Orthogonal Tandem Catalysis involving Au(I)-Hydroacyloxylation and Rh(I)-Hydroformylation reactions

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1. General information

Reagents and dry solvents were obtained from commercial sources and used without further purification. Thin-layer chromatography (TLC) was performed on silica gel 60 F254 plates, was visualized under UV light, and revealed with $KMnO_4$ stain. Crude products were purified by flash column chromatography on Merck silica gel Si 60 (40-63 µm) or by using a CombiFlash Rf (Teledyne Isco) system. NMR spectra were recorded at 400 or 500 MHz for ^{1}H, at 101 or 126 MHz for ^{13}C, at 376 MHz for ^{19}F, and at 400 MHz for ^{31}P. Chemical shifts (δ (ppm)) were reported in ppm relative to residual solvent. Coupling constants (*J*) were reported in hertz (Hz). Assignments of ^{1}H and ^{13}C signal were made by DEPT, COSY, HSQC, HMBC, and NOESY-2D experiments. The following abbreviations were adopted in reporting NMR data: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), broad signal (bs), doublet of doublets (dd), doublet of doublet of doublets (ddd), doublet of triplets (dt), doublet of quartets (dq), triplet of doublets (td), triplet of triplets (tt), quartet of triplets (qt) or multiplet (m). HRMS were performed with a Q-TOF analyzer using electrospray ionization (ESI).

2. Synthesis of 1 and 11

2.1 General Procedures

General procedure for Sonogashira cross-coupling (**A**):

The methyl 2-iodoaryl ester was solubilized in freshly distilled NEt_3 (60 eq) with $PdCl_2(PPh_3)_2$ (2 mol%) and CuI (1 mol%). The gases were eliminated from the mixture using the freeze/pump/thaw method three times before the addition of trimethylsilylacetylene (1.2 eq). The resulting mixture was left under agitation at room temperature overnight. The medium was then diluted with Et_2O and filtered on Celite®. The solvents were then removed under reduced pressure. The crude product was then purified on column chromatography to afford the corresponding methyl 2-(2-(trimethylsilyl)ethynyl)aryl ester.

General procedure for deprotection (**B**):

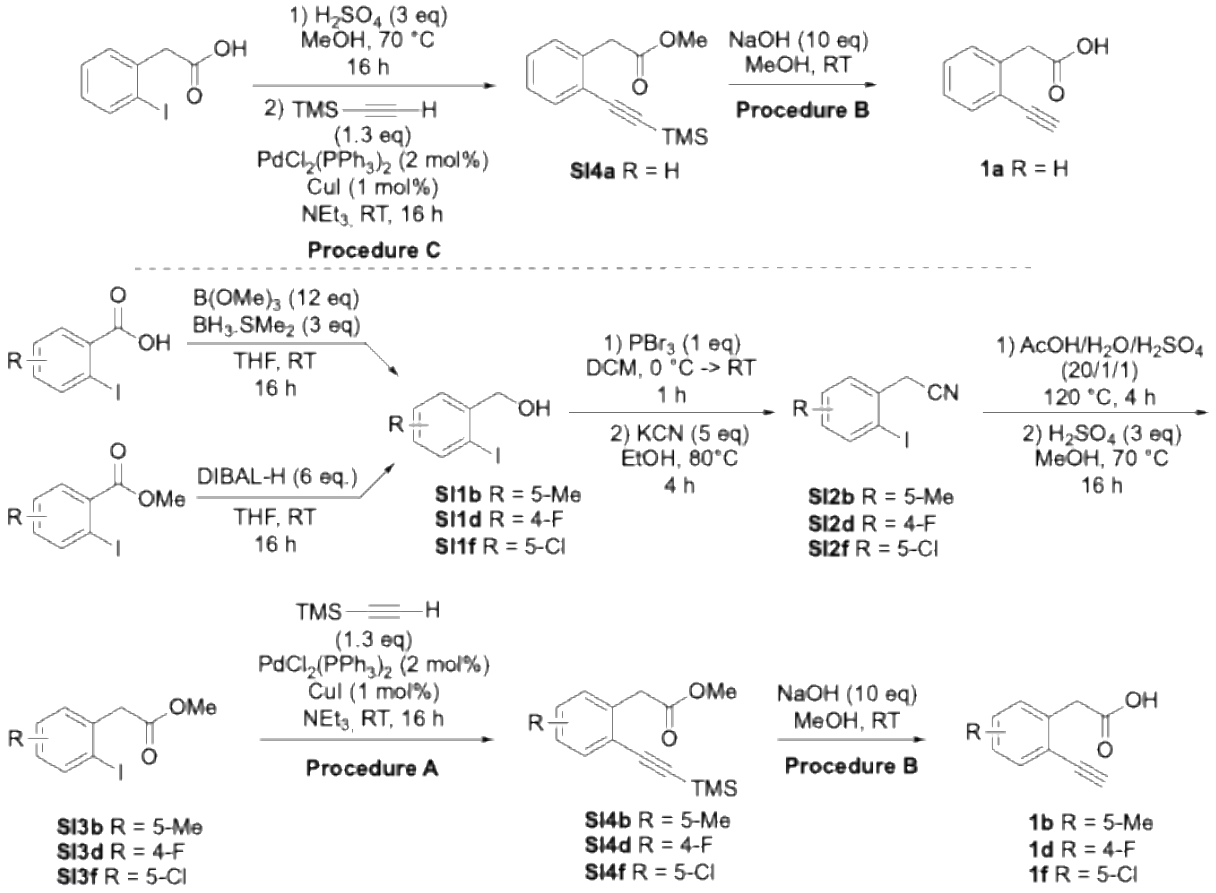
In a round-bottomed flask, the methyl 2-(2-(trimethylsilyl)ethynyl)aryl ester was solubilized in MeOH (100 eq) with NaOH (10 eq) and left under agitation until total consumption of the ester. The medium was then cooled down to T = 0 °C, diluted with deionized water, acidified carefully with a HCl 2 M aqueous solution to pH = 2-3, and the resulting aqueous phase was then extracted thrice using diethyl ether. The organic layers were combined, washed with brine once, and then dried over anhydrous Na_2SO_4. The solvents were finally removed under reduced pressure. The crude product was then optionally purified on column chromatography to afford the corresponding 2-ethynylaryl carboxylic acid.

General procedure for preparation of methyl 2-(2-(trimethylsilyl)ethynyl)aryl ester from commercial 2-iodoaryl carboxylic acid (**C**):

The 2-iodoaryl carboxylic acid was solubilized in anhydrous MeOH (20 eq). The resulting solution was cooled down to T = 0 °C, then 3 equivalents of concentrated H_2SO_4 were added dropwise. Finally, the mixture was left under reflux for 16 h. After cooling down, the mixture was diluted with 40 eq of deionized water and the aqueous phase then was extracted once with ethyl acetate. The resulting organic phase was then washed sequentially using a saturated solution of $NaHCO_3$, and brine. The organic layer was then dried over anhydrous $MgSO_4$ and the solvents were removed under reduced pressure.

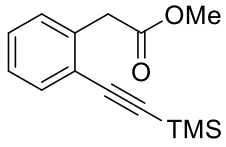
The crude methyl 2-iodoaryl ester obtained was solubilized in freshly distilled NEt_3 (60 eq) with $PdCl_2(PPh_3)_2$ (2 mol%) and CuI (1 mol%). The gases were eliminated from the mixture using the freeze/pump/thaw method three times before the addition of trimethylsilylacetylene (1.2 eq). The resulting mixture was left under agitation at room temperature overnight. The medium was then diluted with Et_2O and filtered on Celite®. The solvents were then removed under reduced pressure. The crude product was then purified on column chromatography to afford the corresponding methyl 2-(2-(trimethylsilyl)ethynyl)aryl ester.

2.2 Synthesis of 1



2.2.1 Synthesis of 1a

methyl 2-(2-((trimethylsilyl)ethynyl)phenyl)acetate (SI4a)



$C_{14}H_{18}O_2Si$

MW: 246.38 g/mol

Compound **SI4a** was synthesized following general procedure **C** from commercially available 2-(2-iodophenyl)acetic acid (3 g, 11.45 mmol), along with conc. H_2SO_4 (3 eq, 1.8 mL, 34.4 mmol) and 9 mL of anhydrous methanol. The crude ester obtained after work-up got used as is in the next step, and solubilized along with $PdCl_2(PPh_3)_2$ (2 mol% , 163.6 mg, 0.23 mmol), CuI (1 mol% , 21.8 mg, 0.11 mmol), trimethylsilylacetylene (1.2 eq, 1.96 mL, 13.74 mmol), in 100 mL of triethylamine. Purification by chromatography on silica gel, with an eluent pentane:AcOEt (98:2), afforded compound **SI4a** (83% in two steps, 1.95 g, 7.91 mmol) as a gold yellow oil.

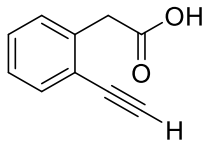
Rf = 0.20 (pentane:AcOEt (98:2)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.50 – 7.43 (m, 1H), 7.32 – 7.23 (m, 2H), 7.21 (td, *J* = 7.1, 2.2 Hz, 1H), 3.83 (s, 2H), 3.69 (s, 3H), 0.25 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 171.4, 136.7, 132.3, 129.9, 128.8, 127.1, 123.5, 103.1, 99.1, 51.9, 39.9, 0.0 (3*C).

HRMS (ESI): calculated for $C_{14}H_{19}O_2Si^+$ $[M+H]^+$, 247.1149 found 247.1160 (Δ = 4.2 ppm)

2-(2-ethynylphenyl)acetic acid (1a)



$C_{10}H_8O_2$

MW: 160.17 g/mol

Compound **1a** was synthesized following general procedure **B** from compound **SI4a** (500 mg, 2.03 mmol) with NaOH (10.7 eq, 866.1 mg, 21.7 mmol) in 8 mL of MeOH. Compound **1a** (92%, 300 mg, 1.87 mmol) was afforded as an orange solid.

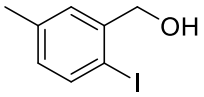
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.56 – 7.49 (m, 1H), 7.38 – 7.22 (m, 3H), 3.90 (s, 2H), 3.29 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 177.3, 135.9, 132.8, 129.9, 129.1, 127.4, 122.6, 81.9, 81.5, 39.4.

HRMS (ESI): calculated for $C_{10}H_9O_2^+$ $[M+H]^+$, 161.0597 found 161.0605 (Δ = 4.4 ppm)

2.2.2 Synthesis of 1b

(2-iodo-5-methylphenyl)methanol (SI1b) [1]



C_8H_9ClO

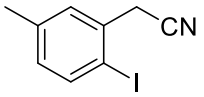
MW: 248.06 g/mol

In a vacuum-dried round-bottomed flask, commercially available met[7]hyl 2-iodo-5-methylbenzoate (400 mg, 1.45 mmol) was solubilized in 3.9 mL of anhydrous THF. The medium was then cooled down to -78 °C. DIBAL-H (6 eq, 1.24 g, 8.69 mmol) was added dropwise as 1 M solution in dichloromethane. The reaction mixture was left under agitation at room temperature overnight. The medium was then cooled down to 0 °C, and the reaction quenched by addition of 8.7 mL of water dropwise. The aqueous phase obtained was acidified to pH = 1 by addition of HCl 2N, then extracted thrice with 20 mL of ethyl acetate. The resulting organic phase was washed with water, then with brine, dried over $MgSO_4$, filtered and evaporated to dryness. Purification by chromatography on silica gel, with an eluent pentane:AcOEt (90:10), afforded compound **SI1b** (97% , 347.7 mg, 1.40 mmol) as a white solid.

Rf = 0.20 (pentane:AcOEt (90:10)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.68 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 3.1 Hz, 1H), 6.83 (dd, *J* = 8.3, 2.1 Hz, 1H), 4.65 (d, *J* = 6.0 Hz, 2H), 2.32 (d, *J* = 0.7 Hz, 3H), 1.94 (t, *J* = 6.2 Hz, 1H).

2-(2-iodo-5-methylphenyl)acetonitrile (SI2b)



C_9H_8IN

MW: 257.07 g/mol

To an ice-cold solution of (2-iodo-5-methylphenyl)methanol **SI1b** (404.3 mg, 1.63 mmol) in 10 mL of anhydrous DCM, was added phosphorus tribromide PBr_3 (1 eq, 150 µL, 1.63 mmol) dropwise. The reaction mixture was then left under stirring for 1 h after which the ice bath was removed and the stirring was furthered overnight at room temperature. The reaction mixture was quenched by addition of 20 mL of deionized H_2O. The aqueous phase was extracted thrice with diethyl ether Et_2O (3 x 20 mL). The organic layers were then combined, washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude product thus obtained was solubilized in 5.4 mL of EtOH. Potassium cyanide KCN (5 eq, 530.7 mg, 8.15 mmol) was then added. The reaction mixture was then stirred under reflux for 4 h, cooled down, and quenched with deionized water. The aqueous phase was extracted thrice with Et_2O (3 x 10mL). The organic layers were reunited, washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. Purification by chromatography on silica gel, with an eluent pentane:AcOEt (95:5), afforded compound **SI2b** (70% in two steps, 291.6 mg, 1.13 mmol) as a white solid.

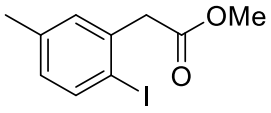
Rf = 0.58 (pentane:AcOEt (95:5)).

[1] G. Chouhan, H. Alper, *J. Org. Chem.* **2009**, *74*, 6181–6189. https://doi.org/10.1021/jo9010574.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.72 (d, *J* = 8.1 Hz, 1H), 7.35 (d, *J* = 2.2 Hz, 1H), 6.86 (dd, *J* = 8.2, 2.1 Hz, 1H), 3.78 (s, 2H), 2.33 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 139.5, 139.3, 132.9, 130.8, 129.9, 117.3, 94.8, 29.8, 20.9.

Methyl 2-(2-iodo-5-methylphenyl)acetate (SI3b)



$C_{10}H_{11}IO_2$

MW: 290.10 g/mol

To a suspension of 2-(2-iodo-5-methylphenyl)acetonitrile **SI2b** (281.6 mg, 1.1 mmol) in 3.5 mL of glacial acetic acid were added successively 0.17 mL of deionized water and 0.17 mL of conc. H_2SO_4. The reaction mixture was then stirred under reflux for 4 h, and then cooled down to room temperature. Crushed ice was then added to the mixture followed by deionized water. The suspension thus obtained was filtered through a Buchner funnel and the product was washed with water. The crude product was then solubilized in DCM, the solution thus obtained subsequently dried over $MgSO_4$, filtered and evaporated to dryness. The crude product obtained was solubilized in 1.8 mL of anhydrous MeOH. The resulting solution was cooled down to 0 °C, then 3 equivalents of concentrated H_2SO_4 were added dropwise. Finally, the mixture was left under reflux for 16 h. After cooling down, the mixture was diluted with 20 mL of deionized water and the aqueous phase then was extracted once with ethyl acetate. The resulting organic phase was then washed sequentially using a saturated solution of $NaHCO_3$, and brine. The organic layer was then dried over anhydrous $MgSO_4$ and the solvents were removed under reduced pressure. Purification by chromatography on silica gel, with an eluent pentane:AcOEt (90:10), afforded compound **SI3b** (62% in two steps, 197.4 mg , 0.68 mmol) as a colourless oil.

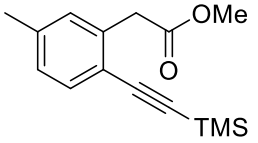
Rf = 0.54 (pentane:AcOEt (90:10)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.70 (d, *J* = 8.1 Hz, 1H), 7.10 (d, *J* = 2.2 Hz, 1H), 6.79 (ddd, *J* = 8.1, 2.3, 0.8 Hz, 1H), 3.77 (s, 2H), 3.73 (s, 3H), 2.29 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 171.1, 139.2, 138.5, 137.4, 131.5, 129.9, 96.8, 52.2, 46.0, 20.9.

HRMS (ESI): calculated for $C_{10}H_{12}IO_2^+$ $[M+H]^+$, 290.9876 found 289.9804 (Δ = 4.0 ppm)

Methyl 2-(5-methyl-2-((trimethylsilyl)ethynyl)phenyl)acetate (SI4b)



$C_{15}H_{20}O_2Si$

MW: 260.41 g/mol

Compound **SI4b** was synthesized following general procedure **A** from methyl 2-(2-iodo-5-methylphenyl)acetate **SI3b** (191.5 mg, 0.66 mmol), solubilized along with $PdCl_2(PPh_3)_2$ (2 mol%, 9.1 mg, 13 µmol), CuI (1 mol%, 1.3 mg, 6.6 µmol), trimethylsilylacetylene (1.2 eq, 0.11 mL, 0.79 mmol), in 3.7 mL of triethylamine. Purification by

chromatography on silica gel, with an eluent pentane:AcOEt (98:2), afforded compound **SI4b** (91% , 157.1 mg, 0.6 mmol) as a yellow oil.

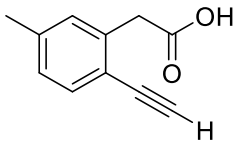
Rf = 0.20 (pentane:AcOEt (98:2)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.36 (d, *J* = 7.8 Hz, 1H), 7.09 – 7.05 (m, 1H), 7.03 (ddd, *J* = 7.8, 1.8, 0.8 Hz, 1H), 3.79 (s, 2H), 3.70 (s, 3H), 2.33 (s, 3H), 0.24 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 171.7, 138.9, 136.5, 132.2, 130.5, 127.9, 120.5, 103.2, 98.3, 52.0, 39.8, 21.5, 0.0 (3*C).

HRMS (ESI): calculated for $C_{15}H_{21}O_2Si^+$ $[M+H]^+$, 260.1233 found 260.1233 (Δ = -0.27 ppm)

2-(2-ethynyl-5-methylphenyl)acetic acid (1b)



$C_{11}H_{10}O_2$

MW: 174.20 g/mol

Compound **1b** was synthesized following general procedure **B** from compound **SI4b** (156.3 mg, 0.6 mmol) with NaOH (10.2 eq, 245 mg, 6.13 mmol) in 2.5 mL of MeOH. Compound **1b** was afforded (97%, 101 mg, 0.58 mmol) as an orange solid.

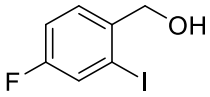
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.41 (d, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 1.7 Hz, 1H), 7.09 – 7.05 (m, 1H), 3.85 (s, 2H), 3.24 (s, 1H), 2.35 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 176.9, 139.3, 135.7, 132.7, 130.7, 128.2, 119.6, 81.6, 81.1, 39.3, 21.4.

HRMS (ESI): calculated for $C_{11}H_{11}O_2^+$ $[M+H]^+$, 194.0135 found 194.0135 (Δ = 0.02 ppm)

2.2.3 Synthesis of 1d

(4-fluoro-2-iodophenyl)methanol (SI1d) [2]



C_7H_6FIO

MW: 252.03 g/mol

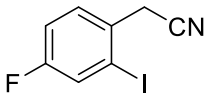
In a vacuum-dried round-bottomed flask, commercially available 4-fluoro-2-iodobenzoic acid (500 mg, 1.88 mmol) was solubilized in 3.3 mL of anhydrous THF. Trimethyl borate $B(OMe)_3$ (12 eq, 2.6 mL, 22.6 mmol) and borane-dimethyl sulfide BH_3-SMe_2 (2 M in THF) (3 eq, 2.8 mL, 5.64 mmol) were successively added to the medium. The reaction mixture was left under agitation at room temperature overnight, then quenched by addition of 2.6 mL of methanol, and concentrated under reduced pressure. The residue obtained was solubilized in 5 mL of ethyl acetate, washed with brine, dried over $MgSO_4$ filtered and then evaporated to dryness. Purification by chromatography on silica gel, with an eluent pentane:AcOEt (80:20), afforded compound **SI1d** (95% , 451.3 mg, 1.79 mmol) as a white solid.

[2] D. Yi, F. Zhu, M. A. Walczak, *Org. Lett.* **2018**, *20*, 4627–4631. https://doi.org/10.1021/acs.orglett.8b01927.

Rf = 0.33 (pentane:AcOEt (80:20)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.56 (dd, *J* = 8.0, 2.6 Hz, 1H), 7.47 – 7.38 (m, 1H), 7.09 (td, *J* = 8.4, 2.6 Hz, 1H), 4.66 (d, *J* = 5.3 Hz, 2H), 1.93 (t, *J* = 6.2 Hz, 1H).

2-(4-fluoro-2-iodophenyl)acetonitrile (SI2d)



C_8H_5FIN

MW: 261.04 g/mol

To an ice-cold solution of (4-fluoro-2-iodophenyl)methanol **SI1d** (451.3 mg, 1.79 mmol) in 10.5 mL of anhydrous DCM, was added phosphorus tribromide PBr_3 (1 eq, 170 µL, 1.79 mmol) dropwise. The reaction mixture was then left under stirring for 1 h after which the ice bath was removed and the stirring was furthered overnight at room temperature. The reaction mixture was quenched by addition of 10 mL of deionized H_2O. The aqueous phase was extracted thrice with diethyl ether Et_2O (3 x 10 mL). The organic layers were then combined, washed with brine, dried over $MgSO_4$ filtered and then evaporated to dryness. The crude product thus obtained was solubilized in 5.9 mL of EtOH. Potassium cyanide (5 eq, 582.8 mg, 8.95 mmol) were then added. The reaction mixture was then stirred under reflux for 4 h, cooled down, and quenched with deionized water. The aqueous phase was extracted thrice with Et_2O (3 x 10 mL). The organic layers were reunited, washed with brine, dried over $MgSO_4$ filtered and then evaporated to dryness. Purification by chromatography on silica gel, with an eluent pentane:AcOEt (95:5), afforded compound **SI2d** (63% in two steps, 294.3 mg, 1.16 mmol) as a white solid.

Rf = 0.20 (pentane:AcOEt (95:5)).

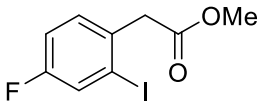
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.61 (dd, *J* = 7.8, 2.7 Hz, 1H), 7.50 (dd, *J* = 8.6, 5.5 Hz, 1H), 7.13 (td, *J* = 8.3, 2.7 Hz, 1H), 3.80 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 161.6 (d, *J* = 253.4 Hz), 129.8 (d, *J* = 8.3 Hz), 129.3 (d, *J* = 3.6 Hz), 126.8 (d, *J* = 24.1 Hz), 117.0, 116.1 (d, *J* = 21.3 Hz), 98.3 (d, *J* = 8.2 Hz), 29.1.

^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -111.80.

HRMS (ESI): calculated for $C_8H_6FIN^+$ $[M+H]^+$, 261.9523 found 261.9529 (Δ = 2.8 ppm)

Methyl 2-(4-fluoro-2-iodophenyl)acetate (SI3d)



$C_9H_8FIO_2$

MW: 294.06 g/mol

To a suspension of 2-(4-fluoro-2-iodophenyl)acetonitrile **SI2d** (290.4 mg, 1.11 mmol) in 4 mL of glacial acetic acid were added successively 0.18 mL of deionized water and 0.18 mL of conc. H_2SO_4. The reaction mixture was then stirred under reflux for 4 h, and then cooled down to room temperature. Crushed ice was then added to the mixture followed by deionized water. The suspension thus obtained was filtered through a Bunchner funnel and the product was washed with water. The crude product was then solubilized in DCM, the solution thus obtained subsequently dried over $MgSO_4$, filtered and evaporated to dryness. The crude product

obtained was solubilized in 2 mL of anhydrous MeOH. The resulting solution was cooled down to 0 °C, then 3 equivalents of concentrated H_2SO_4 were added dropwise. Finally, the mixture was left under reflux for 16 h. After cooling down, the mixture was diluted with 20 mL of deionized water and the aqueous phase then was extracted once with ethyl acetate. The resulting organic phase was then washed sequentially using a saturated solution of $NaHCO_3$, and brine. The organic layer was then dried over anhydrous $MgSO_4$ filtered, and the solvents were removed under reduced pressure. Purification by chromatography on silica gel, with an eluent pentane:AcOEt (90:10), afforded compound **SI3d** (83% in two steps, 281.8 mg, 0.96 mmol) as a colourless oil.

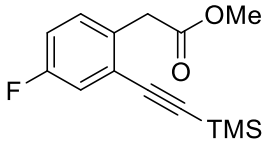
Rf = 0.53 (pentane:AcOEt (90:10)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.57 (dd, *J* = 8.0, 2.6 Hz, 1H), 7.25 (dd, *J* = 8.5, 5.8 Hz, 1H), 7.05 (td, *J* = 8.3, 2.6 Hz, 1H), 3.78 (s, 2H), 3.72 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 170.8, 161.1 (d, *J* = 251.3 Hz), 133.7 (d, *J* = 3.5 Hz), 131.1 (d, *J* = 8.1 Hz), 126.4 (d, *J* = 23.7 Hz), 115.5 (d, *J* = 21.0 Hz), 100.0 (d, *J* = 8.1 Hz), 52.2, 45.1.

^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -113.77.

Methyl 2-(4-fluoro-2-(2-(trimethylsilyl)ethynyl)phenyl)acetate (SI4d)



$C_{14}H_{17}FO_2Si$

MW: 264.37 g/mol

Compound **SI4d** was synthesized following general procedure **A** from methyl 2-(4-fluoro-2-iodophenyl)acetate **SI3d** (274.5 mg, 0.93 mmol), solubilized along with $PdCl_2(PPh_3)_2$ (2 mol%, 13.1 mg, 19 µmol), CuI (1 mol%, 1.8 mg, 9.3 µmol), trimethylsilylacetylene (1.2 eq, 0.16 mL, 1.12 mmol), in 7.8 mL of triethylamine. Purification by chromatography on silica gel, with an eluent pentane:AcOEt (95:5), afforded compound **SI4d** (96% , 237.3 mg, 0.9 mmol) as a yellow oil.

Rf = 0.20 (pentane:AcOEt (95:5)).

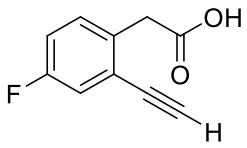
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.22 (dd, *J* = 8.7, 5.5 Hz, 1H), 7.16 (dd, *J* = 9.1, 2.8 Hz, 1H), 6.99 (td, *J* = 8.4, 2.8 Hz, 1H), 3.79 (s, 2H), 3.70 (s, 3H), 0.25 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 171.5, 161.5 (d, *J* = 246.3 Hz), 132.8 (d, *J* = 3.3 Hz), 131.5 (d, *J* = 8.6 Hz), 125.4 (d, *J* = 9.6 Hz), 119.0 (d, *J* = 23.0 Hz), 116.2 (d, *J* = 21.4 Hz), 101.9 (d, *J* = 3.0 Hz), 100.6, 52.2, 39.2, 0.0 (3*C).

^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) - 115.42.

HRMS (ESI): calculated for $C_{14}H_{18}FO_2Si^+$ $[M+H]^+$, 265.1055 found 264.0982 (Δ = -2.6 ppm)

2-(4-fluoro-2-ethynylphenyl)acetic acid (1d)



$C_{10}H_7FO_2$

MW: 178.16 g/mol

Compound **1d** was synthesized following general procedure **B** from compound **SI4d** (100 mg, 0.378 mmol) with NaOH (10 eq, 151.3 mg, 3.78 mmol) in 1.5 mL of MeOH. Compound **1d** was afforded (99%, 66.7 mg, 0.37 mmol) as a light orange solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.25 (dd, *J* = 8.4, 5.6 Hz, 1H), 7.21 (dd, *J* = 8.9, 2.8 Hz, 1H), 7.04 (td, *J* = 8.4, 2.7 Hz, 1H), 3.85 (s, 2H), 3.32 (s, 1H).

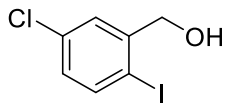
^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 176.6, 161.5 (d, *J* = 247.1 Hz), 131.9, 131.6 (d, *J* = 8.4 Hz), 124.2 (d, *J* = 10.0 Hz), 119.4 (d, *J* = 23.2 Hz), 116.5 (d, *J* = 21.5 Hz), 82.7, 80.4, 38.6.

^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -114.65

HRMS (ESI): calculated for $C_{10}H_8FO_2^+$ $[M+H]^+$, 179.0503 found 178.0430 (Δ = -0.06 ppm)

2.2.4 Synthesis of 1f

(5-chloro-2-iodophenyl)methanol (SI1f) [3]



C_7H_6ClIO

MW: 268.48 g/mol

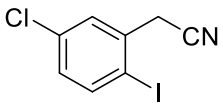
In a vacuum-dried round-bottomed flask, commercially available 5-chloro-2-iodobenzoic acid (250 mg, 0.89 mmol) was solubilized in 1.6 mL of anhydrous THF. Trimethyl borate $B(OMe)_3$ (12 eq, 1.21 mL, 10.62 mmol) and borane-dimethyl sulfide BH_3-SMe_2 (2 M in THF) (3 eq, 1.4 mL, 2.66 mmol) were successively added to the medium. The reaction mixture was left under agitation at room temperature overnight, then quenched by addition of 1.2 mL of methanol and concentrated under reduced pressure. The residue obtained was solubilized in 2.5 mL of ethyl acetate, washed with brine, dried over $MgSO_4$, filtered and then evaporated to dryness. Purification by chromatography on silica gel, with an eluent pentane:AcOEt (90:10), afforded compound **SI1f** (90% , 214.9 mg, 0.8 mmol) as a white solid.

Rf = 0.20 (pentane:AcOEt (90:10)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.72 (d, *J* = 8.3 Hz, 1H), 7.49 (dt, *J* = 2.6, 0.8 Hz, 1H), 7.00 (ddt, *J* = 8.4, 2.7, 0.6 Hz, 1H), 4.64 (d, *J* = 6.0 Hz, 2H), 1.98 (t, *J* = 6.1 Hz, 1H).

[3] M. Reboli, S. Kassamba, M. Durandetti, *Chemistry A European J* **2024**, *30*, e202400440. https://doi.org/10.1002/chem.202400440

2-(5-chloro-2-iodophenyl)acetonitrile (SI2f) [4]



C_8H_5ClIN

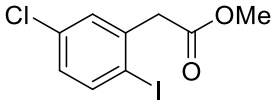
MW: 277.49 g/mol

To an ice-cold solution of (5-chloro-2-iodophenyl)methanol **SI1f** (214.9 mg, 0.8 mmol) in 4.7 mL of anhydrous DCM, was added phosphorus tribromide PBr_3 (1 eq, 75 µL, 0.8 mmol) dropwise. The reaction mixture was then left under stirring for 1 h after which the ice bath was removed and the stirring was furthered overnight at room temperature. The reaction mixture was quenched by addition of 10 mL of deionized H_2O. The aqueous phase was extracted thrice with diethyl ether Et_2O (3 x 10 mL). The organic layers were then combined, washed with brine, dried over $MgSO_4$ filtered and then evaporated to dryness. The crude product thus obtained was solubilized in 2.7 mL of EtOH. KCN (5 eq, 260.6 mg, 4.0 mmol) were then added. The reaction mixture was then stirred under reflux for 4 h, cooled down, and quenched with deionized water. The aqueous phase was extracted thrice with Et_2O (3 x 10 mL). The organic layers were reunited, washed with brine, dried over $MgSO_4$ filtered and then evaporated to dryness. Purification by chromatography on silica gel, with an eluent pentane:AcOEt (95:5), afforded compound **SI2f** (69% in two steps, 153 mg, 0.55 mmol) as a white solid.

Rf = 0.20 (pentane:AcOEt (95:5)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.78 (dt, *J* = 8.4, 1.3 Hz, 1H), 7.53 (tt, *J* = 2.0, 1.1 Hz, 1H), 7.05 (dt, *J* = 8.5, 2.0 Hz, 1H), 3.79 (s, 2H).

Methyl 2-(5-chloro-2-iodophenyl)acetate (SI3f)



$C_9H_8ClIO_2$

MW: 310.52 g/mol

To a suspension of 2-(5-chloro-2-iodophenyl)acetonitrile **SI2f** (265.7 mg, 0.96 mmol) in 3.1 mL of glacial acetic acid were added successively 0.15 mL of deionized water and 0.15 mL of conc. H_2SO_4. The reaction mixture was then stirred under reflux for 4 h, and then cooled down to room temperature. Crushed ice was then added to the mixture followed by deionized water. The suspension thus obtained was filtered through a Buchner funnel and the product was washed with water. The crude product was then solubilized in DCM, the solution thus obtained subsequently dried over $MgSO_4$ filtered and evaporated to dryness. The crude product obtained was solubilized in 5 mL of anhydrous MeOH. The resulting solution was cooled down to 0 °C, then 3 equivalents of concentrated H_2SO_4 were added dropwise. Finally, the mixture was left under reflux for 16 h. After cooling down, the mixture was diluted with 20 mL of deionized water and the aqueous phase then was extracted once with ethyl acetate. The resulting organic phase was then washed sequentially using a saturated solution of $NaHCO_3$, and brine. The organic layer was then dried over anhydrous $MgSO_4$ filtered and the solvents were removed under reduced pressure. Purification by chromatography on silica gel, with an eluent pentane:AcOEt (90:10), afforded compound **SI3f** (64% in two steps, 190 mg , 0.61 mmol) as a colourless oil.

[4] R. Das, M. Kapur, *J. Org. Chem.* **2017**, *82*, 1114–1126. https://doi.org/10.1021/acs.joc.6b02731.

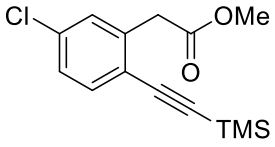
Rf = 0.56 (pentane:AcOEt (90:10)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.75 (d, *J* = 8.4 Hz, 1H), 7.28 (d, *J* = 2.5 Hz, 1H), 6.97 (dd, *J* = 8.5, 2.5 Hz, 1H), 3.77 (s, 2H), 3.73 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 170.3, 140.4, 139.4, 134.7, 130.7, 129.1, 98.0, 52.3, 45.8.

HRMS (ESI): calculated for $C_9H_9ClIO_2^+$ $[M+H]^+$, 310.9330 found 310.9341 (Δ = 3.2 ppm)

Methyl 2-(5-chloro-2-((trimethylsilyl)ethynyl)phenyl)acetate (SI4f)



$C_{14}H_{17}ClO_2Si$

MW: 280.82 g/mol

Compound **SI4f** was synthesized following general procedure **A** from methyl 2-(5-chloro-2-iodophenyl)acetate **SI3f** (190 mg, 0.61 mmol), solubilized along with $PdCl_2(PPh_3)_2$ (2 mol%, 8.4 mg, 12 µmol), CuI (1 mol%, 1.2 mg, 6.1 µmol), trimethylsilylacetylene (1.2 eq, 0.1 mL, 0.70 mmol), in 3.4 mL of triethylamine. Purification by chromatography on silica gel, with an eluent pentane:AcOEt (98:2), afforded compound **SI4f** (97% , 167.1 mg, 0.6 mmol) as a yellow oil.

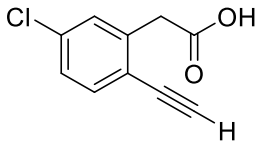
Rf = 0.43 (pentane:AcOEt (98:2)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.39 (d, *J* = 8.2 Hz, 1H), 7.27 (d, *J* = 2.1 Hz, 1H), 7.20 (dd, *J* = 8.3, 2.2 Hz, 1H), 3.79 (s, 2H), 3.71 (s, 3H), 0.24 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 171.0, 138.4, 134.6, 133.5, 130.1, 127.5, 122.2, 101.9, 100.5, 52.2, 39.7, 0.0 (3*C).

HRMS (ESI): calculated for $C_{14}H_{18}ClO_2Si^+$ $[M+H]^+$, 280.0686 found 280.0704 (Δ = 6.4 ppm)

2-(5-chloro-2-ethynylphenyl)acetic acid (1f)



$C_{10}H_7ClO_2$

MW: 194.61 g/mol

Compound **1f** was synthesized following general procedure **B** from compound **SI4f** (167 mg, 0.6 mmol) with NaOH (10 eq, 239.2 mg, 5.98 mmol) in 2.5 mL of MeOH. Compound **1f** was afforded (99% , 114.7 mg, 0.59 mmol) as a light red solid.

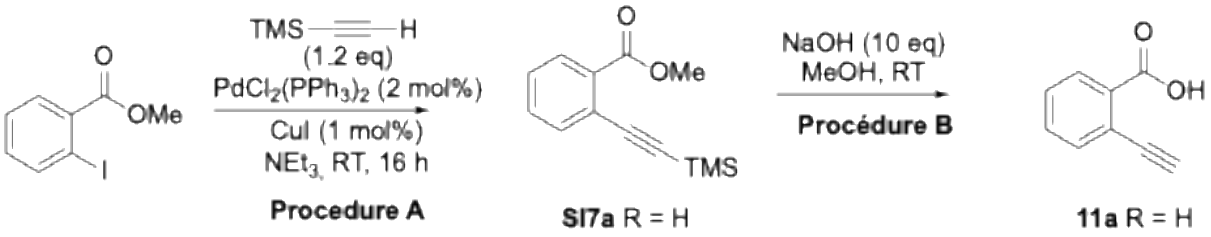
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.44 (d, *J* = 8.3 Hz, 1H), 7.31 (d, *J* = 2.1 Hz, 1H), 7.25 (dd, *J* = 8.2, 2.1 Hz, 1H), 3.86 (s, 2H), 3.32 (s, 1H).

^{13}C NMR. (101 MHz, $CDCl_3$) δ (ppm) 175.8, 137.6, 134.9, 133.9, 130.2, 127.8, 121.1, 82.8, 80.5, 39.0.

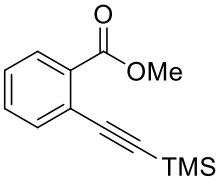
HRMS (ESI): calculated for $C_{10}H_8ClO_2^+$ $[M+H]^+$, 194.0135 found 194.0144 (Δ = 4.6 ppm)

2.3 Synthesis of 11

2.3.1 Synthesis of 11a



Methyl 2-(2-(trimethylsilyl)ethynyl)benzoate (SI7a)



$C_{13}H_{16}O_2Si$

MW: 232.35 g/mol

Compound **SI7a** was synthesized following general procedure **A** from commercially available methyl 2-iodobenzoate (2 g, 7.63 mmol), solubilized along with $PdCl_2(PPh_3)_2$ (2 mol%, 107 mg, 0.15 mmol), copper iodide (1 mol%, 15 mg, 7.6 µmol), trimethylsilylacetylene (1.2 eq, 1.30 mL, 9.16 mmol), in 64 mL of triethylamine. Purification by chromatography on silica gel, with an eluent pentane:AcOEt (98:2), afforded compound **SI7a** (98%, 1.74 g, 7.48 mmol) as a yellow oil.

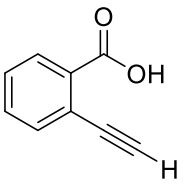
Rf = 0.21 (pentane:AcOEt (98:2)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) (ppm) 7.90 (ddd, *J* = 7.8, 1.5, 0.6 Hz, 1H), 7.58 (ddd, *J* = 7.7, 1.4, 0.6 Hz, 1H), 7.44 (td, *J* = 7.6, 1.5 Hz, 1H), 7.36 (td, *J* = 7.6, 1.4 Hz, 1H), 3.92 (s, 3H), 0.27 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 166.7, 134.5, 132.7, 131.6, 130.3, 128.3, 123.3, 103.5, 99.7, 51.9, 0.0 (3*C).

HRMS (ESI): calculated for $C_{13}H_{17}O_2Si^+$ $[M+H]^+$, 233.0992 found 233.1003 (Δ = 4.5 ppm)

2-ethynylbenzoic acid (11a)[5]



$C_9H_6O_2$

MW: 146.15 g/mol

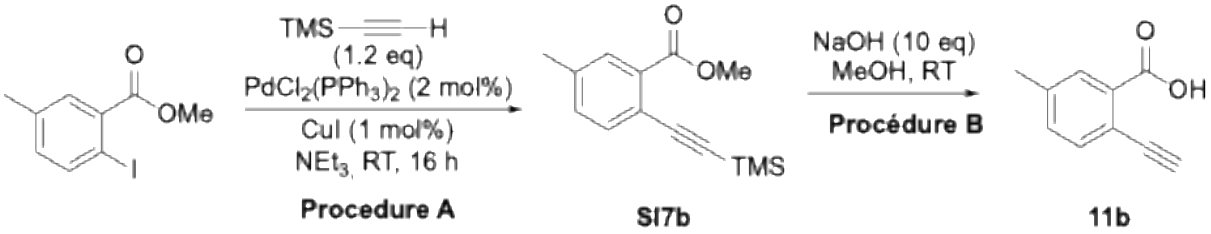
Compound **11a** was synthesized following general procedure **B** from compound **SI7a** (500 mg, 2.16 mmol) with NaOH (10.35 eq, 893.2 mg, 22.33 mmol) in 8.7 mL of MeOH. Compound **11a** (94%, 296.3 mg, 2.03 mmol) was afforded as a yellow solid.

[5] A. S. K. Hashmi, C. Lothschütz, R. Döpp, M. Ackermann, J. De Buck Becker, M. Rudolph, C. Scholz, F. Rominger, *Adv Synth Catal* **2012**, *354*, 133–147. https://advanced.onlinelibrary.wiley.com/doi/abs/10.1002/ adsc.201000044.

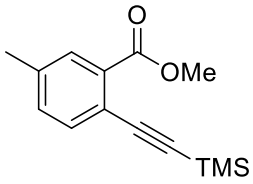
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.09 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.67 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.54 (td, *J* = 7.6, 1.4 Hz, 1H), 7.46 (td, *J* = 7.7, 1.4 Hz, 1H), 3.46 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 170.1, 135.2, 132.6, 131.3, 131.2, 128.7, 123.1, 83.3, 81.8.

2.3.2 Synthesis of 11b



Methyl 5-methyl-2-(2-(trimethylsilyl)ethynyl)benzoate (SI7b)



$C_{14}H_{18}O_2Si$

MW: 246.38 g/mol

Compound **SI7b** was synthesized following general procedure **A** from commercially available methyl 6-iodo-*m*-toluate (250 mg, 0.91 mmol), solubilized along with $PdCl_2(PPh_3)_2$ (2 mol%, 12.8 mg, 18 µmol), copper iodide (1 mol%, 1.7 mg, 9.1 µmol), trimethylsilylacetylene (1.2 eq, 0.15 mL, 1.09 mmol), in 7.6 mL of triethylamine. Purification by chromatography on silica gel, with an eluent pentane:AcOEt (98:2), afforded compound **SI7b** (99% , 220.1 mg, 0.89 mmol) as a yellow oil.

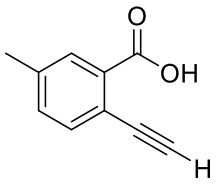
Rf = 0.3 (pentane:AcOEt (98:2)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.72 – 7.67 (m, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.25 – 7.18 (m, 1H), 3.89 (d, *J* = 0.9 Hz, 3H), 2.35 (s, 3H), 0.25 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 167.1, 138.5, 134.5, 132.5, 132.3, 130.8, 120.3, 103.6, 98.6, 51.9, 21.3, 0.0 (3*C).

HRMS (ESI): calculated for $C_{14}H_{19}O_2Si^+$ $[M+H]^+$, 247.1149 found 247.1159 (Δ = 3.8 ppm)

2-ethynyl-5-methylbenzoic acid (11b)



$C_{10}H_8O_2$

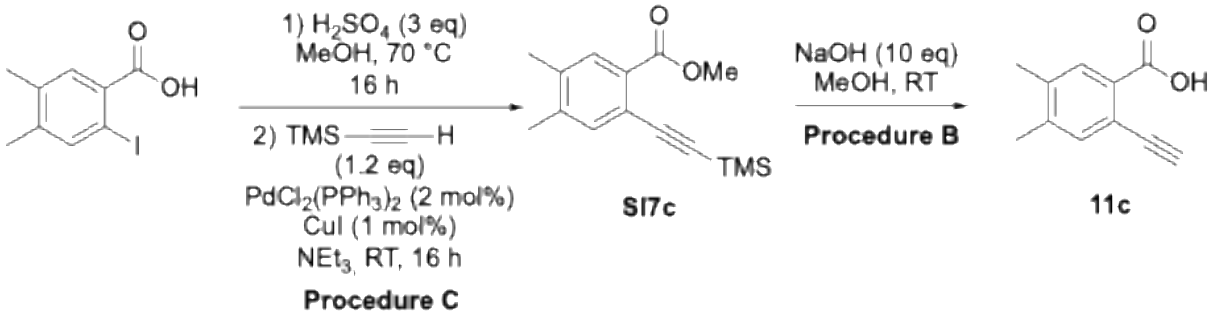
MW: 160.17 g/mol

Compound **11b** was synthesized following general procedure **B** from compound **SI7b** (200 mg, 0.81 mmol) with NaOH (10.2 eq, 329.9 mg, 8.25 mmol) in 3.3 mL of MeOH. Compound **11b** was afforded (97%, 126.5 mg, 0.79 mmol) as a yellowish solid.

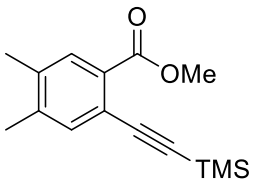
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.64 (d, *J* = 1.9 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.36 (dd, *J* = 7.9, 1.8 Hz, 1H), 4.24 (s, 1H), 2.35 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 167.7, 139.1, 134.7, 134.2, 132.6, 130.7, 119.1, 84.8, 82.7, 21.2.

2.3.3 Synthesis of 11c



methyl 4,5-dimethyl-2-(2-(trimethylsilyl)ethynyl)benzoate (SI7c)



$C_{15}H_{20}O_2Si$

MW: 260.41 g/mol

Compound **SI7c** was synthesized following general procedure **C** from commercially available 2-iodo-4,5-dimethylbenzoic acid (250 mg, 0.906 mmol), along with conc. H_2SO_4 (3 eq, 0.15 mL, 2.72 mmol) and 0.7 mL of anhydrous methanol. The crude ester obtained after work-up got used as is in the next step, and solubilized along with $PdCl_2(PPh_3)_2$ (2 mol%, 12.8 mg, 18 µmol), CuI (1 mol%, 1.7 mg, 9.1 µmol), trimethylsilylacetylene (1.2 eq, 0.15 mL, 1.09 mmol), in 7.6 mL of triethylamine. Purification by chromatography on silica gel, with an eluent pentane:AcOEt (98:2), afforded compound **SI7c** (94% in two steps, 221.9 mg, 0.85 mmol) as a yellow oil.

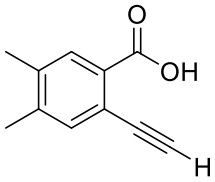
Rf = 0.25 (pentane:AcOEt (98:2)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.72 – 7.67 (m, 1H), 7.36 (s, 1H), 3.90 (s, 3H), 2.28 (s, 3H), 2.26 (s, 3H), 0.26 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 166.9, 140.9, 137.3, 135.6, 131.6, 129.7, 120.7, 103.9, 98.2, 51.8, 19.6, 19.5, 0.0 (3*C).

HRMS (ESI): calculated for $C_{15}H_{21}O_2Si^+$ $[M+H]^+$, 261.1305 found 261.1316 (Δ = 3.7 ppm)

2-ethynyl-4,5-dimethylbenzoic acid (11c)



$C_{11}H_{10}O_2$

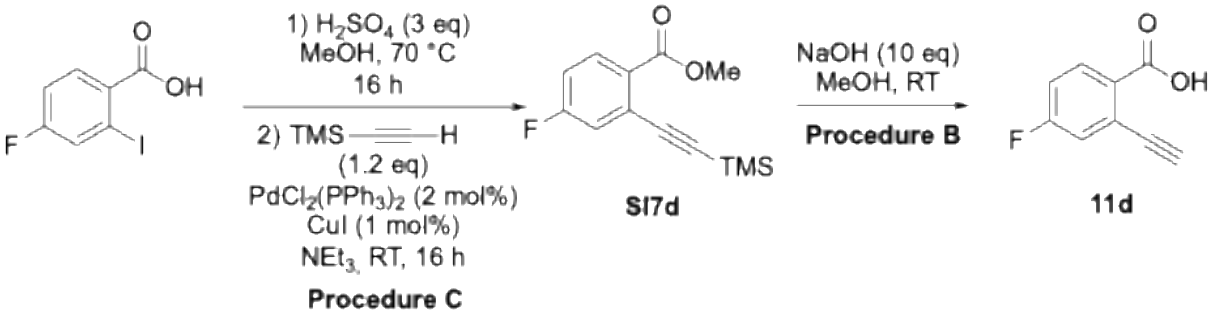
MW: 174.20 g/mol

Compound **11c** was synthesized following general procedure **B** from compound **SI7c** (221.9 mg, 0.85 mmol) with NaOH (10 eq, 340.85 mg, 8.52 mmol) in 3.5 mL of MeOH. Compound **11c** was afforded (86%, 128.2 mg, 0.74 mmol) as a dark red solid.

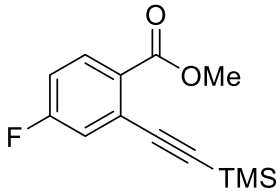
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.86 (s, 1H), 7.42 (s, 1H), 3.37 (s, 1H), 2.31 (s, 3H), 2.29 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 170.8, 142.2, 137.8, 136.3, 132.4, 128.6, 120.5, 82.2, 82.1, 19.7, 19.6.

2.3.4 Synthesis of 11d



Methyl 4-fluoro-2-(2-(trimethylsilyl)ethynyl)benzoate (SI7d)



$C_{13}H_{15}FO_2Si$

MW: 250.34 g/mol

Compound **SI7d** was synthesized following general procedure **C** from commercially available 4-fluoro-2-iodobenzoic acid (500 mg, 1.88 mmol), along with conc. H_2SO_4 (3 eq, 0.3 mL, 5.64 mmol) and 1.1 mL of anhydrous methanol. The crude ester obtained after work-up got used as is in the next step and solubilized along with $PdCl_2(PPh_3)_2$ (2 mol%, 26.5 mg, 38 µmol), copper iodide (1 mol%, 3.6 mg, 19 µmol), trimethylsilylacetylene (1.2 eq, 0.32 mL, 2.26 mmol), in 15.7 mL of triethylamine. Purification by chromatography on silica gel, with an eluent pentane:AcOEt (98:2), afforded compound **SI7d** (83% in two steps, 389.8 mg, 1.56 mmol) as a yellow oil.

Rf = 0.50 (pentane:AcOEt (98:2)).

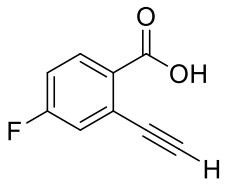
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.92 (ddd, *J* = 8.9, 5.8, 1.3 Hz, 1H), 7.24 (dd, *J* = 9.1, 1.4 Hz, 1H), 7.04 (tdd, *J* = 8.9, 2.6, 1.2 Hz, 1H), 3.89 (d, *J* = 1.1 Hz, 3H), 0.26 (d, *J* = 1.0 Hz, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 166.0 (d, *J* = 1.4 Hz), 164.3 (d, *J* = 253.8 Hz), 133.2 (d, *J* = 9.6 Hz), 128.9 (d, *J* = 3.2 Hz), 126.2 (d, *J* = 10.3 Hz), 121.4 (d, *J* = 23.3 Hz), 115.9 (d, *J* = 21.6 Hz), 102.3 (d, *J* = 2.5 Hz), 101.6, 52.23 (d, *J* = 0.9 Hz), 0.0 (3*C).

^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -107.55.

HRMS (ESI): calculated for $C_{13}H_{16}FO_2Si^+$ $[M+H]^+$, 251.0898 found 251.0908 (Δ = 3.6 ppm)

2-ethynyl-4-fluorobenzoic acid (11d)



$C_9H_5FO_2$

MW: 164.14 g/mol

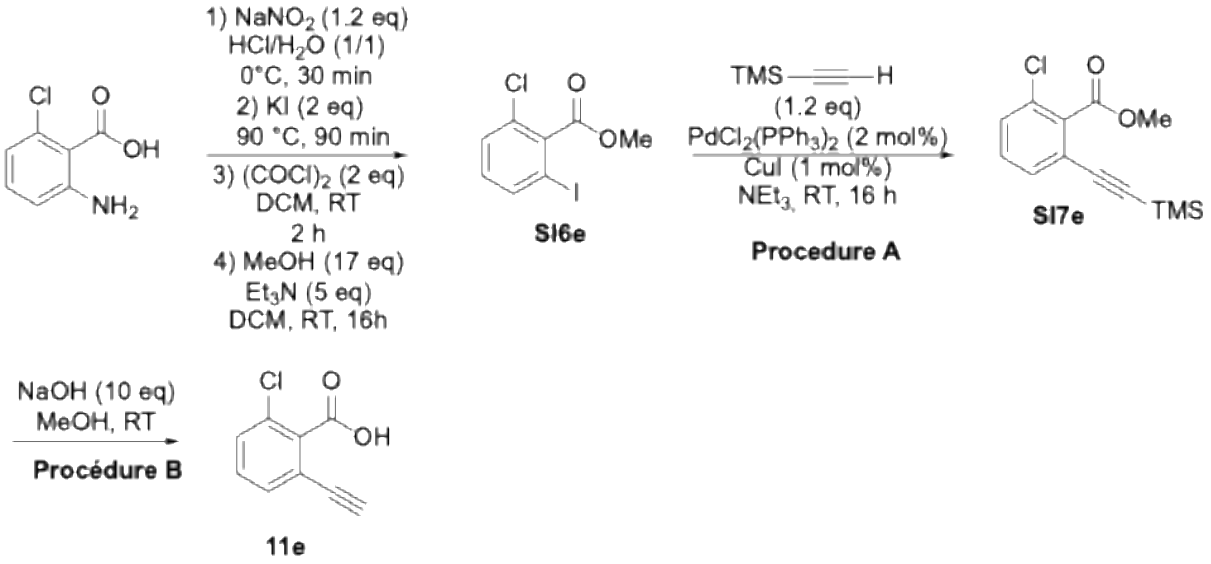
Compound **11d** was synthesized following general procedure **B** from compound **SI7d** (170.3 mg, 0.68 mmol) with NaOH (10.3 eq, 280.2 mg, 7.0 mmol) in 2.8 mL of MeOH. Compound **11d** was afforded (95%, 106 mg, 0.65 mmol) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ (ppm) 12.94 (s, 1H), 7.68 (dd, *J* = 8.8, 5.9 Hz, 1H), 7.22 (dt, *J* = 9.5, 1.9 Hz, 1H), 7.11 (tt, *J* = 8.5, 1.9 Hz, 1H), 4.27 (s, 1H).

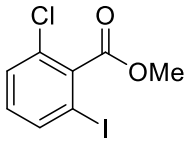
^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ (ppm) 166.5, 163.7 (d, *J* = 250.6 Hz), 133.3 (d, *J* = 9.8 Hz), 130.8 (d, *J* = 3.3 Hz), 124.7 (d, *J* = 10.5 Hz), 121.4 (d, *J* = 23.6 Hz), 116.7 (d, *J* = 21.6 Hz), 87.2, 81.4 (d, *J* = 2.7 Hz).

^{19}F NMR (376 MHz, DMSO-*d*$_6$) δ (ppm) -108.35.

2.3.5 Synthesis of 11e



Methyl 6-chloro-2-iodobenzoate (SI6e)



$C_8H_6ClIO_2$

MW: 296.49 g/mol

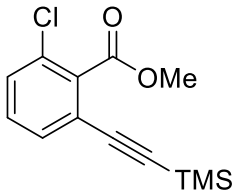
To an ice-cold solution of commercially available 2-amino-6-chlorobenzoic acid (250 mg, 1.46 mmol) in suspension in 4 mL of a 1:1 mixture of 37% HCl and H_2O was slowly added $NaNO_2$ (1.2 eq, 120.6 mg, 1.75 mmol) in 0.75 mL of H_2O. The resulting solution was stirred at 0 °C for 30 min, after which KI (2 eq, 483.8 mg, 2.91 mmol) in 0.75 mL of H_2O was added dropwise. The mixture was stirred at 90 °C for 90 min. The mixture was then cooled down and the reaction was quenched by addition of 10 mL of a saturated $Na_2S_2O_3$ solution. The aqueous phase was then extracted with EtOAc (3 x 25 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was solubilized in dry CH_2Cl_2 (5 mL), then oxalyl chloride (2 eq, 0.25 mL, 2.92 mmol) was added, followed by drops of DMF to catalyse the reaction. The mixture thus obtained was left under stirring for 2 h at room temperature. Solvent and excess oxalyl chloride were removed under reduced pressure. Triethylamine (5 eq, 1 mL, 7.18 mmol) and absolute methanol (17 eq, 1 mL, 24.3 mmol) were added to the residue in 5 mL of CH_2Cl_2. After stirring overnight, the reaction was quenched by addition of a saturated solution of $NaHCO_3$. The aqueous phase was extracted with ethyl acetate (3 x 10 mL), washed with brine, dried over $MgSO_4$ and then evaporated to dryness. Purification by column chromatography on silica gel, with an eluent pentane:AcOEt (95:5), afforded compound **SI6e** (54% in two steps, 233.3 mg, 0.79 mmol) as a yellow oil.

Rf = 0.61 (pentane:AcOEt (95:5)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.72 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.39 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.04 (t, *J* = 8.1 Hz, 1H), 3.98 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 167.1, 139.7, 137.3, 131.5, 131.0, 129.1, 92.0, 53.1.

Methyl 6-chloro-2-(2-(trimethylsilyl)ethynyl)benzoate (SI7e)



$C_{13}H_{15}ClO_2Si$

MW: 266.80 g/mol

Compound **SI7e** was synthesized following general procedure **A** from methyl 6-chloro-2-iodobenzoate **SI6e** (234.2 mg, 0.79 mmol), solubilized along with $PdCl_2(PPh_3)_2$ (2 mol%, 11.1 mg, 16 µmol), CuI (1 mol%, 1.5 mg, 7.9 µmol), trimethylsilylacetylene (1.2 eq, 0.13 mL, 0.95 mmol) in 6.6 mL of triethylamine. Purification by chromatography on silica gel, with an eluent pentane:AcOEt (98:2), afforded compound **SI7e** (89%, 186.6 mg, 0.7 mmol) as a yellow oil.

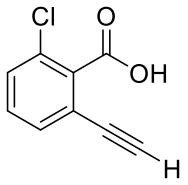
Rf = 0.69 (pentane:AcOEt (98:2)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.39 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.35 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.27 (dd, *J* = 8.2, 7.6 Hz, 1H), 3.95 (s, 3H), 0.23 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 166.7, 136.8, 131.0, 130.8, 130.4, 129.8, 122.9, 100.9, 100.0, , 52.9, 0.0 (3*C).

HRMS (ESI): calculated for $C_{13}H_{16}ClO_2Si^+$ $[M+H]^+$, 267.0603 found 267.0616 (Δ = 4.6 ppm)

6-chloro-2-ethynylbenzoic acid (11e)



$C_9H_5ClO_2$

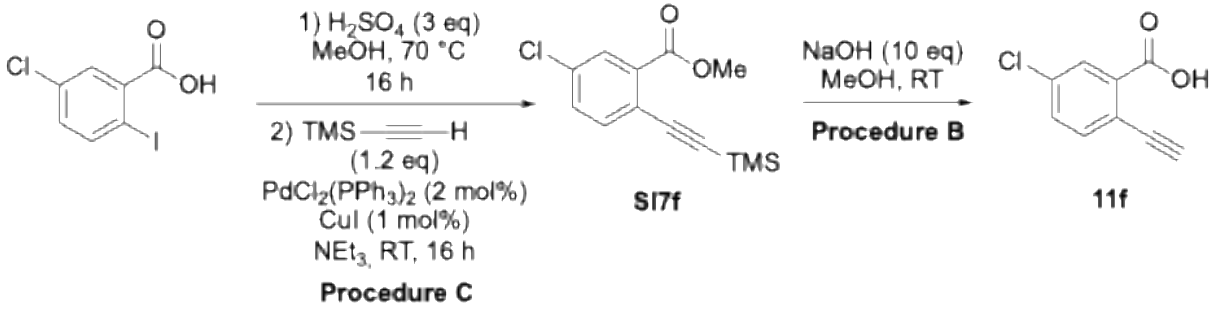
MW: 180.59 g/mol

Compound **11e** was synthesized following general procedure **B** from compound **SI7e** (186.6 mg, 0.7 mmol) with NaOH (10.8 eq, 303.2 mg, 7.58 mmol) in 2.8 mL of MeOH. Purification by chromatography on silica gel, with an eluent pentane:Et_2O (70:30), afforded compound **11e** (27%, 34.5 mg, 0.19 mmol) as a yellowish solid.

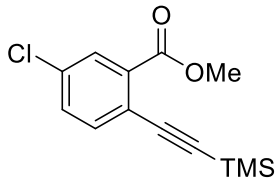
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.48 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.44 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 3.31 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 170.2, 135.5, 131.3, 131.0, 130.6, 130.2, 121.6, 82.4, 79.5.

2.3.6 Synthesis of 11f



Methyl 5-chloro-2-(2-(trimethylsilyl)ethynyl)benzoate (SI7f)



$C_{13}H_{15}ClO_2Si$

MW: 266.80 g/mol

Compound **SI7f** was synthesized following general procedure **C** from commercially available 5-chloro-2-iodobenzoic acid (250 mg, 0.89 mmol), along with conc. H_2SO_4 (3 eq, 0.14 mL, 2.66 mmol) and 0.5 mL of anhydrous methanol. The crude ester obtained after work-up got used as is in the next step, and solubilized along with $PdCl_2(PPh_3)_2$ (2 mol%, 12.5 mg, 18 µmol), CuI (1 mol%, 1.7 mg, 8.9 µmol), trimethylsilylacetylene (1.2 eq, 0.15 mL, 1.07 mmol), in 7.4 mL of triethylamine. Purification by chromatography on silica gel, with an eluent pentane:AcOEt (98:2), afforded compound **SI7f** (80% in two steps, 190 mg, 0.71 mmol) as a brown oil.

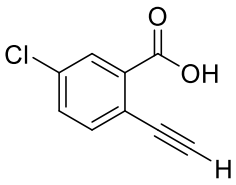
Rf = 0.25 (pentane:AcOEt (98:2)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.89 (dd, *J* = 2.3, 0.5 Hz, 1H), 7.51 (dd, *J* = 8.4, 0.5 Hz, 1H), 7.41 (dd, *J* = 8.4, 2.3 Hz, 1H), 3.92 (s, 3H), 0.27 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 165.7, 135.8, 134.4, 134.1, 131.8, 130.5, 121.9, 102.3, 101.2, 52.4, 0.0 (3*C).

HRMS (ESI): calculated for $C_{13}H_{16}ClO_2Si^+$ $[M+H]^+$, 267.0603 found 267.0613 (Δ = 3.7 ppm)

5-chloro-2-ethynylbenzoic acid (11f)



$C_9H_5ClO_2$

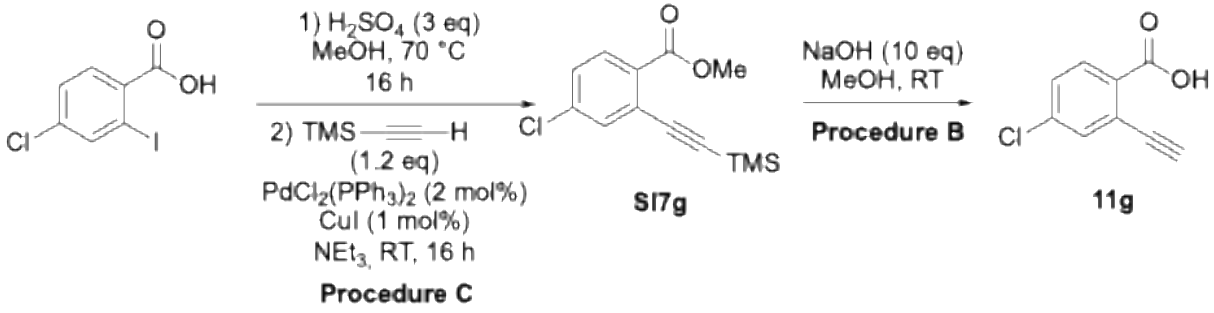
MW: 180.59 g/mol

Compound **11f** was synthesized following general procedure **B** from compound **SI7f** (162.1 mg, 0.61 mmol) with NaOH (8.0 eq, 193.2 mg, 4.83 mmol) in 2.5 mL of MeOH. Compound **11f** was afforded (98%, 107.8 mg, 0.6 mmol) as a beige solid.

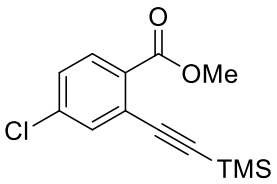
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.05 – 8.01 (m, 1H), 7.85 – 7.80 (m, 2H), 4.67 (s, 1H).

^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 166.3, 160.2, 136.5, 133.8, 131.9, 129.9, 120.8, 86.9, 81.5.

2.3.7 Synthesis of 11g



Methyl 4-chloro-2-(2-(trimethylsilyl)ethynyl)benzoate (SI7g)



$C_{13}H_{15}ClO_2Si$

MW: 266.80 g/mol

Compound **SI7g** was synthesized following general procedure **C** from commercially available 4-chloro-2-iodobenzoic acid (250 mg, 0.89 mmol), along with conc. H_2SO_4 (3 eq, 0.14 mL, 2.66 mmol) and 0.5 mL of anhydrous methanol. The crude ester obtained after work-up got used as is in the next step, and solubilized along with $PdCl_2(PPh_3)_2$ (2 mol%, 12.5 mg, 18 µmol), CuI (1 mol%, 1.7 mg, 8.9 µmol), trimethylsilylacetylene (1.2 eq, 0.15 mL, 1.07 mmol),

in 7.4 mL of triethylamine. Purification by chromatography on silica gel, with an eluent pentane:AcOEt (98:2), afforded compound **SI7g** (79% in two steps, 186.9 mg, 0.7 mmol) as a yellow oil.

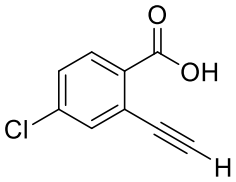
Rf = 0.33 (pentane:AcOEt (98:2)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.86 (d, *J* = 8.5 Hz, 1H), 7.57 (d, *J* = 2.1 Hz, 1H), 7.33 (dd, *J* = 8.5, 2.2 Hz, 1H), 3.91 (s, 3H), 0.27 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 166.1, 138.0, 134.4, 131.9, 130.9, 128.7, 125.2, 102.1, 101.7, 52.3, 0.0 (3*C).

HRMS (ESI): calculated for $C_{13}H_{16}ClO_2Si^+$ $[M+H]^+$, 267.0603 found 267.053 (Δ = - 1.9 ppm)

4-chloro-2-ethynylbenzoic acid (11g)



$C_9H_5ClO_2$

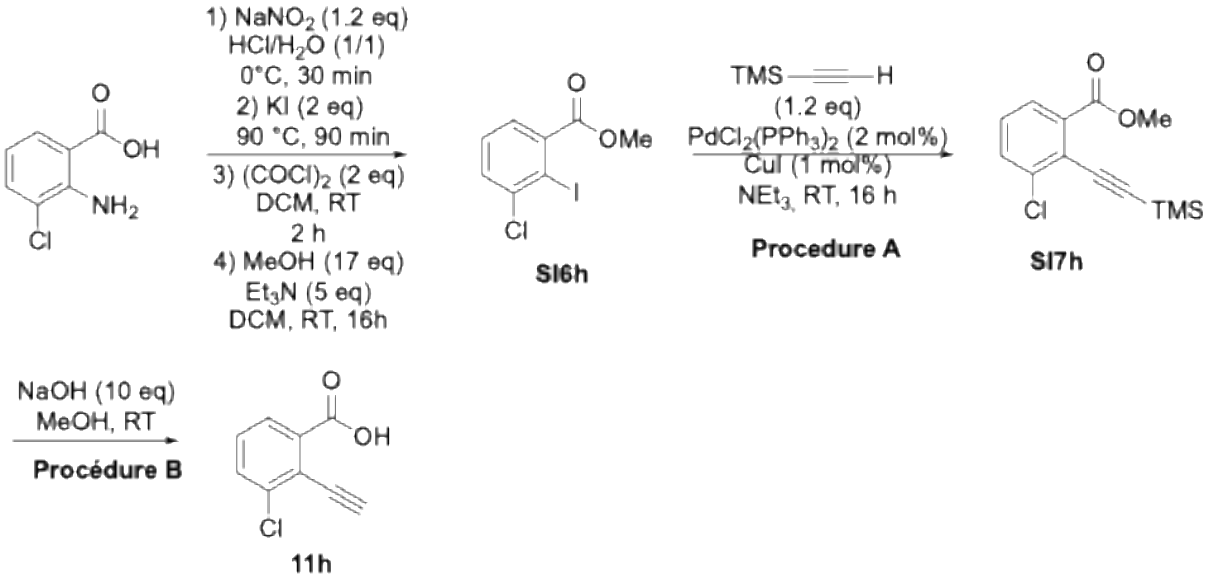
MW: 180.59 g/mol

Compound **11g** was synthesized following general procedure **B** from compound **SI7g** (212.7 mg, 0.80 mmol) with NaOH (8.7 eq, 278.8 mg, 6.97 mmol) in 3.2 mL of MeOH. Compound **11g** was afforded (100%, 144 mg, 0.80 mmol) as a beige solid.

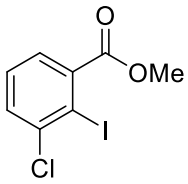
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.02 (d, *J* = 8.5 Hz, 1H), 7.64 (d, *J* = 2.2 Hz, 1H), 7.42 (dd, *J* = 8.5, 2.2 Hz, 1H), 3.50 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 169.6, 139.1, 135.0, 132.6, 131.2, 129.0, 125.0, 84.7, 80.5.

2.3.8 Synthesis of 11h



Methyl 3-chloro-2-iodobenzoate (SI6h)[6]



$C_8H_6ClIO_2$

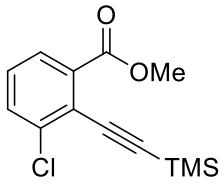
MW: 296.49 g/mol

To an ice-cold solution of commercially available 2-amino-5-methoxybenzoic acid (250 mg, 1.46 mmol) in suspension in 3 mL of H_2O were slowly added H_2SO_4 conc. (19 eq, 1.5 mL, 27.7 mmol) and $NaNO_2$ (1.2 eq, 120.6 mg, 1.75 mmol) in 1.5 mL of H_2O. The solution was left under stirring in the ice bath for 1 h. KI (2 eq, 483.8 mg, 2.91 mmol) in 2 mL of H_2O was slowly added to the solution, which was then transferred in an oil bath and stirred at 60 °C for 2.5 h. The mixture was then cooled down and the reaction was quenched by addition of 10 mL of a saturated $Na_2S_2O_3$ solution. The aqueous phase was then extracted with EtOAc (3 x 25 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was solubilized in dry CH_2Cl_2 (5 mL), then oxalyl chloride (2 eq, 0.25 mL, 2.92 mmol) was added, followed by drops of DMF to catalyse the reaction. The mixture thus obtained was left under stirring for 2 h at room temperature. Solvent and excess oxalyl chloride were removed under reduced pressure. NEt_3 (5 eq, 0.6 mL, 7.3 mmol) and absolute methanol (10 eq, 0.6 mL, 14.6 mmol) were then added to the residue in 5 mL of CH_2Cl_2. After stirring overnight, the reaction was quenched by addition of a saturated solution of $NaHCO_3$. The aqueous phase was extracted with ethyl acetate (3 x 10 mL), washed with brine, dried over $MgSO_4$ and then evaporated to dryness. Purification by chromatography on silica gel, with an eluent pentane:AcOEt (90:10), afforded compound **SI6h** (73% in two steps, 314.3 mg, 1.06 mmol) as a yellowish oil.

Rf = 0.63 (pentane:AcOEt (90:10)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.56 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.45 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.37 – 7.28 (m, 1H), 3.95 (s, 3H).

Methyl 3-chloro-2-(2-(trimethylsilyl)ethynyl)benzoate (SI7h)



$C_{13}H_{15}ClO_2Si$

MW: 266.80 g/mol

Compound **SI7h** was synthesized following general procedure **A** from methyl 3-chloro-2-iodobenzoate **SI6h** (314.3 mg, 1.06 mmol), solubilized along with $PdCl_2(PPh_3)_2$ (2 mol%, 14.9 mg, 21 µmol), CuI (1 mol%, 2.0 mg, 10.6 µmol), trimethylsilylacetylene (1.2 eq, 0.18 mL, 1.27 mmol), in 8.8 mL of triethylamine. In that case, the reaction was conducted at 70 °C for 96 h instead of room temperature overnight. Purification by chromatography on silica gel, with an eluent pentane:AcOEt (98:2), afforded compound **SI7h** (82%, 233.2 mg, 0.87 mmol) as an orange oil.

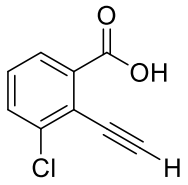
Rf = 0.32 (pentane:AcOEt (98:2)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.74 – 7.67 (m, 1H), 7.55 – 7.48 (m, 1H), 7.27 – 7.18 (m, 1H), 3.88 (s, 3H), 0.26 (s, 9H).

[6] C. Guo, K. Huang, B. Wang, L. Xie, X. Xu, *RSC Adv.* **2013**, *3*, 17271. https://doi.org/10.1039/C3RA42474J.

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 166.4, 138.4, 135.2, 132.5, 128.6, 128.4, 122.8, 107.1, 99.2, 52.4, 0.0 (3*C).

3-chloro-2-ethynylbenzoic acid (11h)



$C_9H_5ClO_2$

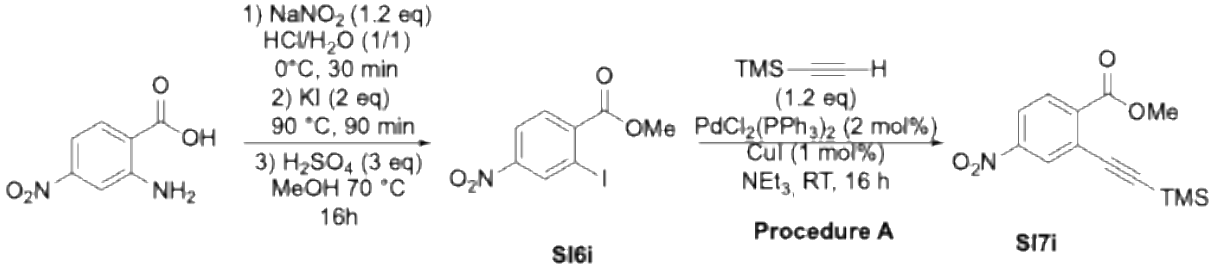
MW: 180.59 g/mol

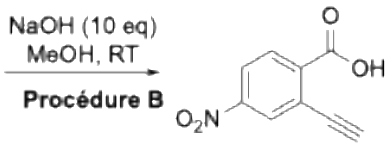
Compound **11h** was synthesized following general procedure **B** from compound **SI7h** (233.2 mg, 0.87 mmol) with NaOH (11.2 eq, 390.4 mg, 9.8 mmol) in 3.5 mL of MeOH. Compound **11h** was afforded (96%, 151.5 mg, 0.84 mmol) as a beige solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.82 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.51 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 3.63 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 170.1, 139.0, 133.7, 133.5, 129.3, 128.9, 122.4, 89.6, 77.9.

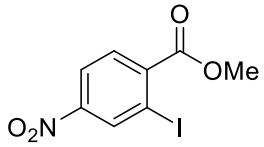
2.3.9 Synthesis of 11i





11i

Methyl 2-iodo-4-nitrobenzoate (SI6i)[7]



$C_8H_6INO_4$

MW: 307.04 g/mol

To a suspension of commercially available 2-amino-4-nitrobenzoic acid (1 eq, 250 mg, 1.37 mmol) in a solution of PTSA (1.2 eq, 283.6 mg, 1.65 mmol) in 1 mL was added $NaNO_2$ (1 eq, 94.7 mg, 1.37 mmol) in 0.25 mL of water. The resulting mixture was left stirring at room

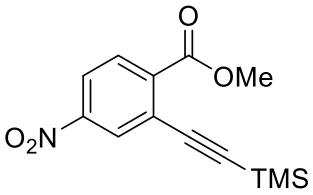
[7] J. M. Cary, J. S. Moore, *Org. Lett.* **2002**, *4*, 4663–4666. https://doi.org/10.1021/ol0270982.

temperature for 15 min. KI (1 eq, 227.9 mg, 1.37 mmol) solubilized in 0.25 mL of water was then added dropwise to the solution, then left under stirring at room temperature for 72 h. Upon completion, the reaction was quenched by addition of 10 mL of a saturated $Na_2S_2O_3$ solution. The aqueous phase was then extracted with EtOAc (3 x 25 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude product obtained was solubilized in 5 mL of anhydrous MeOH. The resulting solution was cooled down to 0 °C, then 3 equivalents of concentrated H_2SO_4 were added dropwise. Finally, the mixture was left under reflux for 16 h. After cooling down, the mixture was diluted with 20 mL of deionized water and the aqueous phase then was extracted once with ethyl acetate. The resulting organic phase was then washed sequentially using a saturated solution of $NaHCO_3$, and brine. The organic layer was then dried over anhydrous $MgSO_4$, filtered and the solvents were removed under reduced pressure. Purification by chromatography on silica gel, with an eluent pentane:AcOEt (90:10), afforded compound **SI6i** (50% in two steps, 193.3 mg , 0.63 mmol) as a white solid.

Rf = 0.34 (pentane:AcOEt (90:10)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.80 (d, *J* = 2.2 Hz, 1H), 8.25 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 3.99 (s, 3H).

Methyl 4-nitro-2-((trimethylsilyl)ethynyl)benzoate (SI7i)



$C_{13}H_{15}NO_4Si$

MW: 277.35 g/mol

Compound **SI7i** was synthesized following general procedure **A** from methyl 2-iodo-4-nitrobenzoate **SI6i** (266.9 mg, 0.87 mmol), solubilized along with $PdCl_2(PPh_3)_2$ (2 mol% , 12.2 mg, 17 µmol), CuI (1 mol% , 1.7 mg, 8.7 µmol), trimethylsilylacetylene (1.2 eq, 0.15 mL, 1.04 mmol), in 7.2 mL of triethylamine. Purification by chromatography on silica gel, with an eluent pentane:AcOEt (98:2), afforded compound **SI7i** (79%, 190.2 mg, 0.69 mmol) as a white solid.

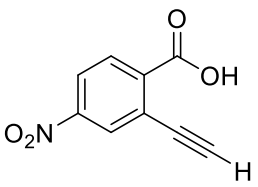
Rf = 0.33 (pentane:AcOEt (98:2)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.39 (dd, *J* = 2.4, 1.0 Hz, 1H), 8.16 (ddd, *J* = 8.7, 2.4, 0.8 Hz, 1H), 8.04 (d, *J* = 8.7 Hz, 1H), 3.96 (s, 3H), 0.29 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 165.6, 149.5, 138.0, 131.7, 129.4, 125.3, 122.9, 103.8, 101.0, , 53.0, 0.0 (3C).

HRMS (ESI): calculated for $C_{13}H_{16}NO_4Si^+$ $[M+H]^+$, 278.0843 found 278.0853 (Δ = 4.2 ppm)

2-ethynyl-4-nitrobenzoic acid (11i)



$C_9H_5NO_4$

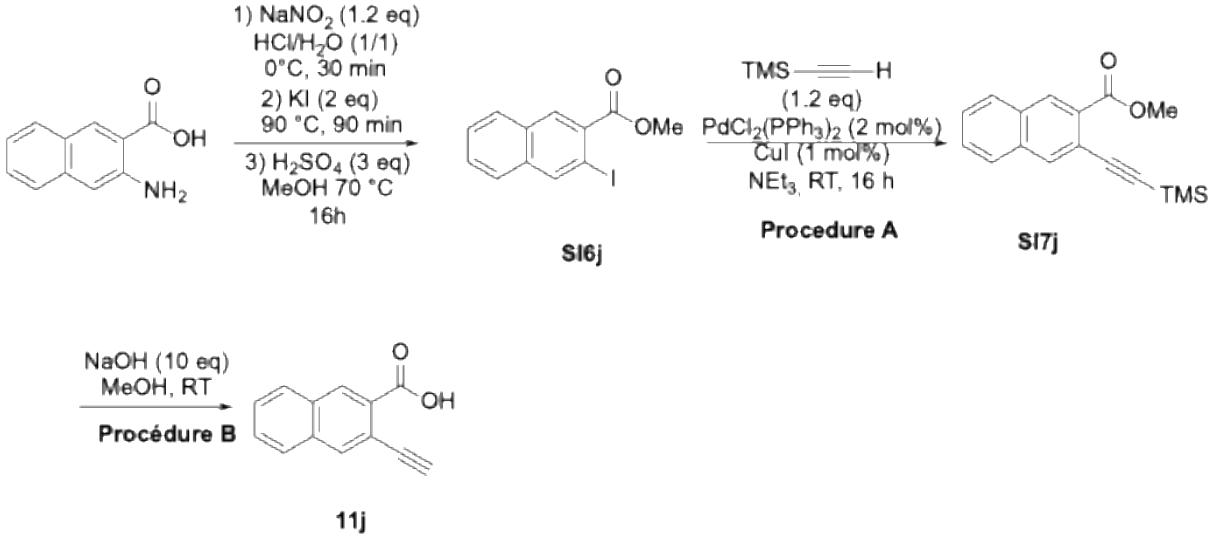
MW: 191.14 g/mol

Compound **11i** was synthesized following general procedure **B** from compound **SI7i** (118.4 mg, 0.43 mmol) with NaOH (11.8 eq, 201.2 mg, 5.03 mmol) in 1.8 mL of MeOH. Compound **11i** was afforded (86%, 70 mg, 0.37 mmol) as a yellowish solid.

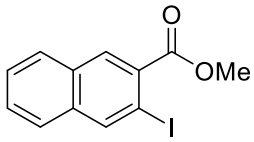
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.41 (d, *J* = 2.2 Hz, 1H), 8.21 – 8.13 (m, 2H), 3.54 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 168.3, 149.9, 136.3, 132.3, 129.8, 125.0, 123.1, 86.2, 79.7.

2.3.10 Synthesis of 11j



Methyl 3-iodo-2-naphthoate (SI6j)[8]



$C_{12}H_9IO_2$

MW: 312.11 g/mol

To an ice-cold solution of commercially available 3-amino-2-naphthoic acid (250 mg, 1.34 mmol) in suspension in 10 mL of a 1:1 mixture of 37% HCl and H_2O was slowly added $NaNO_2$ (2 eq, 184.3 mg, 2.68 mmol) in 2.5 mL of H_2O. The resulting solution was stirred at 0 °C for 2 h, after which KI (6 eq, 1.33 g, 8.01 mmol) in 2.5 mL of H_2O was added dropwise. The mixture was stirred at 0 °C for 30 min, then at room temperature for 1 h, and finally heated at 60 °C for 1 h. EtOAc (2.5 mL) was then poured into the mixture and heating was maintained for an additional 30 min. Powdered $Na_2S_2O_3$ was added until complete discoloration of the solution, and the reaction mixture was then extracted with EtOAc (4 x 10 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude product obtained was solubilized in 5 mL of anhydrous MeOH. The resulting solution was cooled down to 0 °C, then 3 equivalents of concentrated H_2SO_4 were added dropwise. Finally, the mixture was left under reflux for 16 h. After cooling down, the mixture was diluted with 10 mL of deionized water and the aqueous phase then was extracted

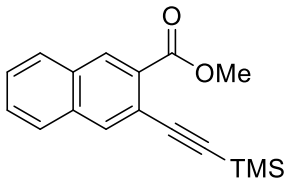
[8] R. R. Kadiyala, D. Tilly, E. Nagaradja, T. Roisnel, V. E. Matulis, O. A. Ivashkevich, Y. S. Halauko, F. Chevallier, P. C. Gros, F. Mongin, *Chemistry A European J* **2013**, *19*, 7944–7960. https://doi.org/10.1002/chem.201300552.

once with ethyl acetate. The resulting organic phase was then washed sequentially using a saturated solution of $NaHCO_3$, and brine. The organic layer was then dried over anhydrous $MgSO_4$ filtered and the solvents were removed under reduced pressure. Purification by chromatography on silica gel, with an eluent pentane:AcOEt (90:10), afforded compound **SI6j** (82% in two steps, 343.5 mg, 1.10 mmol) as a yellow oil.

Rf = 0.43 (pentane:AcOEt (90:10)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.50 (s, 1H), 8.35 (s, 1H), 7.90 – 7.83 (m, 1H), 7.74 (dt, *J* = 8.2, 1.3 Hz, 1H), 7.62-7.52 (m, 2H), 3.99 (s, 3H).

Methyl 3-((trimethylsilyl)ethynyl)-2-naphthoate (SI7j)



$C_{17}H_{18}O_2Si$

MW: 282.41 g/mol

Compound **SI7j** was synthesized following general procedure **A** from methyl 3-iodo-2-naphtohoate **SI6j** (310 mg, 0.99 mmol), solubilized along with $PdCl_2(PPh_3)_2$ (2 mol%, 13.4 mg, 2.0 µmol), CuI (1 mol%, 1.9 mg, 0.99 µmol), trimethylsilylacetylene (1.2 eq, 0.17 mL, 1.19 mmol), in 8.3 mL of triethylamine. Purification by chromatography on silica gel, with an eluent pentane:AcOEt (98:2), afforded compound **SI7j** (90%, 253.6 mg, 0.9 mmol) as a dark brown oil.

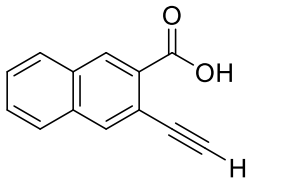
Rf = 0.20 (pentane:AcOEt (98:2)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.45 (s, 1H), 8.10 (s, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 7.9 Hz, 1H), 7.54 (dtd, *J* = 13.4, 7.0, 3.6 Hz, 2H), 3.98 (s, 3H), 0.31 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 167.0, 134.9, 134.1, 131.7, 131.7, 129.1, 128.9, 128.6, 127.5, 127.4, 119.1, 103.7, 98.4, , 52.1, 0.0 (3*C).

HRMS (ESI): calculated for $C_{17}H_{19}O_2Si^+$ $[M+H]^+$, 283.1149 found 282.1161 (Δ = 3.9 ppm)

3-ethynyl-2-naphthoic acid (11j)



$C_{13}H_8O_2$

MW: 196.20 g/mol

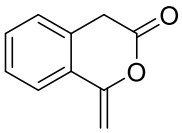
Compound **11j** was synthesized following general procedure **B** from compound **SI7j** (242.0 mg, 0.86 mmol) with NaOH (7.6 eq, 260 mg, 6.5 mmol) in 3.5 mL of MeOH. Compound **11j** was afforded (92%, 155.5 mg, 0.79 mmol) as a bright yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.68 (s, 1H), 8.19 (s, 1H), 7.97 – 7.93 (m, 1H), 7.87 – 7.83 (m, 1H), 7.64 (ddd, *J* = 8.2, 6.9, 1.5 Hz, 1H), 7.59 (ddd, *J* = 8.2, 6.9, 1.5 Hz, 1H), 3.45 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 170.2, 135.8, 134.6, 133.3, 131.9, 129.3, 129.2, 127.9, 127.4 (2*C), 118.3, 82.2, 81.8.

3. Gold-catalyzed hydroacyoxylation of 1a into 2a

1-methyleneisochroman-3-one (2a)



$C_{10}H_8O_2$

MW: 160.17 g/mol

Compound **1a** (150 mg, 0.94 mmol) was solubilized in dry DCE (60 eq, 4.5 mL) in a vacuum-dried flask under inert atmosphere. JohnPhosAu(MeCN)SbF_6 (0.01 eq, 6.8 mg, 9.4 µmol) was then added to the solution. The medium was left under stirring at room temperature until total consumption of the substrate got observed by TLC. The reaction was then quenched using a saturated solution of $NaHCO_3$. The aqueous phase was then extracted thrice using DCM. The organic layers were combined, washed with brine once, and then dried over anhydrous Na_2SO_4. After filtration, the solvents were finally removed under reduced pressure. The crude product was then purified by column chromatography on silica gel, with an eluent pentane:AcOEt (70:30), afforded compound **2a** (92%, 138.7 mg, 0.87 mmol) as a yellow oil that crystallized in the freezer.

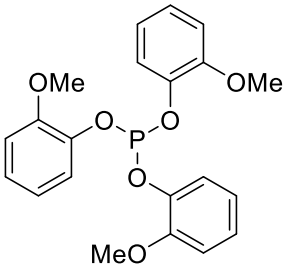
Rf = 0.50 (pentane:AcOEt (70:30)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.59 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.37 (td, *J* = 7.4, 1.6 Hz, 1H), 7.35 – 7.30 (m, 1H), 7.17 (ddt, *J* = 7.5, 1.4, 0.8 Hz, 1H), 5.13 (d, *J* = 2.4 Hz, 1H), 5.03 (d, *J* = 2.4 Hz, 1H), 3.84 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 166.1, 153.7, 129.9, 128.5, 127.8, 127.3, 127.1, 124.7, 94.9, 34.8.

HRMS (ESI): calculated for $C_{10}H_9O_2^+$ $[M+H]^+$, 161.06 found 161.0605 (Δ = 3.1 ppm)

4. Synthesis of the tris(2-methoxyphenyl)phosphiteLigand (L10)



$C_{21}H_{21}O_6P$

MW: 400.37 g/mol

Commercially available guaiacol (3.2 eq, 1.12 g, 1 mL, 9.02 mmol) was solubilized in 10 mL of dry toluene. The solvent was then removed under reduced pressure. Such procedure was repeated thrice to remove all traces of humidity. The resulting dry guaiacol was then solubilized under argon in 50 mL of dry THF. Triethylamine (5 eq, 1.43 g, 2 mL, 14.1 mmol) was added to the mixture. The flask was then cooled down to 0 °C. Commercially available PCl_3 (1 eq, 387.2 mg, 0.25 mL, 2.82 mmol) was finally added dropwise. The resulting mixture was left under agitation at room temperature and under inert atmosphere for 20 h. The medium was then diluted with diethyl ether Et_2O and filtered on Celite®. The solvents were then removed under reduce pressure. Purification by chromatography on silica gel, with an eluent pentane:AcOEt

(80:20), afforded compound **L10** (80% , 908 mg, 2.27 mmol) as a colourless oil that crystallized in the freezer.

Rf = 0.34 (pentane:AcOEt (80:20)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.24 (dt, *J* = 7.9, 1.5 Hz, 3H), 7.06 (dddd, *J* = 8.2, 7.4, 1.6, 0.8 Hz, 3H), 6.94 – 6.85 (m, 6H), 3.73 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 151.0 (3*C), 141.5 (d, *J* = 3.1 Hz) (3*C), 124.4 (3*C), 122.5 (d, *J* = 6.4 Hz) (3*C), 120.8 (3*C), 112.5 (3*C), 55.9 (3*C).

^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 134.

5. OTC of 1a into 4a

In a vacuum-dried adapted vial under an inert atmosphere, positioned inside a Parr reactor, ligand **L10** (0.04 eq) was solubilized in dry DCE (50 eq). $Rh(CO)_2(acac)$ (0.04 eq), **1a** (1 eq), and JohnPhosAu(MeCN)SbF_6 (0.01 eq) were then successively added to the mixture. The reactor was immediately purged twice with 10 bars of syngas and then left stirring under 20 bars of syngas at 70 °C for 16 h. The reactor was then cooled down to room temperature in an ice bath. The vial was retrieved, the solution was diluted with EtOAc and filtered on Celite®. The solvents were then removed under reduced pressure.

The determination of the composition of the crude reaction mixture has been performed by ^{1}H NMR analysis. Below, as examples, the ^{1}H NMR of the crude reaction mixtures from entries 5 and 7 of Table 4.

Table 4, entry 5

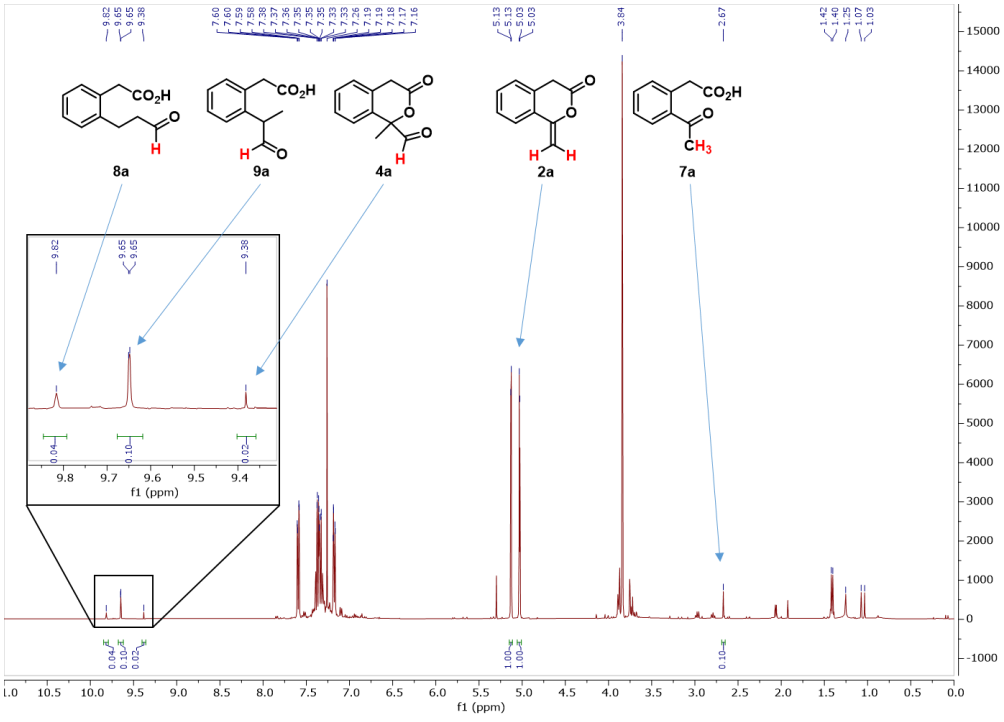
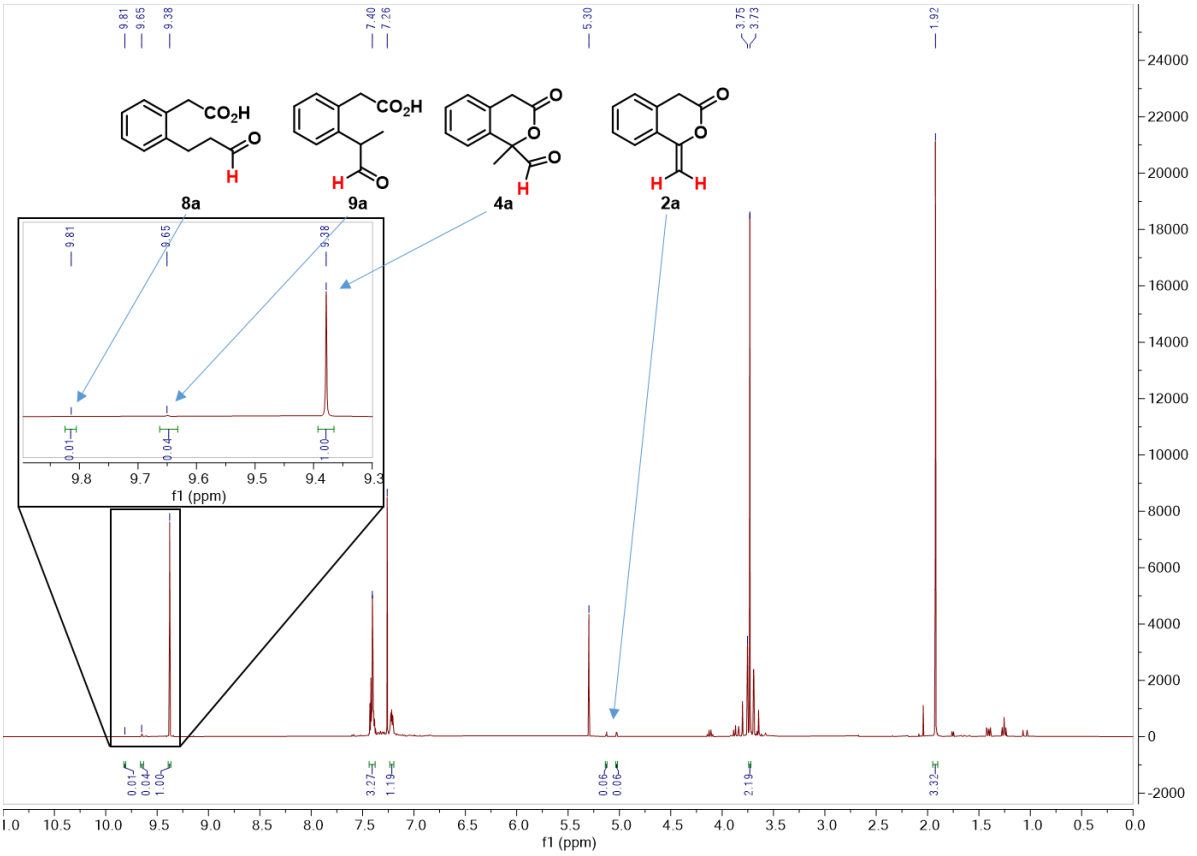


Table 4, entry 7



6. Synthesis of 10 and 13

6.1 General Procedures

General procedure for the Au(I)/Rh(I) OTC + Aldehyde reduction (**E**):

In a vacuum-dried adapted vial under an inert atmosphere, positioned inside a Parr reactor, ligand **L10** (0.04 eq) was solubilized in dry DCE (50 eq). $Rh(CO)_2(acac)$ (0.04 eq), derivative **1** (1 eq), and JohnPhosAu(MeCN)SbF_6 (0.01 eq) were then successively added to the mixture. The reactor was immediately purged twice with 10 bars of syngas and then left stirring under 20 bars of syngas at 70 °C for 16 h. The reactor was then cooled down to room temperature in an ice bath. The vial was retrieved, the solution was diluted with EtOAc and filtered on Celite®. The solvents were then removed under reduced pressure.

The crude product was then solubilized in DCM (190 eq), and cooled down to 0 °C. Sodium cyanoborohydride (2 eq) was then added to the mixture. The overall medium was slowly warmed up to room temperature and then left under stirring until total consumption of the substrate. Afterwards, 2 eq of a HCl 0.1 M solution were added and then the aqueous phase was extracted thrice with ethyl acetate. The organic layers were combined, washed with brine once, and then dried over anhydrous Na_2SO_4. After filtration, the solvents were finally removed under reduced pressure. The crude was finally purified on column chromatography to afford the corresponding alcohol **10**.

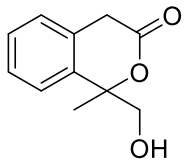
General procedure for the Au(I)/Rh(I) OTC + Aldehyde reduction (**F**):

In a vacuum-dried hydroformylation-adapted vial under inert atmosphere, ligand **L10** (0.04 eq) was solubilized in dry DCE (50 eq). $Rh(CO)_2(acac)$ (0.04 eq), derivative **11** (1 eq), and JohnPhosAu(MeCN)SbF_6 (0.01 eq) were then successively added to the mixture. The vial was then transferred in a hydroformylation reactor, purged twice with 10 bars of syngas and then left stirring under 20 bars of syngas at 70 °C for 16 h. The reactor was then cooled down to room temperature in an ice bath. The vial was retrieved, the solution was diluted with EtOAc and filtered on Celite®. The solvents were then removed under reduced pressure.

The crude product was then solubilized in MeOH (190 eq), and cooled down to 0 °C. $NaBH_4$ (2 eq) was then added to the mixture. The overall medium was slowly warmed up to room temperature and then left under stirring until total consumption of the substrate. Afterwards, the medium was diluted with brine then the aqueous phase was extracted thrice with ethyl acetate. The organic layers were combined, washed with brine once, and then dried over anhydrous Na_2SO_4. After filtration, the solvents were finally removed under reduced pressure. The crude was finally purified on column chromatography to afford the corresponding alcohol **13**.

6.2 Synthesis of 10

1-(hydroxymethyl)-1-methylisochroman-3-one (10a)



$C_{11}H_{12}O_3$

MW: 192.21 g/mol

Compound **10a** was synthesized following general procedure **E** from compound **1a** (50 mg, 0.31 mmol) with ligand **L10** (0.04 eq, 5.0 mg, 12.4 µmol), $Rh(CO)_2(acac)$ (0.04 eq, 3.22 mg, 12.4 µmol), and JohnPhosAu(MeCN)SbF_6 (0.01 eq, 2.41 mg, 3.1 µmol) in dry DCE (50 eq, 1.25 mL). $NaBH_3CN$ (2 eq, 41.5 mg, 0.66 mmol) in DCM (190 eq, 4.0 mL) were used in the reduction step. Purification by chromatography on silica gel, with an eluant pentane:AcOEt (55:45), afforded compound **10a** (52%, 34.6 mg, 0.18 mmol) as a white solid.

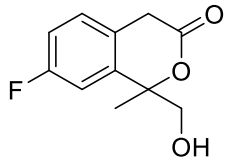
Rf = 0.20 (pentane:AcOEt (55:45)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.40 – 7.27 (m, 2H), 7.34 – 7.23 (m, 1H), 7.22 – 7.13 (m, 1H), 3.91 (s, 2H), 3.91 (d, *J* = 20.4 Hz, 1H), 3.77 (d, *J* = 20.4 Hz, 1H), 2.15 (bs, 1H), 1.70 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 170.0, 134.8, 130.3, 128.7, 127.8, 127.7, 124.1, 86.8, 69.8, 34.8, 23.7.

HRMS (ESI): calculated for $C_{11}H_{13}O_3^+$ $[M+H]^+$, 193.0859 found 193.0866 (Δ = 3.6 ppm)

7-fluoro-1-(hydroxymethyl)-1-methylisochroman-3-one (10d)



$C_{11}H_{11}FO_3$

MW: 210.20 g/mol

Compound **10d** was synthesized following general procedure **E** from compound **1d** (50 mg, 0.28 mmol) with ligand **L10** (0.04 eq, 4.5 mg, 11 µmol), $Rh(CO)_2(acac)$ (0.04 eq, 2.9 mg, 11 µmol), and JohnPhosAu(MeCN)SbF_6 (0.01 eq, 2.17 mg, 2.8 µmol) in dry DCE (50 eq, 1.12 mL). $NaBH_3CN$ (2 eq, 35.2 mg, 0.56 mmol) in DCM (190 eq, 3.4 mL) were used in the reduction step. Purification by chromatography on silica gel, with an eluant pentane:AcOEt (55:45), afforded compound **10d** (35%, 20.6 mg, 0.10 mmol) as a white solid.

Rf = 0.22 (pentane:AcOEt (55:45)).

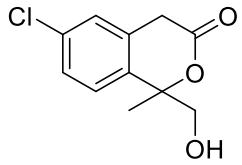
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.14 (dd, *J* = 8.5, 5.4 Hz, 1H), 7.04 (td, *J* = 8.4, 2.5 Hz, 1H), 6.99 (dd, *J* = 9.4, 2.5 Hz, 1H), 3.96 – 3.83 (m, 3H), 3.71 (d, *J* = 20.2 Hz, 1H), 2.42 (s, 1H), 1.68 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 169.8, 162.0 (d, *J* = 246.3 Hz), 136.9 (d, *J* = 7.1 Hz), 129.3 (d, *J* = 8.1 Hz), 126.0 (d, *J* = 3.2 Hz), 115.8 (d, *J* = 21.7 Hz), 111.4 (d, *J* = 23.4 Hz), 86.4 (d, *J* = 2.3 Hz), 69.8, 34.2, 23.6.

^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -113.82.

HRMS (ESI): calculated for $C_{11}H_{12}FO_3^+$ $[M+H]^+$, 211.0765 found 217.0771 (Δ = 2.4 ppm)

6-chloro-1-(hydroxymethyl)-1-methylisochroman-3-one (10f)



$C_{11}H_{11}ClO_3$

MW: 226.66 g/mol

Compound **10f** was synthesized following general procedure **E** from compound **1f** (49.2 mg, 0.25 mmol) with ligand **L10** (0.04 eq, 4.1 mg, 10.1 µmol), $Rh(CO)_2(acac)$ (0.04 eq, 2.6 mg, 10.1 µmol), and JohnPhosAu(MeCN)SbF_6 (0.01 eq, 1.95 mg, 2.5 µmol) in dry DCE (50 eq, 1.12 mL). $NaBH_3CN$ (2 eq, 31.4 mg, 0.5 mmol) in DCM (190 eq, 3.0 mL) were used in the reduction step. Purification by chromatography on silica gel, with an eluant pentane:AcOEt (55:45), afforded compound **10f** (46%, 26.3 mg, 0.12 mmol) as a light yellow solid.

Rf = 0.21 (pentane:AcOEt (55:45)).

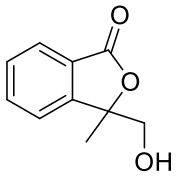
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.31 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.17 (d, *J* = 2.1 Hz, 1H), 3.96 – 3.82 (m, 3H), 3.71 (d, *J* = 20.4 Hz, 1H), 2.39 (s, 1H), 1.68 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 169.4, 134.5, 133.5, 132.4, 127.9, 127.6, 125.6, 86.5, 70.0, 34.6, 23.7.

HRMS (ESI): calculated for $C_{11}H_{12}ClO_3^+$ $[M+H]^+$, 227.0469 found 227.0477 (Δ = 2.7 ppm)

6.3 Synthesis of 13

3-(hydroxymethyl)-3-methylisobenzofuran-1(3H)-one (13a)



$C_{10}H_{10}O_3$

MW: 178.19 g/mol

Compound **13a** was synthesized following general procedure **F** from compound **11a** (50 mg, 0.34 mmol) with ligand **L10** (0.04 eq, 4.93 mg, 12 µmol), $Rh(CO)_2(acac)$ (0.04 eq, 3.2 mg, 12 µmol), and JohnPhosAu(MeCN)SbF_6 (0.01 eq, 2.38 mg, 3.4 µmol) in dry DCE (50 eq, 1.13 mL). $NaBH_3CN$ (2 eq, 33.9 mg, 0.54 mmol) in MeOH (190 eq, 2.1 mL) were used in the reduction step. Purification by chromatography on silica gel, with an eluant pentane:AcOEt (60:40), afforded compound **13a** (50%, 30.5 mg, 0.17 mmol) as a white solid.

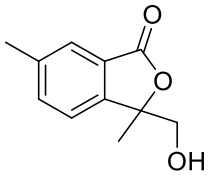
Rf = 0.21 (pentane:AcOEt (60:40)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.90 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.69 (td, *J* = 7.5, 1.1 Hz, 1H), 7.55 (td, *J* = 7.5, 0.9 Hz, 1H), 7.44 (dt, *J* = 7.7, 0.9 Hz, 1H), 3.92 (d, *J* = 12.0 Hz, 1H), 3.82 (d, *J* = 12.0 Hz, 1H), 1.91 (bs, 1H), 1.67 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 170.0, 151.4, 134.3, 129.4, 126.4, 125.8, 121.3, 87.7, 67.8, 21.7.

HRMS (ESI): calculated for $C_{10}H_{11}O_3^+$ $[M+H]^+$ 179.0703, found 179.0698 (Δ = 3.0 ppm)

3-(hydroxymethyl)-3,6-dimethylisobenzofuran-1(3H)-one (13b)



$C_{11}H_{12}O_3$

MW: 192.21 g/mol

Compound **13b** was synthesized following general procedure **F** from compound **11b** (43.25 mg, 0.27 mmol) with ligand **L10** (0.04 eq, 4.32 mg, 10.8 µmol), $Rh(CO)_2(acac)$ (0.04 eq, 2.79 mg, 10.8 µmol), and JohnPhosAu(MeCN)SbF_6 (0.01 eq, 2.1 mg, 2.7 µmol) in dry DCE (50 eq, 1.0 mL). $NaBH_3CN$ (2 eq, 27.7 mg, 0.54 mmol) in MeOH (190 eq, 2.1 mL) were used in the reduction step. Purification by chromatography on silica gel, with an eluant pentane:AcOEt (60:40), afforded compound **13b** (31% , 16.1 mg, 0.08 mmol) as a colourless oil.

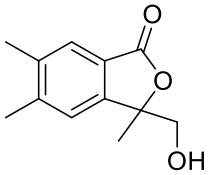
Rf = 0.22 (pentane:AcOEt (60:40)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.66 (s, 1H), 7.49 (d, *J* = 7.3 Hz, 1H), 7.31 (d, *J* = 7.7 Hz, 1H), 3.90 (d, *J* = 11.6 Hz, 1H), 3.78 (d, *J* = 11.8 Hz, 1H), 2.45 (s, 3H), 1.63 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 170.1, 148.7, 139.7, 135.4, 126.6, 125.9, 121.0, 87.5, 67.9, 21.8, 21.3.

HRMS (ESI): calculated for $C_{11}H_{13}O_3^+$ $[M+H]^+$ 193.0859, found 193.0864 (Δ = 2.0 ppm)

3-(hydroxymethyl)-3,5,6-trimethylisobenzofuran-1(3H)-one (13c)



$C_{12}H_{14}O_3$

MW: 206.24 g/mol

Compound **13c** was synthesized following general procedure **F** from compound **11c** (47.7 mg, 0.27 mmol) with ligand **L10** (0.04 eq, 4.4 mg, 10.9 µmol), $Rh(CO)_2(acac)$ (0.04 eq, 2.8 mg, 10.9 µmol), and JohnPhosAu(MeCN)SbF_6 (0.01 eq, 2.11 mg, 2.7 µmol) in dry DCE (50 eq, 1 mL). $NaBH_3CN$ (2 eq, 33.9 mg, 0.54 mmol) in MeOH (190 eq, 2 mL) were used in the reduction step. Purification by chromatography on silica gel, with an eluant pentane:AcOEt (65:35), afforded compound **13c** (24%, 13.4 mg, 0.06 mmol) as a white solid.

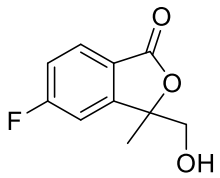
Rf = 0.18 (pentane:AcOEt (65:35)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.62 (s, 1H), 7.18 (s, 1H), 3.90 (d, *J* = 12.0 Hz, 1H), 3.77 (d, *J* = 12.0 Hz, 1H), 2.38 (s, 3H), 2.34 (s, 3H), 1.62 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 170.2, 149.4, 144.5, 138.6, 126.2, 124.2, 122.0, 87.2, 67.9, 21.8, 20.8, 19.9.

HRMS (ESI): calculated for $C_{12}H_{15}O_3^+$ $[M+H]^+$ 207.1016, found 207.1024 (Δ = 3.8 ppm)

5-fluoro-3-(hydroxymethyl)-3-methylisobenzofuran-1(3H)-one (13d)



$C_{10}H_9FO_3$

MW: 196.18 g/mol

Compound **13d** was synthesized following general procedure **F** from compound **11d** (44.32 mg, 0.27 mmol) with ligand **L10** (0.04 eq, 4.32 mg, 10.8 µmol), $Rh(CO)_2(acac)$ (0.04 eq, 2.79 mg, 10.8 µmol), and JohnPhosAu(MeCN)SbF_6 (0.01 eq, 2.1 mg, 2.7 µmol) in dry DCE (50 eq, 1.0 mL). $NaBH_3CN$ (2 eq, 33.9 mg, 0.54 mmol) in MeOH (190 eq, 2.1 mL) were used in the reduction step. Purification by chromatography on silica gel, with an eluant pentane:AcOEt (65:35), afforded compound **13d** (49%, 26.0 mg, 0.13 mmol) as a white solid.

Rf = 0.24 (pentane:AcOEt (65:35)).

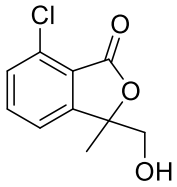
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.87 (ddd, *J* = 6.7, 4.9, 1.7 Hz, 1H), 7.22 (td, *J* = 8.6, 2.1 Hz, 1H), 7.12 (dd, *J* = 7.8, 2.2 Hz, 1H), 3.91 (d, *J* = 12.0 Hz, 1H), 3.82 (d, *J* = 12.0 Hz, 1H), 2.25 (bs, 1H), 1.65 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 168.7 (d, *J* = 5.0 Hz), 166.7 (d, *J* = 256.7 Hz), 154.2 (d, *J* = 10.1 Hz), 128.2 (d, *J* = 10.4 Hz), 122.5 (d, *J* = 2.1 Hz), 117.6 (d, *J* = 24.0 Hz), 109.0, 86.88 (d, *J* = 3.6 Hz), 67.6 (d, *J* = 2.0 Hz), 21.7.

^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -102.18.

HRMS (ESI): calculated for $C_{10}H_{10}FO_3^+$ $[M+H]^+$ 197.0608, found 197.0614 (Δ = 2.3 ppm)

7-chloro-3-(hydroxymethyl)-3-methylisobenzofuran-1(3H)-one (13e)



$C_{10}H_9ClO_3$

MW: 212.63 g/mol

Compound **13e** was synthesized following general procedure **F** from compound **11e** (50 mg, 0.28 mmol) with ligand **L10** (0.04 eq, 4.43 mg, 11 µmol), $Rh(CO)_2(acac)$ (0.04 eq, 2.86 mg, 11 µmol), and JohnPhosAu(MeCN)SbF_6 (0.01 eq, 2.14 mg, 2.8 µmol) in dry DCE (50 eq, 1.0 mL). $NaBH_3CN$ (2 eq, 35.2 mg, 0.56 mmol) in MeOH (190 eq, 2.2 mL) were used in the reduction step. Purification by chromatography on silica gel, with an eluant pentane:AcOEt (55:45), afforded compound **13e** (38%, 22.6 mg, 0.11 mmol) as a colourless oil.

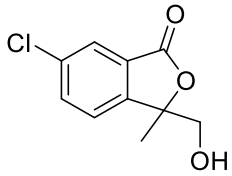
Rf = 0.23 (pentane:AcOEt (55:45)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.37 (t, *J* = 7.7 Hz, 1H), 7.25 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.11 (dd, *J* = 7.7, 0.8 Hz, 1H), 3.70 (d, *J* = 12.1 Hz, 1H), 3.59 (d, *J* = 12.5 Hz, 1H), 2.13 (bs, 1H), 1.42 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 166.9, 153.8, 135.2, 133.4, 130.8, 123.1, 119.8, 86.2, 67.6, 21.7.

HRMS (ESI): calculated for $C_{10}H_{10}ClO_3^+$ $[M+H]^+$ 213.0313, found 213.0318 (Δ = 1.6 ppm)

6-chloro-3-(hydroxymethyl)-3-methylisobenzofuran-1(3H)-one (13f)



$C_{10}H_9ClO_3$

MW: 212.63 g/mol

Compound **13f** was synthesized following general procedure **F** from compound **11f** (50 mg, 0.28 mmol) with ligand **L10** (0.04 eq, 4.43 mg, 11 µmol), $Rh(CO)_2(acac)$ (0.04 eq, 2.86 mg, 11 µmol), and JohnPhosAu(MeCN)SbF_6 (0.01 eq, 2.14 mg, 2.8 µmol) in dry DCE (50 eq, 1.0 mL). $NaBH_3CN$ (2 eq, 35.2 mg, 0.56 mmol) in MeOH (190 eq, 2.2 mL) were used in the reduction step. Purification by chromatography on silica gel, with an eluant pentane:AcOEt (60:40), afforded compound **13f** (44%, 26.2 mg, 0.12 mmol) as a white solid.

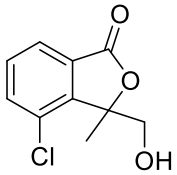
Rf = 0.21 (pentane:AcOEt (60:40)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.84 (d, *J* = 1.8 Hz, 1H), 7.65 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 3.92 (d, *J* = 11.8 Hz, 1H), 3.82 (d, *J* = 11.9 Hz, 1H), 2.10 (bs, 1H), 1.65 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 168.4, 149.5, 135.8, 134.6, 128.3, 125.8, 122.7, 87.6, 67.6, 21.7.

HRMS (ESI): calculated for $C_{10}H_{10}ClO_3^+$ $[M+H]^+$ 213.0313, found 213.0321 (Δ = 3.8 ppm)

4-chloro-3-(hydroxymethyl)-3-methylisobenzofuran-1(3H)-one (13h)



$C_{10}H_9ClO_3$

MW: 212.63 g/mol

Compound **13h** was synthesized following general procedure **F** from compound **11h** (50 mg, 0.28 mmol) with ligand **L10** (0.04 eq, 4.43 mg, 11 µmol), $Rh(CO)_2(acac)$ (0.04 eq, 2.86 mg, 11 µmol), and JohnPhosAu(MeCN)SbF_6 (0.01 eq, 2.14 mg, 2.8 µmol) in dry DCE (50 eq, 1.0 mL). $NaBH_3CN$ (2 eq, 35.2 mg, 0.56 mmol) in MeOH (190 eq, 2.2 mL) were used in the reduction step. Purification by chromatography on silica gel, with an eluant pentane:AcOEt (60:40), afforded compound **13h** (26%, 15.5 mg, 0.07 mmol) as a white solid.

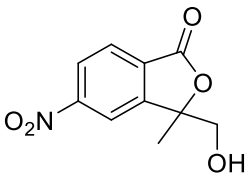
Rf = 0.22 (pentane:AcOEt (60:40)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.81 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.63 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 1H), 4.18 – 4.07 (m, 2H), 1.77 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 168.5, 147.0, 135.1, 131.1, 129.4, 128.4, 124.4, 88.8, 65.1, 19.4.

HRMS (ESI): calculated for $C_{10}H_{13}ClNO_3^+$ $[M+NH_4]^+$, 230.0578 found 230.0582 (Δ = 0.5 ppm)

3-(hydroxymethyl)-3-methyl-5-nitroisobenzofuran-1(3H)-one (13i)



$C_{10}H_9NO_5$

MW: 223.18 g/mol

Compound **13i** was synthesized following general procedure **F** from compound **11i** (50 mg, 0.26 mmol) with ligand **L10** (0.04 eq, 4.19 mg, 10.5 µmol), $Rh(CO)_2(acac)$ (0.04 eq, 2.7 mg, 10.5 µmol), and JohnPhosAu(MeCN)SbF6 (0.01 eq, 2.02 mg, 2.6 µmol) in dry DCE (50 eq, 1 mL). $NaBH_3CN$ (2 eq, 32.7 mg, 0.52 mmol) in MeOH (190 eq, 2 mL) were used in the reduction step. Purification by chromatography on silica gel, with an eluant pentane:AcOEt (65:35), afforded compound **13i** (24%, 13.9 mg, 0.06 mmol) as a yellow solid.

Rf = 0.25 (pentane:AcOEt (65:35)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.40 (dd, *J* = 8.3, 1.9 Hz, 1H), 8.32 (d, *J* = 2.0 Hz, 1H), 8.05 (d, *J* = 8.3 Hz, 1H), 3.99 (d, *J* = 12.0 Hz, 1H), 3.93 (d, *J* = 12.0 Hz, 1H), 2.22 (bs, 1H), 1.72 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 152.5, 151.8, 131.5, 127.1, 125.0, 117.3, 112.9, 87.7, 67.2, 21.7.

HRMS (ESI): calculated for $C_{10}H_{10}NO_5^+$ $[M+H]^+$ 224.0553, found 224.0553 (Δ = 0.4 ppm)

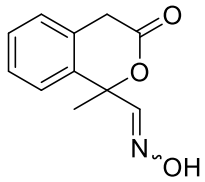
7. Synthesis of 14 and 15

General procedure for the Au(I)/Rh(I) OTC + Hydroxylamine condensation (**G**):

In a vacuum-dried hydroformylation-adapted vial under inert atmosphere, ligand **L10** (0.04 eq) was solubilized in dry DCE (50 eq). $Rh(CO)_2(acac)$ (0.04 eq), derivative **1-11** (1 eq), and JohnPhosAu(MeCN)SbF_6 (0.01 eq) were then successively added to the mixture. The vial was then transferred in a hydroformylation reactor, purged twice with 10 bars of syngas and then left stirring under 20 bars of syngas at 70 °C for 16 h. The reactor was then cooled to room temperature in an ice bath. The vial was retrieved, the solution was diluted with EtOAc and filtered on Celite®. The solvents were then removed under reduced pressure.

The crude product was then solubilized in EtOH (190 eq). Sodium acetate (2eq) and hydroxylammonium chloride (2 eq) were then successively added to the mixture which was then left under stirring at room temperature until total consumption of the substrate. The solvents were then evaporated under reduced pressure. The obtained crude was then solubilized in water. The aqueous phase was then extracted thrice with ethyl acetate. The organic layers were combined, washed with brine once, and then dried over anhydrous Na_2SO_4. After filtration, the solvents were finally removed under reduced pressure. The crude was finally purified on column chromatography to afford the corresponding oxime **14-15**.

1-methyl-3-oxoisochromane-1-carbaldehyde oxime (14a)



$C_{11}H_{11}NO_3$

MW: 205.21 g/mol

Compound **14a** was synthesized following general procedure **G** from compound **1a** (52.3 mg, 0.33 mmol) with ligand **L10** (0.04 eq, 5.23 mg, 13 µmol), $Rh(CO)_2(acac)$ (0.04 eq, 3.37 mg, 13 µmol), and JohnPhosAu(MeCN)SbF_6 (0.01 eq, 2.52 mg, 3.3 µmol) in dry DCE (50 eq, 1.31 mL). NaOAc (2 eq, 54.1 mg, 0.66 mmol) and $NH_2OH.HCl$ (2 eq, 45.9 mg, 0.66 mmol) in EtOH (190 eq, 3.7 mL) were used for the oxime condensation. Purification by chromatography on silica gel, with an eluant pentane:AcOEt (80:20), afforded compound **14a** (69%, 47 mg, 0.23 mmol) as a white solid.

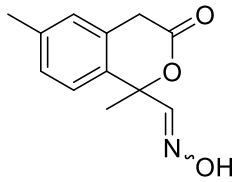
Rf = 0.20 (pentane:AcOEt (80:20)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.89 (bs, 1H), 7.49 (s, 1H), 7.41 – 7.35 (m, 2H), 7.35 – 7.29 (m, 1H), 7.22 – 7.18 (m, 1H), 3.74 (s, 2H), 1.92 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 169.9, 150.8, 134.4, 130.4, 129.4, 127.8, 127.7, 124.3, 82.7, 35.8, 24.2.

HRMS (ESI): calculated for $C_{11}H_{12}NO_3^+$ $[M+H]^+$ 206.0812, found 206.0816 (Δ = 1.5 ppm)

1,6-dimethyl-3-oxoisochromane-1-carbaldehyde oxime (14b)



$C_{12}H_{13}NO_3$

MW: 219.24 g/mol

Compound **14b** was synthesized following general procedure **G** from compound **1b** (51.5 mg, 0.3 mmol) with ligand **L10** (0.04 eq, 4.73 mg, 12 µmol), $Rh(CO)_2(acac)$ (0.04 eq, 3.1 mg, 12 µmol), and JohnPhosAu(MeCN)SbF_6 (0.01 eq, 2.3 mg, 3 µmol) in dry DCE (50 eq, 1.2 mL). NaOAc (2 eq, 49.2 mg, 0.6 mmol) and $NH_2OH.HCl$ (2 eq, 41.7 mg, 0.6 mmol) in EtOH (190 eq, 3.3 mL) were used for the oxime condensation. Purification by chromatography on silica gel, with an eluant pentane:AcOEt (80:20), afforded compound **14b** (35%, 23.3 mg, 0.106 mmol) as a white solid.

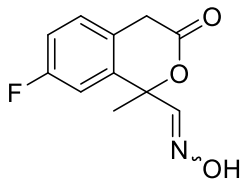
Rf = 0.20 (pentane:AcOEt (80:20)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.57 (bs, 1H), 7.50 (s, 1H), 7.22 – 7.15 (m, 2H), 7.01 (s, 1H), 3.70 (d, *J* = 2.2 Hz, 2H), 2.36 (s, 3H), 1.90 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 170.0, 151.1, 139.4, 131.5, 130.4, 128.4, 128.3, 124.2, 82.6, 35.8, 24.2, 21.1.

HRMS (ESI): calculated for $C_{12}H_{14}NO_3^+$ $[M+H]^+$ 220.0968, found 220.0971 (Δ = 1.1 ppm)

7-fluoro-1-methyl-3-oxoisochromane-1-carbaldehyde oxime (14d)



$C_{11}H_{10}FNO_3$

MW: 223.20 g/mol

Compound **14d** was synthesized following general procedure **G** from compound **1d** (50 mg, 0.28 mmol) with ligand **L10** (0.04 eq, 4.5 mg, 11 µmol), $Rh(CO)_2(acac)$ (0.04 eq, 2.9 mg, 11 µmol), and JohnPhosAu(MeCN)SbF_6 (0.01 eq, 2.2 mg, 2.8 µmol) in dry DCE (50 eq, 1.12 mL). NaOAc (2 eq, 45.9 mg, 0.56 mmol) and $NH_2OH.HCl$ (2 eq, 38.9 mg, 0.56 mmol) in EtOH (190 eq, 3.1 mL) were used for the oxime condensation. Purification by chromatography on silica gel, with an eluant pentane:AcOEt (70:30), afforded compound **14d** (54%, 33.7 mg, 0.15 mmol) as a white solid.

Rf = 0.26 (pentane:AcOEt (70:30)).

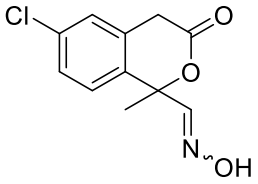
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.32 (s, 1H), 7.57 (s, 1H), 7.38 – 7.19 (m, 3H), 3.85 (d, *J* = 19.5 Hz, 1H), 3.71 (d, *J* = 19.5 Hz, 1H), 1.85 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 169.6, 161.7 (d, *J* = 243.1 Hz), 149.2, 137.6 (d, *J* = 7.7 Hz), 129.9 (d, *J* = 8.3 Hz), 127.2, 116.1 (d, *J* = 21.5 Hz), 112.2 (d, *J* = 24.0 Hz), 82.8 (d, *J* = 2.3 Hz), 34.8, 24.3.

^{19}F NMR (376 MHz, DMSO-d_6) δ (ppm) -114.75 (d, *J* = 2.7 Hz).

HRMS (ESI): calculated for $C_{11}H_{11}FNO_3^+$ $[M+H]^+$, 224.0717 found 224.0719 (Δ = -0.24 ppm)

6-chloro-1-methyl-3-oxoisochromane-1-carbaldehyde oxime (14f)



$C_{11}H_{10}ClNO_3$

MW: 239.66 g/mol

Compound **14f** was synthesized following general procedure **G** from compound **1f** (50 mg, 0.26 mmol) with ligand **L10** (0.04 eq, 4.1 mg, 10 µmol), $Rh(CO)_2(acac)$ (0.04 eq, 2.7 mg, 10 µmol), and JohnPhosAu(MeCN)SbF_6 (0.01 eq, 2.0 mg, 2.6 µmol) in dry DCE (50 eq, 1.0 mL). NaOAc (2 eq, 42.7 mg, 0.52 mmol) and $NH_2OH.HCl$ (2 eq, 36.1 mg, 0.52 mmol) in EtOH (190 eq, 2.9 mL) were used for the oxime condensation. Purification by chromatography on silica gel, with an eluant pentane:AcOEt (80:20), afforded compound **14f** (55%, 34 mg, 0.14 mmol) as a white solid.

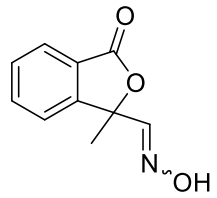
Rf = 0.24 (pentane:AcOEt (80:20)).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.30 (s, 1H), 7.58 (s, 1H), 7.43 (s, 3H), 3.91 (d, *J* = 19.7 Hz, 1H), 3.79 (d, *J* = 19.7 Hz, 1H), 1.85 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 169.2, 149.3, 134.4, 133.7, 133.6, 127.7 (2C), 126.8, 82.9, 35.1, 24.4.

HRMS (ESI): calculated for $C_{11}H_{11}ClNO_3^+$ $[M+H]^+$, 240.0422 found 240.0425 (Δ = -0.85 ppm)

1-methyl-3-oxo-1,3-dihydroisobenzofuran-1-carbaldehyde oxime (15a)



$C_{10}H_9NO_3$

MW: 191.19 g/mol

Compound **15a** was synthesized following general procedure **G** from compound **11a** (45 mg, 0.31 mmol) with ligand **L10** (0.04 eq, 5.0 mg, 12 µmol), $Rh(CO)_2(acac)$ (0.04 eq, 3.2 mg, 12 µmol), and JohnPhosAu(MeCN)SbF_6 (0.01 eq, 2.6 mg, 3.1 µmol) in dry DCE (50 eq, 1.1 mL). NaOAc (2 eq, 50.5 mg, 0.62 mmol) and $NH_2OH.HCl$ (2 eq, 42.8 mg, 0.6 mmol) in EtOH (190 eq, 3.4 mL) were used for the oxime condensation. Purification by chromatography on silica gel, with an eluant pentane:AcOEt (80:20), afforded compound **15a** (60% , 39.1 mg, 0.209 mmol) as a light yellow oil.

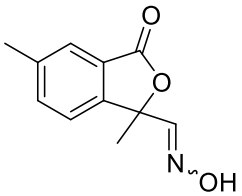
Rf = 0.29 (pentane:AcOEt (80:20))

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.21 (bs, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.70 (t, *J* = 7.4 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.48 (s, 1H), 7.46 (d, *J* = 7.7 Hz, 1H), 1.81 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 169.3, 150.5, 150.1, 134.6, 129.9, 126.0, 125.5, 122.5, 84.4, 23.8.

HRMS (ESI): calculated for $C_{10}H_{10}NO_3^+$ $[M+H]^+$ 192.0655, found 192.0663 (Δ = 4.0 ppm)

1,6-dimethyl-3-oxo-1,3-dihydroisobenzofuran-1-carbaldehyde oxime (15b)



$C_{11}H_{11}NO_3$

MW: 205.21 g/mol

Compound **15b** was synthesized following general procedure **G** from compound **11b** (50 mg, 0.31 mmol) with ligand **L10** (0.04 eq, 5 mg, 12 µmol), $Rh(CO)_2(acac)$ (0.04 eq, 3.22 mg, 12 µmol), and JohnPhosAu(MeCN)SbF_6 (0.01 eq, 2.41 mg, 3.1 µmol) in dry DCE (50 eq, 1.2 mL). NaOAc (2 eq, 43.1 mg, 0.62 mmol) and $NH_2OH.HCl$ (2 eq, 50.9 mg, 0.62 mmol) in EtOH (190 eq, 3.4 mL) were used for the oxime condensation. Purification by chromatography on silica gel, with an eluant pentane:AcOEt (80:20), afforded compound **15b** (28%, 18.1 mg, 0.088 mmol) as a colourless oil.

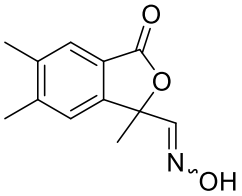
Rf = 0.30 (pentane:AcOEt (80:20)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.93 (bs, 1H), 7.69 (d, *J* = 1.6 Hz, 1H), 7.50 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.46 (s, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 2.46 (s, 3H), 1.79 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 169.4, 150.3, 147.9, 140.3, 135.7, 125.9, 125.6, 122.2, 84.3, 23.8, 21.3.

HRMS (ESI): calculated for $C_{11}H_{12}NO_3^+$ $[M+H]^+$, 206.0812 found 206.0819 (Δ = -3.4 ppm)

1,5,6-trimethyl-3-oxo-1,3-dihydroisobenzofuran-1-carbaldehyde oxime (15c)



$C_{12}H_{13}NO_3$

MW: 219.24 g/mol

Compound **15c** was synthesized following general procedure **G** from compound **11c** (50 mg, 0.29 mmol) with ligand **L10** (0.04 eq, 4.6 mg, 11 µmol), $Rh(CO)_2(acac)$ (0.04 eq, 3.0 mg, 11 µmol), and JohnPhosAu(MeCN)SbF_6 (0.01 eq, 2.2 mg, 2.9 µmol) in dry DCE (50 eq, 1.1 mL). NaOAc (2 eq, 47.6 mg, 0.58 mmol) and $NH_2OH.HCl$ (2 eq, 40.3 mg, 0.58 mmol) in EtOH (190 eq, 3.2 mL) were used for the oxime condensation. Purification by chromatography on silica gel, with an eluant pentane:AcOEt (80:20), afforded compound **15c** (61%, 38.7 mg, 0.18 mmol) as a white solid.

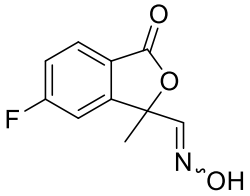
Rf = 0.26 (pentane:AcOEt (80:20)).

^{1}H NMR (400 MHz, $CDCl_3$) 8.31 (bs, 1H), 7.70 (s, 1H), 7.50 (s, 1H), 7.26 (s, 1H), 2.44 (s, 3H), 2.41 (s, 3H), 1.83 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 169.7, 150.4, 148.6, 145.0, 139.2, 126.2, 123.2, 123.1, 84.1, 23.7, 20.8, 20.0.

HRMS (ESI): calculated for $C_{12}H_{14}NO_3^+$ $[M+H]^+$, 220.0968 found 220.0976 (Δ = -3.12 ppm)

5-fluoro-1-methyl-3-oxo-1,3-dihydroisobenzofuran-1-carbaldehyde oxime (15d)



$C_{10}H_8FNO_3$

MW: 209.18 g/mol

Compound **15d** was synthesized following general procedure **G** from compound **11d** (50 mg, 0.31 mmol) with ligand **L10** (0.04 eq, 4.9 mg, 12 µmol), $Rh(CO)_2(acac)$ (0.04 eq, 3.1 mg, 12 µmol), and JohnPhosAu(MeCN)SbF_6 (0.01 eq, 2.3 mg, 3.1 µmol) in dry DCE (50 eq, 1.1 mL). NaOAc (2 eq, 50 mg, 0.61 mmol) and $NH_2OH.HCl$ (2 eq, 42.4 mg, 0.61 mmol) in EtOH (190 eq, 3.4 mL) were used for the oxime condensation. Purification by chromatography on silica gel, with an eluant pentane:AcOEt (80:20), afforded compound **15d** (25%, 16.2 mg, 0.08 mmol) as a white solid.

Rf = 0.31 (pentane:AcOEt (80:20)).

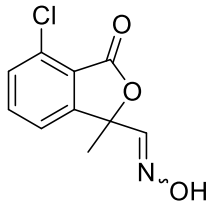
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.21 (bs, 1H), 7.89 (dd, *J* = 8.4, 4.7 Hz, 1H), 7.50 (s, 1H), 7.25 (td, *J* = 8.6, 2.2 Hz, 1H), 7.14 (dd, *J* = 7.6, 2.2 Hz, 1H), 1.81 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 168.0, 166.7 (d, *J* = 257.3 Hz), 153.4 (d, *J* = 10.1 Hz), 149.4, 128.3 (d, *J* = 10.4 Hz), 121.5 (d, *J* = 2.0 Hz), 118.1 (d, *J* = 24.1 Hz), 110.1 (d, *J* = 24.6 Hz), 83.9, 24.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -101.56.

HRMS (ESI): calculated for $C_{10}H_9FNO_3^+$ $[M+H]^+$, 210.0561 found 210.0566 (Δ = -1.87 ppm)

7-chloro-1-methyl-3-oxo-1,3-dihydroisobenzofuran-1-carbaldehyde oxime (15e)



$C_{10}H_8ClNO_3$

MW: 225.63 g/mol

Compound **15e** was synthesized following general procedure **G** from compound **11e** (50 mg, 0.28 mmol) with ligand **L10** (0.04 eq, 4.4 mg, 11 µmol), $Rh(CO)_2(acac)$ (0.04 eq, 2.9 mg, 11 µmol), and JohnPhosAu(MeCN)SbF_6 (0.01 eq, 2.1 mg, 2.8 µmol) in dry DCE (50 eq, 1.0 mL). NaOAc (2 eq, 45.9 mg, 0.56 mmol) and $NH_2OH.HCl$ (2 eq, 38.9 mg, 0.56 mmol) in EtOH (190 eq, 3.1 mL) were used for the oxime condensation. Purification by chromatography on silica gel, with an eluant pentane:AcOEt (80:20), afforded compound **15e** (52%, 33.1 mg, 0.15 mmol) as a white solid.

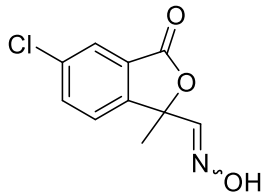
Rf = 0.18 (pentane:AcOEt (80:20)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.71 (bs, 1H), 7.62 (t, *J* = 7.7 Hz, 1H), 7.54 – 7.48 (m, 1H), 7.48 (s, 1H), 7.36 (dd, *J* = 7.5, 0.8 Hz, 1H), 1.81 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 166.1, 152.7, 149.8, 135.4, 133.5, 131.2, 122.2, 121.1, 83.0, 23.9.

HRMS (ESI): calculated for $C_{10}H_9ClNO_3^+$ $[M+H]^+$, 226.0265 found 226.0273 (Δ = -2.68 ppm)

6-chloro-1-methyl-3-oxo-1,3-dihydroisobenzofuran-1-carbaldehyde oxime (15f)



$C_{10}H_8ClNO_3$

MW: 225.63 g/mol

Compound **15f** was synthesized following general procedure **G** from compound **11f** (50 mg, 0.28 mmol) with ligand **L10** (0.04 eq, 4.4 mg, 11 µmol), $Rh(CO)_2(acac)$ (0.04 eq, 2.9 mg, 11 µmol), and JohnPhosAu(MeCN)SbF_6 (0.01 eq, 2.1 mg, 2.8 µmol) in dry DCE (50 eq, 1.0 mL). NaOAc (2 eq, 45.9 mg, 0.56 mmol) and $NH_2OH.HCl$ (2 eq, 38.9 mg, 0.56 mmol) in EtOH (190 eq, 3.1 mL) were used for the oxime condensation. Purification by chromatography on silica gel, with an eluant pentane:AcOEt (80:20), afforded compound **15f** (51%, 32.2 mg, 0.14 mmol) as a yellow oil.

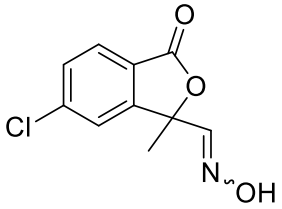
Rf = 0.28 (pentane:AcOEt (80:20)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.86 (d, *J* = 1.8 Hz, 1H), 7.66 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.50 (s, 1H), 7.41 (d, *J* = 8.2 Hz, 1H), 1.81 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 167.8, 149.7, 148.6, 136.3, 134.8, 127.3, 125.8, 124.0, 84.5, 23.9.

HRMS (ESI): calculated for $C_{10}H_9ClNO_3^+$ $[M+H]^+$, 226.0265 found 226.0270 (Δ = -1.16 ppm)

5-chloro-1-methyl-3-oxo-1,3-dihydroisobenzofuran-1-carbaldehyde oxime (15g)



$C_{10}H_8ClNO_3$

MW: 225.63 g/mol

Compound **15g** was synthesized following general procedure **G** from compound **11g** (45 mg, 0.25 mmol) with ligand **L10** (0.04 eq, 4.0 mg, 10 µmol), $Rh(CO)_2(acac)$ (0.04 eq, 2.6 mg, 10 µmol), and JohnPhosAu(MeCN)SbF_6 (0.01 eq, 1.9 mg, 2.5 µmol) in dry DCE (50 eq, 1.0 mL). NaOAc (2 eq, 41.0 mg, 0.50 mmol) and $NH_2OH.HCl$ (2 eq, 34.8 mg, 0.5 mmol) in EtOH (190 eq, 2.8 mL) were used for the oxime condensation. Purification by chromatography on silica gel, with an eluant pentane:AcOEt (90:10), afforded compound **15g** (32%, 17.8 mg, 0.08 mmol) as a white solid.

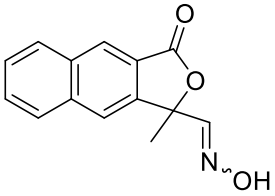
Rf = 0.13 (pentane:AcOEt (90:10)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.83 (d, *J* = 8.2 Hz, 1H), 7.54 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.50 (s, 1H), 7.46 (d, *J* = 1.7 Hz, 1H), 1.82 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ (ppm) 168.0, 152.1, 149.7, 141.3, 130.7, 127.1, 124.0, 123.2, 84.0, 24.0.

HRMS (ESI): calculated for $C_{10}H_9ClNO_3^+$ $[M+H]^+$, 226.0265 found 226.0271 (Δ = -1.91 ppm)

1-methyl-3-oxo-1,3-dihydronaphtho[2,3-c]furan-1-carbaldehyde oxime (15j)



$C_{14}H_{11}NO_3$

MW: 241.25 g/mol

Compound **15j** was synthesized following general procedure **G** from compound **11j** (50 mg, 0.25 mmol) with ligand **L10** (0.04 eq, 4.1 mg, 10.2 µmol), $Rh(CO)_2(acac)$ (0.04 eq, 2.6 mg, 10.2 µmol), and JohnPhosAu(MeCN)SbF_6 (0.01 eq, 2.0 mg, 2.5 µmol) in dry DCE (50 eq, 1.0 mL). NaOAc (2 eq, 41.0 mg, 0.5 mmol) and $NH_2OH.HCl$ (2 eq, 34.8 mg, 0.5 mmol) in EtOH (190 eq, 2.8 mL) were used for the oxime condensation. Purification by chromatography on silica gel, with an eluant pentane:AcOEt (80:20), afforded compound **15j** (50%, 30.4 mg, 0.13 mmol) as a white solid.

Rf = 0.25 (pentane:AcOEt (80:20)).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.49 (s, 1H), 8.05 (d, *J* = 8.1 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.88 (s, 1H), 7.75 (bs, 1H), 7.67 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 1H), 7.61 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1H), 7.57 (s, 1H), 1.92 (s, 3H).

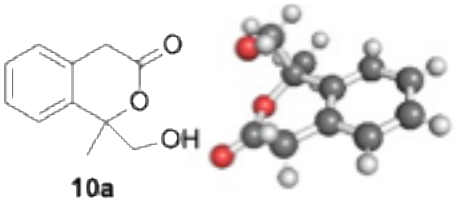
^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 169.2, 150.6, 144.2, 136.4, 133.5, 130.0, 129.3, 128.5, 127.5, 127.4, 123.0, 121.7, 84.5, 24.4.

HRMS (ESI): calculated for $C_{14}H_{12}NO_3^+$ $[M+H]^+$, 242.0812 found 242.0820 (Δ = -3 ppm)

8. X-ray structure of compounds 10a and 13a

8.1 X-ray structure of compounds 10a

These data are provided free of charge by the Cambridge Crystallographic Data Center.
Single crystals of compound **10a** were obtained in cyclopentane/chlorobenzene. CCDC 2384274 for **10a** contains the supplementary crystallographic data for this paper.



10a

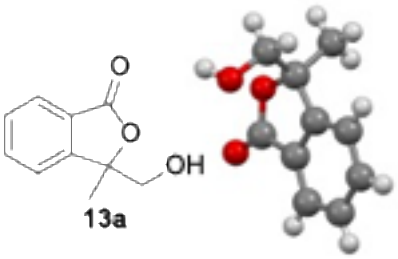
Datablock: mges220617

```
Bond precision:      C-C = 0.0032 A              Wavelength=1.54178
Cell:          a=5.3853(2)     b=6.7196(2)     c=26.2878(8)
               alpha=90        beta=90         gamma=90
Temperature :  120 K

                    Calculated                  Reported
Volume              951.28(5)                   951.28(5)
Space group         P 21 21 21                  P 21 21 21
Hall group          P 2ac 2ab                   P 2ac 2ab
Moiety formula      C11 H12 O3                  C11 H12 O3
Sum formula         C11 H12 O3                  C11 H12 O3
Mr                  192.21                      192.21
Dx,g cm-3           1.342                       1.342
Z                   4                           4
Mu (mm-1)           0.803                       0.803
F000                408.0                       408.0
F000'               409.34
h,k,lmax            6,7,31                      6,7,31
Nref                1672[ 1021]                 1670
Tmin,Tmax           0.891,0.923                 0.600,0.753
Tmin'               0.879
Correction method= # Reported T Limits: Tmin=0.600
Tmax=0.753 AbsCorr = MULTI-SCAN
Data completeness= 1.64/1.00   Theta(max)= 66.553
R(reflections)= 0.0311( 1603)                wR2(reflections)=
                                             0.0840( 1670)
S = 1.064            Npar= 133
```

8.2 X-ray structure of compounds 13a

These data are provided free of charge by the Cambridge Crystallographic Data Center.
Single crystals of compound **13a** were obtained in cyclopentane/ethyl formate. CCDC 2111415 for **13a** contains the supplementary crystallographic data for this paper.



13a

Datablock: mges210916

```
Bond precision:      C-C = 0.0011 A              Wavelength=0.71073
Cell:        a=8.1953(3)     b=7.1751(3)      c=14.7724(5)
             alpha=90        beta=100.927(1)  gamma=90
Temperature: 120 K
                    Calculated                      Reported
Volume              852.90(6)                       852.90(6)
Space group         P 21/c                          P 21/c
Hall group          -P 2ybc                         -P 2ybc
Moiety formula      C10 H10 O3                      C10 H10 O3
Sum formula         C10 H10 O3                      C10 H10 O3
Mr                  178.18                          178.18
Dx,g cm-3           1.388                           1.388
Z                   4                               4
Mu (mm-1)           0.103                           0.103
F000                376.0                           376.0
F000'               376.22
h,k,lmax            12,10,22                        12,10,22
Nref                2968                            2964
Tmin,Tmax           0.986,0.990                     0.719,0.746
Tmin'               0.986
Correction method= # Reported T Limits: Tmin=0.719
Tmax=0.746 AbsCorr = MULTI-SCAN
Data completeness= 0.999        Theta(max)= 32.014
R(reflections)= 0.0340( 2695)                   wR2(reflections)=
                                                0.1012( 2964)
S = 1.075             Npar= 123
```

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9. ^{31}P NMR Spectra for the study of ligand exchange

Figure 1, spectrum **a**: ^{31}P, 162 MHz

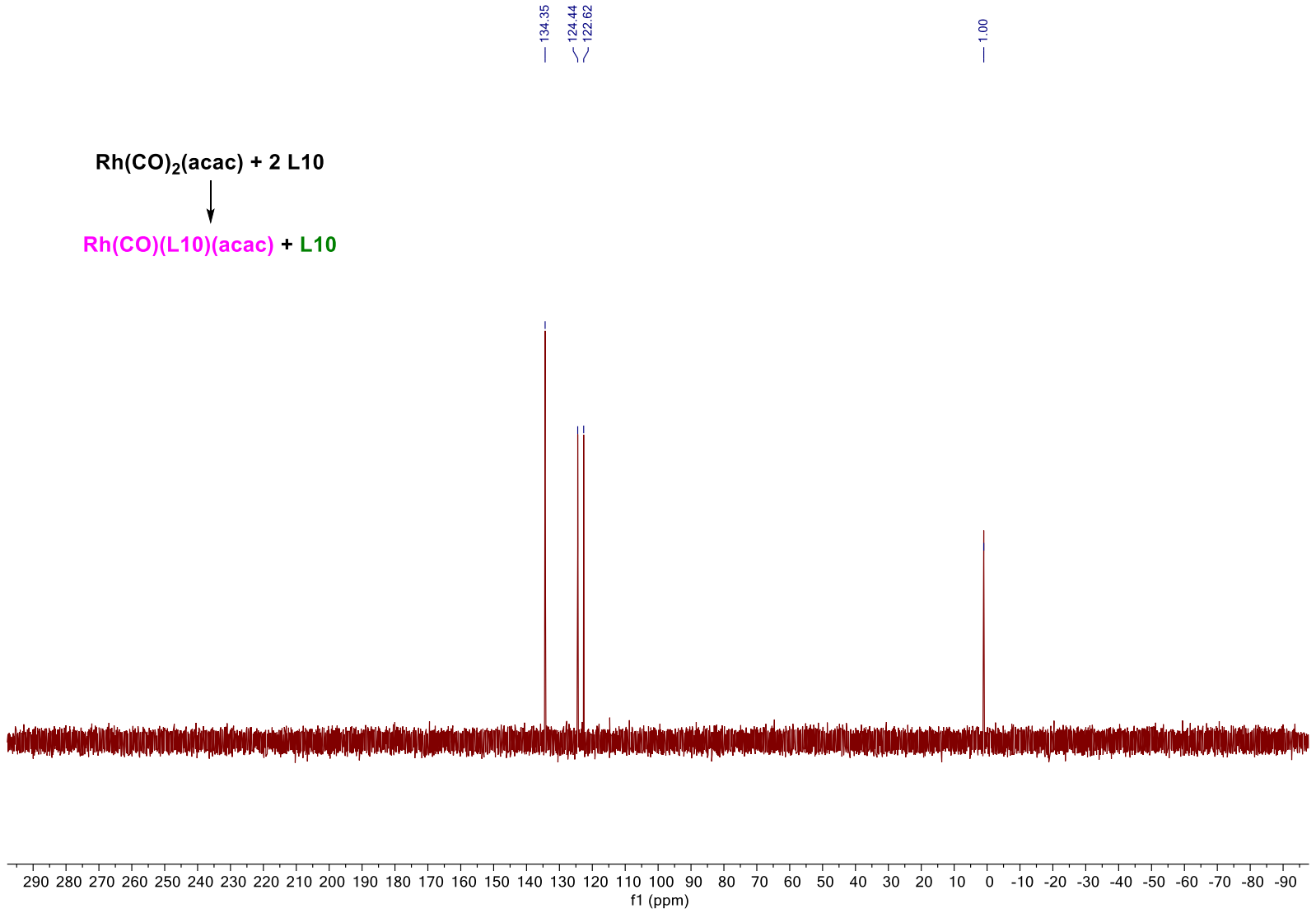


Figure 1, spectrum **b**: ^{31}P, 162 MHz

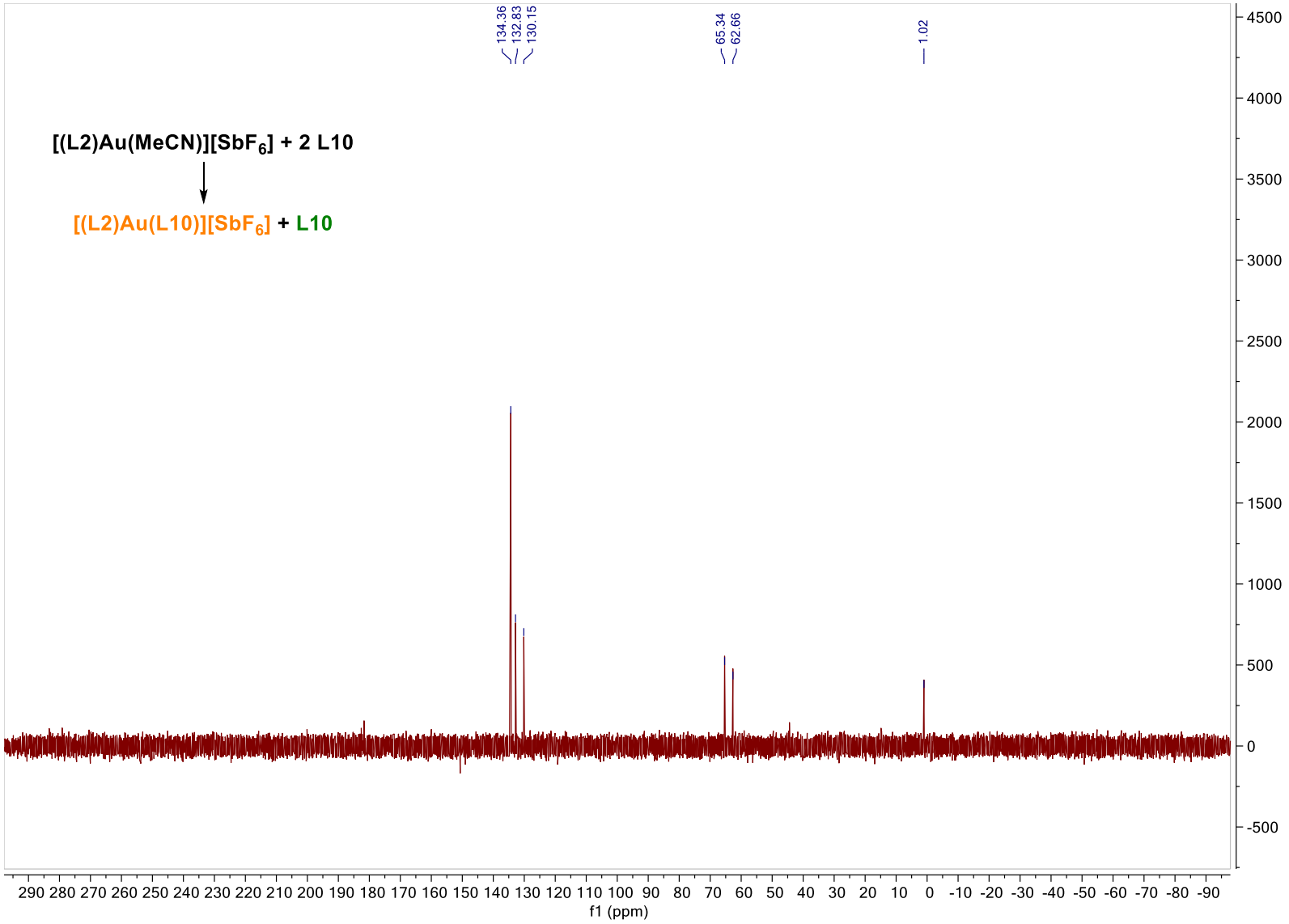


Figure 1, spectrum **c**: ^{31}P, 162 MHz

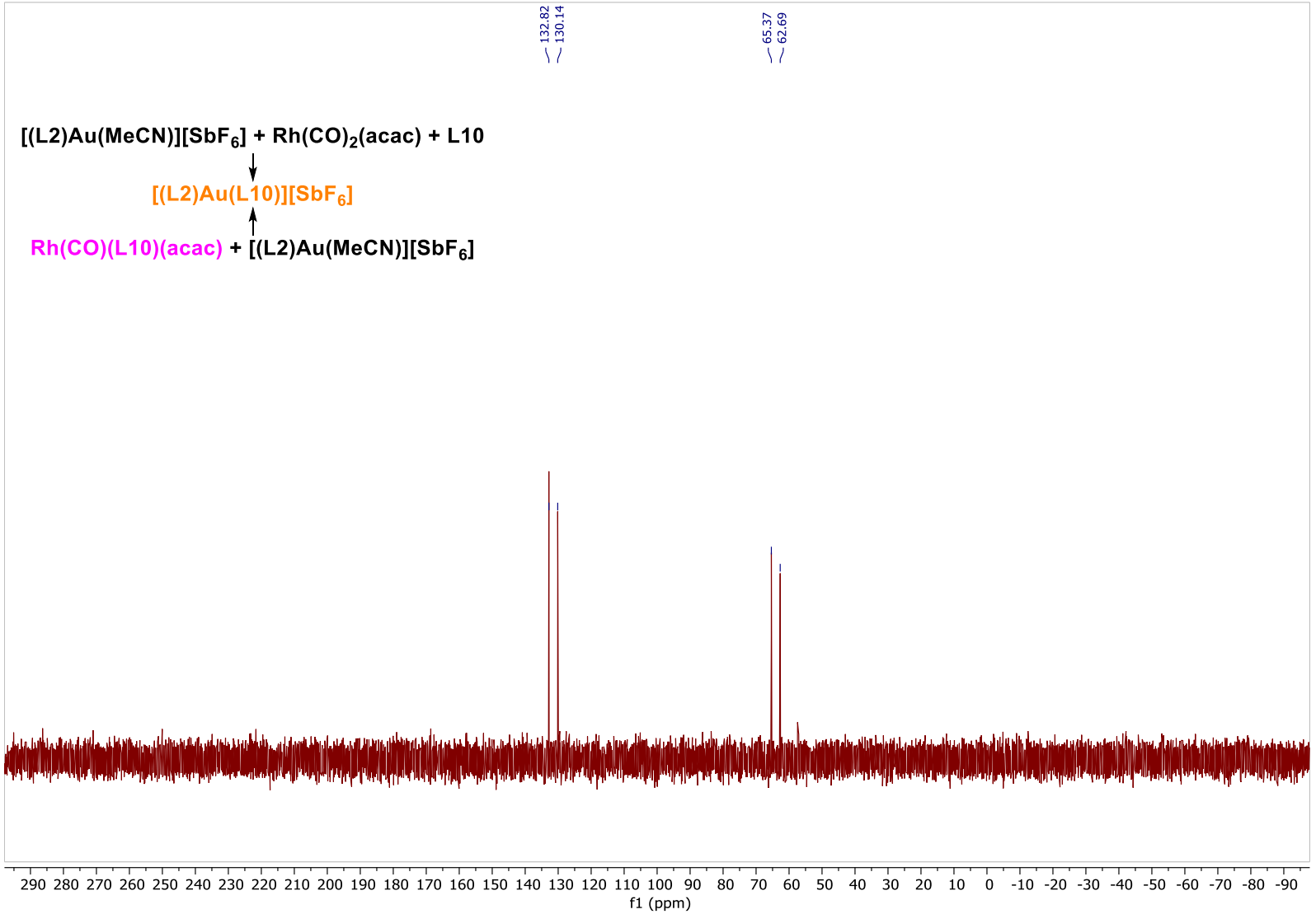
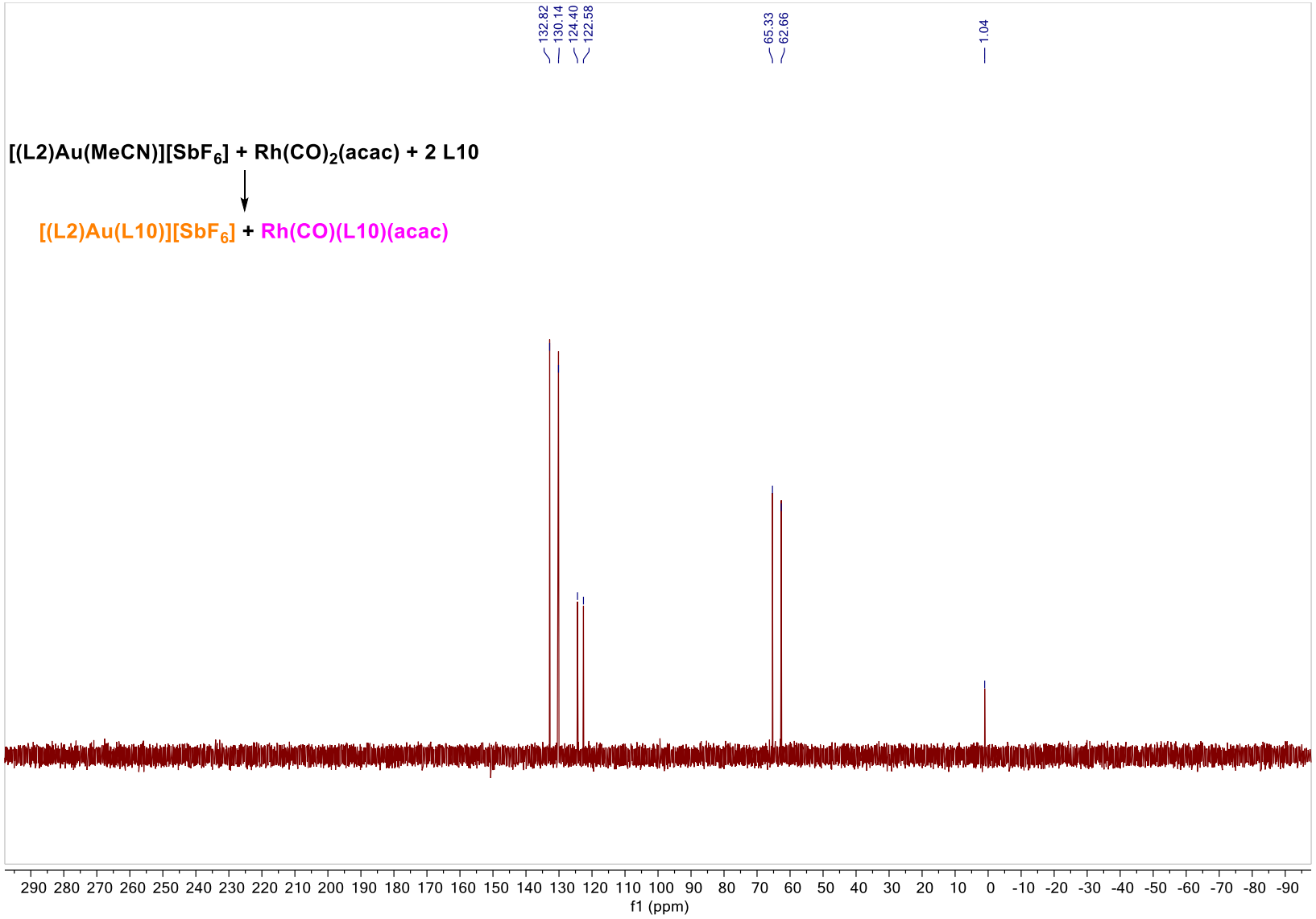
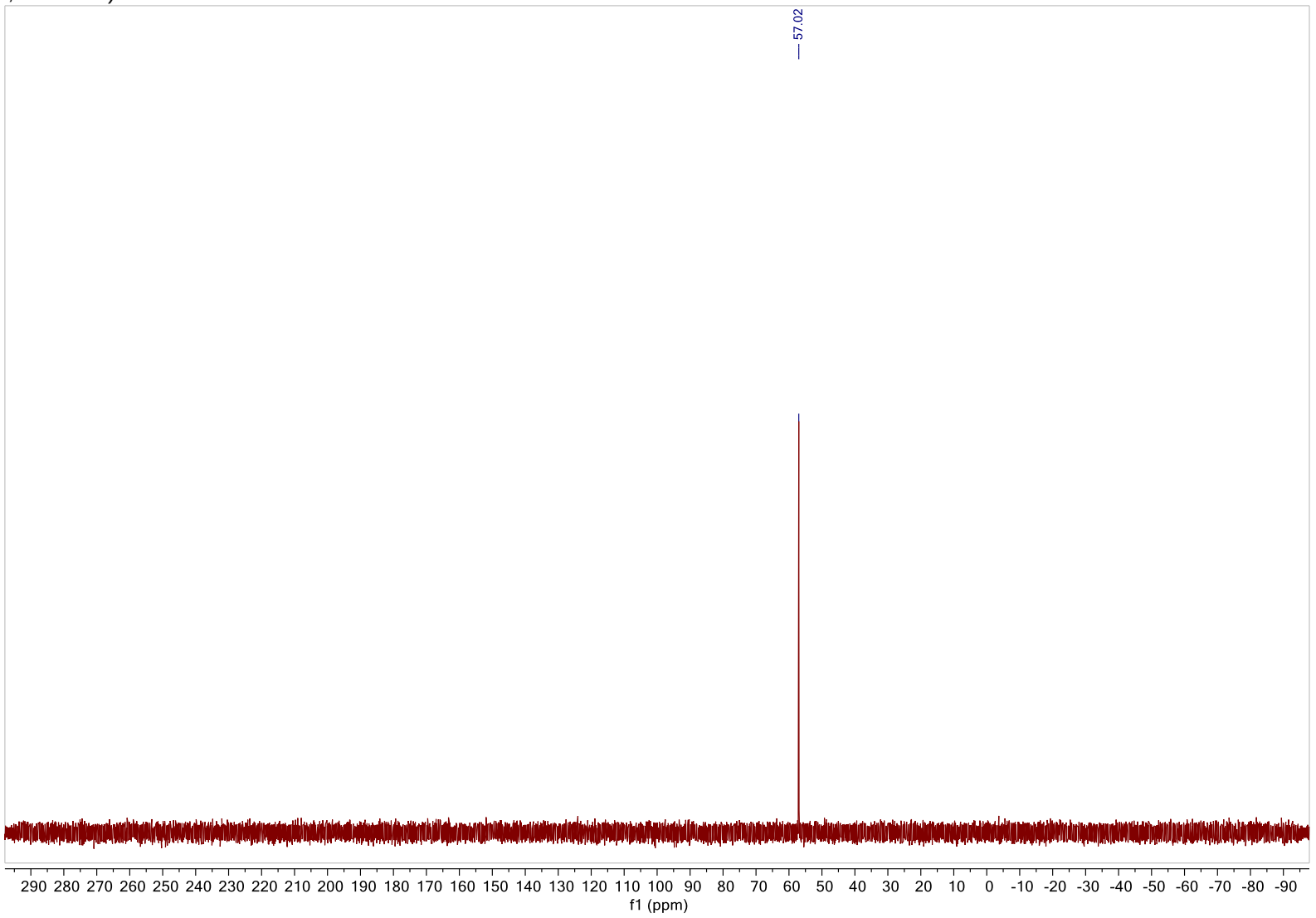


Figure 1, spectrum **d**: ^{31}P, 162 MHz

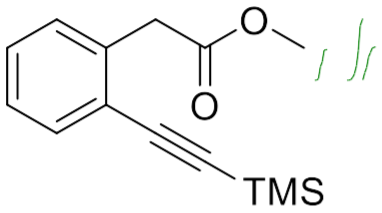


Cat. D, [(**L2**)Au(MeCN)][SbF_6] (^{31}P, 162 MHz):

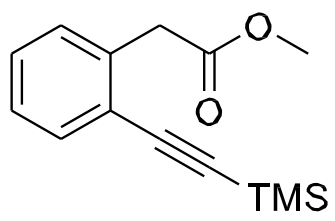


10. NMR Spectra

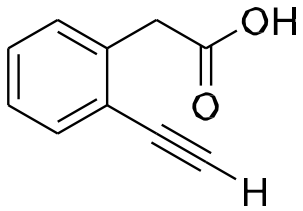
SI4a (^{1}H, 400 MHz):



SI4a (^{13}C, 101 MHz):

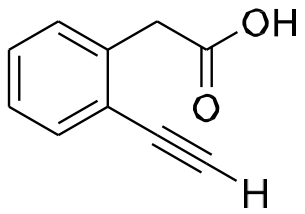


1a (^{1}H, 400 MHz):

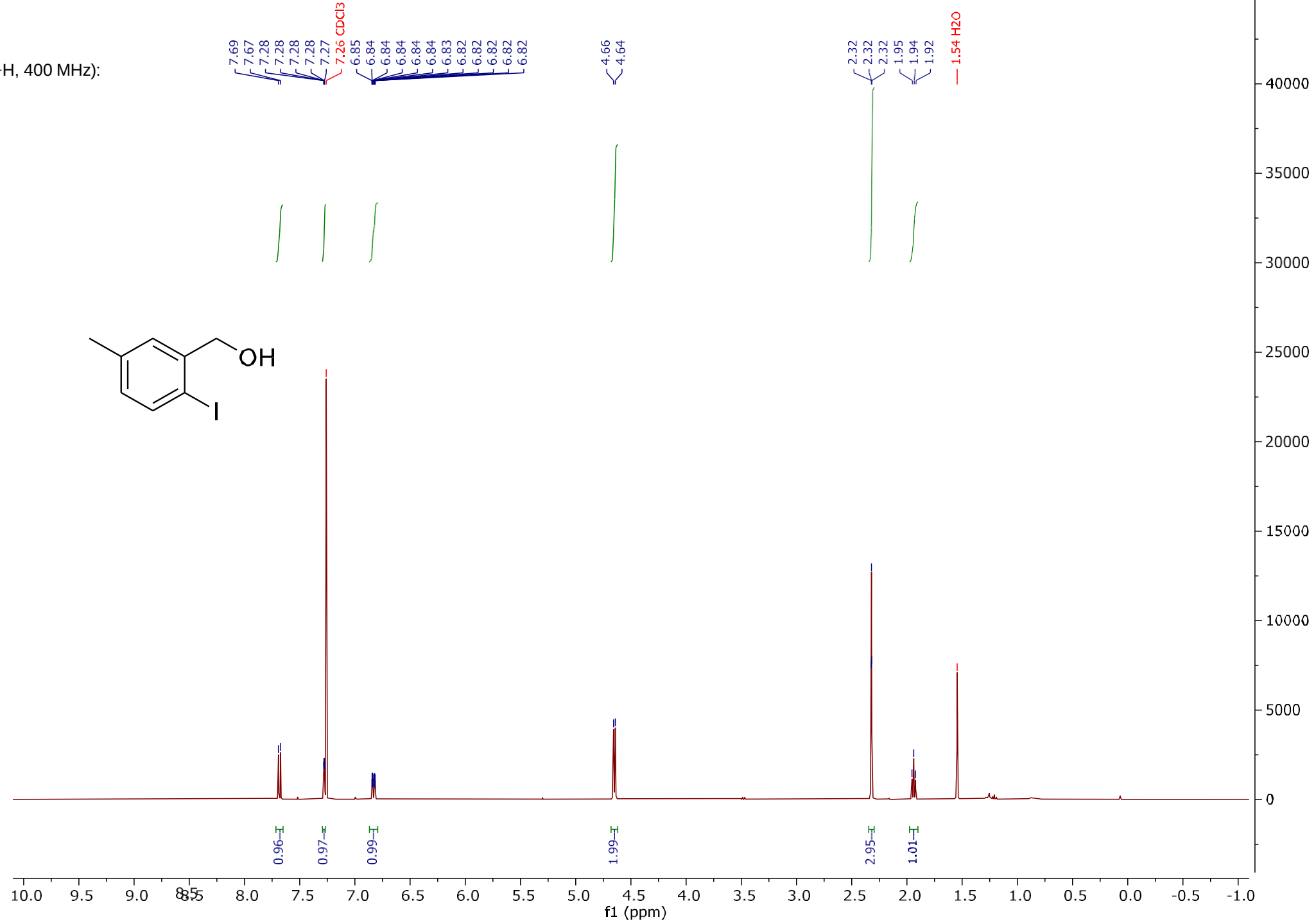

OH
O
H

7.54
7.53
7.53
7.52
7.51
7.36
7.36
7.34
7.34
7.32
7.32
7.31
7.30
7.29
7.28
7.28
7.27
7.26 CDCl3
7.25
7.24
3.90
3.29
1.04
4.04
1.99
1.00
f1 (ppm)

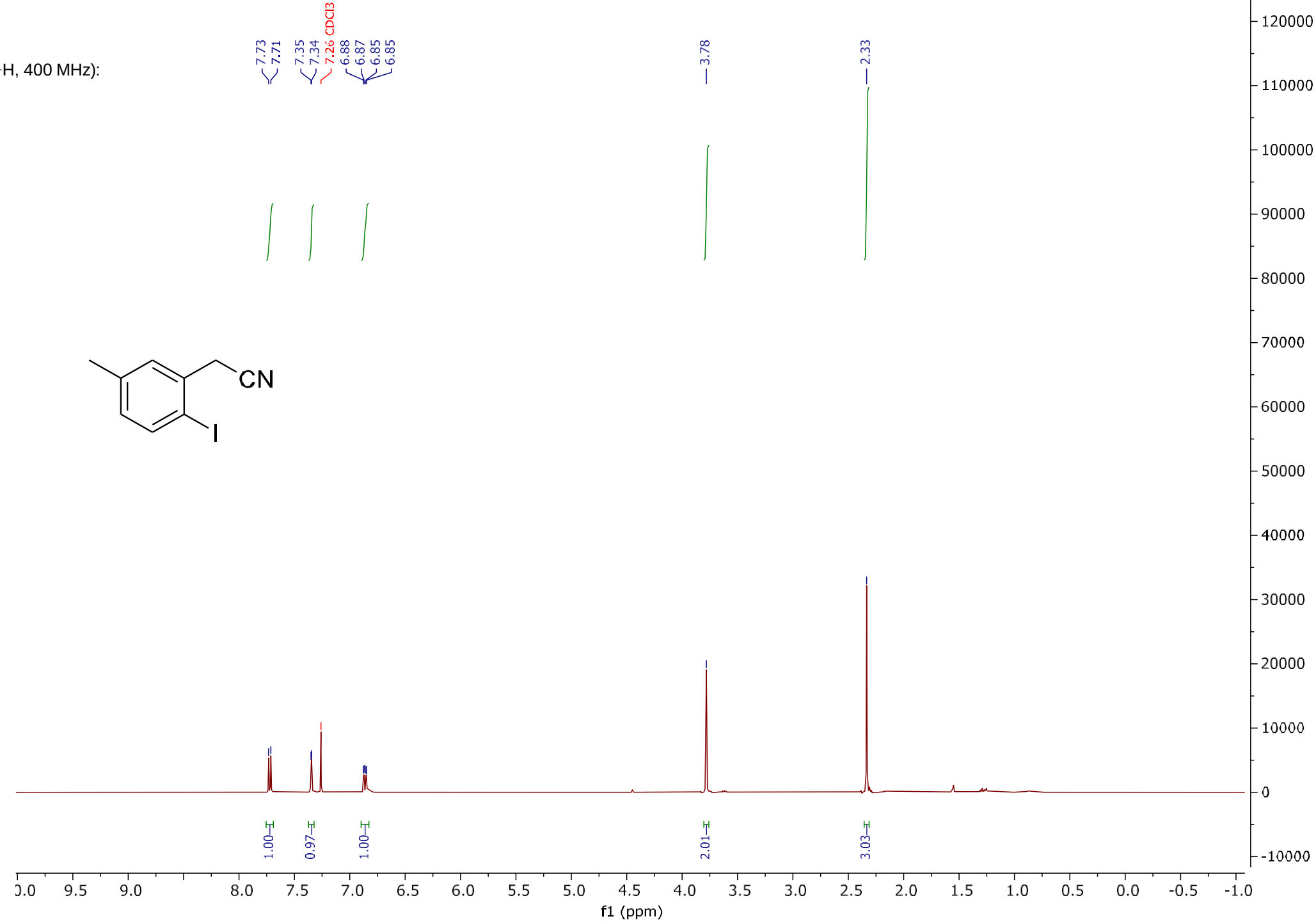
1a (^{13}C, 101 MHz):



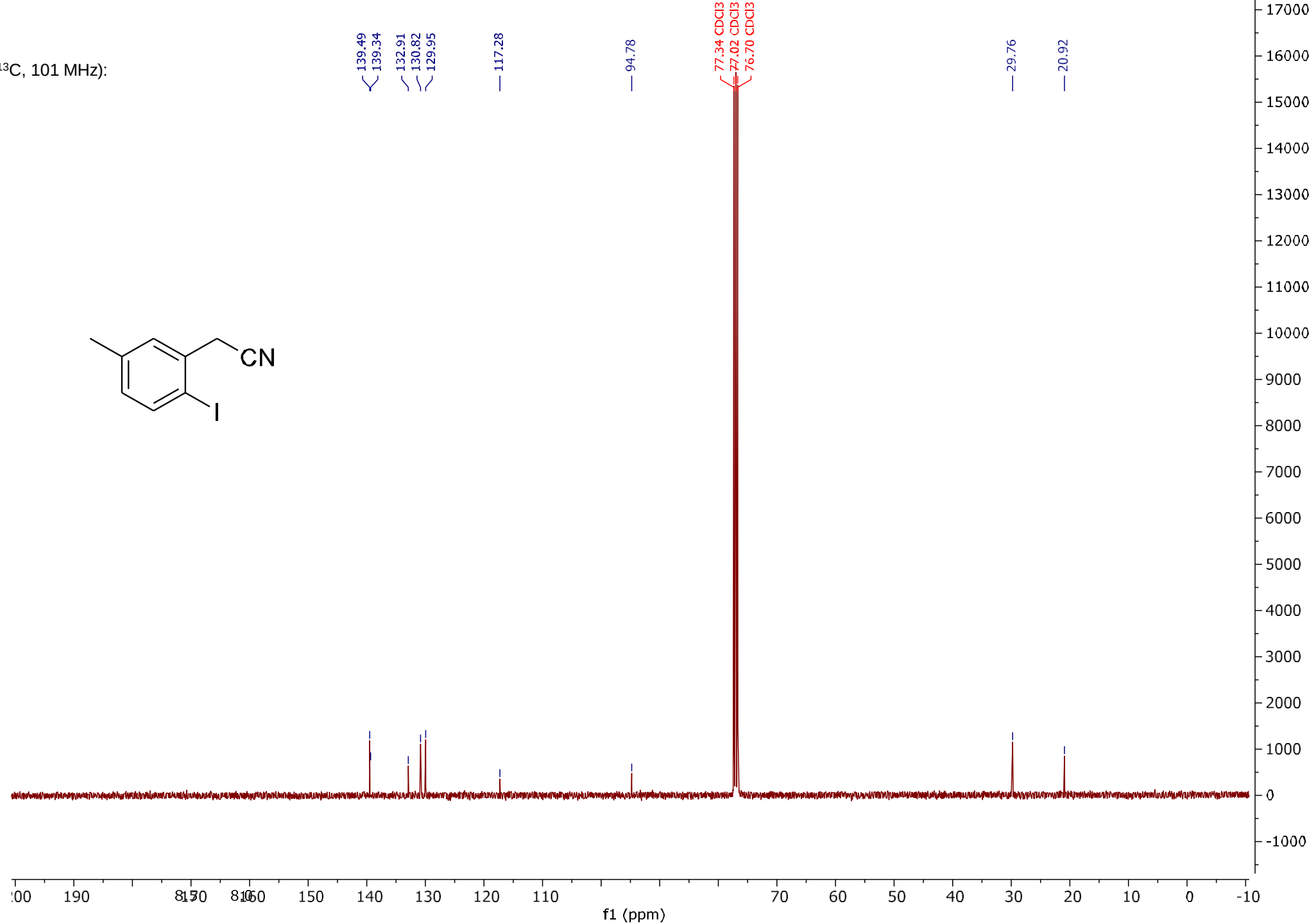
SI1b (^{1}H, 400 MHz):



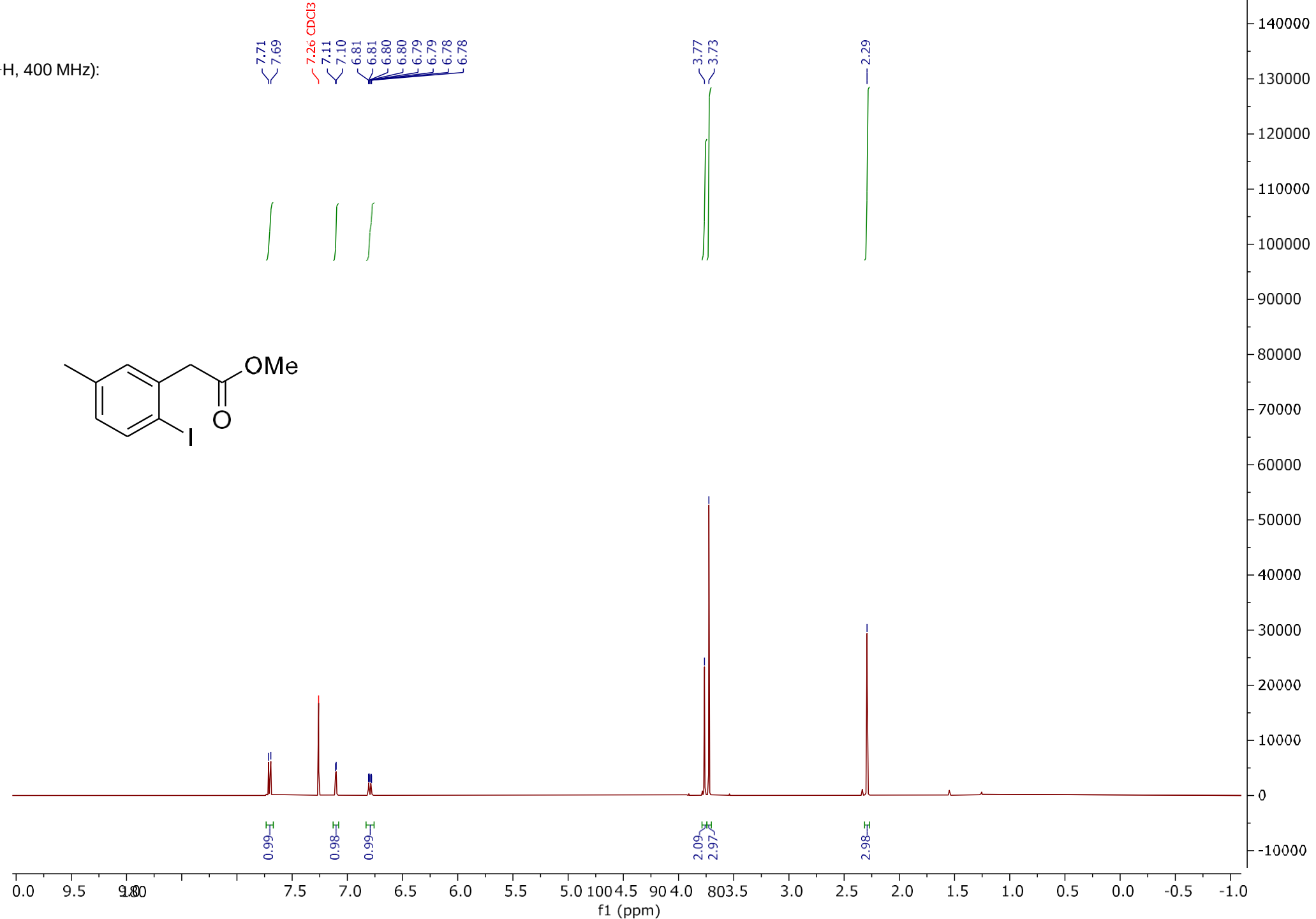
SI2b (^{1}H, 400 MHz):



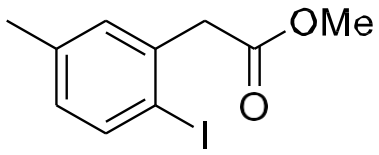
SI2b (^{13}C, 101 MHz):



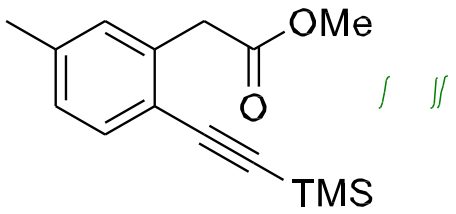
SI3b (^{1}H, 400 MHz):



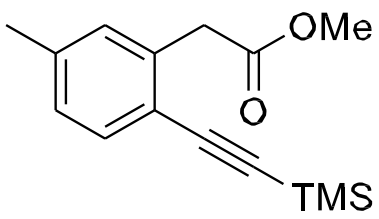
SI3b (^{13}C, 101 MHz):



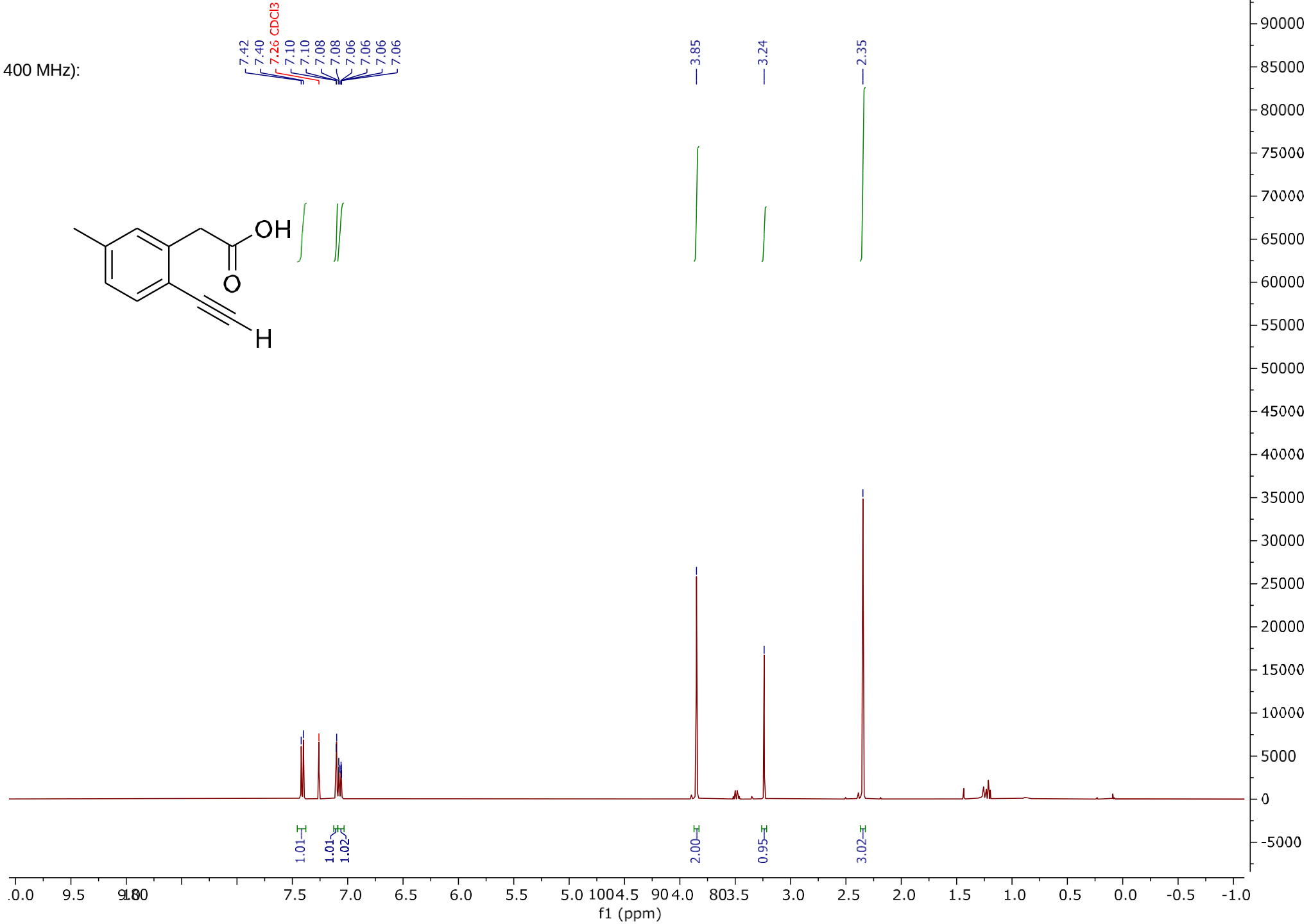
SI4b (^{1}H, 400 MHz):



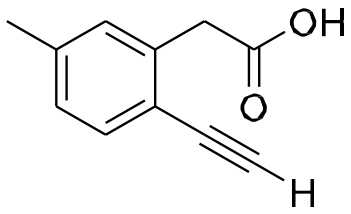
SI4b (^{13}C, 101 MHz):



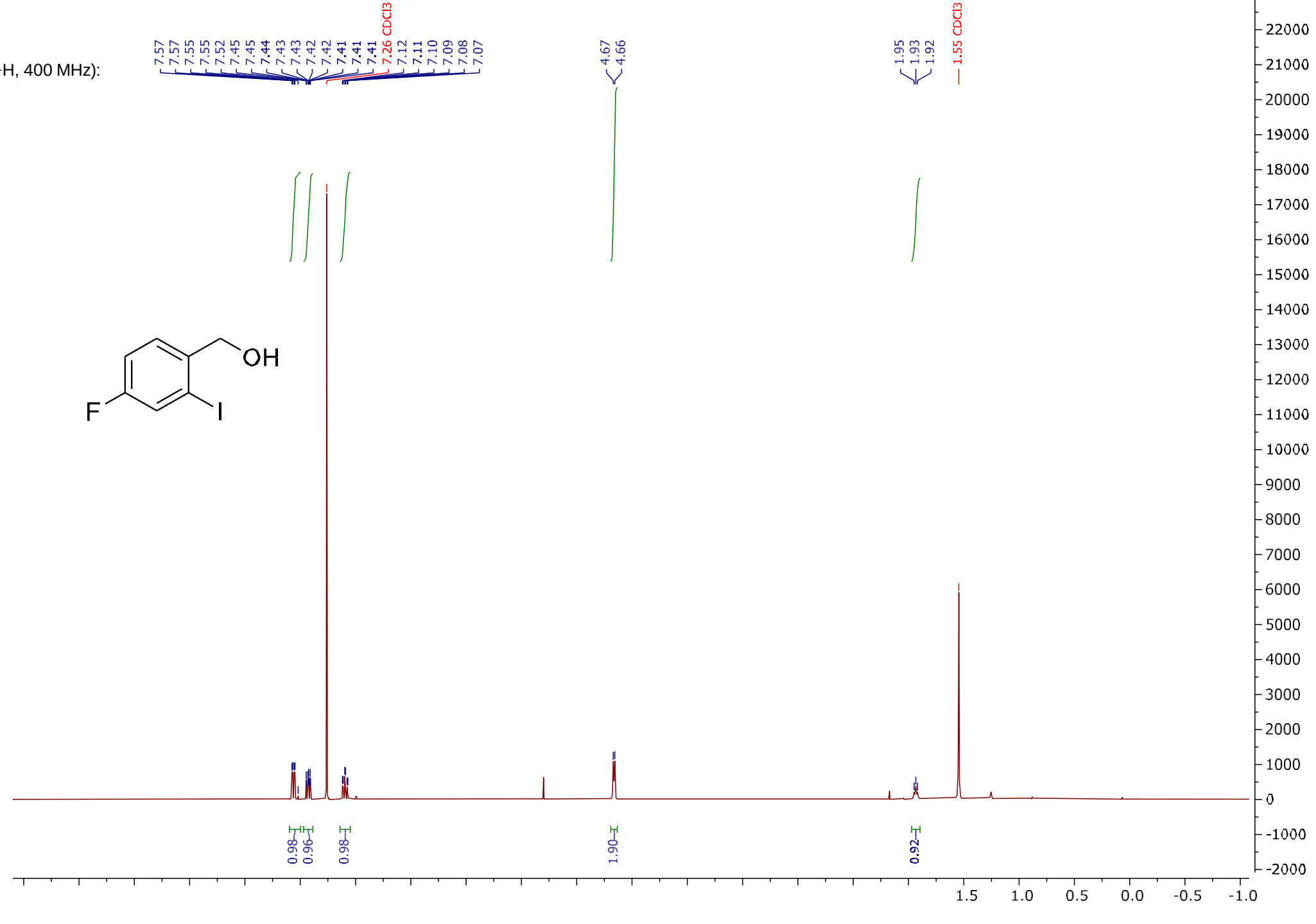
1b (^{1}H, 400 MHz):


7.42
7.40
7.26 CDCl3
7.10
7.10
7.08
7.08
7.06
7.06
7.06
7.06
3.85
3.24
2.35
OH
O
H
1.01
1.01
1.02
2.00
0.95
3.02
f1 (ppm)

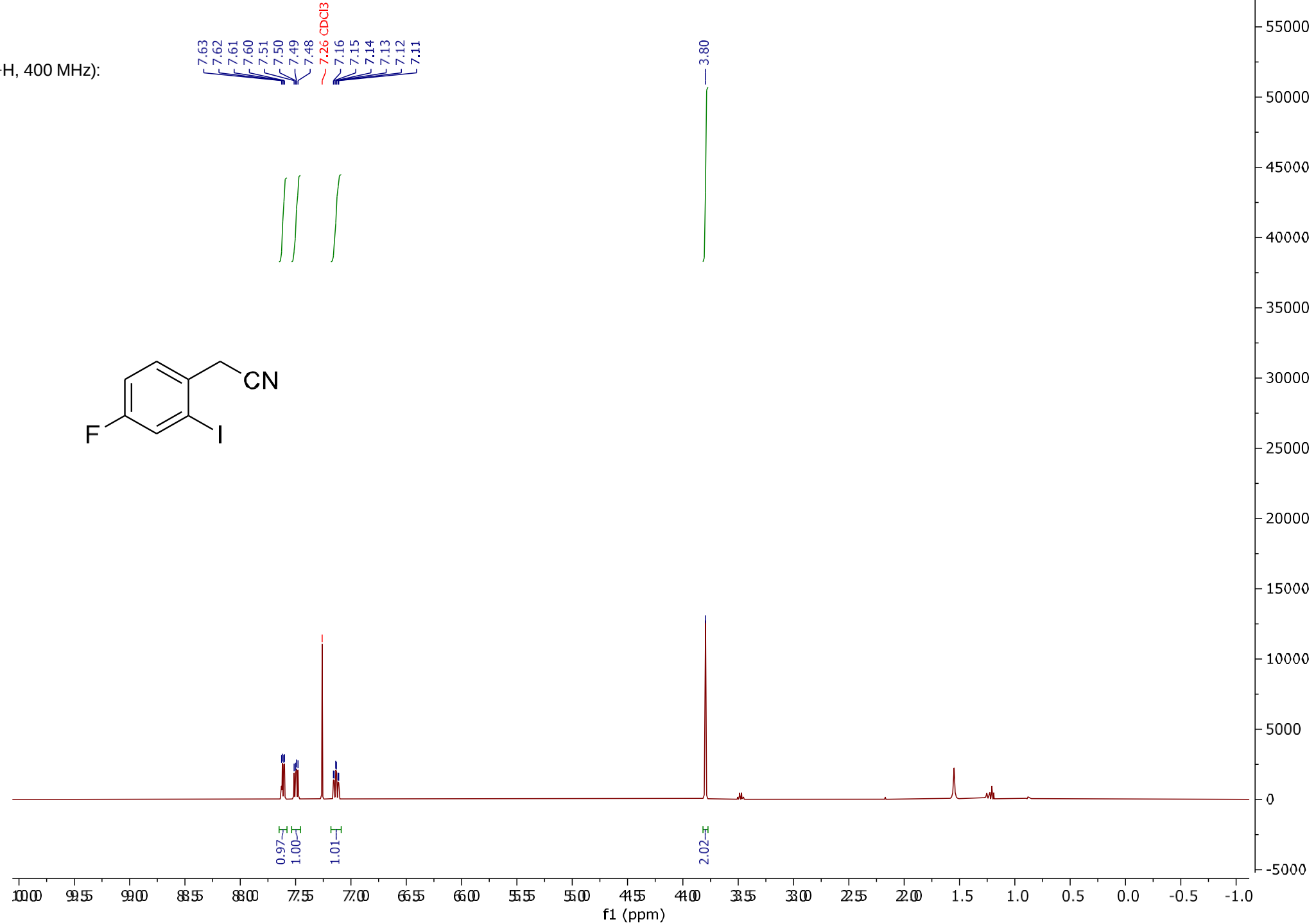
1b (^{13}C, 101 MHz):



SI1d (^{1}H, 400 MHz):

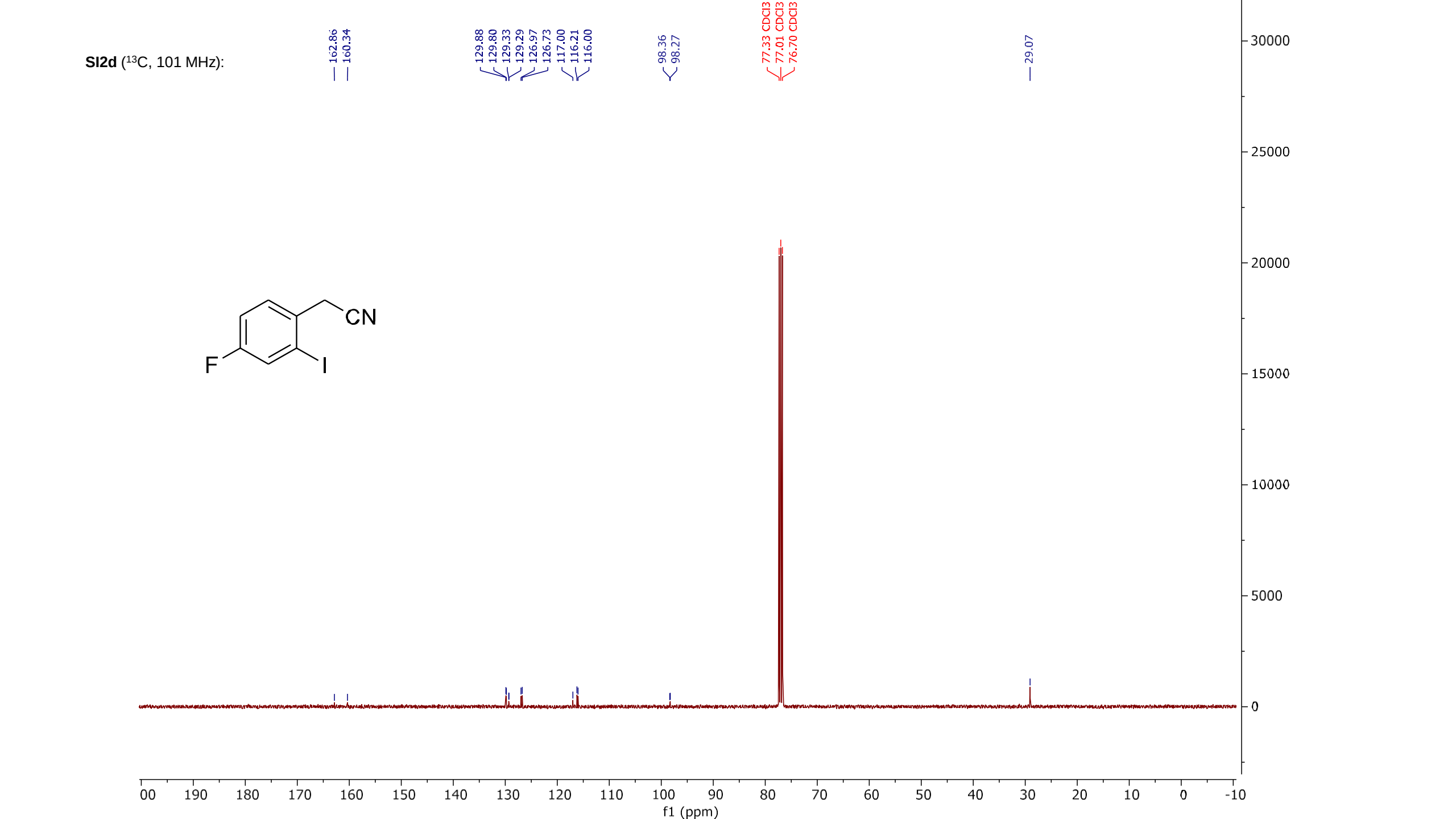


SI2d (^{1}H, 400 MHz):

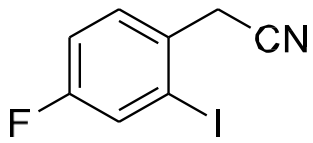


f1 (ppm)

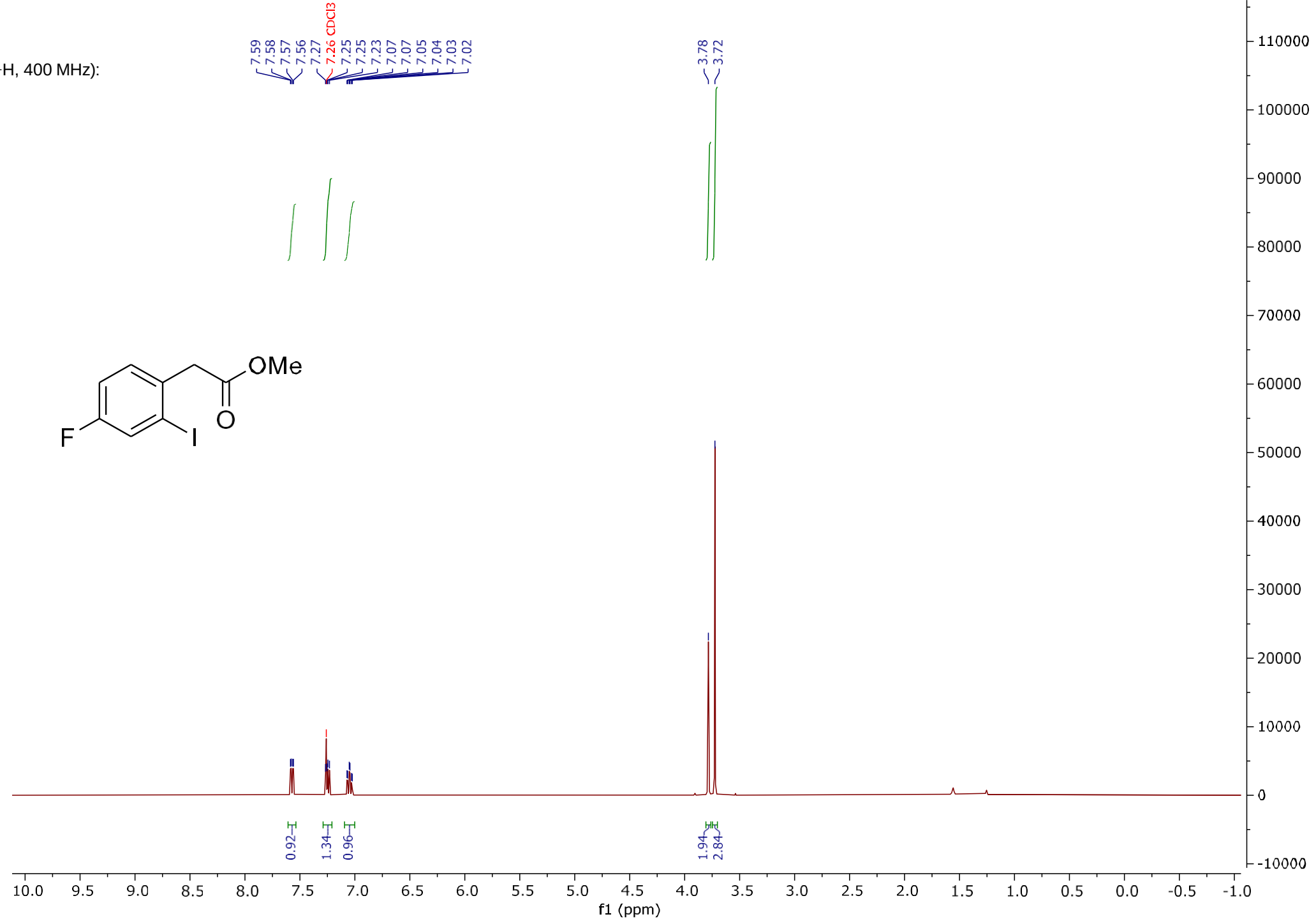
SI2d (^{13}C, 101 MHz):



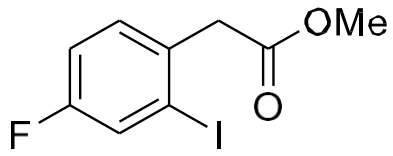
SI2d (^{19}F, 376 MHz):



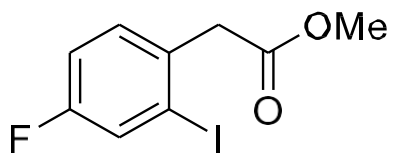
SI3d (^{1}H, 400 MHz):



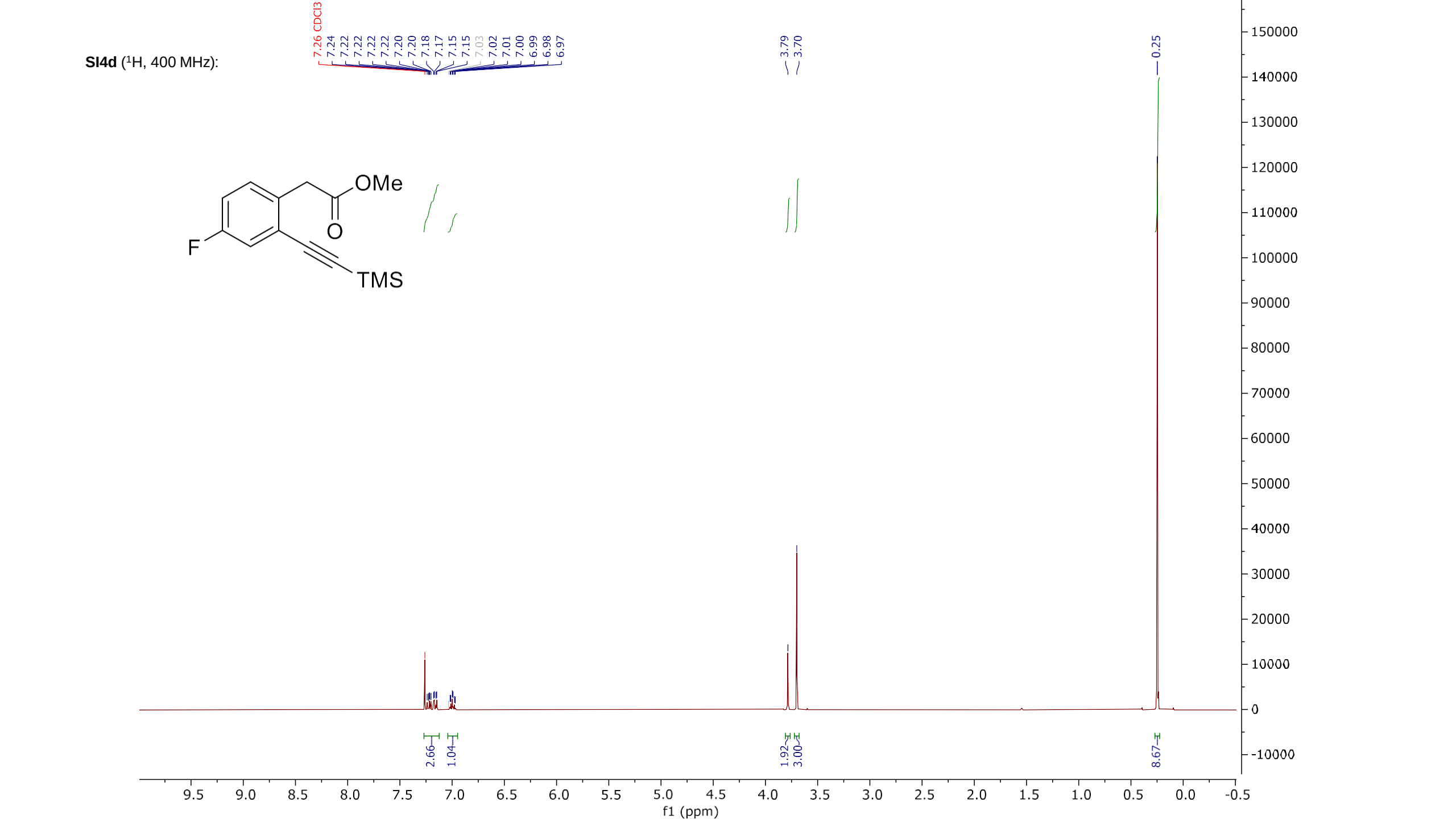
SI3d (^{13}C, 101 MHz):



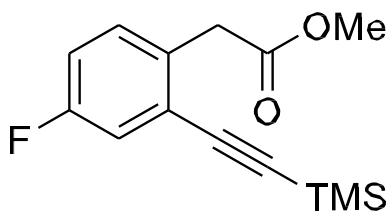
SI3d (^{19}F, 376 MHz):



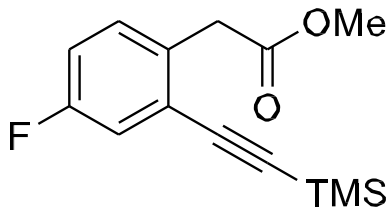
SI4d (^{1}H, 400 MHz):



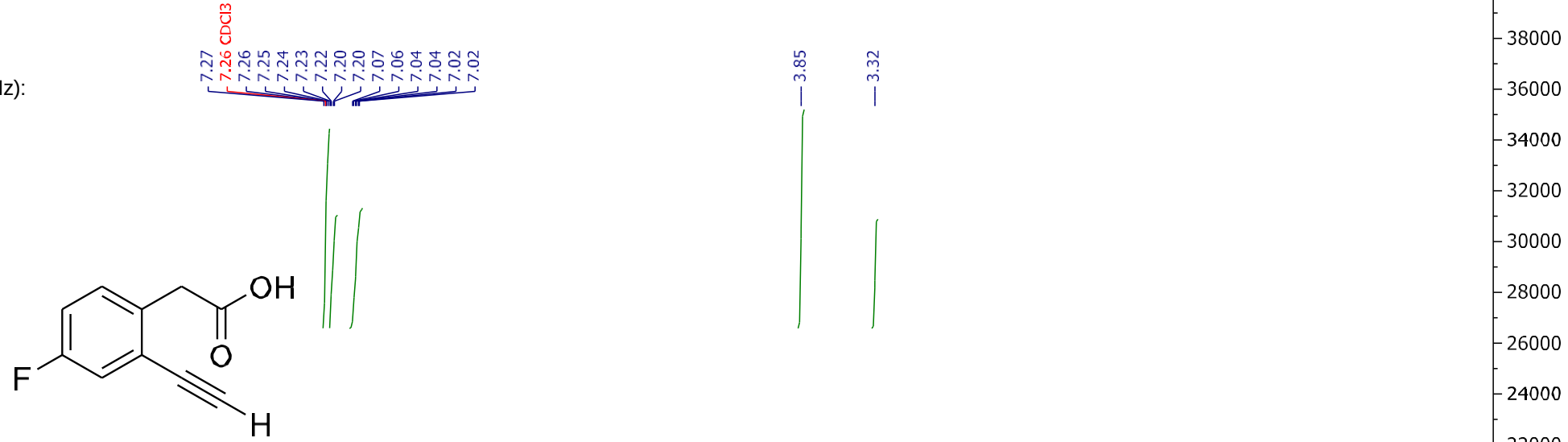
SI4d (^{13}C, 126 MHz):



SI4d (^{19}F, 376 MHz):

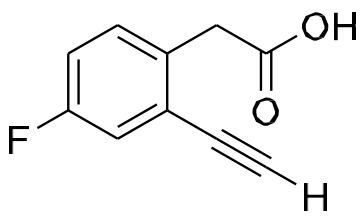


1d (^{1}H, 400 MHz):

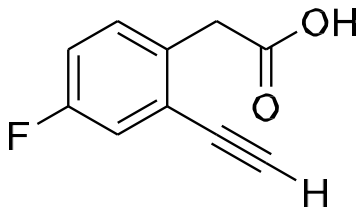

OH
O
F
H

7.27
7.26 CDCl3
7.26
7.25
7.24
7.23
7.22
7.20
7.20
7.07
7.06
7.04
7.04
7.02
7.02
3.85
3.32
1.82
1.03
1.10
2.00
1.00
38000
36000
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
.0.0
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
-1.0
f1 (ppm)

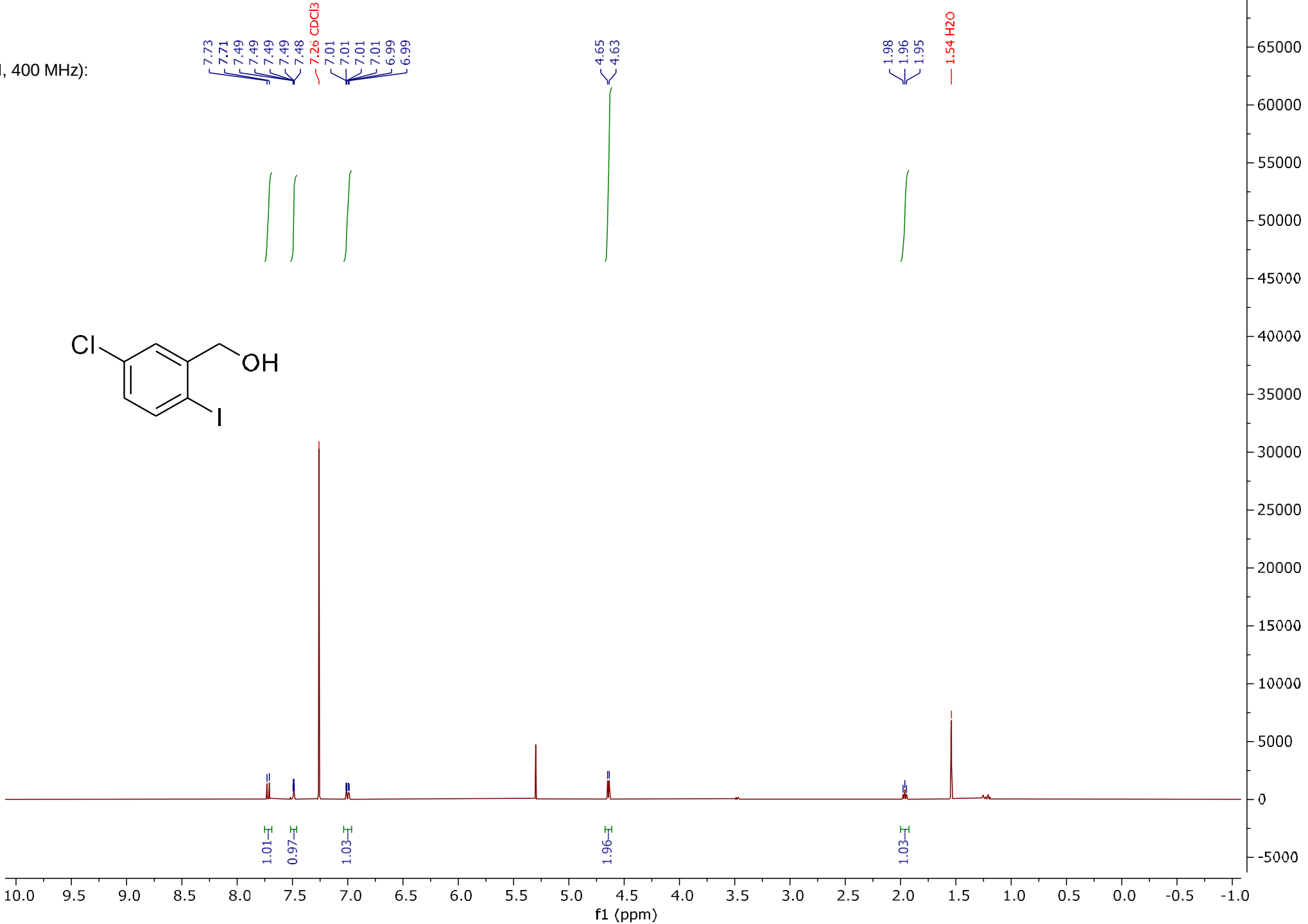
1d (^{13}C, 101 MHz):



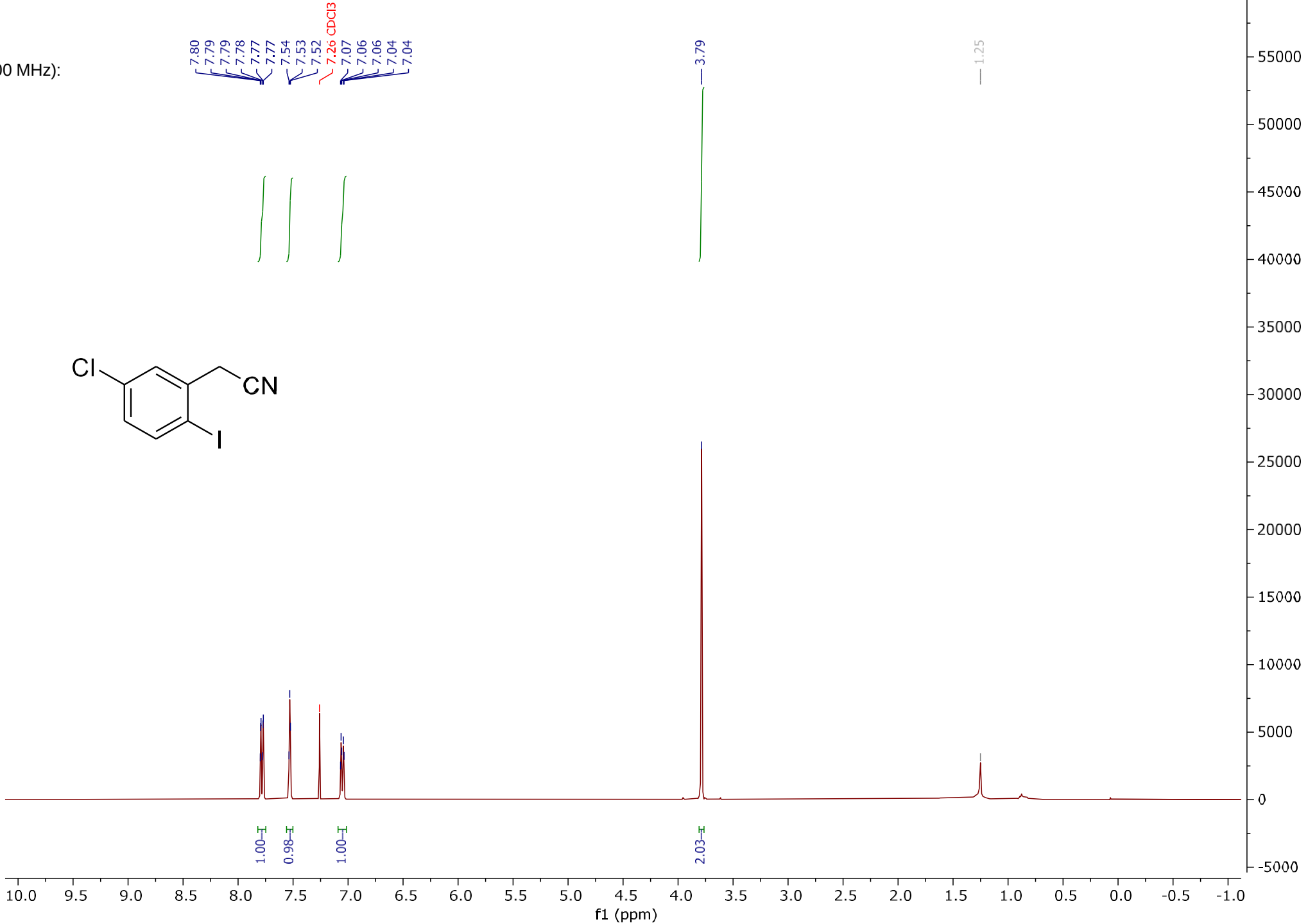
1d (^{19}F, 376 MHz):



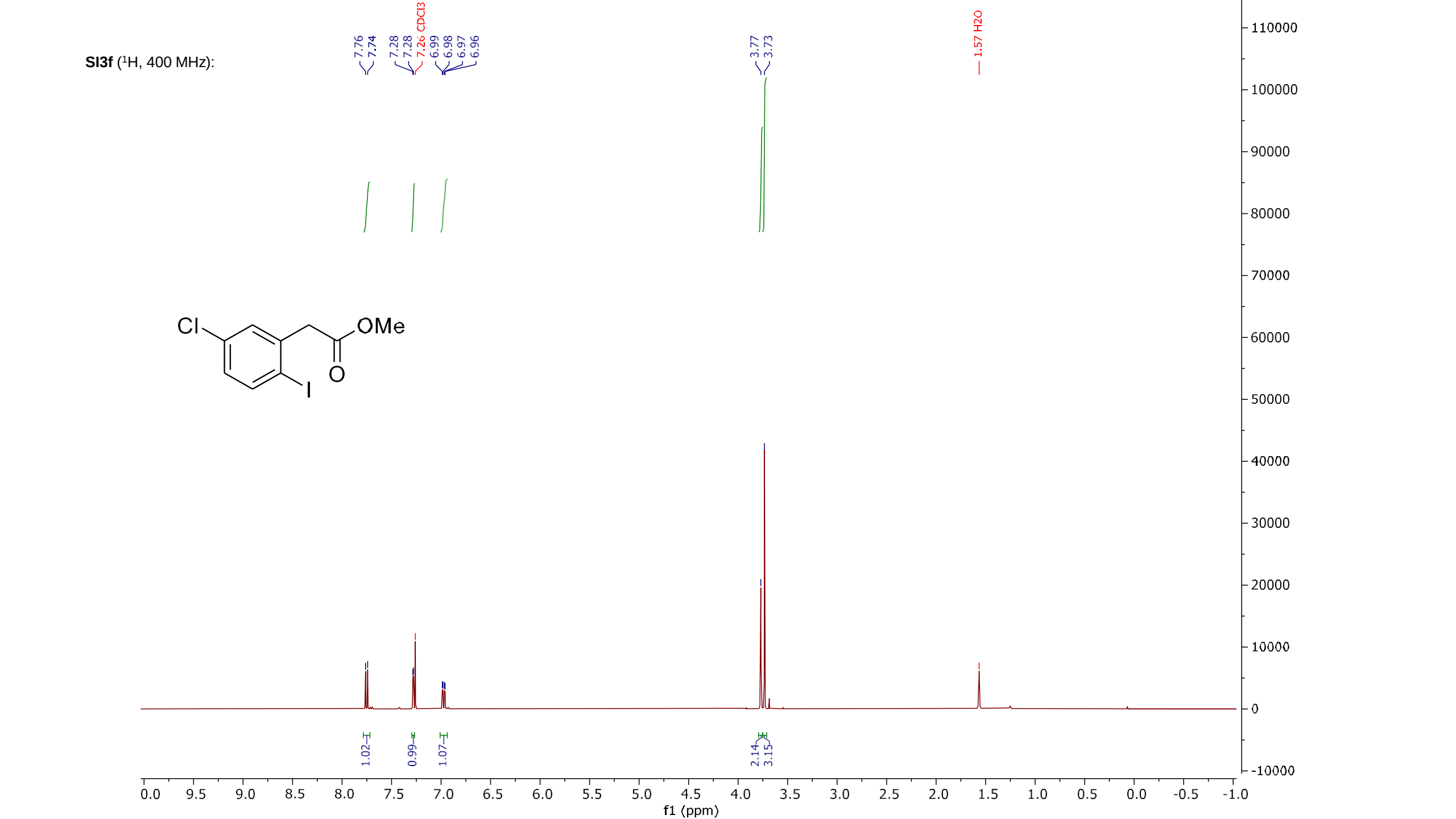
SI1f (^{1}H, 400 MHz):



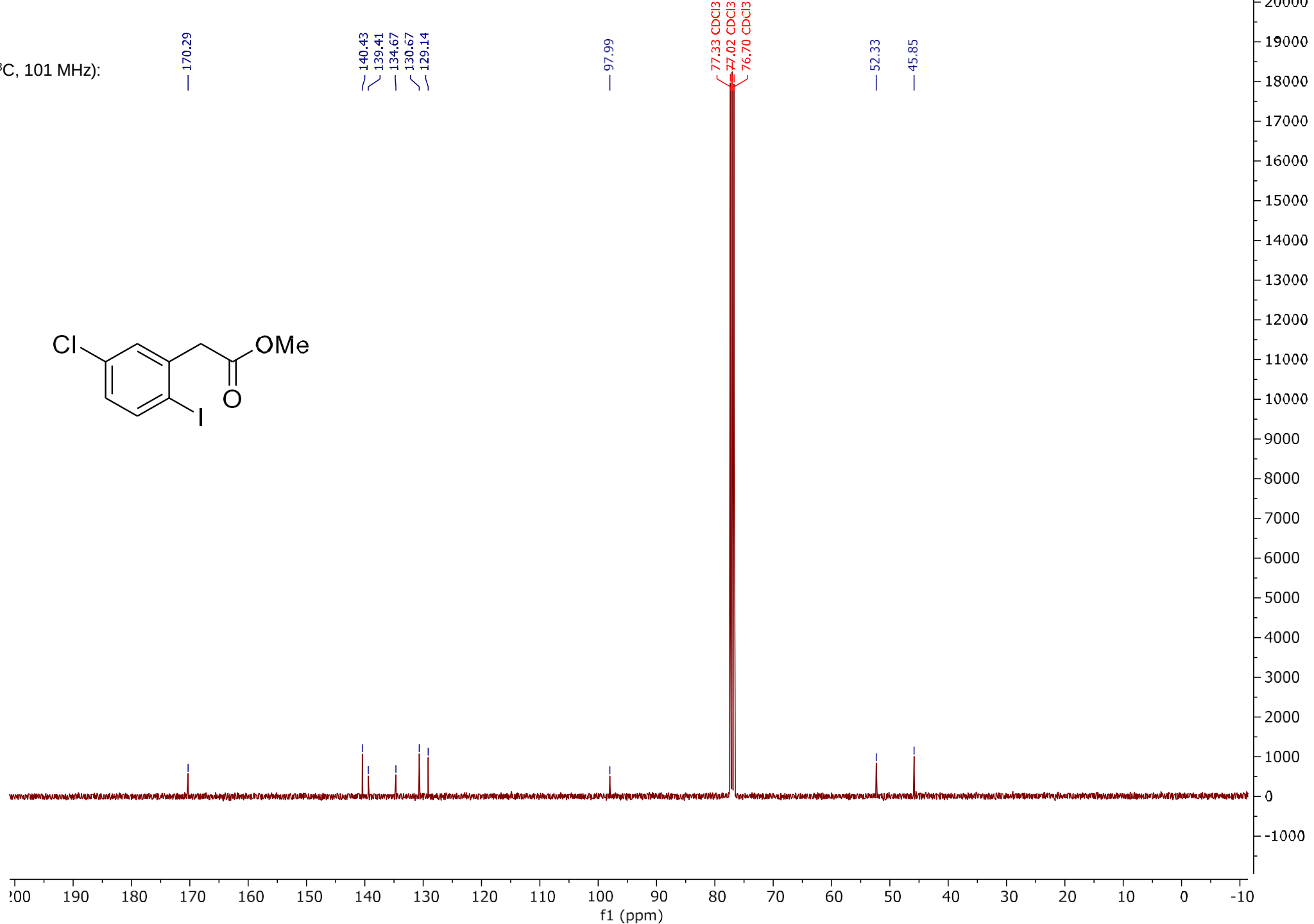
SI2f (400 MHz):


7.80
7.79
7.79
7.78
7.77
7.77
7.54
7.53
7.52
7.26 CDCl3
7.07
7.06
7.06
7.04
7.04
3.79
1.25
Cl
CN
I
1.00
0.98
1.00
2.03
f1 (ppm)

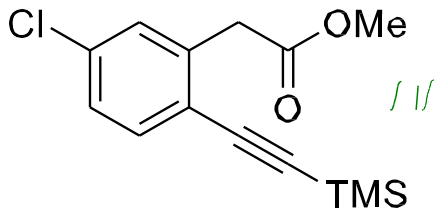
SI3f (^{1}H, 400 MHz):



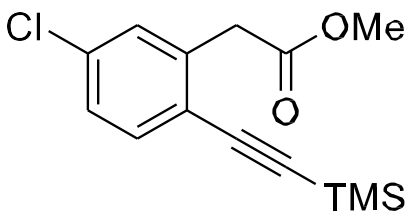
SI3f (^{13}C, 101 MHz):



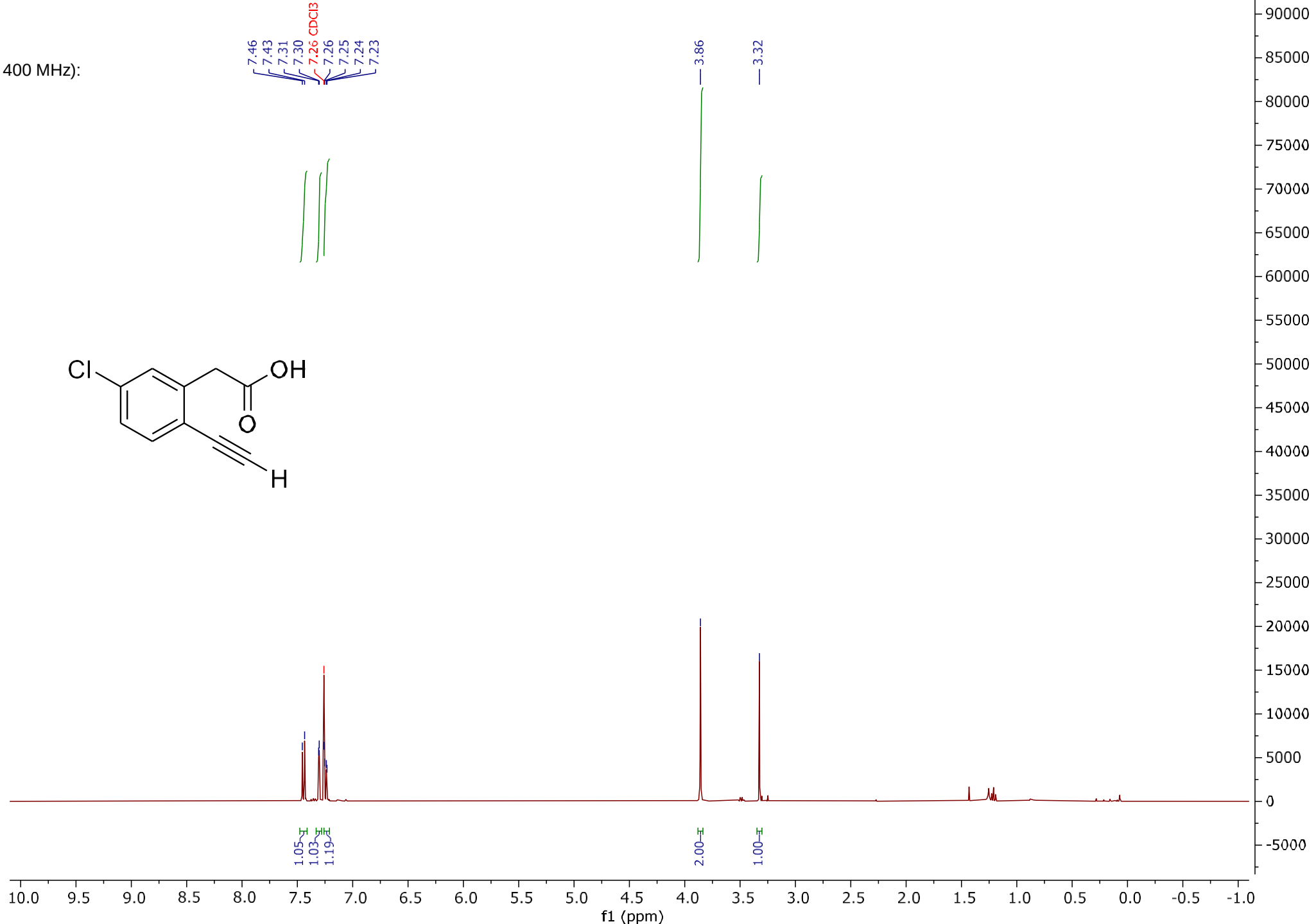
SI4f (^{1}H, 400 MHz):



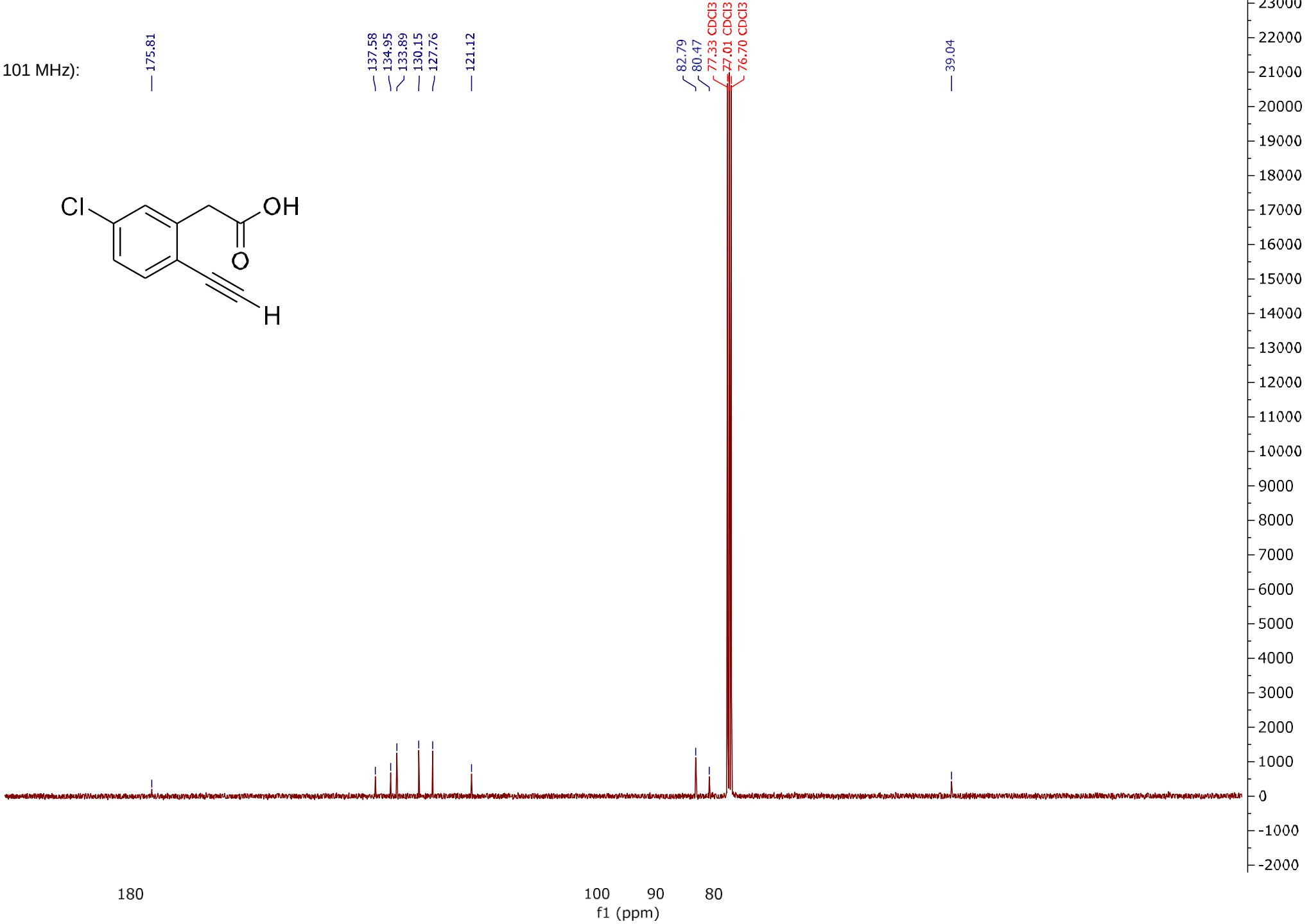
SI4f (^{13}C, 101 MHz):



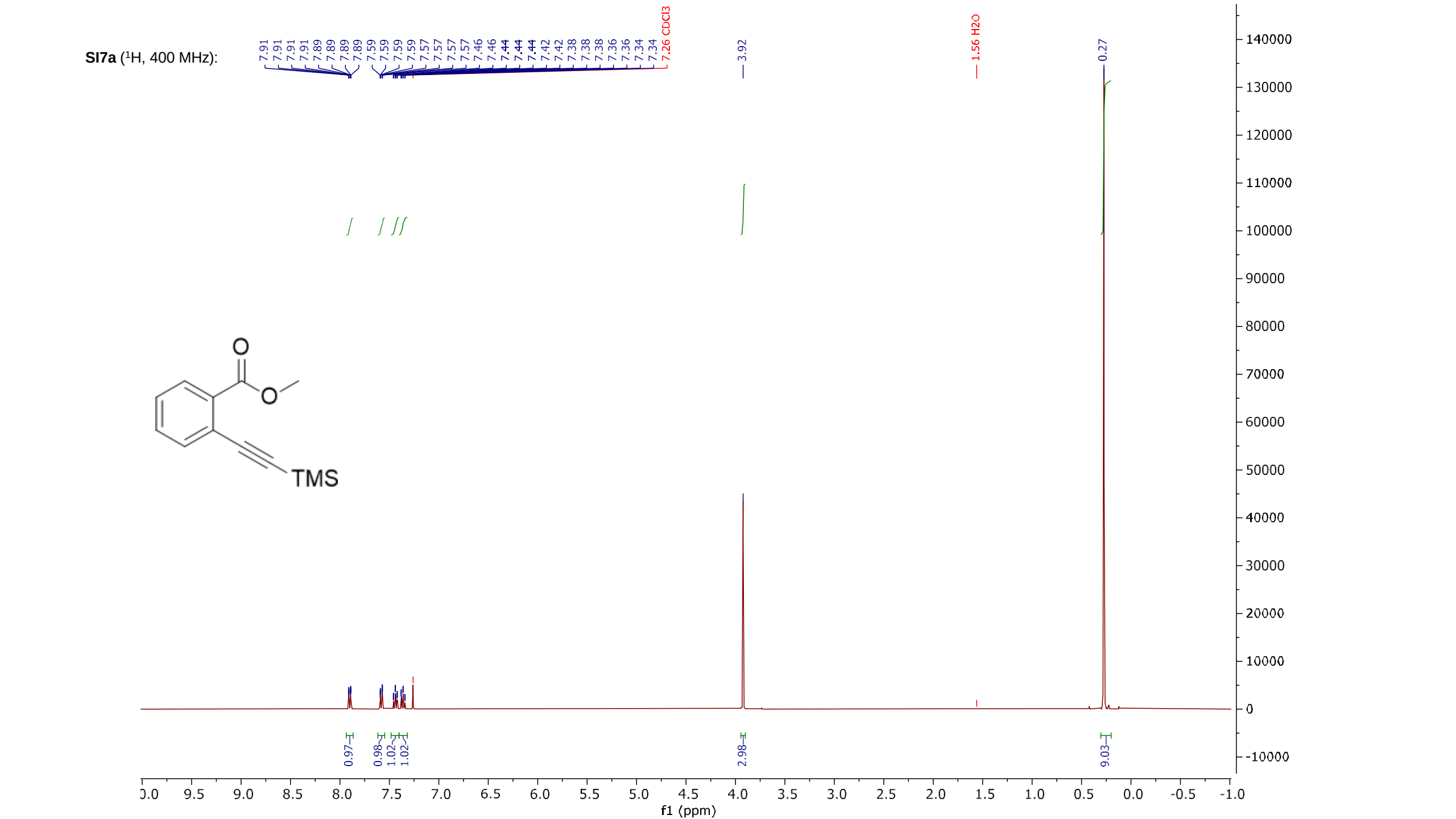
1f (^{1}H, 400 MHz):


7.46
7.43
7.31
7.30
7.26 CDCl3
7.26
7.25
7.24
7.23
3.86
3.32
Cl
OH
O
H
1.05
1.03
1.19
2.00
1.00
f1 (ppm)

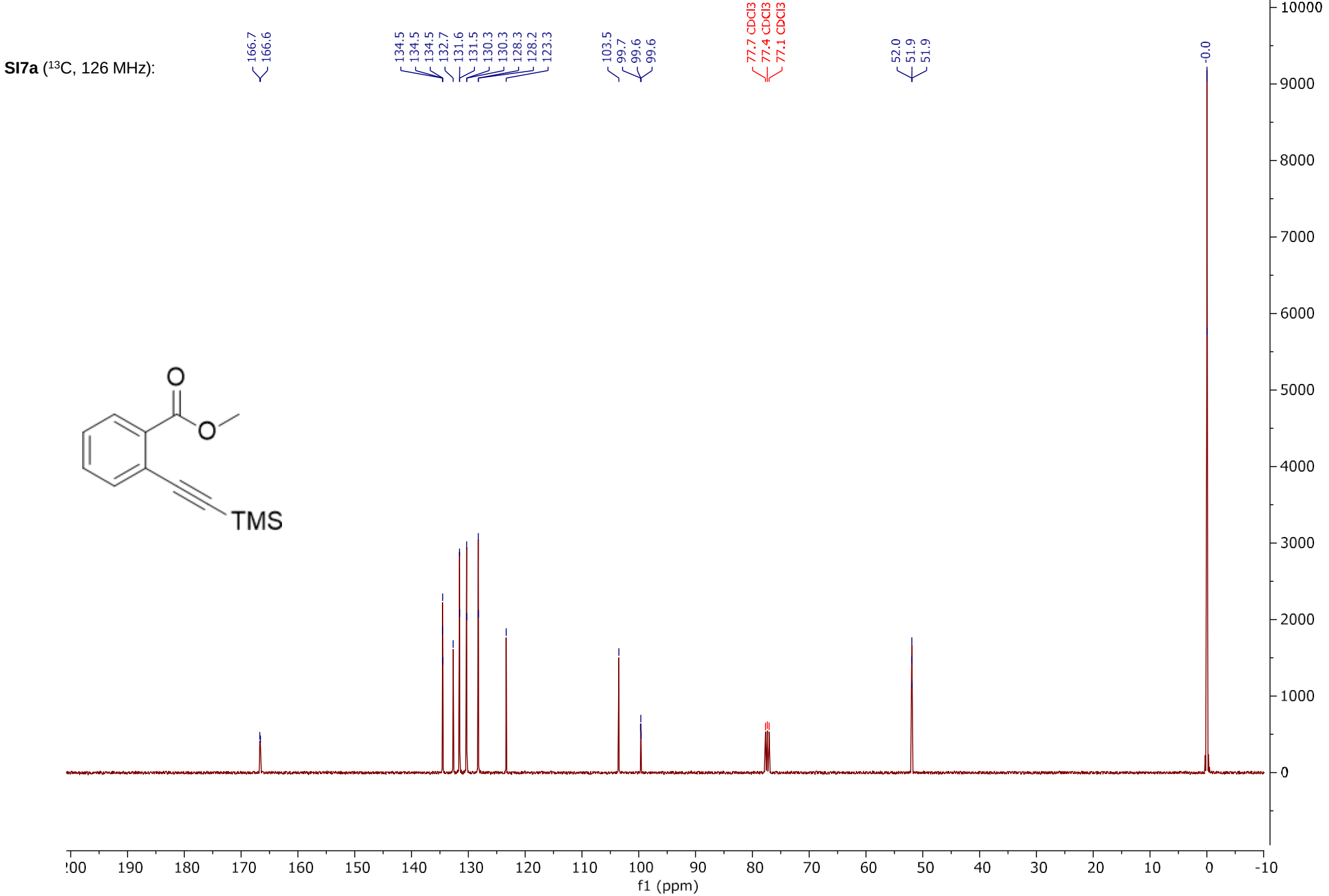
1f (^{13}C, 101 MHz):



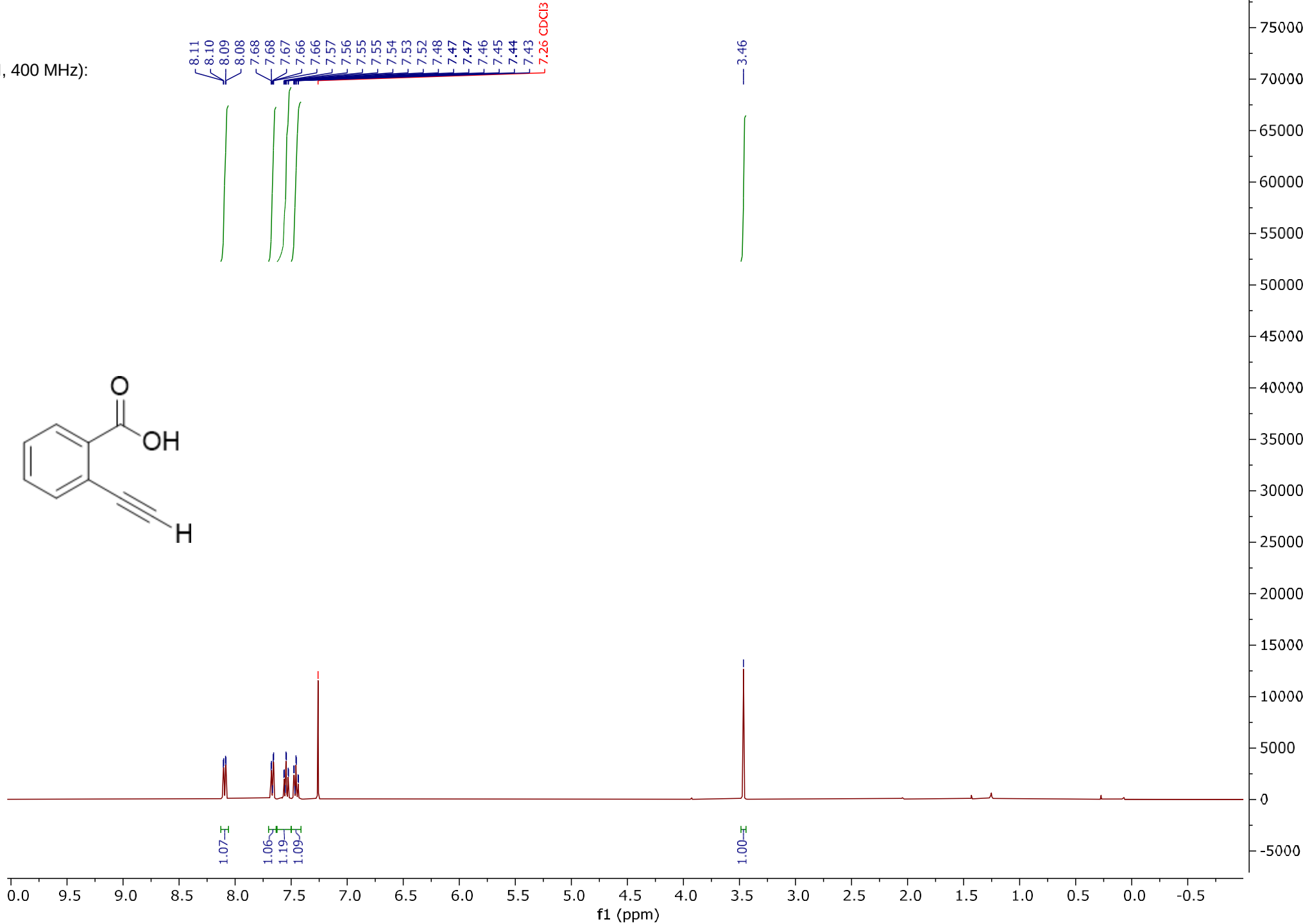
SI7a (^{1}H, 400 MHz):



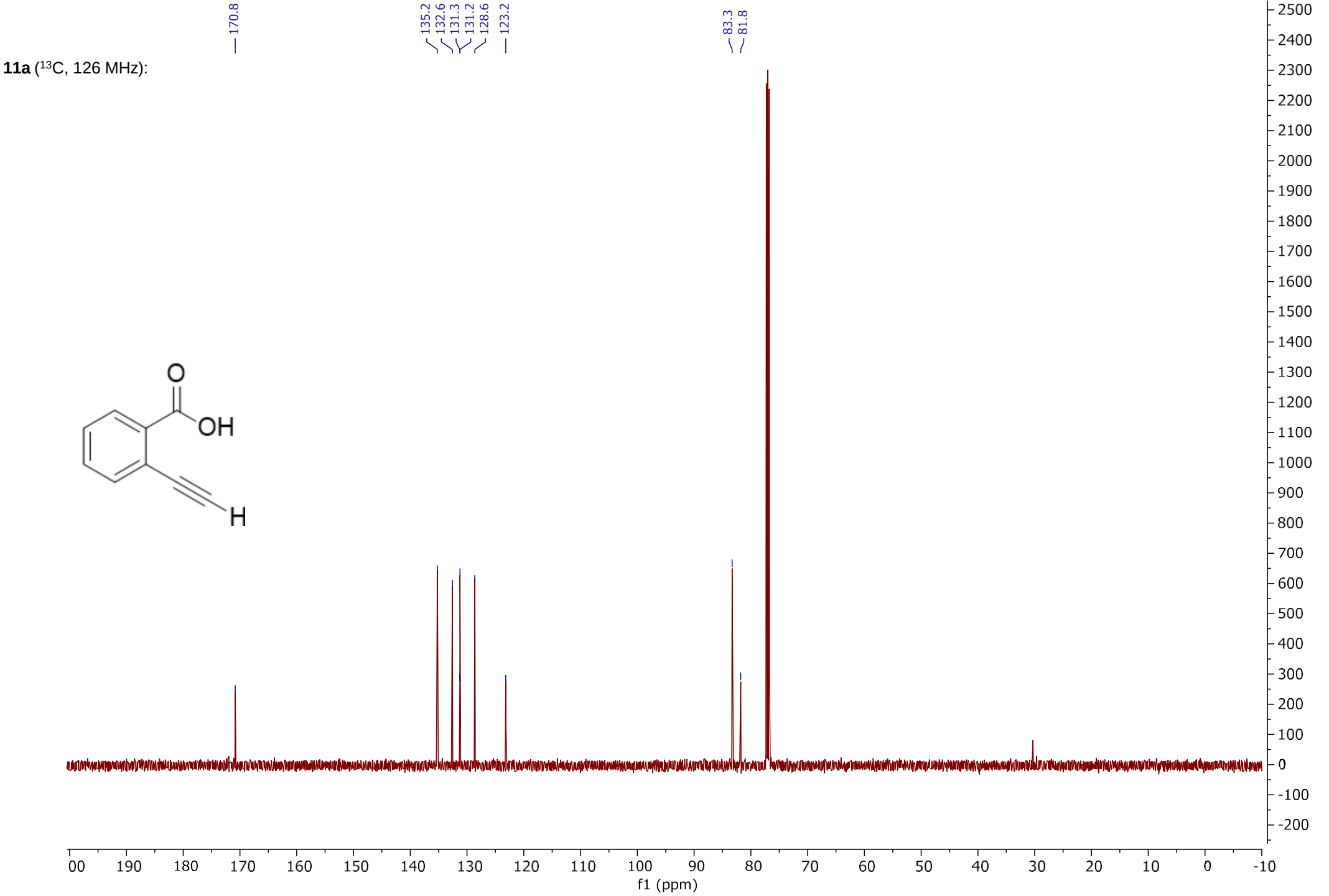
SI7a (^{13}C, 126 MHz):



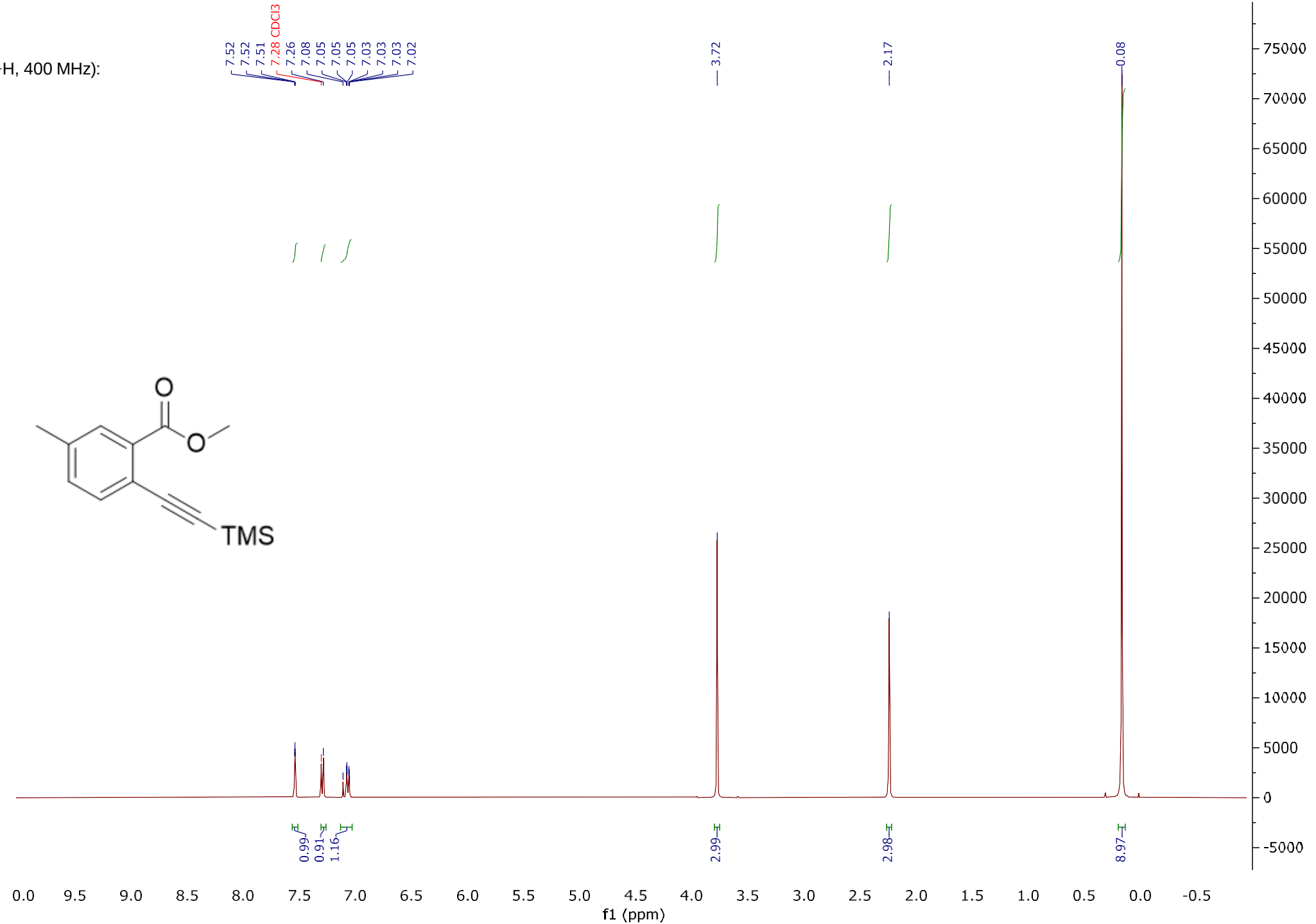
11a (^{1}H, 400 MHz):



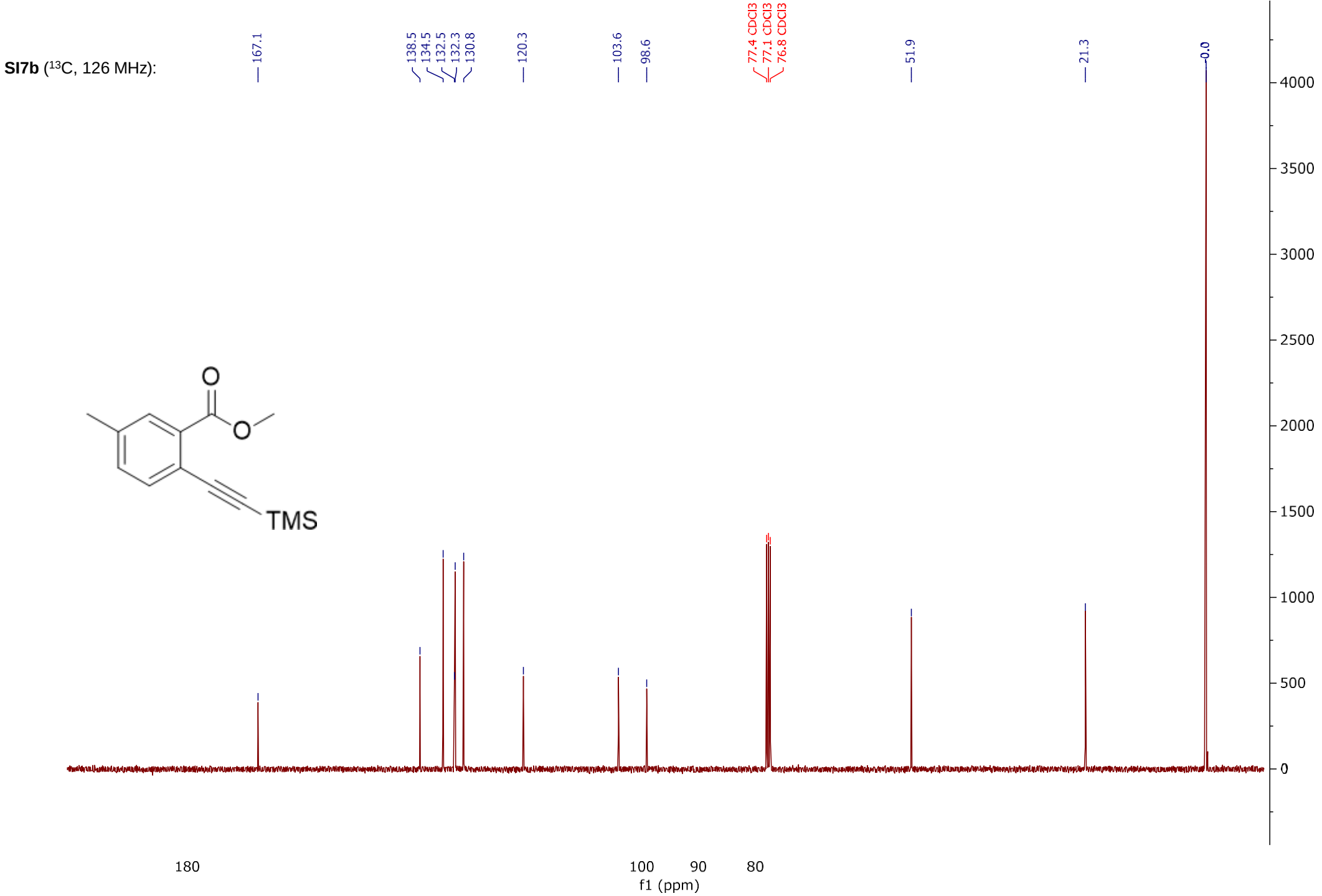
11a (^{13}C, 126 MHz):



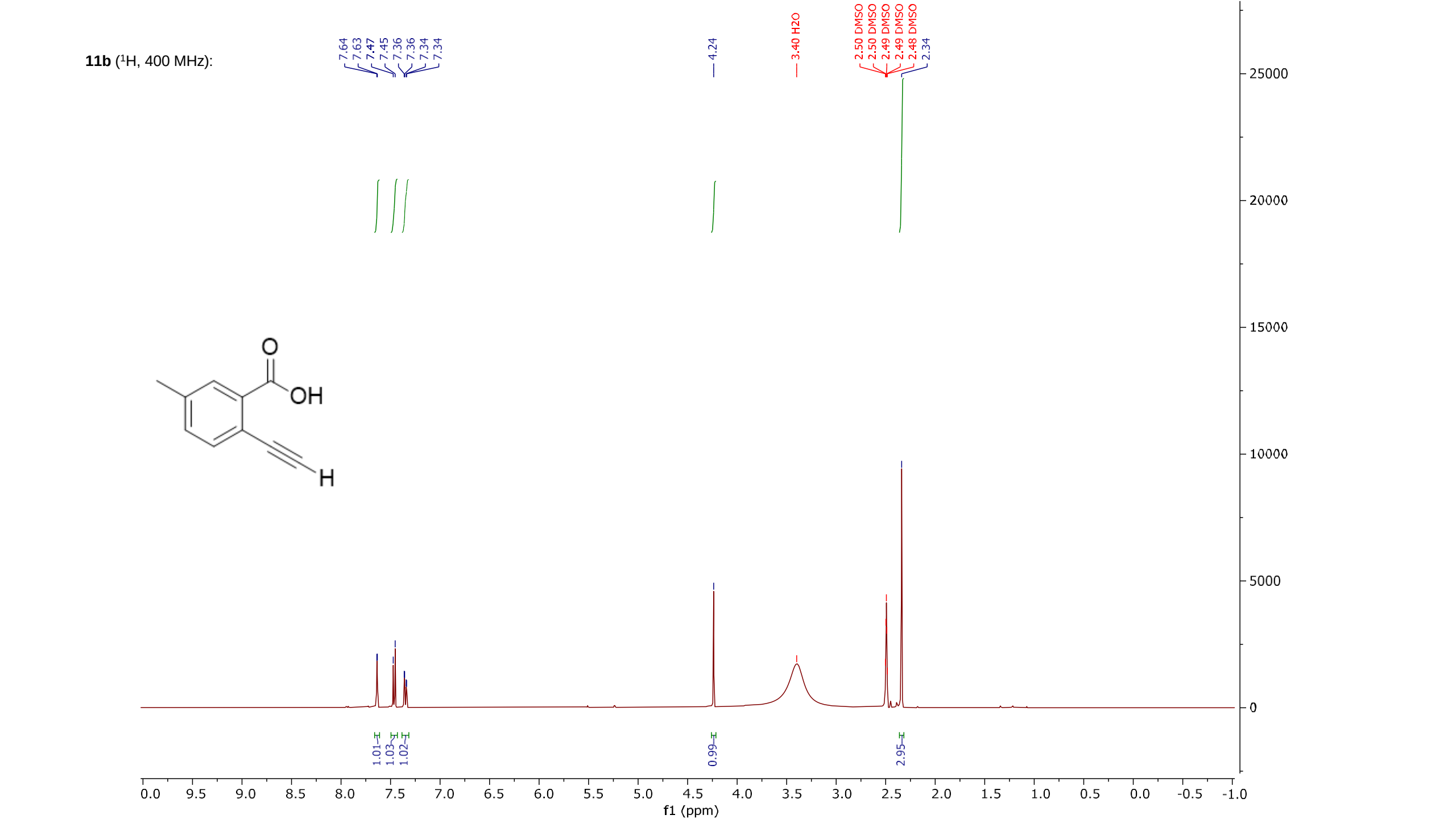
SI7b (^{1}H, 400 MHz):



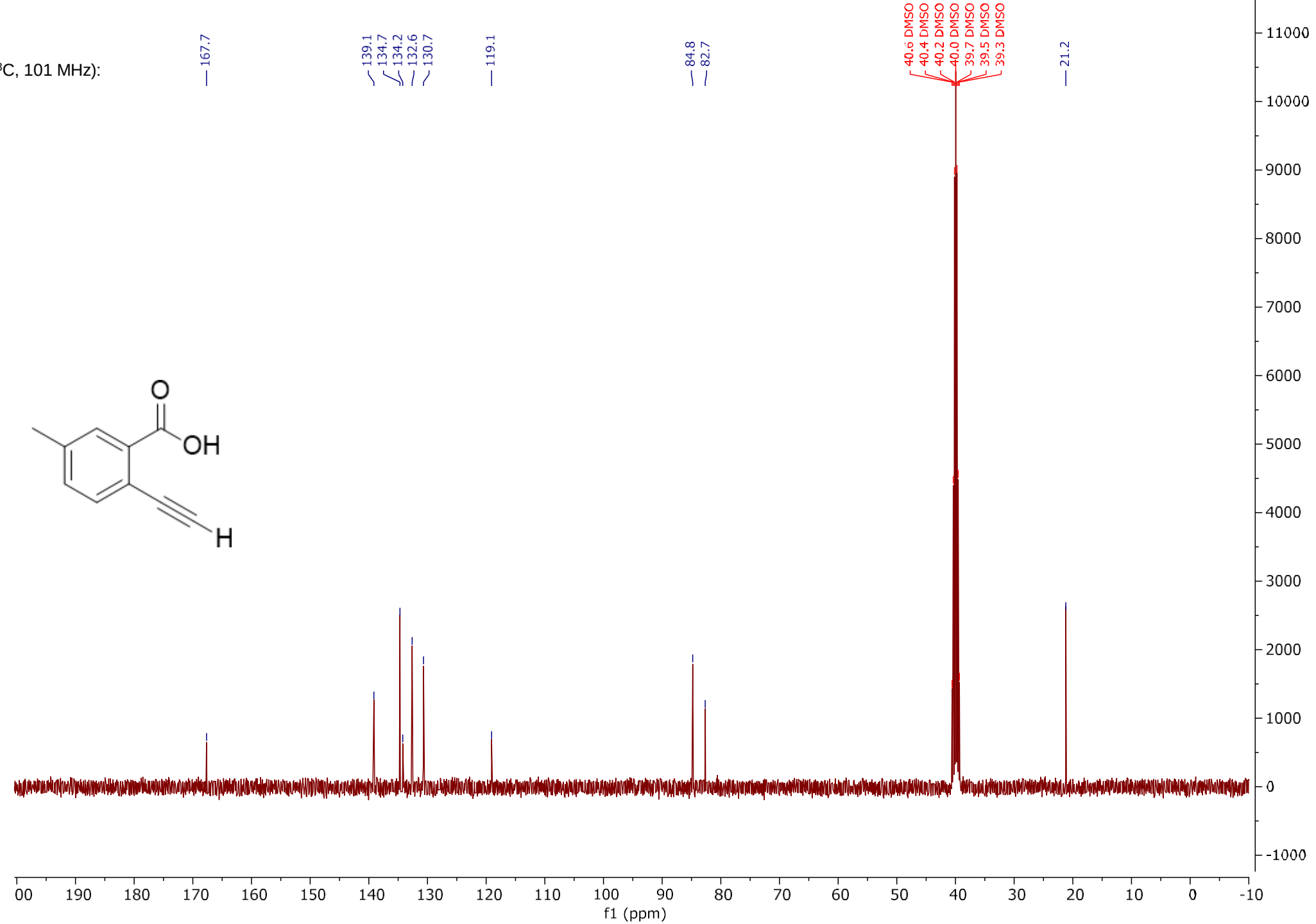
SI7b (^{13}C, 126 MHz):



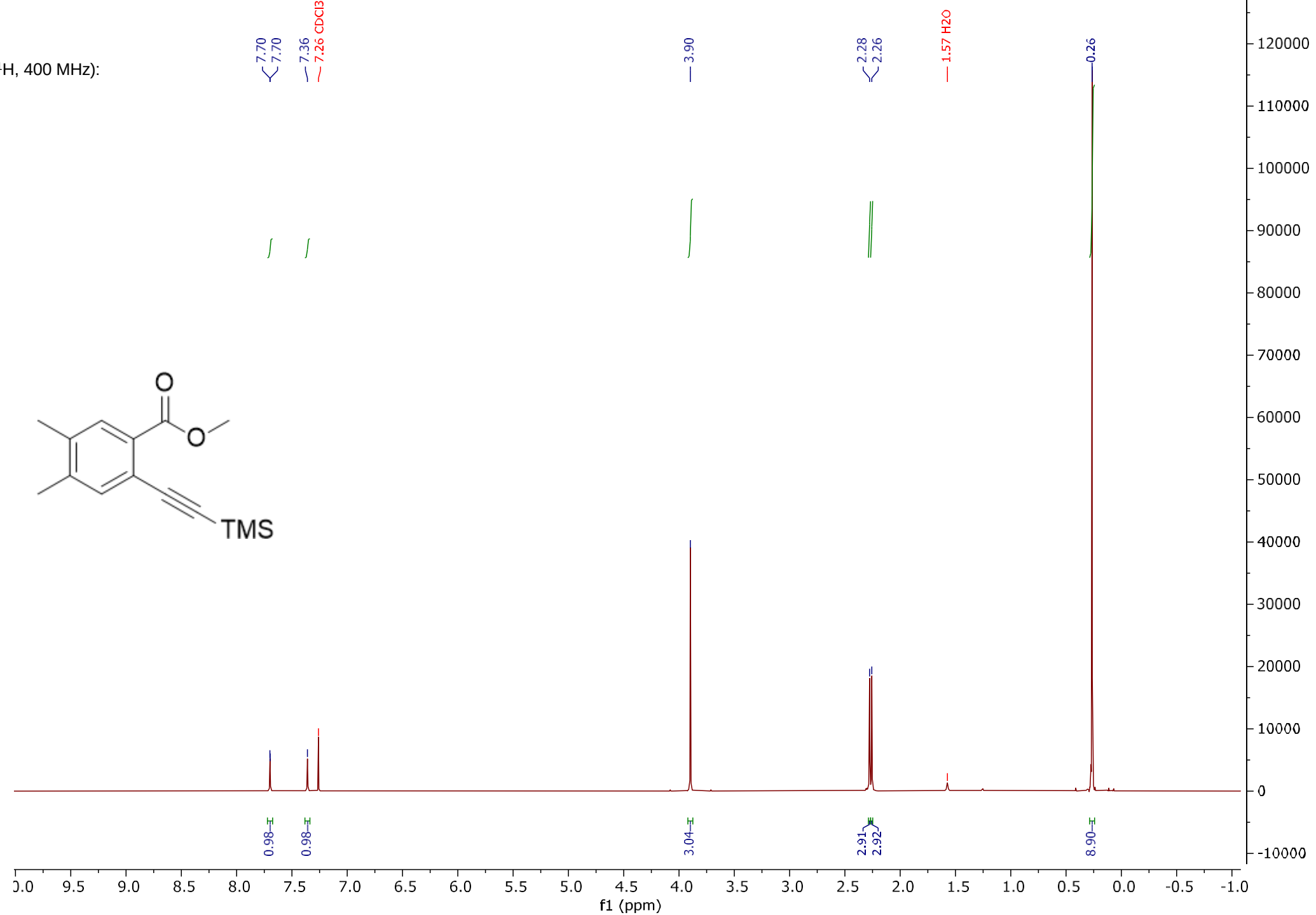
11b (^{1}H, 400 MHz):



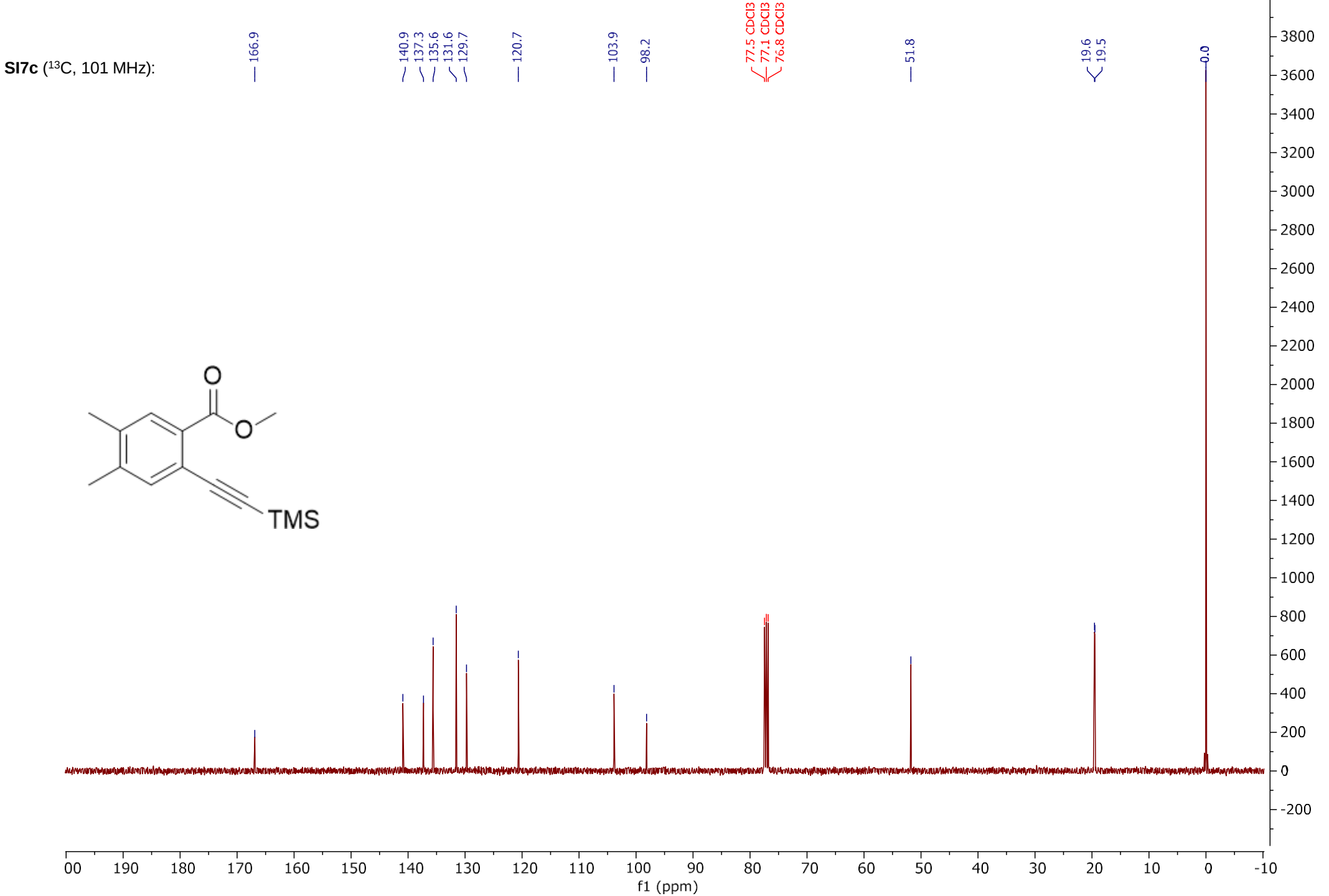
11b (^{13}C, 101 MHz):



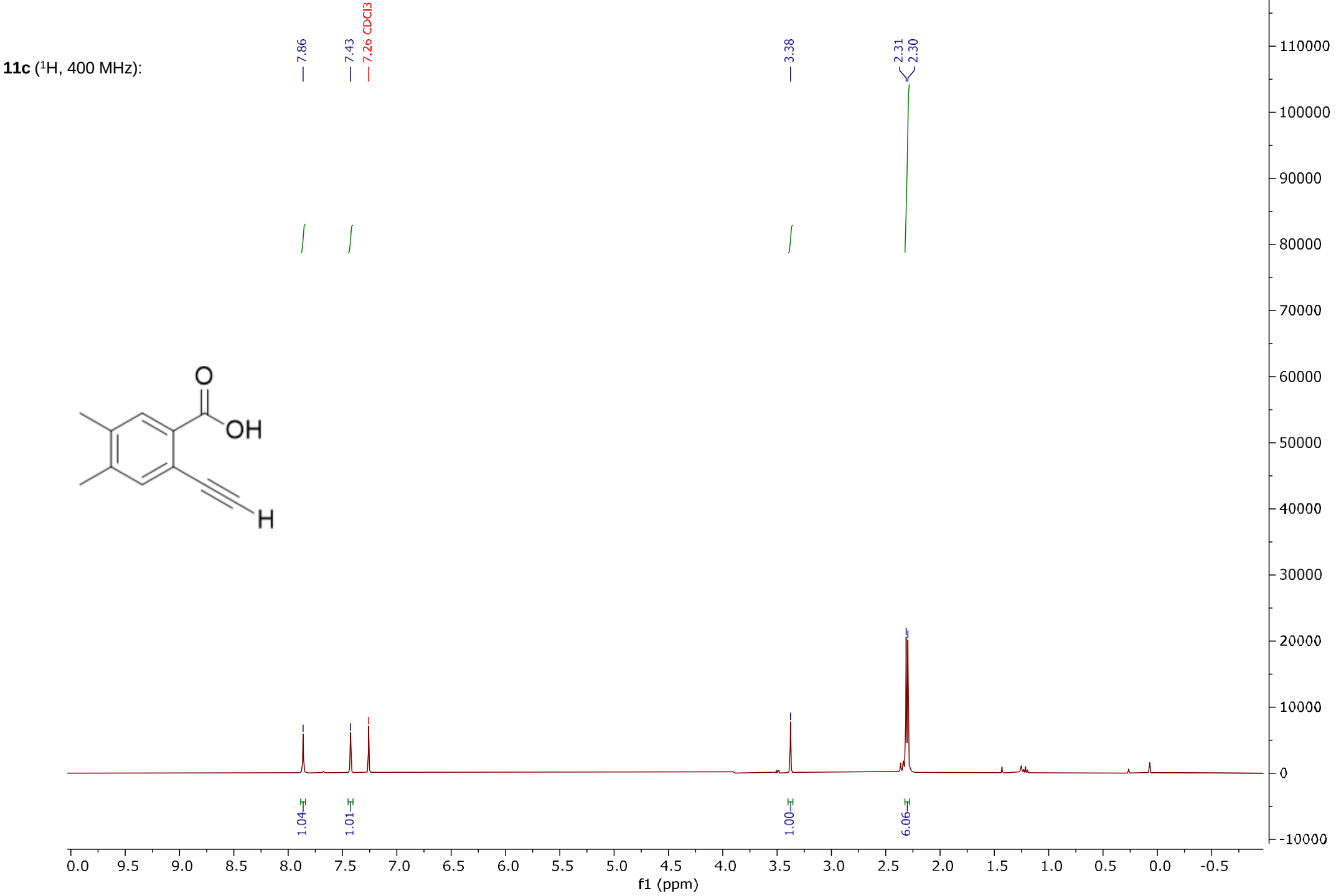
SI7c (^{1}H, 400 MHz):



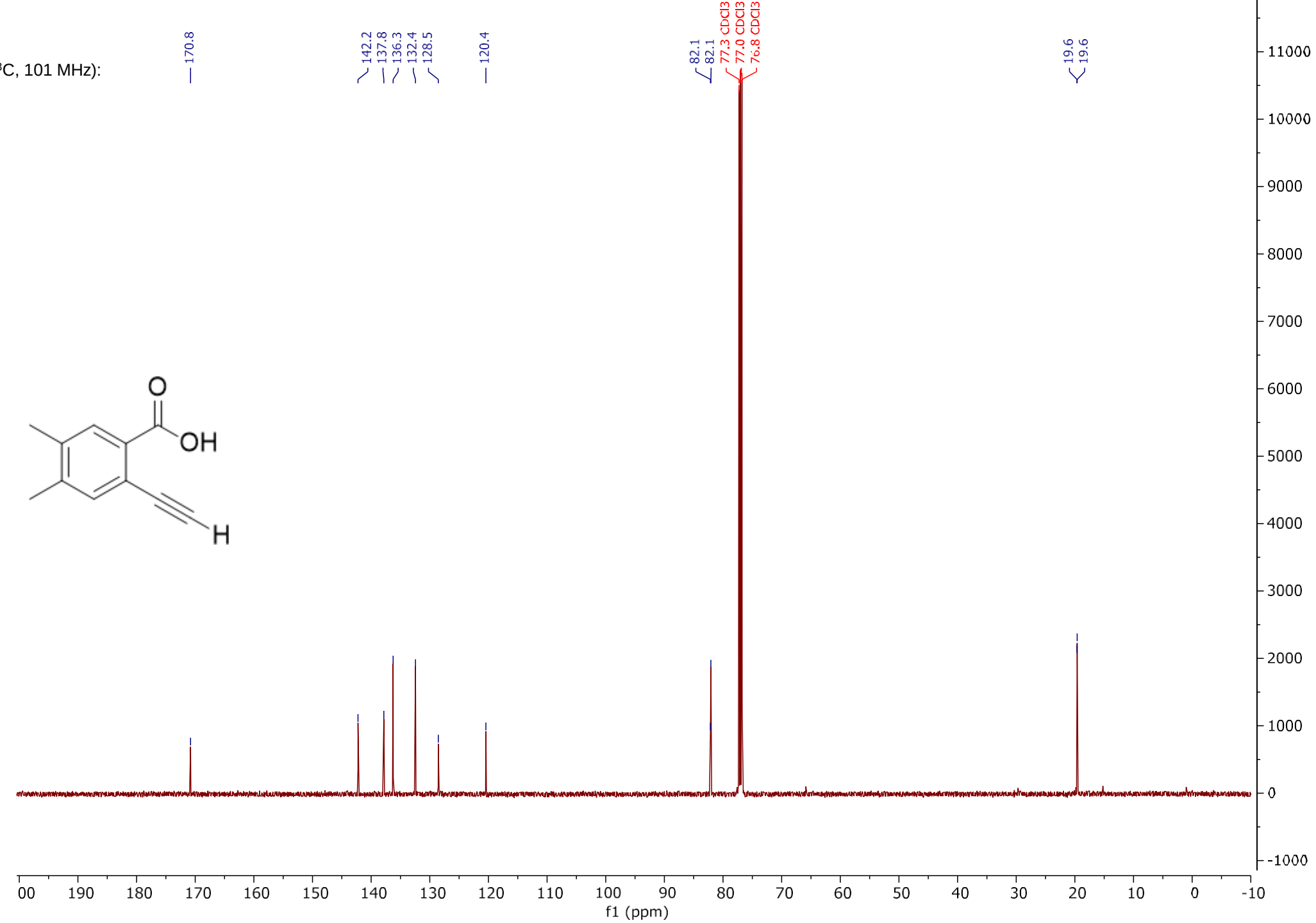
SI7c (^{13}C, 101 MHz):



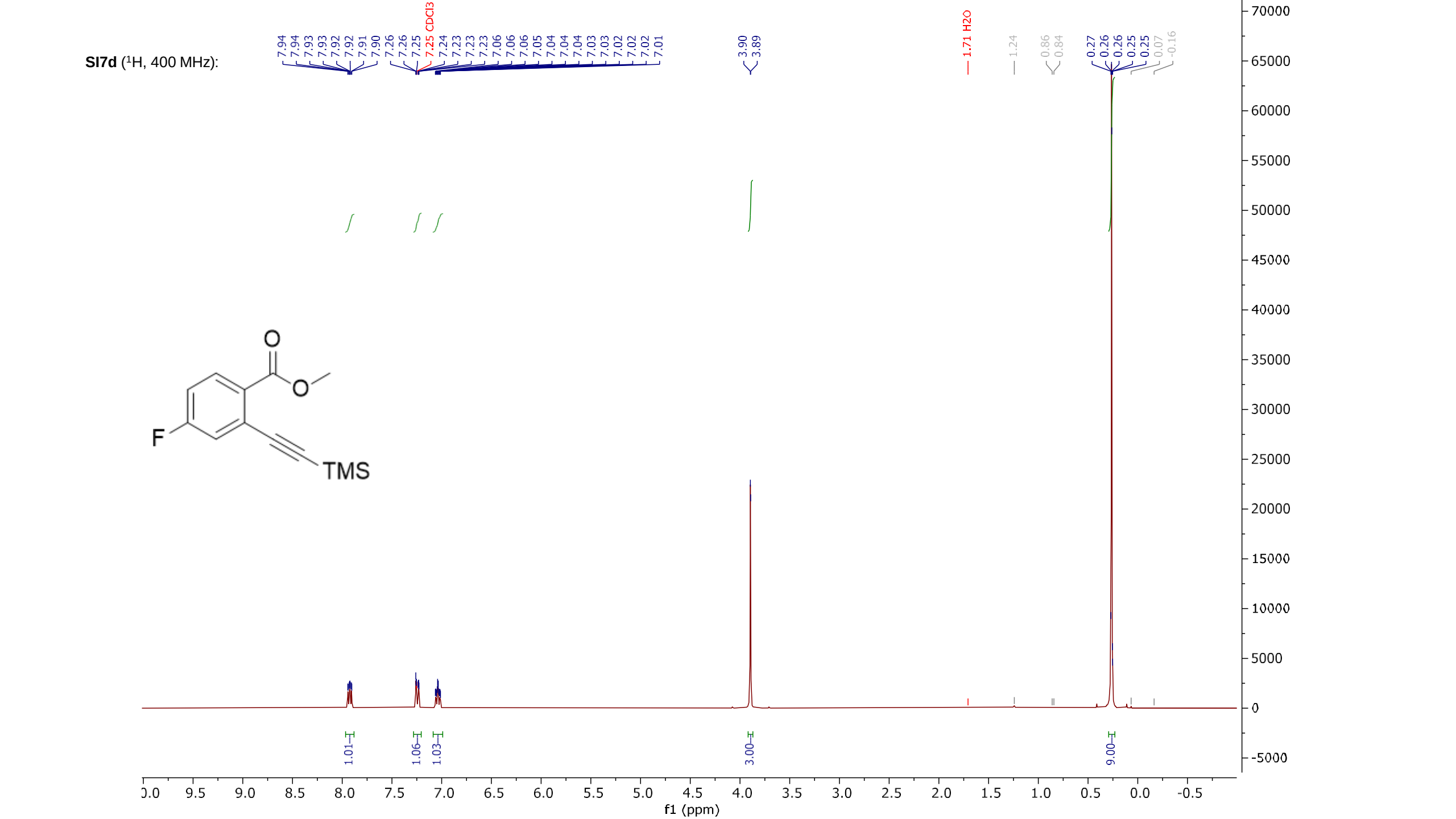
11c (^{1}H, 400 MHz):



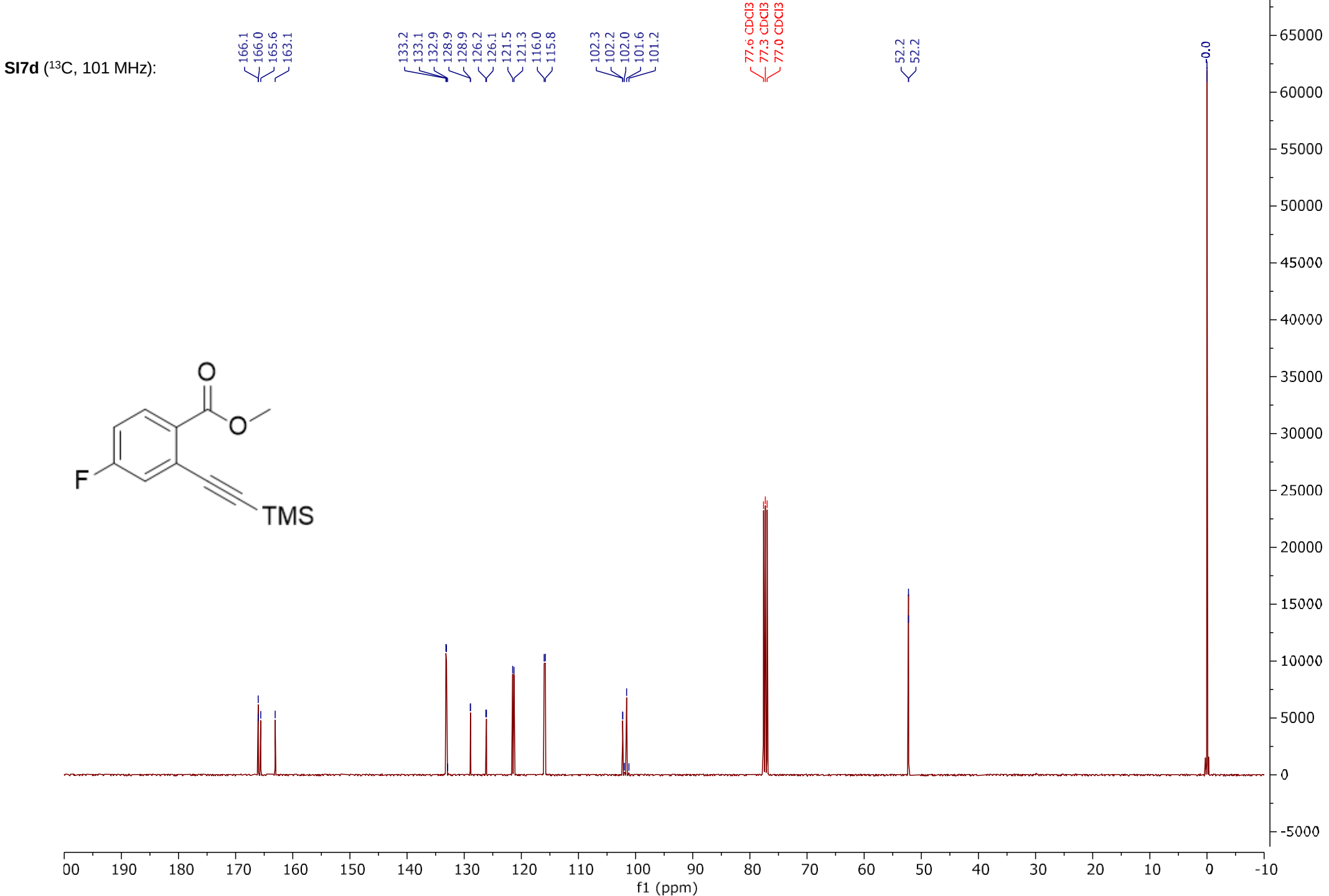
11c (^{13}C, 101 MHz):



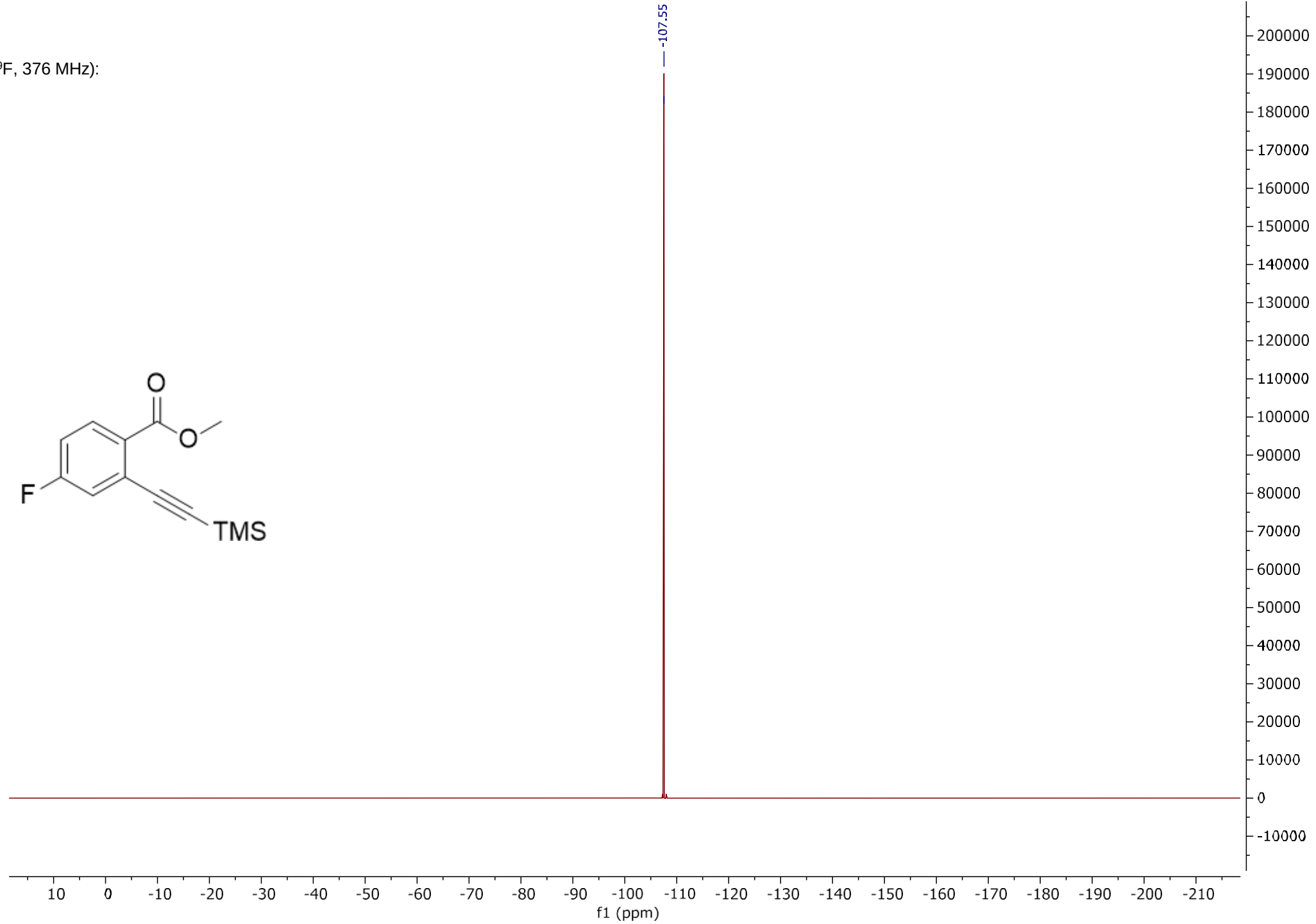
SI7d (^{1}H, 400 MHz):



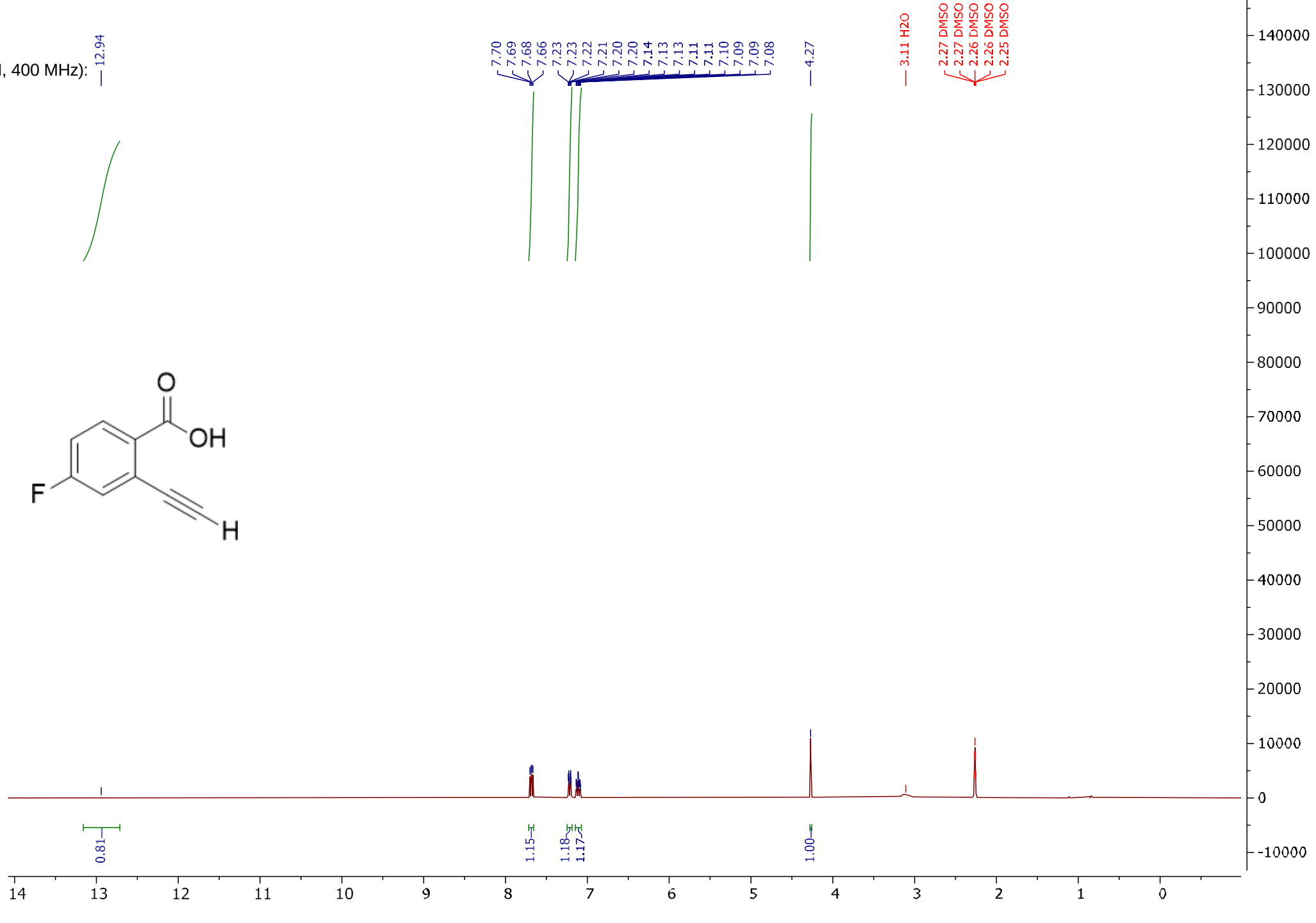
SI7d (^{13}C, 101 MHz):



SI7d (^{19}F, 376 MHz):

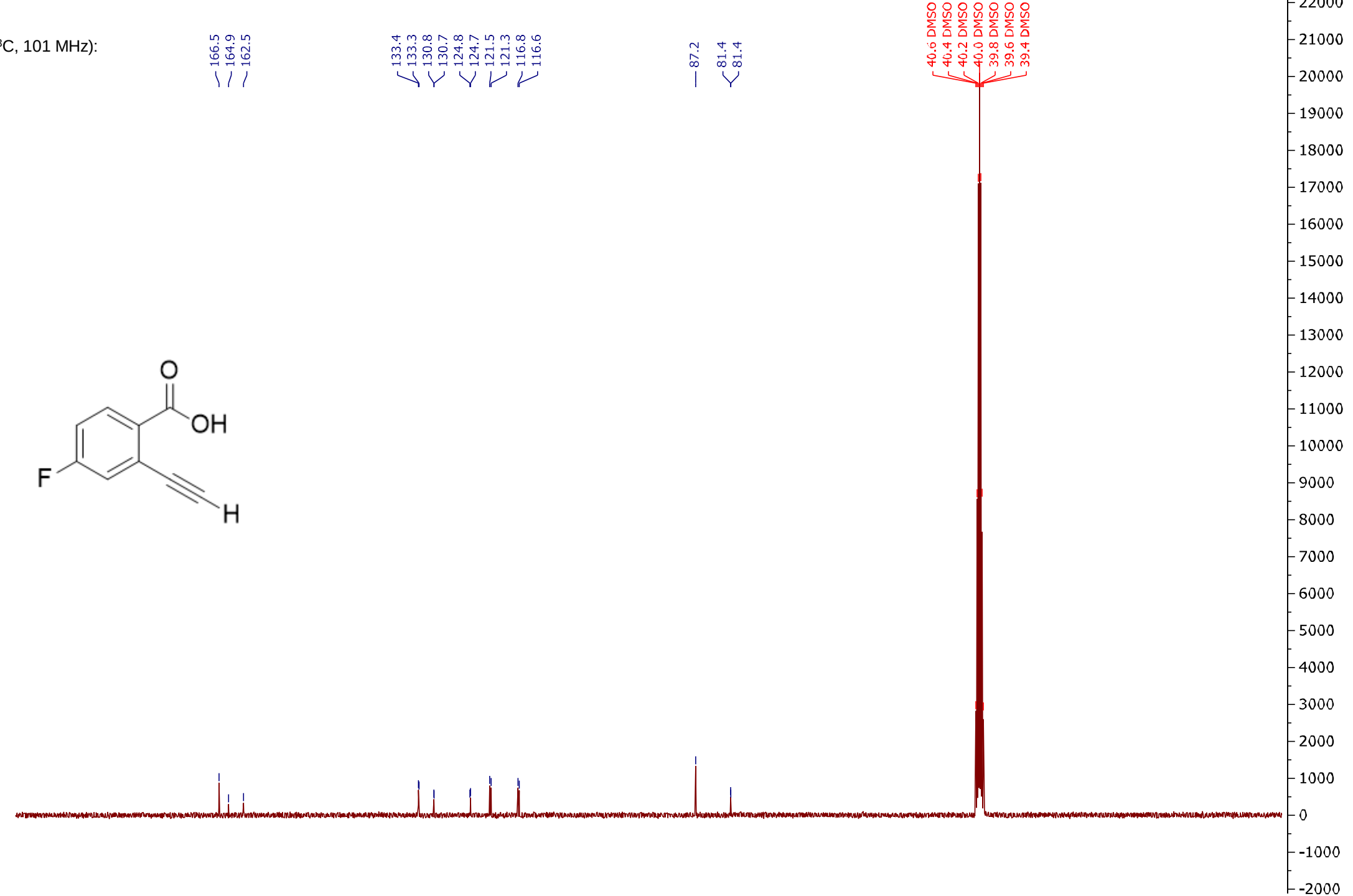


11d (^{1}H, 400 MHz):

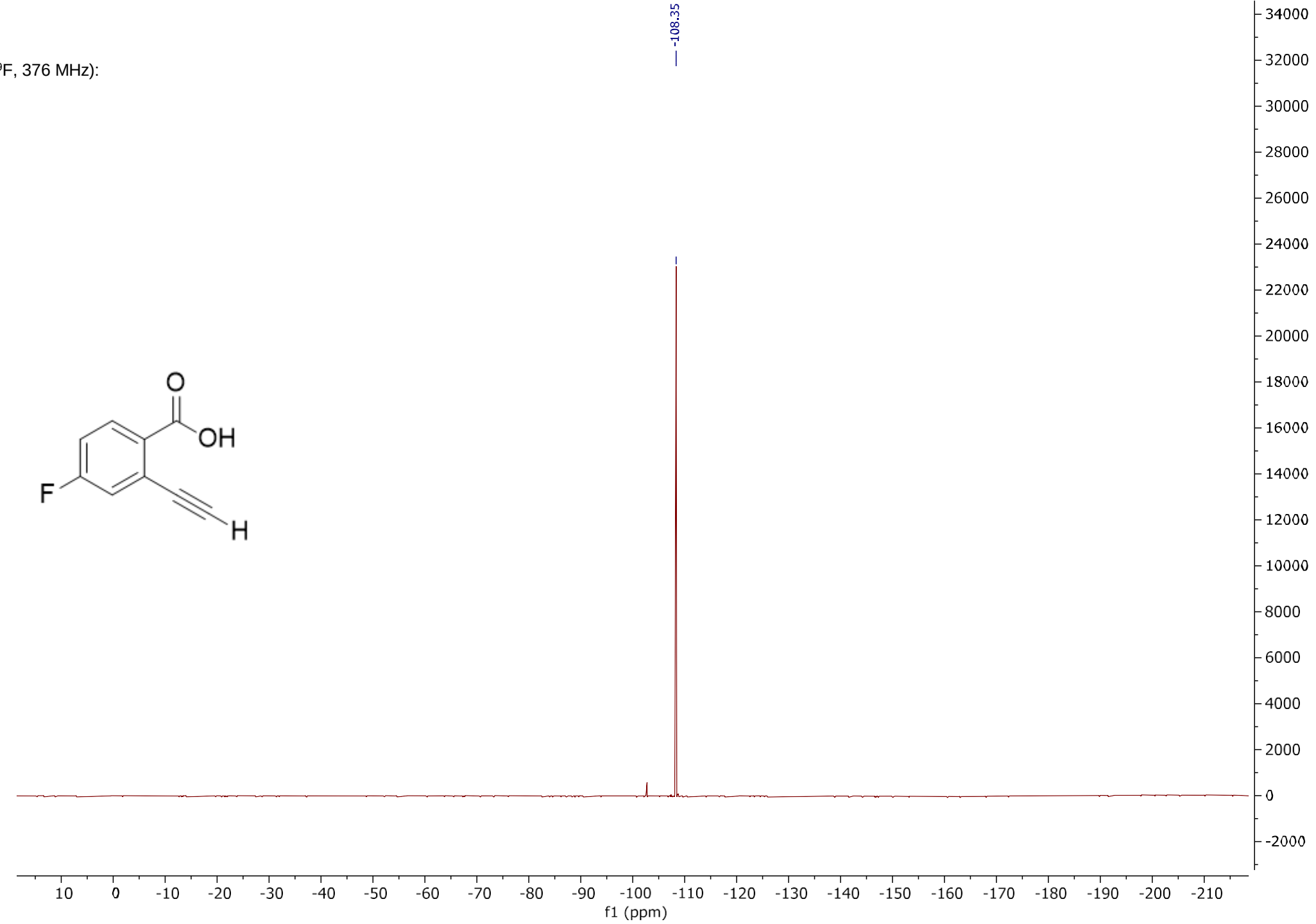


f1 (ppm)

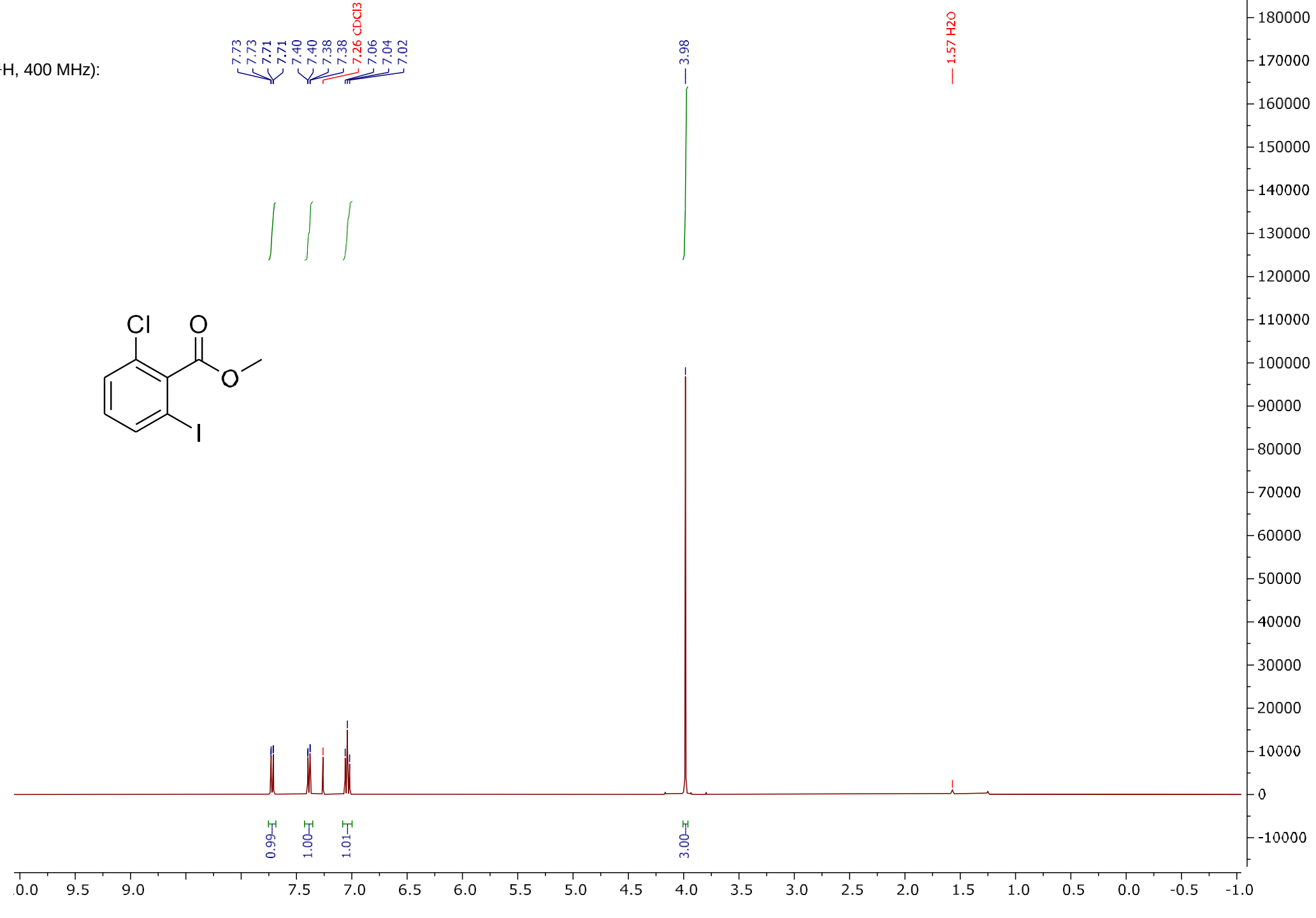
11d (^{13}C, 101 MHz):



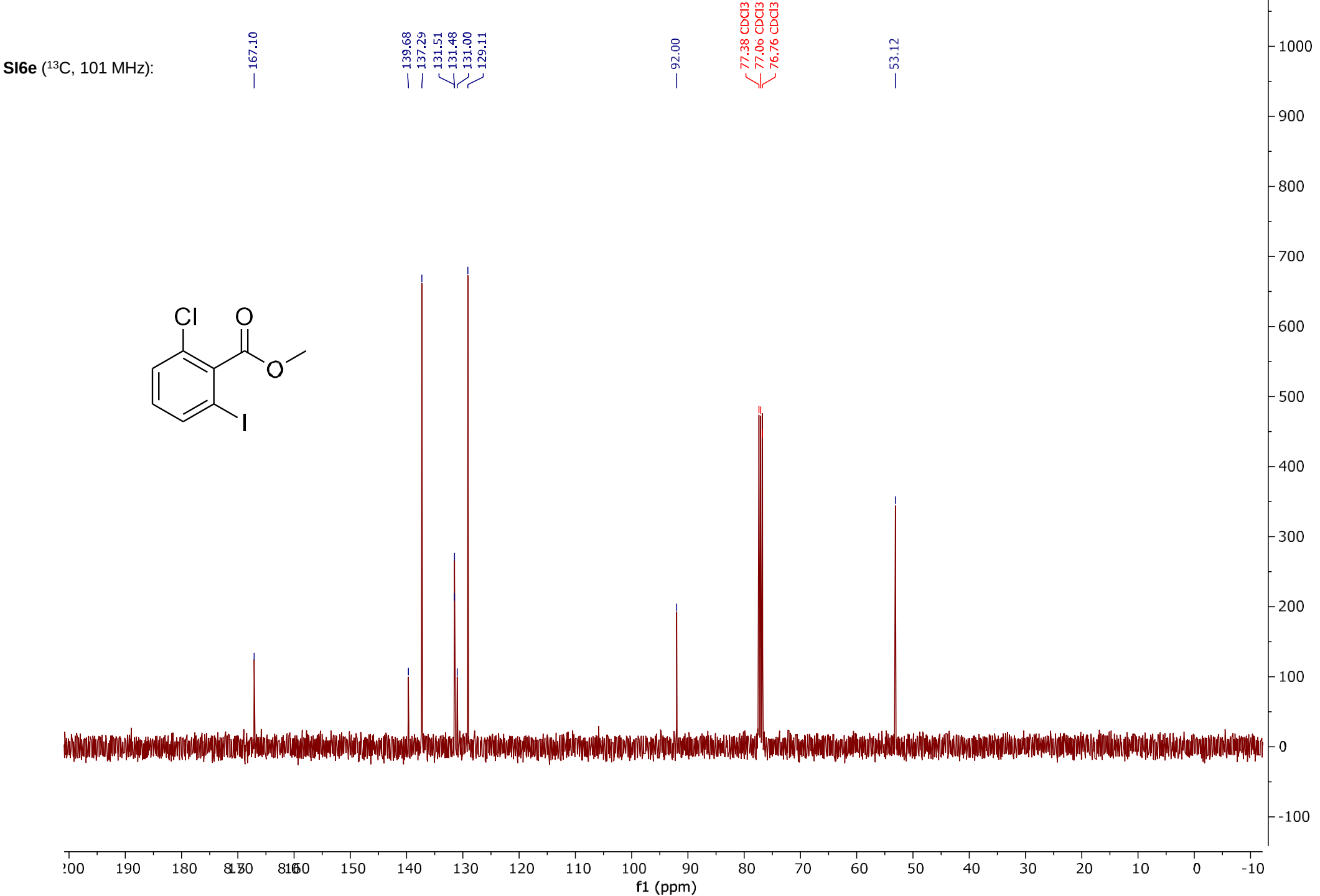
11d (^{19}F, 376 MHz):



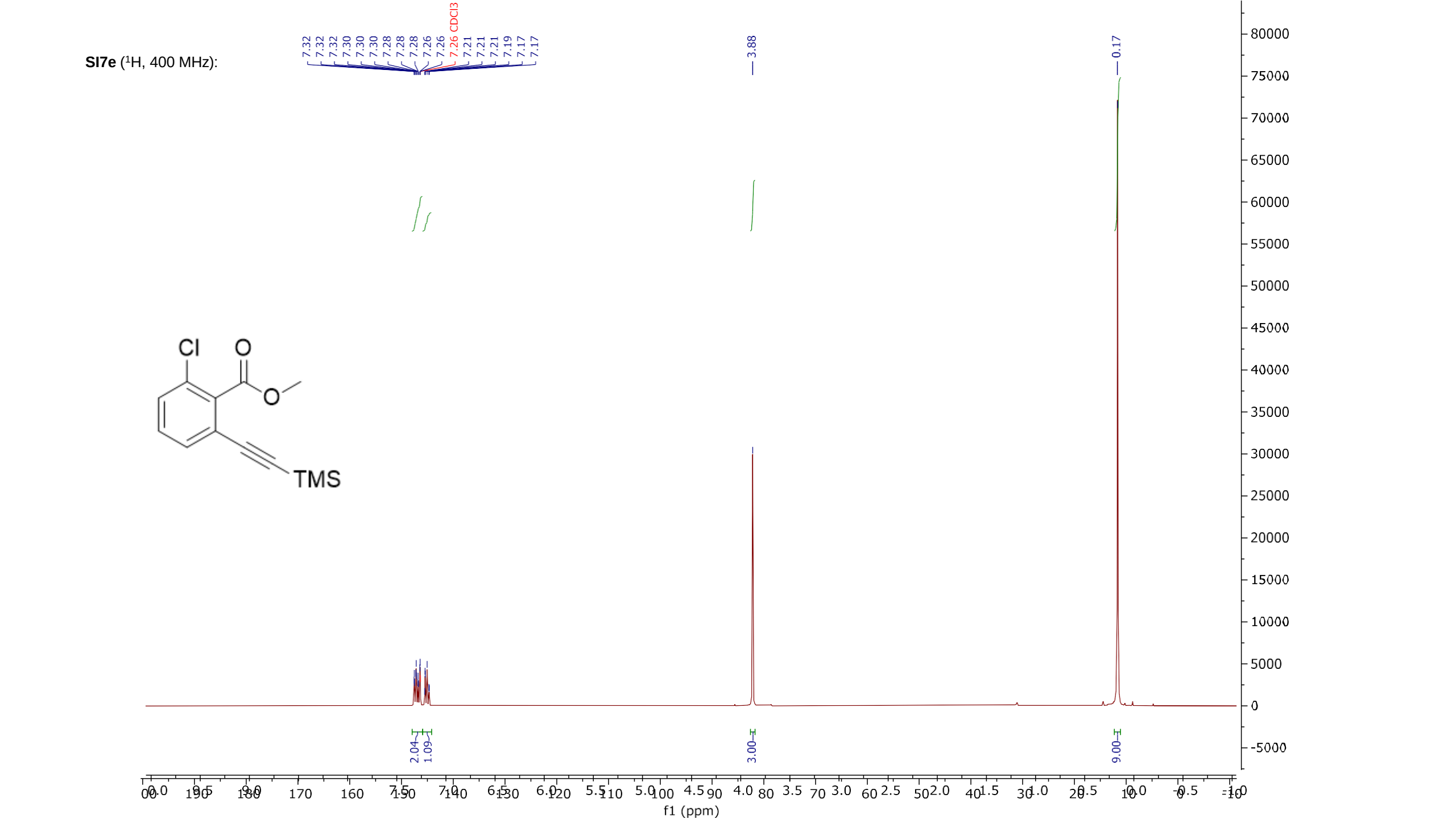
SI6e (^{1}H, 400 MHz):



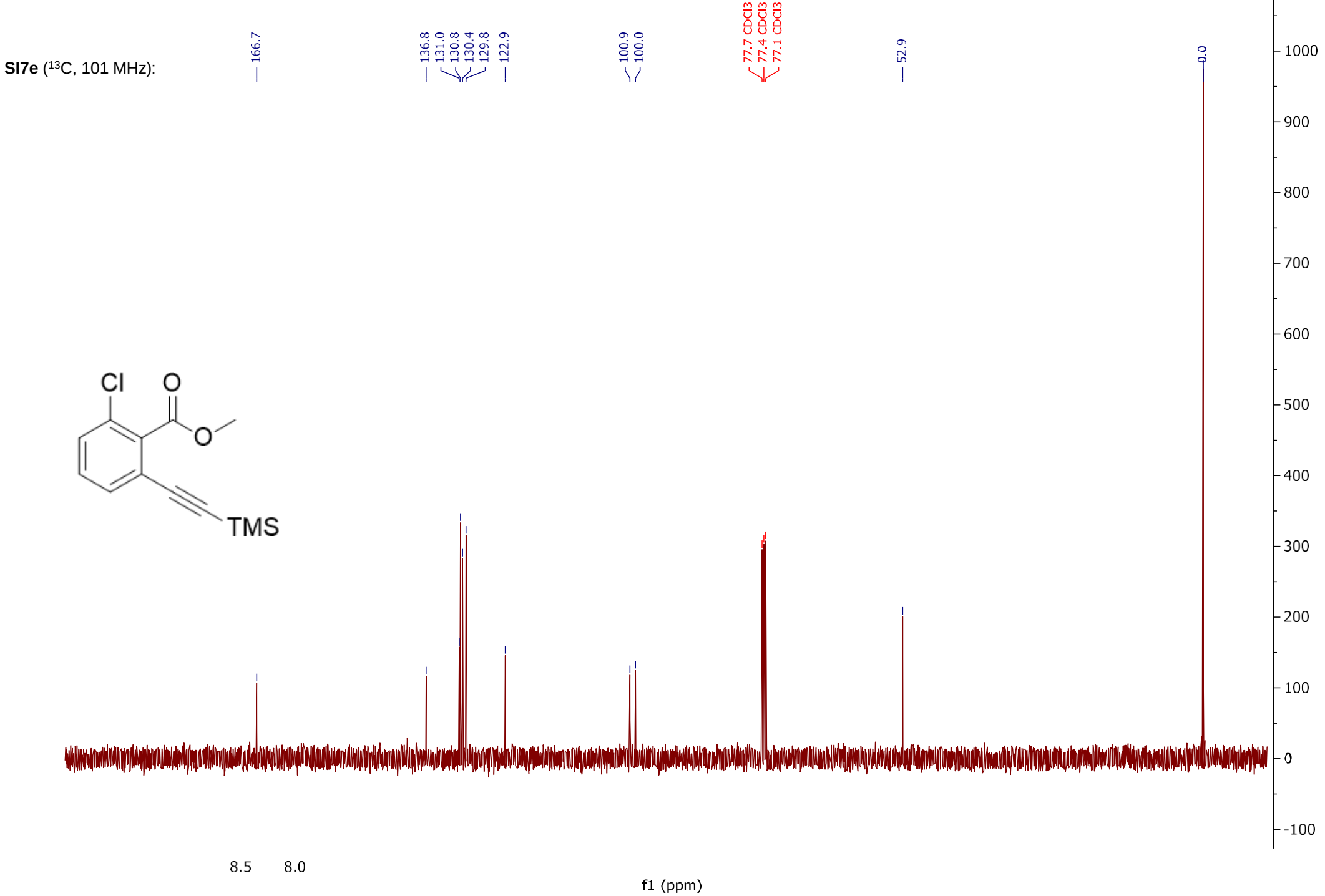
SI6e (^{13}C, 101 MHz):



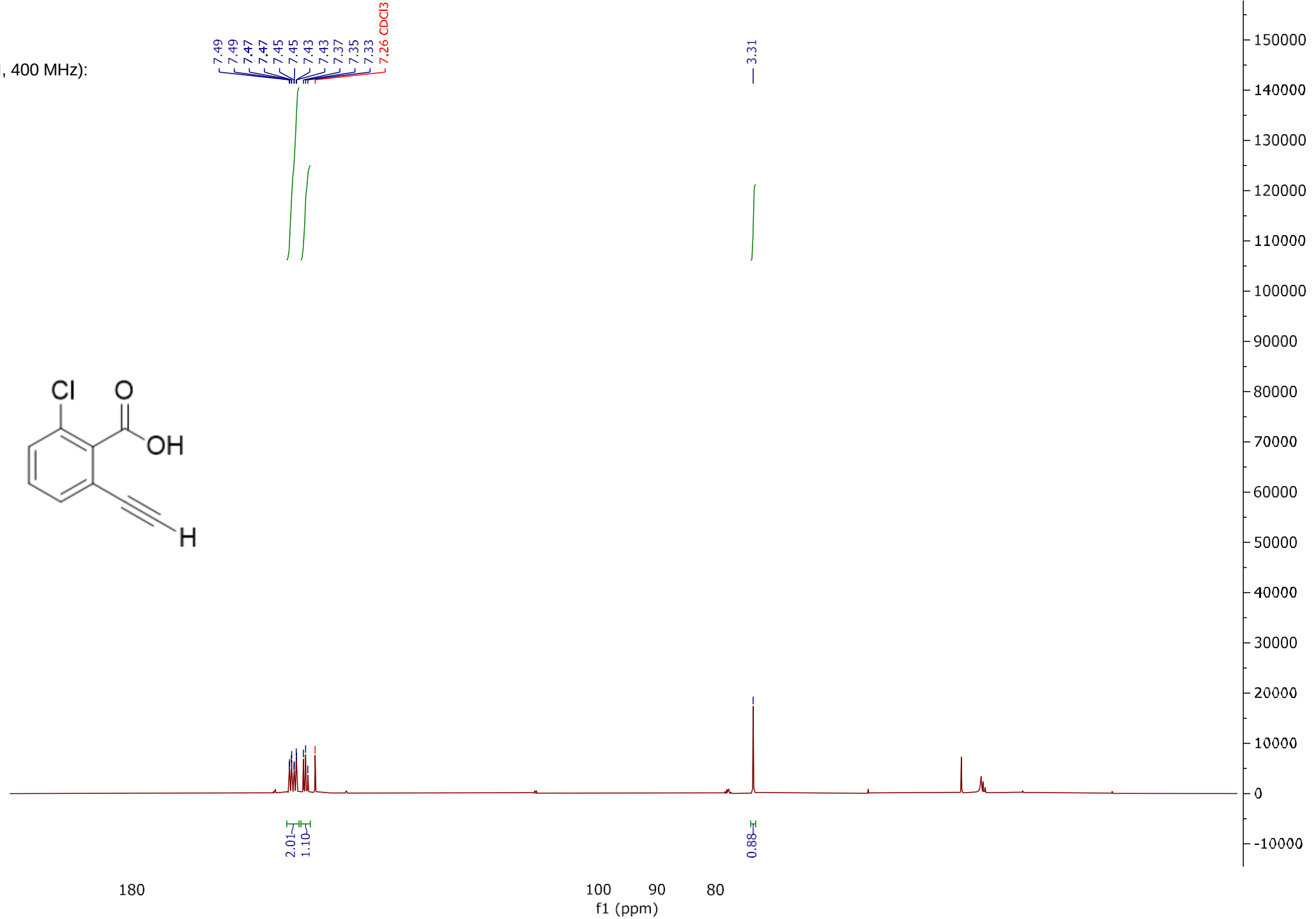
SI7e (^{1}H, 400 MHz):



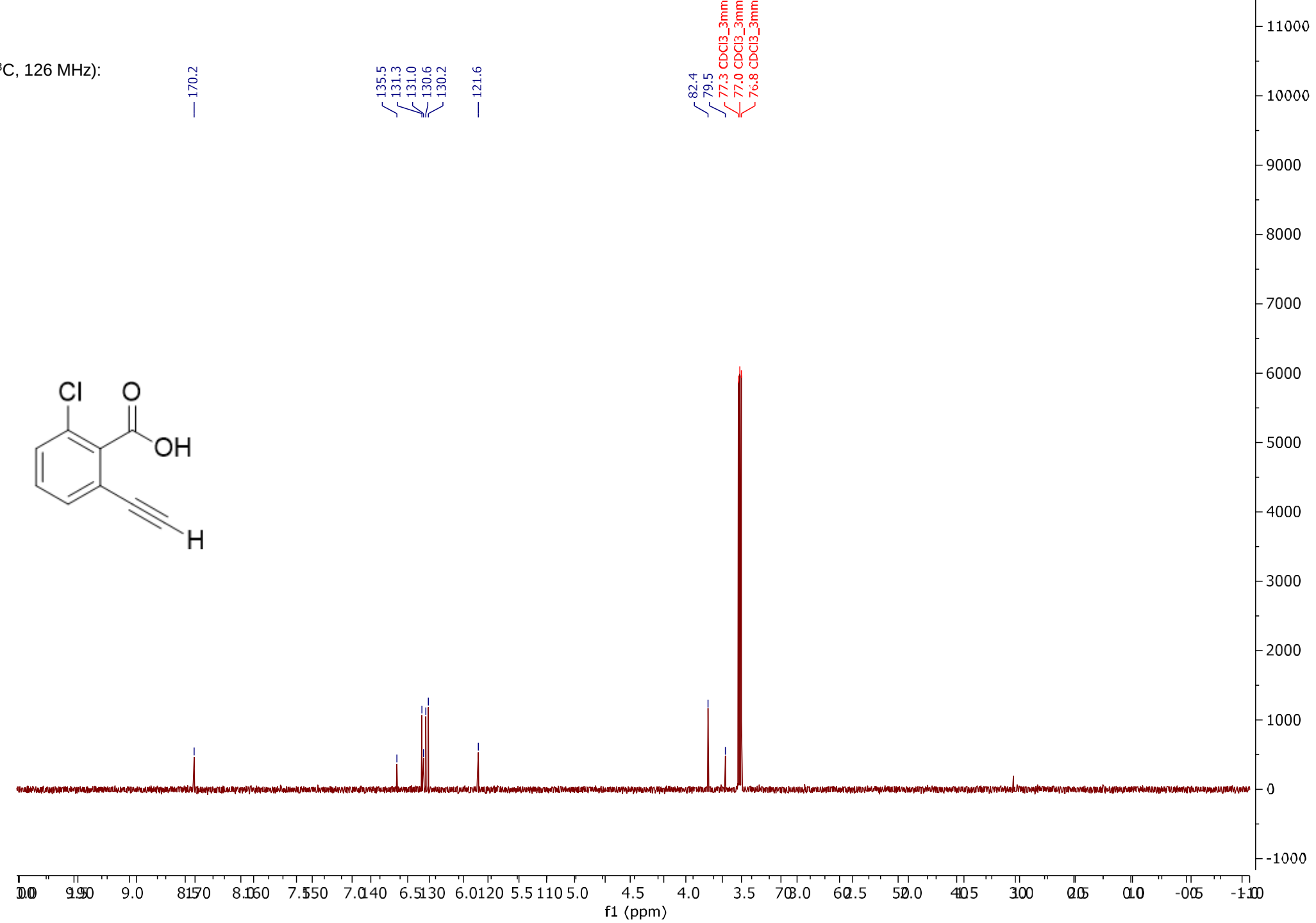
SI7e (^{13}C, 101 MHz):



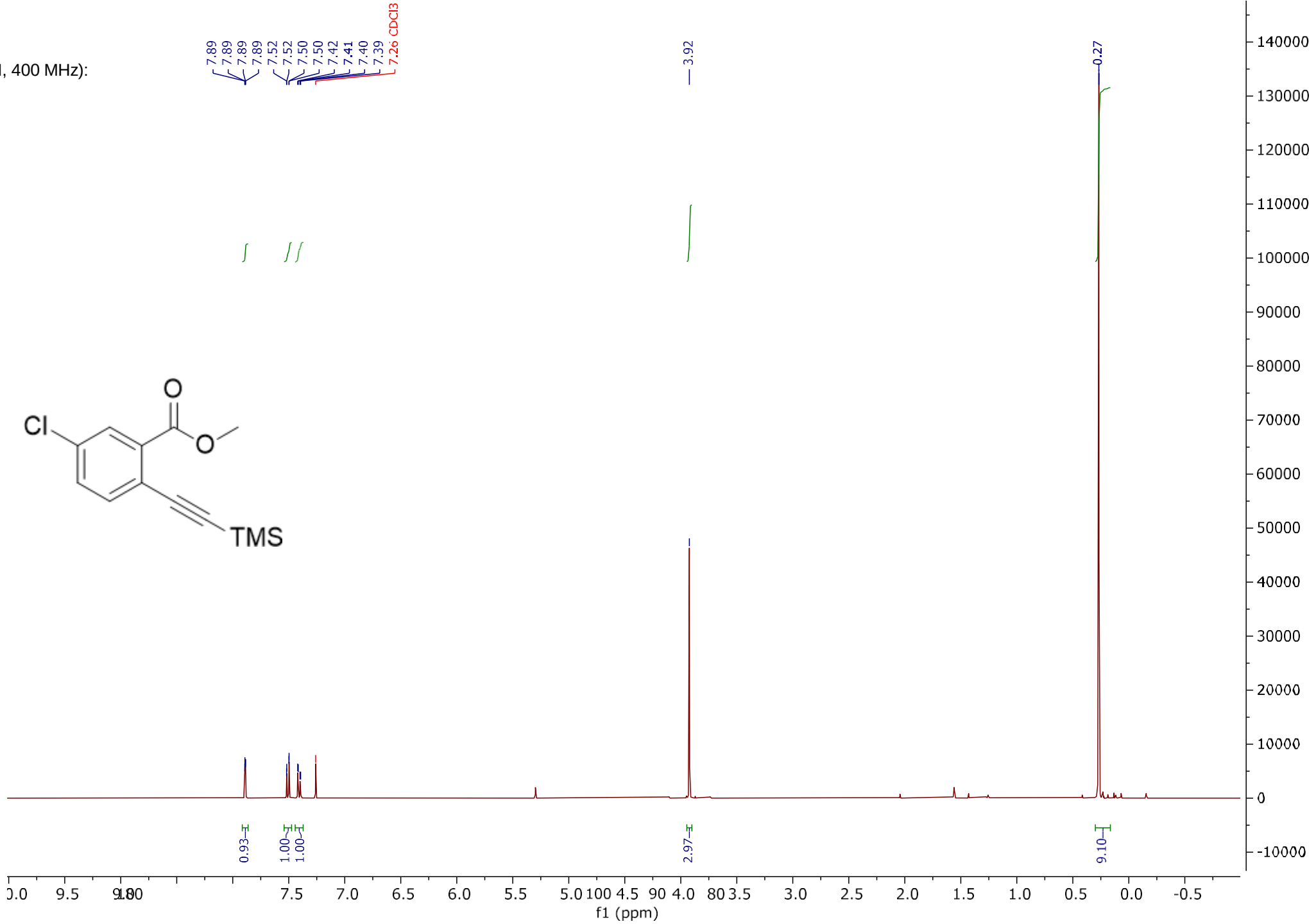
11e (^{1}H, 400 MHz):



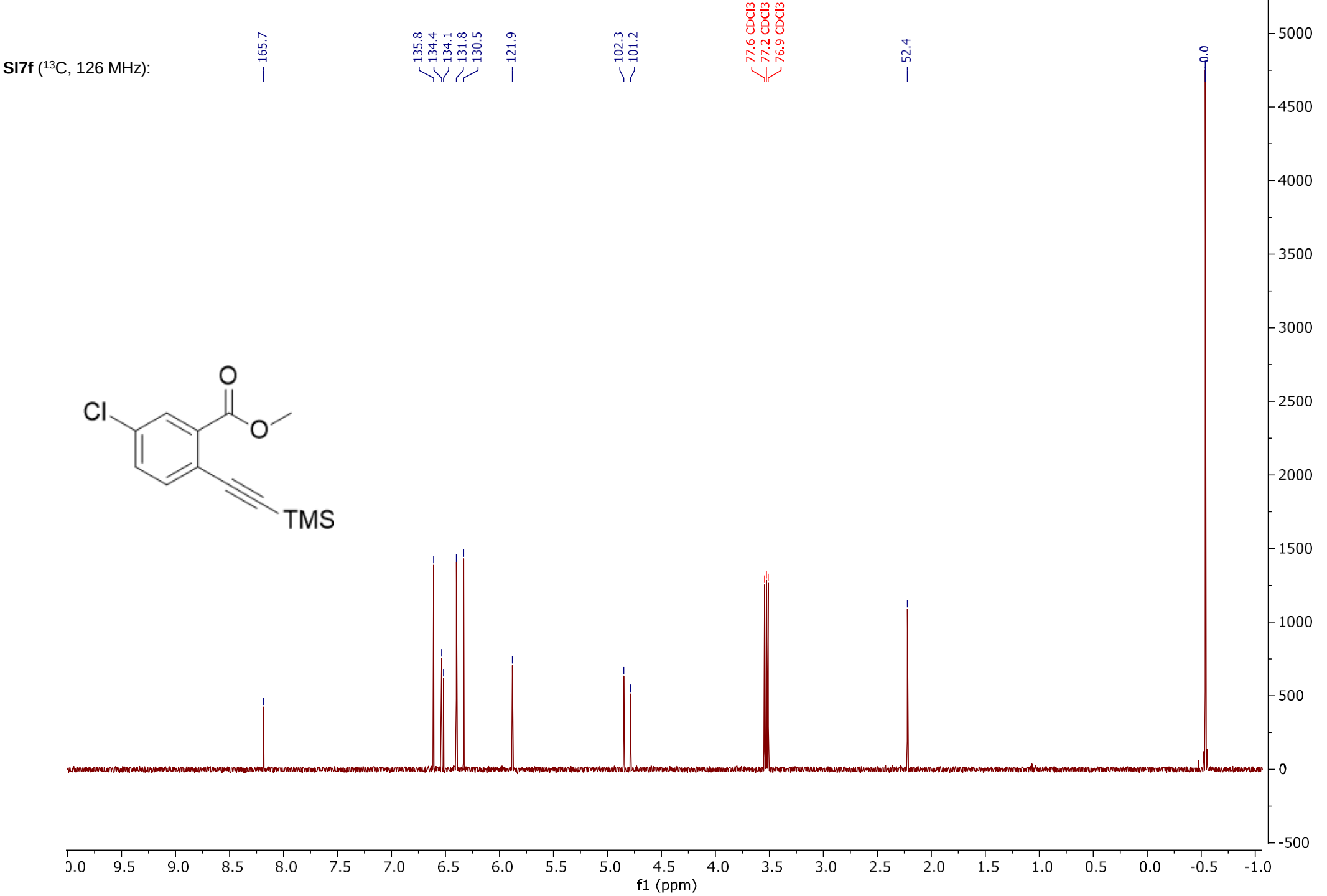
11e (^{13}C, 126 MHz):



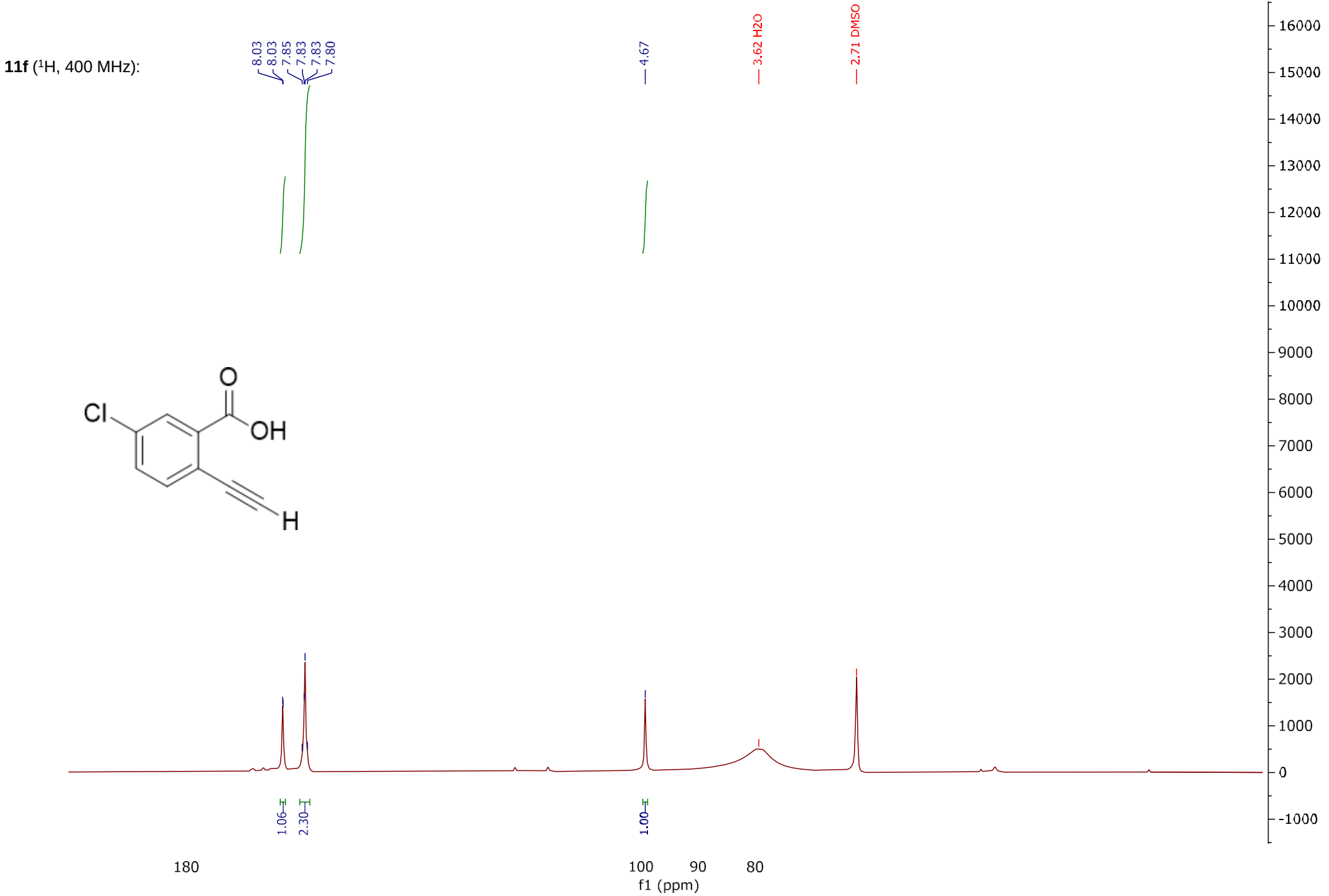
SI7f (^{1}H, 400 MHz):



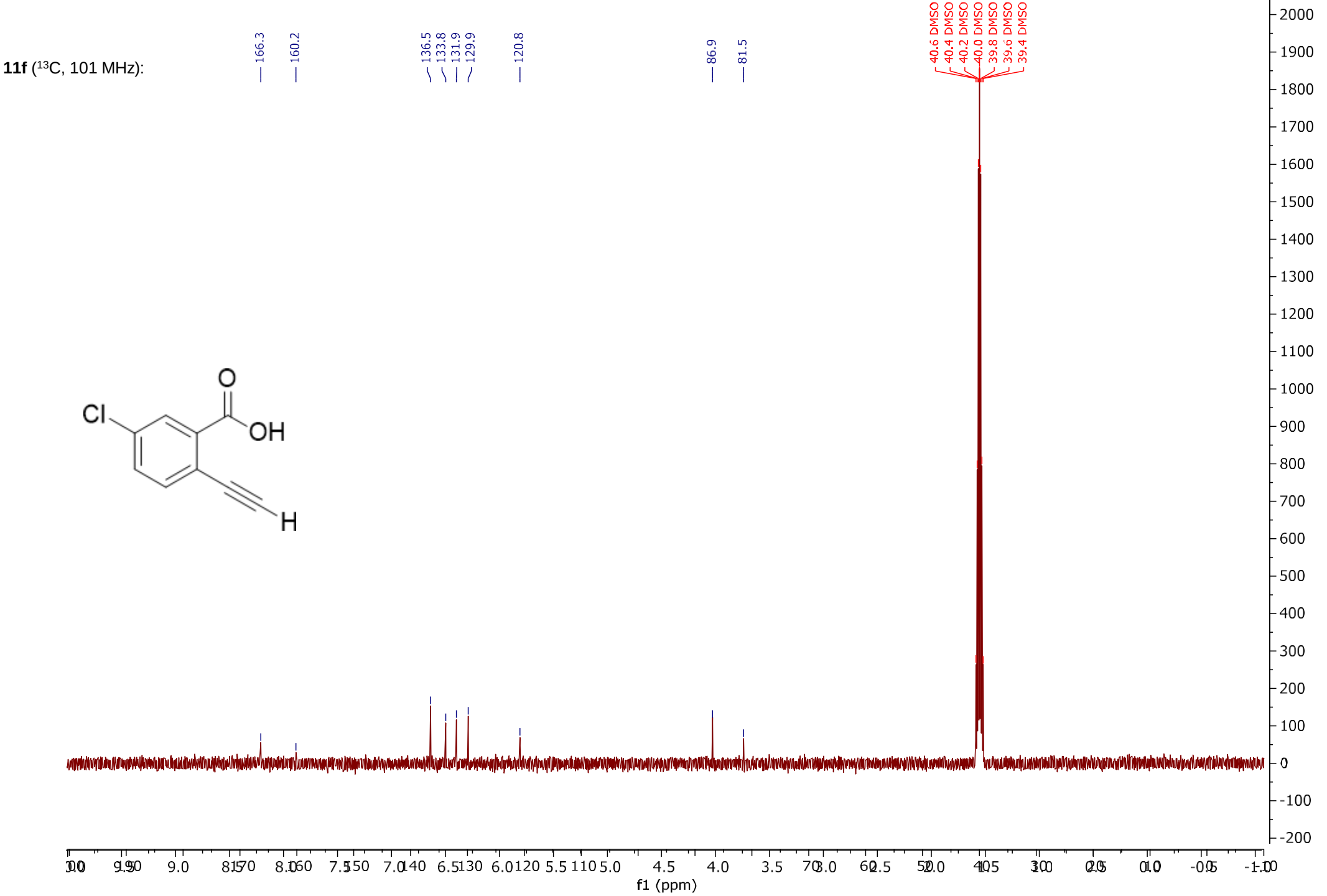
SI7f (^{13}C, 126 MHz):



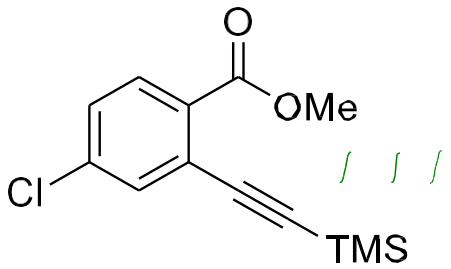
11f (^{1}H, 400 MHz):



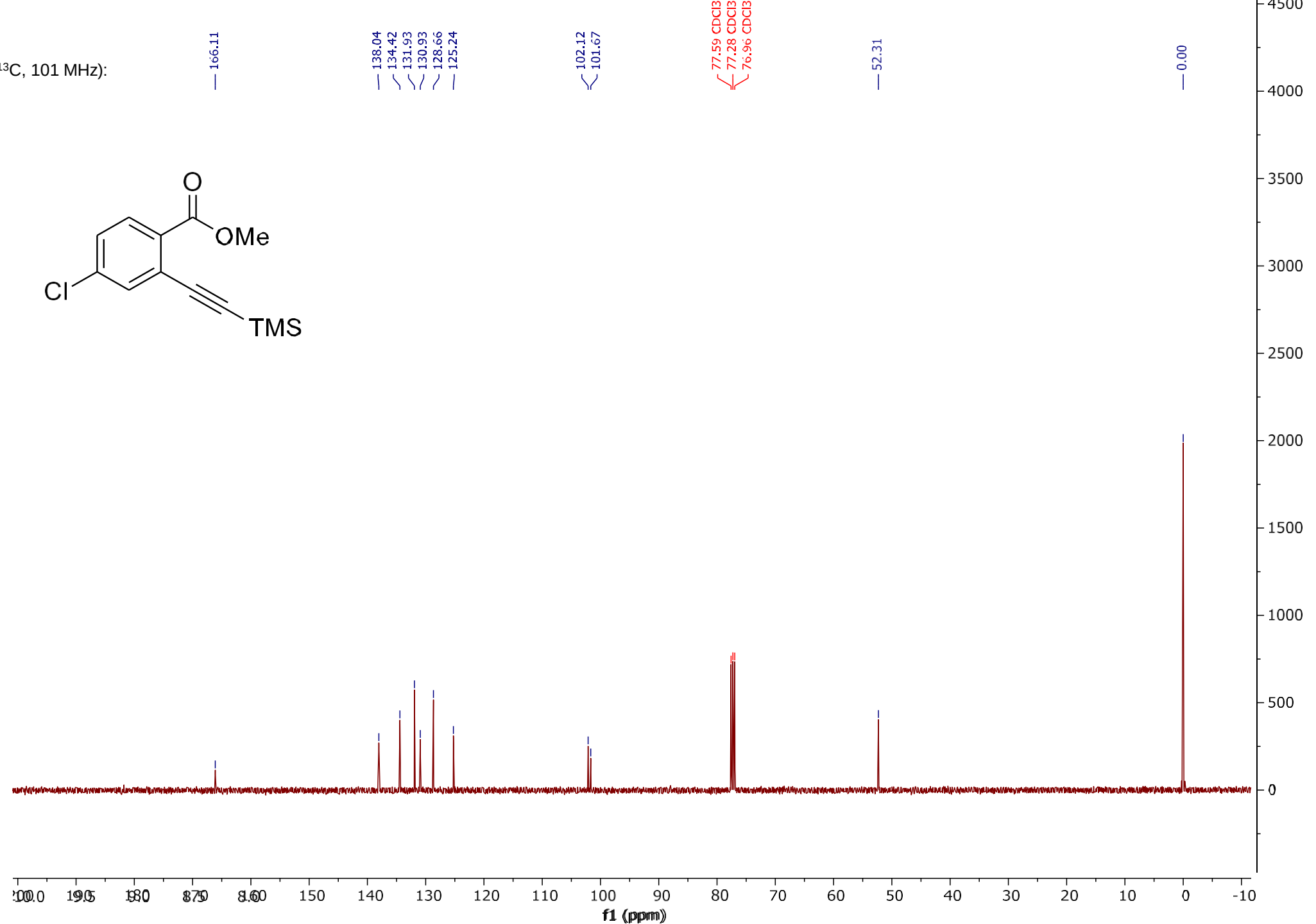
11f (^{13}C, 101 MHz):



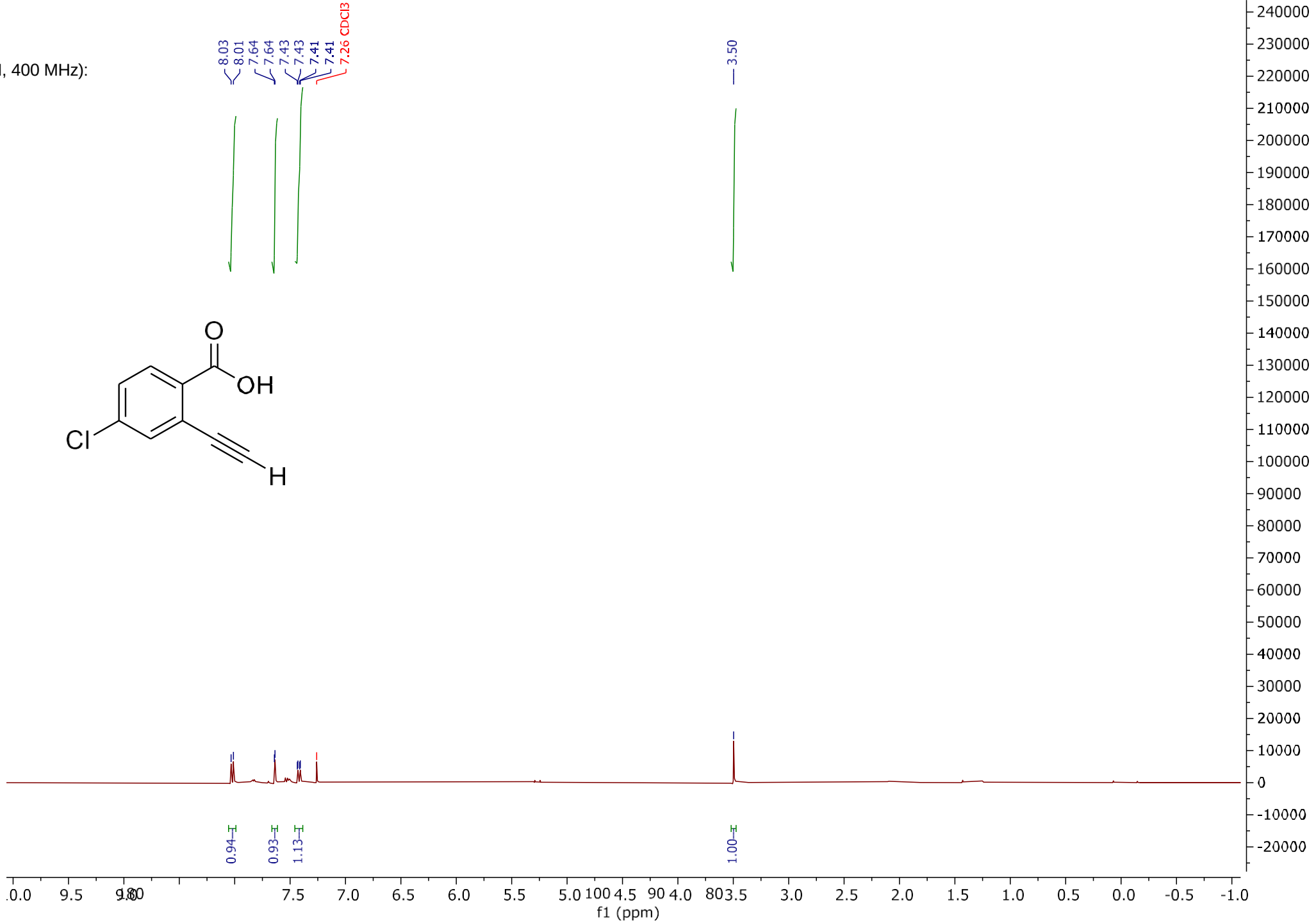
SI7g (^{1}H, 400 MHz):



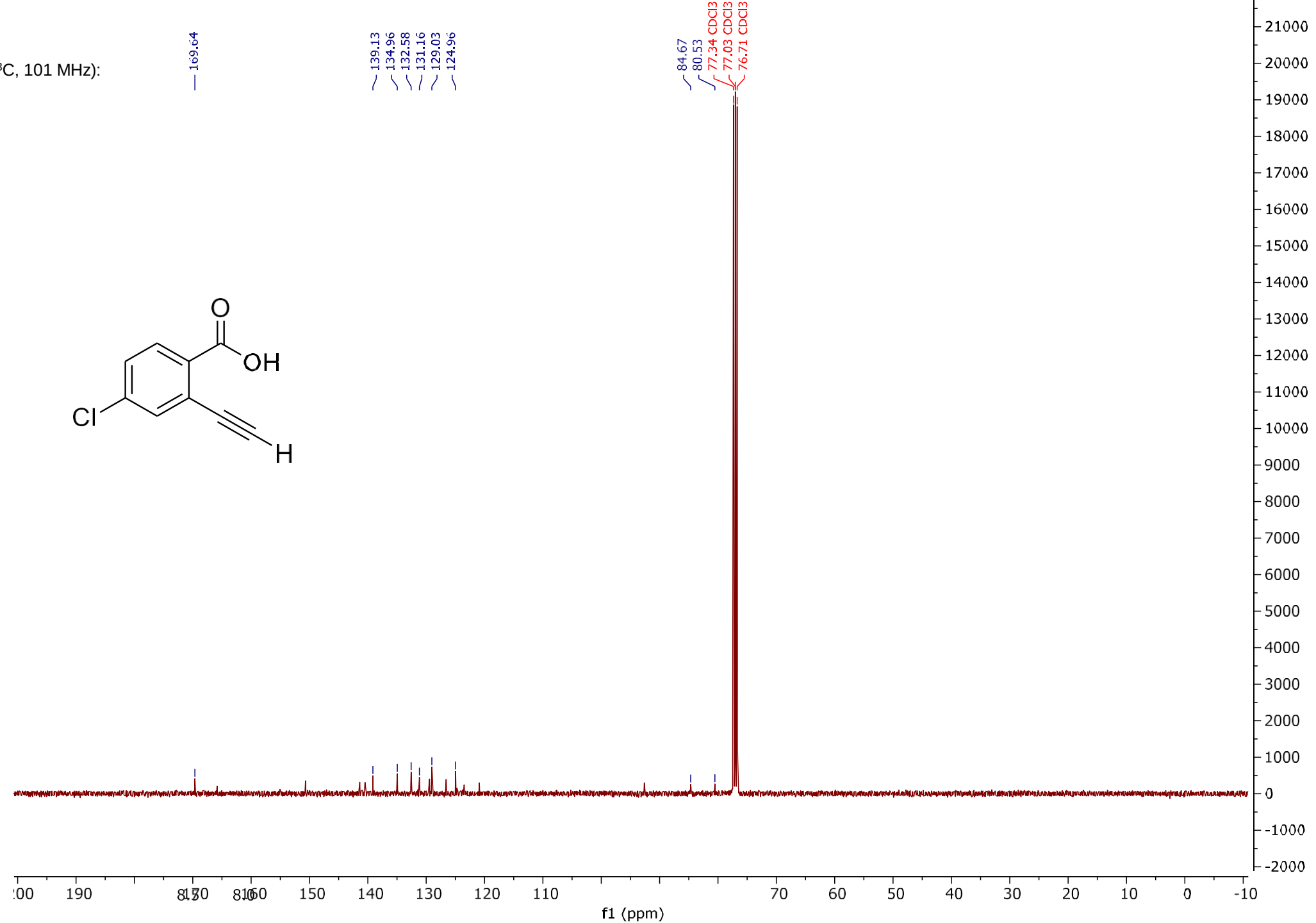
SI7g (^{13}C, 101 MHz):



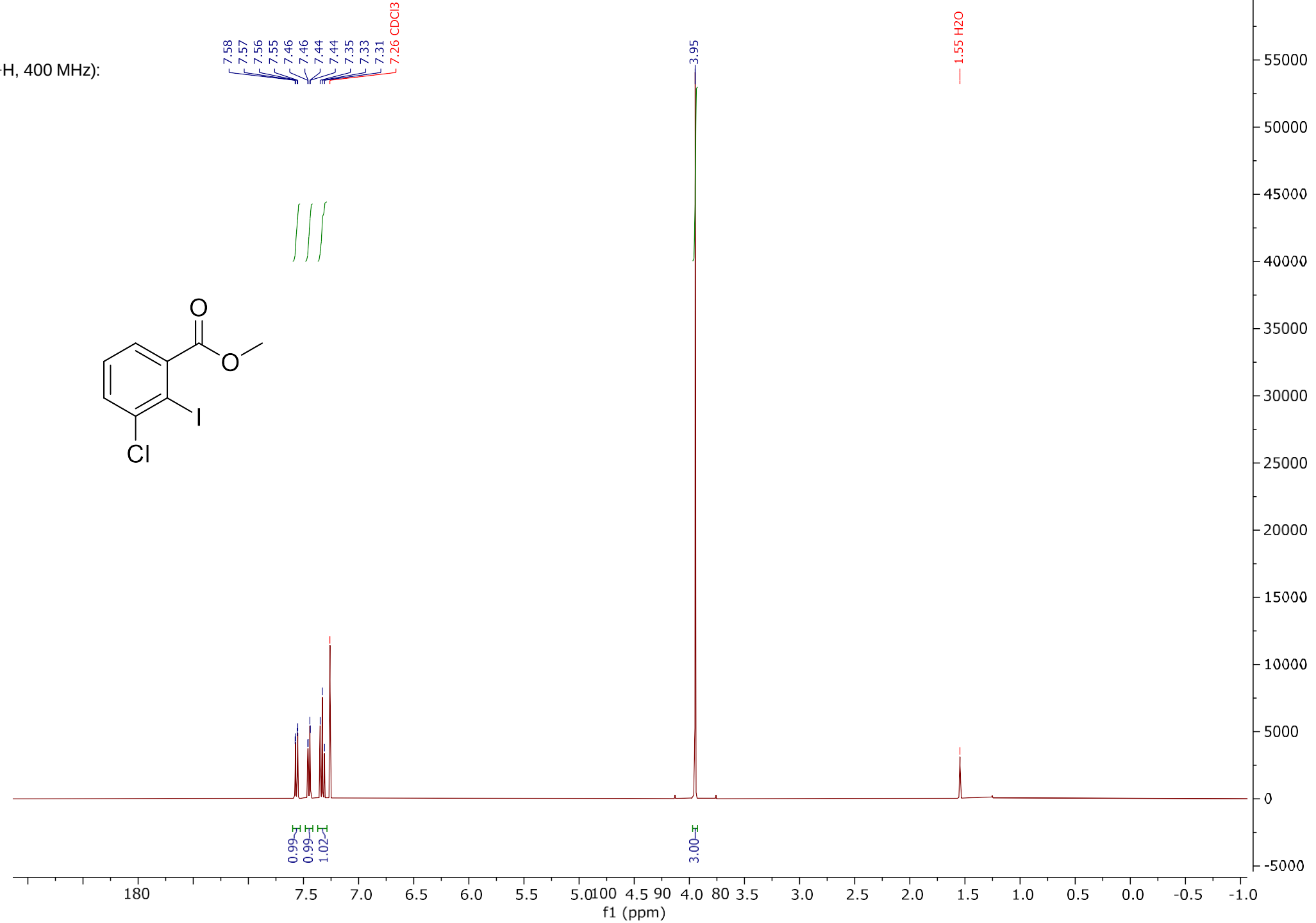
11g (^{1}H, 400 MHz):



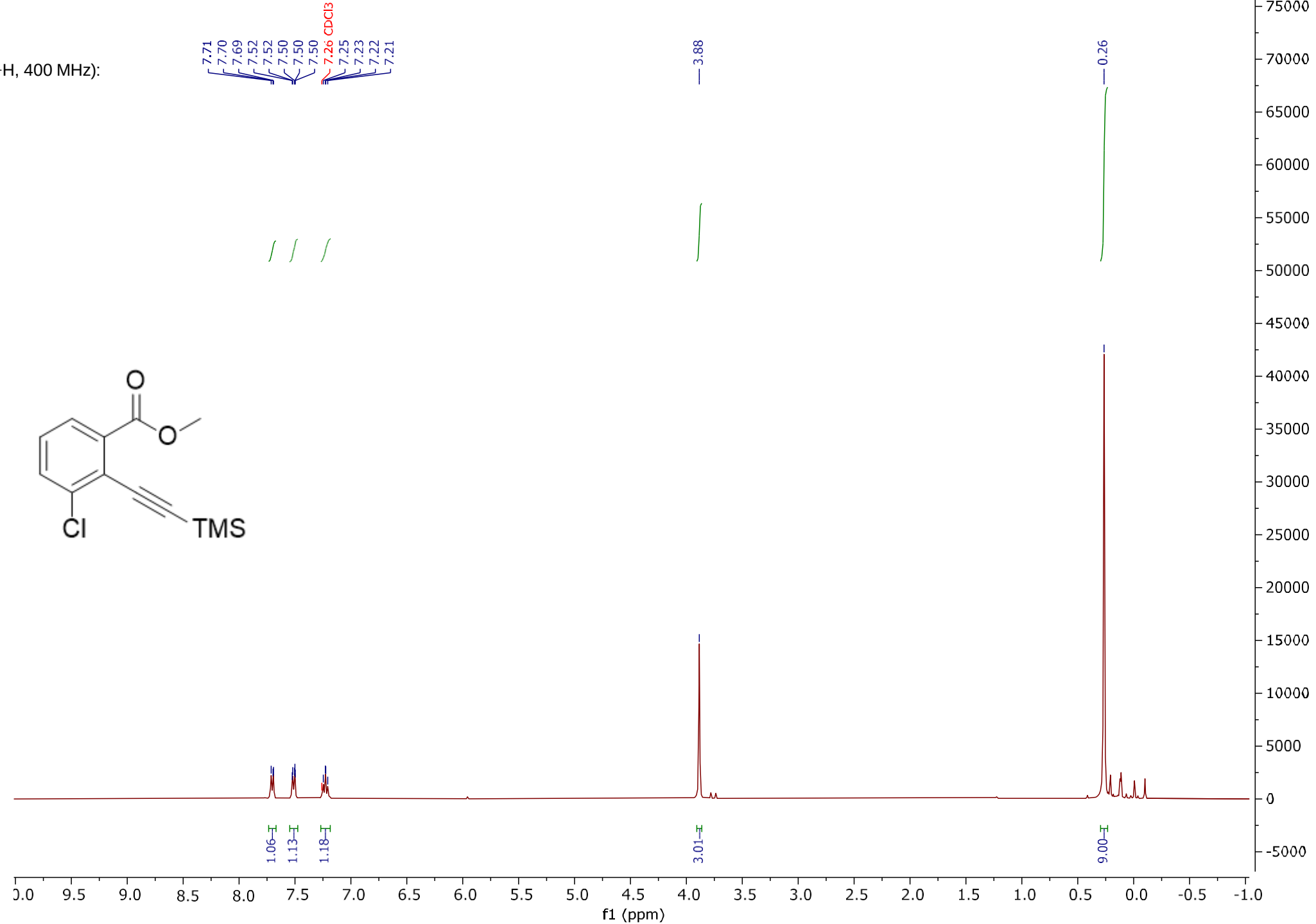
11g (^{13}C, 101 MHz):



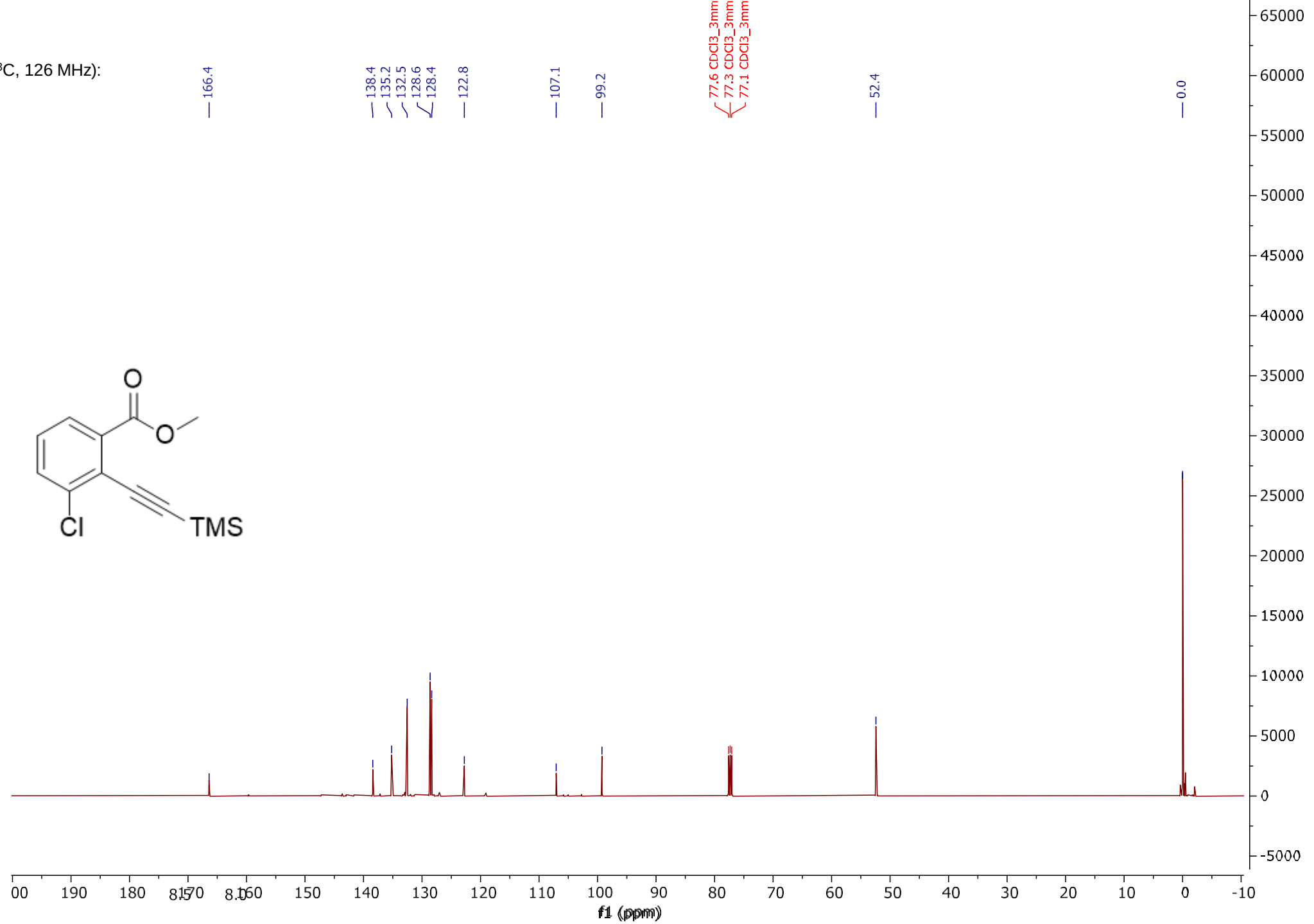
SI6h (^{1}H, 400 MHz):



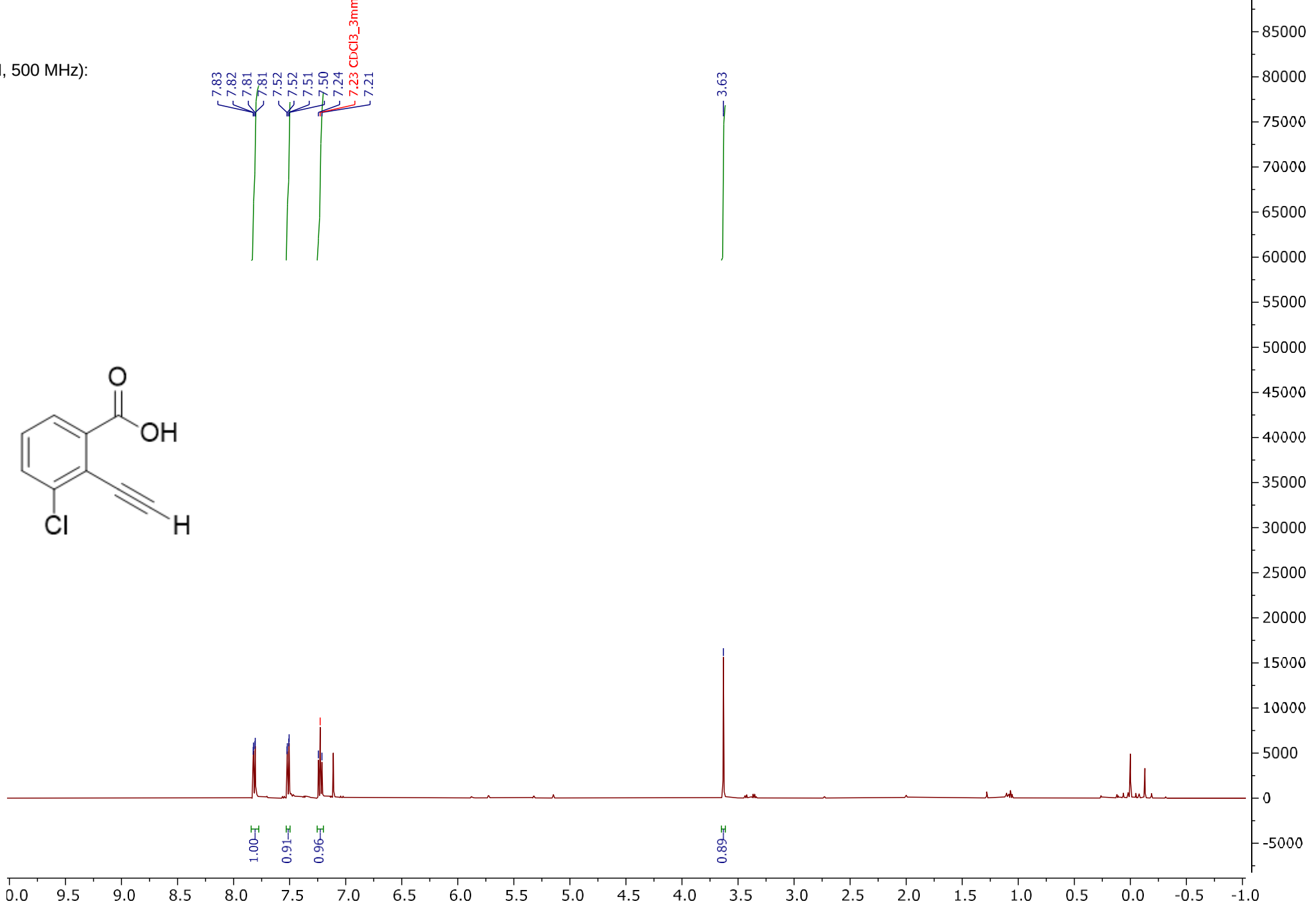
SI7h (^{1}H, 400 MHz):



SI7h (^{13}C, 126 MHz):

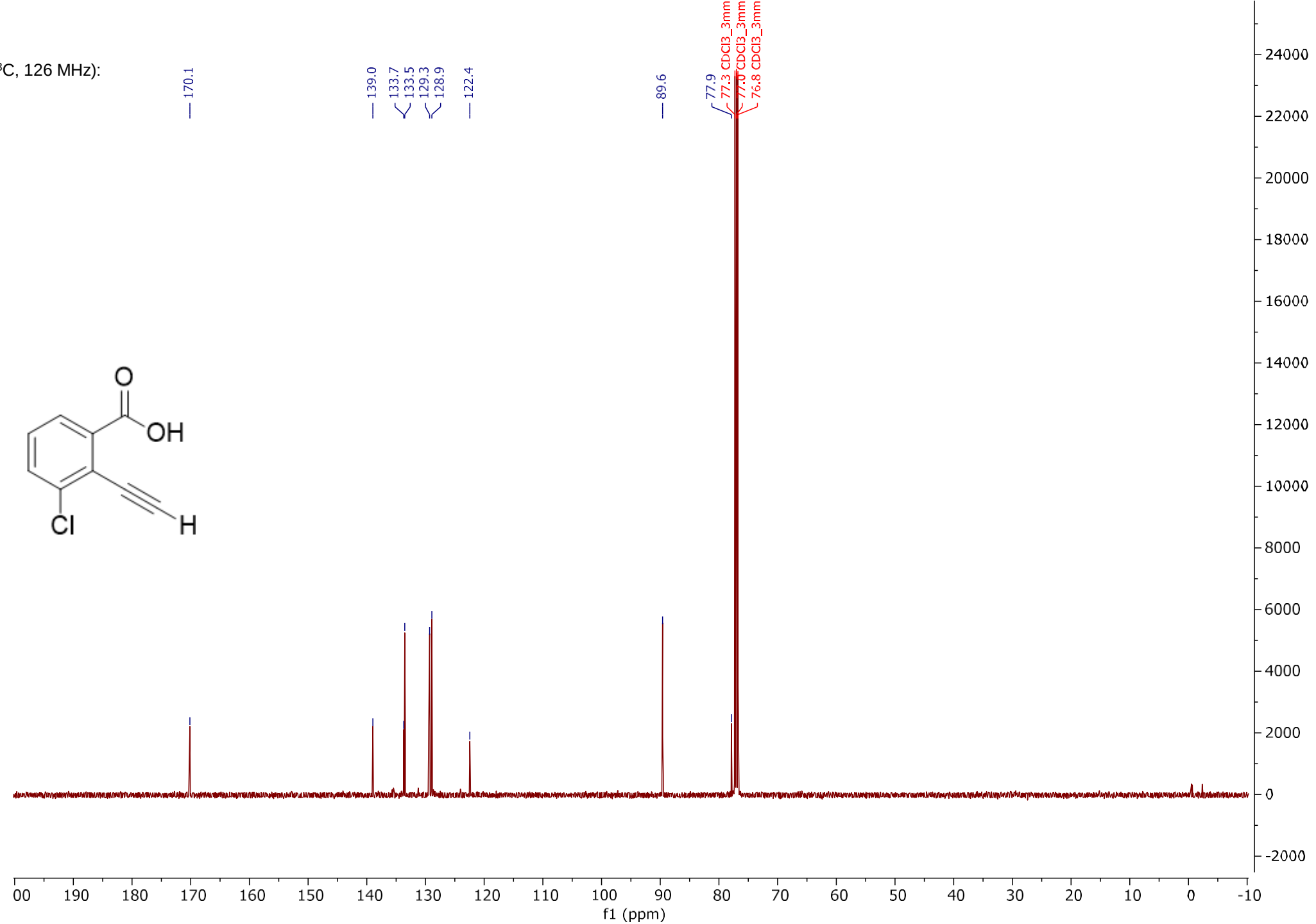


11h (^{1}H, 500 MHz):

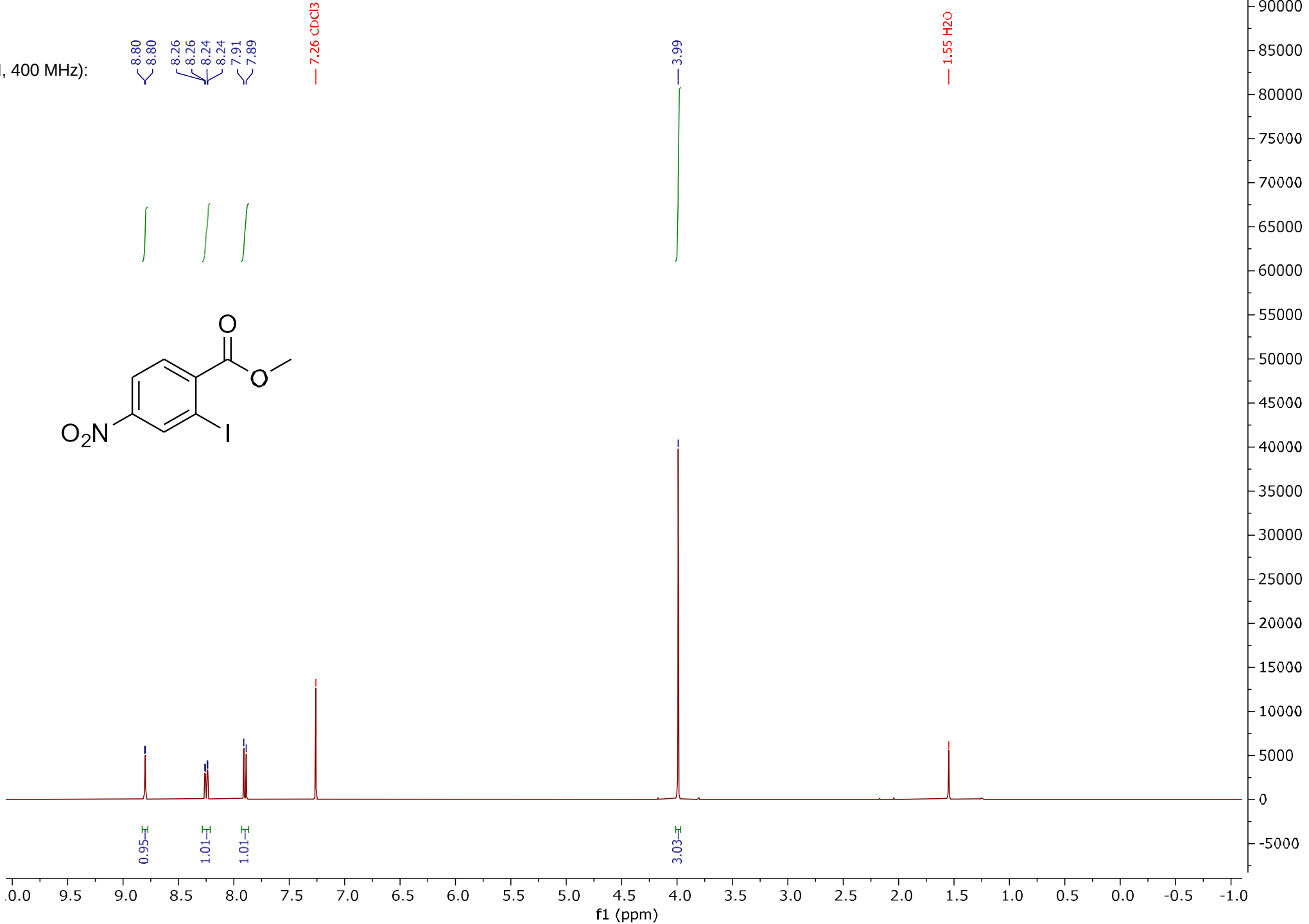


f1 (ppm)

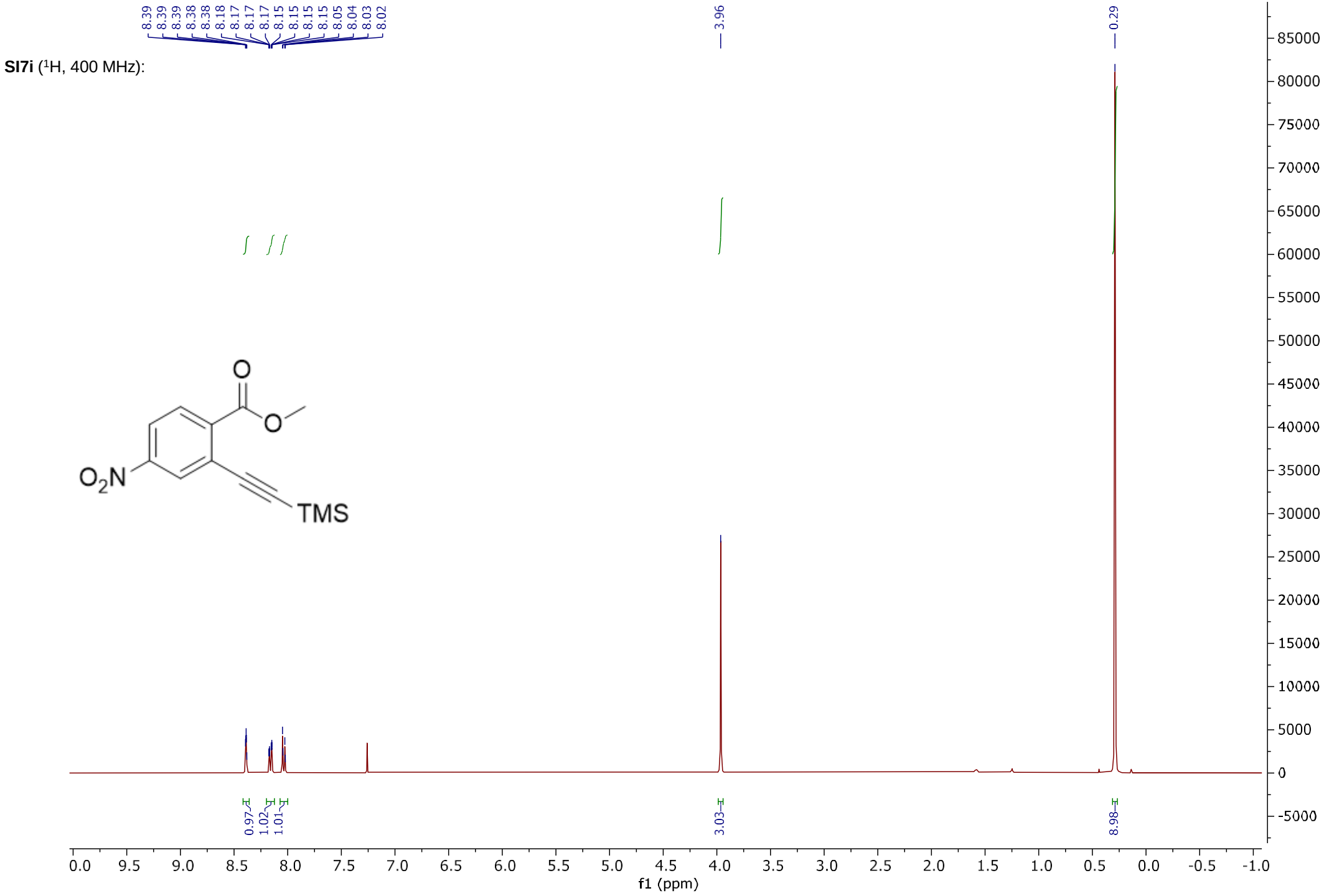
11h (^{13}C, 126 MHz):



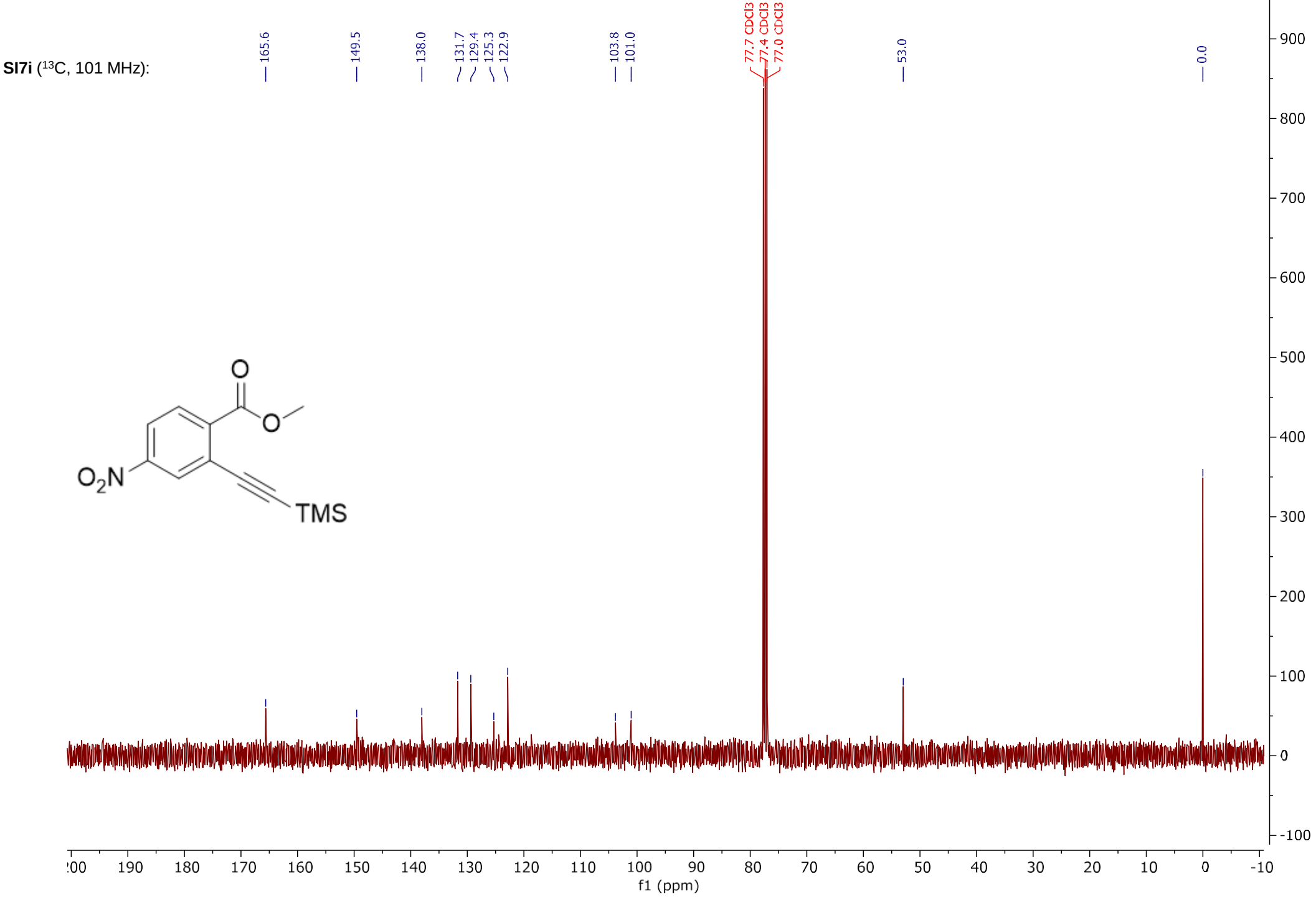
SI6i (^{1}H, 400 MHz):



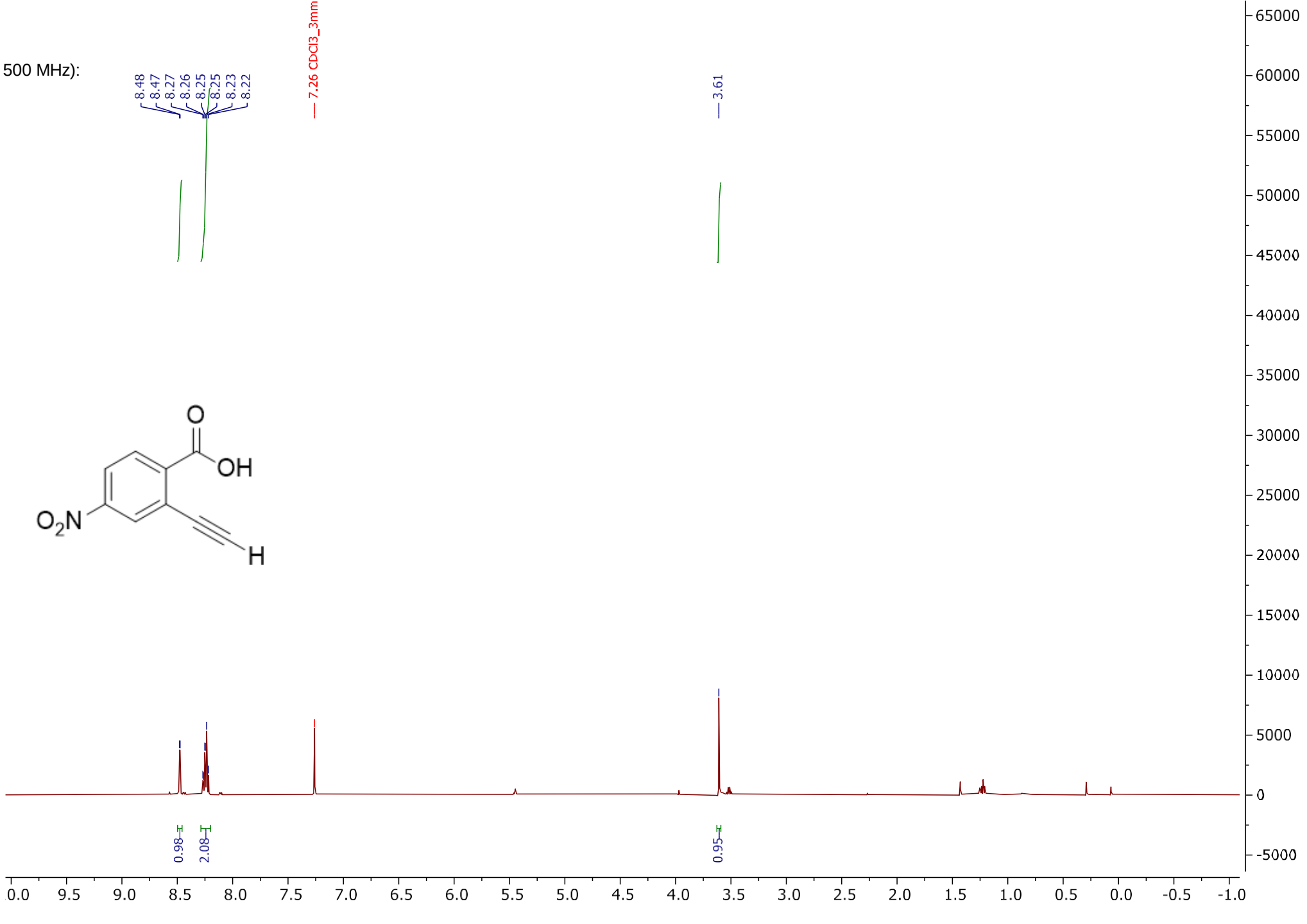
SI7i (^{1}H, 400 MHz):



SI7i (^{13}C, 101 MHz):

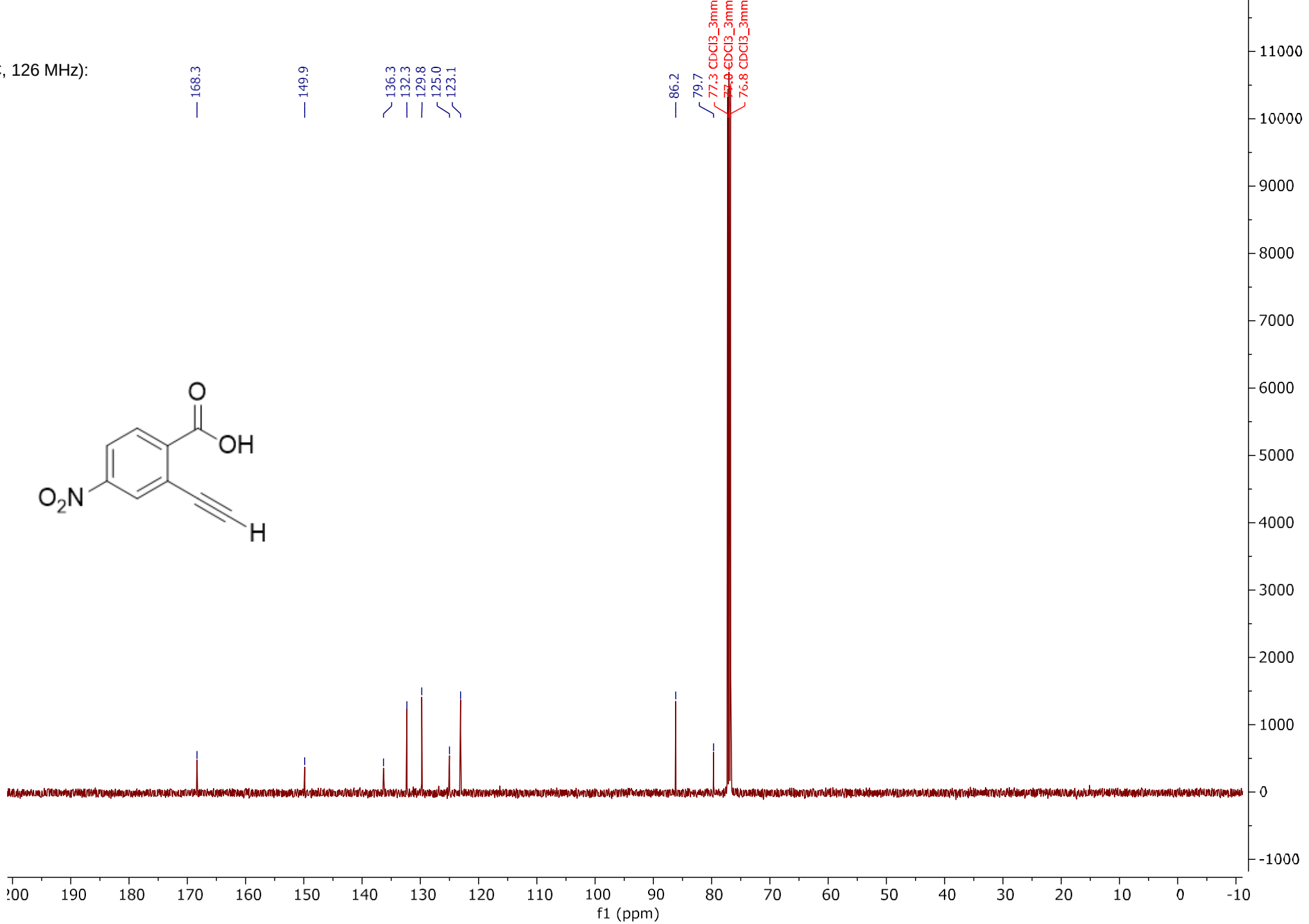


11i (^{1}H, 500 MHz):

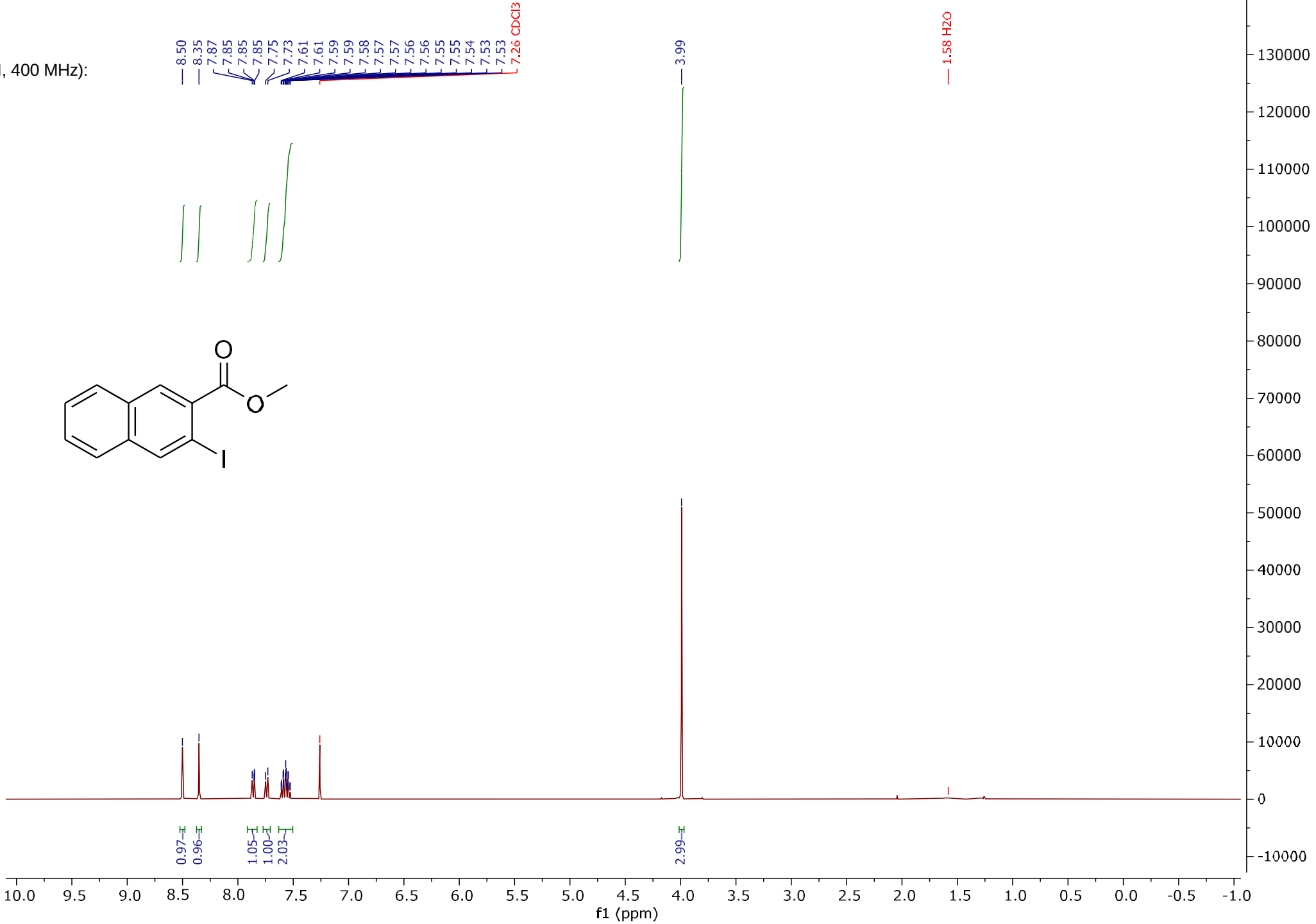


f1 (ppm)

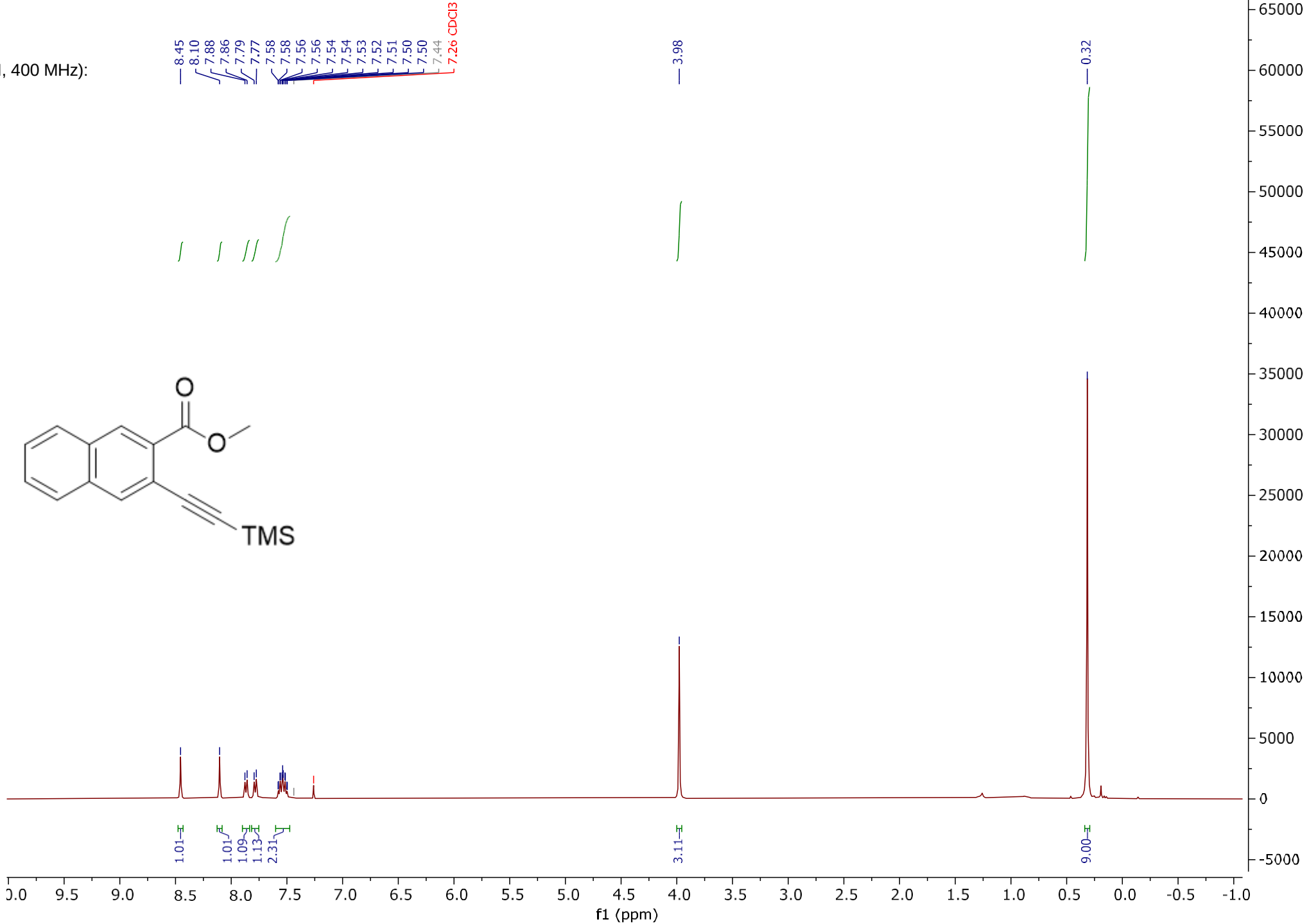
11i (^{13}C, 126 MHz):



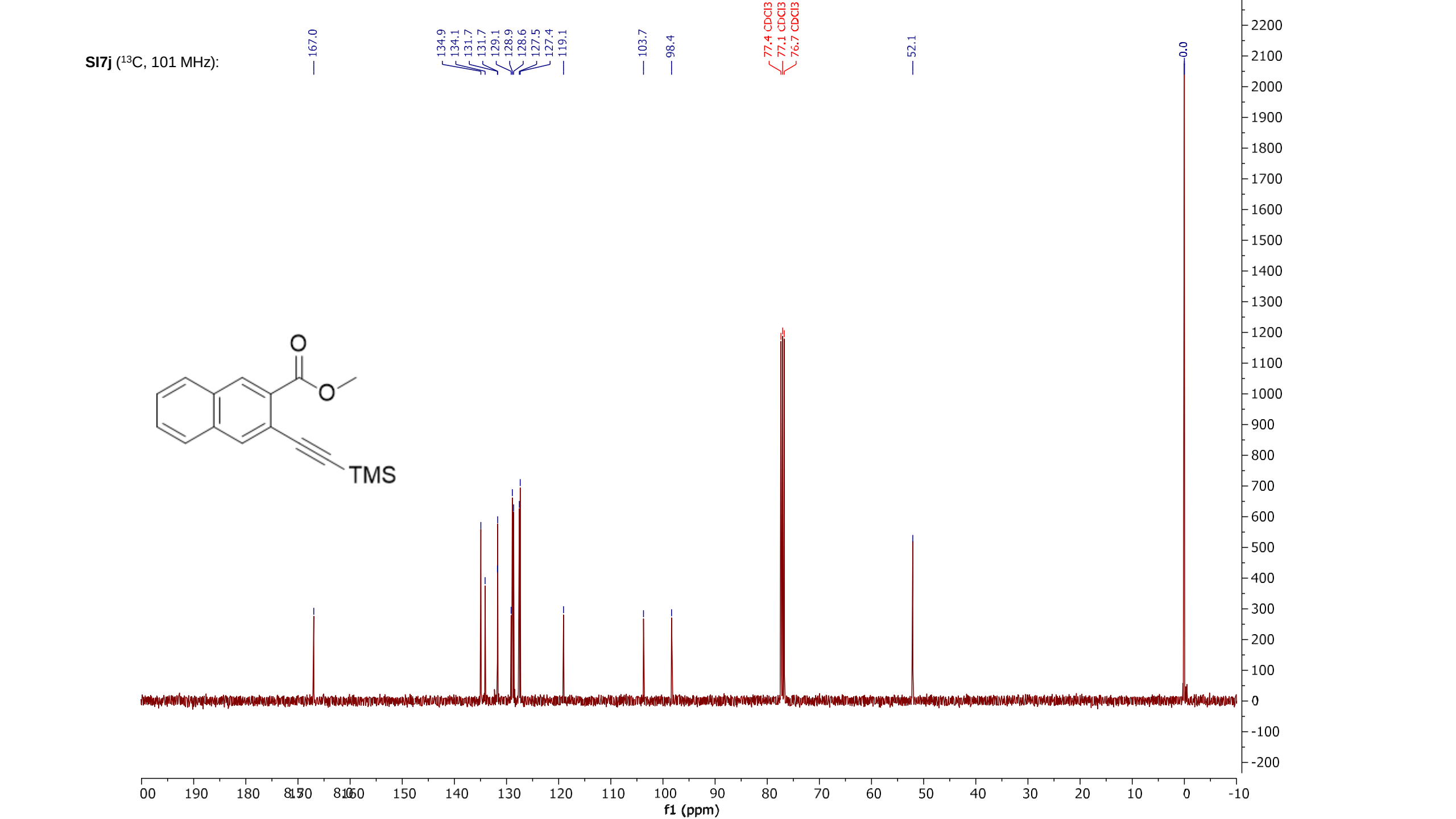
SI6j (^{1}H, 400 MHz):



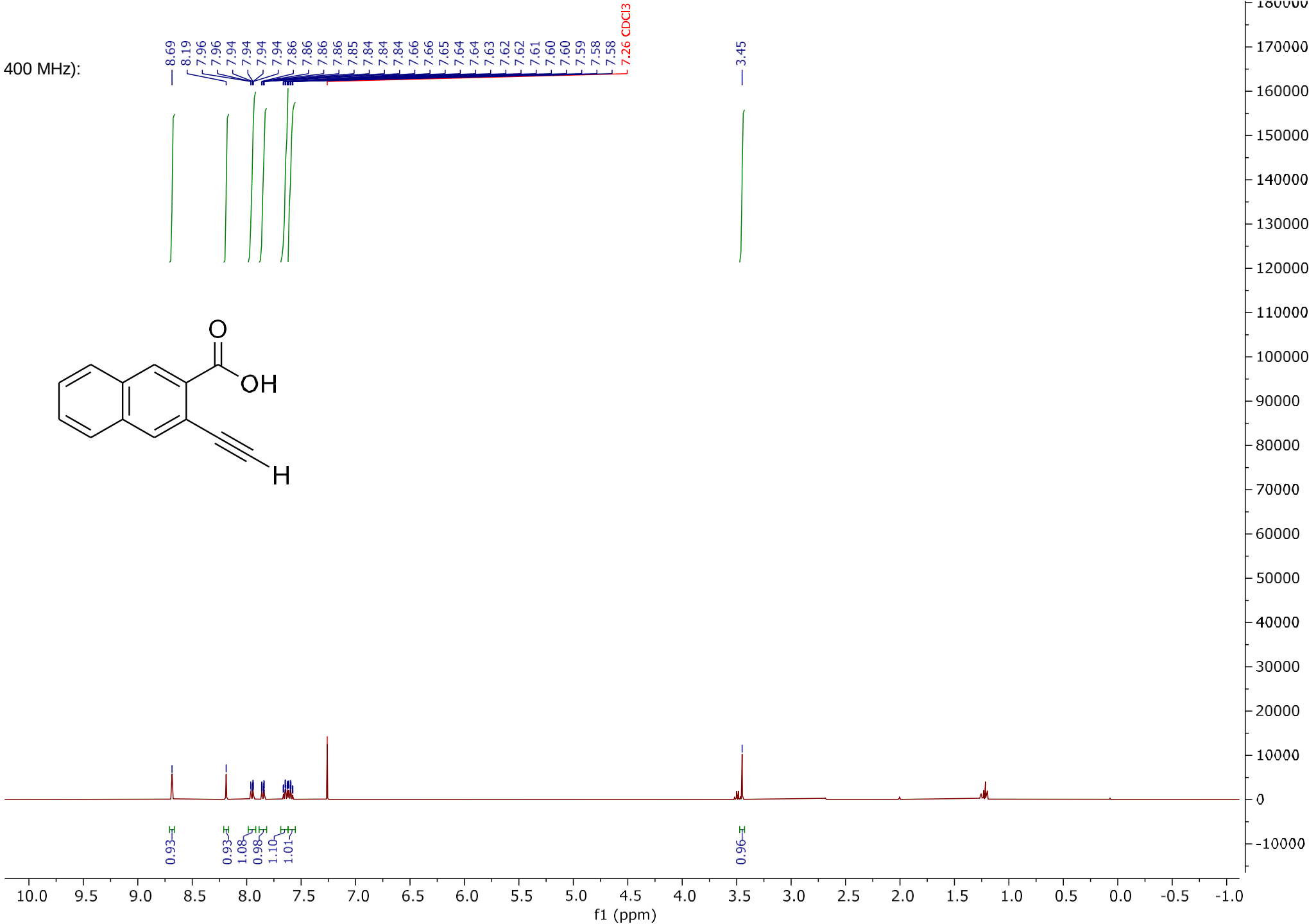
SI7j (^{1}H, 400 MHz):



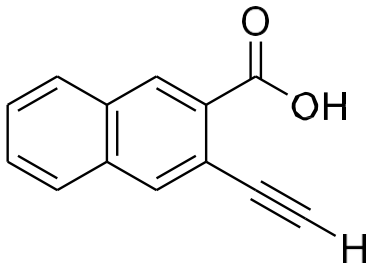
SI7j (^{13}C, 101 MHz):



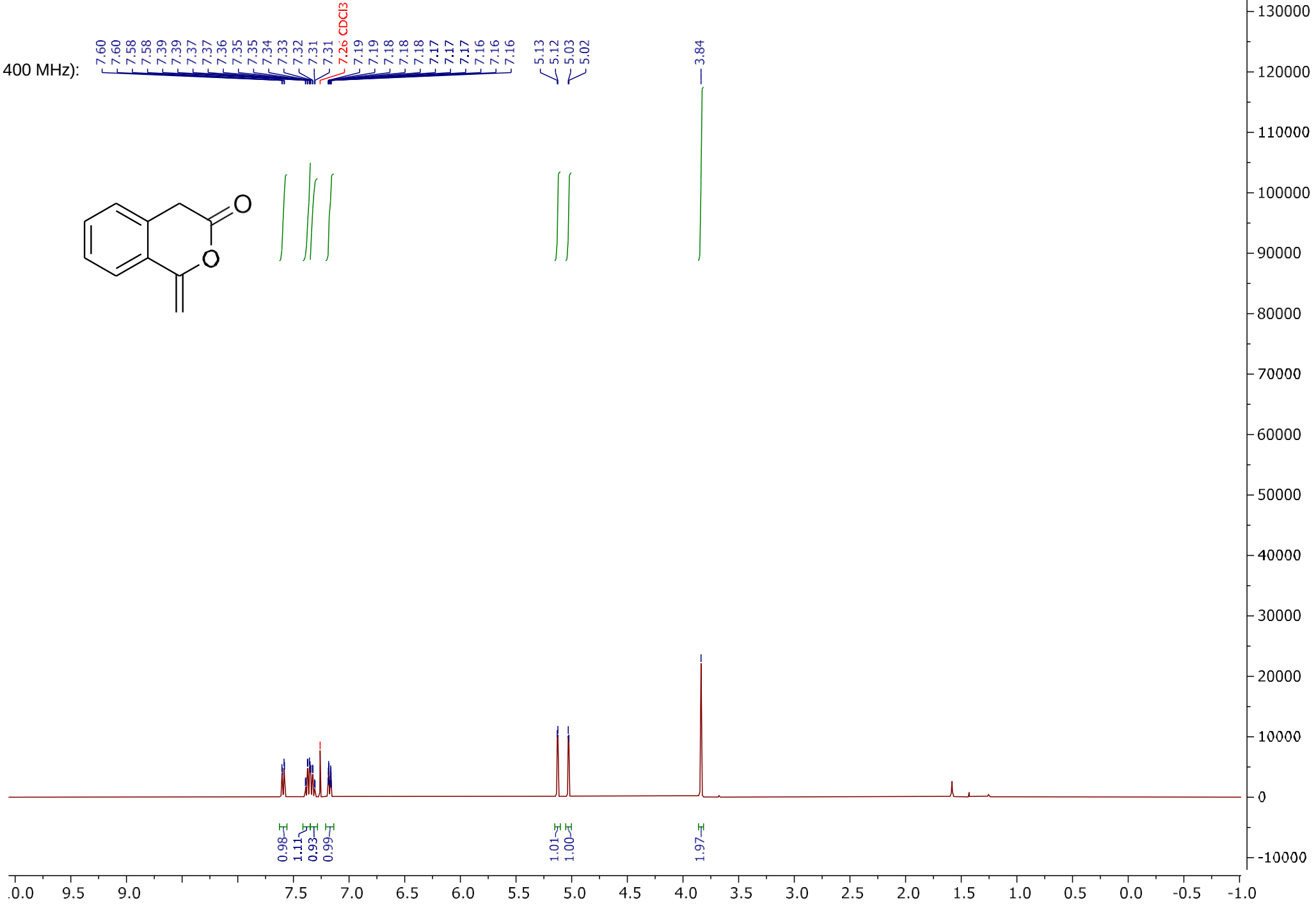
11j (^{1}H, 400 MHz):



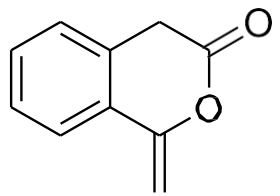
11j (^{13}C, 101 MHz):



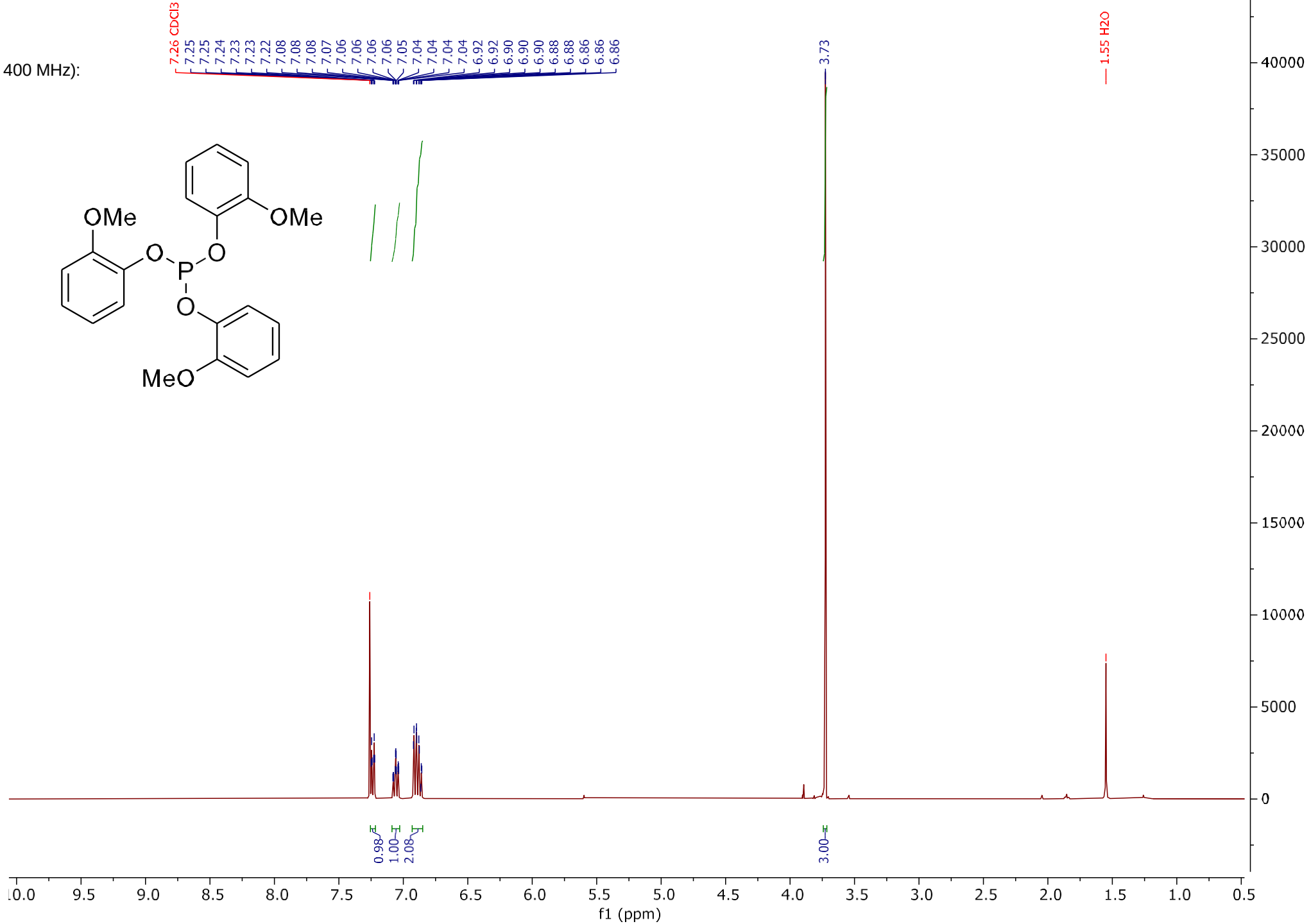
2a (^{1}H, 400 MHz):


7.60
7.60
7.58
7.58
7.39
7.39
7.37
7.37
7.36
7.35
7.35
7.34
7.33
7.32
7.31
7.31
7.26 CDCl3
7.19
7.19
7.18
7.18
7.18
7.17
7.17
7.17
7.16
7.16
7.16
5.13
5.12
5.03
5.02
3.84
O
O
0.98
1.11
0.93
0.99
1.01
1.00
1.97
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
.0.0
9.5
9.0
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
-1.0

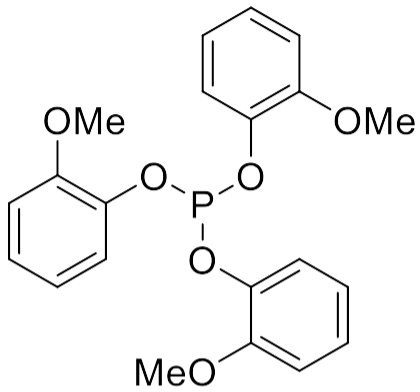
2a (^{13}C, 101 MHz):



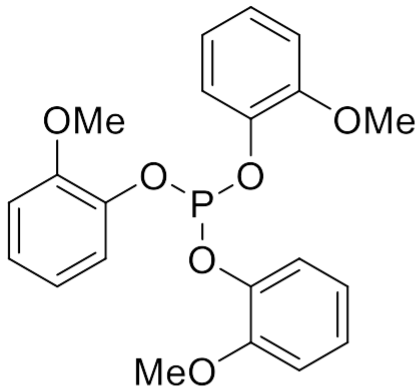
L1 (^{1}H, 400 MHz):


7.26 CDCl3
7.25
7.25
7.24
7.23
7.23
7.22
7.08
7.08
7.08
7.07
7.06
7.06
7.06
7.06
7.05
7.04
7.04
7.04
7.04
6.92
6.92
6.90
6.90
6.90
6.88
6.88
6.86
6.86
6.86
3.73
1.55 H2O
OMe
OMe
O
O
P
O
MeO
40000
35000
30000
25000
20000
15000
10000
5000
0
0.98
1.00
2.08
3.00
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)

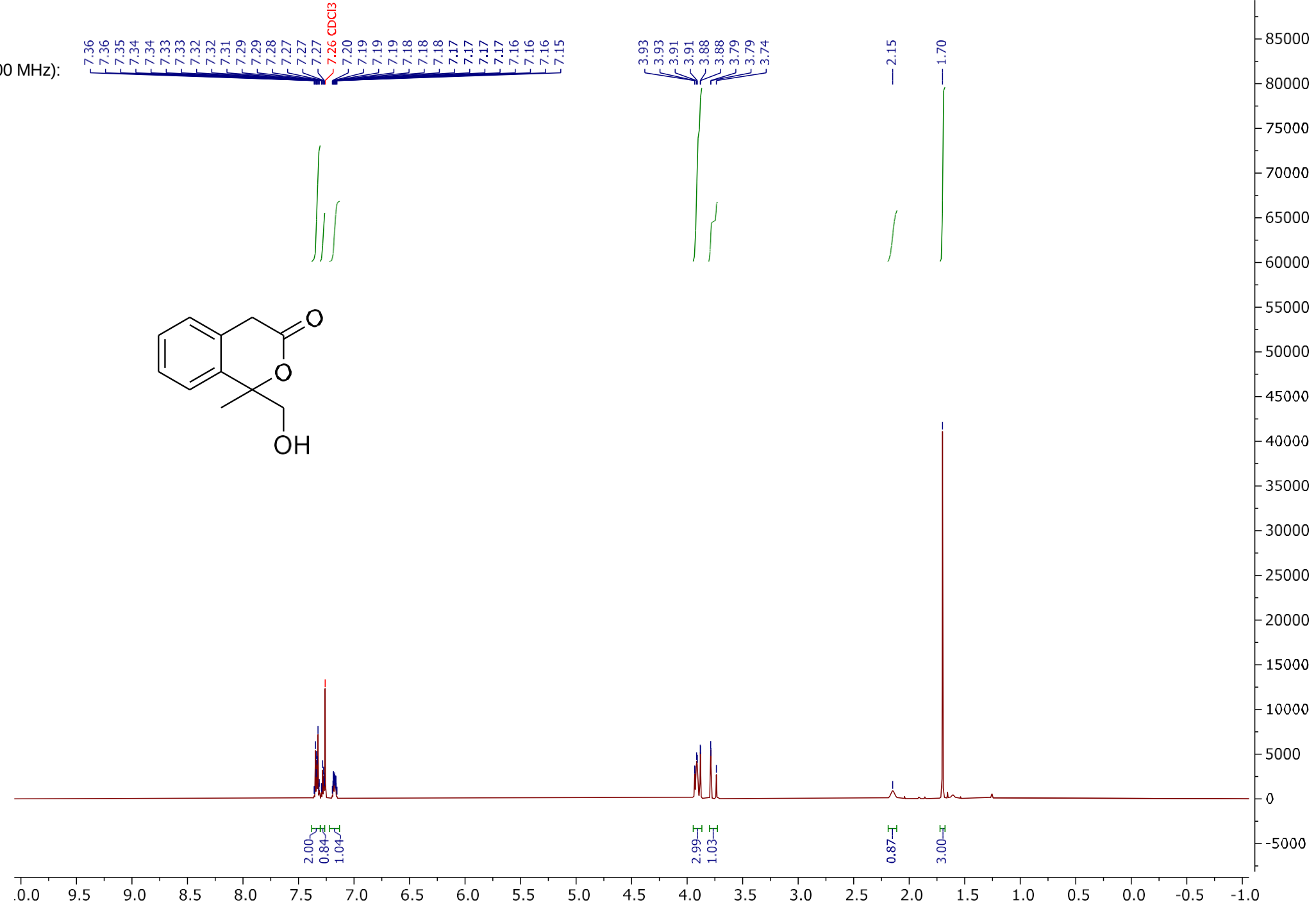
L1 (^{13}C, 126 MHz):



L1 (^{31}P, 162 MHz):

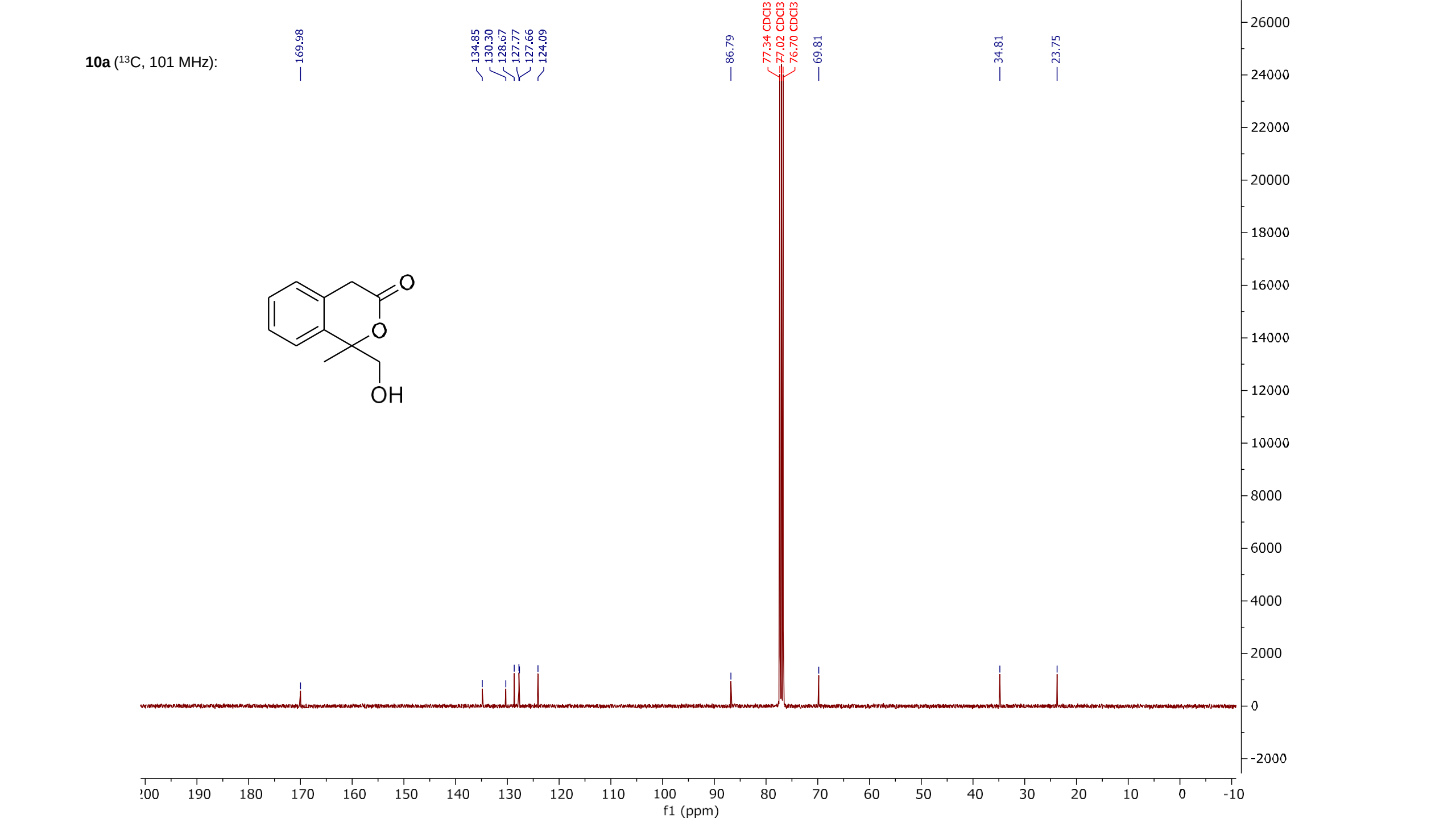


10a (^{1}H, 400 MHz):

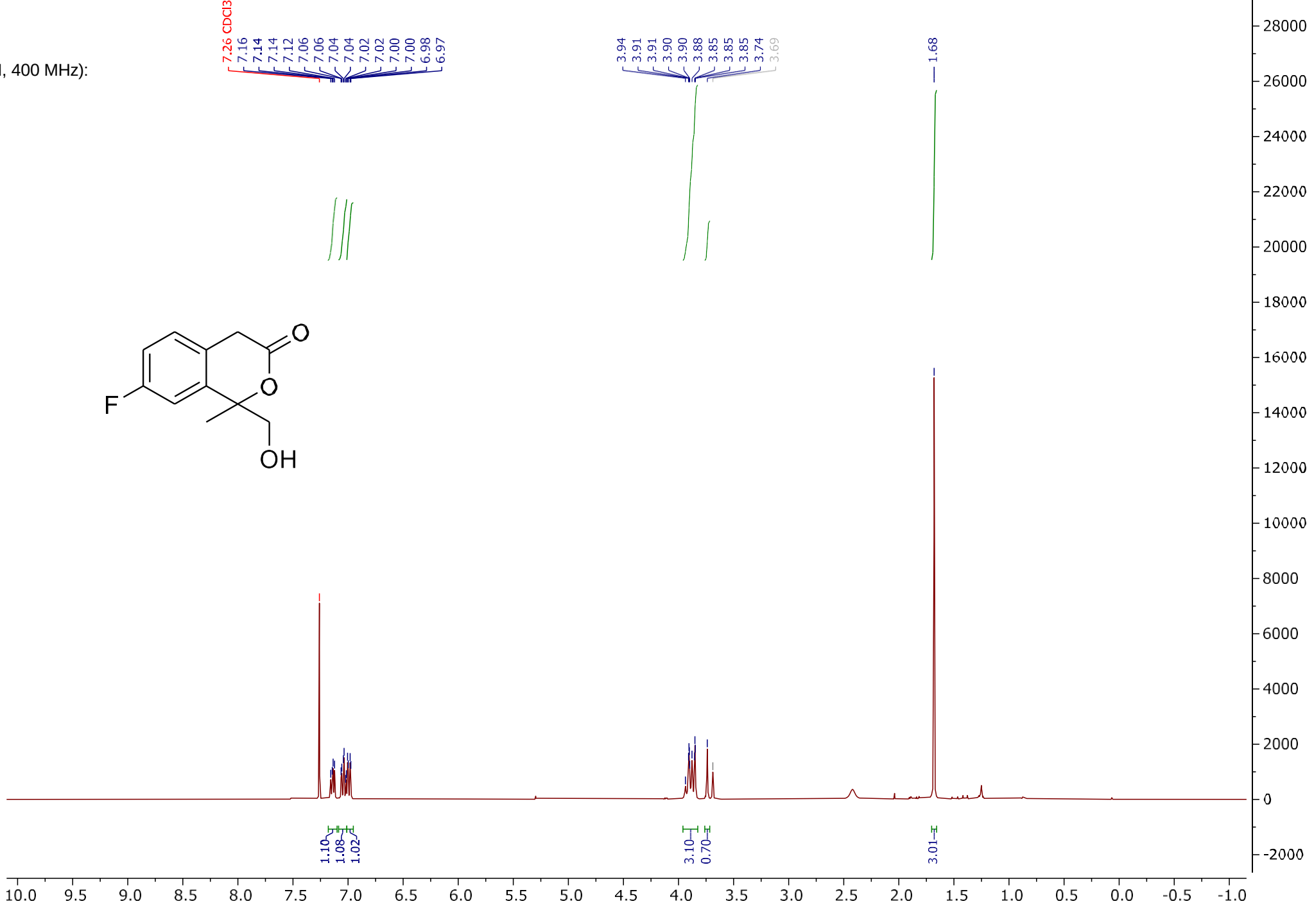


f1 (ppm)

10a (^{13}C, 101 MHz):

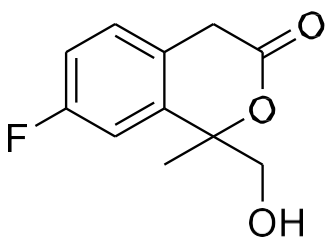


10d (^{1}H, 400 MHz):

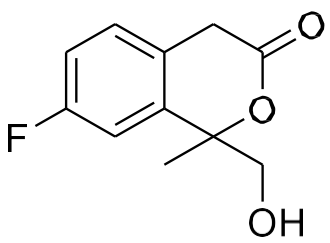


f1 (ppm)

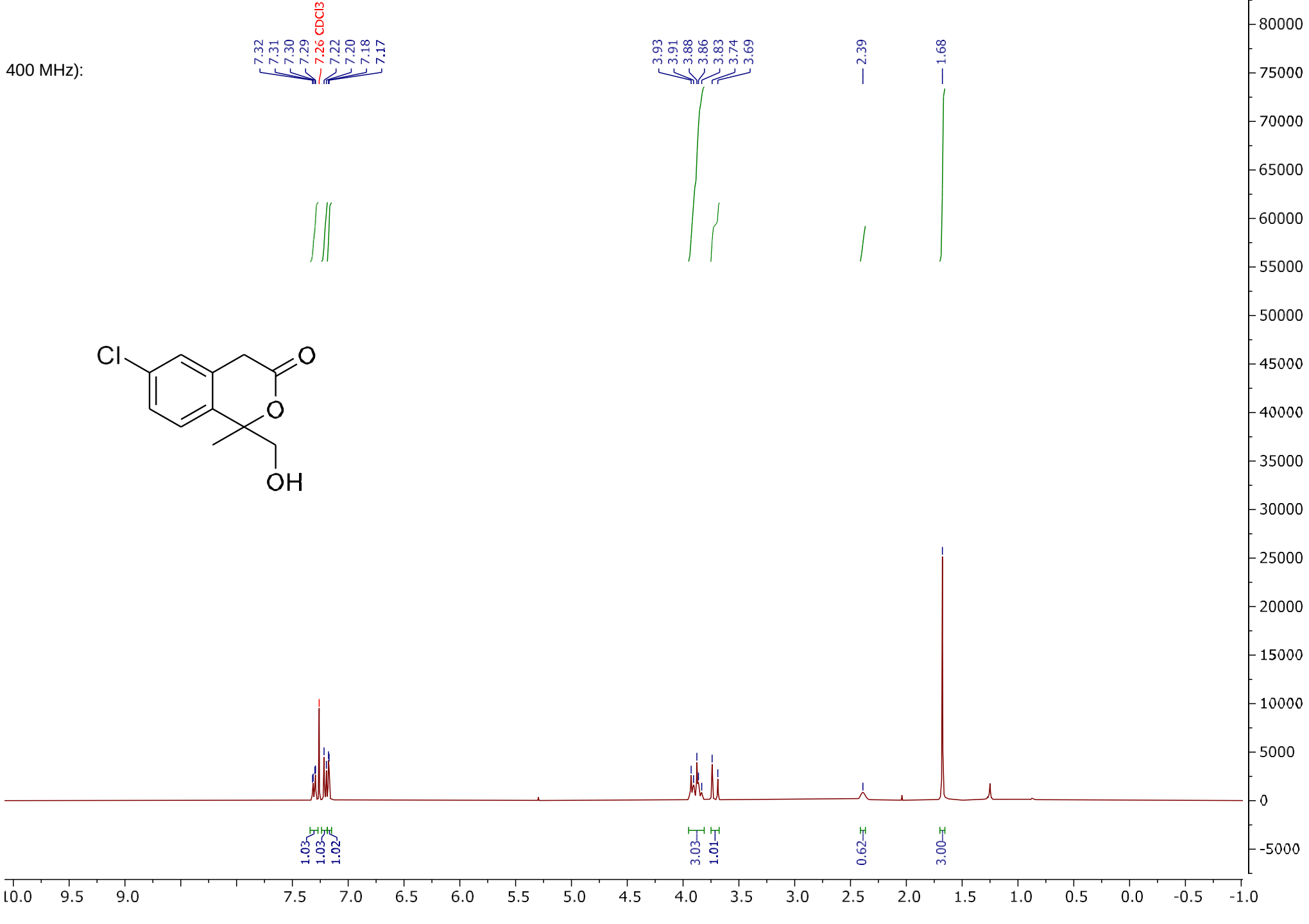
10d (^{13}C, 101 MHz):



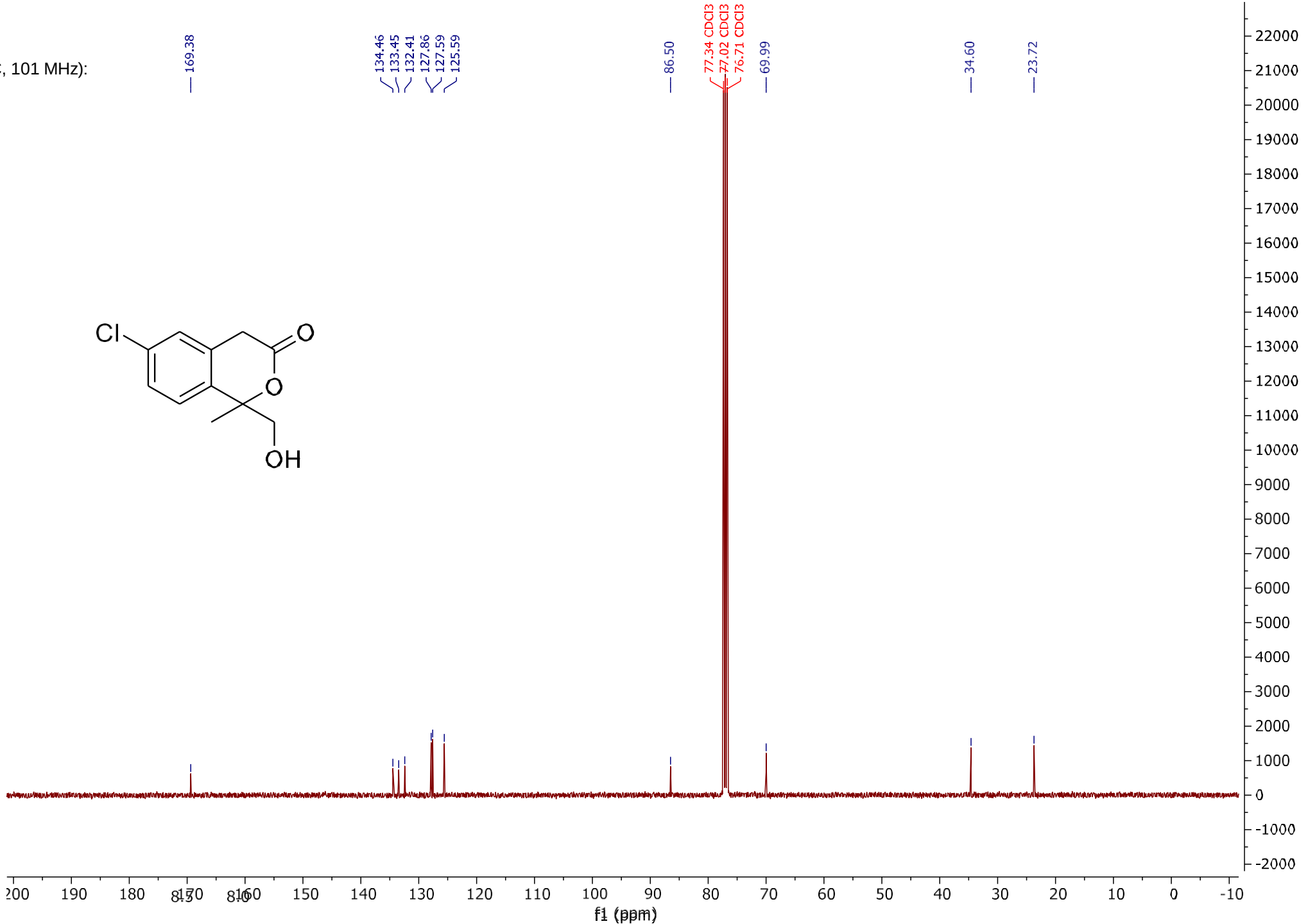
10d (^{19}F, 376 MHz):



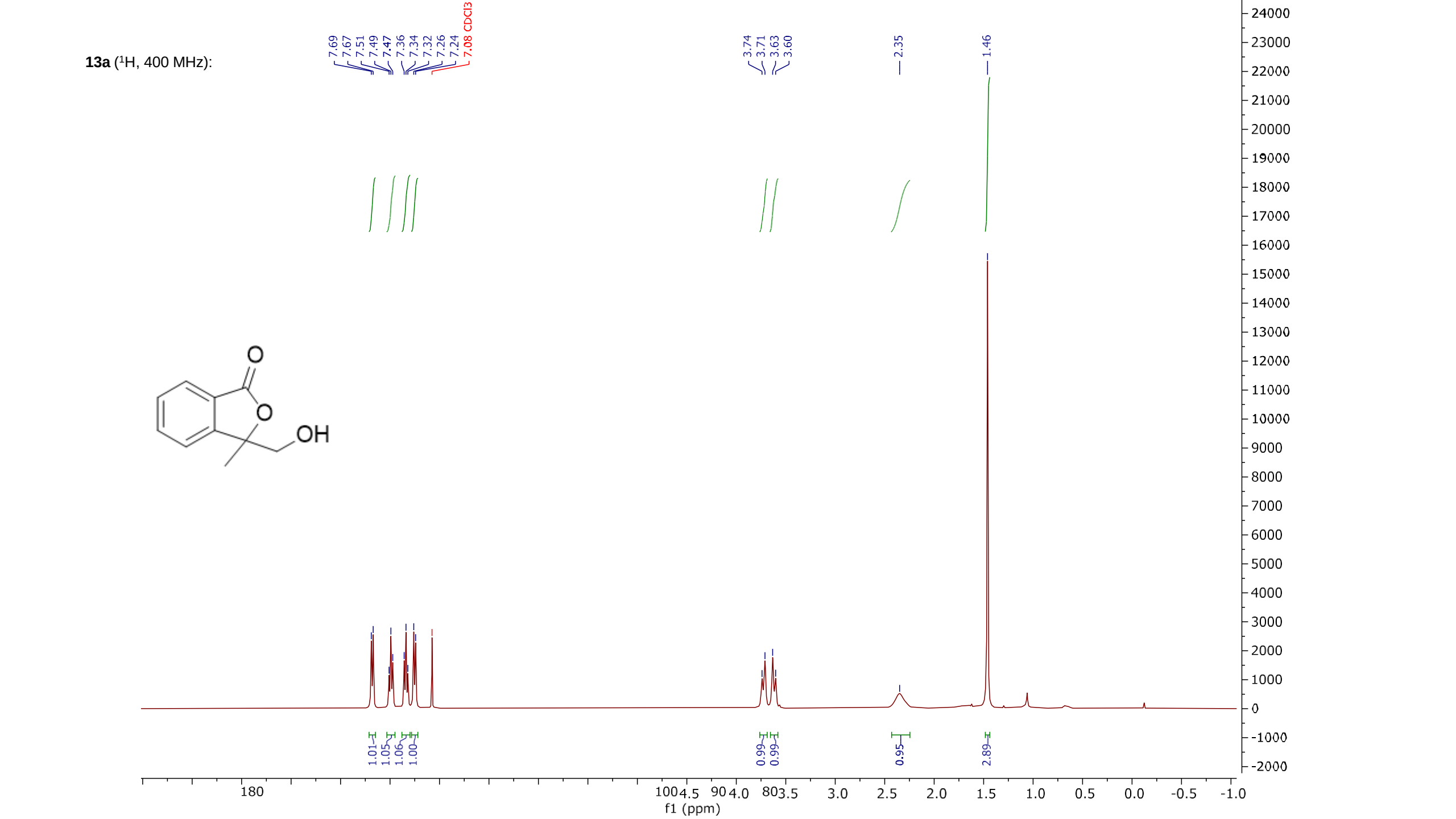
10f (^{1}H, 400 MHz):



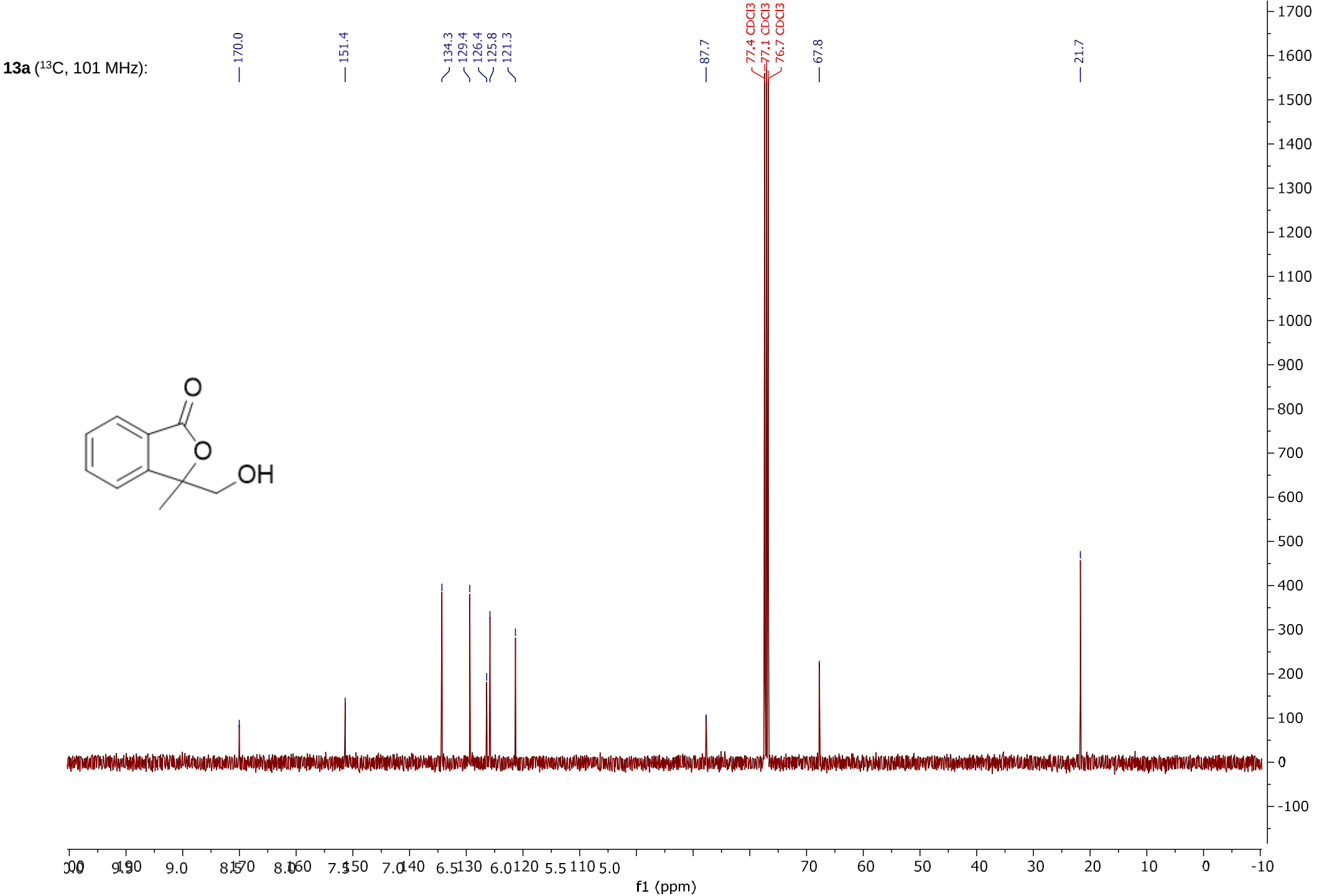
10f (^{13}C, 101 MHz):



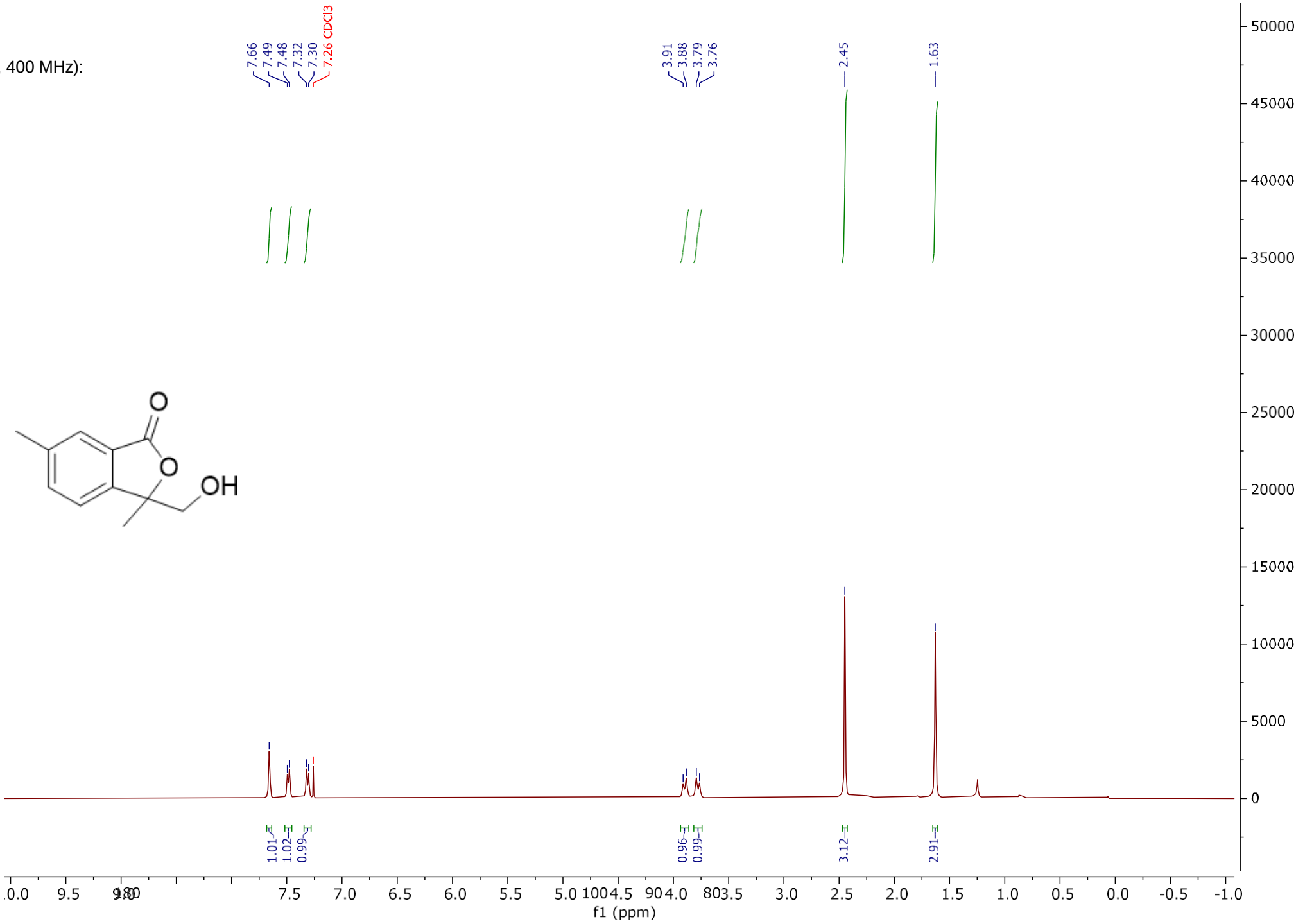
13a (^{1}H, 400 MHz):



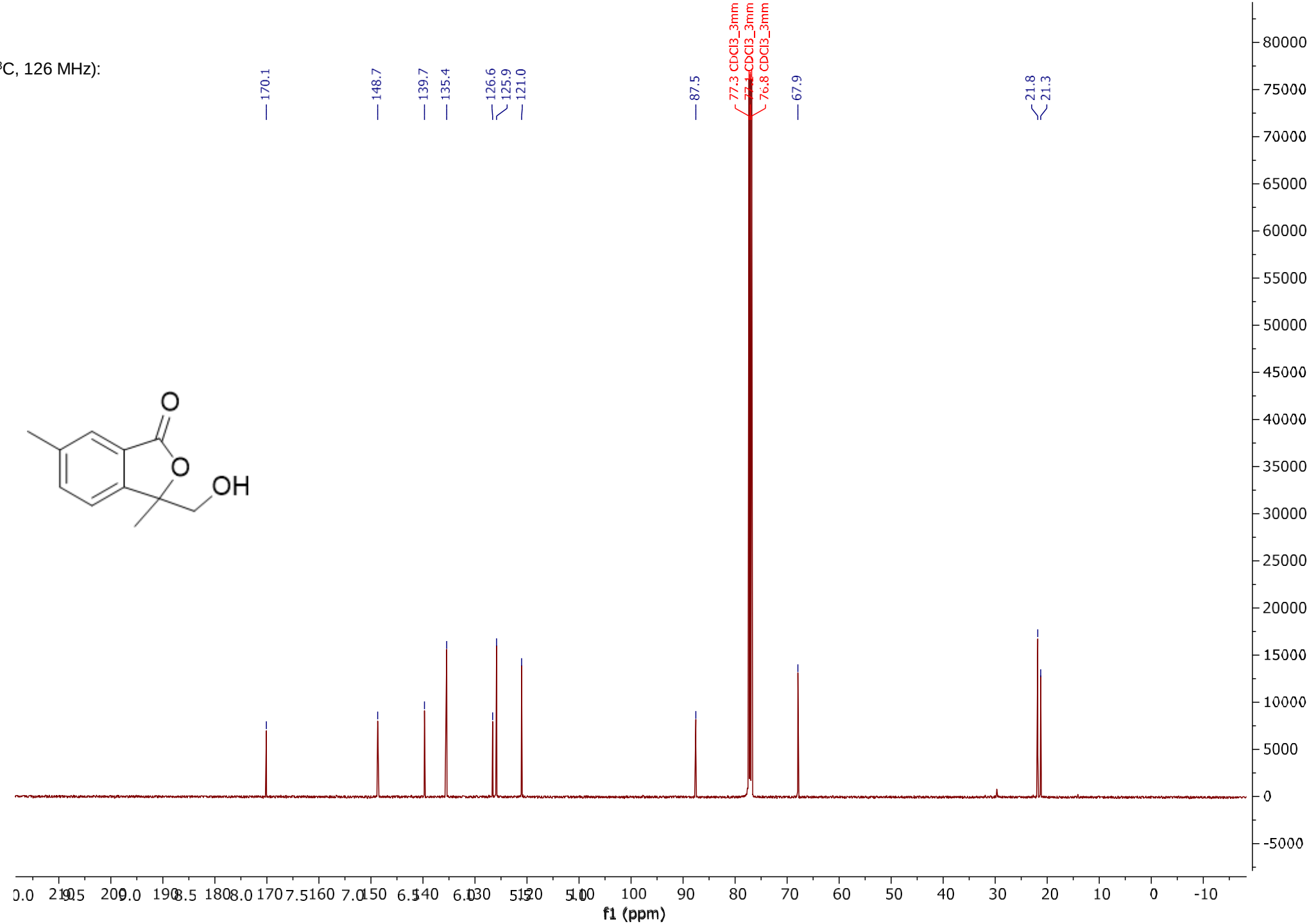
13a (^{13}C, 101 MHz):



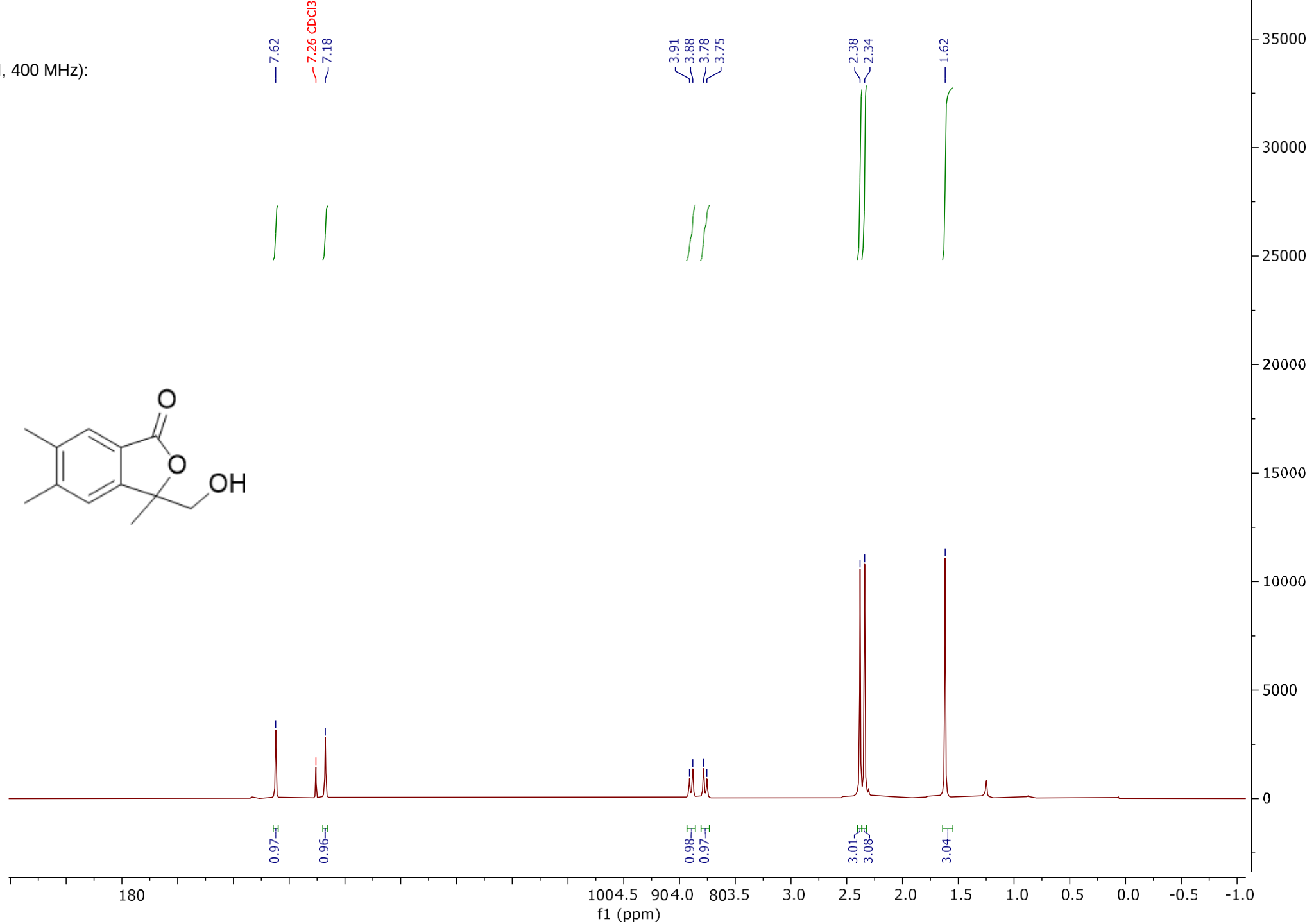
13b (^{1}H, 400 MHz):



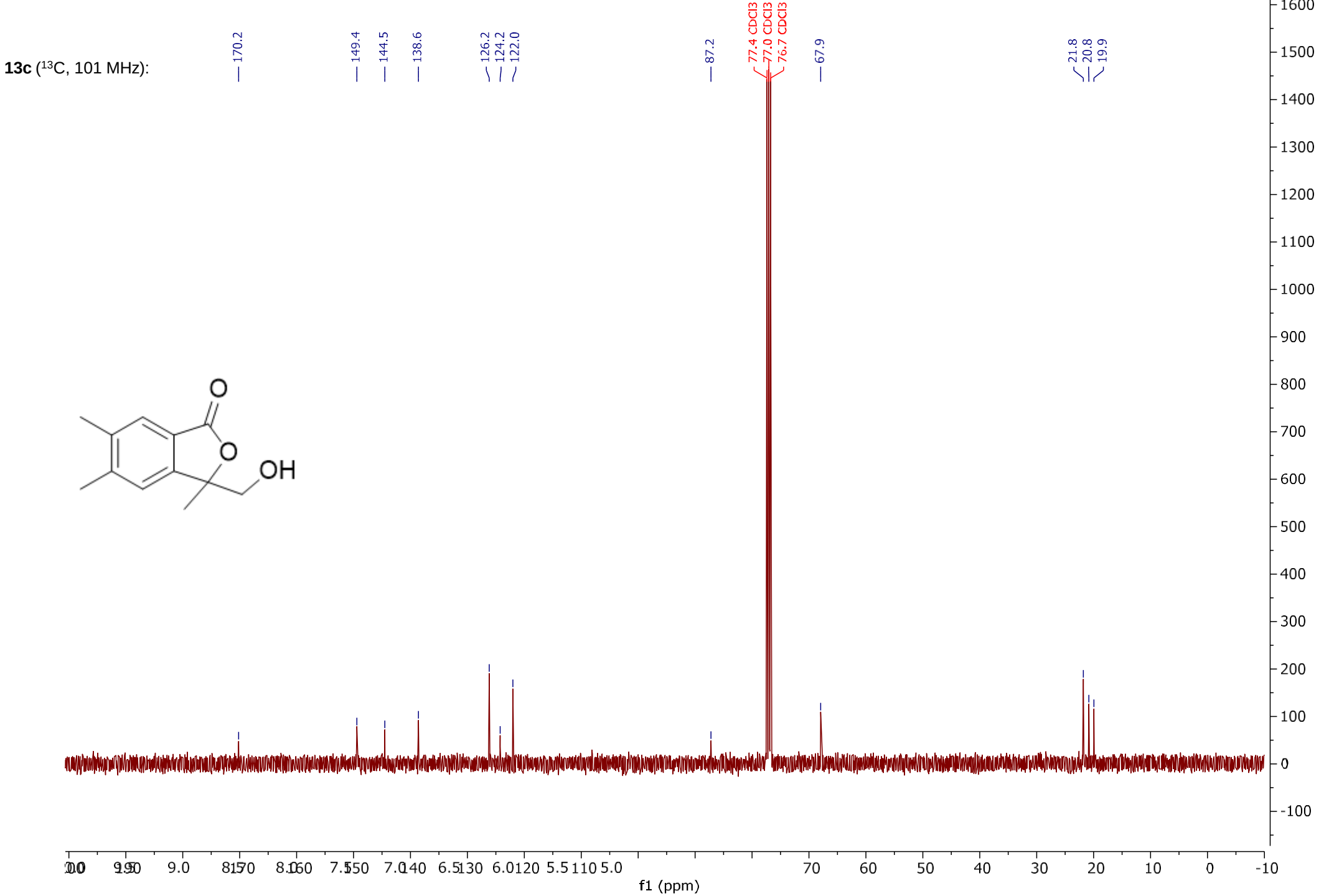
13b (^{13}C, 126 MHz):



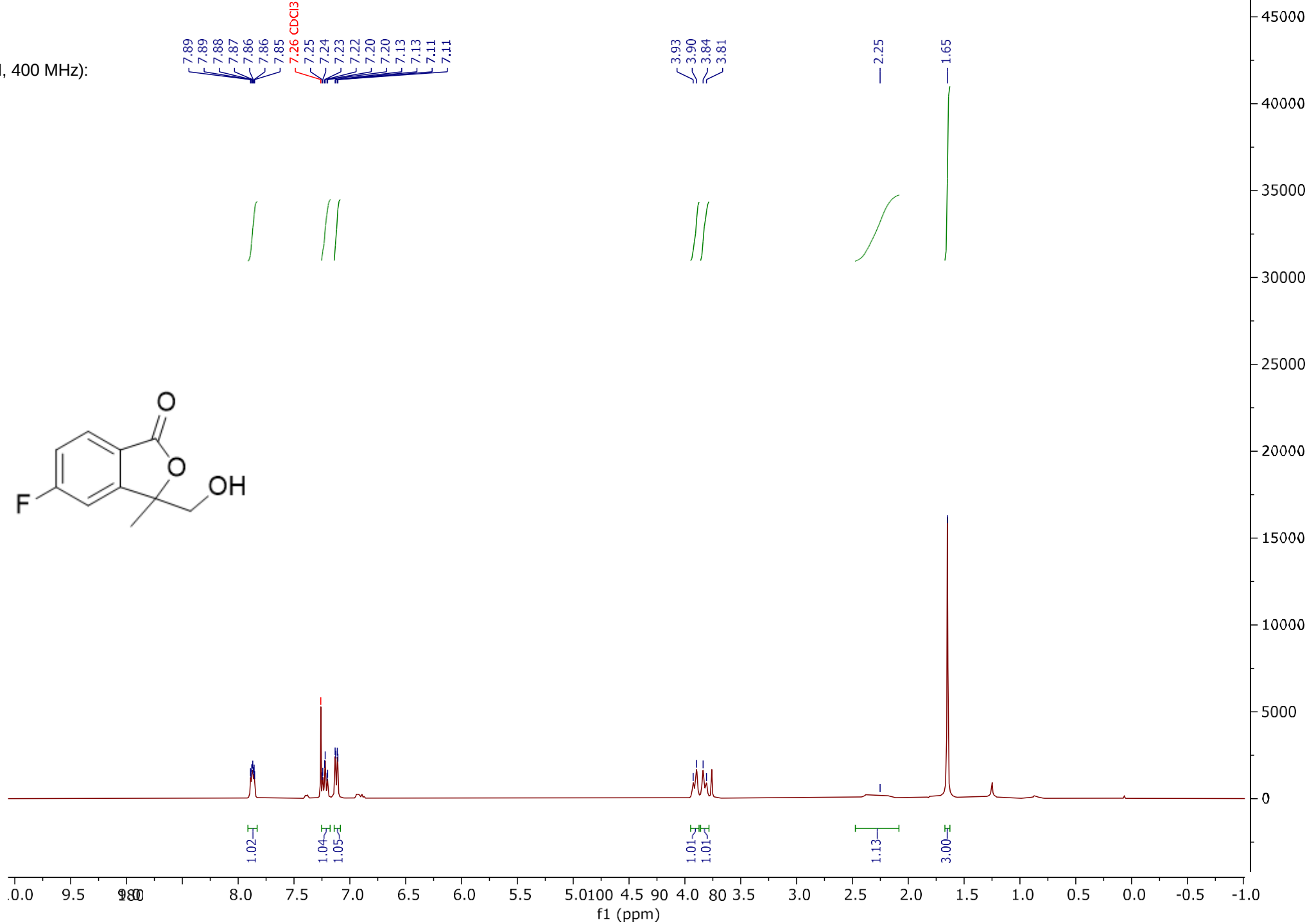
13c (^{1}H, 400 MHz):



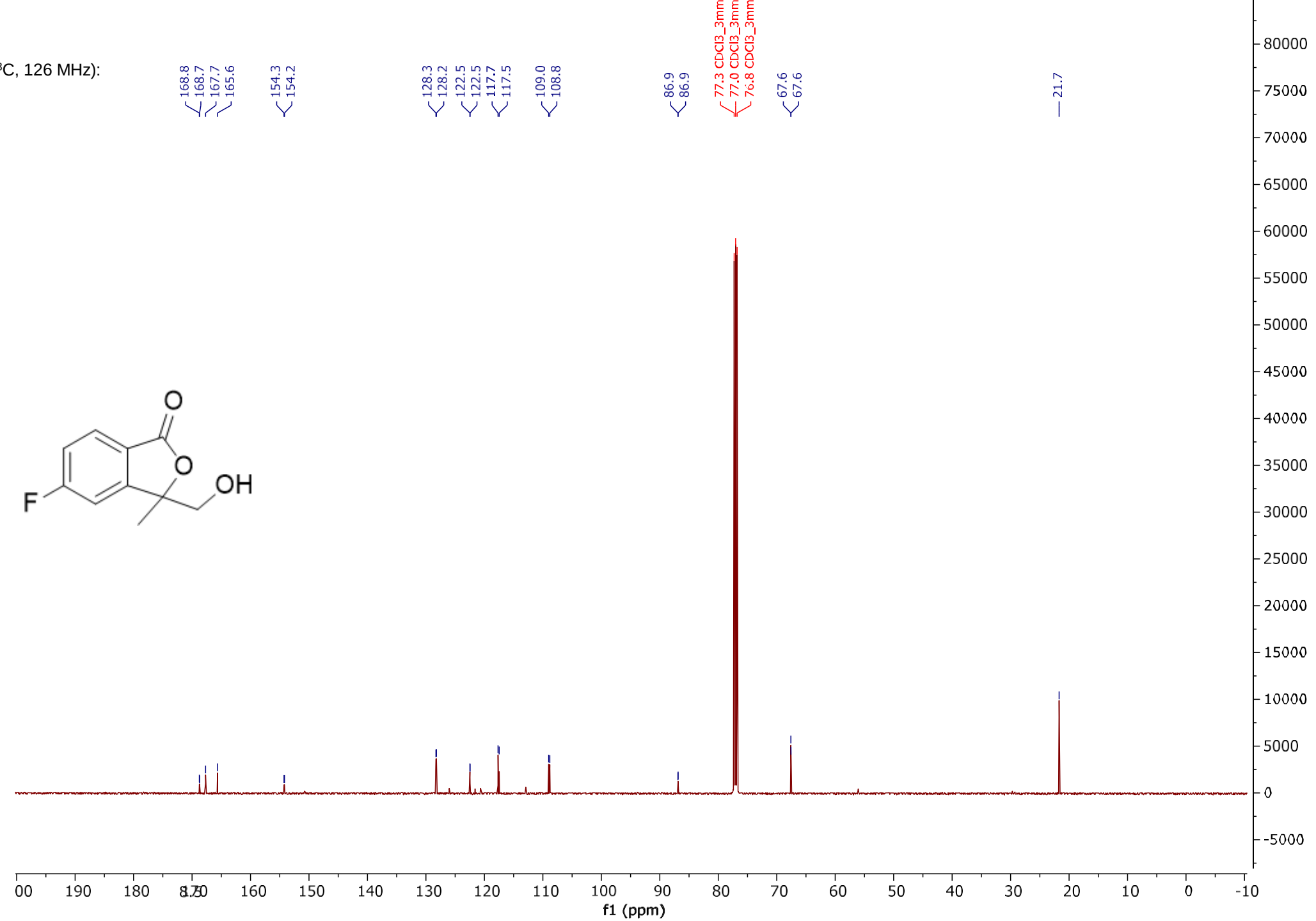
13c (^{13}C, 101 MHz):



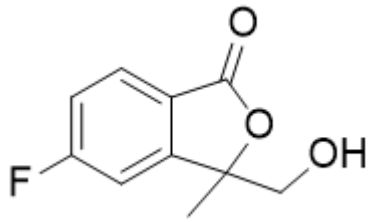
13d (^{1}H, 400 MHz):



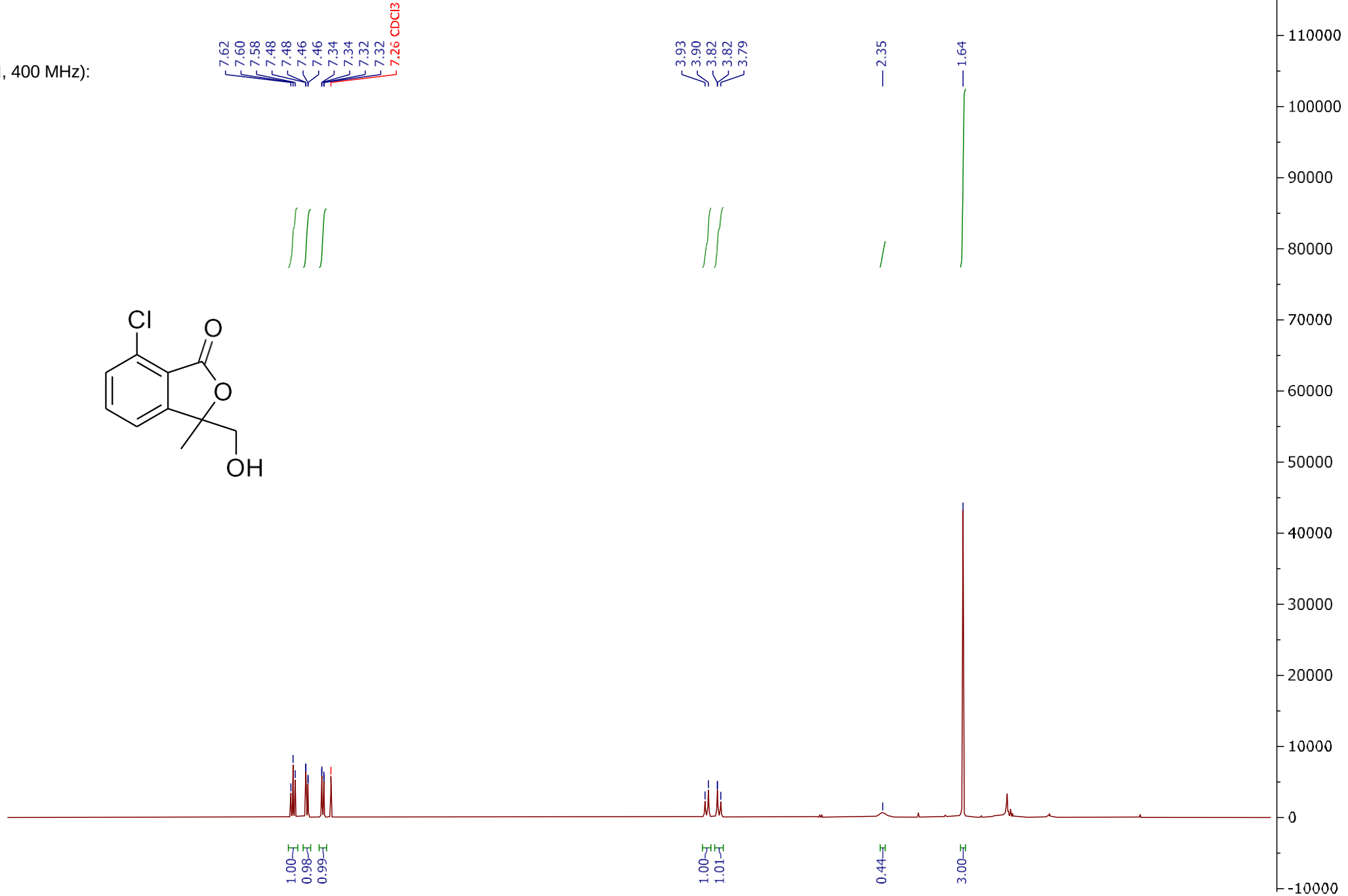
13d (^{13}C, 126 MHz):



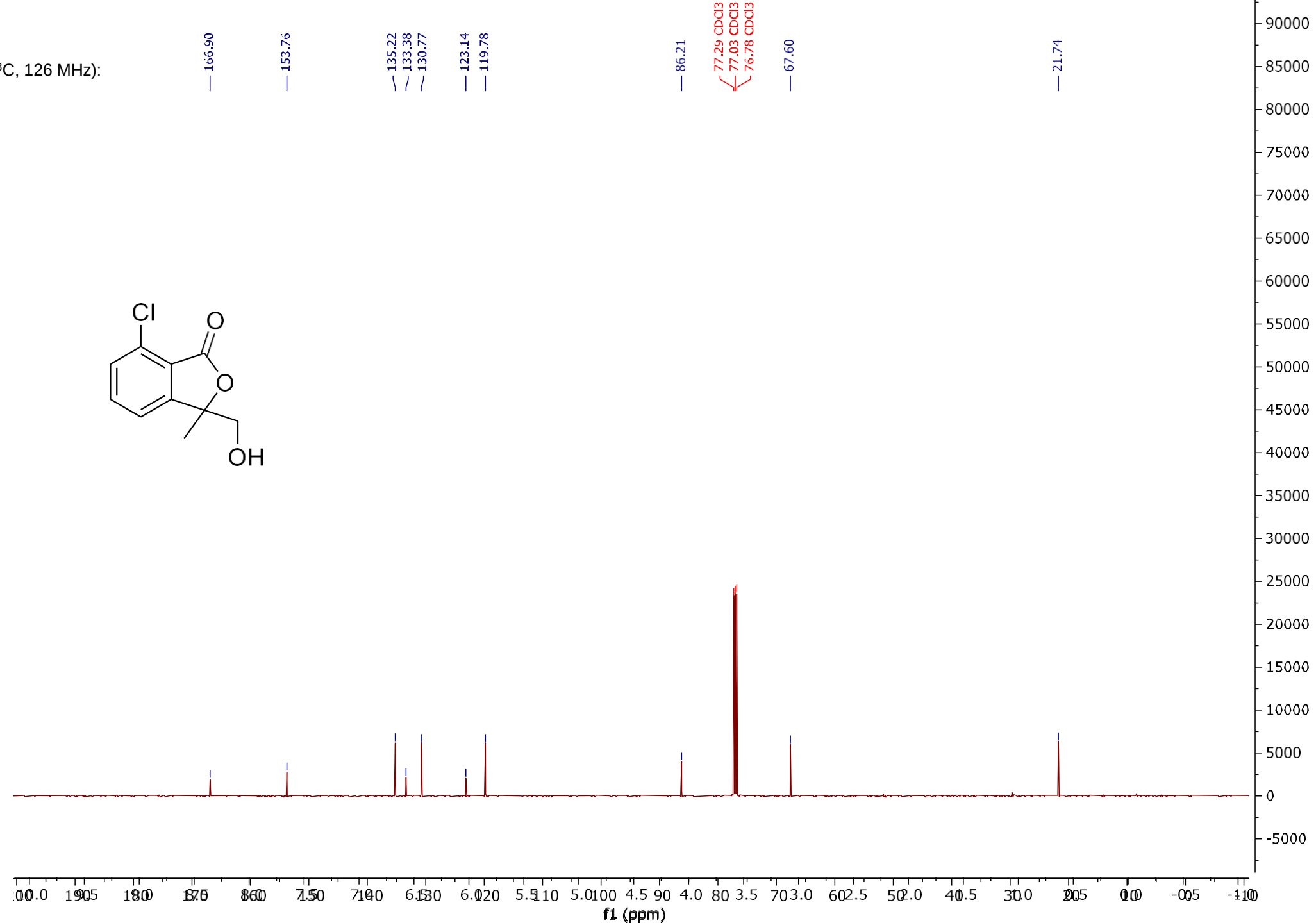
13d (^{19}F, 376 MHz):



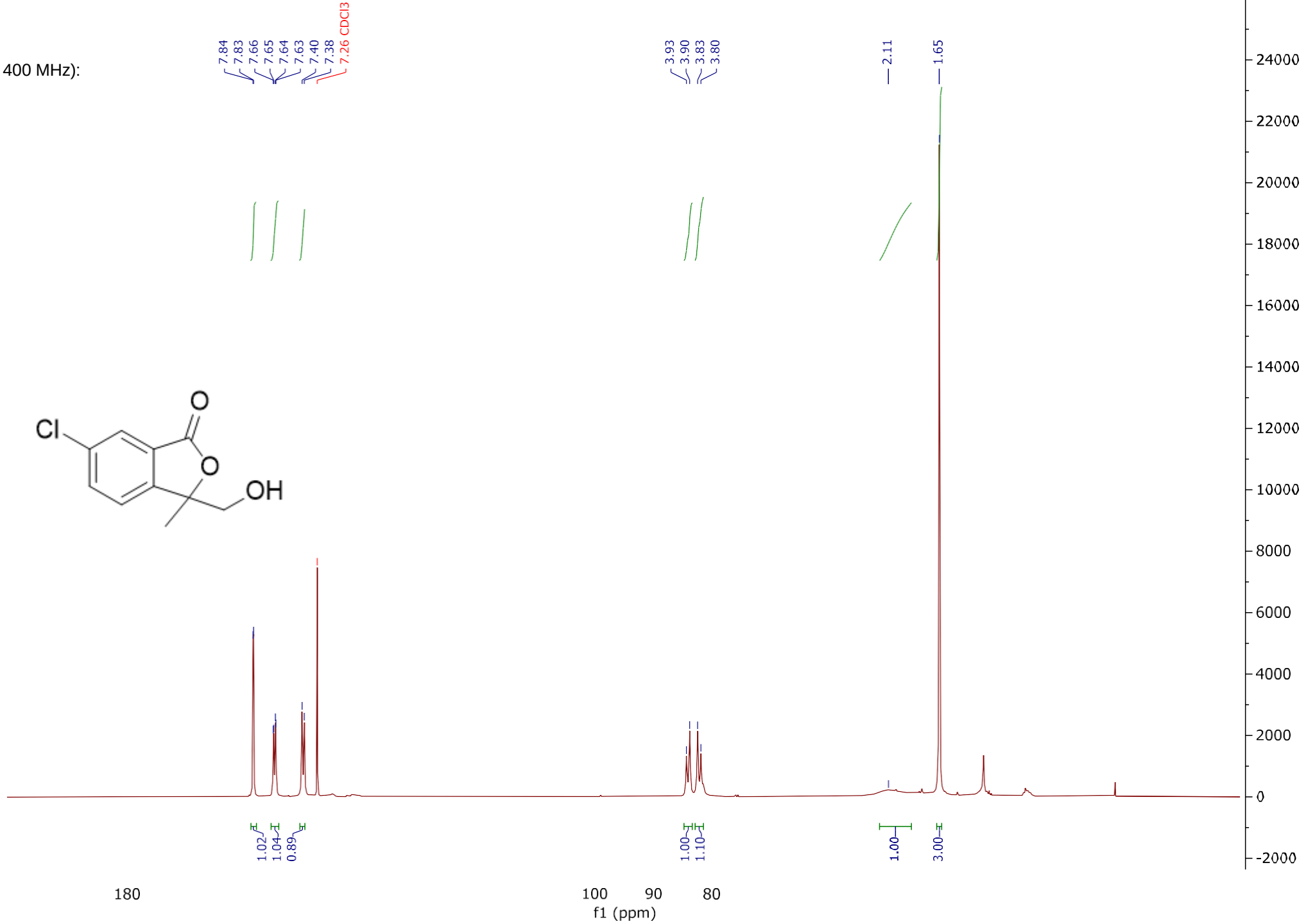
13e (^{1}H, 400 MHz):



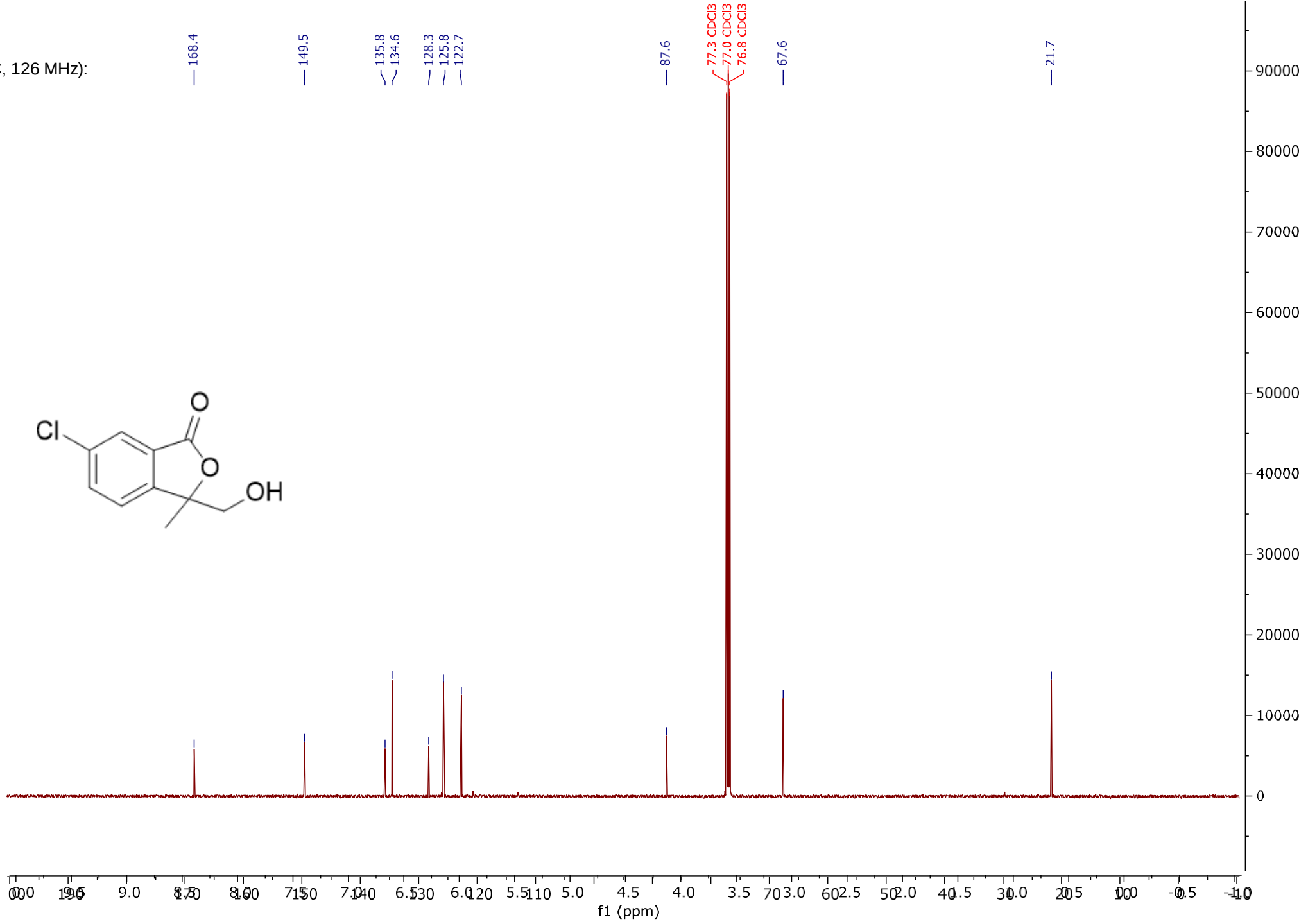
13e (^{13}C, 126 MHz):



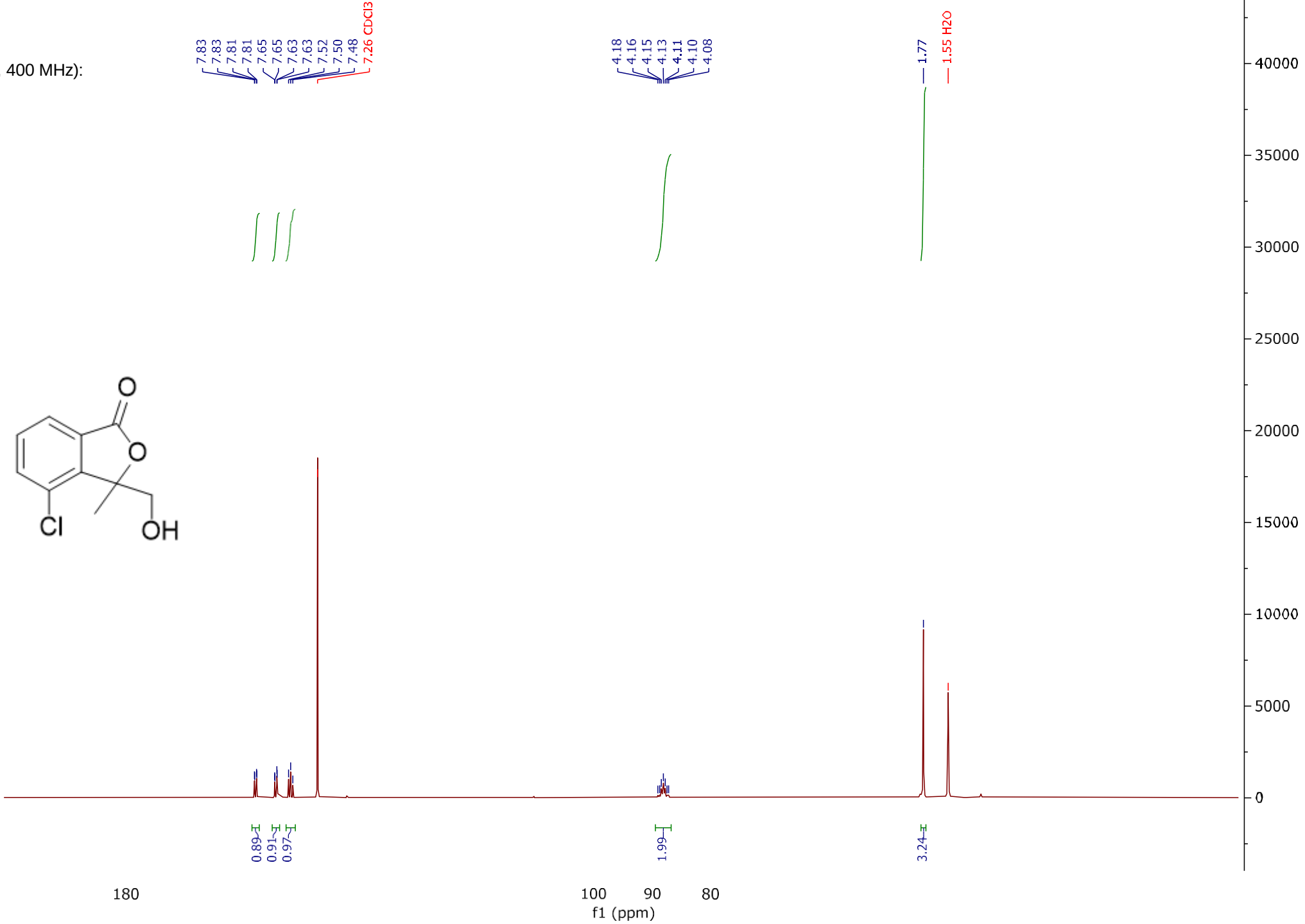
13f (^{1}H, 400 MHz):



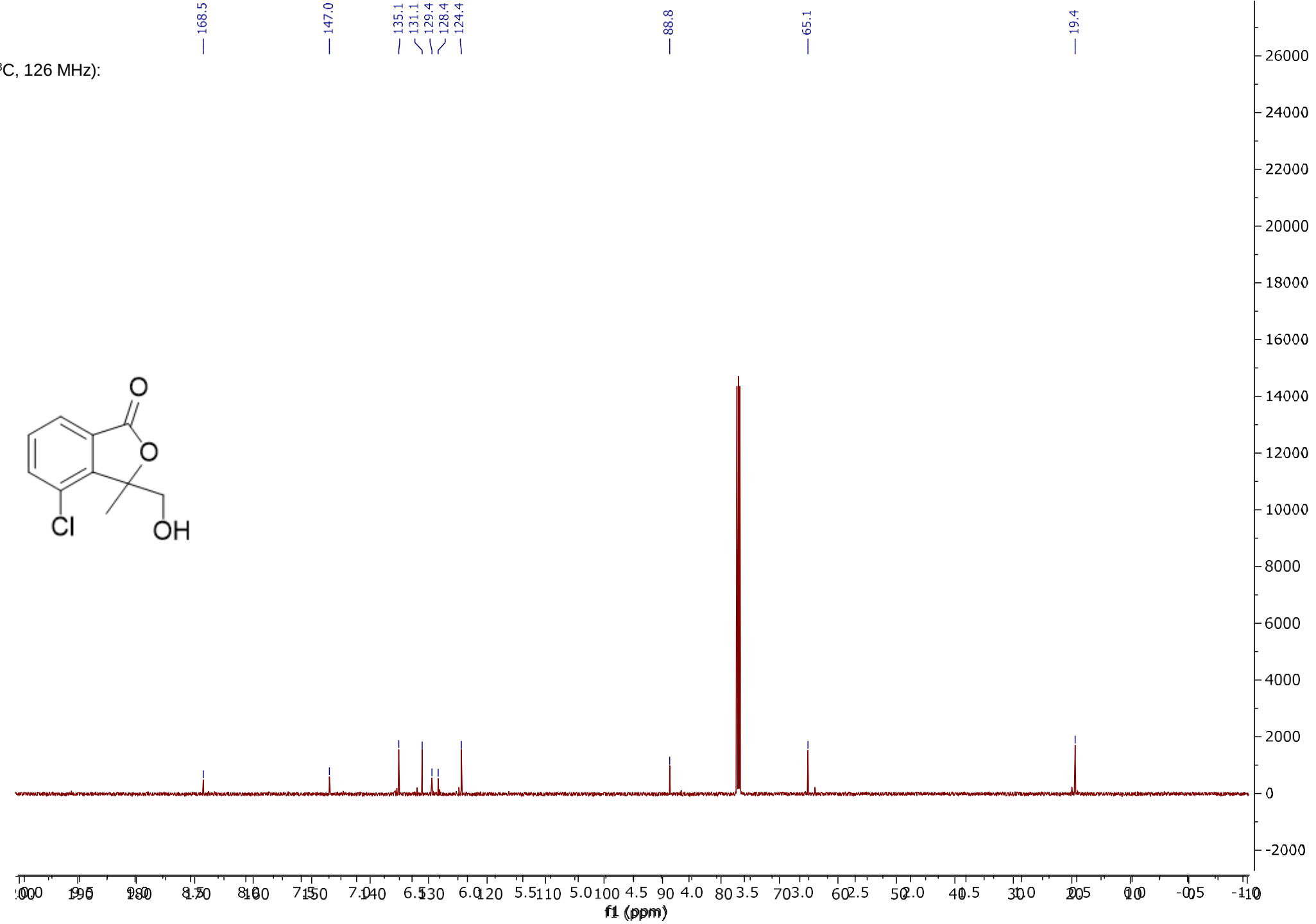
13f (^{13}C, 126 MHz):



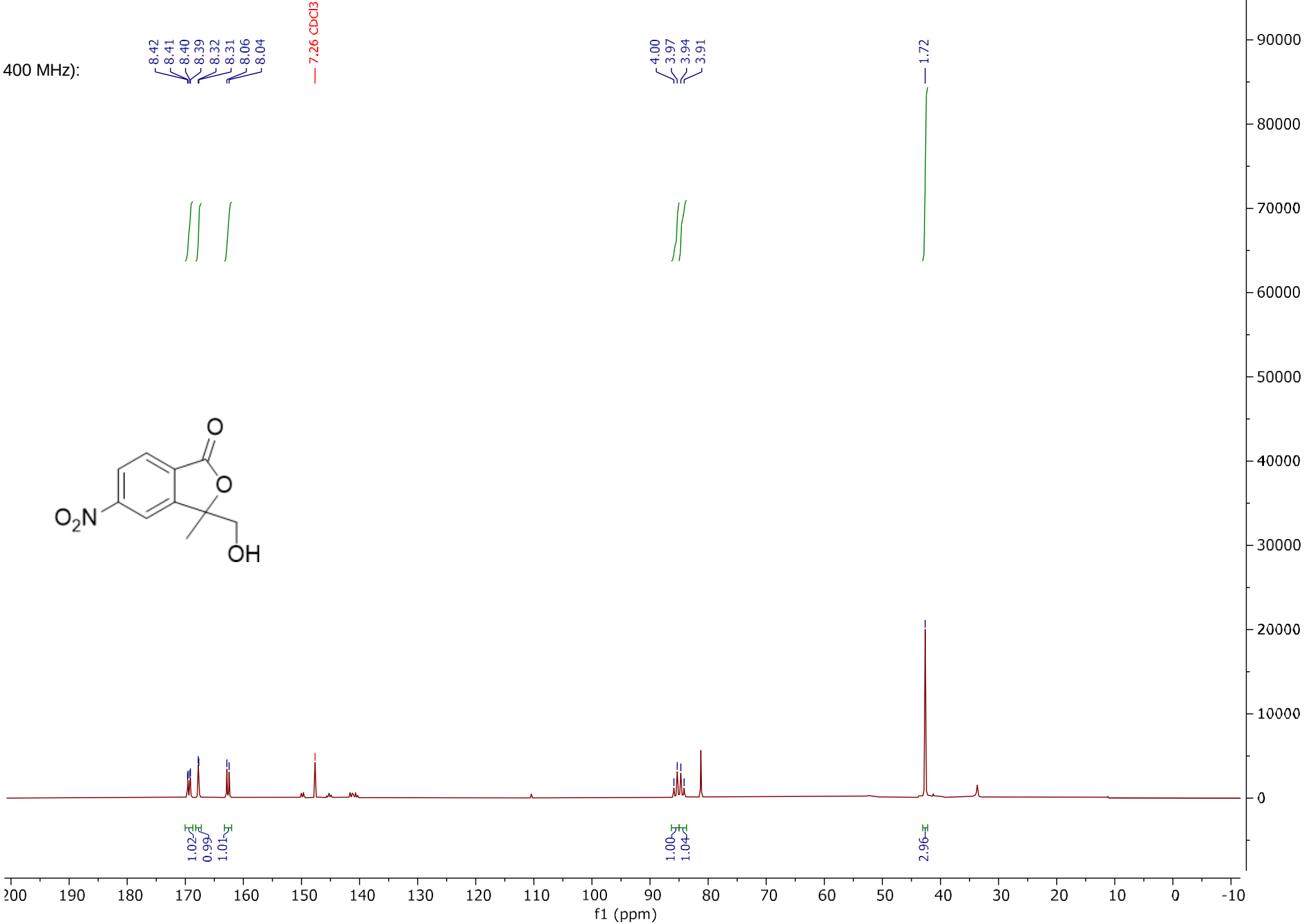
13h (^{1}H, 400 MHz):



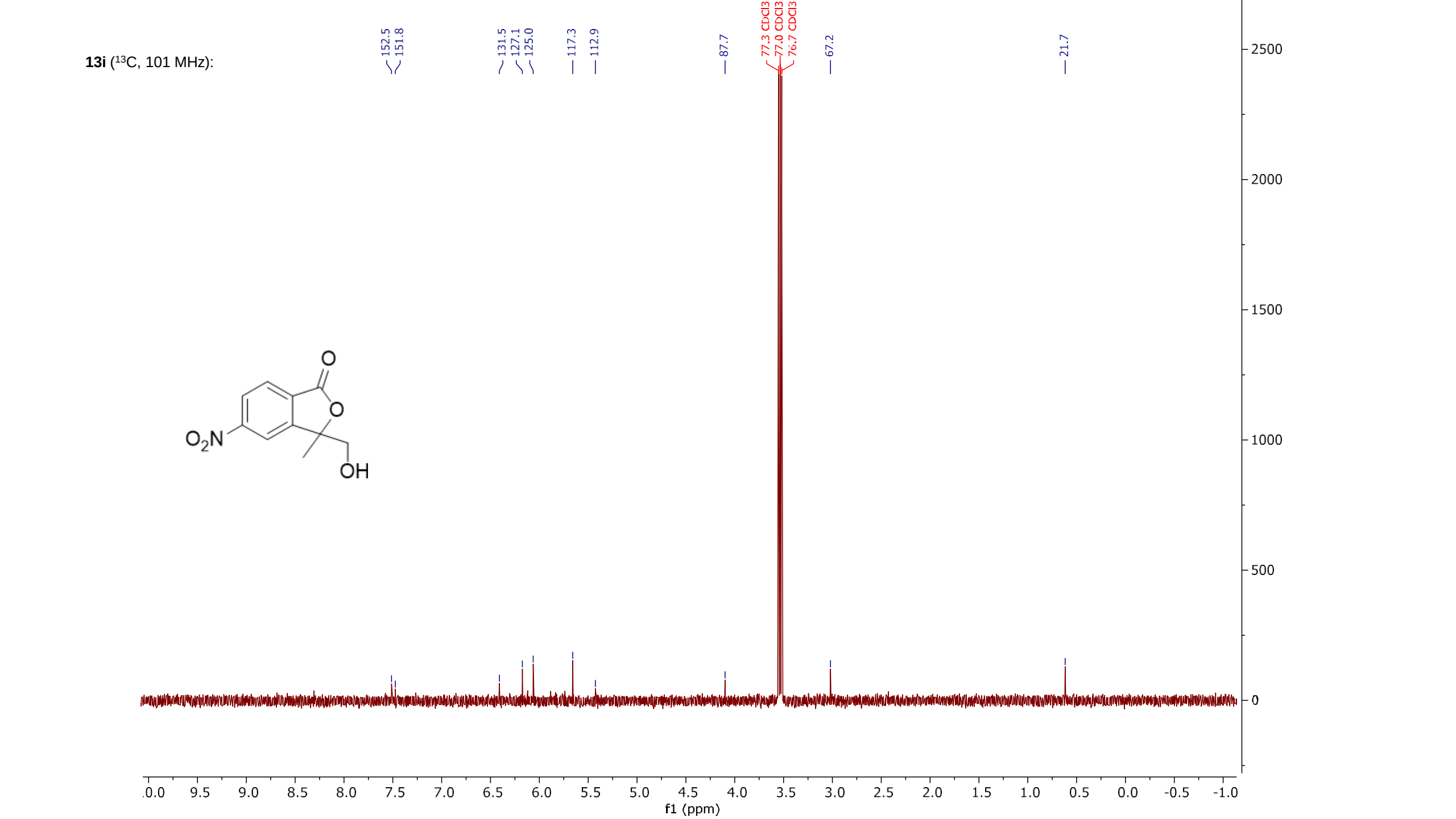
13h (^{13}C, 126 MHz):



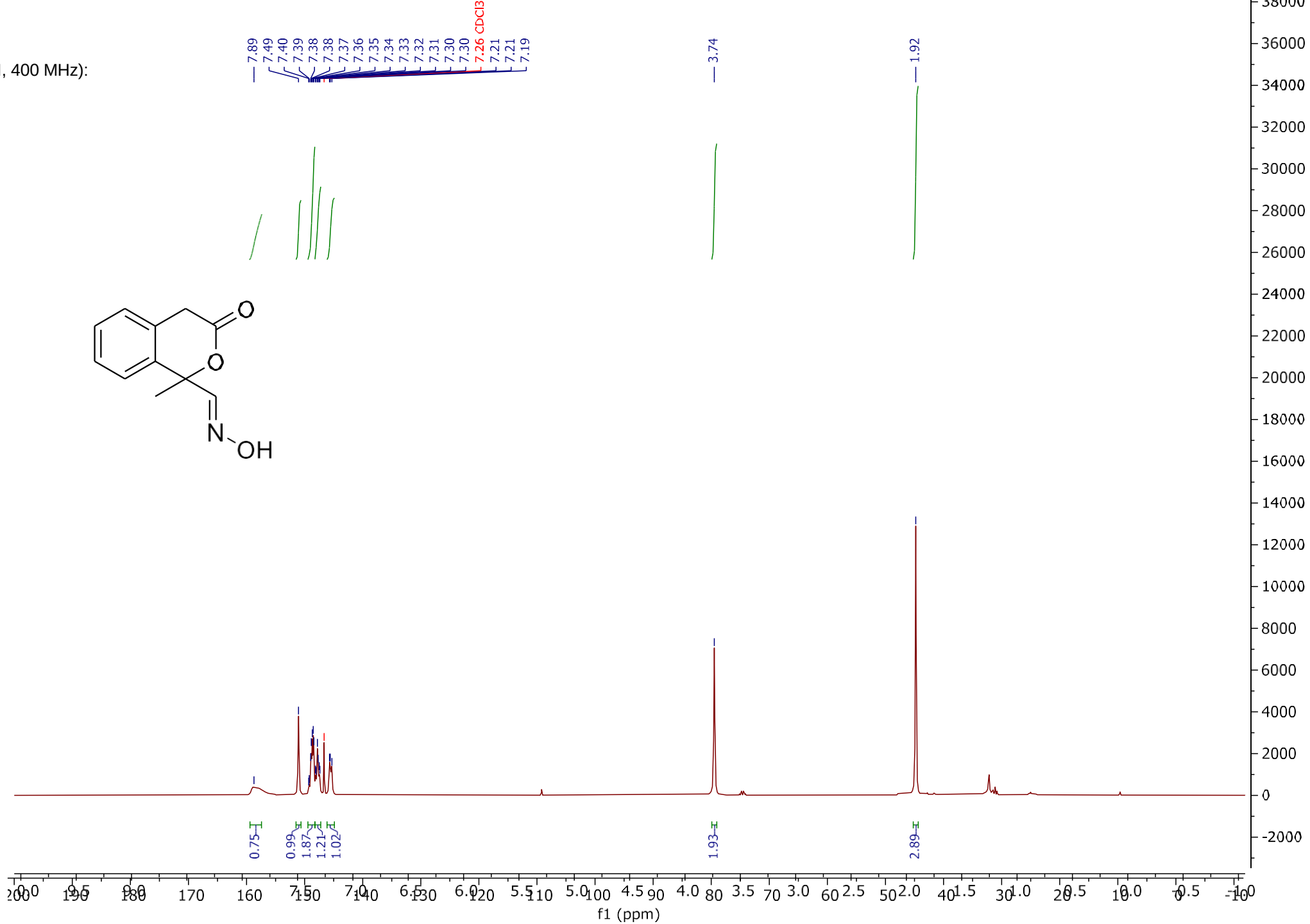
13i (^{1}H, 400 MHz):



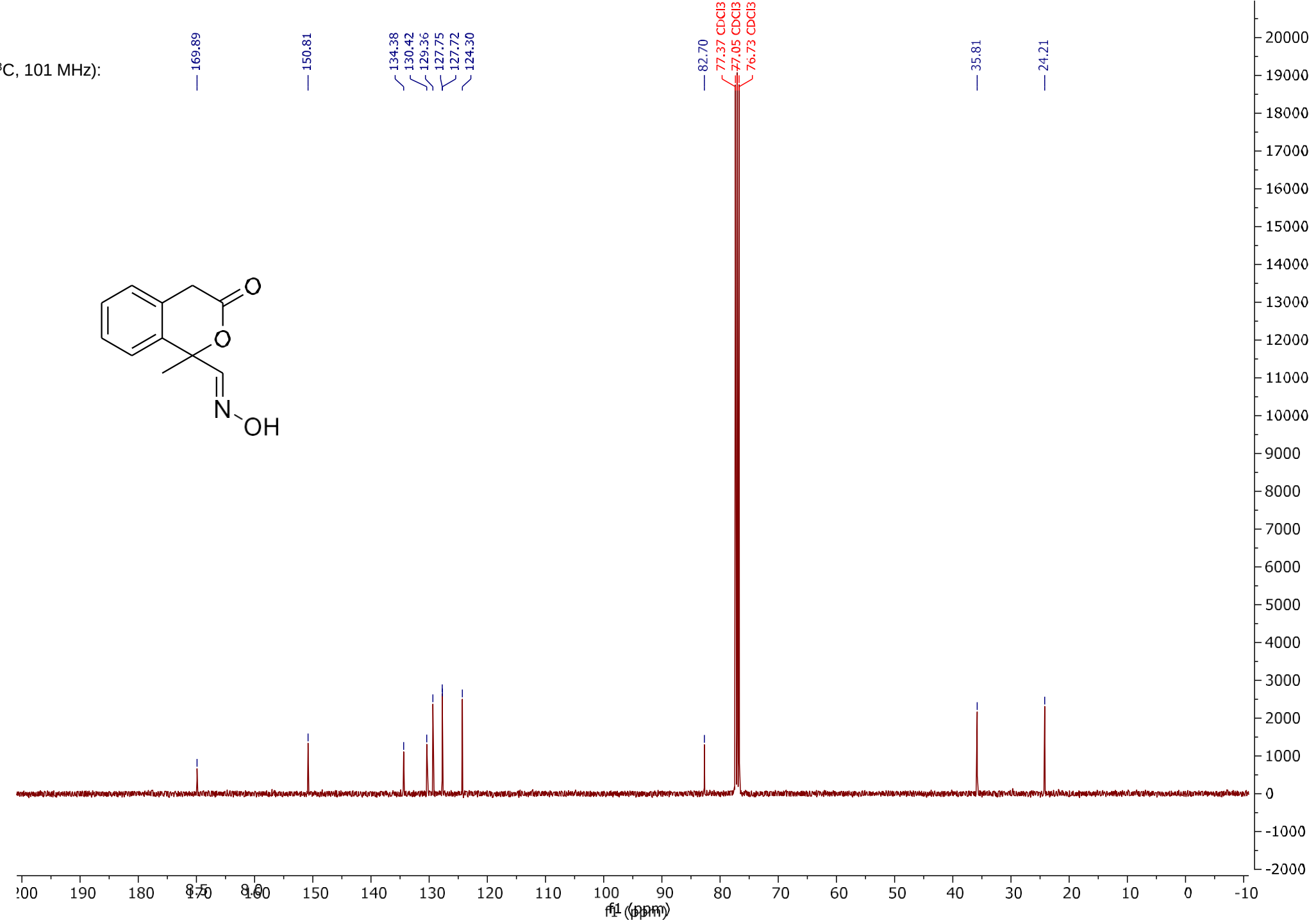
13i (^{13}C, 101 MHz):



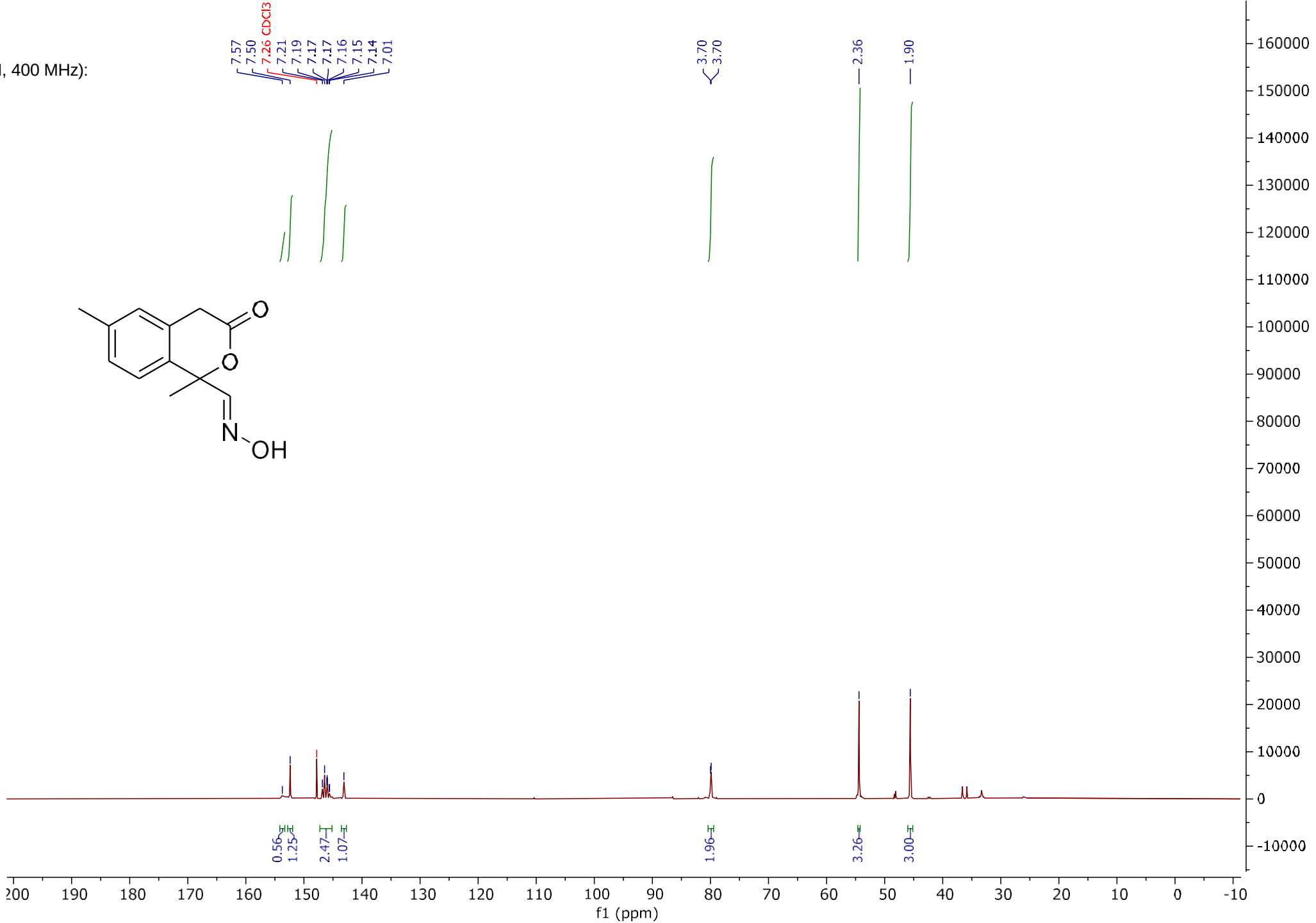
14a (^{1}H, 400 MHz):



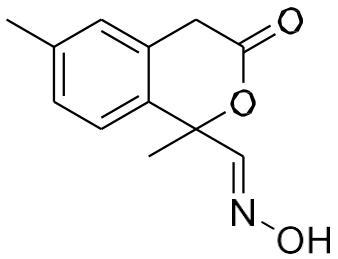
14a (^{13}C, 101 MHz):



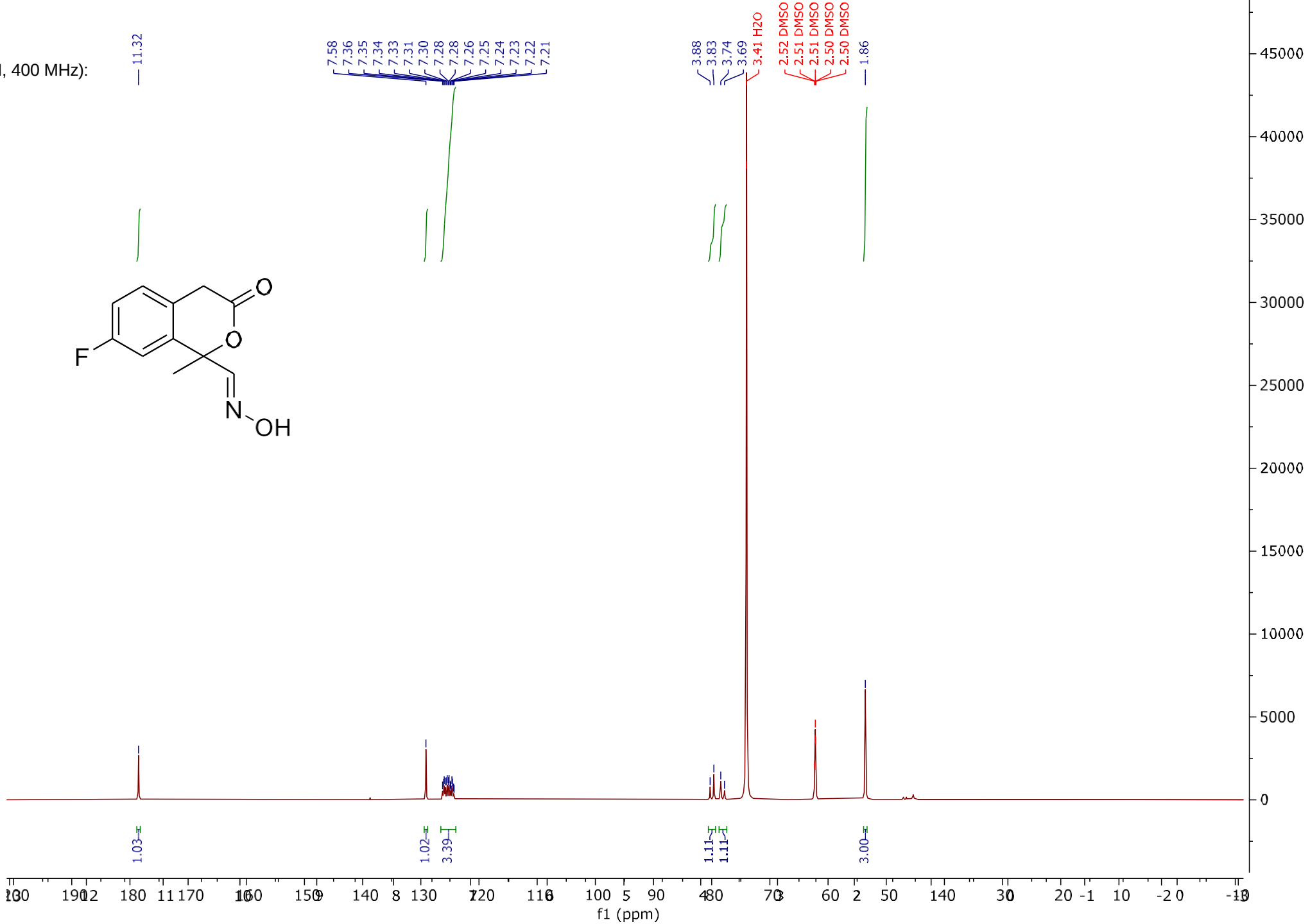
14b (^{1}H, 400 MHz):



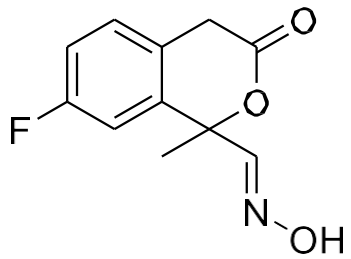
14b (^{13}C, 101 MHz):



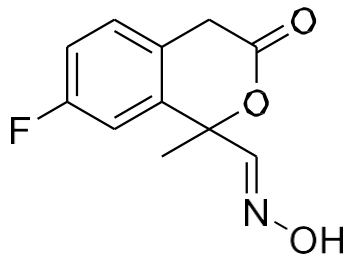
14d (^{1}H, 400 MHz):



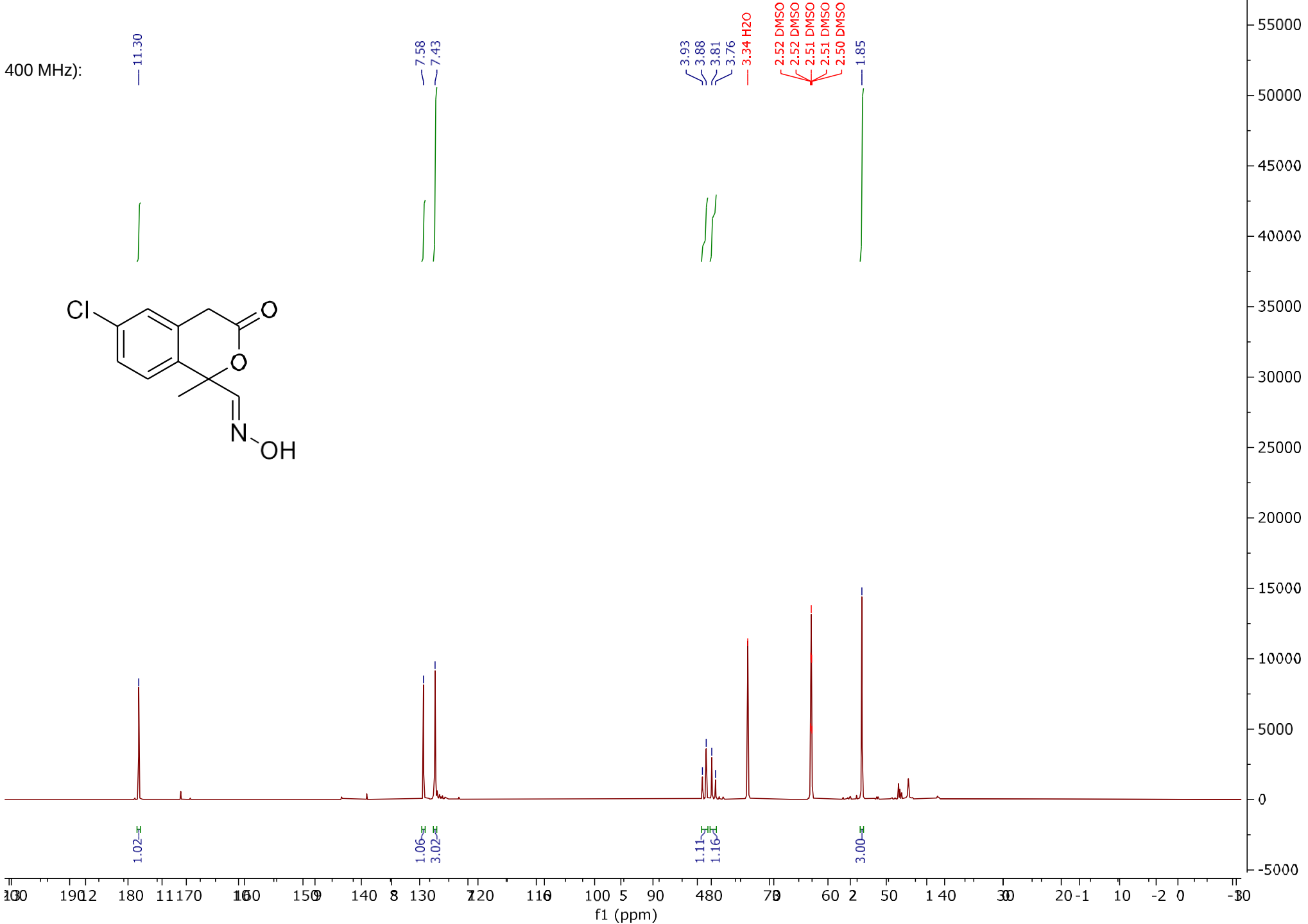
14d (^{13}C, 101 MHz):



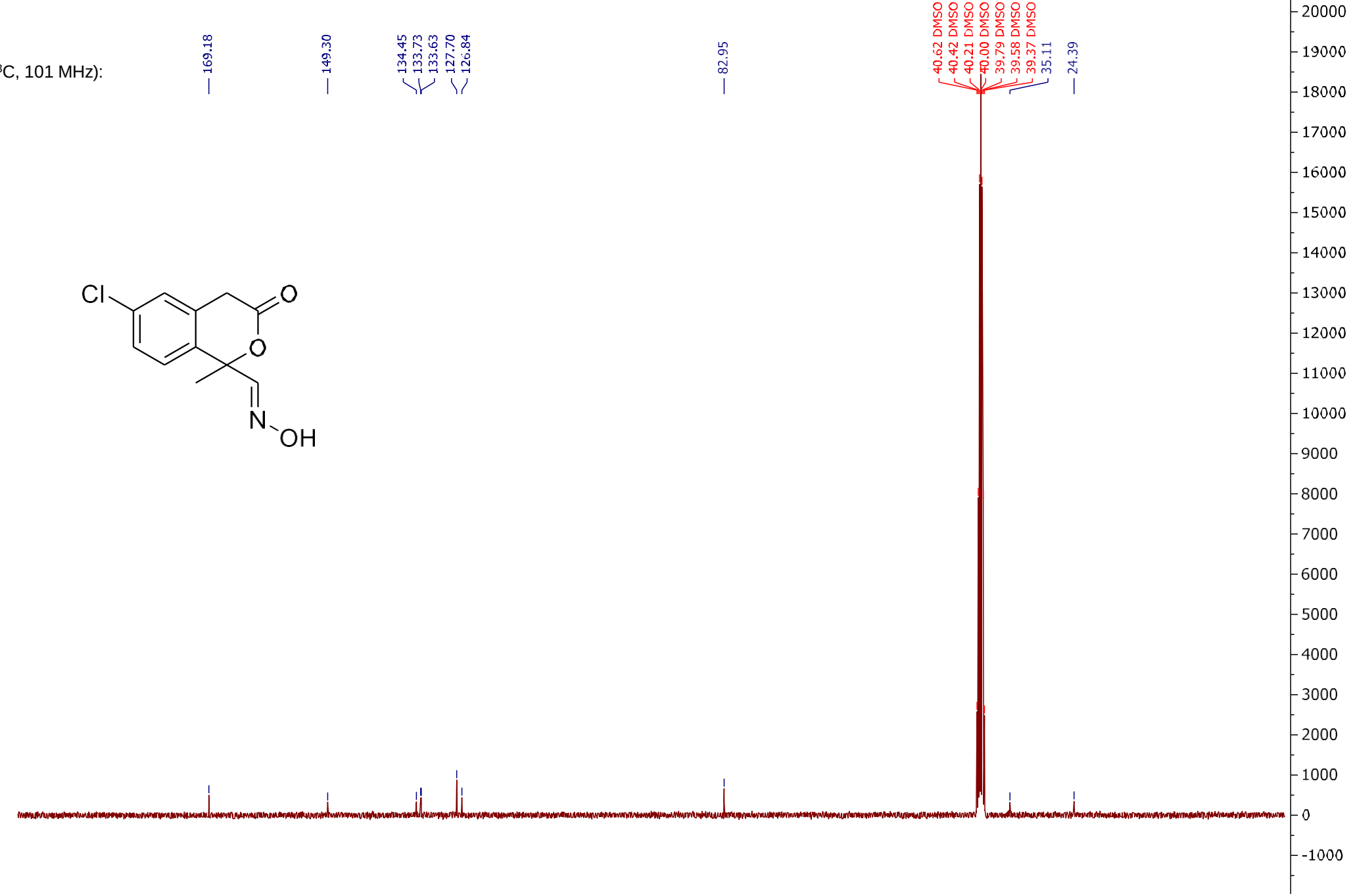
14d (^{19}F, 376 MHz):



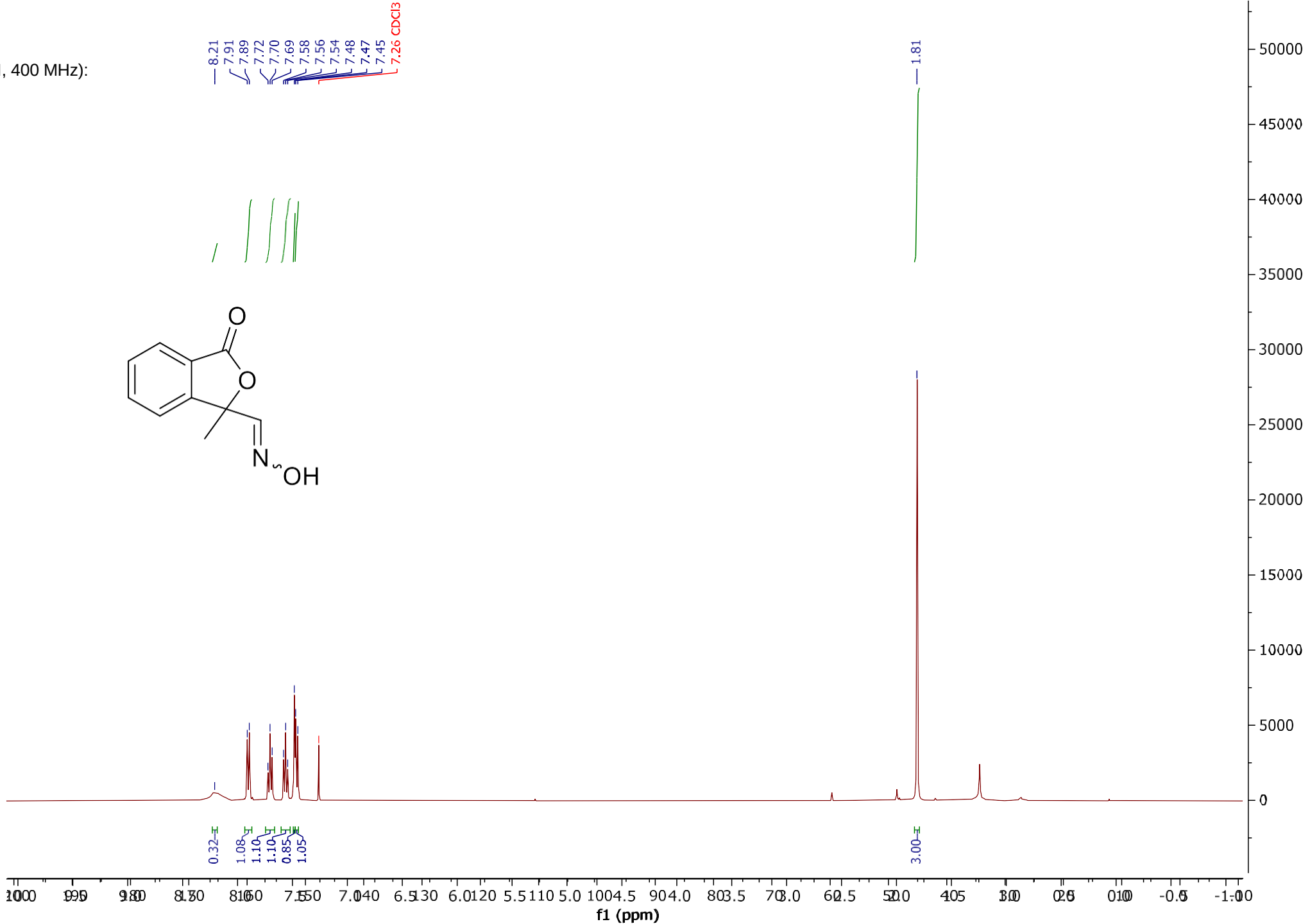
14f (^{1}H, 400 MHz):



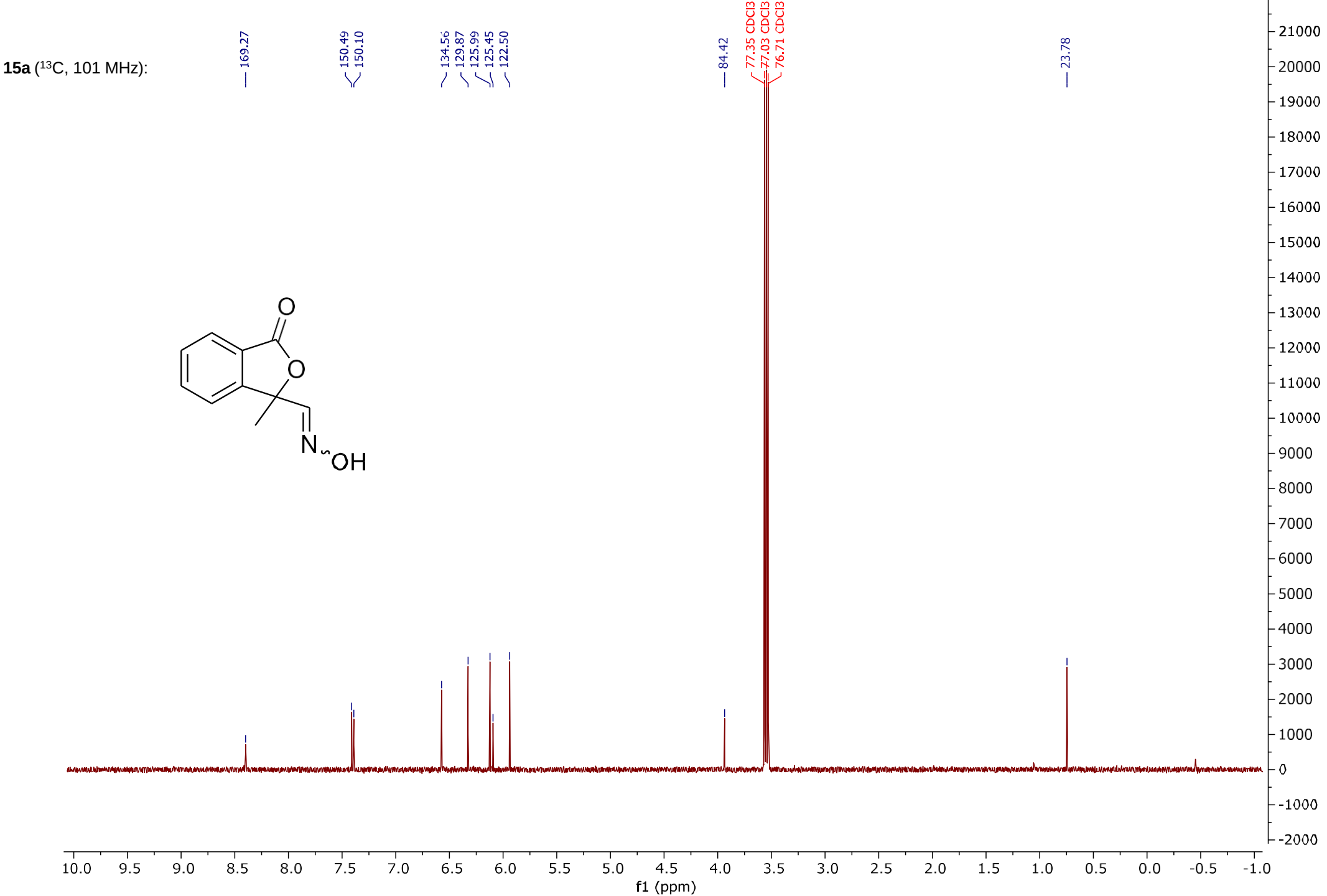
14f (^{13}C, 101 MHz):



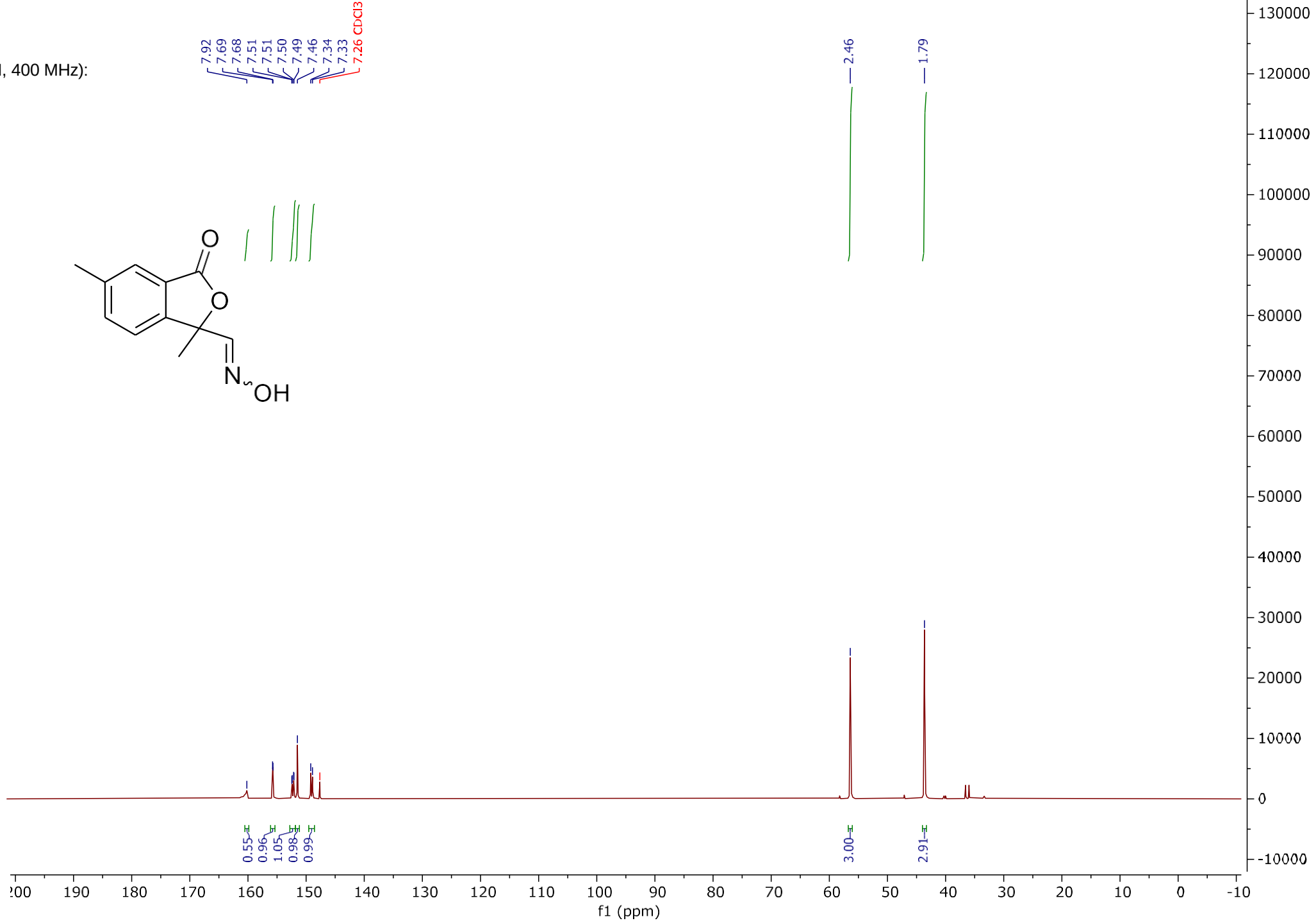
15a (^{1}H, 400 MHz):



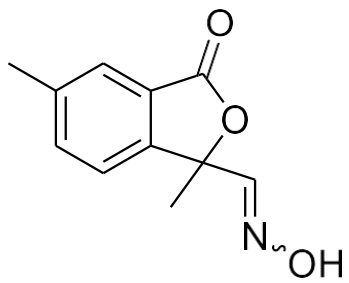
15a (^{13}C, 101 MHz):



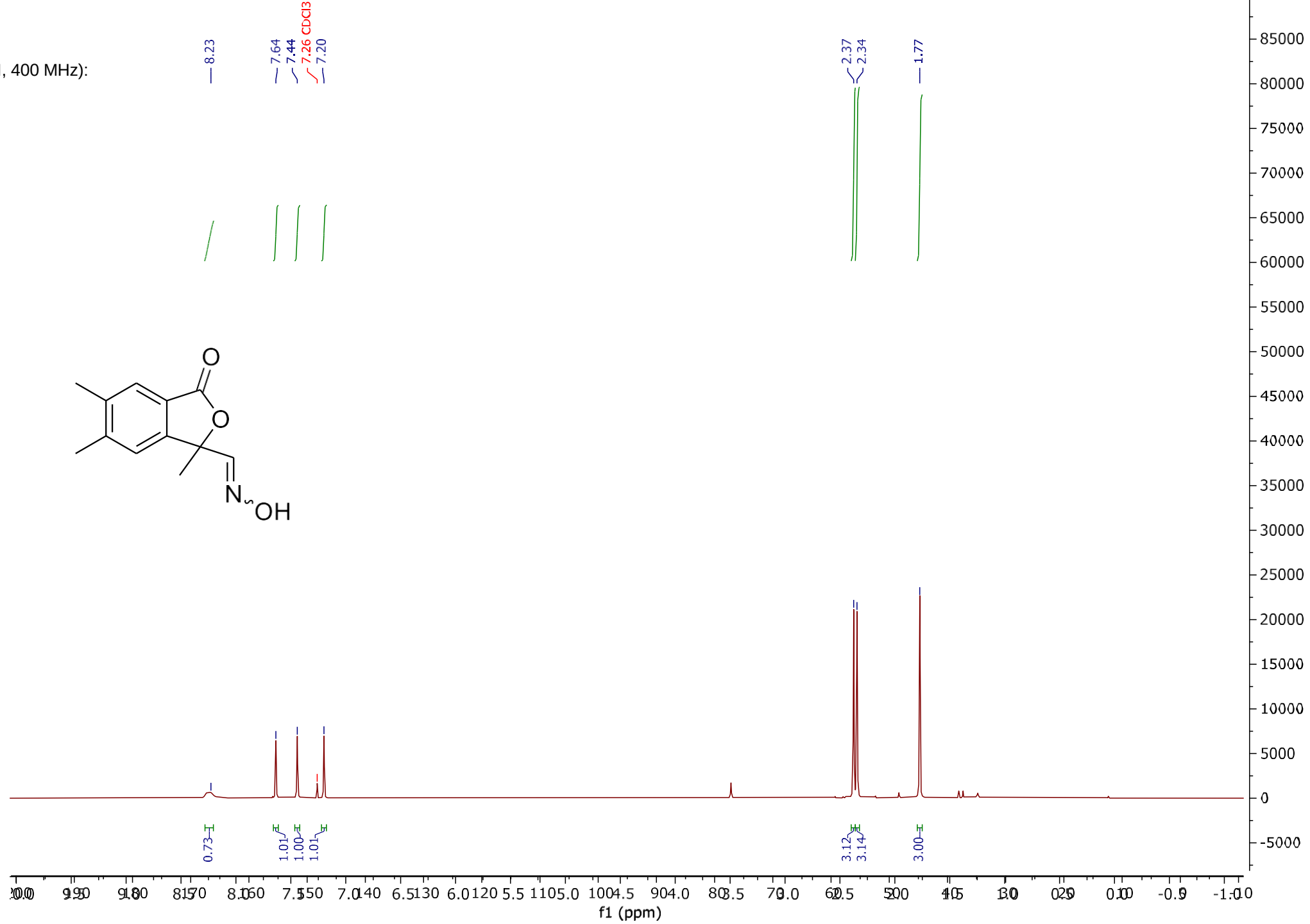
15b (^{1}H, 400 MHz):



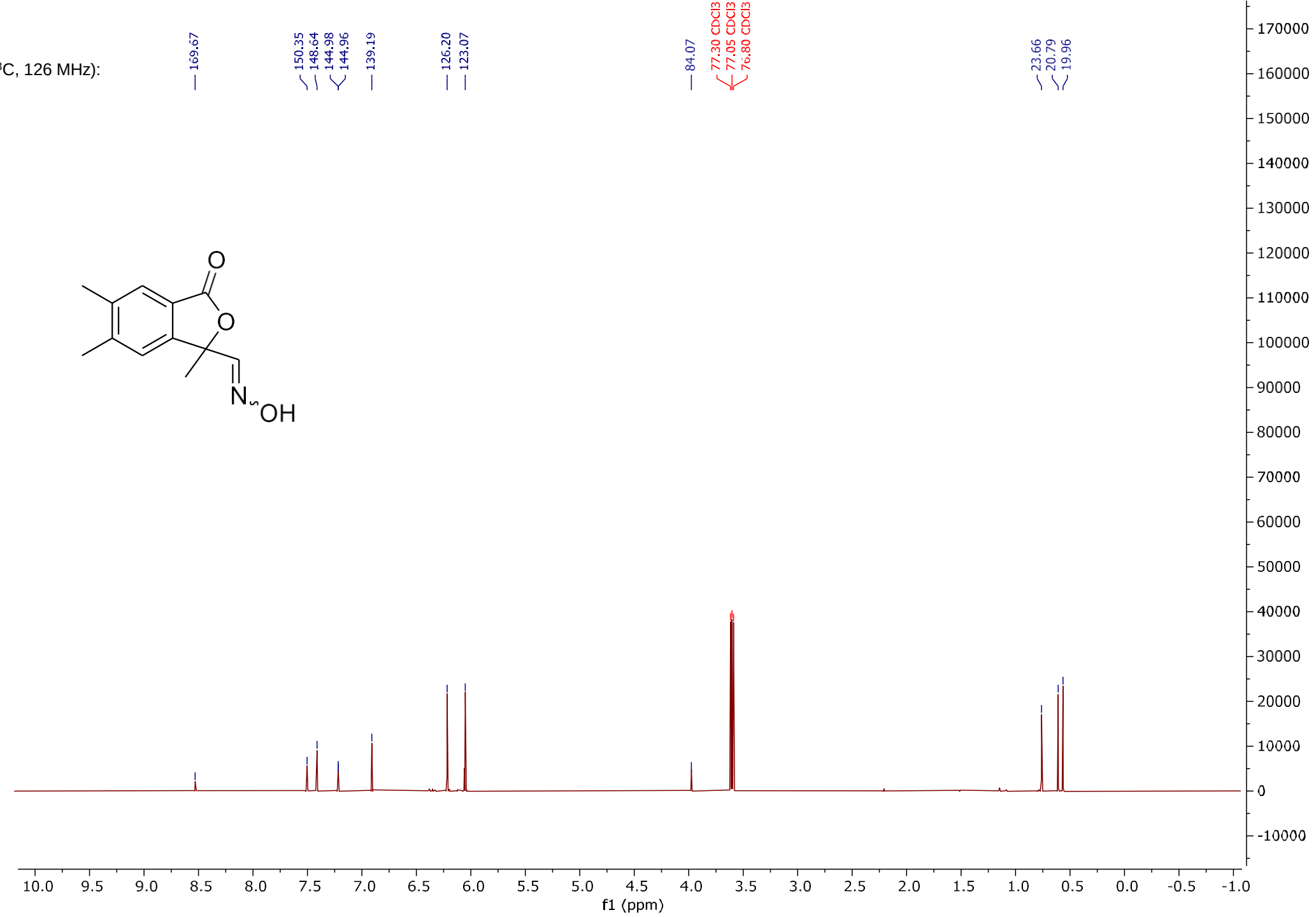
15b (^{13}C, 126 MHz):



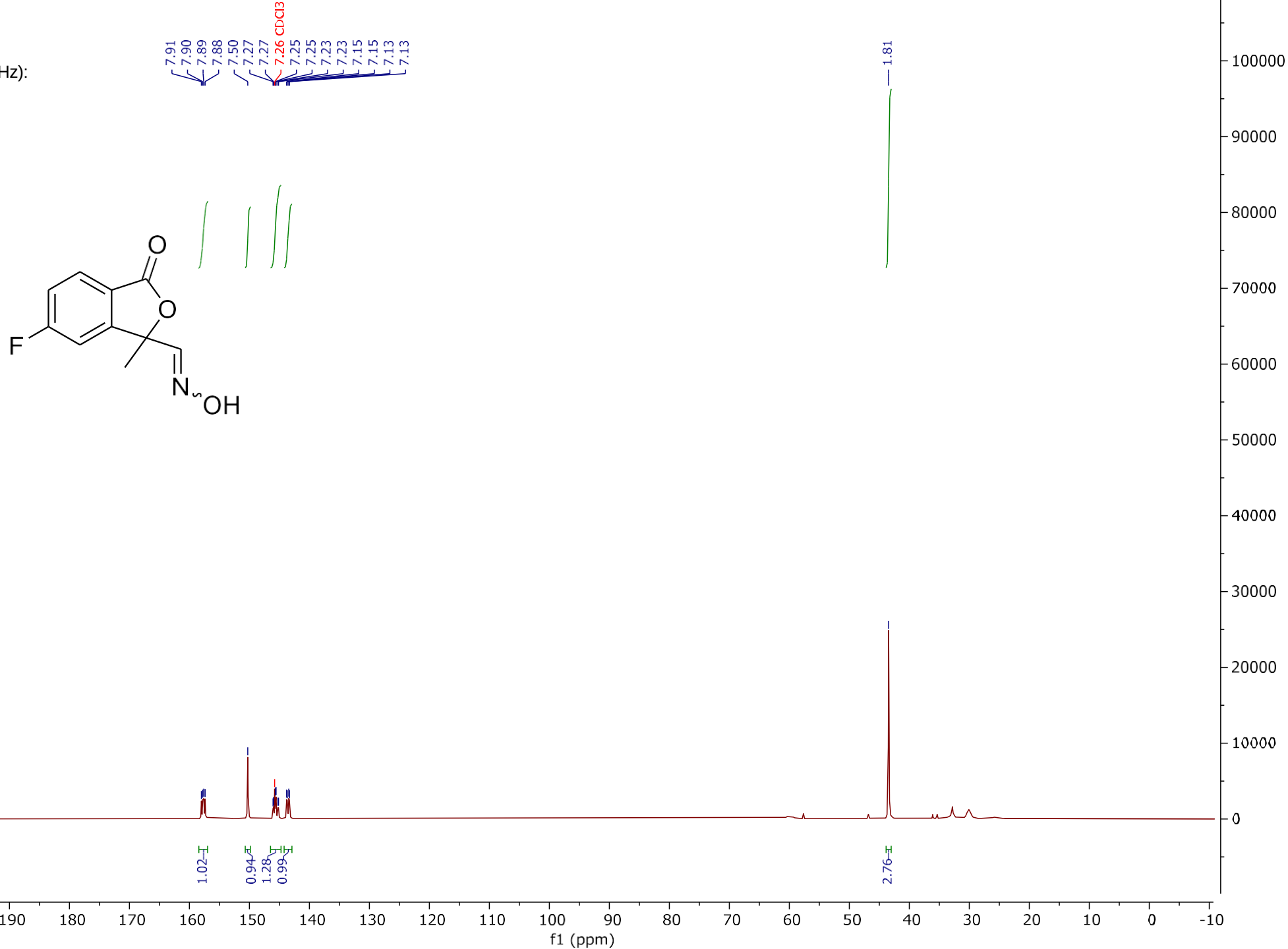
15c (^{1}H, 400 MHz):



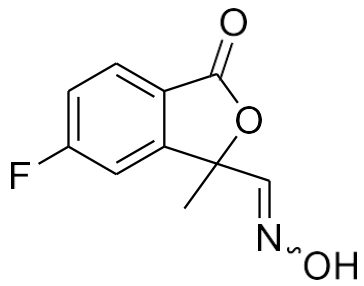
15c (^{13}C, 126 MHz):



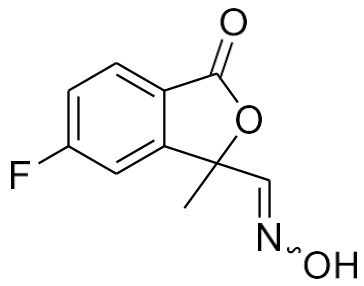
15d (^{1}H, 400 MHz):



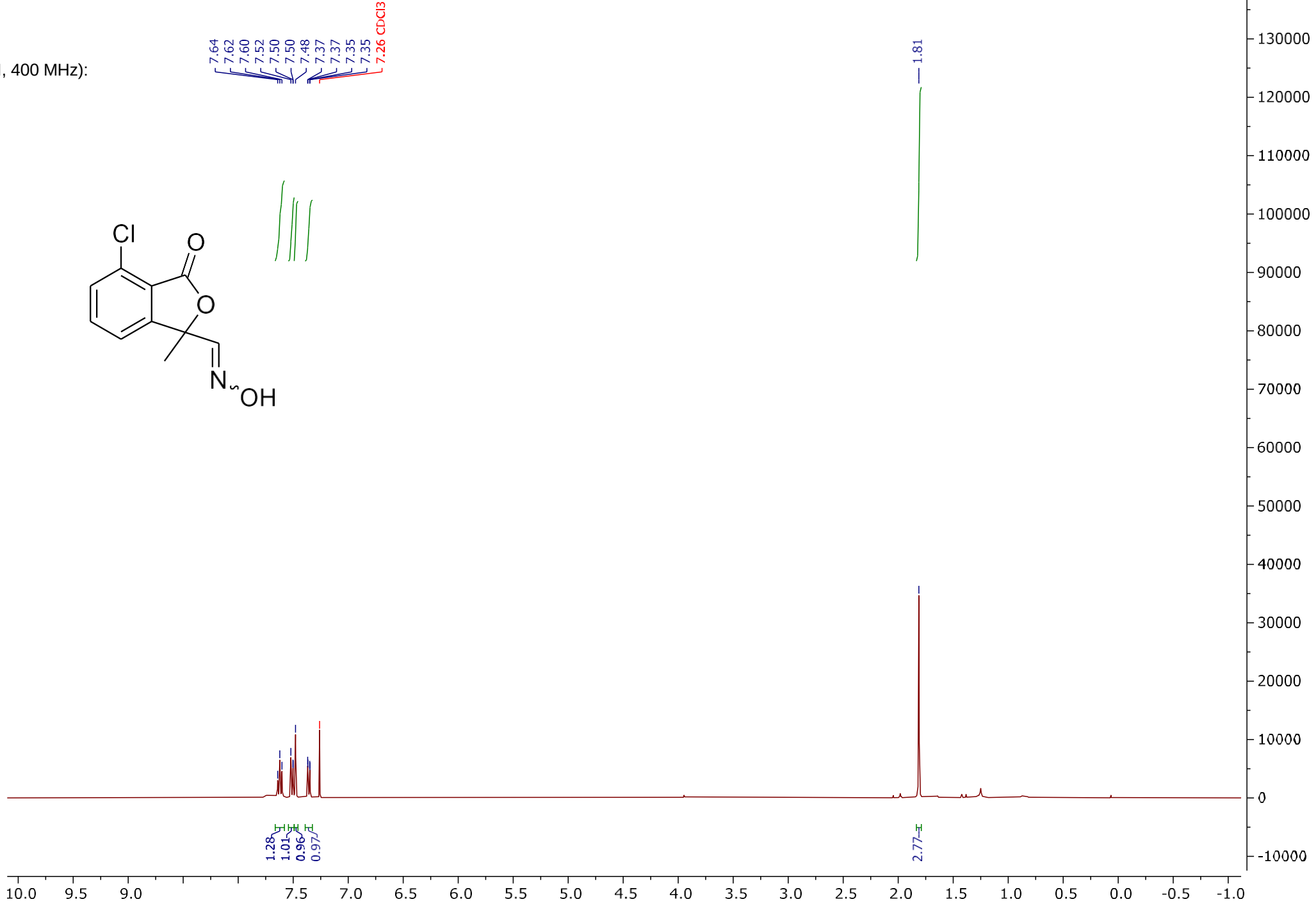
15d (^{13}C, 101 MHz):



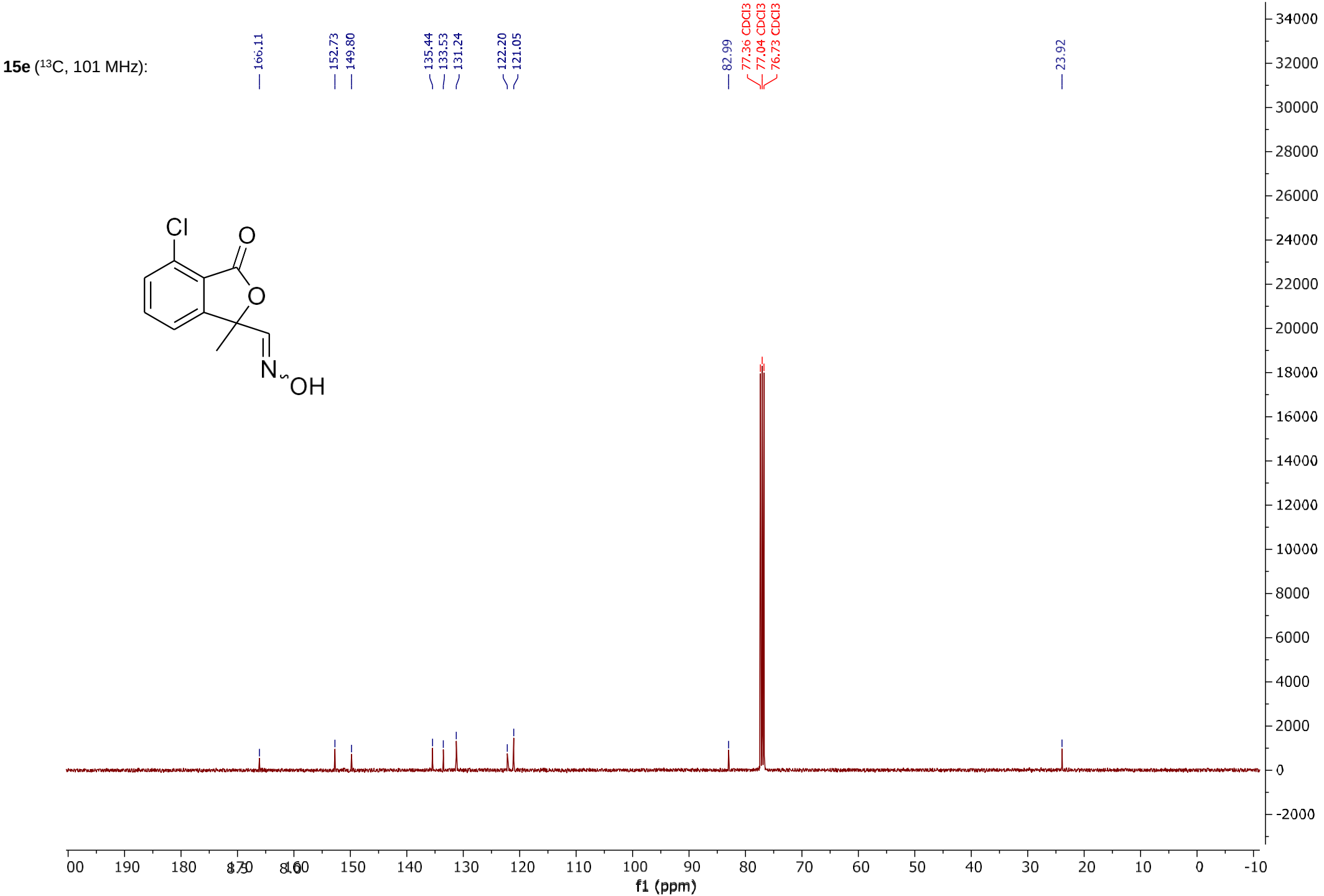
15d (^{19}F, 376 MHz):



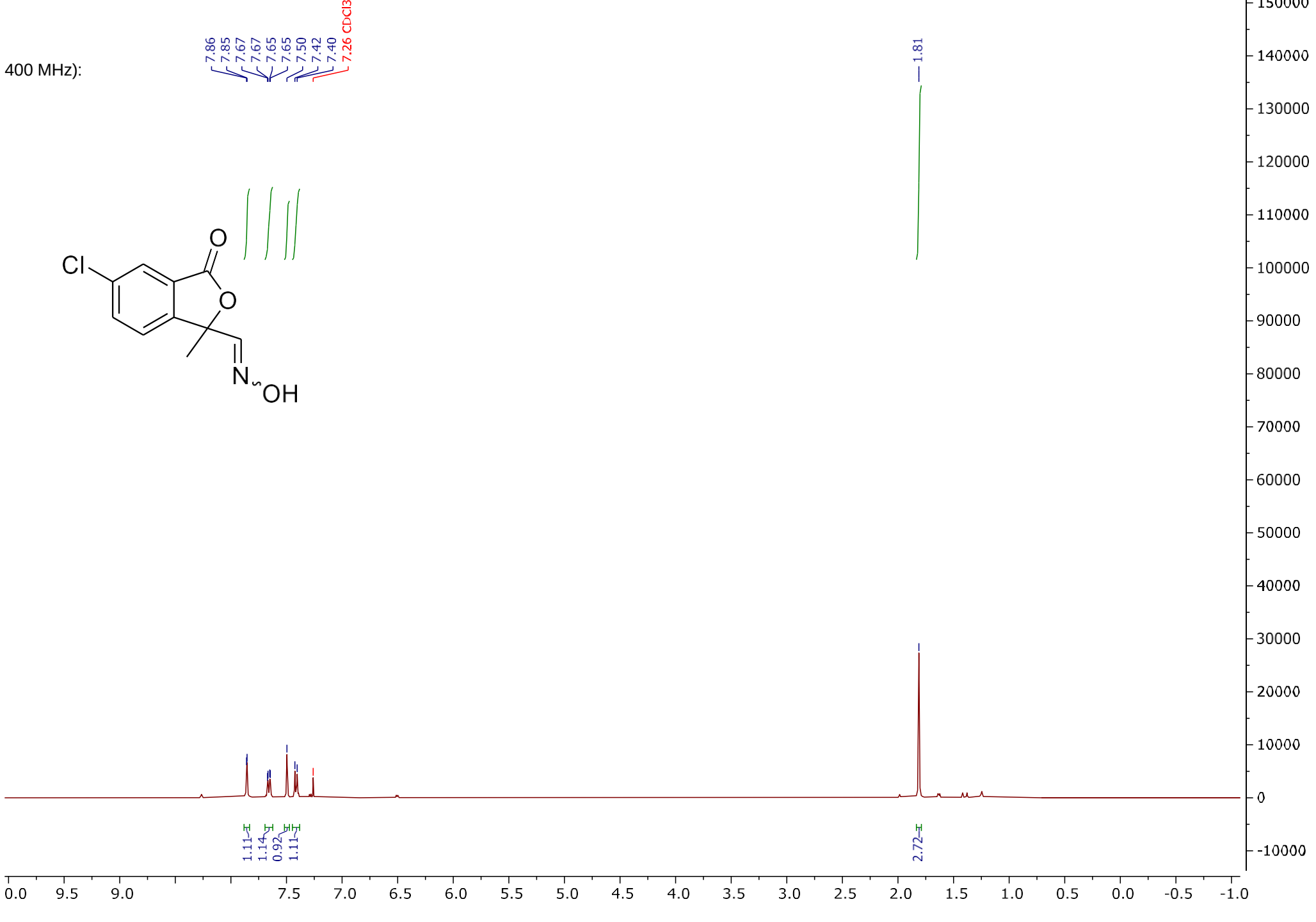
15e (^{1}H, 400 MHz):



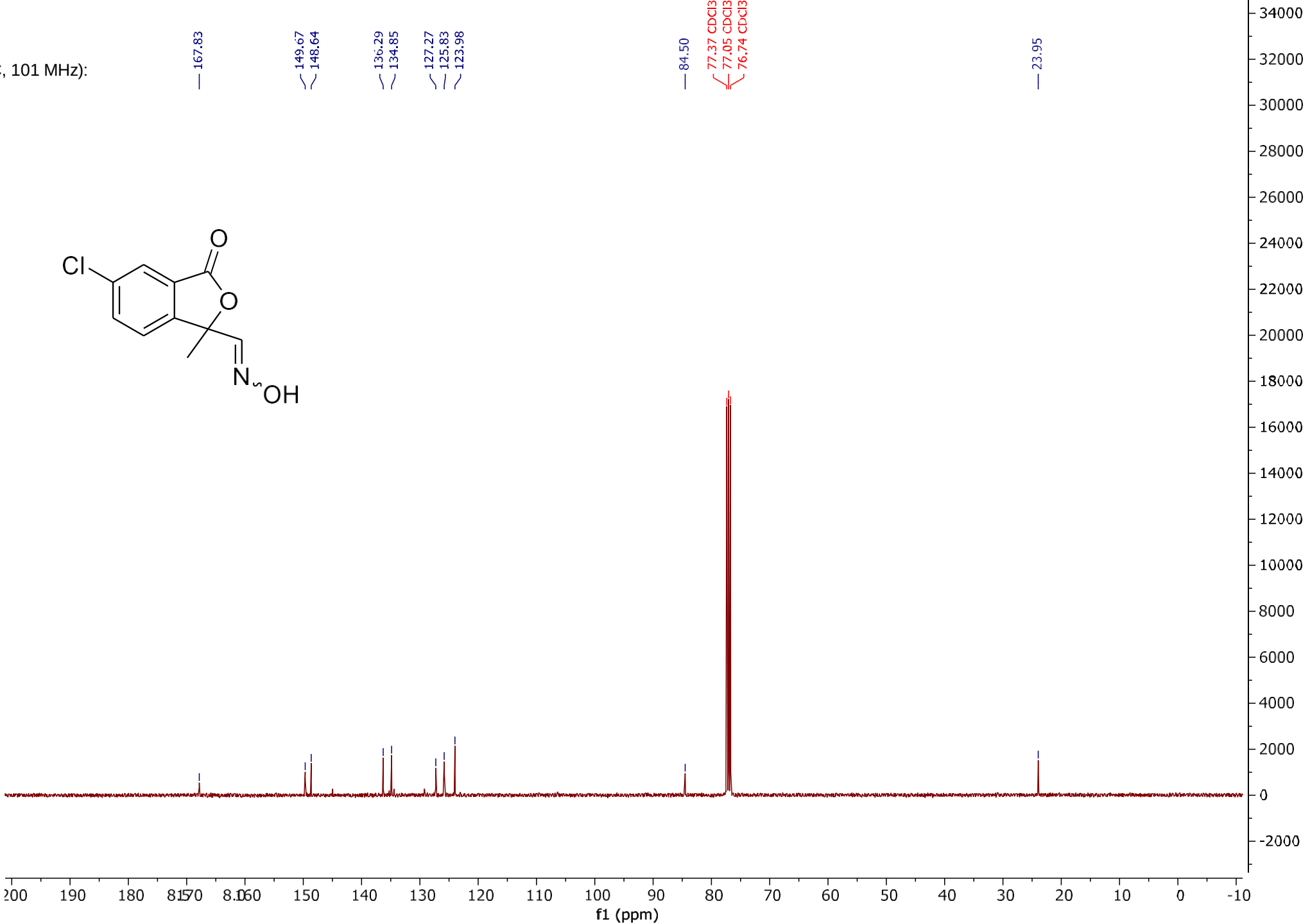
15e (^{13}C, 101 MHz):



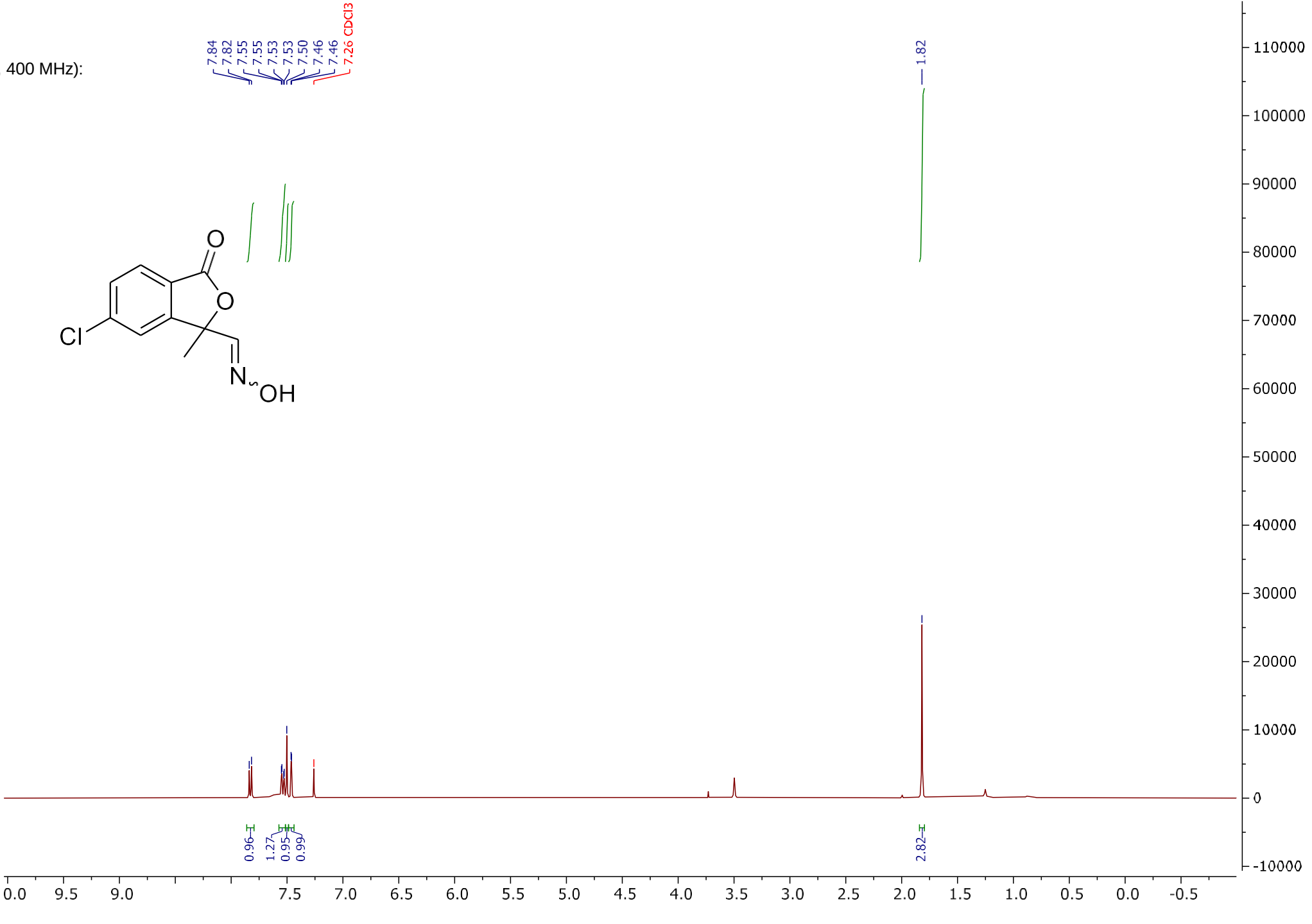
15f (^{1}H, 400 MHz):



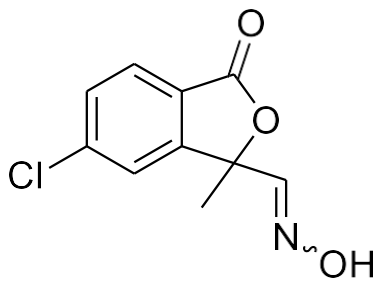
15f (^{13}C, 101 MHz):



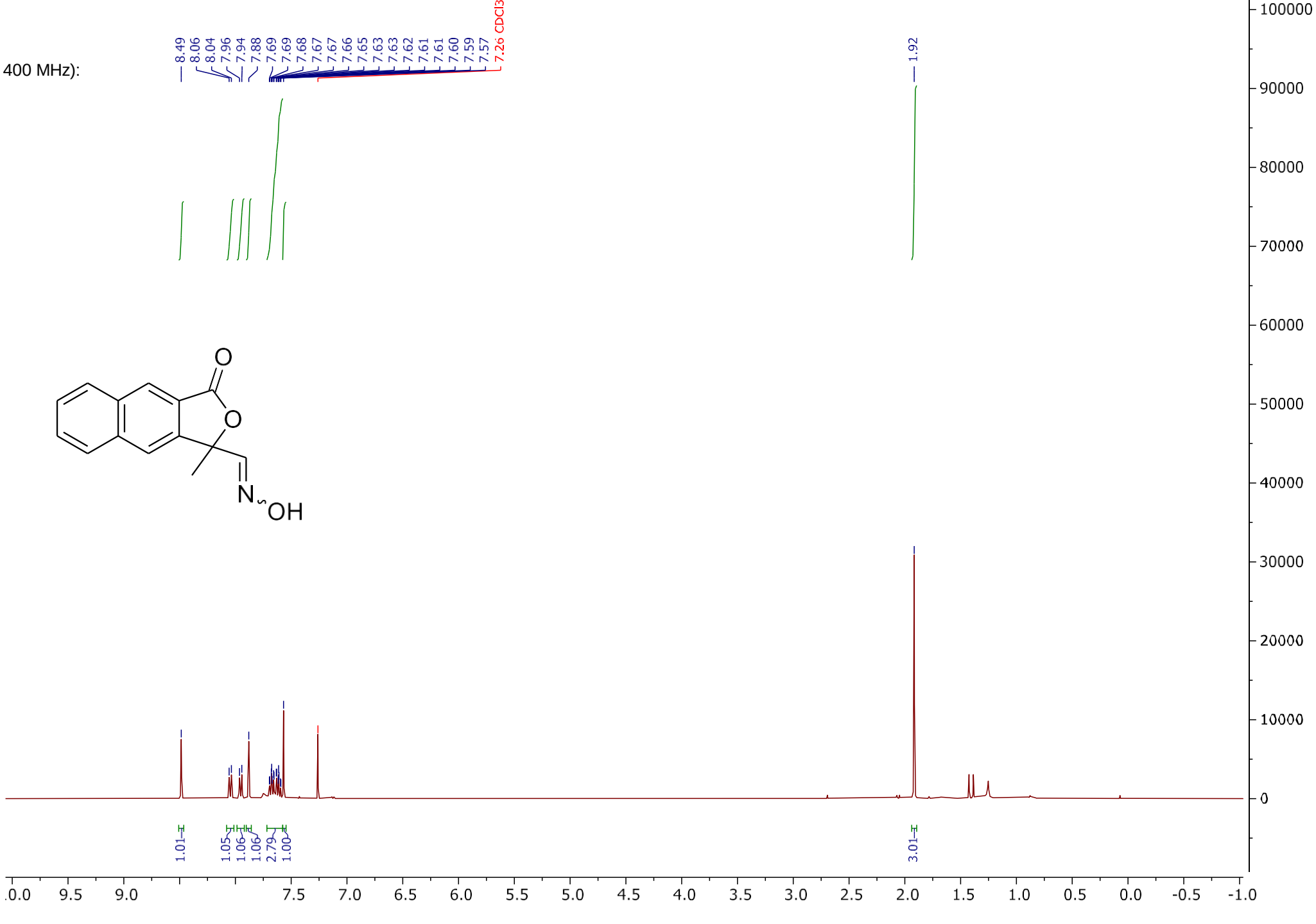
15g (^{1}H, 400 MHz):



15g (^{13}C, 176 MHz):



15j (^{1}H, 400 MHz):



15j (^{13}C, 101 MHz):