)-benzoxazole 3f (Scheme 1):-



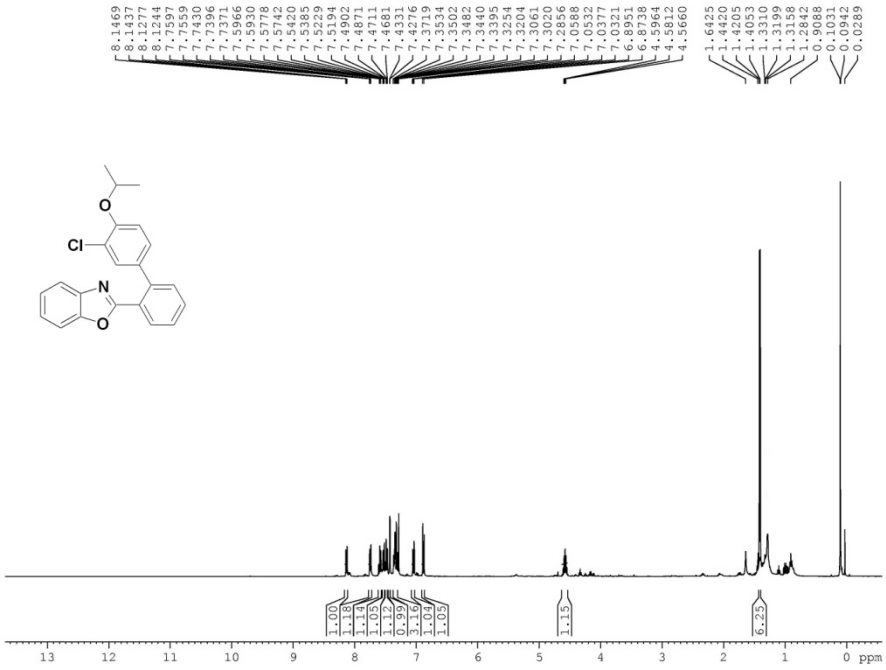
^{1}H NMR of 2-(3'-Chloro-4'-methoxy-biphenyl-2-yl)-benzoxazole 3g (Scheme 1):-



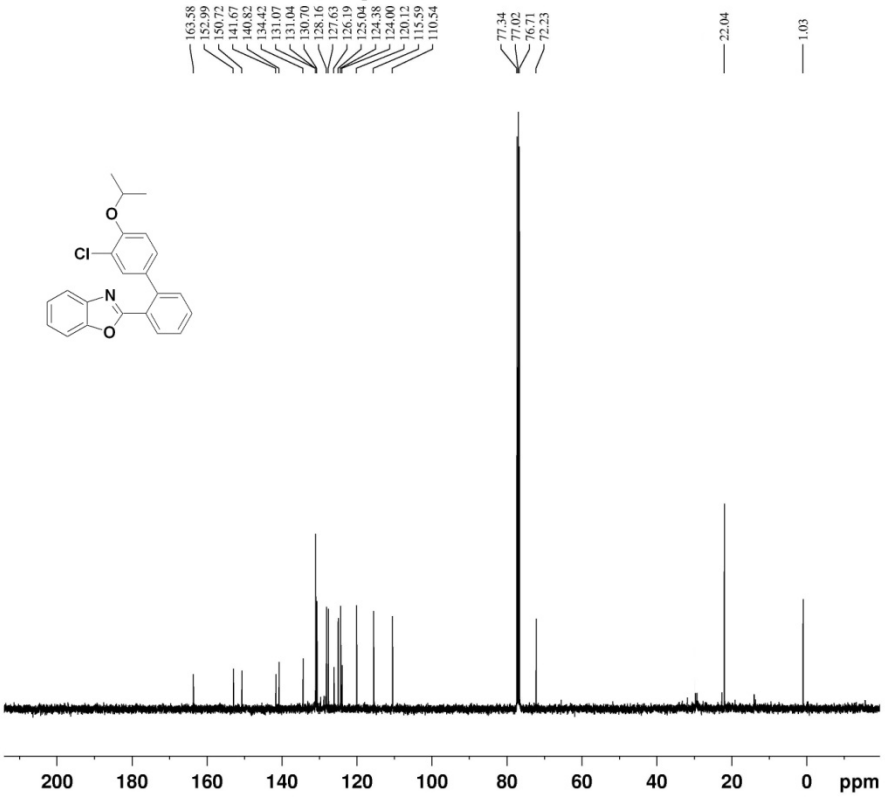
^{13}C NMR of 2-(3'-Chloro-4'-methoxy-biphenyl-2-yl)-benzoxazole 3g (Scheme 1):-



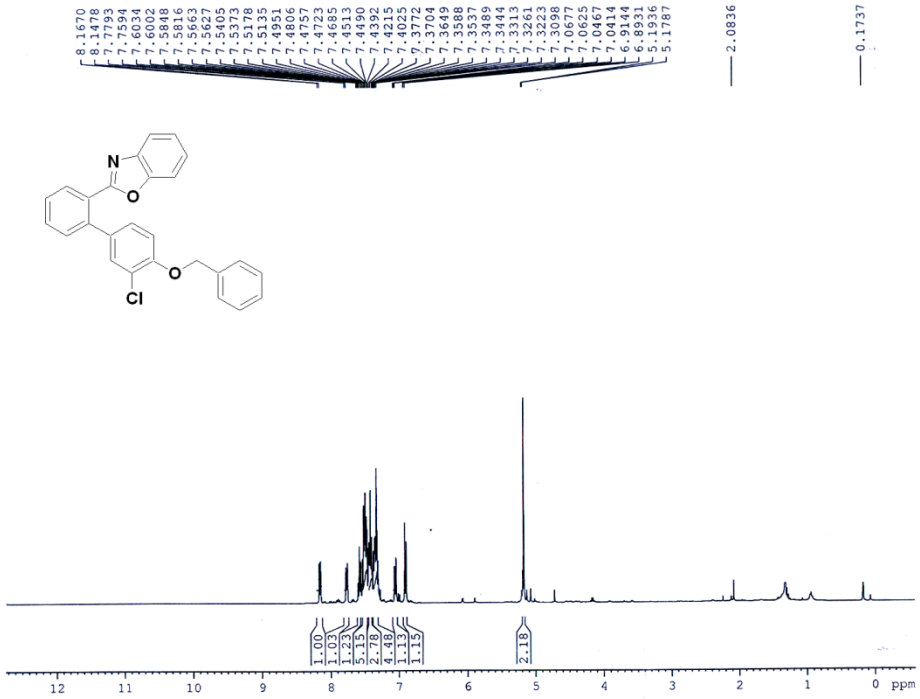
^{1}H NMR of 2-(3'-Chloro-4'-isopropoxy-biphenyl-2-yl)-benzoxazole 3h (Scheme 1):-



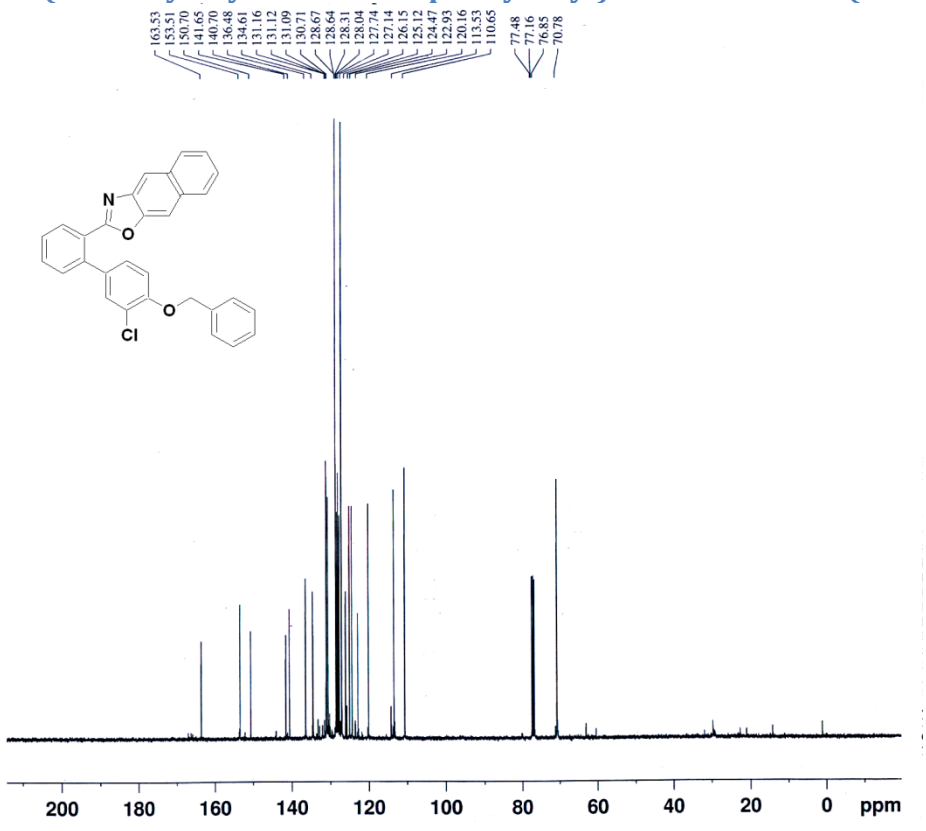
^{13}C NMR of 2-(3'-Chloro-4'-isopropoxy-biphenyl-2-yl)-benzoxazole 3h (Scheme 1):-



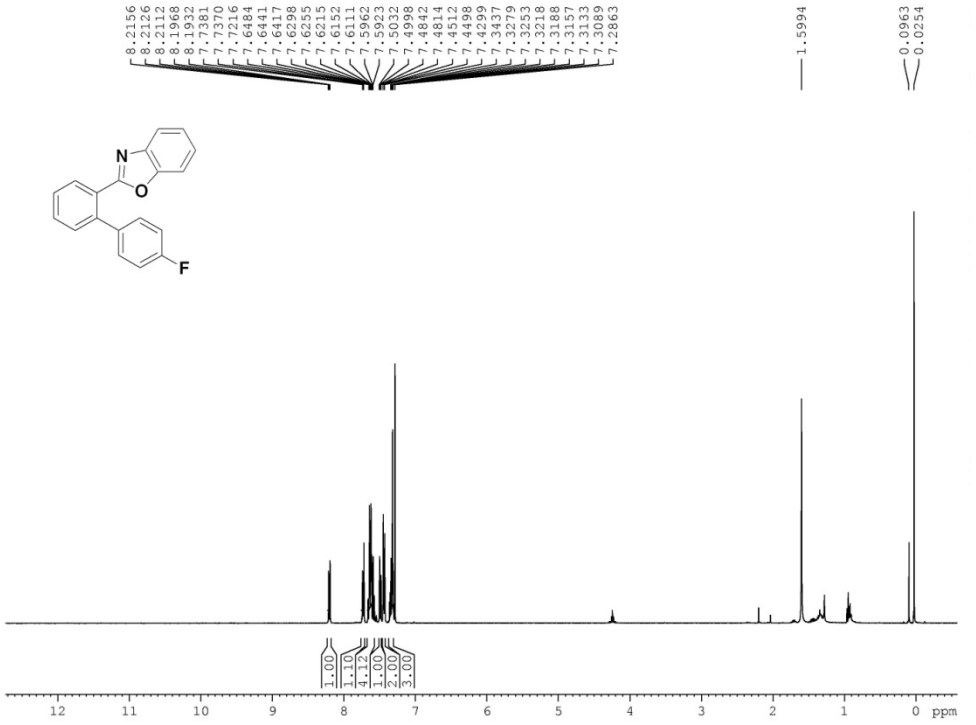
^{1}H NMR of 2-(4'-Benzyloxy-3'-chloro-biphenyl-2-yl)-benzoxazole 3i (Scheme 1):-



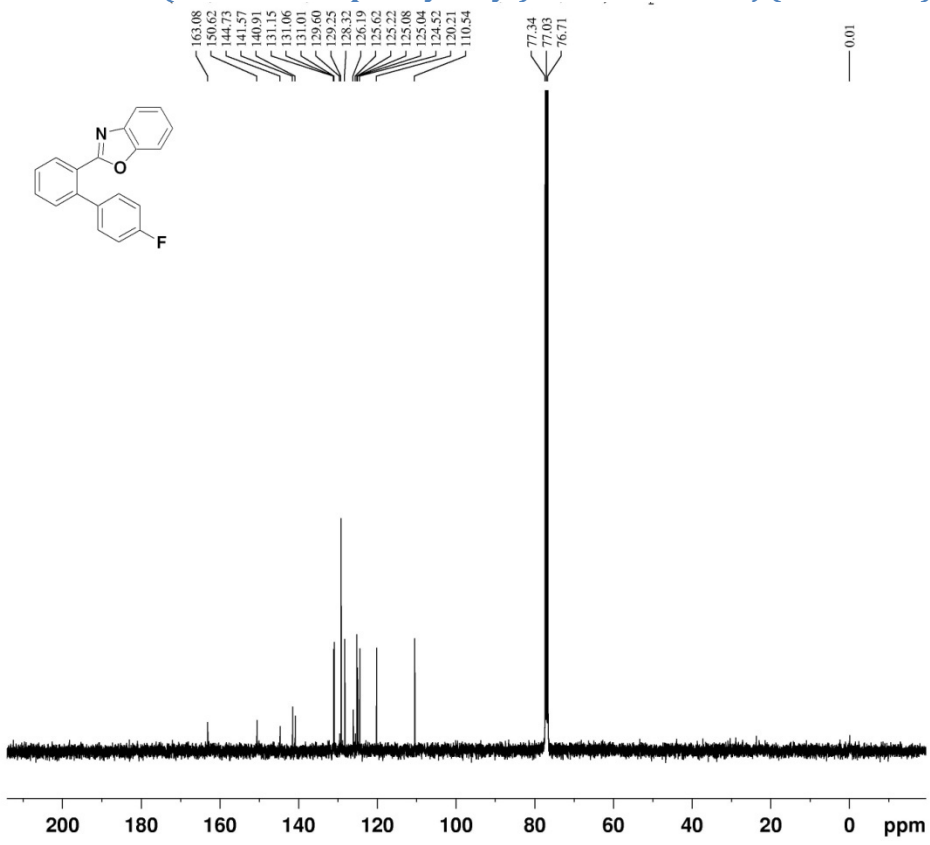
^{13}C NMR of 2-(4'-Benzyloxy-3'-chloro-biphenyl-2-yl)-benzoxazole 3i (Scheme 1):-



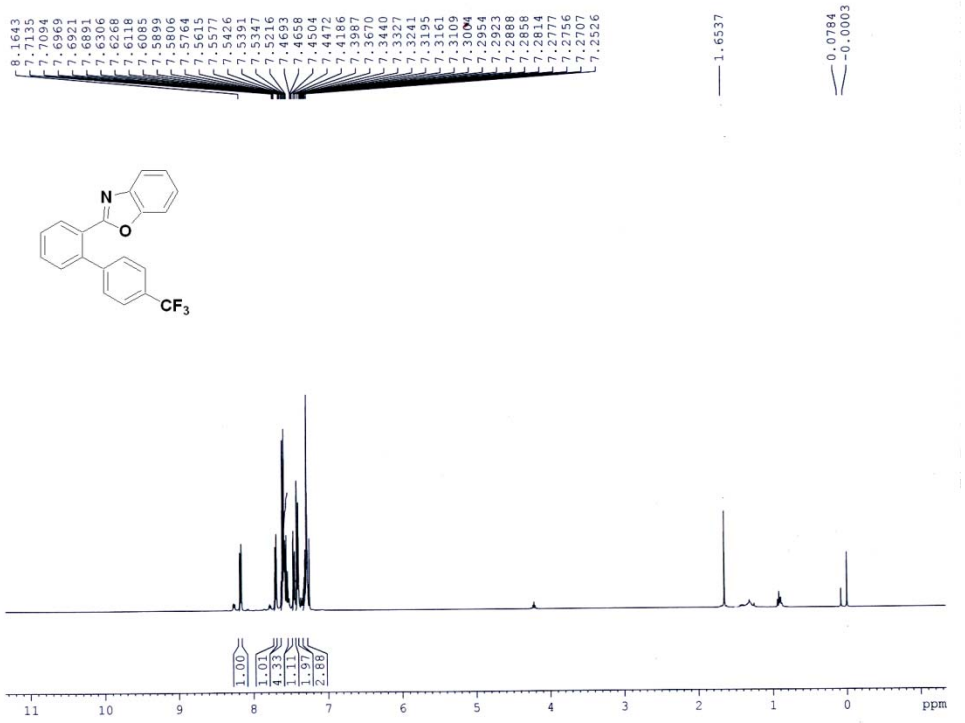
^{1}H NMR of 2-(4'-Fluoro-biphenyl-2-yl)-benzoxazole 3j (Scheme 1):-



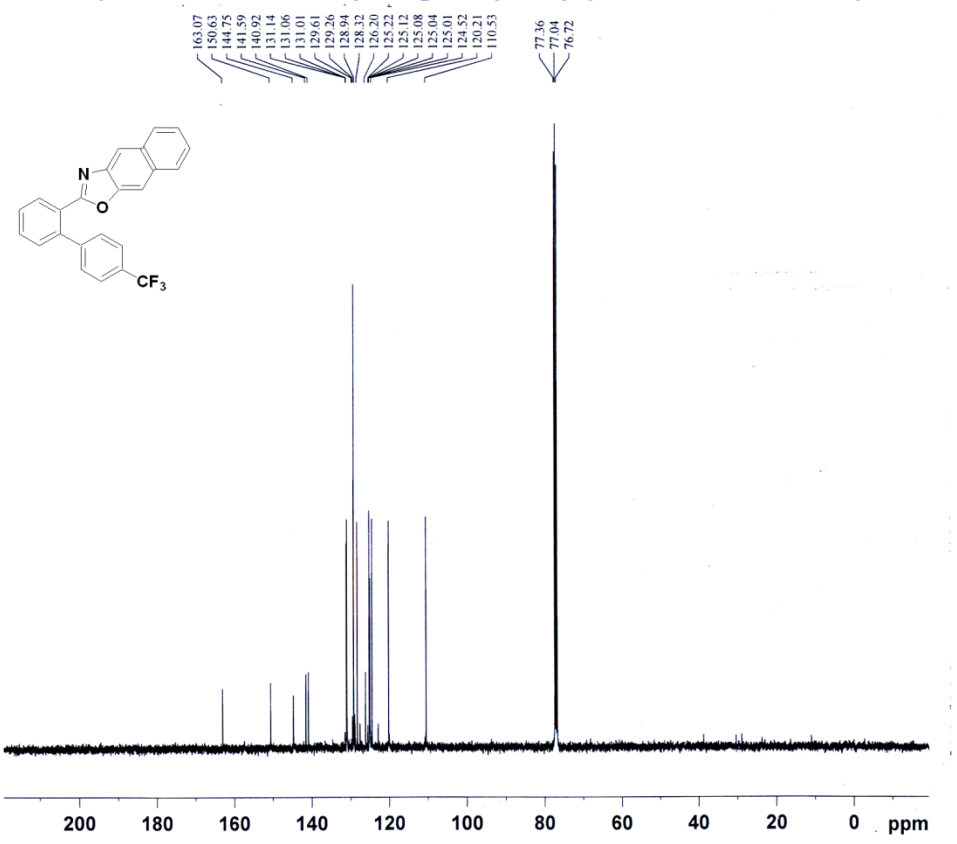
^{13}C NMR of 2-(4'-Fluoro-biphenyl-2-yl)-benzoxazole 3j (Scheme 1):-



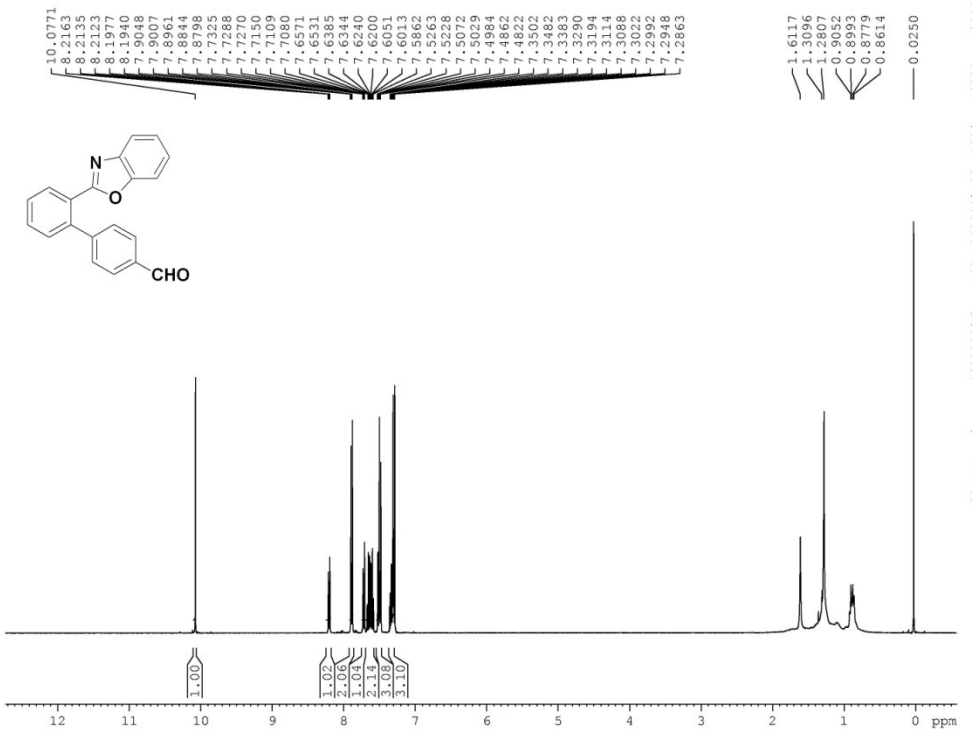
^{1}H NMR of 2-(4'-Trifluoromethyl-biphenyl-2-yl)-benzoxazole 3k (Scheme 1):-



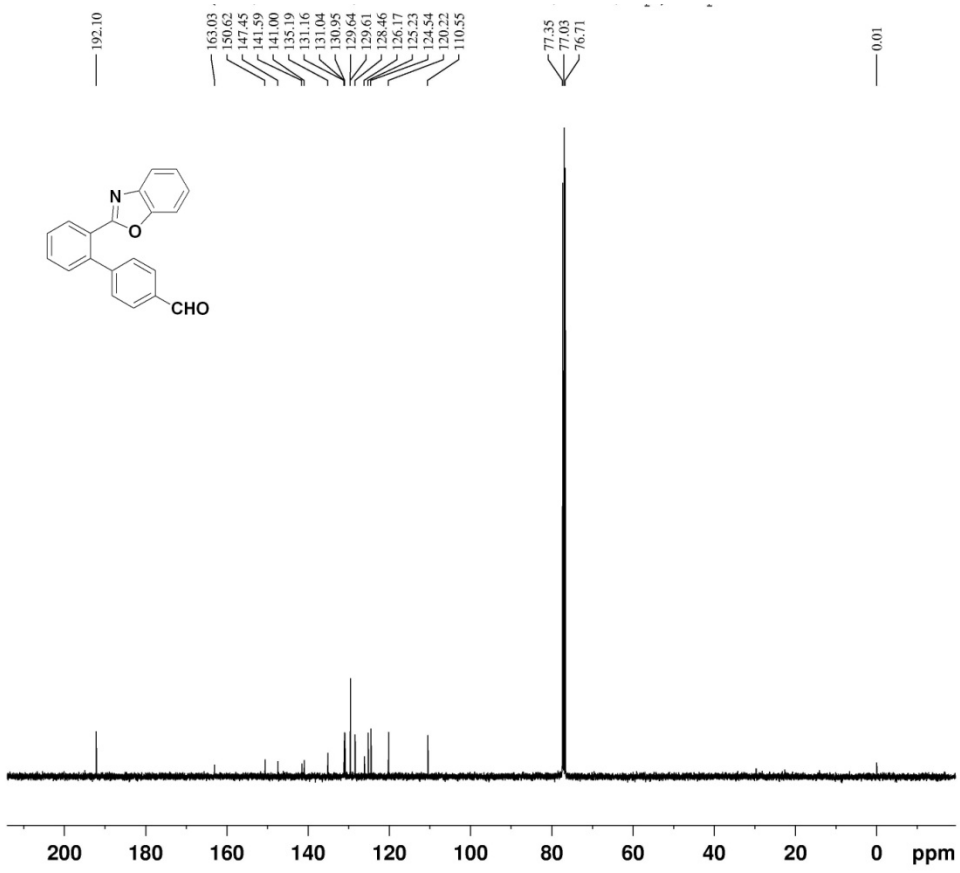
^{13}C NMR of 2-(4'-Trifluoromethyl-biphenyl-2-yl)-benzoxazole 3k (Scheme 1):-



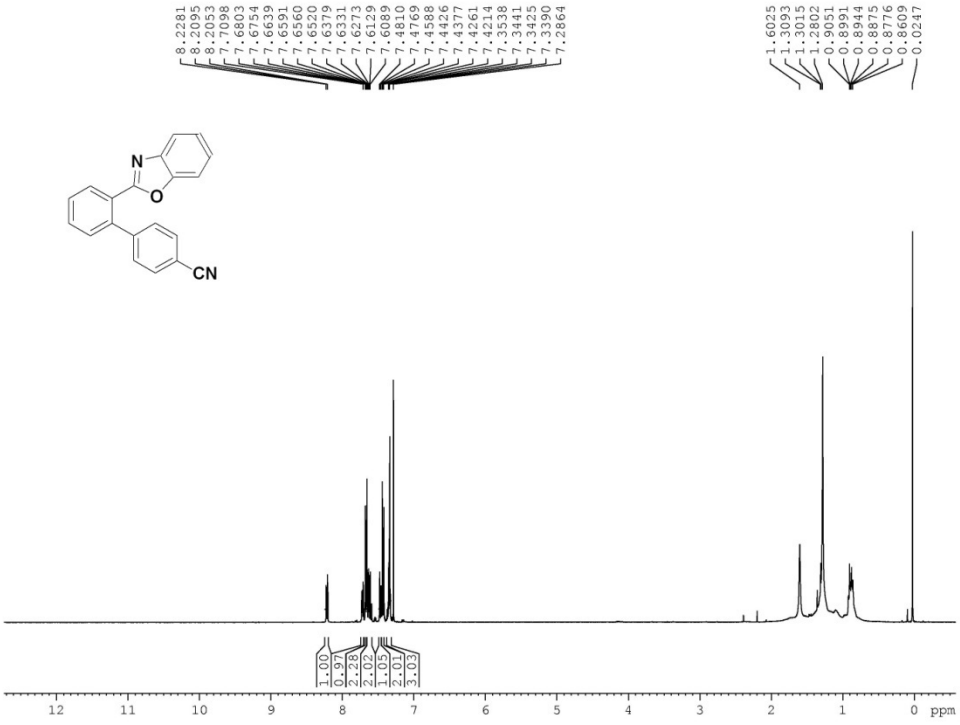
^{1}H NMR of 2'-Benzoxazol-2-yl-biphenyl-4-carbaldehyde 3l (Scheme 1):-



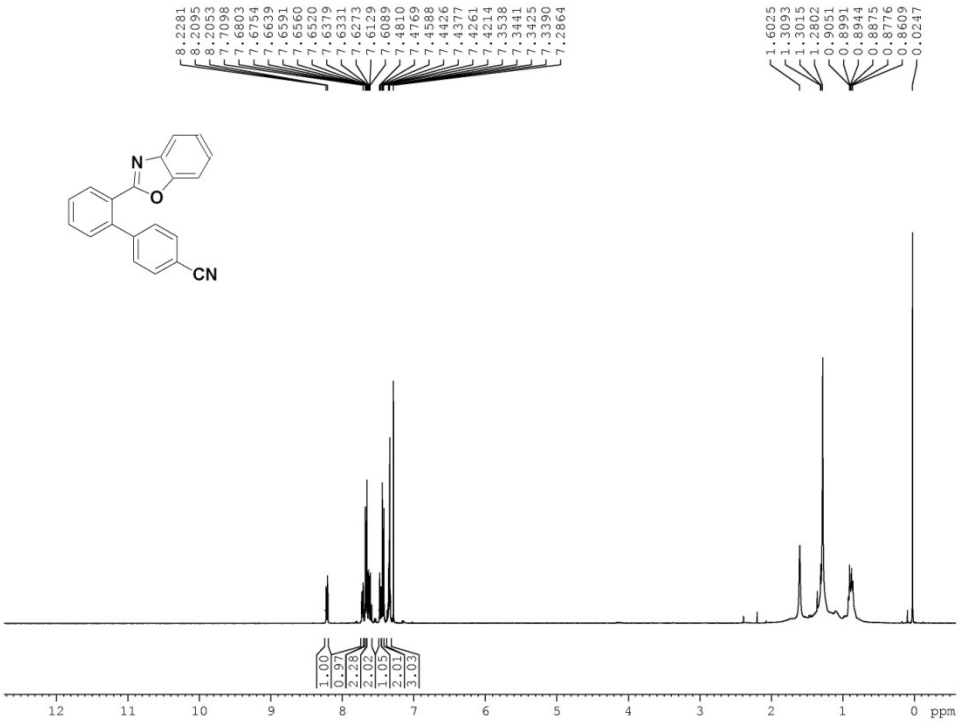
^{13}C NMR of 2'-Benzoxazol-2-yl-biphenyl-4-carbaldehyde 3l (Scheme 1):-



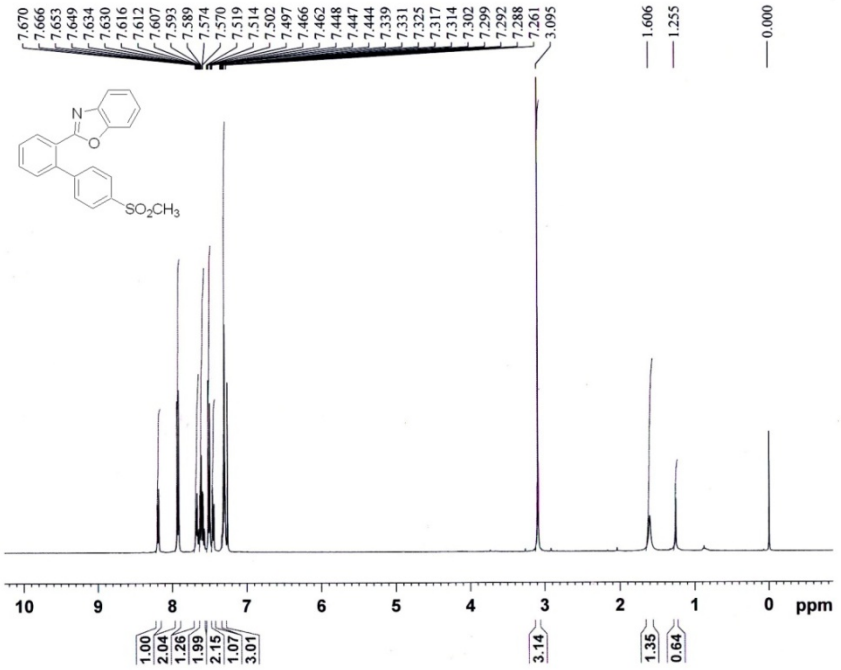
^{1}H NMR of 2'-Benzoxazol-2-yl-biphenyl-4-carbonitrile 3m (Scheme 1):-



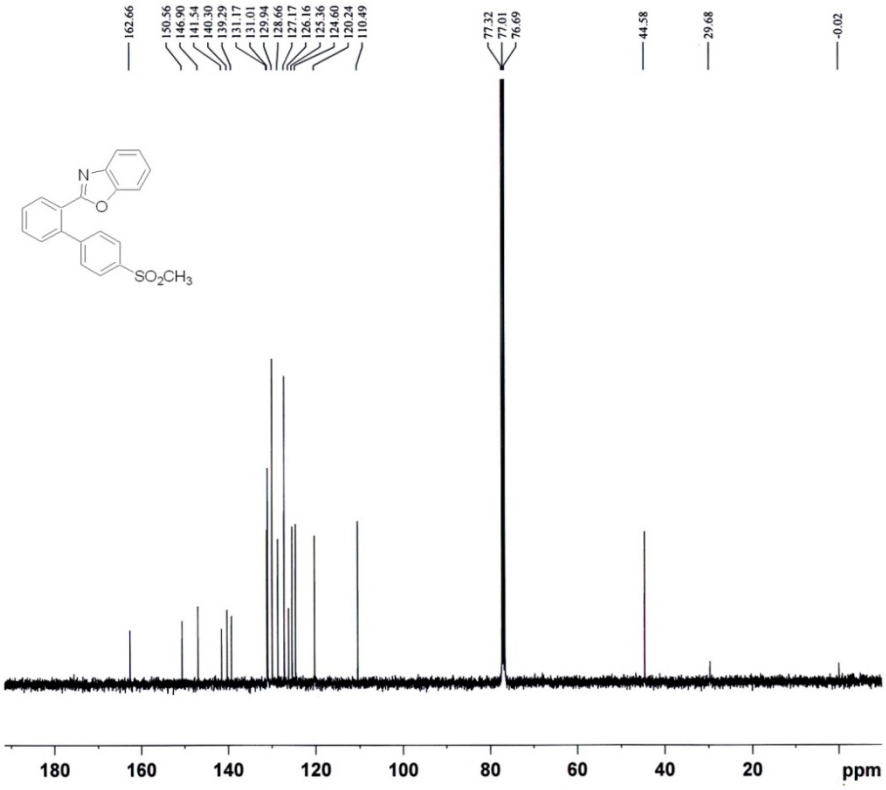
^{13}C NMR of 2'-Benzoxazol-2-yl-biphenyl-4-carbonitrile 3m (Scheme 1):-



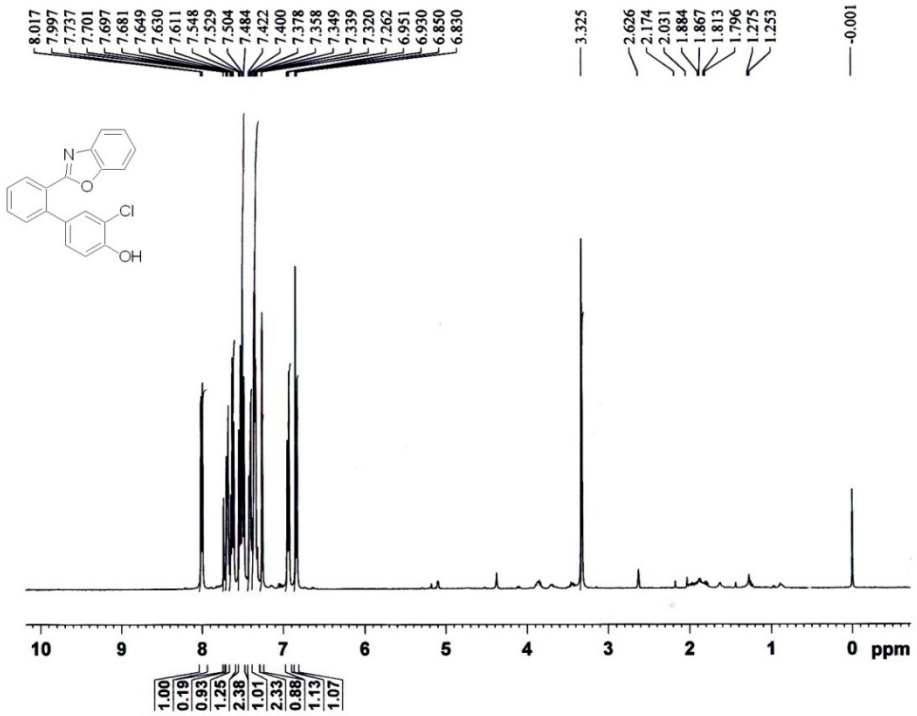
^{1}H NMR of 2-(4'-Methanesulfonyl-biphenyl-2-yl)-benzoxazole 3o (Scheme 2):-



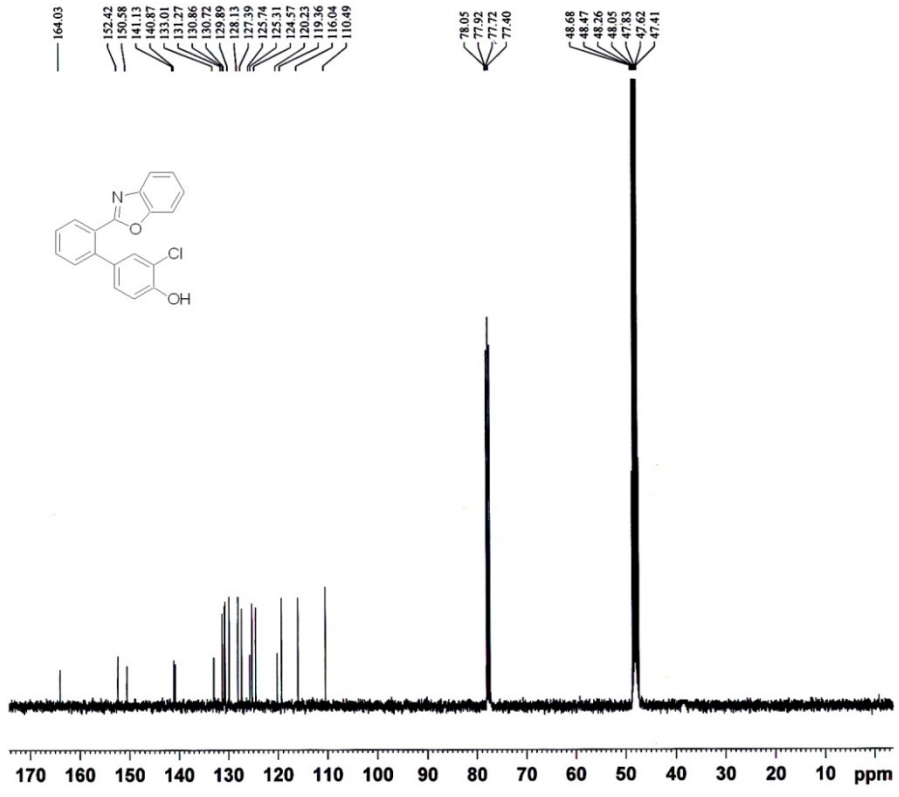
^{13}C NMR of 2-(4'-Methanesulfonyl-biphenyl-2-yl)-benzoxazole 3o (Scheme 2):-



^{1}H NMR of 2'-Benzoxazol-2-yl-3-chloro-biphenyl-4-ol 3n (Scheme 2):-



^{13}C NMR of 2'-Benzoxazol-2-yl-3-chloro-biphenyl-4-ol 3n (Scheme 2):-



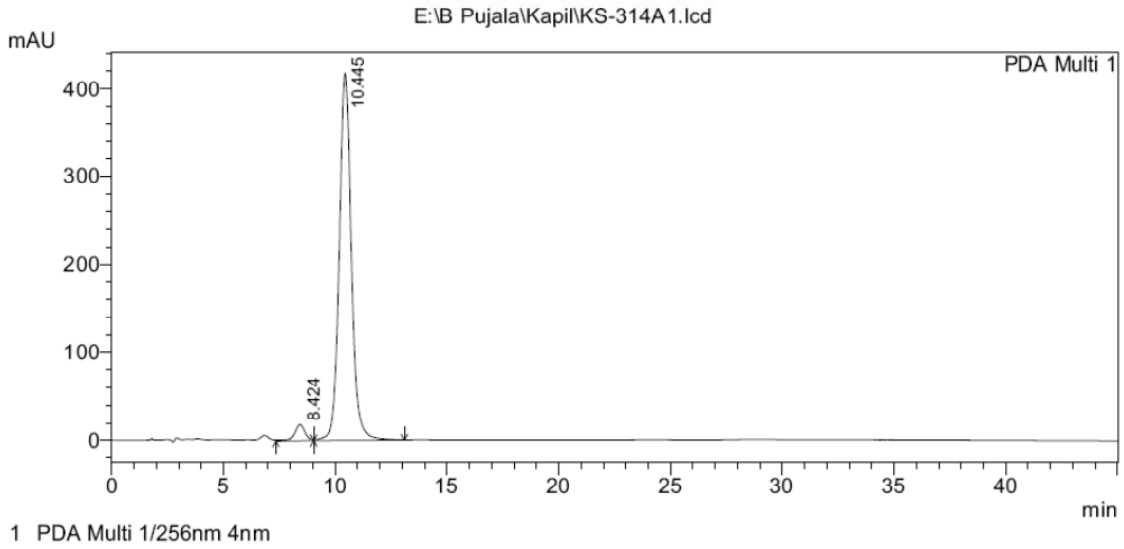
Scanned HPLC Spectra to Determine the Purity of Compounds

HPLC of 2-Biphenyl-2-yl-benzoxazole 3a (Scheme 1):-

E:\B Pujala\Kapil\KS-314A1.lcd

Acquired by	: Admin
Sample Name	: KS-314A
Sample ID	: KS-314A
Vail #	: 32
Injection Volume	: 10 uL
Data File Name	: KS-314A1.lcd
Method File Name	: COAN1.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 4/8/2012 9:27:20 PM
Data Processed	: 4/8/2012 10:12:22 PM

<Chromatogram>



1 PDA Multi 1/256nm 4nm

PeakTable

PDA Ch1 256nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.424	613853	18503	3.759	4.241
2	10.445	15714980	417780	96.241	95.759
Total		16328833	436283	100.000	100.000

HPLC of 2-(4'-Methoxy-biphenyl-2-yl)-benzoxazole 3b (Scheme 1):-

E:\B Pujala\Kapil\KS-309.lcd

Acquired by	: Admin
Sample Name	: KS-309
Sample ID	: KS-309
Vail #	: 31
Injection Volume	: 10 uL
Data File Name	: KS-309.lcd
Method File Name	: COAN1.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 4/8/2012 6:37:13 PM
Data Processed	: 4/8/2012 7:22:16 PM

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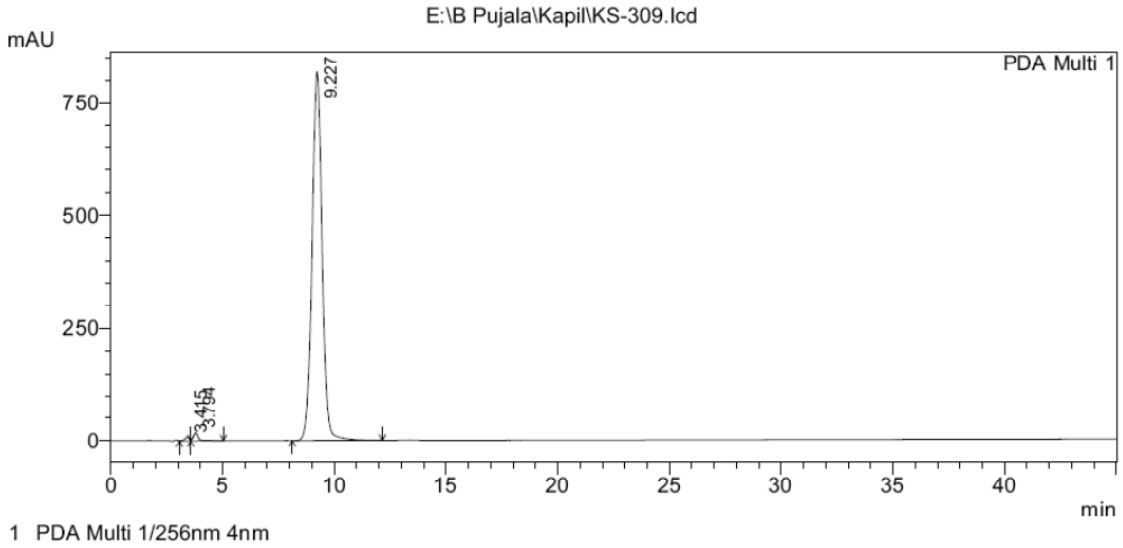

1 PDA Multi 1/256nm 4nm

PeakTable

PDA Ch1 256nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	3.415	132095	8838	0.509	1.048
2	3.794	274031	17473	1.056	2.072
3	9.227	25550927	817160	98.435	96.881
Total		25957053	843471	100.000	100.000

HPLC of 2-(3',4'-Dimethoxy-biphenyl-2-yl)-benzoxazole 3c (Scheme 1):-

E:\B Pujala\Kapil\KS-310.lcd

Acquired by	: Admin
Sample Name	: KS-310
Sample ID	: KS-310
Vail #	: 36
Injection Volume	: 10 uL
Data File Name	: KS-310.lcd
Method File Name	: COAN1.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 4/9/2012 12:23:36 PM
Data Processed	: 4/9/2012 1:08:39 PM

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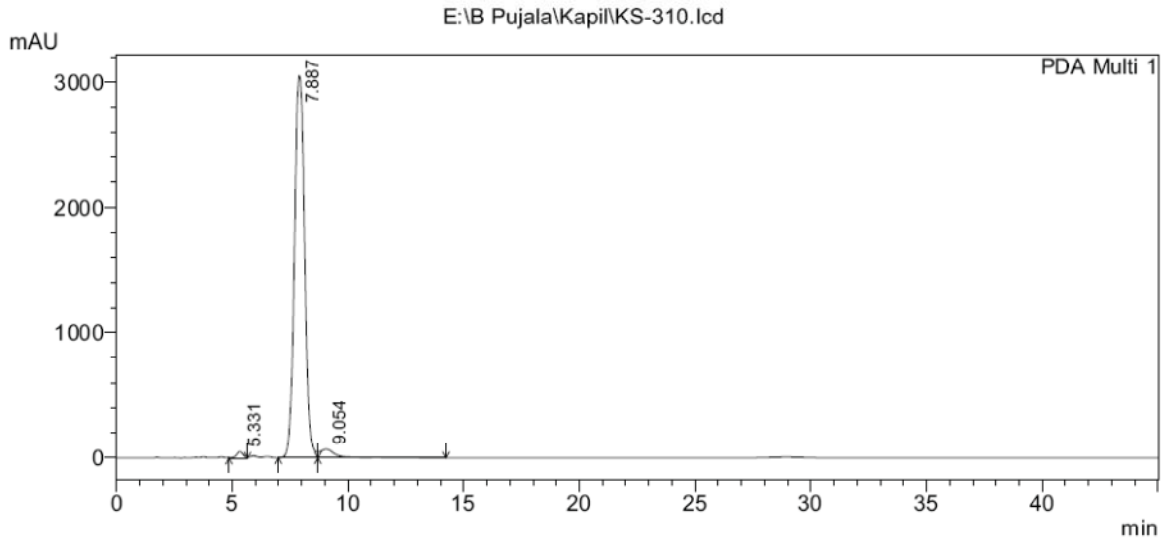

1 PDA Multi 1/256nm 4nm

PeakTable

PDA Ch1 256nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.331	1018910	51212	1.031	1.612
2	7.887	94291851	3054643	95.399	96.164
3	9.054	3528292	70645	3.570	2.224
Total		98839053	3176499	100.000	100.000

HPLC of 2-(2',3'-Dimethoxy-biphenyl-2-yl)-benzoxazole 3d (Scheme 1):-

E:\B Pujala\Kapil\KS-308.lcd

Acquired by	: Admin
Sample Name	: KS-308
Sample ID	: KS-308
Vail #	: 35
Injection Volume	: 10 uL
Data File Name	: KS-308.lcd
Method File Name	: COAN1.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 4/9/2012 11:31:57 AM
Data Processed	: 4/9/2012 12:17:01 PM

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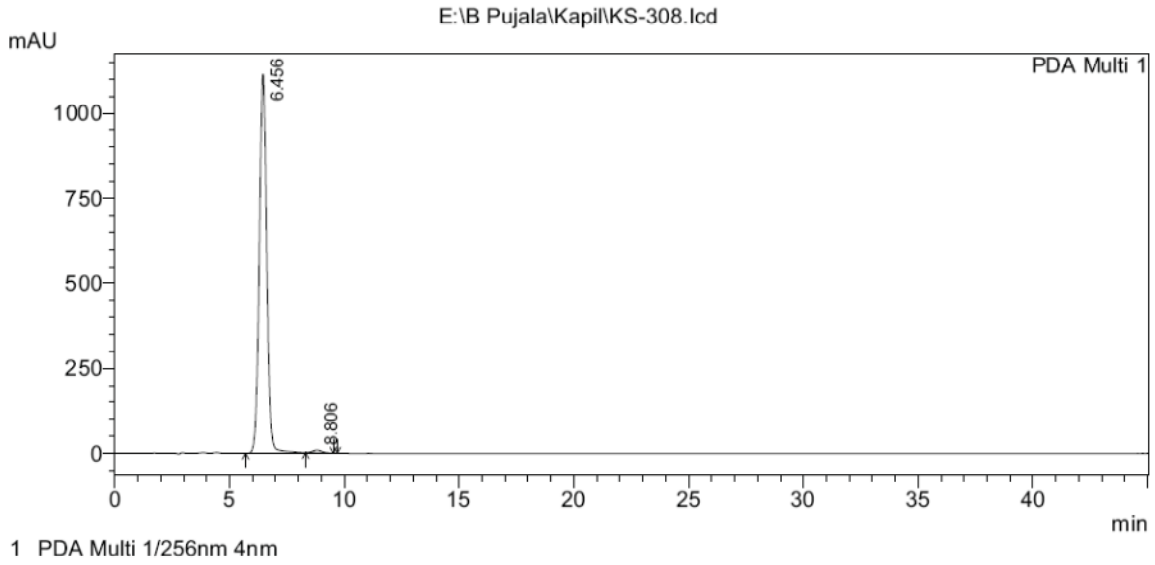

1 PDA Multi 1/256nm 4nm

PeakTable

PDA Ch1 256nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.456	25444160	1114988	99.130	99.283
2	8.806	223290	8055	0.870	0.717
Total		25667450	1123043	100.000	100.000

HPLC of 2-(3'-Cyclopentyloxy-4'-methoxy-biphenyl-2-yl)-benzoxazole 3e (Scheme 1):-

E:\B Pujala\Kapil\KS-303.lcd

Acquired by	: Admin
Sample Name	: KS-303
Sample ID	: KS-303
Vail #	: 39
Injection Volume	: 10 uL
Data File Name	: KS-303.lcd
Method File Name	: COAN1.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 4/9/2012 3:31:56 PM
Data Processed	: 4/9/2012 4:17:01 PM

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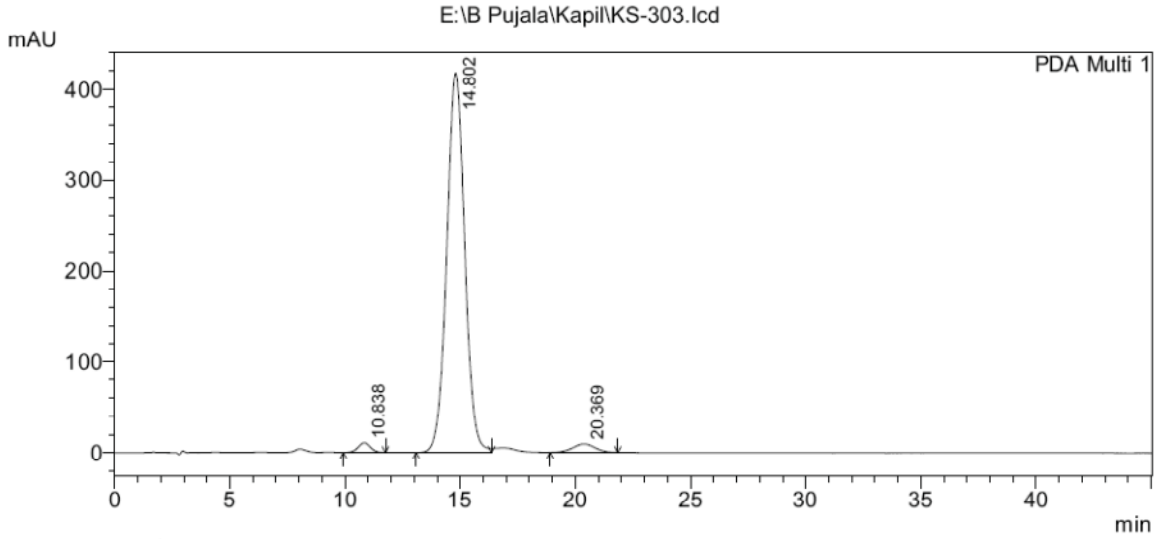


1 PDA Multi 1/256nm 4nm

PeakTable

PDA Ch1 256nm 4nm

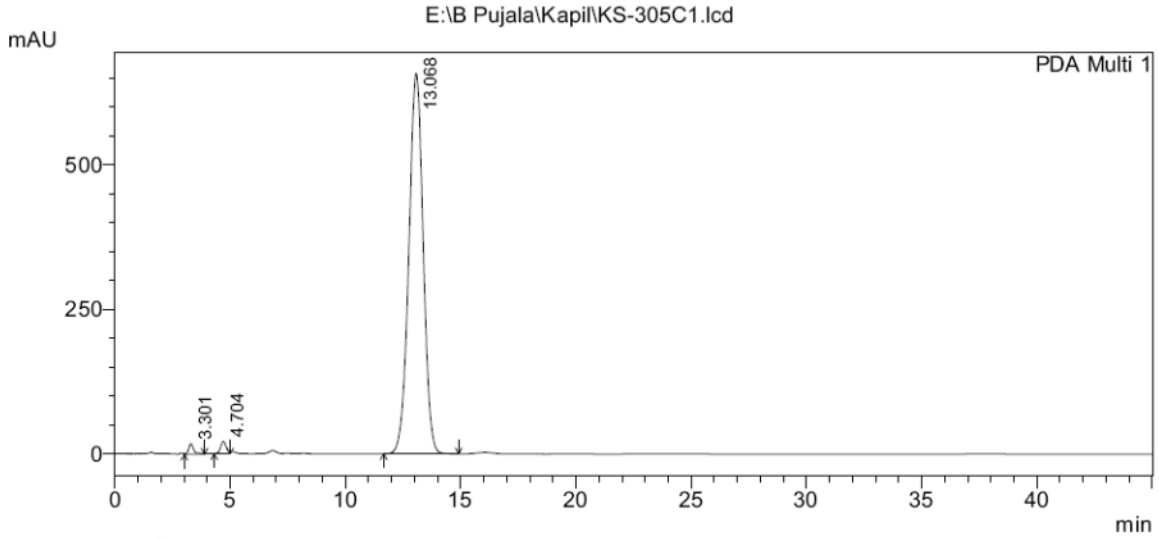
Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.838	391709	10491	1.659	2.403
2	14.802	22612096	417005	95.758	95.511
3	20.369	609970	9108	2.583	2.086
Total		23613775	436604	100.000	100.000

HPLC of 2-(4'-Methylsulfanyl-biphenyl-2-yl)-benzoxazole 3f (Scheme 1):-

E:\B Pujala\Kapil\KS-305C1.lcd

Acquired by	: Admin
Sample Name	: KS-305C
Sample ID	: KS-305C
Vail #	: 30
Injection Volume	: 10 uL
Data File Name	: KS-305C1.lcd
Method File Name	: COAN1.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 4/8/2012 5:39:58 PM
Data Processed	: 4/8/2012 6:25:01 PM

<Chromatogram>



1 PDA Multi 1/256nm 4nm

PeakTable

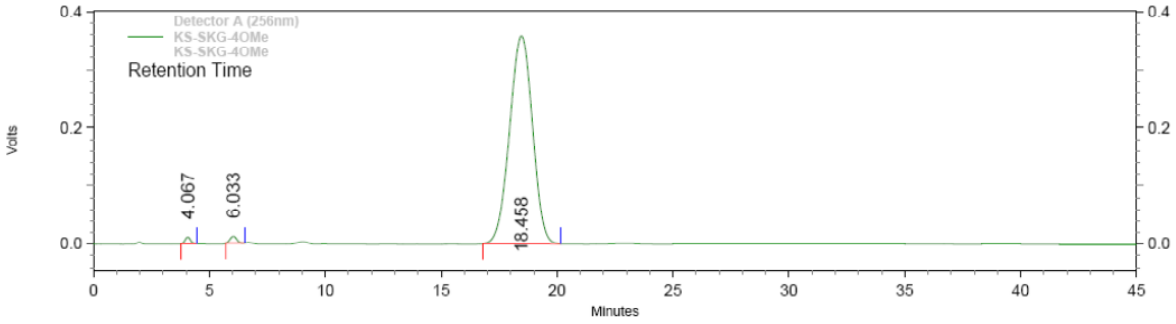
PDA Ch1 256nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	3.301	287226	18001	0.984	2.577
2	4.704	374155	21575	1.281	3.088
3	13.068	28541938	659078	97.735	94.335
Total		29203320	698655	100.000	100.000

HPLC of 2-(3'-Chloro-4'-methoxy-biphenyl-2-yl)-benzoxazole 3g (Scheme 1):-

Shimadzu CLASS-VP V6.14 SP1
Area % Report **Page 1 of 1**

Method Name: C:\CLASS-VP\untitled.met
Data Name: I:\KApil Seth\KS-SKG-4OMe
User: System
Acquired: 4/12/2012 10:38:02 AM
Printed: 10/26/2013 12:37:19 PM



Detector A (256nm)

Pk #	Retention Time	Area	Area %
1	4.067	180423	0.723
2	6.033	237314	0.951
3	18.458	24543688	98.326
Totals		24961425	100.000

HPLC of 2-(3'-Chloro-4'-isopropoxy-biphenyl-2-yl)-benzoxazole 3h (Scheme 1):-

E:\B Pujala\Kapil\KS-312.lcd

Acquired by	: Admin
Sample Name	: KS-312
Sample ID	: KS-312
Vail #	: 33
Injection Volume	: 10 uL
Data File Name	: KS-312.lcd
Method File Name	: COAN1.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 4/8/2012 10:15:41 PM
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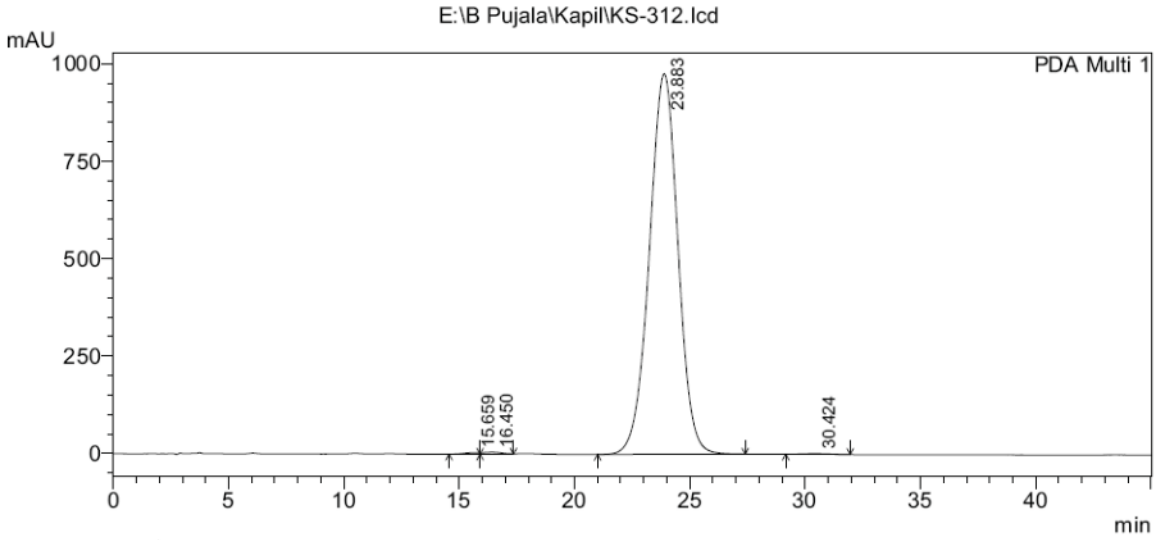

1 PDA Multi 1/256nm 4nm

PeakTable

PDA Ch1 256nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.659	179029	3919	0.211	0.397
2	16.450	303919	5109	0.358	0.518
3	23.883	84244025	975452	99.241	98.894
4	30.424	161129	1881	0.190	0.191
Total		84888103	986361	100.000	100.000

HPLC of 2-(4'-Benzyloxy-3'-chloro-biphenyl-2-yl)-benzoxazole 3i (Scheme 1):-

E:\B Pujala\Kapil\KS-304.lcd

Acquired by	: Admin
Sample Name	: KS-304
Sample ID	: KS-304
Vail #	: 34
Injection Volume	: 10 uL
Data File Name	: KS-304.lcd
Method File Name	: COAN1.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 4/8/2012 11:03:41 PM
Data Processed	: 4/8/2012 11:48:43 PM

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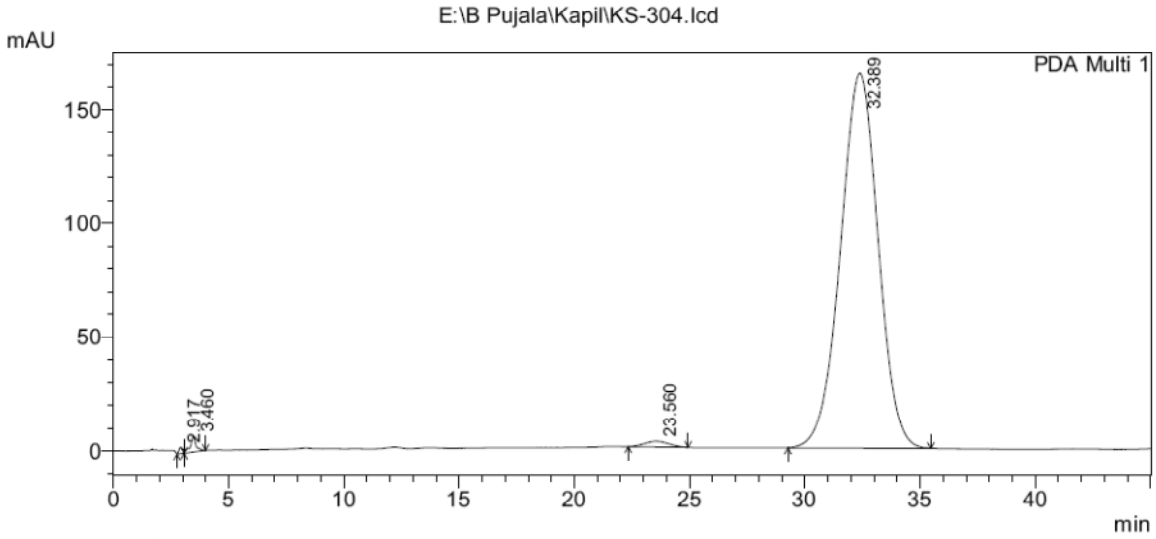

1 PDA Multi 1/256nm 4nm

PeakTable

PDA Ch1 256nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	2.917	32271	2714	0.169	1.536
2	3.460	116712	6606	0.612	3.739
3	23.560	176415	2404	0.925	1.361
4	32.389	18738025	164948	98.293	93.364
Total		19063423	176672	100.000	100.000

HPLC of 2-(4'-Fluoro-biphenyl-2-yl)-benzoxazole 3j (Scheme 1):-

E:\B Pujala\Kapil\KS-315B1.lcd

Acquired by	: Admin
Sample Name	: KS-315B
Sample ID	: KS-315B
Vail #	: 38
Injection Volume	: 10 uL
Data File Name	: KS-315B1.lcd
Method File Name	: COAN1.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 4/9/2012 2:38:43 PM
Data Processed	: 4/9/2012 3:23:48 PM

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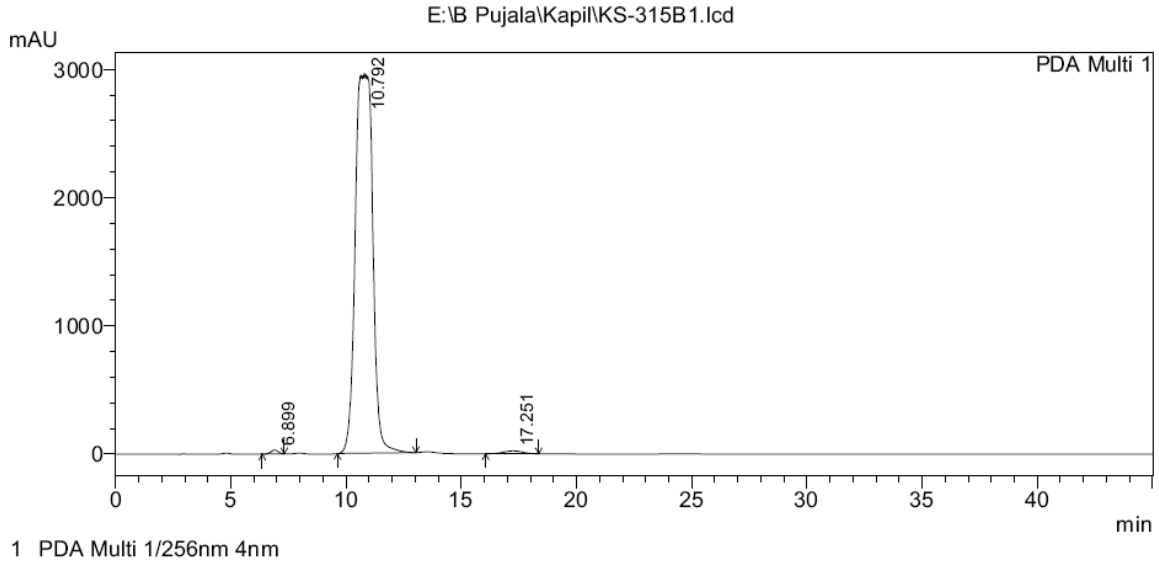

1 PDA Multi 1/256nm 4nm

PeakTable

PDA Ch1 256nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.899	652613	29977	0.411	0.994
2	10.792	156725242	2964514	98.769	98.260
3	17.251	1300302	22520	0.819	0.746
Total		158678157	3017011	100.000	100.000

HPLC of 2-(4'-Trifluoromethyl-biphenyl-2-yl)-benzoxazole 3k (Scheme 1):-

E:\B Pujala\Kapil\KS-313.lcd

Acquired by	: Admin
Sample Name	: KS-313
Sample ID	: KS-313
Vail #	: 37
Injection Volume	: 10 uL
Data File Name	: KS-313.lcd
Method File Name	: COAN1.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 4/9/2012 1:45:49 PM
Data Processed	: 4/9/2012 2:30:53 PM

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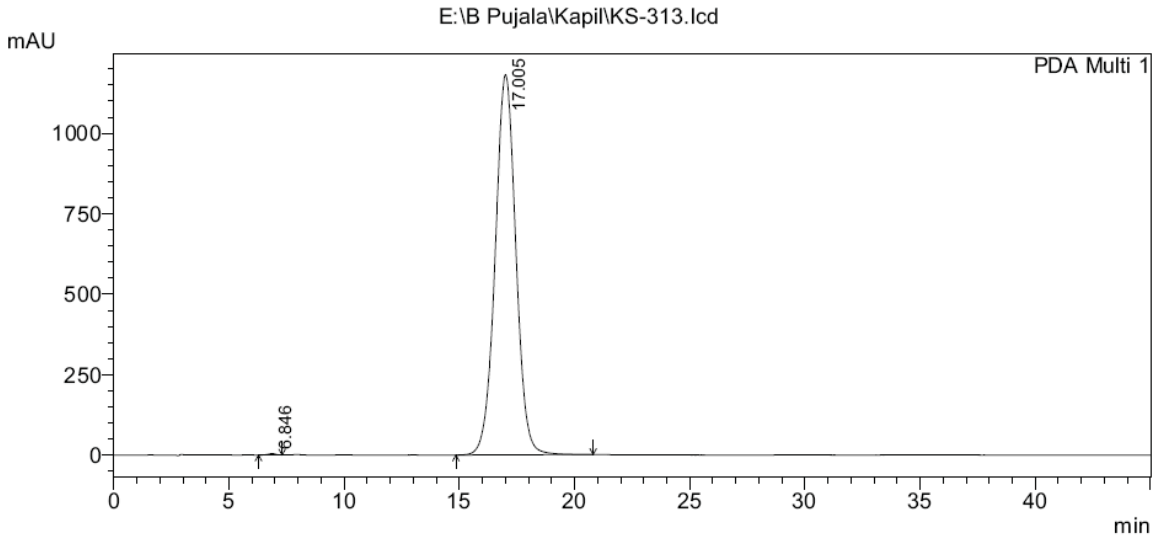


1 PDA Multi 1/256nm 4nm

PeakTable

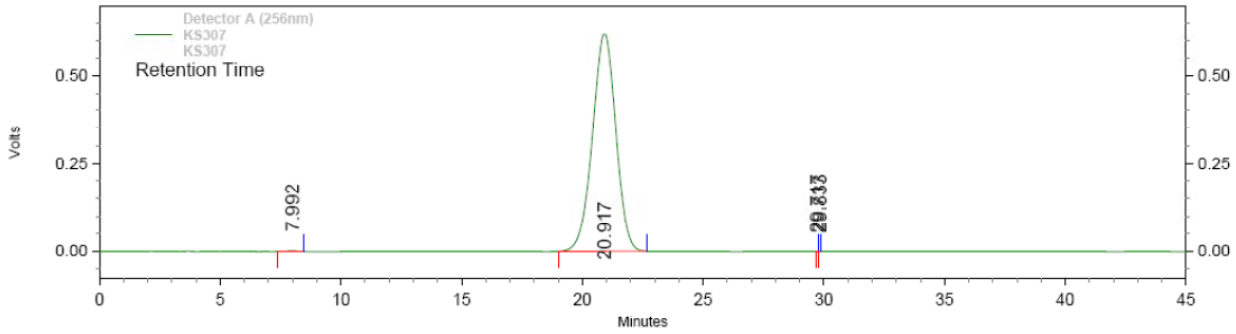
PDA Ch1 256nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.846	98967	4265	0.134	0.360
2	17.005	73754620	1181853	99.866	99.640
Total		73853587	1186118	100.000	100.000

HPLC of 2'-Benzoxazol-2-yl-biphenyl-4-carbaldehyde 3l (Scheme 1):-

Shimadzu CLASS-VP V6.12 SP3
Area % Report

Method Name: C:\CLASS-VP\untitled.met
Data Name: D:\class-vp\DATA\VSM\KApil Seth\KS307
User: System
Acquired: 4/11/2012 8:25:59 PM
Printed: 4/13/2012 11:54:32 AM



Detector A (256nm)

Pk #	Retention Time	Area	Area %	Height	Height %
1	7.992	58843	0.141	2349	0.378
2	20.917	41562589	99.858	618407	99.615
3	29.717	63	0.000	22	0.004
4	29.833	59	0.000	19	0.003
Totals		41621554	100.000	620797	100.000

HPLC of 2'-Benzoxazol-2-yl-biphenyl-4-carbonitrile 3m (Scheme 1):-

Method Name: C:\CLASS-VP\untitled.met
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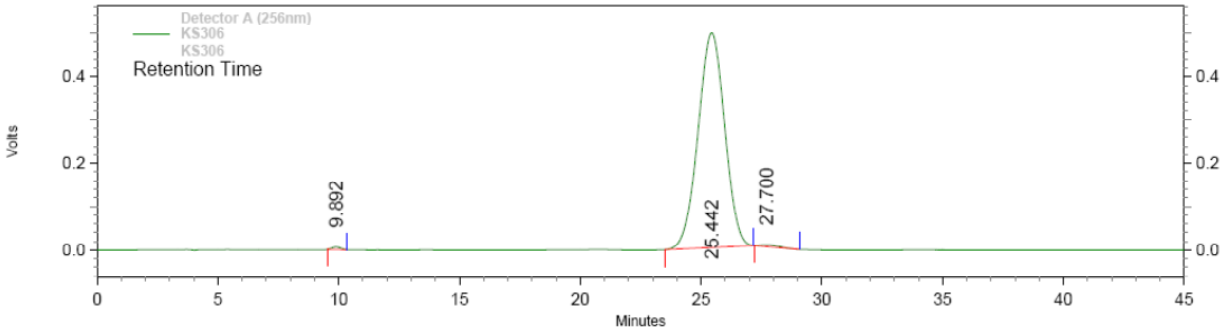


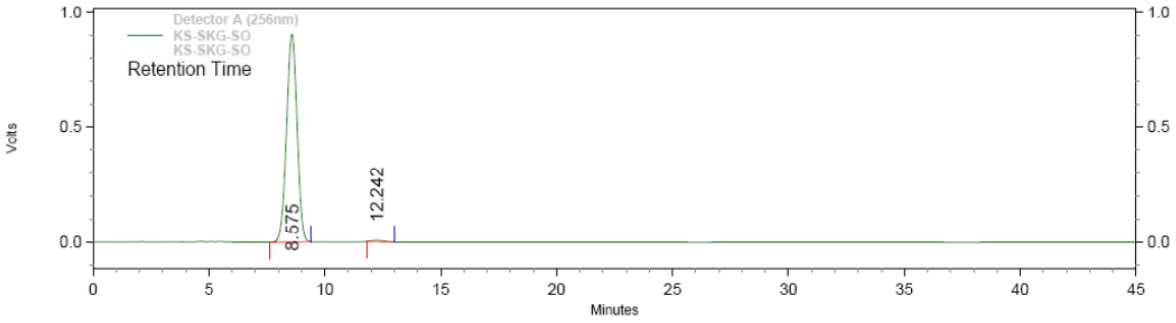
Detector A (256nm)

Pk #	Retention Time	Area	Area %	Height	Height %
1	9.892	150716	0.395	6088	1.208
2	25.442	37777155	99.028	493855	98.006
3	27.700	220237	0.577	3962	0.786
Totals		38148108	100.000	503905	100.000

HPLC of 2-(4'-Methanesulfonyl-biphenyl-2-yl)-benzoxazole 3o (Scheme 2):-

Shimadzu CLASS-VP V6.12 SP3
Area % Report

Method Name: C:\CLASS-VP\untitled.met
Data Name: D:\class-vp\DATA\VSM\KApil Seth\KS-SKG-SO
User: System
Acquired: 4/12/2012 9:51:38 AM
Printed: 4/13/2012 12:15:31 PM



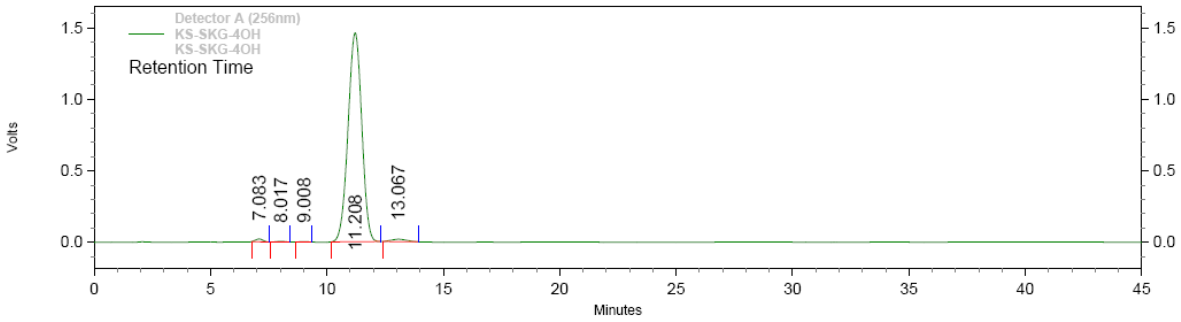
Detector A (256nm)

Pk #	Retention Time	Area	Area %	Height	Height %
1	8.575	28499800	99.327	902763	99.419
2	12.242	193129	0.673	5278	0.581
Totals		28692929	100.000	908041	100.000

HPLC of 2'-Benzoxazol-2-yl-3-chloro-biphenyl-4-ol 3n (Scheme 2):-

Shimadzu CLASS-VP V6.12 SP3
Area % Report

Method Name: C:\CLASS-VP\untitled.met
Data Name: D:\class-vp\DATA\VSM\KApil Seth\KS-SKG-4OH
User: System
Acquired: 4/12/2012 11:24:14 AM
Printed: 4/13/2012 12:04:32 PM



Detector A (256nm)

Pk #	Retention Time	Area	Area %	Height	Height %
1	7.083	427543	0.698	19762	1.313
2	8.017	120556	0.197	4668	0.310
3	9.008	68552	0.112	2857	0.190
4	11.208	59864612	97.734	1460852	97.057
5	13.067	771214	1.259	17013	1.130
Totals		61252477	100.000	1505152	100.000

References

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