

SUPPORTING INFORMATION

Fluoroalkyl Amino Reagents for the Introduction of the Fluoro(trifluoromethoxy)methyl Group onto Arenes and Heterocycles

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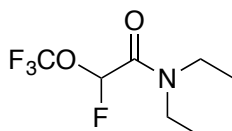
A. General considerations

All reactions were performed in flame-dried glassware using sealed tubes or Schlenk tubes. Liquids and solutions were transferred with syringes. Air- and moisture- sensitive materials were stored protected and handled under an atmosphere of argon, with appropriate glassware. Solvents were purified and dried following standard procedures: tetrahydrofuran (THF) was distilled from sodium or sodium + benzophenone prior to use. Anhydrous MeCN was used from commercial source and was stored under Argon. Technical grade solvents for extraction and chromatography (cyclohexane, dichloromethane, *n*-pentane, ether, toluene, and ethyl acetate) were used without purification. All reagents were purchased from standard suppliers (Sigma Aldrich, ABCR, Alfa Aesar and Apollo scientific). FARs were purchased from ABCR or Aldrich and depicted purities were checked by NMR before use. Yarovenko and Ishikawa reagents were degrading upon storage and purity had to be checked frequently. Starting materials, if commercial, were purchased and used as such, provided that adequate checks (NMR) had confirmed the claimed purity. Analytical thin-layer chromatography (TLC) was performed on silica gel. Flash column chromatography was performed on silica gel 60 (40–63 μm , 230–400 mesh, ASTM) by Merck using the indicated solvents. ^1H , ^{13}C , ^{11}B and ^{19}F -NMR spectra were recorded in CDCl_3 on Bruker AV 400 (^1H : 400MHz, ^{19}F : 376MHz, ^{13}C : 100MHz), AC-300 (^1H : 300MHz) and AC-200 (^1H : 200MHz, ^{19}F : 188MHz, ^{13}C : 50MHz) instruments. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to the residual solvent resonance as the internal standard (chloroform (δ [^1H] = 7.26 and accordingly δ [^{13}C] = 77.16 ppm), CD_3CN (δ [^1H] = 1.94 and accordingly δ [^{13}C] = 1.32 ppm, MeOD-d^4 (δ [^1H] = 3.31 and accordingly δ [^{13}C] = 49.00 ppm), DMSO-d^6 (δ [^1H] = 2.50 and accordingly δ [^{13}C] = 39.52 ppm) or Acetone- d^6 (δ [^1H] = 2.05 and accordingly δ [^{13}C] = 29.84 ppm). Data are reported as follows: chemical shift, multiplicity (br s = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br d = broad doublet), coupling constant (Hz) and integration. Fluorobenzene (δ [^{19}F] = -113.15 ppm) was used as internal standard to measure yields *in-situ*. The spectra were processed with the program NMR Notebook (NMRtec) or with MestreNova (Mestrelab). Experiments under microwave irradiation were carried out on an InitiatorTM apparatus from Biotage, exact parameters are given with the procedures. Melting points (M.p.) were determined for crystalline or solid compounds with a Melting Point Apparatus M-560 and are not corrected. High resolution mass spectrometry (HRMS) analysis and elemental analysis (Anal.) were performed by the analytical facility at the University of Strasbourg (measurement accuracy ≤ 15 ppm). Spectral data were recorded from samples purified by Hickmann distillation when necessary.

B. New FARs (1a,2a) and their activated forms (1b,2b)

Method A – Procedure for the preparation of activated FAR 1b

A tared stopcock-equipped balloon was filled with the required amount of trifluoromethyl trifluorovinyl ether (5 equiv, 830 mg, 5 mmol) then connected to a two-necked round-bottomed flask under inert atmosphere. Diethylamine (1 equiv, 73 mg, 1 mmol) was added *via* syringe, the gas was allowed to enter the flask, the mixture was vigorously stirred until the balloon was empty. Anhydrous DCM (2.5 mL) was added, followed by $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (2.5 equiv, 355 mg, 2.5 mmol). The FAR was activated after 10min.



N,N-Diethyl-2-fluoro-2-(trifluoromethoxy)acetamide (1c) – Hydrolysis product of 1b

Yield: 71% (2.6 mmol, 757 mg). Yellow oil. Rf: 0.54 (pentane/diethylether= 7/3)

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ = 1.08 (dt, J = 12.5 Hz, J = 5.6 Hz, 6H), 3.14-3.50 (m, 4H), 6.08 (d, J = 56.8 Hz, 1H) ppm.

$^{19}\text{F-NMR}$ (188 MHz, CDCl_3): δ = -59.4 (d, J = 4.7 Hz, 3F), -130.0 (dq, J = 56.7 Hz, J = 4.9 Hz, 1F) ppm.

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ = 11.8, 13.6, 40.7, 40.9 (d, J = 4.0 Hz), 100.5 (dq, J = 244.3 Hz, J = 3.7 Hz), 120.7 (qd, J = 262.3 Hz, J = 2.5 Hz), 160.2 (d, J = 25.1 Hz) ppm.

FTIR (cm^{-1} , neat): 2983, 2939, 1669, 1213, 1185, 1042, 824.

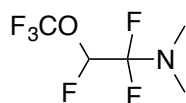
HRMS (ESI) for $\text{C}_7\text{H}_{12}\text{NO}_2\text{F}_4$ [$\text{M} + \text{H}$] $^+$: 218.0804. Found: 218.0794.

Method B – Procedure for the preparation of activated FAR 2b

The estimated amount of 1,1,2-trifluoro-2-(trifluoromethoxy)ethene (0.44 mL) was liquefied at -78°C into a sealed Schlenk vessel under inert atmosphere, then dimethylamine (2M in THF, 2 mL, 4 mmol) was added *via* syringe at -78°C. The cold bath was removed after 10min and the vessel was transferred into a water-bath. BF₃•Et₂O (0.50 mL, 3.95 mmol) was syringed very slowly into the vessel and the resulting bis-layered mixture was vigorously stirred for 15min (polymerization possible at this stage, MeCN can be added to dissolve the polymer) to afford iminium **2b**.

The non-activated FAR (**2a**) was found to be very water sensitive, and partially hydrolysed to the corresponding *N,N*-dimethyl-2-fluoro-2-(trifluoromethoxy)acetamide **2c**.

The activated FAR (**2b**) was either reacted further "as such" or isolated pure as a solid prior to utilization (*vide infra*).



1,1,2-Trifluoro-*N,N*-dimethyl-2-(trifluoromethoxy)ethan-1-amine (2a) (in solution, mixture with **2c**)

¹H-NMR (400 MHz, CDCl₃): δ = 5.85 (dt, CHFOCF₃, ²J_{H-F} = 54.7 Hz, ⁴J_{H-F} = 3.4 Hz), 2.49 (s, 6H, N(CH₃)₂) ppm.

¹⁹F-NMR (376 MHz, CDCl₃): δ = -60.2 (m, OCF₃), -100.4 (m, CF₂), -142.1 (d, CHFOCF₃, ²J_{F-H} = 54.5 Hz) ppm.

¹³C-NMR (100 MHz, CDCl₃): δ = 121.0 (q, OCF₃, ¹J_{C-F} = 262 Hz), 118.9 (td, CF₂, ¹J_{C-F} = 250 Hz, ²J_{C-F} = 26 Hz), 100.0 (ddq CHFOCF₃, ¹J_{C-F} = 241 Hz, ²J_{C-F} = 45 Hz, ³J_{C-F} = 3 Hz), 35.9 (N(CH₃)₂) ppm.

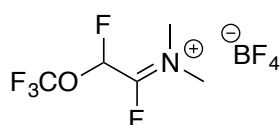
The compound was obtained as a mixture with the corresponding hydrolysis product **2c**.

2-Fluoro-*N,N*-dimethyl-2-(trifluoromethoxy)acetamide (2c) (in solution, mixture with **2a**)

¹H-NMR (400 MHz, CDCl₃): δ = 6.12 (d, CHFOCF₃, ²J_{H-F} = 56.5 Hz), 3.07 (s, 3H, N(CH₃)₂), 2.95 (s, 3H, N(CH₃)₂) ppm.

¹⁹F-NMR (376 MHz, CDCl₃): δ = -60.1 (m, OCF₃), -131.2 (d, CHFOCF₃, ²J_{F-H} = 56.5 Hz) ppm.

¹³C-NMR (100 MHz, CDCl₃): δ = 161.2 (d, C=O, ²J_{C-F} = 24.9 Hz), 121.0 (q, OCF₃, ¹J_{C-F} = 262 Hz), 101.0 (dq CHFOCF₃, ¹J_{C-F} = 246 Hz, ³J_{C-F} = 3 Hz), 36.1, 36.0 (N(CH₃)₂) ppm.



***N*-(1,2-Difluoro-2-(trifluoromethoxy)ethylidene)-*N*-methylmethanaminium tetrafluoroborate (2b)**

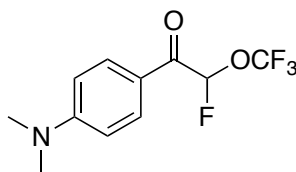
To isolate an accurate amount of iminium salt, the procedure was carried out in a tared reaction vessel (Schlenk tube equipped with a stirring bar and a septum and tared under vacuum) and was completed by the addition of DCM (10-20 mL) instead of MeCN after addition of BF₃•Et₂O. Upon vigorous stirring, the iminium precipitated over several minutes. The suspension was left to decant and the supernatant was removed by cannulation. The resulting solid was dried *in vacuo* to yield a white water-sensitive solid iminium salt, which was weighed under vacuum.

Activation yield: 82-99%.

¹H-NMR (d⁶-DMSO, 400MHz): 6.93 (dd, CHFOCF₃, *J* = 54.6 Hz, *J* = 6.5 Hz), 3.01 and 2.89 (2 x s, 6H, N(CH₃)₂⁺) ppm.

¹⁹F-NMR (d⁶-DMSO, 376MHz): -57.9 (d, OCF₃, *J* = 40 Hz), -134.7 (d, CHFOCF₃, *J* = 55.5 Hz), -148.2 (s, BF₄⁻), -168.6 (s br, F_{iminium}) ppm.

C. Acylation of arenes and heteroarenes



1-(4-(Dimethylamino)phenyl)-2-fluoro-2-(trifluoromethoxy)ethanone (3a)

Trifluoromethyl trifluorovinyl ether (830 mg, 5 mmol, 5 equiv) was added in a Schlenk tube with diethylamine (73 mg, 1 mmol, 1 equiv). The solution was stirred for two hours at room temperature. Then, dry CH₂Cl₂ was added (4 mL) followed by BF₃·Et₂O (170 mg, 1.2 mmol, 1.2 equiv) under argon. The solution was stirred for 15 min at room temperature. Then, *N,N*-dimethylaniline (127 μL, 1 mmol, 1 equiv) was added and the resulting mixture stirred overnight at room temperature. The solution was hydrolysed with water (2.5 mL) and extracted three times with CH₂Cl₂ (3 x 5 mL). The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum. The crude mixture was purified by chromatography on silica gel, using pentane/CH₂Cl₂ (6/4) as eluent. Yield: 96% (0.79 mmol, 211 mg). Yellow oil. Rf: 0.44 (pentane/CH₂Cl₂=6/4).

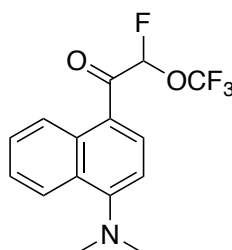
¹H NMR (200 MHz, CDCl₃) (ppm) δ: 3.12 (s, 6H), 6.34 (d, *J* = 56.7 Hz, 1H), 6.69 (d, *J* = 9.2 Hz, 2H), 7.96 (d, *J* = 9.1 Hz, 2H)

¹⁹F NMR (188 MHz, CDCl₃) (ppm) δ: -59.6 (d, *J* = 4.9 Hz, 3F), -131.3 (dq, *J* = 56.7 Hz, *J* = 4.9 Hz, 1F).

¹³C NMR (75 MHz, CDCl₃) (ppm) δ: 39.7, 102.1 (dq, *J* = 244.8 Hz, *J* = 3.3 Hz), 110.8, 118.9, 121.1 (qd, *J* = 261.8 Hz, *J* = 2.0 Hz), 131.8 (d, *J* = 2.4 Hz), 154.3, 183.1 (d, *J* = 24.6 Hz).

FTIR (cm⁻¹, neat): 2920, 1675, 1588, 1546, 1375, 1223, 1169, 1106, 1037, 943, 846, 590.

HRMS (ESI) calcd for C₁₁H₁₂NO₂F₄ [M + H]⁺: 266.0804. Found 266.0800.



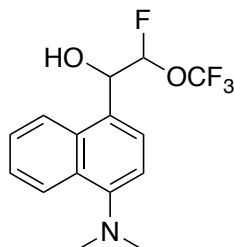
1-(4-(Dimethylamino)naphthalen-1-yl)-2-fluoro-2-(trifluoromethoxy)ethanone (3b)

Trifluoromethyl trifluorovinyl ether (830 mg, 5 mmol, 5 equiv) was added in a Schlenk tube with diethylamine (73 mg, 1 mmol, 1 equiv). The solution was stirred for two hours at room temperature. Then, dry CH₂Cl₂ was added (4 mL) followed by BF₃·Et₂O (170 mg, 1.2 mmol, 1.2 equiv) under argon. The solution was stirred for 15 min at room temperature. Then, 1-(dimethylamino)naphthalene (164 μL, 1 mmol, 1 equiv) was added and the resulting mixture stirred overnight at room temperature. The solution was hydrolysed with water (2.5 mL) and extracted three times with CH₂Cl₂ (3 x 5 mL). The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum. The crude mixture was purified by chromatography on silica gel, using a gradient of pentane/Et₂O as eluent from 95/5 to 80/20. Yield: 80% (0.77 mmol, 245 mg). Yellow oil. Rf: 0.61 (pentane/Et₂O = 8/2).

¹H NMR (300 MHz, CDCl₃) (ppm) δ: 3.07 (s, 6H), 6.53 (d, *J* = 56.5 Hz, 1H), 6.94 (d, *J* = 8.6 Hz, 1H), 7.53 (tt, *J* = 6.9 Hz, *J* = 1.5 Hz, 1H), 7.65 (tt, *J* = 8.3 Hz, *J* = 1.7 Hz, 1H), 8.12 (d, *J* = 8.6 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 9.13 (d, *J* = 8.4 Hz, 1H).

¹⁹F NMR (188 MHz, CDCl₃) (ppm) δ: -59.1 (d, *J* = 4.7 Hz, 3F), -128.5 (dq, *J* = 56.8 Hz, *J* = 4.6 Hz, 1F).

^{13}C NMR (75 MHz, CDCl_3) (ppm) δ : 44.4, 102.3 (dq, $J = 245.8$ Hz, $J = 3.2$ Hz), 110.4, 120.2, 121.2 (qd, $J = 262.1$ Hz, $J = 1.6$ Hz), 125.4, 125.5, 126.2, 127.5, 129.1, 133.7, 133.8, 157.8, 185.6 (d, $J = 23.9$ Hz). FTIR (cm^{-1} , neat): 2948, 2871, 1672, 1564, 1514, 1428, 1214, 1172, 1051, 766, 607. Anal. Calcd. for $\text{C}_{15}\text{H}_{14}\text{NO}_2\text{F}_4$ [$\text{M} + \text{H}$] $^+$: 316.0961. Found 316.095.



1-(4-(Dimethylamino)naphthalen-1-yl)-2-fluoro-2-(trifluoromethoxy)ethanol (**3c**)

To a solution of 1-(4-(dimethylamino)naphthalen-1-yl)-2-fluoro-2-(trifluoromethoxy)ethanone (**3b**) (148 mg, 0.47 mmol) in ethanol (5 ml) at 0°C was slowly added NaBH_4 . The solution was slowly warmed up to room temperature where it was kept for 16 h. After this time, 10 ml of water was added and the mixture was extracted with dichloromethane (3x10 ml). The organic phase was dried with MgSO_4 , filtered and concentrated under reduced pressure. The crude was directly purified by column chromatography on silica gel, using pentane/ Et_2O (7/3) as eluent.

Yield: 82% (0.39 mmol, 123 mg). Colourless oil. Rf: 0.50 (pentane/ Et_2O = 7/3).

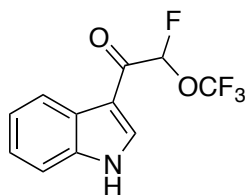
^1H NMR (200 MHz, CDCl_3) (ppm) δ : 2.90 (s, 6H), 3.11 (br s, 1H), 5.54 (dd, $J = 11.9$ Hz, $J = 5.3$ Hz, 1H, 1 dias), 6.02 (dd, $J = 57.7$ Hz, $J = 5.1$ Hz, 1H, 1 dias), 7.03 (d, $J = 7.9$ Hz, 1H), 7.48-7.60 (m, 3H), 8.01 (td, $J = 6.6$ Hz, $J = 3.2$ Hz, 1H), 8.31 (dt, $J = 6.5$ Hz, $J = 3.2$ Hz, 1H).

^{19}F NMR (188 MHz, CDCl_3) (ppm) δ : 2 diastereoisomers. -59.5 (d, $J = 4.8$ Hz, 3F), -59.8 (d, $J = 4.7$ Hz, 3F), -134.2 (dq, $J = 57.2$ Hz, $J = 5.2$ Hz, 3F), -137.2 (dq, $J = 58.7$ Hz, $J = 11.9$ Hz, $J = 5.0$ Hz, 1F).

^{13}C NMR (50 MHz, CDCl_3) (ppm) δ : 45.1, 70.1 (d, $J = 27.2$ Hz, 1 dias), 70.3 (d, $J = 23.1$ Hz, 1 dias), 106.1 (d, $J = 240.6$ Hz, $J = 2.9$ Hz, 1 dias), 106.5 (dq, $J = 235.5$ Hz, $J = 2.8$ Hz, 1 dias), 113.3, 120.9 (qd, $J = 260.4$ Hz, $J = 1.9$ Hz, 1 dias), 122.8 (qd, $J = 259.8$ Hz, $J = 1.6$ Hz, 1 dias), 123.1 (d, $J = 9.1$ Hz), 125.0 (d, $J = 3.1$ Hz), 125.5, 125.9 (d, $J = 3.5$ Hz), 126.2 (d, $J = 24.3$ Hz), 126.4, 128.7, 132.2 (d, $J = 11.1$ Hz), 151.8 (d, $J = 2.8$ Hz).

FTIR (cm^{-1} , neat): 3373, 2943, 2833, 1581, 1221, 1169, 1041, 835, 762, 575

Anal. Calcd. for $\text{C}_{15}\text{H}_{15}\text{NO}_2\text{F}_4$ [$\text{M} + \text{H}$] $^+$ 318.1117, found 318.1119 δ : 0.6 ppm.



2-Fluoro-1-(1H-indol-3-yl)-2-(trifluoromethoxy)ethanone (**4a**)

Trifluoromethyl trifluorovinyl ether (830 mg, 5 mmol, 5 equiv) was added in a Schlenk tube with diethylamine (73 mg, 1 mmol, 1 equiv). The solution was stirred for two hours at room temperature. Then, dry CH_2Cl_2 was added (4 mL) followed by $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (170 mg, 1.2 mmol, 1.2 equiv) under argon. The solution was stirred for 15 min at room temperature. Then, indole (117 mg, 1 mmol, 1 equiv) was added in one portion and the resulting mixture stirred overnight at room temperature. The solution was hydrolysed with water (2.5 mL) and extracted three times with CH_2Cl_2 (3 x 5 mL). The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum. The crude mixture was purified by chromatography on silica gel, using pentane/ Et_2O (6/4) as eluent. Yield: 83% (0.68 mmol, 178 mg). White solid. M.p.: $160\text{--}162^\circ\text{C}$. Rf: 0.42 (pentane/ Et_2O = 6/4).

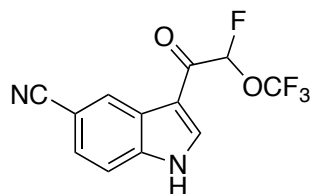
^1H NMR (200 MHz, Acetone) (ppm) δ : 6.64 (d, J = 55.9 Hz, 1H), 7.31-7.89 (m, 2H), 7.55-7.62 (m, 1H), 8.22 (dd, J = 3.4 Hz, J = 1.7 Hz, 1H), 8.26-8.35 (m, 1H), 10.3 (br s, NH)

^{19}F NMR (188 MHz, Acetone) (ppm) δ : -59.5 (d, J = 4.8 Hz, 1F), -133.3 (dq, J = 55.6 Hz, J = 4.8 Hz, J = 1.6 Hz, 3F)

^{13}C NMR (75 MHz, Acetone) (ppm) δ : 102.5 (dq, J = 241.2, J = 2.8 Hz), 112.7, 113.5, 122.4 (qd, J = 259.1 Hz, J = 1.7 Hz), 122.5, 124.2, 125.3, 126.9, 136.4 (d, J = 7.5 Hz), 137.5, 181.7 (d, J = 24.5 Hz)

FTIR (cm^{-1} , neat): 3196, 2957, 1644, 1522, 1461, 1163, 1093, 1164, 1057, 811, 787, 773, 718, 642, 509.

Anal. Calcd. for $\text{C}_{11}\text{H}_8\text{NO}_2\text{F}_4$ [$\text{M} + \text{H}$] $^+$ 262.0491, found 262.0486 δ : -1.9 ppm.



3-(2-Fluoro-2-(trifluoromethoxy)acetyl)-1H-indole-5-carbonitrile (4b)

Trifluoromethyl trifluorovinyl ether (830 mg, 5 mmol, 5 equiv) was added in a Schlenk tube with diethylamine (73 mg, 1 mmol, 1 equiv). The solution was stirred for two hours at room temperature. Then, dry CH_2Cl_2 was added (4 mL) followed by $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (170 mg, 1.2 mmol, 1.2 equiv) under argon. The solution was stirred for 15 min at room temperature. Then, indole-5-carbonitrile (142 mg, 1 mmol, 1 equiv) was added in one portion and the resulting mixture stirred overnight at room temperature. The solution was hydrolysed with water (2.5 mL) and extracted three times with CH_2Cl_2 (3 x 5 mL). The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum. The crude mixture was purified by chromatography on silica gel, using a gradient of pentane/ Et_2O as eluent from 7/3 to 5/5. Yield: 72 % (0.67 mmol, 180 mg). White solid. M.p.: 194-196 °C. Rf: 0.40 (pentane/ Et_2O = 6/4).

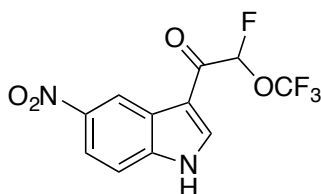
^1H NMR (200 MHz, Acetone) (ppm) δ : 6.87 (d, J = 55.7 Hz, 1H), 7.65 (d, J = 9.2 Hz, 1H), 7.81 (d, J = 8.5 Hz, 1H), 8.65 (s, 2H), 10.66 (br s, NH).

^{19}F NMR (188 MHz, Acetone) (ppm) δ : -59.5 (d, J = 4.25 Hz, 3F), -133.7 (dq, J = 55.6 Hz, J = 4.9 Hz, 1F).

^{13}C NMR (50 MHz, Acetone) (ppm) δ : 101.5 (dq, J = 241.8 Hz, J = 4.0 Hz), 106.2, 111.8 (d, J = 1.4 Hz), 113.8, 119.3, 121.3, (qd, J = 259.1 Hz, J = 1.8 Hz), 125.9, 126.4, 126.9, 137.4 (d, J = 8.2 Hz), 138.3, 180.7 (d, J = 25.5 Hz).

FTIR (cm^{-1} , neat): 3194, 2229, 1652, 1434, 1409, 1229, 1181, 1080, 1032, 889, 813, 795, 669, 630, 608.

Anal. Calcd. for $\text{C}_{12}\text{H}_7\text{N}_2\text{O}_2\text{F}_4$ [$\text{M} + \text{H}$] $^+$: 287.0444, found 287.0446.



2-Fluoro-1-(5-nitro-1H-indol-3-yl)-2-(trifluoromethoxy)ethanone (4c)

Trifluoromethyl trifluorovinyl ether (830 mg, 5 mmol, 5 equiv) was added in a Schlenk tube with diethylamine (73 mg, 1 mmol, 1 equiv). The solution was stirred for two hours at room temperature. Then, dry CH_2Cl_2 was added (4 mL) followed by $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (170 mg, 1.2 mmol, 1.2 equiv) under argon. The solution was stirred for 15 min at room temperature. Then, 5-nitroindole (162 mg, 1 mmol, 1 equiv) was added in one portion and the resulting mixture stirred overnight at room temperature. The solution was hydrolysed with water (2.5 mL) and extracted three times with CH_2Cl_2 (3 x 5 mL).

The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum. The crude mixture was purified by chromatography on silica gel, using pentane/Et₂O (5/5) as eluent. Yield: 27 % (0.3 mmol, 95 mg). Yellow solid. M.p.: 200-202 °C. Rf: 0.37 (pentane/Et₂O = 5/5).

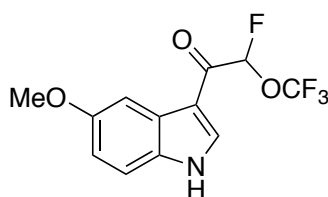
¹H NMR (200 MHz, Acetone) (ppm) δ: 6.89 (d, *J* = 55.5 Hz, 1H), 7.82 (d, *J* = 9.0 Hz, 1H), 8.23 (dd, *J* = 8.9 Hz, *J* = 2.3 Hz, 1H), 8.69 (d, *J* = 1.9 Hz, 1H), 9.19 (d, *J* = 2.2 Hz, 1H), 11.94 (br s, 1H).

¹⁹F NMR (188 MHz, Acetone) (ppm) δ: -59.5 (d, *J* = 4.8 Hz, 3F), -133.7 (dq, *J* = 55.6 Hz, *J* = 4.4 Hz, 1F).

¹³C NMR (50 MHz, Acetone) (ppm) δ: 102.6 (dq, *J* = 240.6 Hz, *J* = 3.0 Hz), 133.8 (d, *J* = 1.2 Hz), 114.1, 118.8, 120.2, 122.3 (dq, *J* = 261.5 Hz, *J* = 1.5 Hz), 126.6, 139.3, 140.6, 145.1, 181.9 (d, *J* = 25.7 Hz).

FTIR (cm⁻¹, neat): 3192, 1640, 1587, 1531, 1437, 1340, 1222, 1064, 821, 806, 631, 583.

Anal. Calcd. for C₁₁H₇N₂O₄F₄ [M + H]⁺: 307.0342, found 307.0335.



2-Fluoro-1-(5-methoxy-1H-indol-3-yl)-2-(trifluoromethoxy)ethanone (4d)

Trifluoromethyl trifluorovinyl ether (830 mg, 5 mmol, 5 equiv) was added in a Schlenk tube with diethylamine (73 mg, 1 mmol, 1 equiv). The solution was stirred for two hours at room temperature. Then, dry CH₂Cl₂ was added (4 mL) followed by BF₃·Et₂O (170 mg, 1.2 mmol, 1.2 equiv) under argon. The solution was stirred for 15 min at room temperature. Then, 5-methoxyindole (147 mg, 1 mmol, 1 equiv) was added in one portion and the resulting mixture stirred overnight at room temperature. The solution was hydrolysed with water (2.5 mL) and extracted three times with CH₂Cl₂ (3 x 5 mL). The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum. The crude mixture was purified by chromatography on silica gel, using a gradient of pentane/Et₂O as eluent from 7/3 to 4/6. Yield: 60% (0.55 mmol, 160 mg). White solid. M.p.: 184-186 °C. Rf: 0.16 (pentane/Et₂O = 6/4)

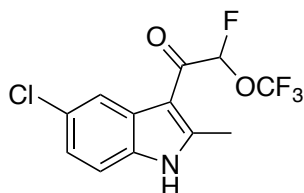
¹H NMR (200 MHz, CD₃CN) (ppm) δ: 3.86 (s, 3H), 6.60 (d, *J* = 55.8 Hz, 1H), 6.97 (dd, *J* = 8.9 Hz, *J* = 2.5 Hz, 1H), 7.47 (d, *J* = 8.9 Hz, 1H), 7.79 (d, *J* = 2.4 Hz, 1H), 8.16 (dd, *J* = 3.5 Hz, *J* = 1.6 Hz, 1H), 10.20 (br s, NH).

¹⁹F NMR (188 MHz, CD₃CN) (ppm) δ: -59.5 (d, *J* = 5.2 Hz, 3F), -135.4 (dq, *J* = 55.9 Hz, *J* = 5.0 Hz, *J* = 1.5 Hz, 1F).

¹³C NMR (50 MHz, CD₃CN) (ppm) δ: 55.2, 101.4 (dq, *J* = 240.9 Hz, *J* = 2.9 Hz), 103.1, 111.5 (d, *J* = 1.1 Hz), 113.2, 114.1, 121.3 (qd, *J* = 260.2 Hz, *J* = 1.8 Hz), 126.9, 131.1, 135.3 (d, *J* = 7.2 Hz), 156.9, 180.5 (d, *J* = 24.7 Hz).

FTIR (cm⁻¹, neat): 3172, 1646, 1624, 1589, 1437, 1225, 1161, 1085, 1026, 846, 802, 650, 629, 598

Anal. Calcd. C₁₂H₁₀NO₃F₄ [M + H]⁺: 292.0589, found 292.0597.



1-(5-Chloro-2-methyl-1H-indol-3-yl)-2-fluoro-2-(trifluoromethoxy)ethanone (4e)

Trifluoromethyl trifluorovinyl ether (830 mg, 5 mmol, 5 equiv) was added in a Schlenk tube with diethylamine (73 mg, 1 mmol, 1 equiv). The solution was stirred for two hours at room temperature. Then, dry CH₂Cl₂ was added (4 mL) followed by BF₃·Et₂O (170 mg, 1.2 mmol, 1.2 equiv) under argon.

The solution was stirred for 15 min at room temperature. Then, 5-chloro-2-methylindole (166 mg, 1 mmol, 1 equiv) in one portion was added and the resulting mixture stirred overnight at room temperature. The solution was hydrolysed with water (2.5 mL) and extracted three times with CH₂Cl₂ (3 x 5 mL). The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum. The crude mixture was purified by chromatography on silica gel, using a gradient of pentane/Et₂O as eluent from 7/3 to 5/5. Yield: 60% (0.36 mmol, 110 mg). Pale yellow solid. M.p.: 172-174 °C. Rf: 0.44 (pentane/Et₂O = 8/2).

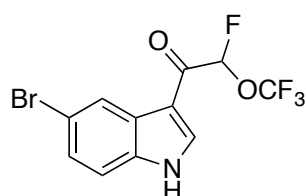
¹H NMR (200 MHz, Acetone) (ppm) δ: 2.81 (s, 3H), 6.69 (d, *J* = 55.8 Hz, 1H), 7.22 (dd, *J* = 8.6 Hz, *J* = 1.8 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 8.09 (d, *J* = 1.1 Hz, 1H), 11.46 (br s, NH).

¹⁹F NMR (188 MHz, Acetone) (ppm) δ: -57.9 (d, *J* = 4.9 Hz, 3F), -134.4 (dq, *J* = 55.9 Hz, *J* = 5.3 Hz, 1F).

¹³C NMR (300 MHz, Acetone) (ppm) δ: 14.5 (d, *J* = 2.7 Hz), 101.5 (dq, *J* = 239.8, *J* = 2.8 Hz), 109.4, 112.8, 120.3 (d, *J* = 2.7 Hz), 121.4 (qd, *J* = 258.1 Hz, *J* = 1.8 Hz), 122.9, 127.8, 128.1, 133.7 (d, *J* = 7.2 Hz), 148.3 (d, *J* = 8.0 Hz), 180.4 (d, *J* = 25.2 Hz).

FTIR (cm⁻¹, neat): 3043, 2952, 2838, 1604.64, 1556, 1480, 1325, 1272, 1230, 1014, 887, 751, 741, 718, 585.

Anal. Calcd. for C₁₂H₉NO₂ClF₄ [M + H]⁺: 310.0258, found 310.0257.



1-(5-Bromo-1H-indol-3-yl)-2-fluoro-2-(trifluoromethoxy)ethanone (4f)

Trifluoromethyl trifluorovinyl ether (830 mg, 5 mmol, 5 equiv) was added in a Schlenk tube with diethylamine (73 mg, 1 mmol, 1 equiv). The solution was stirred for two hours at room temperature. Then, dry CH₂Cl₂ was added (4 mL) followed by BF₃·Et₂O (170 mg, 1.2 mmol, 1.2 equiv) under argon. The solution was stirred for 15 min at room temperature. Then, 5-bromoindole (196 mg, 1 mmol, 1 equiv) was added in one portion and the resulting mixture stirred overnight at room temperature. The solution was hydrolysed with water (2.5 mL) and extracted three times with CH₂Cl₂ (3 x 5 mL). The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum. The crude mixture was purified by chromatography on silica gel, using a gradient of pentane/Et₂O as eluent from 7/3 to 4/6. Yield: 49 % (0.65 mmol, 221 mg). White solid. M.p.: 196-198 °C. Rf: 0.21 (pentane/Et₂O = 6/4).

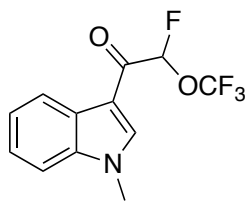
¹H NMR (200 MHz, Acetone) (ppm) δ: 6.83 (d, *J* = 54.6 Hz, 1H), 7.46 (d, *J* = 8.3 Hz, 1H), 7.59 (d, *J* = 8.46 Hz, 1H), 8.40-8.55 (m, 2H), 11.62 (br s, 1H).

¹⁹F NMR (188 MHz, Acetone) (ppm) δ: -59.5 (d, *J* = 4.9 Hz, 3F), -133.33 (dq, *J* = 54.97 Hz, *J* = 5.19 Hz, 1F).

¹³C NMR (50 MHz, Acetone) (ppm) δ: 101.6 (dq, *J* = 241.5 Hz, *J* = 3.8 Hz), 111.2 (d, *J* = 1.3 Hz), 114.3, 116.1, 121.4 (qd, *J* = 260.3, *J* = 2 Hz), 124.0, 126.9, 127.9, 135.5, 136.4 (d, *J* = 8.5 Hz), 180.5 (d, *J* = 25.4 Hz).

FTIR (cm⁻¹, neat): 3274, 1635, 1615, 1519, 1441, 1224, 1185, 1092, 1047, 885, 799, 786, 685, 614

Anal. Calcd. for C₁₁H₇NO₂F₄Br [M + H]⁺ 339.9596, found 339.9598.



2-Fluoro-1-(1-methyl-1H-indol-3-yl)-2-(trifluoromethoxy)ethanone (4g)

Trifluoromethyl trifluorovinyl ether (830 mg, 5 mmol, 5 equiv) was added in a Schlenk tube with diethylamine (73 mg, 1 mmol, 1 equiv). The solution was stirred for two hours at room temperature. Then, dry CH₂Cl₂ was added (4 mL) followed by BF₃.Et₂O (170 mg, 1.2 mmol, 1.2 equiv) under argon. The solution was stirred for 15 min at room temperature. Then, 1-methylindole (125 μL, 1 mmol, 1 equiv) was added and the resulting mixture stirred overnight at room temperature. The solution was hydrolysed with water (2.5 mL) and extracted three times with CH₂Cl₂ (3 x 5 mL). The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum. The crude mixture was purified by chromatography on silica gel, using pentane/Et₂O (6/4) as eluent. Yield: 77% (0.68 mmol, 186 mg). White solid. M.p.: 86-88°C. Rf: 0.39 (pentane/Et₂O = 6/4).

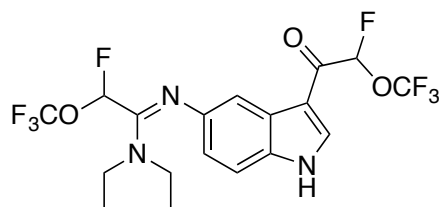
¹H NMR (200 MHz, CDCl₃) (ppm) δ: 3.84 (s, 3H), 6.18 (d, *J* = 56.8 Hz, 1H), 7.33-7.38 (m, 3H), 7.94 (d, *J* = 2.2 Hz, 1H), 8.36-8.43 (m, 1H).

¹⁹F NMR (188 MHz, CDCl₃) (ppm) δ: -59.6 (d, *J* = 4.6 Hz, 3F), -129.9 (dq, *J* = 56.9 Hz, *J* = 4.8 Hz, 1F).

¹³C NMR (75 MHz, CDCl₃) (ppm) δ: 33.8, 103.2 (dq, *J* = 244.5 Hz, *J* = 3.3 Hz), 109.9, 110.3 (d, *J* = 3.0 Hz), 121.1 (qd, *J* = 262.3 Hz, *J* = 1.7 Hz), 122.4, 123.6, 124.2, 126.9, 137.1, 137.8 (d, *J* = 10.2 Hz), 180.9 (d, *J* = 26.3 Hz).

FTIR (cm⁻¹, neat): 3111, 1658, 1535, 1355, 1217, 1181, 1041, 826, 748, 669, 568.

Anal. Calcd. for C₁₂H₁₀NO₂F₄ [M + H]⁺: 276.0648, found 276.0640.



(Z)-N,N-Diethyl-2-fluoro-N'-(3-(2-fluoro-2-(trifluoromethoxy)acetyl)-1H-indol-5-yl)-2-(trifluoromethoxy)acetimidamide (4h)

Trifluoromethyl trifluorovinyl ether (830 mg, 5 mmol, 5 equiv) was added in a Schlenk tube with diethylamine (73 mg, 1 mmol, 1 equiv). The solution was stirred for two hours at room temperature. Then, dry CH₂Cl₂ was added (4 mL) followed by BF₃.Et₂O (170 mg, 1.2 mmol, 1.2 equiv) under argon. The solution was stirred for 15 min at room temperature. Then, 5-aminoindole (132 mg, 1 mmol, 1 equiv) was added in one portion and the resulting mixture stirred overnight at room temperature. The solution was hydrolysed with water (2.5 mL) and extracted three times with CH₂Cl₂ (3 x 5 mL). The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum. The crude mixture was purified by chromatography on silica gel, using pentane/AcOEt (6/4) as eluent. Yield: 48 % (0.27 mmol, 130 mg). White solid. M.p.: 182-184 °C. Rf: 0.67 (pentane/AcOEt = 6/4).

¹H NMR (200 MHz, Acetone) (ppm) δ: 1.25 (t, *J* = 6.9 Hz, 6H), 3.56 (q, *J* = 7.0 Hz, 4H), 6.61 (d, *J* = 55.4 Hz, 1H), 6.74 (dd, *J* = 55.6 Hz, *J* = 1.2 Hz, 1H), 6.78 (dd, *J* = 8.5 Hz, *J* = 2.1 Hz, 1H), 7.52 (d, *J* = 8.3 Hz, 1H), 7.65 (d, *J* = 2.2 Hz, 1H), 8.39 (d, *J* = 1.4 Hz, 1H), 11.4 (br s, NH).

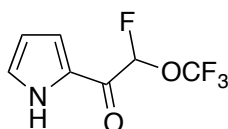
¹⁹F NMR (188 MHz, Acetone) (ppm) δ: -59.5 (d, *J* = 4.6 Hz, 3F), -59.7 (dd, *J* = 4.6 Hz, *J* = 2.4 Hz, 3F), -129.5 (d, *J* = 55.6 Hz, 1F), -133.1 (ddq, *J* = 55.9 Hz, *J* = 13.5 Hz, *J* = 5.3 Hz, 1F).

¹³C NMR (50 MHz, Acetone) (ppm) δ: 12.4, 41.9 (d, *J* = 2.7 Hz), 101.7 (dt, *J* = 242.9 Hz, *J* = 2.8 Hz), 111.7, 112.7, 112.8 (d, *J* = 2.2 Hz), 119.1, 120.9 (d, *J* = 262.8 Hz), 121.4 (dd, *J* = 260.4 Hz, *J* = 2.2 Hz),

127.2, 132.8 (d, $J = 7.8$ Hz), 135.1, 135.3 (d, $J = 8.4$ Hz), 144.9 (d, $J = 1.0$ Hz), 146.8 (d, $J = 20.7$ Hz), 180.2 (dd, $J = 25.0$ Hz, $J = 1.9$ Hz).

FTIR (cm^{-1} , neat): 3173, 2983, 2938, 1644, 1605, 1450, 1433, 1276, 1172, 1033, 893, 902, 640, 592, 461.

Anal. Calcd. for $\text{C}_{18}\text{H}_{18}\text{N}_3\text{O}_3\text{F}_8$ $[\text{M} + \text{H}]^+$: 476.1220, found 476.1221.



2-Fluoro-1-(1H-pyrrol-2-yl)-2-(trifluoromethoxy)ethanone (5a)

Trifluoromethyl trifluorovinyl ether (830 mg, 5 mmol, 5 equiv) was added in a Schlenk tube with diethylamine (73 mg, 1 mmol, 1 equiv). The solution was stirred for two hours at room temperature. Then, dry CH_2Cl_2 was added (4 mL) followed by $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (170 mg, 1.2 mmol, 1.2 equiv) under argon. The solution was stirred for 15 min at room temperature. Then, pyrrole (69 μL , 1 mmol, 1 equiv) was added and the resulting mixture stirred overnight at room temperature. The solution was hydrolysed with water (2.5 mL) and extracted three times with CH_2Cl_2 (3 x 5 mL). The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum. The crude mixture was purified by chromatography on silica gel, using pentane/ Et_2O (8/2) as eluent. Yield: 55% (0.57 mmol, 120 mg). Colourless oil. Rf: 0.40 (pentane/ Et_2O = 8/2).

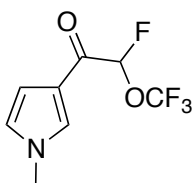
^1H NMR (300 MHz, CDCl_3) (ppm) δ : 6.22 (d, $J = 56.2$ Hz, 1H), 6.41 (dd, $J = 6.4$ Hz, $J = 2.5$ Hz, 1H), 7.22 (dd, $J = 3.8$ Hz, $J = 3.1$ Hz, 1H), 7.26 (t, $J = 6.4$ Hz, 1H), 10.0 (br s, 1H, NH).

^{19}F NMR (188 MHz, CDCl_3) (ppm) δ : -59.7 (d, $J = 4.7$ Hz, 3F), -113.5 (dq, $J = 56$ Hz, $J = 2.7$ Hz, 1F).

^{13}C NMR (75 MHz, CDCl_3) (ppm) δ : 101.2 (dq, $J = 242.3$ Hz, $J = 3.8$ Hz), 112.3, 120.3 (d, $J = 5.3$ Hz), 121.1 (qd, $J = 262.4$ Hz, $J = 1.5$ Hz), 127.1, 128.3, 175.8 (d, $J = 26.3$ Hz).

FTIR (cm^{-1} , neat): 3310, 1649, 1430, 1410, 1260, 1179, 1045, 715, 653, 621, 596.

Anal. Calcd. for $\text{C}_7\text{H}_6\text{NO}_2\text{F}_4$ $[\text{M} + \text{H}]^+$: 212.0335, found 212.0328.



2-Fluoro-1-(1-methyl-1H-pyrrol-2-yl)-2-(trifluoromethoxy)ethanone (5b)

Trifluoromethyl trifluorovinyl ether (830 mg, 5 mmol, 5 equiv) was added in a Schlenk tube with diethylamine (73 mg, 1 mmol, 1 equiv). The solution was stirred for two hours at room temperature. Then, dry CH_2Cl_2 was added (4 mL) followed by $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (170 mg, 1.2 mmol, 1.2 equiv) under argon. The solution was stirred for 15 min at room temperature. Then, 1-methylpyrrole (89 μL , 1 mmol, 1 equiv) was added and the resulting mixture stirred overnight at room temperature. The solution was hydrolysed with water (2.5 mL) and extracted three times with CH_2Cl_2 (3 x 5 mL). The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum. The crude mixture was purified by chromatography on silica gel, using pentane/DCM (8/2) as eluent. Yield: 45 % (0.45 mmol, 102 mg). Colourless oil. Rf: 0.30 (pentane/ CH_2Cl_2 = 8/2).

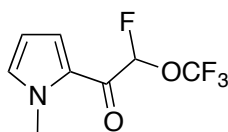
^1H NMR (200 MHz, CDCl_3) (ppm) δ : 3.73 (s, 3H), 6.09 (d, $J = 56.8$ Hz, 1H), 6.63 (dd, $J = 2.7$ Hz, $J = 2$ Hz, 1H), 6.67-6.71 (m, 1H), 7.44 (dd, $J = 3.4$ Hz, $J = 1.7$ Hz, 1H).

^{19}F NMR (188 MHz, CDCl_3) (ppm) δ : -59.6 (d, $J = 4.8$ Hz, 3F), -132.3 (dq, $J = 56.5$ Hz, $J = 4.5$ Hz, 1F).

^{13}C NMR (50 MHz, CDCl_3) (ppm) δ : 36.8, 102.5 (dq, $J = 245.2$ Hz, $J = 3.2$ Hz), 110.6 (d, $J = 1.5$ Hz), 119.3 (d, $J = 2.6$ Hz), 121.1 (qd, $J = 262.4$ Hz, $J = 1.9$ Hz), 124.1, 129.5 (d, $J = 6.5$ Hz), 181.1 (d, $J = 26.4$ Hz).

FTIR (cm^{-1} , neat): 3126, 2967, 1670, 1533, 1226, 1173, 1117, 1042, 822, 719, 605.

Anal. Calcd. for $\text{C}_8\text{H}_8\text{NO}_2\text{F}_4$ $[\text{M} + \text{H}]^+$: 226.0491, found 226.0492.



2-Fluoro-1-(1-methyl-1H-pyrrol-3-yl)-2-(trifluoromethoxy)ethanone (5c)

Separated from **5b** by chromatography. Yield: 41 % (0.41 mmol, 93 mg). Colourless oil. Rf: 0.63 (pentane/CH₂Cl₂ = 8/2).

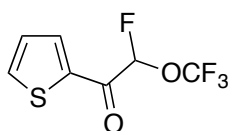
¹H NMR (300 MHz, CDCl₃) (ppm) δ: 3.97 (s, 3H), 6.26 (d, *J* = 56.6 Hz, 1H), 6.25 (dd, *J* = 4.2 Hz, *J* = 2.4 Hz, 1H), 6.97-7.02 (m, 1H), 7.18 (dt, *J* = 3.4 Hz, *J* = 1.4 Hz, 1H).

¹⁹F NMR (188 MHz, CDCl₃) (ppm) δ: -59.7 (d, *J* = 3.8 Hz, 3F), -131.9 (qd, *J* = 56.4 Hz, *J* = 3.8 Hz, 1F).

¹³C NMR (75 MHz, CDCl₃) (ppm) δ: 37.7, 101.2 (dq, *J* = 243.6 Hz, *J* = 3.1 Hz), 109.7, 121.1 (qd, *J* = 160.2 Hz, *J* = 2.2 Hz), 122.4 (d, *J* = 4.5 Hz), 125.9, 133.9, 175.3 (d, *J* = 24.7 Hz).

FTIR (cm⁻¹, neat): 3118, 2960, 1661, 1530, 1408, 1257, 1212, 1171, 1046, 957, 831, 741, 653, 600.

Anal. Calcd. for C₈H₈NO₂F₄ [M + H]⁺: 226.0491, found 226.0486.



2-Fluoro-1-(thiophen-2-yl)-2-(trifluoromethoxy)ethanone (5d)

Trifluoromethyl trifluorovinyl ether (830 mg, 5 mmol, 5 equiv) was added in a Schlenk tube with diethylamine (73 mg, 1 mmol, 1 equiv). The solution was stirred for two hours at room temperature. Then, dry CH₂Cl₂ was added (4 mL) followed by BF₃·Et₂O (170 mg, 1.2 mmol, 1.2 equiv) under argon. The solution was stirred for 15 min at room temperature. Then, thiophene (80 μL, 1 mmol, 1 equiv) was added and the resulting mixture stirred overnight at room temperature. The solution was hydrolysed with water (2.5 mL) and extracted three times with CH₂Cl₂ (3 x 5 mL). The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum. The crude mixture was purified by chromatography on silica gel, using pentane/Et₂O (8/2) as eluent. Yield: 6 % (0.06 mmol, 13 mg). Pale yellow oil. Rf: 0.62 (pentane/Et₂O = 8/2).

¹H NMR (200 MHz, CDCl₃) (ppm) δ: 6.26 (d, *J* = 56.4 Hz, 1H), 7.24 (dd, *J* = 4.9 Hz, *J* = 4.1 Hz, 1H), 7.86 (dd, *J* = 4.9 Hz, *J* = 1.0 Hz, 1H), 8.00 (dt, *J* = 3.9 Hz, *J* = 1.4 Hz, 1H).

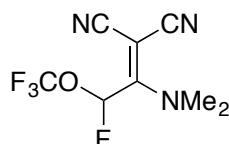
¹⁹F NMR (188 MHz, CDCl₃) (ppm) δ: -59.7 (d, *J* = 4.7 Hz, 3F), -131.5 (dq, *J* = 56.2 Hz, *J* = 4.6 Hz, *J* = 1.2 Hz, 1F).

¹³C NMR (50 MHz, CDCl₃) (ppm) δ: 101.9 (dq, *J* = 245.9 Hz, *J* = 3.3 Hz), 120.9 (qd, *J* = 261.9 Hz, *J* = 1.8 Hz), 128.9 (d, *J* = 1.1 Hz), 135.6 (d, *J* = 4.8 Hz), 136.9 (d, *J* = 1.1 Hz), 137.6 (d, *J* = 2.9 Hz), 179.3 (d, *J* = 27.3 Hz).

FTIR (cm⁻¹, neat): 3103, 2954, 1676, 1515, 1413, 1116, 1058, 895, 812, 726, 592.

Anal. Calcd. for C₇H₅O₂F₄S [M + H]⁺: 228.9946, found 228.9953.

D. Regioselective preparation of 3-(CHFOCF₃)-5-aminopyrazole- and -isoxazolecarbonitrile and -carboxylates (7a-d and 8a-c)



2-(1-(Dimethylamino)-2-fluoro-2-(trifluoromethoxy)ethylidene)malononitrile (6a)

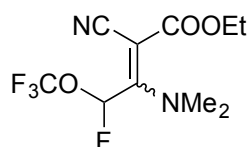
Solid activated FAR **2b** (1.22 equiv, 930 mg, 3.33 mmol) was taken up in dry MeCN (4 mL) at room temperature before a solution of malononitrile (1 equiv, 180 mg, 2.72 mmol) was added *via* syringe. After placing a water-bath, Et₃N (1.51 equiv, 414 mg, 0.57 mL, 4.1 mmol) was carefully added *via* syringe. The mixture was stirred for 1h at room temperature. Internal standard: fluorobenzene (1.17 equiv, 306 mg, 0.3 mL, 3.18 mmol). ¹⁹F NMR yield: 53%. An excess of Al₂O₃ was added and the mixture was concentrated *in vacuo*. The cake was washed twice with cyclohexane and the combined filtrate was concentrated *in vacuo*, to yield 290 mg of orange oil (45%).

¹H-NMR (400 MHz, CDCl₃): δ = 6.76 d, CHFOCF₃, ¹J_{H-F} = 53.5 Hz), 3.40 (s, N(CH₃)₂) ppm.

¹⁹F-NMR (376 MHz, CDCl₃): δ = -59.6 (d, OCF₃, ⁴J_{F-F} = 4.8 Hz), -127.6 (d, CHFOCF₃, ¹J_{F-H} = 53.1 Hz) ppm.

¹³C-NMR (100 MHz, CDCl₃): δ = 158.8 (d, CCHFOCF₃, ²J_{C-F} = 23.1 Hz), 120.8 (q, OCF₃, ¹J_{C-F} = 265.2 Hz), 114.3 and 114.0 (2 x CN), 101.1 (dq, CHFOCF₃, ¹J_{C-F} = 239.5 Hz, ⁴J_{C-F} = 3.7 Hz), 55.7 (d, C(CN)₂, ³J_{C-F} = 6.3 Hz), 44.2 (s br, N(CH₃)₂) ppm.

HRMS (ESI) calcd for C₈H₇F₄N₃NaO [M+Na]⁺: 260.0417. Found: 260.0432.



Ethyl 2-cyano-3-(dimethylamino)-4-fluoro-4-(trifluoromethoxy)but-2-enoate (6b)

Solid activated FAR **2b** (1.22 equiv, 930 mg, 3.33 mmol) was taken up in dry MeCN (4 mL) at room temperature before a solution of ethyl cyanoacetate (1 equiv, 307 mg, 0.27 mL, 2.72 mmol) was added *via* syringe. After placing a water-bath, DIPEA (2 equiv, 703 mg, 0.9 mL, 5.45 mmol) was carefully added *via* syringe. The mixture was stirred for 1h at room temperature. An excess of Al₂O₃ was added and the mixture was concentrated *in vacuo*. The Al₂O₃ cake was washed twice with cyclohexane and the combined filtrate was concentrated *in vacuo*, to yield 815 mg of orange oil (95wt.%, 39%). Clean analytical data were obtained after purification by flash chromatography (AcOEt in cyclohexane 0 to 30%).

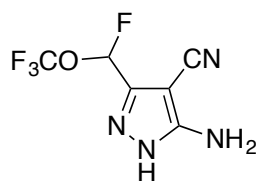
Major isomer:

¹H-NMR (400 MHz, CDCl₃): δ = 8.07 (d, CHFOCF₃, ¹J_{H-F} = 54.1 Hz), 4.20 (q, OCH₂CH₃), 3.33 (s, N(CH₃)₂), 1.28 (t, OCH₂CH₃) ppm.

¹⁹F-NMR (376 MHz, CDCl₃): δ = -59.5 (d, OCF₃, ⁴J_{F-F} = 4.1 Hz), -132.0 (d, CHFOCF₃, ¹J_{F-H} = 54.5 Hz) ppm.

¹³C-NMR (100 MHz, CDCl₃): δ = 165.3 (C=O), 161.5 (d, CCHFOCF₃, ²J_{C-F} = 21.8 Hz), 120.9 (q, OCF₃, ¹J_{C-F} = 263.4 Hz), 117.3 (CN), 98.6 (qd, CHFOCF₃, ¹J_{C-F} = 235.3 Hz, ⁴J_{C-F} = 3.8 Hz), 75.9 (d, CCN, ³J_{C-F} = 5.2 Hz), 61.6 (OCH₂CH₃), 44.7 (s br, N(CH₃)₂), 14.2 (OCH₂CH₃) ppm.

HRMS (ESI) calcd for C₁₀H₁₂F₄N₂NaO₃ [M + Na]⁺: 307.0676. Found: 307.0670.



5-Amino-3-(fluoro(trifluoromethoxy)methyl)-1H-pyrazole-4-carbonitrile (7a)

A solution of 2-[1-(dimethylamino)-2-fluoro-2-(trifluoromethoxy)ethylidene]propanedinitrile **6a** (1 equiv, 400 mg, 1.69 mmol) and boc-hydrazide (1.5 equiv, 335 mg, 2.53 mmol) in dry MeCN (4 mL) was heated at 50 °C for 18h and 2h more at 70 °C. The mixture was concentrated *in vacuo* and purified by flash chromatography (AcOEt in cyclohexane 0 to 50%), to yield 245 mg of colourless solid (99%).

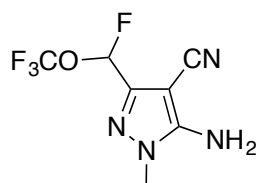
M.p.: 141.6 - 142.1 °C.

¹H-NMR (400 MHz, CD₃CN): δ = 10.55 (s br, NH), 6.80 (d, CHFOCF₃, *J* = 55.5 Hz), 5.36 (s br, NH₂) ppm.

¹⁹F-NMR (376 MHz, CD₃CN): δ = -59.9 (d, OCF₃, *J* = 5.5 Hz), -124.0 (dq, CHFOCF₃, *J* = 55.4 Hz, *J* = 4.7 Hz) ppm.

¹³C-NMR (100 MHz, CD₃CN): δ = 155.0 (CNH₂), 146.7 (d, CCHFOCF₃, *J* = 28 Hz), 121.9 (q, OCF₃, *J* = 260 Hz), 113.4 (CN), 102.5 (dq, CHFOCF₃, *J* = 225 Hz, *J* = 3 Hz) ppm.

Anal. calcd for C₆H₄F₄N₄O: C, 32.16; H, 1.80; F, 33.91; N, 25.00; O, 7.14. Found: C, 32.28; H, 1.99; N, 24.57.



5-Amino-3-(fluoro(trifluoromethoxy)methyl)-1-methyl-1H-pyrazole-4-carbonitrile (7b)

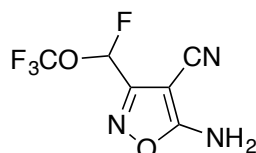
A solution of 2-[1-(dimethylamino)-2-fluoro-2-(trifluoromethoxy)ethylidene]propanedinitrile **6a** (1 equiv, 462 mg, 1.95 mmol) in dry MeCN (5 mL) was treated with methyl hydrazine (1.63 equiv, 146 mg, 0.17 mL, 3.17 mmol) at room temperature. The mixture was stirred for 30min. The mixture was concentrated *in vacuo* and purified by flash chromatography (AcOEt in cyclohexane 0 to 50%) to yield 416 mg of yellow solid (90%). M.p.: 95.0 - 96.4 °C.

¹H-NMR (400 MHz, CDCl₃): δ = 6.58 (d, CHFOCF₃, ¹*J*_{H-F} = 56 Hz), 4.68 (s br, NH₂), 3.66 (NCH₃) ppm.

¹⁹F-NMR (376 MHz, CDCl₃): δ = -59.3 (d, OCF₃, ⁴*J*_{F-F} = 4.8 Hz), -122.5 (qd, CHFOCF₃, ¹*J*_{F-H} = 56.5 Hz, ⁴*J*_{F-F} = 5.2 Hz) ppm.

¹³C-NMR (100 MHz, CDCl₃): δ = 151.6 (CNH₂), 144.6 (d, CCHFOCF₃, ²*J*_{C-F} = 28.8 Hz), 121.0 (q, OCF₃, ¹*J*_{C-F} = 260.6 Hz), 112.5 (CN), 100.6 (qd, CHFOCF₃, *J* = 228.0 Hz, *J* = 3.8 Hz), 73.7 (CCN), 35.1 (NCH₃) ppm.

Anal. calcd for C₇H₆F₄N₄O: C, 35.30; H, 2.54; F, 31.91; N, 23.53; O, 6.72. Found: C, 35.59; H, 2.63; N, 23.56.



5-Amino-3-(fluoro(trifluoromethoxy)methyl)isoxazole-4-carbonitrile (7c)

A solution of 2-[1-(dimethylamino)-2-fluoro-2-(trifluoromethoxy)ethylidene]propanedinitrile **6a** (1 equiv, 50 mg, 0.21 mmol) in dry MeCN (4 mL) was treated with hydroxylamine (50wt.% aqueous, 1.55 equiv, 22 mg, 0.02 mL, 0.32 mmol) at room temperature. The mixture was stirred for 15 min. Internal standard: fluorobenzene (1 equiv, 20 mg, 0.02 mL, 0.21 mmol). ¹⁹F NMR yield: 99%.

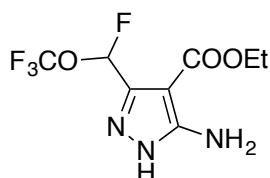
The desired product was isolated after purification by flash chromatography (Et₂O in pentane 0 to 50%), to yield 46 mg of a pale solid (after trituration in pentane) (97%). M.p.: 110.3 - 110.9 °C.

¹H-NMR (400 MHz, d⁶-DMSO): δ = 8.88 (s br, NH₂), 7.53 (d, CHFOCF₃, J = 53.3 Hz) ppm.

¹⁹F-NMR (376 MHz, d⁶-DMSO): δ = -58.0 (m, OCF₃), -129.8 (dq, CHFOCF₃, J = 52.9 Hz, J = 4.5 Hz) ppm.

¹³C-NMR (100 MHz, d⁶-DMSO): δ = 173.5 (OCNH₂), 157.1 (d, CCHFOCF₃, J = 27 Hz), 120.4 (q, OCF₃, J = 263 Hz), 111.0 (CN), 99.5 (d, CHFOCF₃, J = 229 Hz), 61.9 (C-CN) ppm.

Anal. calcd for C₆H₃F₄N₃O₂: C, 32.01; H, 1.34; F, 33.76; N, 18.67; O, 14.21. Found: C, 31.94; H, 1.58; N, 18.13.



Ethyl 5-amino-3-(fluoro(trifluoromethoxy)methyl)-1H-pyrazole-4-carboxylate (8a)

A solution of ethyl 2-cyano-3-(dimethylamino)-4-fluoro-4-(trifluoromethoxy)but-2-enoate **6b** (1 equiv, 480 mg, 1.52 mmol) and hydrazine hydrate (0.9 equiv, 70 μL, 1.43 mmol) in dry MeCN (4 mL) was stirred for 1h at rt, then diluted with DCM, filtered and concentrated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 50%) to yield a yellow solid after trituration in pentane (160 mg, 39%).

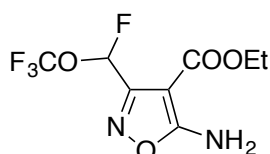
M.p.: 96.0 - 99.0 °C.

¹H-NMR (400 MHz, CDCl₃): δ = 12.5 (s br, NH), 7.25 (d, CHFOCF₃, J = 56.5 Hz), 5.44 (s br, NH₂), 4.32 (q, OCH₂), 1.35 (t, OCH₂CH₃) ppm.

¹⁹F-NMR (376 MHz, CDCl₃): δ = -59.1 (d, OCF₃, J = 5 Hz), -129.3 (d, CHFOCF₃, J = 56.8 Hz) ppm.

¹³C-NMR (100 MHz, CDCl₃): δ = 163.4 (C=O), 152.3 (NC-NH₂), 143.8 (d, CCHFOCF₃, J = 22 Hz), 121.1 (q, OCF₃, J = 262 Hz), 100.8 (dq, CHFOCF₃, J = 225 Hz, J = 3 Hz), 93.2 (d, CCOOEt, J = 3.7 Hz), 60.5 (OCH₂), 14.4 (OCH₂CH₃) ppm.

HRMS (ESI) calcd for C₈H₁₀F₄N₃O₃ [M+H]⁺: 272.0653. Found: 272.0671.



Ethyl 5-amino-3-(fluoro(trifluoromethoxy)methyl)isoxazole-4-carboxylate (8c)

A solution of ethyl 2-cyano-3-(dimethylamino)-4-fluoro-4-(trifluoromethoxy)but-2-enoate **6b** (1 equiv, 410 mg, 1.30 mmol) in dry MeCN (4 mL) was treated with hydroxylamine hydrochloride (1.66 equiv, 150 mg, 2.16 mmol), followed after 1h without reaction by Et₃N (1.0 equiv, 131 mg, 0.18 mL, 1.3 mmol). After 1h at room temperature, the mixture was diluted with DCM, filtered and concentrated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 5%) to yield a white solid (353 mg, 99%) after trituration in pentane. M.p.: 119.6 - 119.8 °C.

¹H-NMR (400 MHz, CDCl₃): δ = 6.92 (d, CHFOCF₃, J = 55.2 Hz), 6.23 (s br, NH₂), 4.32 (m, OCH₂), 1.34 (t, OCH₂CH₃) ppm.

¹⁹F-NMR (376 MHz, CDCl₃): δ = -59.3 (d, OCF₃, J = 5.5 Hz), -131.4 (qd, CHFOCF₃, J = 55.3 Hz, J = 5.1 Hz) ppm.

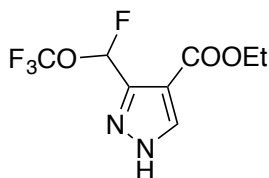
¹³C-NMR (100 MHz, CDCl₃): δ = 172.3 (CNH₂), 162.3 (C=O), 155.7 (d, CCHFOCF₃, J = 24.8 Hz), 121.0 (q, OCF₃, J = 262 Hz), 99.1 (dq, CHFOCF₃, J = 233 Hz, J = 4 Hz), 85.4 (CCOOEt), 61.0 (OCH₂), 14.2 (OCH₂CH₃) ppm.

Anal. calcd for C₈H₈F₄N₂O₄: C, 35.31; H, 2.96; F, 27.92; N, 10.29; O, 23.51. Found: C, 35.31; H, 3.06; N, 10.34.

Crystals of the compound suitable for X-ray crystallographic analysis were obtained by slow evaporation of a concentrated solution in Et₂O/DCM.

E. Preparation of OCF₃-analogues of a key intermediate of Bixafen (9, 10a-b and 11a-b)

Procedures inspired from: Pazenok, S.; Norbert, L.; Neeff, A., WO2008/022777 (Bayer CropScience, filed 25.08.2006).



Ethyl 3-(fluoro(trifluoromethoxy)methyl)-1H-pyrazole-4-carboxylate (9)

The required amount of 1,1,2-trifluoro-2-(trifluoromethoxy)ethene (1.2 equiv, 1.5 g, 1 mL, 9.03 mmol) was condensed at -78°C into a Schlenk vessel under inert atmosphere, then was treated with dimethylamine 2M in THF (1.2 equiv, 2 M, 4.52 mL, 9.04 mmol). After 5min at -78 °C, the Schlenk vessel was placed into a water bath. BF₃•Et₂O (1.2 equiv, 1.29 g, 1.15 mL, 9.08 mmol) was carefully added *via* syringe, the mixture was stirred 15min. A solution of ethyl 3-(dimethylamino)prop-2-enoate (1 equiv, 1.08 g, 7.54 mmol) in dry MeCN (10 mL) was prepared under inert atmosphere into a Schlenk vessel. The first solution was added *via* syringe to the second, the resulting mixture was stirred for 2h at room temperature. A solution of hydrazine hydrate (1.51 equiv, 0.571 g, 0.56 mL, 11.4 mmol) in dry MeCN (5 mL) was then added. After 1h more, the reaction mixture was concentrated *in vacuo*. The crude was purified by silica gel chromatography (Et₂O in pentane 0 to 50%), to yield a beige solid (1.53g, 79%).

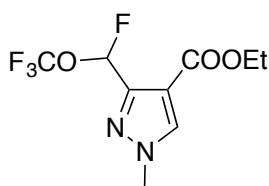
M.p.: 105.7 - 106.2 °C.

¹H-NMR (400 MHz, CDCl₃): δ = 13.7 (s br, NH), 8.17 (d, 5-CH, J = 1.7 Hz), 7.45 (d, CHFOCF₃, J = 56 Hz), 4.37 (q, OCH₂), 1.38 (t, OCH₂CH₃), ppm.

¹⁹F-NMR (376 MHz, CDCl₃): δ = -59.1 (d, OCF₃, J = 4.8 Hz), -127.0 (d, CHFOCF₃, J = 56 Hz) ppm.

¹³C-NMR (100 MHz, CDCl₃): δ = 162.0 (C=O), 145.1 (d, CCHFOCF₃, J = 22.4 Hz), 134.3 (5-CH_{arom}), 121.1 (q, OCF₃, J = 262 Hz), 113.0 (d, CCOOEt, J = 3.6 Hz), 99.9 (qd, CHFOCF₃, J = 228 Hz, J = 3.7 Hz), 61.2 (OCH₂), 14.3 (OCH₂CH₃), ppm.

Anal calcd for C₈H₈F₄N₂O₃: C, 37.51; H, 3.15; F, 29.67; N, 10.94; O, 18.74. Found: C, 37.86; H, 3.14; N, 11.03.



Ethyl 3-(fluoro(trifluoromethoxy)methyl)-1-methyl-1H-pyrazole-4-carboxylate (10a)

The required amount of 1,1,2-trifluoro-2-(trifluoromethoxy)ethene (1.2 equiv, 1.5 g, 1 mL, 9.03 mmol) was condensed at -78°C into a Schlenk vessel under inert atmosphere, then was treated with dimethylamine 2M in THF (1.2 equiv, 2 M, 4.52 mL, 9.04 mmol). After 5min at -78 °C, the Schlenk vessel was placed into a water bath. BF₃•Et₂O (1.2 equiv, 1.29 g, 1.15 mL, 9.08 mmol) was carefully added *via* syringe, the mixture was stirred 15min. A solution of ethyl 3-(dimethylamino)prop-2-enoate (1 equiv, 1.08 g, 7.54 mmol) in dry MeCN (10 mL) was prepared under inert atmosphere into a Schlenk vessel. The first solution was added *via* syringe to the second, the resulting mixture was stirred for 2h at room temperature. A solution of methyl hydrazine (1.53 equiv, 620 μL, 11.6 mmol) in dry MeCN (5 mL) was then added at rt, and the mixture was stirred at rt for 1h. The mixture was

concentrated *in vacuo*. The crude was purified by flash chromatography (Et₂O in pentane 0 to 40%), and both regioisomers (ca. 75/25) were separated (**10b** eluted first, followed by **10a**).

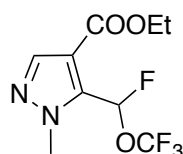
10a: 1.15g (56%), colourless oil.

¹H-NMR (400 MHz, CDCl₃): δ = 7.88 (5-CH), 7.24 (d, CHFOCF₃, *J* = 55.7 Hz), 4.29 (q, OCH₂), 3.94 (NCH₃), 1.32 (OCH₂CH₃), ppm.

¹⁹F-NMR (376 MHz, CDCl₃): δ = -59.2 (d, OCF₃, *J* = 5.5 Hz), -125.3 (qd, CHFOCF₃, *J* = 55.8 Hz, *J* = 5.3 Hz) ppm.

¹³C-NMR (100 MHz, CDCl₃): δ = 161.8 (C=O), 145.2 (d, CCHFOCF₃, *J* = 23.8 Hz), 135.0 (5-CH), 121.1 (q, OCF₃, *J* = 262 Hz), 113.2 (d, CCOOEt, *J* = 2.9 Hz), 99.5 (qd, CHFOCF₃, *J* = 229.4 Hz, *J* = 3.9 Hz), 60.9 (OCH₂), 39.8 (NCH₃), 14.2 (OCH₂CH₃), ppm.

HRMS (ESI) calcd for C₉H₁₀F₄N₂NaO₃ [M+Na]⁺: 293.0520. Found: 293.0497.



Ethyl 5-(fluoro(trifluoromethoxy)methyl)-1-methyl-1H-pyrazole-4-carboxylate (**10b**)

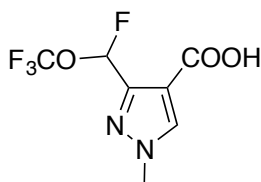
10b: 392 mg (19%), colourless oil.

¹H-NMR (400 MHz, CDCl₃): δ = 1.31 (t, CH₃), 4.02 (d, NCH₃, *J* = 1 Hz), 4.28 (m, OCH₂), 7.64 (d, CHFOCF₃, *J* = 54.3 Hz), 7.81 (d, CH, *J* = 0.7 Hz) ppm.

¹⁹F-NMR (376 MHz, CDCl₃): δ = -59.8 (d, OCF₃, *J* = 4.8 Hz), -126.7 (qd, CHFOCF₃, *J* = 54.5 Hz, *J* = 5.2 Hz) ppm.

¹³C-NMR (100 MHz, CDCl₃): δ = 14.1 (CH₃), 39.1 (d, CH₃, *J* = 3 Hz), 60.9 (OCH₂), 97.8 (qd, CHFOCF₃, *J* = 226 Hz, *J* = 4 Hz), 114.4 (d, CCOOEt, *J* = 4.4 Hz), 120.1 (q, OCF₃, *J* = 262.5 Hz), 135.8 (d, CCHFOCF₃, *J* = 23.7 Hz), 140.3 (CH), 162.3 (C=O) ppm.

HRMS (ESI) calcd for C₉H₁₁F₄N₂O₃ [M+H]⁺: 271.0700. Found: 271.0696.



3-(Fluoro(trifluoromethoxy)methyl)-1-methyl-1H-pyrazole-4-carboxylic acid (**11a**)

A solution of ethyl 3-[fluoro(trifluoromethoxy)methyl]-1-methyl-1H-pyrazole-4-carboxylate **10a** (1 equiv, 810 mg, 3 mmol) in EtOH (6 mL) was treated with NaOH 12.5M (3.04 equiv, 12.5 M, 0.73 mL, 9.13 mmol) and stirred at room temperature for 18h. The mixture was diluted with 1N HCl until pH = 1, then extracted with Et₂O. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The oily residue was triturated in pentane and dried *in vacuo*, to yield a white solid (725 mg, 99%).

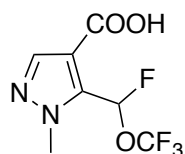
M.p.: 117.2 - 117.6 °C.

¹H-NMR (400 MHz, CDCl₃): δ = 4.00 (s, CH₃), 7.26 (d, CHFOCF₃, *J* = 55.9 Hz), 7.98 (CH_{arom}), 10.3 (s.br, COOH) ppm.

¹⁹F-NMR (376 MHz, CDCl₃): δ = -59.2 (d, OCF₃, *J* = 5.4 Hz), -125.3 (qd, CHFOCF₃, *J* = 55.8 Hz, *J* = 5.5 Hz) ppm.

¹³C-NMR (100 MHz, CDCl₃): δ = 40.1 (CH₃), 99.2 (qd, CHFOCF₃, *J* = 230 Hz, *J* = 4 Hz), 112.1 (d, CCOOH, *J* = 2.7 Hz), 121.1 (q, OCF₃, *J* = 261 Hz), 136.0 (CH_{arom}), 146.2 (CCHFOCF₃, *J* = 24 Hz), 167.2 (COOH) ppm.

Anal. calcd for C₇H₆F₄N₂O₃: C, 34.72; H, 2.50; F, 31.39; N, 11.57; O, 19.82. Found: C, 35.05; H, 2.27; N, 11.66.



5-(Fluoro(trifluoromethoxy)methyl)-1-methyl-1H-pyrazole-4-carboxylic acid (11b)

A solution of ethyl 5-[fluoro(trifluoromethoxy)methyl]-1-methyl-1H-pyrazole-4-carboxylate **10b** (1 equiv, 200 mg, 0.74 mmol) in EtOH (1 mL) was treated with NaOH 12.5M (3.04 equiv, 12.5 M, 0.18 mL, 2.25 mmol) and stirred at rt for 18h. The mixture was diluted with 1N HCl until pH = 1, then extracted with Et₂O. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo* to yield the pure product (177 mg, 0.733 mmol, 99 %) as a white solid.

M.p.: 140.5 - 141.0 °C.

¹H-NMR (400 MHz, CDCl₃): δ = 4.11 (s, CH₃), 7.64 (d, CHFOCF₃, J = 54.3 Hz), 7.97 (s, CH_{arom}), 10.9 (s.br, COOH) ppm.

¹⁹F-NMR (376 MHz, CDCl₃): δ = -59.6 (d, OCF₃, J = 4.8 Hz), -126.6 (qd, CHFOCF₃, J = 54.5 Hz, J = 5.2 Hz) ppm.

¹³C-NMR (100 MHz, CDCl₃): δ = 39.5 (d, CH₃, J = 2.8 Hz), 97.5 (qd, CHFOCF₃, J = 226 Hz, J = 3.6 Hz), 113.4 (d, CH_{arom}, J = 4.3 Hz), 120.9 (q, OCF₃, J = 263 Hz), 136.8 (d, CCHFOCF₃, J = 24 Hz), 141.3 (CCOOH), 167.6 (COOH) ppm.

Anal. calcd for C₇H₆F₄N₂O₃: C, 34.72; H, 2.50; F, 31.39; N, 11.57; O, 19.82. Found: C, 35.01; H, 2.77; N, 10.39.

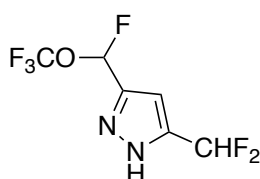
F. Regioselective preparation of 3,5-bis(fluoroalkyl)pyrazoles bearing the –CHFOCF₃ motif (12a-c, 13a-c, 14a)

The experimental details concerning the preparation of pyrazoles **12a-c**, **13a-c**, **14a** and vinamide **15** were previously described in:

Schmitt, E.; Panossian, A.; Vors, J.-P.; Funke, C.; Lui, N.; Pazenok, S.; Leroux, F. R. *Chem. Eur. J.* **2016**, *22*, 11239-11244.

The preparation of 3,5-bis(fluoroalkyl)pyrazoles was also submitted for a patent application:

Pazenok, S.; Lui, N.; Funke, C.; Etzel, W.; Neeff, A. *WO2015144578* (Bayer CropScience, filed 24.03.2014).



5-(Difluoromethyl)-3-(fluoro(trifluoromethoxy)methyl)-1H-pyrazole (**12a**)

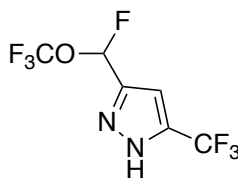
Activated FAR **2b** (1.22 equiv, 930 mg, 3.33 mmol) was taken up in dry MeCN (4 mL) at room temperature under inert atmosphere into a Schlenk vessel before a solution of *N*-benzyl-1,1-difluoropropan-2-imine (1 equiv, 600 mg, 3.27 mmol) in MeCN (4 mL) was carefully added *via* syringe. After 1h at room temperature (step 1), hydrazine hydrate (1.5 equiv, 0.24 mL, 4.89 mmol) was added *via* syringe, rapidly followed by cc H₂SO₄ (0.5 equiv, 0.08 mL, 1.50 mmol). The mixture was stirred at 50 °C for 1h, and was concentrated *in vacuo* (>200 mbar, 40°C max.). The crude was purified by flash chromatography (Et₂O in pentane 0 to 30%). Yield: 650 mg, brown oil (85%).

¹H-NMR (400 MHz, CDCl₃): δ = 12.3 (br s, NH), 6.80 (d, CHFOCF₃, ²J_{H-F} = 57 Hz), 6.74 (t, CHF₂, ²J_{H-F} = 55 Hz), 6.72 (s, 4-CH) ppm.

¹⁹F-NMR (376 MHz, CDCl₃): δ = -59.6 (d, OCF₃, ⁴J_{F-H} = 5.3 Hz), -113.0 (d, CHF₂, ²J_{F-H} = 55 Hz), -120.6 (d, CHFOCF₃, ²J_{F-H} = 57.5 Hz) ppm.

¹³C-NMR (100 MHz, CDCl₃): δ = 142.6 (m, CCHF₂ and CCHFOCF₃), 121.0 (q, OCF₃, ¹J_{C-F} = 262 Hz), 109.1 (t, CHF₂, ¹J_{C-F} = 237 Hz), 103.3 (4-CH), 100.0 (d, CHFOCF₃, ¹J_{C-F} = 228 Hz) ppm.

HRMS (ESI) calcd for C₆H₅F₆N₂O [M+H]: 235.0301. Found: 235.0317.



3-(Fluoro(trifluoromethoxy)methyl)-5-(trifluoromethyl)-1H-pyrazole (**12b**)

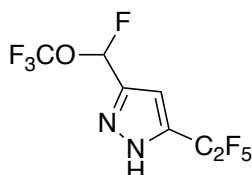
A solution of activated FAR **2b** was prepared from 1,1,2-trifluoro-2-(trifluoromethoxy)ethene (1.21 equiv, 659 mg, 0.44 mL, 3.98 mmol), dimethylamine 2M in THF (1.22 equiv, 2 M, 2 mL, 4 mmol) and BF₃•Et₂O (1.2 equiv, 0.5 mL, 3.95 mmol) (see SI, part B, Method B). The resulting mixture was added to a solution of *N*-benzyl-1,1,1-trifluoropropan-2-imine (1 equiv, 660 mg, 3.28 mmol) in freshly distilled THF (4 mL) at rt, and the mixture was stirred for 30 min. Hydrazine hydrate (1.49 equiv, 0.24 mL, 4.89 mmol) and H₂SO₄ (0.458 equiv, 0.08 mL, 1.5 mmol) were successively added *via* syringe, and the orange mixture was stirred for 1 h at rt. The mixture was diluted with Et₂O, concentrated *in*

vacuo and the crude was purified by flash chromatography (Et₂O in pentane 0 to 20%). Yield: 500 mg, brown oil (60%). ¹⁹F NMR yield: 81%.

¹H-NMR (400 MHz, CDCl₃): δ = 12.2 (br s, NH), 6.78 (d, CHFOCF₃, ²J_{H-F} = 57.5 Hz), 6.77 (s, 4-CH) ppm.
¹⁹F-NMR (376 MHz, CDCl₃): δ = -60.0 (d, OCF₃, ⁴J_{F-H} = 5.5 Hz), -62.3 (s, CF₃), -121.7 (qd, CHFOCF₃, ²J_{F-H} = 57 Hz, ⁴J_{F-H} = 5 Hz) ppm.

¹³C-NMR (100 MHz, CDCl₃): δ = 140.8 (m, CCF₃ and CCHFOCF₃), 120.3 and 121.0 (2 x q, CF₃ and OCF₃, ¹J_{C-F} = 269 and 262 Hz), 104.0 (4-CH), 99.1 (d, CHFOCF₃, ¹J_{C-F} = 230 Hz) ppm.

HRMS (ESI) calcd for C₆H₄F₇N₂O [M+H]: 253.0206. Found: 253.0213.



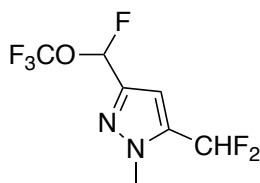
3-(Fluoro(trifluoromethoxy)methyl)-5-(perfluoroethyl)-1H-pyrazole (12c)

A solution of activated FAR **2b** was prepared from 1,1,2-trifluoro-2-(trifluoromethoxy)ethene (1.21 equiv, 345 mg, 0.23 mL, 2.08 mmol), dimethylamine 2M in THF (1.22 equiv, 2 M, 1.04 mL, 2.08 mmol) and BF₃•Et₂O (1.2 equiv, 0.27 mL, 2.13 mmol) (see SI, part B, Method B). The resulting mixture was added to a solution of *N*-benzyl-3,3,4,4,4-pentafluorobutan-2-imine (1 equiv, 500 mg, 1.69 mmol, 85wt.%) in freshly distilled THF (2.11 mL) at rt, and the mixture was stirred for 1 h. Hydrazine hydrate (1.53 equiv, 0.13 mL, 2.65 mmol) and H₂SO₄ (0.542 equiv, 0.05 mL, 0.938 mmol) were successively added via syringe, and the mixture was stirred for 2 h at rt, then for 18 h at 50 °C. The mixture was concentrated *in vacuo* and the crude was purified by flash chromatography (Et₂O in pentane 0 to 20%). Yield: 211 mg, brown oil (40%). ¹⁹F NMR yield: 99%.

¹H-NMR (400 MHz, CDCl₃): δ = 12.59 (br s, NH), 6.82 (s, 4-CH), 6.79 (d, CHFOCF₃, ²J_{H-F} = 57.5 Hz) ppm.
¹⁹F-NMR (376 MHz, CDCl₃): δ = -59.9 (d, OCF₃, ⁴J_{F-H} = 5 Hz), -85.1 (s, CF₃), -113.6 (s, CF₂), -121.8 (dq, CHFOCF₃, ²J_{F-H} = 57.4 Hz, ⁴J_{F-H} = 4.9 Hz) ppm.

¹³C-NMR (100 MHz, CDCl₃): δ = 141.1 and 139.4 (m, CCHFOCF₃ and CC₂F₅), 120.7 (q, OCF₃, ¹J_{C-F} = 263 Hz), 118.4 (qt, CF₃, ¹J_{C-F} = 286 Hz, ²J_{C-F} = 40 Hz), 109.8 (tq, CF₂, ¹J_{C-F} = 252 Hz, ²J_{C-F} = 40 Hz), 105.4 (4-CH), 99.0 (d, CHFOCF₃, ¹J_{C-F} = 230 Hz) ppm.

HRMS (ESI) calcd for C₇H₄F₉N₂O [M+H]: 303.0174. Found: 303.0168.



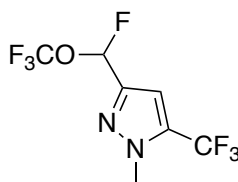
5-(Difluoromethyl)-3-(fluoro(trifluoromethoxy)methyl)-1-methyl-1H-pyrazole (13a)

A solution of activated FAR **2b** was prepared from 1,1,2-trifluoro-2-(trifluoromethoxy)ethene (1.20 equiv, 660 mg, 0.44 mL, 3.98 mmol), dimethylamine 2M in THF (1.22 equiv, 2 M, 2 mL, 4 mmol) and BF₃•Et₂O (1.19 equiv, 0.5 mL, 3.95 mmol) (see SI, part B, Method B). The resulting mixture was added to a solution of *N*-benzyl-1,1-difluoropropan-2-imine (1 equiv, 610 mg, 3.33 mmol) in freshly distilled THF (2 mL) at rt, and the mixture was stirred for 30 min. Methyl hydrazine (1.46 equiv, 0.26 mL, 4.85 mmol) and H₂SO₄ (0.507 equiv, 0.09 mL, 1.69 mmol) were successively added via syringe, and the orange mixture was stirred for 1 h at rt. The mixture was concentrated *in vacuo* and the crude was purified by flash chromatography (Et₂O in pentane 0 to 5%). Yield: **13a**, 320 mg, brown oil (39%); **14a**, 135 mg, brown oil (16%). ¹⁹F NMR yield (**13a/14a**): >99% (71/29).

¹H-NMR (400 MHz, CDCl₃): δ = 6.71 (t, CHF₂, ²J_{H-F} = 53.5 Hz), 6.70 (d, CHFOCF₃, ²J_{H-F} = 57 Hz), 6.68 (s, 4-CH), 4.00 (s, NCH₃) ppm.

^{19}F -NMR (376 MHz, CDCl_3): $\delta = -59.4$ (d, OCF_3 , $^4J_{\text{F-H}} = 5.5$ Hz), -113.4 (d, CHF_2 , $^2J_{\text{F-H}} = 53.5$ Hz), -119.8 (dq, CHFOCF_3 , $^2J_{\text{F-H}} = 57$ Hz, $^4J_{\text{F-H}} = 5.5$ Hz) ppm.

^{13}C -NMR (100 MHz, CDCl_3): $\delta = 144.8$ (d, CCHFOCF_3 , $^2J_{\text{C-F}} = 29$ Hz), 136.9 (t, CCHF_2 , $^2J_{\text{C-F}} = 26$ Hz), 121.1 (q, OCF_3 , $^1J_{\text{C-F}} = 261$ Hz), 108.3 (t, CHF_2 , $^2J_{\text{C-F}} = 237$ Hz), 105.3 (t, 4-CH, $^3J_{\text{C-F}} = 4$ Hz), 101.0 (qd, CHFOCF_3 , $^1J_{\text{C-F}} = 227$ Hz, $^3J_{\text{C-F}} = 4$ Hz), 38.5 (NCH₃) ppm. HRMS (ESI) calcd for $\text{C}_7\text{H}_7\text{F}_6\text{N}_2\text{O}$ [M+H]: 249.0457. Found: 249.0460.



3-(Fluoro(trifluoromethoxy)methyl)-1-methyl-5-(trifluoromethyl)-1H-pyrazole (13b)

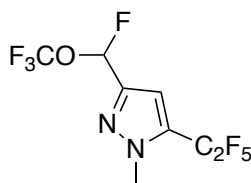
A solution of activated FAR **2b** was prepared from 1,1,2-trifluoro-2-(trifluoromethoxy)ethene (1.19 equiv, 659 mg, 0.44 mL, 3.98 mmol), dimethylamine 2M in THF (1.19 equiv, 2 M, 2 mL, 4 mmol) and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.18 equiv, 0.5 mL, 3.95 mmol) (see SI, part B, Method B). The resulting mixture was added to a solution of *N*-benzyl-1,1,1-trifluoropropan-2-imine (1 equiv, 675 mg, 3.36 mmol) in anhydrous MeCN (4 mL) at rt, and the mixture was stirred for 30 min. Methyl hydrazine (1.50 equiv, 0.27 mL, 5.04 mmol) and H_2SO_4 (0.56 equiv, 0.10 mL, 1.88 mmol) were successively added via syringe, and the orange mixture was stirred for 1 h at rt. The mixture was diluted with DCM, concentrated *in vacuo* and the crude was purified by flash chromatography (Et_2O in pentane 0 to 5%). Yield: 187 mg, brown oil (21%). ^{19}F NMR yield: 61%.

^1H -NMR (400 MHz, CDCl_3): $\delta = 6.84$ (s, 4-CH), 6.71 (d, CHFOCF_3 , $^2J_{\text{H-F}} = 57$ Hz), 4.02 (s, NCH₃) ppm.

^{19}F -NMR (376 MHz, CDCl_3): $\delta = -59.3$ (d, OCF_3 , $^4J_{\text{F-H}} = 5$ Hz), -60.9 (s, CF_3), -120.1 (qd, CHFOCF_3 , $^2J_{\text{F-H}} = 57$ Hz, $^4J_{\text{F-H}} = 5.4$ Hz) ppm.

^{13}C -NMR (100 MHz, CDCl_3): $\delta = 144.8$ (d, CCHFOCF_3 , $^2J_{\text{C-F}} = 30$ Hz), 133.6 (CCF_3 , $^2J_{\text{C-F}} = 40$ Hz), 121.0 and 119.6 (2 x q, OCF_3 and CF_3 , $^1J_{\text{C-F}} = 261$ Hz and $^1J_{\text{C-F}} = 269$ Hz), 105.8 (4-CH), 100.8 (dq, CHFOCF_3 , $^1J_{\text{C-F}} = 227$ Hz, $^3J_{\text{C-F}} = 4$ Hz), 38.6 (NCH₃) ppm.

HRMS (ESI) calcd for $\text{C}_7\text{H}_6\text{F}_7\text{N}_2\text{O}$ [M+H]: 267.0363. Found: 267.0347.



3-(Fluoro(trifluoromethoxy)methyl)-1-methyl-5-(perfluoroethyl)-1H-pyrazole (13c)

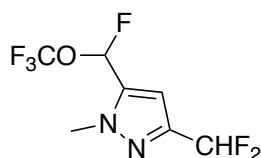
A solution of activated FAR **2b** was prepared from 1,1,2-trifluoro-2-(trifluoromethoxy)ethene (1.28 equiv, 660 mg, 0.44 mL, 3.98 mmol), dimethylamine 2M in THF (1.28 equiv, 2 M, 2 mL, 4 mmol) and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.27 equiv, 0.5 mL, 3.95 mmol) (see SI, part B, Method B). The resulting mixture was added to a solution of *N*-benzyl-3,3,4,4,4-pentafluorobutan-2-imine (1 equiv, 920 mg, 3.11 mmol) in freshly distilled THF (2 mL) at 0 °C, and the mixture was stirred for 1 h. Methyl hydrazine (1.62 equiv, 0.27 mL, 5.04 mmol) and H_2SO_4 (0.542 equiv, 0.09 mL, 1.69 mmol) were successively added via syringe, and the mixture was stirred for 20 h at rt. The mixture was concentrated *in vacuo* and the crude was purified by flash chromatography (Et_2O in pentane 0 to 2%). Yield: 576 mg, brown oil (59%). ^{19}F NMR yield: 81%.

^1H -NMR (400 MHz, CDCl_3): $\delta = 6.84$ (s, 4-CH), 6.72 (d, CHFOCF_3 , $^2J_{\text{H-F}} = 57.2$ Hz), 4.04 (s, NCH₃) ppm.

^{19}F -NMR (376 MHz, CDCl_3): $\delta = -59.3$ (d, OCF_3 , $^4J_{\text{F-H}} = 5.4$ Hz), -83.9 (s, CF_3), -110.7 (CF_2), -120.3 (dq, CHFOCF_3 , $^2J_{\text{F-H}} = 57.2$ Hz, $^4J_{\text{F-H}} = 5.3$ Hz) ppm.

^{13}C -NMR (100 MHz, CDCl_3): δ = 145.2 (d, CCHFOCF_3 , $^2J_{\text{C-F}} = 29.5$ Hz), 131.6 (t, CC_2F_5 , $^2J_{\text{C-F}} = 28.7$ Hz), 121.1 (q, OCF_3 , $^1J_{\text{C-F}} = 262$ Hz), 118.6 (qt, CF_3 , $^1J_{\text{C-F}} = 286.3$ Hz, $^2J_{\text{C-F}} = 37.2$ Hz), 109.9 (tq, CF_2 , $^1J_{\text{C-F}} = 253.5$ Hz, $^2J_{\text{C-F}} = 40$ Hz), 107.4 (4-CH), 100.7 (dq, CHFOCF_3 , $^1J_{\text{C-F}} = 227.4$ Hz, $^3J_{\text{C-F}} = 4.3$ Hz), 39.5 (NCH_3) ppm.

HRMS (ESI) calcd for $\text{C}_8\text{H}_6\text{F}_9\text{N}_2\text{O}$ [M+H]: 317.0331. Found: 317.0298.



3-(Difluoromethyl)-5-(fluoro(trifluoromethoxy)methyl)-1-methyl-1H-pyrazole (14a)

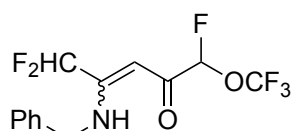
A solution of 4-(benzylamino)-1,5,5-trifluoro-1-(trifluoromethoxy)pent-3-en-2-one **15** (1 equiv, 349 mg, 0.92 mmol) in MeCN (2 mL) was treated with methyl hydrazine (1.6 equiv, 69 mg, 0.08 mL, 1.49 mmol) and cc H_2SO_4 (0.6 equiv 55 mg, 0.03 mL, 0.55 mmol). The mixture was vigorously stirred at 80 °C for 1 h.

The mixture was concentrated *in vacuo* and purified by flash chromatography (Et_2O in pentane 0 to 5%). Yield: 191 mg, colourless oil (84%). ^{19}F NMR yield: 95%.

^1H -NMR (400 MHz, CDCl_3): δ = 6.76 (d, CHFOCF_3 , $^2J_{\text{H-F}} = 56$ Hz), 6.68 (s, 4-CH), 6.64 (t, CHF_2 , $^2J_{\text{H-F}} = 55$ Hz), 3.98 (m, NCH_3) ppm.

^{19}F -NMR (376 MHz, CDCl_3): δ = -59.6 (d, OCF_3 , $^4J_{\text{F-H}} = 5.5$ Hz), -112.2 (d, CHF_2 , $^2J_{\text{F-H}} = 55$ Hz), -121.6 (qd, CHFOCF_3 , $^2J_{\text{F-H}} = 56$ Hz, $^4J_{\text{F-H}} = 5.5$ Hz) ppm.

^{13}C -NMR (100 MHz, CDCl_3): δ = 145.7 (t, CCHF_2 , $^2J_{\text{C-F}} = 30$ Hz), 135.5 (d, CCHFOCF_3 , $^2J_{\text{C-F}} = 26$ Hz), 120.8 (q, OCF_3 , $^1J_{\text{C-F}} = 263$ Hz), 110.5 (t, CHF_2 , $^1J_{\text{C-F}} = 234$ Hz), 104.8 (4-CH), 98.5 (dq, CHFOCF_3 , $^1J_{\text{C-F}} = 228$ Hz, $^3J_{\text{C-F}} = 4$ Hz), 38.5 (NCH_3) ppm. HRMS calcd for $\text{C}_7\text{H}_7\text{F}_6\text{N}_2\text{O}$ [M+H]: 249.0457. Found: 249.0458.



4-(Benzylamino)-1,5,5-trifluoro-1-(trifluoromethoxy)pent-3-en-2-one (15)

A solution of activated FAR **2b** was prepared from 1,1,2-trifluoro-2-(trifluoromethoxy)ethene (1.00 equiv, 660 mg, 0.44 mL, 3.98 mmol), dimethylamine 2M in THF (1.01 equiv, 2 M, 2 mL, 4 mmol) and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.01 equiv, 0.51 mL, 4.02 mmol) (see SI, part B, Method B). The resulting mixture was added to a solution of *N*-benzyl-1,1-difluoropropan-2-imine (1 equiv, 728 mg, 3.97 mmol) in anhydrous MeCN (5 mL) at rt. The mixture was stirred for 30 min, diluted with Et_2O (20 mL) and treated with 1N aq HCl (10 mL). The mixture was vigorously stirred for 15min at room temperature (open flask) and the aqueous layer was extracted with Et_2O . The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Yield 1.08 g, brown oil (83%, 95wt.%).

^1H -NMR (400 MHz, CDCl_3): δ = 10.64 (br s, NH), 7.40 to 7.28 (m, C_6H_5), 6.18 (t, CHF_2 , $^2J_{\text{H-F}} = 53.2$ Hz), 5.81 (d, CHFOCF_3 , $^2J_{\text{H-F}} = 56.9$ Hz), 5.70 (d, CHCO , $^4J_{\text{H-F}} = 1.6$ Hz), 4.65 (d, NHCH_2 , $^3J_{\text{H-H}} = 6.4$ Hz) ppm.

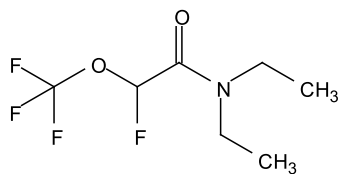
^{19}F -NMR (376 MHz, CDCl_3): δ = -59.4 (d, CHFOCF_3 , $^4J_{\text{F-F}} = 4.7$ Hz), -119.3 (d, CHF_2 , $^2J_{\text{F-H}} = 53.1$ Hz), -135.5 (dq, CHFOCF_3 , $^2J_{\text{F-H}} = 56.9$ Hz, $^4J_{\text{F-F}} = 4.5$ Hz) ppm.

^{13}C -NMR (100 MHz, CDCl_3): δ = 185.5 (d, C=O , $^2J_{\text{C-F}} = 25.3$ Hz), 157.3 (t, CCHF_2 , $^2J_{\text{C-F}} = 22.0$ Hz), 136.1, 129.2, 128.4, 127.3 (C_6H_5), 121.2 (q, CF_3 , $^1J_{\text{C-F}} = 261$ Hz), 111.0 (t, CHF_2 , $^1J_{\text{C-F}} = 245$ Hz), 101.3 (dq, CHFOCF_3 , $^1J_{\text{C-F}} = 243$ Hz, $^3J_{\text{C-F}} = 3$ Hz), 87.8 (t, CHCO , $^3J_{\text{C-F}} = 77.2$ Hz), 48.1 (CH_2NH) ppm.

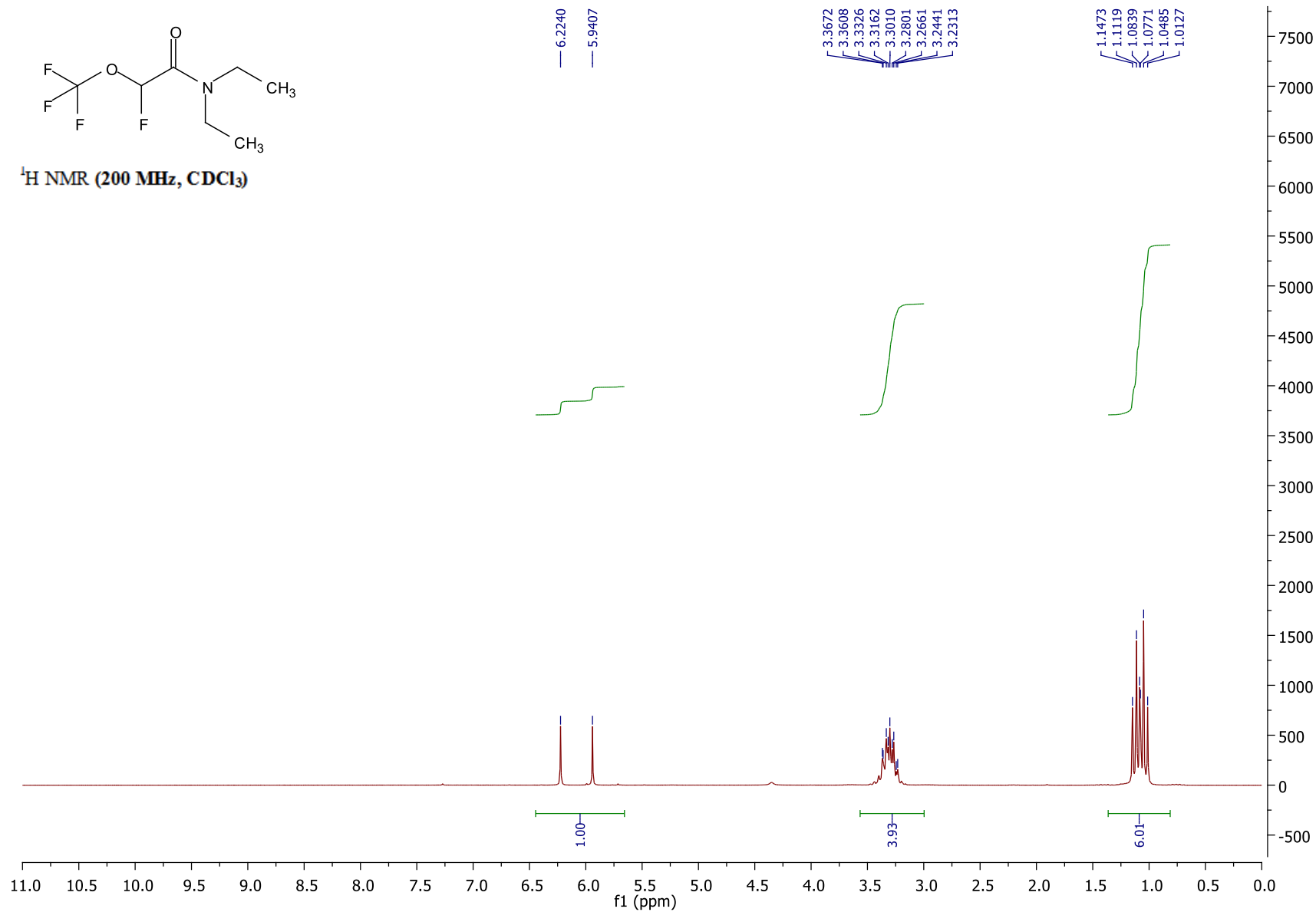
HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{12}\text{F}_6\text{NO}_2$ [M+H]: 328.0767. Found: 328.0728.

G. NMR SPECTRA

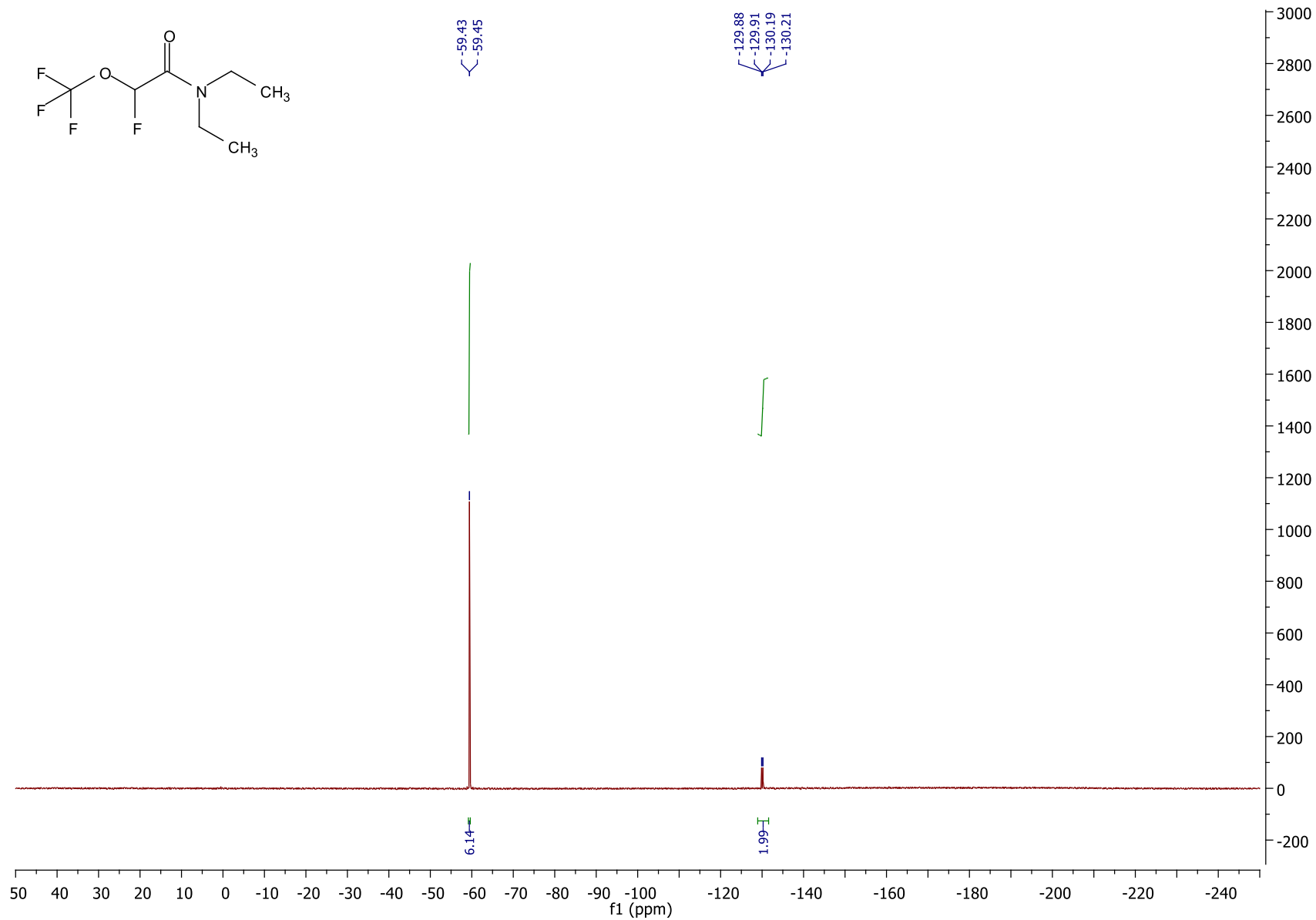
N,N-Diethyl-2-fluoro-2-(trifluoromethoxy)acetamide (**1c**)



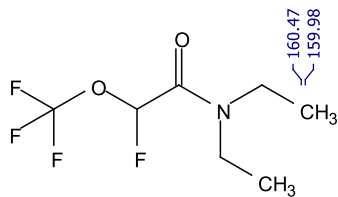
¹H NMR (200 MHz, CDCl₃)



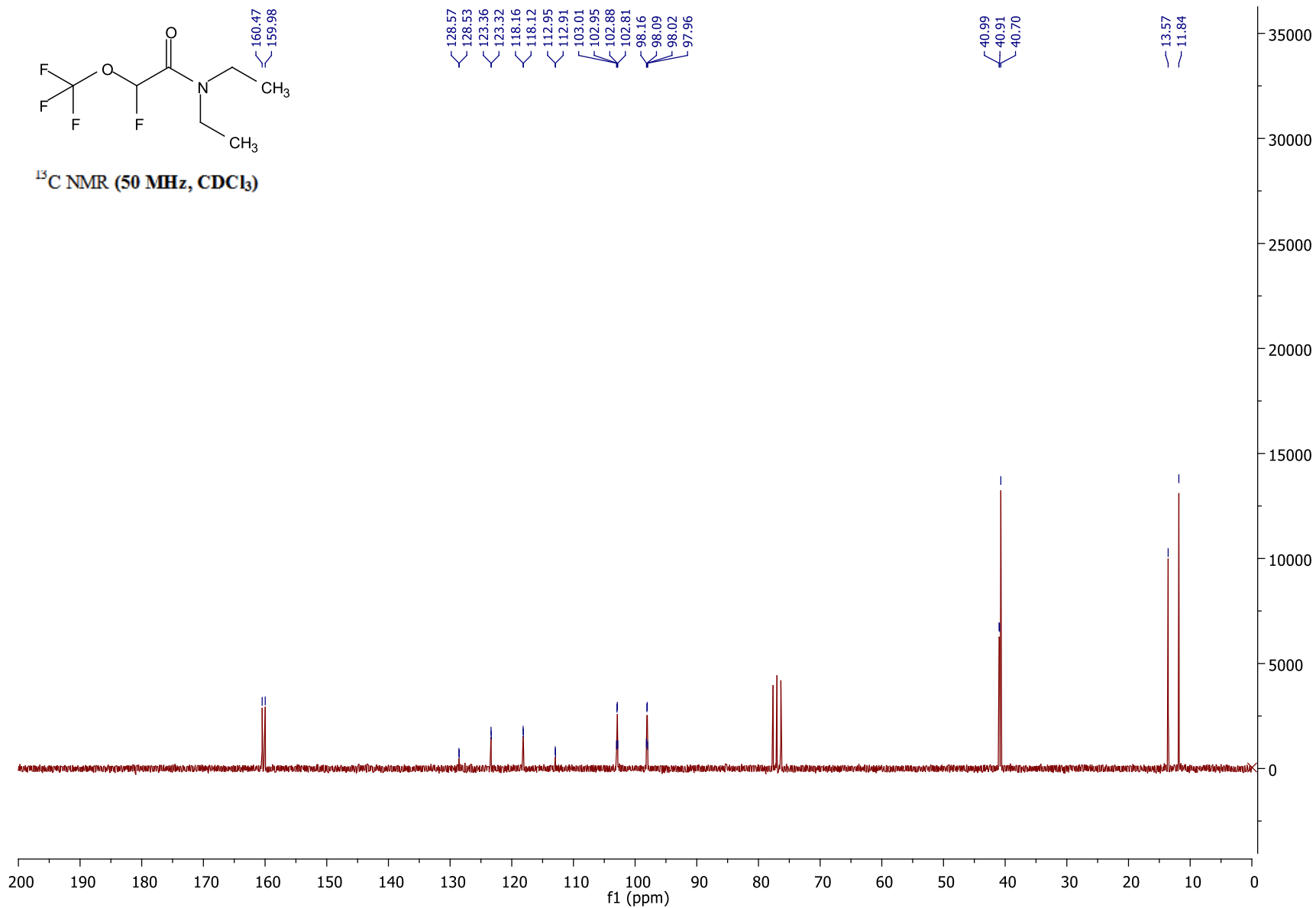
N,N-Diethyl-2-fluoro-2-(trifluoromethoxy)acetamide (**1c**)



N,N-Diethyl-2-fluoro-2-(trifluoromethoxy)acetamide (**1c**)

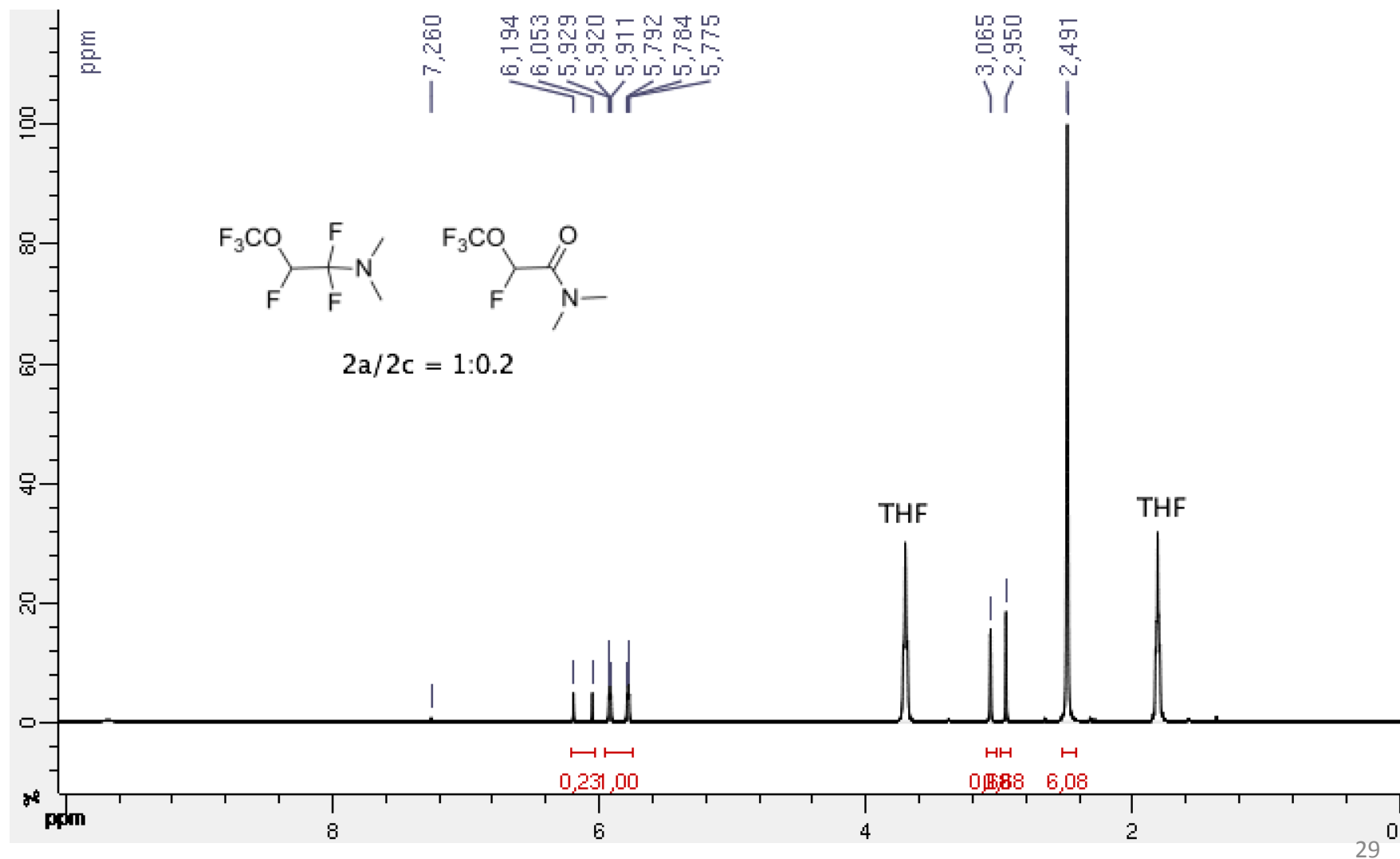


^{13}C NMR (50 MHz, CDCl_3)



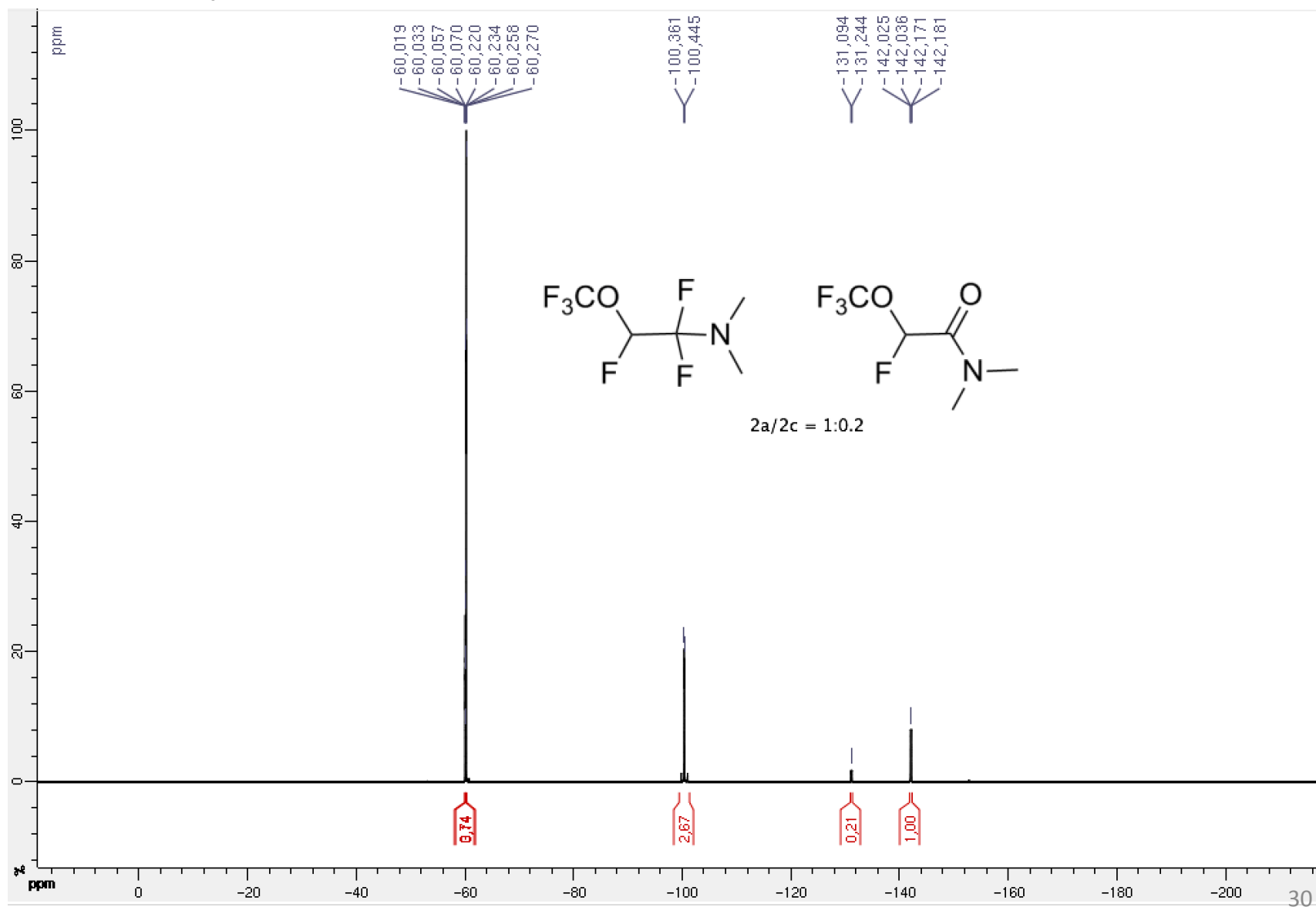
1,1,2-Trifluoro-*N,N*-dimethyl-2-(trifluoromethoxy)ethan-1-amine (**2a**) + 2-Fluoro-*N,N*-dimethyl-2-(trifluoromethoxy)-acetamide (**2c**)

^1H NMR (400 MHz, CDCl_3)



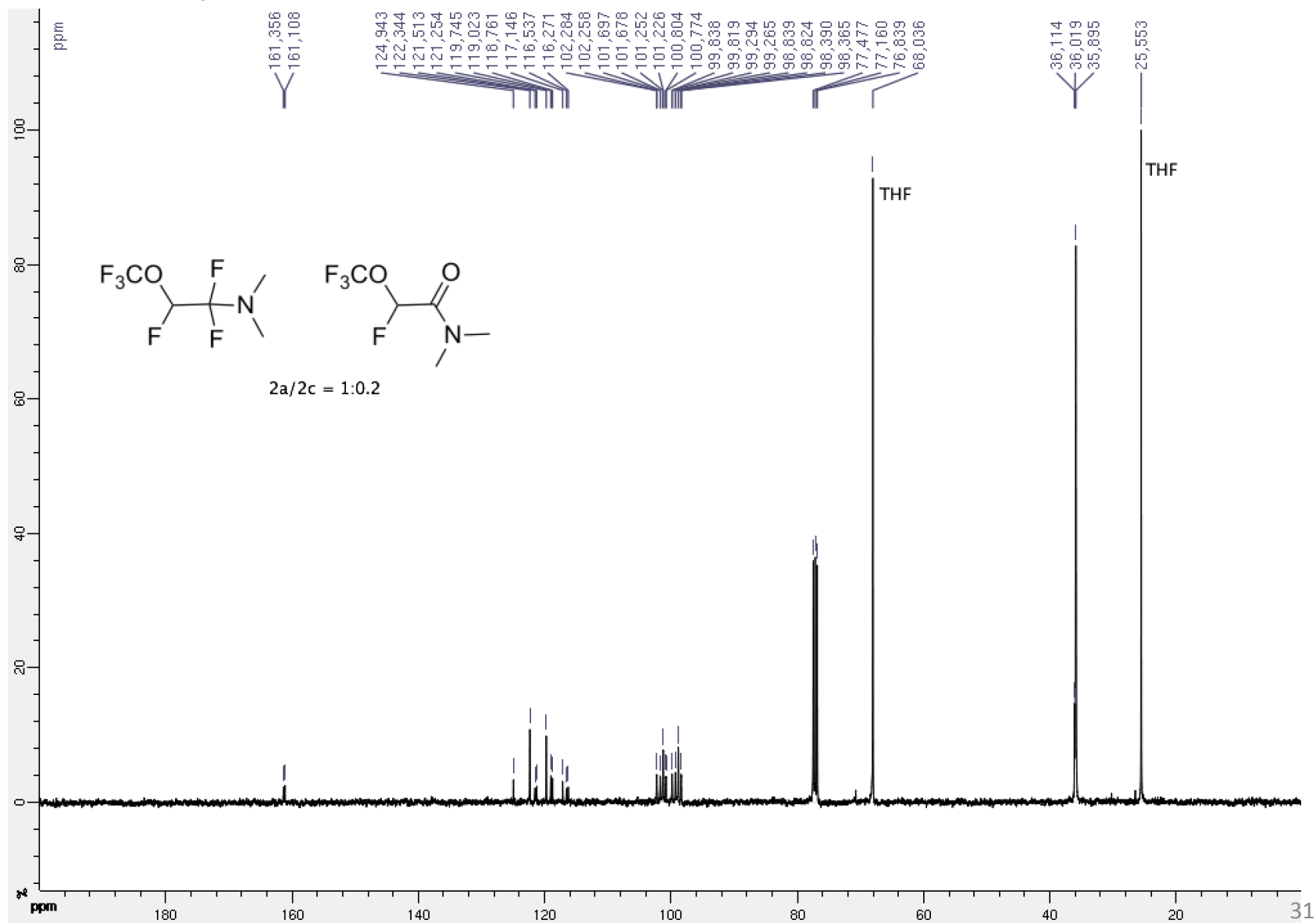
1,1,2-Trifluoro-*N,N*-dimethyl-2-(trifluoromethoxy)ethan-1-amine (**2a**) + 2-Fluoro-*N,N*-dimethyl-2-(trifluoromethoxy)-acetamide (**2c**)

^{19}F NMR (376 MHz, CDCl_3)



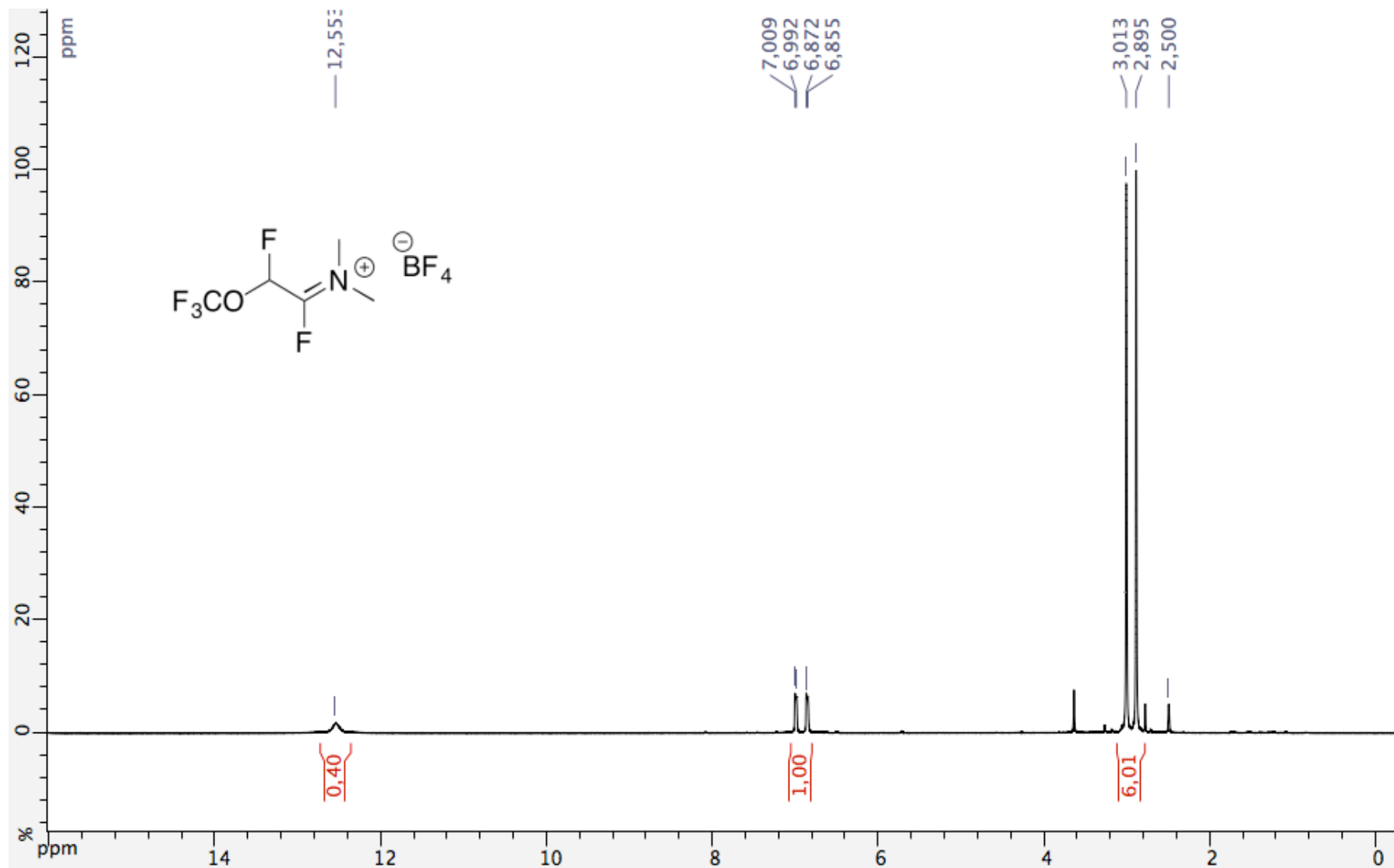
1,1,2-Trifluoro-*N,N*-dimethyl-2-(trifluoromethoxy)ethan-1-amine (**2a**) + 2-Fluoro-*N,N*-dimethyl-2-(trifluoromethoxy)-acetamide (**2c**)

¹³C NMR (100 MHz, CDCl₃)



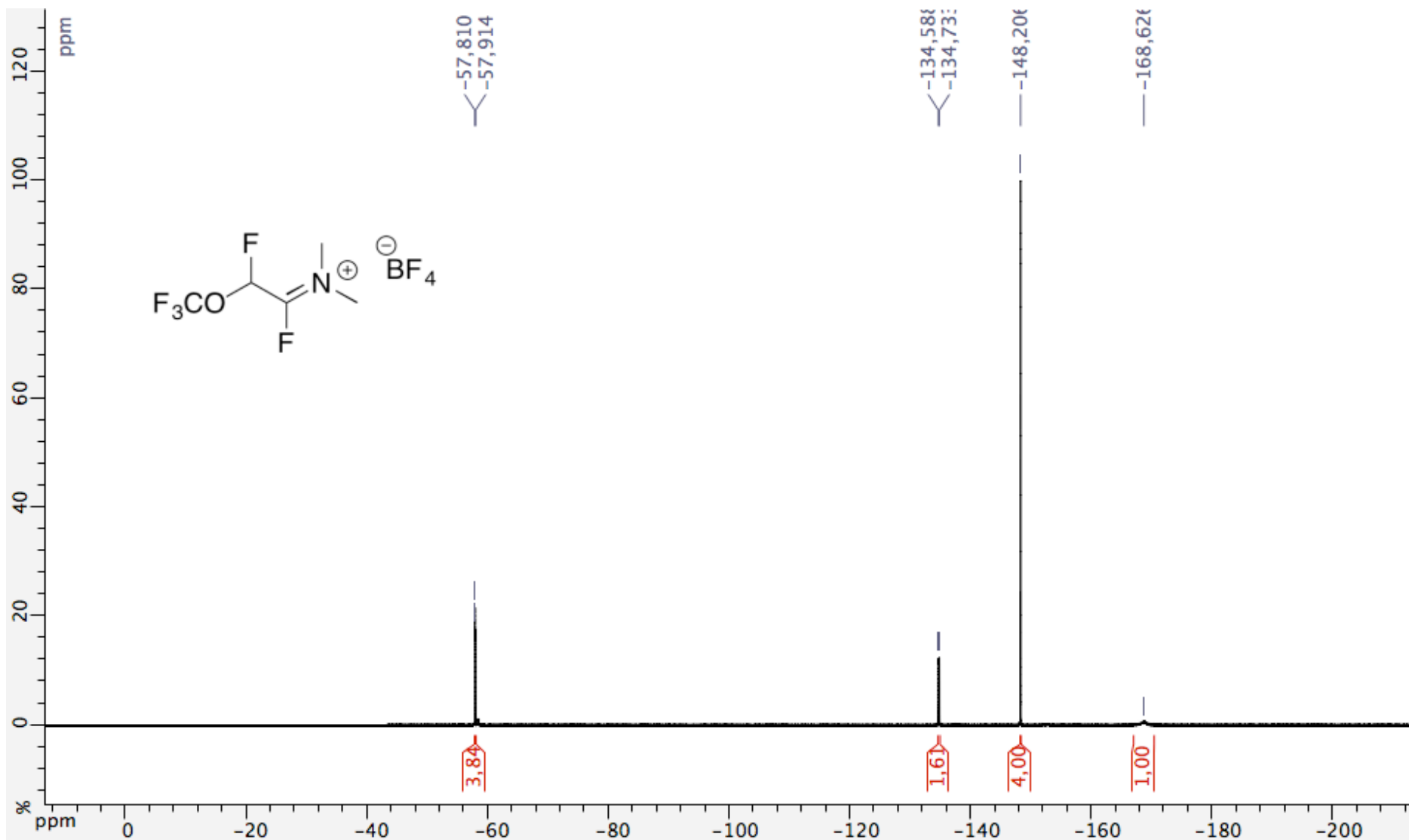
N-(1,2-Difluoro-2-(trifluoromethoxy)ethylidene)-*N*-methylmethanaminium tetrafluoroborate (**2b**)

^1H NMR (400 MHz, CDCl_3)

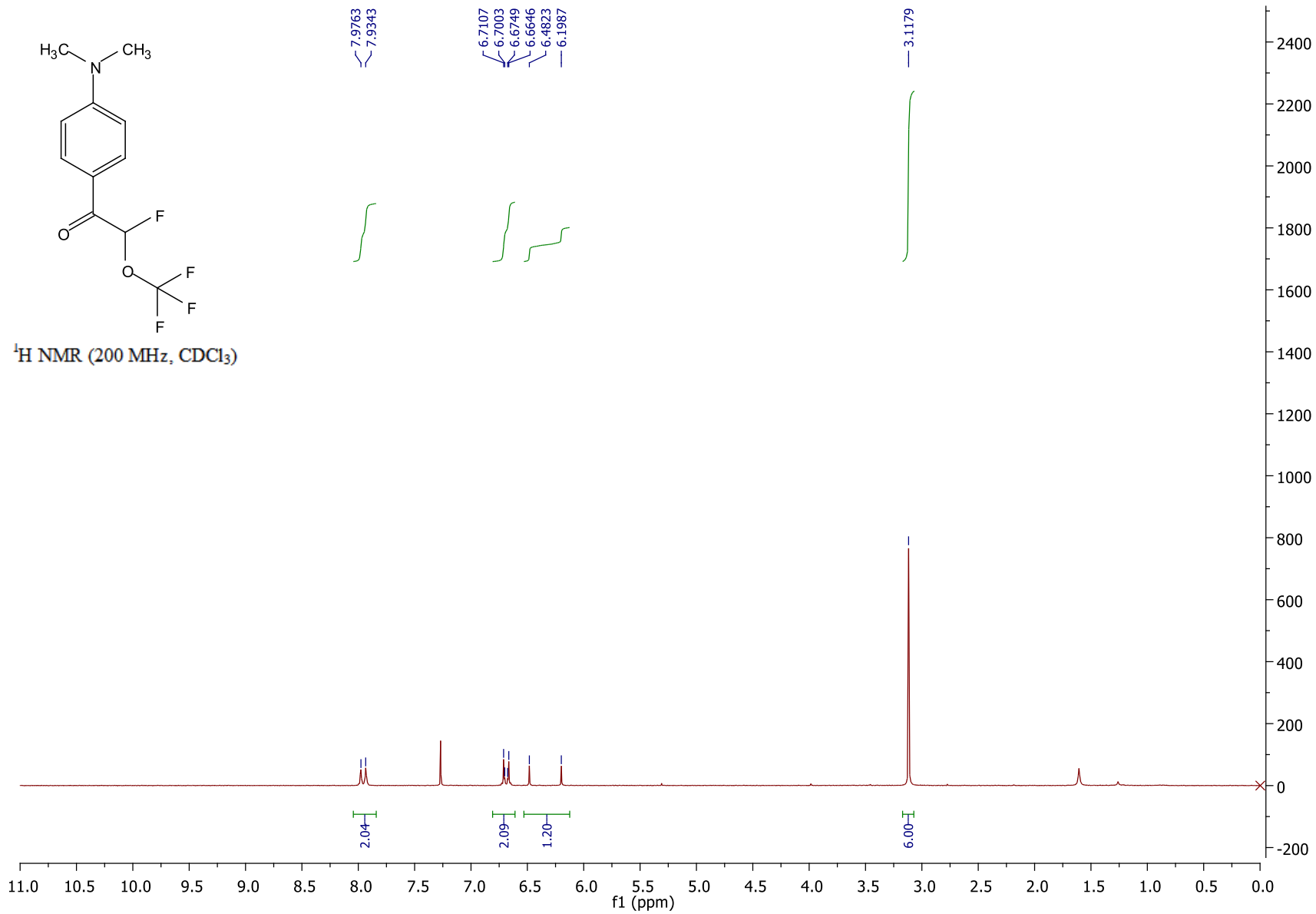


N-(1,2-Difluoro-2-(trifluoromethoxy)ethylidene)-*N*-methylmethanaminium tetrafluoroborate (**2b**)

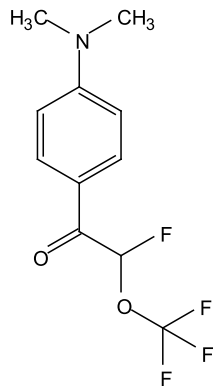
^{19}F NMR (376 MHz, CDCl_3)



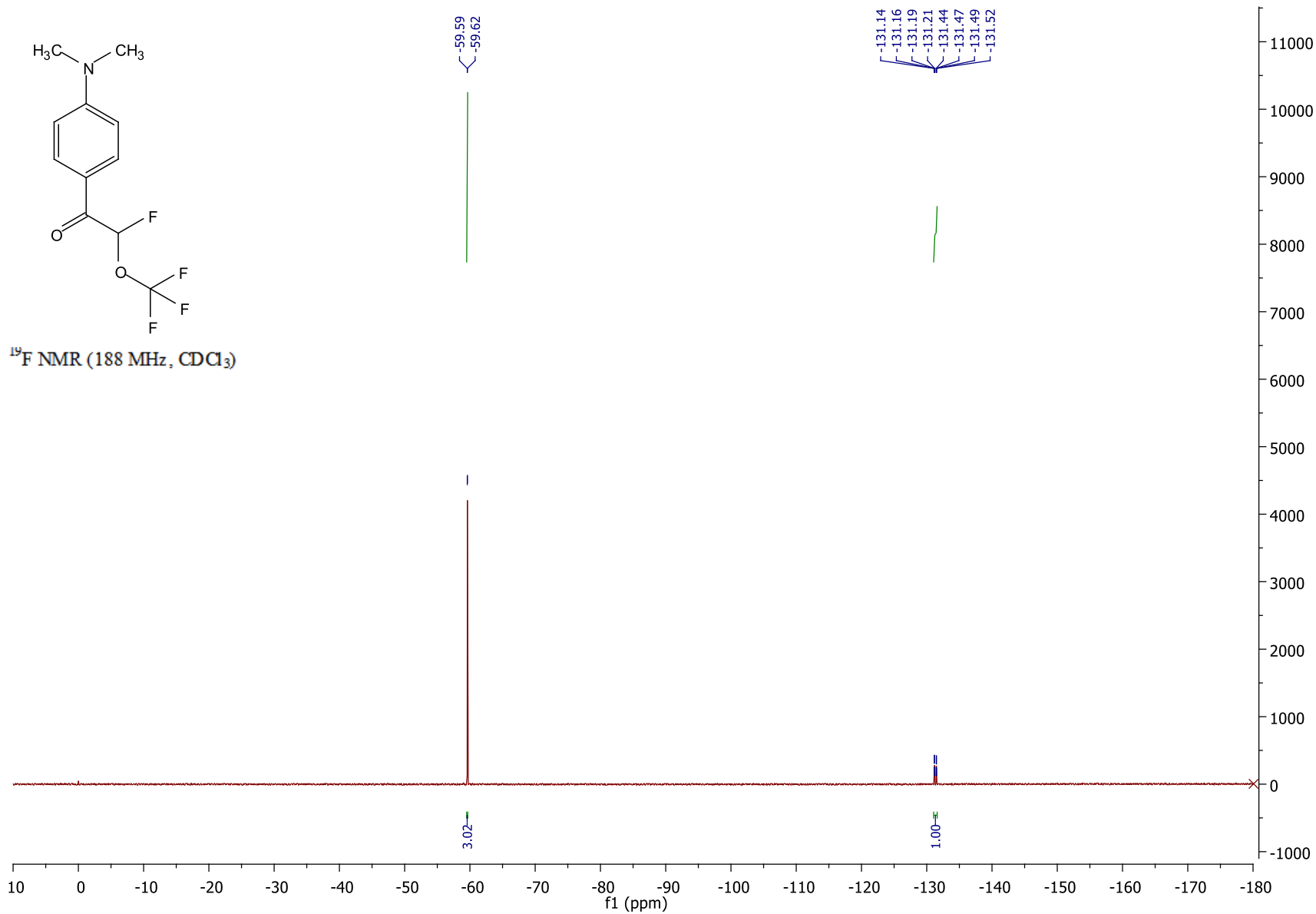
1-(4-(Dimethylamino)phenyl)-2-fluoro-2-(trifluoromethoxy)ethanone (**3a**)



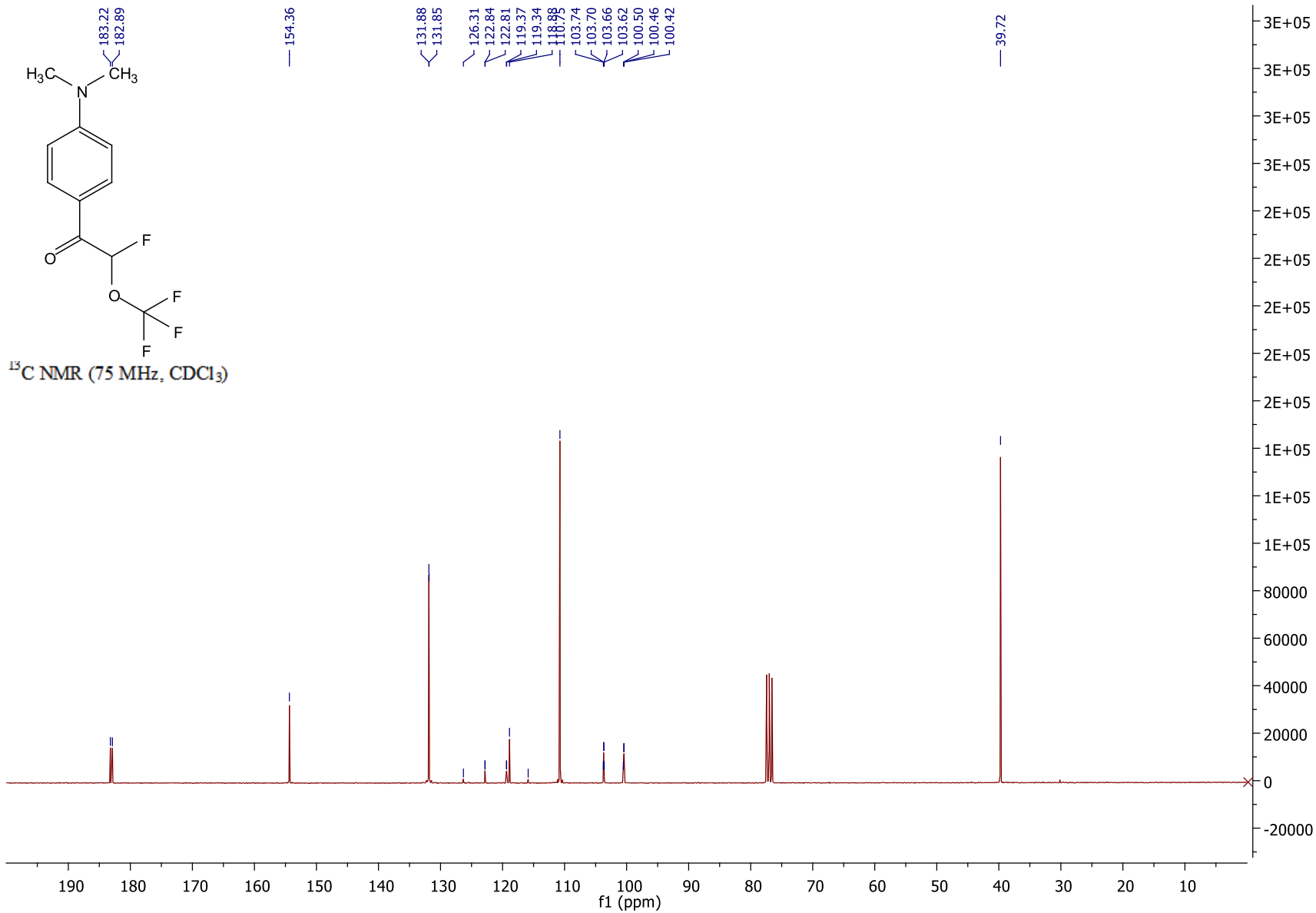
1-(4-(Dimethylamino)phenyl)-2-fluoro-2-(trifluoromethoxy)ethanone (**3a**)



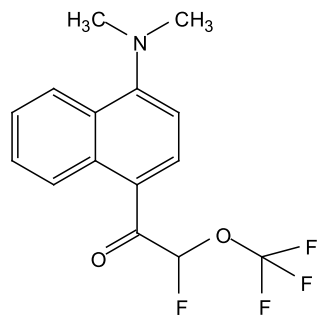
^{19}F NMR (188 MHz, CDCl_3)



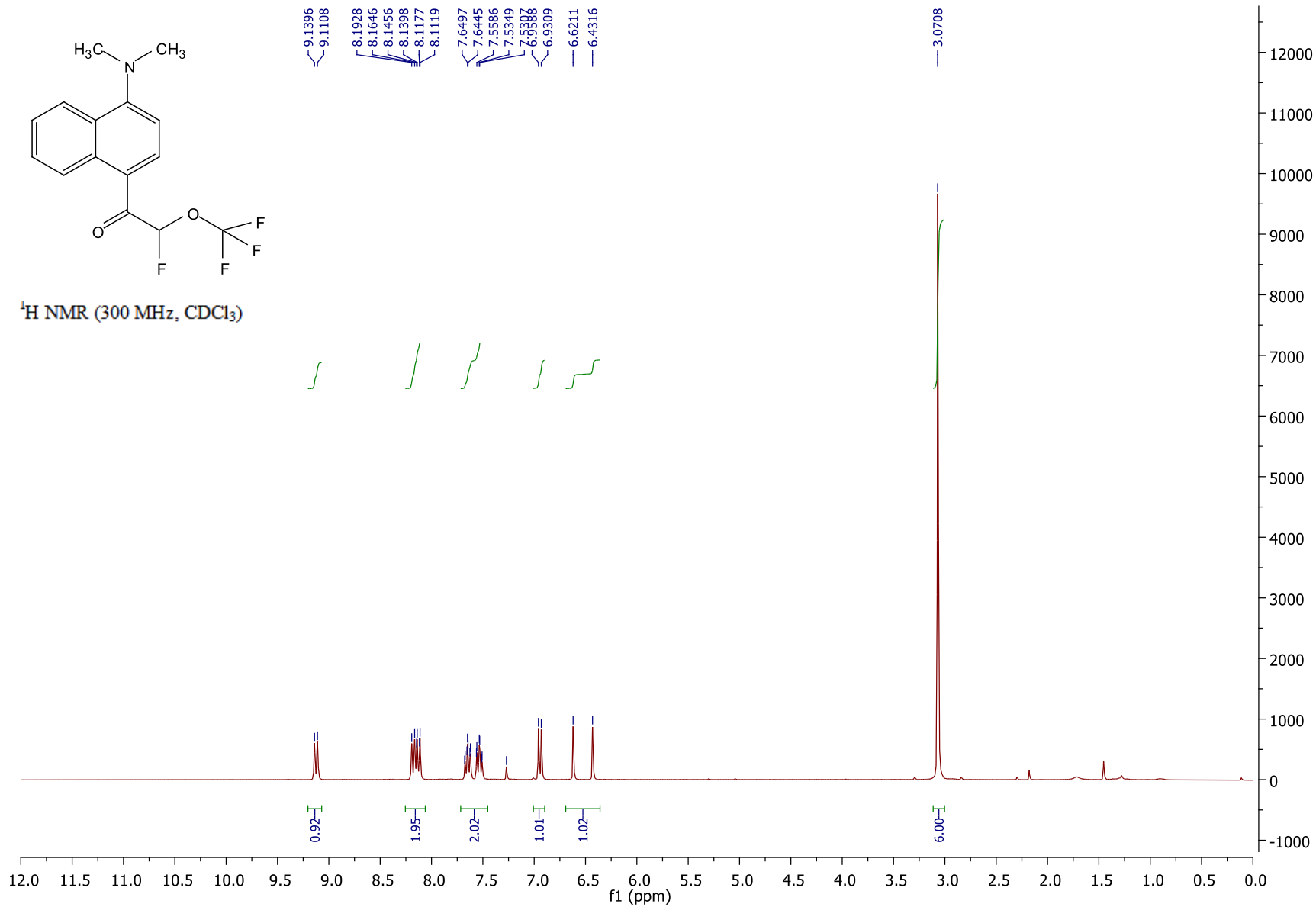
1-(4-(Dimethylamino)phenyl)-2-fluoro-2-(trifluoromethoxy)ethanone (**3a**)



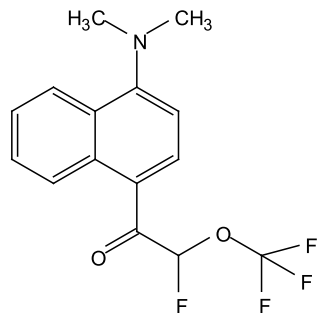
1-(4-(Dimethylamino)naphthalen-1-yl)-2-fluoro-2-(trifluoromethoxy)ethanone (**3b**)



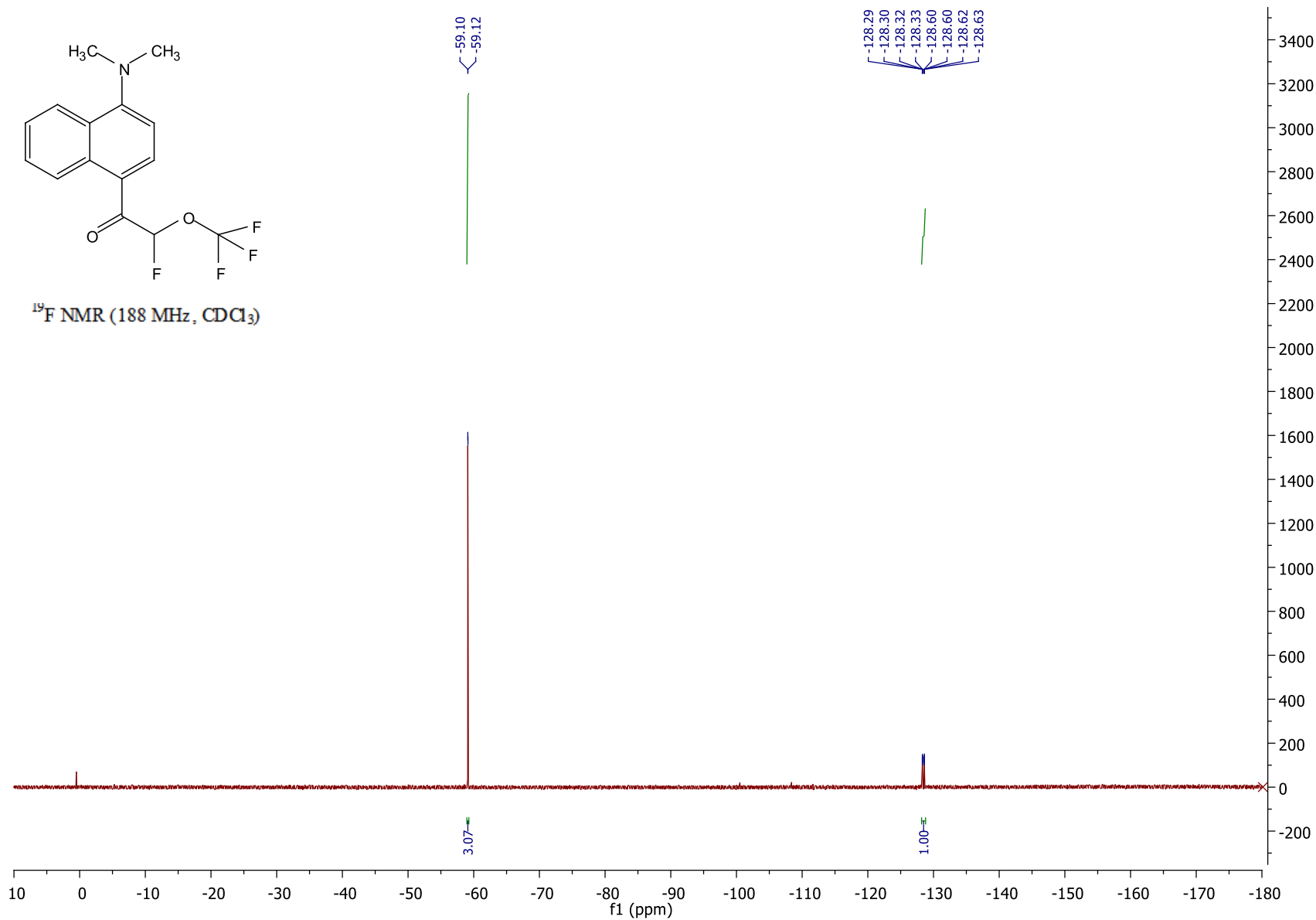
$^1\text{H NMR}$ (300 MHz, CDCl_3)



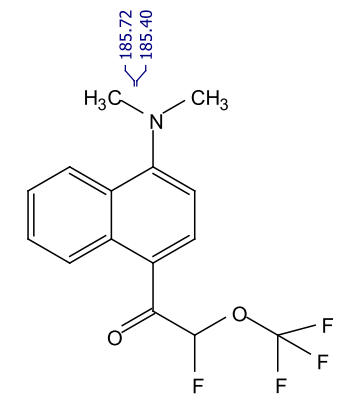
1-(4-(Dimethylamino)naphthalen-1-yl)-2-fluoro-2-(trifluoromethoxy)ethanone (**3b**)



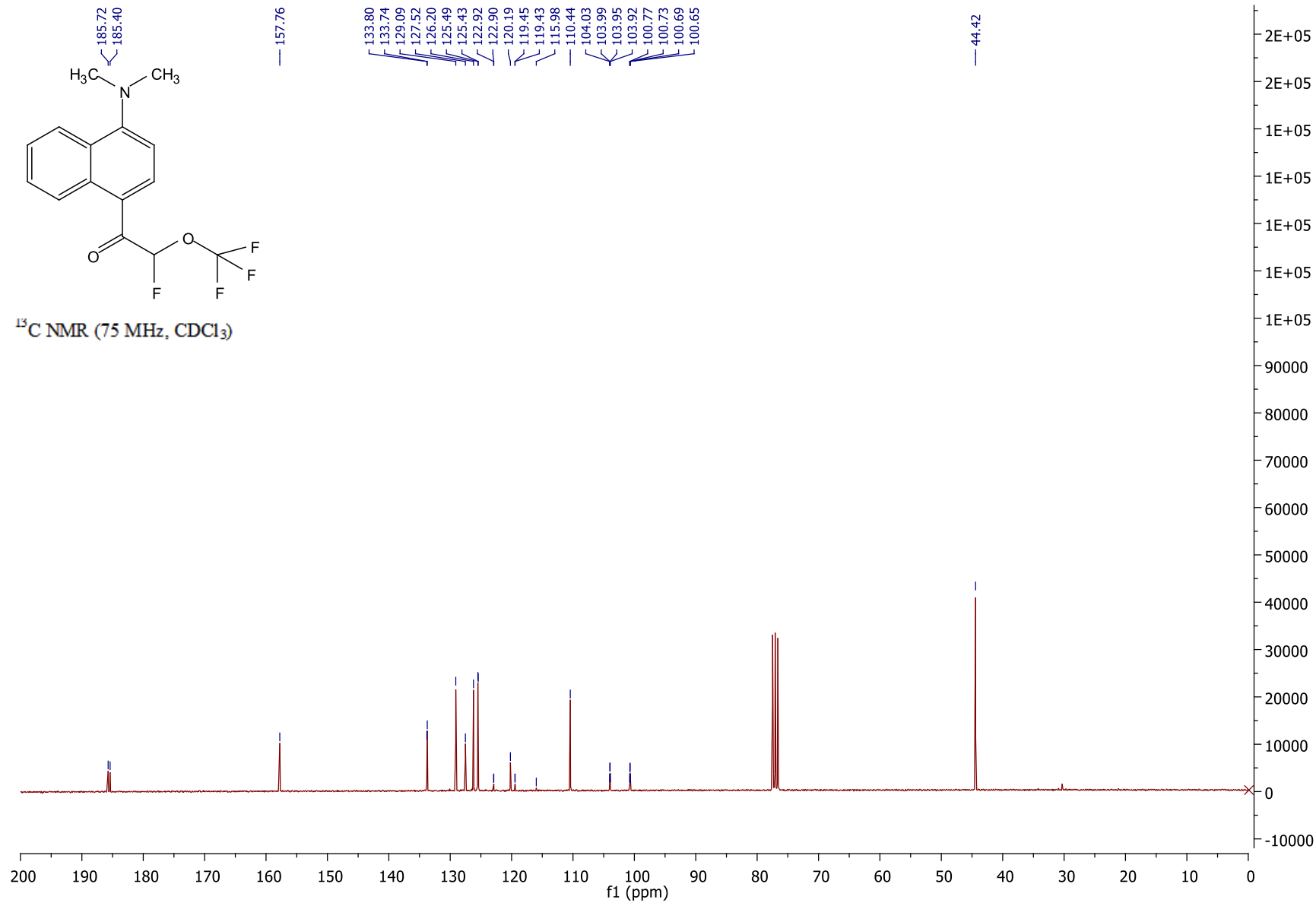
^{19}F NMR (188 MHz, CDCl_3)



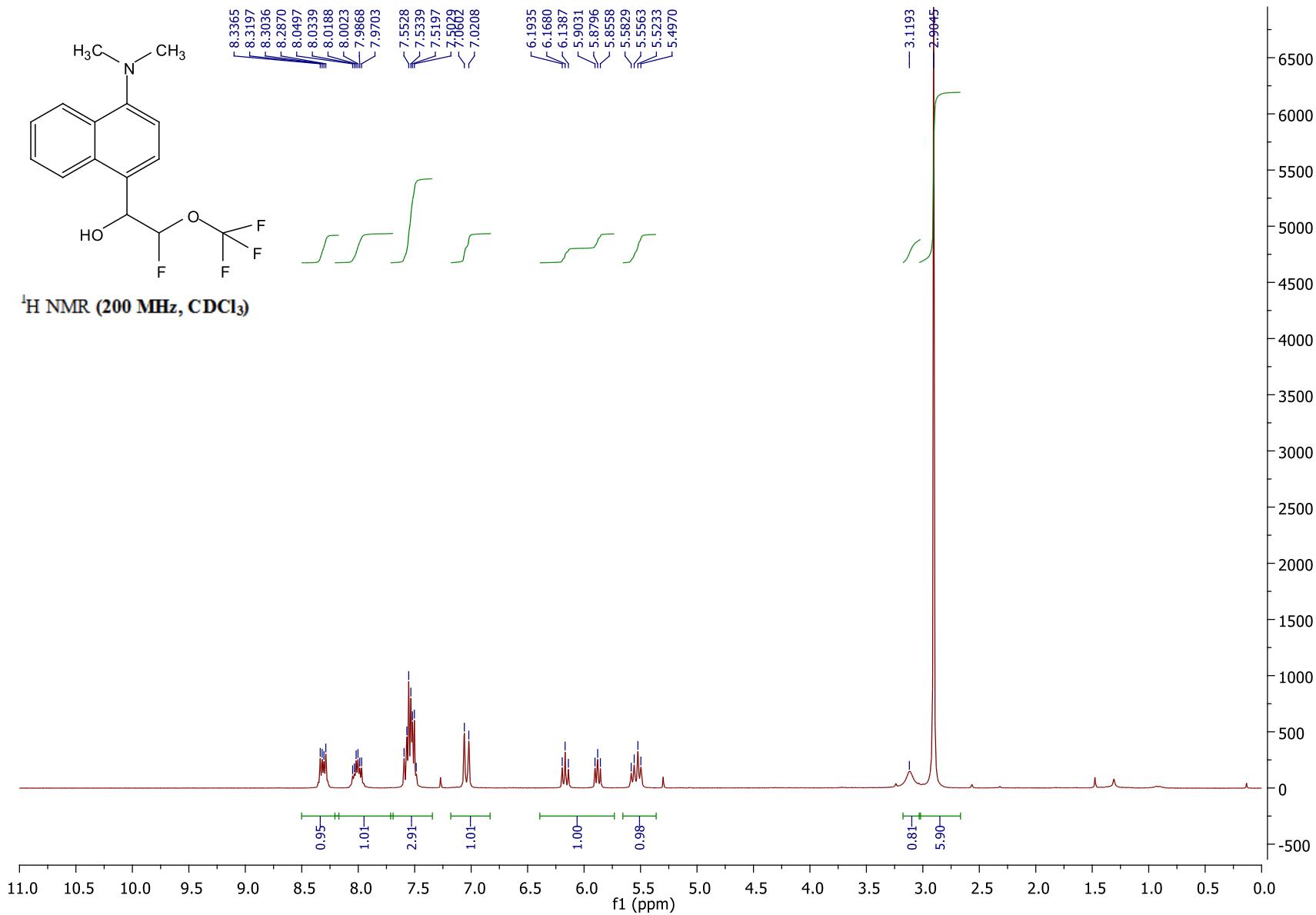
1-(4-(Dimethylamino)naphthalen-1-yl)-2-fluoro-2-(trifluoromethoxy)ethanone (3b)



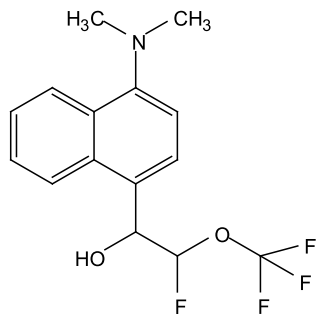
^{13}C NMR (75 MHz, CDCl_3)



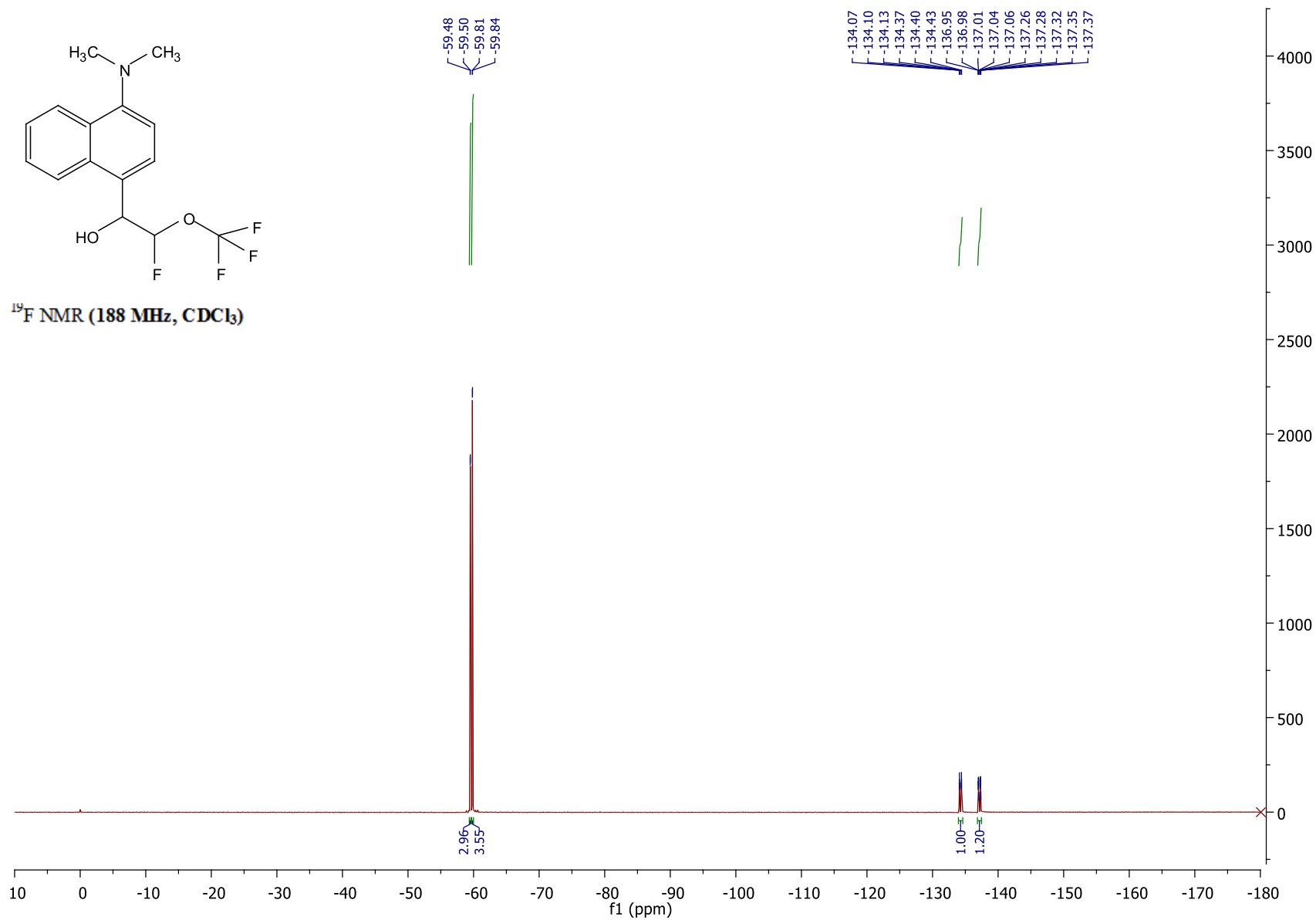
1-(4-(Dimethylamino)naphthalen-1-yl)-2-fluoro-2-(trifluoromethoxy)ethanol (**3c**)



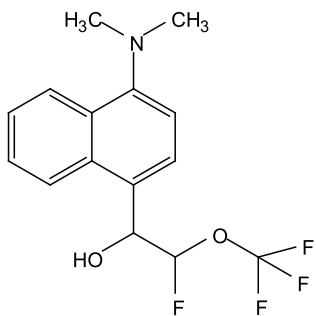
1-(4-(Dimethylamino)naphthalen-1-yl)-2-fluoro-2-(trifluoromethoxy)ethanol (**3c**)



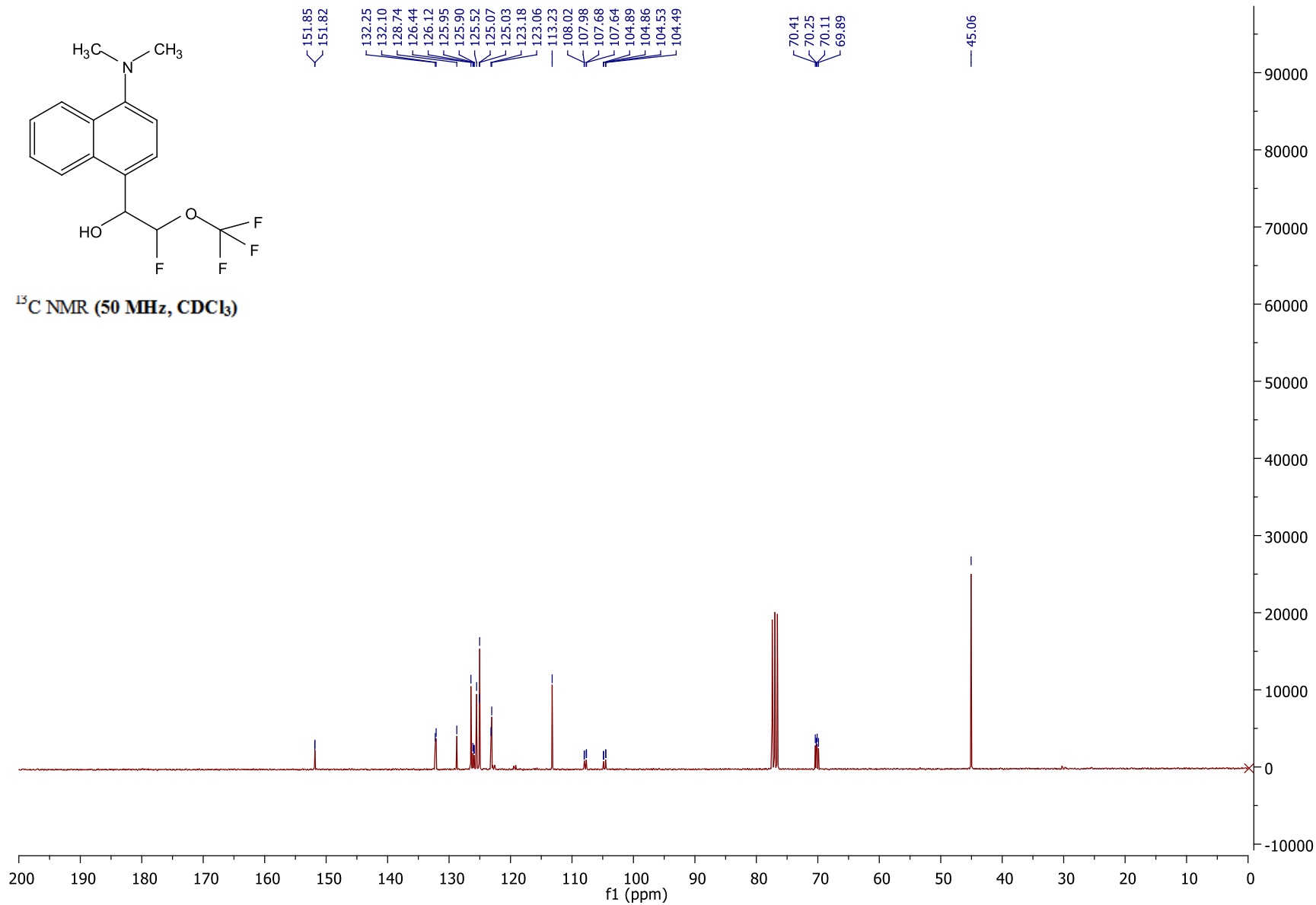
^{19}F NMR (188 MHz, CDCl_3)



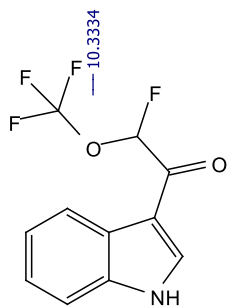
1-(4-(Dimethylamino)naphthalen-1-yl)-2-fluoro-2-(trifluoromethoxy)ethanol (**3c**)



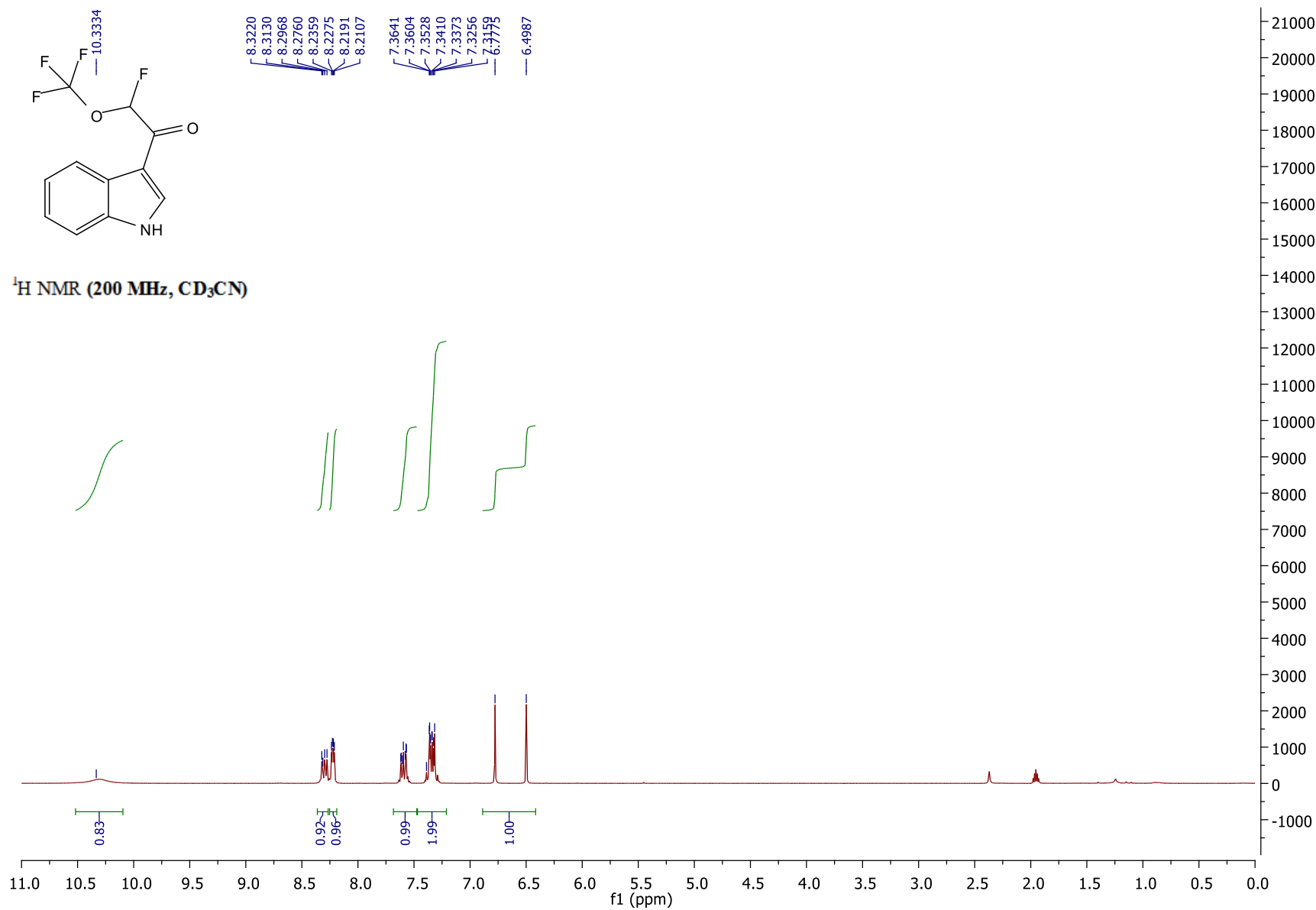
^{13}C NMR (50 MHz, CDCl_3)



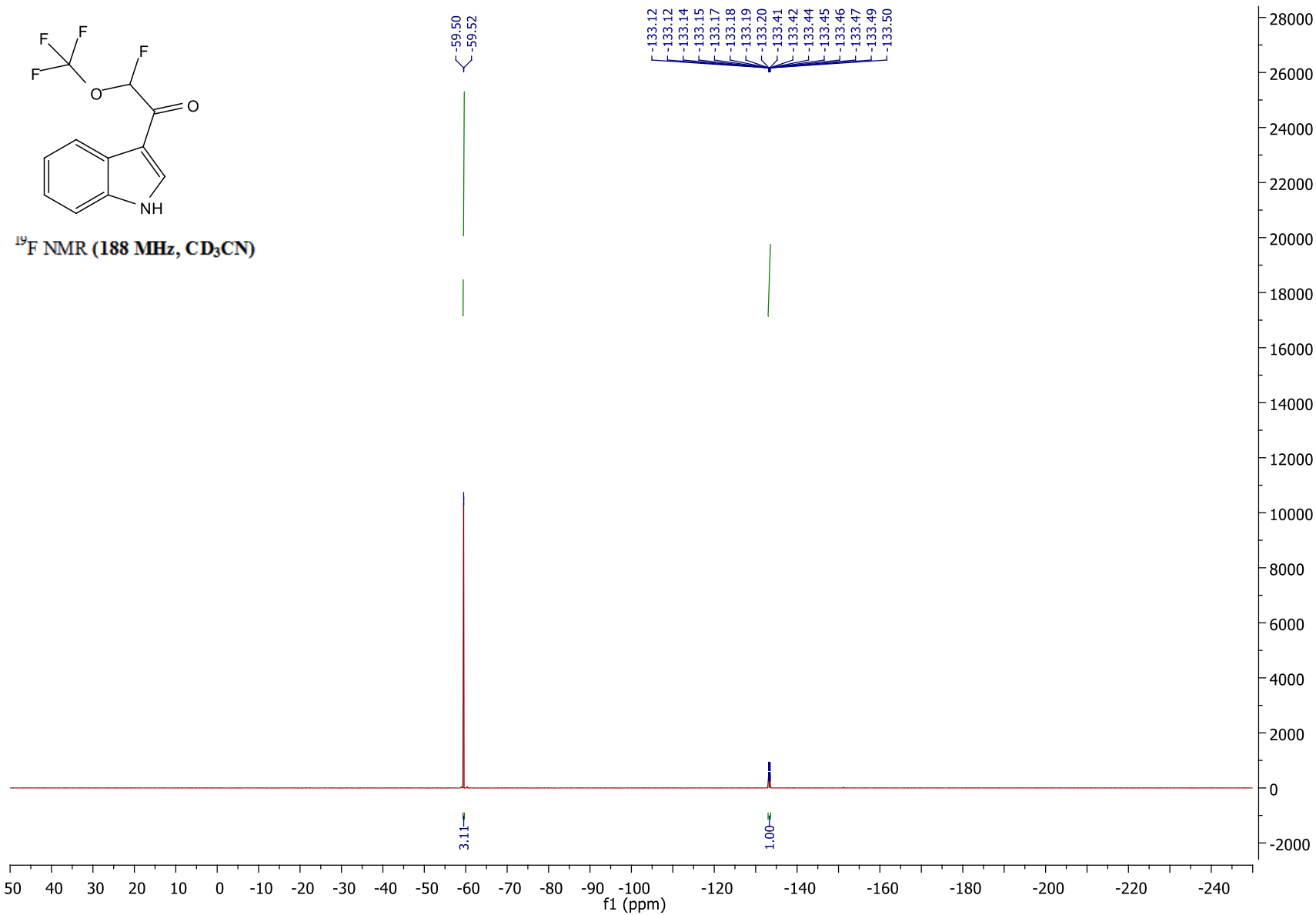
2-Fluoro-1-(1H-indol-3-yl)-2-(trifluoromethoxy)ethanone (4a)



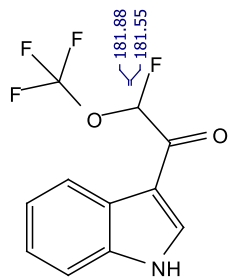
¹H NMR (200 MHz, CD₃CN)



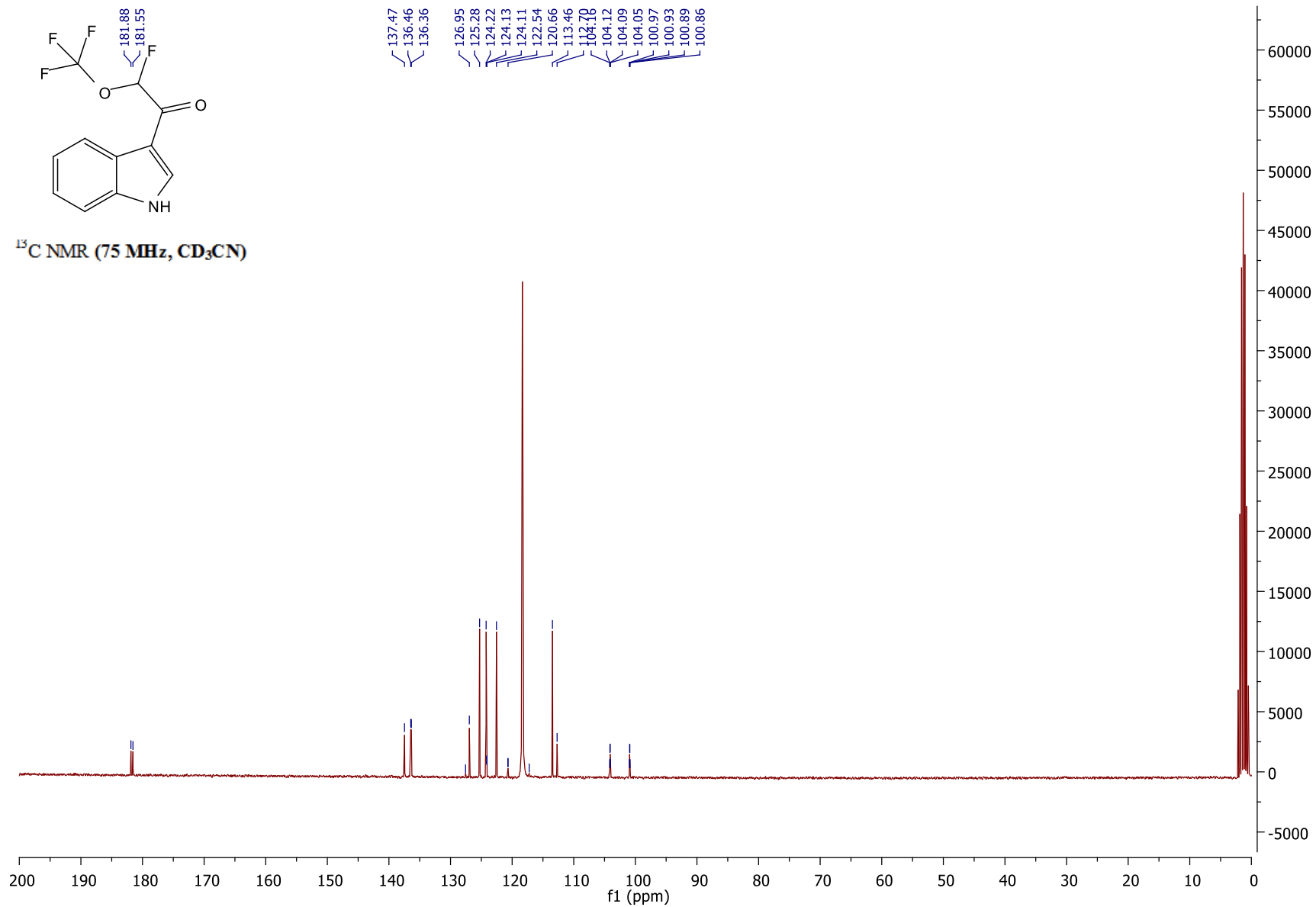
2-Fluoro-1-(1*H*-indol-3-yl)-2-(trifluoromethoxy)ethanone (**4a**)



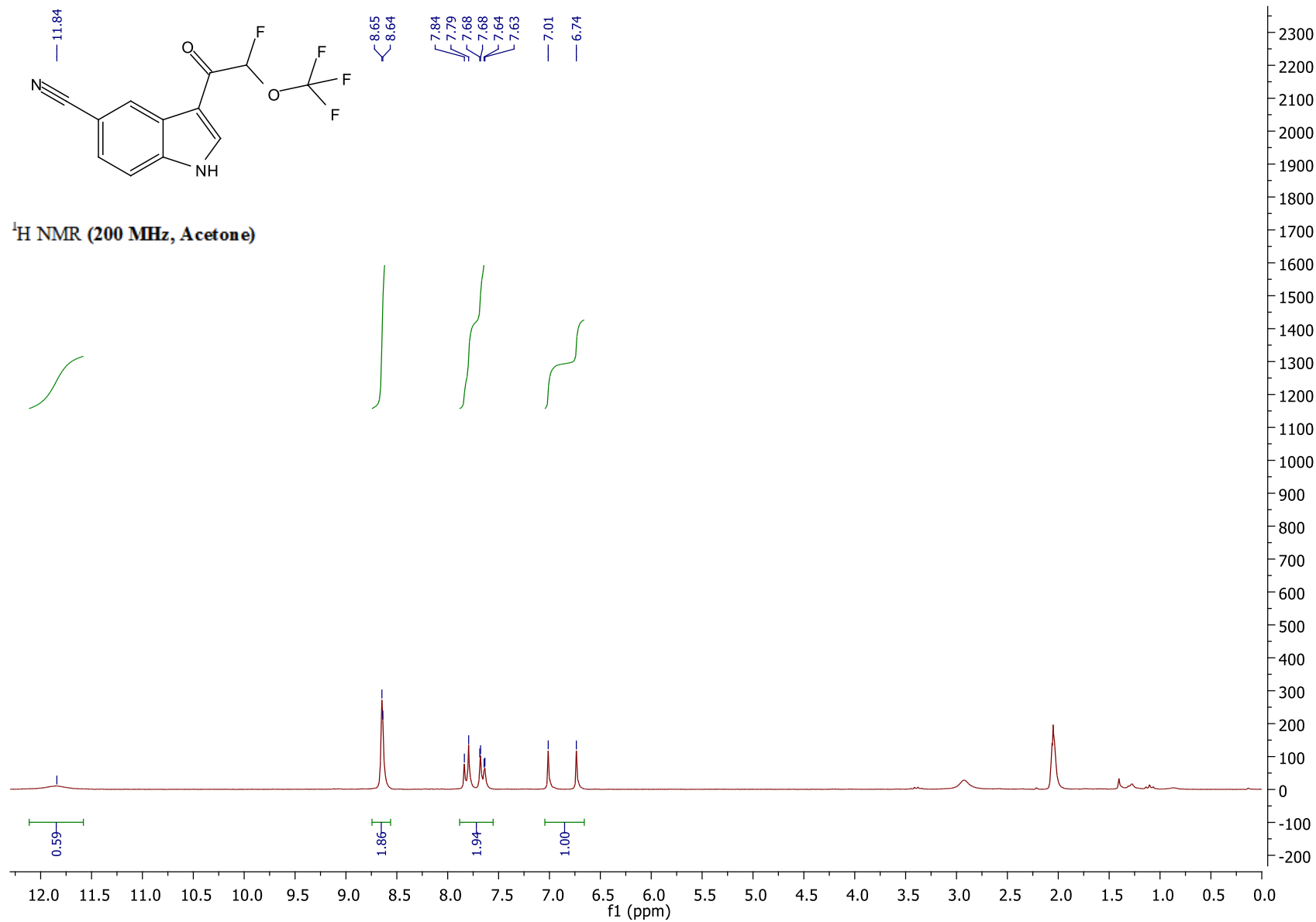
2-Fluoro-1-(1*H*-indol-3-yl)-2-(trifluoromethoxy)ethanone (**4a**)



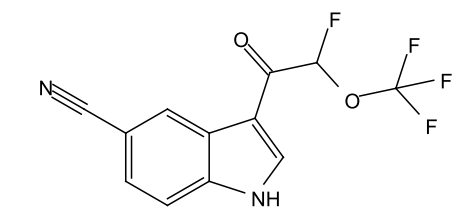
^{13}C NMR (75 MHz, CD_3CN)



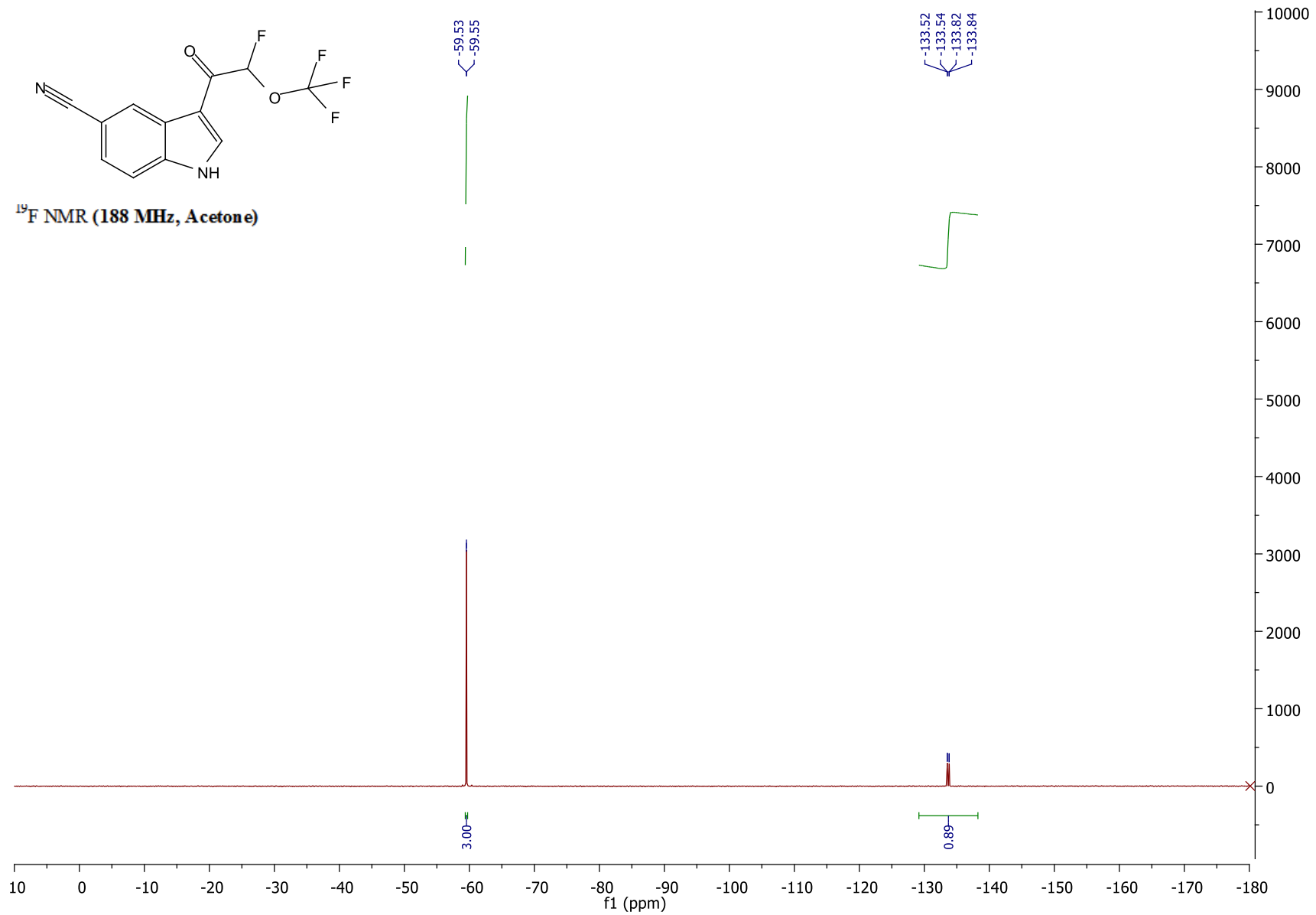
3-(2-Fluoro-2-(trifluoromethoxy)acetyl)-1H-indole-5-carbonitrile (**4b**)



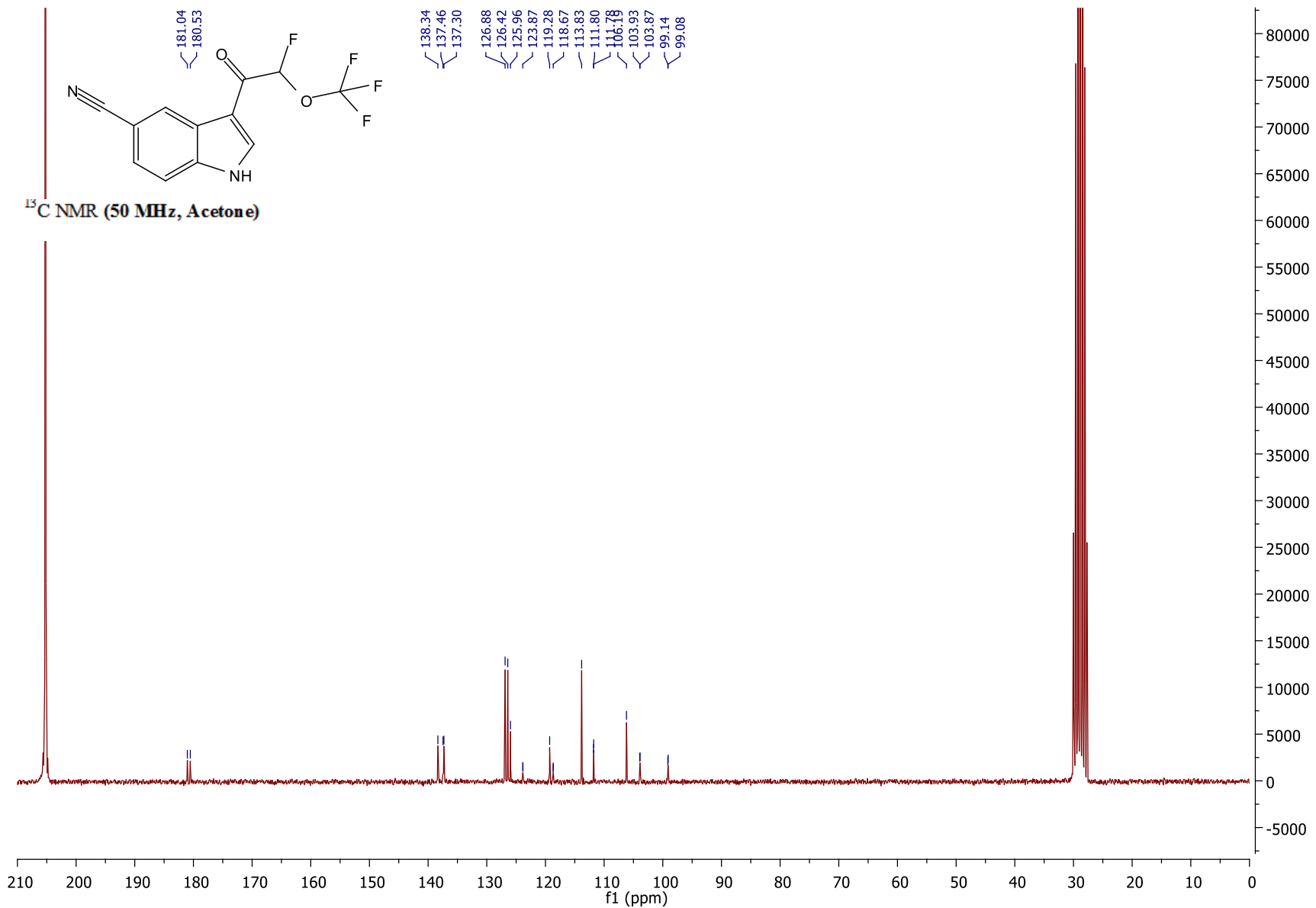
3-(2-Fluoro-2-(trifluoromethoxy)acetyl)-1H-indole-5-carbonitrile (**4b**)



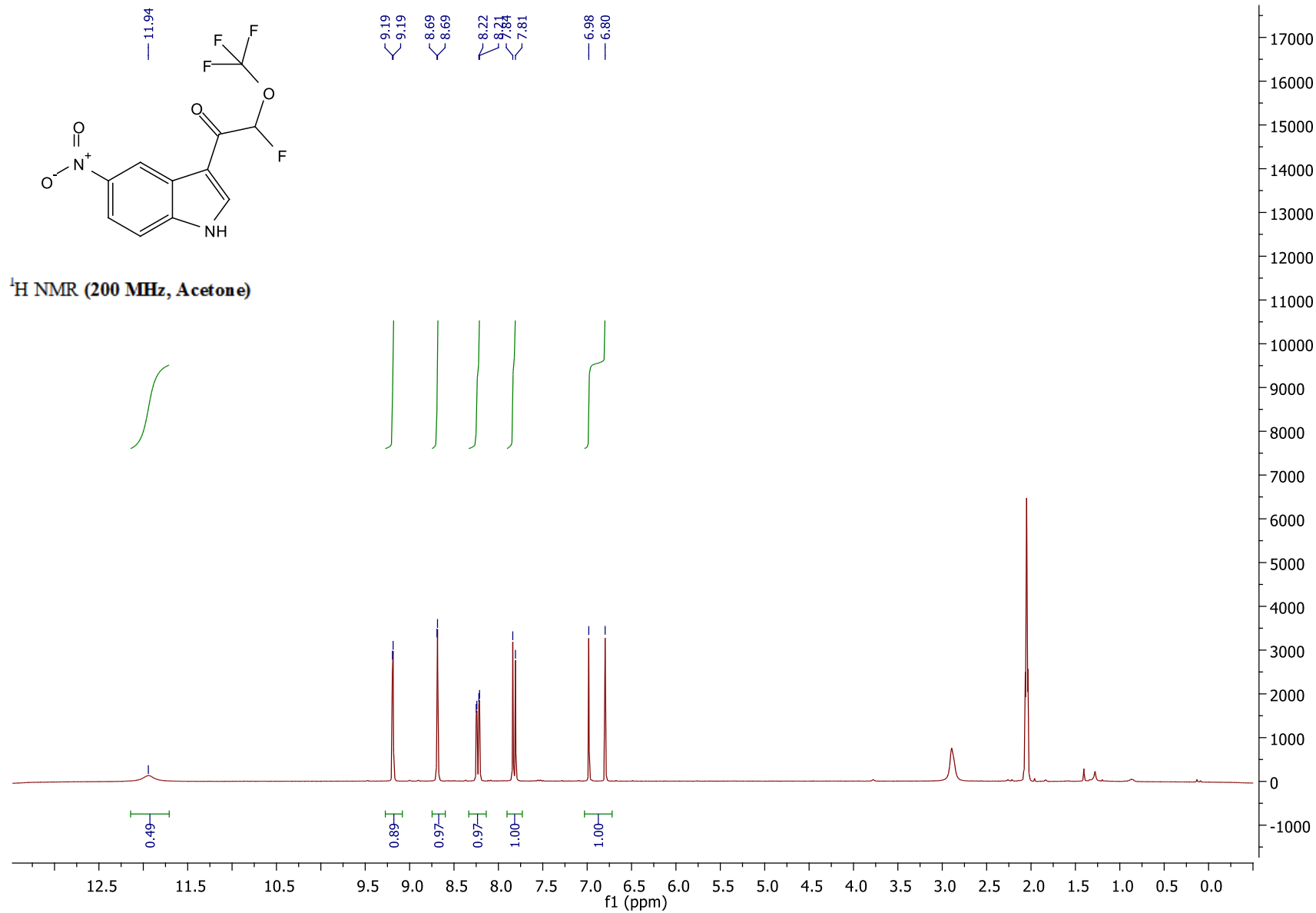
¹⁹F NMR (188 MHz, Acetone)



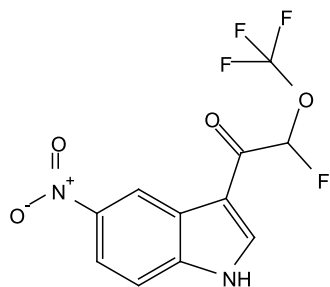
3-(2-Fluoro-2-(trifluoromethoxy)acetyl)-1H-indole-5-carbonitrile (**4b**)



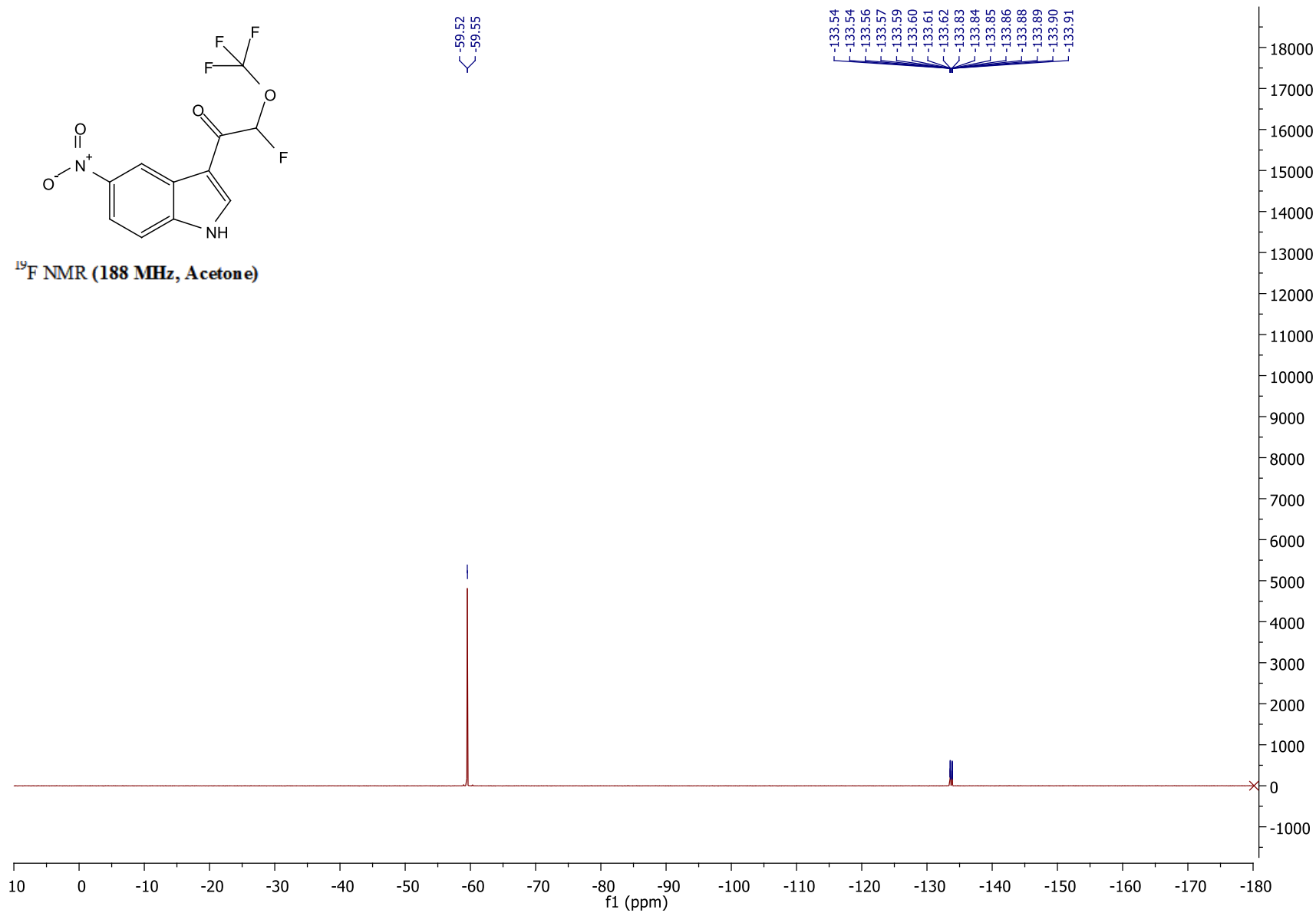
2-Fluoro-1-(5-nitro-1H-indol-3-yl)-2-(trifluoromethoxy)ethanone (4c)



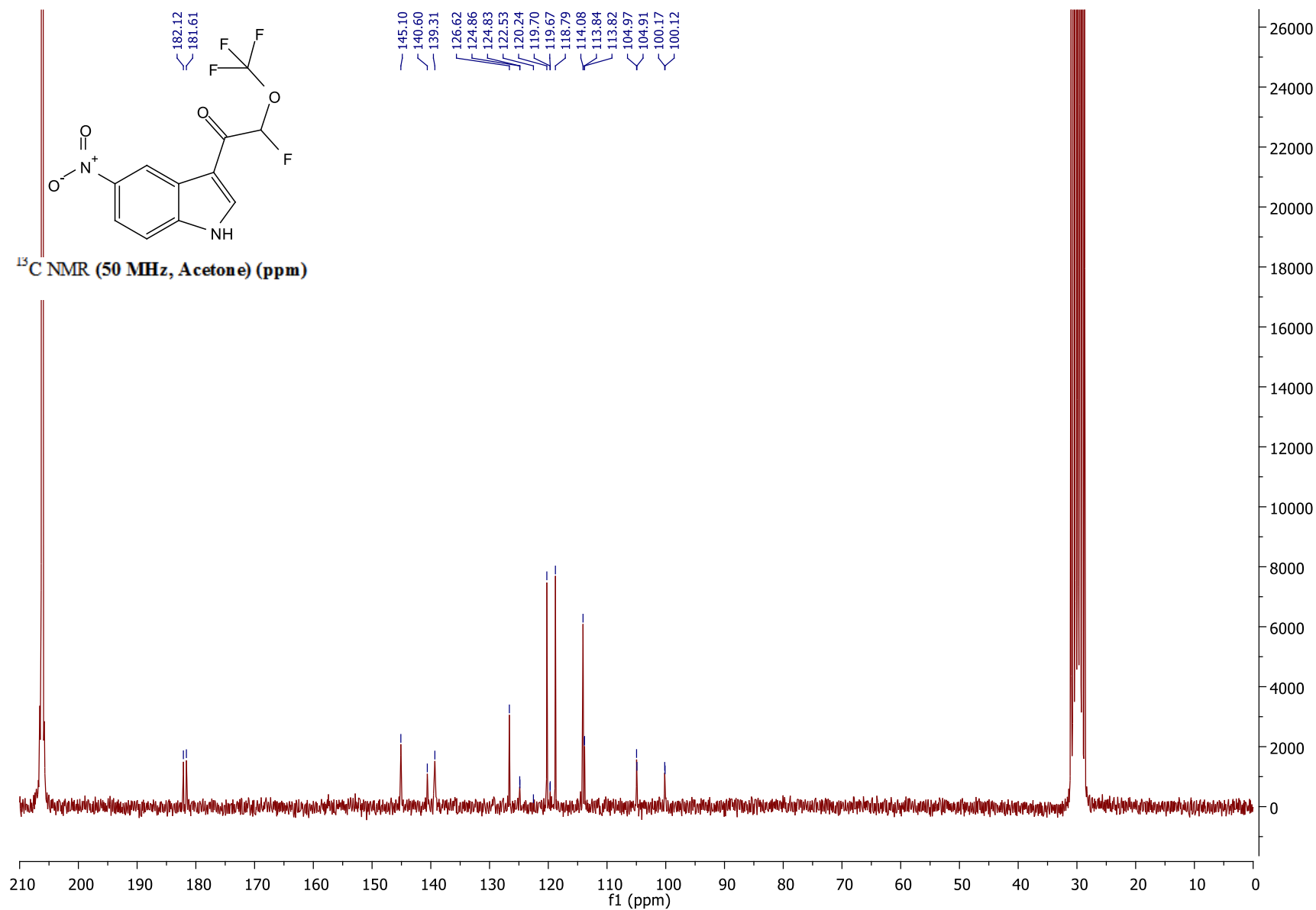
2-Fluoro-1-(5-nitro-1*H*-indol-3-yl)-2-(trifluoromethoxy)ethanone (**4c**)



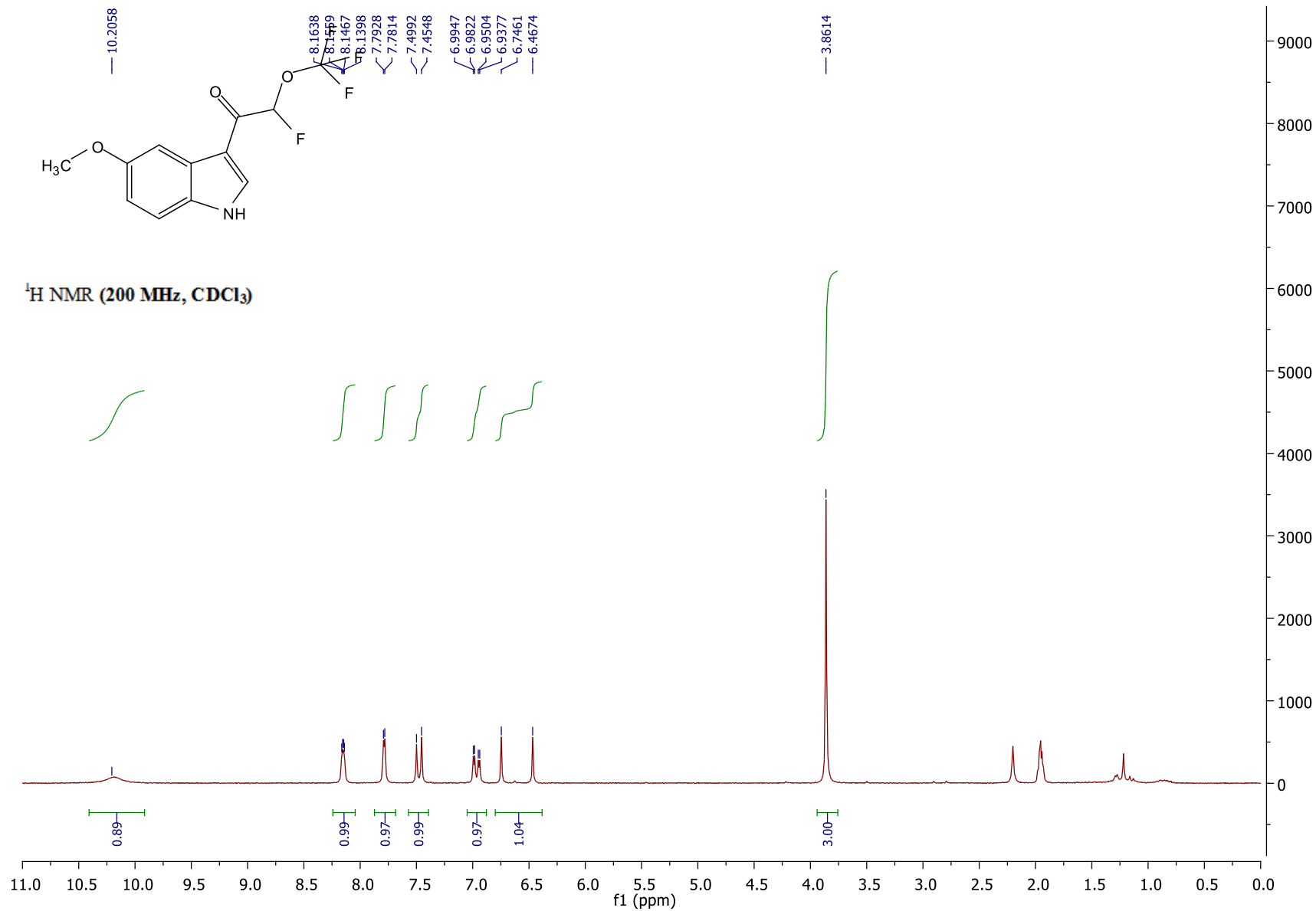
¹⁹F NMR (188 MHz, Acetone)



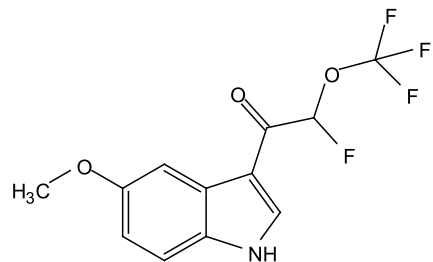
2-Fluoro-1-(5-nitro-1*H*-indol-3-yl)-2-(trifluoromethoxy)ethanone (**4c**)



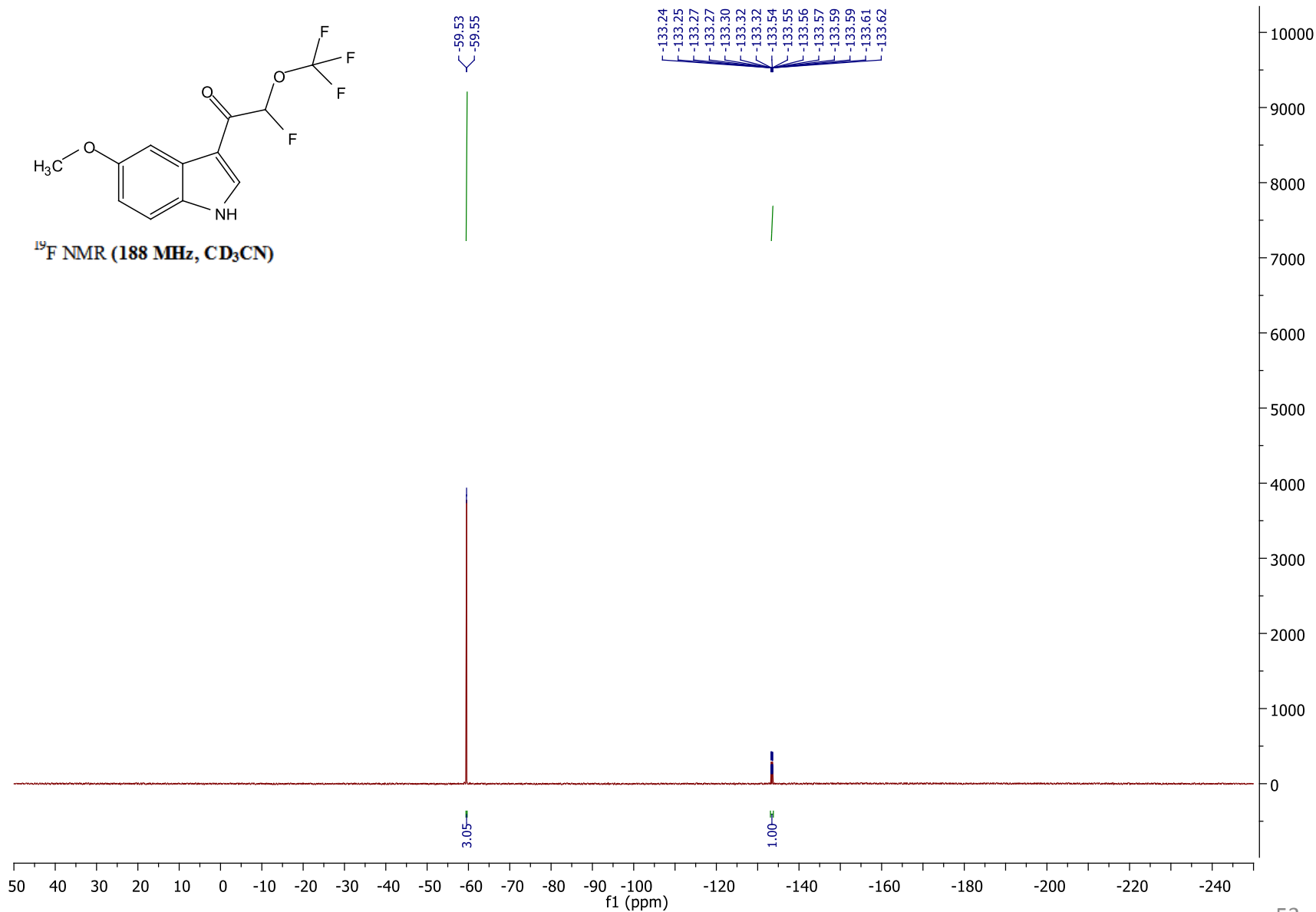
2-Fluoro-1-(5-methoxy-1*H*-indol-3-yl)-2-(trifluoromethoxy)ethanone (**4d**)



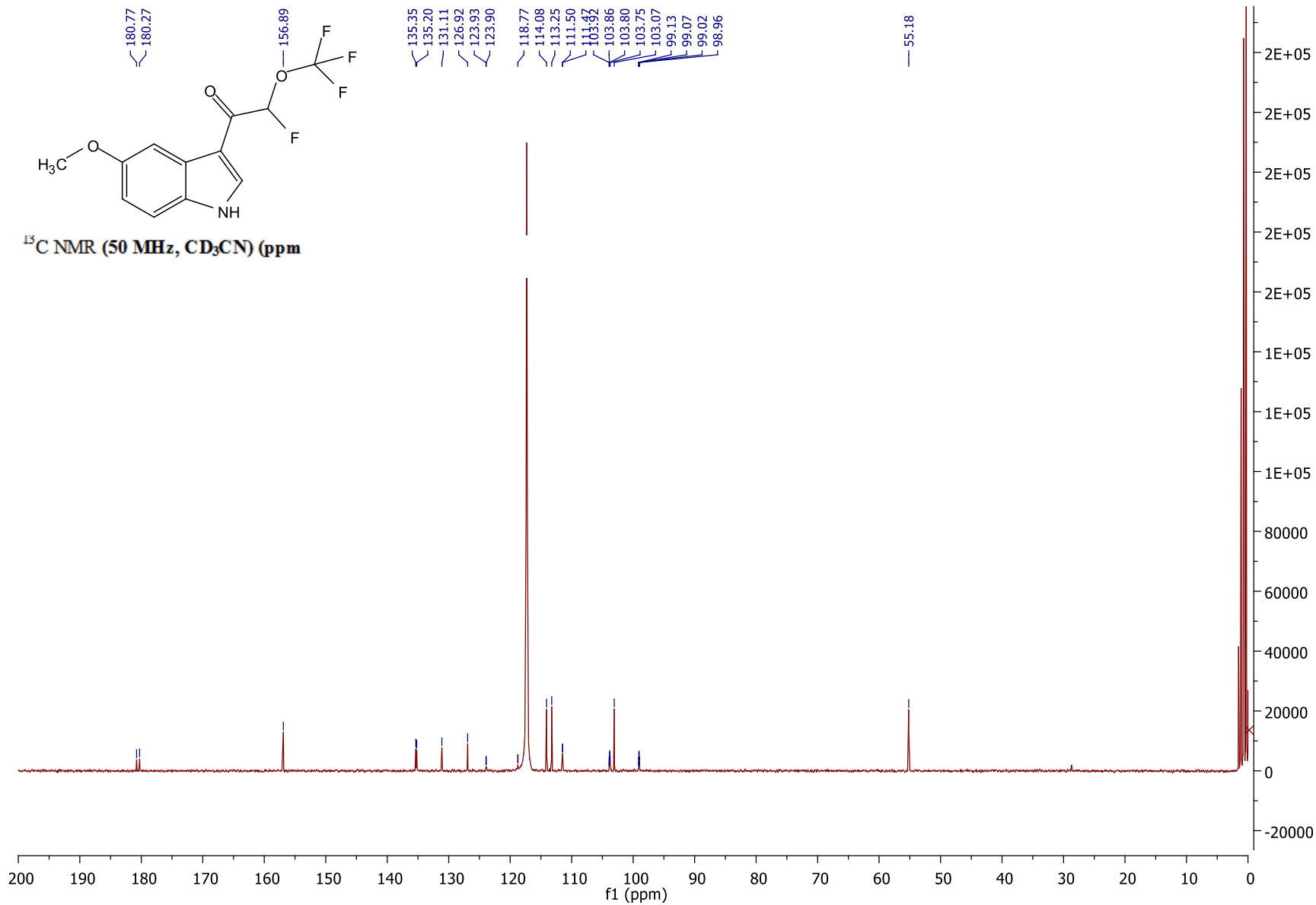
2-Fluoro-1-(5-methoxy-1*H*-indol-3-yl)-2-(trifluoromethoxy)ethanone (**4d**)



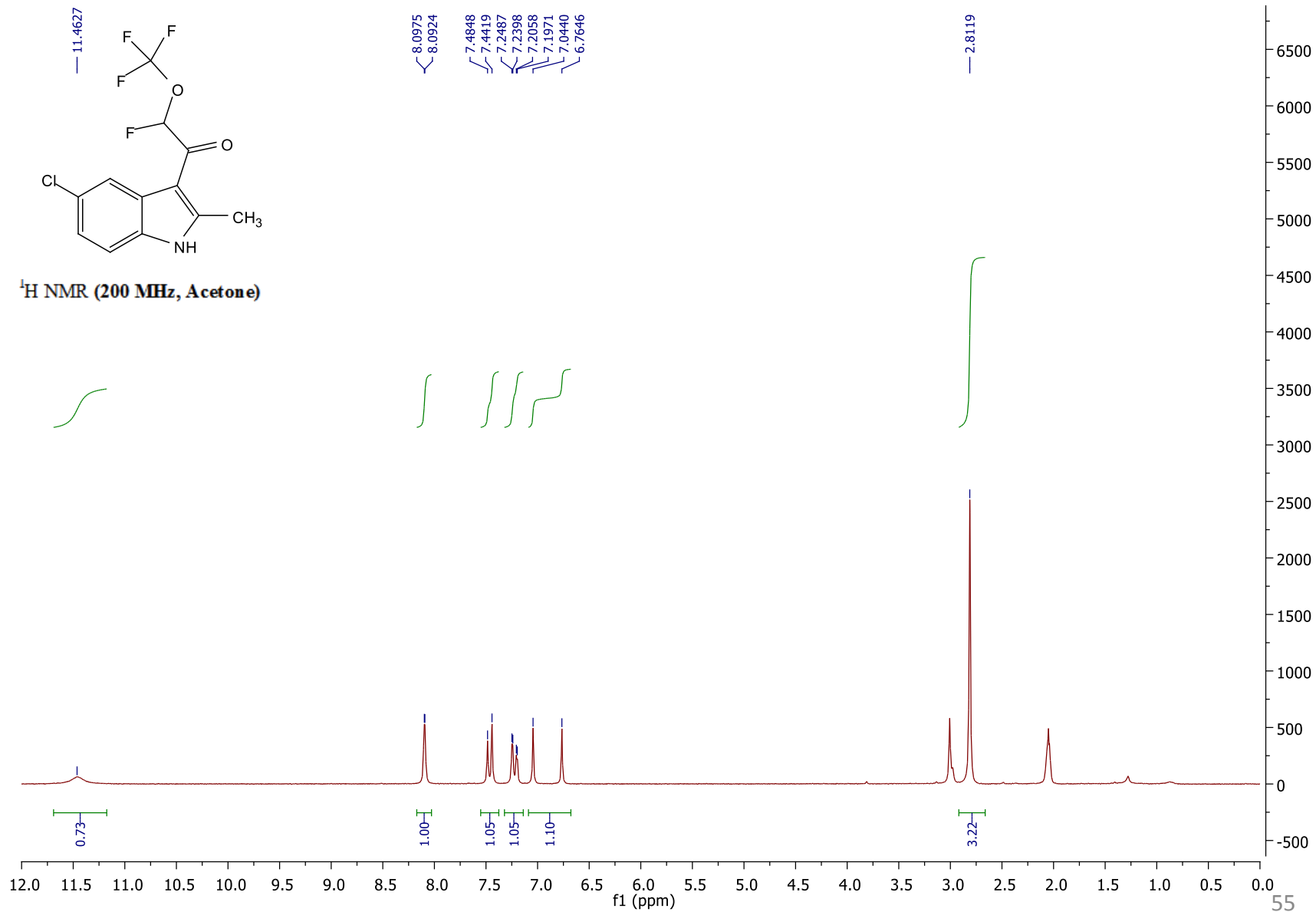
¹⁹F NMR (188 MHz, CD₃CN)



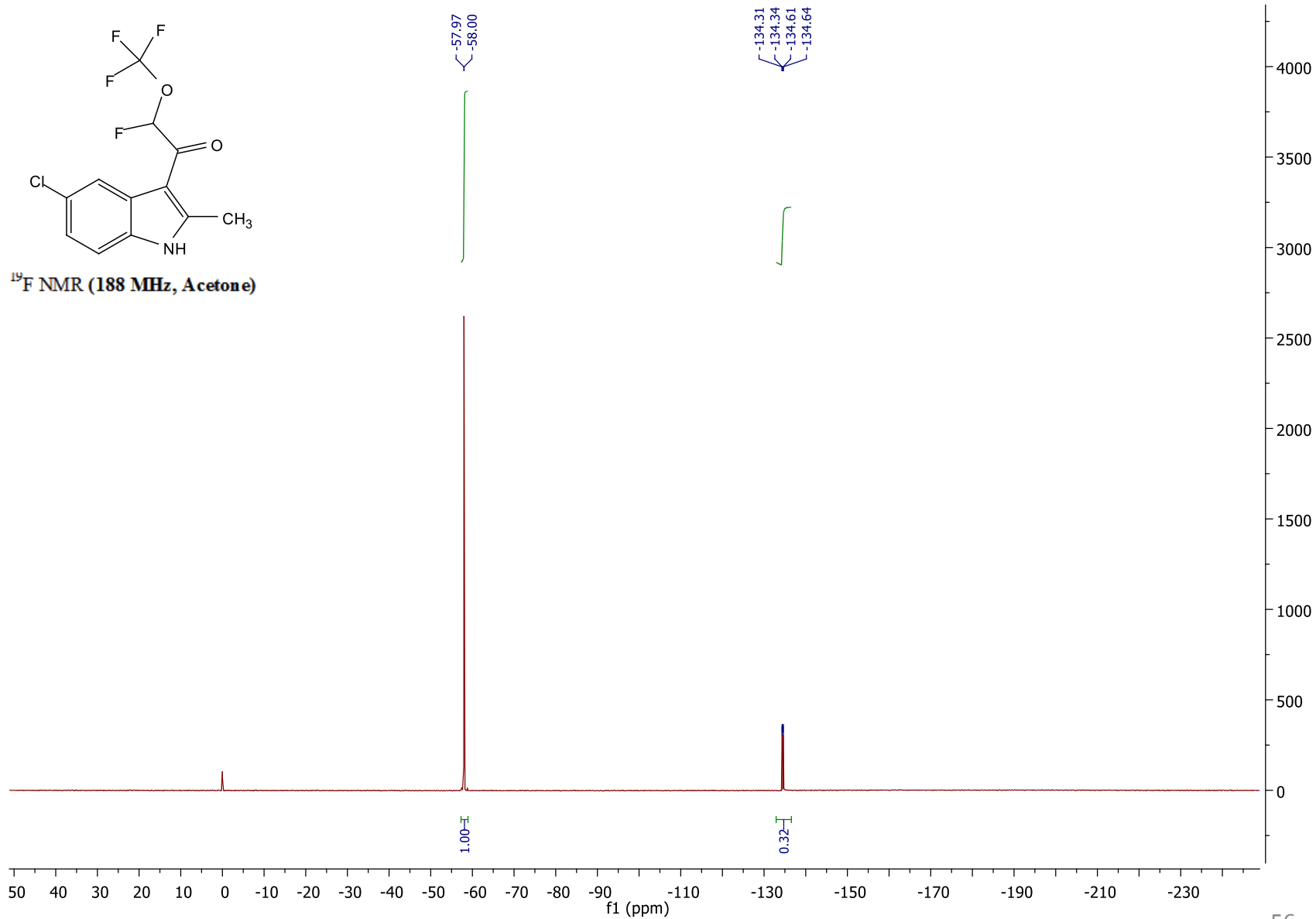
2-Fluoro-1-(5-methoxy-1H-indol-3-yl)-2-(trifluoromethoxy)ethanone (4d)



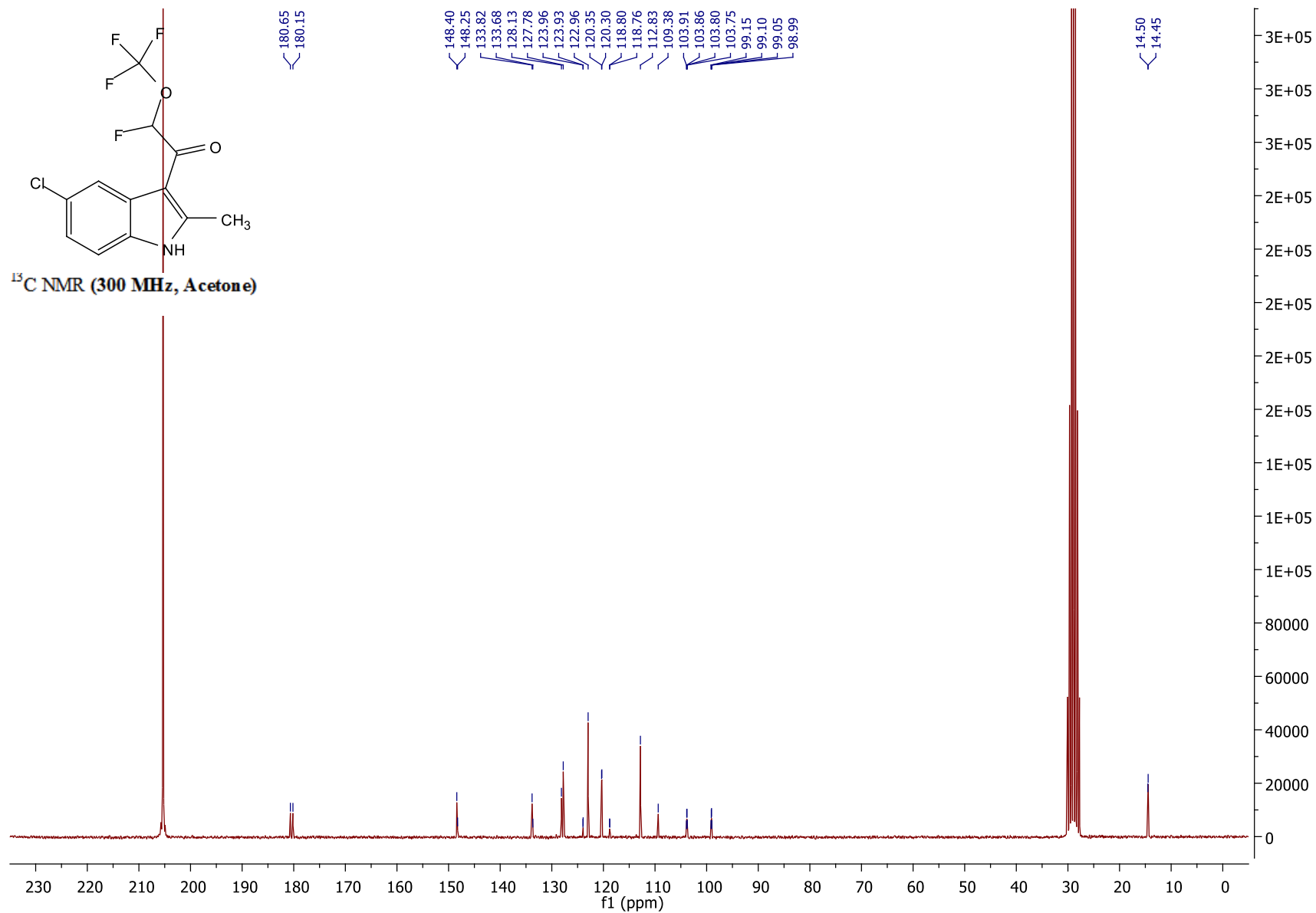
1-(5-Chloro-2-methyl-1H-indol-3-yl)-2-fluoro-2-(trifluoromethoxy)ethanone (**4e**)



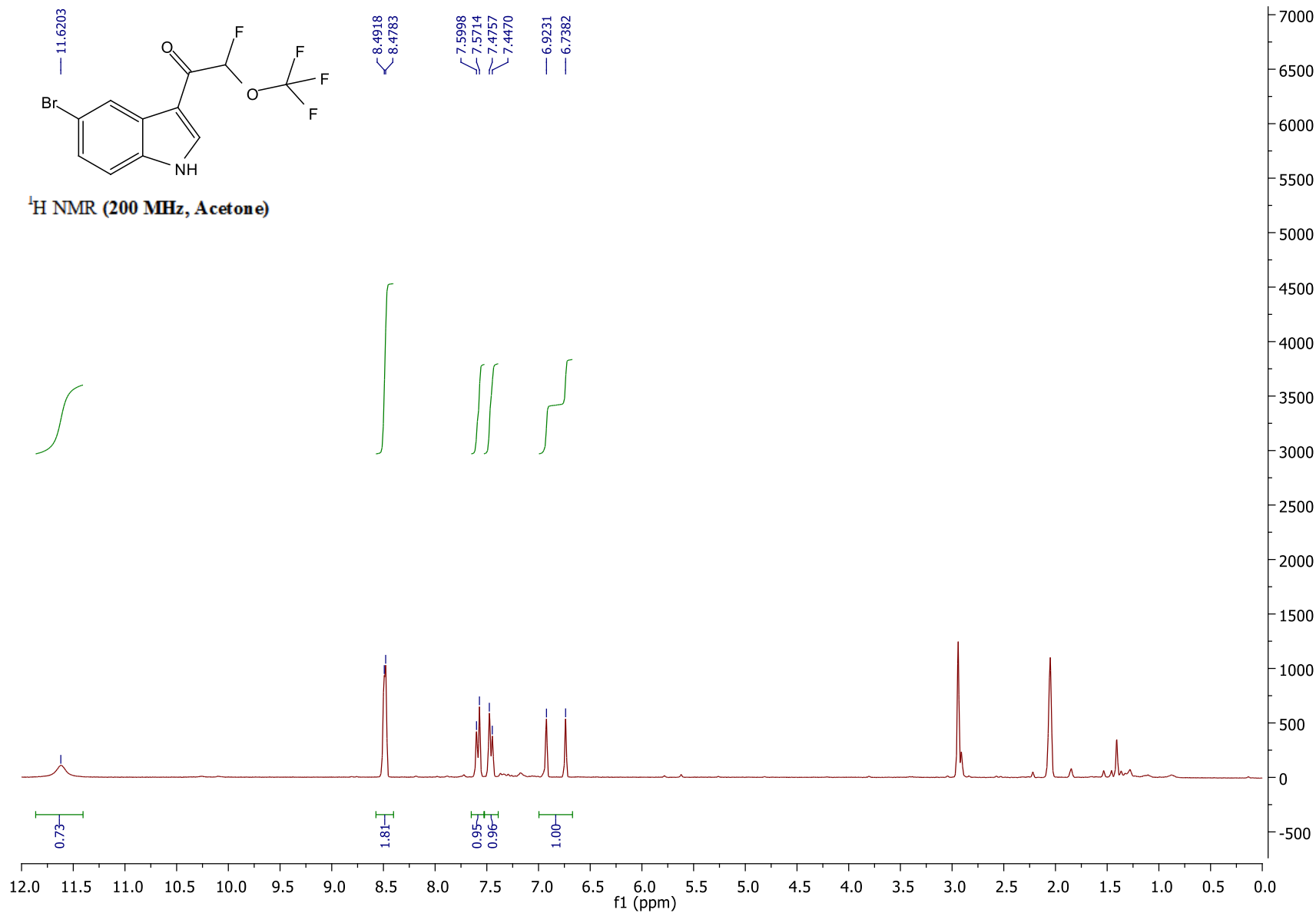
1-(5-Chloro-2-methyl-1H-indol-3-yl)-2-fluoro-2-(trifluoromethoxy)ethanone (**4e**)



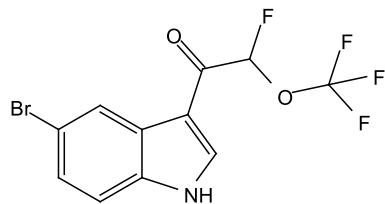
1-(5-Chloro-2-methyl-1H-indol-3-yl)-2-fluoro-2-(trifluoromethoxy)ethanone (**4e**)



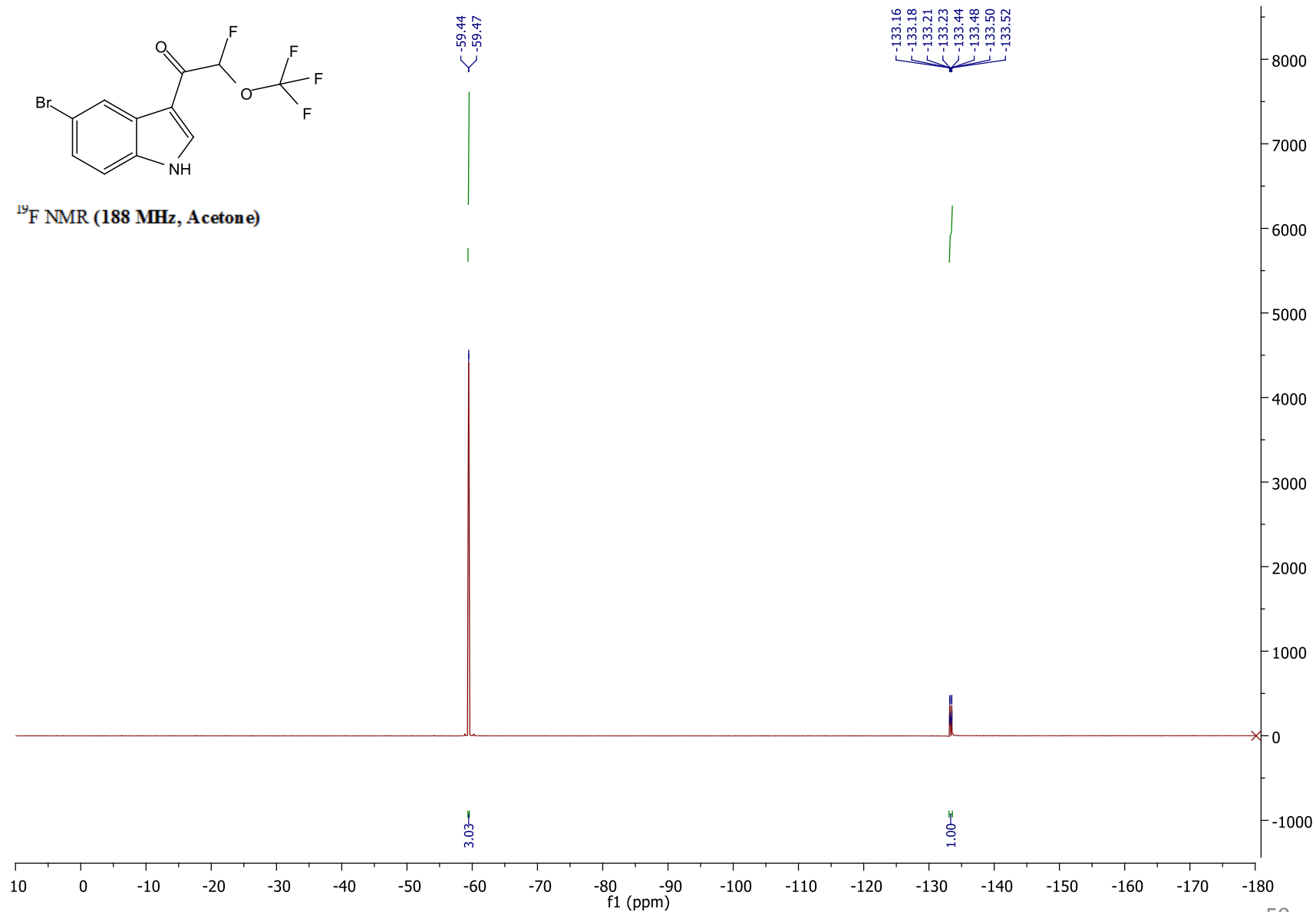
1-(5-Bromo-1*H*-indol-3-yl)-2-fluoro-2-(trifluoromethoxy)ethanone (**4f**)



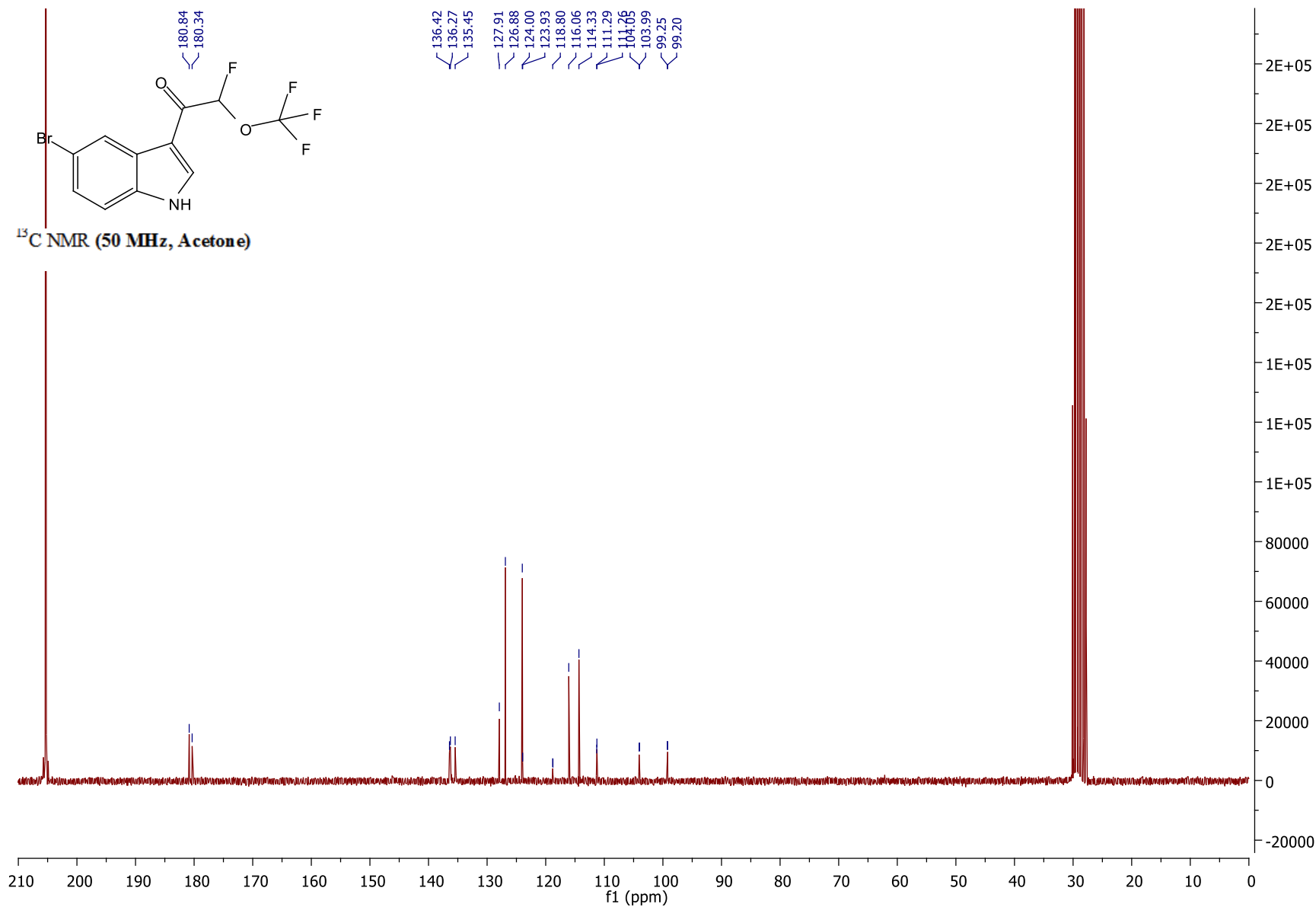
1-(5-Bromo-1*H*-indol-3-yl)-2-fluoro-2-(trifluoromethoxy)ethanone (**4f**)



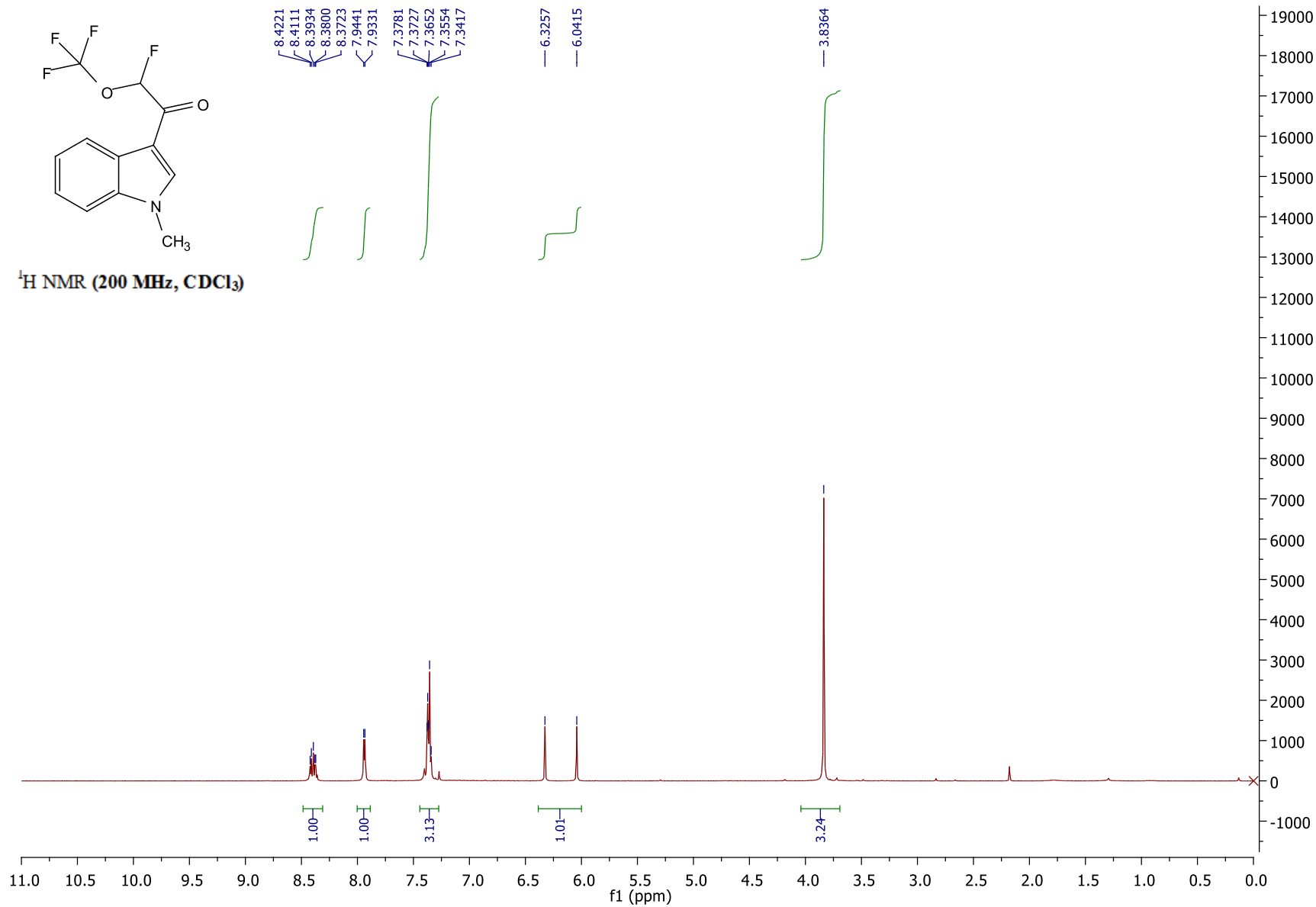
¹⁹F NMR (188 MHz, Acetone)



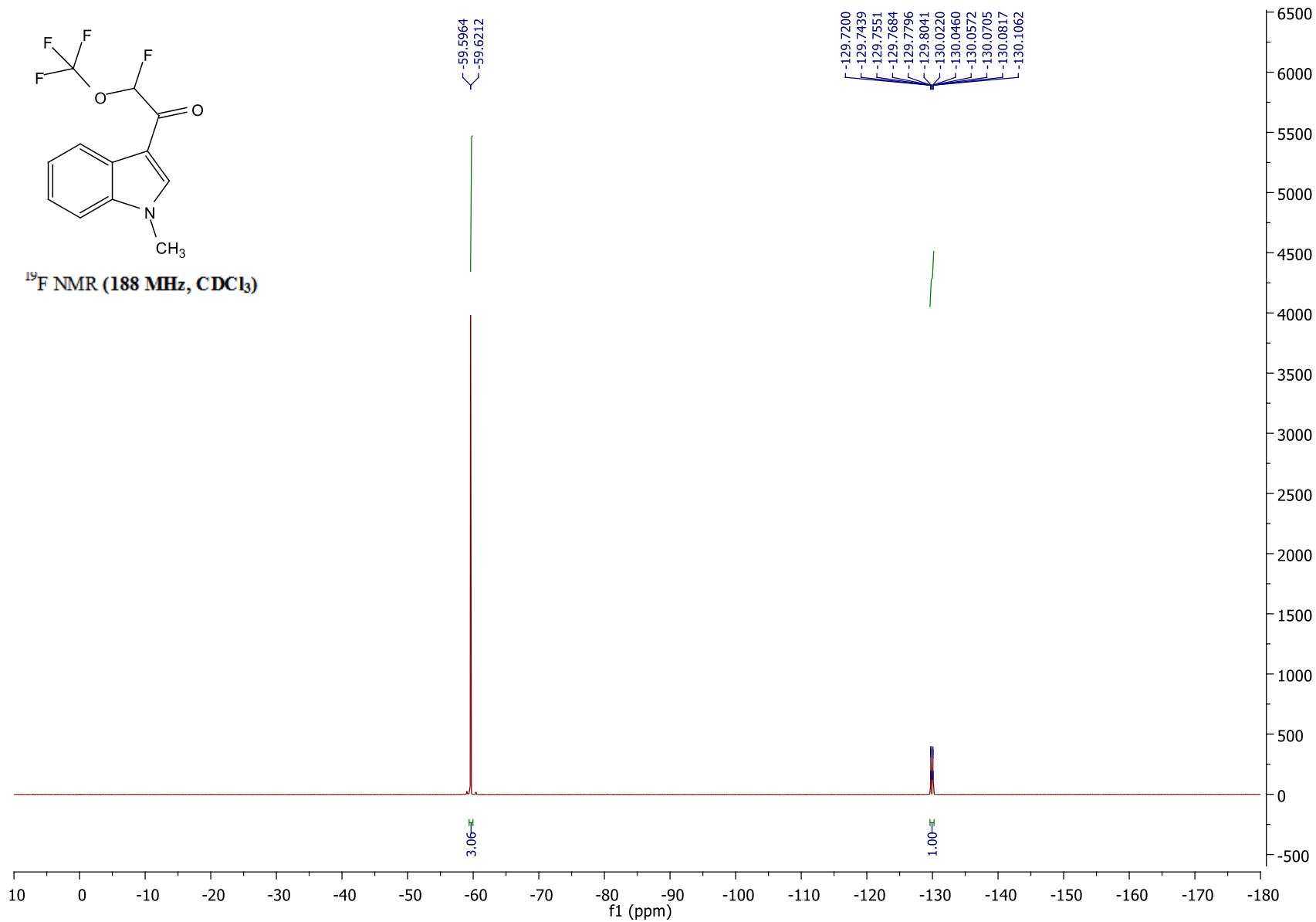
1-(5-Bromo-1*H*-indol-3-yl)-2-fluoro-2-(trifluoromethoxy)ethanone (**4f**)



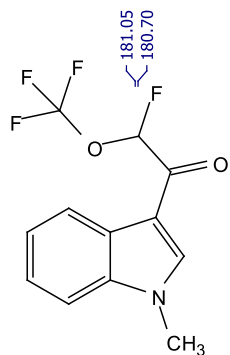
2-Fluoro-1-(1-methyl-1*H*-indol-3-yl)-2-(trifluoromethoxy)ethanone (**4g**)



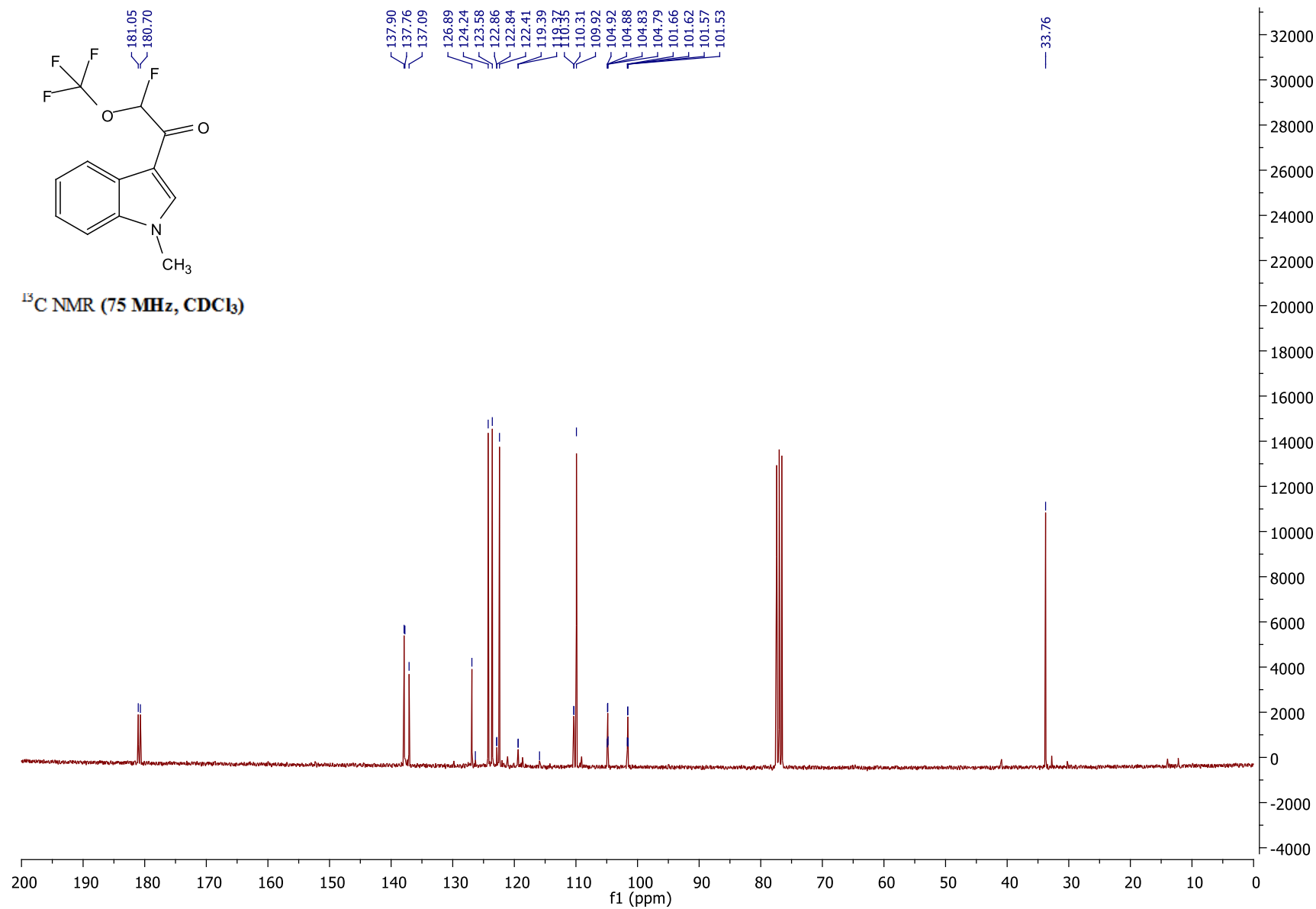
2-Fluoro-1-(1-methyl-1*H*-indol-3-yl)-2-(trifluoromethoxy)ethanone (**4g**)



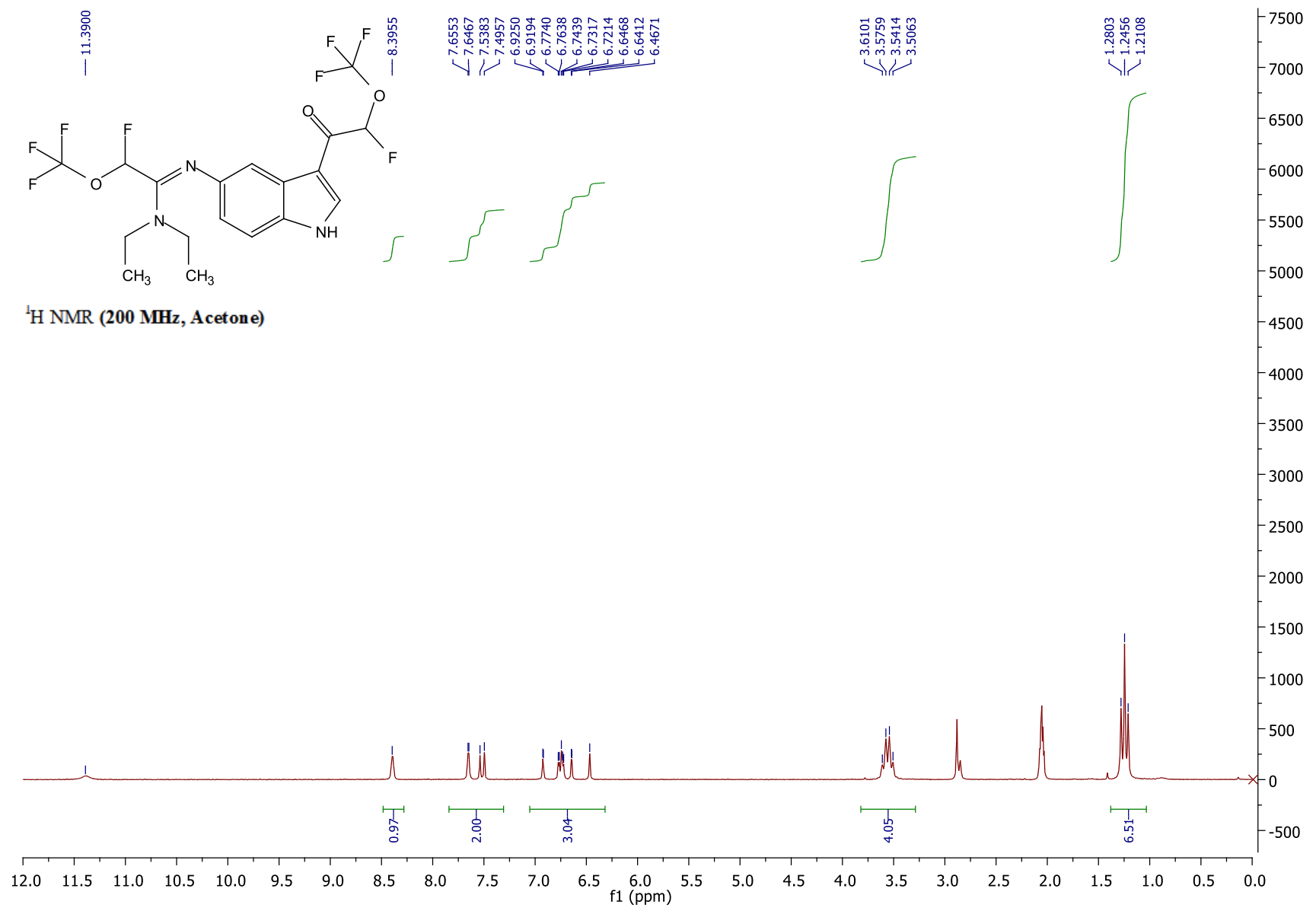
2-Fluoro-1-(1-methyl-1*H*-indol-3-yl)-2-(trifluoromethoxy)ethanone (**4g**)



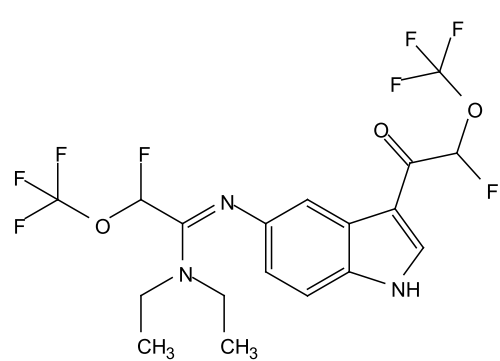
¹³C NMR (75 MHz, CDCl₃)



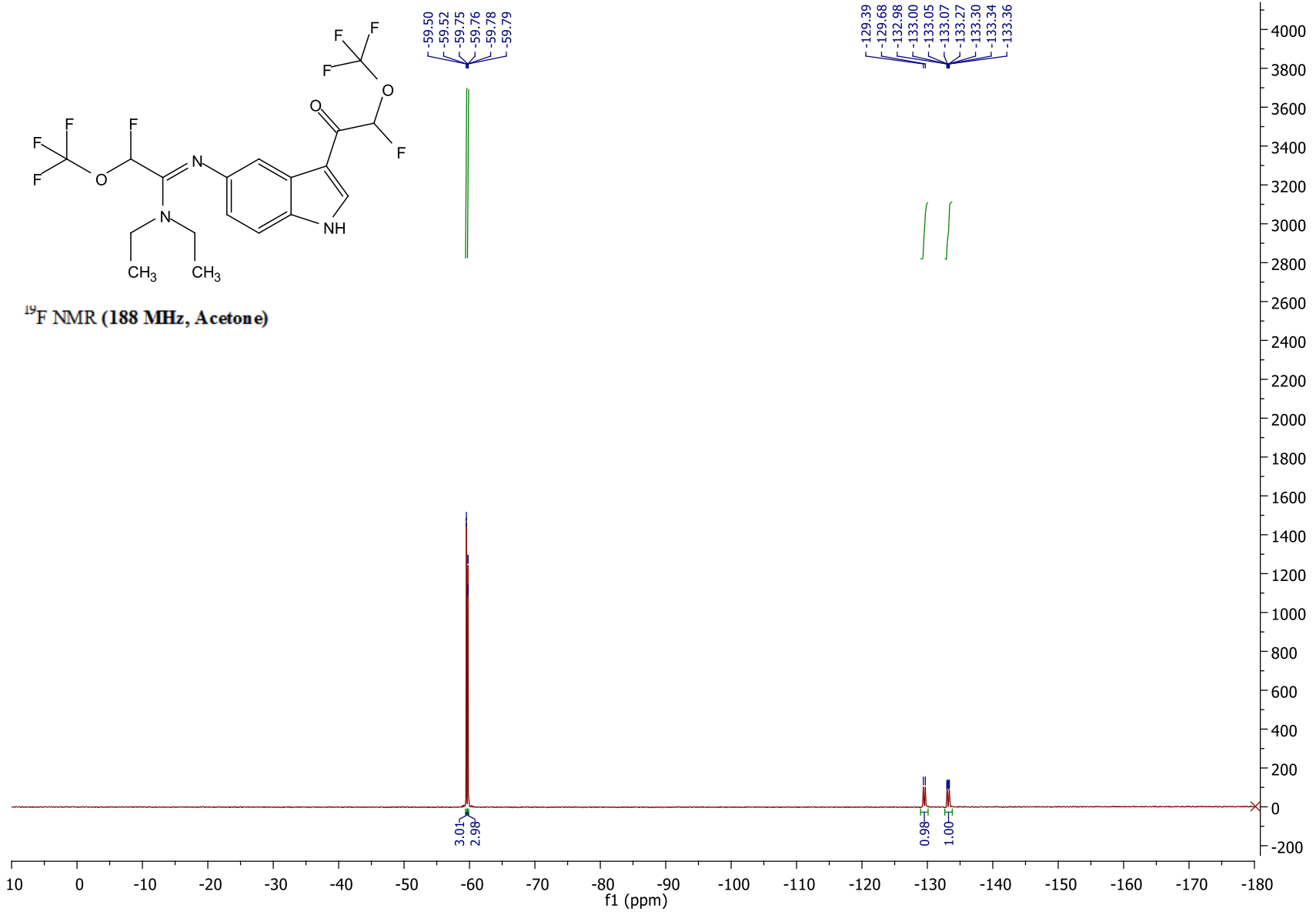
(Z)-N,N-Diethyl-2-fluoro-N'-(3-(2-fluoro-2-(trifluoromethoxy)acetyl)-1H-indol-5-yl)-2-(trifluoromethoxy)acetimidamide (4h)



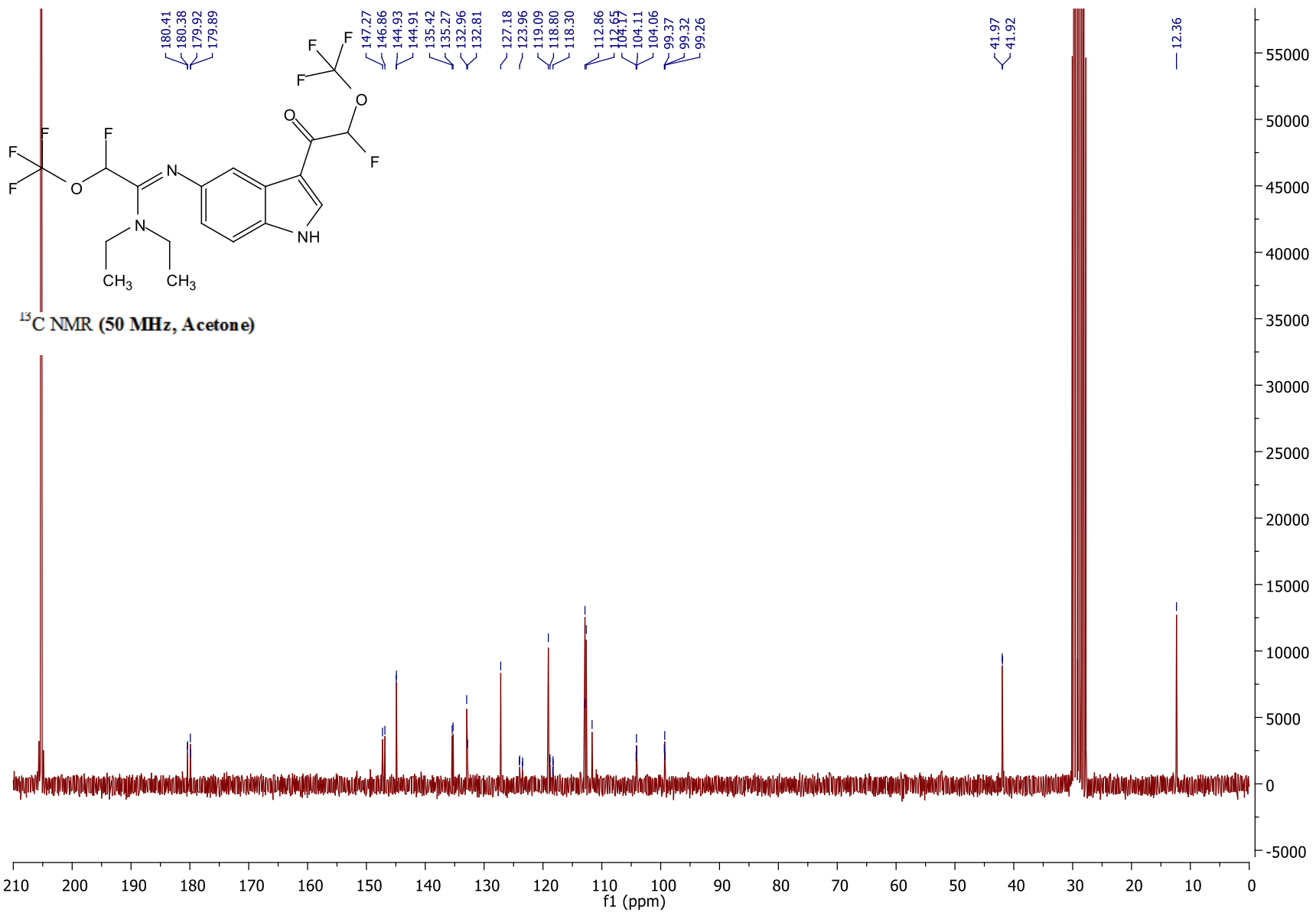
(Z)-N,N-Diethyl-2-fluoro-N'-(3-(2-fluoro-2-(trifluoromethoxy)acetyl)-1H-indol-5-yl)-2-(trifluoromethoxy)acetimidamide (4h)



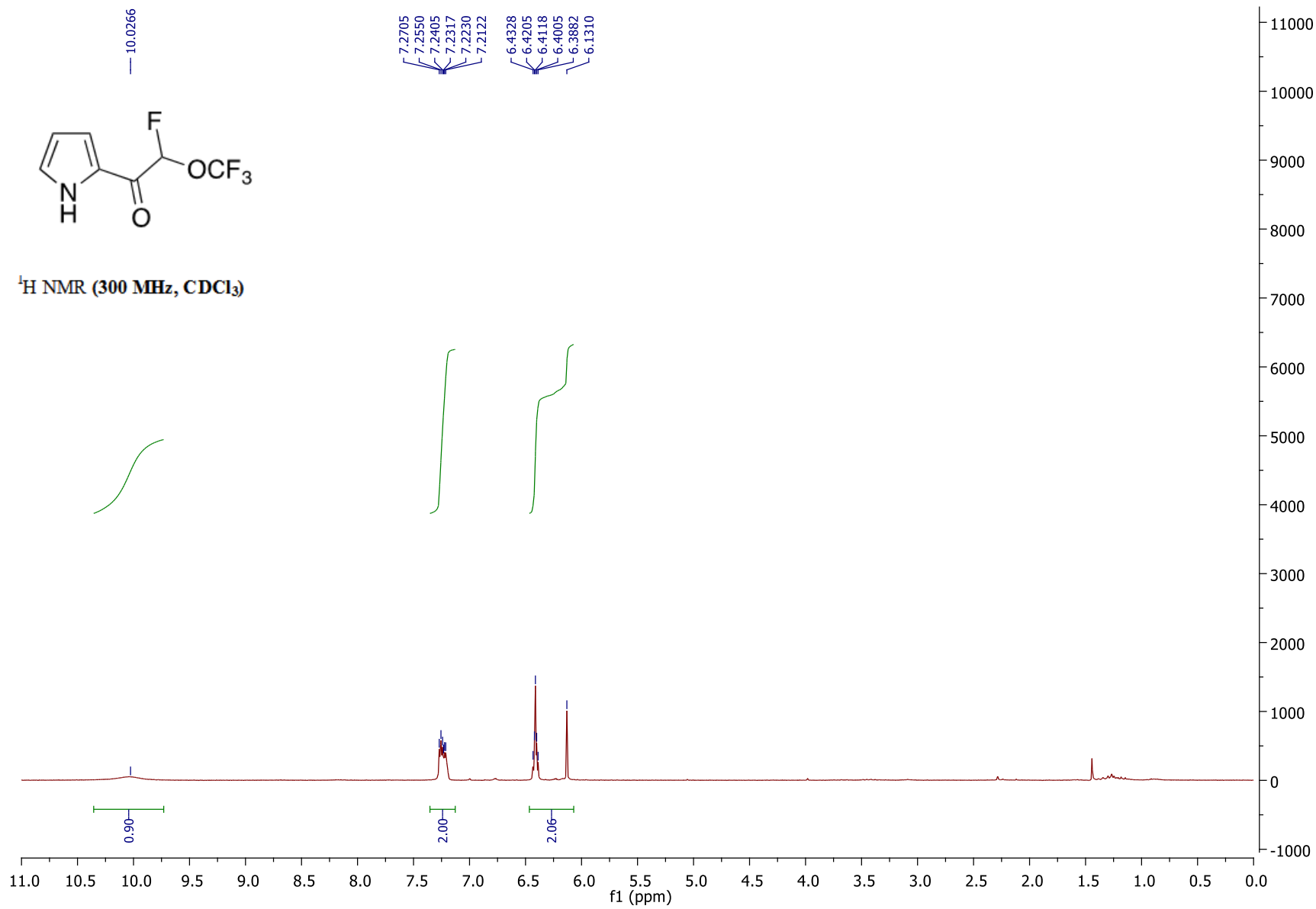
¹⁹F NMR (188 MHz, Acetone)



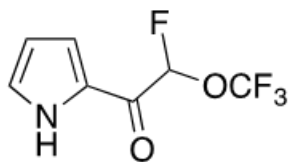
(Z)-N,N-Diethyl-2-fluoro-N'-(3-(2-fluoro-2-(trifluoromethoxy)acetyl)-1H-indol-5-yl)-2-(trifluoromethoxy)acetimidamide (4h)



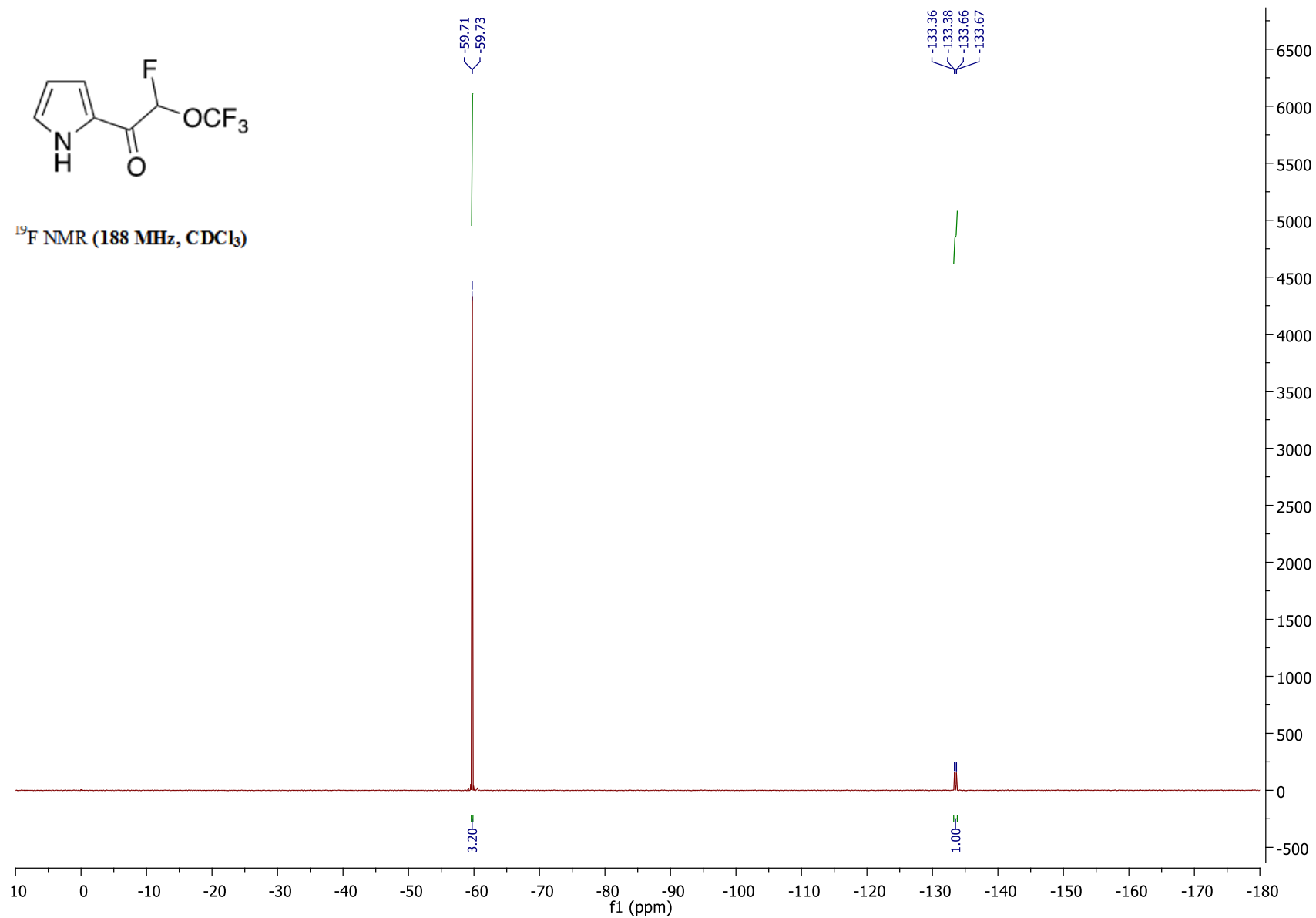
2-Fluoro-1-(1H-pyrrol-2-yl)-2-(trifluoromethoxy)ethanone (5a)



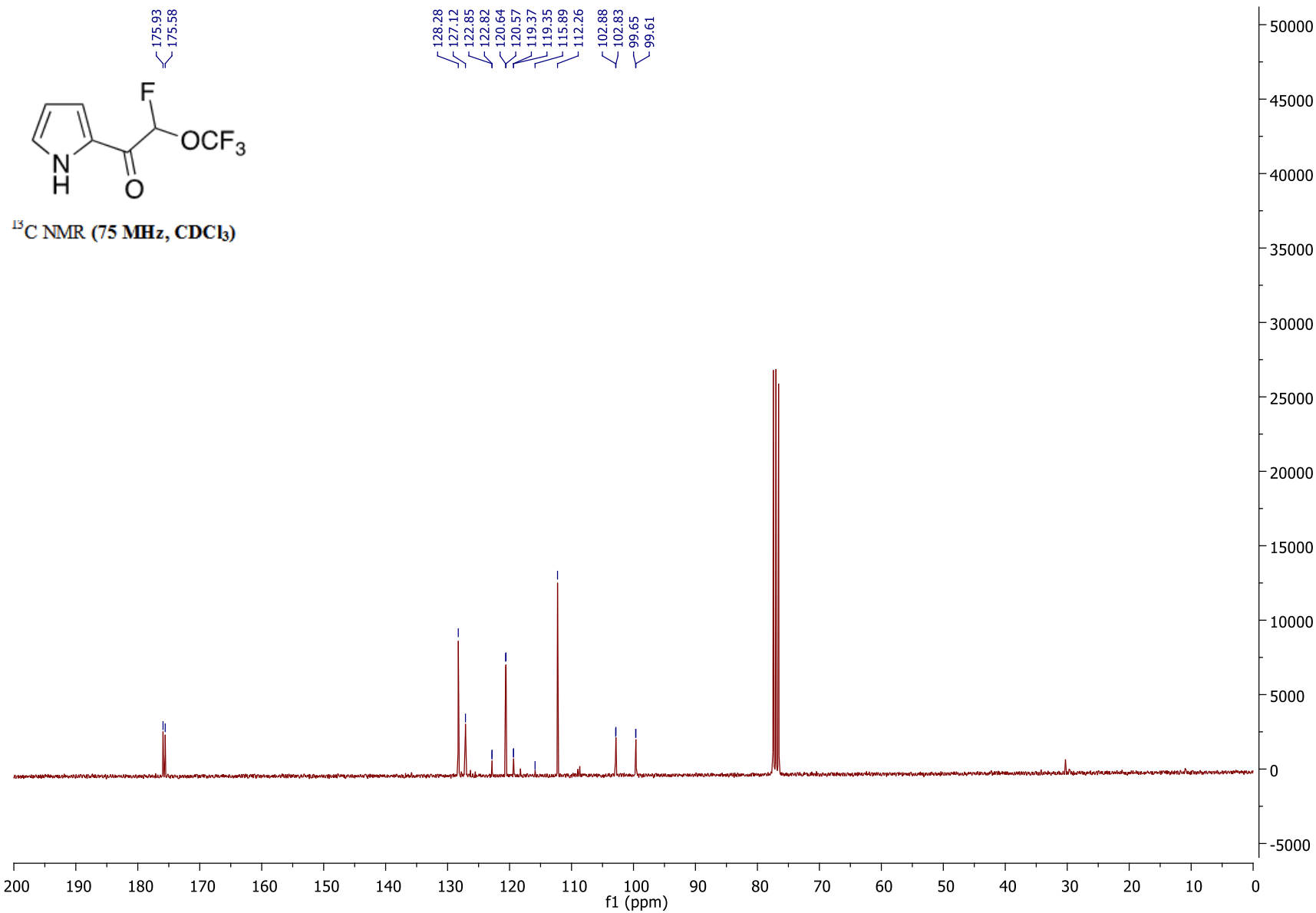
2-Fluoro-1-(1*H*-pyrrol-2-yl)-2-(trifluoromethoxy)ethanone (**5a**)



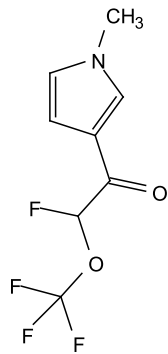
^{19}F NMR (188 MHz, CDCl_3)



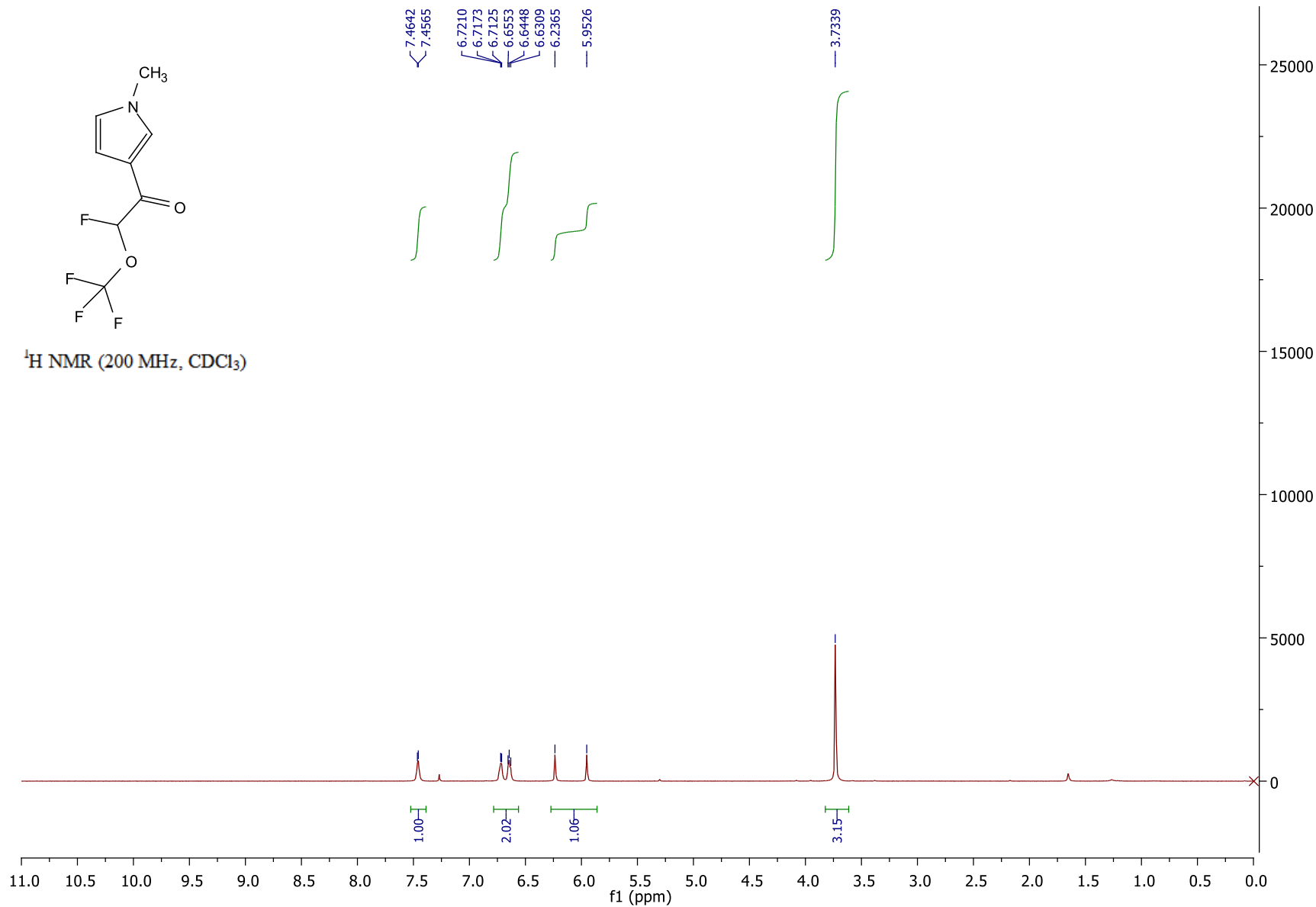
2-Fluoro-1-(1H-pyrrol-2-yl)-2-(trifluoromethoxy)ethanone (5a)



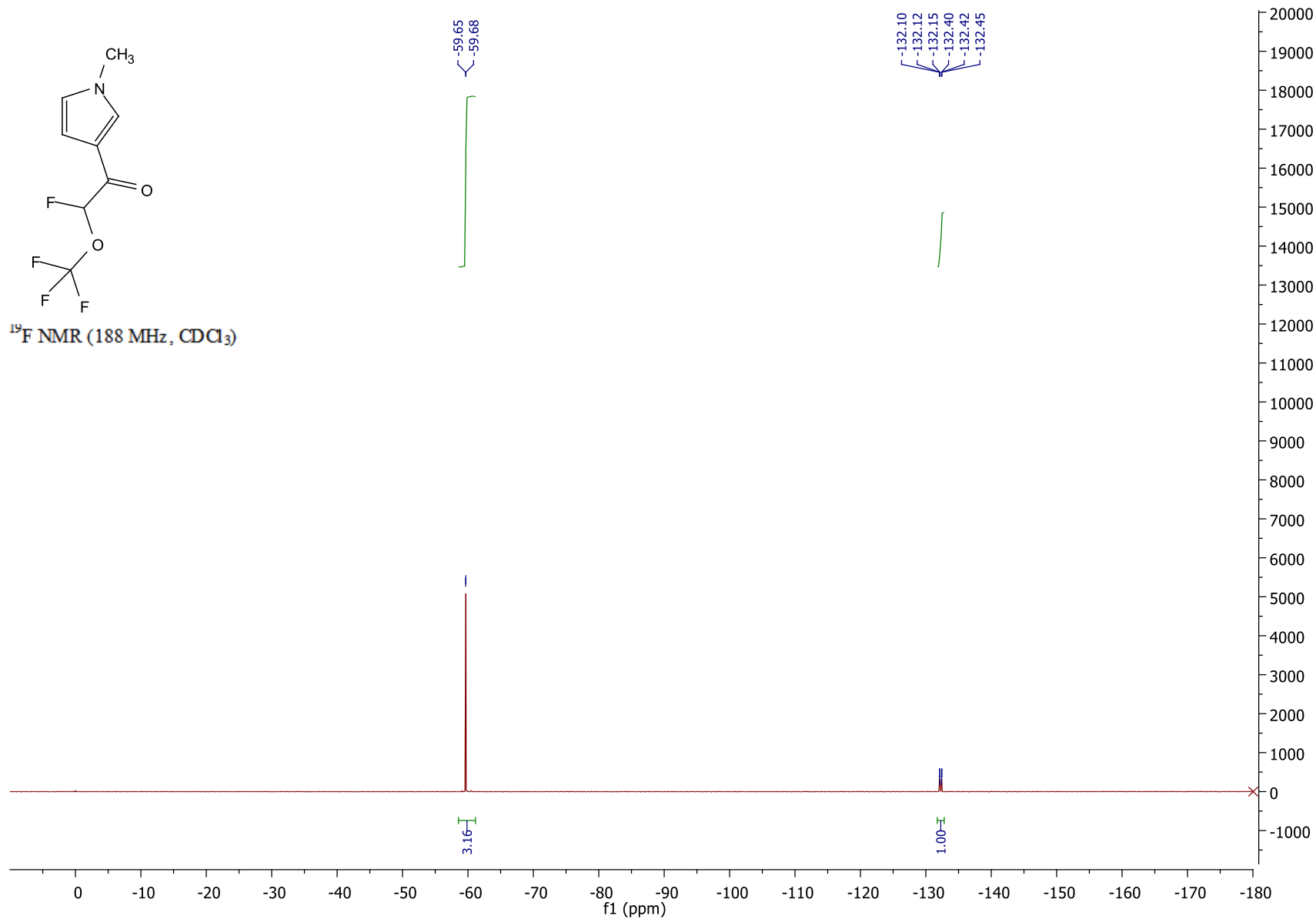
2-Fluoro-1-(1-methyl-1*H*-pyrrol-2-yl)-2-(trifluoromethoxy)ethanone (**5b**)



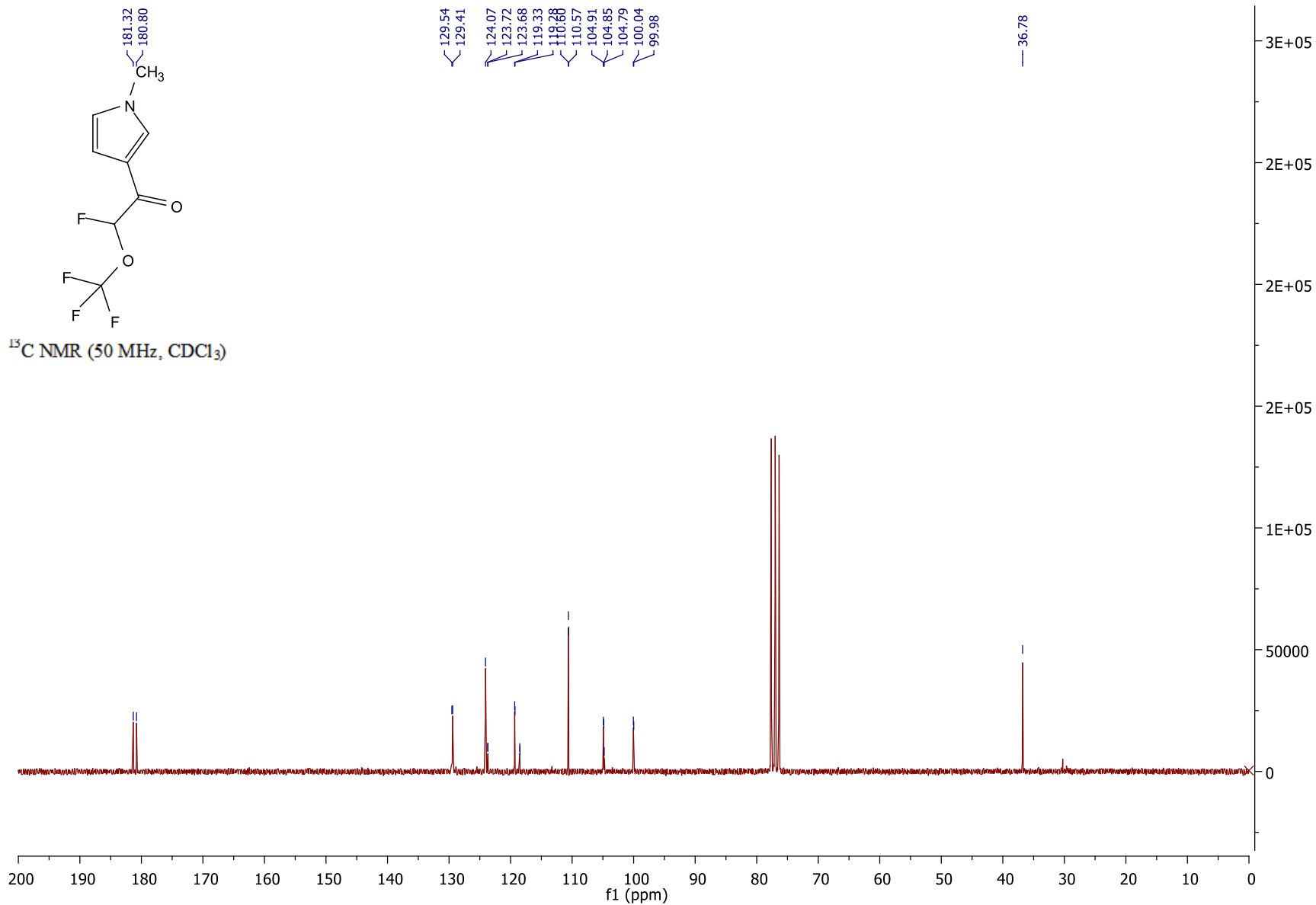
¹H NMR (200 MHz, CDCl₃)



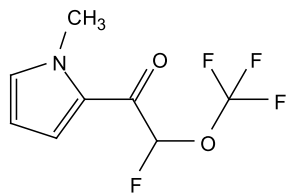
2-Fluoro-1-(1-methyl-1*H*-pyrrol-2-yl)-2-(trifluoromethoxy)ethanone (**5b**)



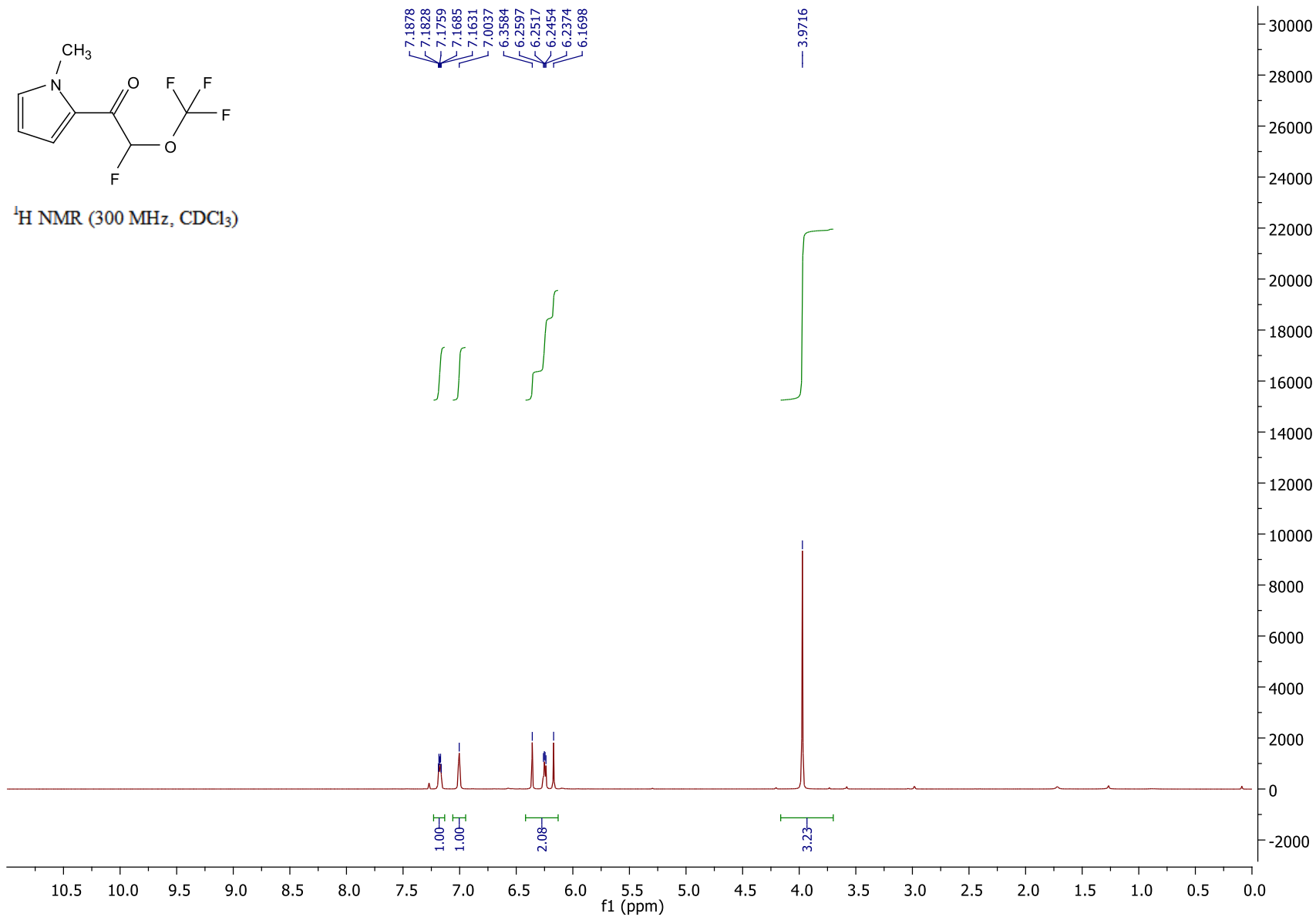
2-Fluoro-1-(1-methyl-1*H*-pyrrol-2-yl)-2-(trifluoromethoxy)ethanone (**5b**)



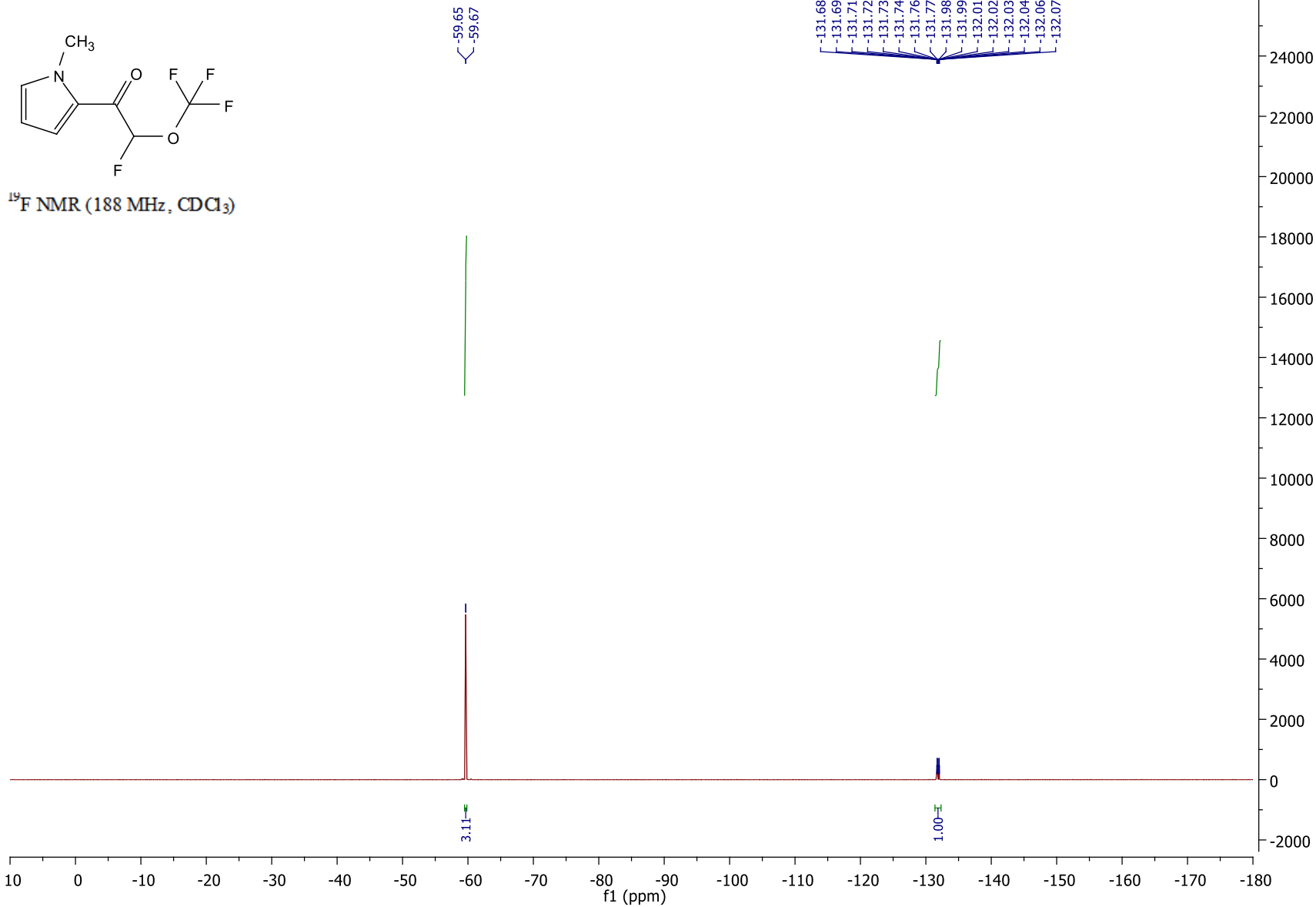
2-Fluoro-1-(1-methyl-1*H*-pyrrol-3-yl)-2-(trifluoromethoxy)ethanone (**5c**)



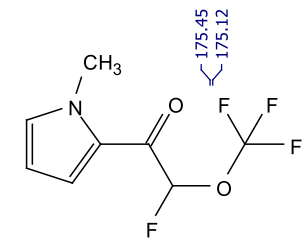
$^1\text{H NMR}$ (300 MHz, CDCl_3)



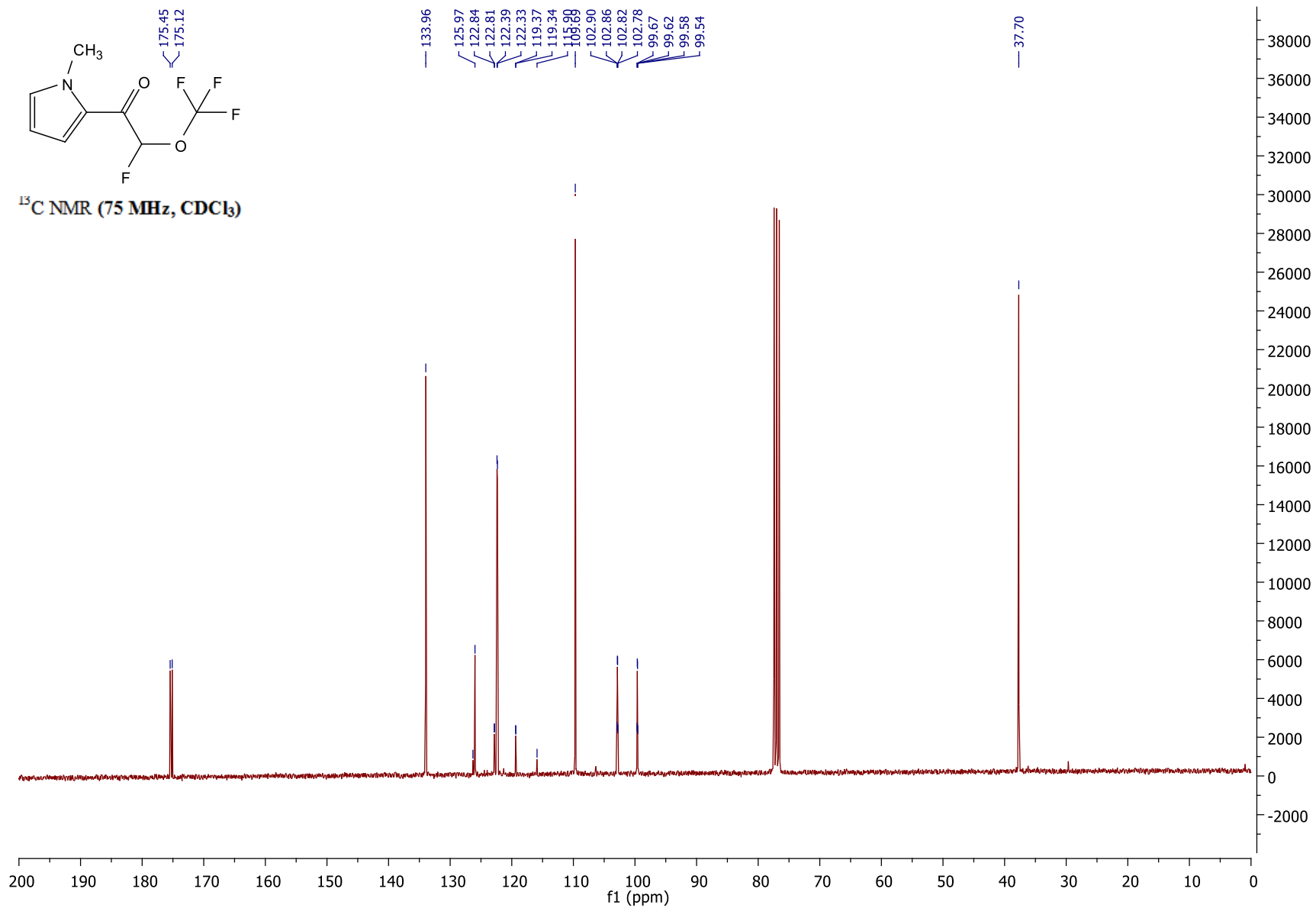
2-Fluoro-1-(1-methyl-1H-pyrrol-3-yl)-2-(trifluoromethoxy)ethanone (**5c**)



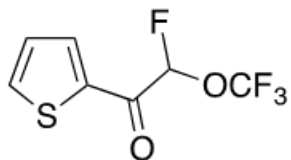
2-Fluoro-1-(1-methyl-1H-pyrrol-3-yl)-2-(trifluoromethoxy)ethanone (**5c**)



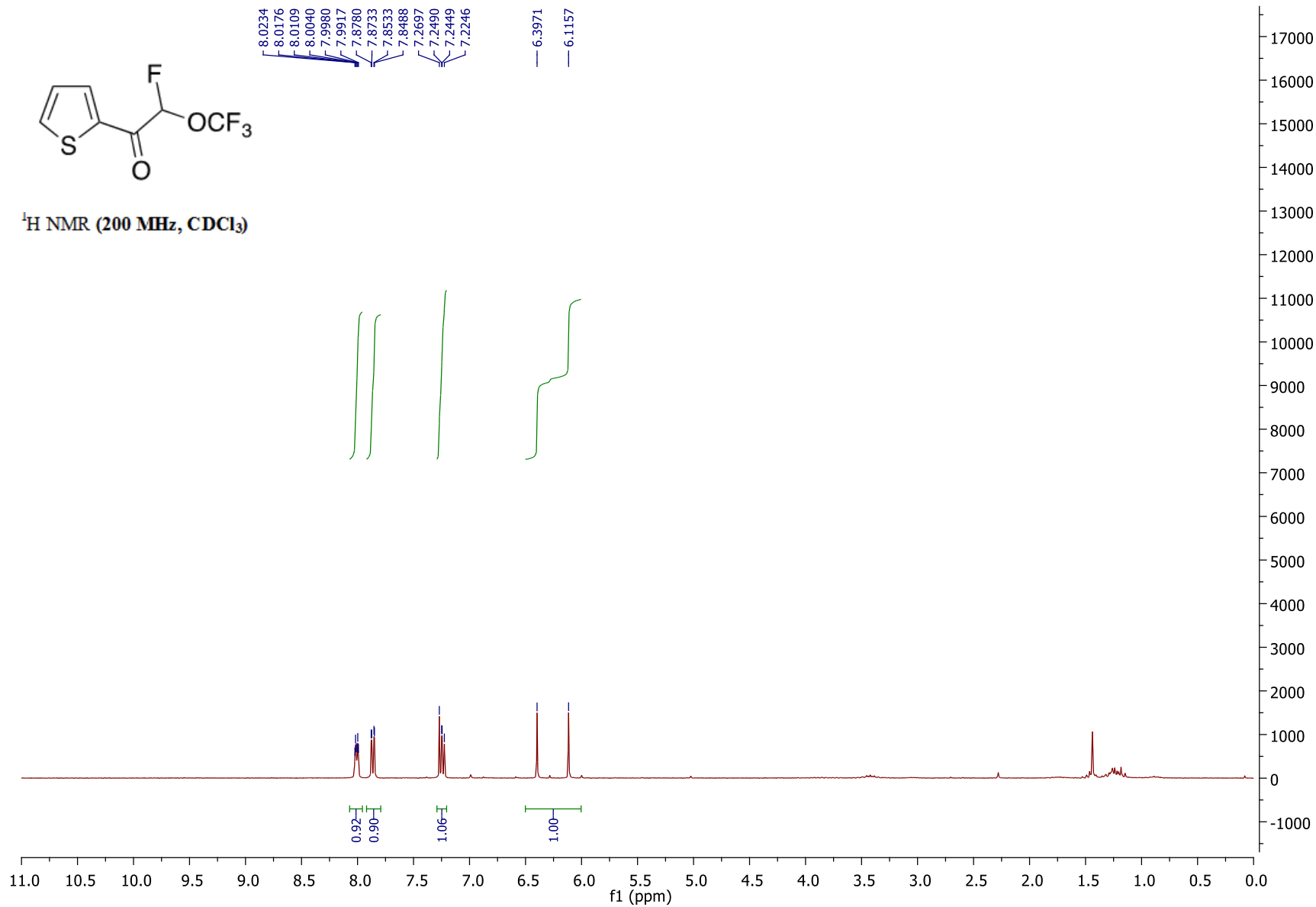
^{13}C NMR (75 MHz, CDCl_3)



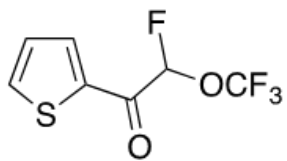
2-Fluoro-1-(thiophen-2-yl)-2-(trifluoromethoxy)ethanone (5d)



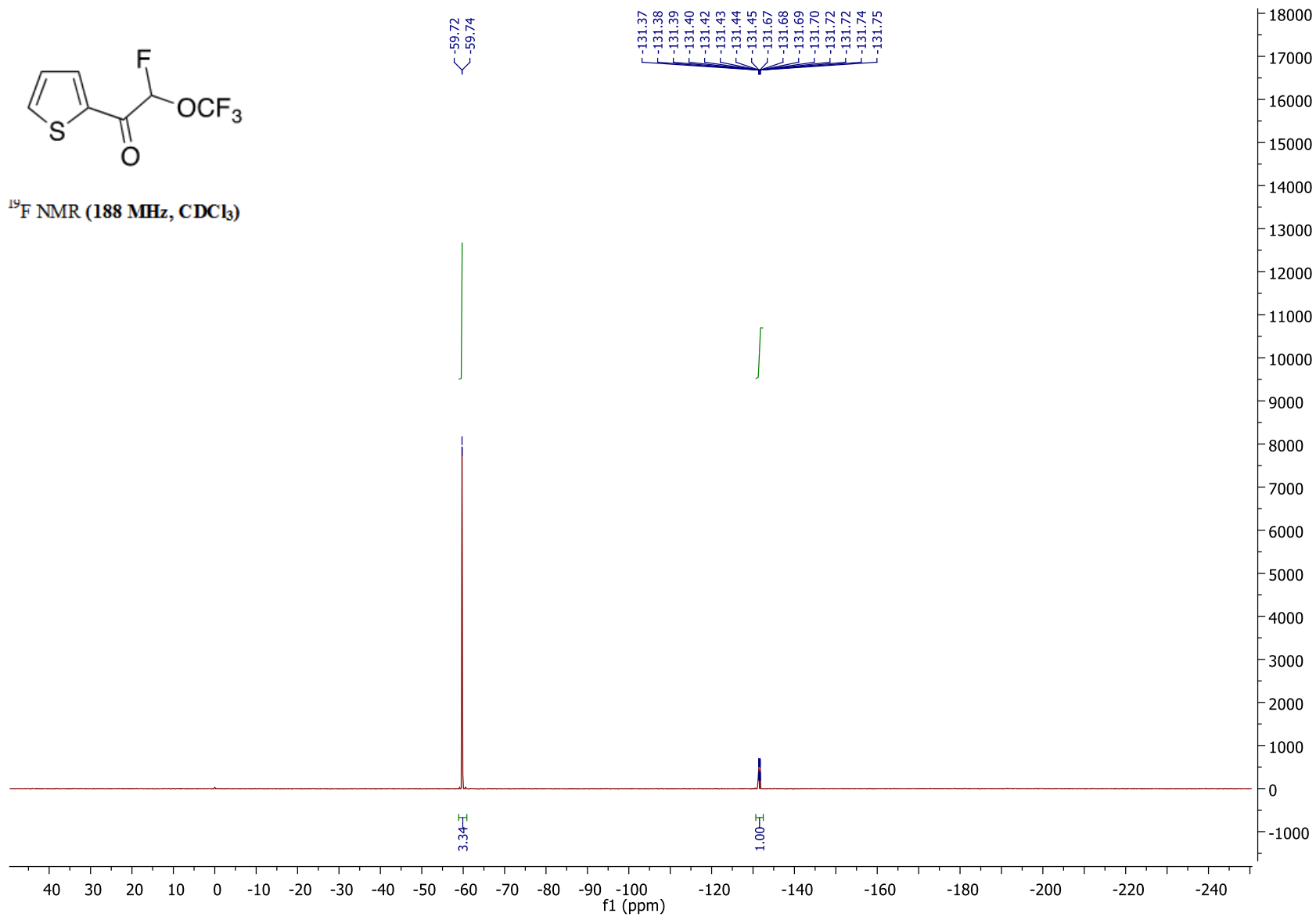
^1H NMR (200 MHz, CDCl_3)



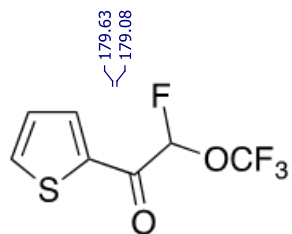
2-Fluoro-1-(thiophen-2-yl)-2-(trifluoromethoxy)ethanone (5d)



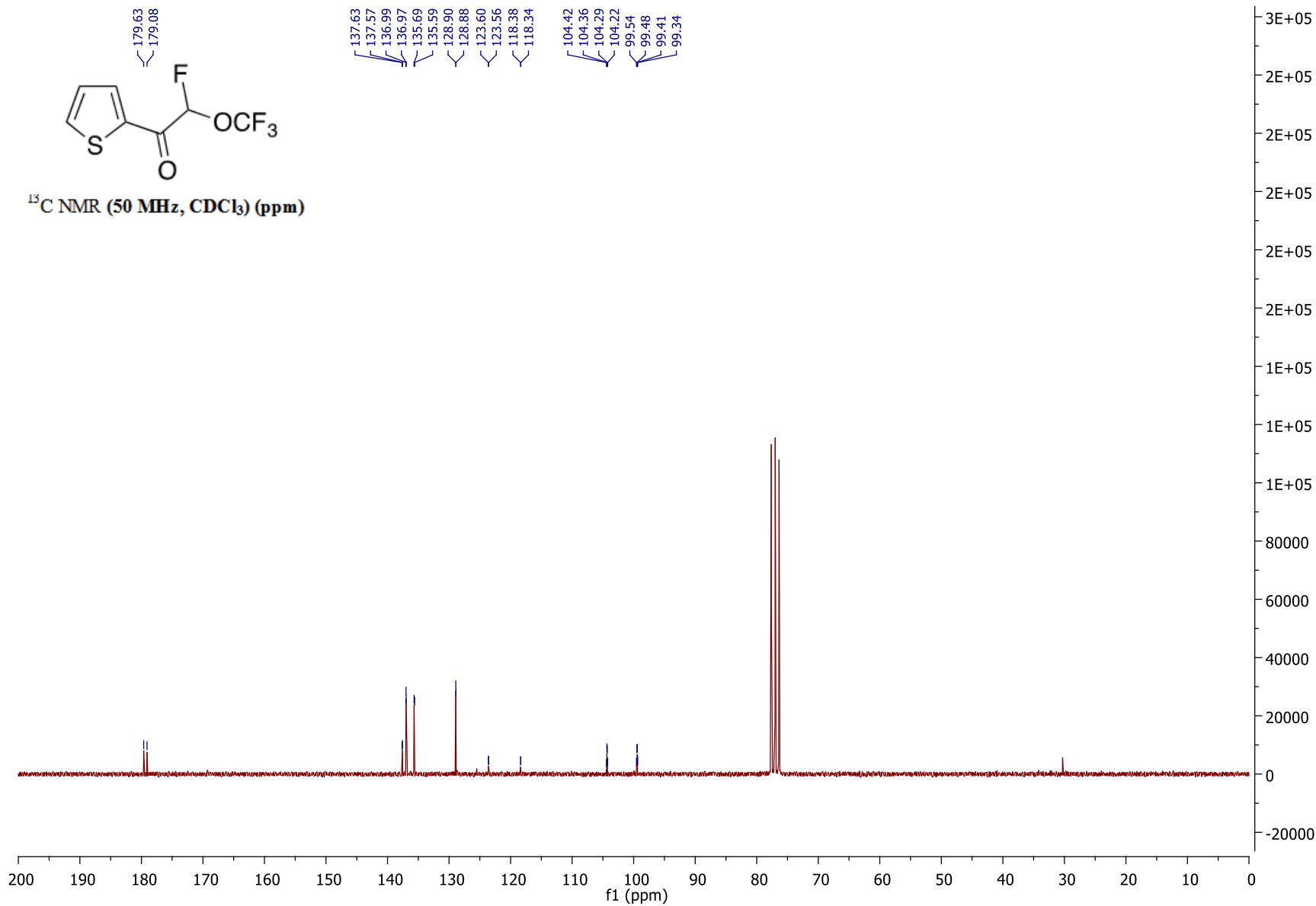
^{19}F NMR (188 MHz, CDCl_3)



2-Fluoro-1-(thiophen-2-yl)-2-(trifluoromethoxy)ethanone (**5d**)

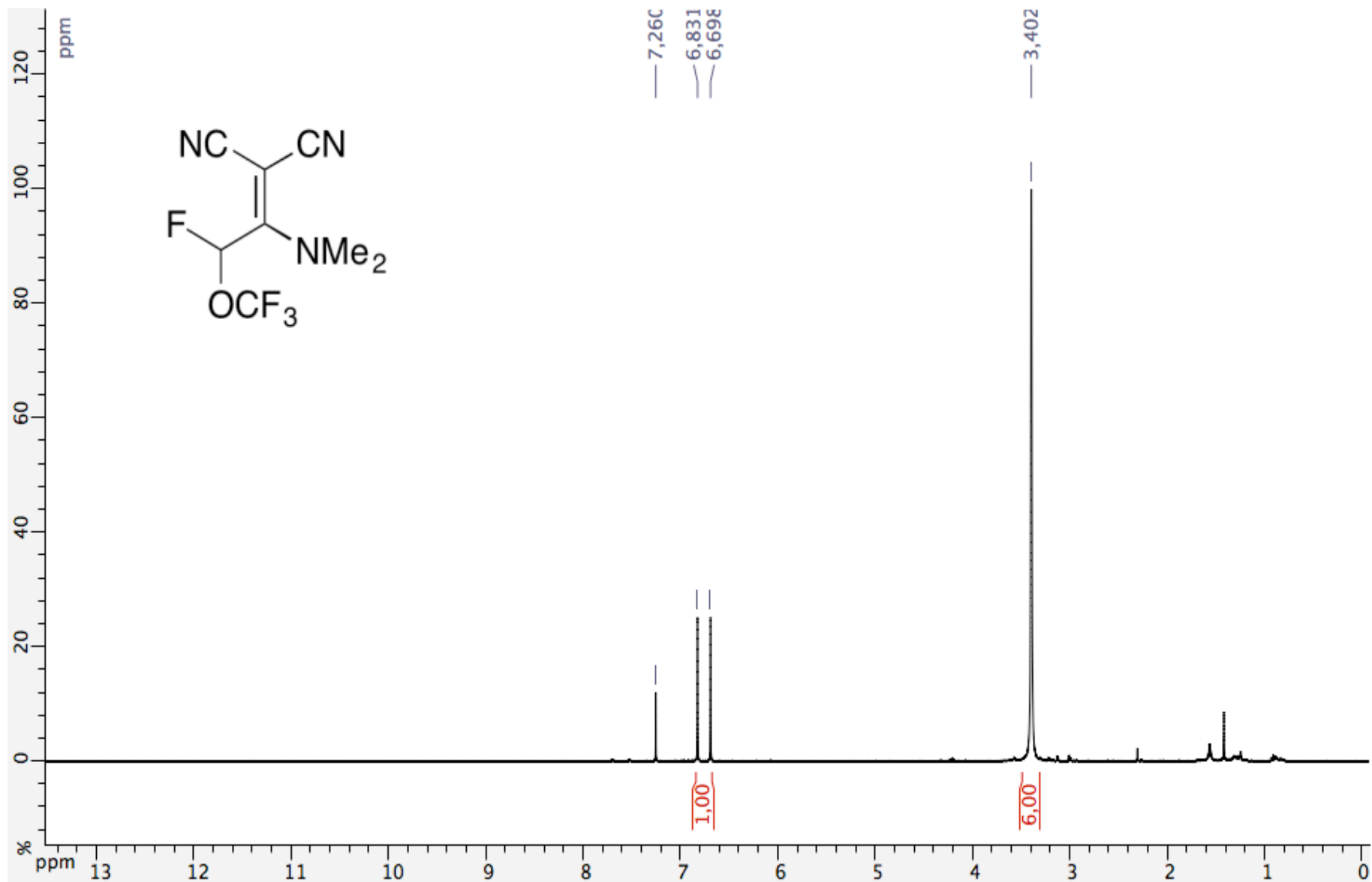
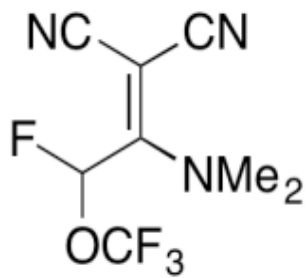


^{13}C NMR (50 MHz, CDCl_3) (ppm)



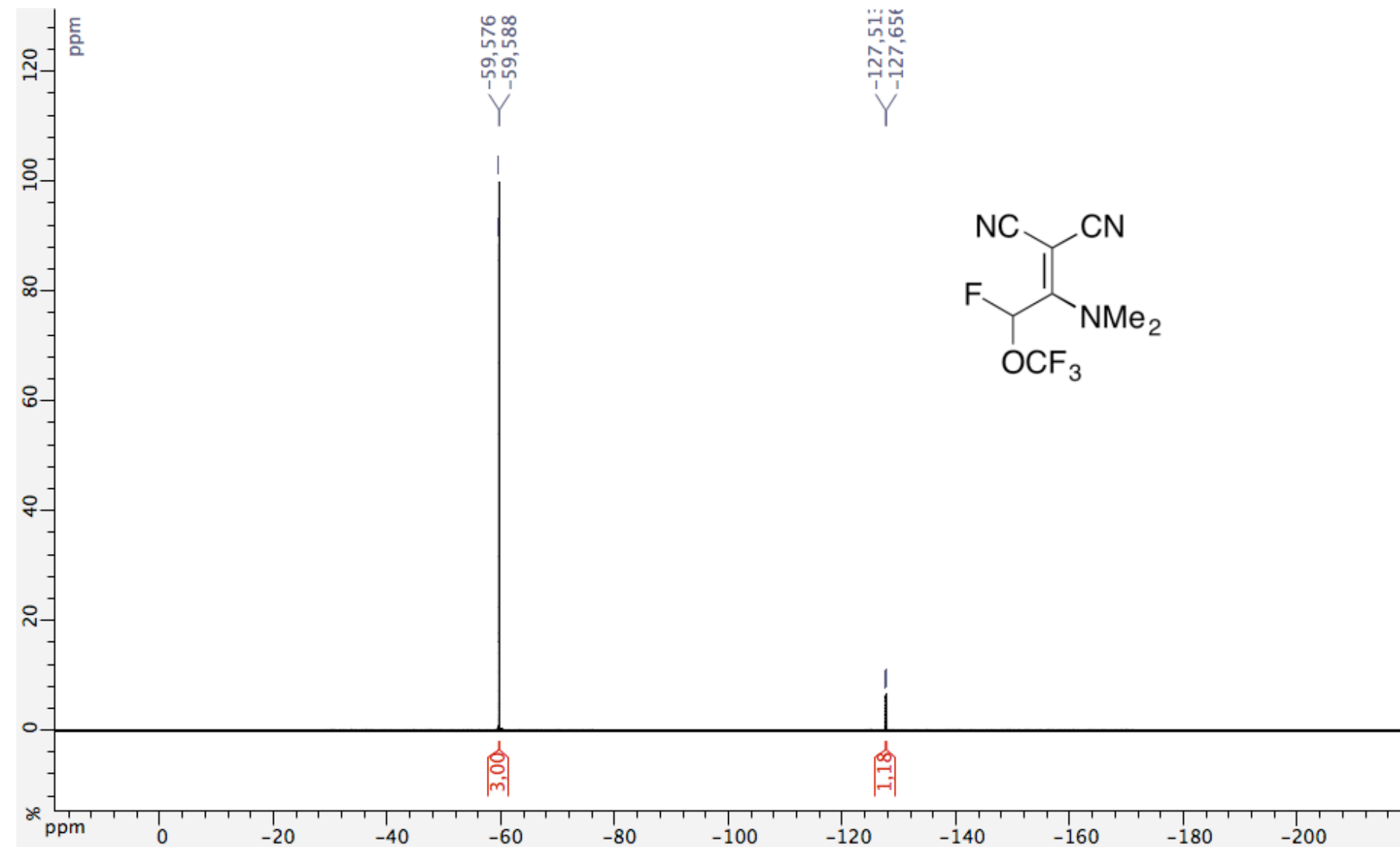
2-(1-(Dimethylamino)-2-fluoro-2-(trifluoromethoxy)ethylidene)malononitrile (**6a**)

^1H NMR (400 MHz, CDCl_3)



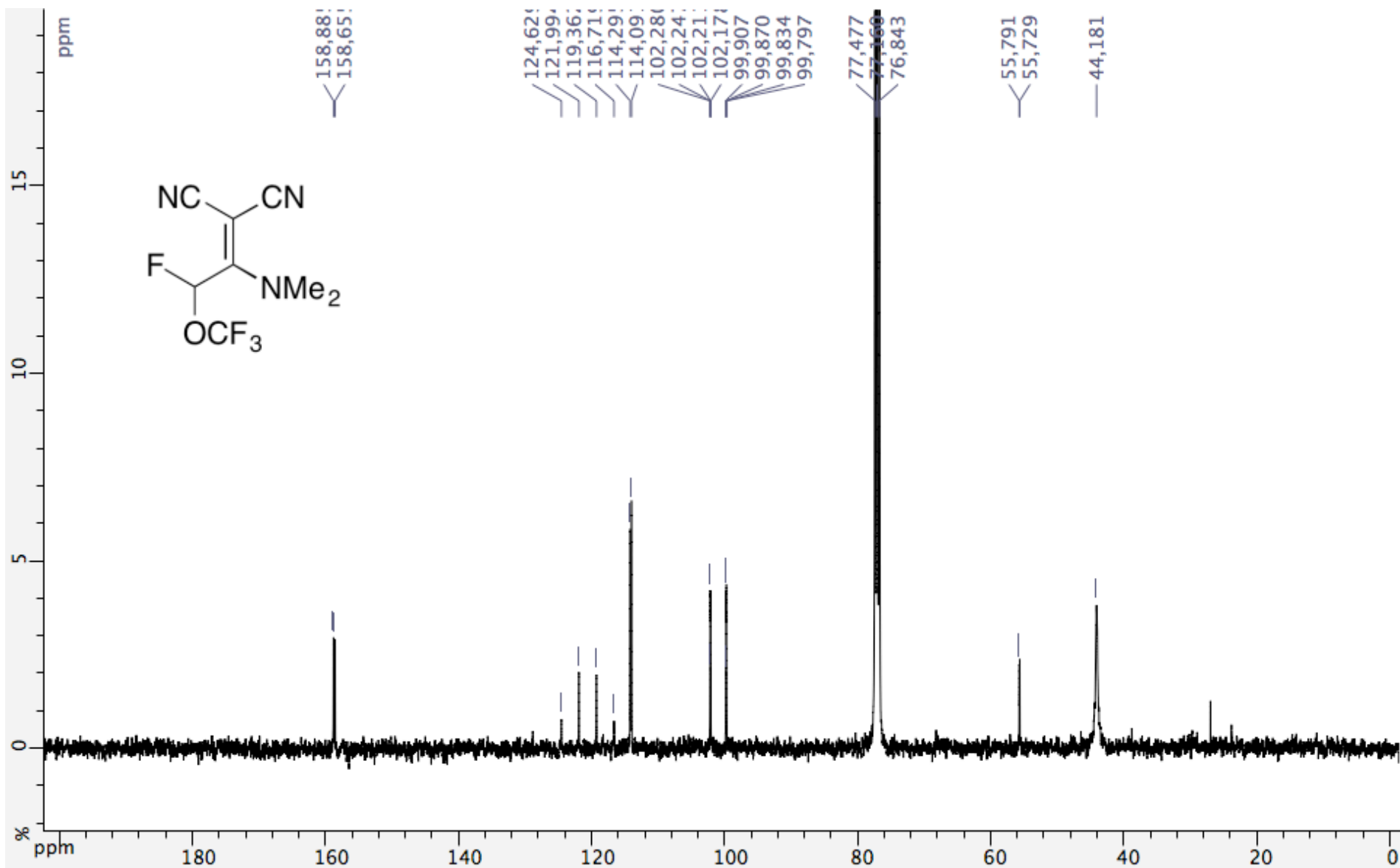
2-(1-(Dimethylamino)-2-fluoro-2-(trifluoromethoxy)ethylidene)malononitrile (**6a**)

^{19}F NMR (376 MHz, CDCl_3)



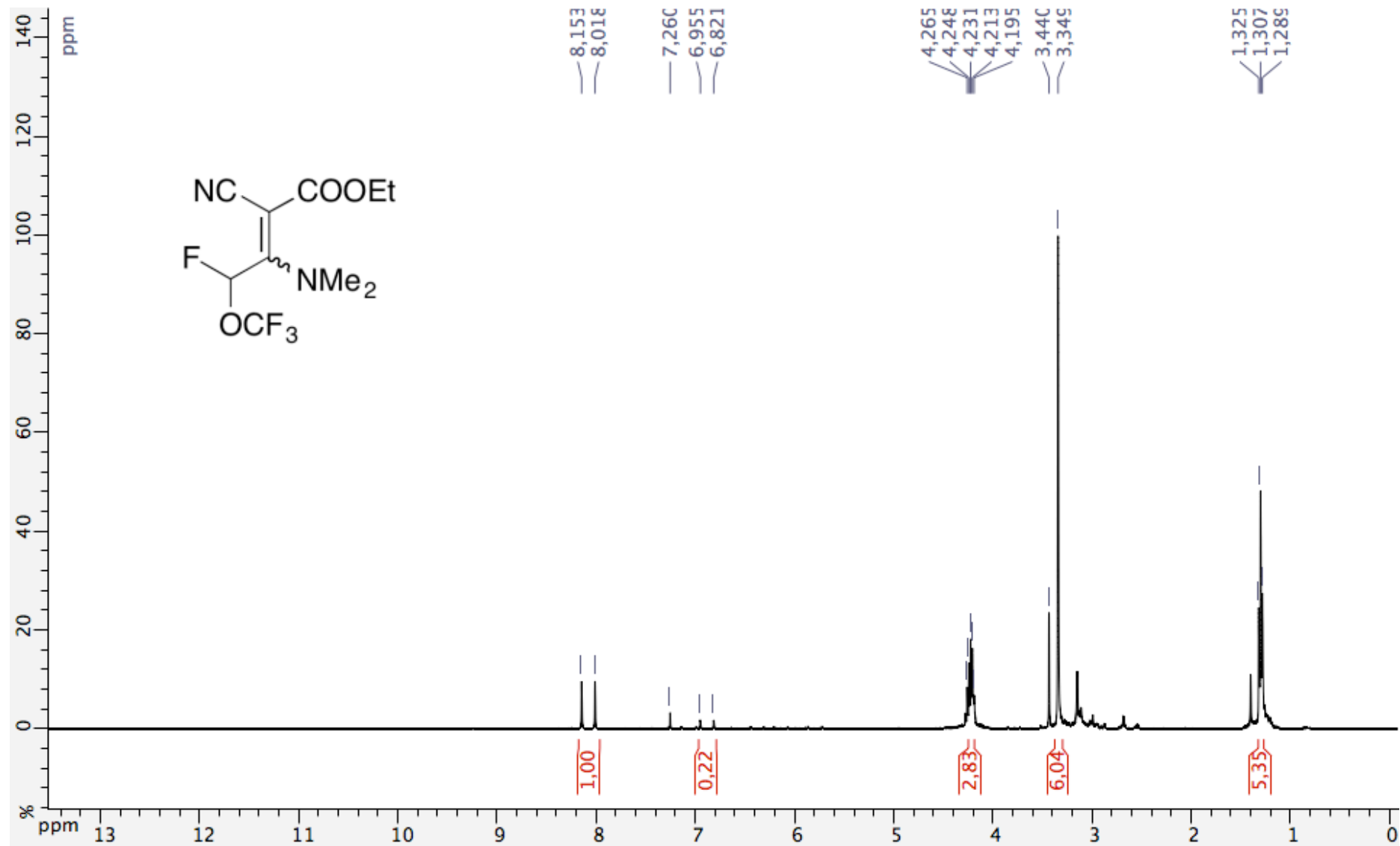
2-(1-(Dimethylamino)-2-fluoro-2-(trifluoromethoxy)ethylidene)malononitrile (6a)

^{13}C NMR (100 MHz, CDCl_3)



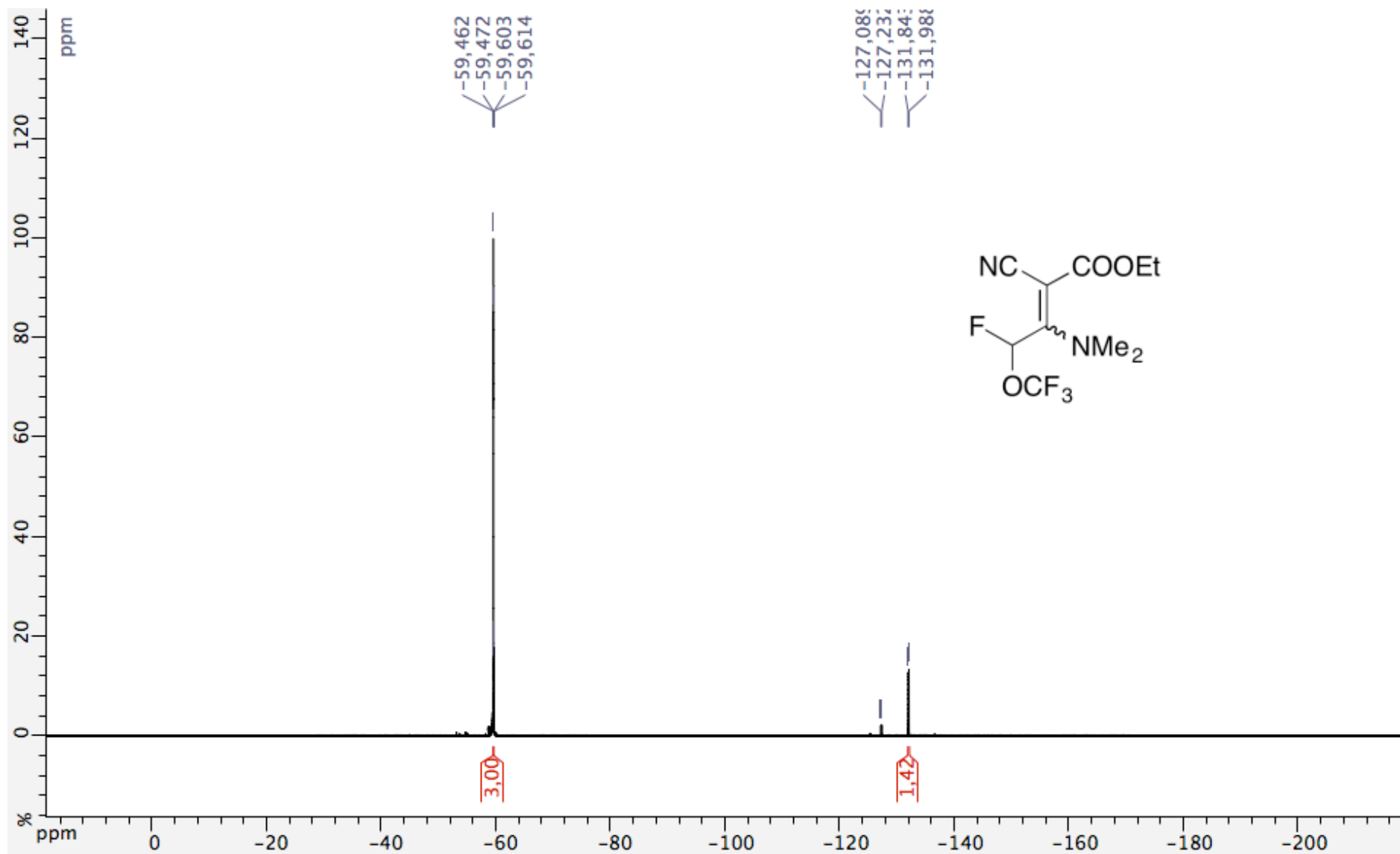
Ethyl 2-cyano-3-(dimethylamino)-4-fluoro-4-(trifluoromethoxy)but-2-enoate (**6b**)

^1H NMR (400 MHz, CDCl_3)



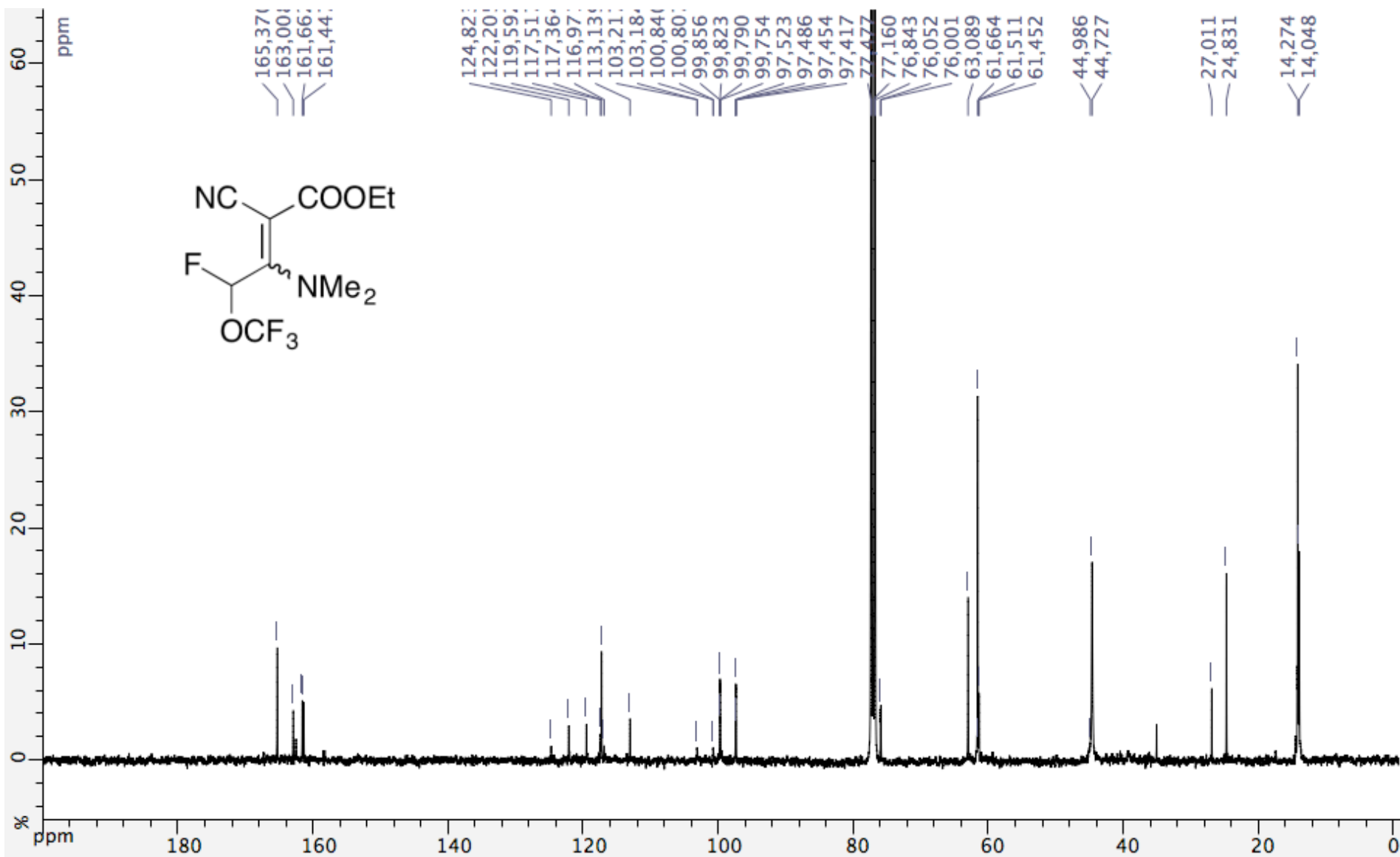
Ethyl 2-cyano-3-(dimethylamino)-4-fluoro-4-(trifluoromethoxy)but-2-enoate (**6b**)

^{19}F NMR (376 MHz, CDCl_3)



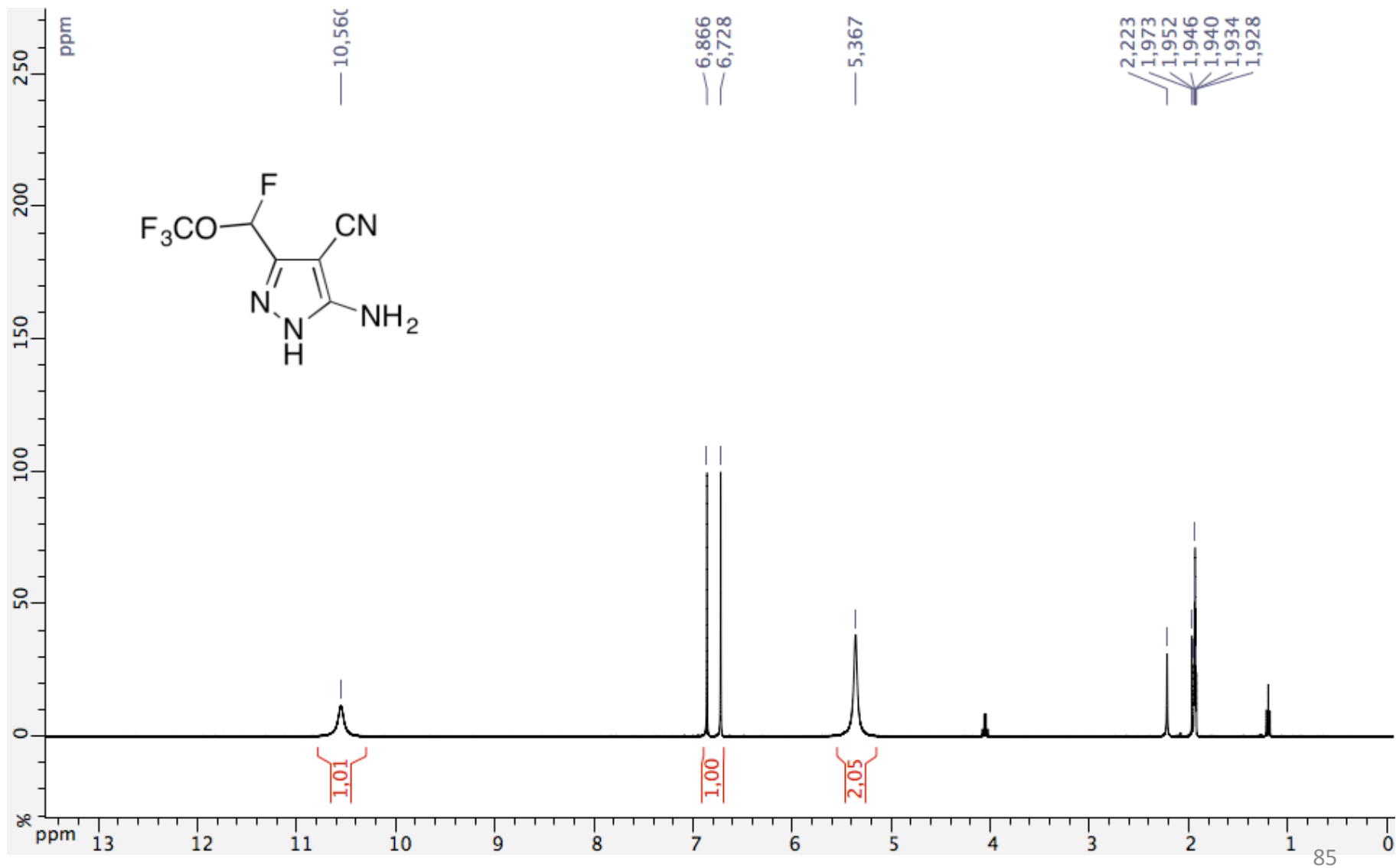
Ethyl 2-cyano-3-(dimethylamino)-4-fluoro-4-(trifluoromethoxy)but-2-enoate (**6b**)

^{13}C NMR (100 MHz, CDCl_3)



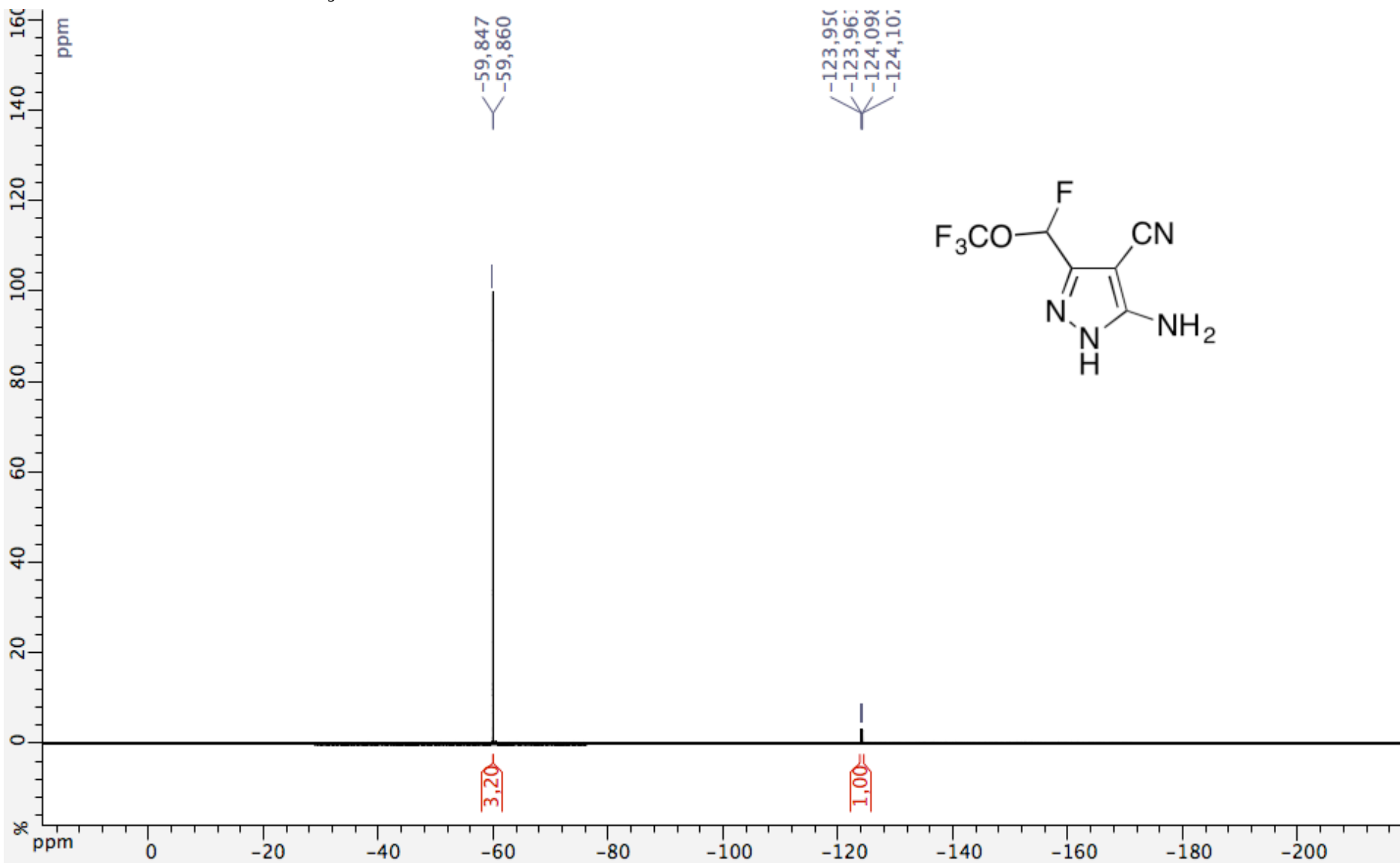
5-Amino-3-(fluoro(trifluoromethoxy)methyl)-1H-pyrazole-4-carbonitrile (**7a**)

^1H NMR (400 MHz, CD_3CN)



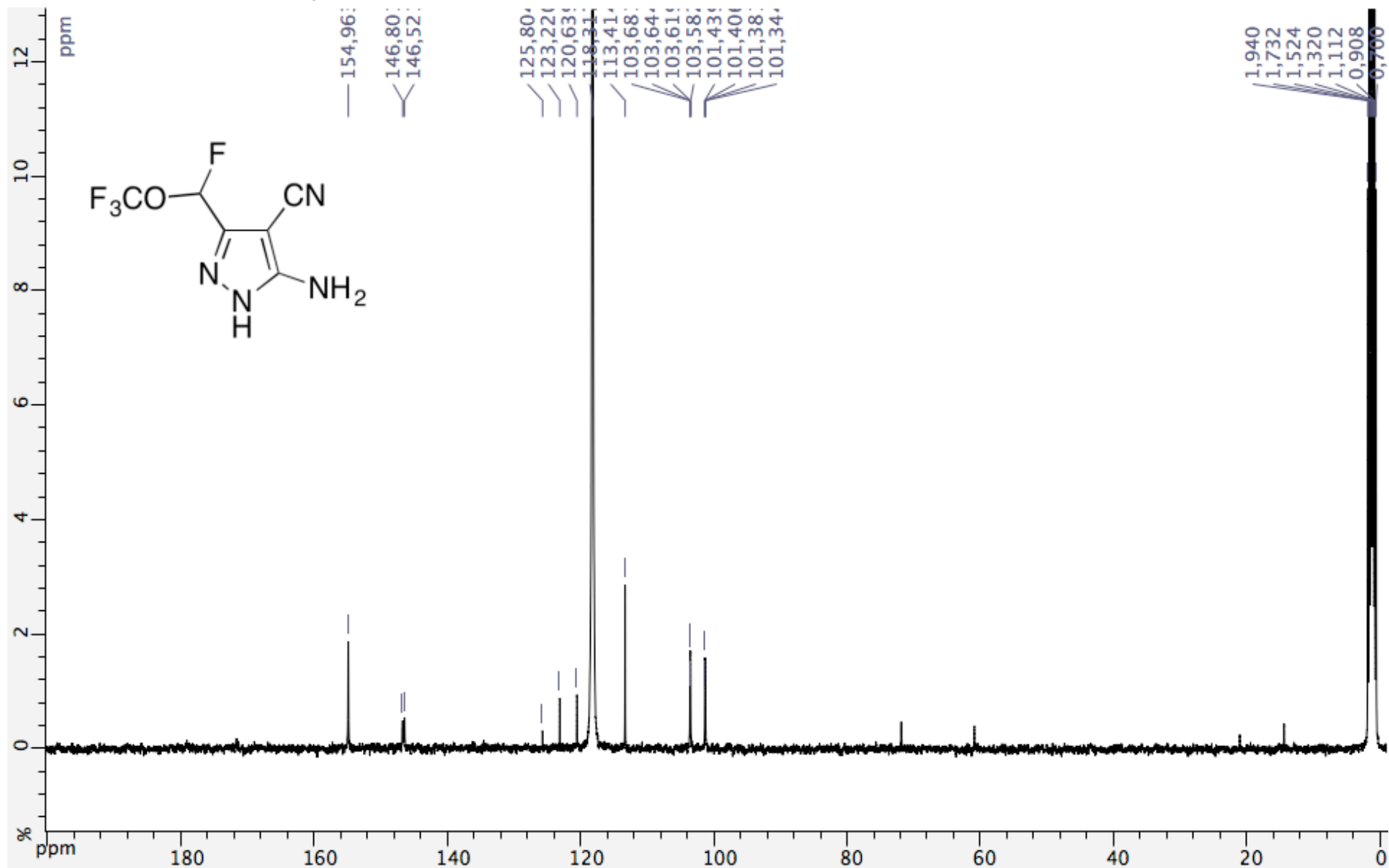
5-Amino-3-(fluoro(trifluoromethoxy)methyl)-1H-pyrazole-4-carbonitrile (**7a**)

^{19}F NMR (376 MHz, CD_3CN)



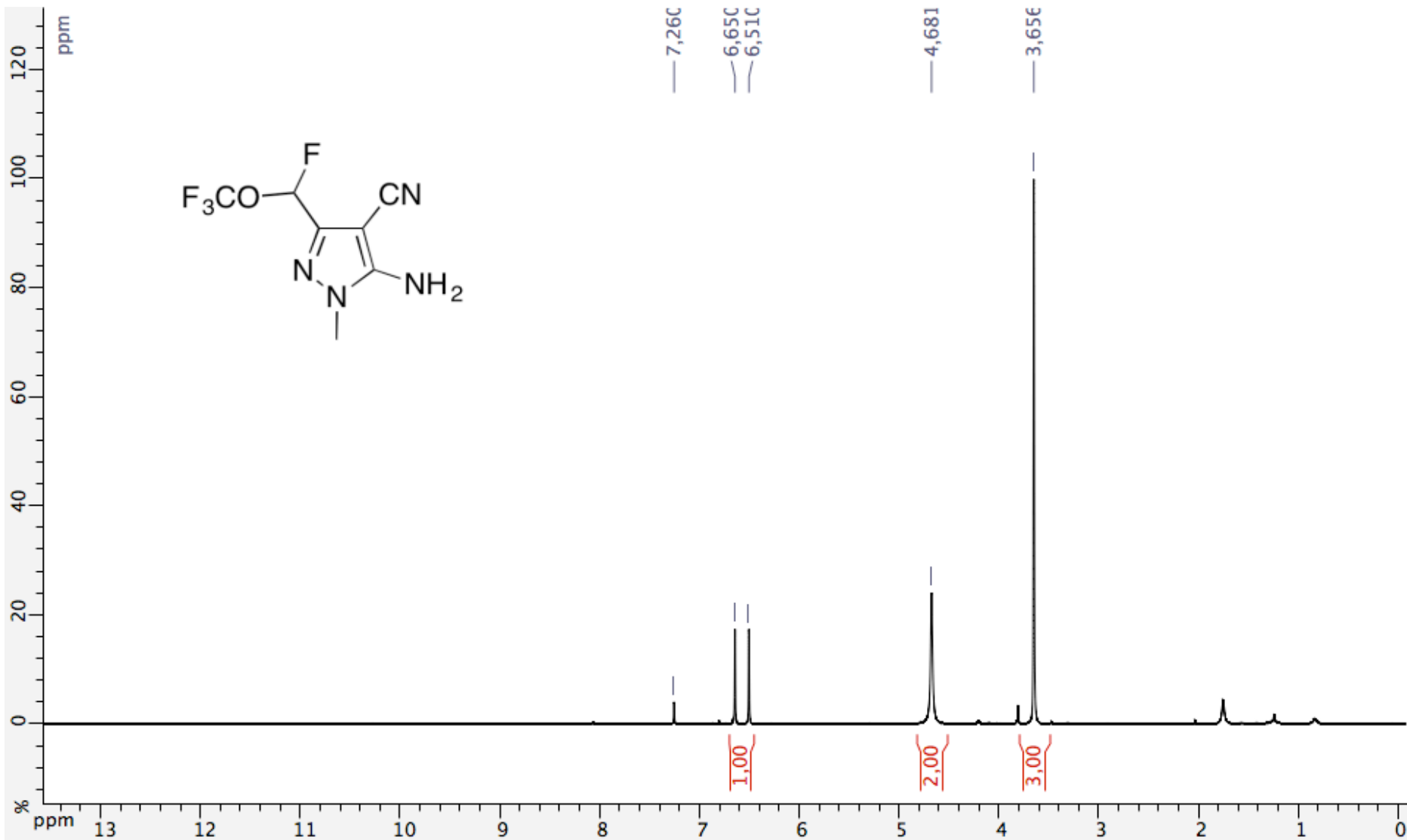
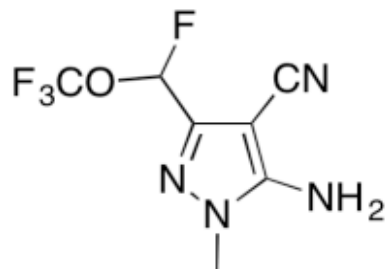
5-Amino-3-(fluoro(trifluoromethoxy)methyl)-1H-pyrazole-4-carbonitrile (**7a**)

^{13}C NMR (100 MHz, CD_3CN)



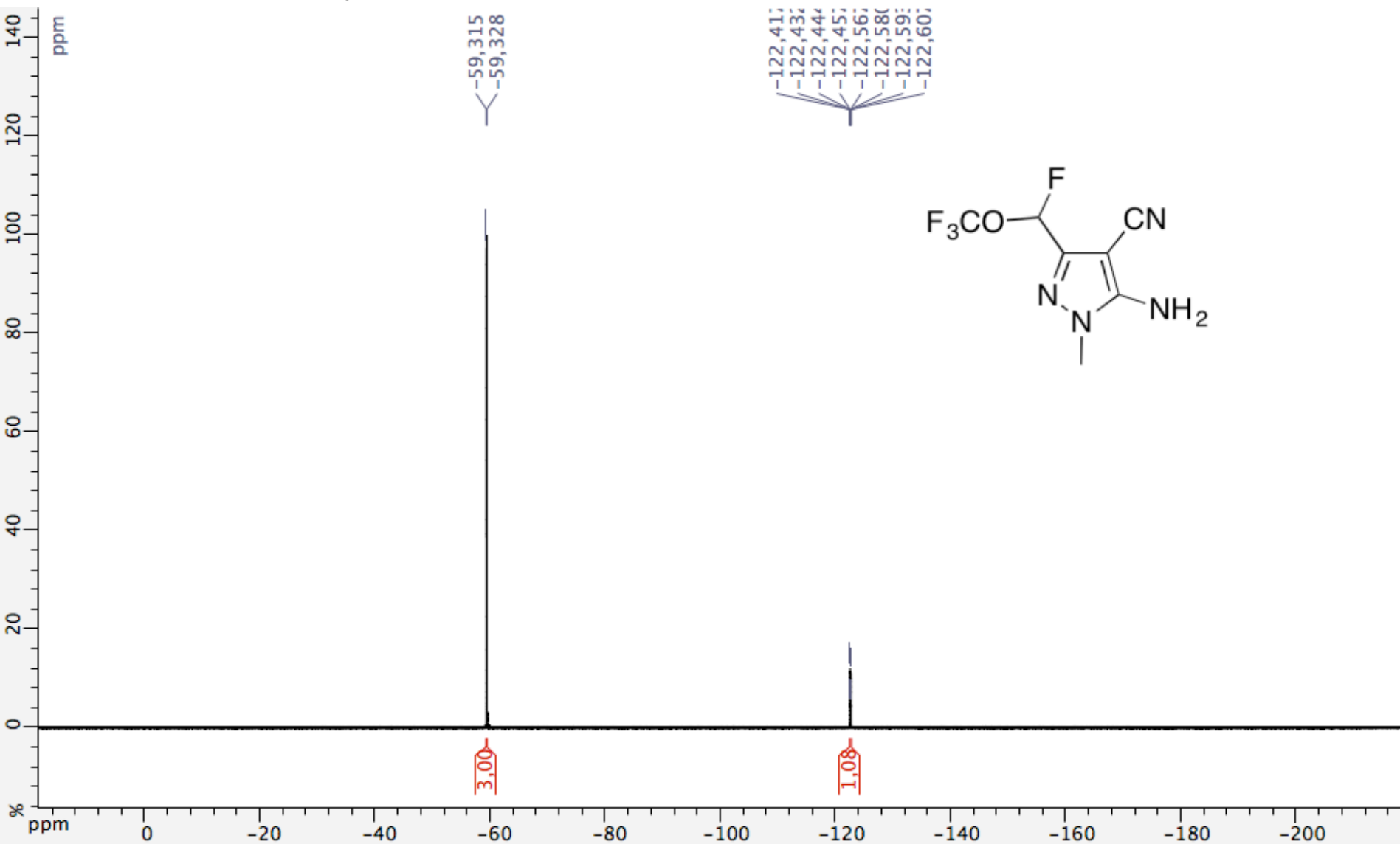
5-Amino-3-(fluoro(trifluoromethoxy)methyl)-1-methyl-1H-pyrazole-4-carbonitrile (**7b**)

^1H NMR (400 MHz, CDCl_3)



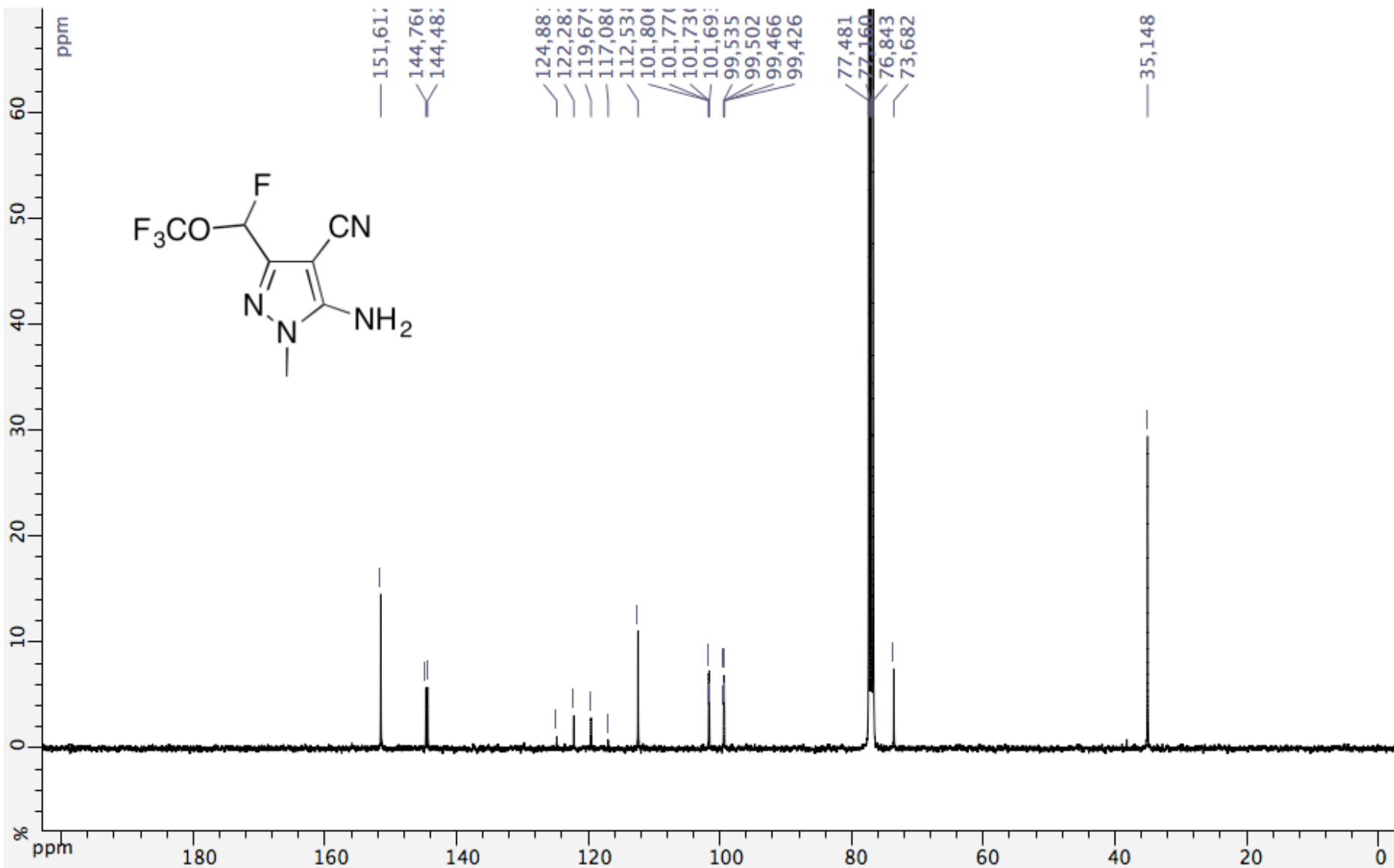
5-Amino-3-(fluoro(trifluoromethoxy)methyl)-1-methyl-1H-pyrazole-4-carbonitrile (**7b**)

^{19}F NMR (376 MHz, CDCl_3)



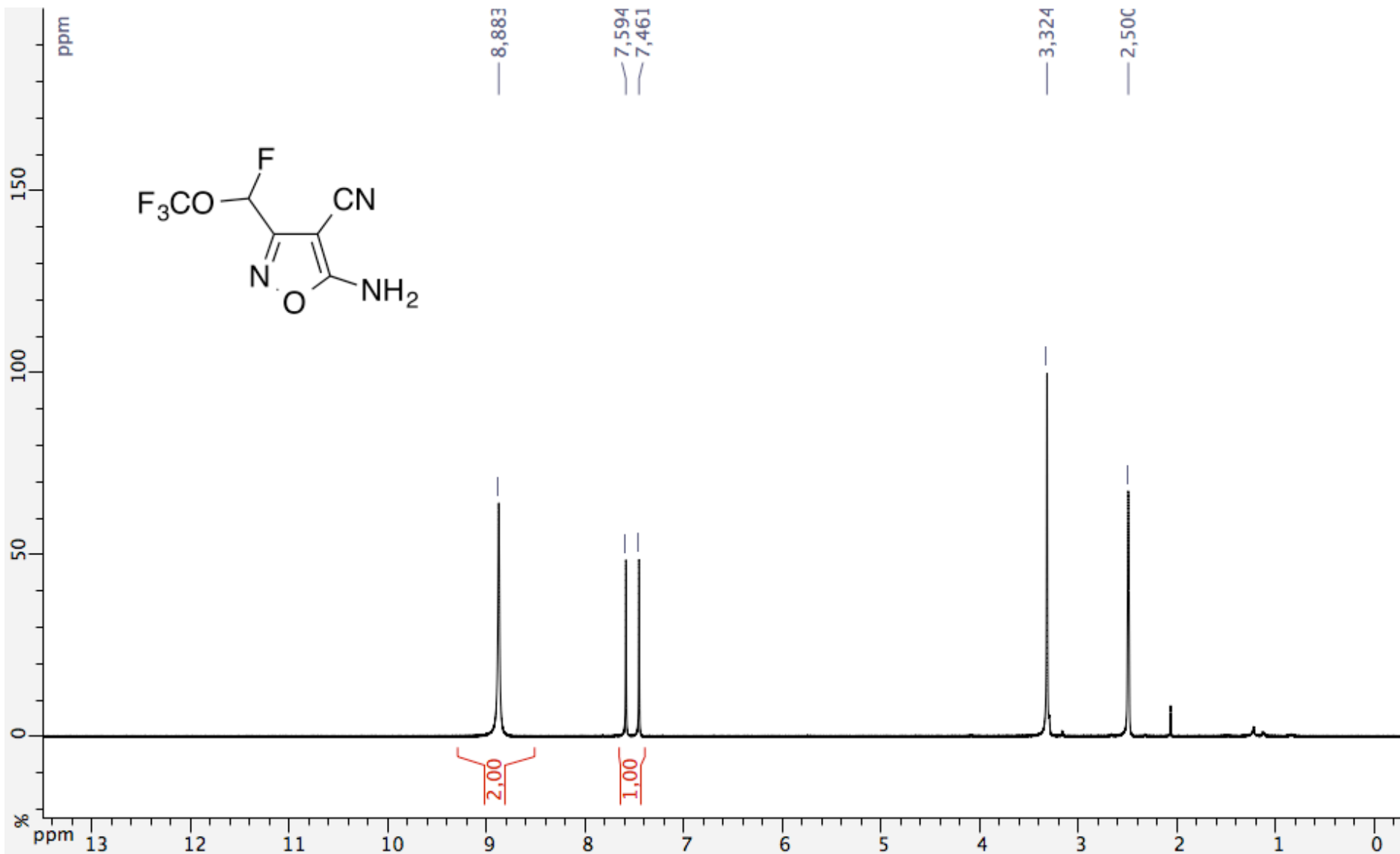
5-Amino-3-(fluoro(trifluoromethoxy)methyl)-1-methyl-1H-pyrazole-4-carbonitrile (**7b**)

^{13}C NMR (100 MHz, CDCl_3)



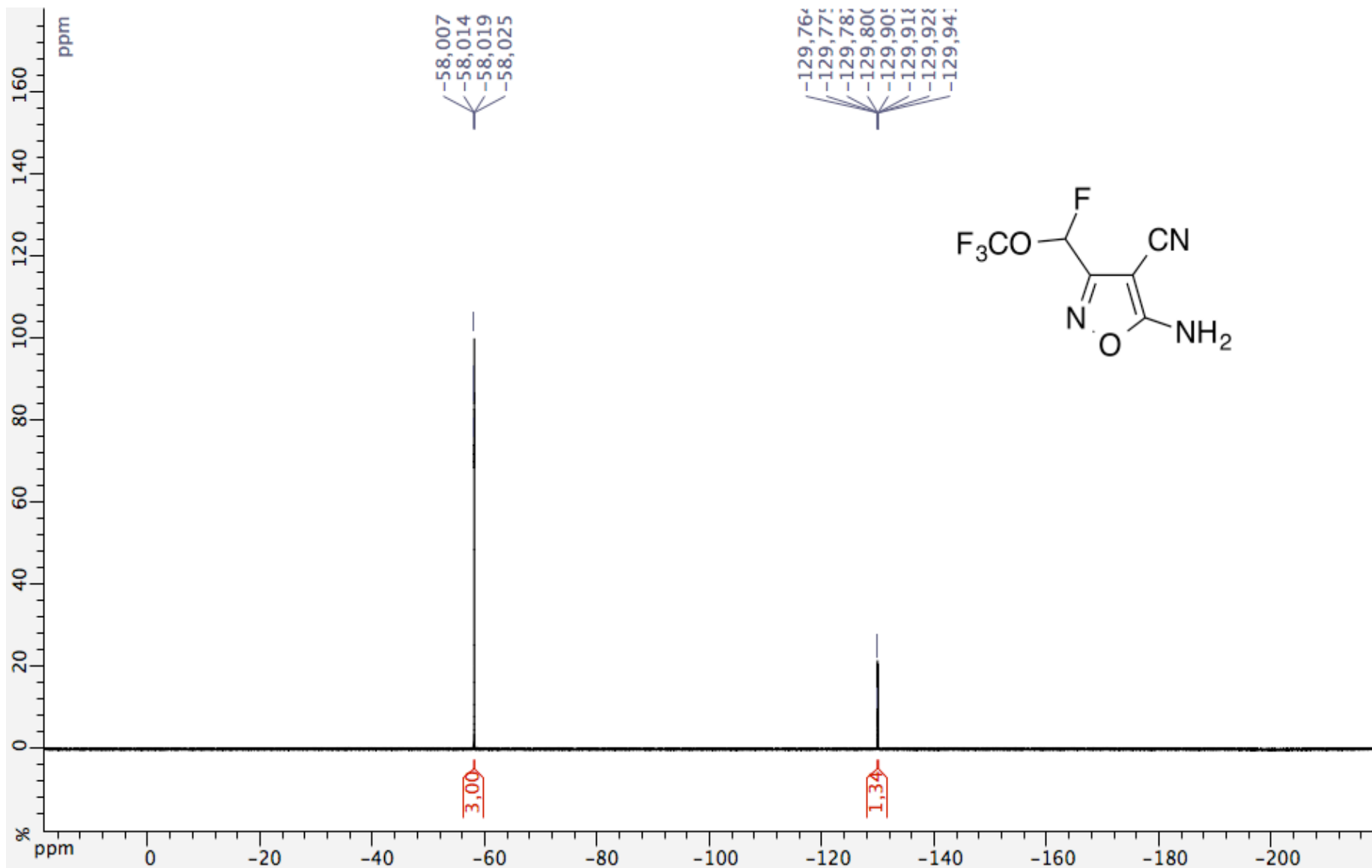
5-Amino-3-(fluoro(trifluoromethoxy)methyl)isoxazole-4-carbonitrile (**7c**)

^1H NMR (400 MHz, DMSO-d_6)



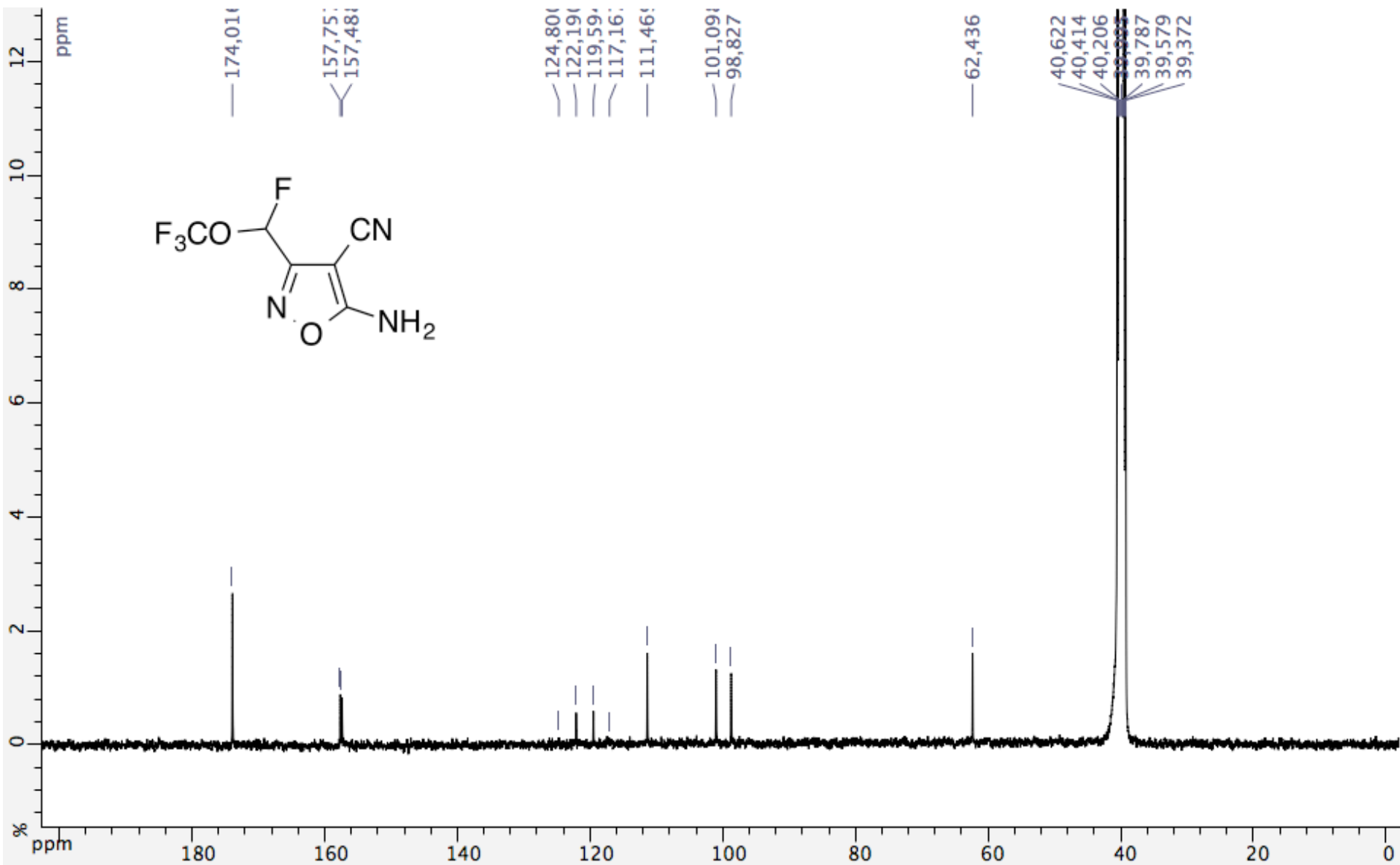
5-Amino-3-(fluoro(trifluoromethoxy)methyl)isoxazole-4-carbonitrile (**7c**)

^{19}F NMR (376 MHz, DMSO-d_6)



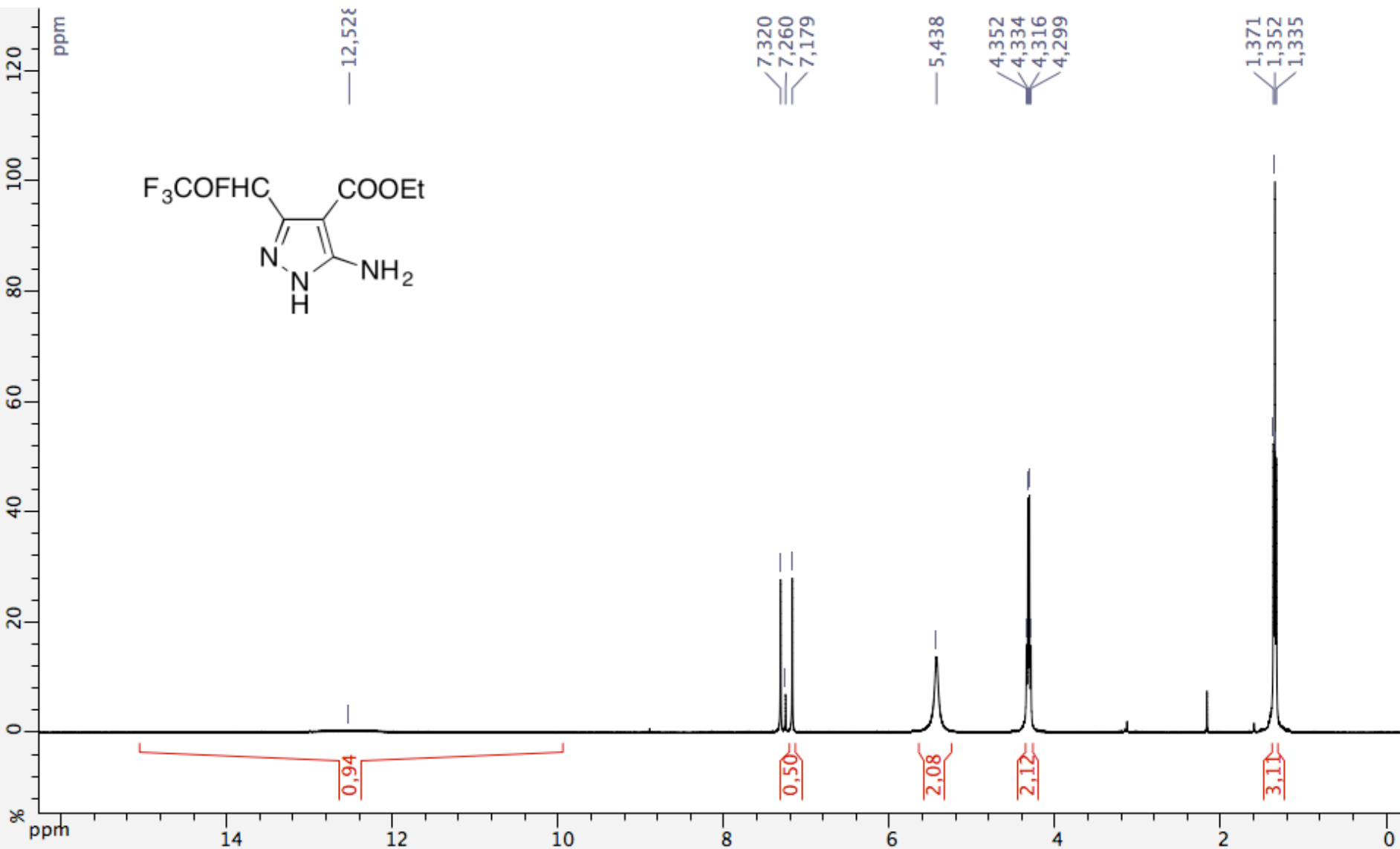
5-Amino-3-(fluoro(trifluoromethoxy)methyl)isoxazole-4-carbonitrile (**7c**)

^{13}C NMR (100 MHz, DMSO-d_6)



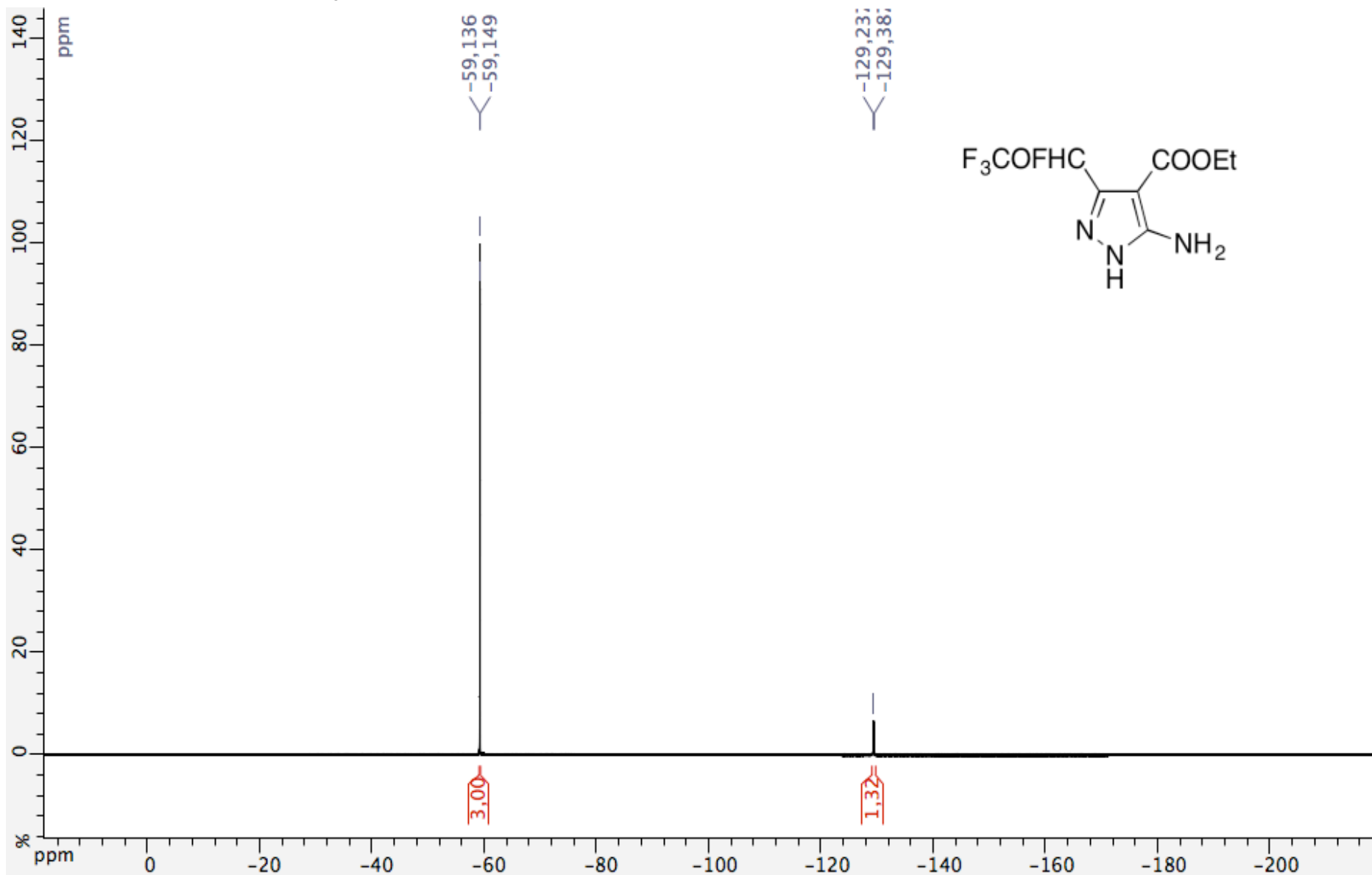
Ethyl 5-amino-3-(fluoro(trifluoromethoxy)methyl)-1H-pyrazole-4-carboxylate (**8a**)

^1H NMR (400 MHz, CDCl_3)

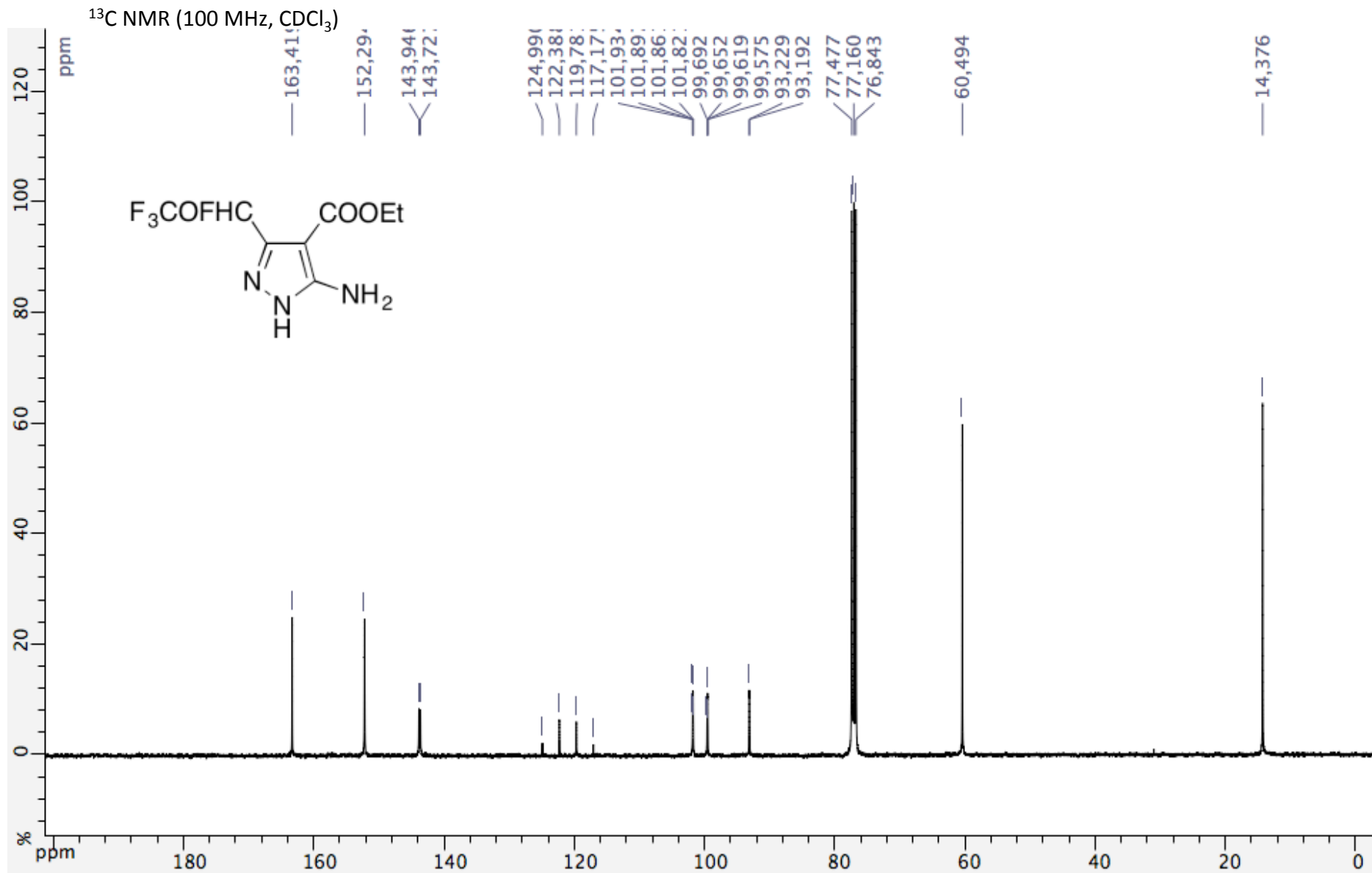


Ethyl 5-amino-3-(fluoro(trifluoromethoxy)methyl)-1H-pyrazole-4-carboxylate (**8a**)

^{19}F NMR (376 MHz, CDCl_3)

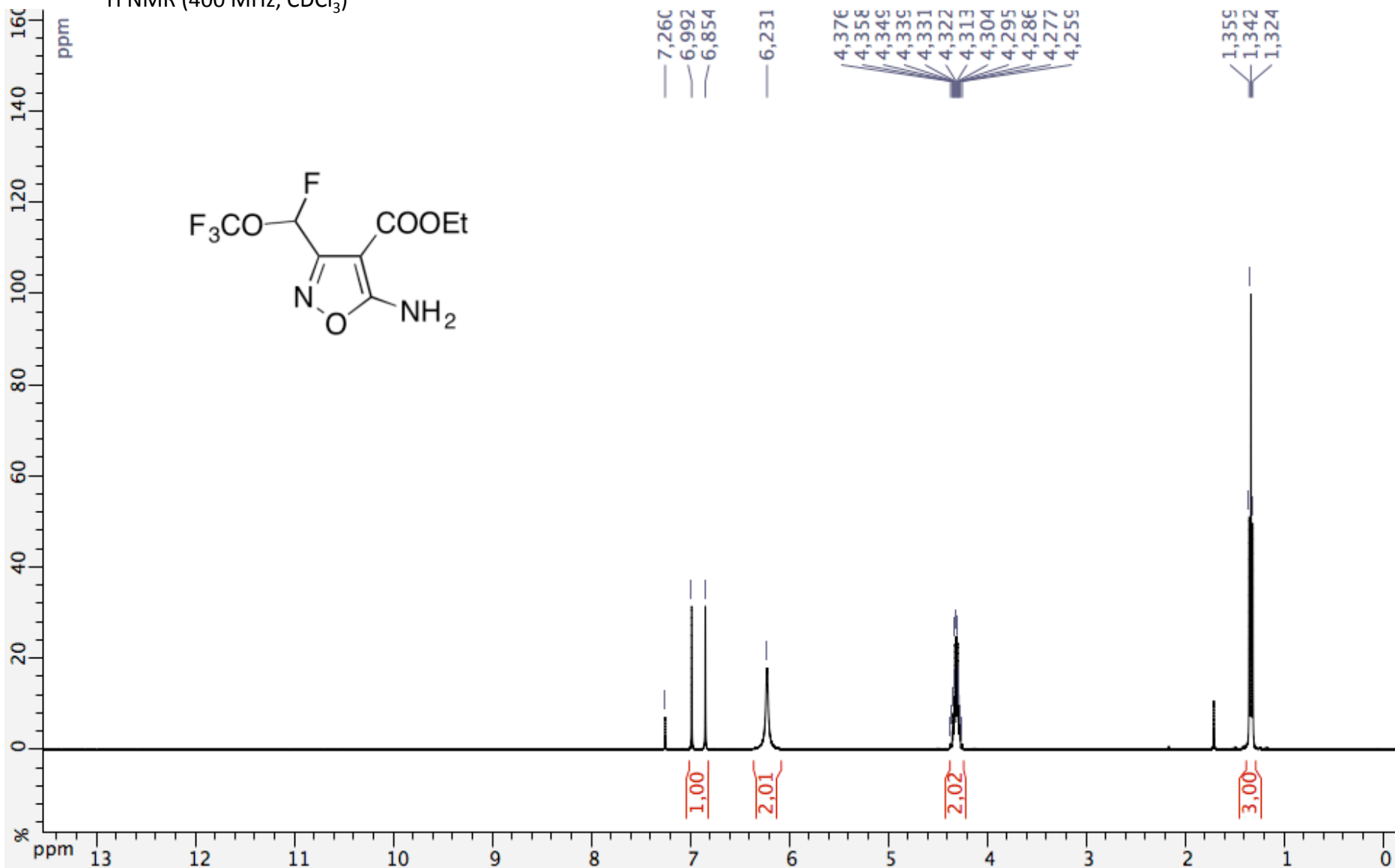
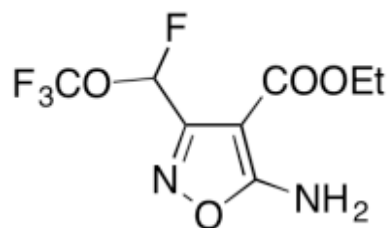


Ethyl 5-amino-3-(fluoro(trifluoromethoxy)methyl)-1H-pyrazole-4-carboxylate (**8a**)



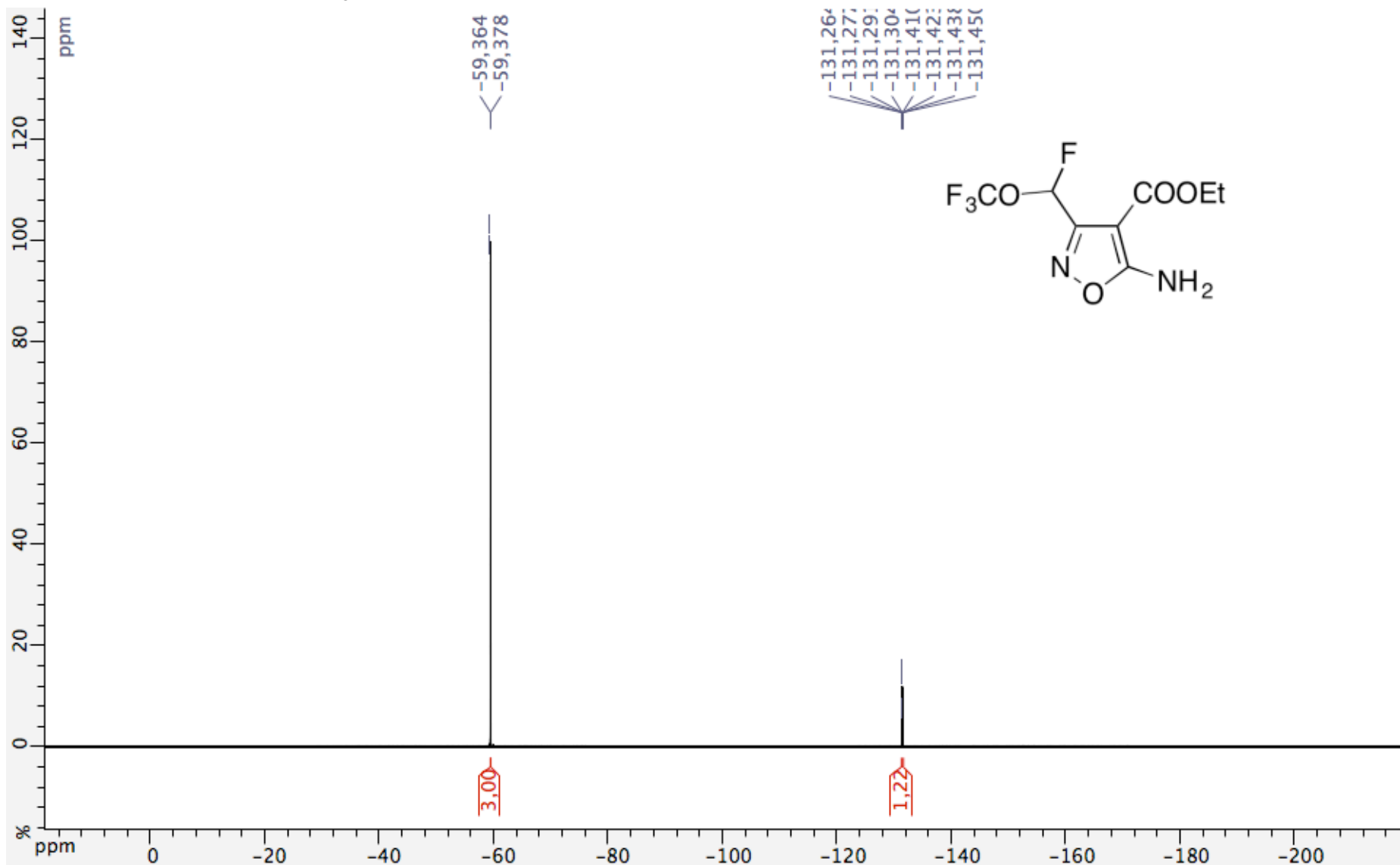
Ethyl 5-amino-3-(fluoro(trifluoromethoxy)methyl)isoxazole-4-carboxylate (**8c**)

¹H NMR (400 MHz, CDCl₃)



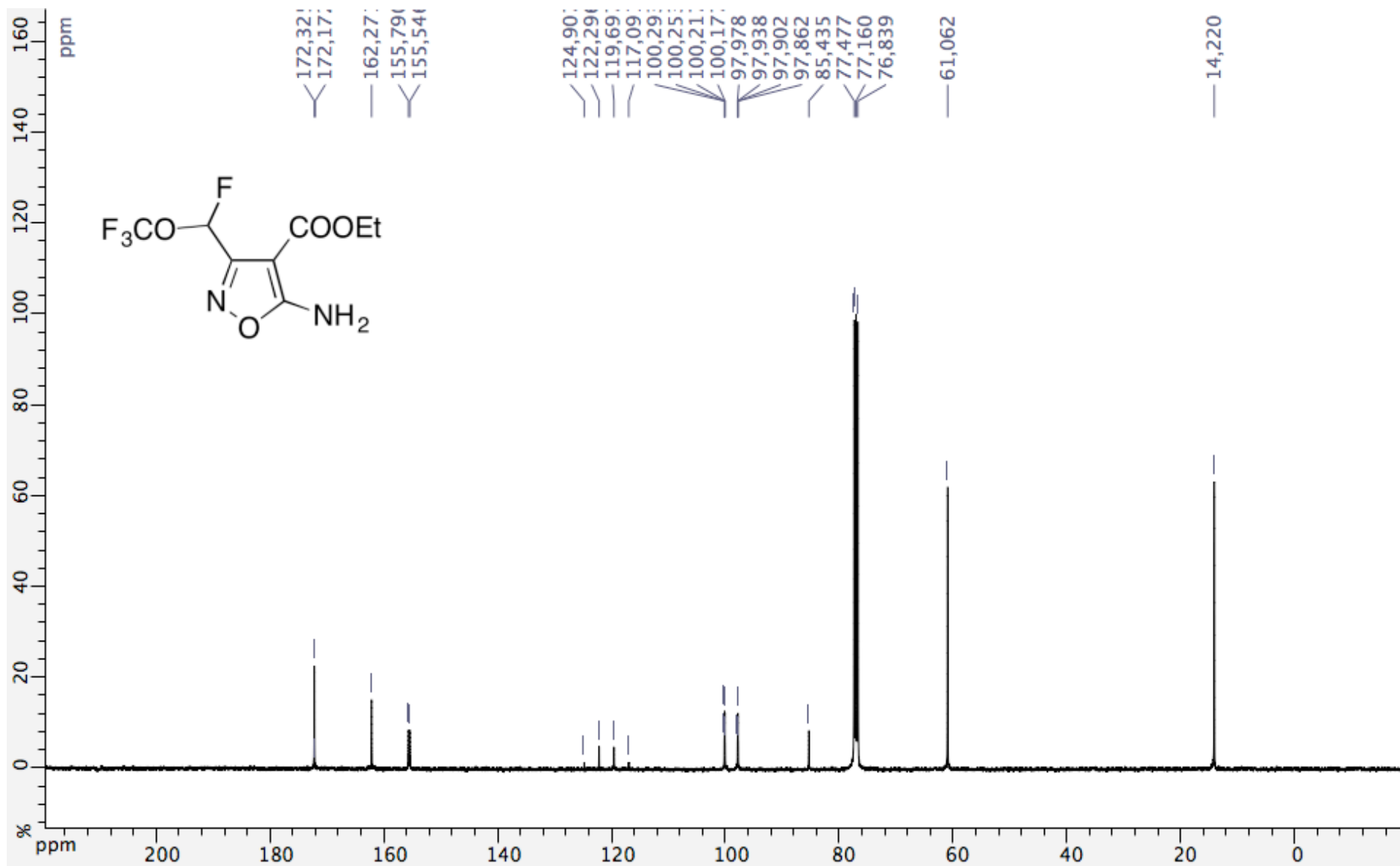
Ethyl 5-amino-3-(fluoro(trifluoromethoxy)methyl)isoxazole-4-carboxylate (**8c**)

^{19}F NMR (376 MHz, CDCl_3)



Ethyl 5-amino-3-(fluoro(trifluoromethoxy)methyl)isoxazole-4-carboxylate (**8c**)

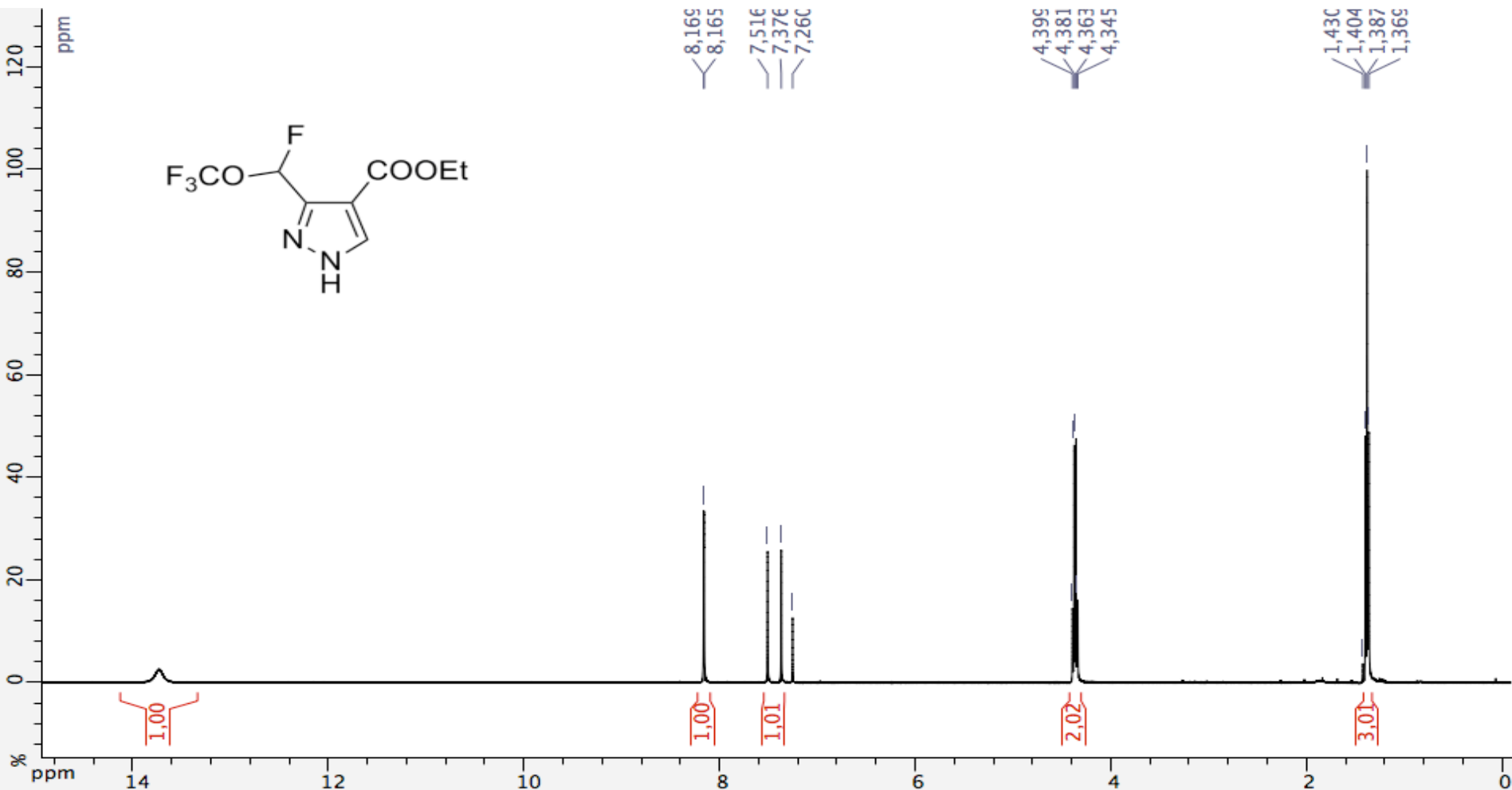
^{13}C NMR (100 MHz, CDCl_3)



Preparation of OCF₃-analogues of a key intermediate of Bixafen

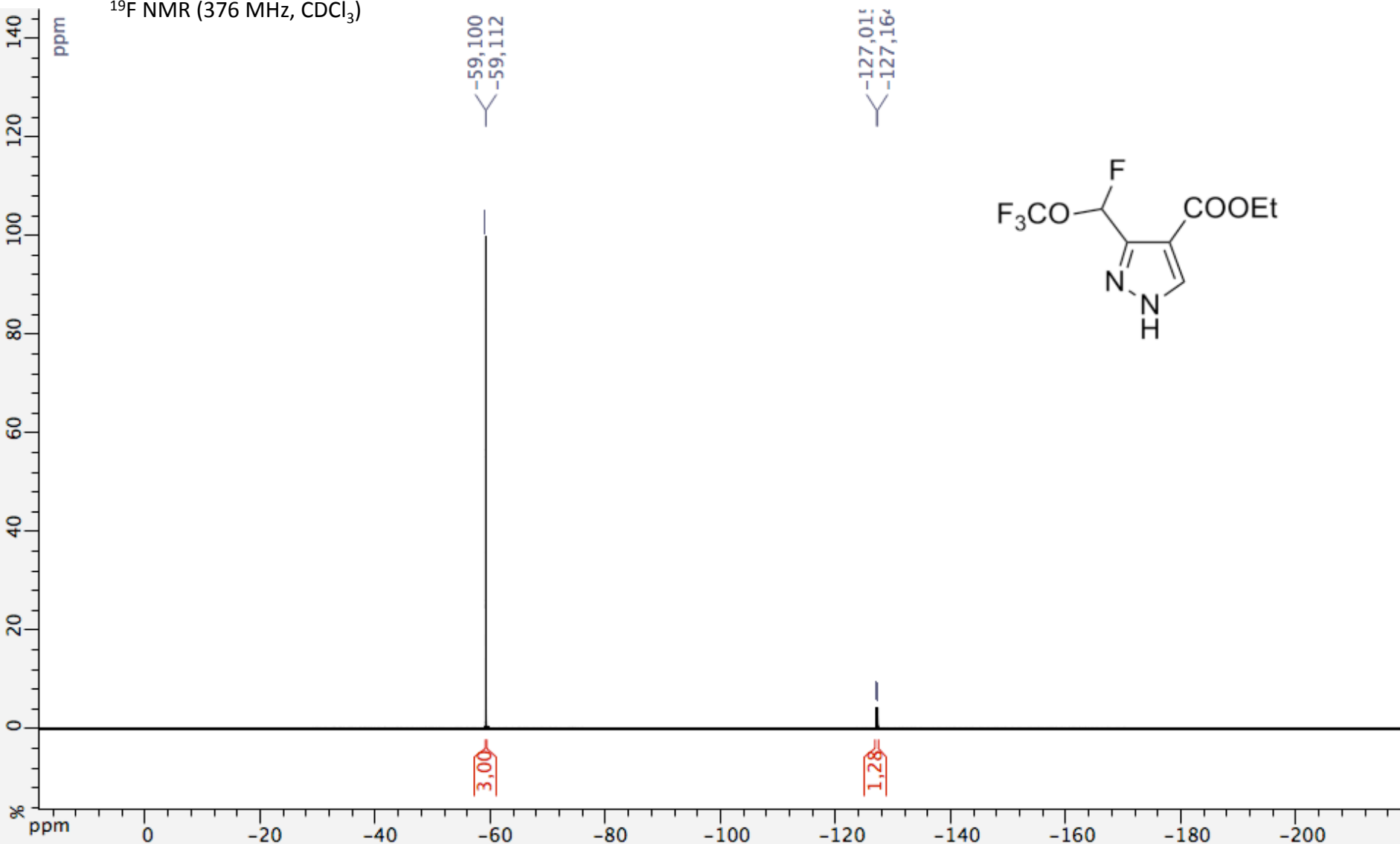
Ethyl 3-(fluoro(trifluoromethoxy)methyl)-1H-pyrazole-4-carboxylate (**9**)

¹H NMR (400 MHz, CDCl₃)



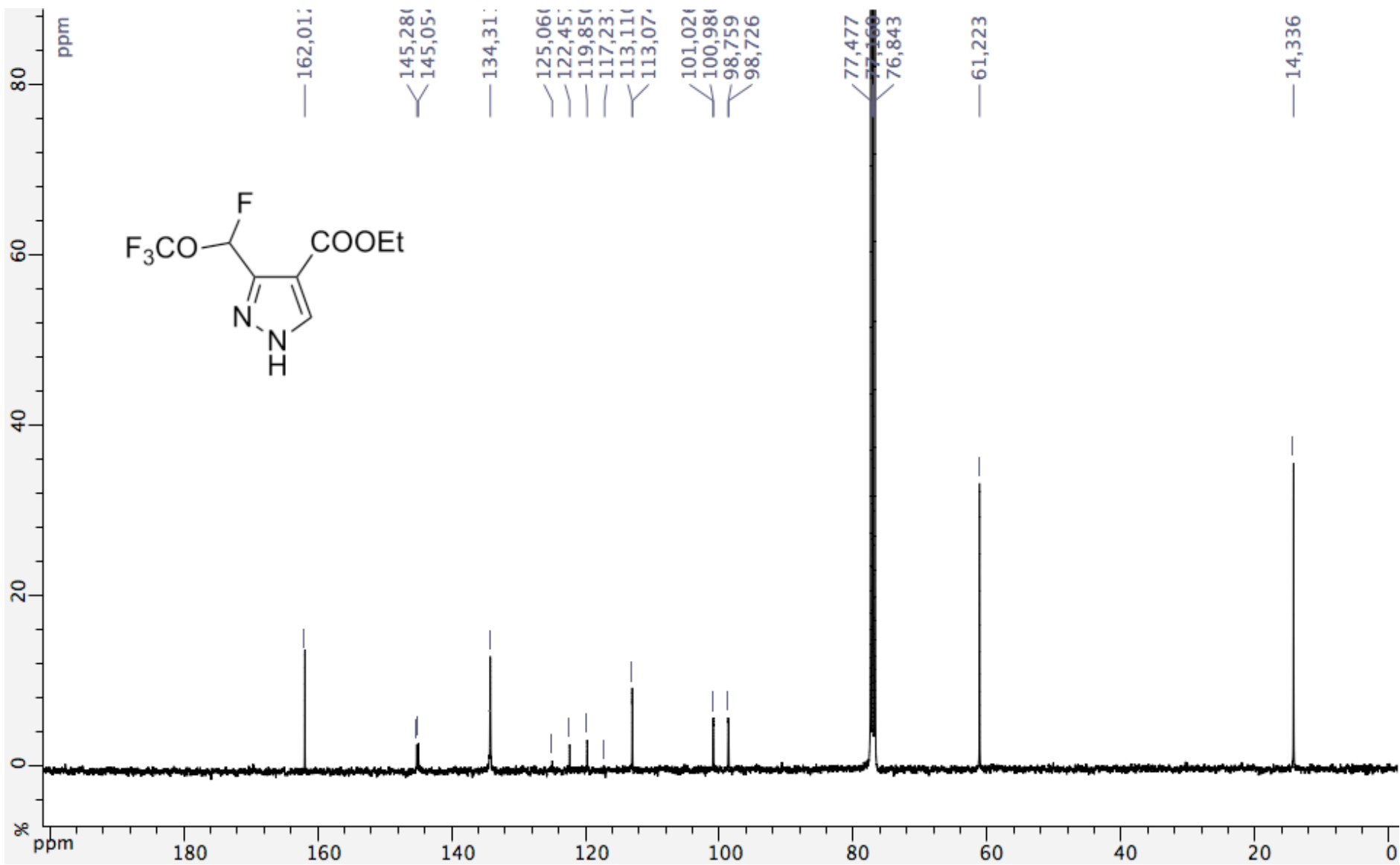
Ethyl 3-(fluoro(trifluoromethoxy)methyl)-1H-pyrazole-4-carboxylate (**9**)

^{19}F NMR (376 MHz, CDCl_3)



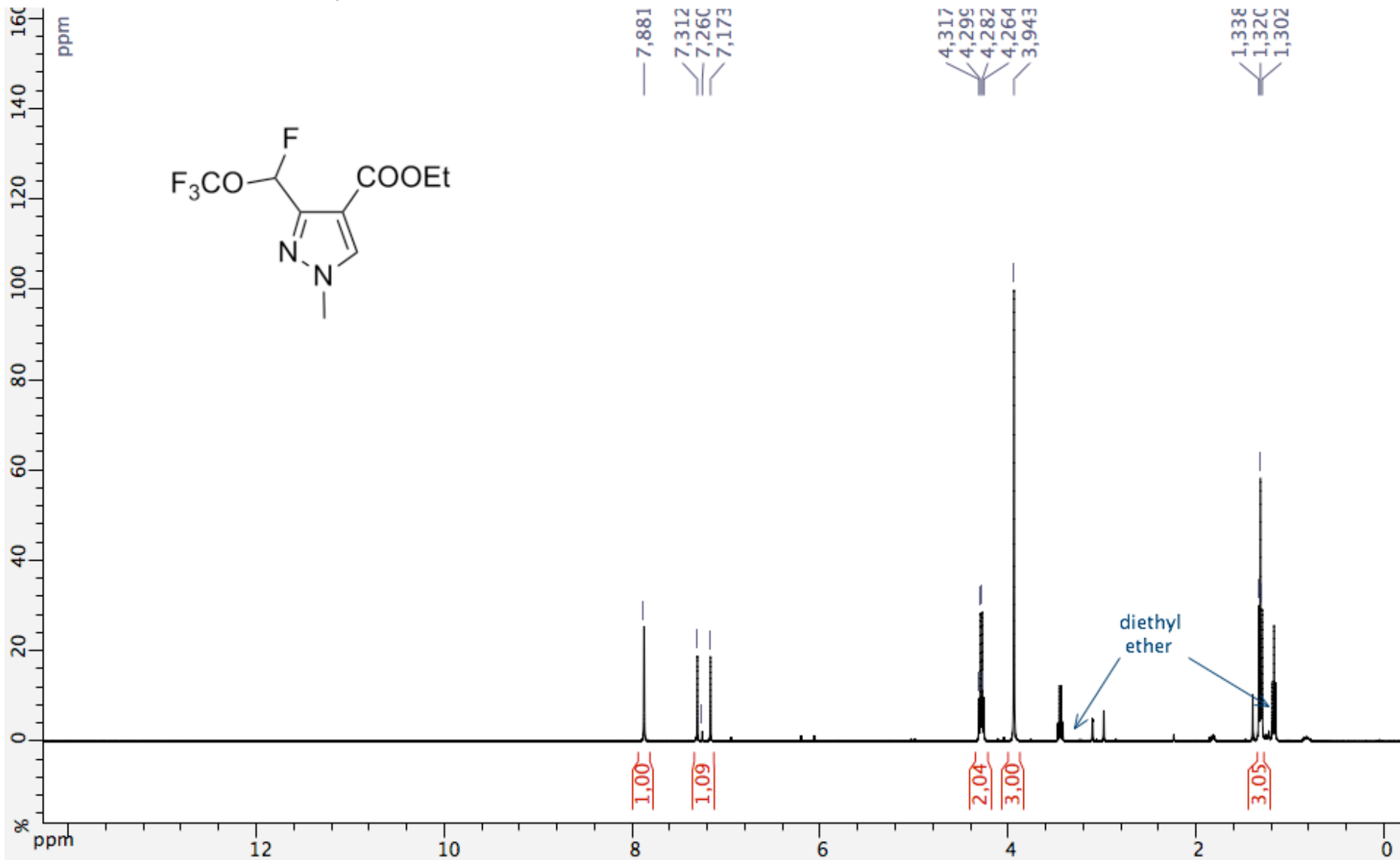
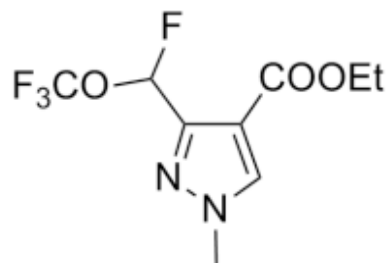
Ethyl 3-(fluoro(trifluoromethoxy)methyl)-1H-pyrazole-4-carboxylate (9)

^{13}C NMR (100 MHz, CDCl_3)



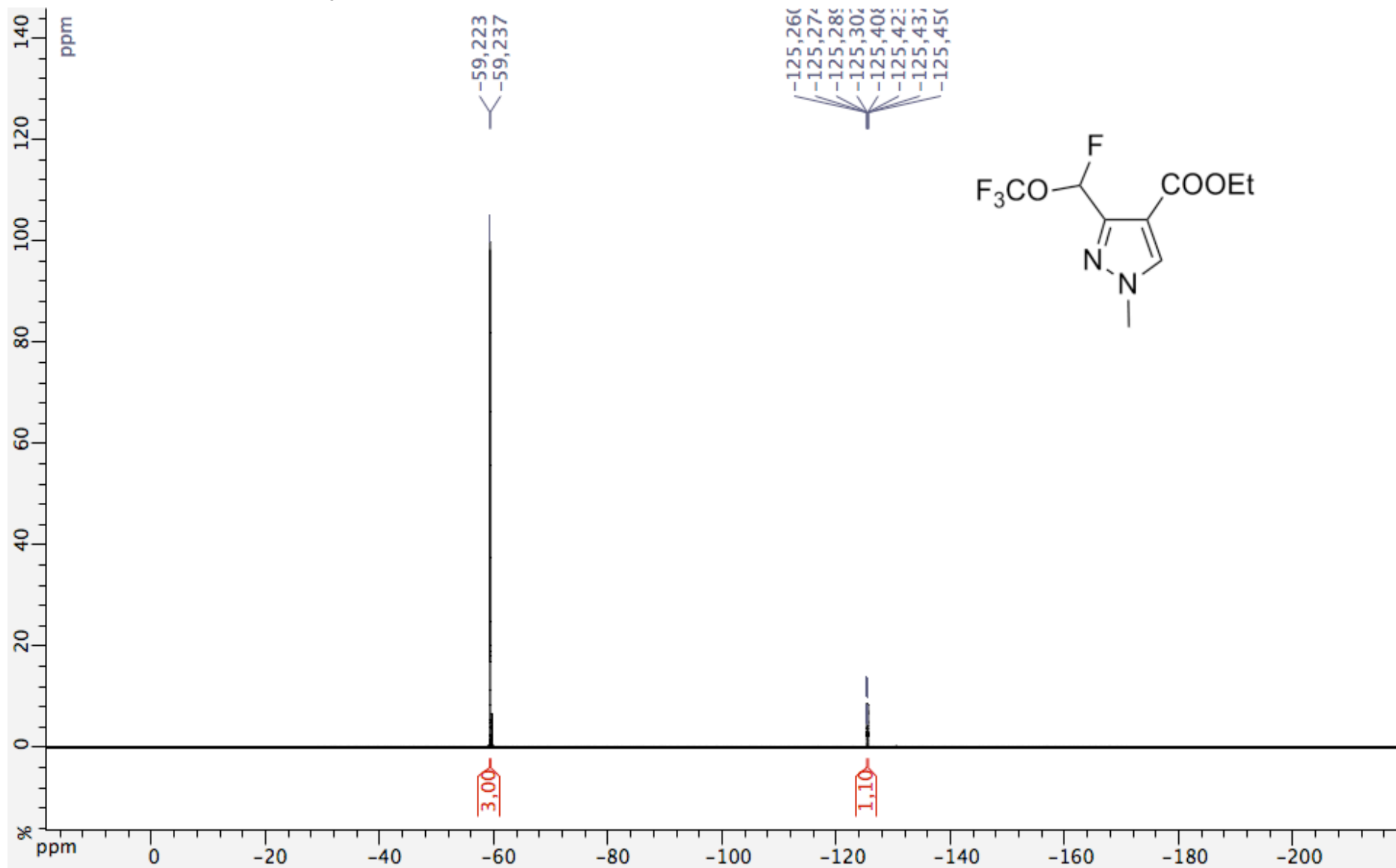
Ethyl 3-(fluoro(trifluoromethoxy)methyl)-1-methyl-1H-pyrazole-4-carboxylate (**10a**)

^1H NMR (400 MHz, CDCl_3)



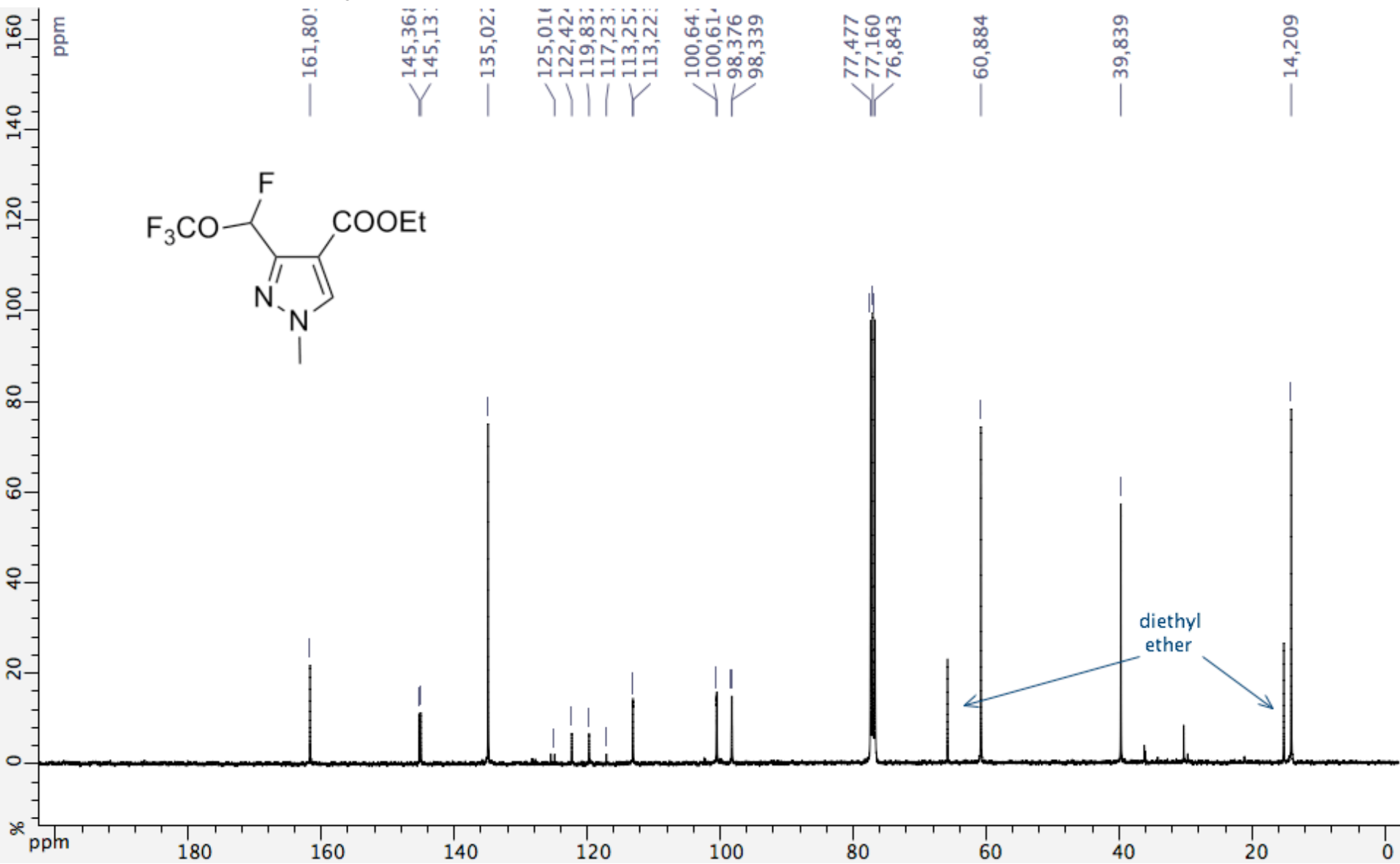
Ethyl 3-(fluoro(trifluoromethoxy)methyl)-1-methyl-1H-pyrazole-4-carboxylate (**10a**)

^{19}F NMR (376 MHz, CDCl_3)



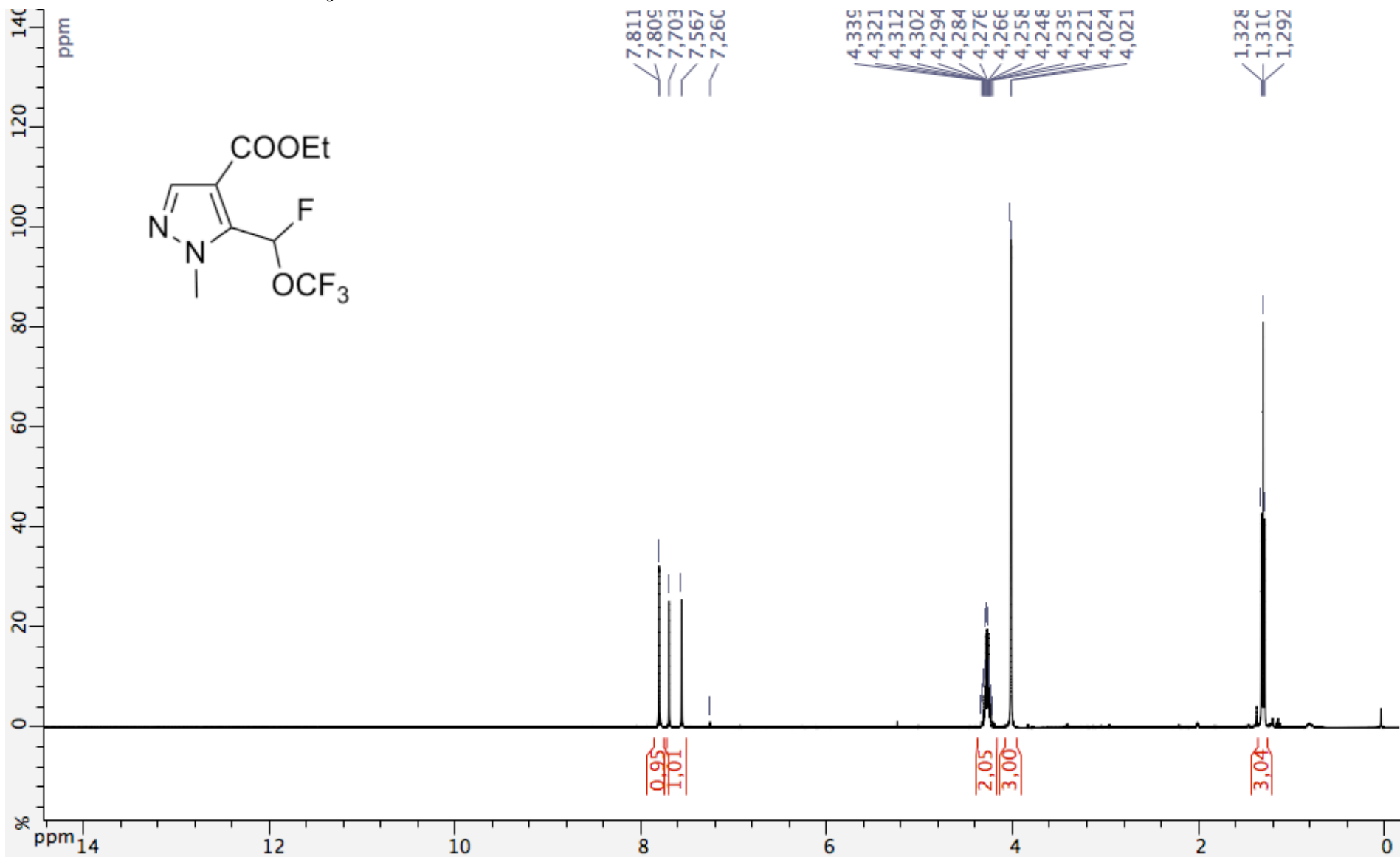
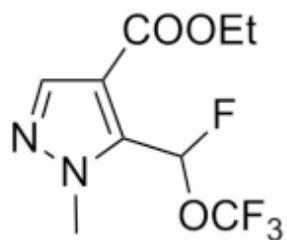
Ethyl 3-(fluoro(trifluoromethoxy)methyl)-1-methyl-1H-pyrazole-4-carboxylate (**10a**)

^{13}C NMR (100 MHz, CDCl_3)



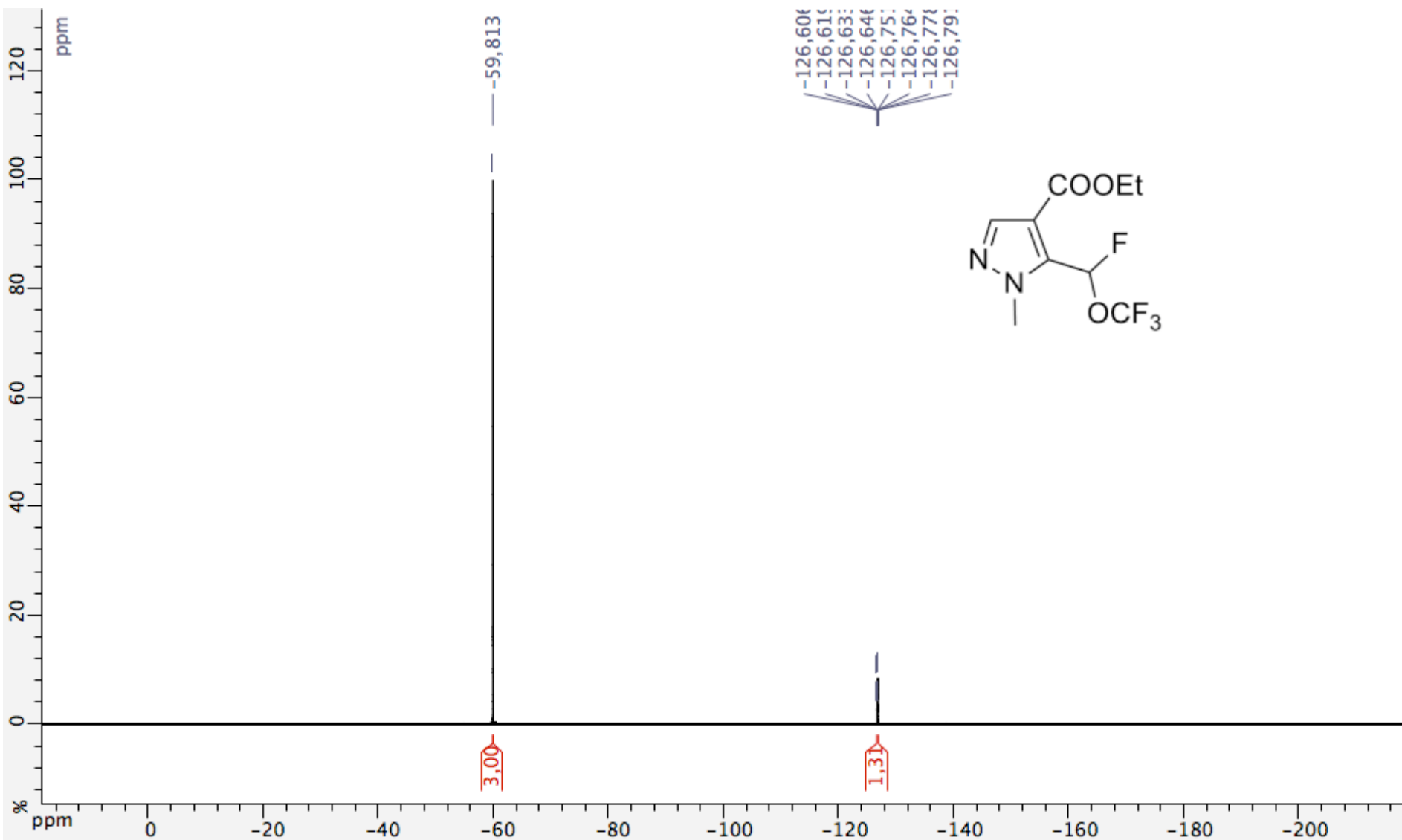
Ethyl 5-(fluoro(trifluoromethoxy)methyl)-1-methyl-1*H*-pyrazole-4-carboxylate (**10b**)

¹H NMR (400 MHz, CDCl₃)



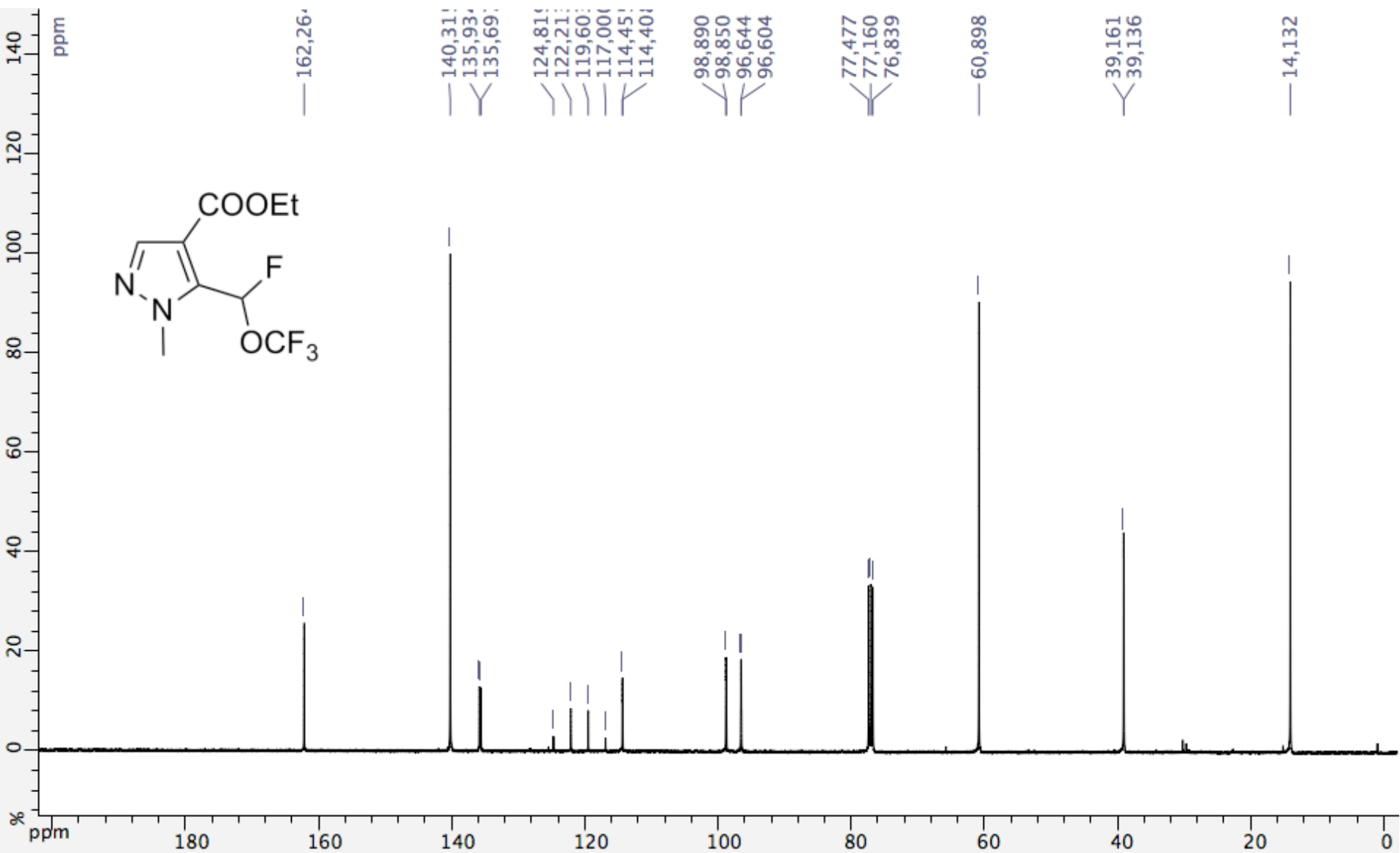
Ethyl 5-(fluoro(trifluoromethoxy)methyl)-1-methyl-1H-pyrazole-4-carboxylate (**10b**)

^{19}F NMR (376 MHz, CDCl_3)



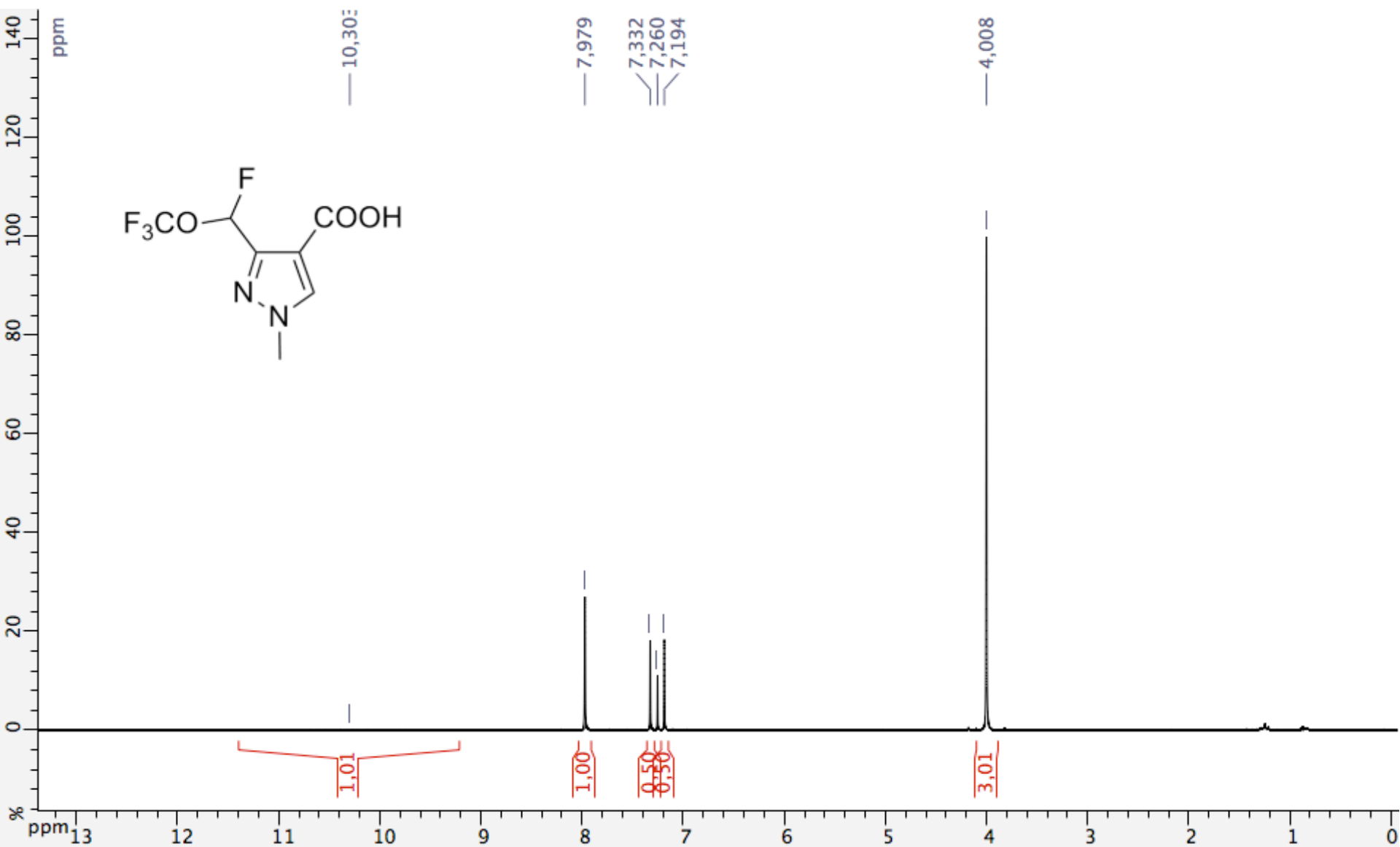
Ethyl 5-(fluoro(trifluoromethoxy)methyl)-1-methyl-1*H*-pyrazole-4-carboxylate (**10b**)

^{13}C NMR (100 MHz, CDCl_3)



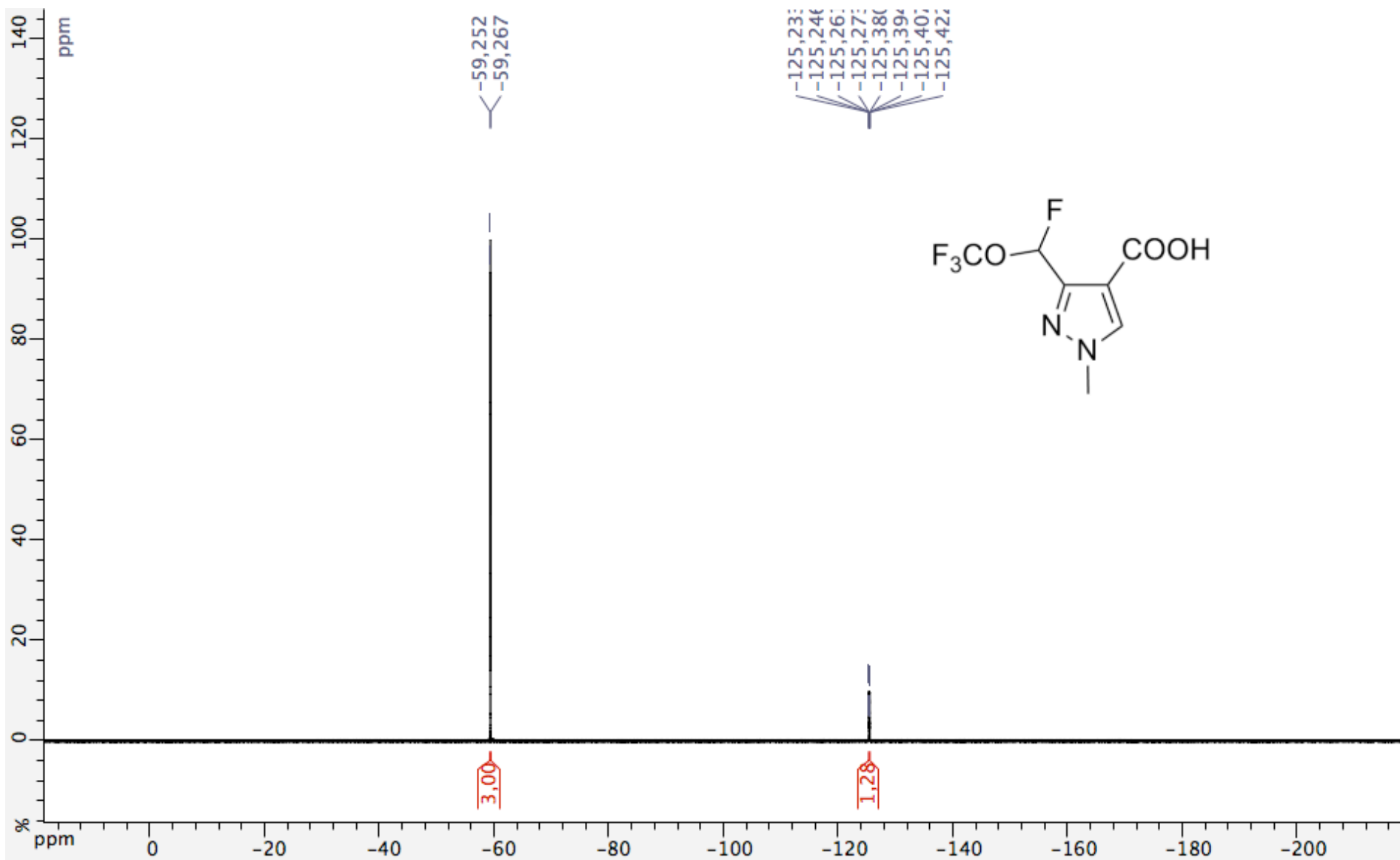
3-(Fluoro(trifluoromethoxy)methyl)-1-methyl-1H-pyrazole-4-carboxylic acid (**11a**)

^1H NMR (400 MHz, CDCl_3)



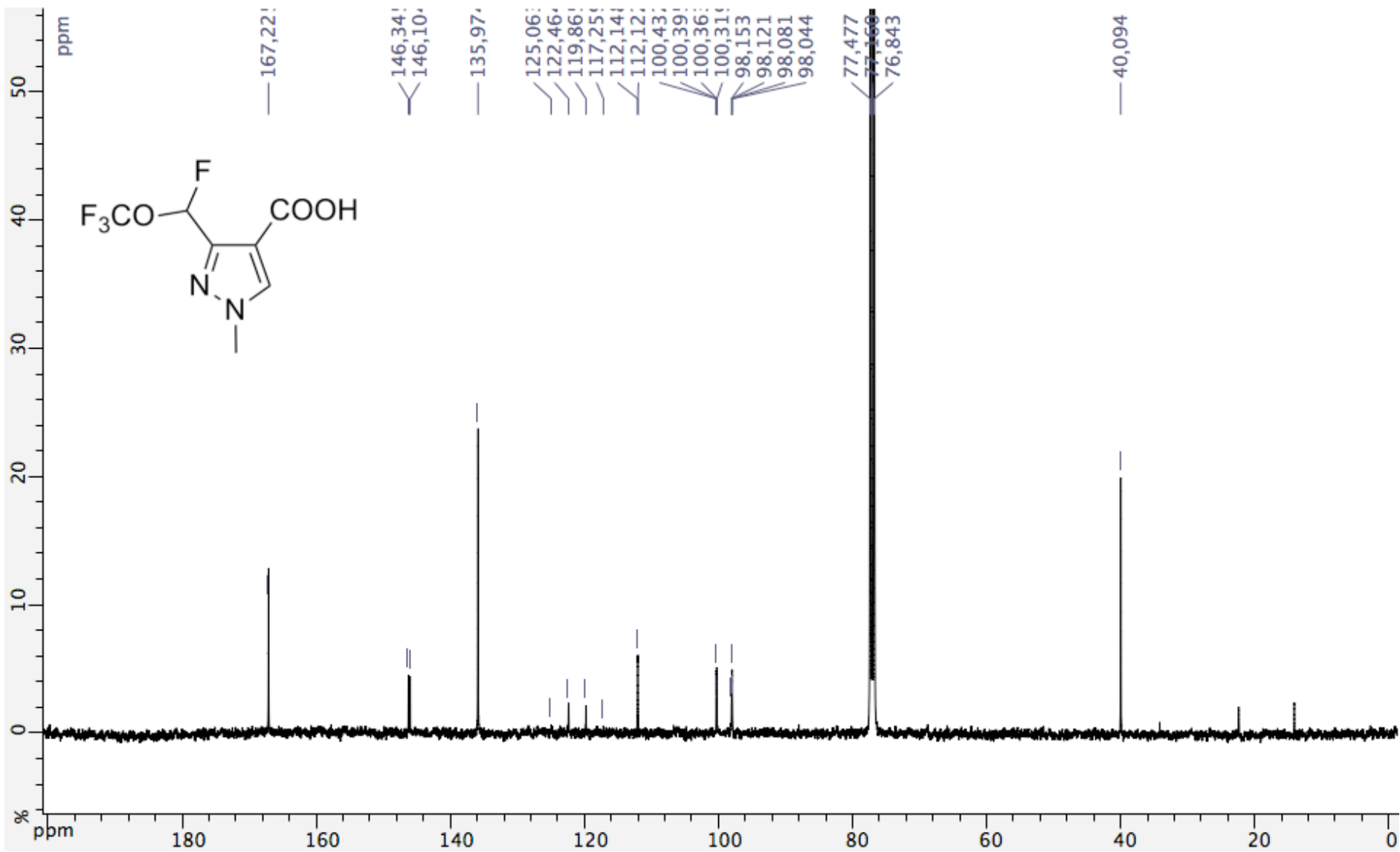
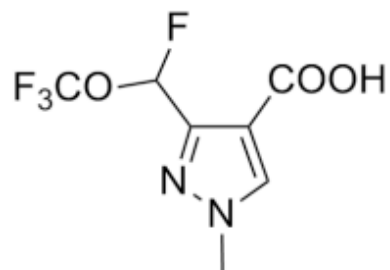
3-(Fluoro(trifluoromethoxy)methyl)-1-methyl-1H-pyrazole-4-carboxylic acid (**11a**)

^{19}F NMR (376 MHz, CDCl_3)



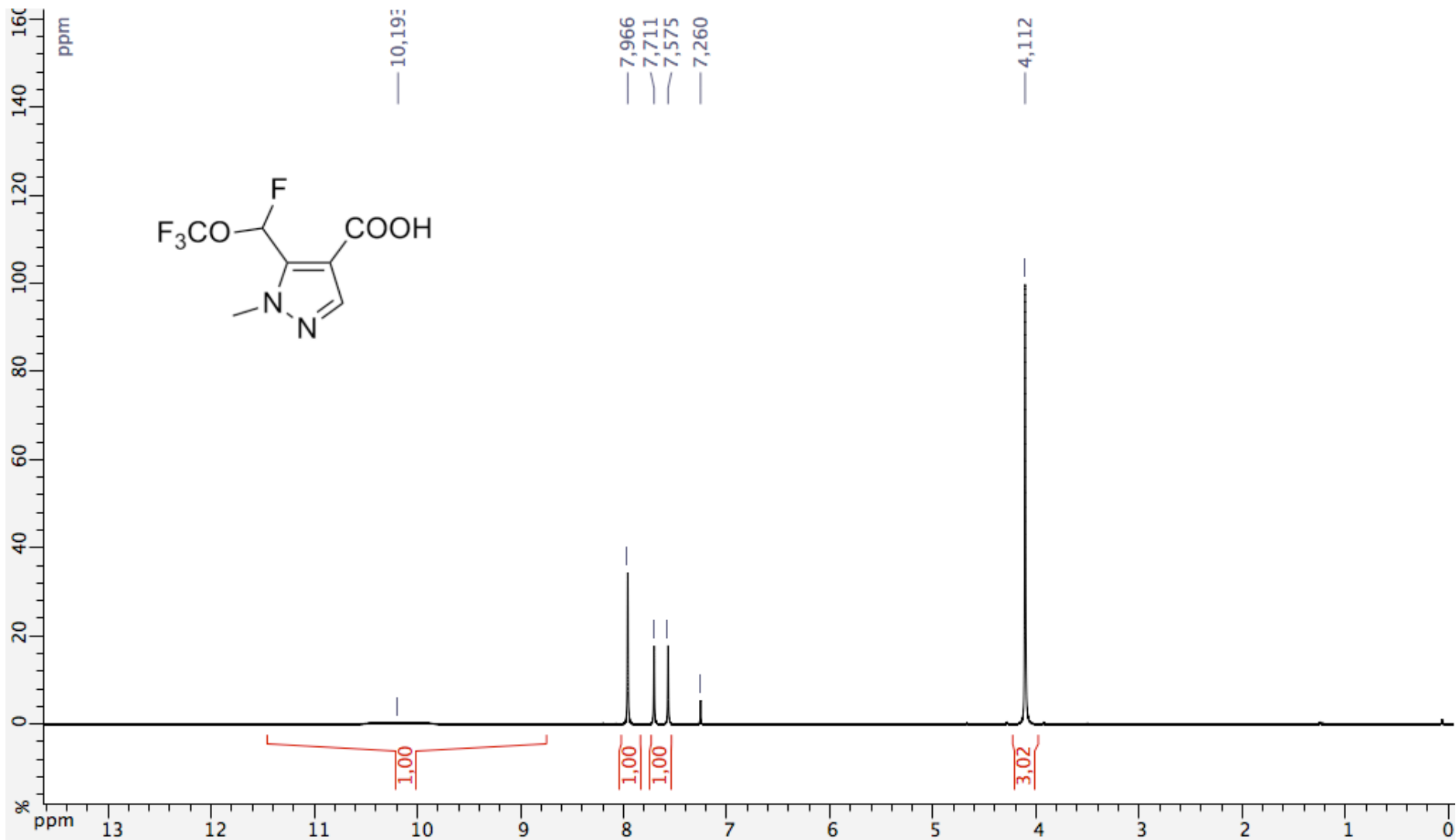
3-(Fluoro(trifluoromethoxy)methyl)-1-methyl-1H-pyrazole-4-carboxylic acid (**11a**)

^{13}C NMR (100 MHz, CDCl_3)



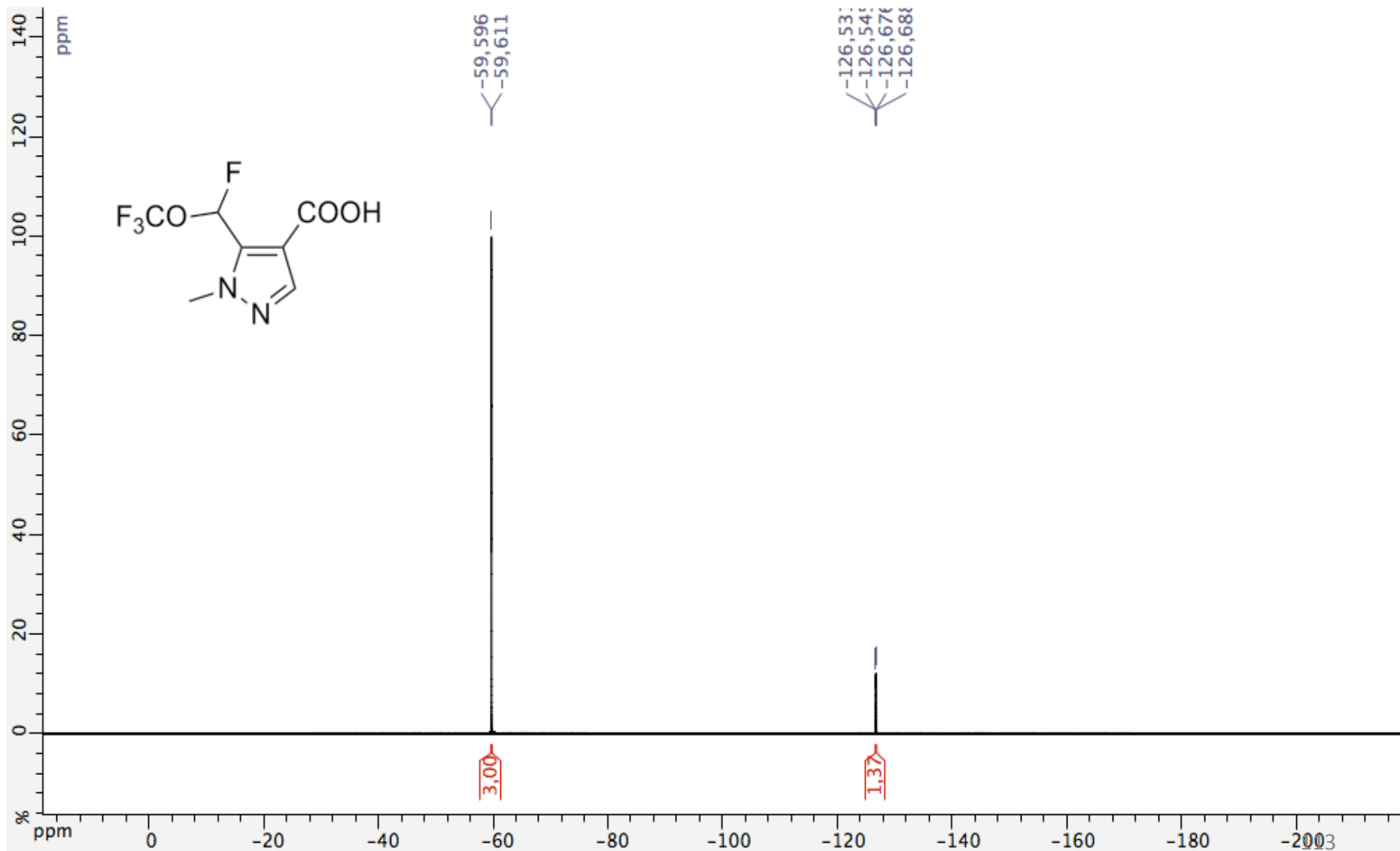
5-(Fluoro(trifluoromethoxy)methyl)-1-methyl-1H-pyrazole-4-carboxylic acid (**11b**)

^1H NMR (400 MHz, CDCl_3)



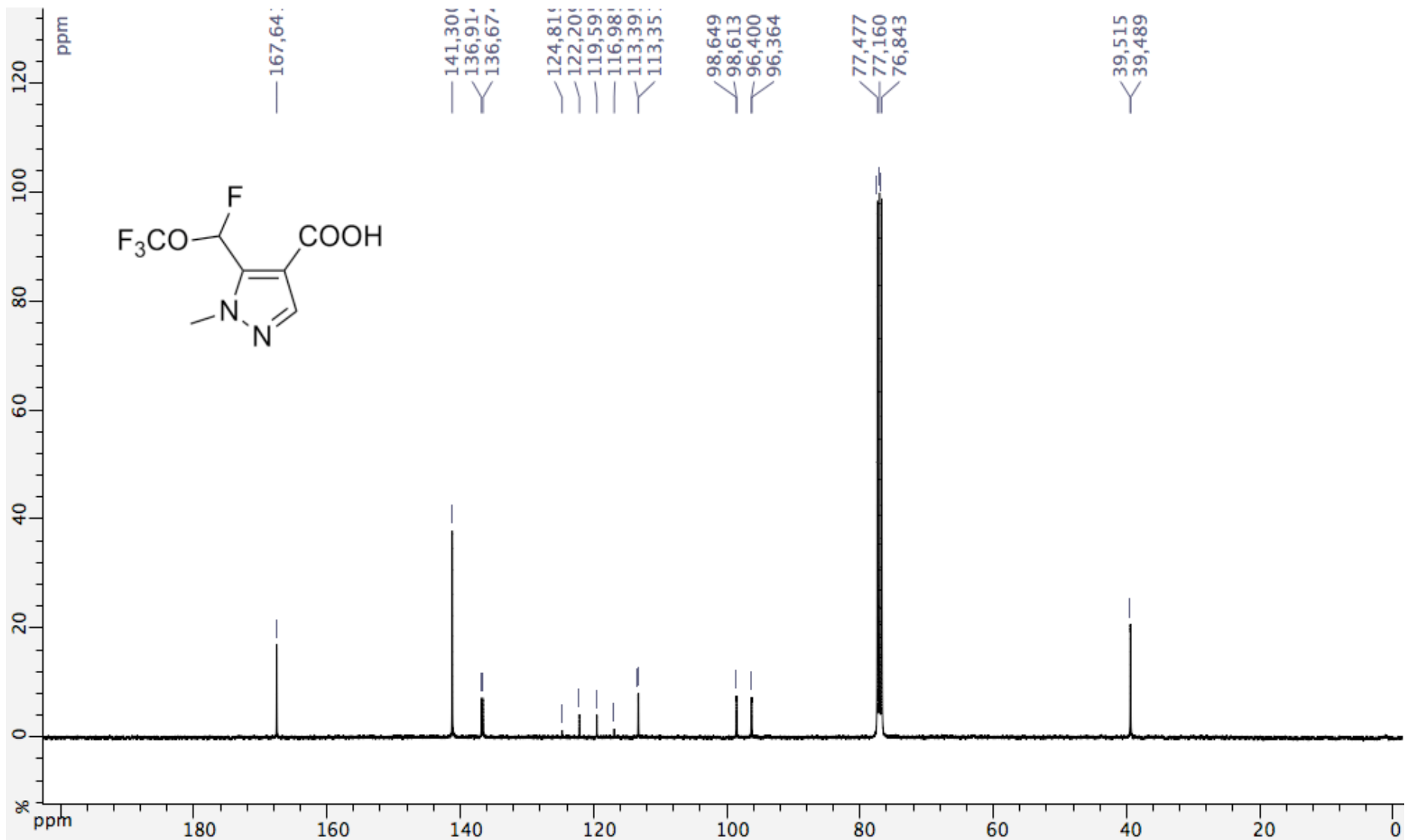
5-(Fluoro(trifluoromethoxy)methyl)-1-methyl-1H-pyrazole-4-carboxylic acid (**11b**)

^{19}F NMR (376 MHz, CDCl_3)



5-(Fluoro(trifluoromethoxy)methyl)-1-methyl-1H-pyrazole-4-carboxylic acid (**11b**)

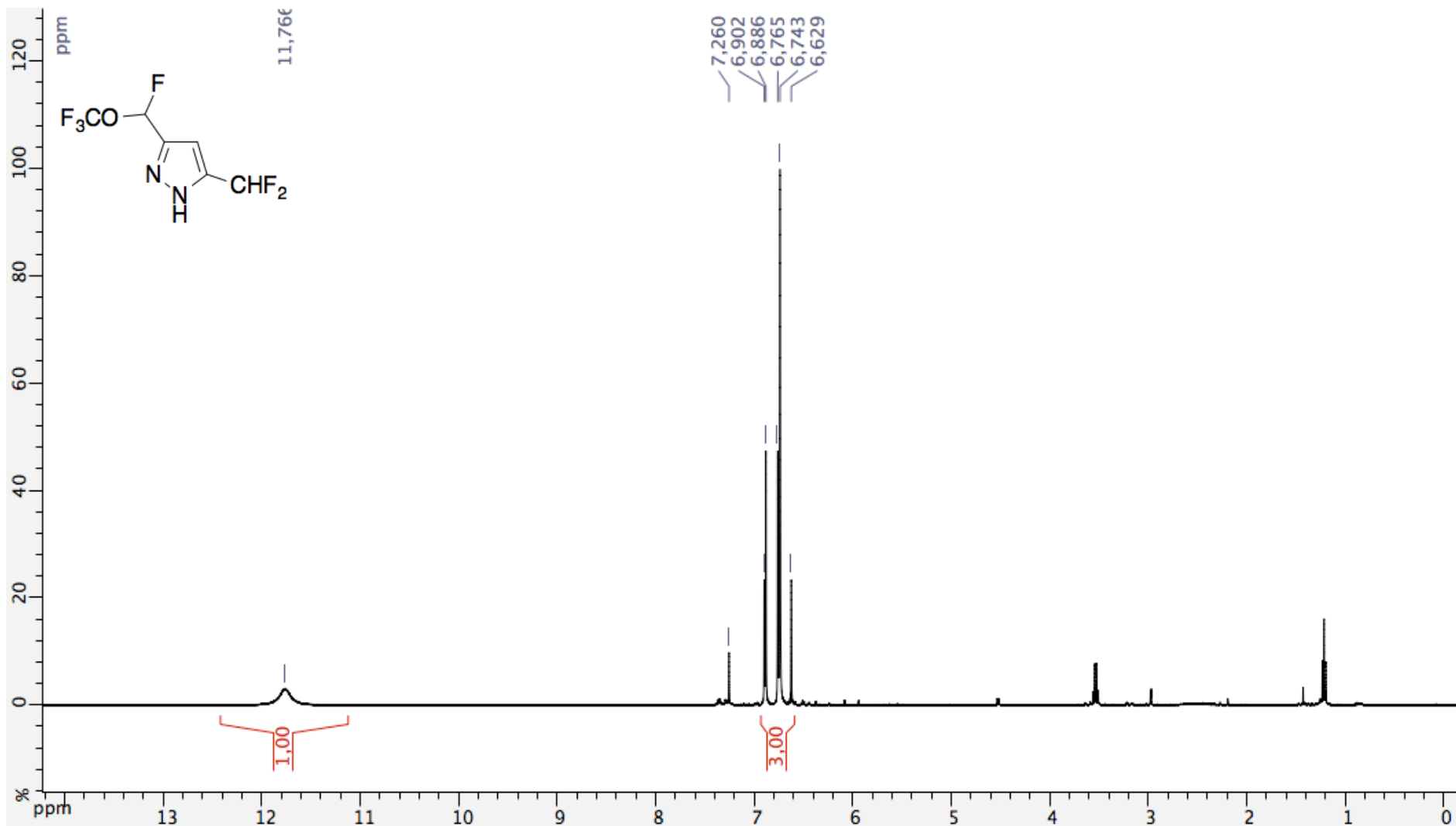
^{13}C NMR (100 MHz, CDCl_3)



Regioselective preparation of 3,5-bis(fluoroalkyl)pyrazoles bearing new –CHFOCF₃ motif.

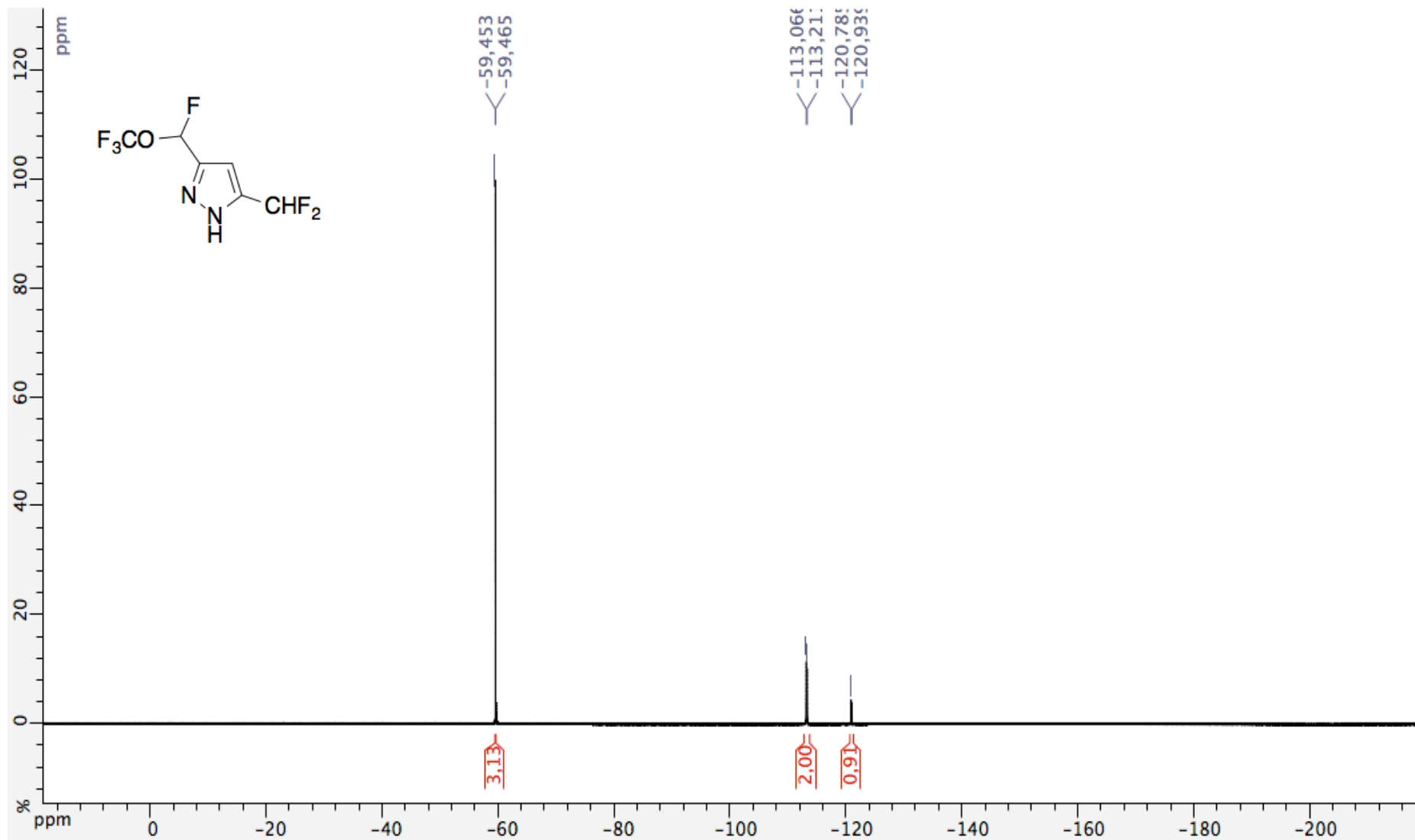
5-(Difluoromethyl)-3-(fluoro(trifluoromethoxy)methyl)-1H-pyrazole (**12a**)

¹H NMR (400 MHz, CDCl₃)



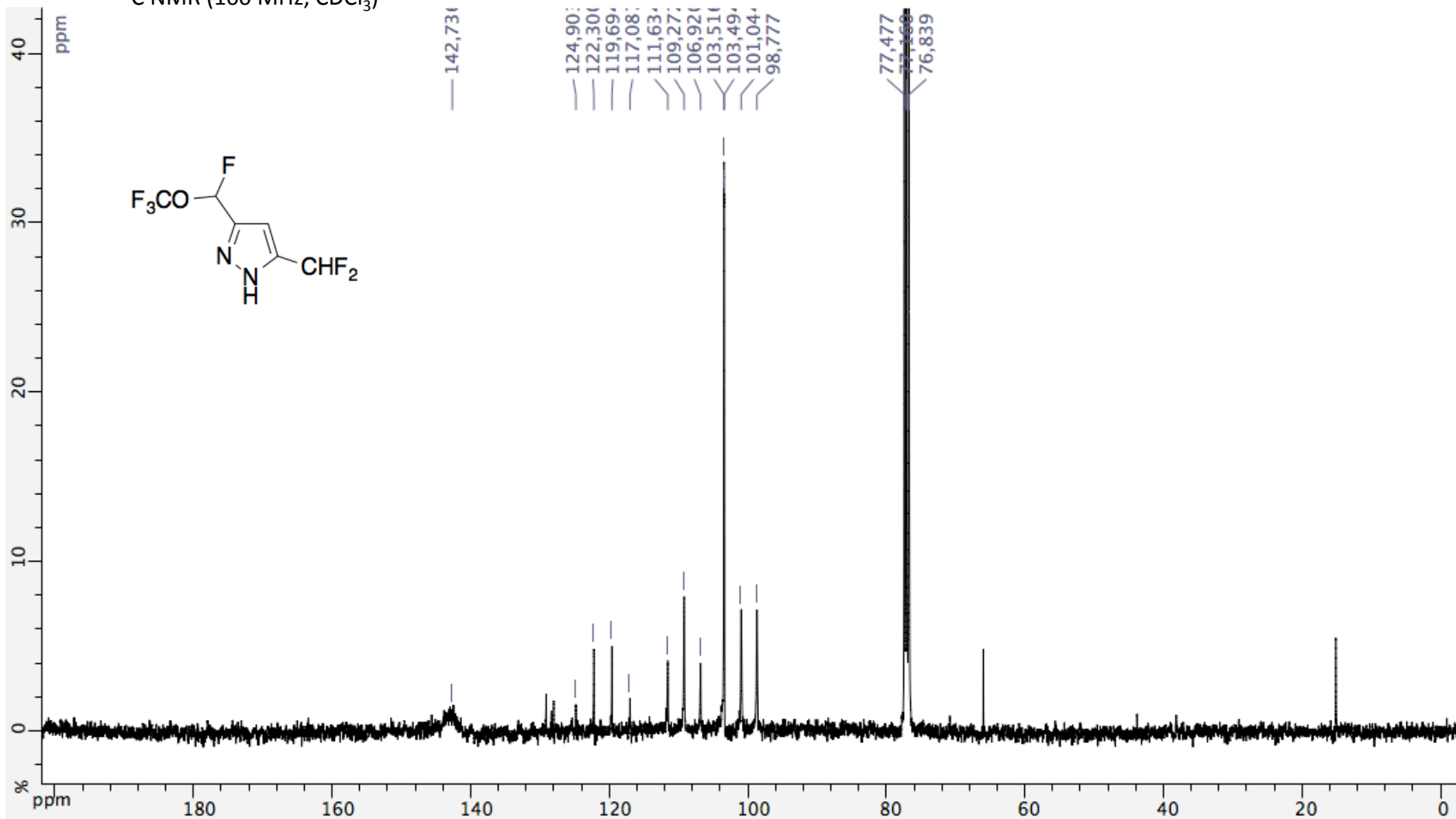
5-(Difluoromethyl)-3-(fluoro(trifluoromethoxy)methyl)-1H-pyrazole (**12a**)

^{19}F NMR (376 MHz, CDCl_3)



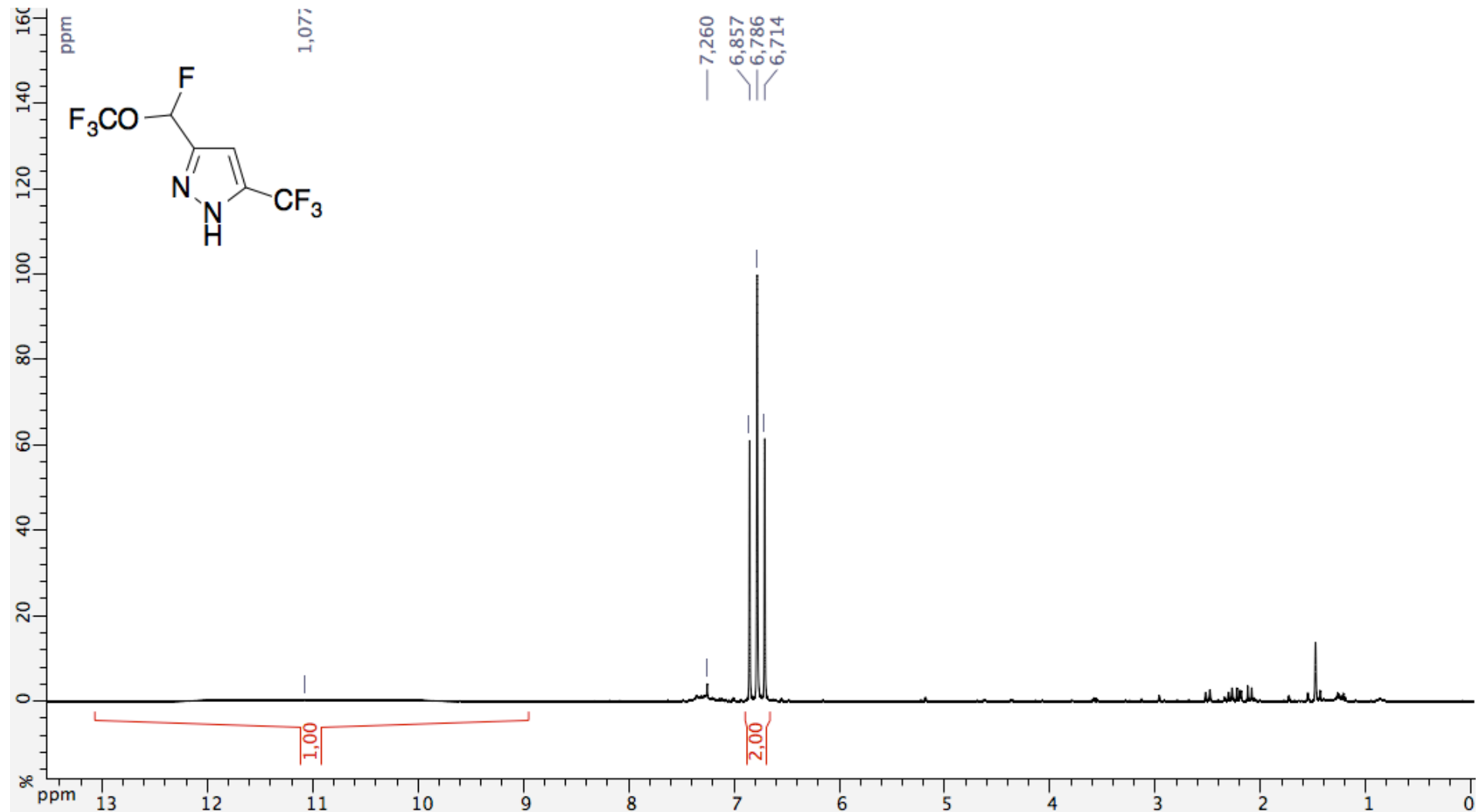
5-(Difluoromethyl)-3-(fluoro(trifluoromethoxy)methyl)-1H-pyrazole (**12a**)

^{13}C NMR (100 MHz, CDCl_3)



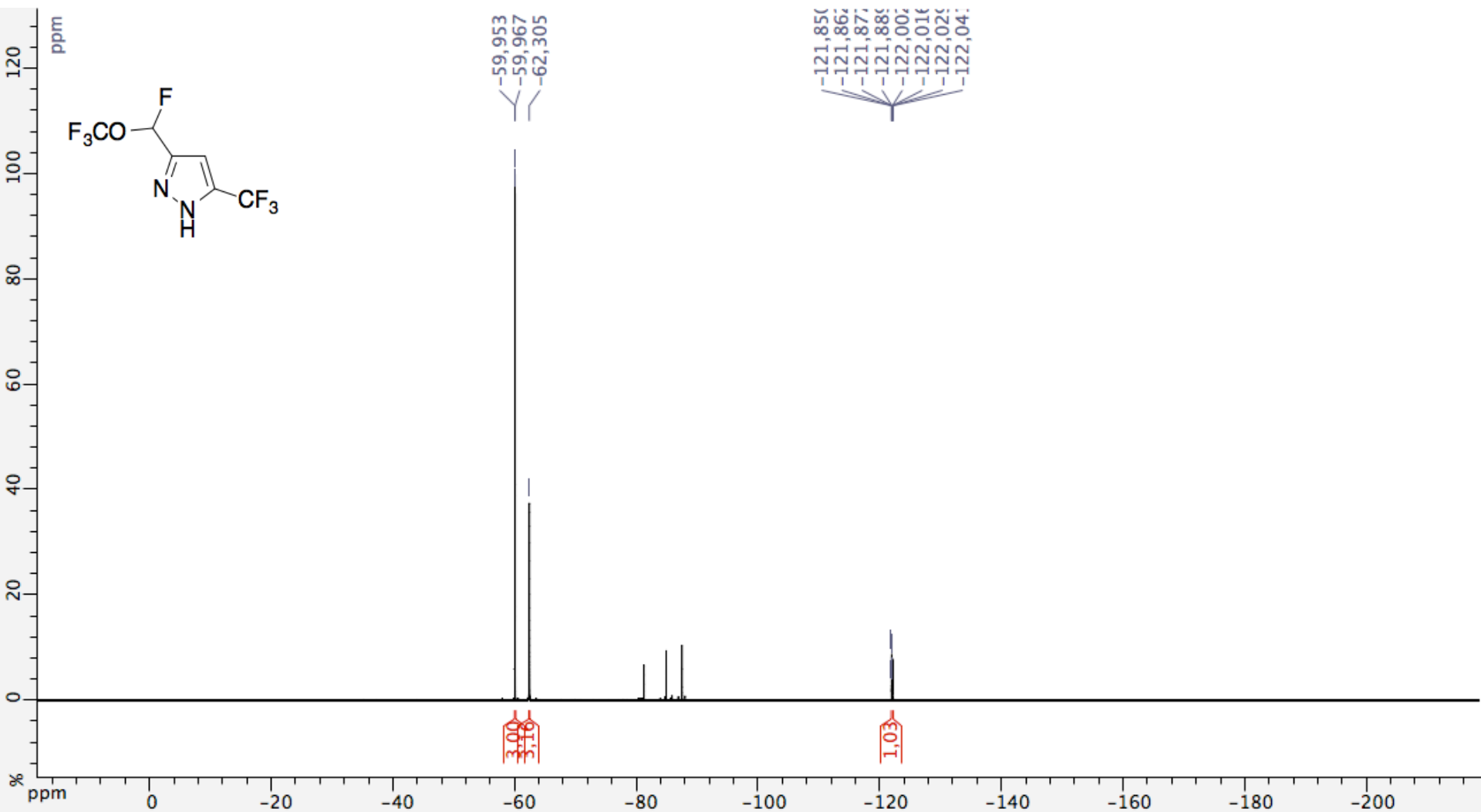
3-(Fluoro(trifluoromethoxy)methyl)-5-(trifluoromethyl)-1H-pyrazole (**12b**)

^1H NMR (400 MHz, CDCl_3)



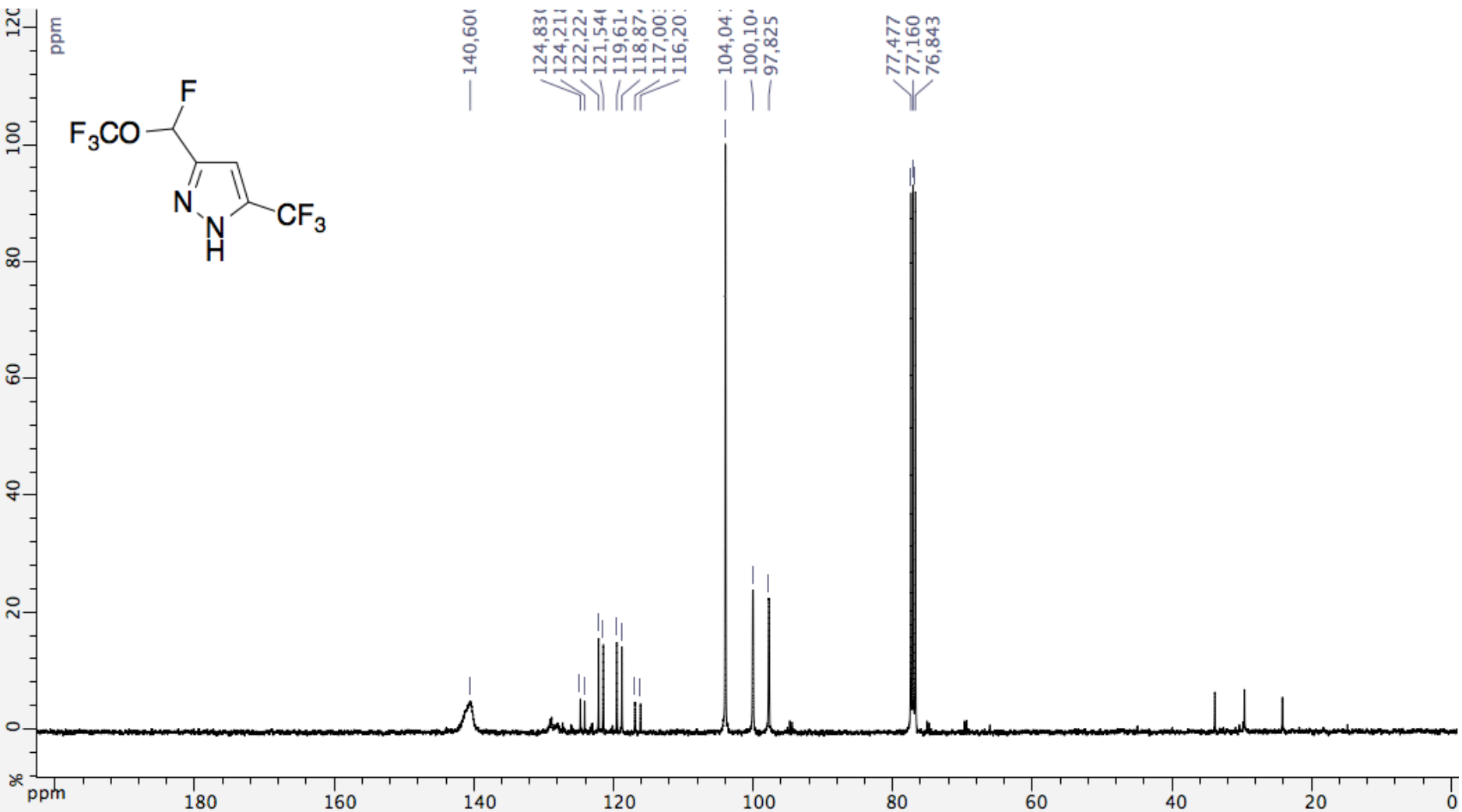
3-(Fluoro(trifluoromethoxy)methyl)-5-(trifluoromethyl)-1H-pyrazole (**12b**)

^{19}F NMR (376 MHz, CDCl_3)



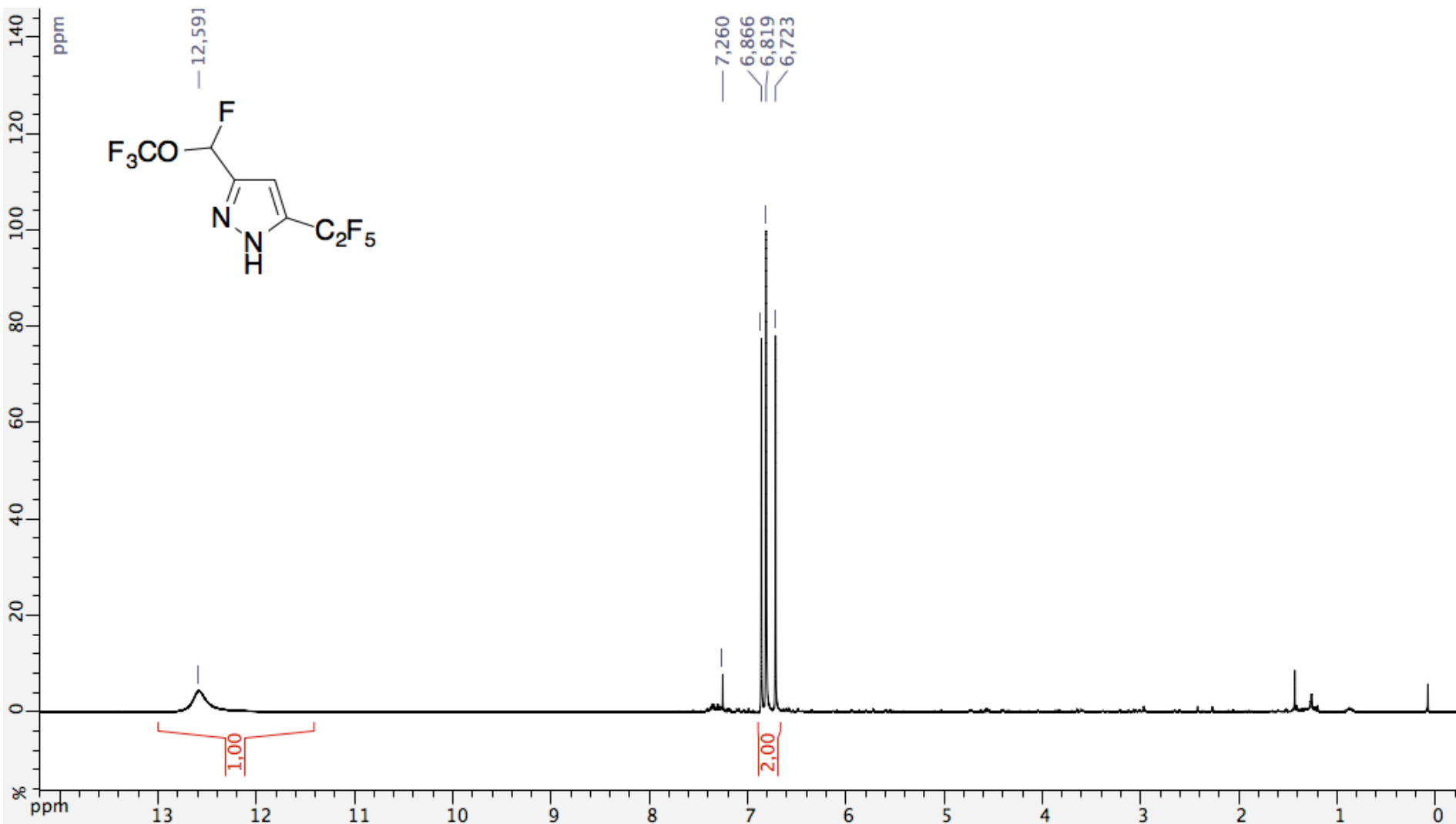
3-(Fluoro(trifluoromethoxy)methyl)-5-(trifluoromethyl)-1H-pyrazole (**12b**)

^{13}C NMR (100 MHz, CDCl_3)



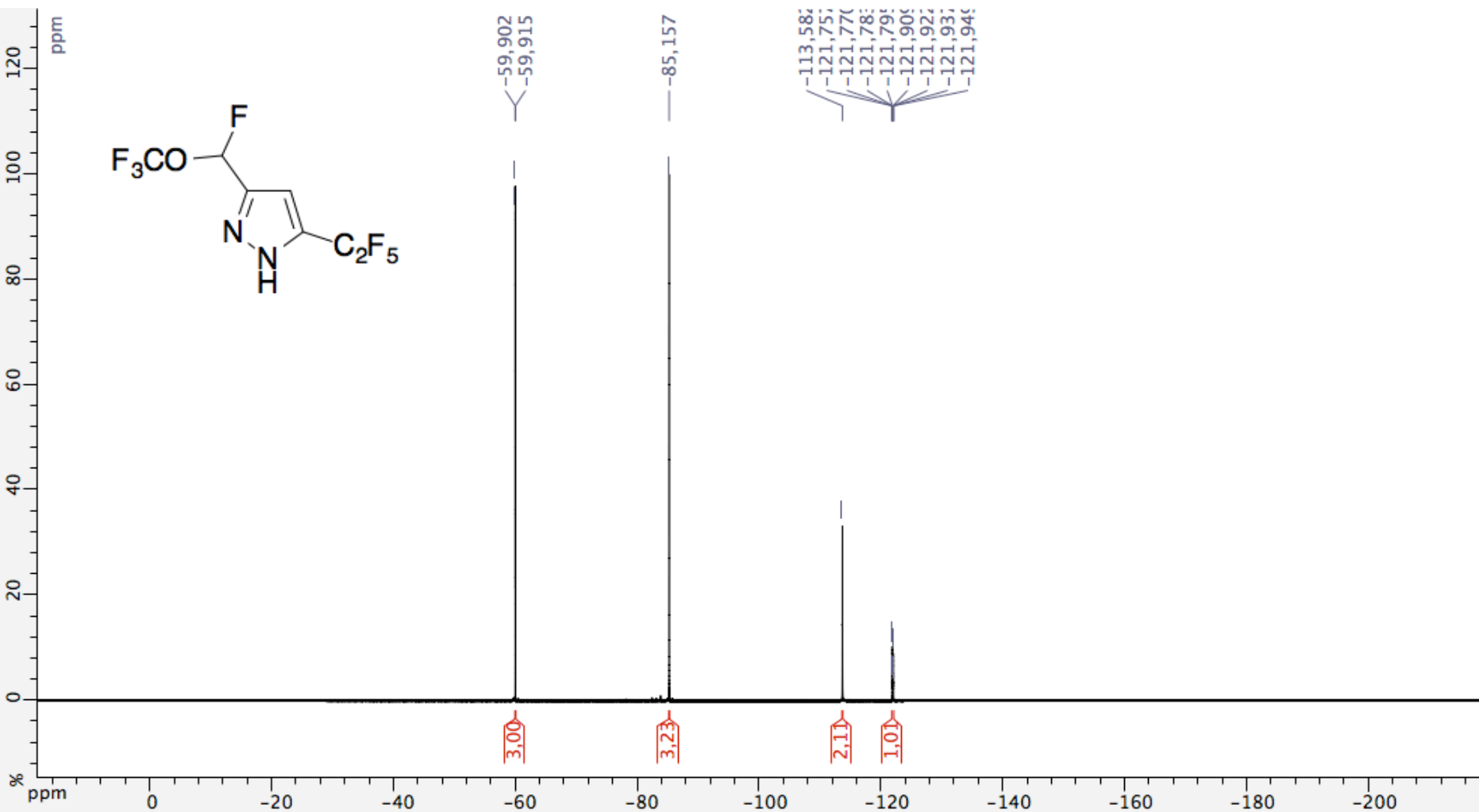
3-(Fluoro(trifluoromethoxy)methyl)-5-(perfluoroethyl)-1H-pyrazole (**12c**)

^1H NMR (400 MHz, CDCl_3)



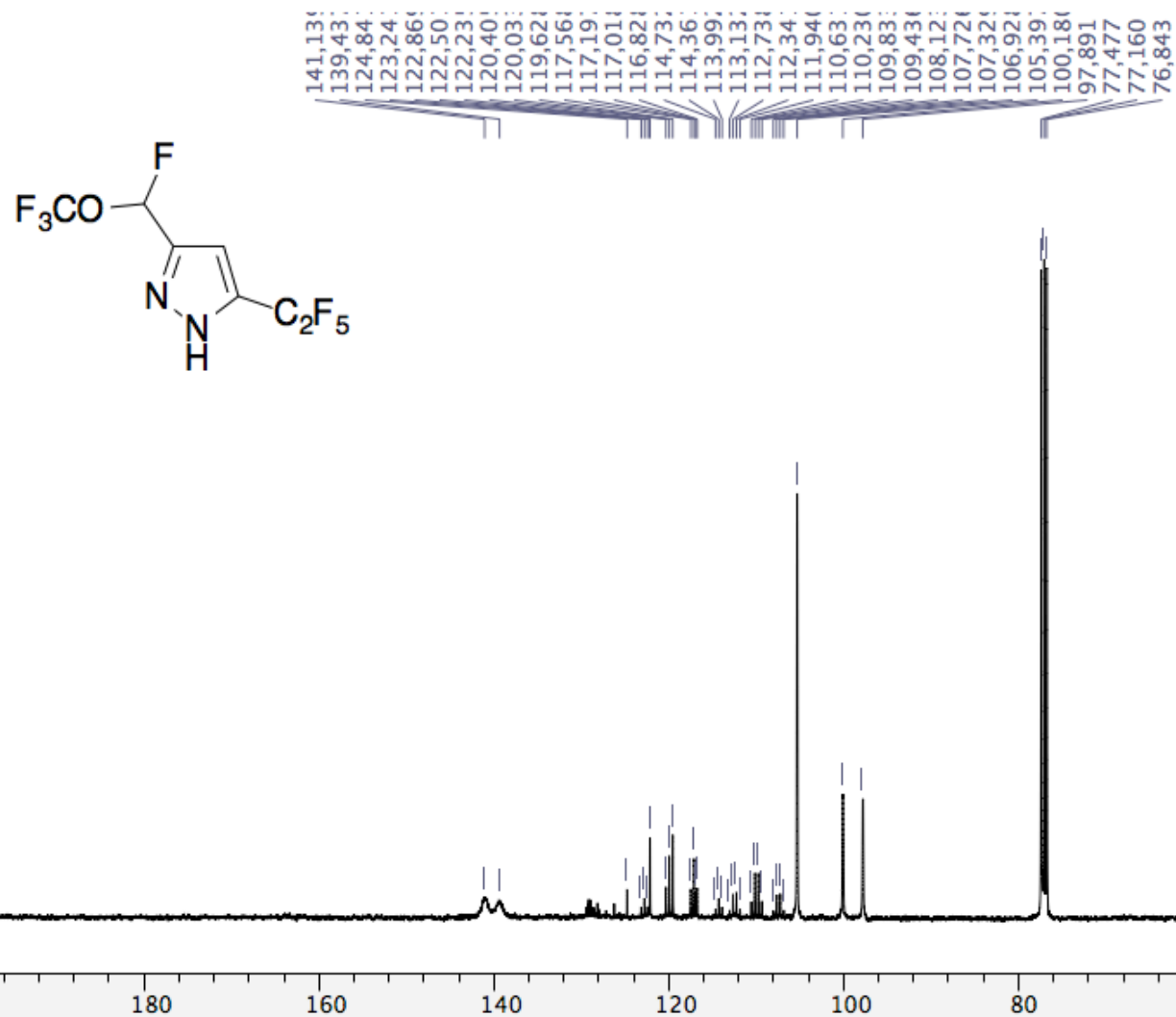
3-(Fluoro(trifluoromethoxy)methyl)-5-(perfluoroethyl)-1H-pyrazole (**12c**)

^{19}F NMR (376 MHz, CDCl_3)



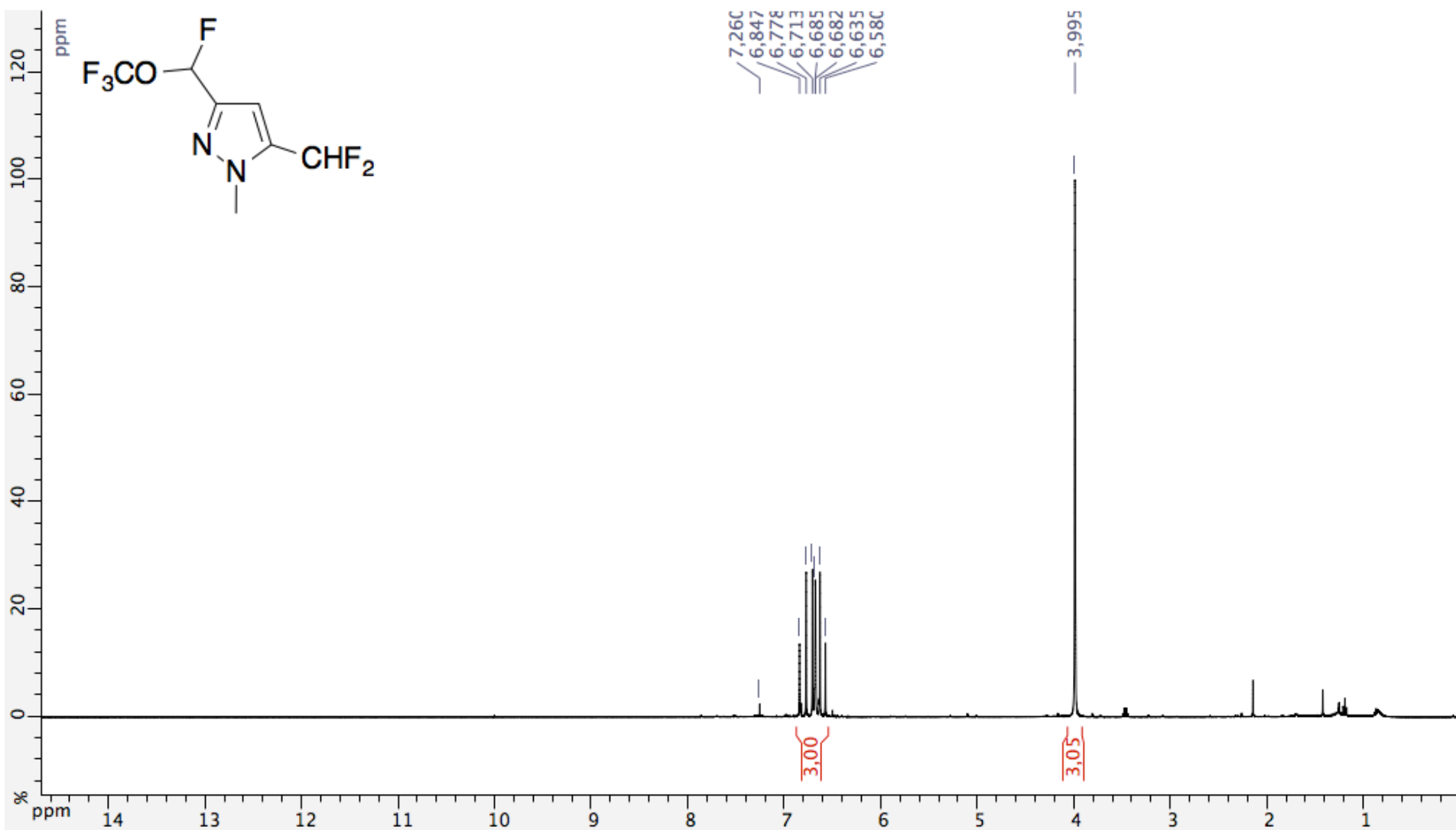
3-(Fluoro(trifluoromethoxy)methyl)-5-(perfluoroethyl)-1H-pyrazole (**12c**)

^{13}C NMR (100 MHz, CDCl_3)



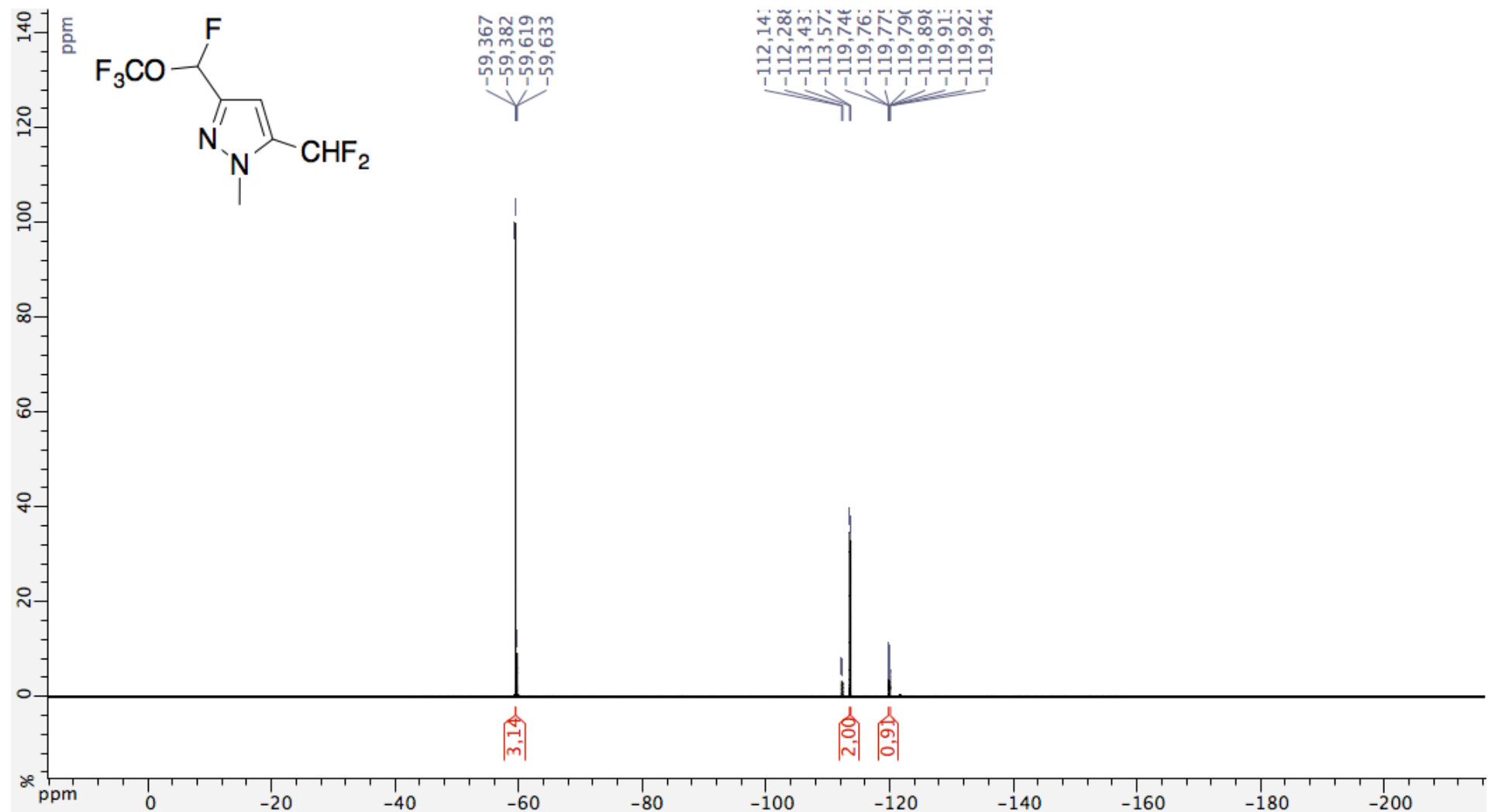
5-(Difluoromethyl)-3-(fluoro(trifluoromethoxy)methyl)-1-methyl-1H-pyrazole (**13a**)

^1H NMR (400 MHz, CDCl_3)



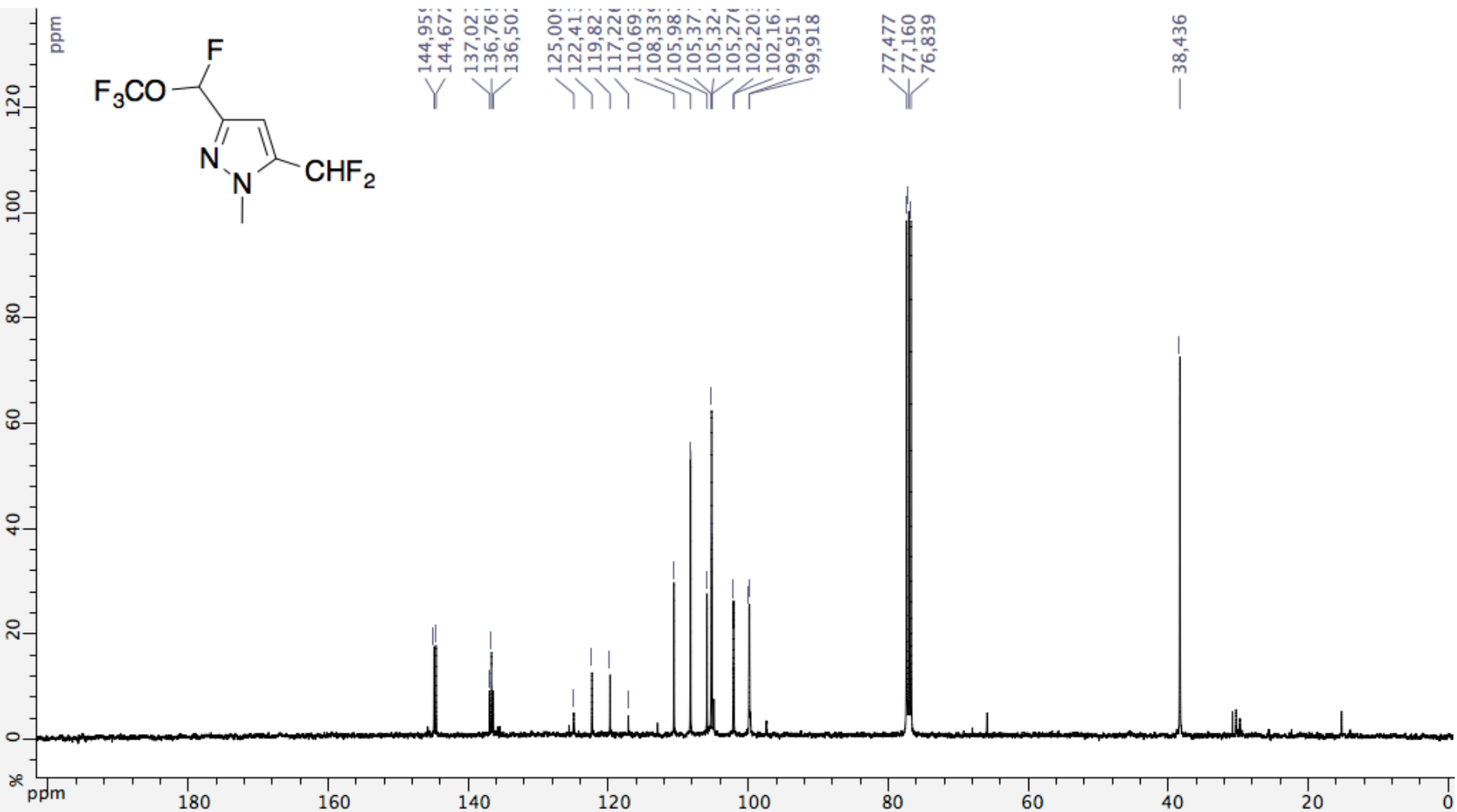
5-(Difluoromethyl)-3-(fluoro(trifluoromethoxy)methyl)-1-methyl-1H-pyrazole (**13a**)

^{19}F NMR (376 MHz, CDCl_3)



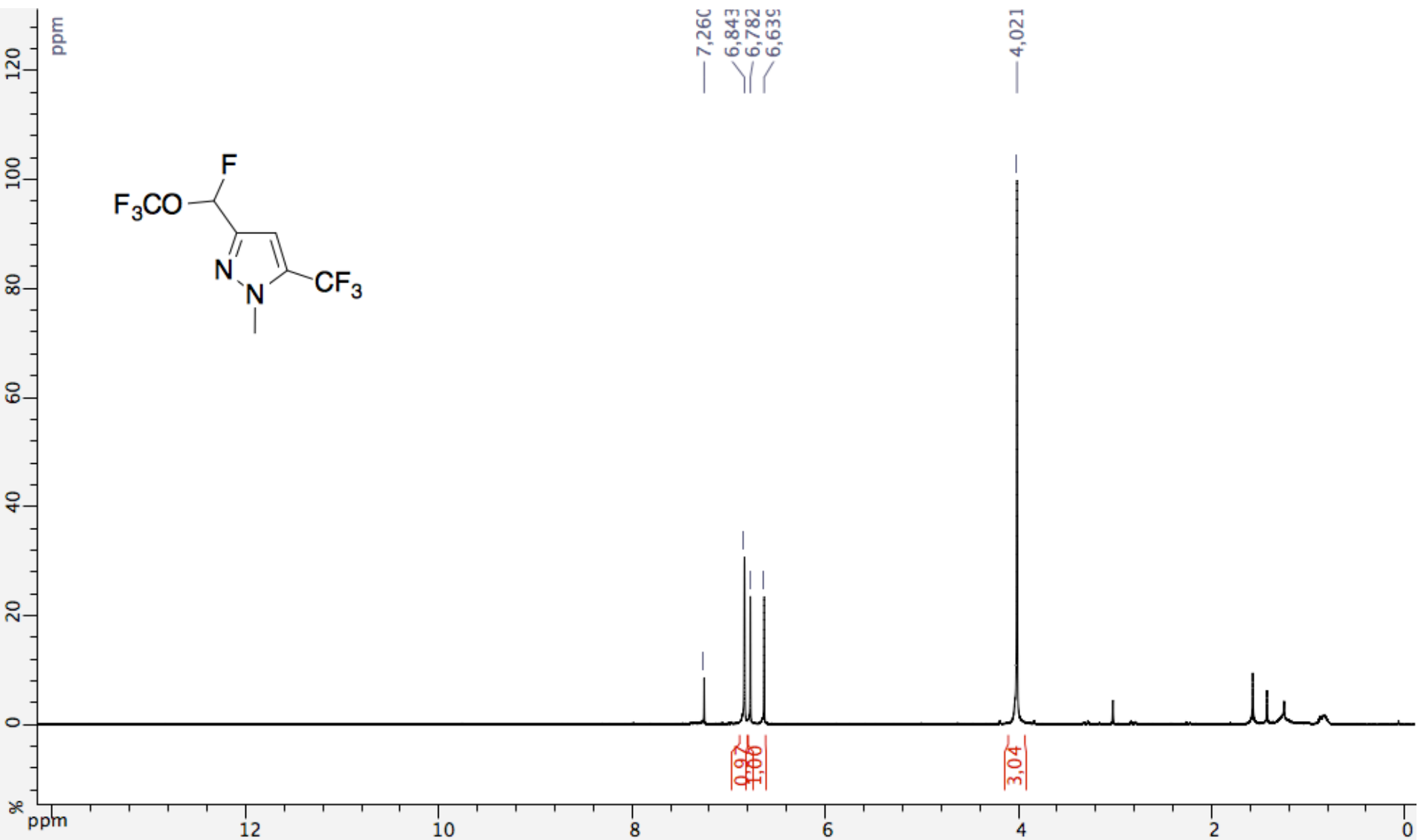
5-(Difluoromethyl)-3-(fluoro(trifluoromethoxy)methyl)-1-methyl-1H-pyrazole (**13a**)

^{13}C NMR (100 MHz, CDCl_3)



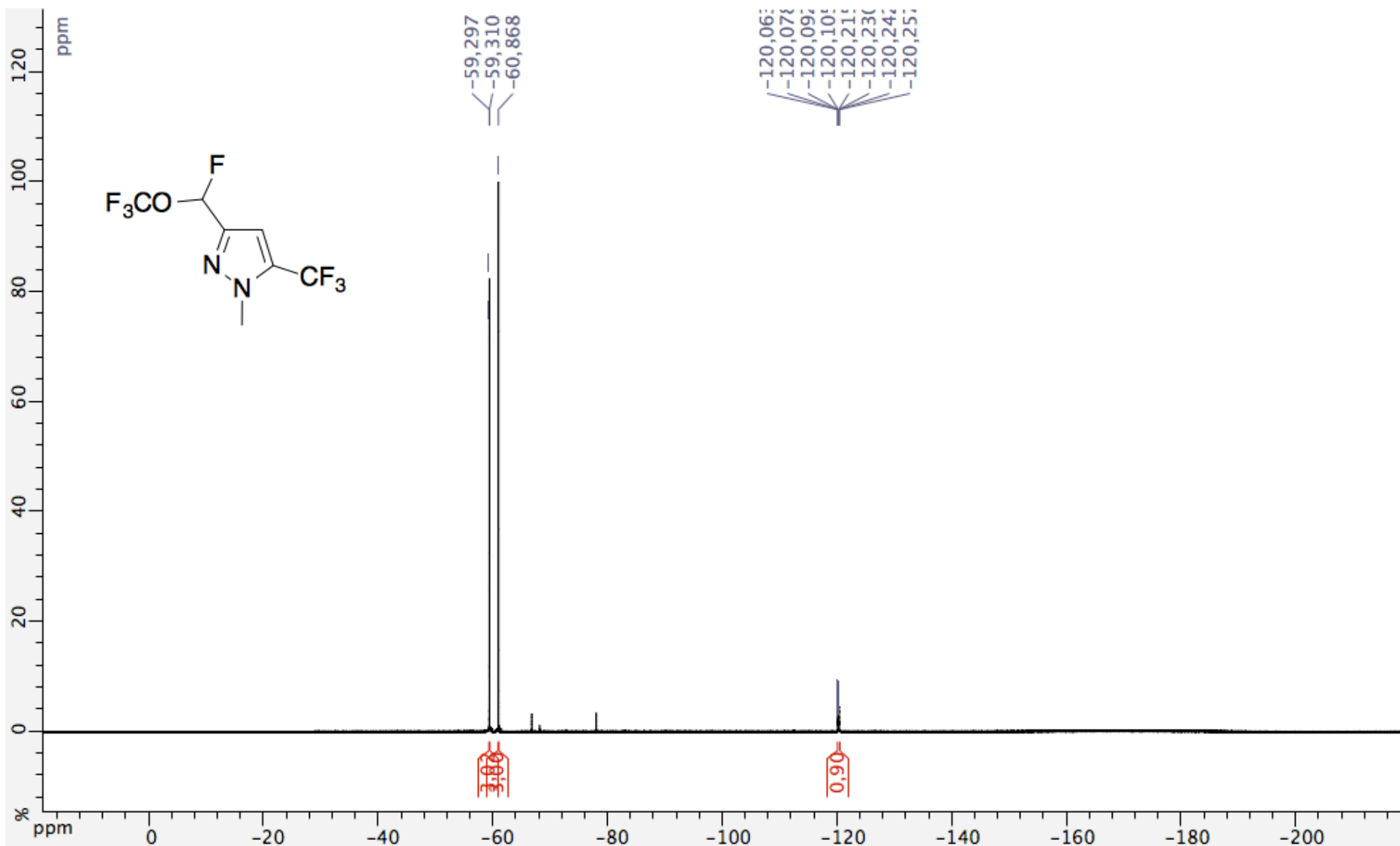
3-(Fluoro(trifluoromethoxy)methyl)-1-methyl-5-(trifluoromethyl)-1H-pyrazole (**13b**)

^1H NMR (400 MHz, CDCl_3)



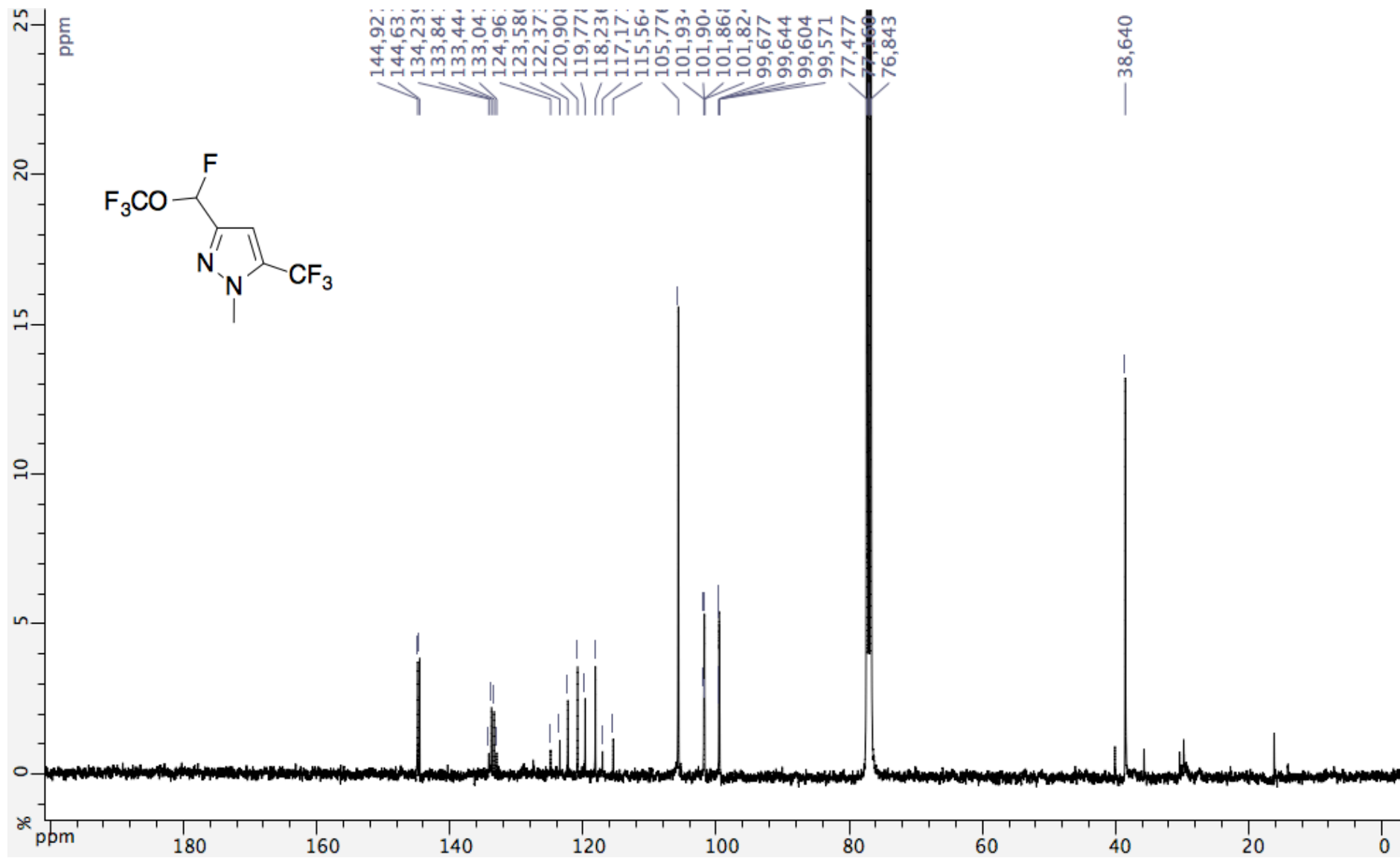
3-(Fluoro(trifluoromethoxy)methyl)-1-methyl-5-(trifluoromethyl)-1H-pyrazole (**13b**)

^{19}F NMR (376 MHz, CDCl_3)



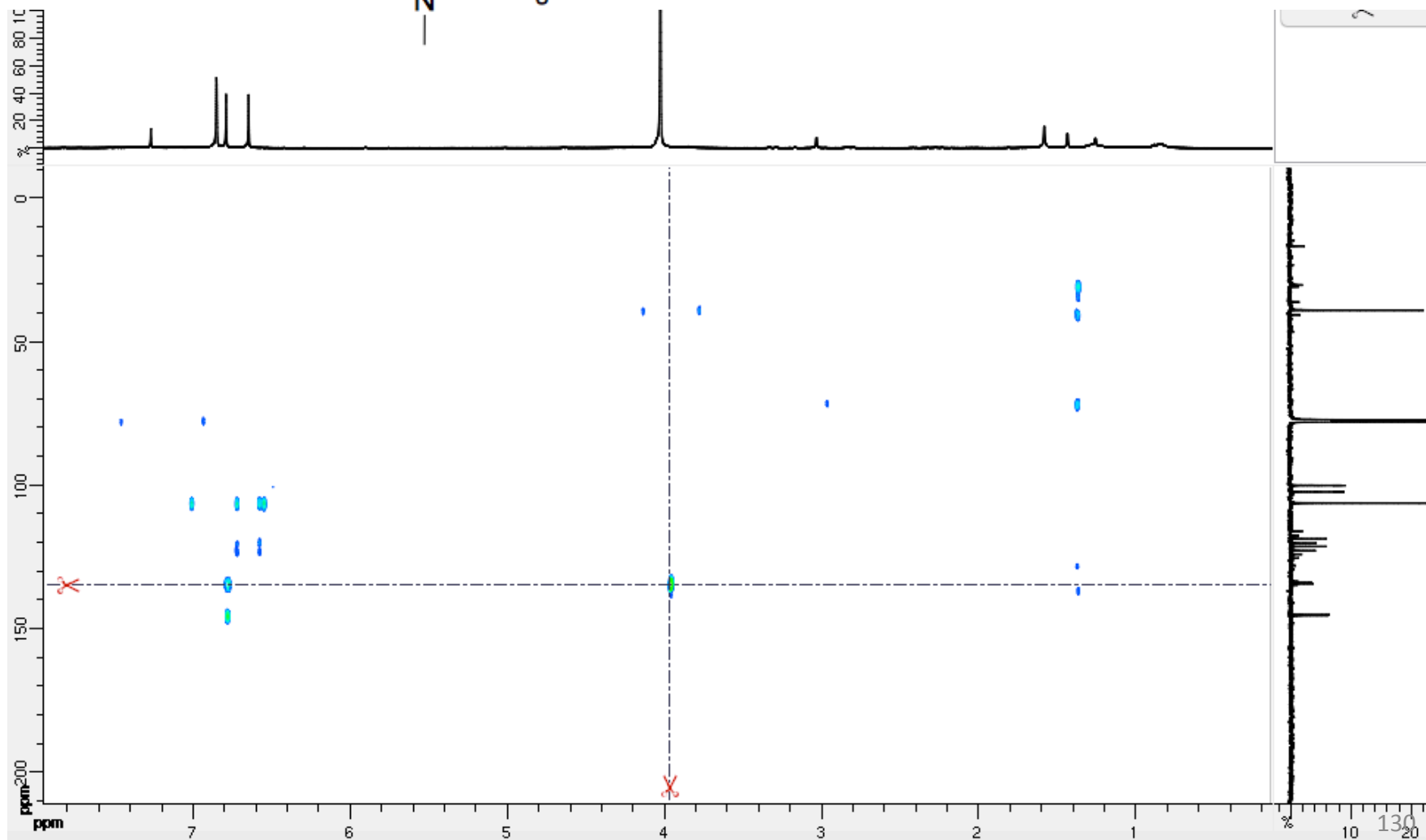
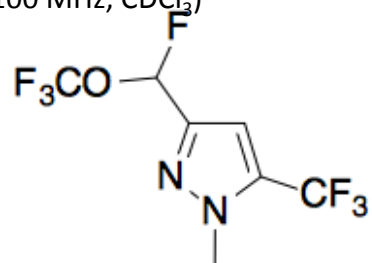
3-(Fluoro(trifluoromethoxy)methyl)-1-methyl-5-(trifluoromethyl)-1H-pyrazole (**13b**)

^{13}C NMR (100 MHz, CDCl_3)



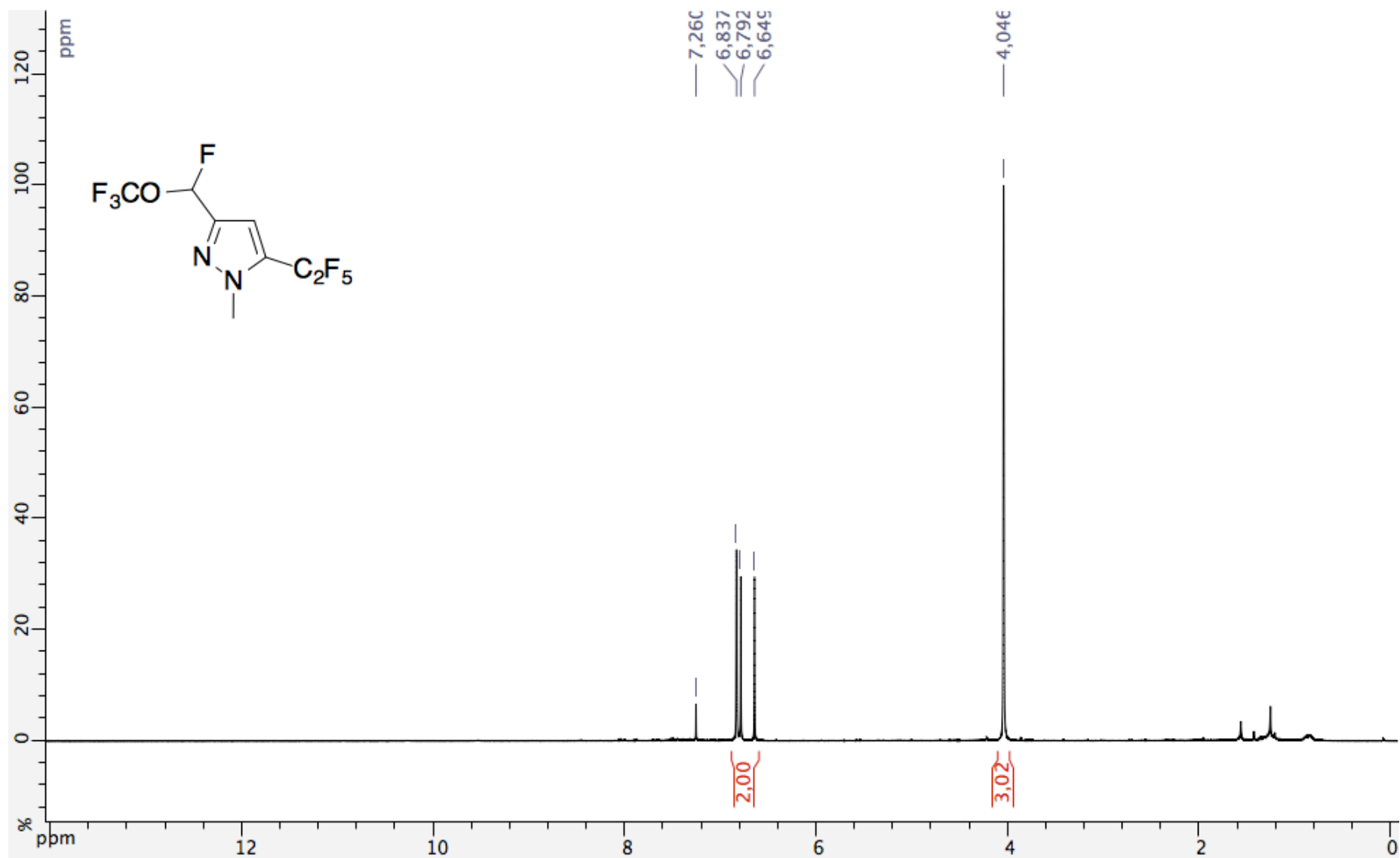
3-(Fluoro(trifluoromethoxy)methyl)-1-methyl-5-(trifluoromethyl)-1H-pyrazole (**13b**)

HMBC (¹H NMR 100 MHz, CDCl₃)



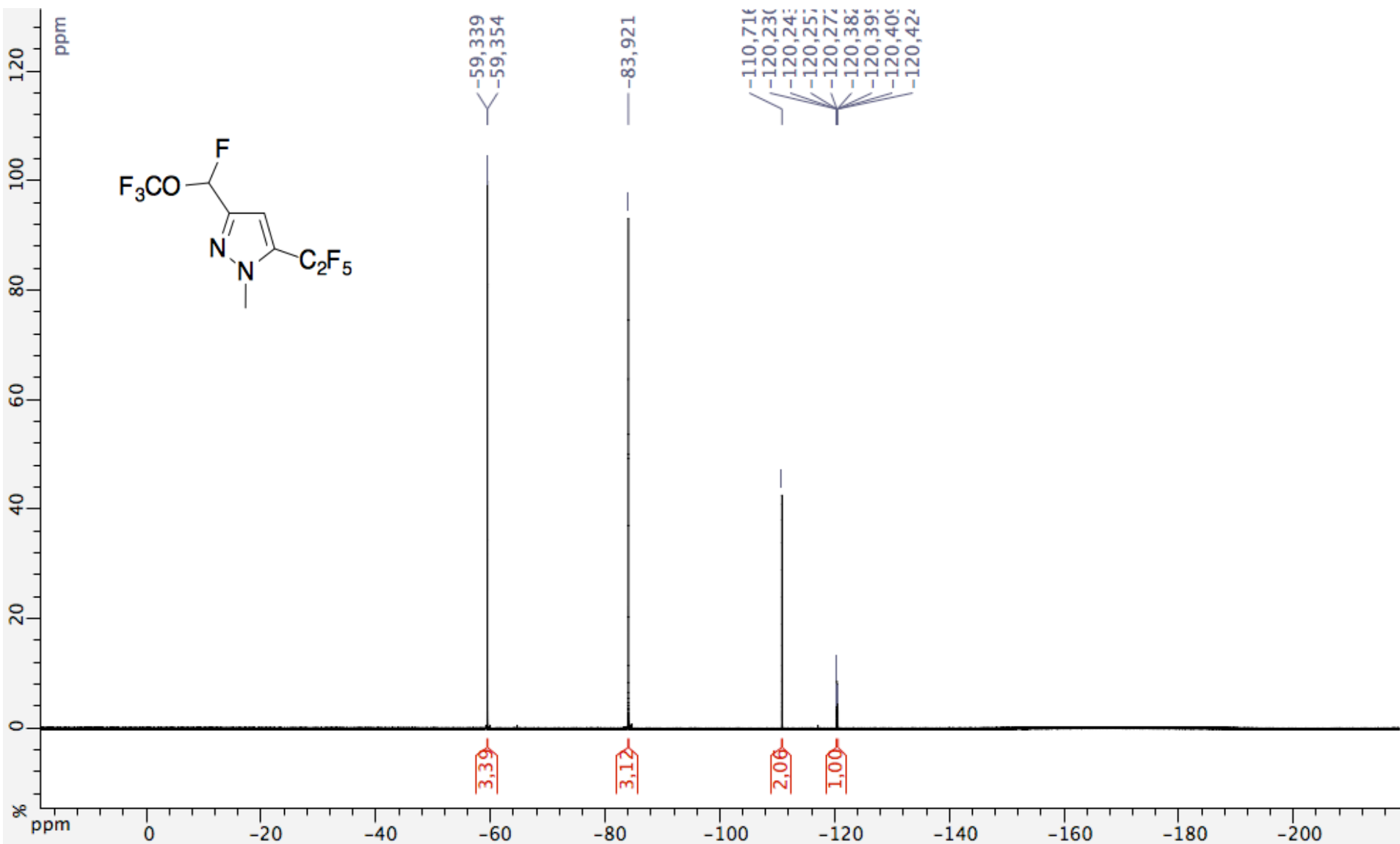
3-(Fluoro(trifluoromethoxy)methyl)-1-methyl-5-(perfluoroethyl)-1H-pyrazole (**13c**)

^1H NMR (400 MHz, CDCl_3)



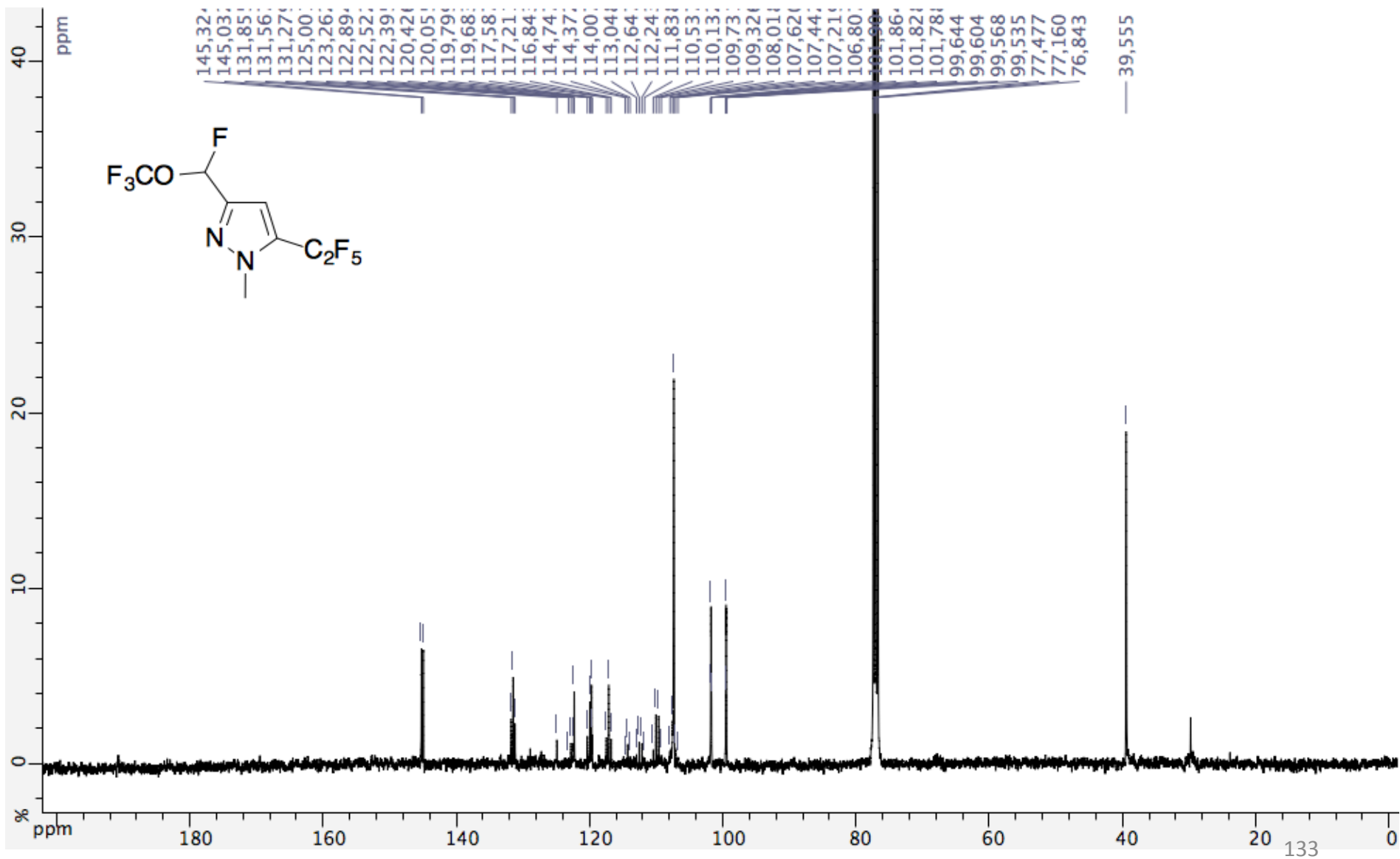
3-(Fluoro(trifluoromethoxy)methyl)-1-methyl-5-(perfluoroethyl)-1H-pyrazole (**13c**)

^{19}F NMR (376 MHz, CDCl_3)



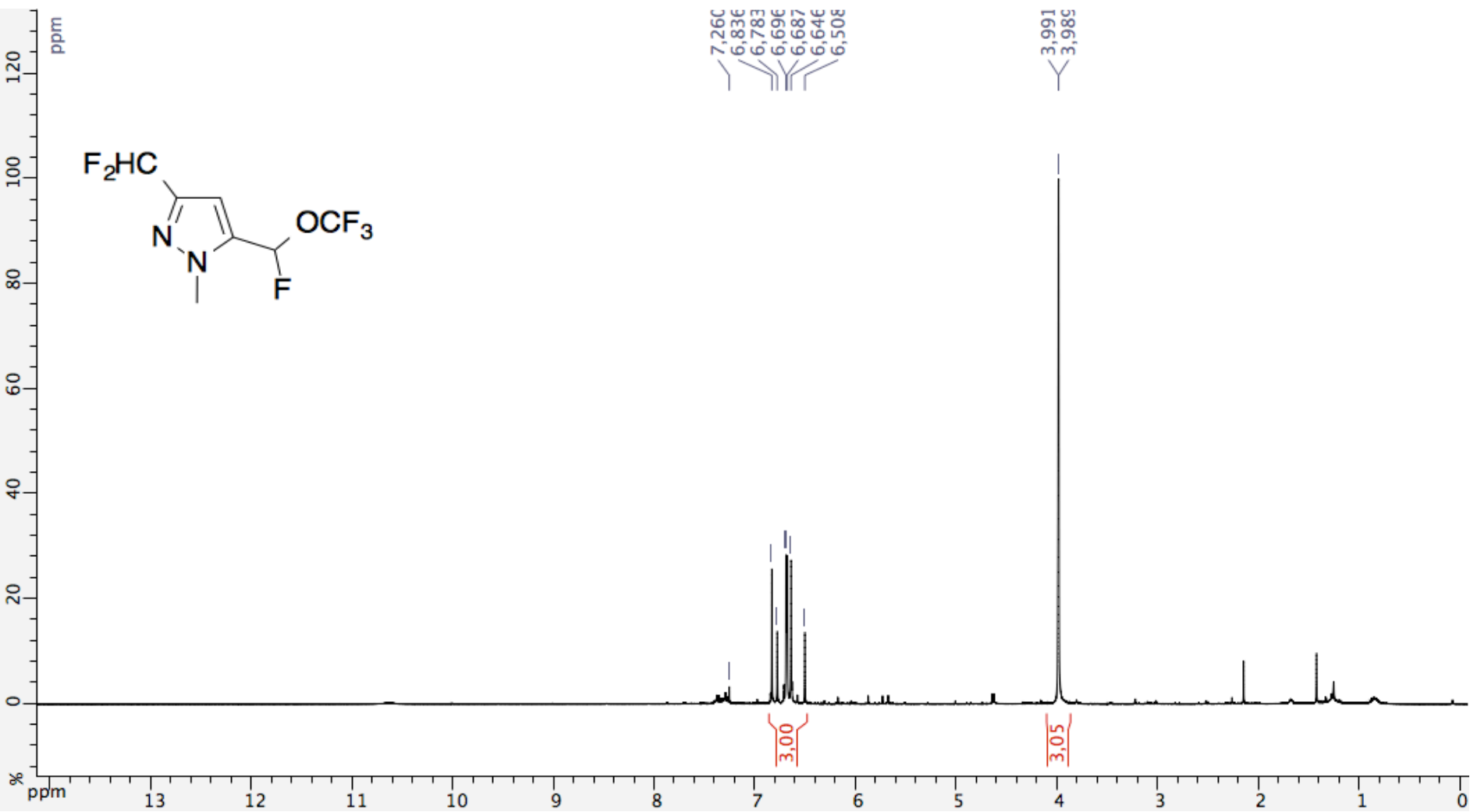
3-(Fluoro(trifluoromethoxy)methyl)-1-methyl-5-(perfluoroethyl)-1H-pyrazole (**13c**)

^{13}C NMR (100 MHz, CDCl_3)



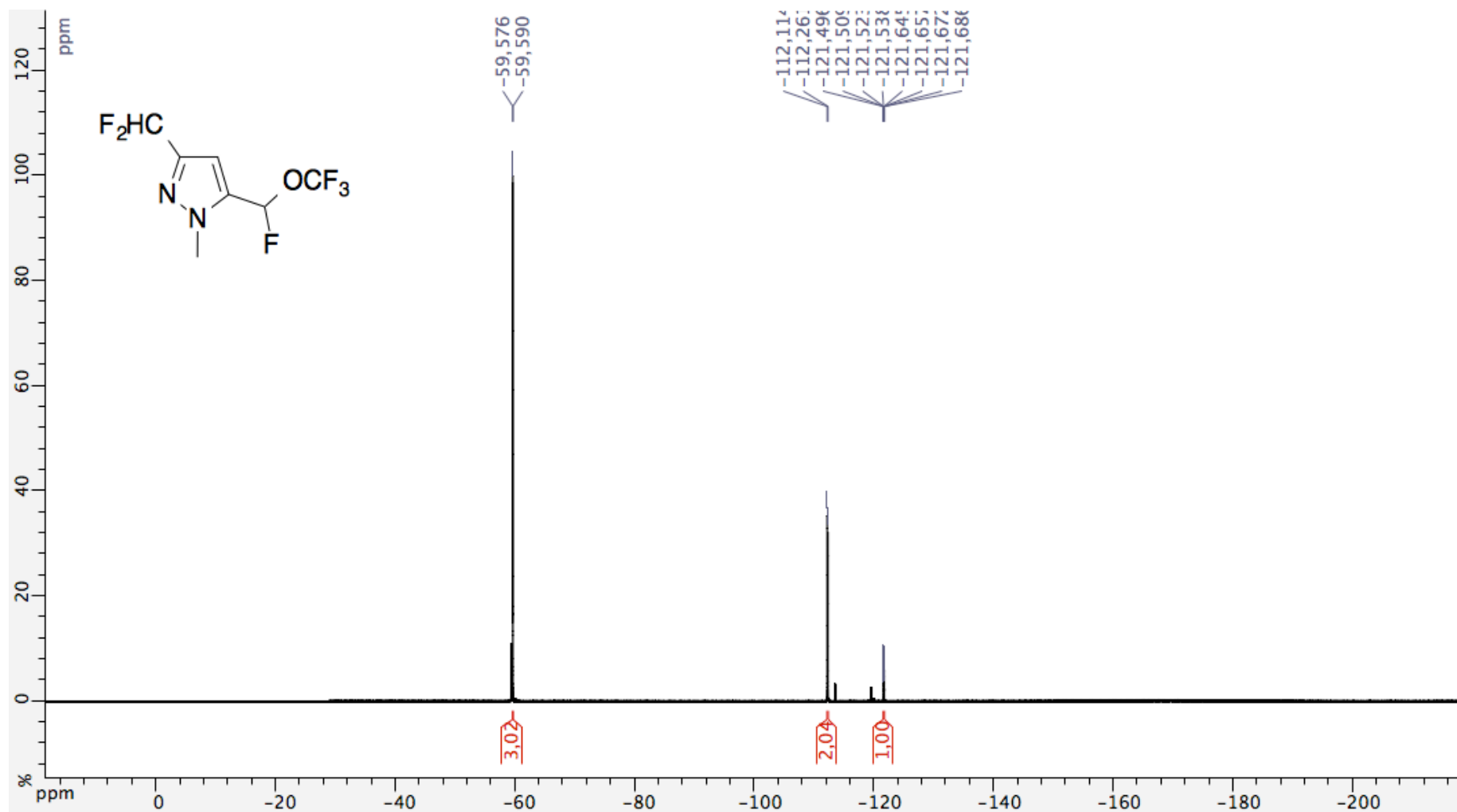
3-(Difluoromethyl)-5-(fluoro(trifluoromethoxy)methyl)-1-methyl-1H-pyrazole (**14a**)

^1H NMR (400 MHz, CDCl_3)



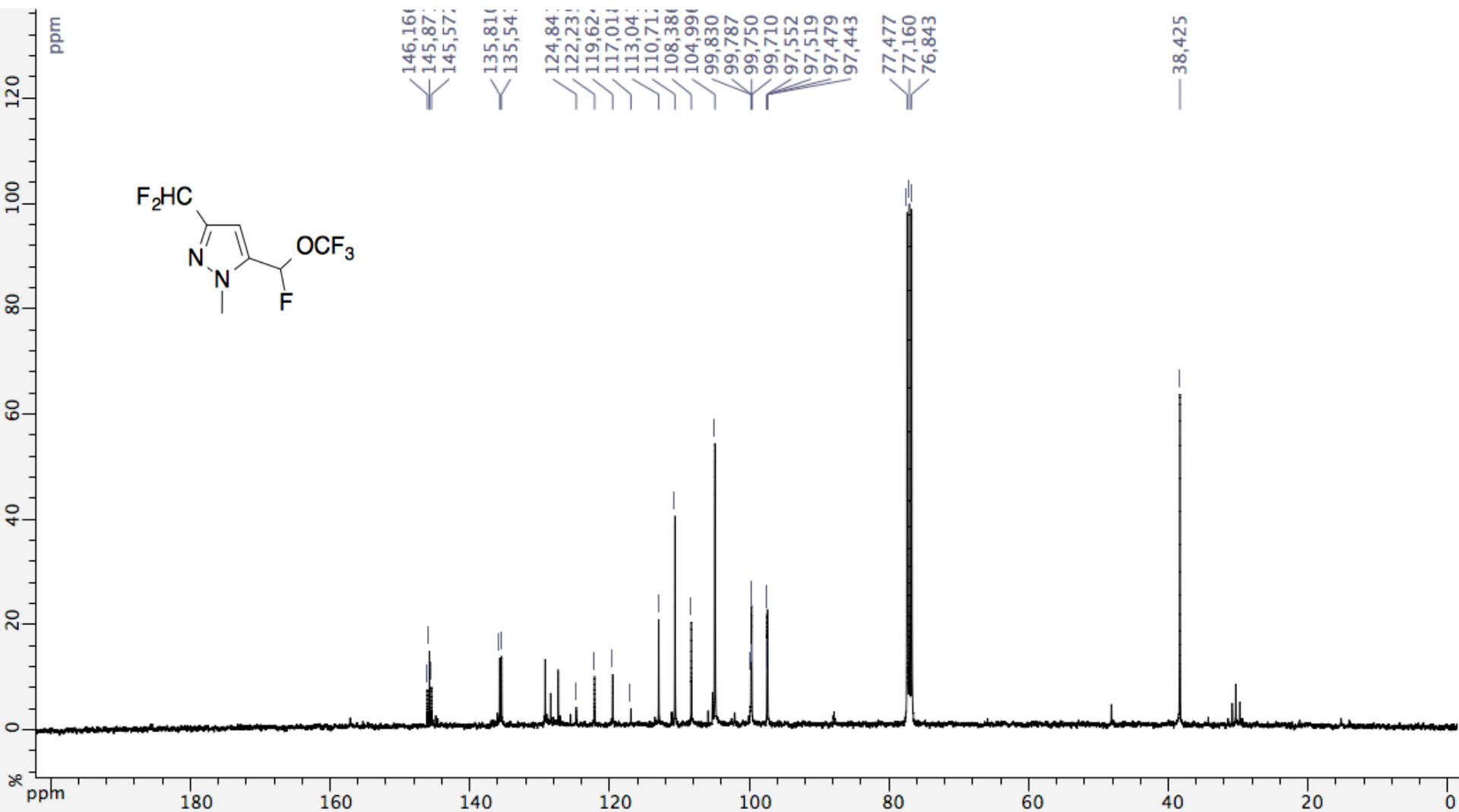
3-(Difluoromethyl)-5-(fluoro(trifluoromethoxy)methyl)-1-methyl-1H-pyrazole (**14a**)

^{19}F NMR (376 MHz, CDCl_3)



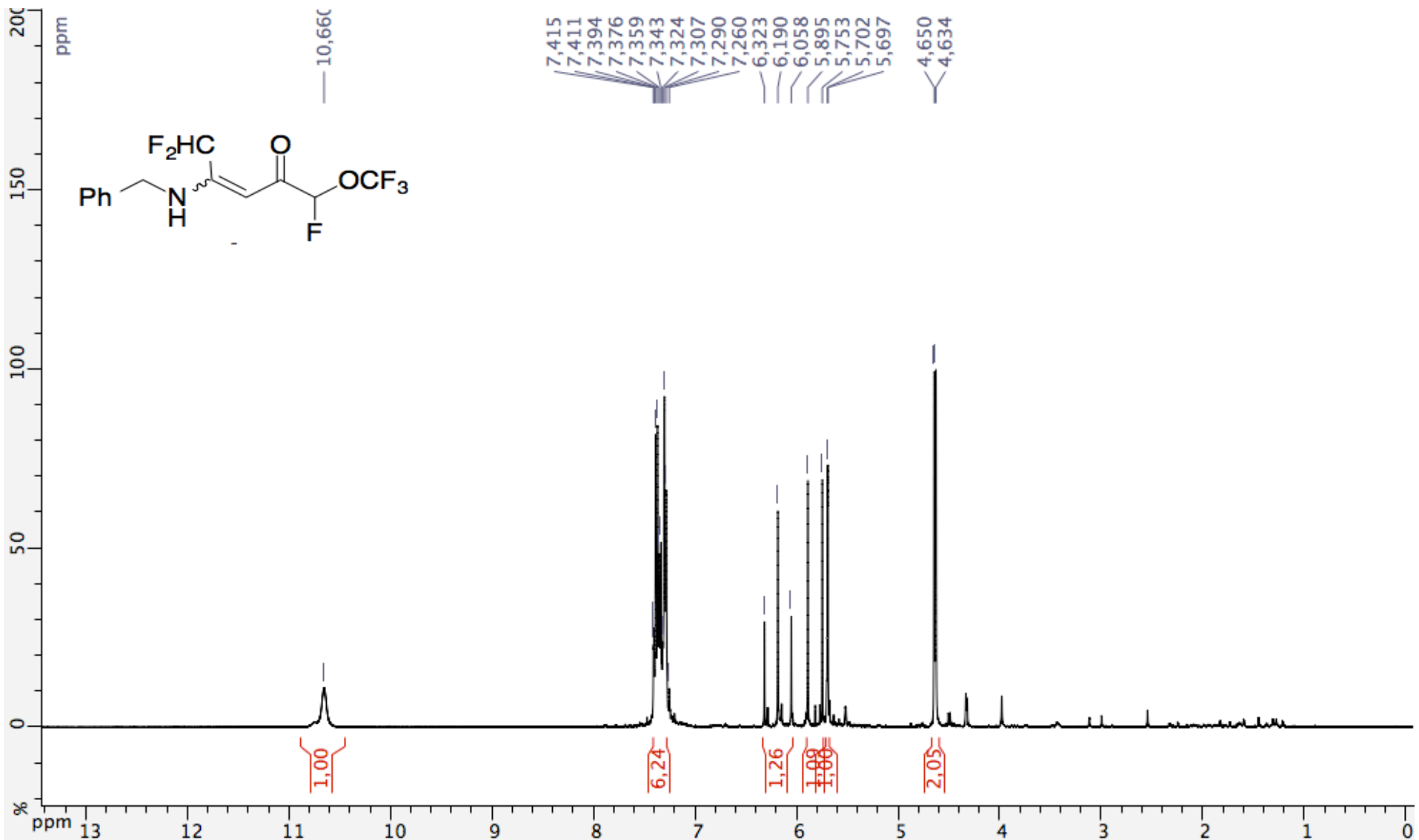
3-(Difluoromethyl)-5-(fluoro(trifluoromethoxy)methyl)-1-methyl-1H-pyrazole (**14a**)

^{13}C NMR (100 MHz, CDCl_3)



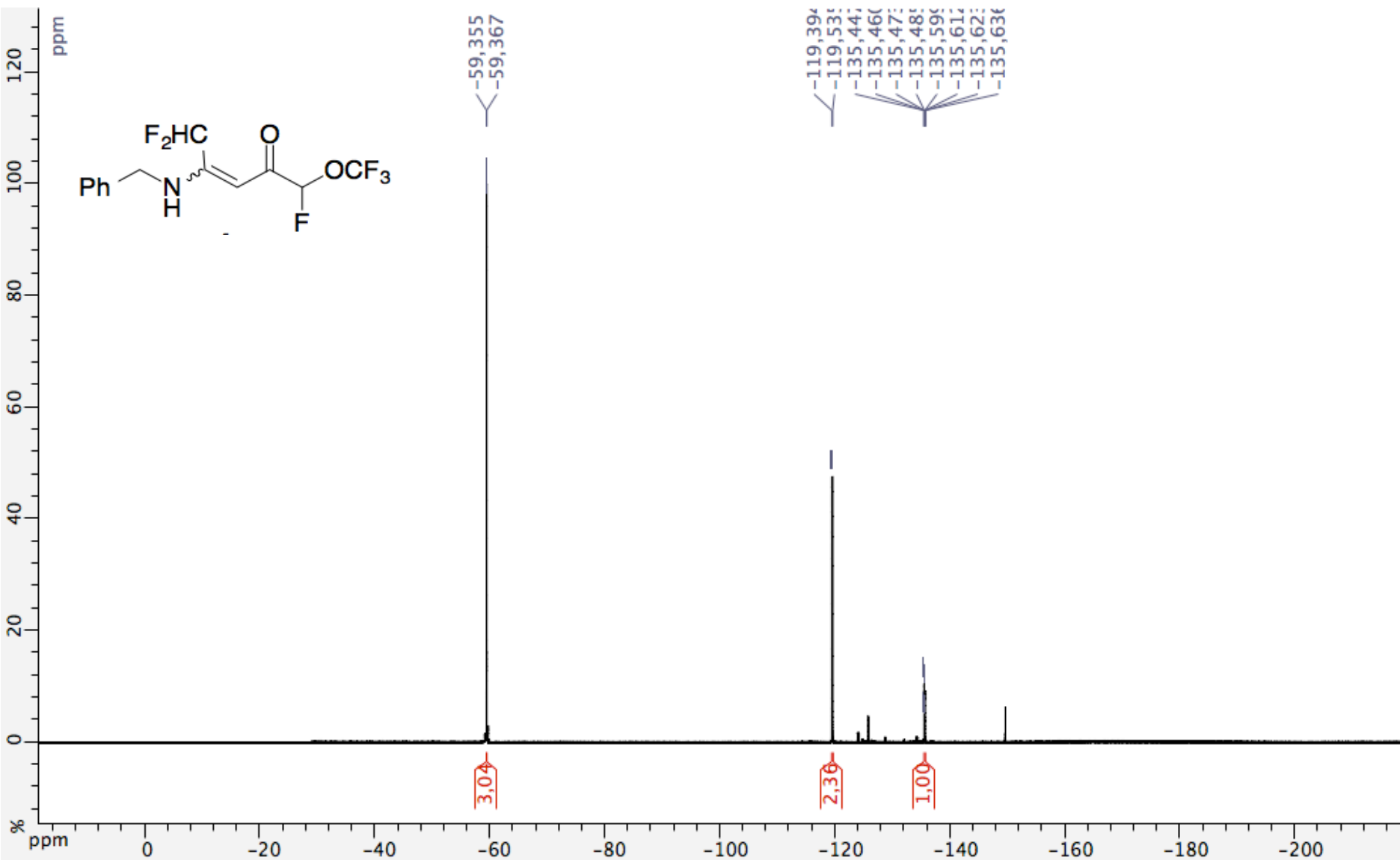
4-(Benzylamino)-1,5,5-trifluoro-1-(trifluoromethoxy)pent-3-en-2-one (**15**)

$^1\text{H NMR}$ (400 MHz, CDCl_3)



4-(Benzylamino)-1,5,5-trifluoro-1-(trifluoromethoxy)pent-3-en-2-one (**15**)

^{19}F NMR (376 MHz, CDCl_3)



4-(Benzylamino)-1,5,5-trifluoro-1-(trifluoromethoxy)pent-3-en-2-one (**15**)

^{13}C NMR (100 MHz, CDCl_3)

