Supplementary Information

Rhodium-mediated ^{18}F-oxyfluorination of diazoketones using fluorine-18-containing hypervalent iodine reagent

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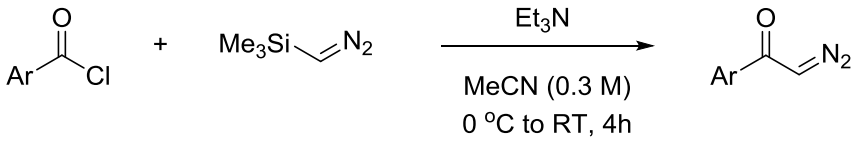
General information

Reagents were used as obtained from commercial suppliers without further purification. Solvents were obtained from commercial suppliers and dried using a Vacuum Atmospheres Solvent Purifier system. IST Phase Separators® were obtained from Biotage. Flash chromatography purifications were carried out on 60 Å (35-70 µm) silica gel (Acros Kieselgel 60) using or *n*-pentane / EtOAc or *n*-pentane / Et_2O mixtures as eluent. $Rh_2(OPiv)_4$ was prepared following a reported literature procedure.[1]

Fluorine-19 experiments. All reactions were carried out in dry closed glass reaction vessels using dry solvents under an atmosphere of dry Ar. Reagents **1** and **5** were prepared following a reported literature procedure.[2] Analytical TLC was carried out on aluminum-backed plates (1.5 Å, 4 cm) pre-coated (0.25 mm) with silica gel (Merck, Silica Gel 60 F254). Compounds were visualized by exposure to UV light (λ = 254 nm) or by dipping the plates in a solution of 0.75% $KMnO_4$ (w/v) in an aqueous solution of K_2CO_3 0.36 M or in a soltion of PMA in EtOH (0.05M). Melting points were recorded in a metal block and are uncorrected. ^{1}H NMR spectra were recorded at 400 MHz, ^{13}C NMR spectra were recorded at 100 MHz and ^{19}F NMR spectra were recorded at 377 MHz with a Bruker Advance spectrometer. ^{1}H and ^{13}C NMR chemical shifts (δ) are reported in ppm from tetramethylsilane, using the residual solvent resonance ($CHCl_3$: δ_H 7.26 and $CDCl_3$: δ_C 77.2) as an internal reference. Coupling constants (*J*) are given in Hz. High-resolution mass spectra (HRMS) were recorded on a Bruker microTOF ESI-TOF mass spectrometer in positive ion mode

Fluorine-18 experiments. The labelling reactions were carried out in dry conical glass vials under an atmosphere of dry N_2. Dry CH_2Cl_2 for the labelling reactions was obtained from commercial suppliers and dried using a Vacuum Atmospheres Solvent Purifier system or by distillation over $LiAlH_4$ and stored in a glovebox. Trimethyl orthoformate was distilled over $CaSO_4$ and stored in a glovebox. Radiochemical units and parameters are used in accordance with the standard of the field.[3] Radiochemical yields were estimated by radio-HPLC analysis of the crude reaction mixture by integration of the product peak relative to that of [^{18}F]fluoride and are decay corrected. The activity yield was determined by dividing the isolated activity obtained after semi-preparative HPLC purification by the starting activity of **[^{18}F]1** and is non-decay corrected.

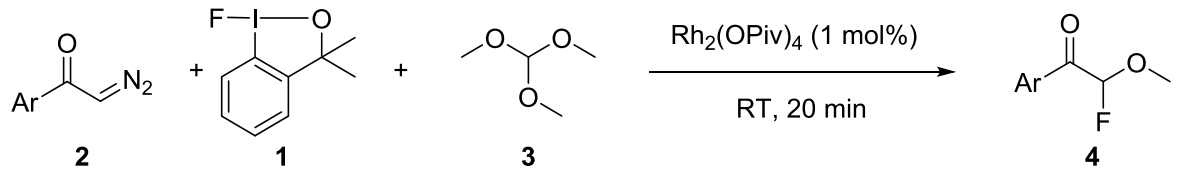
Synthesis of diazoketones (2)



Diazoketones **2k-l** were prepared by reported literature procedures.[4] Diazoketones **2a-j** were synthesized from the corresponding acyl chlorides by modified literature procedures[5]. Accordingly, (trimethylsilyl)diazomethane (2M in Et_2O, 1.2 equiv.) and triethylamine (1.0 equiv.) was dissolved in MeCN at 0 °C. To this mixture the corresponding benzoyl chloride was added dropwise under Ar. The reaction mixture was allowed to warm to room temperature and stirred for 4 hours or until the full consumption of the benzoyl chloride. The solvent was evaporated and Na_2CO_3 (sat. aq.) was added before extracting with Et_2O. The combined organic fractions were dried using an IST Phase Separator® (Biotage) and concentrated. The crude was purified by flash chromatography using *n*-pentane / EtOAc (10:1).

Diazoketones **2a-j** are known compounds. The obtained spectroscopical data matched with the reported literature values.[5-6]

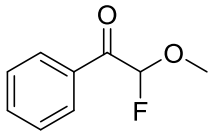
Synthesis and characterization of 2-fluoro-2-methoxy-1-aryl-1-ones (4)



2 1 3 4

A Schlenk flask was loaded with fluorobenziodoxole **1** (0.1 mmol, 1.0 equiv.), $Rh_2(OPiv)_4$ (1 mol%) and trimethyl orthoformate **3** (0.2 M) under Ar. To this was added a solution of diazoketone **2** (1.2 equiv) in trimethyl orthoformate (0.24 M) dropwise at room temperature over 10 minutes. The reaction was stirred for 10 more minutes. The excess of **3** was removed under vacuum and the crude was purified by column chromatography affording the desired 2-fluoro-methoxy-1-aryl-1-ones.

2-fluoro-2-methoxy-1-phenylethan-1-one (4a)



The title compound was prepared starting from 2-diazo-1-phenylethan-1-one (18 mg, 0.12 mmol). The crude was purified by column chromatography (SiO_2; Et_2O / *n*-pentane 1:50) affording the title compound as a colorless oil (3 mg, 18%).

TLC: R_f = 0.52 (Et_2O / *n*-pentane 1:10). UV active.

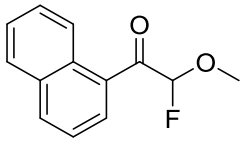
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.11-8.09 (m, 2H), 7.64-7.59 (m, 1H), 7.51-7.46 (m, 2H), 5.79 (d, *J*(H,F) = 63.7 Hz, 1H), 3.75 (d, *J*(H,F) = 1.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 190.1 (d, *J*(C,F) = 27.9 Hz), 134.3, 132.7 (d, *J*(C,F) = 1.8 Hz), 130.0 (d, *J*(C,F) = 2.3 Hz), 128.7, 110.7 (d, *J*(C,F) = 230.0 Hz), 57.9.

^{19}F NMR (377 MHz, $CDCl_3$): δ = −131.90 (d, *J*(F,H) = 63.6 Hz).

HRMS (ESI): m/z calcd for $C_9H_9FO_2$+Na^+: 191.0479, $[M+Na]^+$; found: 191.0480.

2-fluoro-2-methoxy-1-(naphthalen-1-yl)ethan-1-one (4b)



The title compound was prepared starting from 2-diazo-1-(naphthalen-1-yl)ethan-1-one (24 mg, 0.12 mmol). The crude was purified by column chromatography (SiO_2; Et_2O / *n*-pentane 1:50) affording the title compound as a colorless oil (5 mg, 21%).

TLC: R_f = 0.58 (Et_2O / *n*-pentane 1:10). UV active.

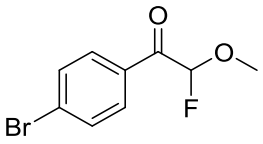
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.76 (d, *J*(H,H) = 8.5 Hz, 1H), 8.24 (d, *J*(H,H) = 7.3 Hz, 1H), 8.07 (d, *J*(H,H) = 8.2 Hz, 1H), 7.90 (d, *J*(H,H) = 8.1 Hz, 1H), 7.65-7.62 (m, 1H), 7.58-7.53 (m, 2H), 5.88 (d, *J*(H,F) = 64.1 Hz, 1H), 3.76 (d, *J*(H,F) = 1.6, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 192.8 (d, *J*(C,F) = 27.3 Hz), 134.5, 134.1, 131.2, 130.9 (d, *J*(C,F) = 3.8 Hz), 129.9, 128.82, 128.78, 126.8, 125.7, 124.3, 110.7 (d, *J*(C,F) = 231.8 Hz), 58.0.

^{19}F NMR (377 MHz, $CDCl_3$): $\delta = -130.58$ (d, *J*(F,H) = 64.2 Hz)

HRMS (ESI): m/z calcd for $C_{13}H_{11}FO_2$+Na^+: 241.0635, $[M+Na]^+$; found: 241.0635.

1-(4-bromophenyl)-2-fluoro-2-methoxyethan-1-one (4c)



The title compound was prepared starting from 1-(4-bromophenyl)-2-diazoethan-1-one (27 mg, 0.12 mmol). The crude was purified by column chromatography (SiO_2; Et_2O / *n*-pentane 1:50) affording the title compound as a white solid (5 mg, 21%).

M.p.: 45.9 - 46.4 °C.

TLC: R_f = 0.55 (Et_2O / n-pentane 1:10). UV active.

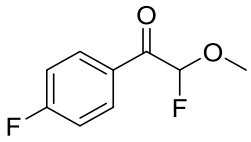
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.99-7.95 (m, 2H), 7.65-7.61 (m, 2H), 5.71 (d, J(H,F) = 63.9 Hz), 3.75 (d, J(H,F) = 1.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 189.3 (d, J(C,F) = 28.8 Hz), 132.1, 131.5 (d, J(C,F) = 2.3 Hz), 131.3 (d, J(C,F) = 2.3 Hz), 129.8, 111.0 (d, J(C,F) = 230.5 Hz), 58.1.

^{19}F NMR (377 MHz, $CDCl_3$): δ = −130.72 (d, J(F,H) = 63.6 Hz).

HRMS (ESI): m/z calcd for $C_9H_8{}^{79}BrFO_2$+Na^+: 268.9584, $[M+Na]^+$; found: 268.9588.

1-(4-fluorophenyl)-2-fluoro-2-methoxyethan-1-one (4d)



The title compound was prepared starting from 1-(4-fluorophenyl)-2-diazoethan-1-one (20 mg, 0.12 mmol). The crude was purified by column chromatography (SiO_2; Et_2O / *n*-pentane 1:50) affording the title compound as a colorless oil (3 mg, 18%).

TLC: R_f = 0.59 (Et_2O / *n*-pentane 1:10). UV active.

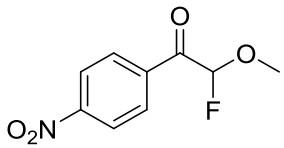
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.18-8.13 (m, 2H), 7.18-7.12 (m, 2H), 5.72 (d, *J*(H,F) = 63.9 Hz, 1H), 3.75 (d, *J*(H,F) = 1.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 188.6 (d, *J*(C,F) = 28.6 Hz), 166.5 (d, *J*(C,F) = 256.8 Hz), 133.0 (dd, *J*(C,F) = 9.3 Hz, 2.6 Hz), 129.0 (t, *J*(C,F) = 2.7 Hz), 116.0 (d, *J*(C,F) = 21.9 Hz), 111.1 (*J*(C,F) = 230.5 Hz), 58.1.

^{19}F NMR (377 MHz, $CDCl_3$): δ = −102.83 (tt, *J*(F,H) = 8.7 Hz, 5.5 Hz), −130.57 (d, *J*(F,H) = 64.0 Hz).

HRMS (ESI): m/z calcd for $C_9H_8F_2O_2$+Na^+: 209.0385, $[M+Na]^+$; found: 209.0384.

1-(4-nitrophenyl)-2-fluoro-2-methoxyethan-1-one (4e)



The title compound was prepared starting from 1-(4-nitrophenyl)-2-diazoethan-1-one (23 mg, 0.12 mmol). The crude was purified by column chromatography (SiO_2; Et_2O / *n*-pentane 1:50) affording the title compound as a yellow solid (7 mg, 32%).

M.p.: 64.6 – 65.4 °C.

TLC: R_f = 0.37 (Et_2O / *n*-pentane 3:6). UV active.

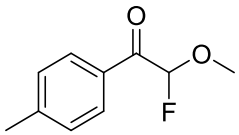
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.33-8.27 (m, 4H), 5.73 (d, *J*(H,F) = 64.0 Hz, 1H), 3.79 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 188.7 (d, *J*(C,F) = 30.1 Hz), 150.9, 137.0 (d, *J*(C,F) = 2.8 Hz), 131.3 (d, *J*(C,F) =2 4 Hz), 123.8, 111.1 (d, *J*(C,F) = 230.4 Hz), 58.4.

^{19}F NMR (377 MHz, $CDCl_3$): $\delta = -129.80$ (d, *J*(F,H) = 64.0 Hz).

HRMS (ESI): m/z calcd for $C_9H_8FNO_4$+Na^+: 236.0330, $[M+Na]^+$; found: 236.0319.

1-(4-methylphenyl)-2-fluoro-2-methoxyethan-1-one (4f)



The title compound was prepared starting from 1-(4-methylphenyl)-2-diazoethan-1-one (19 mg, 0.12 mmol). The crude was purified by column chromatography (SiO_2; Et_2O / *n*-pentane 1:50) affording the title compound as a colorless oil (16 mg, 88%).

TLC: R_f = 0.49 (Et_2O / *n*-pentane 1:10). UV active.

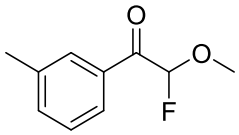
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.99 (d, *J*(H,H) = 8.2 Hz, 2H), 7.28 (d, *J*(H,H) = 8.2 Hz, 2H), 5.77 (d, *J*(H,F) = 63.7 Hz, 1H), 3.74 (d, *J*(H,F) = 1.7 Hz, 3H), 2.43 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 189.7 (d, *J*(C,F) = 27.6 Hz), 145.4, 130,2 (d, *J*(C,F) = 1.7 Hz), 130,1 (d, *J*(C,F) = 2.1 Hz), 129.5, 110.7 (d, *J*(C,F) = 230.2 Hz), 57.8, 22.0.

^{19}F NMR (377 MHz, $CDCl_3$): $\delta = -132.03$ (d, *J*(F,H) = 64.3 Hz).

HRMS (ESI): m/z calcd for $C_{10}H_{11}FO_2$+Na^+: 205.0635, $[M+Na]^+$; found: 205.0641.

1-(3-methylphenyl)-2-fluoro-2-methoxyethan-1-one (4g)



The title compound was prepared starting from 1-(3-methylphenyl)-2-diazoethan-1-one (19 mg, 0.12 mmol). The crude was purified by column chromatography (SiO_2; Et_2O / *n*-pentane 1:50) affording the title compound as a colorless oil (6 mg, 31%).

TLC: R_f = 0.43 (Et_2O / *n*-pentane 1:10). UV active.

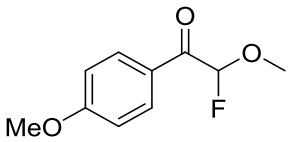
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.90-7.89 (m, 2H), 7.44-7.42 (m, 1H), 7.39-7.35 (m, 1H), 5.79 (d, *J*(H,F) = 63.6 Hz, 1H), 3.74 (d, *J*(H,F) = 1.7 Hz, 3H), 2.42 (s, 3 Hz).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 190.2 (d, *J*(C,F) = 27.7 Hz), 138.6, 135.1, 132.7 (d, *J*(C,F) = 1.7 Hz), 130.3 (*J*(C,F) = 1.9 Hz), 128.6, 127.2 (d, *J*(C,F) = 2.2 Hz), 110.6 (d, *J*(C,F) = 230.3 Hz), 57.9, 21.5.

^{19}F NMR (377 MHz, $CDCl_3$): $\delta = -132.09$ (d, *J*(F,H) = 63.4 Hz).

HRMS (ESI): m/z calcd for $C_{10}H_{11}FO_2$+Na^+: 205.0635, $[M+Na]^+$; found: 205.0634.

1-(4-methoxyphenyl)-2-fluoro-2-methoxyethan-1-one (4h)



The title compound was prepared starting from 1-(4-methoxyphenyl)-2-diazoethan-1-one (21 mg, 0.12 mmol). The crude was purified by column chromatography (SiO_2; Et_2O / *n*-pentane 1:30 to 1:25) affording the title compound as a white solid (4 mg, 20%).

M.p.: 65.1 - 65.7 °C.

TLC: R_f = 0.20 (Et_2O / *n*-pentane 1:9). UV active.

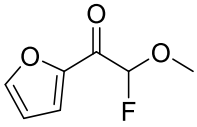
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.09 (d, *J*(H,H) = 8.5 Hz, 2H), 6.95 (d, *J*(H,H) = 9.1 Hz, 2H), 5.75 (d, *J*(H,F) = 63.9 Hz, 1H), 3.89 (s, 3H), 3.73 (d, *J*(H,F) = 1.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 188.7 (d, *J*(C,F) = 27.7 Hz), 164.5, 132.5 (d, *J*(C,F) = 2.3 Hz), 125.6 (d, *J*(C,F) = 1.9 Hz), 114.0, 111.0 (d, *J*(C,F) = 230.3 Hz), 57.9, 55.7.

^{19}F NMR (377 MHz, $CDCl_3$): $\delta = -131.31$ (d, *J*(F,H) = 64.7 Hz).

HRMS (ESI): m/z calcd for $C_{10}H_{11}FO_3$+Na^+: 221.0584, $[M+Na]^+$; found:221.0587.

2-fluoro-2-methoxy-1-(furan-2-yl)ethan-1-one (4i)



The title compound was prepared starting from 2-diazo-1-(furan-2-yl)ethan-1-one (16 mg, 0.12 mmol). The crude was purified by column chromatography (SiO_2; Et_2O / *n*-pentane 1:35) affording the title compound as a yellow oil (3 mg, 16%).

TLC: R_f = 0.43 (Et_2O / *n*-pentane 3:7). UV active.

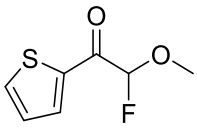
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.71 (dd, *J*(H,H) = 1.7 Hz, 0.8 Hz, 1H), 7.47 (ddd, *J*(H,H) = 3.7 Hz, 1.5 Hz, 0.7 Hz, 1H), 6.60 (dd, *J*(H,H) = 3.7 Hz, 1.7 Hz, 1H), 5.68 (d, *J*(H,F) = 63.4 Hz, 1H), 3.73 (d, *J*(H,F) = 1.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 178.7 (d, *J*(C,F) = 29.1 Hz), 149.1 (d, *J*(C,F) = 1.3 Hz), 148.4, 122.3 (d, *J*(C,F) = 4.4 Hz), 112.7, 109.4 (d, *J*(C,F) = 229.5 Hz), 58.0.

^{19}F NMR (377 MHz, CDCl3): $\delta = -133.55$ (δ, *J*(F,H) = 63.3 Hz).

HRMS (ESI): m/z calcd for $C_7H_7FO_3$+Na^+: 181.0271, $[M+Na]^+$; found: 181.0274.

2-fluoro-2-methoxy-1-(thiophen-2-yl)ethan-1-one (4j)



The title compound was prepared starting from 2-diazo-1-(thiophen-2-yl)ethan-1-one (18 mg, 0.12 mmol). The crude was purified by column chromatography (SiO_2; Et_2O / *n*-pentane 1:30) affording the title compound as a yellow oil (2 mg, 12%).

TLC: R_f = 0.44 (Et_2O / *n*-pentane 1:7). UV active.

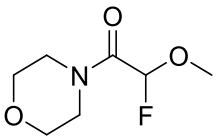
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.02 (dt, *J*(H,H) = 3.8 Hz, 1.1 Hz, 1H), 7.75 (dd, *J*(H,H) = 4.9Hz, 1.1 Hz, 1H), 7.18 (dd, *J*(H,H) = 4.9 Hz, 3.9 Hz, 1H), 5.67 (d, *J*(H,F) = 63.7 Hz, 1H), 3.74 (d, *J*(H,F) = 1.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 183.6 (d, *J*(C,F) = 29.0 Hz), 138.8 (d, *J*(C,F) = 2.4 Hz), 135.8, 135.6 (d, *J*(C,F) = 3.7 Hz), 128.6, 110.3 (d, *J*(C,F) = 230.6 Hz), 57.9.

^{19}F NMR (377 MHz, $CDCl_3$): δ = −130.91 (dt, *J*(F,H) = 64.0 Hz, 1.5 Hz).

HRMS (ESI): m/z calcd for $C_7H_7FO_2S+Na^+$: 197.0043, $[M+Na]^+$; found: 197.0048.

2-fluoro-2-methoxy-1-morpholinoethan-1-one (4k)



The title compound was prepared starting from 2-diazo-1-morpholinoethan-1-one (15 mg, 0.12 mmol). The crude was purified by column chromatography (SiO_2; EtOAc / pentane 1:4) affording the title compound as a pale yellow oil (2 mg, 11%).

TLC: R_f = 0.30 (EtOAc / *n*-pentane 1:1). UV inactive. Stains green with PMA.

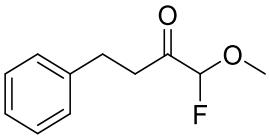
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 5.57 (d, *J*(H,F) = 64.4 Hz, 1H), 3.72-3.56 (m, 11H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 163.2 (d, *J*(C,F) = 27.3 Hz), 110.4 (d, *J*(C,F) = 231.5 Hz), 67.0, 66.9, 58.0, 45.9 (d, *J*(C,F) = 4.3 Hz), 42.8.

^{19}F NMR (377 MHz, $CDCl_3$): δ = −130.00 (d, *J*(F,H) = 64.4 Hz).

HRMS (ESI): m/z calcd for $C_{14}H_{25}F_2N_2O_6$: 355.1675, $[2M+H]^+$; found: 355.1668.

1-fluoro-1-methoxy-4-phenylbutan-2-one (4l)



The title compound was prepared starting from 1-diazo-4-phenylbutan-2-one (21 mg, 0.12 mmol). The crude was purified by column chromatography (SiO_2; Et_2O / pentane 1:50) affording the title compound as a yellow oil (2 mg, 8%).

TLC: R_f = 0.25 (Et_2O / *n*-pentane 1:10). UV inactive. Stains green with PMA.

^{1}H NMR (400 MHz, $(CD_3)_2CO$, TMS): δ = 7.29-7.15 (m, 5H), 5.38 (d, *J*(H,F) = 64.2 Hz, 1H), 3.62 (d, *J*(H,F) = 1.7 Hz, 3H), 2.97-2.93 (m, 2H), 2.89-2.85 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 201.3 (d, *J*(C,F) = 28.3 Hz), 140.7, 128.7, 128.5, 126.4, 109.7 (d, *J*(C,F) = 228.9 Hz), 57.8, 38.1, 28.7.

^{19}F NMR (377 MHz, $(CD_3)_2CO$): $\delta = -137.90$ (d, *J*(F,H) = 64.6 Hz).

HRMS (ESI): m/z calcd for $C_{22}H_{27}F_2O_4$: 393.1872, $[2M+H]^+$; found: 393.1870.

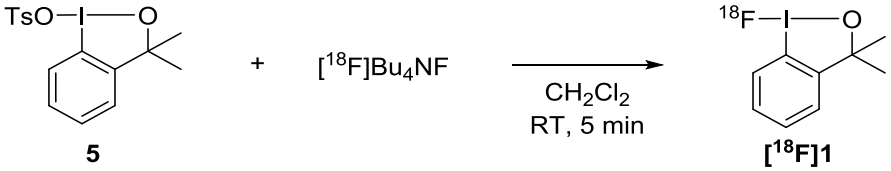
Radiochemistry

Preparation of [^{18F}]Bu_4NF

[^{18}F]Fluoride was produced by the nuclear reaction $^{18}O(p,n)^{18}F$ using [^{18}O]H_2O as target in a Scanditronix MC-17 cyclotron and was separated from [^{18}O]H_2O using a Sep-PAK® Accell Plus QMA Light anion exchange cartridge (Waters, Part No. WAT023525) pretreated with K_2CO_3 (aq. 0.5 M, 10 mL) and later with H_2O (10 mL). [^{18}F]Fluoride was released from the cartridge as [^{18}F]Bu_4NF using an aqueous solution of Bu_4NHCO_3 (ABX; 0.0375 M) in a 1:1 mixture with acetonitrile (450 μL total volume). Acetonitrile was added (200 μL) and the [^{18}F]Bu_4NF was dried at 120 °C under a flow of N_2 for 4 minutes. The drying process was repeated (x2) using 200 μL of acetonitrile for 3 and 2 minutes respectively. The obtained [^{18}F]Bu_4NF was dissolved in dry CH_2Cl_2 and used in the next step.

The activity in the vials was determined using a CRC-15R (Capintec) detector calibrated for fluorine-18.

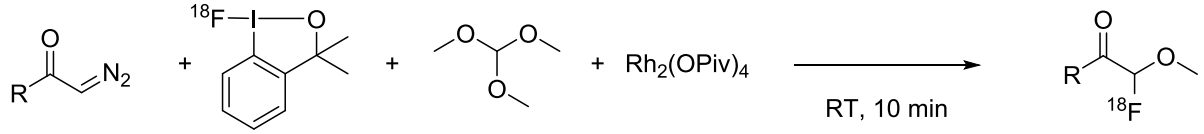
Synthesis of 1-[^{18}F]fluoro-3,3-dimethyl-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodoxole ([^{18}F]1)



5 **[^{18}F]1**

A 0.5 mL conical glass vial containing a magnetic stirrer was loaded with 1-tosyloxy-3,3-dimethyl-1,3-dihydro-λ^3-benzo[d][1,2]iodoxole **5** (5 mg, 0.012 mmol). [^{18}F]Bu_4NF in CH_2Cl_2 was added (500 μL, 1-3 GBq) and the reaction was stirred at room temperature for 5 minutes. After that time, the solvent was evaporated under a stream of N_2 for 10 minutes at room temperature until a solid formed. To ensure the formation of the solid, *n*-hexane (300 μL) was added before the CH_2Cl_2 evaporated completely. To the remaining solid was added *n*-hexane (500 μL) and the mixture was stirred at 70 °C for 1 minute. The *n*-hexane supernatant was extracted by means of a syringe, filtered through a 1 mL IST Phase Separator® (Biotage, Part No. 120-1901-A) and used as such in the labelling reactions.

Synthesis of 2-[^{18}F]fluoro-2-methoxy-1-aryl-1-ones ([^{18}F]4)



2 **[^{18}F]1** **3** **[^{18}F]4**

To a 0.5 mL conical vial containing a magnetic stirrer was added a solution of $Rh_2(OPiv)_4$ in DCM (100 μL, 5 mg/mL). The solvent was removed under a stream of nitrogen at room temperature before adding the labelling reagent **[^{18}F]1** in hexane (100 μL, 100-300 MBq). The solvent was removed under a stream of nitrogen at room temperature for 4 minutes. To the resulting mixture was added a solution of the corresponding diazoketone **2** in trimethyl orthoformate (0.027 M) in one step. In case of radiosynthesis of **[^{18}F]4a-j** the reaction was stirred at room temperature for 10 minutes, while for synthesis of **[^{18}F]4k** the temperature was increased to 90 °C. An aliquot was analyzed by radio-HPLC in order to estimate the radiochemical yield of 2-[^{18}F]fluoro-2-methoxy-1-aryl-1-ones **[^{18}F]4**.

Analysis and radiochemical yield (RCY) determination

Radiochemical yields were determined by HPLC analysis of the crude reaction mixtures. The analyses were performed using a VWR LaChrom ELITE system (L-2200, L2300, L2450) with a built-in PDA detector and in series with a Bioscan Flow-Count PMT radioactivity detector using a Chromolith Performace RP-18 end-capped column (2 μm, 100 x 4.6 mm). The mixtures were eluted with a linear-increase gradients 1 and 2 (mobile phase A: acetonitrile, mobile phase B: ammonium formate 50 mM) at a flow of 4 mL/min.

Gradient 1

Time [min]	Mobile Phase A (MeCN) [%]	Mobile Phase B (AMF) [%]
0	10	90
10	50	50

Gradient 2

Time [min]	Mobile Phase A (MeCN) [%]	Mobile Phase B (AMF) [%]
0	1	99
10	5	95

The ^{18}F-labelled compounds were identified by comparison of the retention time of the labelled compounds **[^{18}F]4** with that of the corresponding references **4**.

Gradient	Compound	Retention time UV detector (^{19}F reference) [min]	Compound	Retention time β^+ flow detector (^{18}F-labelled) [min]
1	**4a**	3.760	**[^{18}F]4a**	3.821
1	**4b**	7.433	**[^{18}F]4b**	7.743
1	**4c**	6.620	**[^{18}F]4c**	6.665
1	**4d**	4.373	**[^{18}F]4d**	4.440
1	**4e**	2.051	**[^{18}F]4e**	2.128
1	**4f**	5.140	**[^{18}F]4f**	5.335
1	**4g**	4.413	**[^{18}F]4g**	4.633
1	**4h**	4.433	**[^{18}F]4h**	4.436
1	**4i**	1.113	**[^{18}F]4i**	1.163
1	**4j**	3.120	**[^{18}F]4j**	3.133
2	**4k**	2.225	**[^{18}F]4k**	2.227

Isolation and determination of activity yield (AY) and molar activity (A_m)

A 0.5 mL conical glass vial containing a magnetic stirrer was loaded with 1-tosyloxy-3,3-dimethyl-1,3-dihydro-λ^3-benzo[d][1,2]iodoxole (5 mg, 0.012 mmol). [^{18}F]Bu_4NF in CH_2Cl_2 was added (500 μL, 6.60 GBq) and the reaction was stirred at room temperature for 5 minutes. After that time, the solvent was evaporated under a stream of N_2 for 10 minutes at room temperature until a solid formed. To ensure the formation of the solid, *n*-hexane (300 μL) was added before the CH_2Cl_2 evaporated completely. To the remaining solid was added *n*-hexane (500 μL) and the mixture was stirred at 70 ^{o}C for 1 minute. The *n*-hexane supernatant was extracted by means of a syringe and filtered through a 1 mL IST Phase Separator® (Biotage, Part No. 120-1901-A) obtaining 2.70 GBq of extracted activity.

To a 0.5 mL conical vial containing a magnetic stirrer was added a solution of $Rh_2(OPiv)_4$ in DCM (100 μL, 5 mg/mL). The solvent was removed under a stream of nitrogen at room temperature before

adding the labelling reagent **[^{18}F]1** in hexane (2.70 GBq). The solvent was removed under a stream of N_2 at room temperature for 7 minutes. To the resulting mixture was added a solution of 1-(4-bromophenyl)-2-diazoethan-1-one **2c** in trimethyl orthoformate (0.027 M) in one step. The reaction was stirred at room temperature for 10 minutes. An aliquote was analyzed by radio-HPLC to confirm product formation and estimate the RCY (RCY = 38%). The labelled compound **[^{18}F]4c** was purified by semi-preparative HPLC. The isolated activity was 253 MBq (9% AY, starting from **[^{18}F]1**, non-decay corrected) with a radiochemical purity of 89% and a molar activity of 216 GBq/μmol, measured 110 minutes after the end of the bombardment.

Purification and analysis procedure:

The crude reaction mixture was purified by semi-preparative HPLC using a VWR LaPrep HPLC system (LP1200) with an in-series UV-detector (λ = 212 nm), in series with a Bioscan Flow-Count PMT radioactivity detector using a reverse phase column (Kinetex 5 μm, C18, 100 Å, 10 × 250 mm) and eluted with a linear increase gradient (mobile phase A: acetonitrile, mobile phase B: ammonium formate 50 mM) at a flow of 5 mL/min.

Time [min]	Mobile Phase A (MeCN) [%]	Mobile Phase B (AMF) [%]
0	10	90
12	50	50
30	50	50

The product was collected in a fraction over 31 seconds with a retention time of 19.3 minutes.

Analysis of the purified product was performed using a VWR LaChrom ELITE system (L-2200, L2300, L2450) with a built-in PDA detector and in series with a Bioscan Flow-Count PMT radioactivity detector using a Chromolith Performace RP-18 end-capped column (2 μm, 100 x 4.6 mm). and eluted with a linear-increase gradient (mobile phase A: acetonitrile, mobile phase B: ammonium formate 50 mM) at a flow of 4 mL/min.

Time [min]	Mobile Phase A (MeCN) [%]	Mobile Phase B (AMF) [%]
0	5	95
10	50	50

The identity of the labelled compound **[^{18}F]4c** was confirmed by co-injection with a true reference of product **4c** (Figure S1).

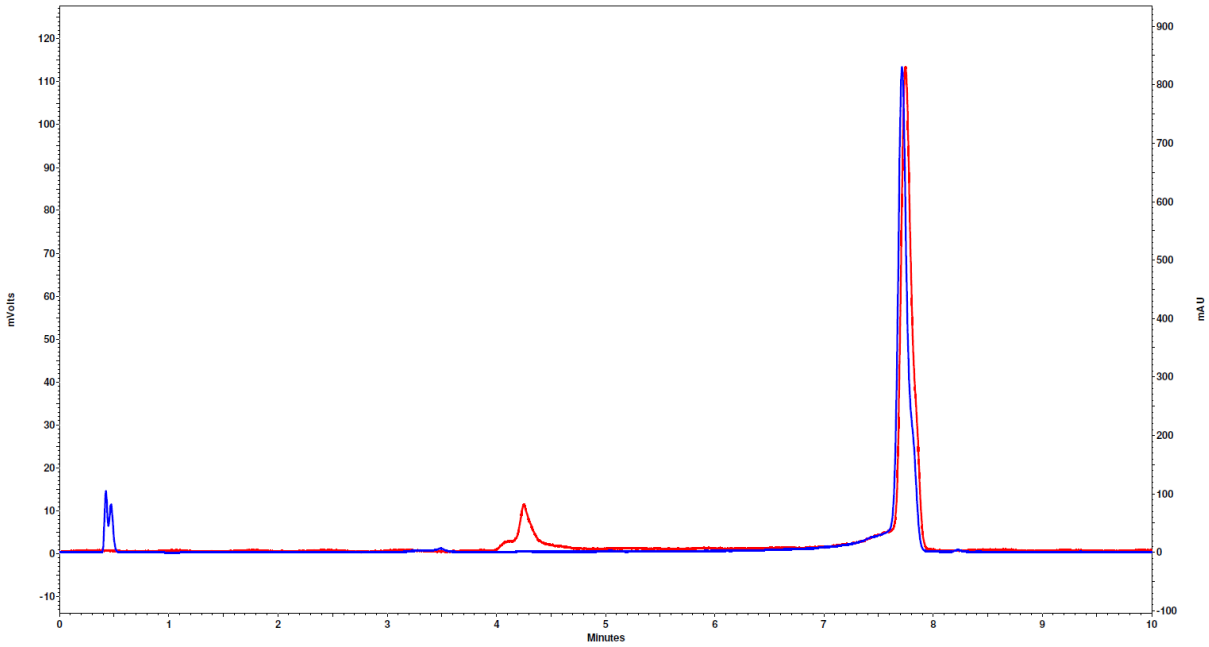


Figure S1. Co-injection of purified product **[^{18}F]4c** and true **4c**.

The molar activity was calculated using a calibration curve (Fig S2). The calibration curve was generated plotting the UV absorption (λ = 253 nm) of known amounts of **4c** against the injected amounts.

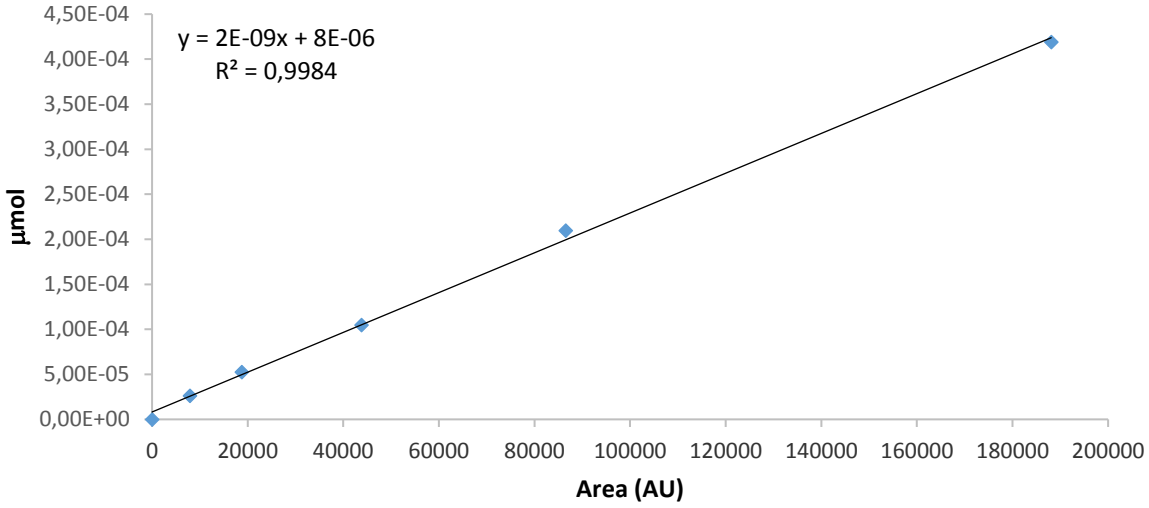
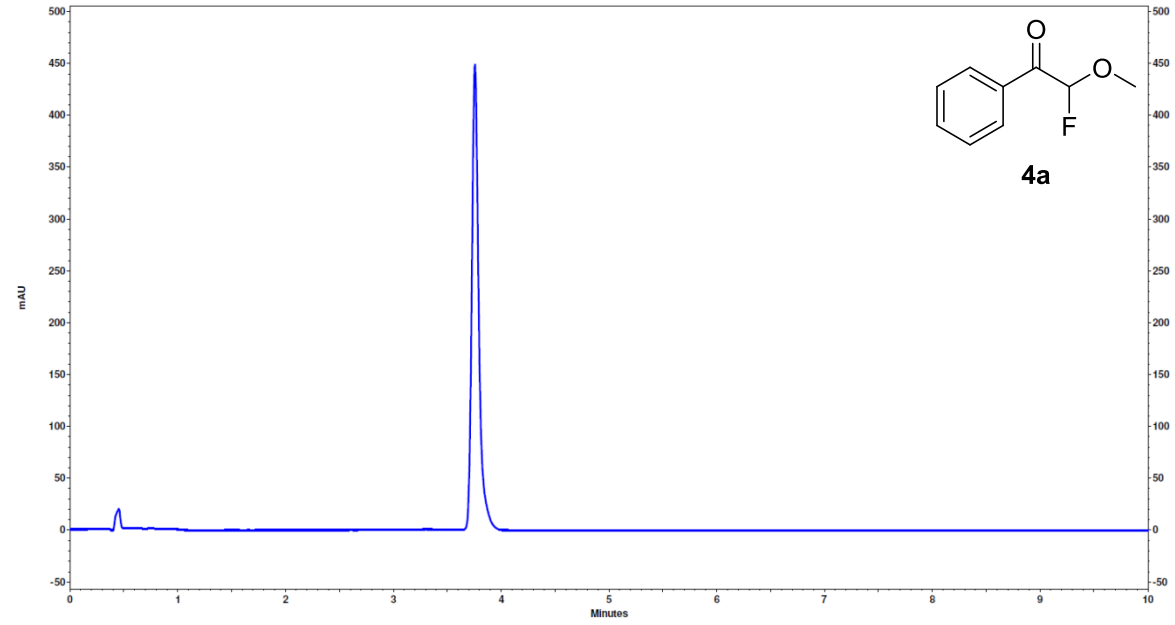
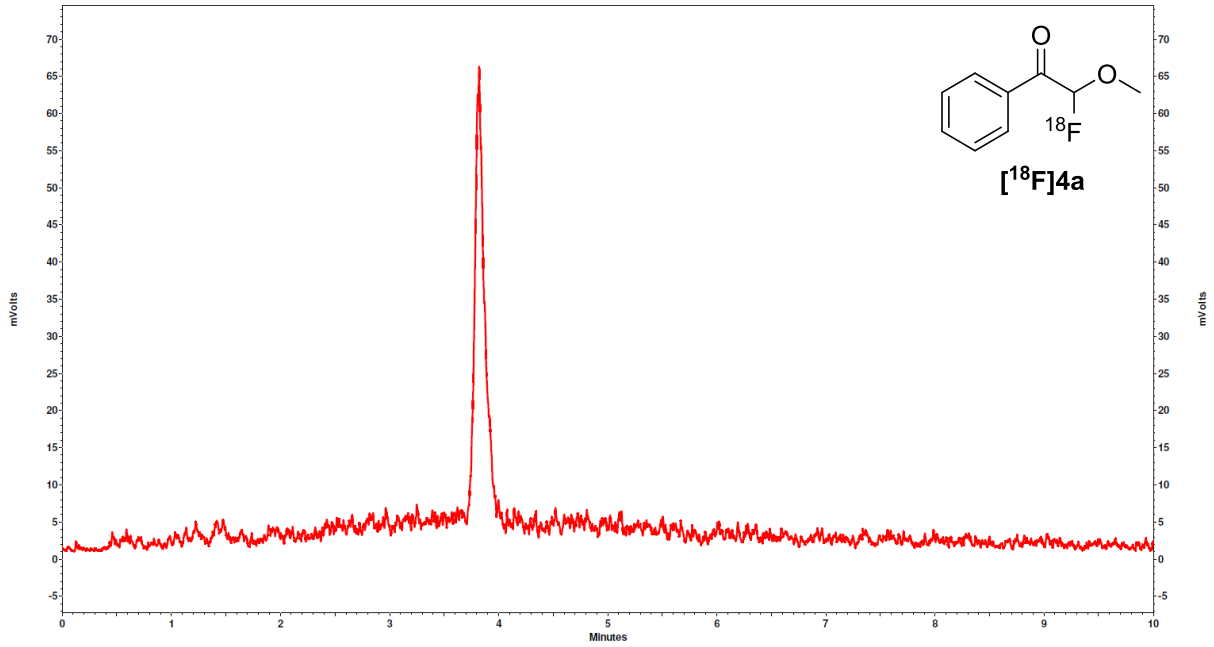
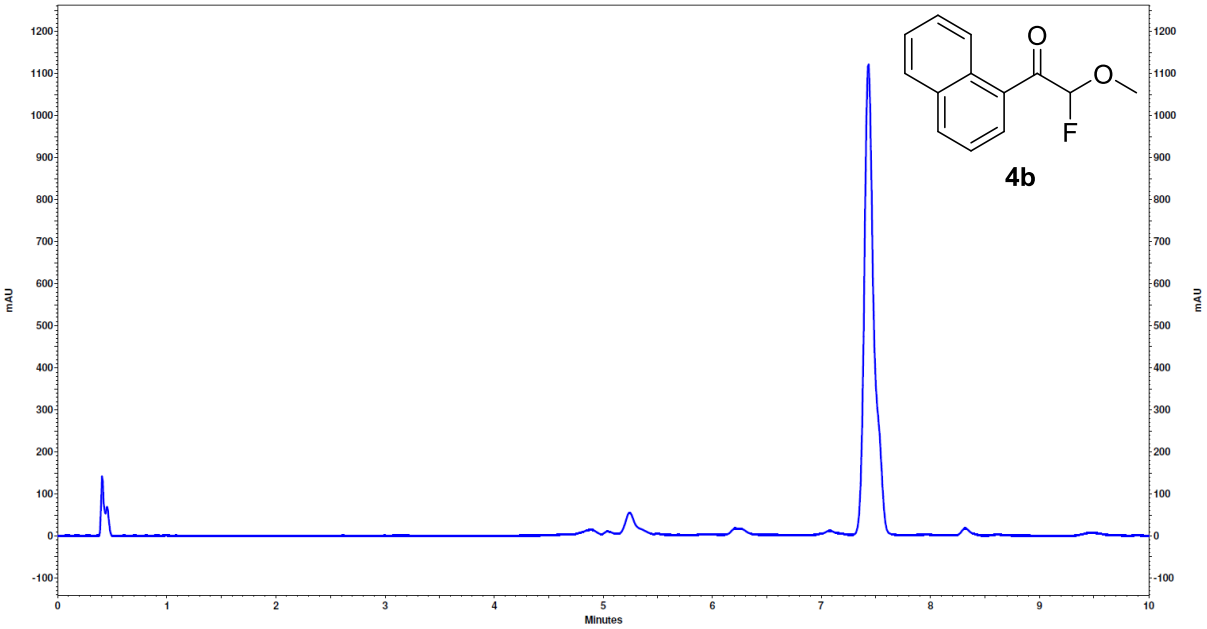


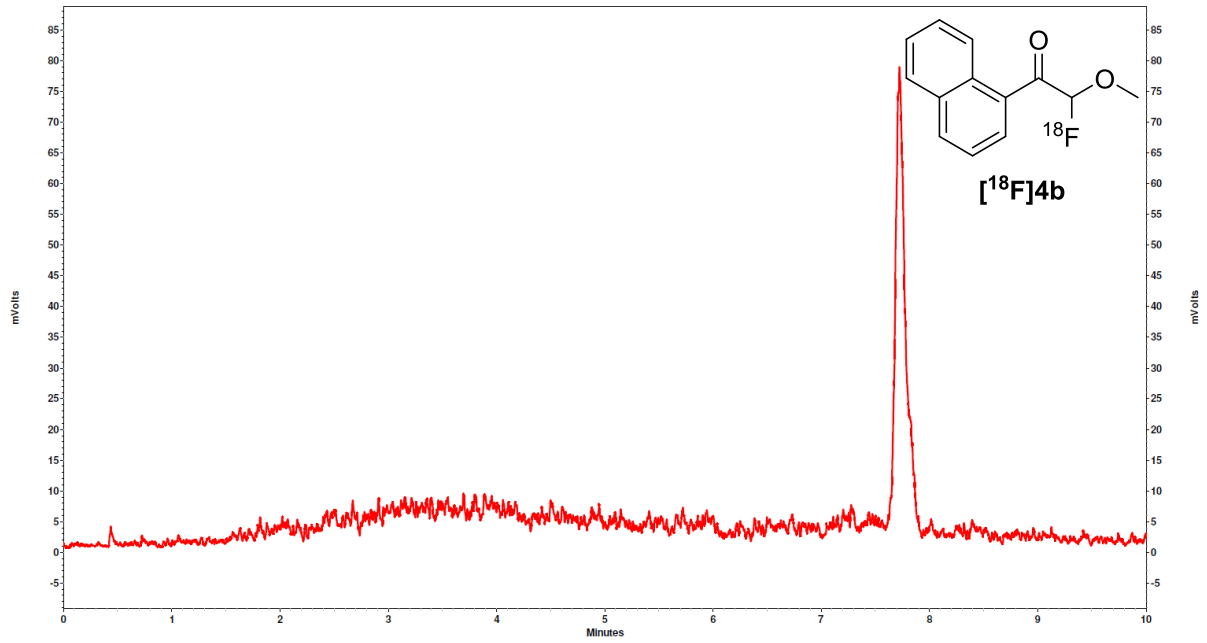
Figure S2. Calibration curve of **4b** for the determination of the molar activity.

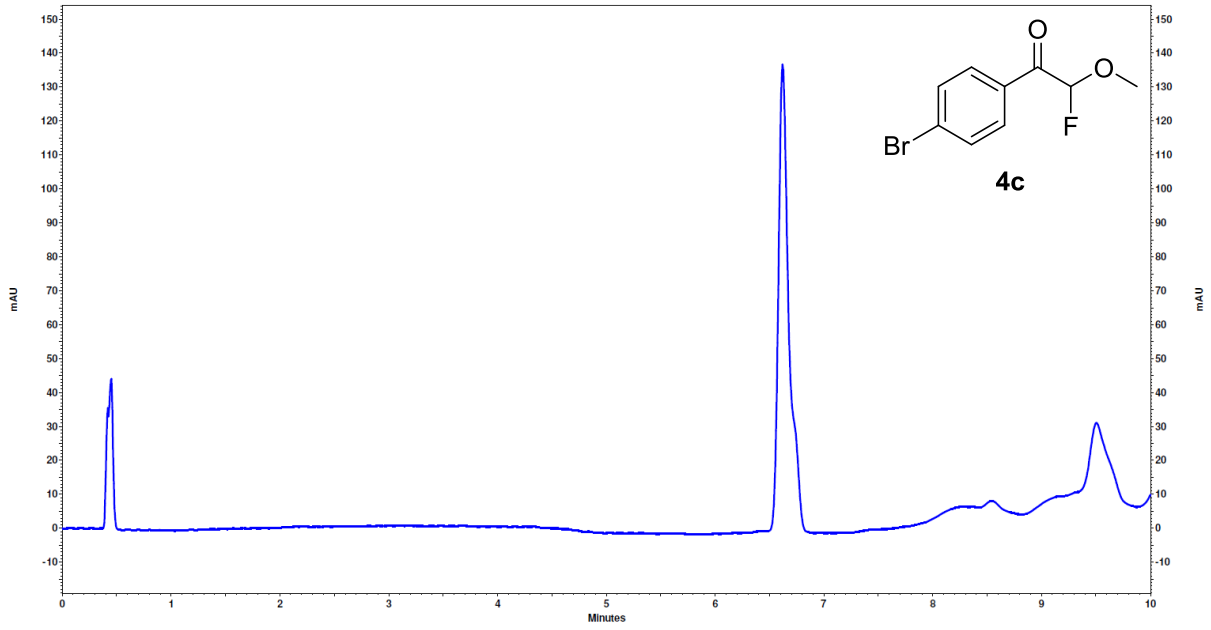
Radio-HPLC chromatograms

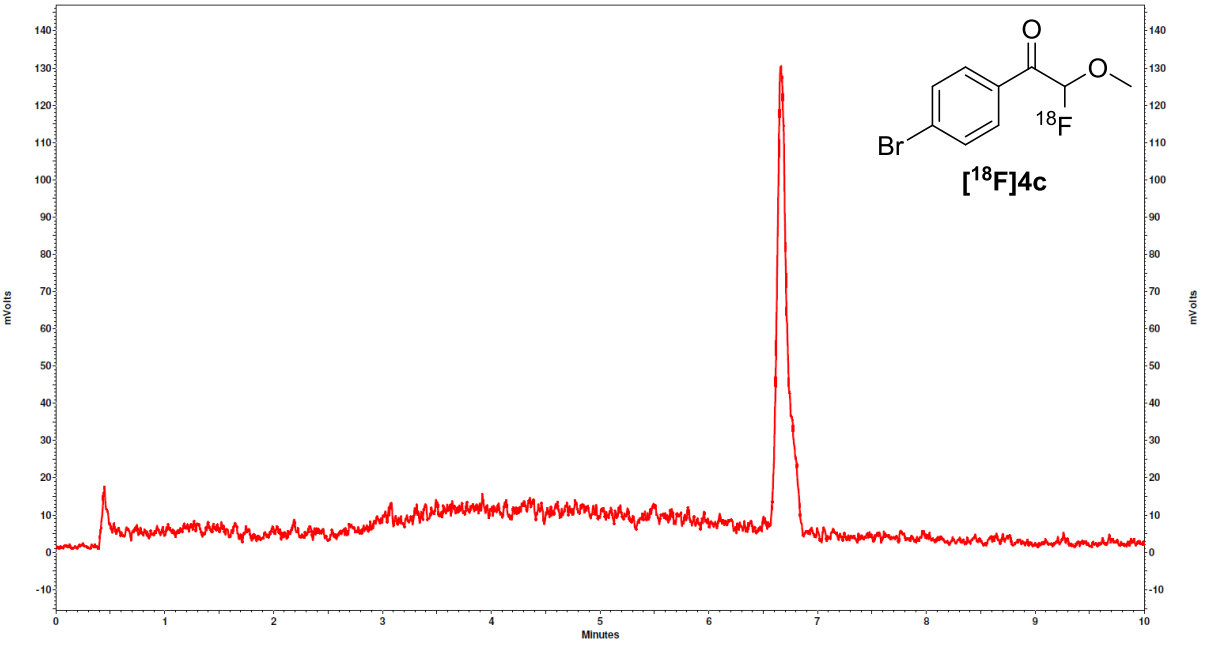


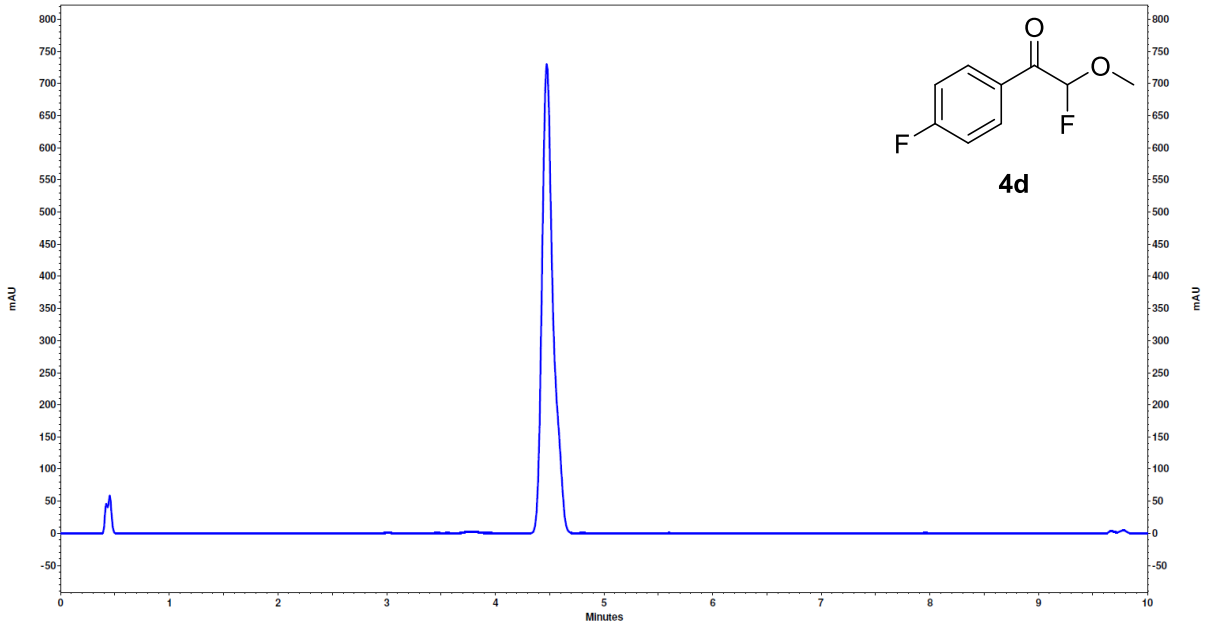


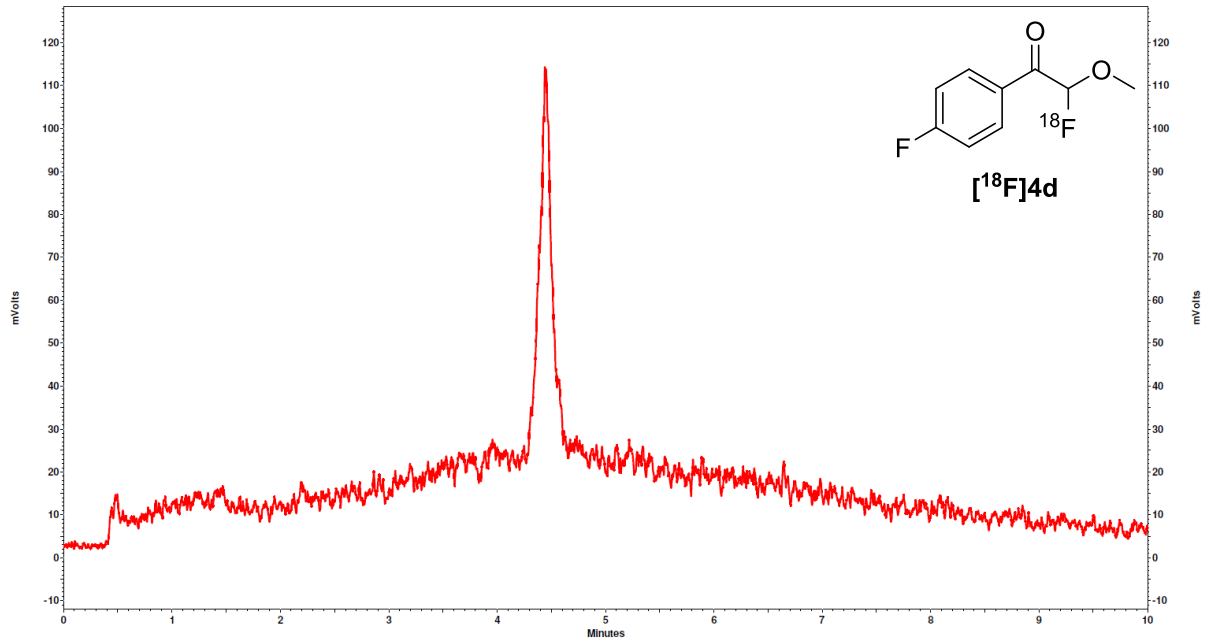

mAU
Minutes
4b

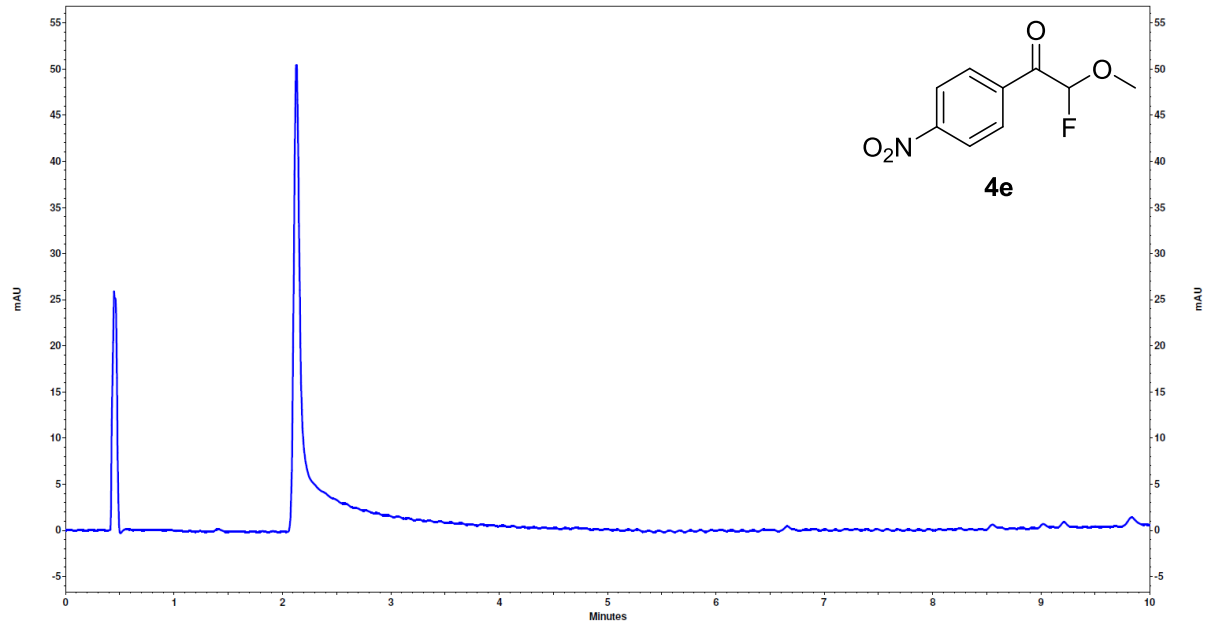

mVolts
Minutes
[18F]4b

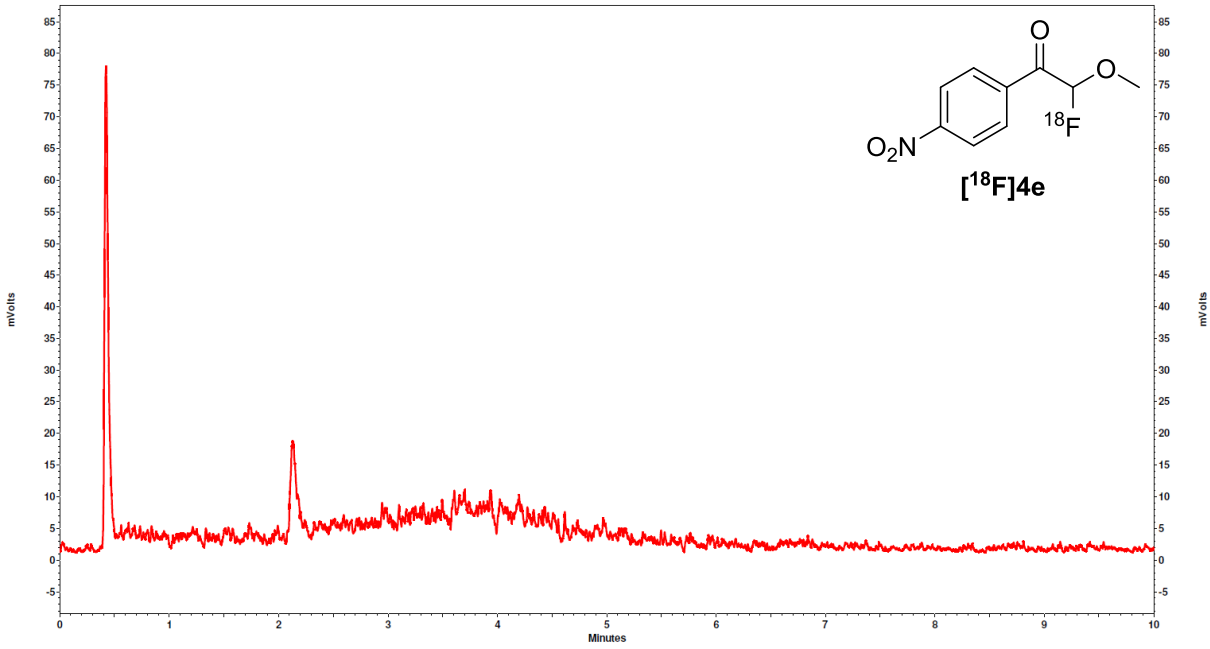

mAU
Minutes
Br
O
O
F
4c

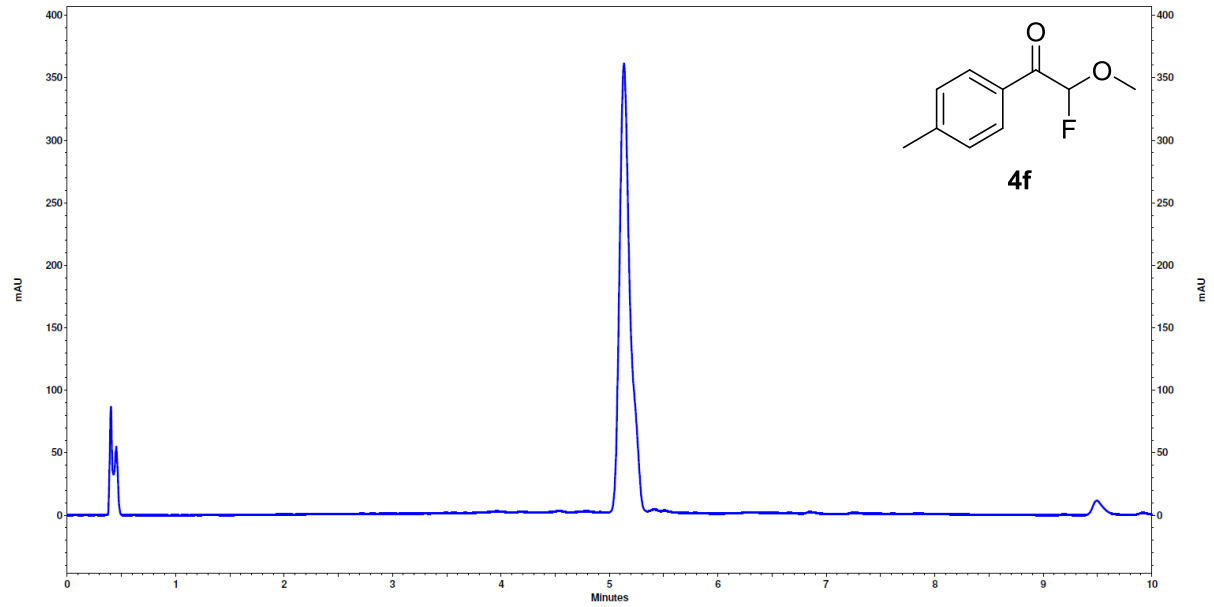

mVolts
Minutes
Br
O
O
18F
[18F]4c

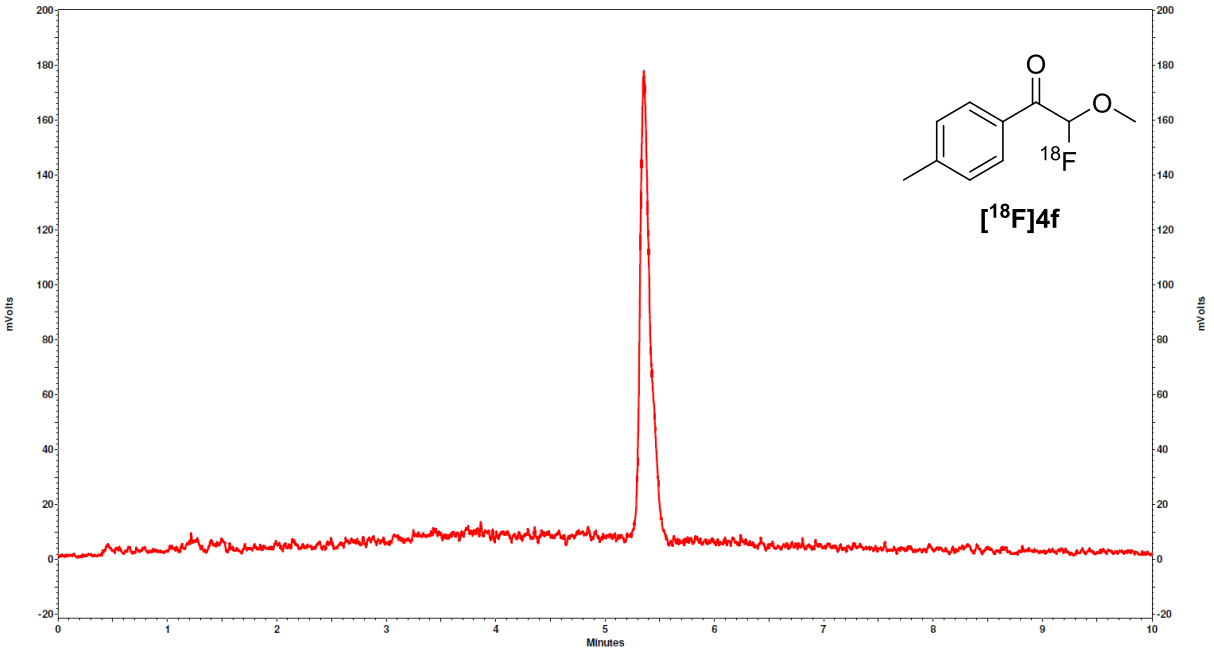

mAU
Minutes
4d

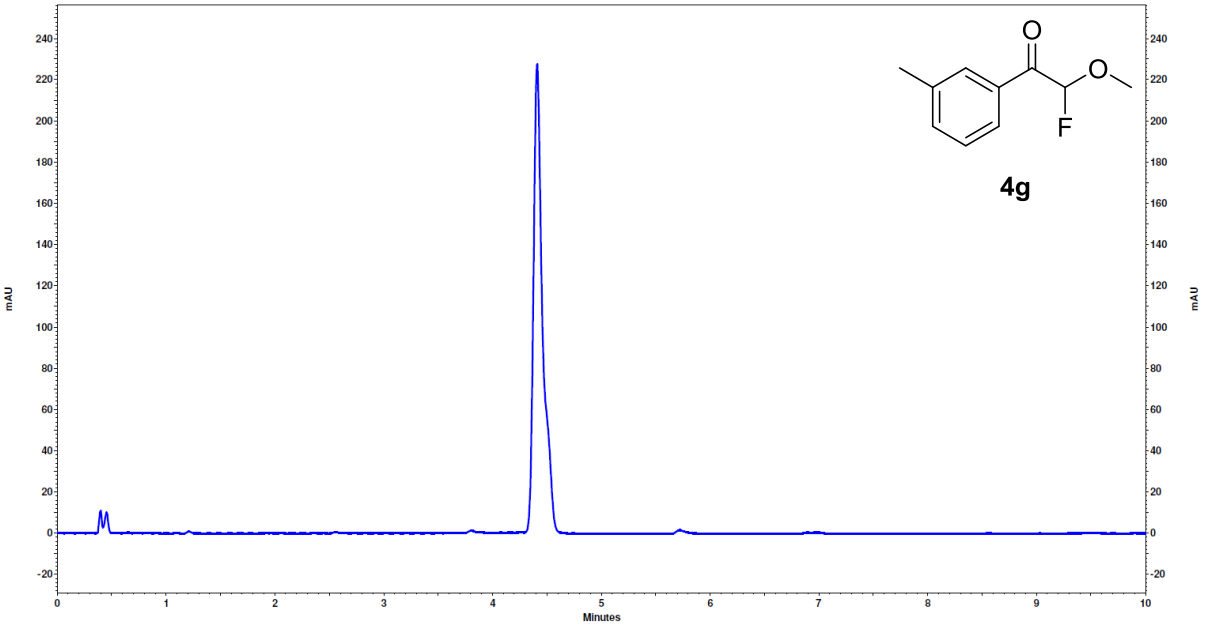

mVolts
Minutes
[18F]4d

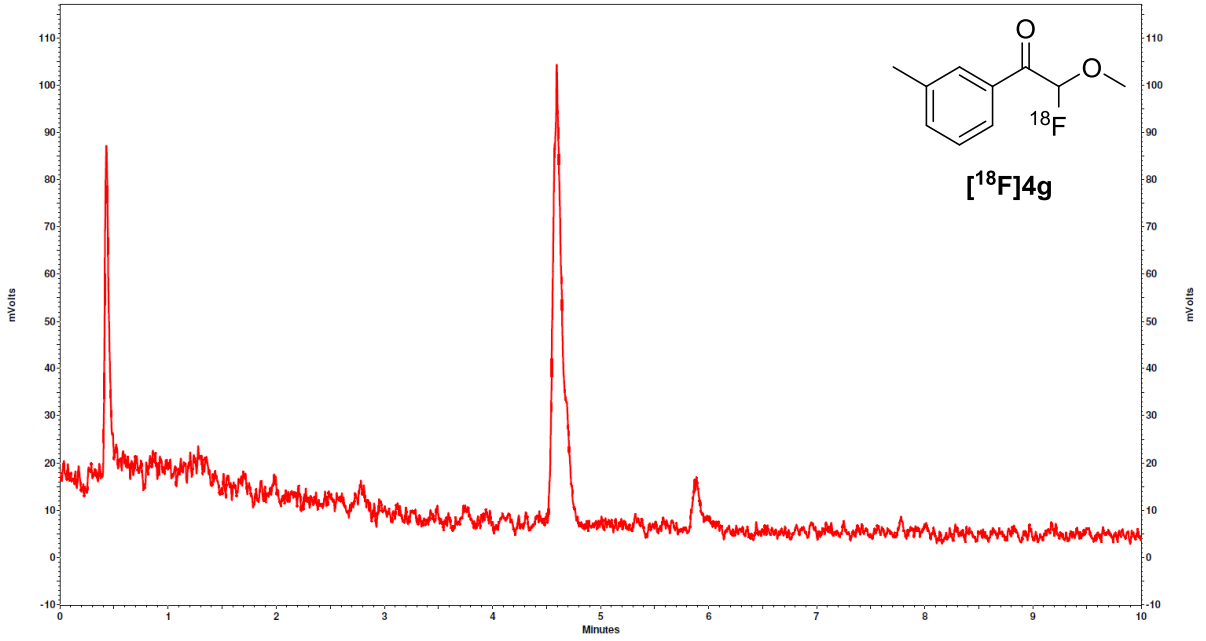

mAU
Minutes
O
O
F
O_2N
4e

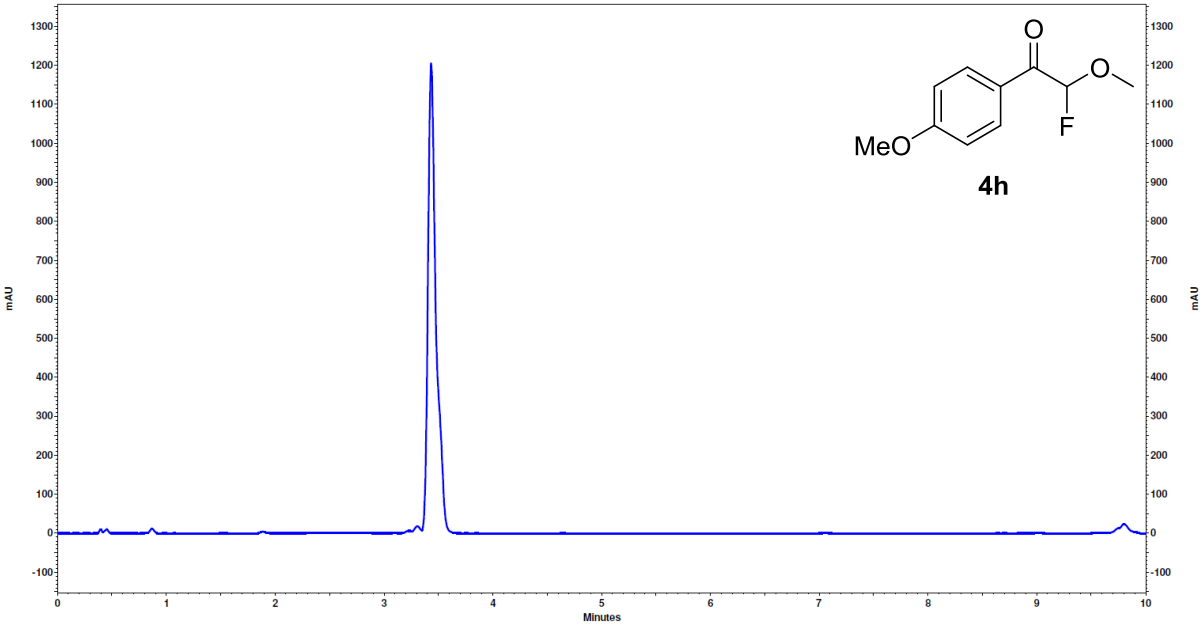

mVolts
Minutes
O
O
^{18}F
O_2N
[^{18}F]4e

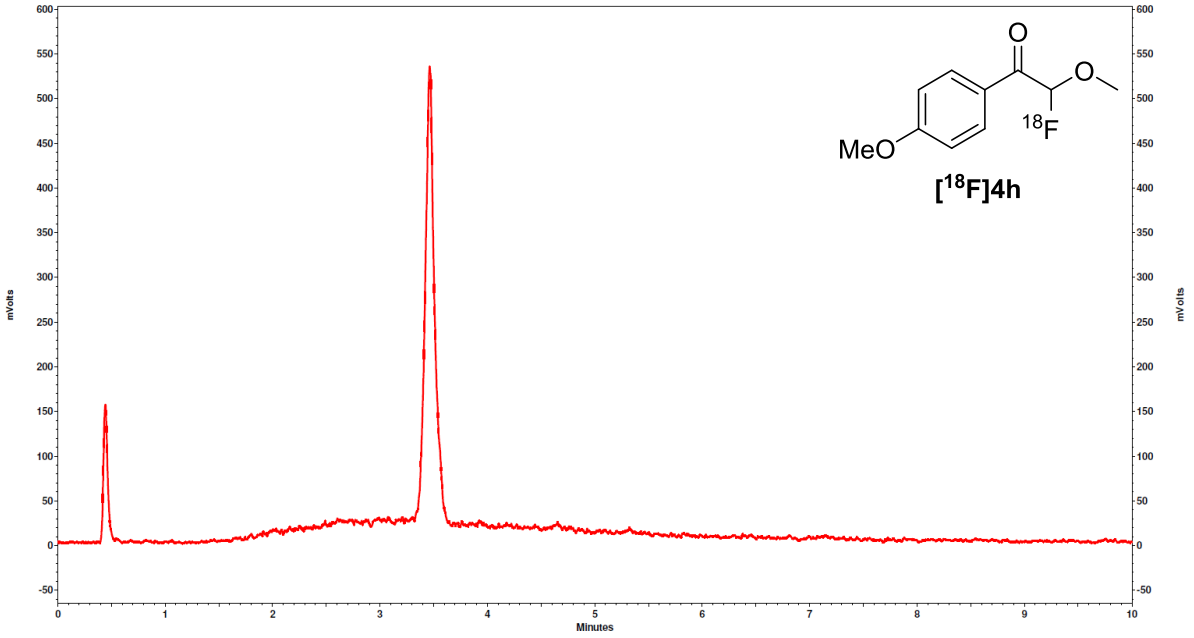

mAU
Minutes
4f

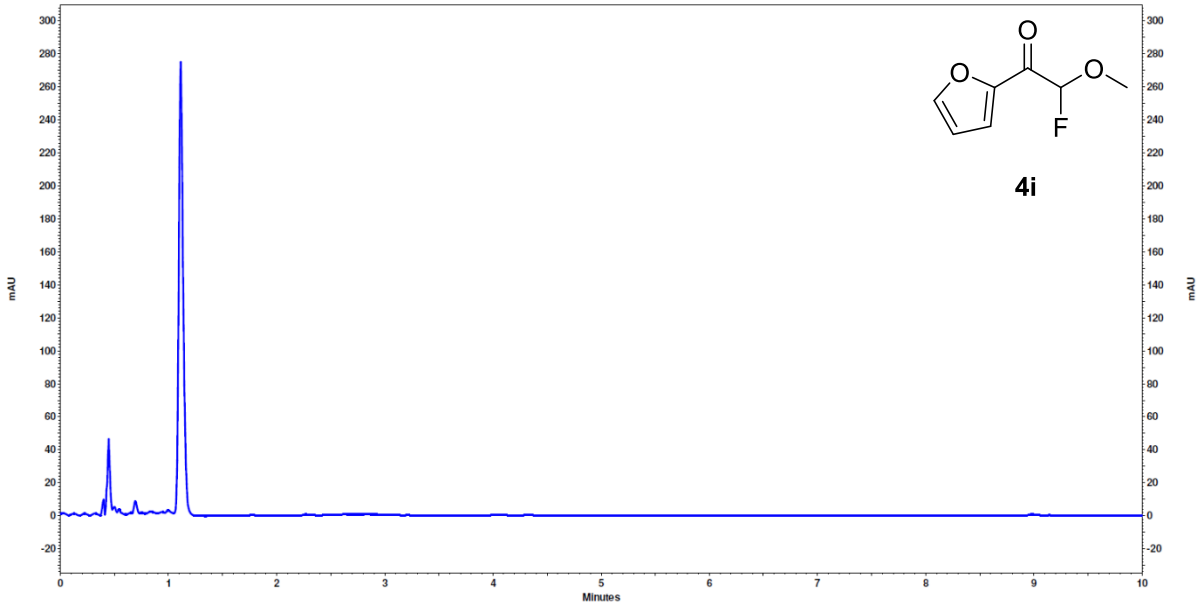

mVolts
Minutes
[18F]4f


mAU
Minutes
4g


mVolts
Minutes
[18F]4g


mAU
Minutes
MeO
O
O
F
4h


mVolts
Minutes
MeO
O
O
18F
[18F]4h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Minutes
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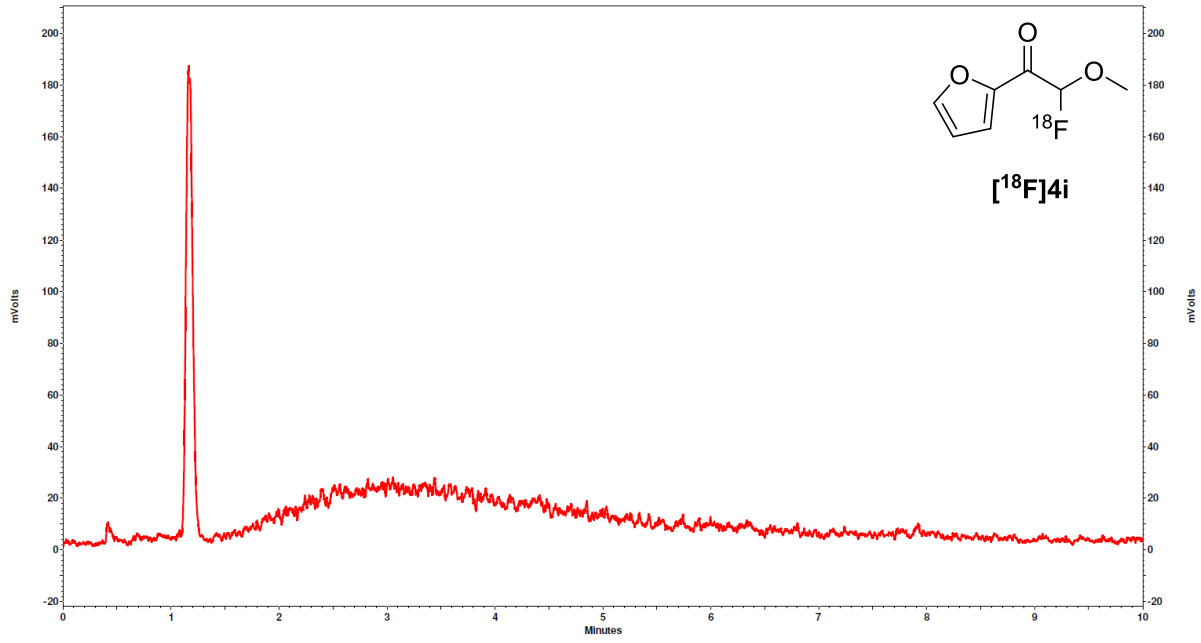
mVolts
Minutes
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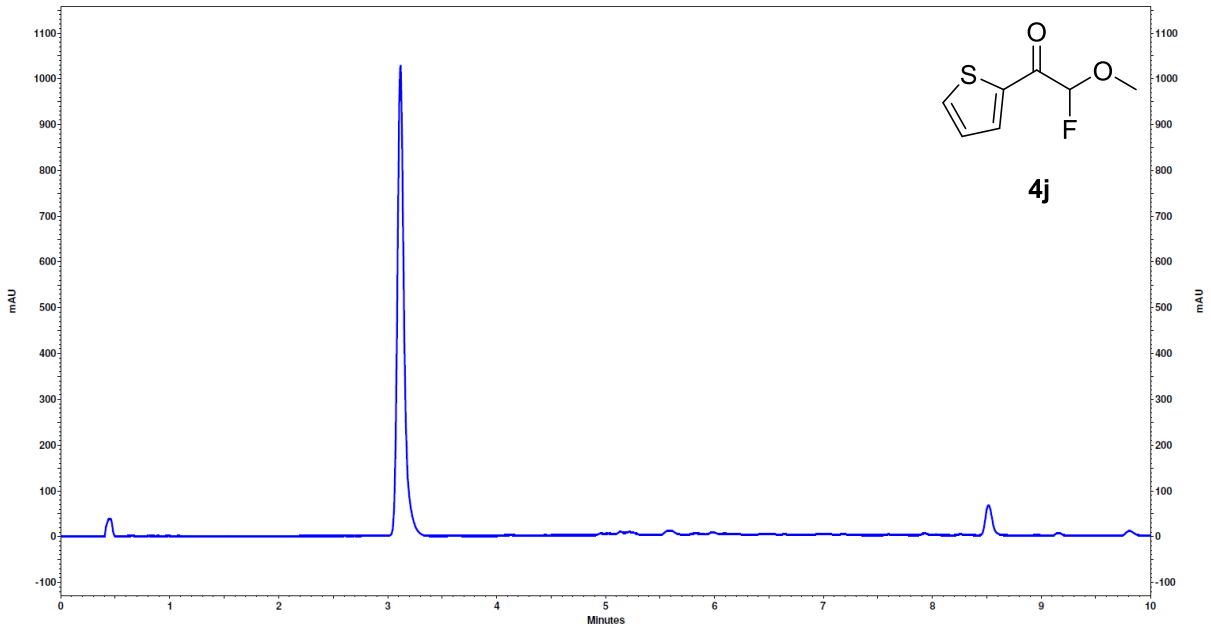
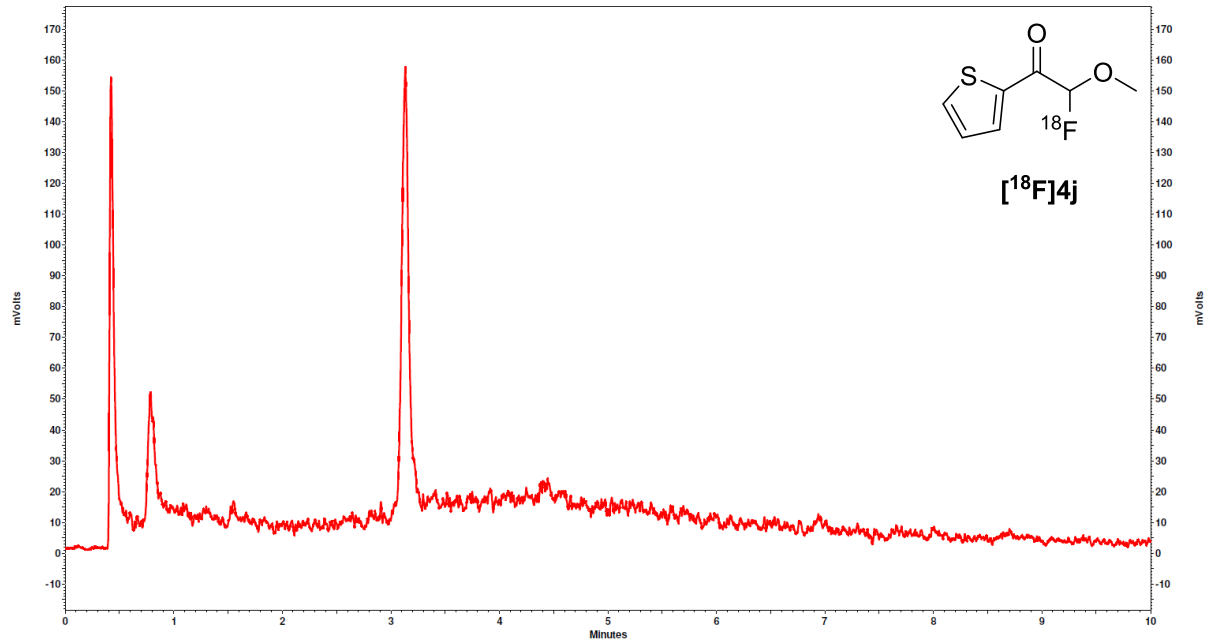

mAU
Minutes
4j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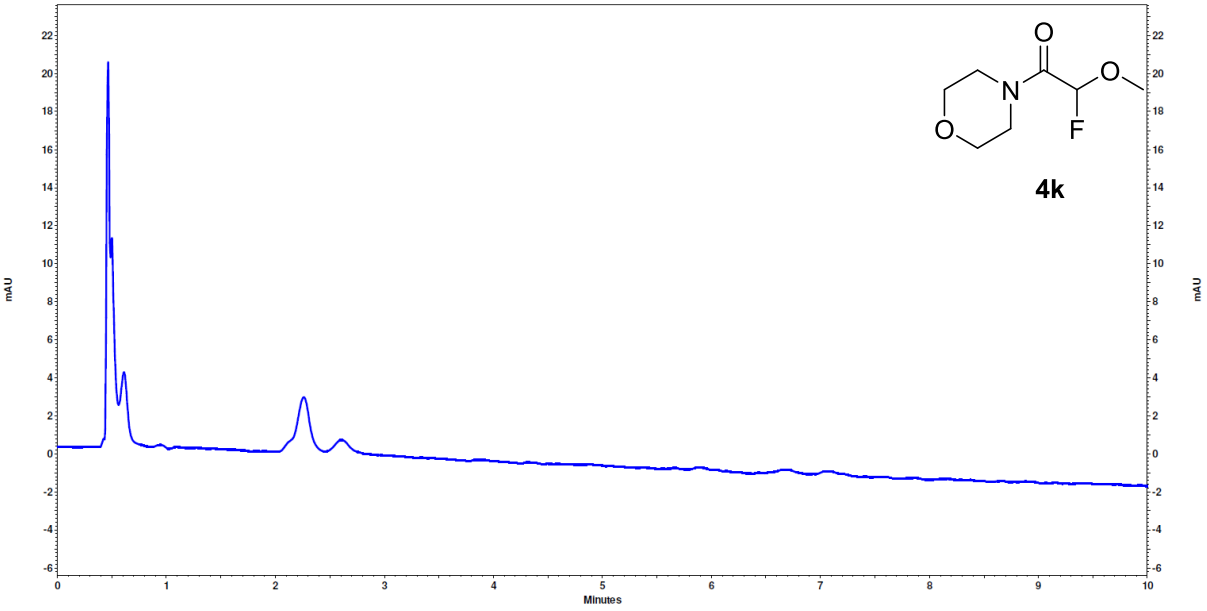
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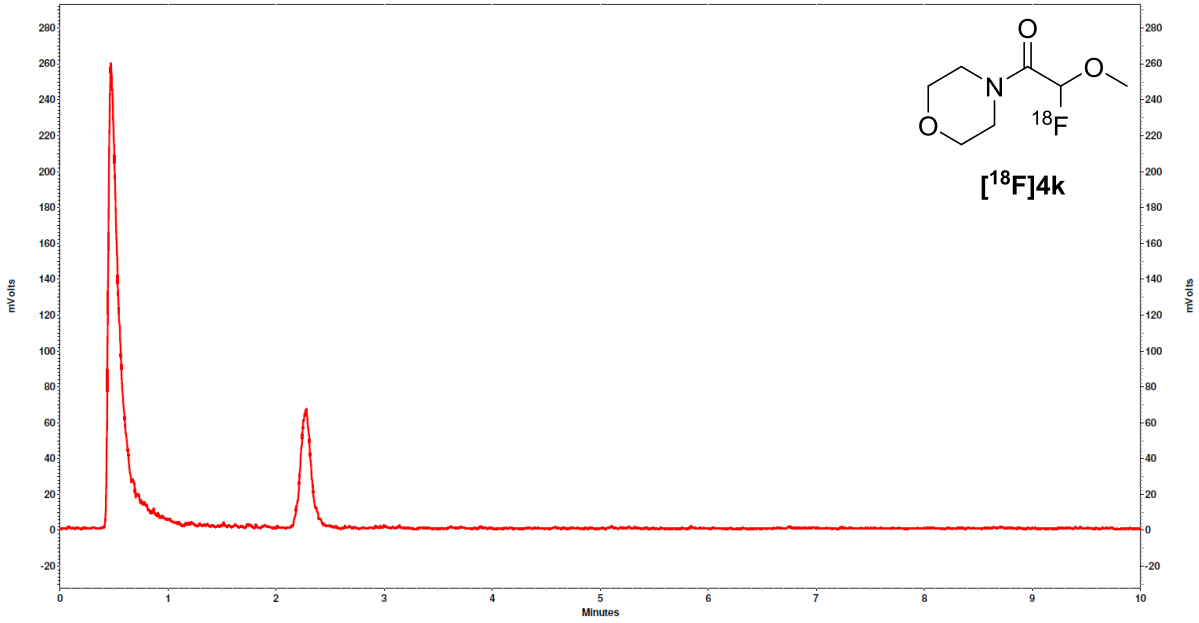
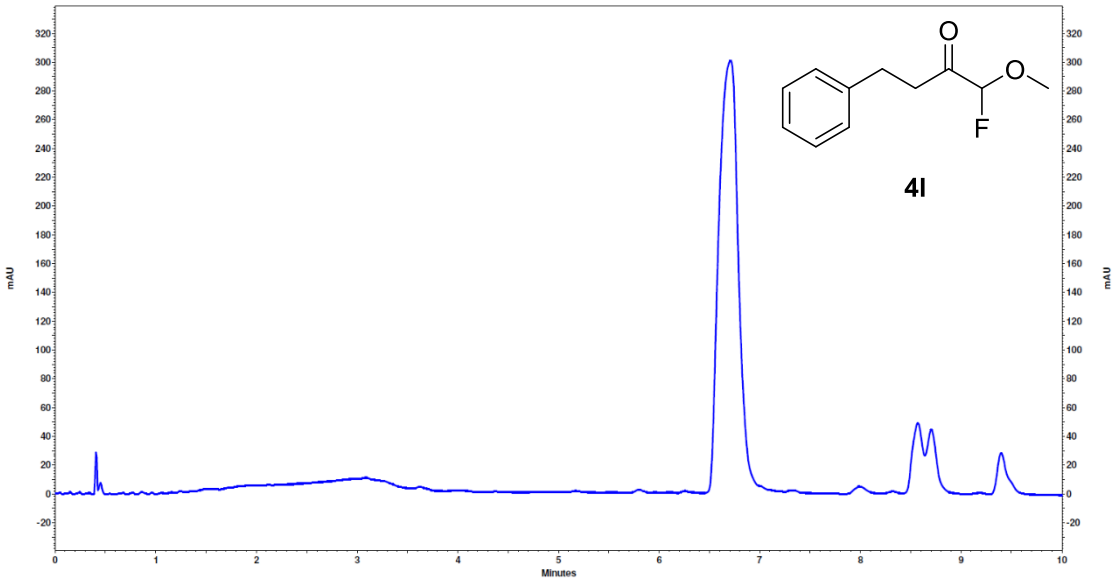
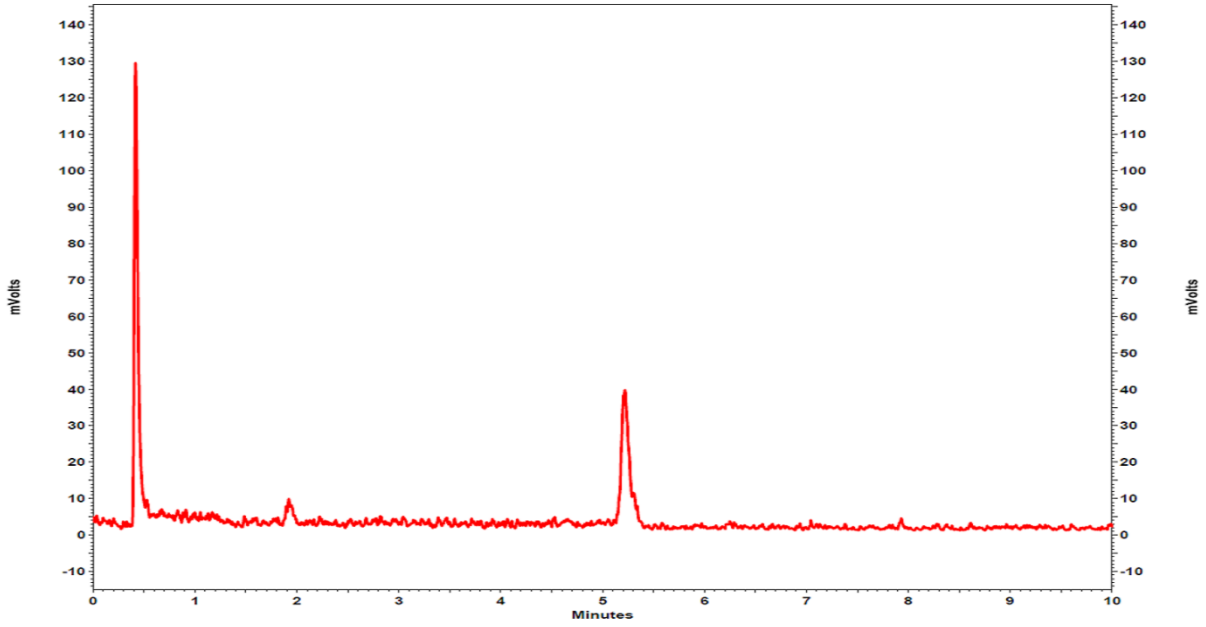
Minutes
4k


mVolts
Minutes
[18F]4k


O
O
F
4l
mAU
Minutes


mVolts
Minutes

References

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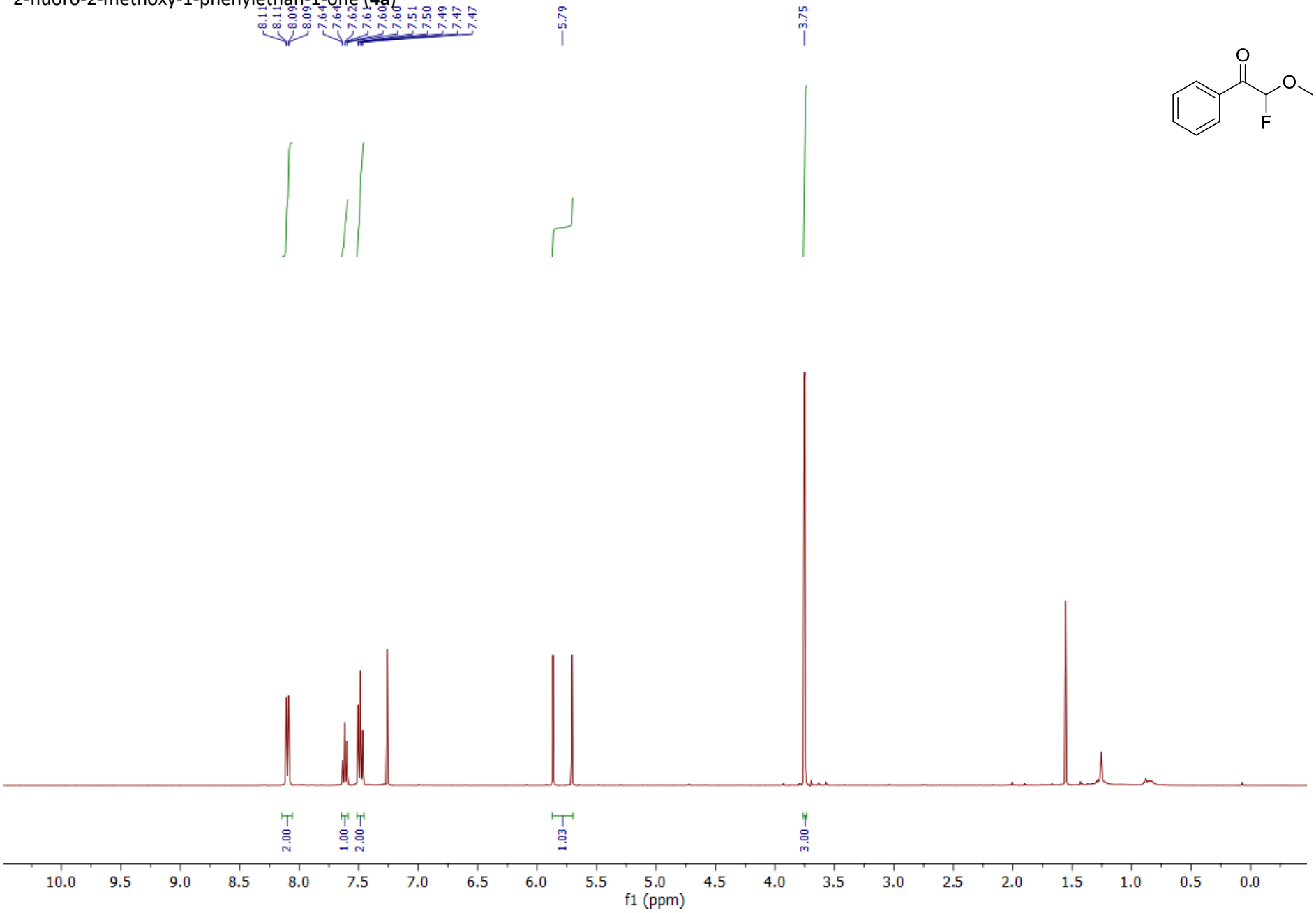
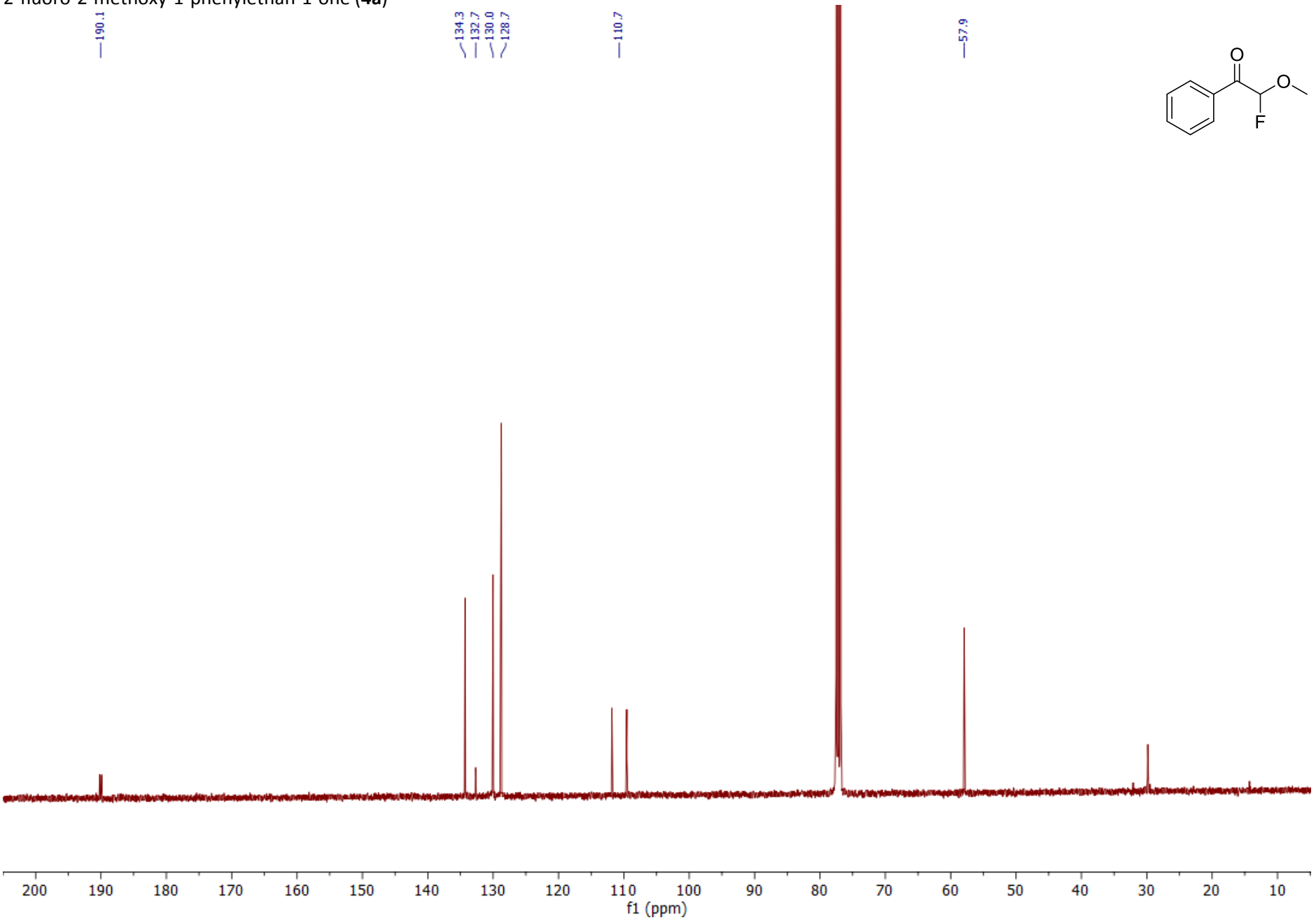
Copies of ^{1}H-, ^{13}C- and ^{19}F-NMR of compounds

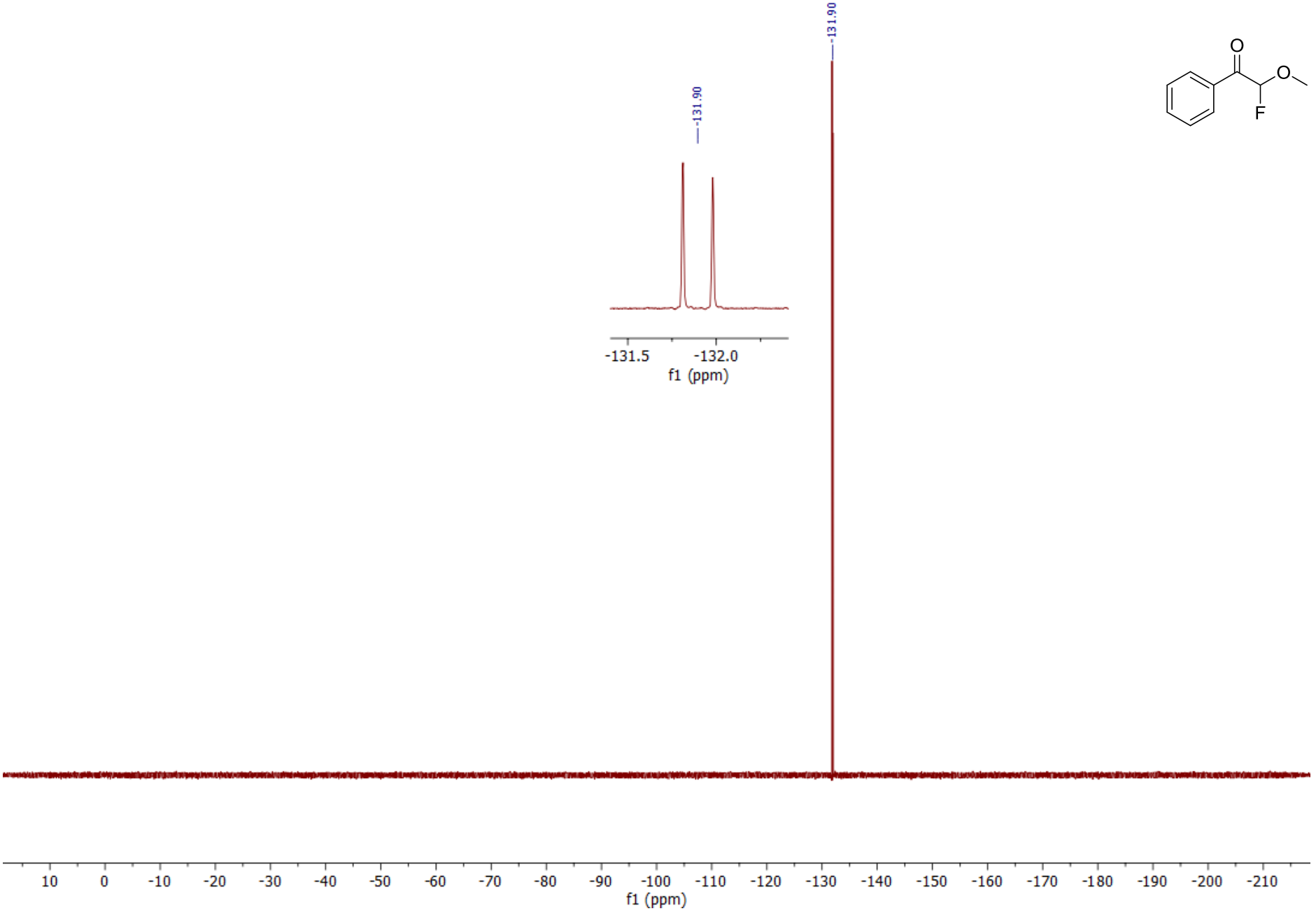
2-fluoro-2-methoxy-1-phenylethan-1-one (**4a**)



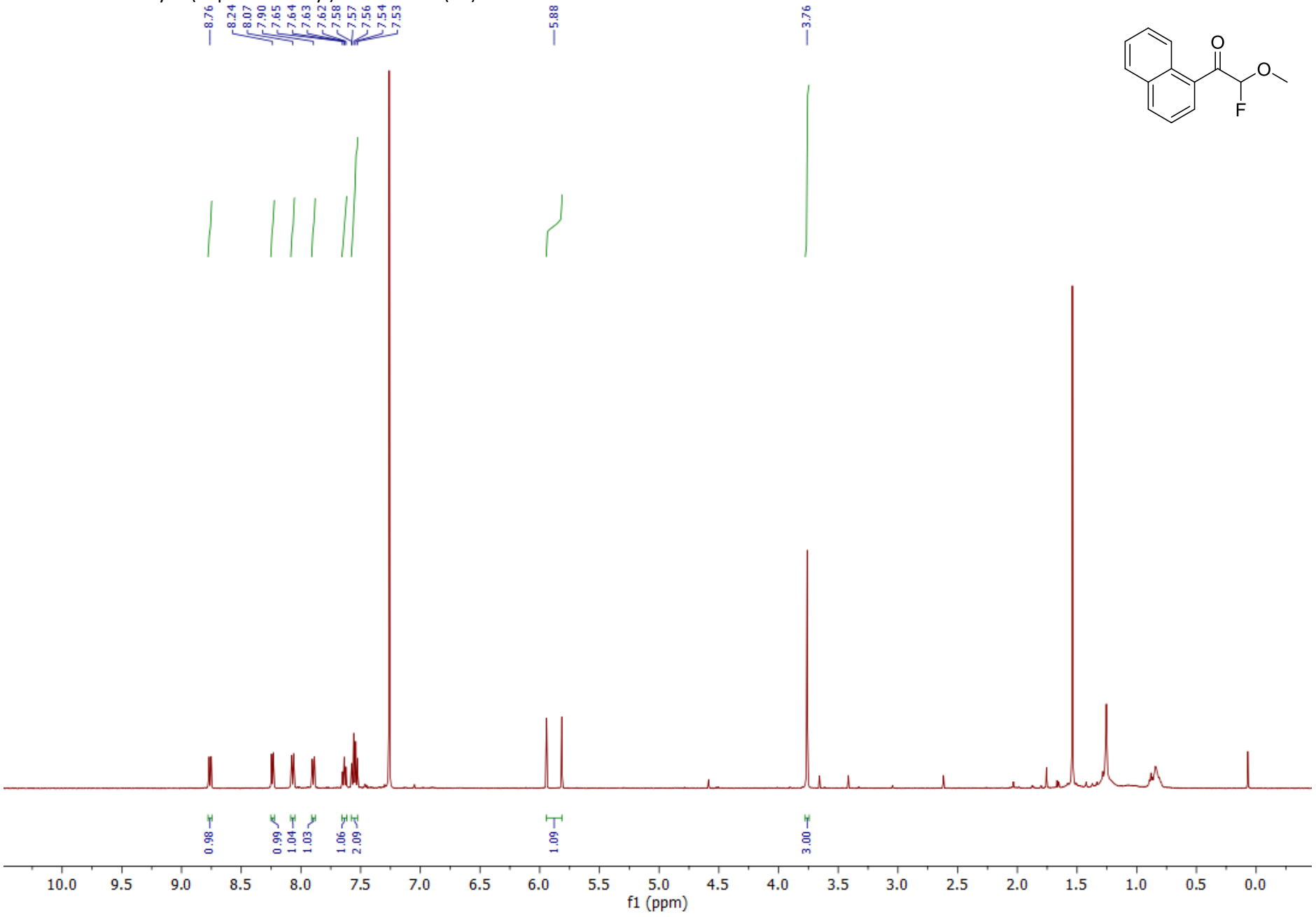
2-fluoro-2-methoxy-1-phenylethan-1-one (**4a**)



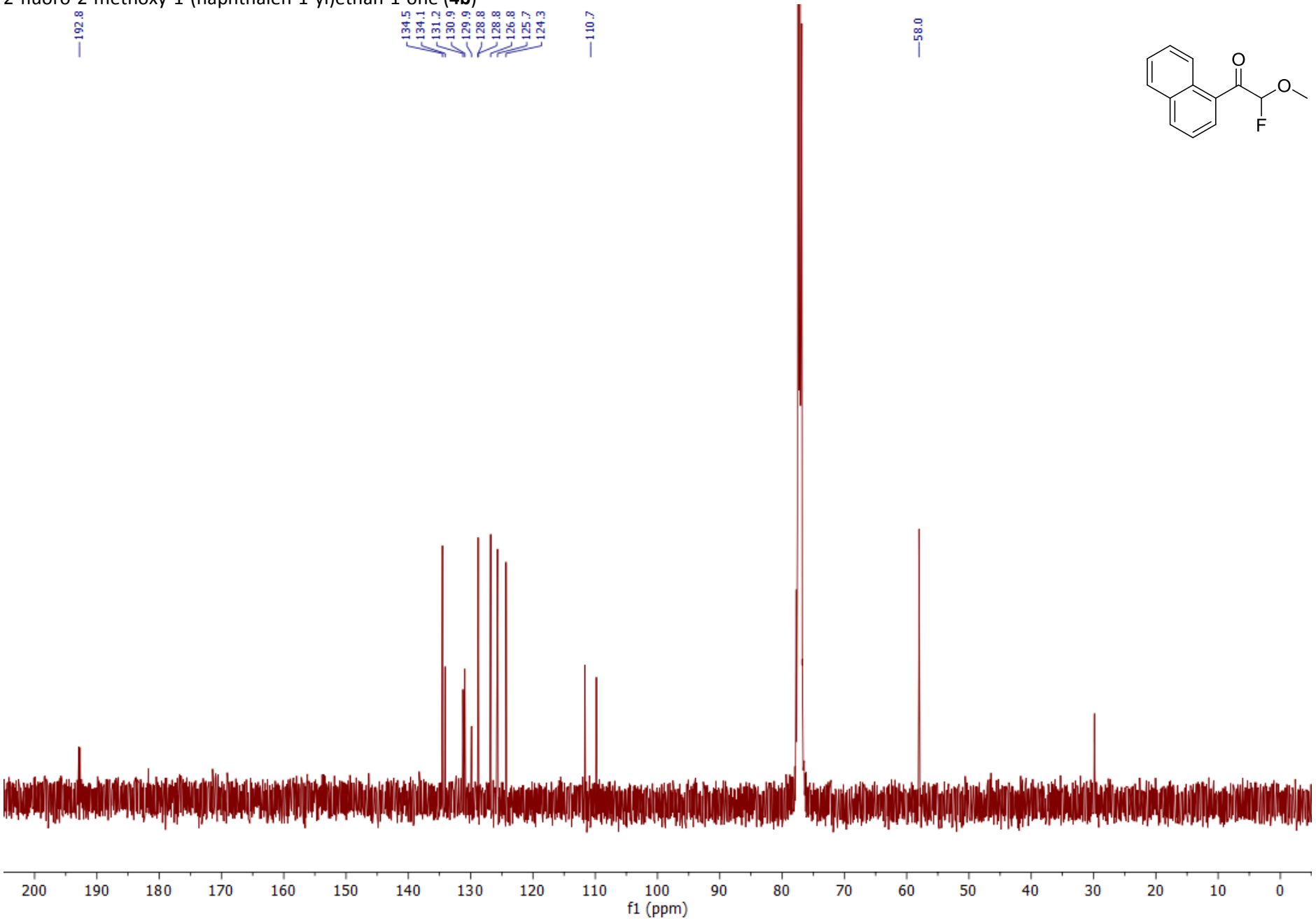
2-fluoro-2-methoxy-1-phenylethan-1-one (**4a**)



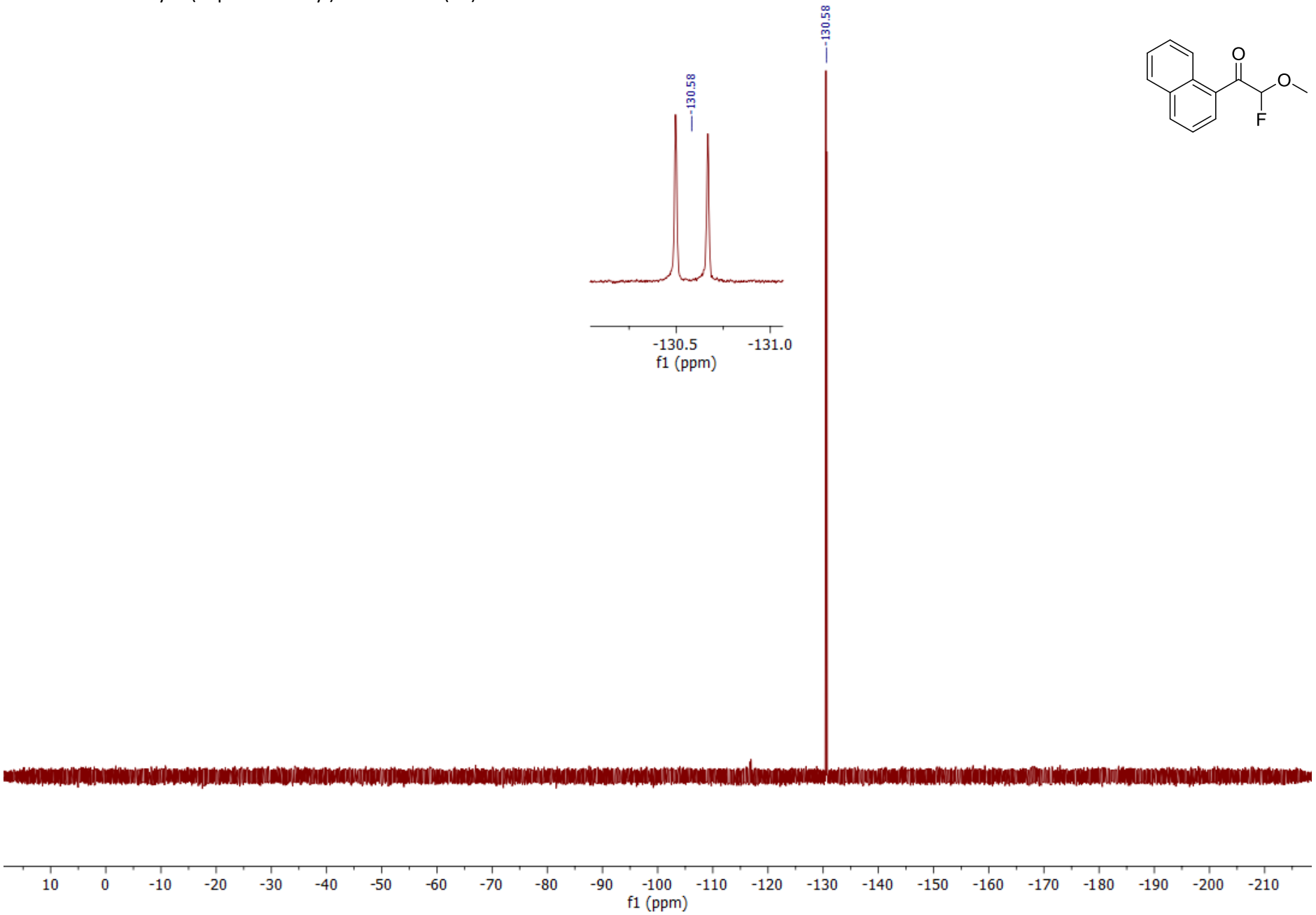
2-fluoro-2-methoxy-1-(naphthalen-1-yl)ethan-1-one (**4b**)



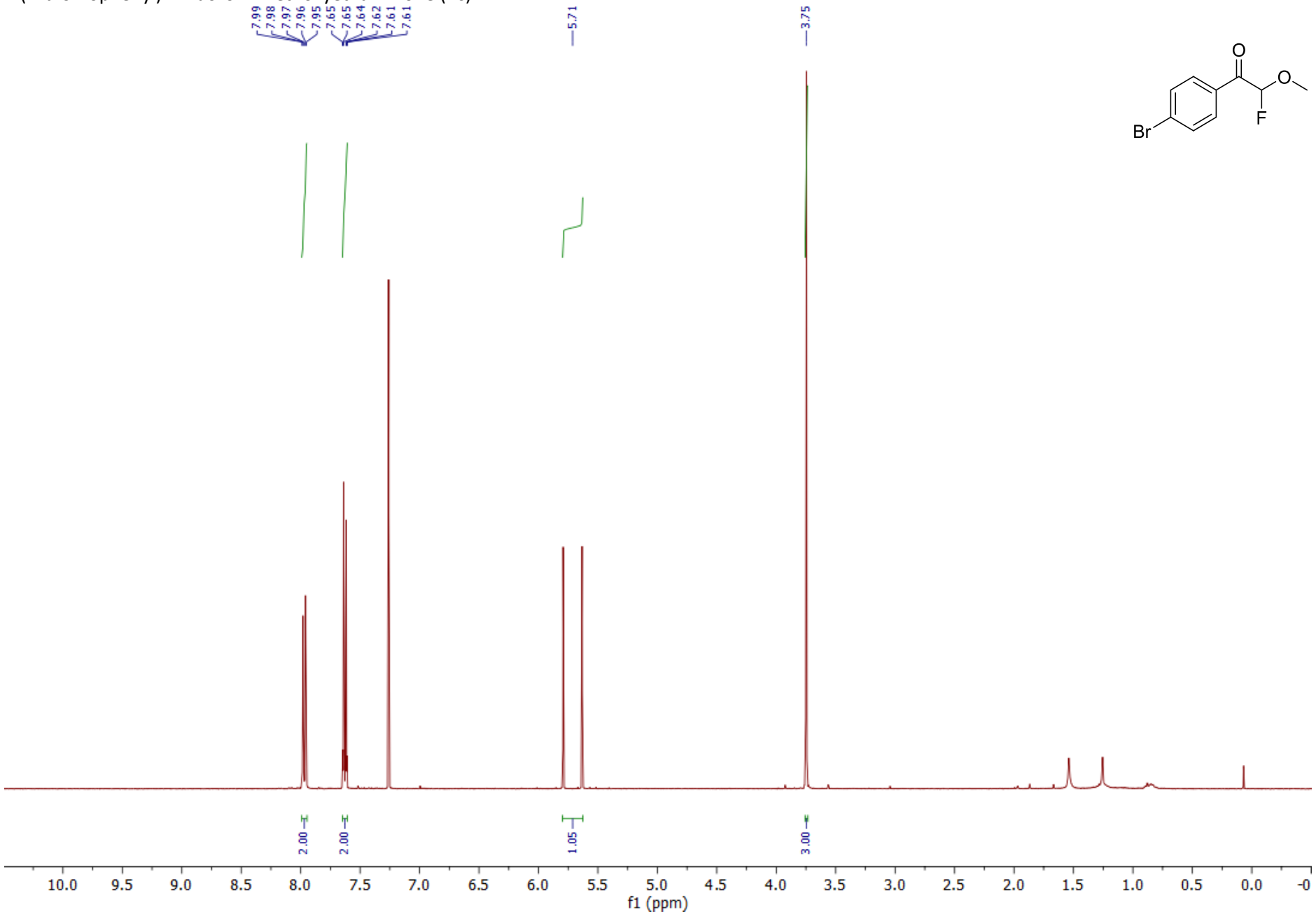
2-fluoro-2-methoxy-1-(naphthalen-1-yl)ethan-1-one (**4b**)



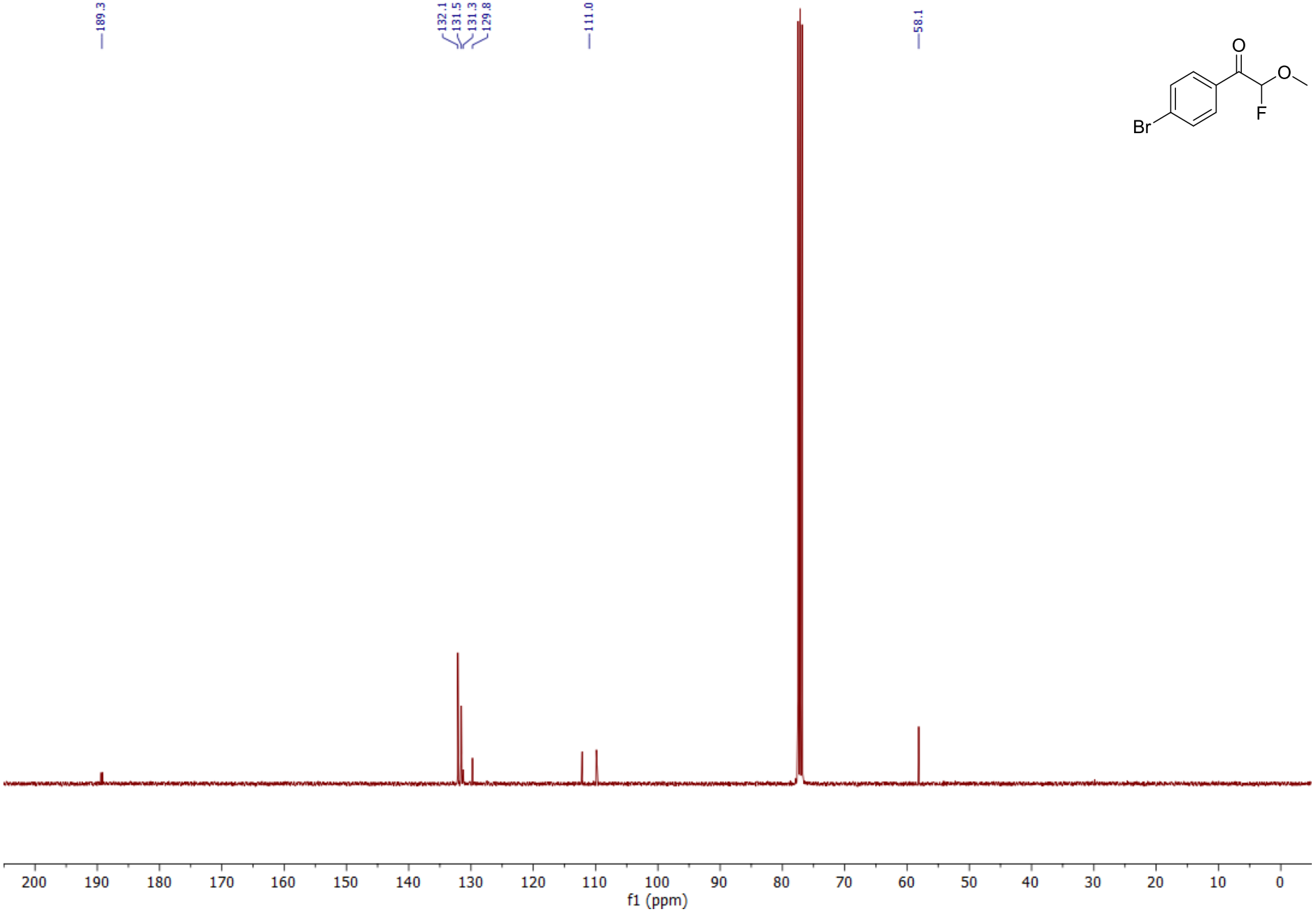
2-fluoro-2-methoxy-1-(naphthalen-1-yl)ethan-1-one (**4b**)



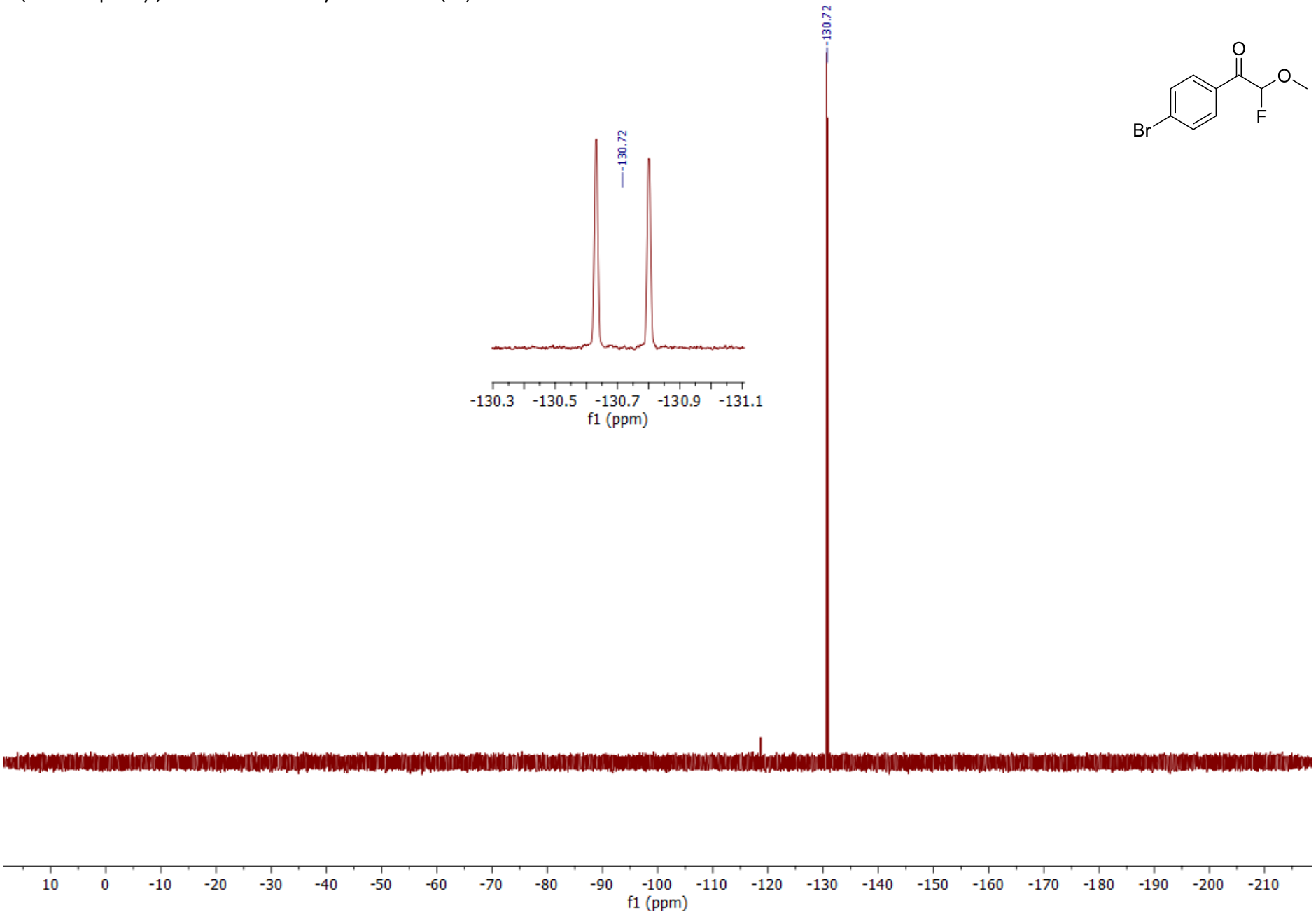
1-(4-bromophenyl)-2-fluoro-2-methoxyethan-1-one (**4c**)



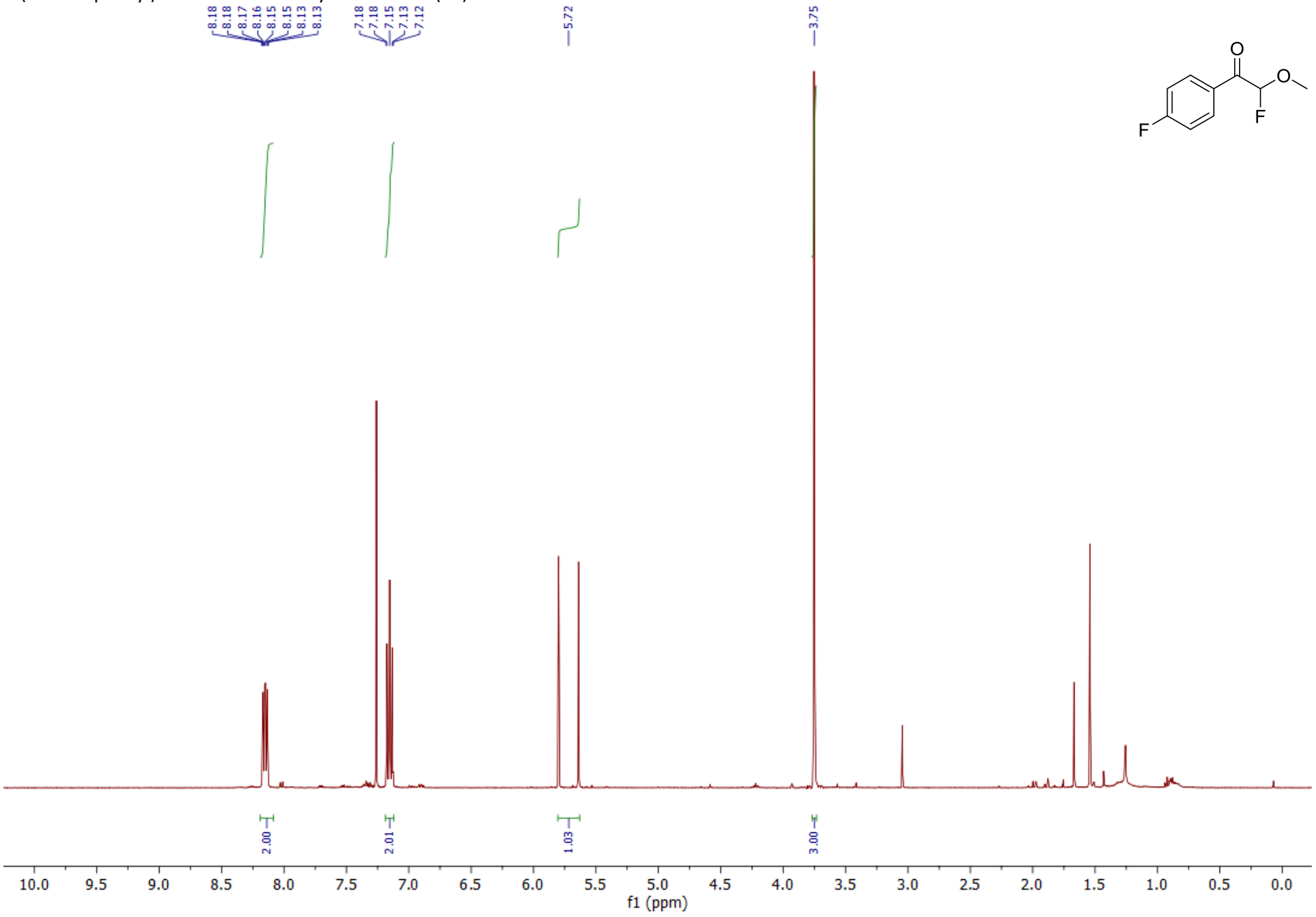
1-(4-bromophenyl)-2-fluoro-2-methoxyethan-1-one (**4c**)



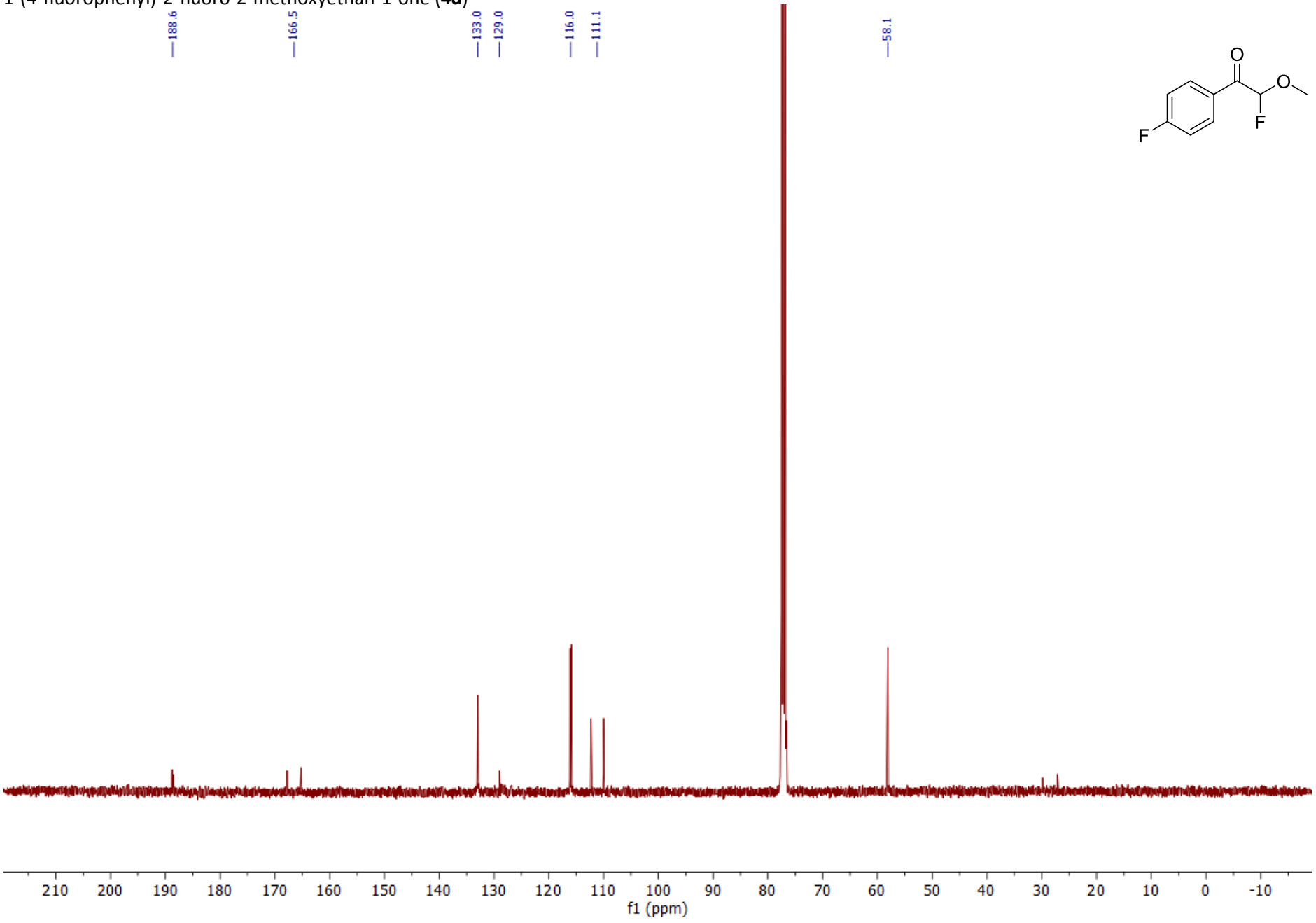
1-(4-bromophenyl)-2-fluoro-2-methoxyethan-1-one (**4c**)



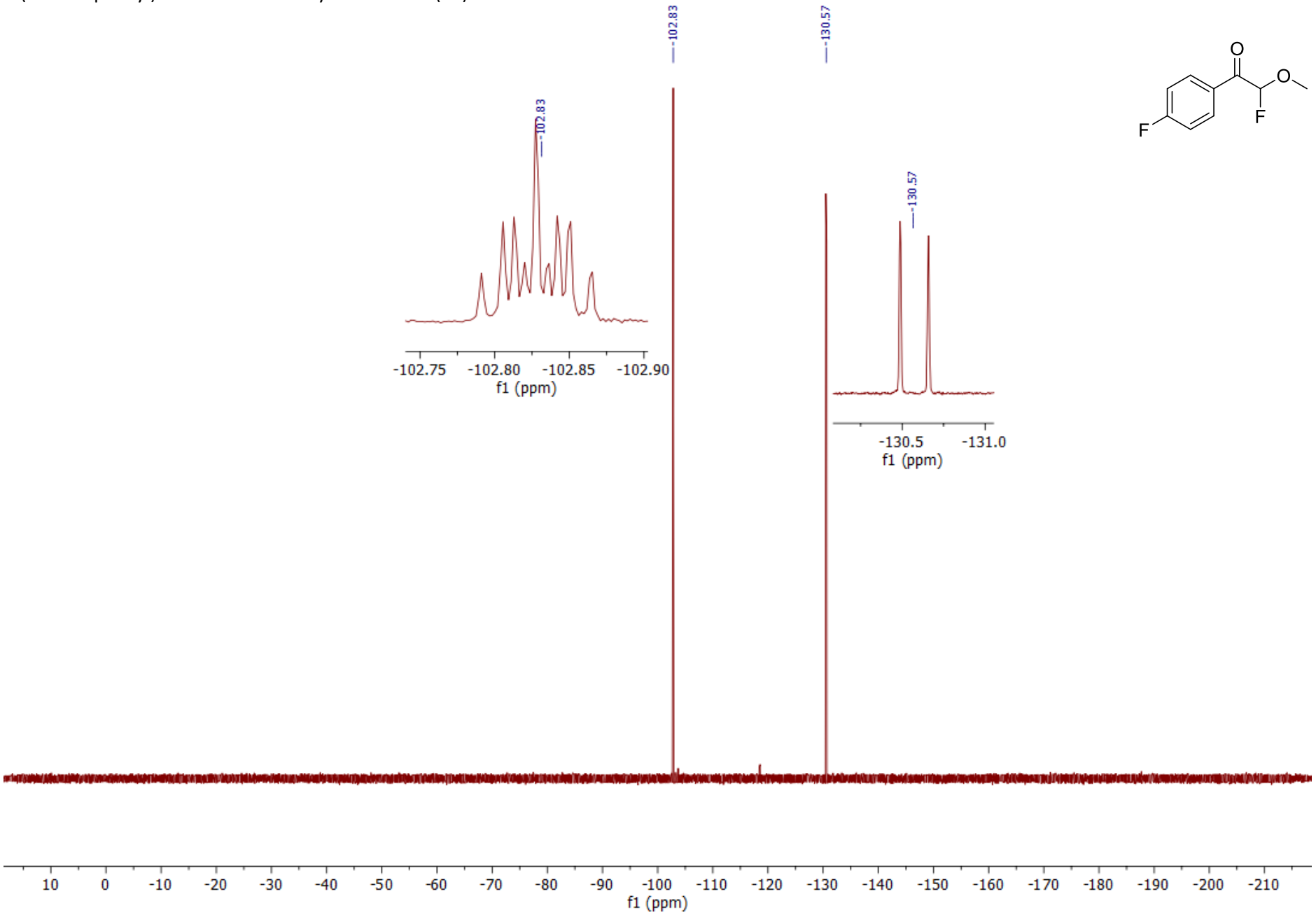
1-(4-fluorophenyl)-2-fluoro-2-methoxyethan-1-one (**4d**)



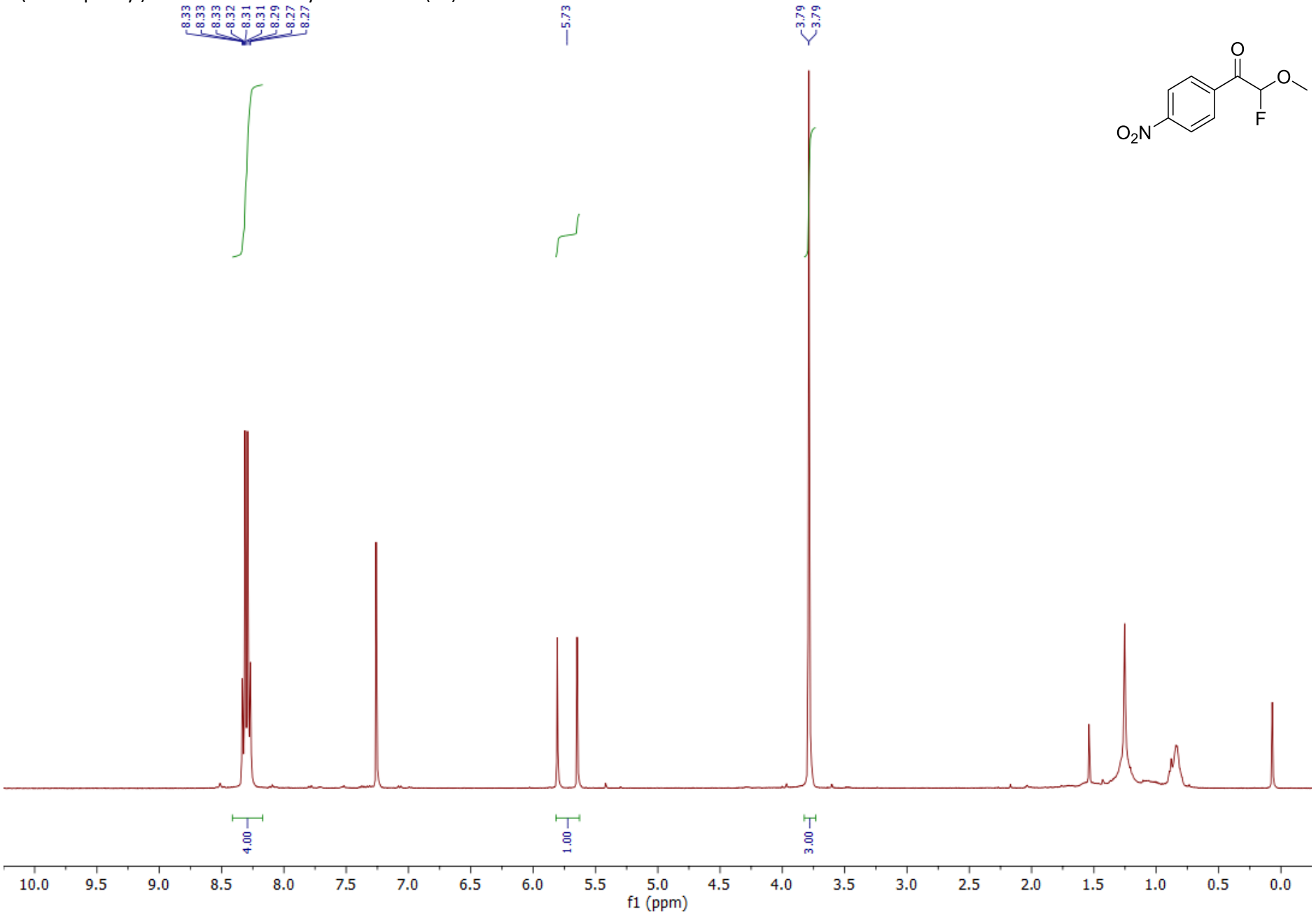
1-(4-fluorophenyl)-2-fluoro-2-methoxyethan-1-one (**4d**)



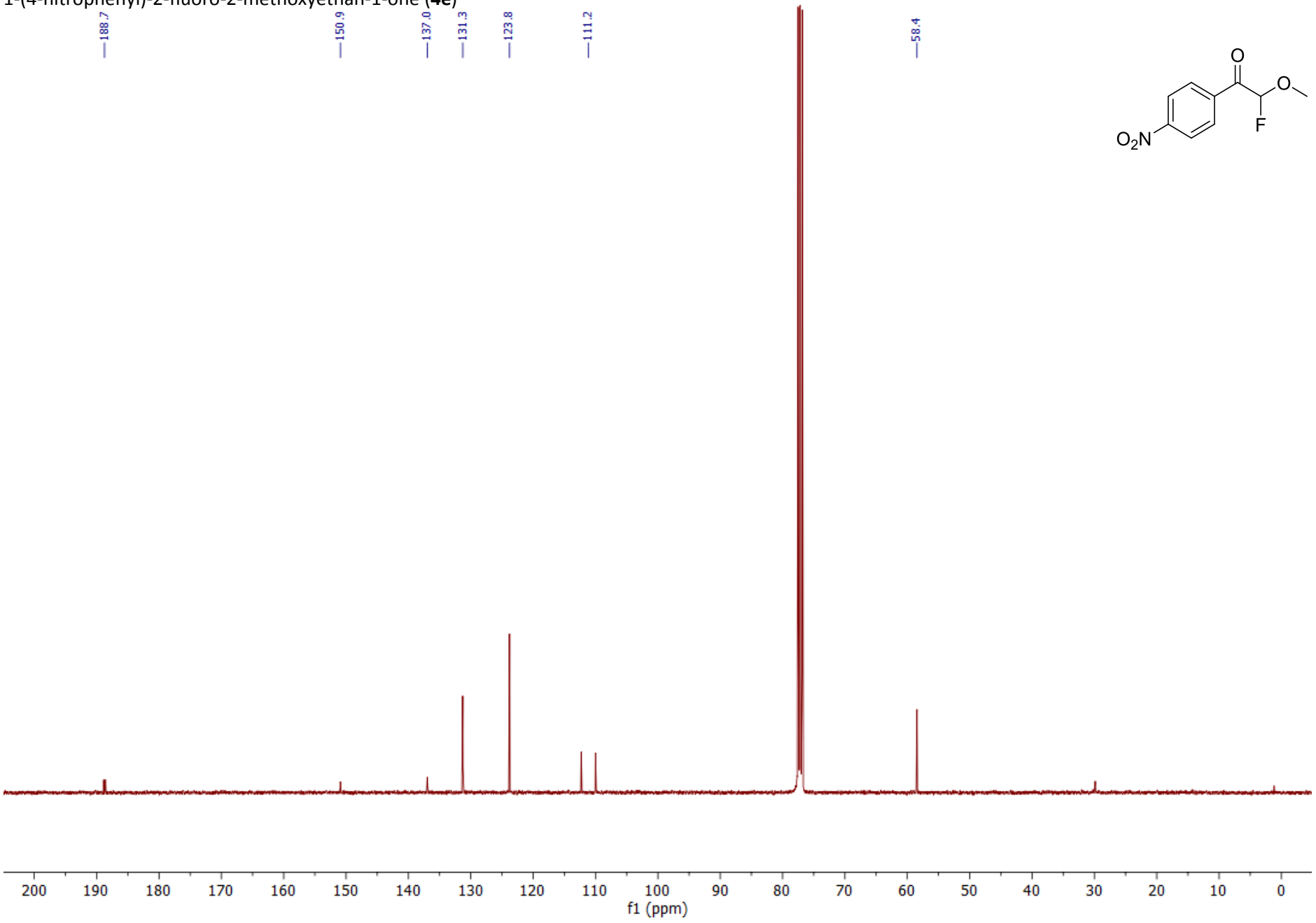
1-(4-fluorophenyl)-2-fluoro-2-methoxyethan-1-one (**4d**)



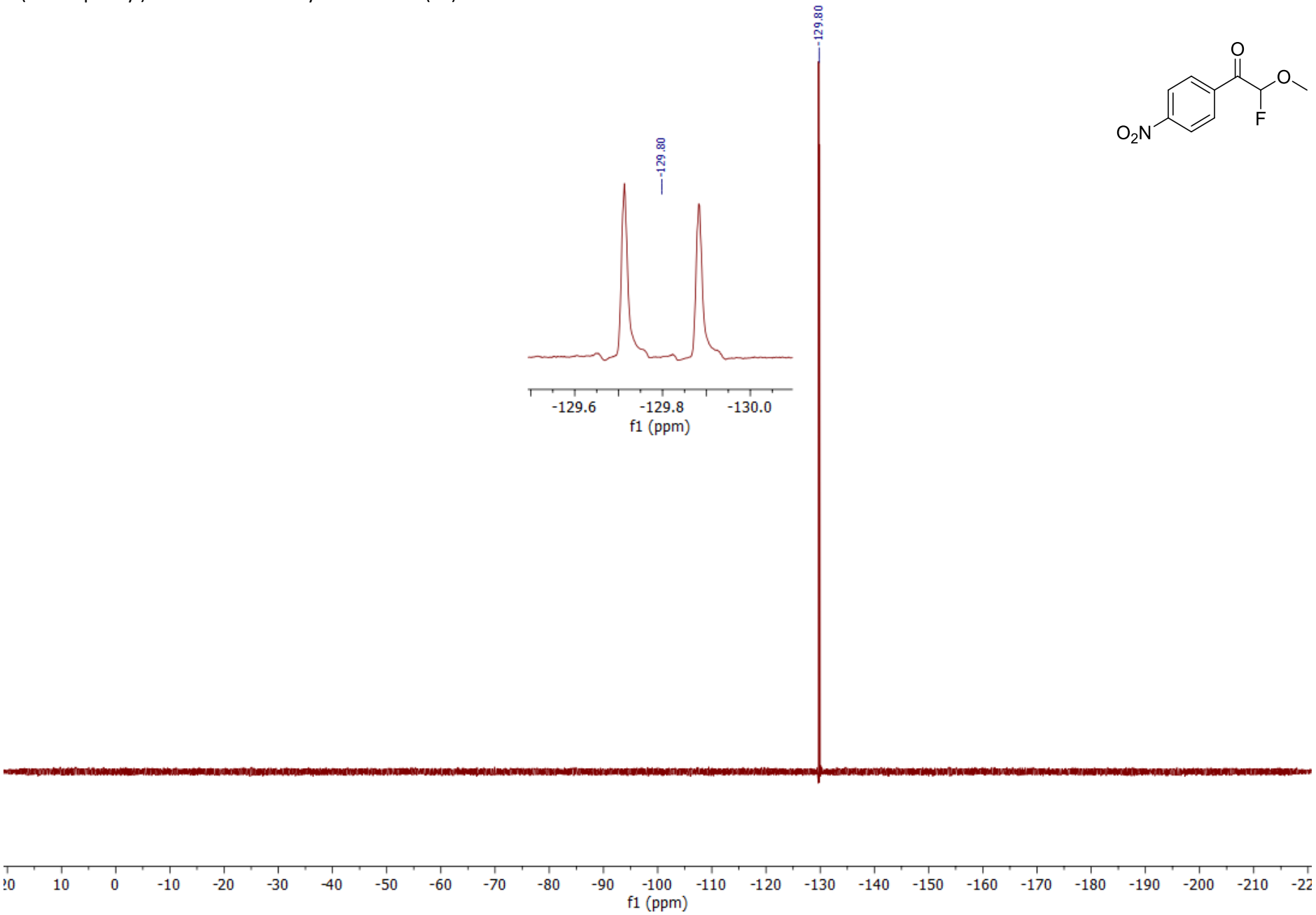
1-(4-nitrophenyl)-2-fluoro-2-methoxyethan-1-one (**4e**)



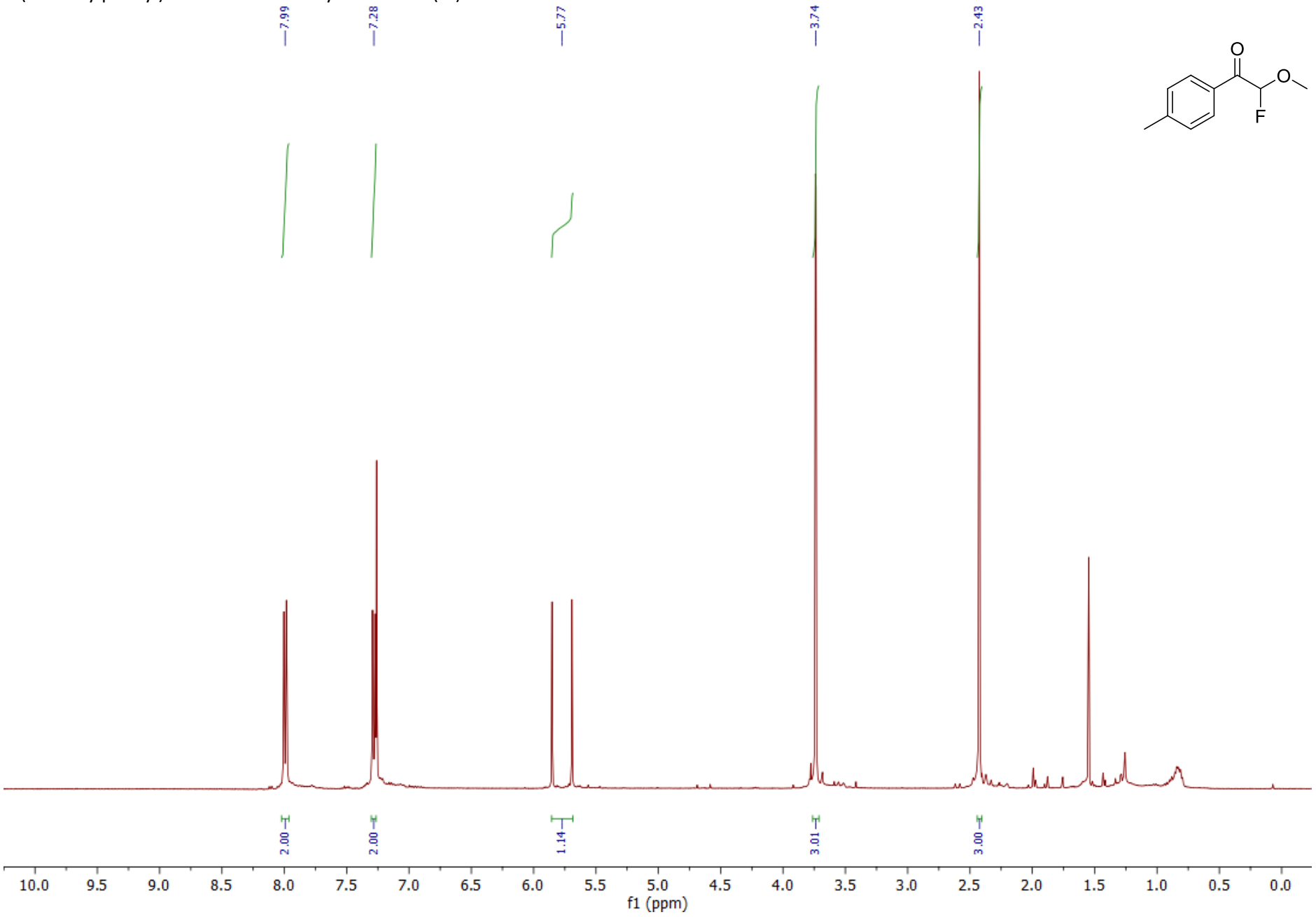
1-(4-nitrophenyl)-2-fluoro-2-methoxyethan-1-one (**4e**)



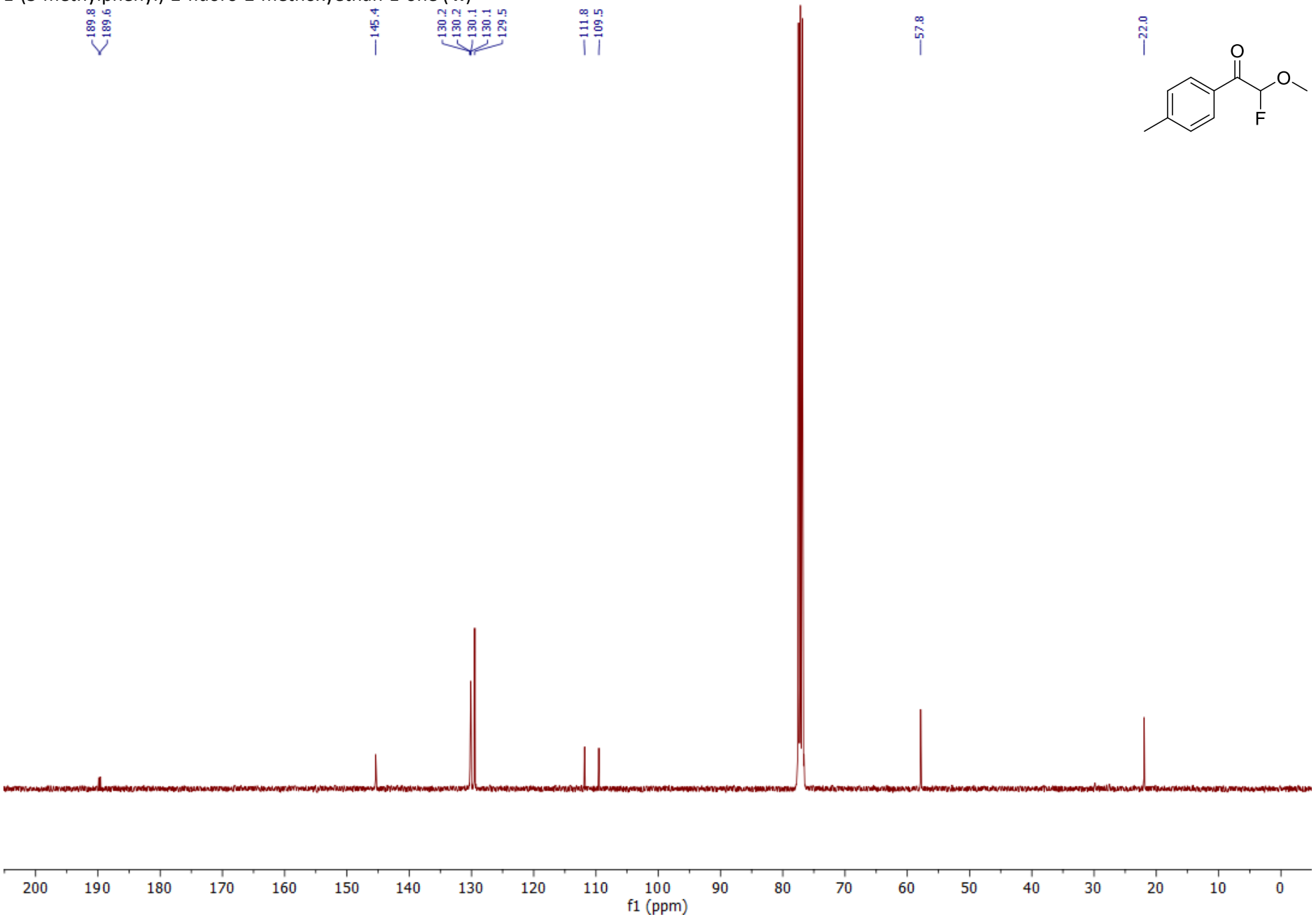
1-(4-nitrophenyl)-2-fluoro-2-methoxyethan-1-one (**4e**)



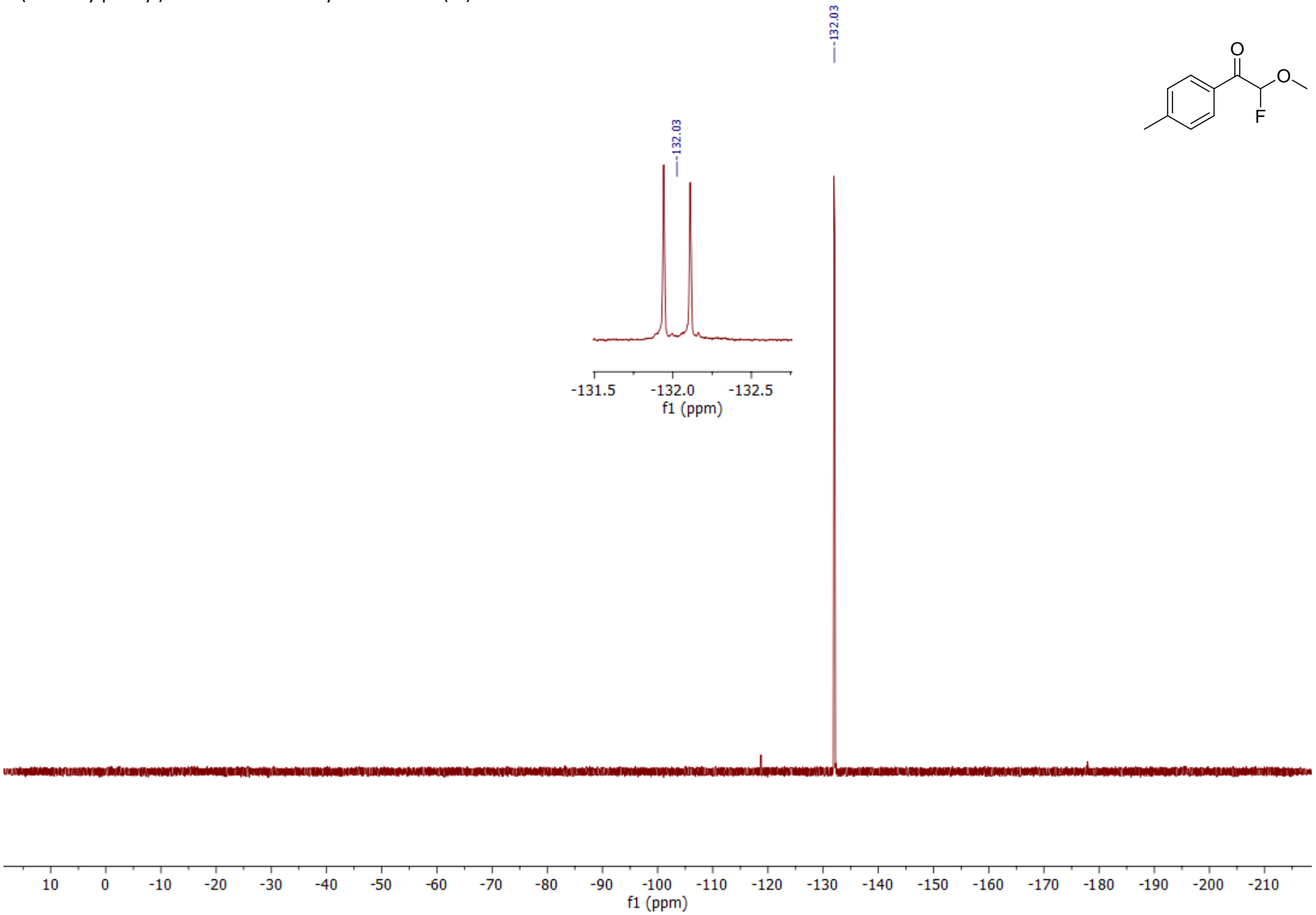
1-(3-methylphenyl)-2-fluoro-2-methoxyethan-1-on (**4f**)



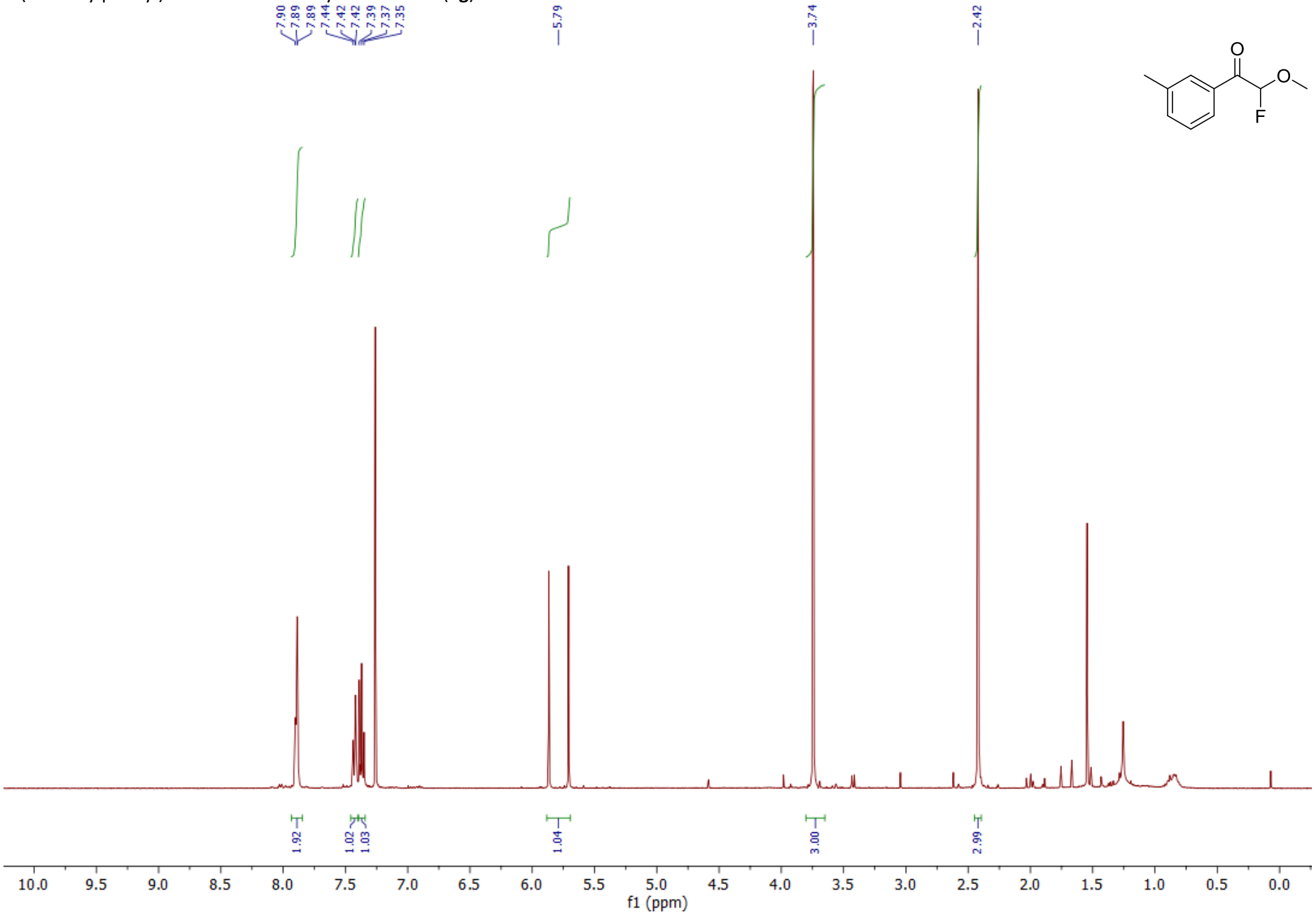
1-(3-methylphenyl)-2-fluoro-2-methoxyethan-1-one (**4f**)



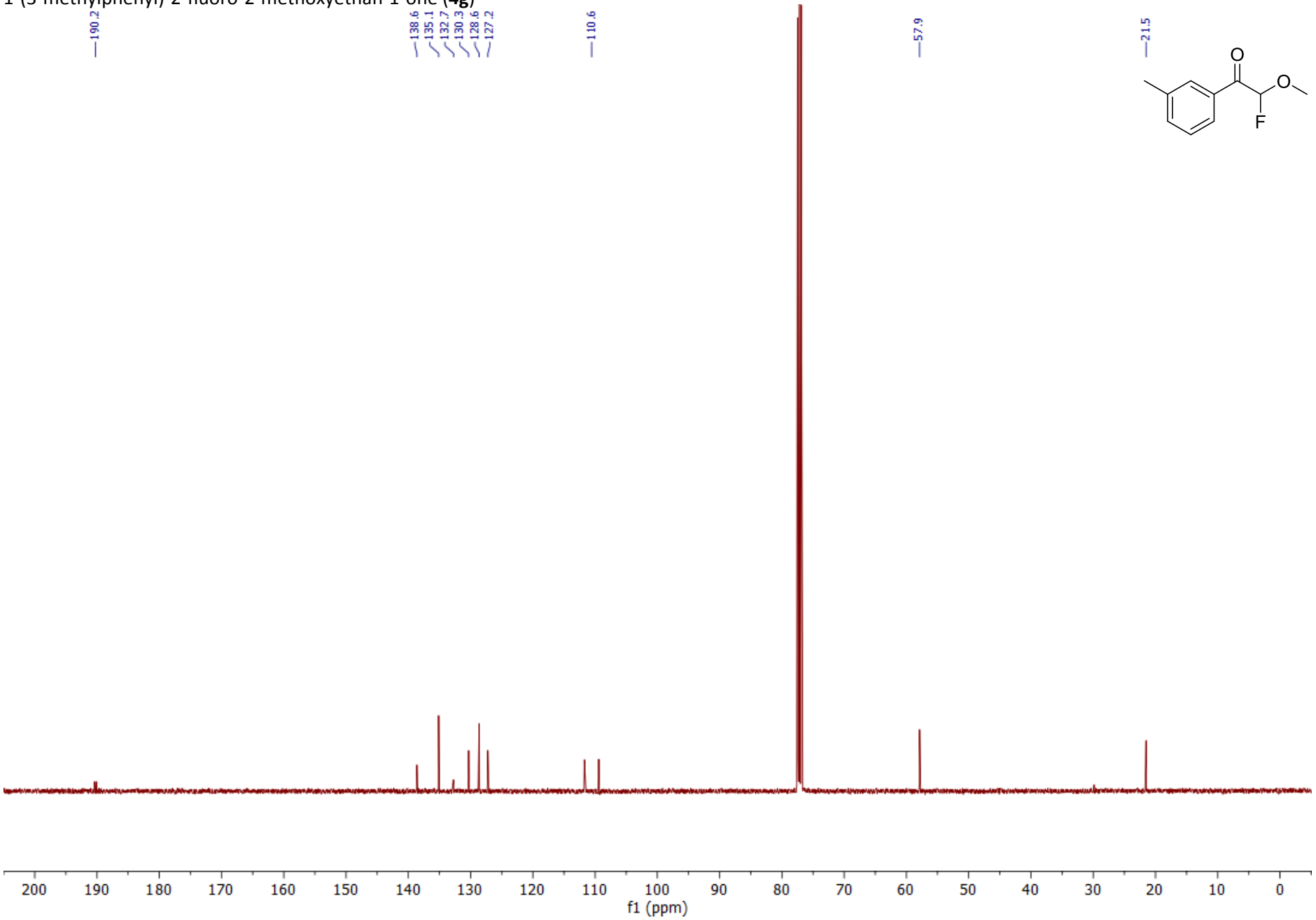
1-(3-methylphenyl)-2-fluoro-2-methoxyethan-1-one (**4f**)



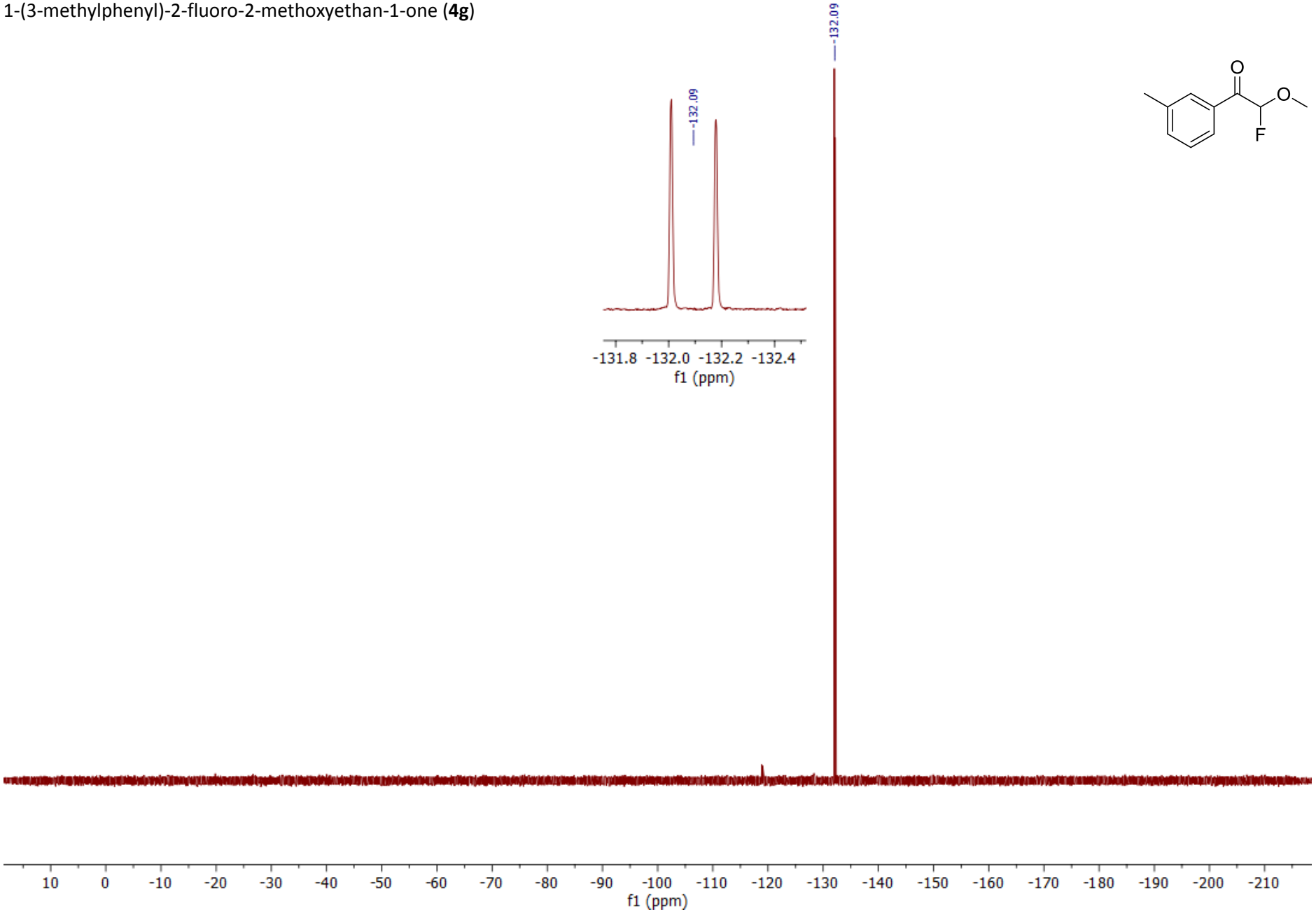
1-(3-methylphenyl)-2-fluoro-2-methoxyethan-1-one (**4g**)



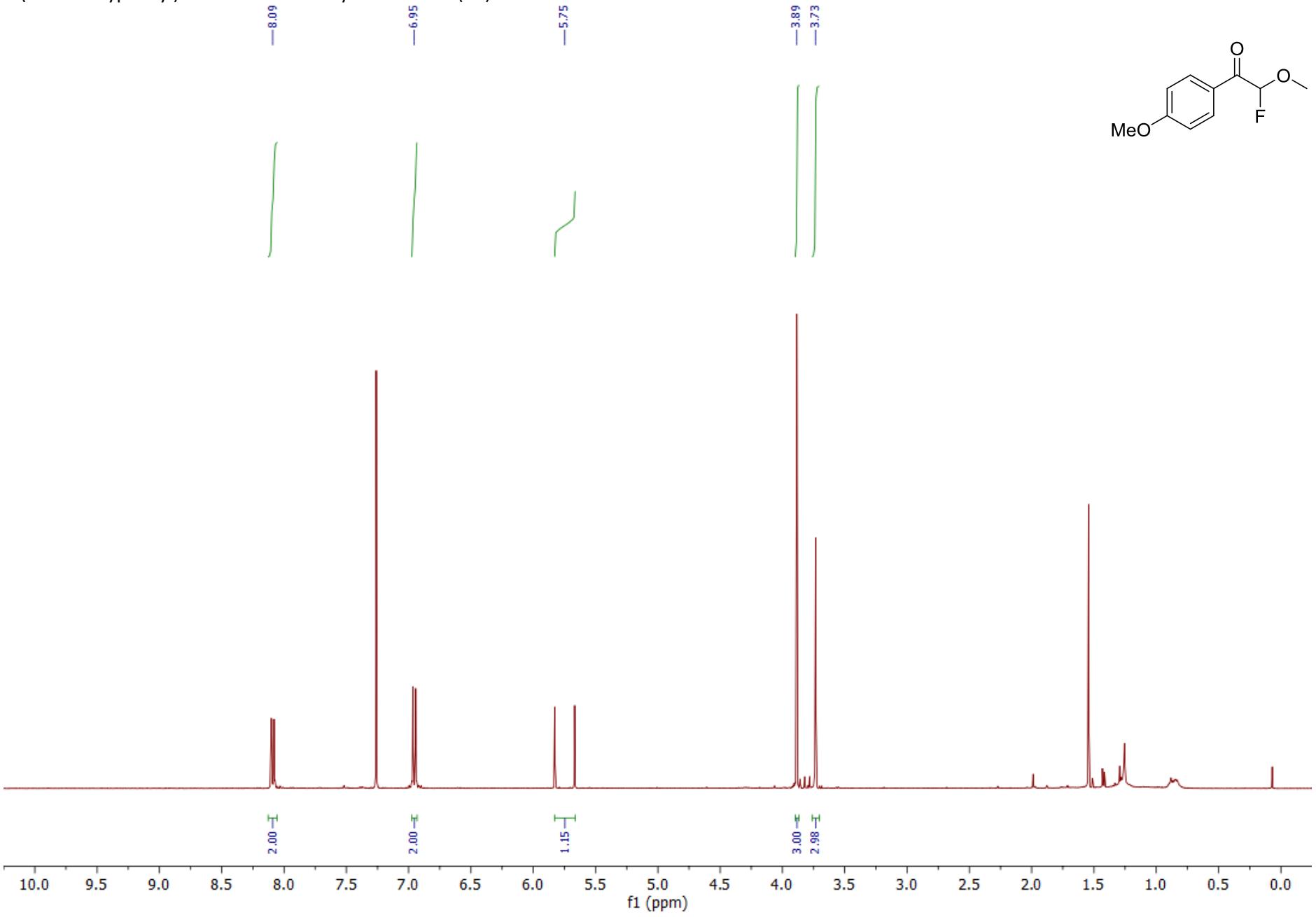
1-(3-methylphenyl)-2-fluoro-2-methoxyethan-1-one (**4g**)



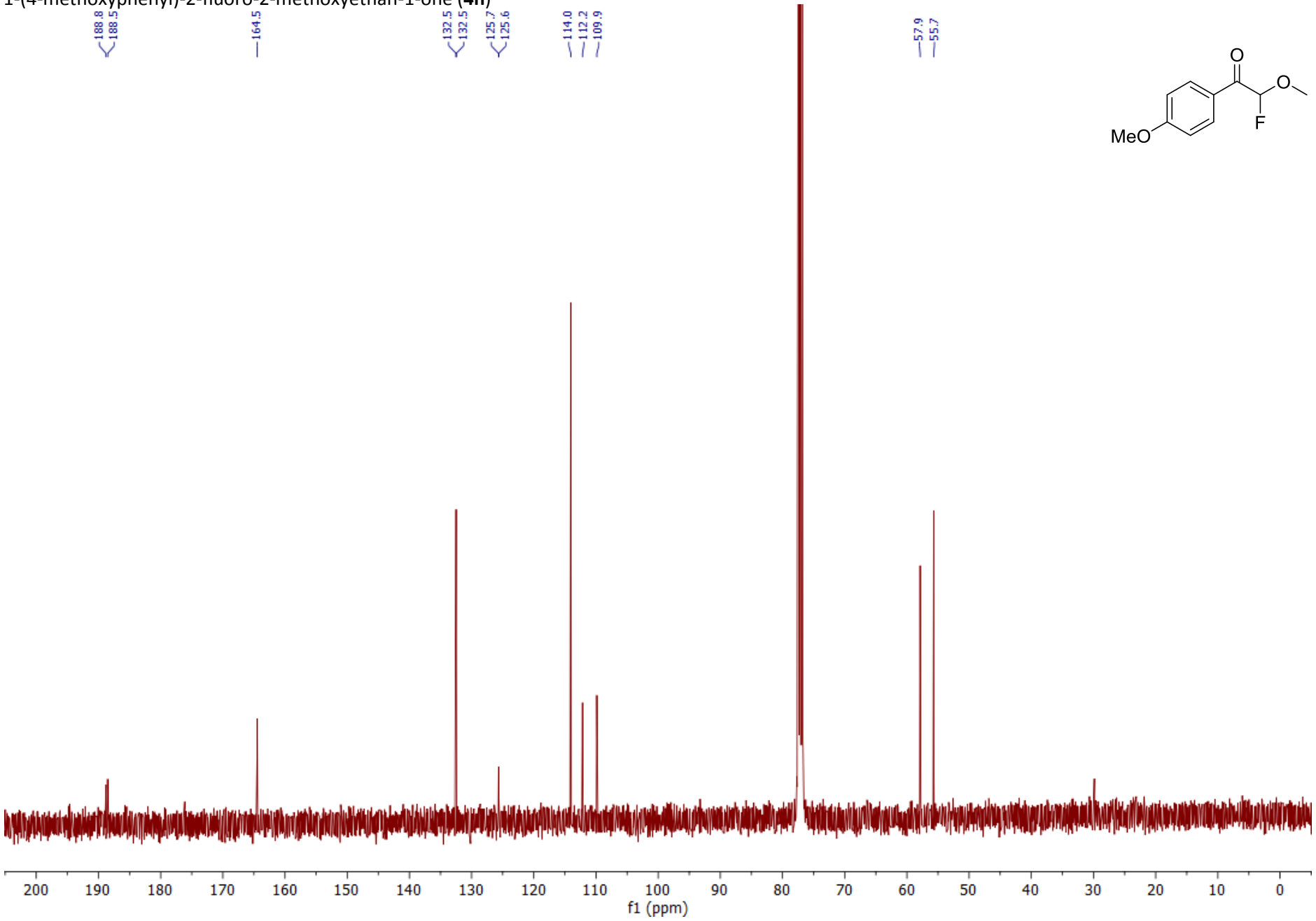
1-(3-methylphenyl)-2-fluoro-2-methoxyethan-1-one (**4g**)



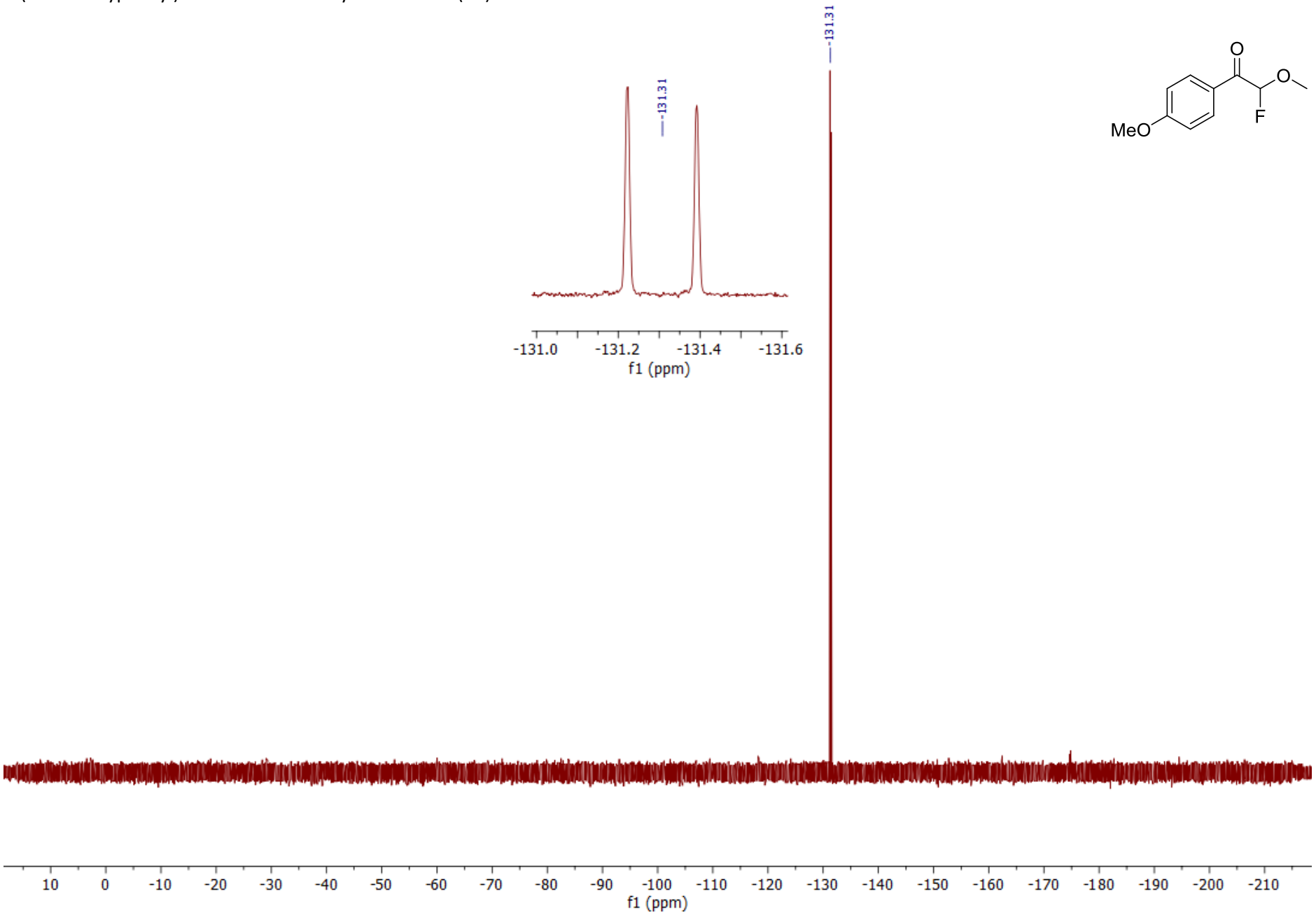
1-(4-methoxyphenyl)-2-fluoro-2-methoxyethan-1-one (**4h**)



1-(4-methoxyphenyl)-2-fluoro-2-methoxyethan-1-one (**4h**)

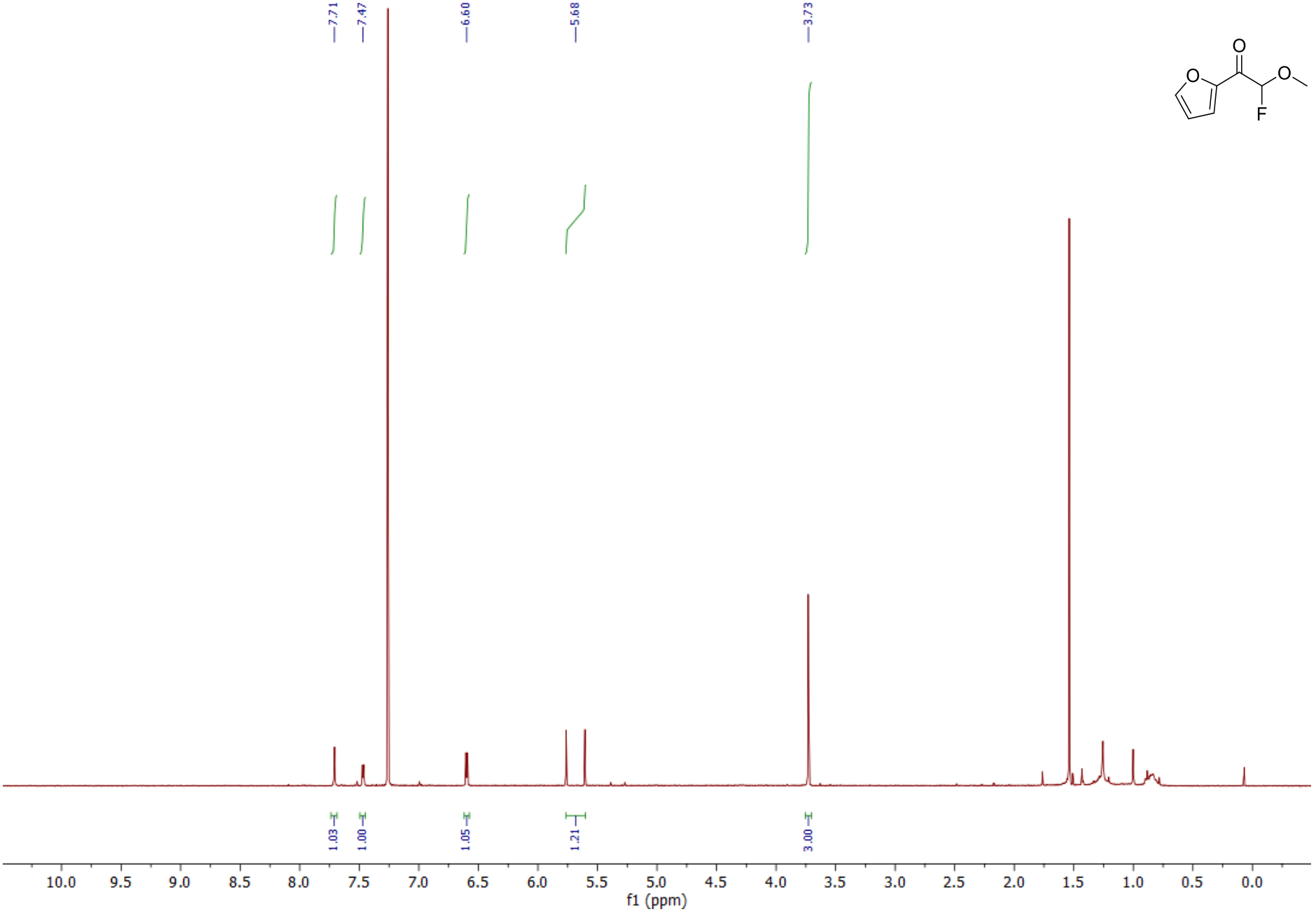


1-(4-methoxyphenyl)-2-fluoro-2-methoxyethan-1-one (**4h**)

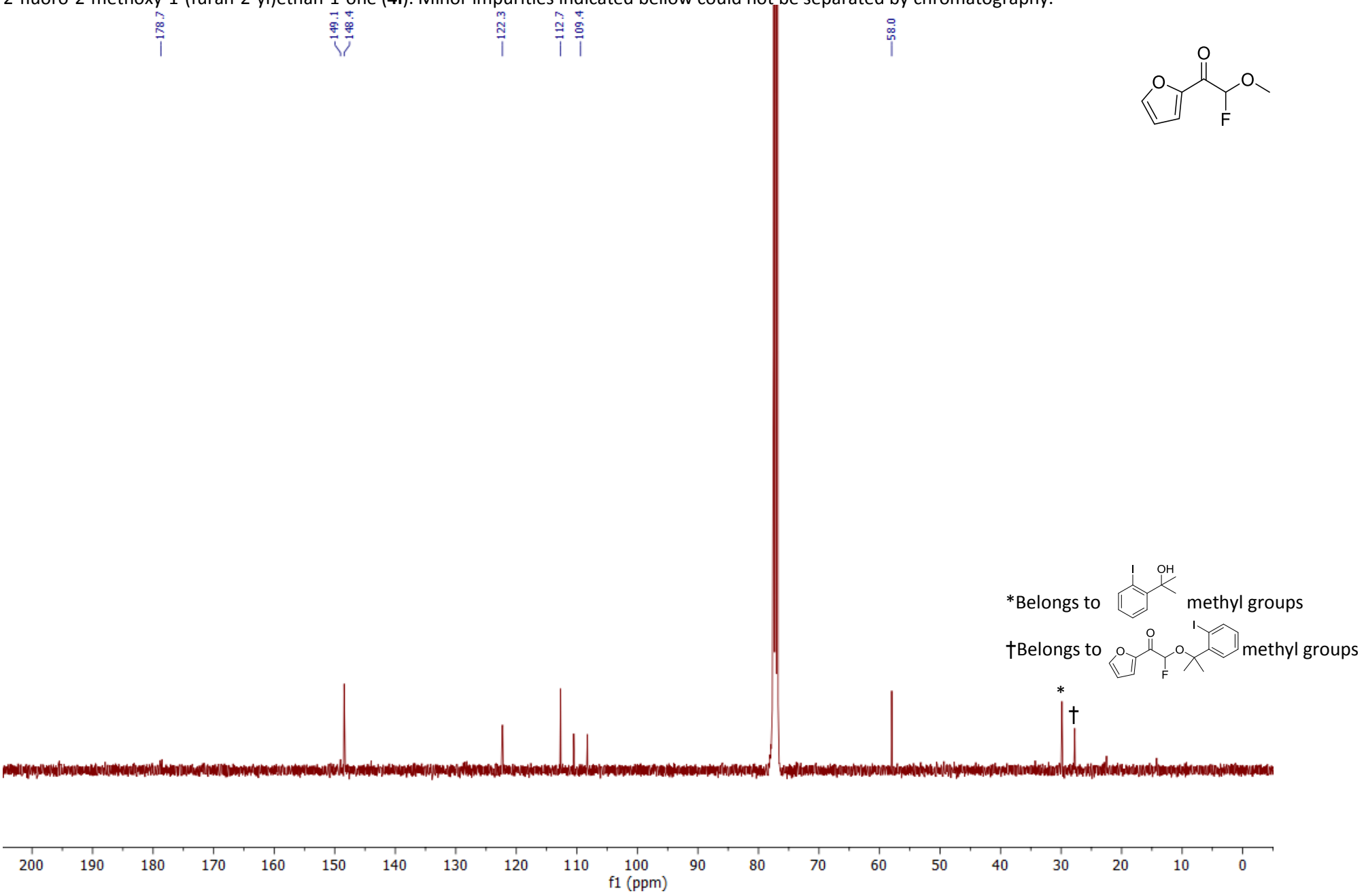


S50

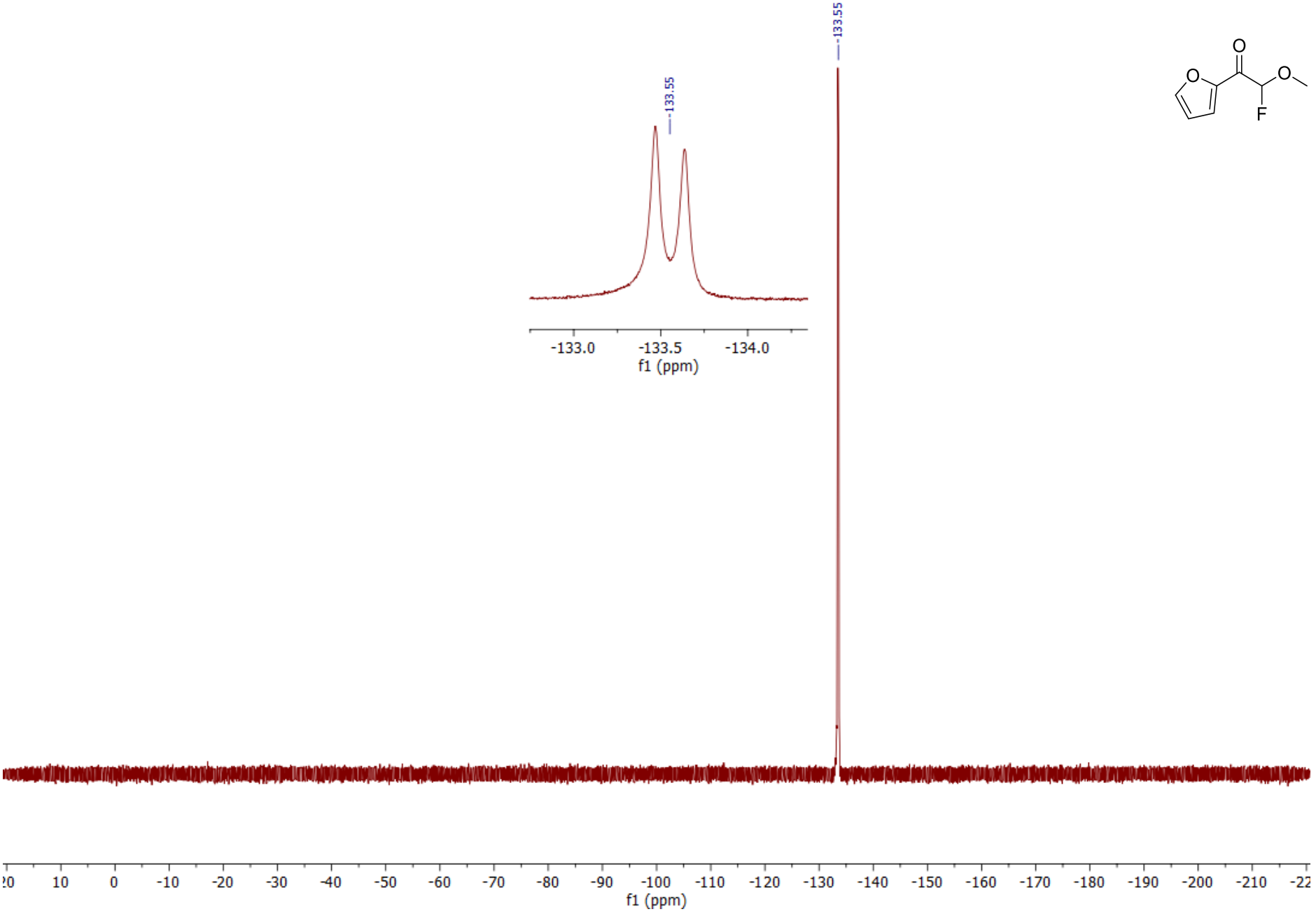
2-fluoro-2-methoxy-1-(furan-2-yl)ethan-1-one (**4i**)



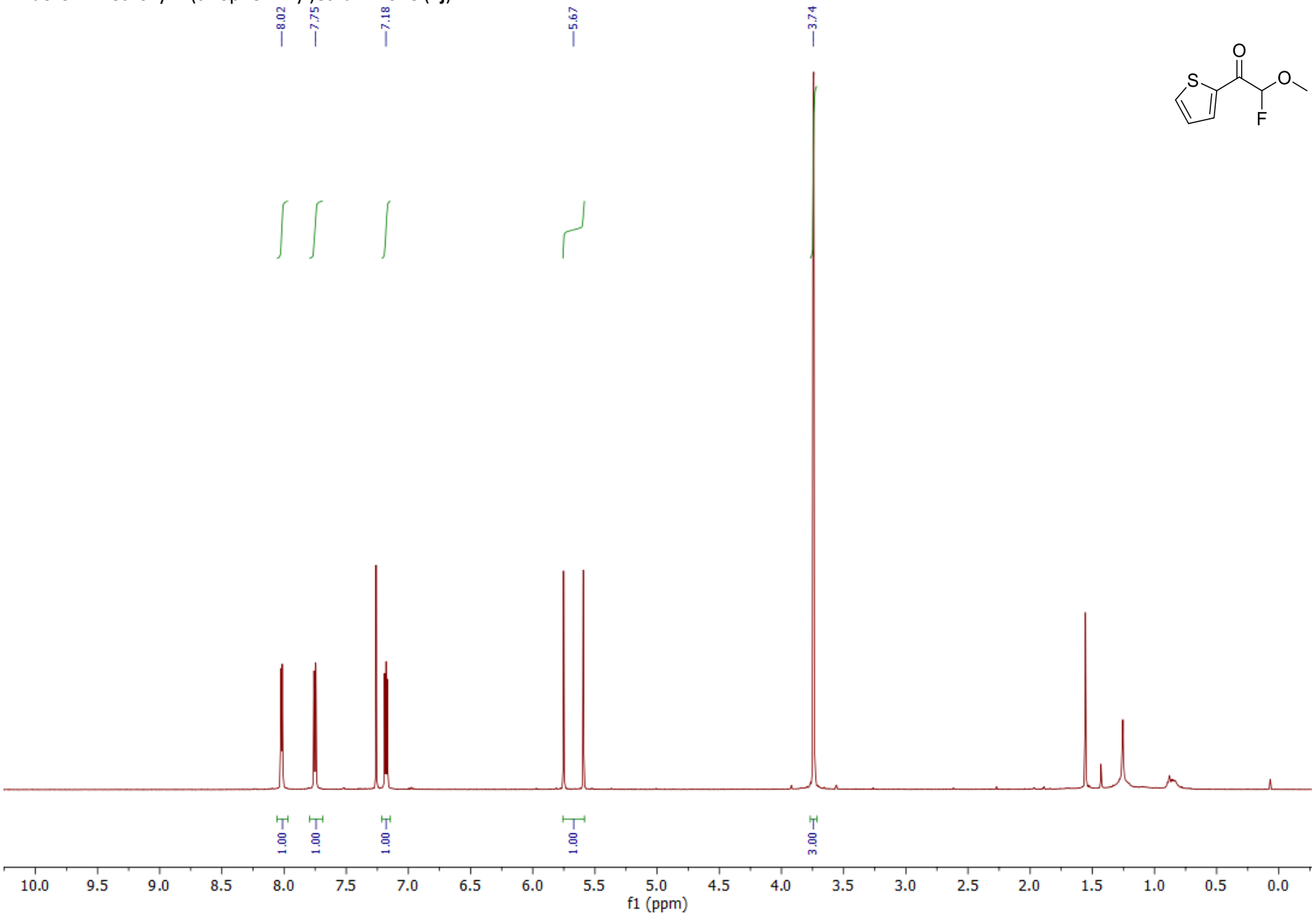
2-fluoro-2-methoxy-1-(furan-2-yl)ethan-1-one (**4i**). Minor impurities indicated bellow could not be separated by chromatography.



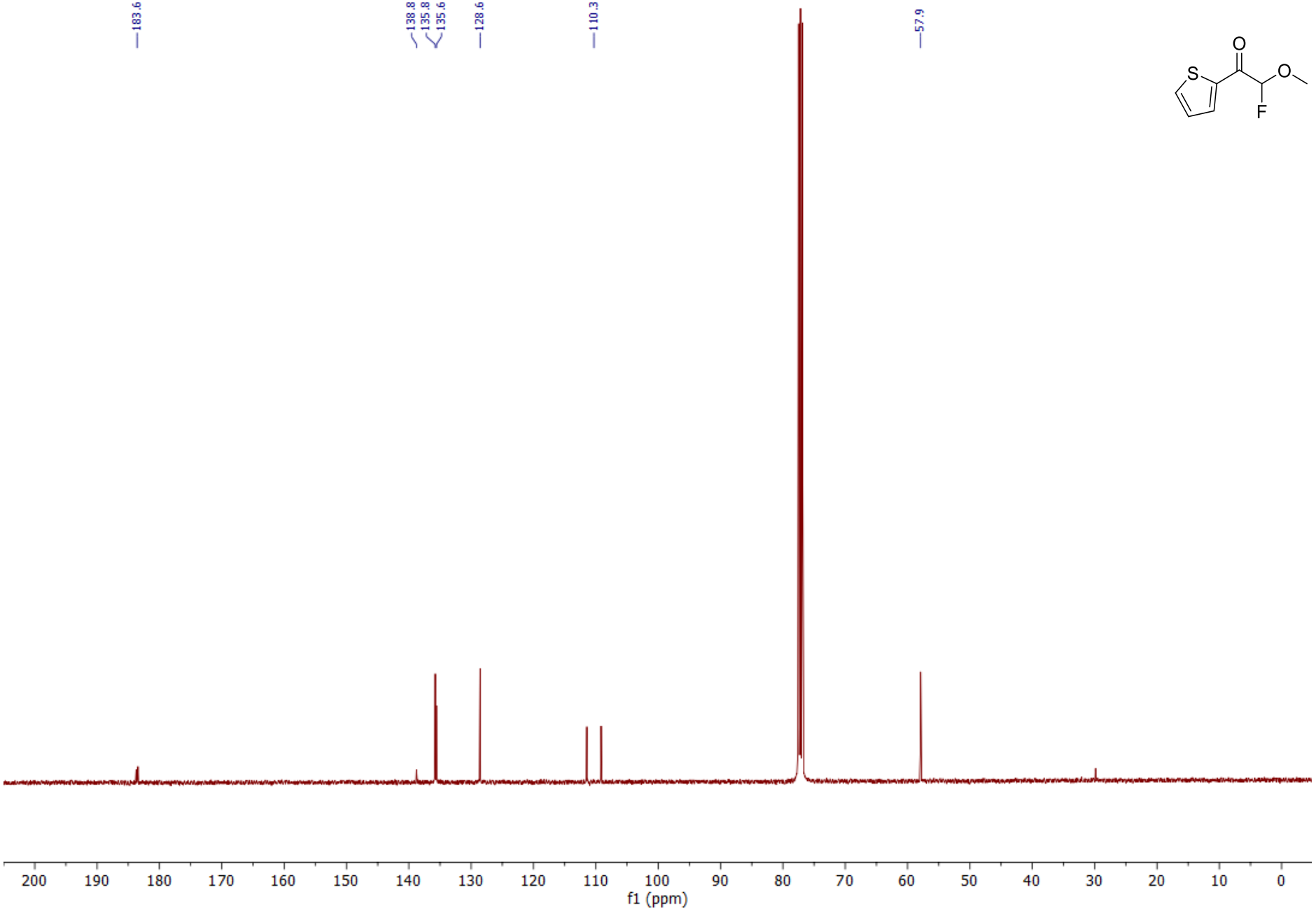
2-fluoro-2-methoxy-1-(furan-2-yl)ethan-1-one (**4i**)



2-fluoro-2-methoxy-1-(thiophen-2-yl)ethan-1-one (**4j**)

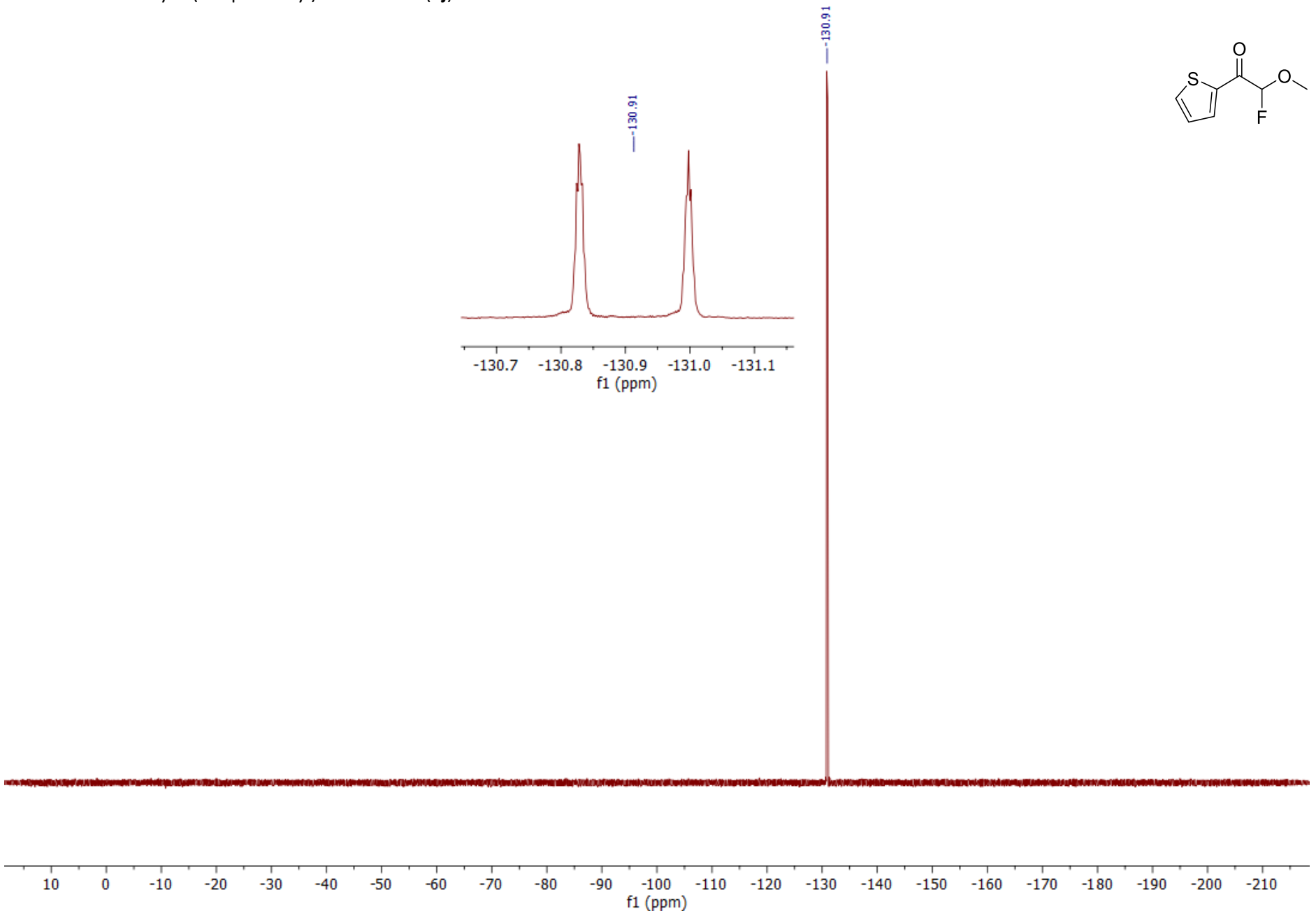


2-fluoro-2-methoxy-1-(thiophen-2-yl)ethan-1-one (**4j**)

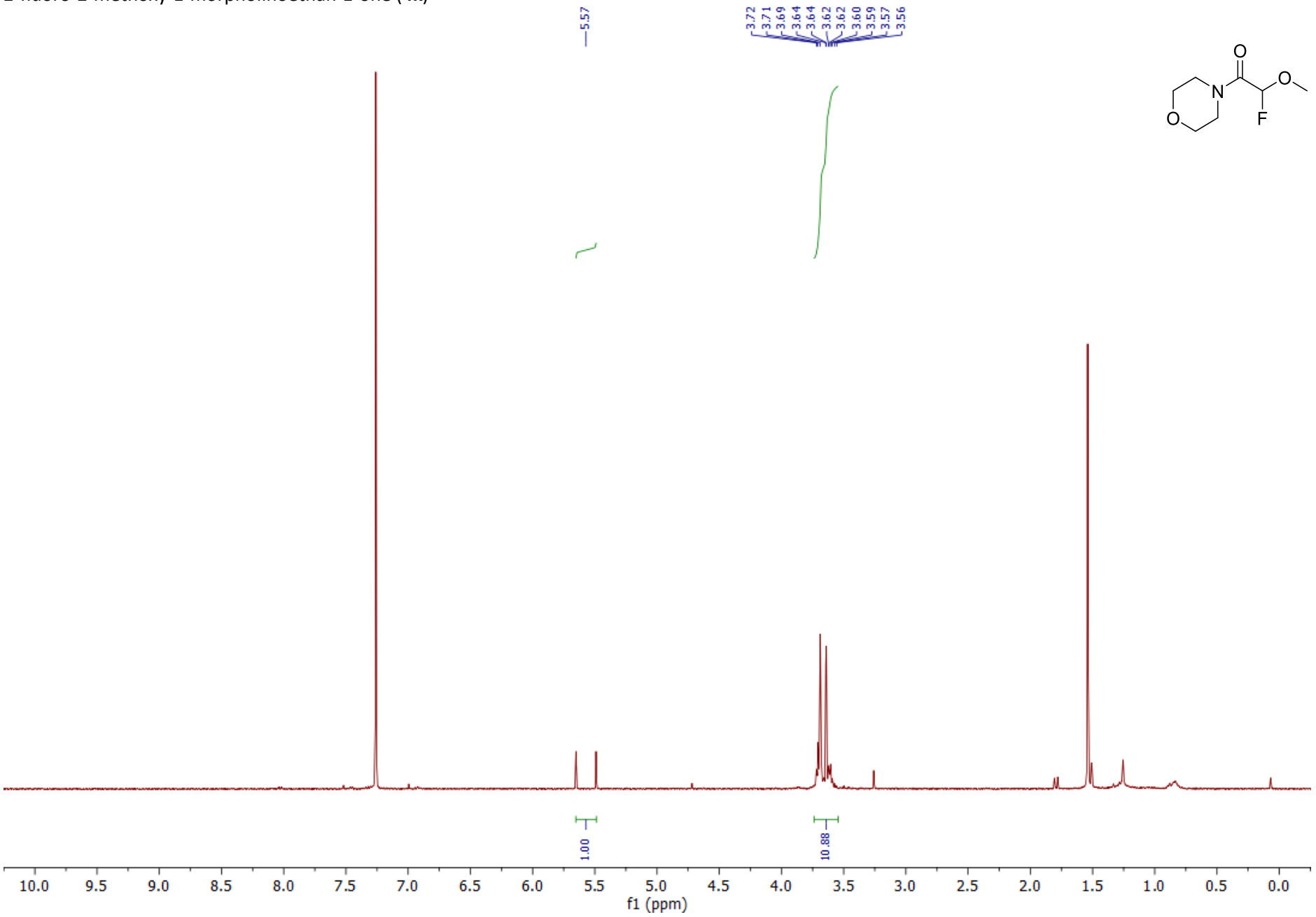


S55

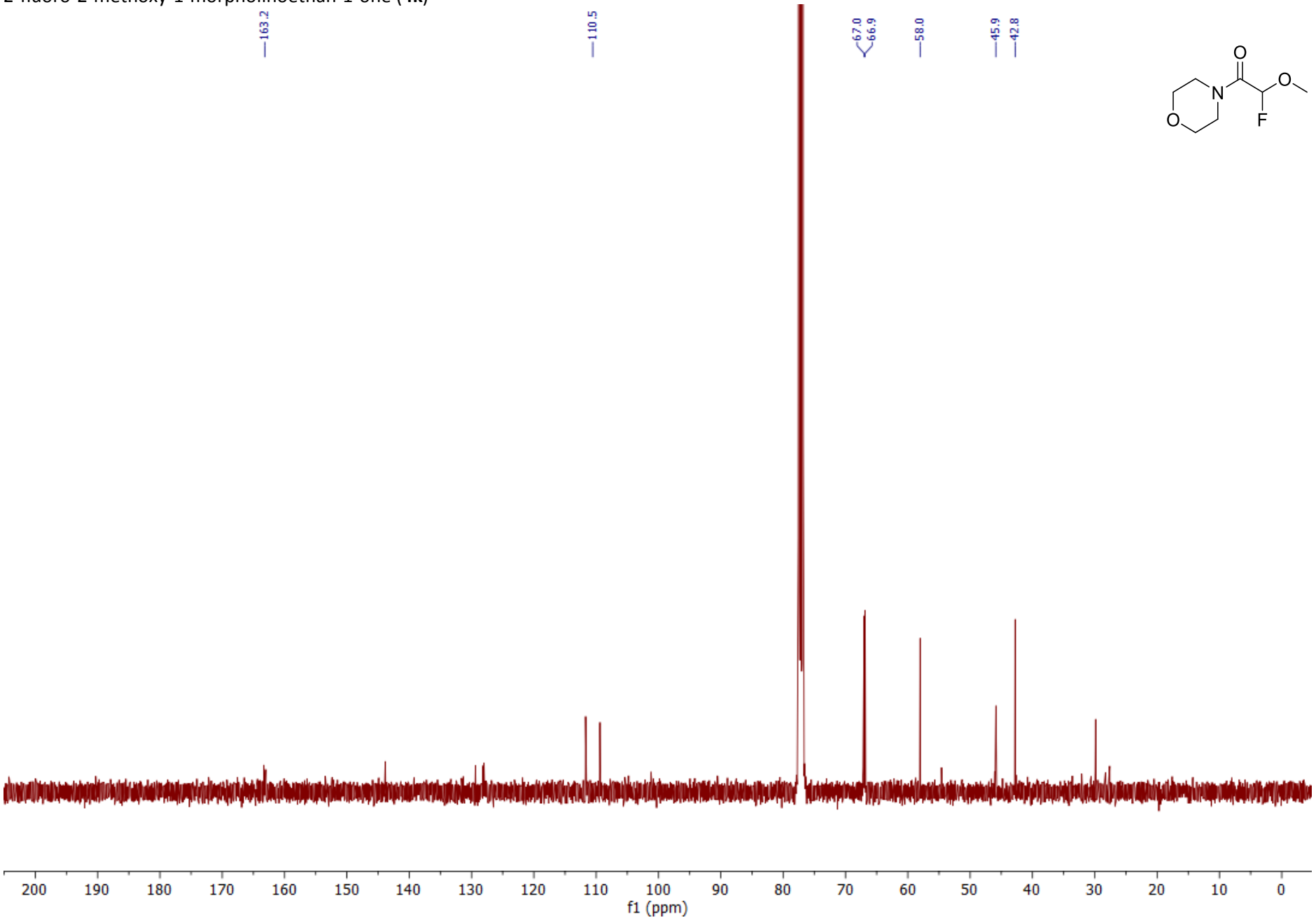
2-fluoro-2-methoxy-1-(thiophen-2-yl)ethan-1-one (**4j**)



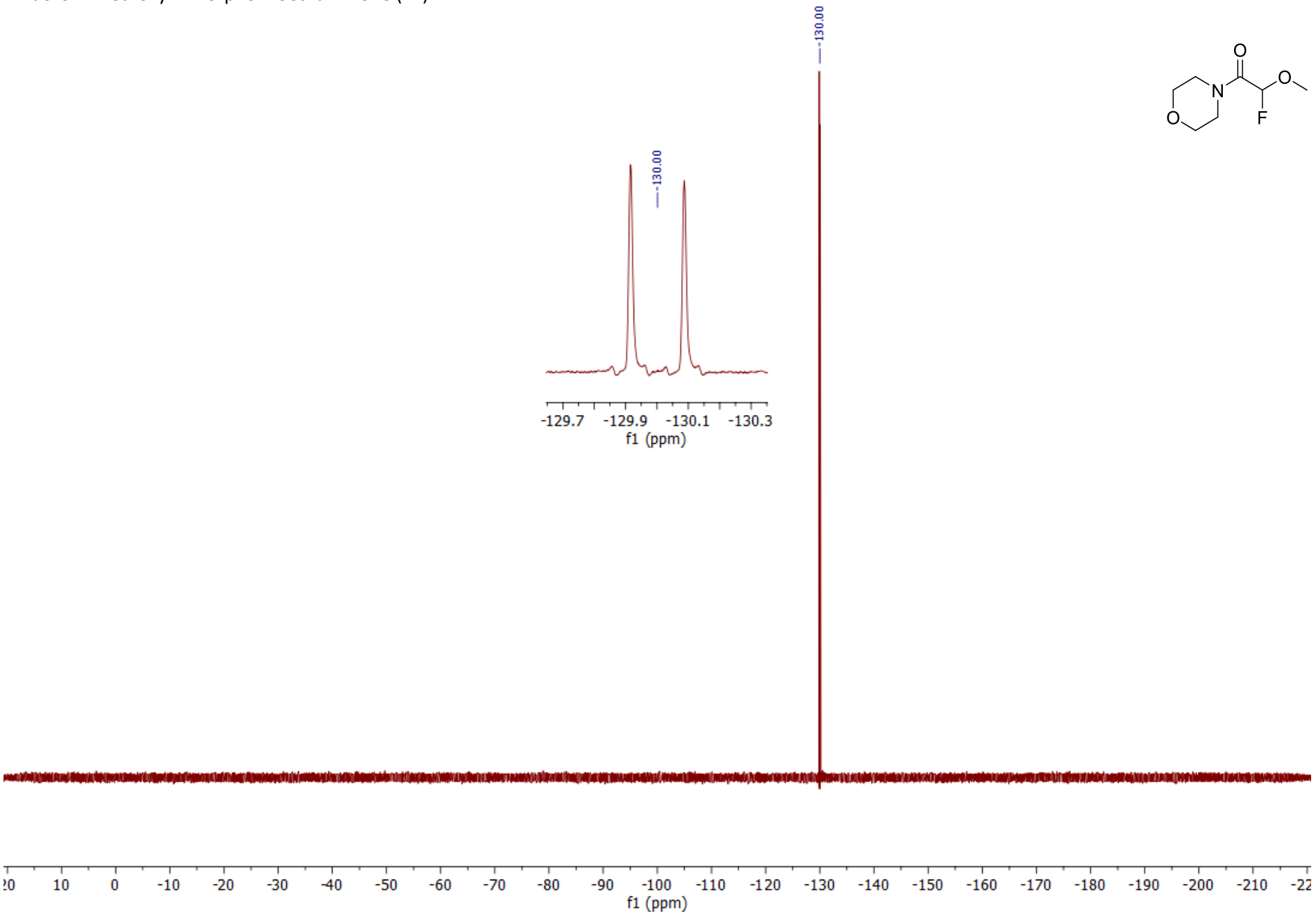
2-fluoro-2-methoxy-1-morpholinoethan-1-one (**4k**)



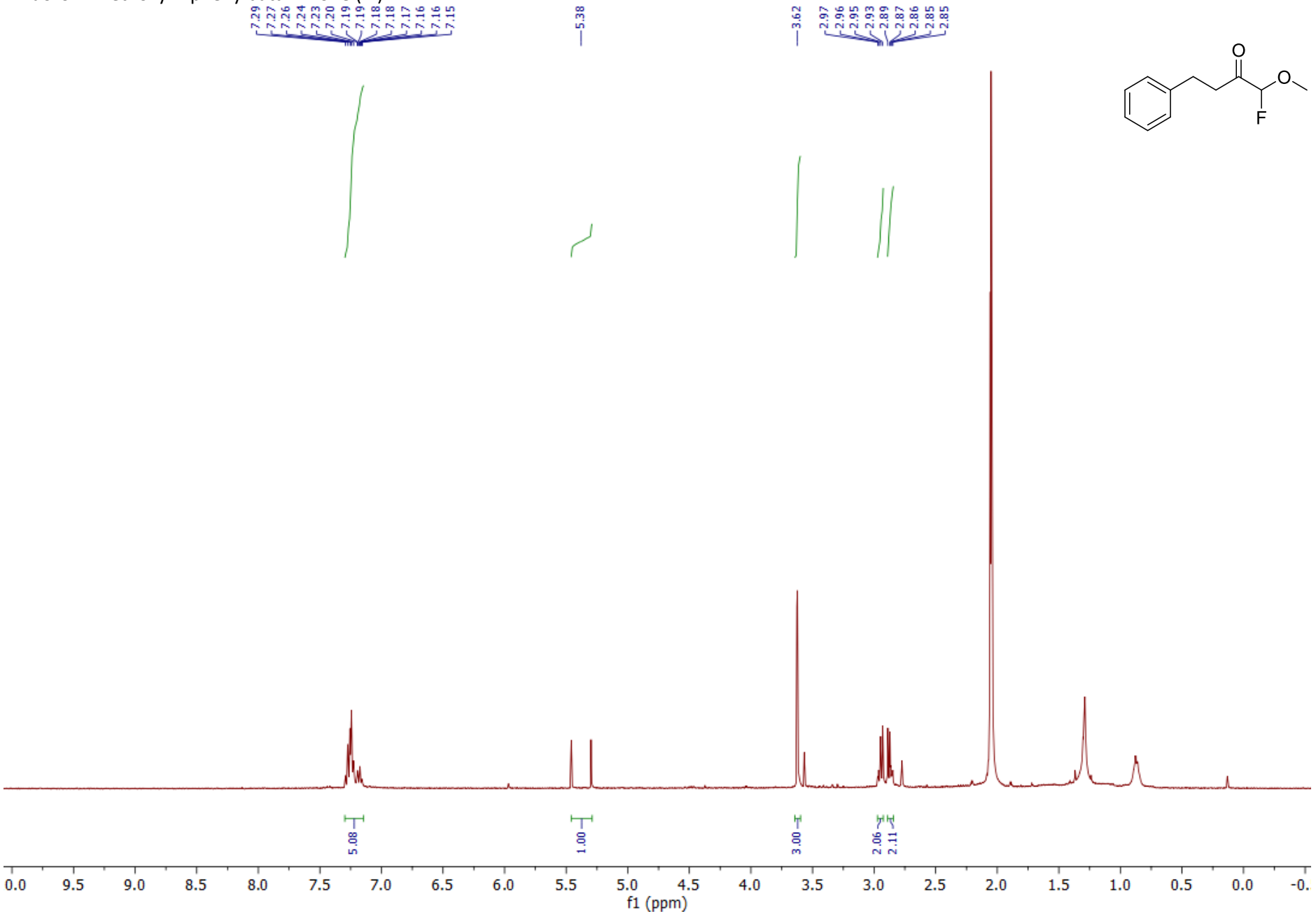
2-fluoro-2-methoxy-1-morpholinoethan-1-one (**4k**)



2-fluoro-2-methoxy-1-morpholinoethan-1-one (**4k**)

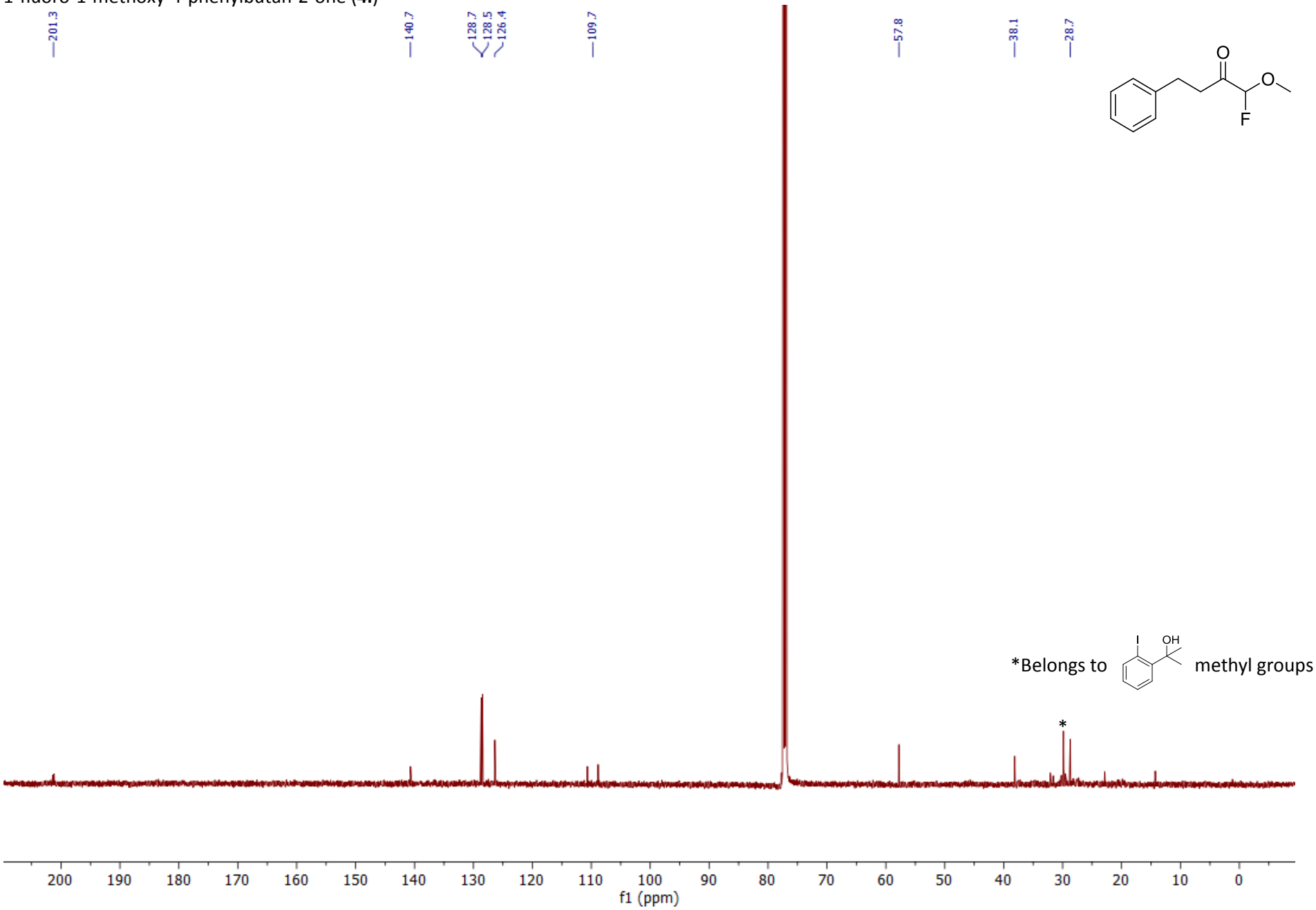


1-fluoro-1-methoxy-4-phenylbutan-2-one (**4l**)



S60

1-fluoro-1-methoxy-4-phenylbutan-2-one (**4l**)



S61

1-fluoro-1-methoxy-4-phenylbutan-2-one (**4l**)