Optimization of Phenyl Indole Inhibitors of the AAA ATPase p97

Matthew G. LaPorte,[‡] James C. Burnett,[‡ Ω] Raffaele Colombo,[‡] Stacie Bulfer,[§] Celeste Alverez,[† ‡] Tsui-Fen Chou,[¶] R. Jeffrey Neitz,[§] Neal Green,[&] William J. Moore,[&] Zhizhou Yue,[‡] Shan Li[¶], Michelle R. Arkin,[§*] Peter Wipf,[† ‡*] Donna M. Huryn[†‡*]

[‡]University of Pittsburgh Chemical Diversity Center, University of Pittsburgh, Pittsburgh, PA 15260; [Ω] Computational Drug Development Group, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD 20892; [§] Department of Pharmaceutical Chemistry, Small Molecule Discovery Center, University of California, San Francisco, CA 94158; [†]Department of Pharmaceutical Sciences, University of Pittsburgh, Pittsburgh, PA 15260; [¶] Division of Medical Genetics, Department of Pediatrics, Harbor–UCLA Medical Center and Los Angeles Biomedical Research Institute, Torrance, CA, USA; [&] Leidos Biomedical Research, Inc., Frederick, MD 21702 United States

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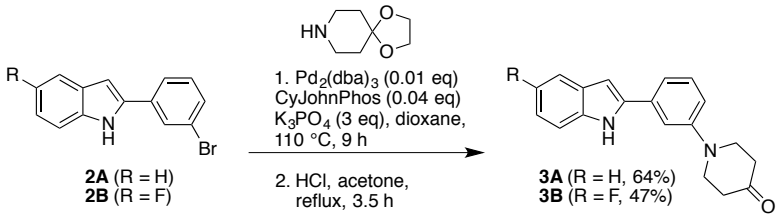
Experimental

General

All glassware was dried in an oven at 140 °C for two hours prior to use. All air- and moisture-sensitive reactions were performed under a dry N_2 atmosphere. The addition of air- and moisture-sensitive catalysts was performed under a dry and inert atmosphere. Reactions carried out at 0 °C or –78 °C employed an ice bath or an acetone/dry ice bath. THF and diethyl ether were distilled over sodium/benzophenone ketyl, Et_3N, CH_2Cl_2 and toluene were distilled from CaH_2. All other materials were obtained from commercial sources and used as received. Microwave reactions were performed in glass microwave vials (cap sealed) with continuous magnetic stirring and an external surface temperature sensor in a Biotage Initiator microwave reactor. Infrared spectra were determined on a Smiths Detection Identify FT-IR spectrometer. ^1H and ^{13}C NMR spectra were obtained either on a Bruker Avance 300/75 MHz, Bruker Avance 400/100 MHz, Bruker Avance 500/125 MHz, or Bruker Avance 700/175 MHz instruments. Chemical shifts (δ) were reported in parts per million, with the residual solvent peak used as an internal standard δ $^1H/^{13}C$ NMR (Solvents); 7.26/77.16 ($CDCl_3$), 2.05/29.84 (acetone-d_6), 2.50/39.52 (DMSO-d_6), 3.31/49.00 (CD_3OD), 5.32/53.84 (CD_2Cl_2); they are tabulated as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, bd = broad doublet, d = doublet, t = triplet, q = quartet, m = multiplet), number of protons, and coupling constant(s). ^{13}C NMR spectra were obtained at 75 MHz, 100 MHz or 125 MHz unless otherwise specified using a proton-decoupled pulse sequence and are tabulated by observed solvent peak. ^{19}F NMR spectra were obtained at 376 MHz unless otherwise specified using a proton-decoupled pulse sequence. Reactions were monitored by thin-layer chromatography analysis using pre-coated silica gel 60 F_{254} plates (EMD, 250 μm thickness), and visualization was accomplished with a 254 nm UV light. Flash chromatography was performed using SiO_2 (SiliaFlash® F60, Silicycle) or using and ISCO-Rf flash chromatography system. LCMS-high resolution LC/MS analyses were completed on a Thermo Scientific Exactive spectrometer with purities determined using an Agilent Technologies 385-ELSD using MeCN/H_2O with 0.1% formic acid; Unless otherwise noted, purities of final products were >95%. Melting points (uncorrected) were determined using a Mel-Temp instrument.



Compound **2A** was prepared according to methods in References 1 and 3.

Compound **2B** was prepared according to methods described in Reference 2.

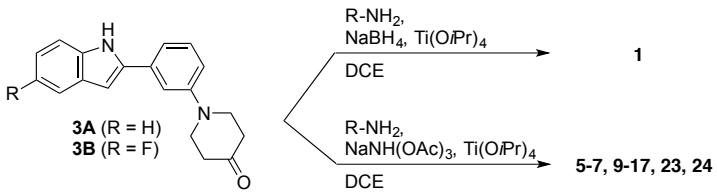
Compound **3A** was prepared according to methods in Reference 3.

Synthesis of Compound **3B**

8-(3-(5-Fluoro-1*H*-indol-2-yl)phenyl)-1,4-dioxa-8-azaspiro[4.5]decane[4]**.** To a solution of 2-(3-bromophenyl)-5-fluoro-1*H*-indole (**2B**, 0.060 g, 0.207 mmol) in deoxygenated dioxane (1.45 mL) was added K_3PO_4 (0.072 g, 0.331 mmol), CyJohnPhos (0.007 g, 0.021 mmol), and Pd_2dba_3 (0.008 g, 0.008 mmol) followed by 1,4-dioxa-8-azaspiro[4.5]decane (0.037 mL, 0.290 mmol). The solution was degassed for 10 min by bubbling with nitrogen and the reaction vial was sealed, and stirred at 120 °C for 12 h. The reaction was cooled to room temperature, sat. $NaHCO_3$ added, and the aqueous extracted with EtOAc (2x). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The product was purified by flash chromatography on SiO_2 (ISCO-Rf, 0-5% MeOH/CH_2Cl_2) to give 8-(3-(5-fluoro-1*H*-indol-2-yl)phenyl)-1,4-dioxa-8-azaspiro[4.5]decane as an orange solid (0.054 g, 74%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (bs, 1 H), 7.35-7.22 (m, 4 H), 7.11 (d, *J* = 7.8 Hz, 1 H), 6.96-6.89 (m, 2 H), 6.74 (d, *J* = 1.2 Hz, 1 H), 4.01 (s, 4 H), 3.41 (t, *J* = 5.7 Hz, 4 H), 1.88 (t, *J* = 5.7 Hz, 4 H); HRMS (ESI) *m/z* calcd for $C_{21}H_{22}N_2FO_2$ $[M+H]^+$ 353.1660, found 353.1659.

1-(3-(5-Fluoro-1*H*-indol-2-yl)phenyl)piperidin-4-one (3B). To a solution of 8-(3-(5-fluoro-1*H*-indol-2-yl)phenyl)-1,4-dioxa-8-azaspiro[4.5]decane (0.050 g, 0.142 mmol) in acetone (17.5 mL) was added 3M HCl (17.5 mL) at room temperature then heated to reflux. After 2.5 h, the solution was cooled to 0 °C, neutralized with Na_2CO_3, and extracted with EtOAc (2x). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on SiO_2 (ISCO-Rf, 5-50% EtOAc/hexanes) to give the product as a pale yellow solid (**3B**, 0.027 g, 63%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (bs, 1 H), 7.58 (d, *J* = 1.6 Hz, 1 H), 7.39 (t, *J* =7.8 Hz, 1 H), 7.32 (m, 2 H), 7.19 (d, *J* = 6.58 Hz, 1 H), 7.15 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.01 (app d, *J* = 8.0 Hz, 1 H), 6.75 (d, *J* =

1.6 Hz, 1 H), 3.70 (t, J = 6.0 Hz, 4 H), 6.66 (t, J = 5.4 Hz, 4 H); HRMS (ESI) m/z calcd for $C_{19}H_{18}N_2FO$ $[M+H]^+$ 309.1398, found 309.1398.



Reductive amination for Compound **1**

1-(3-(1*H*-Indol-2-yl)phenyl)-*N*-(2-(1-methyl-1*H*-1,2,4-triazol-5-yl)ethyl)piperidin-4-amine (1).[5] To a solution of 1-(3-(1*H*-indol-2-yl)phenyl)piperidin-4-one (**3A**, 110 mg, 0.379 mmol) and 2-(1-methyl-1*H*-1,2,4-triazol-5-yl)ethan-1-amine (75 mg, 0.568 mmol) in 1,2-DCE (3.5 mL) was added Ti(O*i*Pr)$_4$ (0.12 mL, 0.42 mmol). The reaction mixture was stirred for 12 h then $NaBH_4$ (26 mg, 0.68 mmol) was added in a single portion. After 2 h, sat. $NaHCO_3$ was added and the mixture was extracted with EtOAc (3x). The organic phases were combined, washed with brine, dried (Na_2SO_4) and concentrated. The crude residue was purified by chromatography on SiO_2 (0-5% MeOH/CH_2Cl_2 with 1% Et_3N) followed by filtration through basic alumina (0-3% MeOH/CH_2Cl_2) to afford the product as a pale yellow solid (**1**, 0.079 g, 52%): Mp 142-143 °C (dec.); IR (neat) 3132, 3064, 3020, 2946, 2901, 2808, 1596, 1421, 1447, 1360, 1185, 805 cm^{-1}; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.91 (s, 1 H), 7.79 (s, 1 H), 7.64 (d, J = 7.8 Hz, 1 H), 7.44 (dd, J = 8.1, 0.5 Hz, 1 H), 7.35 (t, J = 7.9 Hz, 1 H), 7.28 (t, J = 1.8 Hz, 1 H), 7.23-7.11 (m, 3 H), 6.94 (dd, J = 8.2, 2.1 Hz, 1 H), 6.84 (d, J = 1.4 Hz, 1 H), 3.85 (s, 3 H), 3.72 (dt, J = 12.6, 3.3 Hz, 2 H), 3.11 (t, J = 6.6 Hz, 2 H), 2.93-2.84 (m, 4 H), 2.69 (tt, J = 10.1, 4.0 Hz, 1 H), 2.02-1.98 (m, 2 H), 1.62-1.45 (m, 3 H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 154.7, 152.6, 150.3, 139.0, 137.2, 133.4, 130.0, 129.6, 122.4, 120.7, 120.4, 116.26, 116.19, 113.3, 111.2, 99.7, 54.8, 48.6, 44.3, 35.4, 32.8, 27.2; HRMS (ESI) m/z calcd for $C_{24}H_{29}N_6$ $[M+H]^+$ 401.2448, found 401.2445; ELS purity 100%.

General Procedure 1: Reductive amination

A solution of ketone (1 eq.) in 1,2-DCE (0.1 M with respect to ketone) was treated with amine (0.32 mmol) followed by Ti(OiPr)$_4$ (0.22 mmol) at room temperature. After 1 h, $NaBH(OAc)_3$ (1.6 eq.) was added and the solution was stirred for 12 h at room temperature. The reaction was monitored by TLC, and additional quantities of $NaBH(OAc)_3$ were added until the reaction was complete. The reaction was diluted with satd. $NaHCO_3$, extracted with EtOAc (2x), dried (Na_2SO_4), filtered and concentrated. The

residue was purified by chromatography on SiO_2 (MeOH/CH_2Cl_2 with 0.1% Et_3N) followed by filtration through basic alumina (MeOH/CH_2Cl_2) to give the product.

1-(3-(1*H*-Indol-2-yl)phenyl)-*N*-phenethylpiperidin-4-amine (5).[5] Prepared according to General Procedure 1, using 2-phenylethan-1-amine (79 μL, 0.63 mmol). The crude residue was purified by chromatography on SiO_2 (0-3% MeOH/CH_2Cl_2 with 1% Et_3N) followed by filtration through basic alumina (0-7% MeOH/CH_2Cl_2) to afford the desired product as a pale yellow foam (**5**, 0.097 g, 70% over 2 steps): IR (neat) 3415, 3147, 3054, 2920, 2815, 1600, 1450, 1216, 776, 746 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 8.61 (s, 1 H), 7.65 (d, J = 7.8 Hz, 1 H), 7.46 (d, J = 8.0 Hz, 1 H), 7.37-7.33 (m, 3 H), 7.31-7.20 (m, 5 H), 7.15 (dt, J = 8.5, 4.6 Hz, 2 H), 6.95 (dd, J = 8.2, 2.2 Hz, 1 H), 6.85 (d, J = 1.4 Hz, 1 H), 3.76 (dd, J = 9.6, 3.0 Hz, 2 H), 2.99 (t, J = 7.2 Hz, 2 H), 2.93-2.82 (m, 4 H), 2.71 (tt, J = 10.2, 4.0 Hz, 1 H), 2.04-2.00 (m, 2 H), 1.56-1.47 (m, 2 H), 1.06 (bs, 1 H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 152.2, 140.5, 138.6, 136.8, 133.0, 129.6, 129.3, 128.7, 128.4, 126.0, 122.1, 120.4, 120.1, 115.83, 115.81, 113.0, 110.8, 99.5, 54.6, 48.4, 48.1, 36.8, 32.6; HRMS (ESI) m/z calcd for $C_{27}H_{30}N_3$ $[M+H]^+$ 396.2434, found 396.2431; ELS purity 100%.

1-(3-(1*H*-Indol-2-yl)phenyl)-*N*-(2-(pyridin-2-yl)ethyl)piperidin-4-amine (6).[5] Prepared according to General Procedure 1, using 2-(pyridin-2-yl)ethan-1-amine (78 μL, 0.63 mmol). The crude residue was purified by chromatography on SiO_2 (0-5% MeOH/CH_2Cl_2 with 1% Et_3N) followed by filtration through basic alumina (0-7% MeOH/CH_2Cl_2) to afford the desired product as a pale yellow foam (**6**, 0.099 g, 71% over 2 steps): IR (neat) 3166, 3058, 2949, 2893, 2819, 1596, 1477, 1450, 1357, 1293, 1219, 995, 776, 746 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 10.72 (s, 1 H), 8.52 (ddd, J = 4.8, 1.8, 0.9 Hz, 1 H), 7.67 (td, J = 7.6, 1.8 Hz, 1 H), 7.57 (d, J = 7.8 Hz, 1 H), 7.46 (d, J = 1.0 Hz, 1 H), 7.41-7.40 (m, 1 H), 7.28-7.27 (m, 3 H), 7.18 (dd, J = 7.0, 5.3 Hz, 1 H), 7.12-7.09 (m, 1 H), 7.04-7.01 (m, 1 H), 6.92-6.88 (m, 2 H), 3.73 (dt, J = 12.7, 3.4 Hz, 2 H), 3.06-3.03 (m, 2 H), 2.94 (t, J = 7.0 Hz, 2 H), 2.85 (td, J = 11.9, 2.1 Hz, 2 H), 2.67 (tt, J = 9.9, 3.9 Hz, 1 H), 1.96 (dt, J = 9.2, 3.6 Hz, 2 H), 1.49-1.41 (m, 2 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 160.9, 152.3, 149.1, 138.8, 137.4, 136.1, 133.3, 129.44, 129.39, 123.1, 121.5, 121.1, 120.1, 119.5, 115.8, 115.2, 112.7, 111.0, 98.9, 54.5, 47.8, 46.4, 38.7, 32.4; HRMS (ESI) m/z calcd for $C_{26}H_{29}N_4$ $[M+H]^+$ 397.2387, found 397.2381; ELS purity 100%.

1-(3-(1*H*-Indol-2-yl)phenyl)-*N*-(pyridin-2-ylmethyl)piperidin-4-amine (7).[5] Prepared according to General Procedure 1, using pyridin-2-ylmethanamine (69 mg, 0.63 mmol). The crude residue was purified by chromatography on SiO_2 (0-5% MeOH/CH_2Cl_2 with 1% Et_3N) followed by filtration through basic alumina (0-7% MeOH/CH_2Cl_2) to afford the desired product as a pale yellow foam (**7**, 0.090 g, 67% over

2 steps): IR (neat) 3158, 3057, 3013, 2923, 2807, 1596, 1450, 1354, 1216, 1115, 776, 746 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 10.70 (s, 1 H), 8.54 (d, J = 4.3 Hz, 1 H), 7.74 (td, J = 7.7, 1.8 Hz, 1 H), 7.57 (d, J = 7.8 Hz, 1 H), 7.48 (d, J = 7.4 Hz, 2 H), 7.42-7.40 (m, 1 H), 7.29 (d, J = 5.0 Hz, 2 H), 7.23 (dd, J = 7.1, 5.2 Hz, 1 H), 7.13-7.09 (m, 1 H), 7.05-7.01 (m, 1 H), 6.93 (td, J = 4.6, 2.5 Hz, 1 H), 6.89 (d, J = 1.4 Hz, 1 H), 3.97 (s, 2 H), 3.78 (dt, J = 12.7, 3.5 Hz, 2 H), 2.91-2.84 (m, 2 H), 2.72 (tt, J = 9.8, 4.0 Hz, 1 H), 2.06-2.02 (m, 2 H), 1.60-1.51 (m, 2 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 161.1, 152.3, 148.9, 138.8, 137.4, 136.1, 133.3, 129.44, 129.37, 121.9, 121.63, 121.53, 120.1, 119.5, 115.8, 115.3, 112.7, 111.0, 98.9, 54.3, 52.1, 47.8, 32.3; HRMS (ESI) m/z calcd for $C_{25}H_{27}N_4$ $[M+H]^+$ 383.2230, found 383.2226; ELS purity 100%.

1-(3-(1*H*-Indol-2-yl)phenyl)-*N*-(2-(4-methylpiperazin-1-yl)ethyl)piperidin-4-amine (9).[5] Prepared according to General Procedure 1, using 2-(4-methylpiperazin-1-yl)ethan-1-amine (90 mg, 0.63 mmol). The crude residue was purified by chromatography on SiO_2 (0-5% MeOH/CH_2Cl_2 with 1% Et_3N) followed by filtration through basic alumina (0-7% MeOH/CH_2Cl_2) to afford the desired product as a pale yellow foam (**9**, 0.09 g, 62% over 2 steps): IR (neat) 3151, 3057, 2981, 2797, 2688, 1600, 1450, 1353, 1294, 1011, 776, 746 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 10.73 (s, 1 H), 7.59-7.57 (m, 1 H), 7.47 (t, J = 1.3 Hz, 1 H), 7.43-7.41 (m, 1 H), 7.30-7.28 (m, 2 H), 7.11 (ddd, J = 8.1, 7.0, 1.2 Hz, 1 H), 7.04 (ddd, J = 7.9, 7.0, 1.0 Hz, 1 H), 6.94-6.89 (m, 2 H), 3.76 (dt, J = 12.7, 3.4 Hz, 2 H), 2.87 (td, J = 11.9, 2.2 Hz, 2 H), 2.74 (t, J = 6.1 Hz, 2 H), 2.64 (tt, J = 9.9, 3.9 Hz, 1 H), 2.46-2.36 (m, 10 H), 2.19 (s, 3 H), 1.99-1.95 (m, 2 H), 1.52-1.43 (m, 2 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 152.3, 138.8, 137.4, 133.3, 129.45, 129.38, 121.5, 120.1, 119.5, 115.8, 115.3, 112.7, 111.1, 98.9, 58.1, 55.2, 54.8, 53.2, 47.9, 45.5, 43.5, 32.5; HRMS (ESI) m/z calcd for $C_{26}H_{36}N_5$ $[M+H]^+$ 418.2965, found 418.2963; ELS purity 99.4%.

1-(3-(1*H*-Indol-2-yl)phenyl)-*N*-(2-(4-ethylpiperazin-1-yl)ethyl)piperidin-4-amine (10).[5] Prepared according to General Procedure 1, using 2-(4-ethylpiperazin-1-yl)ethan-1-amine (62 mg, 0.39 mmol). The crude residue was purified by chromatography on SiO_2 (0-30% MeOH/CH_2Cl_2 with 1% Et_3N) followed by filtration through basic alumina (0-7% MeOH/CH_2Cl_2) to afford the desired product as a pale yellow foam (**10**, 0.080, 71% over 2 steps): IR (neat) 3173, 2931, 2811, 1600, 1450, 1298, 1115, 776, 746 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 10.76 (s, 1 H), 7.58 (d, J = 7.9 Hz, 1 H), 7.47-7.42 (m, 2 H), 7.30-7.28 (m, 2 H), 7.12 (ddd, J = 8.1, 7.0, 1.1 Hz, 1 H), 7.04 (td, J = 7.4, 0.9 Hz, 1 H), 6.92-6.89 (m, 2 H), 3.75 (dt, J = 12.6, 3.4 Hz, 2 H), 2.90-2.83 (m, 2 H), 2.74 (t, J = 6.1 Hz, 2 H), 2.64 (tt, J = 9.4, 4.4 Hz, 1 H), 2.45-2.30 (m, 12 H), 1.97 (dd, J = 12.8, 2.8 Hz, 2 H), 1.52-1.43 (m, 2 H), 1.03 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 152.3, 138.8, 137.4, 133.4, 129.46, 129.40, 121.5, 120.1, 119.5, 115.9, 115.3, 112.8, 111.1, 98.9, 58.2, 54.8, 53.3, 53.0, 52.0, 47.9, 43.5, 32.5, 11.8; HRMS (ESI) m/z calcd for

$C_{27}H_{38}N_5$ $[M+H]^+$ 432.3122, found 432.3116; ELS purity 100%.

1-(3-(1*H*-Indol-2-yl)phenyl)-*N*-(2-(4-isopropylpiperazin-1-yl)ethyl)piperidin-4-amine (11).[3,5] Prepared according to General Procedure 1, using 2-(4-isopropylpiperazin-1-yl)ethan-1-amine (0.077 g, 0.45 mmol). The crude residue was purified by chromatography on SiO_2 (0-20% MeOH/CH_2Cl_2 with 1% Et_3N) followed by filtration through basic alumina (0-7% MeOH/CH_2Cl_2) to afford the desired product as a pale yellow foam (**11**, 0.095 g, 71% over 2 steps): IR (neat) 3422, 3222, 2957, 2931, 2808, 1600, 1450, 1294, 1144, 776, 746 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.55 (d, J = 7.8 Hz, 1 H), 7.41 (t, J = 7.1 Hz, 2 H), 7.29-7.23 (m, 2 H), 7.13-7.09 (m, 1 H), 7.02 (t, J = 7.4 Hz, 1 H), 6.84 (dt, J = 7.3, 1.9 Hz, 1 H), 6.79 (s, 1 H), 3.70 (d, J = 12.5 Hz, 2 H), 2.72-2.66 (m, 2 H), 2.62-2.38 (m, 14 H), 1.91 (t, J = 8.4 Hz, 2 H), 1.48-1.39 (m, 2 H), 1.03 (d, J = 6.5 Hz, 6 H); ^{13}C NMR (100 MHz, CD_3OD) δ 152.0, 138.5, 137.4, 133.4, 129.2, 121.3, 119.8, 119.2, 116.5, 115.6, 113.2, 110.8, 98.4, 57.0, 54.7, 54.5, 52.7, 42.3, 31.5, 17.4; HRMS (ESI) m/z calcd for $C_{28}H_{40}N_5$ $[M+H]^+$ 446.3278, found 446.3277; ELS purity 100%.

1-(3-(1*H*-Indol-2-yl)phenyl)-*N*-(2-(4-(*tert*-butyl)piperazin-1-yl)ethyl)piperidin-4-amine (12).[3,5] Prepared according to General Procedure 1, using 2-(4-(*tert*-butyl)piperazin-1-yl)ethan-1-amine (0.062 g, 0.34 mmol). The crude residue was purified by chromatography on SiO_2 (0-30% MeOH/CH_2Cl_2 with 1% Et_3N) followed by filtration through basic alumina (0-7% MeOH/CH_2Cl_2) to afford the desired product as a pale yellow foam (**12**, 0.080 g, 78%): IR (neat) 3307, 3058, 2961, 2931, 2811, 1600, 1450, 1357, 1294, 1212, 776, 734 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 10.74 (s, 1 H), 7.58 (d, J = 7.8 Hz, 1 H), 7.47 (s, 1 H), 7.42 (d, J = 8.1 Hz, 1 H), 7.28 (t, J = 6.5 Hz, 2 H), 7.11 (t, J = 7.5 Hz, 1 H), 7.04 (t, J = 7.4 Hz, 1 H), 6.91-6.88 (m, 2 H), 3.76 (d, J = 12.5 Hz, 2 H), 2.87 (t, J = 11.0 Hz, 2 H), 2.73 (t, J = 6.1 Hz, 2 H), 2.64 (tt, J = 9.3, 4.3 Hz, 1 H), 2.61-2.41 (m, 10 H), 1.97 (d, J = 11.0 Hz, 2 H), 1.51-1.44 (m, 2 H), 1.04 (s, 9 H); ^{13}C NMR (125 MHz, acetone-d_6) δ 152.3, 138.8, 137.4, 133.4, 129.45, 129.39, 121.5, 120.1, 119.5, 115.9, 115.3, 112.8, 111.1, 98.9, 58.2, 54.8, 54.3, 52.9, 47.9, 45.7, 43.5, 32.5, 25.4; HRMS (ESI) m/z calcd for $C_{27}H_{35}N_5F_3$ $[M+H]^+$ 460.3435, found 460.3432; ELS purity 99.9%.

1-(3-(1*H*-Indol-2-yl)phenyl)-*N*-(3-(4-isopropylpiperazin-1-yl)propyl)piperidin-4-amine (13).[5] Prepared according to General Procedure 1, using 3-(4-isopropylpiperazin-1-yl)propan-1-amine (146 mg, 0.39 mmol). The crude residue was purified by chromatography on SiO_2 (0-30% MeOH/CH_2Cl_2 with 1% Et_3N) followed by filtration through basic alumina (0-7% MeOH/CH_2Cl_2) to afford the desired product as a pale yellow foam (**13**, 0.062 g, 52% over 2 steps): IR (neat) 3136, 2927, 2804, 1600, 1450, 1294, 1175, 1145, 776, 746 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 10.79 (s, 1 H), 7.59 (d, J = 7.8 Hz, 1 H), 7.50 (s, 1 H), 7.45 (d, J = 8.1 Hz, 1 H), 7.33-7.28 (m, 2 H), 7.15-7.11 (m, 1 H), 7.07-7.03 (m, 1 H), 6.96-6.90 (m,

2 H), 3.78 (dt, *J* = 12.6, 3.5 Hz, 2 H), 2.95-2.88 (m, 2 H), 2.72 (t, *J* = 6.7 Hz, 2 H), 2.63 (dq, *J* = 12.4, 6.0 Hz, 2 H), 2.50-2.37 (m, 10 H), 2.00 (dd, *J* = 12.8, 3.1 Hz, 2 H), 1.65 (quin, *J* = 6.8 Hz, 2 H), 1.54-1.45 (m, 2 H), 1.02 (d, *J* = 6.5 Hz, 6 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 152.3, 138.8, 137.4, 133.3, 129.41, 129.37, 121.5, 120.1, 119.4, 115.8, 115.2, 112.7, 111.1, 98.8, 57.0, 54.7, 54.03, 53.87, 48.6, 47.8, 45.4, 32.4, 27.5, 18.0; HRMS (ESI) *m/z* calcd for $C_{29}H_{42}N_5$ $[M+H]^+$ 460.3435, found 460.3431; ELS purity 99.9%.

1-(3-(5-Fluoro-1*H*-indol-2-yl)phenyl)-*N*-(2-(4-isopropylpiperazin-1-yl)ethyl)piperidin-4-amine (14). Prepared according to methods described in Reference 2.

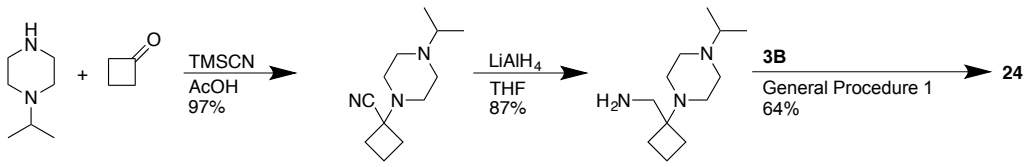
N^1-(1-(3-(5-Fluoro-1*H*-indol-2-yl)phenyl)piperidin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (15).[5] Prepared according to General Procedure 1, using (**3B**, 0.061 g, 0.20 mmol) and N^1,N^1-dimethylethane-1,2-diamine (0.035 mL, 0.31 mmol). The crude residue was purified by chromatography on SiO_2 (0-15% MeOH/CH_2Cl_2 with 0.1% Et_3N) followed by filtration through basic alumina (0-4% MeOH/CH_2Cl_2) to give the product (**15**, 0.042 g, 0.11 mmol, 56%) as a light yellow foamy solid: IR (neat) 3059, 2934, 2816, 1586, 1450, 1215, 1193, 1127, 1077, 839, 767, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1 H), 7.34-7.26 (m, 4 H), 7.10 (d, *J* = 7.2 Hz, 1 H), 6.96-6.92 (m, 2 H), 6.76 (s, 1 H), 3.75 (app d, *J* = 12.4 Hz, 2 H), 2.86 (app t, *J* = 11.6 Hz, 2 H), 2.78 (t, *J* = 6.0 Hz, 2 H), 2.67-2.62 (m, 1 H), 2.47 (t, *J* = 6.0 Hz, 2 H), 2.26 (s, 6 H), 2.03 (app d, *J* = 11.6 Hz, 2 H), 1.61-1.54 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1 (d, J_{CF} = 233 Hz), 152.0, 140.6, 133.3, 132.9, 129.7, 129.6 (d, J_{CF} = 11 Hz), 116.4, 116.1, 113.5, 111.4 (d, J_{CF} = 9 Hz), 110.3 (d, J_{CF} = 26 Hz), 105.2 (d, J_{CF} = 24 Hz), 99.9, 99.8, 59.3, 55.1, 48.5, 45.5, 44.3, 32.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -124.4; HRMS (ESI) *m/z* calcd for $C_{23}H_{30}N_4F$ $[M+H]^+$ 381.2449, found 381.2447; ELS purity 100%.

3-((1-(3-(5-Fluoro-1*H*-indol-2-yl)phenyl)piperidin-4-yl)amino)-1-(4-isopropylpiperazin-1-yl)propan-1-one (16).[5] Prepared according to General Procedure 1 using 3-amino-1-(4-isopropylpiperazin-1-yl)propan-1-one dihydrochloride (0.066 g, 0.24 mmol) and **3B** in 1,2-DCE (1.5 mL). The residue was purified by chromatography on SiO_2 (0-10% MeOH/CH_2Cl_2 with 0.1% Et_3N) followed by filtration through basic alumina (0-5% MeOH/CH_2Cl_2) to give the product (**16**, 0.046 g, 0.094 mmol, 42%) as a light orange foamy solid: IR (neat) 3027, 2974, 2934, 1599, 1450, 1358, 1193, 1127, 1077, 768, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1 H), 7.33-7.23 (m, 4 H), 7.13 (d, *J* = 7.6 Hz, 1 H), 6.95-6.92 (m, 2 H), 6.76 (s, 1 H), 3.71 (d, *J* = 12.4 Hz, 2 H), 3.65 (app t, *J* = 4.8 Hz, 2 H), 3.45 (app t, *J* = 4.8 Hz, 2 H), 2.96 (t, *J* = 6.0 Hz, 2 H), 2.85 (app t, *J* = 11.6 Hz, 2 H), 2.71 (app pent, *J* = 6.8 Hz, 1 H), 2.66-2.60 (m, 1 H), 2.54 (app t, *J* = 6.0 Hz, 2 H), 2.49-2.45 (m, 4 H), 1.99 (app d, *J* = 12.4 Hz, 2 H), 1.56-1.47 (m, 2 H),

1.04 (d, J = 6.4 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 158.1 (d, J_{CF} = 233 Hz), 151.9, 140.5, 133.3, 132.9, 129.7, 129.6 (d, J_{CF} = 11 Hz), 116.3, 116.1, 113.4, 111.5 (d, J_{CF} = 10 Hz), 110.2 (d, J_{CF} = 26 Hz), 105.2 (d, J_{CF} = 24 Hz), 99.8, 99.7, 54.9, 54.5, 48.7, 48.5, 48.3, 45.7, 42.3, 41.9, 33.5, 32.4, 18.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -124.5; HRMS (ESI) *m/z* calcd for $C_{29}H_{39}N_5FO$ $[M+H]^+$ 492.3133, found 492.3133; ELS purity 100%.

1-(3-(5-Fluoro-1*H*-indol-2-yl)phenyl)-*N*-(1-isopropylpiperidin-4-yl)piperidin-4-amine (17).[5] Prepared according to General Procedure 1, using 1-isopropylpiperidin-4-amine (0.046 g, 0.32 mmol) and **3B**. The crude residue was purified by chromatography on SiO_2 (0-20% MeOH/CH_2Cl_2 with 0.1% Et_3N) followed by filtration through basic alumina (0-5% MeOH/CH_2Cl_2) to give the product as a light orange foamy solid (**17**, 0.031 g, 0.12 mmol, 28%): IR (neat) 3027, 2934, 2934, 1605, 1567, 1450, 1359, 1193, 1128, 982, 734, 692 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 1 H), 7.32-7.28 (m, 4 H), 7.11 (d, J = 5.5 Hz, 1 H), 7.02-6.94 (m, 2 H), 6.76 (s, 1 H), 3.75 (d, J = 11.0 Hz, 2 H), 2.87-2.84 (m, 6 H), 2.76-2.74 (m, 2 H), 2.65-2.62 (m, 1 H), 2.20 (app t, J = 11.0 Hz, 2 H), 1.99-1.92 (m, 5 H), 1.55-1.52 (m, 2 H), 1.39-1.36 (m, 2 H), 1.06 (d, J = 4.0 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1 (d, J_{CF} = 235 MHz), 152.1, 140.5, 133.2, 132.9, 129.7, 129.6 (d, J_{CF} = 11 Hz), 116.3, 116.1, 113.4, 111.4 (d, J_{CF} = 10 Hz), 110.3, (d, J_{CF} = 25 Hz), 105.2 (d, J_{CF} = 24 Hz), 99.9, 54.4, 51.7, 51.1, 48.5, 47.8, 33.9, 33.1, 18.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ -124.3; HRMS (ESI) *m/z* calcd for $C_{27}H_{36}N_4F$ $[M+H]^+$ 435.2919, found 435.2915; ELS purity 100%.

1-(3-(5-Fluoro-1*H*-indol-2-yl)phenyl)-*N*-((1-(4-methylpiperazin-1-yl)cyclobutyl)methyl)piperidin-4-amine (23).[5] Prepared according to General Procedure 1, using (1-(4-methylpiperazin-1-yl)cyclobutyl)methanamine (0.033 g, 0.18 mmol). The crude residue was purified by chromatography on SiO_2 (0-10% MeOH/CH_2Cl_2 with 0.1% Et_3N) followed by filtration through basic alumina (0-5% MeOH/CH_2Cl_2) to give the product as an off-white foamy solid (**23**, 0.032 g, 0.067 mmol, 42%): IR (neat) 2934, 2816, 1599, 1450, 1358, 1193, 1127, 982, 768 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (s, 1 H), 7.34-7.28 (m, 3 H), 7.22 (s, 1 H), 7.11 (d, J = 7.5 Hz, 1 H), 6.95-6.94 (m, 2 H), 6.76 (s, 1 H), 3.74 (d, J = 12.5 Hz, 2 H), 2.91-2.85 (m, 4 H), 2.61-2.60 (m, 4 H), 2.55-2.43 (m, 5 H), 2.30 (s, 3 H), 2.21-2.19 (m, 2 H), 2.01 (app d, J = 10.5 Hz, 2 H), 1.76-1.74 (m, 4 H), 1.60-1.56 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1 (d, J_{CF} = 234 Hz), 152.1, 140.5, 133.2, 132.9, 129.7, 129.6 (d, J_{CF} = 10 Hz), 116.2, 116.1, 113.4, 111.4 (d, J_{CF} = 9 Hz), 110.3 (d, J_{CF} = 26 Hz), 105.2 (d, J_{CF} = 23 Hz), 99.9, 62.7, 55.9, 55.3, 50.7, 48.5, 46.1, 45.3, 32.6, 26.9, 13.9; HRMS (ESI) *m/z* calcd for $C_{29}H_{39}N_5F$ $[M+H]^+$ 476.3184, found 476.3182; ELS purity 99.3%.



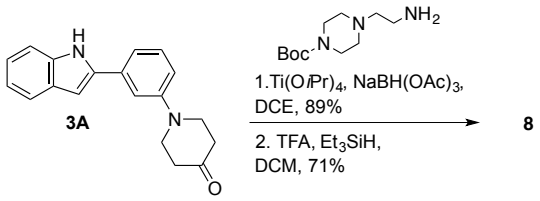
Synthesis of Compound **24**

1-(4-Isopropylpiperazin-1-yl)cyclobutane-1-carbonitrile. Isopropylpiperazine (7.00 mL, 47.4 mmol) was slowly added to acetic acid (20 mL) at 0 °C, followed by cyclobutanone (0.71 mL, 9.45 mmol) and TMSCN (3.10 mL, 23.7 mmol). The mixture was stirred at room temperature overnight and diluted with CH_2Cl_2 (100 mL) and adjusted to pH~9 with 50% NaOH (16 mL). The mixture was extracted with CH_2Cl_2 (2 x). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by chromatography on SiO_2 (3-5% MeOH/CH_2Cl_2) to afford the desired product (1.90 g, 97%) as yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.68 (sept, *J* = 6.6 Hz, 1 H), 2.58-2.52 (m, 4 H), 2.49-2.44 (m, 4 H), 2.42-2.35 (m, 2 H), 2.27-2.07 (m, 3 H), 1.92-1.83 (m, 1 H), 1.03 (d, *J* = 6.6 Hz, 6 H).

(1-(4-Isopropylpiperazin-1-yl)cyclobutyl)methanamine. 1-(4-Isopropylpiperazin-1-yl)cyclobutane-1-carbonitrile (1.90 g, 9.16 mmol) in THF (70 mL) was added to a solution of $LiAlH_4$ (6.90 mL, 27.6 mmol, 4M in Et_2O) in THF (20 mL) at 0-5 °C. The reaction mixture was stirred at room temperature for 12 h, then quenched with H_2O (1.44 mL), 15% NaOH (1.44 mL), and H_2O (4.32 mL), filtered through Celite®, and concentrated to afford the desired product (1.70 g, 88%) as a colorless oil which was used in the next step without any further purification: IR (neat) 2962, 2811, 1677, 1450, 1381, 1328, 1180, 1154, 984 cm-1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.79 (s, 2 H), 2.64-2.52 (m, 9 H), 2.17-2.11 (m, 2 H), 1.83 (bs, 2 H), 1.73-1.57 (m, 4 H), 1.03 (d, *J* = 4.8 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.7, 54.6, 49.5, 45.7, 45.5, 25.9, 18.8, 13.7.

1-(3-(5-Fluoro-1*H*-indol-2-yl)phenyl)-*N*-((1-(4-isopropylpiperazin-1-yl)cyclobutyl)methyl)piperidin-4-amine (24).[5] Prepared according to General Procedure 1, using (1-(4-isopropylpiperazin-1-yl)cyclobutyl)methanamine (0.058 g, 0.27 mmol). The crude residue was purified by chromatography on SiO_2 (0-10% MeOH/CH_2Cl_2 with 0.1% Et_3N) followed by filtration through basic alumina (0-3% MeOH/CH_2Cl_2) to give the product (**24**, 0.077 g, 0.15 mmol, 64%, approx. 5% residual solvent) as a light orange foamy solid: IR (neat) 2975, 2934, 1586, 1450, 1215, 1192, 1128, 982, 767, 734 cm^{-1}; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 8.64 (s, 1 H), 7.34-7.26 (m, 3 H), 7.23 (s, 1 H), 7.11 (d, J = 7.6 Hz, 1 H), 6.96-6.91 (m, 2 H), 6.76 (d, J = 1.2 Hz, 1 H), 3.74 (d, J = 12.4 Hz, 2 H), 2.87-2.85 (m, 3 H), 2.67-2.55 (m, 11 H), 2.24-2.21 (m, 2 H), 2.03-1.99 (m, 2 H), 1.74-1.72 (m, 4 H), 1.62-1.52 (m, 2 H), 1.08 (d, J = 6.8 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1 (d, J_{CF} = 233 Hz), 152.1, 140.5, 133.3, 132.9, 129.7, 129.6 (d, J_{CF} = 11 Hz), 116.3, 116.1, 113.4, 111.4 (d, J_{CF} = 10 Hz), 110.3 (d, J_{CF} = 26 Hz), 105.2 (d, J_{CF} = 24 Hz), 99.9, 62.7, 55.4, 54.5, 50.7, 49.5, 48.5, 45.6, 32.6, 26.8, 18.8, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -124.4; HRMS (ESI) *m/z* calcd for $C_{31}H_{43}N_5F$ $[M+H]^+$ 504.3497, found 504.3493; ELS purity 98.7%.

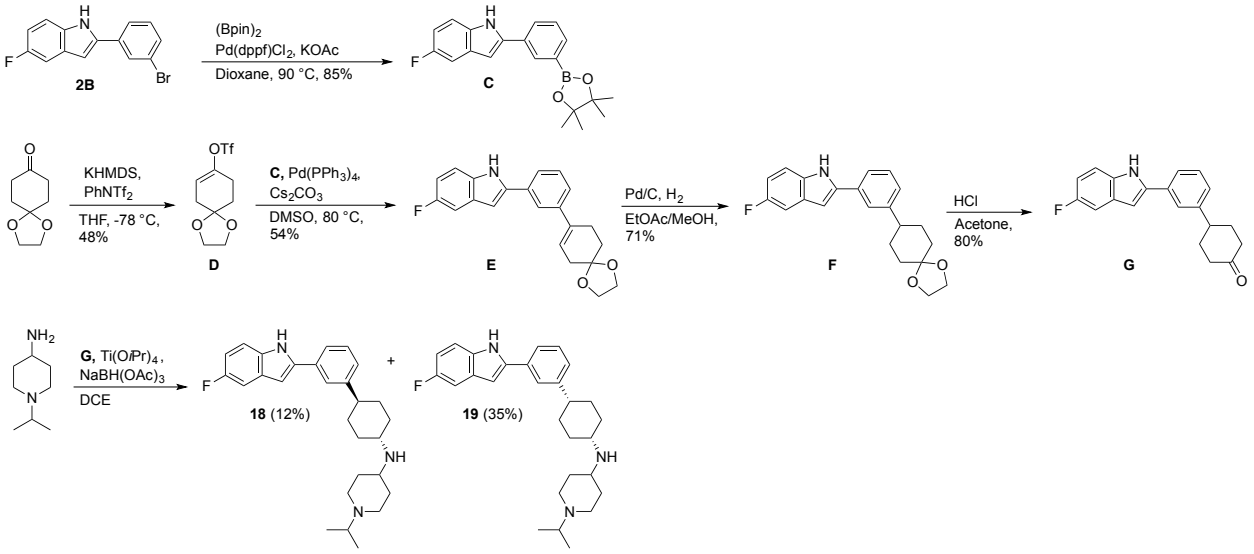


Synthesis of Compound **8**

***tert*-Butyl 4-(2-((1-(3-(1*H*-indol-2-yl)phenyl)piperidin-4-yl)amino)ethyl)piperazine-1-carboxylate**.[5] To a suspension of **3A** (0.11 g, 0.38 mmol) and *tert*-butyl 4-(2-aminoethyl)piperazine-1-carboxylate (0.12 g, 0.57 mmol) in 1,2-DCE (5 mL) was added Ti(O*i*Pr)$_4$ (0.13 mL, 0.41 mmol). The reaction mixture was stirred at room temperature and treated with $NaBH(OAc)_3$ (3 x 55 mg, 0.48 mmol) after 30 min, 1 h and 3 h. The reaction mixture was stirred for an additional 2 h, quenched with sat. $NaHCO_3$ and extracted with EtOAc (3x). The organic phases were combined, washed with brine, dried (Na_2SO_4) and concentrated. The crude residue was purified by chromatography on SiO_2 (10-20% MeOH/CH_2Cl_2) to afford the desired product as a white foam (0.17 g, 89%): IR (neat) 3296, 2931, 2819, 1689, 1667, 1424, 1365, 1242, 1167, 776, 735 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 10.78 (s, 1 H), 7.60-7.58 (m, 1 H), 7.47-7.42 (m, 2 H), 7.28 (q, J = 6.7 Hz, 2 H), 7.13 (td, J = 7.5, 1.0 Hz, 1 H), 7.07-7.03 (m, 1 H), 6.89 (dd, J = 4.9, 1.8 Hz, 2 H), 3.75 (d, J = 12.6 Hz, 2 H), 3.40 (t, J = 4.6 Hz, 4 H), 2.88-2.82 (m, 2 H), 2.74 (t, J = 6.1 Hz, 2 H), 2.66-2.60 (m, 1 H), 2.45 (t, J = 6.1 Hz, 2 H), 2.35 (t, J = 4.9 Hz, 4 H), 1.98-1.95 (m, 2 H), 1.52-1.42 (m, 11 H); ^{13}C NMR (101 MHz, acetone-d_6) δ 154.2, 152.3, 138.8, 137.4, 133.4, 129.49, 129.41, 121.6, 120.2, 119.5, 115.9, 115.3, 112.8, 111.1, 98.9, 78.7, 58.2, 54.8, 53.0, 47.9, 44.2, 43.4, 32.5, 27.8; HRMS (ESI+) *m/z* calcd for $C_{30}H_{42}O_2N_5$ $[M+H]^+$ 504.3333, found 504.3334.

1-(3-(1*H*-Indol-2-yl)phenyl)-*N*-(2-(piperazin-1-yl)ethyl)piperidin-4-amine (8).[5] A solution of trifluoroacetic acid (1.5 mL) and triethylsilane (0.15 mL, 0.93 mmol) in CH_2Cl_2 (1.5 mL) was added to a solution of *tert*-butyl 4-(2-((1-(3-(1*H*-indol-2-yl)phenyl)piperidin-4-yl)amino)ethyl)piperazine-1-

carboxylate (0.14 g, 0.28 mmol) in CH_2Cl_2 (1.5 mL). The reaction mixture was stirred under N_2 at room temperature for 1 h, then concentrated, diluted with $NaHCO_3$, extracted with EtOAc (3x), washed with brine, dried (Na_2SO_4) and concentrated. The crude residue was purified by chromatography on SiO_2 (0-100% MeOH/CH_2Cl_2 with 1% Et_3N) followed by filtration through basic alumina (0-50% MeOH/CH_2Cl_2) to afford the desired product as a yellow oil (**8**, 0.080 g, 71%): IR (neat) 3233, 2938, 2819, 1600, 1450, 1298, 1115, 779, 750 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.54 (d, J = 7.8 Hz, 1 H), 7.41 (t, J = 7.6 Hz, 2 H), 7.27 (q, J = 7.7 Hz, 2 H), 7.11 (t, J = 7.5 Hz, 1 H), 7.02 (t, J = 7.4 Hz, 1 H), 6.85 (d, J = 7.3 Hz, 1 H), 6.79 (s, 1 H), 3.72 (d, J = 12.5 Hz, 2 H), 2.82 (t, J = 4.8 Hz, 4 H), 2.73-2.65 (m, 4 H), 2.54 (tt, J = 10.8, 4.0 Hz, 1 H), 2.42 (t, J = 6.5 Hz, 6 H), 1.93 (d, J = 11.6 Hz, 2 H), 1.47 (qd, J = 11.8, 3.3 Hz, 2 H); ^{13}C NMR (125 MHz, CD_3OD) δ 151.9, 138.5, 137.4, 133.4, 129.24, 129.19, 121.3, 119.8, 119.2, 116.5, 115.6, 113.2, 110.7, 98.4, 57.2, 54.8, 53.1, 48.5, 44.7, 42.0, 31.2; HRMS (ESI) m/z calcd for $C_{25}H_{34}N_5$ $[M+H]^+$ 404.2809, found 404.2807; ELS purity 100%.



Synthesis of Compounds **18** and **19**

5-Fluoro-2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-indole (C)[6]. To a solution of 2-(3-bromophenyl)-5-fluoro-1*H*-indole (**2B**, 0.500 g, 1.72 mmol)[2] in dioxane (17.2 mL) was added 4,4,4′,4′,5,5,5′,5′-octamethyl-2,2′-bi-1,3,2-dioxaborolane (0.656 g, 2.59 mmol), potassium acetate (0.683 g, 6.89 mmol), and Pd(dppf)Cl_2 (0.141 g, 0.172 mmol) and the reaction was stirred under N_2 at 90 °C for 12 h. The reaction was concentrated and the crude mixture was purified by chromatography on SiO_2 (ISCO-Rf, 0-20% EtOAc/hexanes) to give the product as a tan solid (**C**, 0.495 g, 85%): IR (CH_2Cl_2) 3330, 2979, 1626, 1581, 1491, 1362, 1284, 1201, 1171, 1121, 965, 852, 779, 708 cm^{-1}; ^1H NMR (500

MHz, $CDCl_3$) δ 8.43 (bs, 1 H), 8.07 (s, 1 H), 7.778 (d, *J* = 7.5 Hz, 2 H), 7.46 (t, *J* = 7.5 Hz, 1 H), 7.31-7.25 (m, 2 H), 6.93 (td, *J* = 9.0, 2.0 Hz, 1 H), 6.82 (s, 1 H), 1.38 (s, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2 (d, J_{CF} = 234 Hz), 139.6, 134.4, 133.3, 131.4, 131.0, 129.6 (d, J_{CF} = 10 Hz), 128.5, 128.2, 111.4 (d, J_{CF} = 10 Hz), 110.5 (d, J_{CF} = 26 Hz), 105.4 (d, J_{CF} = 24 Hz), 100.1, 100.0, 84.1, 25.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ -124.3; HRMS (ESI) *m/z* calcd for $C_{20}H_{22}O_2NF$ $[M+H]^+$ 338.1722, found 338.1721.

1,4-Dioxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate (D)[7]. To a solution of 1,4-dioxaspiro[4.5]deane-8-one (0.400 g, 2.48 mmol) and 1,1,1-trifluoro-*N*-phenyl-*N*-[(trifluoromethyl)sulfonyl]methanesulfonamide (1.08 g, 2.98 mmol) in THF (15.9 mL) at -78 °C was slowly added KHMDS (0.574 g, 2.73 mmol) in THF (8.9 mL). The reaction was warmed to room temperature over 4 h. The reaction was quenched with sat. NH_4Cl and extracted with Et_2O (3 x 20 mL). The combined organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The product was purified by flash chromatography on SiO_2 (ISCO-Rf, 0-5% EtOAc/hexanes) to give the product as a colorless oil (**D**, 0.560 g, 48%): ^1H NMR (400 MHz, $CDCl_3$) δ 5.67 (t, *J* = 4.0 Hz, 1 H), 3.99 (s, 4 H), 2.56-2.52 (m, 2 H), 2.41 (d, *J* = 2.8 Hz, 2 H), 1.91 (t, *J* = 6.6 Hz, 2 H).

2-(3-(1,4-Dioxaspiro[4.5]dec-7-en-8-yl)phenyl)-5-fluoro-1*H*-indole (E)[7]. A solution of 5-fluoro-2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-indole (**C**, 0.400 g, 1.19 mmol) and 1,4-dioxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate (**D**, 0.560 g, 1.19 mmol) in DMSO (5.9 mL) was degassed by 3 freeze pump/thaw cycles. To this solution was added Cs_2CO_3 (0.773 g, 2.37 mmol) and $Pd(PPh_3)_4$ (0.137 g, 0.119 mmol). The reaction was heated to 85 °C under N_2 for about 2.5 h. After cooling to room temperature, the reaction was quenched with sat. NH_4Cl (12 mL) and H_2O (20 mL). The reaction mixture was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated. The product was purified by flash chromatography on SiO_2 (ISCO-Rf, 0-40% EtOAc/hexanes) to give the product as a white solid (**E**, 0.223 g, 54%): ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (bs, 1 H), 7.64 (s, 1 H), 7.52-7.49 (m, 1 H), 7.40-7.25 (m, 4 H), 7.93 (td, *J* = 9.0, 2.6 Hz, 1 H), 6.77 (d, *J* = 1.6 Hz, 1 H), 6.06-6.04 (m, 1 H), 4.05 (s, 4 H), 2.74-2.71 (m, 2 H), 2.51 (bs, 2 H), 1.96 (t, *J* = 6.4 Hz, 2 H); HRMS (ESI) *m/z* calcd for $C_{22}H_{21}O_2NF$ $[M+H]^+$ 350.1551, found 350.1549.

2-(3-(1,4-Dioxaspiro[4.5]decan-8-yl)phenyl)-5-fluoro-1*H*-indole (F)[8]. To a solution of 2-(3-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)phenyl)-5-fluoro-1*H*-indole (**E**, 0.210 g, 0.601 mmol) in EtOAc (3.3 mL) and MeOH (1 mL) was added Pd/C (10%, 0.130 g, 0.120 mmol). The reaction was kept under H_2 (2 bar) using Parr reactor. After 3 h, additional Pd/C (10%, 0.130 g, 0.120 mmol) was added and the reaction was stirred under H_2 (4 bar) for 1 h. Additional Pd/C (10%, 0.130 g, 0.120 mmol) was added and the reaction

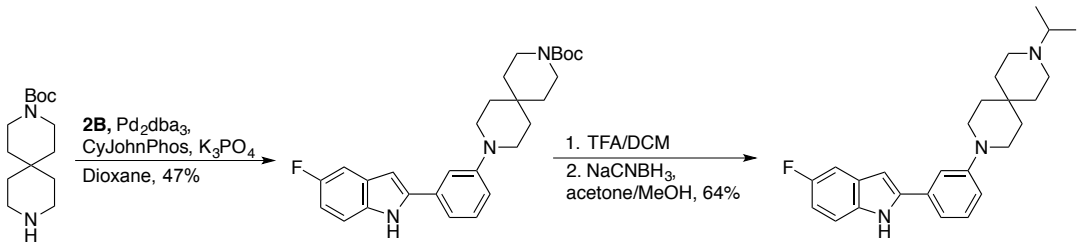
was stirred under H_2 (4 bar) for 12 h. The reaction was filtered through Celite®, rinsed with EtOAc, and concentrated. The product was purified by flash chromatography on SiO_2 (ISCO-Rf, 0-35% EtOAc/hexanes) to give the product as a tan foam (**F**, 0.150 g, 71%): ^{1}H NMR (300 MHz, acetone-d_6) δ 10.81 (bs, 1 H), 7.74 (app s, 1 H), 7.68 (dt, *J* = 7.8, 1.4 Hz, 1 H), 7.42-7.20 (m, 3 H), 6.94-6.84 (m, 3 H), 3.95-3.90 (m, 4 H), 2.71-2.61 (m, 1 H), 1.87-1.81 (m, 6 H), 1.78-1.66 (m, 2 H); HRMS (ESI) *m/z* calcd for $C_{22}H_{23}O_2NF$ $[M+H]^+$ 352.1707, found 352.1707.

4-(3-(5-Fluoro-1*H*-indol-2-yl)phenyl)cyclohexan-1-one (G). To a solution of 2-(3-(1,4-dioxaspiro[4.5]decan-8-yl)phenyl)-5-fluoro-1*H*-indole (**F**, 0.147 g, 0.418 mmol) in acetone (53 mL) was added 3M HCl (53 mL) at room temperature and the reaction was heated to reflux. After 4.75 h, the solution was cooled to room temperature and allowed to stir for 12 h. The reaction was cooled to 0 °C and neutralized with Na_2CO_3. The mixture was extracted with EtOAc, washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on SiO_2 (ISCO-Rf, 0-35% EtOAc/hexanes) to give the product as a yellow solid (**G**, 0.103 g, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (bs, 1 H), 7.54-7.51 (m, 2 H), 7.41 (t, *J* = 7.6 Hz, 1 H), 7.33-7.22 (m, 3 H), 6.94 (td, *J* = 9.0, 2.6 Hz, 1 H), 6.78 (d, *J* = 1.6 Hz, 1 H), 3.11 (tt, *J* = 12, 3.5 Hz, 1 H), 2.57-2.53 (m, 4 H), 2.32-2.26 (m, 2 H), 2.07-1.96 (m, 2 H); HRMS (ESI) *m/z* calcd for $C_{20}H_{19}ONF$ $[M+H]^+$ 308.1445, found 308.1443.

***N*-((1*r*,4*r*)-4-(3-(5-Fluoro-1*H*-indol-2-yl)phenyl)cyclohexyl)-1-isopropylpiperidin-4-amine (18); *N*-((1*s*,4*s*)-4-(3-(5-Fluoro-1*H*-indol-2-yl)phenyl)cyclohexyl)-1-isopropylpiperidin-4-amine (19).**[5] To a solution of 4-(3-(5-fluoro-1*H*-indol-2-yl)phenyl)cyclohexan-1-one (**G**, 0.098 g, 0.319 mmol), 4-amino-1-isopropyl piperidine (0.058 mL, 0.351 mmol) in 1,2-DCE (3.15 mL) was added Ti(O*i*Pr)$_4$ (0.108 mL, 0.351 mmol) at room temperature. After 30 min, $NaBH(OAc)_3$ (0.033 g, 0.151 mmol) was added. After 30 min, additional $NaBH(OAc)_3$ (0.033 g, 0.151 mmol) was added and the solution was stirred at room temperature. After 1 h, additional $NaBH(OAc)_3$ (0.033 g, 0.151 mmol) was added. After 1 h, the solution was diluted with sat. $NaHCO_3$, extracted with EtOAc (2 x 3 mL), dried (Na_2SO_4), filtered, and concentrated. The products were purified by flash chromatography on neutral Al_2O_3 (0-10% MeOH/CH_2Cl_2 with 0.1% Et_3N) followed by filtration through basic alumina (0-5% MeOH/CH_2Cl_2) to give the products (**18**, 0.017 g, 12% and **19**, 0.049 g, 35%) as pale tan foamy solids: **18**: IR (CH_2Cl_2) 3149, 2965, 2927, 1628, 1587, 1447, 1384, 1323, 1248, 1178, 1129, 1110, 956, 844, 797, 774, 784, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (bs, 1 H), 7.49-7.46 (m, 2 H), 7.37 (t, *J* = 7.6 Hz, 1 H), 7.32-7.24 (m, 2 H), 7.19 (d, *J* = 7.6 Hz, 1 H), 6.92 (td, *J* = 9.2, 2.5 Hz, 1 H), 6.77 (d, *J* = 1.2 Hz, 1 H), 2.88 (bd, *J* = 12 Hz, 2 H), 2.76-2.69 (m, 2 H), 2.63-2.54 (m, 2 H), 2.18 (app t, *J* = 12 Hz, 2 H), 2.03-1.93 (m, 6 H), 1.58 (qd, *J* = 13, 2.5 Hz, 2 H), 1.39-1.24 (m, 4 H), 1.04 (d, *J* = 6.4 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 158.2 (d, J_{CF} = 233 Hz), 148.0, 140.0, 133.3, 132.1, 129.6 (d, J_{CF} = 11 Hz), 129.1, 126.6, 123.9, 123.0, 111.4 (d, J_{CF} = 9.0 Hz), 110.4 (d, J_{CF} = 26 Hz), 105.3 (d, J_{CF} = 23 Hz), 99.9 (d, J_{CF} = 4.0 Hz), 54.5, 52.8, 51.7, 47.9, 44.2, 34.3, 33.8, 33.1, 18.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -124.3; HRMS (ESI) *m/z* calcd for $C_{28}H_{37}N_3F$ $[M+H]^+$ 434.2966, found 434.2962; ELS purity 100%;

19: IR (CH_2Cl_2) 3601, 3437, 2926, 1626, 1586, 1449, 1361, 1323, 1248, 1211, 1132, 1109, 1057, 960, 855, 781, 733, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (bs, 1 H), 7.52 (s, 1 H), 7.46 (d, *J* = 8.0 Hz, 1 H), 7.36 (t, *J* = 7.6 Hz, 1 H), 7.31-7.21 (m, 3 H), 6.92 (td, *J* = 9.2, 2.4 Hz, 1 H), 6.76 (d, *J* = 1.6 Hz, 1 H), 3.08 (t, *J* = 3.3 Hz, 1 H), 2.87 (bd, *J* = 12 Hz, 2 H), 2.72 (sept, *J* = 6.5 Hz, 1 H), 2.63 (tt, *J* = 12.0, 4.0, 4.0 Hz, 1 H), 2.50 (tt, *J* = 12.0, 3.4, 3.4 Hz, 1 H), 2.18 (dt, *J* = 11.6, 2.0 Hz, 2 H), 1.97-1.85 (m, 4 H), 1.80-1.76 (m, 2 H), 1.70-1.60 (m, 4 H), 1.37 (qd, *J* = 12.0, 3.1 Hz, 2 H), 1.04 (d, *J* = 6.4 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2 (d, J_{CF} = 233 Hz), 148.2, 140.2, 133.3, 132.1, 129.7 (d, J_{CF} = 10 Hz), 129.0, 126.9, 124.0, 123.0, 111.5 (d, J_{CF} = 9.0 Hz), 110.5 (d, J_{CF} = 27 Hz), 105.3 (d, J_{CF} = 24 Hz), 99.9 (d, J_{CF} = 5.0 Hz), 54.4, 52.2, 48.8, 47.9, 43.6, 33.8, 31.0, 28.2, 18.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -124.3; HRMS (ESI) *m/z* calcd for $C_{28}H_{37}N_3F$ $[M+H]^+$ 434.2966, found 434.2963; ELS purity 100%.



H **20**

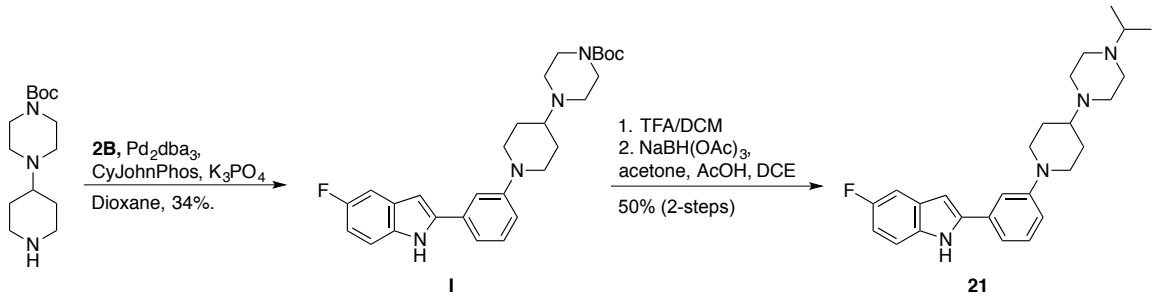
Synthesis of Compound **20**

***tert*-Butyl 9-(3-(5-fluoro-1*H*-indol-2-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (H).**[4] A dry microwave vial was charged with 2-(3-bromophenyl)-5-fluoro-1*H*-indole (**2B**, 0.10 g, 0.36 mmol), K_3PO_4 (0.11 g, 0.50 mmol)[3] and 1,4-dioxane (1.5 mL, degassed for 15 min by N_2 bubbling). To this solution was added CyJohnPhos (0.010 g, 0.029 mmol), Pd_2dba_3 (0.010 g, 0.011 mmol) followed by *tert*-butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate (0.102 g, 0.401 mmol) at room temperature. This solution was degassed for 10 min by N_2 bubbling and the reaction vial was capped and heated at 120 °C. After 17 h, the solution was cooled to room temperature and extracted with EtOAc, washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography on SiO_2 (0-25% EtOAc/hexanes) to give the product (**H**, 0.078 g, 0.168 mmol, 47%, approx. 5% residual solvent) as a light orange foamy solid: IR (neat) 3059, 2934, 1668, 1629, 1450, 1340, 1232, 1163, 768, 734 cm^{-1}; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 8.66 (s, 1 H), 7.36-7.26 (m, 4 H), 7.14 (d, *J* = 8.0 Hz, 1 H), 6.97-6.93 (m, 2 H), 6.77 (d, *J* = 1.6 Hz, 1 H), 3.45 (app t, *J* = 5.6 Hz, 4 H), 3.26 (app t, *J* = 5.6 Hz, 4 H), 1.71 (app t, *J* = 5.6 Hz, 4 H), 1.53 (app t, *J* = 5.6 Hz, 4 H), 1.51 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ171.3, 158.1 (d, J_{CF} = 233 Hz), 155.1, 152.1, 140.4, 133.3, 133.0, 129.7 (d, J_{CF} = 12 Hz), 129.5, 116.4, 115.9, 113.1, 111.4 (d, J_{CF} = 10 Hz), 110.3 (d, J_{CF} = 26 Hz), 105.2 (d, J_{CF} = 24 Hz), 99.9, 99.8, 79.5, 60.5, 45.0, 35.2, 29.6, 28.5, 14.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ -124.4; HRMS (ESI) *m/z* calcd for $C_{28}H_{35}N_3O_2F$ $[M+H]^+$ 464.2708, found 464.2700; ELS purity 100%.

3-(3-(5-Fluoro-1*H*-indol-2-yl)phenyl)-3,9-diazaspiro[5.5]undecane. A solution of *tert*-butyl 9-(3-(5-fluoro-1*H*-indol-2-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (**H**, 0.050 g, 0.11 mmol) in CH_2Cl_2 (2.0 mL) was treated with TFA (0.30 mL, 4.0 mmol) at room temperature. After 2 h, the solution was concentrated and extracted with EtOAc, washed with satd. $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated to give the product as an orange oil that was used without further purification: HRMS (ESI) *m/z* calcd for $C_{23}H_{26}N_3F$ $[M+H]^+$ 364.2184, found 364.2181.

3-(3-(5-Fluoro-1*H*-indol-2-yl)phenyl)-9-isopropyl-3,9-diazaspiro[5.5]undecane (20).[5] A solution of 3-(3-(5-fluoro-1*H*-indol-2-yl)phenyl)-3,9-diazaspiro[5.5]undecane (0.040 g, 0.11 mmol) in dry MeOH (1.5 mL) was added anhydrous acetone (0.10 mL, 1.4 mmol). After 1 h, $NaCNBH_3$ (0.012 g, 0.20 mmol) was added and the reaction was stirred at room temperature for 12 h. The reaction was diluted with H_2O and extracted with EtOAc (2x). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography on SiO_2 (0-5% MeOH/CH_2Cl_2 with 0.1% Et_3N) followed by filtration through basic alumina (0-3% MeOH/CH_2Cl_2) to give **20** (0.029 g, 0.072 mmol, 64%, approx. 5% residual solvent) as a light yellow foamy solid: IR (neat) 2974, 2934, 2328, 1599, 1580, 1450, 1340, 1232, 1193, 1163, 1128, 768, cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 10.86 (bs, 1 H), 7.47 (s, 1 H), 7.42 (dd, *J* = 4.4, 8.8 Hz, 1 H), 7.31-7.29 (m, 2 H), 7.25 (dd, *J* = 2.4, 10 Hz, 1 H), 6.96-6.92 (m, 1 H), 6.91-6.88 (m, 2 H), 3.39 (sept, *J* = 6.4 Hz, 1 H), 3.31 (app t, *J* = 5.6 Hz, 4 H), 3.18-3.16 (m, 4 H), 1.88 (app t, *J* = 4.0 Hz, 4 H), 1.73 (app t, *J* = 5.2 Hz, 4 H), 1.34 (d, *J* = 6.4 Hz, 6 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 157.8 (d, J_{CF} = 231 Hz), 140.6 (d, J_{CF} = 14 Hz), 133.9, 133.8, 132.9, 129.5, 115.9, 115.4, 112.5, 111.9 (d, J_{CF} = 9 Hz), 109.5 (d, J_{CF} = 26 Hz), 104.4 (d, J_{CF} = 23 Hz), 98.9 (d, J_{CF} = 5 Hz), 44.4, 44.3, 33.1, 16.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ -124.3; HRMS (ESI) *m/z* calcd for $C_{26}H_{33}N_3F$ $[M+H]^+$ 406.2653, found 406.2648; ELS purity 97.9%.



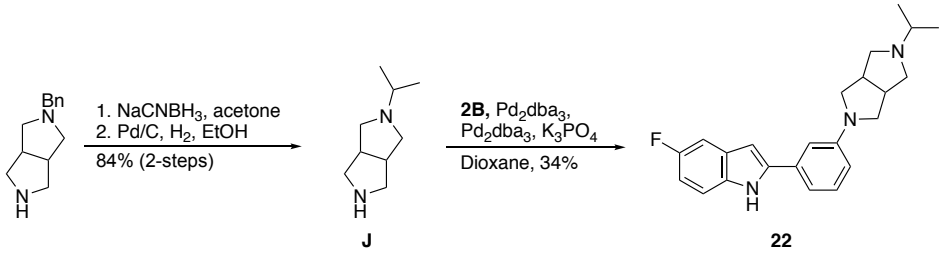
Synthesis of Compound **21**

***tert*-Butyl 4-(1-(3-(5-fluoro-1*H*-indol-2-yl)phenyl)piperidin-4-yl)piperazine-1-carboxylate (I).**[4] A solution of 2-(3-bromophenyl)-5-fluoro-1*H*-indole (**2B**, 0.101 g, 0.348 mmol)[2], K_3PO_4 (0.087 g, 0.41 mmol) was treated with dioxane (1.5 mL, degassed by N_2 bubbling) followed by CyJohnPhos (0.016 g, 0.045 mmol), Pd_2dba_3 (0.012 g, 0.013 mmol) and *tert*-butyl 4-(piperidin-4-yl)piperazine-1-carboxylate (0.094 g, 0.35 mmol). The solution was degassed for 10 min, sealed and heated at 120 °C for 12 h. The solution was cooled to room temperature and extracted with EtOAc, washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography on SiO_2 (0-100% EtOAc/hexanes) to give the product (**I**, 0.057 g, 34%) that was used without further purification: HRMS (ESI) *m/z* calcd for $C_{28}H_{35}N_4FO_2$ $[M+H]^+$ 479.2817, found 479.2816.

5-Fluoro-2-(3-(4-(piperazin-1-yl)piperidin-1-yl)phenyl)-1*H*-indole. To a solution of *tert*-butyl 4-(1-(3-(5-fluoro-1*H*-indol-2-yl)phenyl)piperidin-4-yl)piperazine-1-carboxylate (**I**, 0.057 g, 0.12 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (0.30 mL, 4.0 mmol) at room temperature. After 2 h, the reaction solution was concentrated, diluted with satd. $NaHCO_3$, extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated to give the product as an orange oil that was used without further purification: HRMS (ESI) *m/z* calcd for $C_{23}H_{27}N_4F$ $[M+H]^+$ 379.2293, found 379.2292.

5-Fluoro-2-(3-(4-(4-isopropylpiperazin-1-yl)piperidin-1-yl)phenyl)-1*H*-indole (21).[5] A solution of 5-fluoro-2-(3-(4-(piperazin-1-yl)piperidin-1-yl)phenyl)-1*H*-indole (0.047 g, 0.12 mmol) in 1,2-DCE (1.5 mL) was treated with acetone (0.10 mL, 1.4 mmol), AcOH (0.070 mL, 1.2 mmol). After 10 min, $NaBH(OAc)_3$ (0.027 g, 0.13 mmol) was added at room temperature. After 1 h, an additional $NaBH(OAc)_3$ (0.054 g, 0.25 mmol) was added. The solution was stirred for 12 h at room temperature and diluted with satd. $NaHCO_3$, extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography on SiO_2 (0-5% MeOH/CH_2Cl_2 with 0.1% Et_3N) followed by filtration through basic alumina (0-4% MeOH/CH_2Cl_2) to give the product (**21**, 0.025 g, 0.059 mmol, 50%, 2-steps) as a light orange foamy solid: IR (neat) 2974, 2816, 1591, 1450, 1359, 1193, 1127, 839, 767, 734 cm^{-1}; ^1H NMR

(300 MHz, $CDCl_3$) δ 8.37 (s, 1 H), 7.36-7.26 (m, 2 H), 7.22-7.20 (m, 1 H), 7.13-7.10 (m, 1 H), 6.98-6.91 (m, 2 H), 6.77 (app d, J = 1.5 Hz, 1 H), 3.86-3.82 (m, 2 H), 2.85-2.81 (m, 2 H), 2.78-2.61 (m, 10 H), 2.43-2.40 (m, 1 H), 2.02-1.98 (m, 2 H), 1.79-1.66 (m, 2 H), 1.09 (d, J = 6.6 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1 (d, J_{CF} = 233 Hz), 151.9, 140.4, 133.2, 132.9, 129.7, 129.6 (d, J_{CF} = 10 Hz), 116.4, 116.2, 113.4, 111.4 (d, J_{CF} = 10 Hz), 110.3 (d, J_{CF} = 26 Hz), 105.3 (d, J_{CF} = 24 Hz), 99.9, 99.9, 61.7, 54.5, 49.4, 49.2, 49.1, 28.2, 18.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -124.3; HRMS (ESI) *m/z* calcd for $C_{26}H_{34}N_4F$ $[M+H]^+$ 421.2762, found 421.2759; ELS purity 99.8%.



J **22**

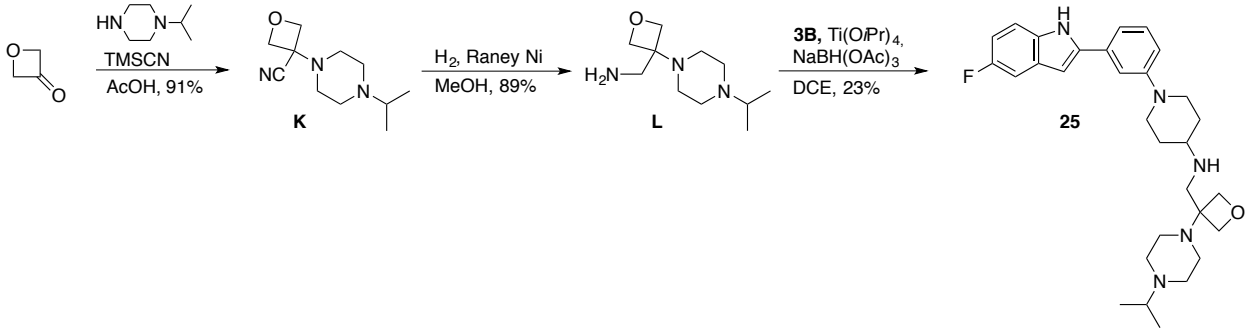
Synthesis of Compound **22**

2-Benzyl-5-isopropyloctahydropyrrolo[3,4-*c*]pyrrole. A solution of 2-benzyloctahydropyrrolo[3,4-*c*]pyrrole (0.434 g, 2.15 mmol) in dry MeOH (2.0 mL) was treated with dry acetone (1.50 mL, 21.5 mmol) at room temperature. After 1 h, $NaCNBH_3$ (0.146 g, 2.40 mmol) was added at room temperature and kept at this temperature for 12 h. The reaction mixture was diluted with H_2O and extracted with EtOAc (2x). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by distillation (Kugelrohr, 170 °C. 0.1 mmHg) to give 2-benzyl-5-isopropyl-octahydropyrrolo[3,4-*c*]pyrrole (0.464 g, 1.9 mmol, 88%) as a colorless oil: IR (neat) 3026, 2974, 2775, 1450, 1359, 1323, 1163, 982, 734, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.25 (m, 5 H), 3.61 (s, 2 H), 2.93 (dd, J = 7.6, 8.8 Hz, 2 H), 2.74-2.69 (m, 2 H), 2.50-2.43 (m, 4 H), 2.33 (sept, J = 6.4 Hz, 1 H), 2.25-2.21 (m, 2 H), 1.11 (d, J = 6.4 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 128.6, 128.2, 126.7, 59.6, 59.4, 58.3, 54.6, 41.8, 22.0; HRMS (ESI) *m/z* calcd for $C_{16}H_{25}N_2$ $[M+H]^+$ 245.2012, found 245.2011.

2-Isopropyloctahydropyrrolo[3,4-*c*]pyrrole (J). To a solution of 2-benzyl-5-isopropyloctahydropyrrolo[3,4-*c*]pyrrole (0.464 g, 1.90 mmol) in EtOH (8.0 mL) was added Pd/C (10%, 0.064 g). The solution was subjected to H_2 (5 psi) using Parr apparatus at 50 °C. After 48 h, the mixture was filtered through Celite® plug, rinsed with MeOH and concentrated to give the product as an off-white solid (**J**, 0.279 g, 1.81 mmol, 84%-2 steps): Mp 122-124 °C; IR (neat) 2974, 2934, 2900, 2762, 1593, 1450, 1420, 1359, 1340, 1215, 1163, 982, 839, 768 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.33 (dd, J = 6.4, 10.0 Hz, 2 H), 2.96-2.92 (m, 2 H), 2.88-2.86 (m, 2 H), 2.64 (app d, J = 9.6 Hz, 2 H), 2.49-2.47 (m, 2 H),

2.41 (sept, J = 6.4 Hz, 1 H), 1.00 (d, J = 6.4 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.2, 53.6, 51.4, 40.9, 21.3; HRMS (ESI) *m/z* calcd for $C_9H_{19}N_2$ $[M+H]^+$ 155.1543, found 155.1539.

5-Fluoro-2-(3-(5-isopropylhexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)phenyl)-1*H*-indole (22).[4] A mixture of 2-(3-bromophenyl)-5-fluoro-1*H*-indole (**2B**, 0.118 g, 0.406 mmol)[2], K_3PO_4 (0.141 g, 0.664 mmol) in degassed 1,4-dioxane (1.0 mL, degassed by N_2 bubbling) was treated with CyJohnPhos (0.013 g, 0.037 mmol) followed by $Pd_2(dba)_3$ (0.011 g, 0.012 mmol) and 2-isopropyloctahydropyrrolo[3,4-*c*]pyrrole (**J**, 0.070 g, 0.45 mmol). in dioxane (1.5 mL). The solution was degassed (10 min) and the reaction vial was capped and heated at 120 °C for 12 h. The reaction mixture was cooled to room temperature, extracted with EtOAc, brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography on SiO_2 (0-5% MeOH/CH_2Cl_2, then 8% MeOH/CH_2Cl_2 with NH_4OH) to give the product (**22**, 0.050 g, 0.137 mmol, 34%) as a light orange foamy solid: IR (neat) 3202, 2974, 1629, 1599, 1450, 1359, 1193, 1128, 982, 768, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1 H), 7.37 (dd, J = 4.4, 8.8 Hz, 1 H), 7.31-7.24 (m, 3 H), 7.07 (d, J = 8.0 Hz, 1 H), 7.01 (s, 1 H), 6.91 (app dt, J = 2.4, 9.2, 9.2 Hz, 1 H), 6.75 (s, 1 H), 6.92 (dd, J = 1.6, 8.0 Hz, 1 H), 3.35-3.33 (m, 4 H), 3.13 (app t, J = 8.4 Hz, 2 H), 3.01-2.99 (m, 2 H), 2.53-2.47 (m, 1 H), 2.43-2.39 (m, 2 H), 1.14 (d, J = 6.4 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 (d, J_{CF} = 234 Hz), 149.1, 140.6, 133.4, 132.9, 129.6 (d, J_{CF} = 17 Hz), 129.4, 114.4, 113.5, 111.6 (d, J_{CF} = 9.0 Hz), 110.7, 110.2 (d, J_{CF} = 26 Hz), 105.1 (d, J_{CF} = 24 Hz), 99.5, 58.3, 55.0, 53.9, 41.2, 21.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -124.5; HRMS (ESI) *m/z* calcd for $C_{23}H_{27}N_3F$ $[M+H]^+$ 364.2184 found 364.2181; ELS purity 100%.



Synthesis of compound **25**.

3-(4-Isopropylpiperazin-1-yl)oxetane-3-carbonitrile (K). To AcOH (3.2 mL) at 0 °C was added 1-isopropylpiperazine (1.49 mL, 10.1 mmol) followed by 3-oxetanone (133 uL, 2.02 mmol) and TMSCN (687 uL, 5.05 mmol). The reaction was warmed to room temperature and stirred for 12 h. The reaction was diluted with CH_2Cl_2 (10 mL) and basified to pH 9 with 32% NaOH. The aqueous was extracted with

CH_2Cl_2 (2 x 5 mL) and the combined organic layer was dried (Na_2SO_4), filtered, and concentrated. The product was purified by flash chromatography on SiO_2 (ISCO-Rf, 0-10% MeOH/CH_2Cl_2) to give a pale yellow crystalline solid (**K**, 0.38 g, 91%): Mp 80-82 °C; IR (neat) 2960, 2884, 2824, 1453, 1365, 1273, 1226, 1178, 1146, 994, 983, 925, 787 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.79 (d, *J* = 6.4 Hz, 2 H), 4.65 (d, *J* = 6.4 Hz, 2 H), 2.71 (sept, *J* = 6.7 Hz, 1 H), 2.62 (bs, 4 H), 2.47 (t, *J* = 4.8 Hz, 4 H), 1.05 (d, *J* = 6.4 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 116.4, 59.0, 54.3, 47.7, 46.2, 18.4; HRMS (ESI) *m/z* calcd for $C_{11}H_{20}ON_3$ $[M+H]^+$ 210.1601, found 210.1600.

(3-(4-Isopropylpiperazin-1-yl)oxetan-3-yl)methanamine (L). To a solution of 3-(4-isopropylpiperazin-1-yl)oxetane-3-carbonitrile (**K**, 0.150 g, 0.717 mmol) in MeOH (12.8 mL) was added a catalytic amount of Raney-Ni (15 drops). The reaction was sparged for 10 sec with H_2 and the reaction was stirred under an atmosphere of H_2 for 12 h. The reaction was filtered through a pad of Celite®, washed with THF, and concentrated. The product was obtained as a yellow oil (**L**, 0.136 g, 89%) and carried on without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 4.74 (d, *J* = 6.6 Hz, 2 H), 4.28 (d, *J* = 6.3 Hz, 2 H), 3.11 (s, 2 H), 2.67-2.56 (m, 9 H), 1.20 (bs, 2 H), 1.06 (d, *J* = 6.6 Hz, 6 H).

1-(3-(5-Fluoro-1*H*-indol-2-yl)phenyl)-N-((3-(4-isopropylpiperazin-1-yl)oxetan-3-yl)methyl)-piperidin-4-amine (25).[5] To a solution of 1-(3-(5-fluoro-1*H*-indol-2-yl)phenyl)piperidin-4-one **(3B)** (0.050 g, 0.162 mmol), (3-(4-isopropylpiperazin-1-yl)oxetan-3-yl)methanamine **(L)** (0.038 g, 0.178 mmol) in 1,2-DCE (1.6 mL) was added $Ti(OiPr)_4$ (0.055 mL, 0.178 mmol) at room temperature. After 30 min, $NaBH(OAc)_3$ (0.019 g, 0.052 mmol) was added. After 1 h, additional $NaBH(OAc)_3$ (0.019 g, 0.052 mmol) was added and the solution was stirred at room temperature. After 8 h, additional $NaBH(OAc)_3$ (0.019 g, 0.052 mmol) was added. After 4 h, the solution was diluted with sat. $NaHCO_3$, extracted with EtOAc (2 x 3 mL), dried (Na_2SO_4), filtered, and concentrated. The product was purified by flash chromatography on SiO_2 (0-10% MeOH/CH_2Cl_2 with 0.1% Et_3N) followed by filtration through basic alumina (0-5% MeOH/CH_2Cl_2) to give a white solid (**25**, 0.019 g, 23%): Mp >235 °C; IR (neat) 2961, 2932, 2819, 2412, 1603, 1577, 1500, 1479, 1462, 1382, 1362, 1281, 1226, 1195, 1143, 1108, 1046, 973, 845, 773, 746, 688 cm^{-1}; ^1H NMR (500 MHz, MeOD/DMSO-d_6) δ 7.47 (s, 1 H), 7.45-7.43 (m, 1 H), 7.49-7.35 (s, 1 H), 7.32-7.29 (m, 2 H), 7.01 (d, *J* = 8.0 Hz, 1 H), 6.96 (td, *J* = 7.8, 2.8 Hz, 1 H), 6.89 (m, 1 H), 4.70 (d, *J* = 6.5 Hz, 2 H), 4.45-4.40 (m, 2 H), 4.39 (d, *J* = 6.0 Hz, 2 H), 3.87 (d, *J* = 13 Hz, 2 H), 3.11 (s, 2 H), 2.93 (t, *J* = 12 Hz, 2 H), 2.72 (bs, 6 H), 2.65 (t, *J* = 1.5 Hz, 2 H), 2.10 (d, *J* = 11 Hz, 2 H), 1.58 (app q, *J* = 11 Hz, 2 H), 1.11 (d, *J* = 6.5 Hz, 6 H); ^{13}C NMR (175 MHz, $CDCl_3$/DMSO-d_6) δ 156.6 (d, J_{CF} = 232 Hz), 151.9, 140.6 (d, J_{CF} = 26 Hz), 133.9 (d, J_{CF} = 26 Hz), 132.9, 129.8, 129.2 (d, J_{CF} = 11 Hz), 116.1, 115.4, 112.8, 112.2 (d, J_{CF} = 8.8 Hz), 109.7 (d, J_{CF} = 25 Hz), 104.7 (d, J_{CF} = 23 Hz), 98.9 (d, J_{CF} = 3.5

Hz), 76.0, 63.2, 60.1, 55.3, 54.9, 54.3, 49.0, 48.4, 48.3, 48.1, 48.0, 45.9, 32.2, 21.1, 18.6, 14.5; ^{19}F NMR (376 MHz, $CDCl_3$/DMSO-d_6) δ -124.9; HRMS (ESI) *m/z* calcd for $C_{30}H_{41}ON_5F$ $[M+H]^+$ 506.3290, found 506.3289; ELS purity 98.3%.

Computational Methods

Protein preparation and small molecule docking and scoring were performed as previously described in detail.[3] Briefly, PDB entry 5FTJ, a co-cryo-EM structure with inhibitor **14** partially bound, was used for protein coordinates. Energy refinement of the protein involved an iterative process with hydrogen only optimization performed first, followed by side-chain relaxation, and finally, a tethered, all atoms minimization procedure.[3] Inhibitor structures were generated using the Discovery Studio 2018 (Dassault Systèmes BIOVIA, San Diego, CA) GUI interface, and energy refined using the cff force field and CFF partial charges, with distance dielectric set to 1.0. Following, 200 hundred steps of steepest descents were applied, followed by conjugate gradients minimization until the RMS gradient was < 0.001 kcal/Å for each compound. For each energy minimized inhibitor, the piperidine ring, which is in a twist chair conformation in **14** in the co-cryo-EM structure, relaxes to a full chair conformation (*e.g.*, compare inhibitor **14** in Figure 2a and 2b).

Inhibitor docking was performed using the Insight 2005 (Dassault Systèmes BIOVIA, San Diego, CA) GUI interface. This program provides a 3D environment and dial box control for detailed small molecule manipulations *(i.e.*, positional and multi-torsional management). To start, the 5-fluoro-phenyl substructure of **14**, which binds deeply in the p97 allosteric site in the co-cryo-EM structure (and is a common component found in all of the inhibitors described in the study), was conservatively repositioned into a biochemically feasible and sterically compatible orientation. Following, binding locations for the extended piperidine-amino-ethyl-isopropyl piperazine side chain of **14** (for which there is no density in the co-cryo-EM structure 5FTJ) were explored, with both inhibitor side chain and residues side chain torsions free to move. Of the numerous inhibitor side chain orientations evaluated, a cleft extending down the length of the p97 helix 16 - 17 interface provided the most chemically compatible and sterically accessible location for the generation of a biochemically feasible inhibitor side chain binding mode. Therefore, this location of the protein was chosen as the binding site for the side chains of all other examined inhibitors.

Following, all initial inhibitor binding models were generated as follows: 1) with the intermolecular van der Waals bump set to 0.25 Å, the 5-fluoro-phenyl indole substructure of each derivative was superimposed onto that of **14** (*i.e.*, in its binding mode described above), and 2) translational, rotational, and torsional adjustments to the inhibitor, as well as side chain torsional adjustments to surrounding protein amino acid residues lining the proposed helix 16 and 17 interface

binding site were concomitantly performed to: a) orient the inhibitor in the binding site, b) eliminate intermolecular atom-atom van der Waals violations, c) provide optimal non-bonded interactions, and d) remove any intramolecular van der Waals clashes within the conformations of the docked inhibitors.

Finally, using the HINT atom-atom contact scoring program (eduSoft LLC, Richmond, VA), inter- and intramolecular scoring of the docked inhibitors was performed and used to optimize final binding modes, as previously described.[3] In brief, iterative rounds of tether minimizations, followed by additional manual adjustments (translational, rotational, and torsional), and subsequent HINT scoring, were used to direct SAR-guided adjustments to optimize inhibitor - protein contacts. This method of inhibitor docking resulted in biochemically feasible inhibitor binding modes to aid in rationalizing the *in vitro* binding data provided in Table 1.

Biological Assays

P97 ADP-Glo assay

Protein Expression, and Purification

Full-length human p97 (residues 1-806) was cloned as previously reported.[9] Recombinant full-length p97 was expressed in *E. coli* Rosetta 2(DE3) by inducing with 0.1 mM IPTG and growing at 25 °C for 16 hours. To generate biotinylated proteins for SPR, AviTagged p97 constructs were expressed as previously described.[9] p97 protein was purified using a combination of Ni-NTA affinity purification, TEV cleavage, and size exclusion chromatography (Superdex 200 16/60) in 25 mM Tris pH 7.8, 150 mM NaCl, 0.5 mM Tris-(2-carboxyethyl) phosphine (TCEP).[9]

Biochemical Assay

The activity of p97 was measured using the ADP-glo™ Max assay (Promega V7002) as described.[9] Compounds (in duplicate or triplicate) or a DMSO control (50 nL) were pinned into white, low volume 384-well plates (Corning) containing 5 μL of ATP substrate (40 μM or 200 μM) in assay buffer (10 mM Tris, pH 7.4, 20 mM $MgCl_2$, 1 mM EDTA, 0.5 mM TCEP, 0.01% Triton X-100). p97 (5 uL at 40 nM) was then dispensed into each well and the reaction was incubated for 90 min at 22 °C. Luminescence was measured on an Envision multi-mode plate reader (Perkin Elmer) and was converted to % inhibition relative to the average negative (0% inhibition; DMSO) and positive (100 % inhibition; no ATP) controls within the plate using Equation 1.

Equation 1: % inhibition = (average $Lum_{neg} - Lum_{well}$)/(average $Lum_{neg} - Lum_{pos}$) x 100.

IC_{50} values were calculated from duplicate or triplicate data by transforming the [compound] to log[compound] and fitting a four-parameter (top set to 100, and bottom set to 0) sigmoidal dose response equation in Prism (GraphPad software).

Solubility

Solubility measurements were based on previously published methods.[10] The solubility assay sample preparation was performed in a 96 well plate on a TECAN GENESIS RSP 150 robotic sample processor, incorporating a 96-well filter plate to remove precipitated solids (Millipore) prior to UV/Vis spectroscopic analysis. 10 mM stock compound solutions (or Nifedipine or Diclofenac controls) in 100% DMSO were plated, followed by an 80:20 0.1 M potassium phosphate buffer:acetonitrile mixture to give 10-pt serial dilutions (500 to 3.13 mM). The plate was scanned from 260 to 500 nm in 10 nm increments and a standard curve was generated using at least 3 standard concentrations to produce a linear relationship with an $r^2 \geq 0.85$. Aqueous solubility (Sol) was determined using a formula Sol = [(A_{max} Filtrate/(slope)].

Metabolic Stability

Metabolic stability assay was based on previously published methods.[11] Sample preparation was performed in a 96-well plate format using a TECAN Genesis robotic sample processor. All incubations were carried out in 0.1 M sodium phosphate buffer (pH 7.4) in the presence of an NADPH-regenerating system (NADP+ sodium salt, $MgCl_2 \bullet 6H_2O$, and glucose-6- phosphate). SMNPIs (10 μM), microsomes (1 mg/mL total protein), buffer, and NADPH regenerating system were warmed to 37 °C, and the reaction was initiated by the addition of glucose-6-phosphate dehydrogenase (G6PD). Samples were quenched at 0, 10, 30, and 60 min using an equal volume of cold acetonitrile. Samples were centrifuged to pellet the proteins, and the supernatant was analyzed by LC-MS/MS using fast LC gradient methods. Depletion of parent SMNPI signal was monitored relative to signal at time 0. Chromatograms were analyzed using the mass spectrometry software Xcalibur QuanBrowser. To calculate SMNPI half-lives, a first-order rate of decay was assumed. A plot of the natural log (LN) of the compound concentration versus time was generated, in which the slope of that line was -k. Half-lives were calculated as 0.693/k.

Ub^{G76V}-GFP

The accumulation assay was performed similar to the published method with minor modification.[12] A stable HeLa cell line with the ubiquitin fusion degradation reporter Ub^{G76V}-GFP were seeded on Greiner

Bio-One μ clear 384-well black plates (Cat # 781091) (4500 cells/well) in custom DMEM (DMEM without phenol red, folic acid, riboflavin, and vitamin B12; 2.5% FBS, 2mM GlutaMAX™-I, 100units Penicillin-Streptomycin) using Biotek MultiFlo Microplate dispenser and grown for 18 hours inside incubator. Serial diluted compounds were transfer from 96 well compound plates to 384 well plates using Sorenson Bioscience Bench Top Pipetter. Cell plates treated with DMSO or a test compound (0.63, 1.25, 2.5, 5, 10, 20 and 40 μM) was grown inside incubator. Plates were imaged on the ImageXpress Micro microscope (Molecular Devices) after 1 hour and 6 hours. EC_{50} values were calculated from quadruplicate data by transforming the [compound] to log[compound] and fitting a four-parameter (top set to 100, and bottom set to 0) sigmoidal dose response equation in Prism (GraphPad software).

Compounds screening in the NCI60 panel are evaluated according to methods described.[13]

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National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

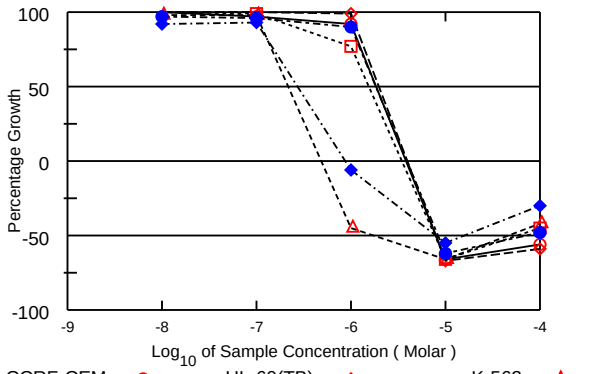
NSC : D - 783212 / 3=Compound 17	Experiment ID : 1508NS50	Test Type : 08	Units : Molar
Report Date : August 01, 2018	Test Date : August 31, 2015	QNS :	MC :
COMI : UPCDC30321-02	Stain Reagent : SRB Dual-Pass Related	SSPL : 0YLV	

Log10 Concentration

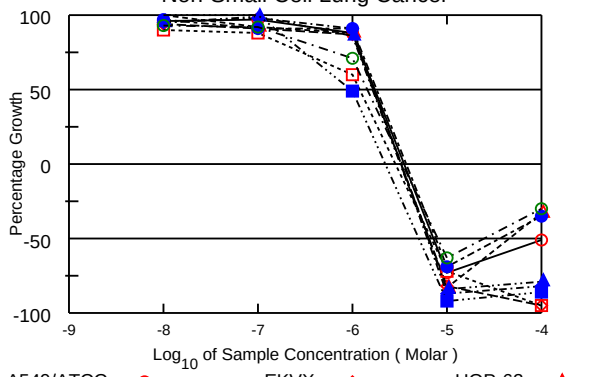
	Time	Mean Optical Densities						Percent Growth							
Panel/Cell Line	Zero	Ctrl	-8.0	-7.0	-6.0	-5.0	-4.0	-8.0	-7.0	-6.0	-5.0	-4.0	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.895	3.351	3.399	3.284	3.154	0.302	0.395	102	97	92	-66	-56	1.84E-6	3.81E-6	7.89E-6
HL-60(TB)	1.036	3.334	3.350	3.370	3.312	0.338	0.427	101	102	99	-67	-59	1.97E-6	3.94E-6	7.86E-6
K-562	0.285	2.485	2.437	2.451	0.158	0.097	0.164	98	98	-45	-66	-42	2.18E-7	4.87E-7	.
MOLT-4	0.768	3.201	3.194	3.173	2.633	0.265	0.423	100	99	77	-66	-45	1.54E-6	3.46E-6	.
RPMI-8226	1.016	3.195	3.140	3.107	2.986	0.390	0.530	97	96	90	-62	-48	1.84E-6	3.93E-6	.
SR	0.358	1.475	1.388	1.396	0.338	0.160	0.251	92	93	-6	-55	-30	2.72E-7	8.75E-7	.
Non-Small Cell Lung Cancer															
A549/ATCC	0.465	2.187	2.124	2.129	1.974	0.127	0.228	96	97	88	-73	-51	1.72E-6	3.52E-6	7.21E-6
EKVX	0.854	2.112	2.037	2.000	1.945	0.154	0.041	94	91	87	-82	-95	1.65E-6	3.27E-6	6.46E-6
HOP-62	0.390	1.473	1.485	1.389	1.339	0.068	0.263	101	92	88	-83	-33	1.66E-6	3.27E-6	.
HOP-92	1.903	2.448	2.394	2.381	2.232	0.535	0.094	90	88	60	-72	-95	1.20E-6	2.86E-6	6.83E-6
NCI-H226	0.760	1.420	1.401	1.360	1.363	0.232	0.498	97	91	91	-69	-35	1.81E-6	3.70E-6	.
NCI-H23	0.717	2.171	2.103	2.145	2.047	0.094	0.126	95	98	91	-87	-82	1.71E-6	3.26E-6	6.21E-6
NCI-H322M	0.608	2.030	1.958	2.015	1.836	0.095	0.129	95	99	86	-84	-79	1.63E-6	3.20E-6	6.28E-6
NCI-H460	0.229	2.510	2.598	2.556	1.346	0.019	0.032	104	102	49	-92	-86	9.56E-7	2.23E-6	5.05E-6
NCI-H522	0.587	1.692	1.613	1.601	1.371	0.216	0.411	93	92	71	-63	-30	1.43E-6	3.38E-6	.
Colon Cancer															
COLO 205	0.480	2.082	2.024	1.952	1.692	0.131	0.173	96	92	76	-73	-64	1.49E-6	3.23E-6	7.03E-6
HCC-2998	0.650	2.081	2.065	2.061	2.035	0.078	0.135	99	99	97	-88	-79	1.79E-6	3.34E-6	6.23E-6
HCT-116	0.270	2.480	2.617	2.582	1.722	0.053	0.155	106	105	66	-80	-43	1.28E-6	2.82E-6	.
HCT-15	0.354	2.202	2.133	2.060	1.166	0.037	0.049	96	92	44	-90	-86	7.49E-7	2.13E-6	5.06E-6
HT29	0.214	1.530	1.513	1.485	0.468	0.122	0.208	99	97	19	-43	-3	4.00E-7	2.04E-6	> 1.00E-4
KM12	0.443	2.712	2.774	2.638	2.353	0.065	0.098	103	97	84	-85	-78	1.59E-6	3.14E-6	6.19E-6
SW-620	0.296	2.112	2.126	2.090	0.609	0.026	0.034	101	99	17	-91	-89	3.97E-7	1.44E-6	4.17E-6
CNS Cancer															
SF-268	0.473	1.976	1.950	1.915	1.690	0.063	0.216	98	96	81	-87	-54	1.53E-6	3.04E-6	6.04E-6
SF-295	0.799	2.573	2.543	2.519	2.534	0.174	0.180	98	97	98	-78	-78	1.87E-6	3.59E-6	6.91E-6
SF-539	0.692	2.320	2.321	2.292	2.122	0.199	0.420	100	98	88	-71	-39	1.73E-6	3.56E-6	.
SNB-19	0.541	1.973	1.913	1.939	1.857	0.121	0.288	96	98	92	-78	-47	1.77E-6	3.48E-6	.
SNB-75	0.803	1.594	1.488	1.467	1.419	0.043	0.113	87	84	78	-95	-86	1.45E-6	2.82E-6	5.51E-6
U251	0.368	1.694	1.660	1.679	1.442	0.053	0.145	97	99	81	-86	-61	1.53E-6	3.06E-6	6.11E-6
Melanoma															
LOX IMVI	0.452	2.806	2.673	2.604	2.145	0.044	0.248	94	91	72	-90	-45	1.36E-6	2.77E-6	.
MALME-3M	0.483	1.067	1.065	1.044	1.043	0.177	0.318	100	96	96	-63	-34	1.94E-6	4.00E-6	.
M14	0.505	2.178	2.110	2.182	2.063	0.081	0.095	96	100	93	-84	-81	1.75E-6	3.36E-6	6.43E-6
MDA-MB-435	0.509	2.775	2.796	2.718	2.259	0.028	0.040	101	97	77	-95	-92	1.44E-6	2.82E-6	5.50E-6
SK-MEL-2	0.964	1.820	1.827	1.841	1.773	0.256	0.308	101	102	95	-73	-68	1.84E-6	3.65E-6	7.25E-6
SK-MEL-28	0.789	2.420	2.456	2.451	2.280	0.160	0.436	102	102	91	-80	-45	1.75E-6	3.42E-6	.
SK-MEL-5	0.644	2.189	2.154	2.054	1.969	0.011	0.067	98	91	86	-98	-90	1.56E-6	2.92E-6	5.46E-6
UACC-62	0.936	2.856	2.747	2.739	2.765	0.187	0.377	94	94	95	-80	-60	1.81E-6	3.50E-6	6.74E-6
Ovarian Cancer															
IGROV1	0.705	2.307	2.357	2.342	2.191	0.235	0.431	103	102	93	-67	-39	1.85E-6	3.82E-6	.
OVCAR-3	0.420	1.549	1.588	1.563	1.419	0.047	0.023	103	101	88	-89	-95	1.65E-6	3.15E-6	6.03E-6
OVCAR-4	0.676	1.545	1.569	1.491	1.509	0.208	0.387	103	94	96	-69	-43	1.89E-6	3.80E-6	.
OVCAR-5	0.827	2.121	2.052	2.049	2.022	0.258	0.276	95	94	92	-69	-67	1.83E-6	3.74E-6	7.64E-6
OVCAR-8	0.570	2.374	2.415	2.372	2.252	0.171	0.447	102	100	93	-70	-22	1.84E-6	3.73E-6	.
NCI/ADR-RES	0.545	1.804	1.805	1.740	1.679	0.076	0.359	100	95	90	-86	-34	1.69E-6	3.24E-6	.
SK-OV-3	0.732	1.642	1.600	1.529	1.521	0.057	0.033	95	88	87	-92	-95	1.60E-6	3.05E-6	5.80E-6
Renal Cancer															
786-0	0.735	2.633	2.633	2.598	2.388	0.127	0.055	100	98	87	-83	-93	1.65E-6	3.26E-6	6.41E-6
A498	1.458	2.230	2.063	1.987	2.063	0.145	0.022	78	68	78	-90	-98	1.47E-6	2.92E-6	5.78E-6
ACHN	0.582	2.460	2.449	2.449	2.413	0.049	0.097	99	99	97	-92	-83	1.78E-6	3.28E-6	6.03E-6
CAKI-1	0.748	2.036	1.903	1.866	1.818	0.058	0.036	90	87	83	-92	-95	1.54E-6	2.98E-6	5.74E-6
RXF 393	0.883	1.308	1.267	1.233	1.245	0.115	0.081	90	82	85	-87	-91	1.60E-6	3.12E-6	6.10E-6
SN12C	0.555	2.019	1.964	2.017	1.763	0.144	0.158	96	100	82	-74	-72	1.61E-6	3.36E-6	7.01E-6
TK-10	0.936	1.956	1.878	1.878	1.818	0.286	0.118	92	92	86	-69	-87	1.71E-6	3.58E-6	7.50E-6
UO-31	0.970	2.869	2.717	2.716	2.660	0.128	0.101	92	92	89	-87	-90	1.67E-6	3.21E-6	6.18E-6
Prostate Cancer															
PC-3	0.926	3.003	2.937	2.931	2.804	0.082	0.086	97	97	90	-91	-91	1.67E-6	3.15E-6	5.93E-6
DU-145	0.473	2.312	2.358	2.388	2.226	0.019	0.006	102	104	95	-96	-99	1.72E-6	3.15E-6	5.75E-6
Breast Cancer															
MCF7	0.486	2.810	2.674	2.676	2.150	0.097	0.224	94	94	72	-80	-54	1.39E-6	2.97E-6	6.34E-6
MDA-MB-231/ATCC	0.652	1.769	1.773	1.732	1.443	0.175	0.159	100	97	71	-73	-76	1.39E-6	3.10E-6	6.90E-6
HS 578T	1.053	2.153	2.101	2.087	2.001	0.336	0.626	95	94	86	-68	-41	1.72E-6	3.62E-6	.
BT-549	1.331	2.536	2.542	2.520	2.458	0.235	0.084	100	99	94	-82	-94	1.77E-6	3.40E-6	6.55E-6
T-47D	0.727	1.874	1.845	1.796	1.654	0.306	0.393	97	93	81	-58	-46	1.67E-6	3.82E-6	.
MDA-MB-468	0.970	2.016	1.921	1.917	1.853	0.168	0.240	91	90	84	-83	-75	1.61E-6	3.20E-6	6.37E-6

National Cancer Institute Developmental Therapeutics Program Dose Response Curves	NSC: D - 783212 / 3	SSPL: 0YLV	EXP. ID: 1508NS50
	Report Date: August 01, 2018	Test Date: August 31, 2015	

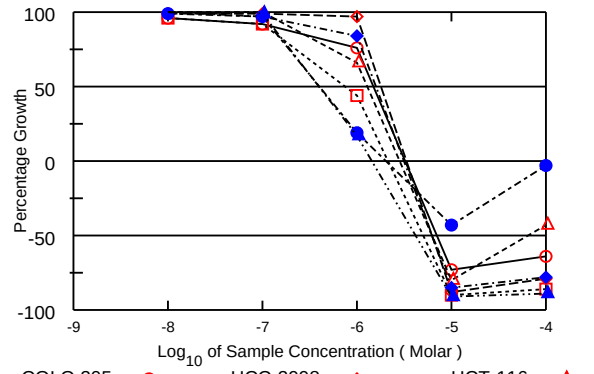
Leukemia



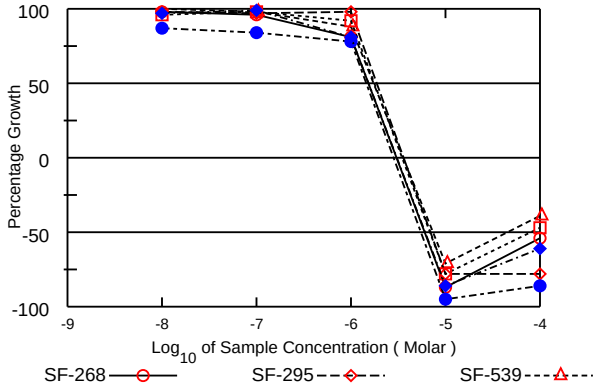
Non-Small Cell Lung Cancer



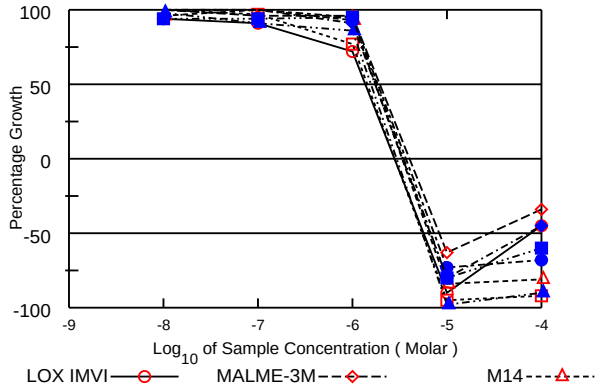
Colon Cancer



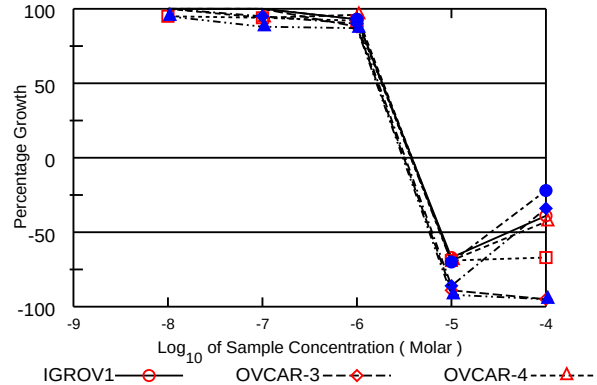
CNS Cancer



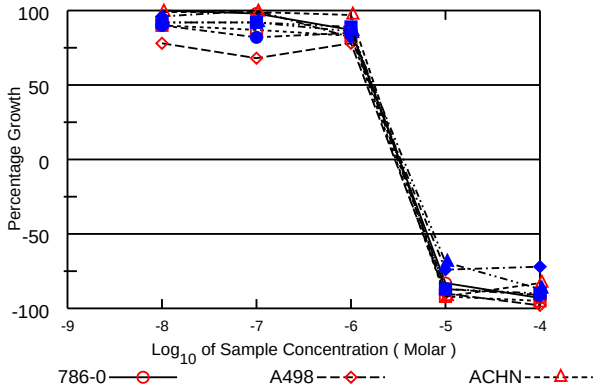
Melanoma



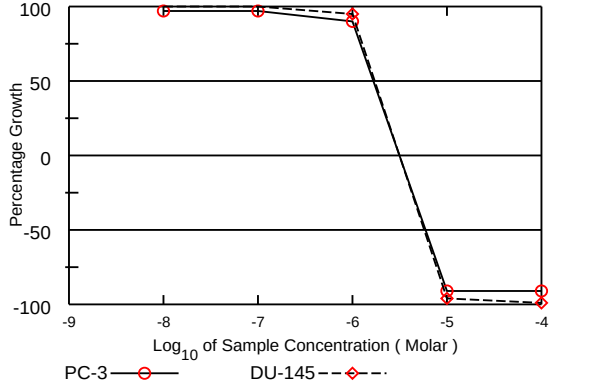
Ovarian Cancer



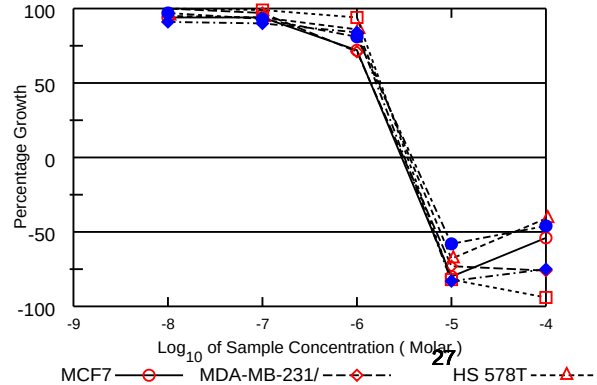
Renal Cancer



Prostate Cancer



Breast Cancer



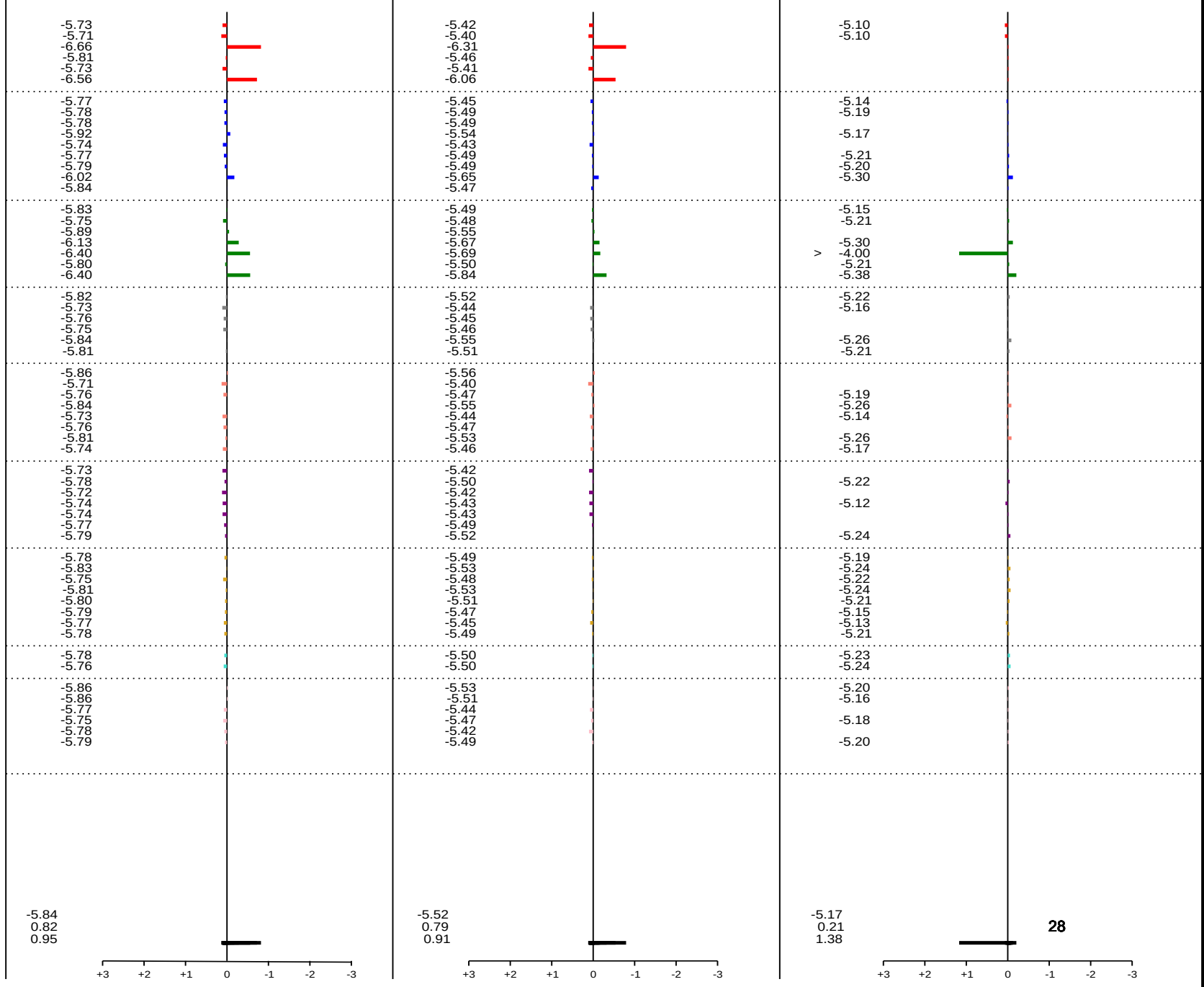
National Cancer Institute Developmental Therapeutics Program

Mean Graphs

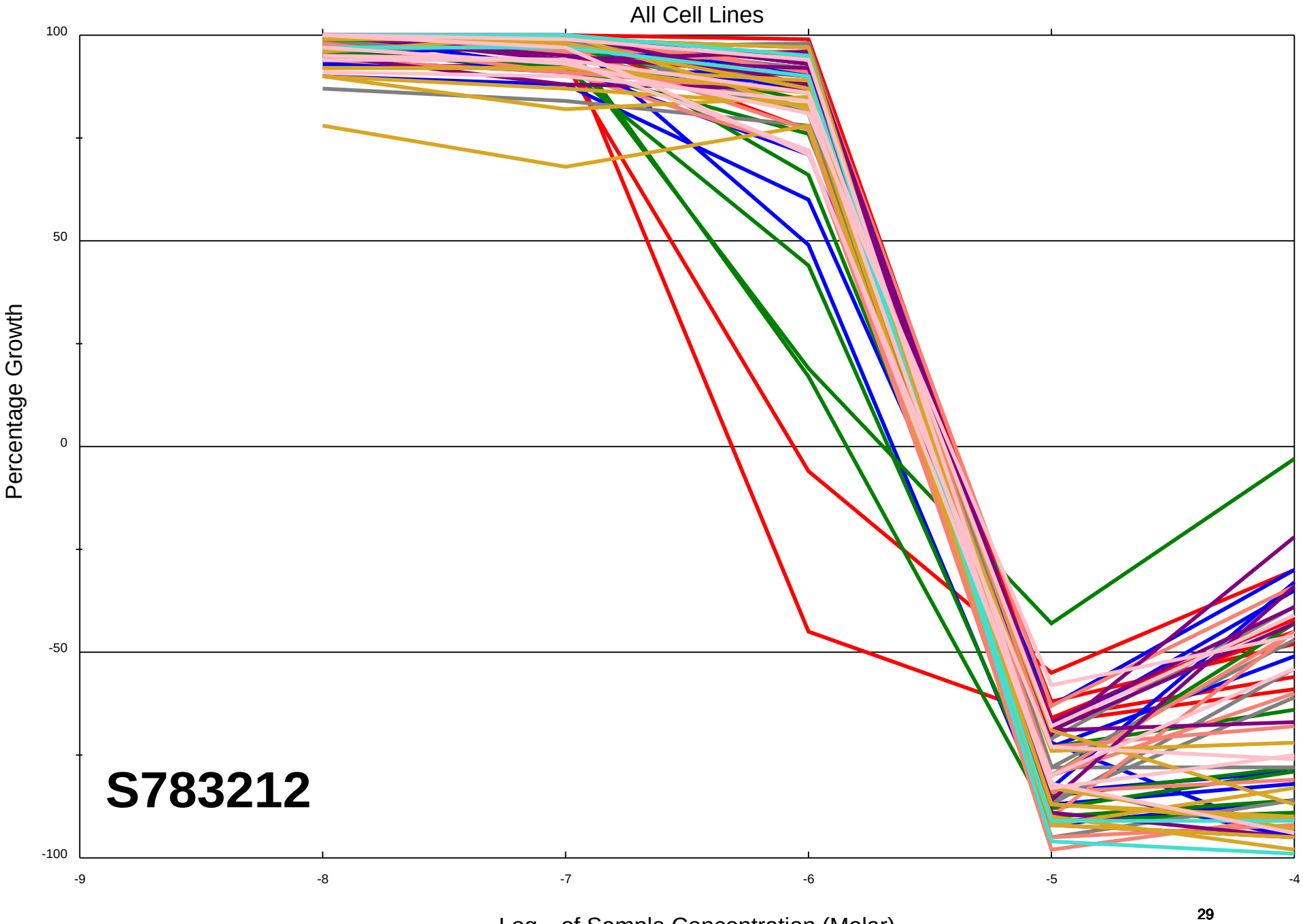
NSC : D - 783212/3 | Units :Molar | SSPL :0YLV | EXP. ID :1508NS50

Report Date :August 01, 2018 | Test Date :August 31, 2015

Panel/Cell Line	Log_{10}GI50	Log_{10}TGI	Log_{10}LC50
Leukemia			
CCRF-CEM	-5.73	-5.42	-5.10
HL-60(TB)	-5.71	-5.40	-5.10
K-562	-6.66	-6.31	
MOLT-4	-5.81	-5.46	
RPMI-8226	-5.73	-5.41	
SR	-6.56	-6.06	
Non-Small Cell Lung Cancer			
A549/ATCC	-5.77	-5.45	-5.14
EKVX	-5.78	-5.49	-5.19
HOP-62	-5.78	-5.49	
HOP-92	-5.92	-5.54	-5.17
NCI-H226	-5.74	-5.43	
NCI-H23	-5.77	-5.49	-5.21
NCI-H322M	-5.79	-5.49	-5.20
NCI-H460	-6.02	-5.65	-5.30
NCI-H522	-5.84	-5.47	
Colon Cancer			
COLO 205	-5.83	-5.49	-5.15
HCC-2998	-5.75	-5.48	-5.21
HCT-116	-5.89	-5.55	
HCT-15	-6.13	-5.67	-5.30
HT29	-6.40	-5.69	> -4.00
KM12	-5.80	-5.50	-5.21
SW-620	-6.40	-5.84	-5.38
CNS Cancer			
SF-268	-5.82	-5.52	-5.22
SF-295	-5.73	-5.44	-5.16
SF-539	-5.76	-5.45	
SNB-19	-5.75	-5.46	
SNB-75	-5.84	-5.55	-5.26
U251	-5.81	-5.51	-5.21
Melanoma			
LOX IMVI	-5.86	-5.56	
MALME-3M	-5.71	-5.40	
M14	-5.76	-5.47	-5.19
MDA-MB-435	-5.84	-5.55	-5.26
SK-MEL-2	-5.73	-5.44	-5.14
SK-MEL-28	-5.76	-5.47	
SK-MEL-5	-5.81	-5.53	-5.26
UACC-62	-5.74	-5.46	-5.17
Ovarian Cancer			
IGROV1	-5.73	-5.42	
OVCAR-3	-5.78	-5.50	-5.22
OVCAR-4	-5.72	-5.42	
OVCAR-5	-5.74	-5.43	-5.12
OVCAR-8	-5.74	-5.43	
NCI/ADR-RES	-5.77	-5.49	
SK-OV-3	-5.79	-5.52	-5.24
Renal Cancer			
786-0	-5.78	-5.49	-5.19
A498	-5.83	-5.53	-5.24
ACHN	-5.75	-5.48	-5.22
CAKI-1	-5.81	-5.53	-5.24
RXF 393	-5.80	-5.51	-5.21
SN12C	-5.79	-5.47	-5.15
TK-10	-5.77	-5.45	-5.13
UO-31	-5.78	-5.49	-5.21
Prostate Cancer			
PC-3	-5.78	-5.50	-5.23
DU-145	-5.76	-5.50	-5.24
Breast Cancer			
MCF7	-5.86	-5.53	-5.20
MDA-MB-231/ATCC	-5.86	-5.51	-5.16
HS 578T	-5.77	-5.44	
BT-549	-5.75	-5.47	-5.18
T-47D	-5.78	-5.42	
MDA-MB-468	-5.79	-5.49	-5.20
MID	-5.84	-5.52	-5.17
Delta	0.82	0.79	0.21
Range	0.95	0.91	1.38



National Cancer Institute Developmental Therapeutics Program Dose Response Curves	NSC : D - 783212/3	SSPL:0YLV	EXP. ID:1508NS50
	Report Date:August 01, 2018	Test Date:August 31, 2015	



National Cancer Institute Developmental Therapeutics Program
Waterfall Graph GI50

NSC : D - 783212/3	Units :Molar	SSPL :0YLV	EXP. ID :1508NS50
Report Date :August 01, 2018		Test Date :August 31, 2015	

Panel	Cell Name	Hollow Fiber	GI50
Leukemia	K-562		-6.66
Leukemia	SR		-6.56
Colon Cancer	SW-620	*	-6.40
Colon Cancer	HT29		-6.40
Colon Cancer	HCT-15		-6.13
Non-Small Cell Lung Cancer	NCI-H460		-6.02
Non-Small Cell Lung Cancer	HOP-92		-5.92
Colon Cancer	HCT-116		-5.89
Melanoma	LOX IMVI	*	-5.86
Breast Cancer	MCF7		-5.86
Breast Cancer	MDA-MB-231/ATCC	*	-5.86
Non-Small Cell Lung Cancer	NCI-H522	*	-5.84
Melanoma	MDA-MB-435	*	-5.84
CNS Cancer	SNB-75		-5.84
Renal Cancer	A498		-5.83
Colon Cancer	COLO 205	*	-5.83
CNS Cancer	SF-268		-5.82
CNS Cancer	U251	*	-5.81
Leukemia	MOLT-4		-5.81
Renal Cancer	CAKI-1		-5.81
Melanoma	SK-MEL-5		-5.81
Colon Cancer	KM12		-5.80
Renal Cancer	RXF 393		-5.80
Ovarian Cancer	SK-OV-3		-5.79
Breast Cancer	MDA-MB-468		-5.79
Renal Cancer	SN12C		-5.79
Non-Small Cell Lung Cancer	NCI-H322M		-5.79
Ovarian Cancer	OVCAR-3	*	-5.78
Non-Small Cell Lung Cancer	EKVX		-5.78
Renal Cancer	786-0		-5.78
Non-Small Cell Lung Cancer	HOP-62		-5.78
Renal Cancer	UO-31		-5.78
Breast Cancer	T-47D		-5.78
Prostate Cancer	PC-3		-5.78
Ovarian Cancer	NCI/ADR-RES		-5.77
Non-Small Cell Lung Cancer	NCI-H23	*	-5.77
Renal Cancer	TK-10		-5.77
Breast Cancer	HS 578T		-5.77
Non-Small Cell Lung Cancer	A549/ATCC		-5.77
Prostate Cancer	DU-145		-5.76
CNS Cancer	SF-539		-5.76
Melanoma	SK-MEL-28		-5.76
Melanoma	M14		-5.76
CNS Cancer	SNB-19		-5.75
Breast Cancer	BT-549		-5.75
Renal Cancer	ACHN		-5.75
Colon Cancer	HCC-2998		-5.75
Non-Small Cell Lung Cancer	NCI-H226		-5.74
Melanoma	UACC-62	*	-5.74
Ovarian Cancer	OVCAR-5	*	-5.74
Ovarian Cancer	OVCAR-8		-5.74
Melanoma	SK-MEL-2		-5.73
Leukemia	CCRF-CEM		-5.73
Leukemia	RPMI-8226		-5.73
Ovarian Cancer	IGROV1		-5.73
CNS Cancer	SF-295	*	-5.73
Ovarian Cancer	OVCAR-4		-5.72
Melanoma	MALME-3M		-5.71
Leukemia	HL-60(TB)		-5.71

Log10 High Conc :-4.0

National Cancer Institute Developmental Therapeutics Program
Waterfall Graph TGI

NSC : D - 783212/3	Units :Molar	SSPL :0YLV	EXP. ID :1508NS50
Report Date :August 01, 2018		Test Date :August 31, 2015	

Panel	Cell Name	Hollow Fiber	TGI
Leukemia	K-562		-6.31
Leukemia	SR		-6.06
Colon Cancer	SW-620	*	-5.84
Colon Cancer	HT29		-5.69
Colon Cancer	HCT-15		-5.67
Non-Small Cell Lung Cancer	NCI-H460		-5.65
Melanoma	LOX IMVI	*	-5.56
Melanoma	MDA-MB-435	*	-5.55
Colon Cancer	HCT-116		-5.55
CNS Cancer	SNB-75		-5.55
Non-Small Cell Lung Cancer	HOP-92		-5.54
Renal Cancer	A498		-5.53
Melanoma	SK-MEL-5		-5.53
Breast Cancer	MCF7		-5.53
Renal Cancer	CAKI-1		-5.53
CNS Cancer	SF-268		-5.52
Ovarian Cancer	SK-OV-3		-5.52
CNS Cancer	U251	*	-5.51
Breast Cancer	MDA-MB-231/ATCC	*	-5.51
Renal Cancer	RXF 393		-5.51
Colon Cancer	KM12		-5.50
Prostate Cancer	PC-3		-5.50
Prostate Cancer	DU-145		-5.50
Ovarian Cancer	OVCAR-3	*	-5.50
Breast Cancer	MDA-MB-468		-5.49
Non-Small Cell Lung Cancer	NCI-H322M		-5.49
Renal Cancer	UO-31		-5.49
Colon Cancer	COLO 205	*	-5.49
Ovarian Cancer	NCI/ADR-RES		-5.49
Renal Cancer	786-0		-5.49
Non-Small Cell Lung Cancer	NCI-H23	*	-5.49
Non-Small Cell Lung Cancer	EKVX		-5.49
Non-Small Cell Lung Cancer	HOP-62		-5.49
Renal Cancer	ACHN		-5.48
Colon Cancer	HCC-2998		-5.48
Melanoma	M14		-5.47
Renal Cancer	SN12C		-5.47
Non-Small Cell Lung Cancer	NCI-H522	*	-5.47
Breast Cancer	BT-549		-5.47
Melanoma	SK-MEL-28		-5.47
Leukemia	MOLT-4		-5.46
CNS Cancer	SNB-19		-5.46
Melanoma	UACC-62	*	-5.46
Non-Small Cell Lung Cancer	A549/ATCC		-5.45
CNS Cancer	SF-539		-5.45
Renal Cancer	TK-10		-5.45
CNS Cancer	SF-295	*	-5.44
Breast Cancer	HS 578T		-5.44
Melanoma	SK-MEL-2		-5.44
Non-Small Cell Lung Cancer	NCI-H226		-5.43
Ovarian Cancer	OVCAR-8		-5.43
Ovarian Cancer	OVCAR-5	*	-5.43
Ovarian Cancer	OVCAR-4		-5.42
Leukemia	CCRF-CEM		-5.42
Ovarian Cancer	IGROV1		-5.42
Breast Cancer	T-47D		-5.42
Leukemia	RPMI-8226		-5.41
Leukemia	HL-60(TB)		-5.40
Melanoma	MALME-3M		-5.40

Log10 High Conc : -4.0

National Cancer Institute Developmental Therapeutics Program
Waterfall Graph LC50

NSC : D - 783212/3	Units :Molar	SSPL :0YLV	EXP. ID :1508NS50
Report Date :August 01, 2018		Test Date :August 31, 2015	

Panel	Cell Name	Hollow Fiber	LC50
Colon Cancer	SW-620	*	-5.38
Non-Small Cell Lung Cancer	NCI-H460		-5.30
Colon Cancer	HCT-15		-5.30
Melanoma	SK-MEL-5		-5.26
Melanoma	MDA-MB-435	*	-5.26
CNS Cancer	SNB-75		-5.26
Renal Cancer	CAKI-1		-5.24
Prostate Cancer	DU-145		-5.24
Renal Cancer	A498		-5.24
Ovarian Cancer	SK-OV-3		-5.24
Prostate Cancer	PC-3		-5.23
Renal Cancer	ACHN		-5.22
Ovarian Cancer	OVCAR-3	*	-5.22
CNS Cancer	SF-268		-5.22
Renal Cancer	RXF 393		-5.21
CNS Cancer	U251	*	-5.21
Renal Cancer	UO-31		-5.21
Colon Cancer	KM12		-5.21
Non-Small Cell Lung Cancer	NCI-H23	*	-5.21
Colon Cancer	HCC-2998		-5.21
Non-Small Cell Lung Cancer	NCI-H322M		-5.20
Breast Cancer	MCF7		-5.20
Breast Cancer	MDA-MB-468		-5.20
Renal Cancer	786-0		-5.19
Melanoma	M14		-5.19
Non-Small Cell Lung Cancer	EKVX		-5.19
Breast Cancer	BT-549		-5.18
Melanoma	UACC-62	*	-5.17
Non-Small Cell Lung Cancer	HOP-92		-5.17
Breast Cancer	MDA-MB-231/ATCC	*	-5.16
CNS Cancer	SF-295	*	-5.16
Renal Cancer	SN12C		-5.15
Colon Cancer	COLO 205	*	-5.15
Non-Small Cell Lung Cancer	A549/ATCC		-5.14
Melanoma	SK-MEL-2		-5.14
Renal Cancer	TK-10		-5.13
Ovarian Cancer	OVCAR-5	*	-5.12
Leukemia	HL-60(TB)		-5.10
Leukemia	CCRF-CEM		-5.10
Colon Cancer	HT29		> -4.00

Log10 High Conc : -4.0

National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

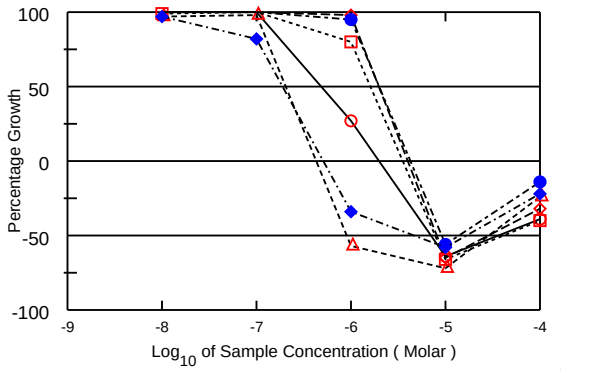
NSC : D - 783211 / 2= Compound 23	Experiment ID : 1504NS69	Test Type : 08	Units : Molar
Report Date : August 01, 2018	Test Date : April 13, 2015	QNS :	MC :
COMI : UPCDC30320-01	Stain Reagent : SRB Dual-Pass Related	SSPL : 0YLV	

Log10 Concentration

	Time	Mean Optical Densities						Percent Growth							
Panel/Cell Line	Zero	Ctrl	-8.0	-7.0	-6.0	-5.0	-4.0	-8.0	-7.0	-6.0	-5.0	-4.0	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.574	2.151	2.171	2.213	0.993	0.208	0.352	101	104	27	-64	-39	4.98E-7	1.97E-6	.
HL-60(TB)	1.047	2.962	3.029	2.986	2.928	0.362	0.709	103	101	98	-65	-32	1.97E-6	3.98E-6	.
K-562	0.333	2.405	2.341	2.367	0.145	0.094	0.253	97	98	-57	-72	-24	2.05E-7	4.31E-7	.
MOLT-4	0.964	3.110	3.087	3.103	2.684	0.332	0.579	99	100	80	-66	-40	1.61E-6	3.55E-6	.
RPMI-8226	0.812	2.991	3.056	3.037	2.882	0.361	0.701	103	102	95	-56	-14	1.99E-6	4.28E-6	.
SR	0.493	1.678	1.637	1.470	0.327	0.207	0.386	97	82	-34	-58	-22	1.90E-7	5.12E-7	.
Non-Small Cell Lung Cancer															
A549/ATCC	0.453	1.749	1.750	1.765	1.724	0.083	0.227	100	101	98	-82	-50	1.85E-6	3.51E-6	.
EKVX	0.829	2.139	2.002	2.013	1.952	0.102	-0.006	89	90	86	-88	-100	1.61E-6	3.12E-6	6.06E-6
HOP-62	0.638	1.642	1.513	1.575	1.531	0.180	0.118	87	93	89	-72	-82	1.75E-6	3.57E-6	7.31E-6
HOP-92	1.340	1.929	1.930	1.931	1.803	0.135	0.211	100	100	79	-90	-84	1.48E-6	2.93E-6	5.79E-6
NCI-H226	0.894	2.334	2.363	2.314	2.365	0.315	0.718	102	99	102	-65	-20	2.05E-6	4.09E-6	.
NCI-H23	0.626	2.060	1.969	1.926	1.885	0.087	0.229	94	91	88	-86	-63	1.65E-6	3.20E-6	6.20E-6
NCI-H322M	1.234	2.816	2.704	2.720	2.802	0.228	0.265	93	94	99	-82	-79	1.87E-6	3.54E-6	6.69E-6
NCI-H460	0.444	3.181	3.238	3.268	3.229	0.156	0.374	102	103	102	-65	-16	2.04E-6	4.08E-6	.
NCI-H522	0.866	1.972	1.899	1.944	1.839	0.229	0.619	93	97	88	-74	-29	1.72E-6	3.50E-6	.
Colon Cancer															
COLO 205	0.359	1.466	1.409	1.425	0.988	0.102	0.241	95	96	57	-72	-33	1.13E-6	2.77E-6	.
HCC-2998	0.425	1.461	1.518	1.455	1.191	0.042	0.184	105	99	74	-90	-57	1.40E-6	2.82E-6	5.69E-6
HCT-116	0.319	2.718	2.660	2.618	1.779	0.059	0.196	98	96	61	-82	-39	1.19E-6	2.68E-6	.
HCT-15	0.264	2.002	1.840	1.962	0.703	0.022	0.088	91	98	25	-92	-67	4.55E-7	1.64E-6	4.39E-6
HT29	0.380	1.912	1.896	1.854	1.181	0.087	0.261	99	96	52	-77	-31	1.04E-6	2.53E-6	.
KM12	0.437	2.452	2.363	2.403	1.937	0.067	0.092	96	98	74	-85	-79	1.42E-6	2.93E-6	6.05E-6
SW-620	0.686	3.195	3.246	3.292	3.200	0.224	0.480	102	104	100	-67	-30	1.99E-6	3.96E-6	.
CNS Cancer															
SF-268	0.763	2.400	2.277	2.270	2.118	0.158	0.257	92	92	83	-79	-66	1.59E-6	3.24E-6	6.60E-6
SF-295	0.867	2.779	2.578	2.703	2.659	0.189	0.069	89	96	94	-78	-92	1.80E-6	3.51E-6	6.85E-6
SF-539	1.112	2.887	2.754	2.795	2.716	0.088	0.362	93	95	90	-92	-67	1.66E-6	3.13E-6	5.88E-6
SNB-19	0.565	2.168	2.202	2.212	2.038	0.184	0.286	102	103	92	-67	-49	1.83E-6	3.77E-6	.
SNB-75	0.683	1.634	1.452	1.511	1.441	0.067	0.308	81	87	80	-90	-55	1.49E-6	2.94E-6	5.79E-6
U251	0.592	2.159	2.182	2.253	2.021	0.098	0.041	101	106	91	-83	-93	1.72E-6	3.33E-6	6.43E-6
Melanoma															
LOX IMVI	0.331	2.425	2.341	2.279	0.392	0.040	0.220	96	93	3	-88	-34	3.00E-7	1.08E-6	.
MALME-3M	0.800	1.555	1.511	1.533	1.560	0.249	0.474	94	97	101	-69	-41	1.99E-6	3.92E-6	.
M14	0.432	1.991	1.825	1.922	1.596	0.113	0.158	89	96	75	-74	-64	1.47E-6	3.18E-6	6.91E-6
MDA-MB-435	0.305	2.040	1.935	2.004	0.848	0.037	0.095	94	98	31	-88	-69	5.23E-7	1.83E-6	4.80E-6
SK-MEL-2	1.421	2.450	2.508	2.550	2.570	0.334	0.329	106	110	112	-77	-77	2.13E-6	3.92E-6	7.23E-6
SK-MEL-28	0.745	2.312	2.224	2.277	2.198	0.103	0.191	94	98	93	-86	-74	1.73E-6	3.30E-6	6.28E-6
SK-MEL-5	0.820	3.196	3.189	3.272	3.085	0.015	0.019	100	103	95	-98	-98	1.71E-6	3.11E-6	5.64E-6
UACC-257	0.990	1.846	1.856	1.908	1.985	0.214	0.086	101	107	116	-78	-91	2.19E-6	3.96E-6	7.15E-6
UACC-62	1.140	3.058	3.053	3.139	3.138	0.420	0.826	100	104	104	-63	-28	2.11E-6	4.19E-6	.
Ovarian Cancer															
IGROV1	0.843	2.806	2.796	2.757	2.664	0.291	0.608	100	98	93	-66	-28	1.86E-6	3.85E-6	.
OVCAR-3	0.780	2.340	2.364	2.241	2.170	0.063	-0.026	102	94	89	-92	-100	1.64E-6	3.11E-6	5.87E-6
OVCAR-4	0.904	2.181	2.148	2.181	2.071	0.360	0.741	97	100	91	-60	-18	1.87E-6	4.01E-6	.
OVCAR-5	0.923	1.934	1.837	1.836	1.852	0.187	0.172	90	90	92	-80	-81	1.75E-6	3.43E-6	6.71E-6
OVCAR-8	0.542	2.026	2.094	2.149	2.094	0.139	0.297	105	108	105	-74	-45	2.02E-6	3.84E-6	.
NCI/ADR-RES	0.634	2.340	2.336	2.285	2.163	0.085	0.409	100	97	90	-87	-36	1.68E-6	3.23E-6	.
SK-OV-3	0.795	1.959	1.879	1.978	1.963	0.085	0.068	93	102	100	-89	-91	1.84E-6	3.38E-6	6.20E-6
Renal Cancer															
786-0	0.666	2.461	2.231	2.252	1.950	0.177	0.010	87	88	72	-73	-98	1.41E-6	3.11E-6	6.89E-6
A498	1.313	2.144	2.121	2.091	2.037	0.304	0.135	97	94	87	-77	-90	1.68E-6	3.40E-6	6.86E-6
ACHN	0.539	2.178	2.090	2.113	2.083	0.042	0.059	95	96	94	-92	-89	1.73E-6	3.20E-6	5.93E-6
CAKI-1	0.830	3.360	3.215	3.291	3.158	0.099	0.134	94	97	92	-88	-84	1.71E-6	3.24E-6	6.14E-6
RXF 393	0.803	1.541	1.560	1.515	1.401	0.110	0.003	103	96	81	-86	-100	1.53E-6	3.05E-6	6.06E-6
SN12C	0.980	3.246	3.250	3.300	3.232	0.326	0.141	100	102	99	-67	-86	1.98E-6	3.96E-6	7.93E-6
TK-10	0.909	1.632	1.587	1.568	1.565	0.147	0.009	94	91	91	-84	-99	1.71E-6	3.31E-6	6.40E-6
UO-31	0.988	2.951	2.853	2.808	2.769	0.159	0.135	95	93	91	-84	-86	1.71E-6	3.31E-6	6.39E-6
Prostate Cancer															
PC-3	0.571	2.395	2.365	2.360	2.254	0.082	0.110	98	98	92	-86	-81	1.73E-6	3.30E-6	6.30E-6
DU-145	0.326	1.480	1.535	1.467	1.320	0.004	-0.017	105	99	86	-99	-100	1.57E-6	2.92E-6	5.45E-6
Breast Cancer															
MCF7	0.400	2.151	1.922	1.971	1.503	0.092	0.251	87	90	63	-77	-37	1.24E-6	2.82E-6	.
MDA-MB-231/ATCC	0.732	1.834	1.887	1.893	1.730	0.230	0.203	105	105	91	-69	-72	1.80E-6	3.71E-6	7.64E-6
HS 578T	1.372	2.580	2.572	2.594	2.568	0.790	1.342	99	101	99	-42	-2	2.22E-6	5.01E-6	> 1.00E-4
BT-549	1.210	2.764	2.566	2.708	2.595	0.274	0.027	87	96	89	-77	-98	1.72E-6	3.43E-6	6.85E-6
T-47D	0.770	1.621	1.532	1.622	1.578	0.299	0.513	90	100	95	-61	-33	1.94E-6	4.05E-6	.
MDA-MB-468	0.790	1.515	1.559	1.599	1.406	0.184	0.366	106	112	85	-77	-54	1.64E-6	3.35E-6	6.83E-6

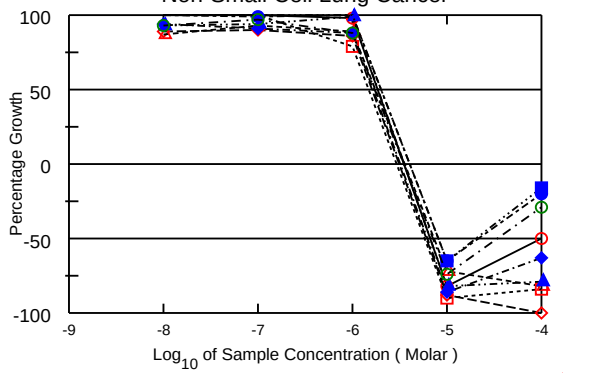
National Cancer Institute Developmental Therapeutics Program Dose Response Curves	NSC: D - 783211 / 2	SSPL: 0YLV	EXP. ID: 1504NS69
	Report Date: August 01, 2018	Test Date: April 13, 2015	

Leukemia



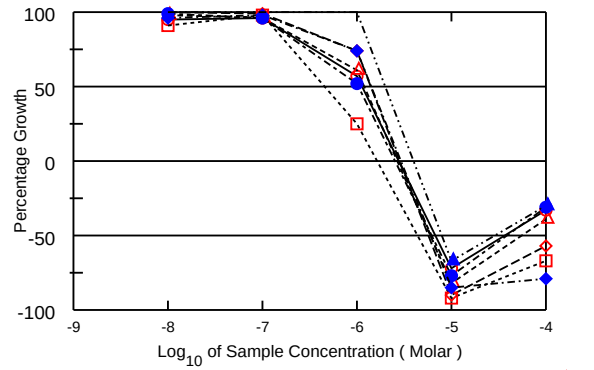
CCRF-CEM, HL-60(TB), K-562, MOLT-4, RPMI-8226, SR

Non-Small Cell Lung Cancer



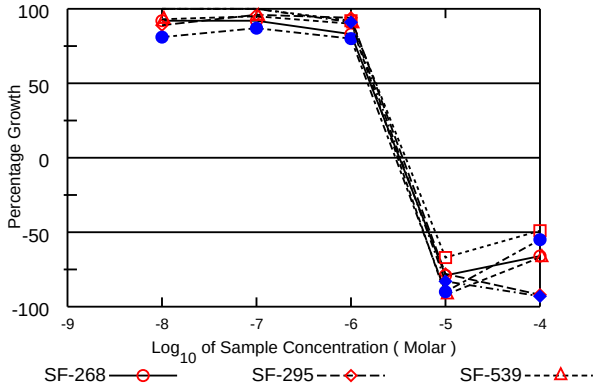
A549/ATCC, EKVX, HOP-62, HOP-92, NCI-H226, NCI-H23, NCI-H322M, NCI-H460, NCI-H522

Colon Cancer



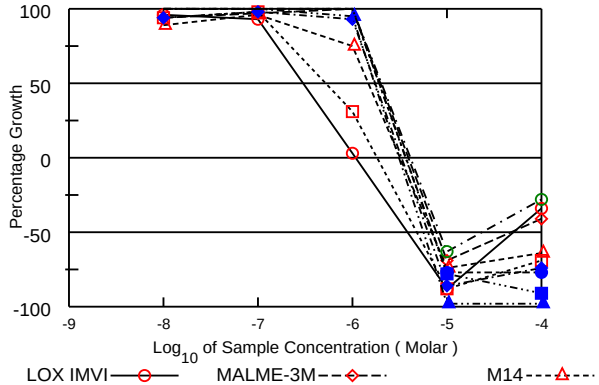
COLO 205, HCC-2998, HCT-116, HCT-15, HT29, KM12, SW-620

CNS Cancer



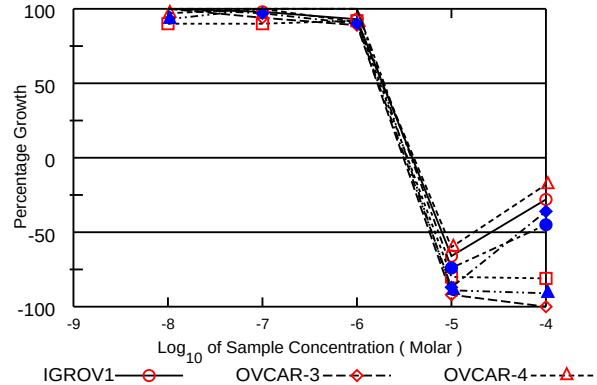
SF-268, SF-295, SF-539, SNB-19, SNB-75, U251

Melanoma



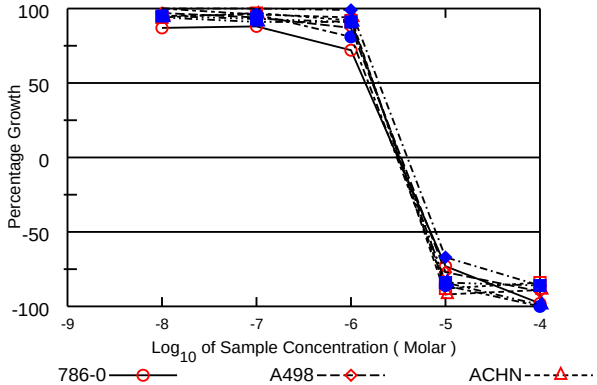
LOX IMVI, MALME-3M, M14, MDA-MB-435, SK-MEL-2, SK-MEL-28, SK-MEL-5, UACC-257, UACC-62

Ovarian Cancer



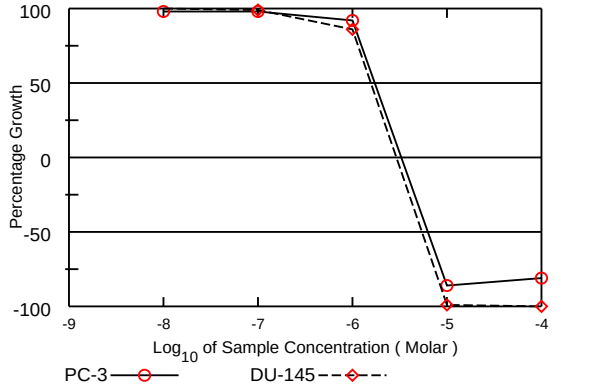
IGROV1, OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, NCI/ADR-RES, SK-OV-3

Renal Cancer



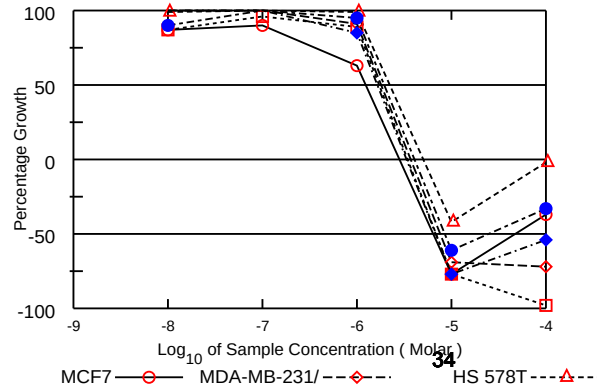
786-0, A498, ACHN, CAKI-1, RXF 393, SN12C, TK-10, UO-31

Prostate Cancer



PC-3, DU-145

Breast Cancer



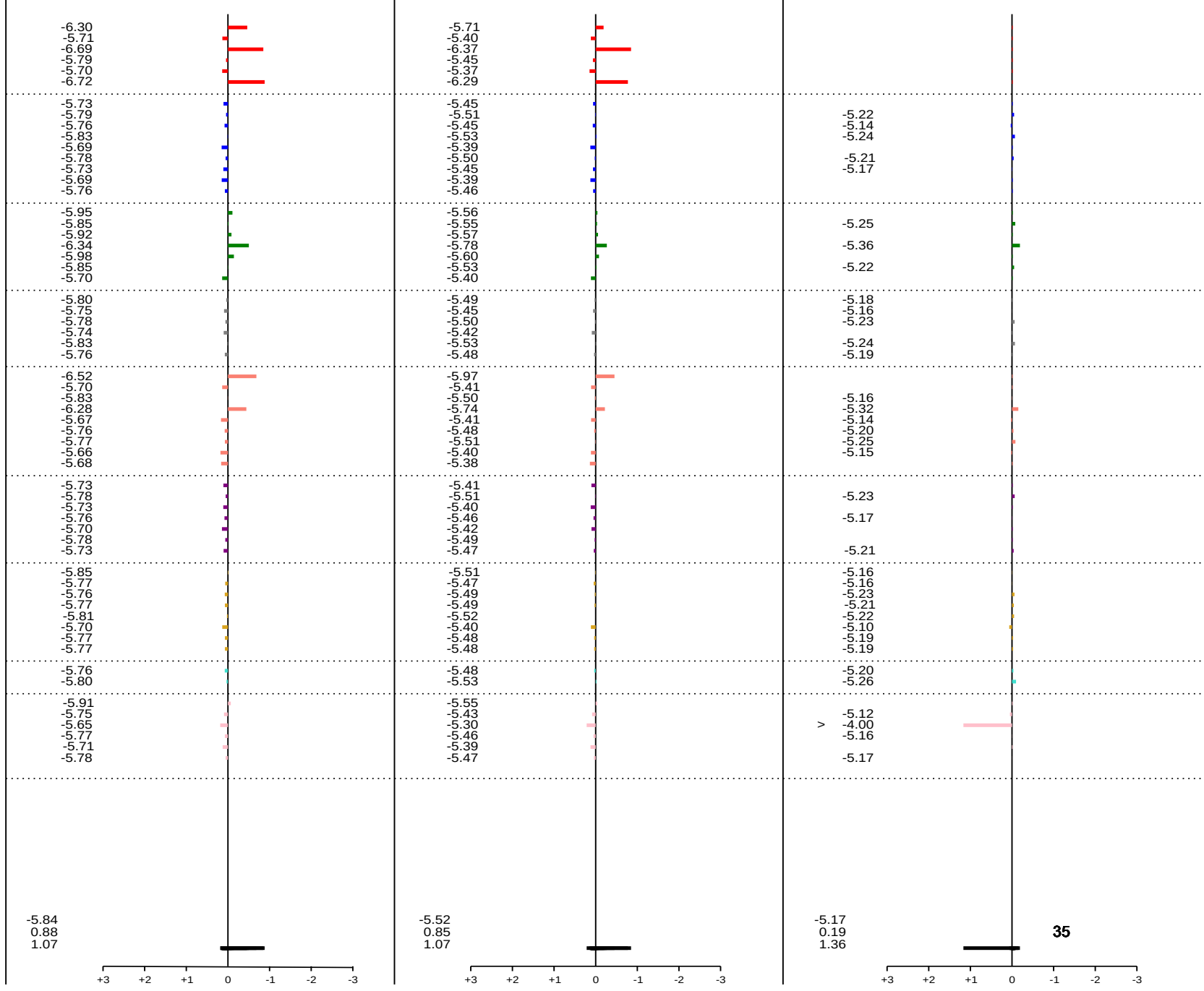
MCF7, MDA-MB-231/, HS 578T, BT-549, T-47D, MDA-MB-468

National Cancer Institute Developmental Therapeutics Program

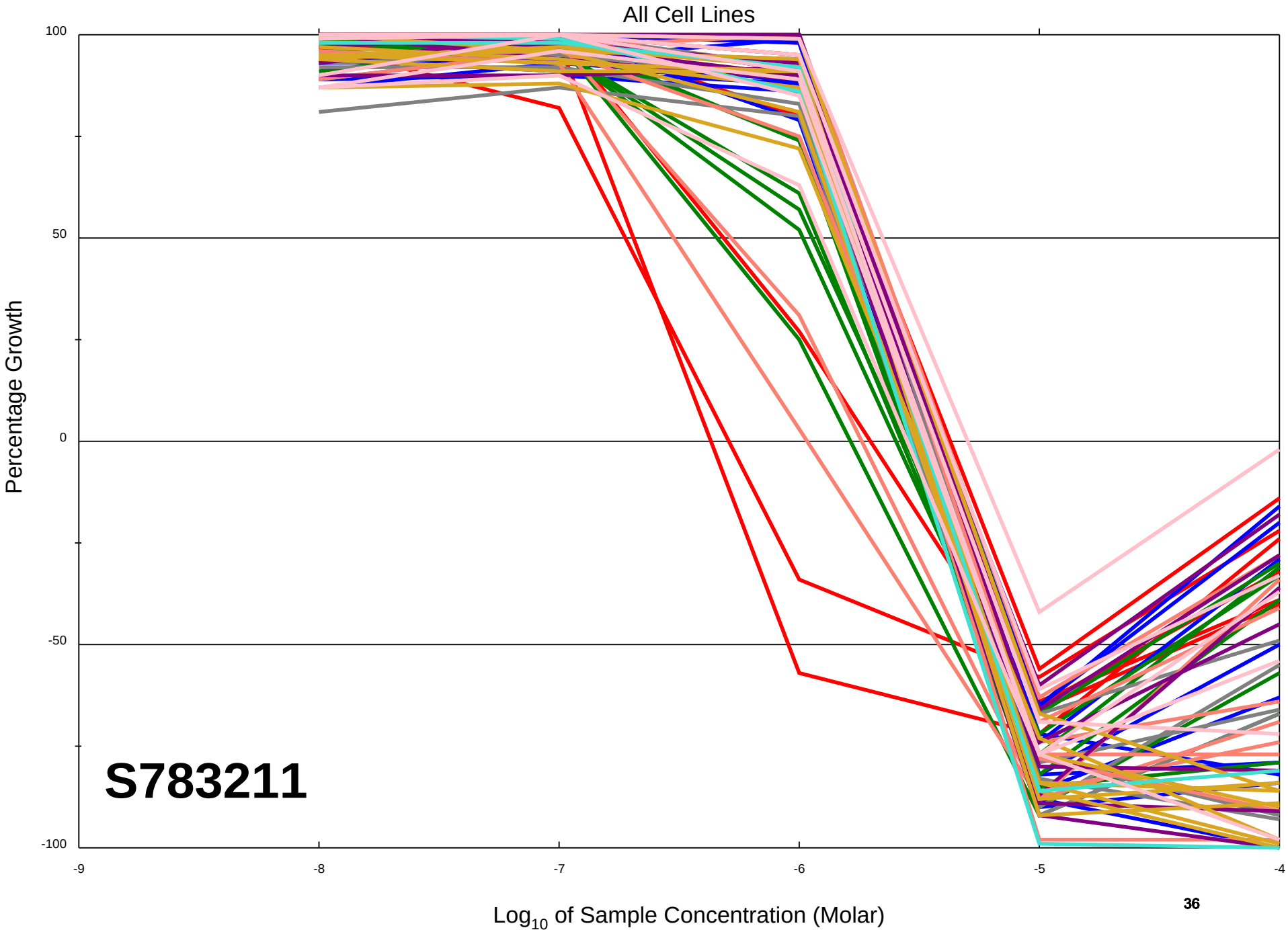
Mean Graphs

NSC : D - 783211/2	Units :Molar	SSPL :0YLV	EXP. ID :1504NS69
Report Date :August 01, 2018		Test Date :April 13, 2015	

Panel/Cell Line	Log_{10}GI50	Log_{10}TGI	Log_{10}LC50
Leukemia			
CCRF-CEM	-6.30	-5.71	
HL-60(TB)	-5.71	-5.40	
K-562	-6.69	-6.37	
MOLT-4	-5.79	-5.45	
RPMI-8226	-5.70	-5.37	
SR	-6.72	-6.29	
Non-Small Cell Lung Cancer			
A549/ATCC	-5.73	-5.45	
EKVX	-5.79	-5.51	-5.22
HOP-62	-5.76	-5.45	-5.14
HOP-92	-5.83	-5.53	-5.24
NCI-H226	-5.69	-5.39	
NCI-H23	-5.78	-5.50	-5.21
NCI-H322M	-5.73	-5.45	-5.17
NCI-H460	-5.69	-5.39	
NCI-H522	-5.76	-5.46	
Colon Cancer			
COLO 205	-5.95	-5.56	
HCC-2998	-5.85	-5.55	-5.25
HCT-116	-5.92	-5.57	
HCT-15	-6.34	-5.78	-5.36
HT29	-5.98	-5.60	
KM12	-5.85	-5.53	-5.22
SW-620	-5.70	-5.40	
CNS Cancer			
SF-268	-5.80	-5.49	-5.18
SF-295	-5.75	-5.45	-5.16
SF-539	-5.78	-5.50	-5.23
SNB-19	-5.74	-5.42	
SNB-75	-5.83	-5.53	-5.24
U251	-5.76	-5.48	-5.19
Melanoma			
LOX IMVI	-6.52	-5.97	
MALME-3M	-5.70	-5.41	
M14	-5.83	-5.50	-5.16
MDA-MB-435	-6.28	-5.74	-5.32
SK-MEL-2	-5.67	-5.41	-5.14
SK-MEL-28	-5.76	-5.48	-5.20
SK-MEL-5	-5.77	-5.51	-5.25
UACC-257	-5.66	-5.40	-5.15
UACC-62	-5.68	-5.38	
Ovarian Cancer			
IGROV1	-5.73	-5.41	
OVCAR-3	-5.78	-5.51	-5.23
OVCAR-4	-5.73	-5.40	
OVCAR-5	-5.76	-5.46	-5.17
OVCAR-8	-5.70	-5.42	
NCI/ADR-RES	-5.78	-5.49	
SK-OV-3	-5.73	-5.47	-5.21
Renal Cancer			
786-0	-5.85	-5.51	-5.16
A498	-5.77	-5.47	-5.16
ACHN	-5.76	-5.49	-5.23
CAKI-1	-5.77	-5.49	-5.21
RXF 393	-5.81	-5.52	-5.22
SN12C	-5.70	-5.40	-5.10
TK-10	-5.77	-5.48	-5.19
UO-31	-5.77	-5.48	-5.19
Prostate Cancer			
PC-3	-5.76	-5.48	-5.20
DU-145	-5.80	-5.53	-5.26
Breast Cancer			
MCF7	-5.91	-5.55	
MDA-MB-231/ATCC	-5.75	-5.43	-5.12
HS 578T	-5.65	-5.30	> -4.00
BT-549	-5.77	-5.46	-5.16
T-47D	-5.71	-5.39	
MDA-MB-468	-5.78	-5.47	-5.17
MID	-5.84	-5.52	-5.17
Delta	0.88	0.85	0.19
Range	1.07	1.07	1.36



National Cancer Institute Developmental Therapeutics Program Dose Response Curves	NSC : D - 783211/2	SSPL:0YLV	EXP. ID:1504NS69
	Report Date:August 01, 2018	Test Date:April 13, 2015	



National Cancer Institute Developmental Therapeutics Program
Waterfall Graph GI50

NSC : D - 783211/2	Units :Molar	SSPL :0YLV	EXP. ID :1504NS69
Report Date :August 01, 2018		Test Date :April 13, 2015	

Panel	Cell Name	Hollow Fiber	GI50
Leukemia	SR		-6.72
Leukemia	K-562		-6.69
Melanoma	LOX IMVI	*	-6.52
Colon Cancer	HCT-15		-6.34
Leukemia	CCRF-CEM		-6.30
Melanoma	MDA-MB-435	*	-6.28
Colon Cancer	HT29		-5.98
Colon Cancer	COLO 205	*	-5.95
Colon Cancer	HCT-116		-5.92
Breast Cancer	MCF7		-5.91
Colon Cancer	HCC-2998		-5.85
Renal Cancer	786-0		-5.85
Colon Cancer	KM12		-5.85
Melanoma	M14		-5.83
Non-Small Cell Lung Cancer	HOP-92		-5.83
CNS Cancer	SNB-75		-5.83
Renal Cancer	RXF 393		-5.81
Prostate Cancer	DU-145		-5.80
CNS Cancer	SF-268		-5.80
Non-Small Cell Lung Cancer	EKVX		-5.79
Leukemia	MOLT-4		-5.79
Ovarian Cancer	OVCAR-3	*	-5.78
Breast Cancer	MDA-MB-468		-5.78
Non-Small Cell Lung Cancer	NCI-H23	*	-5.78
CNS Cancer	SF-539		-5.78
Ovarian Cancer	NCI/ADR-RES		-5.78
Renal Cancer	A498		-5.77
Renal Cancer	UO-31		-5.77
Renal Cancer	CAKI-1		-5.77
Renal Cancer	TK-10		-5.77
Melanoma	SK-MEL-5		-5.77
Breast Cancer	BT-549		-5.77
Non-Small Cell Lung Cancer	NCI-H522	*	-5.76
CNS Cancer	U251	*	-5.76
Renal Cancer	ACHN		-5.76
Prostate Cancer	PC-3		-5.76
Melanoma	SK-MEL-28		-5.76
Non-Small Cell Lung Cancer	HOP-62		-5.76
Ovarian Cancer	OVCAR-5	*	-5.76
CNS Cancer	SF-295	*	-5.75
Breast Cancer	MDA-MB-231/ATCC	*	-5.75
CNS Cancer	SNB-19		-5.74
Ovarian Cancer	SK-OV-3		-5.73
Non-Small Cell Lung Cancer	A549/ATCC		-5.73
Ovarian Cancer	IGROV1		-5.73
Non-Small Cell Lung Cancer	NCI-H322M		-5.73
Ovarian Cancer	OVCAR-4		-5.73
Breast Cancer	T-47D		-5.71
Leukemia	HL-60(TB)		-5.71
Renal Cancer	SN12C		-5.70
Melanoma	MALME-3M		-5.70
Leukemia	RPMI-8226		-5.70
Colon Cancer	SW-620	*	-5.70
Ovarian Cancer	OVCAR-8		-5.70
Non-Small Cell Lung Cancer	NCI-H460		-5.69
Non-Small Cell Lung Cancer	NCI-H226		-5.69
Melanoma	UACC-62	*	-5.68
Melanoma	SK-MEL-2		-5.67
Melanoma	UACC-257		-5.66
Breast Cancer	HS 578T		-5.65

Log10 High Conc :-4.0

National Cancer Institute Developmental Therapeutics Program
Waterfall Graph TGI

NSC : D - 783211/2 | Units :Molar | SSPL :0YLV | EXP. ID :1504NS69

Report Date :August 01, 2018 | Test Date :April 13, 2015

Panel	Cell Name	Hollow Fiber	TGI
Leukemia	K-562		-6.37
Leukemia	SR		-6.29
Melanoma	LOX IMVI	*	-5.97
Colon Cancer	HCT-15		-5.78
Melanoma	MDA-MB-435	*	-5.74
Leukemia	CCRF-CEM		-5.71
Colon Cancer	HT29		-5.60
Colon Cancer	HCT-116		-5.57
Colon Cancer	COLO 205	*	-5.56
Breast Cancer	MCF7		-5.55
Colon Cancer	HCC-2998		-5.55
Prostate Cancer	DU-145		-5.53
Non-Small Cell Lung Cancer	HOP-92		-5.53
Colon Cancer	KM12		-5.53
CNS Cancer	SNB-75		-5.53
Renal Cancer	RXF 393		-5.52
Ovarian Cancer	OVCAR-3	*	-5.51
Melanoma	SK-MEL-5		-5.51
Renal Cancer	786-0		-5.51
Non-Small Cell Lung Cancer	EKVX		-5.51
CNS Cancer	SF-539		-5.50
Melanoma	M14		-5.50
Non-Small Cell Lung Cancer	NCI-H23	*	-5.50
Renal Cancer	ACHN		-5.49
Ovarian Cancer	NCI/ADR-RES		-5.49
CNS Cancer	SF-268		-5.49
Renal Cancer	CAKI-1		-5.49
Prostate Cancer	PC-3		-5.48
Melanoma	SK-MEL-28		-5.48
Renal Cancer	UO-31		-5.48
Renal Cancer	TK-10		-5.48
CNS Cancer	U251	*	-5.48
Breast Cancer	MDA-MB-468		-5.47
Ovarian Cancer	SK-OV-3		-5.47
Renal Cancer	A498		-5.47
Ovarian Cancer	OVCAR-5	*	-5.46
Breast Cancer	BT-549		-5.46
Non-Small Cell Lung Cancer	NCI-H522	*	-5.46
CNS Cancer	SF-295	*	-5.45
Non-Small Cell Lung Cancer	A549/ATCC		-5.45
Non-Small Cell Lung Cancer	NCI-H322M		-5.45
Leukemia	MOLT-4		-5.45
Non-Small Cell Lung Cancer	HOP-62		-5.45
Breast Cancer	MDA-MB-231/ATCC	*	-5.43
CNS Cancer	SNB-19		-5.42
Ovarian Cancer	OVCAR-8		-5.42
Ovarian Cancer	IGROV1		-5.41
Melanoma	SK-MEL-2		-5.41
Melanoma	MALME-3M		-5.41
Melanoma	UACC-257		-5.40
Colon Cancer	SW-620	*	-5.40
Renal Cancer	SN12C		-5.40
Leukemia	HL-60(TB)		-5.40
Ovarian Cancer	OVCAR-4		-5.40
Breast Cancer	T-47D		-5.39
Non-Small Cell Lung Cancer	NCI-H460		-5.39
Non-Small Cell Lung Cancer	NCI-H226		-5.39
Melanoma	UACC-62	*	-5.38
Leukemia	RPMI-8226		-5.37
Breast Cancer	HS 578T		-5.30

Log10 High Conc : -4.0

National Cancer Institute Developmental Therapeutics Program Waterfall Graph LC50	NSC : D - 783211/2	Units :Molar	SSPL :0YLV	EXP. ID :1504NS69
	Report Date :August 01, 2018		Test Date :April 13, 2015	

Panel	Cell Name	Hollow Fiber	LC50
Colon Cancer	HCT-15		-5.36
Melanoma	MDA-MB-435	*	-5.32
Prostate Cancer	DU-145		-5.26
Melanoma	SK-MEL-5		-5.25
Colon Cancer	HCC-2998		-5.25
Non-Small Cell Lung Cancer	HOP-92		-5.24
CNS Cancer	SNB-75		-5.24
Ovarian Cancer	OVCAR-3	*	-5.23
CNS Cancer	SF-539		-5.23
Renal Cancer	ACHN		-5.23
Colon Cancer	KM12		-5.22
Non-Small Cell Lung Cancer	EKVX		-5.22
Renal Cancer	RXF 393		-5.22
Renal Cancer	CAKI-1		-5.21
Non-Small Cell Lung Cancer	NCI-H23	*	-5.21
Ovarian Cancer	SK-OV-3		-5.21
Melanoma	SK-MEL-28		-5.20
Prostate Cancer	PC-3		-5.20
Renal Cancer	UO-31		-5.19
Renal Cancer	TK-10		-5.19
CNS Cancer	U251	*	-5.19
CNS Cancer	SF-268		-5.18
Non-Small Cell Lung Cancer	NCI-H322M		-5.17
Ovarian Cancer	OVCAR-5	*	-5.17
Breast Cancer	MDA-MB-468		-5.17
Breast Cancer	BT-549		-5.16
CNS Cancer	SF-295	*	-5.16
Renal Cancer	A498		-5.16
Renal Cancer	786-0		-5.16
Melanoma	M14		-5.16
Melanoma	UACC-257		-5.15
Melanoma	SK-MEL-2		-5.14
Non-Small Cell Lung Cancer	HOP-62		-5.14
Breast Cancer	MDA-MB-231/ATCC	*	-5.12
Renal Cancer	SN12C		-5.10
Breast Cancer	HS 578T		> -4.00

Log10 High Conc : -4.0

National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

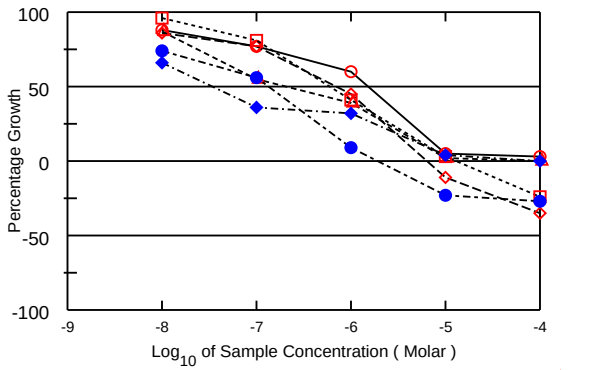
NSC : D - 775402 / 2= NMS-873	Experiment ID : 1406NS10	Test Type : 08	Units : Molar
Report Date : August 01, 2018	Test Date : June 30, 2014	QNS :	MC :
COMI : GPHR-00223549-06	Stain Reagent : SRB Dual-Pass Related	SSPL : 0YZE	

Log10 Concentration

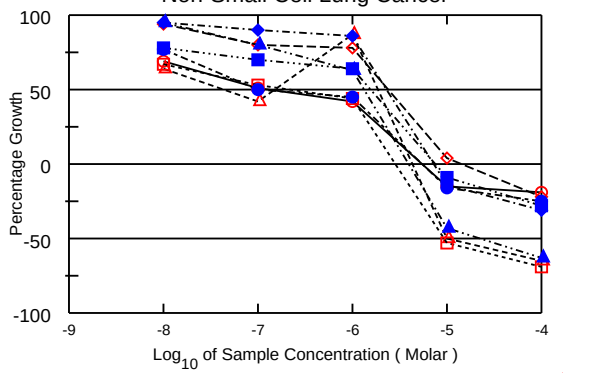
Panel/Cell Line	Time Zero	Mean Optical Densities Ctrl	-8.0	-7.0	-6.0	-5.0	-4.0	Percent Growth -8.0	-7.0	-6.0	-5.0	-4.0	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.593	2.718	2.460	2.225	1.877	0.689	0.667	88	77	60	5	3	1.54E-6	> 1.00E-4	> 1.00E-4
HL-60(TB)	0.777	2.748	2.471	2.300	1.665	0.691	0.502	86	77	45	-11	-35	7.02E-7	6.35E-6	> 1.00E-4
K-562	0.358	2.475	2.206	1.530	1.178	0.397	0.367	87	55	39	2	0	2.10E-7	> 1.00E-4	> 1.00E-4
MOLT-4	0.624	2.589	2.517	2.210	1.428	0.681	0.475	96	81	41	3	-24	5.91E-7	1.28E-5	> 1.00E-4
RPMI-8226	0.899	2.788	2.302	1.957	1.076	0.696	0.657	74	56	9	-23	-27	1.34E-7	1.96E-6	> 1.00E-4
SR	0.404	1.848	1.358	0.921	0.867	0.468	0.408	66	36	32	4	0	3.40E-8	> 1.00E-4	> 1.00E-4
Non-Small Cell Lung Cancer															
EKVX	0.699	1.894	1.522	1.309	1.203	0.596	0.566	69	51	42	-15	-19	1.30E-7	5.50E-6	> 1.00E-4
HOP-62	0.511	1.882	1.805	1.614	1.579	0.563	0.401	94	80	78	4	-22	2.38E-6	1.41E-5	> 1.00E-4
HOP-92	1.575	1.924	1.798	1.721	1.880	0.792	0.556	64	42	87	-50	-65	.	4.34E-6	1.04E-5
NCI-H226	1.458	3.122	2.579	2.339	2.194	0.679	0.455	67	53	44	-53	-69	2.16E-7	2.84E-6	9.22E-6
NCI-H23	0.585	1.882	1.579	1.229	1.172	0.492	0.441	77	50	45	-16	-25	9.71E-8	5.48E-6	> 1.00E-4
NCI-H322M	0.779	2.313	2.229	2.166	2.093	0.667	0.541	95	90	86	-14	-31	2.27E-6	7.17E-6	> 1.00E-4
NCI-H460	0.342	3.208	3.071	2.631	2.146	0.195	0.127	95	80	63	-43	-63	1.32E-6	3.92E-6	2.22E-5
NCI-H522	0.911	2.703	2.306	2.160	2.065	0.832	0.656	78	70	64	-9	-28	1.57E-6	7.61E-6	> 1.00E-4
Colon Cancer															
COLO 205	0.485	2.147	2.053	1.954	1.548	0.457	0.454	94	88	64	-6	-6	1.58E-6	8.26E-6	> 1.00E-4
HCC-2998	0.720	2.408	2.430	2.099	1.594	0.109	0.173	101	82	52	-85	-76	1.03E-6	2.39E-6	5.55E-6
HCT-116	0.302	2.822	2.473	2.023	1.443	0.176	0.227	86	68	45	-42	-25	6.22E-7	3.31E-6	> 1.00E-4
HCT-15	0.303	2.164	1.877	1.794	1.364	0.249	0.243	85	80	57	-18	-20	1.24E-6	5.78E-6	> 1.00E-4
HT29	0.205	1.560	1.469	1.441	1.126	0.244	0.188	93	91	68	3	-8	1.89E-6	1.80E-5	> 1.00E-4
KM12	0.502	2.744	2.718	2.507	2.059	0.235	0.189	99	89	69	-53	-62	1.44E-6	3.68E-6	9.40E-6
SW-620	0.348	2.758	2.646	2.321	2.152	0.255	0.170	95	82	75	-27	-51	1.76E-6	5.46E-6	8.86E-5
CNS Cancer															
SF-268	0.880	2.473	2.439	2.266	2.024	0.221	0.290	98	87	72	-75	-67	1.41E-6	3.09E-6	6.76E-6
SF-295	0.628	2.460	2.059	1.615	1.249	0.198	0.246	78	54	34	-68	-61	1.56E-7	2.14E-6	6.60E-6
SF-539	1.038	2.922	2.608	2.378	2.191	0.354	0.405	83	71	61	-66	-61	1.22E-6	3.03E-6	7.50E-6
SNB-75	0.981	1.892	1.677	1.717	1.584	0.105	0.076	76	81	66	-89	-92	1.27E-6	2.66E-6	5.59E-6
Melanoma															
LOX IMVI	0.263	1.792	1.668	1.446	0.782	0.110	0.139	92	77	34	-58	-47	4.26E-7	2.33E-6	.
MALME-3M	0.682	1.594	1.491	1.375	1.263	0.090	0.132	89	76	64	-87	-81	1.23E-6	2.65E-6	5.69E-6
M14	0.506	2.248	2.064	1.803	1.634	0.364	0.364	89	74	65	-28	-28	1.44E-6	4.98E-6	> 1.00E-4
MDA-MB-435	0.623	3.075	2.874	2.364	1.872	0.137	0.301	92	71	51	-78	-52	1.02E-6	2.48E-6	6.06E-6
SK-MEL-2	0.896	2.559	2.401	2.174	2.077	0.718	0.578	90	77	71	-20	-36	1.70E-6	6.04E-6	> 1.00E-4
SK-MEL-28	0.737	1.963	1.770	1.799	1.788	0.200	0.082	84	87	86	-73	-89	1.68E-6	3.47E-6	7.18E-6
SK-MEL-5	0.919	3.258	2.698	1.620	1.100	0.065	0.070	76	30	8	-93	-92	3.67E-8	1.19E-6	3.74E-6
UACC-257	1.065	2.508	2.421	2.027	1.775	0.754	0.660	94	67	49	-29	-38	8.99E-7	4.24E-6	> 1.00E-4
UACC-62	0.998	3.045	2.551	2.130	2.076	0.303	0.484	76	55	53	-70	-52	1.05E-6	2.69E-6	6.90E-6
Ovarian Cancer															
IGROV1	0.472	2.130	2.151	1.826	1.532	0.223	0.284	101	82	64	-53	-40	1.32E-6	3.53E-6	.
OVCAR-3	0.579	1.779	1.776	1.602	1.408	0.159	0.166	100	85	69	-73	-71	1.36E-6	3.07E-6	6.93E-6
OVCAR-4	0.633	1.690	1.393	1.216	1.117	0.583	0.476	72	55	46	-8	-25	3.54E-7	7.11E-6	> 1.00E-4
OVCAR-5	0.770	2.115	1.891	1.869	1.962	0.305	0.342	83	82	89	-60	-56	1.82E-6	3.93E-6	8.51E-6
OVCAR-8	0.486	2.157	2.073	1.856	1.275	0.493	0.403	95	82	47	0	-17	8.32E-7	1.06E-5	> 1.00E-4
NCI/ADR-RES	0.494	1.677	1.636	1.464	0.875	0.523	0.372	97	82	32	2	-25	4.39E-7	1.23E-5	> 1.00E-4
SK-OV-3	0.813	2.033	1.954	1.925	1.841	1.063	0.783	94	91	84	21	-4	3.45E-6	7.04E-5	> 1.00E-4
Renal Cancer															
A498	1.420	2.544	2.371	2.090	1.846	0.039	0.084	85	60	38	-97	-94	2.76E-7	1.91E-6	4.47E-6
ACHN	0.482	1.922	1.655	1.495	1.275	0.204	0.152	81	70	55	-58	-68	1.11E-6	3.08E-6	8.53E-6
CAKI-1	0.746	2.693	2.222	1.913	1.778	0.806	0.568	76	60	53	3	-24	1.15E-6	1.30E-5	> 1.00E-4
RXF 393	0.737	1.372	1.307	1.269	1.062	0.178	0.283	90	84	51	-76	-62	1.02E-6	2.53E-6	6.26E-6
SN12C	0.724	2.651	2.495	2.250	1.803	0.323	0.368	92	79	56	-55	-49	1.13E-6	3.18E-6	.
TK-10	0.765	2.308	2.094	1.974	1.789	0.851	0.812	86	78	66	6	3	1.86E-6	> 1.00E-4	> 1.00E-4
UO-31	0.637	2.143	1.914	1.784	1.522	0.045	0.171	85	76	59	-93	-73	1.14E-6	2.44E-6	5.21E-6
Prostate Cancer															
PC-3	0.571	1.697	1.511	1.442	1.271	0.535	0.529	83	77	62	-6	-7	1.51E-6	8.07E-6	> 1.00E-4
DU-145	0.420	1.790	1.768	1.679	1.221	0.480	0.529	98	92	58	4	8	1.43E-6	> 1.00E-4	> 1.00E-4
Breast Cancer															
MCF7	0.338	2.030	1.645	1.388	0.931	0.413	0.337	77	62	35	4	0	2.80E-7	8.65E-5	> 1.00E-4
MDA-MB-231/ATCC	0.663	1.634	1.627	1.485	1.312	0.141	0.184	99	85	67	-79	-72	1.31E-6	2.88E-6	6.35E-6
HS 578T	1.105	2.319	2.256	2.113	2.001	1.118	0.904	95	83	74	1	-18	2.12E-6	1.14E-5	> 1.00E-4
BT-549	1.140	2.676	2.319	2.010	1.610	0.555	0.701	77	57	31	-51	-39	1.80E-7	2.36E-6	.
T-47D	0.584	1.550	1.356	1.228	1.116	0.693	0.588	80	67	55	11	0	1.30E-6	> 1.00E-4	> 1.00E-4
MDA-MB-468	0.771	1.746	1.364	1.023	0.875	0.359	0.422	61	26	11	-53	-45	2.04E-8	1.47E-6	.

National Cancer Institute Developmental Therapeutics Program Dose Response Curves	NSC: D - 775402 / 2	SSPL: 0YZE	EXP. ID: 1406NS10
	Report Date: August 01, 2018	Test Date: June 30, 2014	

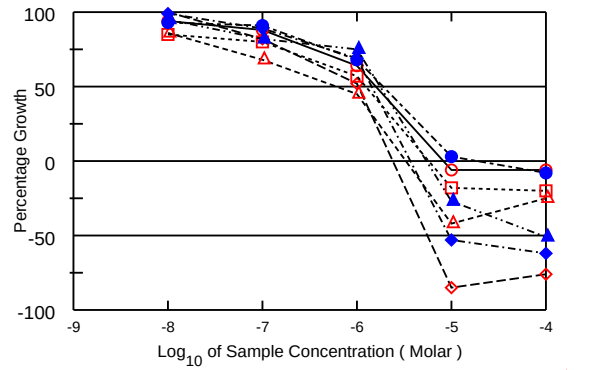
Leukemia



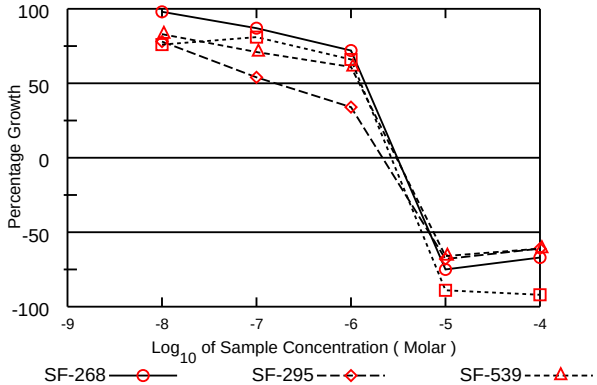
Non-Small Cell Lung Cancer



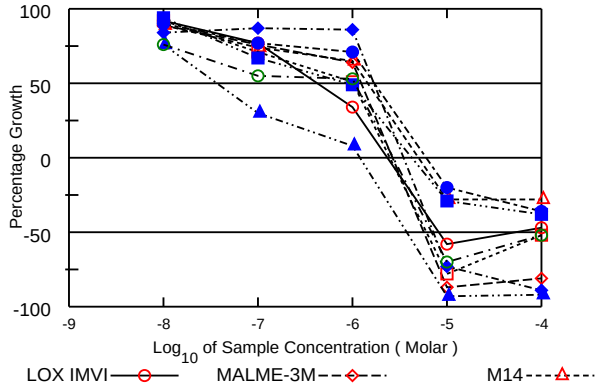
Colon Cancer



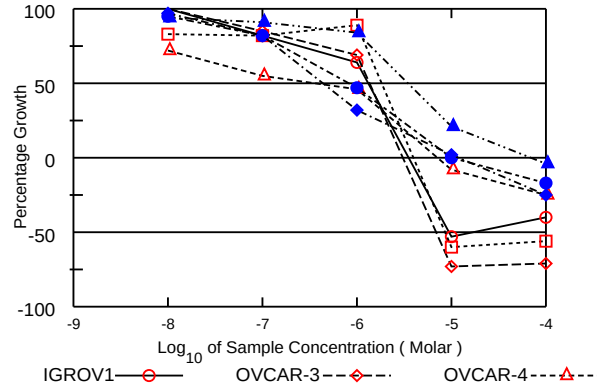
CNS Cancer



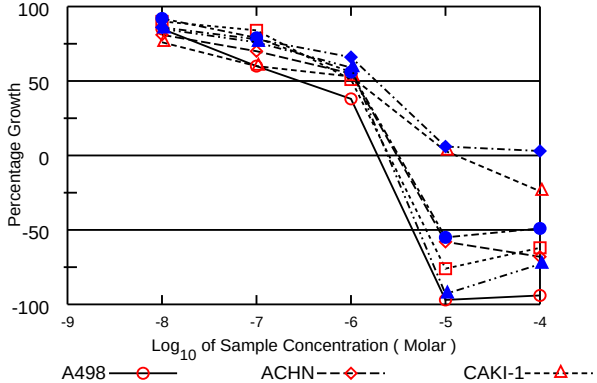
Melanoma



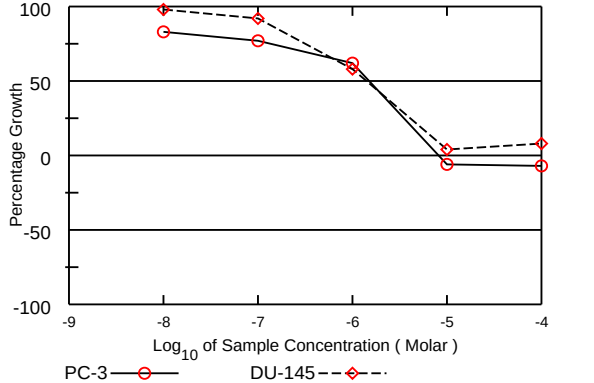
Ovarian Cancer



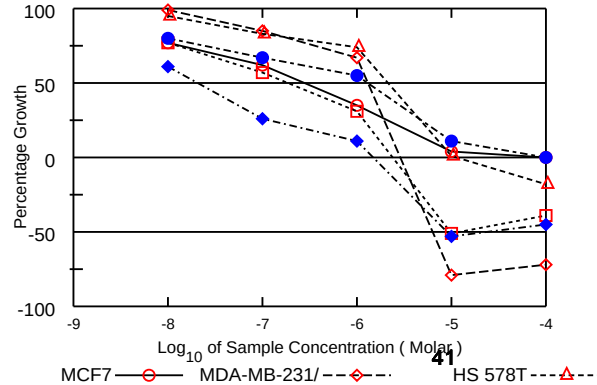
Renal Cancer



Prostate Cancer



Breast Cancer



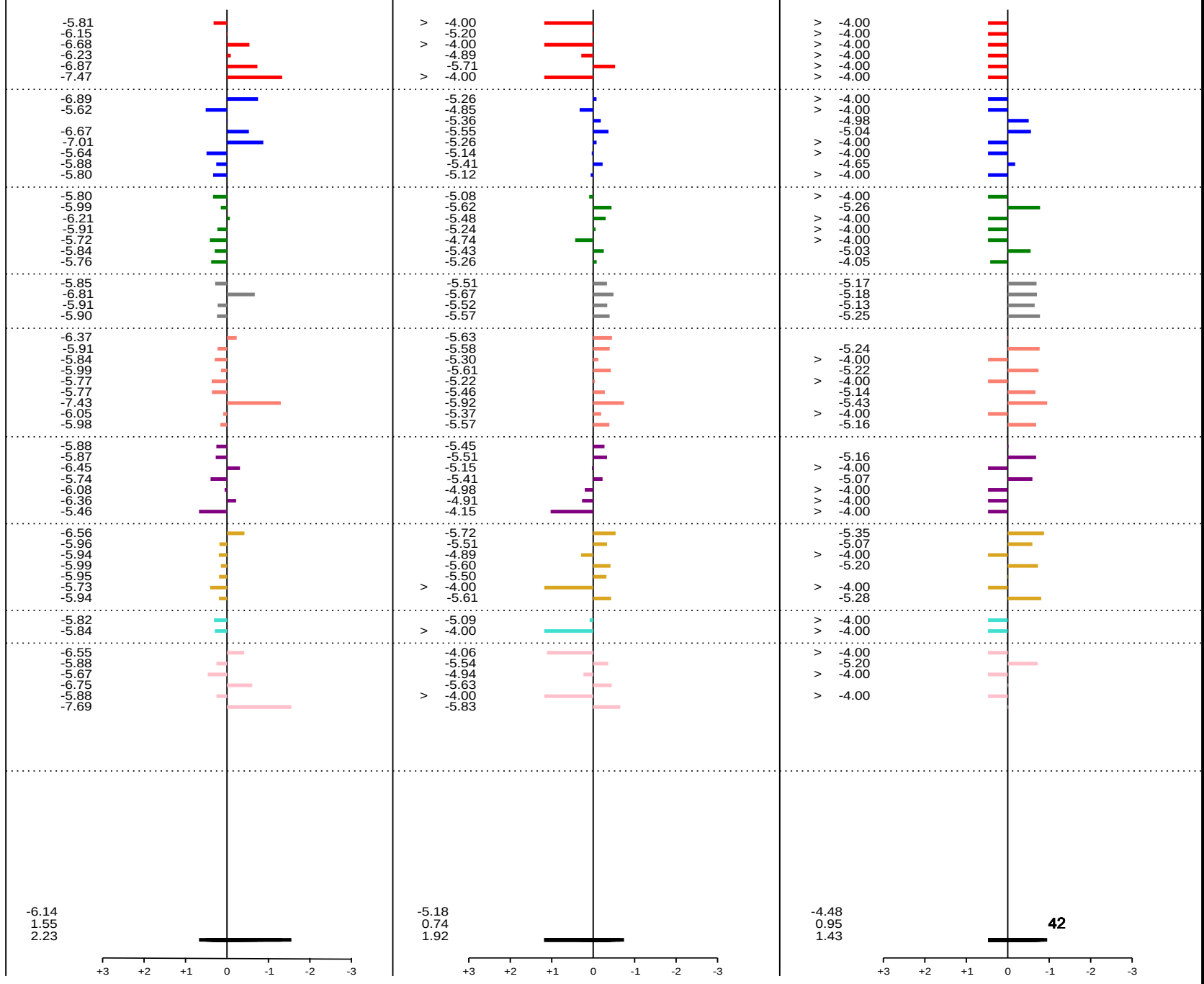
National Cancer Institute Developmental Therapeutics Program

Mean Graphs

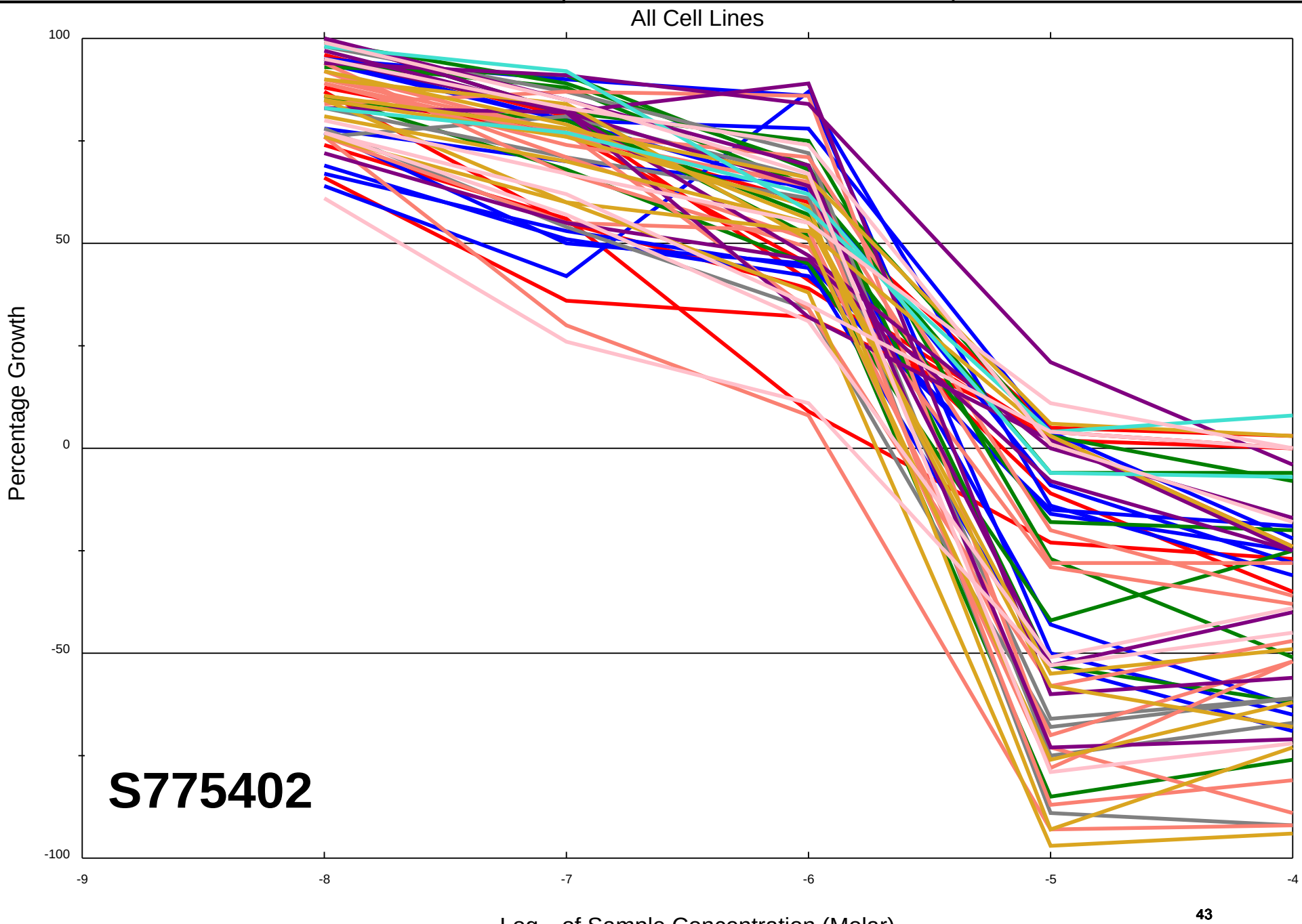
NSC : D - 775402/2 | Units :Molar | SSPL :0YZE | EXP. ID :1406NS10

Report Date :August 01, 2018 | Test Date :June 30, 2014

Panel/Cell Line	Log_{10}GI50	GI50	Log_{10}TGI	TGI	Log_{10}LC50	LC50
Leukemia						
CCRF-CEM	-5.81		> -4.00		> -4.00	
HL-60(TB)	-6.15		-5.20		> -4.00	
K-562	-6.68		> -4.00		> -4.00	
MOLT-4	-6.23		-4.89		> -4.00	
RPMI-8226	-6.87		-5.71		> -4.00	
SR	-7.47		> -4.00		> -4.00	
Non-Small Cell Lung Cancer						
EKVX	-6.89		-5.26		> -4.00	
HOP-62	-5.62		-4.85		> -4.00	
HOP-92			-5.36		-4.98	
NCI-H226	-6.67		-5.55		-5.04	
NCI-H23	-7.01		-5.26		> -4.00	
NCI-H322M	-5.64		-5.14		> -4.00	
NCI-H460	-5.88		-5.41		-4.65	
NCI-H522	-5.80		-5.12		> -4.00	
Colon Cancer						
COLO 205	-5.80		-5.08		> -4.00	
HCC-2998	-5.99		-5.62		-5.26	
HCT-116	-6.21		-5.48		> -4.00	
HCT-15	-5.91		-5.24		> -4.00	
HT29	-5.72		-4.74		> -4.00	
KM12	-5.84		-5.43		-5.03	
SW-620	-5.76		-5.26		-4.05	
CNS Cancer						
SF-268	-5.85		-5.51		-5.17	
SF-295	-6.81		-5.67		-5.18	
SF-539	-5.91		-5.52		-5.13	
SNB-75	-5.90		-5.57		-5.25	
Melanoma						
LOX IMVI	-6.37		-5.63			
MALME-3M	-5.91		-5.58		-5.24	
M14	-5.84		-5.30		> -4.00	
MDA-MB-435	-5.99		-5.61		-5.22	
SK-MEL-2	-5.77		-5.22		> -4.00	
SK-MEL-28	-5.77		-5.46		-5.14	
SK-MEL-5	-7.43		-5.92		-5.43	
UACC-257	-6.05		-5.37		> -4.00	
UACC-62	-5.98		-5.57		-5.16	
Ovarian Cancer						
IGROV1	-5.88		-5.45			
OVCAR-3	-5.87		-5.51		-5.16	
OVCAR-4	-6.45		-5.15		> -4.00	
OVCAR-5	-5.74		-5.41		-5.07	
OVCAR-8	-6.08		-4.98		> -4.00	
NCI/ADR-RES	-6.36		-4.91		> -4.00	
SK-OV-3	-5.46		-4.15		> -4.00	
Renal Cancer						
A498	-6.56		-5.72		-5.35	
ACHN	-5.96		-5.51		-5.07	
CAKI-1	-5.94		-4.89		> -4.00	
RXF 393	-5.99		-5.60		-5.20	
SN12C	-5.95		-5.50			
TK-10	-5.73		> -4.00		> -4.00	
UO-31	-5.94		-5.61		-5.28	
Prostate Cancer						
PC-3	-5.82		-5.09		> -4.00	
DU-145	-5.84		> -4.00		> -4.00	
Breast Cancer						
MCF7	-6.55		-4.06		> -4.00	
MDA-MB-231/ATCC	-5.88		-5.54		-5.20	
HS 578T	-5.67		-4.94		> -4.00	
BT-549	-6.75		-5.63			
T-47D	-5.88		> -4.00		> -4.00	
MDA-MB-468	-7.69		-5.83			
MID	-6.14		-5.18		-4.48	
Delta	1.55		0.74		0.95	
Range	2.23		1.92		1.43	



National Cancer Institute Developmental Therapeutics Program Dose Response Curves	NSC : D - 775402/2	SSPL:0YZE	EXP. ID:1406NS10
	Report Date:August 01, 2018	Test Date:June 30, 2014	

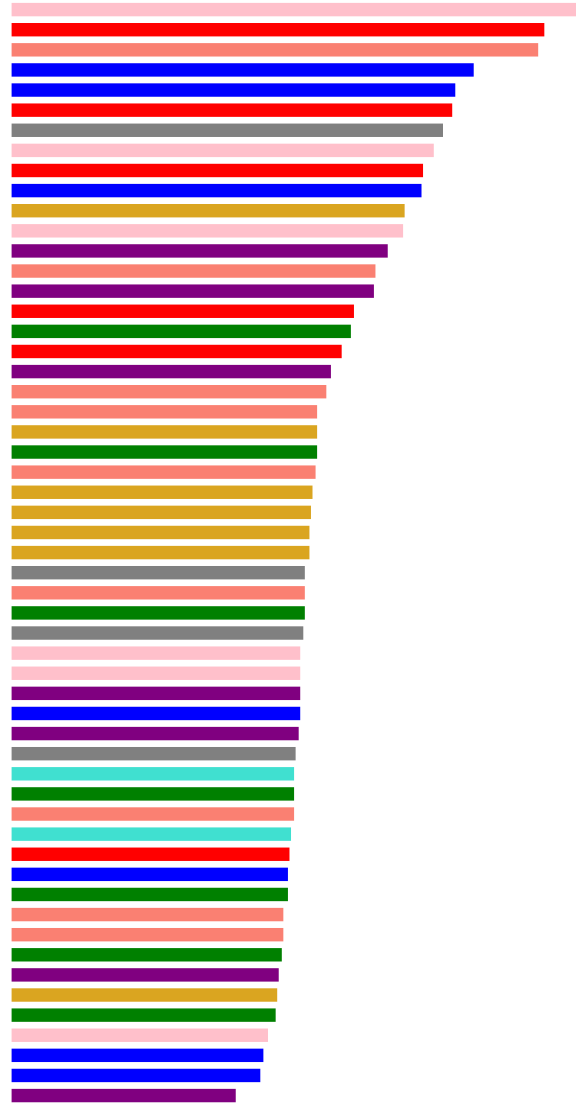


National Cancer Institute Developmental Therapeutics Program
Waterfall Graph GI50

NSC : D - 775402/2 | Units :Molar | SSPL :0YZE | EXP. ID :1406NS10

Report Date :August 01, 2018 | Test Date :June 30, 2014

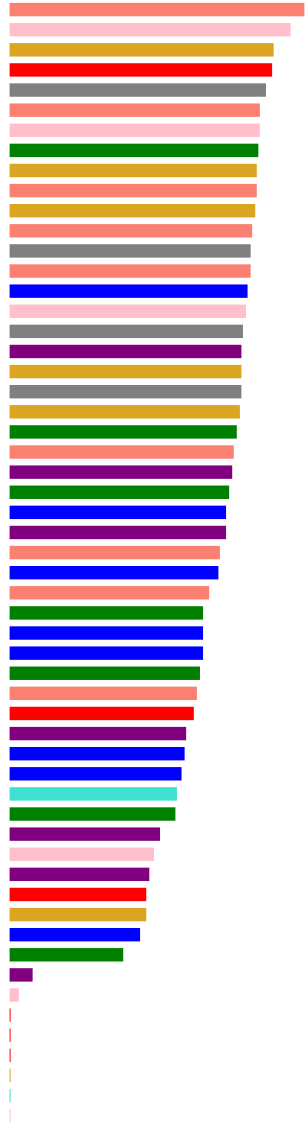
Panel	Cell Name	Hollow Fiber	GI50
Breast Cancer	MDA-MB-468		-7.69
Leukemia	SR		-7.47
Melanoma	SK-MEL-5		-7.43
Non-Small Cell Lung Cancer	NCI-H23	*	-7.01
Non-Small Cell Lung Cancer	EKVX		-6.89
Leukemia	RPMI-8226		-6.87
CNS Cancer	SF-295	*	-6.81
Breast Cancer	BT-549		-6.75
Leukemia	K-562		-6.68
Non-Small Cell Lung Cancer	NCI-H226		-6.67
Renal Cancer	A498		-6.56
Breast Cancer	MCF7		-6.55
Ovarian Cancer	OVCAR-4		-6.45
Melanoma	LOX IMVI	*	-6.37
Ovarian Cancer	NCI/ADR-RES		-6.36
Leukemia	MOLT-4		-6.23
Colon Cancer	HCT-116		-6.21
Leukemia	HL-60(TB)		-6.15
Ovarian Cancer	OVCAR-8		-6.08
Melanoma	UACC-257		-6.05
Melanoma	MDA-MB-435	*	-5.99
Renal Cancer	RXF 393		-5.99
Colon Cancer	HCC-2998		-5.99
Melanoma	UACC-62	*	-5.98
Renal Cancer	ACHN		-5.96
Renal Cancer	SN12C		-5.95
Renal Cancer	UO-31		-5.94
Renal Cancer	CAKI-1		-5.94
CNS Cancer	SF-539		-5.91
Melanoma	MALME-3M		-5.91
Colon Cancer	HCT-15		-5.91
CNS Cancer	SNB-75		-5.90
Breast Cancer	T-47D		-5.88
Breast Cancer	MDA-MB-231/ATCC	*	-5.88
Ovarian Cancer	IGROV1		-5.88
Non-Small Cell Lung Cancer	NCI-H460		-5.88
Ovarian Cancer	OVCAR-3	*	-5.87
CNS Cancer	SF-268		-5.85
Prostate Cancer	DU-145		-5.84
Colon Cancer	KM12		-5.84
Melanoma	M14		-5.84
Prostate Cancer	PC-3		-5.82
Leukemia	CCRF-CEM		-5.81
Non-Small Cell Lung Cancer	NCI-H522	*	-5.80
Colon Cancer	COLO 205	*	-5.80
Melanoma	SK-MEL-28		-5.77
Melanoma	SK-MEL-2		-5.77
Colon Cancer	SW-620	*	-5.76
Ovarian Cancer	OVCAR-5	*	-5.74
Renal Cancer	TK-10		-5.73
Colon Cancer	HT29		-5.72
Breast Cancer	HS 578T		-5.67
Non-Small Cell Lung Cancer	NCI-H322M		-5.64
Non-Small Cell Lung Cancer	HOP-62		-5.62
Ovarian Cancer	SK-OV-3		-5.46



Log10 High Conc :-4.0

National Cancer Institute Developmental Therapeutics Program Waterfall Graph TGI	NSC : D - 775402/2	Units :Molar	SSPL :0YZE	EXP. ID :1406NS10
	Report Date :August 01, 2018		Test Date :June 30, 2014	

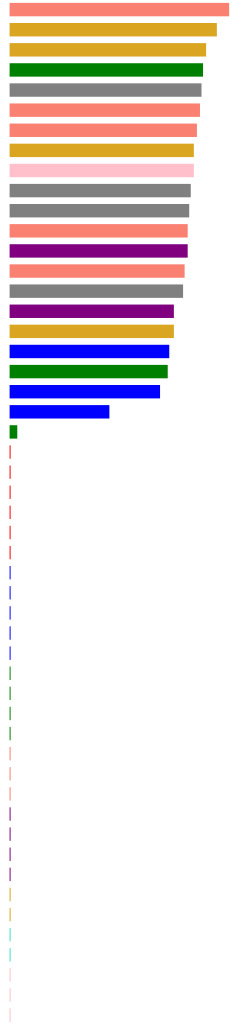
Panel	Cell Name	Hollow Fiber	TGI
Melanoma	SK-MEL-5		-5.92
Breast Cancer	MDA-MB-468		-5.83
Renal Cancer	A498		-5.72
Leukemia	RPMI-8226		-5.71
CNS Cancer	SF-295	*	-5.67
Melanoma	LOX IMVI	*	-5.63
Breast Cancer	BT-549		-5.63
Colon Cancer	HCC-2998		-5.62
Renal Cancer	UO-31		-5.61
Melanoma	MDA-MB-435	*	-5.61
Renal Cancer	RXF 393		-5.60
Melanoma	MALME-3M		-5.58
CNS Cancer	SNB-75		-5.57
Melanoma	UACC-62	*	-5.57
Non-Small Cell Lung Cancer	NCI-H226		-5.55
Breast Cancer	MDA-MB-231/ATCC	*	-5.54
CNS Cancer	SF-539		-5.52
Ovarian Cancer	OVCAR-3	*	-5.51
Renal Cancer	ACHN		-5.51
CNS Cancer	SF-268		-5.51
Renal Cancer	SN12C		-5.50
Colon Cancer	HCT-116		-5.48
Melanoma	SK-MEL-28		-5.46
Ovarian Cancer	IGROV1		-5.45
Colon Cancer	KM12		-5.43
Non-Small Cell Lung Cancer	NCI-H460		-5.41
Ovarian Cancer	OVCAR-5	*	-5.41
Melanoma	UACC-257		-5.37
Non-Small Cell Lung Cancer	HOP-92		-5.36
Melanoma	M14		-5.30
Colon Cancer	SW-620	*	-5.26
Non-Small Cell Lung Cancer	NCI-H23	*	-5.26
Non-Small Cell Lung Cancer	EKVX		-5.26
Colon Cancer	HCT-15		-5.24
Melanoma	SK-MEL-2		-5.22
Leukemia	HL-60(TB)		-5.20
Ovarian Cancer	OVCAR-4		-5.15
Non-Small Cell Lung Cancer	NCI-H322M		-5.14
Non-Small Cell Lung Cancer	NCI-H522	*	-5.12
Prostate Cancer	PC-3		-5.09
Colon Cancer	COLO 205	*	-5.08
Ovarian Cancer	OVCAR-8		-4.98
Breast Cancer	HS 578T		-4.94
Ovarian Cancer	NCI/ADR-RES		-4.91
Leukemia	MOLT-4		-4.89
Renal Cancer	CAKI-1		-4.89
Non-Small Cell Lung Cancer	HOP-62		-4.85
Colon Cancer	HT29		-4.74
Ovarian Cancer	SK-OV-3		-4.15
Breast Cancer	MCF7		-4.06
Leukemia	CCRF-CEM		> -4.00
Leukemia	K-562		> -4.00
Leukemia	SR		> -4.00
Renal Cancer	TK-10		> -4.00
Prostate Cancer	DU-145		> -4.00
Breast Cancer	T-47D		> -4.00



Log10 High Conc : -4.0

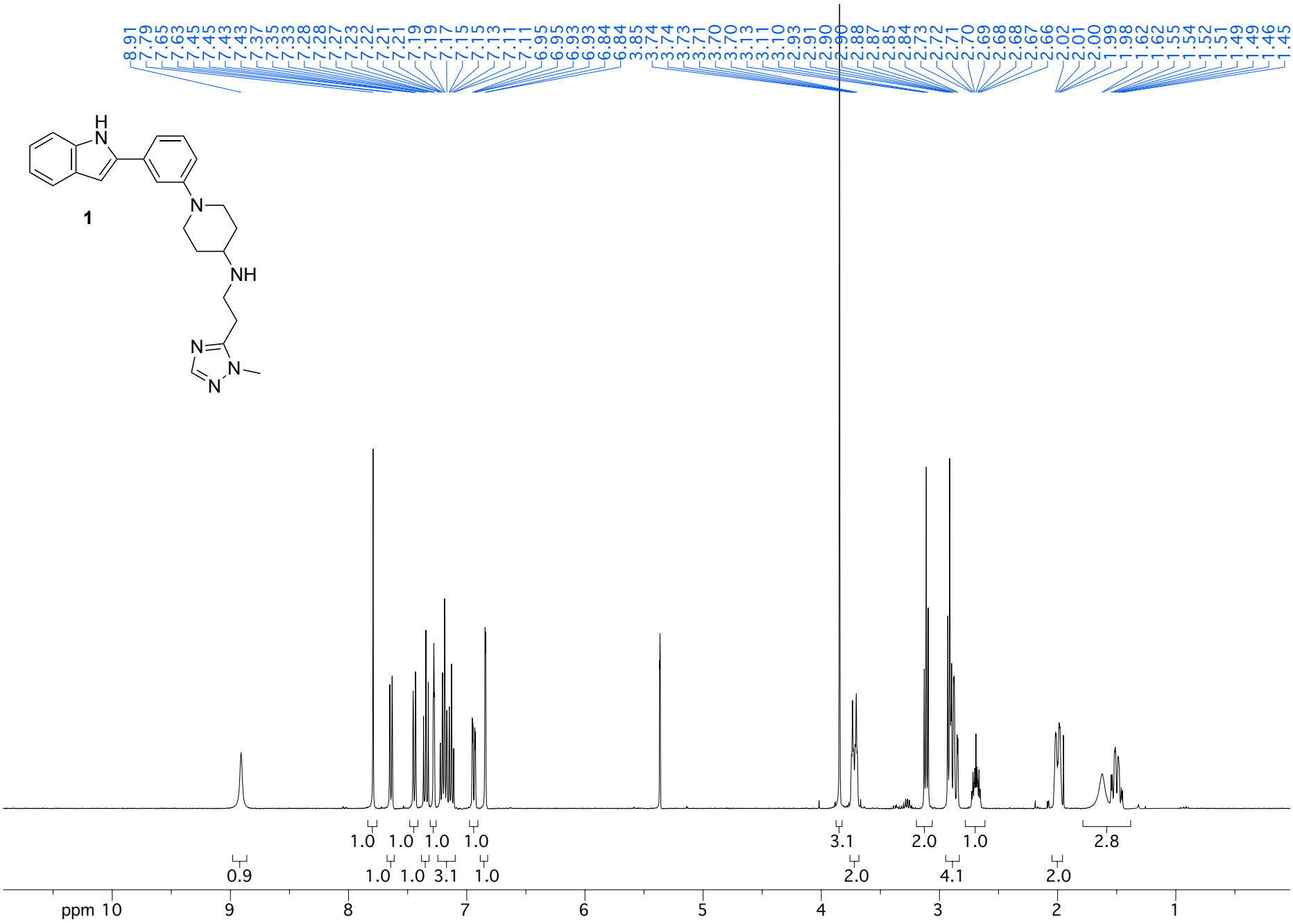
National Cancer Institute Developmental Therapeutics Program Waterfall Graph LC50	NSC : D - 775402/2	Units :Molar	SSPL :0YZE	EXP. ID :1406NS10
	Report Date :August 01, 2018		Test Date :June 30, 2014	

Panel	Cell Name	Hollow Fiber	LC50
Melanoma	SK-MEL-5		-5.43
Renal Cancer	A498		-5.35
Renal Cancer	UO-31		-5.28
Colon Cancer	HCC-2998		-5.26
CNS Cancer	SNB-75		-5.25
Melanoma	MALME-3M		-5.24
Melanoma	MDA-MB-435	*	-5.22
Renal Cancer	RXF 393		-5.20
Breast Cancer	MDA-MB-231/ATCC	*	-5.20
CNS Cancer	SF-295	*	-5.18
CNS Cancer	SF-268		-5.17
Melanoma	UACC-62	*	-5.16
Ovarian Cancer	OVCAR-3	*	-5.16
Melanoma	SK-MEL-28		-5.14
CNS Cancer	SF-539		-5.13
Ovarian Cancer	OVCAR-5	*	-5.07
Renal Cancer	ACHN		-5.07
Non-Small Cell Lung Cancer	NCI-H226		-5.04
Colon Cancer	KM12		-5.03
Non-Small Cell Lung Cancer	HOP-92		-4.98
Non-Small Cell Lung Cancer	NCI-H460		-4.65
Colon Cancer	SW-620	*	-4.05
Leukemia	CCRF-CEM		> -4.00
Leukemia	HL-60(TB)		> -4.00
Leukemia	K-562		> -4.00
Leukemia	MOLT-4		> -4.00
Leukemia	RPMI-8226		> -4.00
Leukemia	SR		> -4.00
Non-Small Cell Lung Cancer	EKVX		> -4.00
Non-Small Cell Lung Cancer	HOP-62		> -4.00
Non-Small Cell Lung Cancer	NCI-H23	*	> -4.00
Non-Small Cell Lung Cancer	NCI-H322M		> -4.00
Non-Small Cell Lung Cancer	NCI-H522	*	> -4.00
Colon Cancer	COLO 205	*	> -4.00
Colon Cancer	HCT-116		> -4.00
Colon Cancer	HCT-15		> -4.00
Colon Cancer	HT29		> -4.00
Melanoma	M14		> -4.00
Melanoma	SK-MEL-2		> -4.00
Melanoma	UACC-257		> -4.00
Ovarian Cancer	OVCAR-4		> -4.00
Ovarian Cancer	OVCAR-8		> -4.00
Ovarian Cancer	NCI/ADR-RES		> -4.00
Ovarian Cancer	SK-OV-3		> -4.00
Renal Cancer	CAKI-1		> -4.00
Renal Cancer	TK-10		> -4.00
Prostate Cancer	PC-3		> -4.00
Prostate Cancer	DU-145		> -4.00
Breast Cancer	MCF7		> -4.00
Breast Cancer	HS 578T		> -4.00
Breast Cancer	T-47D		> -4.00

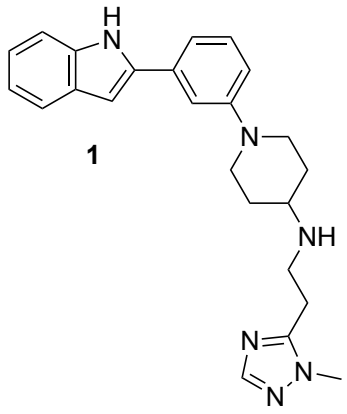


Log10 High Conc : -4.0

1H NMR (400 MHz, CD2Cl2)

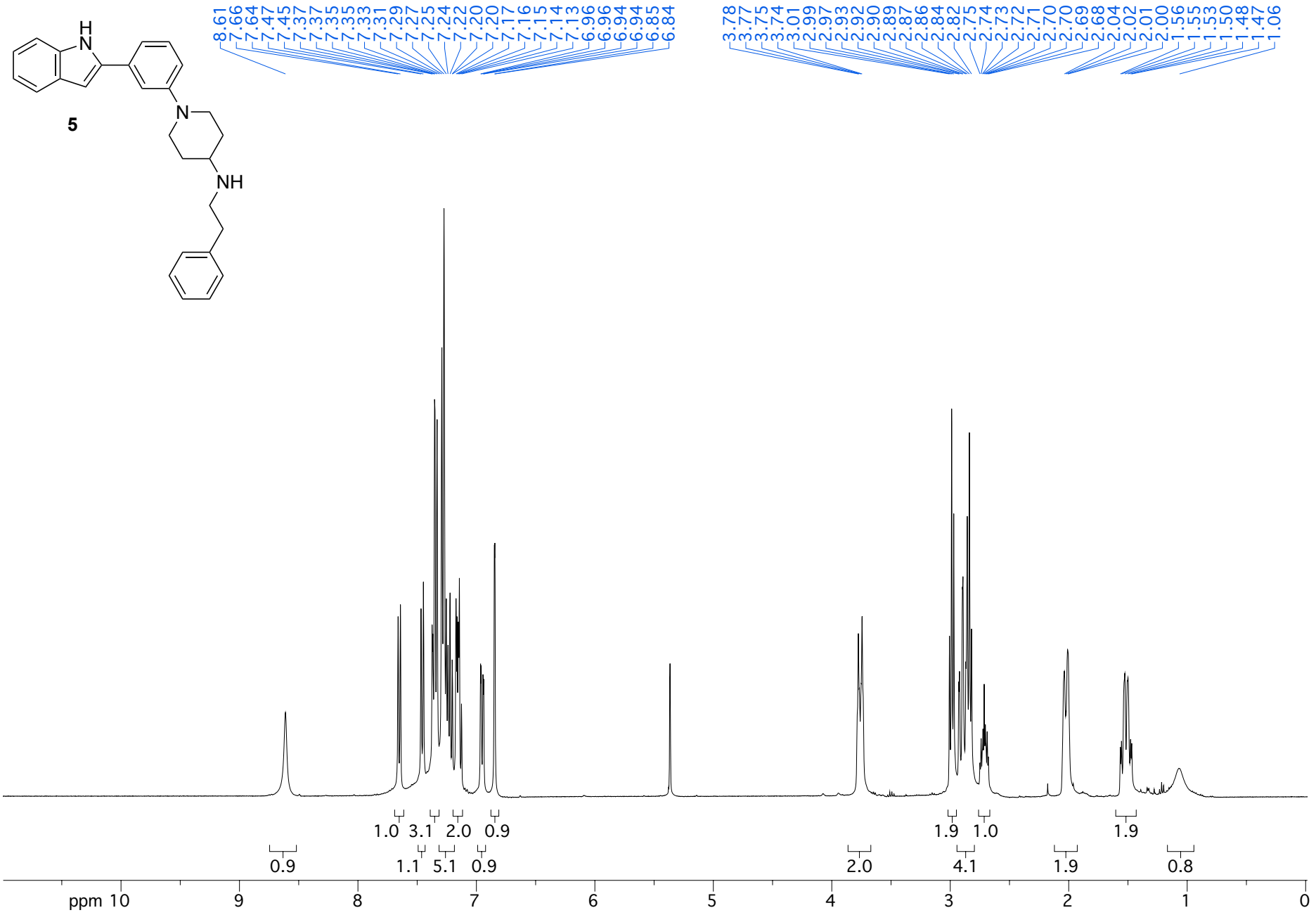


13C NMR (100 MHz, CD2Cl2)

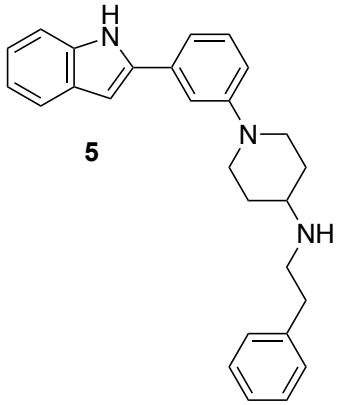


1

1H NMR (400 MHz, CD2Cl2)

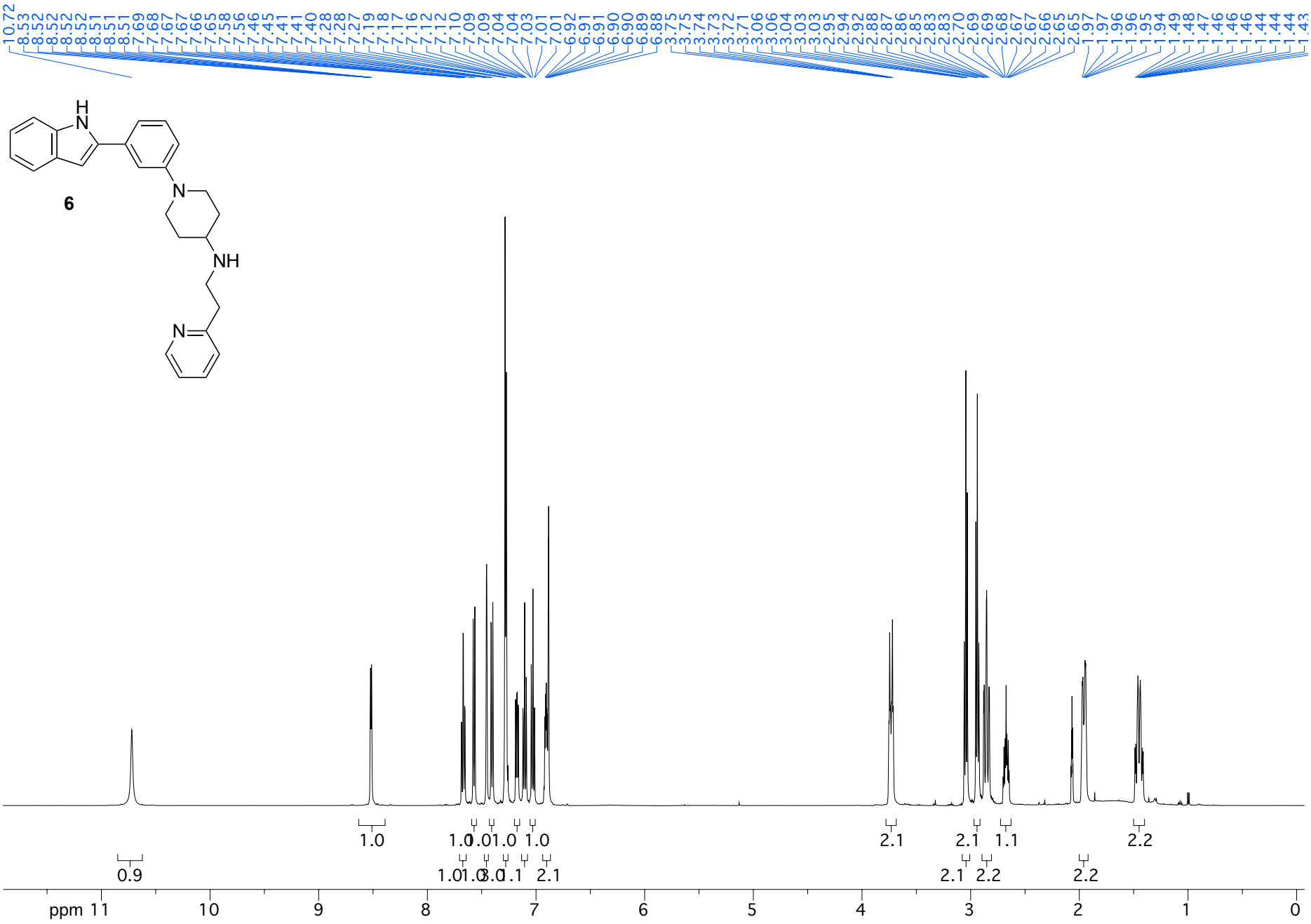


13C NMR (100 MHz, CD2Cl2)

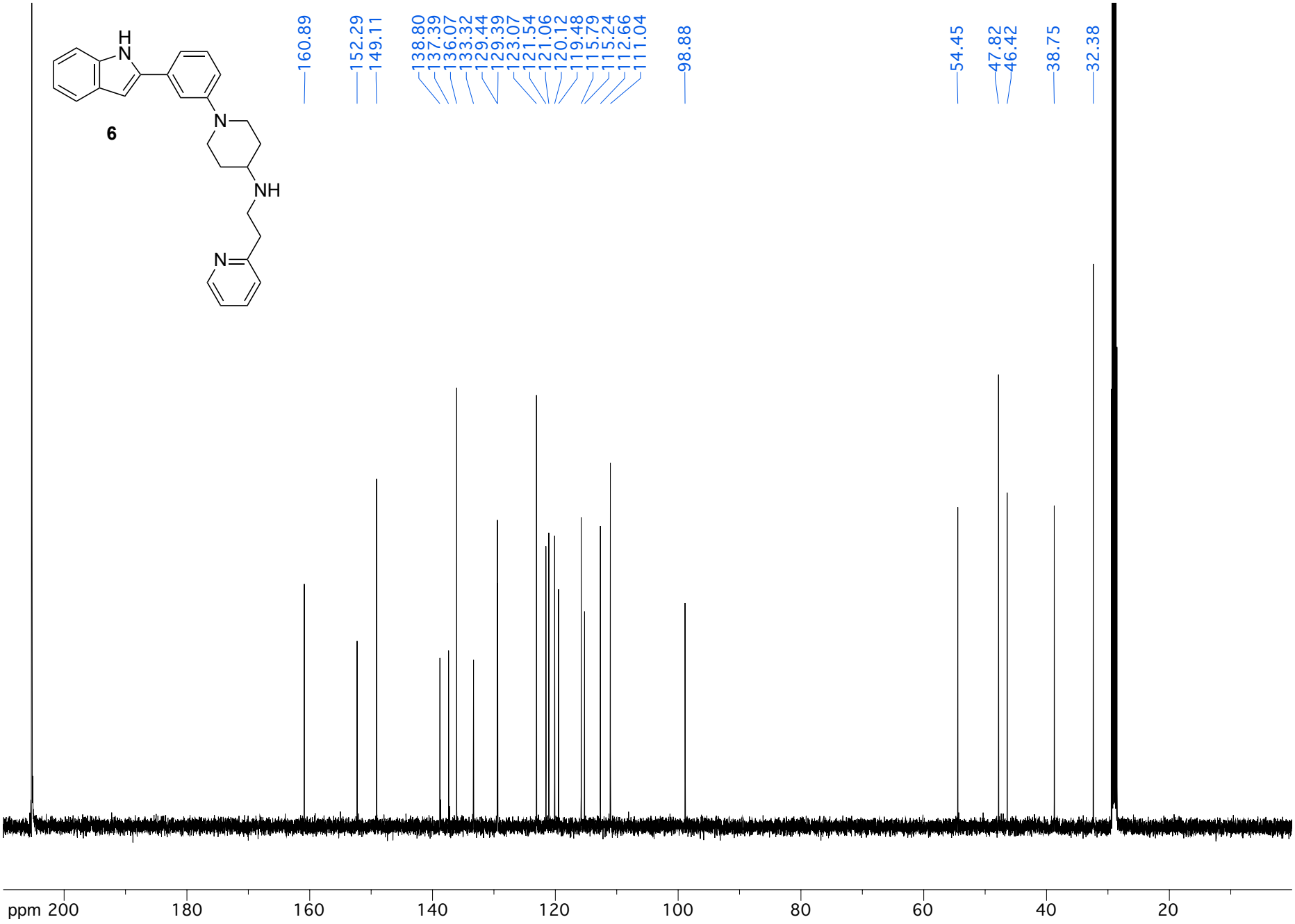


5

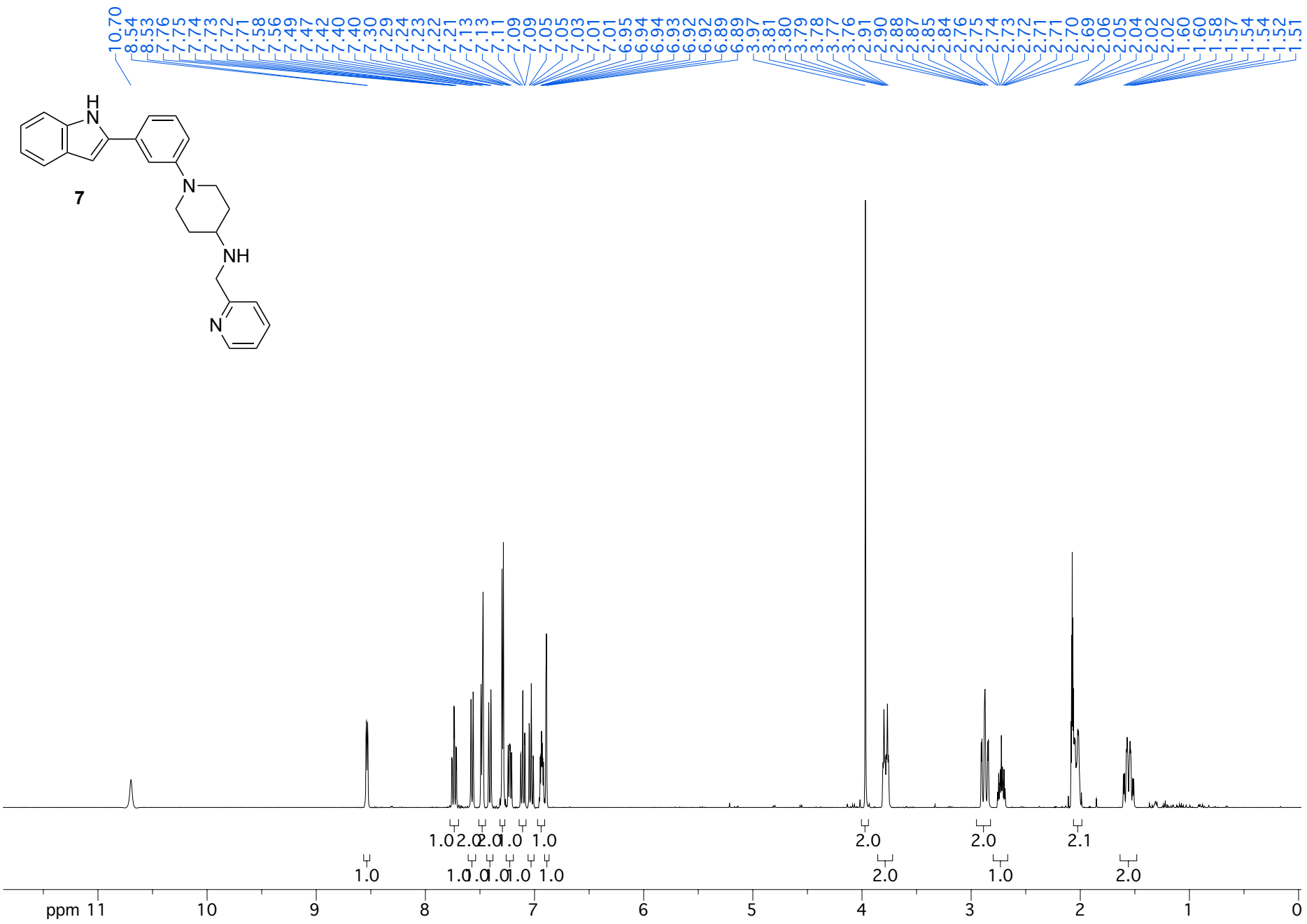
1H NMR (400 MHz, acetone-d6)



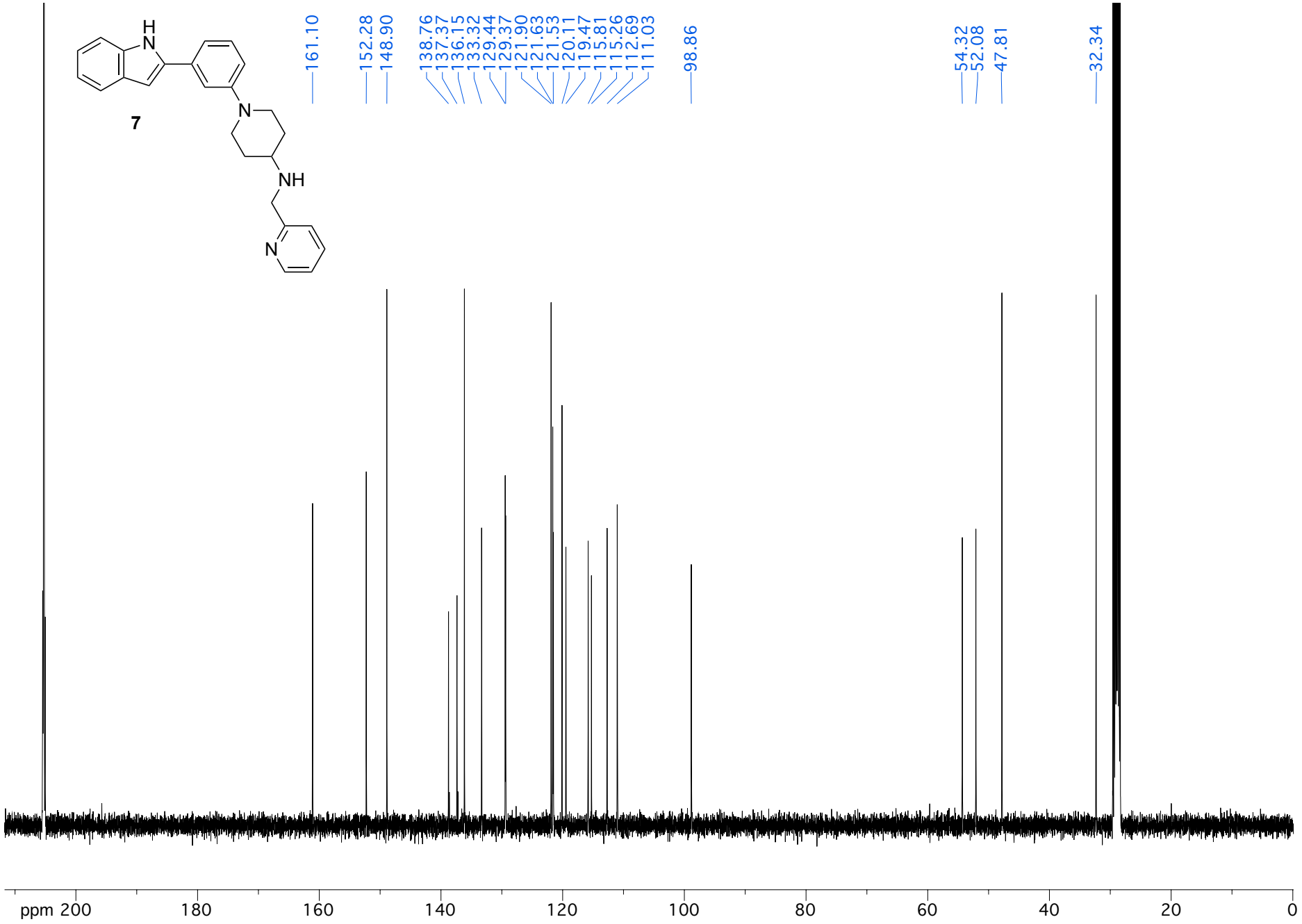
13C NMR (100 MHz, acetone-d6)



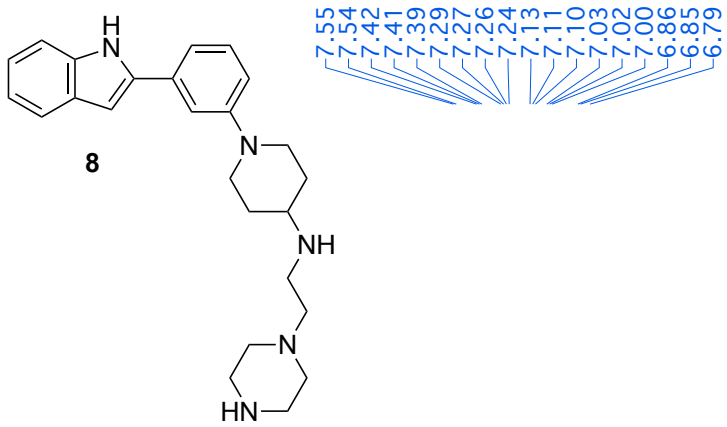
1H NMR (400 MHz, acetone-d6)



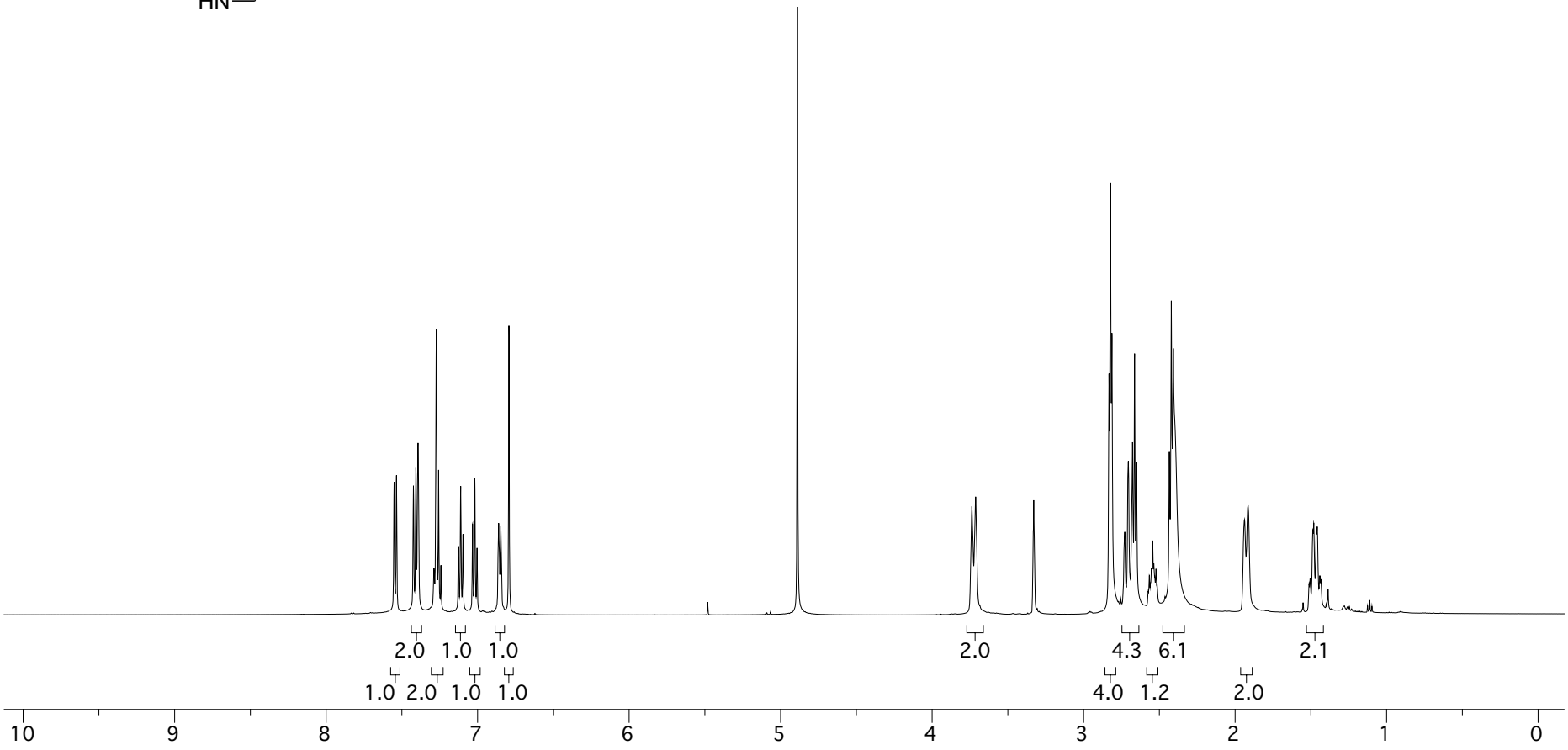
13C NMR (100 MHz, acetone-d6)



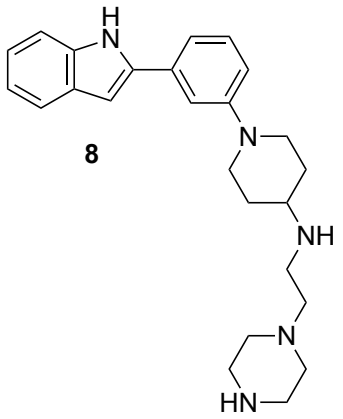
1H NMR (500 MHz, CD3OD)



8

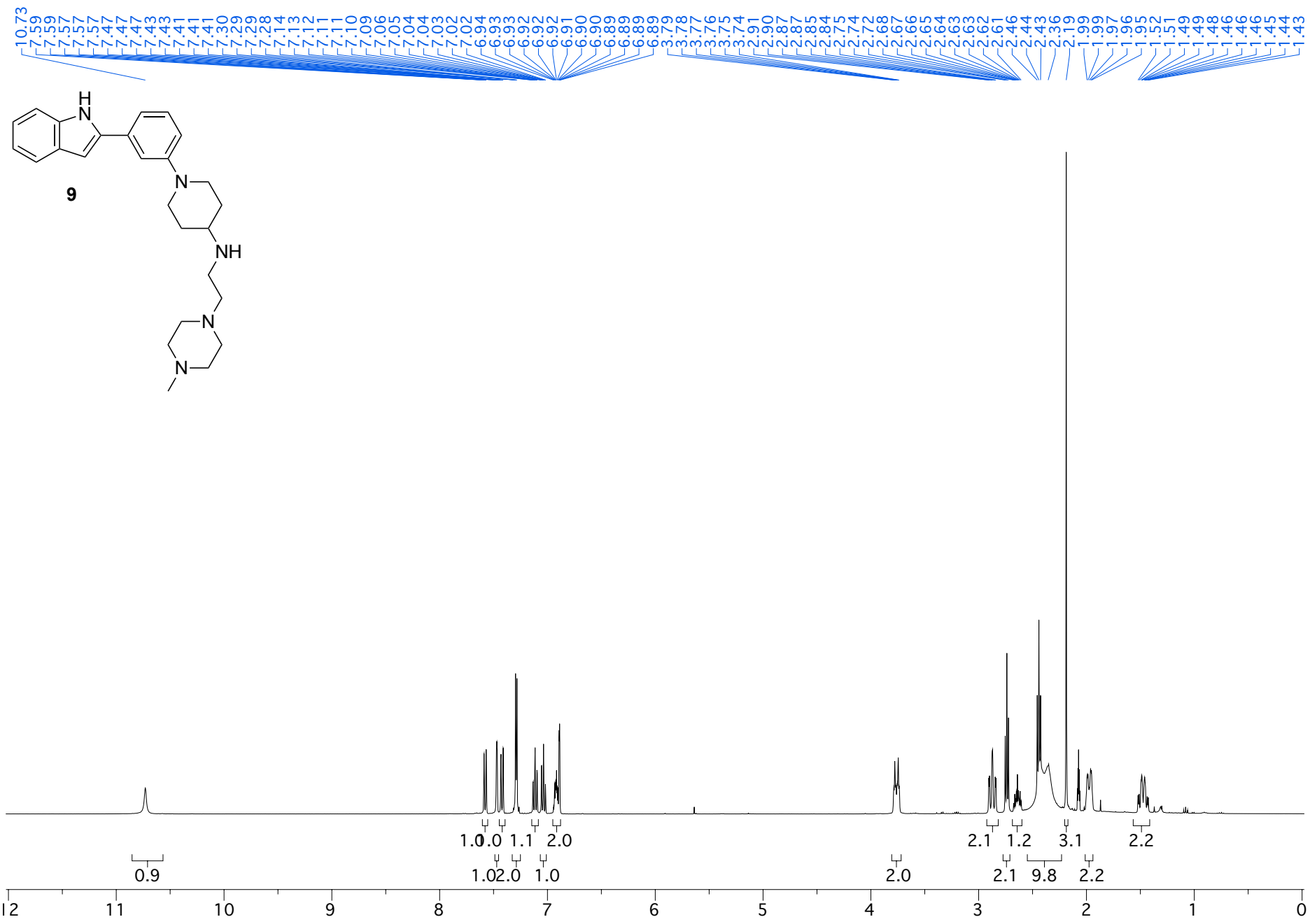


13C NMR (125 MHz, CD3OD)

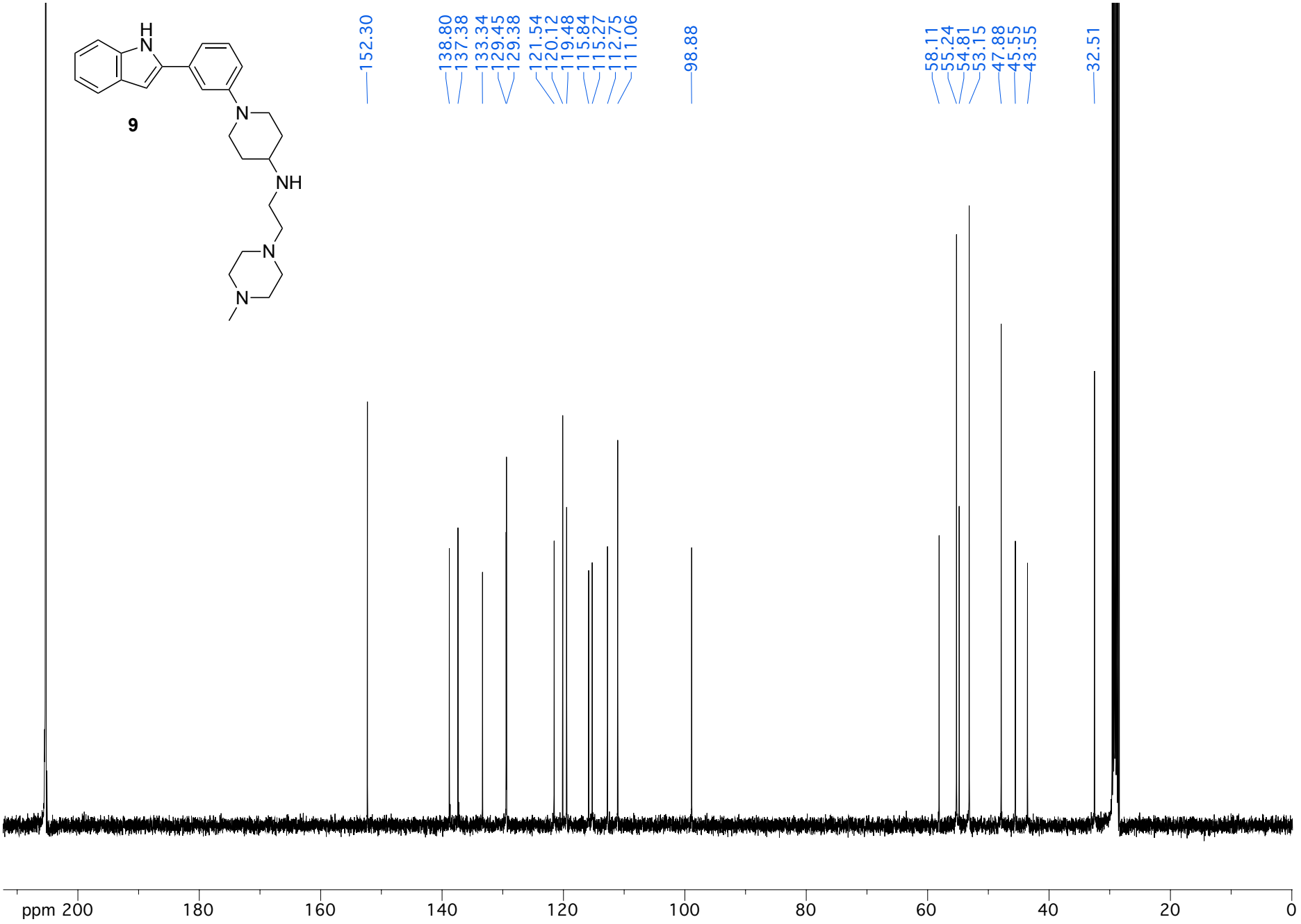


8

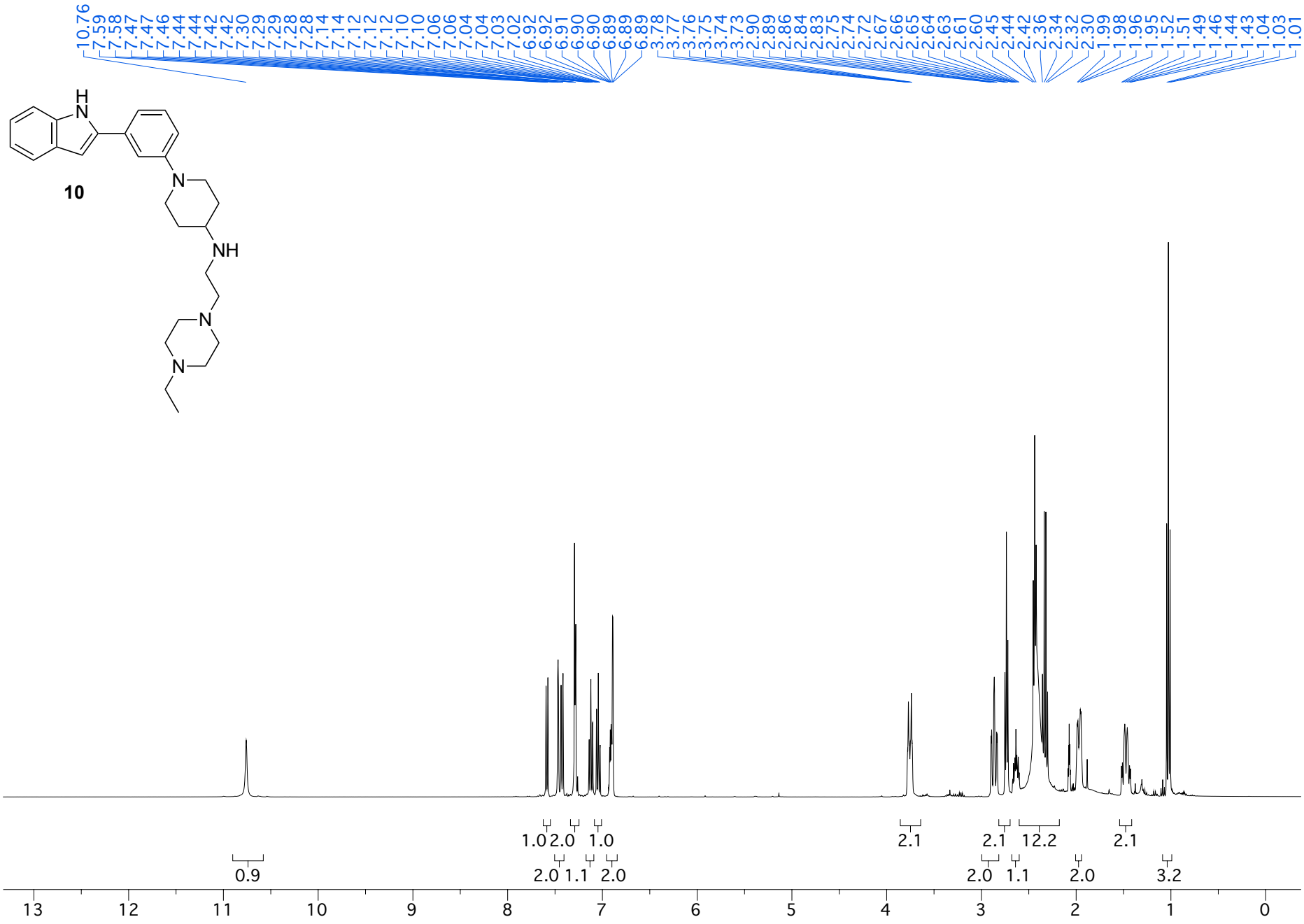
1H NMR (400 MHz, acetone-d6)



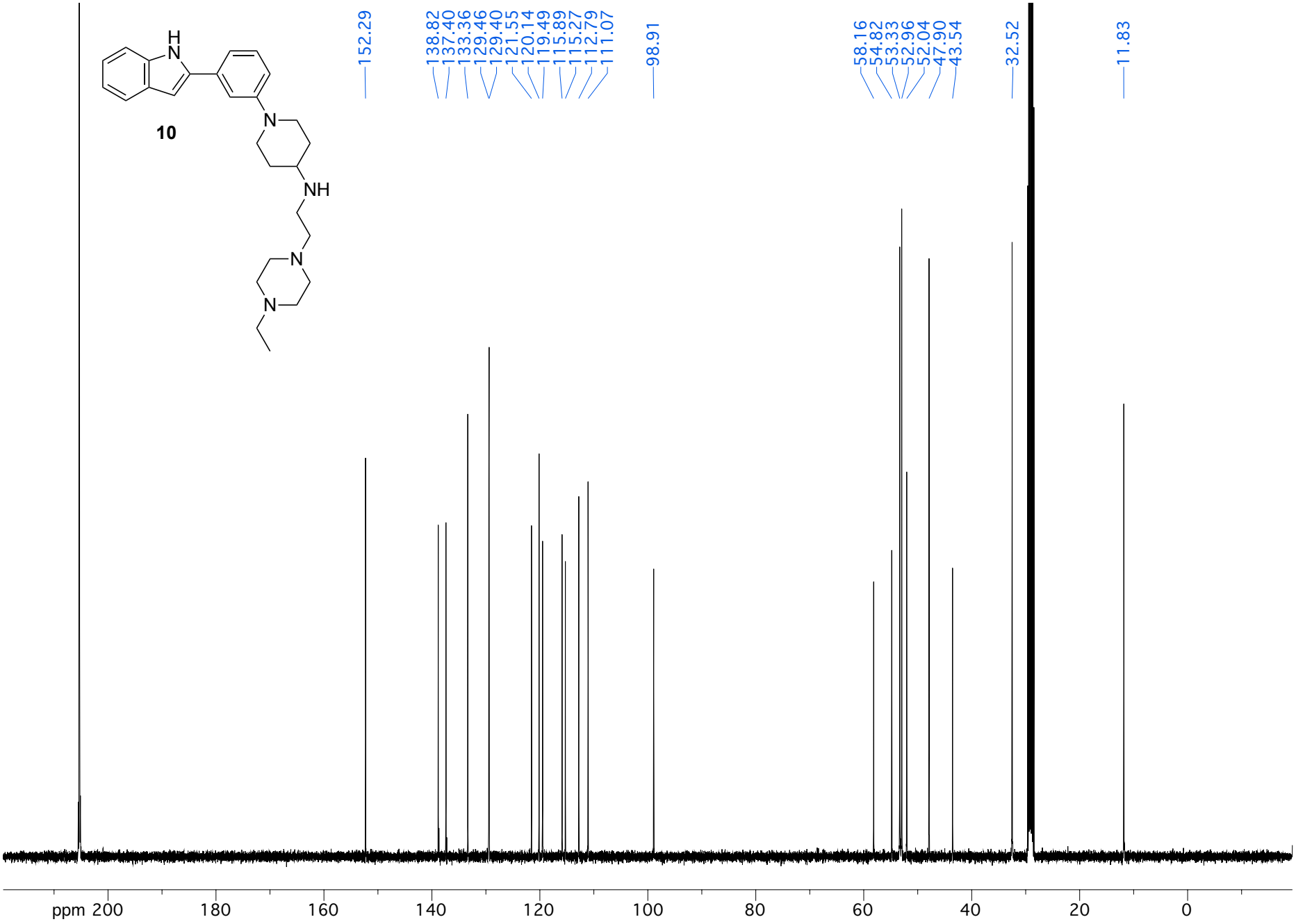
13C NMR (100 MHz, acetone-d6)



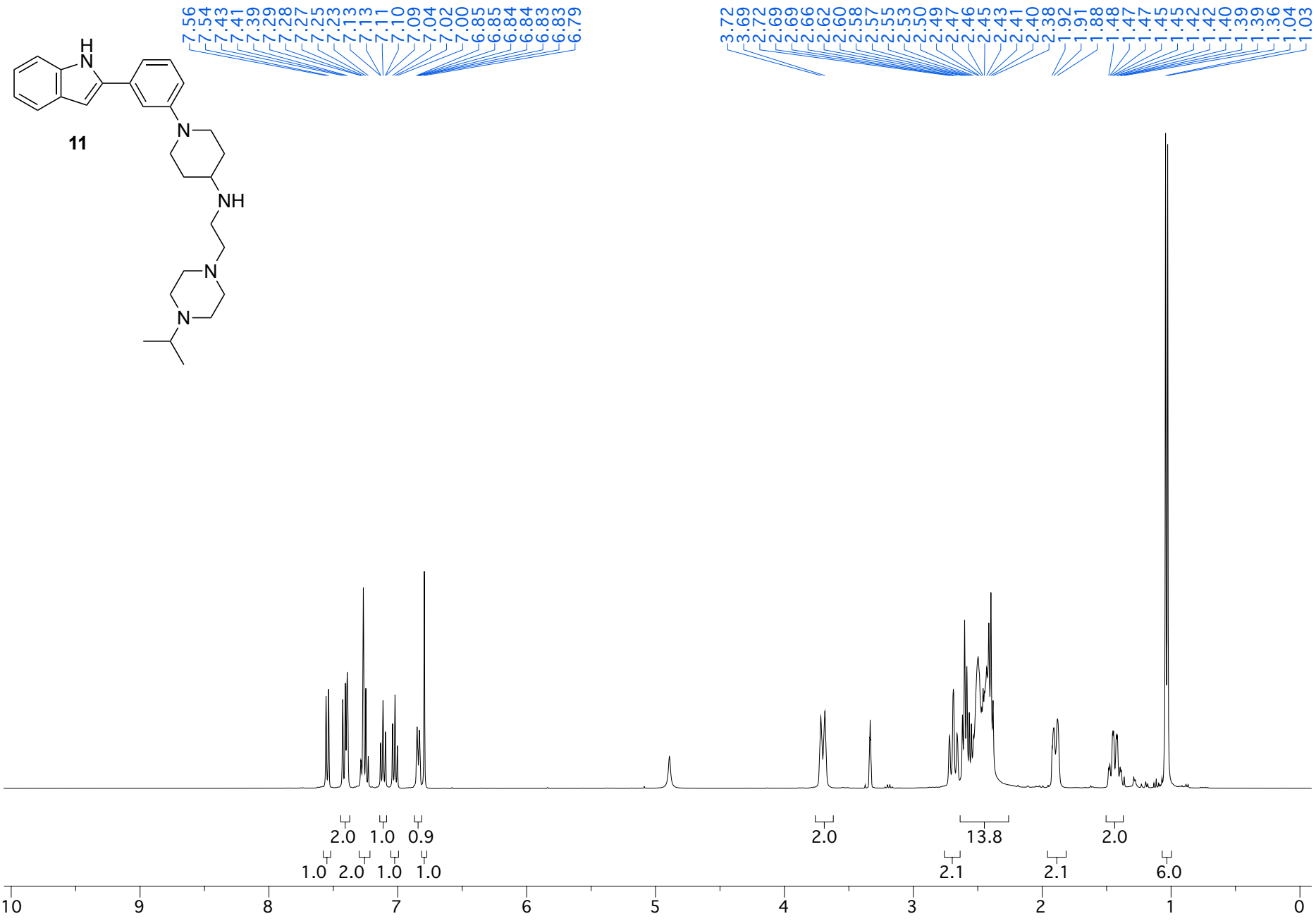
1H NMR (400 MHz, acetone-d6)



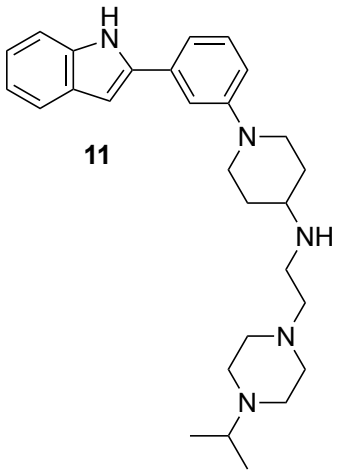
13C NMR (100 MHz, acetone-d6)



1H NMR (400 MHz, CD3OD)

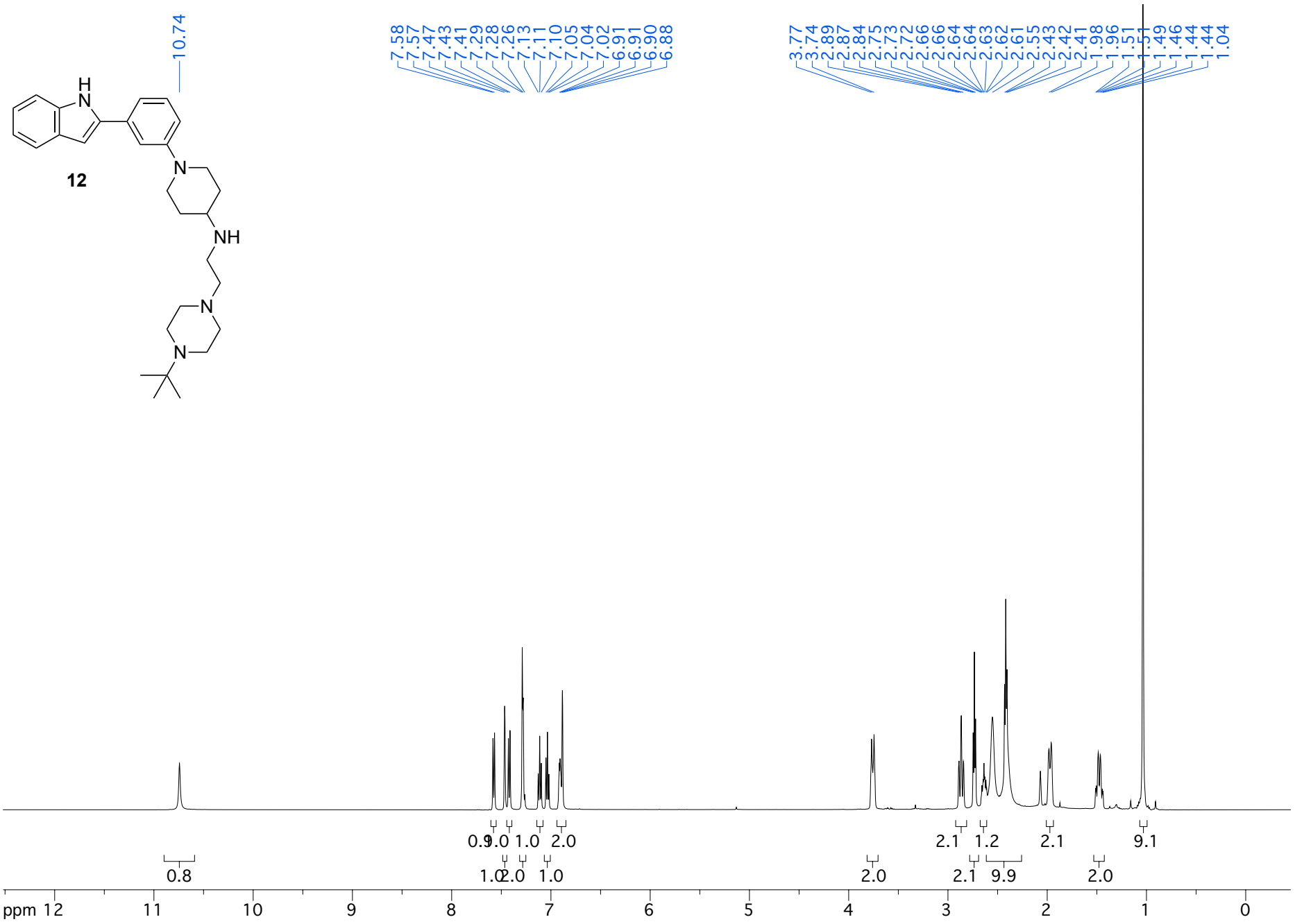


13C NMR (100 MHz, CD3OD)

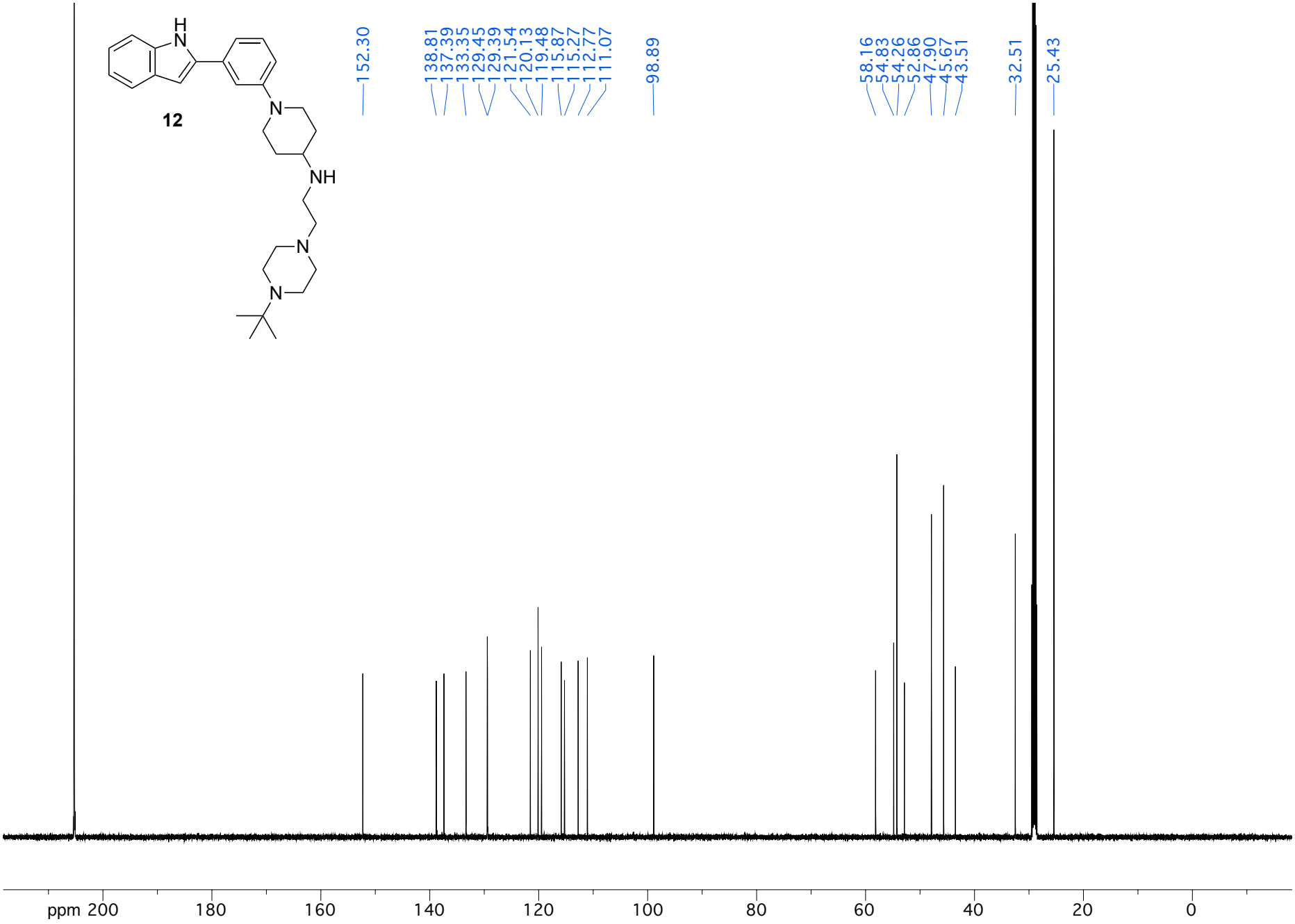


11

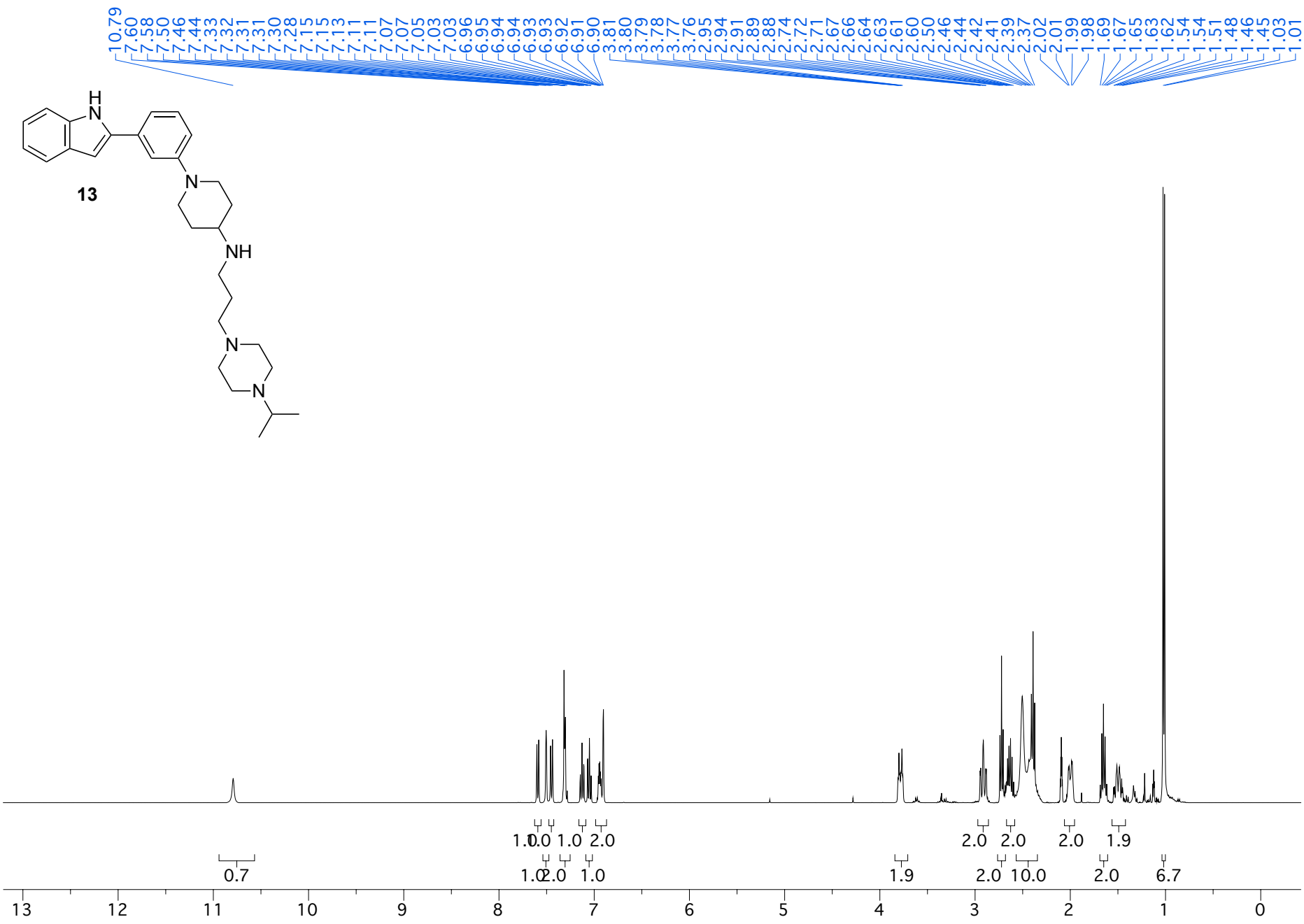
1H NMR (500 MHz, acetone-d6)



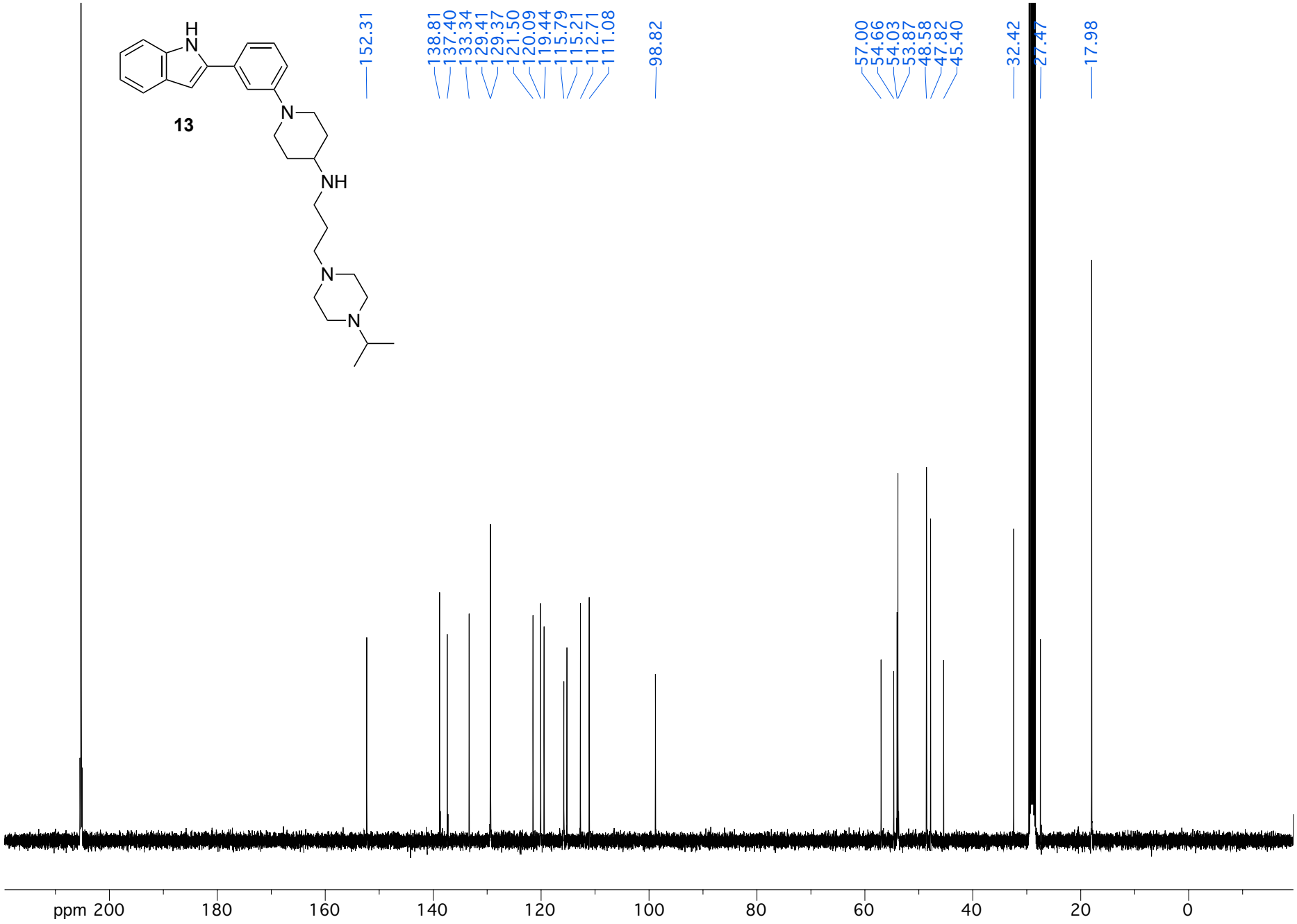
13C NMR (125 MHz, acetone-d6)



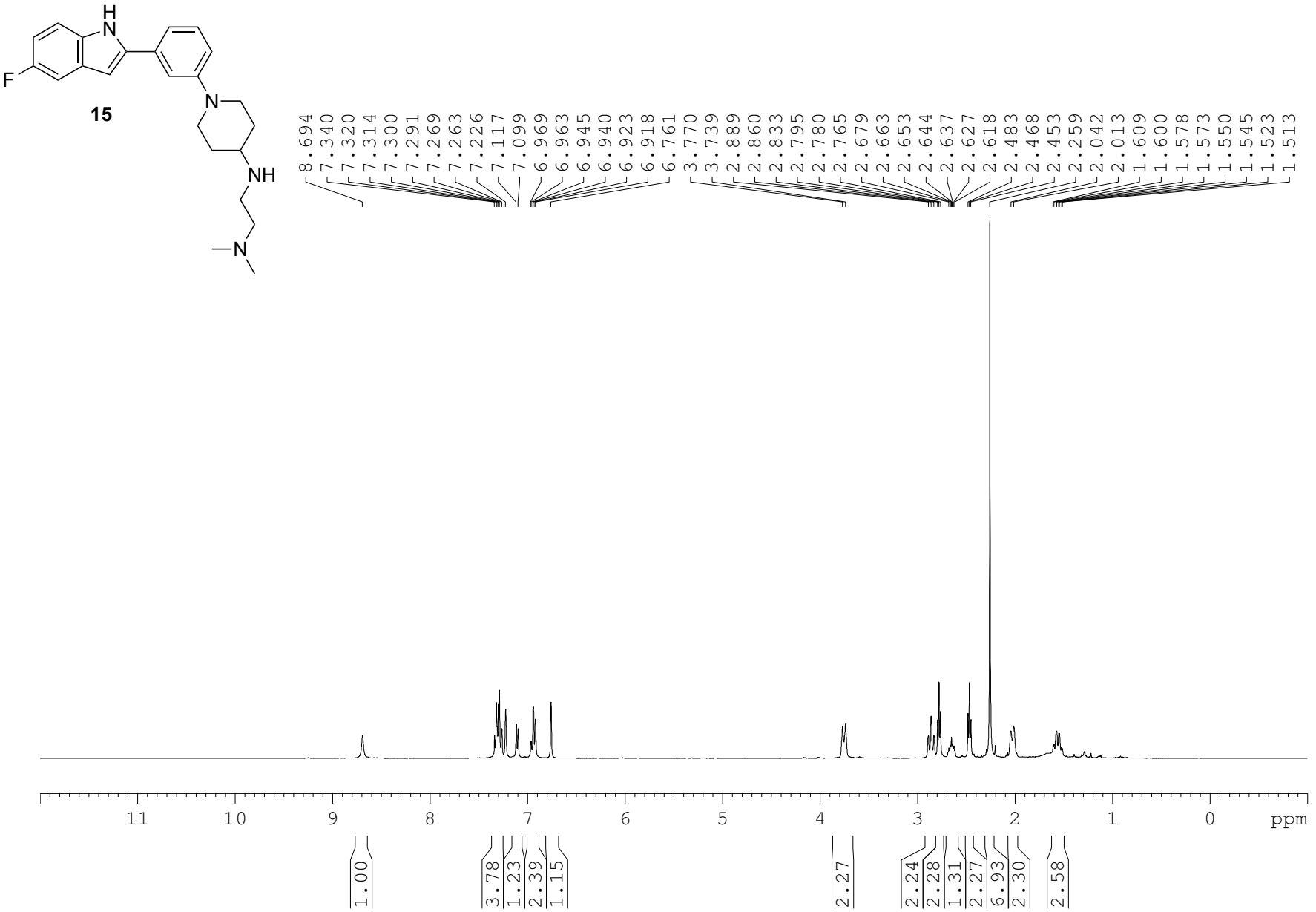
1H NMR (400 MHz, acetone-d6)



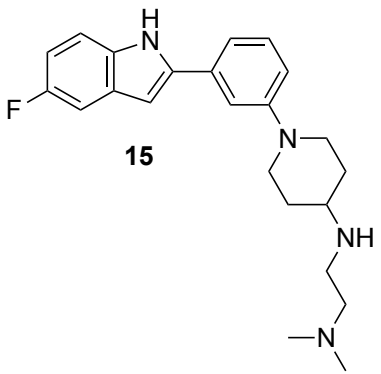
13C NMR (100 MHz, acetone-d6)



1H NMR (400 MHz, CDCl3)

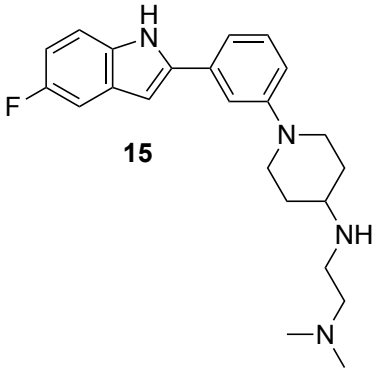


13C NMR (100 MHz, CDCl3)



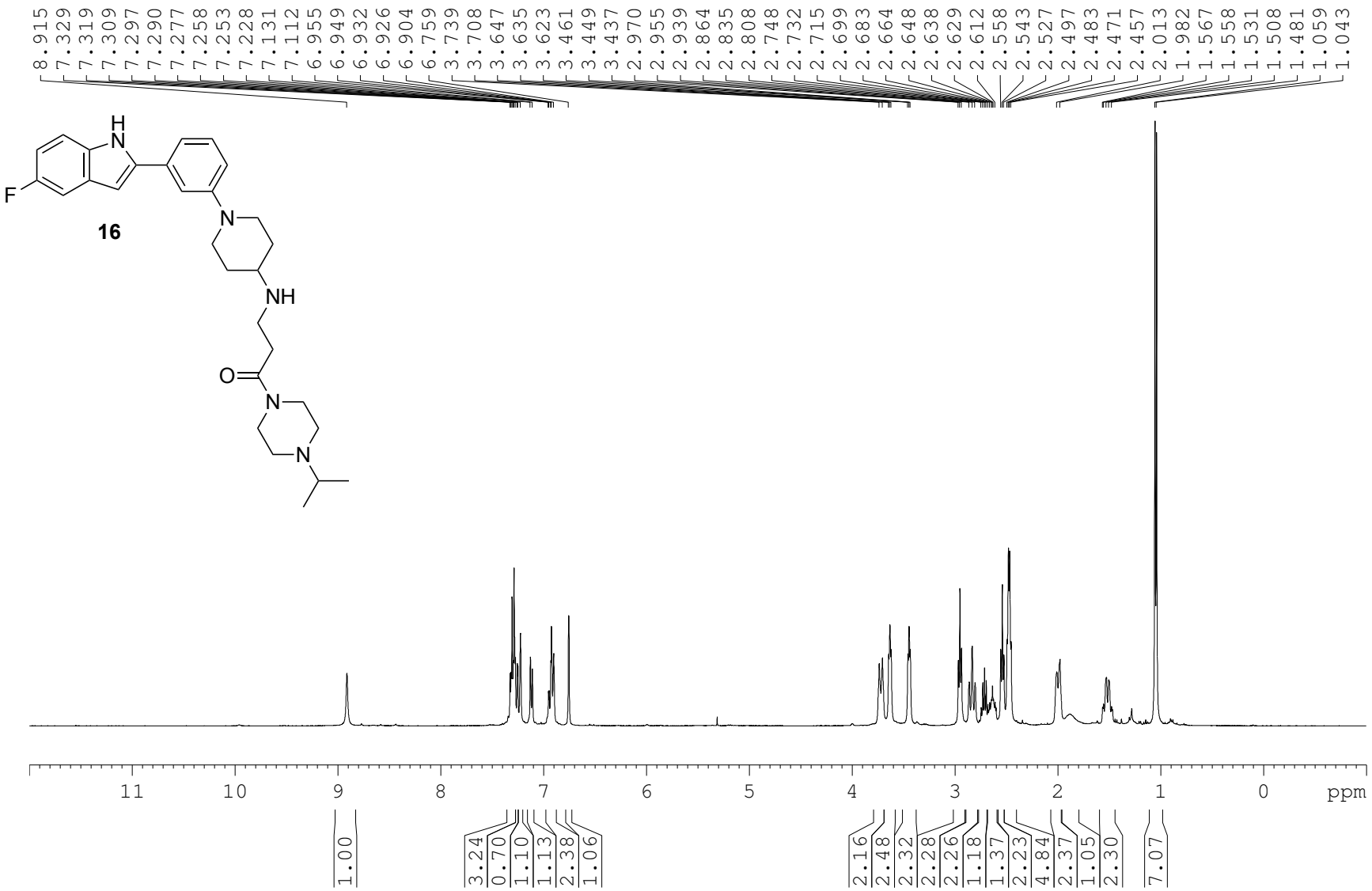
15

19F NMR (376 MHz, CDCl3)

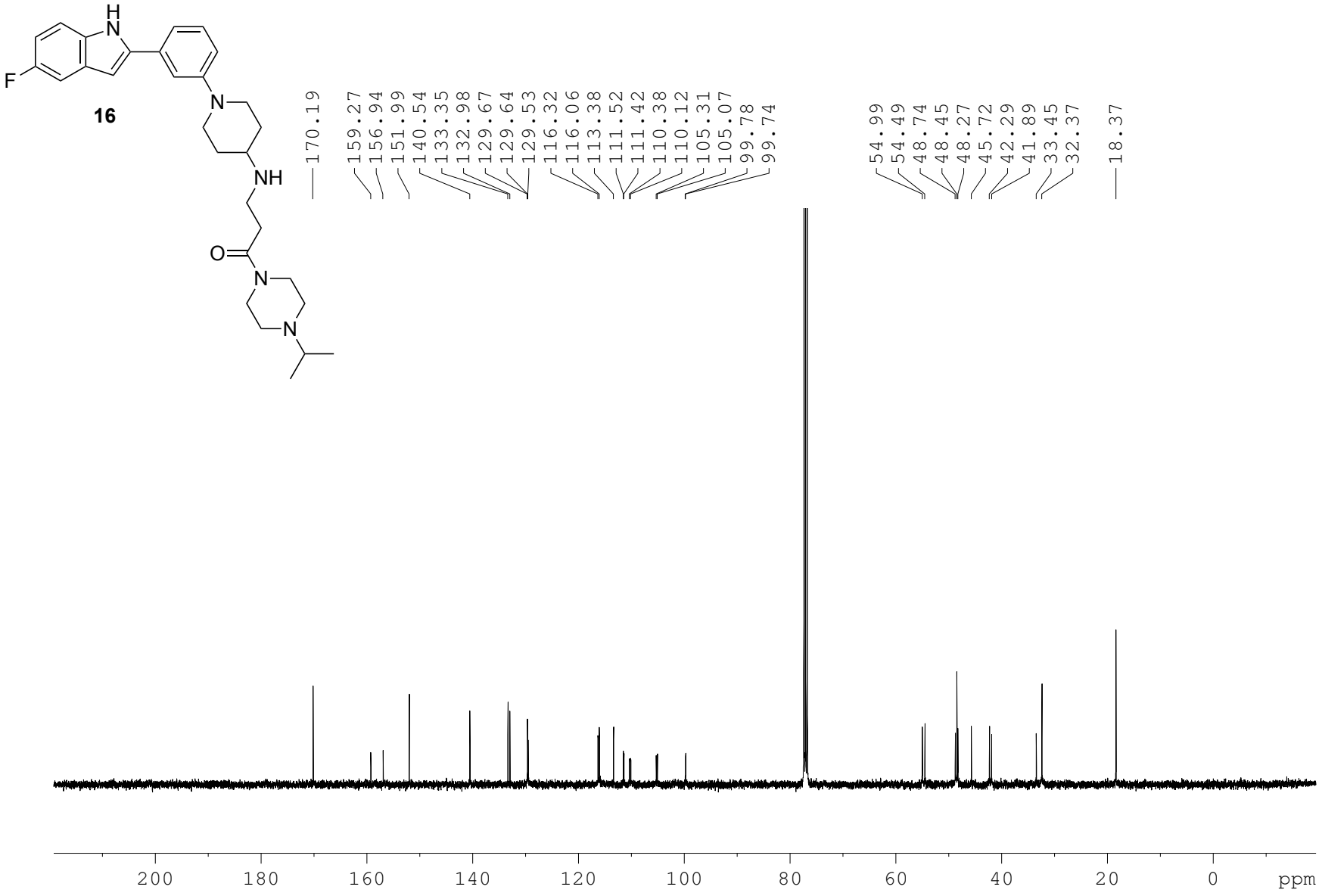


15

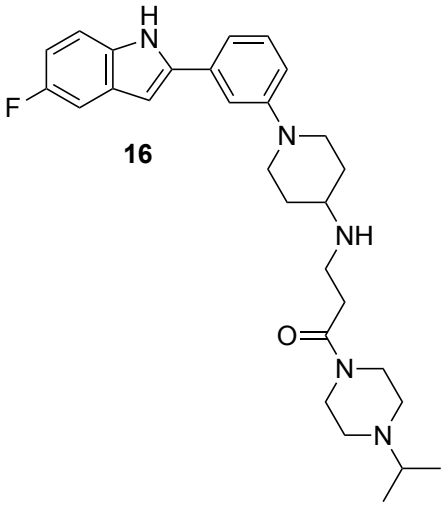
1H NMR (400 MHz, CDCl3)



13C NMR (100 MHz, CDCl3)

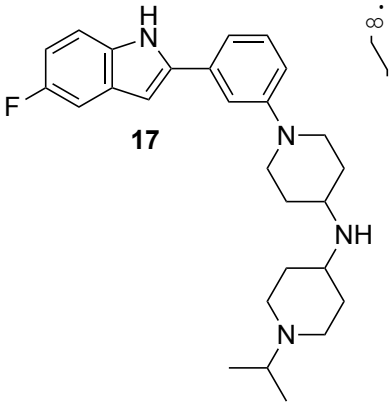


19F NMR (376 MHz, CDCl3)



16

MGl-622-035
CDCl3



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BRUKER

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PROCNO                 1

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PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
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DS                     2
SWH            10000.000 Hz
FIDRES         0.152588 Hz
AQ             3.2767999 sec
RG                  45.2
DW                50.000 usec
DE                 6.50 usec
TE                298.3 K
D1           1.00000000 sec
TD0                    1

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SFO1         500.1630887 MHz
NUC1                   1H
P1                 11.45 usec
PLW1         18.00000000 W

F2 - Processing parameters
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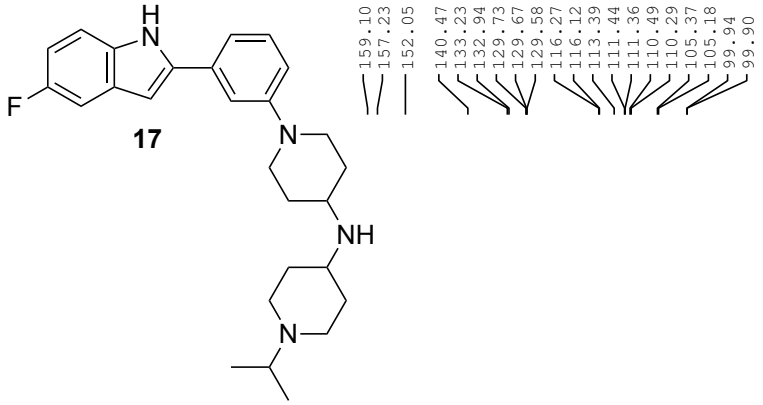
MGl-622-035
CDCl3



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110.29
105.37
105.18
99.94
99.90
54.42
51.66
51.12
48.54
47.83
33.87
33.07
18.49

Current Data Parameters
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EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
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Time 10.57
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PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1765
DS 2
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010048 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 298.7 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
SFO1 125.7779080 MHz
NUC1 13C
P1 10.50 usec
PLW1 110.00000000 W

======== CHANNEL f2 ========
SFO2 500.1620006 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 18.00000000 W
PLW12 0.36873001 W
PLW13 0 W

F2 - Processing parameters
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SF 125.7653320 MHz
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SSB 0
LB 1.00 Hz
GB 0
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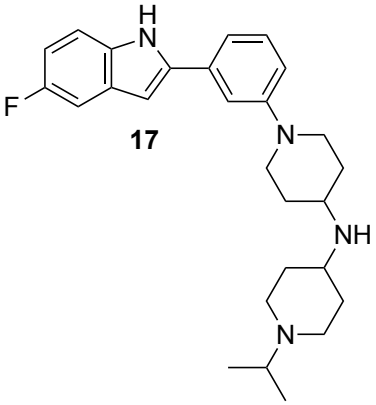
MGl-622-035
CDCl3



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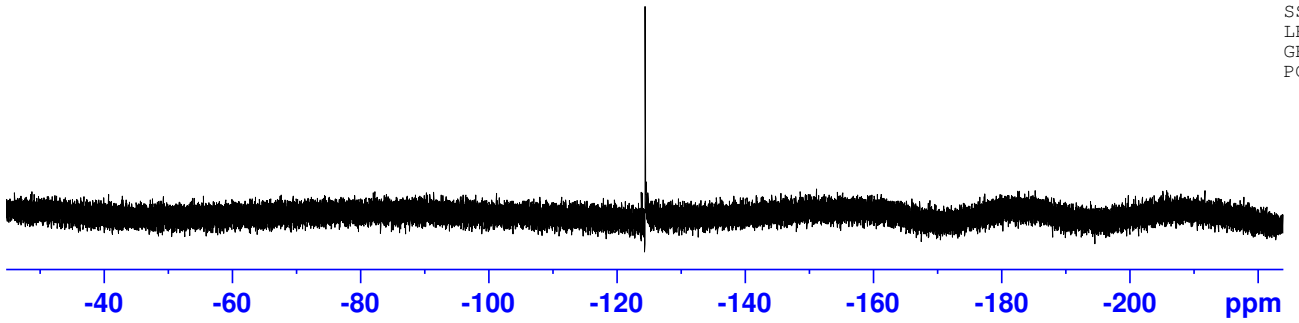


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PROCNO                  1

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PULPROG         zgflqn
TD              131072
SOLVENT           CDCl3
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FIDRES         0.715256 Hz
AQ            0.6990507 sec
RG                  203
DW                5.333 usec
DE                6.50 usec
TE                298.3 K
D1           1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
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NUC1               19F
P1                5.00 usec
PLW1        10.00000000 W

F2 - Processing parameters
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WDW                EM
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GB        0
PC                1.00
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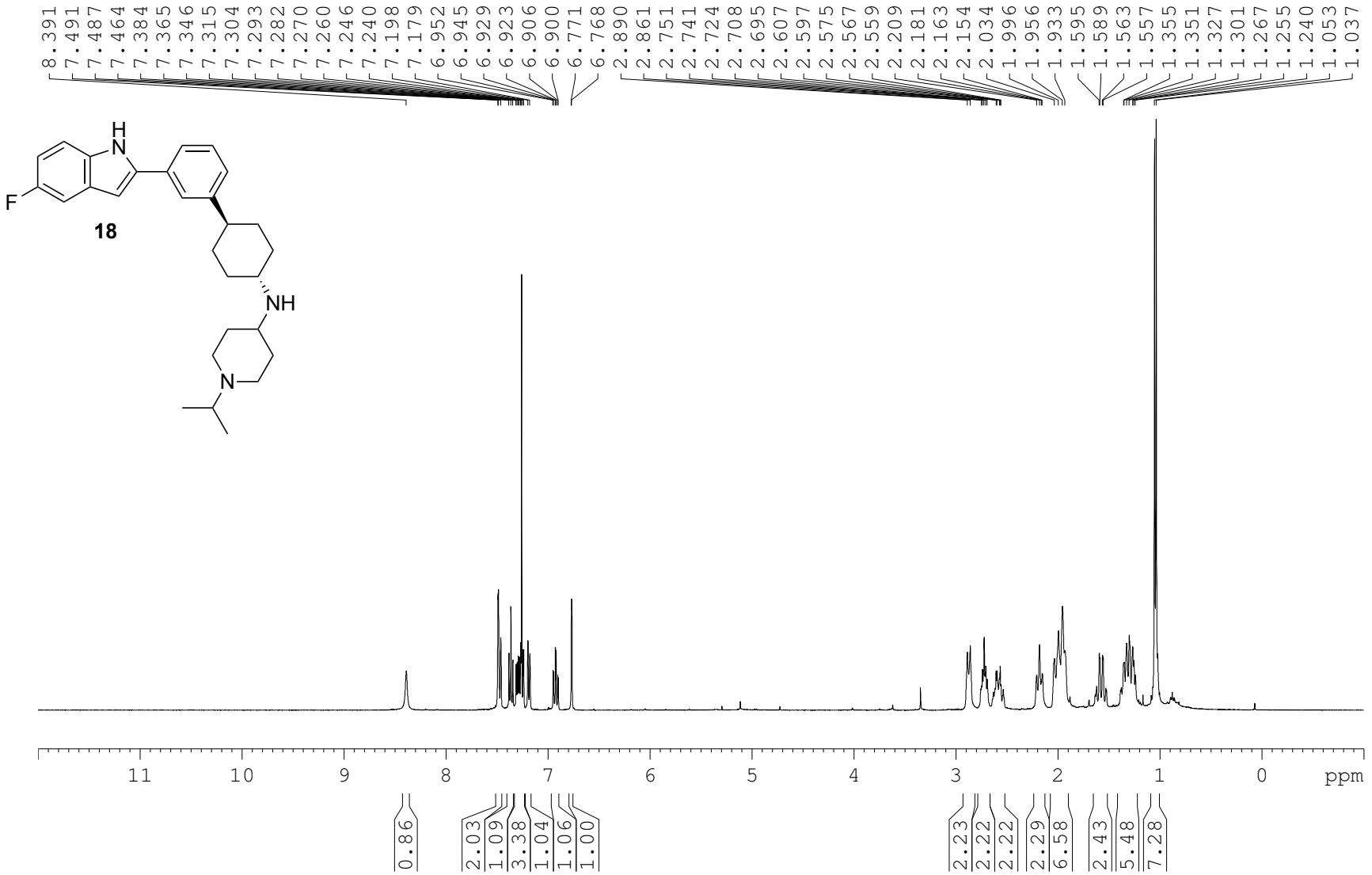
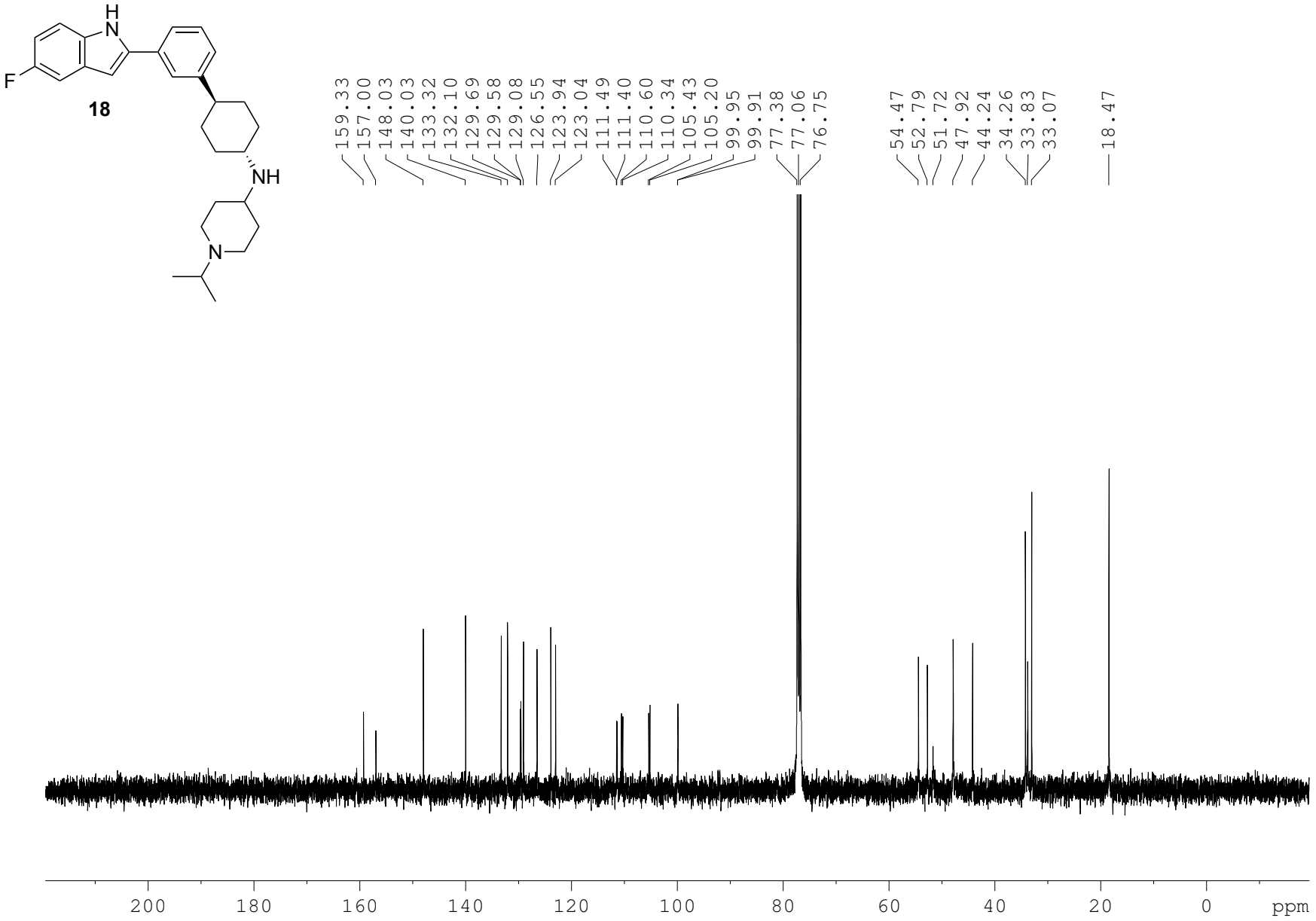
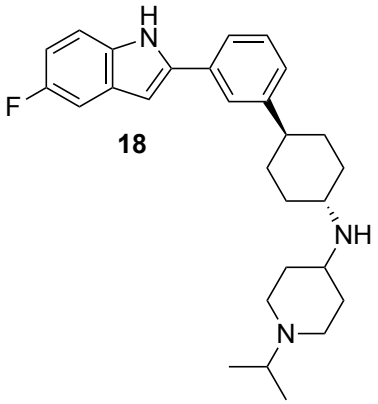
1H NMR (400 MHz, CDCl3)



13C NMR (100 MHz, CDCl3)

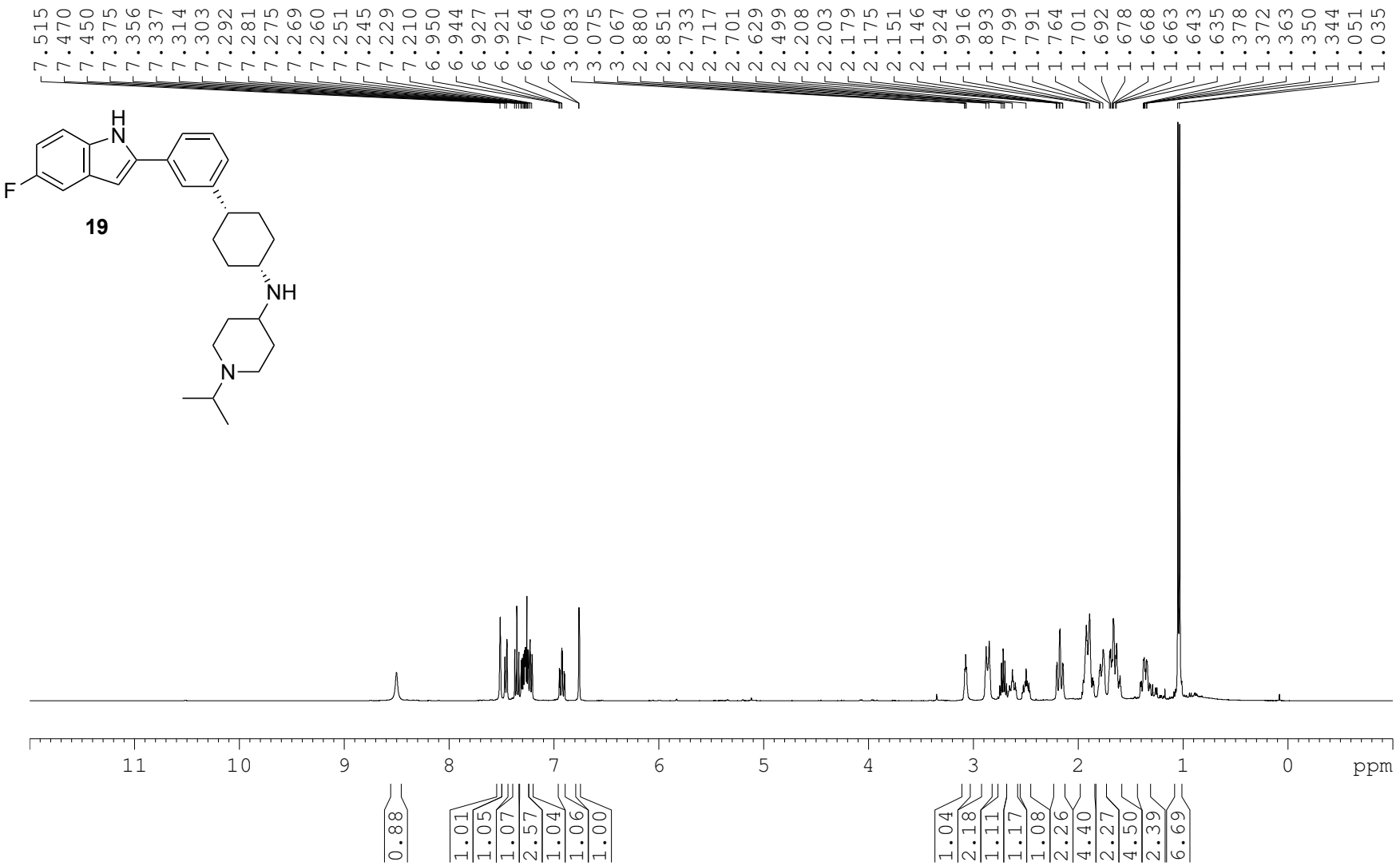


19F NMR (376 MHz, CDCl3)

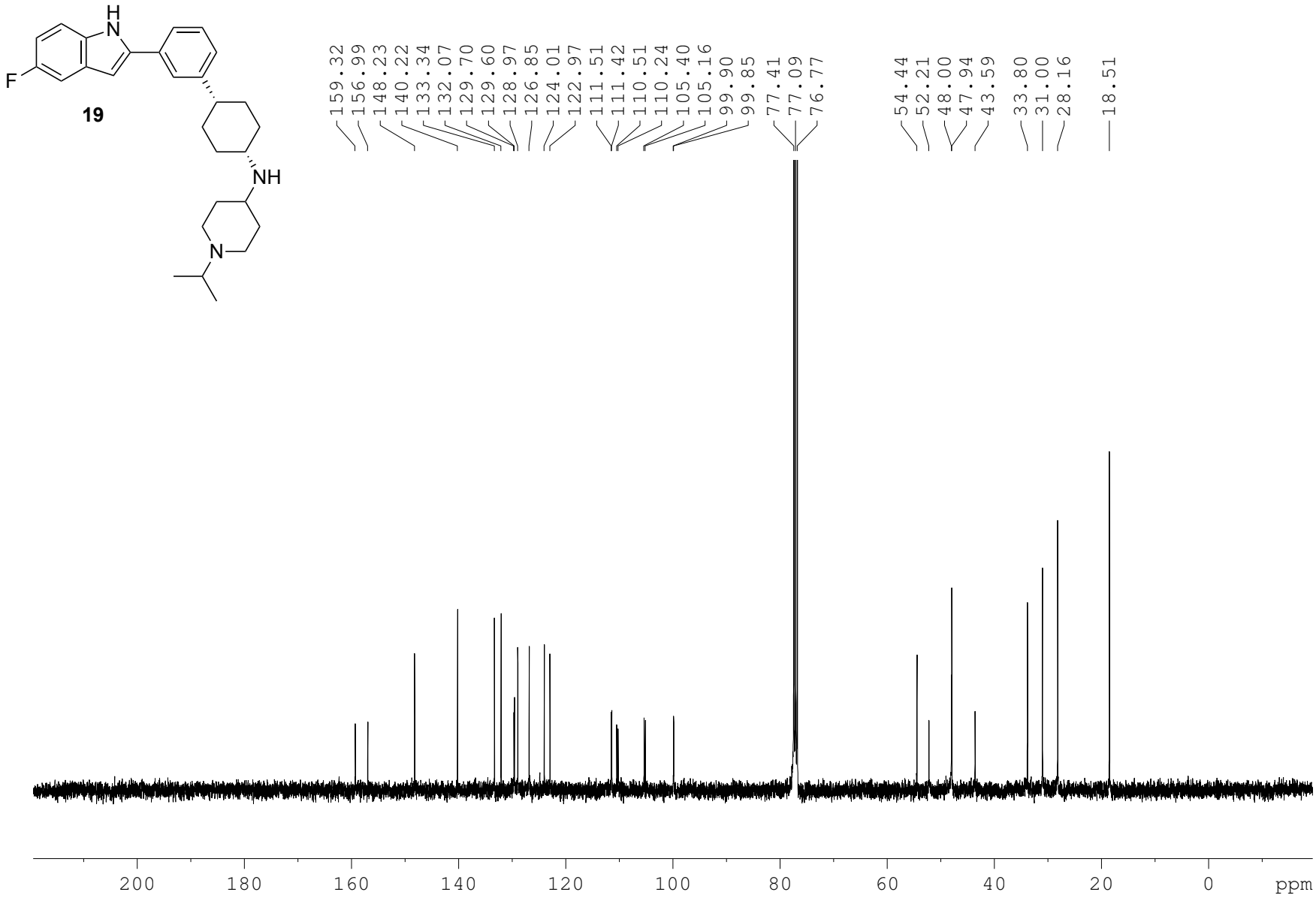


18

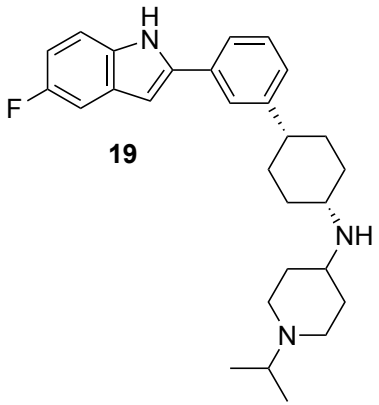
1H NMR (400 MHz, CDCl3)



13C NMR (100 MHz, CDCl3)

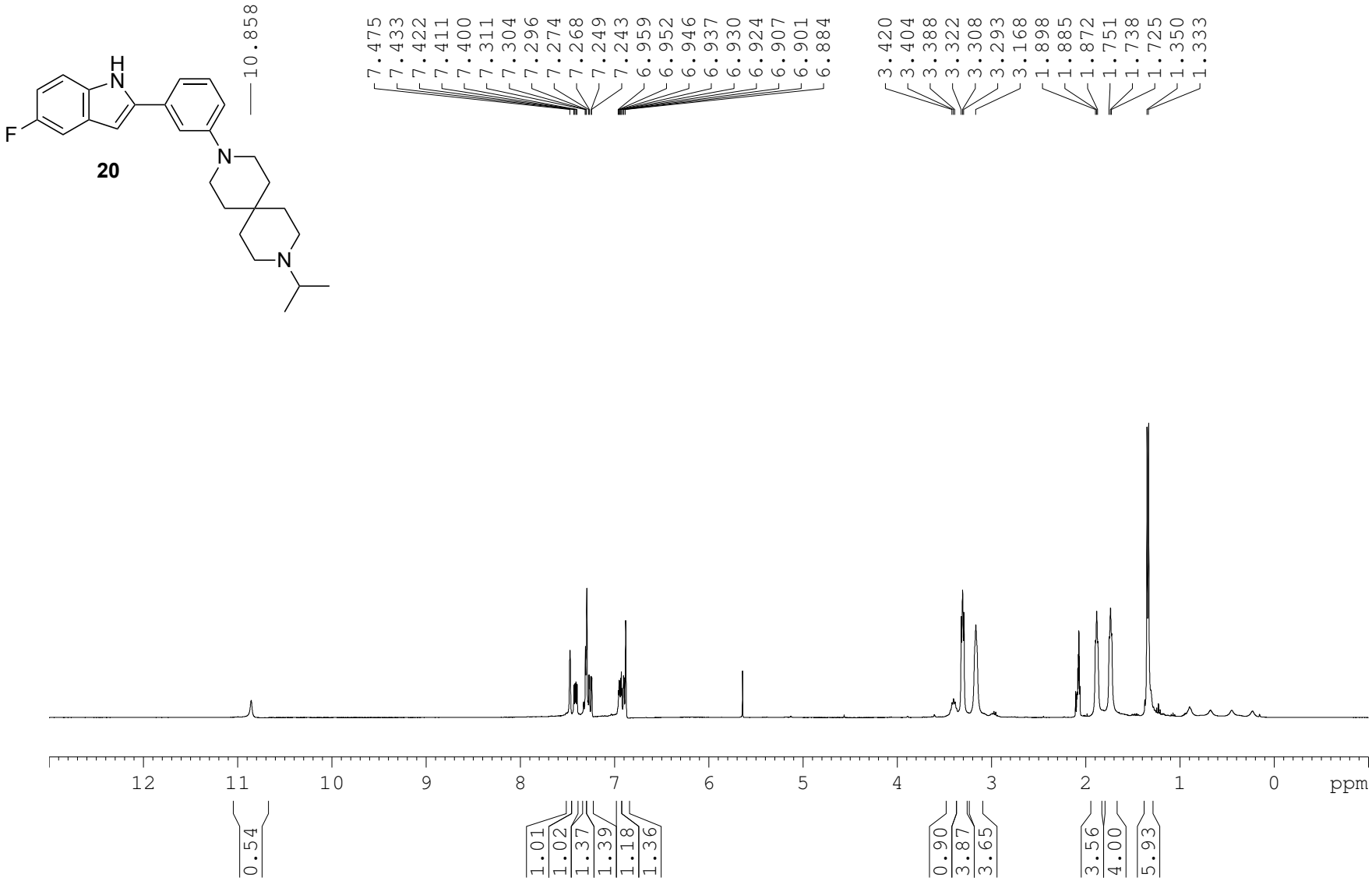


19F NMR (376 MHz, CDCl3)

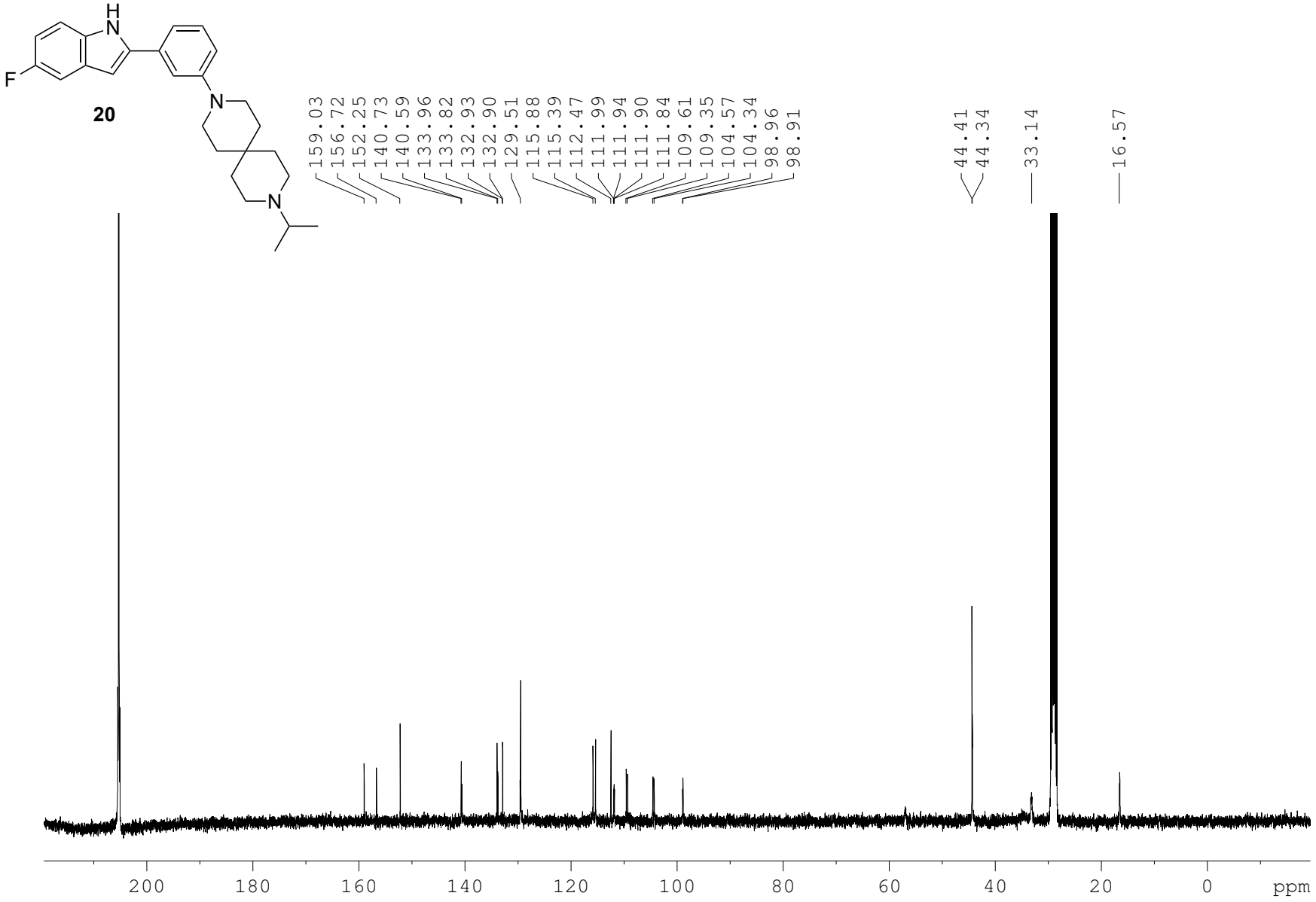


19

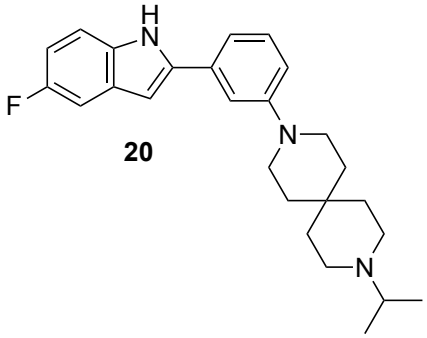
1H NMR (400 MHz, acetone-d6)



13C NMR (100 MHz, acetone-d6)

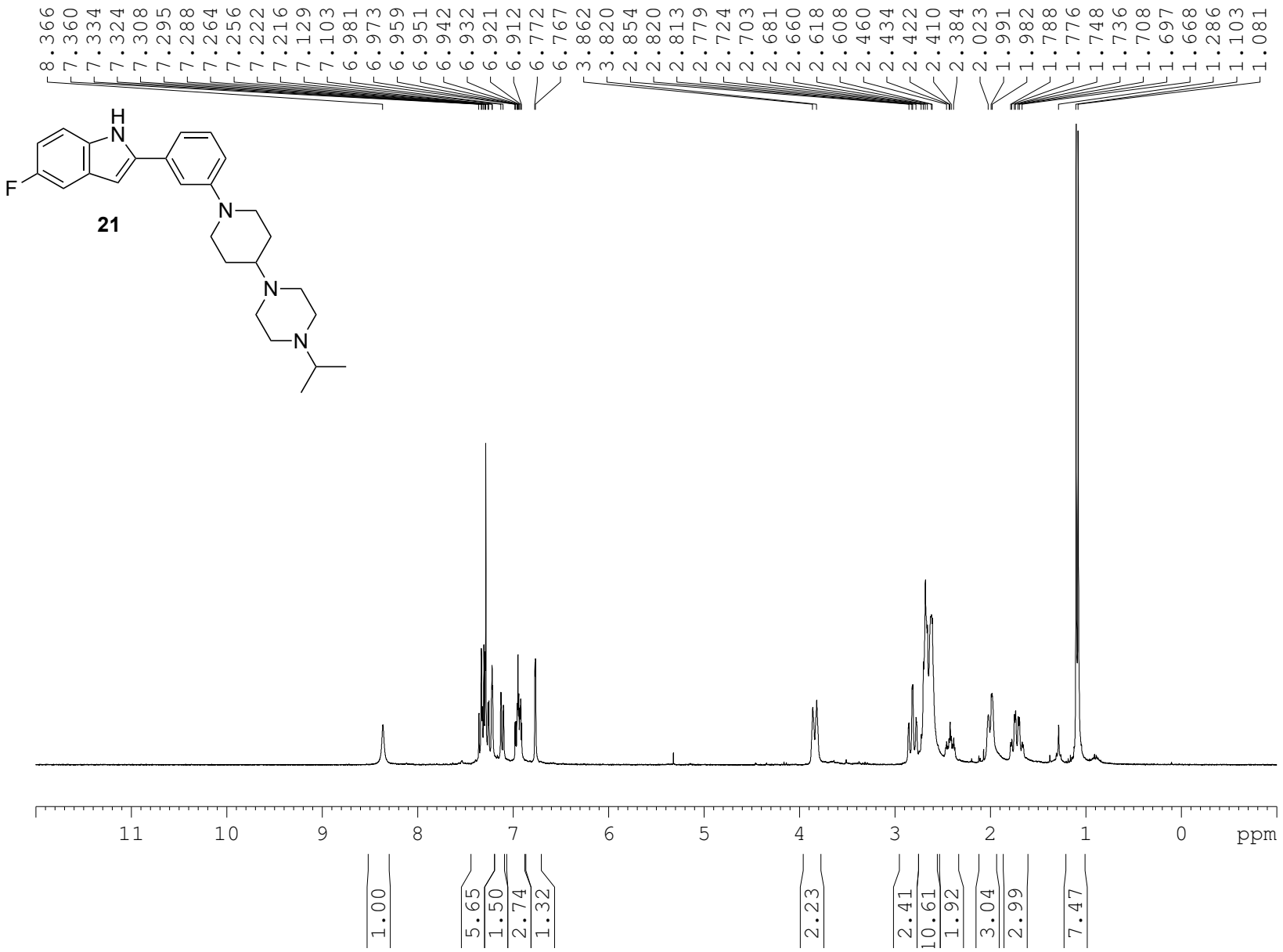


19F NMR (470 MHz, CDCl3)

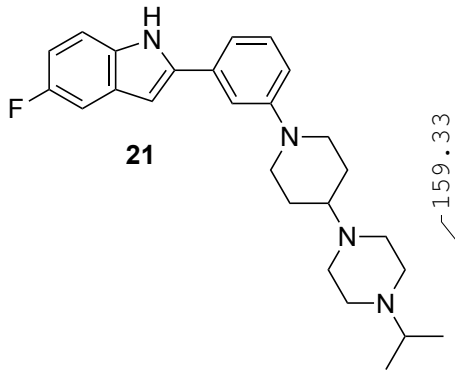


20

1H NMR (300 MHz, CDCl3)

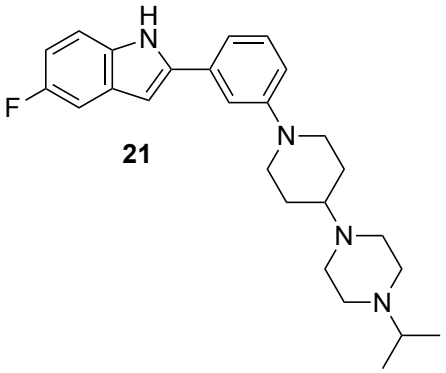


13C NMR (100 MHz, CDCl3)



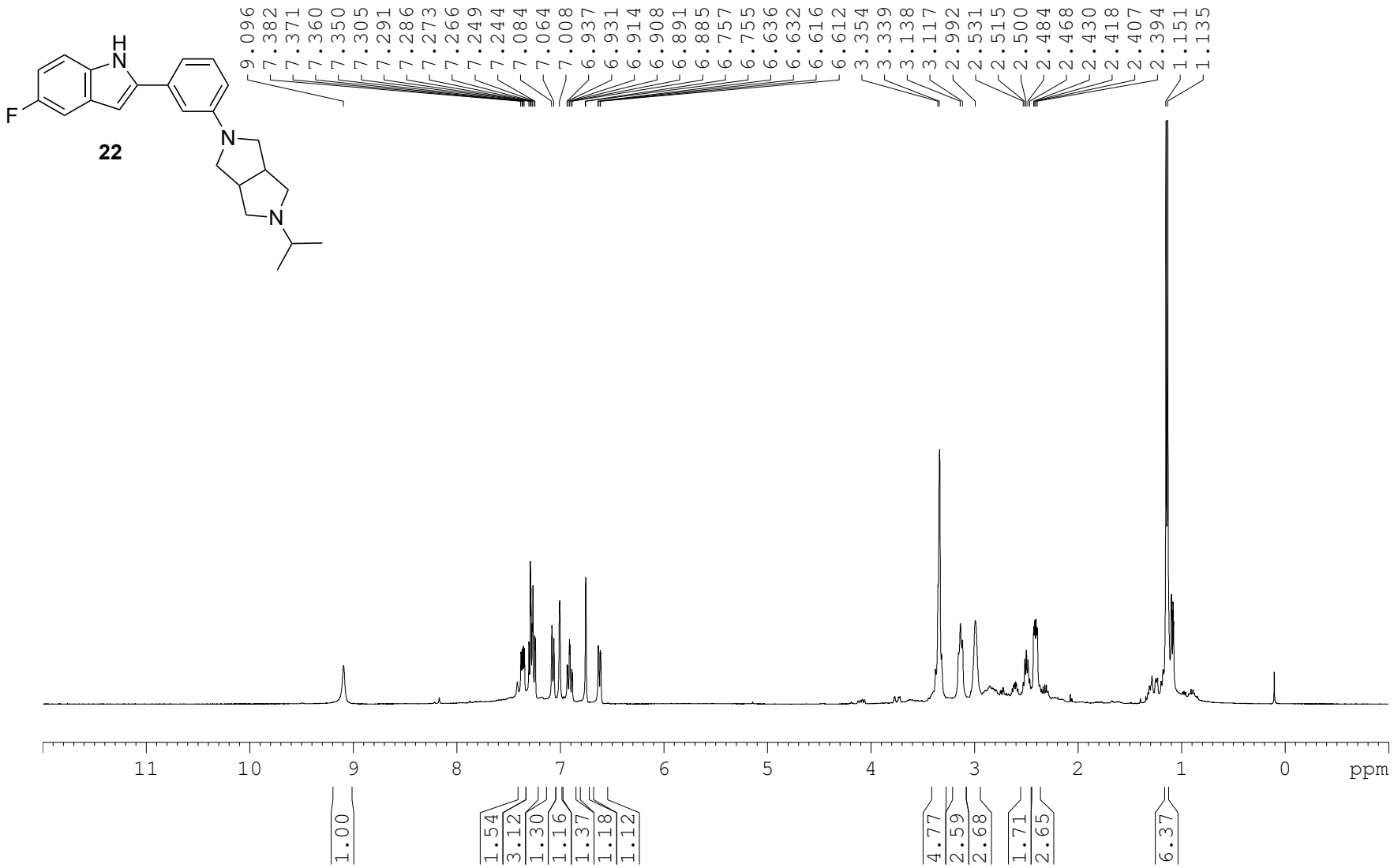
21

19F NMR (376 MHz, CDCl3)

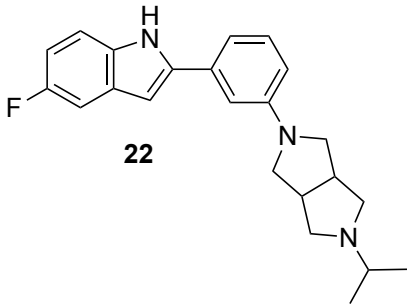


21

1H NMR (400 MHz, CDCl3)

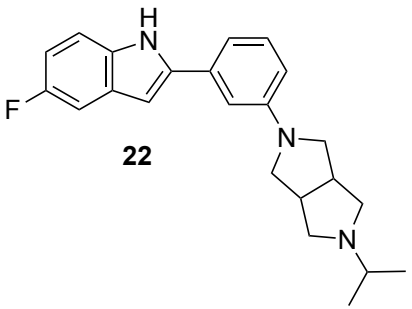


13C NMR (100 MHz, CDCl3)



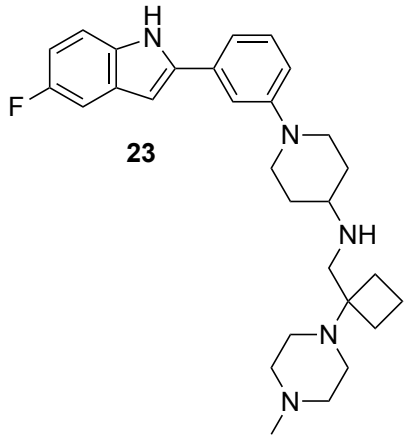
22

19F NMR (376 MHz, CDCl3)



22

1H NMR (500 MHz, CDCl3)



23

8.481
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7.303
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7.266
7.225
7.115
7.100
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6.766

3.758
3.733
2.912
2.890
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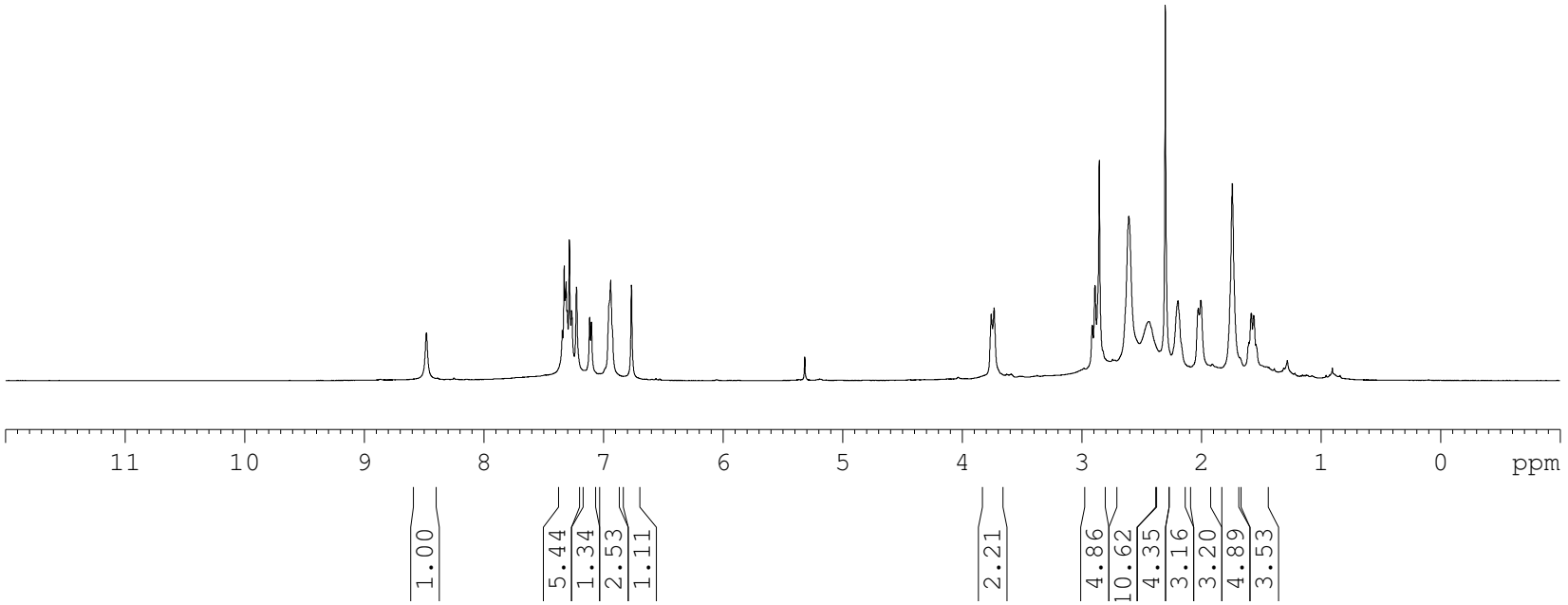
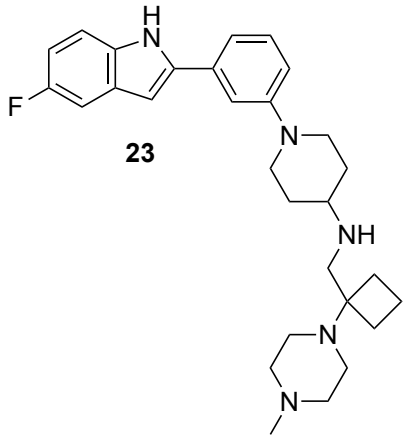


13C NMR (125 MHz, CDCl3)



23

159.09
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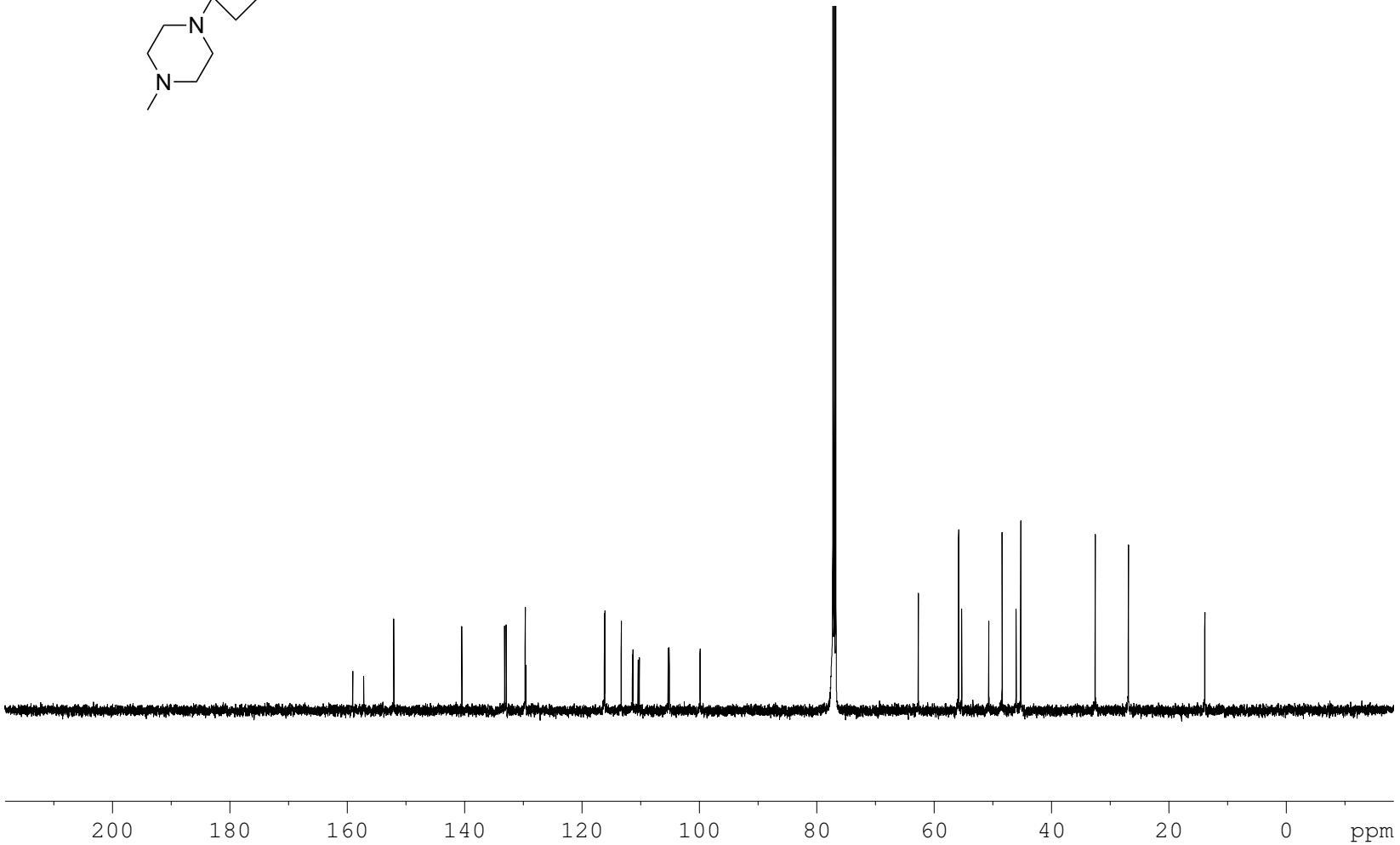
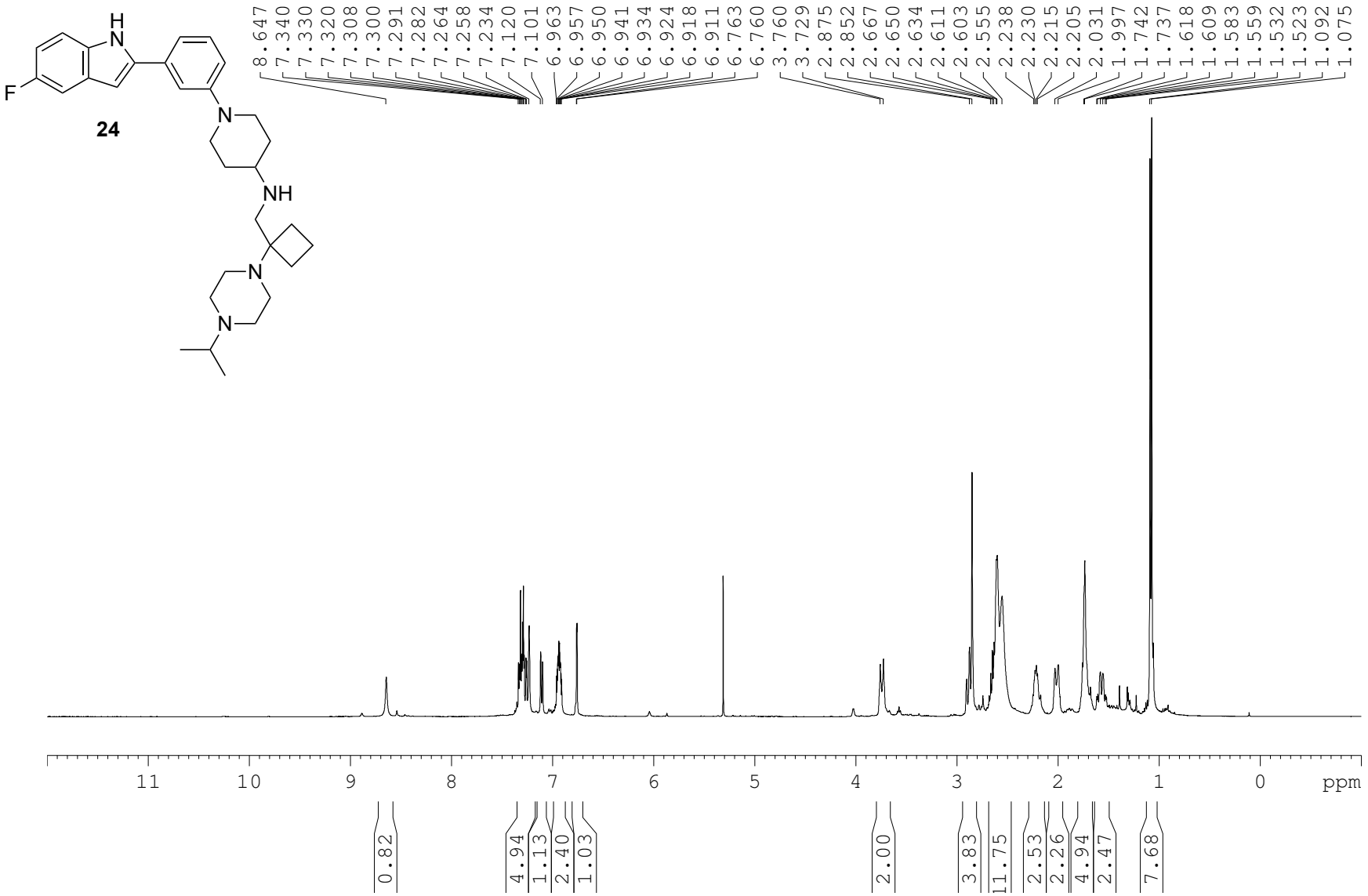
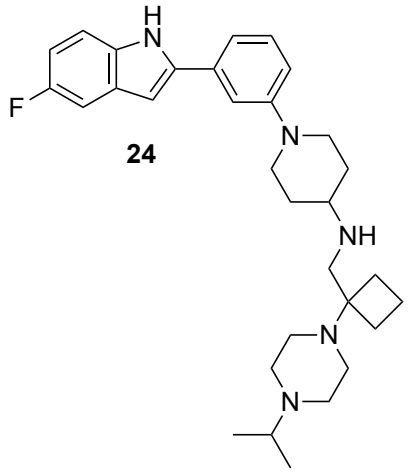


1H NMR (400 MHz, CDCl3)



13C NMR (100 MHz, CDCl3)



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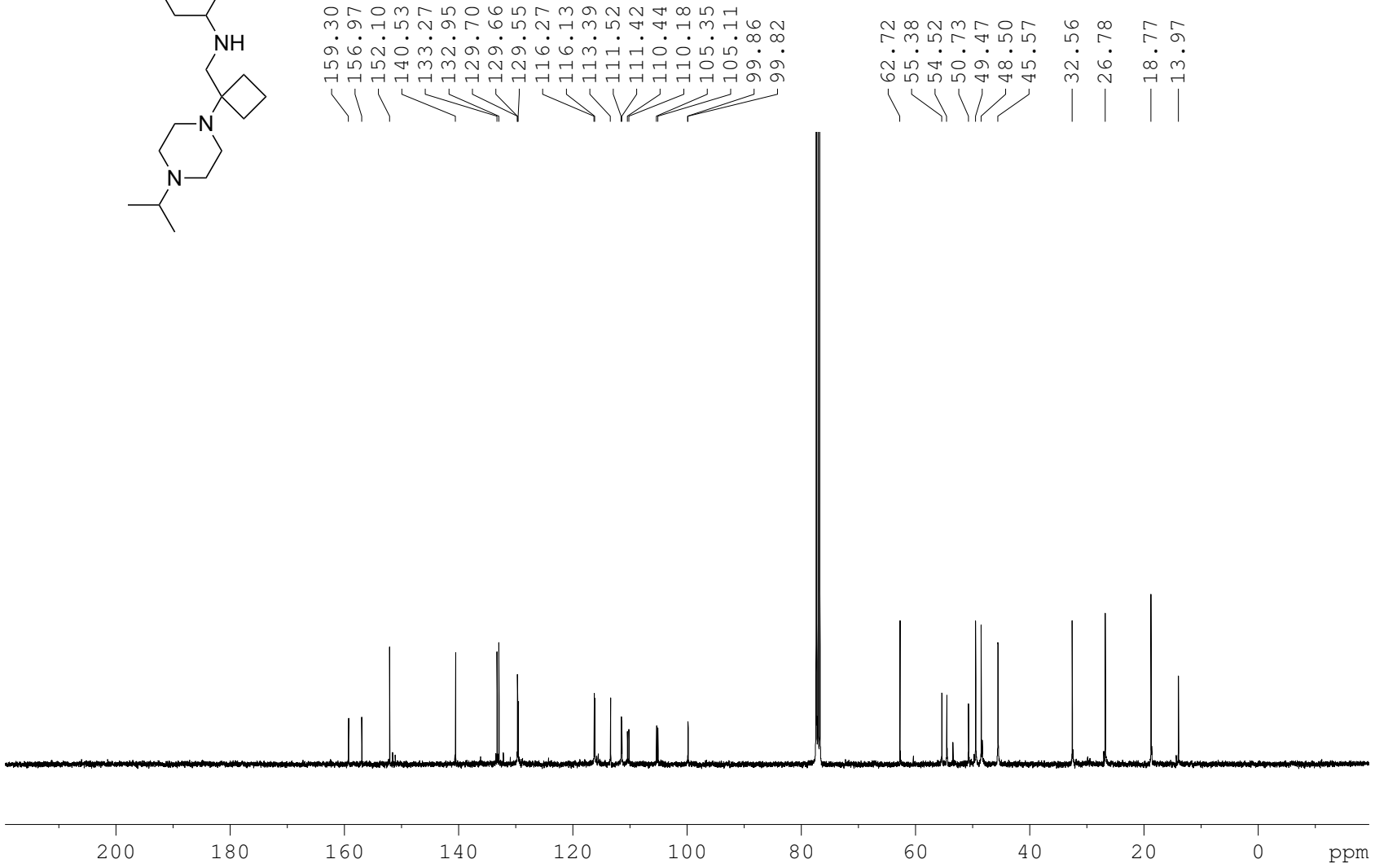
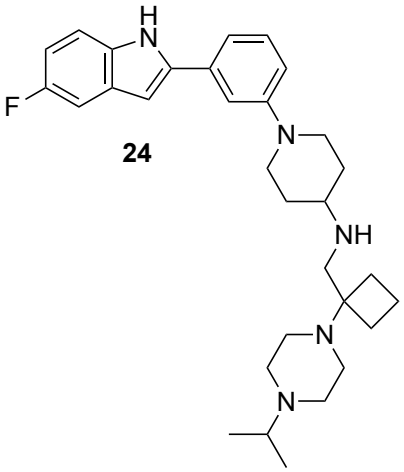
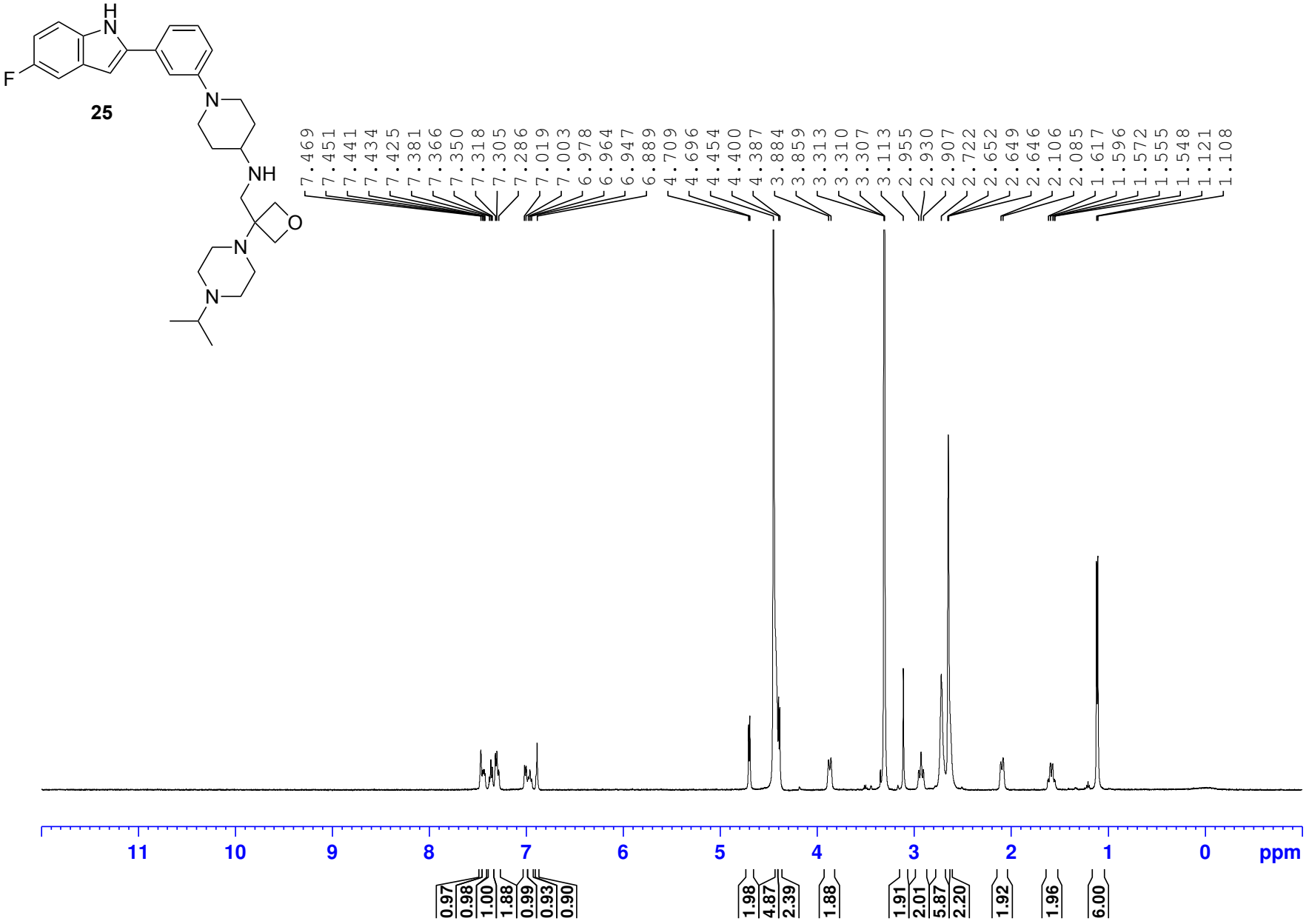


19F NMR (376 MHz, CDCl3)

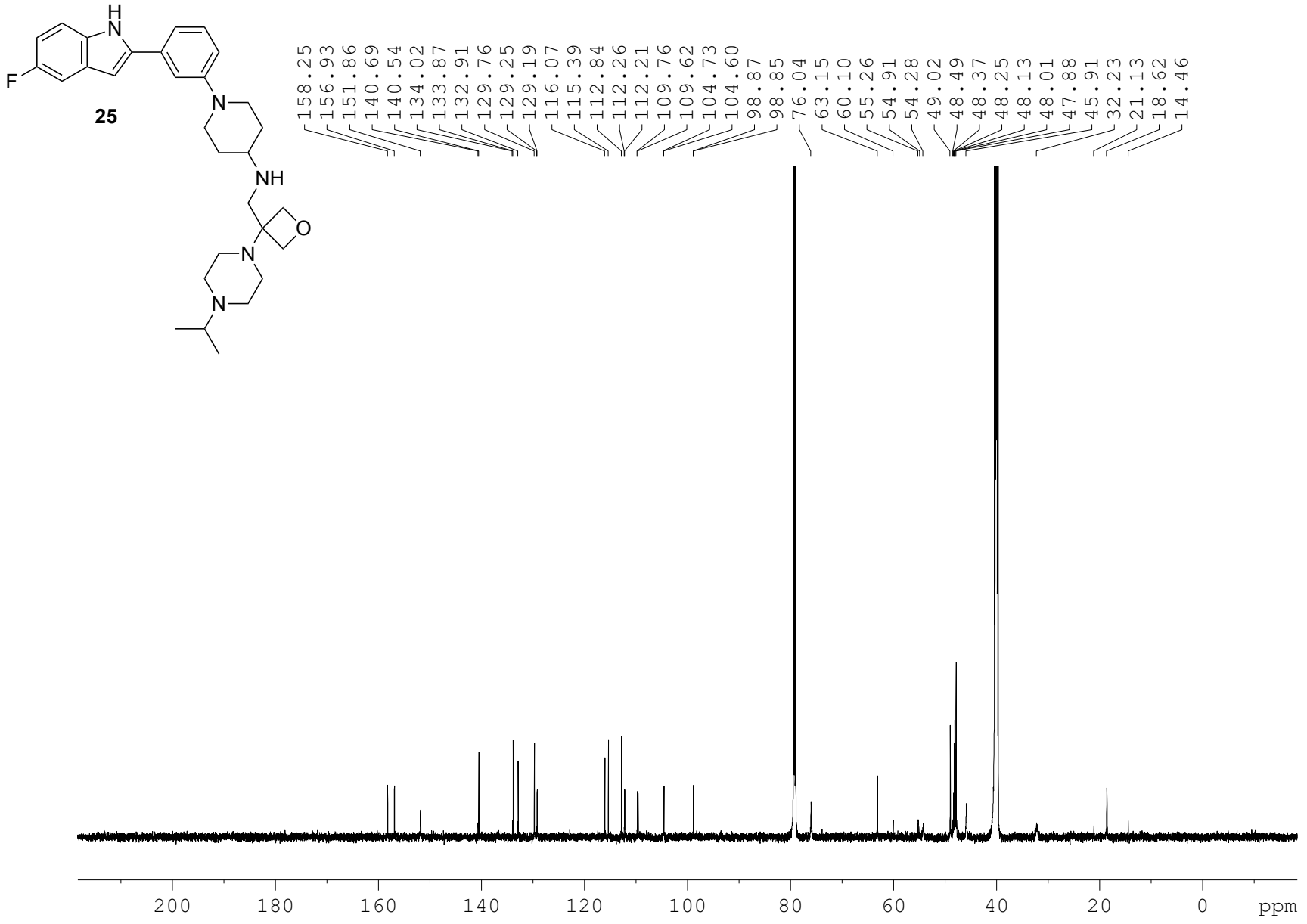


24

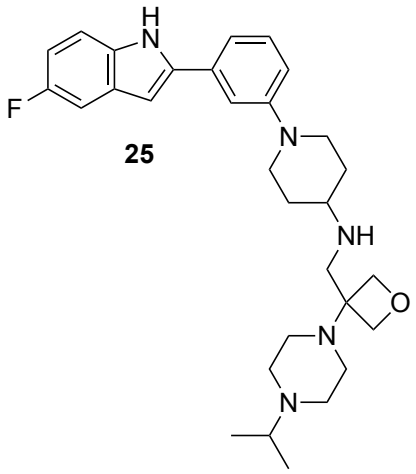
1H NMR (500 MHz, CD3OD/DMSO-d6)



13C NMR (175 MHz, CDCl3/DMSO-d6)



19F NMR (376 MHz, CDCl3/DMSO-d6)



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