Supporting Information
for

Design, Synthesis, and Evaluation of Novel Anti-Trypanosomal Compounds

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General. Tetrahydrofuran and diethyl ether were dried by filtration through two columns of activated, neutral alumina prior to use. Methanol, acetonitrile and dimethylformamide were dried by filtration through two columns of activated molecular sieves, and toluene was dried by filtration through one column of activated, neutral alumina followed by one column of Q5 reactant. Benzene was distilled from sodium and benzophenone. Methylene chloride, diisopropylamine, triethylamine, and diisopropylethylamine were distilled from calcium hydride immediately prior to use. Pyridine was distilled from potassium hydroxide (KOH) and calcium hydride and stored over KOH. Dioxane was distilled from sodium metal and benzophenone prior to use. All solvents were determined to have less than 50 ppm H_2O by Karl Fischer coulometric moisture analysis. All reagents were reagent grade and used without purification unless otherwise noted. All reactions involving air or moisture sensitive reagents or intermediates were performed under an inert atmosphere of nitrogen or argon in glassware that was flame dried. Solutions were degassed using three freeze-thaw cycles under vacuum. Reaction temperatures refer to the temperature of the cooling/heating bath. Volatile solvents were removed under reduced pressure using a Büchi rotary evaporator at 25–30 °C. Thin layer chromatography was performed using run on pre-coated plates of silica gel with a 0.25 mm thickness containing 60F-254 indicator (Merck). Chromatography was performed using forced flow (flash chromatography) and the indicated solvent system on 230-400 mesh silica gel (E. Merck reagent silica gel 60) according to the method of Still,[1] unless otherwise noted.

Infrared (IR) spectra were obtained either neat on sodium chloride or as solutions in the solvent indicated and reported as wavenumbers (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were obtained at the specified field as solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are referenced to the deuterated solvent and are reported in parts per million (ppm, δ) downfield from tetramethylsilane (TMS, δ = 0.00 ppm). Coupling constants (*J*) are reported in Hz and the splitting abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, overlapping multiplets of magnetically nonequivalent protons; br, broad; app, apparent. In reporting the HRMS for compounds containing chlorine, the calculated and measured masses are for the isotope ^{35}Cl.

(±)-(3*R*,4*S*)-1-(2-(1*H*-Indol-3-yl)ethyl)-4-((3-chloro-5-methoxybenzyl)(methyl)amino)-3-((*R*)-1-hydroxyethyl)piperidin-2-one (14b). Prepared according to representative procedure for compound **14a**. The crude material was purified via flash column chromatography eluting with a gradient with hexanes : ethyl acetate (1 : 1) → ethyl acetate : methanol (20 : 1). To give 30 mg (27%) of **14b** as an amorphous white solid. ^{1}H NMR (400 MHz) δ 8.24 (s, 1 H), 7.57 (d, *J* = 7.6 Hz, 1 H), 7.33 (d, *J* = 7.6 Hz, 1 H), 7.18 (td, *J* = 7.2, 1.2 Hz, 1 H), 7.10 (td, *J* = 8.0, 1.2 Hz, 1 H), 7.01 (d, *J* = 2.4 Hz, 1 H), 6.80 (t, *J* = 1.6 Hz, 1 H), 6.78 (t, *J* = 1.6 Hz, 1 H), 6.67 (t, *J* = 1.6 Hz, 1 H), 4.33 (p, *J* = 6.4 Hz, 1 H), 3.79 - 3.72 (comp, 4 H), 3.61 (p, *J* = 6.4 Hz, 1 H), 3.47 – 3.30 (comp, 3 H), 3.23 (dt, *J* = 12.4, 4.8 Hz, 1 H), 3.10 (dt, *J* = 12.4, 9.2 Hz, 1 H), 3.02 - 2.90 (comp, 2 H), 2.38 (t, *J* = 6.0 Hz, 1 H), 2.06 (s, 3 H), 1.91 - 1.85 (comp, 2 H), 1.18 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz) δ 170.9, 160.5, 139.6, 136.2, 135.0, 127.3, 122.3, 122.1, 121.4, 119.3, 118.4, 113.6, 113.4, 112.4, 111.4, 66.3, 59.0, 58.0, 55.6, 48.5, 47.4, 45.0, 37.5, 23.1, 22.1, 20.5; HRMS (ESI) *m/z* calcd for $C_{26}H_{32}ClN_3O_3$ $(M+H)^+$, 470.2205; found, 470.2207.

(3*R*,4*S*)-1-(2-(1*H*-Indol-3-yl)ethyl)-4-((3-chlorobenzyl)(methyl)amino)-3-((*R*)-1-hydroxyethyl)piperidin-2-one (14c). Prepared according to representative procedure for compound **14a**. The crude material was purified via flash column chromatography eluting along a gradient with hexanes : ethyl acetate (3 : 1 → 0 : 1) to give 26 mg (37%) of **14c** as an amorphous white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.58 (d, *J* = 7.6 Hz, 1 H), 7.33 (d, *J* = 7.4 Hz, 1 H), 7.31 – 7.26 (comp, 3 H), 7.18 (dt, *J* = 6.8, 1.6 Hz, 1 H), 7.11 – 7.07 (comp, 2 H), 7.02 (ddd, *J* = 7.6, 6.8, 0.8 Hz, 1 H), 4.22 (dq, *J* = 8.8, 6.0 Hz, 1 H), 3.77 (dt, *J* = 13.2, 7.2 Hz, 1 H), 3.57 – 3.51 (comp, 2 H), 3.44 (d, *J* = 12.8 Hz, 1 H), 3.35 - 3.32 (m, 1 H), 3.18 – 2.90 (comp, 4 H), 2.59 (dd, *J* = 8.4, 5.2 Hz, 1 H), 2.07 (s, 3 H), 2.04 - 1.98 (m, 1 H), 1.94 - 1.87 (m, 1 H), 1.20 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, CD_3OD) δ 171.8, 141.6, 138.1, 135.5, 131.1, 130.0, 128.9, 128.5, 123.7, 122.4, 119.7, 119.3, 112.8, 112.3, 67.9, 61.2, 58.9, 51.0, 46.6, 38.3, 24.0, 22.8, 22.4; HRMS (ESI) *m/z* calcd for $C_{25}H_{30}ClN_3O_2$ $(M+H)^+$, 440.2099; found, 440.2099.

(3*R*,4*S*)-1-(2-(1*H*-Indol-3-yl)ethyl)-4-((3,5-dimethoxybenzyl)(methyl)amino)-3-((*R*)-1-hydroxyethyl)piperidin-2-one (14d). Prepared according to representative procedure for compound **14a**. The crude material was purified via flash column chromatography eluting with a gradient with hexanes : ethyl acetate (1 : 1 → 0 : 1) to give 37 mg (50%) of **14d** as an amorphous white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.58 (dt, *J* = 8.0, 0.8 Hz, 1 H), 7.33 (dt, *J* = 8.0, 0.8 Hz, 1 H), 7.11 - 7.07 (comp, 2 H), 7.01 (td, *J* = 8.0, 6.8, 1.2 Hz, 1 H), 6.42 (d, *J* = 2.4 Hz, 2 H), 6.38 (t, *J* = 2.4 Hz, 1 H), 4.23 (dq, *J* = 14.0, 6.0 Hz, 1 H), 3.81 - 3.71 (comp, 7 H), 3.57 - 3.51 (m, 1 H), 3.47, 3.41 (ABq, J_{AB} = 12.8 Hz, 2 H), 3.34 - 3.30 (m, 1 H), 3.17 - 2.93 (comp, 4 H), 2.58 (dd, *J* = 8.8, 5.6 Hz, 1 H), 2.09 (s, 3 H), 2.04 - 1.98 (m, 1 H), 1.95 - 1.85 (m, 1 H), 1.19 (d, *J* = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz, CD_3OD) δ 171.9, 162.5, 141.4, 138.1, 128.9, 123.7, 122.4, 119.7, 119.3, 112.8, 112.3, 107.8, 100.3, 68.0, 61.0, 59.8, 55.7, 50.9, 46.7, 38.4, 24.0, 22.8, 22.3; HRMS (ESI) *m/z* calcd for $C_{27}H_{35}N_3O_4$ $(M+H)^+$, 466.2700; found, 466.2701.

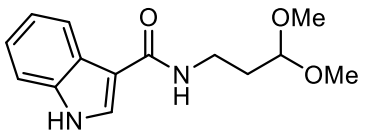
(3*R*,4*S*)-1-(2-(1*H*-Indol-3-yl)ethyl)-3-((*R*)-1-hydroxyethyl)-4-((3-methoxybenzyl)(methyl)amino)piperidin-2-one (14e). Prepared according to representative procedure for compound **14a**. The crude material was purified via flash column chromatography eluting with a gradient with hexanes : ethyl acetate (1 : 1) → ethyl acetate : methanol (20 : 1) to give 18 mg (26%) of **14e** as an off-white, amorphous solid. ^{1}H NMR (400 MHz) δ 8.19 (s, 1 H), 7.58 (d, *J* = 8.0 Hz, 1 H), 7.34 (d, *J* = 8.0 Hz, 1 H), 7.24 – 7.16 (comp, 2 H), 7.10 (td, *J* = 8.0, 1.2 Hz, 1 H), 7.03 (d, *J* = 2.4 Hz, 1 H), 6.82 (d, *J* = 2.0 Hz, 1 H), 6.80 (d, *J* = 2.0 Hz, 1 H), 6.77 (t, *J* = 2.0 Hz, 1 H), 4.33 (p, *J* = 6.4 Hz, 1 H), 3.81 - 3.74 (comp, 4 H), 3.60 (p, *J* = 6.4 Hz, 1 H), 3.50, 3.43 (ABq, J_{AB} = 12.8 Hz, 2 H), 3.37 - 3.32 (m, 1 H), 3.24 (dt, *J* = 12.0, 4.4 Hz, 1 H), 3.11 (dt, *J* = 12.0, 8.0 Hz, 1 H), 3.04 - 2.92 (comp, 2 H), 2.41 (t, *J* = 7.2 Hz, 1 H), 2.07 (s, 3 H), 1.95 - 1.89 (comp, 2 H), 1.19 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, CD_3OD) δ 171.8, 161.4, 140.3, 137.6, 130.6, 128.9, 123.7, 122.4, 122.3, 119.7, 119.3, 115.5, 114.2, 112.8, 112.3, 68.0, 61.2, 59.6, 55.6, 50.9, 46.6, 38.3, 24.0, 22.9, 22.3; HRMS (ESI) *m/z* calcd for $C_{26}H_{33}N_3O_3$ $(M+H)^+$, 436.2595; found, 436.2599.

(3*R*,4*S*)-1-(2-(1*H*-Indol-3-yl)ethyl)-4-((benzo[*d*][1,3]dioxol-5-ylmethyl)(methyl)amino)-3-((*R*)-1-hydroxyethyl)piperidin-2-one (14f). Prepared according to representative procedure for compound **14a**. The crude material was purified via flash column chromatography eluting with a gradient with hexanes : ethyl acetate (3 : 1 → 0 : 1) to give 30 mg (28%) of **14f** as an off-white, an amorphous solid; ^{1}H NMR (400 MHz) δ 8.35 (s, 1 H), 7.63 (d, *J* = 7.6 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 7.19 (t, *J* = 7.2 Hz, 1 H), 7.12 (t, *J* = 7.6 Hz, 1 H), 7.02 (d, *J* = 2.0 Hz, 1 H), 6.74 – 6.72 (comp, 2 H), 6.67 (d, *J* = 8.0 Hz, 1 H), 4.28 (dq *J* = 6.4, 6.0 Hz, 1 H), 3.81 (p, *J* = 7.6 Hz, 1 H), 3.54 (p, *J* = 6.4 Hz, 1 H), 3.48, 3.37 (ABq, J_{AB} = 12.4 Hz, 2 H), 3.28 - 3.23 (m, 1 H), 3.16 - 3.10 (comp, 2 H), 3.07 - 2.98 (comp, 2 H), 2.65 (dd, *J* = 8.8, 5.2 Hz, 1 H), 2.10 (s, 3 H), 1.99 - 1.96 (comp, 2 H), 1.32 (d, *J* = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz) δ 170.1, 148.0, 147.1, 136.4, 131.2, 127.5, 122.4, 122.2, 122.1, 119.4, 118.7, 112.8, 111.4, 109.4, 108.3, 101.1, 66.8, 59.8, 58.6, 50.1, 47.6, 45.6, 38.0, 23.3, 22.8, 21.6; HRMS (ESI) *m/z* calcd for $C_{26}H_{31}N_3O_4$ $(M+H)^+$, 450.2387; found, 450.2394.

(3*R*,4*S*)-1-(2-(1*H*-Indol-3-yl)ethyl)-3-((*R*)-1-hydroxyethyl)-4-(methyl(3-(methylthio)benzyl)amino)piperidin-2-one (14g). Prepared according to representative procedure for compound **14a**. The crude material was purified via flash column chromatography eluting with a gradient with hexanes : ethyl acetate (1 : 1 → 0 : 1) to give 45 mg (49%) of **14g** as a fluffy white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.58 (d, *J* = 7.6 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.26 (td, *J* = 7.6, 0.8 Hz, 1 H), 7.17 - 7.15 (comp, 2 H), 7.09 (ddd, *J* = 8.0, 7.6, 0.8 Hz, 1 H), 7.07 (s, 1 H), 7.03 - 6.99 (comp, 2 H), 4.22 (dq, *J* = 8.8, 6.0 Hz, 1 H), 3.77 (dt, *J* = 13.2, 7.6 Hz, 1 H), 3.56 - 3.49 (comp, 2 H), 3.43 (d, *J* = 12.8, 1 H), 3.34 - 3.28 (m, 1 H), 3.17 - 2.92 (comp, 4 H), 2.58 (dd, *J* = 8.8, 5.6 Hz, 1 H), 2.45 (s, 3 H), 2.07 (s, 3 H), 2.02 - 1.86 (comp, 2 H), 1.19 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, CD_3OD) δ 171.8, 140.6, 139.7,

138.1, 130.0, 128.8, 127.8, 126.7, 125.4, 123.7, 122.4, 119.7, 119.3, 112.8, 112.3, 67.9, 61.1, 59.4, 50.9, 46.5, 38.3, 24.0, 22.9, 22.3, 15.5; HRMS (ESI) *m/z* calcd for $C_{26}H_{33}N_3O_2S$ $(M+Na)^+$, 474.2186; found, 474.2187.

(±)-(3*R*,4*S*)-1-(2-(1*H*-Indol-3-yl)ethyl)-4-(benzyl(methyl)amino)-3-((*R*)-1-hydroxyethyl)piperidin-2-one (14h). Prepared according to representative procedure for compound **14a**. The crude material was purified via flash column chromatography eluting with a gradient with hexanes : ethyl acetate (1 : 1) → ethyl acetate : methanol (20 : 1). To give 31 mg (48%) of **14h** as an off-white, amorphous solid. ^{1}H NMR (500 MHz) δ 8.13 (brs, 1 H), 7.58 (d, *J* = 7.9 Hz, 1 H), 7.35 (d, *J* = 7.9 Hz, 1 H), 7.33 – 7.26 (comp, 3 H), 7.21 (d, *J* = 6.6 Hz, 2 H), 7.19 (t, *J* = 7.1 Hz, 1 H), 7.11 (t, *J* = 7.1 Hz, 1 H), 7.03 (d, *J* = 2.2 Hz, 1 H), 4.34 (p, *J* = 6.1 Hz, 1 H), 3.76 (p, *J* = 7.6 Hz, 1 H), 3.64 (p, *J* = 6.4 Hz, 1 H), 3.52, 3.47 (ABq, J_{AB} = 12.7 Hz, 2 H), 3.42 (q, *J* = 7.6 Hz, 1 H), 3.26 (ddd, *J* = 13.7, 6.6, 3.4 Hz, 1 H), 3.16 - 3.10 (m, 1 H), 3.04 - 2.93 (comp, 2 H), 2.35 (t, *J* = 5.6 Hz, 1 H), 2.06 (s, 3 H), 1.96 - 1.90 (comp, 2 H), 1.16 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (125 MHz) δ 171.7, 136.7, 136.3, 129.3, 128.7, 127.9, 127.3, 122.3, 122.1, 119.4, 118.4, 112.4, 111.4, 66.4, 60.0, 48.3, 47.4, 45.1, 37.2, 29.7, 23.2, 21.9, 20.1; HRMS (ESI) *m/z* calcd for $C_{25}H_{31}N_3O_2$ $(M+H)^+$, 406.2489; found, 406.2490.



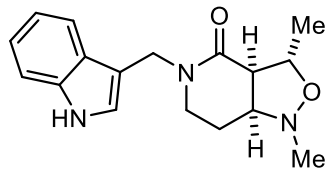
S1

***N*-(3,3-Dimethoxypropyl)-1*H*-indole-3-carboxamide (S1).** Freshly distilled thionyl chloride (0.37 g, 3.2 mmol) was added dropwise over 10 min, followed by addition of DMF (3 drops), to a solution of indole-3-carboxylic acid (0.42 g, 2.6 mmol) in THF (13 mL) at 0 ºC. The reaction was stirred for 1.5 h at 0 ºC and for an additional 0.5 h at room temperature. The solvent was removed *in vacuo*, whereupon the crude material was taken up in CH_2Cl_2 (5 mL), and added dropwise over 10 min to a solution of **9** (0.52 g, 2.6 mmol) and triethylamine (0.79 g, 7.8 mmol) in CH_2Cl_2 (50 mL) at 0 ºC. The reaction was stirred for 1 h at 0 ºC, then warmed to room temperature and stirred for an additional 1 h. The mixture was diluted with CH_2Cl_2 (100 mL), and successively washed with saturated aqueous NH_4Cl (100 mL), saturated aqueous Na_2CO_3 (100 mL), water (100 mL) and brine (100 mL). The organic fraction was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give 0.60 g (88%) of **S1** as a viscous oil (>95% purity, by ^{1}H NMR): ^{1}H NMR (400 MHz) δ 9.94 (brs, 1 H), 7.95 - 7.93 (m, 1 H), 7.72 (d, *J* = 2.9 Hz, 1 H), 7.44 - 7.42 (m, 1 H), 7.25 - 7.20 (comp, 2 H), 6.85 (t, *J* = 4.9 Hz, 1 H), 4.54 (t, *J* = 5.4 Hz, 1 H), 3.64 (q, *J* = 5.4 Hz, 2 H), 3.40 (s, 6 H), 1.98 (q, *J* = 5.4 Hz, 2 H); ^{13}C NMR (100 MHz) δ 165.7, 136.8, 128.9, 124.5, 122.7, 121.5, 119.5, 112.4,

112.2, 104.9, 53.8, 35.6, 32.2; HRMS (ESI) *m/z* calcd for $C_{14}H_{18}N_2O_3$ $(M+Na)^+$, 285.1210; found, 285.1212.

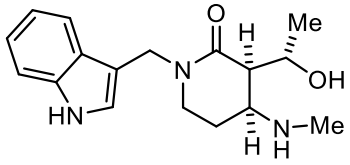
(*E*)-*N*-((1*H*-Indol-3-yl)methyl)-*N*-(3,3-dimethoxypropyl)but-2-enamide (16a). A solution of **S1** (140 mg, 0.53 mmol) in THF (3 mL) was added dropwise over 10 min to a stirred suspension of lithium aluminum hydride (100 mg, 2.7 mmol) in THF (10 mL) at 0 ºC. The reaction heated to 65 ºC for 48 h, then cooled to 0 ºC, and the Fieser work-up was performed by successive addition of water (0.1 mL), aqueous NaOH (15%, 0.1 mL), and water (1 mL). The suspension was warmed to room temperature and $MgSO_4$ was added, followed by removal of solids by vacuum filtration through a fritted funnel, and washing with copious amounts of ether and CH_2Cl_2. The filtrate was concentrated *in vacuo* to give 132 mg (quant.) of crude *N*-((1H-indol-3-yl)methyl)-3,3-dimethoxypropan-1-amine as an opaque viscous oil which was found to be unstable to acid/base extraction and chromatographic conditions, and was immediately carried on to the next step without further purification.

Crotonoyl chloride (66 mg, 0.64 mmol) was added dropwise over 5 min to a stirred solution of crude *N*-((1H-indol-3-yl)methyl)-3,3-dimethoxypropan-1-amine (130 mg, 0.53 mmol) and Hünig's base (165 mg, 1.28 mmol) in CH_2Cl_2 (5 mL) at -78 ºC. The solution was stirred for 2 h at -78 ºC, then partitioned between saturated aqueous $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL). The phases were separated, and the aqueous phase extracted with CH_2Cl_2 (2 x 10 mL). The combined organic fractions were successively washed with water (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give crude **16a** as a viscous yellow oil. The crude material was purified via silica gel flash column chromatography eluting with hexanes : ethyl acetate (2 : 1 →1 : 1 along a gradient) to give 141 mg (86%, two-steps) of **16a** as a yellow amorphous solid: ^{1}H NMR (400 MHz) (1:1 rotamer mixture) δ 9.04 (brs, 0.5 H), 8.85 (brs, 0.5 H), 7.69 (d, *J* = 7.8 Hz, 0.5 H), 7.53 (d, *J* = 7.8 Hz, 0.5 H), 7.38 (d, *J* = 8.1 Hz, 0.5 H), 7.34 (d, *J* = 8.1 Hz, 0.5 H), 7.23 - 6.96 (comp, 4 H), 6.41 (dd, *J* = 14.9, 1.2 Hz, 0.5 H), 6.34 (dd, *J* = 14.9, 1.2 Hz, 0.5 H), 4.85 (s, 1 H), 4.75 (s, 1 H), 4.40 (t, *J* = 5.5 Hz, 0.5 H), 4.30 (t, *J* = 5.5 Hz, 0.5 H), 3.53 (t, *J* = 7.4 Hz, 1 H), 3.40 (t, *J* = 7.4 Hz, 1 H) 3.28 (s, 6 H), 1.97 - 1.81 (comp, 5 H); ^{13}C NMR (100 MHz) (1 : 1 rotamer mixture) δ 166.0, 165.4, 141.0, 140.9, 135.7, 135.3, 125.9, 124.9, 123.2, 121.5, 121.3, 121.1, 121.1, 120.9, 118.6, 118.2, 117.3, 111.0, 110.6, 110.2, 101.9, 101.3, 52.2, 51.9, 43.5, 41.5, 41.0, 38.9, 31.1, 29.8, 17.3, 17.2; HRMS (ESI) *m/z* calcd for $C_{18}H_{24}N_2O_3$ $(M+Na)^+$, 339.1679; found, 339.1680.



S2

(3*R*,3a*R*,7a*S*)-5-((1*H*-Indol-3-yl)methyl)-1,3-dimethylhexahydroisoxazolo[4,3-*c*]pyridin-4(1*H*)-one (S2). A solution of trifluoroacetic acid (36 mg, 0.32 mmol) and **16a** (100 mg, 0.32 mmol) in a mixture of acetone/water (2 : 1, 6 mL) was stirred for 3 h at room temperature. Saturated aqueous $NaHCO_3$ (20 mL) was added, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue was dissolved in toluene (5 mL), followed by the addition of *N*-methylhydroxylamine hydrochloride (40 mg, 0.47 mmol) and triethylamine (81 mg, 0.80 mmol). The resulting solution was heated under reflux for 1 h, at which point the solution was cooled to room temperature, and partitioned between saturated aqueous $NaHCO_3$ (20 mL), ethyl acetate (20 mL) and methanol (1 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 x 20 mL). The combined organic fractions were washed successively with water (50 mL) and brine (50 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give 76 mg (81%, two-steps) of **S2** as a colorless oil (>95% purity, by ^{1}H NMR): ^{1}H NMR (400 MHz, CD_3OD) δ 7.57 (dt, *J* = 8.0, 1.0 Hz, 1 H), 7.35 (dt, *J* = 8.2, 0.8 Hz, 1 H), 7.26 (s, 1 H), 7.11 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1 H), 7.00 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1 H), 4.78 (s, 2 H), 3.93 - 3.87 (m, 1 H), 3.40 - 3.33 (m, 1 H), 3.20 (dt, *J* = 12.8, 4.3 Hz, 1 H), 2.97 - 2.88 (comp, 2 H), 2.62 (s, 3 H), 1.79 (tt, *J* = 14.4, 4.0 Hz, 1 H), 1.63 (dq, *J* = 14.4, 3.9 Hz, 1 H), 1.45 (d, *J* = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz, CD_3OD) δ 169.2, 136.9, 126.5, 124.5, 121.4, 118.7, 118.4, 111.0, 109.8, 77.3, 66.2, 54.9, 41.4, 41.1, 24.1, 24.1, 18.1; HRMS (ESI) *m/z* calcd for $C_{17}H_{21}N_3O_2$ $(M+Na)^+$, 322.1526; found, 322.1529.



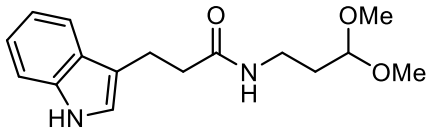
S3

(3*R*,4*S*)-1-((1*H*-Indol-3-yl)methyl)-3-((*R*)-1-hydroxyethyl)-4-(methylamino)piperidin-2-one (S3). A mixture of **S2** (100 mg, 0.35 mmol) and zinc (dust, 680 mg, 10.4 mmol) in acetic acid (aq 80%, 21 mL) was stirred for 48 h at room temperature. Excess zinc was removed via vacuum filtration, and washed with ethyl acetate (150 mL), whereupon zinc acetate immediately precipitated out of solution as a fluffy

white solid. The zinc acetate was removed by vacuum filtration and washed with ethyl acetate. The combined filtrate and washes were concentrated *in vacuo*, and the residue dissolved in aqueous HCl (1 M, 50 mL). The resulting solution was washed with ether (50 mL), and basified to pH ~14 with solid NaOH. The basic solution was extracted with CH_2Cl_2 (3 x 75 mL). The combined organic fractions were washed with brine (100 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give 150 mg (quant) of crude **S3** as the acetate salt with residual acetic acid. The crude material was taken up in aqueous HCl (1 M, 50 mL) and washed with ether (2 x 50 mL). The aqueous fraction was basified to pH ~14 with solid NaOH, and extracted with CH_2Cl_2 (3 x 75 mL). The combined organic fractions were successively washed with aqueous NaOH (1 M, 100 mL), saturated aqueous $NaHCO_3$ (100 mL), water (100 mL), and brine (100 mL). The organic fraction was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give 69 mg (66%) of pure **S3** as an off-white, amorphous solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.59 (dt, *J* = 7.9, 0.9 Hz, 1 H), 7.35 (dt, *J* = 8.1, 0.9 Hz, 1 H), 7.24 (s, 1 H), 7.09 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1 H), 6.98 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1 H), 4.89 (d, *J* = 14.4 Hz, 1 H), 4.56 (d, *J* = 14.4, 1 H), 4.42 (p, *J* = 6.4 Hz, 1 H), 3.38 (dt, *J* = 12.9, 6.6 Hz, 1 H), 3.28 - 3.21 (comp, 2 H), 2.55 (dd, *J* = 6.5, 4.1 Hz, 1 H), 2.43 (s, 3 H), 2.10 - 2.02 (m, 1 H), 1.88 - 1.83 (m, 1 H), 1.33 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, CD_3OD) δ 169.7, 136.8, 126.7, 124.4, 121.3, 118.7, 118.4, 110.9, 110.1, 66.3, 54.8, 50.1, 42.1, 40.8, 32.4, 23.8, 21.0; HRMS (ESI) *m/z* calcd for $C_{17}H_{23}N_3O_2$ $(M+Na)^+$, 324.1682; found, 324.1686.

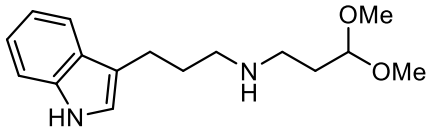
(3*R*,4*S*)-1-((1*H*-Indol-3-yl)methyl)-4-((3,5-dichlorobenzyl)(methyl)amino)-3-((*R*)-1-hydroxyethyl)piperidin-2-one (14i). A solution of **S3** (75 mg, 0.25 mmol) and 3,5-dichlorobenzaldehyde (130 mg, 0.75 mmol) in acetonitrile (2 mL) was heated under reflux for 5 h. The reaction was cooled to room temperature, and sodium borohydride (28 mg, 0.75 mmol) was added. The solution was stirred at room temperature for 14 h, at which point, LC/MS analysis showed no trace of the desired product. Methanol (1 mL) and acetic acid (0.2 mL) were added, and the solution was stirred for 24 h at room temperature, no product detected by LC/MS. Acetic acid (0.1 mL) and $NaBH_3CN$ (62 mg, 1.0 mmol) were added, and the solution was stirred for an additional 24 h at room temperature. LC/MS analysis showed complete conversion to product and the reaction mixture was partitioned between aqueous NaOH (1 M, 20 mL) and CH_2Cl_2 (25 mL). The two phases were separated, and the aqueous phase extracted with CH_2Cl_2 (2 x 25 mL). The combined organic fractions were washed with water (50 mL), brine (50 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give crude **14i** as an amorphous solid. The crude material was purified via silica gel flash column chromatography eluting with CH_2Cl_2 : methanol (1 : 0 → 95 : 5 along a gradient) to give 59 mg (51%) of **14i** as an amorphous white solid: ^{1}H NMR (400 MHz) δ 8.54 (brs, 1 H), 7.68 (d, *J* = 8.0 Hz, 1 H), 7.38 (d, *J* = 8.4 Hz, 1 H), 7.25 - 7.18 (comp, 3 H), 7.09 (ddd, *J* = 8.0, 7.2, 0.8 Hz, 1 H), 7.06 (d, *J* = 2.0 Hz, 2 H), 4.96 (d, *J* = 14.4 Hz, 1 H), 4.51 (d, *J* = 14.4 Hz, 1 H), 4.36 (dq, *J* = 8.4, 5.6 Hz, 1 H), 3.42 - 3.35 (comp, 3 H), 3.23 - 3.11 (comp, 2 H), 2.75 (dd, *J* = 8.8, 6.0 Hz, 1 H), 2.06 (s, 3 H), 1.99 - 1.92

(m, 1 H), 1.86 - 1.78 (m, 1 H), 1.41 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz) δ 169.7, 141.2, 136.3, 135.1, 127.7, 127.0, 126.8, 124.3, 122.4, 119.9, 119.3, 111.5, 111.3, 66.5, 60.4, 57.5, 50.3, 43.5, 40.8, 38.6, 22.6, 21.6; HRMS (ESI) *m/z* calcd for $C_{26}H_{31}Cl_2N_3O_3$ $(M+Na)^+$, 482.1373 and 484.1348; found, 482.1373 and 484.1349.



S4

***N*-(3,3-Dimethoxypropyl)-3-(1*H*-indol-3-yl)propanamide (S4).** Thionyl chloride (1.1 g, 9.6 mmol) was added dropwise over 10 min to a solution of **15b** (1.5 g, 8.0 mmol) and DMF (3 drops) in THF (40 mL) at 0 ºC. The reaction was stirred for 2 h at 0 ºC, whereupon all volatiles were removed *in vacuo*. The crude material was dissolved in CH_2Cl_2 (20 mL) and added dropwise over 20 min to a solution of **9** (1.46 g, 7.3 mmol) and triethylamine (3.30 g, 32.8 mmol) in CH_2Cl_2 (120 mL) at 0 ºC. The reaction was stirred for 1 h at 0 ºC, followed by stirring for 2 h at room temperature. The solution was diluted with CH_2Cl_2 (300 mL) and washed successively with saturated aqueous NH_4Cl (150 mL), aqueous Na_2CO_3 (5% w/v, 150 mL), and brine (150 mL). The organic fraction was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give crude **S4** as a viscous yellow oil. The crude material was purified via silica gel flash column chromatography eluting with hexanes : ethyl acetate (1 : 1 → 1 : 3 along a gradient) to give 2.05 g (97%) of **S4** as a viscous yellow oil. ^{1}H NMR (400 MHz) δ 8.42 (brs, 1 H), 7.59 (d, J = 8.0 Hz, 1 H), 7.33 (d, J = 8.0 Hz, 1 H), 7.18 (td, J = 8.0, 1.2 Hz, 1 H), 7.11 (ddd, J = 8.0, 7.2, 0.8 Hz, 1 H), 6.96 (d, J = 2.4 Hz, 1 H), 5.94 (brs, 1 H), 4.26 (t, J = 5.2 Hz, 1 H), 3.30 - 3.25 (comp, 8 H), 3.10 (t, J = 7.2 Hz, 2 H), 2.55 (t, J = 7.2 Hz, 2 H), 1.69 (q, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz) δ 172.7, 136.4, 127.1, 121.9, 121.8, 119.2, 118.6, 114.7, 111.3, 103.9, 53.3, 37.4, 35.3, 31.9, 21.4; HRMS (ESI) *m/z* calcd for $C_{16}H_{22}N_2O_3$ $(M+Na)^+$, 313.1523; found, 313.1524.

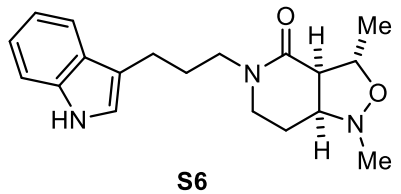


S5

***N*-(3-(1*H*-Indol-3-yl)propyl)-3,3-dimethoxypropan-1-amine (S5).** A solution of **S4** (400 mg, 1.4 mmol) in THF (5 mL) was added dropwise over 15 min to a suspension of lithium aluminum hydride (120 mg, 3.0 mmol) in THF (30 mL) at 0 ºC. The reaction was heated at 65 ºC for 14 h, at which point the

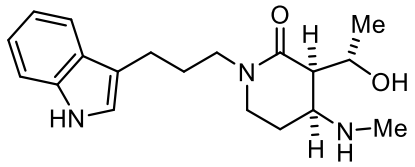
reaction was cooled to 0 ºC, and the Fieser work-up was performed by successive addition of water (0.1 mL), aqueous NaOH (15% w/v, 0.1 mL), and water (1 mL). The suspension was warmed to room temperature and $MgSO_4$ was added. The solids were removed by filtration through a fritted funnel, and washed with copious amounts of CH_2Cl_2. The filtrate was concentrated *in vacuo* to give crude **S5** as an opaque viscous oil. The crude material was taken up into aqueous HCl (0.2 M, 150 mL) and washed with ether (2 x 100 mL). The aqueous fraction was basified to pH ~ 12-14 by dropwise addition of aqueous NaOH (40% w/v), and extracted with CH_2Cl_2 (4 x 150 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ (200 mL), water (200 mL), and brine (200 mL). The organic fraction was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give 331 mg (87%) of **S5** as an oil (>95% purity, by ^{1}H NMR). ^{1}H NMR (400 MHz) δ 8.43 (brs, 1 H), 7.60 (d, *J* = 7.6 Hz, 1 H), 7.33 (dt, *J* = 8.0, 1.2 Hz, 1 H), 7.18 (td, *J* = 6.8, 1.2 Hz, 1 H), 7.10 (td, *J* = 6.8, 1.2 Hz, 1 H), 6.94 (d, *J* = 2.0 Hz, 1 H), 4.46 (t, *J* = 5.6 Hz, 1 H), 3.33 (s, 6 H), 2.80 (t, *J* = 7.6 Hz, 2 H), 2.72 - 2.68 (comp, 4 H), 1.92 (p, *J* = 7.6 Hz, 2 H), 1.82 (q, *J* = 6.0 Hz, 2 H); ^{13}C NMR (100 MHz) δ 136.4, 127.5, 121.8, 121.2, 119.0, 118.8, 116.1, 111.1, 103.6, 52.9, 49.9, 45.5, 32.8, 30.4, 22.9; HRMS (ESI) *m/z* calcd for $C_{16}H_{24}N_2O_2$ $(M+H)^+$, 277.1911; found 277.1912.

(*E*)-*N*-(3-(1*H*-Indol-3-yl)propyl)-*N*-(3,3-dimethoxypropyl)but-2-enamide (16b). Crotonoyl chloride (200 mg, 1.9 mmol) was added dropwise over 10 min to a stirred solution of **S5** (440 mg, 1.6 mmol) and Hünig's base (500 mg, 3.8 mmol) in CH_2Cl_2 (16 mL) at -78 ºC. The solution was stirred for 2 h at -78 ºC, then partitioned between saturated aqueous $NaHCO_3$ solution (50 mL) and CH_2Cl_2 (50 mL). The two phases were separated and the aqueous phase extracted with CH_2Cl_2 (2 x 50 mL). The combined organic fractions were successively washed with water (50 mL), brine (50 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give crude **16b** as a colorless oil. The crude material was purified via silica gel flash column chromatography eluting with a gradient hexanes : ethyl acetate (3 : 1 →1 : 1 along a gradient) to give 340 mg (62%) of **16b** as an opaque viscous oil. ^{1}H NMR (400 MHz) (1:1 rotamer mixture) δ 8.69 (brs, 0.5 H), 8.54 (brs, 0.5 H), 7.57 (dd, *J* = 8.0, 0.4 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 0.5 H), 7.32 (d, *J* = 8.0 Hz, 0.5 H), 7.20 - 7.06 (comp, 2 H), 7.00 - 6.95 (comp, 1.5 H), 6.85 (dq, *J* = 14.2, 6.8 Hz, 0.5 H), 6.32 (dd, *J* = 14.2, 1.6 Hz, 0.5 H), 5.98 (dd, *J* = 14.2, 1.6 Hz, 0.5 H), 4.38 (t, *J* = 6.0 Hz, 0.5 H), 4.33 (t, *J* = 6.0 Hz, 0.5 H), 3.50 - 3.39 (comp, 3 H), 3.36 - 3.28 (comp, 7 H), 2.77 (app q, *J* = 7.2 Hz, 2 H), 2.01 (q, *J* = 7.2 Hz, 2 H), 1.90 - 1.83 (comp, 3.5 H), 1.68 (dd, *J* = 6.8, 1.6 Hz, 1.5 H); ^{13}C NMR (400 MHz) (1:1 rotamer mixture) δ 166.5, 166.4, 141.8, 141.5, 136.6, 136.4, 127.4, 127.2, 121.9, 121.8, 121.6, 121.5, 119.1, 118.9, 118.7, 118.6, 115.3, 114.6, 111.3, 111.2, 102.9, 102.2, 53.2, 53.0, 48.0, 46.5, 43.6, 42.3, 32.5, 31.0, 29.6, 28.0, 22.6, 22.3, 18.3, 18.0; HRMS (ESI) *m/z* calcd for $C_{20}H_{28}N_2O_2$ $(M+Na)^+$, 367.1992; found, 367.1994.



S6

(3*R*,3a*R*,7a*S*)-5-(3-(1*H*-Indol-3-yl)propyl)-1,3-dimethylhexahydroisoxazolo[4,3-*c*]pyridin-4(1*H*)-one (S6). A solution of trifluoroacetic acid (5 drops) and **16b** (50 mg, 0.14 mmol) in TFE/water (3 : 1, 4 mL) was stirred for 1 h at room temperature. Saturated aqueous $NaHCO_3$ (10 mL) was added, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was dissolved in toluene (2 mL), followed by the addition of N-methylhydroxylamine hydrochloride (18 mg, 0.22 mmol) and triethylamine (37 mg, 0.36 mmol). The reaction was heated under reflux for 1.5 h. After cooling the to room temperature, the reaction was partitioned between saturated aqueous $NaHCO_3$ (10 mL), ethyl acetate (20 mL), and methanol (1 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic fractions were washed successively with water (40 mL) and brine (40 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give 49 mg (quant) of **16b** as an oil of ~80 – 90% purity, as judged by ^{1}H NMR. The crude material was taken up in aqueous HCl (1 M, 10 mL), and washed with ether (2 x 10 mL). The aqueous fraction was basified to pH 12-14 by dropwise addition of aqueous NaOH (40% w/v), as judged by pH paper. The basic solution was extracted with CH_2Cl_2 (2 x 30 mL) and ethyl acetate (2 x 30 mL). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give 33 mg (68%) of **16b** as a colorless oil. ^{1}H NMR (400 MHz) δ 8.24 (brs, 1 H), 7.57 (d, J = 7.6 Hz, 1 H), 7.35 (dt, J = 8.4, 1.2 Hz, 1 H), 7.18 (ddd, J = 8.4, 7.2, 1.2, 1 H), 7.10 (ddd, J = 8.0, 7.2, 1.2 Hz, 1 H), 7.03 (d, J = 2.0 Hz, 1 H), 3.94 (dq, J = 7.2, 6.0 Hz, 1 H), 3.68 - 3.55 (comp, 2 H), 3.44 - 3.37 (m, 1 H), 3.07 (dt, J = 12.4, 4.0 Hz, 1 H), 2.91 - 2.87 (m, 1 H), 2.84 - 2.70 (comp, 3 H), 2.69 (s, 3 H), 2.00 - 1.85 (comp, 3 H), 1.71 (dq, J = 14.4, 3.6 Hz, 1 H), 1.47 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz) δ 169.0, 136.4, 127.3, 121.8, 121.5, 119.1, 118.7, 115.4, 111.1, 77.6, 66.1, 55.4, 47.3, 46.0, 43.2, 27.6, 25.2, 22.4, 19.2; HRMS (ESI) *m/z* calcd for $C_{19}H_{25}N_3O_2$ $(M+Na)^+$, 350.1839; found, 350.1845.

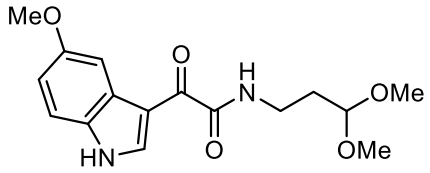


S7

(3*R*,4*S*)-1-(3-(1*H*-Indol-3-yl)propyl)-3-((*R*)-1-hydroxyethyl)-4-(methylamino)piperidin-2-one (S7). A suspension of zinc (dust, 7.0 g, 84 mmol) and **S6** (1.4 g, 4.2 mmol) in acetic acid (aq 80%, 200 mL)

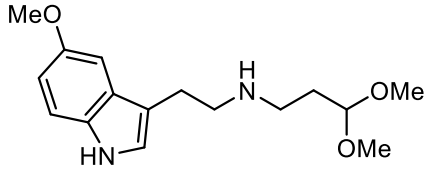
was stirred for 3 h at 65 ºC, at which point the reaction was cooled to room temperature. Excess zinc was removed via vacuum filtration and washed with ethyl acetate (200 mL), whereupon zinc acetate immediately precipitated out of solution as a fluffy white solid. The zinc acetate was removed by vacuum filtration and washed with ethyl acetate. The combined filtrate and washes were concentrated *in vacuo*. The resulting residue was dissolved in aqueous HCl (1 M, 300 mL), and washed with ether (150 mL). The aqueous fraction was basified to pH ~14 with solid NaOH, and extracted with CH_2Cl_2 (3 x 300 mL). The combined organic fractions were washed with brine (200 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was purified via silica gel flash column chromatography eluting with CH_2Cl_2 : methanol (98 : 2 → 9 : 1 along a gradient) to give 791 mg (57%) of **S7** as a yellow oil. ^{1}H NMR (500 MHz, CD_3OD) δ 7.51 (dt, *J* = 8.0, 1.5 Hz, 1 H), 7.30 (dt, *J* = 8.5, 1.0 Hz, 1 H), 7.06 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1 H), 7.03 (s, 1 H), 6.97 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1 H), 4.41 (t, *J* = 6.2 Hz, 1 H), 3.54 (ddd, *J* = 13.4, 8.4, 6.8 Hz, 1 H), 3.38 (ddd, *J* = 12.7, 7.5, 6.3 Hz, 1 H), 3.28 - 3.20 (comp, 2 H), 3.16 (p, *J* = 3.8 Hz, 1 H), 2.75 (t, *J* = 7.4 Hz, 2 H), 2.37 (s, 3 H), 2.34 (dd, *J* = 5.9, 4.1 Hz, 1 H), 2.09 - 2.02 (m, 1 H), 1.99 - 1.93 (comp, 2 H), 1.79 (dtd, *J* = 14.3, 7.4, 3.6 Hz, 1 H), 1.25 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 171.2, 138.2, 128.7, 122.8, 122.2, 119.4, 119.3, 115.7, 112.2, 67.4, 56.1, 51.4, 48.3, 45.0, 33.7, 28.4, 25.2, 23.7, 22.3; HRMS (ESI) *m/z* calcd for $C_{19}H_{27}N_3O_2$ $(M+Na)^+$, 352.1995; found, 352.2000.

(3*R*,4*S*)-1-(3-(1*H*-Indol-3-yl)propyl)-4-((3,5-dichlorobenzyl)(methyl)amino)-3-((*R*)-1-hydroxyethyl)piperidin-2-one (14j). A solution of **S7** (100 mg, 0.30 mmol) and 3,5-dichlorobenzaldehyde (159 mg, 0.91 mmol) in acetonitrile (2 mL) was heated under reflux for 2 h. The reaction was cooled to room temperature, at which time $NaBH_3CN$ (22 mg, 0.35 mmol) and acetic acid (glacial, 53 μL, 0.89 mmol) were added. The reaction was stirred for 20 h at room temperature, then partitioned between aqueous NaOH (1 M, 15 mL) and CH_2Cl_2 (30 mL). The two phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic fractions were washed with brine (15 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified via silica gel flash column chromatography eluting with hexanes : ethyl acetate (1 : 1 → 0 : 1 along a gradient) to give 30 mg (20%) of **14j** as an amorphous white solid. ^{1}H NMR (400 MHz) δ 8.10 (brs, 1 H), 7.57 (d, *J* = 7.6 Hz, 1 H), 7.36 (dt, *J* = 8.4, 0.8 Hz, 1 H), 7.27 (t, *J* = 2.0 Hz, 1 H), 7.21 - 7.17 (m, 1 H), 7.14 (d, *J* = 2.0 Hz, 2 H), 7.11 (ddd, *J* = 8.0, 7.2, 0.8 Hz, 1 H), 7.04 (d, *J* = 2.0 Hz, 1 H), 7.33 (dq, *J* = 8.8, 6.4 Hz, 1 H), 3.62 - 3.55 (comp, 2 H), 3.45 (d, *J* = 13.2 Hz, 1 H), 3.39 - 3.24 (comp, 3 H), 3.14 (dt, *J* = 10.4, 5.6 Hz, 1 H), 2.77 (t, *J* = 7.2 Hz, 2 H), 2.70 (dd, *J* = 8.4, 5.6 Hz, 1 H), 2.16 (s, 3 H), 2.13 - 2.05 (comp, 2 H), 1.99 - 1.92 (comp, 2 H), 1.34 (d, *J* = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz) δ 169.9, 141.2, 136.3, 135.2, 127.8, 127.3, 127.1, 121.9, 121.4, 119.2, 118.7, 115.4, 111.2, 66.5, 60.3, 57.9, 50.2, 46.6, 44.9, 39.5, 27.5, 22.5, 22.5, 21.8; HRMS (ESI) *m/z* calcd for $C_{26}H_{31}Cl_2N_3O_2$ $(M+Na)^+$, 510.1686 and 512.1662; found, 510.1690 and 512.1695.



S8

***N*-(3,3-Dimethoxypropyl)-2-(5-methoxy-1*H*-indol-3-yl)-2-oxoacetamide (S8).** Oxalyl chloride (0.95 g, 7.5 mmol) was added dropwise over 10 min to a solution of 5-methoxyindole (1.0 g, 6.8 mmol) in ether (15 mL) at 0 ºC, whereupon a red precipitate immediately crashed out of solution and the resulting suspension was stirred for 1 h at room temperature. The precipitate was collected via vacuum filtration, and dried *in vacuo* to give 1.21 g (75%) of 5-methoxyindole-3-glyoxal chloride as a red powder. A slurry of 5-methoxyindole-3-glyoxal chloride (1.20 g, 5.1 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 10 min to a solution of **9** (1.0 g, 5.1 mmol) and triethylamine (1.3 g, 13 mmol) in CH_2Cl_2 (50 mL) at 0 ºC, and the reaction was stirred for 2 h at room temperature. Saturated aqueous $NaHCO_3$ (50 mL) was added, the two phases were separated, and the aqueous phase extracted with CH_2Cl_2 (3 x 100 mL). The combined organic fractions were washed with water (100 mL), brine (100 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give 1.59 g (98%) of **S8** as a pale-yellow, amorphous solid of (>95% purity, by ^{1}H NMR). ^{1}H NMR (400 MHz) δ 9.10 (brs, 1 H), 9.03 (d, *J* = 3.2 Hz, 1 H), 7.93 (d, *J* = 2.5 Hz, 1 H), 7.87 (t, *J* = 5.3 Hz, 1 H), 7.32 (d, *J* = 8.8 Hz, 1 H), 6.93 (dd, *J* = 8.8, 2.5 Hz, 1 H) 4.50 (t, *J* = 5.4 Hz, 1 H), 3.90 (s, 3 H), 3.49 (t, *J* = 6.1 Hz, 2 H), 3.39 (s, 6 H), 1.92 (q, *J* = 5.8 Hz, 2 H); ^{13}C NMR (125 MHz) δ 180.6, 162.5, 156.9, 138.2, 130.4, 127.6, 114.3, 113.2, 112.4, 103.9, 103.6, 55.8, 53.4, 35.2, 31.8; HRMS (ESI) *m/z* calcd for $C_{16}H_{20}N_2O_5$ $(M+Na)^+$, 343.1264; found, 343.1264.



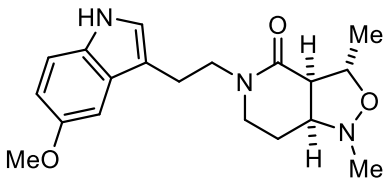
S9

3,3-Dimethoxy-*N*-(2-(5-Methoxy-1*H*-indol-3-yl)ethyl)propan-1-amine (S9).

A solution of **S8** (200 mg, 0.62 mmol) in THF (5 mL) was added dropwise over 5 min to a suspension of lithium aluminum hydride (230 mg, 6.2 mmol) in THF (15 mL) at 0 ºC. The reaction heated to 65 ºC for 14 h. The reaction was then cooled to 0 ºC, and the Fieser work-up was performed by successive addition of water (0.25 mL), aqueous NaOH (15%, 0.25 mL), and water (1 mL). The suspension was warmed to room temperature, and $MgSO_4$ was added. The solids were removed by vacuum filtration through a fritted funnel and washed with copious amounts of CH_2Cl_2. The filtrate was concentrated *in vacuo* to give crude

S9 as an opaque viscous oil. The crude material was purified via acid/base extraction. The crude oil was taken up into aqueous HCl (0.2 M, 100 mL) and washed with ether (2 x 75 mL). The aqueous fraction was basified to pH 12 - 14 by dropwise addition of aqueous NaOH (40% w/v). The basic solution was extracted with CH_2Cl_2 (4 x 100 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ (200 mL), water (200 mL), brine (200 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give 164 mg (90%) of **S9** as an oil (>95% purity, by ^{1}H NMR). ^{1}H NMR (400 MHz) δ 8.58 (brs, 1 H), 7.23 (dd, *J* = 8.0, 0.5 Hz, 1 H), 7.05 (d, *J* = 2.4 Hz, 1 H), 6.99 (d, *J* = 2.4 Hz, 1 H), 6.83 (dd, *J* = 8.0, 2.4 Hz, 1 H), 4.38 (t, *J* = 5.6 Hz, 1 H), 3.85 (s, 3 H), 3.24 (s, 6 H), 2.95 (app s, 4 H), 2.72 (t, *J* = 7.2 Hz, 2 H), 1.80 (td, *J* = 7.2, 5.6 Hz, 2 H); ^{13}C NMR (100 MHz) δ 153.8, 131.6, 127.7, 123.0, 113.0, 112.1, 111.9, 103.6, 100.6, 55.9, 53.0, 49.8, 45.2, 32.5, 25.4; HRMS (ESI) *m/z* calcd for $C_{16}H_{24}N_2O_3$ $(M+H)^+$, 293.1860; found, 293.1870.

(*E*)-*N*-(3,3-Dimethoxypropyl)-*N*-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)but-2-enamide (18a). Crotonoyl chloride (0.53 g, 5.1 mmol) was added dropwise over 5 min to a solution of **S9** (1.2 g, 4.2 mmol) and Hünig's base (1.3 g, 11 mmol) in CH_2Cl_2 (42 mL) at -78 ºC. The reaction was stirred for 2 h at -78 ºC. Saturated aqueous $NaHCO_3$ (40 mL) was added and the mixture was stirred for 20 min at room temperature. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic fractions were washed with saturated aqueous NH_4Cl (100 mL), water (100 mL), brine (100 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified via silica gel flash column chromatography eluting with hexanes : ethyl acetate (1 : 1 → 1 : 2 along a gradient) to give 1.08 g (71%) of **18a** as an oil: ^{1}H NMR (400 MHz) (1:1 mixture of rotamers) δ 8.78 (brs, 0.5 H), 8.65 (brs, 0.5 H), 7.21 (app t, *J* = 8.9 Hz, 1H), 7.11 (d, *J* = 2.2 Hz, 0.5 H), 7.05 - 6.74 (comp, 3.5 H), 6.30 (dd, *J* = 14.9, 1.6 Hz, 0.5 H), 6.02 (dd, *J* = 14.9, 1.6 Hz, 0.5 H), 4.39 (t, *J* = 5.6 Hz, 0.5 H), 4.31 (t, *J* = 5.6 Hz, 0.5 H), 3.87 (s, 1.5 H), 3.84 (s, 1.5 H), 3.66 (t, *J* = 7.1 Hz, 1 H), 3.61 (t, *J* = 7.1 Hz, 1 H), 3.44 (t, *J* = 7.3 Hz, 1 H), 3.35 (t, *J* = 7.3 Hz, 1 H), 3.30 (s, 3 H), 3.28 (s, 3 H), 3.01 (t, *J* = 7.1 Hz, 1 H), 2.96 (t, *J* = 7.1 Hz, 1 H) 1.94 - 1.79 (comp, 3.5 H), 1.66 (dd, *J* = 6.8, 1.4 Hz, 1.5 H); ^{13}C NMR (100 MHz) (1:1 mixture of rotamers) δ 166.7, 166.5, 154.0, 153.8, 141.9, 141.0, 131.6, 131.5, 127.8, 127.5, 123.3, 122.9, 121.8, 121.7, 112.7, 112.2, 112.1, 112.0, 111.4, 102.9, 102.1, 100.5, 100.1, 55.9, 55.9, 53.1, 53.0, 48.6, 47.7, 44.2, 42.9, 32.5, 30.9, 25.4, 23.7, 18.3, 18.0; HRMS (ESI) *m/z* calcd for $C_{20}H_{28}N_2O_4$ $(M+Na)^+$, 383.1941; found, 383.1943.



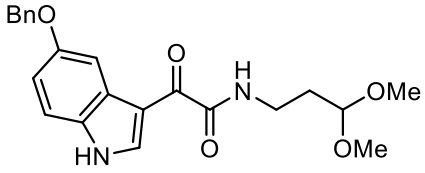
S10

(3*R*,3a*R*,7a*S*)-5-(2-(5-Methoxy-1*H*-indol-3-yl)ethyl)-1,3-dimethylhexahydroisoxazolo[4,3-*c*]pyridin-4(1*H*)-one (S10). A solution of **18a** (250 mg, 0.69 mmol) and TFA (5 drops) in a mixture of TFE/water (3 : 1, 12 mL) was stirred for 1 h at room temperature. The reaction was poured into saturated aqueous $NaHCO_3$ (30 mL), and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic fractions were washed with water (50 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue was dissolved in toluene (10 mL), followed by the addition of *N*-methylhydroxylamine hydrochloride (86 mg, 1.0 mmol) and triethylamine (175 mg, 1.73 mmol). The reaction was heated under reflux for 2 h, whereupon the mixture was cooled to room temperature, and partitioned between saturated aqueous $NaHCO_3$ (50 mL), ethyl acetate (50 mL) and methanol (2 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organic fractions were washed with water (100 mL), brine (100 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give 202 mg (85%) of **S10** as a viscous oil (>95% purity, by ^{1}H NMR). ^{1}H NMR (400 MHz) δ 8.11 (brs, 1 H), 7.25 (d, J = 8.8 Hz, 1 H), 7.07 (d, J = 2.4 Hz, 1 H), 7.01 (d, J = 2.1 Hz, 1 H), 6.85 (dd, J = 8.8, 2.4 Hz, 1 H), 3.92 - 3.87 (comp, 4 H), 3.76 (dt, J = 13.3, 7.7 Hz, 1 H), 3.65 (dt, J = 13.3, 7.0 Hz, 1 H), 3.56 (td, J = 11.8, 3.0 Hz, 1 H), 3.01 - 2.95 (comp, 3 H), 2.87 - 2.79 (comp, 2 H), 2.66 (s, 3 H), 1.79 (tt, J = 11.2, 4.2 Hz, 1 H), 1.61 (dq, J = 11.2, 3.4 Hz, 1 H), 1.46 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (100 MHz) δ 169.1, 154.0, 131.6, 127.8, 123.0, 112.5, 112.13, 112.06, 100.7, 77.5, 66.2, 56.1, 55.4, 48.5, 44.1, 43.3, 25.1, 23.5, 19.4; HRMS (ESI) *m/z* calcd for $C_{19}H_{25}N_3O_3$ $(M+Na)^+$, 366.1788; found, 266.1794.

(3*R*,4*S*)-3-((*R*)-1-Hydroxyethyl)-1-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)-4-(methylamino)piperidin-2-one (19a). Zinc (powder, 588 mg, 9.00 mmol) was added in three portions over 1.5 h to a solution of **S10** (100 mg, 0.30 mmol) in acetic acid (aq 80%, 20 mL) at 60 ºC. The reaction was stirred for 1 h at 60 ºC. The suspension was cooled to room temperature, excess zinc was filtered and washed with ethyl acetate. To the filtrate was added ethyl acetate (100 mL), upon which zinc acetate immediately precipitated out of solution as a fluffy white solid. The zinc acetate was filtered and washed with ethyl acetate, and the solvent was removed *in vacuo*. The crude material was taken up in aqueous HCl (1 M, 30 mL), and washed with ether (2 x 30 mL). The aqueous fraction was basified to pH ~14 with aqueous NaOH (40% w/v), and extracted with CH_2Cl_2 (4 x 50 mL). The organic fractions were washed with saturated aqueous $NaHCO_3$ (100 mL), water (100 mL), and brine (1 x 100 mL). The organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give 86 mg (85%) of **19a** as an oil (>95% purity, by ^{1}H

NMR). ^{1}H NMR (400 MHz, CD_3OD) δ 7.22 (d, *J* = 8.8 Hz, 1 H), 7.08 (d, *J* = 2.3 Hz, 1 H), 7.04 (s, 1 H), 6.75 (dd, *J* = 8.8, 2.3 Hz, 1 H), 4.40 (p, *J* = 6.2 Hz, 1 H), 3.83 (s, 3 H), 3.71 - 3.65 (m, 1 H), 3.52 (dt, *J* = 13.2, 7.2 Hz, 1 H), 3.14 - 2.92 (comp, 5 H), 2.38 (dd, *J* = 5.8, 4.1 Hz, 1 H), 2.33 (s, 3 H), 1.97 (dq, *J* = 13.7, 6.1 Hz, 1 H), 1.70 (dtd, *J* = 13.7, 6.9, 3.5 Hz, 1 H), 1.23 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, CD_3OD) δ 169.7, 135.6, 131.9, 127.8, 123.0, 111.6, 111.4, 111.2, 99.9, 66.1, 54.9, 54.6, 50.0, 48.2, 44.3, 32.2, 23.6, 22.3, 21.0; HRMS (ESI) *m/z* calcd for $C_{19}H_{27}N_3O_3$ $(M+H)^+$, 346.2125; found, 346.2124.

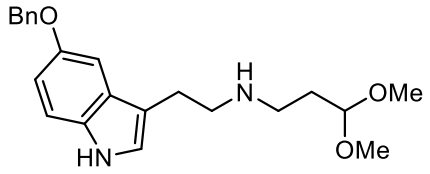
(3*R*,4*S*)-4-((3,5-Dichlorobenzyl)(methyl)amino)-3-((*R*)-1-hydroxyethyl)-1-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)piperidin-2-one (14k). Prepared according to the representative procedure for compound **14a**. The crude material was purified via silica gel flash column chromatography eluting with hexanes : ethyl acetate (3 : 1 → 1 : 3 along a gradient) to give 97 mg (89%) of **14k** as a white solid. ^{1}H NMR (600 MHz, CD_3OD) δ 7.34 (t, *J* = 1.9 Hz, 1 H), 7.22 - 7.21 (comp, 3 H), 7.07 (d, *J* = 2.1 Hz, 1 H), 7.04 (s, 1 H), 6.76 (ddd, *J* = 8.7, 2.4, 0.3 Hz, 1 H), 4.22 (dq, *J* = 8.7, 6.1, 1 H), 3.82 (s, 3 H), 3.76 (dt, *J* = 13.3, 7.6 Hz, 1 H), 3.55 (ddd, *J* = 13.4, 7.7, 5.8 Hz, 1 H), 3.50 (d, *J* = 13.4 Hz, 1 H), 3.41 (d, *J* = 13.4 Hz, 1 H), 3.36 - 3.32 (m, 1 H), 3.17 - 3.08 (comp, 2 H), 3.02 (p, *J* = 7.2 Hz, 1 H), 2.93 (ddd, *J* = 13.7, 7.8, 5.9 Hz, 1 H), 2.58 (dd, *J* = 8.4, 5.7 Hz, 1 H), 2.07 (s, 3 H), 1.99 (dt, *J* = 12.3, 5.7 Hz, 1 H), 1.96 - 1.91 (m, 1 H), 1.21 (d, *J* = 6.1 Hz, 3 H); ^{13}C NMR (150 MHz, CD_3OD) δ 172.0, 155.0, 143.7, 136.2, 133.4, 129.2, 128.5, 128.5, 124.5, 113.0, 112.6, 112.6, 101.5, 67.7, 61.2, 58.4, 56.4, 51.2, 48.8, 46.6, 38.5, 24.0, 22.8, 22.5; HRMS (ESI) *m/z* calcd for $C_{26}H_{31}Cl_2N_3O_3$ $(M+H)^+$, 504.1815 and 506.1792; found, 504.1815 and 506.1795.



S11

2-(5-(Benzyloxy)-1*H*-indol-3-yl)-*N*-(3,3-dimethoxypropyl)-2-oxoacetamide (S11). Oxalyl chloride (1.3 g, 9.9 mmol) was added dropwise over 10 min to a solution of 5-benzyloxyindole (2.0 g, 9.0 mmol) in ether (18 mL) at 0 ºC. The solution was stirred for 2 h at 0 ºC, whereupon a red precipitate was isolated via vacuum filtration, and dried *in vacuo* to give 2.37 g (84%) of 5-benzyloxyindole-3-glyoxal chloride. A suspension of 5-benzyloxyindole-3-glyoxal chloride (0.97 g, 3.1 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 10 min to a solution of **9** (0.62 g, 3.1 mmol) and triethylamine (0.78 g, 7.8 mmol) in CH_2Cl_2 (30 mL) at 0 ºC. The reaction was stirred for 2 h at 0 ºC. The reaction was poured into saturated aqueous $NaHCO_3$ (40 mL), the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic fractions were washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give 1.16 (95%) of **S11** as a yellow amorphous solid (>95%

purity, by ^{1}H NMR). ^{1}H NMR (400 MHz) δ 9.16 (brs, 1 H), 9.03 (d, *J* = 2.8 Hz, 1 H), 8.05 (d, *J* = 2.5 Hz, 1 H), 7.88 (t, *J* = 5.6 Hz, 1 H), 7.50 (d, *J* = 7.1 Hz, 2 H), 7.40 (t, *J* = 7.1 Hz, 2 H), 7.35 - 7.32 (comp, 2 H), 7.02 (dd, *J* = 8.7, 2.5 Hz, 1 H), 5.16 (s, 2 H), 4.51 (t, *J* = 5.4 Hz, 1 H), 3.59 (q, *J* = 6.7 Hz, 2 H), 3.39 (s, 6 H), 1.93 (q, *J* = 6.7 Hz, 2 H); ^{13}C NMR (100 MHz, CD_3CN) δ 181.5, 162.9, 155.9, 139.2, 138.0, 131.3, 128.7, 128.1, 127.9, 126.3, 114.4, 113.4, 112.7, 105.2, 103.7, 70.3, 53.0, 35.1, 32.3; HRMS (ESI) *m/z* calcd for $C_{22}H_{24}N_2O_5$ $(M+Na)^+$, 419.1577; found, 419.1575.

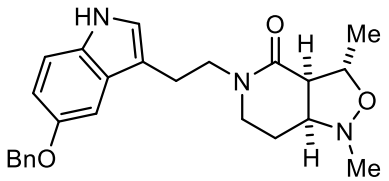


S12

***N*-(2-(5-(Benzyloxy)-1*H*-indol-3-yl)ethyl)-3,3-dimethoxypropan-1-amine (S12).** A solution of **S11** (1.16 g, 2.93 mmol) in THF (15 mL) was added dropwise over 20 min to a suspension of lithium aluminum hydride (1.10 g, 29.3 mmol) in THF (70 mL) at 0 ºC. The reaction heated under reflux for 14 h, whereupon the reaction was cooled to 0 ºC, and the Fieser work-up was performed by successive addition of water (1.1 mL), aqueous NaOH (15%, 1.1 mL), and water (3.3 mL). The suspension was warmed to room temperature and $MgSO_4$ was added. The solids were removed by vacuum filtered through a fritted funnel, and washed with copious amounts of CH_2Cl_2. The filtrate was concentrated *in vacuo* to give crude **S12** as an opaque viscous oil. The crude oil was taken up into aqueous HCl (0.2 M, 200 mL) and washed with ether (2 x 150 mL). The aqueous fraction was basified to pH 12-14 by addition of solid NaOH, as judged by pH paper. The basic solution was extracted with CH_2Cl_2 (4 x 200 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ (400 mL), water (400 mL), brine (400 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give 1.02 g (94%) of **S12** as an oil (>95% purity, by ^{1}H NMR). ^{1}H NMR (400 MHz) δ 8.41 (brs, 1 H), 7.49 (d, *J* = 7.2 Hz, 2 H), 7.34 (td, *J* = 7.2, 1.6 Hz, 2 H), 7.33 (tt, *J* = 7.2, 1.6 Hz, 1 H), 7.23 (d, *J* = 8.8 Hz, 1 H), 7.16 (d, *J* = 2.4 Hz, 1 H), 6.97 (d, *J* = 2.0 Hz, 1 H), 6.94 (dd, *J* = 8.8, 2.4 Hz, 1 H), 5.11 (s, 2 H), 4.41 (t, *J* = 5.6 Hz, 1 H), 3.28 (s, 6 H), 2.94 (app s, 4 H), 2.72 (t, *J* = 7.2 Hz, 2 H), 1.82 (td, *J* = 7.2, 5.6 Hz, 2 H); ^{13}C NMR (100 MHz) δ 153.0, 137.7, 131.8, 128.5, 127.82, 127.77 127.6, 123.0, 113.5, 112.8, 111.9, 103.6, 102.5, 71.0, 52.9, 49.9, 45.3, 32.8, 25.7; HRMS (CI) *m/z* calcd for $C_{22}H_{28}N_2O_3$ $(M+H)^+$, 369.2178; found, 369.2181.

(*E*)-*N*-(2-(5-(Benzyloxy)-1*H*-indol-3-yl)ethyl)-*N*-(3,3-dimethoxypropyl)but-2-enamide (18b). Crotonoyl chloride (0.35 g, 3.3 mmol) was added dropwise over 5 min to a solution of **S12** (1.0 g, 2.8 mmol) and Hünig's base (0.85 g, 6.6 mmol) in CH_2Cl_2 (30 mL) at -78 ºC. The reaction was stirred for 2 h at –78 ºC, whereupon saturated aqueous $NaHCO_3$ (30 mL) was added, and the resulting solution was stirred

for 20 min at room temperature. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic fractions were washed with, water (50 mL), brine (50 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified via silica gel flash column chromatography eluting with hexanes : ethyl acetate (2 : 1 → 1 : 1 along a gradient) to give 0.73 g (61%) of **18b** as an oil. ^{1}H NMR (400 MHz) (1:1 mixture of rotamers) δ 8.65 (brs, 0.5 H), 8.53 (brs, 0.5), 7.50 - 7.48 (comp, 2 H), 7.41 - 7.37 (comp, 2 H), 7.34 - 7.30 (m ,1 H), 7.26 - 7.23 (comp, 1.5 H), 7.11 (d, *J* = 2.2 Hz, 0.5), 7.02 (dq, *J* = 13.8, 6.9 Hz, 0.5 H), 6.96 - 6.88 (comp, 2 H), 6.78 (dq, *J* = 13.8, 6.9 Hz, 0.5 H), 6.32 (dd, *J* = 14.9, 1.6 Hz, 0.5 H), 5.98 (dd, *J* = 14.9, 1.6 Hz, 0.5 H), 5.13 (s, 1 H), 5.10 (s, 1 H), 4.41 (t, *J* = 5.6 Hz, 0.5 H), 4.33 (t, *J* = 5.6 Hz, 0.5 H), 3.67 (t, *J* = 7.3 Hz, 1 H), 3.60 (t, *J* = 7.3 Hz, 1 H), 3.45 (t, *J* = 7.5 Hz, 1 H), 3.37 - 3.30 (comp, 7 H), 3.03 (t, *J* = 7.3 Hz, 1 H), 2.96 (t, *J* = 7.3 Hz, 1 H), 1.96 - 1.90 (comp, 2 H), 1.85 - 1.80 (comp, 1.5 H), 1.66 (dd, *J* = 6.8, 1.5 Hz, 1.5); ^{13}C NMR (100 MHz) (1:1 mixture of rotamers) δ 166.7, 166.6, 153.1, 153.1, 141.9, 141.0, 137.7, 137.6, 131.8, 131.7, 128.5, 128.5, 127.8, 127.7, 127.6, 127.5, 123.4, 123.0, 121.8, 121.8, 112.9, 112.8, 112.7, 112.0, 111.4, 102.9, 102.1, 102.0, 71.1, 70.9, 53.2, 53.0, 48.6, 47.8, 44.2, 42.9, 32.5, 31.0, 25.4, 23.7, 18.3, 18.1; HRMS (ESI) *m/z* calcd for $C_{26}H_{32}N_2O_4$ $(M+Na)^+$, 459.2254; found, 459.2253.



S13

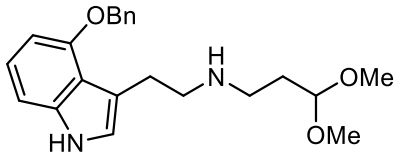
(3*R*,3a*R*,7a*S*)-5-(2-(5-(Benzyloxy)-1*H*-indol-3-yl)ethyl)-1,3-dimethylhexahydroisoxazolo[4,3-*c*]pyridin-4(1*H*)-one (S13). A solution of **18b** (250 mg, 0.57 mmol) and TFA (65 mg, 0.57 mmol) in TFE/water (3 : 1, 12 mL) was stirred for 1 h at room temperature. The reaction was poured into saturated aqueous $NaHCO_3$ (30 mL), and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic fractions were washed with water (50 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue was dissolved in toluene (8 mL), followed by addition of *N*-methylhydroxylamine hydrochloride (71 mg, 0.86 mmol) and triethylamine (130 mg, 1.30 mmol). The reaction was heated under reflux for 2 h, then cooled to room temperature, and partitioned between saturated aqueous $NaHCO_3$ (50 mL), ethyl acetate (50 mL) and methanol (2 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organic fractions were washed with water (100 mL), brine (100 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified via silica gel flash column chromatography eluting with hexanes : ethyl acetate (1 : 1 → 0 : 1 along a gradient) to give 163 mg (68%, two-steps) of **S13** as a viscous oil. ^{1}H NMR (400 MHz) δ 8.52 (brs, 1 H), 7.50 - 7.48 (comp, 2 H), 7.41 -

7.35 (comp, 2 H), 7.32 (tt, *J* = 7.2, 1.4 Hz, 1 H), 7.22 (d, *J* = 8.8 Hz, 1 H), 7.16 (d, *J* = 2.3 Hz, 1 H), 6.95 (s, 1 H), 5.11 (s, 2 H), 3.93 (p, *J* = 6.2 Hz, 1 H), 3.74 (dt, *J* = 13.3, 7.5 Hz, 1 H), 3.61 (dt, *J* = 13.3, 7.2 Hz, 1 H), 3.52 (td, *J* = 11.6, 2.5 Hz, 1 H), 2.99 - 2.92 (comp, 3 H), 2.83 - 2.79 (comp, 2 H), 2.66 (s, 3 H), 1.76 (tt, *J* = 11.1, 4.0 Hz, 1 H), 1.58 (dq, *J* = 11.1, 2.9 Hz, 1 H), 1.47 (d, *J* = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz) δ 169.0, 153.0, 137.7, 131.7, 128.5, 127.8, 127.7, 127.7, 123.1, 112.7, 112.4, 112.0, 102.3, 77.5, 71.0, 66.1, 55.3, 48.4, 44.0, 43.2, 25.1, 23.5, 19.3; HRMS (ESI) *m/z* calcd for $C_{25}H_{29}N_3O_3$ $(M+Na)^+$, 442.2101; found, 442.2106.

(3*R*,4*S*)-1-(2-(5-(Benzyloxy)-1*H*-indol-3-yl)ethyl)-3-((*R*)-1-hydroxyethyl)-4-(methylamino)piperidin-2-one (19b). Zinc (dust, 590 mg, 9.0 mmol) was slowly added to a solution of **S13** (130 mg, 0.30 mmol) in acetic acid (aq, 80%, 18 mL), and the mixture was stirred for 48 h at room temperature. Excess zinc was filtered, and washed with ethyl acetate. To the filtrate was added ethyl acetate (200 mL), at which point zinc acetate immediately precipitated out of solution as a fluffy white solid. The zinc acetate was removed by vacuum filtration, and the solvent was removed *in vacuo*. The resulting residue was dissolved in aqueous HCl (1 M, 30 mL), and washed with ether (30 mL). The aqueous fraction was basified to pH ~12-14 by addition of solid NaOH, as judged by pH paper. The basic solution was extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic fractions were washed with brine (100 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified via silica gel flash column chromatography eluting with CH_2Cl_2 : methanol (1 : 0 → 9 : 1 along a gradient) to give 106 mg (85%) of **19b** as an off white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.48 - 7.46 (comp, 2 H), 7.38 - 7.34 (comp, 2 H), 7.29 (tt, *J* = 7.4, 1.4 Hz, 1 H), 7.24 (dd, *J* = 8.8, 0.4 Hz, 1 H), 7.17 (d, *J* = 2.1 Hz, 1 H), 7.04 (s, 1 H), 6.85 (dd, *J* = 8.8, 2.1 Hz, 1 H), 5.09 (s, 2 H), 4.27 (dq, *J* = 7.3, 6.4 Hz, 1 H), 3.62 - 3.52 (comp, 2 H), 3.31 - 3.26 (comp, 2 H), 3.14 - 3.06 (m, 1 H), 3.03 - 2.88 (comp, 2 H), 2.54 (dd, *J* = 6.8, 3.4 Hz, 1 H), 2.50 (s, 3 H), 2.07 - 2.01 (m, 1 H), 1.91 - 1.81 (m, 1 H), 1.24 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 169.4, 154.0, 139.4, 133.6, 129.4, 129.1, 128.7, 124.6, 113.4, 113.1, 112.6, 103.3, 72.1, 67.2, 56.6, 51.0, 49.3, 45.5, 32.5, 23.6, 23.0, 23.0; HRMS (ESI) *m/z* calcd for $C_{25}H_{31}N_3O_3$ $(M+H)^+$, 422.2438; found, 422.2447.

(3*R*,4*S*)-1-(2-(5-(Benzyloxy)-1*H*-indol-3-yl)ethyl)-4-((3,5-dichlorobenzyl)(methyl)amino)-3-((*R*)-1-hydroxyethyl)piperidin-2-one (14l). Prepared according to representative procedure for compound **14a**. The crude material was purified via silica gel flash column chromatography eluting with hexanes : ethyl acetate (2 : 1 → 0 : 1 along a gradient) to give 50 mg (37%) of **14l** as a white solid. ^{1}H NMR (600 MHz) δ 8.07 (brs, 1 H), 7.47 (d, *J* = 7.5 Hz, 2 H), 7.38 - 7.35 (comp, 2 H), 7.31 - 7.28 (m, 1 H), 7.25 - 7.23 (comp, 2 H), 7.13 (d, *J* = 2.4 Hz, 1 H), 7.08 (d, *J* = 1.9 Hz, 2 H), 6.99 (d, *J* = 2.3 Hz, 1 H), 6.93 (dd, *J* = 8.7, 2.3 Hz, 1 H), 5.11 (s, 2 H), 4.26 (dq, *J* = 8.8, 6.1 Hz, 1 H), 3.77 (dt, *J* = 13.4, 7.7 Hz, 1 H), 3.49 (dq, *J* = 7.8, 6.1 Hz, 1 H), 3.42 (d, *J* = 13.3, 1 H), 3.34 (d, *J* = 13.3, 1 H), 3.21 (ddd, *J* = 12.8, 6.7, 2.3 Hz, 1 H), 3.12 - 3.03 (comp, 2 H), 2.99 (p, *J* = 7.3 Hz, 1 H), 2.91 (p, *J* = 7.3 Hz, 1 H) 2.65 (dd, *J* = 8.7, 5.8 Hz, 1 H), 2.07

(s, 3 H), 1.96 - 1.84 (comp, 2 H), 1.31 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (150 MHz) δ 169.8, 153.1, 141.2, 137.6, 135.1, 131.6, 128.5, 127.8, 127.8, 127.7, 127.6, 127.1, 123.0, 112.7, 112.5, 111.9, 102.4, 71.0, 66.5, 60.3, 57.6, 50.1, 47.2, 45.3, 38.6, 23.1, 22.5, 21.8; HRMS (ESI) *m/z* calcd for $C_{32}H_{35}Cl_2N_3O_3$ $(M+Na)^+$, 602.1948 and 604.1927; found, 602.1950 and 604.1931.



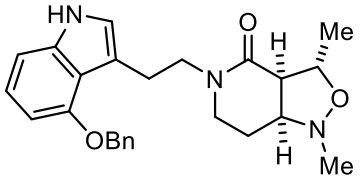
S14

***N*-(2-(4-(Benzyloxy)-1*H*-indol-3-yl)ethyl)-3,3-dimethoxypropan-1-amine (S14).** A solution of oxalyl chloride (0.57 g, 4.5 mmol) in ether (1 mL) was added dropwise over 20 min to a solution of 4-benzyloxyindole (1.40 g, 4.5 mmol) in ether (10 mL) at 0 ºC. The reaction was stirred for 2 h at 0 ºC, at which point the solution was transferred dropwise over 20 min via cannula into a solution of **9** (0.73 g, 3.7 mmol) and triethylamine (1.9 g, 19 mmol) in CH_2Cl_2 (50 mL) at 0 ºC. During the transfer, HCl gas was removed from the reaction through intermittent ventilation with a stream of nitrogen. The reaction was warmed to room temperature and stirred for 1 h. Saturated aqueous $NaHCO_3$ (100 mL) was added, and the solution was stirred for 20 min at room temperature. The mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic fractions were washed with aqueous NaOH (1 M, 100 mL), water (100 mL), brine (100 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give crude 2-(4-(benzyloxy)-1H-indol-3-yl)-N-(3,3-dimethoxypropyl)-2-oxoacetamide as a thick orange semi-solid, which was carried onto the next step without further purification.

A solution of crude 2-(4-(benzyloxy)-1H-indol-3-yl)-N-(3,3-dimethoxypropyl)-2-oxoacetamide (0.37 g, 0.93 mmol) in THF (5 mL) was added dropwise over 10 min to a suspension of lithium aluminum hydride (0.35 g, 9.3 mmol) in THF (20 mL) at 0 ºC. The reaction was heated to 60 ºC for 14 h. The reaction was then cooled to 0 ºC, and the Fieser work-up was performed by successive addition of water (0.3 mL), aqueous NaOH (15%, 0.3 mL), and water (1 mL). The suspension was warmed to room temperature, and $MgSO_4$ was added. The solids were removed by vacuum filtration through a fritted funnel and washed with copious amounts of CH_2Cl_2. The filtrate was concentrated *in vacuo* to give crude **S14** as an opaque viscous oil. The crude residue was taken up into aqueous HCl (0.2 M, 100 mL), and washed with ether (2 x 50 mL). The aqueous fraction was basified to pH 12-14 by dropwise addition of aqueous NaOH (40% w/v), as judged by pH paper. The basic solution was extracted with CH_2Cl_2 (4 x 100 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ (100 mL), water (100 mL), brine (100 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give 230 mg (67%) of **S14** as a viscous oil (>95% purity,

by ^{1}H NMR). ^{1}H NMR (400 MHz) δ 8.31 (brs, 1 H), 7.51 (d, *J* = 6.8 Hz, 2 H), 7.40 (td, *J* = 6.8, 1.4 Hz, 2 H), 7.34 (tt, *J* = 6.8, 1.4 Hz, 1 H), 7.06 (t, *J* = 7.8 Hz, 1 H), 6.98 (dd, *J* = 7.8 Hz, 0.7 Hz, 1 H), 6.91 (d, *J* = 2.1 Hz, 1 H), 6.55 (dd, *J* = 7.8, 0.7 Hz, 1 H), 5.17 (s, 2 H), 4.38 (t, *J* = 5.6 Hz, 1 H), 3.27 (s, 6 H), 3.06 (t, *J* = 6.8 Hz, 2 H), 2.89 (t, *J* = 6.8 Hz, 2 H), 2.58 (t, *J* = 7.2 Hz, 2 H), 1.71 (td, *J* = 7.2, 5.6 Hz, 2 H); ^{13}C NMR (100 MHz) δ 153.8, 138.4, 137.5, 128.5, 127.8, 127.4, 122.7, 121.0, 117.4, 114.5, 104.7, 103.5, 100.4, 69.8, 52.7, 51.1, 45.1, 33.0, 27.4; HRMS (CI) *m/z* calcd for $C_{22}H_{28}N_2O_3$ $(M+H)^+$, 369.2178 found, 369.2180.

(*E*)-*N*-(2-(4-(Benzyloxy)-1*H*-indol-3-yl)ethyl)-*N*-(3,3-dimethoxypropyl)but-2-enamide (18c). Crotonoyl chloride (200 mg, 1.90 mmol) was added dropwise over 5 min to a solution of **S14** (588 mg, 1.60 mmol) and Hünig's base (495 mg, 3.80 mmol) in CH_2Cl_2 (16 mL) at -78 ºC. The reaction was stirred for 1 h at –78 ºC. Saturated aqueous $NaHCO_3$ (20 mL) was added, and the resulting solution was stirred for 20 min at room temperature. The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were washed with water (25 mL), brine (25 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified via silica gel flash column chromatography eluting with hexanes : ethyl acetate (2 : 1 → 1 : 1 along a gradient) to give 590 mg (86%) of **18c** as an oil. ^{1}H NMR (400 MHz) (1:1 mixture of rotamers) δ 8.51 (brs, 1 H), 7.50 - 7.47 (comp, 2 H), 7.39 (app td, *J* = 7.0, 1.4 Hz, 2 H), 7.35 - 7.31 (m, 1 H), 7.06 - 7.02 (comp, 1 H), 6.98 - 6.94 (comp, 1 H), 6.84 (d, *J* = 1.9 Hz, 0.5), 6.73 (d, *J* = 1.9 Hz, 0.5 H), 6.64 (dq, *J* = 13.6, 6.7 Hz, 1 H), 6.57 - 6.53 (comp, 1 H), 6.26 (dd, *J* = 13.6, 1.6 Hz, 0.5 H), 5.92 (dd, *J* = 13.6, 1.6 Hz, 0.5 H), 5.25 (s, 1 H), 5.22 (s, 1 H), 4.32 (t, *J* = 5.7 Hz, 0.5 H), 4.09 (t, *J* = 5.7 Hz, 0.5 H), 3.63 - 3.59 (comp, 2 H), 3.31 - 3.27 (comp, 4 H), 3.19 (s, 3 H), 3.17 - 3.04 (comp, 3 H), 1.88 (dd, *J* = 6.8, 1.5 Hz, 1.5 H), 1.82 (q, *J* = 7.0 Hz, 1 H), 1.58 (q, *J* = 7.0 Hz, 1 H), 1.50 (dd, *J* = 6.8, 1.5 Hz, 1.5 H); ^{13}C NMR (100 MHz) (1 : 1 mixture of rotamers) δ 166.8, 166.3, 153.6, 153.5, 141.3, 140.3, 138.3, 138.2, 137.5, 137.3, 128.6, 128.6, 127.9, 127.9, 127.5, 127.3, 122.8, 122.5, 121.8, 121.8, 117.4, 117.3, 113.4, 112.3, 105.0, 102.8, 101.9, 100.6, 100.4, 70.0, 69.9, 52.9, 52.8, 49.7, 48.8, 43.8, 42.7, 32.2, 30.8, 27.0, 25.2, 18.3, 18.2, 17.8; HRMS (ESI) *m/z* calcd for $C_{26}H_{32}N_2O_4$ $(M+Na)^+$, 459.2254; found, 459.2262



S15

(3*R*,3a*R*,7a*S*)-5-(2-(4-(Benzyloxy)-1*H*-indol-3-yl)ethyl)-1,3-dimethylhexahydroisoxazolo[4,3-*c*]pyridin-4(1*H*)-one (S15). A solution of **18c** (150 mg, 0.34 mmol) and TFA (5 drops) in TFE/water (3 : 1, 6 mL) was stirred for 1 h at room temperature. The reaction was poured into saturated aqueous $NaHCO_3$

(20 mL), and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were washed with water (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue was dissolved in toluene (4 mL), followed by addition of *N*-methylhydroxylamine hydrochloride (34 mg, 0.41 mmol) and triethylamine (70 mg, 0.69 mmol). The reaction was heated under reflux for 1 h, at which point the reaction was cooled to room temperature, and portioned between saturated aqueous $NaHCO_3$ (20 mL), ethyl acetate (20 mL) and methanol (1 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 x 20 mL). The combined organic fractions were washed with water (40 mL), brine (40 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give 133 mg (93%) of **S15** as an oil (>95% purity, by ^{1}H NMR). ^{1}H NMR (600 MHz) δ 8.12 (brs, 1 H), 7.49 - 7.47 (comp, 2 H), 7.40 - 7.38 (comp, 2 H), 7.32 (tt, *J* = 7.4, 1.3 Hz, 1 H), 7.06 (t, *J* = 8.0 Hz, 1 H), 6.98 (dd, *J* = 8.0, 0.6 Hz, 1 H), 6.90 (d, *J* = 2.3 Hz, 1 H), 5.57 (d, *J* = 8.0 Hz, 1 H), 5.14 (s, 2 H), 3.94 (p, *J* = 6.2 Hz, 1 H), 3.62 (ddd, *J* = 12.9, 9.7, 5.9 Hz, 1 H), 3.45 (ddd, *J* = 12.9, 9.7, 5.6 Hz, 1 H), 3.09 - 3.02 (comp, 2 H), 2.95 (ddd, *J* = 13.7, 9.5, 5.8 Hz, 1 H), 2.78 - 2.69 (comp, 2 H), 2.62 (s, 3 H), 2.41 (dt, *J* = 12.9, 4.2 Hz, 1 H), 1.57 - 1.52 (m, 1 H), 1.41 (d, *J* = 6.1 Hz, 3 H), 1.29 (dq, *J* = 14.3, 3.6 Hz, 1 H); ^{13}C NMR (150 MHz) δ 168.7, 153.8, 138.2, 137.2, 128.6, 128.4, 128.0, 122.7, 121.6, 117.2, 113.3, 104.9, 100.3, 77.5, 77.4, 70.2, 66.2, 55.2, 49.7, 43.2, 25.1, 25.0, 19.2; HRMS (ESI) *m/z* calcd for $C_{25}H_{29}N_3O_3$ $(M+H)^+$, 420.2282; found, 420.2289

(3*R*,4*S*)-1-(2-(4-(Benzyloxy)-1*H*-indol-3-yl)ethyl)-3-((*R*)-1-hydroxyethyl)-4-(methylamino)piperidin-2-one (19c). Zinc (powder, 584 mg, 9.00 mmol) was added in three portions over 1.5 h to a solution of **S15** (130 mg, 0.30 mmol) in acetic acid (aq 80%, 18 mL) at 60 ºC. The suspension was stirred for 1 h at 60 ºC. The suspension was cooled to room temperature, followed by the removal of excess zinc by filtration. Ethyl acetate (100 mL) was added to the filtrate, upon which zinc acetate immediately precipitated out of solution as a fluffy white solid. The zinc acetate was filtered and washed with ethyl acetate. The filtrate was concentrated *in vacuo* to give crude **19c**. the crude material was taken up in aqueous HCl (1 M, 30 mL), and washed with ether (2 x 30 mL). The aqueous fraction was basified to pH ~14 with aqueous NaOH (40% w/v). The basic solution was extracted with CH_2Cl_2 (4 x 50 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ (100 mL), water (100 mL), and brine (1 x 100 mL). The organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give 72 mg (57%) of **19c** as an oil (>95% purity, by ^{1}H NMR). ^{1}H NMR (500 MHz, CD_3OD) δ 7.47 (d, *J* = 7.0 Hz, 2 H) 7.39 – 7.33 (comp, 3 H), 7.03 (t, *J* = 8.0 Hz, 1 H), 6.98 (dd, *J* = 8.0, 0.5 H, 1 H), 6.90 (s, 1 H), 6.55 (dd, *J* = 8.0, 0.5 Hz, 1 H), 5.13 (s, 2 H), 4.39 (p, *J* = 6.0 Hz, 1 H), 3.48 – 3.44 (comp, 2 H), 3.03 – 2.98 (comp, 3 H), 2.80 – 2.78 (m, 1 H), 2.63 – 2.58 (m, 1 H), 2.27 – 2.23 (comp, 4 H), 1.73 (dq, *J* = 13.5, 6.0 Hz, 1 H), 1.46 – 1.40 (m, 1 H), 1.20 (d, *J* = 6.0 Hz, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 169.5, 153.6,

138.3, 137.3, 128.5, 128.3, 128.0, 122.2, 122.0, 117.1, 112.2, 105.1, 99.9, 70.1, 66.4, 54.4, 50.0, 43.6, 33.3, 24.4, 23.3, 20.9; HRMS (ESI) *m/z* calcd for $C_{25}H_{31}N_3O_3$ $(M+H)^+$, 422.2438; found, 422.2442.

(3*R*,4*S*)-1-(2-(4-(Benzyloxy)-1*H*-indol-3-yl)ethyl)-4-((3,5-dichlorobenzyl)(methyl)amino)-3-((*R*)-1-hydroxyethyl)piperidin-2-one (14m). Prepared according to the representative procedure for compound **14a**. The crude material was purified via flash column chromatography eluting with CH_2Cl_2 : acetone : methanol (9 : 1 : 0 → 5 : 4 : 1 along a gradient) to give 26 mg (19%) of **14m** as a white solid. ^{1}H NMR (400 MHz) δ 9.14 (brs, 1 H), 7.38 (dd, *J* = 8.4, 1.6 Hz, 2 H), 7.30 - 7.28 (comp, 2 H), 7.23 (d, *J* = 7.2 Hz, 1 H), 7.13 (s, 1 H), 7.01 (s, 2 H), 6.94 - 6.87 (comp, 2 H), 6.77 (d, *J* = 2.4 Hz, 1 H), 6.44 (dd, *J* = 7.2, 0.8 Hz, 1 H), 5.01 (s, 2 H), 4.09 (dq, *J* = 9.2, 6.8 Hz, 1 H), 3.55 - 3.48 (m, 1 H), 3.36 (d, *J* = 12.4 Hz, 1 H), 3.28 - 3.1 (comp, 2 H), 2.90 - 2.84 (comp, 3 H), 2.59 - 2.54 (m, 1 H), 1.97 (s, 3 H), 1.55 - 1.50 (comp, 2 H), 1.22 (d, *J* = 6.0 Hz, 3 H); ^{13}C NMR (125 MHz) δ 169.6, 153.8, 141.4, 138.2, 137.3, 135.2, 128.6, 128.5, 128.1, 127.8, 126.6, 122.8, 121.6, 117.2, 113.1, 105.0, 100.3, 70.2, 66.4, 60.4, 57.7, 50.1, 48.7, 44.6, 24.7, 22.5, 21.9; HRMS (ESI) *m/z* calcd for $C_{32}H_{35}Cl_2N_3O_3$ $(M+Na)^+$, 602.1948 and 604.1945; found, 602.1927 and 604.1954.

(3*R*,4*S*)-4-((3,5-Dichlorobenzyl)(methyl)amino)-1-(2-(5-hydroxy-1*H*-indol-3-yl)ethyl)-3-((*R*)-1-hydroxyethyl)piperidin-2-one (14n). A solution of **S13** (150 mg, 0.36 mmol) in ethanol (2 mL) was added over 5 min to a degassed of ethanol (12 mL) and Pd/C (10% w/w, 150 mg) at room temperature. A balloon of hydrogen gas was bubbled through the suspension, followed immediately by addition of TFA (3 drops), and the reaction was stirred for 5 h at 60 ºC. The suspension was then cooled to room temperature and filtered through a pad of Celite, washing with copious amounts of methanol. The solvent was removed *in vacuo,* followed by azeotropic removal of water with toluene. The crude mixture was dissolved in acetonitrile (10 mL), and 3,5-dichlorobenzaldehyde (190 mg, 1.1 mmol) was added in one portion. The reaction was held under reflux for 2 h, after which the solution was cooled to room temperature. $NaBH_3CN$ (68 mg, 1.1 mmol) and acetic acid (glacial, 130 µL, 2.2 mmol) were added, and the reaction was stirred for 14 h at room temperature. Saturated aqueous $NaHCO_3$ (30 mL) was added to the mixture, followed by extraction with CH_2Cl_2 (3 x 30 mL). The combined organic fractions were washed with water (30 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified via flash column chromatography eluting with hexanes : ethyl acetate (1 : 1 → 0 : 1 along a gradient) to give 48 mg (28%, two-steps) of **14n** as an amorphous white solid. ^{1}H NMR (600 MHz, CD_3OD) δ 7.32 (t, *J* = 1.9 Hz, 1 H), 7.20 (d, *J* = 1.9 Hz, 1 H), 7.15 (dd, *J* = 8.6, 0.4 Hz, 1 H), 7.00 (s, 1 H), 6.94 (d, *J* = 2.0 Hz, 1 H), 6.67 (dd, *J* = 8.6, 2.3 Hz, 1 H), 4.20 (dq, *J* = 8.6, 6.1 Hz, 1 H), 3.67 (dt, *J* = 13.2, 7.6 Hz, 1 H), 3.52 (ddd, *J* = 13.3, 7.6, 5.8 Hz, 1 H), 3.46 (d, *J* = 13.4 Hz, 1 H), 3.36 (d, *J* = 13.4 Hz, 1 H), 3.28 - 3.25 (m, 1 H), 3.09 - 3.01 (comp, 2 H), 2.96 (p, *J* = 7.1 Hz, 1 H), 2.88 - 2.84 (m, 1 H), 2.57 (dd, *J* = 8.0, 5.2 Hz, 1 H), 2.03 (s, 3 H), 1.94 - 1.91 (m, 1 H), 1.86 - 1.80 (m, 1 H), 1.21 (d, *J* = 6.1 Hz, 3 H); ^{13}C NMR (150 MHz, CD_3OD) δ 171.9,

151.3, 143.7, 136.2, 133.0, 129.6, 128.5, 128.4, 124.5, 112.8, 112.5, 112.1, 103.5, 67.7, 61.2, 58.4, 51.1, 49.8, 46.6, 38.5, 24.0, 22.8, 22.5; HRMS (ESI) *m/z* calcd for $C_{25}H_{29}Cl_2N_3O_3$ $(M+H)^+$, 512.1478 and 514.1455; found, 512.1483 and 514.1459.

1-(2-(1H-Indol-3-yl)ethyl)-4-((3-chloro-5-methoxybenzyl)(methyl)amino)piperidin-2-one (25b). The title compound was prepared following the general procedure of **25a**. The crude material was purified via flash column chromatography, eluting with EtOAc:Et_3N (99:1) to furnish 19 mg (64%) of **25b** as a pale yellow amorphous solid. ^{1}H NMR (400 MHz) δ 8.16 (s, 1 H), 7.65 (d, *J* = 7.8 Hz, 1 H), 7.36 (dt, *J* = 8.1, 0.9 Hz, 1 H), 7.19 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1 H), 7.11 (ddd, *J* = 7.8, 7.0, 1.1 Hz, 1 H), 7.03 (d, *J* = 2.4 Hz, 1 H), 6.90 (app s, 1 H), 6.79 (t, *J* = 2.1 Hz, 1 H), 6.75 (app s, 1 H), 3.79 (s, 3 H), 3.73 – 3.59 (comp, 2 H), 3.47 (s, 2 H), 3.22 – 2.99 (comp, 4 H), 2.79 (tdd, *J* = 11.0, 5.2, 3.1 Hz, 1 H), 2.62 (ddd, *J* = 17.0, 5.2, 2.2 Hz, 1 H), 2.43 (dd, *J* = 17.0, 10.8 Hz, 1 H), 2.17 (s, 3 H), 1.90 (dt, *J* = 9.8, 3.6 Hz, 1 H), 1.60 (dtd, *J* = 12.8, 11.1, 5.7 Hz, 1 H); ^{13}C NMR (100 MHz) δ 169.1, 160.3, 142.6, 136.2, 134.7, 127.5, 122.03, 121.94 120.8, 119.3, 118.8, 113.2, 112.73, 112.69, 111.2, 57.6, 56.7, 55.5, 48.1, 46.7, 37.4, 34.9, 26.3, 23.0; IR (NaCl, film) 3262, 3056, 2933, 2853, 2361, 1623, 1576, 1498, 1459, 1431, 1344, 1312, 1271, 1233, 1150, 1097, 1053, 980, 845, 743, 679, 621 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{24}H_{28}ClN_3O_2$ (M+Na)+ 448.1762; found, 448.1758.

1-(2-(1H-Indol-3-yl)ethyl)-4-((3-chlorobenzyl)(methyl)amino)piperidin-2-one (25c). The title compound was prepared following the general procedure of **25c**. The crude material was purified via flash column chromatography, eluting with hexanes:EtOAc:Et_3N (50:50:1) to furnish 29 mg (81%) **25c** as a pale yellow amorphous solid. ^{1}H NMR (400 MHz) δ 8.15 (s, 0.89 H), 7.65 (d, *J* = 8 Hz, 1.24 H), 7.27 (m, 4.76 H), 7.21 (t, *J* = 7 Hz, 1.59 H), 7.13 (t, *J* = 7 Hz, 1.37 H), 7.05 (d, *J* = 2 Hz, 1.31 H), 3.74 (comp, 3.96 H), 3.12 (comp, 5.07 H), 2.69 (d, *J* = 18 Hz, 0.99 H), 2.53 (m, 0.83 H), 2.25 (s, 2.93 H), 2.10 (m, 1.21 H), 1.69 (m, 1.49 H); ^{13}C NMR (100 MHz) δ 135.2, 133.3, 128.6, 127.6, 126.4, 123.8, 121.0, 120.9, 118.3, 117.7, 112.2, 110.2, 56.4, 55.8, 47.1, 45.6, 36.2, 33.7, 25.3, 22.0; IR (NaCl, film) 3251, 3055, 2925, 2853, 1742, 1626, 1575, 1497, 1456, 1433, 1344, 1303, 1260, 1231, 1161, 1097, 1075, 1030, 784, 742, 684 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{23}H_{26}ClN_3O$ (M+Na)+ 418.1657; found 418.1649.

1-(2-(1H-Indol-3-yl)ethyl)-4-((3,5-dimethoxybenzyl)(methyl)amino)piperidin-2-one (25d). The title compound was prepared following the general procedure of **25a**. The crude material was purified via flash column chromatography, eluting with hexanes:EtOAc:Et_3N (50:50:1 → 0:99:1) to furnish 31 mg (67%) of **25d** as an amorphous white solid. ^{1}H NMR (400 MHz) δ 8.31 (s, 1 H), 7.64 (d, *J* = 7.9 Hz, 1 H), 7.35 (dt, *J* = 8.1, 1.0 Hz, 1 H), 7.18 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1 H), 7.11 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1 H), 6.99 (d, *J* = 2.4 Hz, 1 H), 6.49 (d, *J* = 2.3 Hz, 2 H), 6.37 (t, *J* = 2.3 Hz, 1 H), 3.79 (s, 6 H), 3.73 – 3.57 (comp, 2 H), 3.49 (s, 2 H), 3.16 (ddd, *J* = 12.1, 5.5, 3.1 Hz, 1 H), 3.11 – 2.95 (comp, 3 H), 2.81 (tdd, *J* = 10.9, 5.0, 3.0 Hz, 1 H), 2.62 (ddd, *J* = 17.0, 5.2, 2.2 Hz, 1 H), 2.45 (dd, *J* = 17.0, 10.8 Hz, 1 H), 2.20 (s, 3

H), 1.94 – 1.86 (m, 1 H), 1.61 (dtd, *J* = 12.8, 11.2, 5.6 Hz, 1 H); ^{13}C NMR (100 MHz) δ 170.1, 161.6, 137.0, 128.1, 122.64, 122.58, 119.9, 119.3, 113.7, 111.8, 107.0, 99.5, 58.5, 56.7, 55.6, 48.3, 46.9, 37.6, 35.1, 26.2, 23.1; IR (NaCl, film) 3261, 3057, 2936, 2840, 2792, 2243, 1613, 1498, 1457, 1430, 1344, 1299, 1234, 1204, 1154, 1101, 1065, 983, 910, 836, 739 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{25}H_{31}N_3O_3$ (M+Na)+ 444.2258; found 444.2252.

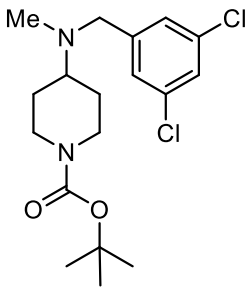
1-(2-(1H-Indol-3-yl)ethyl)-4-((3-methoxybenzyl)(methyl)amino)piperidin-2-one (25e). The title compound was prepared following the general procedure of **25a**. The crude material was purified via flash column chromatography, eluting with EtOAc:Et_3N (99:1) to furnish 26 mg (60%) of **25e** as an amorphous white solid. ^{1}H NMR (400 MHz) δ 8.28 (s, 1 H), 7.64 (d, *J* = 7.6 Hz, 1 H), 7.35 (dt, *J* = 8.1, 0.9 Hz, 1 H), 7.23 (t, *J* = 8.0 Hz, 1 H), 7.18 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1 H), 7.11 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1 H), 7.00 (d, *J* = 2.4 Hz, 1 H), 6.92 – 6.84 (comp, 2 H), 6.81 (ddd, *J* = 8.2, 2.6, 1.1 Hz, 1 H), 3.81 (s, 3 H), 3.72 – 3.58 (comp, 2 H), 3.53 (s, 2 H), 3.16 (ddd, *J* = 12.1, 5.6, 3.1 Hz, 1 H), 3.13 – 2.95 (comp, 3 H), 2.81 (tdd, *J* = 11.0, 5.1, 3.1 Hz, 1 H), 2.64 (ddd, *J* = 16.9, 5.2, 2.2 Hz, 1 H), 2.46 (dd, *J* = 16.9, 10.8 Hz, 1 H), 2.19 (s, 3 H), 1.92 (d, *J* = 12.7 Hz, 1 H), 1.62 (dtd, *J* = 12.8, 11.2, 5.6 Hz, 1 H); ^{13}C NMR (100 MHz) δ 169.2, 159.7, 136.3, 129.3, 127.5, 122.02, 121.97, 121.0, 119.3, 118.7, 114.2, 113.1, 112.5, 111.2, 58.0, 56.5, 55.2, 48.1, 46.7, 37.3, 34.9, 26.2, 23.0; IR (NaCl, film) 3261, 3055, 2935, 2852, 2791, 2360, 2242, 1624, 1491, 1456, 1344, 1304, 1268, 1152, 1011, 1043, 978, 910, 784, 743, 695 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{24}H_{29}N_3O_2$ (M+H)+ 392.2333; found 392.2329.

1-(2-(1H-Indol-3-yl)ethyl)-4-((benzo[d][1,3]dioxol-5- ylmethyl)(methyl)amino)piperidin-2-one (25f). The title compound was prepared following the general procedure of **25a**. The crude material was purified by flash column chromatography, eluting with hexanes:EtOAc:Et_3N (33:66:1) to furnish 14 mg (58%) of **25f** as an amorphous white solid. ^{1}H NMR (400 MHz) δ 8.16 (s, 1 H), 7.65 (d, *J* = 7.8 Hz, 1 H), 7.36 (d, J = 8.2 Hz, 1 H), 7.19 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1 H), 7.11 (ddd, *J* = 7.8, 7.0, 1.1 Hz, 1 H), 7.03 (d, *J* = 2.3 Hz, 1 H), 6.82 (d, *J* = 1.5 Hz, 1 H), 6.77 – 6.69 (comp, 2 H), 5.94 (s, 2 H), 3.74 – 3.58 (comp, 2 H), 3.45 (s, 2 H), 3.21 – 3.09 (comp, 2 H), 3.09 – 2.99 (comp, 2 H), 2.80 (dtd, *J* = 11.0, 5.8, 5.2, 3.5 Hz, 1 H), 2.62 (ddd, *J* = 16.9, 5.2, 2.2 Hz, 1 H), 2.44 (dd, *J* = 17.0, 10.8 Hz, 1 H), 2.16 (s, 3 H), 1.91 (d, *J* = 12.7 Hz, 1 H), 1.61 (dtd, *J* = 12.8, 11.1, 5.7 Hz, 1 H); ^{13}C NMR (100 MHz) δ 169.4, 148.0, 146.9, 136.5, 127.8, 122.3, 122.2, 122.0, 119.6, 119.0, 113.5, 111.5, 109.3, 108.2, 101.2, 58.0, 56.7, 48.4, 47.0, 37.4, 35.1, 26.6, 23.3; IR (film, NaCl) 3260, 2927, 1625, 1489, 1442, 1343, 1302, 1240, 1096, 1038, 929, 807, 741 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{24}H_{27}N_3O_3$ (M+Na)+ 428.1945; found 428.1939.

1-(2-(1H-Indol-3-yl)ethyl)-4-(methyl(3-(methylthio)benzyl)amino)piperidin-2-one (25g). The title compound was prepared following the general procedure of **25a**. The crude material was purified via flash column chromatography, eluting with EtOAc:Et_3N (99:1) to furnish 32 mg (71%) of **25g** as an amorphous, off-white solid. ^{1}H NMR (400 MHz) δ 8.28 (s, 1 H), 7.64 (d, *J* = 7.8 Hz, 1 H), 7.35 (dt, *J* = 8.1,

1.0 Hz, 1 H), 7.26 – 7.08 (comp, 5 H), 7.06 (dt, *J* = 7.5, 1.4 Hz, 1 H), 6.99 (d, *J* = 2.4 Hz, 1 H), 3.66 (t, *J* = 7.5 Hz, 2 H), 3.51 (s, 2 H), 3.16 (ddd, *J* = 12.1, 5.5, 3.1 Hz, 1 H), 3.12 – 2.96 (comp, 3 H), 2.80 (tdd, *J* = 11.0, 5.1, 3.1 Hz, 1 H), 2.63 (ddd, *J* = 16.9, 5.2, 2.2 Hz, 1 H), 2.48 (comp, 4 H), 2.18 (s, 3 H), 1.90 (dt, *J* = 12.8, 3.4 Hz, 1 H), 1.61 (dtd, *J* = 12.8, 11.2, 5.6 Hz, 1 H); ^{13}C NMR (100 MHz) δ 169.2, 140.0, 138.4, 136.3, 128.8, 127.4, 126.6, 125.4, 125.1, 121.96, 119.26, 118.7, 113.1, 111.2, 57.8, 56.5, 48.1, 46.7, 37.3, 34.9, 26.3, 23.0, 15.8; IR (NaCl, film) 3261, 3054, 2922, 2854, 1622, 1498, 1456, 1344, 1303, 1232, 1158, 1100, 1030, 780, 743, 686 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{24}H_{29}N_3OS$ (M+Na)+ 430.1924; found 430.1920.

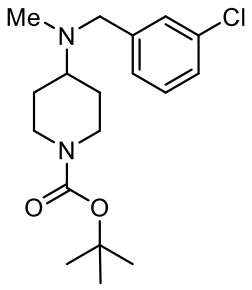
1-(2-(1H-Indol-3-yl)ethyl)-4-(benzyl(methyl)amino)piperidin-2-one (25h). The title compound was prepared following the general procedure of **25a**. The crude material was purified via flash column chromatography, eluting with EtOAc:Et_3N (99:1) to furnish 23 mg (70%) of **25h** as an amorphous white solid. ^{1}H NMR (400 MHz) δ 8.03 (s, 1 H), 7.65 (d, *J* = 7.8 Hz, 1 H), 7.36 (d, *J* = 8.2 Hz, 1 H), 7.34 – 7.26 (comp, 5 H), 7.19 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1 H), 7.12 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1 H), 7.03 (d, *J* = 2.3 Hz, 1 H), 3.66 (hept, *J* = 6.8, 6.1 Hz, 2 H), 3.56 (s, 2 H), 3.21 – 2.99 (comp, 4 H), 2.87 – 2.77 (m, 1 H), 2.69 – 2.61 (m, 1 H), 2.47 (dd, *J* = 17.0, 10.8 Hz, 1 H), 2.19 (s, 3 H), 1.98 – 1.89 (m, 1 H), 1.63 (qd, *J* = 11.5, 5.6 Hz, 1 H); ^{13}C NMR (100 MHz) δ 136.2, 128.9, 128.4, 127.5, 122.05, 121.91, 119.4, 118.8, 113.2, 111.2, 57.9, 56.6, 48.1, 46.7, 26.3, 23.0; IR (NaCl, film) 2923, 2851, 2793, 2242, 1625, 1496, 1456, 1343, 1302, 1260, 1233, 1159, 1101, 1074, 1025, 909, 813, 741, 700 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{23}H_{27}N_3O$ (M+Na)+ 384.2046; found 384.2039.



S16

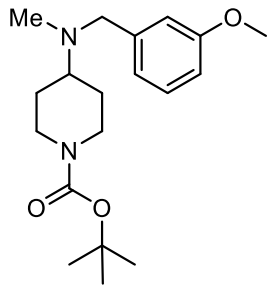
***tert*-Butyl 4-((3,5-dichlorobenzyl)(methyl)amino)piperidine-1-carboxylate (S16).** A solution of **26** (44 mg, 0.2 mmol), 3,5-dichlorobenzaldehyde (50 mg, 0.3 mmol), acetic acid (10 mg, 0.2 mmol), and sodium triacetoxyborohydride (90 mg, 0.4 mmol) in 1,2-dichloroethane (2 mL) was stirred at room temperature for 18 h, whereupon the solution was diluted with 1 M NaOH (15 mL) and extracted with Et_2O (3 x 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated via rotary evaporation. The crude material was purified by flash chromatography eluting with hexane:EtOAc:Et_3N (95:5:1) to give 48 mg (64%) of **S16** as an opaque white oil. ^{1}H NMR (400 MHz) δ 7.23 – 7.19 (comp, 3 H), 4.16 (s, 2 H),

3.50 (s, 2 H), 2.75 – 2.61 (comp, 2 H), 2.55 (tt, *J* = 11.5, 3.6 Hz, 1 H), 2.17 (s, 3 H), 1.83 – 1.70 (comp, 2 H), 1.45 (comp, 11 H). ^{13}C NMR (101 MHz) δ 154.7, 143.9, 134.7, 126.9, 126.7, 79.4, 61.1, 57.0, 43.1, 37.7, 28.4, 27.9; IR (NaCl, film) 2975, 2940, 2854, 2788, 1694, 1590, 1569, 1451, 1425, 1365, 1330, 1275, 1244, 1159, 1111, 1046, 1004 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{18}H_{26}Cl_2N_2O_2$ (M+H)+ 373.1444; found 373.1454.



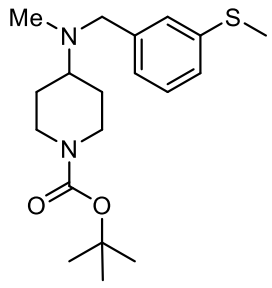
S17

***tert*-Butyl 4-((3-chlorobenzyl)(methyl)amino)piperidine-1-carboxylate (S17).** The title compound was prepared following the general procedure of **S16**. The crude material was dissolved in hexanes and a solution of HCl in 1,4-dioxane was added until the HCl salt of **S17** precipitated out of solution. The suspension was decanted and washed with additional hexanes (2 x 10 mL), and the resultant residue was resuspended in 1M aq. NaOH (20 mL). The aqueous layer was extracted with Et_2O (3 x 15 mL), dried (Na_2SO_4) and concentrated via rotary evaporation to give 48 mg (71%) of **S17** as a clear oil. ^{1}H NMR (300 MHz) δ 7.33 (s, 1 H), 7.25 – 7.16 (comp, 3 H), 4.17 (s, 2 H), 3.54 (s, 2 H), 2.82 – 2.45 (comp, 3 H), 2.19 (s, 3 H), 1.79 (d, *J* = 12.6 Hz, 2 H), 1.46 (comp, 11 H); ^{13}C NMR (101 MHz) δ 154.7, 142.2, 134.1, 129.4, 128.5, 127.0, 126.6, 79.4, 60.9, 57.4, 43.4 37.6, 28.4, 28.0; IR (NaCl, film) 2937, 2853, 2788, 1694, 1598, 1574, 1475, 1452, 1424, 1365, 1330, 1275, 1243, 1158, 1111, 1075, 1043, 1001 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{18}H_{27}ClN_2O_2$ (M+H)+ 339.1834; found 339.1842.



S18

***tert*-Butyl 4-((3-methoxybenzyl)(methyl)amino)piperidine-1-carboxylate (S18).** The title compound was prepared following the general procedure of **S16**. The crude material was purified by flash chromatography eluting with hexane/EtOAc/Et_3N (90:10:1) to give 44 mg (69%) of **S18** as a clear oil. ^{1}H NMR (400 MHz) δ 7.22 (t, J = 8.0 Hz, 1 H), 6.89 (dt, J = 3.6, 1.5 Hz, 2 H), 6.78 (ddd, J = 8.1, 2.6, 1.0 Hz, 1 H), 4.15 (s, 2 H), 3.80 (s, 3 H), 3.55 (s, 2 H), 2.67 (d, J = 13.4 Hz, 2 H), 2.62 – 2.51 (m, 1 H), 2.20 (s, 3 H), 1.79 (d, *J* = 12.6 Hz, 2H), 1.46 (s, 11 H); ^{13}C NMR (101 MHz) δ 159.6, 154.7, 141.6, 129.1, 120.9, 114.0, 112.2, 79.3, 60.6, 57.9, 55.1, 43.4, 37.6, 28.4, 27.9; IR (NaCl, film) 2940, 2853, 2787, 1695, 1601, 1587, 1488, 1454, 1425, 1365, 1330, 1274, 1243, 1158, 1110, 1046, 1003 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{19}H_{30}N_2O_3$ (M+H)+ 335.2329; found 335.2324.



S19

***tert*-Butyl 4-(methyl(3-(methylthio)benzyl)amino)piperidine-1-carboxylate (S19).** The title compound was prepared following the general procedure of **S16**. The crude material was purified by flash chromatography eluting with hexane/EtOAc/Et_3N (90:10:1) to give 45 mg 967%) of **S19** as an off-white oil. ^{1}H NMR (400 MHz) δ 7.22 (s, 2 H), 7.12 (dt, *J* = 7.9, 1.3 Hz, 1 H), 7.10 – 7.05 (m, 1 H), 4.16 (s, 2 H), 3.53 (s, 2 H), 2.68 (t, *J* = 12.5 Hz, 2 H), 2.56 (tt, *J* = 11.3, 3.6 Hz, 1 H), 2.48 (s, 3 H), 2.19 (s, 3 H), 1.79 (d, *J* = 12.8 Hz, 2 H) 1.46 (comp, 11 H). ^{13}C NMR (101 MHz) δ 154.7, 140.7, 138.2, 128.6, 126.7, 125.4, 124.9, 79.3, 60.8, 57.8, 43.4, 37.6, 28.4, 27.9, 15.8. IR (NaCl, film) 2975, 2929, 2854, 2787, 1695, 1592, 1574, 1474, 1425, 1365, 1330, 1275, 1243, 1159, 1110, 1082, 1043, 1001 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{19}H_{30}N_2O_2S$ (M+Na)+ 373.1920; found 373.1934.

N-(3,5-Dichlorobenzyl)-N-methylpiperidin-4-amine (27a). A solution of **S16** (52 mg, 0.14 mmol) and trifluoroacetic acid (160 mg, 1.4 mmol) in CH_2Cl_2 (2.8 mL) was stirred at room temperature for 24 h, whereupon the solvent was removed by rotary evaporation. The resulting solid was resuspended in 1 M HCl (20 mL) and washed with Et_2O (20 mL). 3 M NaOH was added to the aqueous layer until the solution became cloudy, whereupon it was extracted with CH_2Cl_2 (3 x 20 mL), dried (Na_2SO_4) and concentrated via rotary evaporation to give 29 mg (76%) of **27a** as a yellow paste. ^{1}H NMR (400 MHz) δ 7.22 (t, *J* = 0.6 Hz, 3 H), 3.52 (s, 2 H), 3.18 (d, *J* = 12.2 Hz, 2 H), 2.66 – 2.46 (m, 4 H), 2.19 (s, 3 H), 1.51 (qd, *J* = 12.1, 4.1 Hz, 3 H); ^{13}C NMR (100 MHz) δ 144.1, 134.7, 126.9, 126.8, 61.1, 56.9, 46.1, 37.7, 29.0; IR (NaCl, film) 2941, 2851, 2791, 1589, 1568, 1449, 1432, 1384, 1353, 1273, 1208, 1045 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{18}Cl_2N_2$ (M+H)+ 273.0920; found 273.0923.

N-(3-Chlorobenzyl)-N-methylpiperidin-4-amine (27b). The title compound was prepared following the general procedure of **27a** to give 15 mg (79%) of **27b** as a yellow oil. ^{1}H NMR (400 MHz) δ 7.34 – 7.31 (m, 1 H), 7.25 – 7.16 (comp, 3 H), 3.54 (s, 2 H), 3.15 (dt, J = 12.7, 3.4 Hz, 2 H), 2.64 – 2.46 (comp, 3 H), 2.19 (s, 3 H), 1.82 (dt, J = 12.7, 2.7 Hz, 2 H), 1.49 (qd, J = 12.3, 4.3 Hz, 2 H). ^{13}C NMR (101 MHz) δ 142.5, 134.1, 129.4, 128.6, 126.9, 126.6, 61.2, 57.2, 46.3, 37.6, 29.3. IR (NaCl, film) 3291, 3061, 2939, 2850, 2789, 1597, 1574, 1472, 1451, 1429, 1356, 1324, 1260, 1209, 1147, 1075, 1043, 1003 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{13}H_{19}ClN_2$ (M+H)+ 239.1310; found 239.1313.

N-(3-Methoxybenzyl)-N-methylpiperidin-4-amine (27c). The title compound was prepared following the general procedure of **27a** to give 15 mg (79%) of **27c** as a yellow oil. ^{1}H NMR (400 MHz) δ 7.21 (t, *J* = 8.0 Hz, 1 H), 6.92 – 6.87 (comp, 2 H), 6.78 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1 H), 3.80 (s, 3 H), 3.55 (s, 2 H), 3.19 – 3.09 (d, *J* = 12.3 Hz, 2 H), 2.62 – 2.47 (comp, 3 H), 2.21 (s, 3 H), 1.87 – 1.79 (br, 2 H), 1.51 (td, *J* = 12.1, 4.0 Hz, 2 H). ^{13}C NMR (101 MHz) δ 159.6, 141.8, 129.1, 121.0, 114.1, 112.2, 61.0, 57.7, 55.1, 46.4, 37.6, 29.3. IR (NaCl, film) 3306, 2939, 2839, 2788, 1691, 1600, 1488, 1454, 1361, 1318, 1269, 1150, 1046 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{14}H_{22}N_2O$ (M+H)+ 235.1805; found 235.1805.

N-Methyl-N-(3-(methylthio)benzyl)piperidin-4-amine (27d). The title compound was prepared following the general procedure of **27c** to give 23 mg (87%) of **27d** as a pale yellow oil. ^{1}H NMR (400 MHz) δ 7.25 – 7.19 (comp, 2 H), 7.12 (ddd, *J* = 7.8, 2.0, 1.2 Hz, 1 H), 7.10 – 7.06 (m, 1 H), 3.54 (s, 2 H), 3.19 – 3.08 (comp, 2 H), 2.62 – 2.45 (comp, 6 H), 2.19 (s, 3 H), 1.85 (d, *J* = 8.8 Hz, 2 H), 1.56 – 1.42 (comp, 2 H); ^{13}C NMR (101 MHz) δ 140.9, 138.1, 128.6, 126.8, 125.5, 124.9, 61.0, 57.6, 46.4, 37.6, 29.3, 15.8; IR (NaCl, film) 3292, 2938, 2850, 2790, 1591, 1572, 1471, 1422, 1356, 1325, 1273, 1213, 1147, 1084, 1042 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{14}H_{22}N_2S$ (M+H)+ 251.1576; found 251.1584.

1-(4-((3,5-Dichlorobenzyl)(methyl)amino)piperidin-1-yl)-2-(1H-indol-3-yl)ethan-1-one (28a). A solution **27a** (33 mg, 0.12 mmol), indole-3-acetic acid (32 mg, 0.18 mmol), EDCI·HCl (35 mg, 0.18 mmol), and iPr_2NEt (0.8 mL, 0.5 mmol) in THF (1.2 mL) was stirred at rt for 2 h. The reaction was then

diluted with 1 M aq. NaOH (20 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated via rotary evaporation. The crude material was purified by flash chromatography, eluting with hexanes:EtOAc:Et_3N (40:60:1) to give 28a (40 mg, 78%) as an amorphous white solid. ^{1}H NMR (400 MHz) δ 8.17 (s, 1 H), 7.65 (dq, *J* = 7.9, 0.9 Hz, 1 H), 7.35 (dt, *J* = 8.1, 1.0 Hz, 1 H), 7.22 (t, *J* = 2.0 Hz, 1 H), 7.19 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1 H), 7.16 - 7.14 (m, 2 H), 7.13 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1 H), 7.09 (dd, *J* = 2.3, 1.1 Hz, 1 H), 4.74 (d, *J* = 13.7 Hz, 1 H), 4.05 – 3.93 (m, 1 H), 3.86 (dd, *J* = 4.4, 1.0 Hz, 2 H), 3.37 (s, 2 H), 2.93 (td, *J* = 12.9, 2.7 Hz, 1 H), 2.55 (td, *J* = 11.2, 10.6, 3.0 Hz, 2 H), 2.07 (s, 3 H), 1.80 (d, *J* = 13.0 Hz, 1 H), 1.58 (d, *J* = 13.0 Hz, 1 H), 1.40 (qd, *J* = 12.3, 4.4 Hz, 1 H), 1.12 (qd, *J* = 12.3, 4.3 Hz, 1 H) ppm; ^{13}C NMR (126 MHz) δ 170.1, 144.0, 136.4, 135.0, 127.3, 127.3, 126.9, 122.6, 122.5, 119.9, 119.1, 111.4, 109.8, 61.1, 57.1, 46.1, 41.8, 37.9, 31.9, 28.7, 27.7 ppm; IR (NaCl, film) 3058, 2926, 2857, 2790, 1624, 1568, 1454, 1434, 1353, 1268, 1227, 1149, 1125, 1098, 1047 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{23}H_{25}Cl_2N_3O$ (M+Na)+ 452.1267; found, 452.1268.

1-(4-((2-Chlorobenzyl)(methyl)amino)piperidin-1-yl)-2-(5-methoxy-1H-indol-3-yl)ethan-1-one (28b). The title compound was prepared following a procedure analogous to that of **28a**. The crude material was purified by flash chromatography eluting with EtOAc/Et_3N (100:1) to give 40 mg (70%) of **28b** as an amorphous yellow solid. ^{1}H NMR (400 MHz) δ 8.00 (s, 1 H), 7.29 – 7.27 (m, 1 H), 7.24 (dd, J = 8.8, 0.6 Hz, 1 H), 7.22 – 7.19 (m, 2 H), 7.15 – 7.11 (m, 1 H), 7.10 (d, J = 2.5 Hz, 1 H), 7.07 (d, J = 2.2 Hz, 1 H), 6.89 – 6.82 (m, 1 H), 4.73 (d, J = 13.5 Hz, 1 H), 4.02 (d, J = 16.7 Hz, 1 H), 3.86 (s, 3 H), 3.83 (dd, J = 2.9, 1.0 Hz, 2 H), 3.42 (s, 2 H), 2.93 (s, 1 H), 2.63 – 2.50 (m, 2 H), 2.08 (s, 3 H), 1.82 (d, J = 13.1 Hz, 1 H), 1.64 (d, J = 12.8 Hz, 1 H), 1.43 (qd, J = 12.1, 4.3 Hz, 1 H), 1.22 – 1.10 (m, 1 H). ^{13}C NMR (101 MHz) δ 169.8, 154.1, 142.1, 134.2, 131.3, 129.5, 128.5, 127.4, 127.0, 126.6, 123.0, 112.5, 111.9, 109.2, 100.5, 60.6, 57.3, 55.9, 45.9, 41.6, 37.6, 31.8, 28.5, 27.4. IR (NaCl, flim) 3267, 3056, 2941, 2858, 2244, 2127, 1625, 1486, 1451, 1357, 1332, 1302, 1267, 1216, 1171, 1097, 1055 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{24}H_{28}ClN_3O_2$ (M+Na)+ 448.1762; found 448.1774.

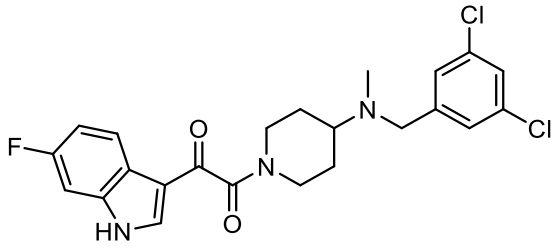
3-(1H-Benzo[d]imidazol-2-yl)-1-(4-((3,5-dichlorobenzyl)(methyl)amino)piperidin-1-yl)propan-1-one (28c). The title compound was prepared following a procedure analogous to that of **28a**. The crude material was purified by flash chromatography eluting with EtOAc/Et_3N (100:1) to give 82 mg (87%) of **28c** as an amorphous white solid. ^{1}H NMR (400 MHz) δ 10.31 (s, 1 H), 7.74 – 7.38 (m, 2 H), 7.24 – 7.17 (comp, 5 H), 4.71 (d, *J* = 13.1 Hz, 1 H), 3.90 (d, *J* = 13.6 Hz, 1 H), 3.48 (s, 2 H), 3.32 – 3.23 (comp, 2 H), 3.06 – 2.94 (m, 1 H), 2.84 (dd, *J* = 7.3, 4.2 Hz, 2 H), 2.70 – 2.57 (comp, 2 H), 2.15 (s, 3 H), 1.91 – 1.81 (comp, 2 H), 1.45 (qd, *J* = 14.2, 12.9, 6.2 Hz, 2 H). ^{13}C NMR (101 MHz) δ 170.6, 154.6, 143.6, 134.8, 127.1, 126.7, 122.0, 60.7, 57.0, 45.0, 41.6, 37.6, 31.6, 28.4, 27.7, 24.5; IR (NaCl, film) 3200, 3057, 2945, 2857, 2789, 2360, 2344, 1631, 1568, 1538, 1450, 1353, 1271, 1226, 1152, 1098, 1046 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{23}H_{26}Cl_2N_4O$ (M+Na)+ 467.1376; found 467.1385.

1-(2-(1H-Indol-3-yl)ethyl)-N-(3,5-dichlorobenzyl)-N-methylpiperidin-4-amine (29a). To a solution of **28a** (20 mg, 0.05 mmol) in THF (1 mL) was added a 0.5 M solution of alane in toluene (0.15 mmol, 0.30 mL) and stirred for 3 h at rt. The reaction was then diluted with 1 M NaOH (20 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated via rotary evaporation. The crude material purified by flash chromatography eluting with hexanes/EtOAc/Et_3N (40:60:1) to give 15 mg (70%) of **29a** as a yellow paste. ^{1}H NMR (400 MHz) δ 8.13 – 8.05 (s, 1 H), 7.61 (d, *J* = 7.8 Hz, 1 H), 7.34 (dt, *J* = 8.0, 0.9 Hz, 1 H), 7.23 (s, 3 H), 7.21 – 7.16 (m, 1 H), 7.15 – 7.09 (m, 1 H), 7.01 (d, *J* = 2.2 Hz, 1 H), 3.80 – 3.71 (m, 1 H), 3.53 (s, 2 H), 3.21 – 3.11 (comp, 2 H), 3.02 – 2.93 (comp, 2 H), 2.75 – 2.65 (comp, 2 H), 2.46 (tt, *J* = 11.5, 3.8 Hz, 1 H), 2.21 (s, 3 H), 2.05 (td, *J* = 11.8, 2.4 Hz, 2 H), 1.85 (comp, 3 H), 1.70 (qd, *J* = 12.0, 3.8 Hz, 2 H). ^{13}C NMR (101 MHz) δ 144.2, 136.2, 134.7, 127.4, 126.9, 126.8, 122.0, 121.4, 119.2, 118.8, 114.5, 111.1, 61.3, 59.3, 57.0, 53.4, 37.9, 27.9, 23.2. IR (NaCl, film) 3412, 3179, 3057, 2943, 2853, 2808, 2360, 1620, 1589, 1568, 1455, 1433, 1376, 1353, 1303, 1228, 1145, 1097, 1049, 1014 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{23}H_{27}Cl_2N_3$ (M+H)+ 416.1655; found 416.1656.

N-(3-Chlorobenzyl)-1-(2-(5-methoxy-1H-indol-3-yl)ethyl)-N-methylpiperidin-4-amine (29b). The title compound was prepared following a procedure analogous to that of **29a**. The crude material was purified by flash chromatography eluting with EtOAc/Et_3N (100:1) to give 13 mg (62%) of **29b** as a yellow paste. ^{1}H NMR (400 MHz) δ 7.97 (s, 1 H), 7.34 (t, *J* = 1.8 Hz, 1 H), 7.25 – 7.17 (comp, 4 H), 7.05 (d, *J* = 2.4 Hz, 1 H), 6.99 (d, *J* = 2.2 Hz, 1 H), 6.84 (dt, *J* = 8.9, 2.3 Hz, 1 H), 3.85 (s, 3 H), 3.56 (s, 2 H), 3.18 (d, *J* = 11.3 Hz, 2 H), 2.99 – 2.90 (comp, 2 H), 2.74 – 2.65 (comp, 2 H), 2.56 – 2.40 (m, 1 H), 2.21 (s, 3 H), 2.12 – 2.02 (comp, 2 H), 1.85 (d, *J* = 12.5 Hz, 2 H), 1.80 – 1.66 (comp, 2 H). ^{13}C NMR (101 MHz) δ 153.9, 142.5, 134.1, 131.3, 129.4, 128.6, 127.8, 126.9, 126.7, 122.3, 114.1, 112.1, 111.8, 100.7, 61.0, 59.2, 57.4, 56.0, 53.4, 37.8, 27.8, 23.2. IR (NaCl, film) 3156, 3049, 2939, 2853, 2808, 2249, 1625, 1581, 1484, 1453, 1356, 1301, 1261, 1216, 1172, 1144, 1119, 1068, 1040 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{24}H_{30}ClN_3O$ (M+Na)+ 434.1970; found 434.1977.

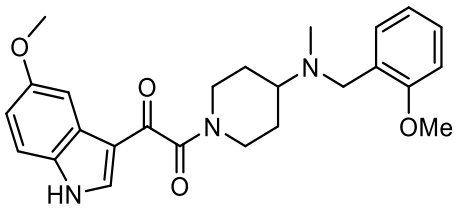
1-(3-(1H-Benzo[d]imidazol-2-yl)propyl)-N-(3,5-dichlorobenzyl)-N-methylpiperidin-4-amine (29c). To a stirred suspension of $NaBH_4$ (32 mg, 0.85 mmol) in THF (0.7 mL) was added a solution of I_2 (99 mg, 0.39 mmol) in THF (0.7 mL) while cooling at 0 ˚C. Once the solution turned clear, **28c** (40 mg, 0.09 mmol) was added, and the solution was warmed to room temperature and stirred overnight, whereupon the reaction was quenched via the slow addition of MeOH (1 mL). The mixture was concentrated via rotary evaporation, resuspended in 3 M HCl (3 mL), and heated under reflux for an additional 6 h. The reaction was then cooled to room temperature, 1 M NaOH (20 mL) was added, and the aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated via rotary evaporation, and the crude material was purified via column chromatography, eluting with

EtOAc:MeOH:Et_3N (100:0:1 → 95:5:1) to give 32 mg (82%) of **29c** as a white solid. ^{1}H NMR (400 MHz) δ 7.52 (dd, *J* = 6.0, 3.2 Hz, 2 H), 7.26 – 7.24 (comp, 3 H), 7.19 (dd, *J* = 6.0, 3.2 Hz, 2 H), 3.57 (s, 2 H), 3.17 – 3.04 (comp, 4 H), 2.61 – 2.54 (comp, 2 H), 2.50 (ddt, *J* = 11.4, 7.6, 3.8 Hz, 1 H), 2.27 (s, 3 H), 2.07 (td, *J* = 12.0, 2.4 Hz, 2 H), 2.02 – 1.95 (comp, 2 H), 1.91 (d, *J* = 13.0, 2.8 Hz, 2 H), 1.81 – 1.68 (comp, 2 H); ^{13}C NMR (101 MHz) δ 155.7, 143.9, 134.8, 127.1, 126.8, 121.7, 114.6, 60.7, 59.0, 57.4, 53.3, 37.8, 29.5, 28.2, 23.7; IR (NaCl, film) 3056, 2944, 2785, 2248, 2192, 1622, 1590, 1568, 1541, 1451, 1431, 1379, 1352, 1304, 1272, 1211, 1123, 1098, 1051, 1026 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{23}H_{28}Cl_2N_4$ (M+H)+ 431.1764; found 431.1785.



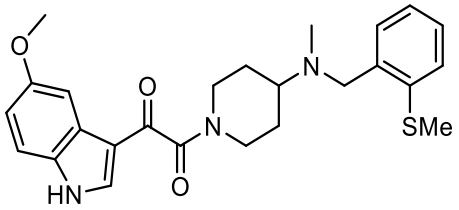
S20

1-(4-((3,5-Dichlorobenzyl)(methyl)amino)piperidin-1-yl)-2-(6-fluoro-1H-indol-3-yl)ethane-1,2-dione (S20). To a solution of **28a** (30 mg, 0.09 mmol) and iPr_2NEt (0.03 mL, 0.2 mmol) in CH_2Cl_2 (1 mL) was added 2-(5-fluoro-1H-indol-3-yl)-2-oxoacetyl chloride (29 mg, 0.13 mmol) , and the reaction was stirred at rt for 48 h. The reaction was then diluted with 1 M aq. NaOH (20 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated via rotary evaporation. The crude material was purified by flash chromatography, eluting with hexanes:EtOAc:Et_3N (50:50:1) to give 36 mg (86%) of **S20** as a white paste. ^{1}H NMR (500 MHz) δ 10.14 (s, 1 H), 8.24 (dd, *J* = 8.5, 5.3 Hz, 1 H), 7.76 (s, 1 H), 7.25 – 7.18 (comp, 3 H), 7.09 – 6.96 (comp, 2 H), 4.69 (ddt, *J* = 13.3, 4.7, 2.5 Hz, 1 H), 3.91 (ddt, *J* = 13.6, 5.0, 2.6 Hz, 1 H), 3.52 (s, 2 H), 3.10 – 2.99 (m, 1 H), 2.84 – 2.75 (m, 1 H), 2.70 (tt, *J* = 11.4, 3.6 Hz, 1 H), 2.18 (s, 3 H), 1.97 – 1.93 (m, 1 H), 1.85 – 1.78 (m, 1 H), 1.59 (pd, *J* = 12.5, 4.3 Hz, 2 H); ^{13}C NMR (126 MHz) δ 185.9, 166.1, 161.6, 159.7, 143.6, 136.9, 136.8, 135.8, 135.8, 134.8, 127.2, 126.7, 125.5, 123.0, 123.0, 121.6, 114.5, 111.9, 111.7, 98.7, 98.5, 60.8, 57.1, 56.0, 45.8, 45.6, 41.1, 37.7, 34.6, 34.2, 30.3, 29.7, 28.6, 27.9, 23.4, 22.7, 21.2, 14.8, 14.2, 14.1; IR (NaCl, film) 2926, 2855, 1623, 1595, 1568, 1525, 1504, 1446, 1432, 1372, 1268, 1232, 1150, 1091, 1046 cm $^{-1}$; HRMS (ESI) *m/z* calcd $C_{23}H_{22}Cl_2FN_3O_2$ (M+H)+ 462.1146; found 462.1156.



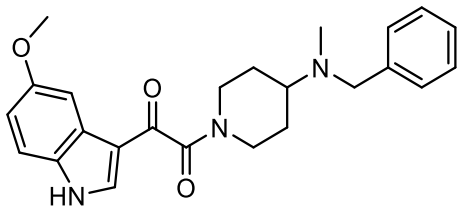
S21

1-(5-Methoxy-1H-indol-3-yl)-2-(4-((2-methoxybenzyl)(methyl)amino)piperidin-1-yl)ethane-1,2-dione (S21). The title compound was prepared following a procedure analogous to that of **S20**. The crude material was purified by flash chromatography eluting with EtOAc/Et_3N (100:1) to give 82 mg (75%) of **S21** as a white foam. ^{1}H NMR (400 MHz) δ 10.12 (s, 1 H), 7.78 (d, J = 2.5 Hz, 1 H), 7.65 (s, 1 H), 7.22 (t, J = 8.3 Hz, 2 H), 6.91 – 6.85 (comp, 3 H), 6.78 (ddd, J = 8.2, 2.5, 1.1 Hz, 1 H), 4.66 (d, J = 13.4 Hz, 1 H), 3.87 (comp, 4 H), 3.79 (s, 3 H), 3.55 (s, 2 H), 3.02 (td, J = 13.8, 13.0, 2.7 Hz, 1 H), 2.83 – 2.64 (comp, 2 H), 2.20 (s, 3 H), 1.97 (dd, J = 10.1, 5.7 Hz, 1 H), 1.81 (d, J = 12.7 Hz, 1 H), 1.61 (dtd, J = 16.1, 12.3, 4.2 Hz, 2 H). ^{13}C NMR (101 MHz) δ 186.1, 166.4, 159.7, 156.7, 141.2, 135.5, 131.4, 129.3, 126.1, 121.0, 114.7, 114.3, 114.1, 112.9, 112.3, 103.1, 60.2, 58.0, 55.8, 55.2, 45.88, 41.1, 37.7, 28.6, 27.8. IR (NaCl, film) 3231, 2949, 2362, 2249, 1628, 1519, 1487, 1439, 1364, 1299, 1211, 1179, 1149, 1089, 1042 cm^{-1}. HRMS (ESI) *m/z* calcd $C_{25}H_{29}N_3O_4$ (M+H)+ 436.2231; found 436.2232.



S22

1-(5-Methoxy-1H-indol-3-yl)-2-(4-(methyl(3-(methylthio)benzyl)amino)piperidin-1-yl)ethane-1,2-dione (S22). The title compound was prepared following a procedure analogous to that of **S20**. The crude material was purified by flash chromatography eluting with EtOAc/Et_3N (100:1) to give 32 mg (79%) of **S22** as a light tan foam. ^{1}H NMR (400 MHz) δ 8.99 (s, 1 H), 7.85 (d, *J* = 3.0 Hz, 2 H), 7.14 (d, *J* = 7.5 Hz, 1 H), 7.08 (d, J = 7.6 Hz, 1 H), 6.95 (dd, J = 8.9, 2.5 Hz, 1 H), 4.71 (d, *J* = 13.4 Hz, 1 H), 3.91 (d, *J* = 1.8 Hz, 4 H), 3.56 (s, 2 H), 3.06 (t, *J* = 11.7 Hz, 1 H), 2.84 – 2.67 (comp, 2 H), 2.49 (d, J = 0.6 Hz, 3 H), 2.21 (s, 3 H), 2.01 – 1.94 (m, 1 H), 1.84 (d, *J* = 13.0 Hz, 1 H), 1.68-1.52 (comp, 2 H). ^{13}C NMR (101 MHz) δ 186.1, 166.3, 156.8, 140.3, 138.4, 131.4, 128.8, 126.6, 126.1, 125.4, 125.0, 114.7, 114.3, 112.8, 103.2, 60.4, 57.8, 55.8, 45.9, 41.1, 37.7, 28.6, 27.8, 15.8. IR (NaCl, film) 3225, 2947, 2248, 1627, 1518, 1474, 1439, 1367, 1298, 1268, 1243, 1211, 1179, 1128, 1088, 1033 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{25}H_{29}N_3O_3S$ (M+H)+ 452.2002; found 452.2019.



S23

1-(4-(Benzyl(methyl)amino)piperidin-1-yl)-2-(5-methoxy-1H-indol-3-yl)ethane-1,2-dione (S23). The title compound was prepared following a procedure analogous to that of **S20**. The crude material was purified by flash chromatography eluting with EtOAc/Et_3N (100:1) to give 80 mg (80%) of **S23** as a white foam. ^{1}H NMR (400 MHz) δ 9.85 (s, 1 H), 7.80 (d, J = 2.5 Hz, 1 H), 7.70 (d, J = 1.9 Hz, 1 H), 7.33 – 7.27 (comp, 4 H), 7.26 – 7.21 (comp, 2 H), 6.89 (ddd, *J* = 8.9, 2.5, 0.3 Hz, 1 H), 3.88 (comp, 4 H), 3.57 (s, 2 H), 3.03 (ddd, *J* = 13.8, 12.1, 2.8 Hz, 1 H), 2.83 – 2.65 (comp, 2 H), 2.20 (s, 3 H), 2.03 – 1.93 (m, 1 H), 1.83 (d, *J* = 12.7 Hz, 1 H), 1.71 – 1.53 (comp, 2 H). ^{13}C NMR (101 MHz) δ 186.08, 166.27, 156.77, 139.46, 135.33, 131.34, 128.64, 128.30, 126.96, 126.11, 114.72, 114.44, 112.73, 103.24, 60.33, 58.04, 55.76, 45.84, 41.06, 37.58, 28.67, 27.83. IR (NaCl, film) 3216, 2948, 1627, 1518, 1487, 1442, 1365, 1299, 1268, 1243, 1211, 1179, 1129, 1089, 1030, 958 cm^{-1}. HRMS (ESI) *m/z* calcd $C_{24}H_{27}N_3O_3$ (M+Na)+ 428.1945; found 428.1960.

N-(3,5-Dichlorobenzyl)-1-(2-(6-fluoro-1H-indol-3-yl)ethyl)-N-methylpiperidin-4-amine (29d). To a stirred suspension of $NaBH_4$ (20 mg, 0.53 mmol) in THF (2 mL) was added I_2 (63 mg, 0.25 mmol) while cooling at 0 ˚C. Once the solution turned clear, **S20** (46 mg, 0.10 mmol) was added at 0 ˚C, and the solution was then heated under reflux overnight, whereupon saturated aq. $NaHCO_3$ (10 mL) was added and the solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried (Na_2SO_4) to give a white paste which was then dissolved in EtOH (5 mL) and treated with CsF (60 mg, 0.39 mmol) and Na_2CO_3 (60 mg, 0.57 mmol), and the resulting solution was heated under reflux for 24 h, whereupon it was cooled to room temperature and filtered over celite, rinsing with EtOAc. The solution was concentrated via rotary evaporation and the resultant crude material was purified via column chromatography, eluting with hexanes:EtOAc:Et_3N (20:80:1) to give 19 mg (44%) of the title compound as a clear paste. ^{1}H NMR (500 MHz) δ 8.02 (s, 1 H), 7.50 (dd, *J* = 8.7, 5.3 Hz, 1 H), 7.23 (s, 3 H), 7.06 – 6.98 (comp, 2 H), 6.88 (td, *J* = 9.2, 2.2 Hz, 1 H), 3.53 (s, 2 H), 3.15 (d, *J* = 10.8 Hz, 2 H), 2.98 – 2.92 (comp, 2 H), 2.69 (dd, *J* = 9.8, 6.6 Hz, 2 H), 2.47 (tt, *J* = 11.4, 3.7 Hz, 1 H), 2.21 (s, 3 H), 2.07 (t, *J* = 11.6 Hz, 2 H), 1.87 – 1.80 (comp, 2 H), 1.71 (qd, *J* = 12.2, 3.6 Hz, 2 H); ^{13}C NMR (126 MHz) δ 161.0, 159.1, 144.2, 136.2, 136.1, 134.7, 127.0, 126.8, 124.1, 121.7, 121.6, 119.6, 119.5, 114.6, 108.1, 107.9, 97.5, 97.3, 61.2, 59.2, 57.0, 53.4, 37.9, 27.9, 23.1; IR (NaCl, film) 2918, 2849, 1567, 1457, 1432, 1245, 1140 cm^{-1} HRMS (ESI) *m/z* calcd $C_{23}H_{26}Cl_2FN_3$ (M+H)+ 434.1561; found 434.1571.

4-((3,5-Dichlorobenzyl)(methyl)amino)-N-phenylpiperidine-1-carboxamide (29e). A solution of **27a** (28 mg, 0.10 mmol), phenyl isocyanate (24 mg, 0.20 mmol) and (*i*-Pr)$_2$NEt (13 mg, 0.10 mmol) in CH_2Cl_2 was stirred overnight at room temperature, and the solvent was removed via rotary evaporation. The crude material was resuspended in 1 M aq. HCl (10 mL) and washed with Et_2O (2 x 20 mL). The aqueous layer was then made basic via the addition of 3 M aq. NaOH (10 mL) and extracted with CH_2Cl_2 (5 x 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated via rotary evaporation to give 22 mg (56%) of the title compound as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.37 – 7.29 (comp, 5 H), 7.29 – 7.20 (comp, 2 H), 7.04 – 6.97 (m, 1 H), 4.24 (d, *J* = 13.2 Hz, 2 H), 3.61 (s, 2 H), 2.87 (td, *J* = 13.7, 2.5 Hz, 2 H), 2.69 (tt, *J* = 11.5, 3.7 Hz, 1 H), 2.21 (s, 3 H), 1.90 (d, *J* = 12.9 Hz, 2 H), 1.57 (qd, *J* = 12.4, 4.2 Hz, 2 H); ^{13}C NMR (101 MHz, CD_3OD) δ 156.4, 144.0, 139.6, 134.6, 128.1, 126.9, 126.5, 122.6, 120.8, 60.9, 56.5, 43.5, 36.6, 27.7; IR (NaCl, film) 3625, 3127, 3054, 2944, 2855, 2796, 2360, 1636, 1595, 1569, 1536, 1501, 1447, 1353, 1329, 1306, 1243, 1160, 1100, 1041 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{20}H_{23}Cl_2N_3O$ (M+Na)+ 414.1110; found 414.1121.

1-(2-(1H-Pyrrolo[2,3-b]pyridin-3-yl)ethyl)-N-(3,5-dichlorobenzyl)-N-methylpiperidin-4-amine (29f). A solution of **27a** (50 mg, 0.18 mmol) and **31** (25 mg, 0.11 mmol) in MeCN (1 mL) was stirred under reflux and stirred for 8 h, whereupon the reaction was cooled to room temperature and stirred for an additional 72 h. The reaction mixture was concentrated via rotary evaporation, and the crude material was purified by flash chromatography eluting with Et_2O/CH_2Cl_2/Et_3N (100:0:1 → 66:33:1) to give 15 mg (33%) of **29f** as an amorphous white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.20 (d, *J* = 4.3 Hz, 1 H), 8.09 (dd, *J* = 7.9, 1.5 Hz, 1 H), 7.35 (comp, 4 H), 7.14 (dd, *J* = 7.9, 4.8 Hz, 1 H), 4.60 (s, 3 H), 3.65 (s, 3 H), 3.38 (s, 1 H), 3.27 – 3.18 (comp, 4 H), 3.06 (s, 2 H), 2.80 (s, 1 H), 2.25 (s, 3 H), 2.12 (d, *J* = 13.2 Hz, 2 H), 1.88 (s, 2 H). ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 198.2, 170.8, 148.9, 143.0, 134.3, 127.3, 127.0, 126.8, 123.9, 119.5, 115.3, 60.2, 56.4, 52.4, 37.8, 21.2, 14.5, 7.6. IR (NaCl, film) 3144, 3096, 3036, 2928, 2856, 2477, 2632, 1570, 1459, 1422,1344, 1288, 1203, 1126, 1103, 1044 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{22}H_{26}Cl_2N_4$ (M+H)+ 417.1607; found 417.1623.

1-(2-(5-Methoxy-1H-indol-3-yl)ethyl)-N-methyl-N-(3-(methylthio)benzyl)piperidin-4-amine (29h). A solution of **S22** (68 mg, 0.15 mmol) in THF (0.5 mL) was added to a stirred suspension of $LiAlH_4$ (57 mg, 1.5 mmol) in THF (1.0 mL) while cooling at 0 ˚C. The reaction vessel was removed from the ice bath and stirred while heating under reflux for 19 hours. The reaction vessel was then cooled to 0 ˚C, whereupon H_2O (0.06 mL) was added, followed by 3M NaOH (0.06 mL) and H_2O (0.18 mL). The mixture was stirred at room temperature for 30 min, during which time the visible precipitate turned from grey to white. $MgSO_4$ was added, and the mixture was stirred for an additional 30 minutes, and then filtered over a pad of celite, washing with EtOAc. The solution was concentrated via rotary evaporation, and the crude material was purified by flash chromatography eluting with hexanes/EtOAc/Et_3N (25:75:1 → 0:100:1) to

give 42 mg (66%) of **29h** as an amorphous off-white solid. ^{1}H NMR (400 MHz) δ 7.87 (s, 1 H), 7.25 – 7.20 (comp, 2 H), 7.11 (comp, 2 H), 7.05 (d, *J* = 2.4 Hz, 1 H), 7.00 (d, *J* = 2.4 Hz, 1 H), 6.85 (dd, *J* = 8.8, 2.4 Hz, 1 H), 3.86 (d, *J* = 0.6 Hz, 3 H), 3.56 (s, 2 H), 3.15 (d, *J* = 11.3 Hz, 2 H), 2.98 – 2.90 (comp, 2 H), 2.71 – 2.63 (comp, 2 H), 2.49 (comp, 4 H), 2.25 – 2.19 (s, 3 H), 2.04 (t, *J* = 11.2 Hz, 2 H), 1.85 (d, *J* = 12.1 Hz, 2 H), 1.74 (td, *J* = 12.0, 3.9 Hz, 2 H). ^{13}C NMR (101 MHz) δ 153.9, 140.9, 138.2, 131.3, 128.7, 127.8, 126.8, 125.5, 124.9, 122.3, 114.2, 112.1, 111.8, 110.0, 100.7, 59.2, 57.8, 56.0, 53.5, 37.8, 27.8, 23.2, 15.8. IR (NaCl, film) 3415, 3163, 3047, 2926, 2854, 2807, 1624, 1587, 1484, 1452, 1356, 1301, 1261, 1216, 1172, 1144, 1099, 1037 cm^{-1}. LRMS (ESI) *m/z* calcd for $C_{25}H_{33}N_3OS$ (M+Na)+ 446.2237; found 446.2249.

1-(2-(5-Methoxy-1H-indol-3-yl)ethyl)-N-(3-methoxybenzyl)-N-methylpiperidin-4-amine (29g). The title compound was prepared following the procedure described for **29h**. The crude material purified by flash chromatography eluting with hexanes/EtOAc/Et_3N (25:75:1 → 0:100:1) to give 23 mg (62%) of **29g** as a yellow paste. ^{1}H NMR (400 MHz) δ 7.85 (s, 1 H), 7.25 – 7.20 (comp, 2 H), 7.05 (d, *J* = 2.4 Hz, 1 H), 7.01 (d, *J* = 2.3 Hz, 1 H), 6.94 – 6.89 (comp, 2 H), 6.85 (dd, *J* = 8.8, 2.5 Hz, 1 H), 6.79 (dd, *J* = 8.1, 2.6 Hz, 1 H), 3.86 (s, 3 H), 3.81 (s, 3 H), 3.58 (s, 2 H), 3.16 (d, *J* = 11.2 Hz, 2 H), 2.98 – 2.91 (comp, 2 H), 2.72 – 2.63 (comp, 2 H), 2.56-2.44 (m, 1 H), 2.24 (s, 3 H), 2.10 – 2.00 (comp, 2 H), 1.86 (d, *J* = 12.6 Hz, 2 H), 1.80 – 1.68 (comp, 2 H). ^{13}C NMR (101 MHz) δ 159.7, 153.9, 141.9, 131.4, 129.1, 127.9, 122.3, 121.1, 114.1, 112.3, 112.1, 111.8, 100.7, 60.8, 59.2, 57.9, 56.0, 55.2, 53.5, 37.8, 27.8, 23.2. IR (NaCl, film) 3415, 3154, 3046, 2941, 2831, 1587, 1487, 1455, 1357, 1308, 1267, 1216, 1170, 1147, 1120, 1045 cm^{-1}. LRMS (ESI) *m/z* calcd for $C_{25}H_{33}N_3O_2$ (M+H)+ 408.2646; found 408.2643.

N-Benzyl-1-(2-(5-methoxy-1H-indol-3-yl)ethyl)-N-methylpiperidin-4-amine (29i). The title compound was prepared following the procedure described for **29h**. The crude material purified by flash chromatography eluting with hexanes/EtOAc/Et_3N (25:75:1 → 0:100:1) to give 43 mg (96%) of **29i** as a yellow paste. ^{1}H NMR (400 MHz) δ 7.85 (s, 1 H), 7.35 – 7.29 (comp, 5 H), 7.24 – 7.21 (m, 1 H), 7.05 (d, *J* = 2.5 Hz, 1 H), 7.00 (d, *J* = 2.4 Hz, 1 H), 6.85 (dd, *J* = 8.8, 2.4 Hz, 1 H), 3.86 (s, 3 H), 3.60 (s, 2 H), 3.16 (d, *J* = 11.2 Hz, 2 H), 2.98 – 2.90 (comp, 2 H), 2.71 – 2.63 (comp, 2 H), 2.55-2.45 (m, 1 H), 2.22 (s, 3 H), 2.09 – 2.00 (comp, 2 H), 1.86 (d, *J* = 12.6 Hz, 2 H), 1.79 – 1.73 (comp, 2 H). ^{13}C NMR (101 MHz) δ 153.9, 140.0, 131.4, 128.8, 128.2, 127.9, 126.8, 122.3, 114.1, 112.1, 111.8, 100.7, 60.8, 59.2, 57.9, 56.0, 53.5, 37.8, 27.8, 23.2. IR (NaCl, film 3416, 3155, 3030, 2942, 2801, 1625, 1584, 1487, 1452, 1360, 1305, 1261, 1216, 1173, 1143, 1118, 1035 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{24}H_{31}N_3O$ (M+H)+ 378.2540; found 378.2550.

***T. brucei* proliferation inhibition assay**

High-throughput proliferation assays were performed as described with minor alterations.[2] Bloodstream form Lister 427 T. brucei was maintained in log phase growth (<10^6 cells/mL) in HMI-9 medium. Cultures for proliferation assays were inoculated at 4 x 10^3 trypanosomes/mL and 50 µL was dispensed into a black 384-well microplate with a MultiDrop Combi (Thermo Scientific). An additional 50 µL of cell culture was manually added to each well of the first row of the plate. Solvent (50% DMSO) or 10 mM compound was added to each well of the first row of the plate to a final concentration of 0.5% or 100 µM, respectively. Two technical replicates were prepared for each sample. Using an Eppendorf Xplorer automated multi-channel pipette, 50 µL was taken from each well of the first row and transferred to the corresponding well in the second row. This was repeated down the rows of the plate, and 50 µL was discarded from the last row. DNA content in each well was measured and plotted as a function of compound concentration.

Expression and purification of recombinant *Tb*MetRS

A 30 mL solution of LB-ampicillin (100 mg/L) was inoculated with one colony of BL21 (de3) transformed with his-tagged *T. brucei* MetRS plasmid (plasmid was a generous gift from Prof. Wim J. G. Hol). The inoculated solution was cultured overnight at 30 °C, 150 RPM in a shaking incubator. The saturated culture was then diluted 100 x (10 mL : 1000 mL) in 3 x 1 L sterile LB and cultured at 37 °C, 200 RPM until an OD_{600} of 0.6 was reached. At this time, IPTG was added to a final concentration of 0.5 mM, and the temperature of the incubator was reduced to 15 °C. Expression continued for 24 h, at which time the cells were harvested via centrifugation (15 min, 4000 x g) and the resulting cell pellet was stored at -80 °C until further use. Frozen cell pellets from 3 L culture were thawed and re-suspended in 30 mL of lysis buffer (25 mM HEPES pH 7.0, 500 mM NaCl, 5% glycerol, 10 mM imidazole, 10 mM $MgCl_2$, 10 mM L-Met, 0.025% NaN_3), DNAse I (240 µL) and phenylmethylsulfonyl fluoride (4 mg) were added, and the cells were lysed 2x in a cell press at 1200 psi and 1 drop/secflow rate. The lysate was clarified via centrifugation for 45 min at 12000 RPM, and the supernatant was purified on an NiNTA FPLC column (10 → 30 → 250 mM imidazole step gradient). Peak fractions were pooled and dialyzed into anion exchange buffer (25 mM HEPES pH 7.0, 5% glycerol, 10 mM L-Met, 0.025% NaN_3), and then ran on an SP/HP FPLC column (0 → 1M NaCl anion exchange buffer gradient). Peak fractions were concentrated via centrifugation, diluted (1:1) with glycerol and stored at -80 ˚C until use.

***Tb*MetRS aminoacylation assay**

Protocol was adapted from the procedure of Cestari and Stuart.[3] Reactions were performed in 25 mM HEPES pH 9, 100 mM NaCl, 10 mM MgCl, 50 mM KCl, 1 mM DTT and 3% glycerol with 0.8 mg/mL yeast tRNA (Sigma), 0.2 mM L-methionine, 0.2 mM ATP, 0.1 µM recombinant *Tb*MetRS, and 2 U/mL pyrophosphatase (Sigma) in 50 µL total volume. The reactions were performed in clear, flat-bottom 96-

well plates and incubated for 2 h at room temperature, whereupon 75 µL of a 2:1 mixture of H_2O and freshly prepared malachite green reagent[4] was added, and the mixture was incubated for 20 min. Absorbances were measured at 620 nM using a plate reader.

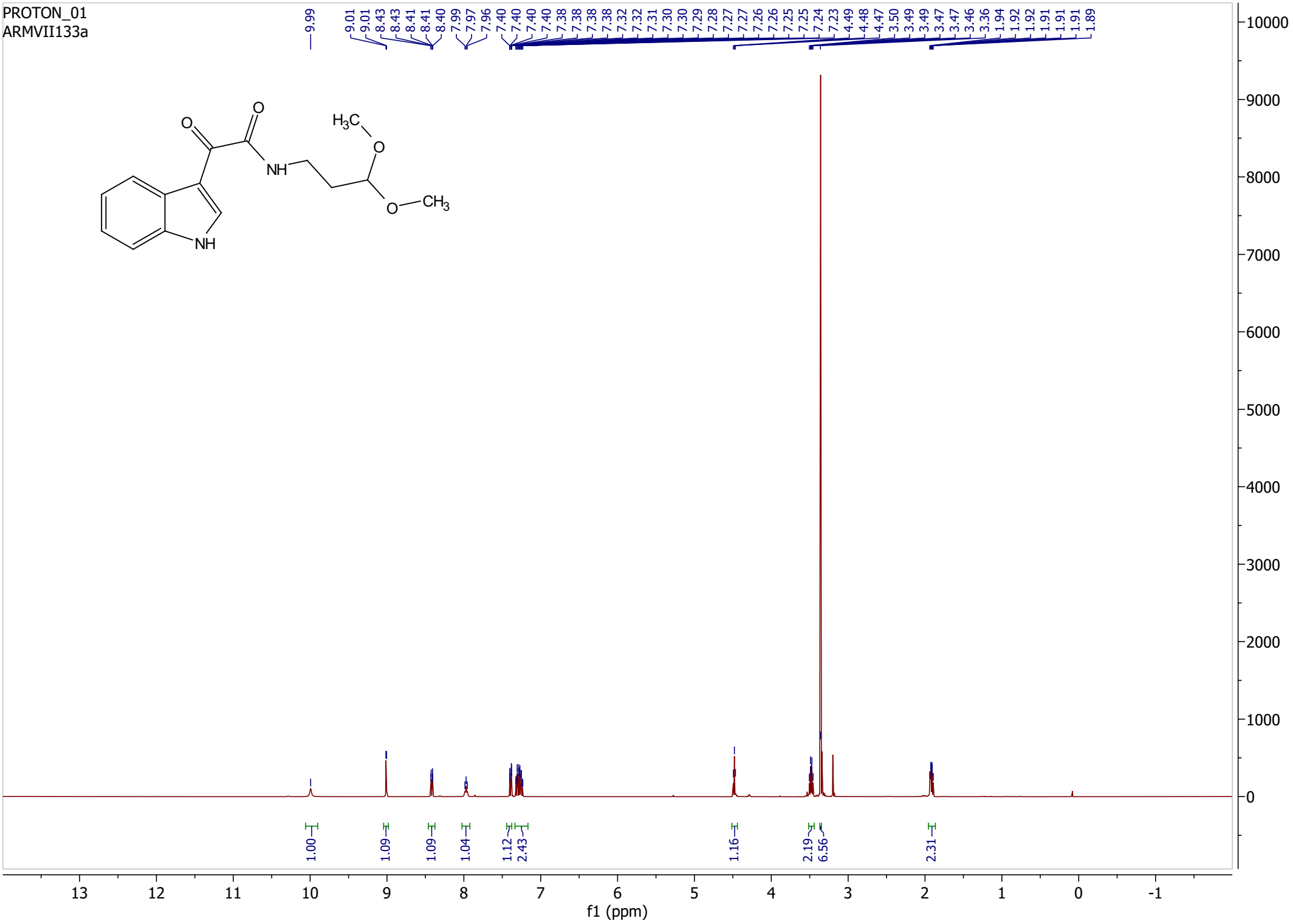
References

1. Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* **1978**, *43*, 2923–2925.

2. Thomas, S. M.; Purmal, A.; Pollastri, M.; Mensa-Wilmot, K. Discovery of a Carbazole-Derived Lead Drug for Human African Trypanosomiasis. *Sci. Rep*. **2016**, *6*, 32083.

3. Cestari, I.; Stuart, K. A Spectrophotometric Assay for Quantitative Measurement of Aminoacyl-TRNA Synthetase Activity. *J Biomol Screen* **2012**, 1087057112465980.

4. Baykov, A. A.; Evtushenko, O. A.; Avaeva, S. M. A Malachite Green Procedure for Orthophosphate Determination and Its Use in Alkaline Phosphatase-Based Enzyme Immunoassay. *Anal. Biochem.* **1988**, *171*, 266–270.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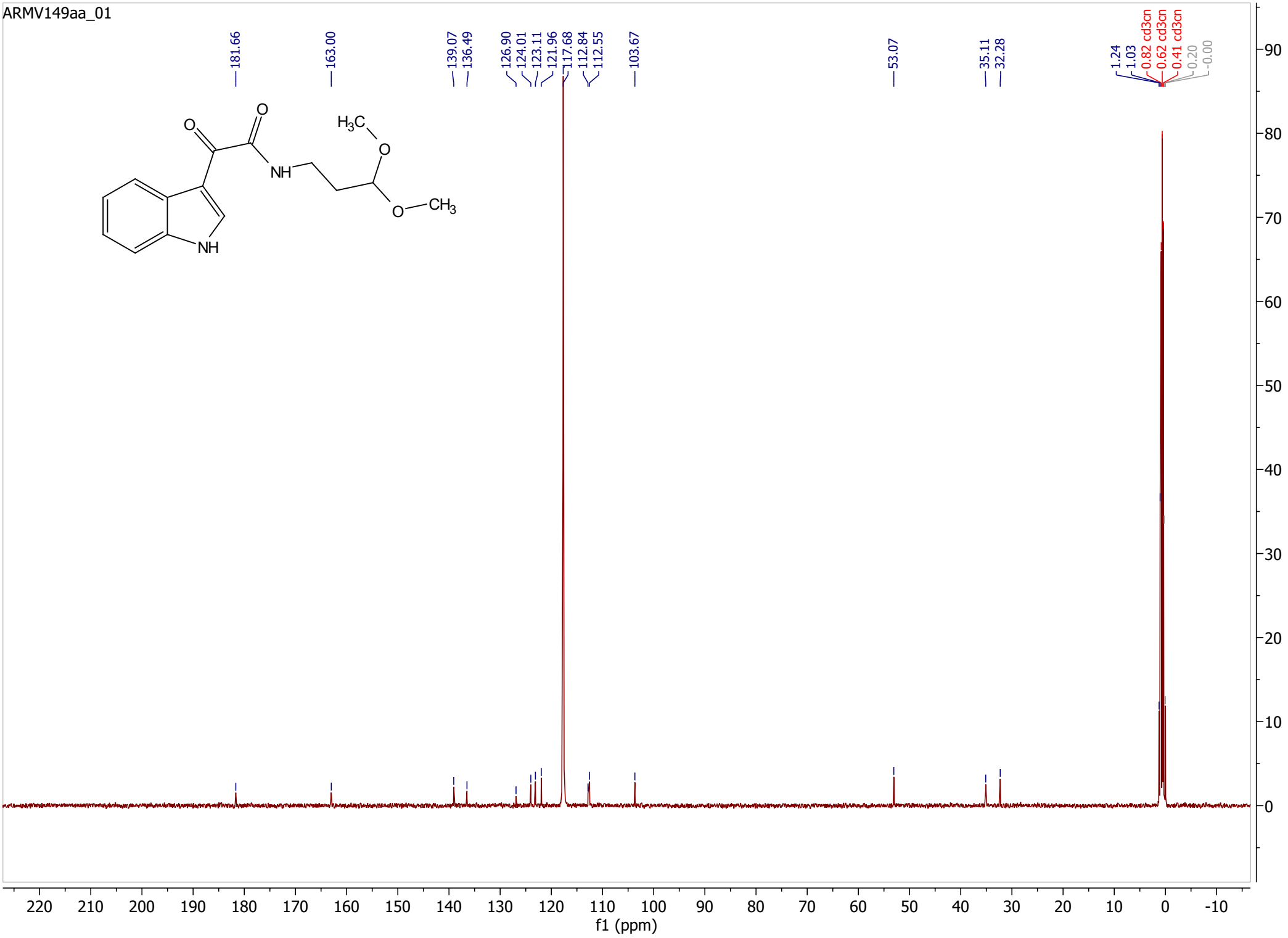
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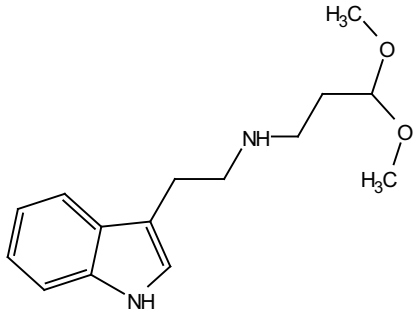

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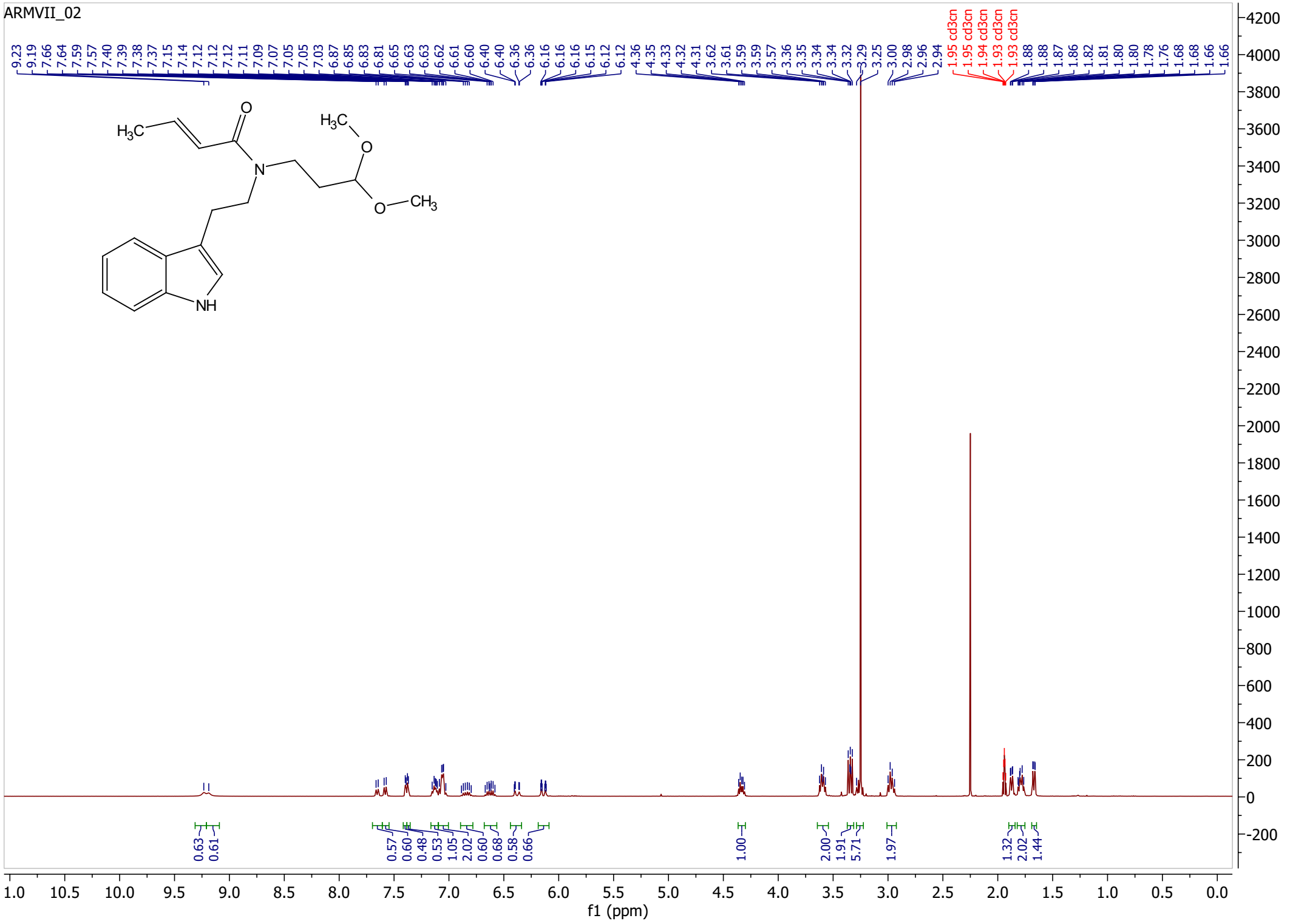
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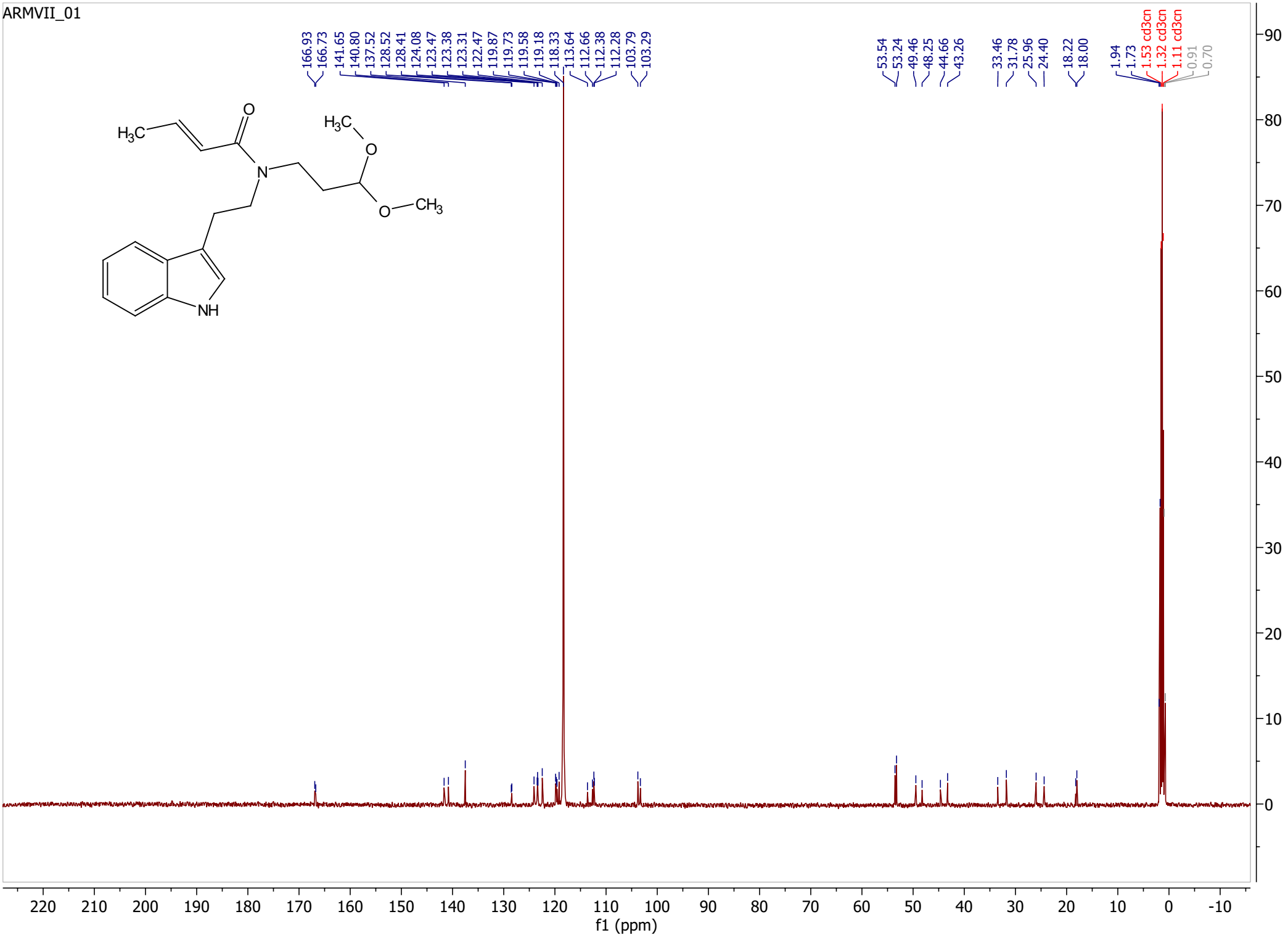
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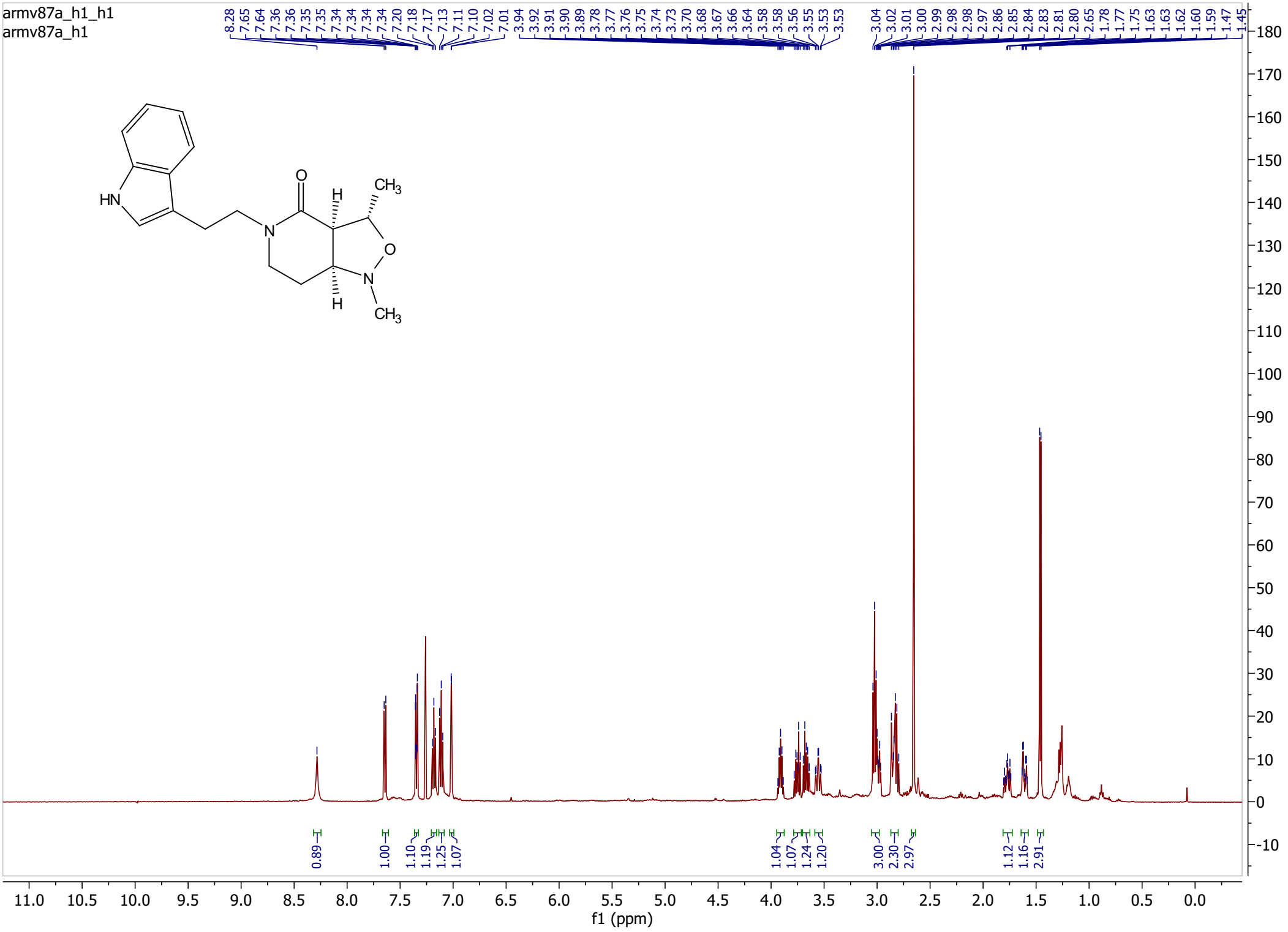
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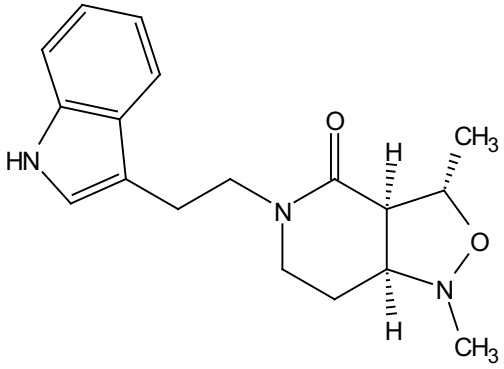

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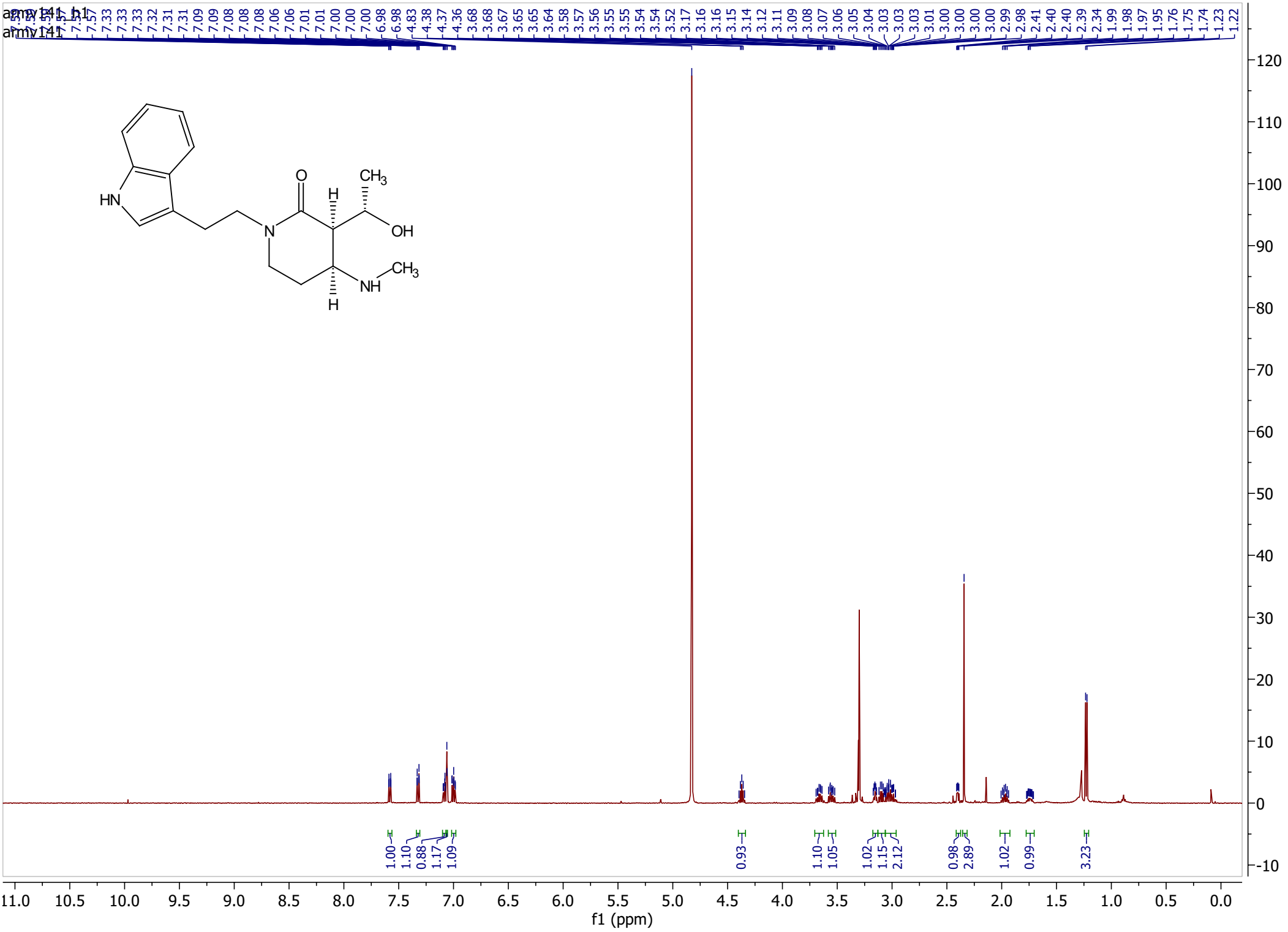
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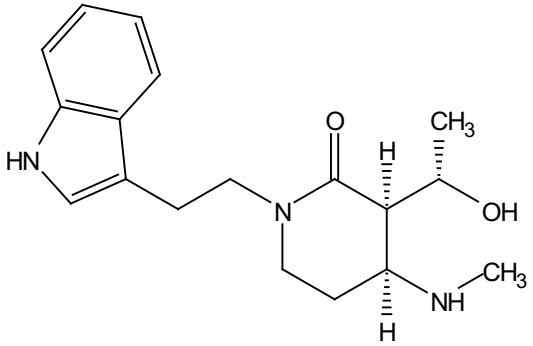
CH3
NH
H
f1 (ppm)

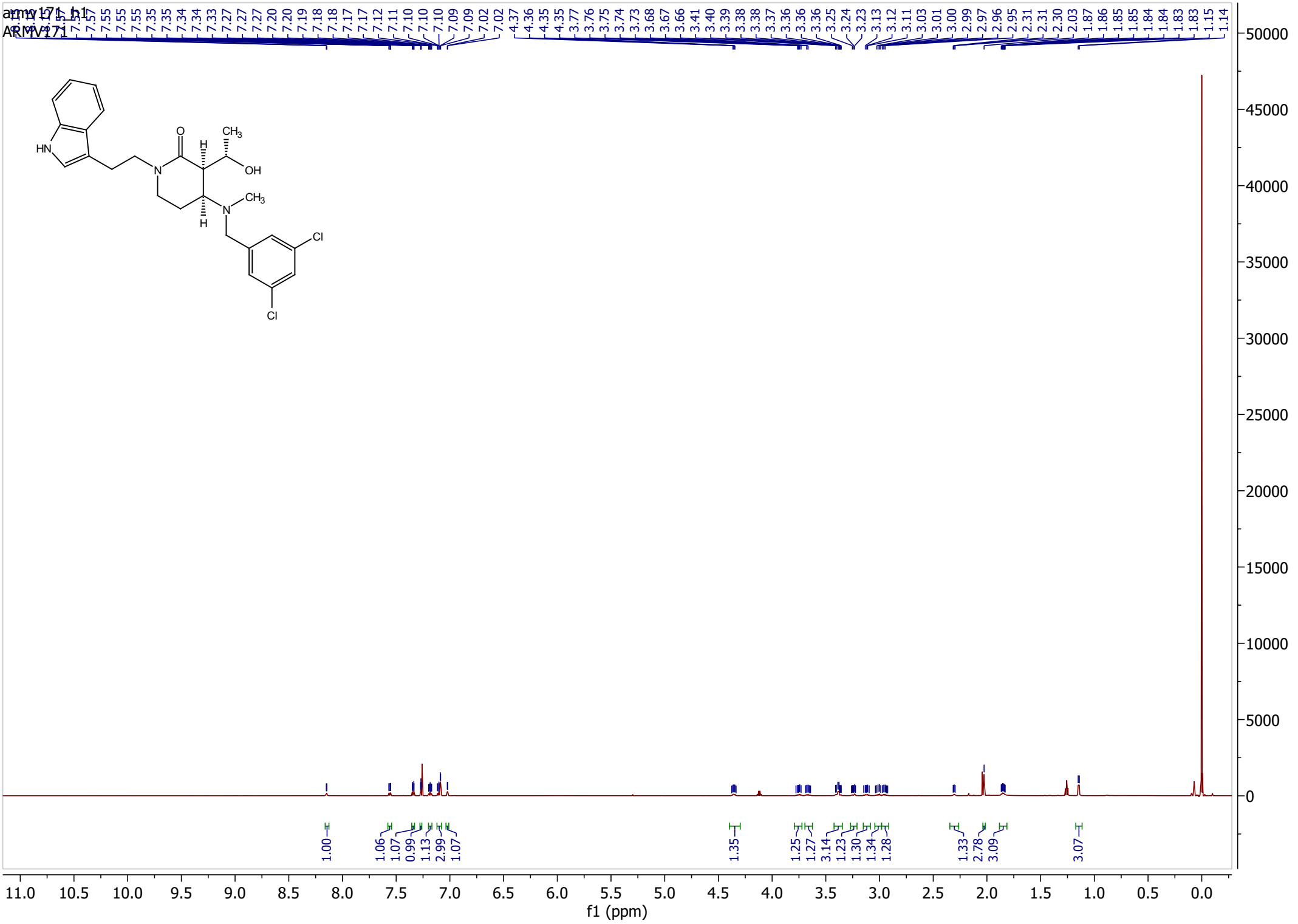
armv141_c13
armv141



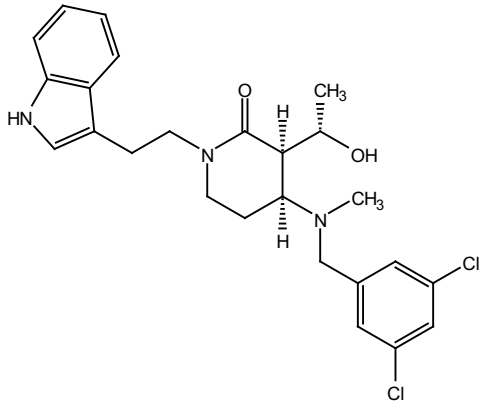
170.96
138.12
128.89
123.64
122.40
119.67
119.31
113.09
112.32
67.50
56.11
51.37
49.69
49.51 cd3od
49.34 cd3od
49.17 cd3od
49.00 cd3od
48.83 cd3od
48.66 cd3od
48.49 cd3od
45.69
33.48
30.77
24.81
23.73
22.46

24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


arm171_h1
ARMV171
HN
O
H
CH3
OH
N
CH3
N
H
Cl
Cl
7.57 7.55 7.55 7.55 7.35 7.35 7.34 7.34 7.33 7.27 7.27 7.27 7.20 7.20 7.19 7.18 7.18 7.17 7.17 7.12 7.11 7.10 7.10 7.10 7.09 7.09 7.02 7.02 4.37 4.36 4.35 4.35 3.77 3.76 3.75 3.74 3.73 3.68 3.67 3.66 3.41 3.40 3.39 3.38 3.38 3.37 3.36 3.36 3.36 3.25 3.24 3.23 3.13 3.12 3.11 3.03 3.01 3.00 2.99 2.97 2.96 2.95 2.31 2.31 2.30 2.03 1.87 1.86 1.85 1.85 1.84 1.84 1.83 1.83 1.15 1.14
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
1.00
1.06
1.07
0.99
1.13
2.99
1.07
1.35
1.25
1.27
3.14
1.23
1.30
1.34
1.28
1.33
2.78
3.09
3.07
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

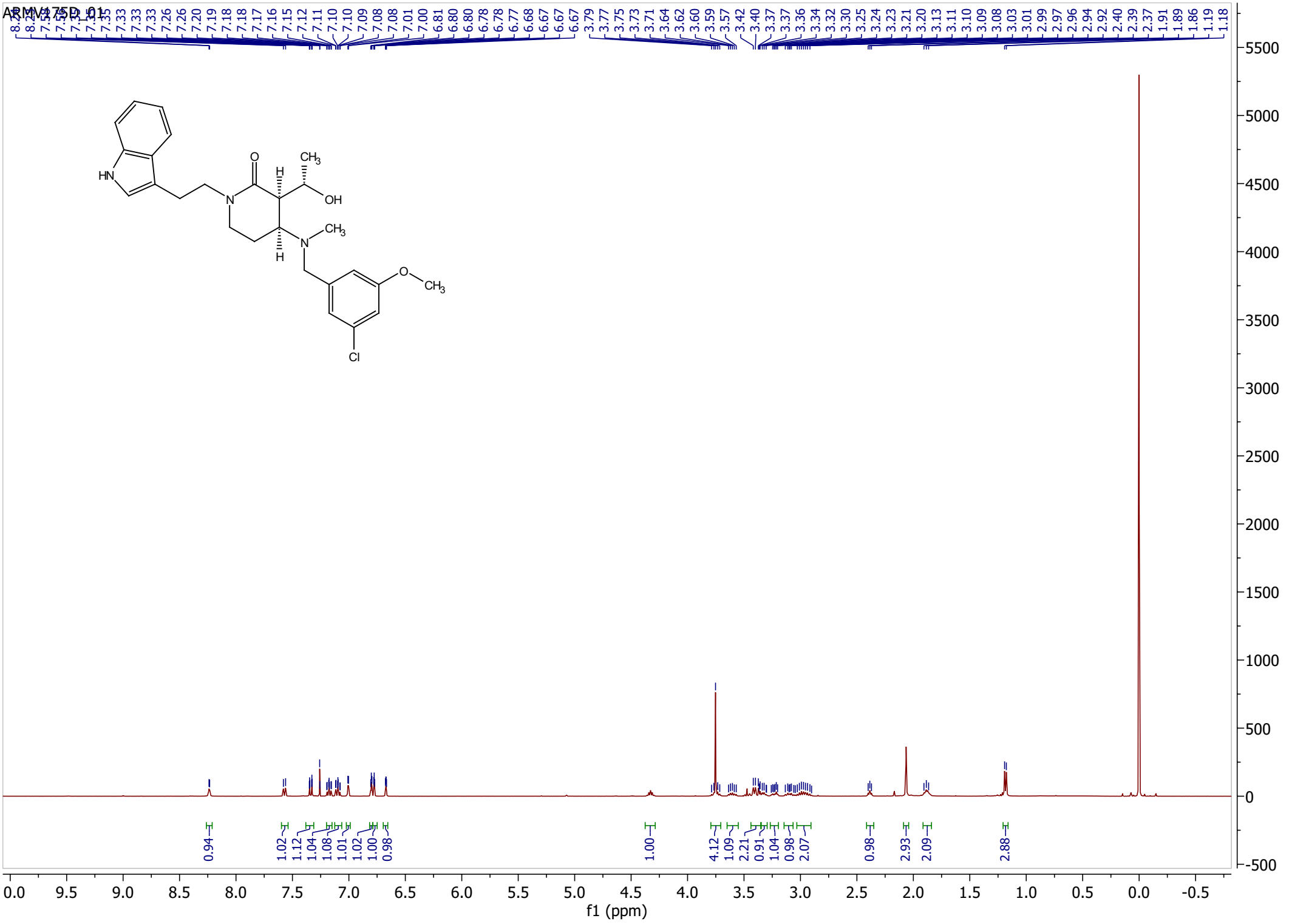
armv171_c13 1
ARMV171

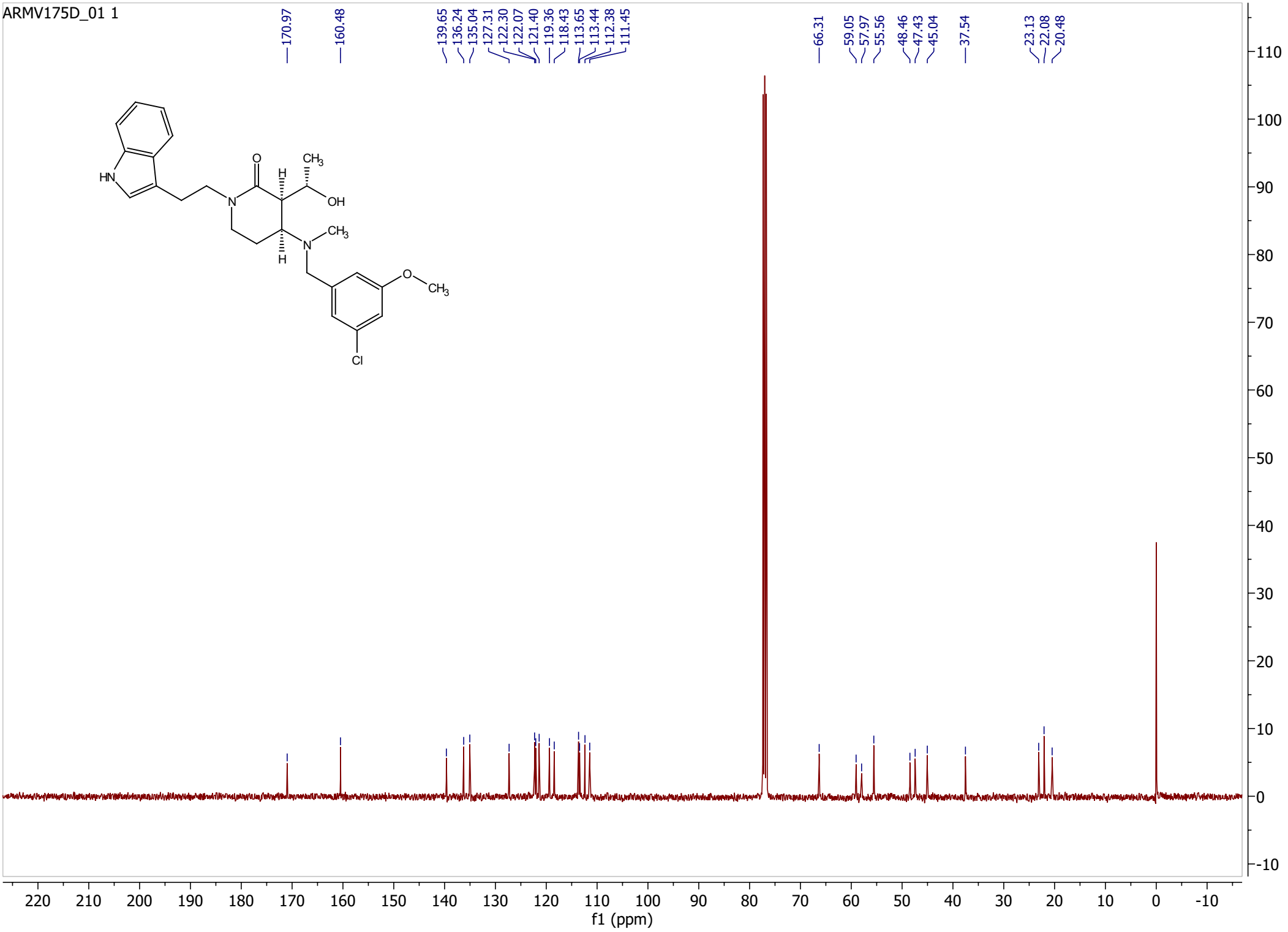


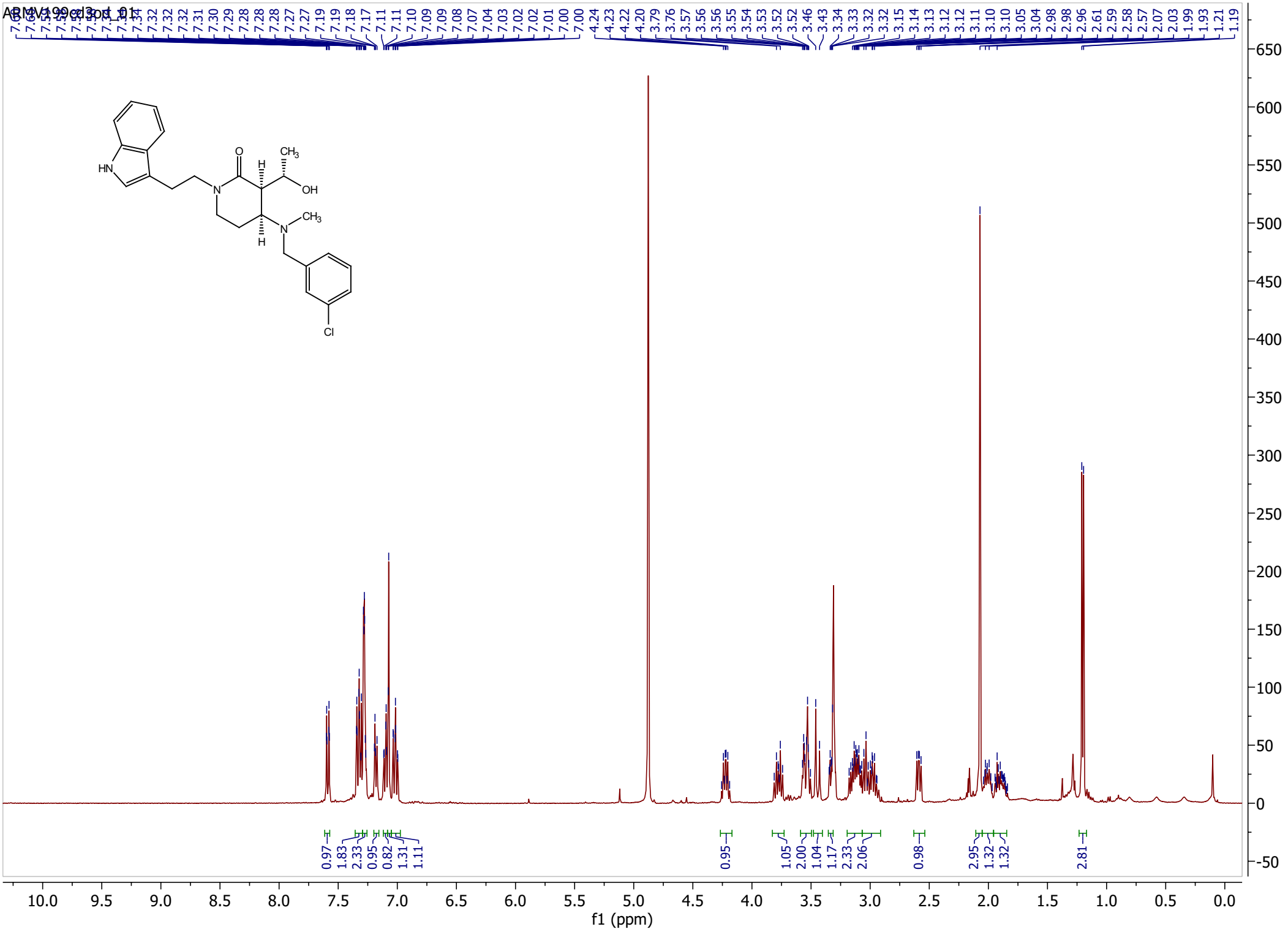
171.73
140.60
136.25
135.21
128.08
127.58
127.25
122.36
122.14
119.40
118.36
112.29
111.53
77.23 cdcl3
77.02 cdcl3
76.81 cdcl3
66.15
60.44
58.93
47.96
47.39
44.92
37.33
29.71
23.18
21.74
21.07
14.20
-0.00

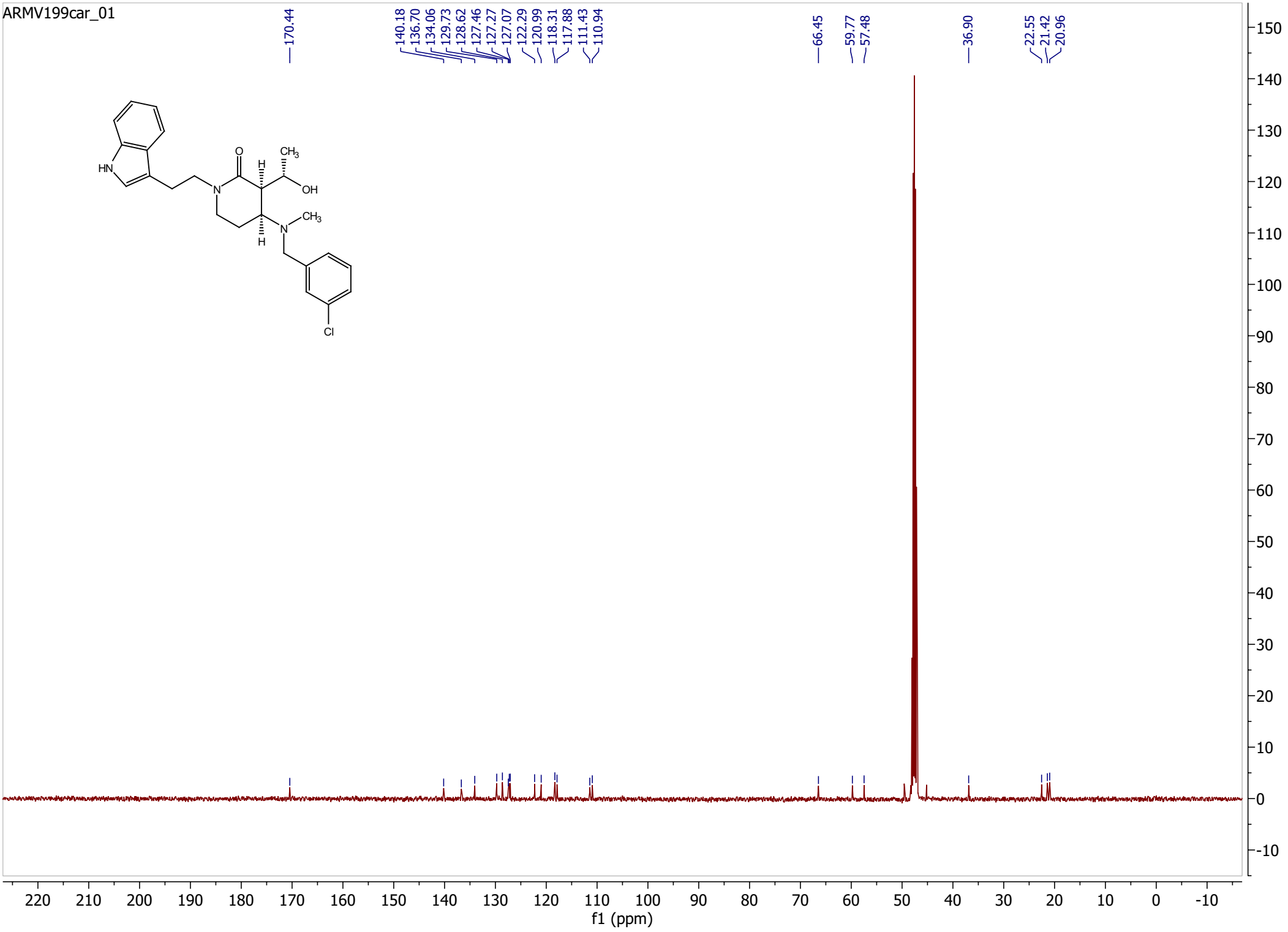
1100
1000
900
800
700
600
500
400
300
200
100
0
-100

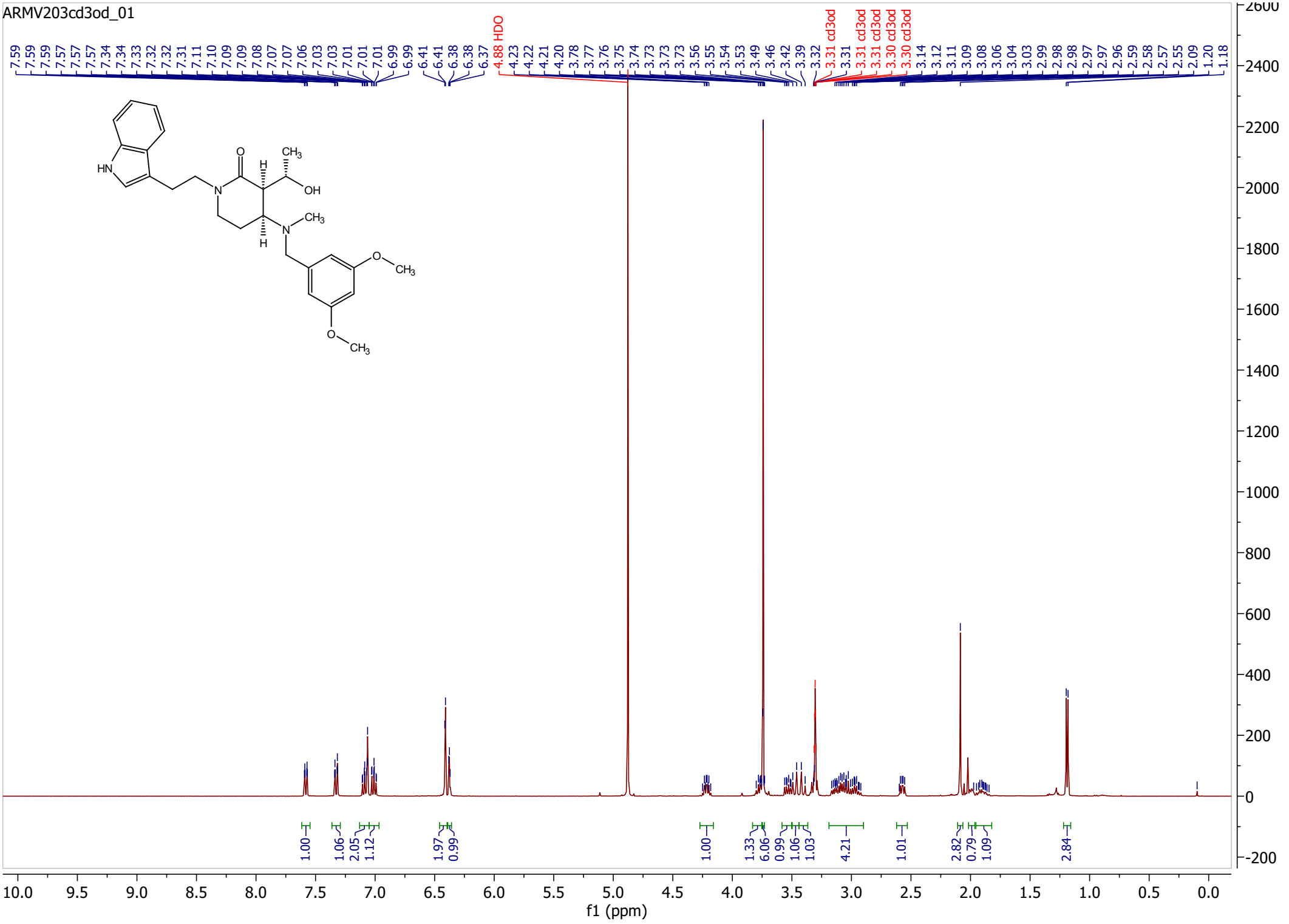
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

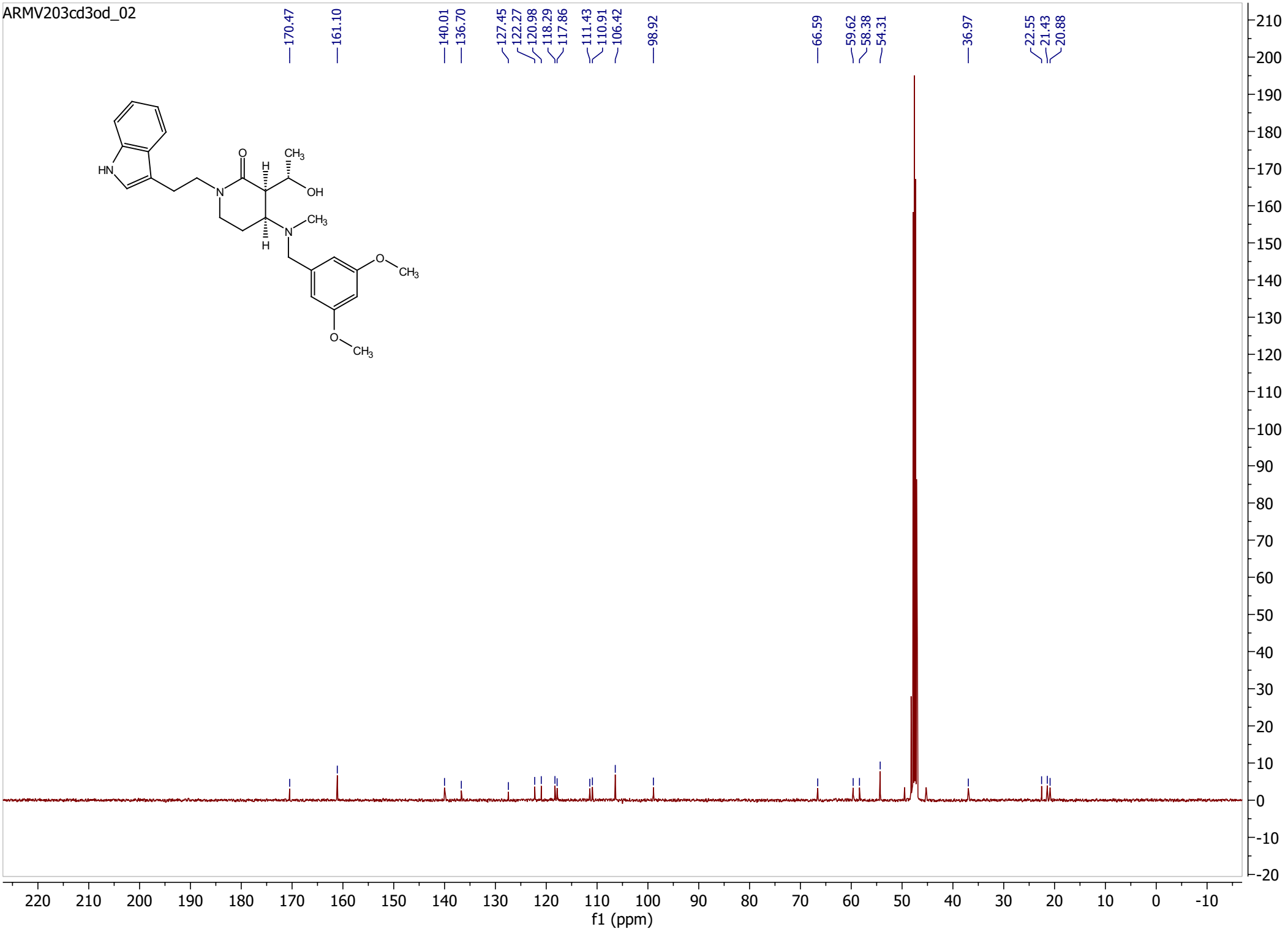

ARMV175D_01
HN
O
H
CH3
OH
N
CH3
N
H
O
CH3
Cl
f1 (ppm)


ARMV175D_01 1
170.97
160.48
139.65
136.24
135.04
127.31
122.30
122.07
121.40
119.36
118.43
113.65
113.44
112.38
111.45
66.31
59.05
57.97
55.56
48.46
47.43
45.04
37.54
23.13
22.08
20.48
HN
O
H
CH3
OH
N
CH3
N
H
O
CH3
Cl
f1 (ppm)

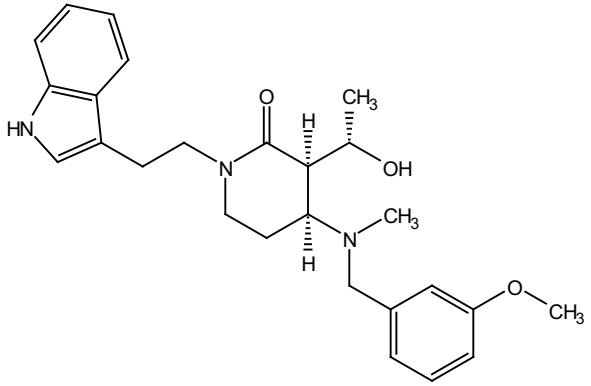

ABMV199cdcl3od_01
HN
O
CH3
H
OH
N
CH3
N
H
Cl
0.97
1.83
2.33
0.95
0.82
1.31
1.11
0.95
1.05
2.00
1.04
1.17
2.33
2.06
0.98
2.95
1.32
1.32
2.81
f1 (ppm)


ARMV199car_01
170.44
140.18
136.70
134.06
129.73
128.62
127.46
127.27
127.07
122.29
120.99
118.31
117.88
111.43
110.94
66.45
59.77
57.48
36.90
22.55
21.42
20.96
HN
O
H
CH3
OH
N
CH3
N
H
Cl
f1 (ppm)

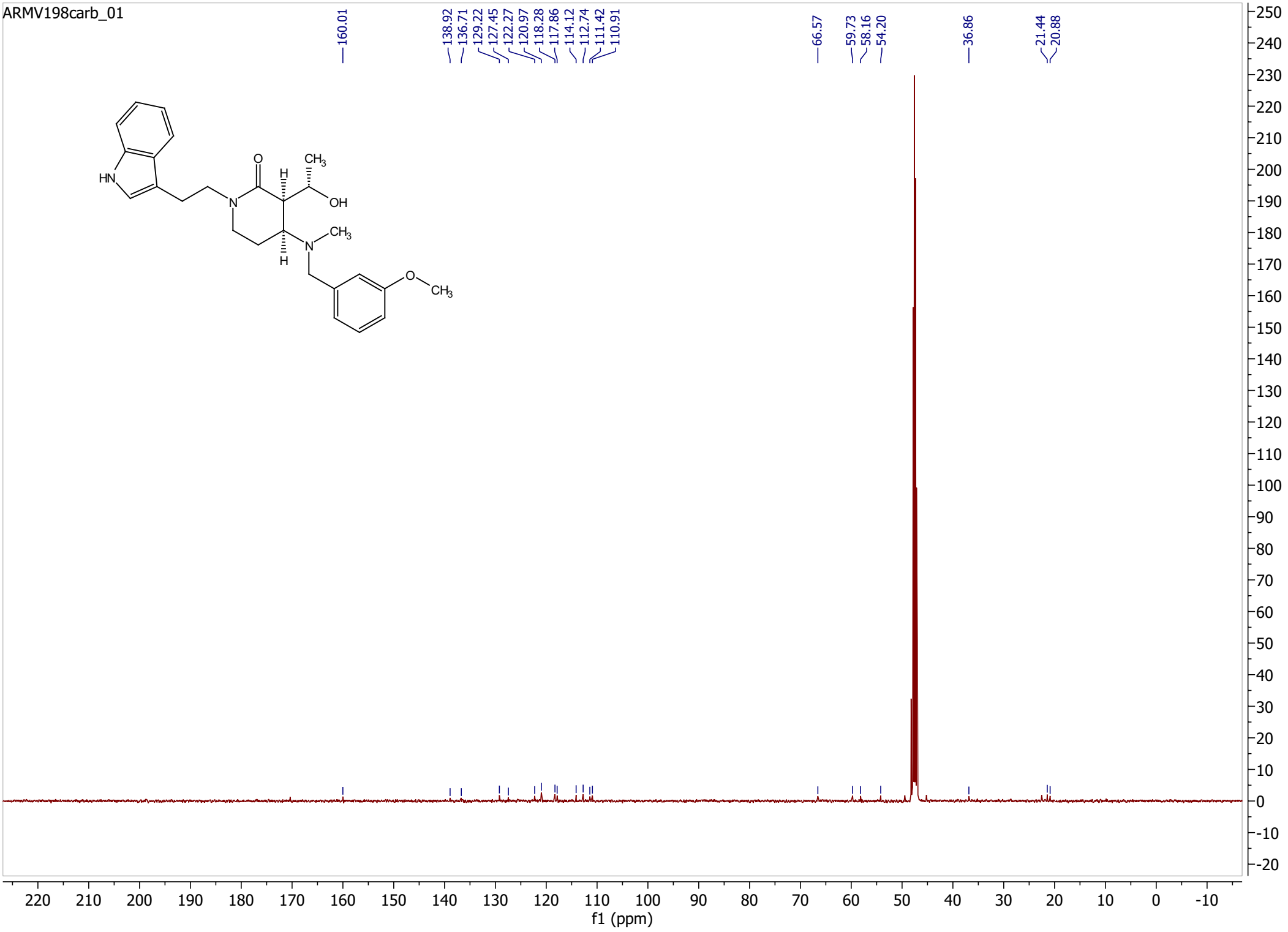

ARMV203cd3od_01
7.59 7.59 7.59 7.57 7.57 7.57 7.34 7.34 7.33 7.32 7.32 7.31 7.11 7.10 7.09 7.09 7.08 7.07 7.07 7.06 7.03 7.03 7.01 7.01 7.01 6.99 6.99 6.41 6.41 6.38 6.38 6.37
4.88 HDO
4.23 4.22 4.21 4.20 3.78 3.77 3.76 3.75 3.74 3.73 3.73 3.73 3.56 3.55 3.54 3.53 3.49 3.46 3.42 3.39 3.32
3.31 cd3od 3.31 3.31 cd3od 3.31 cd3od 3.31 cd3od 3.30 cd3od 3.30 cd3od
3.14 3.12 3.11 3.09 3.08 3.06 3.04 3.03 2.99 2.98 2.98 2.97 2.97 2.96 2.59 2.58 2.57 2.55 2.09 1.20 1.18
HN
O
H
CH3
OH
N
CH3
N
H
O
CH3
O
CH3
1.00 1.06 2.05 1.12 1.97 0.99 1.00 1.33 6.06 0.99 1.06 1.03 4.21 1.01 2.82 0.79 1.09 2.84
2600 2400 2200 2000 1800 1600 1400 1200 1000 800 600 400 200 0 -200
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


ARMV203cd3od_02
170.47
161.10
140.01
136.70
127.45
122.27
120.98
118.29
117.86
111.43
110.91
106.42
98.92
66.59
59.62
58.38
54.31
36.97
22.55
21.43
20.88
HN
O
H
CH3
OH
N
CH3
N
H
O
CH3
O
CH3
f1 (ppm)

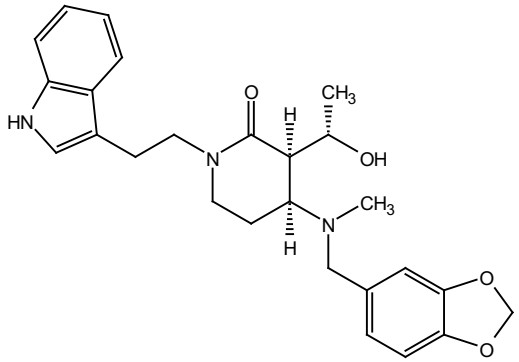
ARMV198
STANDARD 1H OBSERVE



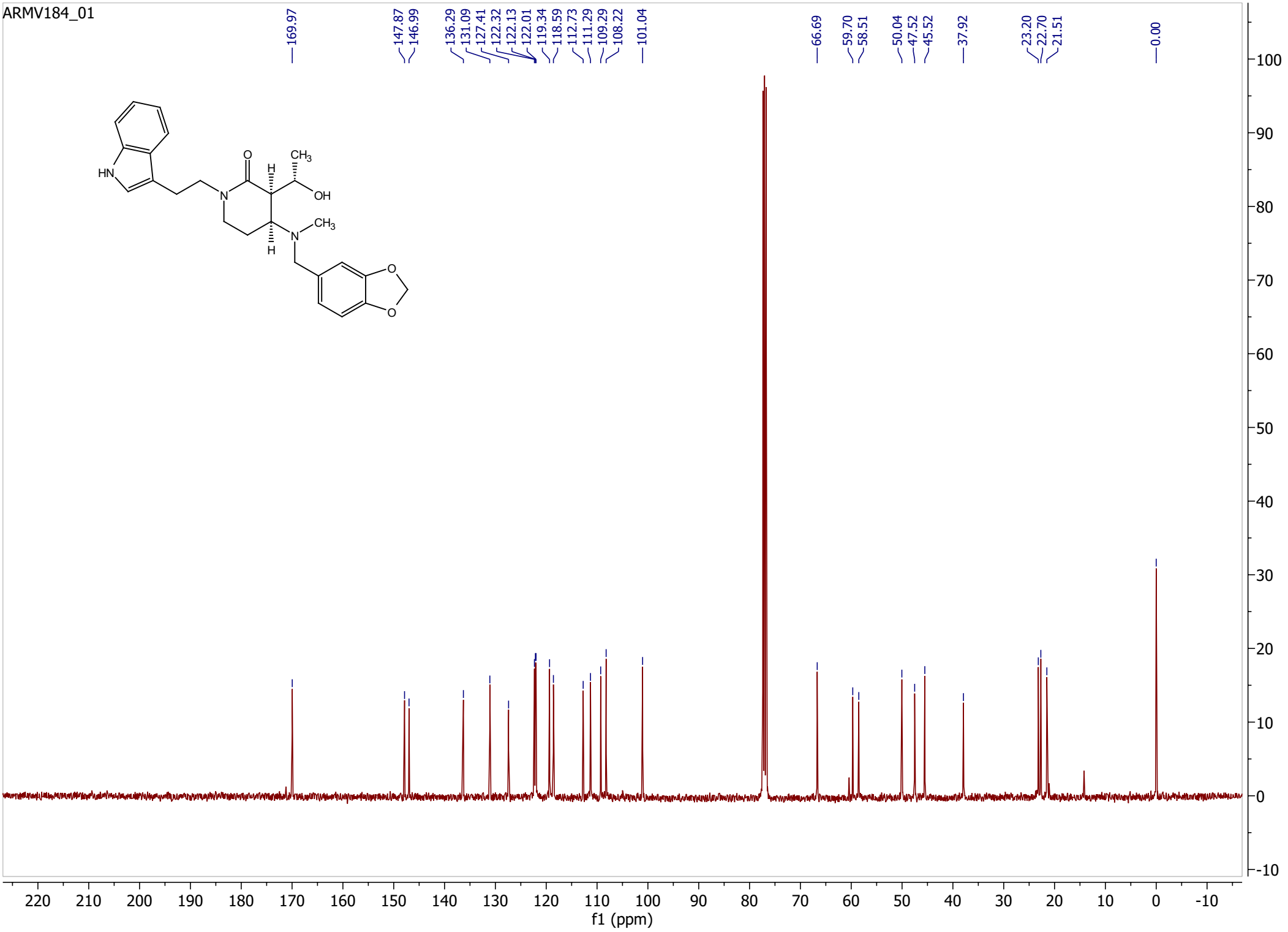
f1 (ppm)

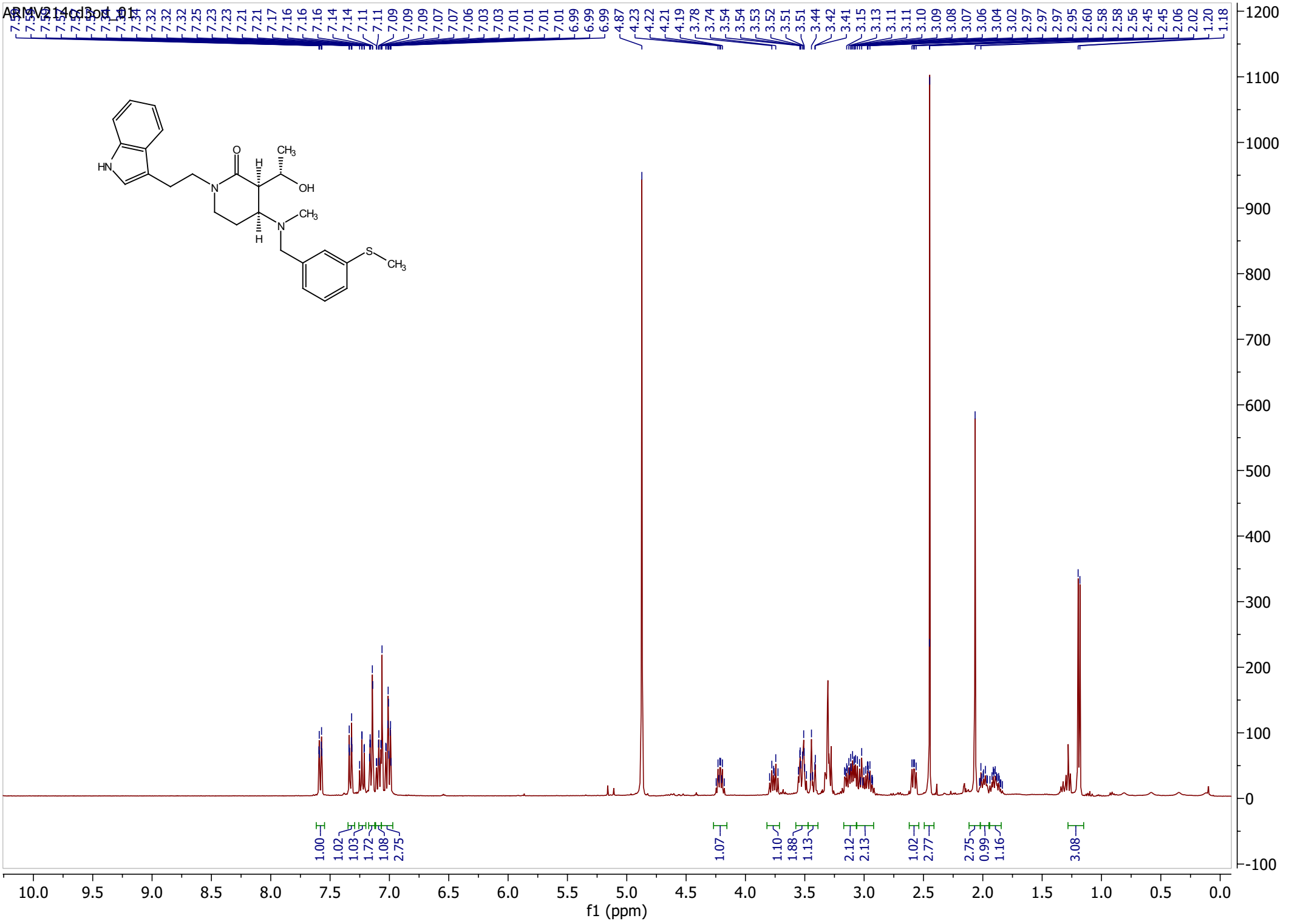

ARMV198carb_01
160.01
138.92
136.71
129.22
127.45
122.27
120.97
118.28
117.86
114.12
112.74
111.42
110.91
66.57
59.73
58.16
54.20
36.86
21.44
20.88
HN
O
H
CH3
OH
N
CH3
N
H
O
CH3
f1 (ppm)

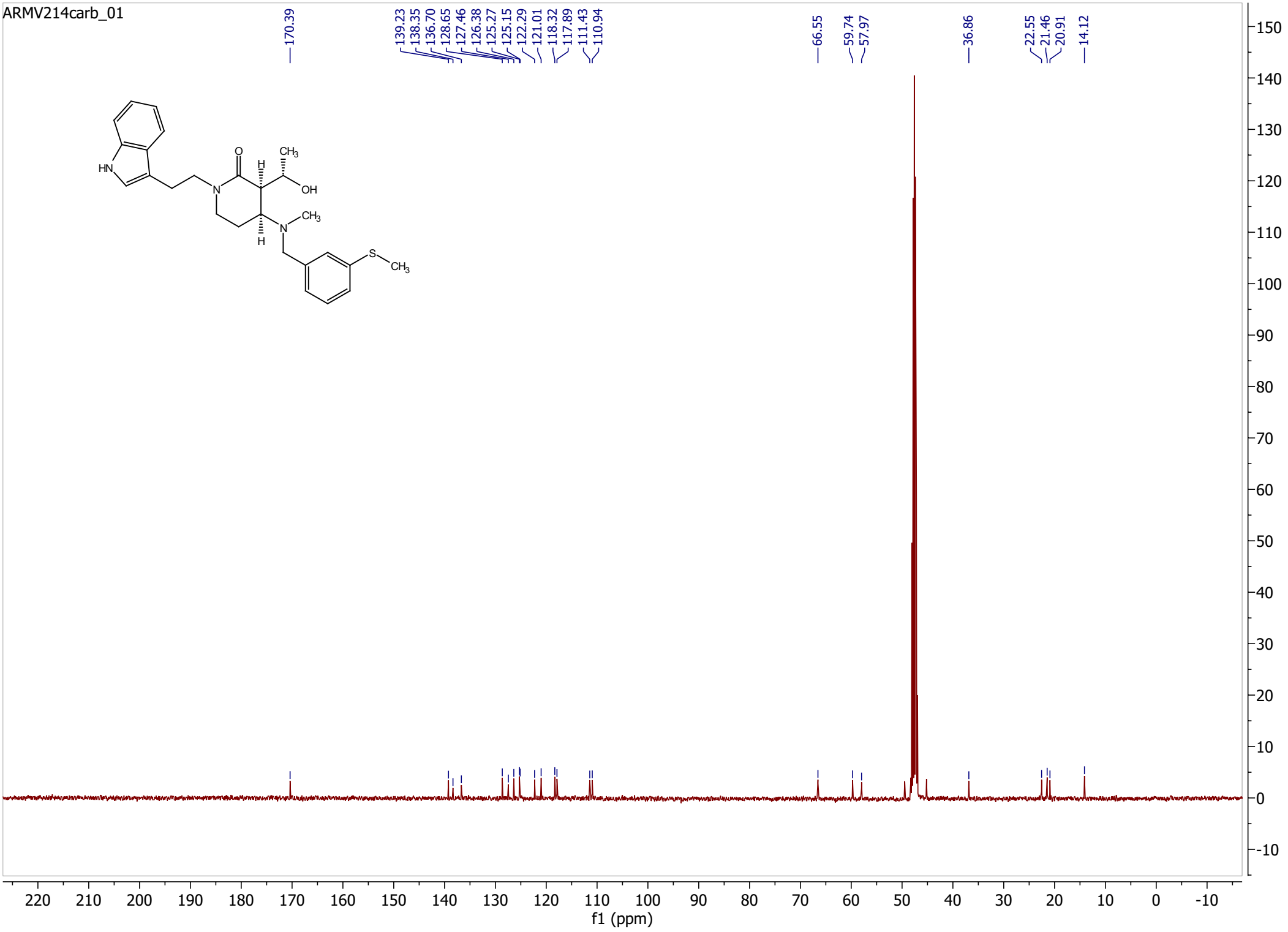
ARMV184
STANDARD 1H OBSERVE

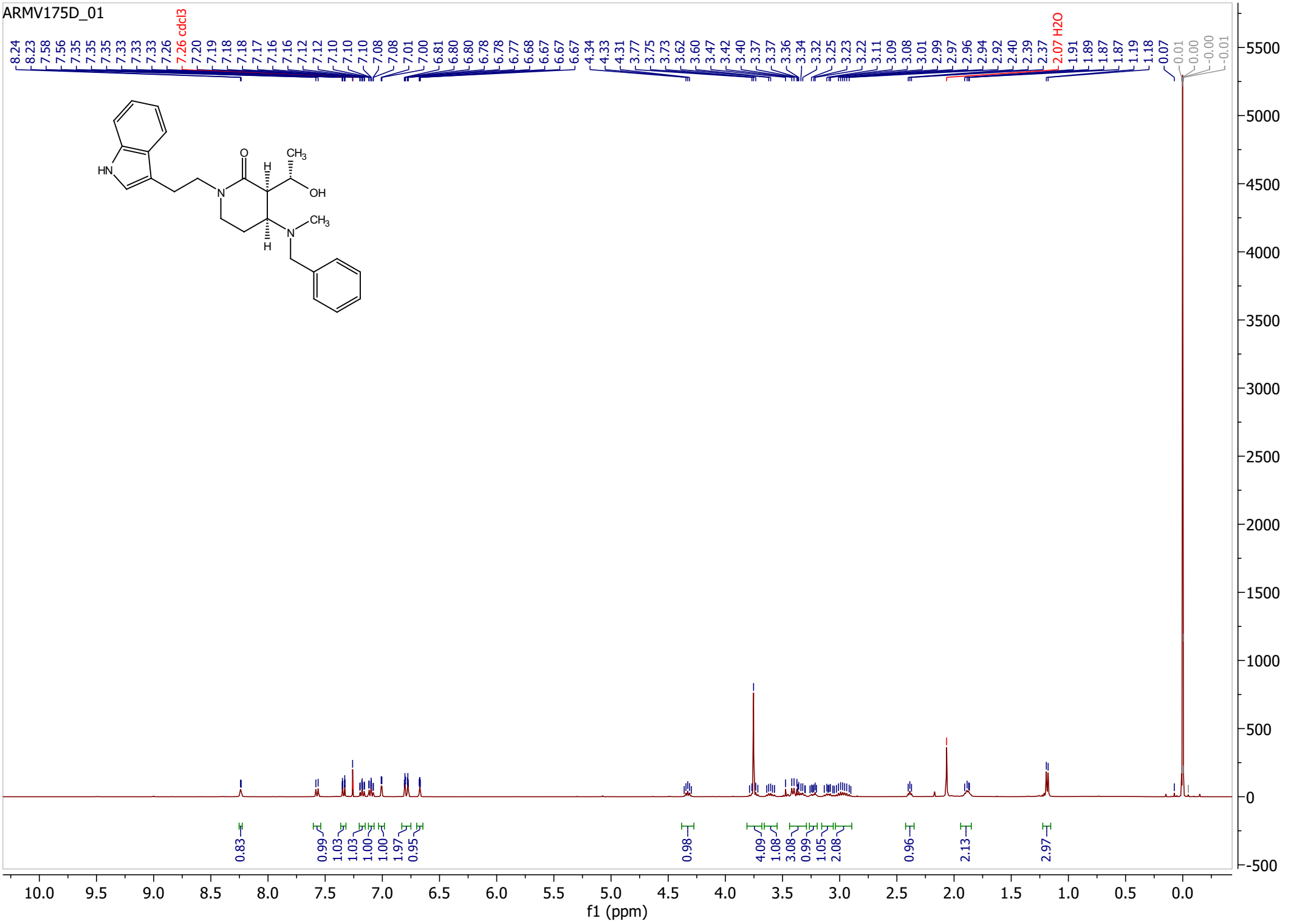


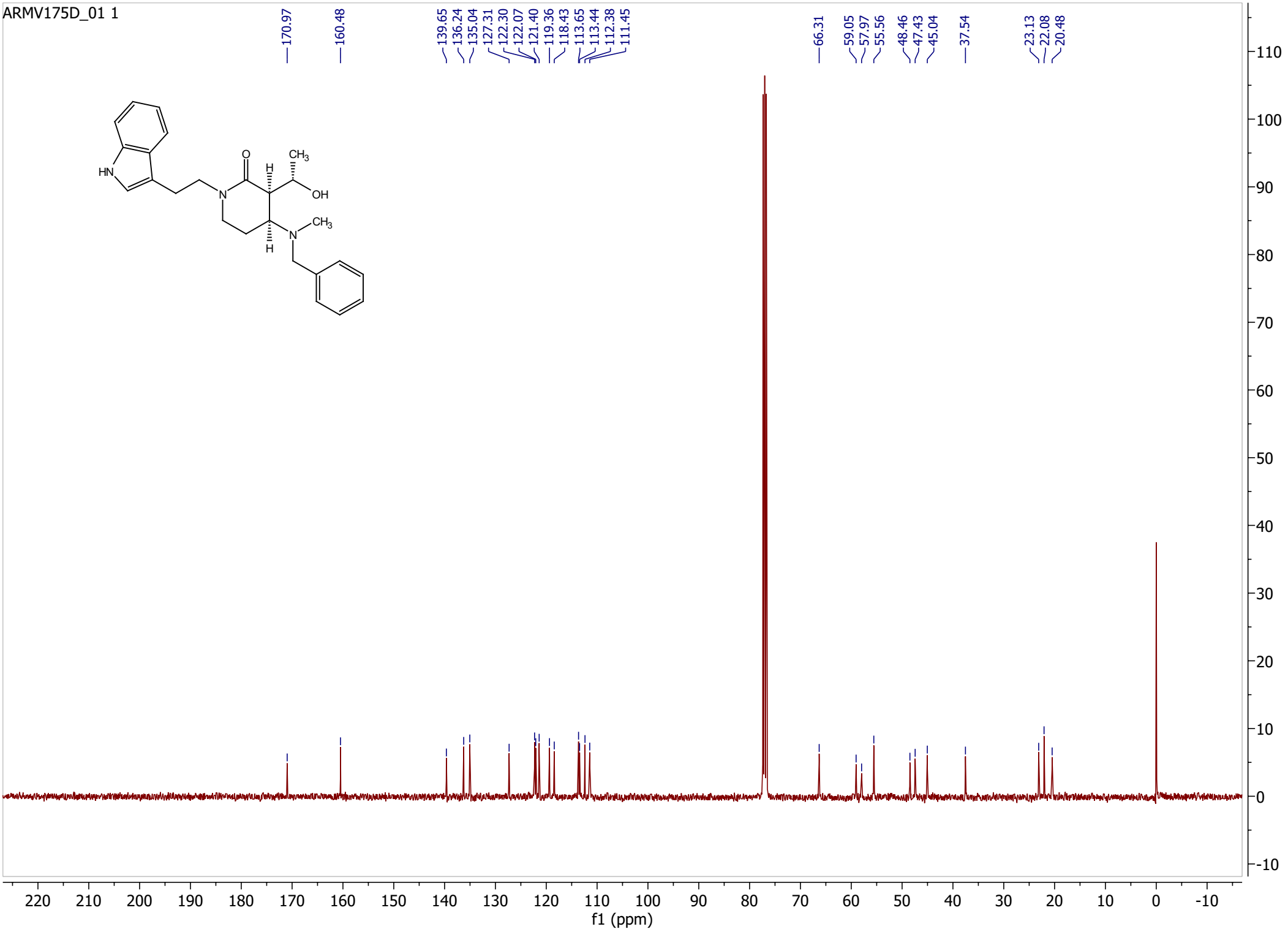
f1 (ppm)

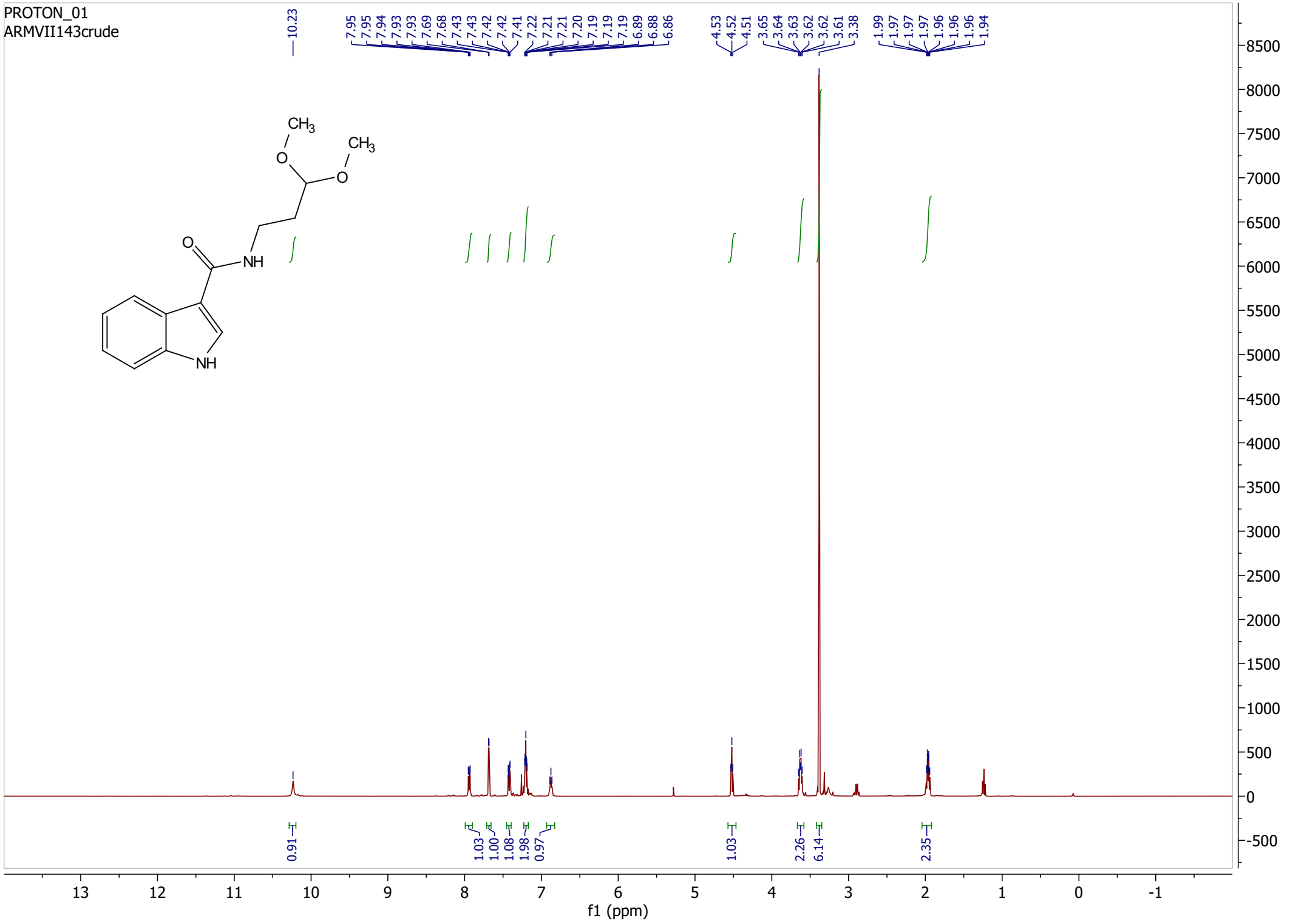

ARMV184_01
169.97
147.87
146.99
136.29
131.09
127.41
122.32
122.13
122.01
119.34
118.59
112.73
111.29
109.29
108.22
101.04
66.69
59.70
58.51
50.04
47.52
45.52
37.92
23.20
22.70
21.51
0.00
HN
O
H
CH3
OH
N
CH3
N
H
O
O
f1 (ppm)

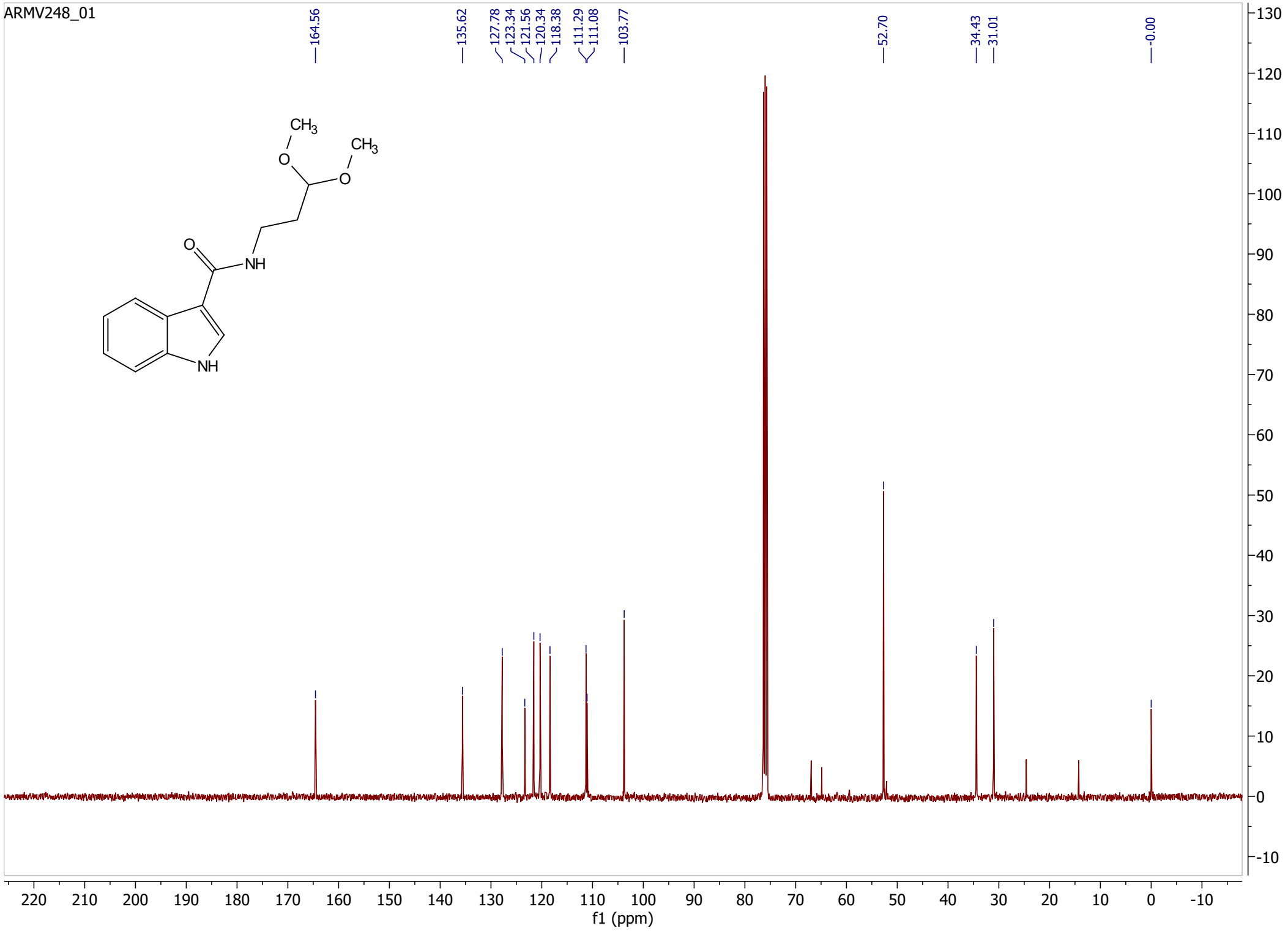

ARMV214cd3od_01
HN
O
CH3
H
OH
N
CH3
N
H
S
CH3
7.54 7.54 7.53 7.53 7.34 7.34 7.32 7.32 7.32 7.25 7.23 7.23 7.21 7.21 7.17 7.16 7.16 7.16 7.14 7.14 7.11 7.11 7.09 7.09 7.09 7.07 7.07 7.06 7.03 7.03 7.01 7.01 7.01 7.01 6.99 6.99 6.99 4.87 4.23 4.22 4.21 4.19 3.78 3.74 3.54 3.54 3.53 3.52 3.51 3.51 3.44 3.42 3.41 3.15 3.13 3.11 3.11 3.10 3.09 3.08 3.07 3.06 3.04 3.02 2.97 2.97 2.97 2.95 2.60 2.58 2.58 2.56 2.45 2.45 2.06 2.02 1.20 1.18
1.00 1.02 1.03 1.72 1.08 2.75 1.07 1.10 1.88 1.13 2.12 2.13 1.02 2.77 2.75 0.99 1.16 3.08
f1 (ppm)

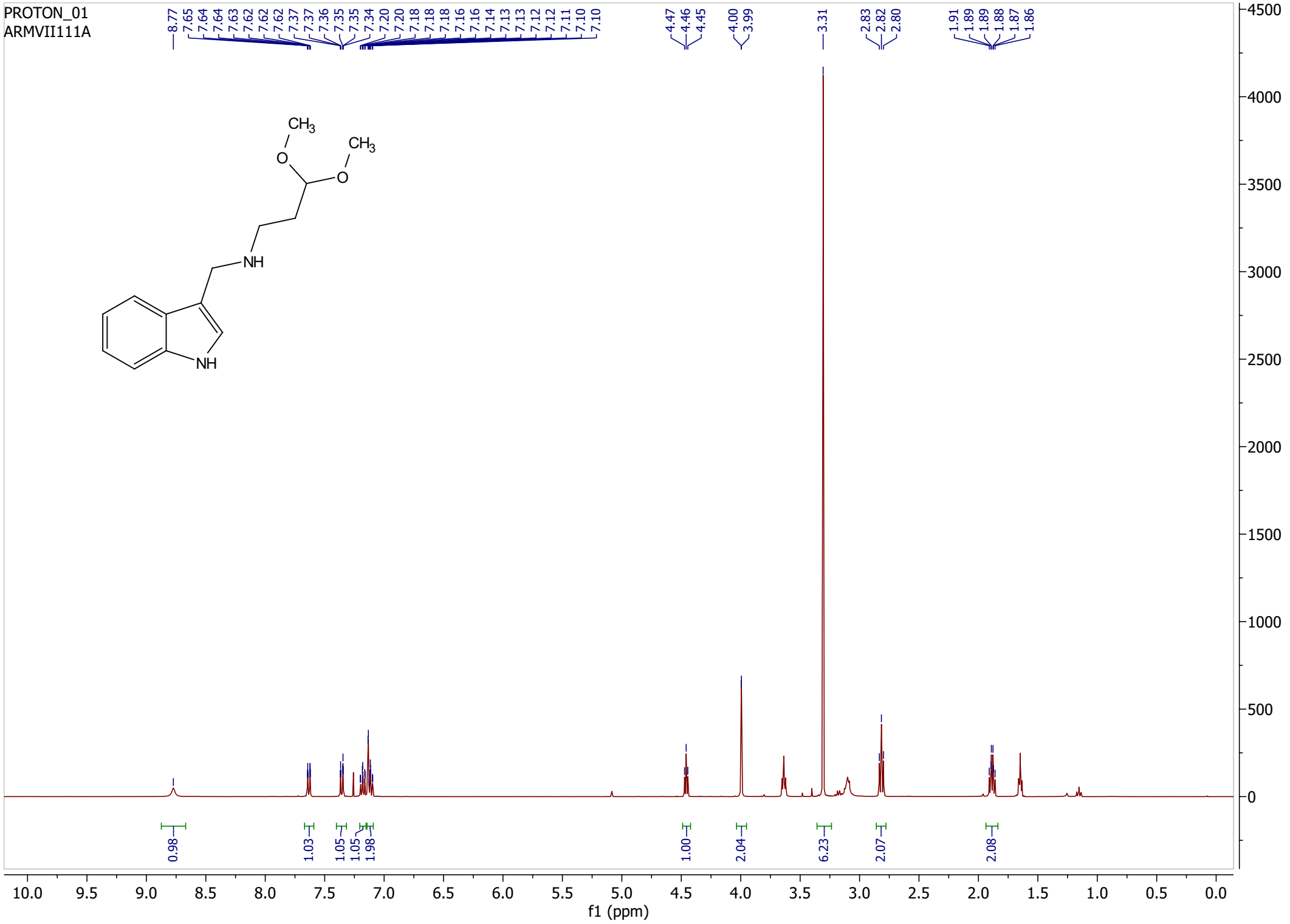

ARMV214carb_01
170.39
139.23
138.35
136.70
128.65
127.46
126.38
125.27
125.15
122.29
121.01
118.32
117.89
111.43
110.94
66.55
59.74
57.97
36.86
22.55
21.46
20.91
14.12
HN
O
H
CH3
OH
N
CH3
N
H
S
CH3
f1 (ppm)

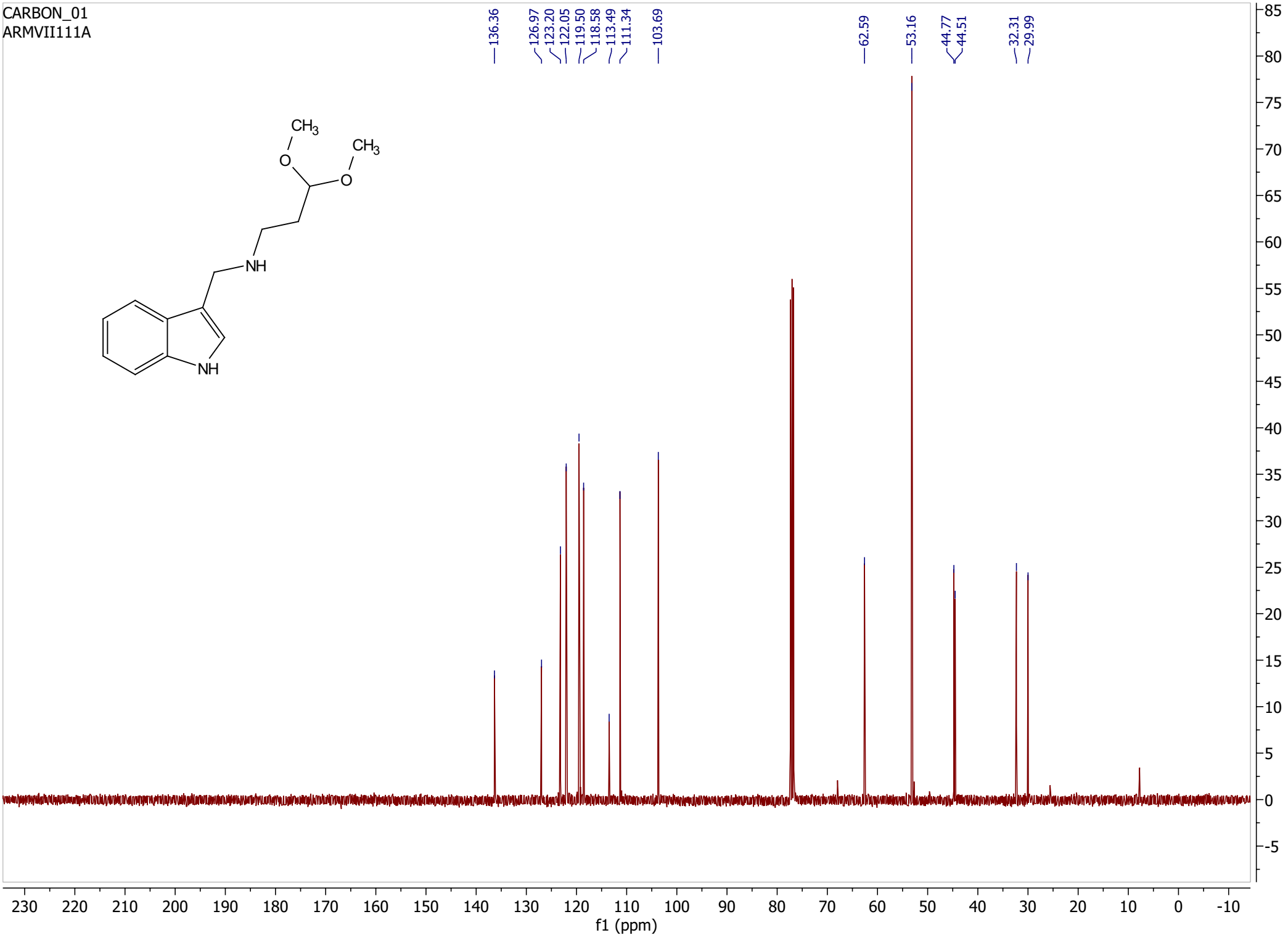

ARMV175D_01
8.24 8.23 7.58 7.56 7.35 7.35 7.35 7.33 7.33 7.33 7.26 7.26 cdcl3 7.20 7.19 7.18 7.18 7.17 7.16 7.16 7.12 7.12 7.10 7.10 7.10 7.08 7.08 7.01 7.00 6.81 6.80 6.80 6.78 6.78 6.77 6.68 6.67 6.67 6.67 4.34 4.33 4.31 3.77 3.75 3.73 3.62 3.60 3.47 3.42 3.40 3.37 3.37 3.36 3.34 3.32 3.25 3.23 3.22 3.11 3.09 3.08 3.01 2.99 2.97 2.96 2.94 2.92 2.40 2.39 2.37 2.07 H2O 1.91 1.89 1.87 1.87 1.19 1.18 0.07 0.01 0.00 -0.00 -0.01
HN
O
H
CH3
OH
N
CH3
N
H
0.83 0.99 1.03 1.03 1.00 1.00 1.97 0.95 0.98 4.09 1.08 3.08 0.99 1.05 2.08 0.96 2.13 2.97
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
5500 5000 4500 4000 3500 3000 2500 2000 1500 1000 500 0 -500

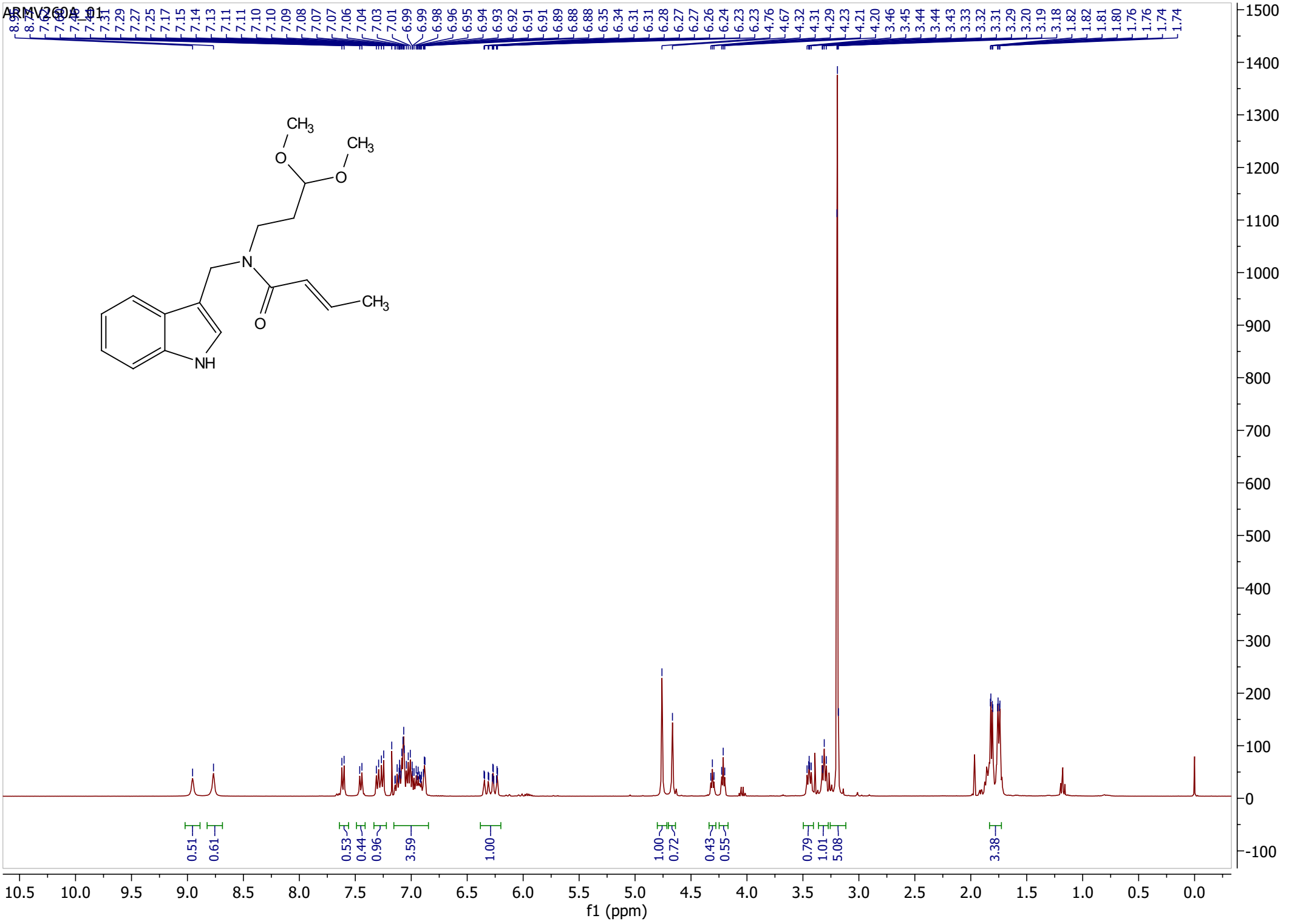

ARMV175D_01 1
170.97
160.48
139.65
136.24
135.04
127.31
122.30
122.07
121.40
119.36
118.43
113.65
113.44
112.38
111.45
66.31
59.05
57.97
55.56
48.46
47.43
45.04
37.54
23.13
22.08
20.48
HN
O
H
CH3
OH
N
CH3
N
H
f1 (ppm)

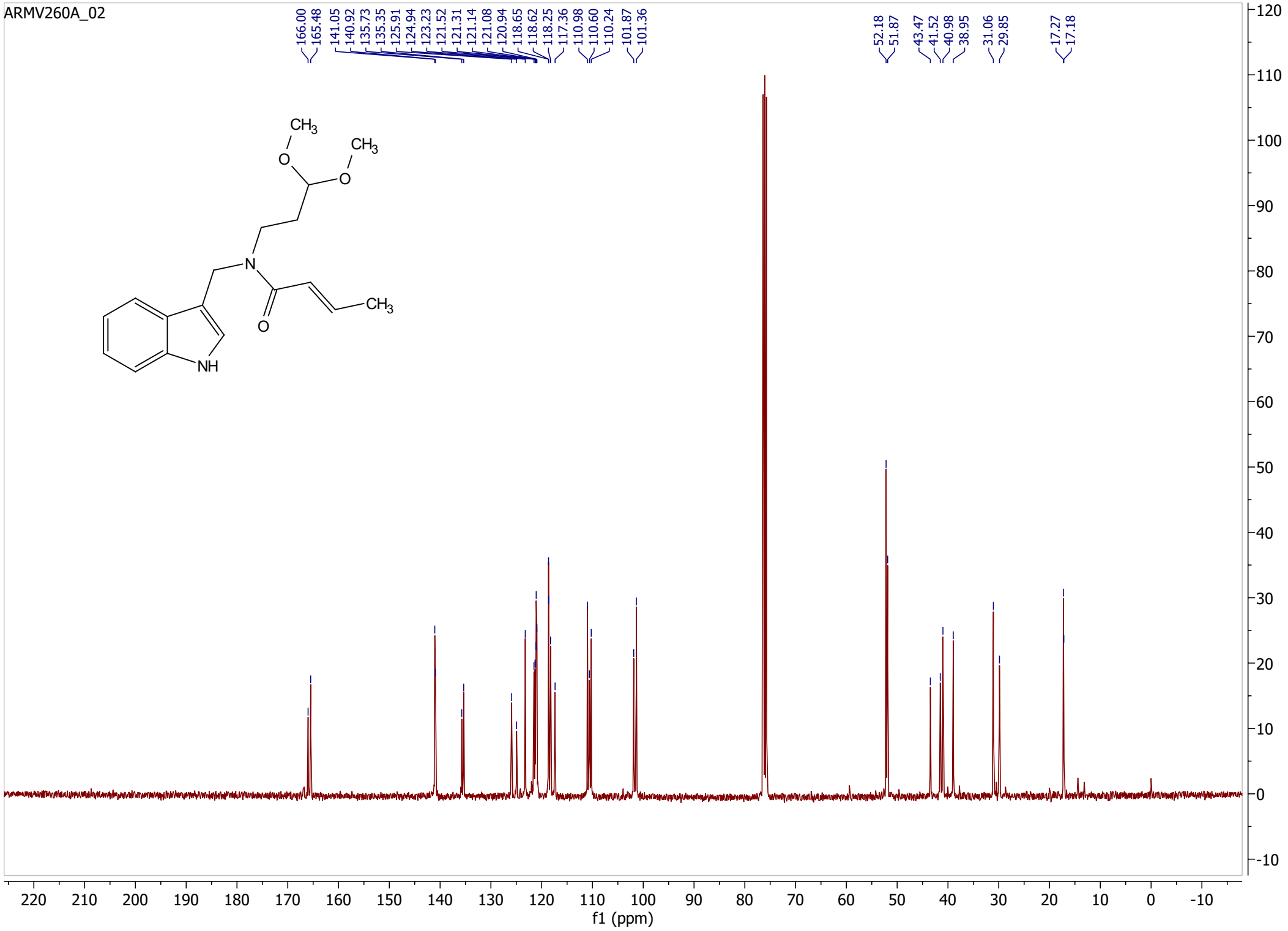

PROTON_01
ARMVII143crude
10.23
7.95 7.95 7.94 7.93 7.93 7.69 7.68 7.43 7.43 7.42 7.42 7.41 7.22 7.21 7.21 7.20 7.19 7.19 7.19 6.89 6.88 6.86
4.53 4.52 4.51
3.65 3.64 3.63 3.62 3.62 3.61 3.38
1.99 1.97 1.97 1.97 1.96 1.96 1.96 1.94
CH3
CH3
O
O
O
NH
NH
0.91
1.03
1.00
1.08
1.98
0.97
1.03
2.26
6.14
2.35
f1 (ppm)

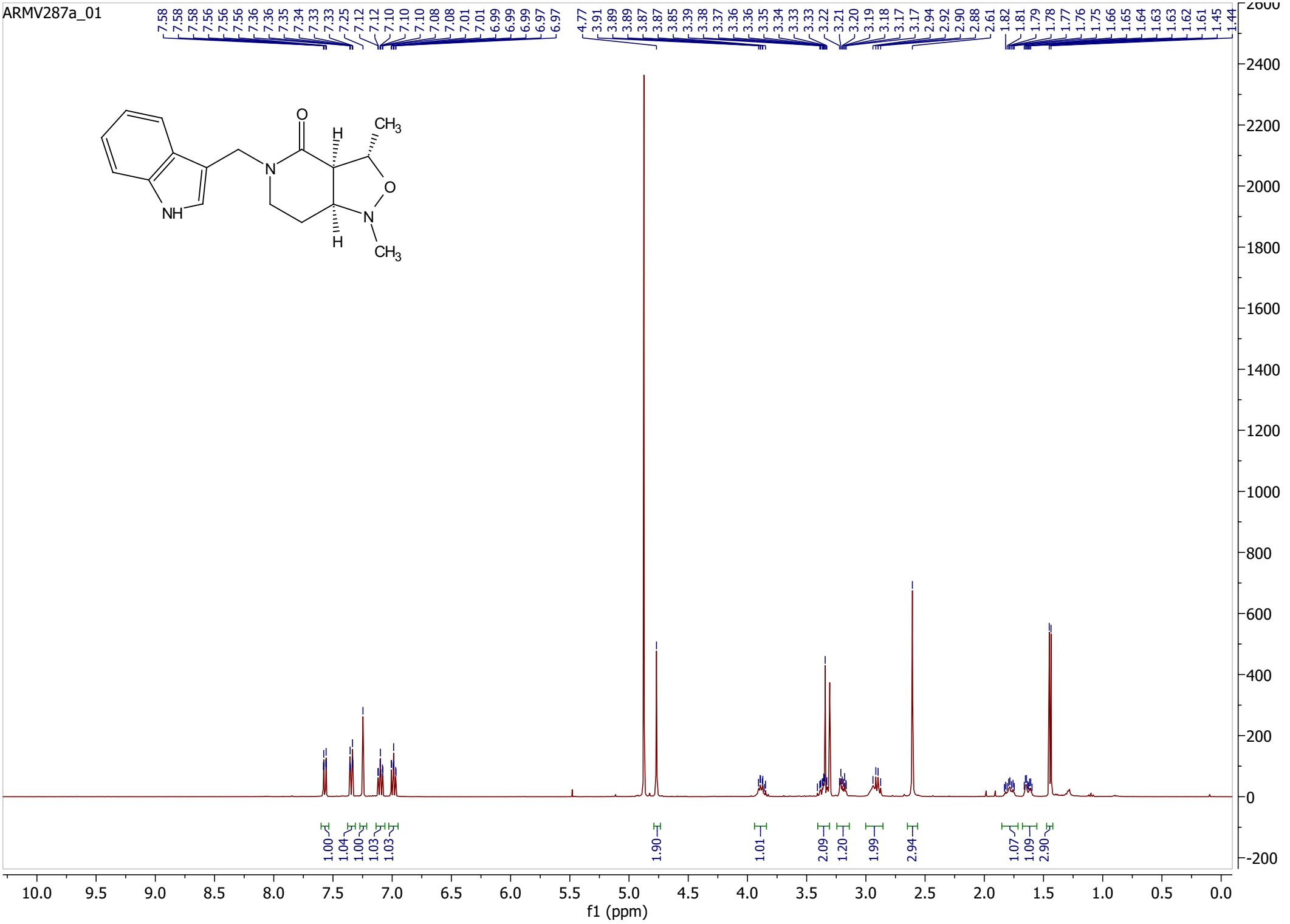

ARMV248_01
164.56
135.62
127.78
123.34
121.56
120.34
118.38
111.29
111.08
103.77
52.70
34.43
31.01
-0.00
CH3
CH3
O
O
O
NH
NH
f1 (ppm)


PROTON_01
ARMVII111A
8.77
7.65
7.64
7.64
7.63
7.62
7.62
7.62
7.37
7.37
7.36
7.35
7.35
7.34
7.20
7.20
7.18
7.18
7.16
7.16
7.14
7.13
7.13
7.12
7.12
7.11
7.10
7.10
4.47
4.46
4.45
4.00
3.99
3.31
2.83
2.82
2.80
1.91
1.89
1.89
1.88
1.87
1.86
CH3
CH3
O
O
NH
NH
0.98
1.03
1.05
1.05
1.98
1.00
2.04
6.23
2.07
2.08
4500
4000
3500
3000
2500
2000
1500
1000
500
0
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

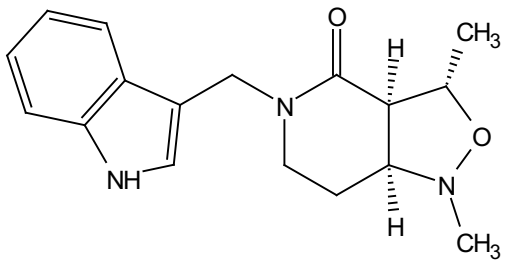

CARBON_01
ARMVII111A
136.36
126.97
123.20
122.05
119.50
118.58
113.49
111.34
103.69
62.59
53.16
44.77
44.51
32.31
29.99
CH3
CH3
O
O
NH
NH
f1 (ppm)


ARMV2604_01
CH3
CH3
O
O
N
O
CH3
NH
f1 (ppm)


ARMV260A_02
166.00
165.48
141.05
140.92
135.73
135.35
125.91
124.94
123.23
121.52
121.31
121.14
121.08
120.94
118.65
118.62
118.25
117.36
110.98
110.60
110.24
101.87
101.36
52.18
51.87
43.47
41.52
40.98
38.95
31.06
29.85
17.27
17.18
CH3
CH3
O
O
N
O
CH3
NH
f1 (ppm)


ARMV287a_01
7.58 7.58 7.58 7.56 7.56 7.56 7.36 7.36 7.35 7.34 7.33 7.33 7.25 7.12 7.10 7.10 7.10 7.08 7.08 7.01 7.01 6.99 6.99 6.97 6.97
4.77 3.91 3.89 3.89 3.87 3.87 3.85 3.39 3.38 3.37 3.36 3.36 3.35 3.34 3.33 3.33 3.22 3.21 3.20 3.19 3.18 3.17 3.17 2.94 2.92 2.90 2.88 2.61 1.82 1.81 1.79 1.78 1.77 1.76 1.75 1.66 1.65 1.64 1.63 1.63 1.62 1.61 1.45 1.44
O
H
CH3
N
O
NH
N
H
CH3
1.00 1.04 1.00 1.03 1.03 1.90 1.01 2.09 1.20 1.99 2.94 1.07 1.09 2.90
2600 2400 2200 2000 1800 1600 1400 1200 1000 800 600 400 200 0 -200
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

ARMV287a_02

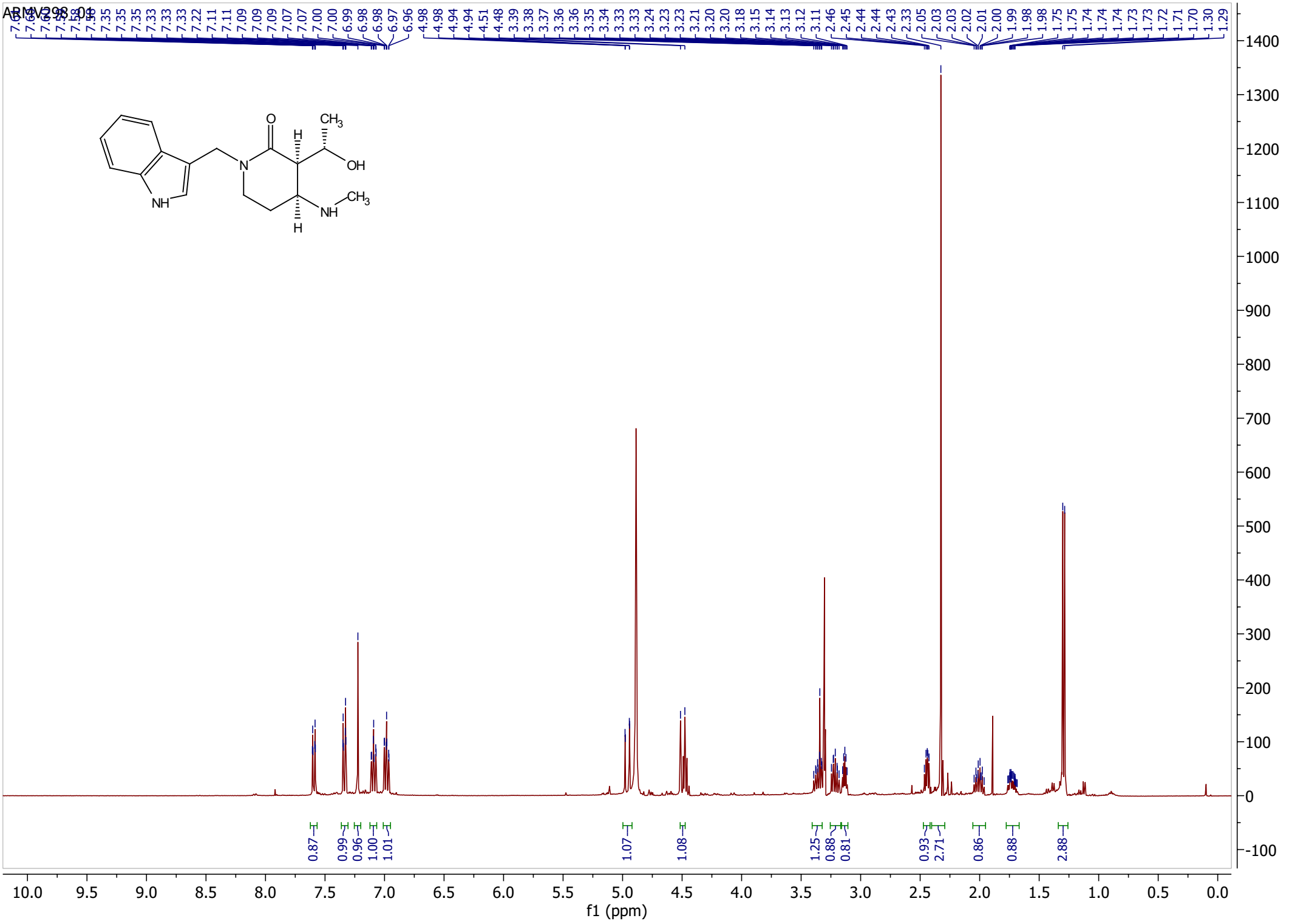


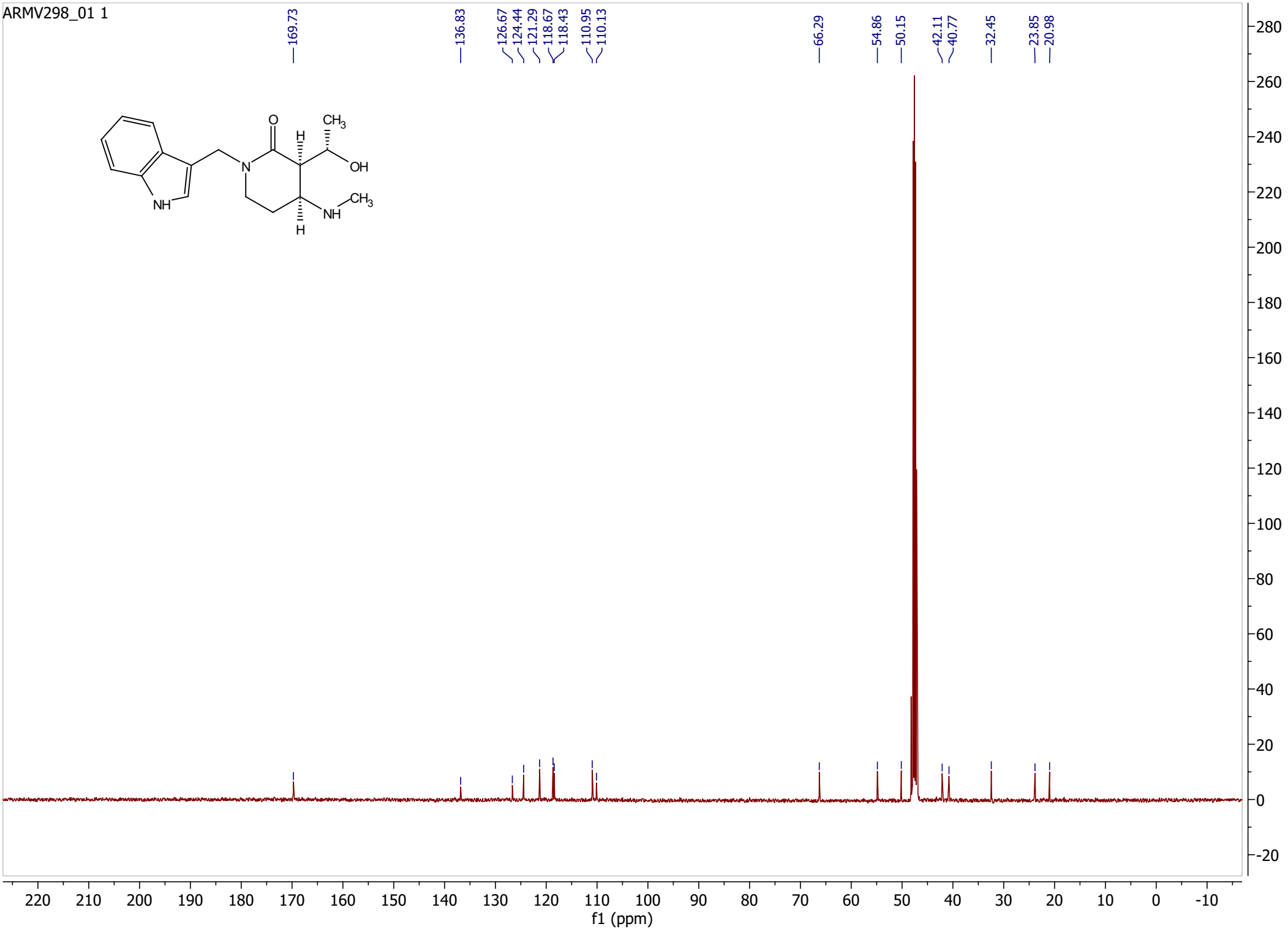
169.26
136.94
126.52
124.52
121.38
118.72
118.44
111.01
109.80
77.36
66.19
54.91
41.39
41.12
24.10
18.09

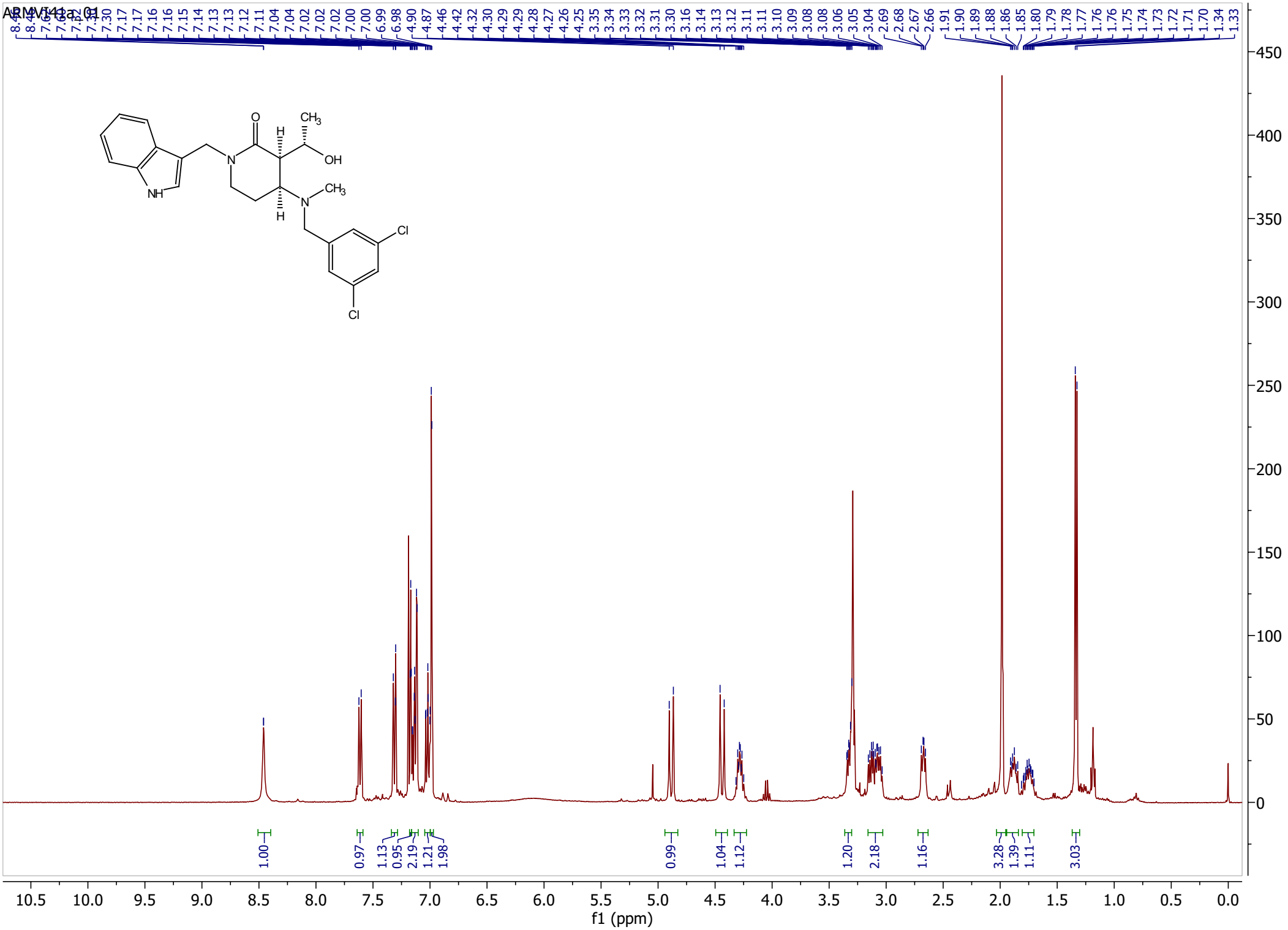
250
200
150
100
50
0

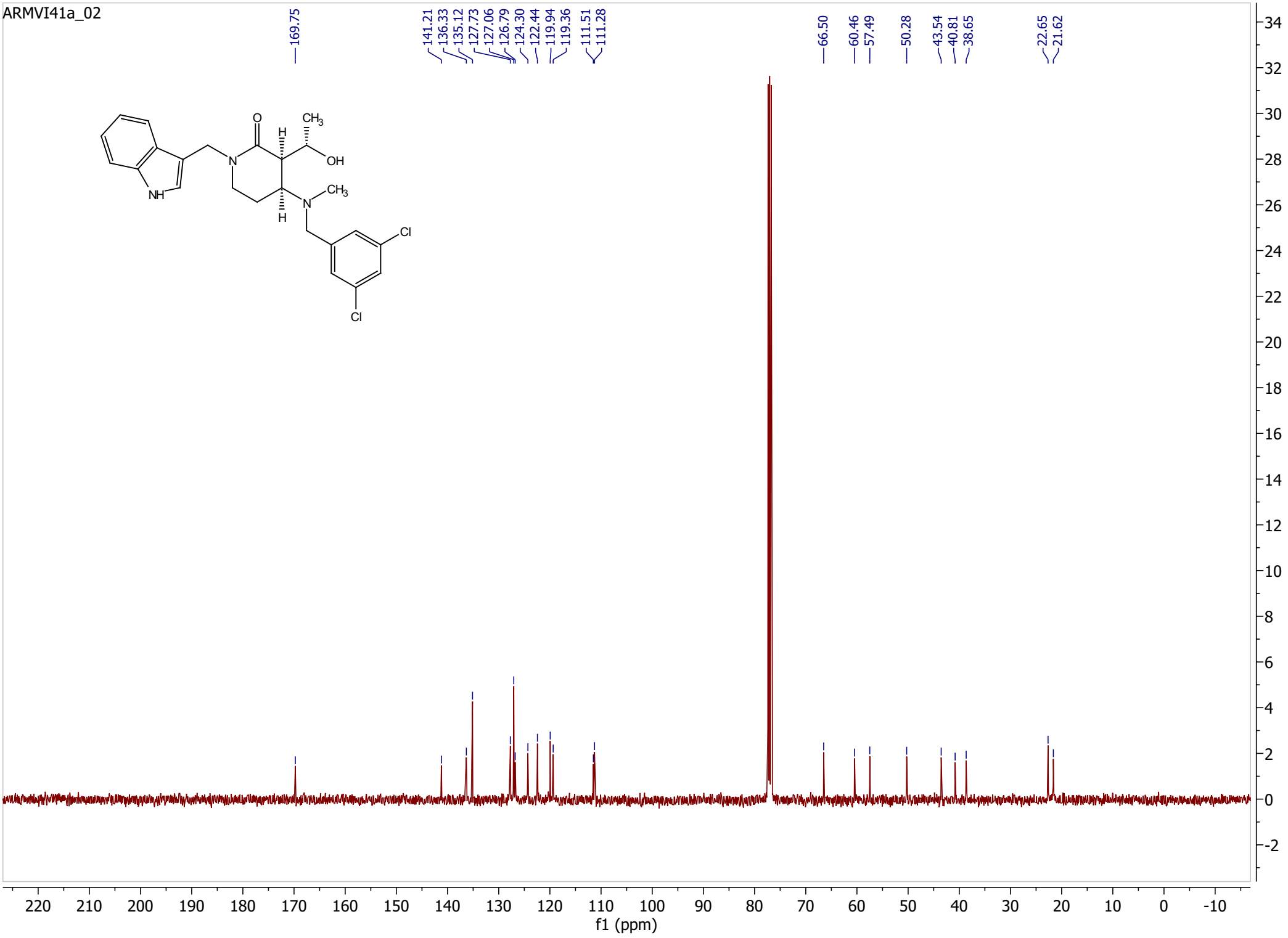
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

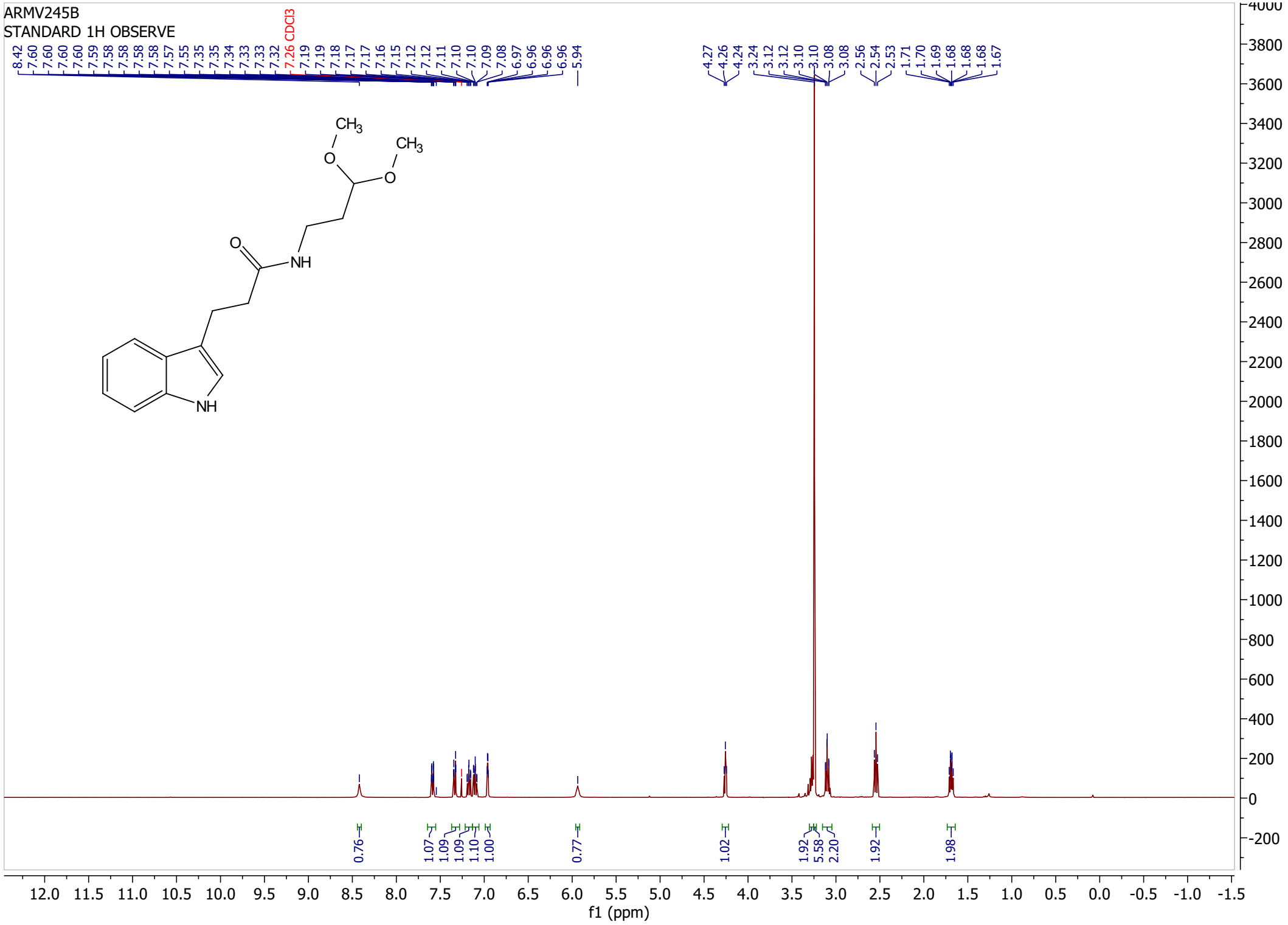
f1 (ppm)

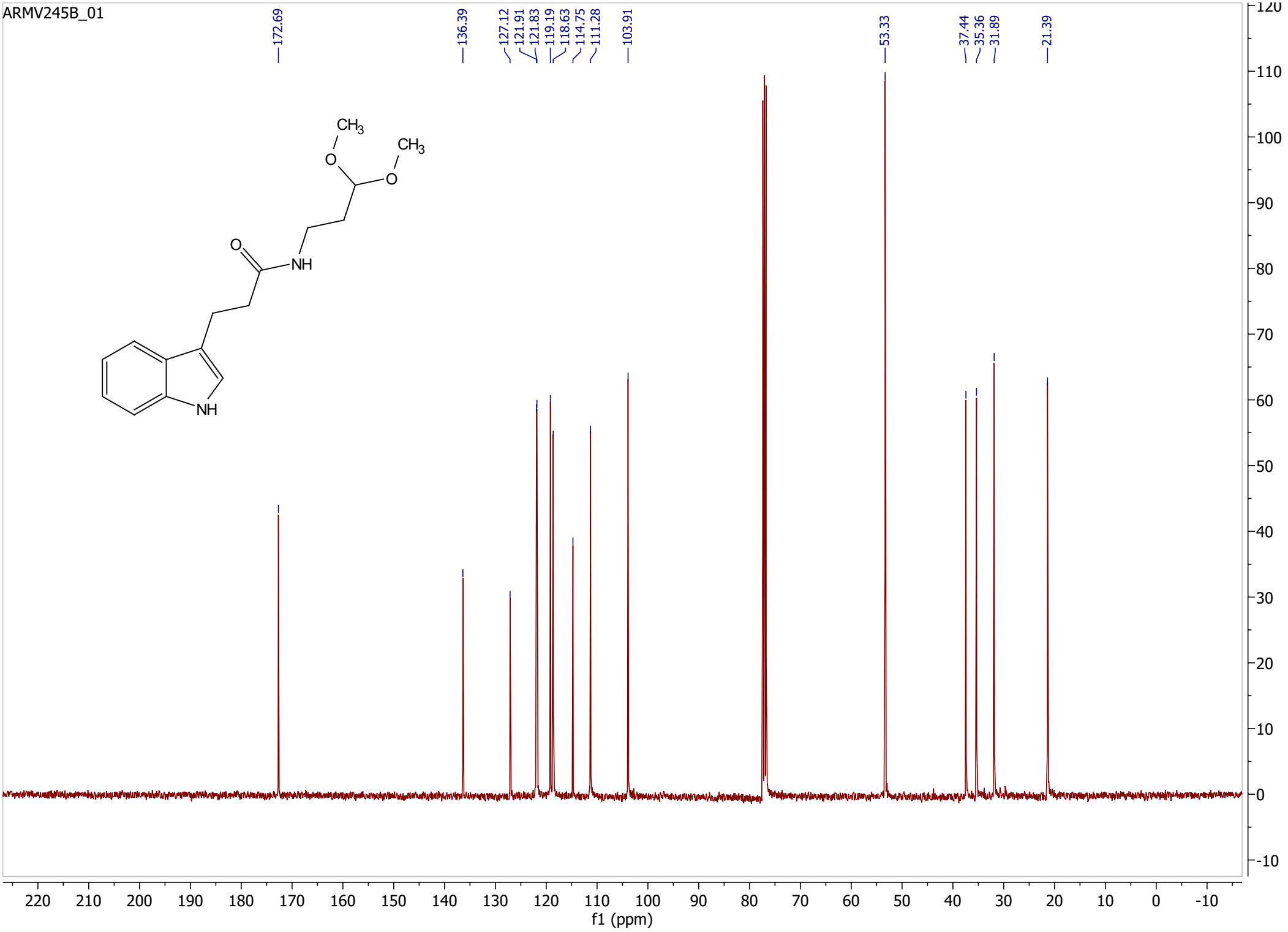

ABMV398-01
O
H
CH3
OH
N
NH
CH3
NH
H
0.87
0.99
0.96
1.00
1.01
1.07
1.08
1.25
0.88
0.81
0.93
2.71
0.86
0.88
2.88
f1 (ppm)

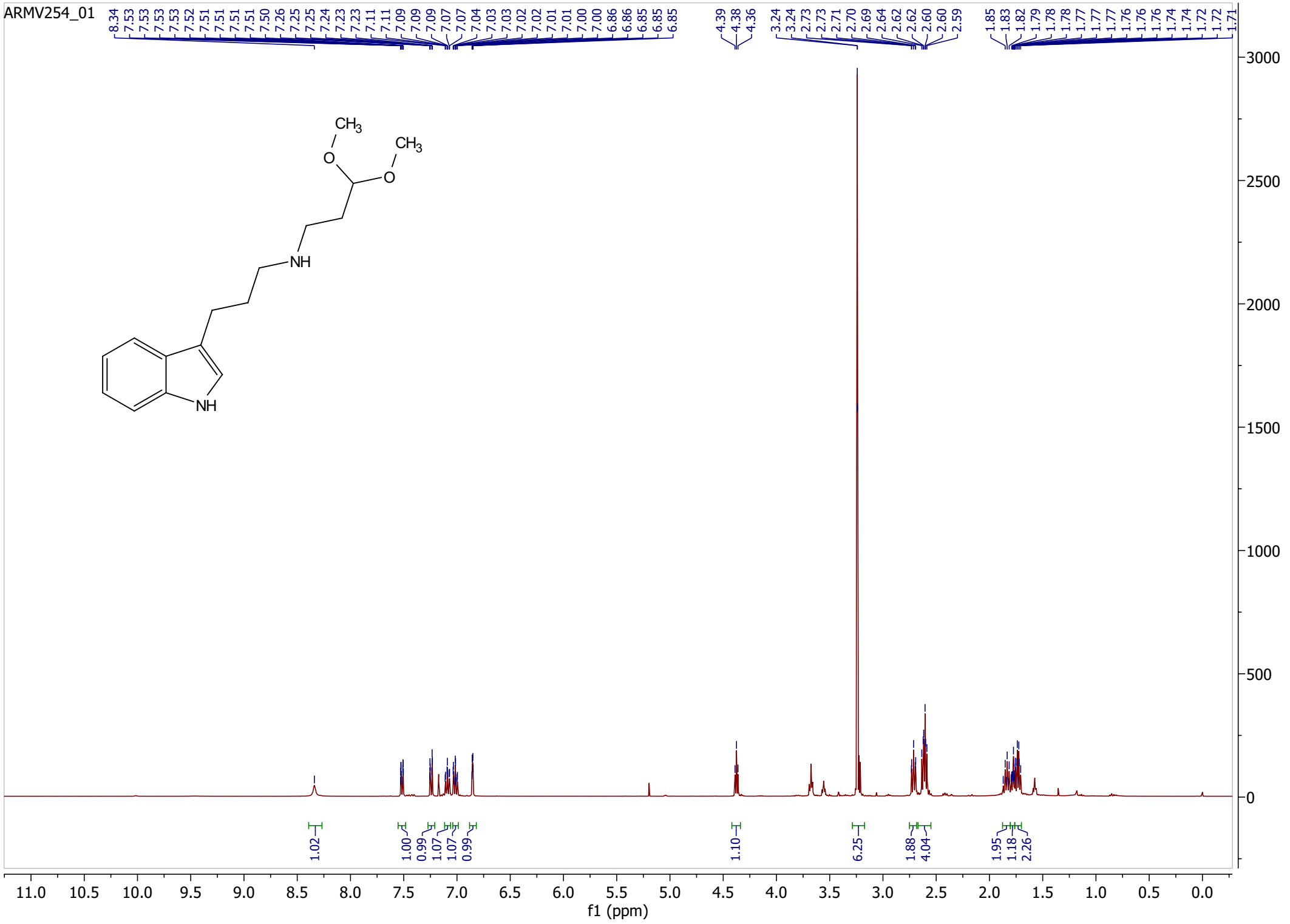

ARMV298_01 1
169.73
136.83
126.67
124.44
121.29
118.67
118.43
110.95
110.13
66.29
54.86
50.15
42.11
40.77
32.45
23.85
20.98
O
H
CH3
OH
N
NH
CH3
NH
H
f1 (ppm)

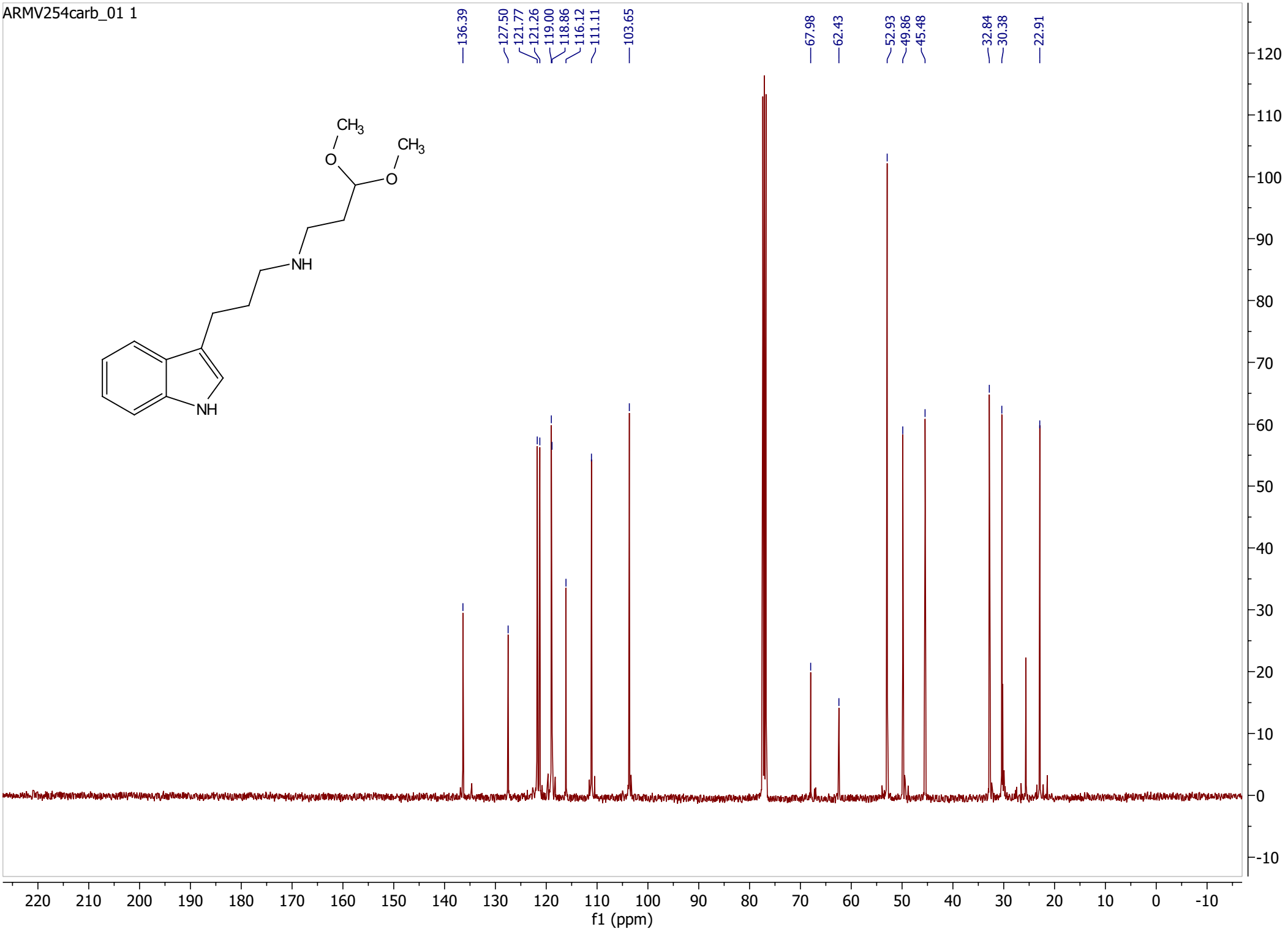

ARMV143a_01
O
H
CH3
OH
N
NH
CH3
N
H
Cl
Cl
1.00
0.97
1.13
0.95
2.19
1.21
1.98
0.99
1.04
1.12
1.20
2.18
1.16
3.28
1.39
1.11
3.03
f1 (ppm)


ARMVI41a_02
169.75
141.21
136.33
135.12
127.73
127.06
126.79
124.30
122.44
119.94
119.36
111.51
111.28
66.50
60.46
57.49
50.28
43.54
40.81
38.65
22.65
21.62
O
H
CH3
OH
N
NH
CH3
N
H
Cl
Cl
f1 (ppm)

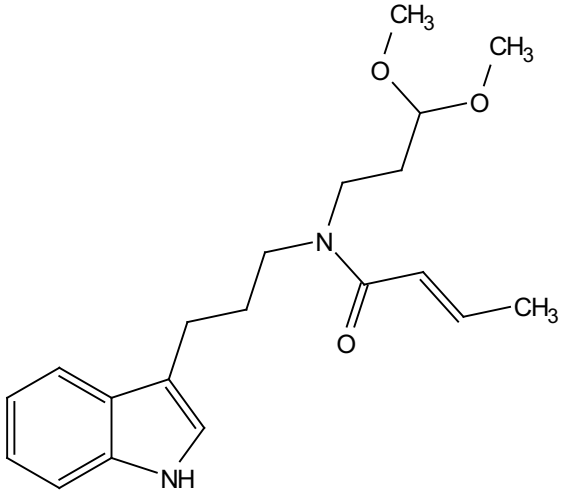

ARMV245B
STANDARD 1H OBSERVE
7.26 CDCl3
CH3
CH3
O
O
O
NH
NH
f1 (ppm)

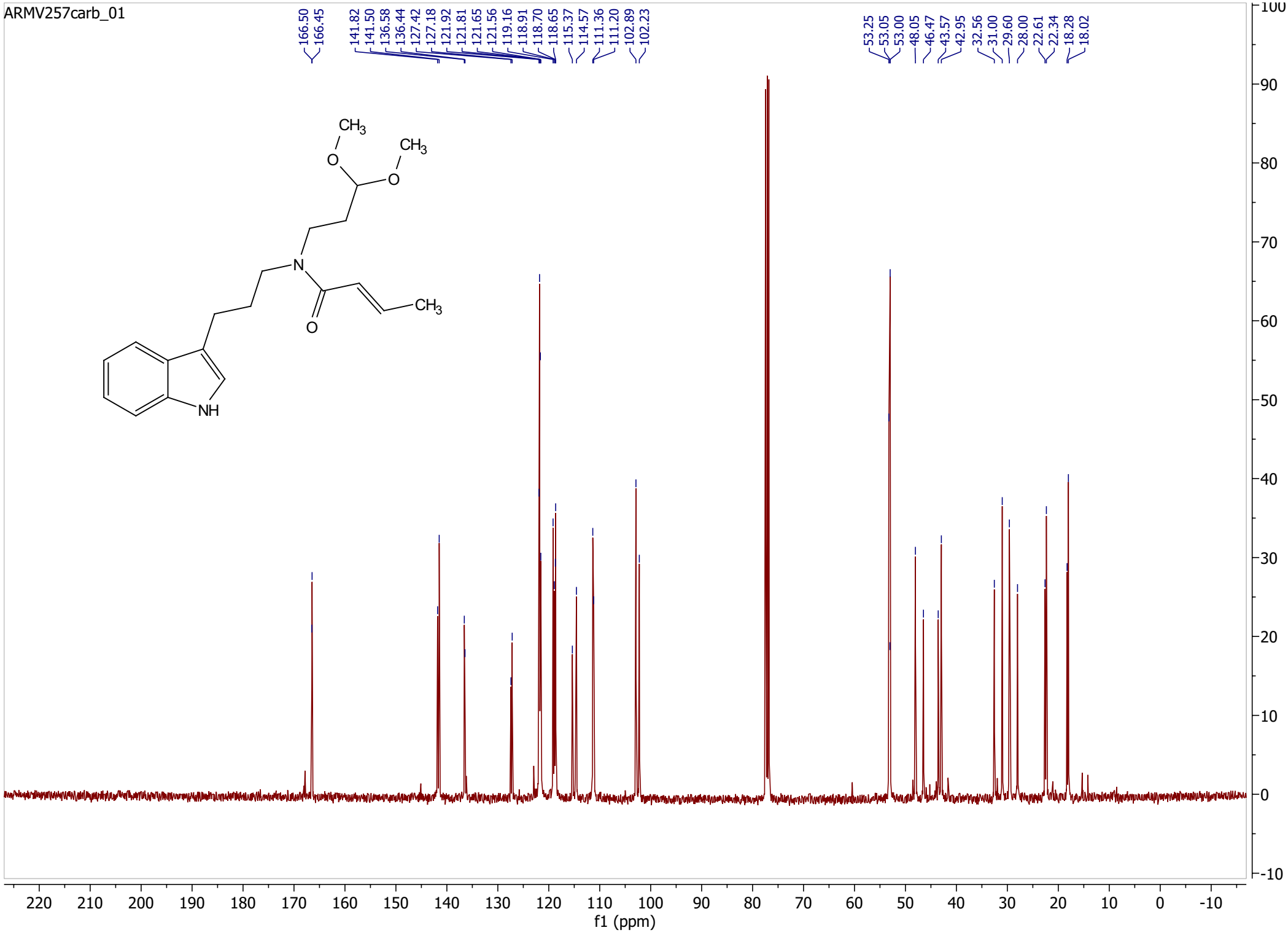

ARMV245B_01
172.69
136.39
127.12
121.91
121.83
119.19
118.63
114.75
111.28
103.91
53.33
37.44
35.36
31.89
21.39
CH3
CH3
O
O
O
NH
NH
f1 (ppm)

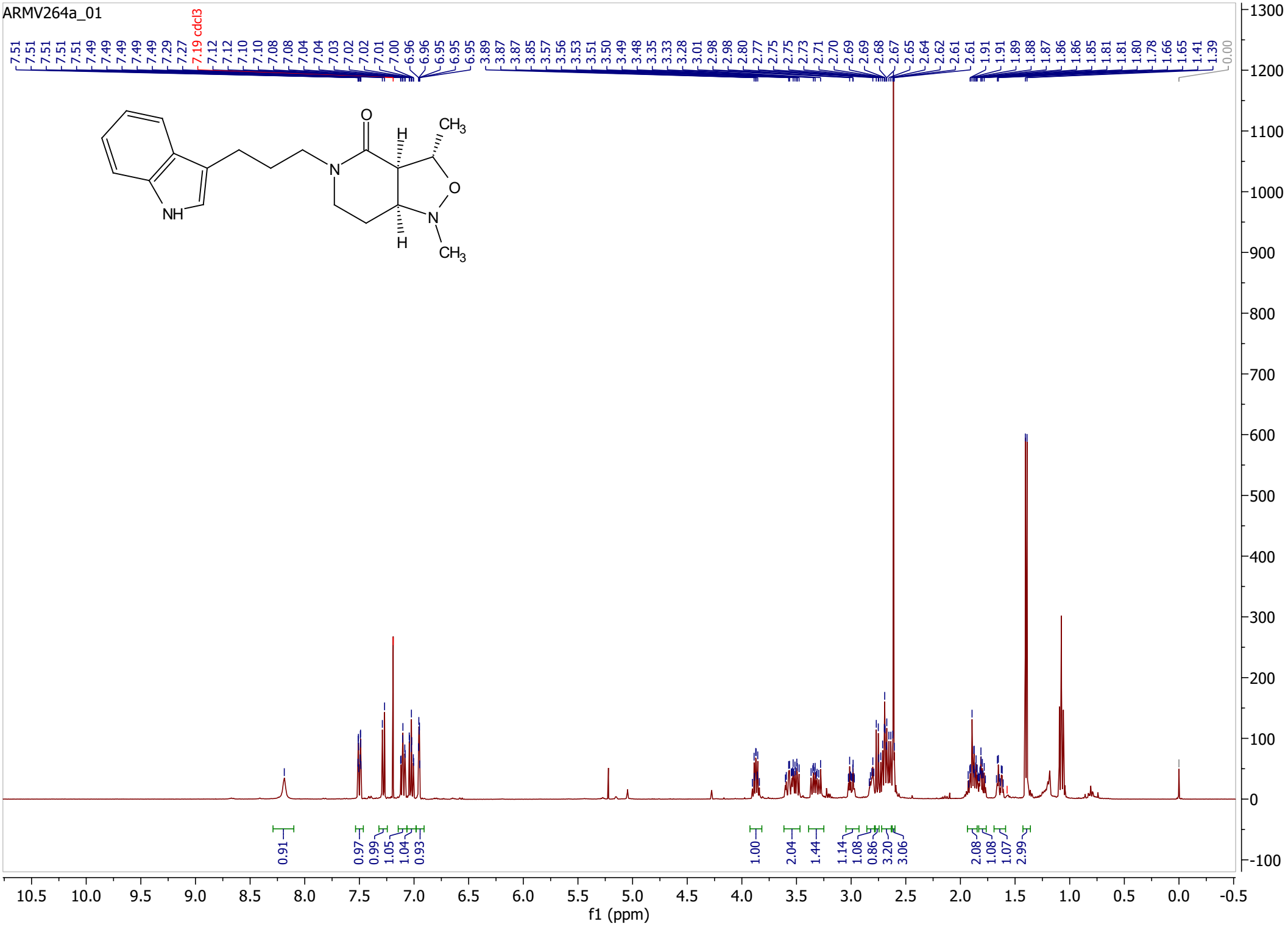

ARMV254_01
8.34 7.53 7.53 7.53 7.53 7.52 7.51 7.51 7.51 7.51 7.50 7.26 7.25 7.25 7.24 7.23 7.23 7.11 7.11 7.09 7.09 7.09 7.07 7.07 7.04 7.03 7.03 7.02 7.02 7.01 7.01 7.00 7.00 6.86 6.86 6.85 6.85 6.85
4.39 4.38 4.36
3.24 3.24 2.73 2.73 2.71 2.70 2.69 2.64 2.62 2.62 2.60 2.60 2.59
1.85 1.83 1.82 1.79 1.78 1.78 1.77 1.77 1.77 1.76 1.76 1.74 1.74 1.72 1.72 1.71
CH3
CH3
O
O
NH
NH
3000
2500
2000
1500
1000
500
0
1.02
1.00
0.99
1.07
1.07
0.99
1.10
6.25
1.88
4.04
1.95
1.18
2.26
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

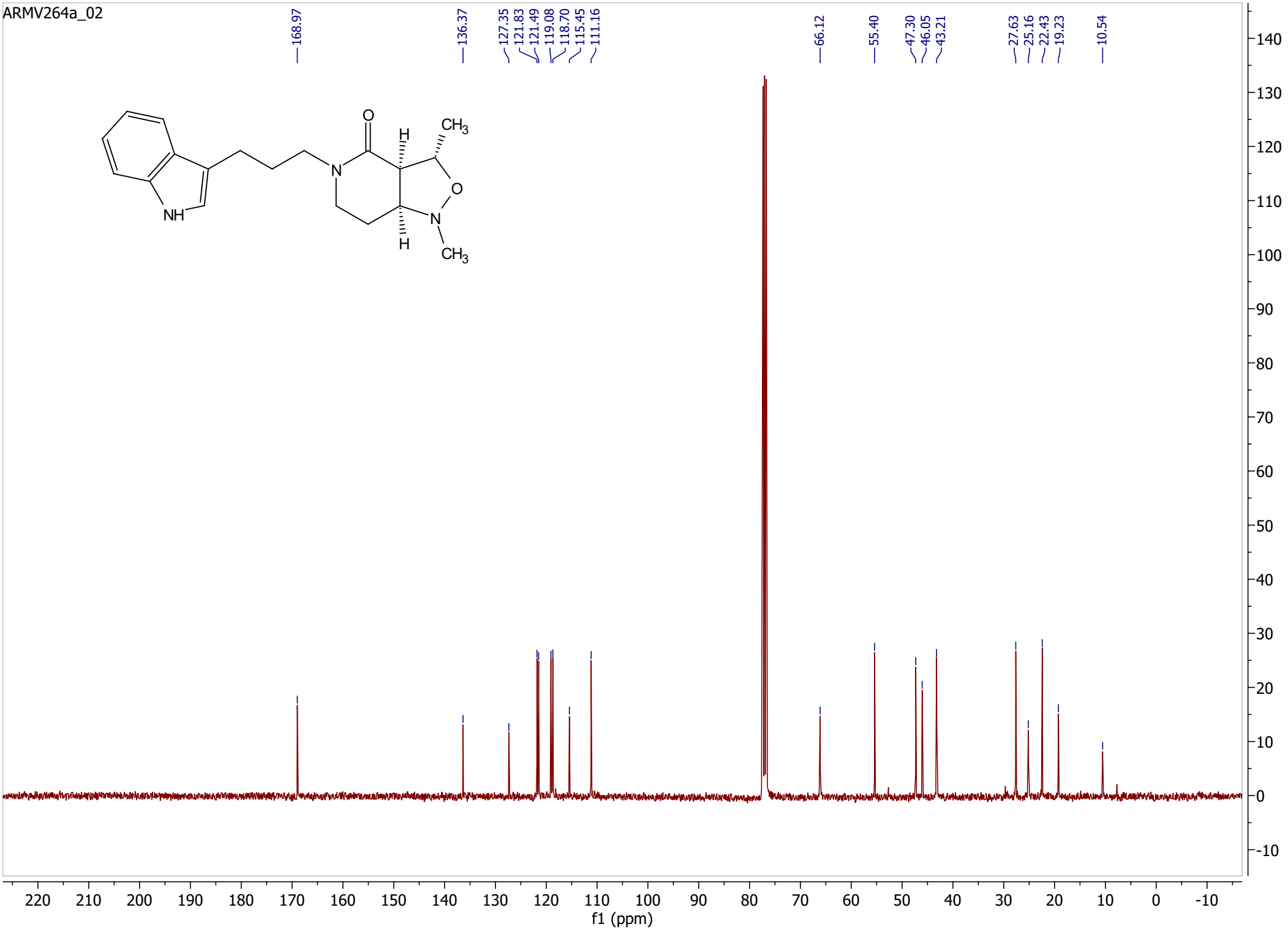

ARMV254carb_01 1
136.39
127.50
121.77
121.26
119.00
118.86
116.12
111.11
103.65
67.98
62.43
52.93
49.86
45.48
32.84
30.38
22.91
CH3
CH3
O
O
NH
NH
f1 (ppm)

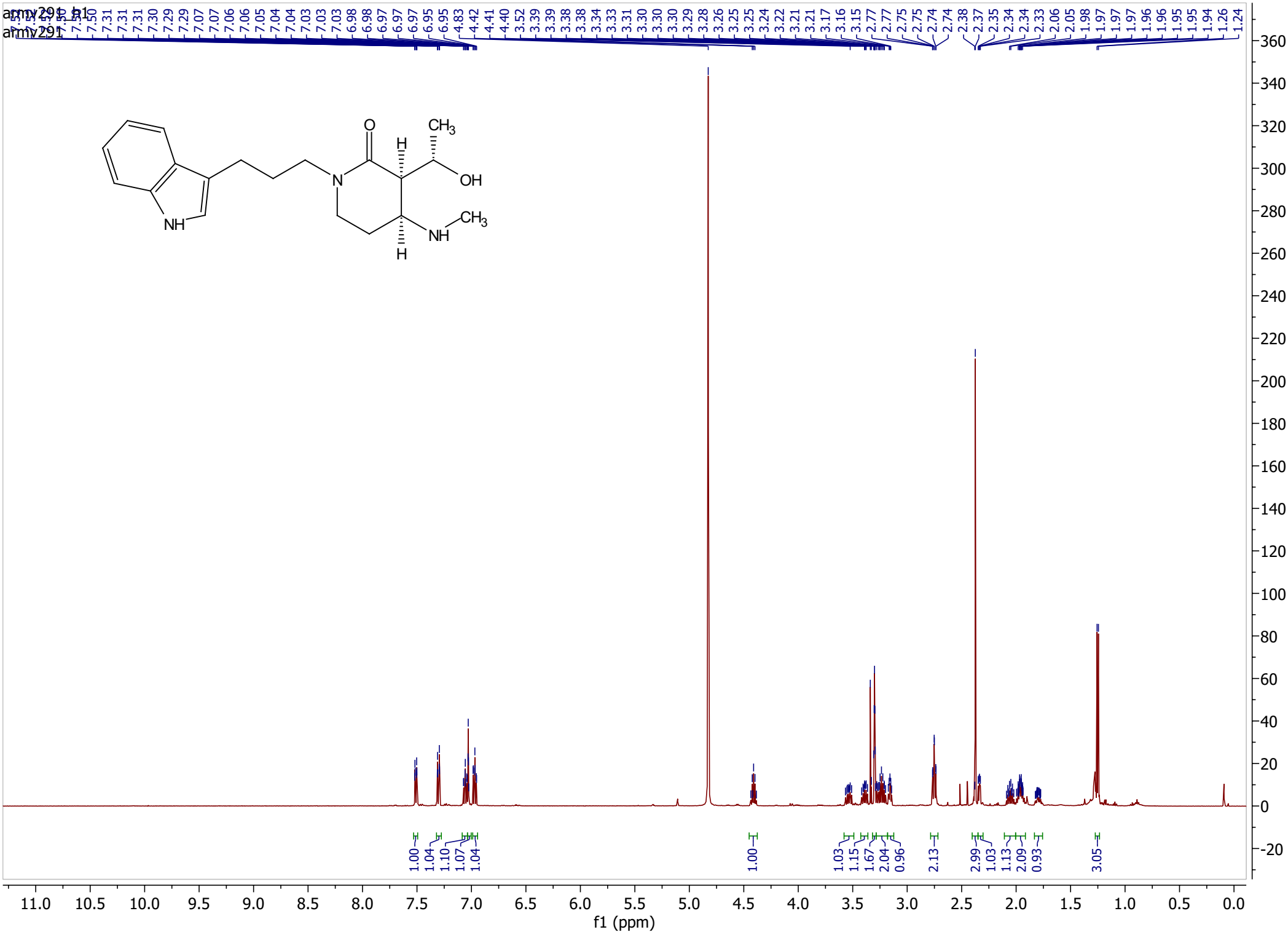
ARMV257A
STANDARD 1H OBSERVE



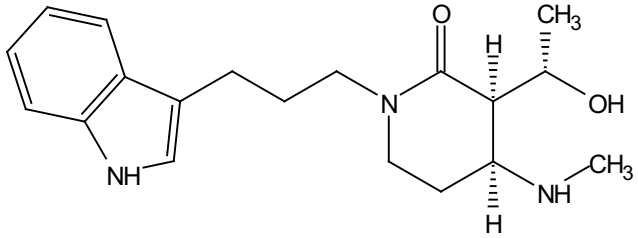

ARMV257carb_01
166.50
166.45
141.82
141.50
136.58
136.44
127.42
127.18
121.92
121.81
121.65
121.56
119.16
118.91
118.70
118.65
115.37
114.57
111.36
111.20
102.89
102.23
53.25
53.05
53.00
48.05
46.47
43.57
42.95
32.56
31.00
29.60
28.00
22.61
22.34
18.28
18.02
CH3
CH3
O
O
N
O
CH3
NH
f1 (ppm)


ARMV264a_01
7.51 7.51 7.51 7.51 7.51 7.49 7.49 7.49 7.49 7.49 7.29 7.27 7.19 cdcl3 7.12 7.12 7.10 7.10 7.08 7.08 7.04 7.04 7.03 7.02 7.02 7.01 7.00 6.96 6.96 6.95 6.95 6.95
3.89 3.87 3.87 3.85 3.57 3.56 3.53 3.51 3.50 3.49 3.48 3.35 3.33 3.28 3.01 2.98 2.98 2.80 2.77 2.75 2.75 2.73 2.71 2.70 2.69 2.69 2.68 2.67 2.65 2.64 2.62 2.61 2.61 1.91 1.91 1.89 1.88 1.87 1.86 1.86 1.85 1.81 1.81 1.80 1.78 1.66 1.65 1.41 1.39 0.00
O
H
CH3
N
O
NH
N
H
CH3
0.91
0.97
0.99
1.05
1.04
0.93
1.00
2.04
1.44
1.14
1.08
0.86
3.20
3.06
2.08
1.08
1.07
2.99
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)
1300 1200 1100 1000 900 800 700 600 500 400 300 200 100 0 -100


ARMV264a_02
168.97
136.37
127.35
121.83
121.49
119.08
118.70
115.45
111.16
66.12
55.40
47.30
46.05
43.21
27.63
25.16
22.43
19.23
10.54
O
H
CH3
N
O
NH
N
H
CH3
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


amv291 h1
amv291
O
CH3
H
OH
N
NH
CH3
NH
H
1.00
1.04
1.10
1.07
1.04
1.00
1.03
1.15
1.67
2.04
0.96
2.13
2.99
1.03
1.13
2.09
0.93
3.05
f1 (ppm)

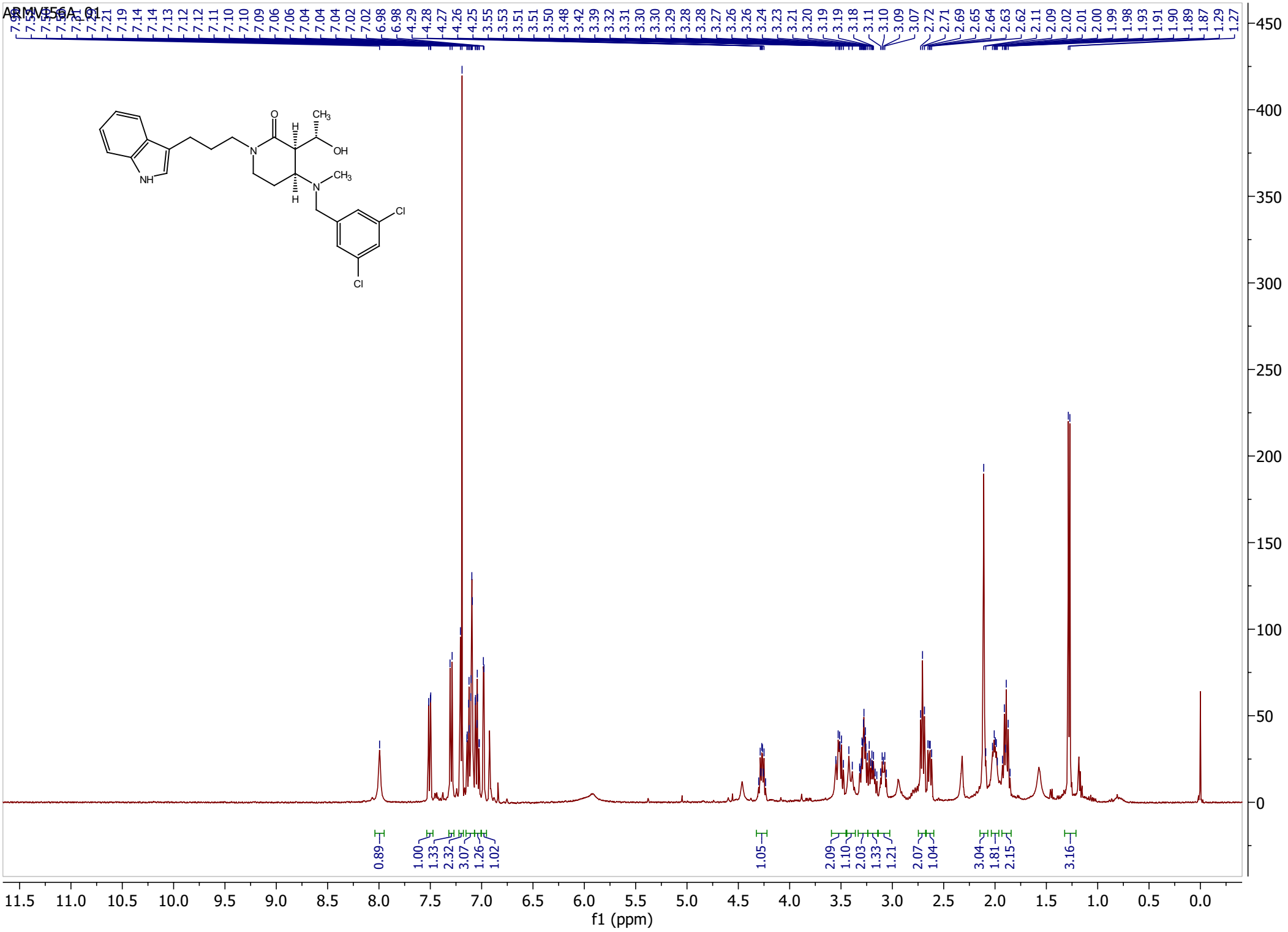
armv291_c13
armv291

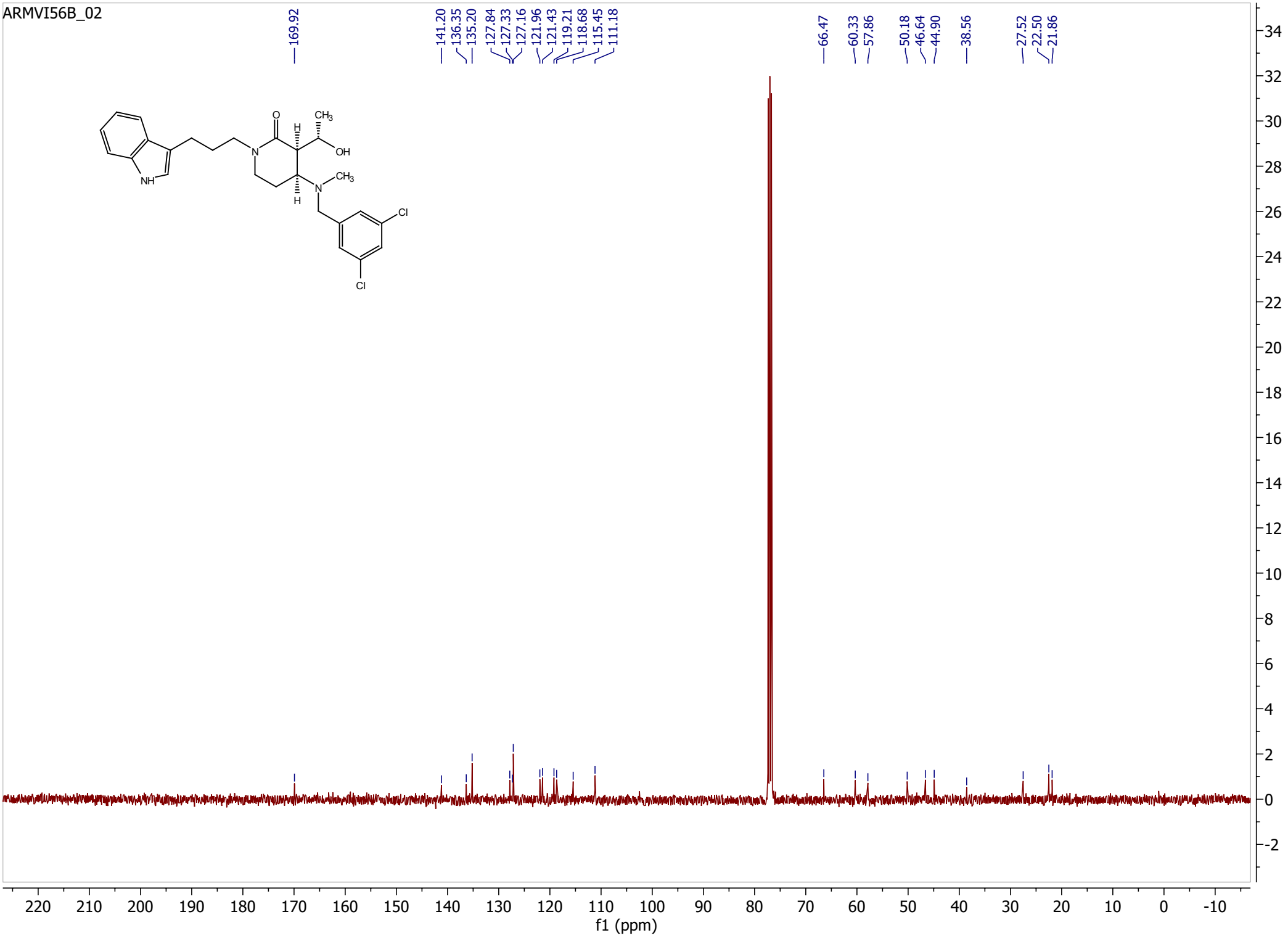


171.24
138.21
128.73
122.81
122.21
119.41
119.35
115.70
112.17
67.43
56.08
51.41
44.97
33.71
28.44
25.18
23.69
22.31

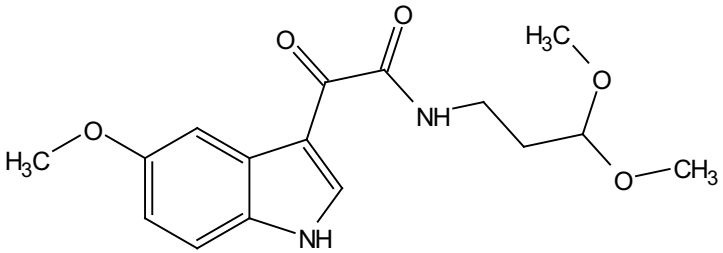
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


ARMV56A_01
O
CH3
H
OH
N
NH
CH3
N
H
Cl
Cl
0.89
1.00
1.33
2.32
3.07
1.26
1.02
1.05
2.09
1.10
2.03
1.33
1.21
2.07
1.04
3.04
1.81
2.15
3.16
f1 (ppm)


ARMVI56B_02
169.92
141.20
136.35
135.20
127.84
127.33
127.16
121.96
121.43
119.21
118.68
115.45
111.18
66.47
60.33
57.86
50.18
46.64
44.90
38.56
27.52
22.50
21.86
O
H
CH3
OH
N
NH
CH3
N
H
Cl
Cl
f1 (ppm)

ARMV236
STANDARD 1H OBSERVE

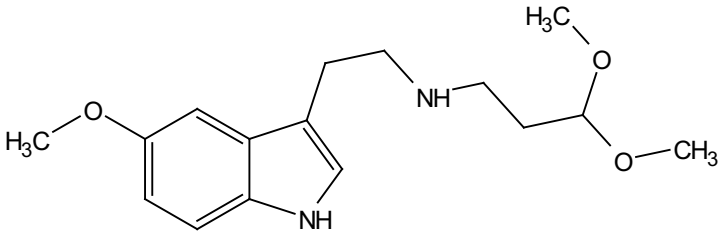


9.10 9.03 9.02 7.93 7.92 7.87 7.34 7.31 7.31 6.95 6.94 6.93 6.92 3.90 3.38 1.95 1.94 1.93 1.92 1.90

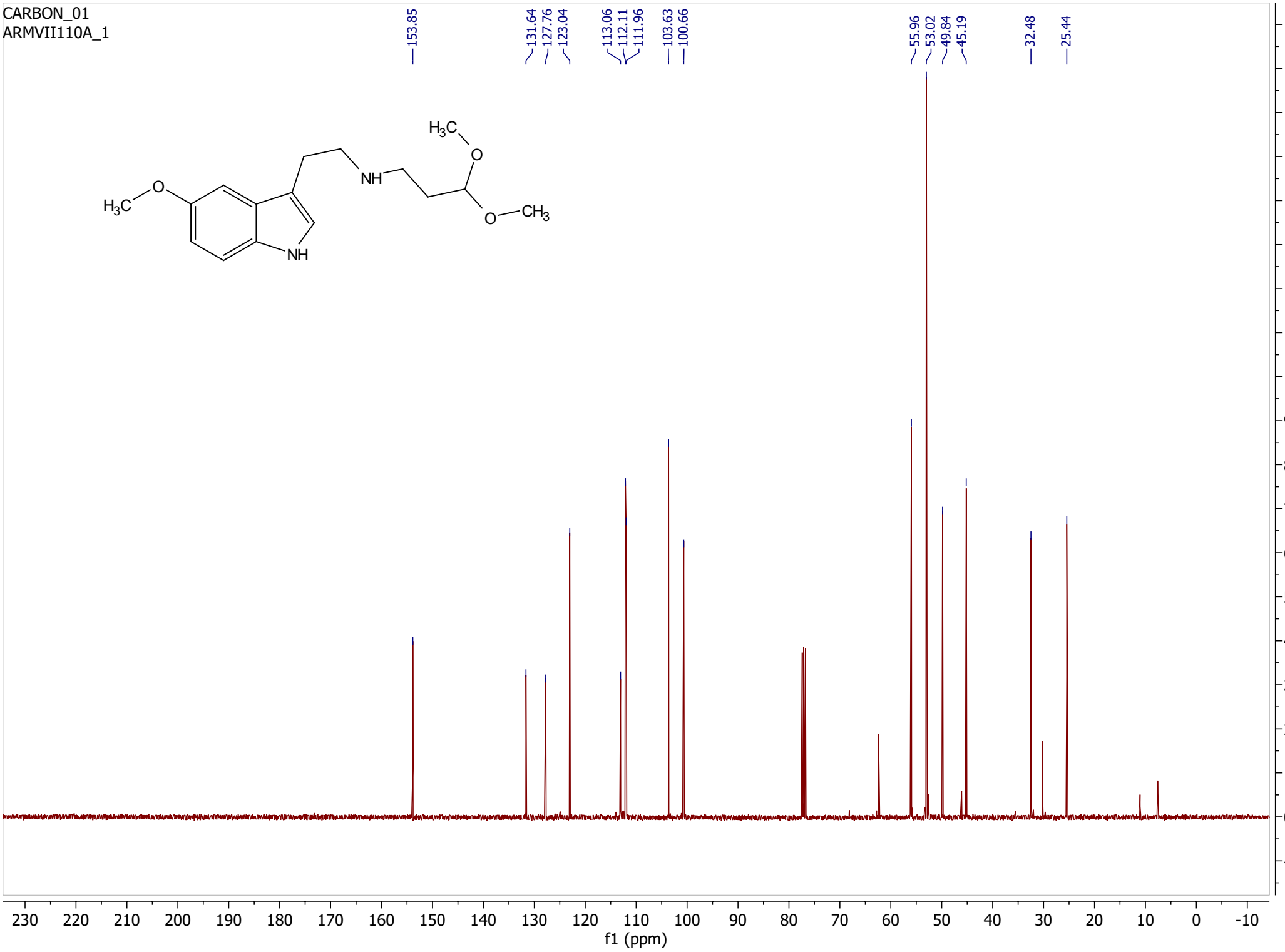
1.09 1.00 0.98 1.01 1.05 1.10 1.06 2.79 2.05 5.02 1.99

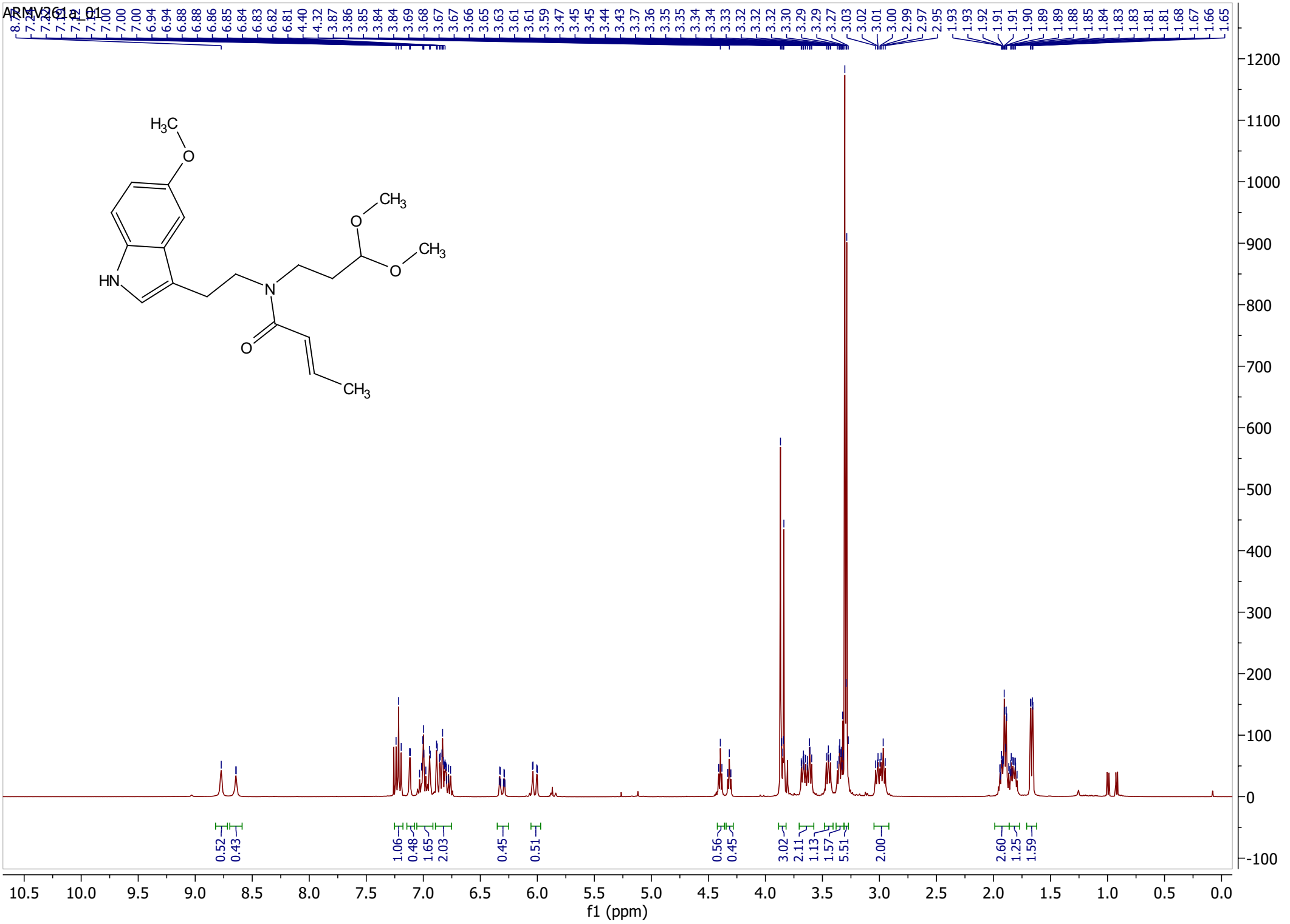
f1 (ppm)

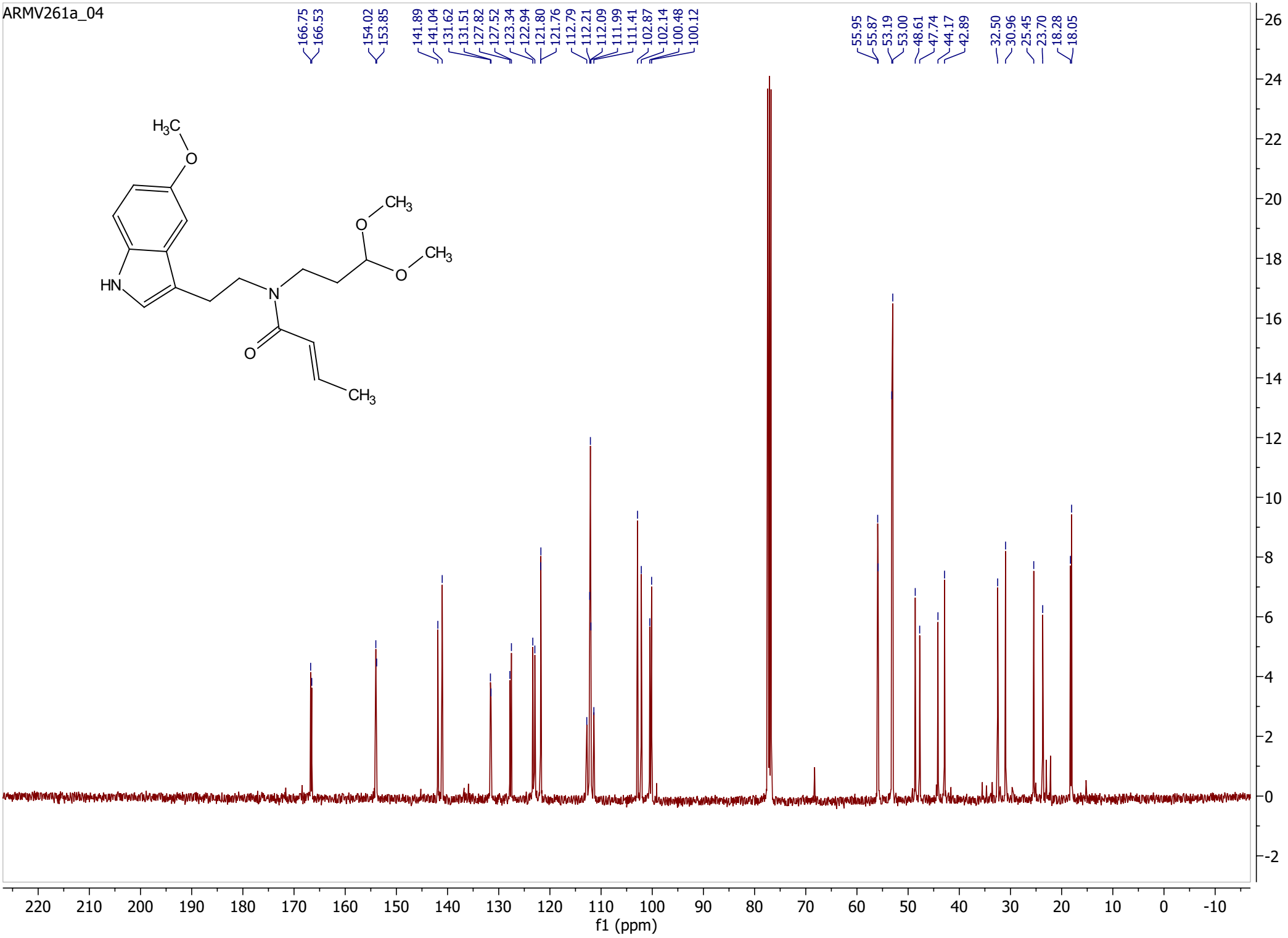
PROTON_01
ARMVII110B

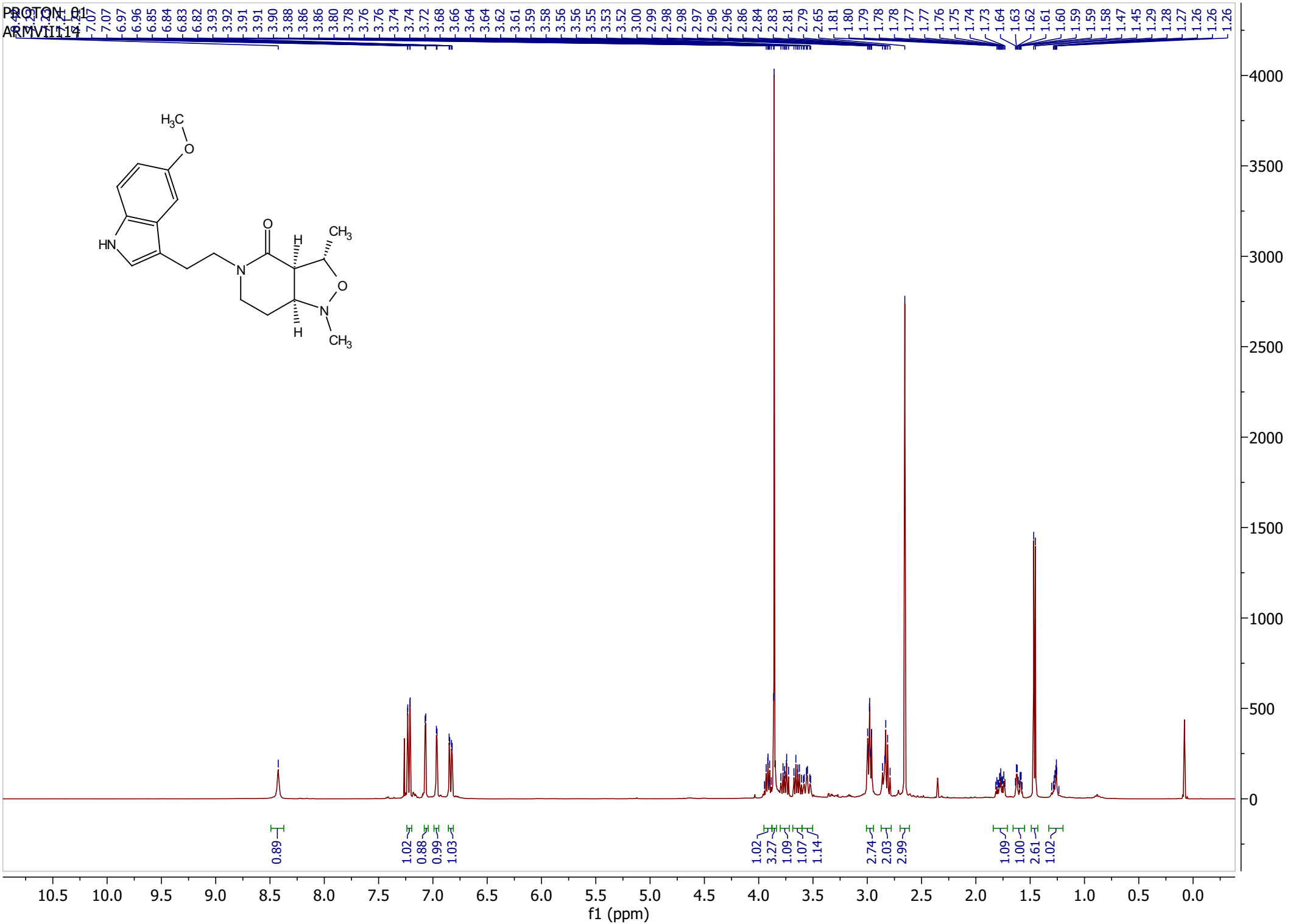


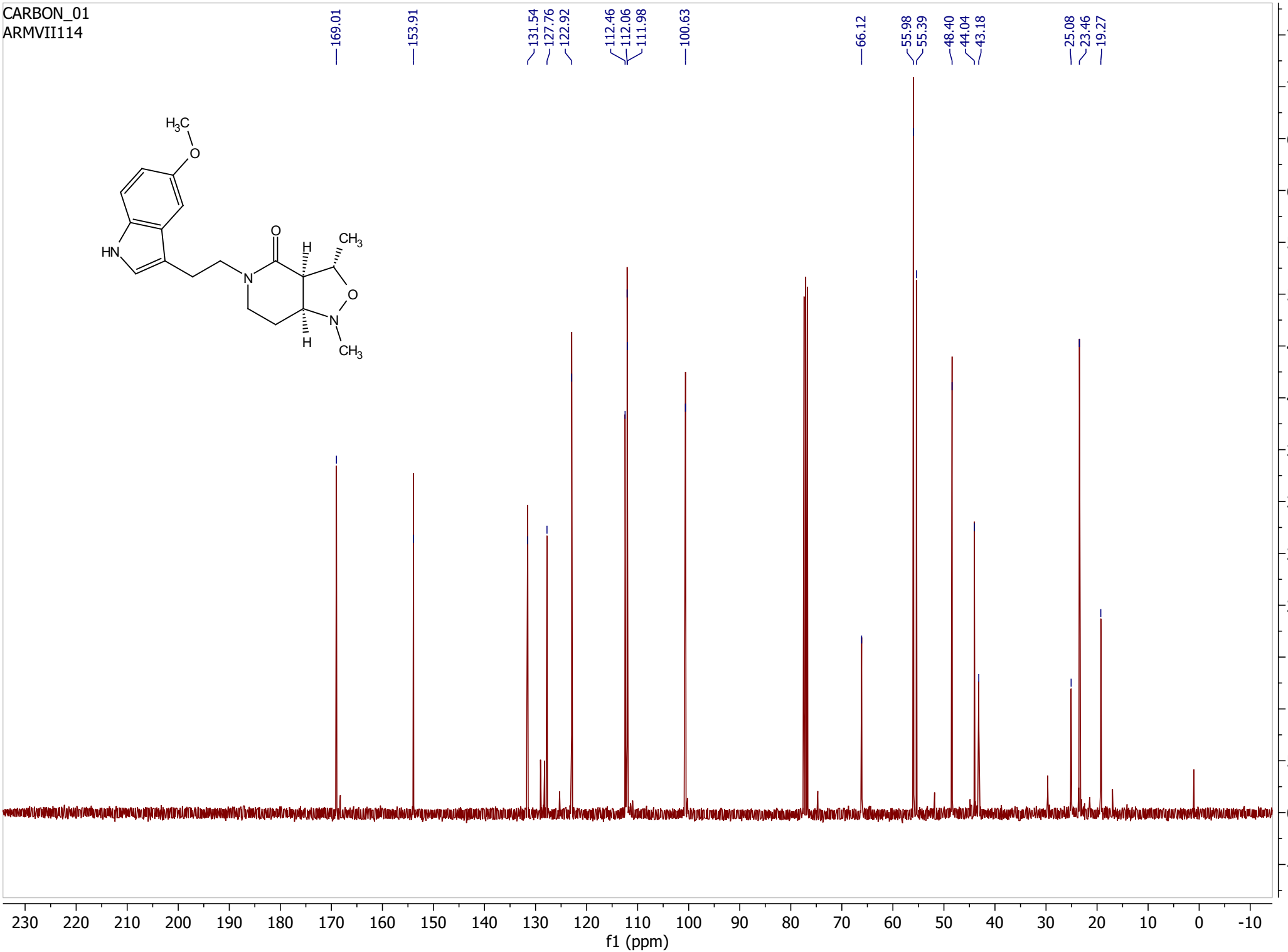
f1 (ppm)

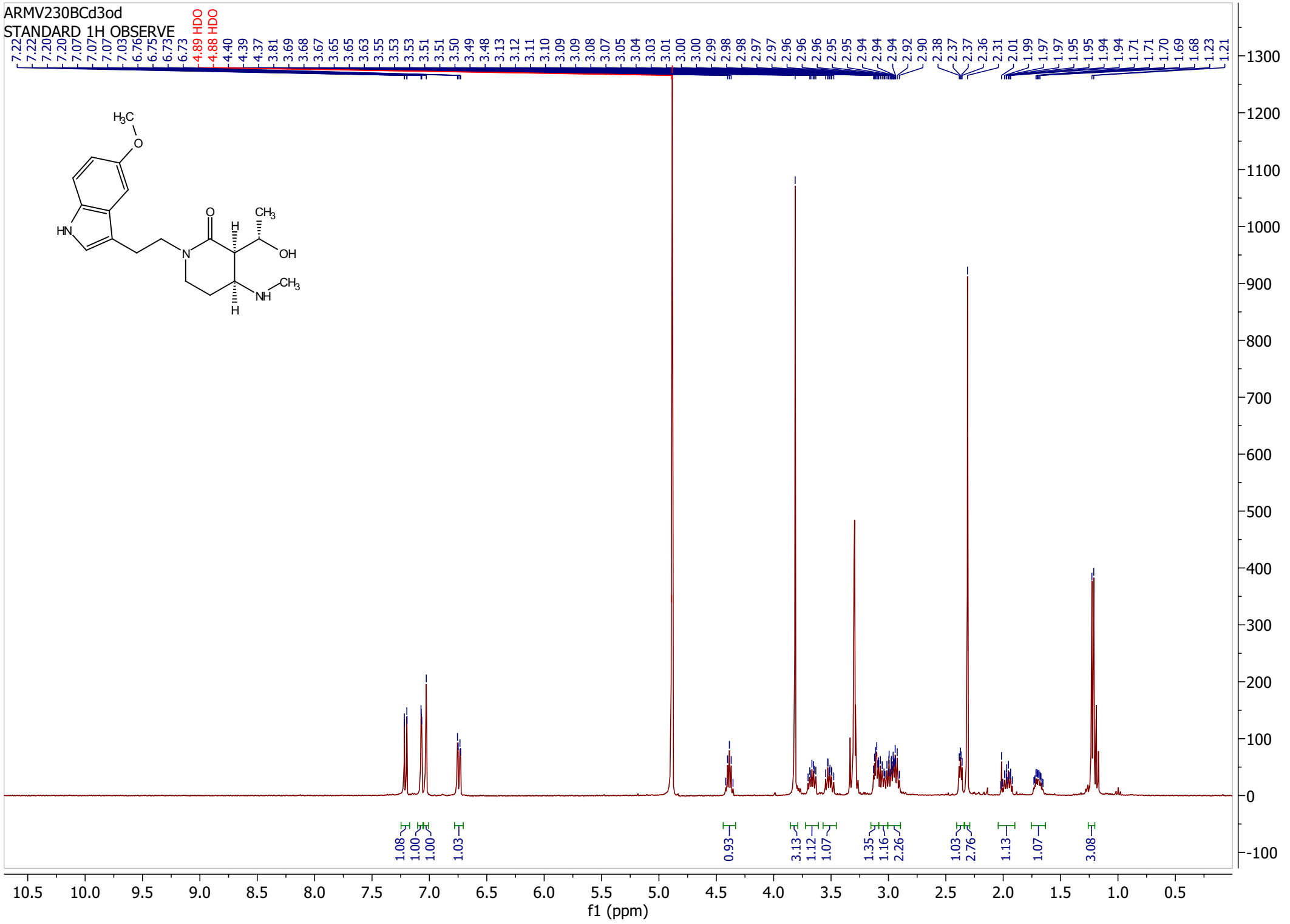

CARBON_01
ARMVII110A_1
153.85
131.64
127.76
123.04
113.06
112.11
111.96
103.63
100.66
55.96
53.02
49.84
45.19
32.48
25.44
H3C
O
NH
O
CH3
H3C
O
NH
f1 (ppm)

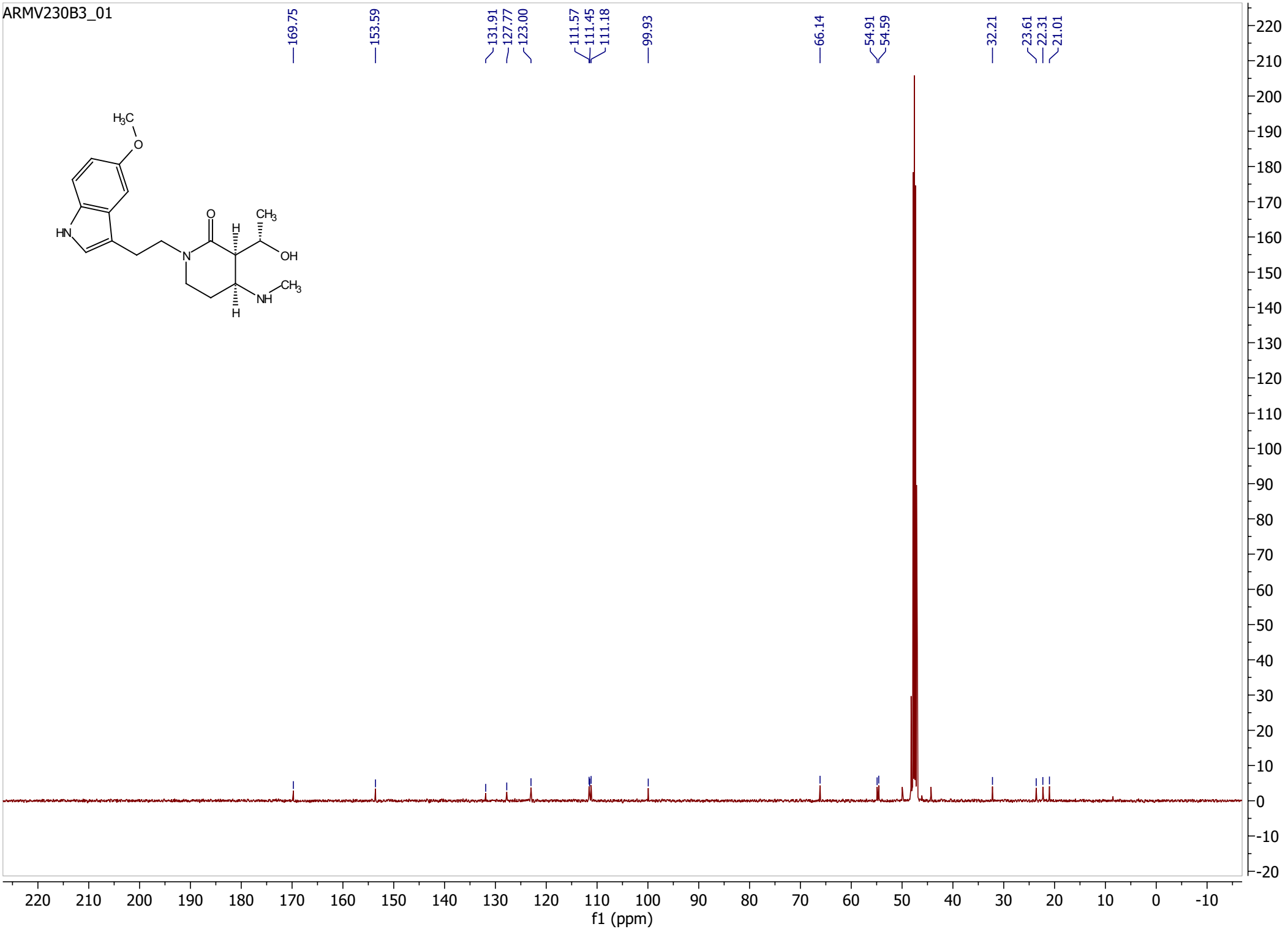

ARMV261a_01
H3C
O
HN
N
O
O
CH3
O
CH3
O
CH3
f1 (ppm)

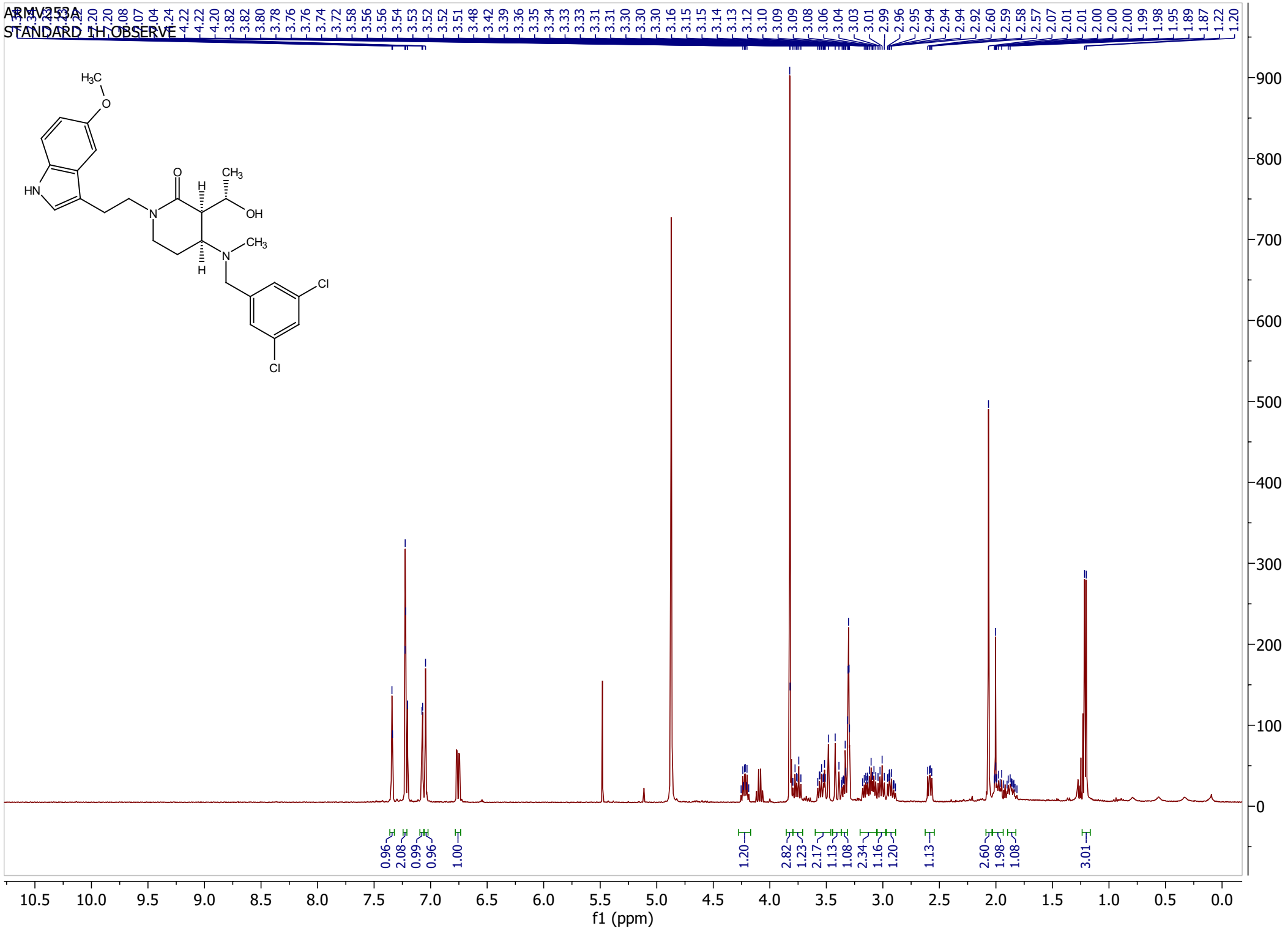

ARMV261a_04
166.75
166.53
154.02
153.85
141.89
141.04
131.62
131.51
127.82
127.52
123.34
122.94
121.80
121.76
112.79
112.21
112.09
111.99
111.41
102.87
102.14
100.48
100.12
55.95
55.87
53.19
53.00
48.61
47.74
44.17
42.89
32.50
30.96
25.45
23.70
18.28
18.05
H3C
O
CH3
O
CH3
O
HN
N
O
CH3
f1 (ppm)

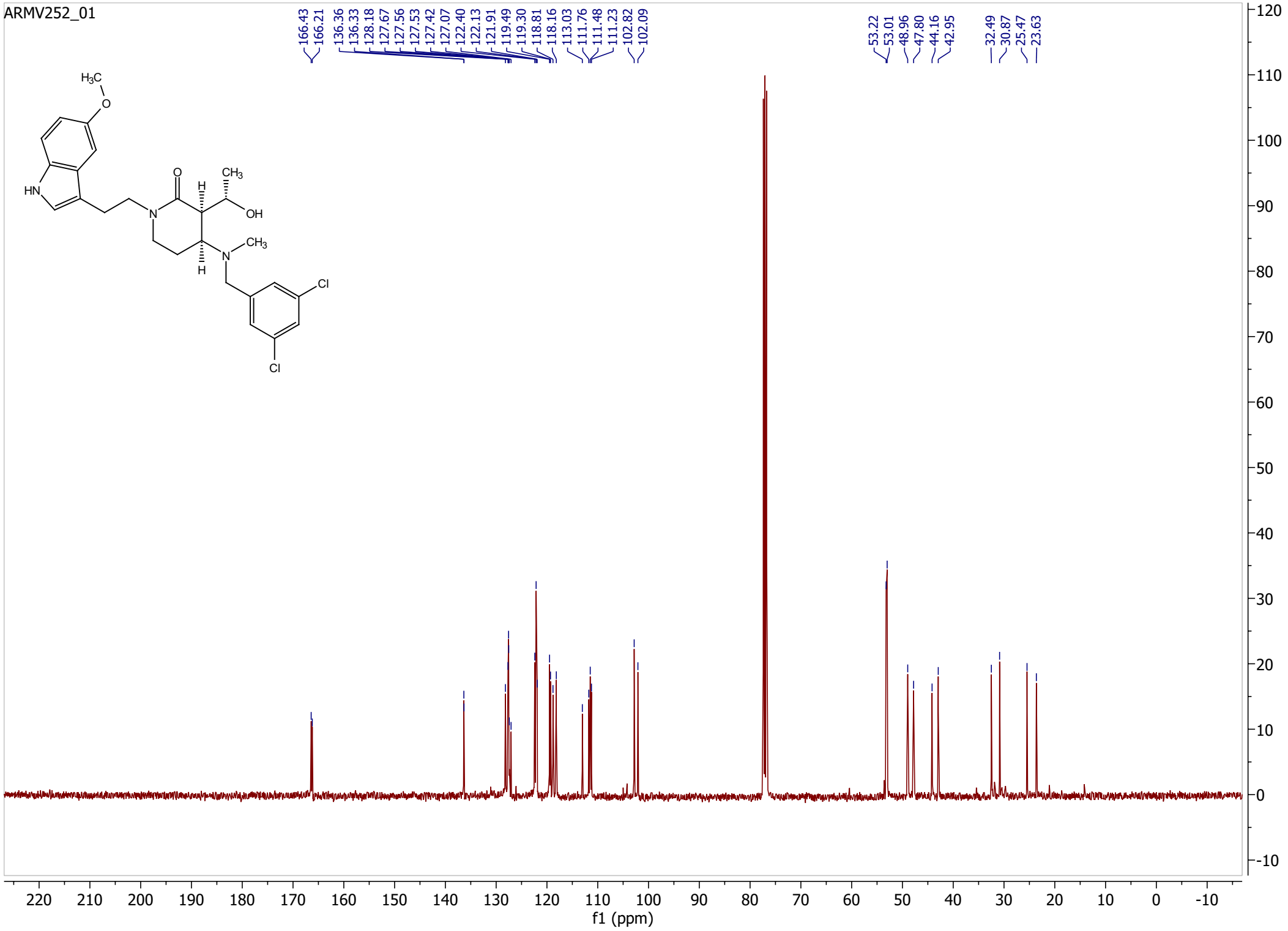

PROTON-01
ARMVII114
7.07 7.07 6.97 6.96 6.85 6.84 6.83 6.82 3.93 3.92 3.91 3.91 3.90 3.88 3.86 3.86 3.80 3.78 3.76 3.76 3.74 3.72 3.68 3.66 3.64 3.64 3.62 3.61 3.59 3.58 3.56 3.56 3.55 3.53 3.52 3.00 2.99 2.98 2.97 2.96 2.96 2.86 2.84 2.83 2.81 2.79 2.65 1.81 1.80 1.79 1.78 1.78 1.77 1.77 1.76 1.75 1.74 1.73 1.64 1.63 1.62 1.61 1.60 1.59 1.59 1.58 1.47 1.45 1.29 1.28 1.27 1.26 1.26 1.26
H3C
O
HN
O
H
CH3
N
O
N
H
CH3
4000
3500
3000
2500
2000
1500
1000
500
0
0.89
1.02
0.88
0.99
1.03
1.02
3.27
1.09
1.07
1.14
2.74
2.03
2.99
1.09
1.00
2.61
1.02
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

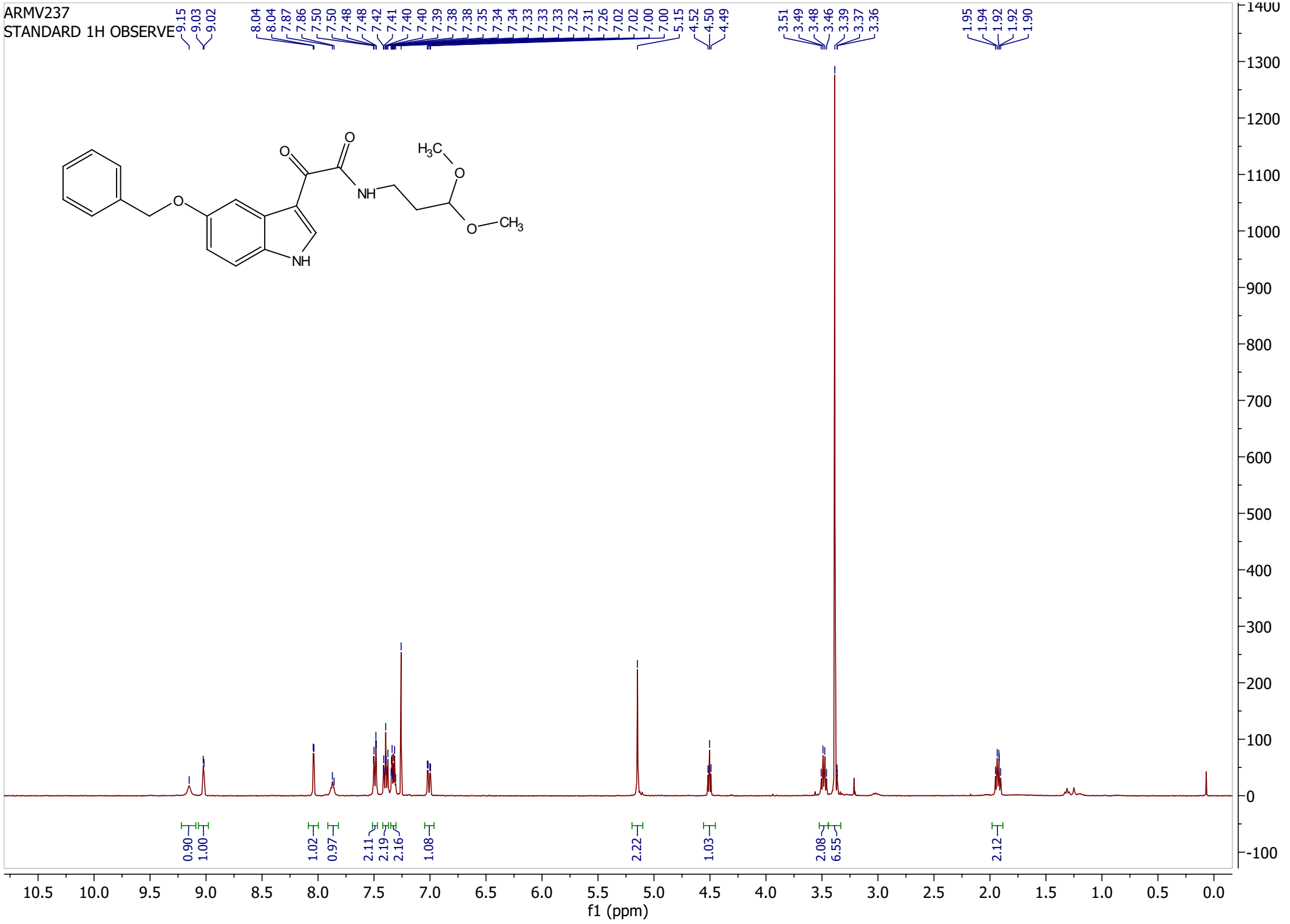

CARBON_01
ARMVII114
169.01
153.91
131.54
127.76
122.92
112.46
112.06
111.98
100.63
66.12
55.98
55.39
48.40
44.04
43.18
25.08
23.46
19.27
H3C
O
HN
O
H
CH3
N
O
N
H
CH3
f1 (ppm)


ARMV230BCd3od
STANDARD 1H OBSERVE
7.22 7.22 7.20 7.20 7.07 7.07 7.07 7.03 6.76 6.75 6.73 6.73 4.89 HDO 4.88 HDO 4.40 4.39 4.37 3.81 3.69 3.68 3.67 3.65 3.65 3.63 3.55 3.53 3.53 3.51 3.51 3.50 3.49 3.48 3.13 3.12 3.11 3.10 3.09 3.09 3.08 3.07 3.05 3.04 3.03 3.01 3.00 3.00 2.99 2.98 2.98 2.97 2.97 2.96 2.96 2.96 2.95 2.95 2.94 2.94 2.94 2.94 2.92 2.90 2.38 2.37 2.37 2.36 2.31 2.01 1.99 1.97 1.97 1.95 1.95 1.94 1.94 1.71 1.71 1.70 1.69 1.68 1.23 1.21
H3C
O
HN
O
CH3
H
OH
N
NH
CH3
H
1.08 1.00 1.00 1.03 0.93 3.13 1.12 1.07 1.35 1.16 2.26 1.03 2.76 1.13 1.07 3.08
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)
1300 1200 1100 1000 900 800 700 600 500 400 300 200 100 0 -100

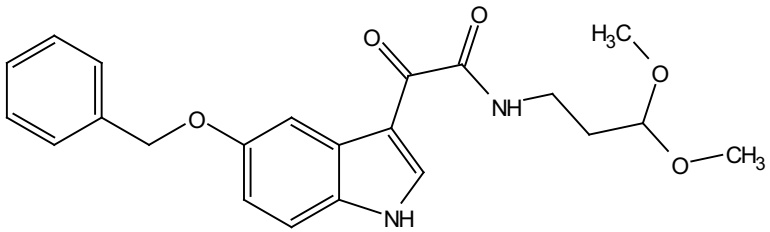

ARMV230B3_01
169.75
153.59
131.91
127.77
123.00
111.57
111.45
111.18
99.93
66.14
54.91
54.59
32.21
23.61
22.31
21.01
H3C
O
HN
O
H
CH3
OH
N
NH
CH3
H
f1 (ppm)


ARMV253A
STANDARD 1H OBSERVE
f1 (ppm)


ARMV252_01
166.43
166.21
136.36
136.33
128.18
127.67
127.56
127.53
127.42
127.07
122.40
122.13
121.91
119.49
119.30
118.81
118.16
113.03
111.76
111.48
111.23
102.82
102.09
53.22
53.01
48.96
47.80
44.16
42.95
32.49
30.87
25.47
23.63
H3C
O
HN
O
CH3
H
OH
N
CH3
N
H
Cl
Cl
f1 (ppm)

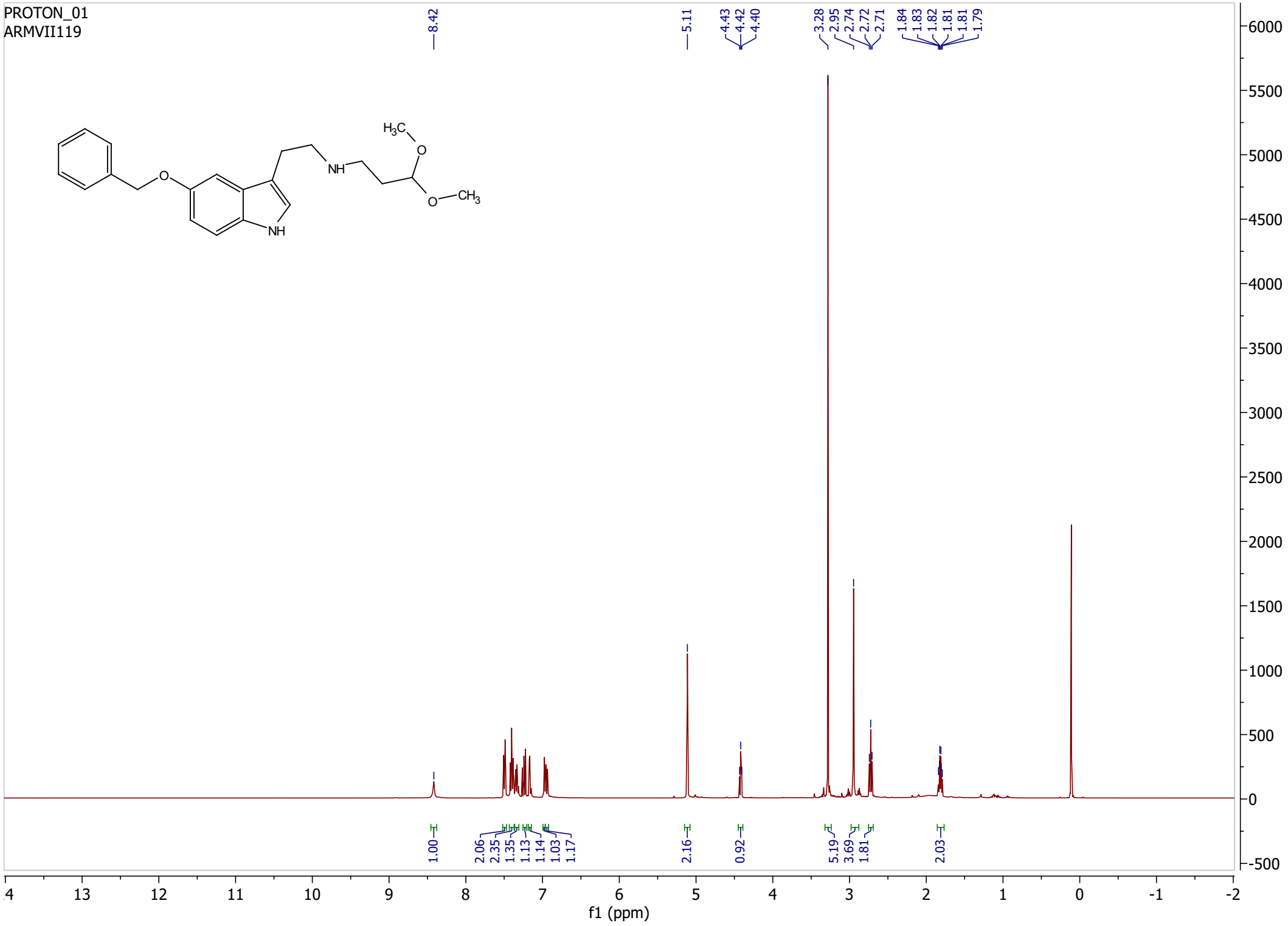

ARMV237
STANDARD 1H OBSERVE
9.15 9.03 9.02
8.04 8.04 7.87 7.86 7.50 7.50 7.48 7.48 7.42 7.41 7.40 7.40 7.39 7.38 7.38 7.35 7.34 7.34 7.33 7.33 7.33 7.32 7.31 7.26 7.02 7.02 7.00 7.00 5.15
4.52 4.50 4.49
3.51 3.49 3.48 3.46 3.39 3.37 3.36
1.95 1.94 1.92 1.92 1.90
O
O
NH
O
H3C
O
O
CH3
NH
0.90 1.00 1.02 0.97 2.11 2.19 2.16 1.08 2.22 1.03 2.08 6.55 2.12
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
1400 1300 1200 1100 1000 900 800 700 600 500 400 300 200 100 0 -100

ARMV227B_01

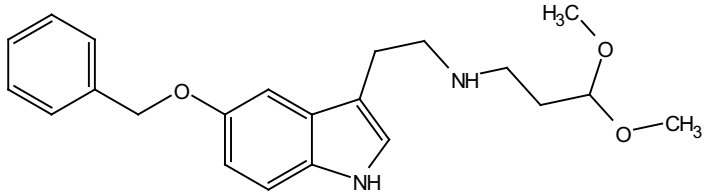


162.94
155.95
139.19
138.04
131.34
128.75
128.07
127.94
114.38
113.41
112.72
105.22
103.67
70.35
53.06
35.08
32.30
1.24
1.03
0.82 cd3cn
0.62 cd3cn
0.41 cd3cn
0.20
-0.00

f1 (ppm)


PROTON_01
ARMVII119
8.42
5.11
4.43
4.42
4.40
3.28
2.95
2.74
2.72
2.71
1.84
1.83
1.82
1.81
1.81
1.79
H3C
O
NH
O
O
CH3
NH
1.00
2.06
2.35
1.35
1.13
1.14
1.03
1.17
2.16
0.92
5.19
3.69
1.81
2.03
f1 (ppm)

CARBON_01
ARMVII119

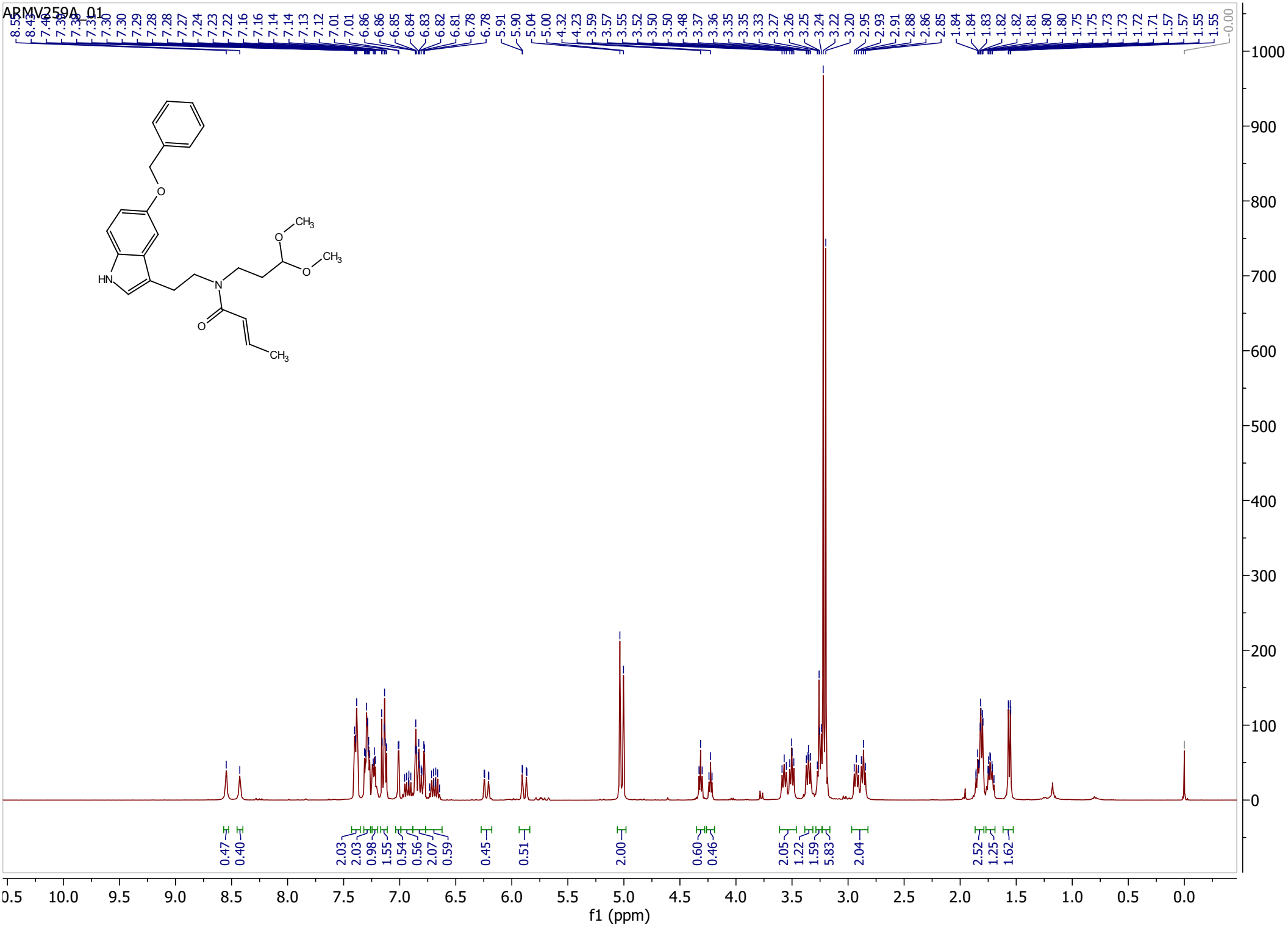


153.05
137.72
131.84
128.52
127.79
127.64
122.99
113.48
112.82
111.90
103.66
102.48
71.05
52.94
49.93
45.35
32.79
25.72

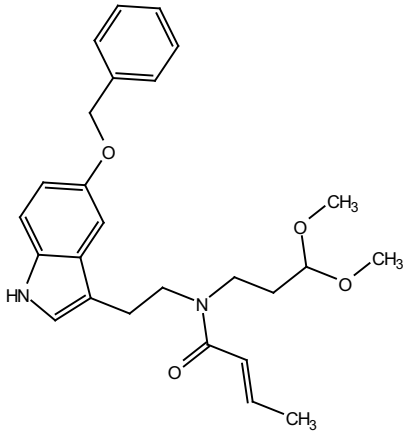
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

f1 (ppm)


ARMV259A_01
f1 (ppm)

ARMV259A_02



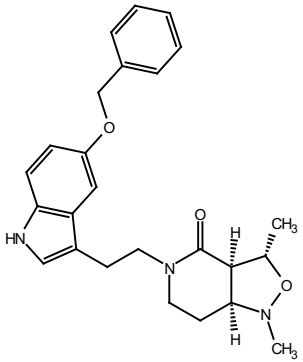
166.77 166.52 153.16 153.08 141.91 140.98 137.73 137.63 131.84 131.72 128.54 128.48 127.85 127.75 127.61 127.55 123.45 123.05 121.83 121.78 112.87 112.76 112.20 111.99 111.47 102.89 102.16 102.01 71.09 70.93 53.21 53.02 48.56 47.80 44.20 42.90 32.52 30.98 25.46 23.72 18.31 18.07

110 100 90 80 70 60 50 40 30 20 10 0 -10

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

f1 (ppm)

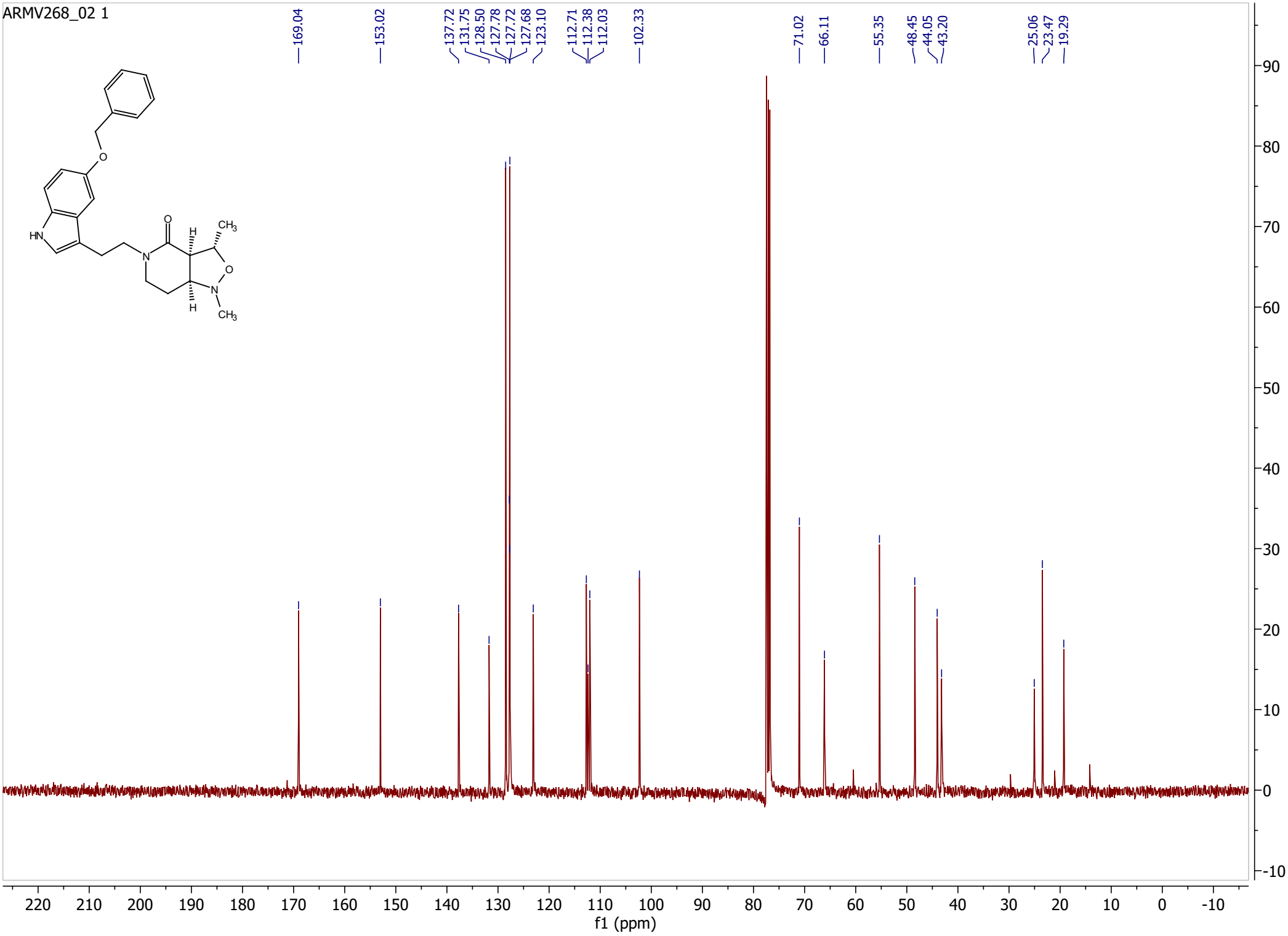
ARMV268
STANDARD 1H OBSERVE

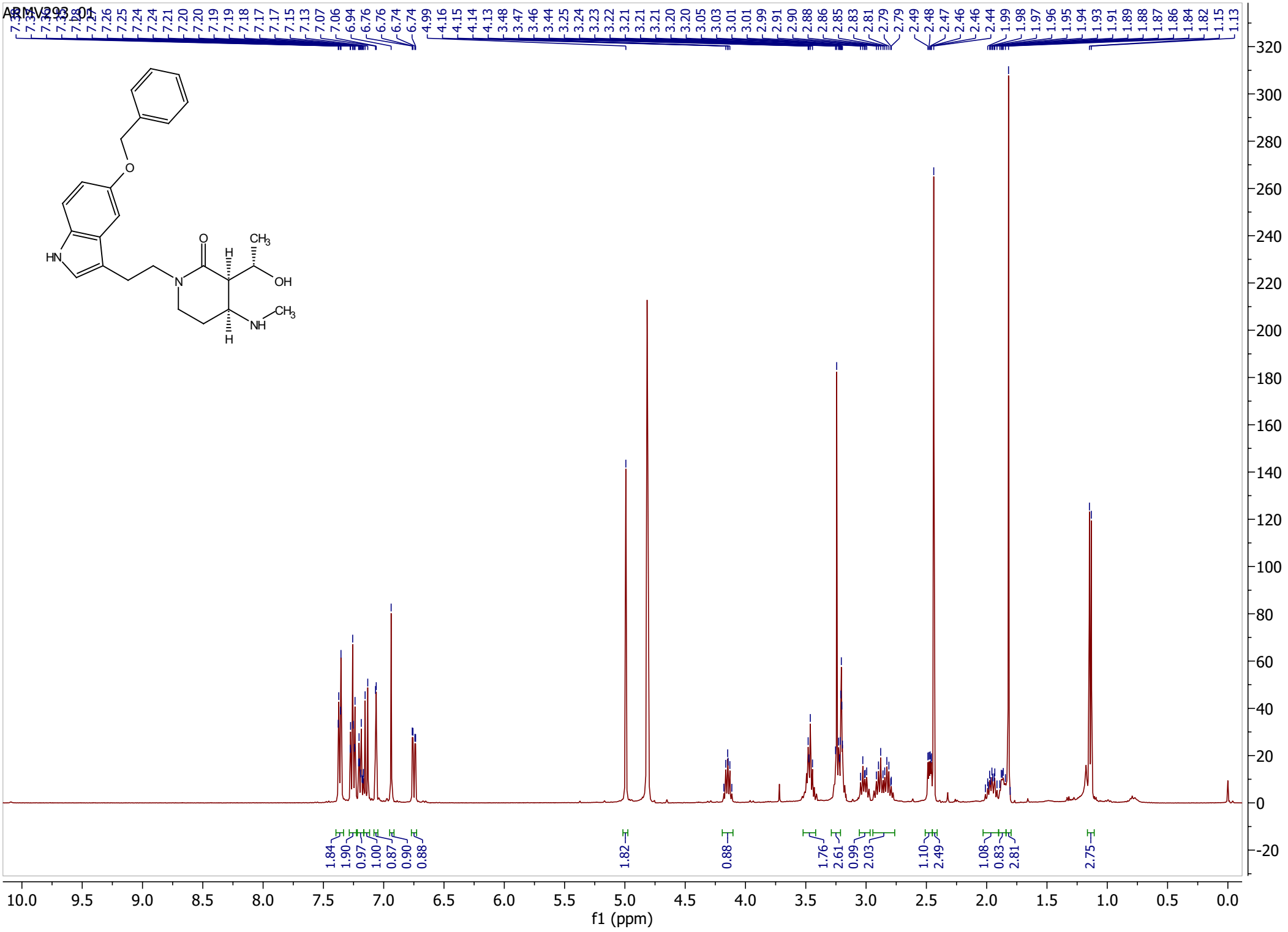


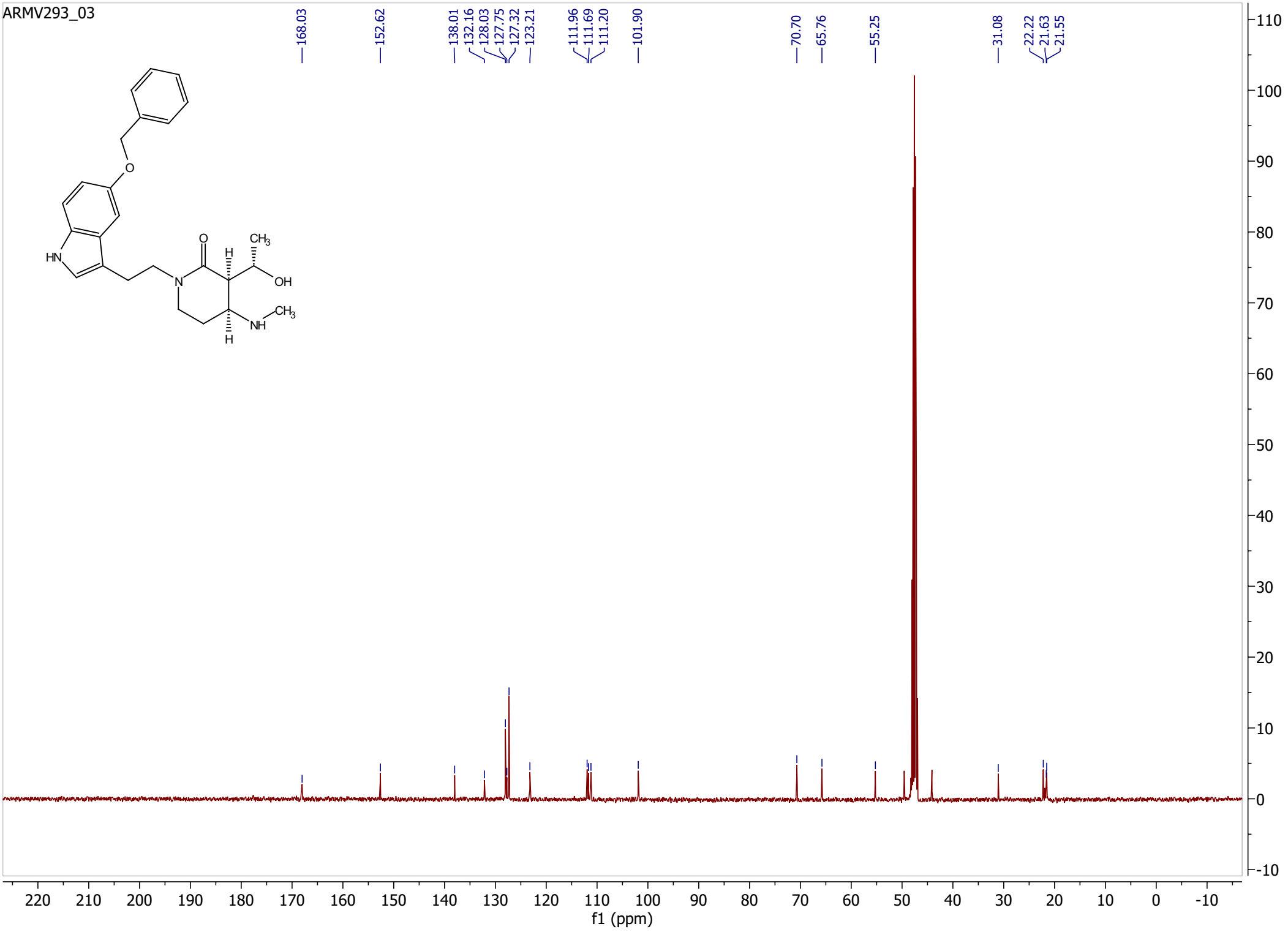
8.39 8.39 8.39 7.50 7.49 7.48 7.47 7.47 7.40 7.40 7.39 7.38 7.38 7.37 7.36 7.33 7.31 7.26 7.24 7.21 7.16 7.15 6.96 6.95 6.93 6.93 6.91 6.91 5.11 3.94 3.92 3.90 3.75 3.74 3.73 3.72 3.70 3.64 3.62 3.61 3.59 3.57 3.55 3.55 3.52 3.52 3.49 3.49 2.98 2.96 2.95 2.84 2.83 2.81 2.66 2.05 1.77 1.76 1.74 1.73 1.62 1.61 1.60 1.58 1.57 1.47 1.46

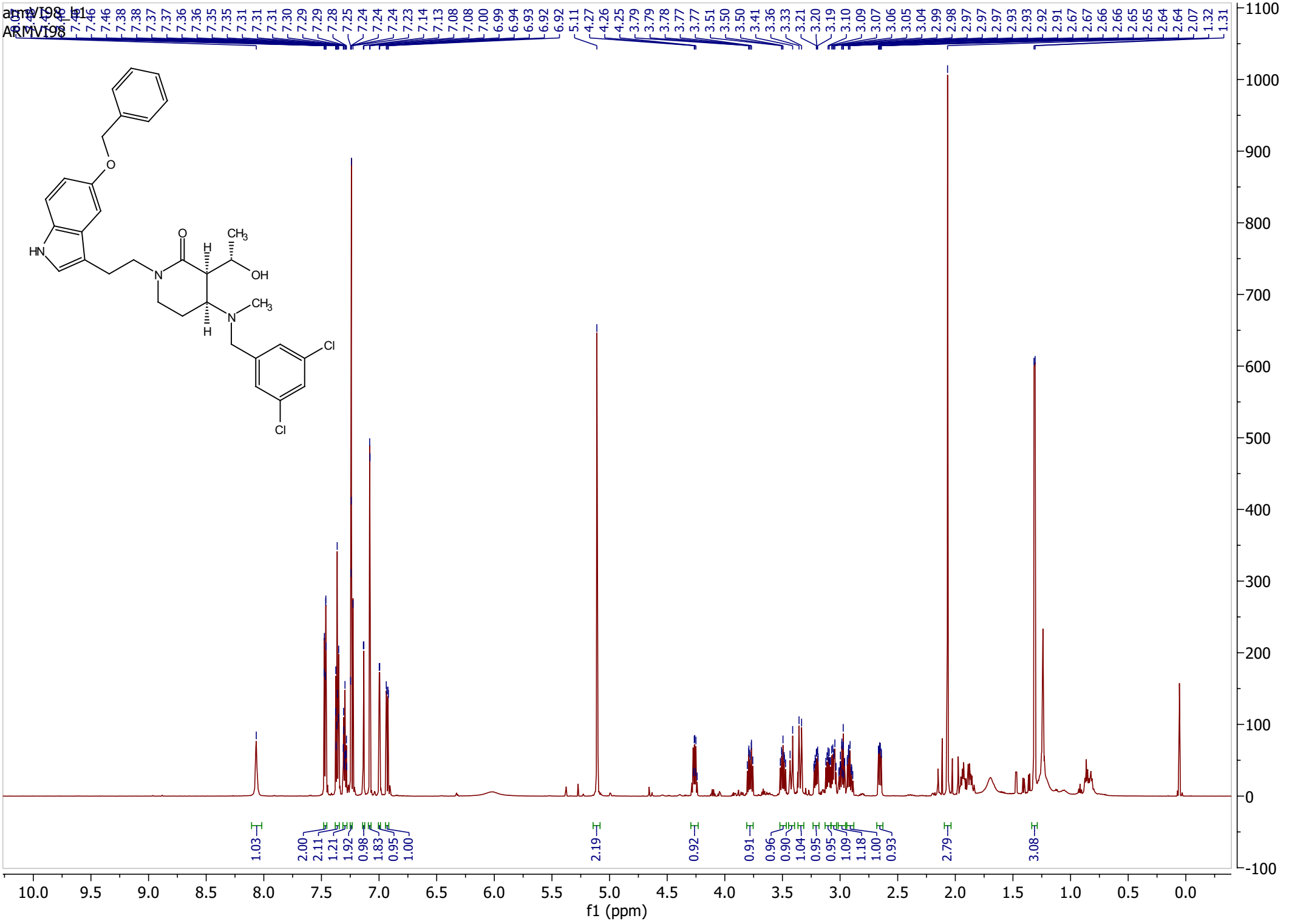
0.95 2.15 2.26 1.27 1.33 1.08 2.15 2.00 1.18 1.26 1.33 1.12 2.99 1.88 2.87 1.30 1.25 2.94

f1 (ppm)

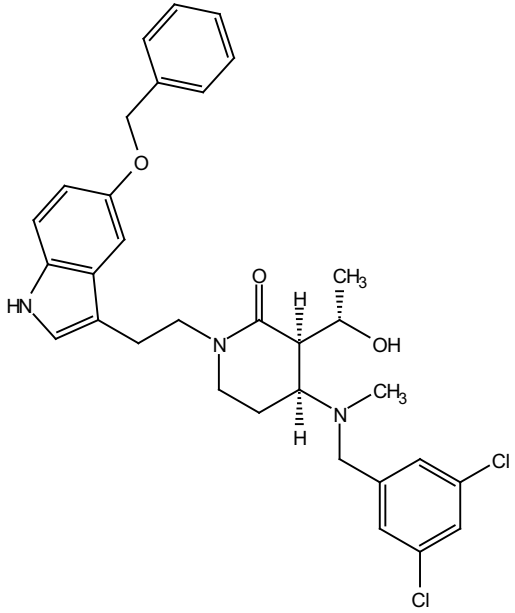

ARMV268_02 1
169.04
153.02
137.72
131.75
128.50
127.78
127.72
127.68
123.10
112.71
112.38
112.03
102.33
71.02
66.11
55.35
48.45
44.05
43.20
25.06
23.47
19.29
HN
O
O
H
CH3
N
O
N
CH3
H
f1 (ppm)


ARMV293-01
HN
O
N
H
CH3
OH
NH
CH3
H
f1 (ppm)


ARMV293_03
168.03
152.62
138.01
132.16
128.03
127.75
127.32
123.21
111.96
111.69
111.20
101.90
70.70
65.76
55.25
31.08
22.22
21.63
21.55
O
HN
N
O
H
CH3
OH
NH
CH3
H
110
100
90
80
70
60
50
40
30
20
10
0
-10
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

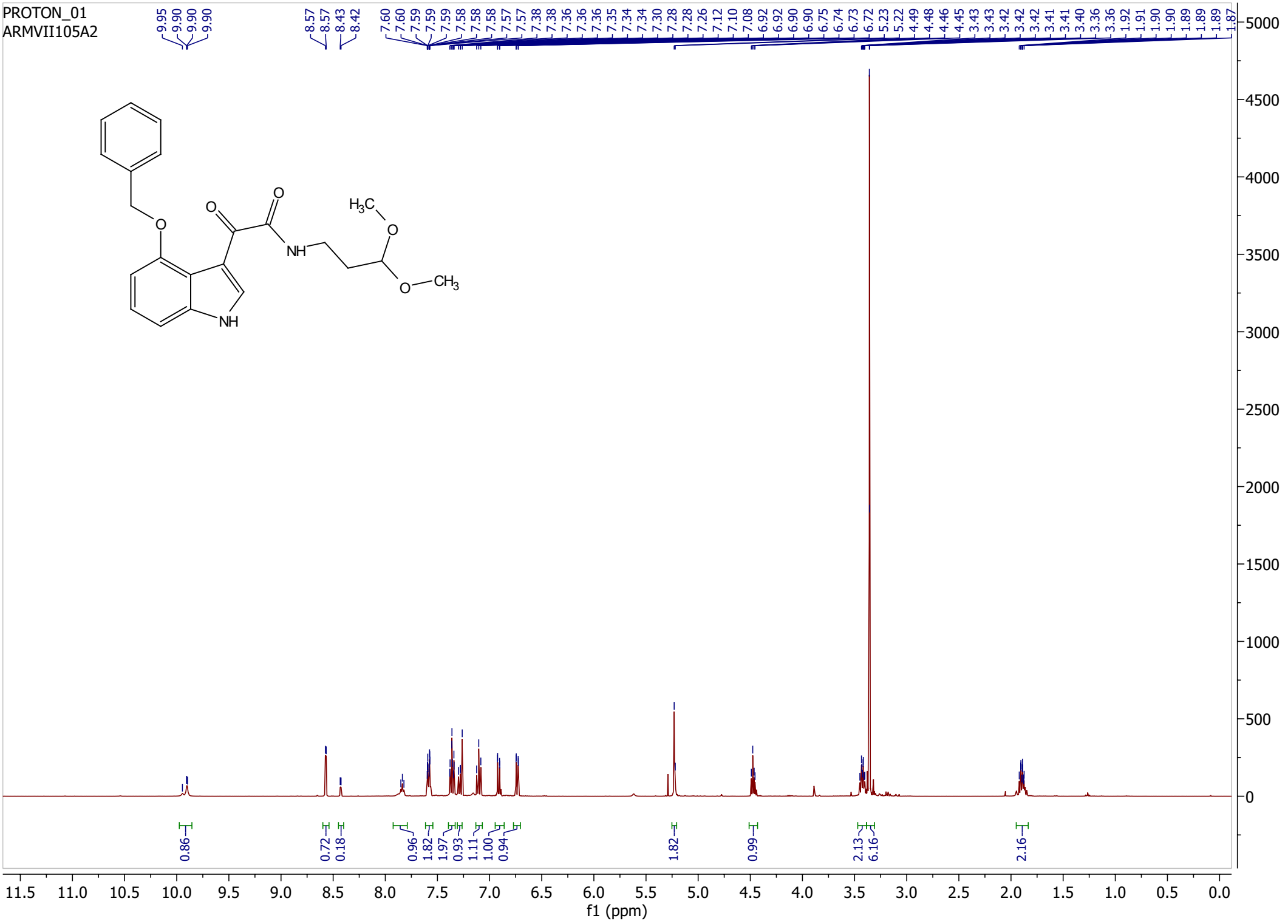

arm\VI98_h1
ARMVI98
7.46 7.46 7.46 7.38 7.38 7.37 7.37 7.36 7.36 7.35 7.35 7.31 7.31 7.30 7.29 7.29 7.28 7.25 7.24 7.24 7.24 7.23 7.14 7.13 7.08 7.08 7.00 6.99 6.94 6.93 6.92 6.92 5.11 4.27 4.26 4.25 3.79 3.79 3.78 3.77 3.77 3.51 3.50 3.50 3.41 3.36 3.33 3.21 3.20 3.19 3.10 3.09 3.07 3.06 3.05 3.04 2.99 2.98 2.97 2.97 2.97 2.93 2.93 2.92 2.91 2.67 2.67 2.66 2.66 2.65 2.65 2.64 2.64 2.07 1.32 1.31
HN
O
N
H
CH3
OH
N
CH3
H
Cl
Cl
1.03 2.00 2.11 1.21 1.92 0.98 1.83 0.95 1.00 2.19 0.92 0.91 0.96 0.90 1.04 0.95 0.95 1.09 1.18 1.00 0.93 2.79 3.08
f1 (ppm)

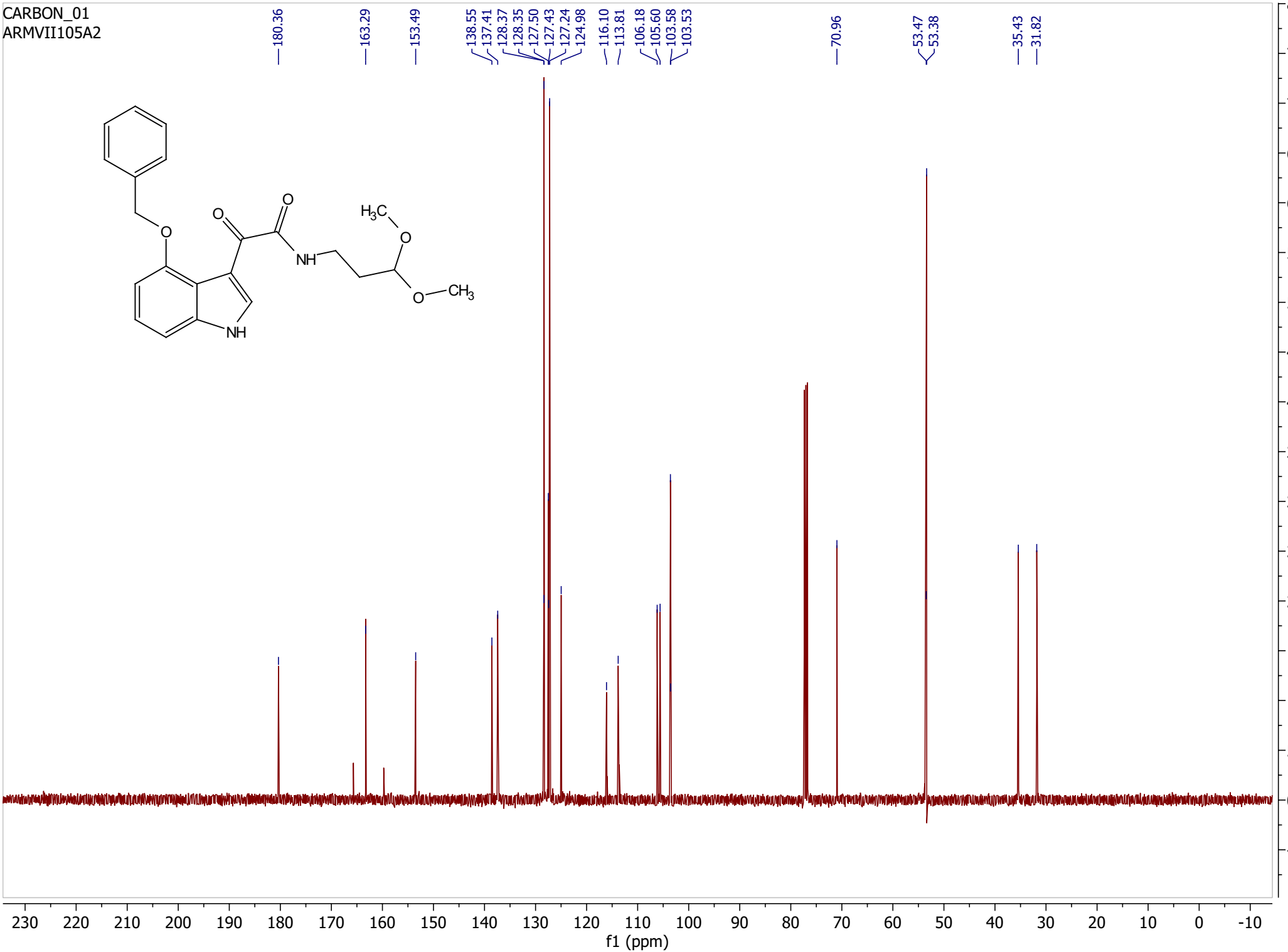
armVI98_c13
ARMVI98



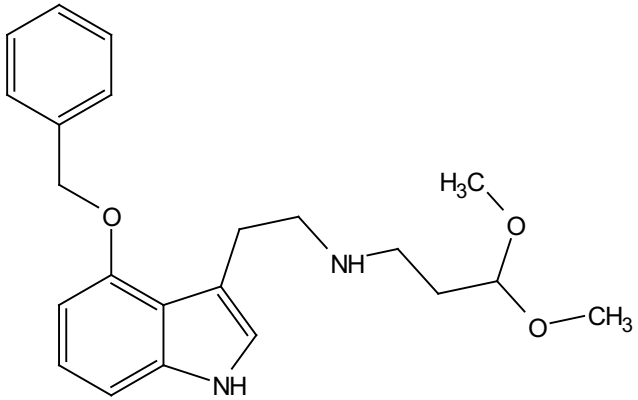
169.83
153.12
137.64
135.14
131.62
128.48
128.47
127.83
127.77
127.76
127.58
127.13
122.99
112.75
112.48
111.94
102.43
71.03
66.45
60.29
57.60
50.14
47.19
45.32
38.55
23.14
22.53
21.75

f1 (ppm)

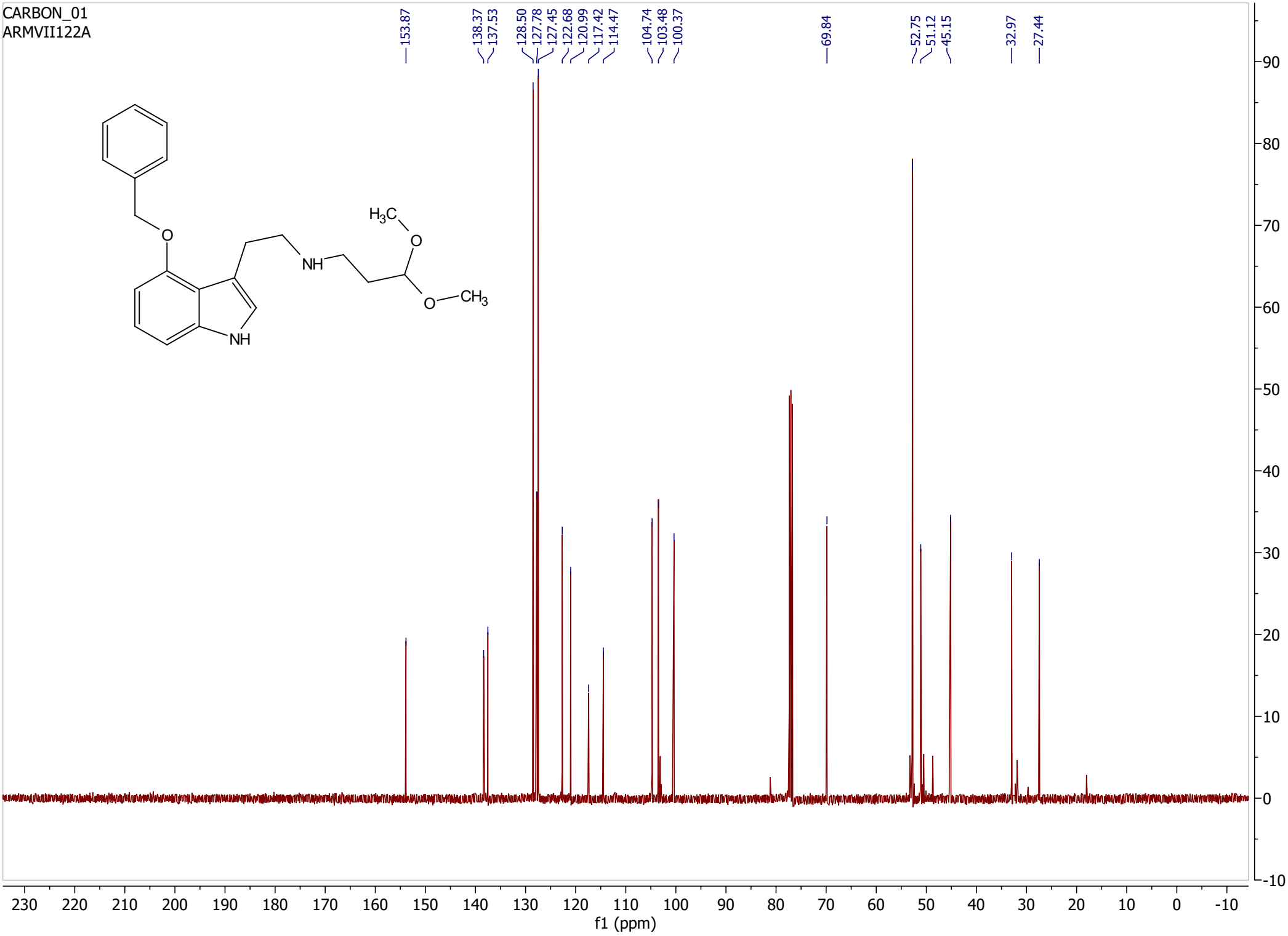

PROTON_01
ARMVII105A2
f1 (ppm)

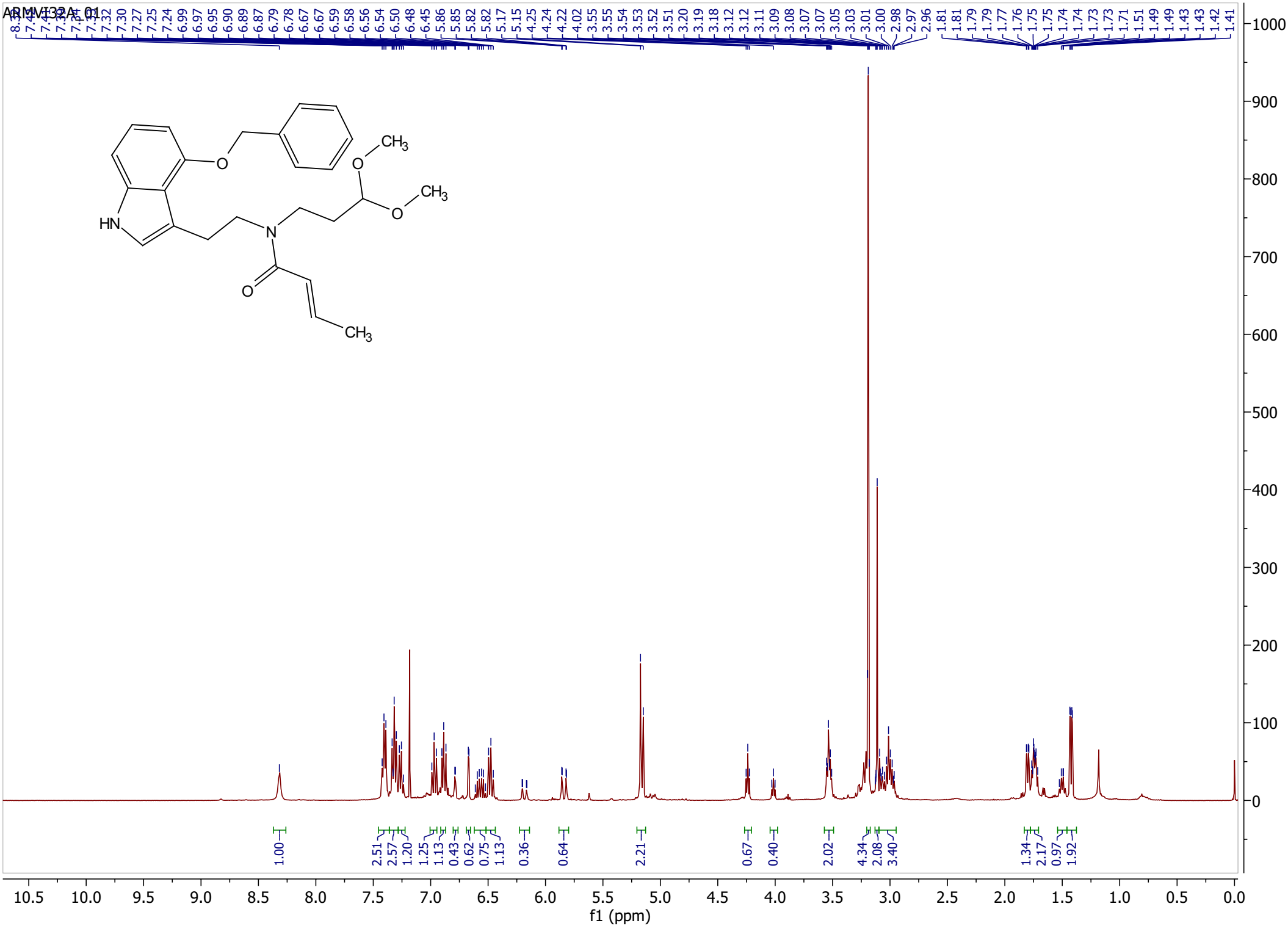

CARBON_01
ARMVII105A2
180.36
163.29
153.49
138.55
137.41
128.37
128.35
127.50
127.43
127.24
124.98
116.10
113.81
106.18
105.60
103.58
103.53
70.96
53.47
53.38
35.43
31.82
O
O
O
NH
H3C
O
O
CH3
NH
f1 (ppm)

PROTON_01
ARMVII122A

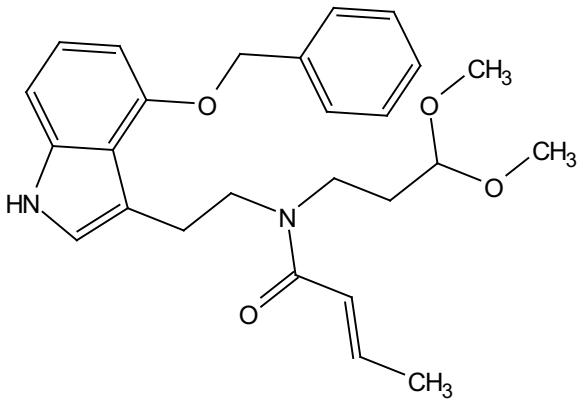


f1 (ppm)


CARBON_01
ARMVII122A
153.87
138.37
137.53
128.50
127.78
127.45
122.68
120.99
117.42
114.47
104.74
103.48
100.37
69.84
52.75
51.12
45.15
32.97
27.44
H3C
O
O
NH
O
CH3
NH
f1 (ppm)

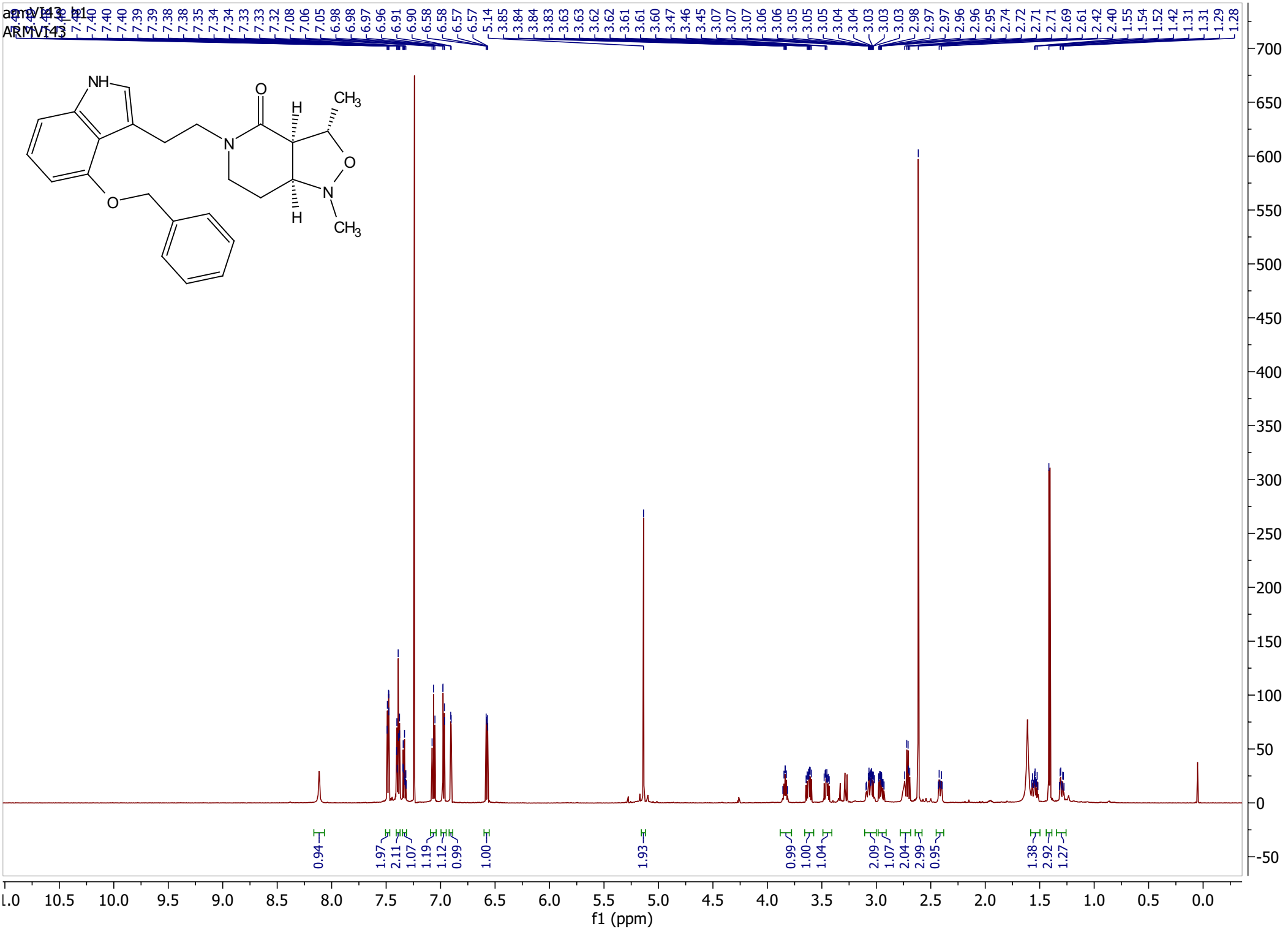

ARMVT32A-01
HN
O
O
CH3
O
CH3
N
O
CH3
f1 (ppm)

ARMVI32A_02

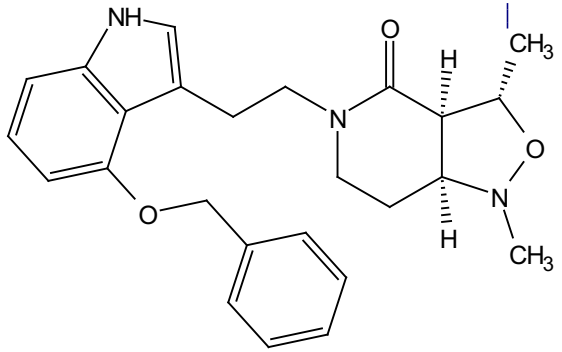


166.86
153.51
141.37
140.20
138.35
137.35
128.61
127.92
127.51
127.30
122.79
121.86
117.41
112.36
104.98
102.80
101.97
100.65
100.45
69.95
52.94
52.80
49.69
48.78
43.76
42.68
32.16
30.79
27.04
18.24
17.78

f1 (ppm)

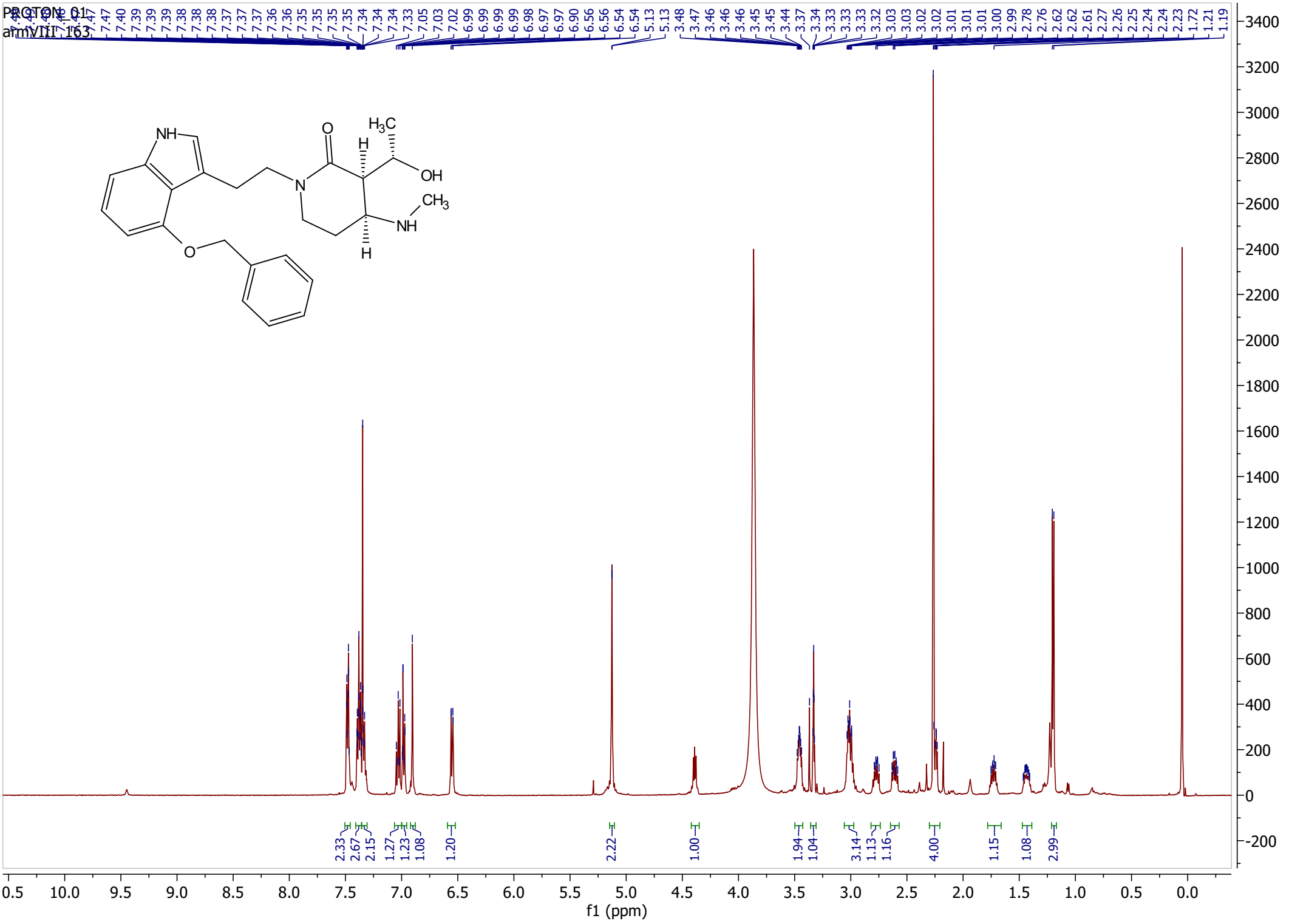

ARMVI43
NH
O
H
CH3
N
O
N
H
CH3
O
f1 (ppm)

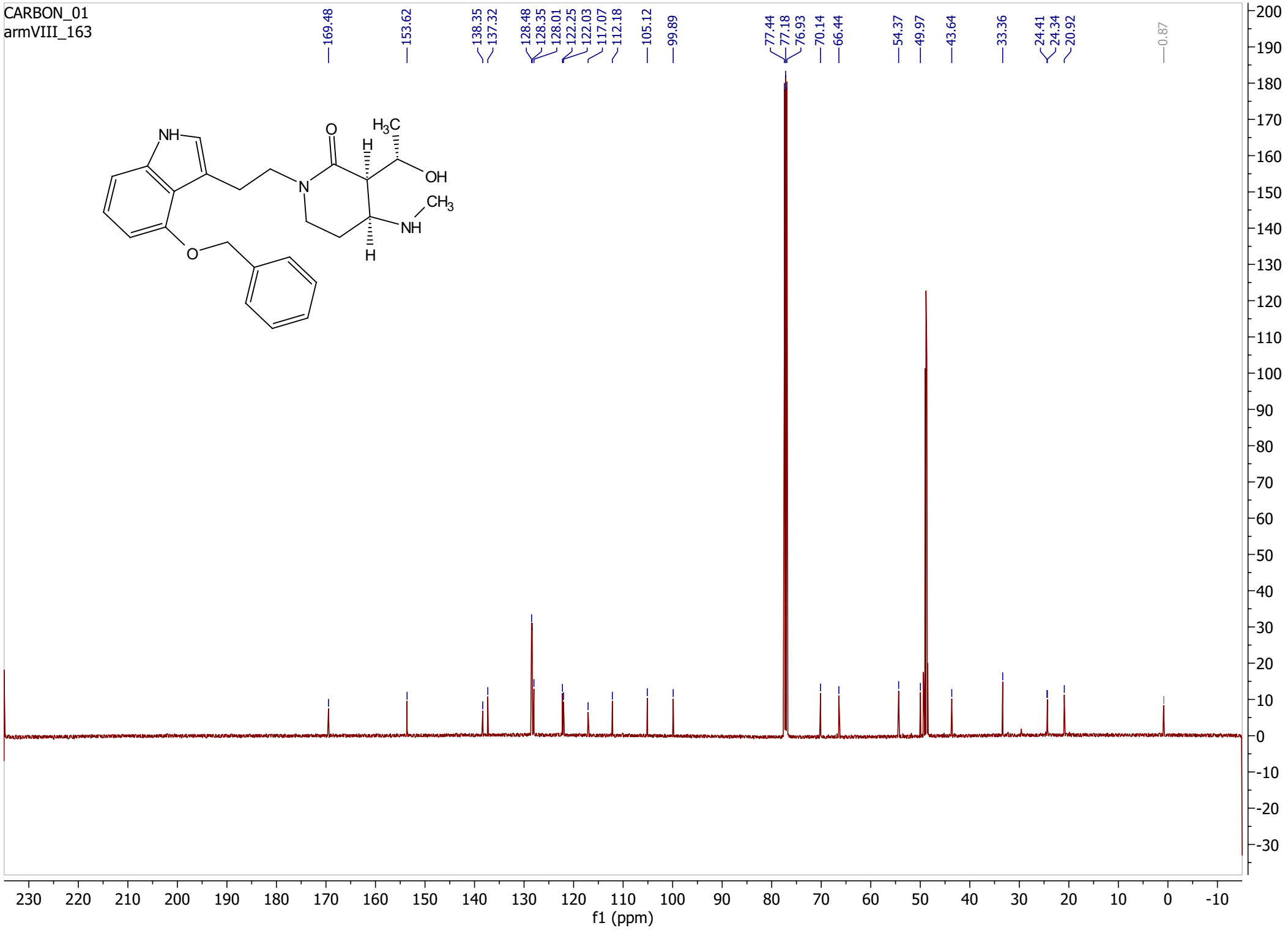
armVI43_c13
ARMVI43

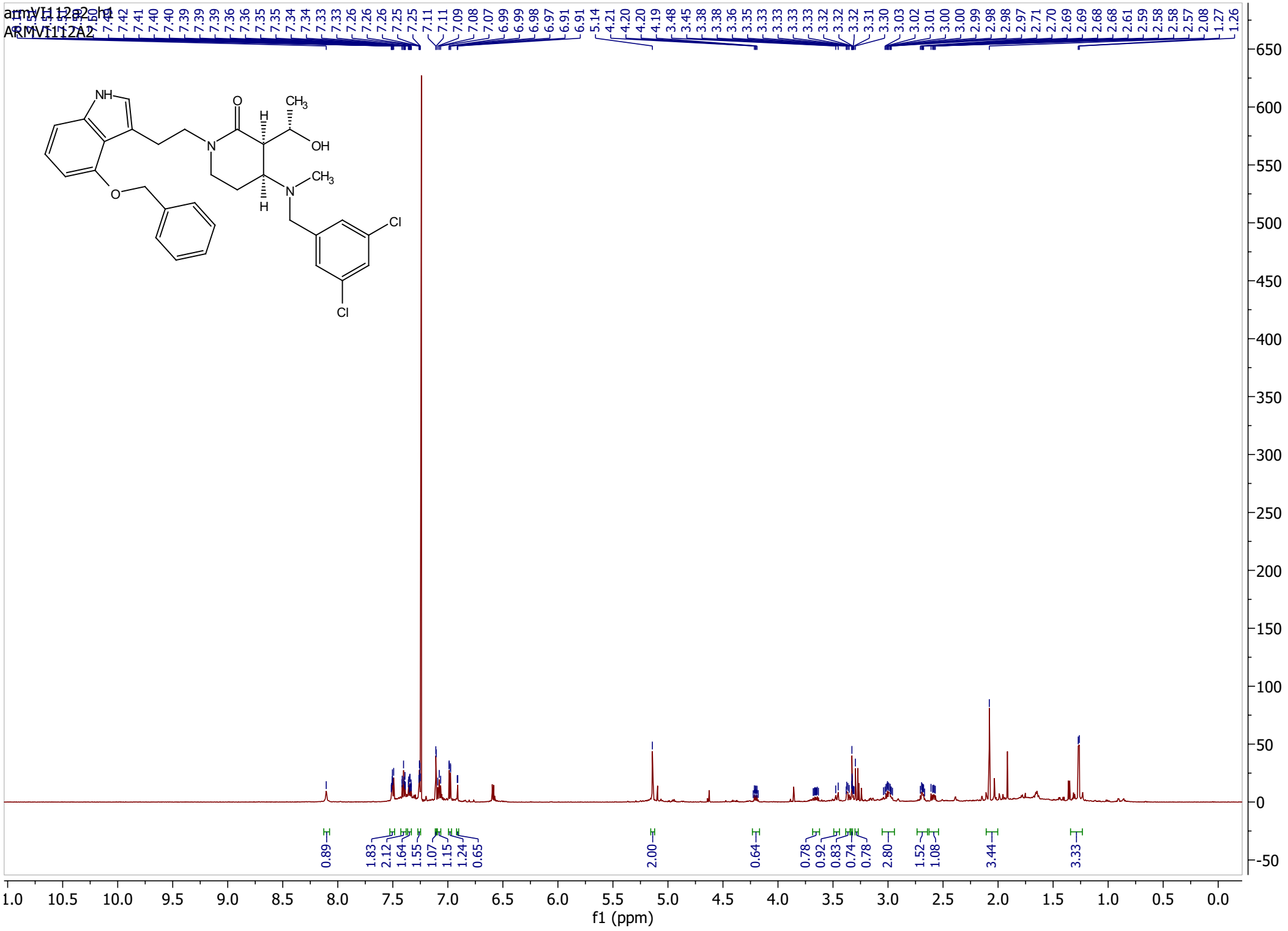


168.71
153.78
138.23
137.23
128.60
128.41
128.05
122.71
121.62
117.20
113.28
104.92
100.29
77.48
77.21 cdcl3
77.00 cdcl3
76.79 cdcl3
70.20
55.23
49.69
43.17
25.02

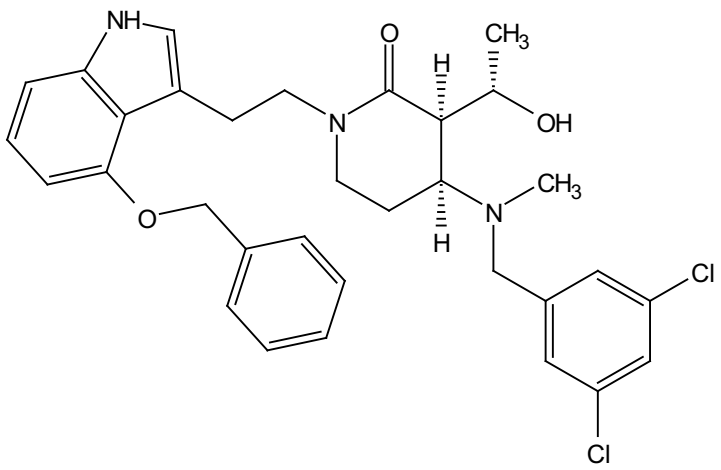
f1 (ppm)


PROTON 01
amVII 163
NH
O
H3C
H
OH
N
CH3
NH
H
O
f1 (ppm)


CARBON_01
armVIII_163
169.48
153.62
138.35
137.32
128.48
128.35
128.01
122.25
122.03
117.07
112.18
105.12
99.89
77.44
77.18
76.93
70.14
66.44
54.37
49.97
43.64
33.36
24.41
24.34
20.92
0.87
NH
O
H
H3C
OH
N
CH3
NH
H
O
f1 (ppm)


ARMVI112A2
NH
O
CH3
H
OH
N
CH3
O
N
H
Cl
Cl
0.89
1.83
2.12
1.64
1.55
1.07
1.15
1.24
0.65
2.00
0.64
0.78
0.92
0.83
0.74
0.78
2.80
1.52
1.08
3.44
3.33
f1 (ppm)

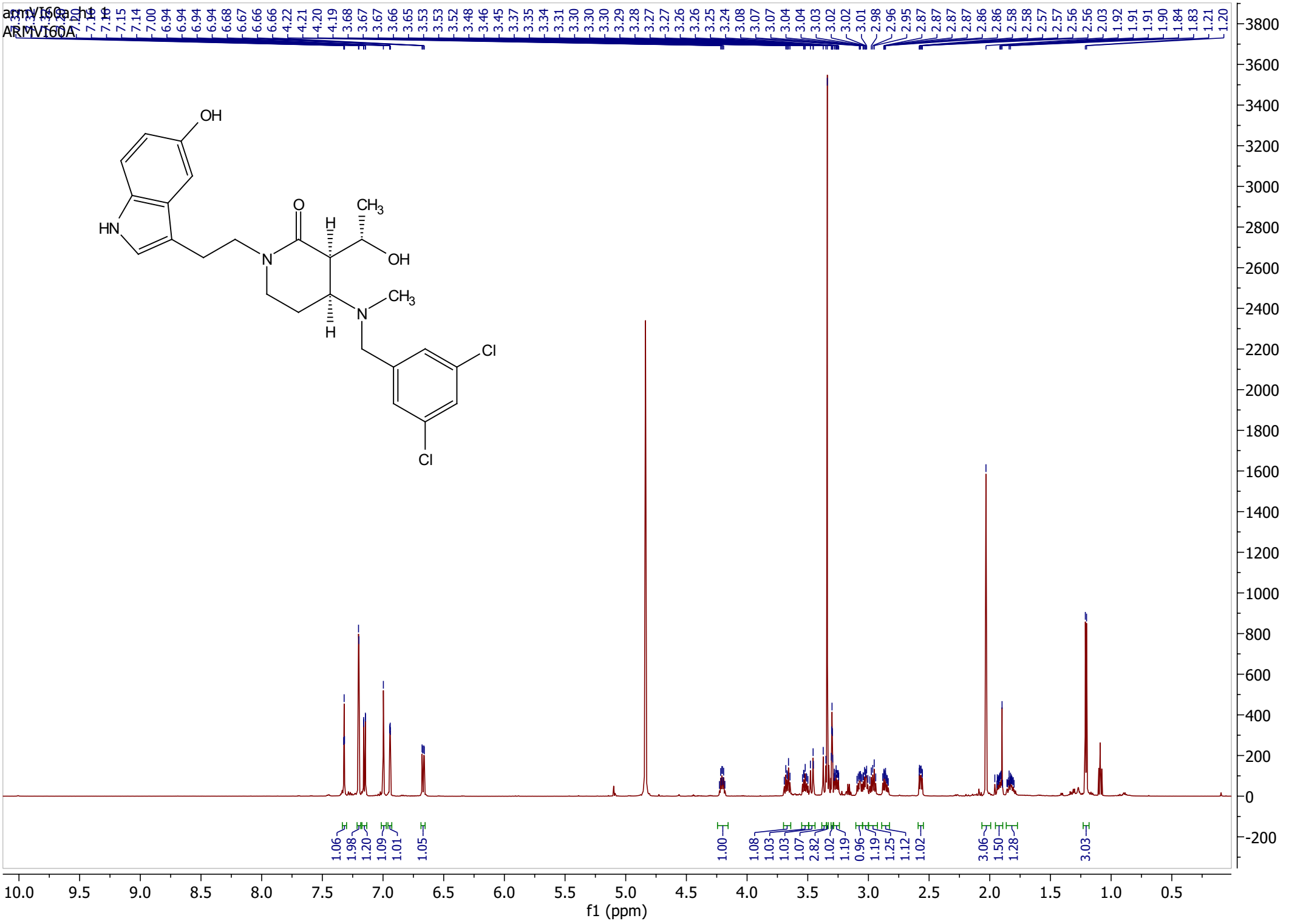
armVI112a2_c13
ARMVI112A2



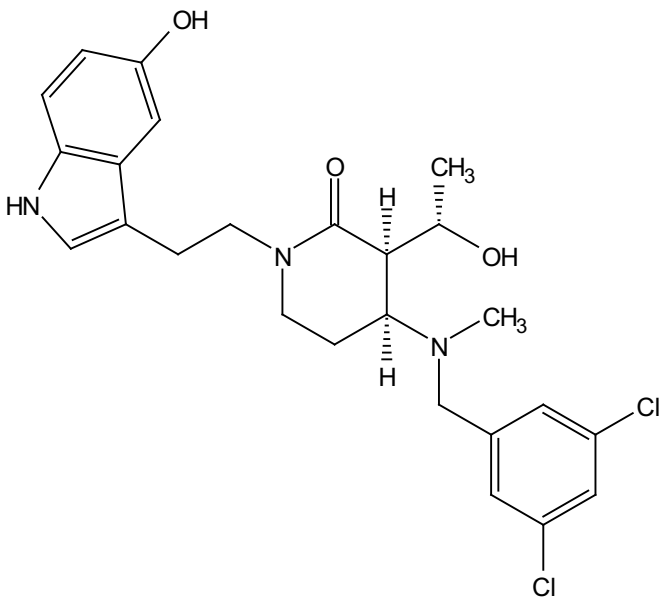
169.60
153.79
137.29
135.17
128.60
128.48
128.12
127.76
127.13
122.77
121.59
113.15
105.01
100.34
77.21 cdcl3
77.00 cdcl3
76.79 cdcl3
70.24
66.45
50.06
48.75
44.61
24.72
22.48
21.89

1000 900 800 700 600 500 400 300 200 100 0

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


ARMVI60A
OH
HN
O
H
CH3
OH
N
CH3
N
H
Cl
Cl
f1 (ppm)

armVI60a_c13
ARMVI60A

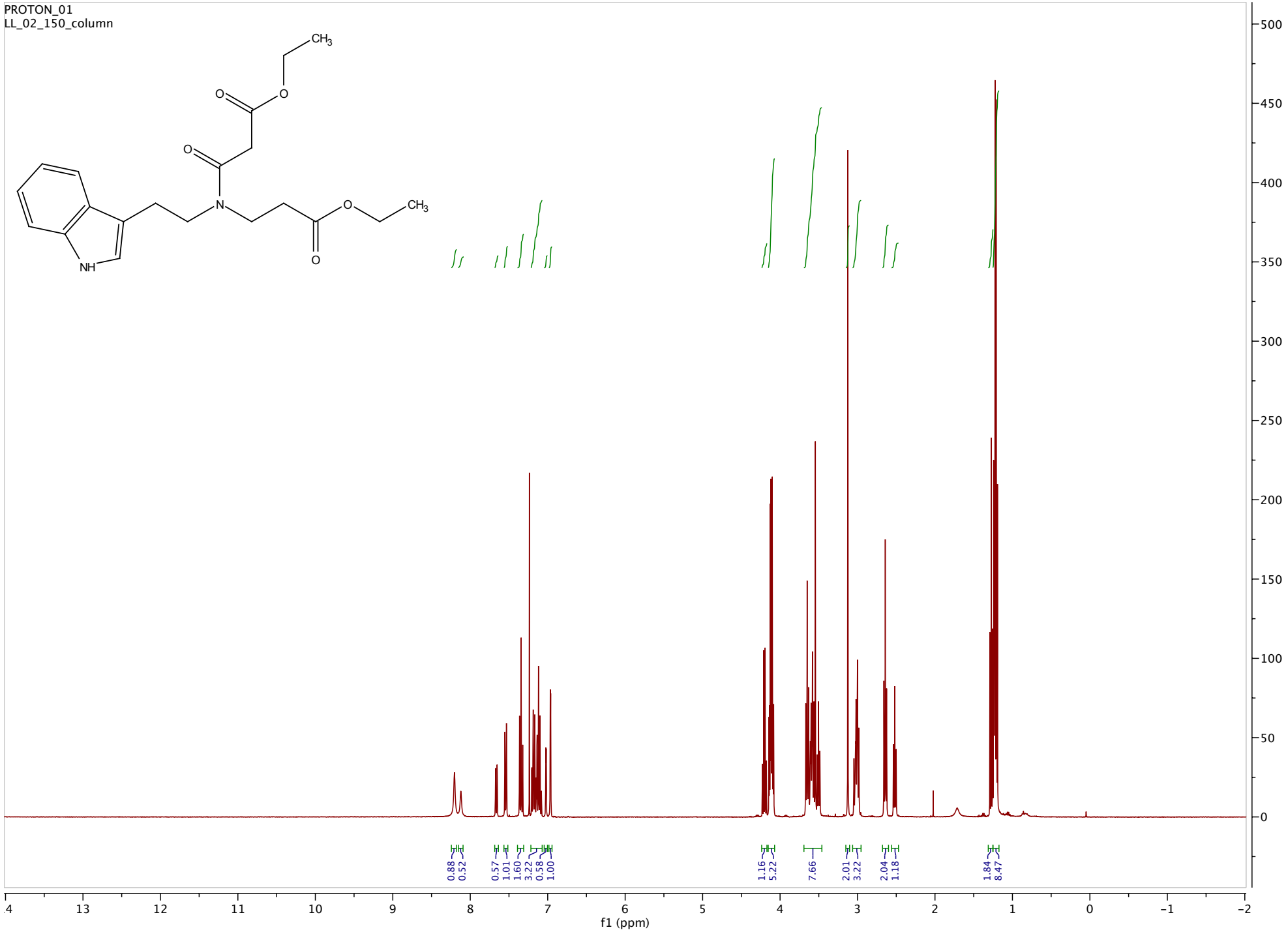


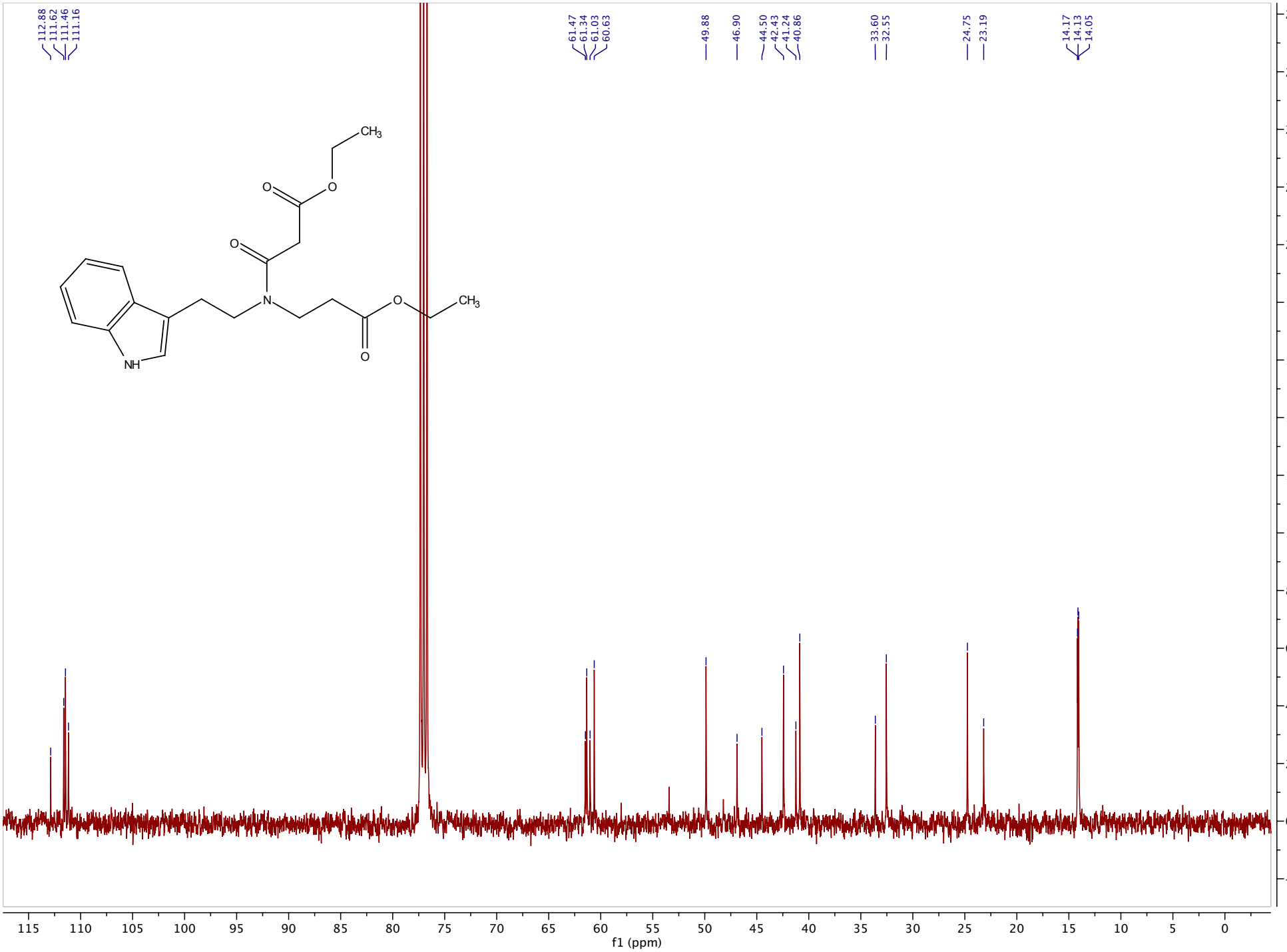
171.89 151.27 143.71 136.20 132.98 129.59 128.51 128.43 124.52 112.84 112.48 112.13 103.51 67.71 61.18 58.44 51.14 49.28 cd3od 49.14 cd3od 49.00 cd3od 48.86 cd3od 48.72 cd3od 48.57 cd3od 46.62 38.47 24.00 22.83 22.52 22.47

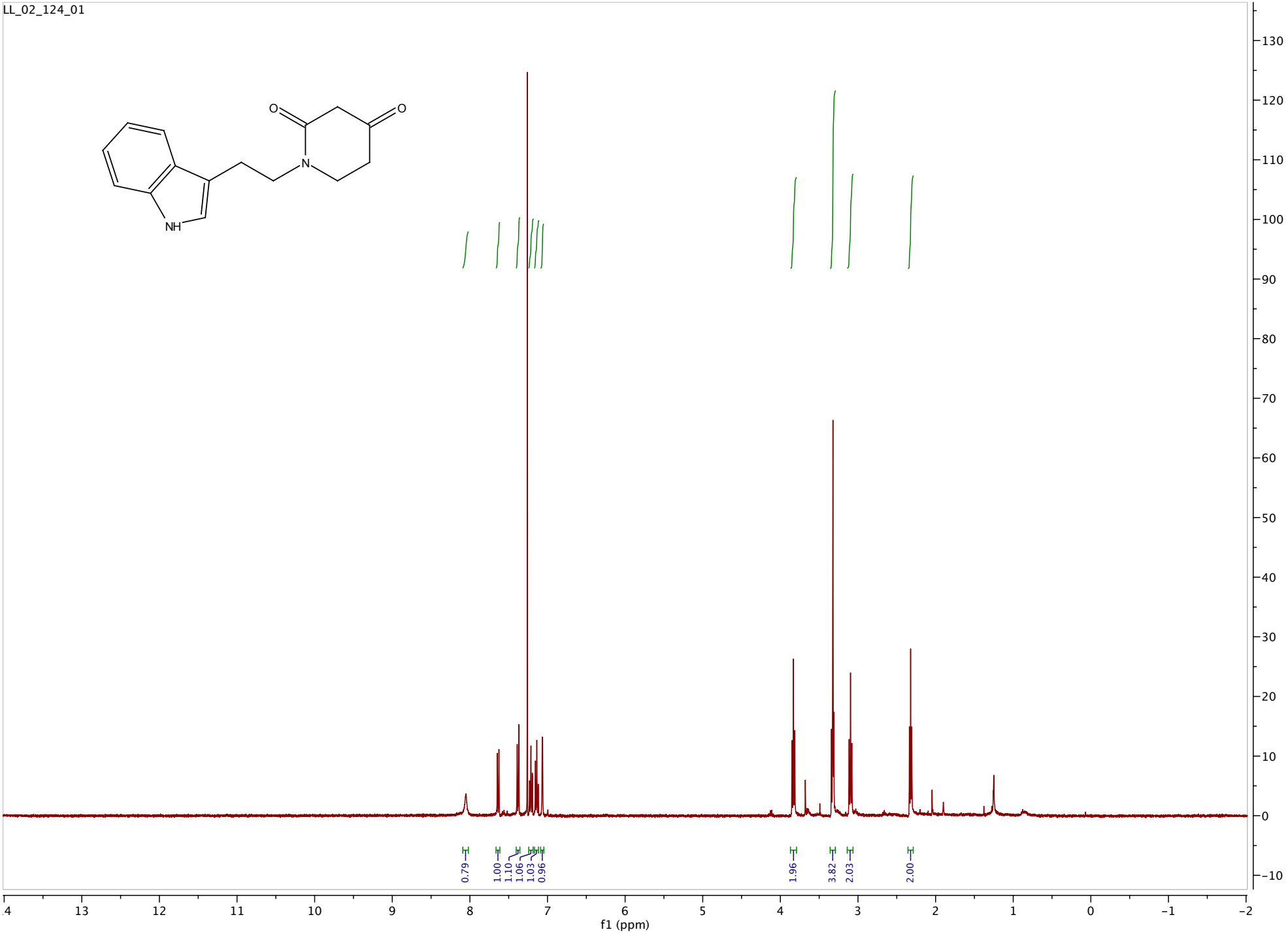
1100 1000 900 800 700 600 500 400 300 200 100 0 -100

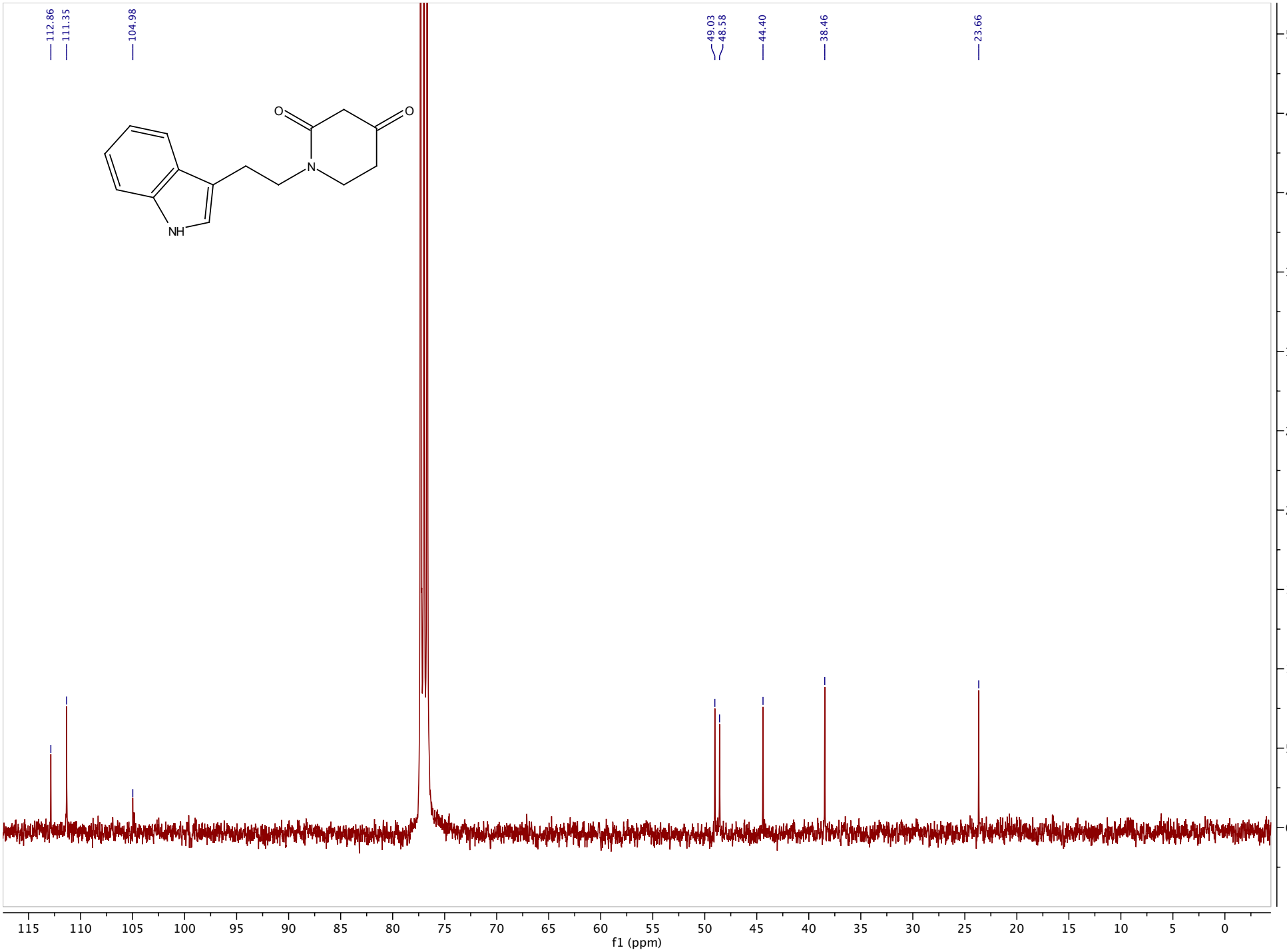
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

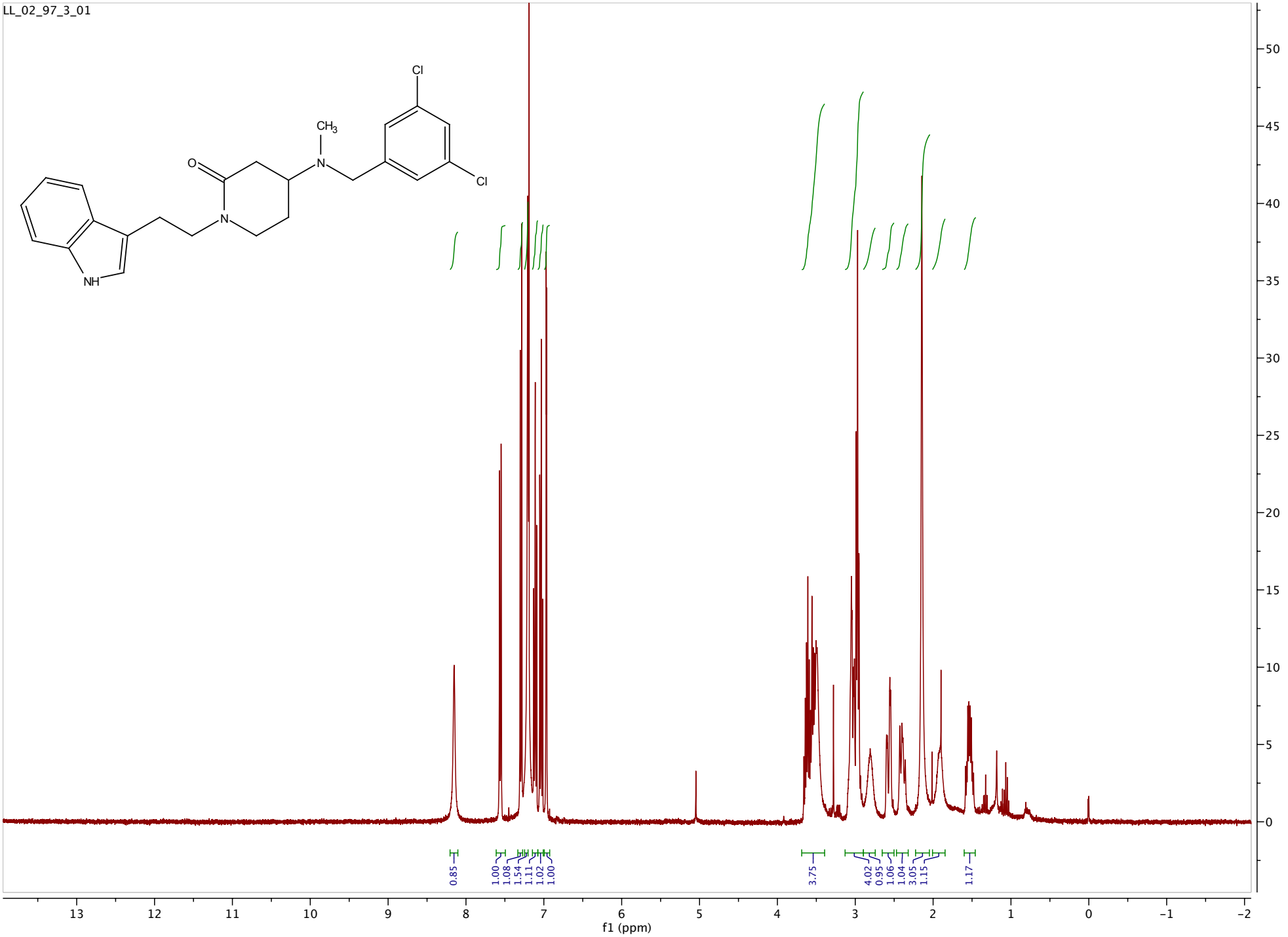
f1 (ppm)

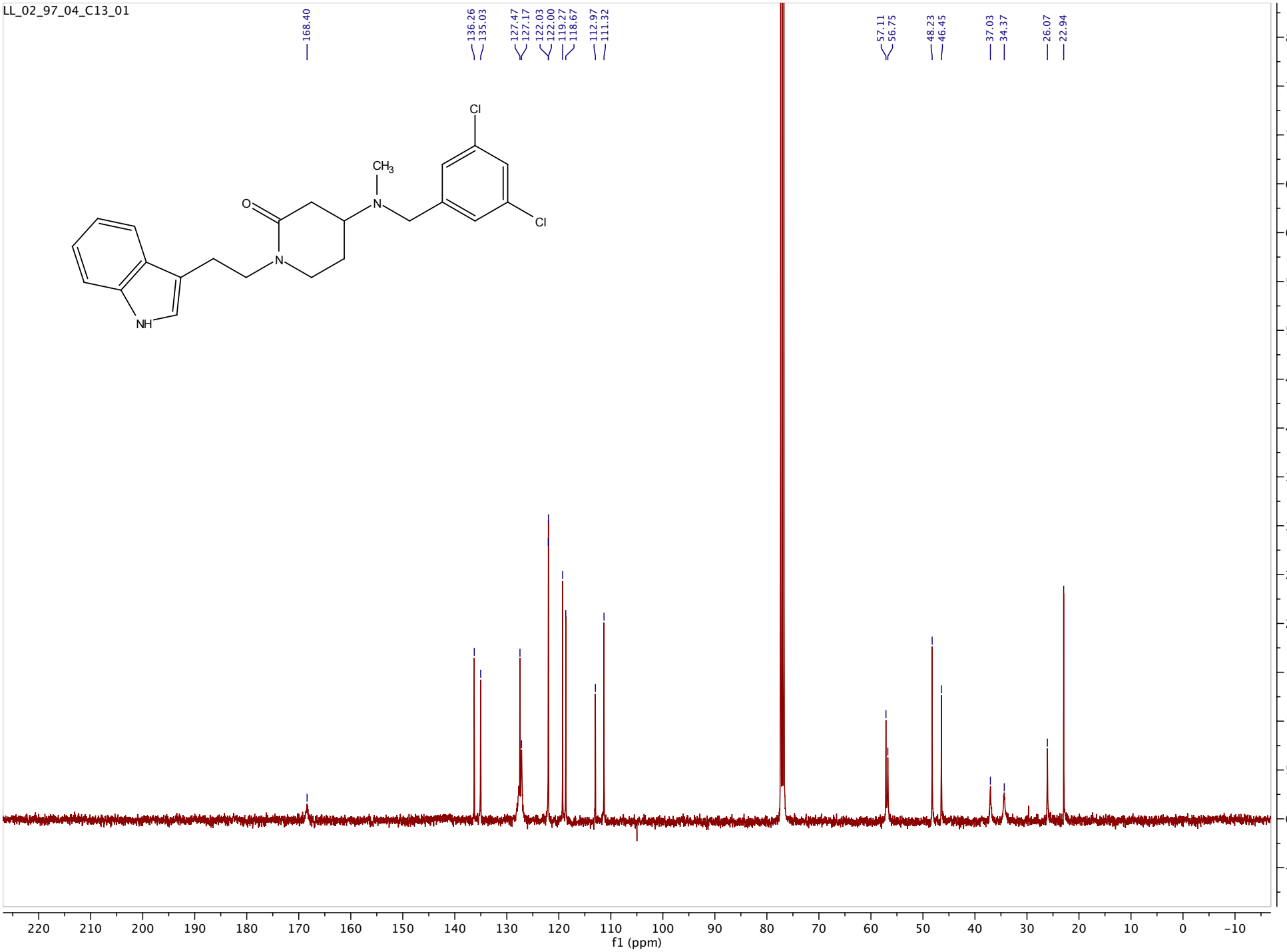

PROTON_01
LL_02_150_column
CH3
O
O
O
N
O
CH3
O
NH
0.88
0.52
0.57
1.01
1.60
3.22
0.58
1.00
1.16
5.22
7.66
2.01
3.22
2.04
1.18
1.84
8.47
500
450
400
350
300
250
200
150
100
50
0
13
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
−2
f1 (ppm)

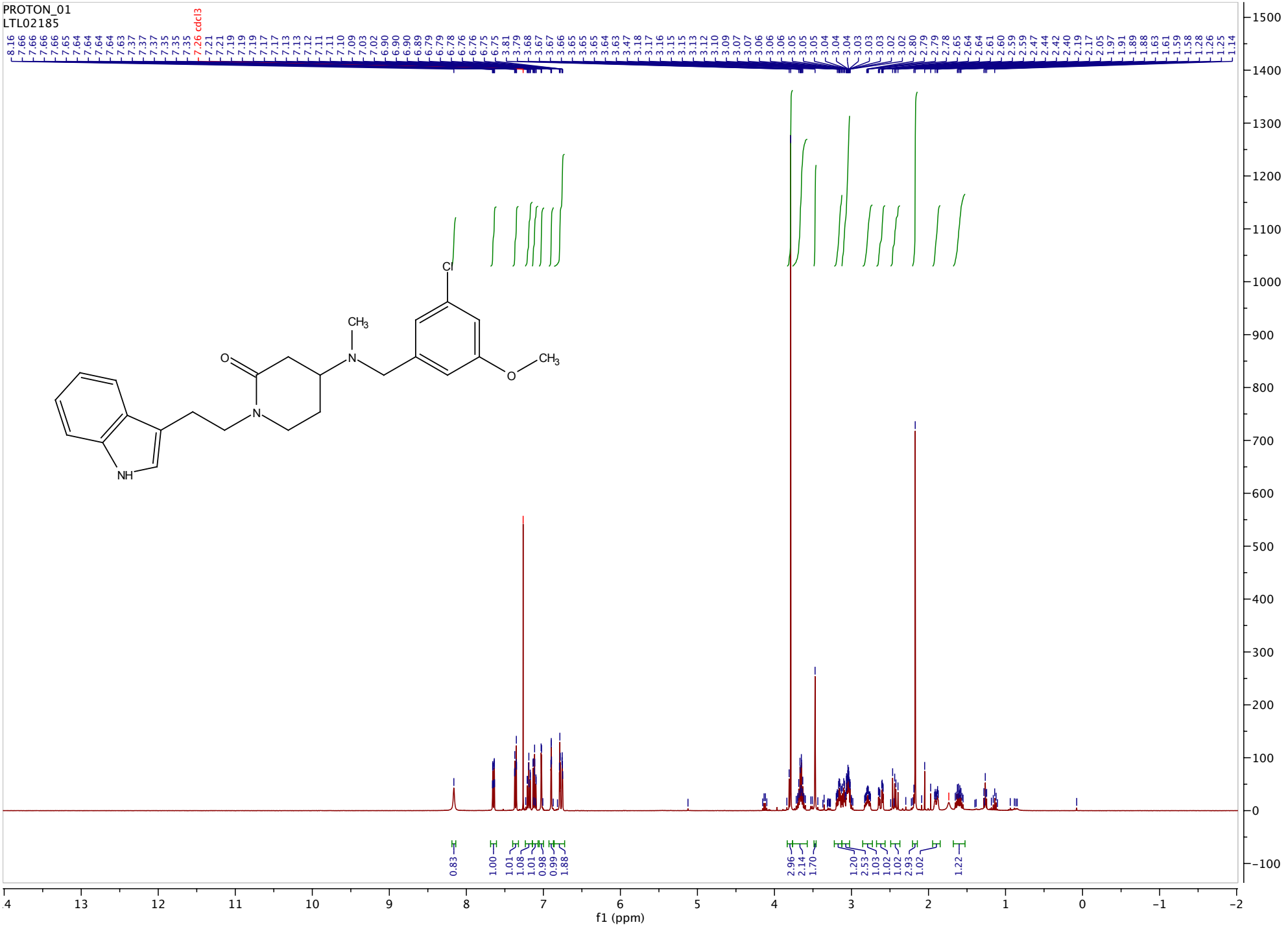

112.88
111.62
111.46
111.16
61.47
61.34
61.03
60.63
49.88
46.90
44.50
42.43
41.24
40.86
33.60
32.55
24.75
23.19
14.17
14.13
14.05
CH3
O
O
O
N
O
CH3
O
NH
f1 (ppm)

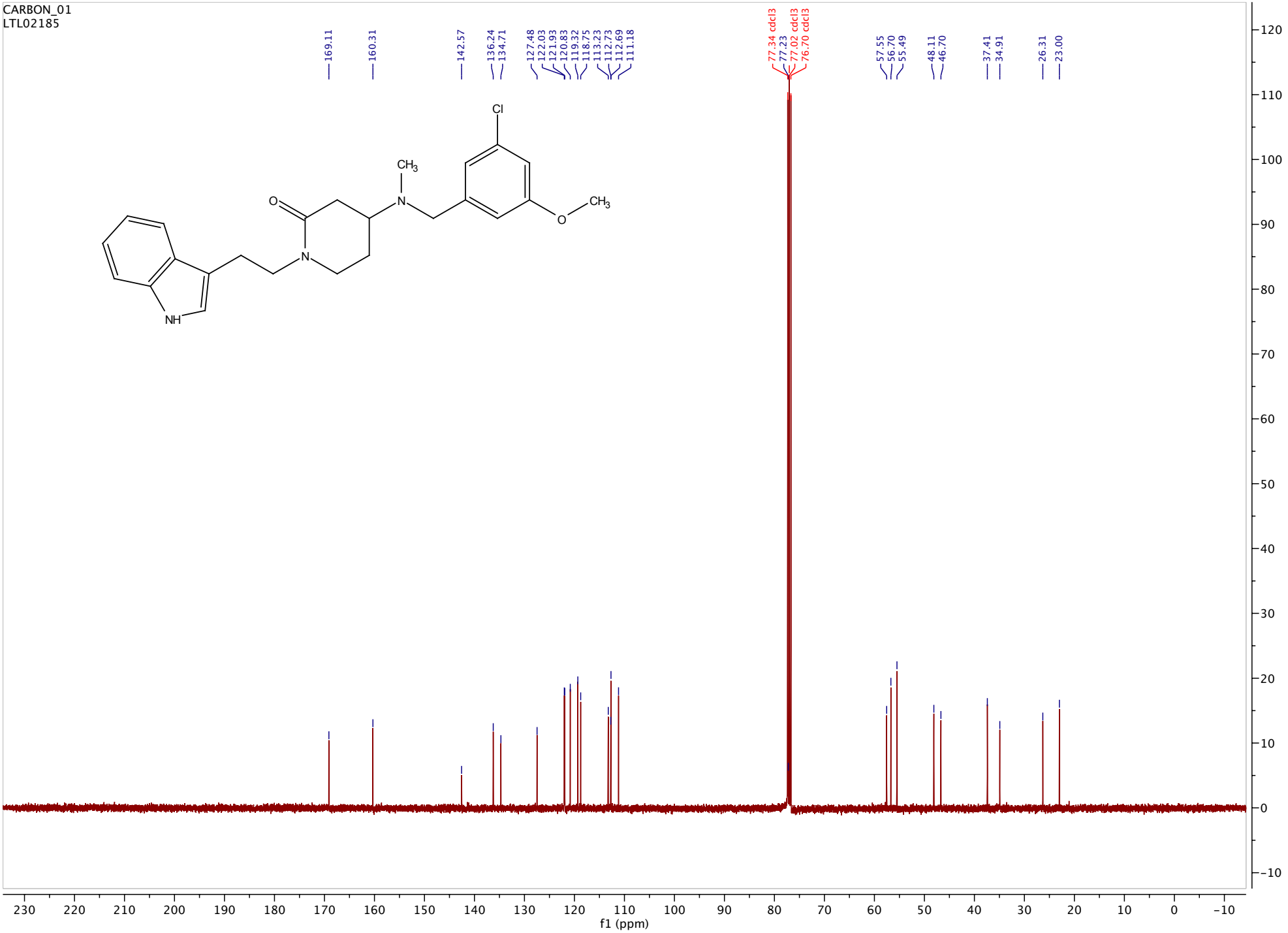

LL_02_124_01
O
O
N
NH
0.79
1.00
1.10
1.06
1.03
0.96
1.96
3.82
2.03
2.00
f1 (ppm)

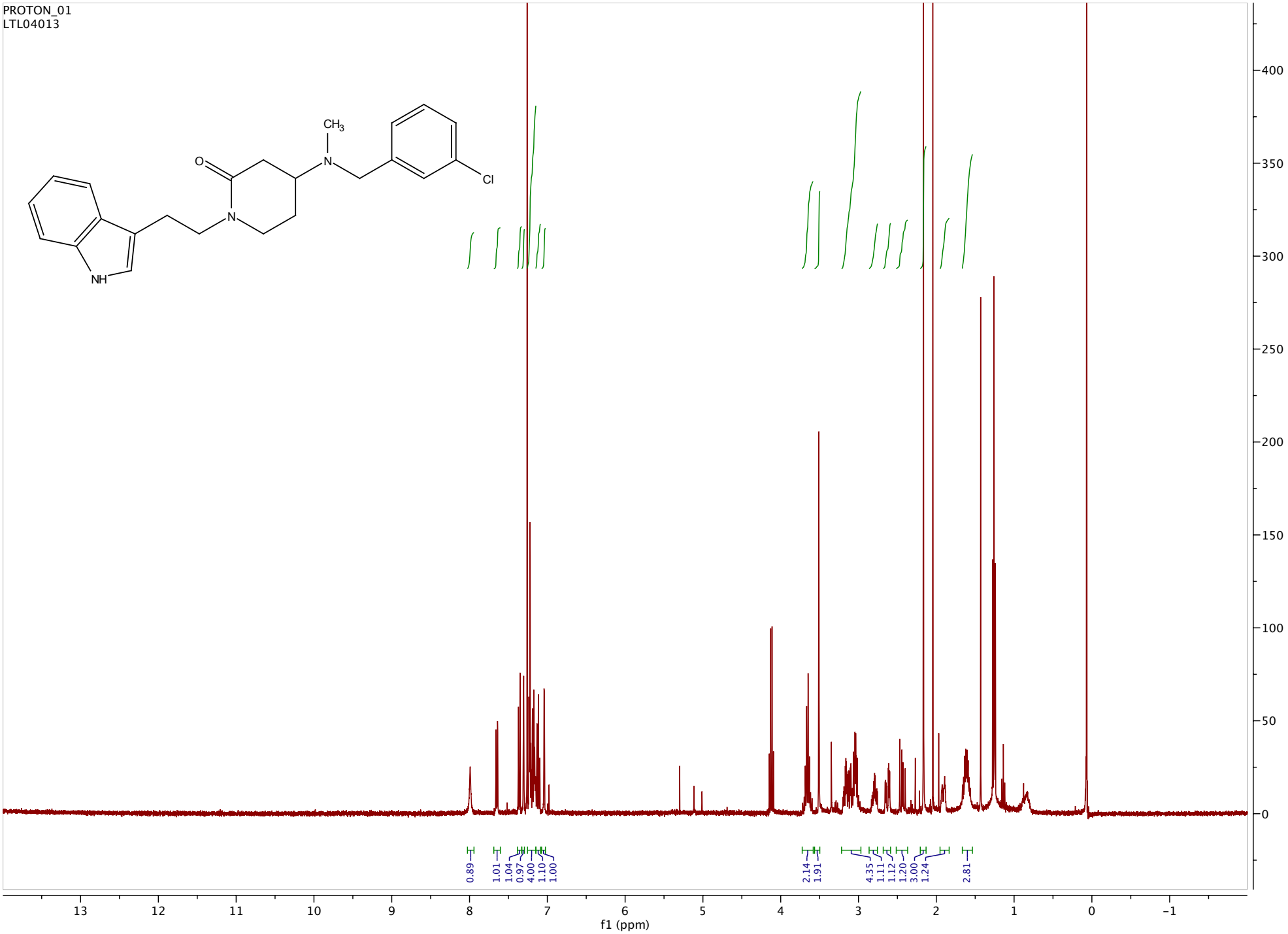

112.86
111.35
104.98
49.03
48.58
44.40
38.46
23.66
O
O
N
NH
50
45
40
35
30
25
20
15
10
5
0
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
f1 (ppm)

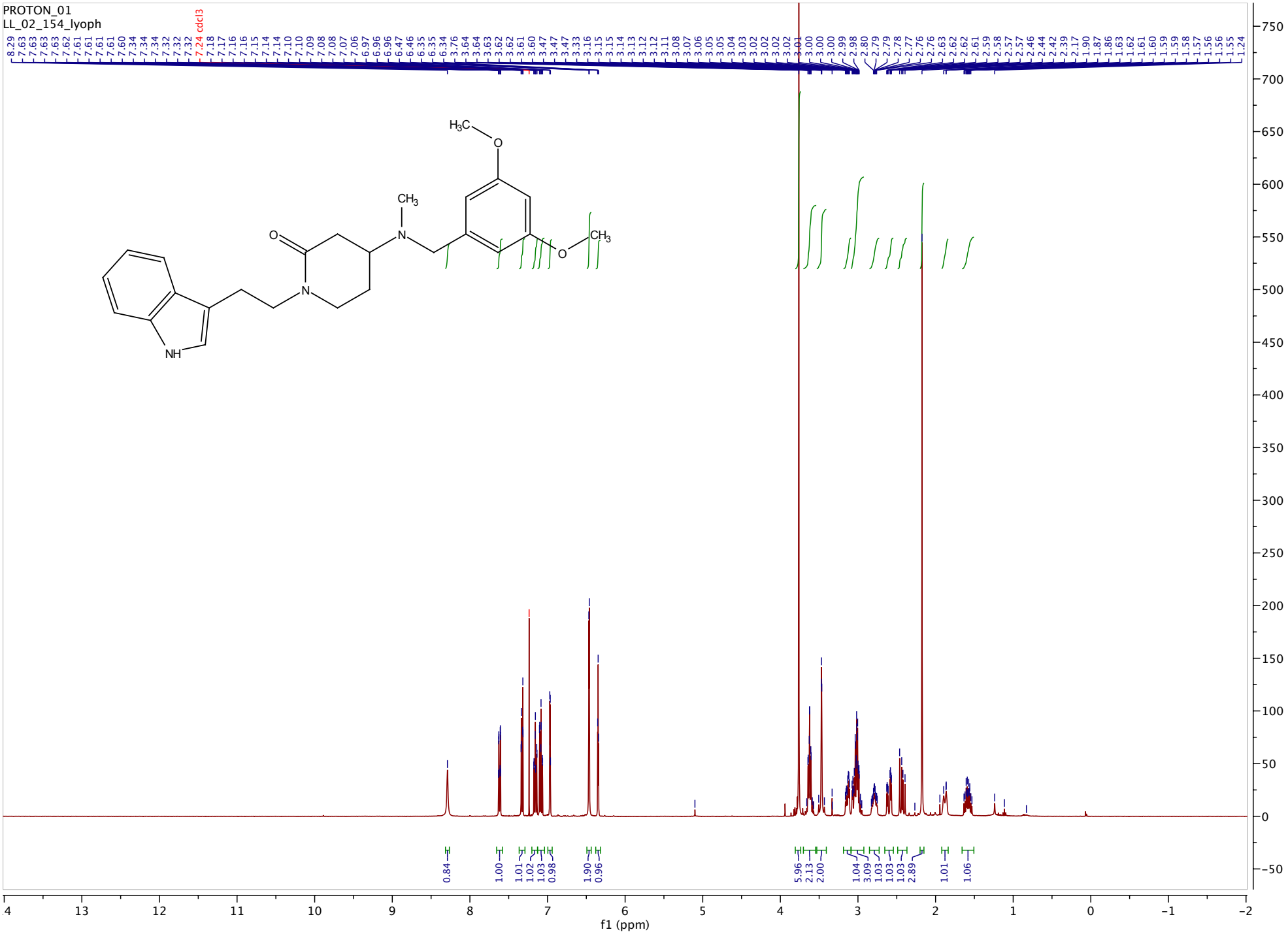

LL_02_97_3_01
Cl
CH3
O
N
Cl
N
NH
0.85
1.00
1.08
1.54
1.11
1.02
1.00
3.75
4.02
0.95
1.06
1.04
3.05
1.15
1.17
f1 (ppm)

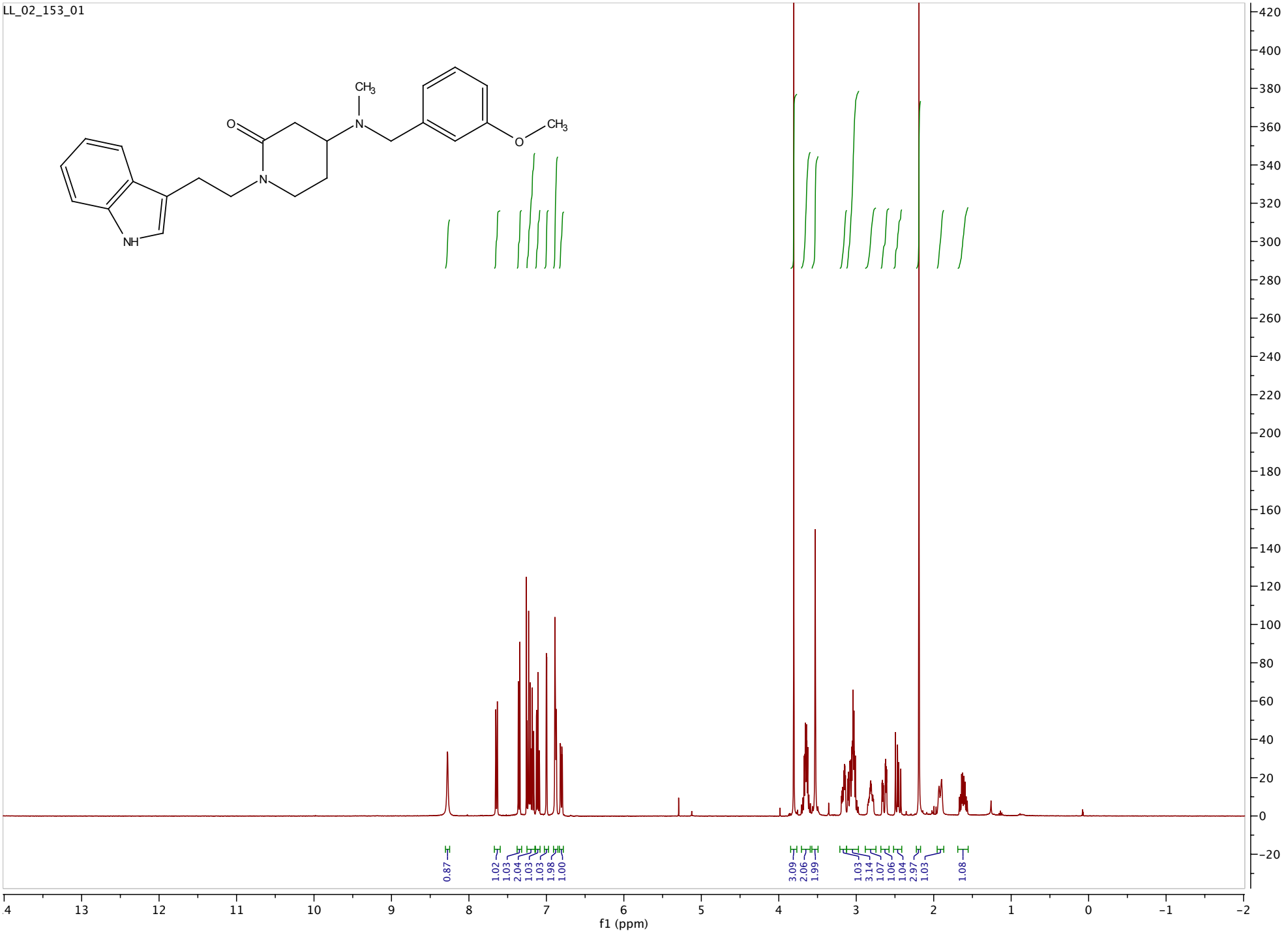

LL_02_97_04_C13_01
168.40
136.26
135.03
127.47
127.17
122.03
122.00
119.27
118.67
112.97
111.32
57.11
56.75
48.23
46.45
37.03
34.37
26.07
22.94
Cl
CH3
O
N
N
Cl
NH
f1 (ppm)

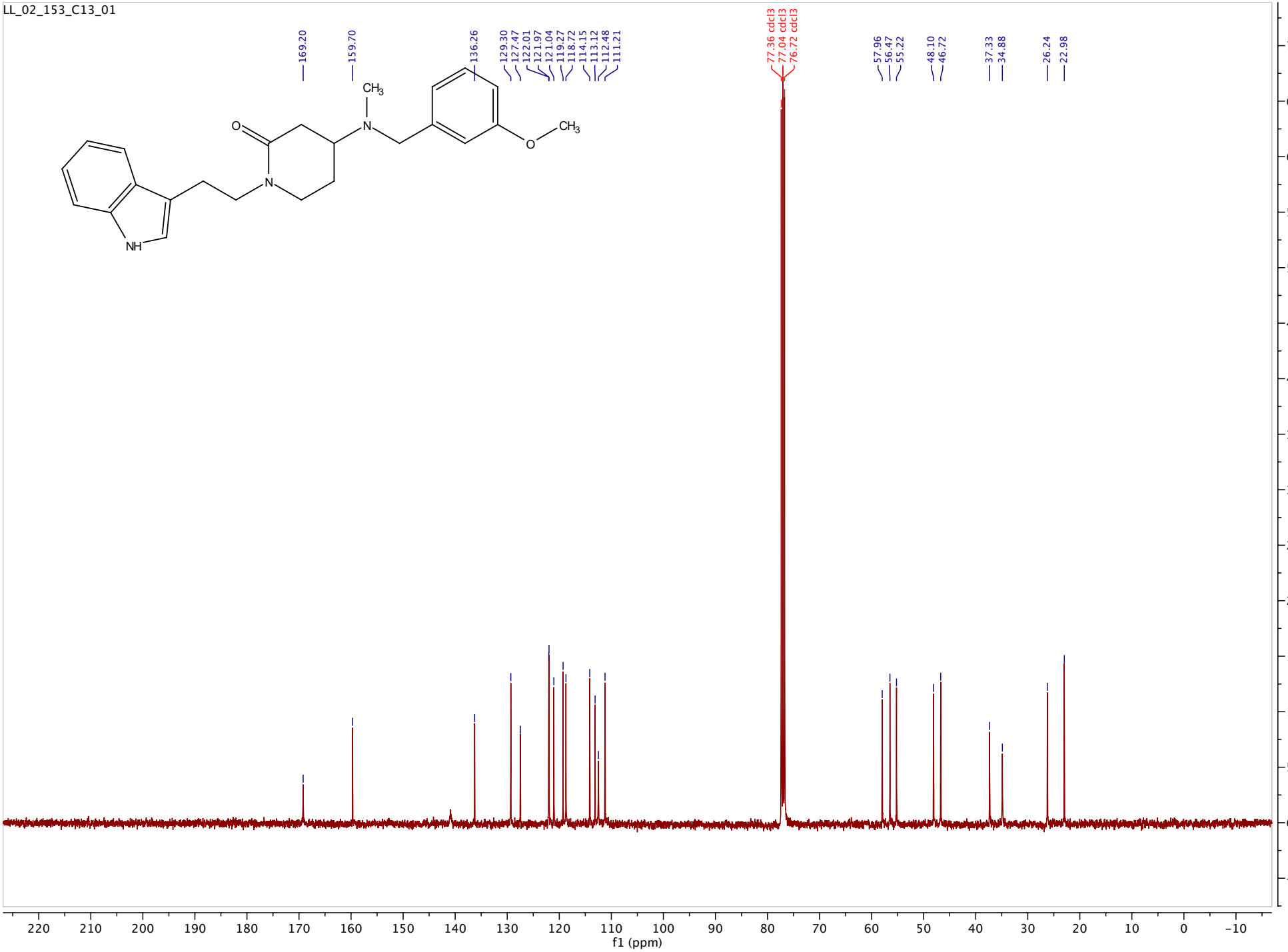

PROTON_01
LTL02185
cdcl3
Cl
CH3
O
N
O
CH3
N
NH
f1 (ppm)

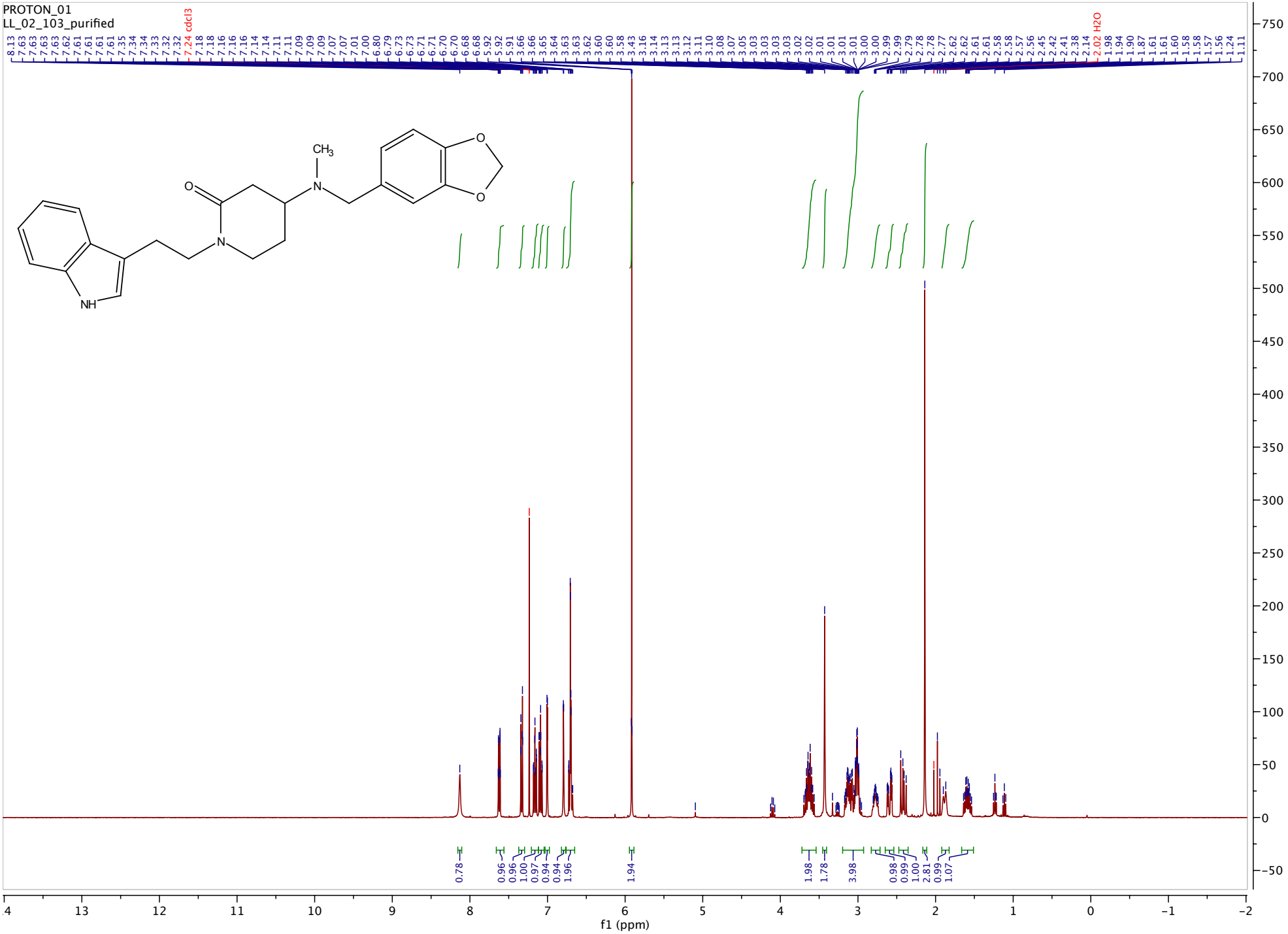

CARBON_01
LTL02185
169.11
160.31
142.57
136.24
134.71
127.48
122.03
121.93
120.83
119.32
118.75
113.23
112.73
112.69
111.18
77.34 cdcl3
77.23
77.02 cdcl3
76.70 cdcl3
57.55
56.70
55.49
48.11
46.70
37.41
34.91
26.31
23.00
Cl
CH3
O
N
CH3
O
O
N
NH
f1 (ppm)

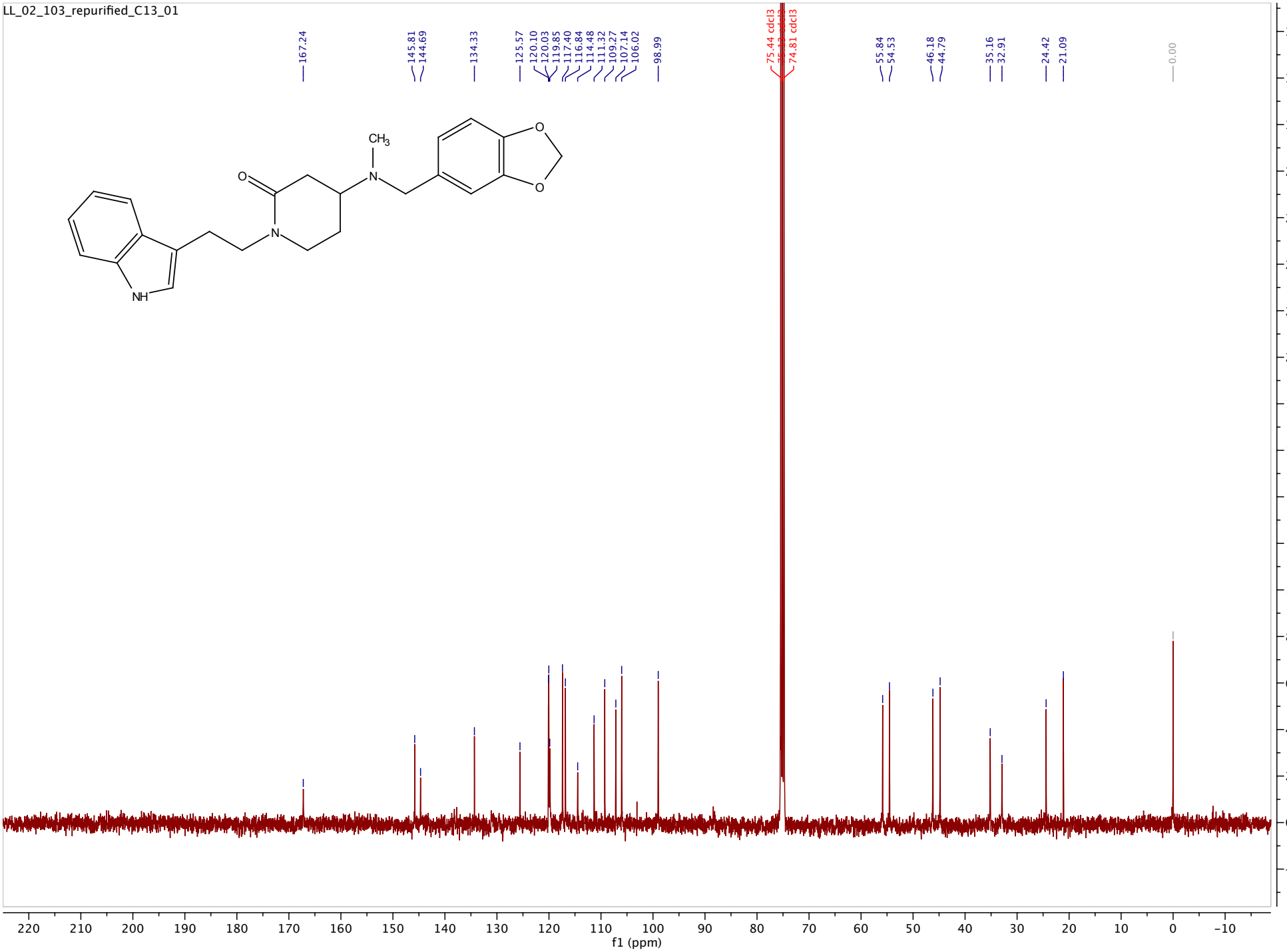

PROTON_01
LTL04013
CH3
O
N
N
Cl
NH
0.89
1.01
1.04
0.97
4.00
1.10
1.00
2.14
1.91
4.35
1.11
1.12
1.20
3.00
1.24
2.81
f1 (ppm)

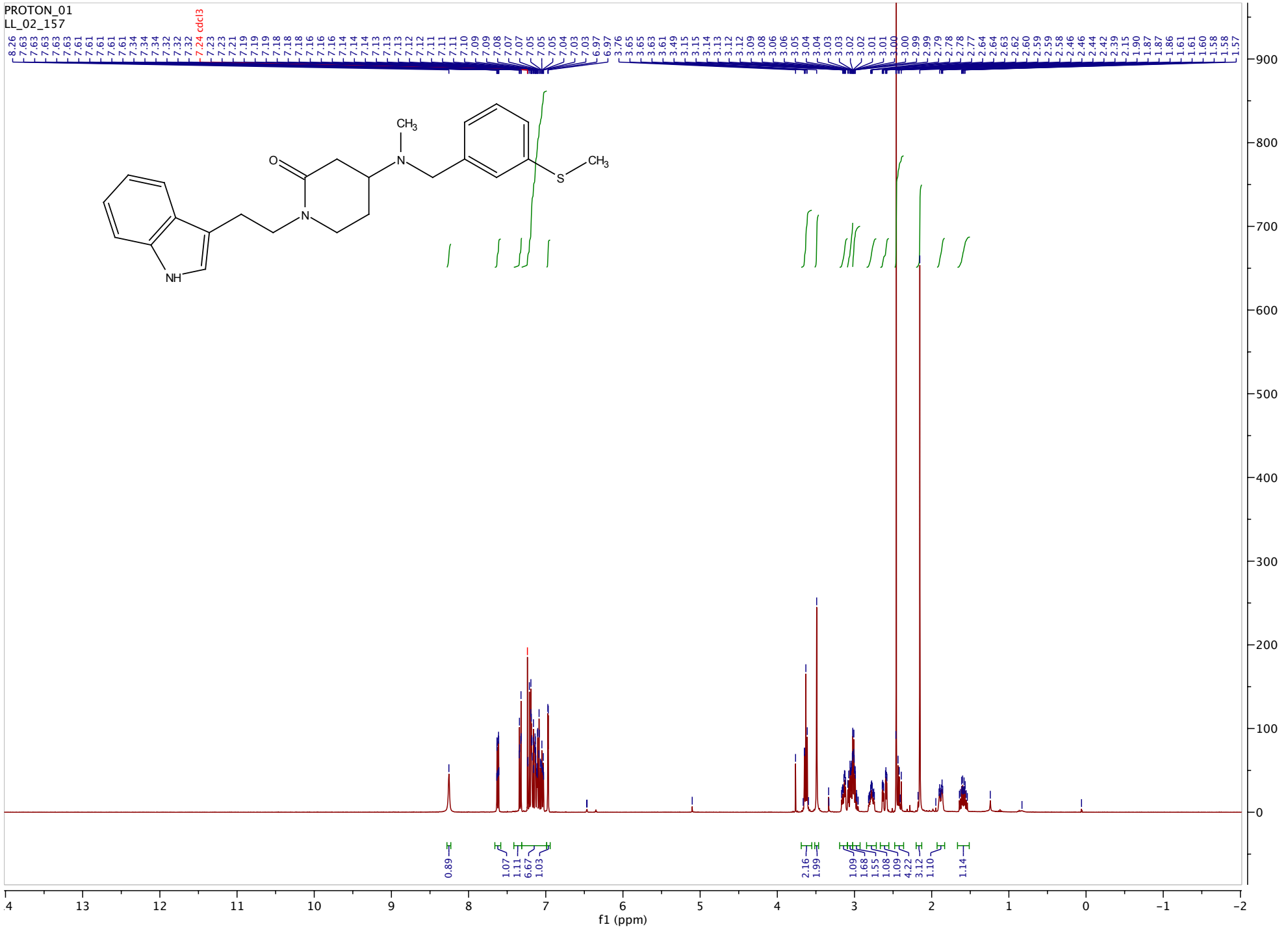

PROTON_01
LL_02_154_lyoph
cdcl3
H3C
O
CH3
N
O
CH3
O
O
N
NH
f1 (ppm)

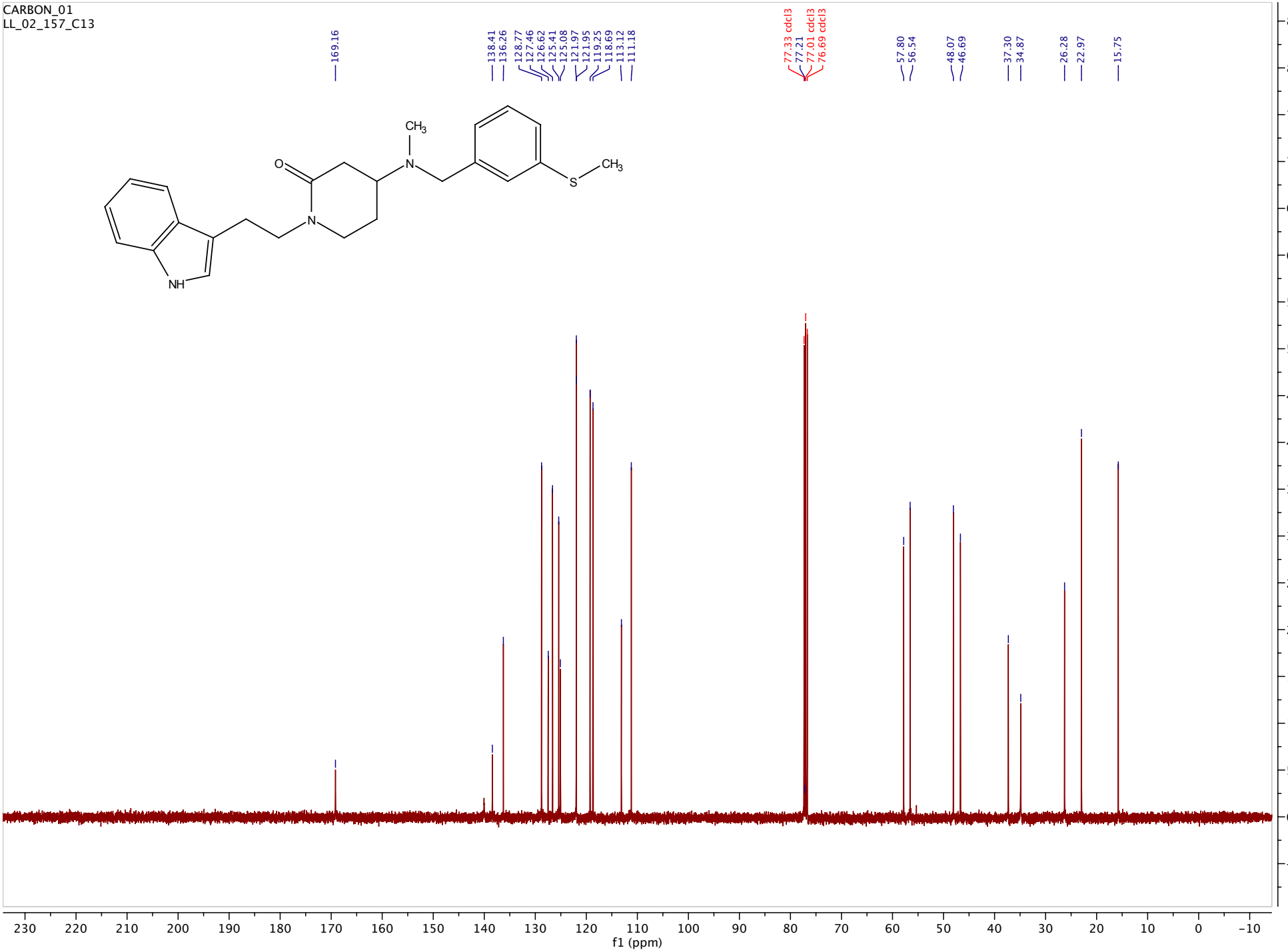

LL_02_153_01
CH3
O
N
CH3
O
N
NH
0.87
1.02
1.03
2.04
1.03
1.03
1.98
1.00
3.09
2.06
1.99
1.03
3.14
1.07
1.06
1.04
2.97
1.03
1.08
f1 (ppm)

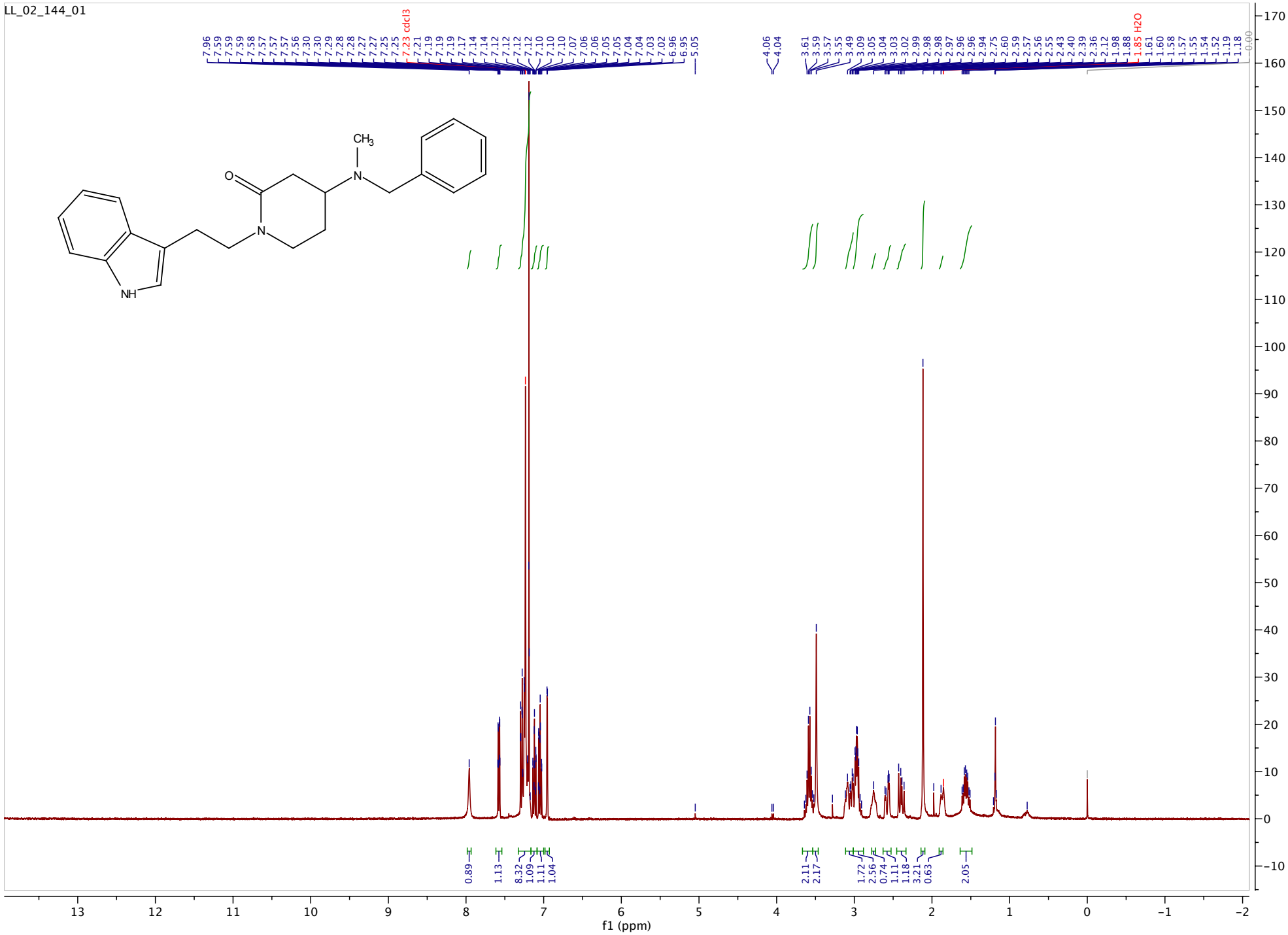

LL_02_153_C13_01
169.20
159.70
136.26
129.30
127.47
122.01
121.97
121.04
119.27
118.72
114.15
113.12
112.48
111.21
77.36 cdcl3
77.04 cdcl3
76.72 cdcl3
57.96
56.47
55.22
48.10
46.72
37.33
34.88
26.24
22.98
CH3
O
N
O
CH3
N
NH
f1 (ppm)

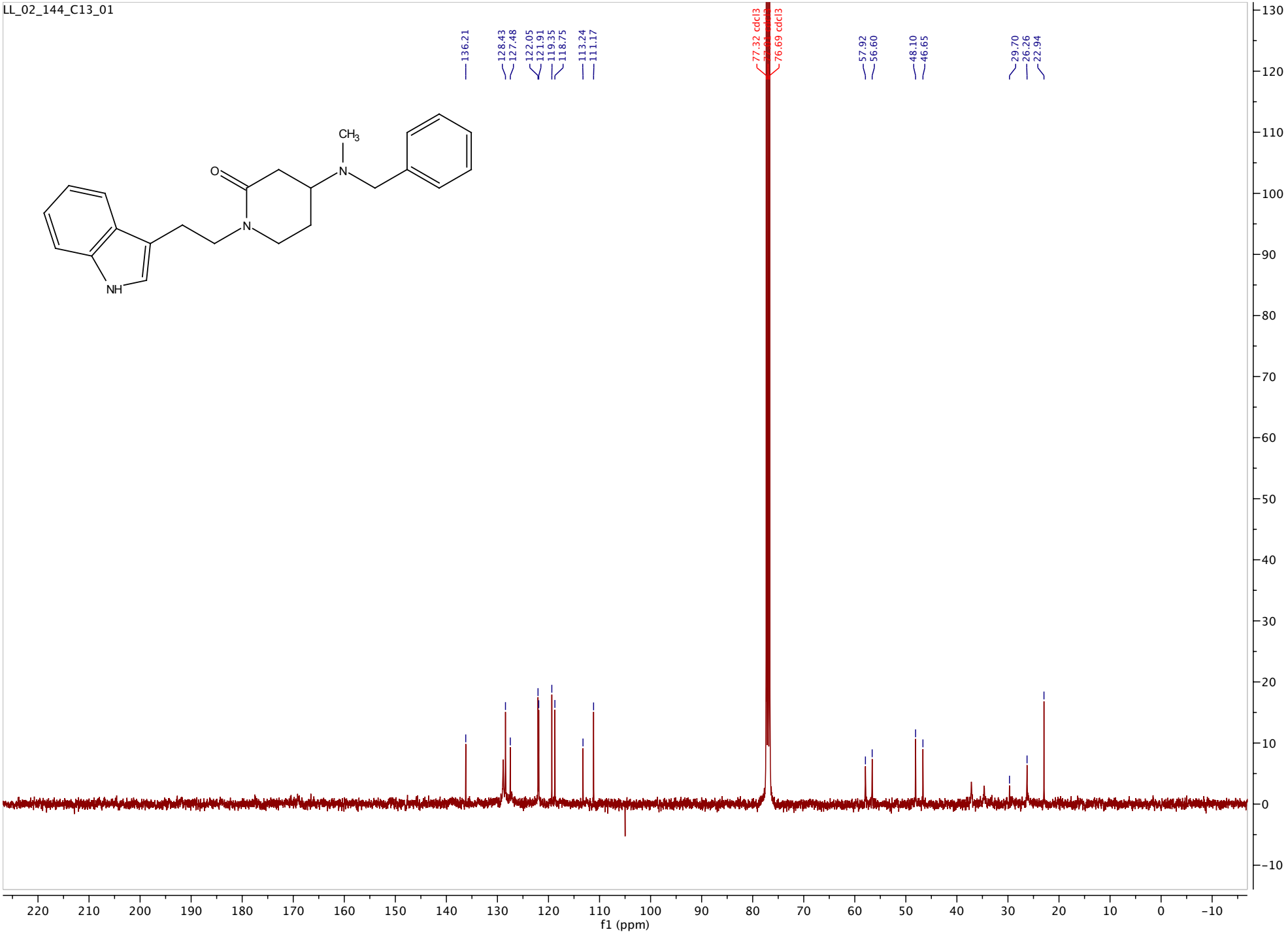

PROTON_01
LL_02_103_purified
cdcl3
H2O
CH3
O
N
NH
f1 (ppm)

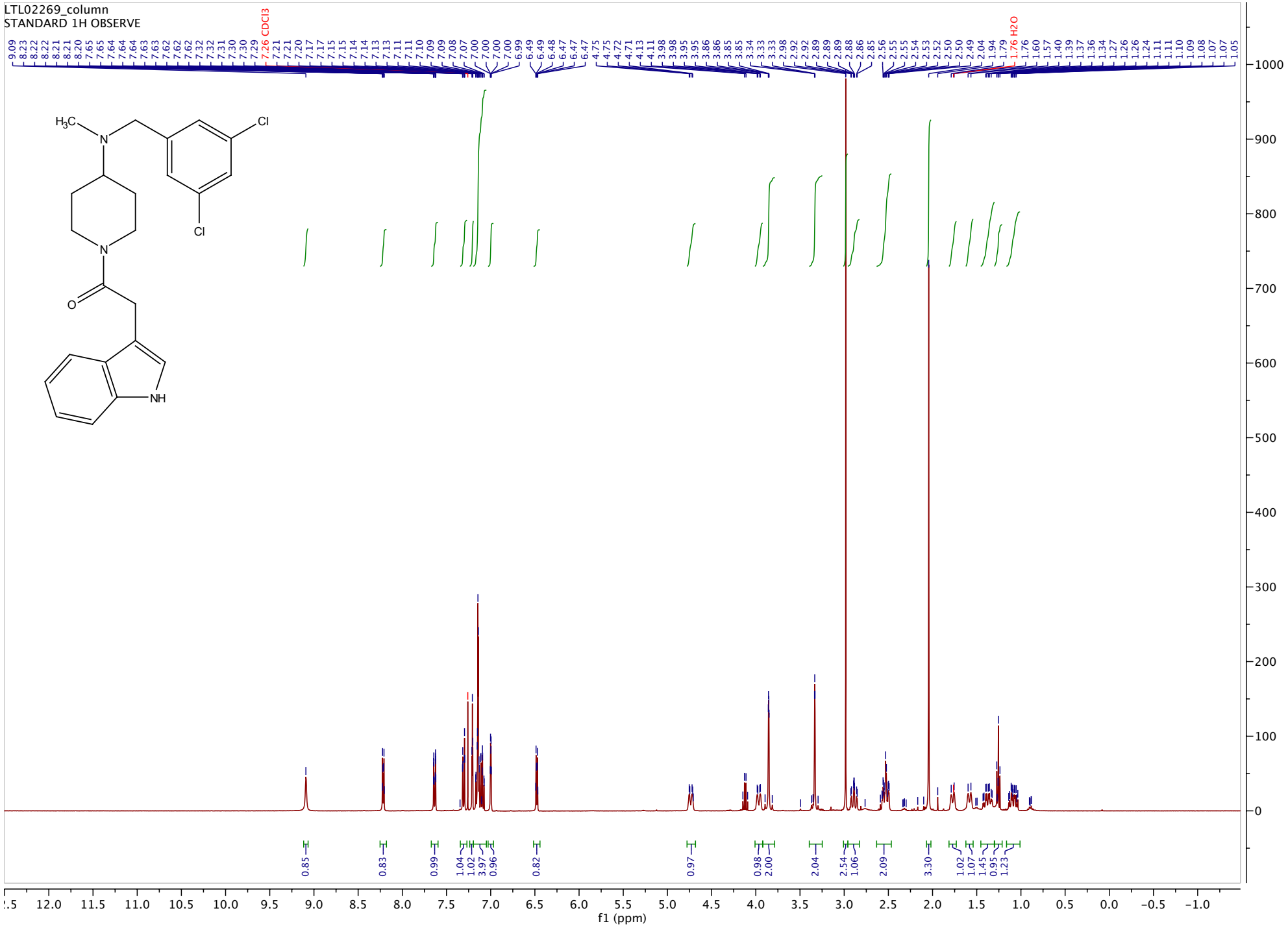

LL_02_103_repurified_C13_01
167.24
145.81
144.69
134.33
125.57
120.10
120.03
119.85
117.40
116.84
114.48
111.32
109.27
107.14
106.02
98.99
75.44 cdcl3
74.81 cdcl3
55.84
54.53
46.18
44.79
35.16
32.91
24.42
21.09
0.00
CH3
O
N
O
O
N
NH
f1 (ppm)

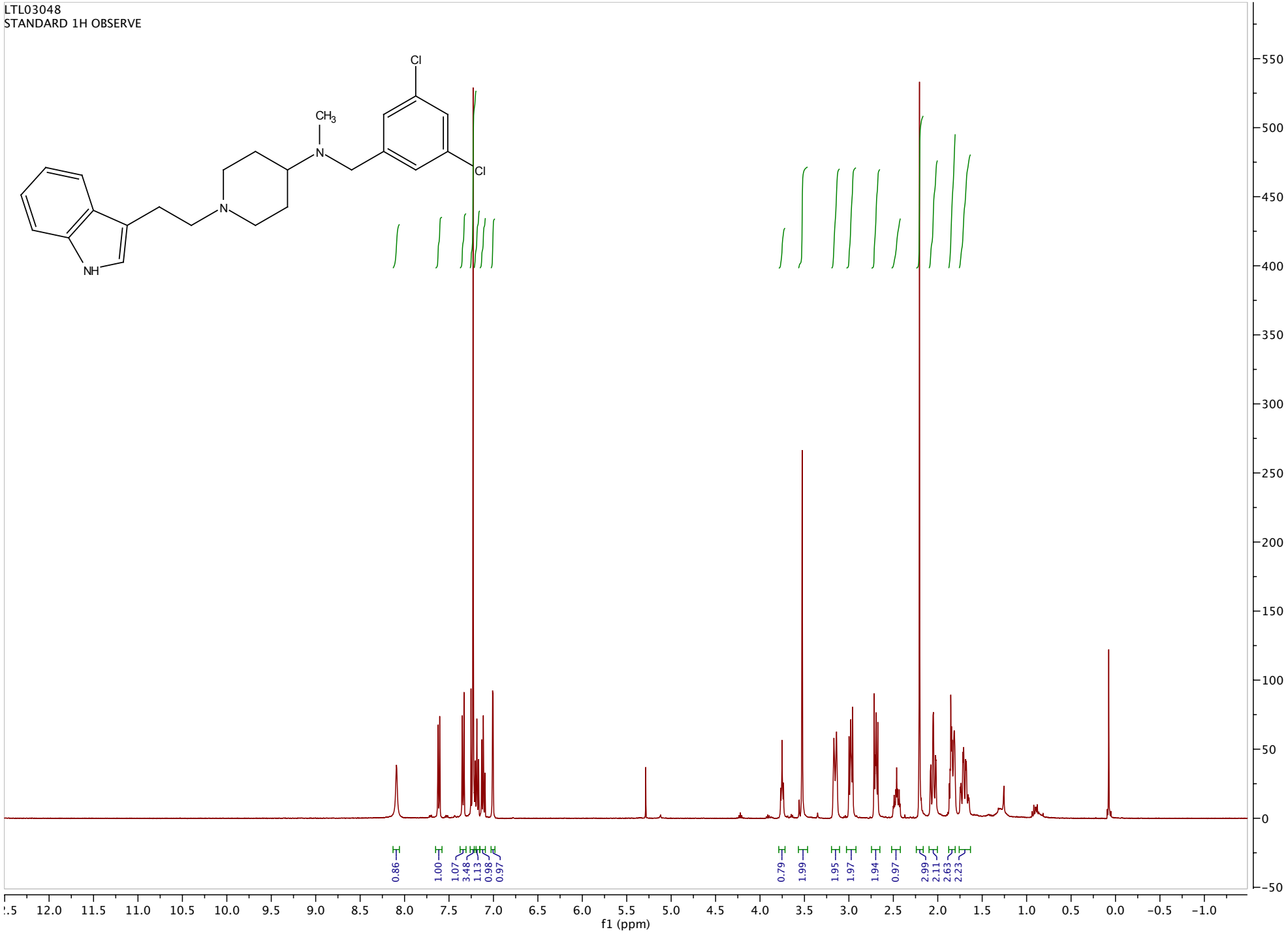

PROTON_01
LL_02_157
cdcl3
f1 (ppm)

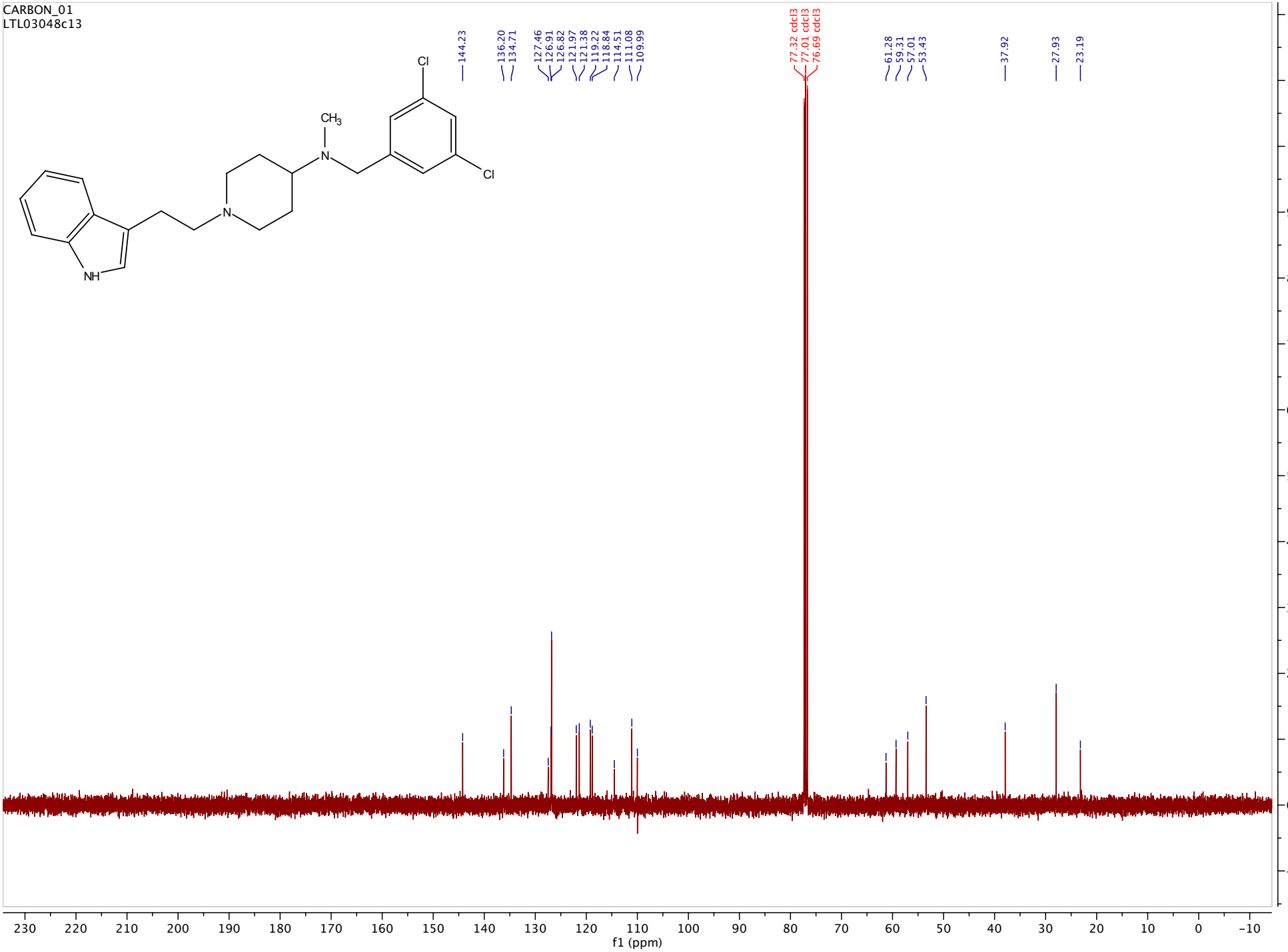

CARBON_01
LL_02_157_C13
169.16
138.41
136.26
128.77
127.46
126.62
125.41
125.08
121.97
121.95
119.25
118.69
113.12
111.18
77.33 cdcl3
77.21
77.01 cdcl3
76.69 cdcl3
57.80
56.54
48.07
46.69
37.30
34.87
26.28
22.97
15.75
CH3
O
N
N
S
CH3
NH
f1 (ppm)

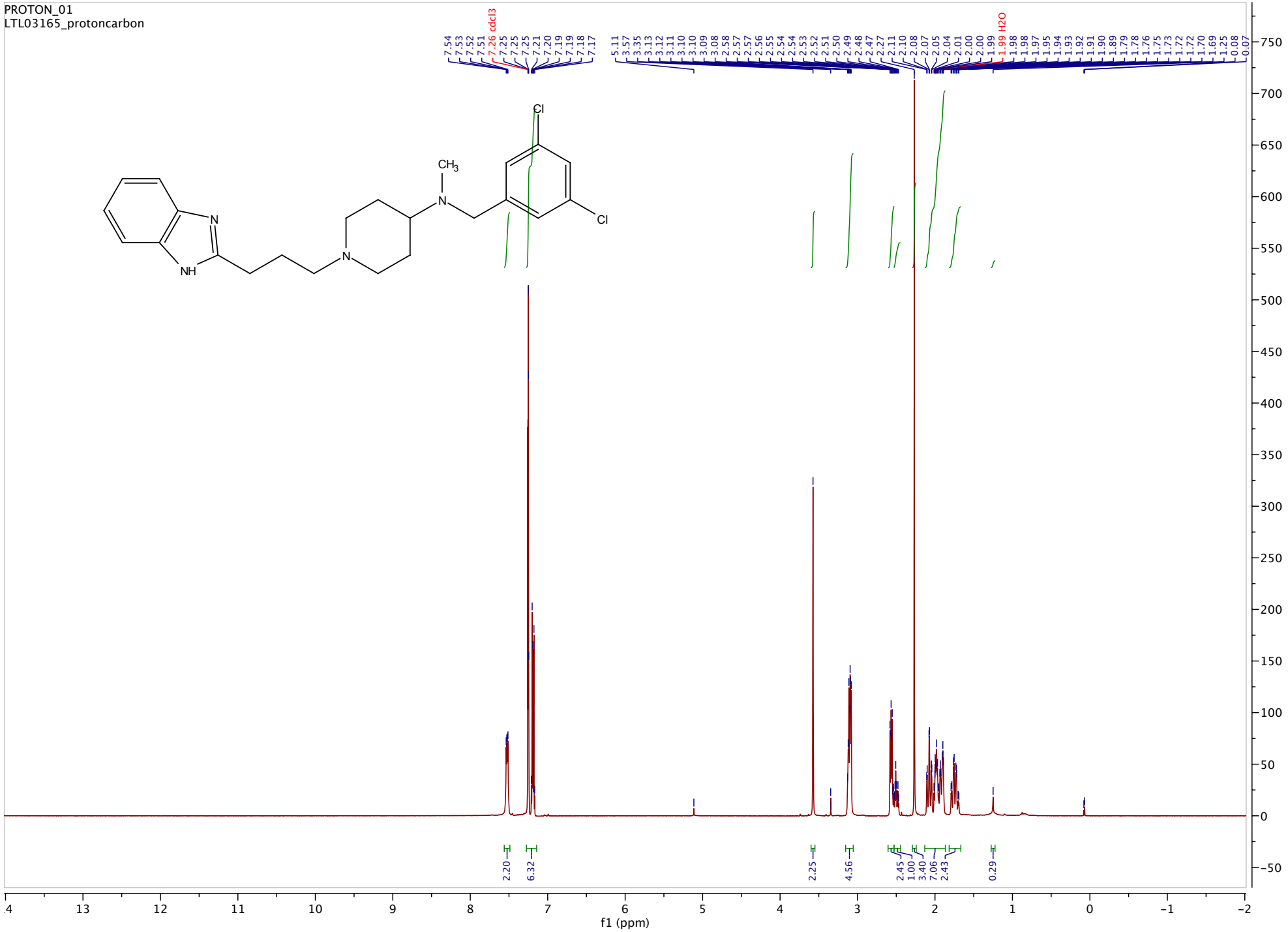

LL_02_144_01
7.96 7.59 7.59 7.59 7.58 7.57 7.57 7.57 7.56 7.30 7.30 7.29 7.28 7.28 7.27 7.25 7.25 7.23 cdcl3 7.21 7.19 7.19 7.19 7.17 7.14 7.14 7.12 7.12 7.12 7.12 7.10 7.10 7.10 7.07 7.06 7.06 7.05 7.05 7.04 7.04 7.03 7.02 6.96 6.95 5.05
4.06 4.04
3.61 3.59 3.57 3.55 3.49 3.09 3.05 3.04 3.03 3.02 2.99 2.98 2.98 2.97 2.96 2.96 2.94 2.75 2.60 2.59 2.57 2.56 2.55 2.43 2.40 2.39 2.36 2.12 1.98 1.88 1.85 H2O 1.61 1.60 1.58 1.57 1.55 1.54 1.52 1.19 1.18 0.00
CH3
O
N
N
NH
0.89 1.13 8.32 1.09 1.11 1.04
2.11 2.17 1.72 2.56 0.74 1.11 1.18 3.21 0.63 2.05
f1 (ppm)

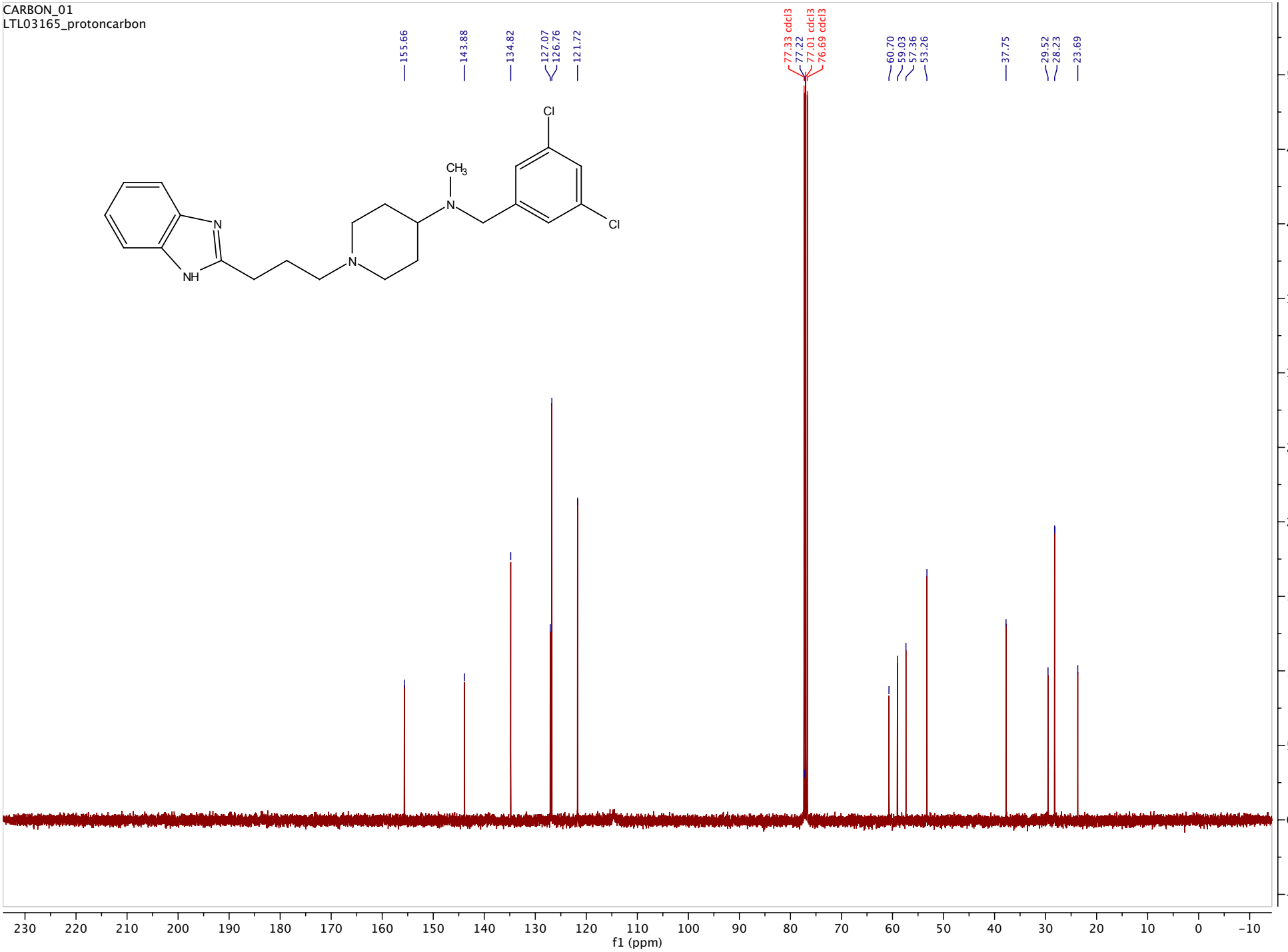

LL_02_144_C13_01
136.21
128.43
127.48
122.05
121.91
119.35
118.75
113.24
111.17
77.32 cdcl3
76.69 cdcl3
57.92
56.60
48.10
46.65
29.70
26.26
22.94
CH3
N
O
N
NH
f1 (ppm)

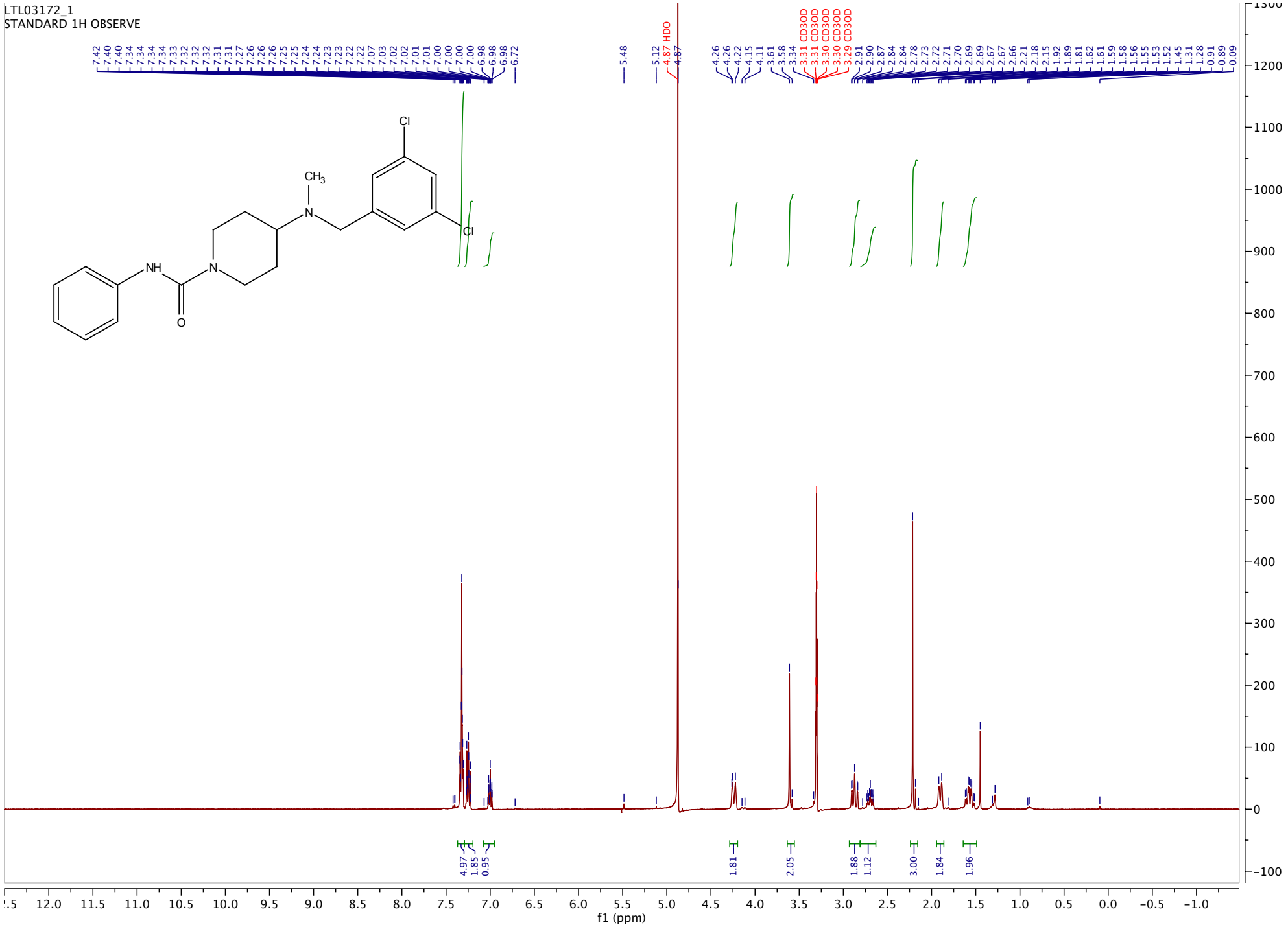

LTL02269_column
STANDARD 1H OBSERVE
7.26 CDCl3
1.76 H2O
H3C
N
Cl
Cl
N
O
NH
f1 (ppm)

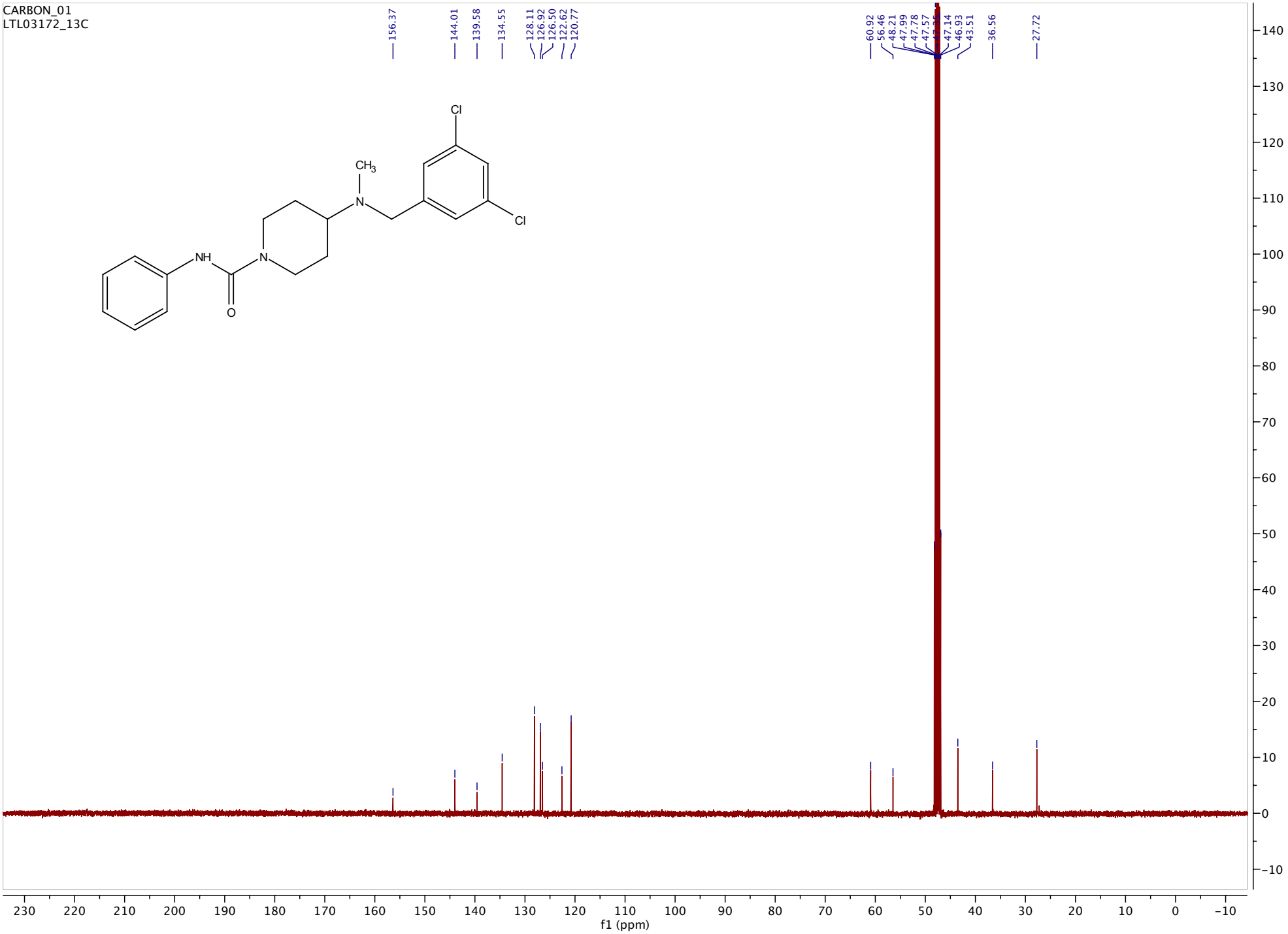

LTL03048
STANDARD 1H OBSERVE
Cl
CH3
N
Cl
N
NH
0.86
1.00
1.07
3.48
1.13
0.98
0.97
0.79
1.99
1.95
1.97
1.94
0.97
2.99
2.11
2.63
2.23
f1 (ppm)

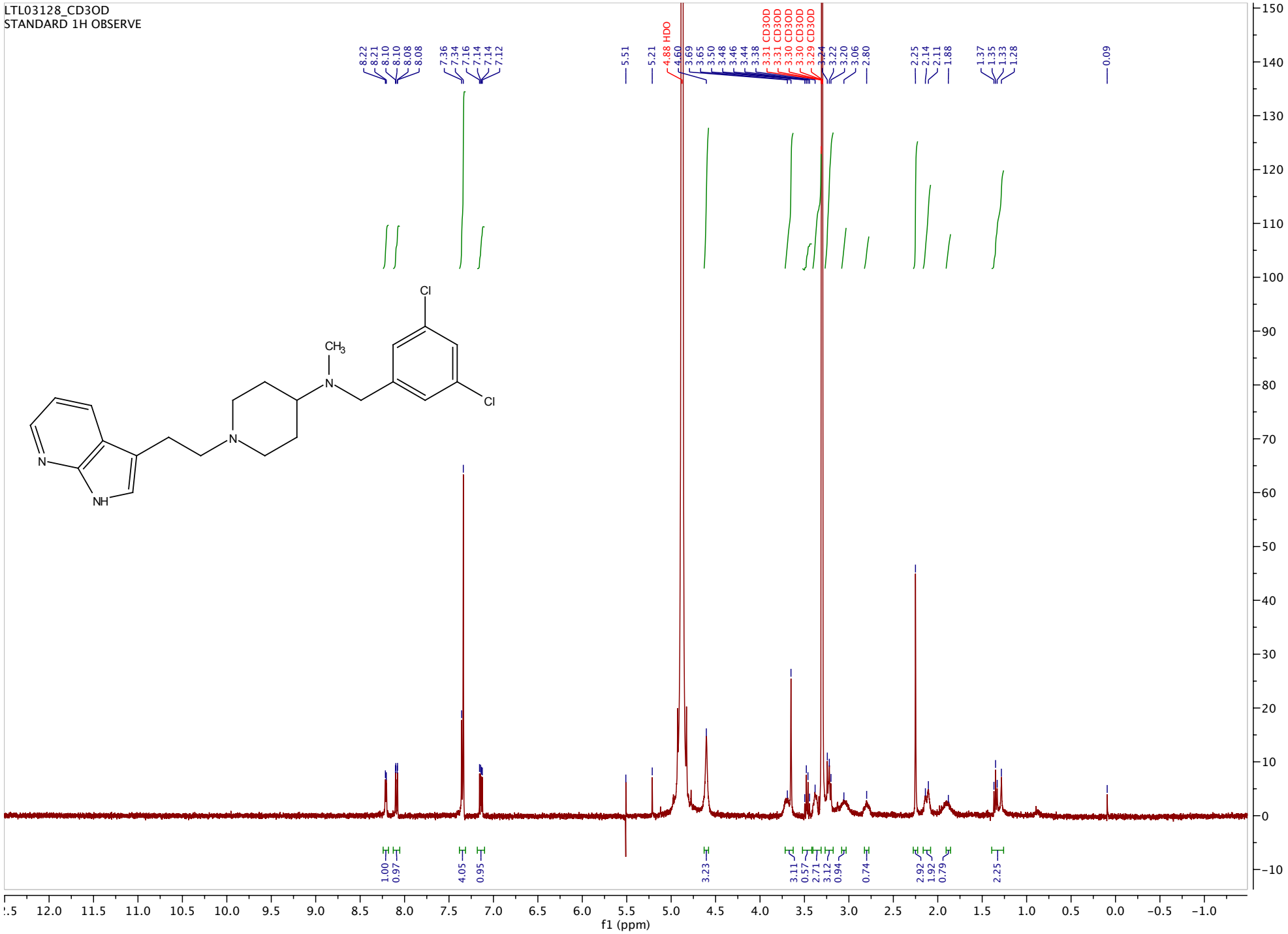

CARBON_01
LTL03048c13
144.23
136.20
134.71
127.46
126.91
126.82
121.97
121.38
119.22
118.84
114.51
111.08
109.99
77.32 cdcl3
77.01 cdcl3
76.69 cdcl3
61.28
59.31
57.01
53.43
37.92
27.93
23.19
Cl
Cl
CH3
N
N
NH
f1 (ppm)

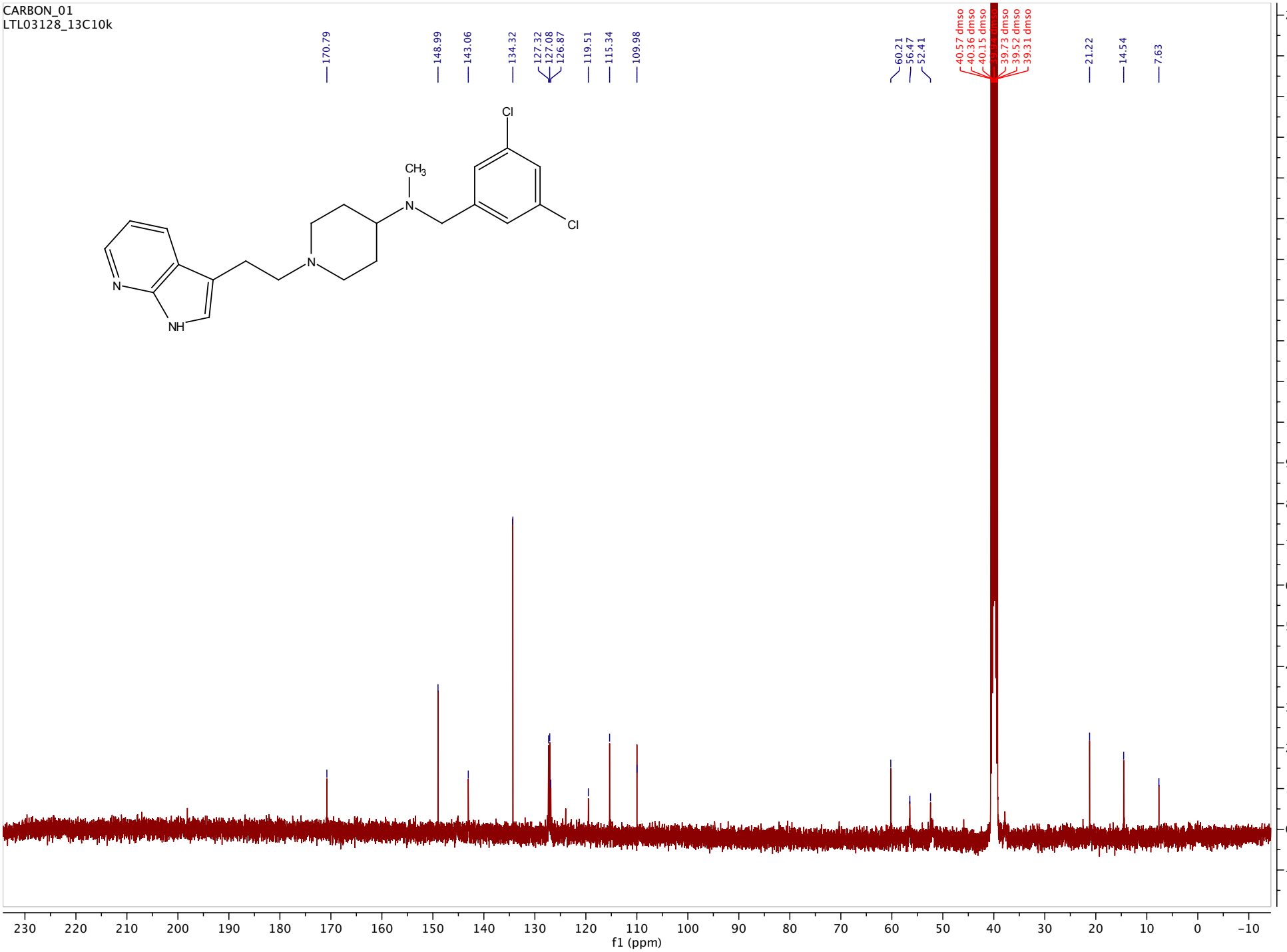

PROTON_01
LTL03165_protoncarbon
7.54 7.53 7.52 7.51 7.26 cdcl3 7.25 7.25 7.25 7.21 7.20 7.19 7.19 7.18 7.17
5.11 3.57 3.35 3.13 3.12 3.11 3.10 3.10 3.09 3.08 2.58 2.57 2.57 2.56 2.55 2.54 2.54 2.53 2.52 2.51 2.50 2.49 2.48 2.47 2.27 2.11 2.10 2.08 2.07 2.05 2.04 2.01 2.00 2.00 1.99 1.99 H2O 1.98 1.98 1.97 1.95 1.94 1.93 1.92 1.91 1.90 1.89 1.79 1.78 1.76 1.75 1.73 1.72 1.72 1.70 1.69 1.25 0.08 0.07
Cl
CH3
N
N
Cl
N
NH
2.20 6.32 2.25 4.56 2.45 1.00 3.40 7.06 2.43 0.29
f1 (ppm)

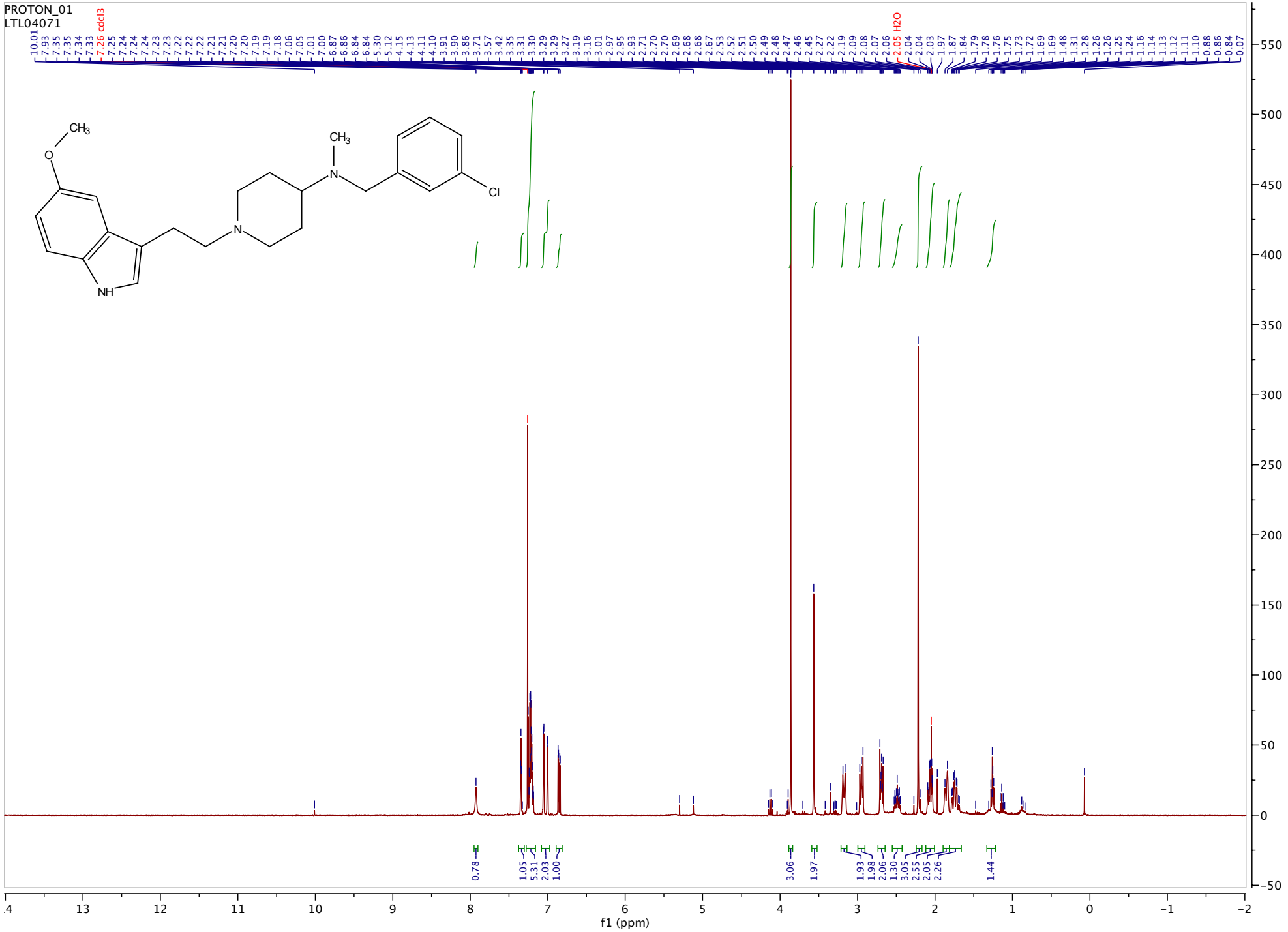

CARBON_01
LTL03165_protoncarbon
155.66
143.88
134.82
127.07
126.76
121.72
77.33 cdcl3
77.22
77.01 cdcl3
76.69 cdcl3
60.70
59.03
57.36
53.26
37.75
29.52
28.23
23.69
Cl
CH3
N
N
NH
N
Cl
f1 (ppm)

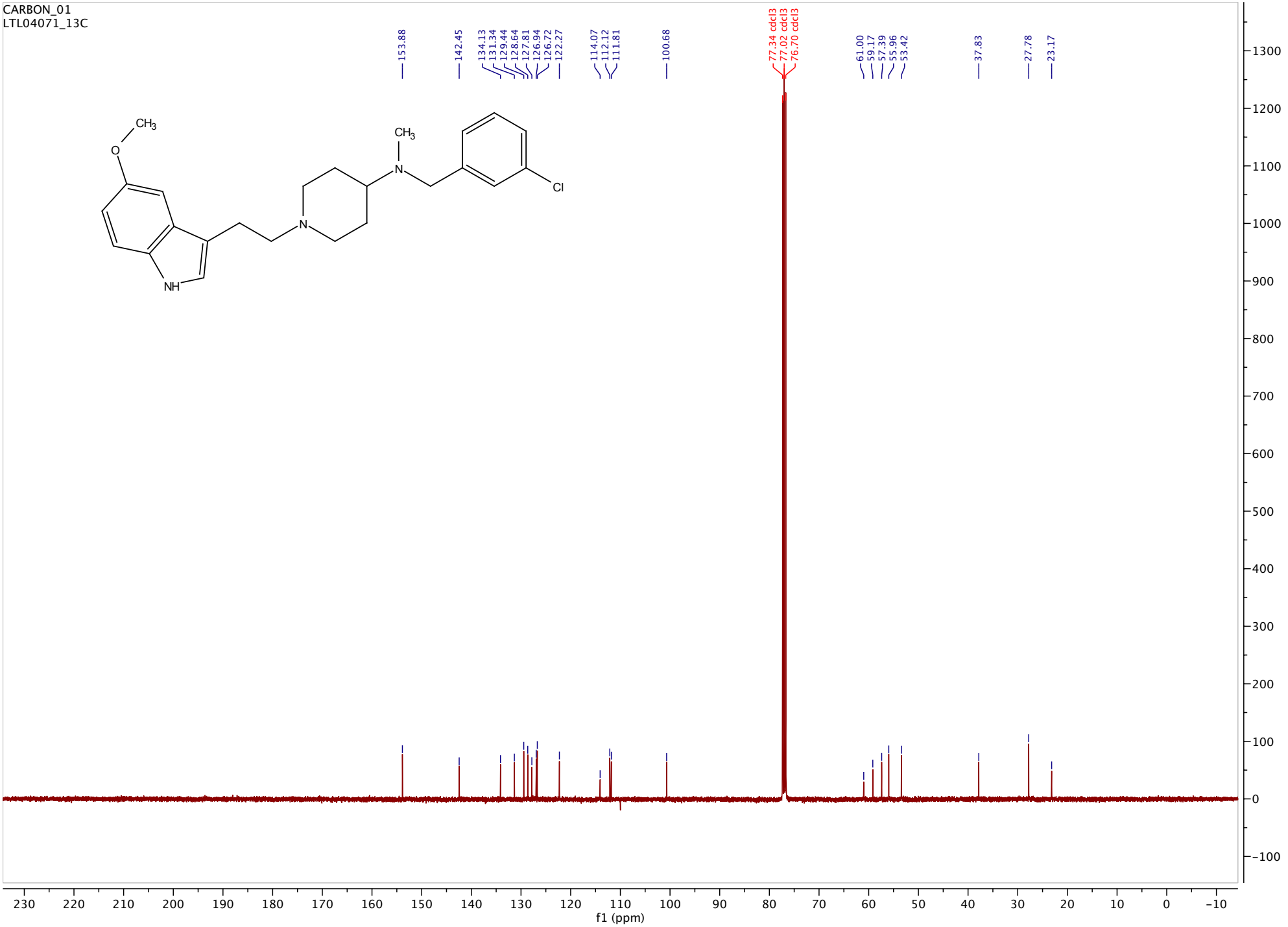

LTL03172_1
STANDARD 1H OBSERVE
7.42 7.40 7.40 7.34 7.34 7.34 7.33 7.32 7.32 7.32 7.31 7.31 7.27 7.26 7.26 7.25 7.25 7.24 7.24 7.23 7.23 7.22 7.22 7.07 7.03 7.02 7.02 7.01 7.01 7.00 7.00 7.00 7.00 6.98 6.98 6.72
5.48
5.12
4.87 HDO
4.87
4.26 4.26 4.22 4.15 4.11 3.61 3.58 3.34 3.31 CD3OD 3.31 CD3OD 3.30 CD3OD 3.30 CD3OD 3.29 CD3OD 2.91 2.90 2.87 2.84 2.84 2.78 2.73 2.72 2.71 2.70 2.69 2.69 2.67 2.67 2.66 2.21 2.18 2.15 1.92 1.89 1.81 1.62 1.61 1.59 1.58 1.56 1.55 1.53 1.52 1.45 1.31 1.28 0.91 0.89 0.09
Cl
CH3
N
Cl
NH
N
O
4.97
1.85
0.95
1.81
2.05
1.88
1.12
3.00
1.84
1.96
f1 (ppm)

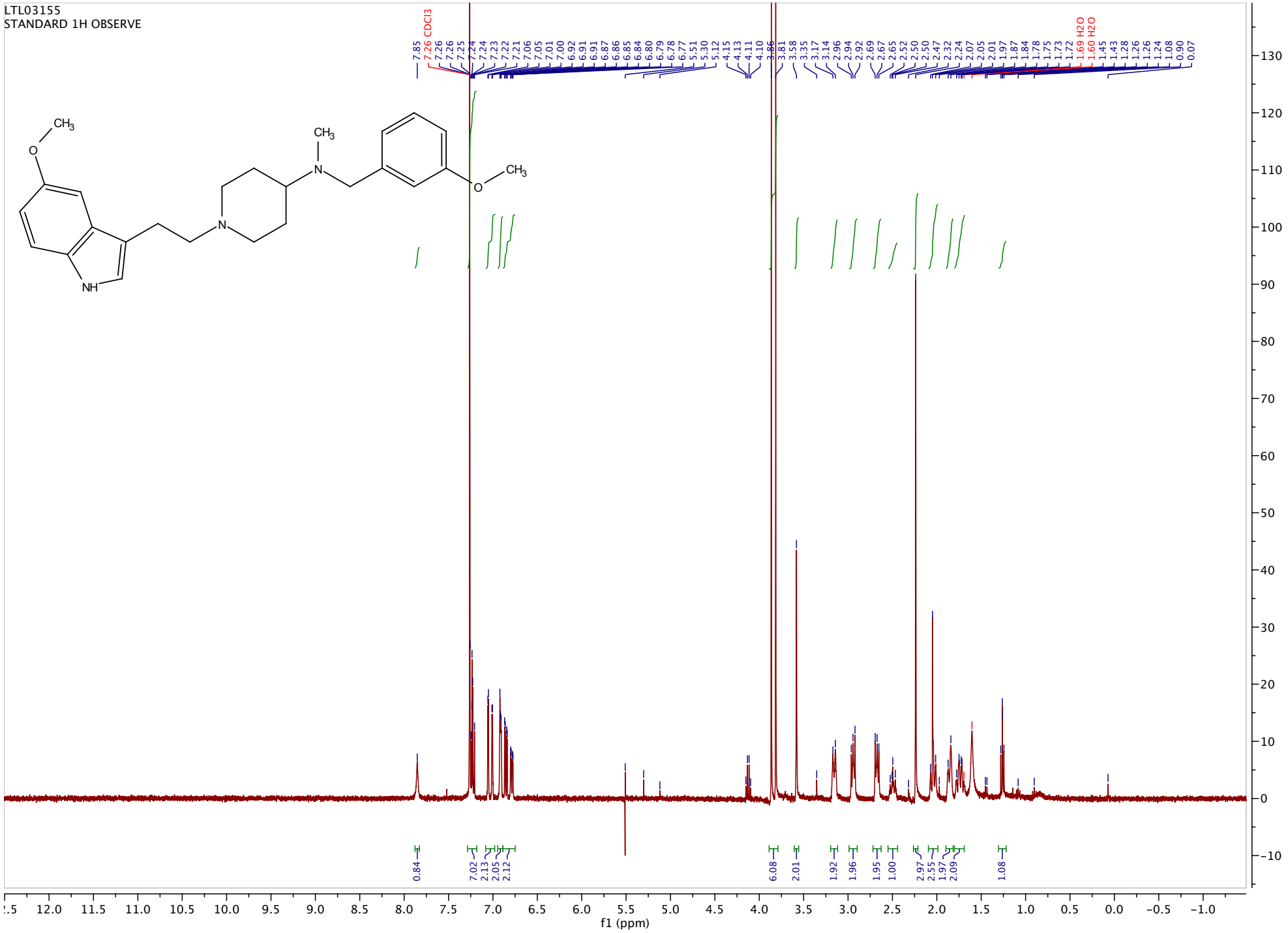

CARBON_01
LTL03172_13C
156.37
144.01
139.58
134.55
128.11
126.92
126.50
122.62
120.77
60.92
56.46
48.21
47.99
47.78
47.57
47.14
46.93
43.51
36.56
27.72
Cl
CH3
N
Cl
NH
N
O
f1 (ppm)

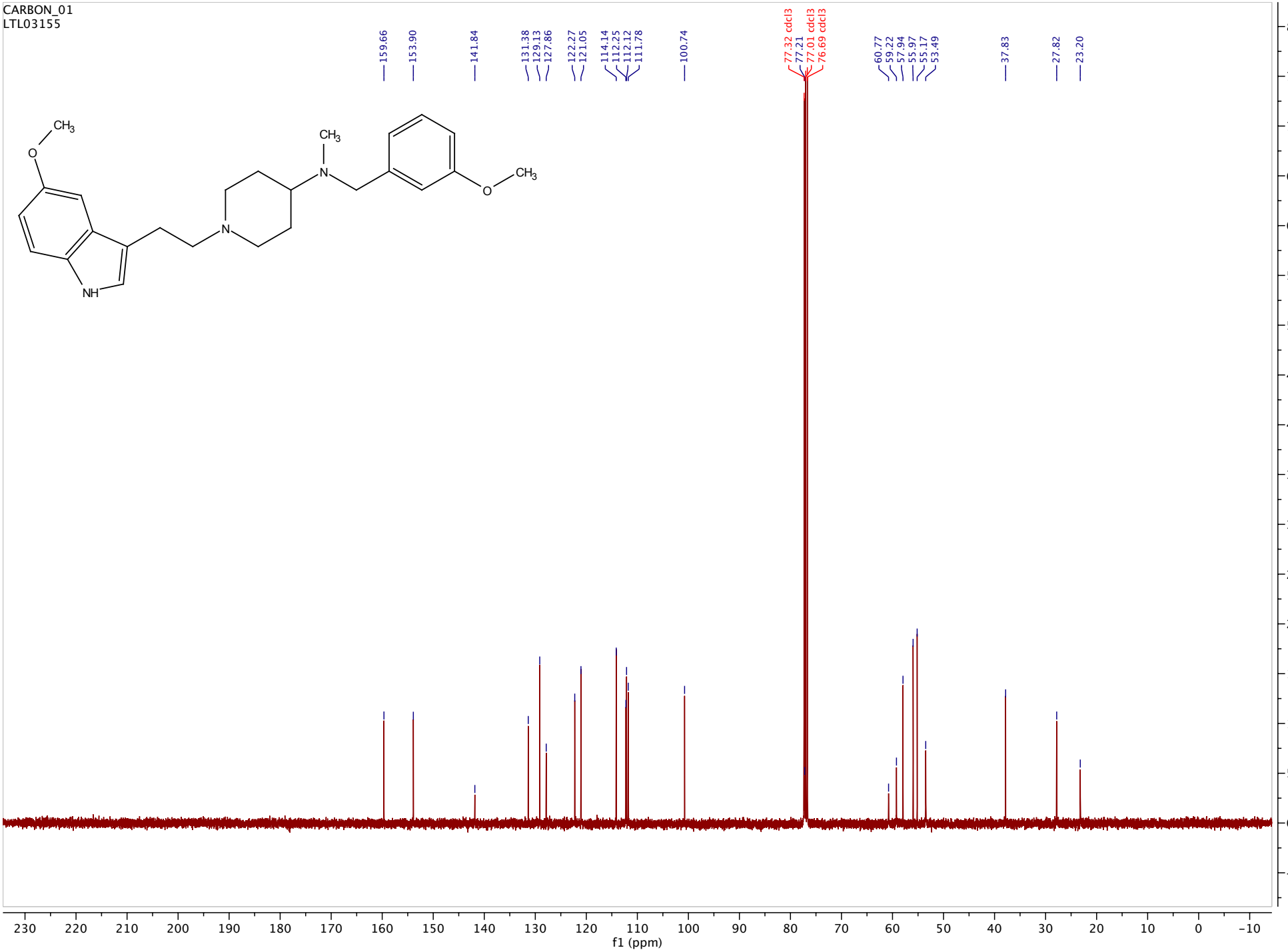

LTL03128_CD3OD
STANDARD 1H OBSERVE
8.22
8.21
8.10
8.10
8.08
8.08
7.36
7.34
7.16
7.14
7.14
7.12
5.51
5.21
4.88 HDO
4.60
3.69
3.65
3.50
3.48
3.46
3.44
3.38
3.31 CD3OD
3.31 CD3OD
3.30 CD3OD
3.30 CD3OD
3.29 CD3OD
3.24
3.22
3.20
3.06
2.80
2.25
2.14
2.11
1.88
1.37
1.35
1.33
1.28
0.09
Cl
CH3
N
Cl
N
N
NH
1.00
0.97
4.05
0.95
3.23
3.11
0.57
2.71
3.12
0.94
0.74
2.92
1.92
0.79
2.25
f1 (ppm)

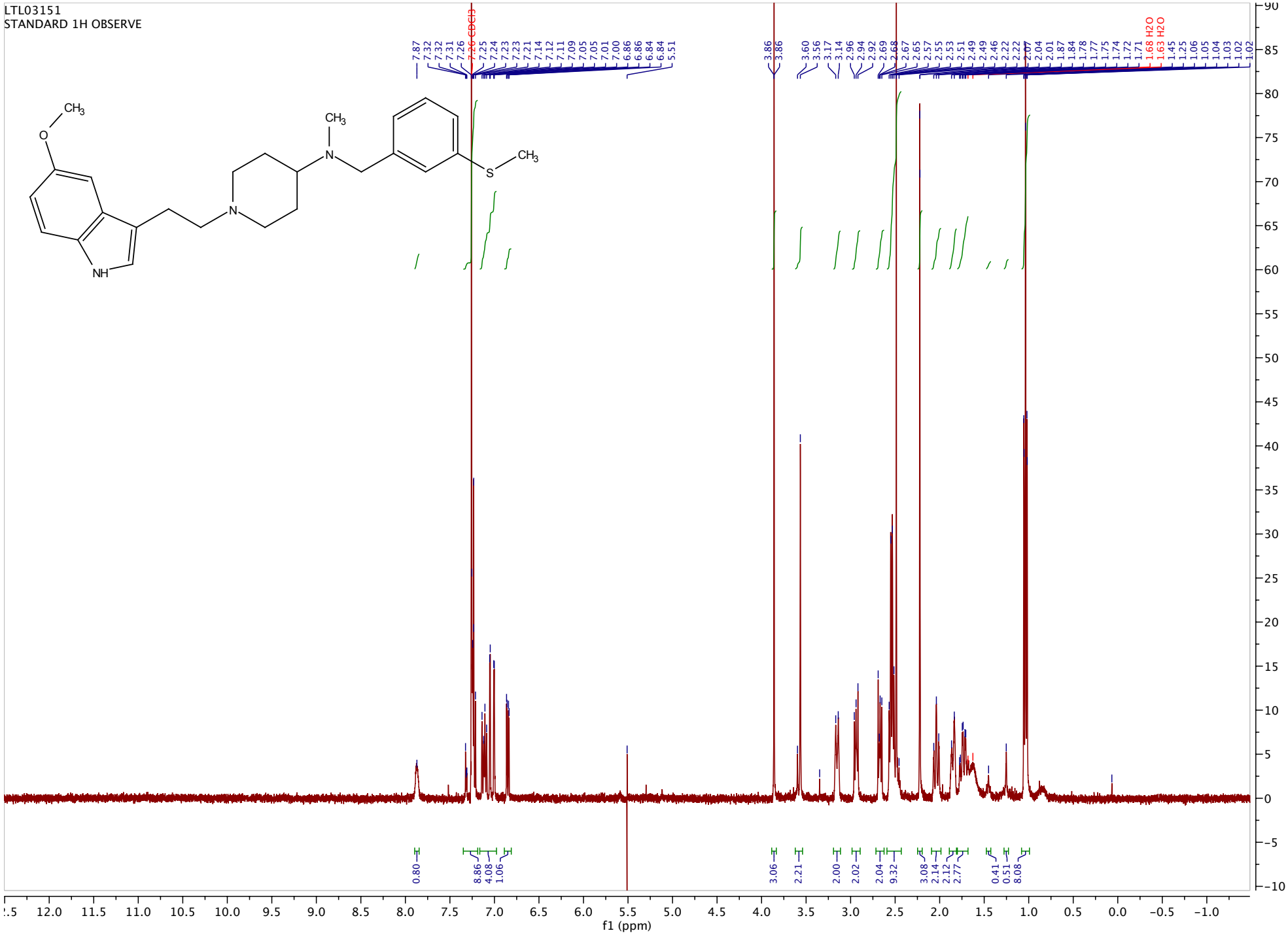

CARBON_01
LTL03128_13C10k
170.79
148.99
143.06
134.32
127.32
127.08
126.87
119.51
115.34
109.98
60.21
56.47
52.41
40.57 dmso
40.36 dmso
40.15 dmso
39.73 dmso
39.52 dmso
39.31 dmso
21.22
14.54
7.63
Cl
CH3
N
N
N
NH
Cl
f1 (ppm)

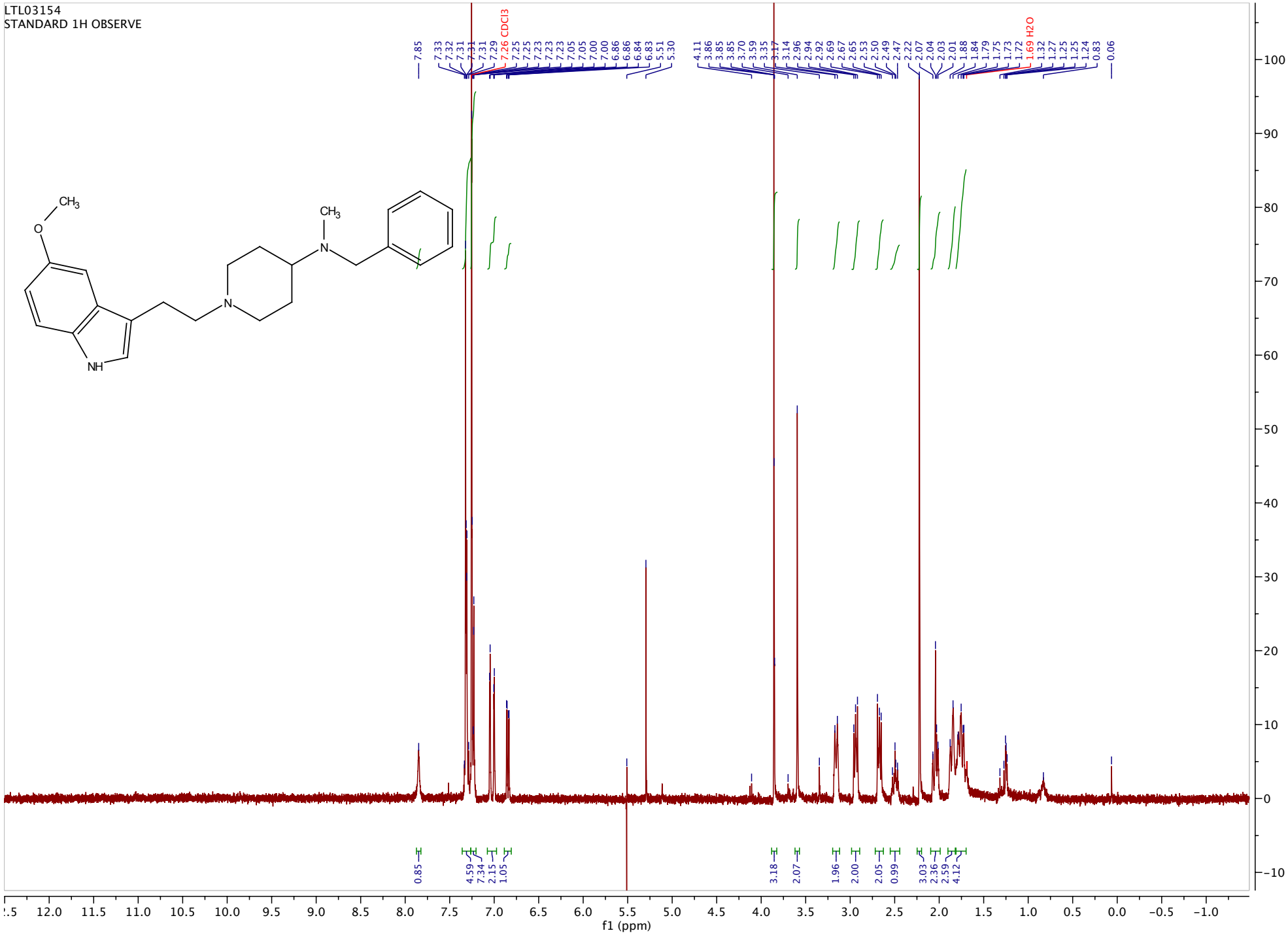

PROTON_01
LTL04071
CH3
O
N
CH3
N
Cl
NH
f1 (ppm)

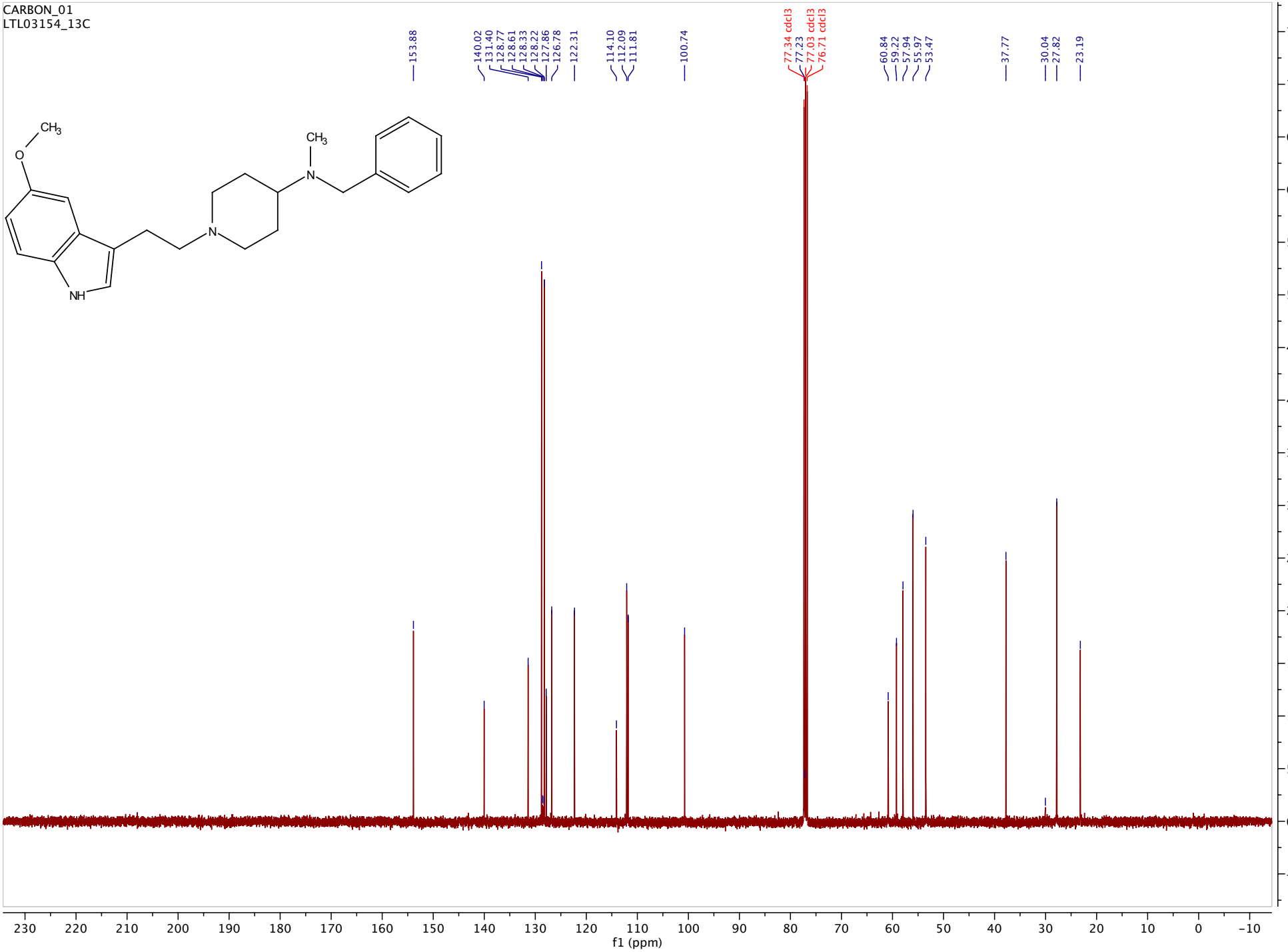

CARBON_01
LTL04071_13C
153.88
142.45
134.13
131.34
129.44
128.64
127.81
126.94
126.72
122.27
114.07
112.12
111.81
100.68
77.34 cdcl3
77.02 cdcl3
76.70 cdcl3
61.00
59.17
57.39
55.96
53.42
37.83
27.78
23.17
CH3
O
CH3
N
N
Cl
NH
f1 (ppm)

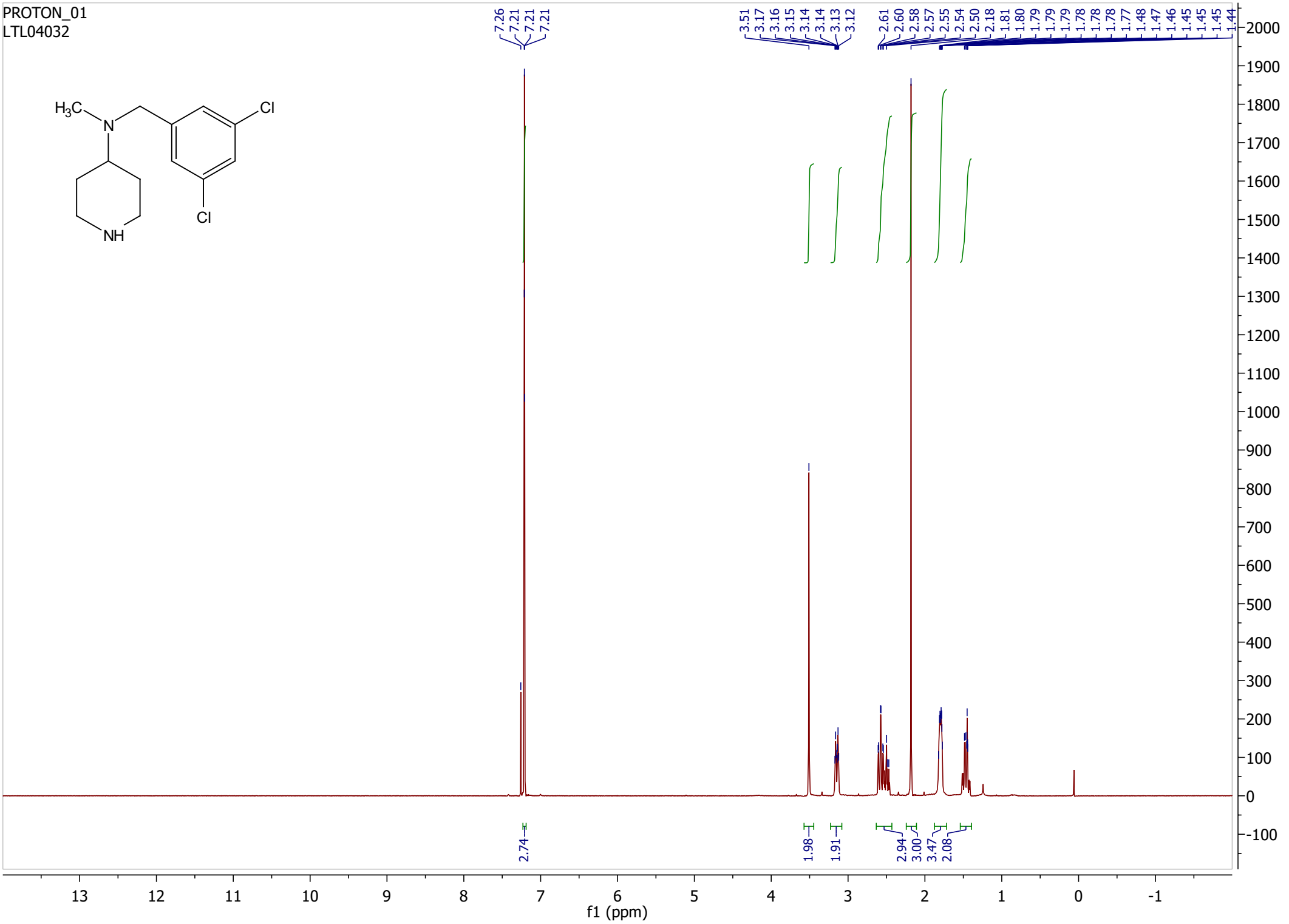

LTL03155
STANDARD 1H OBSERVE
f1 (ppm)

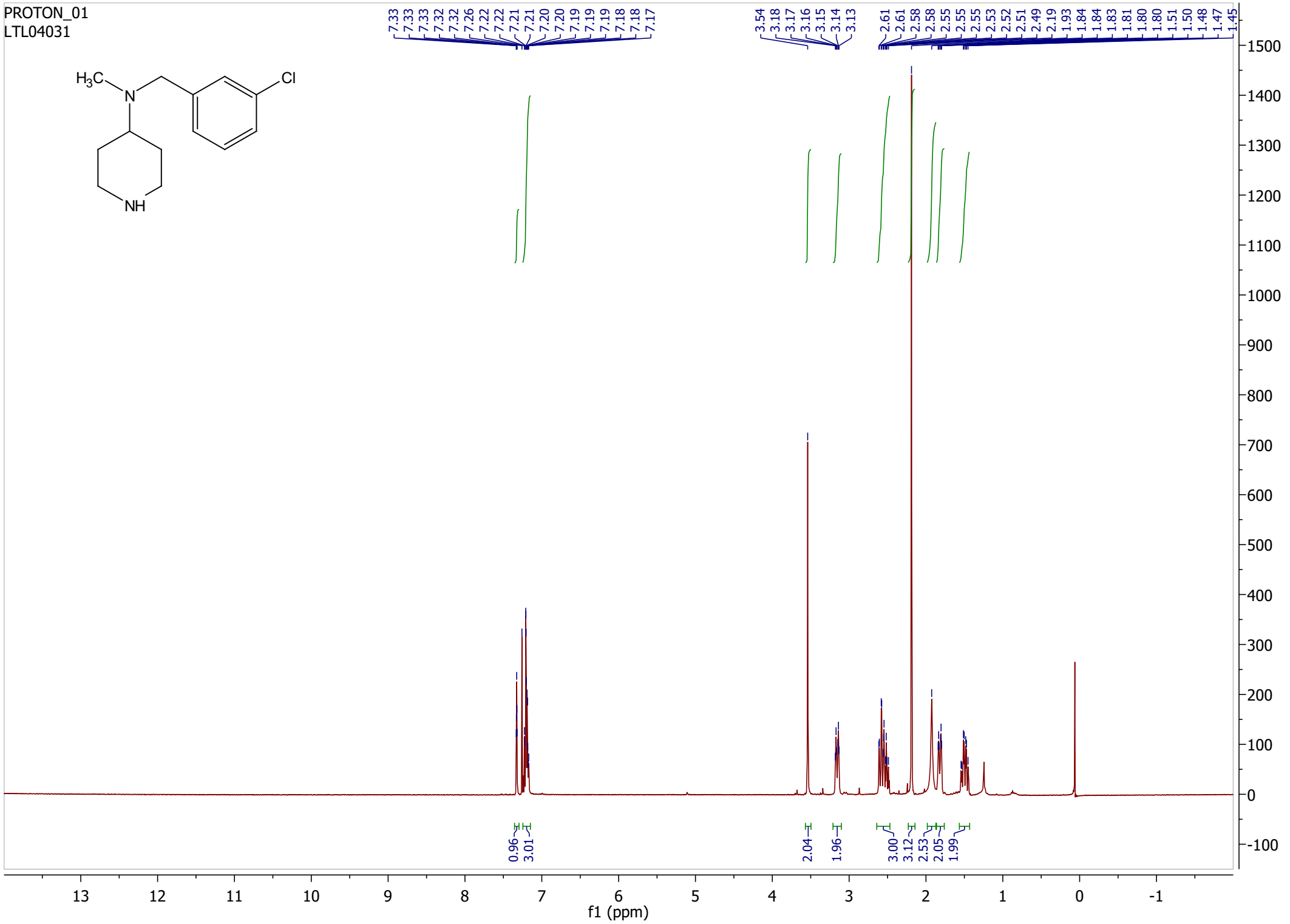

CARBON_01
LTL03155
159.66
153.90
141.84
131.38
129.13
127.86
122.27
121.05
114.14
112.25
112.12
111.78
100.74
77.32 cdcl3
77.21
77.01 cdcl3
76.69 cdcl3
60.77
59.22
57.94
55.97
55.17
53.49
37.83
27.82
23.20
CH3
O
N
NH
f1 (ppm)

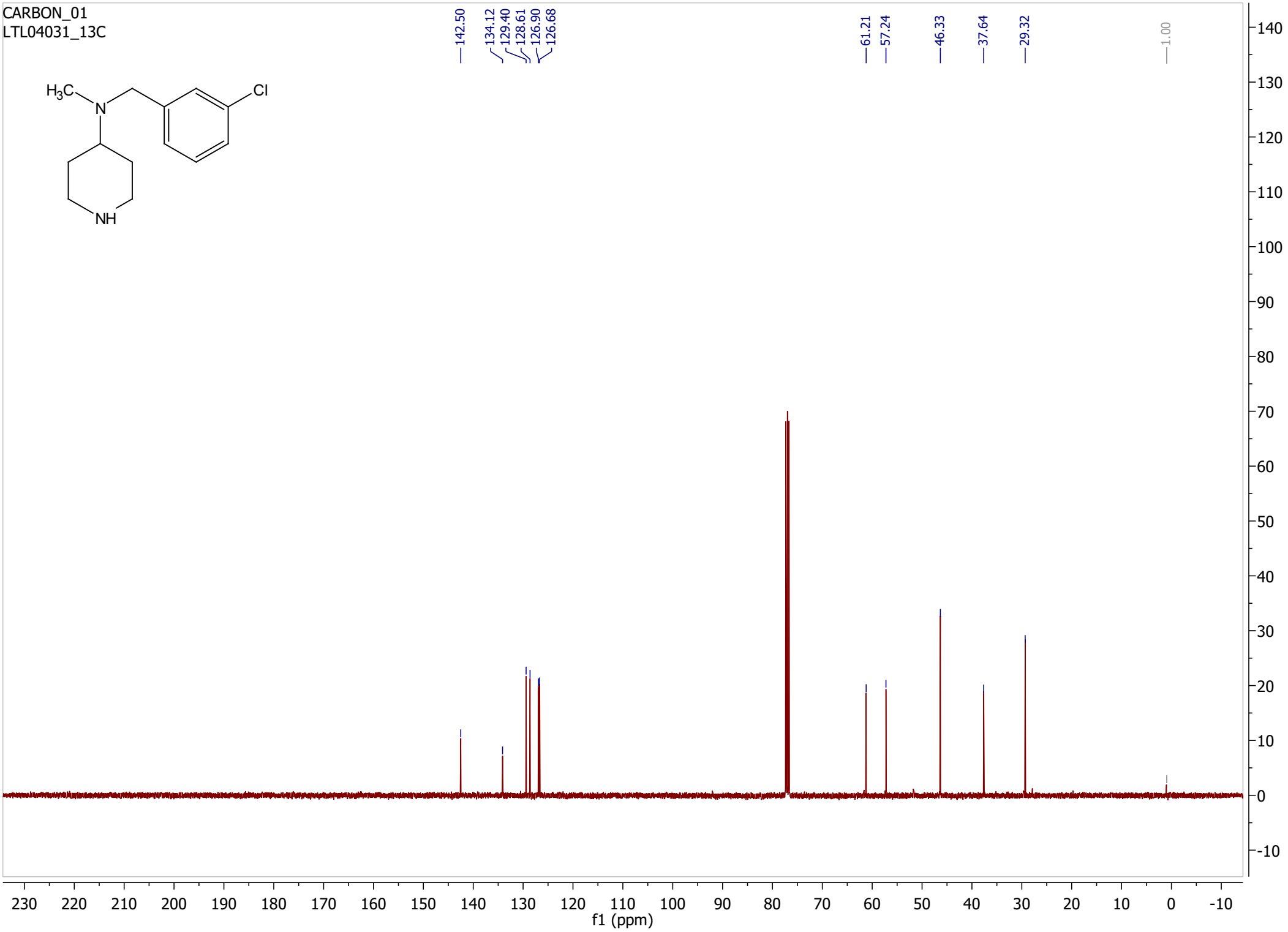

LTL03151
STANDARD 1H OBSERVE
f1 (ppm)

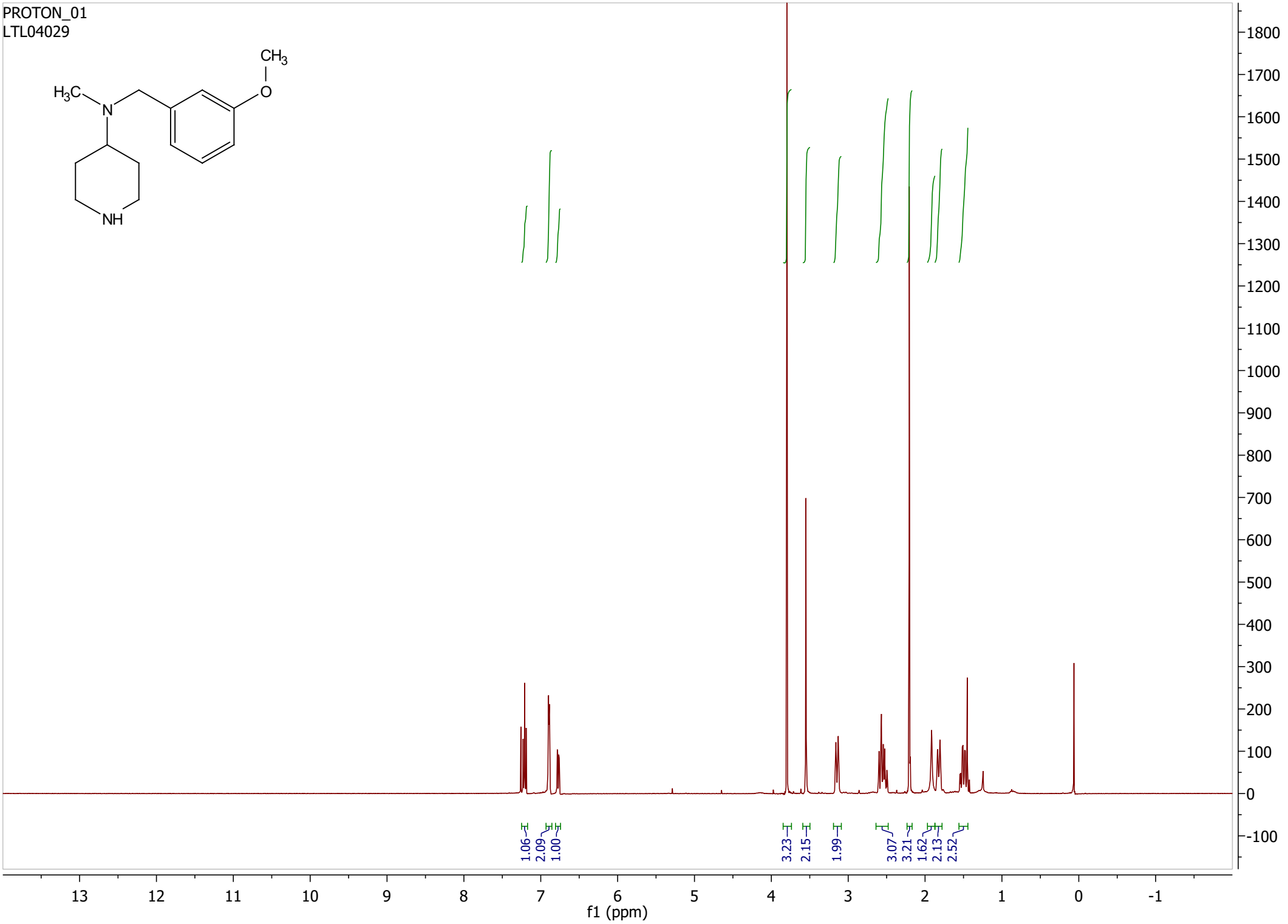

LTL03154
STANDARD 1H OBSERVE
7.85
7.33
7.32
7.31
7.31
7.29
7.26 CDCl3
7.25
7.25
7.23
7.23
7.23
7.05
7.05
7.00
7.00
6.86
6.84
6.83
5.51
5.30
4.11
3.86
3.85
3.85
3.70
3.59
3.35
3.17
3.14
2.96
2.94
2.92
2.69
2.67
2.65
2.53
2.50
2.49
2.47
2.22
2.07
2.04
2.03
2.01
1.88
1.84
1.79
1.75
1.73
1.72
1.69 H2O
1.32
1.27
1.25
1.25
1.24
0.83
0.06
CH3
O
CH3
N
N
NH
0.85
4.59
7.34
2.15
1.05
3.18
2.07
1.96
2.00
2.05
0.99
3.03
2.36
2.59
4.12
f1 (ppm)

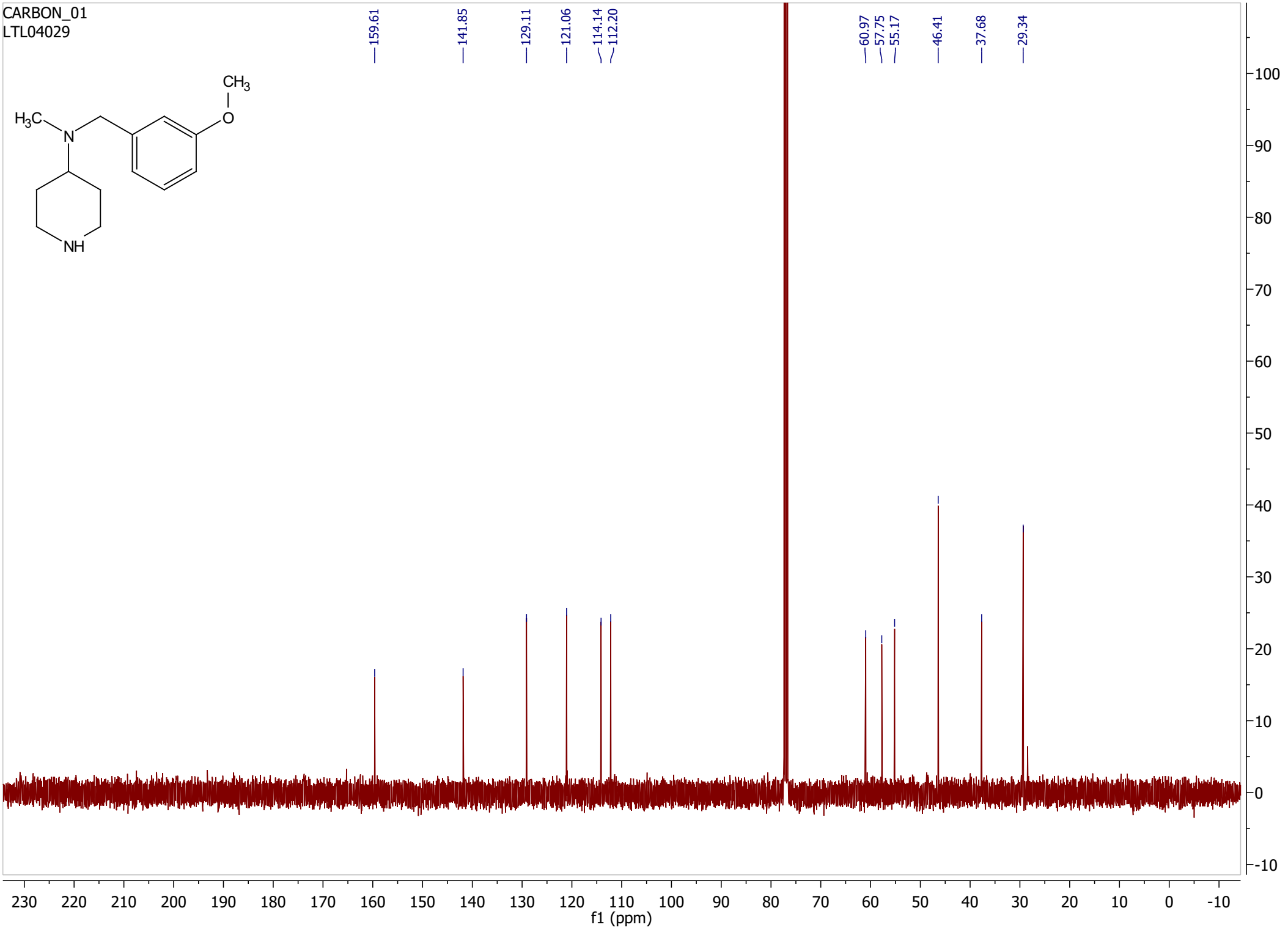

CARBON_01
LTL03154_13C
153.88
140.02
131.40
128.77
128.61
128.33
128.22
127.86
126.78
122.31
114.10
112.09
111.81
100.74
77.34 cdcl3
77.23
77.03 cdcl3
76.71 cdcl3
60.84
59.22
57.94
55.97
53.47
37.77
30.04
27.82
23.19
CH3
O
N
CH3
N
NH
f1 (ppm)

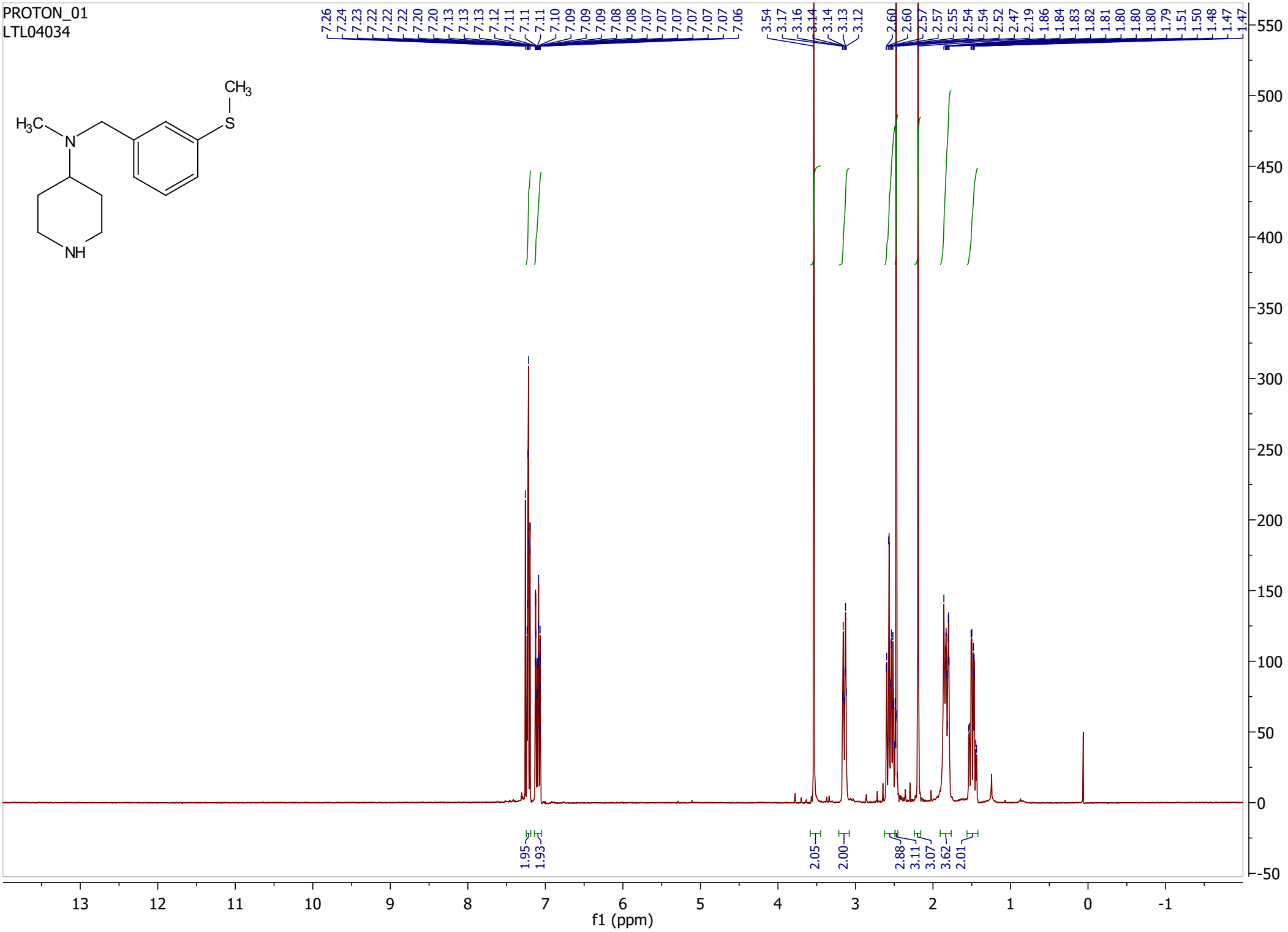

PROTON_01
LTL04032
7.26
7.21
7.21
7.21
3.51
3.17
3.16
3.15
3.14
3.14
3.13
3.12
2.61
2.60
2.58
2.57
2.55
2.54
2.50
2.18
1.81
1.80
1.79
1.79
1.79
1.78
1.78
1.78
1.77
1.48
1.47
1.46
1.45
1.45
1.45
1.44
H3C
N
Cl
Cl
NH
2.74
1.98
1.91
2.94
3.00
3.47
2.08
f1 (ppm)

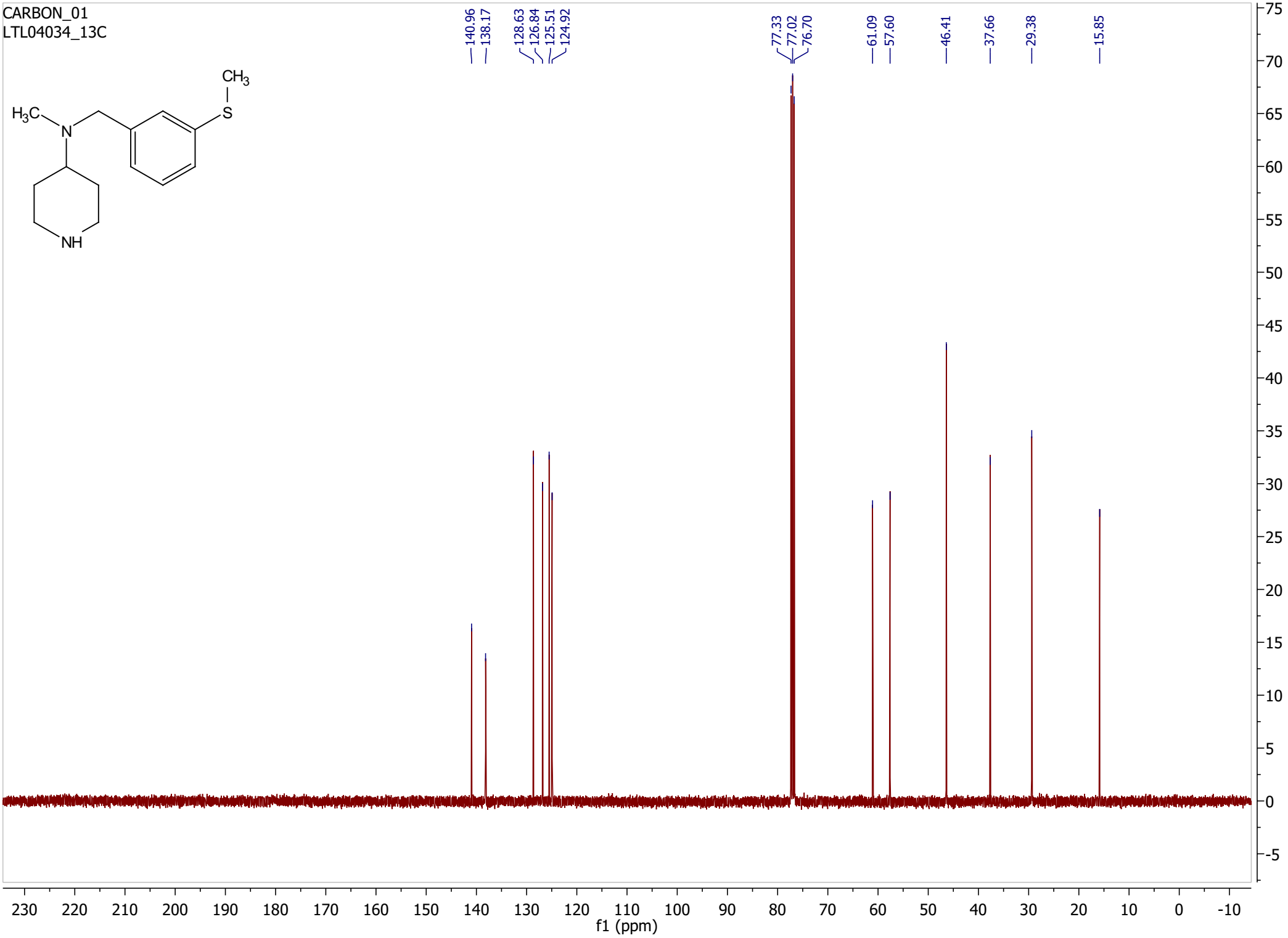

PROTON_01
LTL04031
H3C
N
Cl
NH
7.33 7.33 7.33 7.32 7.32 7.26 7.22 7.22 7.21 7.21 7.20 7.20 7.19 7.19 7.19 7.18 7.18 7.17
3.54 3.18 3.17 3.16 3.15 3.14 3.13
2.61 2.61 2.58 2.58 2.55 2.55 2.55 2.53 2.52 2.51 2.49 2.19 1.93 1.84 1.84 1.83 1.81 1.80 1.80 1.51 1.50 1.48 1.47 1.45
0.96 3.01 2.04 1.96 3.00 3.12 2.53 2.05 1.99
f1 (ppm)

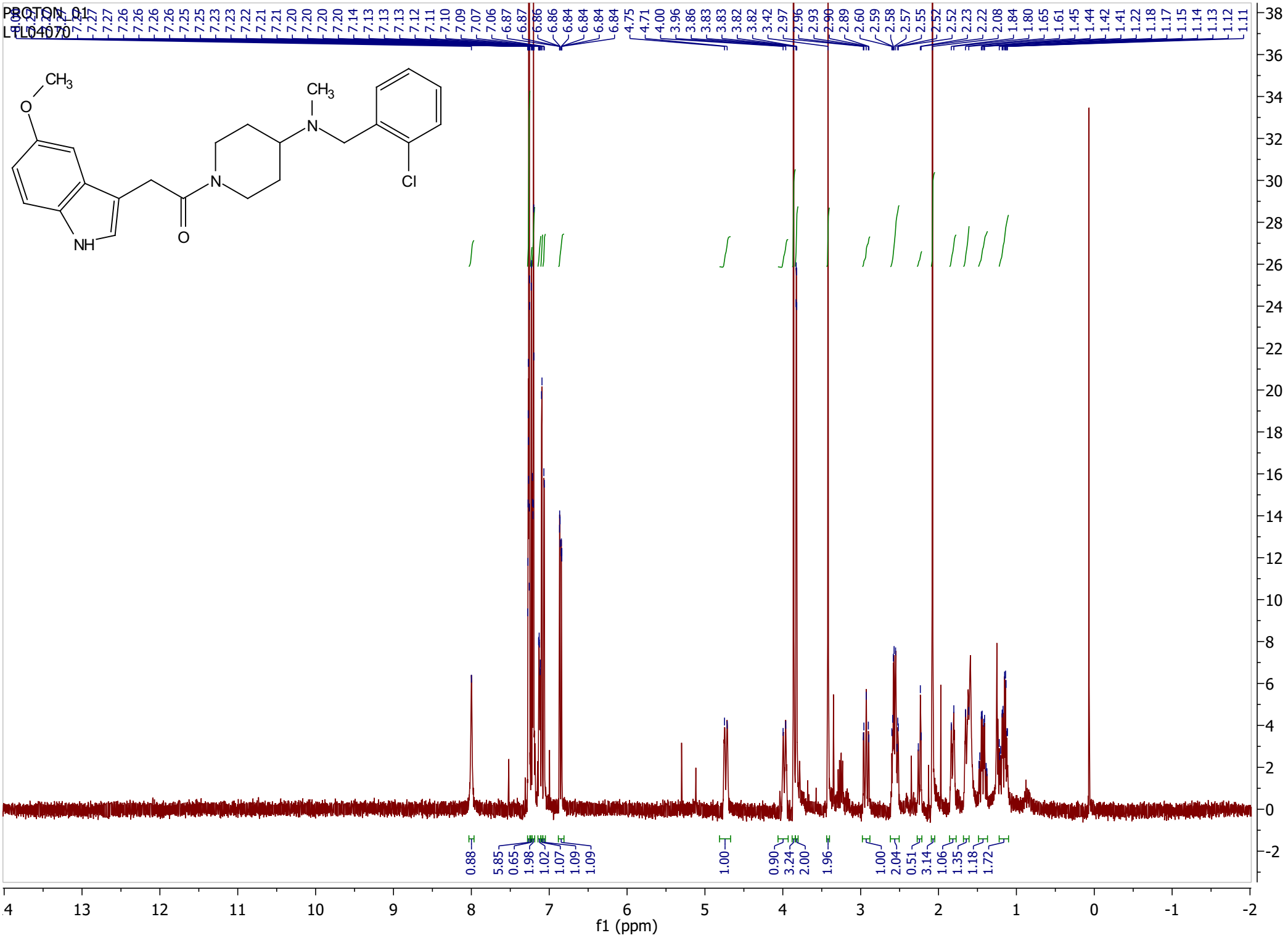

CARBON_01
LTL04031_13C
142.50
134.12
129.40
128.61
126.90
126.68
61.21
57.24
46.33
37.64
29.32
1.00
H3C
N
Cl
NH
f1 (ppm)

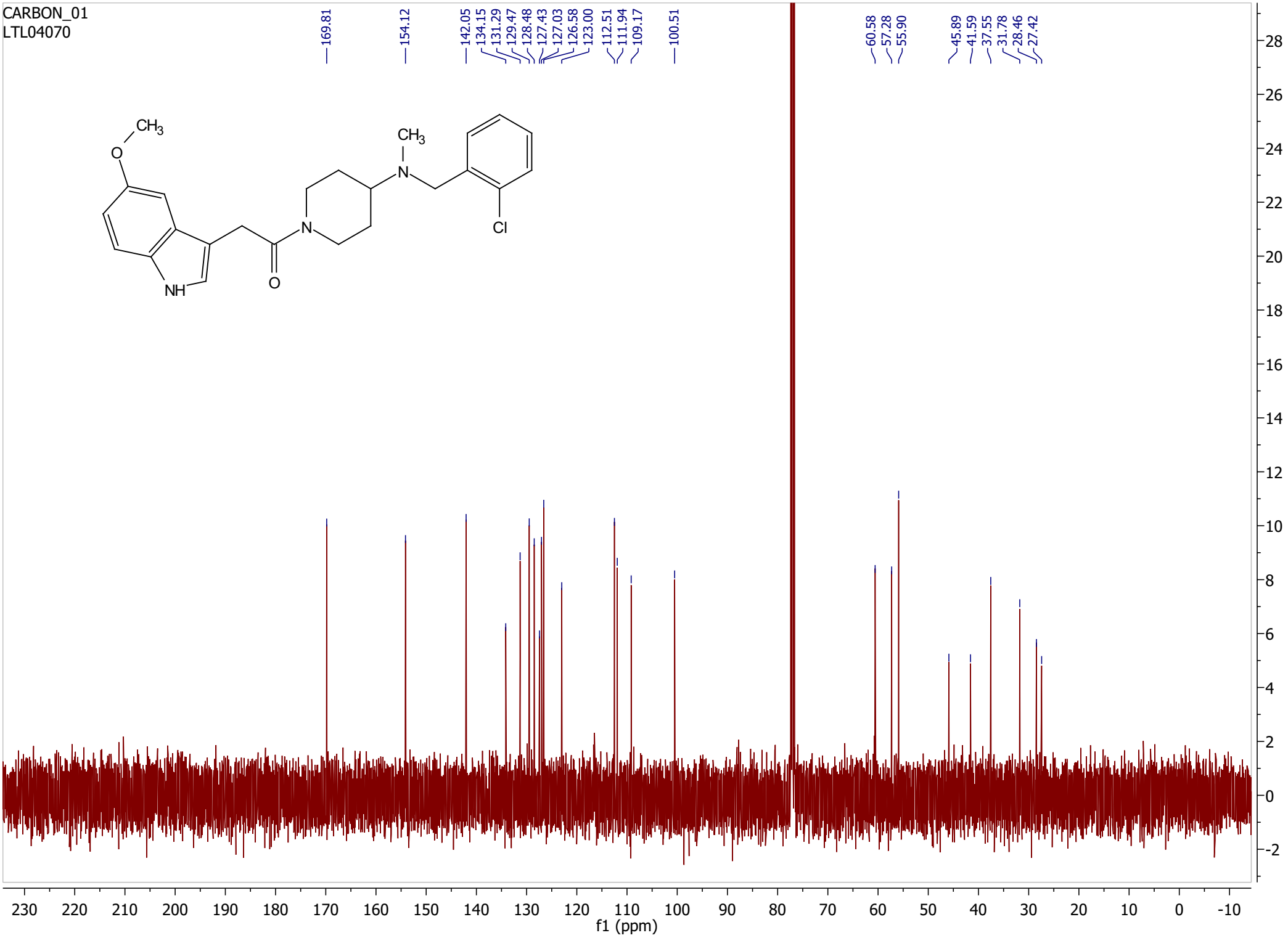

PROTON_01
LTL04029
CH3
H3C
N
O
NH
1.06
2.09
1.00
3.23
2.15
1.99
3.07
3.21
1.62
2.13
2.52
f1 (ppm)

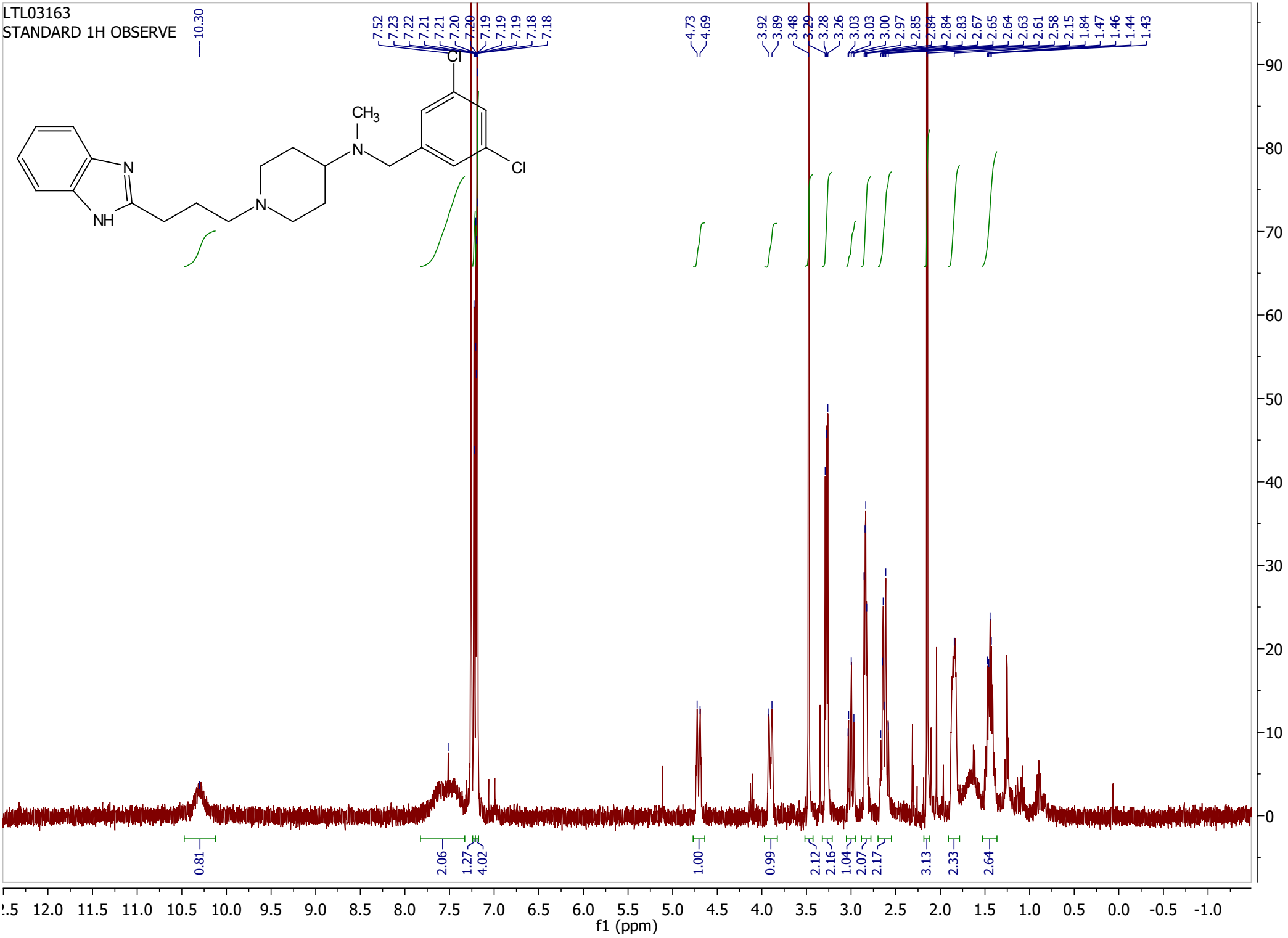

CARBON_01
LTL04029
159.61
141.85
129.11
121.06
114.14
112.20
60.97
57.75
55.17
46.41
37.68
29.34
CH3
H3C
N
O
NH
f1 (ppm)

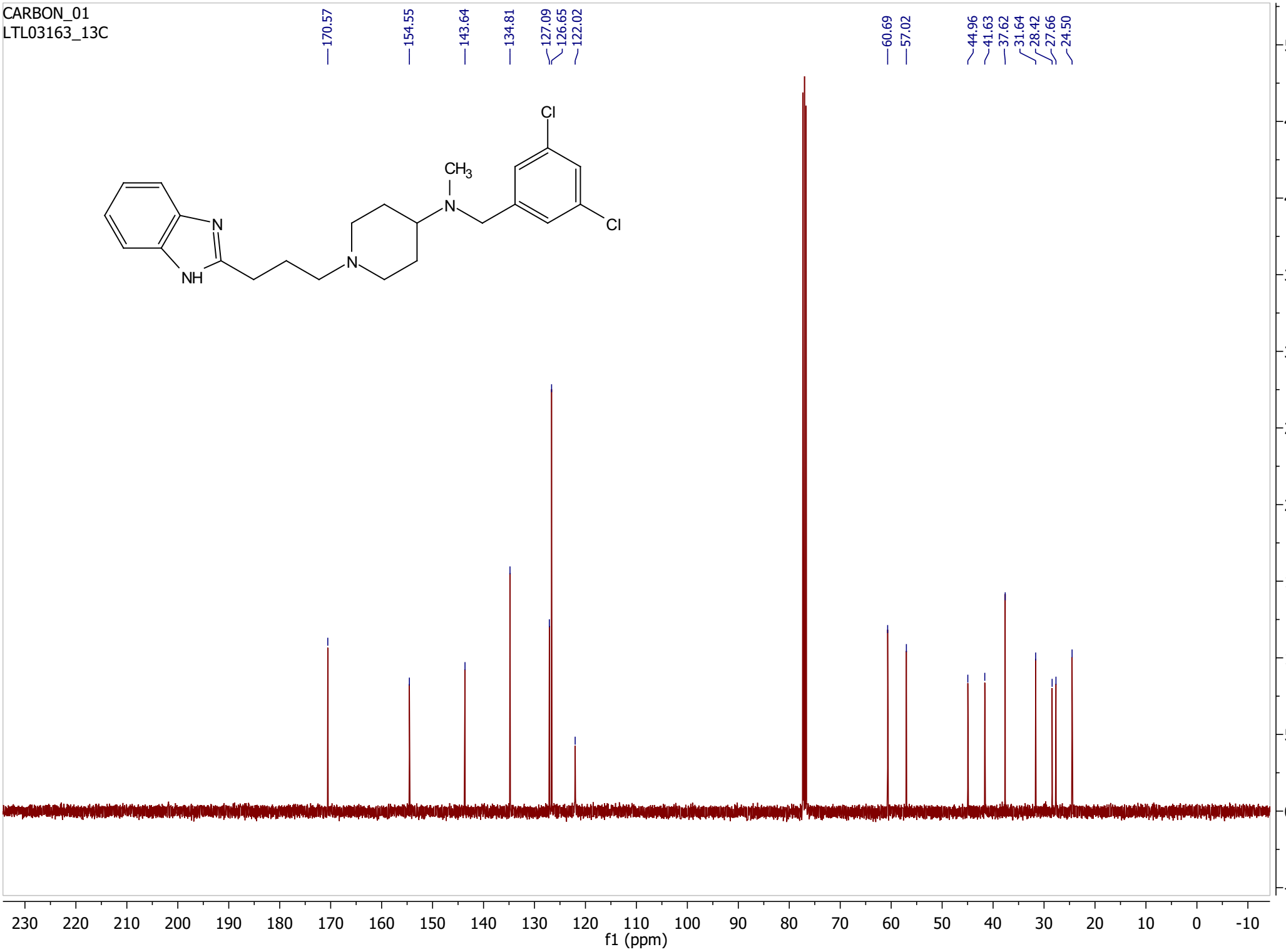

PROTON_01
LTL04034
CH3
H3C
N
S
NH
7.26 7.24 7.23 7.22 7.22 7.22 7.20 7.20 7.13 7.13 7.12 7.11 7.11 7.11 7.10 7.09 7.09 7.09 7.08 7.08 7.07 7.07 7.07 7.07 7.07 7.06
3.54 3.17 3.16 3.14 3.14 3.13 3.12
2.60 2.60 2.57 2.57 2.55 2.54 2.54 2.52 2.47 2.19 1.86 1.84 1.83 1.82 1.81 1.80 1.80 1.80 1.79 1.51 1.50 1.48 1.47 1.47
1.95 1.93 2.05 2.00 2.88 3.11 3.07 3.62 2.01
550 500 450 400 350 300 250 200 150 100 50 0 -50
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)

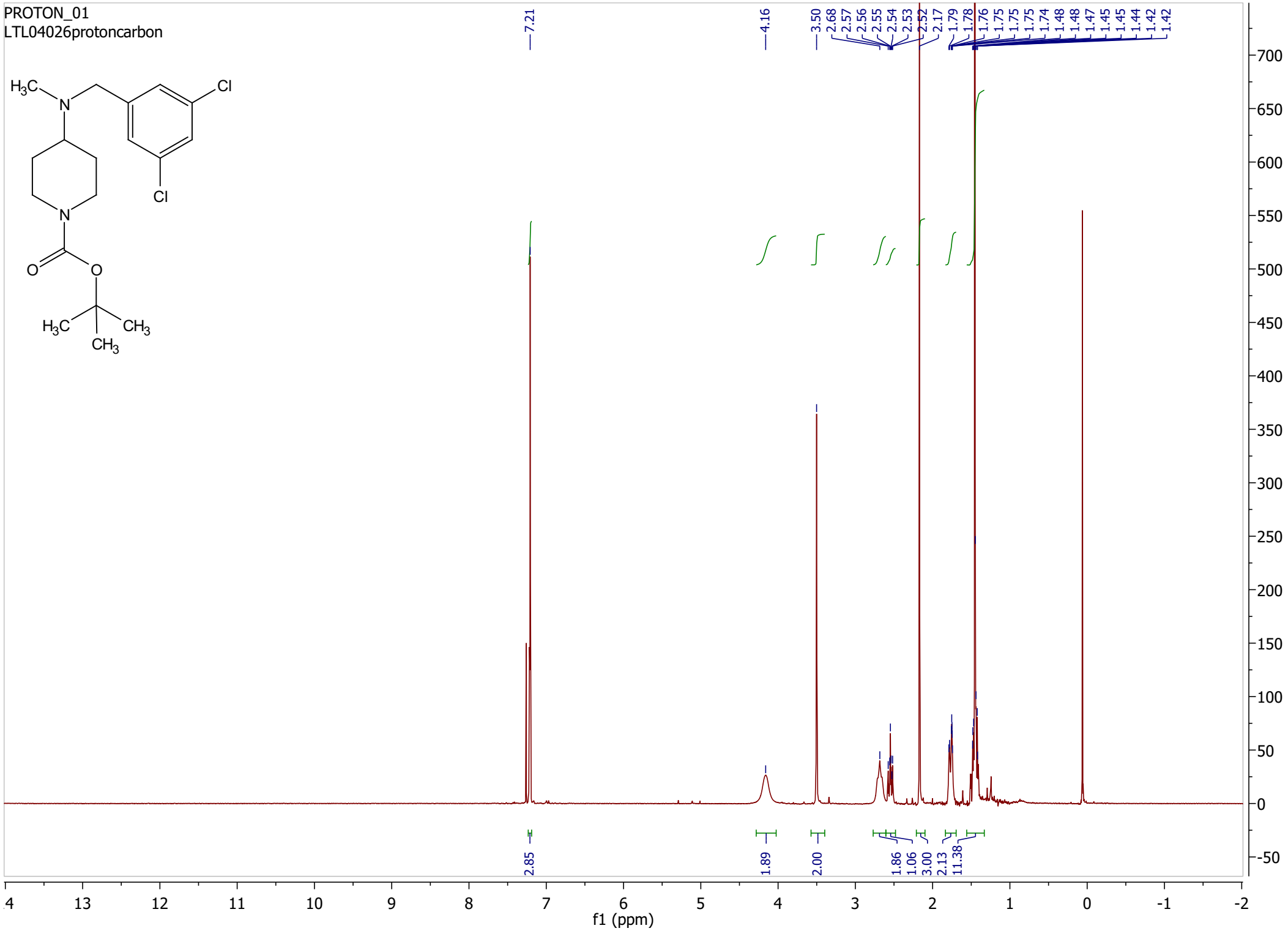

CARBON_01
LTL04034_13C
140.96
138.17
128.63
126.84
125.51
124.92
77.33
77.02
76.70
61.09
57.60
46.41
37.66
29.38
15.85
CH3
H3C
N
S
NH
f1 (ppm)

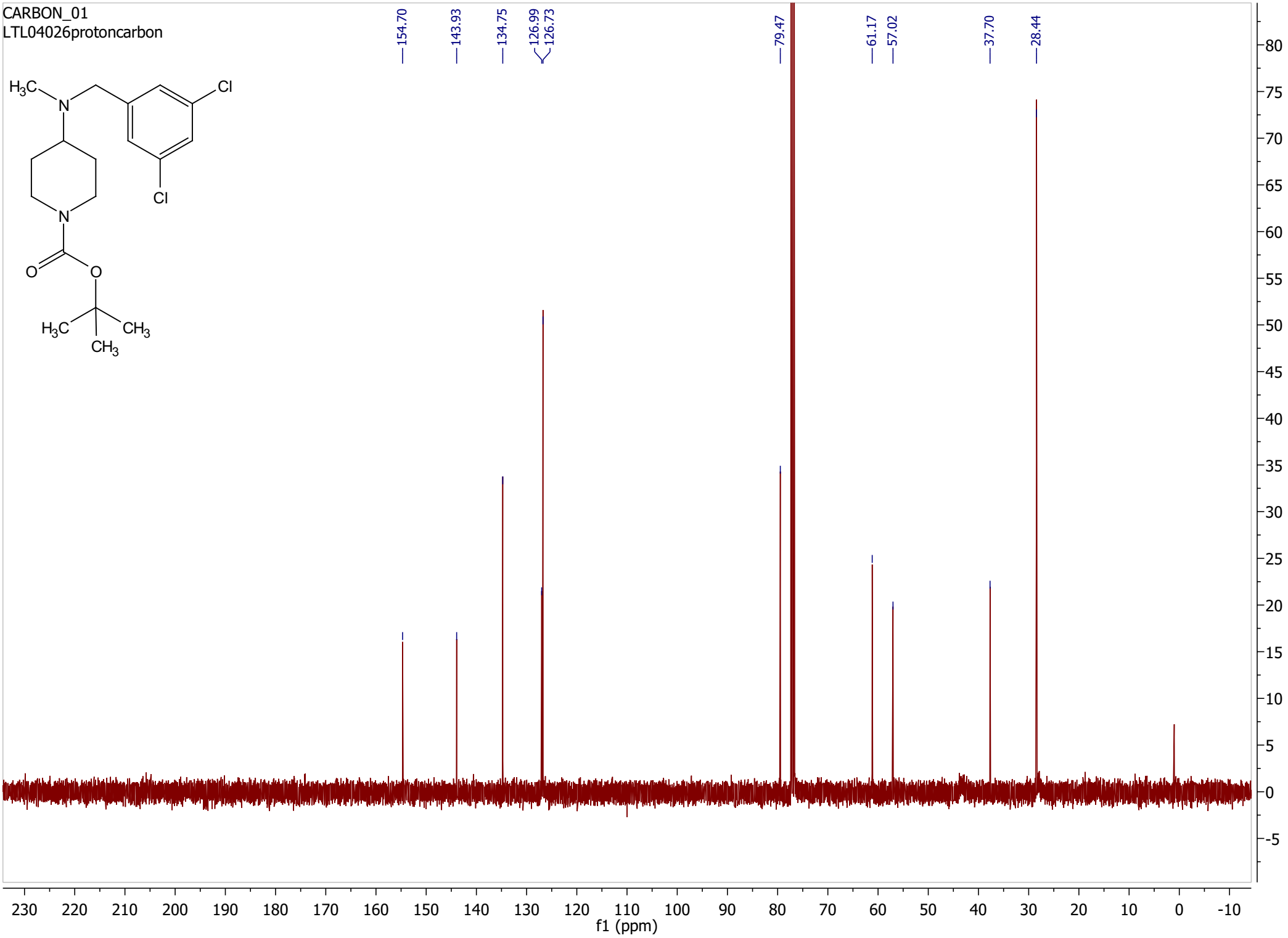

PROTON_01
LTL04070
CH3
O
N
CH3
N
Cl
O
NH
f1 (ppm)

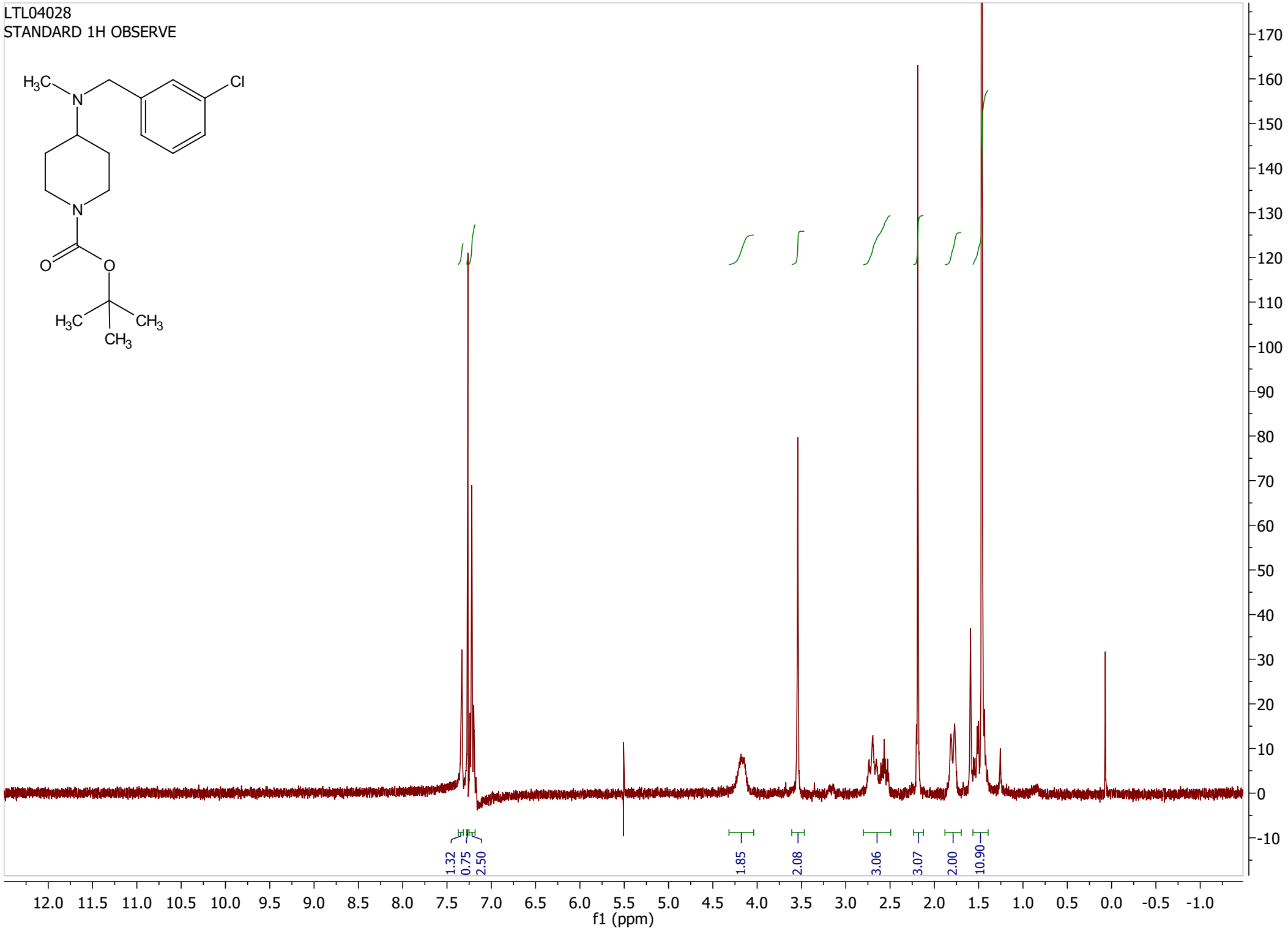

CARBON_01
LTL04070
169.81
154.12
142.05
134.15
131.29
129.47
128.48
127.43
127.03
126.58
123.00
112.51
111.94
109.17
100.51
60.58
57.28
55.90
45.89
41.59
37.55
31.78
28.46
27.42
CH3
O
CH3
N
N
Cl
O
NH
f1 (ppm)


LTL03163
STANDARD 1H OBSERVE
10.30
7.52 7.23 7.22 7.21 7.21 7.20 7.20 7.19 7.19 7.19 7.18 7.18
4.73 4.69
3.92 3.89 3.48 3.29 3.28 3.26 3.03 3.03 3.00 2.97 2.85 2.84 2.84 2.83 2.67 2.65 2.64 2.63 2.61 2.58 2.15 1.84 1.47 1.46 1.44 1.43
Cl
CH3
N
N
NH
N
Cl
0.81
2.06
1.27
4.02
1.00
0.99
2.12
2.16
1.04
2.07
2.17
3.13
2.33
2.64
f1 (ppm)

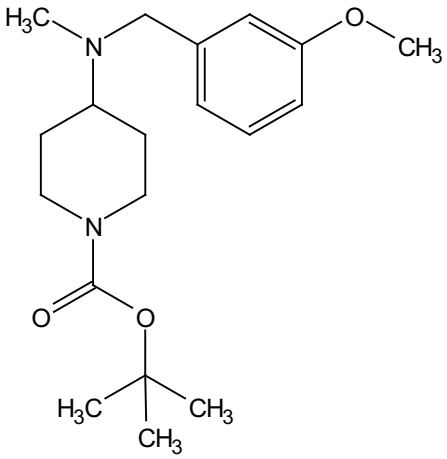

CARBON_01
LTL03163_13C
170.57
154.55
143.64
134.81
127.09
126.65
122.02
60.69
57.02
44.96
41.63
37.62
31.64
28.42
27.66
24.50
Cl
CH3
N
Cl
N
N
NH
f1 (ppm)


PROTON_01
LTL04026protoncarbon
H3C
N
Cl
Cl
N
O
O
H3C
CH3
CH3
7.21
4.16
3.50
2.68
2.57
2.56
2.55
2.54
2.53
2.52
2.17
1.79
1.78
1.76
1.75
1.75
1.75
1.74
1.48
1.48
1.47
1.45
1.45
1.44
1.42
1.42
2.85
1.89
2.00
1.86
1.06
3.00
2.13
11.38
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)


CARBON_01
LTL04026protoncarbon
154.70
143.93
134.75
126.99
126.73
79.47
61.17
57.02
37.70
28.44
f1 (ppm)


LTL04028
STANDARD 1H OBSERVE
H3C
N
Cl
N
O
O
H3C
CH3
CH3
1.32
0.75
2.50
1.85
2.08
3.06
3.07
2.00
10.90
f1 (ppm)

PROTON_01
LTL04016
cdcl3

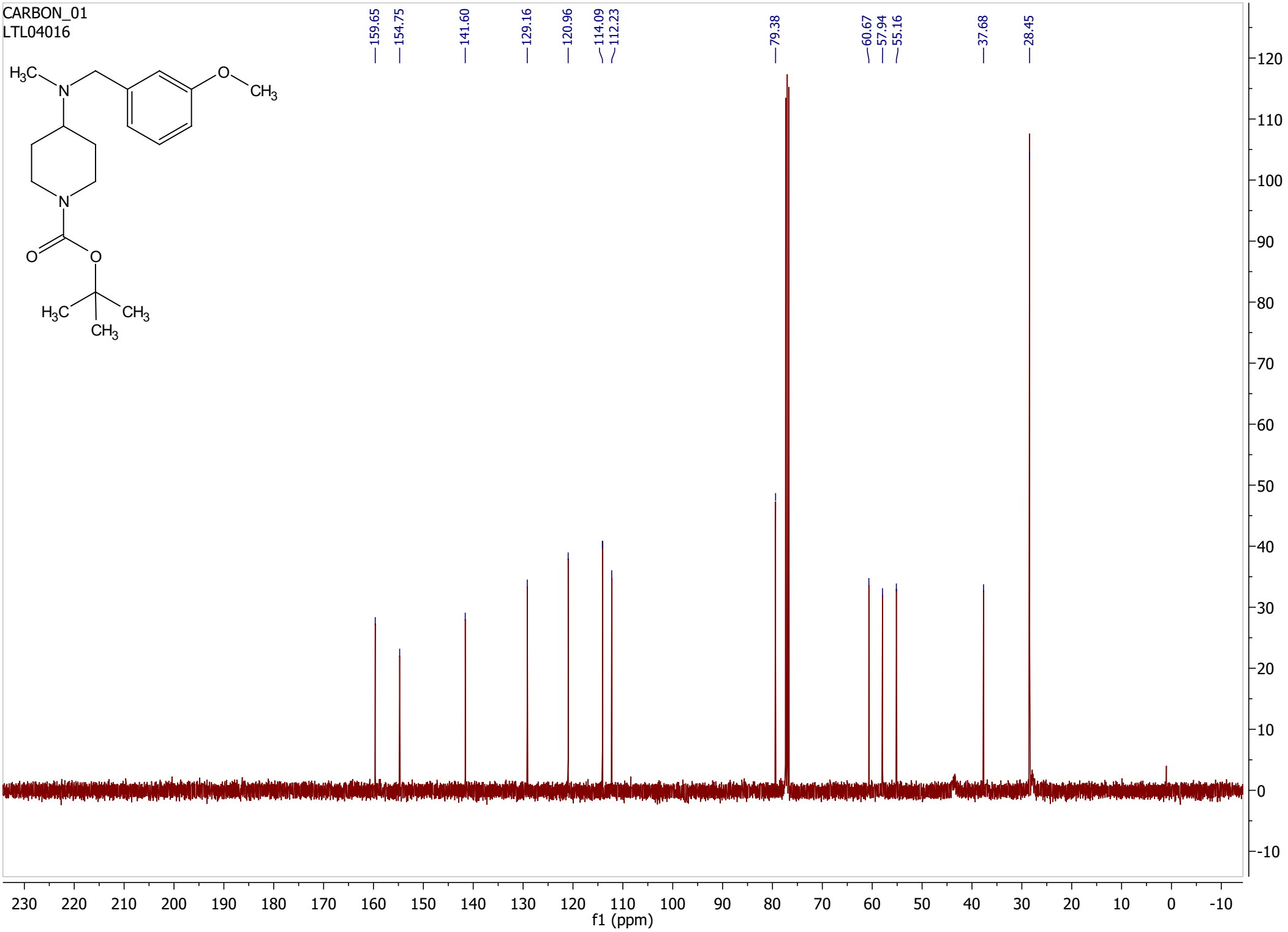


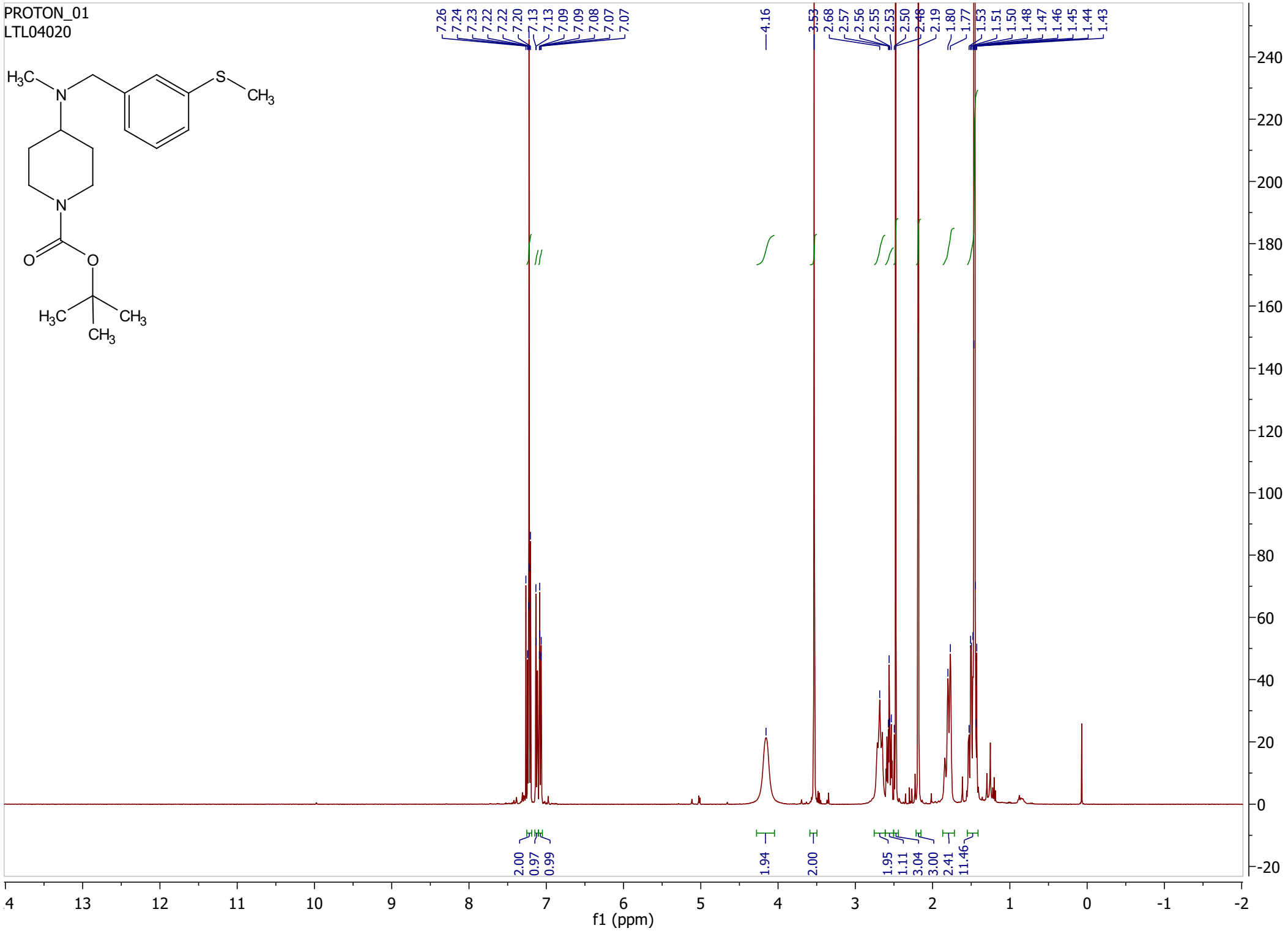
7.26 7.24 7.22 7.20 6.90 6.90 6.89 6.88 6.88 6.80 6.79 6.79 6.79 6.77 6.77 6.77 6.77

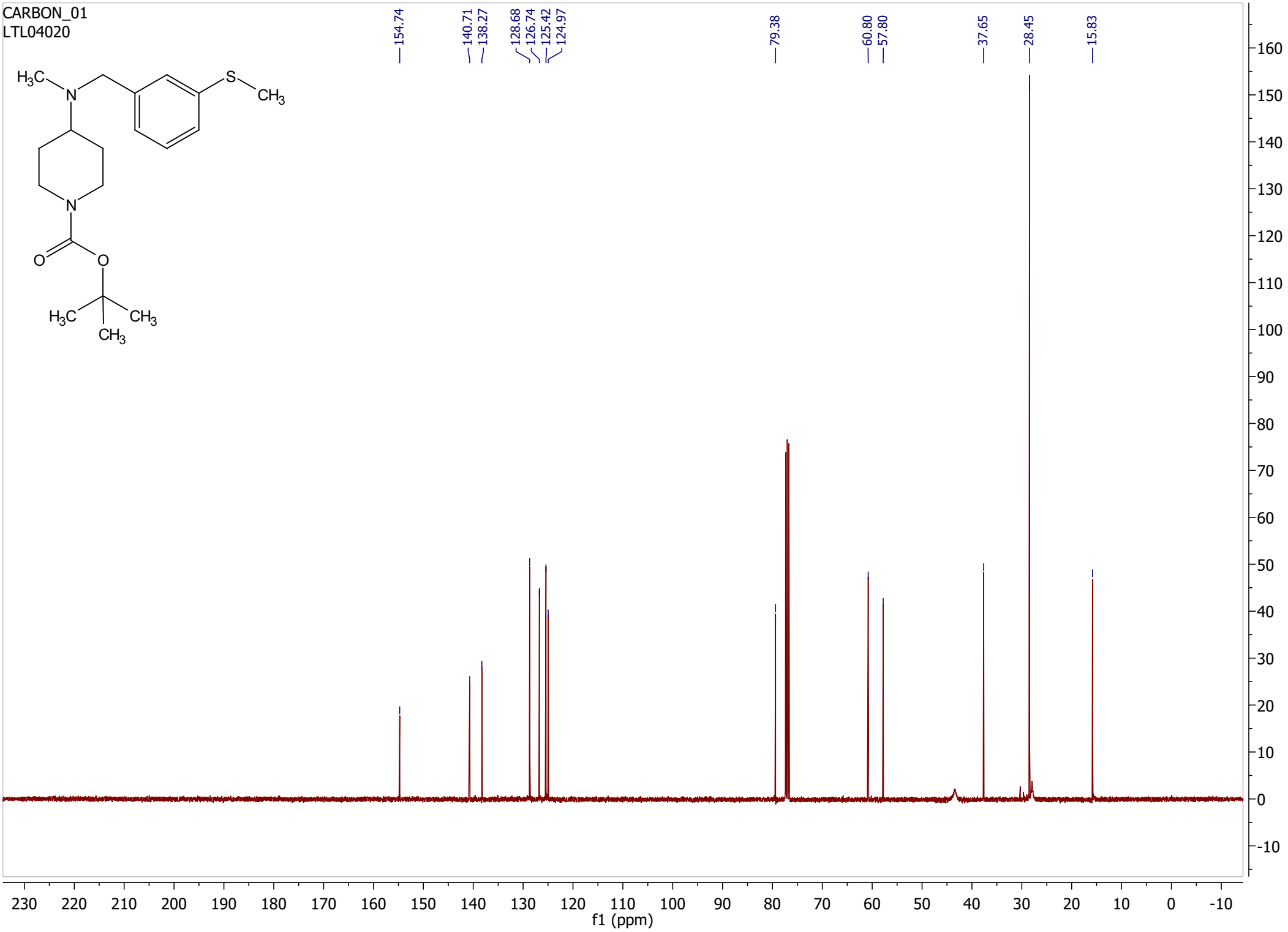
4.15 3.82 3.80 3.55 2.68 2.60 2.58 2.57 2.56 2.54 2.20 1.80 1.77 1.61 1.60 1.54 1.53 1.51 1.50 1.48 1.47 1.47 1.47 1.46 1.44 1.43

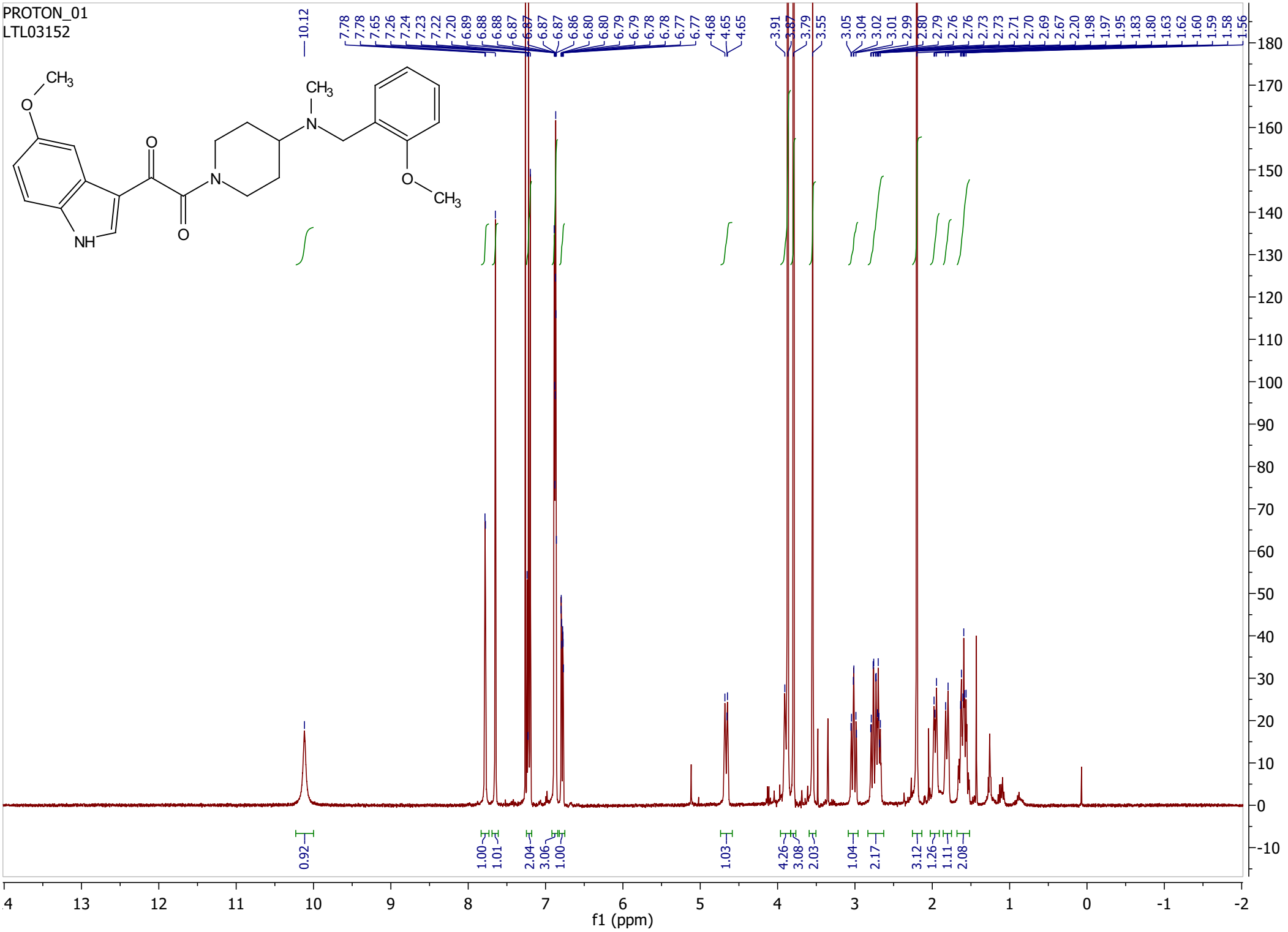
1.00 2.01 0.98 1.84 3.15 2.07 1.96 1.17 3.11 2.05 0.84 11.44

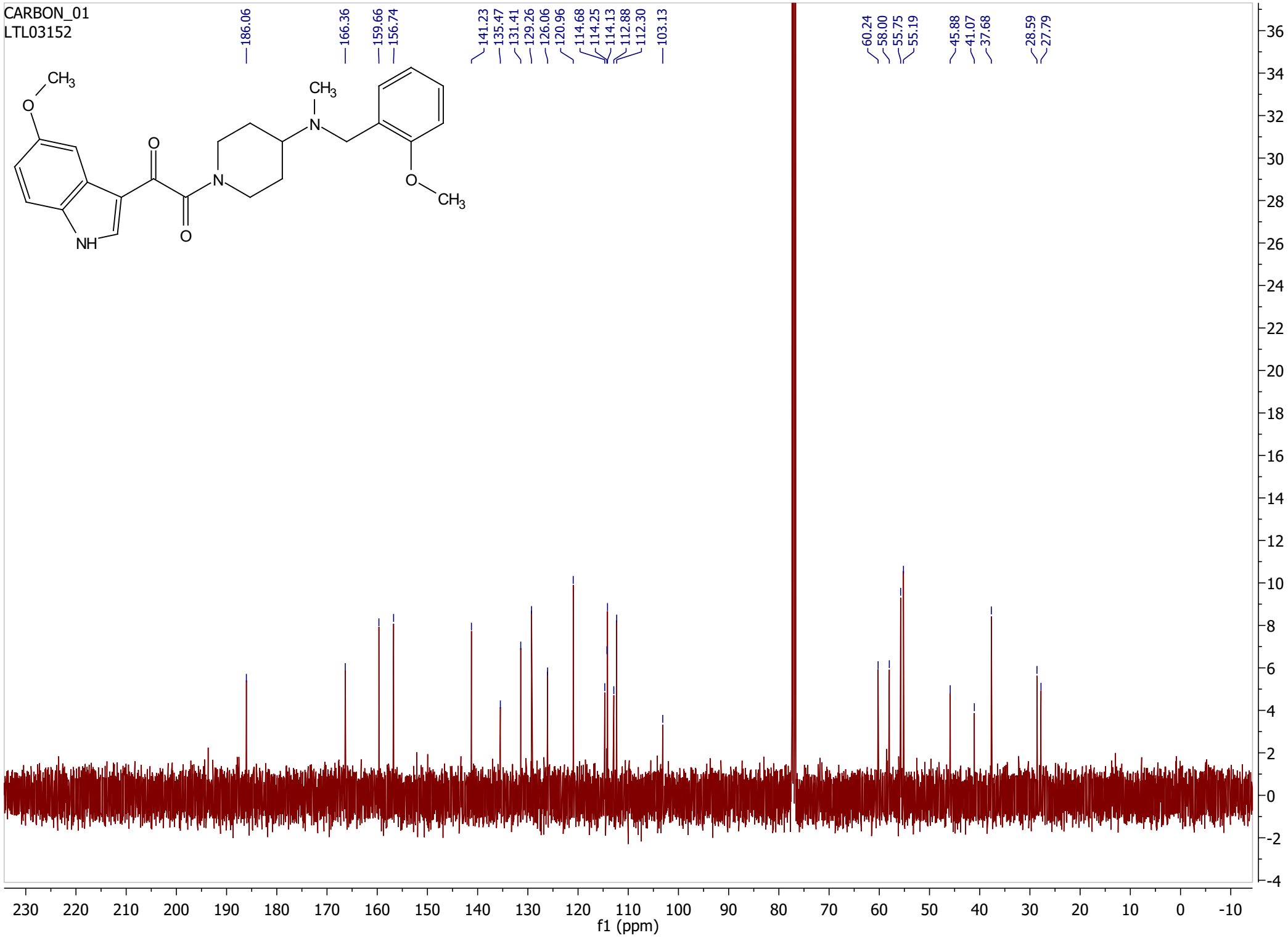
f1 (ppm)

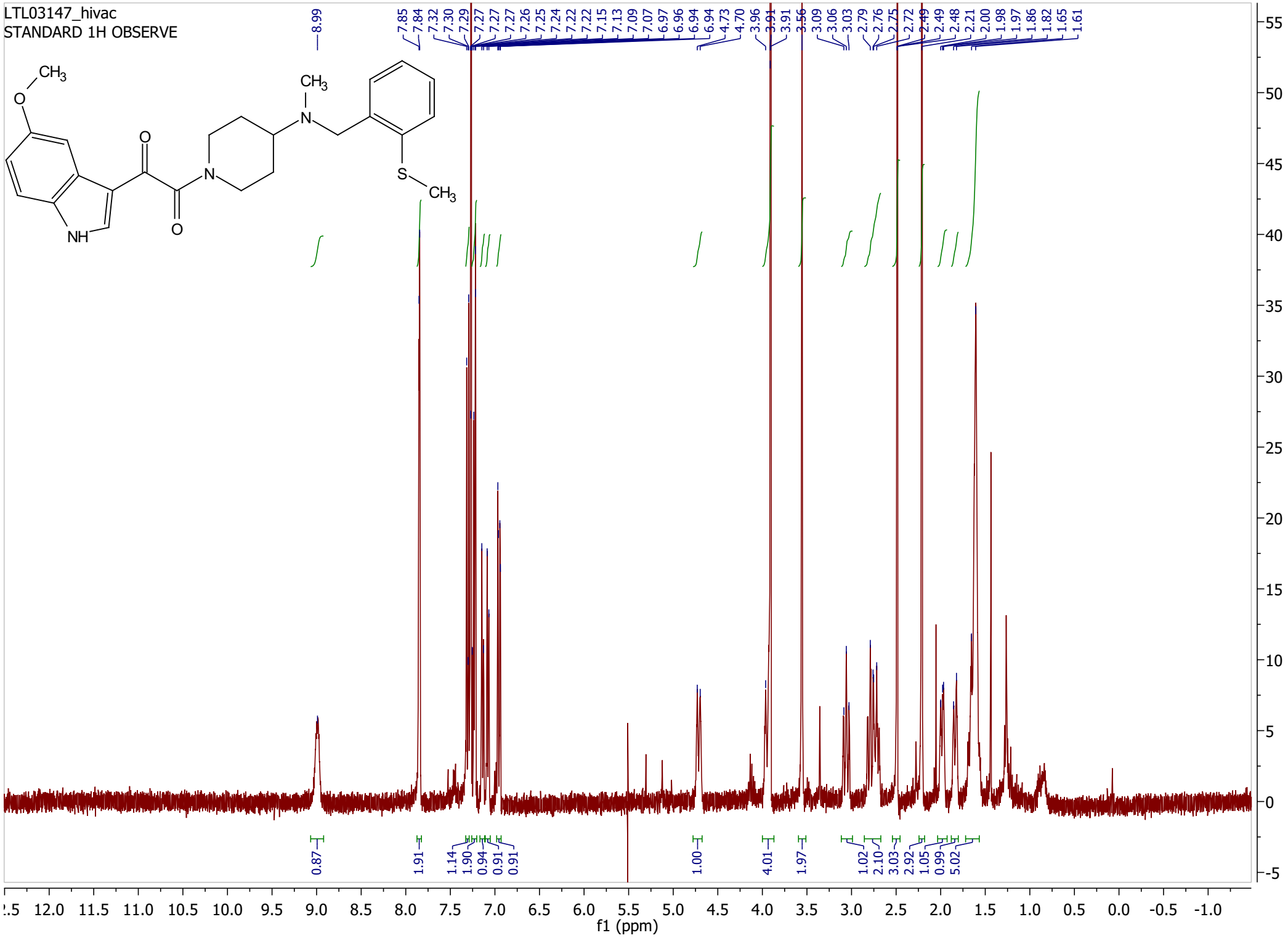

CARBON_01
LTL04016
159.65
154.75
141.60
129.16
120.96
114.09
112.23
79.38
60.67
57.94
55.16
37.68
28.45
f1 (ppm)

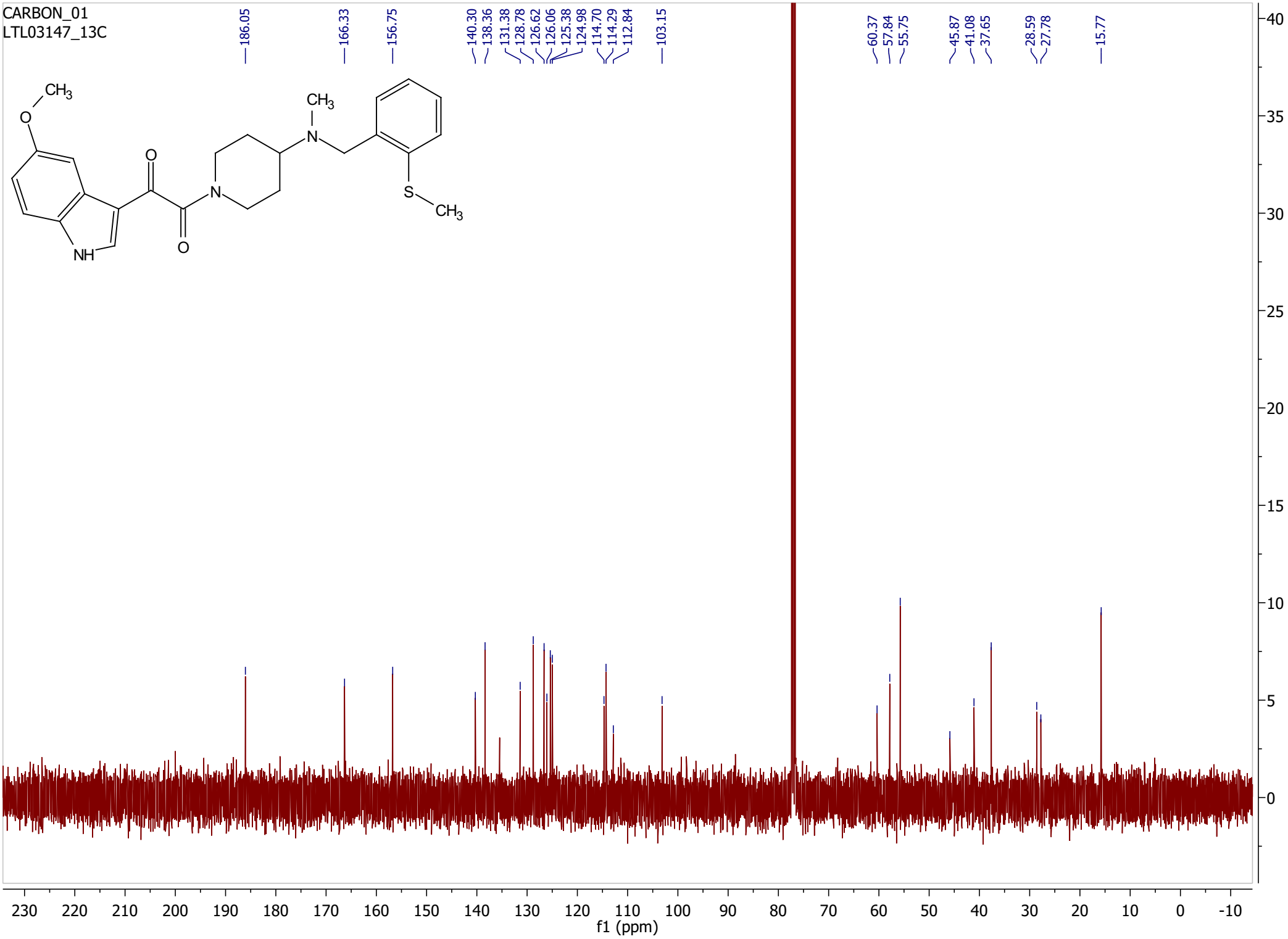

PROTON_01
LTL04020
7.26 7.24 7.23 7.22 7.22 7.20 7.13 7.13 7.09 7.09 7.08 7.07 7.07
4.16
3.53
2.68 2.57 2.56 2.55 2.53 2.50 2.48 2.19 1.80 1.77 1.53 1.51 1.50 1.48 1.47 1.46 1.45 1.44 1.43
2.00 0.97 0.99
1.94
2.00
1.95 1.11 3.04 3.00 2.41 11.46
f1 (ppm)

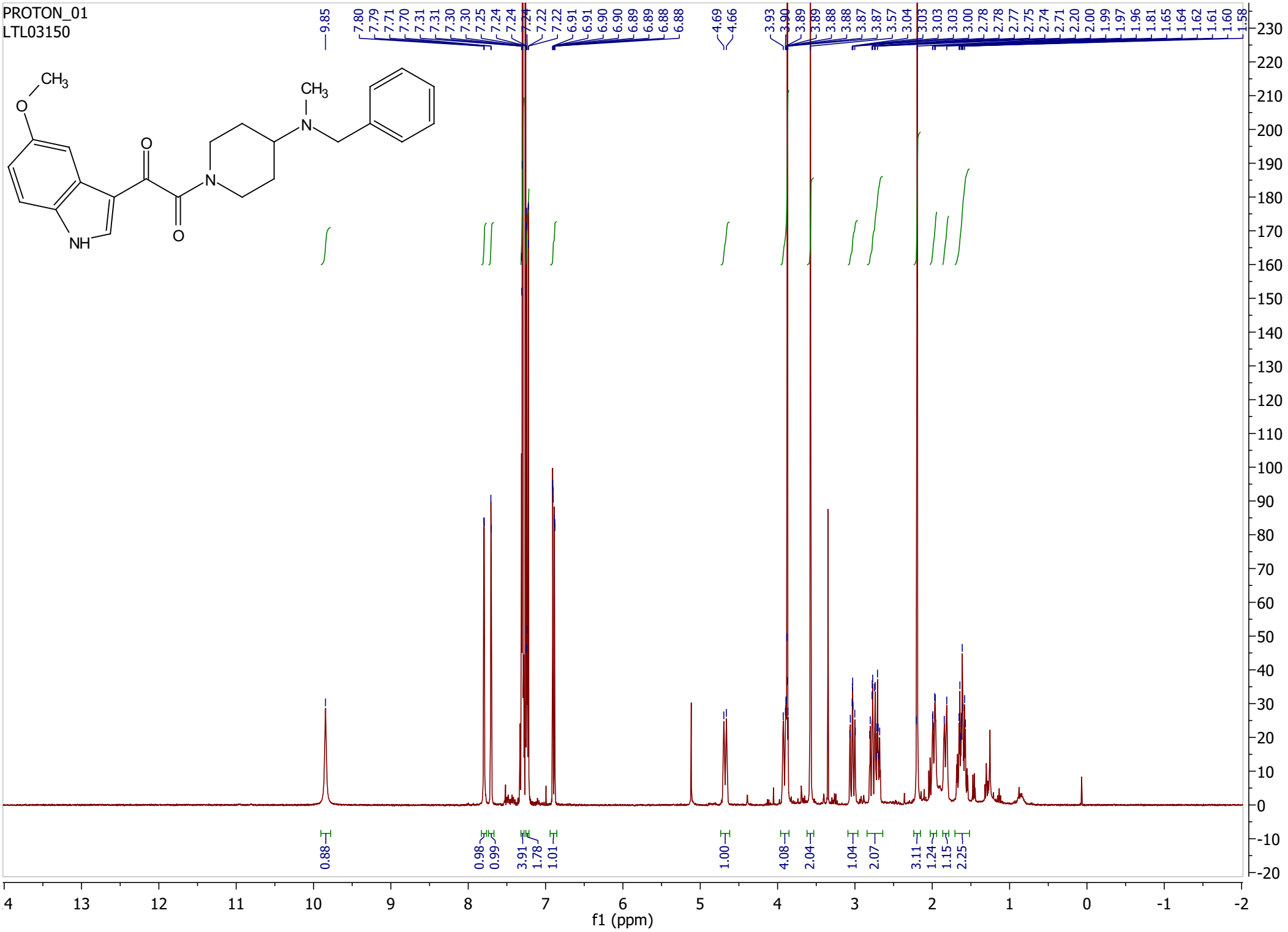

CARBON_01
LTL04020
154.74
140.71
138.27
128.68
126.74
125.42
124.97
79.38
60.80
57.80
37.65
28.45
15.83
f1 (ppm)

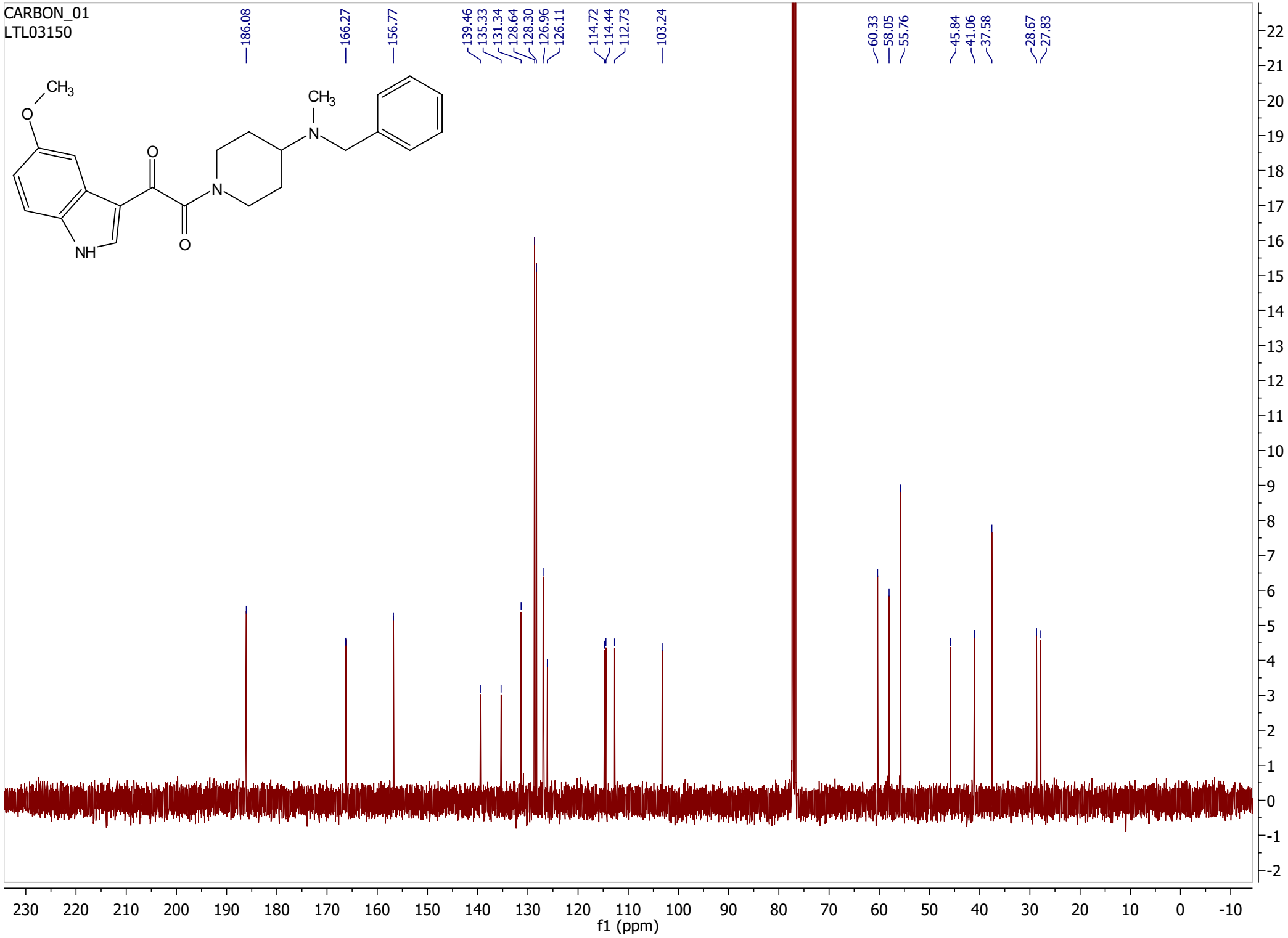

PROTON_01
LTL03152
f1 (ppm)


CARBON_01
LTL03152
186.06
166.36
159.66
156.74
141.23
135.47
131.41
129.26
126.06
120.96
114.68
114.25
114.13
112.88
112.30
103.13
60.24
58.00
55.75
55.19
45.88
41.07
37.68
28.59
27.79
f1 (ppm)


LTL03147_hivac
STANDARD 1H OBSERVE
8.99
7.85
7.84
7.32
7.30
7.29
7.27
7.27
7.27
7.26
7.25
7.24
7.22
7.22
7.15
7.13
7.09
7.07
6.97
6.96
6.94
6.94
4.73
4.70
3.96
3.91
3.91
3.56
3.09
3.06
3.03
2.79
2.76
2.75
2.72
2.49
2.49
2.48
2.21
2.00
1.98
1.97
1.86
1.82
1.65
1.61
CH3
O
O
N
CH3
N
S
CH3
O
NH
0.87
1.91
1.14
1.90
0.94
0.91
0.91
1.00
4.01
1.97
1.02
2.10
3.03
2.92
1.05
0.99
5.02
f1 (ppm)


CARBON_01
LTL03147_13C
186.05
166.33
156.75
140.30
138.36
131.38
128.78
126.62
126.06
125.38
124.98
114.70
114.29
112.84
103.15
60.37
57.84
55.75
45.87
41.08
37.65
28.59
27.78
15.77
CH3
O
O
N
CH3
N
S
CH3
O
NH
40
35
30
25
20
15
10
5
0
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


PROTON_01
LTL03150
f1 (ppm)


CARBON_01
LTL03150
186.08
166.27
156.77
139.46
135.33
131.34
128.64
128.30
126.96
126.11
114.72
114.44
112.73
103.24
60.33
58.05
55.76
45.84
41.06
37.58
28.67
27.83
CH3
O
O
N
O
NH
CH3
N
f1 (ppm)