

Synthesis of Polycyclic Benzonitriles via a One-Pot Aryl Alkylation/Cyanation Reaction

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General Experimental

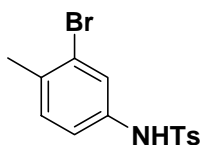
Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrometer, SPECTRUM 1000. ^1H and ^{13}C NMR spectra were measured on Varian Unity 500, Varian Mercury 400, Varian 400 MHz NMR System, Varian Mercury 300 spectrometer. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. For thin layer chromatography (TLC) analysis throughout this work, Silicycle precoated TLC plates (silica gel 60 F₂₅₄ on aluminum sheet) were used. The products were purified by preparative column chromatography on silica gel (60Å, ultrapure silica gel, SILICYCLE). The high-resolution mass spectra (HRMS) analysis was performed at the Department of Chemistry, University of Toronto (EI and ESI). Microwave-assisted reactions were performed in Emrys Liberator model from Personal Chemistry. Reactants were filled into appropriate microwave process vials. Dimethoxyethane was distilled from calcium hydride still under nitrogen prior to use. 3-Iodo-4-methyl-phenol, 3-Bromo-4-methyl-phenylamine, 3,5-dimethoxyphenylmagnesium chloride and 2,4,5-triiodophenol were purchased from Aldrich and used as received. N-(3-Iodo-4-methyl-phenyl)-4-methyl-benzenesulfonamide, 3-Iodo-4-methoxy-phenol, and 3-Iodo-4-nitro-phenol were made according to literature procedure^{1,2,3} respectively.

¹ Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148-13149.

² Hoeger, S. *Liebigs Annalen/ Recueil* **1997**, *1*, 273-277.

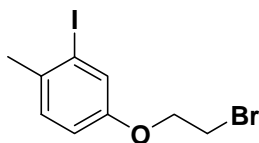
³ Shen, Y.; Xie, Q.; Norberg, M.; Sausville, E.; Vande Woude, G.; Wenkert, D. *Bioorg. Med. Chem.* **2005**, *13*, 4960-4971.

Synthesis of Bicyclic Substrates

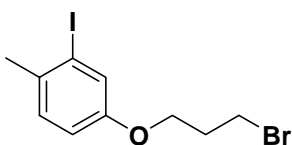


***N*-(3-Bromo-4-methyl-phenyl)-4-methyl-benzenesulfonamide (28):** To a solution of 3-Bromo-4-methyl-phenylamine (1 g, 5.37 mmol) in pyridine (10 mL) was added para-toluenesulfonyl chloride (1.05 g, 5.5 mmol). The resulting solution was heated at 70 °C for 8 hours and the concentrated under reduced pressure, dissolved in dichloromethane and washed with 10% aqueous hydrochloric acid, brine and dried over magnesium sulfate. The solution was concentrated under reduced pressure to give 1.78 g (95% yield) of **28** as a pale brown solid, mp= 139-140 °C. ¹H NMR (CDCl₃, 400 MHz) δ 7.69 (d, *J*=8.4 Hz, 2H), 7.38 (br s, 1H), 7.29 (d, *J*=2.2 Hz, 1H), 7.22 (d, *J*=8.0 Hz, 2H), 7.04 (d, *J*=8.2 Hz, 1H), 6.96 (dd, *J*=8.3 Hz, *J*=2.2 Hz, 1H), 2.37 (s, 3H), 2.28 (s, 3H); ¹³C-NMR (CDCl₃, 100 MHz) 144.1, 135.7, 135.3, 134.8, 131.1, 129.8, 127.3, 125.1, 124.9, 120.4, 22.2, 21.6; δ IR (film) 3250, 2920, 2360, 1603, 1490, 1457, 1374, 1323, 1160, 1091, 1038, 927, 812 cm⁻¹; HRMS-ESI (m/z): [M⁺] calcd for [C₁₄H₁₄NO₂NaSBr]⁺: 361.9820, found 361.9838;

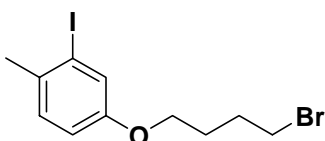
General procedure for bicyclic precursors: To the corresponding phenol or tosylated aniline was added 5 equivalents K₂CO₃ and 10 equivalents of dibromoalkane (1M in acetone). The resulting solution was refluxed under argon for 60 hours. The mixture was diluted with water and extracted with dichloromethane. The organic phase was dried over magnesium sulfate and evaporated under reduced pressure.



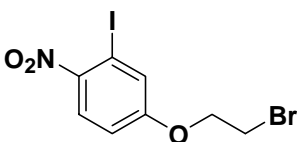
4-(2-Bromoethoxy)-2-iodo-1-methyl-benzene (1): Following the general procedure above on 1 g (4.27 mmol) of 3-Iodo-4-methyl-phenol, the crude product was purified by column chromatography using 10% ether in hexanes to give 827 mg (57% yield) of **1** as a white solid, mp= 27-28 °C. ¹H NMR (CDCl₃, 400 MHz) δ 7.37 (d, *J*=2.6 Hz, 1H), 7.12 (d, *J*=8.4 Hz, 1H), 6.82 (dd, *J*=8.4 Hz, *J*=2.6 Hz, 1H), 4.24 (t, *J*=7.2 Hz, 2H), 3.61 (t, *J*=6.3 Hz, 2H), 2.37 (s, 3H); ¹³C-NMR (CDCl₃, 100 MHz) δ 156.3, 134.3, 129.8, 125.1, 115.0, 100.8, 68.2, 28.9, 26.9; IR (film) 3057, 3018, 2967, 2917, 2858, 1596, 1565, 1486, 1453, 1420, 1380, 1287, 1234, 1076, 1016, 896, 862, 841, 802, 763, 688, 668 cm⁻¹; HRMS-EI (m/z): [M⁺] calcd for C₉H₁₀BrIO: 339.8959, found 339.8960.



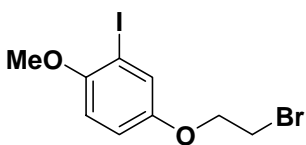
4-(3-Bromo-propoxy)-2-iodo-1-methyl-benzene (3): Following the general procedure above on 1 g (4.27 mmol) of 3-Iodo-4-methyl-phenol, the crude product was purified by column chromatography using 10% ether in hexanes to give 992 mg (66% yield) of **3** as a clear, colorless oil. ^1H NMR (CDCl_3 , 400 MHz) δ 7.39 (d, $J=2.6$ Hz, 1H), 7.12 (d, $J=8.2$ Hz, 1H), 6.82 (dd, $J=8.3$ Hz, $J=2.6$ Hz, 1H), 4.05 (t, $J=5.8$ Hz, 2H), 3.59 (t, $J=6.4$ Hz, 2H), 2.38 (s, 3H), 2.34-2.25 (m, 2H); ^{13}C -NMR (CDCl_3 , 100 MHz) δ 156.8, 133.5, 129.7, 124.7, 114.7, 100.9, 65.6, 32.3, 29.9, 26.9; IR (film) 2925, 2920, 1596, 1560, 1489, 1467, 1437, 1380, 1284, 1234, 1200, 1153, 1020, 936, 856, 804, 708 cm^{-1} ; HRMS-EI (m/z): [M^+] calcd for $\text{C}_{10}\text{H}_{12}\text{BrIO}$: 353.9116, found 353.9114.



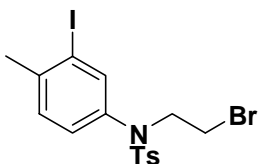
4-(4-Bromo-butoxy)-2-iodo-1-methyl-benzene (5): Following the general procedure above on 1 g (4.27 mmol) of 3-Iodo-4-methyl-phenol, the crude product was purified by column chromatography using 10% ether in hexanes to give 1127 mg (72% yield) of **5** as a clear colorless oil. ^1H NMR (CDCl_3 , 400 MHz) δ 7.33 (d, $J=2.6$ Hz, 1H), 7.08 (d, $J=8.4$ Hz, 1H), 6.77 (dd, $J=8.4$ Hz, $J=2.6$ Hz, 1H), 3.91 (t, $J=6.0$ Hz, 2H), 3.45 (t, $J=6.6$ Hz, 2H), 2.34 (s, 3H), 2.10-1.96 (m, 2H), 1.95-1.84 (m, 2H); ^{13}C -NMR (CDCl_3 , 100 MHz) δ 157.0, 133.3, 129.7, 124.6, 114.6, 100.8, 67.1, 33.4, 29.4, 27.8, 26.9; IR (film) 2942, 2930, 1596, 1560, 1489, 1469, 1437, 1380, 1285, 1233, 1201, 1021, 946, 908, 861, 812, 732 cm^{-1} ; HRMS-EI (m/z): [M^+] calcd for $\text{C}_{11}\text{H}_{14}\text{BrIO}$: 367.9272, found 367.9278.



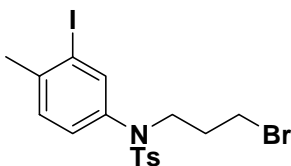
4-(2-Bromo-ethoxy)-2-iodo-1-nitro-benzene (7): Following the general procedure above on 1 g (3.77 mmol) of 3-Iodo-4-nitro-phenol, the crude product was purified by column chromatography using 10% ether in hexanes to give 569 mg (41% yield) of **7** as a bright yellow solid, mp=73-75 $^{\circ}\text{C}$. ^1H NMR (CDCl_3 , 400 MHz) δ 7.95 (d, $J=9.1$ Hz, 1H), 7.53 (d, $J=2.6$ Hz, 1H), 6.95 (dd, $J=9.0$ Hz, $J=2.7$ Hz, 1H), 4.35 (t, $J=6.0$ Hz, 2H), 3.65 (t, $J=6.0$ Hz, 2H); ^{13}C -NMR (CDCl_3 , 100 MHz) δ 160.9, 145.8, 127.7, 127.5, 114.5, 88.2, 68.5, 28.2; IR (film) 3628, 2942, 2252, 1587, 1539, 1521, 1453, 1369, 1341, 1278, 1247, 1227, 1014, 908, 850, 734, 650 cm^{-1} ; HRMS-EI (m/z): [M^+] calcd for $\text{C}_8\text{H}_7\text{BrINO}_3$: 370.8654, found 370.8655.



4-(2-Bromo-ethoxy)-2-iodo-1-methoxy-benzene (9): Following the general procedure above on 1 g (4.00 mmol) of 3-Iodo-4-methoxy-phenol, the crude product was purified by column chromatography using 10% ether in hexanes to give 1135 mg (79% yield) of **9** as a clear, light yellow oil. ^1H NMR (CDCl_3 , 400 MHz) δ 7.36 (d, $J=2.9$ Hz, 1H), 6.88 (dd, $J=8.9$ Hz, $J=2.8$ Hz, 1H), 6.74 (d, $J=8.9$ Hz, 1H), 4.21 (t, $J=6.2$ Hz, 2H), 3.82 (s, 3H), 3.59 (t, $J=6.3$ Hz, 2H); ^{13}C -NMR (CDCl_3 , 75 MHz) δ 153.5, 152.8, 126.4, 116.1, 111.6, 86.2, 69.1, 57.1, 29.3; IR (film) 2946, 2834, 1598, 2224, 1598, 1572, 1489, 1457, 1437, 1420, 1384, 1271, 1212, 1180, 1077, 1047, 1014, 909, 867, 804, 758, 734, 648cm^{-1} ; HRMS-EI (m/z): [M^+] calcd for $\text{C}_9\text{H}_{10}\text{BrIO}_2$: 355.8908, found 355.8910.

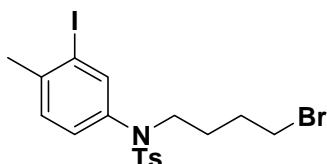


***N*-(2-Bromo-ethyl)-*N*-(3-iodo-4-methyl-phenyl)-4-methyl-benzenesulfonamide (11a):** Following the general procedure above on 1 g (2.58 mmol) of *N*-(3-Iodo-4-methyl-phenyl)-4-methyl-benzenesulfonamide, the crude product was purified by column chromatography using 20% ether in hexanes to give 1128 mg (88% yield) of **11** as a white solid, mp= 75-76 °C. ^1H NMR (CDCl_3 , 400 MHz) δ 7.50 (d, $J=8.3$ Hz, 2H), 7.42 (d, $J=2.2$ Hz, 1H), 7.29 (d, $J=8.0$ Hz, 2H), 7.18 (d, $J=8.1$ Hz, 1H), 6.99 (dd, $J=7.9$ Hz, $J=2.2$ Hz, 1H), 3.81 (t, $J=7.4$ Hz, 2H), 3.38 (t, $J=7.4$ Hz, 2H), 2.45 (s, 3H), 2.42 (s, 3H); ^{13}C -NMR (CDCl_3 , 100 MHz) δ 144.0, 142.0, 138.9, 137.5, 134.8, 129.8, 129.6, 128.8, 127.7, 100.3, 52.6, 28.7, 27.7, 21.6; IR (film) 3054, 2971, 2919, 1917, 1592, 1556, 1481, 1445, 1349, 1304, 1275, 1250, 1220, 1032, 1017, 965, 903, 814, 736, 706, 683, 668, 634cm^{-1} ; HRMS-EI (m/z): [M^+] calcd for $\text{C}_{16}\text{H}_{17}\text{BrINO}_2\text{S}$: 492.9208, found 492.9206.



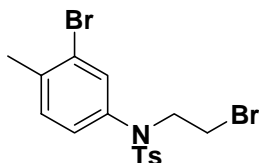
***N*-(3-Bromo-propyl)-*N*-(3-iodo-4-methyl-phenyl)-4-methyl-benzenesulfonamide (13a):** Following the general procedure above on 1 g (2.58 mmol) of *N*-(3-Iodo-4-methyl-phenyl)-4-methyl-benzenesulfonamide, the crude product was purified by column chromatography using 20% ether in hexanes to give 1227 mg (94% yield) **13** clear colorless oil. ^1H NMR (CDCl_3 , 400 MHz) δ 7.46 (d, $J=7.7$ Hz, 2H), 7.40 (d, $J=1.5$ Hz,

1H), 7.27 (d, $J=8.1$ Hz, 2H), 7.17 (d, $J=8.1$ Hz, 1H), 6.96 (dd, $J=8.0$ Hz, $J=1.5$ Hz, 1H), 3.60 (t, $J=6.4$ Hz, 2H), 3.41 (t, $J=6.5$ Hz, 2H), 2.44 (s, 3H), 2.42 (s, 3H), 2.05-1.94 (m, 2H); ^{13}C -NMR (CDCl_3 , 100 MHz) δ 143.8, 141.6, 138.4, 137.6, 134.5, 129.6, 129.5, 128.4, 127.7, 100.3, 49.1, 31.5, 29.8, 27.6, 21.5; IR (film) 2954, 2943, 2932, 2255, 1744, 1592, 1554, 1482, 1445, 1348, 1304, 1237, 1184, 1165, 1090, 1031, 911, 814, 731, 707, 684, 669 cm^{-1} ; HRMS-EI (m/z): $[\text{M}^+]$ calcd for $\text{C}_{17}\text{H}_{19}\text{BrINO}_2\text{S}$: 506.9364, found 506.9377.



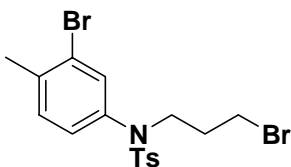
***N*-(4-Bromo-butyl)-*N*-(3-iodo-4-methyl-phenyl)-4-methyl-benzenesulfonamide**

(15a): Following the general procedure above on 1 g (2.58 mmol) of *N*-(3-Iodo-4-methyl-phenyl)-4-methyl-benzenesulfonamide, the crude product was purified by column chromatography using 20% ether in hexanes to give 1209 mg (92% yield) of **15** as a white solid, mp= 66-68 °C. ^1H NMR (CDCl_3 , 300 MHz) δ 7.46 (d, $J=8.3$ Hz, 2H), 7.39 (d, $J=2.2$ Hz, 1H), 7.27 (d, $J=8.0$ Hz, 2H), 7.18 (d, $J=8.1$ Hz, 1H), 6.96 (dd, $J=8.1$ Hz, $J=2.2$ Hz, 1H), 3.49 (t, $J=7.4$ Hz, 2H), 3.40 (t, $J=7.4$ Hz, 2H), 2.44 (s, 3H), 2.42 (s, 3H), 1.92 (m, 2H), 1.55 (m, 2H); ^{13}C -NMR (CDCl_3 , 75 MHz) δ 143.9, 141.8, 138.8, 137.6, 135.0, 129.9, 129.7, 1.8, 128.0, 100.5, 49.6, 33.3, 29.4, 27.9, 26.5, 21.8; IR (film) 2943, 2255 1740, 1592, 1554, 1477, 1444, 1379, 1348, 1304, 1255, 1184, 1164, 1090, 1030, 910, 814, 707, 684, 669 cm^{-1} ; HRMS-EI (m/z): $[\text{M}^+]$ calcd for $\text{C}_{18}\text{H}_{21}\text{BrINO}_2\text{S}$: 520.9521, found 520.9525.



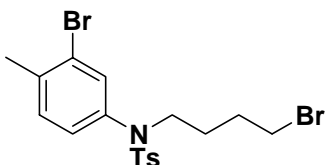
***N*-(2-Bromo-ethyl)-*N*-(3-bromo-4-methyl-phenyl)-4-methyl-benzenesulfonamide**

(11b): Following the general procedure above on 1 g (2.93 mmol) of **28**, the crude product was purified by column chromatography using 20% ether in hexanes to give 1043 mg (80% yield) of **11b** as a white solid, mp= 81-82 °C. ^1H NMR (CDCl_3 , 400 MHz) δ 7.49 (d, $J=8.3$ Hz, 2H), 7.27 (d, $J=8.2$ Hz, 2H), 7.21 (d, $J=8.0$ Hz, 1H), 7.18 (d, $J=8.1$ Hz, 1H), 6.93 (dd, $J=8.1$ Hz, $J=2.2$ Hz, 1H), 3.82 (t, $J=7.4$ Hz, 2H), 3.37 (t, $J=7.4$ Hz, 2H), 2.43 (s, 3H), 2.38 (s, 3H); ^{13}C -NMR (CDCl_3 , 75 MHz) δ 144.2, 138.7, 137.9, 135.0, 132.7, 131.2, 129.8, 128.0, 127.9, 124.9, 52.7, 28.9, 22.8, 21.8; IR (film) 3025, 2922, 2256, 1597, 1560, 1487, 1447, 1350, 1305, 1250, 1222, 1160, 1089, 1038, 1018, 965, 908, 804, 732, 707, 668, 635, 601 cm^{-1} ; HRMS-EI (m/z): $[\text{M}^+]$ calcd for $\text{C}_{16}\text{H}_{17}\text{Br}_2\text{NO}_2\text{S}$: 444.9346, found 444.9350.



***N*-(3-Bromo-4-methyl-phenyl)-*N*-(3-bromo-propyl)-4-methyl-benzenesulfonamide**

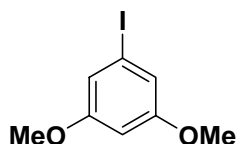
(13b): Following the general procedure above on 0.5 g (1.46 mmol) of **28**, the crude product was purified by column chromatography using 20% ether in hexanes to give 608 mg (89% yield) of **13b** as a thick colourless oil. ^1H NMR (CDCl_3 , 400 MHz) δ 7.47 (d, $J=8.3$ Hz, 2H), 7.27 (d, $J=10.3$ Hz, 2H), 7.17-7.19 (m, 2H), 6.91 (dd, $J=7.9$ Hz, $J=2.2$ Hz, 1H), 3.62 (t, $J=6.7$ Hz, 2H), 3.42 (t, $J=6.7$ Hz, 2H), 2.44 (s, 3H), 2.38 (s, 3H), 2.00 (m, 2H); ^{13}C -NMR (CDCl_3 , 100 MHz) δ 143.8, 138.1, 137.8, 134.4, 132.0, 130.9, 129.5, 127.7, 127.4, 124.6, 49.0, 31.4, 29.8, 22.5, 21.5; IR (film) 2921, 2865, 2361 1733, 1597, 1558, 1489, 1349, 1304, 1238, 1184, 1163, 1090, 1037, 913, 814, 707, 694, 676, 652, 605 cm^{-1} ; HRMS-EI (m/z): [M^+] calcd for $\text{C}_{17}\text{H}_{20}\text{Br}_2\text{NO}_2\text{S}$: 459.9575, found 459.9564.



***N*-(4-Bromo-butyl)-*N*-(3-bromo-4-methyl-phenyl)-4-methyl-benzenesulfonamide**

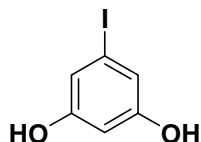
(15b): Following the general procedure above on 0.5 g (1.46 mmol) of **28**, the crude product was purified by column chromatography using 20% ether in hexanes to give 640 mg (92% yield) of **15b** as a white solid, mp= 67-69 $^{\circ}\text{C}$. ^1H NMR (CDCl_3 , 400 MHz) δ 7.46 (d, $J=8.3$ Hz, 2H), 7.27 (d, $J=7.2$ Hz, 2H), 7.18 (m, 2H), 6.92 (dd, $J=8.1$ Hz, $J=2.0$ Hz, 1H), 3.50 (t, $J=6.8$ Hz, 2H), 3.40 (t, $J=6.7$ Hz, 2H), 2.43 (s, 3H), 2.38 (s, 3H), 1.93 (m, 2H), 1.55 (m, 2H); ^{13}C -NMR (CDCl_3 , 100 MHz) δ 143.9, 138.2, 137.7, 134.8, 132.3, 131.1, 129.7, 127.9, 127.8, 124.7, 49.4, 33.3, 29.3, 26.4, 22.8, 21.8; IR (film) 3027, 2922, 2867, 2255, 1917, 1734, 1597, 1558, 1489, 1447, 1379, 1348, 1304, 1286, 1255, 1230, 1183, 1162, 1090, 1037, 927, 814, 735, 707, 694, 675, 652, 600 cm^{-1} ; HRMS-EI (m/z): [M^+] calcd for $\text{C}_{18}\text{H}_{22}\text{Br}_2\text{NO}_2\text{S}$: 473.9732, found 473.9721.

Synthesis of Tricyclic Substrates

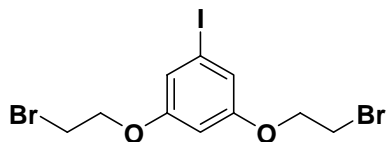


1-Iodo-3,5-dimethoxybenzene (29): To a solution of 3,5-dimethoxyphenylmagnesium chloride (50.0 mL, 50.0 mmol, 1 M in THF, 1 equiv) was added drop wise a solution of iodine (8.38 g, 33.0 mL, 0.66 equiv) in THF (30 mL). The resulting mixture was stirred

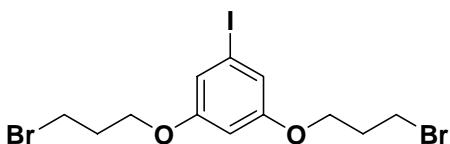
at 0 °C for 2 h then quenched with 1 M aqueous HCl (30 mL). Ether (25 mL) was added and the organic layer was separated and washed with 1 M aqueous Na₂S₂O₃ solution (2 × 30 mL). After drying with anhydrous Magnesium sulfate, removal of the solvent gave a crude solid that was purified by column chromatography using 10% EtOAc in hexanes to give 11 g (93% yield) of **30** as a white solid, mp= 74-75 °C. ¹H NMR (300 MHz, CDCl₃) δ 6.85 (d, 2H, *J* = 2.2 Hz), 6.40 (t, 1H, *J* = 2.2 Hz), 3.76 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 161.2, 116.0, 100.8, 94.3, 55.7; IR (film) 1577, 1425, 1294, 1199, 1164, 1032 cm⁻¹; HRMS (*m/z*): calcd for C₈H₉IO₂ [M]⁺ 263.9654, found 263.9647.



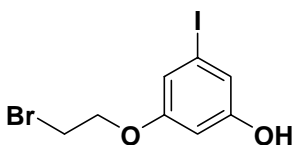
5-Iodobenzene-1,3-diol (30): A solution of **29** (8.30 g, 31.4 mmol, 1 equiv) and HI (47 wt % in water, 75 mL) was heated at reflux for 24 h. The solution was cooled to rt and water (100 mL) and ether (100 mL) were added. The organic layer was separated and washed with 1 M sodium thiosulfate solution (2 × 75 mL) and once with water (50 mL). After drying with anhydrous Magnesium sulfate, removal of the solvent gave a crude oil that was purified by column chromatography using 25% EtOAc in hexanes to give 6.90 g (97% yield) of **30** as a white solid, mp= 94-95 °C. ¹H NMR (300 MHz, acetone-*d*₆) δ 8.40 (br s, 2OH), 6.33 (s, 2H), 6.72 (s, 1H); ¹³C NMR (75 MHz, acetone-*d*₆) δ 159.3, 116.3, 106.8, 93.8; IR (film) 3330, 1591, 1470, 1294, 1152, cm⁻¹; HRMS (*m/z*): calcd for C₆H₅IO₂ [M]⁺ 235.9334, found 235.9334.



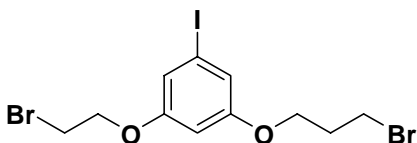
1,3-Bis-(2-bromo-ethoxy)-5-iodo-benzene (17): To a solution of **30** (8.00 g, 33.9 mmol, 1 equiv) and 1,2-dibromoethane (44.0 mL, 508 mmol, 15 equiv) in acetone (70 mL) was added K₂CO₃ (23.4 g, 170 mmol, 5 equiv). The mixture was heated at reflux for 36 h. The reaction was cooled to rt and filtered through Celite™. Distillation of the excess 1,2-dibromoethane gave a crude oil that was purified by column chromatography using 10% EtOAc in hexanes to give 9.3 g (62% yield) of **17** as a white solid, mp= 97-98 °C. ¹H NMR (300 MHz, CDCl₃) δ 6.89 (s, 2H), 6.44 (s, 1H), 4.24 (t, 4H, *J* = 6.0 Hz), 3.61 (t, 4H, *J* = 6.0 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 159.8, 117.4, 102.3, 94.3, 68.3, 28.9; IR (film) 1421, 1168, 1052 cm⁻¹; HRMS (*m/z*): calcd for C₁₀H₁₁Br₂IO₂ [M]⁺ 447.8161, found 447.8170.



1,3-Bis-(3-bromopropoxy)-5-iodobenzene (19): To a solution of **30** (1.24 g, 5.25 mmol, 1 equiv) and 1,3-dibromopropane (5.30 mL, 52.5 mmol, 10 equiv) in acetone (15 mL) was added K_2CO_3 (3.63 g, 26.3 mmol, 5 equiv). The mixture was heated at reflux for 36 h. The reaction was cooled to rt and filtered through Celite™. Distillation of the excess 1,3-dibromopropane gave a crude oil that was purified by column chromatography using 10% EtOAc in hexanes to give 1.5 g (60% yield) of **19** as a white solid, mp= 62-63 °C. 1H NMR (300 MHz, $CDCl_3$) δ 6.87 (d, 2H, J = 2.2 Hz), 6.42 (t, 1H, J = 2.2 Hz), 4.06 (t, 4H, J = 5.8 Hz), 3.58 (t, 4H, J = 6.4 Hz), 2.29 (quintet, 4H, J = 0.015 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 116.8, 160.3, 116.8, 101.8, 94.3, 65.8, 32.4, 29.9; IR (film) 1593, 1434, 1166, 1053 cm^{-1} ; HRMS (m/z): calcd for $C_{12}H_{15}Br_2IO_2$ $[M]^+$ 475.8477, found 475.8483.

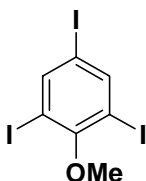


3-(2-Bromoethoxy)-5-iodophenol (31) : To a solution of **30** (2.75 g, 11.6 mmol, 1 equiv) and 1,2-dibromoethane (7.0 mL, 81.6 mmol, 7 equiv) in acetone (20 mL) was added K_2CO_3 (2.10 g, 15.1 mmol, 1.3 equiv). The mixture was heated at reflux for 24 h. The reaction was cooled to rt and filtered through Celite™. Distillation of the excess 1,2-dibromoethane gave a crude oil that was purified by column chromatography using 10% EtOAc in hexanes to give 1.3 g (34% yield) of **31** as a white solid, mp= 139-141 °C. 1H NMR (400 MHz, $CDCl_3$) δ 6.83 (m, 2H), 6.36 (t, 1H, J = 2.2 Hz), 4.89 (br s, 1OH), 4.21 (t, 2H, J = 6.2 Hz), 3.59 (t, 2H, J = 6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 157.2, 118.3, 116.8, 102.6, 94.3, 68.2, 28.9; IR (film) 3385, 1596, 1493, 1279, 1148 cm^{-1} ; HRMS (m/z): calcd for $C_8H_8BrIO_2$ $[M]^+$ 341.8752, found 341.8752.

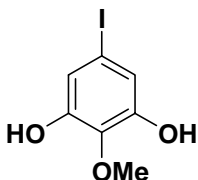


1-(2-Bromoethoxy)-3-(3-bromopropoxy)-5-iodobenzene (21): To a solution of **31** (1.88 g, 5.48 mmol, 1 equiv) and 1,3-dibromopropane (5.6 mL, 54.8 mmol, 10 equiv) in acetone (15 mL) was added K_2CO_3 (2.27 g, 16.4 mmol, 3 equiv). The mixture was heated at reflux for 36 h. The reaction was cooled to rt and filtered through Celite™. Distillation of the excess 1,3-dibromopropane gave a crude oil that was purified by column chromatography using 10% EtOAc in hexanes to give 1.0 g (40% yield) of **21** as

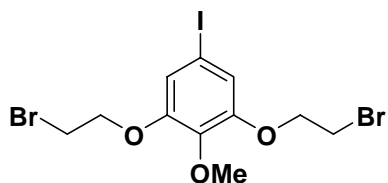
a white solid, mp= 63-64 °C. ^1H NMR (400 MHz, CDCl_3) δ 6.90 (m, 1H), 6.86 (m, 1H), 6.43 (t, 1H, $J = 2.7$ Hz), 4.24 (t, 2H, $J = 6.2$ Hz), 4.06 (t, 2H, $J = 6.2$ Hz), 3.61 (t, 2H, $J = 2.7$ Hz), 3.56 (t, 2H, $J = 6.2$ Hz), 2.29 (quint, 2H, $J = 6.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 160.4, 159.7, 117.4, 116.9, 102.1, 94.3, 68.2, 65.8, 32.3, 29.9, 28.9; IR (film) 1574, 1434, 1277, 1163 cm^{-1} ; HRMS(m/z): calcd for $\text{C}_{11}\text{H}_{13}\text{Br}_2\text{IO}_2$ $[\text{M}]^+$ 461.8333, found 461.8327.



1,3,5-Triiodo-2-methoxybenzene (32): To a solution of 2,4,5-triodophenol (10.0 g, 21.2 mmol, 1 equiv) in acetone (175 mL) was added K_2CO_3 (4.40 g, 31.8 mmol, 1.5 equiv). The mixture was stirred at rt for 30 min then iodomethane (2.00 mL, 31.8 mmol, 1.5 equiv) was added. The mixture was heated at reflux for 3 h, cooled to rt and filtered through CeliteTM. Evaporation of the volatiles gave a crude product that was purified by column chromatography using 10% EtOAc in hexanes to give 10 g (98% yield) of **32** as a pale yellow solid, mp= 93-94 °C. ^1H NMR (300 MHz, CDCl_3) δ 8.05 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.3, 147.5, 91.9, 89.5, 61.0; IR (film) 1455, 1402 cm^{-1} ; HRMS (m/z): calcd for $\text{C}_7\text{H}_5\text{I}_3\text{O}$ $[\text{M}]^+$ 485.7481, found 485.7474.



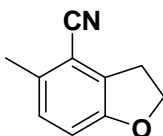
5-Iodo-2-methoxybenzene-1,3-diol (33): To a -78 °C solution of **32** (8.61 g, 17.7 mmol, 1 equiv) in ether (165 mL) was added drop wise *n*-BuLi (24.4 mL, 38.9 mmol, 1.6 M in hexanes, 2.2 equiv). The mixture was stirred at -78 °C for 1 h then trimethyl borate (20.0 mL, 17.7 mmol, 10 equiv) was added at once. The reaction was warmed to rt over 16 h then cooled to 0 °C. Peracetic acid solution (12.0 mL, 17.7 mmol, 32 wt% in dilute acetic acid, 10 equiv) was added drop wise. The reaction was stirred at 0 °C for 30 min then quenched with saturated aqueous NaHCO_3 (12 mL) and then warmed to rt. Water (170 mL) and ether (170 mL) were added and the organic layer was washed with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$, brine, dried with Magnesium sulfate, filtered, and concentrated. The crude mixture was purified by column chromatography using 25% EtOAc in hexanes to give 3.6 g (77% yield) of **33** as a pale yellow solid, mp= 90-91 °C. ^1H NMR (300 MHz, CDCl_3) δ 6.87 (s, 2H), 5.93 (br s, 2OH), 3.85 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 149.8, 135.0, 117.9, 87.2, 61.4; IR (film) 3395, 1582, 1487, 1161 cm^{-1} ; HRMS (m/z): calcd for $\text{C}_7\text{H}_7\text{IO}_3$ $[\text{M}]^+$ 265.9439, found 265.9440.



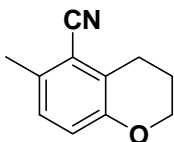
1,3-Bis(2-bromoethoxy)-5-iodo-2-methoxybenzene (23): To a solution of **33** (4.00 g, 19.4 mmol, 1 equiv) and 1,2-dibromoethane (25.0 mL, 291 mmol, 15 equiv) in acetone (35 mL) was added K_2CO_3 (13.5 g, 97.1 mmol, 5 equiv). The mixture was heated at reflux for 36 h. The reaction was cooled to rt and filtered through Celite™. Distillation of the excess 1,2-dibromoethane gave a crude oil that was purified by column chromatography using 10% EtOAc in hexanes to give 7.8 g (84% yield) of **23** as a white solid, mp= 82-83 °C. 1H NMR (300 MHz, $CDCl_3$) δ 6.92 (s, 2H), 4.24 (t, 4H, J = 6.1 Hz), 3.87 (s, 3H), 3.65 (t, 4H, J = 6.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 140.1, 118.3, 85.9, 69.6, 61.5, 29.2; IR (film) 1581, 1496, 1417, 1128 cm^{-1} ; HRMS (m/z): calcd for $C_{11}H_{13}Br_2IO_3$ $[M]^+$ 477.8283, found 477.8276.

Tandem Ortho Alkylation/Cyanation Reaction

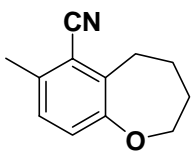
General Procedure for Cyanation Reaction: To a 5 ml microwave vial containing a magnetic stir bar was added 1 equivalent substrate, 0.1 equivalents palladium acetate, 0.22 equivalents triphenylphosphine, 1 equivalent zinc cyanide, 3 equivalents norbornene and 2 equivalents cesium carbonate. The vial was sealed and flushed with argon. Dimethoxyethane was added to give a final substrate concentration of 0.05M. The resulting solution was then purged with argon for 5 minutes followed by microwave irradiation at 150 °C for 4000 seconds. The pressure noted at this temperature was 5.5 bars. The mixture was then diluted with water and extracted with dichloromethane. The combined organic phases were dried with magnesium sulphate and evaporated under reduced pressure.



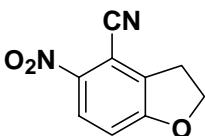
5-Methyl-2,3-dihydro-benzofuran-4-carbonitrile (2): Following the general procedure above on 0.2 mmol of **1**, the crude product was purified by column chromatography using 10% ether in hexanes to give 29.0 mg (91% Yield) of **2** as a white solid, mp= 46-48 °C. Alternatively the sealed vial could be placed in a 150 °C preheated oil bath for 4000 seconds to give 24.5mg (77% yield) of **2**. ¹H NMR (CDCl₃, 400 MHz) δ 7.02 (d, *J*=8.2 Hz, 1H), 6.86 (d, *J*=8.2 Hz, 1H), 4.64 (t, *J*=8.8 Hz, 2H), 3.37 (t, *J*=8.8 Hz, 2H), 2.44 (s, 3H); ¹³C-NMR (CDCl₃, 75 MHz) δ 158.3, 133.1, 131.5, 129.6, 116.6, 113.5, 109.3, 71.5, 29.7, 19.5;; IR (film) 2960, 2224, 1739, 1605, 1480, 1470, 1438, 1144, 1035, 976, 945, 820 cm⁻¹; HRMS-EI (m/z): [M⁺] calcd for C₁₀H₉NO: 159.0684, found 159.0688.



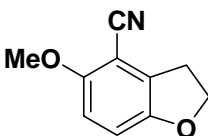
6-Methyl-chroman-5-carbonitrile (4): Following the general procedure above on 0.2 mmol of **3**, the crude product was purified by column chromatography using 10% ether in hexanes to give 27.0 mg (78% Yield) of **4** as a white solid, mp= 34-35 °C. ¹H NMR (CDCl₃, 400 MHz) δ 7.00 (d, *J*=8.4 Hz, 1H), 6.90 (d, *J*=8.4 Hz, 1H), 4.19-4.15 (m, 2H), 2.94 (t, *J*=6.6 Hz, 2H), 2.45 (s, 3H), 2.09-2.02 (m, 2H); ¹³C-NMR (CDCl₃, 100 MHz) δ 153.0, 134.0, 128.6, 125.2, 121.2, 116.7, 113.2, 66.1, 23.9, 21.6, 19.8; IR (film) 2950, 2871, 2219, 1739, 1601, 1485, 1442, 1384, 1365, 1344, 1299, 1257, 1208, 1161, 1089, 1068, 956, 893, 858, 822, 739 cm⁻¹; HRMS-EI (m/z): [M⁺] calcd for C₁₁H₁₁NO: 173.0840, found 173.0842.



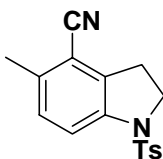
7-Methyl-2,3,4,5-tetrahydro-benzo[b]oxepine-6-carbonitrile (6): Following the general procedure above on 0.2 mmol of **5**, the crude product was purified by column chromatography using 10% ether in hexanes to give 23.0 mg (62% Yield) of **6** as a clear colorless oil. ^1H NMR (CDCl_3 , 400 MHz) δ 7.08 (d, $J=8.2$ Hz, 1H), 7.03 (d, $J=8.2$ Hz, 1H), 4.00-3.96 (m, 2H), 3.1-3.07 (m, 2H), 2.48 (s, 3H), 2.02-1.96 (m, 2H), 1.80-1.73 (m, 2H); ^{13}C -NMR (CDCl_3 , 75 MHz) δ 158.6, 139.2, 137.2, 128.7, 125.7, 117.2, 113.6, 73.8, 32.0, 31.8, 25.3, 20.4; IR (film) 2936, 2869, 2220, 1734, 1609, 1576, 1480, 1383, 1308, 1244, 1174, 1099, 1033, 995, 927, 877, 824 cm^{-1} ; HRMS-EI (m/z): $[\text{M}^+]$ calcd for $\text{C}_{12}\text{H}_{13}\text{NO}$: 187.0997, found 187.0995.



5-Nitro-2,3-dihydro-benzofuran-4-carbonitrile (8): Following the general procedure above on 0.2 mmol of **7**, the crude product was purified by column chromatography using 20% ether in hexanes to give 27.5 mg (73% Yield) of **8** as a yellow solid, mp= 144-145 $^{\circ}\text{C}$. ^1H NMR (CDCl_3 , 400 MHz) δ 8.22 (d, $J=8.9$ Hz, 1H), 7.03 (d, $J=8.9$ Hz, 1H), 5.87 (t, $J=8.8$ Hz, 2H), 3.54 (t, $J=8.8$ Hz, 2H); ^{13}C -NMR (CDCl_3 , 100 MHz) δ 164.9, 141.2, 136.0, 127.8, 113.6, 112.4, 105.9, 73.4, 29.3; IR (film) 2978, 2279, 1586, 1526, 1340, 993, 981, 807 cm^{-1} ; HRMS-EI (m/z): $[\text{M}^+]$ calcd for $\text{C}_9\text{H}_6\text{N}_2\text{O}_3$: 19.0378, found 190.0379.

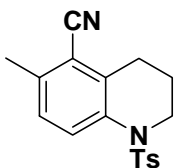


5-Methoxy-2,3-dihydro-benzofuran-4-carbonitrile (10): Following the general procedure above on 0.2 mmol of **9**, the crude product was purified by column chromatography using 10% ether in hexanes to give 29.0 mg (83% Yield) of **10** as a white solid, mp= 131-133 $^{\circ}\text{C}$. ^1H NMR (CDCl_3 , 400 MHz) δ 6.90 (d, $J=8.8$ Hz, 1H), 6.68 (d, $J=8.8$ Hz, 1H), 4.62 (t, $J=8.8$ Hz, 2H), 3.86 (s, 3H), 3.35 (t, $J=8.7$ Hz, 2H); ^{13}C -NMR (CDCl_3 , 100 MHz) δ 155.5, 154.0, 132.6, 115.0, 113.9, 110.5, 98.7, 71.5, 56.6, 29.9; IR (film) 2959, 2229, 1603, 1481, 1464, 1437, 1420, 1319, 1238, 1074, 993, 982, 810 cm^{-1} ; HRMS-EI (m/z): $[\text{M}^+]$ calcd for $\text{C}_{10}\text{H}_9\text{NO}_2$: 175.0633, found 175.0633.



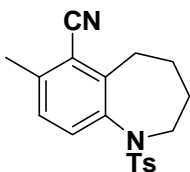
5-Methyl-1-(toluene-4-sulfonyl)-2,3-dihydro-1H-indole-4-carbonitrile (12):

Following the general procedure above on 0.2 mmol of **11a**, the crude product was purified by column chromatography using 30% ether in hexanes to give 49.0 mg (79% Yield) and, 36.0 mg (57% yield) utilizing aryl bromide **11b**, of **12** as a white solid, mp=196-197 °C. ¹H NMR (CDCl₃, 400 MHz) δ 7.73 (d, *J*=8.4 Hz, 1H), 7.64 (d, *J*=8.4 Hz, 2H), 7.25 (d, *J*=8.3 Hz, 2H), 7.13 (d, *J*=8.5 Hz, 1H), 3.97 (t, *J*=8.5 Hz, 2H), 3.03 (t, *J*=8.5 Hz, 2H), 2.45 (s, 3H), 2.39 (s, 3H); ¹³C-NMR (CDCl₃, 100 MHz) δ 144.6, 140.7, 136.6, 136.3, 133.4, 129.8, 129.5, 127.2, 118.7, 116.0, 109.8, 49.7, 27.8, 21.5, 19.7; IR (thin film) 2956, 2224, 1597, 1472, 1357, 1168, 1092, 813, 673 cm⁻¹; HRMS-EI (*m/z*): [*M*⁺] calcd for C₁₇H₁₆N₂O₂S: 312.0932, found 312.0928.



6-Methyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydroquinoline-5-carbonitrile (14):

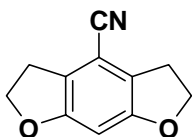
Following the general procedure above on 0.2 mmol of **13a**, the crude product was purified by column chromatography using 30% ether in hexanes to give 51.0 mg (78 % Yield) and, 36.0 (55% yield) utilizing aryl bromide **13b**, of **14** as a white solid, mp= 172-173°C. ¹H NMR (CDCl₃, 400 MHz) δ 7.94 (d, *J*=8.6 Hz, 1H), 7.45 (d, *J*=8.3 Hz, 2H), 7.22 (d, *J*=8.0 Hz, 2H), 7.14 (d, *J*=8.6 Hz, 1H), 3.78-3.75 (m, 2H), 2.65 (t, *J*=6.8 Hz, 2H), 2.50 (s, 3H), 2.40 (s, 3H), 1.64-1.58 (m, 2H); ¹³C-NMR (CDCl₃, 100 MHz) δ 144.0, 139.1, 136.2, 135.4, 133.7, 129.8, 129.3, 128.0, 127.0, 116.3, 113.1, 45.8, 25.6, 21.5, 20.3, 20.2; IR (film) 2952, 2941, 2221, 1736, 1597, 1479, 1450, 1352, 1305, 1163, 1089, 999, 863, 814, 783, 736, 695, 665 cm⁻¹; HRMS-EI (*m/z*): [*M*⁺] calcd for C₁₈H₁₈N₂O₂S: 326.1089, found 326.1089.



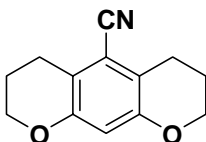
7-Methyl-1-(toluene-4-sulfonyl)-2,3,4,5-tetrahydro-1H-benzo[b]azepine-6-carbonitrile (16):

Following the general procedure above on 0.2 mmol of **15a**, the crude product was purified by column chromatography using 30% ether in hexanes to give 45.5 mg (67% Yield) and, 32.0mg (47% yield) utilizing aryl bromide **15b**, of **16** as a clear, colorless oil. ¹H NMR (CDCl₃, 500 MHz, 45 °C) δ 7.63 (d, *J*=8.0 Hz, 1H), 7.47 (d, *J*=8.1 Hz, 2H), 7.31 (d, *J*=9.6 Hz, 2H), 7.16 (d, *J*=8.1 Hz, 1H), 3.70 (br s, 2H), 2.69 (br

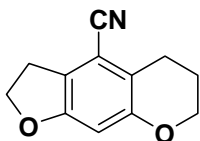
s, 2H), 2.57 (s, 3H), 2.47 (s, 3H), 1.81 (br s, 2H), 1.62 (br s, 2H); ^{13}C -NMR (CDCl_3 , 75 MHz) δ 145.4, 143.8, 142.3, 138.7, 138.5, 134.0, 130.0, 128.8, 127.2, 116.9, 113.9, 50.6, 31.6, 29.0, 24.7, 21.7, 21.1; IR (film) 3423, 3029, 2926, 2857, 2220, 1918, 1738, 1597, 1493, 1479, 1446, 1401, 1366, 1346, 1304, 1264, 1249, 1232, 1158, 1094, 1066, 1042, 989, 949, 815802, 786, 760, 707, 685, 644, 620 cm^{-1} ; HRMS-EI (m/z): $[\text{M}^+]$ calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$: 340.1245, found 340.1246.



2,3,5,6-Tetrahydro-benzo[1,2-b;5,4-b']difuran-4-carbonitrile (18): Following the general procedure above on 0.2 mmol of **17**, the crude product was purified by column chromatography using 10% ether in hexanes to give 30.5 mg (88% Yield) of **18** as a white solid, mp=173-175 $^{\circ}\text{C}$. ^1H NMR (300 MHz, CDCl_3) δ 6.44 (s, 1H), 4.65 (t, 4H, J = 8.8 Hz), 3.27 (t, 4H, J = 8.8 Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 161.2, 122.4, 116.3, 104.8, 97.5, 72.6, 29.1; IR (film) 2221, 1609, 1477, 1438, 1168, 1069 cm^{-1} ; HRMS-EI (m/z): $[\text{M}^+]$ calcd for $\text{C}_{11}\text{H}_9\text{NO}_2$: 187.0641, found 187.0633.

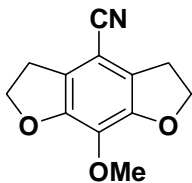


3,4,7,8-Tetrahydro-2H,6H-pyrano[3,2-g]chromene-5-carbonitrile (20): Following the general procedure above on 0.2 mmol of **19**, the crude product was purified by column chromatography using 10% ether in hexanes to give 32.0 mg (75% Yield) of **20** as a white solid, mp= 149-150 $^{\circ}\text{C}$. ^1H NMR (CDCl_3 , 400 MHz) δ 6.48 (s, 1H), 4.16-4.13 (m, 4H), 2.87 (t, J =6.6 Hz, 4H), 2.06-1.99 (m, 4H); ^{13}C -NMR (CDCl_3 , 100 MHz) δ 154.0, 118.6, 116.1, 112.9, 109.2, 66.3, 23.3, 21.7; IR (film) 2980, 2221, 1611, 1477, 1465, 1420, 1301, 1143, 958 cm^{-1} ; HRMS-EI (m/z): $[\text{M}^+]$ calcd for $\text{C}_{13}\text{H}_{13}\text{NO}_2$: 215.0946, found 215.0951.



2,3,6,7-Tetrahydro-5H-furo[3,2-g]chromene-4-carbonitrile (22): Following the general procedure above on 0.13 mmol of **21**, the crude product was purified by column chromatography using 10% ether in hexanes to give 14.5 mg (56% Yield) of **22** as a white solid, mp= 133-135 $^{\circ}\text{C}$. ^1H NMR (CDCl_3 , 400 MHz) δ 6.46 (s, 1H), 4.61 (t, J =8.6 Hz, 2H), 4.17-4.14 (m, 2H), 3.29 (t, J =8.7 Hz, 2H), 2.86 (t, J =6.5 Hz, 2H), 2.05-1.99 (m, 2H); ^{13}C -NMR (CDCl_3 , 100 MHz) δ 159.3, 155.3, 124.0, 116.6, 116.2, 108.7, 103.0,

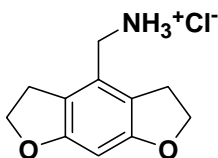
71.8, 66.4, 29.0, 23.3, 21.6; IR (film) 2979, 2223, 1734, 1615, 1474, 1460, 1442, 1395, 1361, 1339, 1320, 1230, 1192, 1167, 1118, 1082, 982, 945, 855 cm^{-1} ; HRMS-EI (m/z): [M^+] calcd for $\text{C}_{12}\text{H}_{11}\text{NO}_2$: 201.0789, found 201.0789.



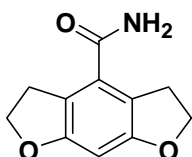
8-Methoxy-2,3,5,6-tetrahydro-benzo[1,2-b;5,4-b']difuran-4-carbonitrile (24):

Following the general procedure above on 0.2 mmol of **23**, the crude product was purified by column chromatography using 10% ether in hexanes to give 32.0 mg (74 % Yield) of **24** as a white solid, mp= 160-161 $^{\circ}\text{C}$. ^1H NMR (CDCl_3 , 400 MHz) δ 4.68 (t, $J=8.8$ Hz, 4H), 4.05 (s, 3H), 3.29 (t, $J=8.8$ Hz, 4H); ^{13}C -NMR (CDCl_3 , 100 MHz) δ 150.4, 133.8, 124.7, 116.3, 97.2, 72.8, 60.2, 29.4; IR (film) 2964, 2218, 1734, 1718, 1610, 1584, 1502, 1473, 1458, 1447, 1424, 1387, 1345, 1263, 1192, 1131, 1064, 1015, 999, 982, 895, 878, 747, 702 cm^{-1} ; HRMS-ESI (m/z): [M^+] calcd for $[\text{C}_{12}\text{H}_{12}\text{NO}_3]^+$: 218.0811, found 218.0819.

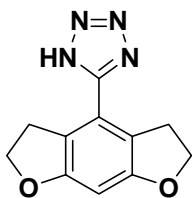
Modification of Benzonitrile Products



2,3,5,6-Tetrahydro-benzo[1,2-b;5,4-b']difuran-4-ylmethyl-ammonium; chloride (25): To a solution of **18** (56.1 mg, 0.3 mmol) in 6ml anhydrous THF at 0 °C under nitrogen was added LiAlH₄ (34.2 mg, 0.3 mmol). The reaction was warmed to room temperature and stirred for 6 hours. Solid sodium potassium tartrate (100 mg) was added followed by 5 ml of a saturated sodium potassium tartrate solution and stirring continued for 1 hour. The resulting solution was extracted with ether. The organic phase was washed with water and brine and then dried over magnesium sulfate. The clear solution was then concentrated under reduced pressure and the redissolved in anhydrous ether. To this clear solution was added a 1M solution of hydrogen chloride in ether (1 ml). The precipitate formed was filter and washed with anhydrous ether to give 64 mg (94% yield) of **25** as a pale yellow solid, decomposition 230 °C. ¹H NMR (D₂O, 300 MHz) δ 6.38 (s, 1H), 4.65 (t, *J*=8.6 Hz, 4H), 4.11 (br s, 2H), 3.20 (t, *J*=8.6 Hz, 4H); ¹³C-NMR (D₂O, 75 MHz) δ 159.7, 125.1, 119.5, 93.4, 72.7, 38.7, 27.1 ; IR (film) 2908, 2366, 2096, 1605, 1458, 1448, 1387, 1319, 1257, 1213, 1175, 1062, 981, 938, 833 cm⁻¹; HRMS-EI (m/z): [M⁺] calcd for [C₁₁H₁₄NO₂]⁺: 191.0946, found 196.0949.



2,3,5,6-Tetrahydro-benzo[1,2-b;5,4-b']difuran-4-carboxylic acid amide (26): To a solution of **18** (37.4 mg, 0.2mmol) in 95% ethanol was added a 5M solution of sodium hydroxide (16 uL, 0.12 mmol) and hydrogen peroxide (100 uL, 1.5 mmol) and stirred for 8 hours at 60 °C. The resulting solution was concentrated under reduced pressure to give a off white solid which was washed with water and dried under reduced pressure to give 31.5 mg (77% yield) of **26**, decomposition 217 °C. ¹H NMR (DMSO, 400 MHz) δ 7.46 (br s, 1H), 7.42 (br s, 1H), 6.30 (s, 1H), 4.50 (t, *J*=8.7 Hz, 4H), 3.16 (t, *J*=8.7 Hz, 4H); ¹³C-NMR (DMSO, 100 MHz) δ 168.4, 159.9, 129.8, 116.3, 93.1, 71.6, 28.4; IR (film) 3361, 2958, 2934, 2254, 2127, 1653, 1587, 1472, 1450, 1412, 1368, 1312, 1263, 1156, 1124, 1083, 1025, 1008, 951, 824, 763 cm⁻¹; HRMS-EI (m/z): [M⁺] calcd for C₁₁H₁₂NO₃: 206.0811, found 206.0814.

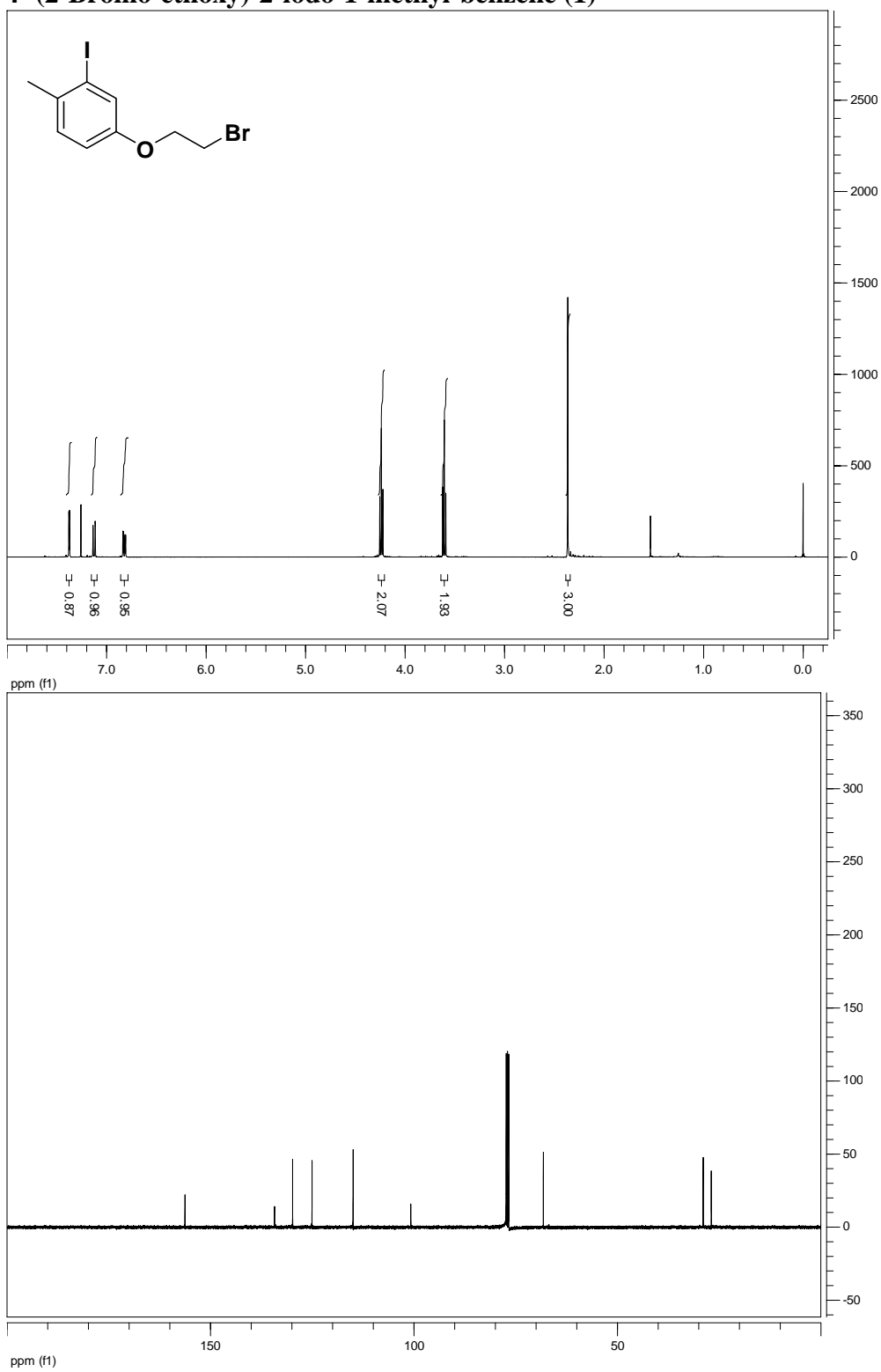


5-(2,3,5,6-Tetrahydro-benzo[1,2-b;5,4-b']difuran-4-yl)-1H-tetrazole (27): To a microwave vial with magnetic stir bar was added **18** (37.4 mg 0.2 mmol) was added sodium azide (156 mg, 2.4mmol) and ammonium chloride (128mg,2.4 mmol). The vial was sealed and 2 ml of anhydrous DMF was added. The vial was purged with nitrogen for 5 minutes and irradiated for 25 minutes at 220 °C. The resulting solution was extracted with chloroform, washed with water and brine and concentrated under reduced pressure. The crude product was purified by preparatory TLC using ethyl acetate to give 16.0 mg (35% yield) of **27** as a off-white solid, mp= 114-115 °C. ¹H NMR (CDCl₃, 400 MHz) δ 6.45 (s, 1H), 4.67 (t, *J*=8.7 Hz, 4H), 3.50 (t, *J*=8.7 Hz, 4H), 1.26 (s,1H) (CDCl₃, 100 MHz) δ 161.3, 117.8, 94.9, 77.2, 72.3, 30.5, 29.7; IR (film) 3449, 2981, 2972, 2252, 1792, 1700, 1609, 1545, 1482, 1458, 1382, 1317, 1297, 1263, 1163, 1095, 1069, 1042, 990, 729, 685 cm⁻¹; HRMS-EI (m/z): [M⁺] calcd for [C₁₁H₁₁N₄O₂]⁺: 231.0876, found 231.0874.

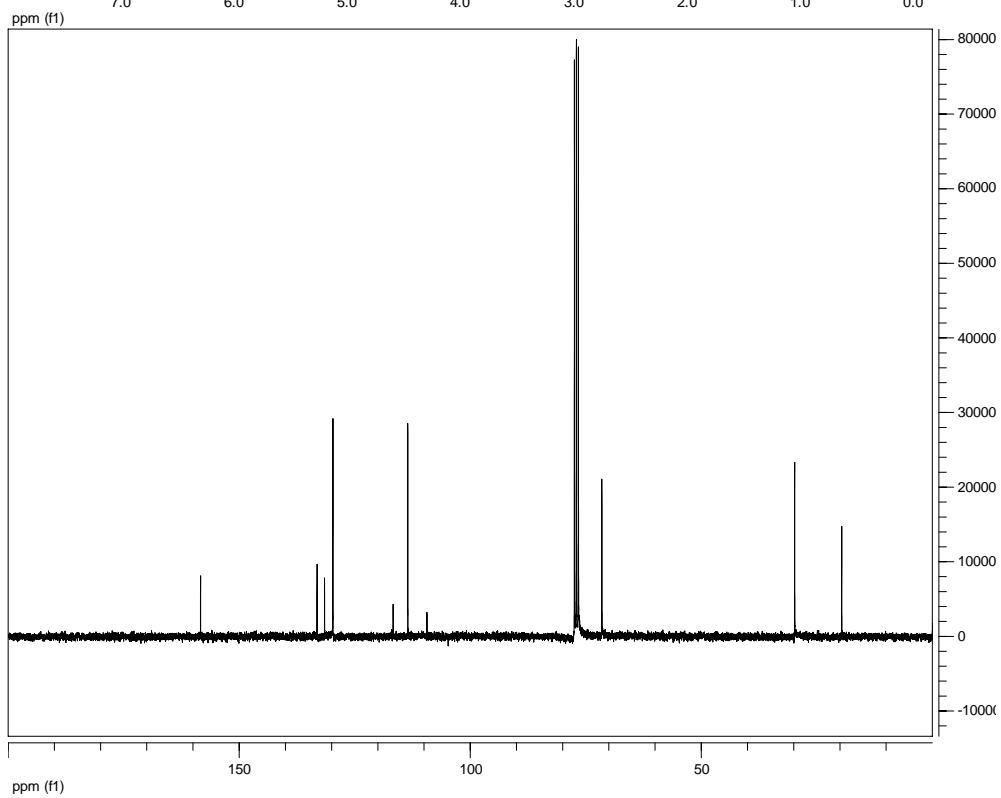
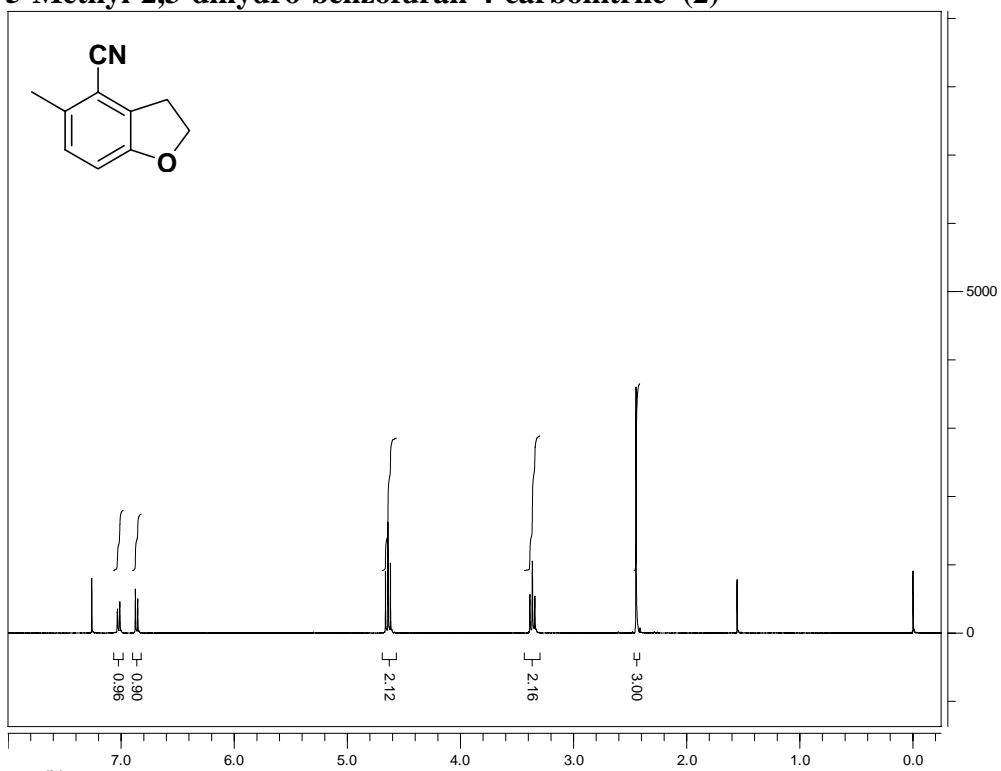
Spectral Data

(In numerical order)

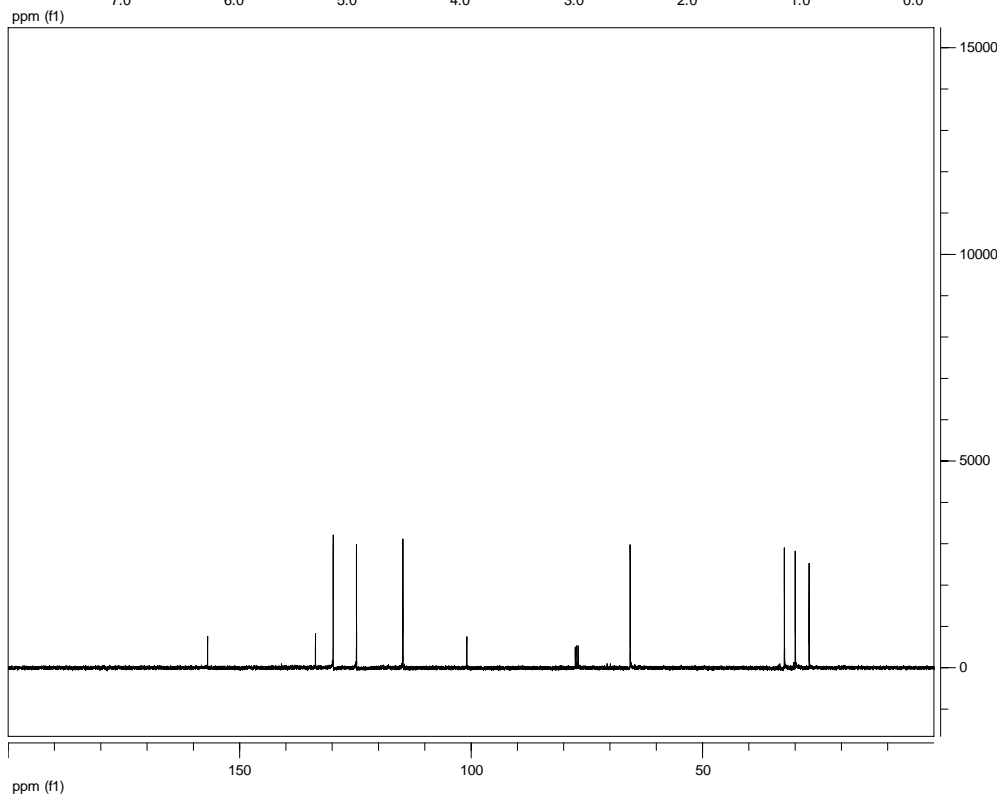
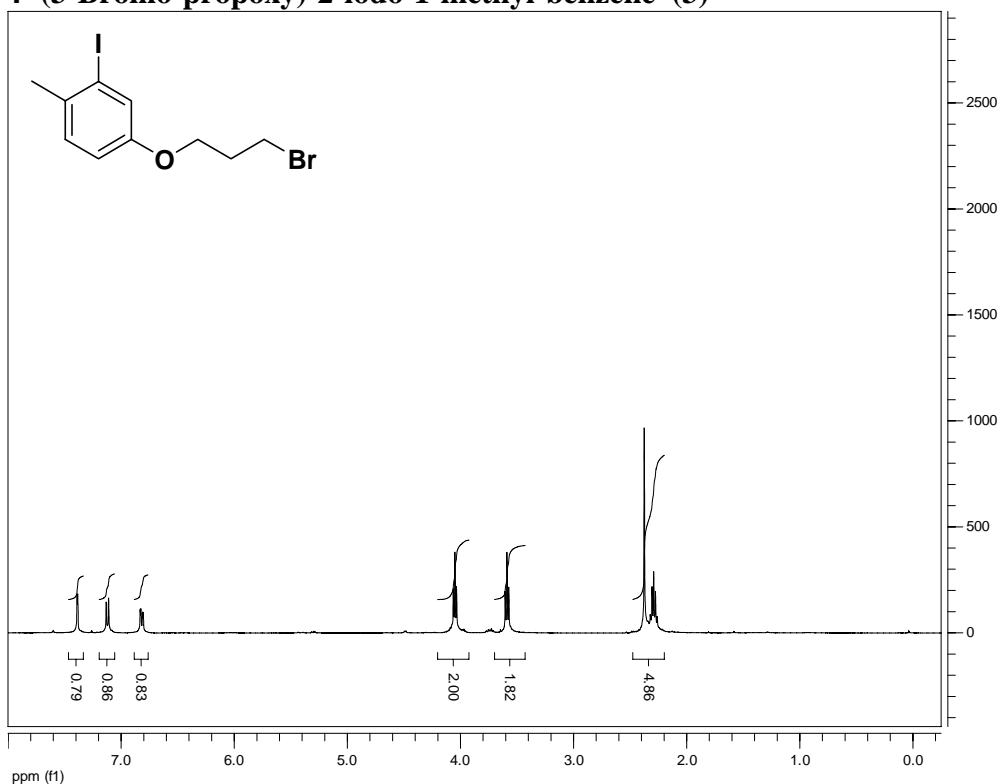
4- (2-Bromo-ethoxy)-2-iodo-1-methyl-benzene (1)



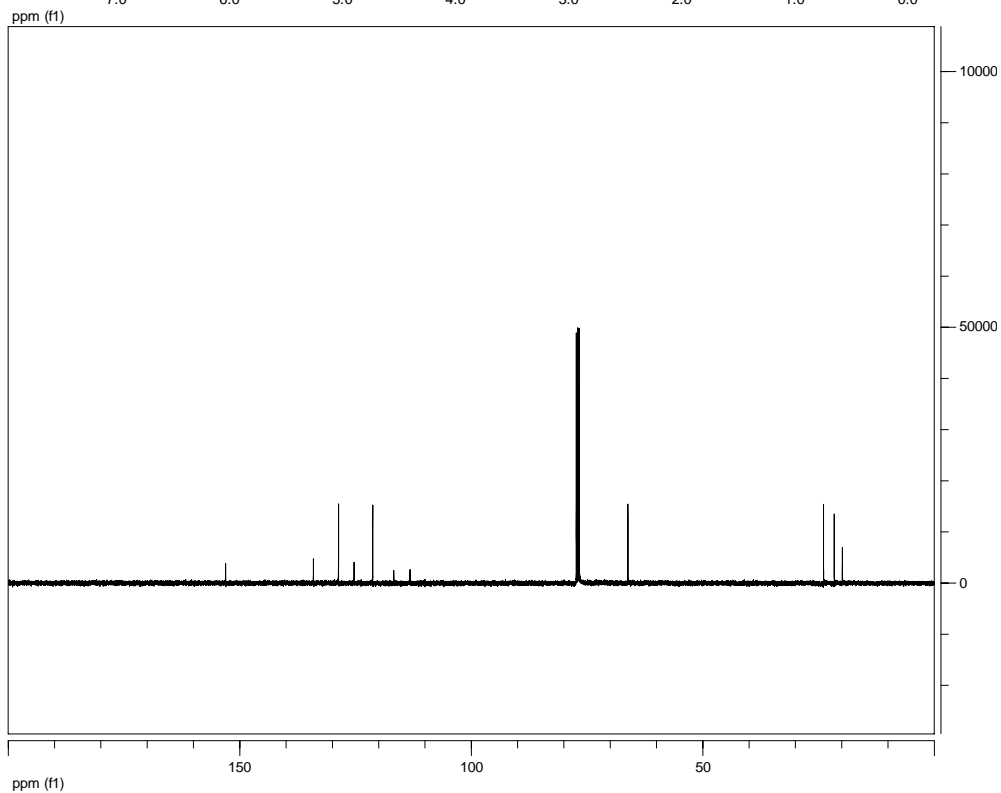
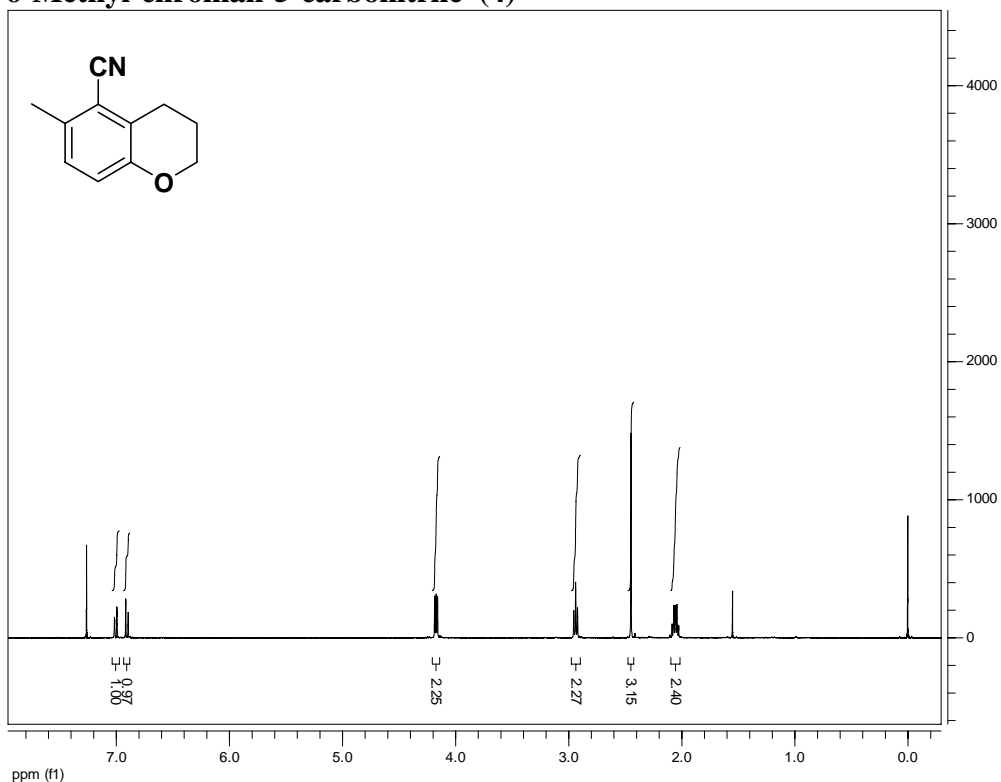
5-Methyl-2,3-dihydro-benzofuran-4-carbonitrile (2)



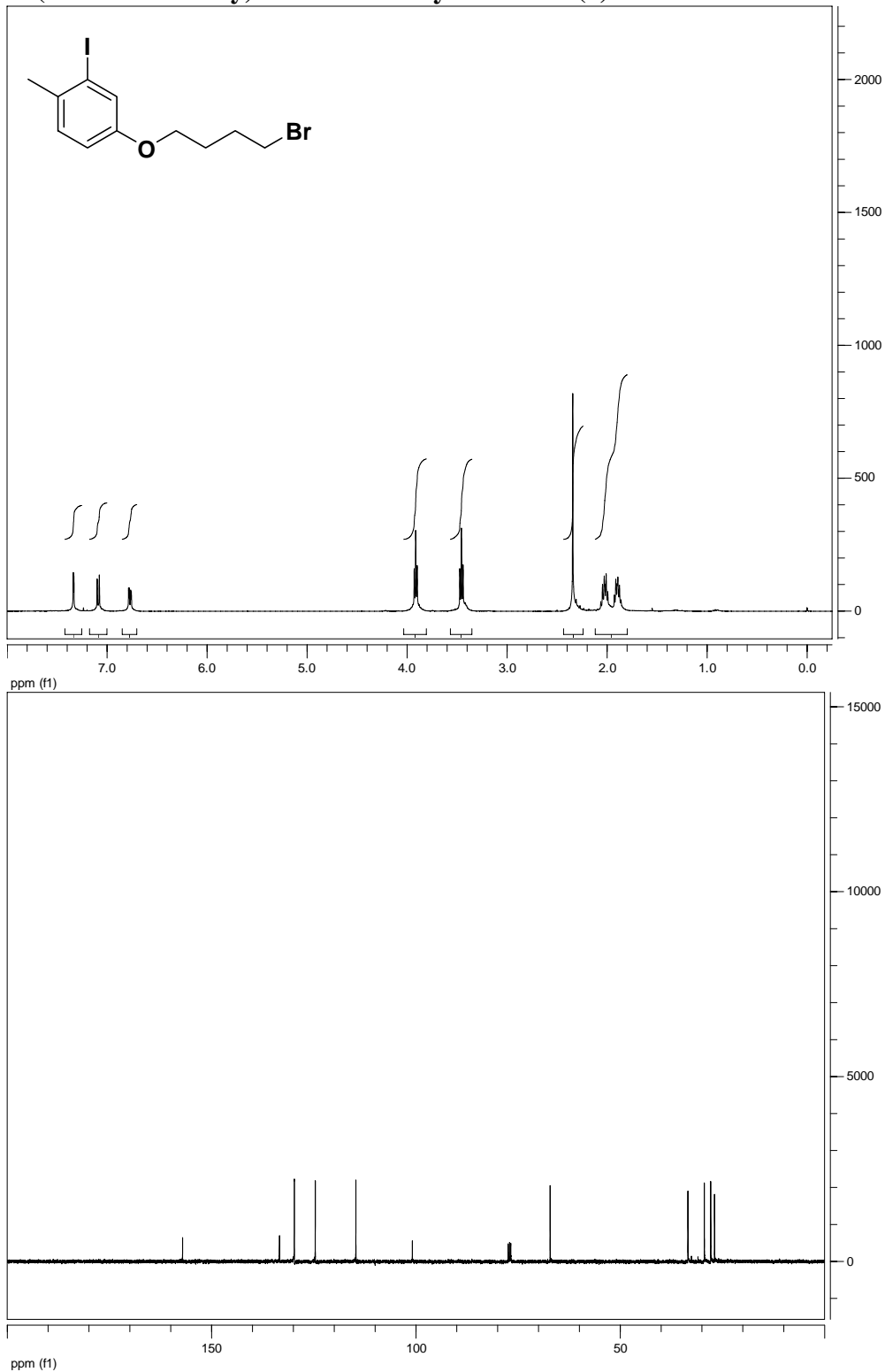
4- (3-Bromo-propoxy)-2-iodo-1-methyl-benzene (3)



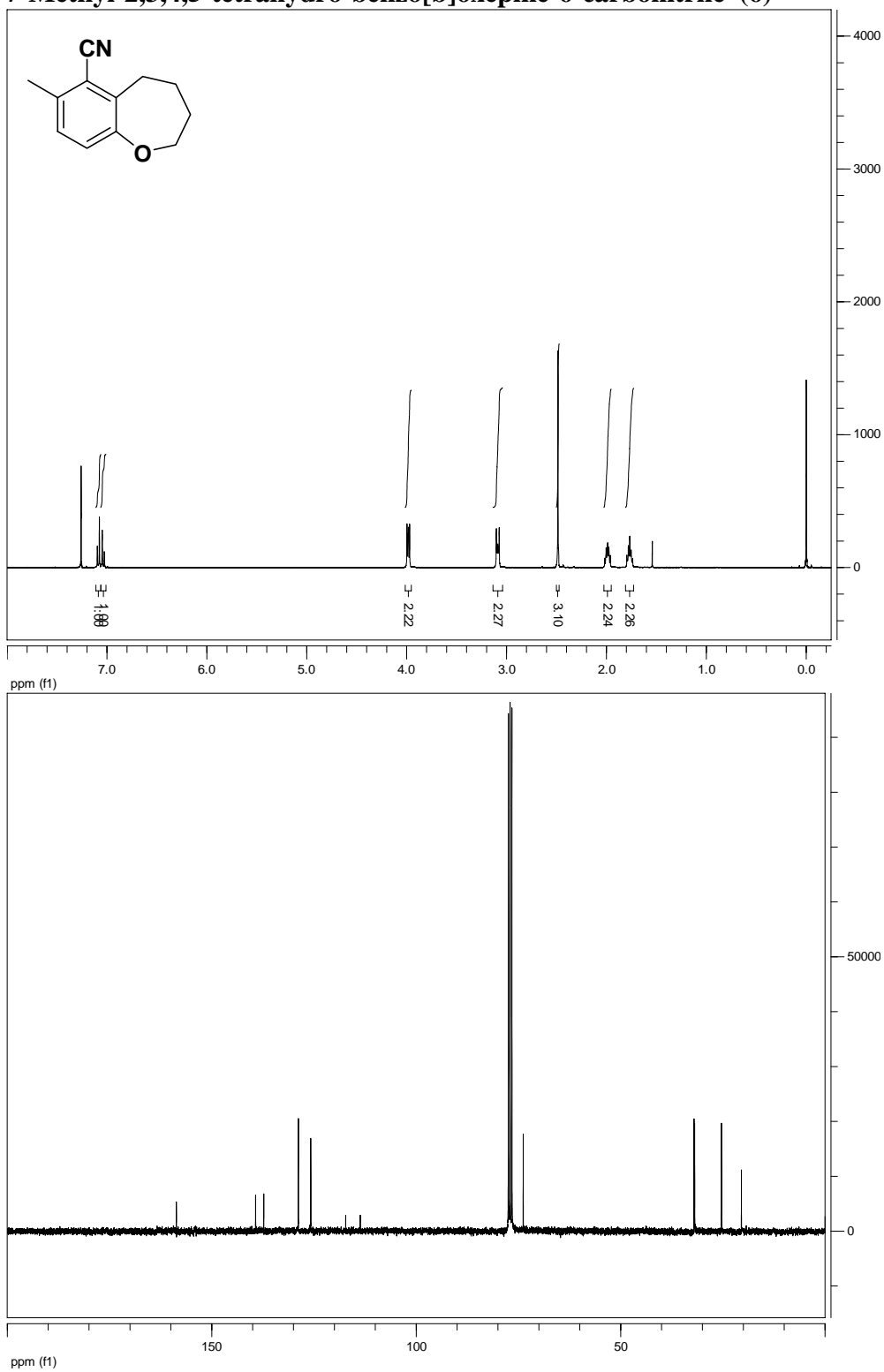
6-Methyl-chroman-5-carbonitrile (4)



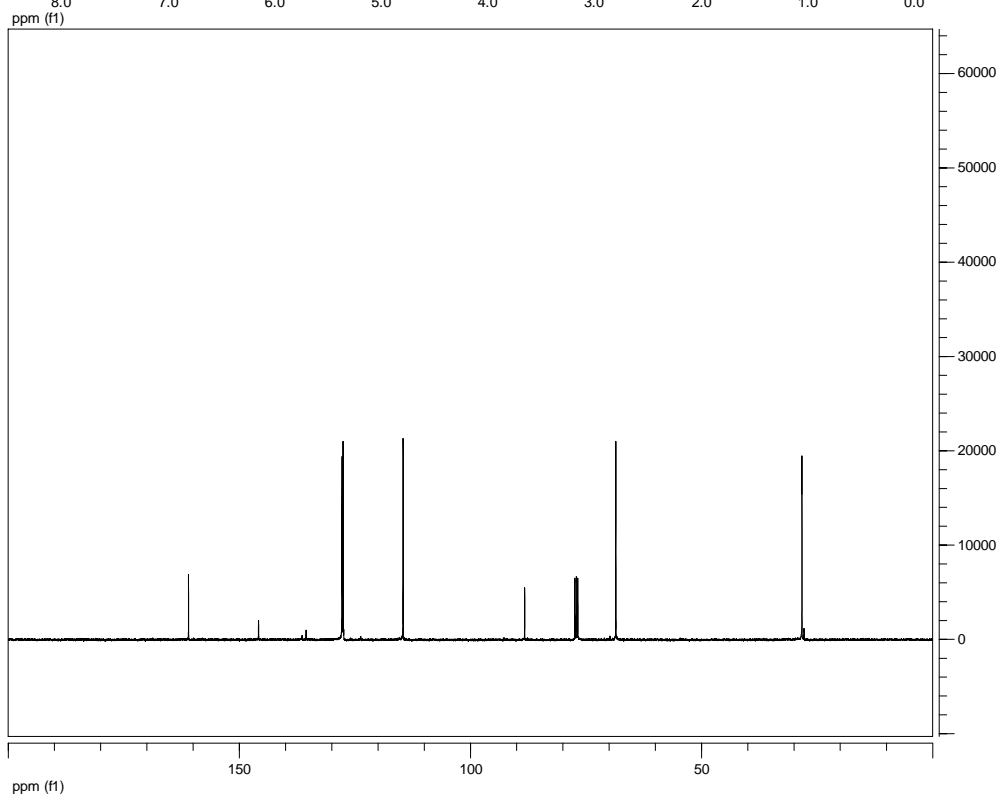
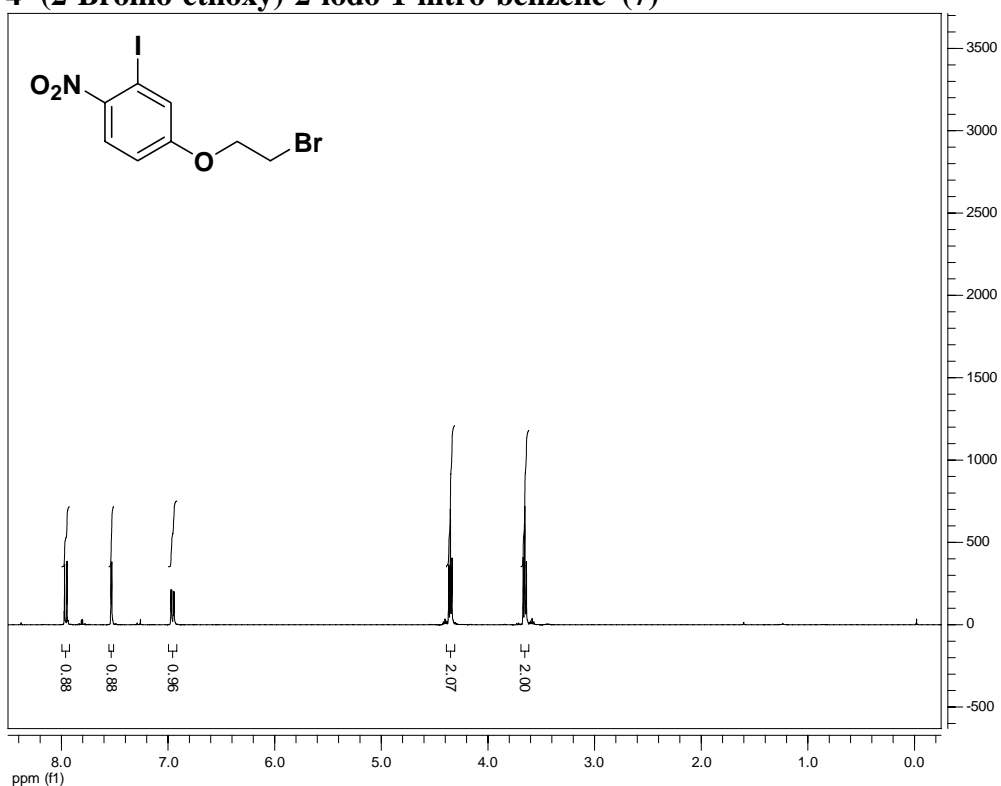
4- (4-Bromo-butoxy)-2-iodo-1-methyl-benzene (5)



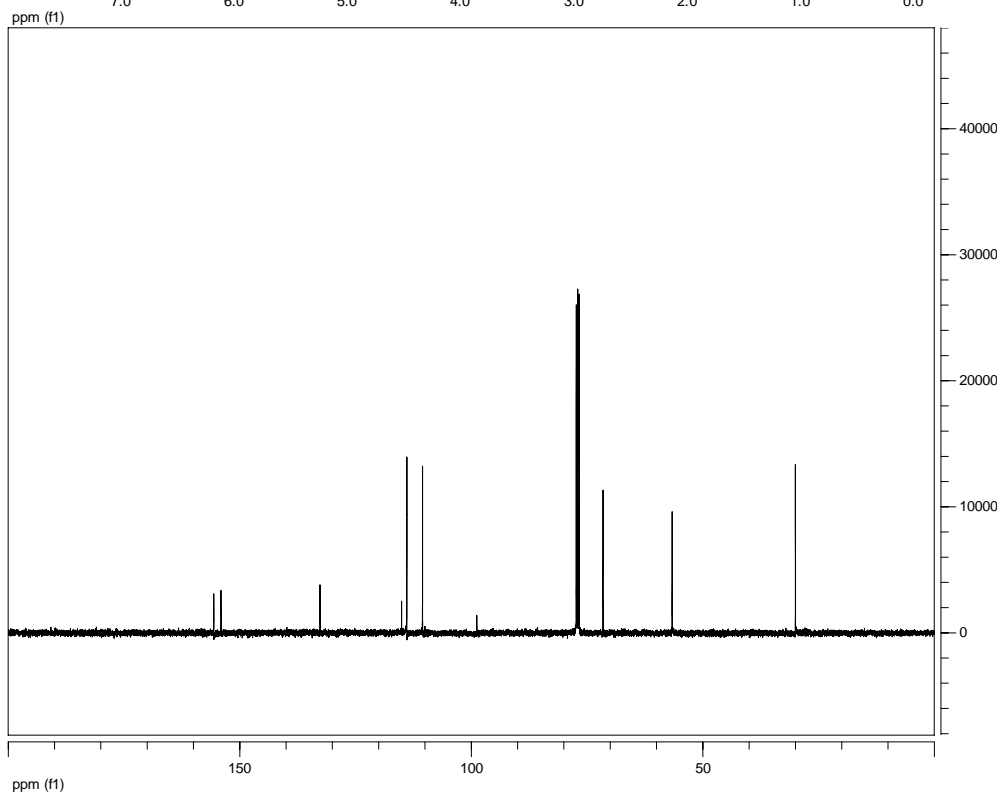
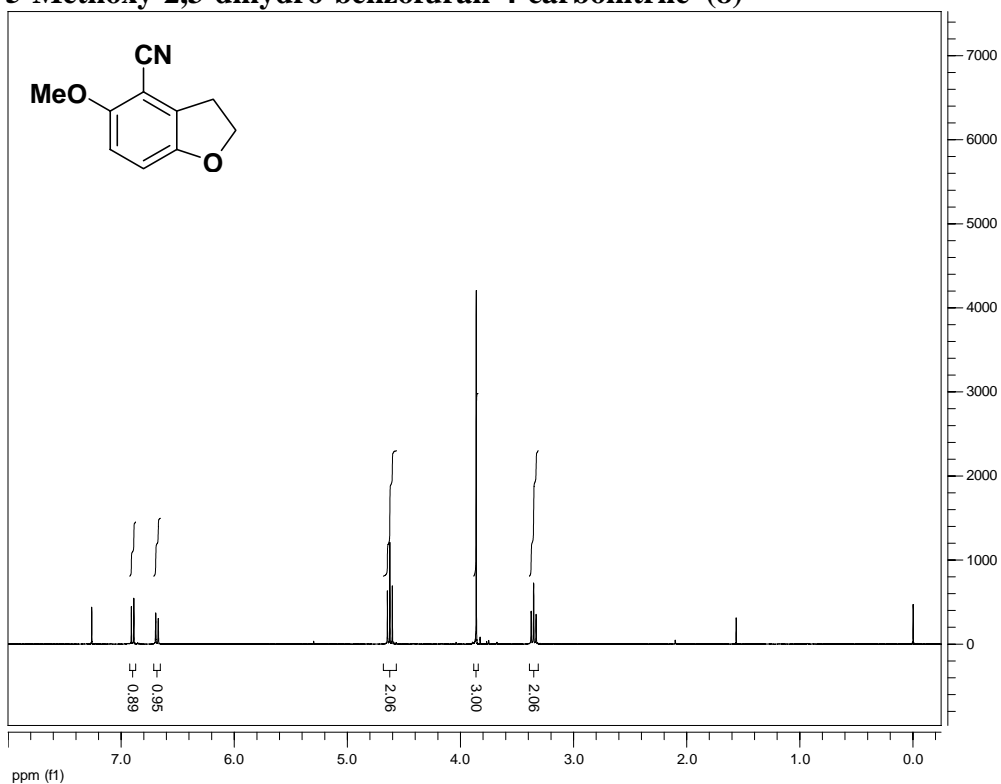
7-Methyl-2,3,4,5-tetrahydro-benzo[b]oxepine-6-carbonitrile (6)



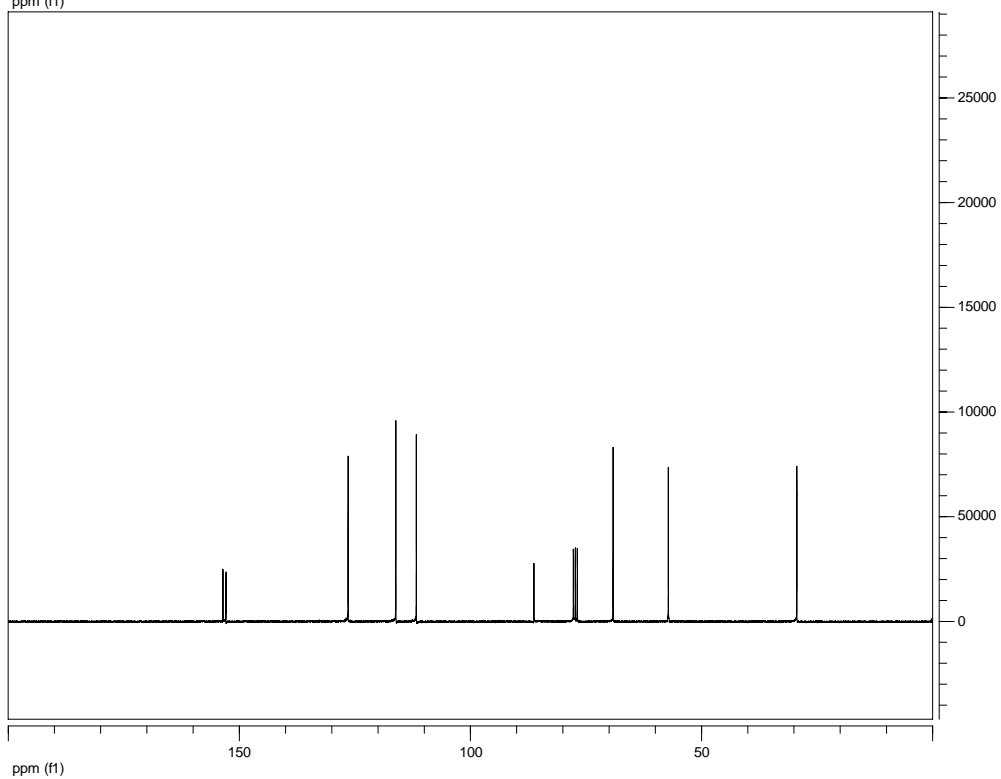
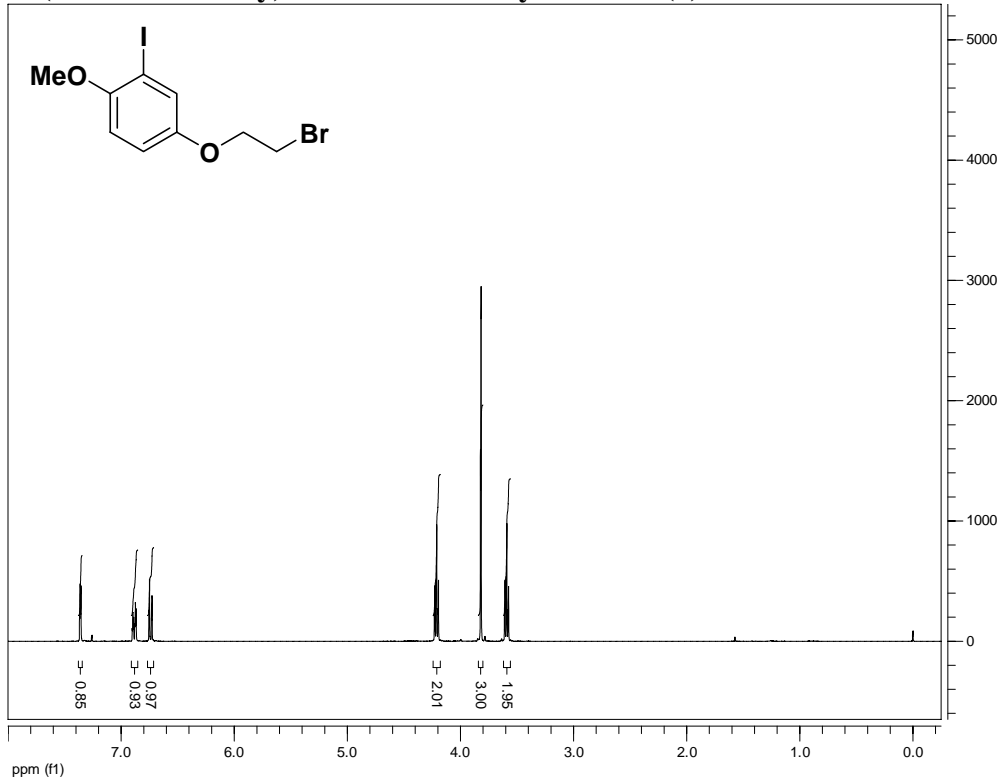
4- (2-Bromo-ethoxy)-2-iodo-1-nitro-benzene (7)



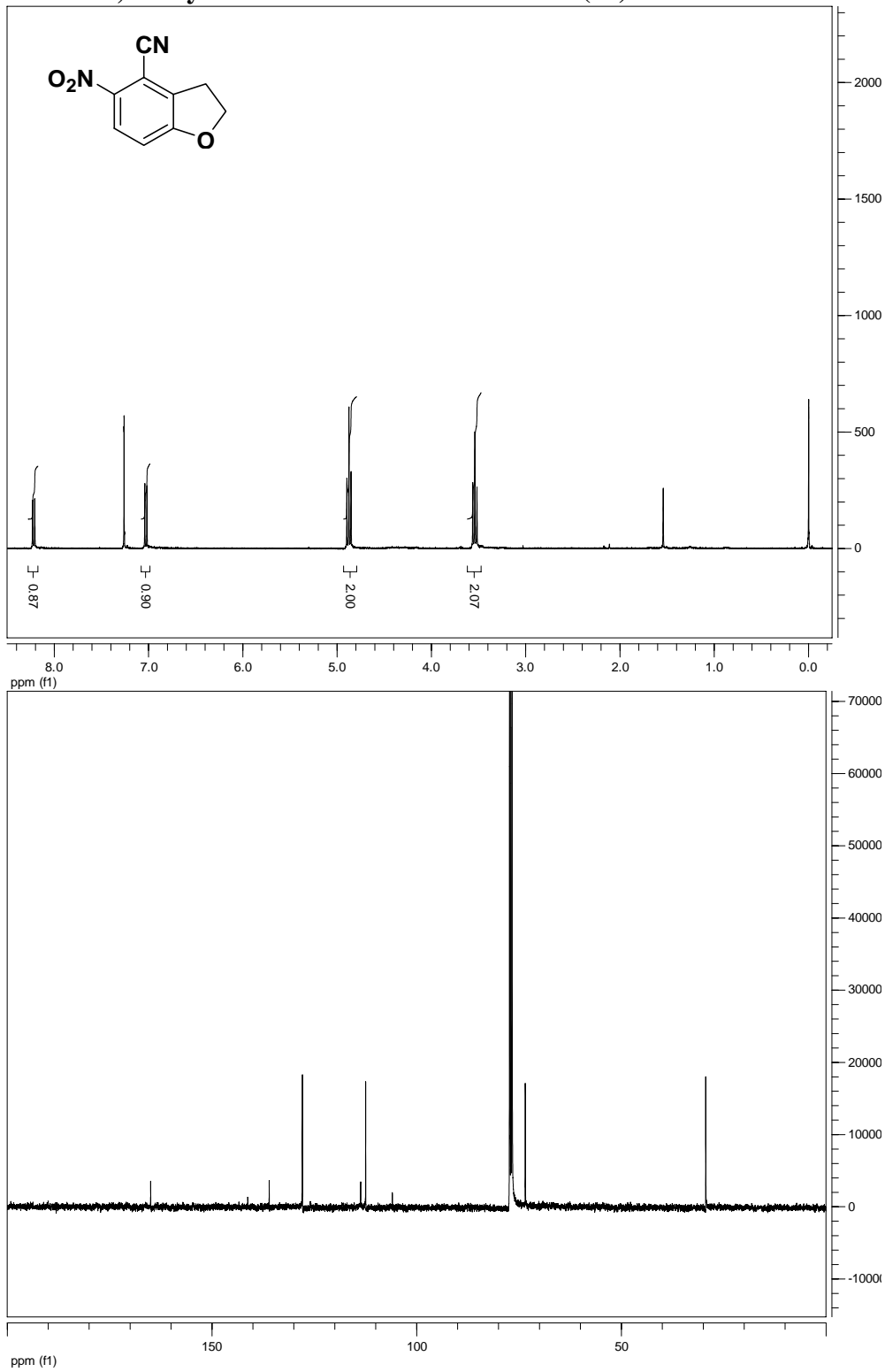
5-Methoxy-2,3-dihydro-benzofuran-4-carbonitrile (8)



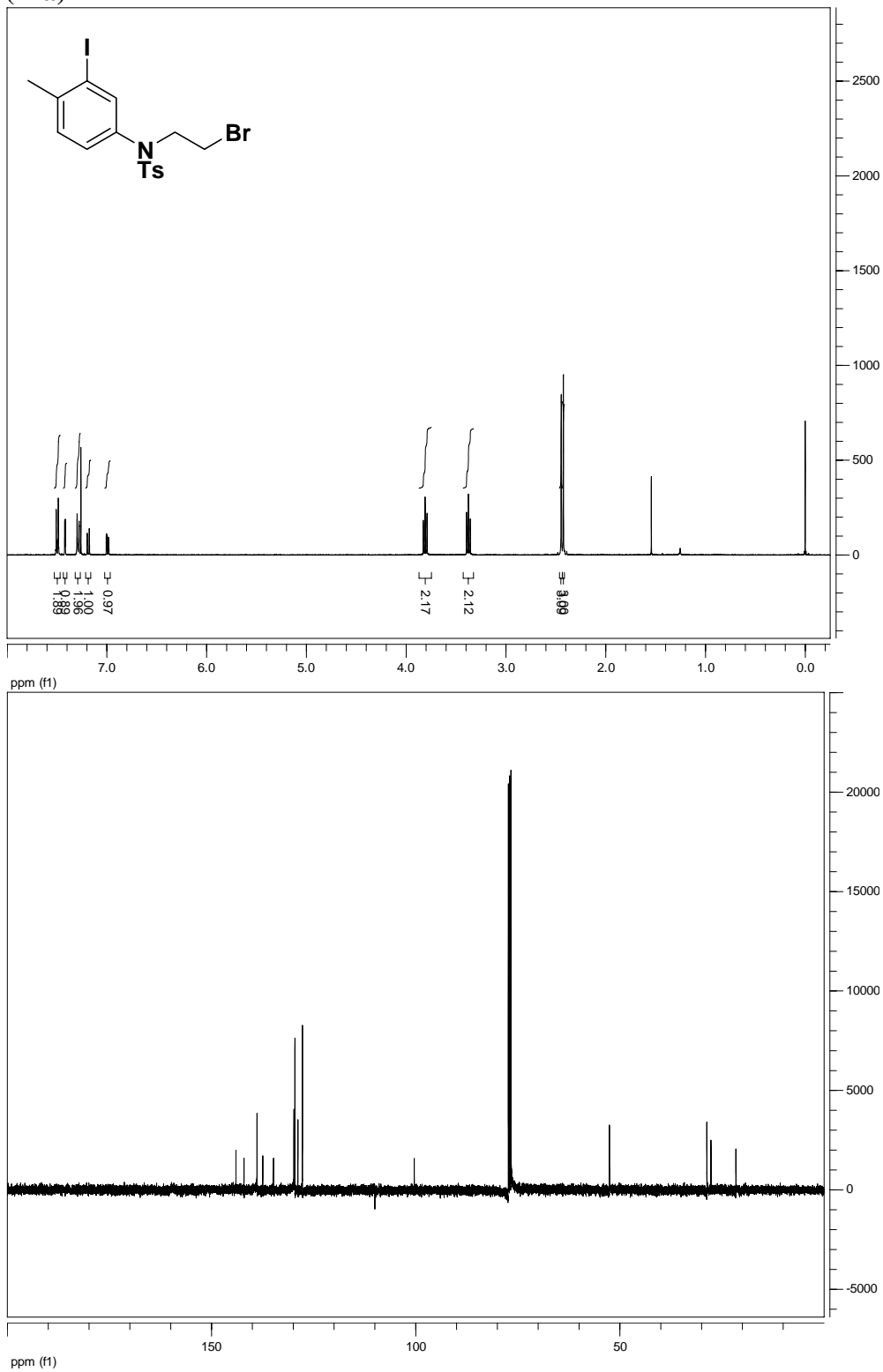
4- (2-Bromo-ethoxy)-2-iodo-1-methoxy-benzene (9)



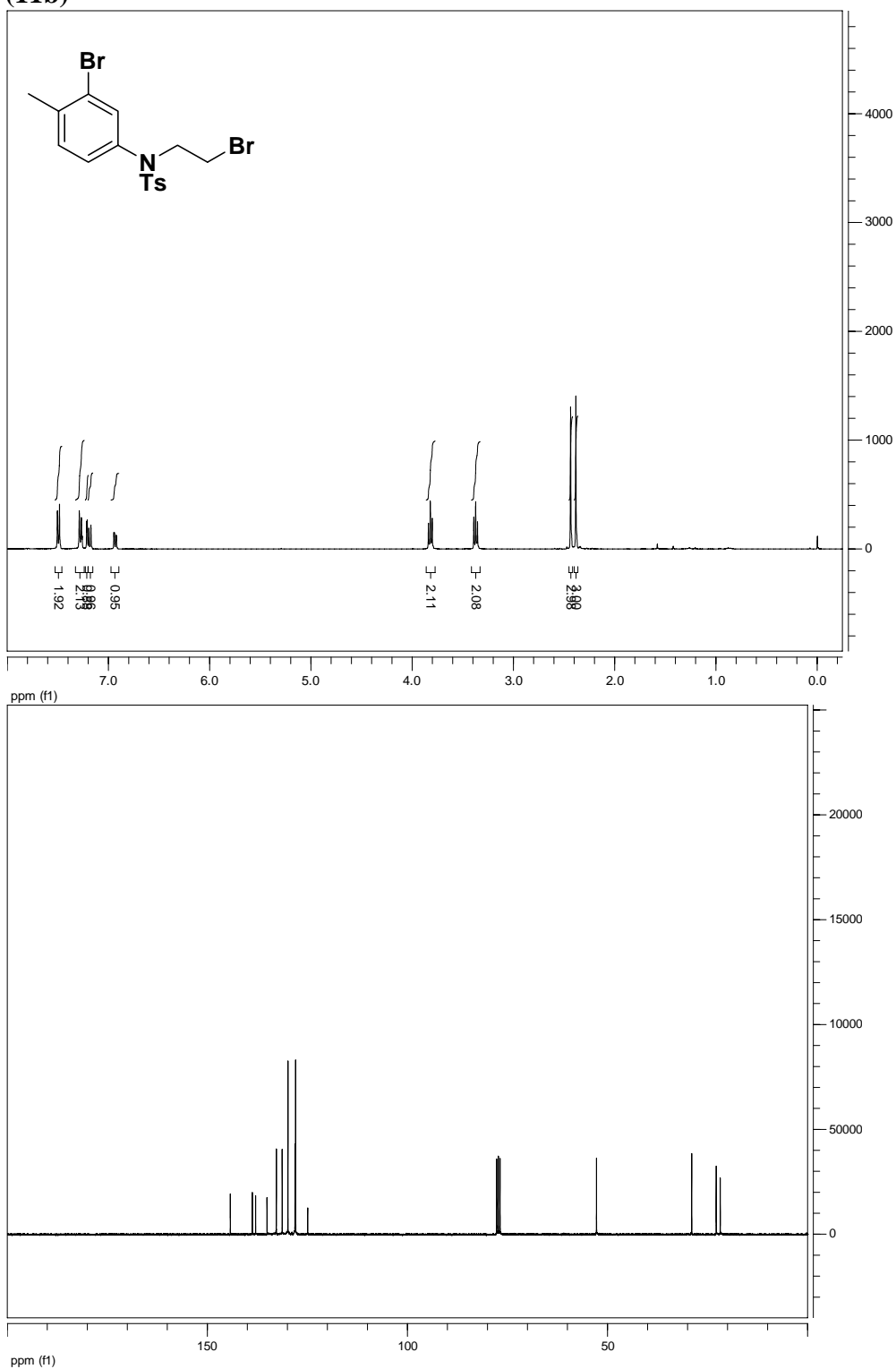
5-Nitro-2,3-dihydro-benzofuran-4-carbonitrile (10)



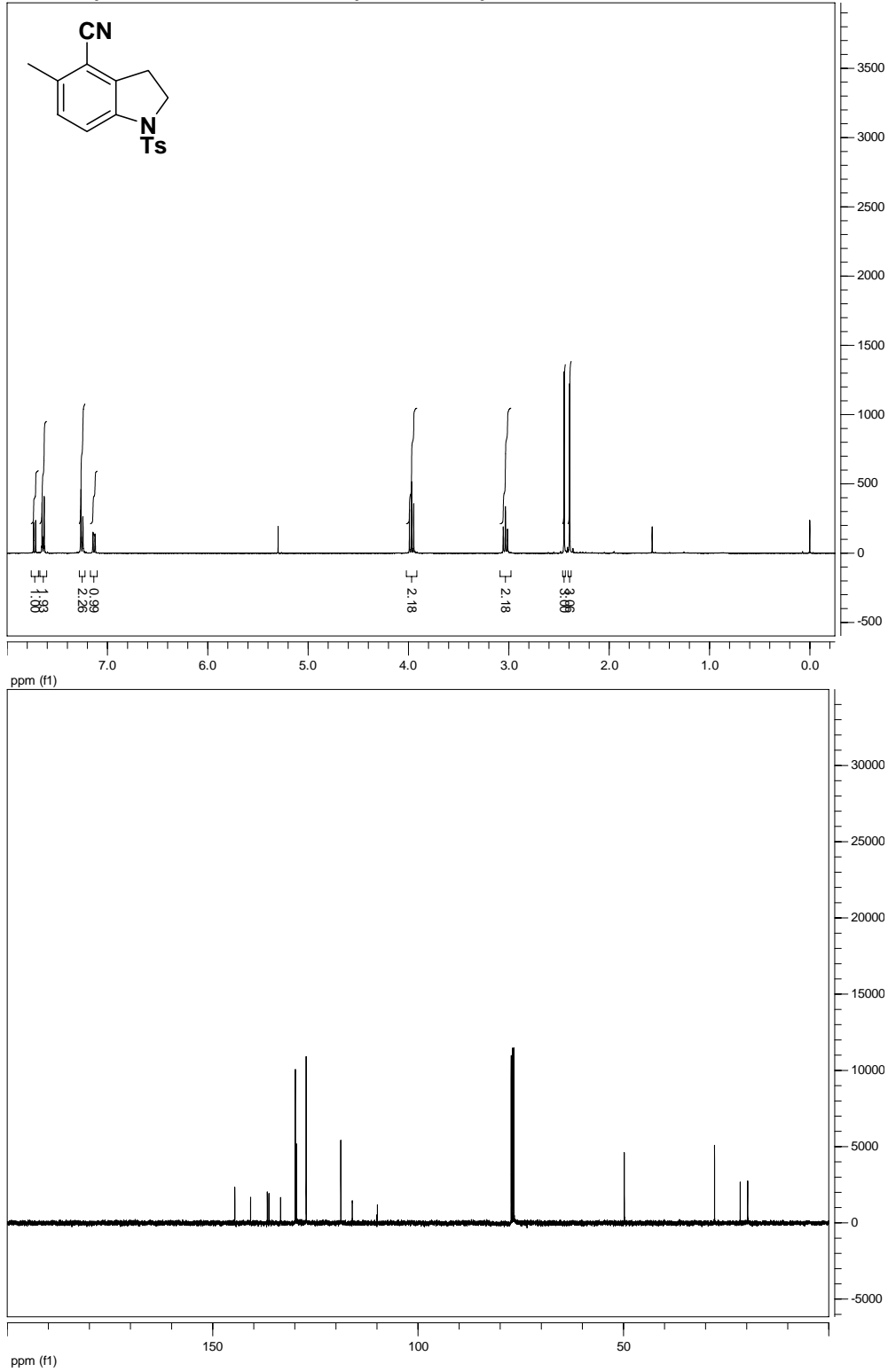
***N*-(2-Bromo-ethyl)-*N*-(3-iodo-4-methyl-phenyl)-4-methyl-benzenesulfonamide (11a)**



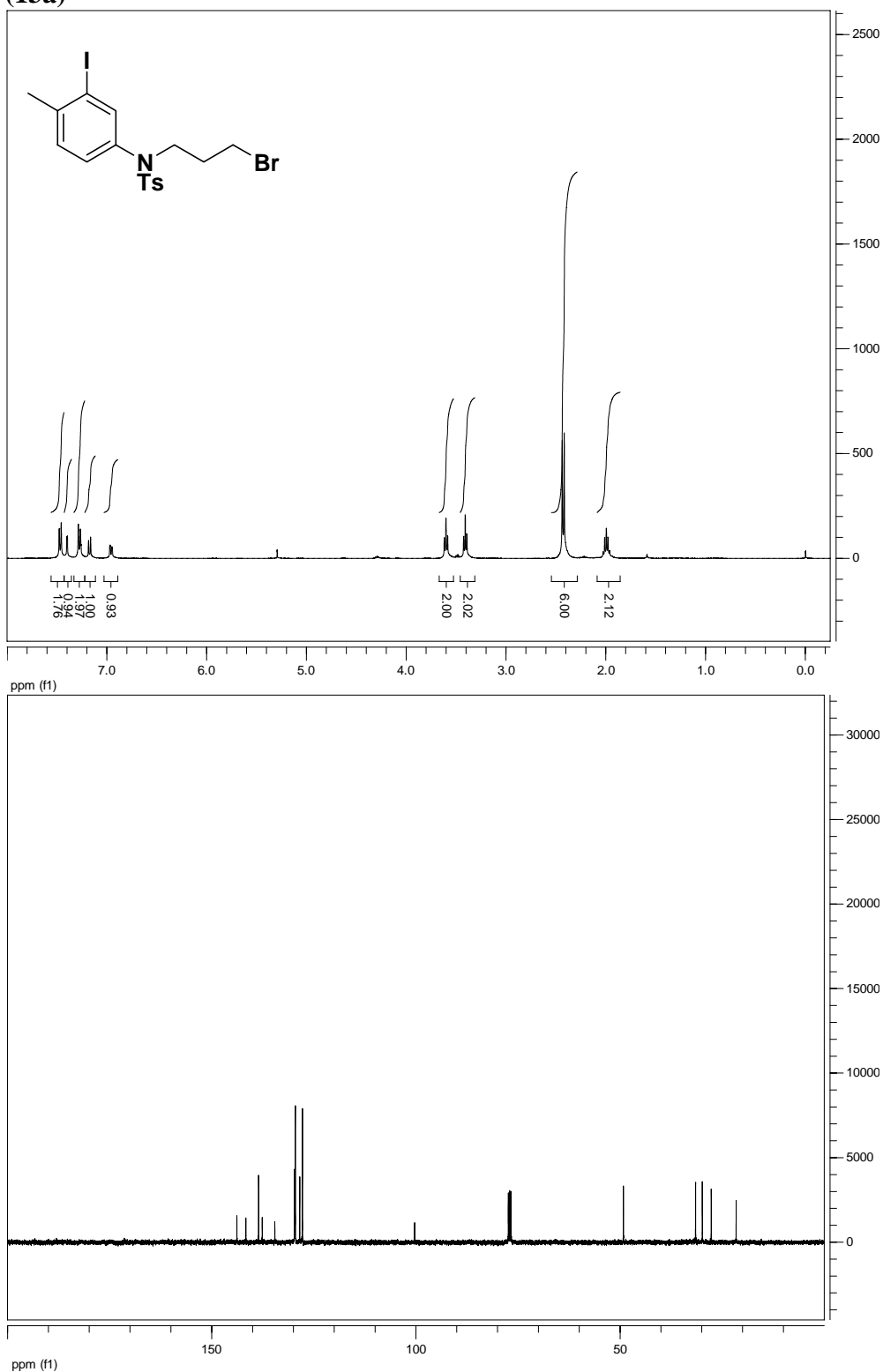
***N*-(2-Bromo-ethyl)-*N*-(3-bromo-4-methyl-phenyl)-4-methyl-benzenesulfonamide (11b)**



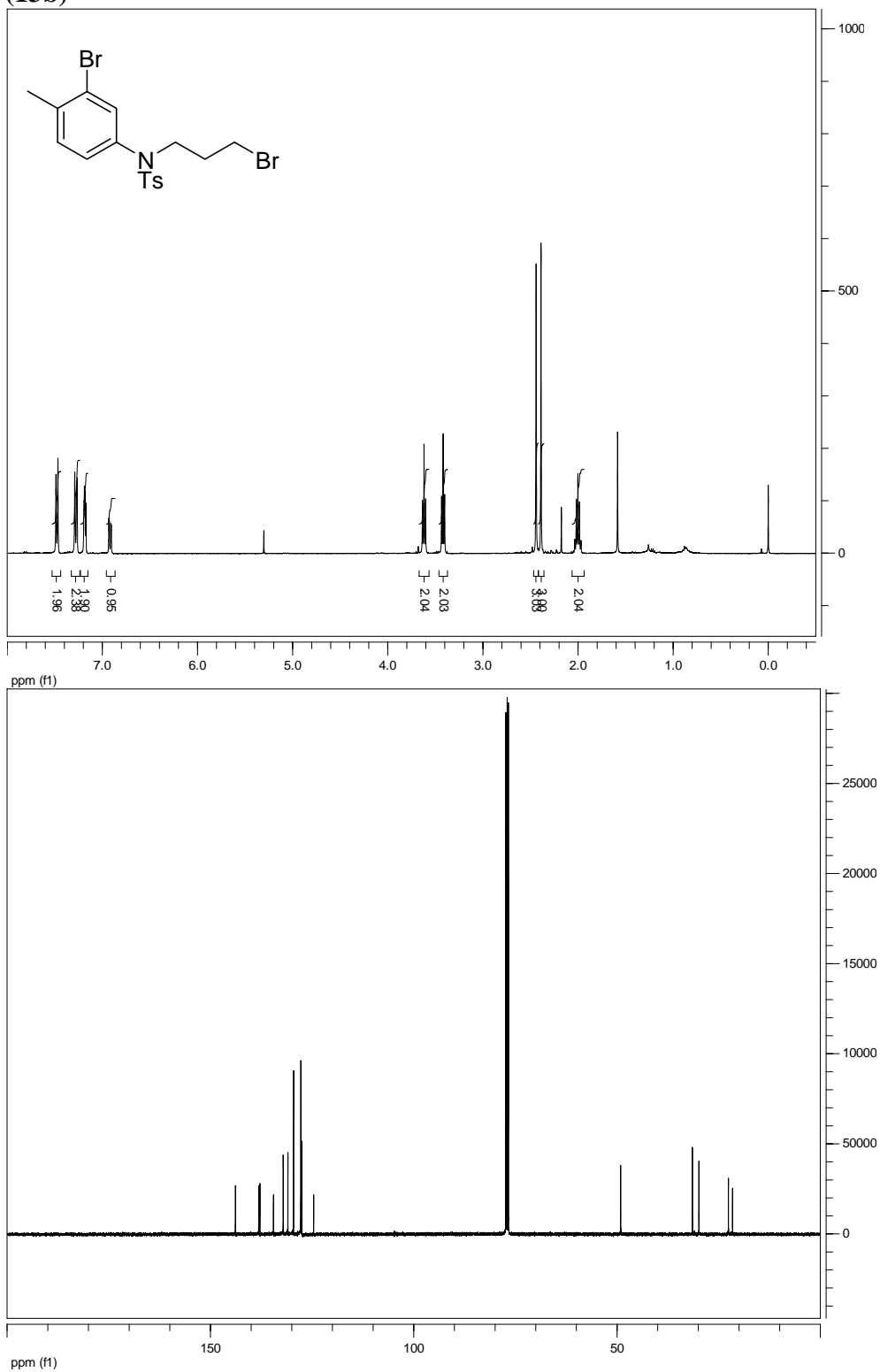
5-Methyl-1-(toluene-4-sulfonyl)-2,3-dihydro-1H-indole-4-carbonitrile (12)



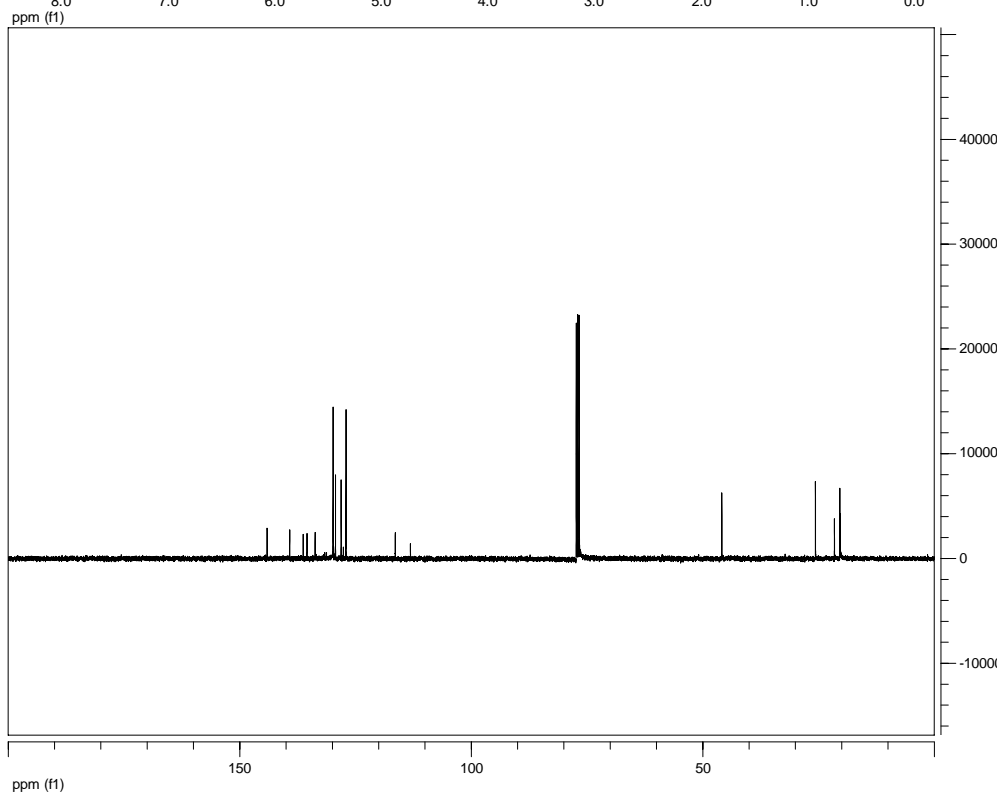
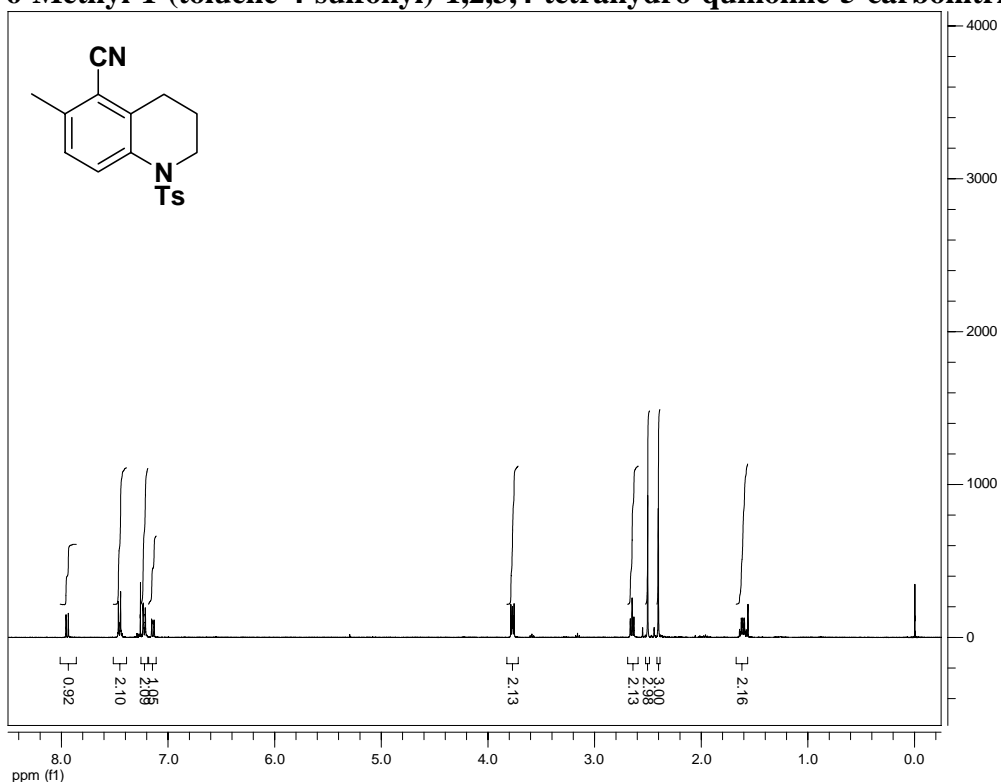
***N*-(3-Bromo-propyl)-*N*-(3-iodo-4-methyl-phenyl)-4-methyl-benzenesulfonamide (13a)**



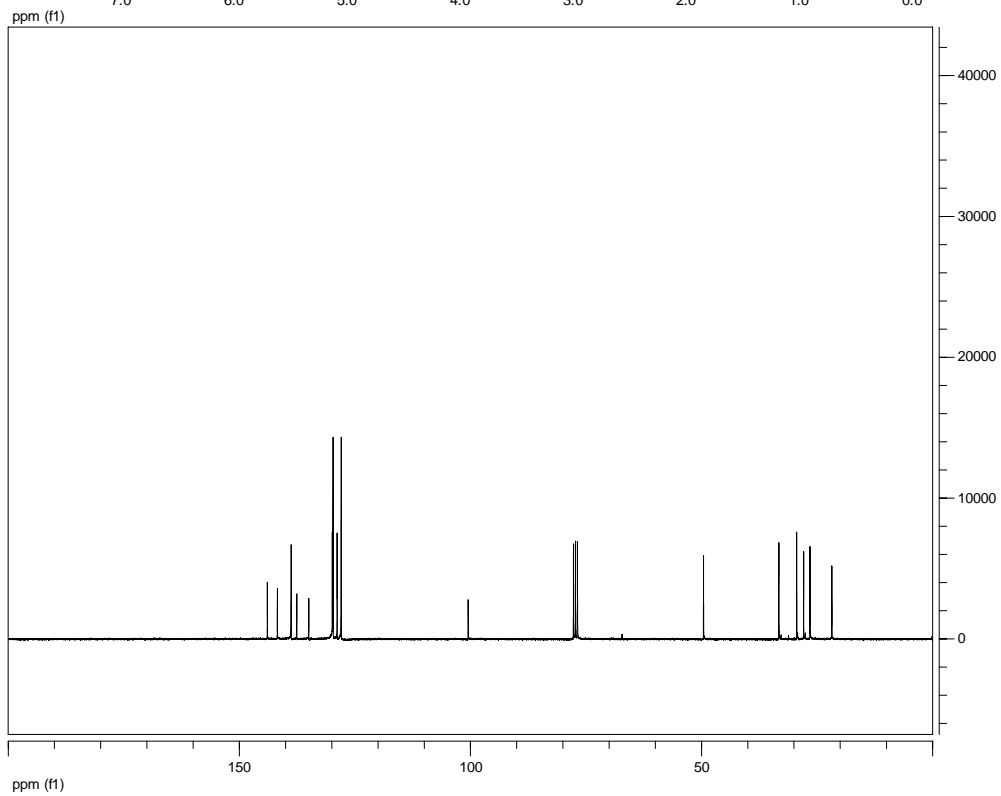
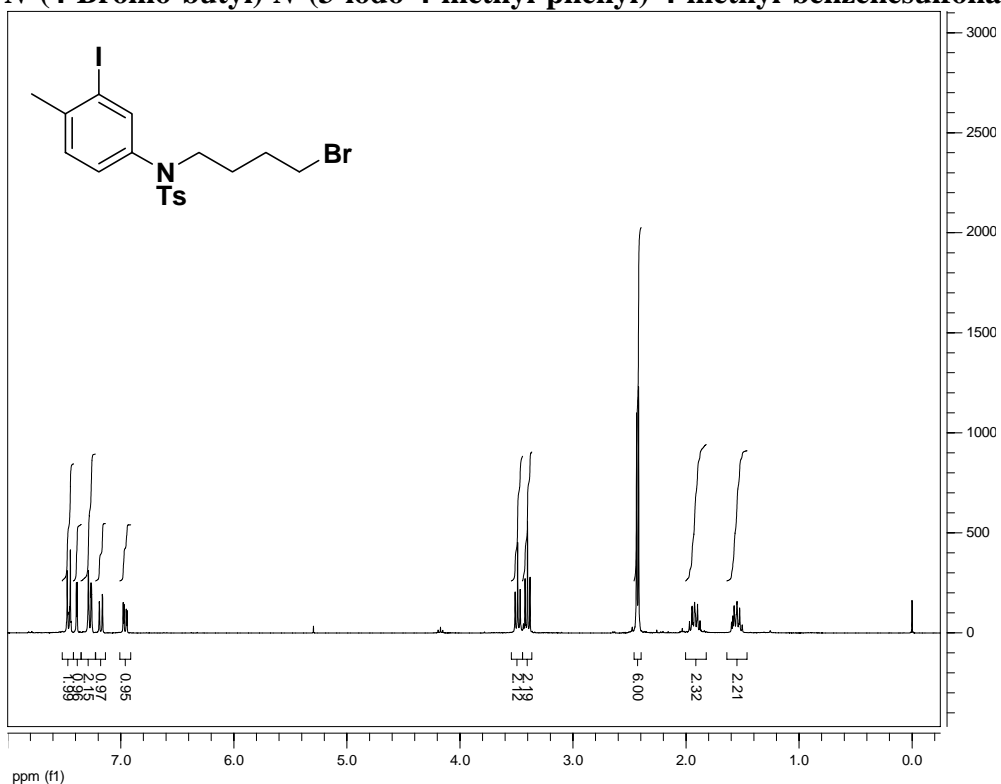
***N*-(3-Bromo-4-methyl-phenyl)-*N*-(3-bromo-propyl)-4-methyl-benzenesulfonamide (13b)**



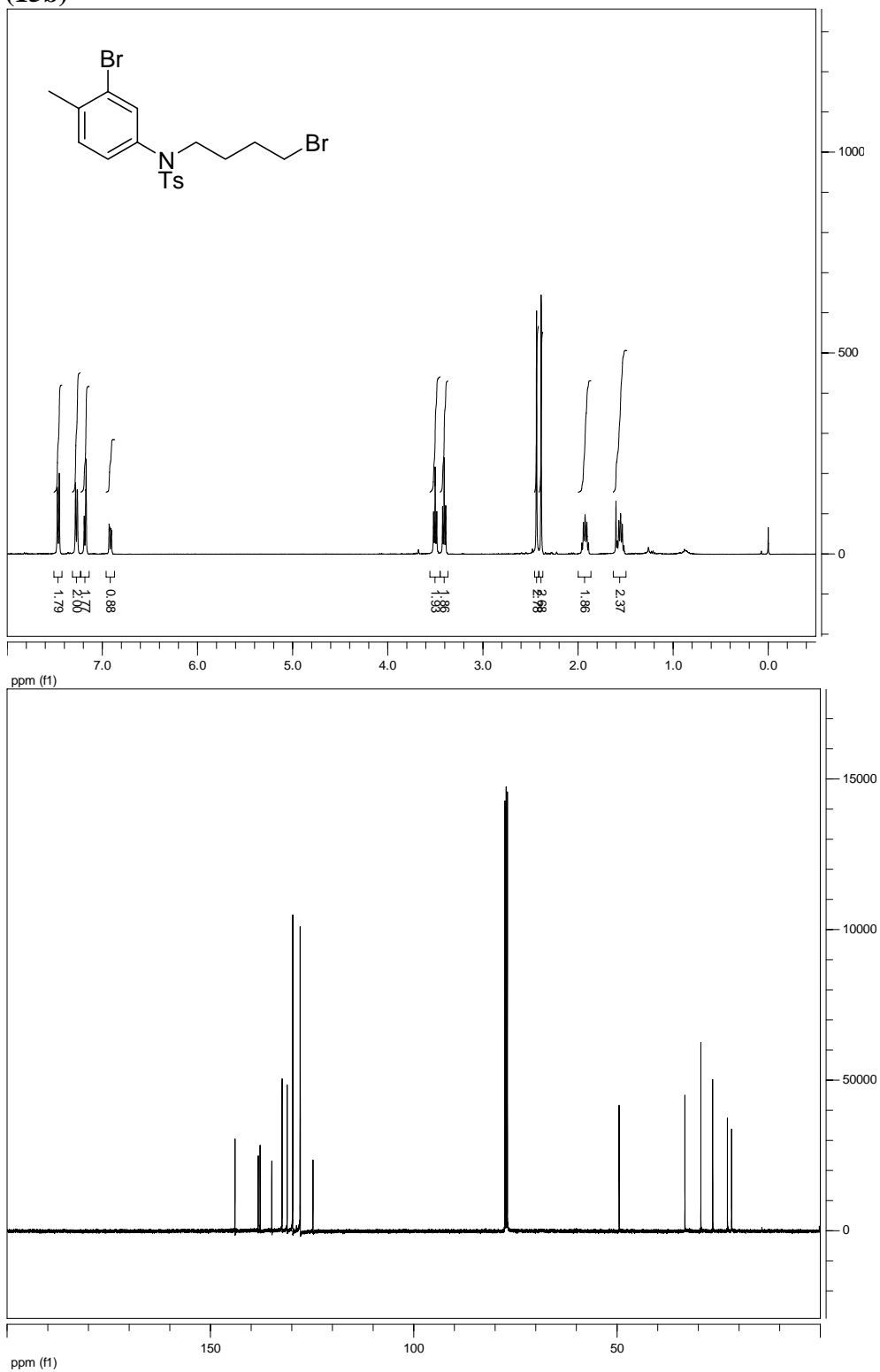
6-Methyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-quinoline-5-carbonitrile (14)



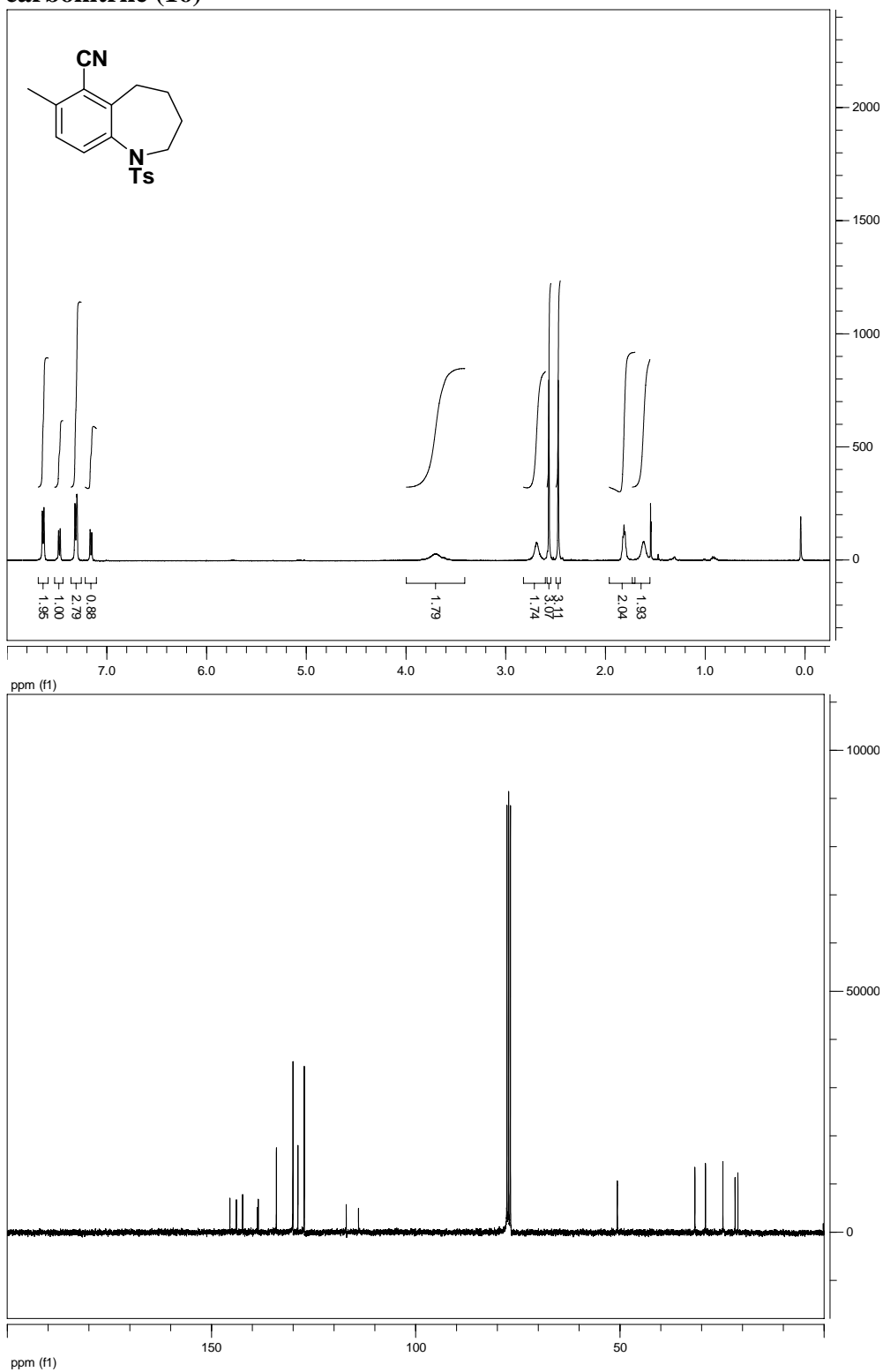
***N*-(4-Bromo-butyl)-*N*-(3-iodo-4-methyl-phenyl)-4-methyl-benzenesulfonamide (15a)**



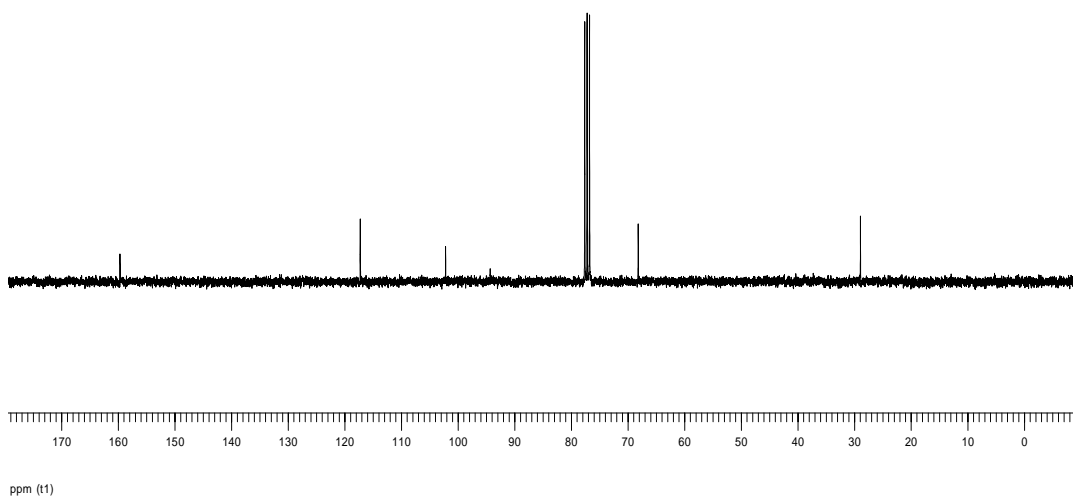
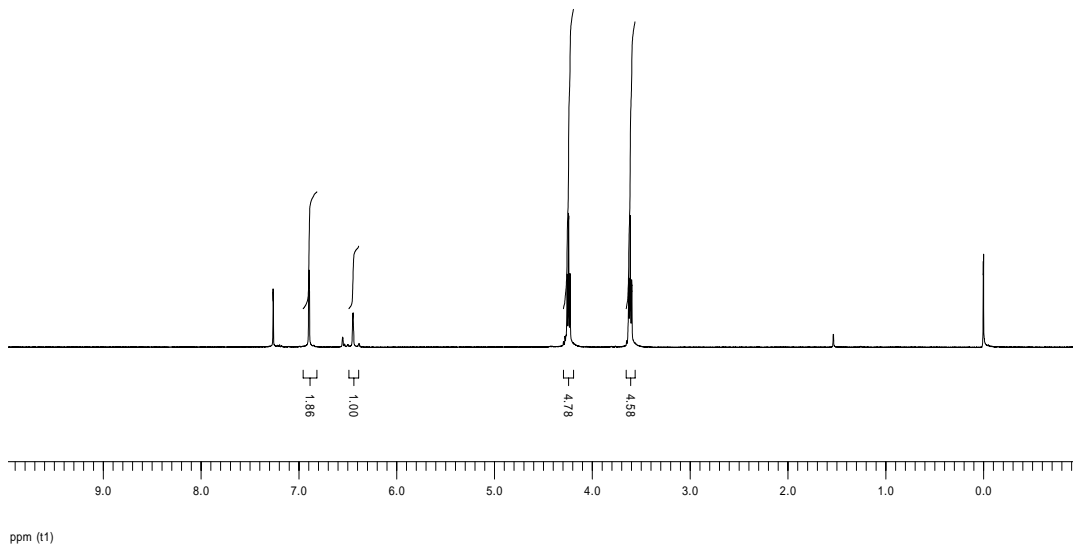
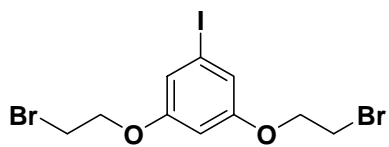
***N*-(4-Bromo-butyl)-*N*-(3-bromo-4-methyl-phenyl)-4-methyl-benzenesulfonamide (15b)**



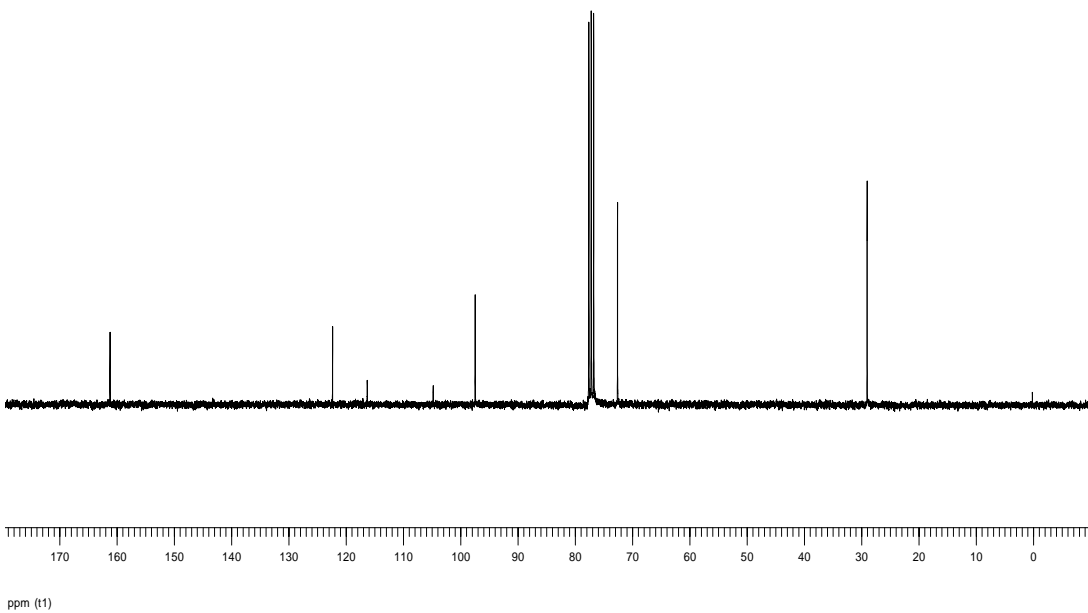
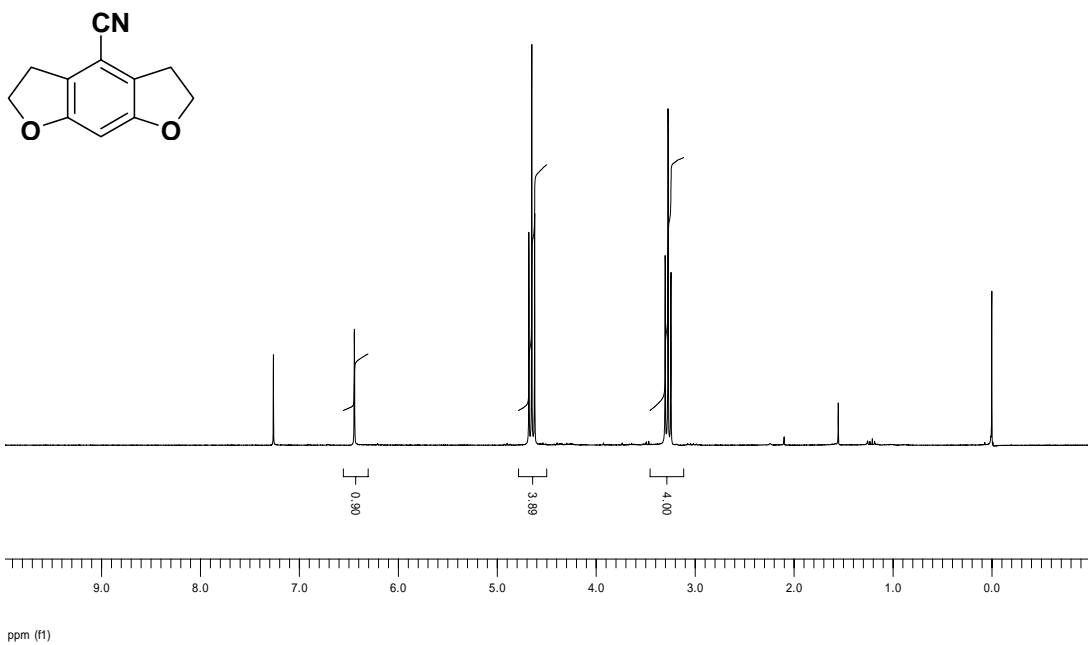
7-Methyl-1-(toluene-4-sulfonyl)-2,3,4,5-tetrahydro-1H-benzo[b]azepine-6-carbonitrile (16)



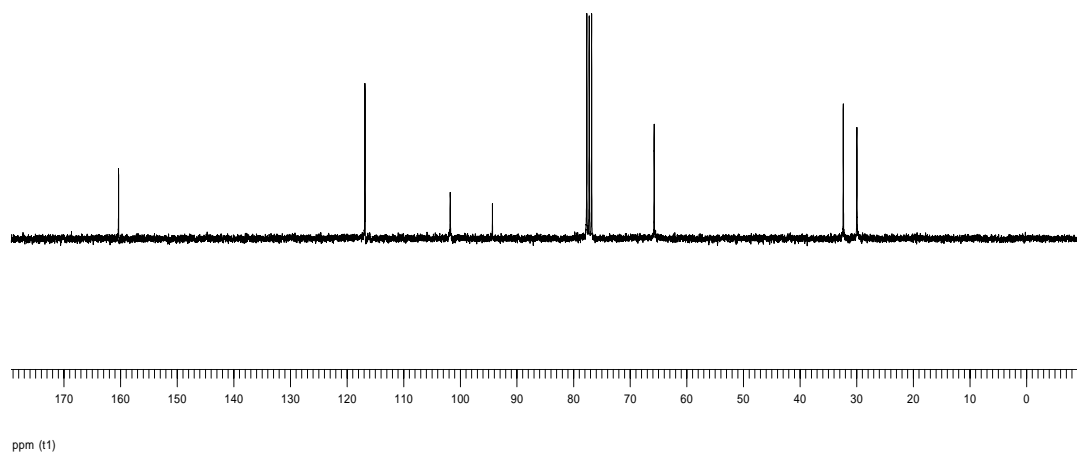
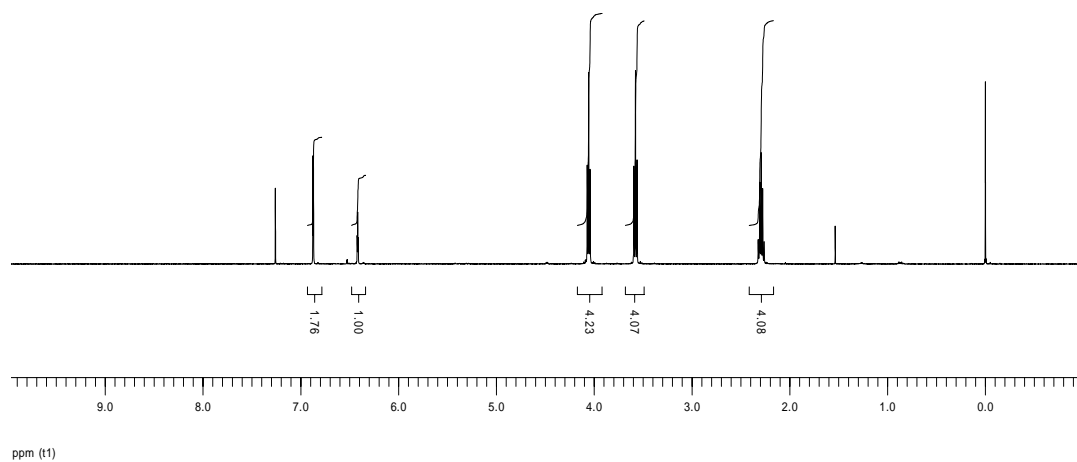
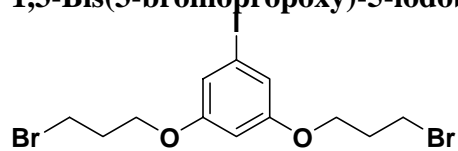
1,3-Bis(2-bromoethoxy)-5-iodobenzene (17)



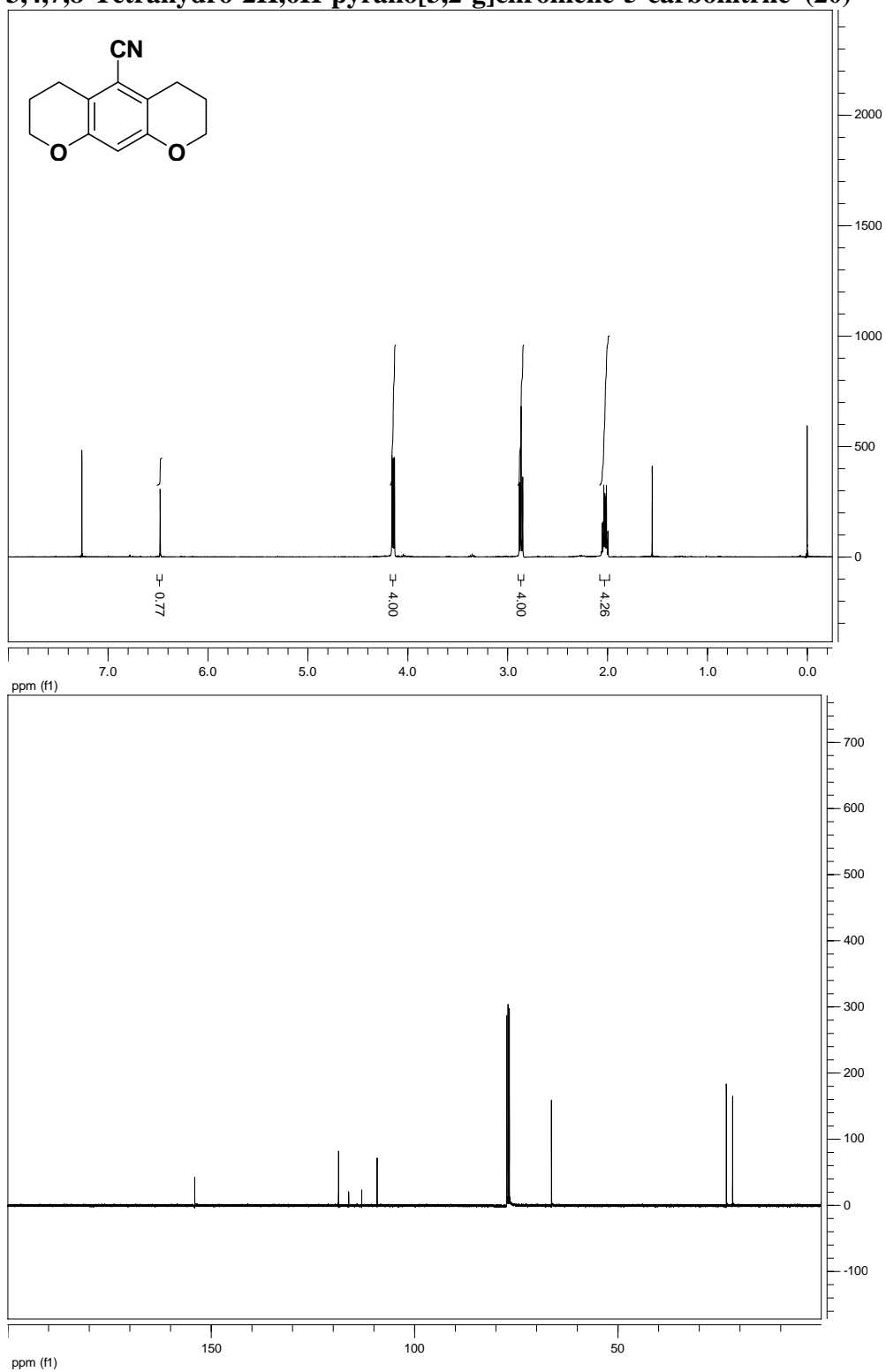
2,3,5,6-Tetrahydro-benzo[1,2-*b*;5,4-*b'*]difuran-4-carbonitrile (18)



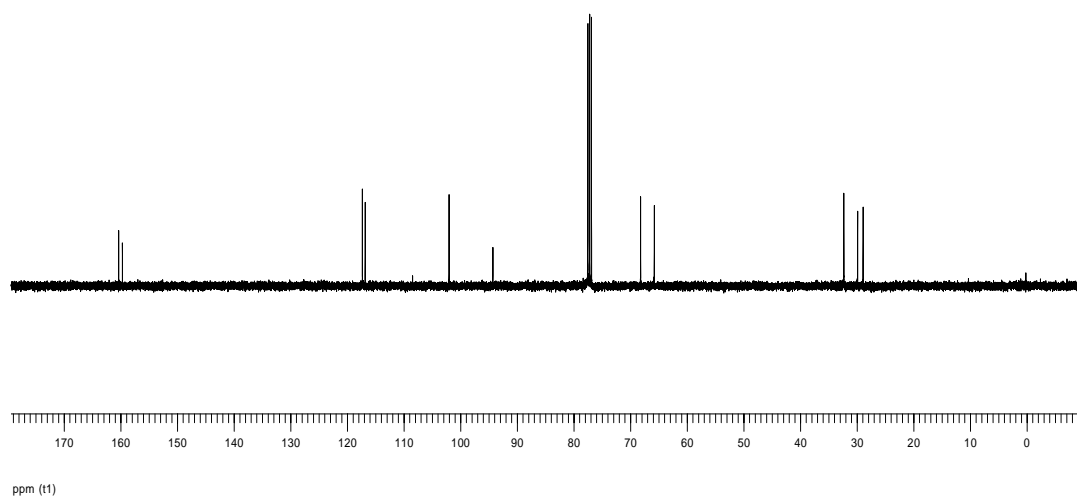
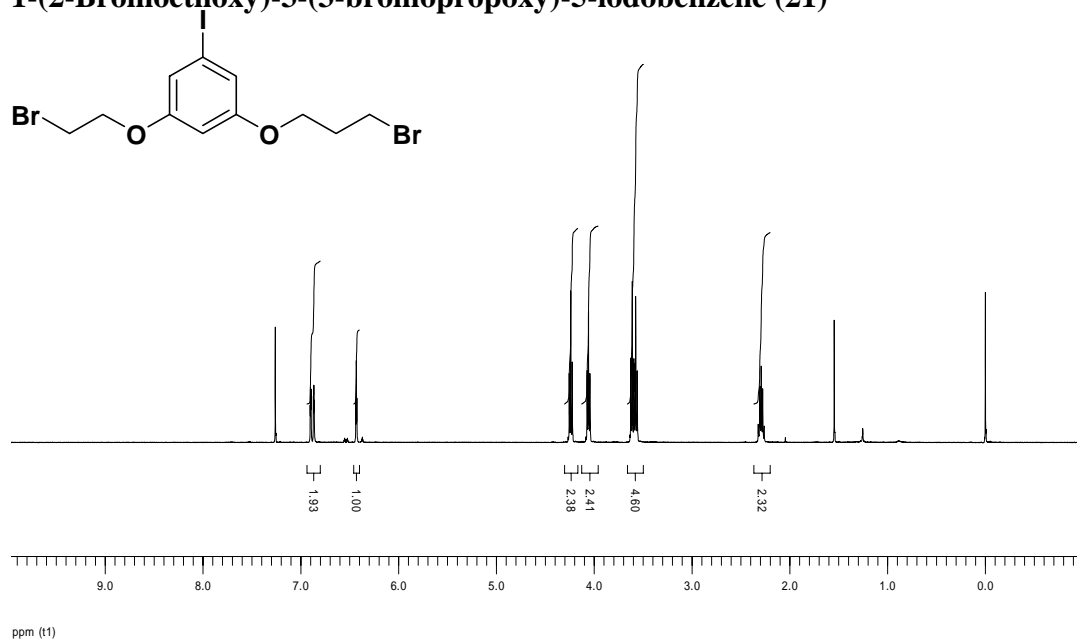
1,3-Bis(3-bromopropoxy)-5-iodobenzene (19)



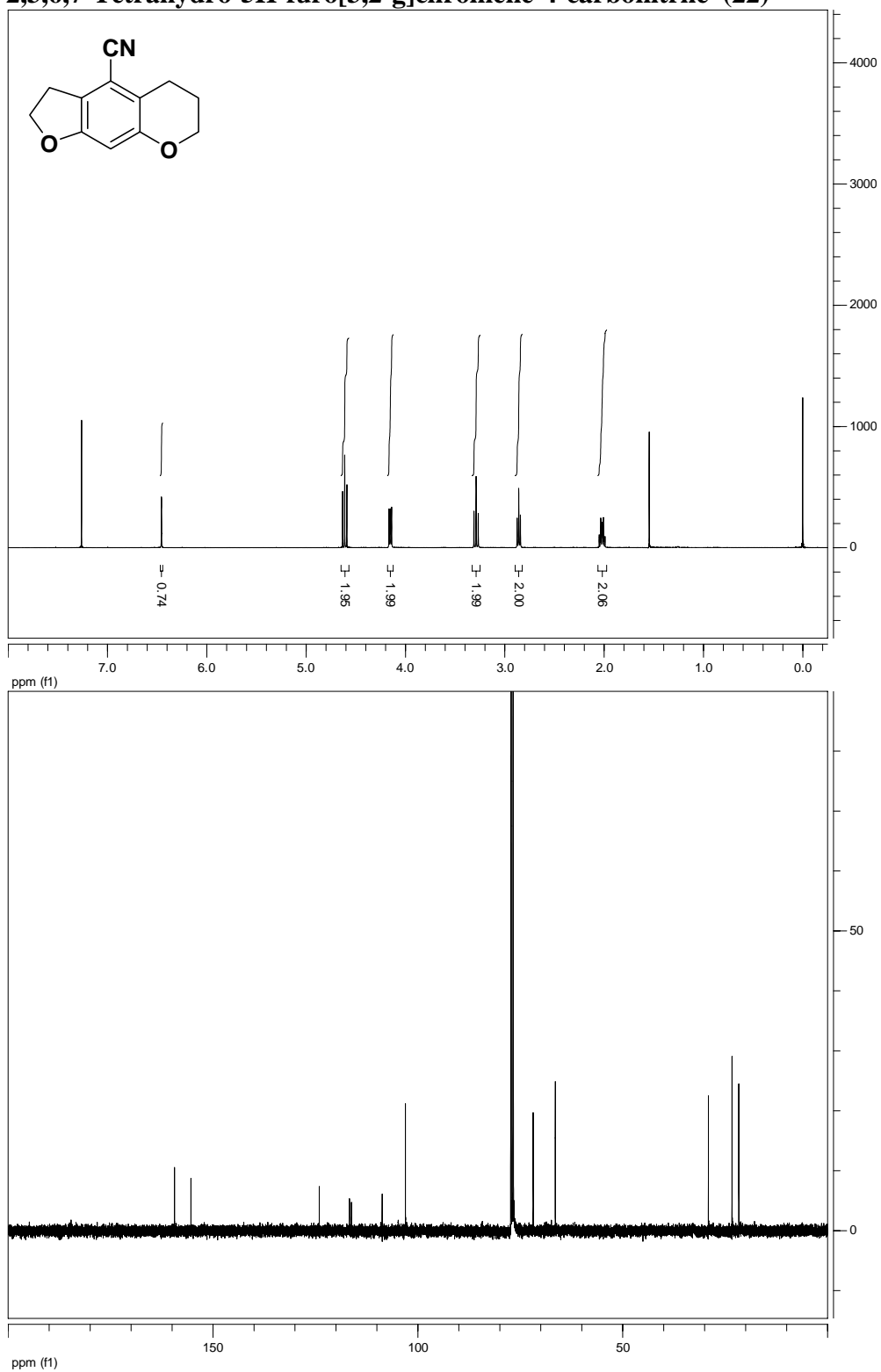
3,4,7,8-Tetrahydro-2H,6H-pyrano[3,2-g]chromene-5-carbonitrile (20)



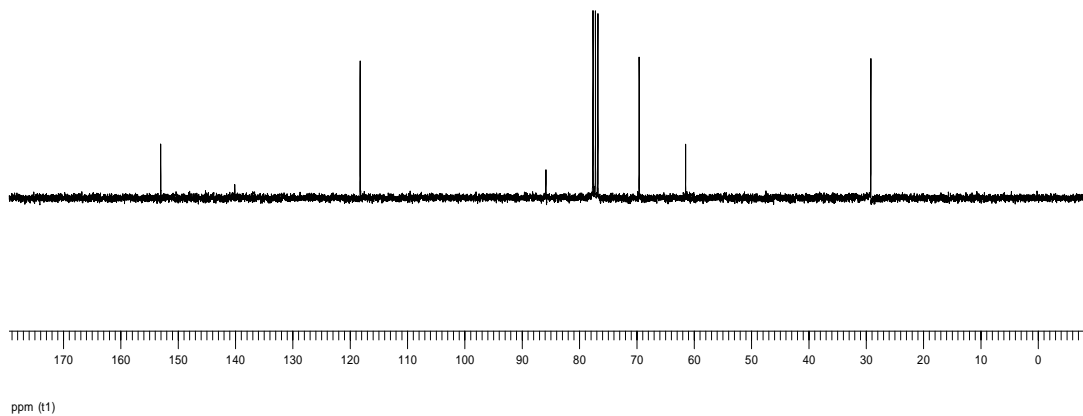
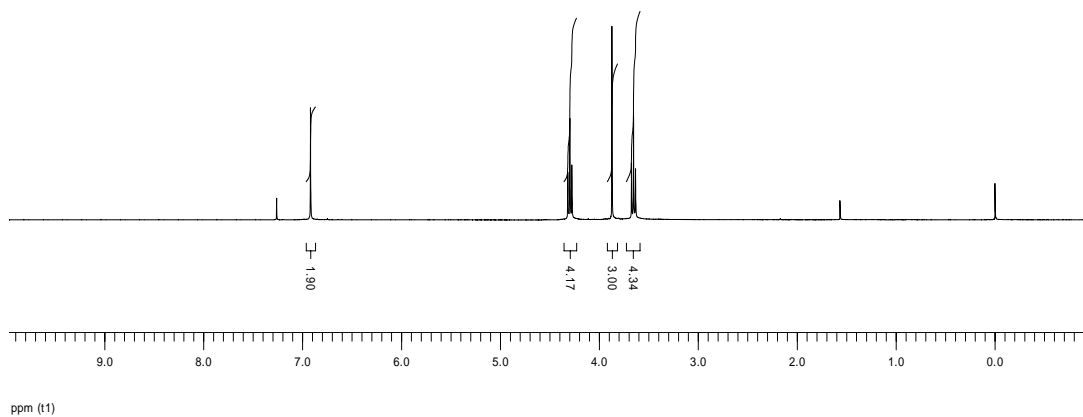
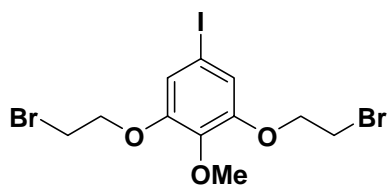
1-(2-Bromoethoxy)-3-(3-bromopropoxy)-5-iodobenzene (21)



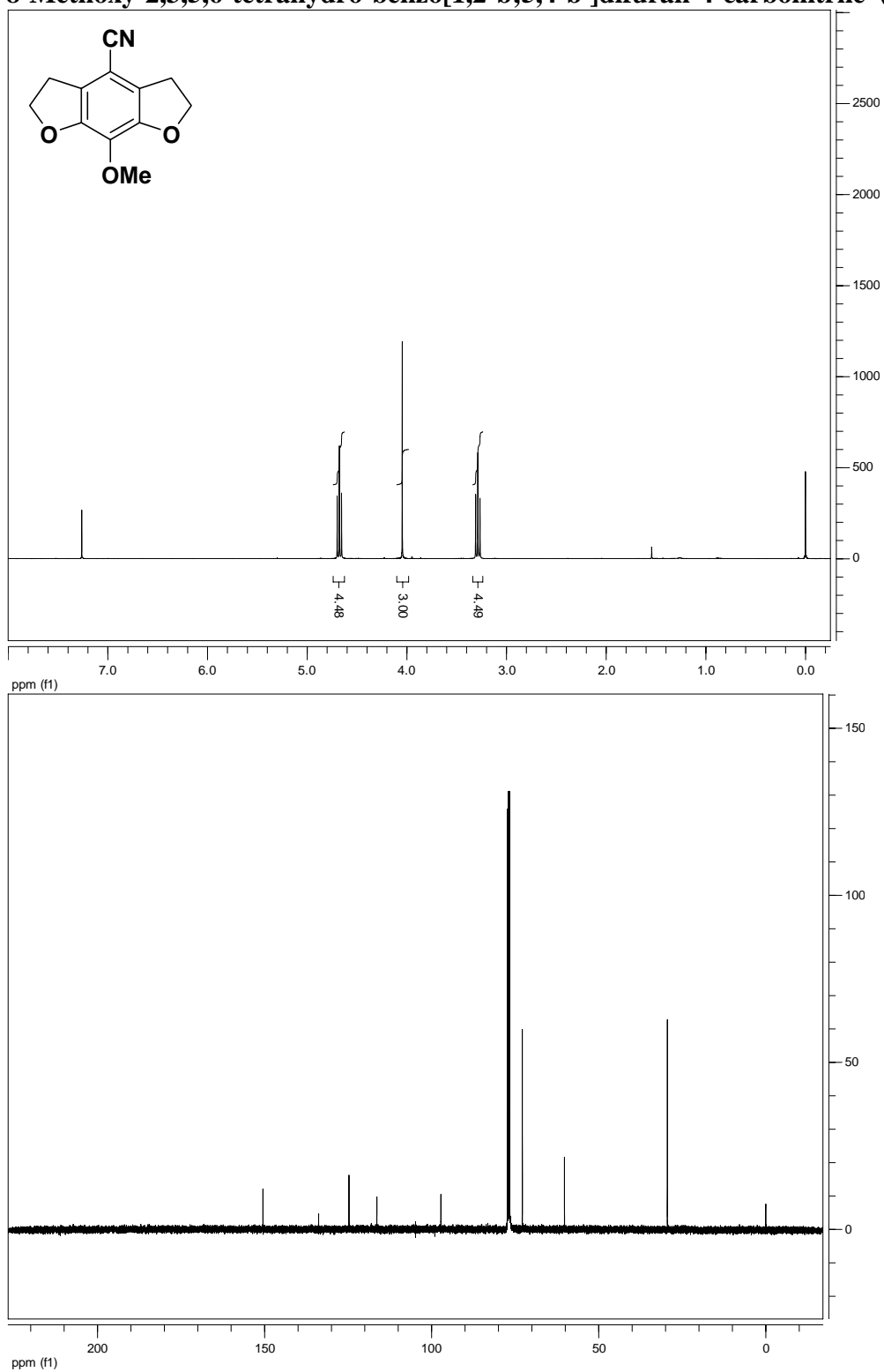
2,3,6,7-Tetrahydro-5H-furo[3,2-g]chromene-4-carbonitrile (22)



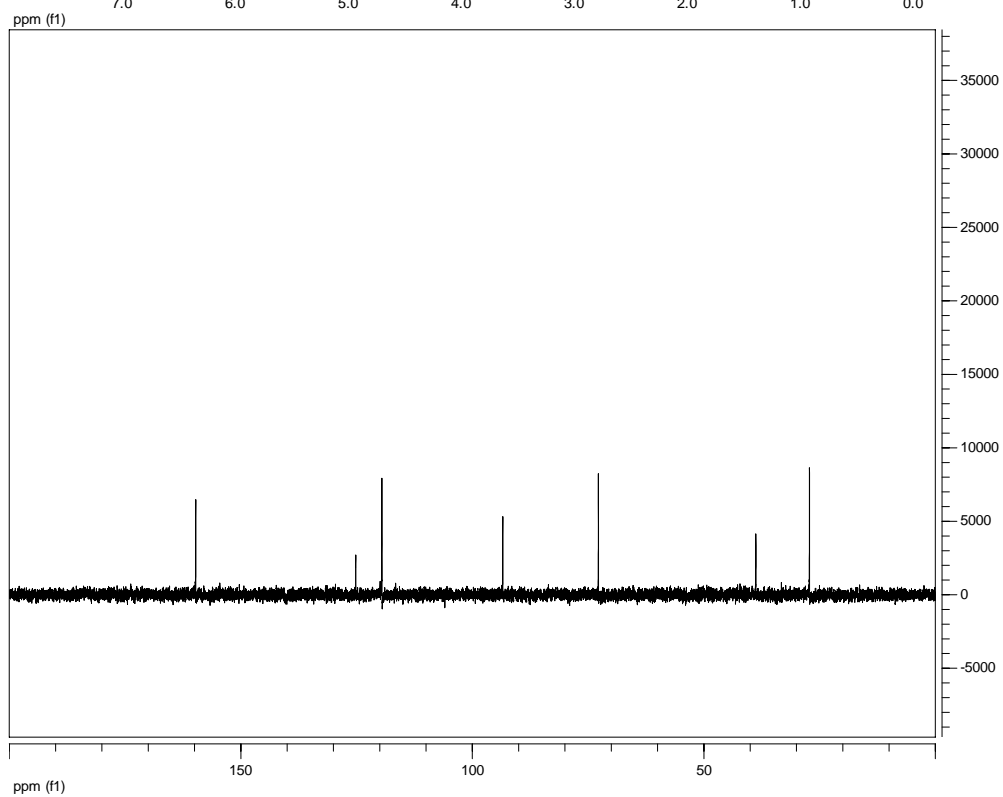
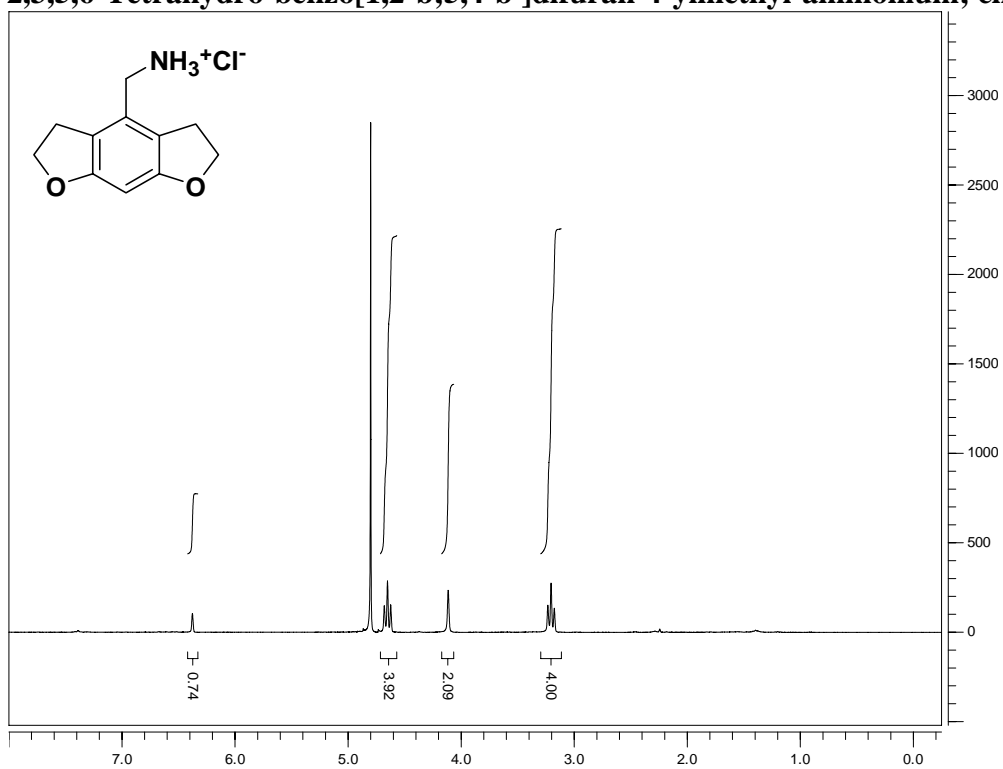
1,3-Bis(2-bromoethoxy)-5-iodo-2-methoxybenzene (23)



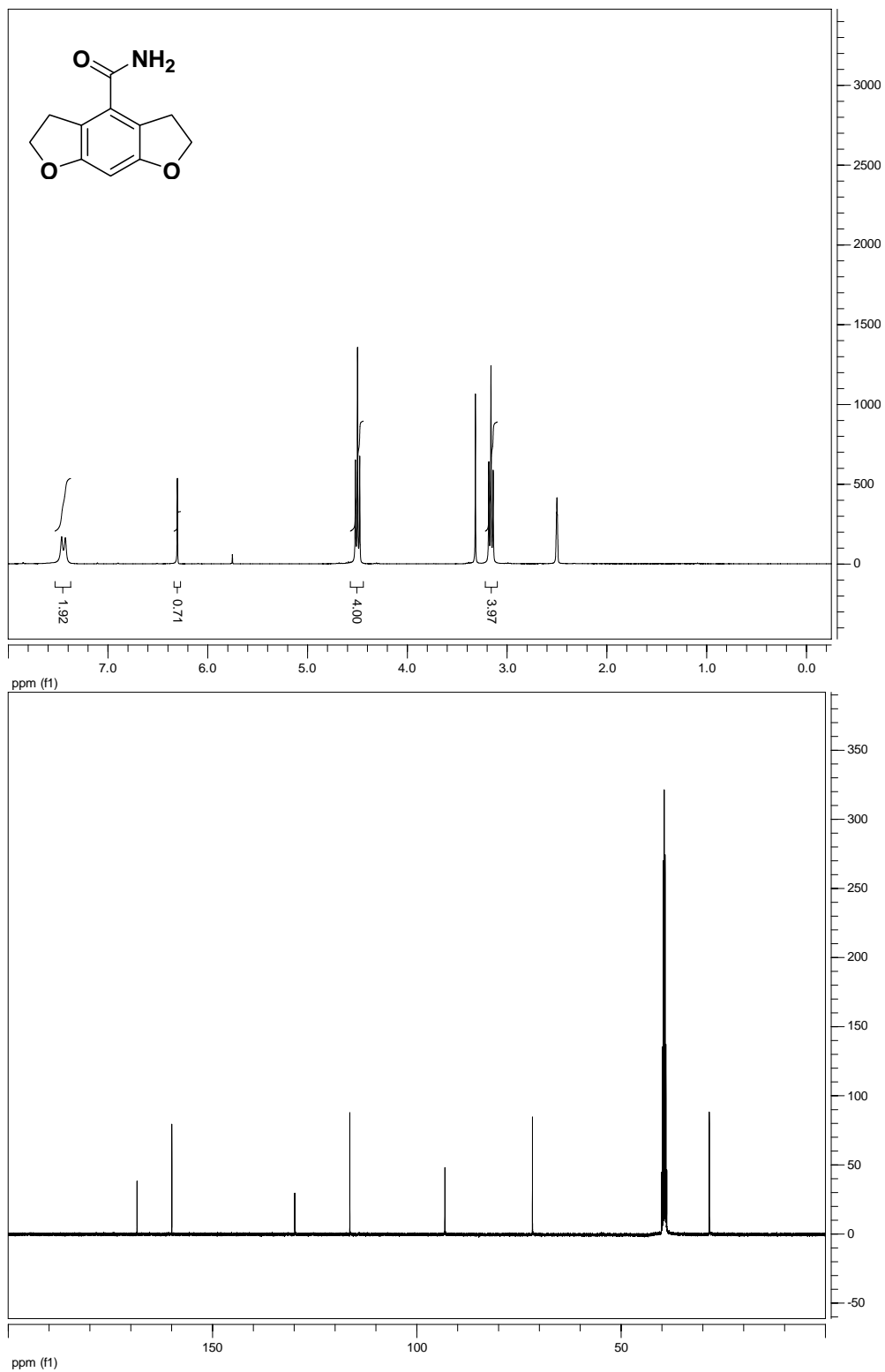
8-Methoxy-2,3,5,6-tetrahydro-benzo[1,2-b;5,4-b']difuran-4-carbonitrile (24)



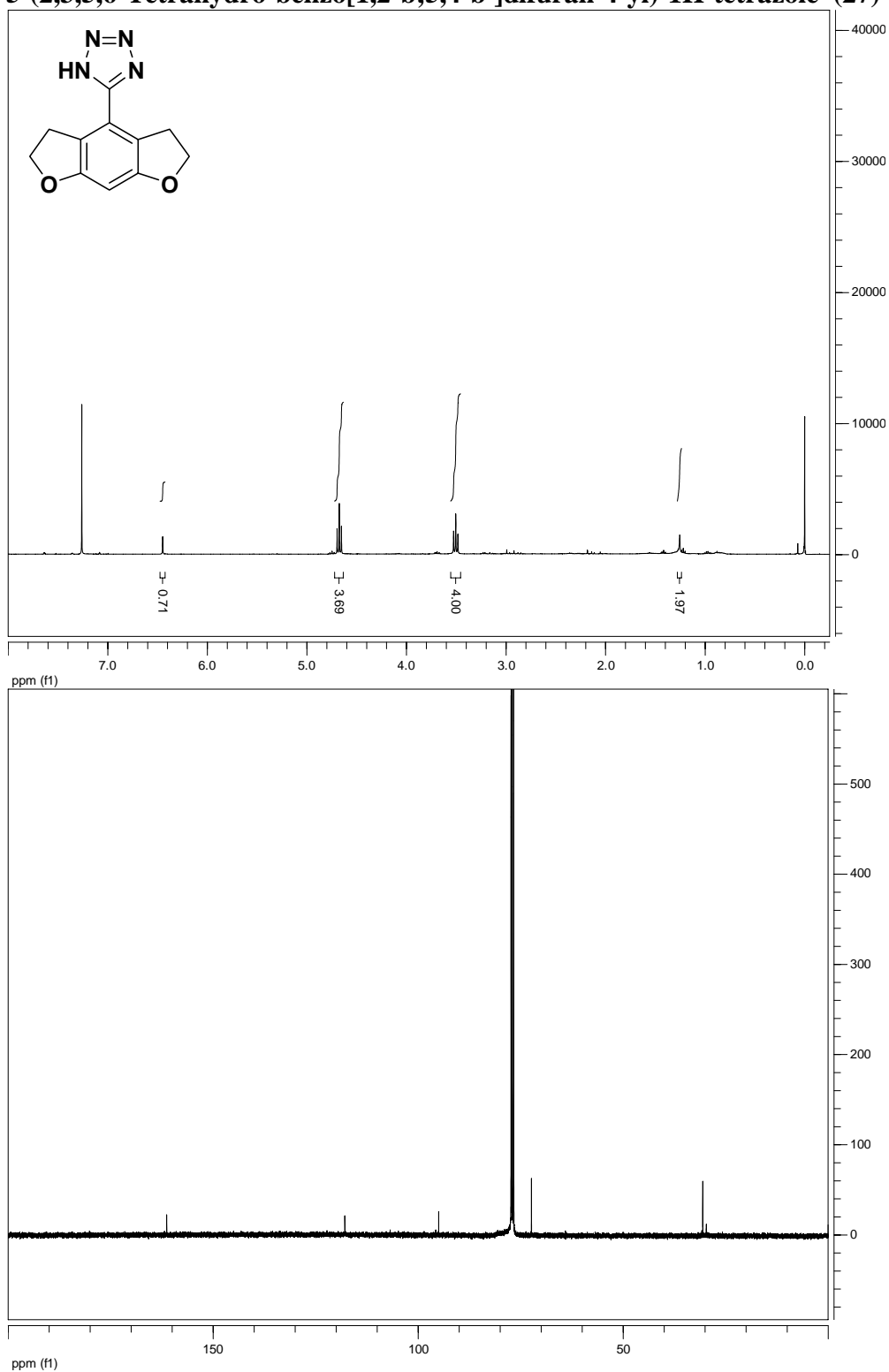
2,3,5,6-Tetrahydro-benzo[1,2-b;5,4-b']difuran-4-ylmethyl-ammonium; chloride (25)



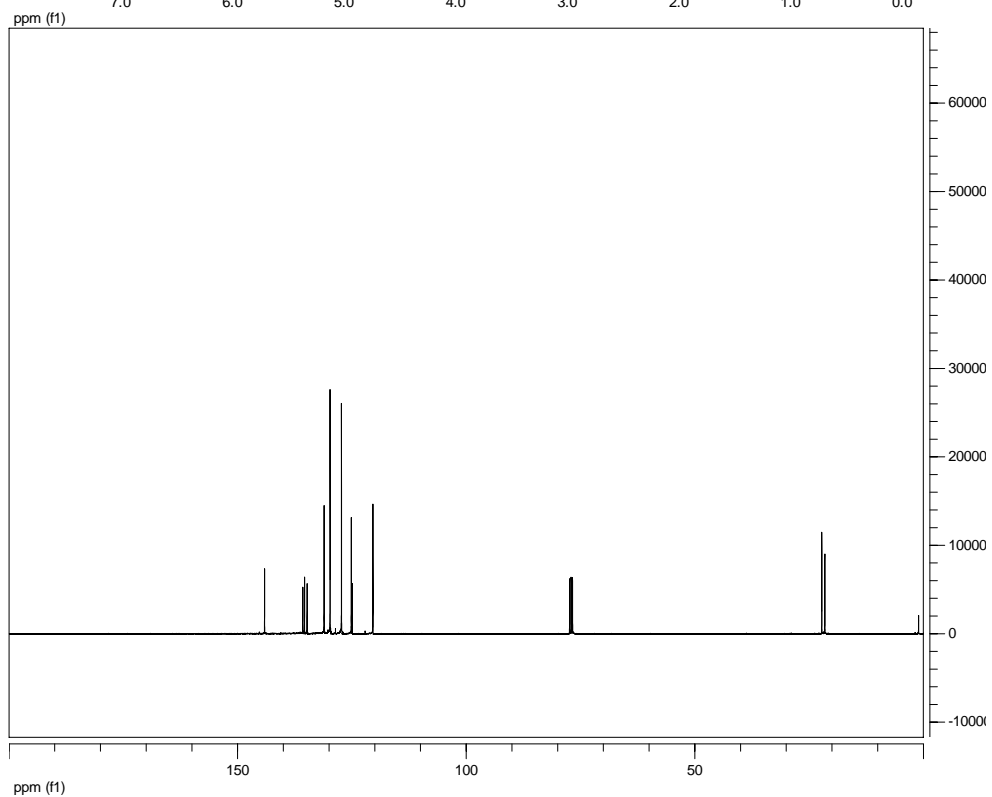
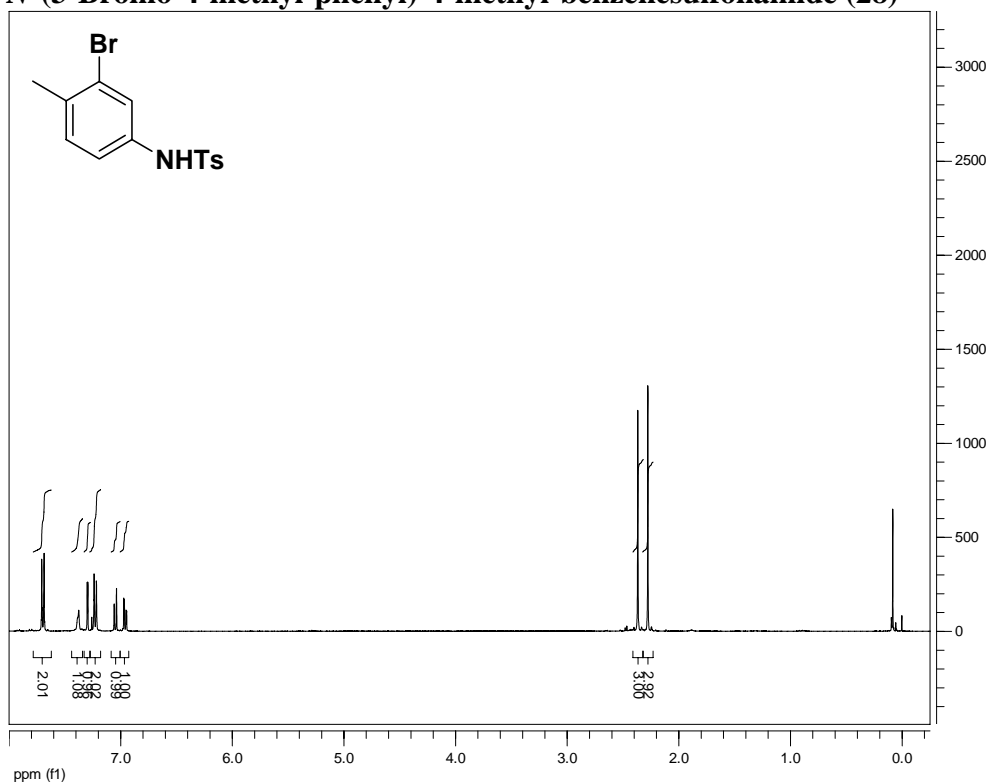
2,3,5,6-Tetrahydro-benzo[1,2-b;5,4-b']difuran-4-carboxylic acid amide (26)



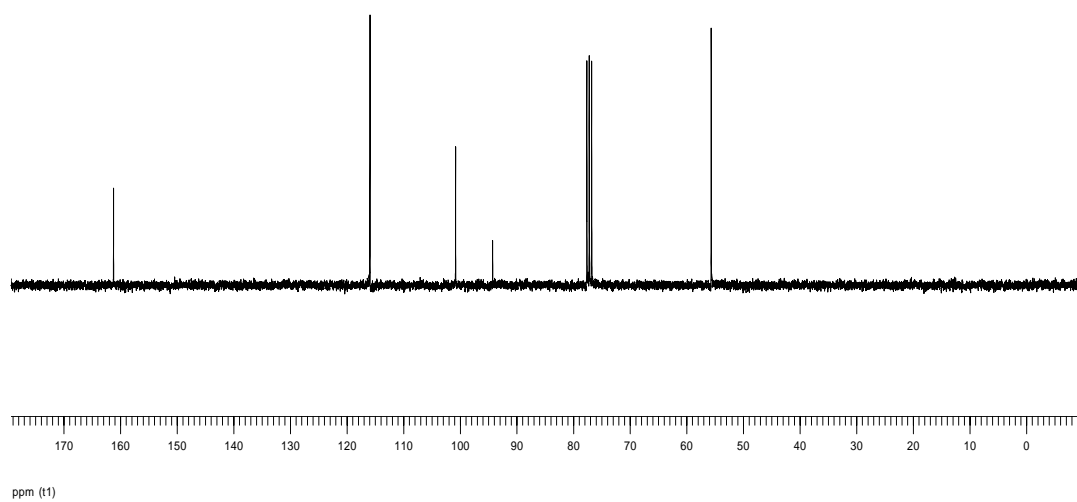
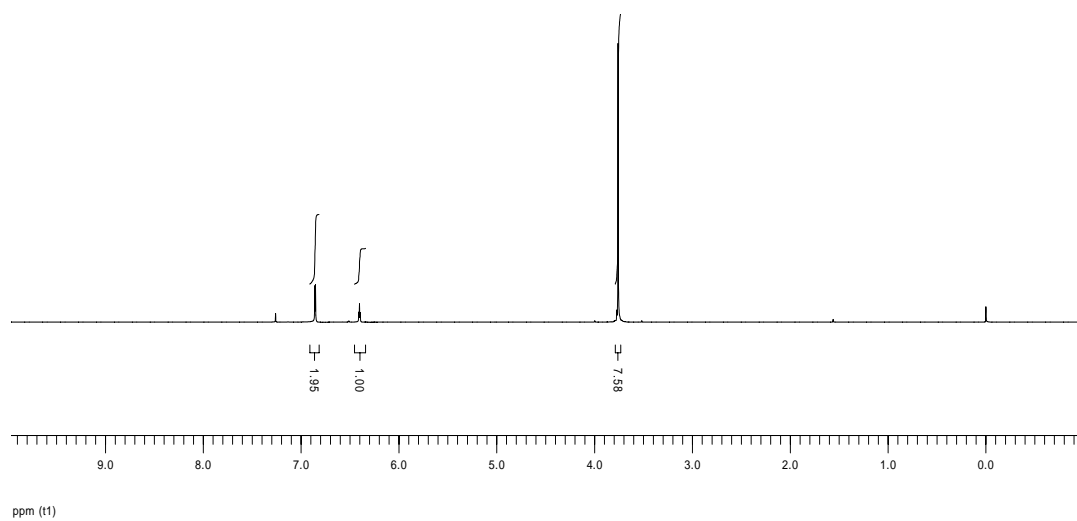
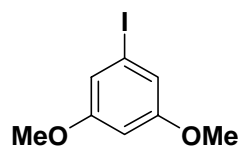
5-(2,3,5,6-Tetrahydro-benzo[1,2-b;5,4-b']difuran-4-yl)-1H-tetrazole (27)



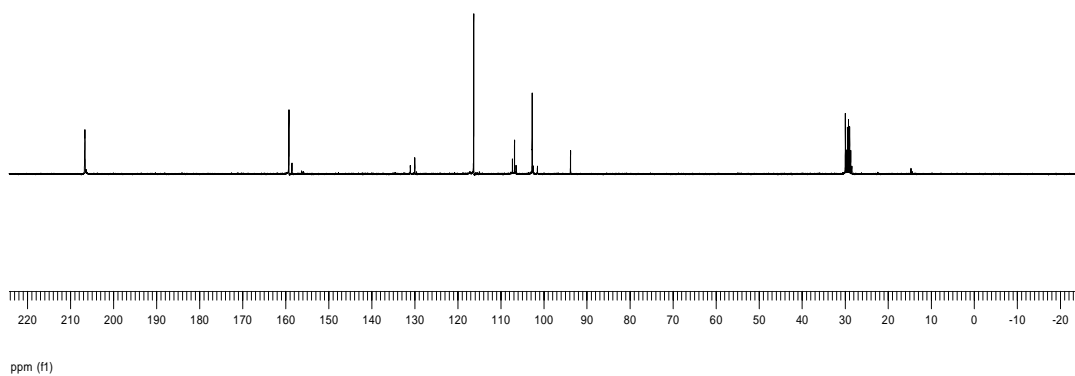
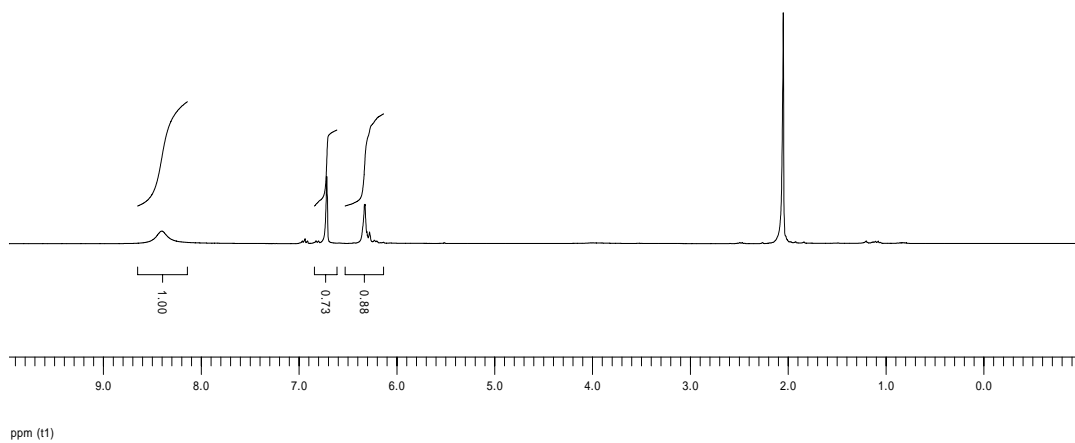
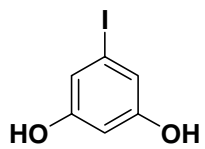
***N*-(3-Bromo-4-methyl-phenyl)-4-methyl-benzenesulfonamide (28)**



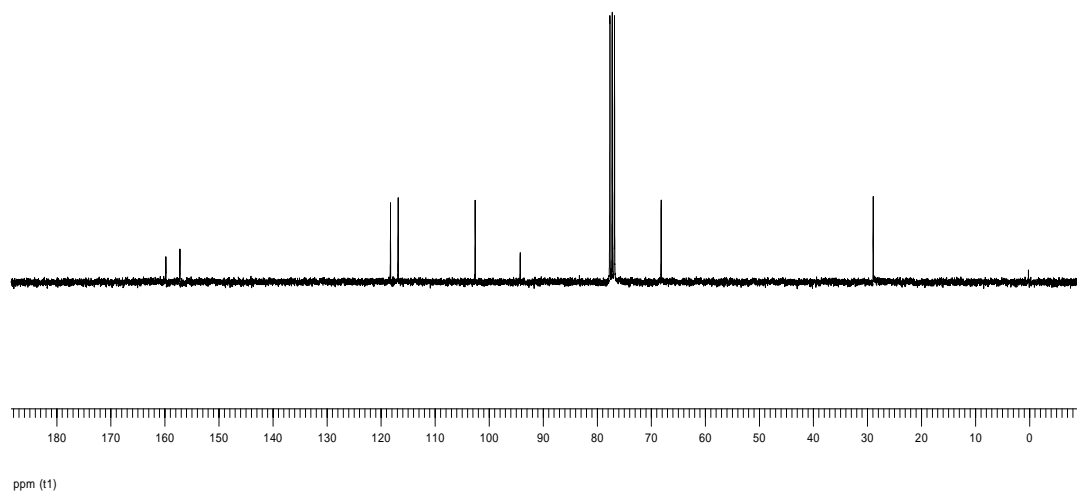
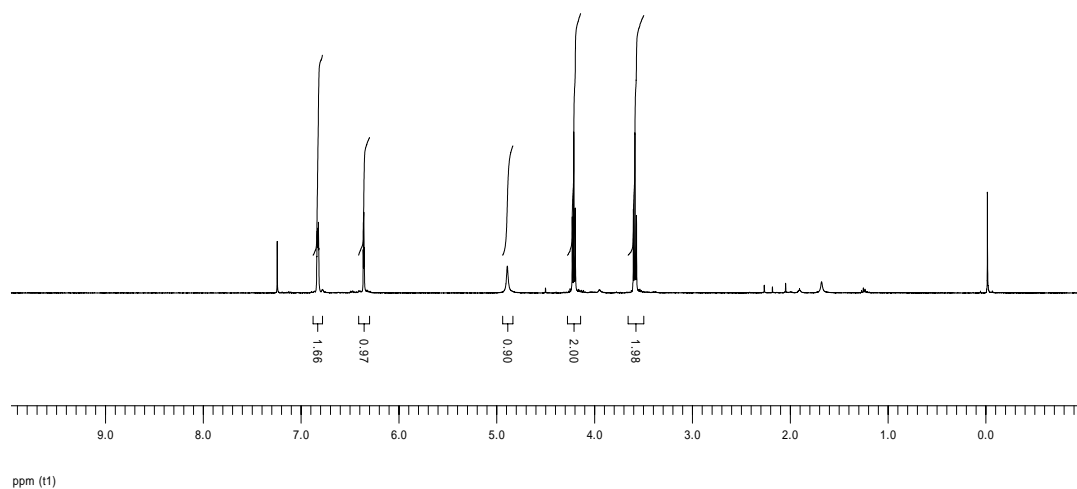
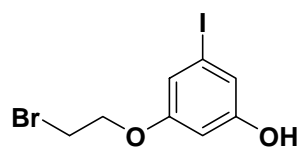
1-Iodo-3,5-dimethoxybenzene (29)



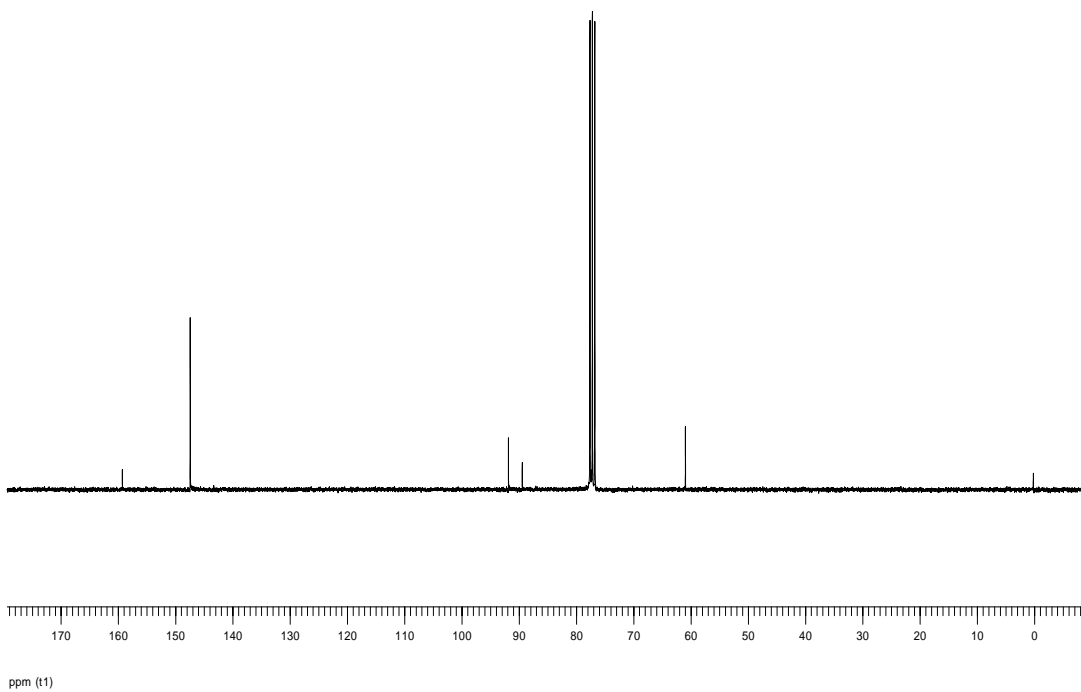
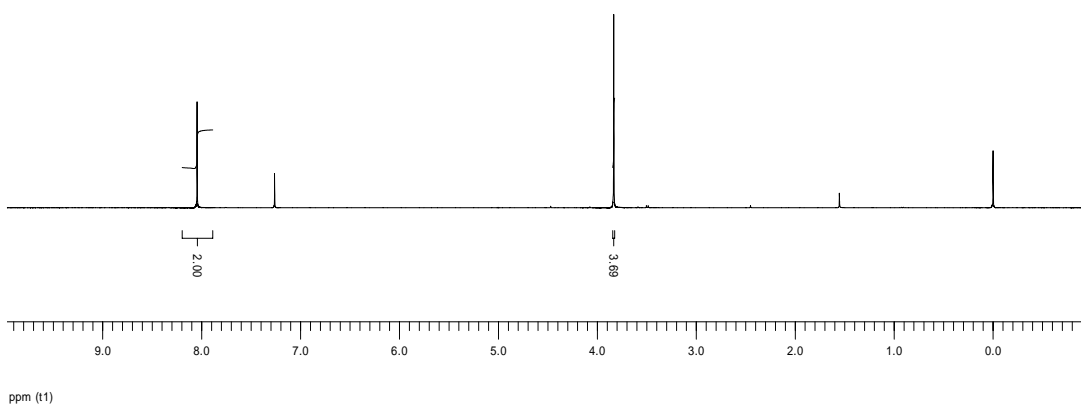
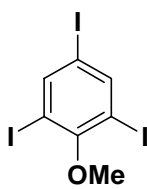
5-Iodobenzene-1,3-diol (30)



3-(2-Bromoethoxy)-5-iodophenol (31)



1,3,5-Triiodo-2-methoxybenzene (32)



5-Iodo-2-methoxybenzene-1,3-diol (33)

