Electronic Supplementary Material (ESI) for Chemical Science.

Cobalt-Catalyzed Decarboxylative Difluoroalkylation of Nitrophenylacetic Acid Salts

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Supporting Information

Table of Contents:

1. General considerations

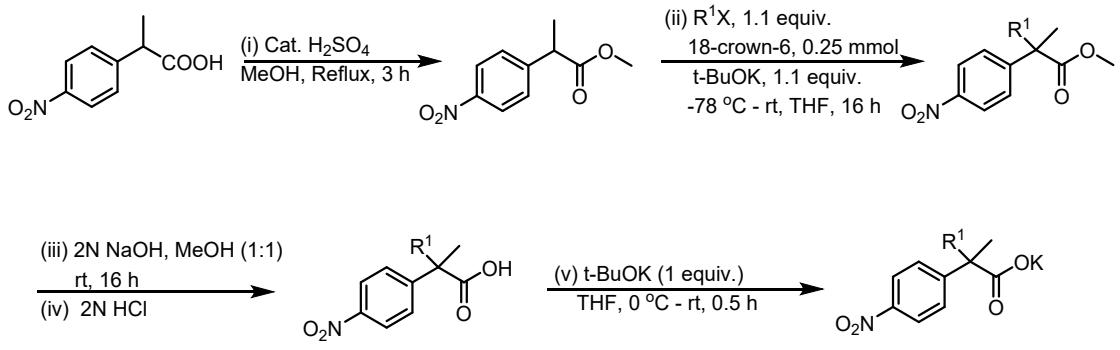
All air and moisture-sensitive reactions were carried out with the standard Schlenk technique or in an Argon-filled glove box. All phenylacetic acids, amines, and ethyl difluorobromoacetate are commercially available and were used without further purification. Unless otherwise stated, all reagents were commercially available and used as received without purification. Fluoxetine and Gabapentin were purchased from Sigma-Aldrich and Combi-Blocks respectively and, were used as received. Other chemicals were obtained from Sigma-Aldrich, Combi-Blocks, Acros, Oakwood, TCI, and Alfa-Aesar. The $CoBr_2$ (reagent grade, 99%) pre-catalyst was purchased from Sigma-Aldrich. The dppBz ligand (97%) was purchased from Sigma-Aldrich. Anhydrous acetonitrile was purchased from Fischer (AC610220010). Other anhydrous solvents were purchased from Alfa-Aesar or Sigma-Aldrich. The final decarboxylative difluoroalkylation reactions were run in a screw-threaded tube from Chemglass (CLS-4208).

Purification was accomplished with column chromatography using silica gel (60 Å porosity, 230 x 400 mesh, standard grade) which was purchased from Sorbent Technologies (catalog # 30930M-25). TLC analysis was performed (fluorescence quenching and potassium permanganate acid stain) with silica gel HL TLC plates with UV254 purchased from Sorbent Technologies. ^{1}H, ^{13}C & ^{19}F NMR spectra were obtained on a Bruker AVIIIHD 400 MHz NMR with a broadband X-channel detect gradient probe or Bruker ADVANCE 500 DRX equipped with a QNP cryoprobe. These spectra were referenced to residual protio solvent signals. The infrared (IR) spectra were measured on a Shimadzu FTIR spectrometer with 16 scans between wavenumbers of 4000 cm^{-1} and 400 cm^{-1}. HRMS data were obtained on an ESI LC-TOF Micromass LCT (Waters). GC/MS data were acquired on Shimadzu GCMS-QP2010 SE.

2. Experimental Procedures

2.1 General procedure for the synthesis of Carboxylate salts

2.1.1 Method A



Step 1: Solid 4-nitrophenylpropionic acid (975 mg, 5 mmol) was added to a round bottom flask and stirred in methanol (20 mL, 0.25 M). Sulfuric acid (0.5 mL) was added dropwise to the stirring solution, and the mixture was heated to reflux for 3 hr. After this, the reaction mixture was allowed to cool to r.t and the reaction volume was decreased by evaporating off the solvent. The remaining solution was then transferred dropwise into a stirring solution of saturated sodium bicarbonate (20 mL), crushed ice, and ethyl acetate (20 mL). The bicarbonate layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over magnesium sulfate, filtered, and evaporated. The crude ester was purified *via* flash chromatography on silica gel in 1:20 EtOAc:Hexanes.

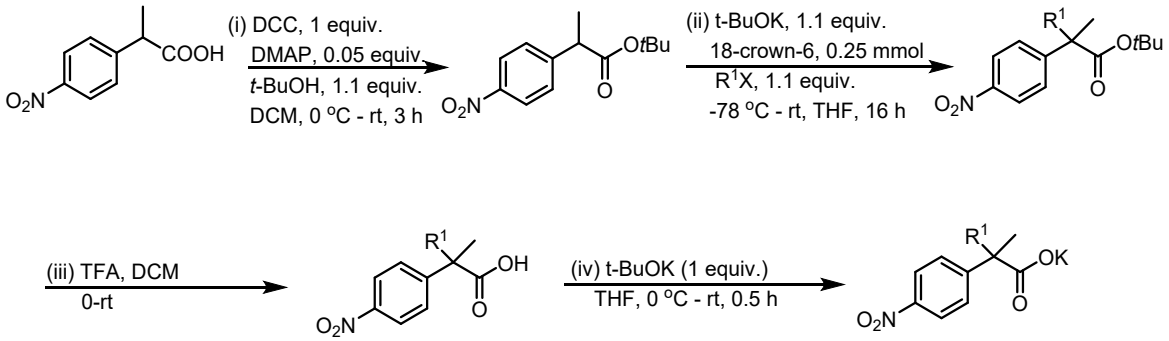
Step 2: To a flame-dried Schlenk flask equipped with a stir bar under an atmosphere of N_2 was added the methyl ester (1 equiv.), 18-crown-6 (0.25 mmol), and anhydrous THF (0.2 M). The reaction solution was cooled to -78 °C and then *t*-BuOK (1.1 equiv.) was added. The reaction was allowed to warm to room temperature and stirred at room temperature for 45 minutes. After this time, the reaction mixture was cooled to -78 °C, and alkyl halide (1.1 equiv.) was added. The reaction mixture was then warmed to room temperature and stirred overnight. Upon completion, the reaction was cooled to -78 °C, and quenched with a saturated NH_4Cl solution (20 mL). After warming the solution to room temperature, it was extracted with Et_2O (3 x 30 mL). The combined organic extracts were then washed with H_2O (1 x 10 mL) and brine (1 x 10 mL). The organic layers were then combined and dried over $MgSO_4$, filtered, and concentrated. The residue was purified *via* silica flash chromatography in 1:20 EtOAc:Hexanes.

Step 3: The hydrolysis of the ester was carried out according to a modified literature procedure.[1] To a solution of the substituted methyl ester (3 mmol) in methanol (15 mL, 0.2 M), was added 2N NaOH solution (15 mL). The resulting suspension was stirred at room temperature for 16 hours. After this time, the resulting mixture was cooled to room temperature and the reaction volume was decreased by evaporating off the solvent. The aqueous solution was then extracted with EtOAc (2 x 10 mL) and the organic extracts were discarded. The resulting aqueous solution was then acidified to pH 1-2 with 2N HCl and extracted with EtOAc (3 x 10 mL). The organic extracts were combined, washed with saturated NaCl solution (1 x 10 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to afford the acid as a crystalline white solid.

Step 4: The potassium salt of the substituted nitrophenylacetic acids was prepared by the neutralization of the acid. A flame-dried Schlenk flask with a stir bar under N_2 was charged with the acid (2 mmol) and THF (10 mL). The solution was cooled to 0 °C and *t*-BuOK (2 mmol) was added in one portion. The resulting

suspension was warmed to room temperature, stirred for 30 minutes, and then concentrated in *vacuo*. The resulting powder was washed with diethyl ether, decanted, and dried under vacuum to afford the potassium salts as solids.

2.1.2 Method B



Step 1: DCC coupling of the carboxylic acids was performed according to a literature procedure.[2] To a flame-dried Schlenk flask with a magnetic stir bar under N_2 were added the commercially available nitrophenylacetic acids (1 equiv.) and dry DCM (0.2 M). The solution was cooled to 0 °C and then *t*-butyl alcohol (1.1 equiv.), DCC (1 equiv.) and DMAP (0.05 equiv.) were added. The reactions were then warmed to room temperature and allowed to stir for 3 hours. Upon completion, the reaction mixture was filtered through a bed of Celite, and the resulting filtrate was evaporated under reduced pressure to afford the crude reaction mixture, which was purified *via* flash silica column chromatography.

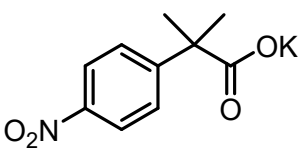
Step 2: Followed the same alkylating procedure as in Step 2, **Method A.**

Step 3: The hydrolysis of the ester was performed according to a modified literature procedure.[3] To a solution of *t*-butyl ester (3 mmol) in DCM (15 mL, 0.2 M), was added TFA (4 equiv.) at 0 °C. The resulting solution was stirred at room temperature until completion. After this time, the resulting mixture was concentrated and purified *via* flash column chromatography to afford the acids as crystalline solids. Alternatively, the resulting carboxylic acids can be purified using acid-base extractions. The crude acid was dissolved in DCM (10 mL) and washed with saturated $NaHCO_3$ solution (3 x 15 mL). The resulting aqueous solution was then acidified to pH 1-2 with 2N HCl and extracted with EtOAc (3 x 10 mL). The organic extracts were combined, washed with saturated NaCl solution (1 x 10 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to afford the carboxylic acids as crystalline solids.

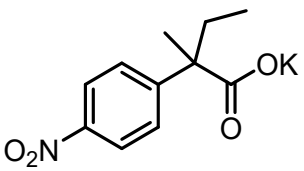
Step 4:** The potassium salts of the substituted nitrophenylacetic acids were prepared following the procedure outlined in **2.1.1**, **Method A.**

General Note: Most of these carboxylic acid salts are hygroscopic and hence shouldn't be exposed out open for longer periods. Additionally, they decompose over time and hence should be stored in the refrigerator.*

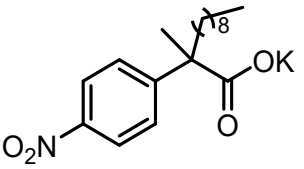
The residual solvent (diethyl ether) after the ether washes in Step 4,* ***2.1.1*,* ***Method A****, was challenging to be removed completely. Thus, the residual solvent peaks can be seen in the NMR spectra for salts* ***1h****,* ***1k****,* ***1m*** *&* ***1n****.*



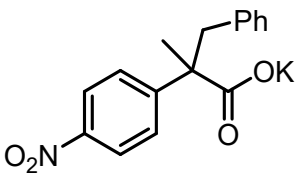
potassium 2-methyl-2-(4-nitrophenyl)propanoate (**1a**). General procedure **2.1.1**, **Method A** provided the title compound using MeI as the alkylating agent in 73% yield (20 mmol scale, over 4 steps); white solid. The product matched the previously reported literature specification.[4] **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.17 – 8.10 (m, 2H), 7.66 – 7.60 (m, 2H), 1.54 (s, 6H).**^{13}C NMR** (126 MHz, Methanol-d_4) δ 183.6, 157.9, 147.3, 128.4, 123.9, 50.1, 28.1.



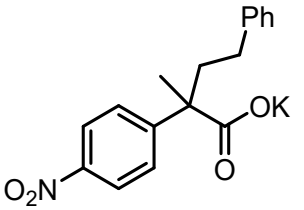
potassium 2-methyl-2-(4-nitrophenyl)butanoate (**1b**). General procedure **2.1.1, Method A** provided the title compound using bromoethane as the alkylating agent in 59% yield (5 mmol scale, over 4 steps); white solid. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.13 (dd, *J* = 9.6, 2.1 Hz, 2H), 7.62 (dd, *J* = 9.2, 2.3 Hz, 2H), 2.08 (qd, *J* = 7.5, 5.9 Hz, 1H), 2.01 – 1.87 (m, 1H), 1.49 (s, 3H), 0.84 (td, *J* = 7.3, 1.6 Hz, 3H).**^{13}C NMR** (126 MHz, Methanol-d_4) δ 182.8, 157.1, 147.3, 129.0, 123.9, 54.3, 33.6, 24.0, 10.0.



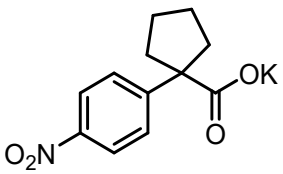
potassium 2-methyl-2-(4-nitrophenyl)undecanoate (**1c**). General procedure **2.1.2, Method B** provided the title compound using bromononane as the alkylating agent in 37% yield (3 mmol scale, over 4 steps); green solid. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.17 – 8.09 (m, 2H), 7.65 – 7.57 (m, 2H), 2.03 (td, *J* = 13.4, 10.1, 3.5 Hz, 1H), 1.90 (td, *J* = 13.0, 12.2, 4.3 Hz, 1H), 1.49 (s, 3H), 1.40 – 1.08 (m, 19H), 0.92 – 0.84 (m, 3H). **^{13}C NMR** (126 MHz, Methanol-d_4) δ 183.0, 157.5, 147.2, 128.9, 123.8, 54.0, 41.2, 33.0, 31.5, 30.7, 30.4, 26.3, 24.7, 23.7, 14.4.



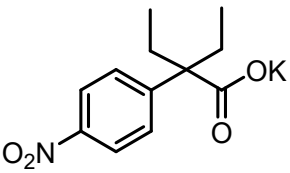
potassium 2-methyl-2-(4-nitrophenyl)-3-phenylpropanoate (**1d**). General procedure **2.1.1**, **Method A** provided the title compound using benzylbromide as the alkylating agent in 61% yield (4 mmol scale, over 4 steps); pale-yellow powder. The product matched the previously reported literature specification.[5] **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.13 – 8.06 (m, 2H), 7.57 – 7.48 (m, 2H), 7.16 – 7.05 (m, 3H), 6.98 – 6.85 (m, 2H), 3.38 (d, *J* = 13.2 Hz, 1H), 3.23 (d, *J* = 13.2 Hz, 1H), 1.44 (s, 3H). **^{13}C NMR** (126 MHz, Methanol-d_4) δ 182.6, 156.4, 147.4, 140.0, 131.6, 129.4, 128.6, 127.0, 123.7, 54.9, 47.5, 23.6.



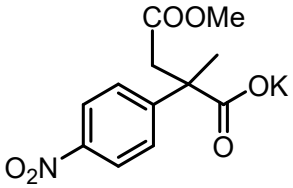
potassium 2-methyl-2-(4-nitrophenyl)-4-phenylbutanoate (**1e**). General procedure **2.1.1**, **Method A** provided the title compound using (2-bromoethyl)benzene as the alkylating agent in 43% yield (4 mmol scale, over 4 steps); pale-yellow solid. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.20 – 8.11 (m, 2H), 7.70 – 7.62 (m, 2H), 7.26 – 7.07 (m, 5H), 2.59 (td, *J* = 12.7, 4.6 Hz, 1H), 2.46 (td, *J* = 12.7, 4.6 Hz, 1H), 2.33 (td, *J* = 12.7, 4.6 Hz, 1H), 2.18 (td, *J* = 12.8, 4.6 Hz, 1H), 1.61 (s, 3H). **^{13}C NMR** (126 MHz, Methanol-d_4) δ 182.6, 157.1, 147.3, 144.3, 129.4, 129.3, 128.9, 126.6, 124.0, 54.1, 43.7, 32.9, 24.8.



potassium 1-(4-nitrophenyl)cyclopentane-1-carboxylate (**1f**). General procedure **2.1.2**, **Method B** provided the title compound using 1,4-dibromobutane as the alkylating agent in 27% yield (4 mmol scale, over 4 steps); white solid. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.16 – 8.08 (m, 2H), 7.68 – 7.57 (m, 2H), 2.73 – 2.65 (m, 2H), 1.89 – 1.63 (m, 6H). **^{13}C NMR** (126 MHz, Methanol-d_4) δ 182.1, 156.4, 147.3, 129.1, 123.8, 63.2, 38.0, 24.8.

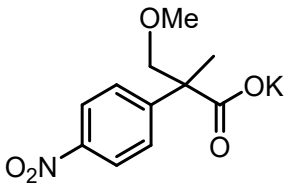


potassium 2-ethyl-2-(4-nitrophenyl)butanoate (**1g**). General procedure **2.1.2**, **Method B** provided the title compound using ethyl bromide as the alkylating agent starting from 4-nitrophenylbutyric acid in 61% yield (2 mmol scale, over 4 steps); white solid. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.18 – 8.09 (m, 2H), 7.62 – 7.54 (m, 2H), 2.25 – 2.04 (m, 2H), 1.99 (dt, *J* = 13.9, 7.4 Hz, 2H), 0.74 (t, *J* = 7.4 Hz, 6H). **^{13}C NMR** (126 MHz, Methanol-d_4) δ 182.4, 156.2, 147.2, 129.5, 123.7, 58.4, 28.4, 9.3.

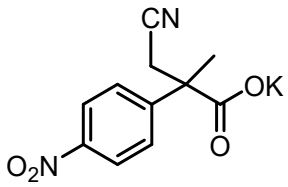


potassium 4-methoxy-2-methyl-2-(4-nitrophenyl)-4-oxobutanoate (**1h**). General procedure **2.1.2**, **Method B** provided the title compound using bromomethyl acetate as the alkylating agent in 53% yield (2 mmol scale, over 4 steps); brown solid. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.20 – 8.05 (m, 2H), 7.73 – 7.62 (m, 2H),

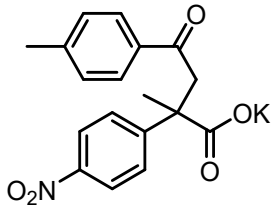
3.53 (s, 3H), 3.07 (d, *J* = 15.6 Hz, 1H), 2.99 (d, *J* = 15.7 Hz, 1H), 1.70 (s, 3H). **^{13}C NMR** (126 MHz, Methanol-d_4) δ 181.3, 174.0, 155.4, 147.6, 128.9, 123.9, 51.7, 45.5, 31.1, 24.6.



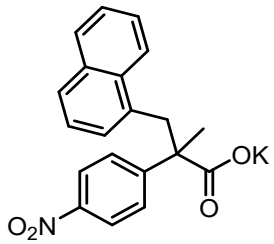
potassium 3-methoxy-2-methyl-2-(4-nitrophenyl)propanoate (**1i**). General procedure **2.1.2**, **Method B** provided the title compound using bromomethyl methylether as the alkylating agent in 33 % yield (4 mmol scale, over 4 steps); pale yellow solid. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.13 (d, *J* = 8.9 Hz, 2H), 7.63 (d, *J* = 9.0 Hz, 2H), 3.86 (d, *J* = 9.1 Hz, 1H), 3.76 (d, *J* = 9.1 Hz, 1H), 3.28 (s, 3H), 1.59 (s, 3H). **^{13}C NMR** (126 MHz, Methanol-d_4) δ 181.0, 154.6, 147.5, 129.2, 123.7, 80.7, 59.4, 54.8, 22.6.



potassium 3-cyano-2-methyl-2-(4-nitrophenyl)propanoate (**1j**). General procedure **2.1.1**, **Method A** provided the title compound using bromoacetonitrile as the alkylating agent in 54% yield (4 mmol scale, over 4 steps); dark green solid. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.20 (d, *J* = 9.0 Hz, 2H), 7.69 (d, *J* = 9.2 Hz, 2H), 3.06 (d, *J* = 1.7 Hz, 2H), 1.75 (s, 3H). **^{13}C NMR** (126 MHz, Methanol-d_4) δ 177.8, 151.6, 146.7, 127.5, 122.9, 118.6, 50.3, 28.5, 22.5.

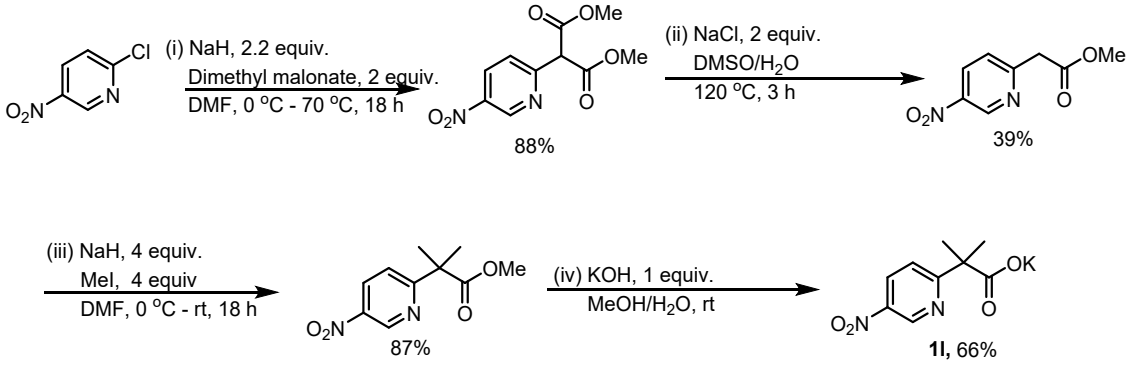


potassium 2-methyl-2-(4-nitrophenyl)-4-oxo-4-(p-tolyl)butanoate (**1k**). General procedure **2.1.2**, **Method B** provided the title compound using 2-Bromo-4'-methylacetophenone as the alkylating agent in 65% yield (4 mmol scale, over 4 steps); dark green solid. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.17 – 8.09 (m, 2H), 7.89 – 7.82 (m, 2H), 7.79 – 7.69 (m, 2H), 7.29 – 7.22 (m, 2H), 3.78 (dd, *J* = 17.4, 8.0 Hz, 2H), 2.38 (s, 3H), 1.73 (s, 3H). **^{13}C NMR** (126 MHz, Methanol-d_4) δ 200.3, 181.9, 156.3, 147.4, 145.0, 136.8, 130.1, 129.2, 128.9, 123.9, 52.1, 31.1, 25.0, 21.5.



potassium 2-methyl-3-(naphthalen-1-yl)-2-(4-nitrophenyl)propanoate (**1m**). General procedure **2.1.1, Method A** provided the title compound using naphthyl bromide as the alkylating agent in 38% yield (4 mmol scale, over 4 steps); pale yellow powder. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.12 (dd, *J* = 9.2, 2.3 Hz, 2H), 7.76 – 7.69 (m, 1H), 7.68 – 7.61 (m, 1H), 7.61 – 7.54 (m, 3H), 7.42 (s, 1H), 7.37 (td, *J* = 6.1, 5.5, 3.2 Hz, 2H), 7.02 (dd, *J* = 8.4, 1.6 Hz, 1H), 3.57 (d, *J* = 13.1 Hz, 1H), 3.39 (d, *J* = 13.2 Hz, 1H), 1.49 (s, 3H).**^{13}C NMR** (126 MHz, Methanol-d_4) δ 182.5, 156.4, 147.4, 137.6, 134.6, 133.6, 130.2, 130.1, 129.4, 128.5, 128.4, 127.8, 126.6, 126.1, 123.7, 55.1, 47.6, 23.7.

2.1.3 *Potassium 2-methyl-2-(5-nitropyridin-2-yl)propanoate* (**1l**)



The synthesis of potassium 2-methyl-2-(5-nitropyridin-2-yl)propanoate was carried out according to a modified literature procedure.[6]

Step 1*: Dimethyl malonate (7.21 ml, 63.1 mmol) was added dropwise to a suspension of sodium hydride (1.6 g, 66.7 mmol) in dry DMF (26 mL) with vigorous stirring at 0 °C for 1 hour. To the stirred reaction mixture, a solution of 2-chloro-5-nitropyridine (5.00 g, 31.5 mmol) in dry DMF (52 mL) was added dropwise and then the stirring was continued at 70 °C for 18 h. After cooling to rt, the reaction mixture was quenched with saturated aq. NH_4Cl solution (150 mL). Filtration followed by drying under vacuum afforded the product (7 g, 27.7 mmol, 88%) as a yellow solid.

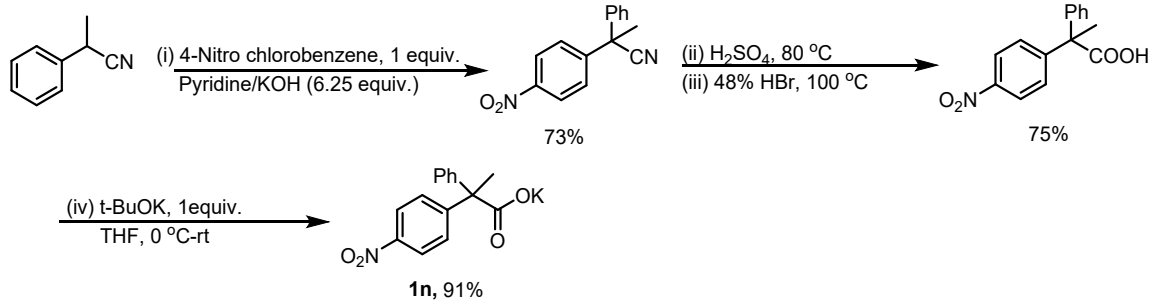
Step 2: A solution of NaCl (3.23 g, 55.4 mmol) in water (15 mL) was added to dimethyl 2-(5-nitropyridin-2-yl)malonate (7g, 27.7 mmol) in DMSO (15 mL) in a round-bottomed flask equipped with a condenser. The reaction mixture was heated at 120 °C for 3 hours. After cooling to rt, the mixture was diluted with water, extracted with ethyl acetate, dried with $MgSO_4$, and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography through silica gel using (eluent = pentane:ether, 3.5:1.5) to afford methyl 2-(5-nitropyridin-2-yl)acetate (2.11 g, 10.8 mmol, 39%) as a yellow oil.

Step 3: To a flame-dried Schlenk flask equipped with a stir bar under an atmosphere of N_2 was added methyl 2-(5-nitropyridin-2-yl)acetate (1.1 g, 5.6 mmol), MeI (1.4 ml, 22.4 mmol), and anhydrous THF (0.2 M). The reaction solution was cooled to 0 °C and then NaH (537 mg, 22.4 mmol) was added. The reaction mixture was then warmed to room temperature and stirred overnight. Upon completion, the reaction was cooled to -78 °C, and quenched with a saturated NH_4Cl solution (20 mL). The reaction mixture was extracted with Et_2O (3 x 30 mL), and the combined organic extracts were then washed with H_2O (1 x 15 mL) and brine (1 x 15 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was then purified *via* silica flash chromatography in 1:5 EtOAc:Hexanes

Step 4: To a solution of methyl 2-methyl-2-(5-nitropyridin-2-yl)propanoate (224 mg, 1 mmol) in MeOH (5 mL) was added KOH (56 mg, 1 mmol) in water (3 mL). The reaction mixture was stirred at room temperature for 20 hours. After this time, the solvent was evaporated under reduced pressure to afford a yellow solid which was washed several times with diethyl ether and dried under vacuum to afford the title salt as a pale-yellow solid in 66% yield. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 9.26 (d, *J* = 2.7 Hz, 1H), 8.46 (ddd, *J* = 8.8, 2.7, 0.9 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 1H), 1.58 (s, 6H).**^{13}C NMR** (126 MHz, Methanol-d_4) δ 183.1, 175.0, 144.5, 143.9, 132.2, 122.9, 53.3, 27.2.

***** *This step may be hazardous at a larger scale due to the danger of runaway exotherm of high equivalency of NaH in DMF.*[7]

2.1.4 *Potassium 2-(4-nitrophenyl)-2-phenylpropanoate* (**1n**)



The synthesis of potassium potassium 2-(4-nitrophenyl)-2-phenylpropanoate was carried out according to a modified literature procedure.[8]

Step 1: A solution of 4-chloronitrobenzene (3.15 g, 20 mmol) in pyridine (10 mL) was added dropwise to a vigorously stirred suspension of KOH (fine powder, 7 g) and α-methylbenzyl cyanide (2.62 g, 20 mmol) in

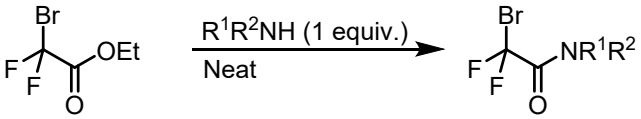
pyridine (15 mL), with the reaction temperature being maintained at 0 °C. The reaction mixture was then stirred for 24 h at 25 °C and poured onto an excess of HCl-ice mixture. The acidic aqueous mixture was extracted with DCM, and the organic phase was washed with brine, dried over anhydrous Na_2SO_4, and the solvent evaporated under vacuum. The residue was then purified via column chromatography in Hex: EtOAc, 10: to afford 2-(4-nitrophenyl)-2-phenylpropanenitrile as a white solid in 73% yield.

Step 2: 2-(4-nitrophenyl)-2-phenylpropanenitrile (500 mg, 2 mmol) was dissolved in concentrated H_2SO_4 (2 ml, 98%) and the mixture was heated at 80 °C for 2 h. The resulting pale-yellow solution was then poured onto ice and extracted with ethyl acetate (2 x 10 mL). The organic solvent was evaporated under reduced pressure, and 48% HBr solution (10 mL) was added to the remaining viscous residue. After refluxing for 8 h, the viscous oil turned to a white crystalline material. The aqueous acidic phase was then removed by decantation, and the crystalline material was washed and recrystallized with H_2O to give 2-(4-nitrophenyl)-2-phenylpropanoic acid as a white solid in 75% yield.

Step 3: The potassium salt of the 2-(4-nitrophenyl)-2-phenylpropanoic acid was prepared following the procedure outlined in **2.1.1**, **Method A, Step 4. ^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.09 (dd, *J* = 8.7, 1.7 Hz, 2H), 7.48 (dd, *J* = 8.9, 1.9 Hz, 2H), 7.35 (dt, *J* = 8.3, 1.2 Hz, 2H), 7.32 – 7.26 (m, 2H), 7.24 – 7.16 (m, 1H), 1.90 (s, 3H). **^{13}C NMR** (126 MHz, Methanol-d_4) δ 181.1, 157.8, 147.9, 147.2, 130.7, 129.4, 129.0, 127.2, 123.4, 60.4, 28.6.

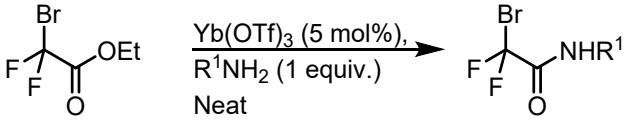
2.2 General procedure for the synthesis of bromodifluoroacetamides.

2.2.1 Method A



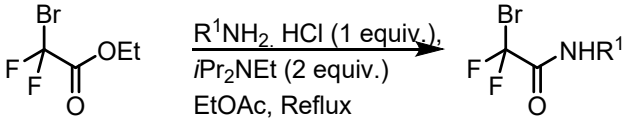
Bromodifluoroacetamides **2b**-**2h,** and **2p** were prepared according to a modified literature procedure.[9] To a round-bottom flask equipped with a stir bar was added ethyl bromodifluoroacetate (5 mmol) and equimolar amount of amine under air (5 mmol). The mixture was then stirred at room temperature and monitored by TLC. Upon complete consumption of the amine, the mixture was quenched with 10% aqueous HCl and extracted with DCM (3 x 10 mL). The combined organic extracts were then washed with H_2O (1 x 5 mL) and brine (1 x 5 mL). The organic layers were then combined and dried over $MgSO_4$, filtered, and concentrated. The resulting residue was then purified by silica flash chromatography in Hexanes: EtOAc to give the corresponding amide.

2.2.2 Method B

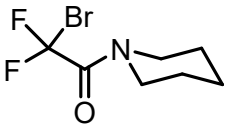


Bromodifluoroacetamides **2i**-**2m** were prepared according to a modified reported procedure.[9] To a round-bottom flask equipped with stir bar was charged ytterbium trifluoromethanesulfonate (5 mol %), ethyl bromodifluoroacetate (5 mmol), and an equimolar amount of amine under air (5 mmol). After the amine was completely consumed, the reaction mixture was quenched by adding 10% aqueous HCl and extracted with DCM (3 x 10 mL). The combined organic extracts were then washed with H_2O (1 x 5 mL) and brine (1 x 5 mL). The organic layers were then combined and dried over $MgSO_4$, filtered, and concentrated. The resulting residue was then purified by silica flash chromatography in Hexanes: EtOAc.

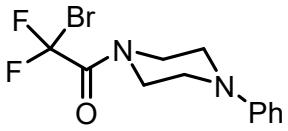
2.2.3 Method C



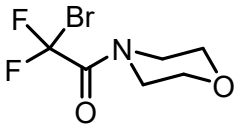
Bromodifluoroacetamides **2n** and **2o** were prepared according to a modified literature procedure.[9] To a solution of the amine hydrochloride salt (5 mmol) and diisopropylethylamine (10 mmol) in ethyl acetate (15 mL) was added ethyl bromodifluoroacetate (5 mmol). The mixture was heated to 80 °C for 7h. Upon completion, reaction mixture was cooled to room temperature and washed with 10% aqueous HCl and extracted with EtOAc (3 x 15 mL). The combined extracts were then washed with brine (1 x 5 mL) and dried over $MgSO_4$, and the solvent removed under reduced pressure. The residue was then purified by column chromatography on silica gel to give the corresponding amide.



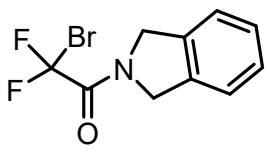
2-bromo-2,2-difluoro-1-(piperidin-1-yl)ethan-1-one (**2b**). General procedure **2.2.1**, **Method A** provided the title compound from piperidine as a colorless liquid in 89% yield. Product matched the previously reported literature specification.[9] **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 3.61 (dt, *J* = 7.6, 3.9 Hz, 4H), 1.66 (ddt, *J* = 15.3, 8.6, 4.3 Hz, 6H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 157.8 (t, *J* = 26.0 Hz), 111.0 (t, *J* = 314.6 Hz), 47.8 (t, *J* = 4.3 Hz), 45.1, 26.0, 25.6, 24.3. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -53.84.



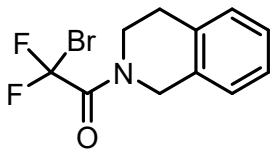
2-bromo-2,2-difluoro-1-(4-phenylpiperazin-1-yl)ethan-1-one (**2c**). General procedure **2.2.1**, **Method A** provided the title compound from N-phenylpiperazine as a white solid in 66% yield. Product matched the previously reported literature specification.[9] **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.31 (t, *J* = 8.0 Hz, 2H), 6.95 (dt, *J* = 7.6, 3.9 Hz, 3H), 3.86 (t, *J* = 5.6 Hz, 4H), 3.29 – 3.22 (m, 4H).**^{13}C NMR** (126 MHz, Chloroform-*d*) δ 157.9 (t, *J* = 26.4 Hz), 150.6, 129.5, 121.1, 116.9, 110.7 (t, *J* = 314.5Hz), 49.4, 49.3, 46.7, 43.7. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -54.2.



2-bromo-2,2-difluoro-1-morpholinoethan-1-one (**2d**). General procedure **2.2.1**, **Method A** provided the title compound from morpholine as a colorless liquid in 88% yield. Product matched the previously reported literature specification.[9] **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 3.74 (t, *J* = 4.6 Hz, 4H), 3.73 – 3.67 (m, 4H).**^{13}C NMR** (126 MHz, Chloroform-*d*) δ 158.0 (t, *J* = 26.5 Hz), 110.5 (t, *J* = 314.5Hz), 66.6, 66.2, 47.5 – 47.2 (m), 44.0. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -54.50.

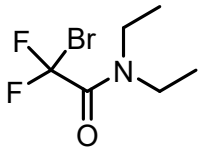


2-bromo-2,2-difluoro-1-(isoindolin-2-yl)ethan-1-one (**2e**). General procedure **2.2.1**, **Method A** provided the title compound from isoindoline as a white solid in 91% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.34 (d, *J* = 3.2 Hz, 3H), 7.32 – 7.27 (m, 1H), 5.05 (s, 2H), 4.92 (s, 2H).**^{13}C NMR** (126 MHz, Chloroform-*d*) δ 158.5 (t, *J* = 27.9 Hz), 135.8, 134.4, 128.3, 128.2, 122.9, 122.7, 111.3 (t, *J* = 315.2 Hz), 54.5, 53.4 (t, *J* = 5.0 Hz). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -57.34.

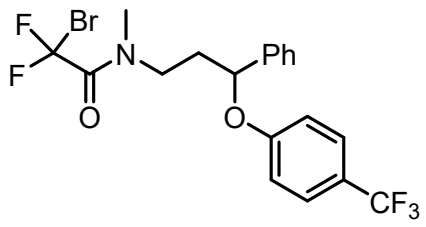


2-bromo-1-(3,4-dihydroisoquinolin-2(1H)-yl)-2,2-difluoroethan-1-one (**2f**). General procedure **2.2.1**, **Method A** provided the title compound from tetrahydroisoquinoline as a pale-yellow liquid in 85% yield. Product matched the previously reported literature specification.[10] **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.28 – 7.08 (m, 4H), 4.81 (d, *J* = 15.1 Hz, 2H), 3.97 – 3.85 (m, 2H), 2.98 (dt, *J* = 11.9,

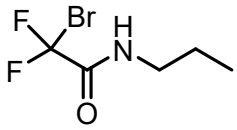
6.0 Hz, 2H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 158.5 (t, *J* = 27.9 Hz), 134.3, 133.4, 131.7, 131.6, 128.9, 128.7, 127.6, 127.2, 127.0, 126.9, 126.7, 126.2, 113.7 – 107.9 (m), 48.2 (t, *J* = 4.6 Hz), 46.1, 44.3 (t, *J* = 4.1 Hz), 42.5, 29.0, 27.9.**^{19}F NMR** (376 MHz, Chloroform-*d*) δ -54.52, -54.70.



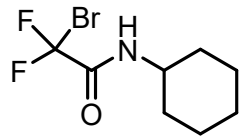
2-bromo-N,N-diethyl-2,2-difluoroacetamide (**2g**). General procedure **2.2.1**, **Method A** provided the title compound from N,N-diethyl amine as a colorless liquid in 92% yield. Product matched the previously reported literature specification.[9] **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 3.51 (qt, *J* = 7.1, 1.5 Hz, 2H), 3.42 (q, *J* = 7.1 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H).**^{13}C NMR** (126 MHz, Chloroform-*d*) δ 158.8 (t, *J* = 26.1 Hz), 111.2 (t, *J* = 315.3 Hz), 43.0 (t, *J* = 4.0 Hz), 42.2, 13.7, 12.0. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -54.39.



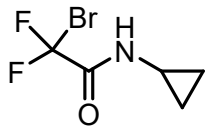
2-bromo-2,2-difluoro-N-methyl-N-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)acetamide (**2h**). General procedure **2.2.1**, **Method A** provided the title compound from Fluoxetine as a colorless oil in 63% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.51 – 7.27 (m, 7H), 6.92 – 6.85 (m, 2H), 5.21 (td, *J* = 8.1, 7.5, 4.0 Hz, 1H), 3.82 – 3.58 (m, 2H), 3.18 (t, *J* = 1.9 Hz, 2H), 3.04 (s, 1H), 2.49 – 2.13 (m, 2H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 160.2, 160.1, 159.4 (t, *J* = 26.8 Hz), 140.3, 139.8, 129.2, 129.1, 128.5, 128.3, 127.0 (q, *J* = 3.6 Hz), 125.8, 125.6, 123.9 – 122.7 (m), 115.89, 115.8, 115.7 – 108.2 (m), 78.1, 77.9, 47.9, 47.4 (t, *J* = 3.9 Hz), 37.3, 36.9 (t, *J* = 4.5 Hz), 35.6, 35.5. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -54.02, -54.05, -54.75, -61.62, -61.64. **IR** (film): 3064, 3005, 2942, 1693, 1590, 1516, 1158, 1068, 947, 879, 836 cm^{-1}. **HRMS** Calcd for $C_{19}H_{17}BrF_5NO_2$ (M+Na) = 488.0261, found 488.0254.



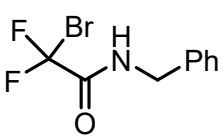
2-bromo-2,2-difluoro-N-propylacetamide (**2i**). General procedure **2.2.2**, **Method B** provided the title compound from propyl amine as a colorless oil in 73% yield.[11] Product matched the previously reported literature specification. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 6.31 (s, 1H), 3.38 – 3.28 (m, 2H), 1.69 – 1.57 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 160.2 (t, *J* = 27.2 Hz), 112.0 (t, *J* = 316.1 Hz), 42.0, 22.4, 11.2. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -60.49.



2-bromo-N-cyclohexyl-2,2-difluoroacetamide (**2j**). General procedure **2.2.2, Method B** provided the title compound from cyclohexyl amine as a white solid in 89% yield. Product matched the previously reported literature specification.[12] **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 6.07 (s, 1H), 3.86 – 3.72 (m, 1H), 1.97 (dq, *J* = 12.2, 3.7 Hz, 2H), 1.80 – 1.70 (m, 2H), 1.69 – 1.60 (m, 1H), 1.46 – 1.31 (m, 2H), 1.30 – 1.11 (m, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 159.1 (t, *J* = 27.2 Hz), 112.1 (t, *J* = 316.5 Hz), 49.6, 32.5, 25.4, 24.7. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -60.51.

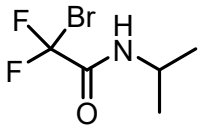


2-bromo-N-cyclopropyl-2,2-difluoroacetamide (**2k**). General procedure **2.2.2, Method B** provided the title compound from cyclopropyl amine as a white solid in 83% yield. Product matched the previously reported literature specification.[11] **^{1}H NMR**. (400 MHz, Chloroform-*d*) δ 6.35 (s, 1H), 2.81 (dq, *J* = 7.2, 3.6 Hz, 1H), 0.89 (dq, *J* = 7.1, 1.4 Hz, 2H), 0.70 – 0.61 (m, 2H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 161.1 (t, *J* = 26.6 Hz), 111.9 (t, *J* = 316.3 Hz), 23.2, 6.8, 6.7. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -60.66.

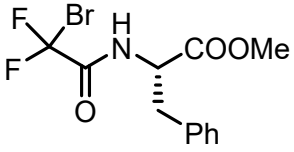


N-benzyl-2-bromo-2,2-difluoroacetamide (**2l**). General procedure **2.2.2, Method B** provided the title compound from benzyl amine as a white solid in 89% yield. Product matched the previously reported literature specification.[12] **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.43 – 7.27 (m,5H), 6.48 (s, 1H), 4.54 (d, *J* = 5.7 Hz, 2H). **^{13}C NMR** (126

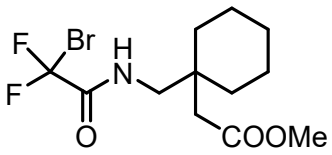
MHz, Chloroform-*d*) δ 160.03 (t, *J* = 27.6 Hz), 136.1, 129.2, 128.4, 128.0, 111.9 (t, *J* = 316.1 Hz), 44.3. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -60.57.



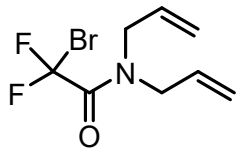
2-bromo-2,2-difluoro-N-isopropylacetamide (**2m**). General procedure **2.2.2, Method B** provided the title compound from isopropyl amine as a white solid in 71% yield. Product matched the previously reported literature specification.[9] **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 5.96 (s, 1H), 4.63 – 3.88 (m, 1H), 1.25 (d, *J* = 6.6 Hz, 6H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 159.2 (t, *J* = 27.2 Hz), 112.1 (t, *J* = 316.5 Hz), 43.0, 22.2. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -60.59.



methyl (2-bromo-2,2-difluoroacetyl)-L-phenylalaninate (**2n**). General procedure **2.2.3, Method C** provided the title compound from L-phenylalanine as a white solid in 45% yield. Product matched the previously reported literature specification.[9] **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.36 – 7.23 (m, 3H), 7.14 – 7.05 (m, 2H), 6.70 (d, *J* = 7.5 Hz, 1H), 4.87 (dt, *J* = 7.7, 5.5 Hz, 1H), 3.79 (s, 3H), 3.31 – 3.15 (m, 2H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 170.6, 159.4 (t, *J* = 28.5 Hz), 134.7, 129.4, 129.0, 127.7, 111.4 (t, *J* = 315.7 Hz), 53.8, 53.0, 37.4. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -60.61 (d, *J* = 161.4 Hz), -60.85 (d, *J* = 161.3 Hz).

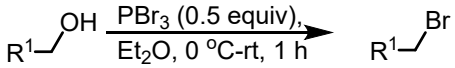


methyl 2-(1-((2-bromo-2,2-difluoroacetamido)methyl)cyclohexyl)acetate (**2o**). General procedure **2.2.3, Method C** provided the title compound from Gabapentin as a colorless oil in 77% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.50 (d, *J* = 13.0 Hz, 1H), 3.71 (s, 3H), 3.37 (d, *J* = 6.4 Hz, 2H), 2.38 (s, 2H), 1.70 – 1.22 (m, 10H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 173.7, 160.4 (t, *J* = 27.2 Hz), 112.0 (t, *J* = 316.5 Hz), 52.0, 47.0, 42.1, 37.8, 34.3, 25.7, 21.3. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -60.44. **IR** (film): 3332, 3078, 2931, 1716, 1537, 1439, 1343, 1154, 1014, 969, 898 cm^{-1}. **HRMS** Calcd for $C_{12}H_{18}BrF_2NO_3$ (M+Na) = 364.0336, found 364.0338.



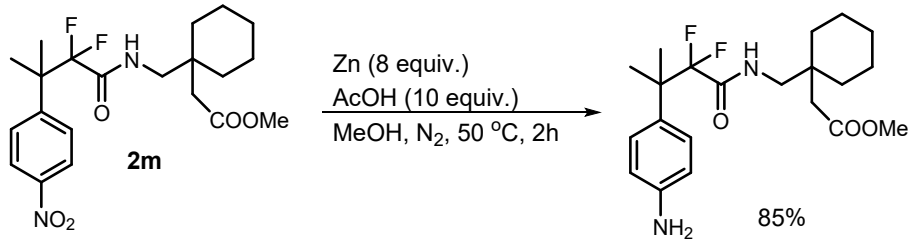
N,N-diallyl-2-bromo-2,2-difluoroacetamideacetate (**2p**). General procedure **2.2.1, Method A** provided the title compound from diallyl amine as a colorless liquid in 92% yield. Product matched the previously reported literature specification.[13] **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 5.77 (ddt, *J* = 16.8, 10.1, 5.7 Hz, 2H), 5.33 – 5.16 (m, 4H), 4.09 (dp, *J* = 5.9, 1.5 Hz, 2H), 4.00 (dt, *J* = 5.8, 1.5 Hz, 2H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 159.3 (t, *J* = 26.4 Hz), 132.0, 131.0, 119.3, 118.6, 112.0 (t, *J* = 315.1 Hz), 50.3 (t, *J* = 3.6 Hz), 48.6. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -54.31.

2.3 General Procedure for the synthesis of alkyl halides



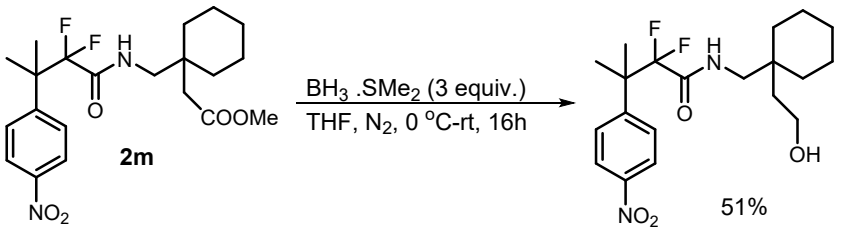
The alkyl halides were prepared according to a modified literature procedure.[14] To a flame-dried Schlenk flask with a magnetic bar under N_2, was added alcohol (3 mmol, 1 equiv.) and anhydrous ether (10 ml, 0.2M). The solution was cooled to 0 °C and 0.5 equiv. of PBr_3 was added dropwise and stirred at room temperature for 1 h. After this time, the reaction was quenched by pouring the reaction mixture into a flask containing ice-cold water and was extracted with Et_2O (3 x 20ml). The combined extracts were washed with saturated $NaHCO_3$, dried over anhydrous $MgSO_4$, and filtered. The resulting alkyl halides were then used without further purification.

2.4 Procedure for the synthesis of methyl 2-(1-((3-(4-aminophenyl)-2,2-difluoro-3-methylbutanamido)methyl)cyclohexyl)acetate (**4a**)



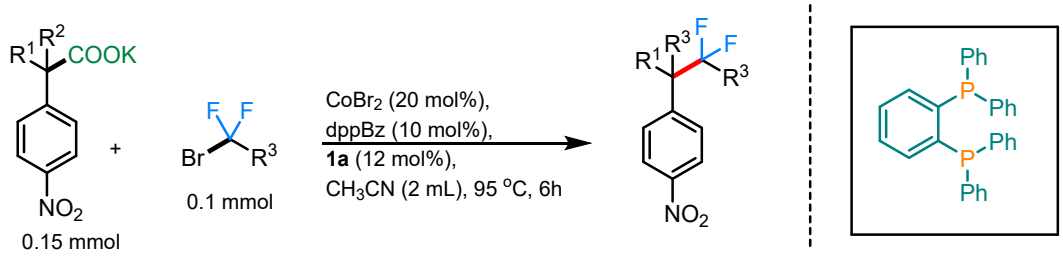
The title compound was prepared using a modified literature procedure.[15] To a solution of **2m** (0.2 mmol) in MeOH (5mL) was added activated Zn dust (1.6 mmol, 8 equiv.) and AcOH (2 mmol, 10 equiv.) under N_2 atmosphere. The mixture was stirred and heated at reflux for 2 h at 50 °C. The resulting mixture was filtered through a bed of Celite and washed with MeOH. The resulting crude mixture was purified using flash gel silica gel column chromatography in Hex:EtOAc – 3:2 to afford the title compound **4a** as a white solid in 85% yield (67.3 mg). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.26 (d, *J* = 2.0 Hz, 2H), 6.91 – 6.39 (m, 3H), 3.63 (s, 3H), 3.07 (d, *J* = 6.6 Hz, 2H), 1.98 (s, 2H), 1.56 (d, *J* = 1.3 Hz, 6H), 1.45 (q, *J* = 9.3, 8.6 Hz, 2H), 1.35 (d, *J* = 4.9 Hz, 4H), 1.13 (t, *J* = 5.4 Hz, 4H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 173.1, 164.0 (t, *J* = 29.1 Hz), 145.3, 131.4, 128.9, 119.5 (t, *J* = 259.9 Hz), 115.0 (t, *J* = 4.1 Hz), 51.7, 46.1, 43.6 (t, *J* = 21.5 Hz), 40.9, 37.5, 34.2, 25.9, 22.9 (t, *J* = 4.5 Hz), 21.4. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -112.20. **IR** (film): 3447, 3363, 3241, 3061, 2985, 2931, 1722, 1625, 1520, 1216, 829 cm^{-1}. **HRMS** Calcd for $C_{21}H_{31}F_2N_2O_3$ (M+H) = 397.2303, found 397.2318.

2.5 Procedure for the synthesis of 2,2-difluoro-N-((1-(hydroxymethyl)cyclohexyl)methyl)-3-methyl-3-(4-nitrophenyl)butanamide (**4b**)



The title alcohol was prepared according to a modified literature procedure.[16] **2m** (0.15 mmol) was dissolved in anhydrous tetrahydrofuran (4 mL) in a dry Schlenk flask under N_2. The solution was cooled to 0 °C and $BH_3.SMe_2$ (2M sol. in THF; 3 equiv.) was added dropwise to the vigorously stirred solution, at 0 °C. The resulting solution was warmed to room temperature and stirred overnight. The reaction was then quenched by the addition of MeOH (3 mL) and the resulting mixture was concentrated under reduced pressure. The pale yellow residue was purified by flash column chromatography on silica gel in Hex:EtOAc – 2:1 to obtain the title alcohol **4b** as a white solid in 51% yield (30.4 mg). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.21 – 8.13 (m, 2H), 7.69 – 7.63 (m, 2H), 7.41 (s, 1H), 3.64 (t, *J* = 5.4 Hz, 2H), 3.10 (d, *J* = 6.5 Hz, 2H), 1.81 (s, 1H), 1.65 (d, *J* = 1.3 Hz, 6H), 1.45 – 1.21 (m, 8H), 1.18 – 0.99 (m, 4H).**^{13}C NMR** (126 MHz, Chloroform-*d*) δ 163.1 (t, *J* = 29.0 Hz), 149.1, 147.2, 129.1, 123.2, 118.6 (t, *J* = 260.6 Hz), 58.5, 46.0, 44.9 (t, *J* = 22.2 Hz), 39.0, 36.1, 34.2, 26.2, 23.1 (t, *J* = 4.4 Hz), 21.4. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -111.56. **IR** (film): 3378, 3007, 2930, 1682, 1520, 1236, 1156, 859, 700 cm^{-1}. **HRMS** Calcd for $C_{20}H_{28}F_2N_2O_4$ (M+H) = 399.2095, found 399.2110.

2.6 Procedure for Cobalt-catalyzed decarboxylative difluoroalkylation.

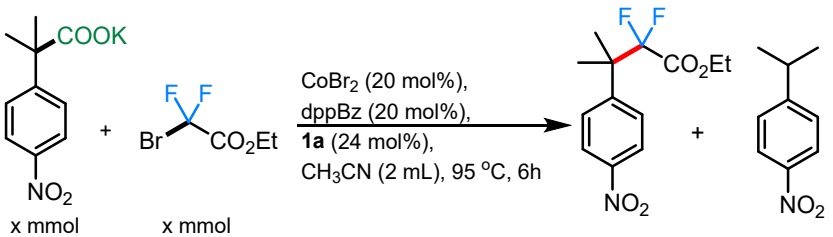


In an argon atmosphere glove box, a 10 mL screw-threaded glass tube equipped with stir bar was charged with $CoBr_2$ (20 mol%, 0.02 mmol, 0.0043 g), dppBz (10 mol%, 0.01 mmol, 0.0044 g), potassium 2-methyl-2-(4-nitrophenyl)propanoate (12 mol%, 0.012 mmol, 0.003 g), and degassed MeCN (1 mL). The reaction vessel was sealed and removed from the glovebox. The reaction mixture was then stirred for 15 minutes at 120 °C. After the pre-reduction, the reaction tube was removed from the heating source, cooled to room temperature, and brought back into the glove box. After this, the corresponding carboxylate salt (0.15 mmol) and the fluoroalkylating reagent (0.1 mmol) were added to the reaction tube followed by an additional 1 mL of degassed CH_3CN. The reaction vessel was sealed, removed from the glove box, and stirred for 6 hours at 95 °C. After this time, the reaction tube was removed from the heating source and the solvent was removed under reduced pressure. The resulting product was purified via silica gel flash chromatography in 1:5-1:40 EtOAc:Hexanes.

2.7 Procedure for larger scale decarboxylative difluoroalkylation.

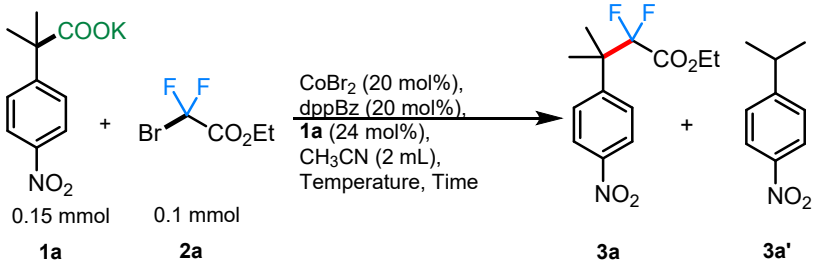
The procedure outlined in 2.4 was utilized but with a 20 mL borosilicate glass Biotage microwave vial (Biotage no. 355631) sealed with Biotage cap (Biotage no. 352298). The vial was charged with $CoBr_2$ (20 mol%, 0.2 mmol, 0.043 g), dppBz (10 mol%, 0.1 mmol, 0.044 g), potassium 2-methyl-2-(4-nitrophenyl)propanoate (6 mol%, 0.12 mmol, 0.030 g), and degassed MeCN (9 mL). After the pre-reduction, **1a** (1.5 mmol), **2o** (1 mmol) and degassed CH_3CN (9 mL) were added. The vial was sealed with the crimper and stirred for 6 hours at 95 °C. After such time, the reaction tube was removed from the heating source, cooled to room temperature, and the solvent removed under reduced pressure. The resulting product **3ac** was purified via silica gel flash chromatography in 1:40 EtOAc:Hexanes.

3. Additional Reaction Optimization Tables



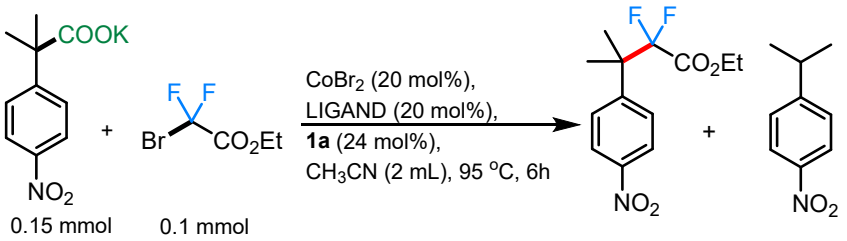
Entry	1a (x mmol)	2a (x mmol)	% Yield (3a/3a')[a]
1	0.2	0.1	74/68
2	0.1	0.2	29/19
3	0.125	0.1	56/20
4	0.15	0.1	81/36
5	0.1	0.1	52/18

Table S1: Reagents loading screening. [a] Yields determined by quantitative ^{1}H NMR analysis using anisole as a standard.



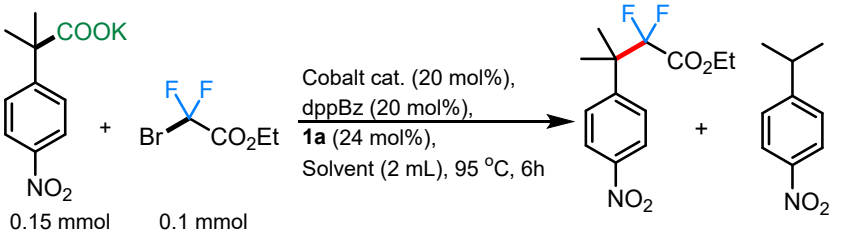
Entry	Temperature (x °C)	Time (x hrs)	% Yield (3a/3a')[a]
1	60	6	40/18
2	85	6	75/18
3	95	6	81/36
4	105	6	81/37
5	120	6	78/31
6	95	3	57/44
7	95	16	79/33

Table S2: Temperature and time screening. [a] Yields determined by quantitative ^{1}H NMR analysis using anisole as a standard.



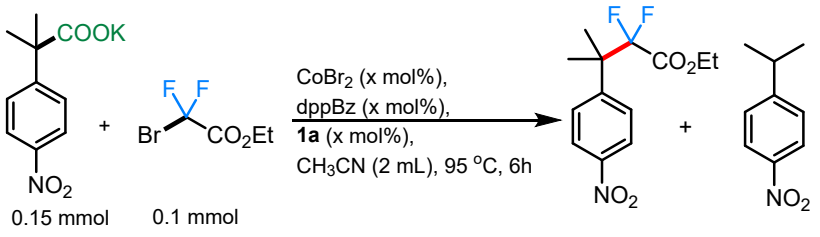
Entry	Ligand	% Yield (3a/3a')[a]
1	None	-/36
2	dppBz	81/37
3	dppe	31/52
4	dppb	<5
5	dppp	12/29
6	dppf	45/50
7	DavePhos	23/85
8	BINAP	36/84
9	DPEPhos	35/78
10	MorDalPhos	14/19
11	dtbbpy	42/28

Table S3: Ligands screened. [a] Yields determined by quantitative ^{1}H NMR analysis using anisole as a standard.



Entry	Cobalt cat.	Solvent	% Yield (3a/3a')[a]
1	No Cobalt	CH_3CN	-/36
2	$Co(BF_4)_2 .xH_2O$	CH_3CN	40/80
3	$Co(acac)_2$	CH_3CN	-/100
4	$Co(OAc)_2$	CH_3CN	79/35
5	$CoBr_2$	CH_3CN	81/36
6	$CoCl_2$	CH_3CN	17/47
7	CoI_2	CH_3CN	54/19
8	$CoBr_2$	DMF	20/94
9	$CoBr_2$	DMSO	16/92
10	$CoBr_2$	Dioxane	22/37
11	$CoBr_2$	THF	24/36
12	$CoBr_2$	Et_2O	-/-

Table S4: Solvents and Cobalt sources screened. [a] Yields determined by quantitative ^{1}H NMR analysis using anisole as a standard.

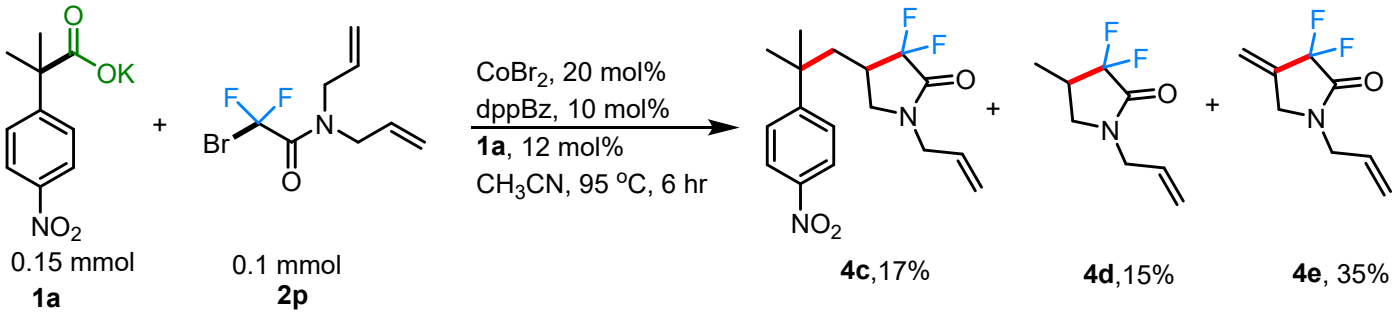


Entry	$CoBr_2$ (x mol%)	dppbz (x mol %)	1a (x mol%)	% Yield (3a/3a')[a]
1	20	20	24	81/24
2	10	10	12	15/30
3	15	15	18	24/36
4	20	40	24	62/35
5	10	20	24	31/22
6	20	10	24	85/13
7	20	10	12	84/17
8	10	5	12	18/31

Table S5: Catalyst, ligand and additive loading screening. [a] Yields determined by quantitative ^{1}H NMR analysis using anisole as a standard.

4. Mechanistic Studies

4.1 Radical clock experiment



$CoBr_2$ (4.3 mg, 0.02 mmol), dppBz (4.4 mg, 0.01 mmol) and potassium 2-methyl-2-(4-nitrophenyl)propanoate (3.0 mg, 0.012 mmol) were dissolved in degassed acetonitrile (1 mL) in a 10 mL screw-threaded glass tube under argon atmosphere. The reaction tube was sealed and removed from the glovebox and heated at 120 °C for 15 minutes to form the dark green colored solution. Upon forming the dark green colored solution, the reaction tube was cooled and taken to the glove box. Potassium 2-methyl-2-(4-nitrophenyl)propanoate (37.5 mg, 0.15 mmol), **2p** (25.4 mg, 0.1 mmol) and 1 mL of degassed CH_3CN were then added to this mixture, sealed, removed from the glovebox, and heated at 95 °C for 6 hours. The solvent was evaporated, and the crude mixture was purified via silica gel flash column chromatography (Hex/EtOAc 4:1) to isolate product **4c** (17%), product **4d** (15%) and product **4e** (35%) as inseparable mixtures.

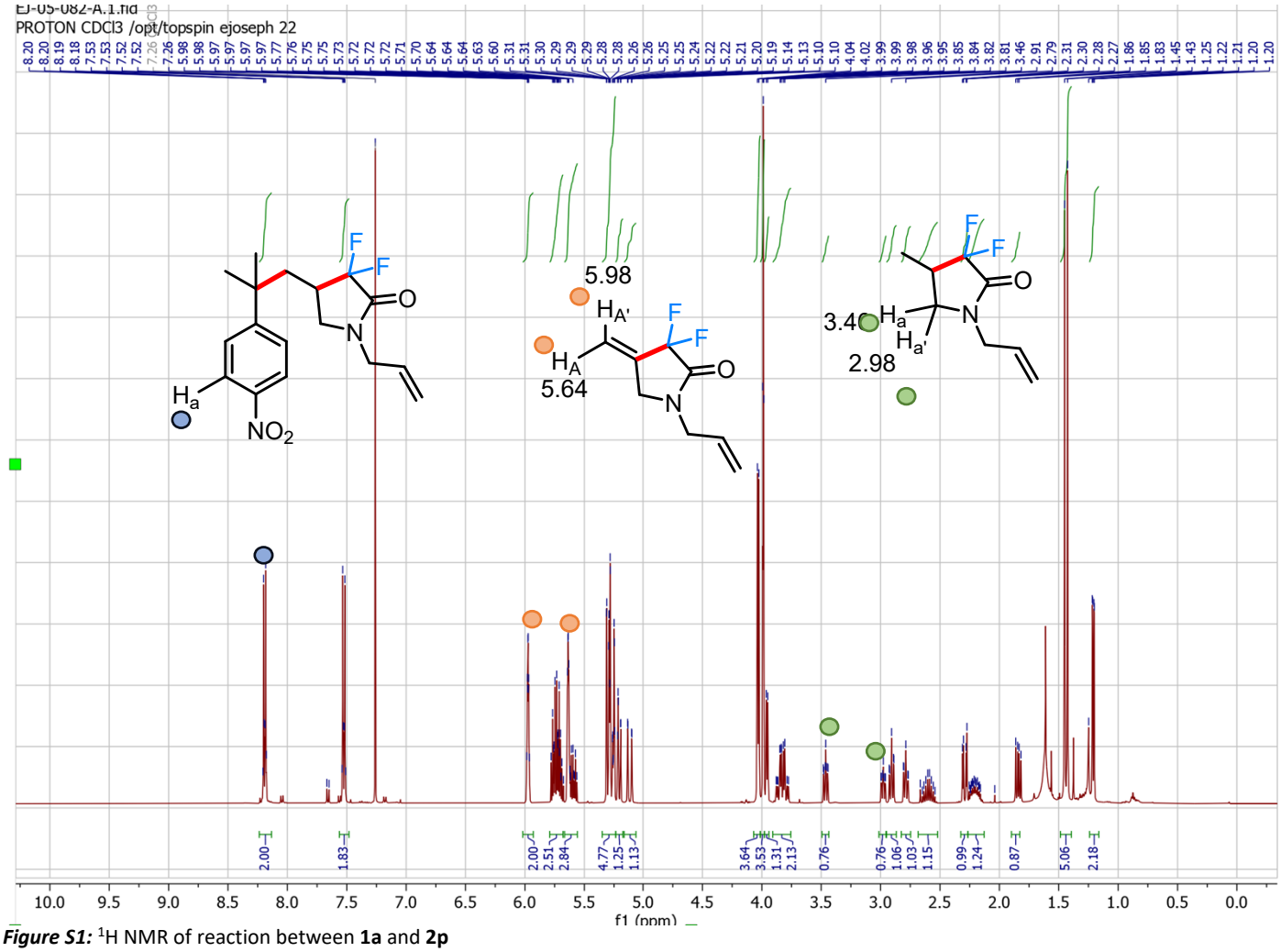


Figure S1: ^{1}H NMR of reaction between **1a** and **2p**

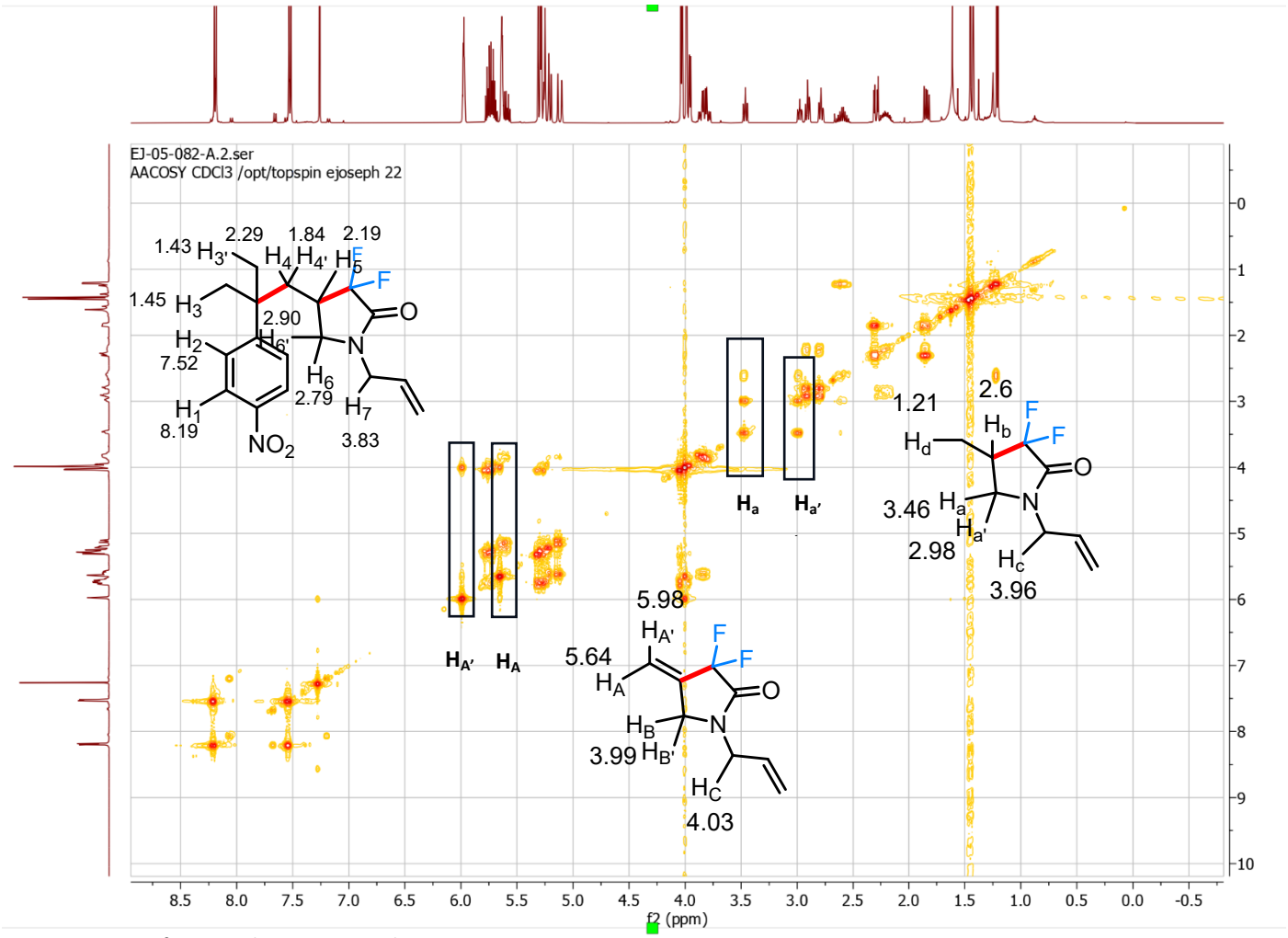
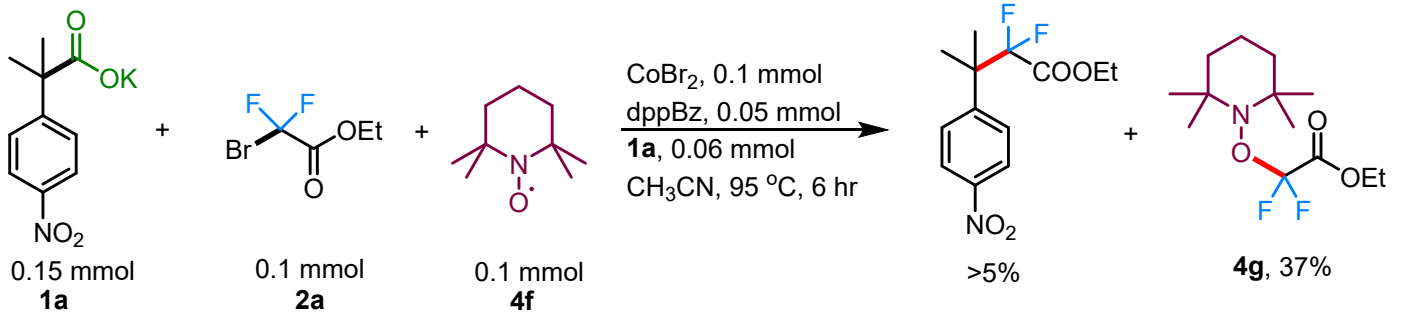


Figure S2: COSY of reaction between **1a** and **2p**

4.2 TEMPO trapping



$CoBr_2$ (22 mg, 0.1 mmol), dppBz (44 mg, 0.05 mmol) and potassium 2-methyl-2-(4-nitrophenyl)propanoate (30 mg, 0.06 mmol) were dissolved in degassed acetonitrile (5 mL) in a 20 mL Biotage microwave sealed with Biotage cap under argon atmosphere. The reaction tube was sealed and removed from the glovebox and heated at 120 °C for 15 minutes to form the dark green colored solution. Upon forming the dark green colored solution, the reaction tube was cooled and taken to the glove box. **1a** (37.5 mg, 0.15 mmol), **2a** (20.1 mg, 0.1 mmol), TEMPO (15.6 mg, 0.1 mmol) and 5 mL of CH_3CN were then added and was heated at 95 °C for 6 hours. The solvent was evaporated, and the crude mixture was purified via silica gel flash column chromatography (Hex/EtOAc 4:1) to isolate product **3a** (<5%), and product **4g** (35%) as a mixture with 42% of **3a'**.

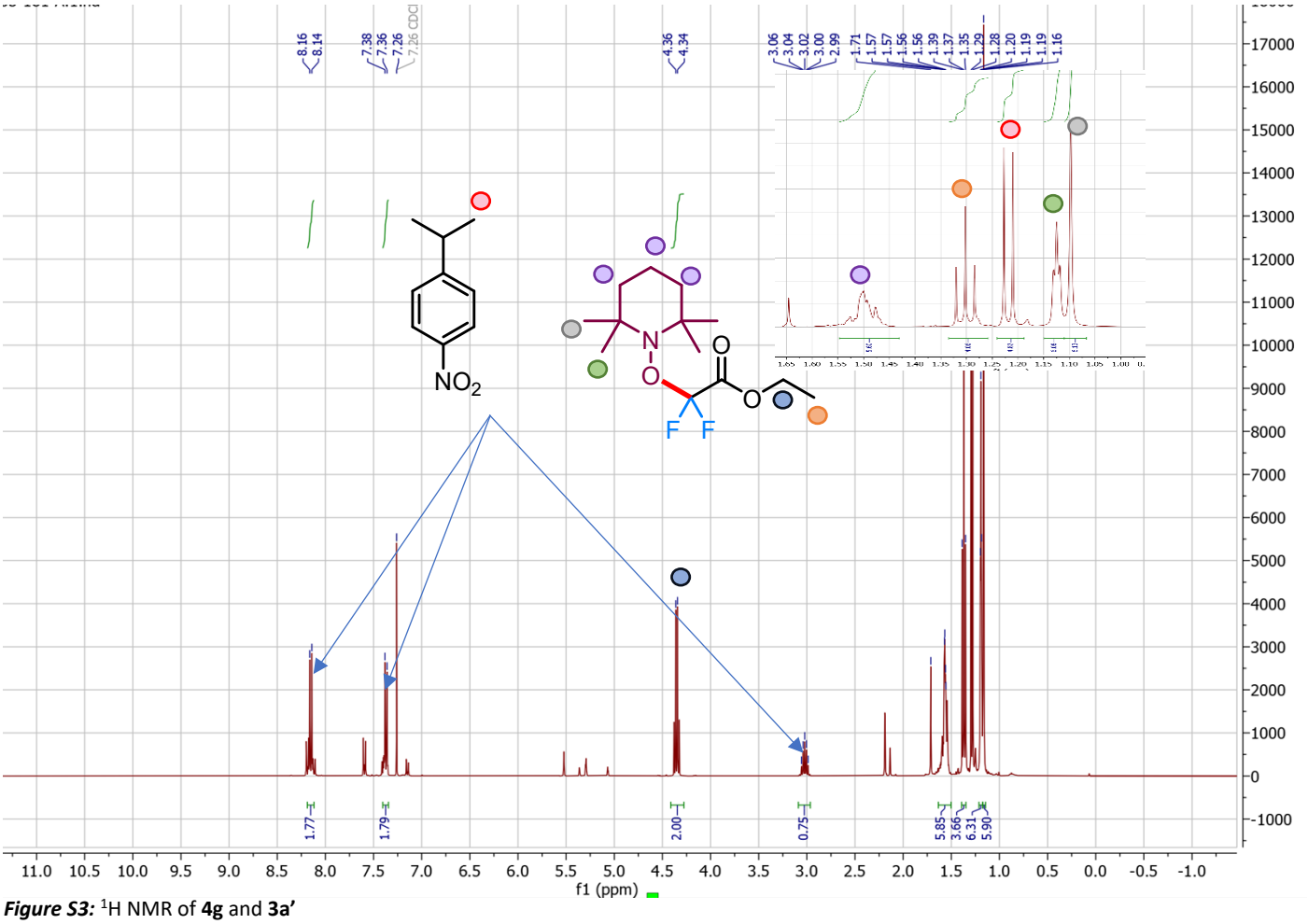
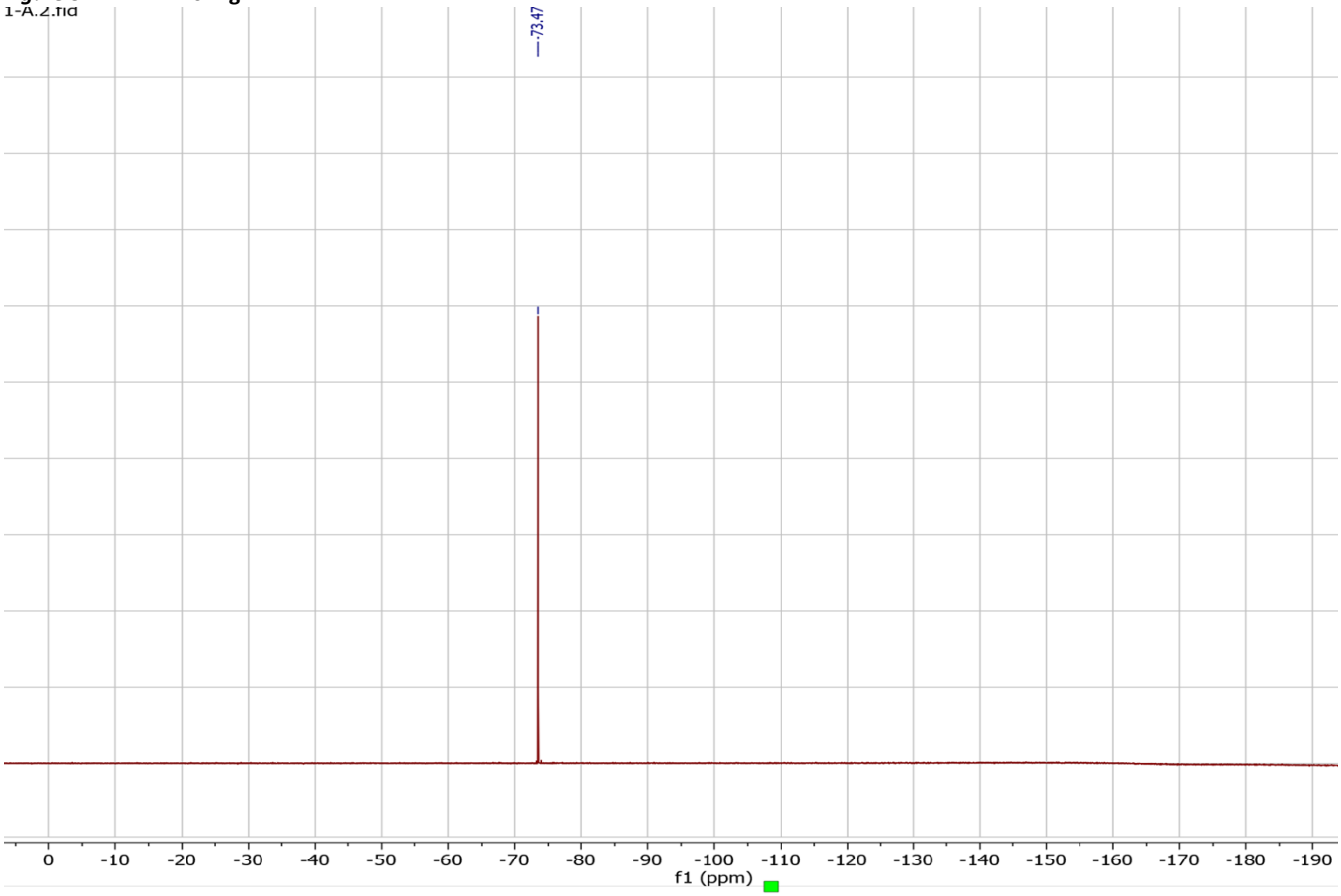
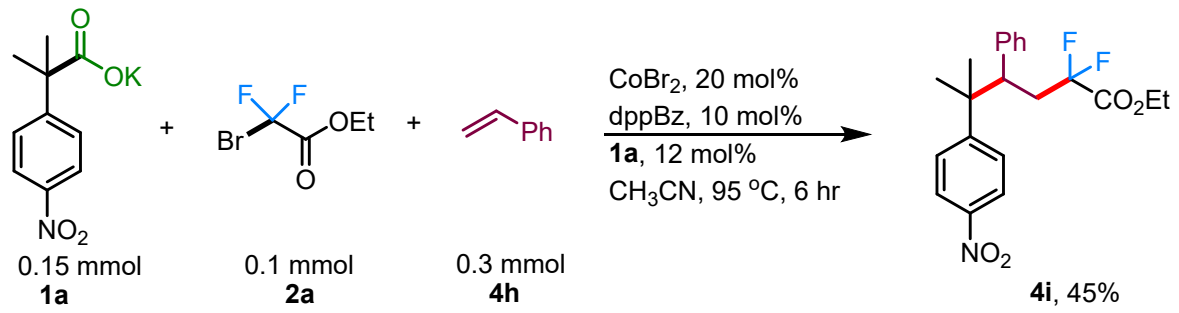


Figure S3: ^{1}H NMR of **4g** and **3a'**

Figure S4: ^{19}F NMR of **4g**



4.3 Intercepted Radical Trapping



$CoBr_2$ (4.3 mg, 0.02 mmol), dppBz (4.4 mg, 0.01 mmol) and potassium 2-methyl-2-(4-nitrophenyl)propanoate (3.0 mg, 0.012 mmol) were dissolved in degassed acetonitrile (1 mL) in a 10 mL screw-threaded glass tube under argon atmosphere. The reaction tube was sealed and removed from the glovebox and heated at 120 °C for 15 minutes to form the dark green colored solution. Upon forming the dark green colored solution, the reaction tube was cooled and taken to the glove box. **1a** (37.5 mg, 0.15 mmol), **2a** (20.1 mg, 0.1 mmol), **4h** (10.4 mg, 0.1 mmol) and 1 mL of CH_3CN were then added and was heated at 95 °C for 6 hours. The solvent was evaporated, and the crude mixture was purified via silica gel flash column chromatography (Hex/EtOAc 4:1) to isolate product **4i** in 45% yield.

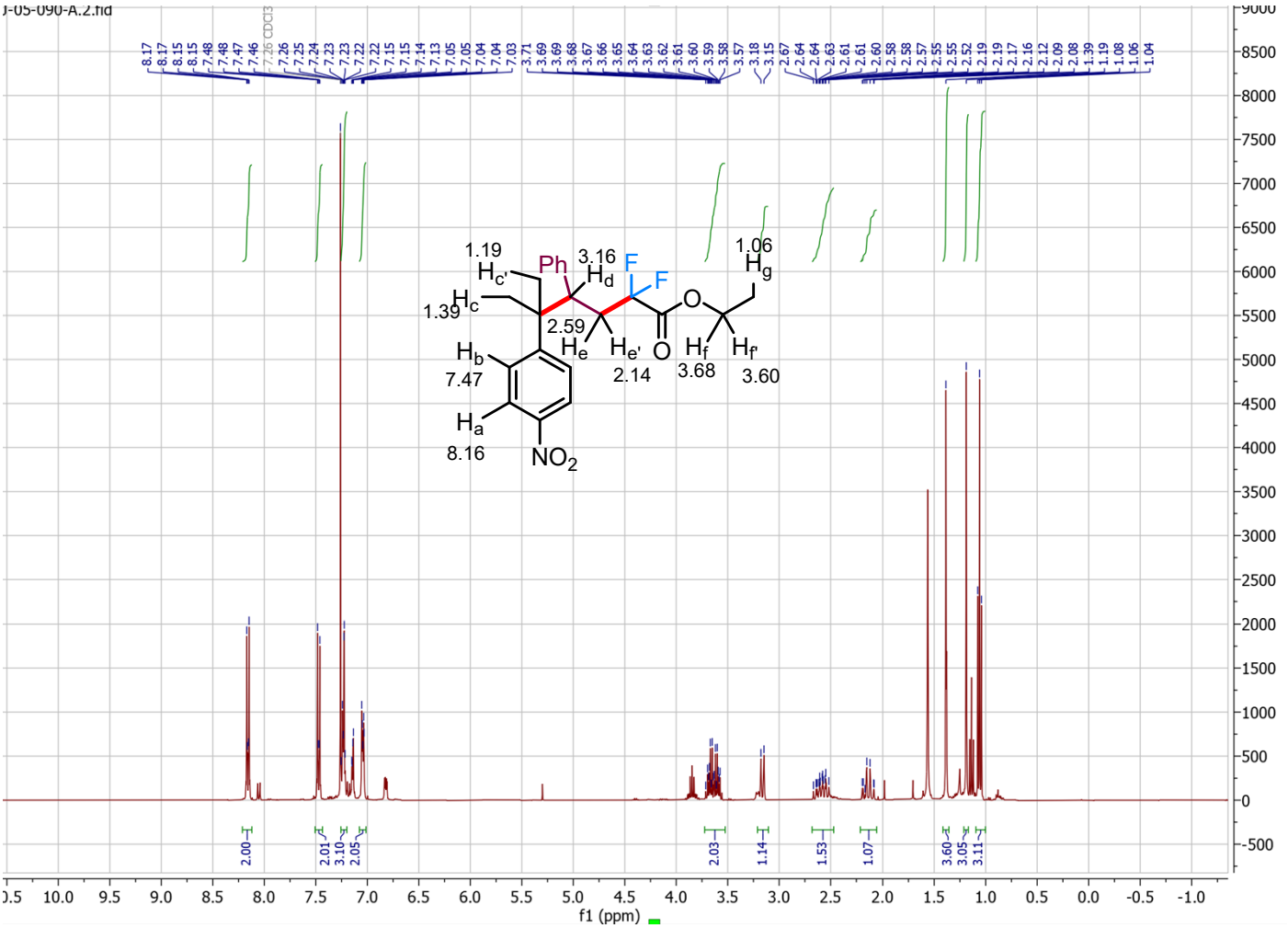


Figure S5: ^{1}H NMR of **4i**

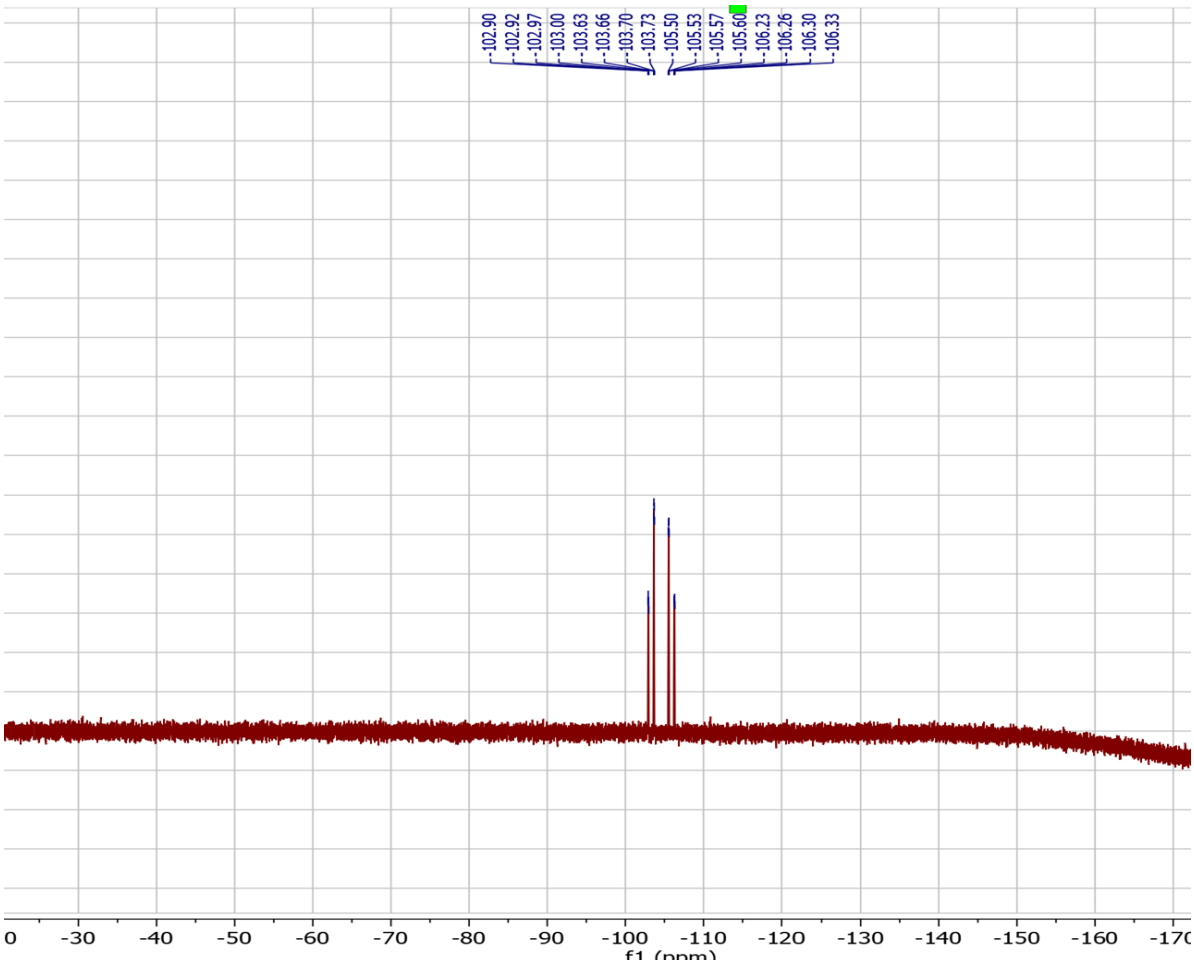


Figure S6: ^{19}F NMR of **4i**

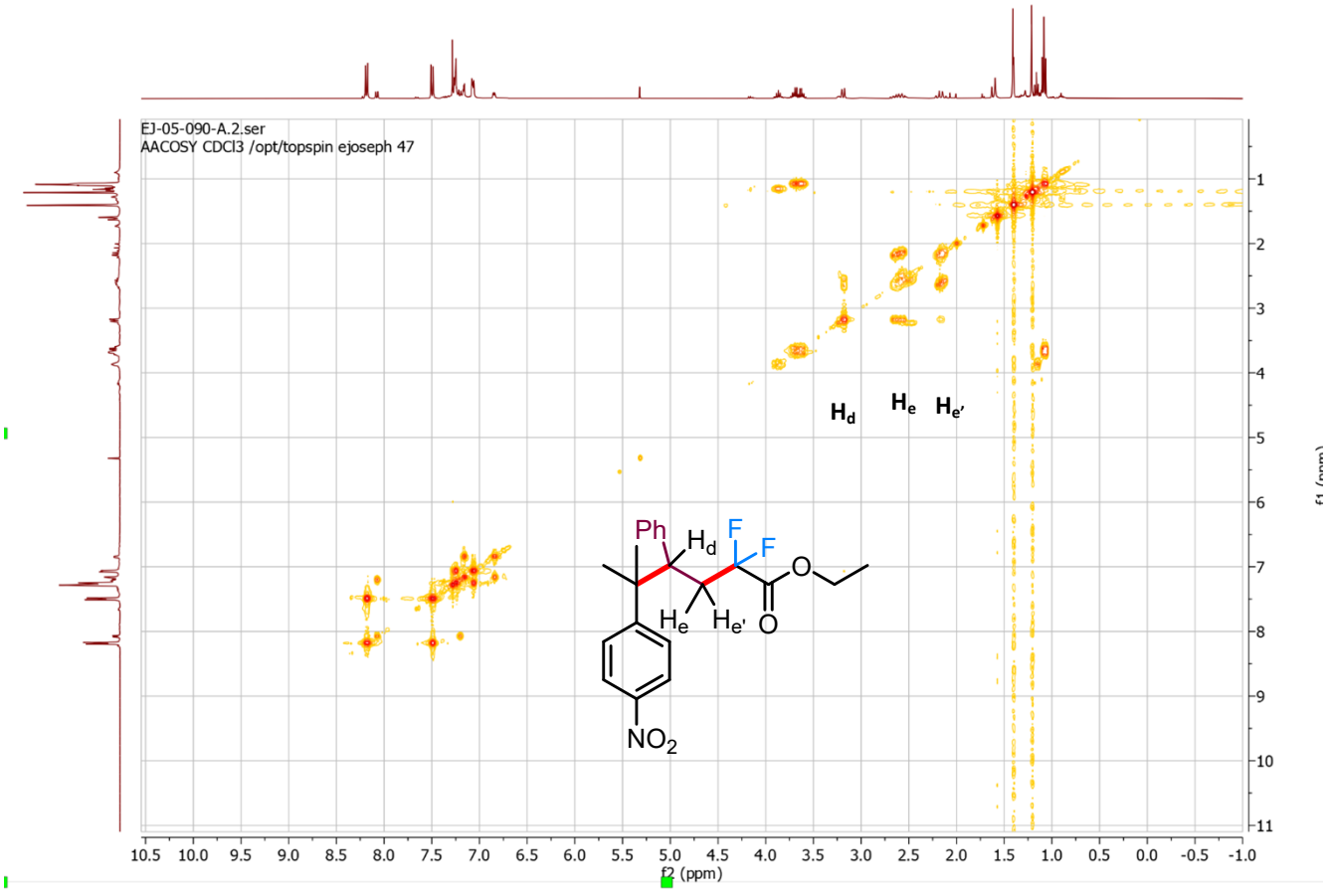


Figure S7: COSY spectra of **4i**

4.4 Sequence of SET

$CoBr_2$ (22 mg, 0.1 mmol), dppbz (44 mg, 0.05 mmol) and potassium 2-methyl-2-(4-nitrophenyl)propanoate (30 mg, 0.06 mmol) were dissolved in degassed CD_3CN (1 mL) in a 10 mL screw-threaded glass tube under argon atmosphere. The reaction tube was sealed and removed from the glovebox and heated at 120 °C for 15 minutes to form the dark green colored solution. Upon forming the dark green colored solution, the reaction tube was cooled and taken to the glove box. **2a** (20.1 mg, 0.1 mmol) and 1 mL of CD_3CN were then added and was heated at 95 °C for 2 hours.

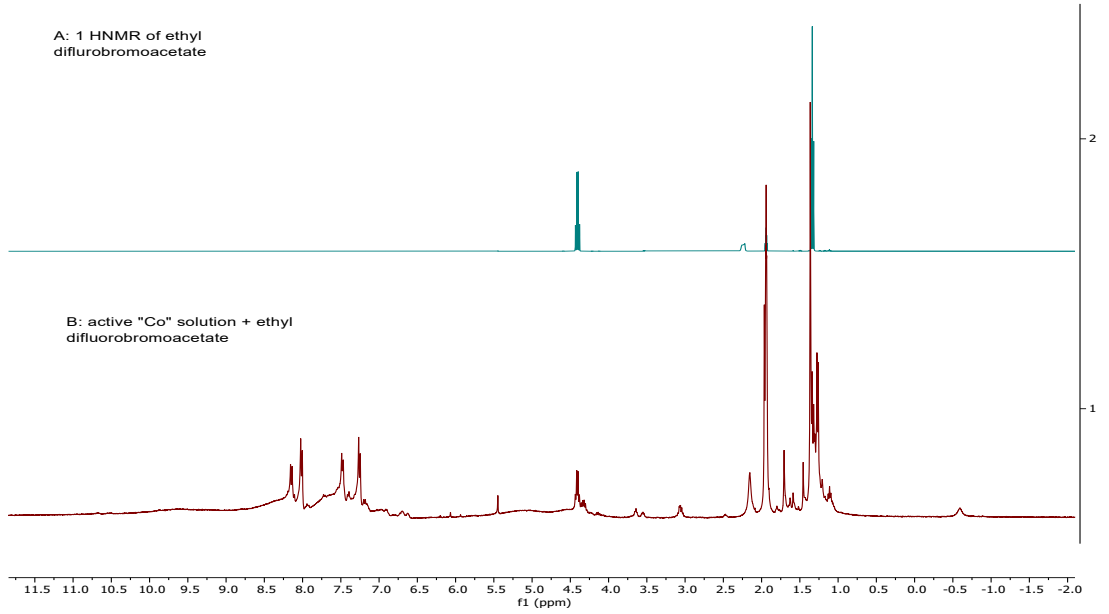
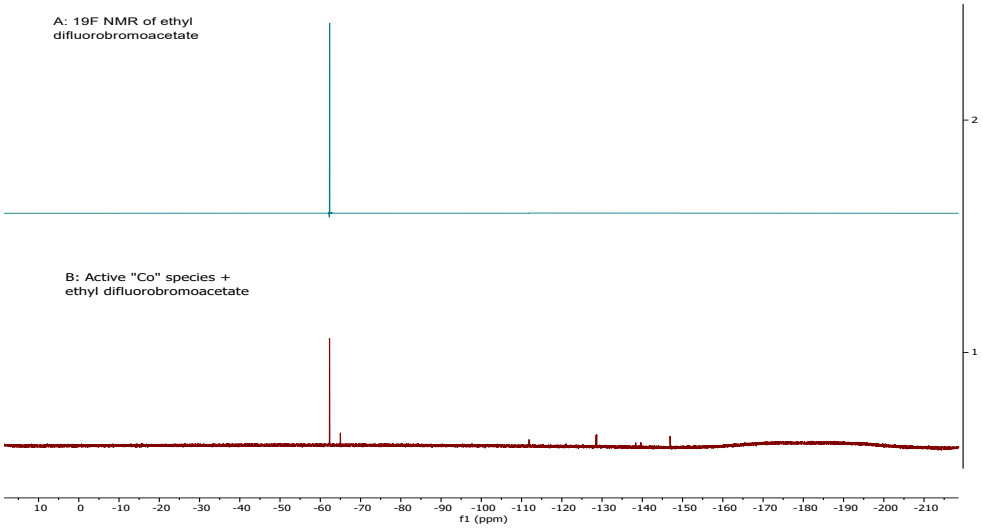


Figure S8: ^1H NMR study of the SET sequence

A: ^1H NMR of ethyl difluorobromoacetate
B: ^1H NMR of $CoBr_2$ (0.1 mmol), dppbz (0.05 mmol), **1a** (0.06 mmol), and ethyl difluorobromoacetate after stirring at 95 °C for 2 hours.

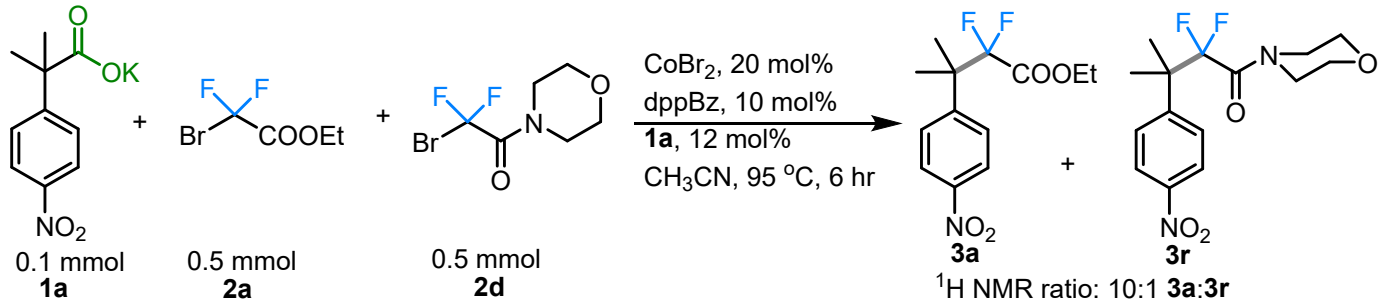


A: ^{19}F NMR of ethyl difluorobromoacetate
B: ^{19}F NMR of $CoBr_2$ (0.1 mmol), dppbz (0.05 mmol), **1a** (0.06 mmol), and ethyl difluorobromoacetate after stirring at 95 °C for 2 hours.

Figure S9: ^{19}F NMR study of the SET sequence

The NMR analysis of the reaction mixture suggested no SET and showed peaks that corresponded to free ethyl difluorobromoacetate in solution than a cobalt bound one. Moreover, NMR did not show evidence of irreversible bond scission products when subjected to Co(I)-solution. These results imply that decarboxylation followed by transmetallation has to occur prior to SET.

4.5 Competition Experiment



$CoBr_2$ (4.3 mg, 0.02 mmol), dppBz (4.4 mg, 0.01 mmol) and potassium 2-methyl-2-(4-nitrophenyl)propanoate (3.0 mg, 0.012 mmol) were dissolved in degassed acetonitrile (1 mL) in a 10 mL screw-threaded glass tube under argon atmosphere. The reaction tube was sealed and removed from the glovebox and heated at 120 °C for 15 minutes to form the dark green colored solution. Upon forming the dark green colored solution, the reaction tube was cooled and taken to the glove box. **1a** (25.0 mg, 0.1 mmol), **2a** (100.5 mg, 0.5 mmol), **2d** (122.0 mg, 0.5 mmol) and 1 mL of CH_3CN were then added to this solution, sealed, and was heated at 95 °C for 6 hours. The solvent was evaporated, and the crude mixture ran through a small plug of silica to remove cobalt salt. The product ratios were determined using ^1H NMR of the crude reaction mixture.

This experiment demonstrates that the product-determining step might be the Single Electron Transfer from Co(I)-species onto the fluoroalkanes.

4.6 Hypothetical Catalyst Activation Pathway

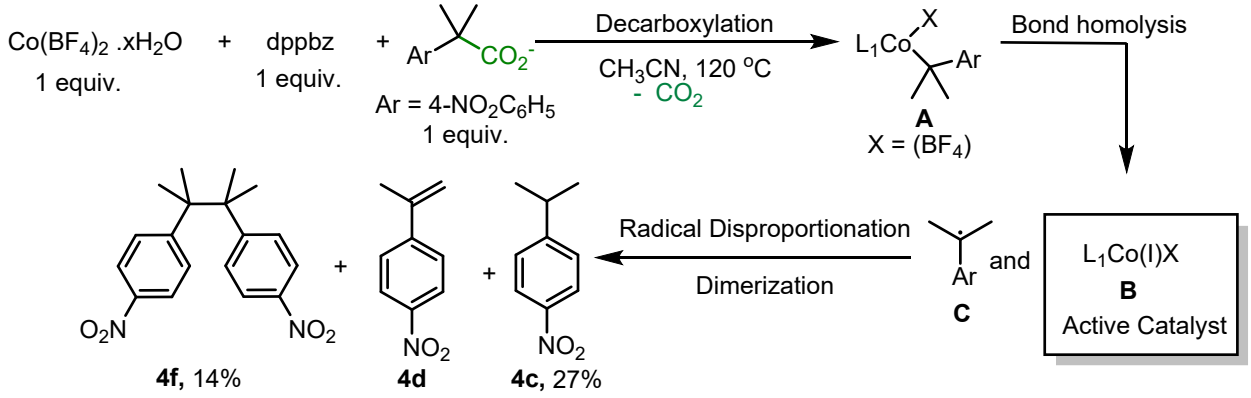
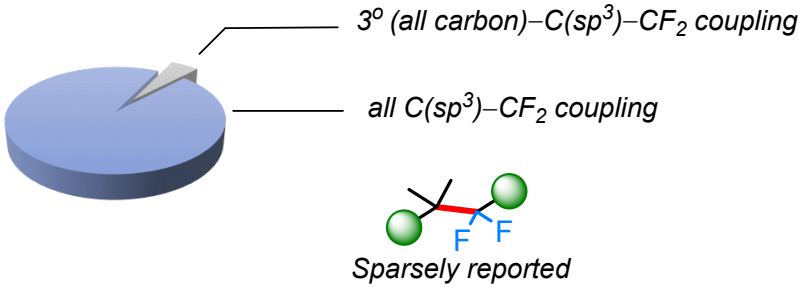


Figure S10: *Mechanism for catalyst activation*

Detailed mechanistic studies for this activation pathway was carried out in a previous publication.[4]

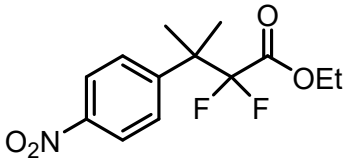
Pie-Chart

This Pie-chart was generated from a pool of 616 references obtained from a search in Sci-finder using the keyword "difluoroalkylation". "Only 7 reports involved difluoroalkylation of all carbon tertiary coupling partners".

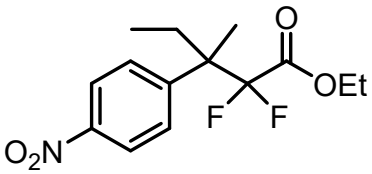


5. Compound Characterization

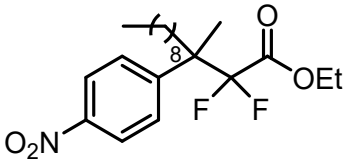
5.1 Difluoroalkanes synthesized by procedures 2.8



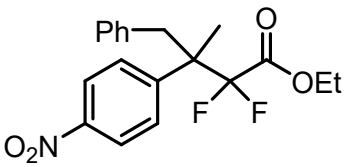
ethyl 2,2-difluoro-3-methyl-3-(4-nitrophenyl)butanoate (**3a**). General procedure 2.6 provided the difluorinated product as a white solid in 77% yield (22.1 mg, Hex:EtOAc – 15:1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.19 (d, *J* = 9.1 Hz, 2H), 7.63 (d, *J* = 9.2 Hz, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 1.61 (t, *J* = 1.1 Hz, 6H), 1.14 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 163.3 (t, *J* = 32.7 Hz), 148.3, 147.3, 129.0, 123.2, 117.1 (t, *J* = 259.7 Hz), 62.9, 44.7 (t, *J* = 21.8 Hz), 22.8 (t, *J* = 4.1 Hz), 13.9. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -111.29. **IR** (film): 3081, 2988, 1759, 1607, 1521, 1214, 1130, 859 cm^{-1}. **HRMS** Calcd for $C_{13}H_{15}F_2NO_4$ (M+H) = 288.1047, found 288.1037.



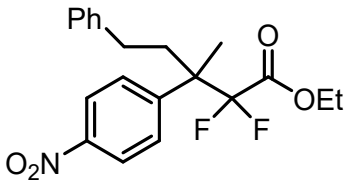
ethyl 2,2-difluoro-3-methyl-3-(4-nitrophenyl)pentanoate (**3b**). General procedure 2.6 provided the difluorinated product as a white solid in 66% yield as a white solid (19.8 mg, Hex:EtOAc – 10:1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.24 – 8.16 (m, 2H), 7.61 – 7.54 (m, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 2.34 (dq, *J* = 14.8, 7.5 Hz, 1H), 1.90 (dq, *J* = 14.8, 7.5 Hz, 1H), 1.58 (t, *J* = 1.1 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H), 0.71 (t, *J* = 7.5 Hz, 3H).**^{13}C NMR** (126 MHz, Chloroform-*d*) δ 163.4 (t, *J* = 32.9 Hz), 147.3, 146.2, 129.7, 123.2, 117.5 (t, *J* = 259.8 Hz), 62.8, 48.6 (t, *J* = 20.6 Hz), 26.8 (t, *J* = 3.6 Hz), 18.3 (t, *J* = 4.6 Hz), 13.9, 7.8. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -110.74 (d, *J* = 246.5 Hz), -111.57 (d, *J* = 248.4 Hz). **IR** (film): 3028, 2981, 1759, 1605, 1522, 1348, 1216, 849 cm^{-1}. **HRMS** Calcd for $C_{14}H_{17}F_2NO_4$ (M+Li) = 308.1286, found 308.1295.



ethyl 2,2-difluoro-3-methyl-3-(4-nitrophenyl)dodecanoate (**3c**). General procedure 2.6 provided the difluorinated product as a pale-yellow oil in 36% yield (14.4 mg, Hex:EtOAc – 20:1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.23 – 8.13 (m, 2H), 7.60 – 7.54 (m, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.29 – 2.17 (m, 1H), 1.84 (ddd, *J* = 13.5, 12.3, 4.3 Hz, 1H), 1.59 (s, 3H), 1.37 – 1.17 (m, 14H), 1.13 (t, *J* = 7.1 Hz, 3H), 0.86 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 163.3 (t, *J* = 154.3 Hz), 147.1, 146.5, 129.4, 123.1, 118.3 (t, *J* = 259.9 Hz), 62.7, 48.2 (t, *J* = 20.9 Hz), 33.9, 31.8, 30.0, 29.5, 29.3, 29.2, 23.3, 22.6, 18.7 (t, *J* = 4.2 Hz), 14.08, 13.77. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -110.78 (d, *J* = 248.0 Hz), -111.64 (d, *J* = 246.6 Hz). **IR** (film): 3030, 2984, 2923, 1759, 1605, 1521, 1213, 1153, 854 cm^{-1}. **HRMS** Calcd for $C_{21}H_{31}F_2NO_4$ (M+Na) = 422.2119, found 422.2102.

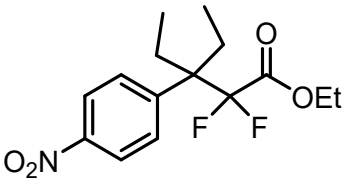


ethyl 2,2-difluoro-3-methyl-3-(4-nitrophenyl)-4-phenylbutanoate (**3d**). General procedure 2.6 provided the difluorinated product as a white solid in 45% yield (16.5 mg, Hex:EtOAc – 10:1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.23 – 8.15 (m, 2H), 7.65 – 7.59 (m, 2H), 7.18 – 7.04 (m, 3H), 6.75 – 6.68 (m, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.58 (d, *J* = 13.7 Hz, 1H), 3.21 (d, *J* = 13.8 Hz, 1H), 1.50 – 1.46 (m, 3H), 1.08 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 163.1 (t, *J* = 33.0 Hz), 147.4, 146.3 (d, *J* = 3.6 Hz), 135.2, 130.6, 129.8 (t, *J* = 3.3 Hz), 128.1, 127.0, 123.1, 117.7 (t, *J* = 261.7 Hz), 62.9, 51.9 – 47.3 (m), 40.45 (d, *J* = 2.6 Hz), 40.40 (d, *J* = 2.7 Hz), 18.6 (t, *J* = 4.1 Hz), 13.8. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -109.12 (d, *J* = 249.3 Hz), -110.78 (d, *J* = 249.3 Hz). **IR** (film): 3088, 2985, 1759, 1605, 1514, 1348, 1216, 852 cm^{-1}. **HRMS** Calcd for $C_{19}H_{19}F_2NO_4$ (M+Na) = 386.1180, found 386.1188.

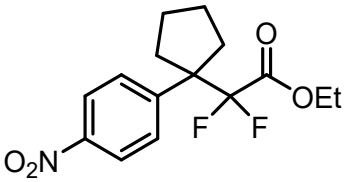


ethyl 2,2-difluoro-3-methyl-3-(4-nitrophenyl)-5-phenylpentanoate (**3e**). General procedure 2.6 provided the difluorinated product as a yellow oil in 56% yield (21.1 mg, Hex:EtOAc – 10:1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.28 – 8.20 (m, 2H), 7.66 (d, *J* = 7.9 Hz, 2H), 7.32 – 7.25 (m, 2H), 7.24 – 7.15 (m, 1H), 7.13 –

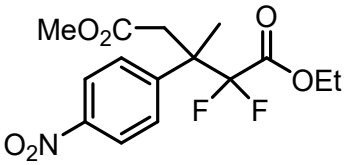
7.06 (m, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.52 (dd, *J* = 12.3, 8.8 Hz, 2H), 2.23 (dd, *J* = 12.4, 8.7 Hz, 1H), 2.14 (dd, *J* = 12.6, 8.8 Hz, 1H), 1.72 (t, *J* = 1.2 Hz, 3H), 1.12 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 163.2 (t, *J* = 32.8 Hz), 147.4, 146.2 (d, *J* = 3.1 Hz), 141.2, 129.5, 128.7, 128.3, 126.4, 123.4, 117.3 (t, *J* = 260.2 Hz), 62.9, 48.5 (t, *J* = 21.3, 20.7 Hz), δ 36.23 (d, *J* = 2.7 Hz), 36.20 (d, *J* = 2.7 Hz), 29.9, 18.9 (t, *J* = 4.1 Hz), 13.9. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -110.52 (d, *J* = 248.0 Hz), -111.51 (d, *J* = 248.0 Hz). **IR** (film): 3053, 2985, 2935, 1759, 1604, 1523, 1211, 853 cm^{-1}. **HRMS** Calcd for $C_{20}H_{21}F_2NO_4$ (M+Na) = 400.1336, found 400.1340.



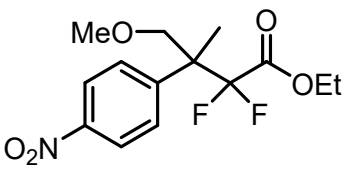
ethyl 3-ethyl-2,2-difluoro-3-(4-nitrophenyl)pentanoate (**3f**). General procedure 2.1.2 provided the difluorinated product as a colorless oil in 51% yield (16.0 mg, Hex:EtOAc – 20:1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.19 (d, *J* = 9.2 Hz, 2H), 7.63 – 7.56 (m, 2H), 4.07 (q, *J* = 7.1 Hz, 2H), 2.29 (dt, *J* = 14.7, 7.4 Hz, 2H), 2.07 (dt, *J* = 14.7, 7.4 Hz, 2H), 1.09 (t, *J* = 7.2 Hz, 3H), 0.96 – 0.84 (m, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 163.4 (t, *J* = 33.6 Hz), 147.1, 146.7 (t, *J* = 2.5 Hz), 129.9, 123.1, 117.1 (t, *J* = 261.6 Hz), 62.8, 51.0 (t, *J* = 19.5 Hz), 23.0 (t, *J* = 3.2 Hz), 13.8, 8.3. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -107.20. **IR** (film): 3028, 2947, 1755, 1603, 1532, 1211, 1132, 864 cm^{-1}. **HRMS** Calcd for $C_{15}H_{19}F_2NO_4$ (M+H) = 316.1360, found 316.1374.



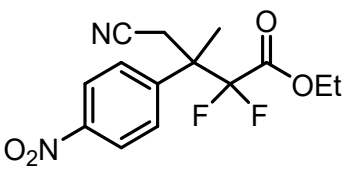
ethyl 2,2-difluoro-2-(1-(4-nitrophenyl)cyclopentyl)acetate (**3g**). General procedure 2.1.2 provided the difluorinated product as a white solid in 60% yield (18.8 mg, Hex:EtOAc – 20:1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.21 – 8.14 (m, 2H), 7.59 (d, *J* = 8.9 Hz, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 2.58 – 2.45 (m, 2H), 2.29 – 2.19 (m, 2H), 1.90 – 1.76 (m, 2H), 1.67 – 1.50 (m, 2H), 1.11 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 163.6 (t, *J* = 33.2 Hz), 147.7 (t, *J* = 3.1 Hz), 147.3, 129.8, 123.3, 117.3 (t, *J* = 258.0Hz), 62.8, 57.3 (t, *J* = 21.3 Hz), 33.4 (t, *J* = 3.2 Hz), 24.1, 13.9. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -108.98. **IR** (film): 3007, 2930, 1682, 1520, 1232, 1156, 859 cm^{-1}. **HRMS** Calcd for $C_{15}H_{17}F_2NO_4$ (M+Na) = 336.1023, found 336.1023.



1-ethyl 5-methyl 2,2-difluoro-3-methyl-3-(4-nitrophenyl)pentanedioate (**3h**). General procedure 2.1.2 provided the difluorinated product as a pale-brown oil in 55% yield (19 mg, Hex:EtOAc – 4:2). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.24 – 8.16 (m, 2H), 7.60 (d, *J* = 9.0 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.52 (s, 3H), 3.46 (d, *J* = 16.9 Hz, 1H), 2.92 (d, *J* = 16.4 Hz, 1H), 1.82 (s, 3H), 1.13 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 170.0, 162.7 (t, *J* = 32.7 Hz), 147.5, 145.4, 129.1, 123.3, 116.5 (t, *J* = 261.4 Hz), 63.2, 51.9, 47.0 (t, *J* = 20.9 Hz), 41.2 – 36.7 (m), 19.2 (t, *J* = 3.6 Hz), 13.9. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -110.88 (d, *J* = 248.0 Hz), -111.77 (d, *J* = 248.0 Hz). **IR** (film): 3025, 2994, 2953, 1759, 1738, 1524, 1232, 1152, 859 cm^{-1}. **HRMS** Calcd for $C_{15}H_{17}F_2NO_6$ (M+Na) = 368.0922, found 368.0919.

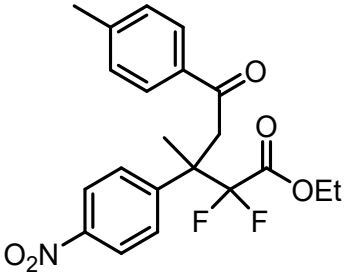


ethyl 2,2-difluoro-4-methoxy-3-methyl-3-(4-nitrophenyl)butanoate (**3i**). General procedure 2.1.2 provided the difluorinated product as a yellow oil in 51% yield as a pale-yellow oil (16.1 mg, Hex:EtOAc – 10:1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.24 – 8.13 (m, 2H), 7.63 (d, *J* = 9.0 Hz, 2H), 4.15 (qd, *J* = 7.1, 1.1 Hz, 2H), 3.93 – 3.80 (m, 2H), 3.34 (s, 3H), 1.65 (t, *J* = 1.2 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 163.1 (t, *J* = 32.3 Hz), 147.3, 145.8, 129.4, 123.2, 116.2 (t, *J* = 259.0 Hz), 74.47 (d, *J* = 3.7 Hz), 74.43 (d, *J* = 3.6 Hz), 62.9, 59.5, 49.6 (t, *J* = 20.6 Hz), 29.9, 18.3 (t, *J* = 4.4 Hz), 13.9. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -109.46 (d, *J* = 254.8 Hz), -111.49 (d, *J* = 253.4 Hz). **IR** (film): 3033, 2989, 1759, 1607, 1517, 1223, 1013, 859 cm^{-1}. **HRMS** Calcd for $C_{14}H_{17}F_2NO_5$ (M+H) = 318.1153, found 318.1161.

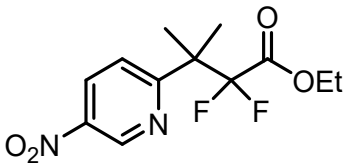


ethyl 4-cyano-2,2-difluoro-3-methyl-3-(4-nitrophenyl)butanoate (**3j**). General procedure 2.1.2 provided the difluorinated product as a viscous yellow oil in 61%

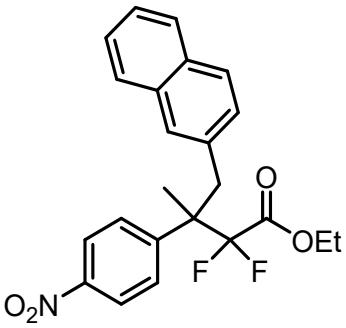
yield (19.0 mg, Hex:EtOAc – 4:1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.31 – 8.24 (m, 2H), 7.63 (d, *J* = 9.0 Hz, 2H), 4.15 (qd, *J* = 7.1, 0.9 Hz, 2H), 3.43 – 3.36 (m, 1H), 3.06 (d, *J* = 17.1 Hz, 1H), 1.86 (q, *J* = 1.2 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 162.2 (t, *J* = 32.2 Hz), 148.1, 143.0, 129.1, 123.9, 115.9, 115.7 (t, *J* = 262.3 Hz), 63.7, 47.2 (t, *J* = 21.8 Hz), 25.3 (t, *J* = 5.5 Hz), 19.8 (t, *J* = 3.6 Hz), 13.8. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -110.47 (d, *J* = 252.0 Hz), -111.18 (d, *J* = 253.3 Hz). **IR** (film): 3018, 2994, 2250, 1759, 1608, 1524, 1213, 1153, 859 cm^{-1}. **HRMS** Calcd for $C_{14}H_{14}F_2N_2O_4$ (M+Na) = 335.0819, found 335.0831.



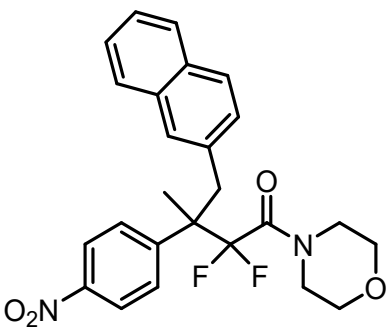
ethyl 2,2-difluoro-3-methyl-3-(4-nitrophenyl)-5-oxo-5-(p-tolyl)pentanoate (**3k**). General procedure 2.1.2 provided the difluorinated product as a yellow oil in 71% yield (28.8 mg, Hex:EtOAc – 5:1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.22 – 8.12 (m, 2H), 7.88 – 7.77 (m, 2H), 7.59 – 7.52 (m, 2H), 7.36 – 7.23 (m, 2H), 4.24 (d, *J* = 18.5 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.62 (d, *J* = 18.5 Hz, 1H), 2.42 (s, 3H), 1.87 (q, *J* = 1.1 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 194.9, 163.2 (t, *J* = 32.2 Hz), 147.1, 146.4, 144.7, 134.56, 129.6, 128.7, 128.1, 123.3, 117.0 (t, *J* = 260.7 Hz), 63.1, 47.3 (t, *J* = 20.5 Hz), 41.9, 21.8, 19.1 (t, *J* = 3.9 Hz), 13.9. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -110.95 (d, *J* = 246.6 Hz), -111.89 (d, *J* = 246.6 Hz). **IR** (film): 3124, 3090, 2987, 1759, 1689, 1605, 1518, 1219, 1030, 854 cm^{-1}. **HRMS** Calcd for $C_{21}H_{21}F_2NO_5$ (M+Na) = 428.1285, found 428.1296.



ethyl 2,2-difluoro-3-methyl-3-(5-nitropyridin-2-yl)butanoate (**3l**). General procedure 2.1.2 provided the difluorinated product as a colorless liquid in 82% yield (24.5 mg, Hex:EtOAc – 10:1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.32 (dd, *J* = 2.6, 0.6 Hz, 1H), 8.46 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.69 (dd, *J* = 8.8, 0.6 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 1.66 – 1.62 (m, 6H), 1.24 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 167.0 (t, *J* = 2.7 Hz), 163.3 (t, *J* = 32.2 Hz), 143.6, 143.2, 131.5, 122.7 (t, *J* = 2.3 Hz), 117.2 (t, *J* = 258.4 Hz), 62.9, 48.4 (t, *J* = 22.3 Hz), 22.2 (t, *J* = 4.1 Hz), 14.0. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -111.73. **IR** (film): 3080, 2987, 1761, 1582, 1525, 1370, 1150, 859, 771 cm^{-1}. **HRMS** Calcd for $C_{12}H_{14}F_2N_2O_4$ (M+H) = 289.1000, found 289.0999.

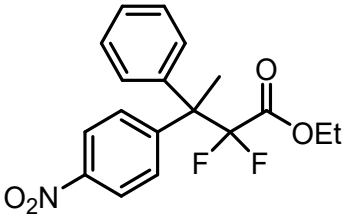


ethyl 2,2-difluoro-3-methyl-4-(naphthalen-2-yl)-3-(4-nitrophenyl)butanoate (**3m**). General procedure 2.1.2 provided the difluorinated product as a white solid in 28% yield (11.6 mg, Hex:EtOAc – 10:1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.24 – 8.16 (m, 2H), 7.76 – 7.68 (m, 1H), 7.68 – 7.58 (m, 3H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.45 – 7.36 (m, 2H), 7.28 – 7.26 (m, 1H), 6.74 (dd, *J* = 8.4, 1.8 Hz, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.74 (d, *J* = 13.7 Hz, 1H), 3.39 (d, *J* = 13.8 Hz, 1H), 1.52 (t, *J* = 1.1 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 163.2 (t, *J* = 32.8 Hz), 147.4, 146.4, 146.4, 133.1, 132.7, 132.4, 129.9 (t, *J* = 3.2 Hz), 129.7, 128.5, 127.7, 127.6, 126.3, 126.0, 123.2, 117.7 (t, *J* = 261.8, Hz), 63.0, 49.5 (t, *J* = 20.6 Hz), 40.79 (d, *J* = 2.7 Hz), 40.75 (d, *J* = 1.9 Hz), 18.7 (t, *J* = 4.1 Hz), 13.9. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -108.96 (d, *J* = 250.7 Hz), -110.66 (d, *J* = 249.3 Hz). **IR** (film): 3058, 2990, 2937, 1759, 1605, 1522, 1209, 858, 751 cm^{-1}. **HRMS** Calcd for $C_{23}H_{21}F_2NO_4$ (M+Na) = 436.1336, found 436.1344.

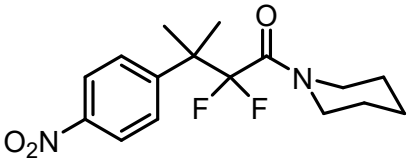


2,2-difluoro-3-methyl-1-morpholino-4-(naphthalen-2-yl)-3-(4-nitrophenyl)butan-1-one (**3n**). General procedure 2.1.2 provided the difluorinated product as a white solid in 33% yield as a white solid (15 mg, Hex:EtOAc – 5:1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.21 – 8.13 (m, 2H), 7.76 – 7.70 (m, 1H), 7.67 – 7.58 (m, 3H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.45 – 7.36 (m, 2H), 7.24 – 7.20 (m, 1H), 6.68 (dd, *J* = 8.5, 1.8 Hz, 1H), 3.76 – 3.56 (m, 7H), 3.51 (t, *J* = 4.8 Hz, 2H), 3.41 (d, *J* = 13.4 Hz, 1H), 1.63 (s, 3H). **^{13}C NMR** (126

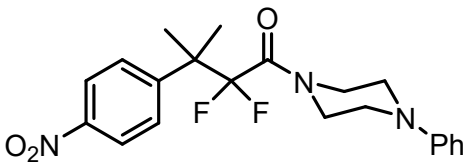
MHz, Chloroform-*d*) δ 160.4 (t, *J* = 30.1 Hz), 148.7, 146.8, 133.1, 132.9, 132.3, 129.9, 129.3 (t, *J* = 3.6 Hz), 128.8, 127.7, 127.6, 127.4, 126.2, 125.9, 123.1, 120.3 (t, *J* = 264.6 Hz), 66.9, 66.9, 50.3 (t, *J* = 19.5 Hz), 47.0, 43.5, 41.68 (d, *J* = 4.5 Hz), 41.65 (d, *J* = 4.4 Hz), 18.9 (t, *J* = 5.2 Hz). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -100.17 (d, *J* = 285.9 Hz), -101.11 (d, *J* = 284.9 Hz). **IR** (film): 3057, 2954, 1846, 1666, 1520, 1236, 1214, 859, 750 cm^{-1}. **HRMS** Calcd for $C_{25}H_{24}F_2N_2O_4$ (M+Na) = 477.1602, found 477.1621.



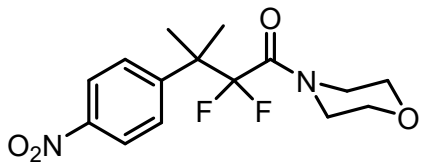
ethyl 2,2-difluoro-3-(4-nitrophenyl)-3-phenylbutanoate (**3o**). General procedure 2.1.2 provided the difluorinated product as a colorless oil in 28% yield (9.8 mg, Hex:EtOAc – 10:1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.18 – 8.10 (m, 2H), 7.51 (d, *J* = 9.0 Hz, 2H), 7.38 – 7.27 (m, 5H), 3.98 (qd, *J* = 7.2, 3.0 Hz, 2H), 2.00 (t, *J* = 1.4 Hz, 3H), 0.99 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 163.0 (t, *J* = 32.5 Hz), 150.7, 146.9, 140.3, 129.9, 129.1, 128.5,123.3, 118.1 (t, *J* = 264.2 Hz), 62.9, 54.7 (t, *J* = 24.4 Hz), 24.8 (t, *J* = 4.5 Hz), 13.6. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -103.41 (d, *J* = 248.0 Hz), -106.62 (d, *J* = 249.3 Hz). **IR** (film): 3060, 2988, 1758, 1608, 1520, 1383, 1128, 859 cm^{-1}. **HRMS** Calcd for $C_{18}H_{17}F_2NO_4$ (M+H) = 350.1204, found 350.1201.



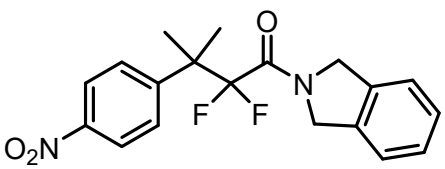
2,2-difluoro-3-methyl-3-(4-nitrophenyl)-1-(piperidin-1-yl)butan-1-one (**3p**). General procedure 2.1.2 provided the difluorinated product as a white solid in 66% yield (21.5 mg, Hex:EtOAc – 10:1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.20 – 8.12 (m, 2H), 7.72 – 7.65 (m, 2H), 3.43 (td, *J* = 8.5, 5.1 Hz, 4H), 1.64 (t, *J* = 1.2 Hz, 6H), 1.63 – 1.57 (m, 2H), 1.55 – 1.45 (m, 4H).**^{13}C NMR** (126 MHz, Chloroform-*d)* δ 160.5 (t, *J* = 29.7 Hz), 150.8, 146.7, 128.9, 123.0, 119.9 (t, *J* = 264.1), 47.1 (t, *J* = 7.7 Hz), 45.9 (t, *J* = 21.5), 44.6, 26.6, 25.7, 24.5, 23.7 (t, *J* = 4.6 Hz). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -102.35. **IR** (film): 3027, 2994, 1662, 1601, 1517, 1294, 852 cm^{-1}. **HRMS** Calcd for $C_{16}H_{20}F_2N_2O_3$ (M+Na) = 349.1340, found 349.1329.



2,2-difluoro-3-methyl-3-(4-nitrophenyl)-1-(4-phenylpiperazin-1-yl)butan-1-one (**3q**). General procedure 2.1.2 provided difluorinated product as a yellow solid in 64% yield (25.8 mg, Hex:EtOAc – 10:1.5). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.18 (d, *J* = 9.0 Hz, 2H), 7.93 – 7.56 (m, 2H), 7.32 – 7.23 (m, 2H), 6.95 – 6.86 (m, 3H), 3.69 (dt, *J* = 16.8, 5.1 Hz, 4H), 3.12 (dt, *J* = 8.2, 5.0 Hz, 4H), 1.67 (t, *J* = 1.3 Hz, 6H).**^{13}C NMR** (126 MHz, Chloroform-*d*) δ 160.7 (t, *J* = 30.3 Hz), 150.7, 150.3, 146.8, 129.4, 128.9, 123.1, 120.9, 119.7 (t, *J* = 263.7Hz), 116.7, 49.9, 49.4, 46.0 (t, *J* = 7.57 Hz), 45.8 (t, *J* = 20.9 Hz), 43.1, 23.7 (t, *J* = 4.9 Hz).**^{19}F NMR** (376 MHz, Chloroform-*d*) δ -102.11. **IR** (film): 3078, 2990, 1666, 1599, 1520, 1216, 998, 859 cm^{-1}. **HRMS** Calcd for $C_{21}H_{23}F_2N_3O_3$ (M+Na) = 426.1605, found 426.1612.

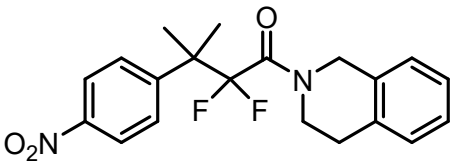


2,2-difluoro-3-methyl-1-morpholino-3-(4-nitrophenyl)butan-1-one (**3r**). General procedure 2.1.2 provided the difluorinated product as a white solid in 77% yield (25.2 mg, Hex:EtOAc – 5:1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.46 – 8.07 (m, 2H), 7.69 (dt, *J* = 8.2, 1.0 Hz, 2H), 3.67 – 3.61 (m, 2H), 3.57 (q, *J* = 2.4 Hz, 4H), 3.50 (t, *J* = 4.9 Hz, 2H), 1.65 (t, *J* = 1.1 Hz, 6H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 160.7 (t, *J* = 30.6 Hz), 150.3, 146.9, 128.95 (t, *J* = 2.0 Hz), 123.1, 119.7 (t, *J* = 263.0 Hz), 66.8, 66.8, 46.8 (t, *J* = 7.6 Hz), 45.8 (t, *J* = 20.9 Hz), 43.4, 23.6 (t, *J* = 4.9 Hz). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -102.35. **IR** (film): 3084, 2987, 1666, 1520, 1350, 1219, 996, 852 cm^{-1}. **HRMS** Calcd for $C_{15}H_{18}F_2N_2O_4$ (M+Na) = 351.1131, found 351.1119.

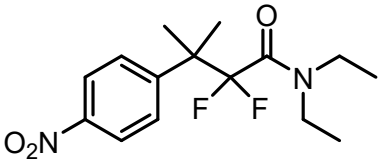


2,2-difluoro-1-(isoindolin-2-yl)-3-methyl-3-(4-nitrophenyl)butan-1-one (**3s**). General procedure 2.1.2 provided the difluorinated product as a

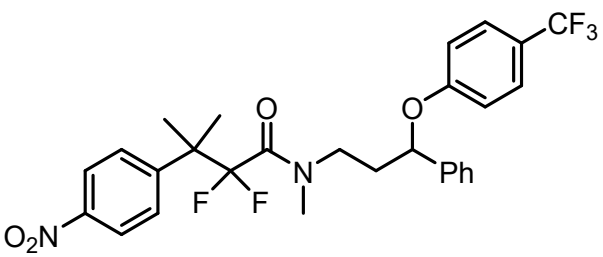
white solid in 70% yield (25.2 mg, Hex:EtOAc – 10:1.5). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.14 (d, *J* = 9.0 Hz, 2H), 7.70 (d, *J* = 9.1 Hz, 2H), 7.29 – 7.11 (m, 3H), 7.15 – 7.09 (m, 1H), 4.75 (s, 2H), 4.72 (s, 2H), 1.70 (t, *J* = 1.2 Hz, 6H).**^{13}C NMR** (126 MHz, Chloroform-*d*) δ 161.6 (t, *J* = 31.1 Hz), 149.5, 147.0 , 136.3 (t, *J* = 2.8 Hz), 134.2, 129.0, 128.0, 127.9, 123.1, 122.8, 122.4, 119.2 (t, *J* = 261.2 Hz), 54.1, 52.7 (t, *J* = 8.2 Hz), 45.7 (t, *J* = 21.8 Hz), 23.3 (t, *J* = 4.4 Hz). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -107.08. **IR** (film): 3027, 2994, 1662, 1517, 1209, 988, 852 cm^{-1}. **HRMS** Calcd for $C_{19}H_{18}F_2N_2O_3$ (M+Na) = 383.1183, found 383.1171.



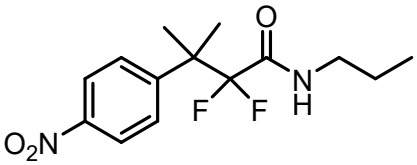
1-(3,4-dihydroisoquinolin-2(1H)-yl)-2,2-difluoro-3-methyl-3-(4-nitrophenyl)butan-1-one (**3t**). General procedure 2.1.2 provided the difluorinated product as a white solid in 75% yield (28.0 mg, Hex:EtOAc – 10:1.5). **^{1}H NMR** (400 MHz, Chloroform-*d*) (1:1 ratio of rotamers) δ 8.18 – 8.10 (m, 2H), 8.00 – 7.92 (m, 2H), 7.70 (d, *J* = 8.9 Hz, 2H), 7.65 – 7.58 (m, 2H), 7.22 – 7.03 (m, 7H), 6.79 – 6.73 (m, 1H), 4.60 (s, 2H), 4.43 (s, 2H), 3.73 (t, *J* = 6.1 Hz, 4H), 2.83 (t, *J* = 5.8 Hz, 2H), 2.79 (t, *J* = 6.0 Hz, 2H), 1.68 (s, 6H), 1.66 (d, *J* = 1.2 Hz, 6H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 161.2 (t, *J* = 30.3 Hz), 161.2 (t, *J* = 30.2 Hz) 150.3, 149.3, 146.8, 146.7, 133.9, 133.8, 132.4, 132.1, 129.5, 128.9, 128.8, 128.7, 128.5, 127.3, 127.0, 126.7, 126.7, 126.4, 125.8, 123.1, 123.0, 122.2, 119.7 (t, *J* = 261.3 Hz), 119.7 (t, *J* = 264.1 Hz), 47.5 (t, *J* = 8.8 Hz), 46.1, 45.9, 45.9, 45.8, 45.7, 45.6, 43.6 (t, *J* = 7.8 Hz), 42.0, 29.5, 28.0, 23.6 (t, *J* = 4.6 Hz), 23.3 (t, *J* = 4.5 Hz).**^{19}F NMR** (376 MHz, Chloroform-*d*) δ -103.30, -103.37. **IR** (film): 3085, 2993, 1698, 1652, 1520, 1209, 858, 754 cm^{-1}. **HRMS** Calcd for $C_{20}H_{20}F_2N_2O_3$ (M+Na) = 397.1340, found 397.1347.



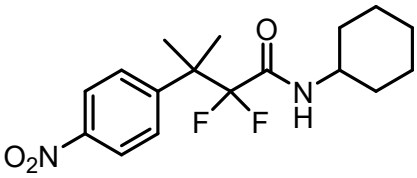
N,N-diethyl-2,2-difluoro-3-methyl-3-(4-nitrophenyl)butanamide (**3u**). General procedure 2.1.2 provided the difluorinated product as a white solid in 68% yield (21.4 mg, Hex:EtOAc – 10:1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.16 (d, *J* = 9.0 Hz, 2H), 7.95 – 7.55 (m, 2H), 3.25 (q, *J* = 7.1 Hz, 2H), 3.17 (qt, *J* = 7.0, 1.8 Hz, 2H), 1.65 (t, *J* = 1.2 Hz, 6H), 1.11 (t, *J* = 7.0 Hz, 3H), 1.05 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 161.6 (t, *J* = 29.8 Hz), 150.8, 146.8, 128.9, 123.0, 119.7 (t, *J* = 263.0 Hz), 46.0 (t, *J* = 21.8 Hz), 42.1 (t, *J* = 7.3 Hz), 42.0, 23.6 (t, *J* = 4.8 Hz), 14.5, 12.3. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -103.53. **IR** (film): 3034, 2988, 1659, 1520, 1348, 1216, 859, 754 cm^{-1}. **HRMS** Calcd for $C_{15}H_{20}F_2N_2O_3$ (M+Na) = 337.1340, found 337.1340.



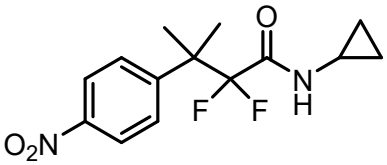
2,2-difluoro-N,3-dimethyl-3-(4-nitrophenyl)-N-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)butanamide (**3v**). General procedure 2.1.2 provided the difluorinated product as a pale-yellow oil in 67% yield as a mixture of rotamers (2:1) (37.0 mg, Hex:EtOAc – 5:1). **^{1}H NMR** (400 MHz, Chloroform-*d*) **major:** δ 8.15 (d, *J* = 9.0 Hz, 2H), 7.73 – 7.61 (m, 2H), 7.48 – 7.35 (m, 4H), 7.38 – 7.29 (m, 3H), 6.92 – 6.80 (m, 2H), 5.10 (ddd, *J* = 9.0, 7.1, 3.8 Hz, 1H), 3.46 (dd, *J* = 8.2, 6.4 Hz, 2H), 2.95 (t, *J* = 2.6 Hz, 3H), 2.29 – 1.94 (m, 2H), 1.60 (s, 6H). **minor:** δ 8.11 (d, *J* = 9.0 Hz, 2H), 7.59 (d, *J* = 9.0 Hz, 2H), 7.48 – 7.35 (m, 4H), 7.38 – 7.29 (m, 3H), 6.92 – 6.80 (m, 2H), 5.10 (ddd, *J* = 9.0, 7.1, 3.8 Hz, 1H), 3.40 – 3.30 (m, 2H), 2.84 (s, 3H), 2.29 – 1.94 (m, 2H), 1.60 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.3, 162.2, 162.1, 162.0, 160.1, 160.1, 150.2, 150.1, 146.7, 140.3, 139.9, 129.0, 128.9, 128.7, 128.2, 128.1, 126.9, 126.8, 126.8, 126.8, 126.7, 125.6, 125.5, 123.2, 122.9, 122.9, 121.5, 119.5, 115.7, 115.6, 78.1, 77.8, 77.3, 77.0, 76.8, 47.3, 46.6, 46.5, 45.9, 45.7, 45.5, 37.5, 35.8, 35.7, 35.7, 35.6, 35.2, 23.4, 23.4, 23.4, 23.3, 23.3. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -61.61, -102.78, -103.44. **IR** (film): 3080, 3060, 2937, 1666, 1518, 1350, 1327, 858, 837, 700 cm^{-1}. **HRMS** Calcd for $C_{28}H_{27}F_5N_2O_4$ (M+Na) = 573.1789, found 573.1774.



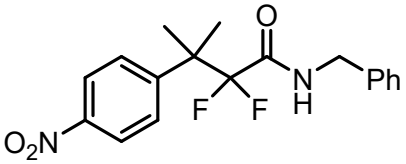
2,2-difluoro-3-methyl-3-(4-nitrophenyl)-N-propylbutanamide (**3w**). General procedure 2.1.2 provided the difluorinated product as a white solid in 67% yield (20.2 mg, Hex:EtOAc – 5:1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.22 – 8.14 (m, 2H), 7.68 – 7.61 (m, 2H), 5.98 (s, 1H), 3.10 (q, *J* = 6.9 Hz, 2H), 1.65 (d, *J* = 1.2 Hz, 6H), 1.35 (h, *J* = 7.4 Hz, 2H), 0.77 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 162.9 (t, *J* = 29.0 Hz), 148.8, 147.2, 129.0, 123.2, 118.4 (t, *J* = 260.7 Hz), 44.9 (t, *J* = 21.8 Hz), 41.1, 22.9 (t, *J* = 4.1 Hz), 22.4, 11.2. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -112.08. **IR** (film): 3369, 3081, 2964, 1682, 1525, 1348, 1222, 858 cm^{-1}. **HRMS** Calcd for $C_{14}H_{18}F_2N_2O_3$ (M+H) = 301.1364, found 301.1372.



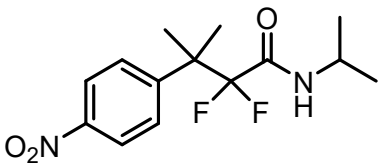
N-cyclohexyl-2,2-difluoro-3-methyl-3-(4-nitrophenyl)butanamide (**3x**). General procedure 2.1.2 provided the difluorinated product as a pale-yellow solid in 77% yield (26.1 mg, Hex:EtOAc – 10:1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.21 – 8.14 (m, 2H), 7.64 (d, *J* = 9.1 Hz, 2H), 5.79 (s, 1H), 3.61 (tdt, *J* = 11.3, 8.1, 3.9 Hz, 1H), 1.74 – 1.51 (m, 11H), 1.35 – 1.21 (m, 2H), 1.17 – 1.01 (m, 1H), 0.94 (dq, *J* = 11.9, 3.4 Hz, 2H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 161.9 (t, *J* = 29.0 Hz), 148.9, 147.1, 129.0, 123.2, 118.2 (t, *J* = 261.0 Hz), 48.4, 44.9 (t, *J* = 21.8 Hz), 32.5, 25.3, 24.6, 22.9 (t, *J* = 4.2 Hz). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -112.41. **IR** (film): 3350, 1088, 2995, 2936, 1682, 1515, 1348, 1219, 859 cm^{-1}. **HRMS** Calcd for $C_{17}H_{22}F_2N_2O_3$ (M+Na) = 363.1496, found 363.1512.



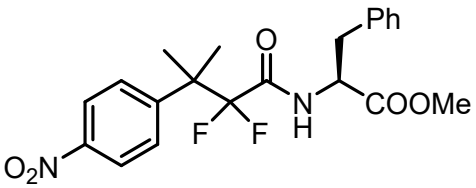
N-cyclopropyl-2,2-difluoro-3-methyl-3-(4-nitrophenyl)butanamide (**3y**). General procedure 2.1.2 provided the difluorinated product as a white solid in 78% yield (23.2 mg, Hex:EtOAc – 4:1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.22 – 8.14 (m, 2H), 7.64 (d, *J* = 9.2 Hz, 2H), 6.01 (s, 1H), 2.55 (dq, *J* = 7.2, 3.5 Hz, 1H), 1.64 (t, *J* = 1.1 Hz, 6H), 0.78 – 0.69 (m, 2H), 0.34 – 0.25 (m, 2H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 164.3 (t, *J* = 28.8 Hz), 148.7, 147.2, 129.0, 123.2, 118.2 (t, *J* = 260.9 Hz), 44.9 (t, *J* = 21.9 Hz), 22.8 (t, *J* = 4.2 Hz), 22.4, 6.6. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -112.27. **IR** (film): 3345, 3082, 2993, 1689, 1518, 1348, 1207, 859 cm^{-1}. **HRMS** Calcd for $C_{14}H_{16}F_2N_2O_3$ (M+Na) = 321.1027, found 321.1039.



N-benzyl-2,2-difluoro-3-methyl-3-(4-nitrophenyl)butanamide (**3z**). General procedure 2.1.2 provided the difluorinated product as a white solid in 71% yield (24.7 mg, Hex:EtOAc – 10:1.5). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.11 – 8.03 (m, 2H), 7.62 – 7.55 (m, 2H), 7.32 – 7.20 (m, 3H), 7.02 – 6.95 (m, 2H), 6.18 (s, 1H), 4.27 (d, *J* = 5.9 Hz, 2H), 1.66 (t, *J* = 1.2 Hz, 6H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 162.8 (t, *J* = 29.2 Hz), 148.5, 147.2, 136.5, 128.9, 128.2, 128.0, 123.3, 120.5, 118.4 (t, *J* = 260.8 Hz), 44.9 (t, *J* = 21.8 Hz), 43.5, 22.8 (t, *J* = 4.1 Hz). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -112.22. **IR** (film): 3323, 3060, 2893, 1681, 1601, 1509, 1421, 1348, 1148, 861, 778 cm^{-1}. **HRMS** Calcd for $C_{18}H_{18}F_2N_2O_3$ (M+Na) = 371.1183, found 371.1186.

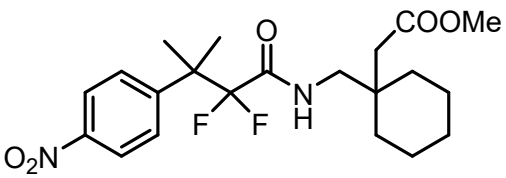


2,2-difluoro-N-isopropyl-3-methyl-3-(4-nitrophenyl)butanamide (**3aa**). General procedure 2.1.2 provided the difluorinated product as a pale-yellow oil in 60% yield (18.0 mg, Hex:EtOAc – 10:1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.21 – 8.14 (m, 2H), 7.65 (d, *J* = 9.0 Hz, 2H), 5.72 (s, 1H), 3.91 (dq, *J* = 13.3, 6.6 Hz, 1H), 1.65 (s, 6H), 0.98 (d, *J* = 6.6 Hz, 6H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 161.99 (t, *J* = 29.1 Hz), 148.84, 147.20, 129.03, 123.19, 118.19 (t, *J* = 260.7 Hz), 44.89 (t, *J* = 21.8 Hz), 41.77, 22.86 (t, *J* = 4.5 Hz), 22.24. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -112.50. **IR** (film): 3338, 3077, 2977, 1682, 1524, 1230, 1150, 854 cm^{-1}. **HRMS** Calcd for $C_{14}H_{18}F_2N_2O_3$ (M+Na) = 323.1183, found 323.1196.

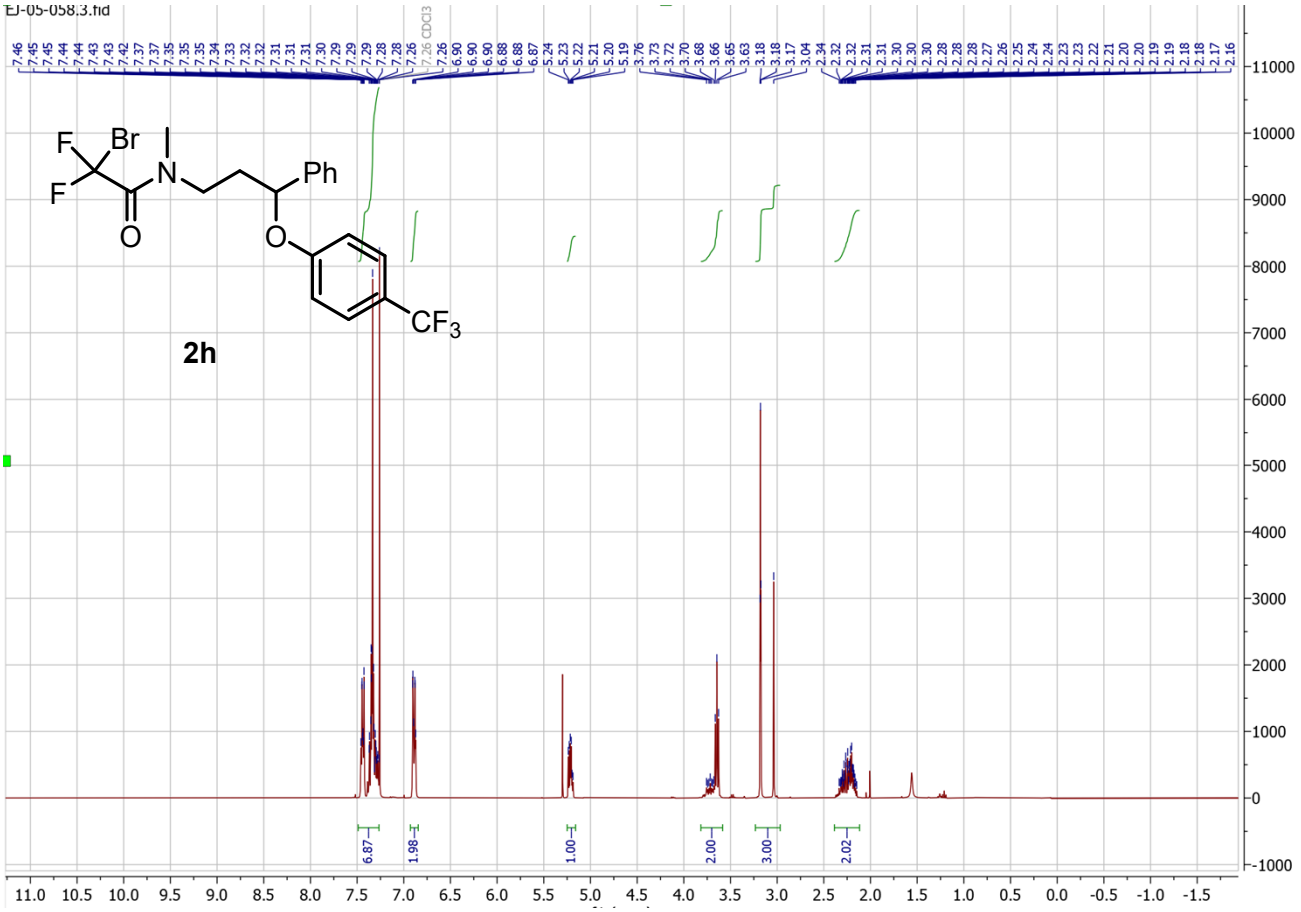


methyl (2,2-difluoro-3-methyl-3-(4-nitrophenyl)butanoyl)-L-phenylalaninate (**3ab**). General procedure 2.1.2 provided the difluorinated product as a pale-yellow solid in 88% yield (98% e.e, 37.2 mg, Hex:EtOAc – 5:1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.17 – 8.07 (m, 2H), 7.61 – 7.54 (m, 2H), 7.31 – 7.20 (m, 3H), 7.02 – 6.92 (m, 2H), 6.40 (d, *J* = 7.9 Hz, 1H), 4.70 (dt, *J* = 7.8, 6.0 Hz, 1H), 3.69 (s, 3H), 3.02 (dd, *J* = 6.0, 5.1 Hz, 2H), 1.58 (s, 3H), 1.57 (s, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 170.8, 162.6 (t, *J* = 29.8 Hz), 148.4, 147.2, 135.0, 129.1, 128.9, 128.9, 127.6, 123.2, 118.2 (t, *J* = 260.6 Hz), 53.1, 52.7, 44.7 (t, *J* = 21.7 Hz), 37.7, 22.8 (dt, *J* = 9.2, 4.2 Hz). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -111.77. **IR** (film): 3358, 3031, 2988, 1748, 1702, 1513, 1216, 959, 700 cm^{-1}. **HRMS** Calcd for $C_{21}H_{22}F_2N_2O_5$ (M+Na) = 443.1394, found 443.1404.

The enantiomeric purity of the title compound was determined by HPLC analyses [DAICEL CHIRALPAK IA column, hexane : 2-propanol = 95 : 5, flow rate = 0.5 mL/min, retention time; 41.1 min (major) and 43.6 min (minor)].

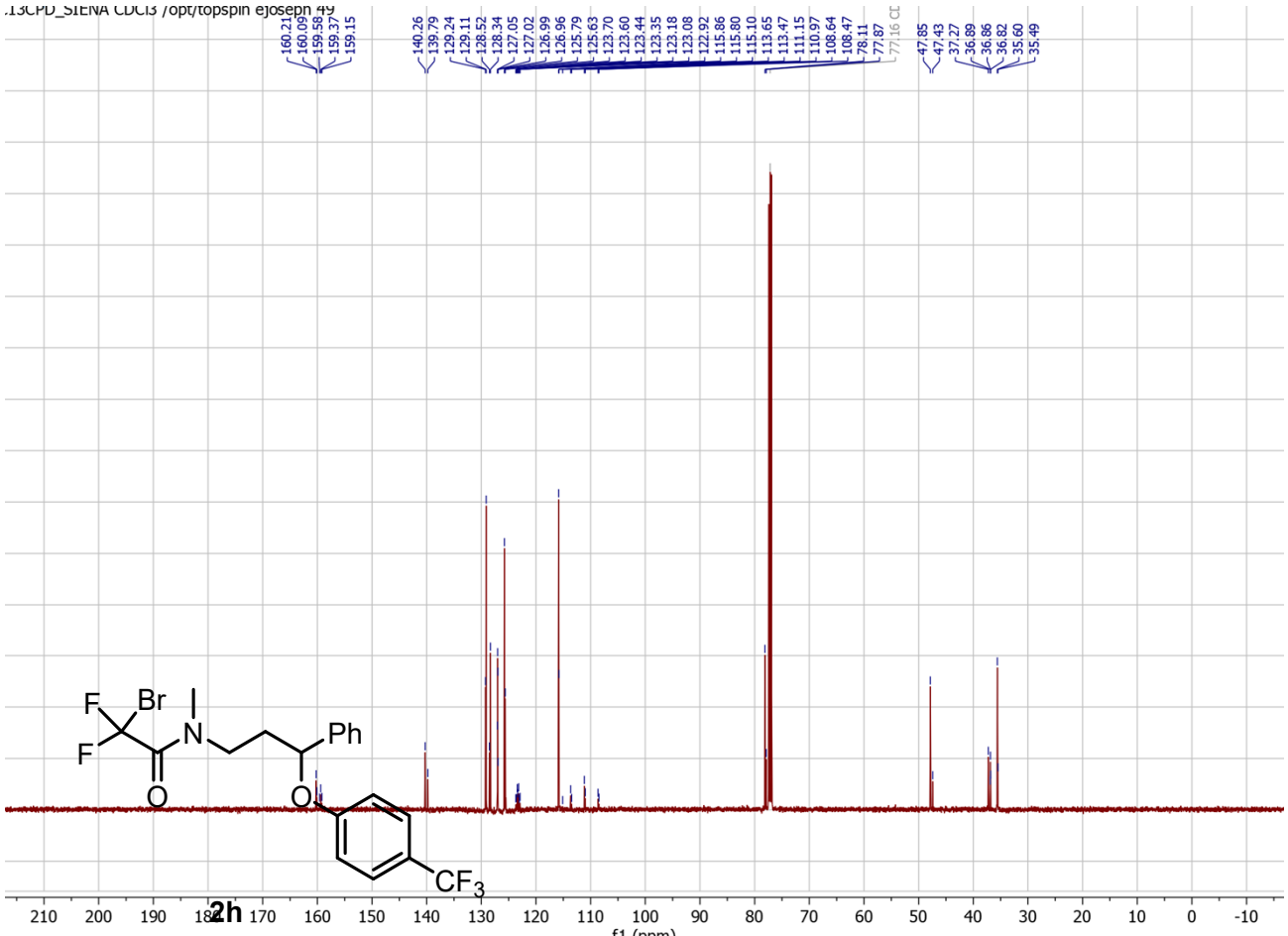


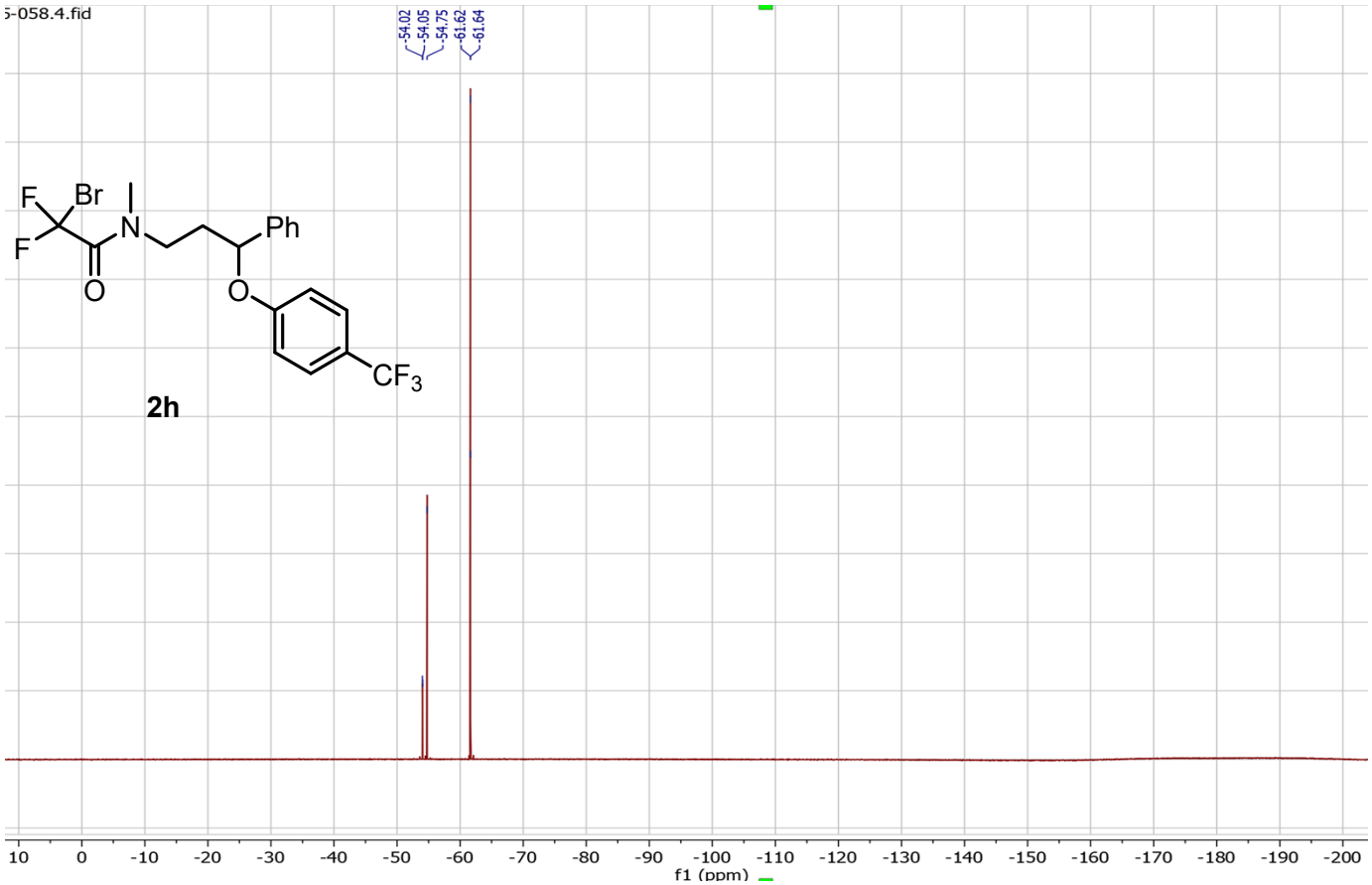
methyl 2-(1-((2,2-difluoro-3-methyl-3-(4-nitrophenyl)butanamido)methyl)cyclohexyl)acetate (**3ac**). General procedure 2.1.2 provided the difluorinated product as a white solid in 79% yield (33.7 mg, Hex:EtOAc – 10:1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.21 – 8.14 (m, 2H), 7.67 (dq, *J* = 7.9, 0.9 Hz, 2H), 7.10 (s, 1H), 3.65 (s, 3H), 3.12 (d, *J* = 6.4 Hz, 2H), 2.08 (s, 2H), 1.66 (t, *J* = 1.1 Hz, 6H), 1.46 – 1.33 (m, 6H), 1.14 (dd, *J* = 6.1, 4.1 Hz, 4H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 173.4, 163.3 (t, *J* = 29.1 Hz), 149.0, 147.2, 129.09, 123.2, 118.5 (t, *J* = 260.6 Hz), 51.9, 46.4, 45.0 (t, *J* = 21.8 Hz), 41.9, 37.3, 34.3, 25.8, 23.0 (t, *J* = 4.1 Hz), 21.3. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -111.60. **IR** (film): 3375, 3085, 2990, 2927, 1704, 1698, 1524, 1209, 859, 701 cm^{-1}. **HRMS** Calcd for $C_{21}H_{28}F_2N_2O_5$ (M+H) = 427.2045, found 427.2039.



^{1}H NMR spectrum of 2h (400 MHz, Chloroform-*d*)

^{13}C NMR spectrum of 2h (126 MHz, Chloroform-*d*)

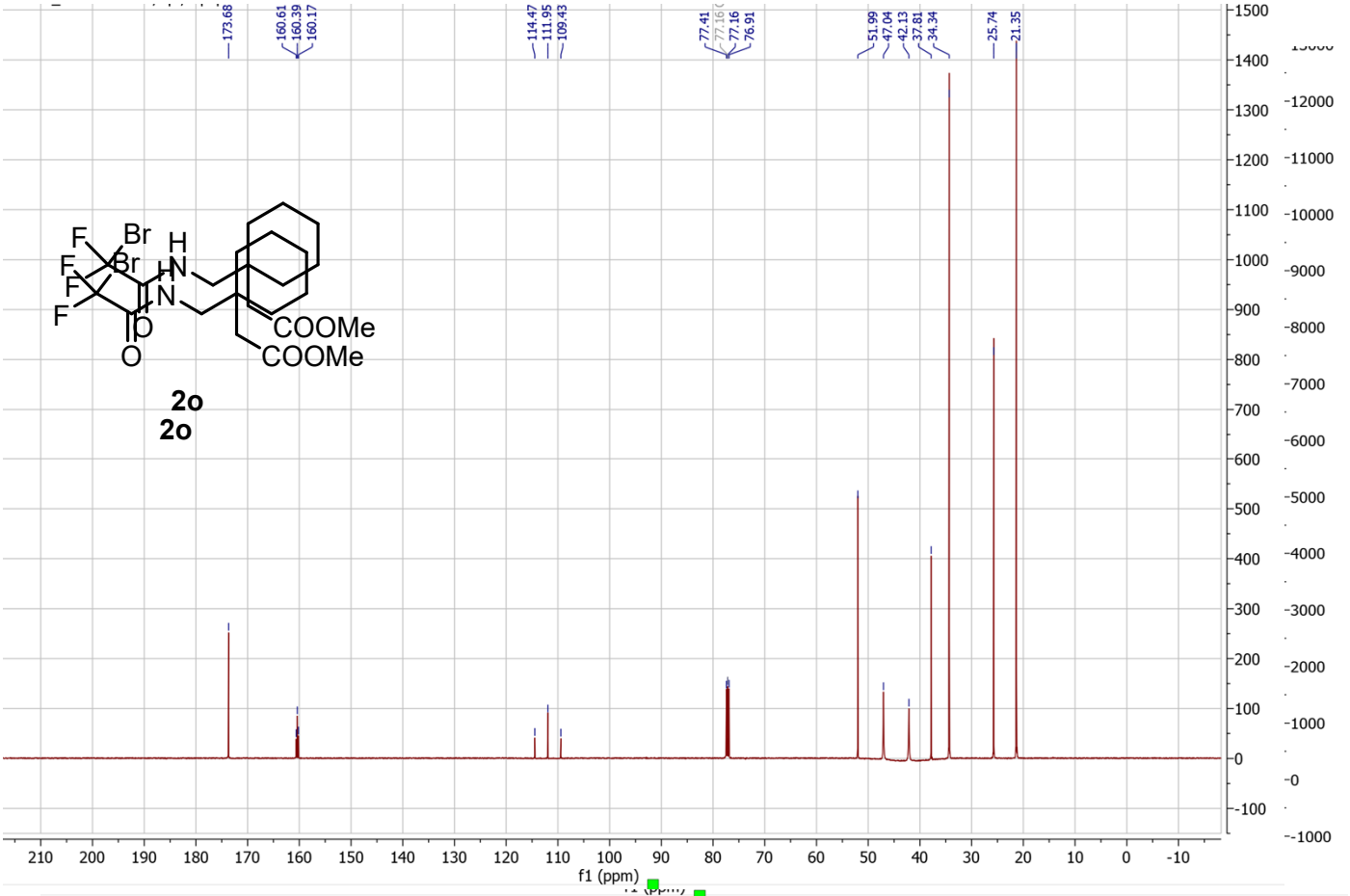




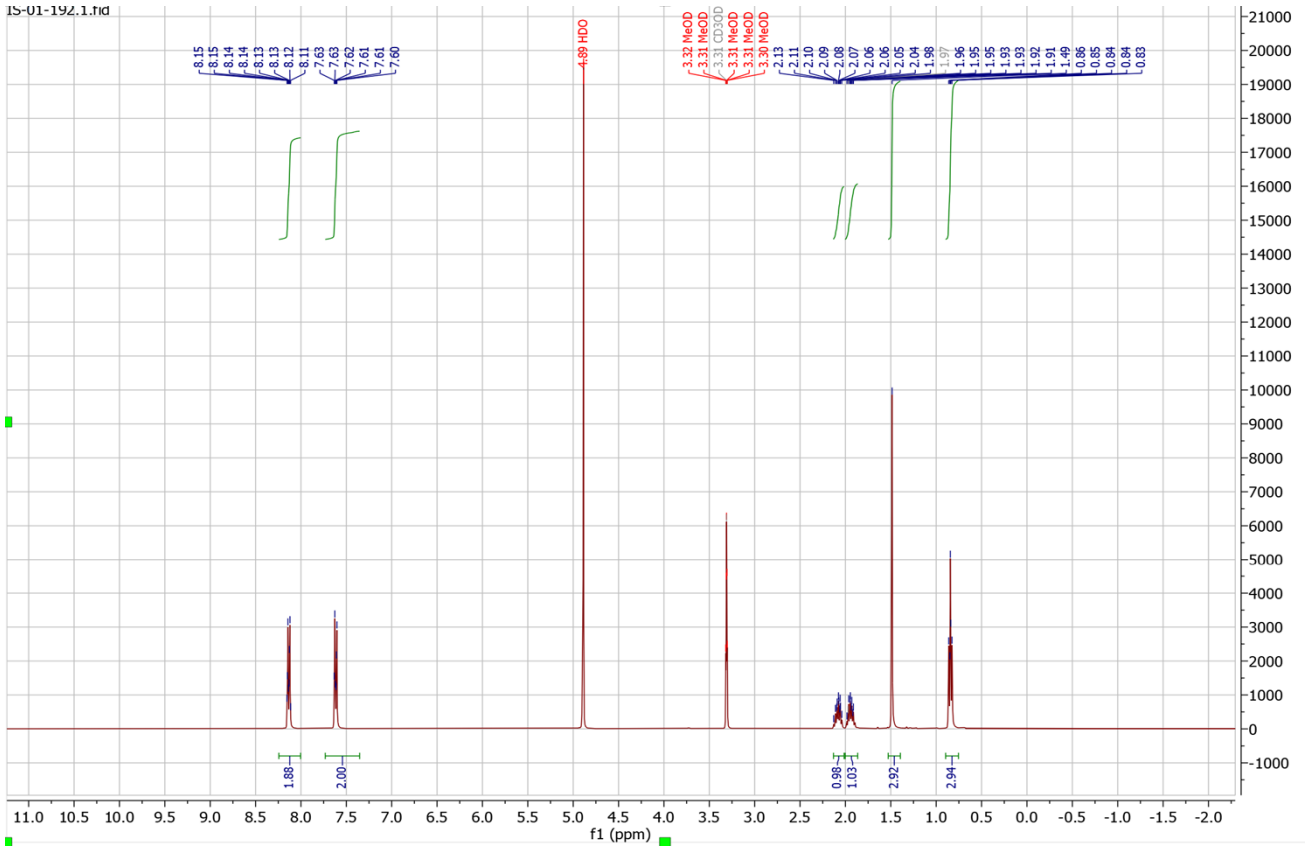
^{19}F NMR spectrum of 2h (376 MHz, Chloroform-*d*)

^{1}H NMR spectrum of 2o (400 MHz, Chloroform-*d*)

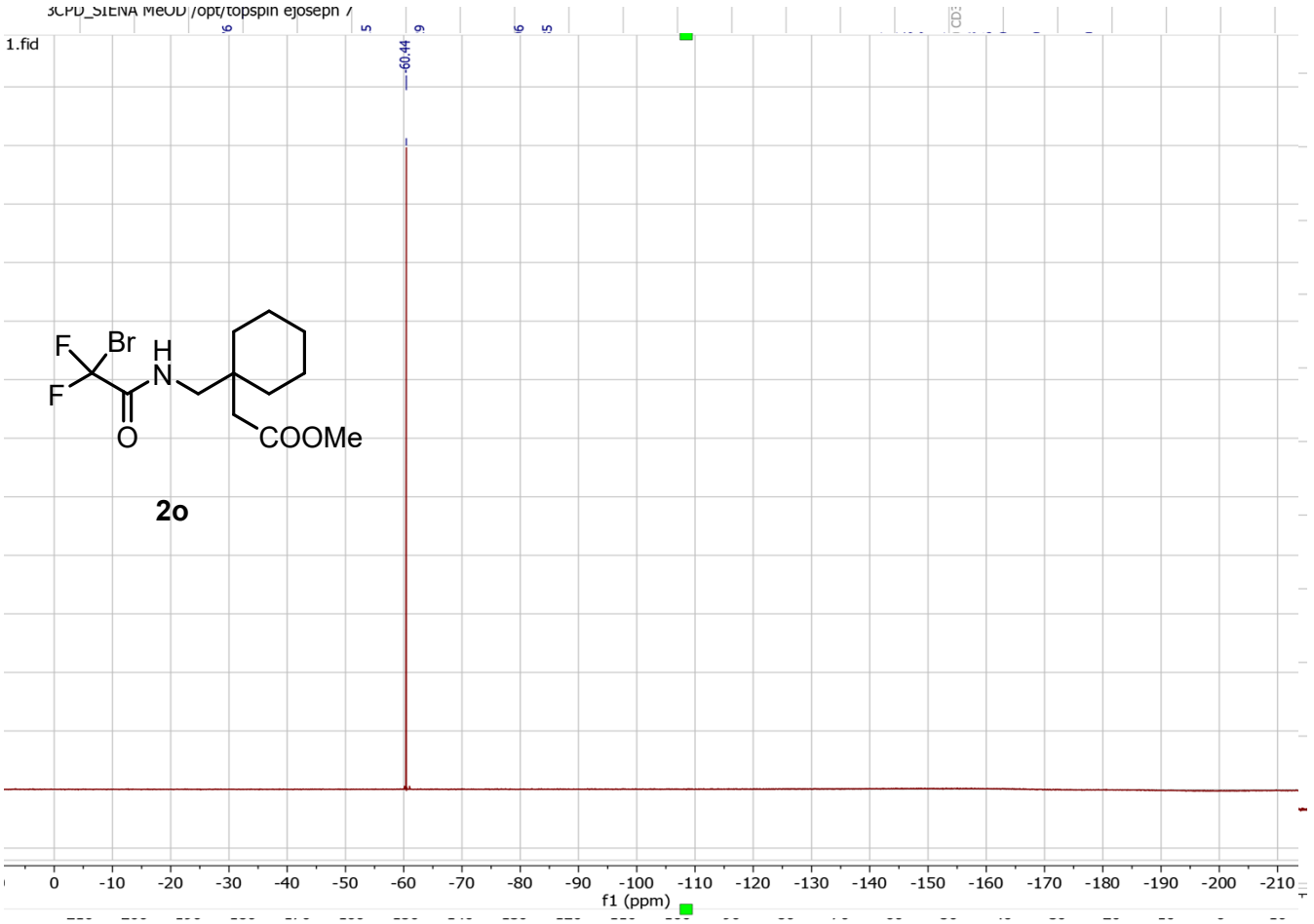
^{13}C NMR spectrum of 2o (126 MHz, Chloroform-*d*)



^{19}F NMR spectrum of 2o (376 MHz, Chloroform-*d*)



^{1}H NMR spectrum of 1b (400 MHz, Methanol-d_4)

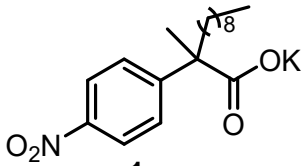


2o

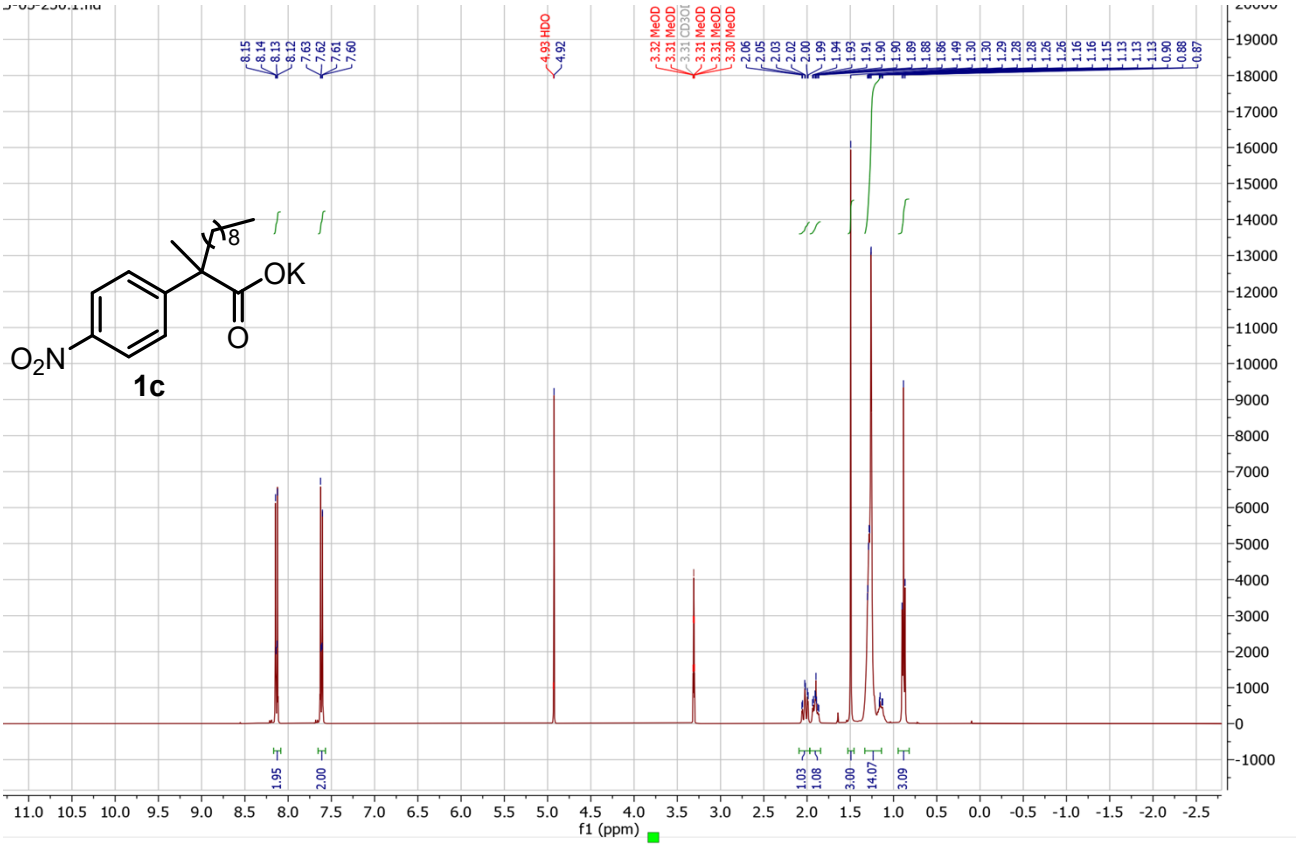
^{13}C NMR spectrum of 1b (126 MHz, Methanol-d_4)

1b

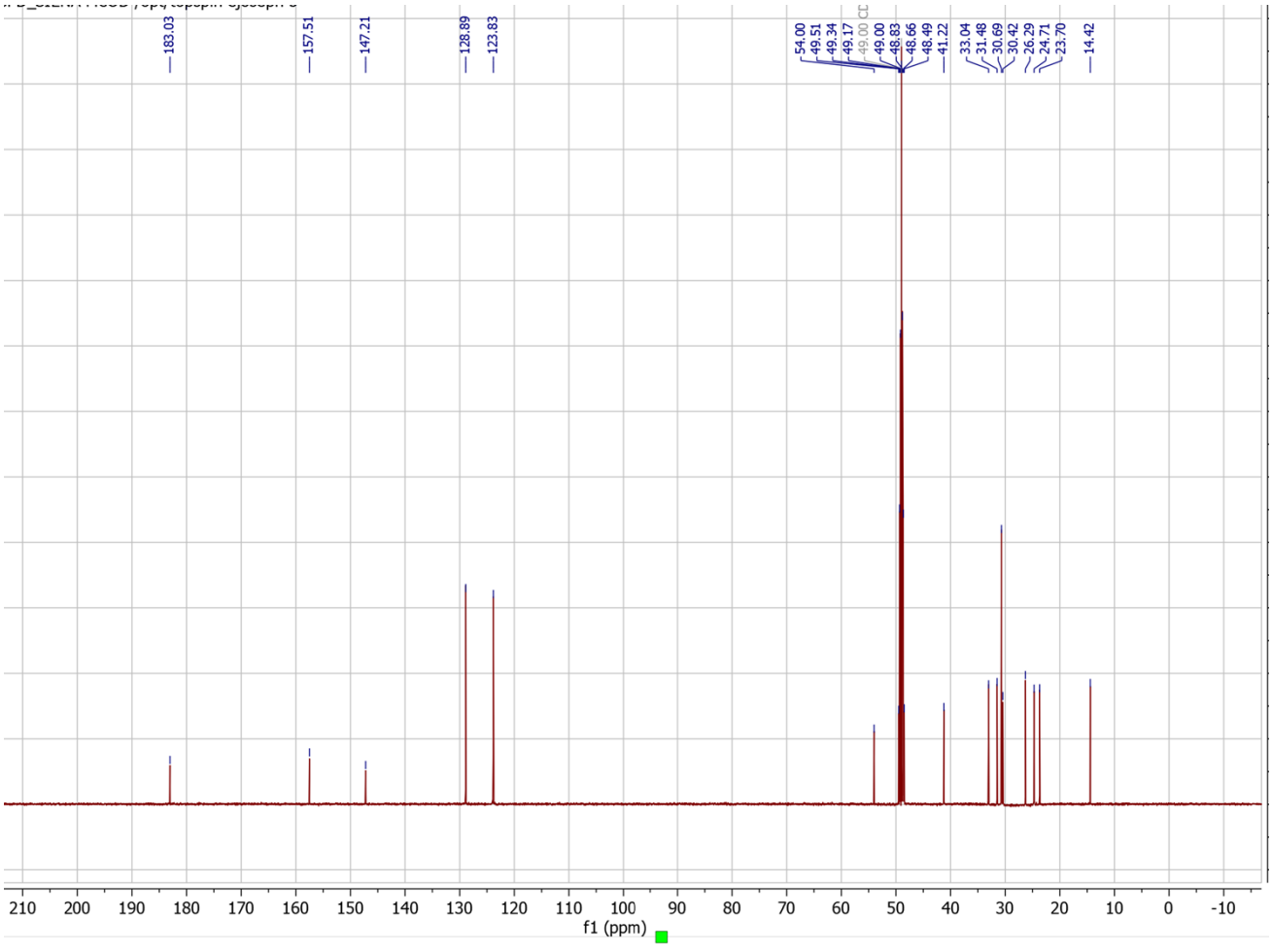
^{1}H NMR spectrum of 1c (400 MHz, Methanol-d_4)

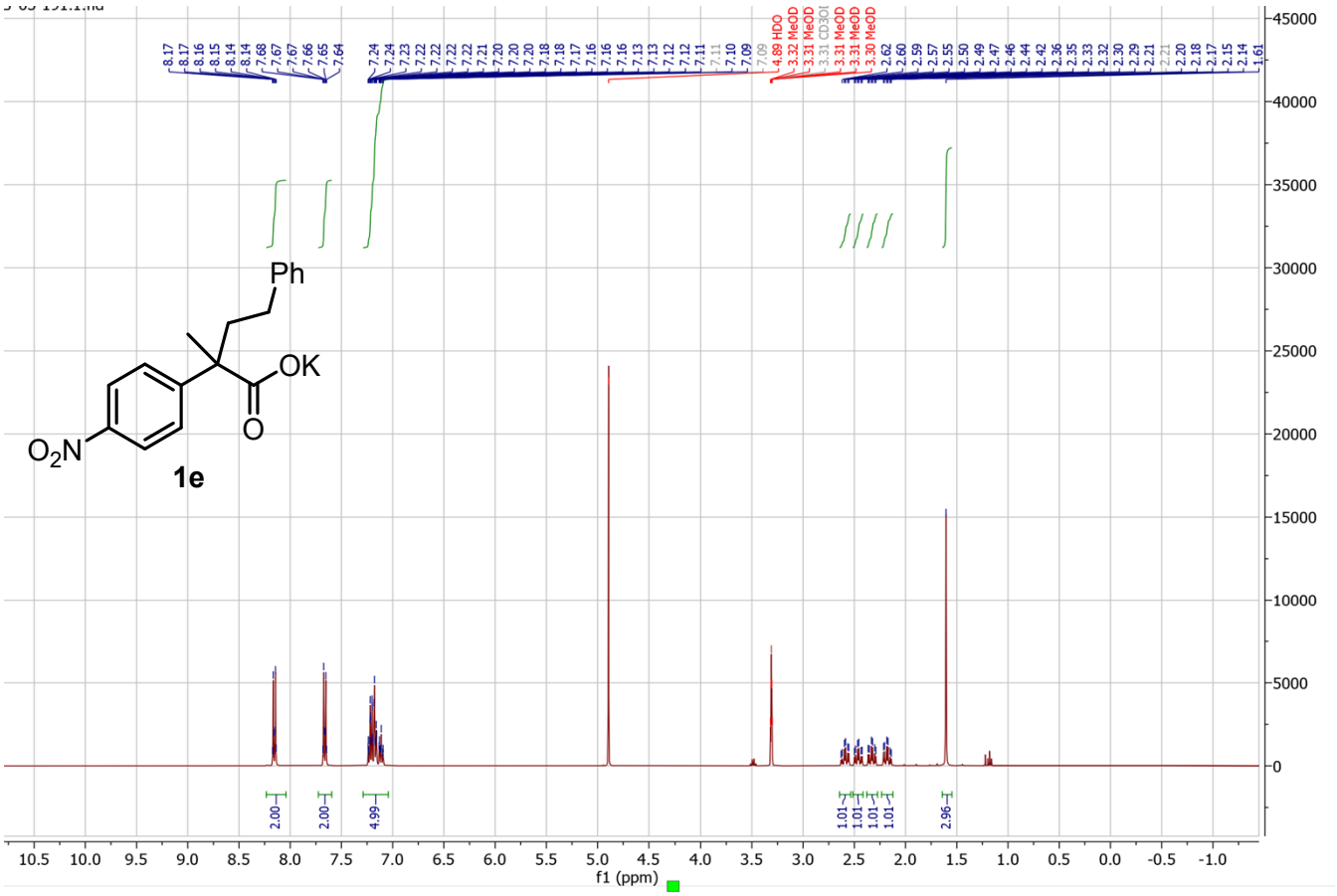


1c



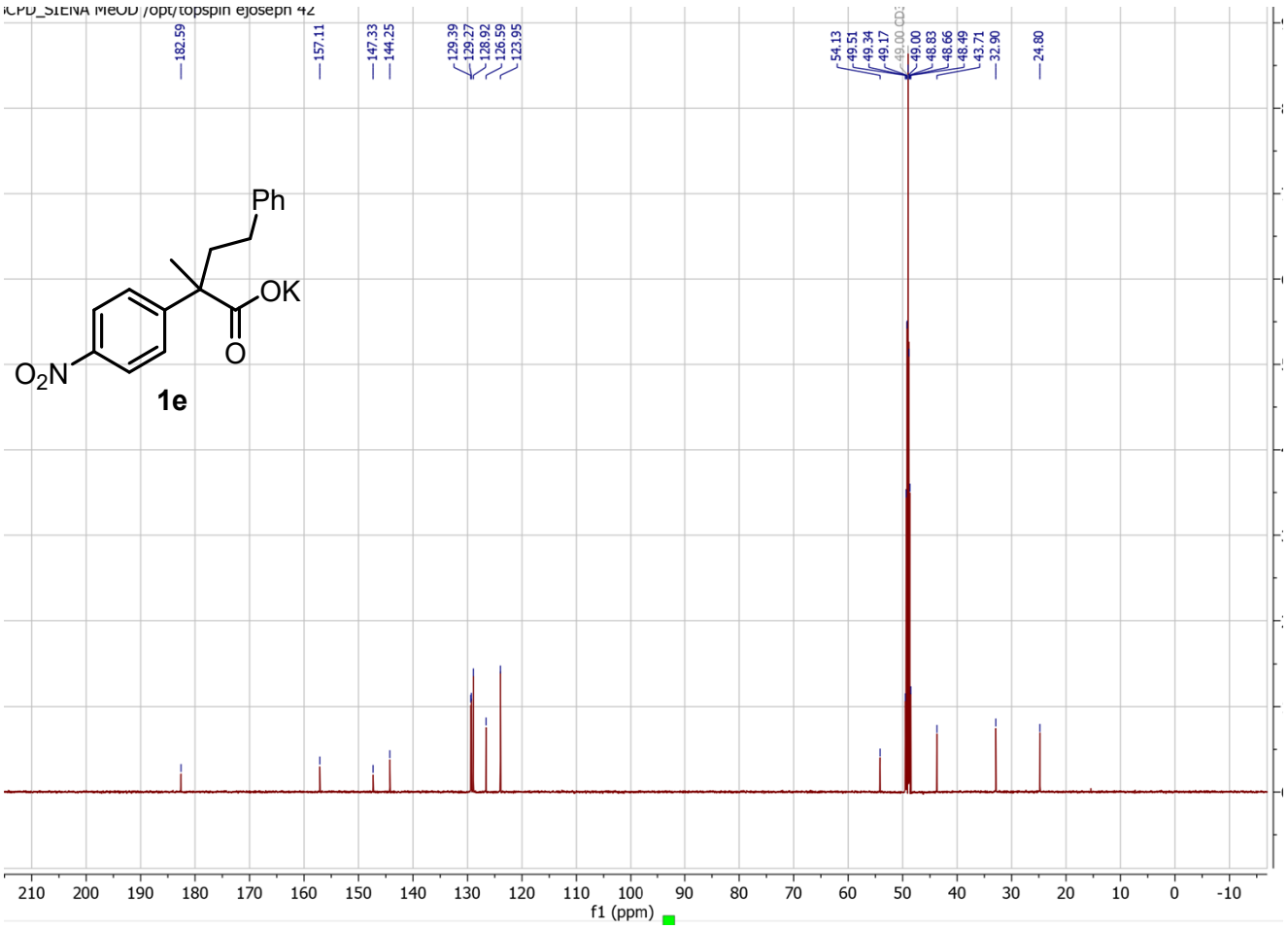
^{13}C NMR spectrum of 1c (126 MHz, Methanol-d_4)

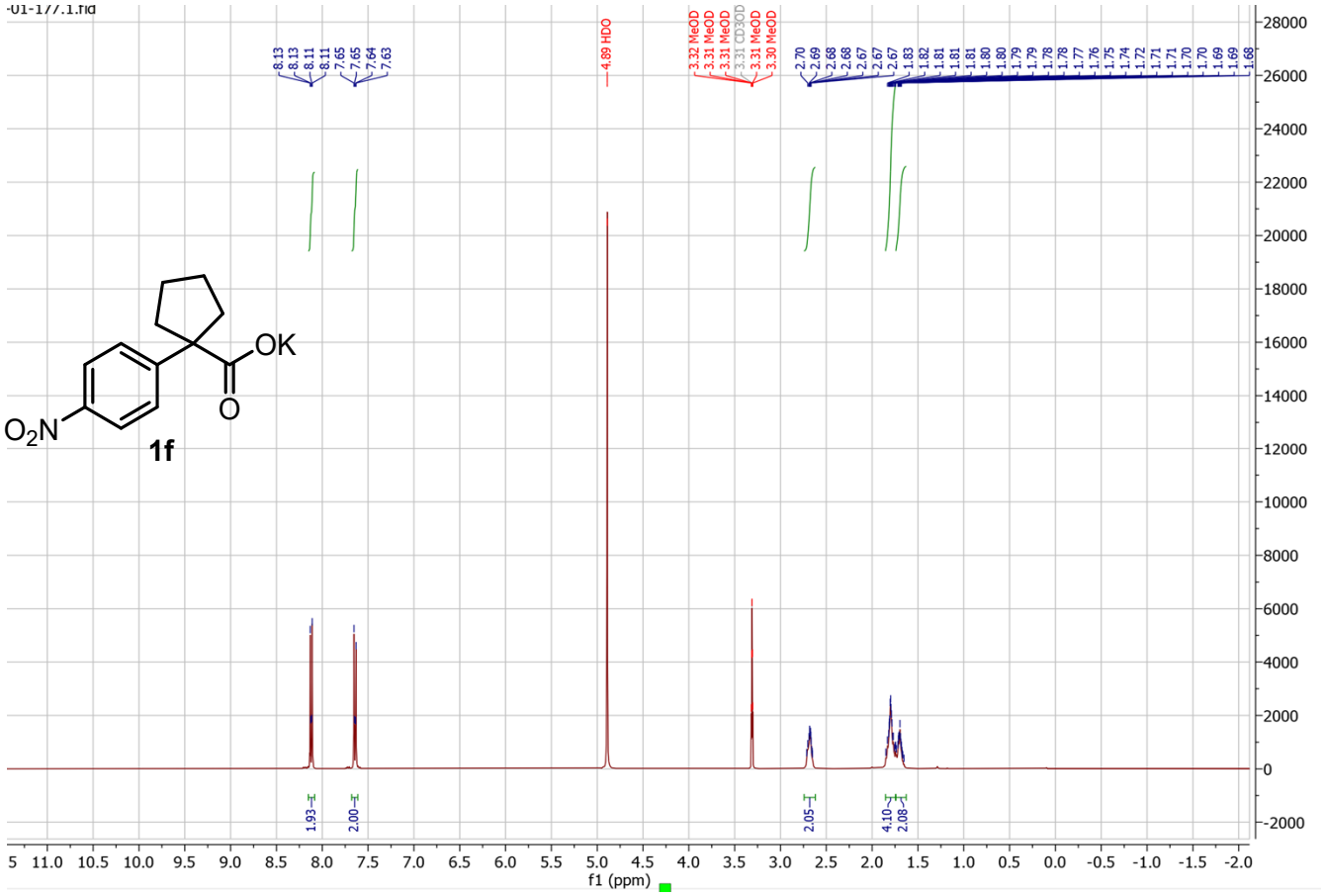




^{1}H NMR spectrum of 1e (400 MHz, Methanol-d_4)

^{13}C NMR spectrum of 1e (126 MHz, Methanol-d_4)

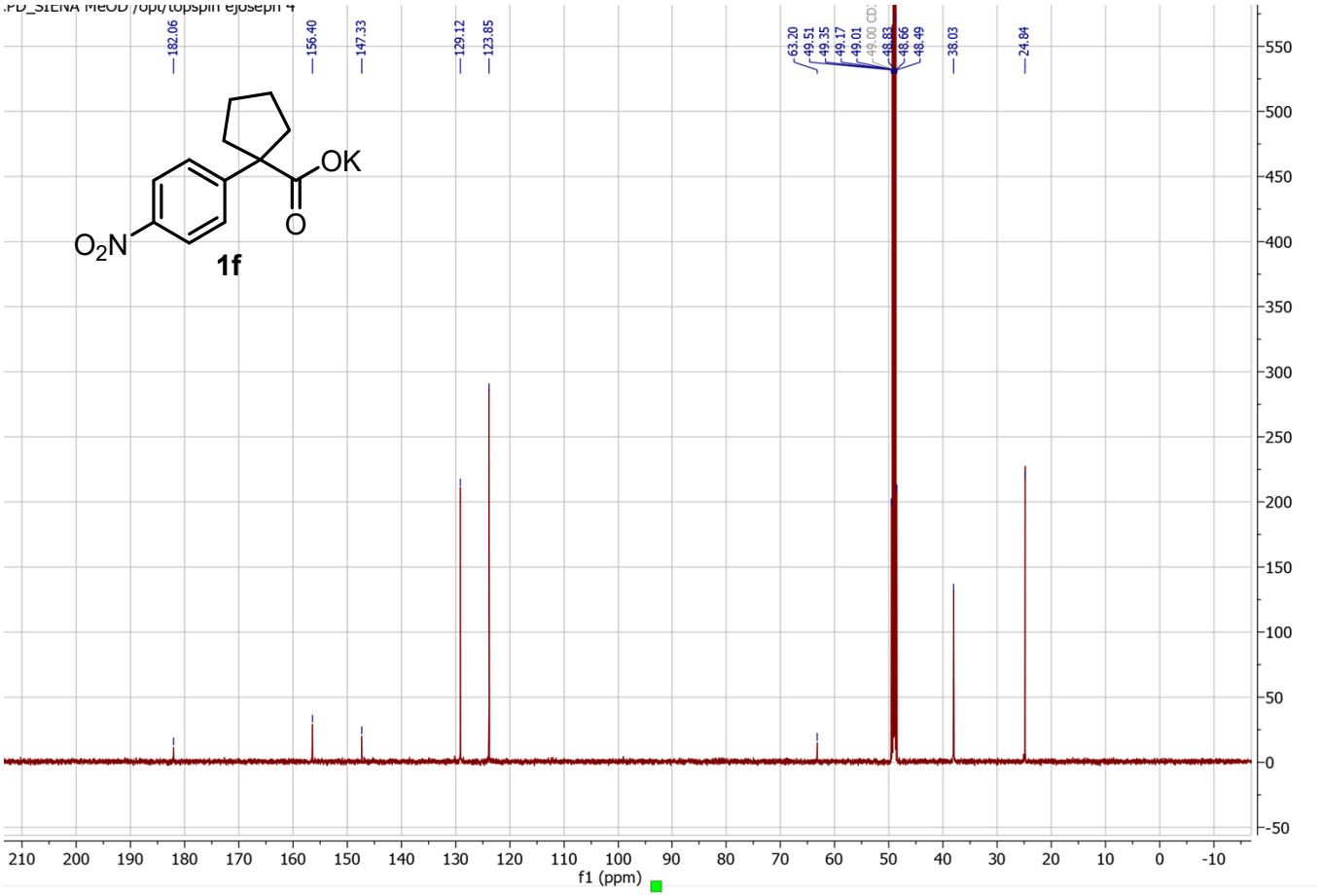




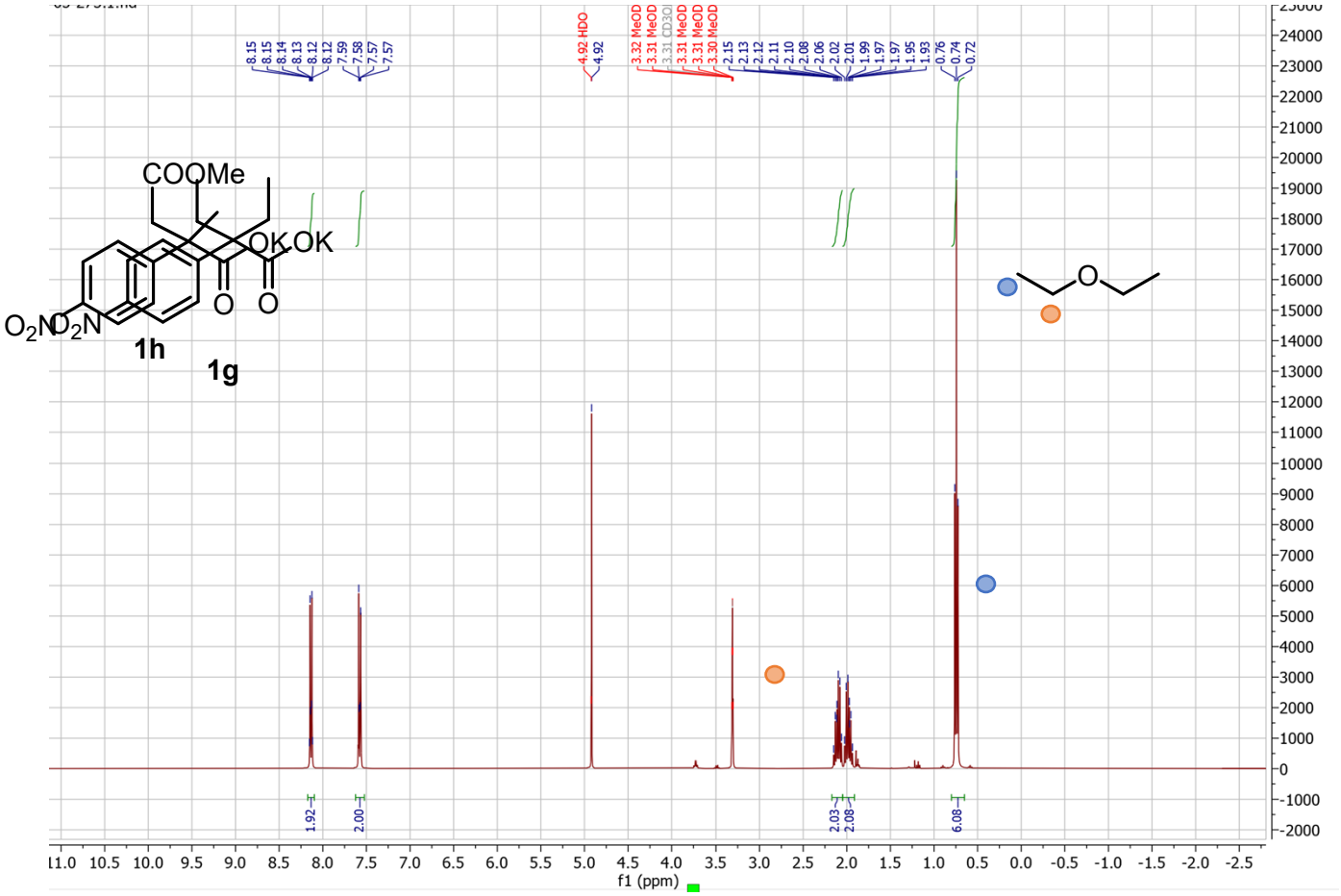
^{1}H NMR spectrum of 1f (400 MHz, Methanol-d_4)

^{13}C NMR spectrum of 1f (126 MHz, Methanol-d_4)

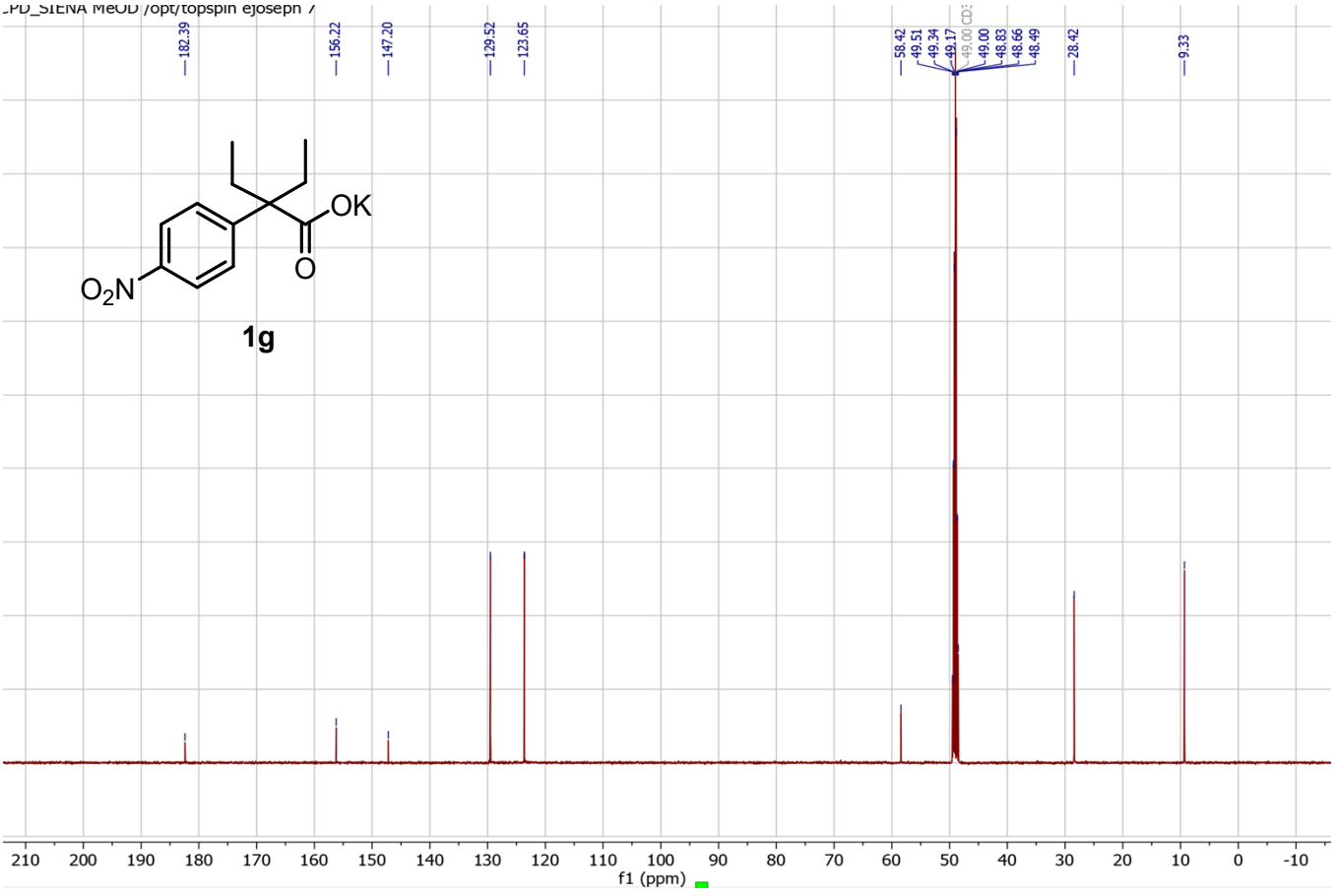
^{1}H NMR spectrum of 1g (400 MHz, Methanol-d_4)

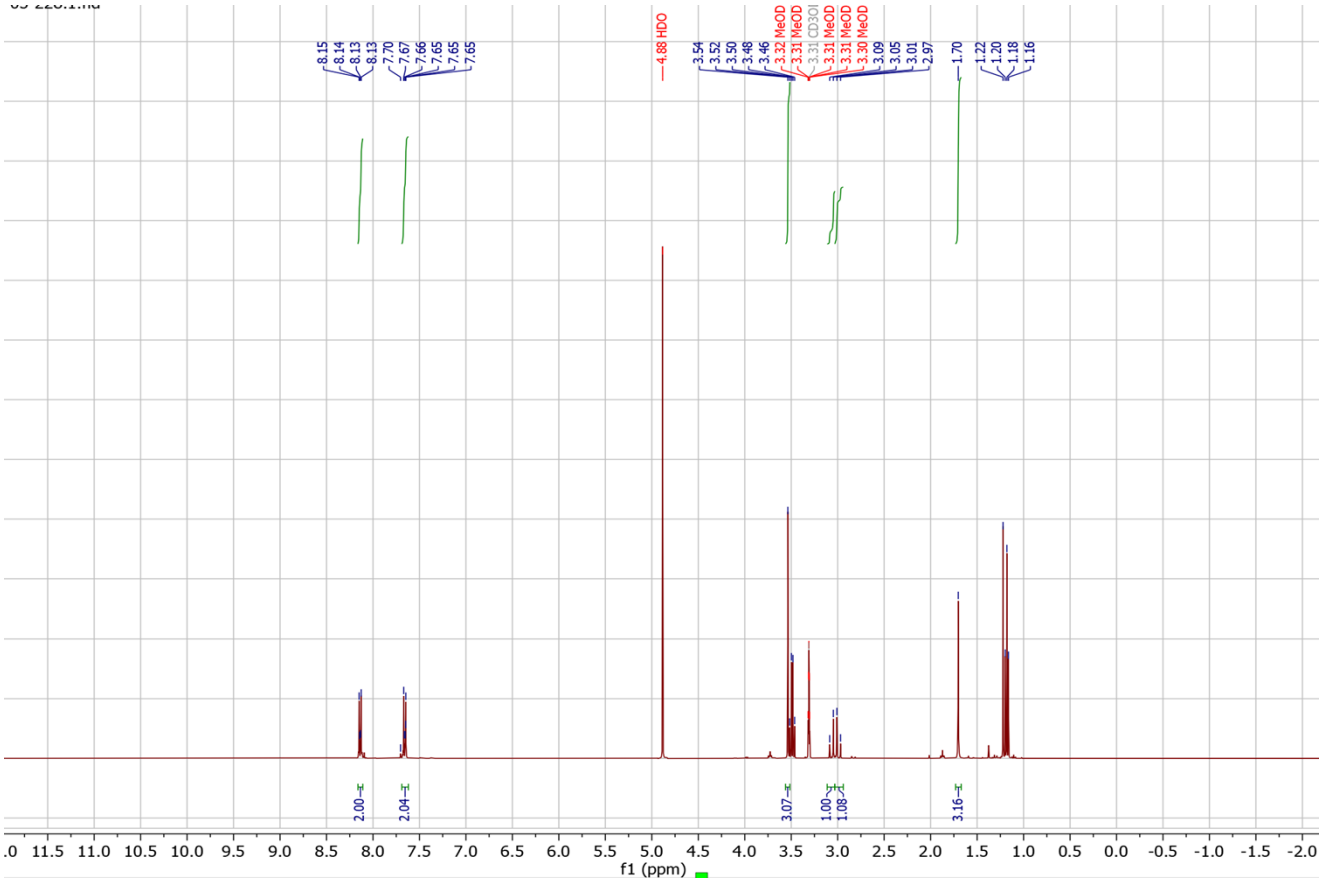


^{13}C NMR spectrum of 1g (126 MHz, Methanol-d_4)

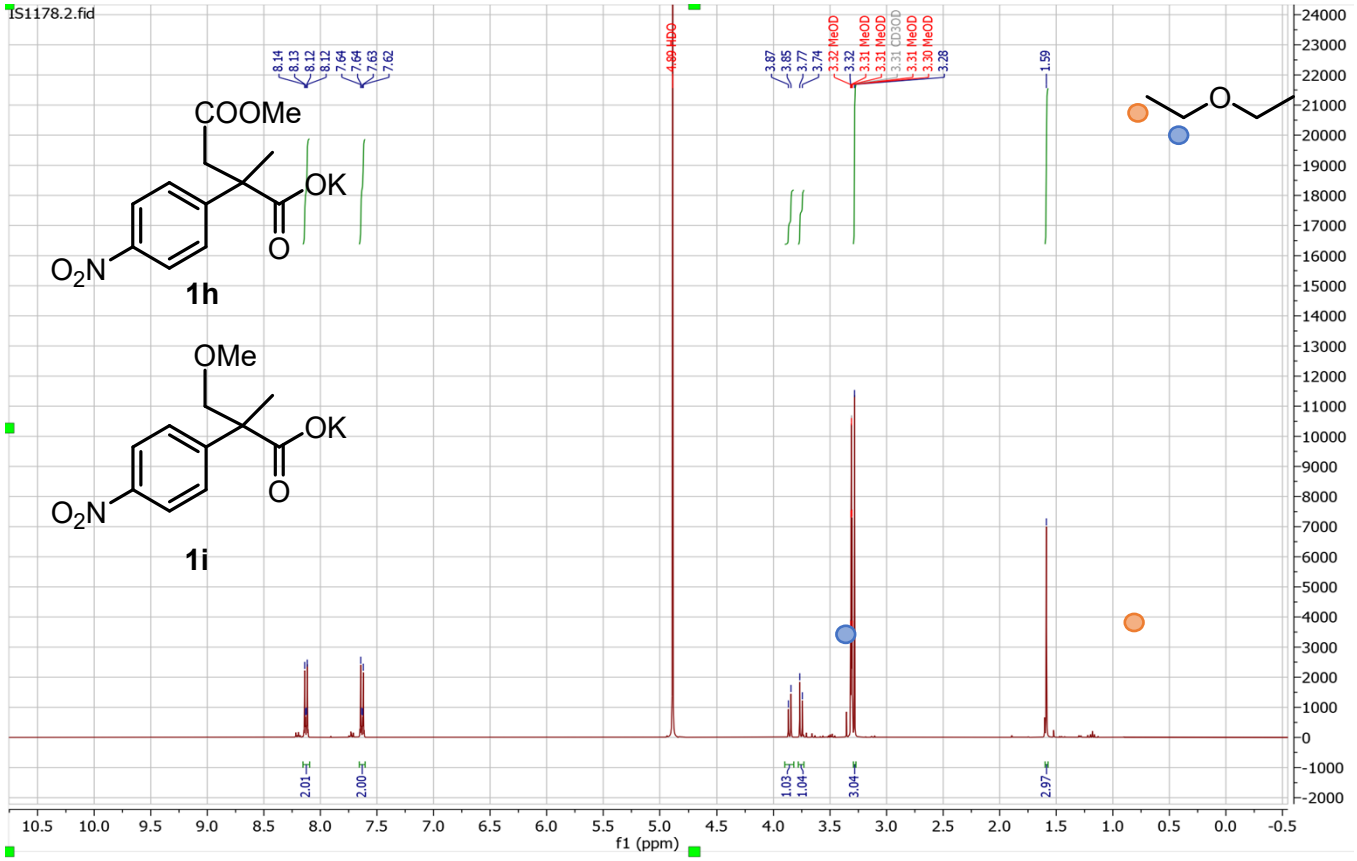


^{1}H NMR spectrum of 1h (400 MHz, Methanol-d_4)

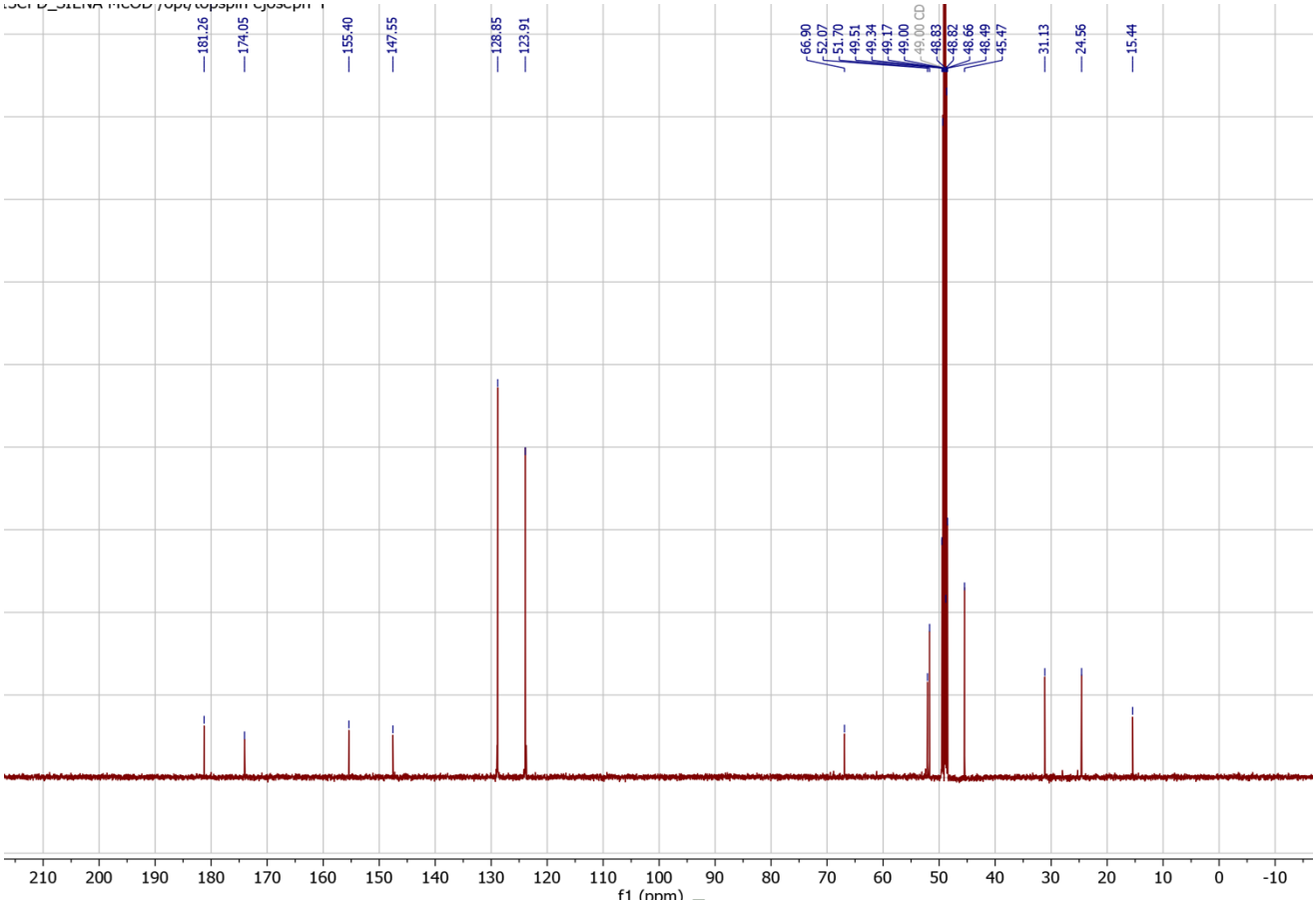


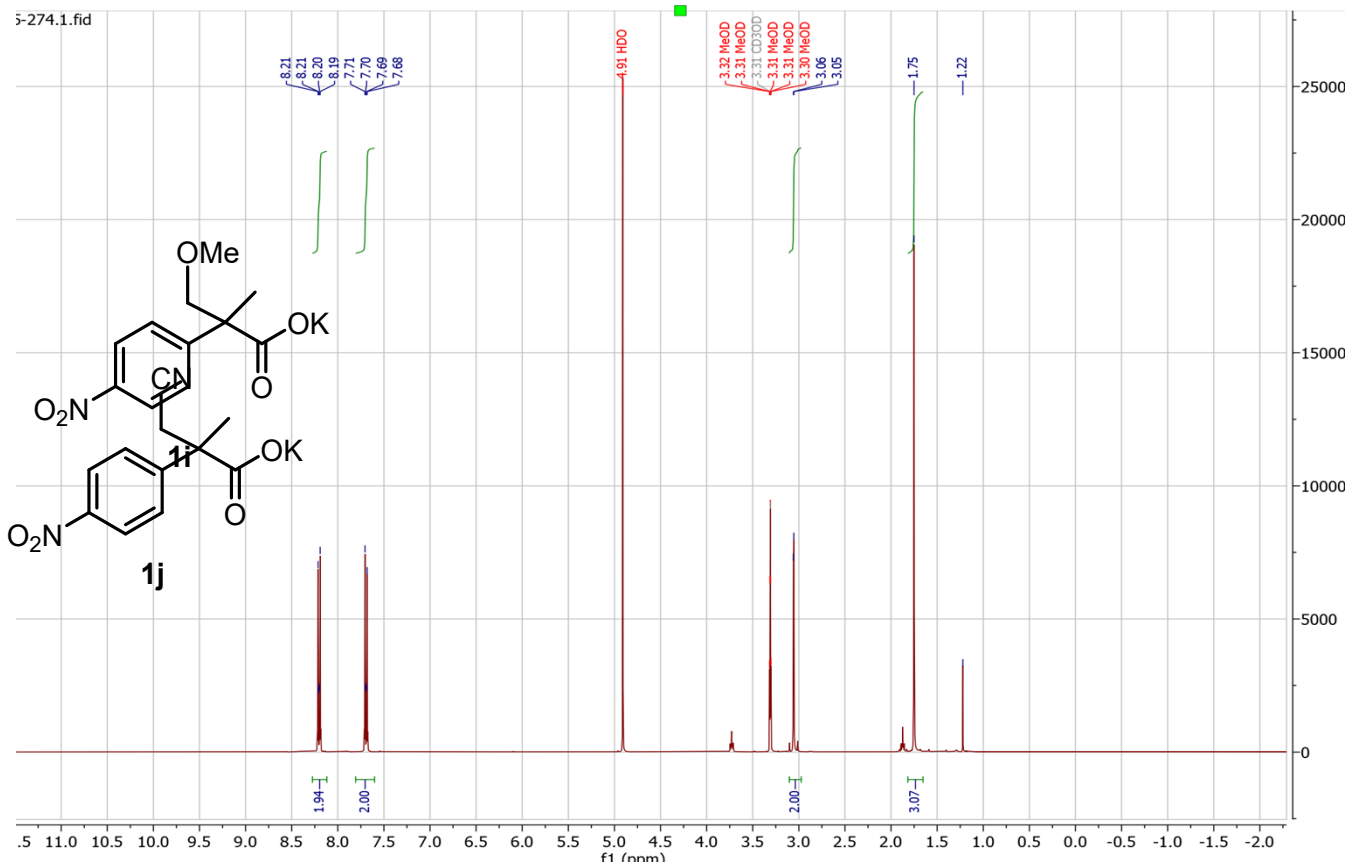


^{13}C NMR spectrum of 1h (126 MHz, Methanol-d_4)

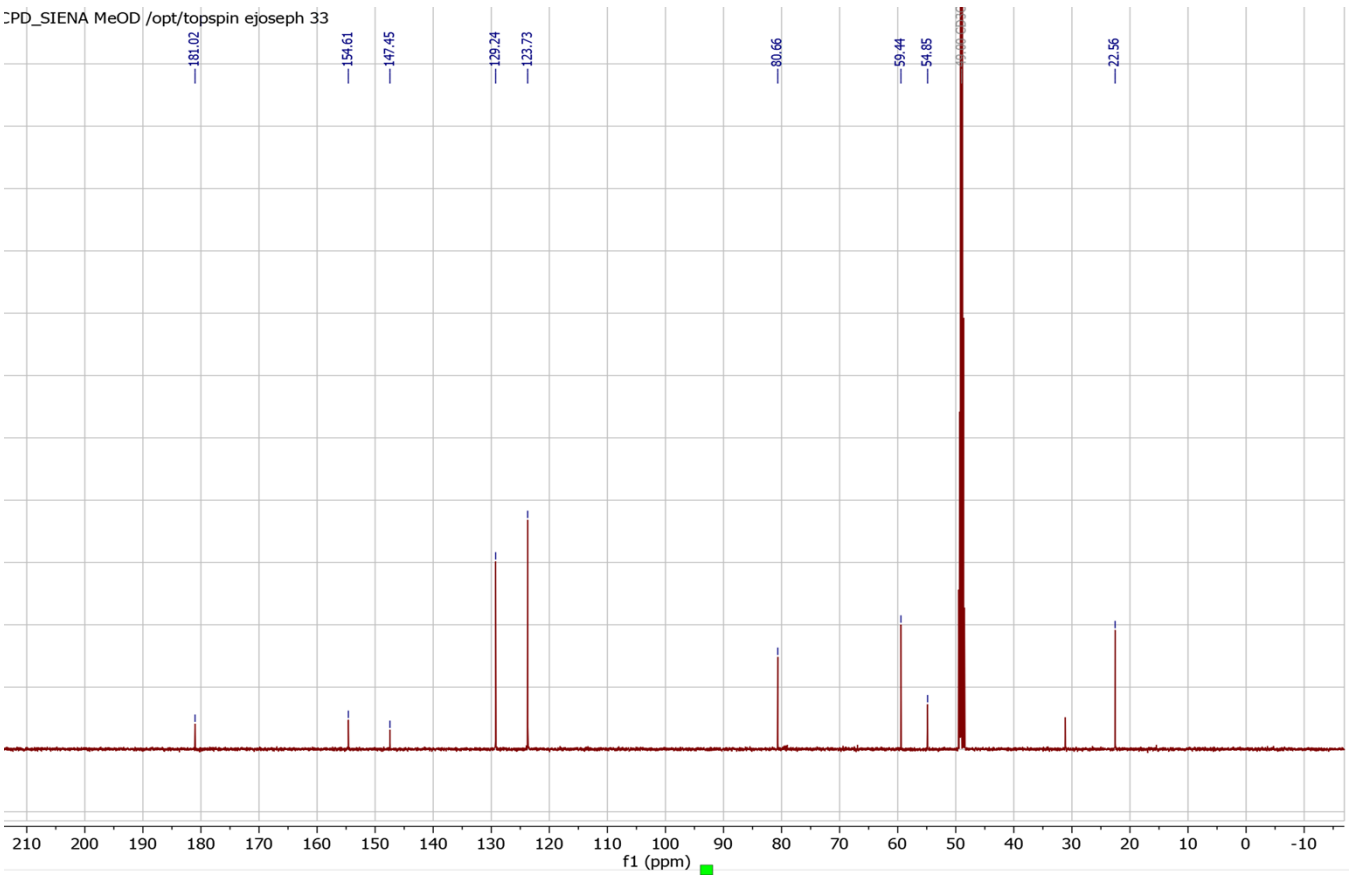


^{1}H NMR spectrum of 1i (400 MHz, Methanol-d_4)



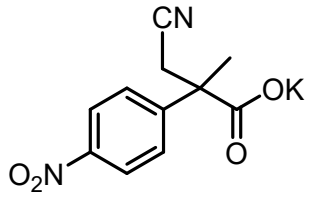


^{13}C NMR spectrum of 1i (126 MHz, Methanol-d_4)

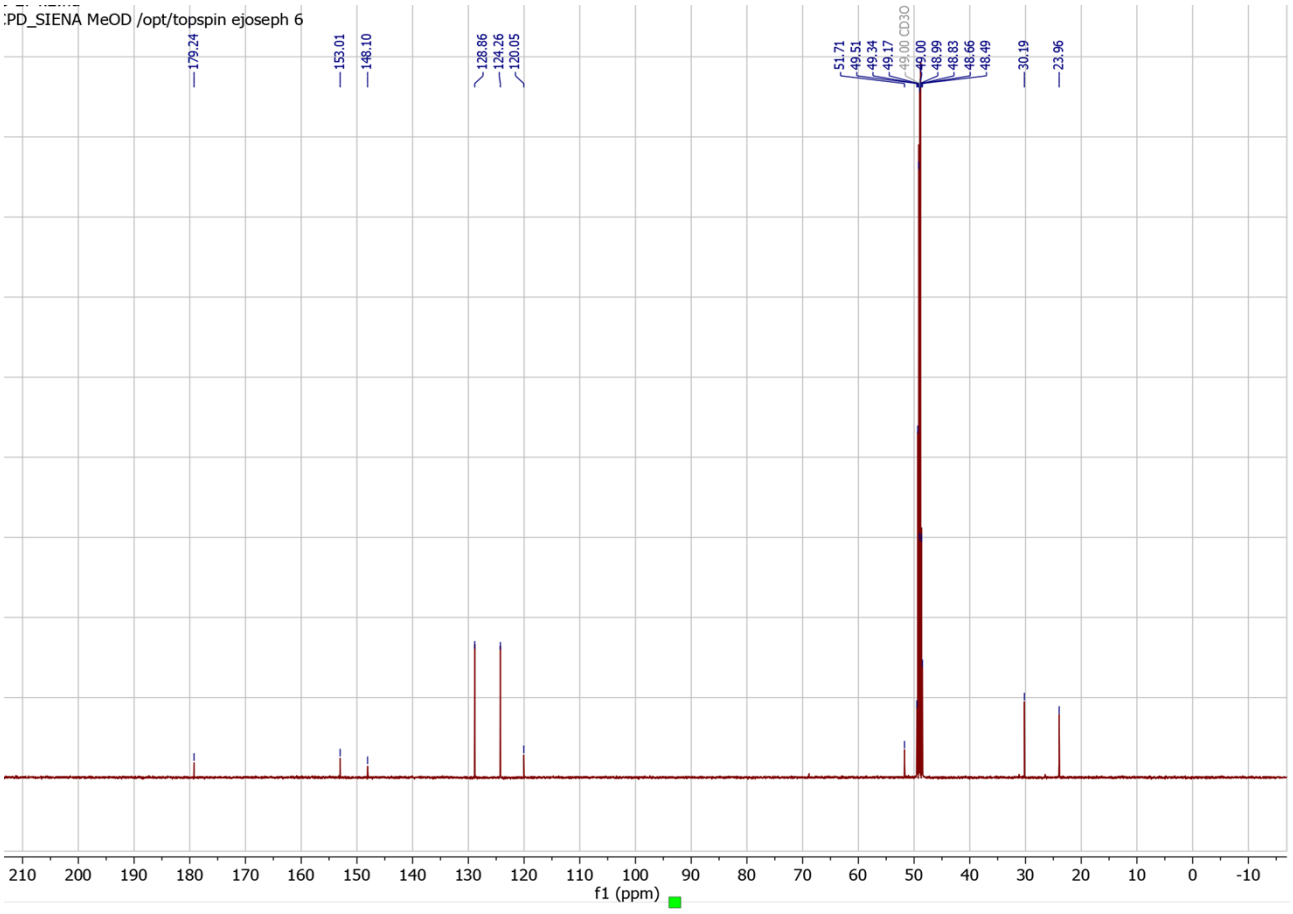


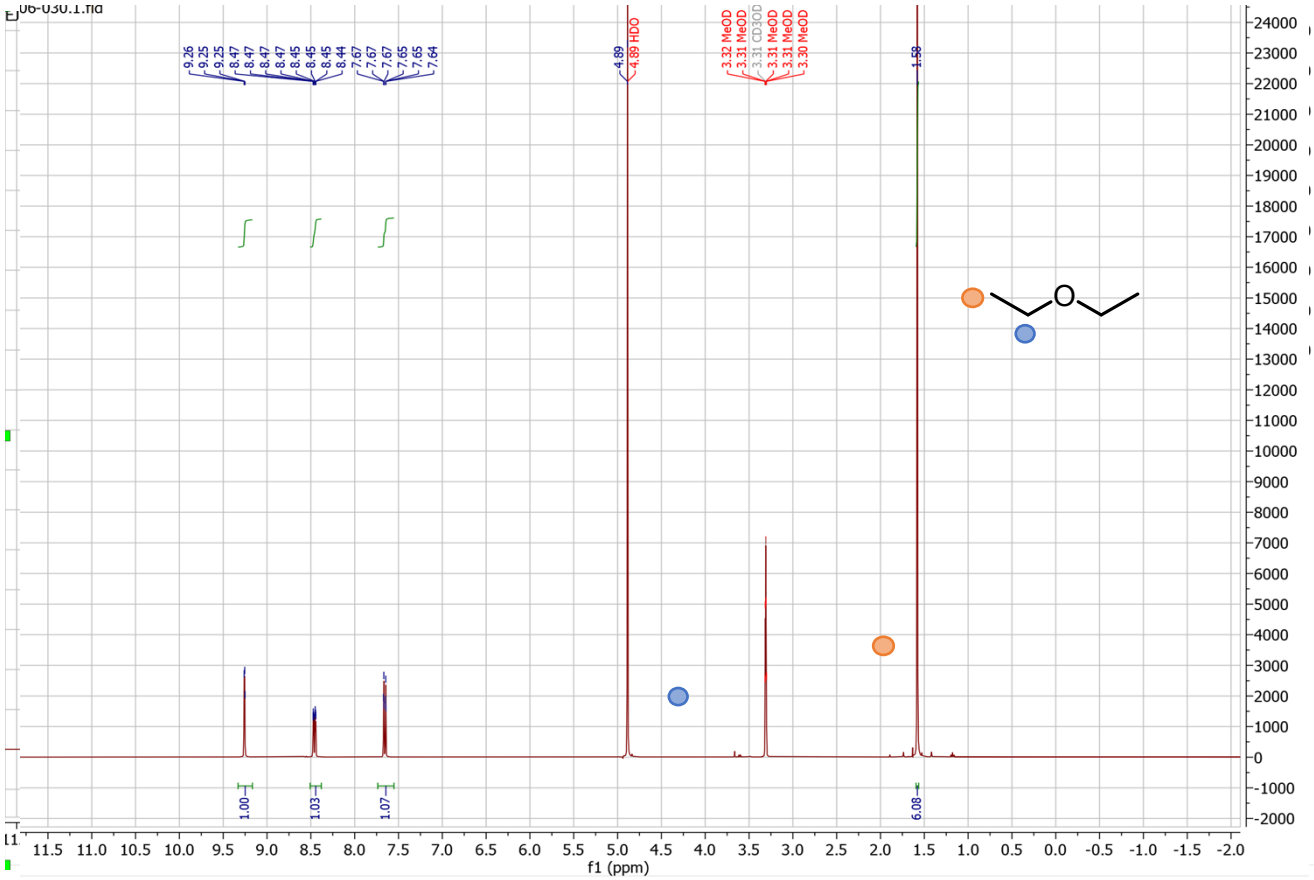
^{1}H NMR spectrum of 1j (400 MHz, Methanol-d_4)

^{13}C NMR spectrum of 1j (126 MHz, Methanol-d_4)

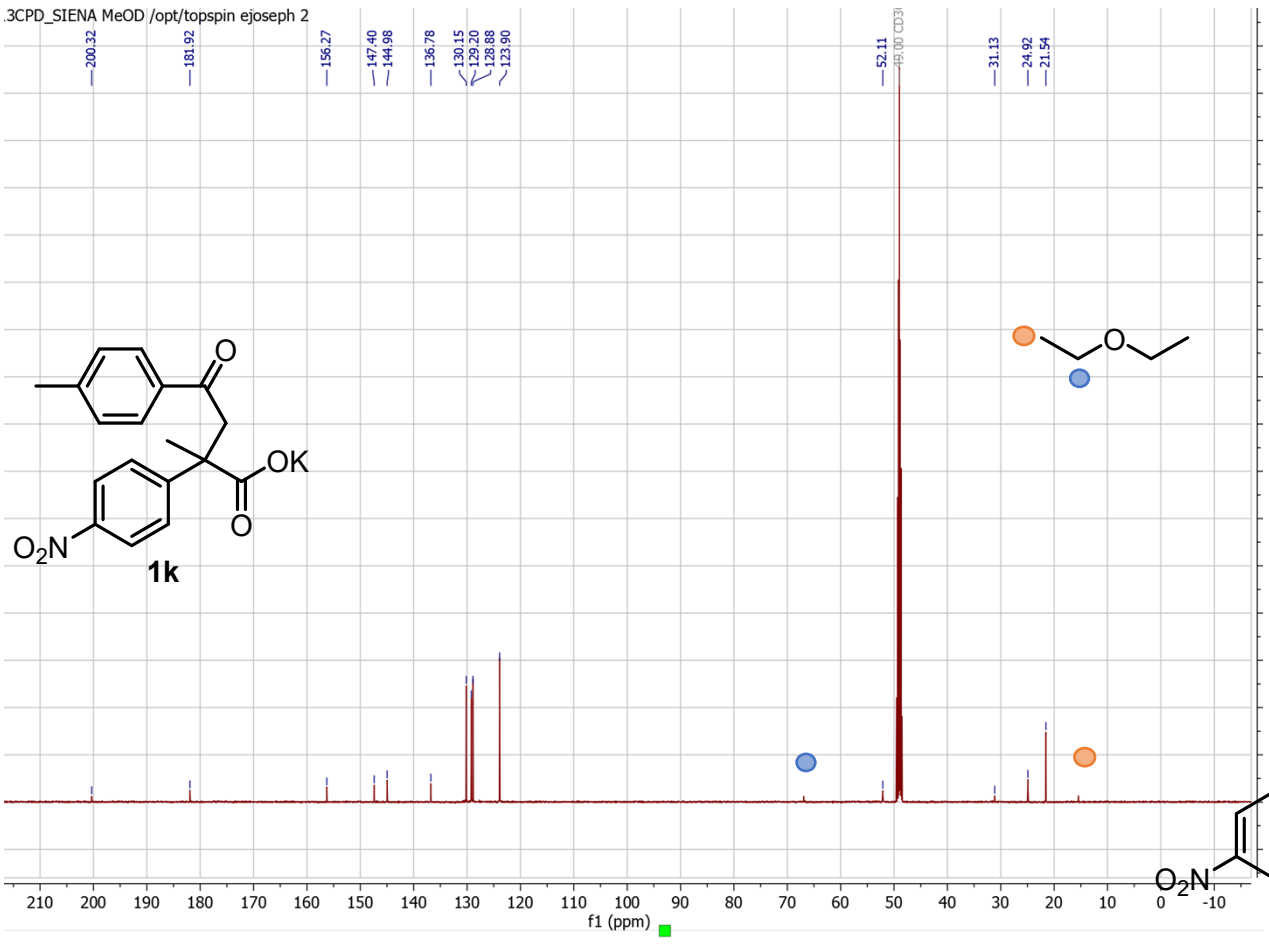


1j

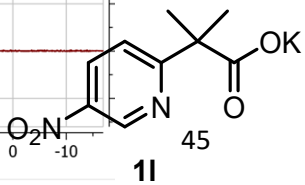




^{1}H NMR spectrum of 1k (400 MHz, Methanol-d_4)



^{13}C NMR spectrum of 1k (126 MHz, Methanol-d_4)



45

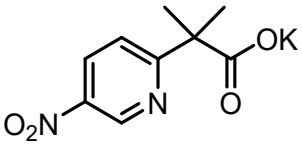
1l

^{13}C NMR spectrum of 1l (400 MHz, Meth

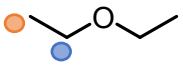
anol-d_4)

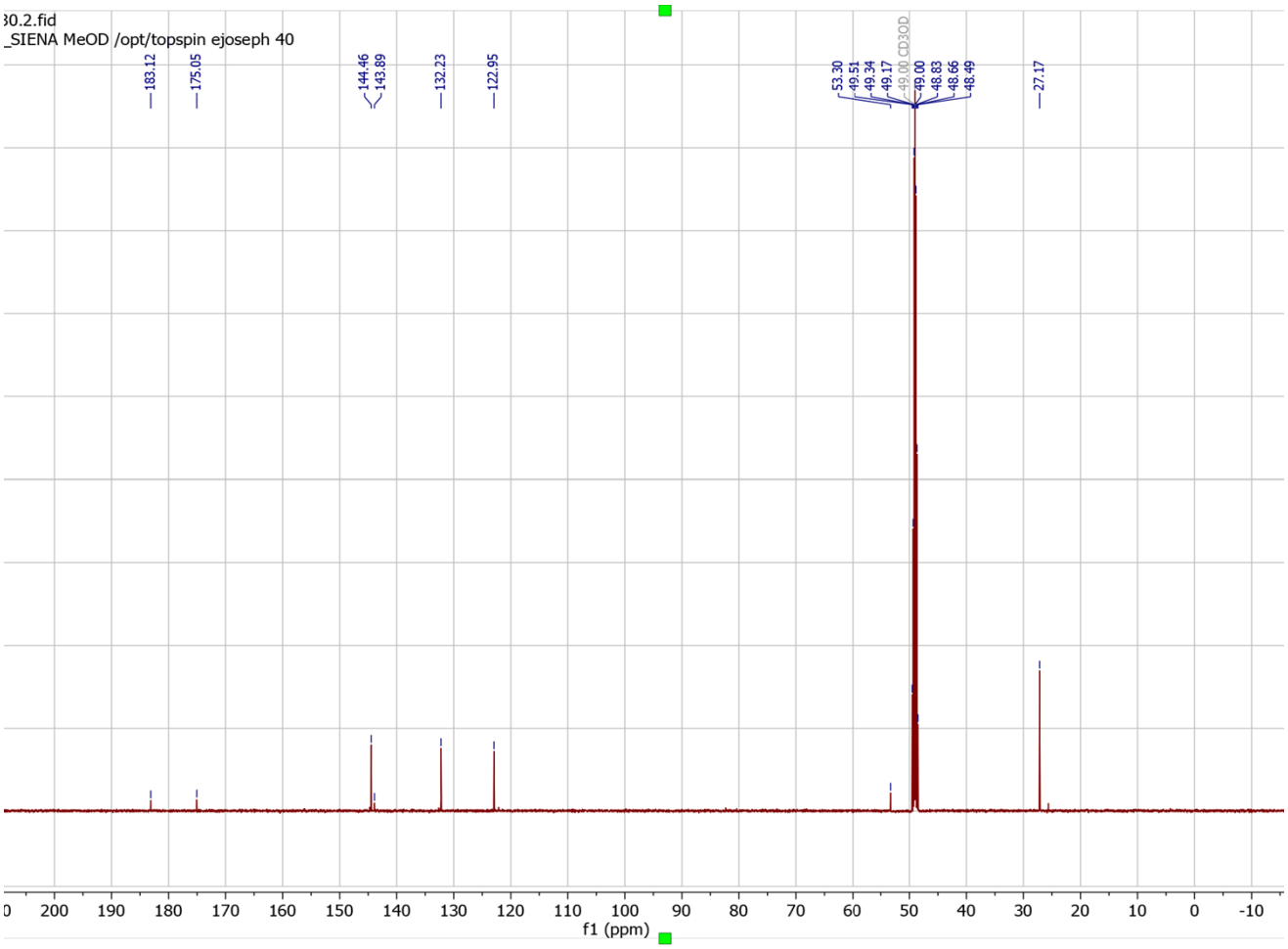
^{13}C NMR spectrum of 1l (126 MHz, Methanol-d_4)

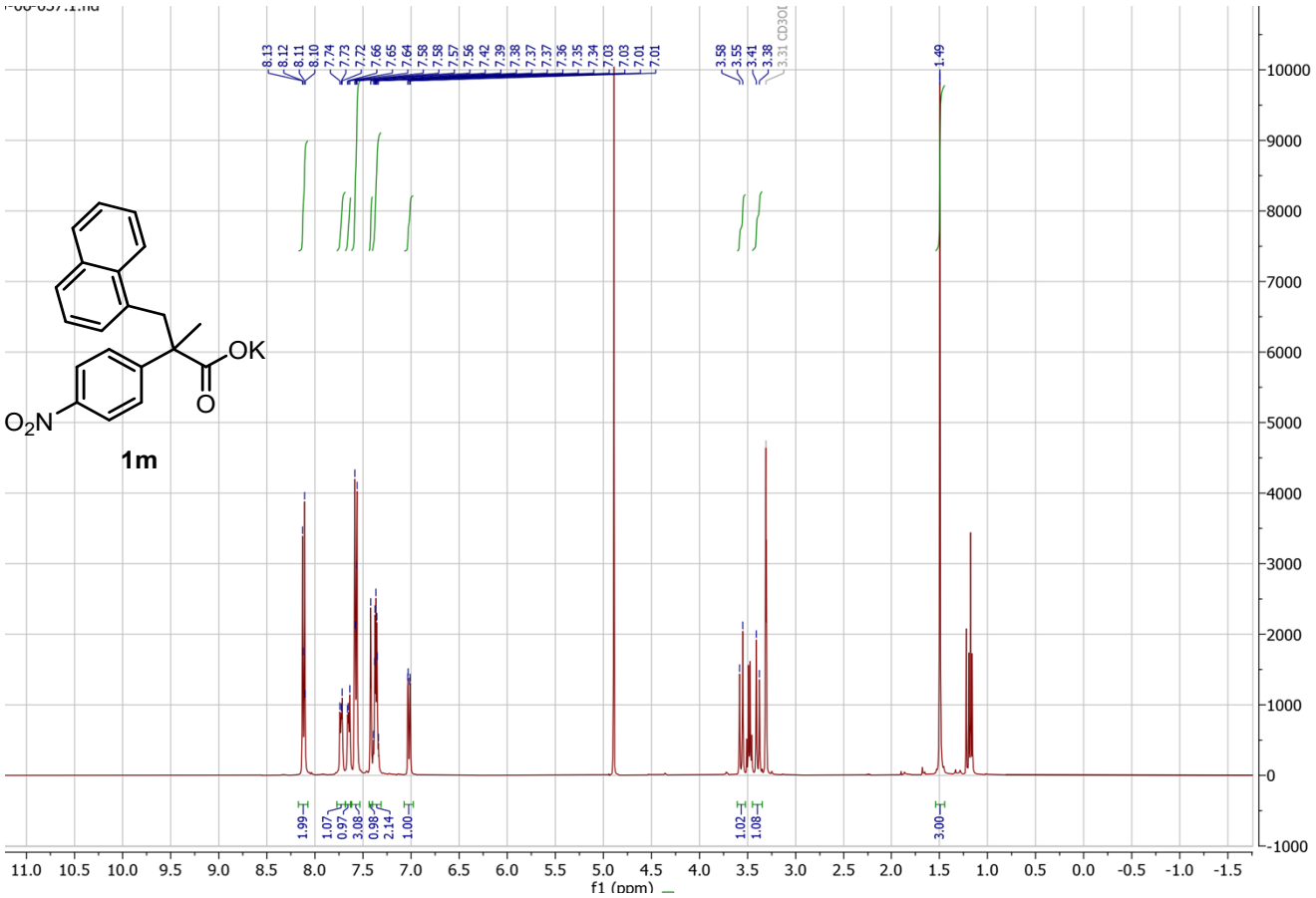
^{1}H NMR spectrum of 1m (400 MHz, Methanol-d_4)



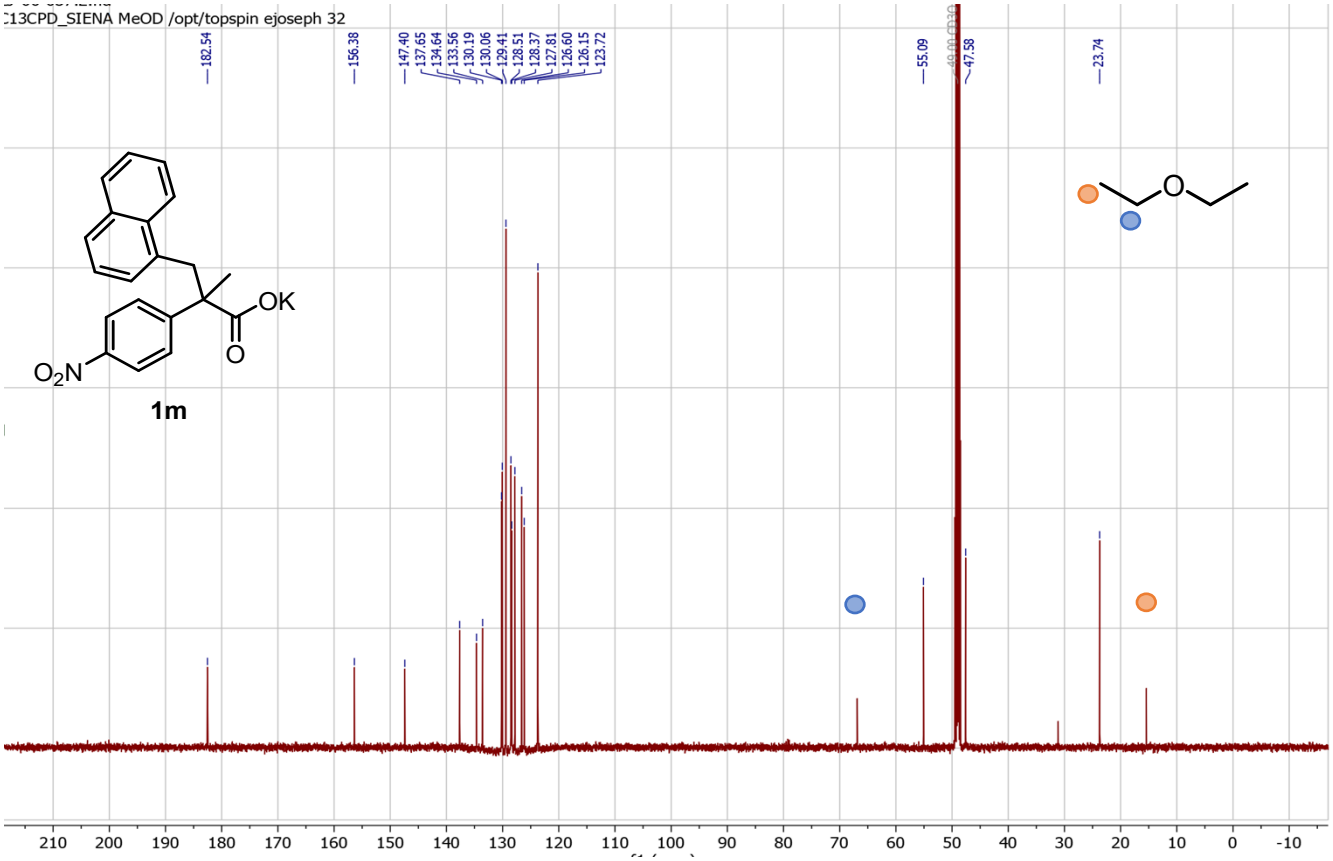
1l

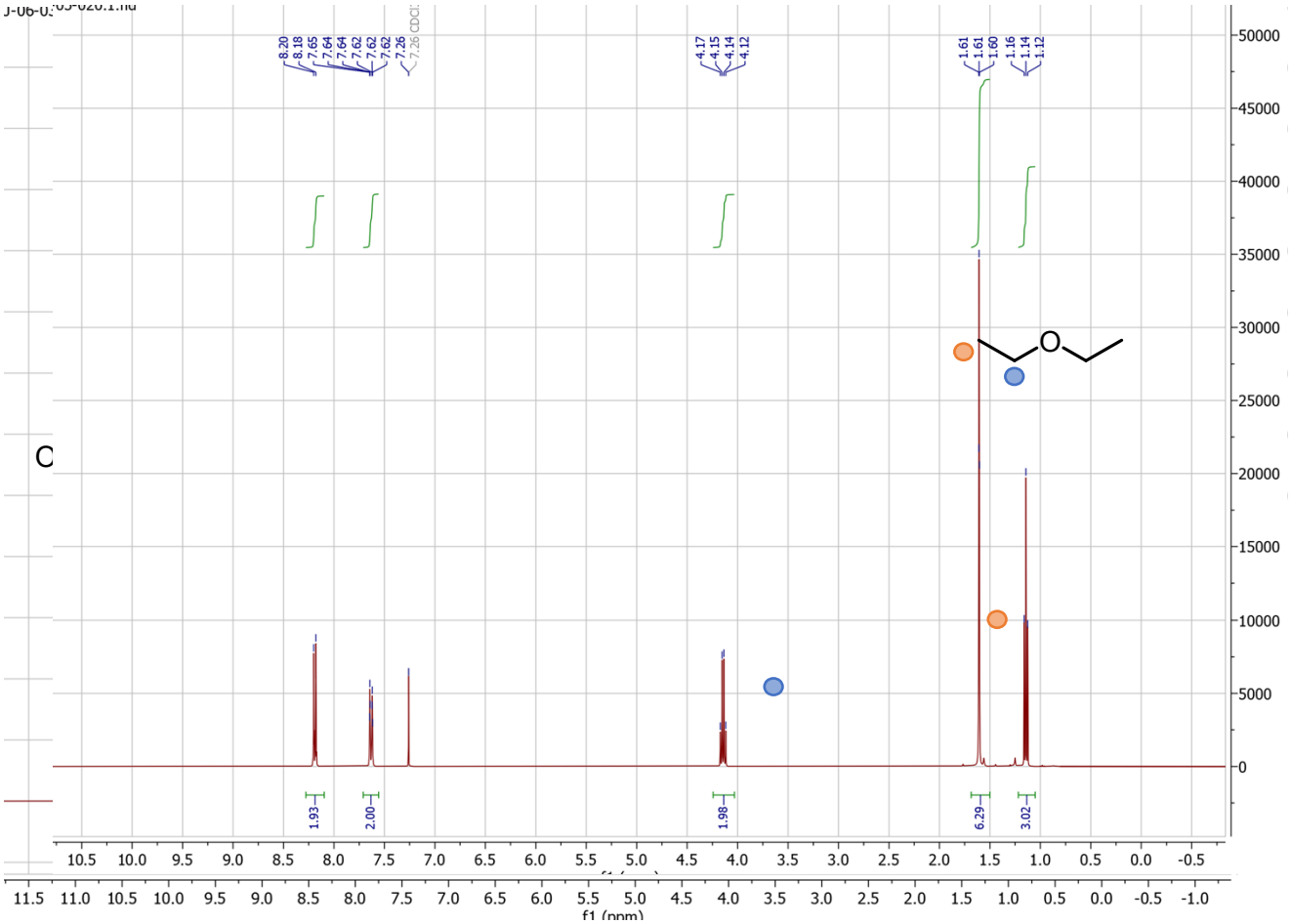






^{13}C NMR spectrum of 1m (126 MHz, Methanol-d_4)

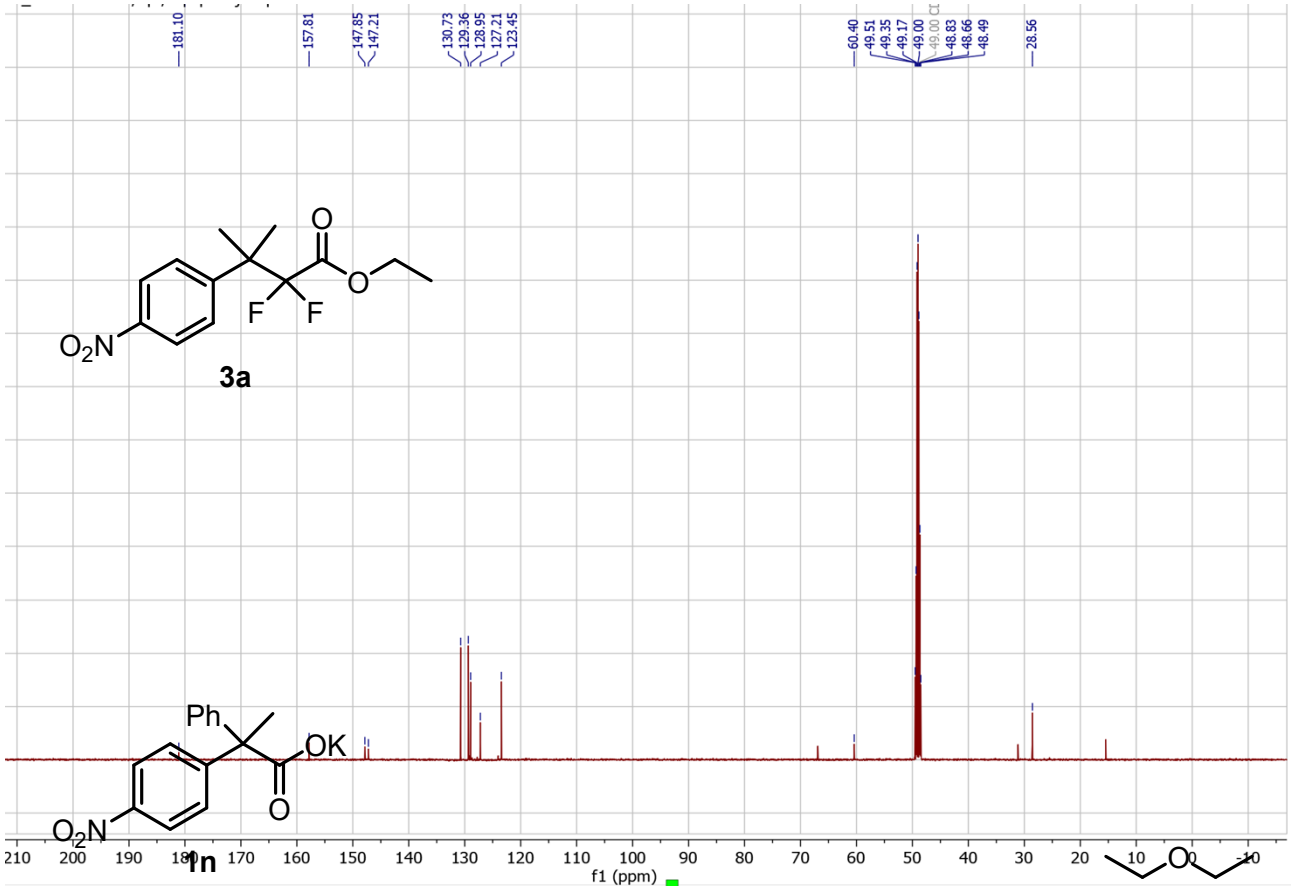




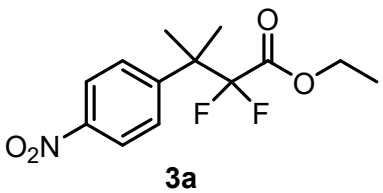
^{1}H NMR spectrum of 1n (400 MHz, Methanol-d_4)

^{13}C NMR spectrum of 1n (126 MHz, Methanol-d_4)

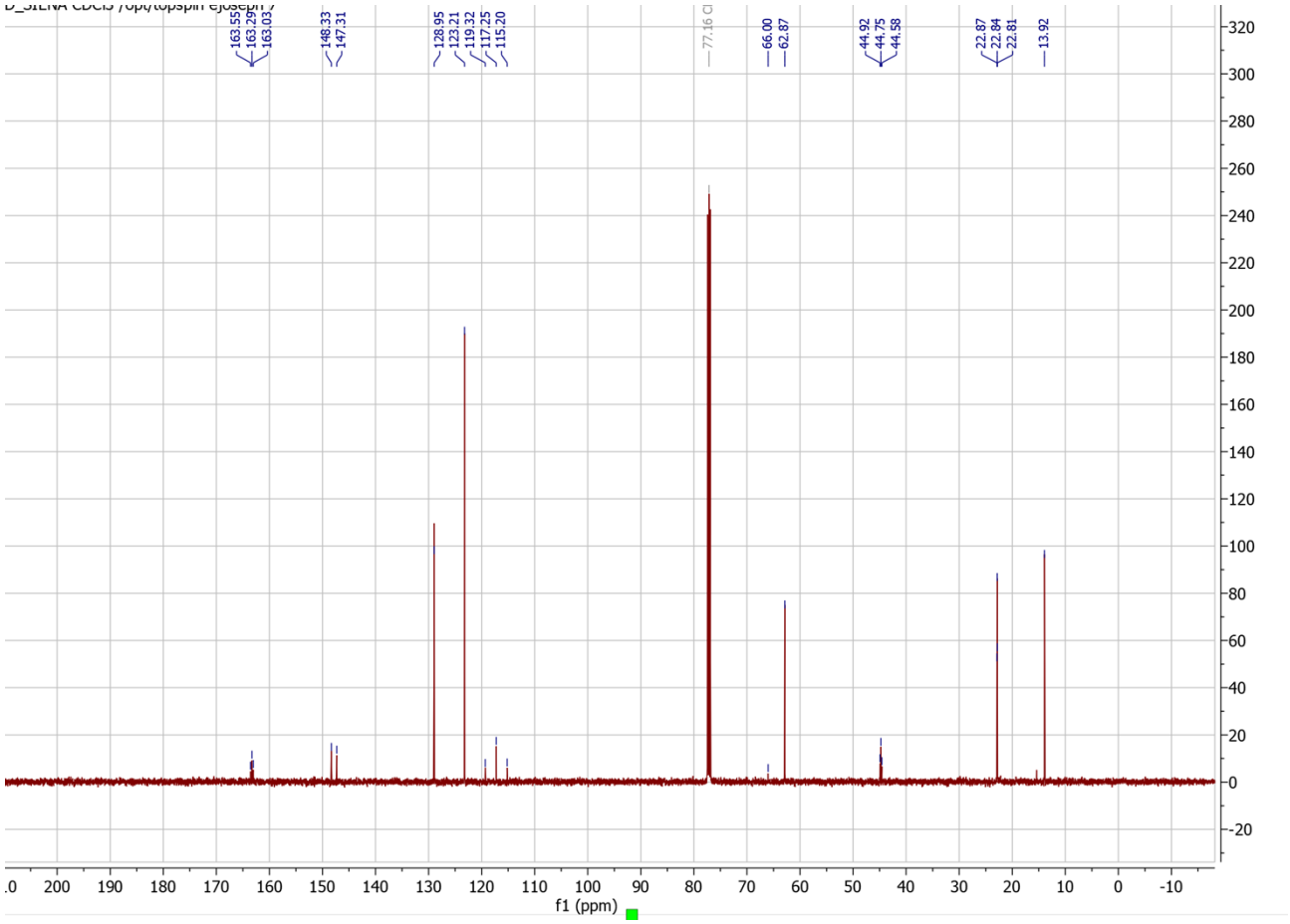
^{1}H NMR spectrum of 3a (400 MHz, Chloroform-d)



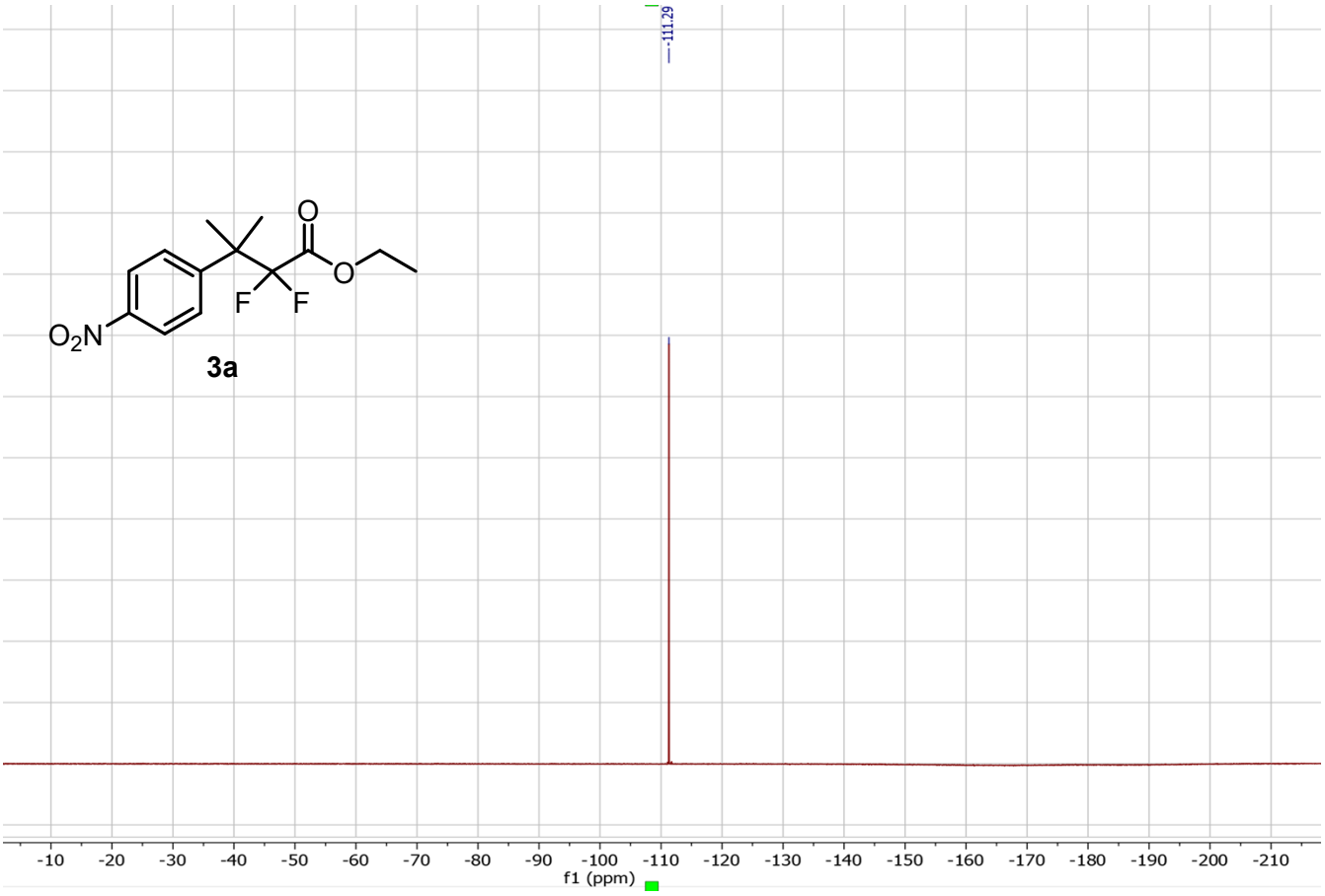
^{13}C NMR spectrum of 3a (126 MHz, Chloroform-*d*)



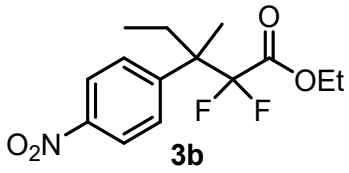
3a



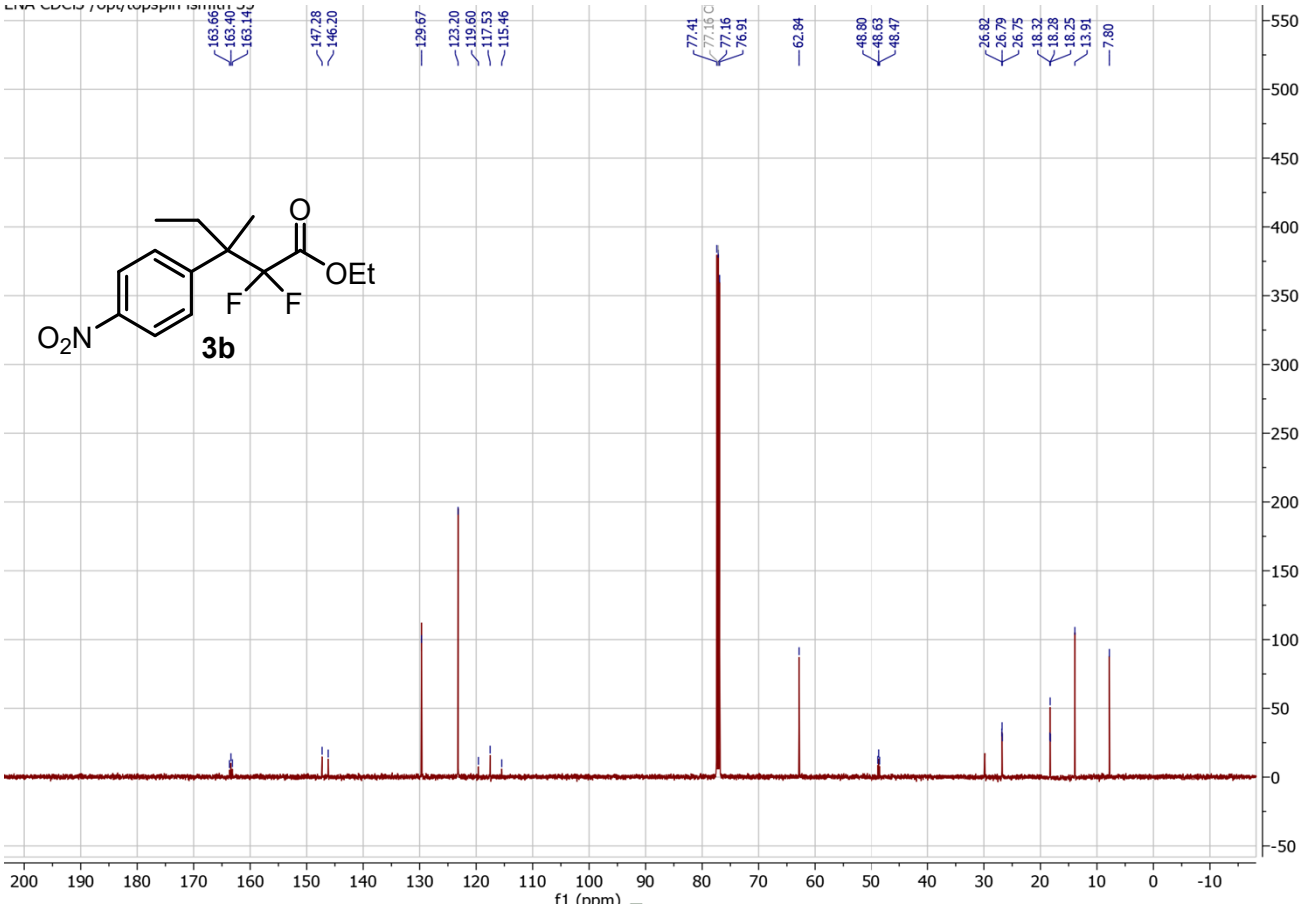
^{19}F NMR spectrum of 3a (376 MHz, Chloroform-*d*)



3a

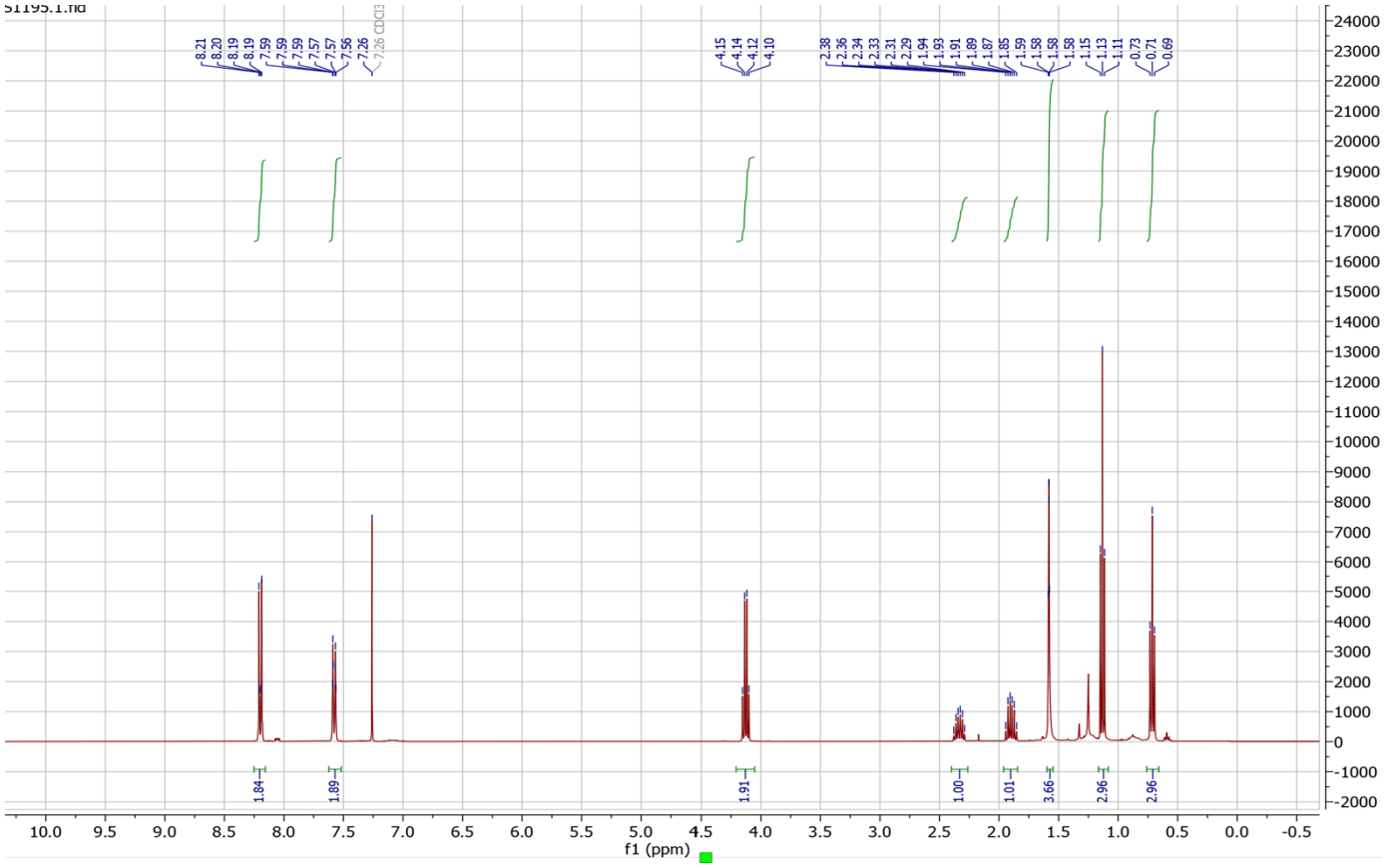


3b

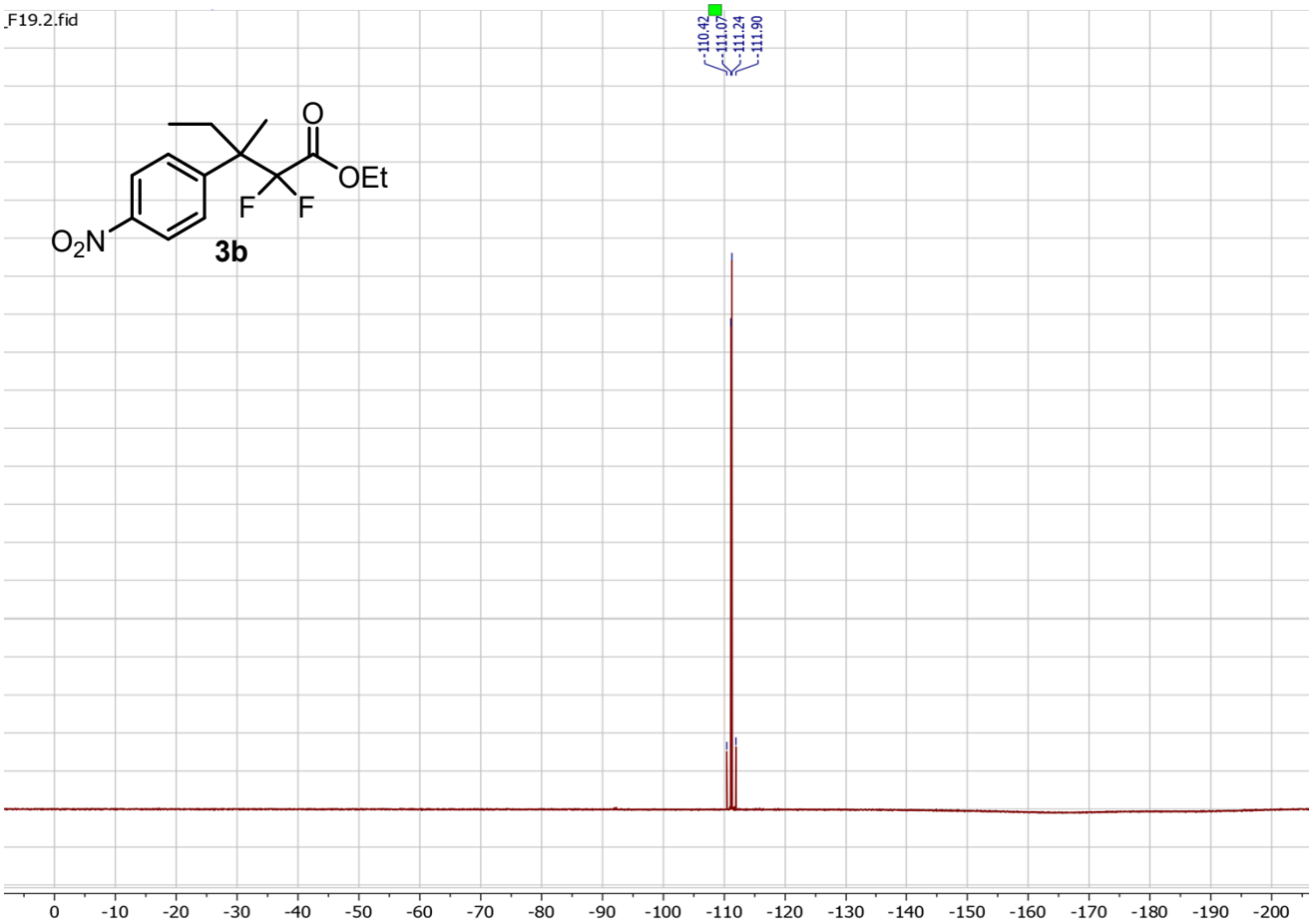


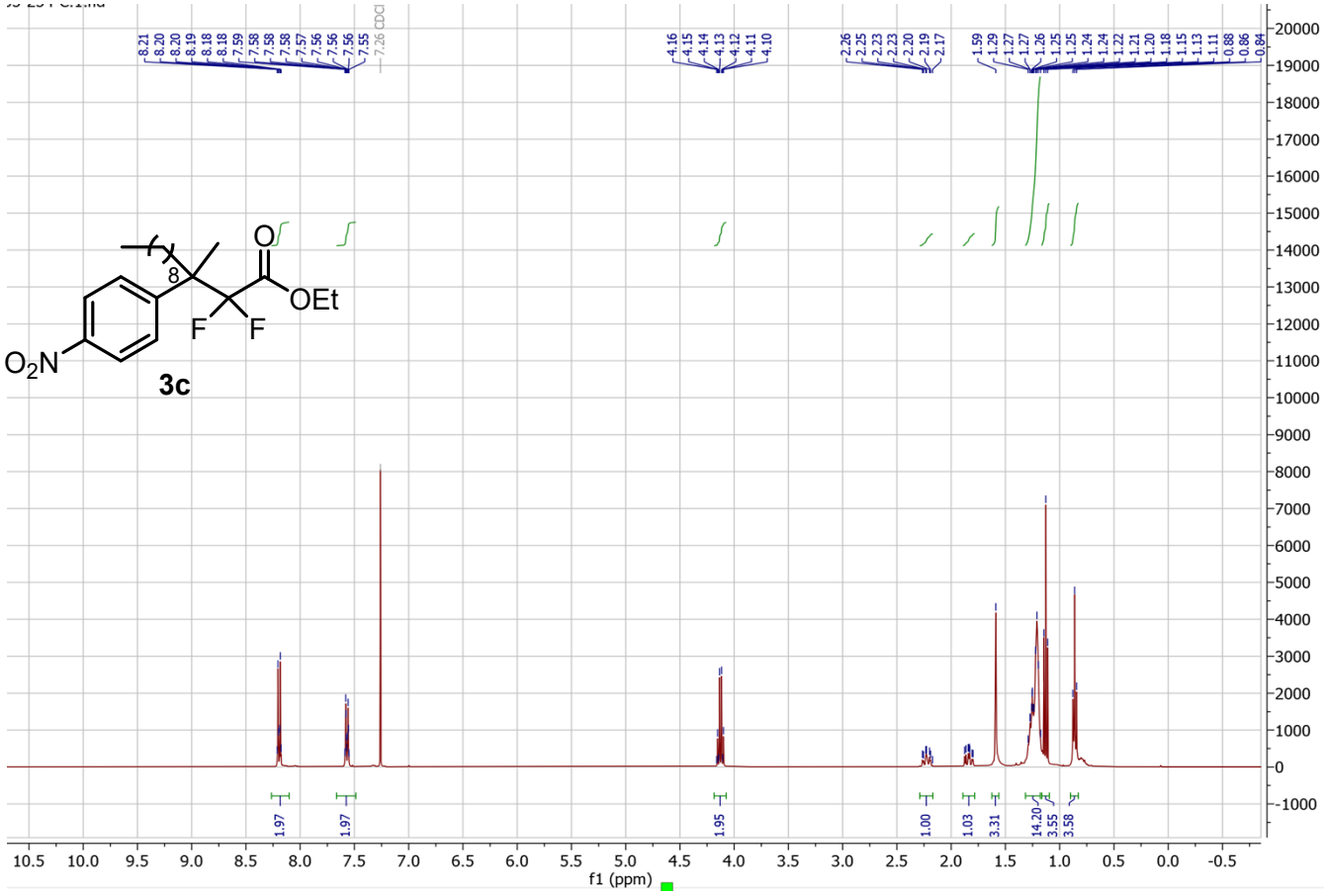
^{1}H NMR spectrum of 3b (400 MHz, Chloroform-d)

^{13}C NMR spectrum of 3b (126 MHz, Chloroform-*d*)



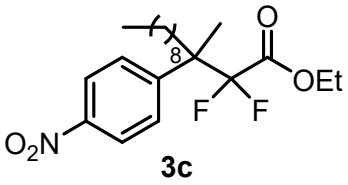
^{19}F NMR spectrum of 3b (376 MHz, Chloroform-*d*)



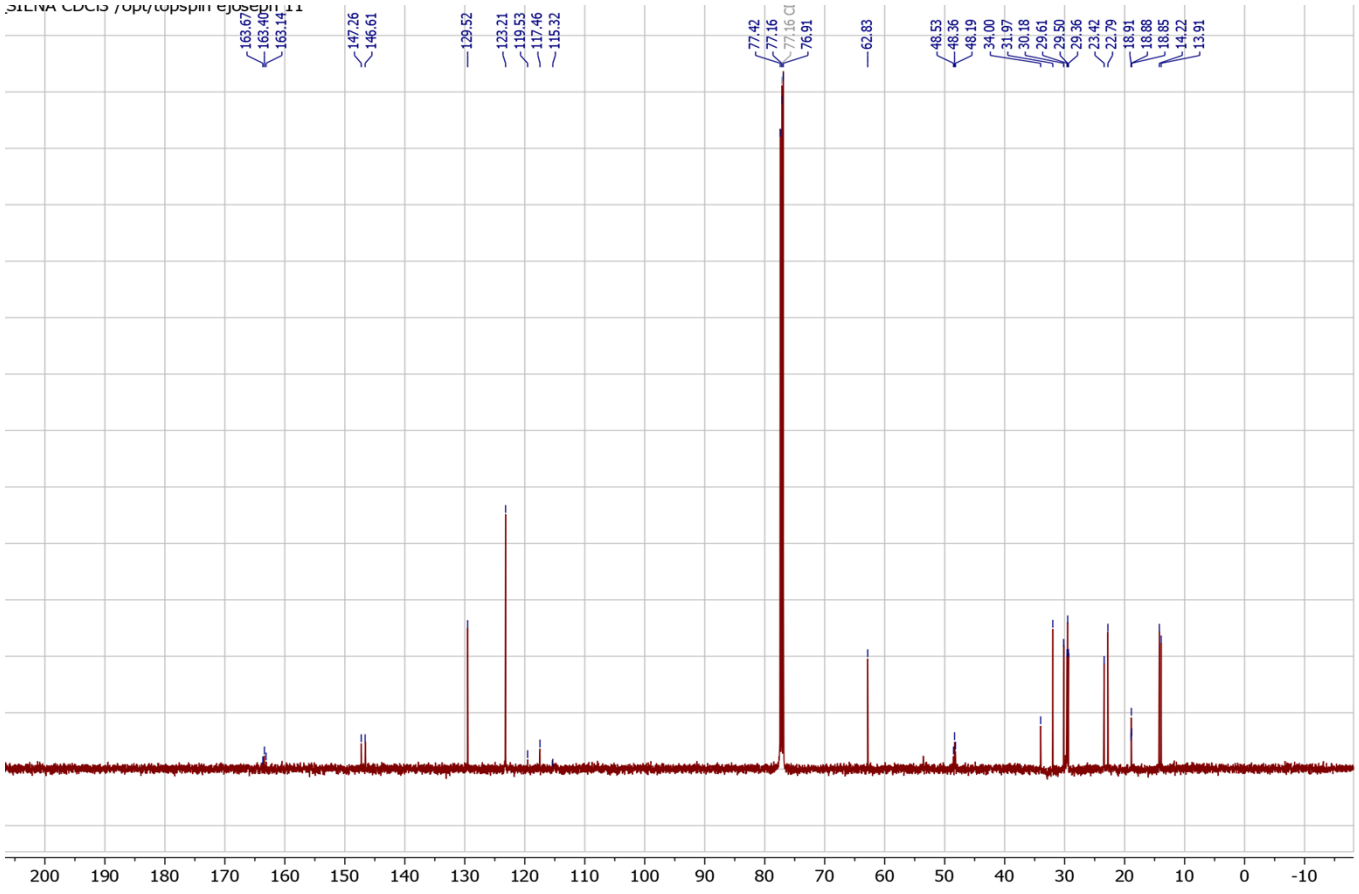


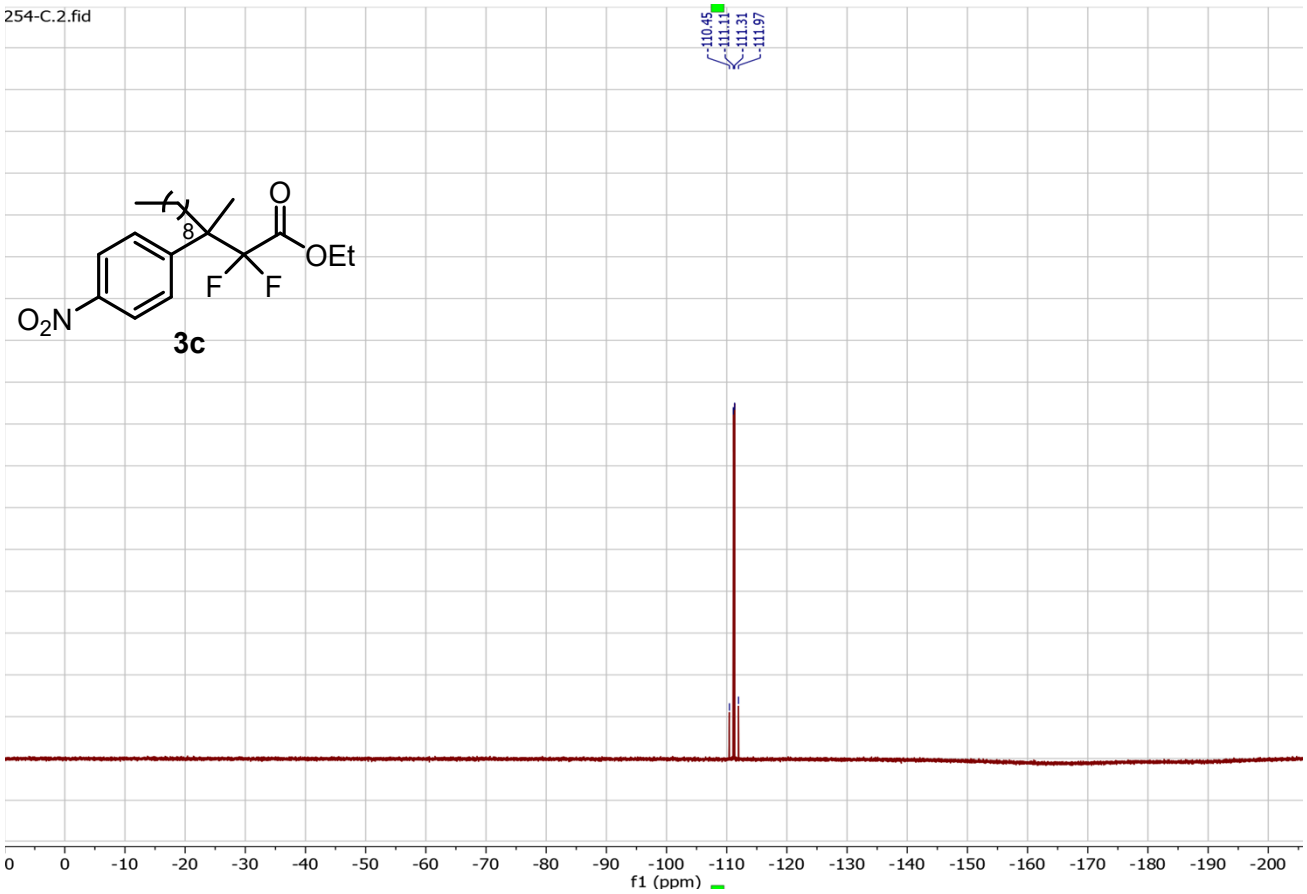
^{1}H NMR spectrum of 3c (400 MHz, Chloroform-d)

^{13}C NMR spectrum of 3c (126 MHz, Chloroform-*d*)

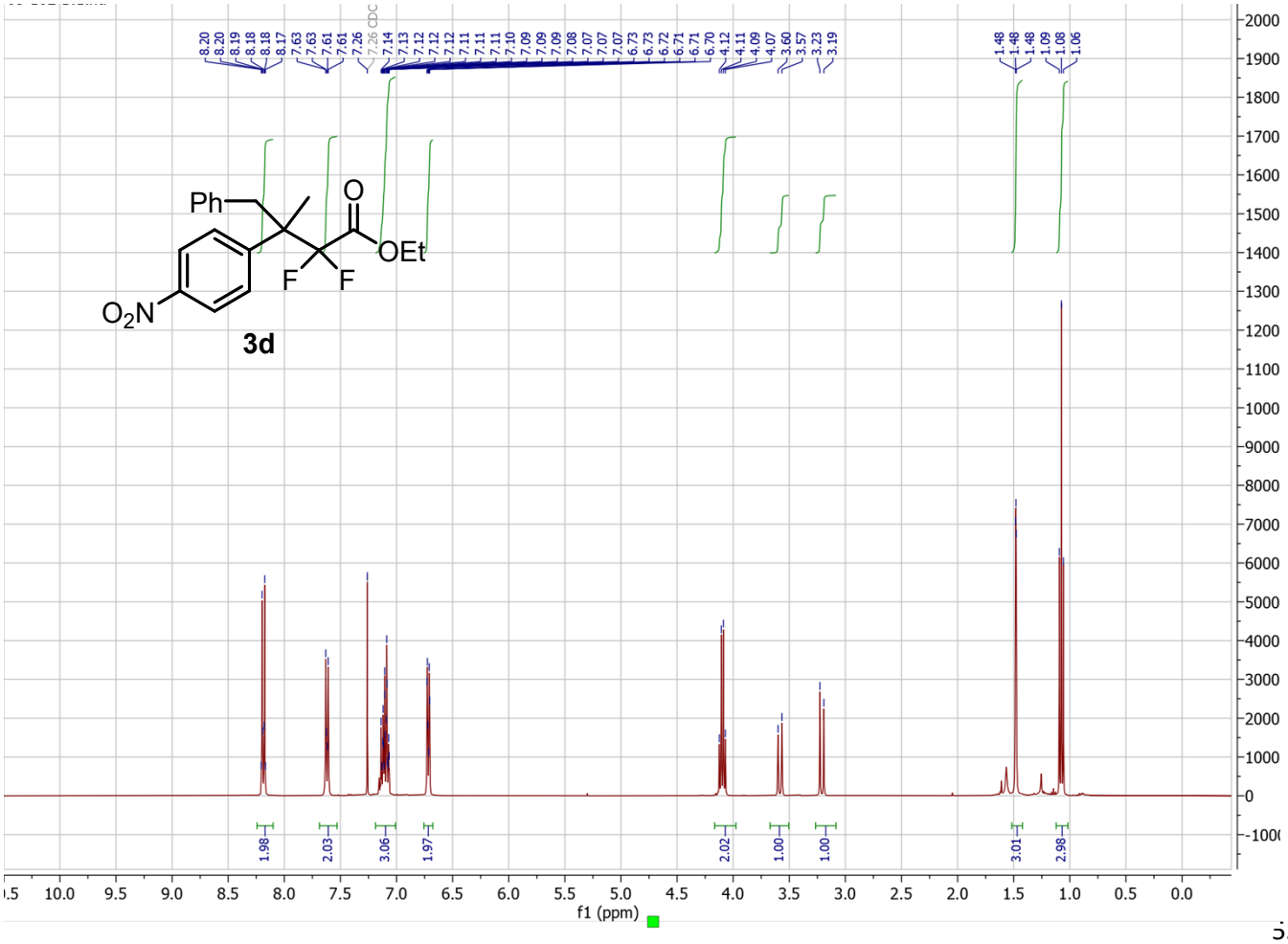


3c



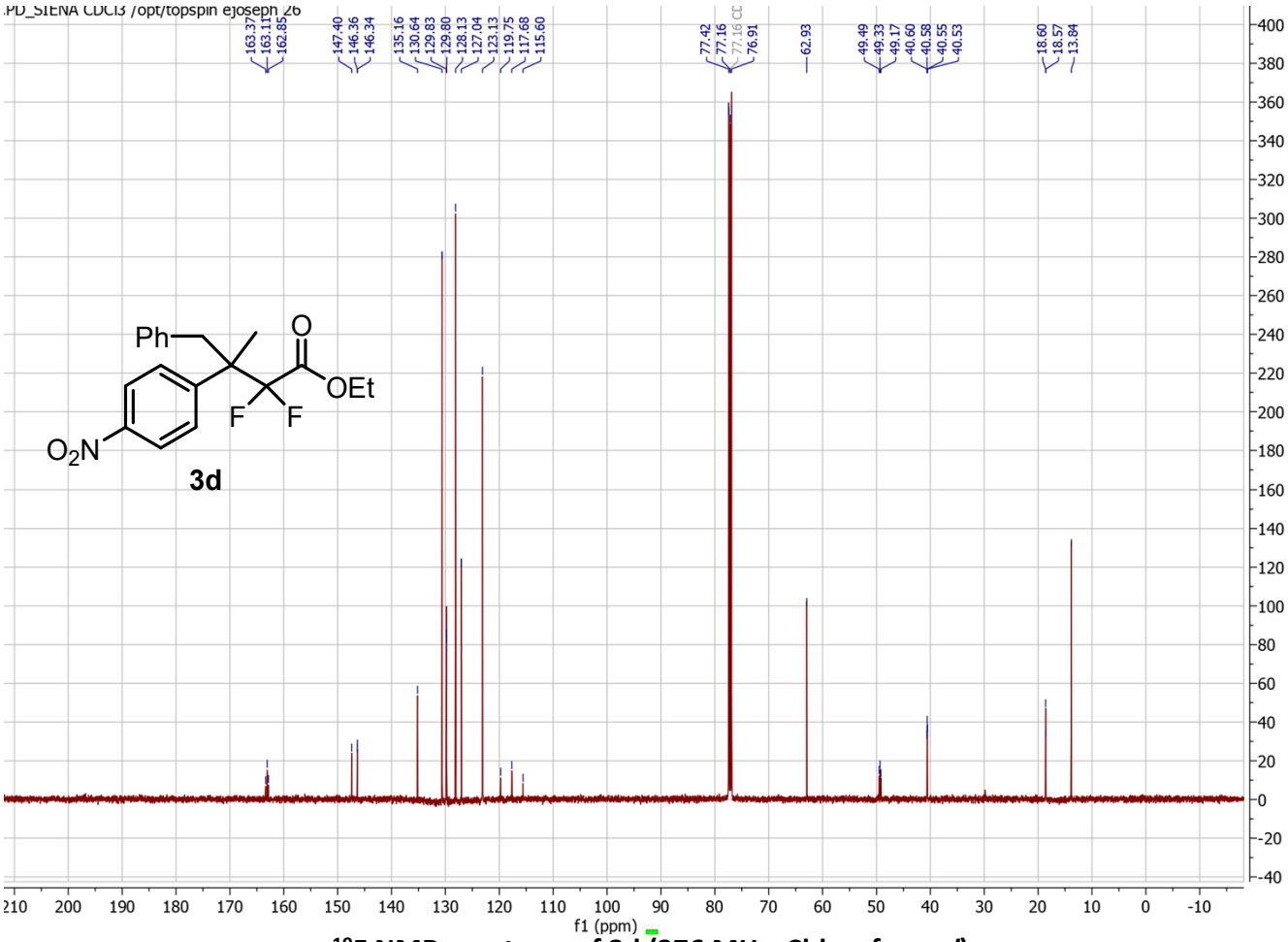


^{19}F NMR spectrum of 3c (376 MHz, Chloroform-*d*)

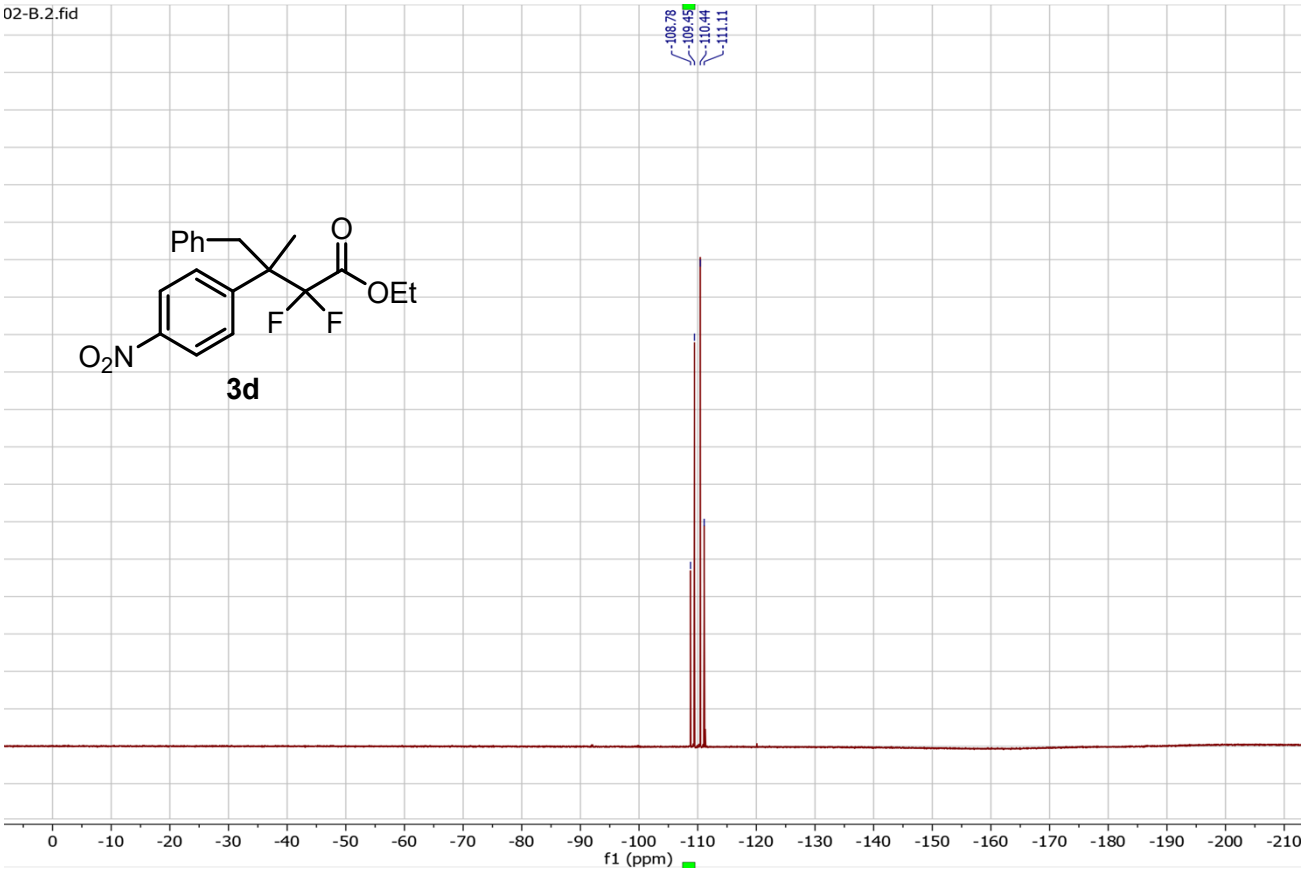


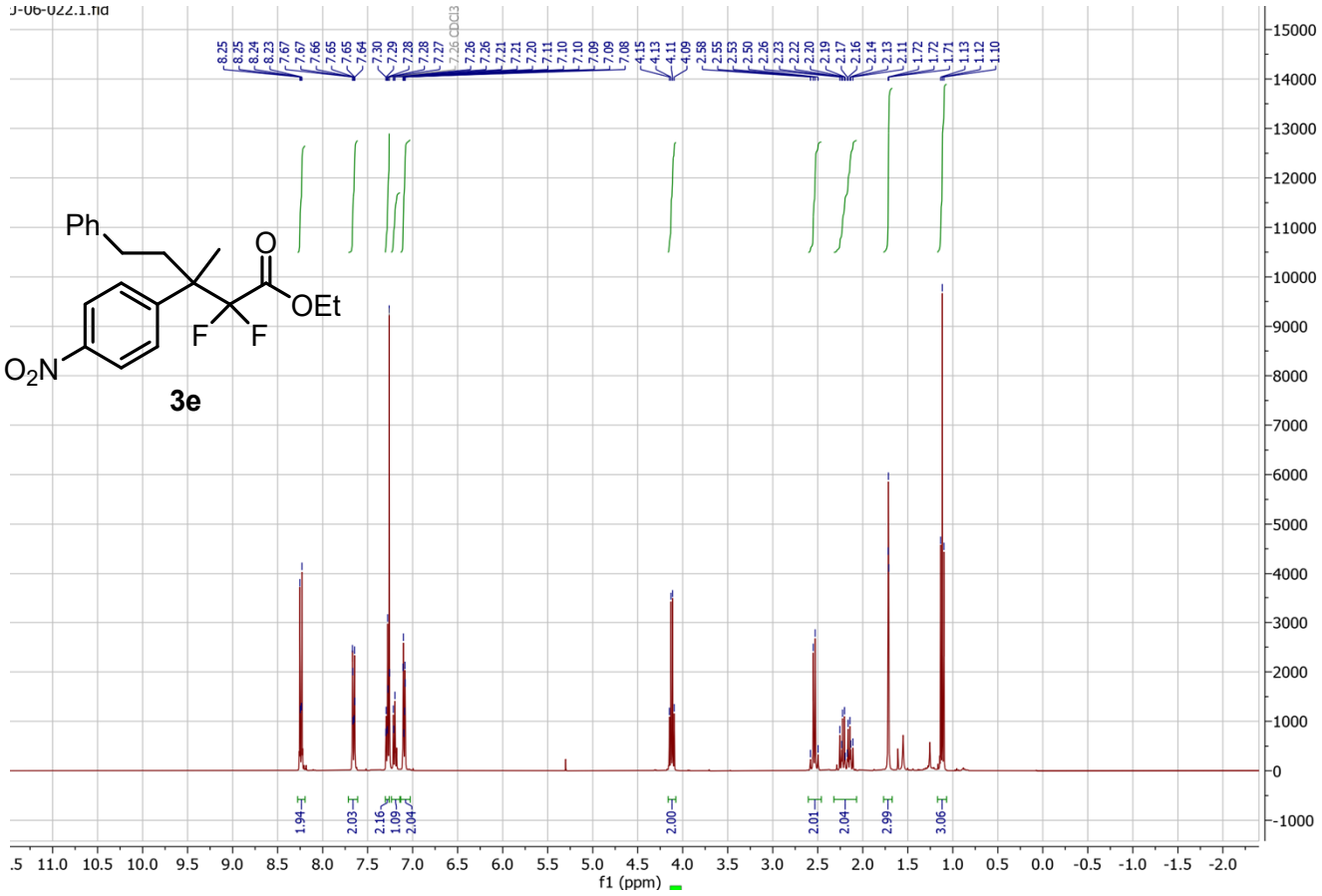
^{1}H NMR spectrum of 3d (400 MHz, Chloroform-d)

^{13}C NMR spectrum of 3d (126 MHz, Chloroform-*d*)



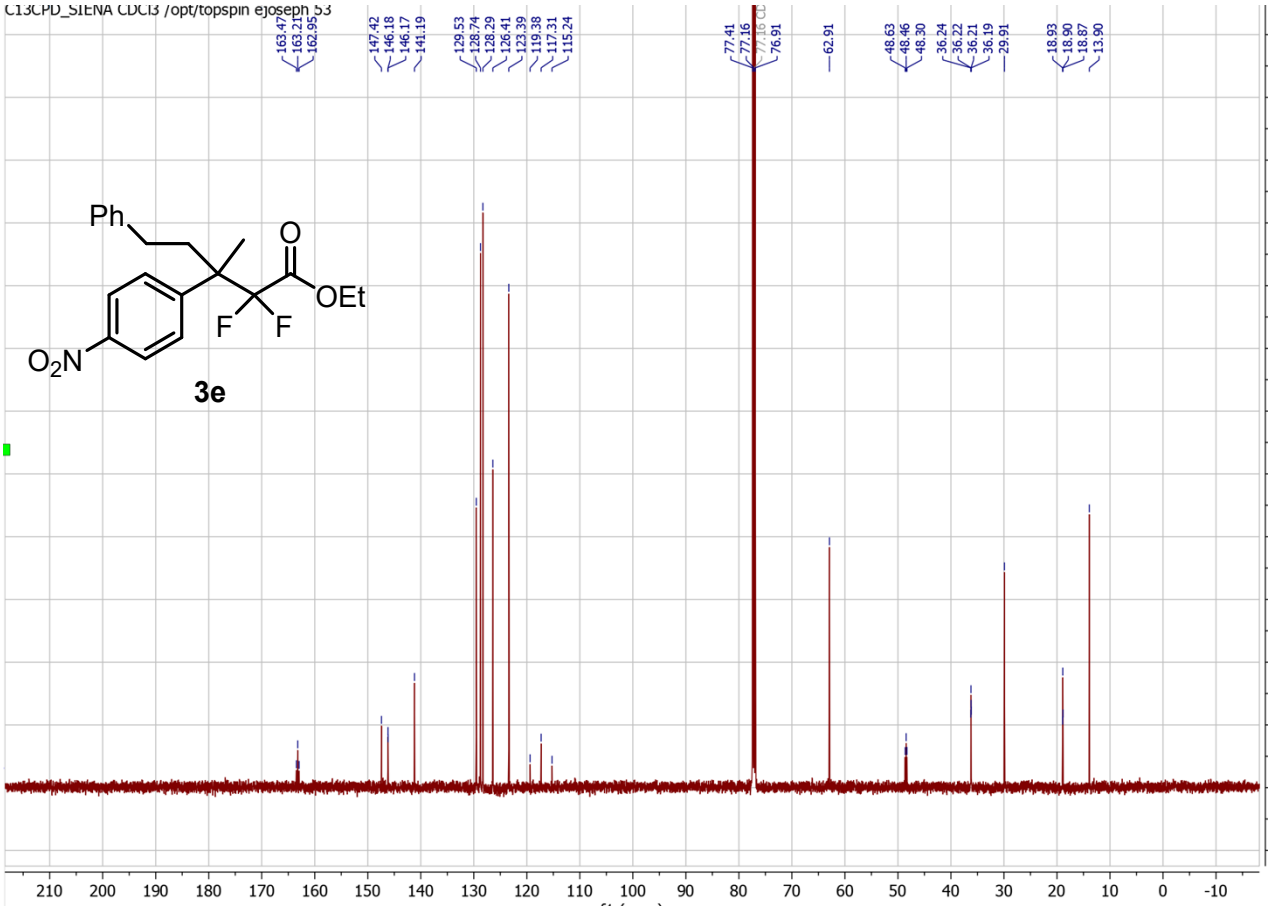
^{19}F NMR spectrum of 3d (376 MHz, Chloroform-*d*)

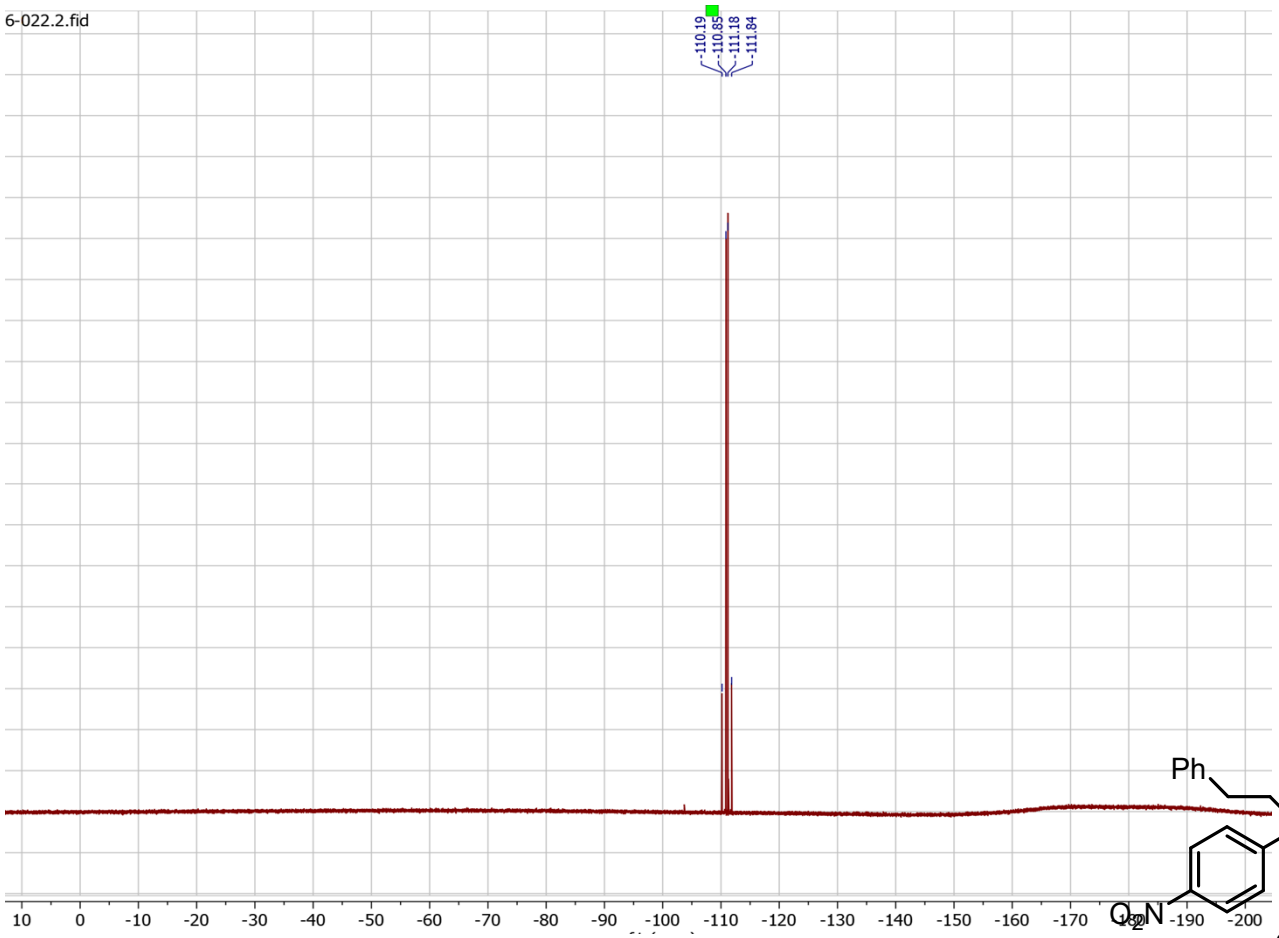




^{1}H NMR spectrum of 3e (400 MHz, Chloroform-d)

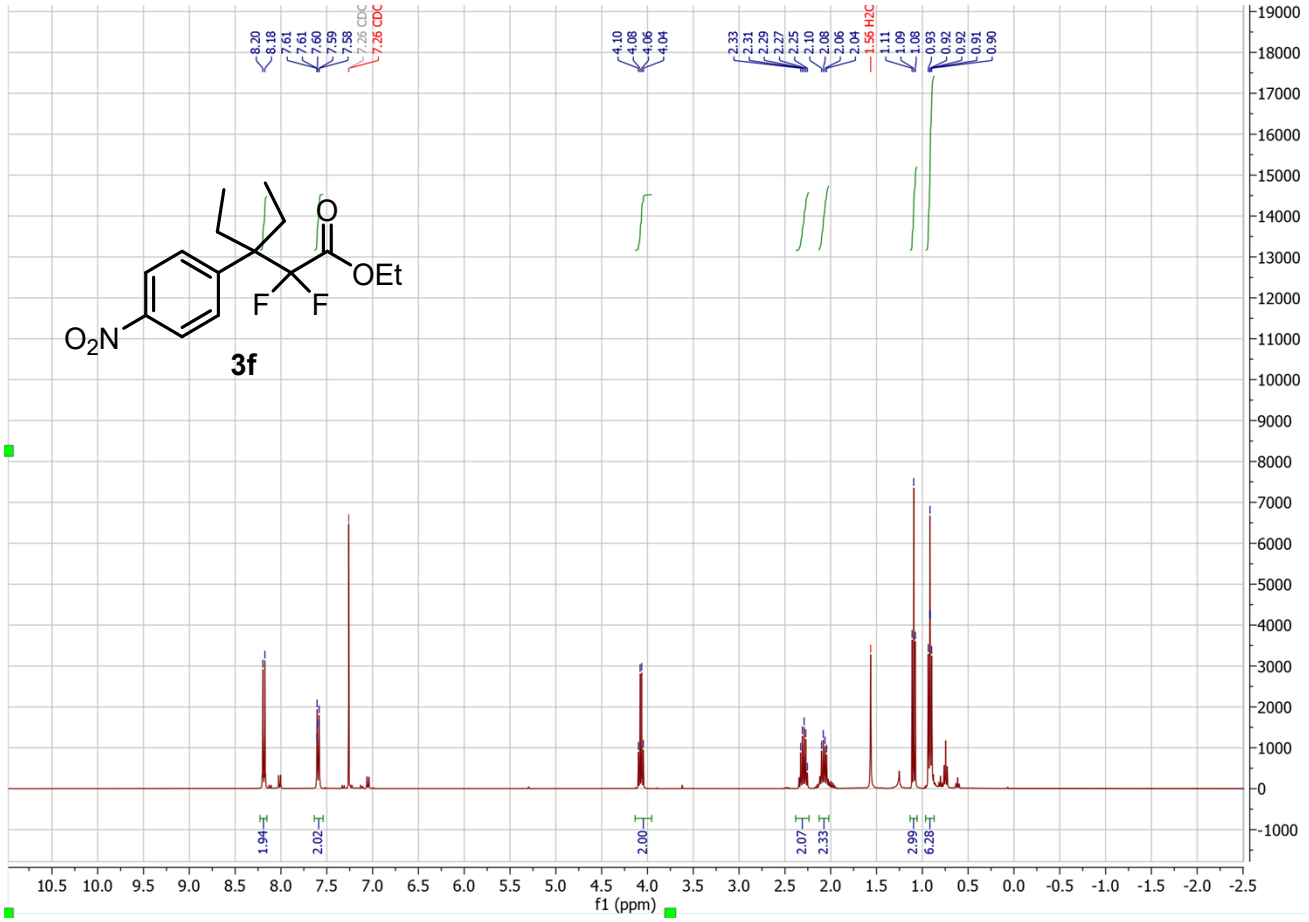
^{13}C NMR spectrum of 3e (126 MHz, Chloroform-*d*)





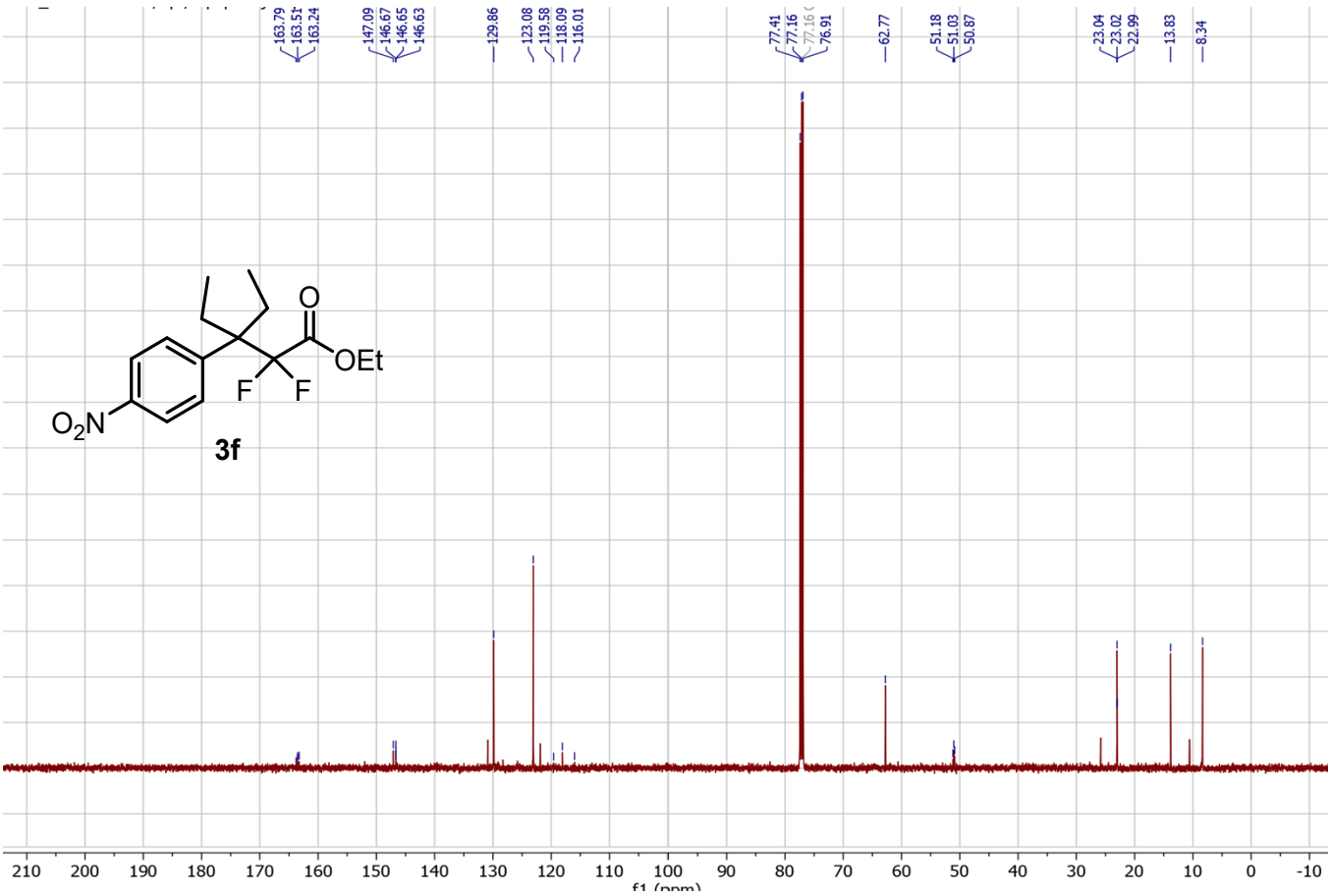
^{19}F NMR spectrum of 3e (376 MHz, Chlorofo rm-*d*)

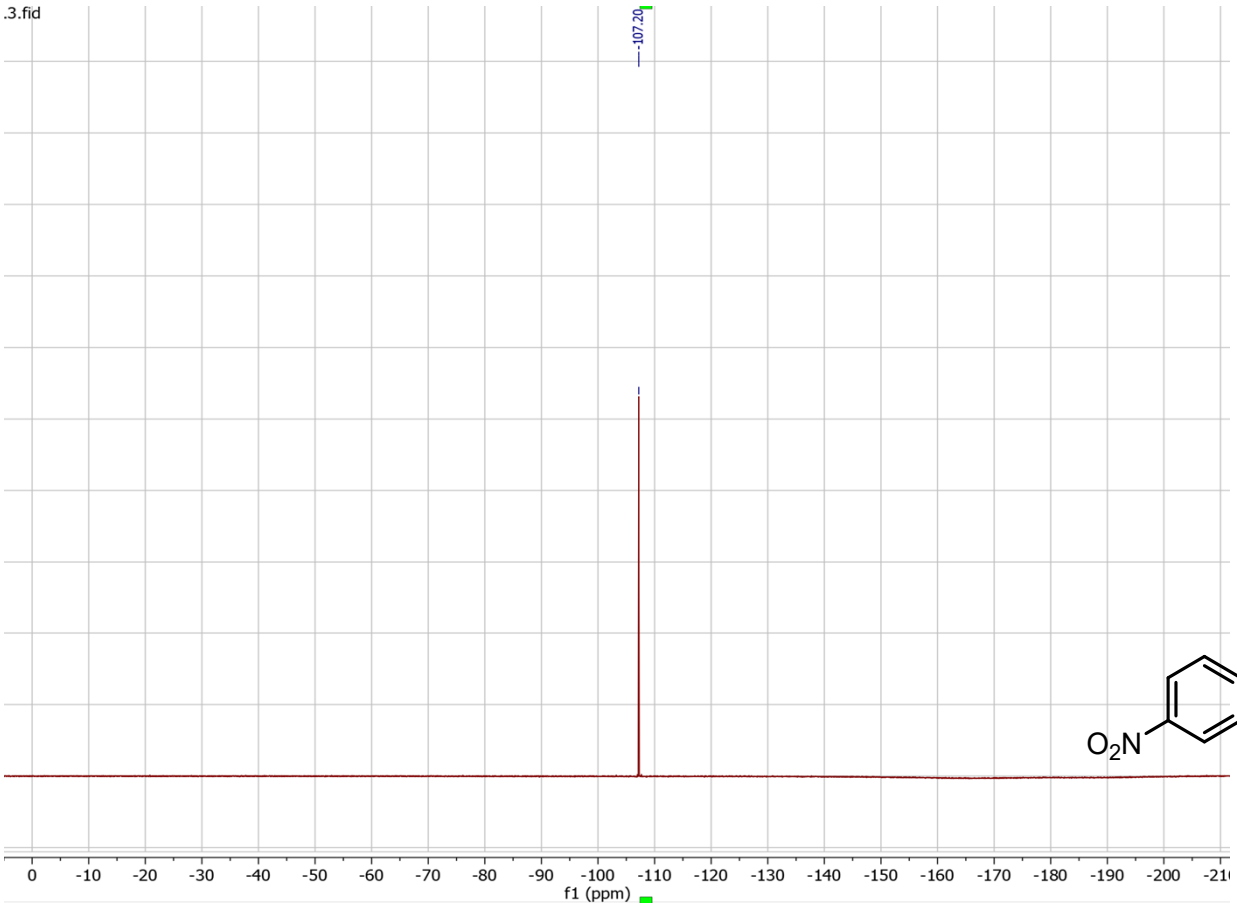
3e



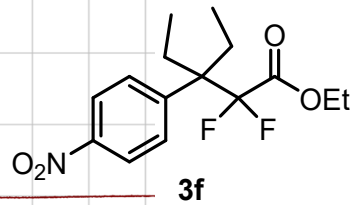
^{1}H NMR spectrum of 3f (400 MHz, Chloroform-d)

^{13}C NMR spectrum of 3f (126 MHz, Chloroform-*d*)

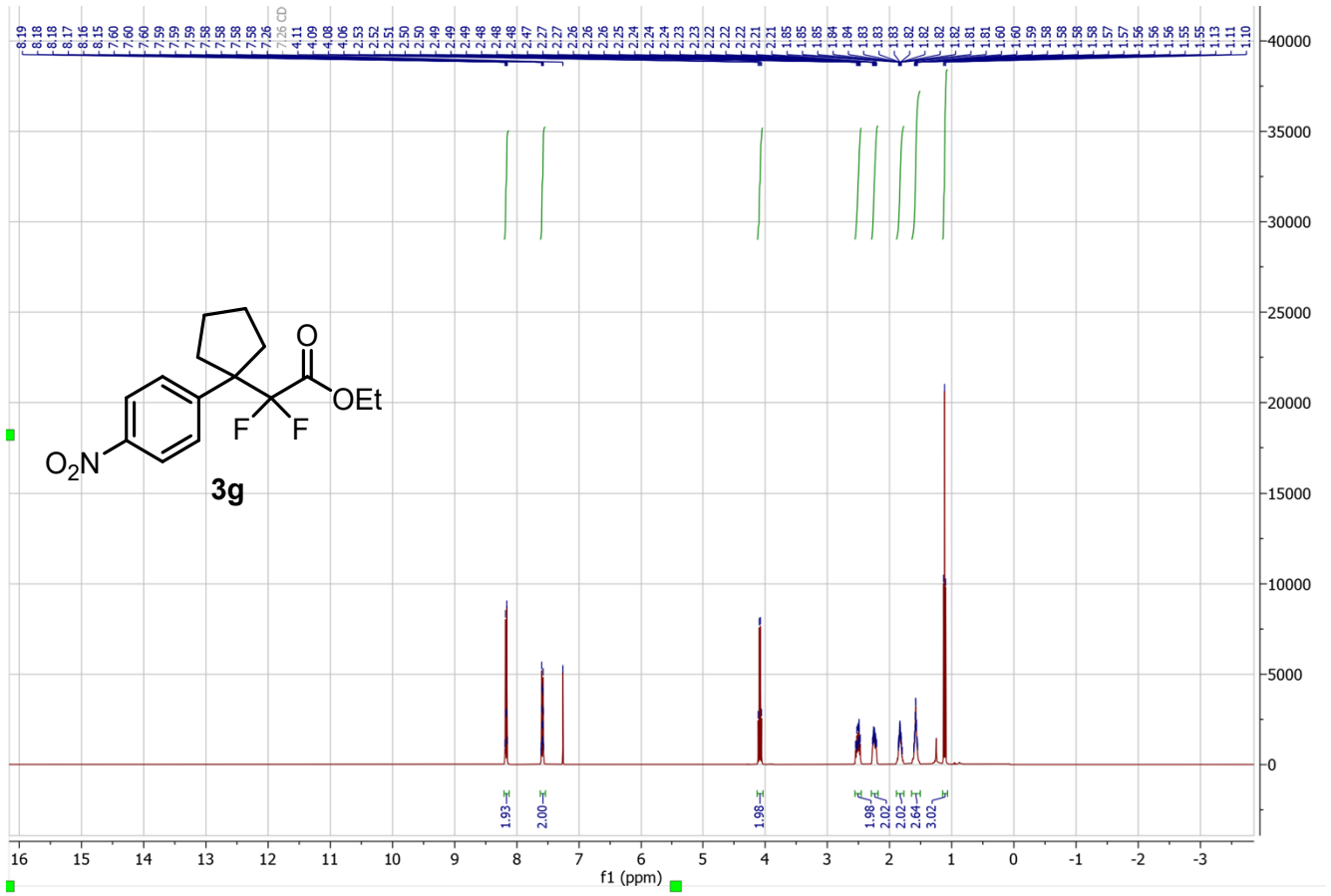




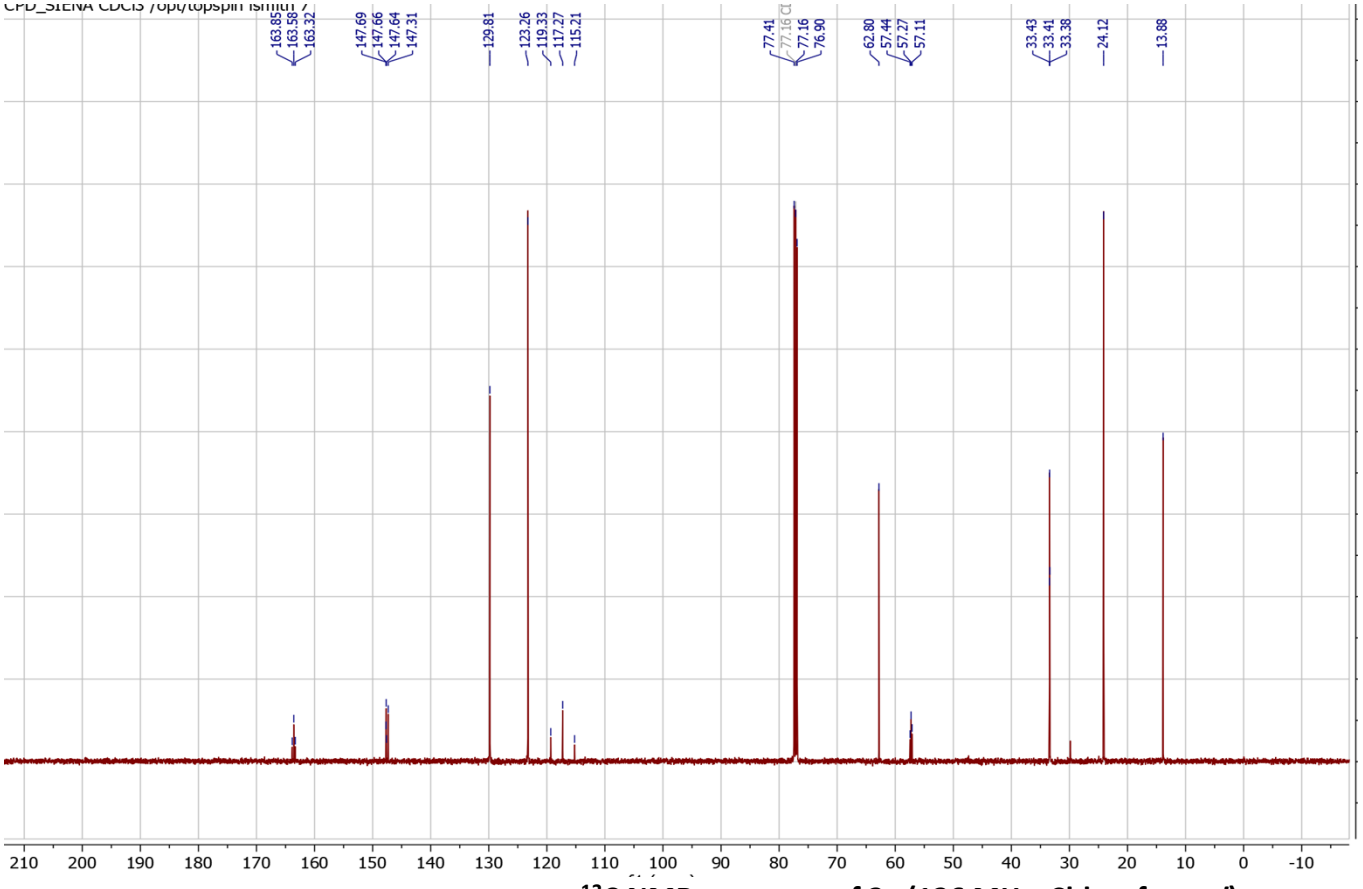
^{19}F NMR spectrum of 3f (376 MHz, Chloroform-*d*)



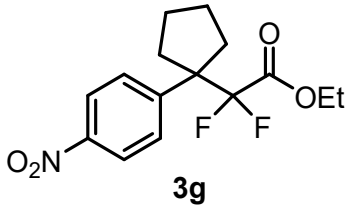
3f

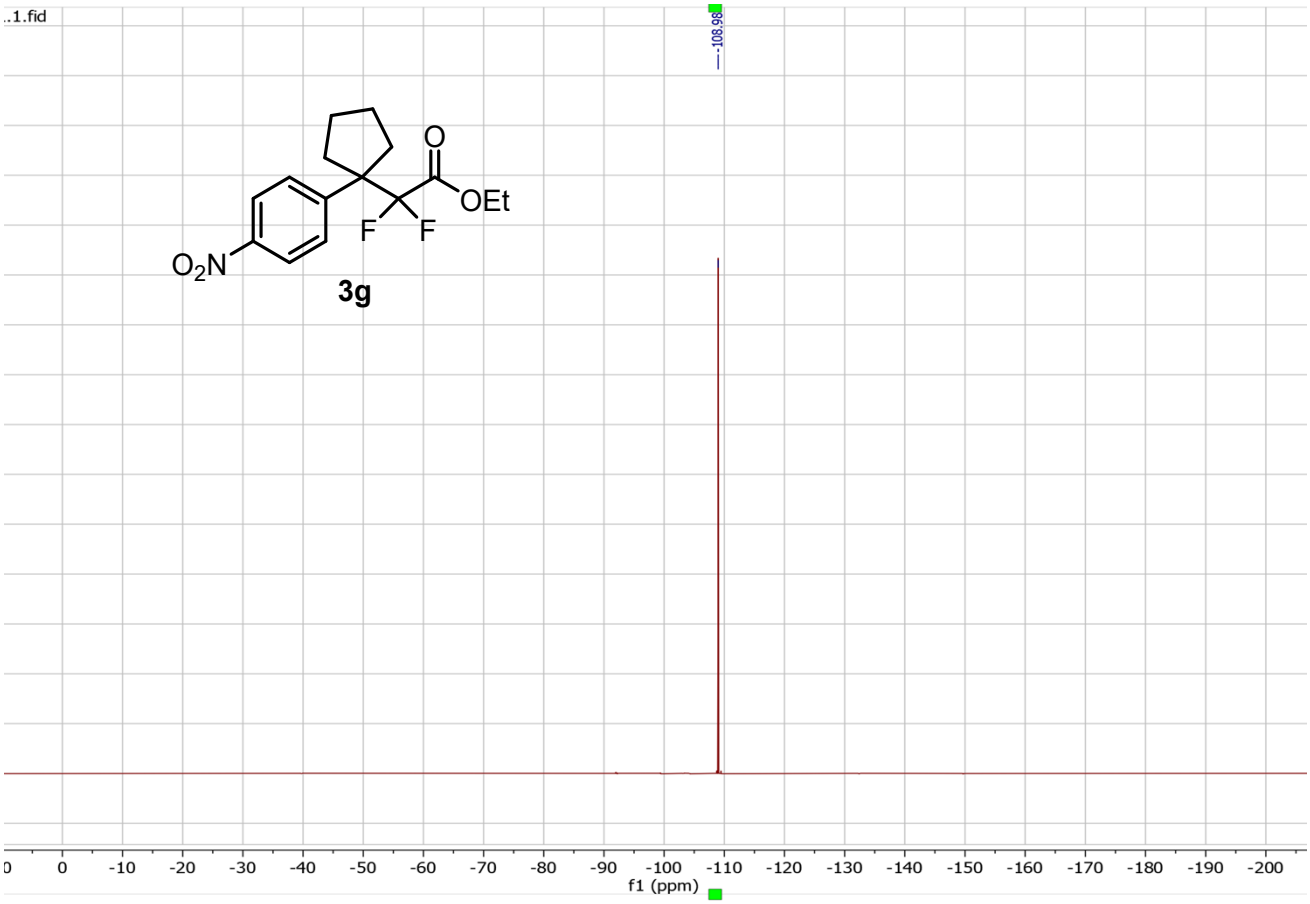


^{1}H NMR spectrum of 3g (400 MHz, Chloroform-d)

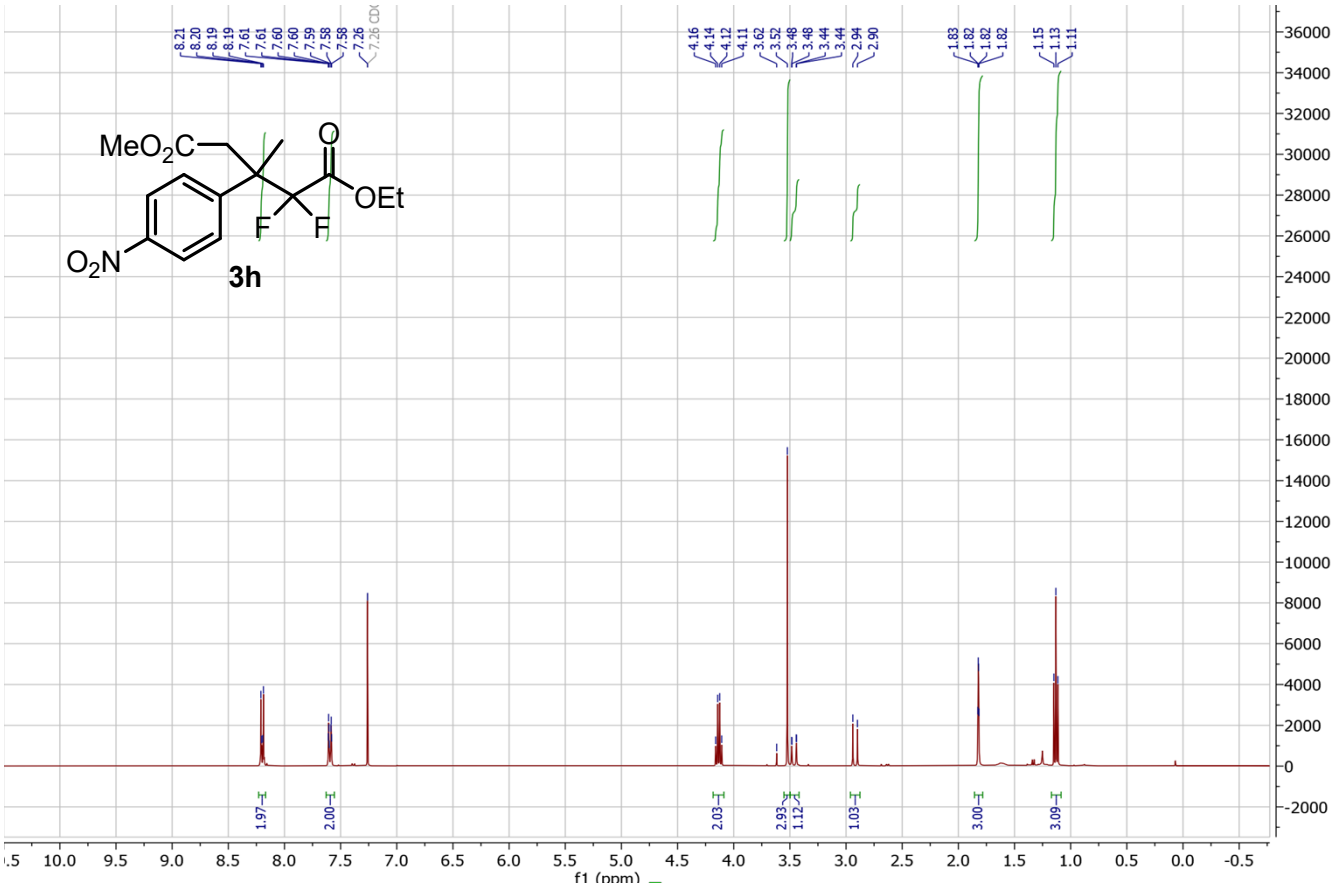


^{13}C NMR spectrum of 3g (126 MHz, Chloroform-*d*)



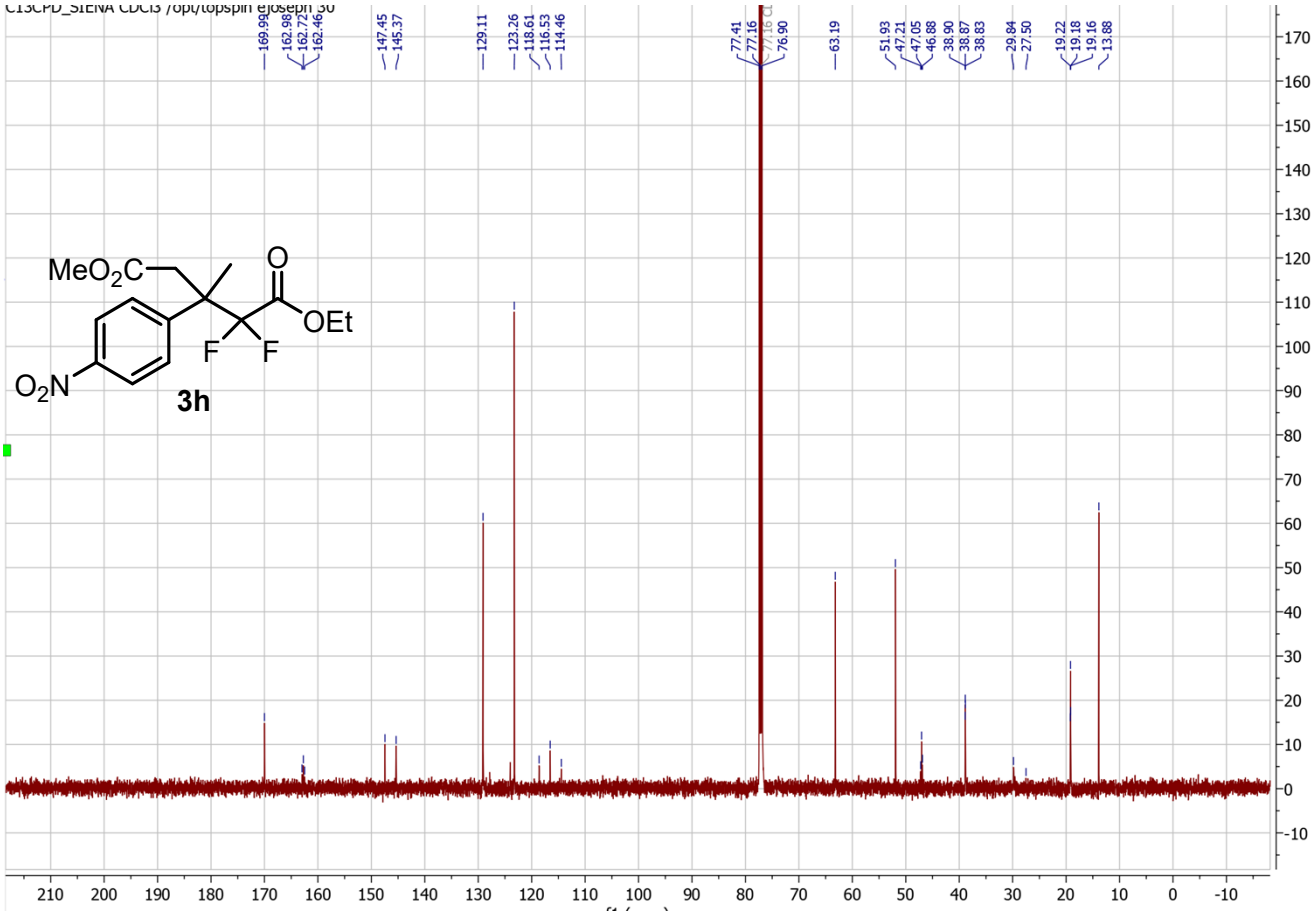


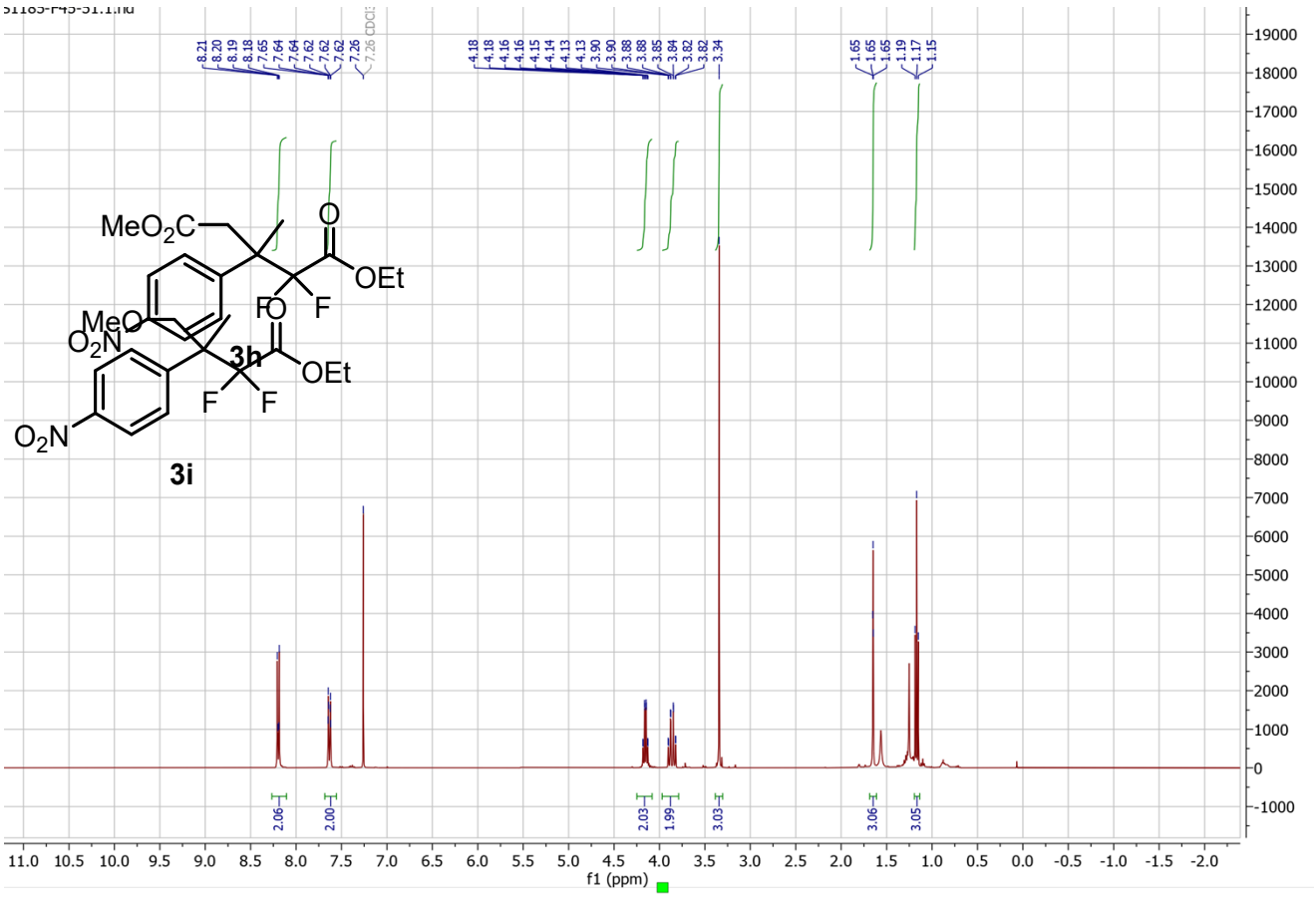
^{19}F NMR spectrum of 3g (376 MHz, Chloroform-*d*)



^{1}H NMR spectrum of 3h (400 MHz, Chloroform-d)

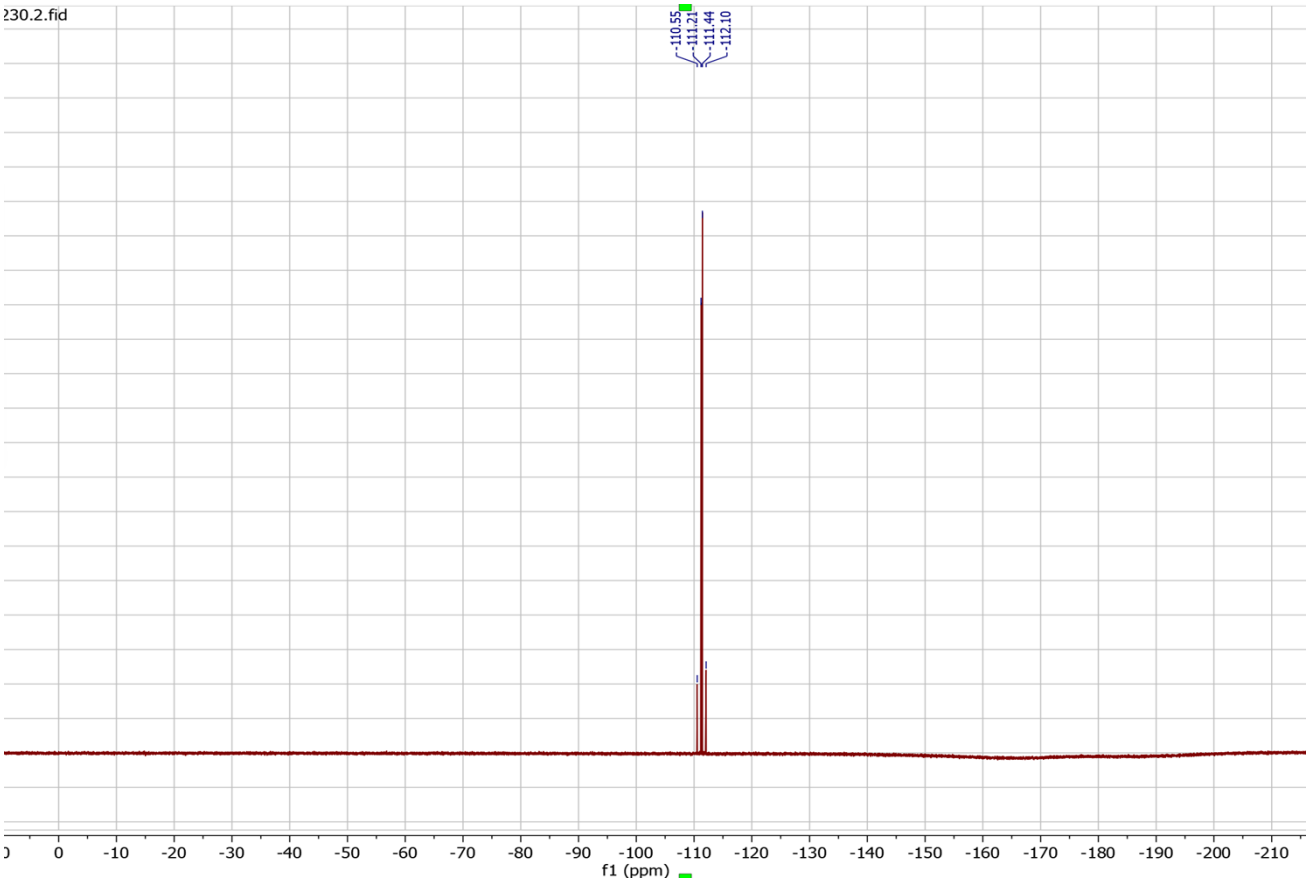
^{13}C NMR spectrum of 3h (126 MHz, Chloroform-*d*)

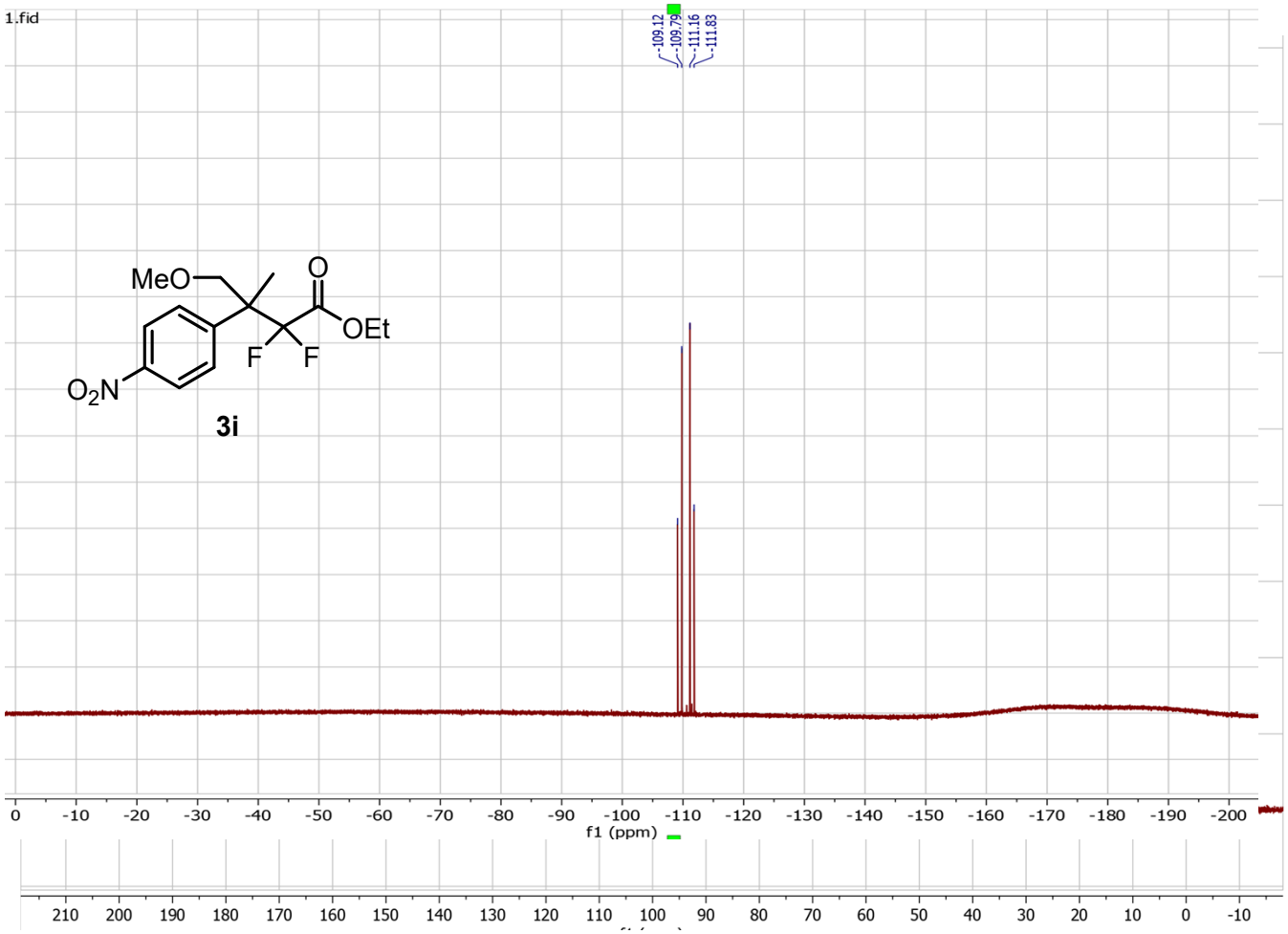




^{19}F NMR spectrum of 3h (376 MHz, Chloroform-*d*)

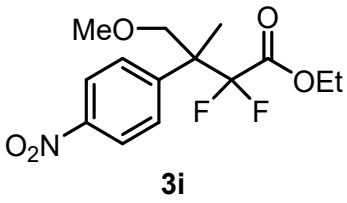
^{1}H NMR spectrum of 3i (400 MHz, Chloroform-d)





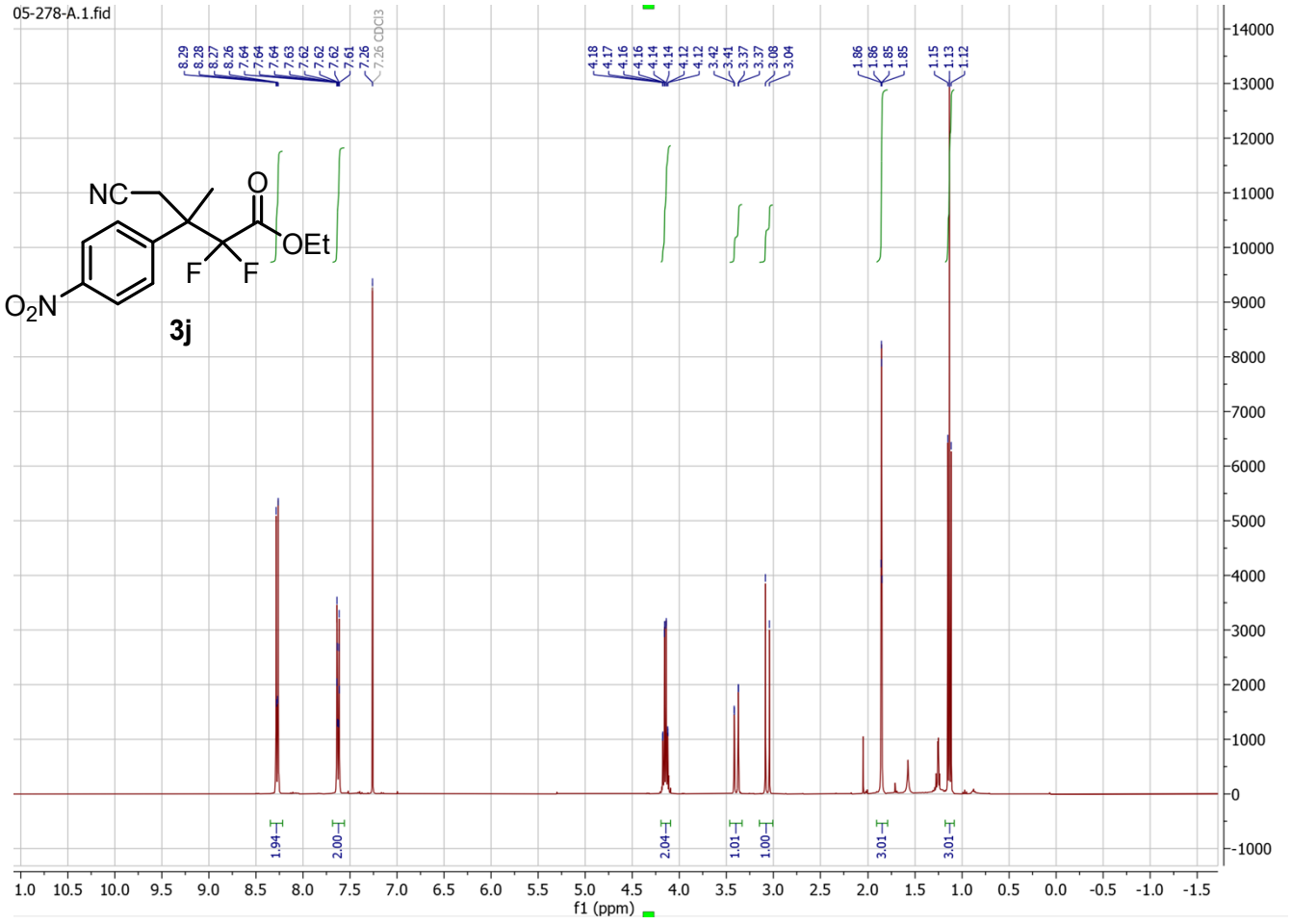
^{13}C NMR spectrum of 3i (126 MHz, Chloroform-*d*)

^{19}F NMR spectrum of 3i (376 MHz, Chloroform-*d*)

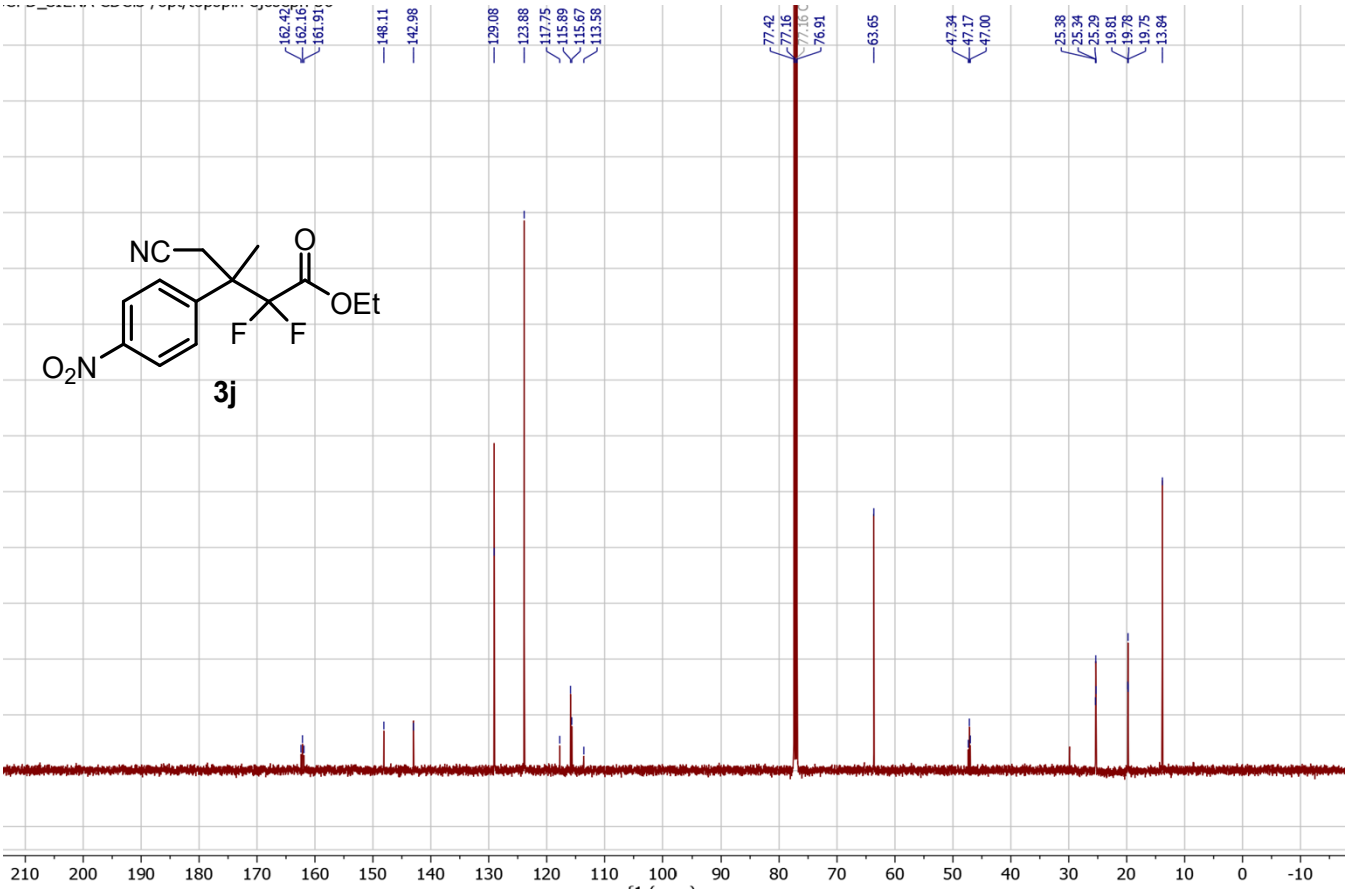


3i

^{1}H NMR spectrum of 3j (400 MHz, Chloroform-d)

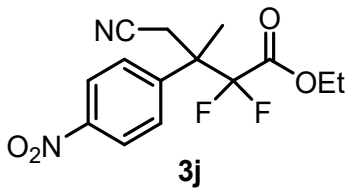


^{13}C NMR spectrum of 3j (126 MHz, Chloroform-*d*)

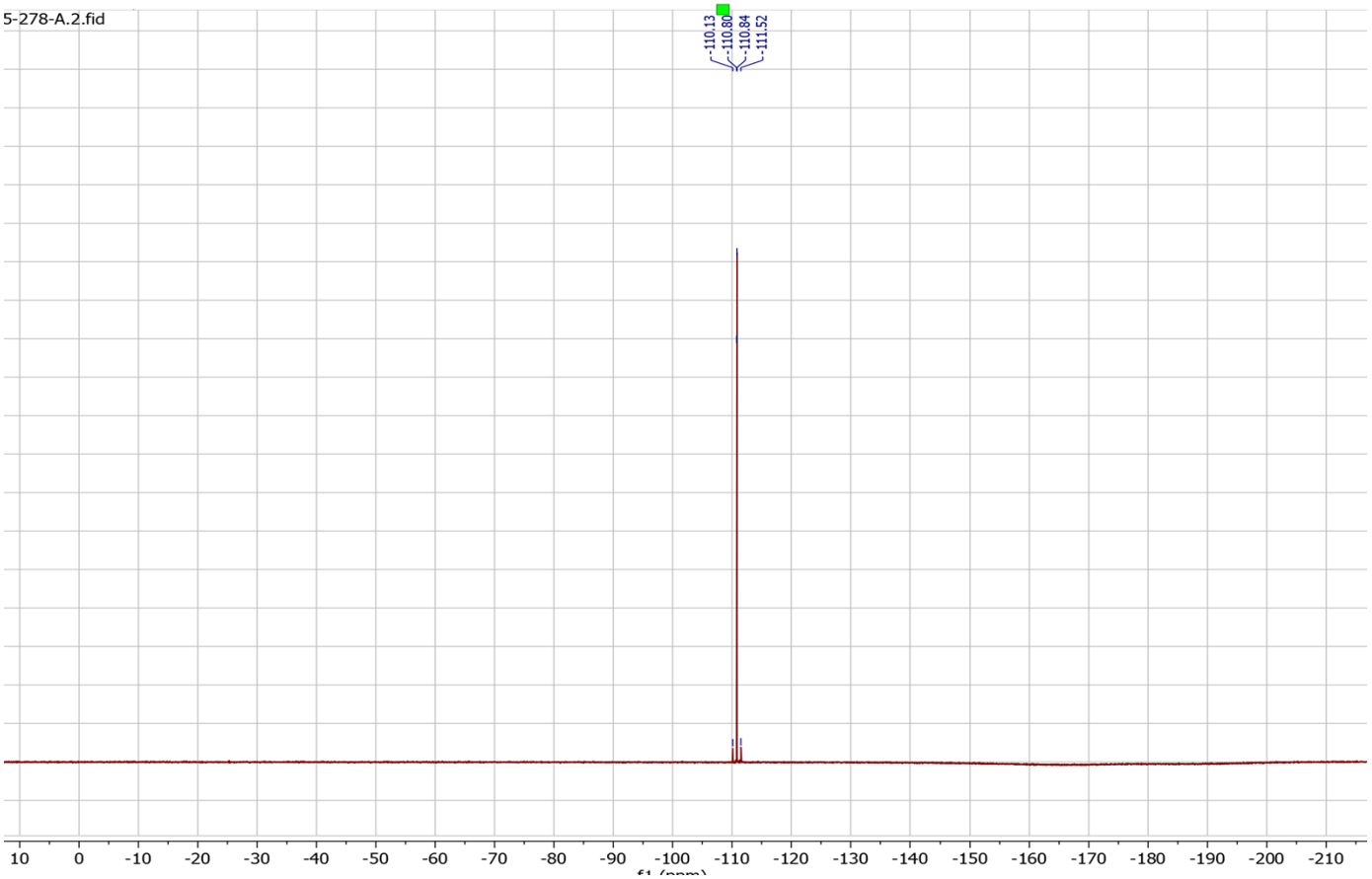


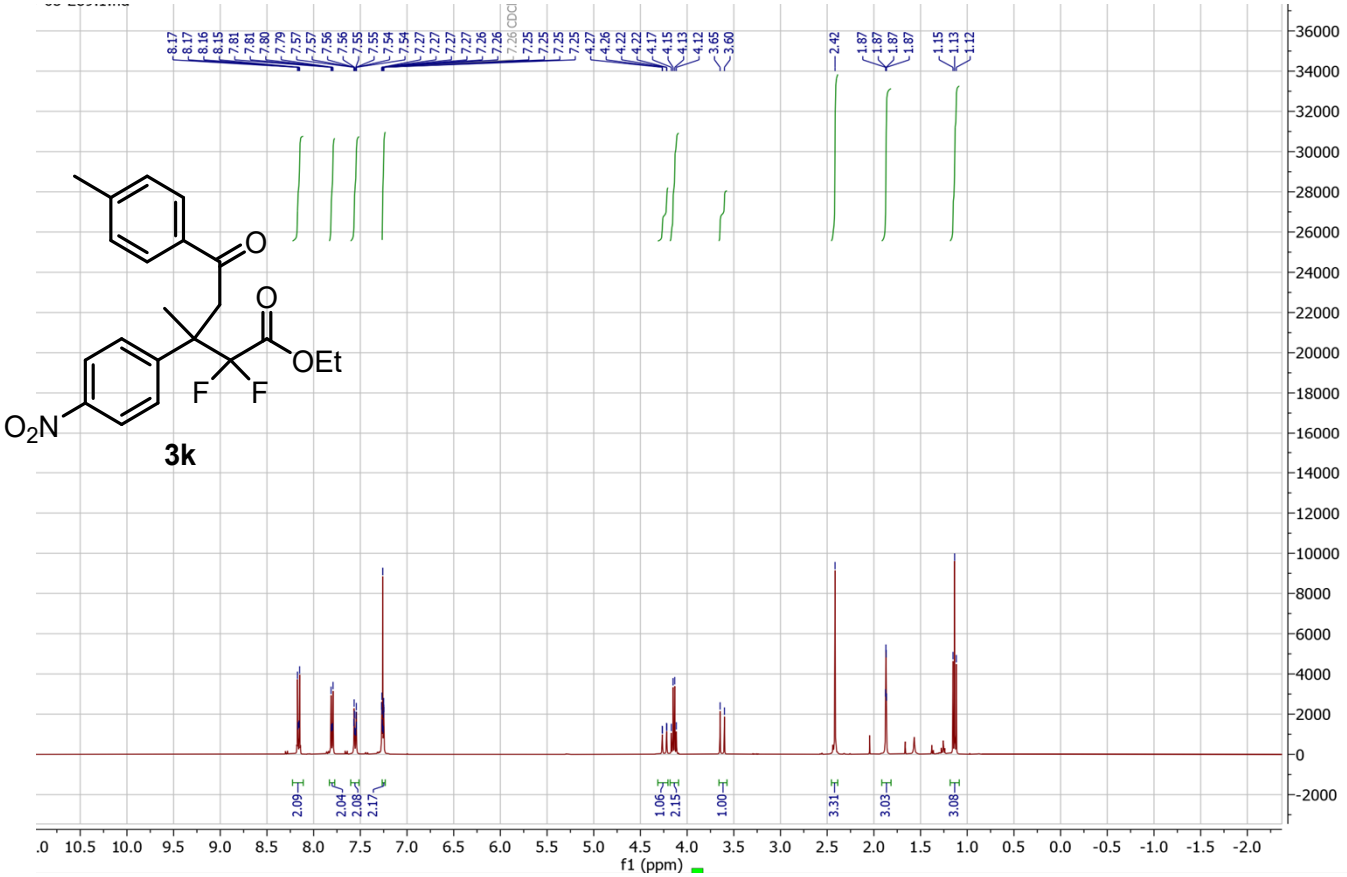
^{19}F NMR spectrum of 3j (376 MHz, Chloroform-*d*)

^{1}H NMR spectrum of 3k (400 MHz, Chloroform-d)

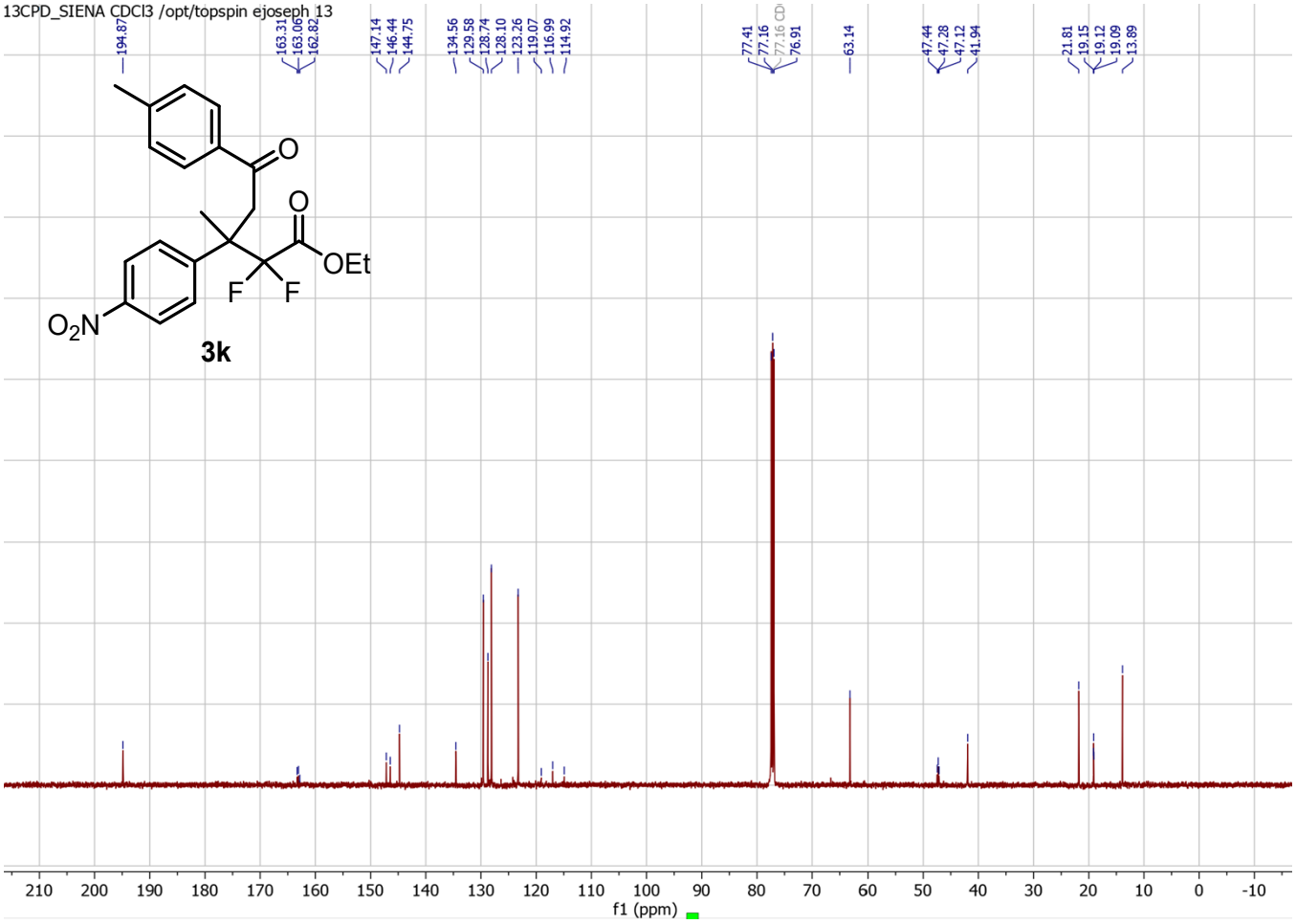


3j

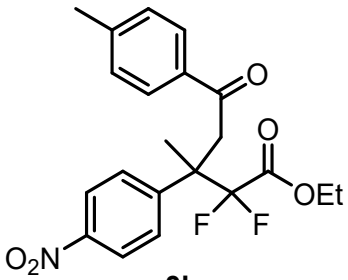




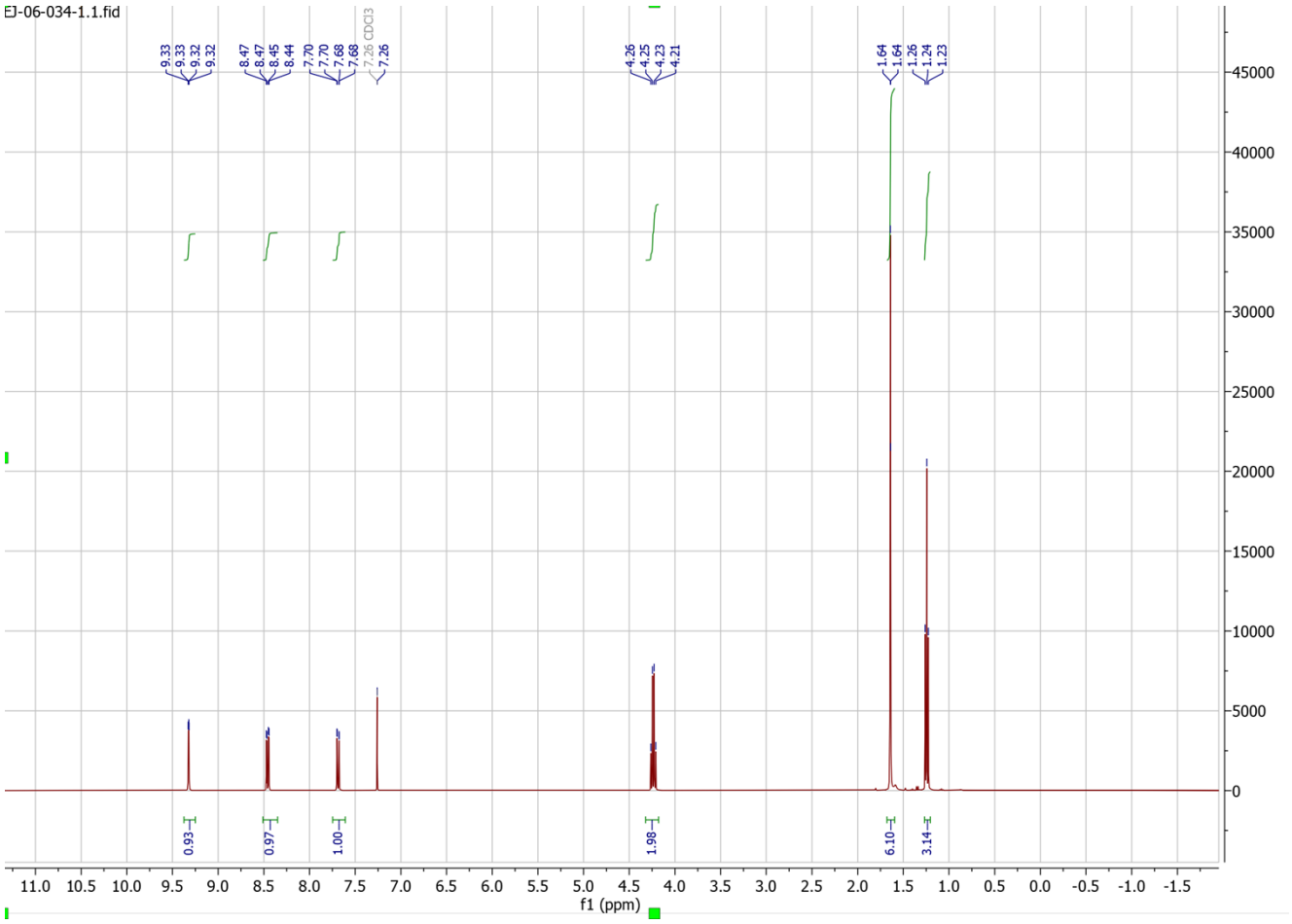
^{13}C NMR spectrum of 3k (126 MHz, Chloroform-*d*)

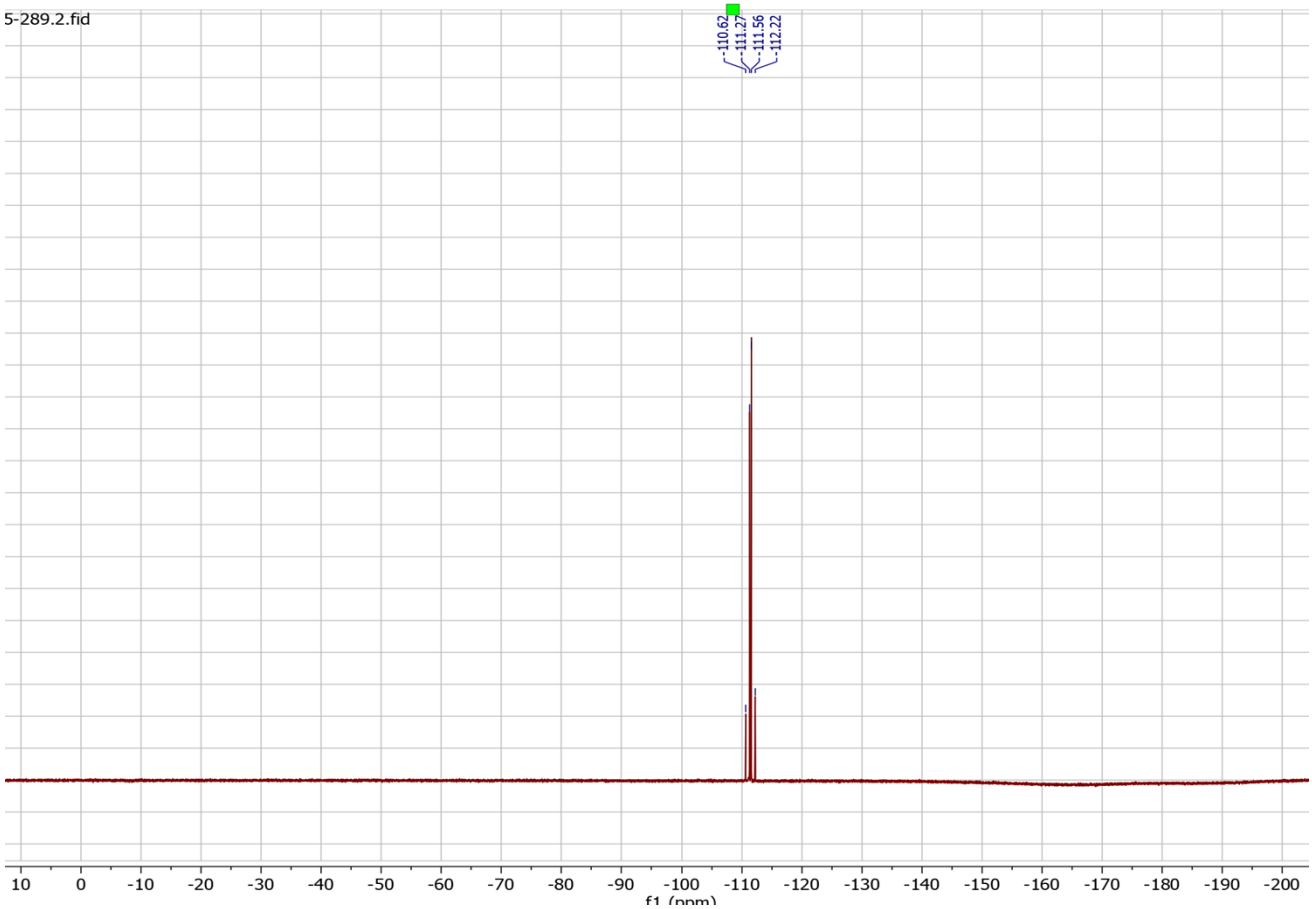


^{19}F NMR spectrum of 3k (376 MHz, Chloroform-*d*)

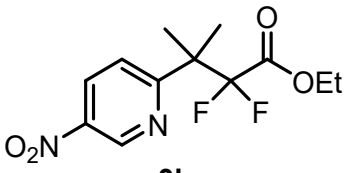


3k

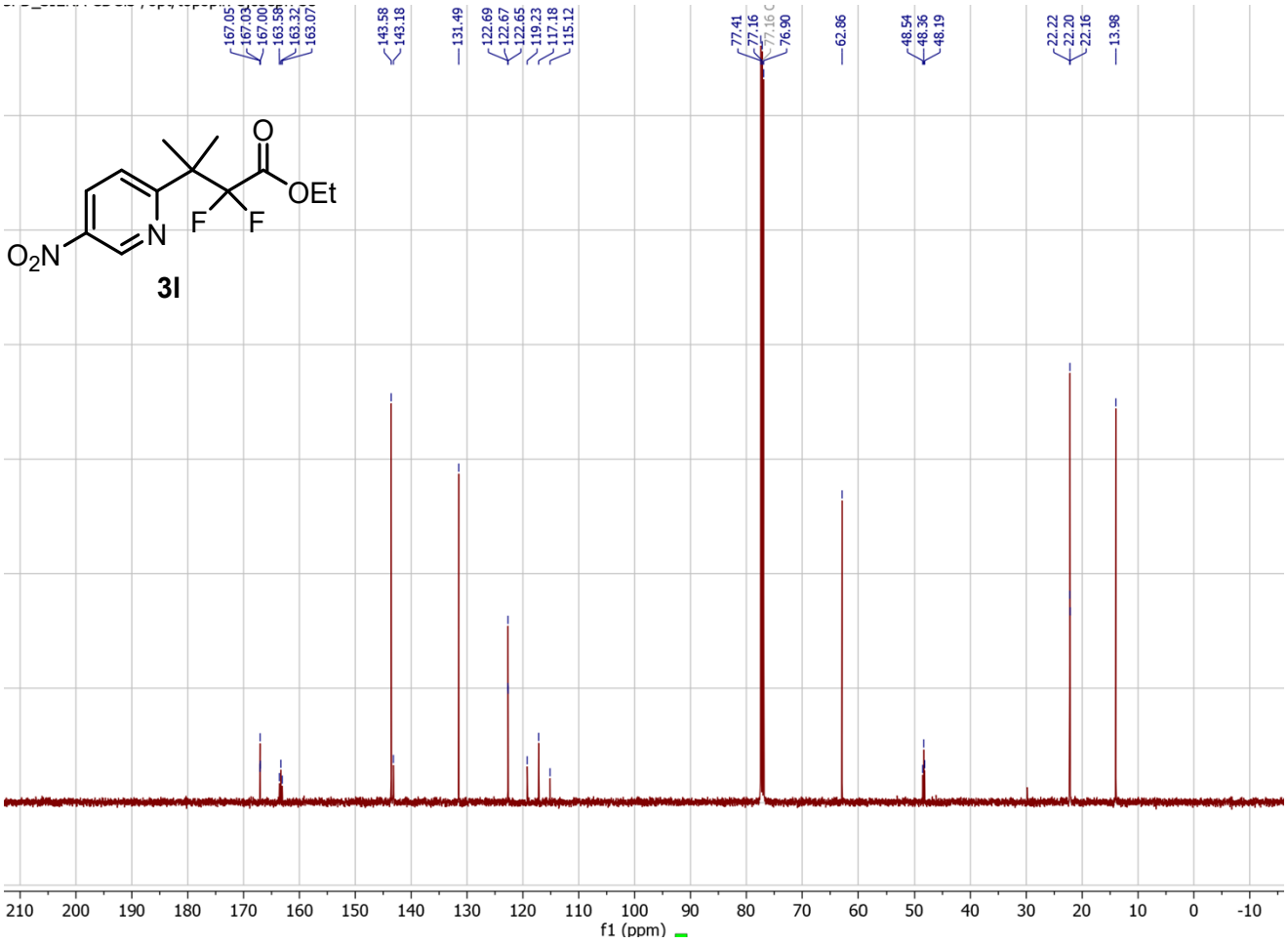




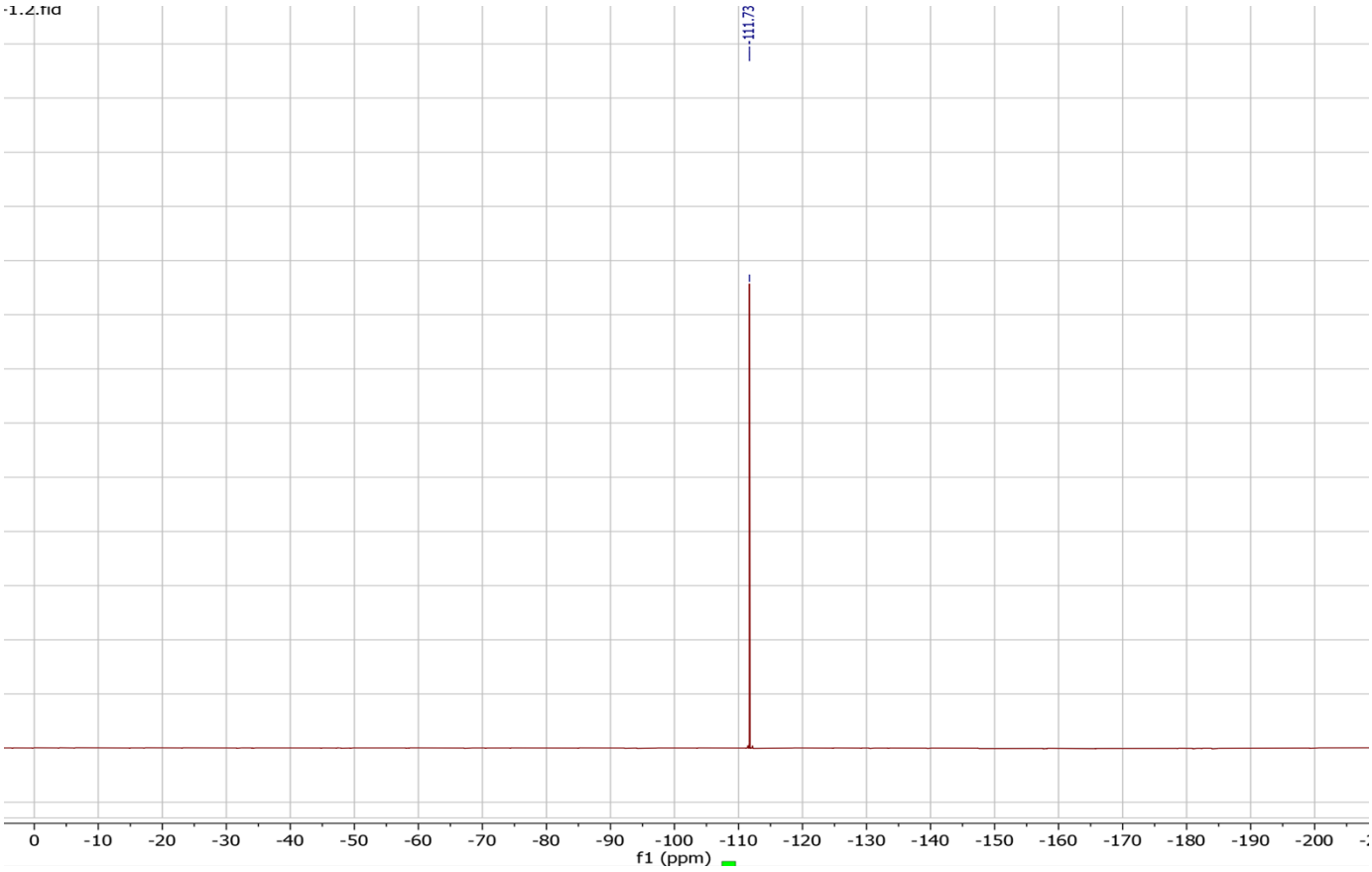
^{1}H NMR spectrum of 3l (400 MHz, Chloroform-d)

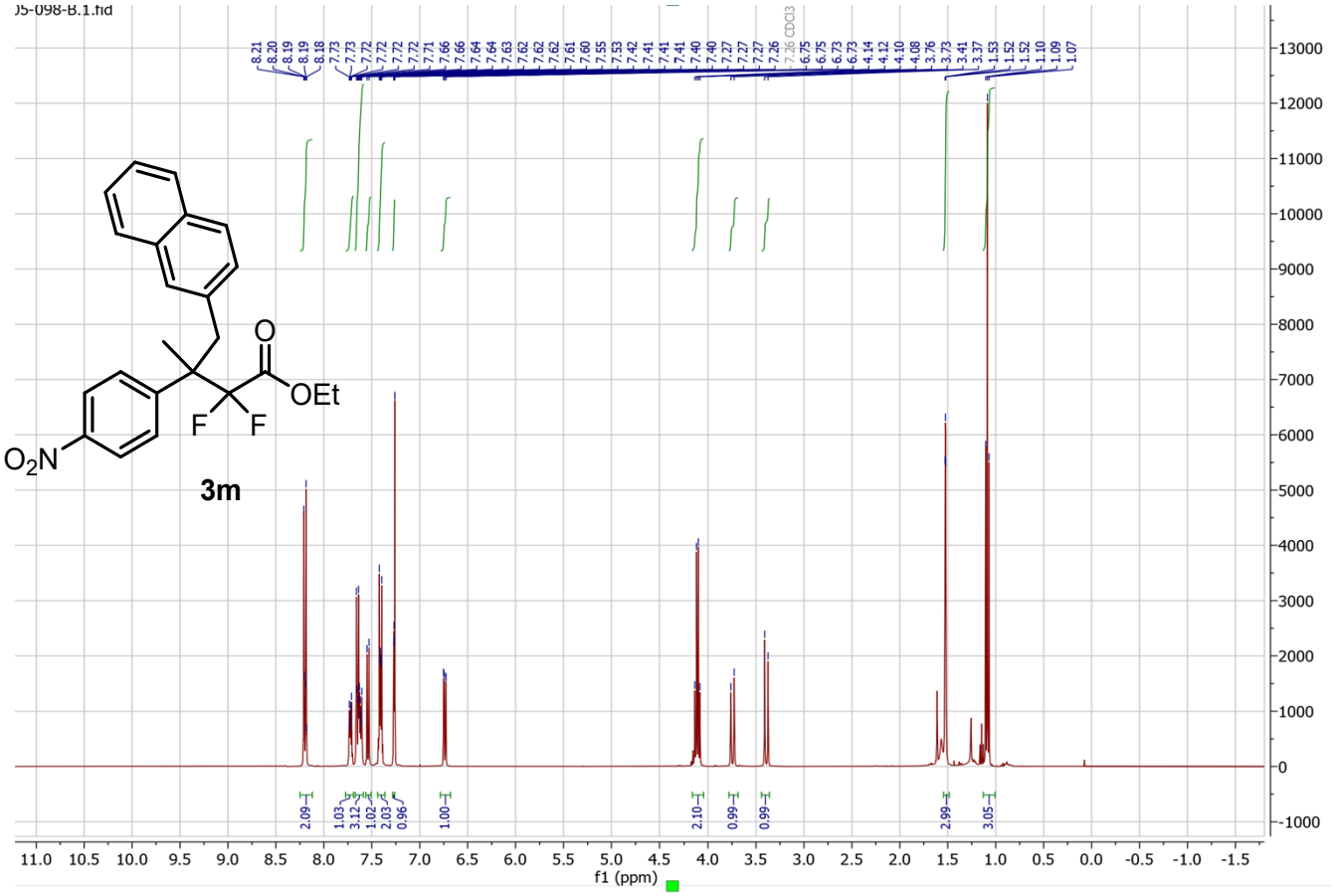


3l



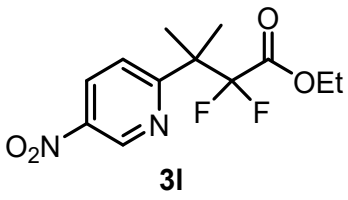
^{13}C NMR spectrum of 3l (126 MHz, Chloroform-*d*)





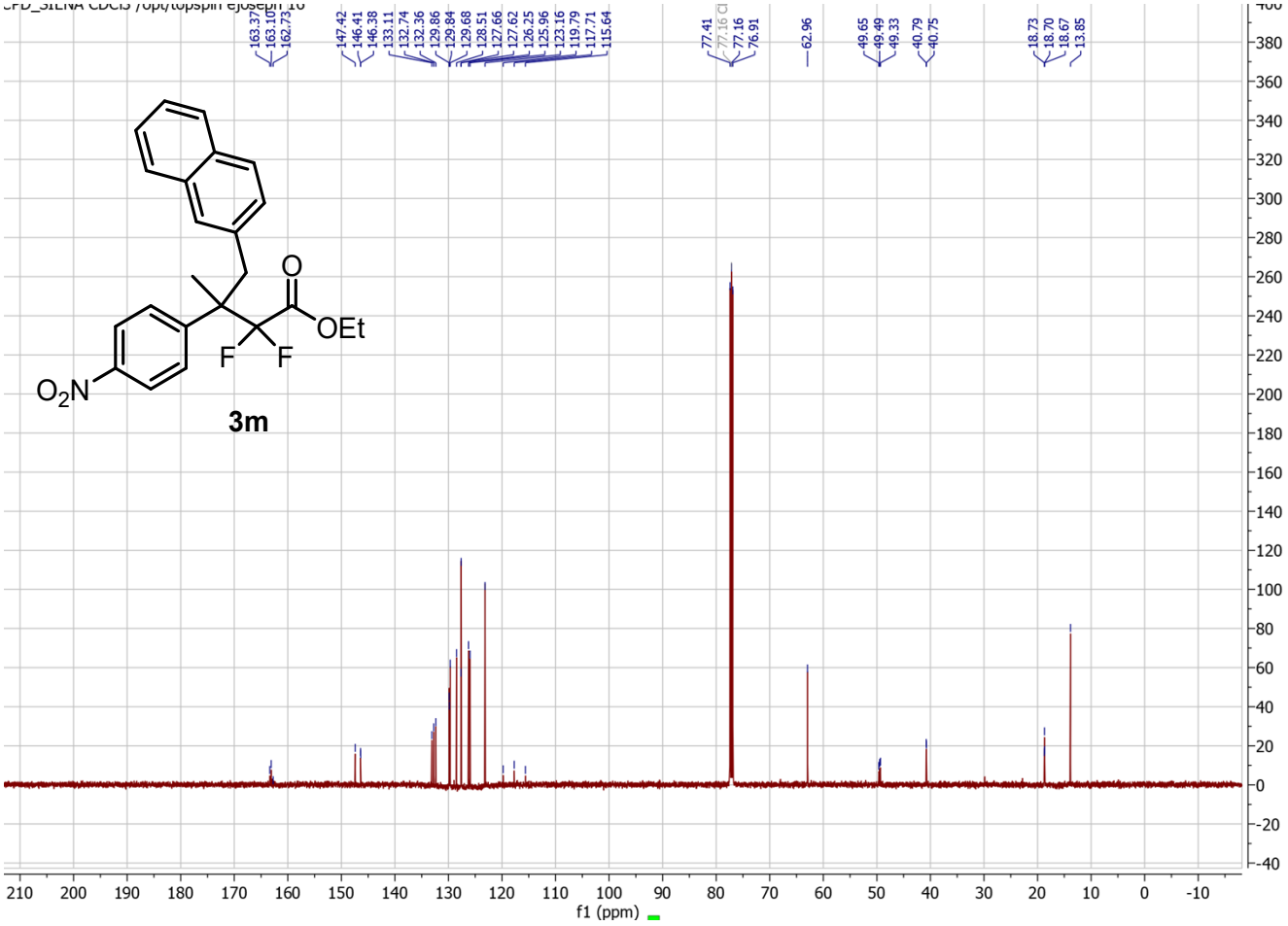
^{19}F NMR spectrum of 3l (376 MHz, Chloroform-*d*)

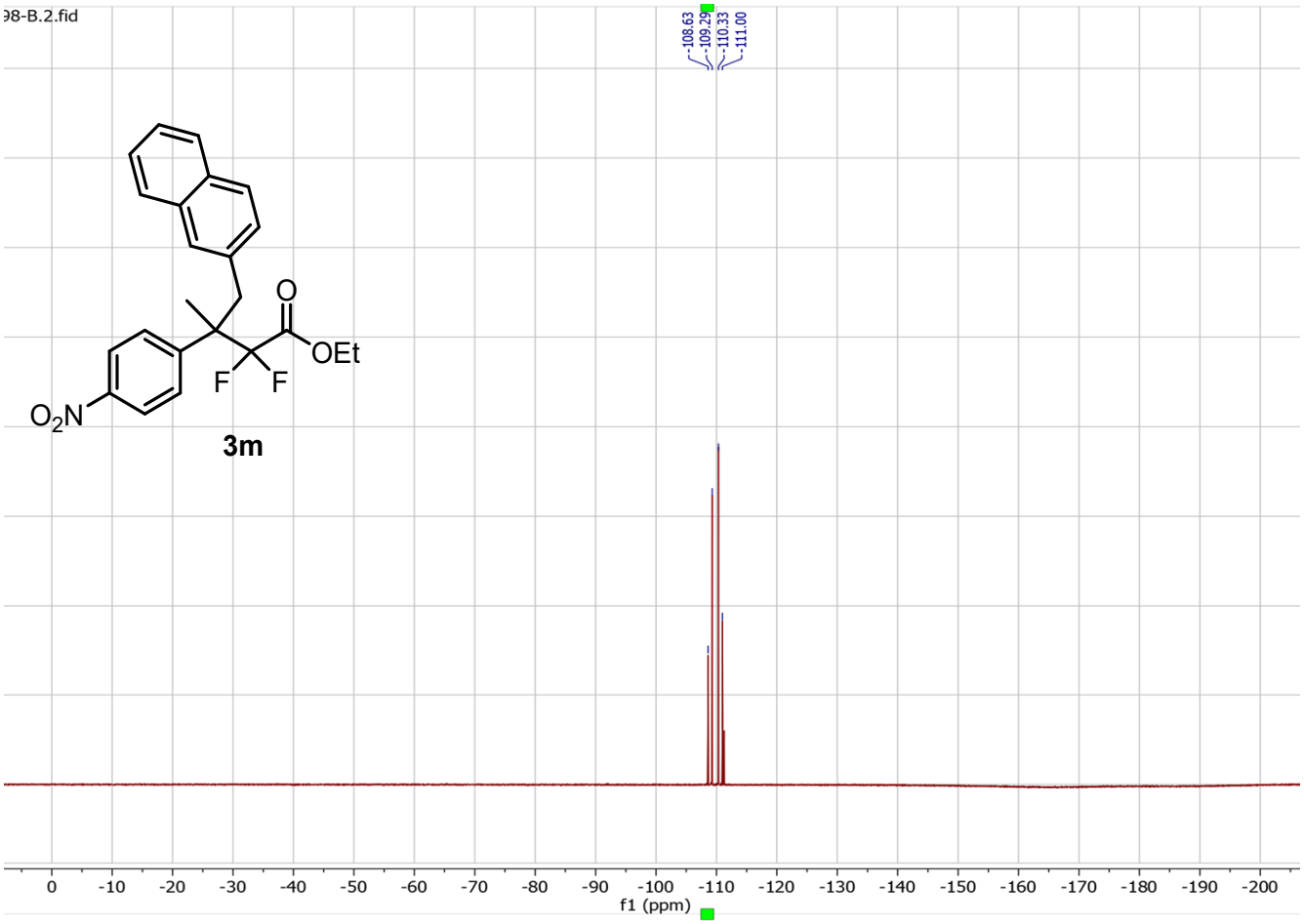
^{1}H NMR spectrum of 3m (400 MHz, Chloroform-d)



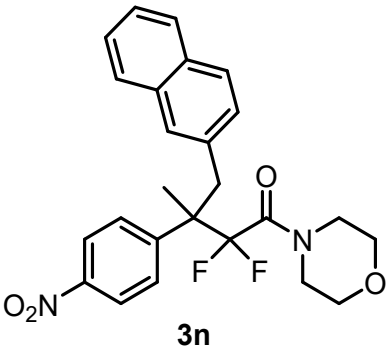
3l

^{13}C NMR spectrum of 3m (126 MHz, Chloroform-*d*)





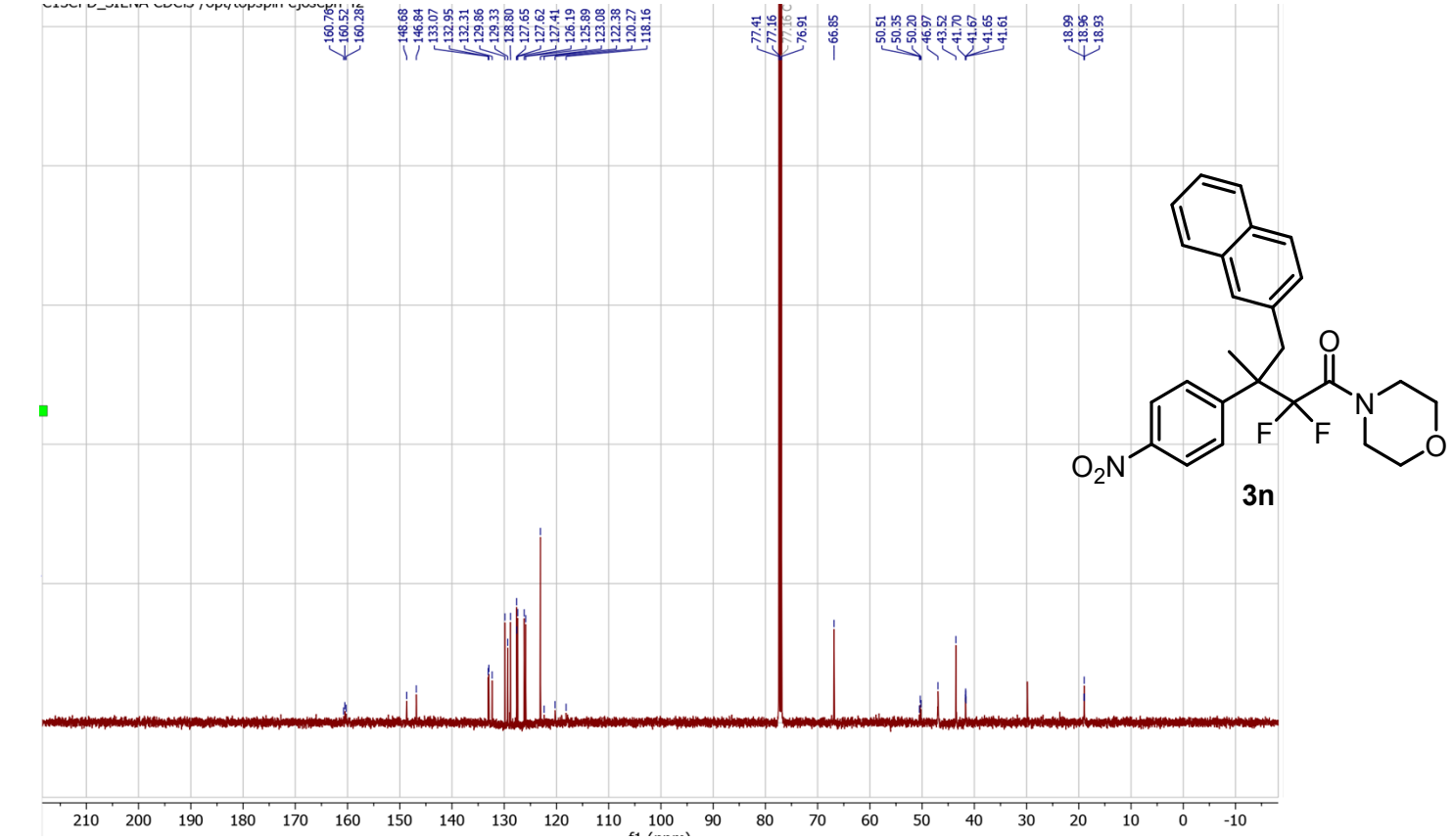
^{19}F NMR spectrum of 3m (376 MHz, Chloroform-*d*)

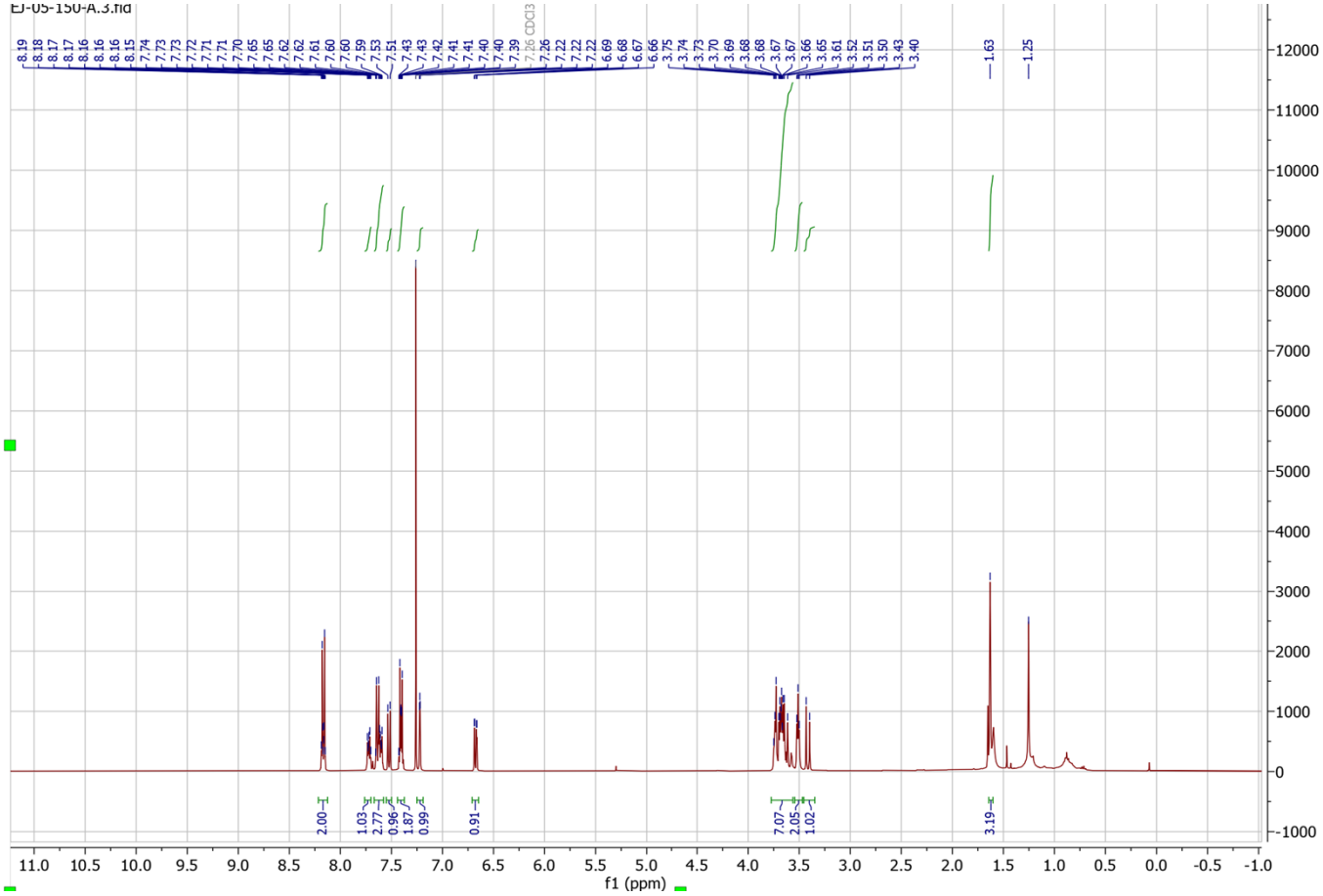


3n

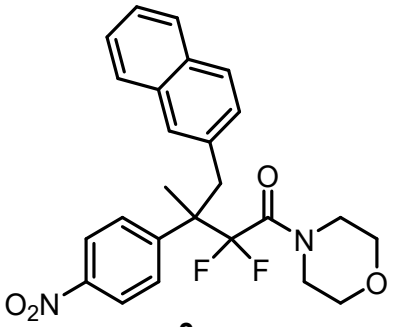
^{1}H NMR spectrum of 3n (400 MHz, Chloroform-d)

^{13}C NMR spectrum of 3n (126 MHz, Chloroform-*d*)

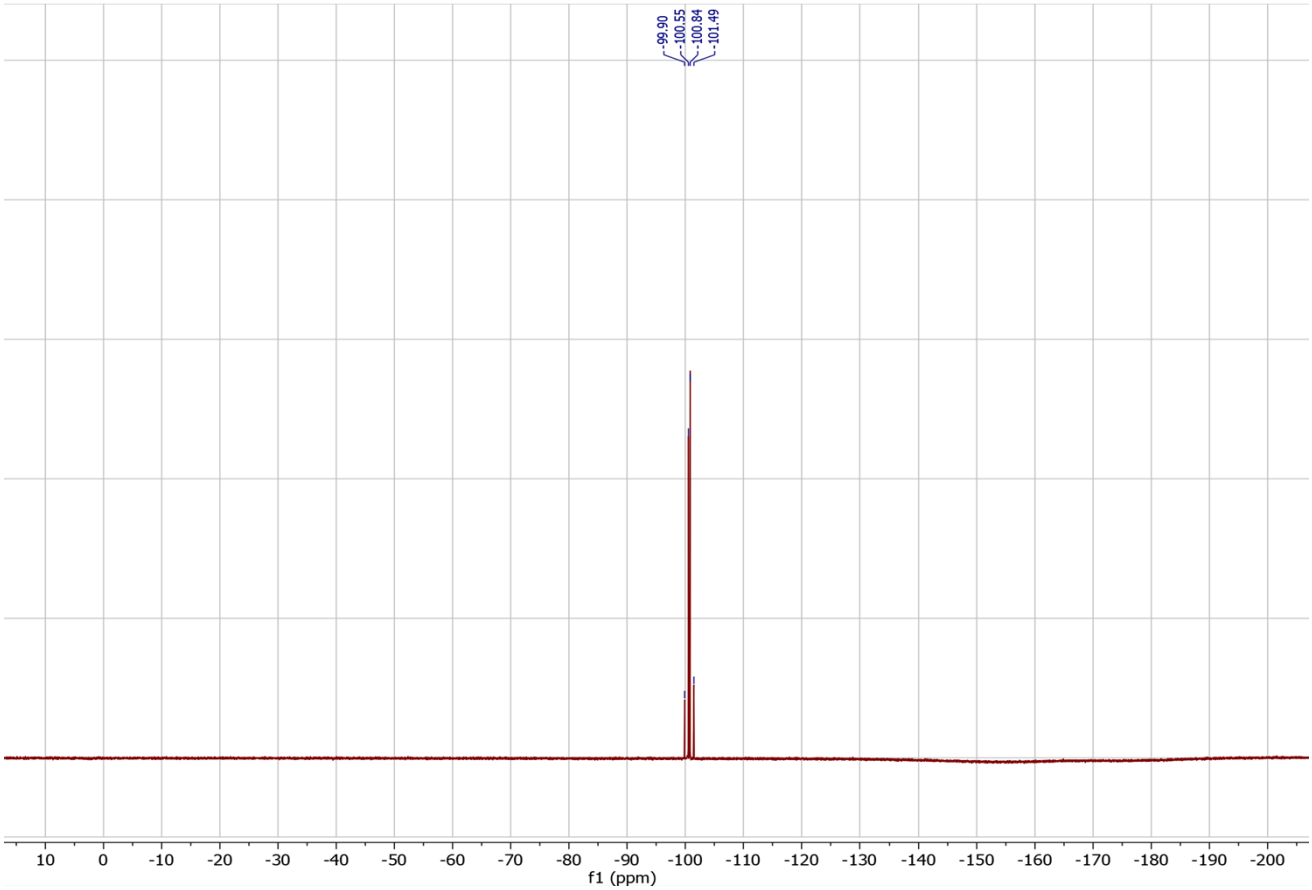


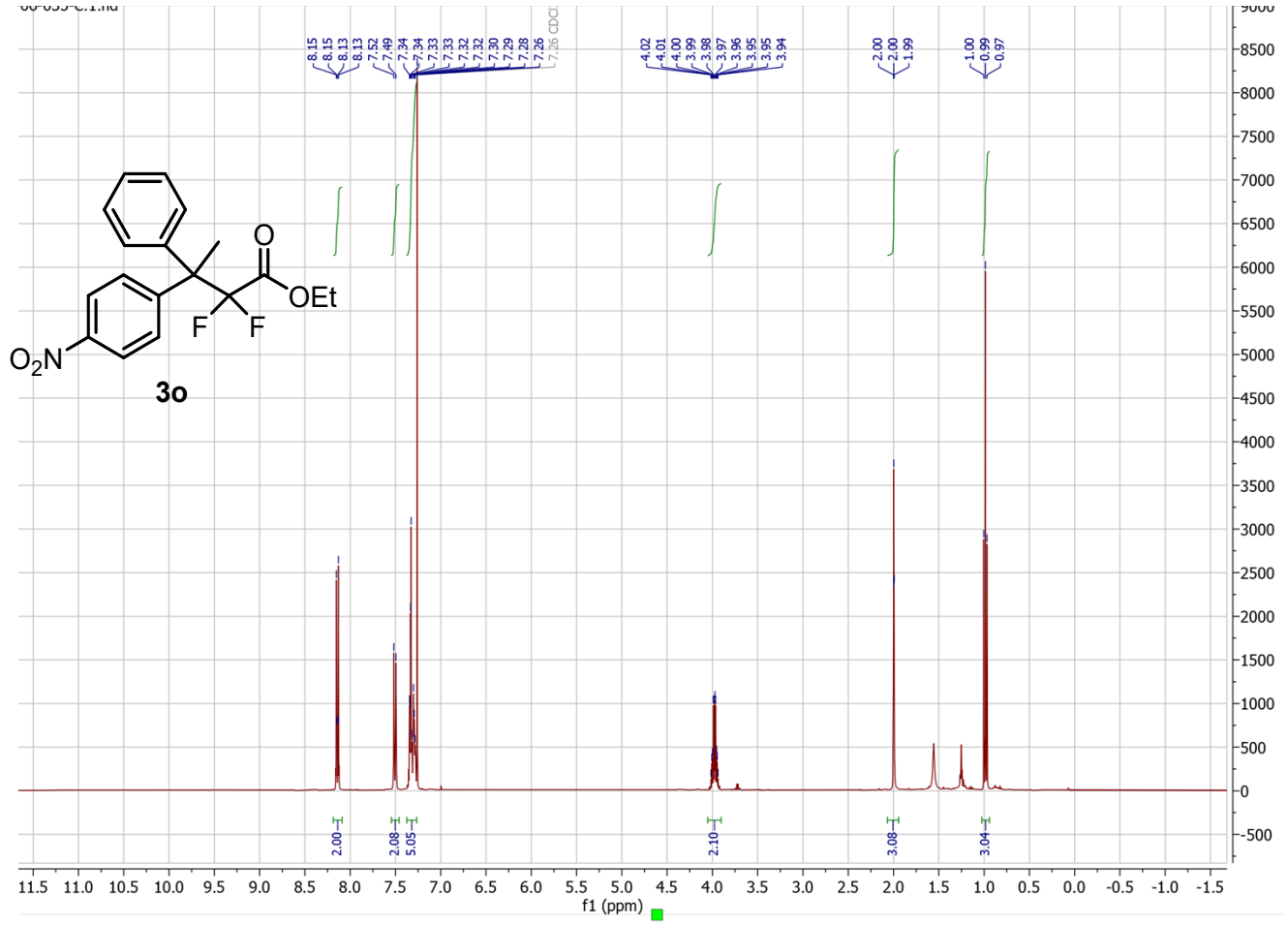


^{19}F NMR spectrum of 3n (376 MHz, Chloroform-*d*)

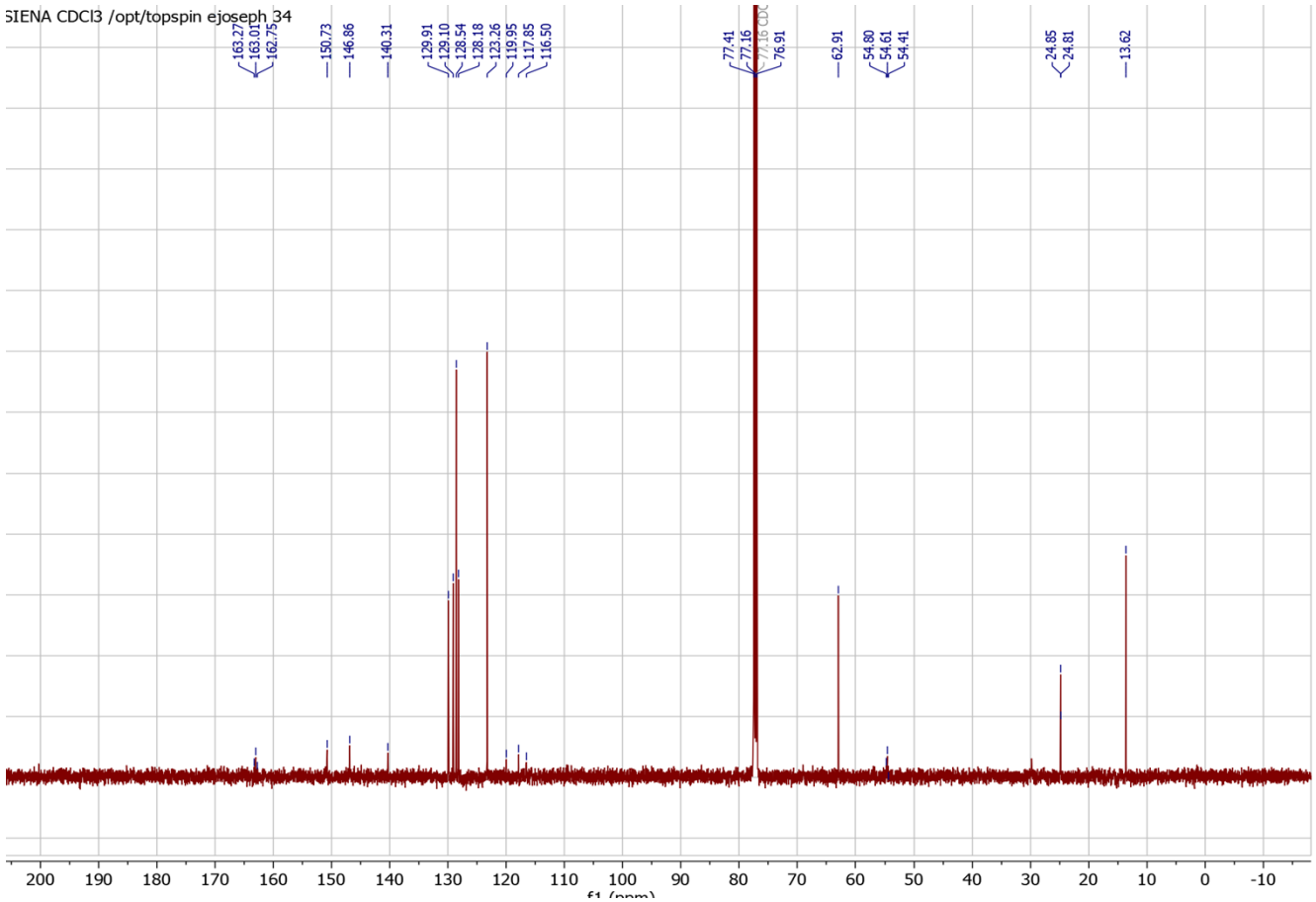


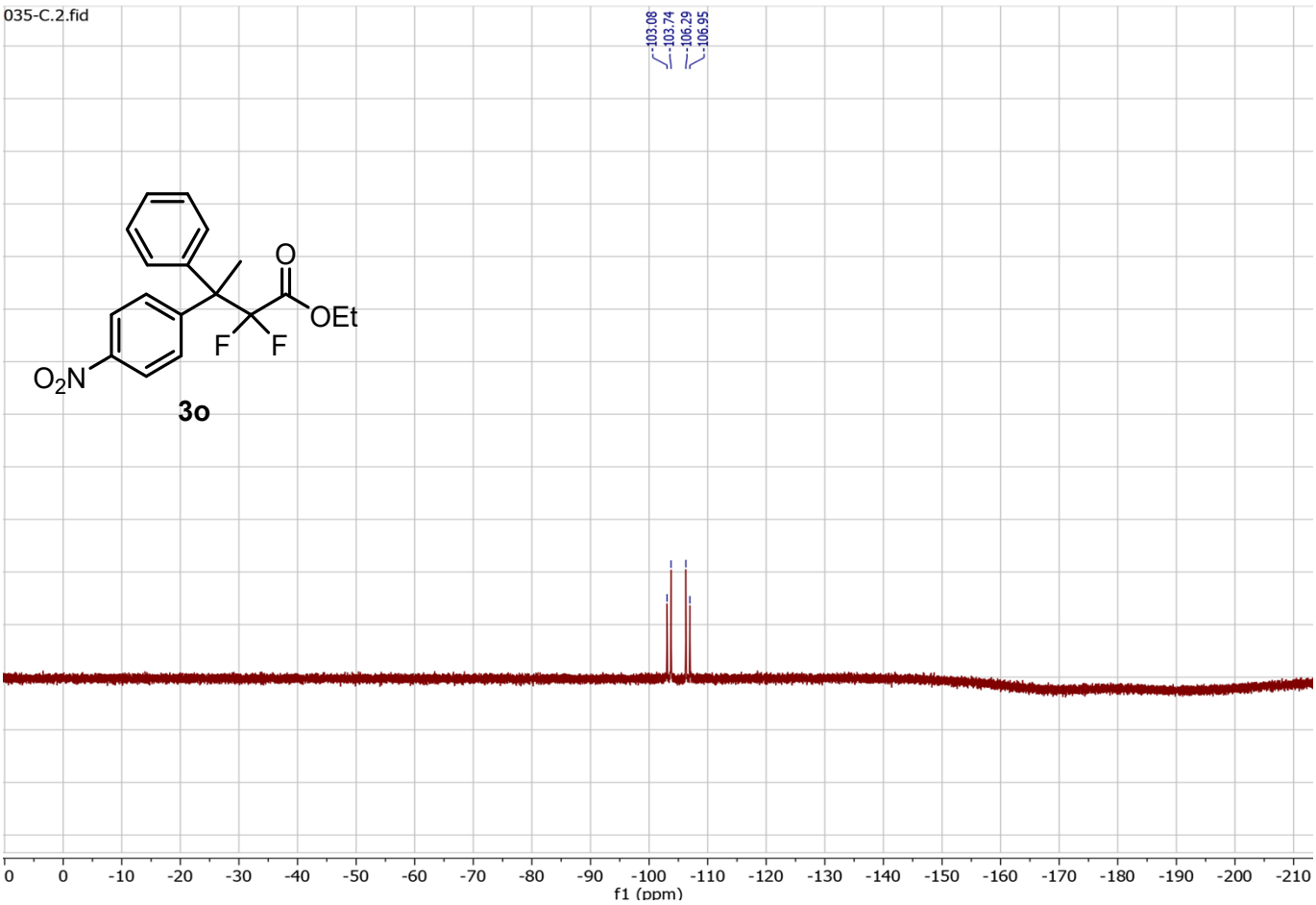
3n





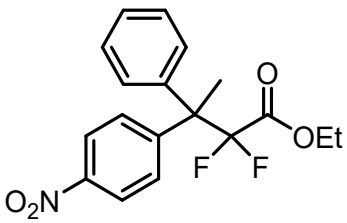
^{1}H NMR spectrum of 3o (400 MHz, Chloroform-d)





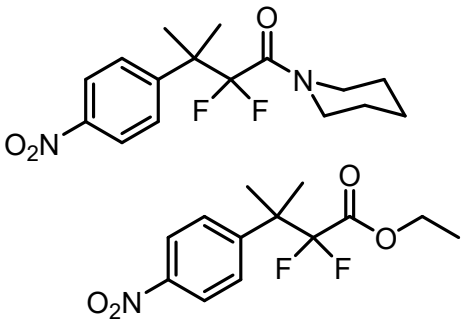
^{13}C NMR spectrum of 3o (126 MHz, Chloroform-*d*)

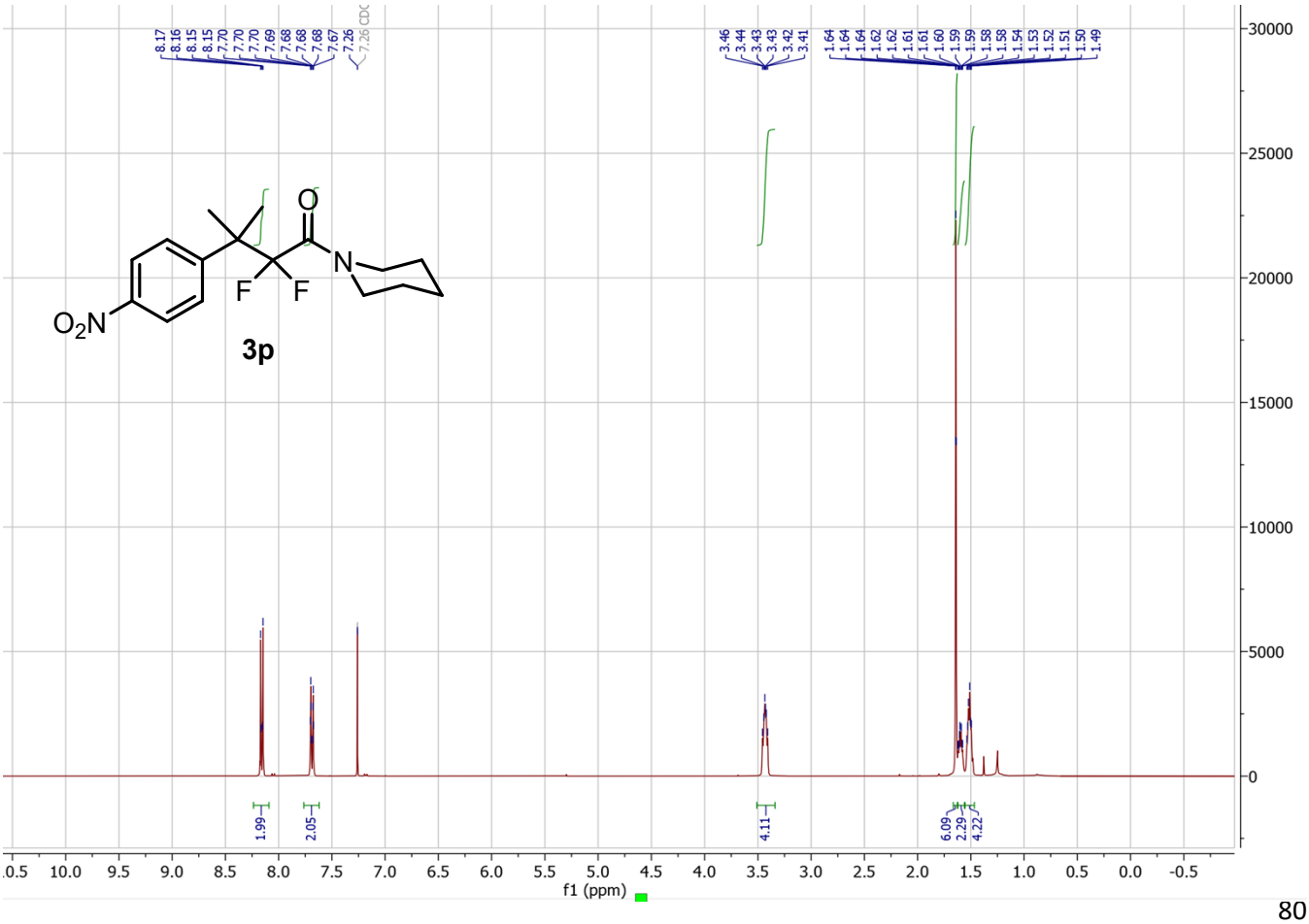
^{19}F NMR spectrum of 3o (376 MHz, Chloroform-*d*)

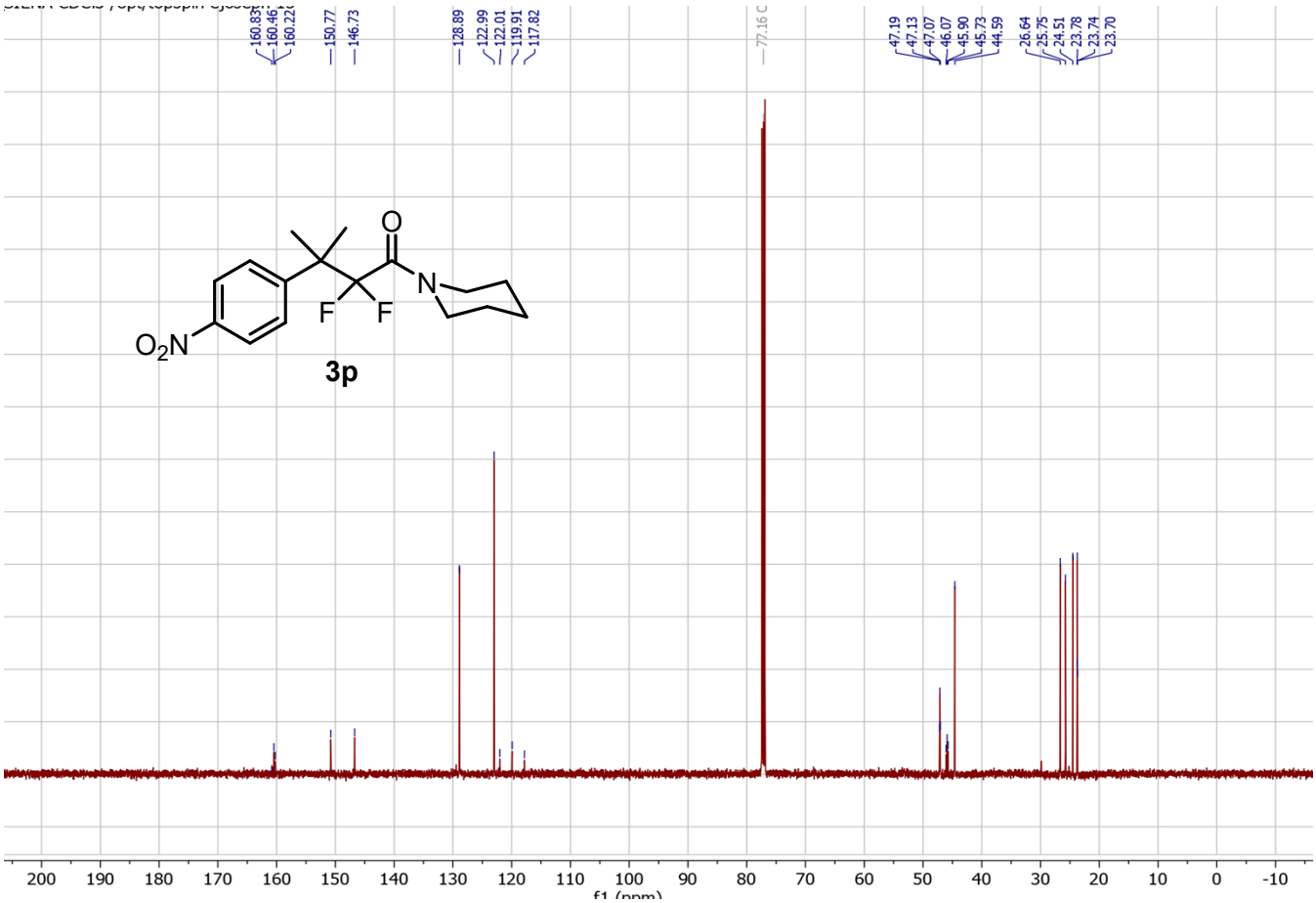


3o

^{1}H NMR spectrum of 3p (400 MHz, Chloroform-d)



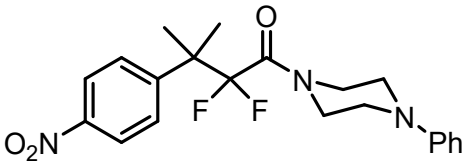




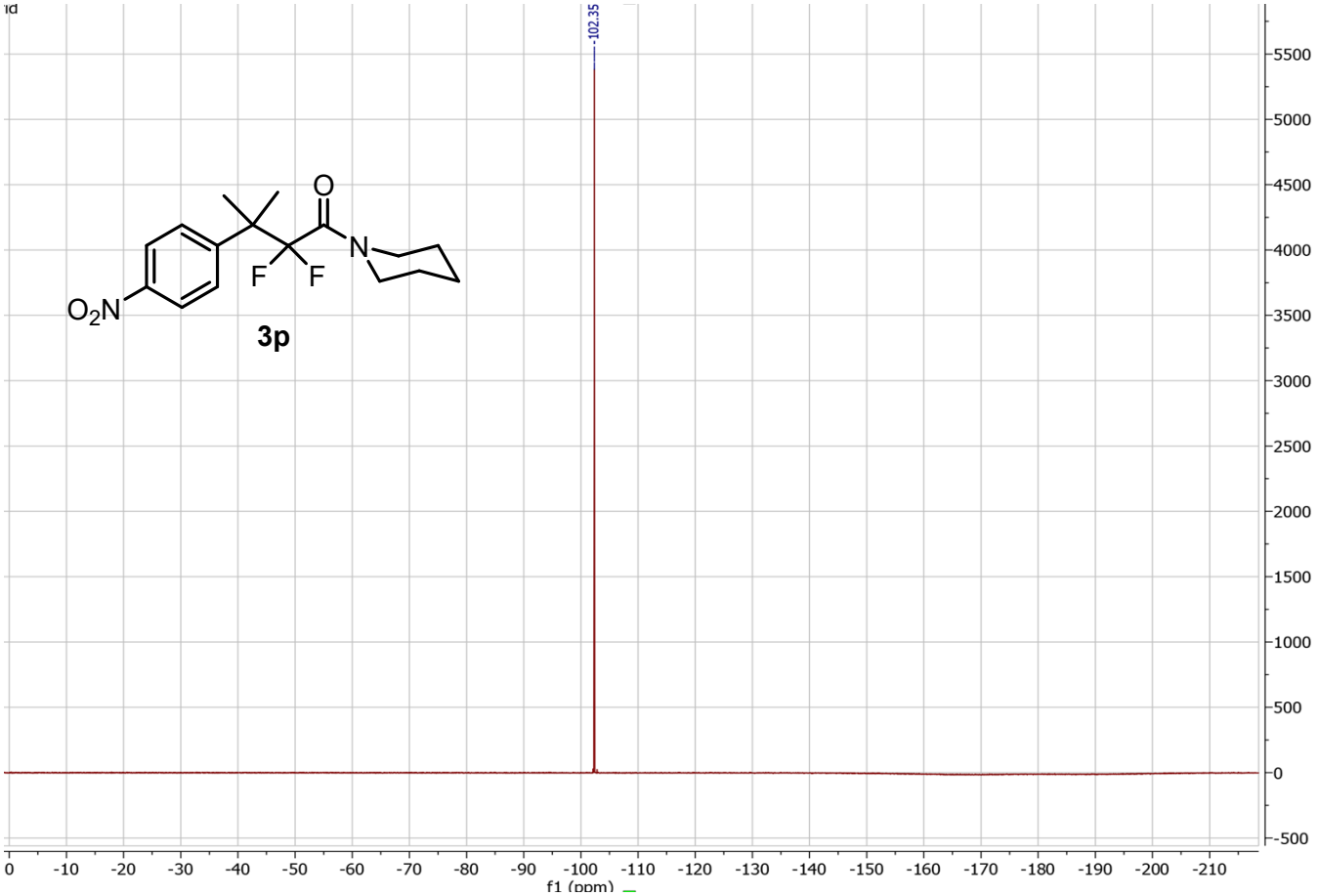
^{13}C NMR spectrum of 3p (126 MHz, Chloroform-*d*)

^{19}F NMR spectrum of 3p (376 MHz, Chloroform-*d*)

^{1}H NMR spectrum of 3q (400 MHz, Chloroform-d)

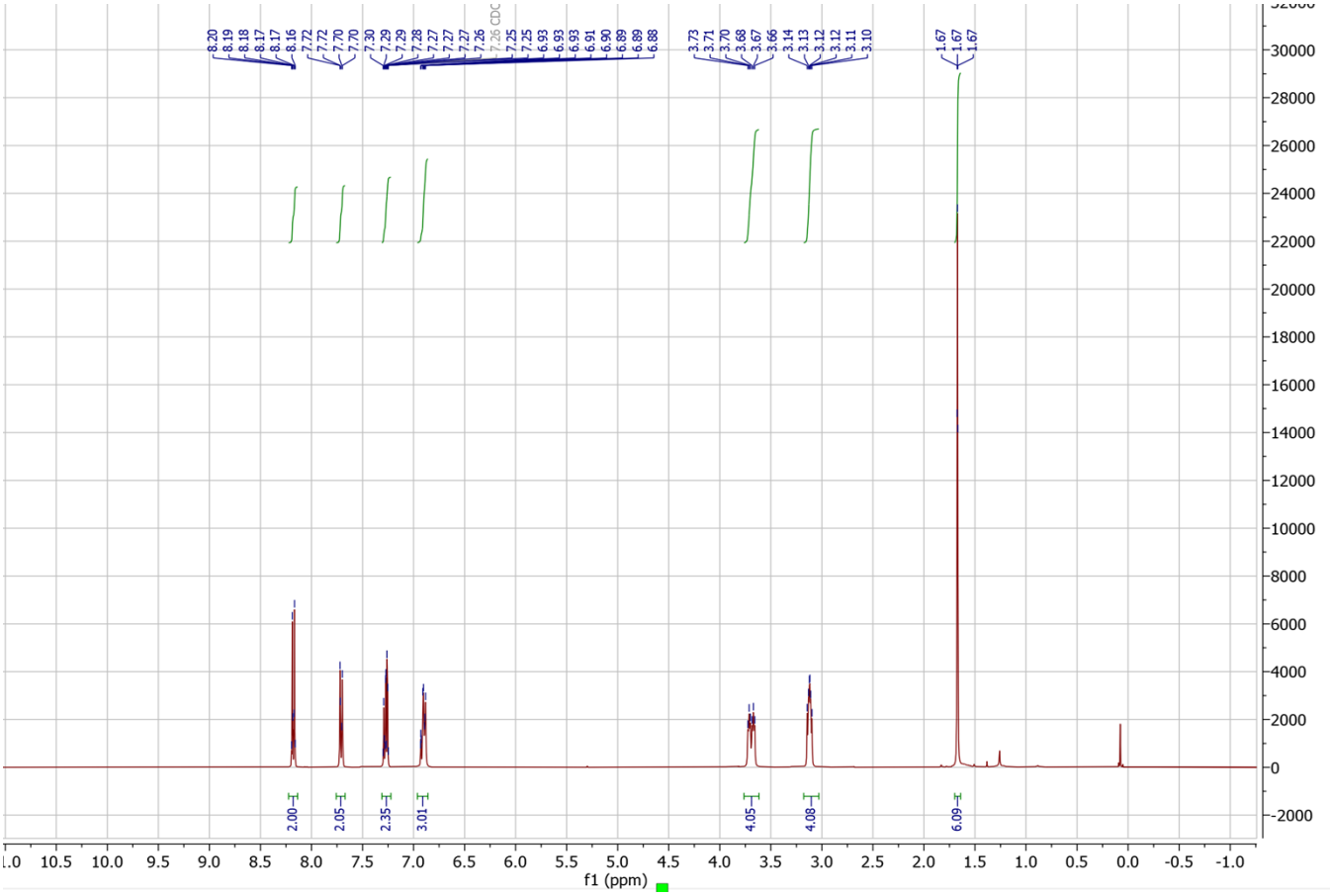


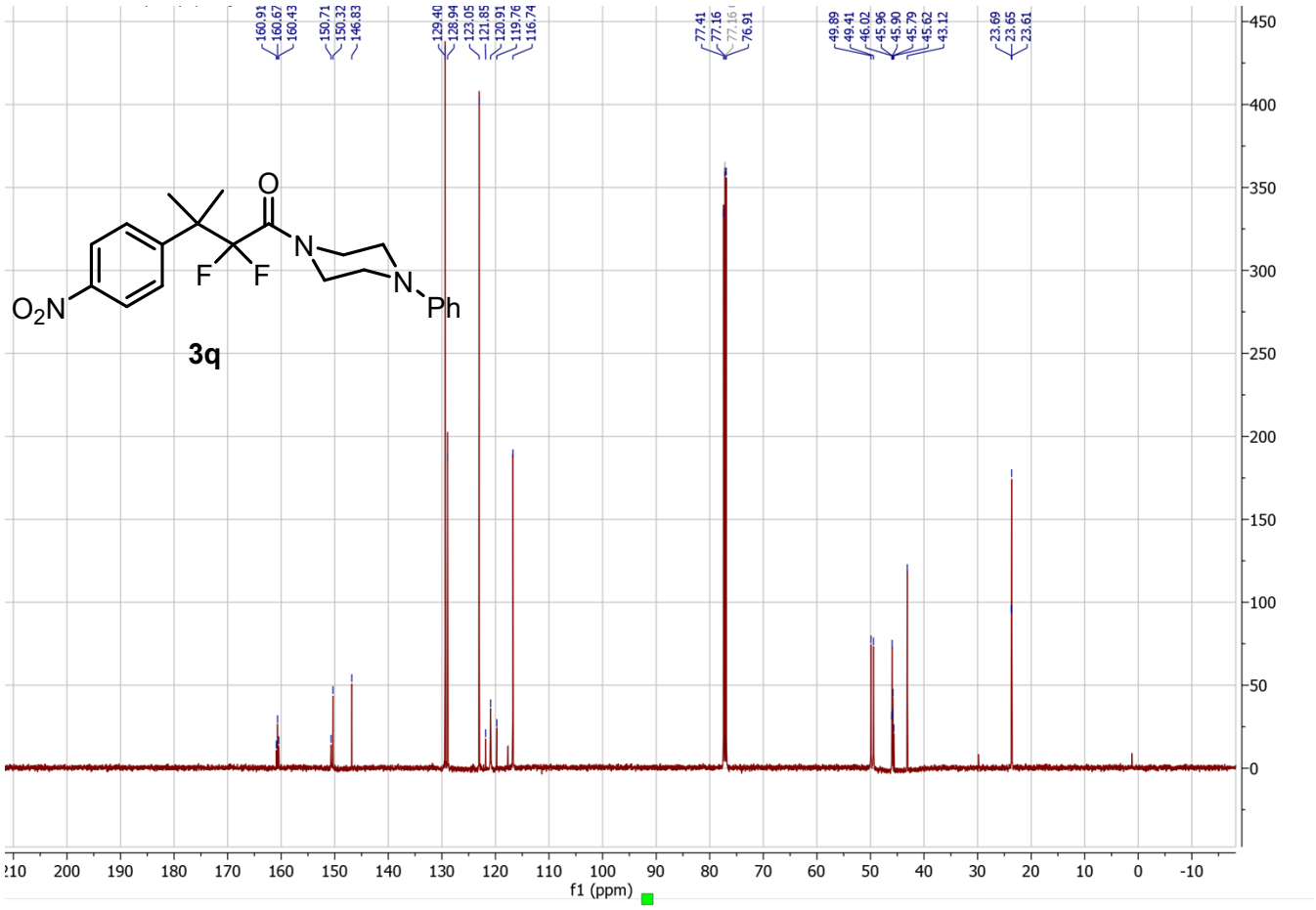
3q



3p

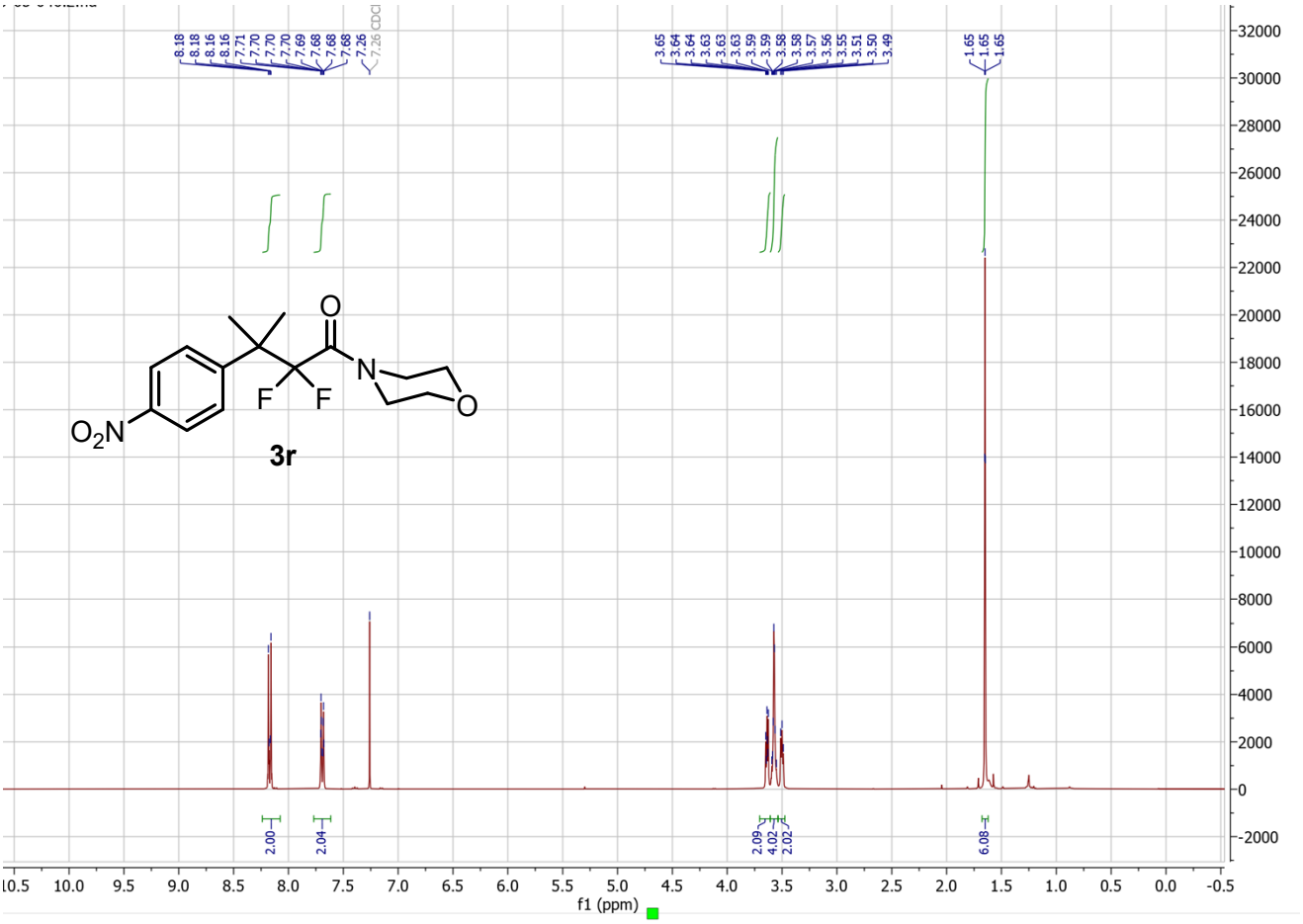
^{13}C NMR spectrum of 3q (126 MHz, Chloroform-*d*)



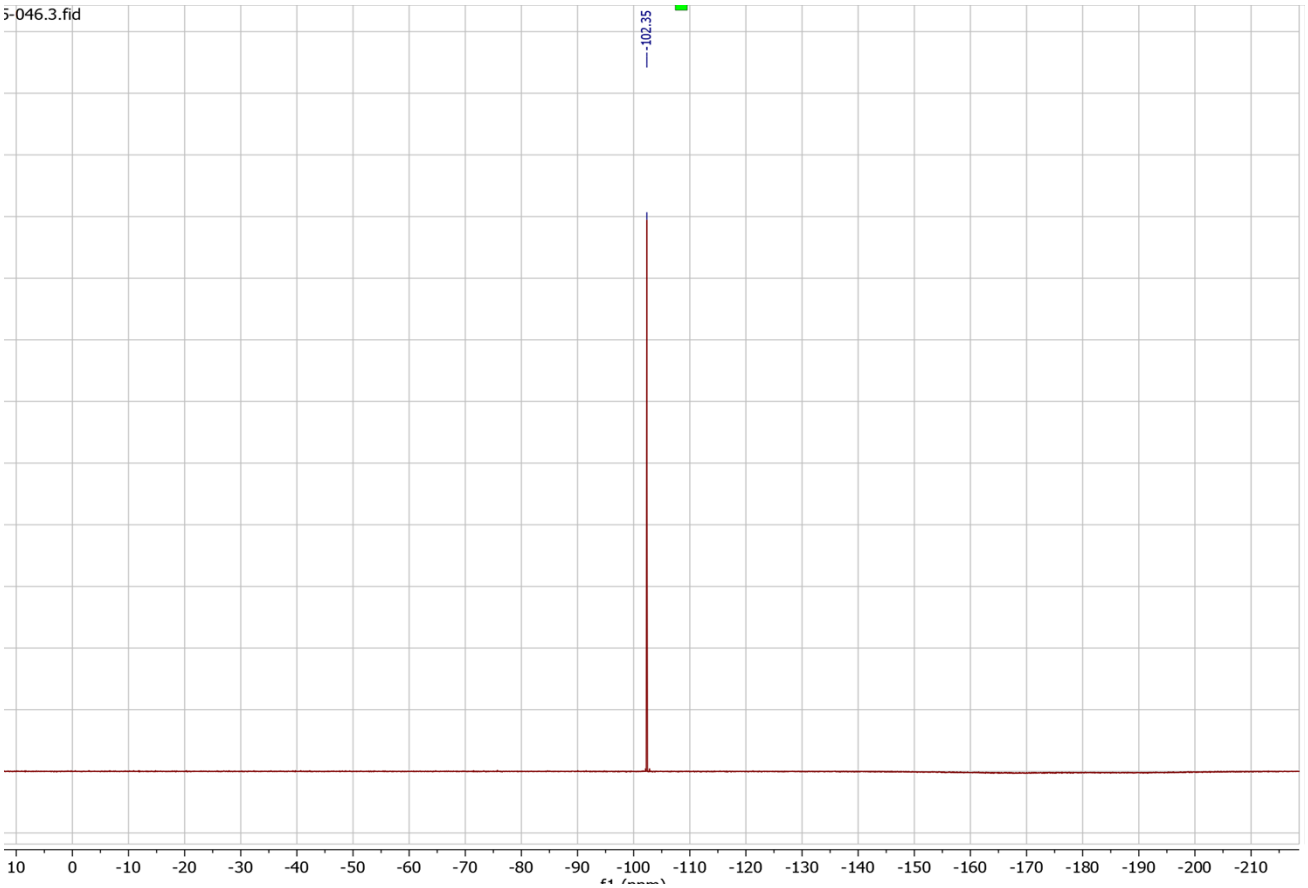


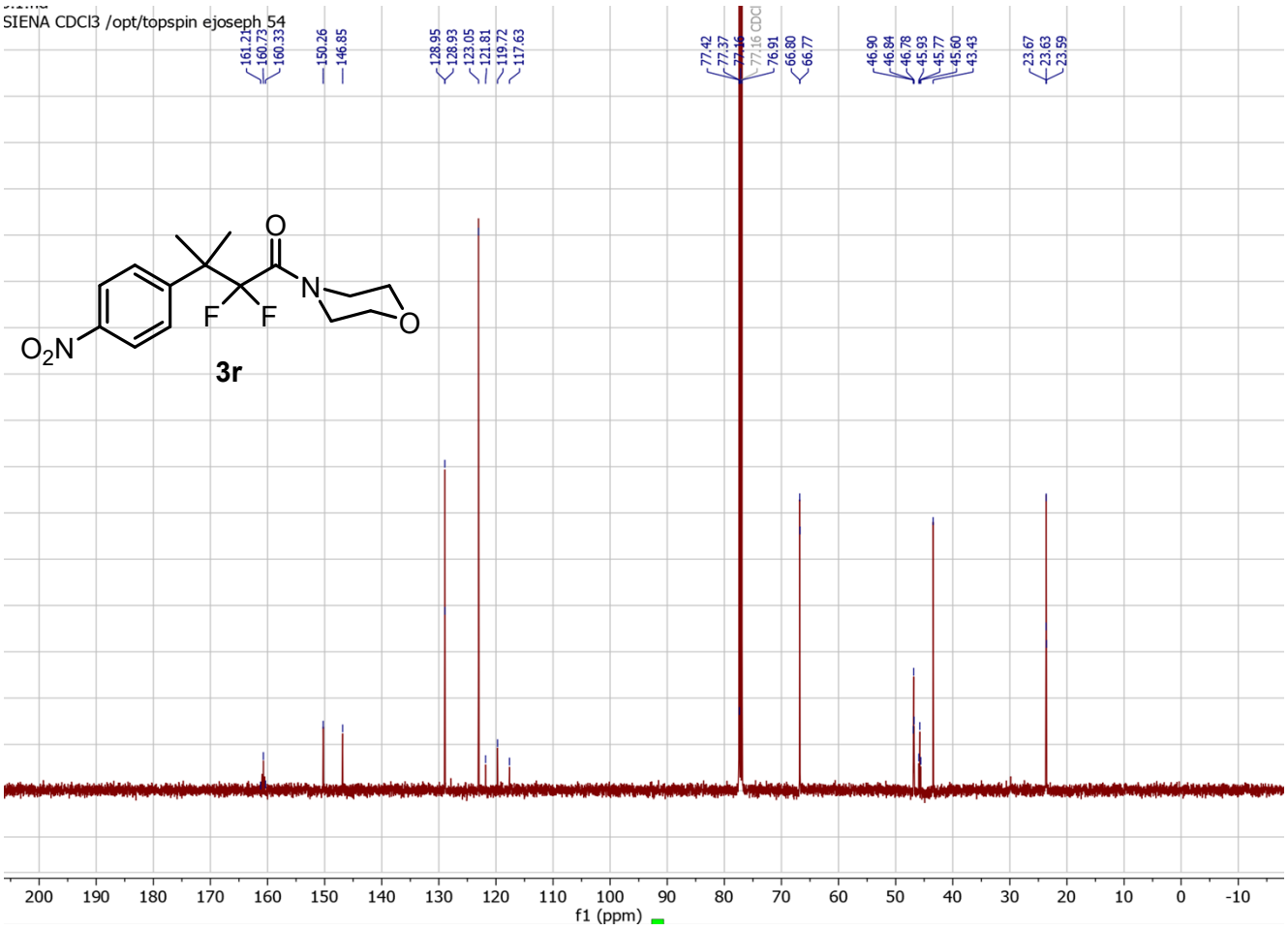
^{19}F NMR spectrum of 3q (376 MHz, Chloroform-*d*)

^{1}H NMR spectrum of 3r (400 MHz, Chloroform-d)



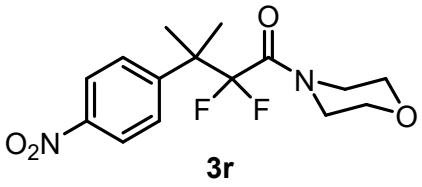
^{13}C NMR spectrum of 3r (126 MHz, Chloroform-*d*)



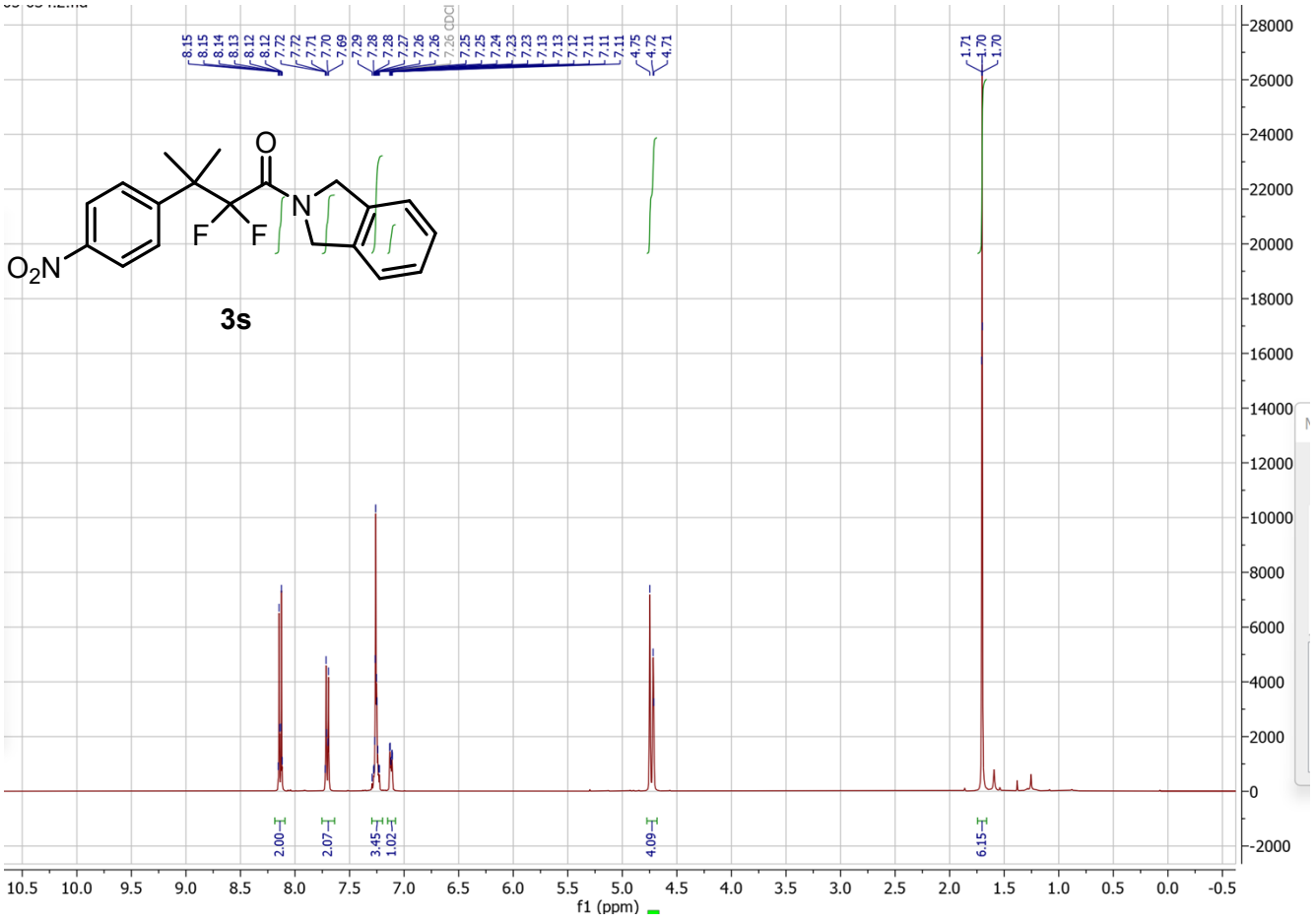


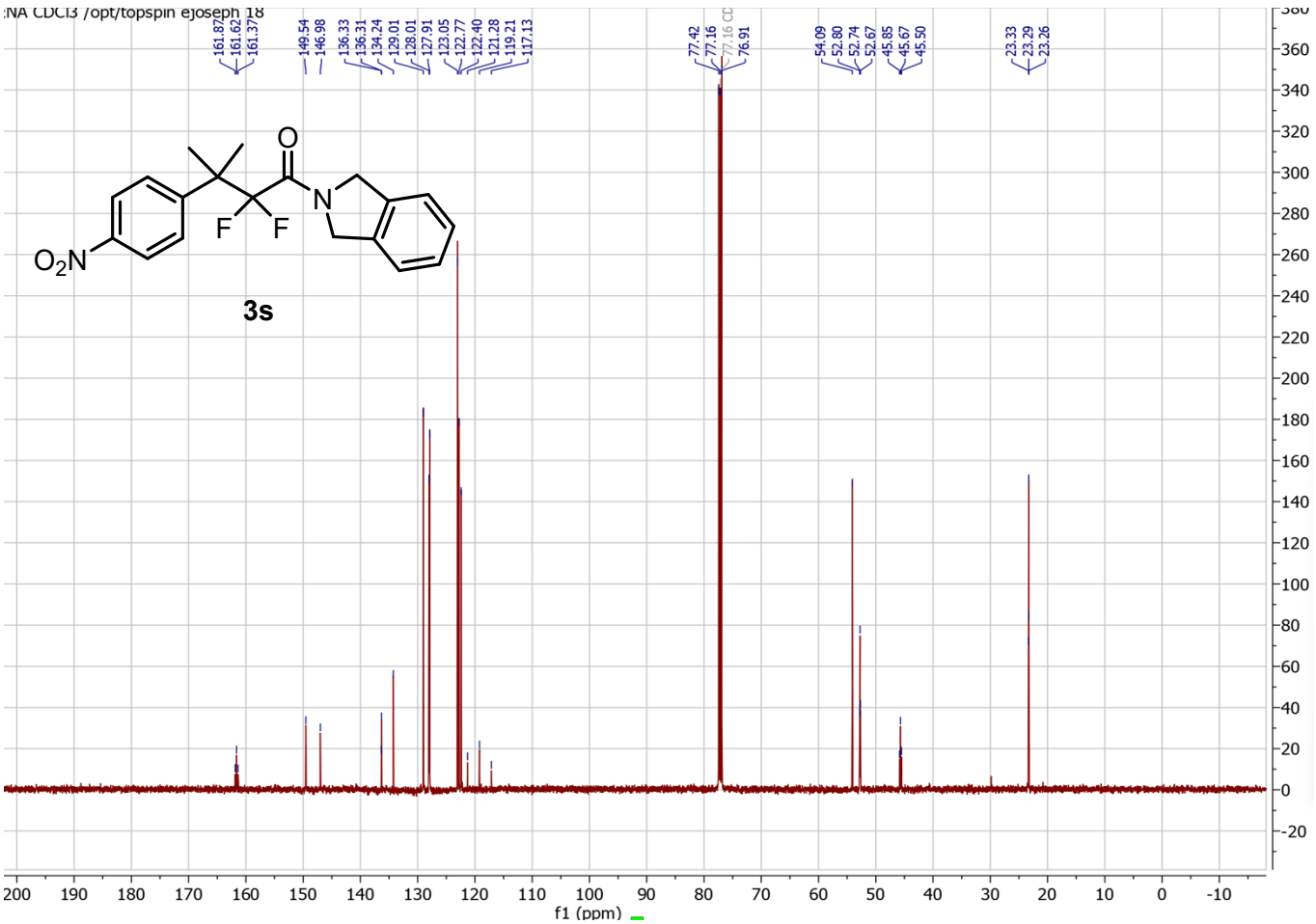
^{19}F NMR spectrum of 3r (376 MHz, Chloroform-*d*)

^{1}H NMR spectrum of 3s (400 MHz, Chloroform-d)

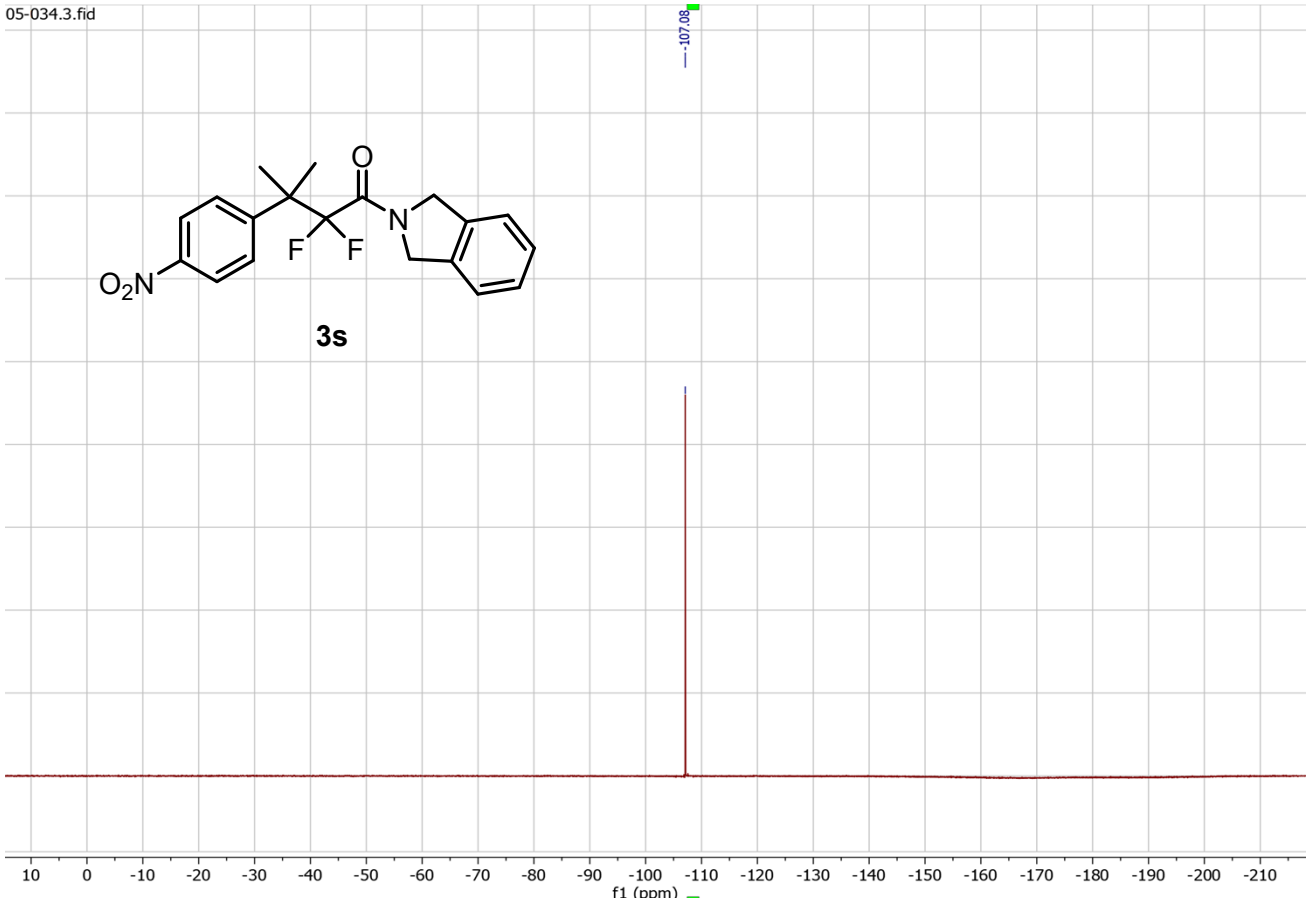


3r



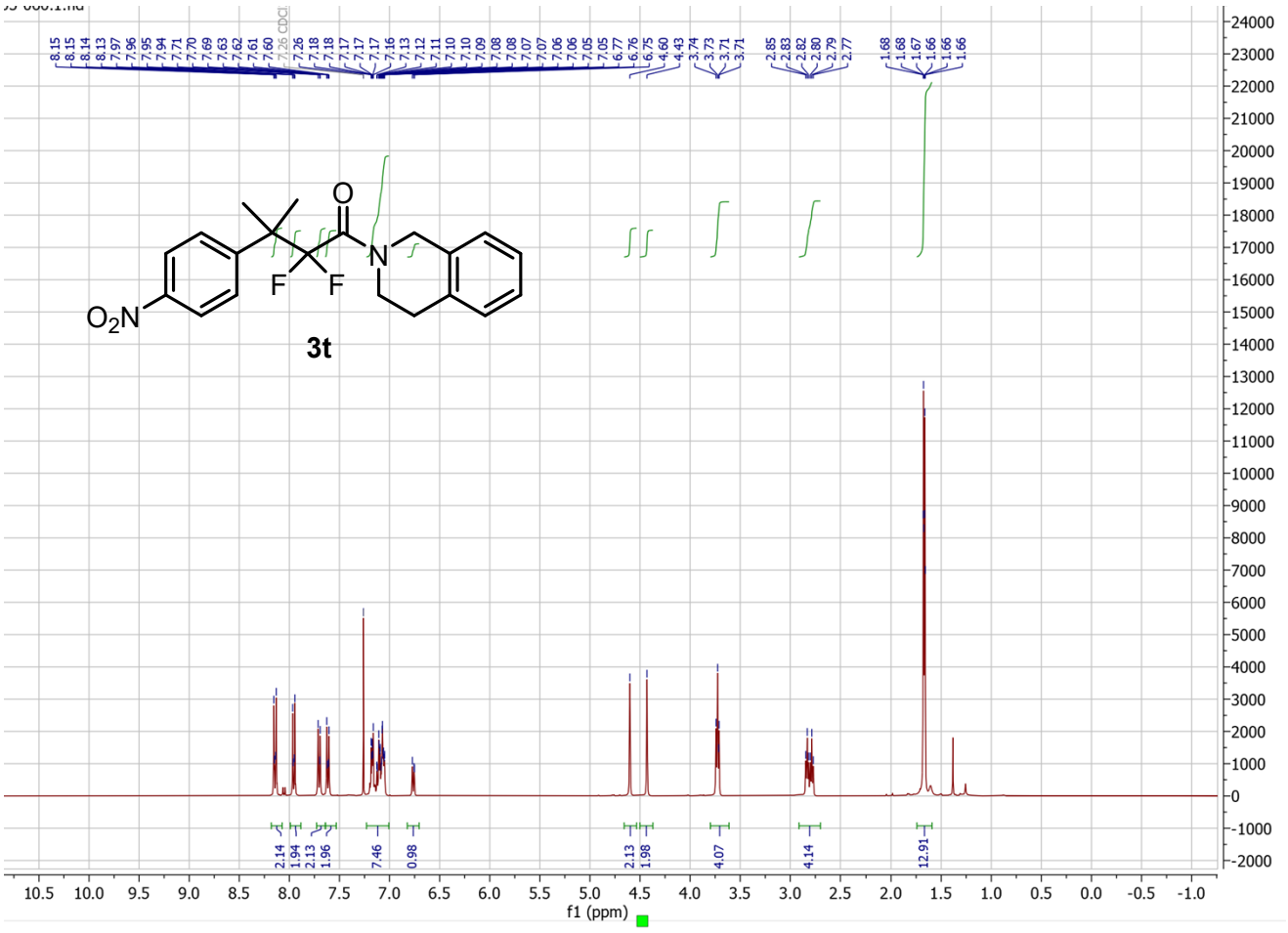


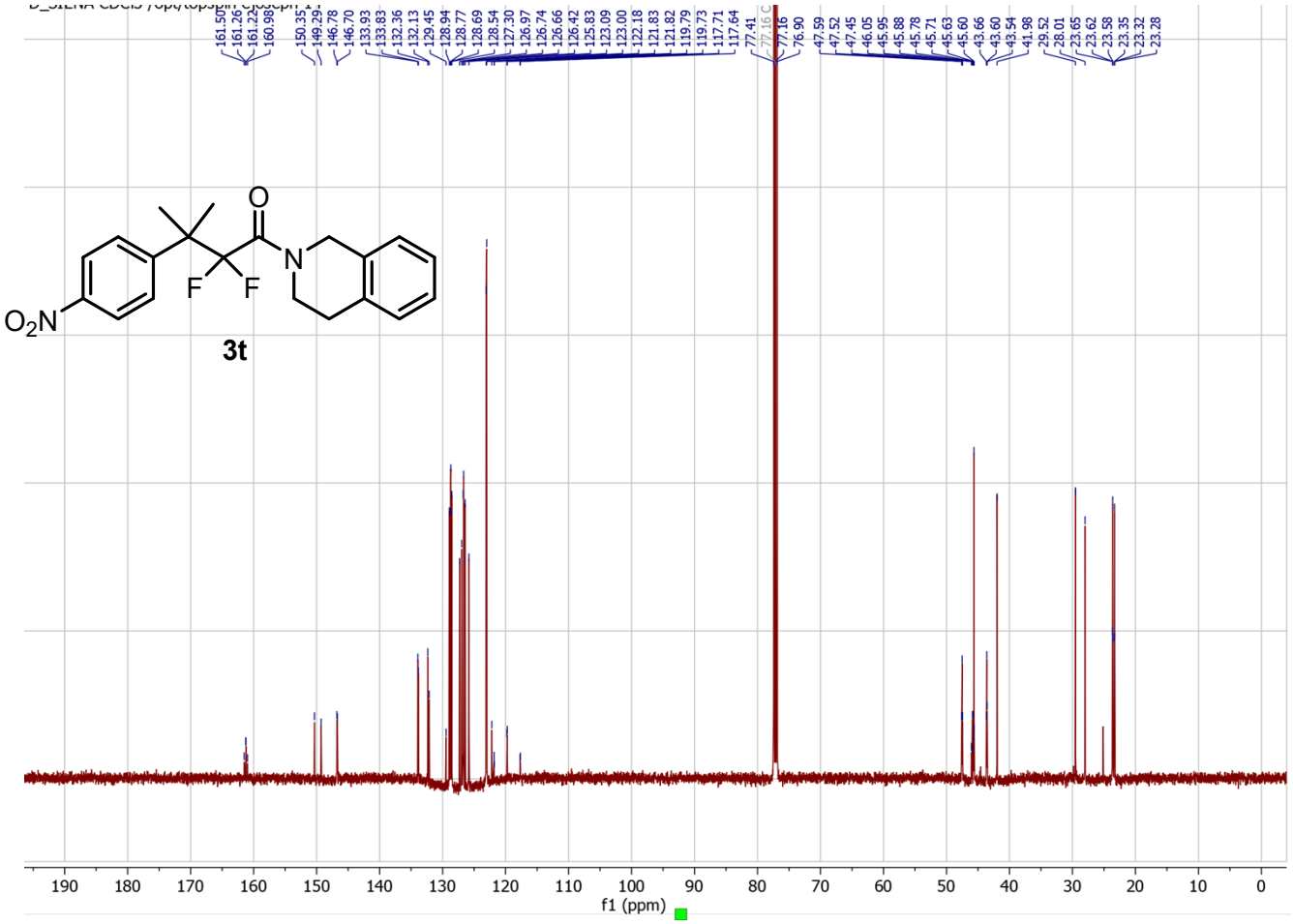
^{13}C NMR spectrum of 3s (126 MHz, Chloroform-*d*)



^{19}F NMR spectrum of 3s (376 MHz, Chloroform-*d*)

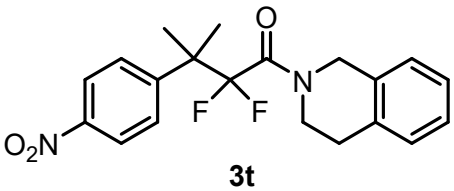
^{1}H NMR spectrum of 3t (400 MHz, Chloroform-d)



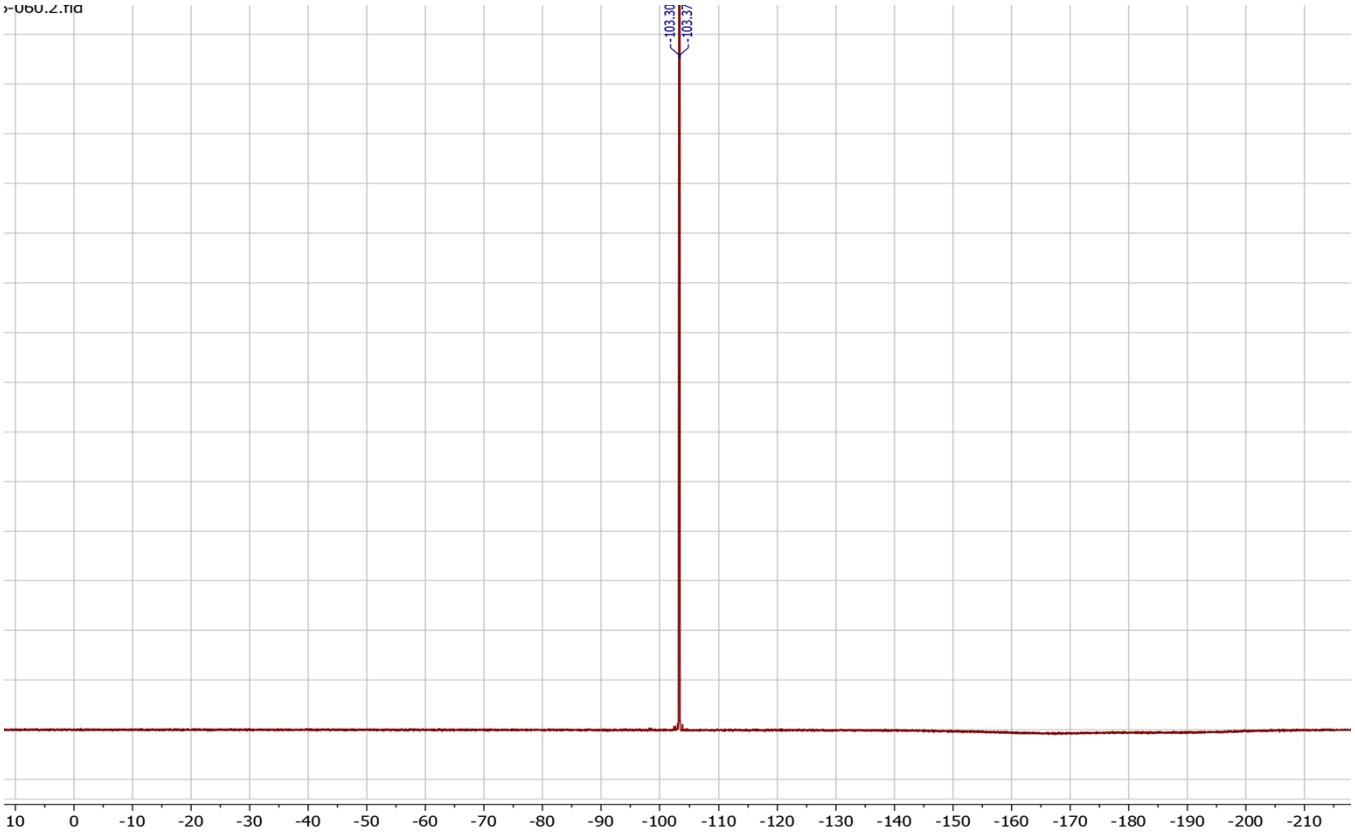


^{13}C NMR spectrum of 3t (126 MHz, Chloroform-*d*)

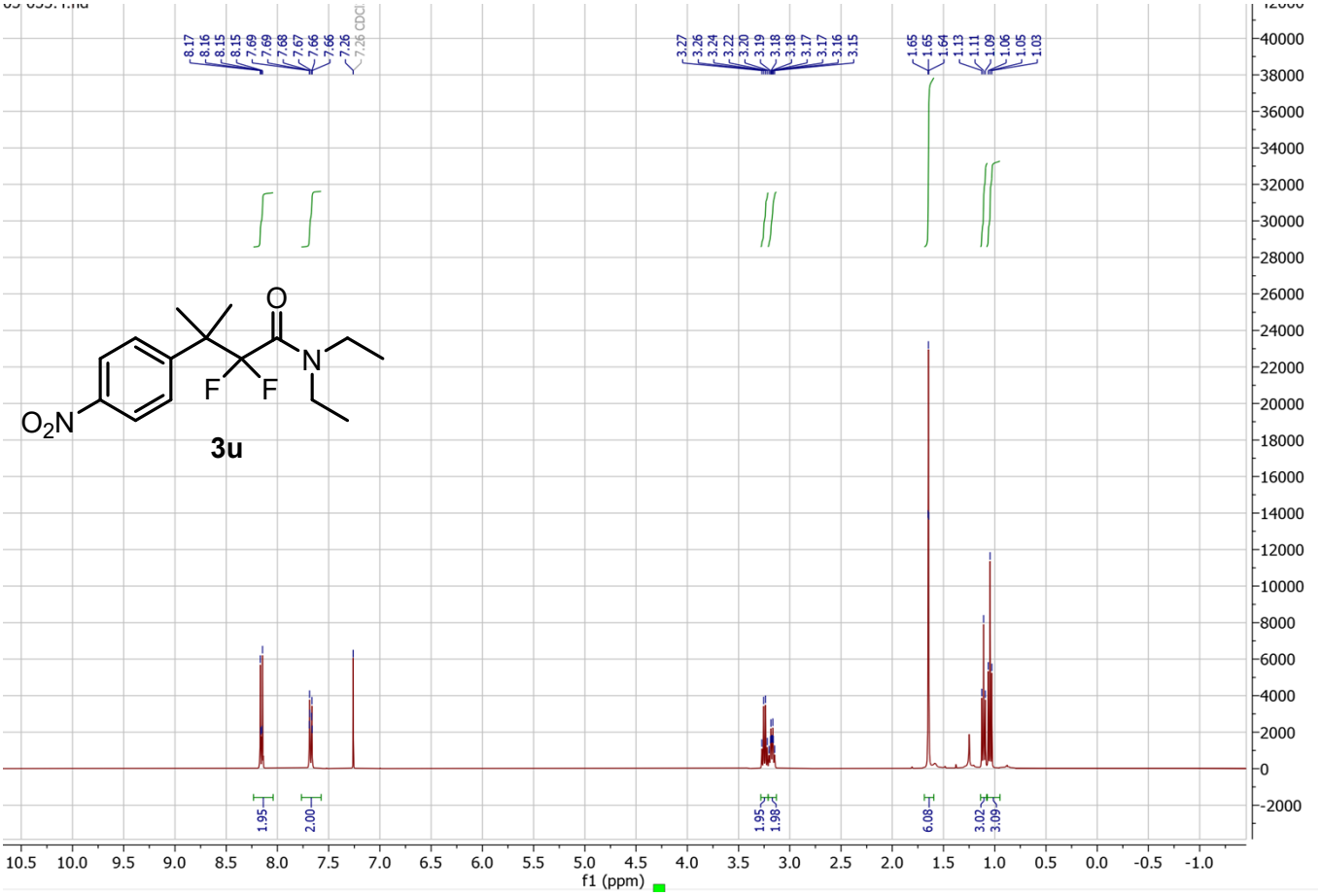
^{19}F NMR spectrum of 3t (376 MHz, Chloroform-*d*)



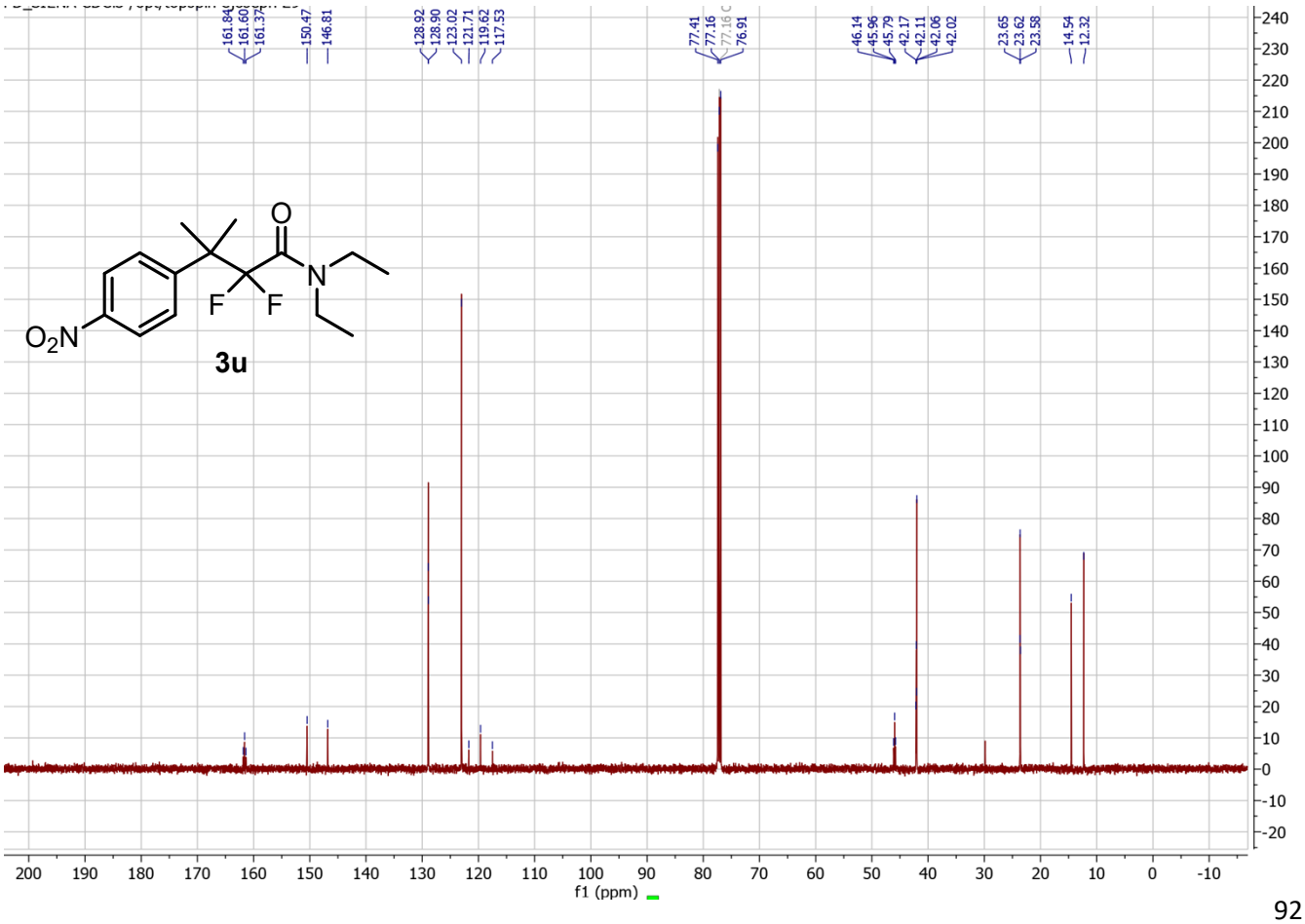
3t

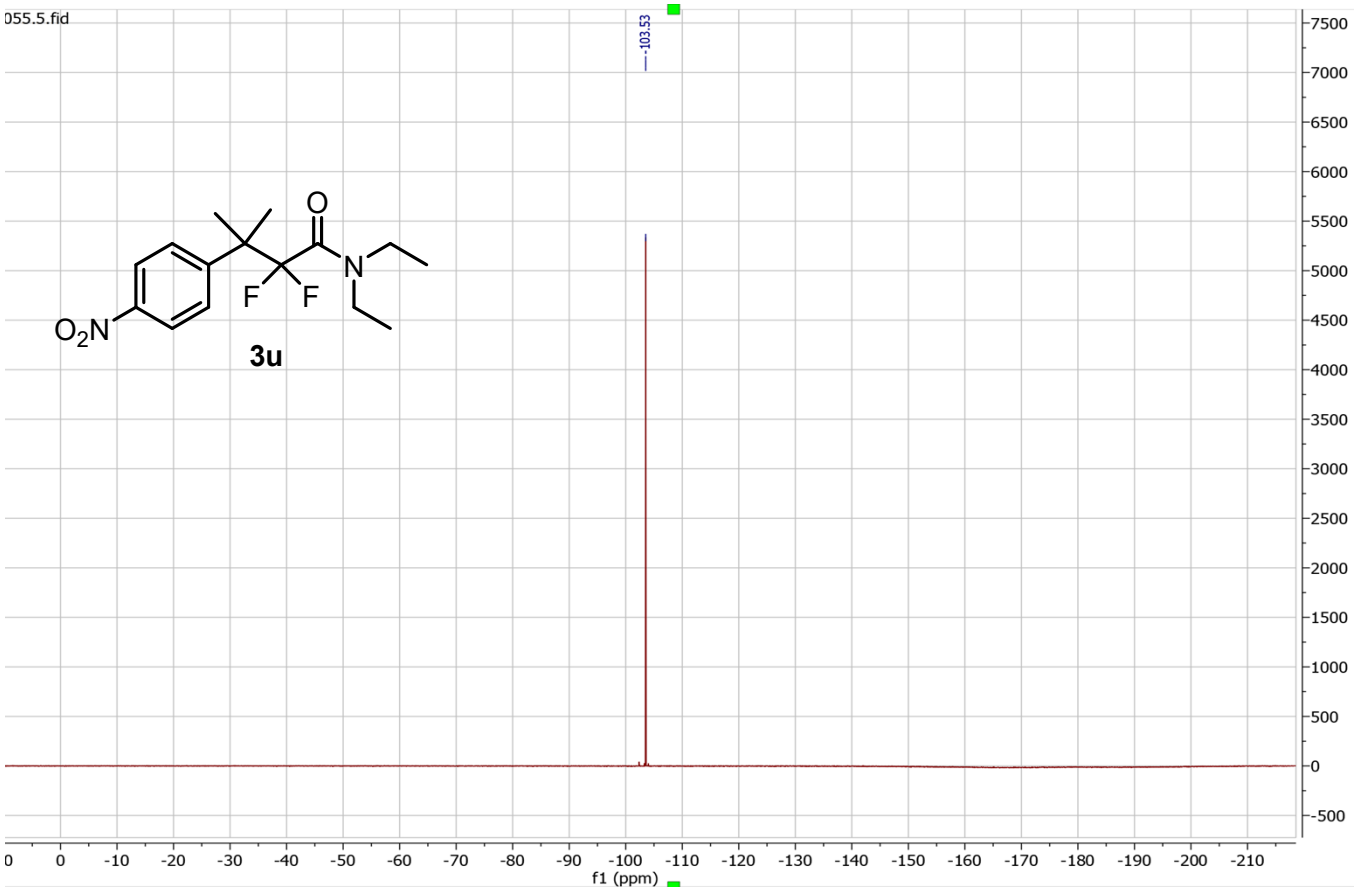


^{1}H NMR spectrum of 3u (400 MHz, Chloroform-d)



^{13}C NMR spectrum of 3u (126 MHz, Chloroform-*d*)

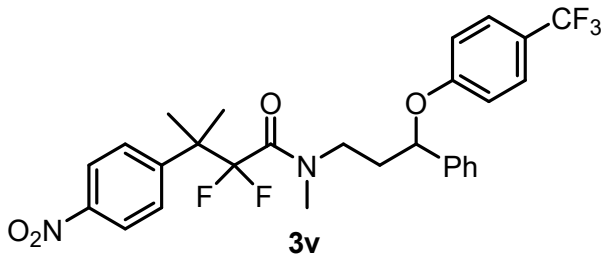




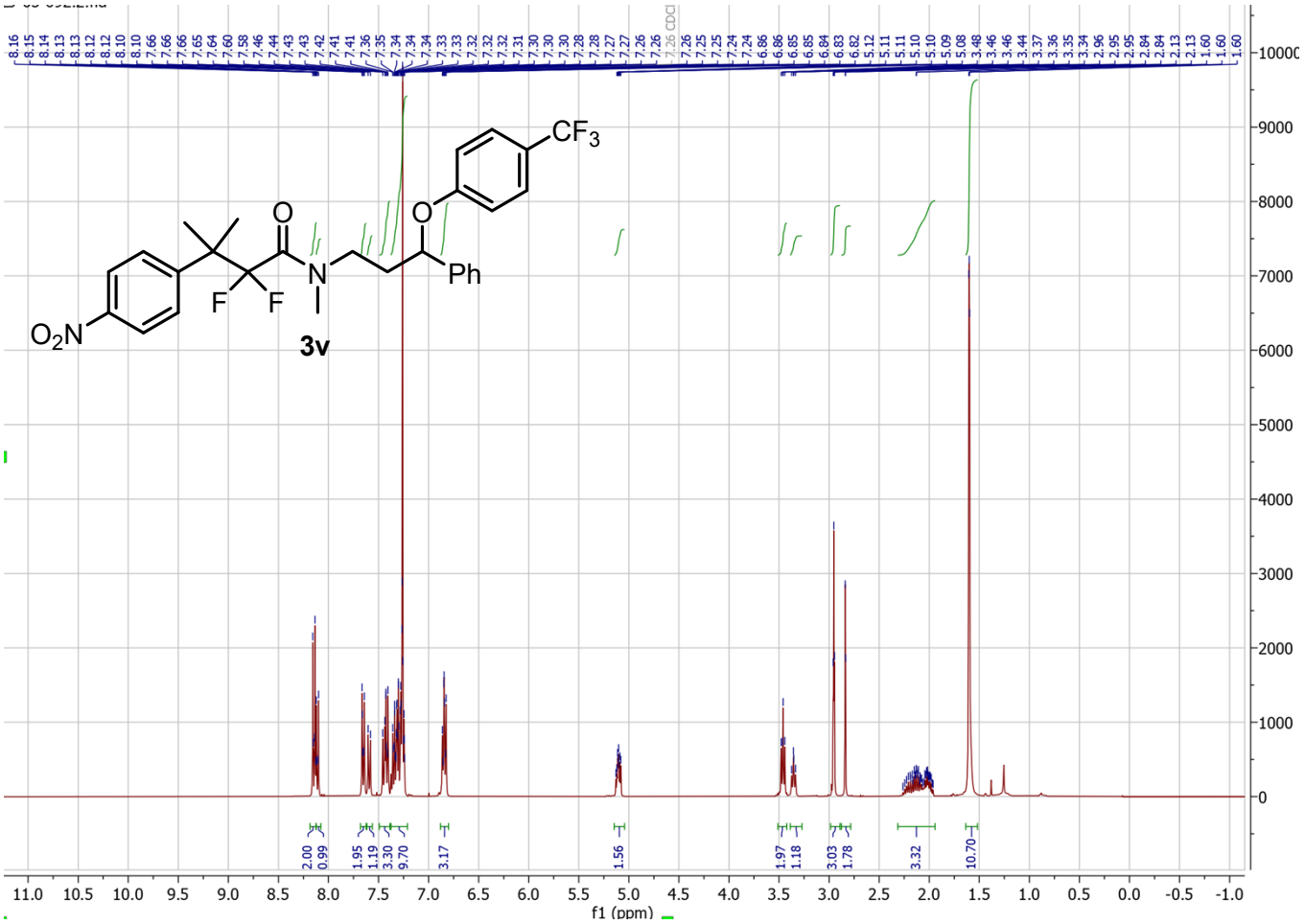
^{19}F NMR spectrum of 3u (376 MHz, Chloroform-*d*)

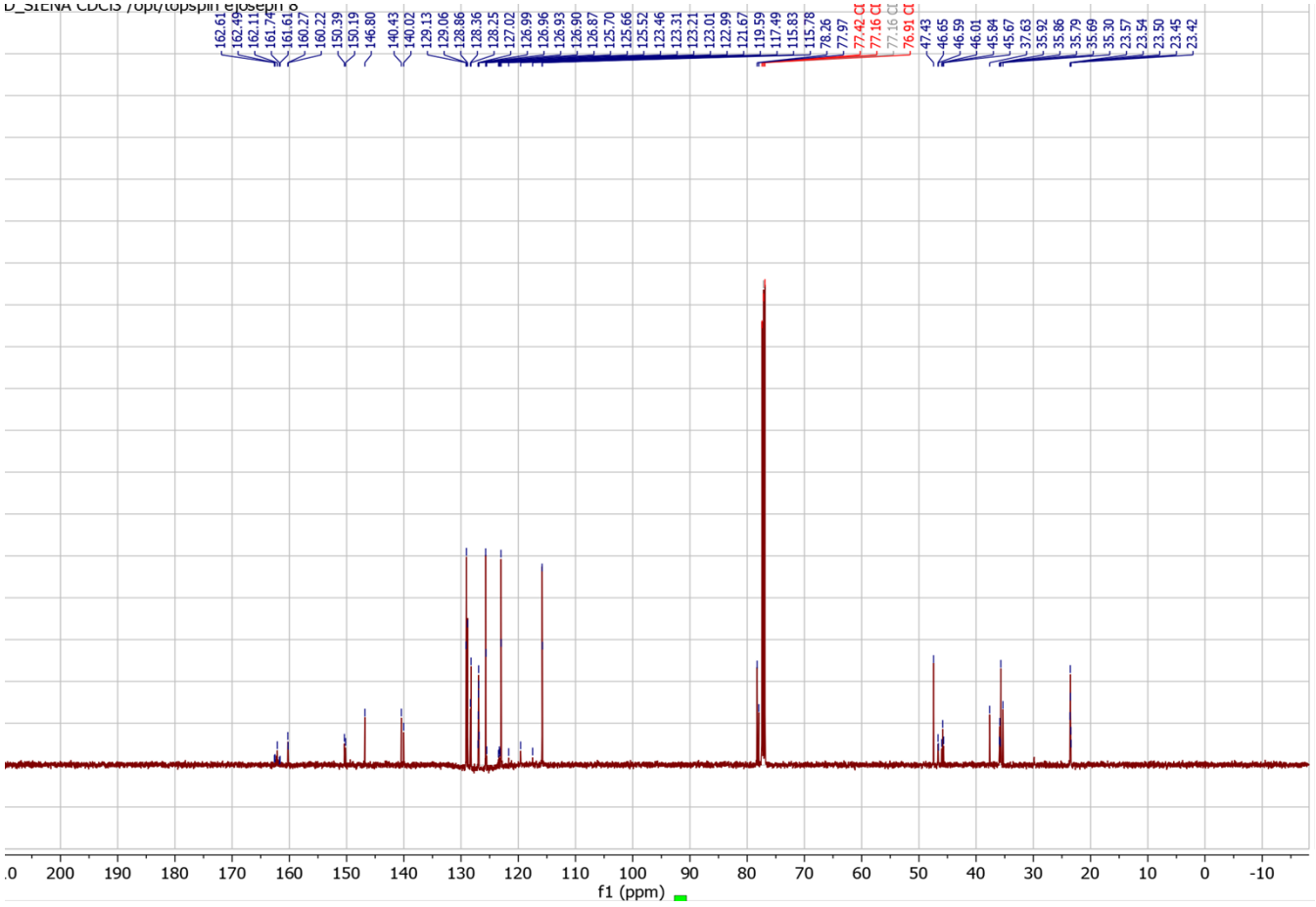
^{1}H NMR spectrum of 3v (400 MHz, Chloroform-d)

^{13}C NMR spectrum of 3v (126 MHz, Chloroform-*d*)

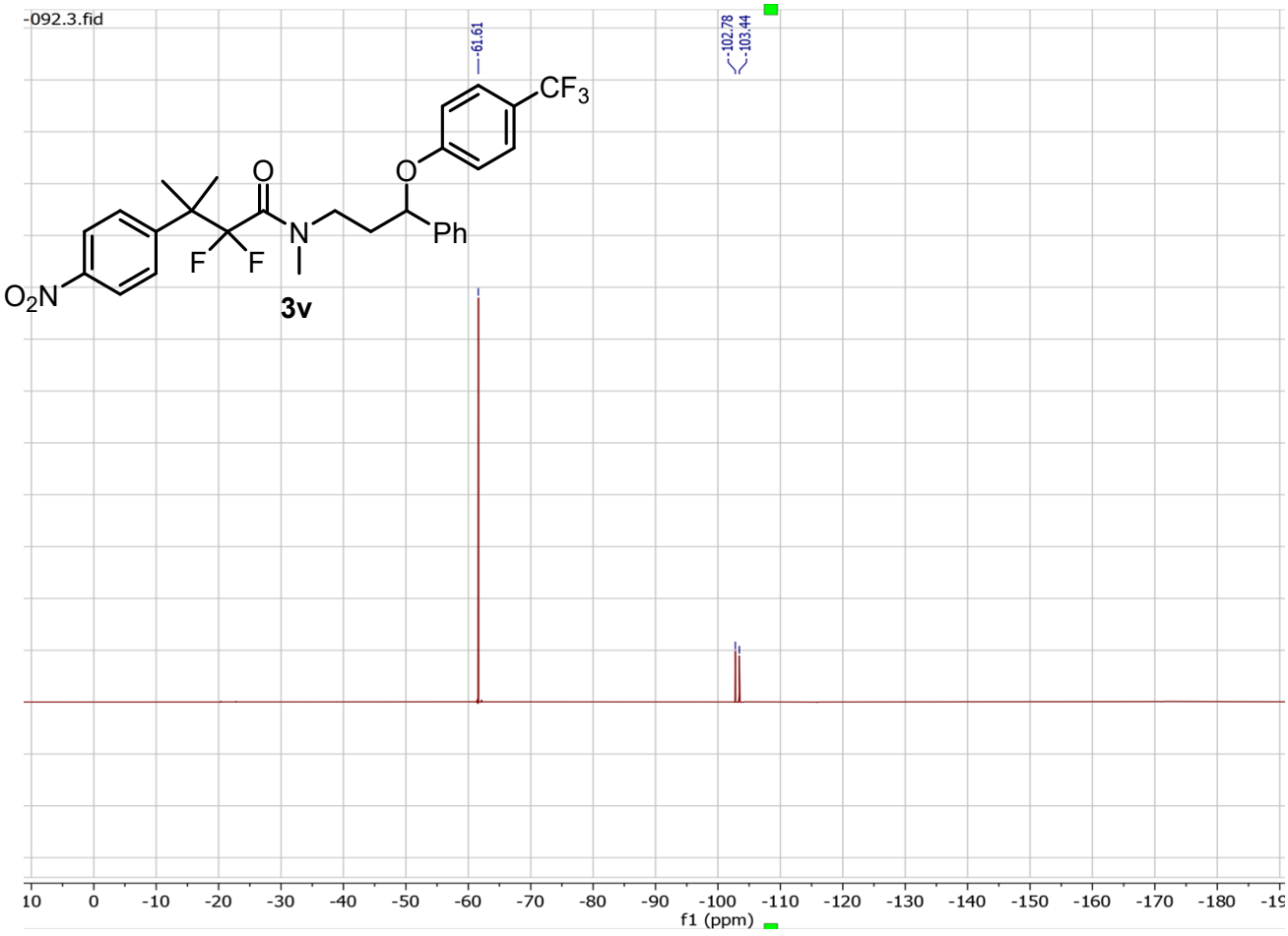


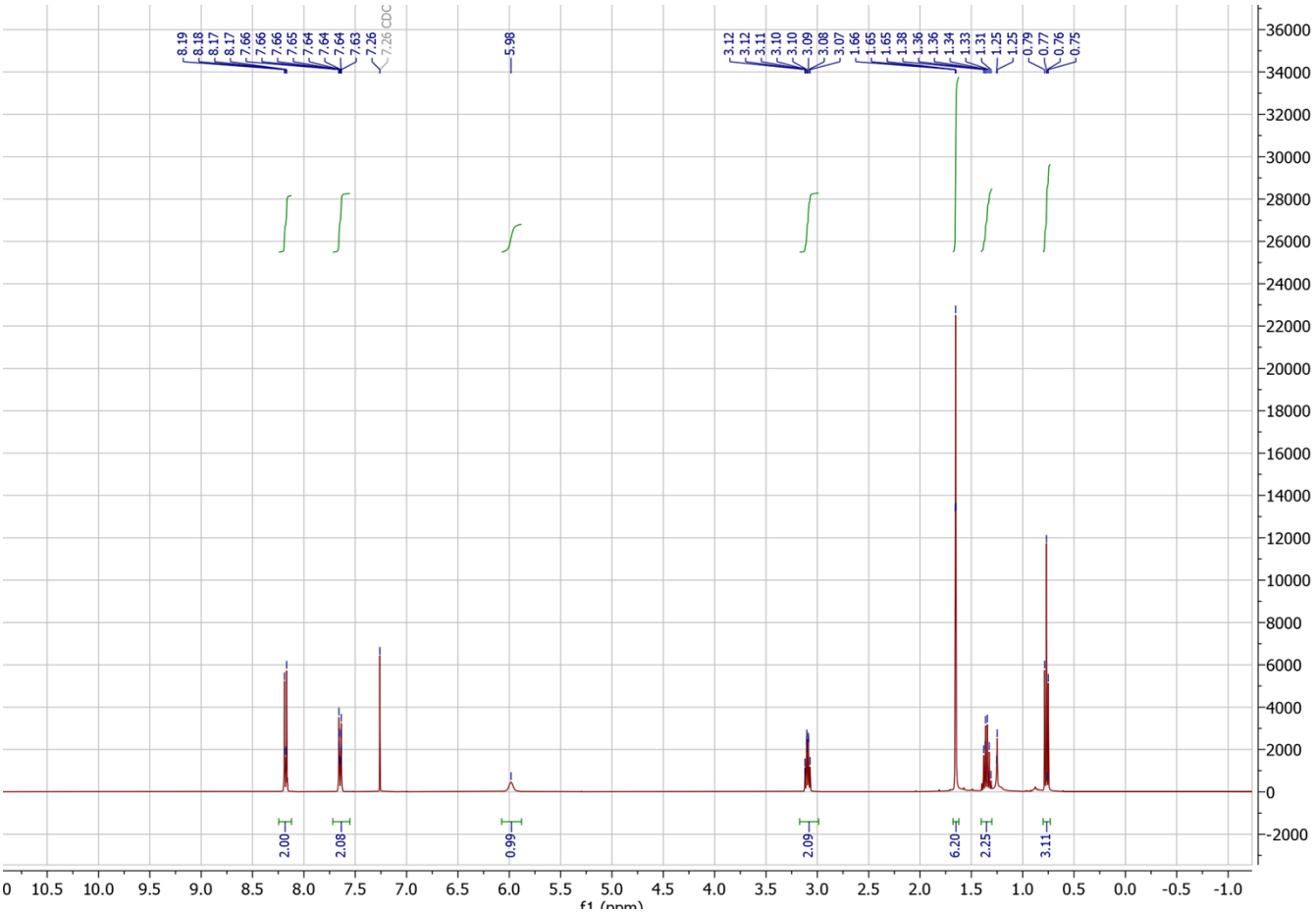
3v





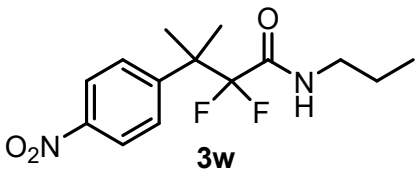
^{19}F NMR spectrum of 3v (376 MHz, Chloroform-*d*)



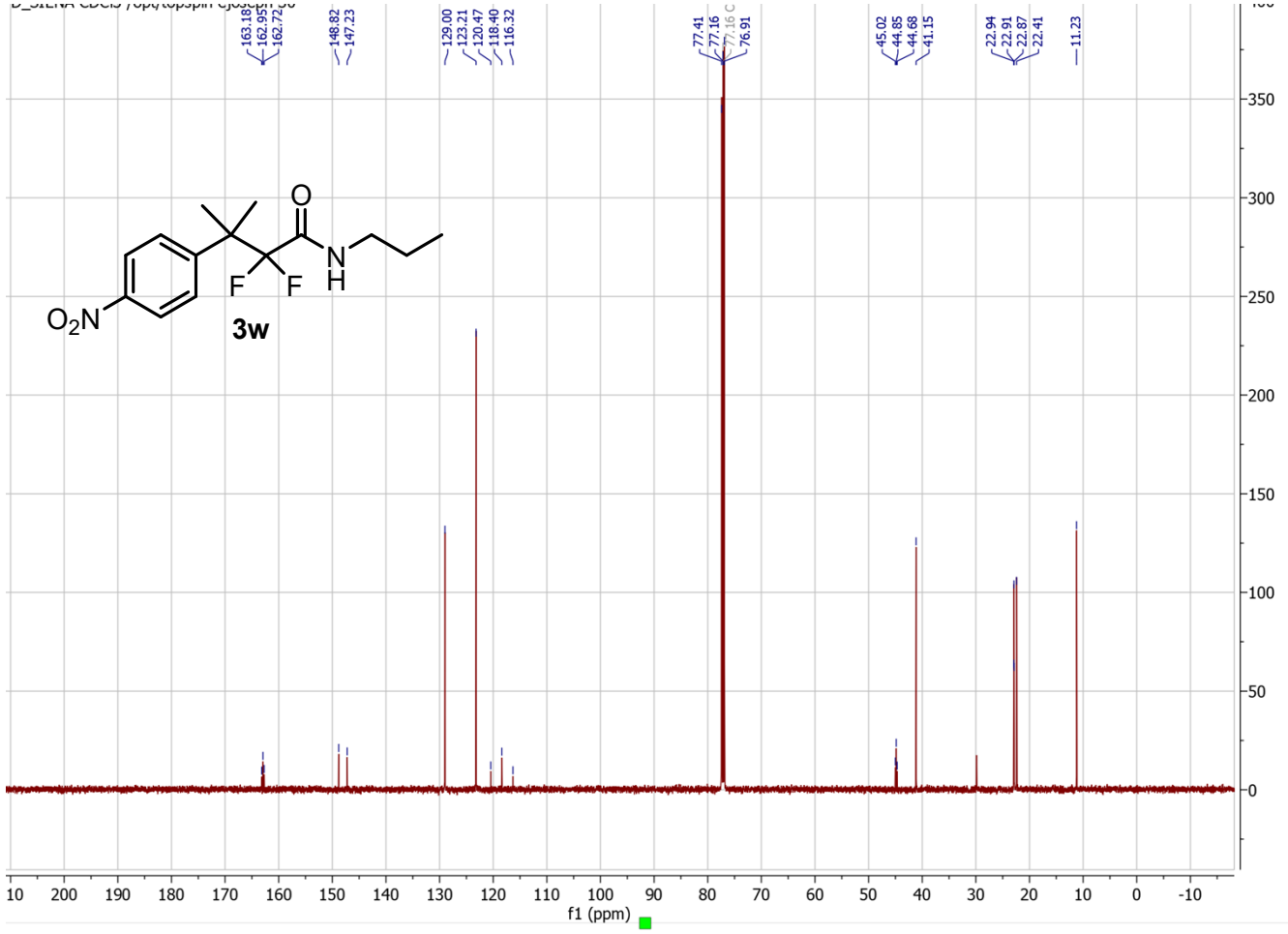


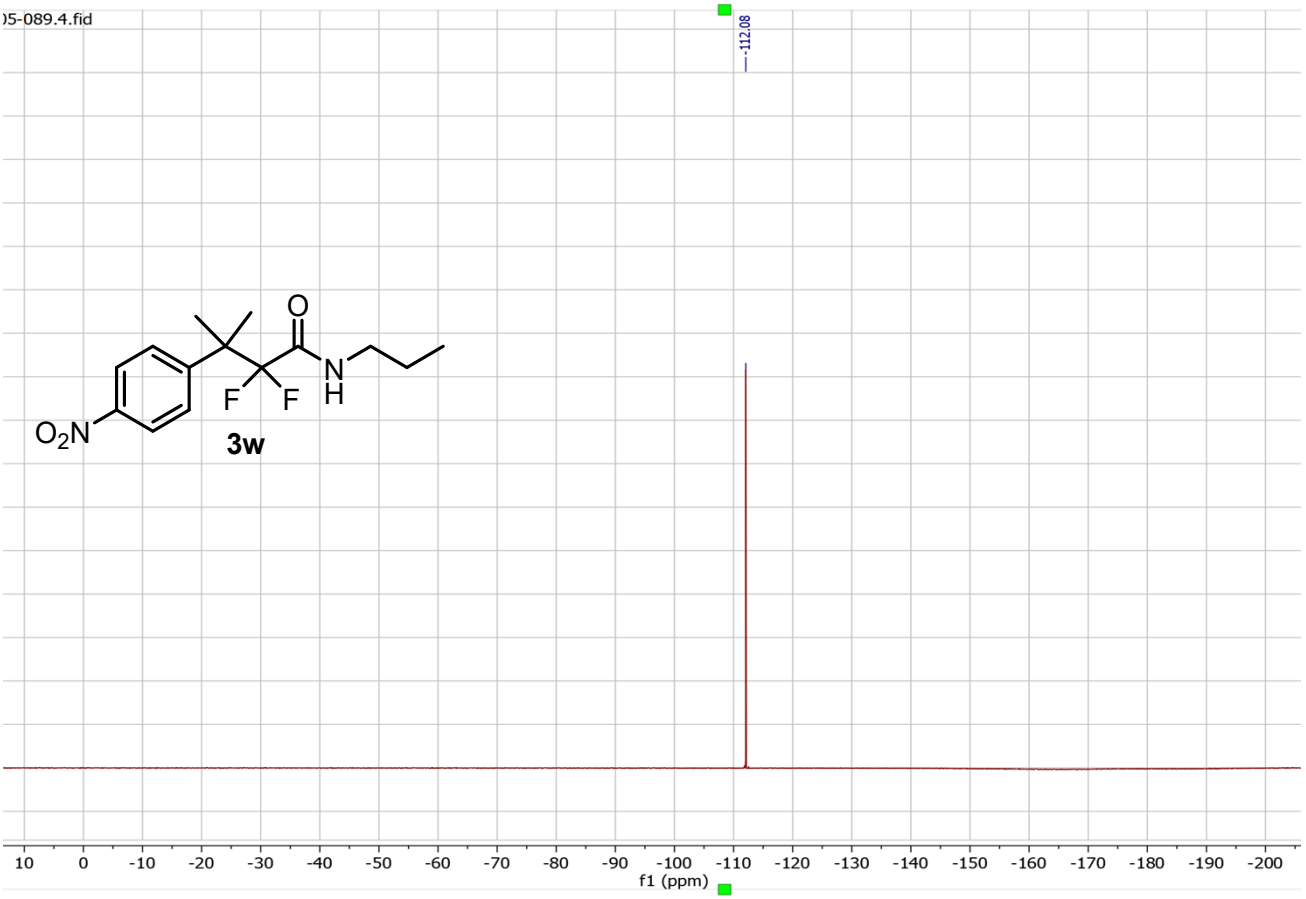
^{1}H NMR spectrum of 3w (400 MHz, Chloroform-d)

^{13}C NMR spectrum of 3w (126 MHz, Chloroform-*d*)

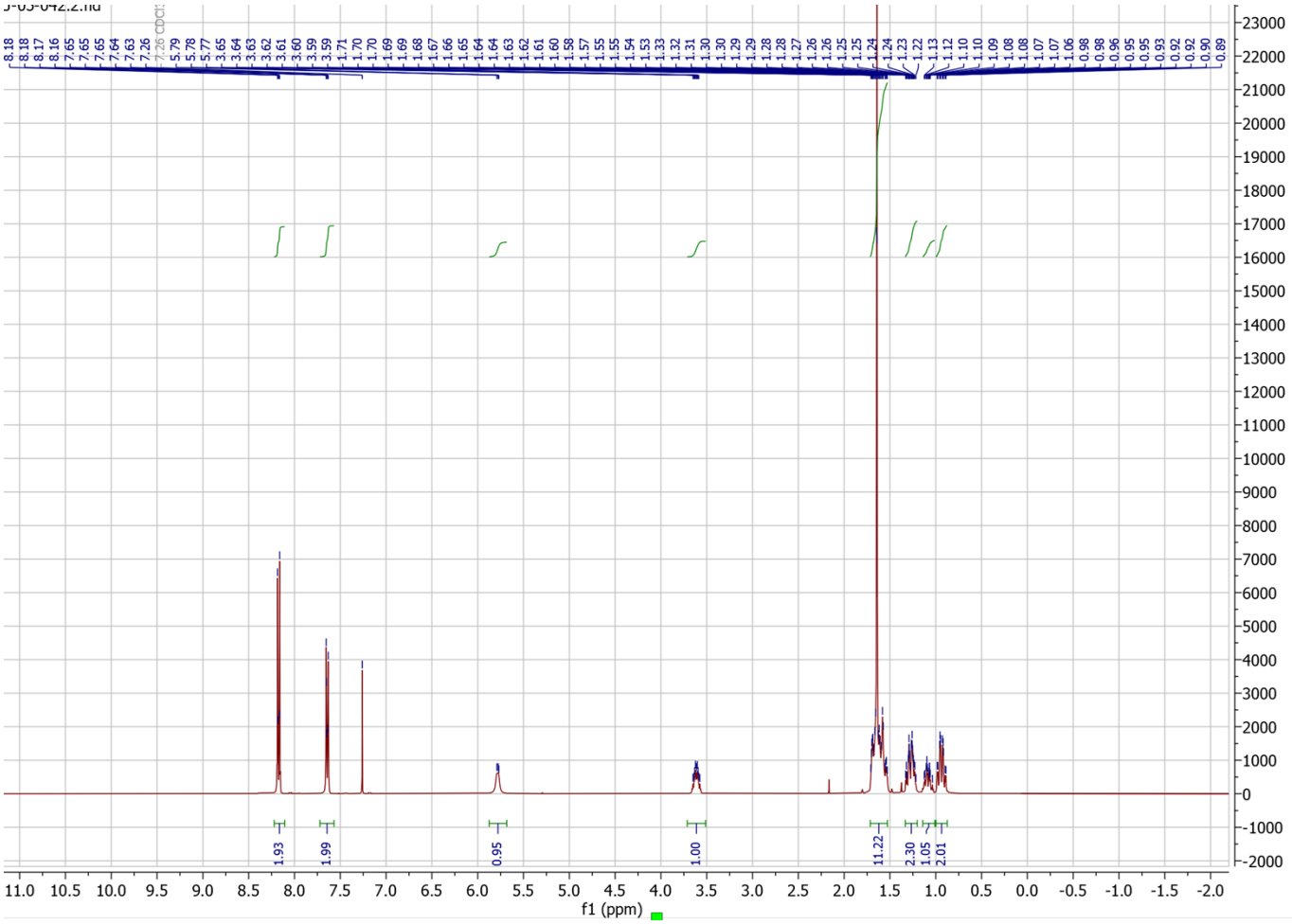


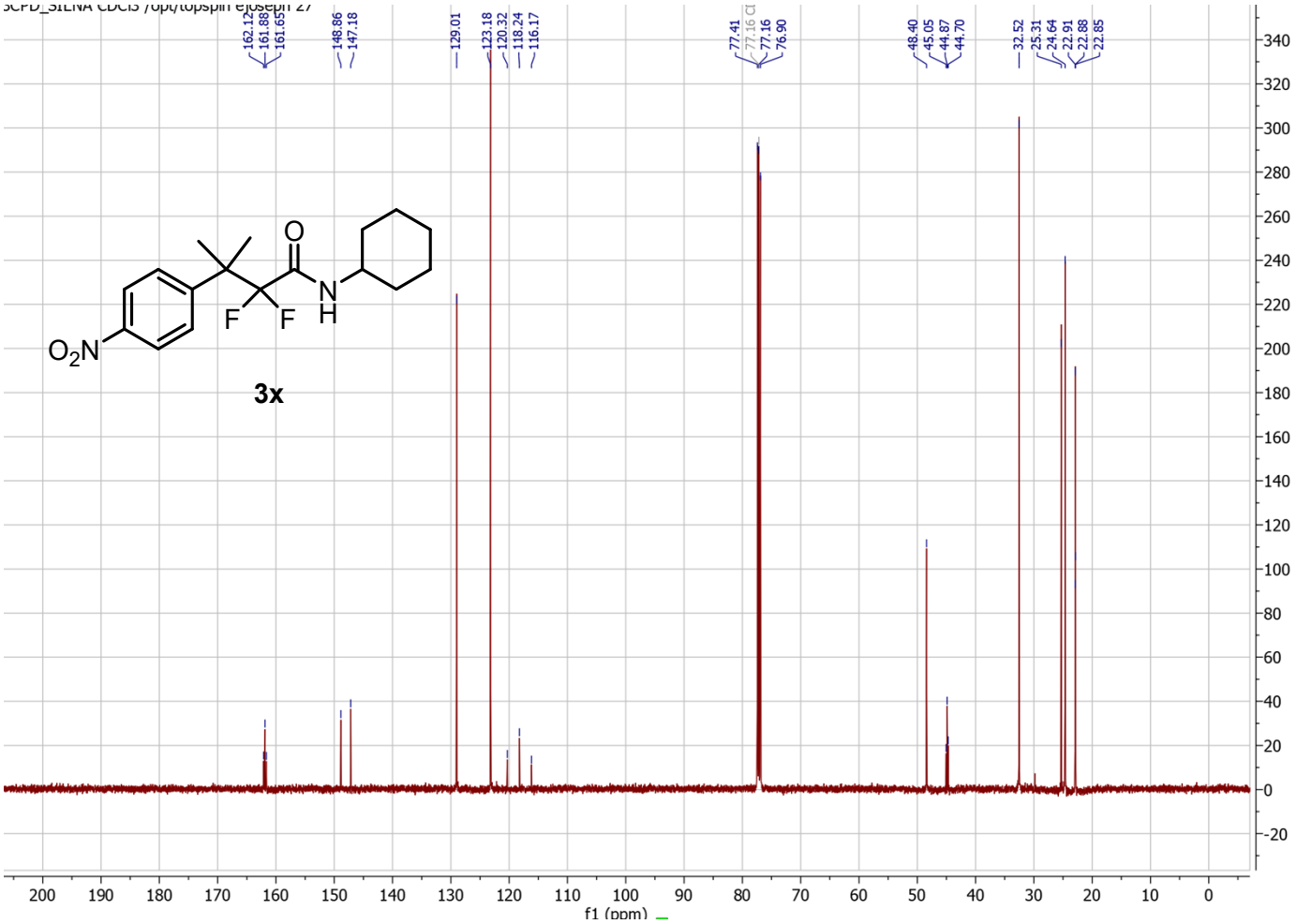
3w





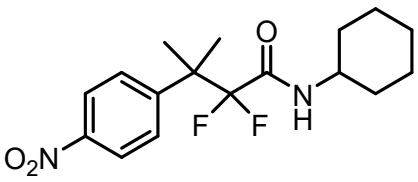
^{19}F NMR spectrum of 3w (376 MHz, Chloroform-*d*)





^{1}H NMR spectrum of 3x (400 MHz, Chloroform-d)

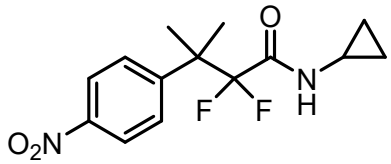
^{13}C NMR spectrum of 3x (126 MHz, Chloroform-*d*)



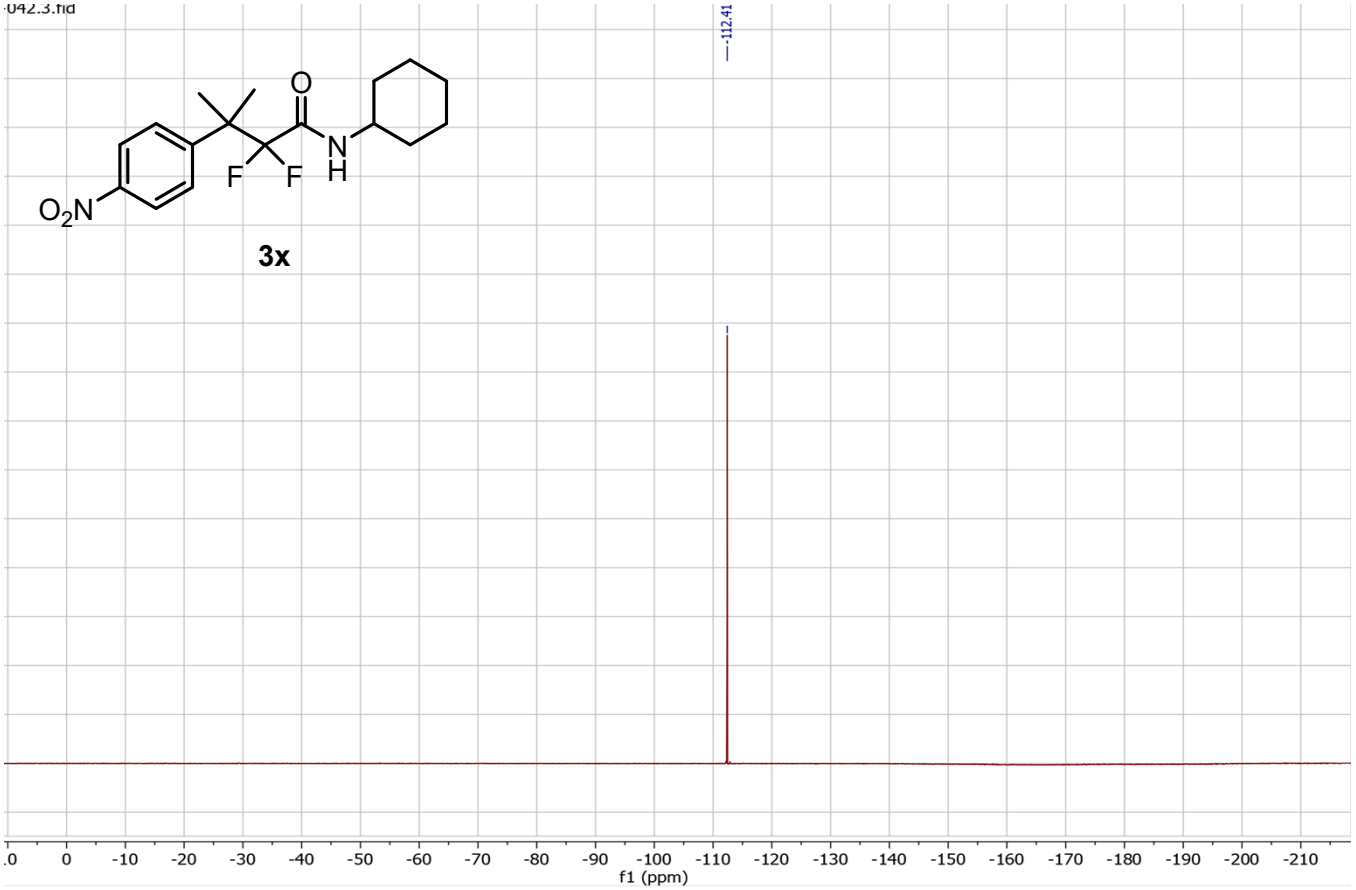
3x

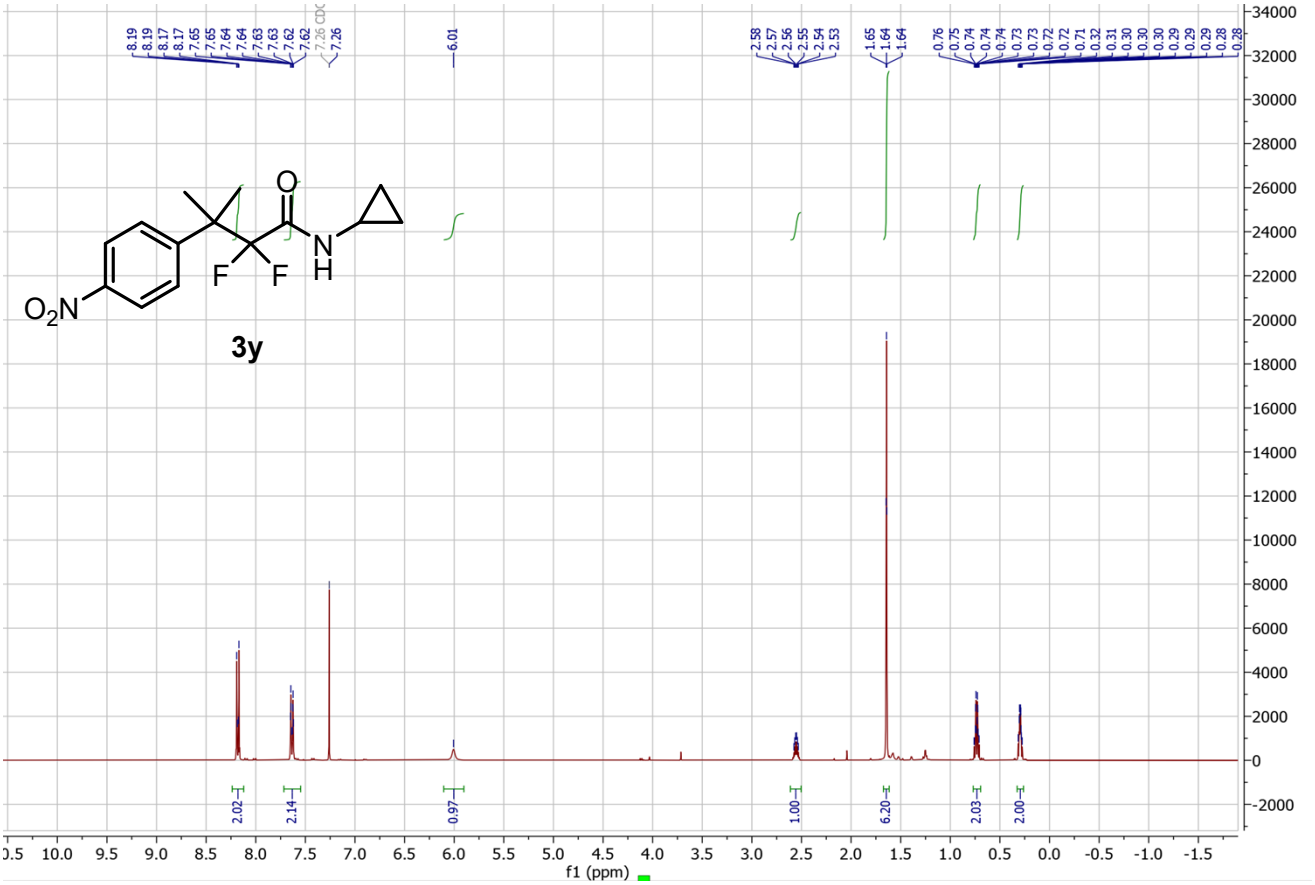
^{19}F NMR spectrum of 3x (376 MHz, Chloroform-*d*)

^{1}H NMR spectrum of 3y (400 MHz, Chloroform-d)

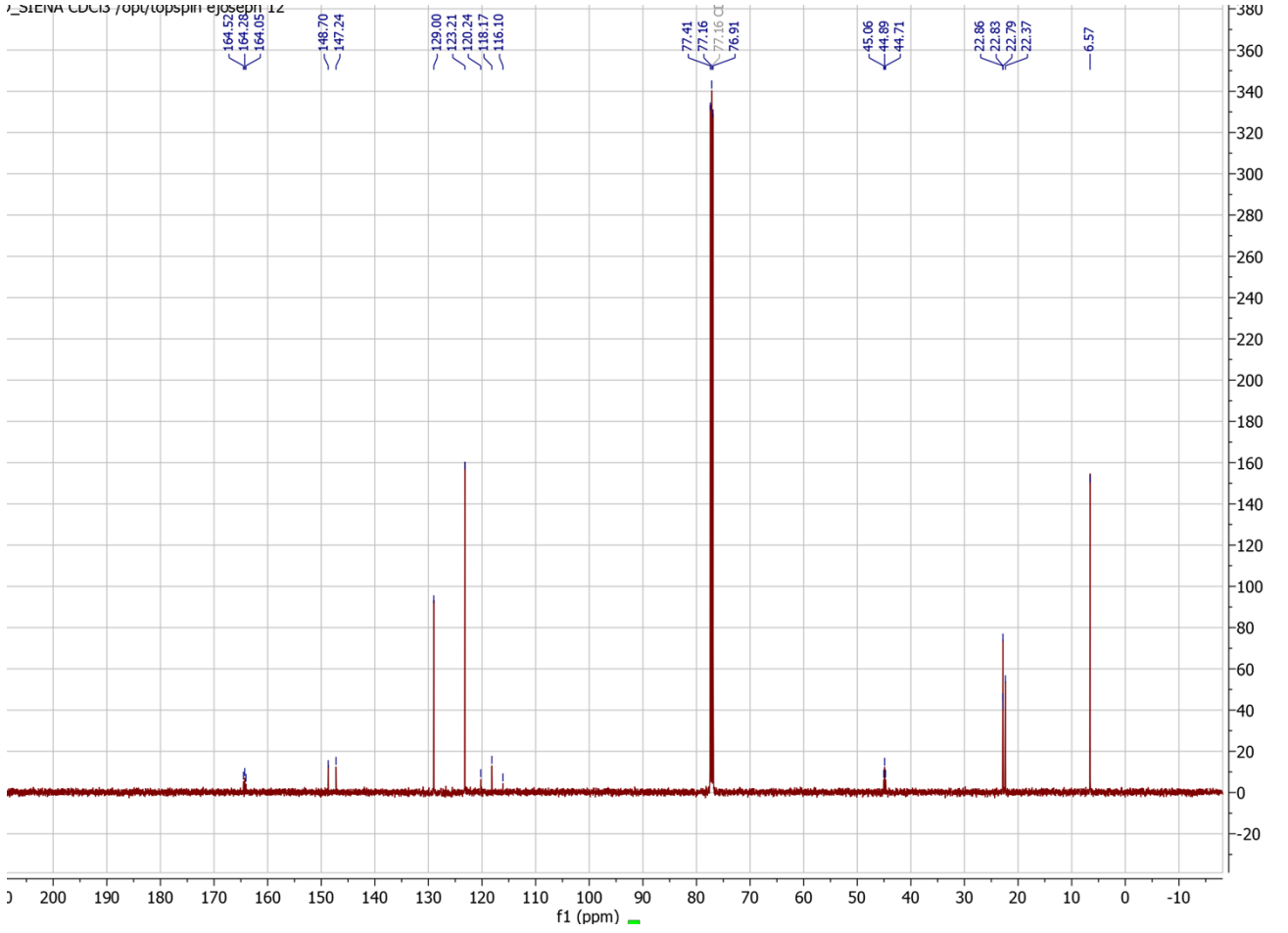


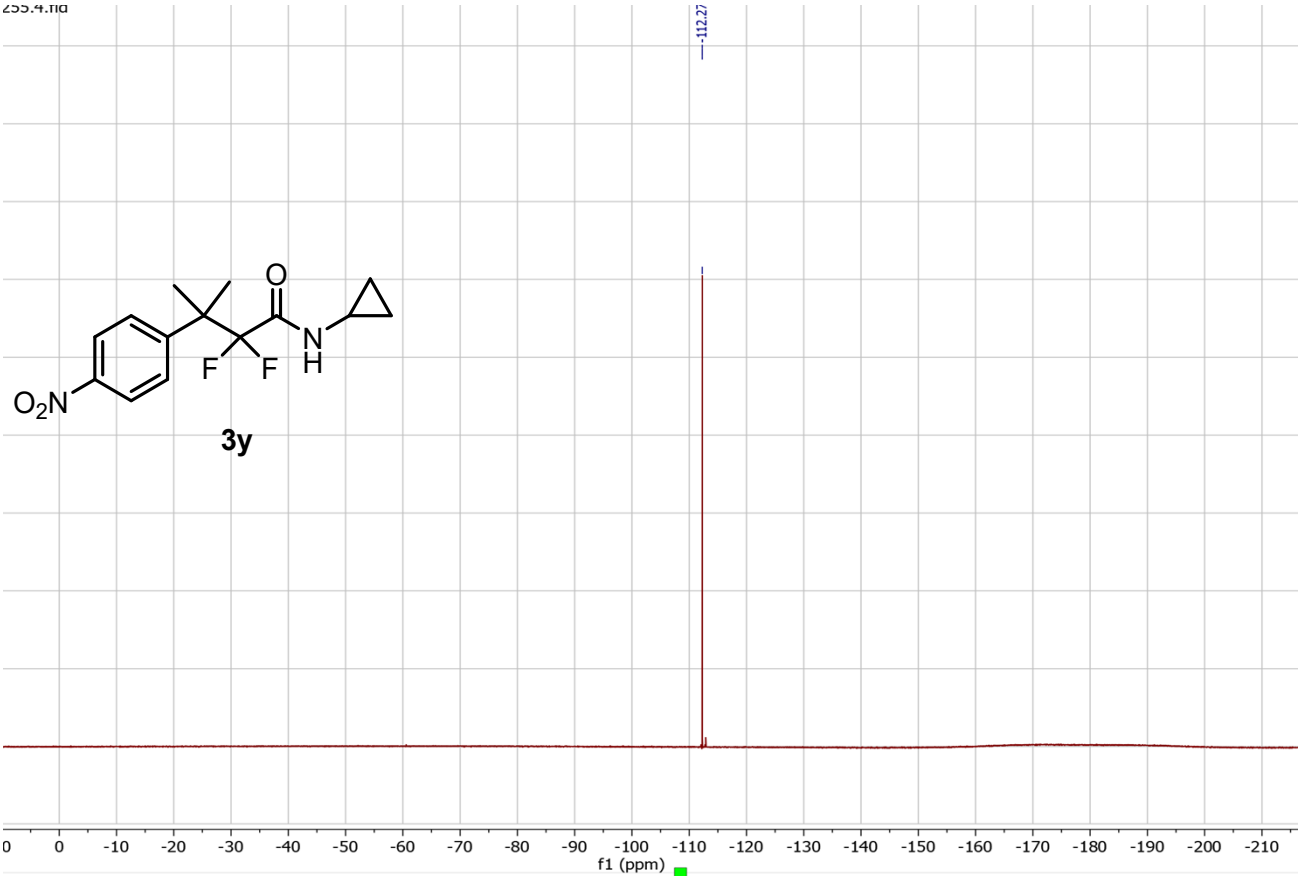
3y





^{13}C NMR spectrum of 3y (126 MHz, Chloroform-*d*)

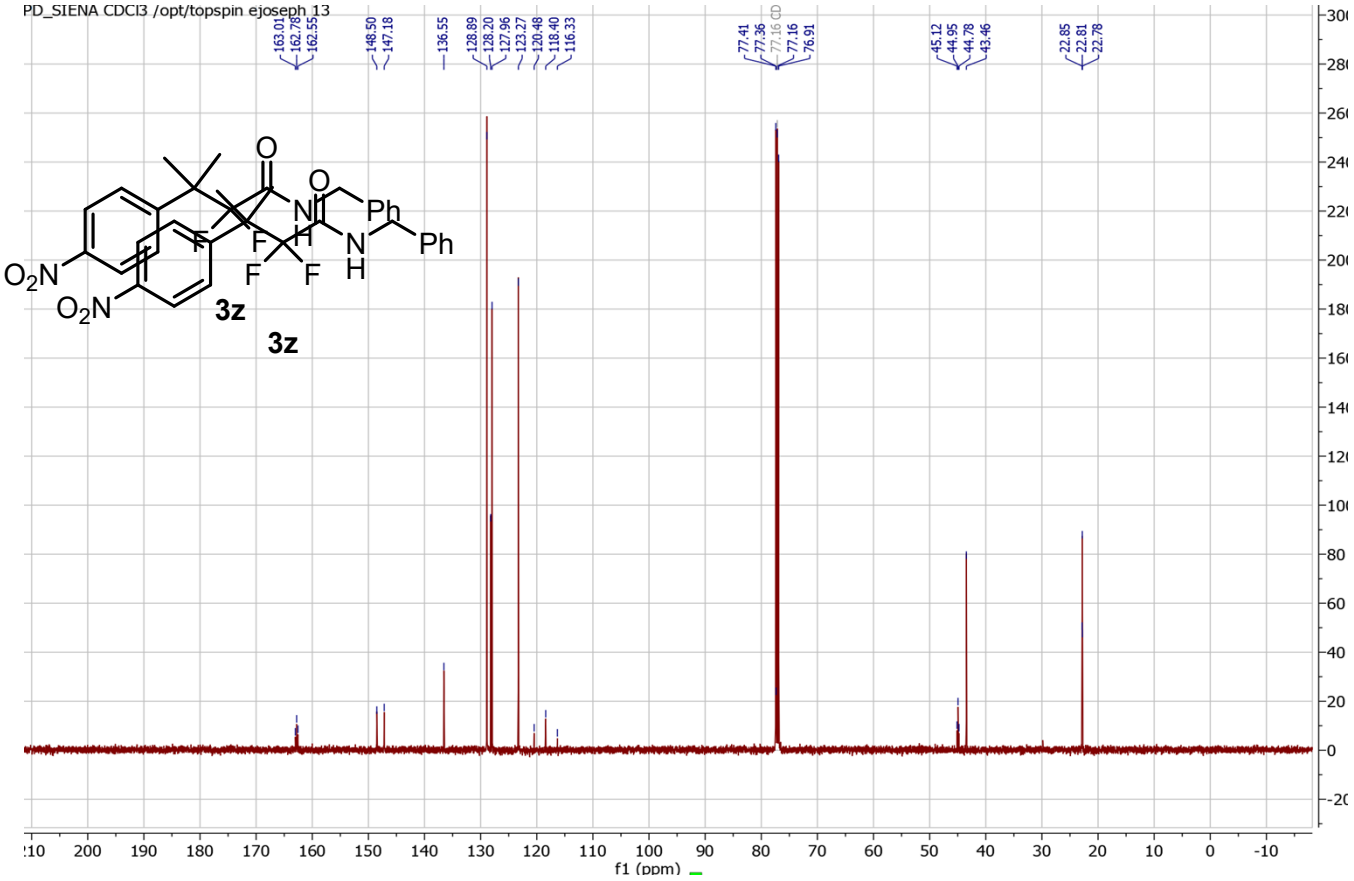


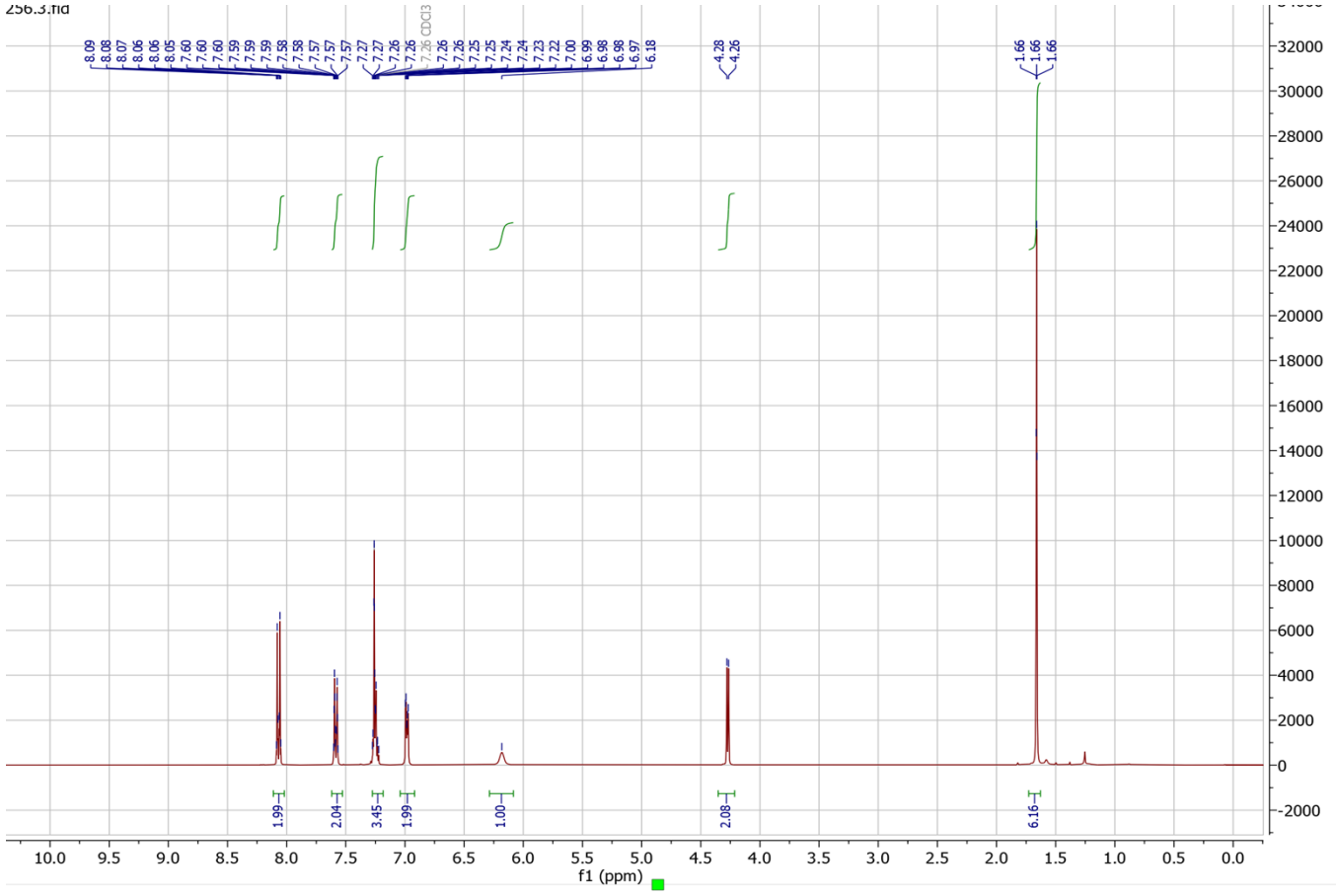


^{19}F NMR spectrum of 3y (376 MHz, Chloroform-*d*)

^{1}H NMR spectrum of 3z (400 MHz, Chloroform-d)

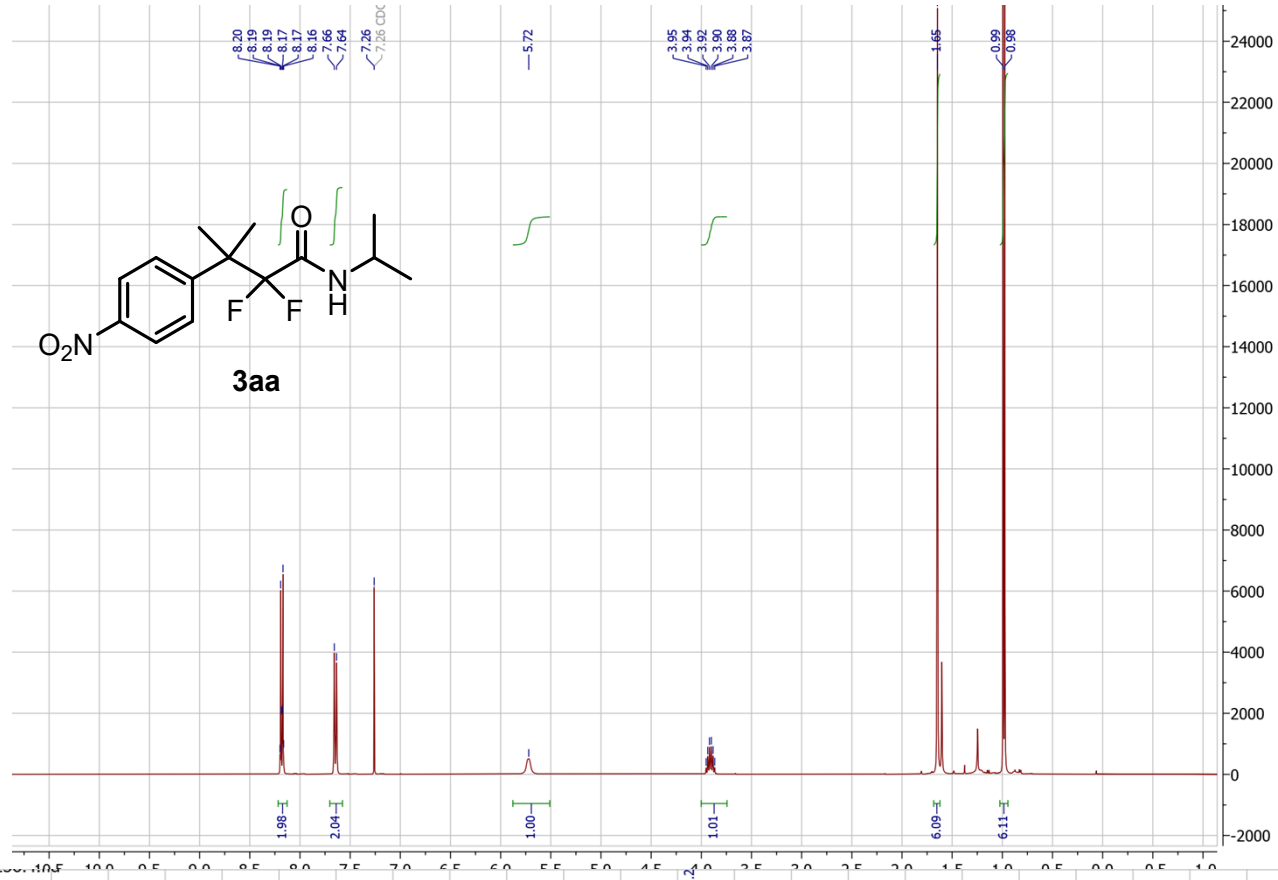
^{13}C NMR spectrum of 3z (126 MHz, Chloroform-*d*)

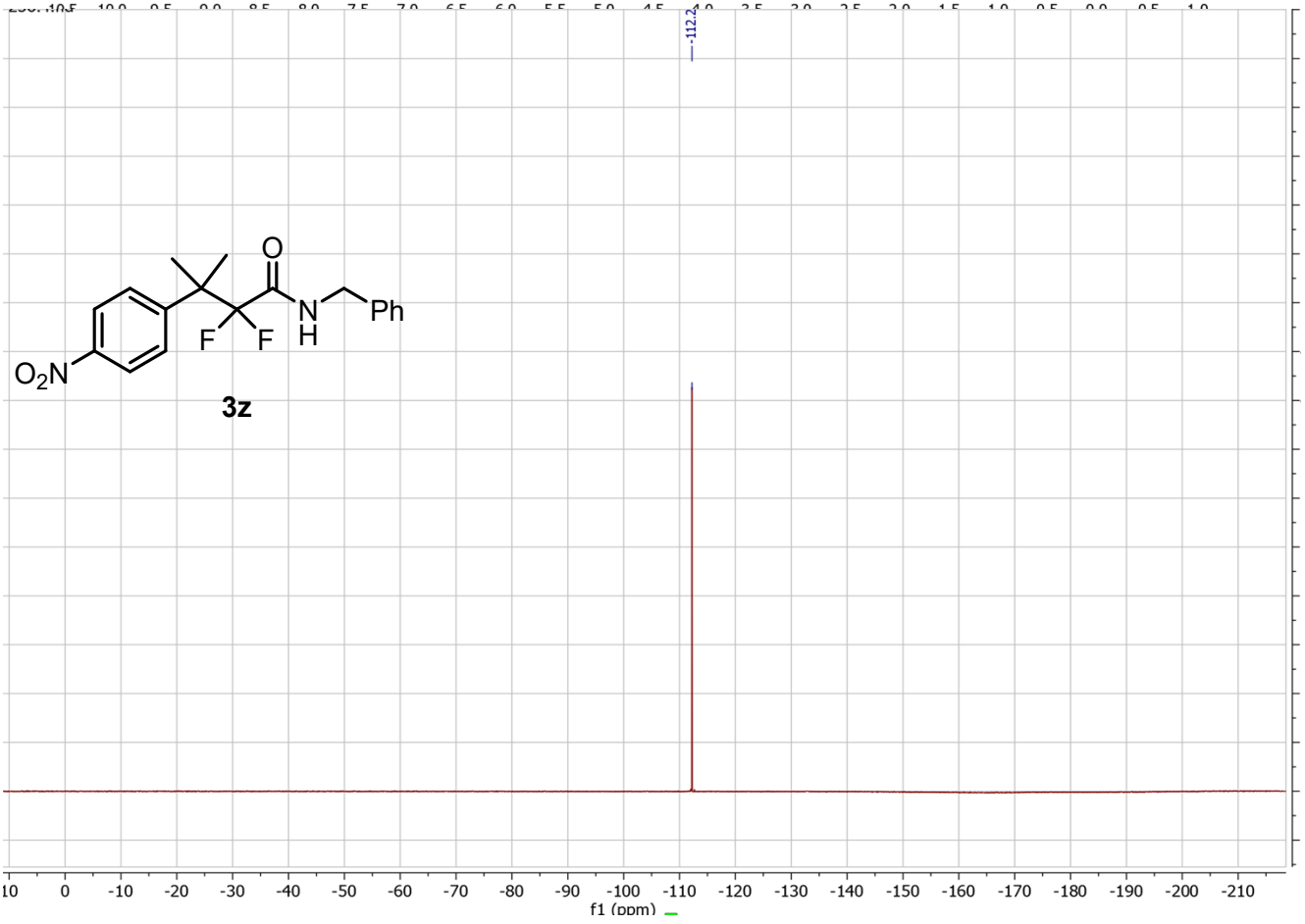




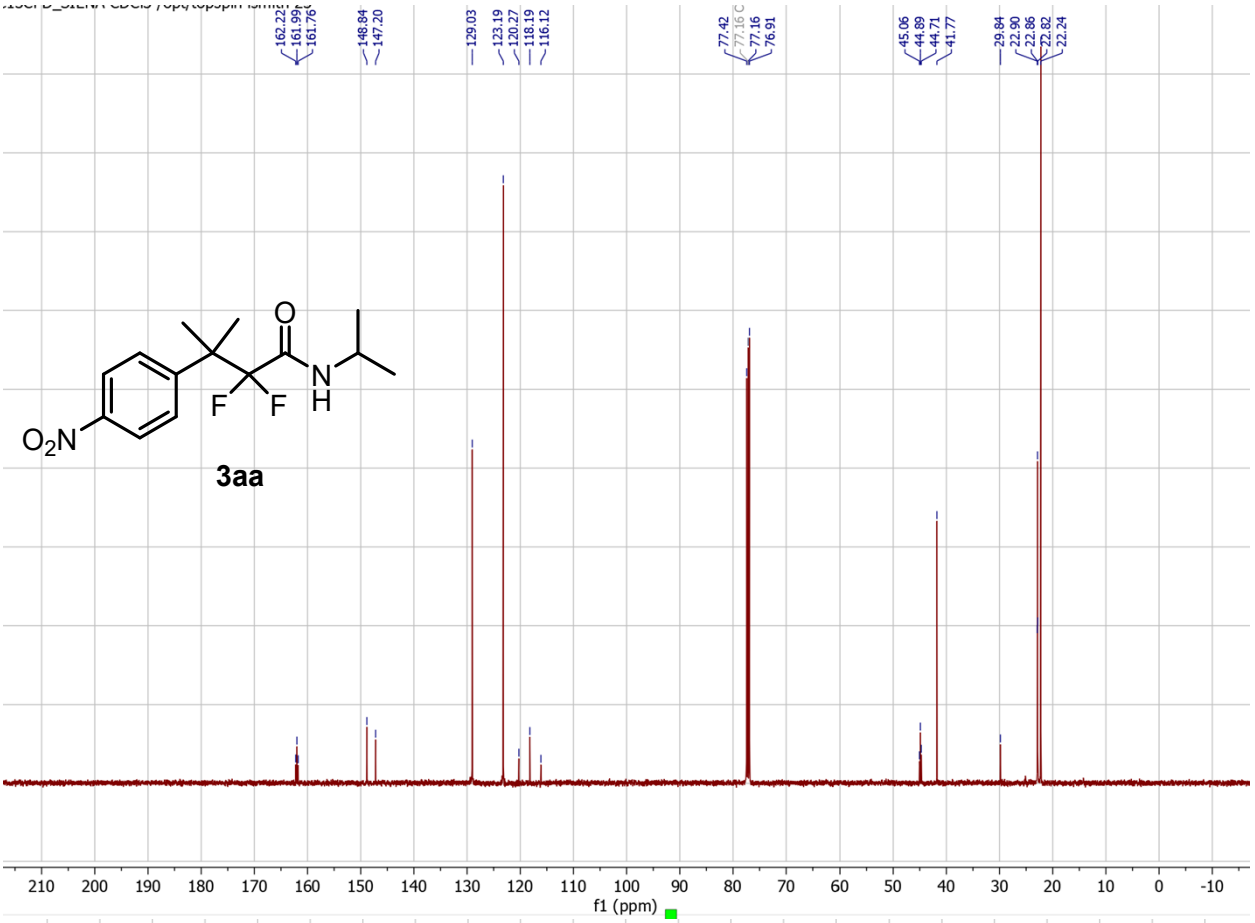
^{19}F NMR spectrum of 3z (376 MHz, Chloroform-*d*)

^{1}H NMR spectrum of 3aa (400 MHz, Chloroform-d)



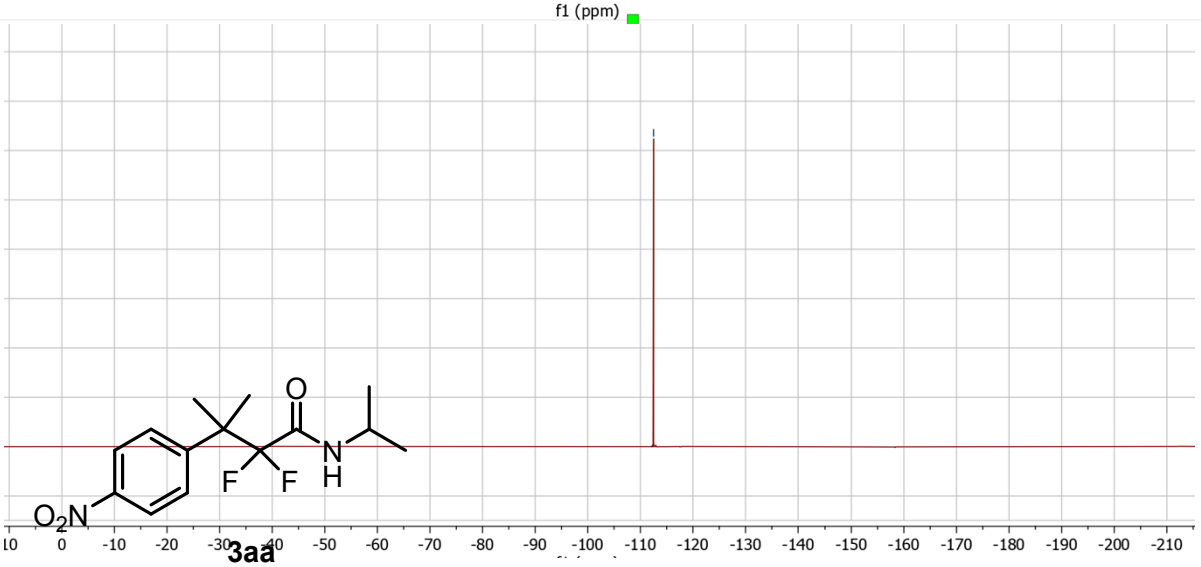


^{13}C NMR spectrum of 3aa (126 MHz, Chloroform-*d*)

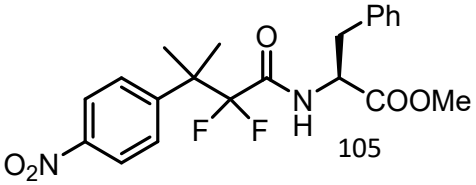


3aa

^{19}F NMR spectrum of 3aa (376 MHz, Chloroform-*d*)



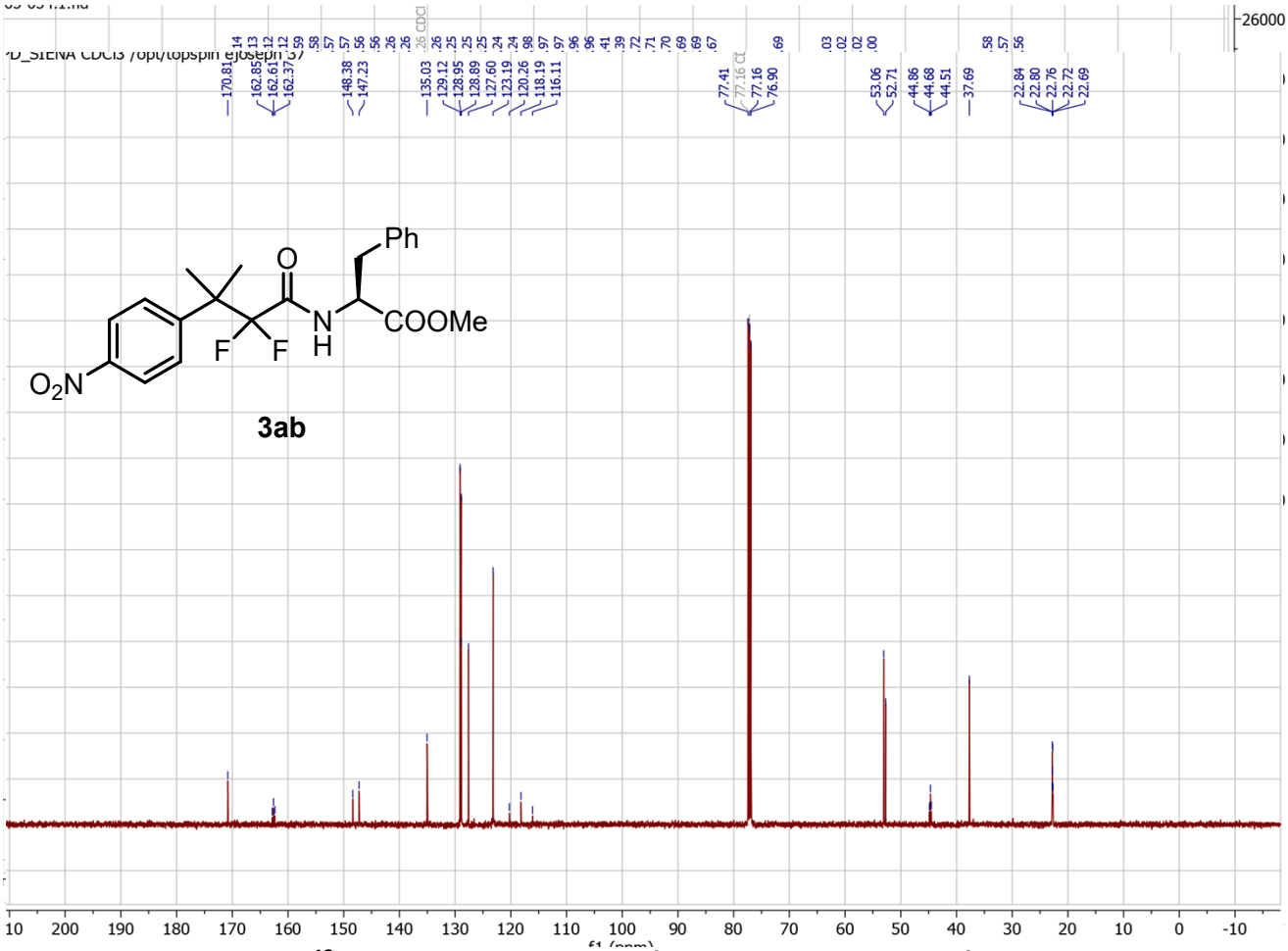
3aa



105

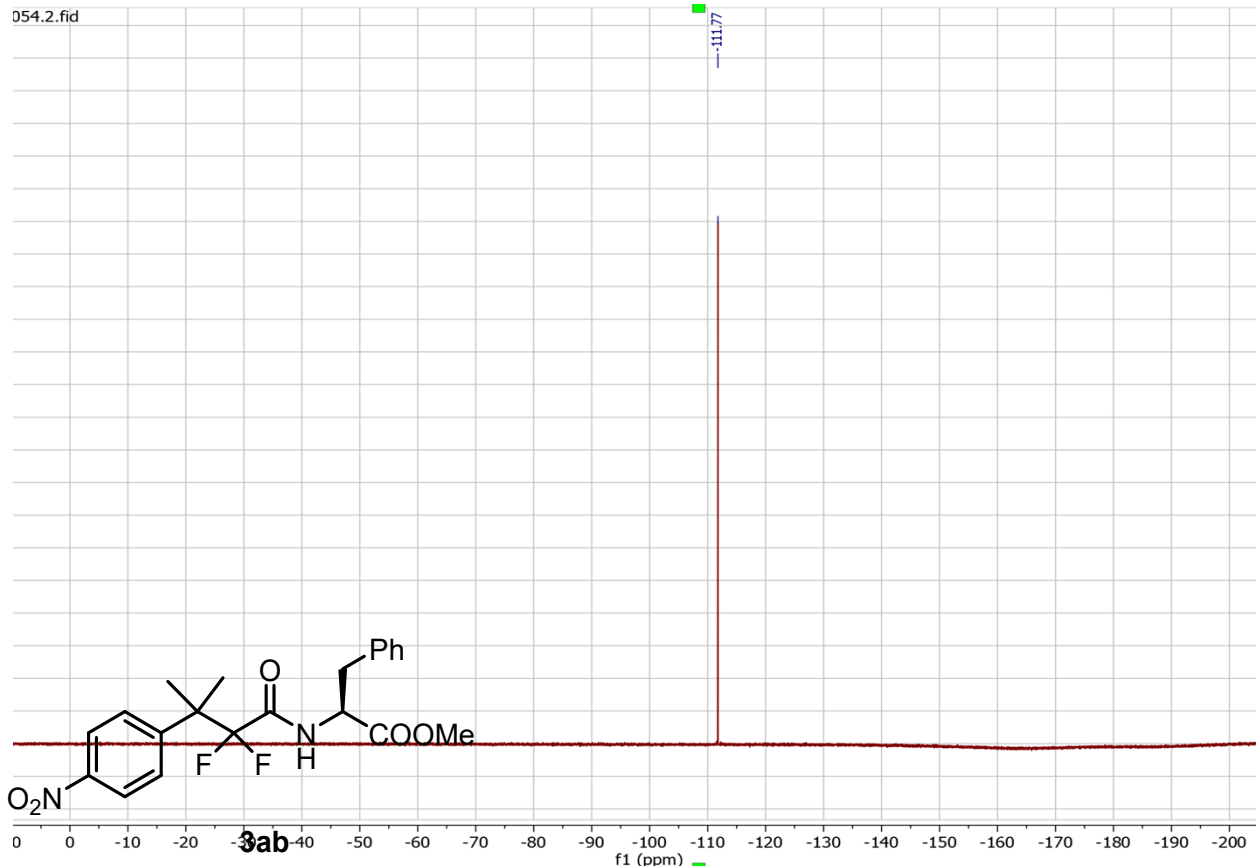
3ab

^{1}H NMR spectrum of 3ab (400 MHz, Chloroform-d)

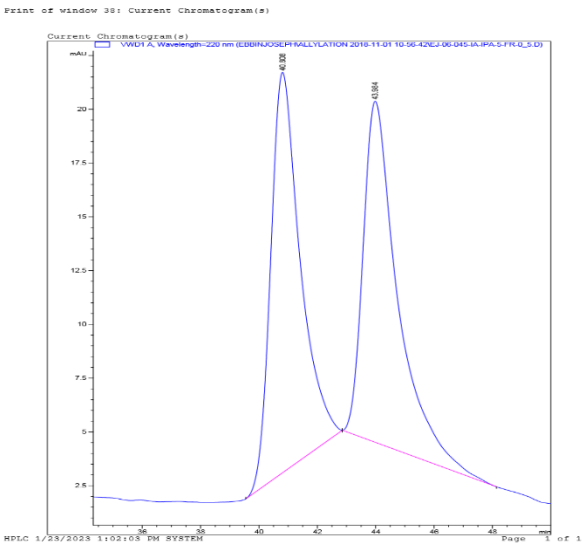


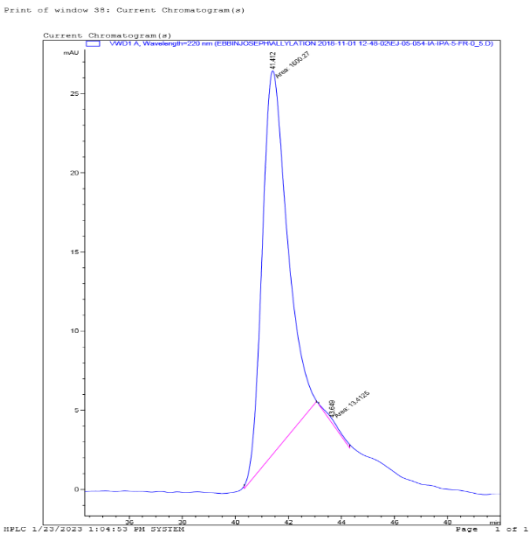
^{13}C NMR spectrum of 3ab (126 MHz, Chloroform-*d*)

^{19}F NMR spectrum of 3ab (376 MHz, Chloroform-*d*)



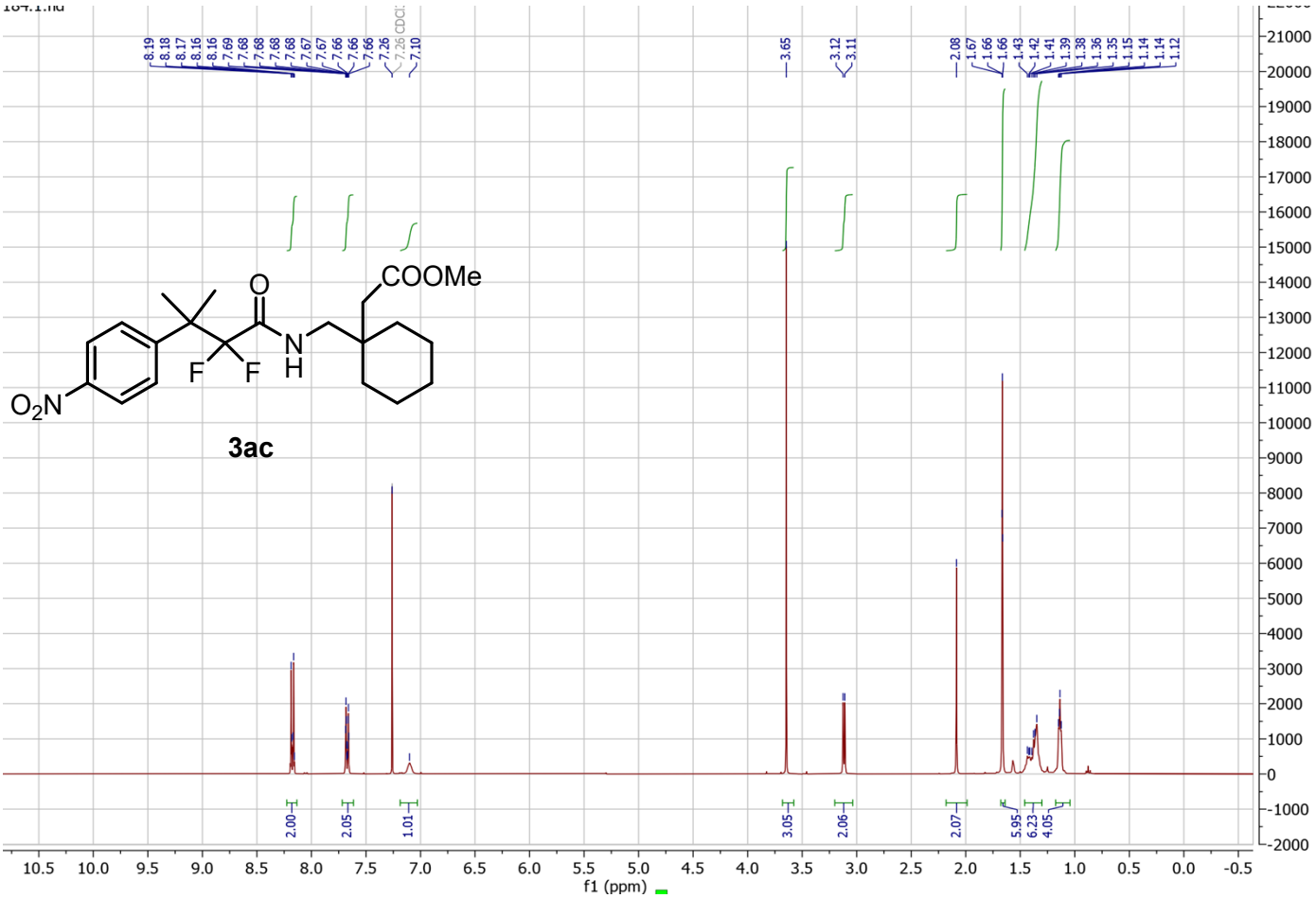
HPLC trace of Racemic and enantiopure 3ab



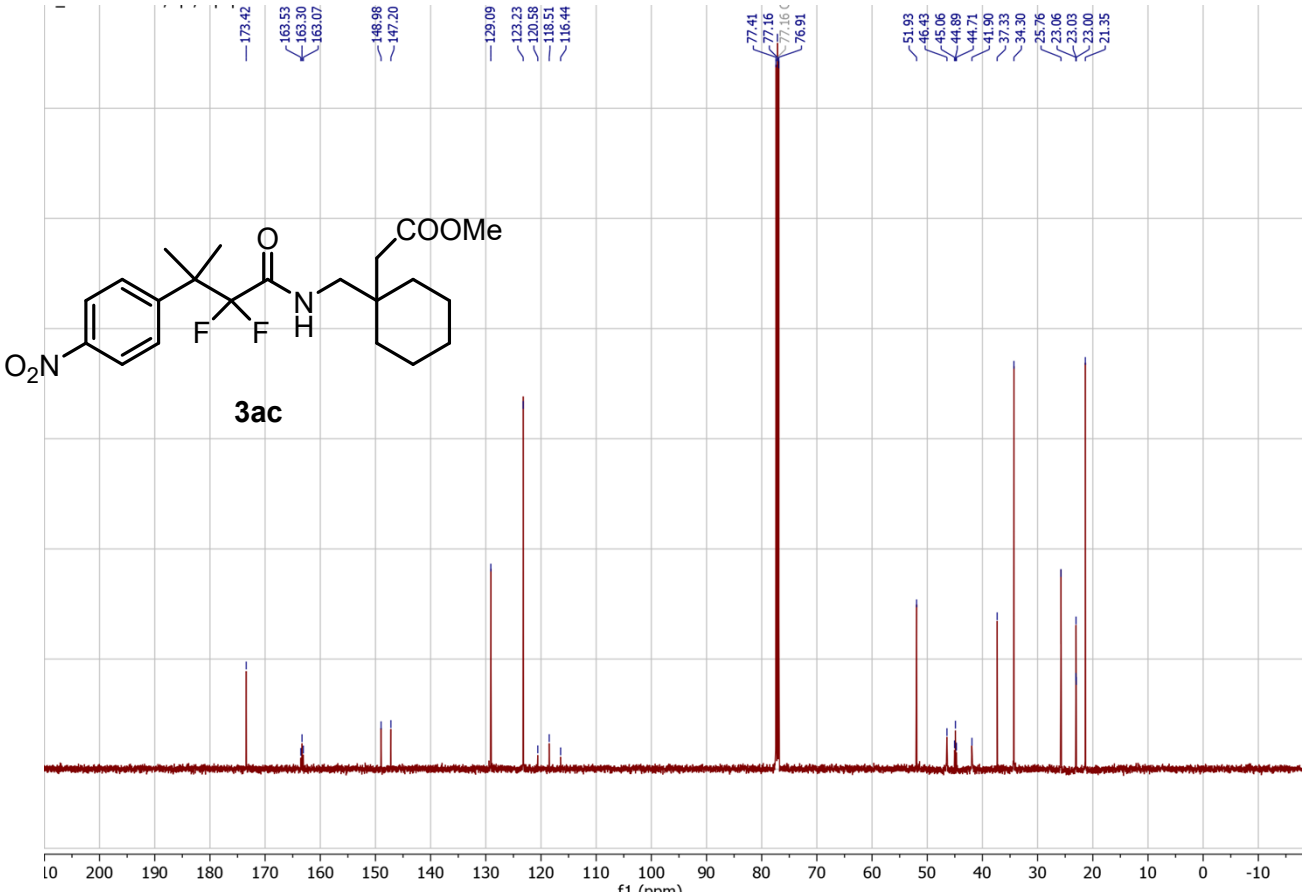


Peak	Retention time (mins)	Area (%)
1	40.8	50.170
2	43.9	49.830

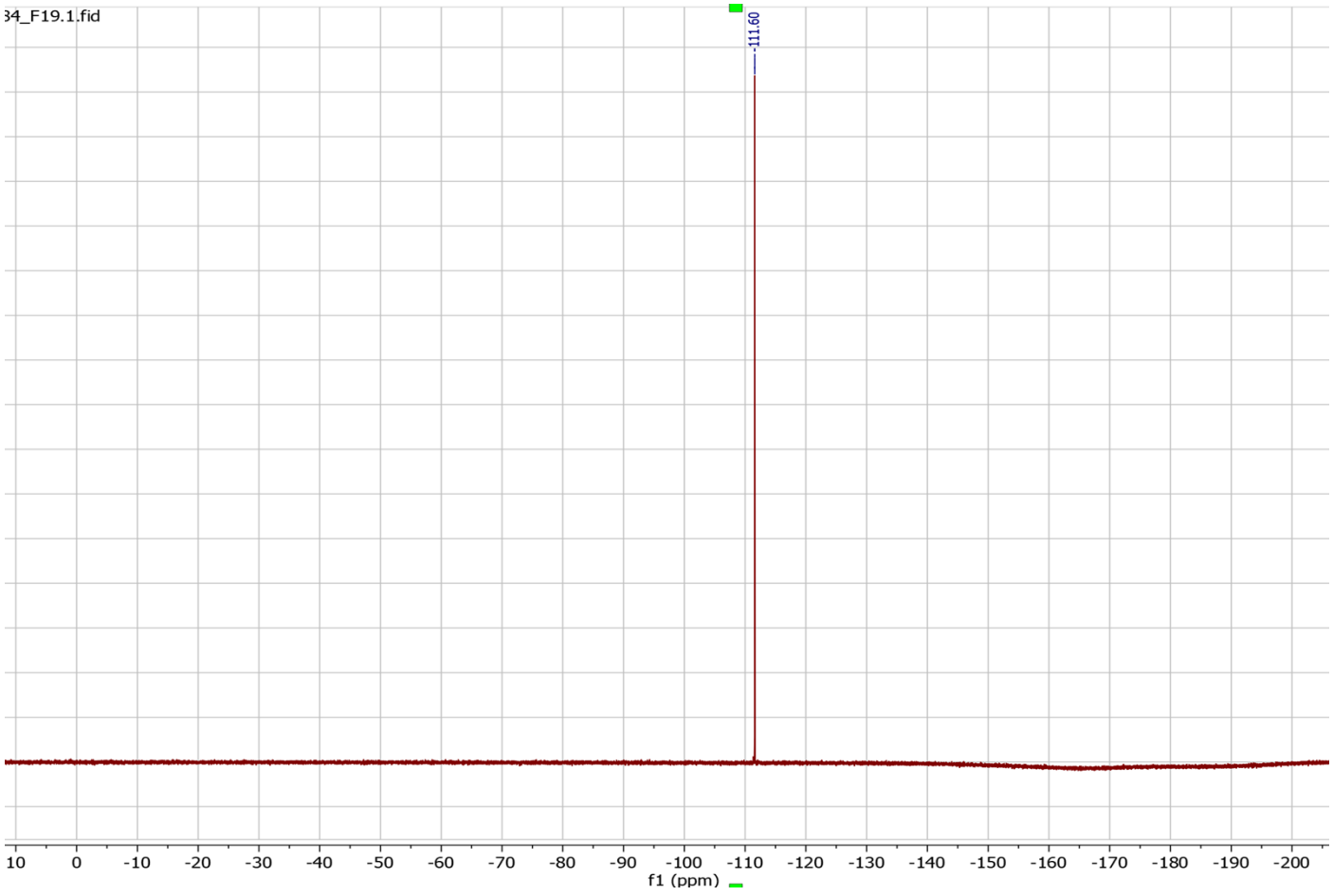
Peak	Retention time (mins)	Area (%)
1	41.1	99.168
2	43.6	0.831



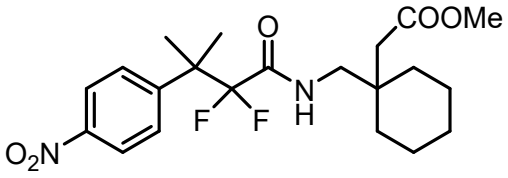
^{1}H NMR spectrum of 3ac (400 MHz, Chloroform-d)



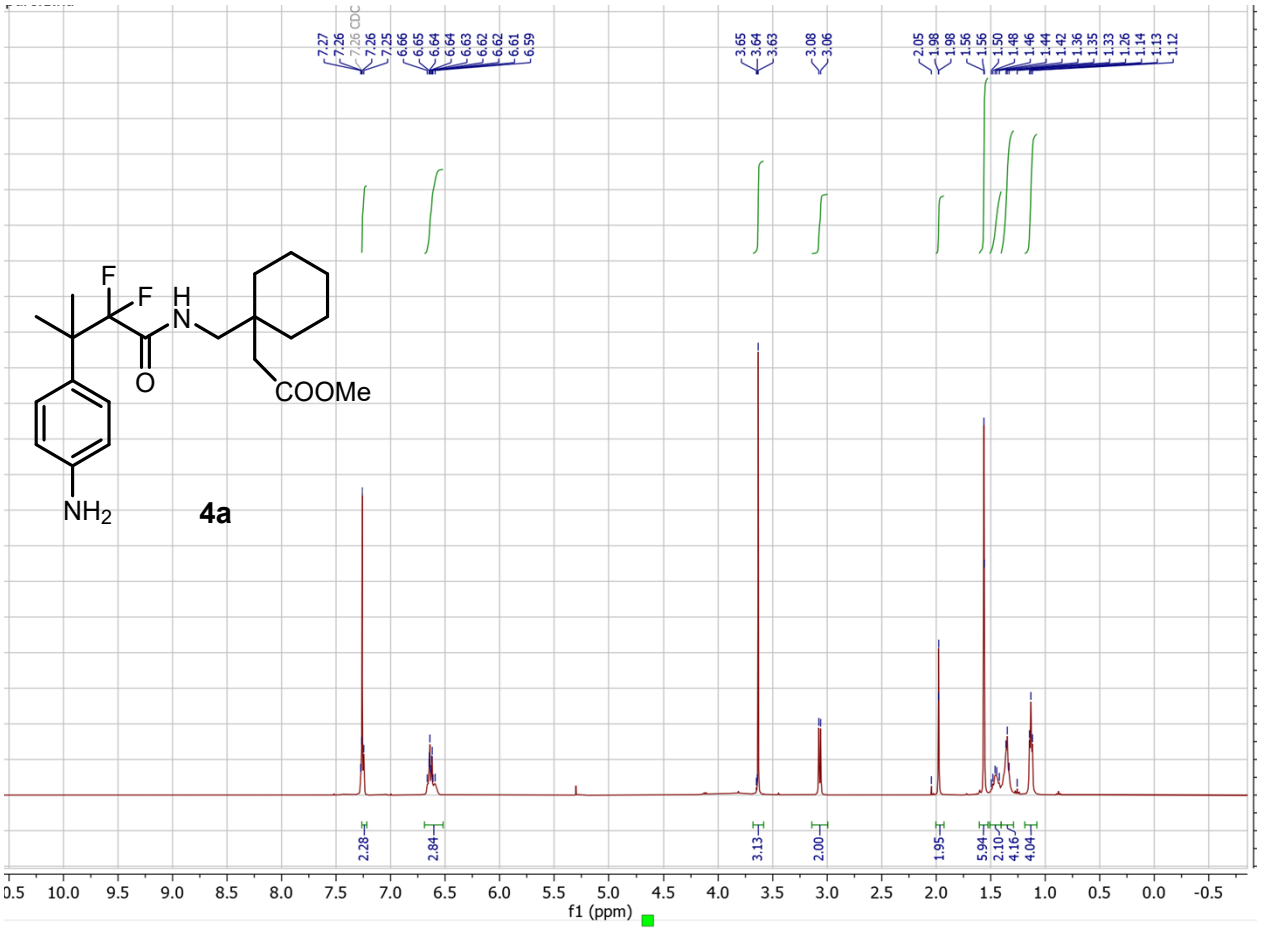
^{13}C NMR spectrum of 3ac (126 MHz, Chloroform-*d*)



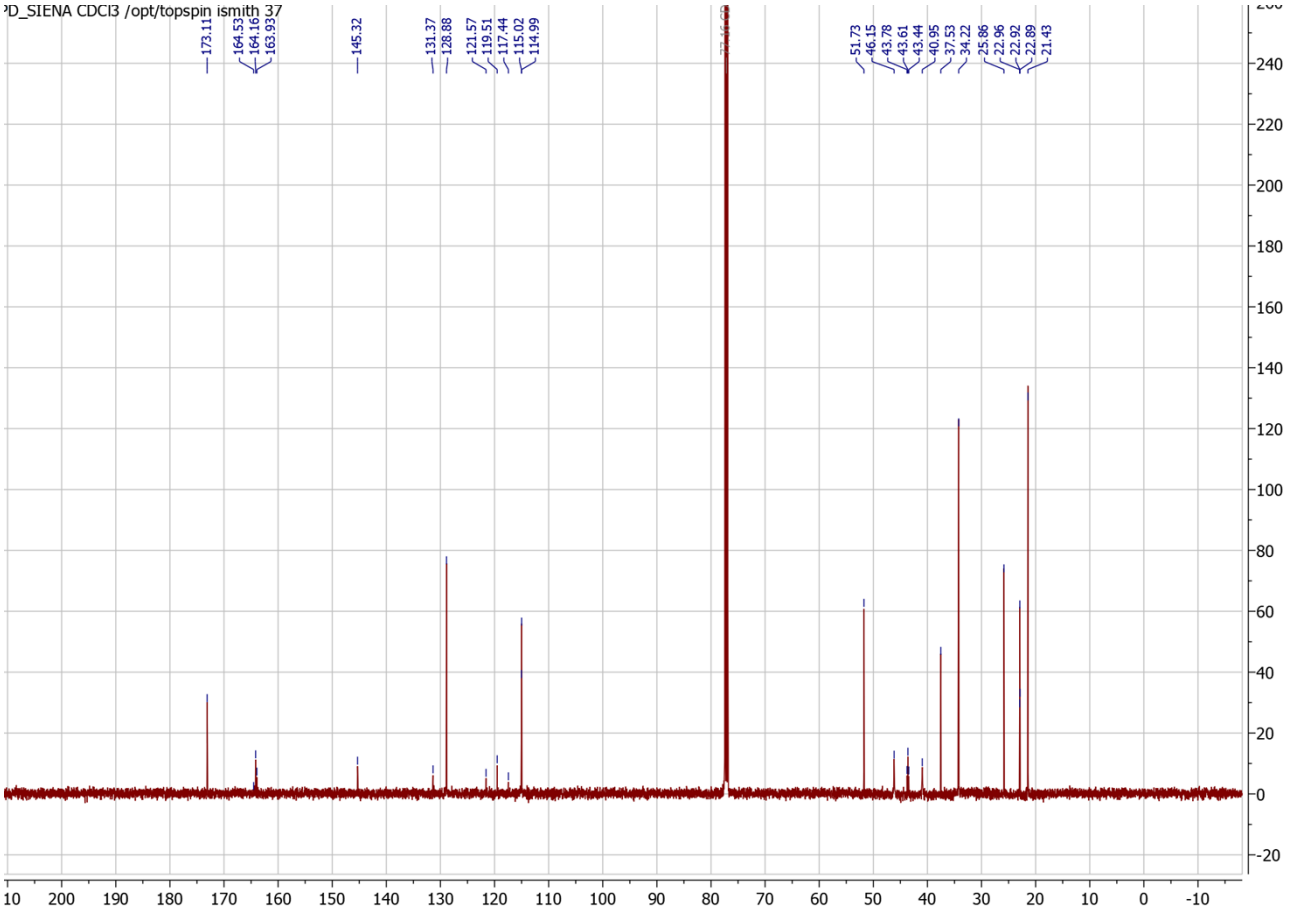
^{19}F NMR spectrum of 3ac (376 MHz, Chloroform-*d*)



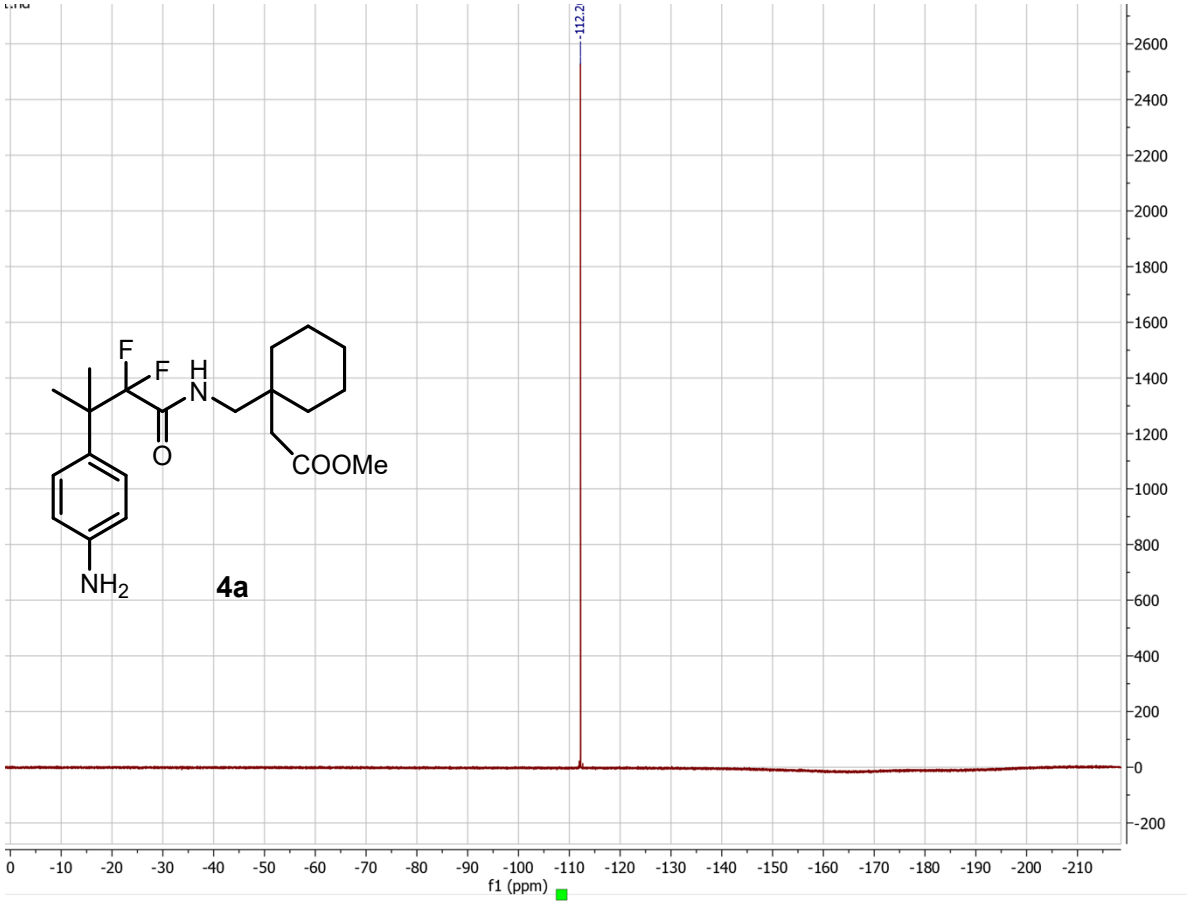
3ac



^{1}H NMR spectrum of 4a (400 MHz, Chloroform-d)

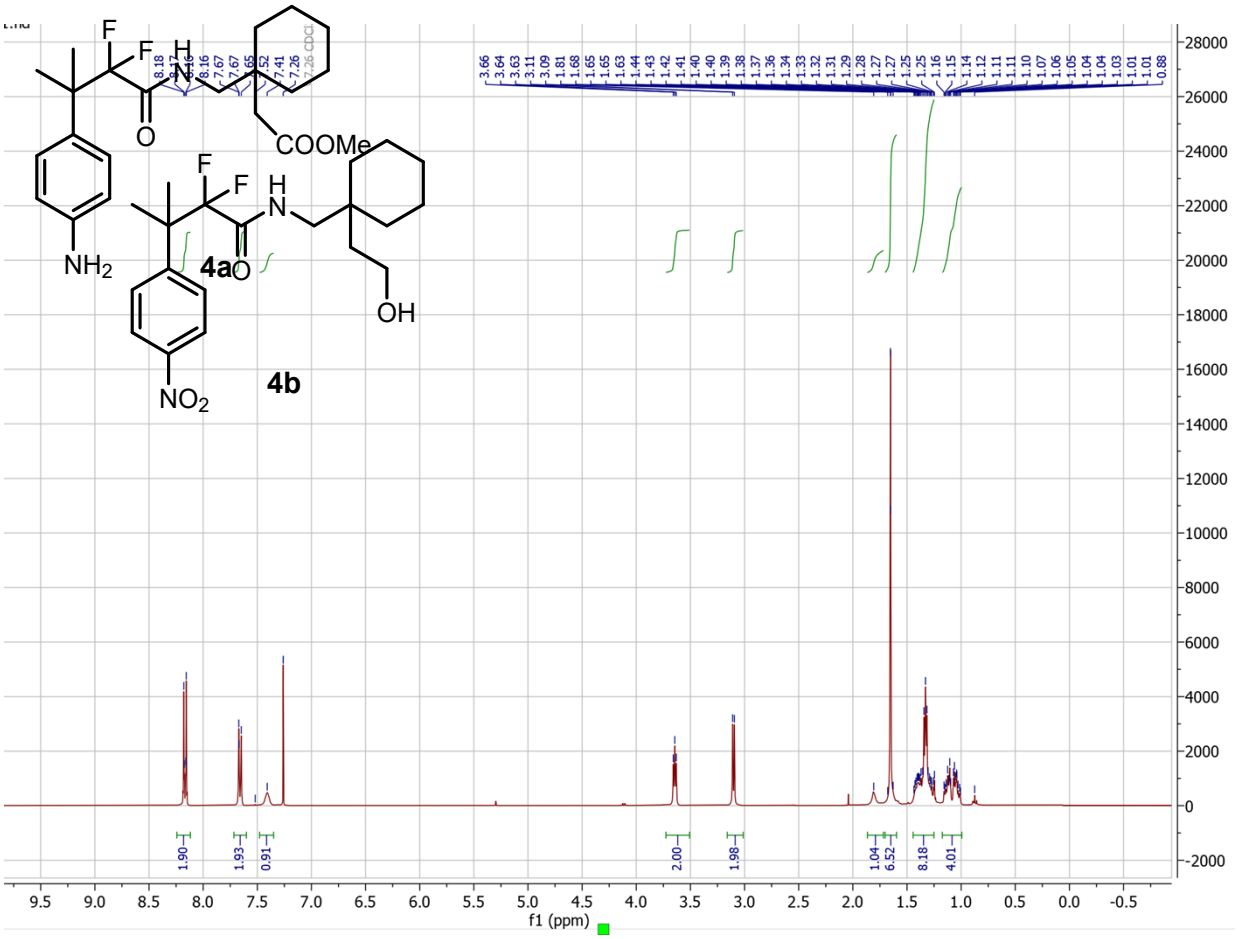


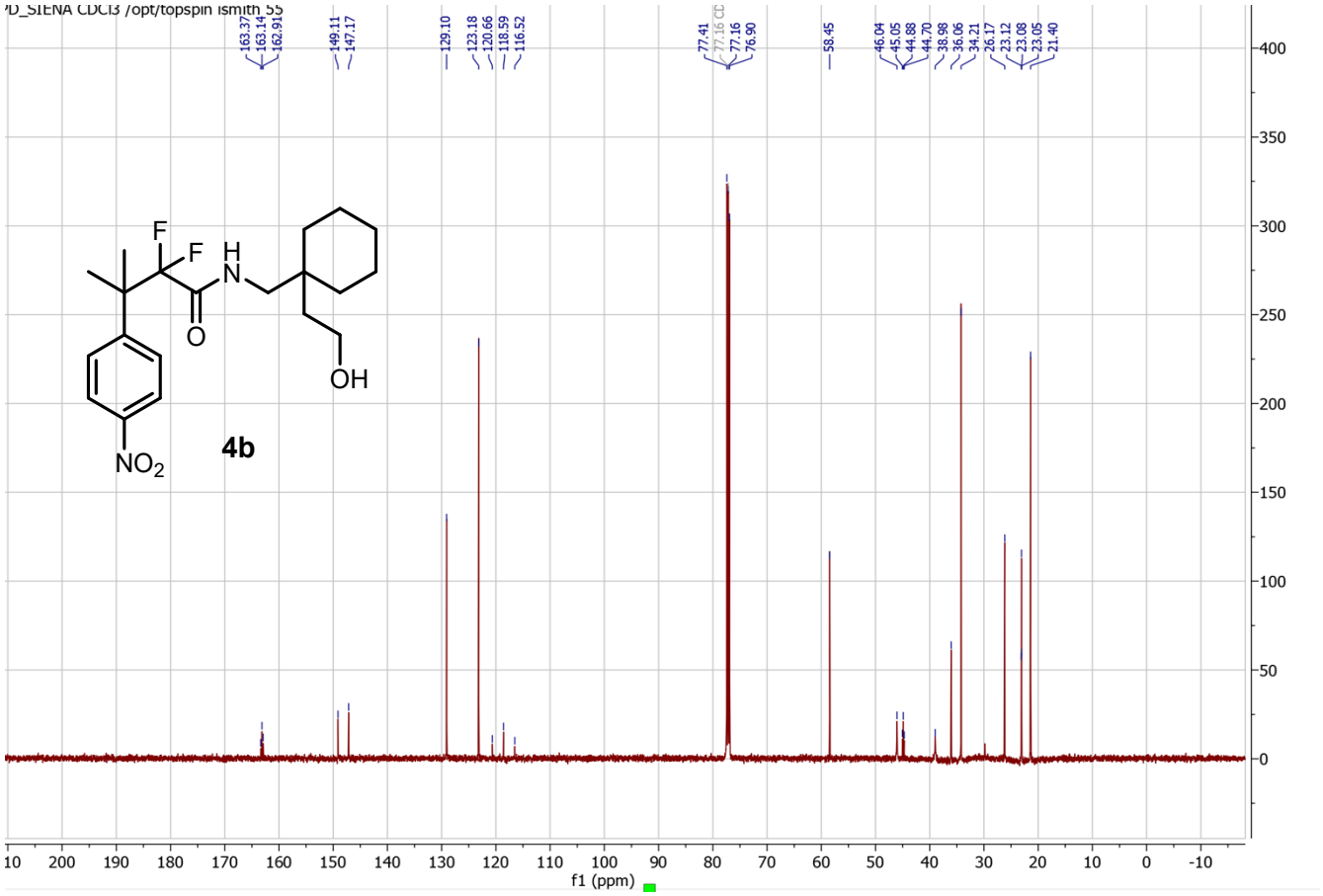
^{13}C NMR spectrum of 4a (126 MHz, Chloroform-*d*)



^{19}F NMR spectrum of 4a (376 MHz, Chloroform-*d*)

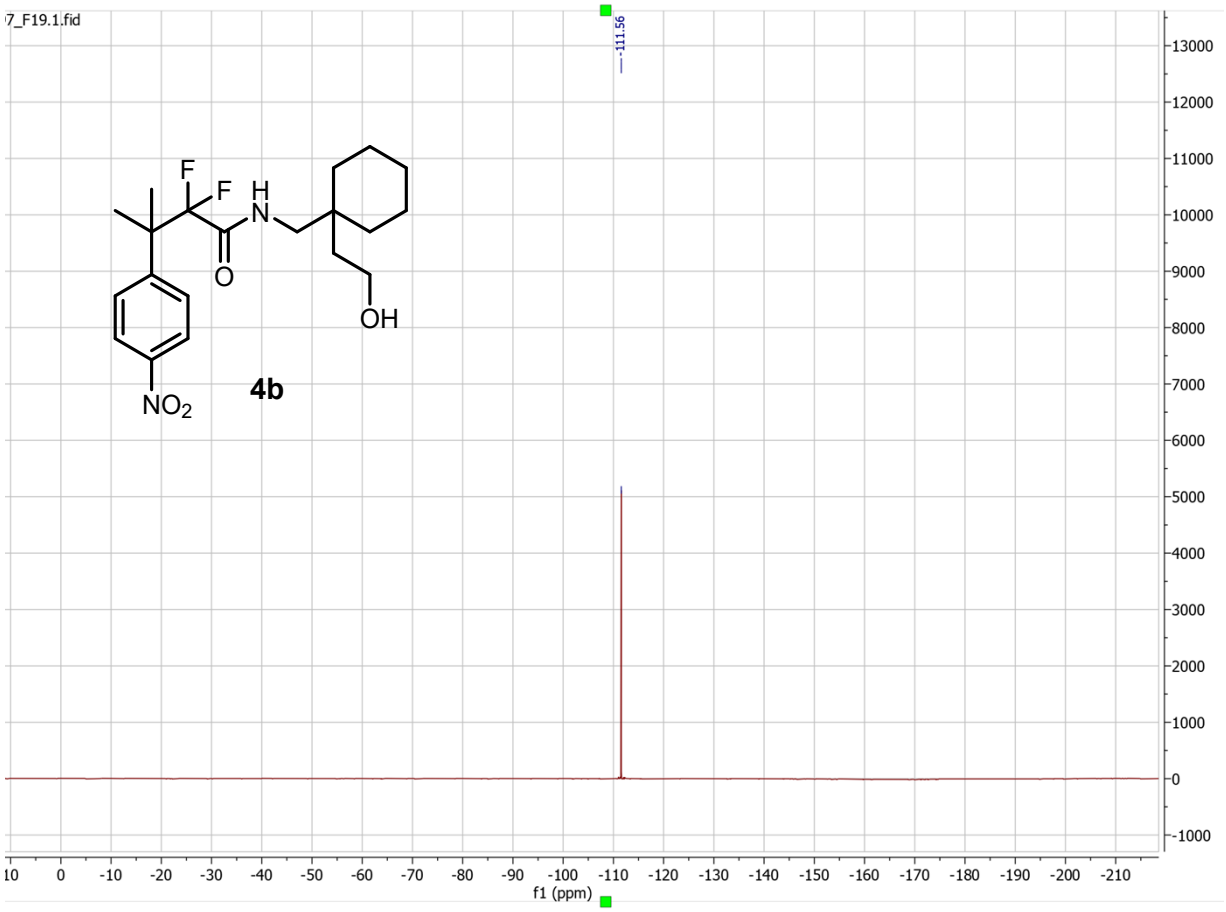
^{1}H NMR spectrum of 4b (400 MHz, Chloroform-d)





^{13}C NMR spectrum of 4b (126 MHz, Chloroform-*d*)

^{19}F NMR spectrum of 4b (376 MHz, Chloroform-*d*)



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