Electronic Supplementary Material (ESI) for ChemComm.

Synthesis and indole coupling reactions of azetidine and oxetane sufinate salts

Supporting Information

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1. General experimental

All reactions were conducted in flame-dried glassware under ambient conditions unless otherwise stated.

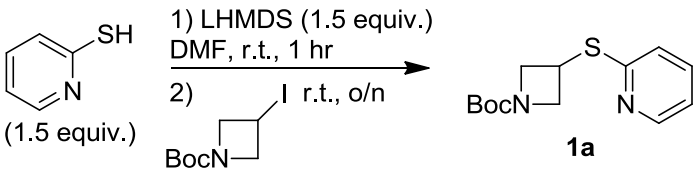
Infrared (IR) spectra were recorded on a Perkin Elmer Paragon 100 FTIR spectrophotometer or Elmer Spectrum 100 spectrophotometer, ν_{max} in cm^{-1}. Samples were recorded neat or as thin films using sodium chloride plates, as a CH_2Cl_2 or MeOH solution. Bands are characterized as broad (br), strong (s), medium (m), or weak (w). ^1H NMR spectra were recorded on a Bruker AMX-400 (400 MHz) or Avance-400 (400 MHz) supported by an Aspect 3000 data system. Chemical shifts are reported in ppm from trimethylsilane with the residual protic solvent resonance as the internal standard ($CHCl_3$: δ 7.27 ppm) unless otherwise stated. Data are reported as follows: chemical shift (integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant (Hz)). ^{13}C NMR spectra were recorded on a Bruker AMX-400 (100.6 MHz) or Avance-400 (101 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from trimethylsilane with the solvent as the internal reference ($CDCl_3$: δ 77.0 ppm) unless otherwise stated. High-resolution mass spectra (HRMS) recorded for accurate mass analysis, were performed on either a MicroMass LCT operating in Electrospray mode (TOF ES+) or on a MicroMass Prospec operating in FAB (FAB+), EI (EI+) or CI (CI+) mode.

Thin layer chromatography (TLC) was performed on pre-coated glass plates with silica (Merck DC Kieselgel 60 F_{254}) which were developed using standard visualizing agents: Ultraviolet light or potassium permanganate. Flash chromatography was performed on silica-gel (BDH Silica Gel 60 43-60 or Davisil 60A). Melting points, performed on recrystallized solids, were recorded on a Gallenkamp melting point apparatus and are uncorrected.

Tetrahydrofuran was purified using standard laboratory techniques according to methods published in "Purification of Laboratory Chemicals" by Perrin, Armarego and Perrin (Pergamon Press, 1966). Unless otherwise stated, all other solvents and materials were used as supplied.

2. Synthesis of sodium sulfinate salts

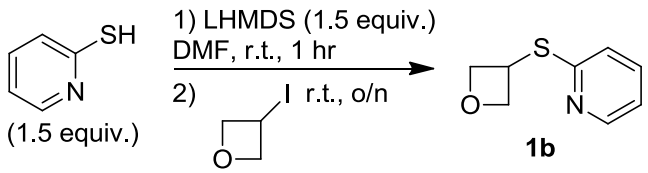
Synthesis of *tert*-butyl 3-(pyridin-2-ylthio)azetidine-1-carboxylate (1a)



LHMDS (1 M in THF, 25.9 mL, 25.9 mmol) was added to pyridine-2-thiol (1.2 g, 17.27 mmol) in DMF (45 mL) at room temperature and the resulting solution was stirred at r.t. for 1 h. *tert*-Butyl 3-iodoazetidine-1-carboxylate (3.0 mL, 17.27 mmol) was then added and the mixture was stirred at r.t. overnight. A saturated aqueous solution of $NaHCO_3$ was added and the solution was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and evaporated to afford crude product. The residue was purified via flash chromatography on silica gel eluting with a gradient from 10% to 30% ethyl acetate in petroleum ether affording *tert*-butyl 3-(pyridin-2-ylthio)azetidine-1-carboxylate (**1a**) as a white solid (4.42 g, 96%).

Mp = 48 – 49 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (1H, ddd, *J* = 5.0, 1.5, 1.0 Hz), 7.51 – 7.42 (1H, m), 7.11 (1H, dd, *J* = 8.0, 1.0 Hz), 6.97 (1H, ddd, *J* = 7.5, 5.0, 1.0 Hz), 4.46 – 4.36 (3H, m), 3.92 – 3.82 (2H, m), 1.42 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 156.1, 149.8, 136.2, 122.0, 119.8, 79.7, 56.3 (br), 31.4, 28.5; FTIR: 3512 (br), 3391 (w), 3047 (m), 2975 (s), 2882 (s), 1707 (s), 1578 (s), 1556 (s), 1477 (s), 1452 (s), 1391 (s), 1302 (m), 1280 (m), 1248 (s), 1130 (s), 1044 (m), 986 (s), 900 (m), 857 (s), 761 (s), 725 (s), 621 (m); HRMS: m/z [M+H]+ calcd. for $C_{13}H_{19}N_2O_2S$: 267.1177, found: 267.1167.

Synthesis of 2-(oxetan-3-ylthio)pyridine (1b)

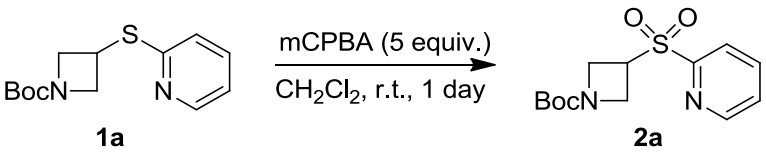


LHMDS (1 M in THF, 28.1 mL, 28.11 mmol) was added to pyridine-2-thiol (3.12 g, 28.11 mmol) in DMF (35 mL) at room temperature and the resulting solution was stirred at r.t. for 1

h. 3-iodooxetane (1.65 mL, 18.74 mmol) was then added and the mixture was stirred at r.t. overnight. A saturated aqueous solution of $NaHCO_3$ was added and the solution was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and evaporated to afford crude product. The residue was purified via flash chromatography on silica gel eluting with a gradient from 10% to 30% ethyl acetate in petroleum ether affording 2-(oxetan-3-ylthio)pyridine (**1b**) as a yellow oil (2.50 g, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (1H, ddd, *J* = 5.0, 2.0, 1.0 Hz), 7.48 – 7.41 (1H, m), 7.09 (1H, dt, *J* = 8.0, 1.0 Hz), 6.94 (1H, ddd, *J* = 7.5, 5.0, 1.0 Hz), 5.10 (2H, dd, *J* = 7.5, 6.5 Hz), 4.92 – 4.83 (1H, m), 4.63 (2H, app t, *J* = 6.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0 149.6, 136.1, 121.9, 119.7, 78.2, 36.8; FTIR: 3487 (br), 3047 (m), 2950 (s), 2871 (s), 1664 (w), 1578 (s), 1556 (s), 1456 (s), 1416 (s), 1280 (m), 1255 (m), 1126 (s), 1087 (w), 1044 (m), 976 (s), 904 (s), 822 (s), 761 (s), 725 (s), 621 (w); HRMS: m/z [M+H]+ calcd. for $C_8H_{10}NOS$: 168.0491, found: 168.0483.

Synthesis of *tert*-butyl 3-(pyridin-2-ylsulfonyl)azetidine-1-carboxylate (2a)



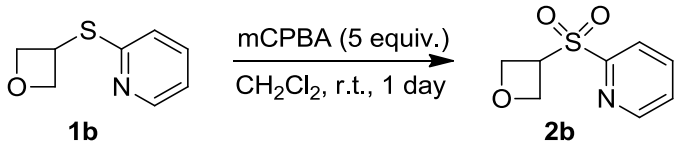
1a **2a**

mCPBA (3.223 g, 18.7 mmol) was added to *tert*-butyl 3-(pyridin-2-ylthio)azetidine-1-carboxylate (**1a**) (0.995 g, 3.7 mmol) in CH_2Cl_2 (20 mL) at room temperature. The resulting solution was stirred at r.t. for 1 day. A saturated aqueous solution of sodium bisulfite was then added and the solution was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and evaporated to afford crude product. The residue was purified via flash chromatography on silica gel eluting with a gradient from 10% to 50% ethyl acetate in dichloromethane affording *tert*-butyl 3-(pyridin-2-ylsulfonyl)azetidine-1-carboxylate (**2a**) as a beige solid (1.050 g, 94%).

Mp = 68 – 69 °C ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (1H, ddd, *J* = 4.5, 1.5, 1.0 Hz), 8.07 (1H, dt, *J* = 8.0, 1.0 Hz), 7.97 (1H, ddd, *J* = 8.0, 6.0, 1.5 Hz), 7.56 (1H, ddd, *J* = 8.0, 4.5, 1.0 Hz), 4.48 – 4.26 (3H, m), 4.15 (2H, app t, *J* = 9.0 Hz), 1.40 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5, 155.8, 150.4, 138.5, 127.9, 122.4, 80.5, 49.5 (br), 48.2, 28.3; FTIR: 2982 (m), 2889 (w), 1703 (s), 1581 (m), 1456 (m), 1431 (m), 1395 (s), 1320 (s), 1259 (m), 1166

(s), 1116 (m), 1087 (m), 990 (m), 897 (m), 779 (m), 746 (m); HRMS: m/z [M+H]+ calcd. for $C_{13}H_{19}N_2O_4S$: 299.1076, found: 299.1066.

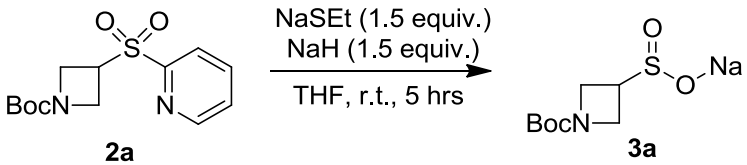
Synthesis of 2-(oxetan-3-ylsulfonyl)pyridine (2b)



mCPBA (2.734 g, 73.79 mmol) was added to 2-(oxetan-3-ylthio)pyridine (**1b**) (2.468 g, 14.76 mmol) in CH_2Cl_2 (80 mL) at room temperature. The resulting solution was stirred at r.t. for 1 day. A saturated aqueous solution of sodium bisulfite was then added and the solution was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and evaporated to afford crude product. The residue was purified via flash chromatography on silica gel eluting with a gradient from 10% to 30% ethyl acetate in dichloromethane affording 2-(oxetan-3-ylsulfonyl)pyridine (**2b**) as a colorless oil (2.854 g, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (1H, ddd, *J* = 5.0, 1.5, 1.0 Hz), 8.09 (1H, dt, *J* = 8.0, 1.0 Hz), 7.99 (1H, td, *J* = 8.0, 1.5 Hz), 7.60 – 7.54 (1H, m), 5.13 – 5.07 (2H, m), 4.93 – 4.88 (3H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.8, 150.3, 138.5, 127.9, 122.2, 70.3, 54.3; FTIR: 3616 (br), 3061 (w), 2961 (m), 2889 (m), 1721 (w), 1578 (m), 1456 (m), 1424 (m), 1313 (s), 1266 (m), 1162 (s), 1108 (s), 1083 (m), 994 (s), 904 (s), 779 (m), 746 (s), 664 (m); HRMS: m/z [M+H]+ calcd. for $C_8H_{10}NO_3S$: 200.0385, found: 200.0381.

Synthesis of sodium 1-(*tert*-butoxycarbonyl)azetidine-3-sulfinate (3a)

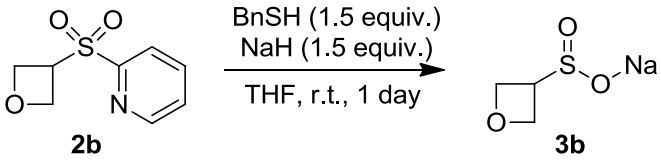


Sodium hydride (1.54 g, 38.51 mmol) was added to *tert*-butyl 3-(pyridin-2-ylsulfonyl)azetidine-1-carboxylate (**2a**) (7.66 g, 25.67 mmol) and sodium ethanethiolate (3.24 g, 38.51 mmol) in THF (120 mL) at room temperature. The resulting solution was stirred at r.t. for 5 h. A saturated aqueous solution of potassium carbonate and water were then added. Volatiles were then removed in vacuo and the solution was extracted with CH_2Cl_2. The

aqueous layer was concentrated to afford crude product. The residue was purified via flash chromatography on silica gel eluting with a gradient from 20% to 50% methanol in dichloromethane affording sodium 1-(*tert*-butoxycarbonyl)azetidine-3-sulfinate (**3a**) as a beige solid (6.14 g, 98%).

Mp = 48 – 50 ^{o}C ; ^{1}H NMR (400 MHz, D_2O) δ 4.13 – 3.89 (4H, m), 3.19 – 3.06 (1H, m), 1.39 (9H, s); ^{13}C NMR (101 MHz, D_2O) δ 157.9, 81.9, 52.3, 48.0 (br), 27.6; FTIR: 3394 (s), 2979 (w), 2875 (w), 1714 (s), 1674 (s), 1477 (w), 1424 (s), 1391 (s), 1370 (m), 1248 (w), 1151 (m), 1055 (m), 1019 (s), 976 (s), 771 (w); HRMS: m/z [M-Na]- calcd. for $C_8H_{14}NO_4S$: 220.0644, found: 220.0637.

Synthesis of sodium oxetane-3-sulfinate (3b)



2b **3b**

Sodium hydride (0.578 g, 14.44 mmol) was added to 2-(oxetan-3-ylsulfonyl)pyridine (**2b**) (1.918 g, 9.63 mmol) and benzyl mercaptan (1.7 mL, 14.44 mmol) in THF (80 mL) at room temperature. The resulting solution was stirred at r.t. for 1 day. Water was then added. Volatiles were removed in vacuo and the solution was extracted with CH_2Cl_2. The aqueous layer was concentrated to afford crude product. The residue was purified via flash chromatography on silica gel eluting with a gradient from 20% to 50% methanol in dichloromethane affording sodium oxetane-3-sulfinate (**3b**) as a beige solid (1.292 g, 93%).

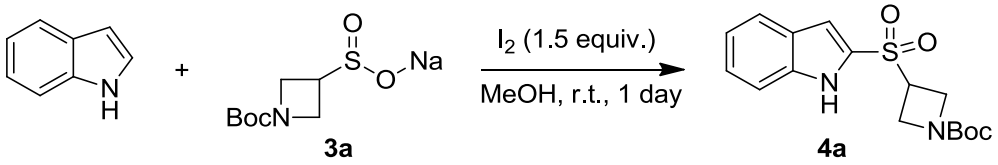
Mp = 223 - 224 ^{o}C ; ^{1}H NMR (400 MHz, MeOD) δ 4.82 – 4.77 (4H, m), 3.49 – 3.37 (1H, m); ^{13}C NMR (101 MHz, MeOD) δ 72.1, 61.1; FTIR: 2962 (w), 2889 (w), 1650 (s), 1028 (s), 964 (s), 904 (m), 775 (w); HRMS: m/z [M+Na]+ calcd. for $C_3H_5O_3SNa_2$: 166.9755, found: 166.9751.

3. Coupling of azetidine sodium sulfinate salt to the position 2 of indoles

<u>General procedure 1:</u> sodium sulfinate of azetidine coupling to position 2 of indole

Iodine (39 mg, 0.154 mmol, 1.5 equiv.) was added to a mixture of indole (0.103 mmol, 1 equiv.) and sodium 1-(*tert*-butoxycarbonyl)azetidine-3-sulfinate (**3a**) (75 mg, 0.309 mmol, 3 equiv.) in MeOH (0.5 mL) at room temperature. The resulting solution was stirred at r.t. for 1 day. All volatiles were removed *in vacuo* and the residue was purified via flash chromatography on silica gel to provide the title product (**4**).

Synthesis of *tert*-butyl 3-((1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (4a)

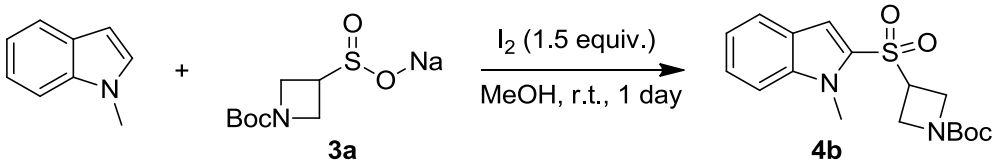


3a **4a**

Using general procedure 1 with indole (12 mg), the product was purified eluting with a gradient from 20% to 30% ethyl acetate in petroleum ether affording *tert*-butyl 3-((1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (**4a**) as a grey-brown solid (33 mg, 94%).

Mp = 138 - 139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (1H, s), 7.73 (1H, d, *J* = 8.0 Hz), 7.50 (1H, d, *J* = 8.5 Hz), 7.44 – 7.38 (1H, m), 7.25 – 7.20 (2H, m), 4.33 (2H, dd, *J* = 9.5, 4.5 Hz), 4.17 – 4.04 (3H, m), 1.40 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 137.5, 129.6, 127.2, 126.8, 123.0, 122.1, 112.6, 110.8, 80.9, 52.3, 49.9, 28.4; FTIR: 3318 (br), 2975 (w), 2928 (w), 1680 (s), 1414 (m), 1328 (m), 1136 (s), 900 (w), 741 (m), 702 (m), 630 (m); HRMS: m/z [M+Na]- calcd. for $C_{16}H_{20}N_2O_4SNa$: 359.1041, found: 359.1046.

Synthesis of *tert*-butyl 3-((1-methyl-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (4b)

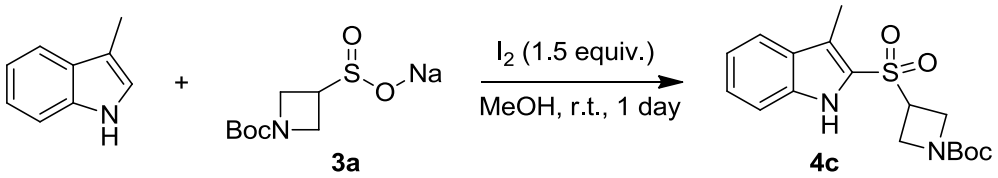


3a **4b**

Using general procedure 1 with 1-methylindole (13 µL), the product was purified eluting with a gradient from 20% to 30% ethyl acetate in petroleum ether affording *tert*-butyl 3-((1-methyl-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (**4b**) as a pale brown solid (28 mg, 77%).

Mp = 104 - 106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (1H, d, *J* = 8.0 Hz), 7.48 – 7.39 (2H, m), 7.32 (1H, s), 7.24 (1H, ddd, *J* = 8.0, 6.5, 1.0 Hz), 4.31 (2H, dd, *J* = 9.0, 5.0 Hz), 4.13 – 3.99 (6H, m), 1.42 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 140.1, 130.6, 126.6, 125.3, 123.2, 121.7, 112.9, 110.7, 80.7, 52.1, 49.8, 31.5, 28.4; FTIR: 2972 (w), 2925 (w), 1704 (s), 1469 (m), 1396 (s), 1323 (s), 1148 (s), 1071 (w), 899 (w), 805 (w), 737 (m), 685 (w); HRMS: m/z [M+Na]- calcd. for $C_{17}H_{22}N_2O_4SNa$: 373.1198, found: 373.1186.

Synthesis of *tert*-butyl 3-((3-methyl-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (4c)

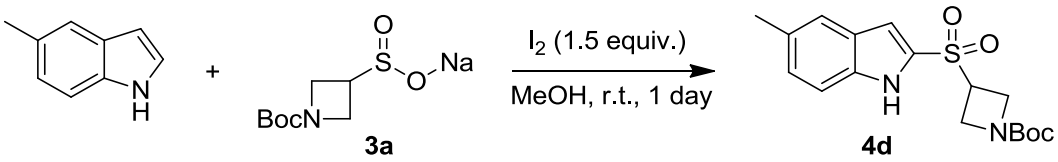


3a **4c**

Using general procedure 1 with 3-methylindole (13.5 mg), the product was purified eluting with a gradient from 20% to 30% ethyl acetate in petroleum ether affording *tert*-butyl 3-((3-methyl-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (**4c**) as an orange oil (29.5 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (1H, s), 7.66 (1H, d, *J* = 8.0 Hz), 7.45 (1H, d, *J* = 8.0 Hz), 7.41 – 7.35 (1H, m), 7.21 (1H, ddd, *J* = 8.0, 7.0, 1.0 Hz), 4.39 – 4.26 (2H, m), 4.18 – 4.02 (3H, m), 2.61 (3H, s), 1.39 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0, 136.6, 128.2, 126.8, 125.2, 121.1, 121.0, 120.8, 112.6, 80.8, 52.4, 49.7, 28.3, 9.3; FTIR: 3335 (br), 2983 (w), 2921 (w), 1689 (s), 1406 (s), 1320 (s), 1208 (w), 1144 (s), 904 (w), 801 (w), 750 (m), 694 (m); HRMS: m/z [M+Na]- calcd. for $C_{17}H_{22}N_2O_4SNa$: 373.1198, found: 373.1184.

Synthesis of *tert*-butyl 3-((5-methyl-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (4d)

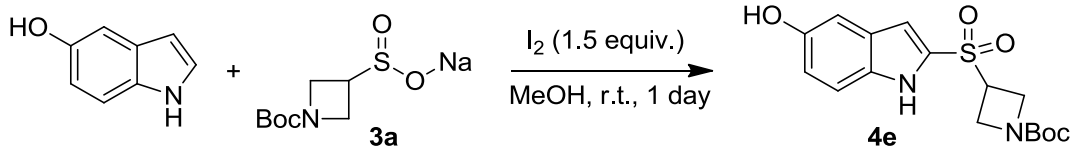


3a **4d**

Using general procedure 1 with 5-methylindole (13.5 mg), the product was purified eluting with a gradient from 20% to 30% ethyl acetate in petroleum ether affording *tert*-butyl 3-((5-methyl-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (**4d**) as a beige solid (33 mg, 91%).

Mp = 143 - 144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (1H, s), 7.47 (1H, s), 7.38 (1H, d, *J* = 8.5 Hz), 7.22 (1H, dd, *J* = 8.5, 1.5 Hz), 7.15 (1H, d, *J* = 1.5 Hz), 4.37 – 4.28 (2H, m), 4.16 – 4.02 (3H, m), 2.44 (3H, s), 1.39 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0, 136.2, 131.4, 129.2, 128.7, 127.3, 122.0, 112.4, 110.3, 80.8, 52.2, 49.9, 28.3, 21.5; FTIR: 3323 (br), 2976 (s), 2925 (s), 2891 (m), 1683 (s), 1516 (s), 1405 (s), 1315 (s), 1255 (m), 1135 (s), 1092 (s), 951 (m), 904 (s), 818 (m), 724 (s), 634 (m); HRMS: m/z [M+Na]- calcd. for $C_{17}H_{22}N_2O_4SNa$: 373.1198, found: 373.1183.

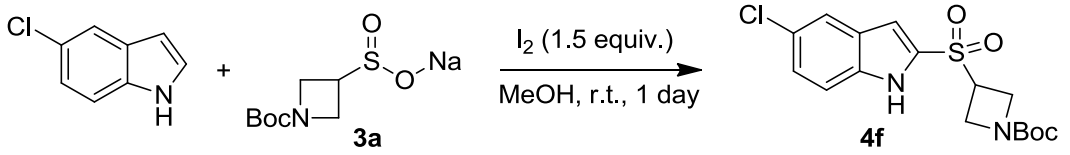
Synthesis of *tert*-butyl 3-((5-hydroxy-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (4e)



Using general procedure 1 with 5-hydroxyindole (13.7 mg), the product was purified eluting with a gradient from 40% to 50% ethyl acetate in petroleum ether affording *tert*-butyl 3-((5-hydroxy-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (**4e**) as a brown solid (34.5 mg, 95%).

M.p. = 158 - 160 °C; ^{1}H NMR (400 MHz, MeOD) δ 7.34 (d, *J* = 9.0 Hz, 1H), 7.06 – 7.01 (m, 2H), 6.95 (dd, *J* = 9.0, 2.5 Hz, 1H), 4.28 – 4.07 (m, 6H), 1.36 (s, 9H); ^{13}C NMR (101 MHz, MeOD) δ 157.6, 153.2, 134.7, 130.9, 128.8, 118.5, 114.3, 110.2, 106.0, 81.8, 53.1, 50.9 (br), 28.4; FTIR: 3412 (br), 2982 (w), 1651 (s), 1517 (m), 1414 (m), 1318 (m), 1173 (m), 1132 (m), 1091 (w), 953 (w), 854 (w); HRMS: m/z [M+Na]+ calcd. for $C_{16}H_{20}N_2O_5SNa$: 375.0991, found: 375.0988.

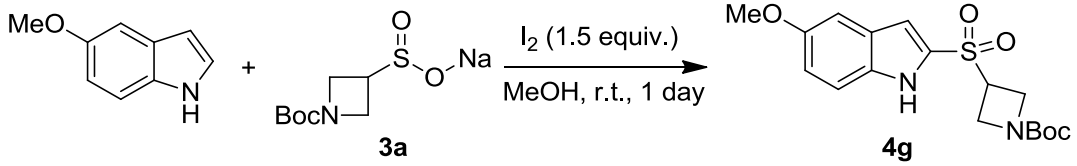
Synthesis of *tert*-butyl 3-((5-chloro-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (4f)



Using general procedure 1 with 5-chloroindole (15.6 mg), the product was purified eluting with a gradient from 20% to 30% ethyl acetate in petroleum ether affording *tert*-butyl 3-((5-chloro-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (**4f**) as a brown gum (23.1 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 7.70 (d, *J* = 2.0 Hz, 1H), 7.43 (d, J = 9.0 Hz, 1H), 7.36 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.17 (dd, *J* = 2.0, 0.5 Hz, 1H), 4.32 (dd, *J* = 9.5, 5.0 Hz, 2H), 4.18 – 4.09 (m, 3H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 135.8, 131.0, 128.0, 127.9, 127.5, 122.2, 113.8, 109.9, 81.0, 52.4, 49.9, 28.4; FTIR: 2975 (w), 2930 (w), 1679 (s), 1407 (s), 1325 (s), 1139 (s), 916 (w), 809 (m), 699 (m); HRMS: m/z [M+Na]+ calcd. for $C_{16}H_{19}N_2O_4S^{35}ClNa$: 393.0652, found: 393.0638.

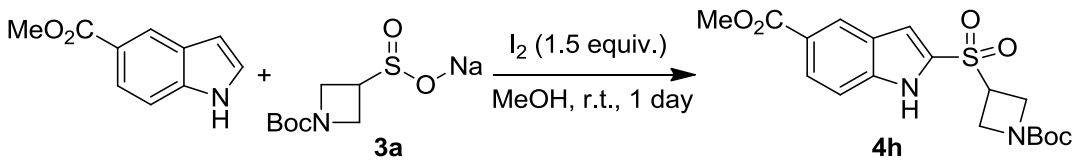
Synthesis of *tert*-butyl 3-((5-methoxy-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (4g)



Using general procedure 1 with 5-methoxyindole (15 mg), the product was purified eluting with a gradient from 40% to 50% ethyl acetate in petroleum ether affording *tert*-butyl 3-((5-methoxy-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (**4g**) as a grey solid (38 mg, 100%).

Mp = 116 – 118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (1H, s), 7.38 (1H, d, *J* = 9.5 Hz), 7.14 (1H, d, *J* = 1.5 Hz), 7.07 – 7.02 (2H, m), 4.32 (2H, dd, *J* = 9.0, 4.0 Hz), 4.16 – 4.05 (3H, m), 3.83 (3H, s), 1.38 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0, 155.4, 133.2, 129.4, 127.4, 118.6, 113.7, 110.2, 102.4, 80.9, 55.8, 52.2, 49.9, 28.3; FTIR: 2979 (w), 2889 (w), 2829 (w), 1676 (s), 1521 (m), 1401 (m), 1324 (m), 1161 (m), 1136 (m), 1028 (w), 955 (m), 835 (m), 694 (m); HRMS: m/z [M+Na]- calcd. for $C_{17}H_{22}N_2O_5SNa$: 389.1147, found: 389.1130.

Synthesis of methyl 2-((1-(*tert*-butoxycarbonyl)azetidin-3-yl)sulfonyl)-1*H*-indole-5-carboxylate (4h)

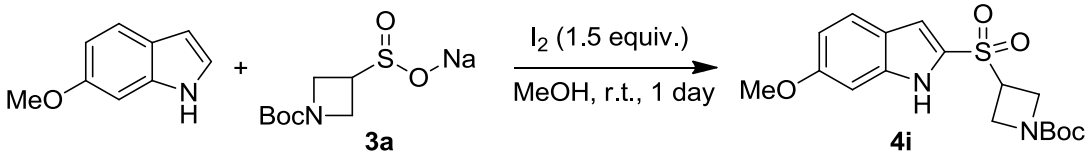


Using general procedure 1 with methyl 1*H*-indole-5-carboxylate (30 mg, 0.171 mmol) and sodium 1-(*tert*-butoxycarbonyl)azetidine-3-sulfinate (125 mg, 0.514 mmol), the product was purified eluting with a gradient from 20% to 30% ethyl acetate in petroleum ether affording

methyl 2-((1-(*tert*-butoxycarbonyl)azetidin-3-yl)sulfonyl)-1*H*-indole-5-carboxylate (**4h**) as a yellow solid (23.6 mg, 35%).

M.p. = 108 - 110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H), 8.50 (s, 1H), 8.08 (dd, *J* = 9.0, 1.5 Hz, 1H), 7.52 (d, *J* = 9.0 Hz, 1H), 7.32 (dd, *J* = 1.5, 0.5 Hz, 1H), 4.34 (dd, *J* = 9.5, 4.5 Hz, 2H), 4.18 – 4.10 (m, 3H), 3.95 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 156.0, 139.8, 131.3, 127.5, 126.6, 126.1, 124.3, 112.6, 111.8, 81.0, 52.3, 49.8, 28.5, 28.4.; FTIR: 3257 (br), 2975 (w), 2930 (w), 1706 (s), 1617 (m), 1404 (m), 1311 (s), 1256 (m), 1139 (s), 905 (w), 768 (w); HRMS: m/z [M+Na]+ calcd. for $C_{18}H_{22}N_2O_6SNa$: 417.1096, found: 417.1090.

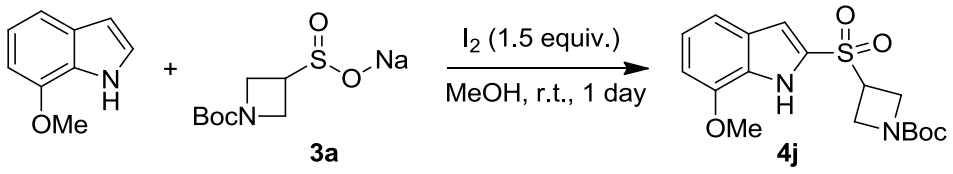
Synthesis of *tert*-butyl 3-((6-methoxy-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (4i)



Using general procedure 1 with 6-methoxyindole (15 mg), the product was purified eluting with a gradient from 40% to 50% ethyl acetate in petroleum ether affording *tert*-butyl 3-((6-methoxy-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (**4i**) as a grey solid (34 mg, 90%).

Mp = 178 - 180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (1H, s), 7.55 (1H, d, *J* = 9.0 Hz), 7.17 (1H, d, *J* = 1.5 Hz), 6.91 – 6.84 (2H, m), 4.33 (2H, dd, *J* = 9.5, 4.5 Hz), 4.16 – 4.03 (3H, m), 3.84 (3H, s), 1.39 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 156.0, 139.2, 127.5, 123.6, 121.2, 113.9, 111.4, 94.0, 80.8, 55.6, 52.3, 49.9, 28.3; FTIR: 2985 (w), 2933 (w), 1674 (s), 1632 (s), 1507 (m), 1409 (m), 1310 (m), 1233 (m), 1139 (s), 959 (w), 899 (w), 826 (m), 702 (m); HRMS: m/z [M+H]- calcd. for $C_{17}H_{23}N_2O_5S$: 367.1328, found: 367.1330.

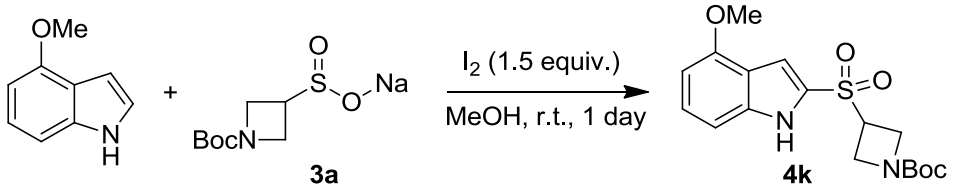
Synthesis of *tert*-butyl 3-((7-methoxy-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (4j)



Using general procedure 1 with 7-methoxyindole (13.5 µL), the product was purified eluting with a gradient from 20% to 30% ethyl acetate in petroleum ether affording *tert*-butyl 3-((7-methoxy-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (**4j**) as a beige solid (31.7 mg, 84%).

M.p. = 128 – 130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 2.0 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 4.32 (dd, *J* = 9.0, 4.5 Hz, 2H), 4.15 – 4.08 (m, 3H), 3.98 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 146.8, 129.3, 128.9, 128.3, 122.6, 114.9, 110.9, 105.1, 80.8, 55.7, 52.2, 49.8, 28.3; FTIR: 3309 (br), 2978 (m), 2934 (m), 2889 (w), 1696 (s), 1583 (m), 1524 (m), 1411 (s), 1321 (s), 1256 (s), 1139 (s), 1108 (s), 974 (m), 905 (m), 771 (m), 726 (s), 695 (m), 606 (m); HRMS: m/z [M+Na]+ calcd. for $C_{17}H_{22}N_2O_5SNa$: 389.1147, found: 389.1130.

Synthesis of *tert*-butyl 3-((4-methoxy-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (4k)



Using general procedure 1 with 4-methoxyindole (15 mg), the product was purified eluting with a gradient from 30% to 40% ethyl acetate in petroleum ether affording *tert*-butyl 3-((4-methoxy-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (**4k**) as a brown foam (37.0 mg, 98%).

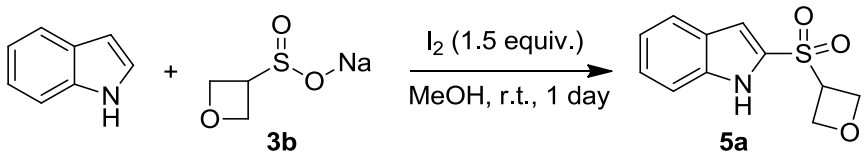
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 7.36 – 7.32 (m, 1H), 7.31 – 7.29 (m, 1H), 7.06 (d, *J* = 8.5 Hz, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 4.35 – 4.26 (m, 2H), 4.15 – 4.05 (m, 3H), 3.95 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 154.7, 138.9, 128.0 (2 carbons), 118.9, 108.6, 105.3, 100.7, 80.8, 55.6, 52.3, 49.9, 28.4; FTIR: 3241 (br), 2978 (m), 2934 (m), 2844 (w), 1688 (s), 1622 (m), 1588 (m), 1518 (m), 1411 (s), 1368 (s), 1331 (s), 1261 (s), 1137 (s), 1117 (s), 977 (w), 950 (w), 777 (m), 736 (s); HRMS: m/z [M+Na]+ calcd. for $C_{17}H_{22}N_2O_5SNa$: 389.1147, found: 389.1147.

4. Coupling of oxetane sodium sulfinate salt to the position 2 of indoles

<u>General procedure 2:</u> sodium sulfinate of oxetane coupling to position 2 of indole

Iodine (39 mg, 0.154 mmol, 1.5 equiv.) was added to a mixture of indole (0.103 mmol, 1 equiv.) and sodium oxetane-3-sulfinate (**3b**) (75 mg, 0.309 mmol, 3 equiv.) in MeOH (0.5 mL) at room temperature. The resulting solution was stirred at r.t. for 1 day. Volatiles were removed *in vacuo* and the residue was purified via flash chromatography on florisil to provide the title product.

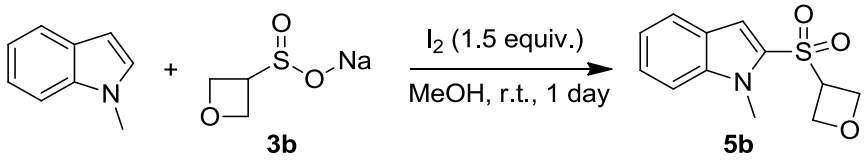
Synthesis of 2-(oxetan-3-ylsulfonyl)-1*H*-indole (5a)



Using general procedure 2 with indole (12 mg), the product was purified eluting with a gradient from 20% to 40% ethyl acetate in petroleum ether affording 2-(oxetan-3-ylsulfonyl)-1*H*-indole (**5a**) as a brown solid (24.5 mg, 100%).

M.p. = 136 - 138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.41 (m, 1H), 7.24 (m, 2H), 5.04 – 4.98 (m, 2H), 4.85 (t, *J* = 8.0 Hz, 2H), 4.58 (tt, *J* = 8.0, 6.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6, 129.7, 127.2, 126.8, 123.0, 122.1, 112.6, 110.7, 70.4, 58.2; FTIR: 3435 (br), 2953 (w), 2933 (w), 2853 (w), 1623 (w), 1320 (m), 1136 (s), 980 (w), 906 (w), 746 (m), 693 (m); HRMS: m/z [M+H]+ calcd. for $C_{11}H_{12}NO_3S$: 238.0538, found: 238.0529.

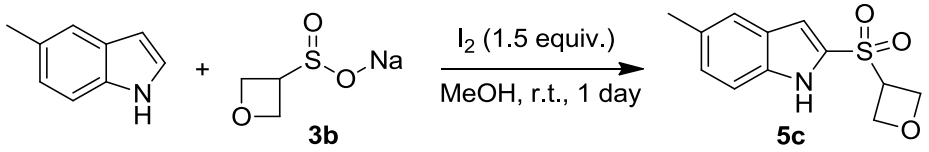
Synthesis of 1-methyl-2-(oxetan-3-ylsulfonyl)-1H-indole (5b)



Using general procedure 2 with *N*-methyl indole (13 µL), the product was purified eluting with a gradient from 10% to 40% ethyl acetate in petroleum ether affording 1-methyl-2-(oxetan-3-ylsulfonyl)-1*H*-indole (**5b**) as a brown solid (24.8 mg, 96%).

M.p. = 100 - 102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.0 Hz, 1H), 7.49 – 7.40 (m, 2H), 7.31 (s, 1H), 7.26 – 7.20 (m, 1H), 5.04 – 4.97 (m, 2H), 4.82 (t, *J* = 8.0 Hz, 2H), 4.55 (tt, *J* = 8.0, 6.0 Hz, 1H), 4.01 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.0, 130.8, 126.5, 125.3, 123.1, 121.7, 112.7, 110.7, 70.3, 57.9, 31.5; FTIR:2953 (m), 2923 (m), 2890 (m), 2850 (w), 1613 (w), 1506 (m), 1466 (s), 1323 (s), 1146 (s), 986 (m), 910 (s), 806 (s), 750 (s), 676 (s), 626 (s); HRMS: m/z [M+H]+ calcd. for $C_{12}H_{14}NO_3S$: 252.0694, found: 252.0682.

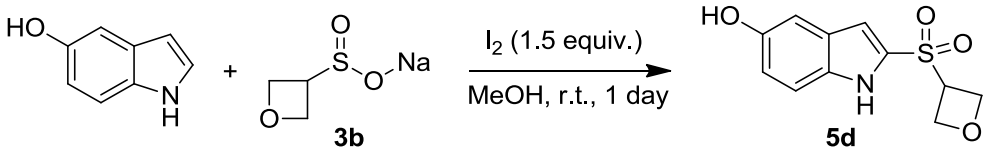
Synthesis of 5-methyl-2-(oxetan-3-ylsulfonyl)-1*H*-indole (5c)



Using general procedure 2 with 5-methyl indole (13.5 mg), the product was purified eluting with a gradient from 10% to 40% ethyl acetate in petroleum ether affording 5-methyl-2-(oxetan-3-ylsulfonyl)-1*H*-indole (**5c**) as a brown solid (26.2 mg, 100%).

M.p. = 132 - 134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.15 (d, *J* = 1.5 Hz, 1H), 4.99 (dd, *J* = 7.5, 6.5 Hz, 2H), 4.90 – 4.79 (m, 2H), 4.62 - 4.52 (m, 1H), 2.45 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.9, 131.7, 129.6, 128.9, 127.5, 122.2, 112.2, 110.2, 70.5, 58.2, 21.5; FTIR: 3410 (br), 2960 (w), 2926 (w), 1636 (m), 1513 (w), 1316 (m), 1133 (m), 906 (w); HRMS: m/z [M+H]+ calcd. for $C_{12}H_{14}NO_3S$: 252.0694, found: 252.0682.

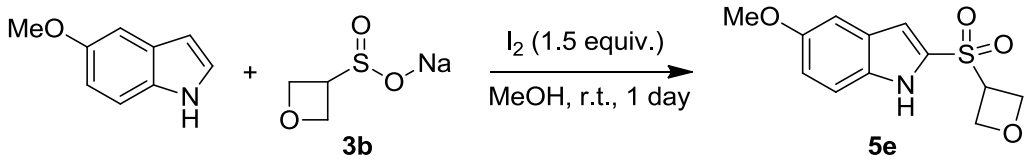
Synthesis of 2-(oxetan-3-ylsulfonyl)-1*H*-indol-5-ol (5d)



Using general procedure 2 with 5-hydroxyindole (13.7 mg), the product was purified eluting with a gradient from 30% to 60% ethyl acetate in petroleum ether affording 2-(oxetan-3-ylsulfonyl)-1*H*-indol-5-ol (**5d**) as a brown solid (16.8 mg, 64%).

M.p. = 120 - 122 °C; ^{1}H NMR (400 MHz, MeOD) δ 7.33 (dd, *J* = 9.0, 0.5 Hz, 1H), 7.04 - 7.00 (m, 2H), 6.93 (ddd, *J* = 9.0, 2.5, 1.5 Hz, 1H), 5.02 - 4.81 (m, 5H), 4.73 – 4.66 (m, 1H); ^{13}C NMR (101 MHz, MeOD) δ 153.2, 134.6, 131.5, 128.8, 118.4, 114.3, 109.8, 106.0, 71.5, 58.9; FTIR: 3425 (br), 2961 (w), 2538 (s), 1644 (s), 1442 (s), 1314 (m), 1173 (m), 1129 (m), 967 (w), 902 (w); HRMS: m/z [M+H]+ calcd. for $C_{11}H_{11}NO_4S$: 254.0487, found: 254.0495.

Synthesis of 5-methoxy-2-(oxetan-3-ylsulfonyl)-1*H*-indole (5e)

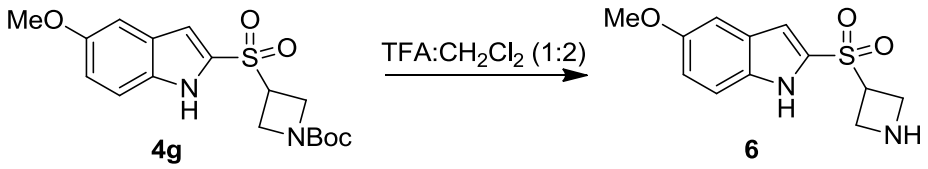


Using general procedure 2 with 5-methoxyindole (15.1 mg), the product was purified eluting with a gradient from 10% to 40% ethyl acetate in petroleum ether affording 5-methoxy-2-(oxetan-3-ylsulfonyl)-1*H*-indole (**5e**) as a brown gum (27.8 mg, 100 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1H), 7.39 – 7.34 (m, 1H), 7.15 (d, *J* = 1.5 Hz, 1H), 7.09 – 7.04 (m, 2H), 5.00 (dd, *J* = 7.5, 6.0 Hz, 2H), 4.85 (t, *J* = 7.5 Hz, 2H), 4.57 (tt, *J* = 7.5, 6.0 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5, 133.0, 129.6, 127.6, 118.7, 113.6, 110.2, 102.5, 70.5, 58.2, 55.8; FTIR: 3423 (br), 2953 (w), 2920 (w), 1633 (m), 1513 (m), 1316 (m), 1200 (m), 1166 (m), 1136 (m), 906 (w); HRMS: m/z [M+H]+ calcd. for $C_{12}H_{14}NO_4S$: 268.0644, found: 268.0632.

5. Synthesis of Atevirdine analogue

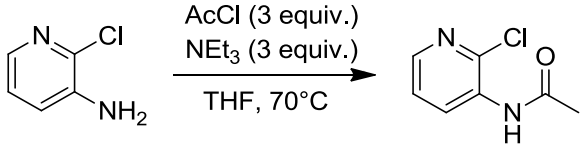
Synthesis 2-(azetidin-3-ylsulfonyl)-5-methoxy-1*H*-indole (6)



TFA (0.25 mL) was added to *tert*-butyl 3-((5-methoxy-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (36.6 mg, 0.1 mmol) in CH_2Cl_2 (0.5 mL) at room temperature. The resulting solution was stirred at 40 °C for 1 day. Volatiles were removed in vacuo and the residue was purified via flash chromatography on silica gel eluting with a gradient from 10% to 15% methanol in dichloromethane affording 2-(azetidin-3-ylsulfonyl)-5-methoxy-1*H*-indole (**6**) as a beige solid (26.5 mg, 100%).

M.p. = 102 - 104 °C; ^{1}H NMR (400 MHz, MeOD) δ 7.40 (d, *J* = 9.0 Hz, 1H), 7.21 (d, *J* = 1.0 Hz, 1H), 7.15 (d, *J* = 2.5 Hz, 1H), 7.04 (dd, *J* = 9.0, 2.5 Hz, 1H), 4.57 – 4.47 (m, 1H), 4.43 – 4.39 (m, 4H), 3.82 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 156.7, 135.3, 130.1, 128.4, 119.5, 114.7, 111.4, 103.1, 56.0, 55.1, 47.4; FTIR: 3296 (br), 2916 (w), 2846 (w), 1670 (s), 1513 (m),1436 (m), 1316 (m), 1203 (s), 1136 (s), 1033 (w), 790 (w); HRMS: m/z [M+H]+ calcd. for $C_{12}H_{15}N_2O_3S$: 267.0803, found: 267.0796.

Synthesis of *N*-(2-chloropyridin-3-yl)acetamide

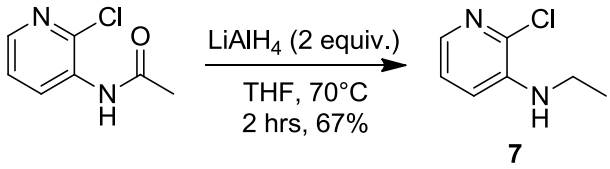


Acetyl chloride (0.21 mL, 3 mmol) was added to 2-chloropyridin-3-amine (128.6 mg, 1 mmol) and triethylamine (0.42 mL, 3 mmol) in THF (3 mL) at room temperature. The resulting solution was stirred at 70 °C for 8 hours and cooled to r.t.. Volatiles were then removed in vacuo and the residue was diluted with CH_2Cl_2. Water was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified via flash chromatography on silica gel eluting with a gradient from 40% to 50% ethyl acetate in petroleum ether affording *N*-(2-chloropyridin-3-yl)acetamide as a beige solid (144.3 mg, 84%)

M.p. = 68 - 70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (td, *J* = 8.0, 1.5 Hz, 1H), 8.13 – 8.06 (m, 1H), 7.65 (s, 1H), 7.28 – 7.19 (m, 1H), 2.26 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 143.9, 132.0, 129.1, 123.5, 26.5, 25.0; FTIR: 3350 (s), 3021 (w), 2927 (w), 2874 (w),

1695 (s), 1582 (s), 1519 (s), 1452 (s), 1362 (s), 1299 (s), 1236 (s), 1082 (m), 1039 (s), 1013 (s) 952 (m), 803 (s), 729 (s), 643 (s); HRMS: m/z [M+H]+ calcd. for $C_7H_8N_2O^{35}Cl$: 171.0324, found: 171.0325.

Synthesis of 2-chloro-*N*-ethylpyridin-3-amine (7)

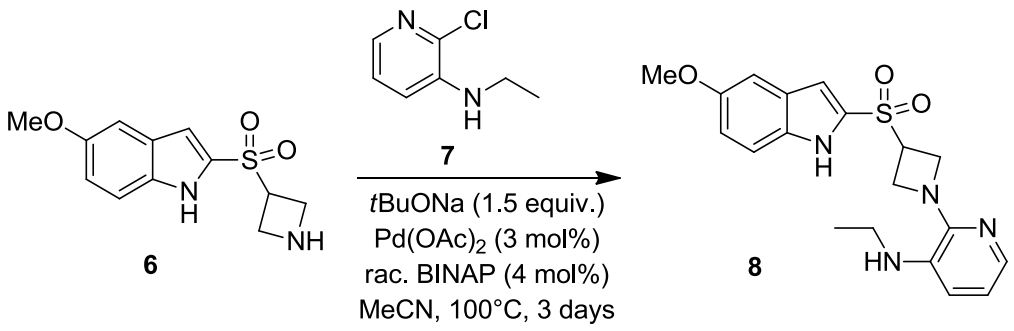


7

$LiAlH_4$ (17.8 mg, 0.469 mmol) was added to *N*-(2-chloropyridin-3-yl)acetamide (40 mg, 0.234 mmol) in THF (1 mL) at room temperature. The resulting solution was stirred at 70 °C for 2 hours and cooled to r.t.. Water was then added and the mixture was extracted with CH_2Cl_2. The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified via flash chromatography on silica gel eluting with 30% ethyl acetate in petroleum ether affording 2-chloro-*N*-ethylpyridin-3-amine (**7**) as an orange oil (24.5 mg, 67%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 4.5, 1.5 Hz, 1H), 7.08 (dd, *J* = 8.0, 4.5 Hz, 1H), 6.86 (dd, *J* = 8.0, 1.5 Hz, 1H), 4.26 (s, 1H), 3.22 – 3.11 (m, 2H), 1.31 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0, 137.0, 136.2, 123.5, 117.3, 38.0, 14.6; FTIR: 3420 (s), 3063 (w), 2973 (s), 2876 (m), 1586 (s), 1493 (s), 1383 (s), 1323 (s), 1273 (m), 1213 (s), 1150 (s), 1120 (m), 1076 (m), 1053(s), 790 (s), 730 (m), 710 (m); HRMS: m/z [M+H]+ calcd. for $C_7H_{10}N_2{}^{35}Cl$: 157.0533, found: 157.0535.

Synthesis of *N*-ethyl-2-(3-((5-methoxy-1*H*-indol-2-yl)sulfonyl)azetidin-1-yl)pyridin-3-amine (8)



Into a flame-dried Schlenk tube were introduced 2-chloro-*N*-ethylpyridin-3-amine (15.6 mg, 0.1 mmol), *t*BuONa (7.2 mg, 0.075 mmol), $Pd(OAc)_2$ (0.4 mg, 0.0015 mmol) and dppf (1.1 mg, 0.002 mmol) under argon. The Schlenk tube was sealed, and the atmosphere was evacuated and purged 3 times with argon. 2-(Azetidin-3-ylsulfonyl)-5-methoxy-1*H*-indole (34 mg, 0.128 mmol) and acetonitrile were then added. The Schlenk tube was sealed, and the atmosphere was evacuated and purged 3 times with argon. The resulting solution was stirred at 100 °C for 3 days, cooled to r.t. and concentrated *in vacuo*. The residue was purified via flash chromatography on silica gel eluting with a gradient from 30% to 50% ethyl acetate in petroleum ether affording *N*-ethyl-2-(3-((5-methoxy-1*H*-indol-2-yl)sulfonyl)azetidin-1-yl)pyridin-3-amine (**8**) as a beige solid (10.2 mg, 53%).

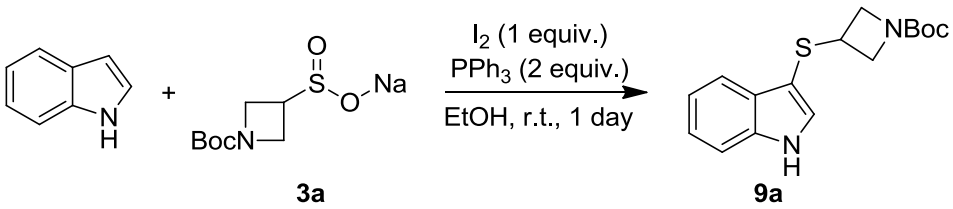
M.p. = 110 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 7.63 (dd, *J* = 4.5, 1.5 Hz, 1H), 7.34 (d, *J* = 9.0 Hz, 1H), 7.19 – 7.16 (m, 1H), 7.09 – 7.03 (m, 2H), 6.79 – 6.71 (m, 2H), 4.44 – 4.38 (m, 2H), 4.30 – 4.17 (m, 4H), 3.85 (s, 3H), 3.01 (q, *J* = 7.0 Hz, 2H), 1.21 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4, 149.5, 135.6, 132.8, 130.4, 129.4, 127.7, 118.4, 118.2, 116.6, 113.5, 110.0, 102.6, 55.8, 54.4, 51.5, 38.4, 14.8; FTIR: 3367 (w), 2954 (w), 2861 (w), 1575 (m), 1479 (m), 1445 (m), 1422 (s), 1282 (s), 1136 (m), 1096 (m), 1029 (m), 956 (m), 896 (m), 789 (m), 716 (s); HRMS: m/z [M+H]+ calcd. for $C_{19}H_{23}N_4O_3S$: 387.1491, found: 387.1492.

6. Coupling of azetidine sodium sulfinate salt to the position 3 of indoles

General procedure 3:

Iodine (26.1 mg, 0.206 mmol) was added to indole (12 mg, 0.103 mmol), triphenylphosphine (54 mg, 0.206 mmol) and sodium 1-(*tert*-butoxycarbonyl)azetidine-3-sulfinate (**3b**) (50.1 mg, 0.206 mmol) in EtOH (0.5 mL) at room temperature. The resulting solution was stirred at 70 °C for 1.5 days. All volatiles were removed *in vacuo* and the residue was purified via flash chromatography on silica gel to provide the title product.

Synthesis of *tert*-butyl 3-((1*H*-indol-3-yl)thio)azetidine-1-carboxylate (9a)

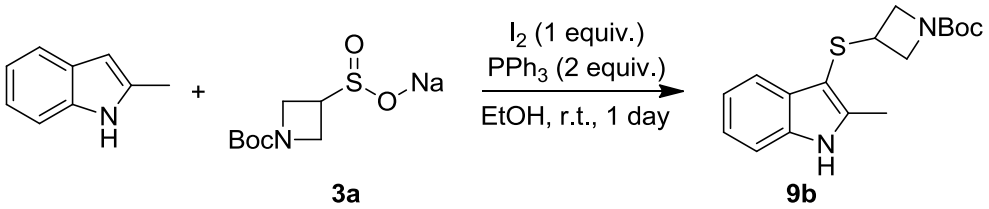


3a **9a**

Using general procedure 3 with indole (12 mg), the product was purified eluting with a gradient from 20% to 30% ethyl acetate in petroleum ether affording *tert*-butyl 3-((1*H*-indol-3-yl)thio)azetidine-1-carboxylate (**9a**) as a brown gum (26.3 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.77 – 7.71 (m, 1H), 7.42 – 7.37 (m, 2H), 7.28 – 7.19 (m, 2H), 4.15 – 4.10 (m, 2H), 3.85 (dd, *J* = 9.0, 5.5 Hz, 2H), 3.78 – 3.70 (m, 1H), 1.35 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4, 136.4, 130.6, 129.9, 123.0, 120.9, 119.3, 111.8, 102.7, 79.7, 56.2 (br), 35.7, 28.4; FTIR: 3278 (s), 2975 (s), 2882 (s), 1675 (s), 1407 (s), 1249 (m), 1156 (s), 1008 (m), 977 (w), 898 (w), 857 (m), 744 (s); HRMS: m/z [M+H]+ calcd. for $C_{16}H_{21}N_2O_2S$: 305.1324, found: 305.1319.

Synthesis of *tert*-butyl 3-((2-methyl-1*H*-indol-3-yl)thio)azetidine-1-carboxylate (9b)

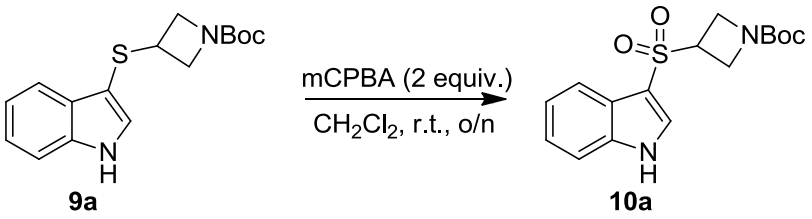


3a **9b**

Using general procedure 3 with 2-methylindole (13.5 mg), the product was purified eluting with a gradient from 20% to 30% ethyl acetate in petroleum ether affording *tert*-butyl 3-((2-methyl-1*H*-indol-3-yl)thio)azetidine-1-carboxylate (**9b**) as a brown solid (33.1 mg, 100%).

M.p. = 130 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.68 – 7.62 (m, 1H), 7.32 – 7.28 (m, 1H), 7.19 – 7.15 (m, 2H), 4.12 (t, *J* = 9.0 Hz, 2H), 3.84 (dd, *J* = 9.0, 5.5 Hz, 2H), 3.77 – 3.69 (m, 1H), 2.54 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4, 141.2, 135.4, 131.1, 122.1, 120.6, 118.6, 110.9, 99.5, 79.8, 56.4 (br), 36.2, 28.4, 12.4; FTIR: 3283 (m), 2976 (m), 2880 (w), 1676 (s), 1473 (m), 1453 (m), 1413 (s), 1363 (m), 1230 (w), 1153 (m), 743 (m); HRMS: m/z [M+H]+ calcd. for $C_{17}H_{23}N_2O_2S$: 319.1480, found: 319.1485.

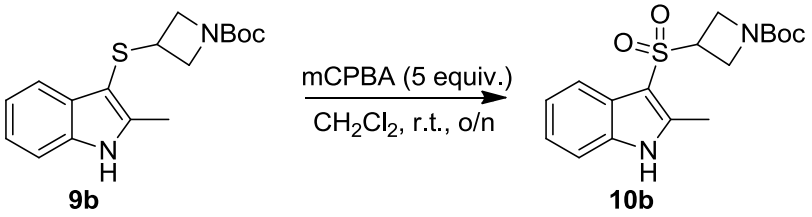
Synthesis of *tert*-butyl 3-((1*H*-indol-3-yl)sulfonyl)azetidine-1-carboxylate (10a)



mCPBA (17.2 mg, 0.1 mmol) was added to a solution of (**9a**) (15.2 mg, 0.05 mmol) in dichloromethane (1 mL). The resulting mixture was stirred at room temperature over night before being quenched with a saturated solution of sodium nitrite. The resulting mixture was extracted with dichloromethane. The combined organic layers was dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography eluting with a gradient from 50 to 100% ethyl acetate in petroleum ether to afford *tert*-butyl 3-((1*H*-indol-3-yl)sulfonyl)azetidine-1-carboxylate (**10a**), (12.1 mg, 72%) as a white solid.

M.p. = 166 – 168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 7.93 – 7.89 (m, 1H), 7.75 (m, 1H), 7.47 (dd, J = 7.0, 1.5 Hz, 1H), 7.35 – 7.27 (m, 2H), 4.36 – 3.98 (m, 5H), 1.42 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4, 136.6, 131.6, 124.4, 124.0, 123.0, 119.3, 112.8, 111.2, 81.0, 51.8, 50.0, 28.4; FTIR: 3281 (br), 2978 (m), 2930 (w), 2893 (w), 1679 (s), 1418 (s), 1369 (m), 1301 (s), 1246 (m), 1129 (s), 1019 (w), 905 (w), 747 (m), 702 (m); HRMS: m/z [M+Na]+ calcd. for $C_{16}H_{20}N_2O_4SNa$: 359.1041, found: 359.1024.

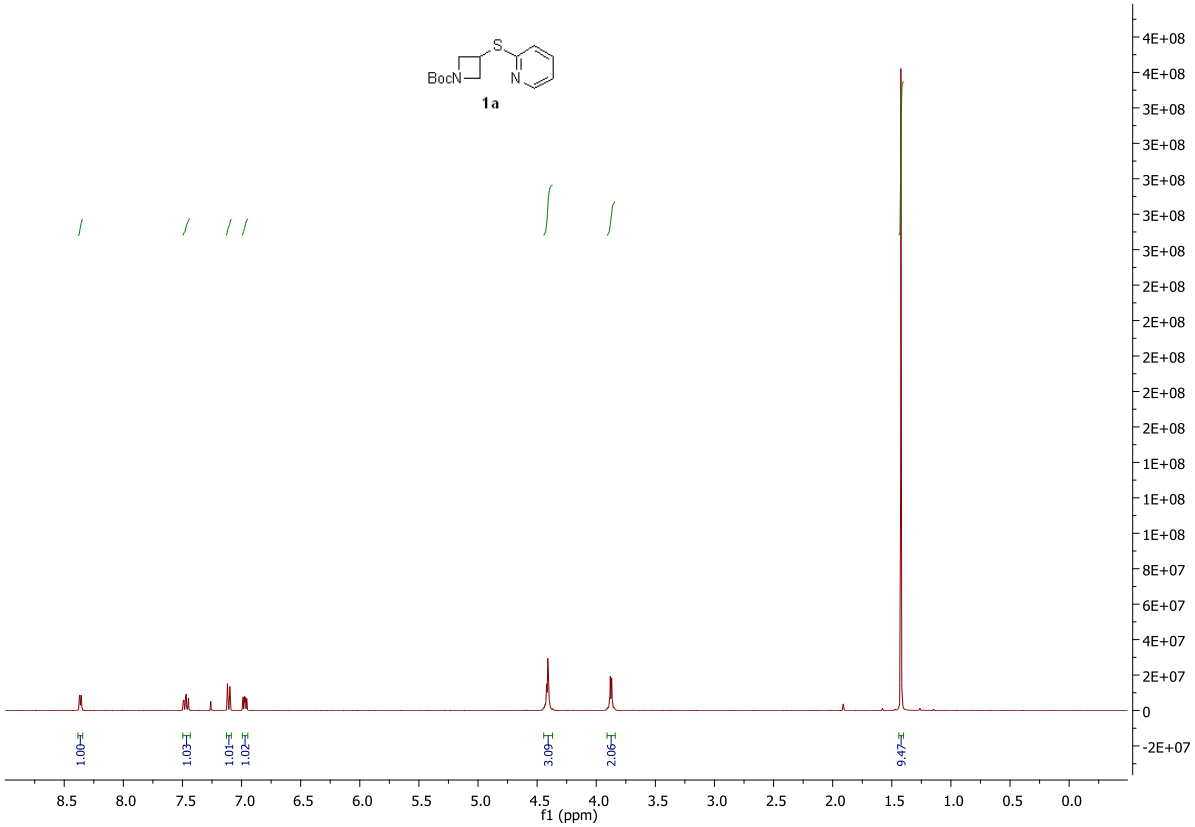
Synthesis of *tert*-butyl 3-((2-methyl-1*H*-indol-3-yl)sulfonyl)azetidine-1-carboxylate (10b)

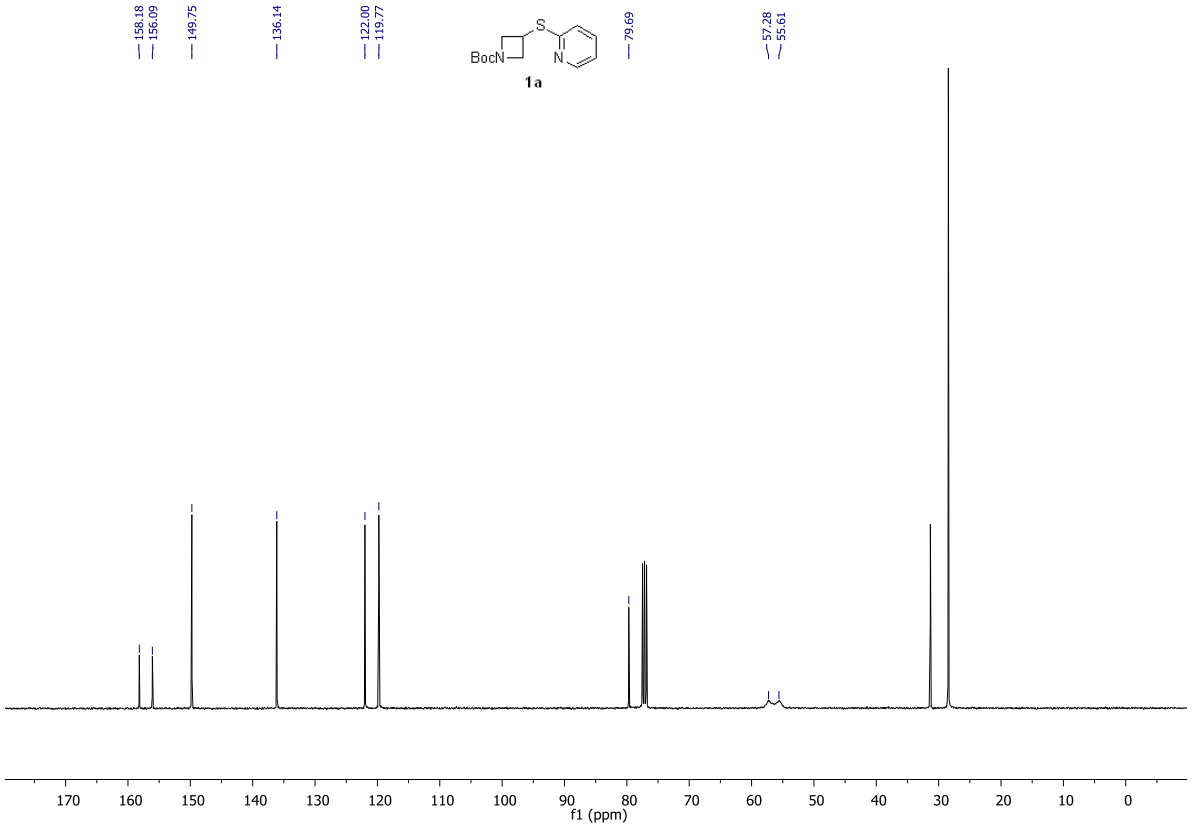


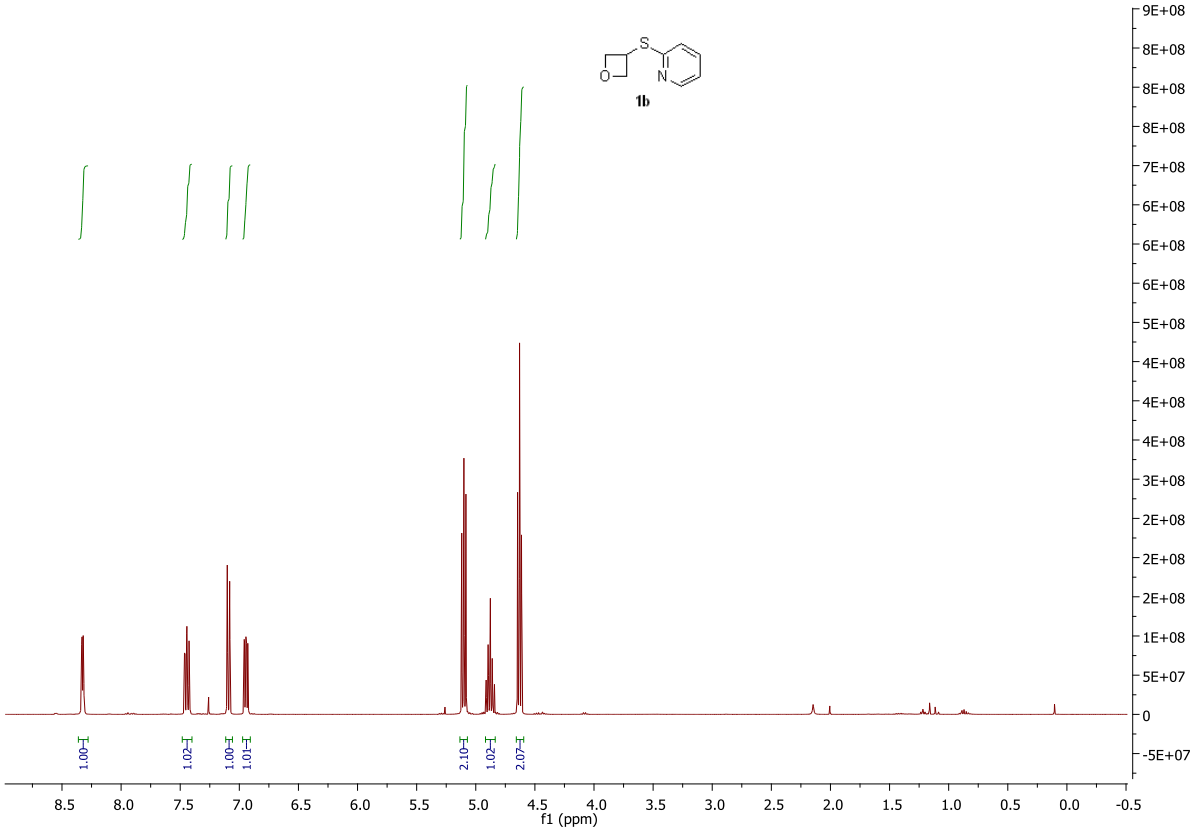
mCPBA (40.6 mg, 0.235 mmol) was added to a solution of **9b** (15.0 mg, 0.047 mmol) in dichloromethane (1 mL). The resulting mixture was stirred at room temperature over night before being quenched with a saturated solution of sodium nitrite. The resulting mixture was extracted with dichloromethane. The combined organic layers was dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography eluting with a gradient from 50 to 100% ethyl acetate in petroleum ether to afford *tert*-butyl 3-((2-methyl-1*H*-indol-3-yl)sulfonyl)azetidine-1-carboxylate (**10b**), (12.2 mg, 74%) as a white solid.

M.p. 128 – 130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 7.92 – 7.88 (m, 1H), 7.36 – 7.32 (m, 1H), 7.26 – 7.22 (m, 2H), 4.26 (br, 2H), 4.11 – 3.93 (m, 3H), 2.70 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2, 142.8, 134.6, 125.9, 123.7, 122.7, 119.4, 111.4, 107.0, 80.7, 52.2, 49.8 (br), 28.4, 13.2; FTIR: 3274 (br), 2978 (m), 2930 (m), 2857 (m), 1679 (s), 1536 (w), 1453 (m), 1412 (s), 1303 (s), 1256 (m), 1144 (s), 1112 (m), 1084 (m), 909 (m), 858 (w); HRMS: m/z [M+H]+ calcd. for $C_{17}H_{23}N_2O_4S$: 351.1379, found: 351.1391.

7. NMR spectra



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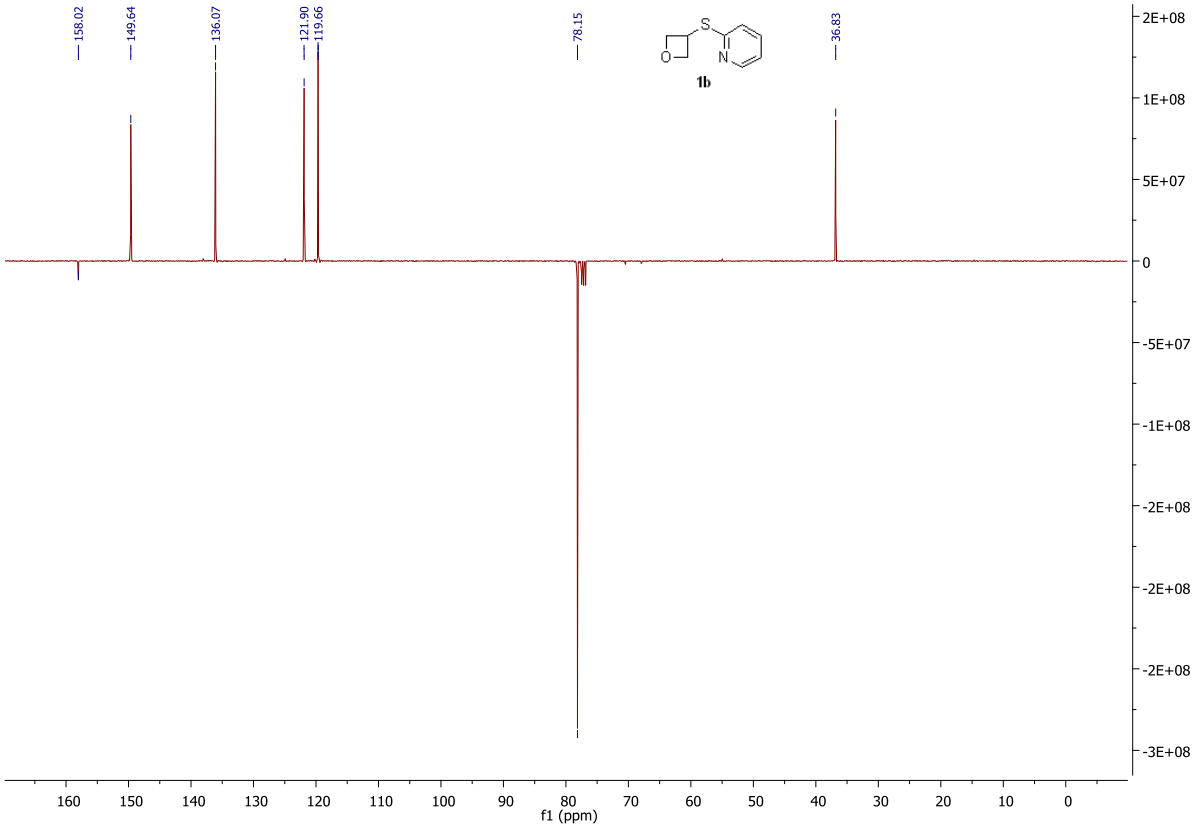
1.00
1.01
2.10
1.02
2.07
f1 (ppm)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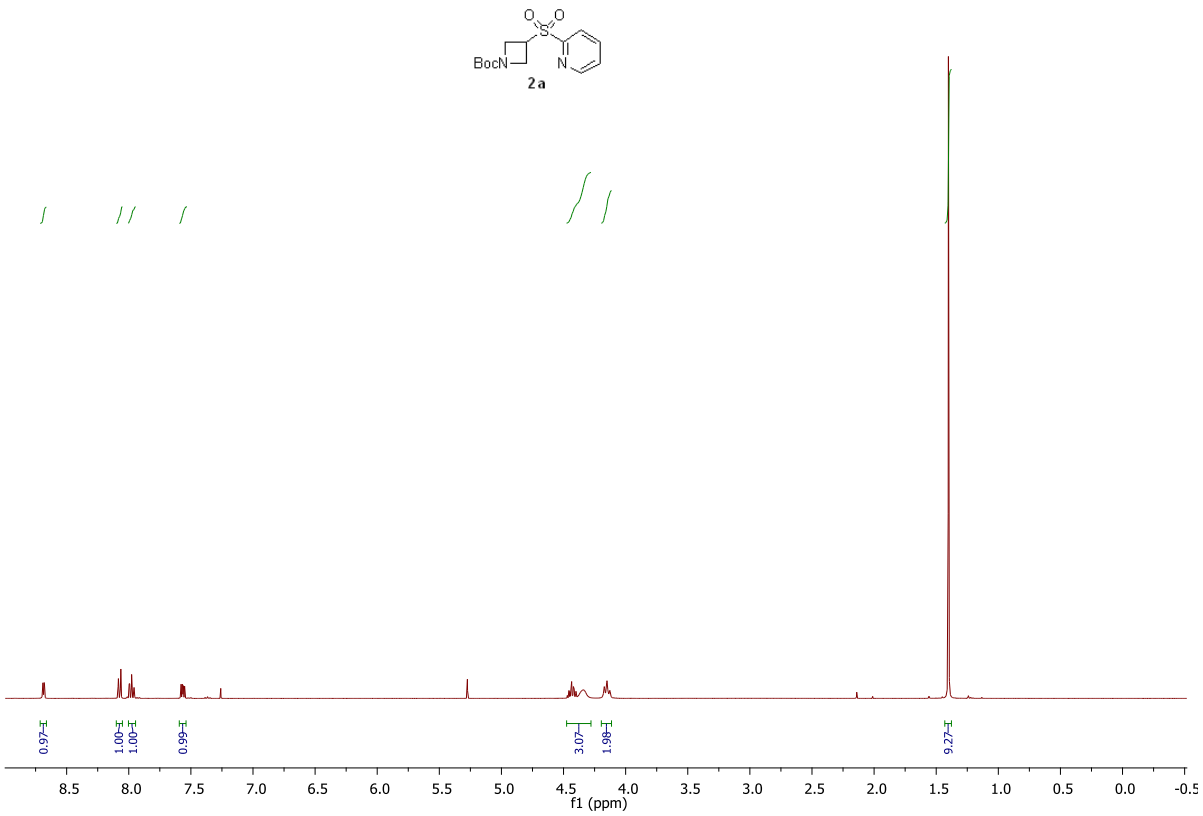
121.90
119.66
78.15
36.83
1b
f1 (ppm)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N
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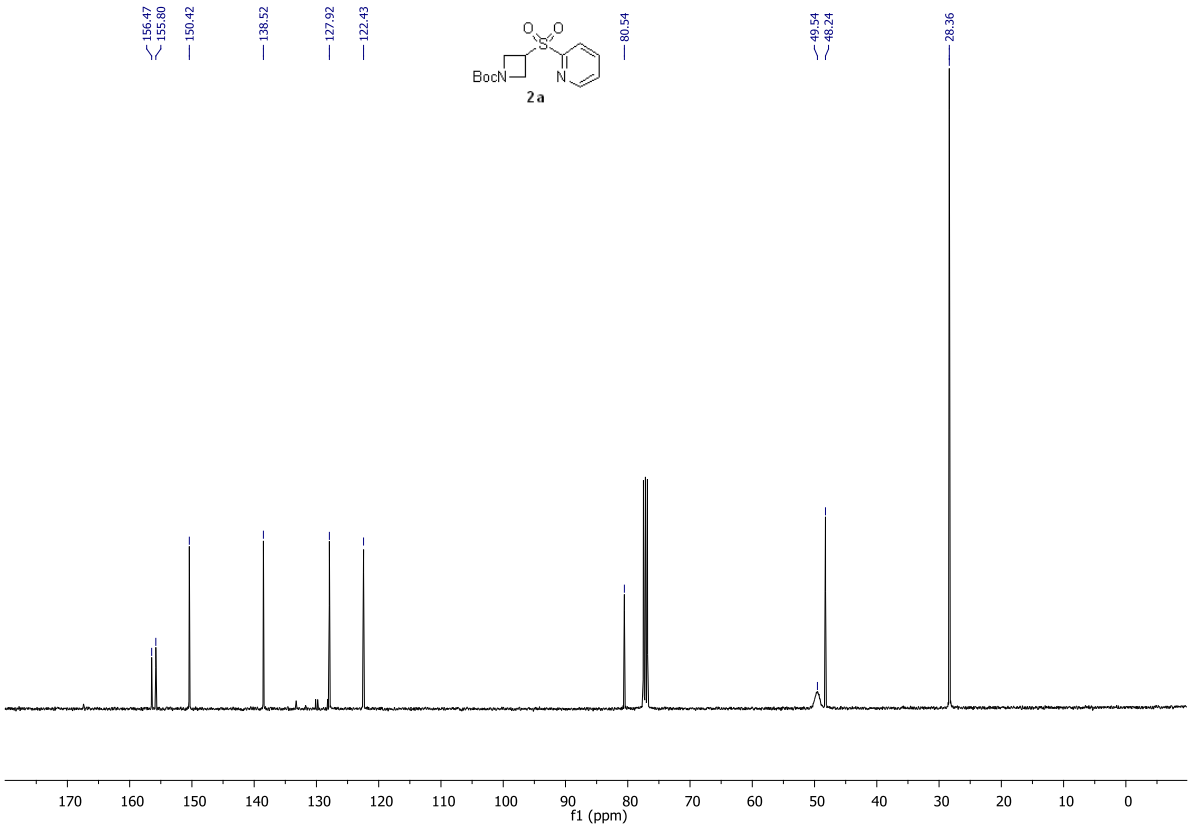
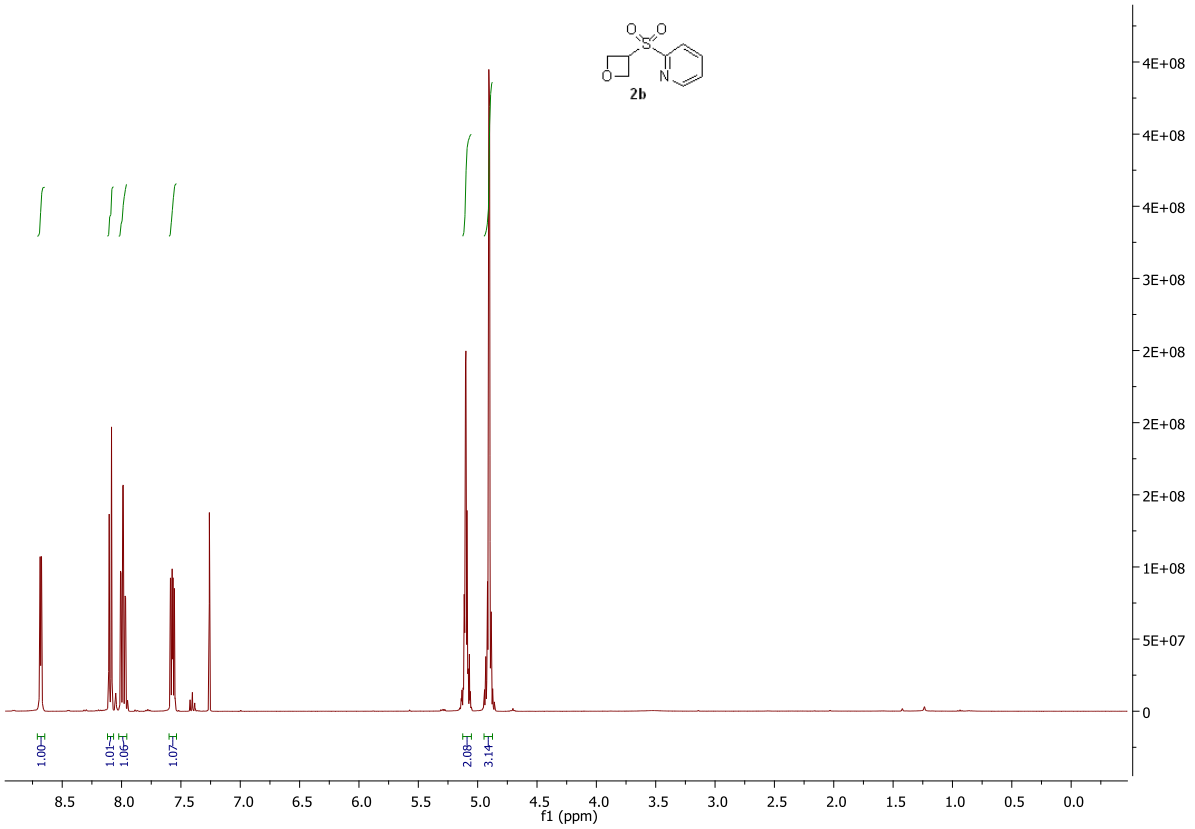
1.00
0.99
3.07
1.98
9.27
f1 (ppm)


156.47
155.80
150.42
138.52
127.92
122.43
80.54
49.54
48.24
28.36
BocN
N
2a
f1 (ppm)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3.14
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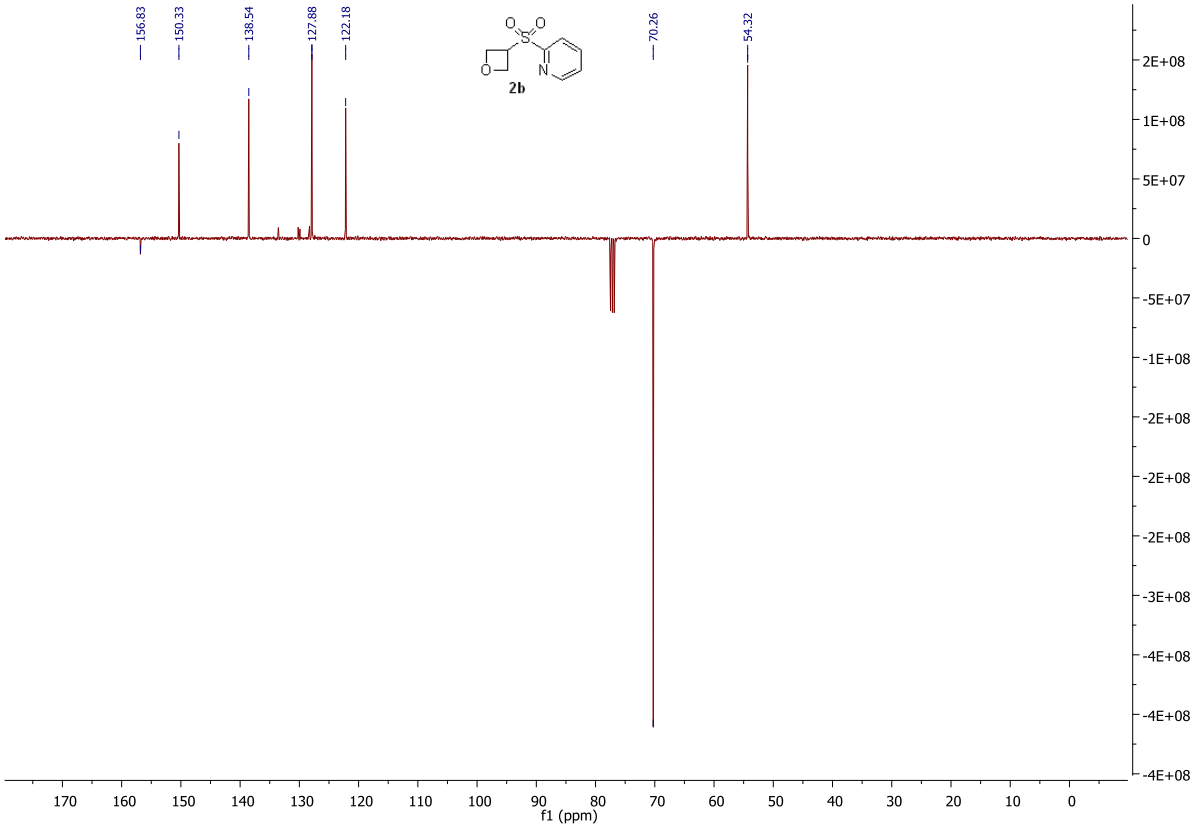
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54.32
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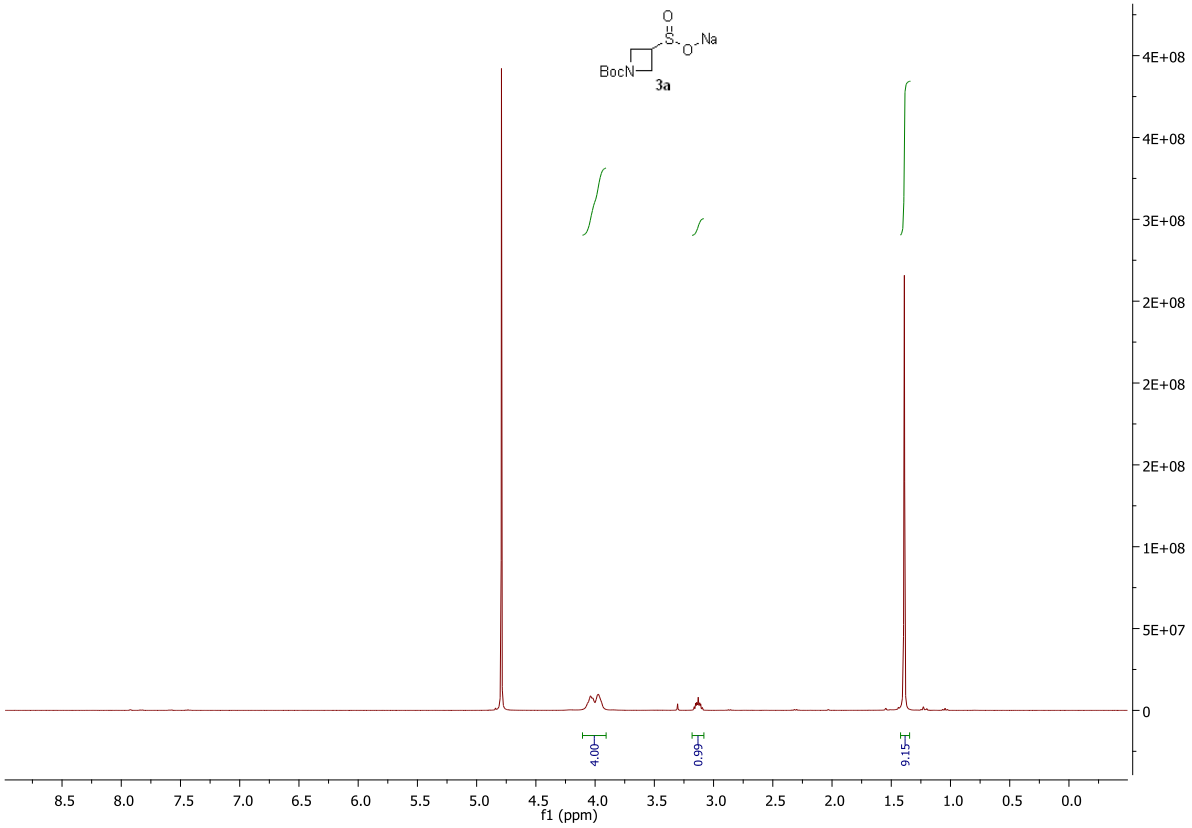
f1 (ppm)


O
O
Na
BocN
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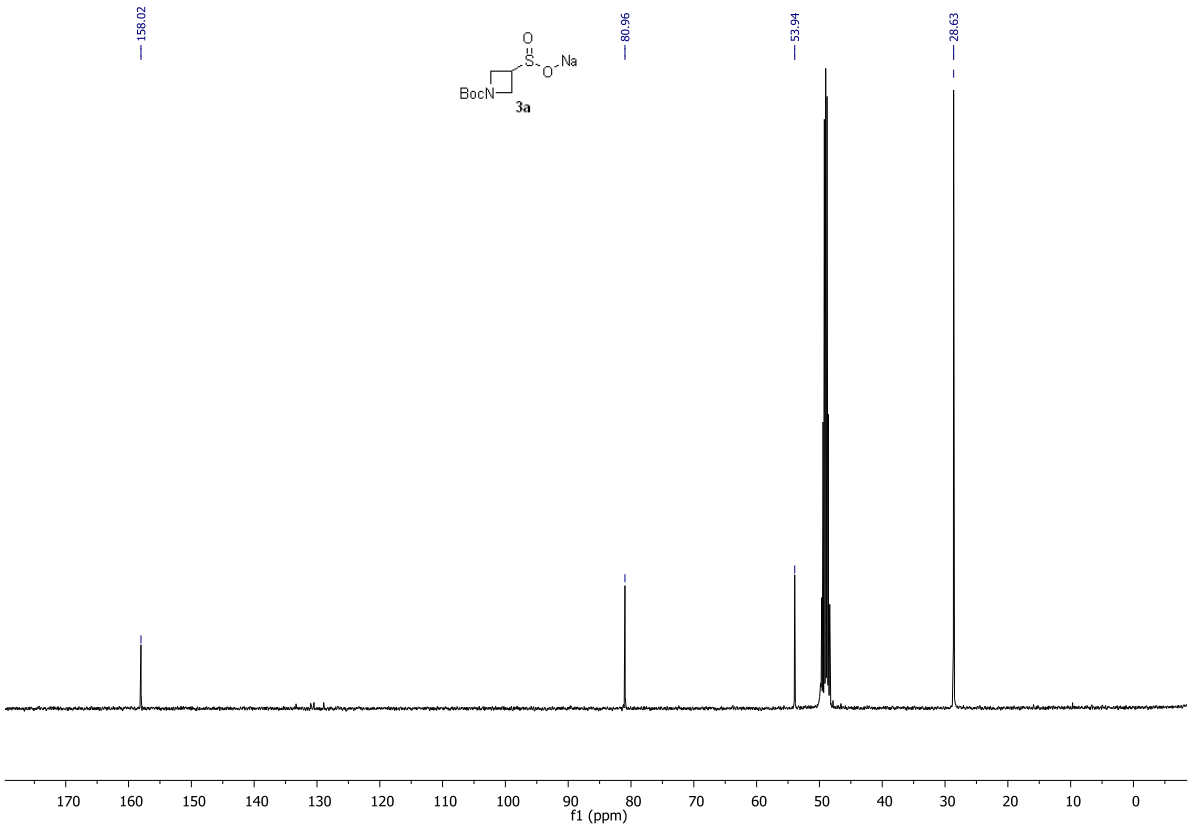
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
4.00
0.99
9.15
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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O
Na
BocN
3a
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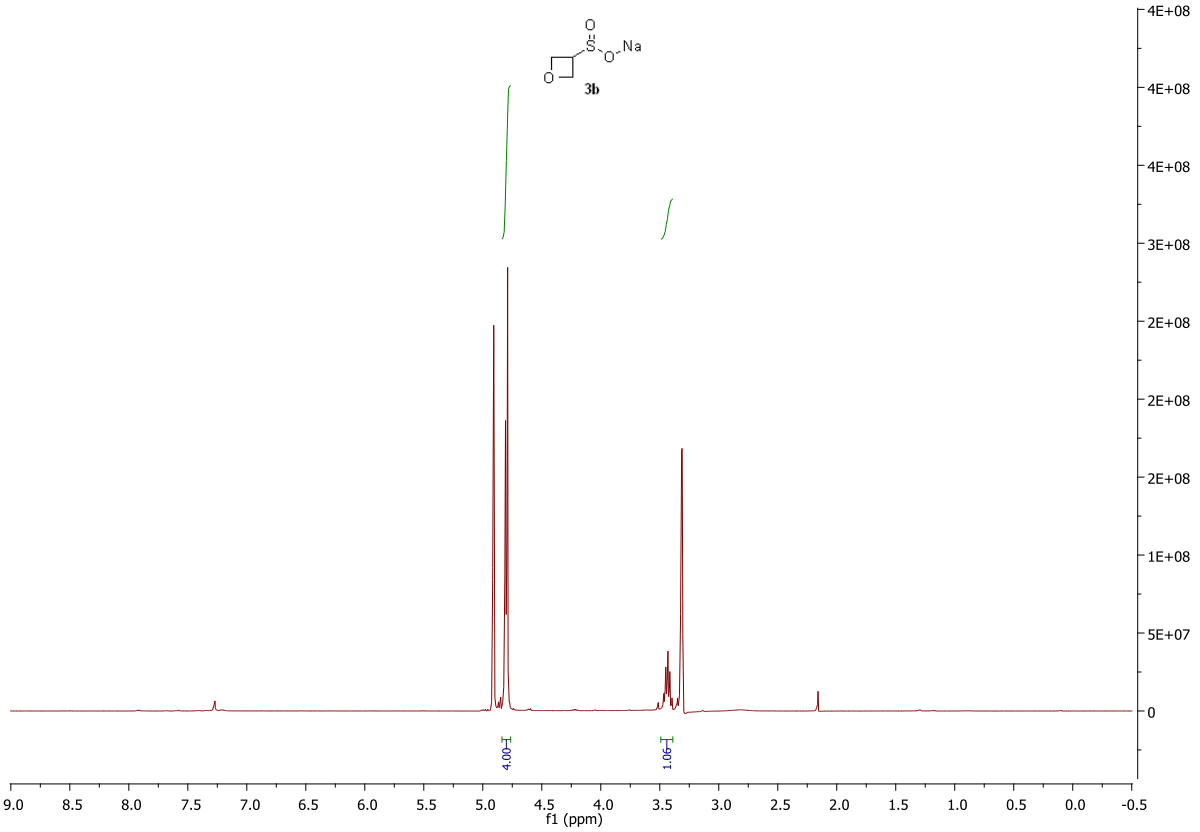
f1 (ppm)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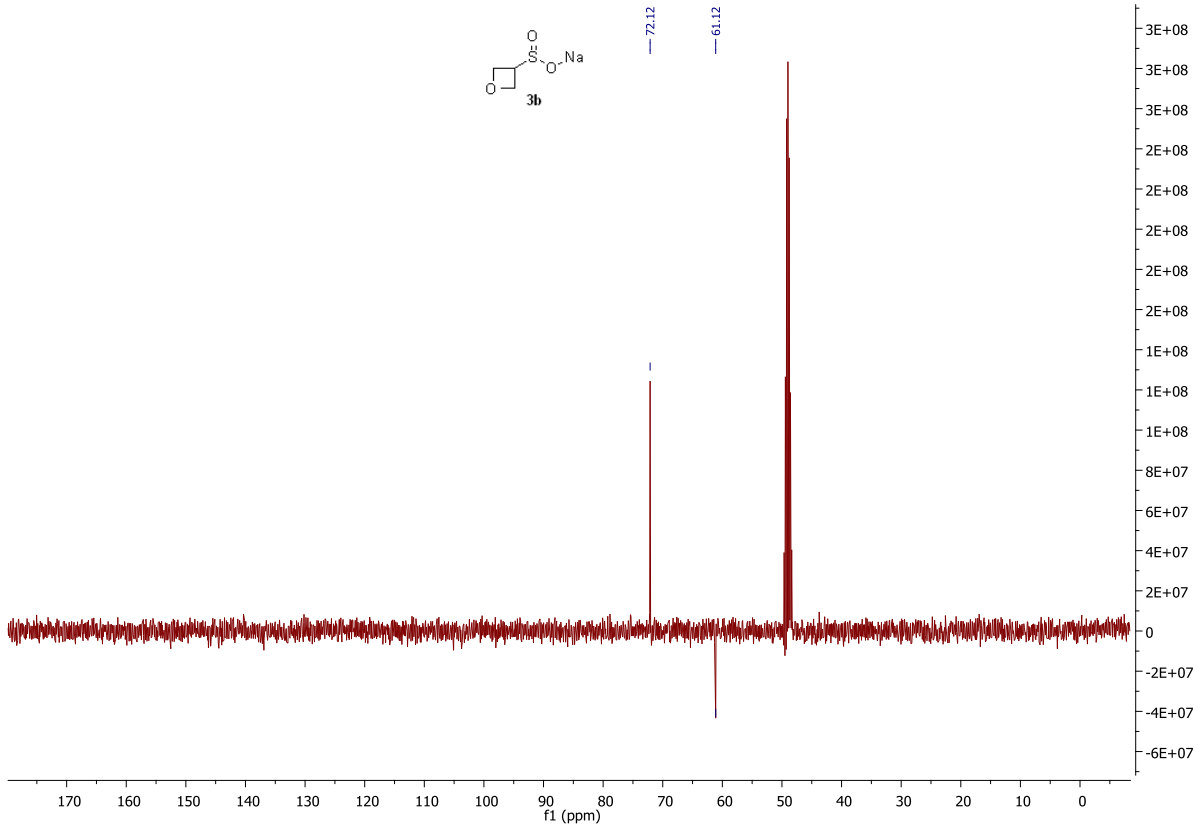
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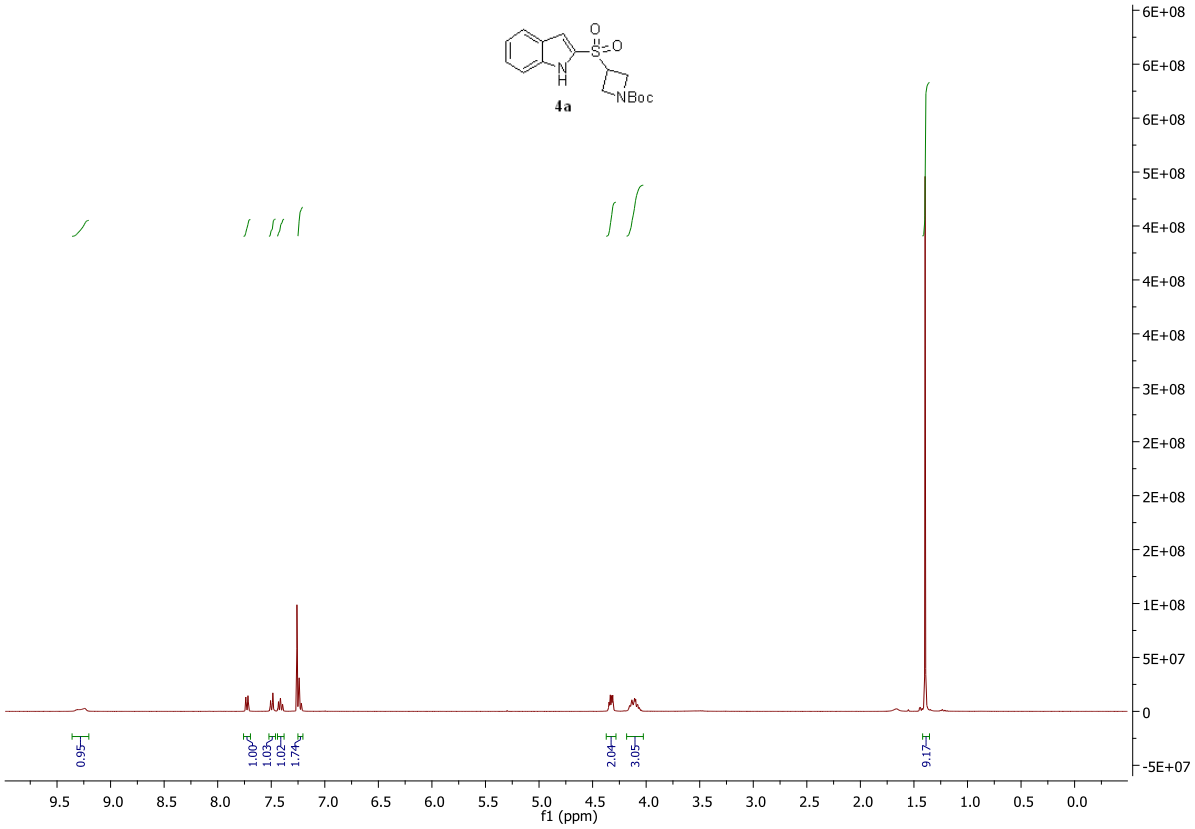
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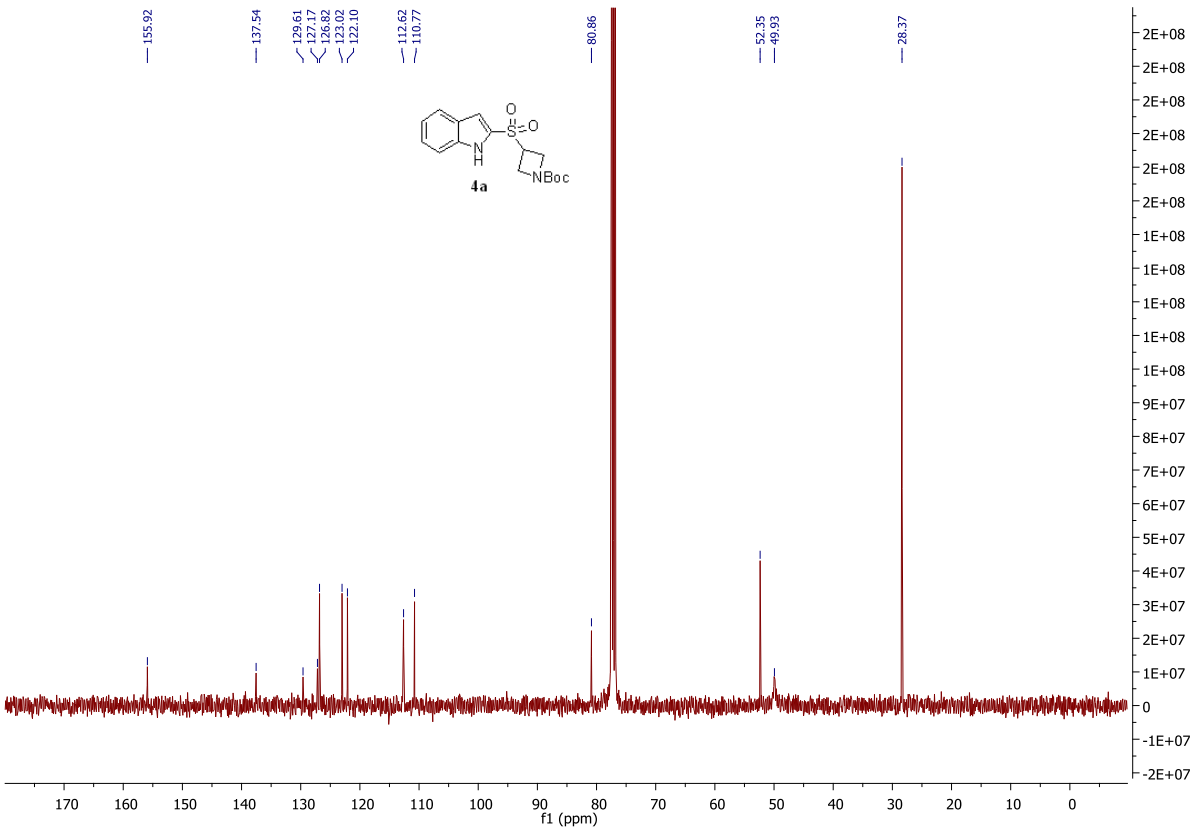
1.02
1.74
2.04
3.05
9.17
f1 (ppm)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127.17
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122.10
112.62
110.77
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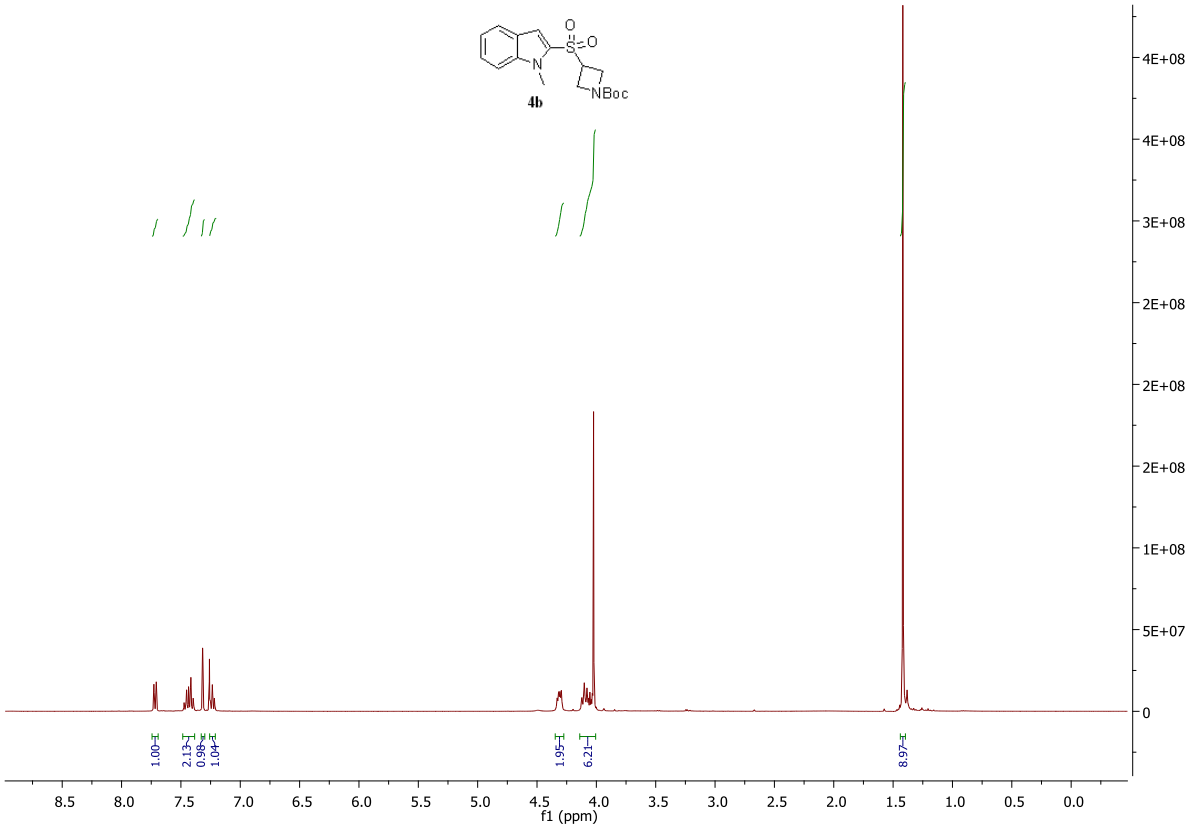
52.35
49.93
28.37
4a
NBoc
f1 (ppm)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8.97
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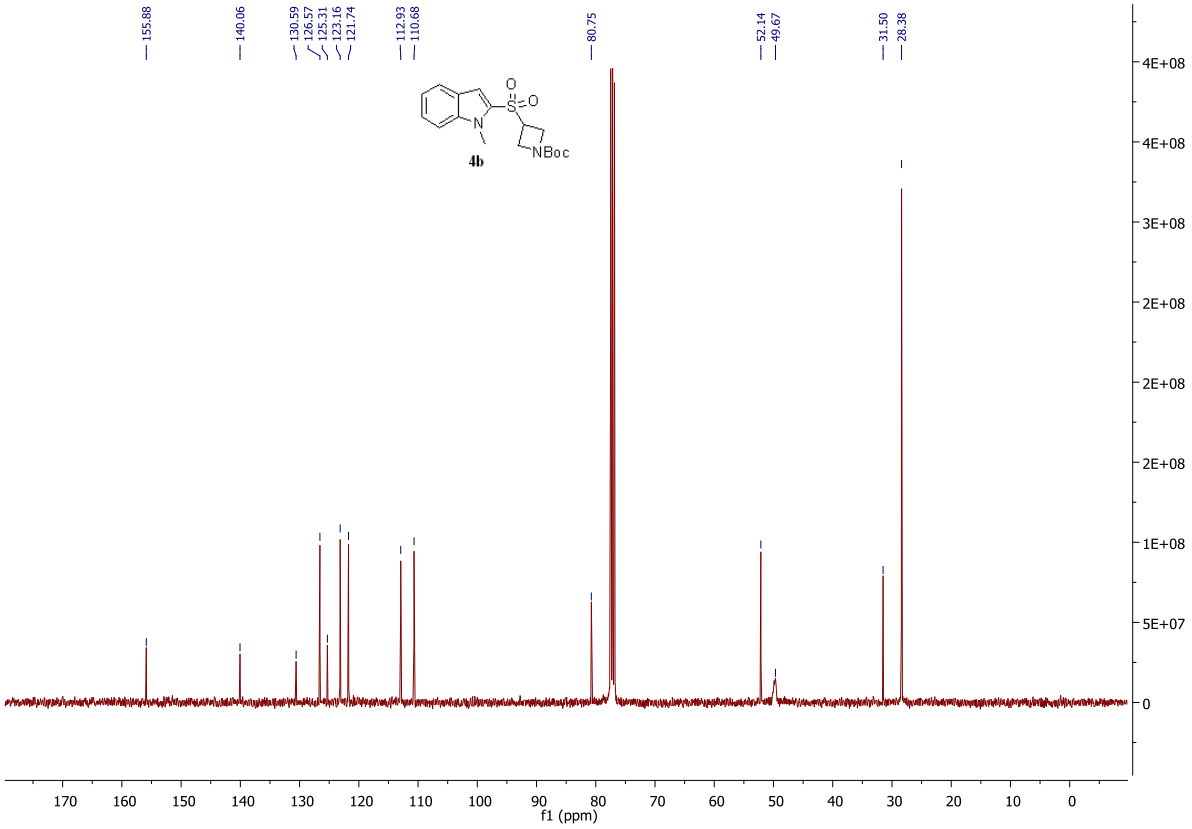
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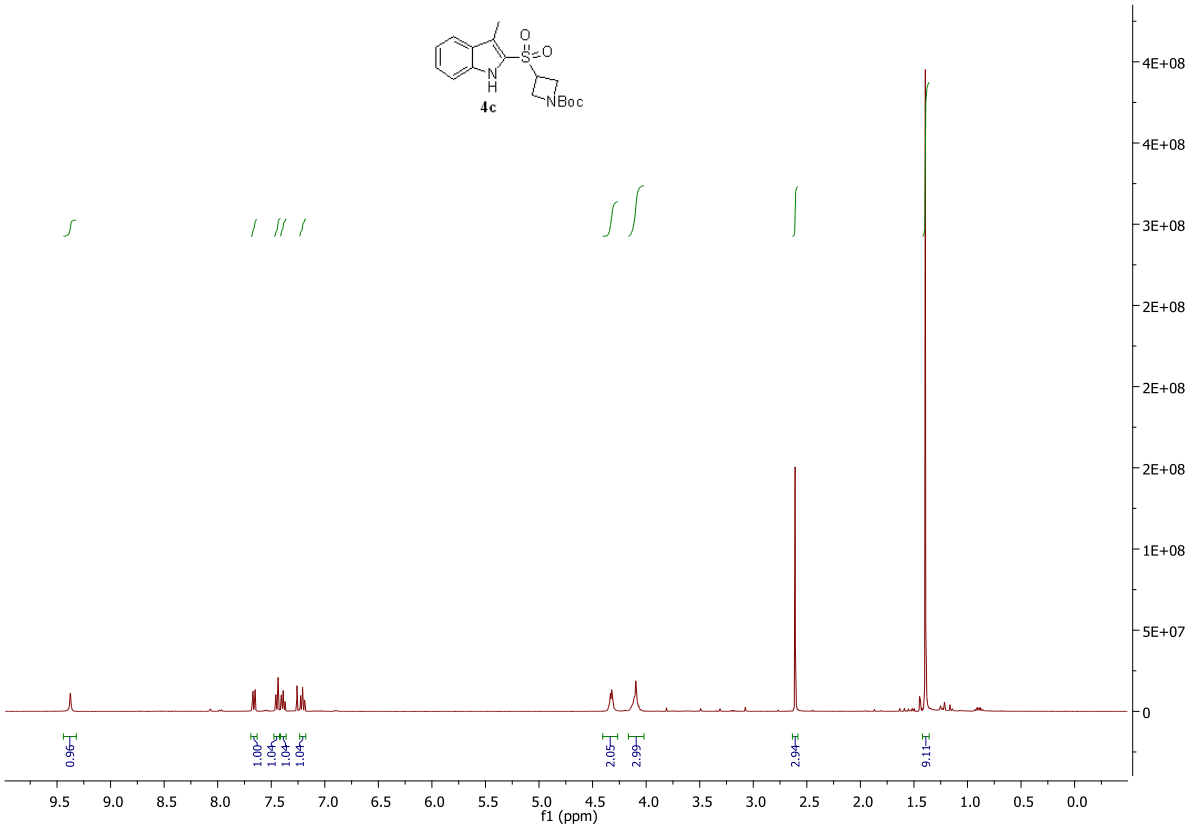
4b
NBoc
f1 (ppm)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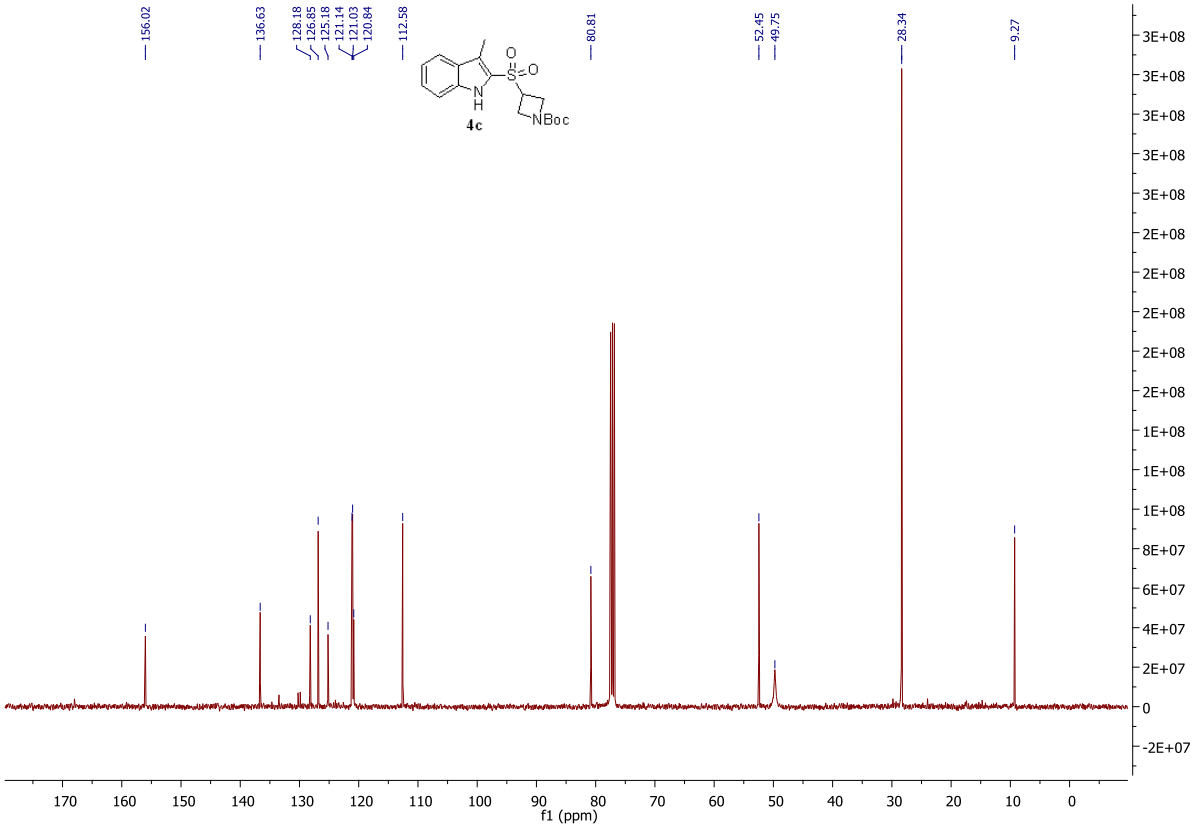
2.99
2.94
9.11
f1 (ppm)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126.85
125.18
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120.84
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28.34
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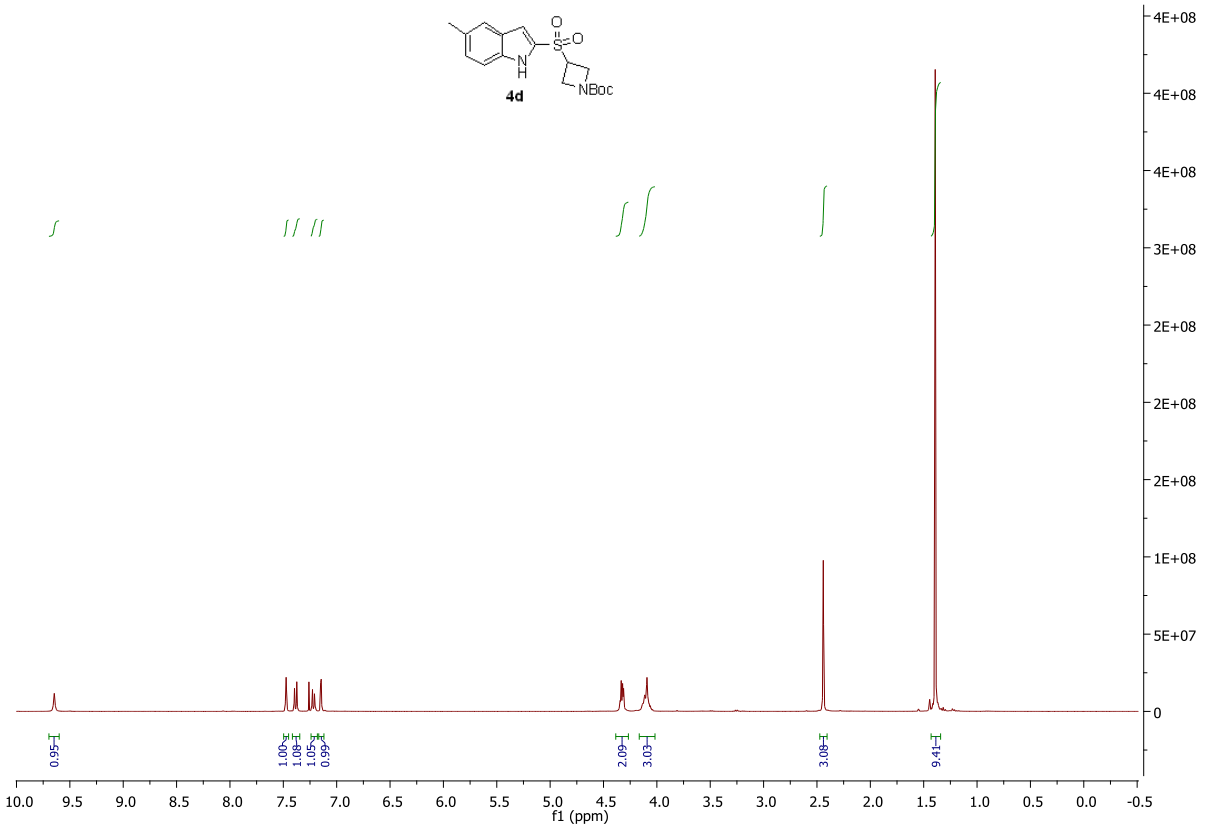
4c
NBoc
f1 (ppm)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3.08
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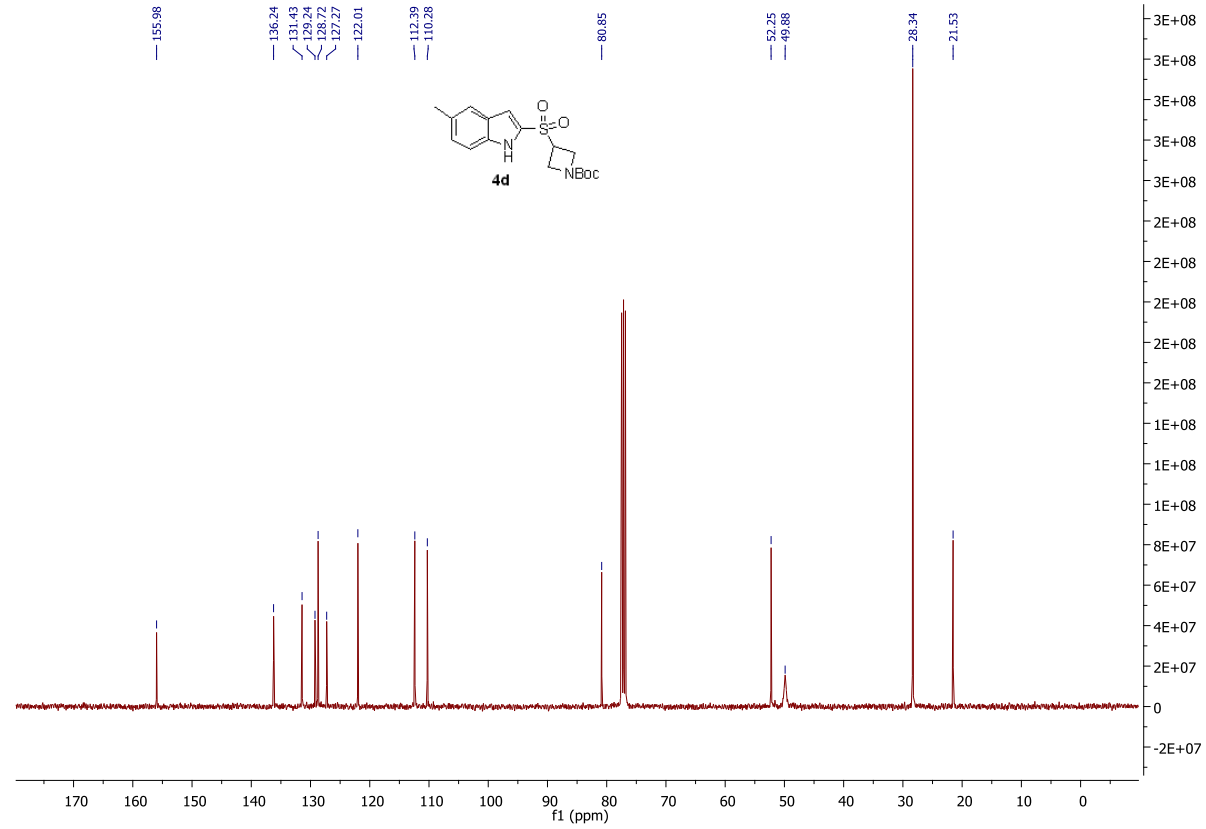
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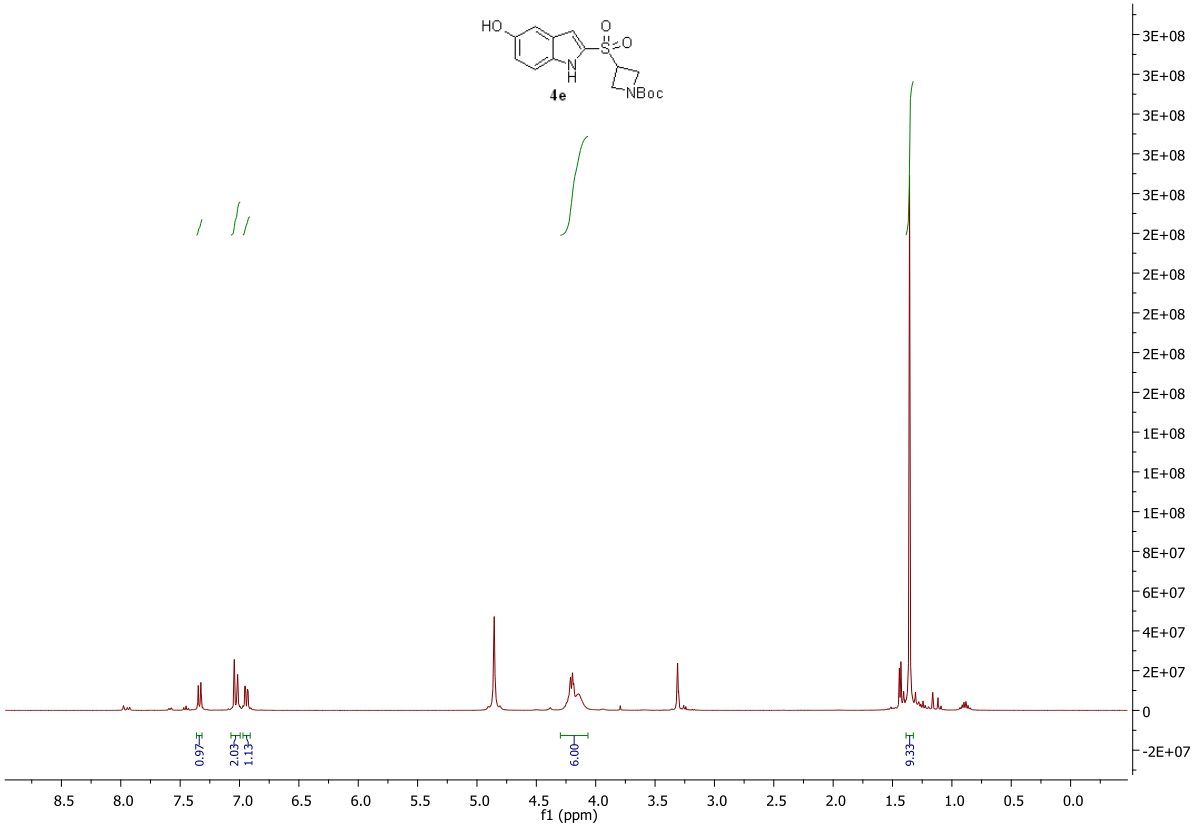
4d
NBoc
f1 (ppm)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N
H
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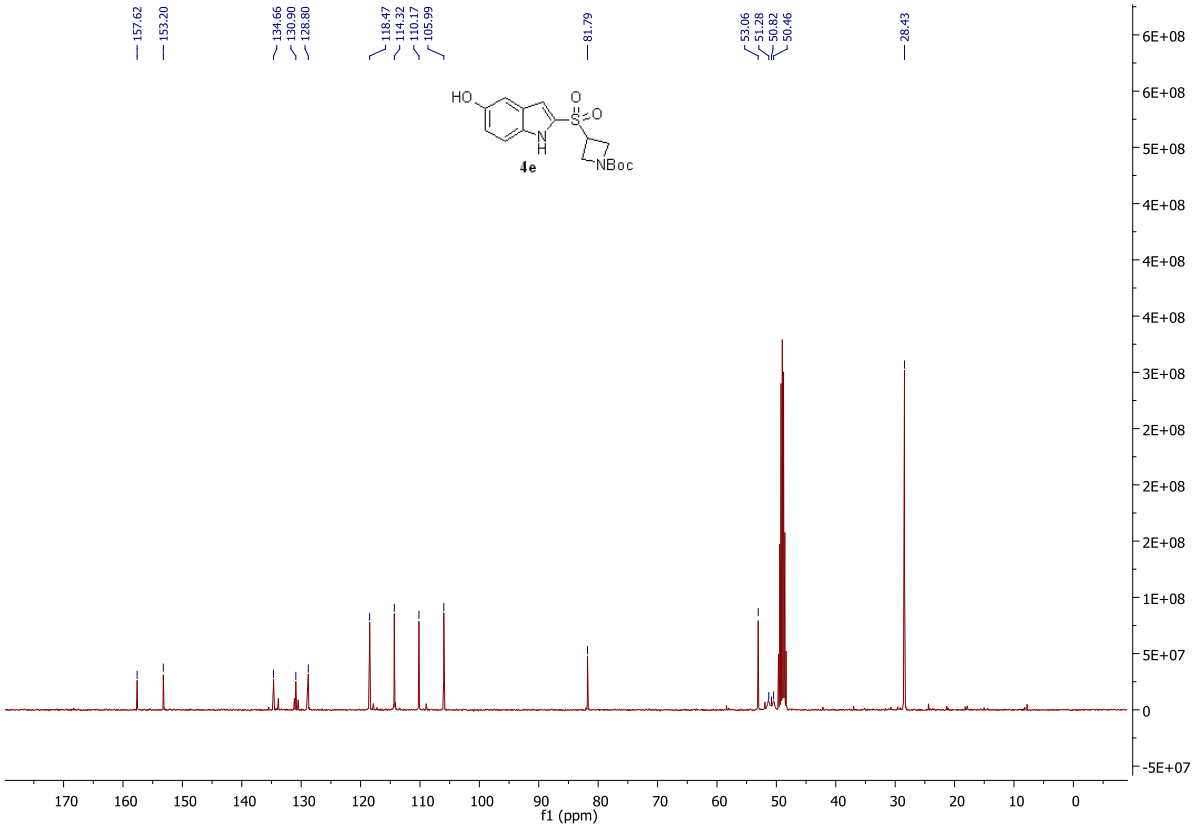
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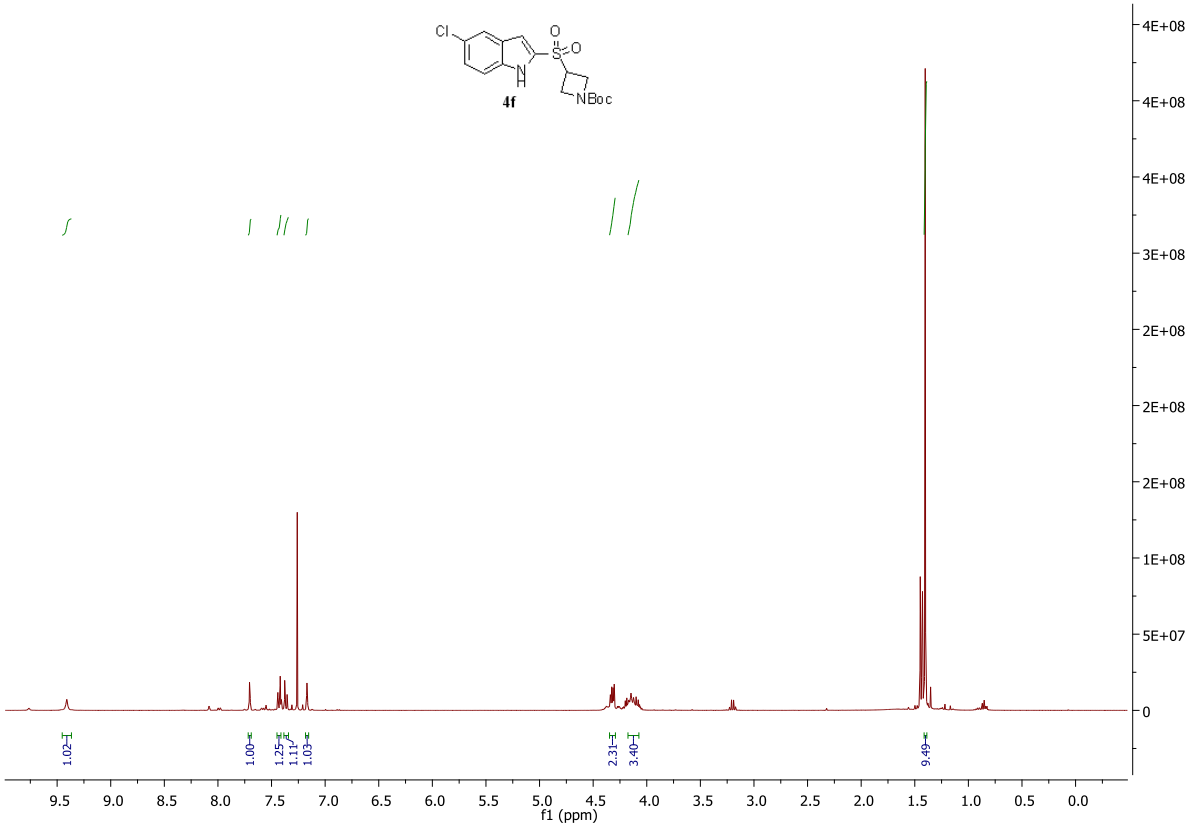
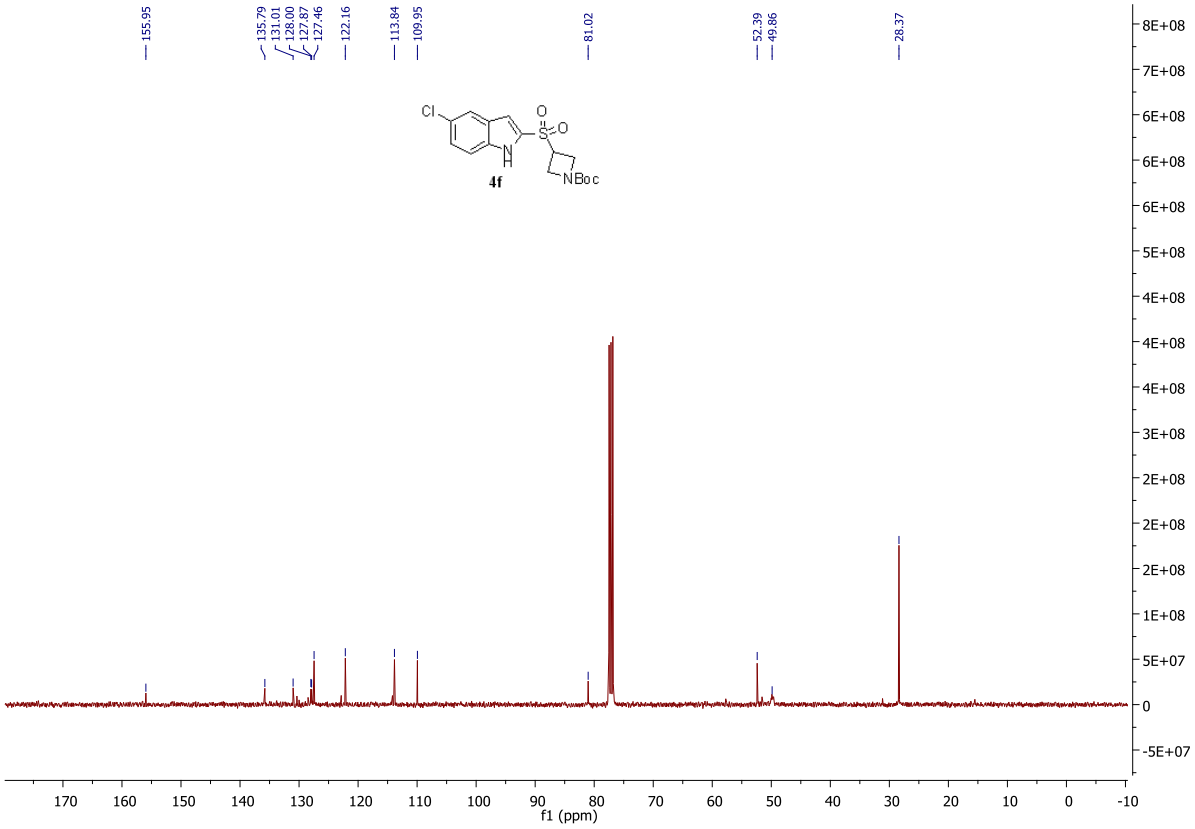
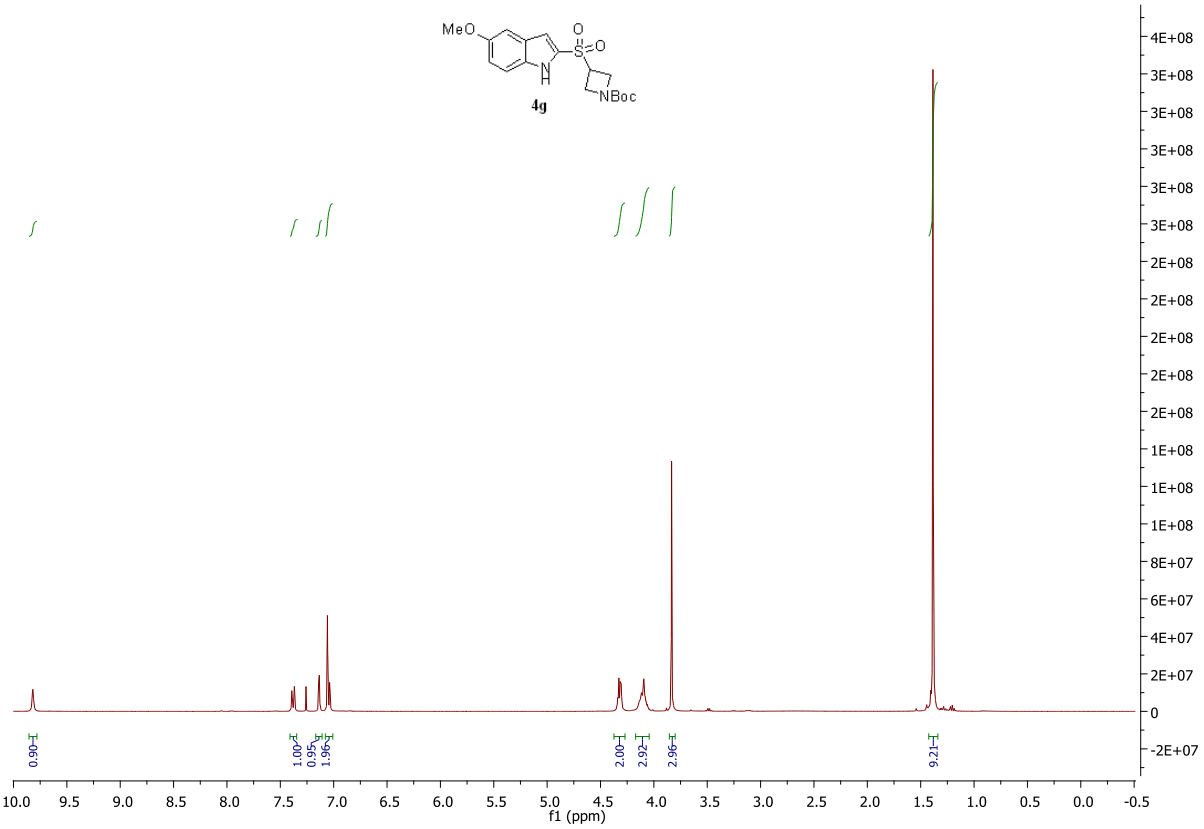
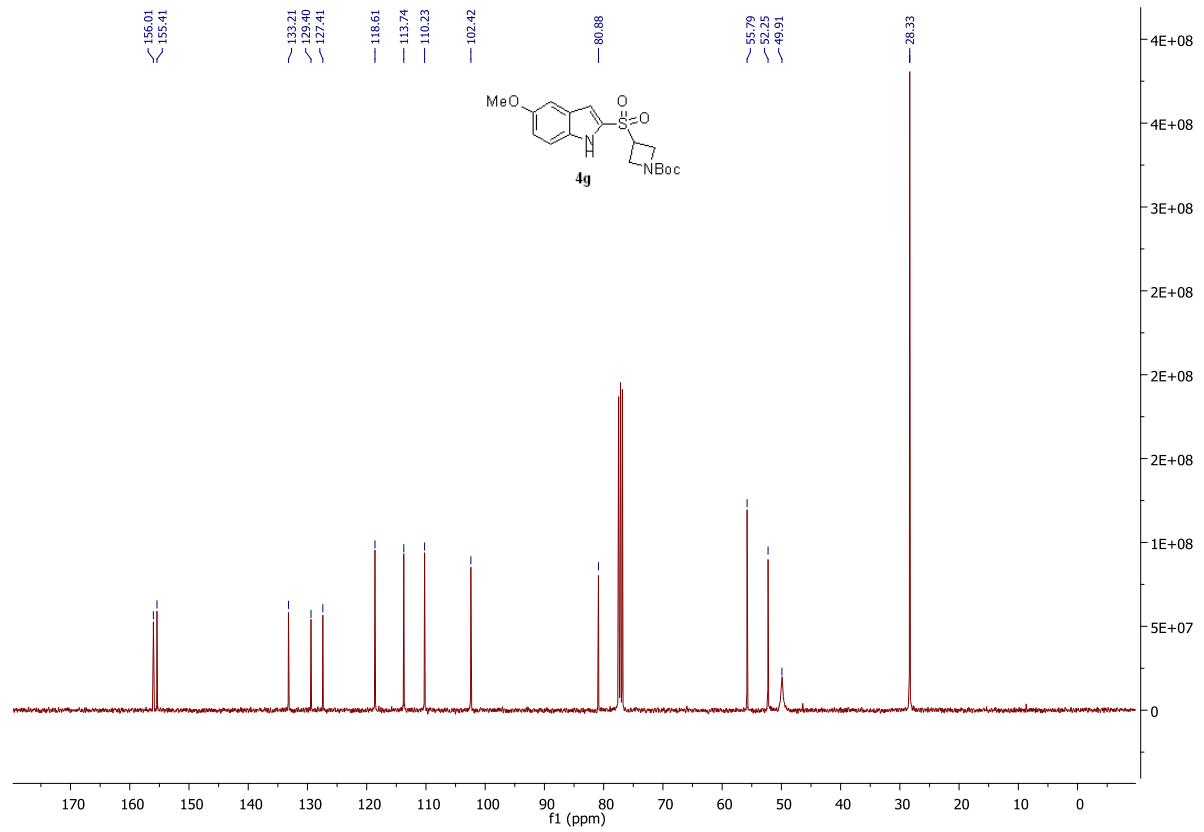
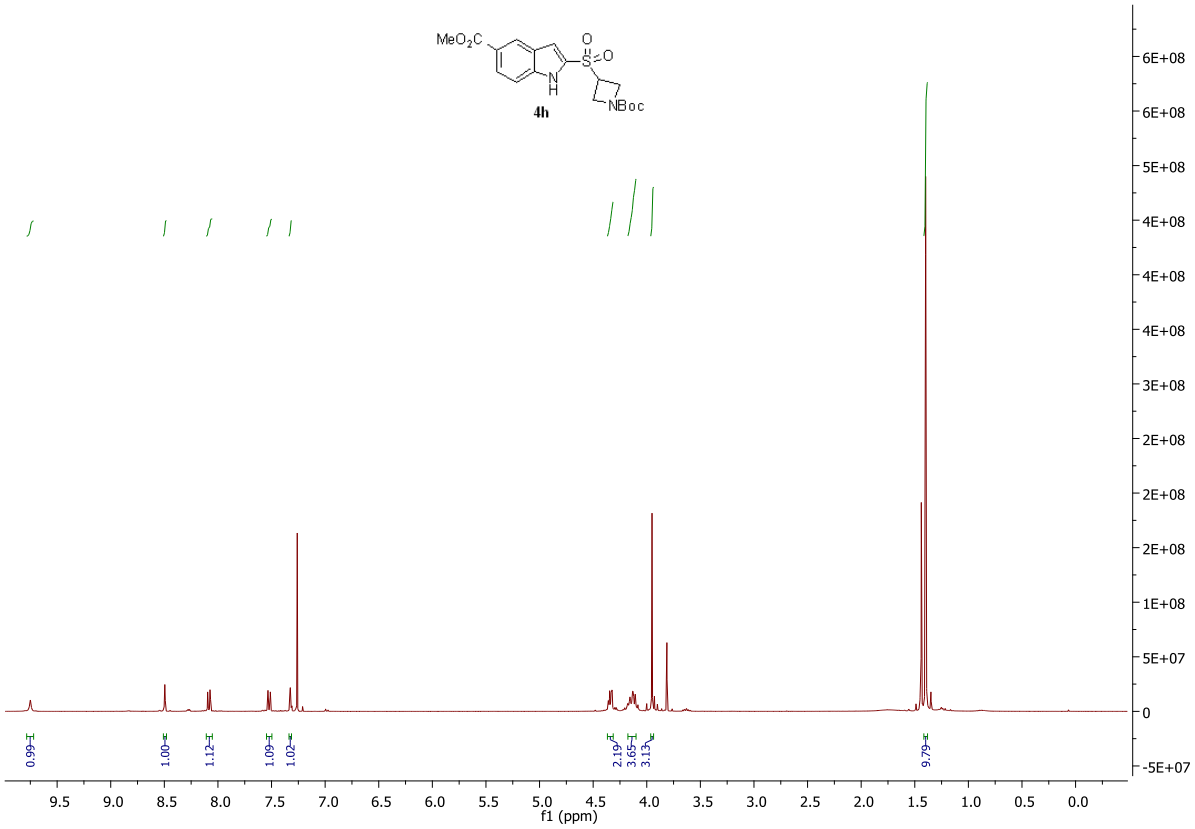
50.46
28.43
HO
O
S
O
N
H
NBoc
4e
f1 (ppm)

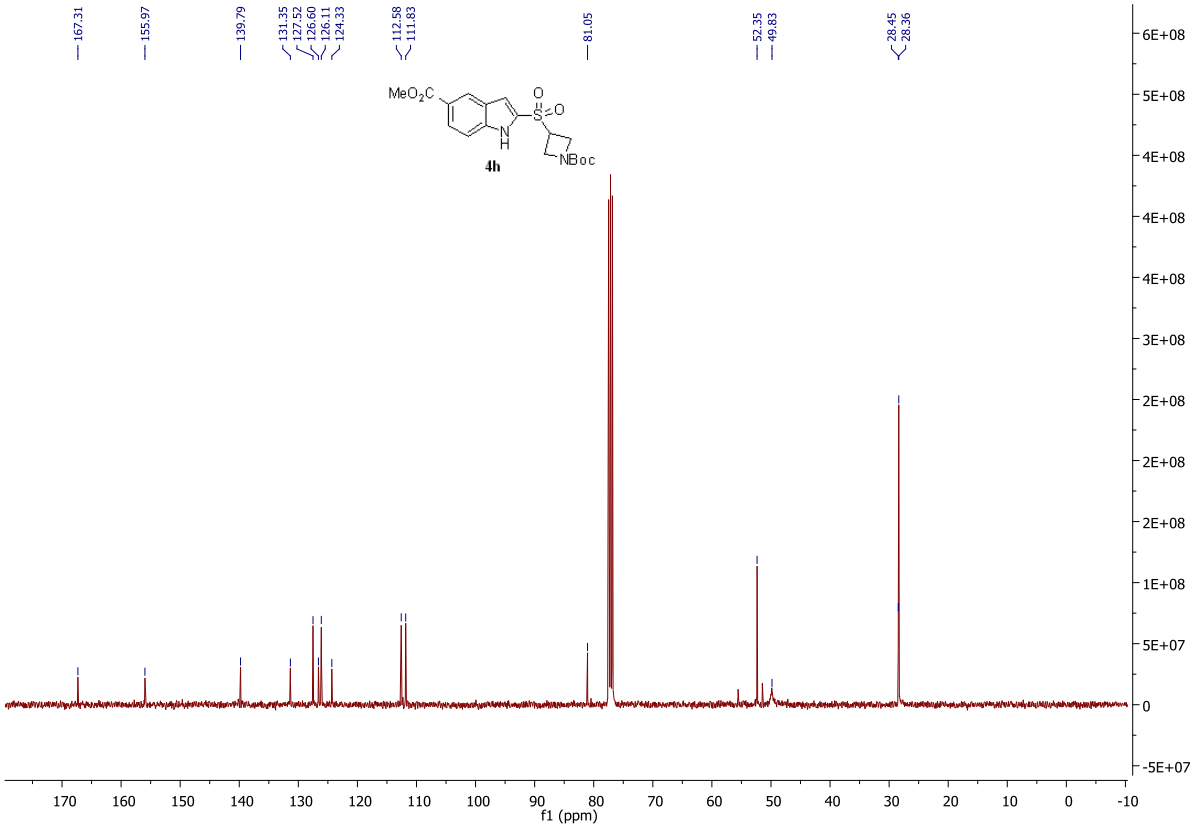

Cl
O
S
O
N
H
NBoc
4f
1.02
1.00
1.25
1.11
1.03
2.31
3.40
9.49
f1 (ppm)

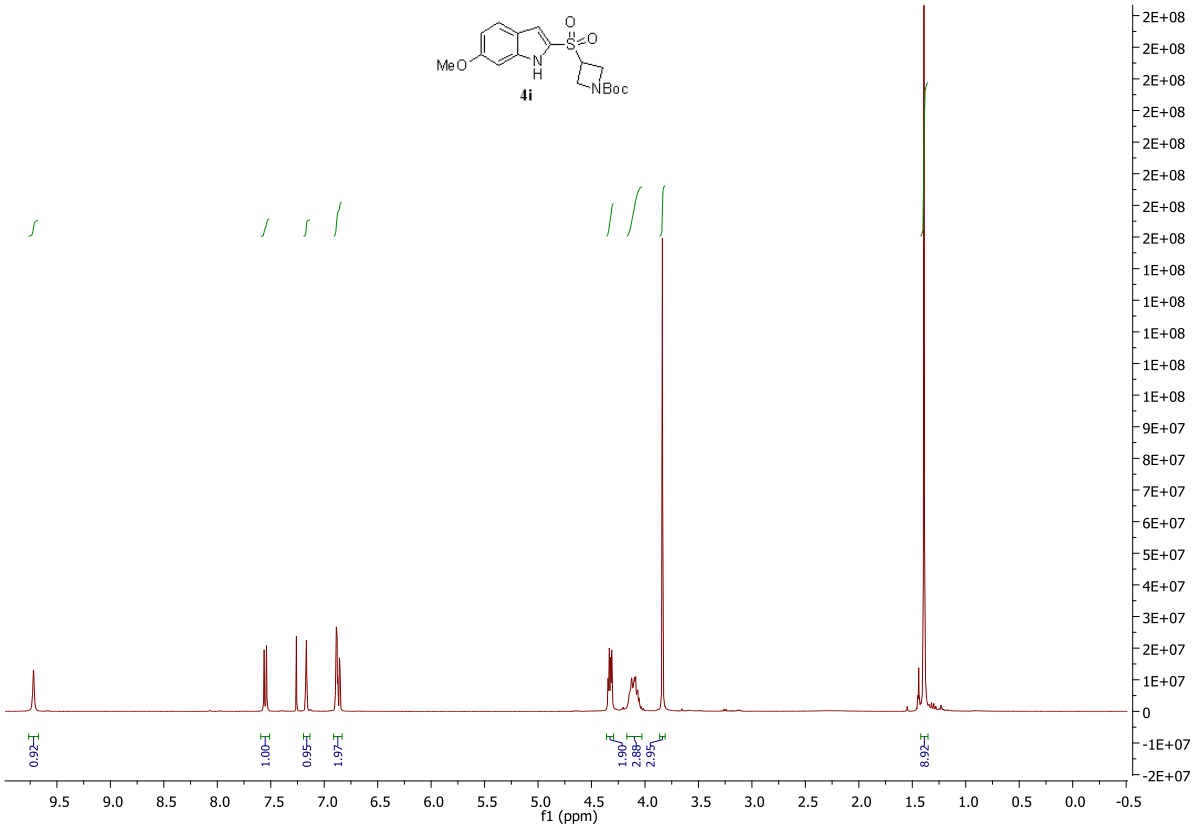

155.95
135.79
131.01
128.00
127.87
127.46
122.16
113.84
109.95
81.02
52.39
49.86
28.37
Cl
O
S
O
N
H
NBoc
4f
f1 (ppm)

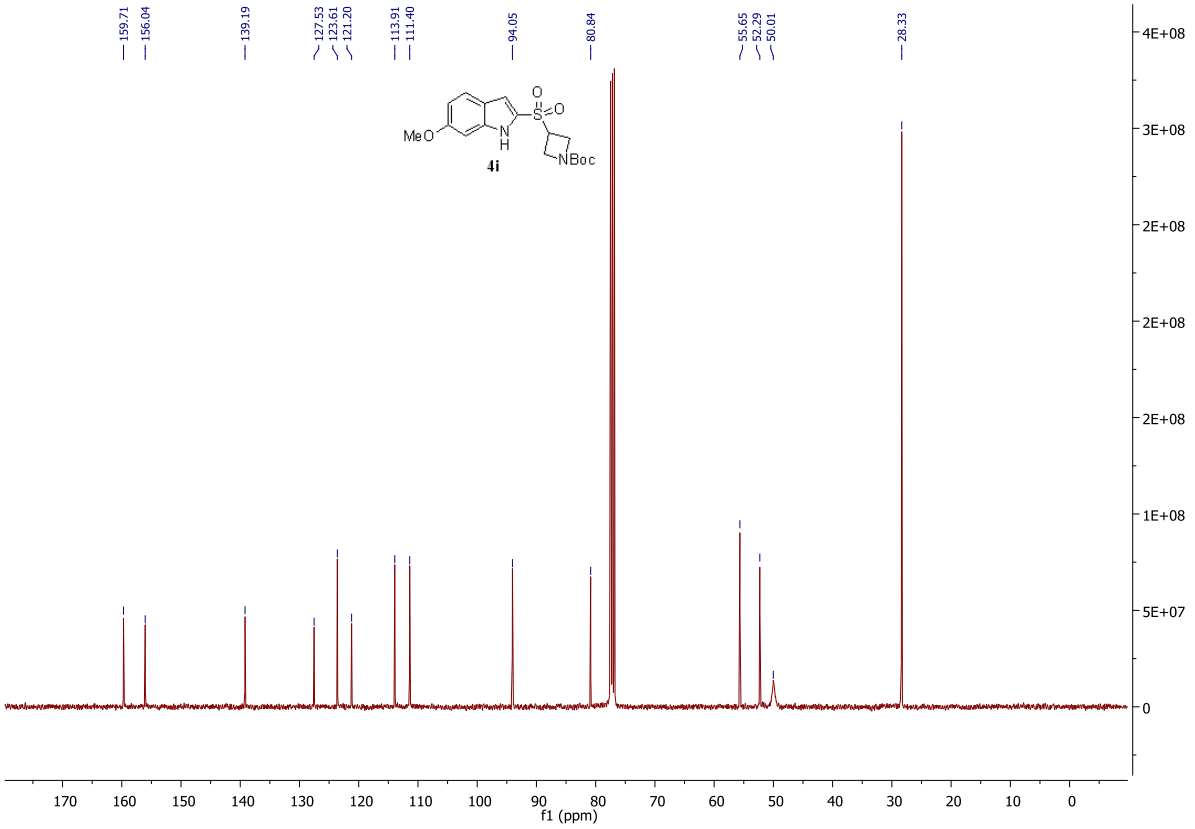

MeO
O
S
O
N
H
NBoc
4g
0.90
1.00
0.95
1.96
2.00
2.92
2.96
9.21
f1 (ppm)

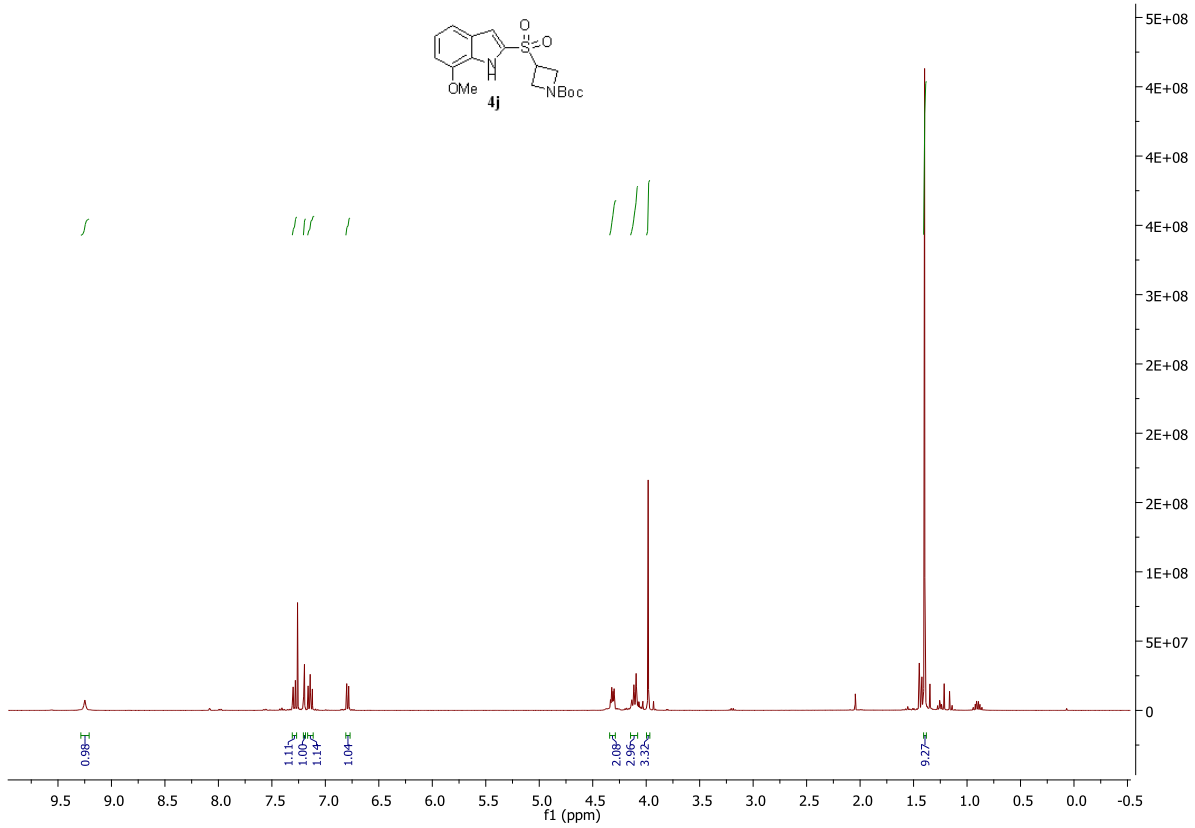

156.01
155.41
133.21
129.40
127.41
118.61
113.74
110.23
102.42
80.88
55.79
52.25
49.91
28.33
MeO
O
S
O
N
H
NBoc
4g
f1 (ppm)

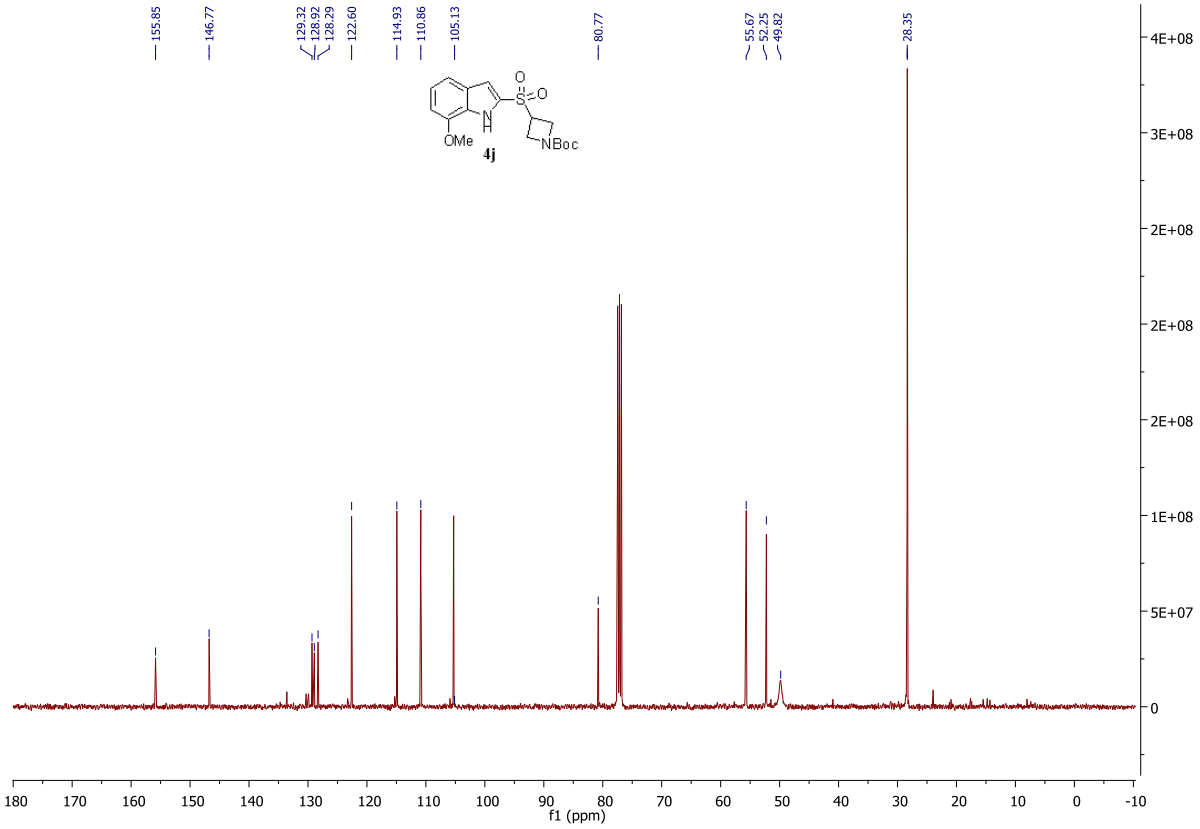

MeO2C
O
S
O
N
H
NBoc
4h
0.99
1.00
1.12
1.09
1.02
2.19
3.65
3.13
9.79
f1 (ppm)

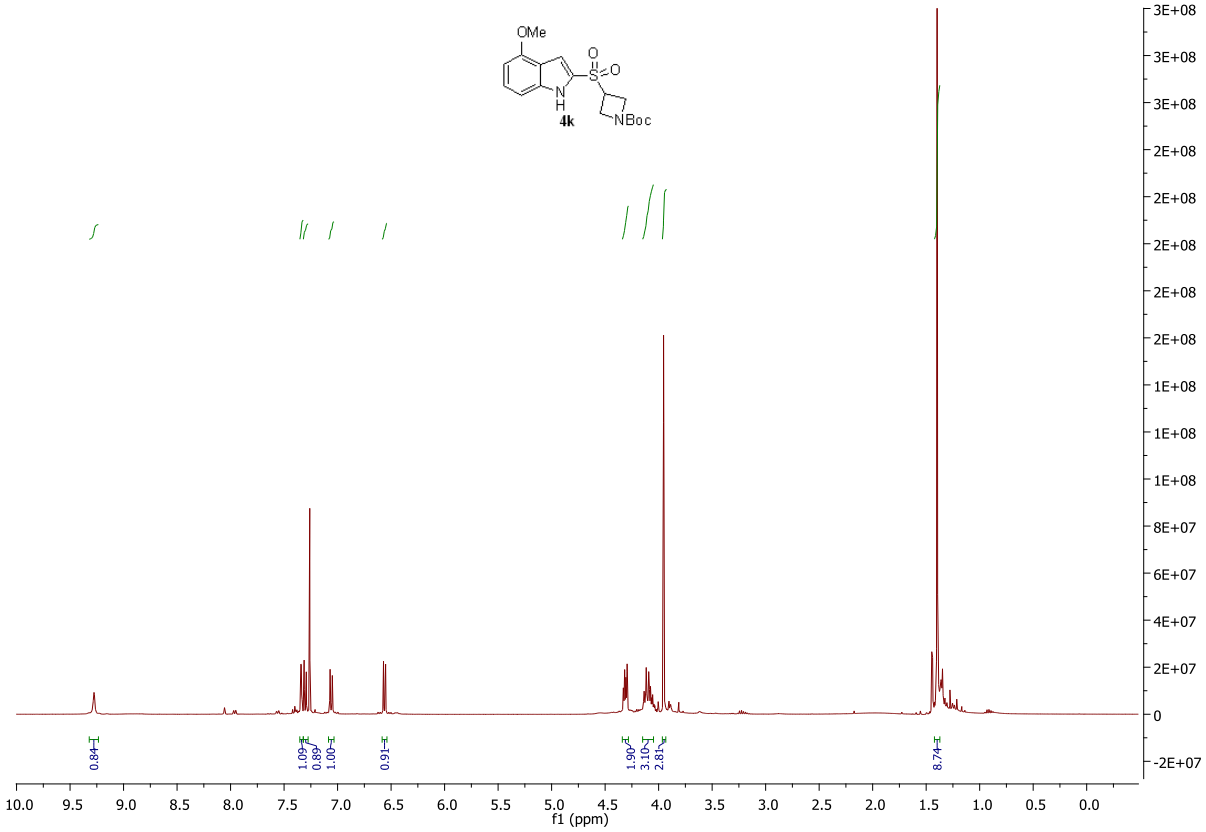

167.31
155.97
139.79
131.35
127.52
126.60
126.11
124.33
112.58
111.83
81.05
52.35
49.83
28.45
28.36
MeO2C
O
S
O
N
H
NBoc
4h
f1 (ppm)

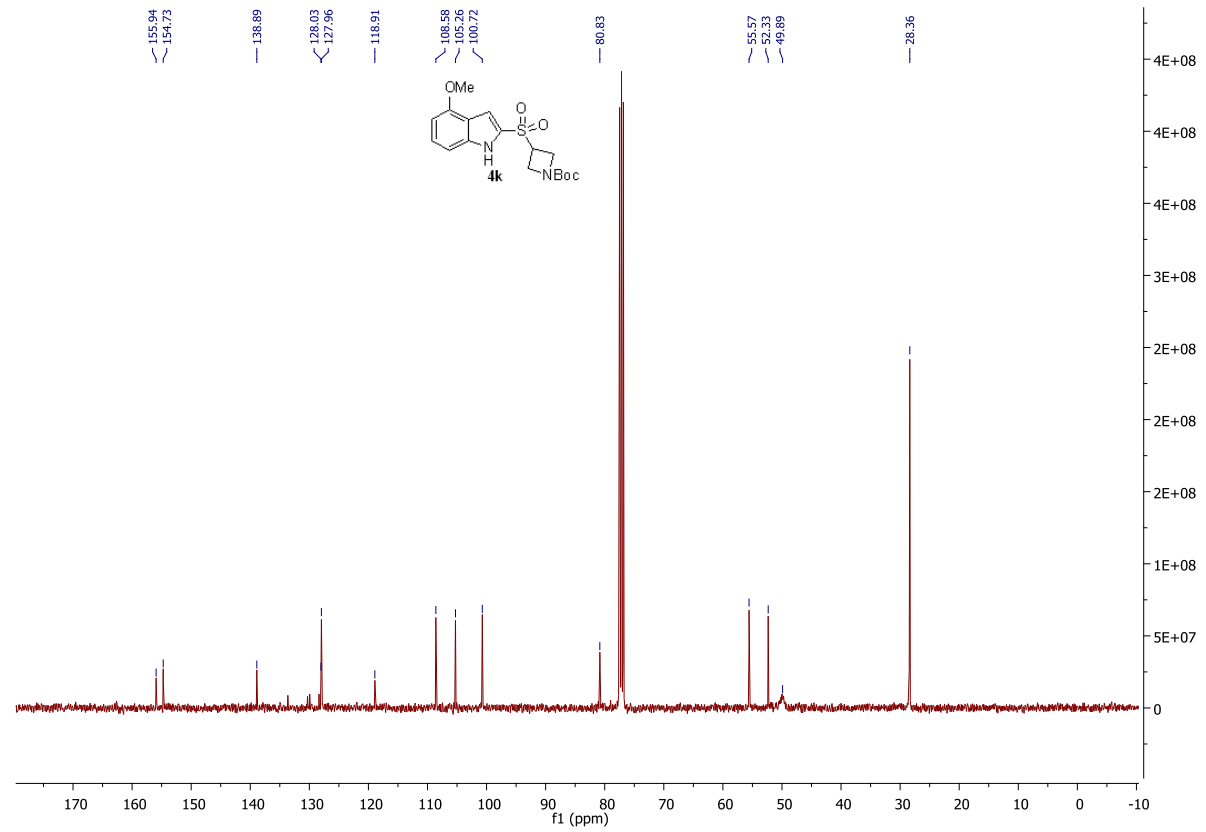

MeO
N
H
O
S
O
NBoc
4i
0.92
1.00
0.95
1.97
1.90
2.88
2.95
8.92
f1 (ppm)

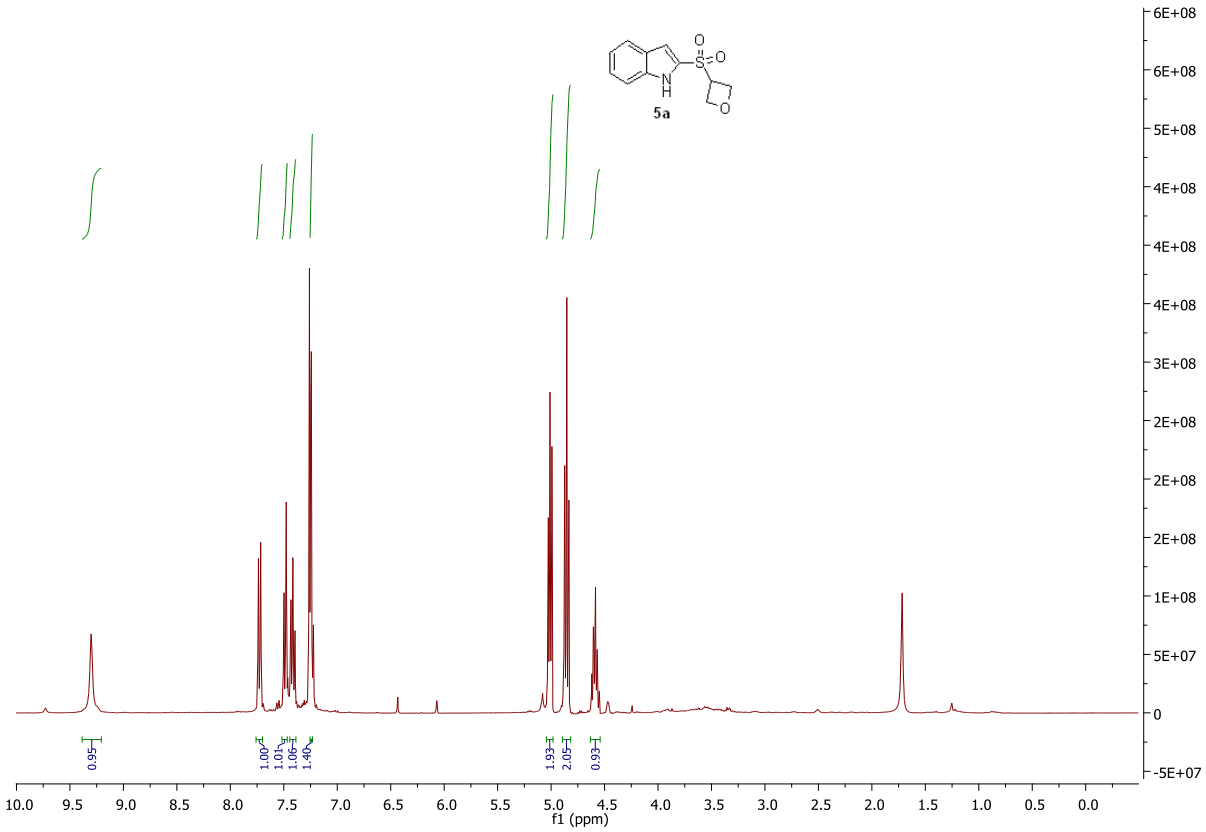

159.71
156.04
139.19
127.53
123.61
121.20
113.91
111.40
94.05
80.84
55.65
52.29
50.01
28.33
MeO
N
H
O
S
O
NBoc
4i
f1 (ppm)

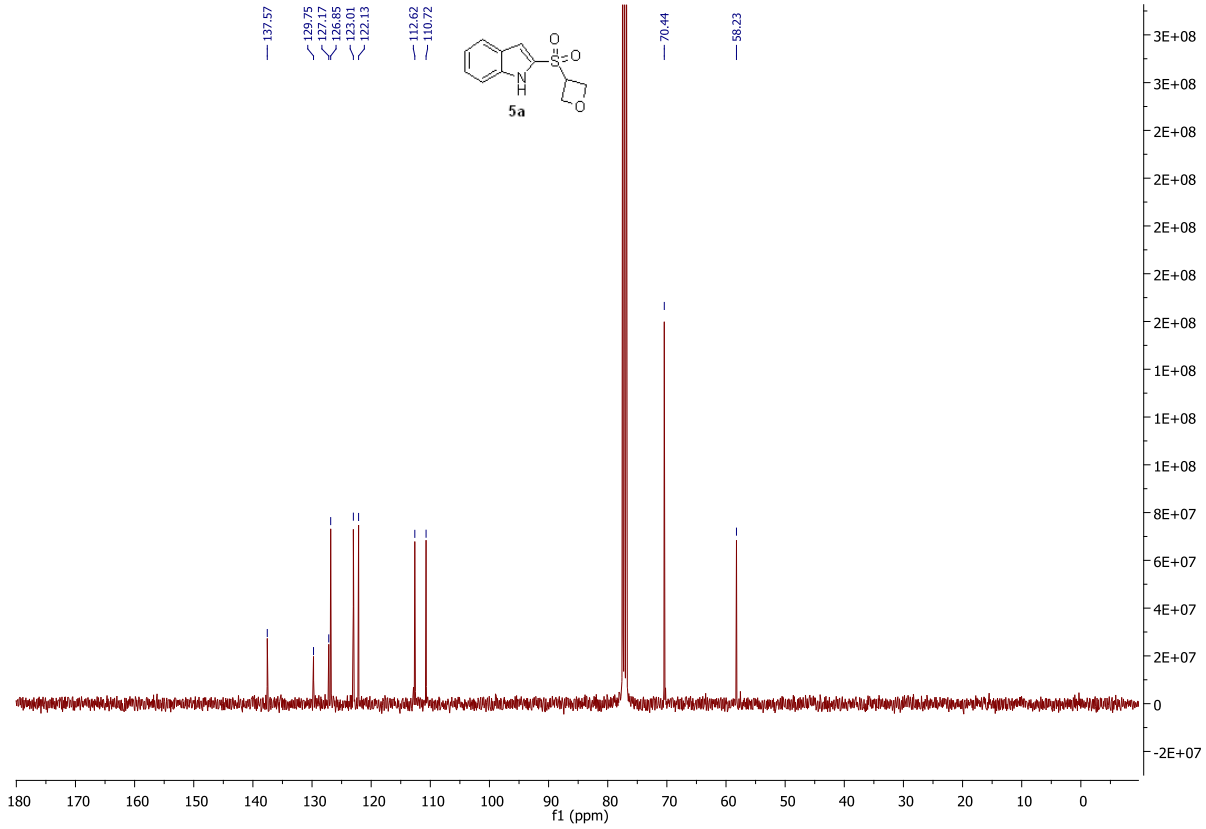

OMe
NBoc
4j
0.98
1.11
1.00
1.14
1.04
2.08
2.96
3.32
9.27
f1 (ppm)

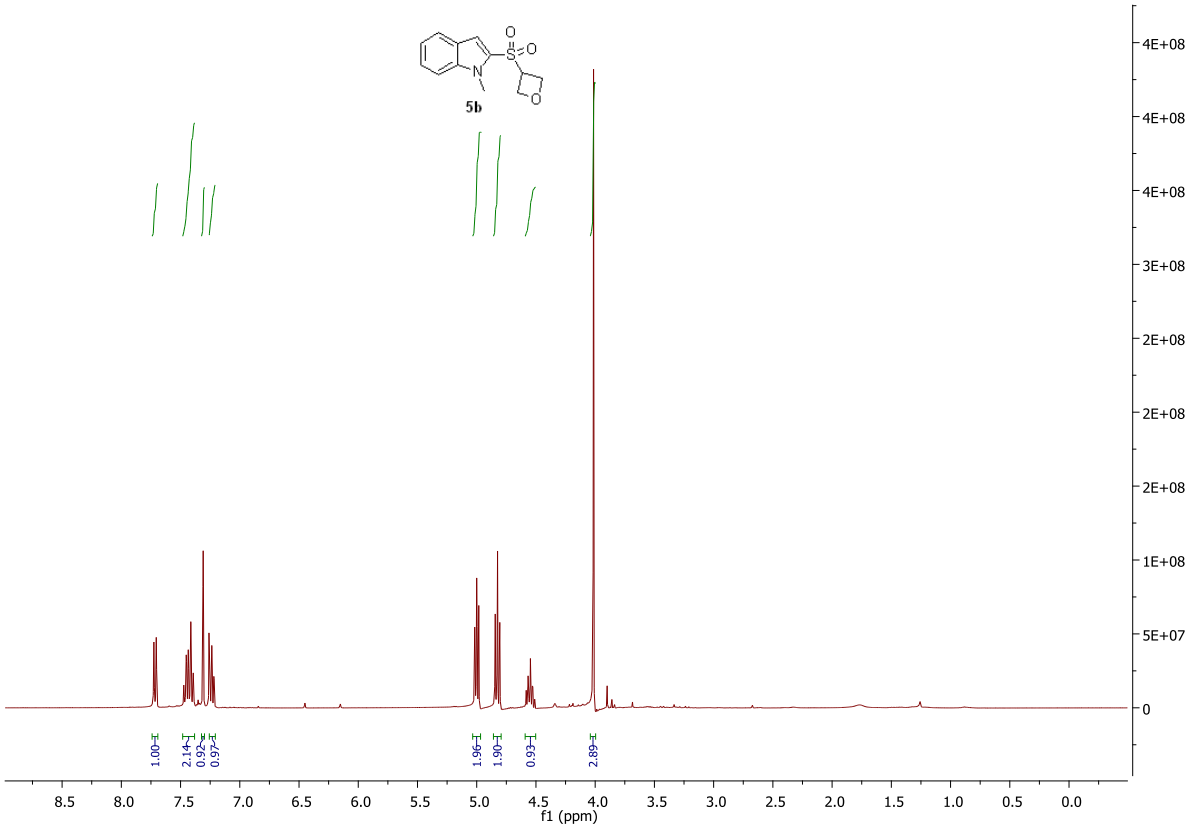

155.85
146.77
129.32
128.92
128.29
122.60
114.93
110.86
105.13
80.77
55.67
52.25
49.82
28.35
OMe
NBoc
4j
f1 (ppm)

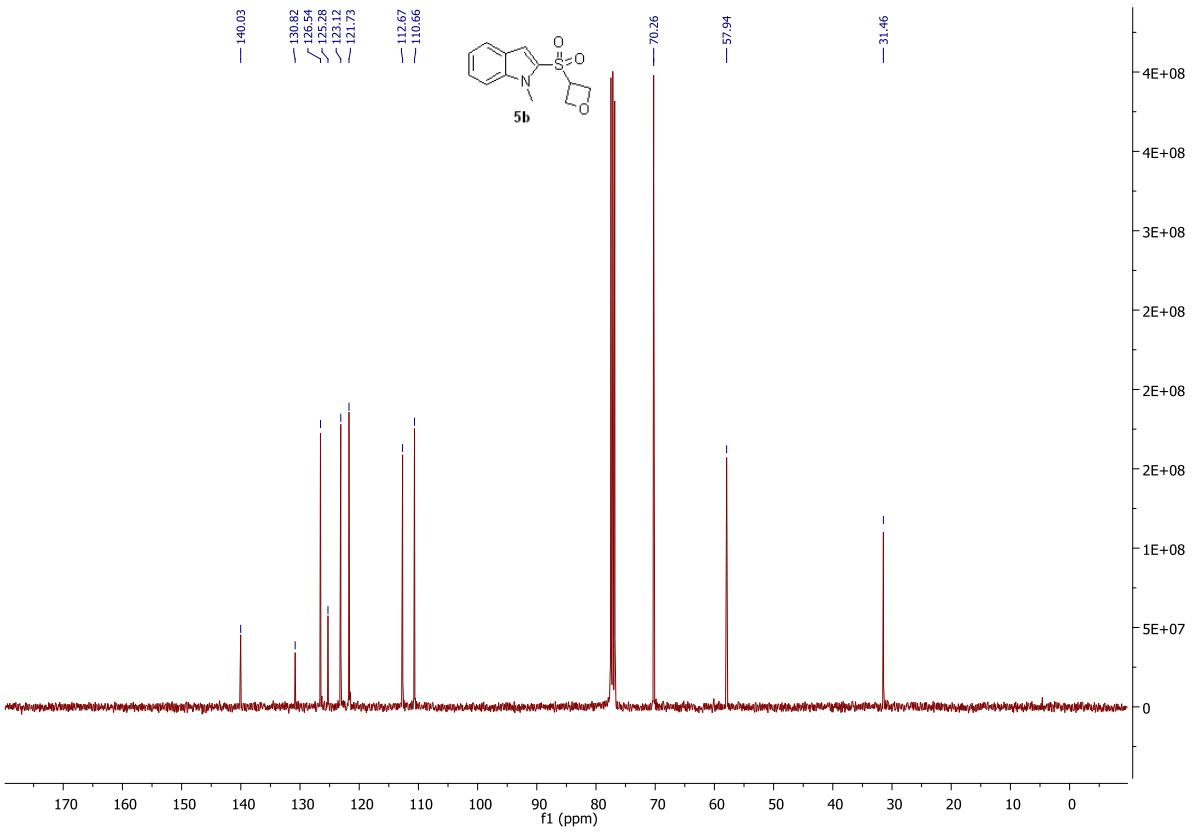

OMe
O
S
O
N
H
NBoc
4k
0.84
1.09
0.89
1.00
0.91
1.90
3.10
2.81
8.74
f1 (ppm)

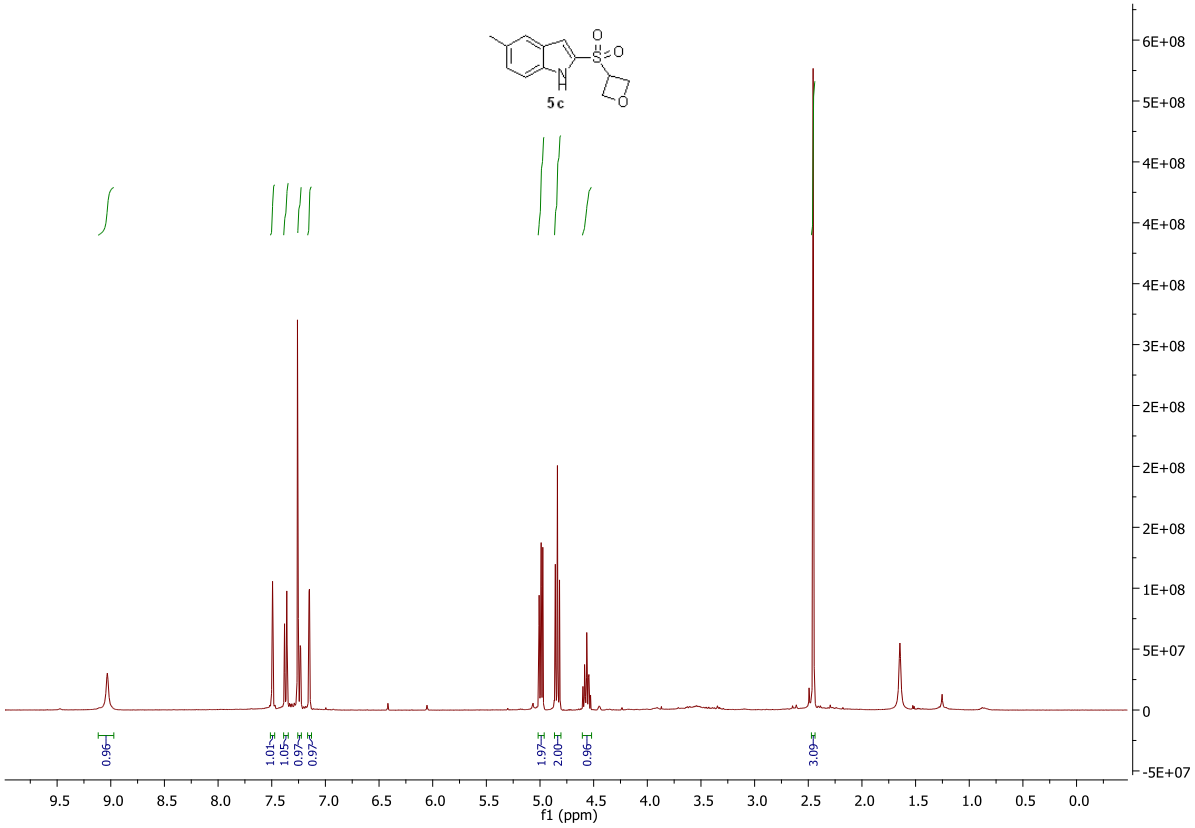

155.94
154.73
138.89
128.03
127.96
118.91
108.58
105.26
100.72
80.83
55.57
52.33
49.89
28.36
OMe
O
S
O
N
H
NBoc
4k
f1 (ppm)

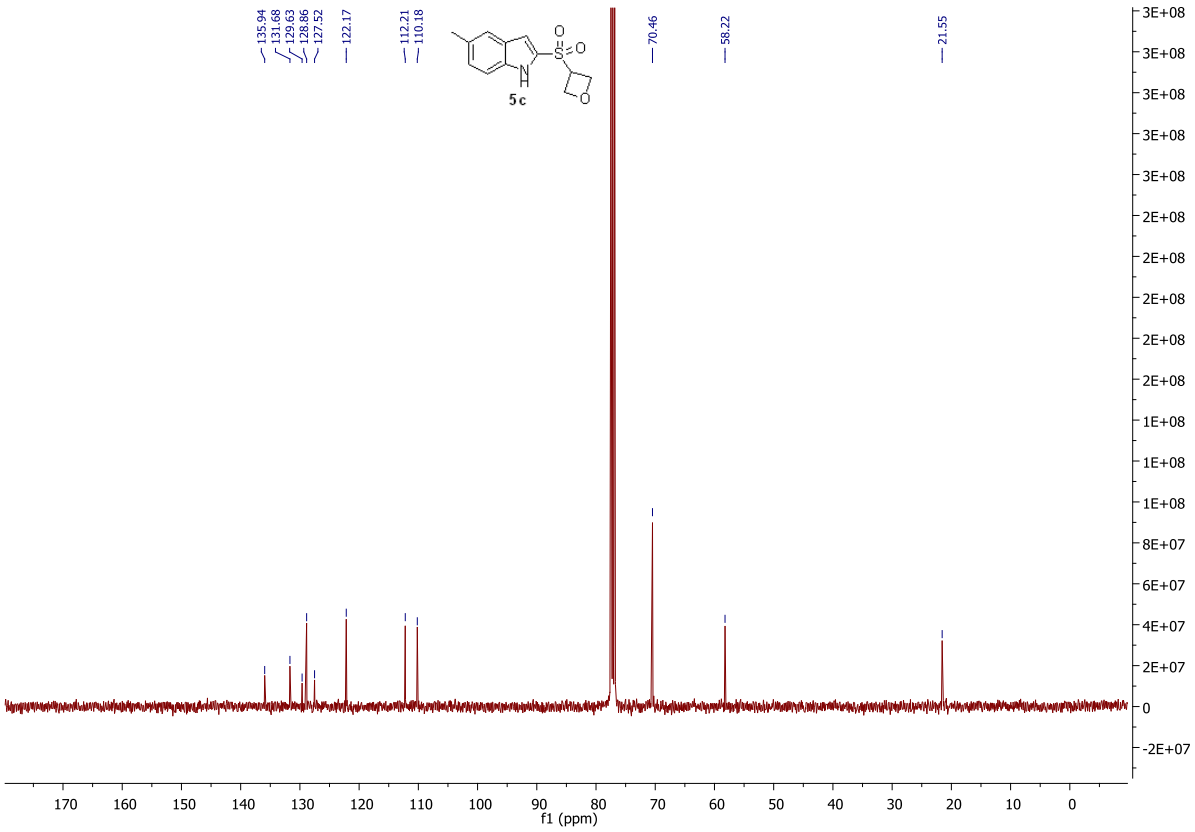

5a
0.95
1.00
1.01
1.06
1.40
1.93
2.05
0.93
f1 (ppm)

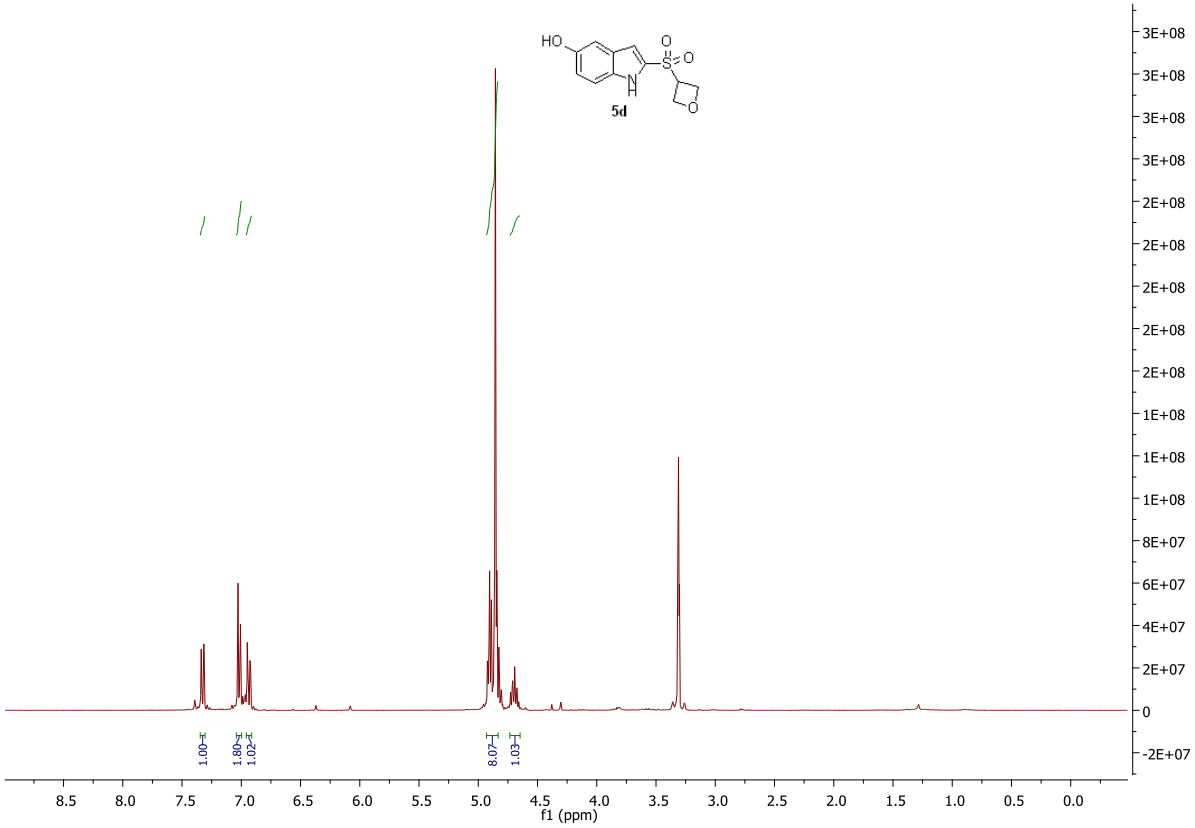

137.57
129.75
127.17
126.85
123.01
122.13
112.62
110.72
70.44
58.23
5a
f1 (ppm)

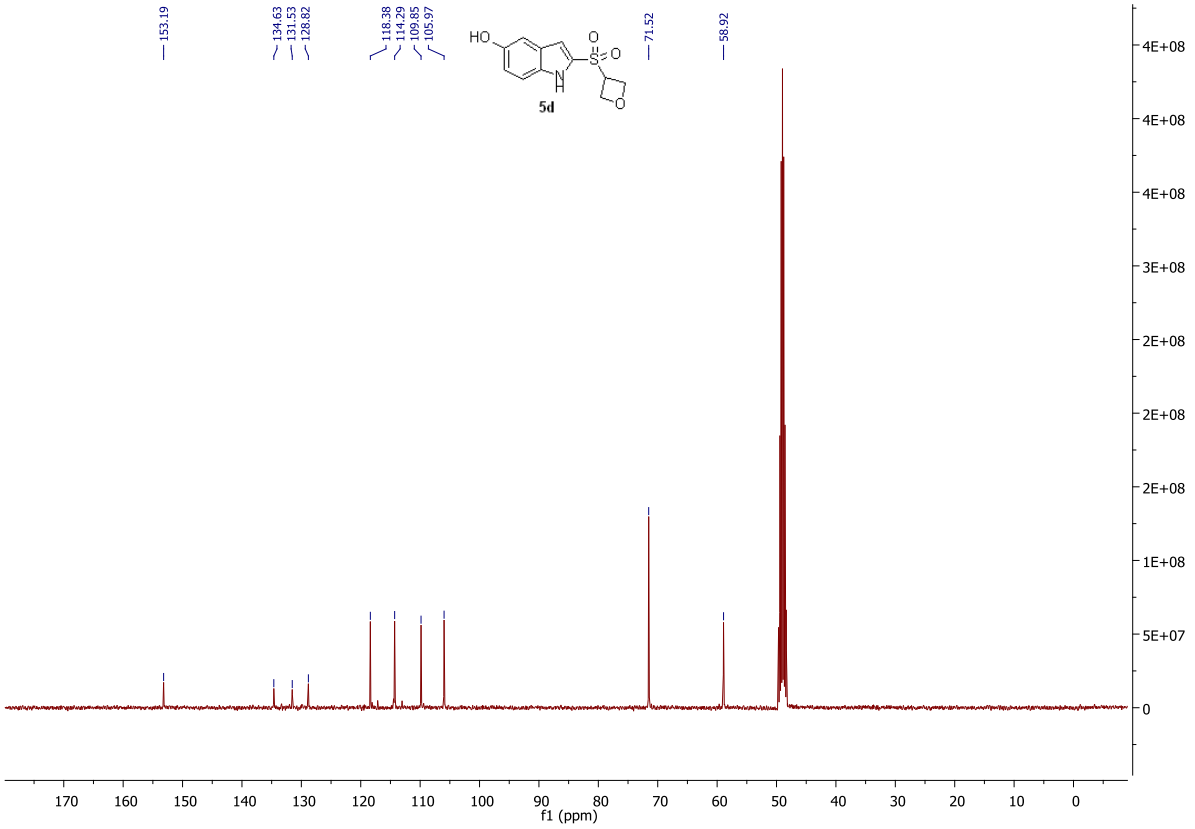

5b
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
1.00
2.14
0.92
0.97
1.96
1.90
0.93
2.89
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

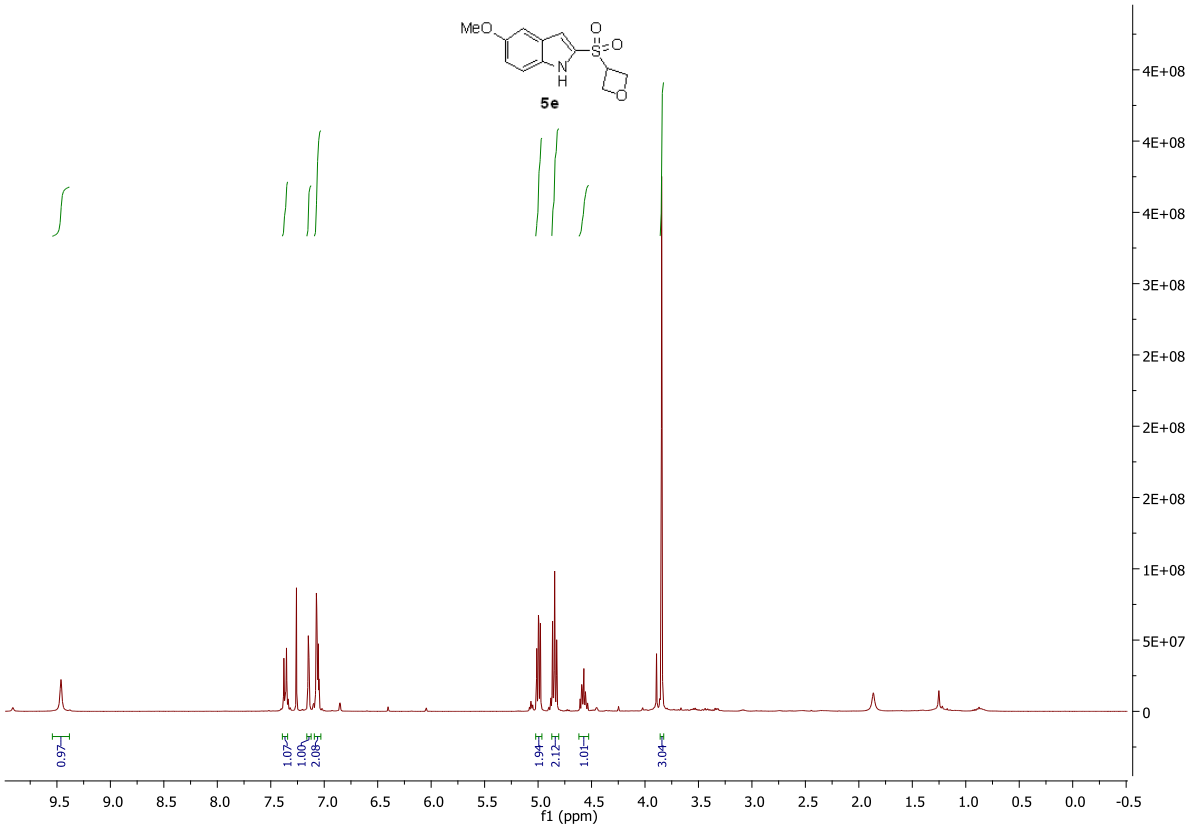

140.03
130.82
126.54
125.28
123.12
121.73
112.67
110.66
70.26
57.94
31.46
5b
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

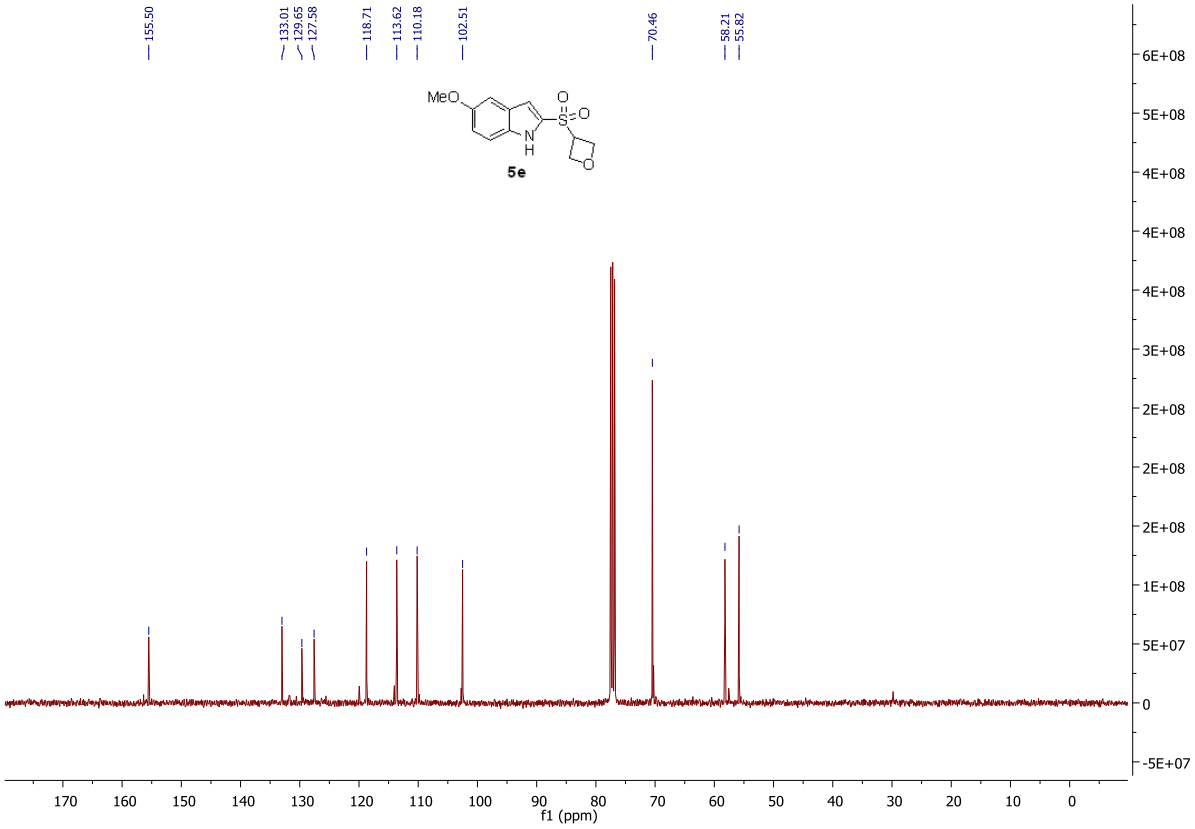

5c
0.96
1.01
1.05
0.97
0.97
1.97
2.00
0.96
3.09
f1 (ppm)

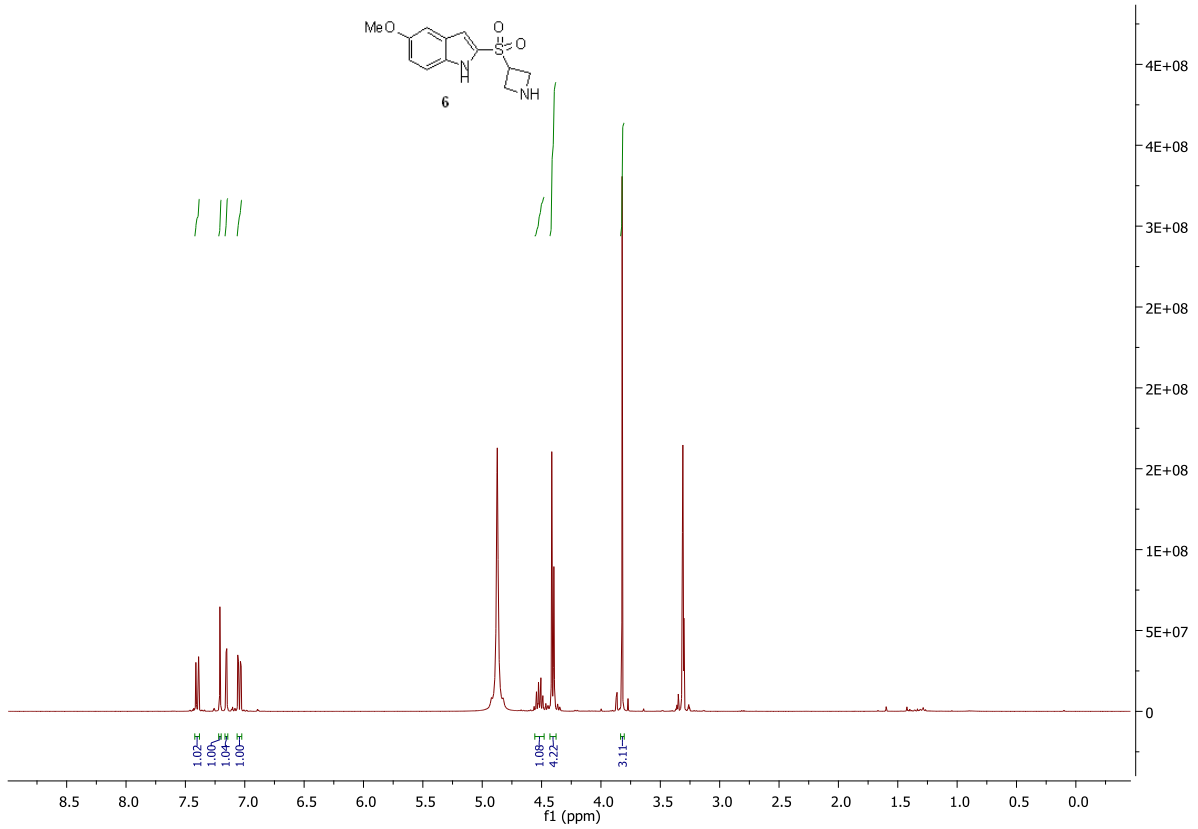

135.94
131.68
129.63
128.86
127.52
122.17
112.21
110.18
70.46
58.22
21.55
5c
f1 (ppm)

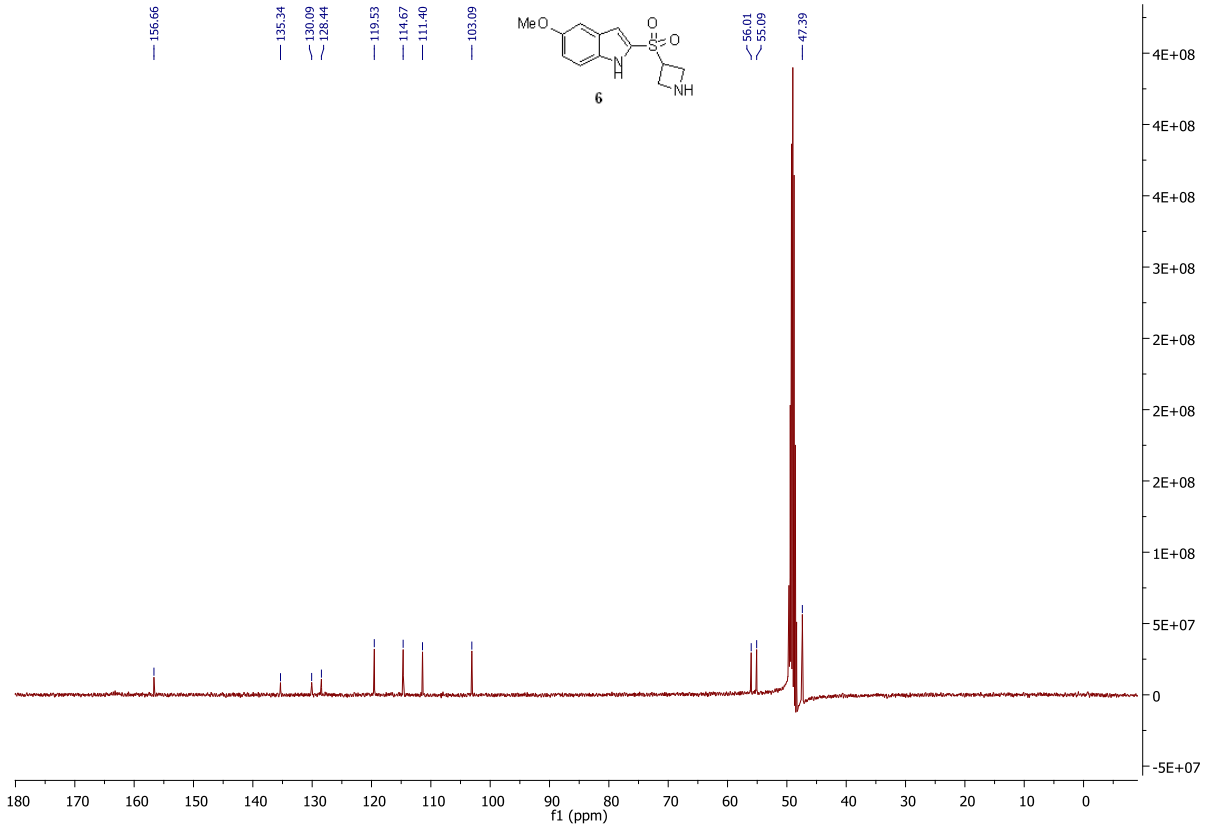

HO
O
S
O
N
H
O
5d
1.00
1.80
1.02
8.07
1.03
f1 (ppm)

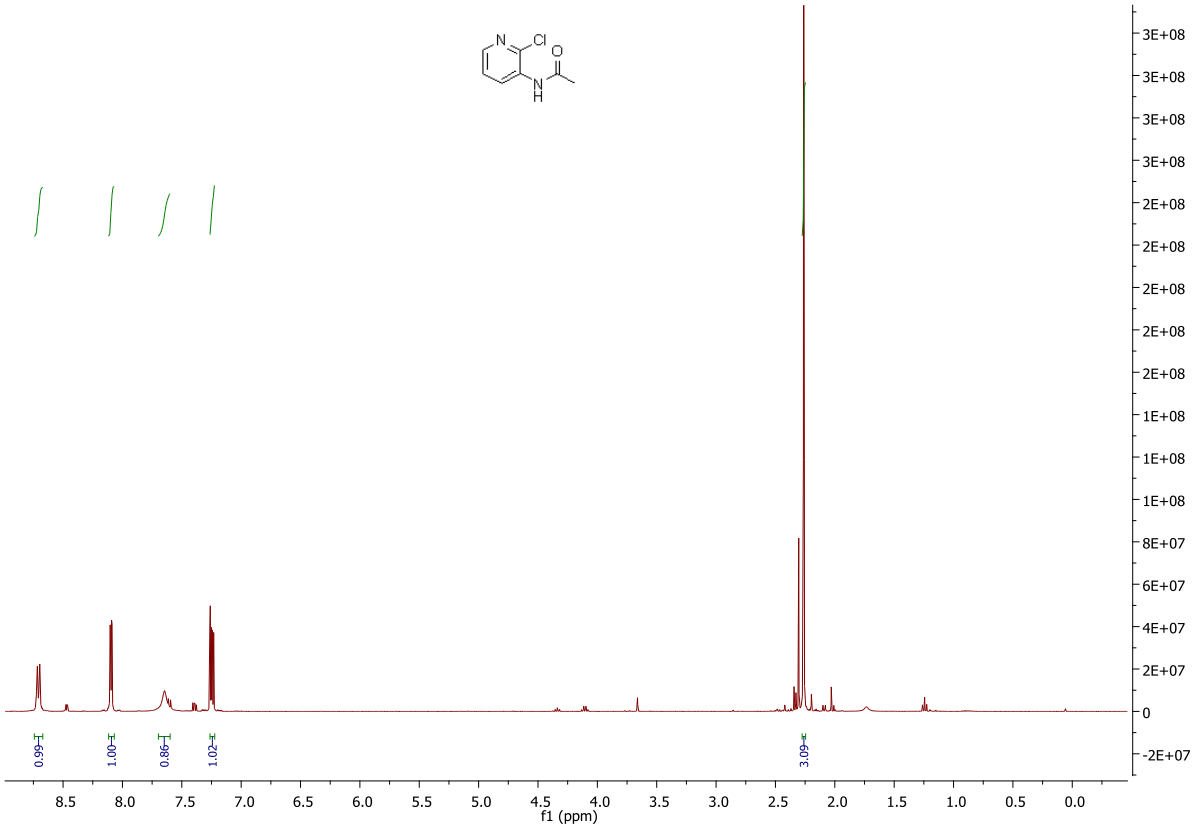

153.19
134.63
131.53
128.82
118.38
114.29
109.85
105.97
71.52
58.92
HO
O
S
O
N
H
O
5d
f1 (ppm)

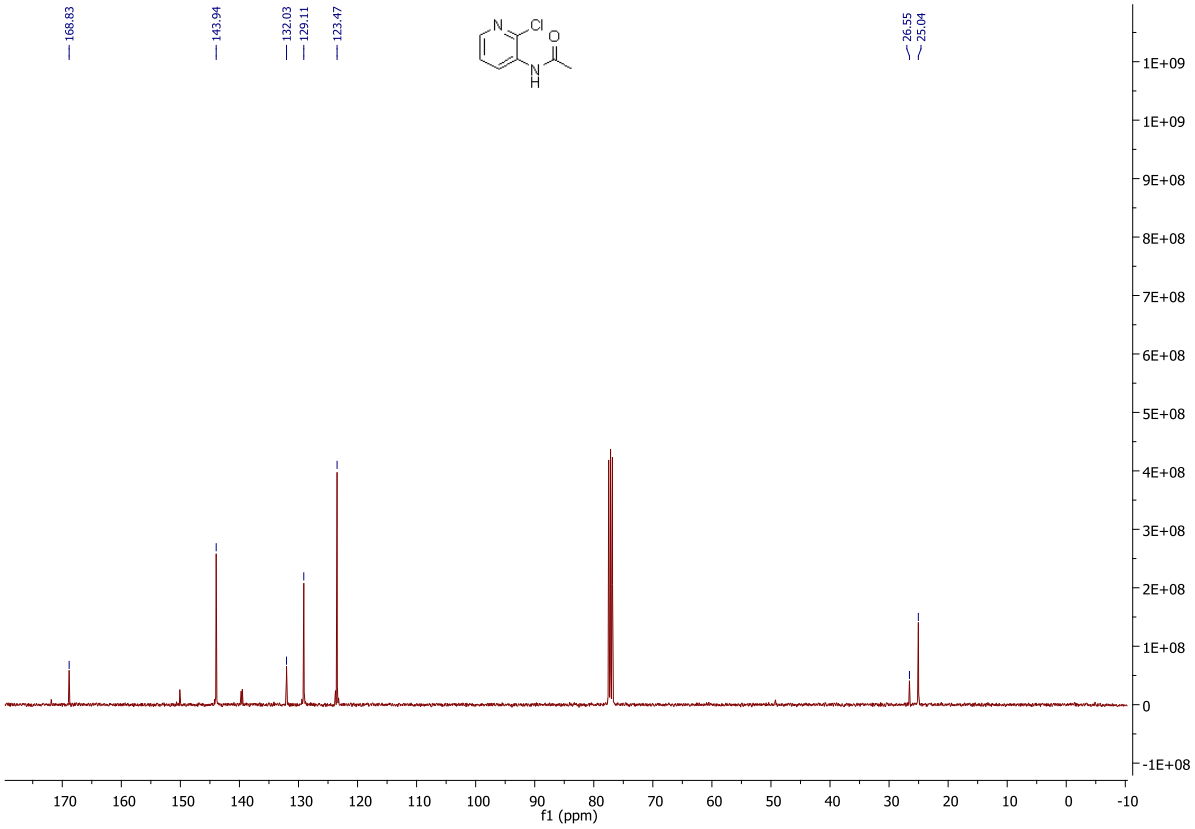

MeO
O
S
O
N
H
O
5e
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
0.97
1.07
1.00
2.08
1.94
2.12
1.01
3.04
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

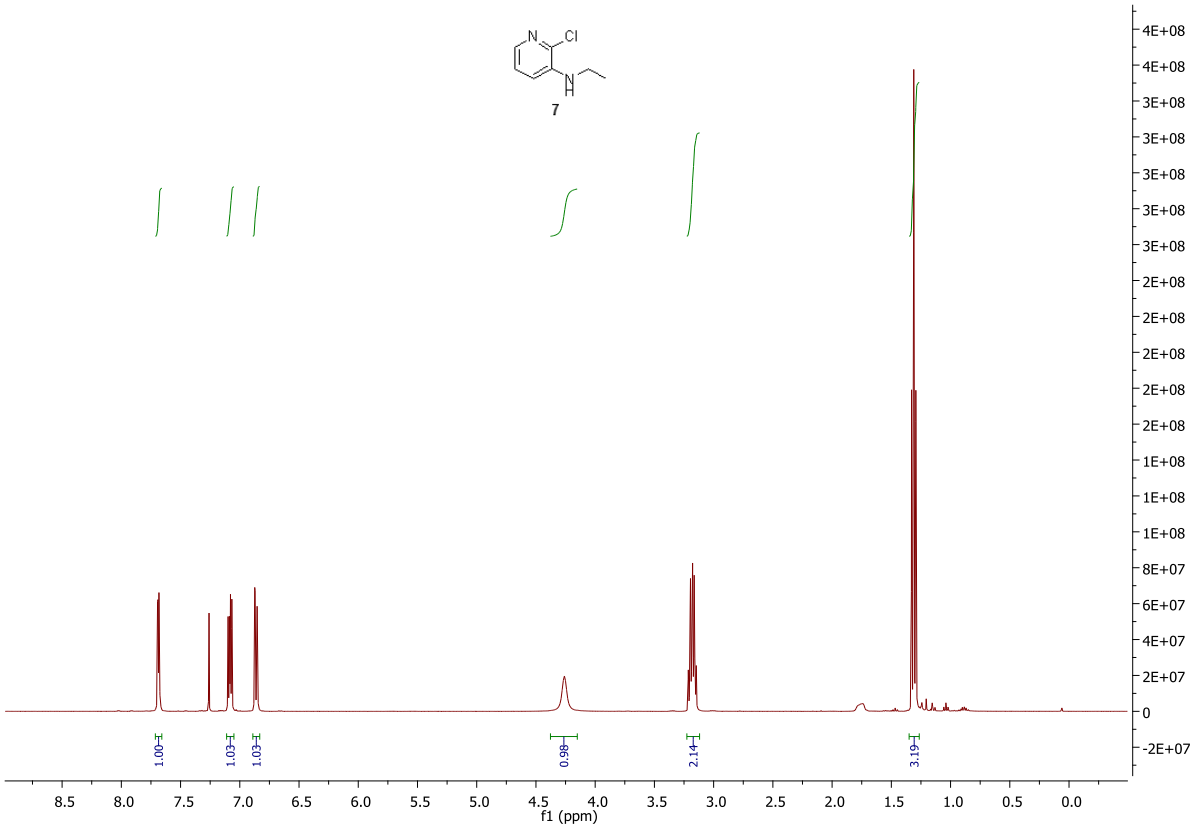

155.50
133.01
129.65
127.58
118.71
113.62
110.18
102.51
70.46
58.21
55.82
MeO
O
S
O
N
H
O
5e
6E+08
5E+08
4E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

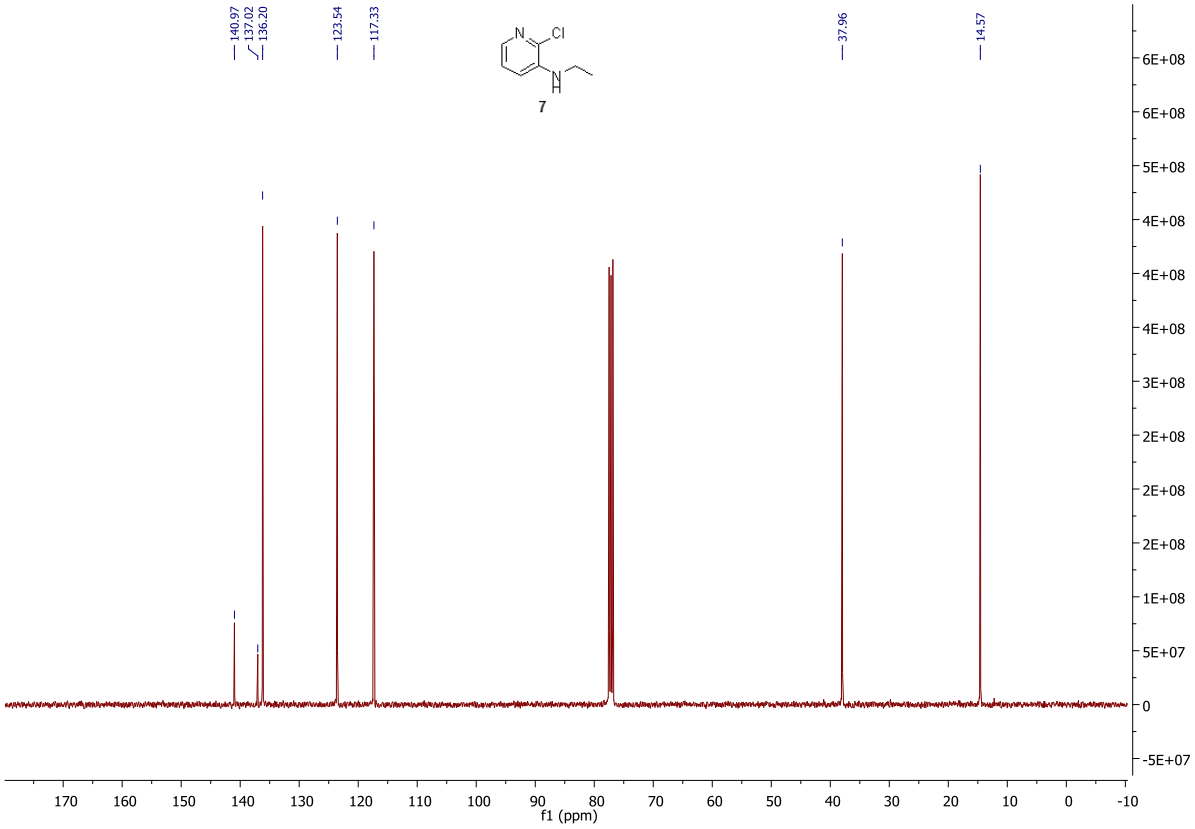

MeO
O
S
O
N
H
NH
6
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
1.02
1.00
1.04
1.00
1.08
4.22
3.11
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

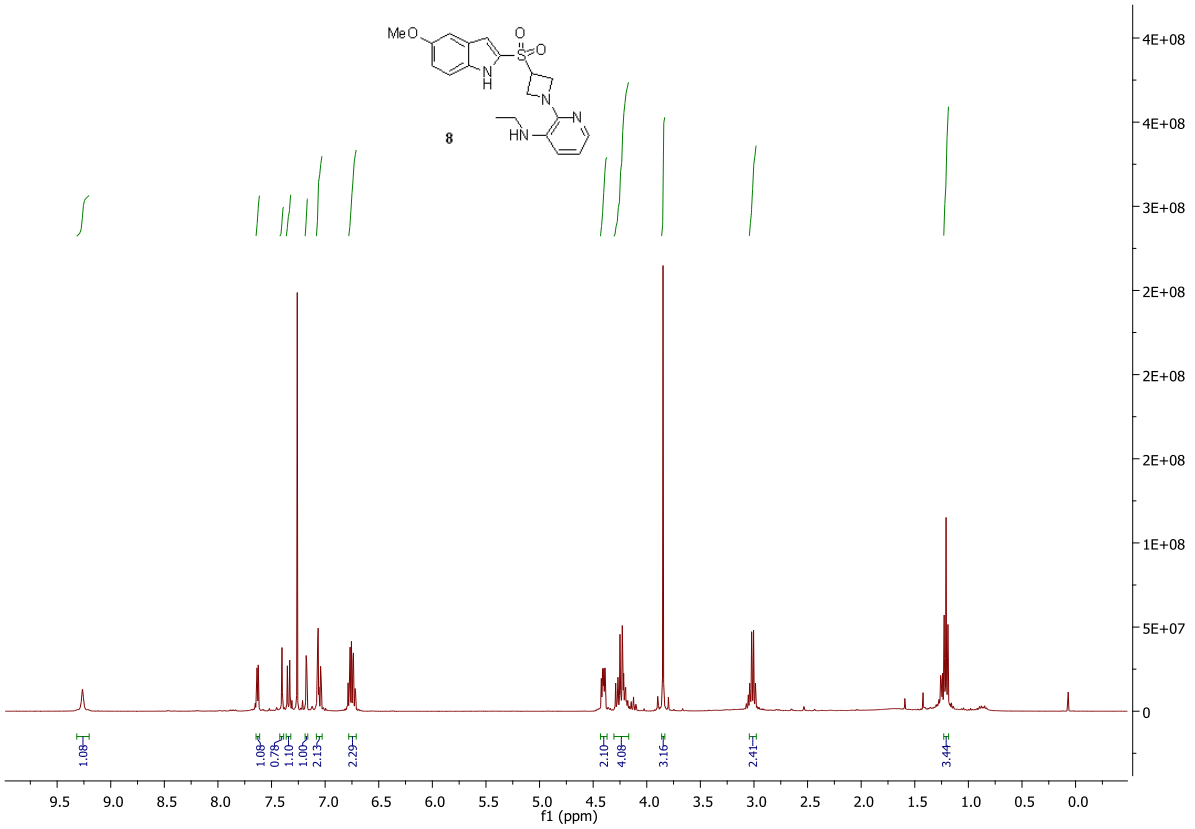

156.66
135.34
130.09
128.44
119.53
114.67
111.40
103.09
56.01
55.09
47.39
MeO
O
S
O
N
H
NH
6
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

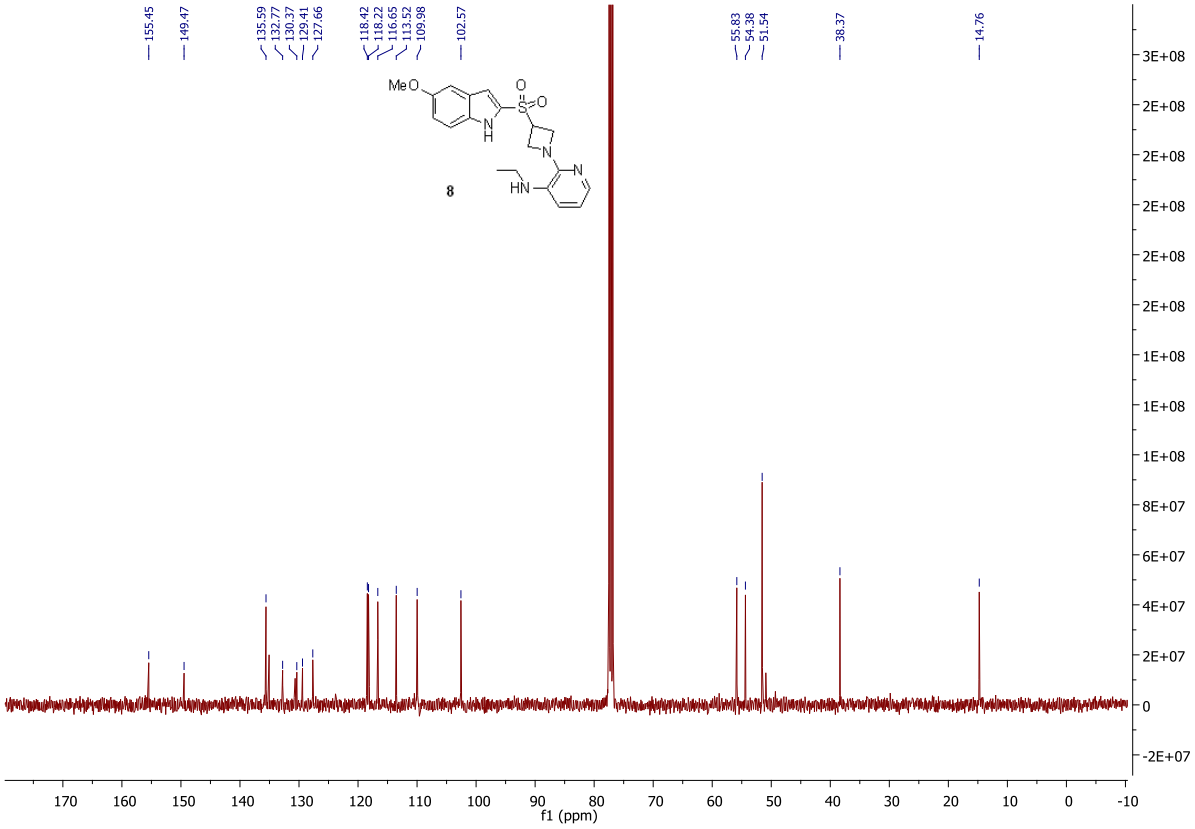

0.99
1.00
0.86
1.02
3.09
f1 (ppm)

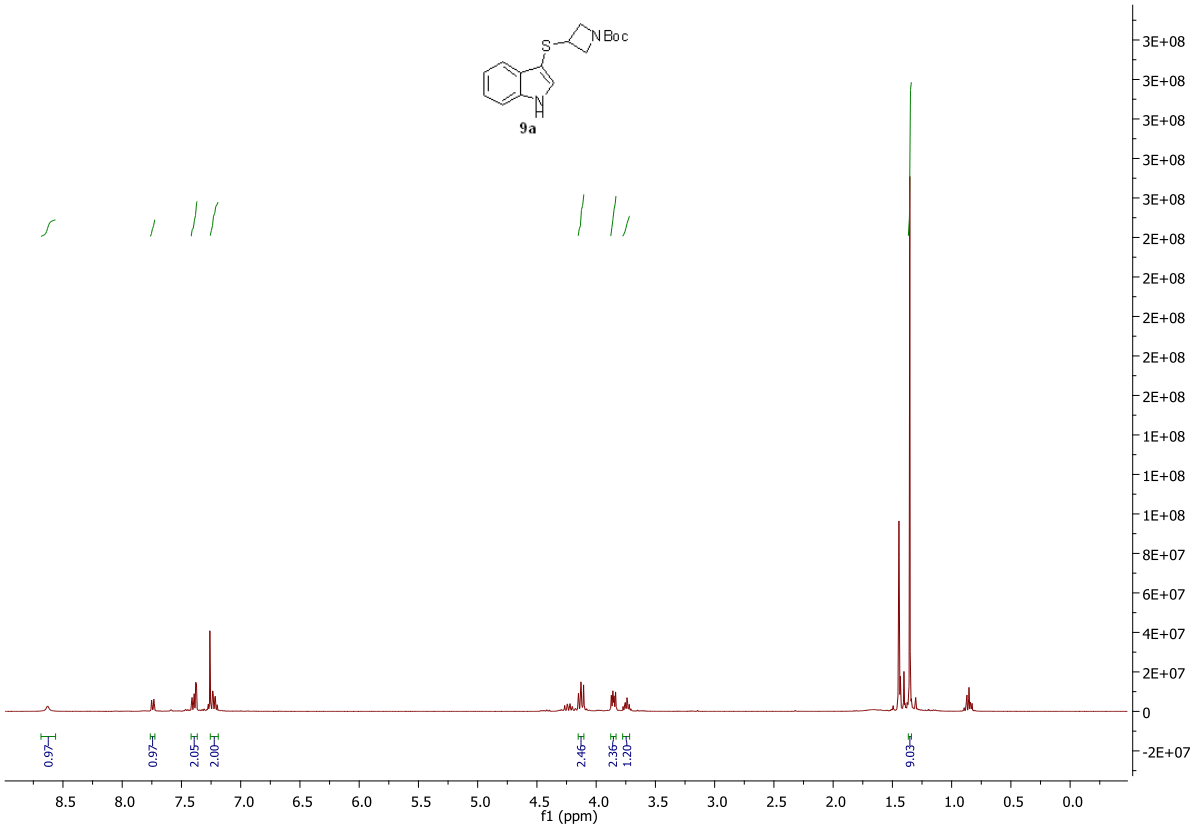

168.83
143.94
132.03
129.11
123.47
26.55
25.04
f1 (ppm)

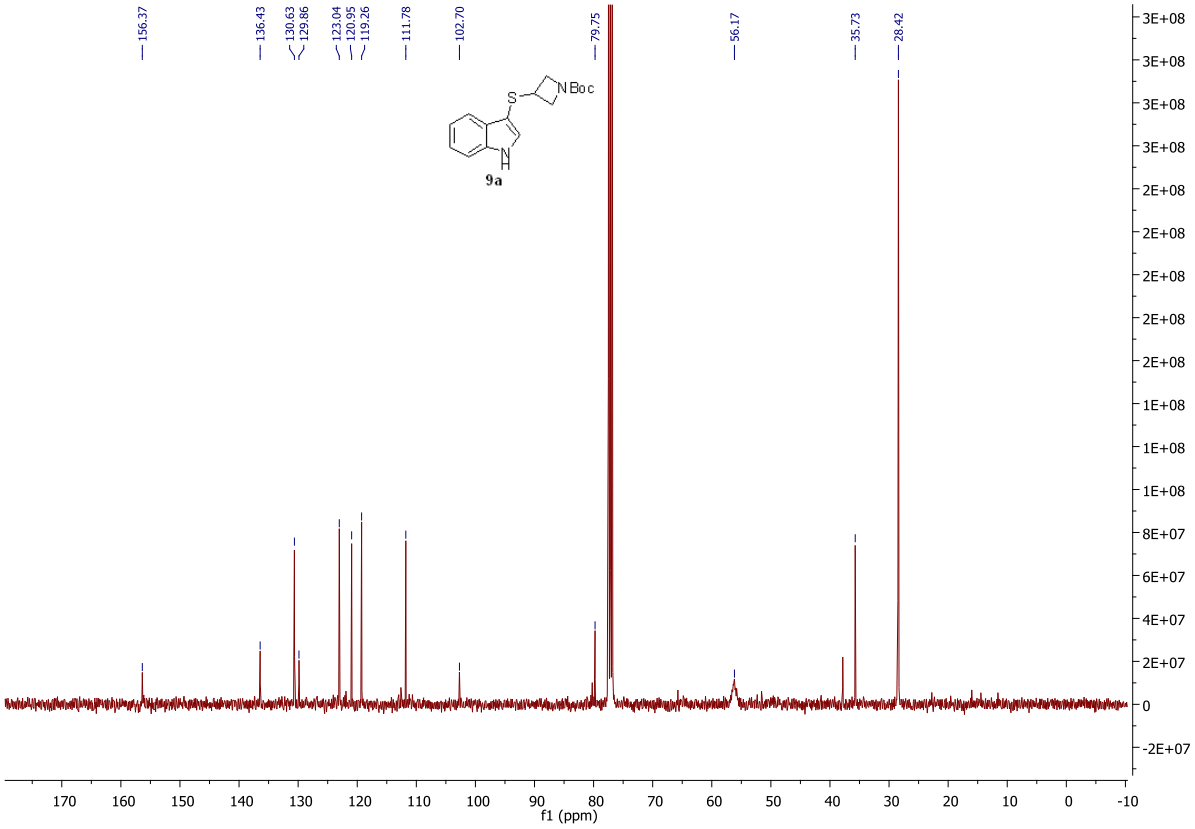

7
1.00
1.03
1.03
0.98
2.14
3.19
f1 (ppm)

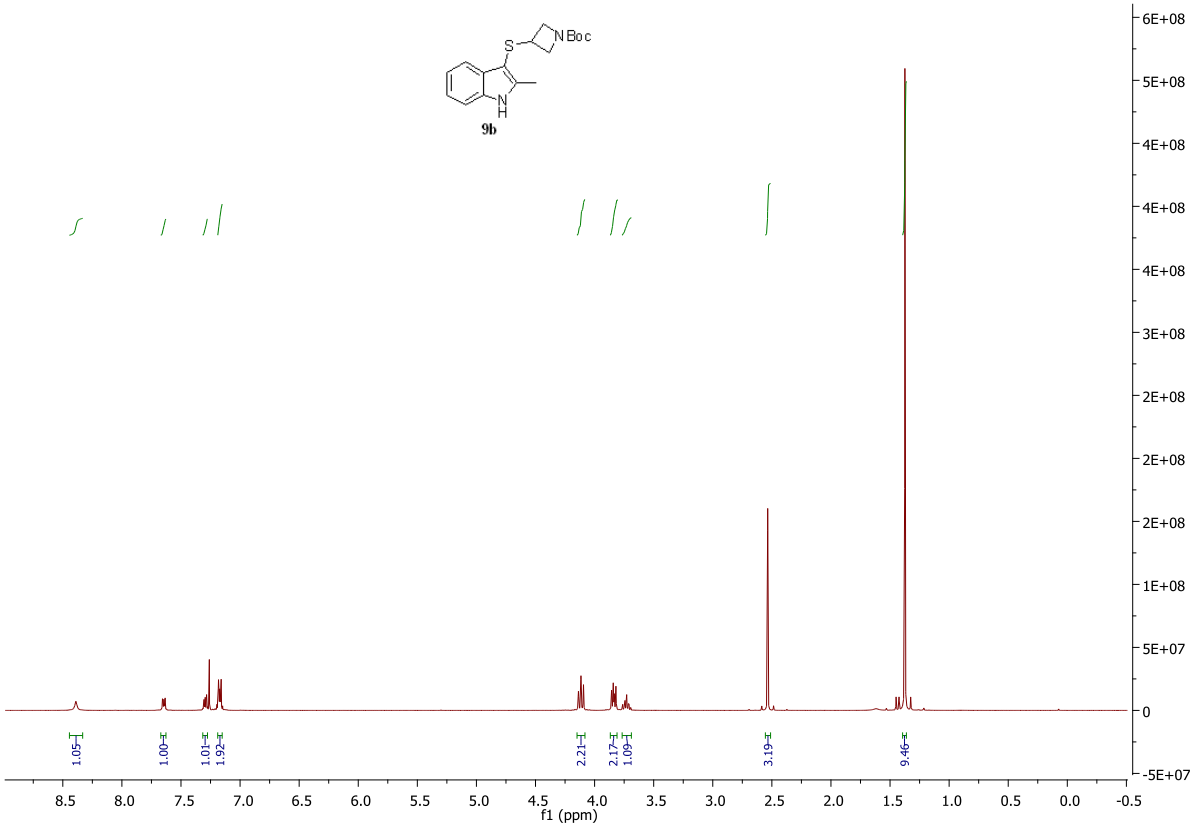

140.97
137.02
136.20
123.54
117.33
37.96
14.57
7
f1 (ppm)

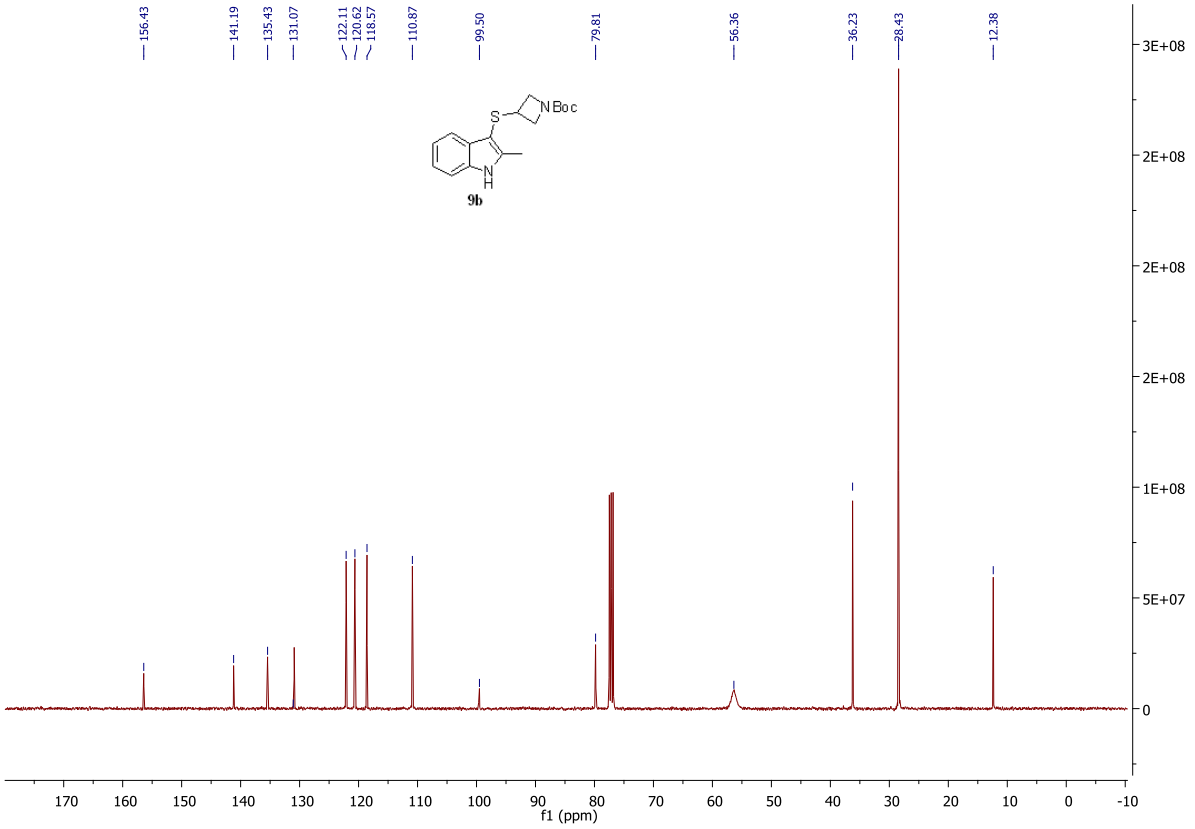

MeO
O
S
O
N
H
N
N
HN
8
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
1.08
1.08
0.78
1.10
1.00
2.13
2.29
2.10
4.08
3.16
2.41
3.44
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

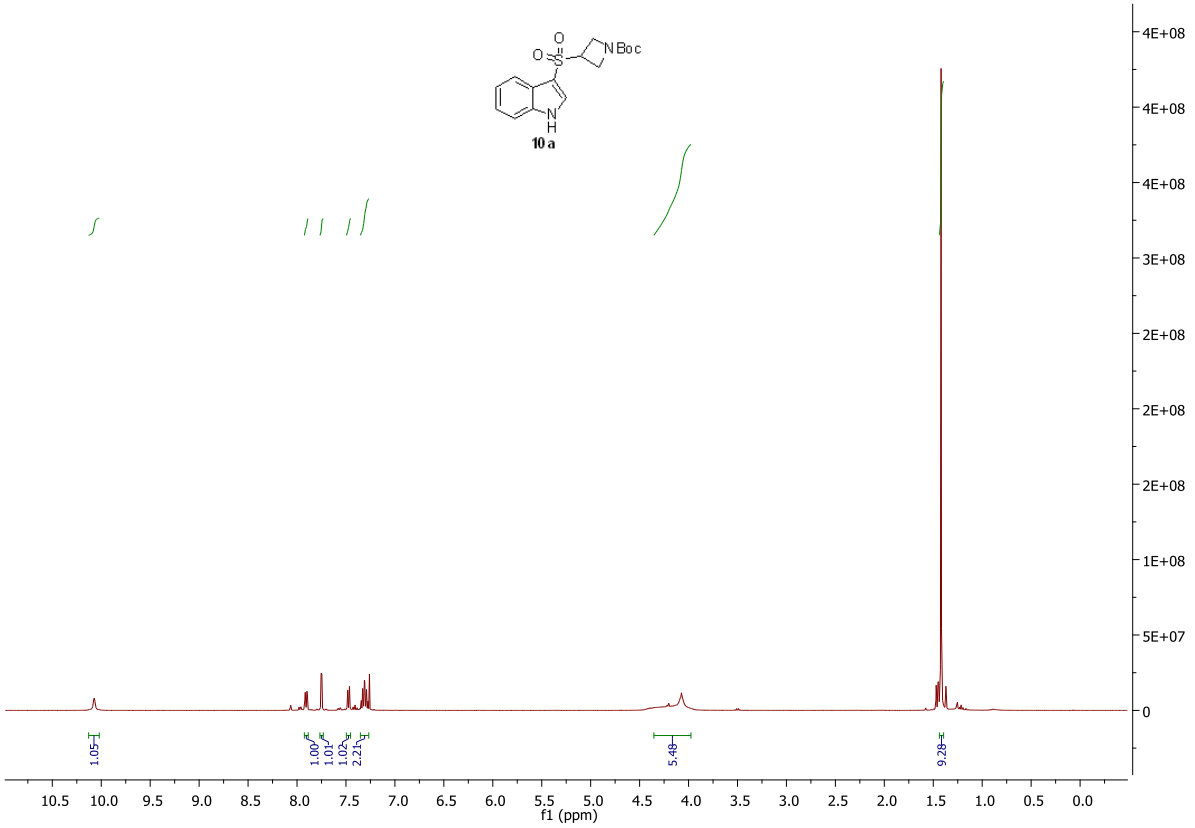

155.45
149.47
135.59
132.77
130.37
129.41
127.66
118.42
118.22
116.65
113.52
109.98
102.57
55.83
54.38
51.54
38.37
14.76
MeO
O
S
O
N
H
N
N
HN
8
3E+08
2E+08
2E+08
2E+08
2E+08
2E+08
2E+08
1E+08
1E+08
1E+08
8E+07
6E+07
4E+07
2E+07
0
-2E+07
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

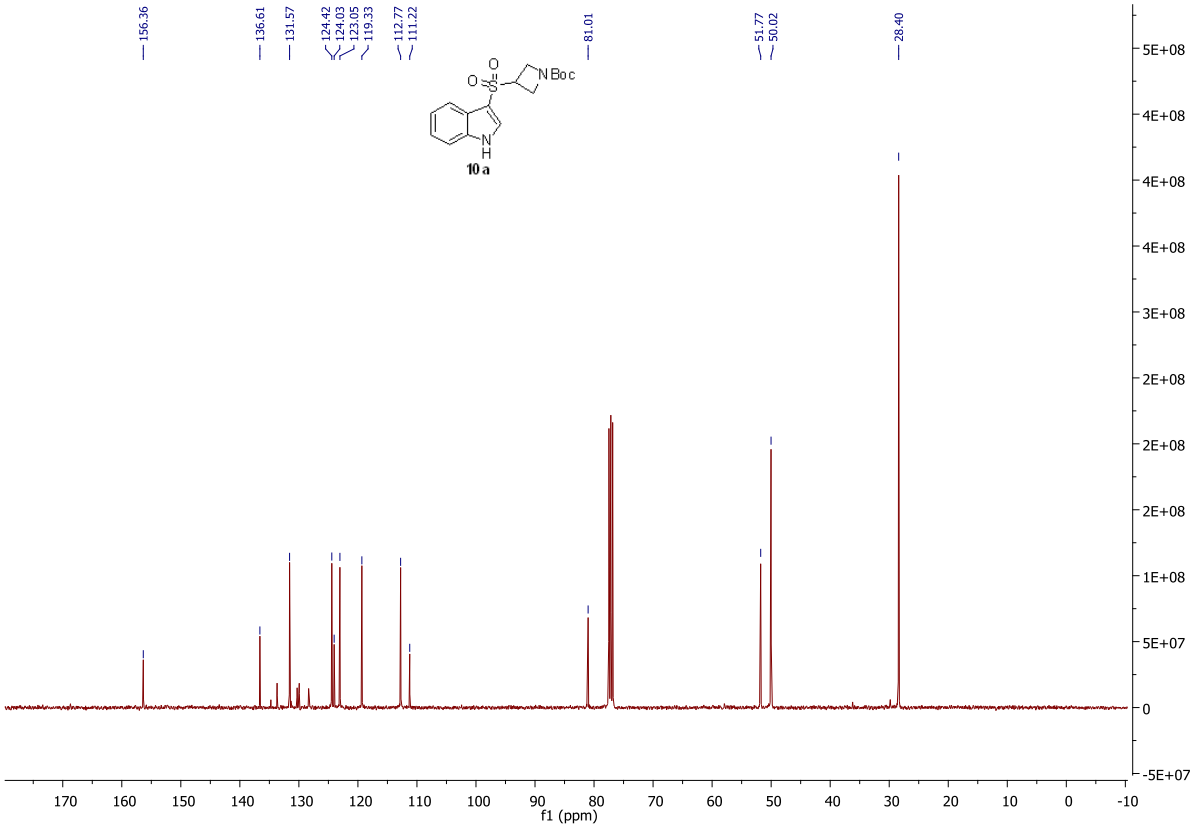

N Boc
S
N
H
9a
0.97
0.97
2.05
2.00
2.46
2.36
1.20
9.03
f1 (ppm)

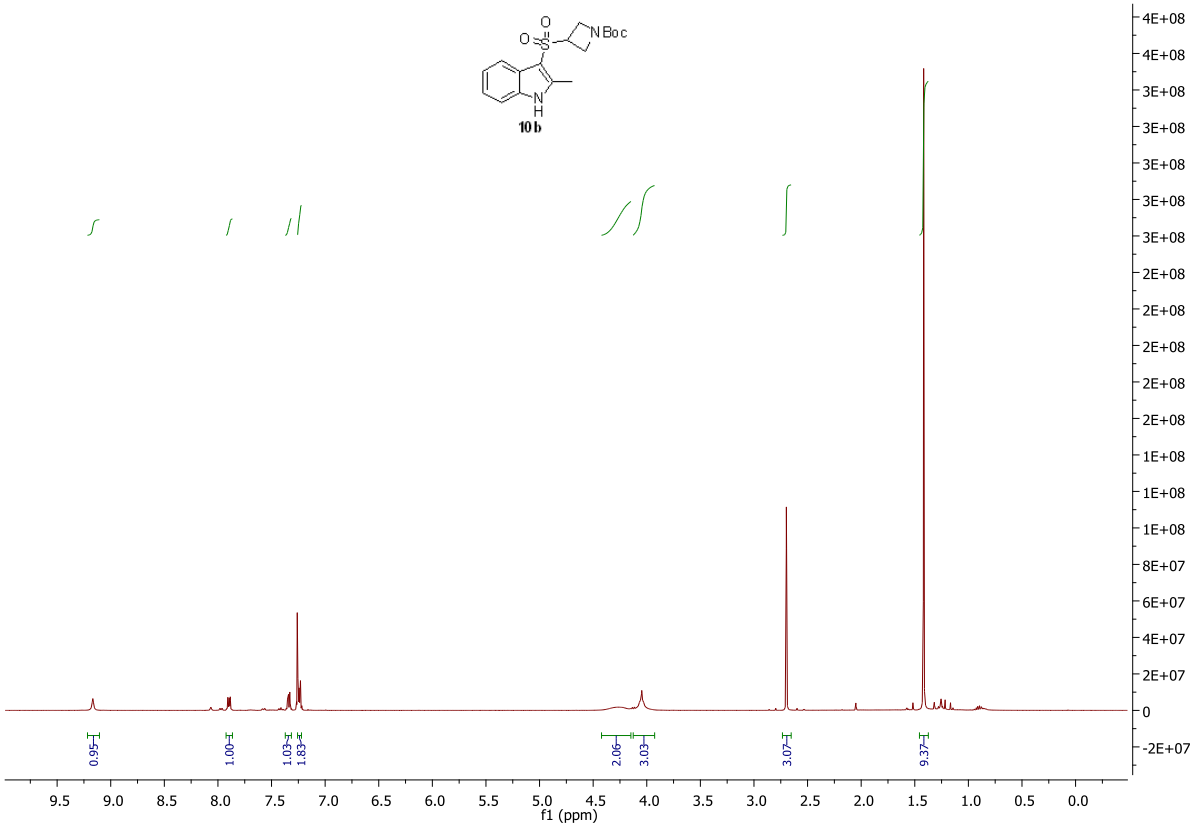

156.37
136.43
130.63
129.86
123.04
120.95
119.26
111.78
102.70
79.75
56.17
35.73
28.42
N Boc
S
N
H
9a
f1 (ppm)

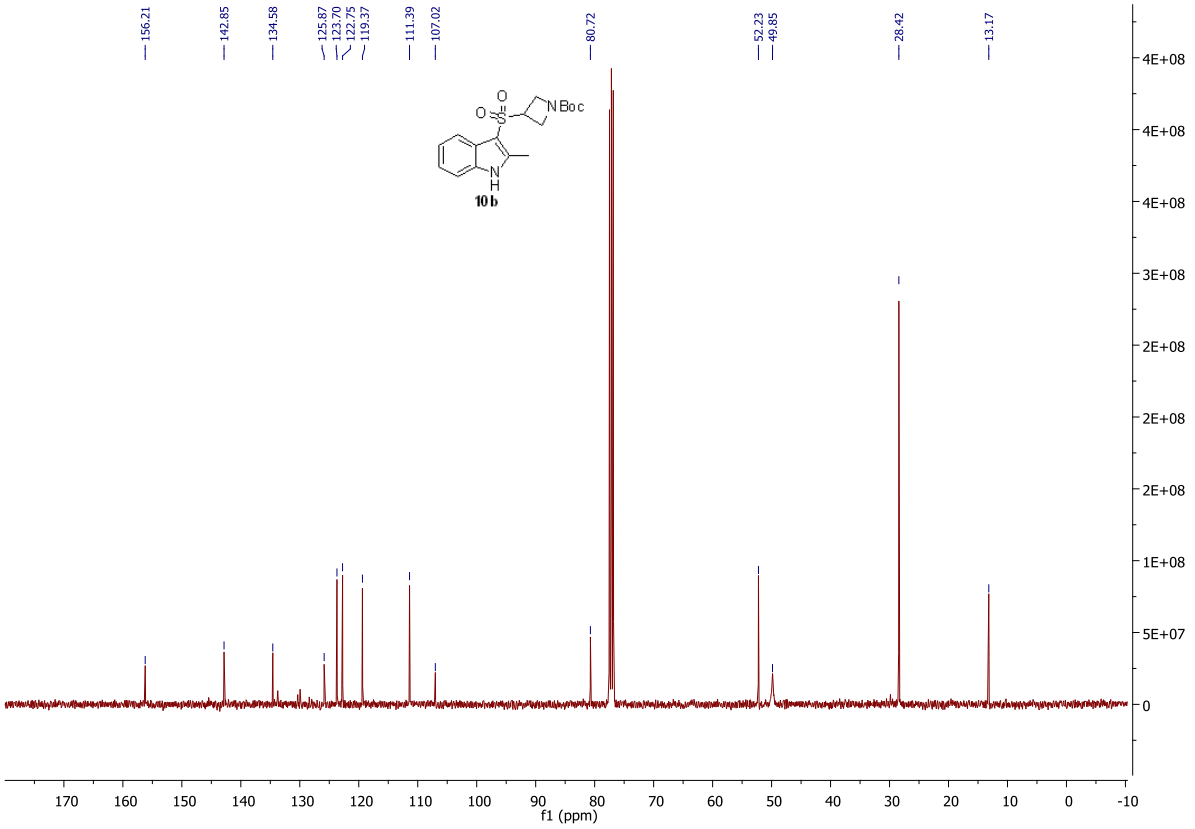

N Boc
S
N
H
9b
1.05
1.00
1.01
1.92
2.21
2.17
1.09
3.19
9.46
f1 (ppm)


156.43
141.19
135.43
131.07
122.11
120.62
118.57
110.87
99.50
79.81
56.36
36.23
28.43
12.38
N Boc
S
N
H
9b
f1 (ppm)


10 a
1.05
1.00
1.01
1.02
2.21
5.48
9.28
f1 (ppm)


156.36
136.61
131.57
124.42
124.03
123.05
119.33
112.77
111.22
81.01
51.77
50.02
28.40
10 a
f1 (ppm)


10b
0.95
1.00
1.03
1.83
2.06
3.03
3.07
9.37
f1 (ppm)


156.21
142.85
134.58
125.87
123.70
122.75
119.37
111.39
107.02
80.72
52.23
49.85
28.42
13.17
10b
f1 (ppm)