Electronic Supplementary Material (ESI) for ChemComm.

Efficient DBU accelerated synthesis of ^{18}F-labelled trifluoroacetamides

Antonio Bermejo Gómez,[a],[b],[c] Miguel A. Cortés González,[b],[c] Marvin Lübcke,[b],[c] Magnus J. Johansson,[d] Christer Halldin[e], Kálmán J. Szabó[b],[c] and Magnus Schou*[a],[c],[e]

[a]Dr A. Bermejo Gómez, Dr M. Schou
AstraZeneca Personalised Healthcare and Biomarkers. PET Centre at Karolinska Institutet, Karolinska Universitetssjukhuset Solna, R5:U1, SE-171 76 Stockholm, Sweden

[b]Dr A. Bermejo Gómez, M. A. Cortés González, M. Lübcke, Prof. K. J. Szabó
Department of Organic Chemistry, Stockholm University
Arrhenius Laboratory, SE-106 91 Stockholm, Sweden

[c]Dr A. Bermejo Gómez, M. A. Cortés González, M. Lübcke, Prof. K. J. Szabó, Dr M. Schou
Stockholm Brain Institute, Karolinska Institutet, SE-171 77 Stockholm, Sweden

[d]Dr M. J. Johansson
CVMD iMed, Medicinal Chemistry AstraZeneca R&D, Mölndal, SE-431 83, Sweden

[e]Prof. C. Halldin, Dr M. Schou, Dept of Clinical Neuroscience, Karolinska Institutet, SE-17176 Stockholm, Sweden

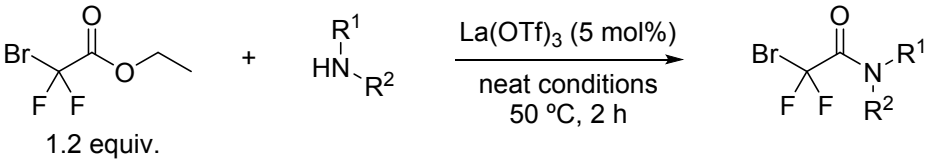
E-mail: magnus.schou@astrazeneca.com

Table of contents for Supporting Information

General Information:

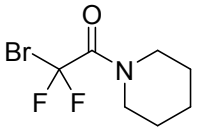
All reactions were carried out in closed glass reaction vials under an atmosphere of dry Ar. Reagents were used as obtained from commercial suppliers without further purification. Dry DMF was used as obtained from a commercial supplier (puriss p. a.). Flash chromatography was carried out on 60 Å (35-70 μm) silica gel (Acros Kieselgel 60) using *n*-pentane or *n*-pentane / EtOAc, *n*-pentane / Et_2O or *n*-pentane / acetone mixtures as eluent. Analytical TLC was carried out on aluminum-backed plates (1.5 Å, ~ 5 cm) pre-coated (0.25 mm) with silica gel (Merck, Silica Gel 60 F254). Compounds were visualized by exposure to UV light or by dipping the plates in a solution of 0.75% $KMnO_4$ (w/v) in a aqueous solution of K_2CO_3 0.36 M. Melting points were recorded in a metal block and are uncorrected. ^1H NMR spectra were recorded at 400 MHz; ^{13}C NMR spectra were recorded at 100 MHz, ^{19}F NMR spectra were recorded at 377 MHz with a Bruker Advance spectrometer. ^1H and ^{13}C NMR chemical shifts (δ) are reported in ppm from tetramethylsilane, using the residual solvent resonance ($CHCl_3$: δ_H 7.26 and $CDCl_3$: δ_C 77.0) as an internal reference. Coupling constants (*J*) are given in Hz. High-resolution mass spectra (HRMS) were recorded with a Bruker microTOF ESI-TOF mass spectrometer. We were not able to obtain high-resolution mass data for some of the compounds. Therefore, we provide EI mass data in the characterization.

Synthesis and characterization of bromodifluoroacetamides 2x-x:



Following the procedure describe in the literature. [1,2] In a 5 mL sealed glass vial the corresponding amine (2.5 mmol, 1 equiv.), ethyl 2-bromo-2,2-difluoroacetate (3.0 mmol, 1.2 equiv., 609 mg) and $La(OTf)_3$ (0.125 mmol, 0.05 equiv., 73 mg) were stirred under an atmosphere of argon at 50 ºC for 2 h. Purification by column chromatography afforded the desired amide.

2-Bromo-2,2-difluoro-1-(piperidin-1-yl)ethan-1-one (1a)



From piperidine (213 mg). Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 1:9) afforded the title compound as a colorless oil (617 mg, 85%).

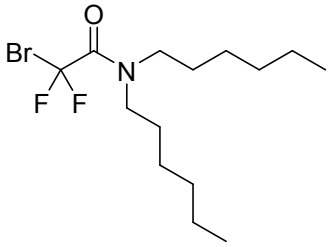
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 3.64-3.59 (m, 4H), 1.73-1.62 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 157.8 (t, *J*(C,F) = 26.1 Hz), 111.0 (t, *J*(C,F) = 314.3 Hz), 47.8 (t, *J*(C,F) = 4.1 Hz), 45.1, 26.0, 25.6, 24.3.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -53.80.

HRMS (ESI): m/z calcd for $C_7H_{10}NO^{79}BrF_2$+Na^+: 263.9806 [*M*+Na]$^+$; found: 263.9812.

2-Bromo-2,2-difluoro-*N*,*N*-dihexylacetamide (1b)



From *N*,*N*-dihexylamine (463 mg). Purification by column chromatography (SiO_2; EtOAc / *n* -pentane 1:9) afforded the title compound as a colorless oil (785 mg, 92%).

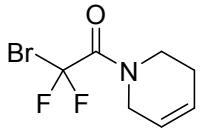
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 3.42-3.33 (m, 4H), 1.64-1.54 (m, 4H), 1.35-1.25 (m, 12H), 0.92-0.86 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 159.0 (t, *J*(C,F) = 26.1 Hz), 111.4 (t, *J*(C,F) = 315.1 Hz), 48.7 (t, *J*(C,F) = 3.5 Hz), 47.6, 31.6, 31.5, 28.7, 26.7, 26.5, 26.4, 22.6, 14.1, 14.0.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -53.91.

HRMS (ESI): m/z calcd for $C_{14}H_{26}NO^{79}BrF_2$+Na^+: 364.1058 [*M*+Na]$^+$; found: 364.1052.

2-Bromo-1-(5,6-dihydropyridin-1(2*H*)-yl)-2,2-difluoroethanone (1c)



From 1,2,3,6-tetrahydropyridine (208 mg). Purification by column chromatography (SiO_2; EtOAc / *n* -pentane 1:10) afforded the title compound as a colorless oil (572 mg, 95%).

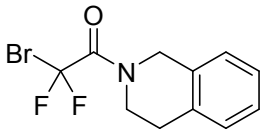
^{1}H NMR (400 MHz, $CDCl_3$, TMS, mixture of two rotamers): δ = 5.95-5.84 (m, 1H), 5.73-5.64 (m, 1H), 4.18-4.08 (m, 2H), 3.76-3.72 (m, 2H), 2.30-2.22 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS, mixture of two rotamers): δ(major) = 158.3 (t, *J*(C,F) = 26.4 Hz), 125.1, 123.4, 110.9 (t, *J*(C,F) = 314.4 Hz), 43.7, 43.7 (t, *J*(C,F) = 4.8 Hz), 25.3. δ(minor) = 158.3 (t, *J*(C,F) = 26.4 Hz), 126.4, 122.6, 111.0 (t, *J*(C,F) = 314.4 Hz), 45.9 (t, *J*(C,F) = 4.8 Hz), 41.0, 24.6.

^{19}F NMR (377 MHz, $CDCl_3$, mixture of two rotamers): δ(major) = -54.40. δ(minor) = -54.74.

HRMS (ESI): m/z calcd for $C_7H_8NO^{79}BrF_2$+Na^+: 261.9650 [*M*+Na]$^+$; found: 261.9649.

2-Bromo-1-(3,4-dihydroisoquinolin-2(1*H*)-yl)-2,2-difluoroethan-1-one (1d)



From 1,2,3,4-tetrahydroisoquinoline (358 mg). Purification by column chromatography (SiO_2; EtOAc / *n* -pentane 1:9) afforded the title compound as a colorless oil (601 mg, 83%).

^{1}H NMR (400 MHz, $CDCl_3$, TMS, mixture of two rotamers): δ(major) = 7.25-7.10 (m, 4H), 4.79 (s, 2H), 3.93 (t, *J*(H,H) = 5.9 Hz, 2H), 2.99 (t, *J*(H,H) = 5.9 Hz, 2H). δ(minor) = 7.25-7.10 (m, 4H), 4.83 (s, 2H), 3.89 (t, *J*(H,H) = 6.1 Hz, 2H), 2.96 (t, *J*(H,H) = 6.1 Hz, 2H).

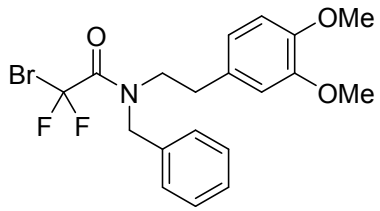
^{13}C NMR (100 MHz, $CDCl_3$, TMS, mixture of two rotamers): δ(major) = 158.4 (t, *J*(C,F) =

26.4 Hz), 133.4, 131.7, 128.6, 127.1, 126.9, 126.6, 110.9 (t, *J*(C,F) = 312.2 Hz), 46.1, 44.3 (t, *J*(C,F) = 4.2 Hz), 29.0. δ(minor) = 158.3 (t, *J*(C,F) = 26.4 Hz), 134.2, 131.6, 128.9, 127.6, 126.8, 126.1, 110.9 (t, *J*(C,F) = 312.6 Hz), 48.2 (t, *J*(C,F) = 4.6 Hz), 42.5, 27.9.

^{19}F NMR (377 MHz, $CDCl_3$, mixture of two rotamers): δ(major) = -54.47. δ(minor) = -54.64.

HRMS (ESI): m/z calcd for $C_{11}H_{10}NO^{79}BrF_2$+Na^+: 311.9806 [*M*+Na]$^+$; found: 311.9793.

_N_-Benzyl-2-bromo-_N_-(3,4-dimethoxyphenethyl)-2,2-difluoroacetamide (1f)



From *N*-benzyl-2-(3,4-dimethoxyphenyl)ethan-1-amine (678 mg). Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 1:9) afforded the title compound as a yellow oil (424 mg, 40%).

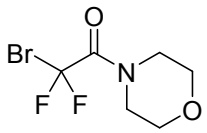
^{1}H NMR (400 MHz, $CDCl_3$, TMS, mixture of two rotamers): δ(major) 7.41 – 7.27 (m, 3H), 7.27 – 7.20 (m, 1H), 7.18 – 7.11 (m, 1H), 6.80 (dd, *J*(H,H) = 8.1, 2.5 Hz, 1H), 6.71 – 6.58 (m, 2H), 4.48 (s, 2H), 3.85 (s, 6H), 3.49 (t, *J*(H,H) = 7.3 Hz, 2H), 2.81 (t, *J*(H,H) = 7.3 Hz, 2H). δ(minor) 7.41 – 7.27 (m, 3H), 7.27 – 7.20 (m, 1H), 7.18 – 7.11 (m, 1H), 6.80 (dd, *J*(H,H) = 8.1, 2.5 Hz, 1H), 6.71 – 6.58 (m, 2H), 4.65 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.64 – 3.56 (m, 2H), 2.88 – 2.82 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS, mixture of two rotamers): δ(major) = 159.4 (t, *J*(C,F) = 26.3 Hz), 149.0, 147.8, 134.9, 130.8, 12.9 (d, *J*(C,F) = 7.4 Hz), 127.30 , 120.8, 112.0, 111.3, 111.0 (t, *J*(C,F) = 314.8 Hz), 55.9, 55.9, 52.5 (t, *J*(C,F) = 3.8 Hz), 49.0, 32.3. δ(minor) = 159.7 (t, *J* = 26.4 Hz), 149.1, 148.1, 135.6, 129.9, 128.9, 128.1, 120.0, 120.7, 111.8, 111.5, 111.3 (t, *J* = 314.8 Hz), 55.9, 55.9, 50.0, 49.3 (t, *J* = 3.5 Hz), 34.7.

^{19}F NMR (377 MHz, $CDCl_3$, mixture of two rotamers): δ(major) = -53.65. δ(minor) = -54.09.

HRMS (ESI): m/z calcd for $C_{19}H_{20}NO_3{}^{79}BrF_2$+$Na^+$: 450.0487 [*M*+Na]$^+$; found: 450.0481.

2-Bromo-2,2-difluoro-1-morpholinoethan-1-one (1g)



From morpholine (218 mg). Purification by column chromatography (SiO_2; EtOAc / *n* -pentane 1:3) afforded the title compound as a colorless oil (465 mg, 76%).

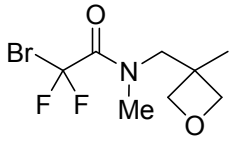
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 3.77-3.66 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 158.0 (t, *J*(C,F) = 26.6 Hz), 110.6 (t, *J*(C,F) = 314.4 Hz), 66.6, 66.2, 47.4 (t, *J*(C,F) = 3.8 Hz), 44.0.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -54.48.

HRMS (ESI): m/z calcd for $C_6H_8NO_2{}^{79}BrF_2$+Na^+: 265.9599 [*M*+Na]$^+$; found: 265.9596.

2-Bromo-2,2-difluoro-*N*-methyl-*N*-((3-methyloxetan-3-yl)methyl)acetamide (1h)



From *N*-methyl-1-(oxetan-yl)-methanamine (288 mg). Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 3:2) afforded the title compound as a colorless oil (465 mg, 68%).

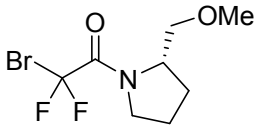
^{1}H NMR (400 MHz, $CDCl_3$, TMS, mixture of two rotamers): δ(major) = 4.60 (d, *J*(H,H) = 6.1 Hz, 2H), 4.31 (d, *J*(H,H) = 6.1 Hz, 2H), 3.65 (s, 2H), 3.14 (t, *J*(H,F) = 1.6Hz, 3H), 1.34 (s, 3H). δ(minor) = 4.58 (d, *J*(H,H) = 6.1 Hz, 2H), 4.34 (d, *J*(H,H) = 6.2 Hz, 2H), 3.69 (s, 2H), 2.89 (s, 3H), 1.35 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS, mixture of two rotamers): δ(major) = 159.9 (t, *J*(C,F) = 26.4 Hz), 110.9 (t, *J*(C,F) = 314.7 Hz), 81.4, 56.5, 40.5, 37.7 (t, *J*(C,F) = 4.8 Hz), 21.4. δ(minor) = 159.9 (t, *J*(C,F) = 26.4 Hz), 110.9 (t, *J*(C,F) = 314.2 Hz), 81.3, 55.9 (t, *J*(C,F) = 3.6 Hz), 39.5, 34.5, 21.2.

^{19}F NMR (377 MHz, $CDCl_3$, mixture of two rotamers): δ(major) = -54.64. δ(minor) = -52.49.

HRMS (ESI): m/z calcd for $C_6H_{12}NO_2{}^{79}BrF_2$+$Na^+$: 293.9912 [*M*+Na]$^+$; found: 293.9906.

(*S*)-2-Bromo-2,2-difluoro-1-(2-(methoxymethyl)pyrrolidin-1-yl)ethanone (1i)



From (*S*)-2-(methoxymethyl)pyrrolidine (288 mg). Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 1:5) afforded the title compound as a colorless oil (642 mg, 94%).

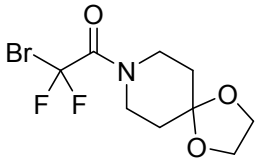
^{1}H NMR (400 MHz, $CDCl_3$, TMS, mixture of two rotamers): δ = 4.35-4.24 (m, 1H), 3.72-3.65 (m, 1H), 3.61-3.55 (m, 1H), 3.54-3.47 (m, 2H), 3.31 (s, 3H), 2.12-1.82 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS, mixture of two rotamers): δ(major) = 158.1 (dd, *J*(C,F) = 27.1, 27.1 Hz), 111.5 (dd, *J*(C,F) = 314.3, 312.7 Hz), 71.4, 59.2, 59.1, 48.4 (t, *J*(C,F) = 4.5 Hz), 26.7, 24.8. δ(minor) = 158.1 (dd, *J*(C,F) = 27.1, 27.1 Hz), 111.6 (dd, *J*(C,F) = 317.4, 314.1 Hz), 73.2, 58.1 (t, *J*(C,F) = 2.9 Hz), 48.1, 28.7, 20.5.

^{19}F NMR (377 MHz, $CDCl_3$, mixture of two rotamers): δ(major) = -56.38 (d, *J*(F,F) = 156.1 Hz, 1F), -56.99 (d, *J*(F,F) = 156.1 Hz, 1F). δ(minor) = -54.61 (d, *J*(F,F) = 156.5 Hz, 1F), -56.24 (d, *J*(F,F) = 156.5 Hz, 1F).

HRMS (ESI): m/z calcd for $C_8H_{12}NO_2{}^{79}BrF_2$+$Na^+$: 293.9912 [*M*+Na]$^+$; found: 293.9922.

2-Bromo-2,2-difluoro-1-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)ethan-1-one (1j)



From 1,4-dioxa-8-azaspiro[4.5]decane (358 mg). Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 1:3) afforded the title compound as a white solid (566 mg, 75%). M.p. = 74-75 ºC.

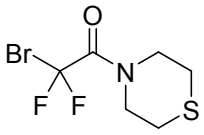
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 3.99 (s, 4H), 3.78-3.74 (m, 4H), 1.81-1.75 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 157.0 (t, *J*(C,F) = 26.3 Hz), 110.7 (t, *J*(C,F) = 314.3 Hz), 106.2, 64.6, 44.6 (t, *J*(C,F) = 4.2 Hz), 42.3, 35.0, 34.7.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -54.01.

HRMS (ESI): m/z calcd for $C_9H_{12}NO_3{}^{79}BrF_2$+$Na^+$: 321.9861 [*M*+Na]$^+$; found: 321.9852.

2-Bromo-2,2-difluoro-1-thiomorpholinoethan-1-one (1k)



From tiomorpholine (258 mg). Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 1:2) afforded the title compound as a colorless oil (649 mg, >99%).

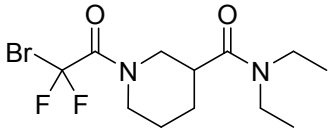
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 3.94-3.90 (m, 4H), 2.73-2.67 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 157.9 (t, *J*(C,F) = 26.5 Hz), 110.6 (t, *J*(C,F) = 314.2 Hz), 49.3 (t, *J*(C,F) = 3.9 Hz), 46.5, 27.5, 27.3.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -54.05.

HRMS (ESI): m/z calcd for $C_6H_8NOS^{79}BrF_2$+Na^+: 281.9370 [*M*+Na]$^+$; found: 281.9357.

1-(2-Bromo-2,2-difluoroacetyl)-*N*,*N*-diethylpiperidine-3-carboxamide (1l)



From *N*,*N*-diethylpiperidine-3-carboxamide (321 mg). Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 1:2) afforded the title compound as a colorless oil (486 mg, 82%).

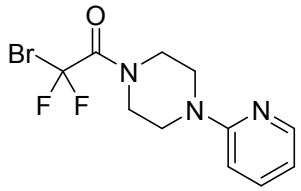
^{1}H NMR (400 MHz, $CDCl_3$, TMS, mixture of two rotameres): δ (major) = 4.61-4.46 (m, 1H), 4.25-4.12 (m, 1H), 3.58-2.60 (m, 7H), 1.98-1.77 (m, 3H), 1.73-1.51 (m, 1H), 1.22 (t, *J*(H,H) = 7.2 Hz, 3H), 1.11 (t, *J*(H,H) = 7.1 Hz, 3H). δ (minor) = 4.61-4.46 (m, 1H), 4.25-4.12 (m, 1H), 3.58-2.60 (m, 7H), 1.98-1.77 (m, 3H), 1.73-1.51 (m, 1H), 1.22 (t, *J*(H,H) = 7.2 Hz, 3H), 1.12 (t, *J*(H,H) = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS, mixture of two rotameres): δ(major) = 171.4 (s, broad), 157.8 (t, *J*(C,F) = 25.7 Hz), 110.6 (t, *J*(C,F) = 314.2 Hz), 47.1 (t, *J*(C,F) = 4.0 Hz) 46.9, 41.9, 40.2, 38.9, 27.5, 24.9, 14.8, 12.9. δ(minor) = 171.4 (s, broad), 157.5 (t, *J*(C,F) = 25.7 Hz), 110.7 (t, *J*(C,F) = 314.2 Hz), 49.1 (t, *J*(C,F) = 4.0 Hz) 44.3, 41.7, 40.2, 39.4, 28.2, 24.3, 14.9, 12.9.

^{19}F NMR (377 MHz, $CDCl_3$, mixture of two rotamers): δ(major) = -53.65 (d, *J*(F,F) = 159.4 Hz, 1F), -54.32 (d, *J*(F,F) = 159.4 Hz, 1F). δ(minor) = -53.54 (d, *J*(F,F) = 159.4 Hz, 1F), -54.13 (d, *J*(F,F) = 159.4 Hz, 1F).

HRMS (ESI): m/z calcd for $C_{12}H_{19}N_2O_2{}^{79}BrF_2$+$Na^+$: 363.0490 [*M*+Na]$^+$; found: 363.0498.

2-Bromo-2,2-difluoro-1-(4-(pyridin-2-yl)piperazin-1-yl)ethan-1-one (1m)



From 1-(pyridin-2-yl)piperazine (408 mg). Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 1:2) afforded the title compound as a white solid (652 mg, 81%). M.p. = 115-116 ºC.

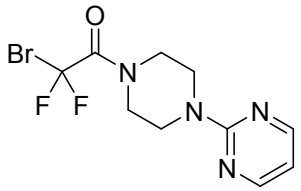
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.22 (bs, 1H), 7.55-7.51 (m, 1H), 6.72-6.67 (m, 1H), 3.84-3.80 (m, 4H), 3.69-3.61 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 158.9, 158.1 (t, *J*(C,F) = 26.6 Hz), 148.2, 137.9, 114.6, 110.7 (t, *J*(C,F) = 314.5 Hz), 107.5, 46.5 (t, *J*(C,F) = 3.9 Hz), 45.1, 45.0, 43.6.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -54.27.

HRMS (ESI): m/z calcd for $C_{11}H_{12}N_3O^{79}BrF_2$+$H^+$: 320.0205 [*M*+H]$^+$; found: 320.0209.

2-Bromo-2,2-difluoro-1-(4-(pyrimidin-2-yl)piperazin-1-yl)ethan-1-one (1n)



From 2-(piperazin-1-yl)pyrimidine (411 mg). Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 1:1) afforded the title compound as a white solid (657 mg, 82%). M.p. = 115-116 ºC.

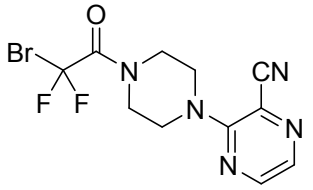
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.33 (d, *J*(H,H) =4.8 Hz, 2H), 6.56 (t, *J*(H,H) =4.7 Hz, 1H), 3.92-3.91 (m, 4H), 3.76-3.74 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 161.5, 158.2 (t, *J*(C,F) = 26.5 Hz), 157.9, 111.0, 110.7 (t, *J*(C,F) = 315.4 Hz), 46.6 (t, *J*(C,F) = 3.8 Hz), 43.7, 43.4, 43.3.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -54.25.

HRMS (ESI): m/z calcd for $C_{10}H_{11}N_4O^{79}BrF_2$+$Na^+$: 342.9977 [*M*+Na]$^+$; found: 342.9987.

3-(4-(2-Bromo-2,2-difluoroacetyl)piperazin-1-yl)pyrazine-2-carbonitrile (1o)



From 3-(piperazin-1-yl)pyrazine-2-carbonitrile (193 mg). Purification by column

chromatography (SiO_2; EtOAc / *n*-pentane 1:4) afforded the title compound as a yellow solid (241 mg, 68%). M.p. = 93-94 ºC.

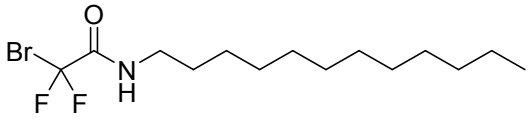
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.32 (d, *J*(H,H) =2.2 Hz, 1H), 8.15 (d, *J*(H,H) =2.2 Hz, 1H), 3.93-3.84 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 158.2 (t, *J*(C,F) = 26.7 Hz), 157.1, 145.1, 136.3, 116.9, 116.5, 110.5 (t, *J*(C,F) = 314.5 Hz), 47.2, 46.9, 46.3 (t, *J*(C,F) = 4.2 Hz), 43.4.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -54.54.

HRMS (ESI): m/z calcd for $C_{11}H_{10}N_5O^{79}BrF_2$+$Na^+$: 367.9934 [*M*+Na]$^+$; found: 367.9947.

2-Bromo-*N*-dodecyl-2,2-difluoroacetamide (1p)



From *N*-dodecylamine (463 mg). Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 1:9) afforded the title compound as a white solid (695 mg, 81%). M.p. = 46-48 ºC.

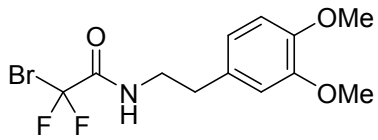
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 6.15 (bs, 1H), 3.38-3.33 (m, 2H), 1.62-1.55 (m, 2H), 1.36-1.23 (m, 18H), 0.90-0.86 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 160.1 (t, *J*(C,F) = 27.2 Hz), 112.0 (t, *J*(C,F) = 316.2 Hz), 40.4, 32.0, 29.8, 29.7, 29.6, 29.5, 29.3, 29.1, 26.8, 22.8, 14.2.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -60.42.

HRMS (ESI): m/z calcd for $C_{14}H_{26}NO^{79}BrF_2$+Na^+: 364.1058 [*M*+Na]$^+$; found: 364.1056.

2-Bromo-*N*-(3,4-dimethoxyphenethyl)-2,2-difluoroacetamide (1r)



From 2-(3,4-dimethoxyphenyl)ethan-1-amine (453 mg). Purification by column chromatography (SiO_2, EtOAc / *n*-pentane 1:2) afforded the title compound as a white solid (653 mg, 77%). M.p. = 78.1-78.3 ºC.

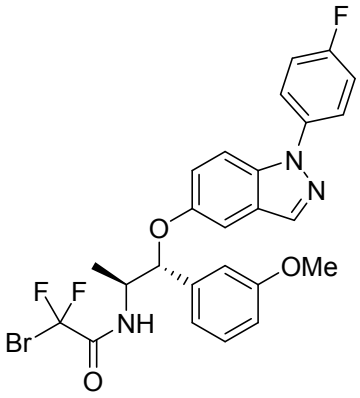
^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ = 6.84-6.82 (m, 1H), 6.75-6.72 (m, 1H), 6.70 (m, 1H), 6.27 (bs, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.62-3.57 (m, 2H), 2.85-2.82 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 160.0 (t, *J* = 27.3 Hz), 149.3, 148.2, 130.2, 120.8, 112.0, 111.9 (t, *J* = 314.0 Hz), 111.7, 56.1, 56.0 , 41.5 , 34.7.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -60.47.

HRMS (ESI): m/z calcd for $C_{12}H_{14}NO_3{}^{79}BrF_2$+$Na^+$: 360.0017 [*M*+Na]$^+$; found: 360.0014.

2-Bromo-2,2-difluoro-*N*-((1*R*,2*S*)-1-((1-(4-fluorophenyl)-1*H*-indazol-5-yl)oxy)-1-(3-methoxyphenyl)propan-2-yl)acetamide (1t)



From (1*R*,2*S*)-1-((1-(4-fluorophenyl)-1*H*-indazol-5-yl)oxy)-1-(3-methoxyphenyl)propan-2-amine (150 mg) using toluene as solvent (1 mL). Purification by column chromatography (SiO_2, EtOAc / *n*-pentane 1:2) afforded the title compound as a white foam (156 mg, 74%).

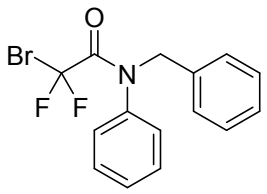
^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ = 7.97 (s, 1H), 7.64 – 7.59 (m, 2H), 7.55 – 7.53 (m, 1H), 7.30 (t, *J* = 7.9 Hz, 1H), 7.23 – 7.18 (m, 2H), 7.16 (dd, *J* = 9.1, 2.4 Hz, 1H), 7.00 – 6.97 (m, 2H), 6.94 – 6.93 (m, 1H), 6.86 – 6.84 (m, 1H), 6.55 (d, *J* = 8.7 Hz, 1H), 5.36 (d, *J* = 3.2 Hz, 1H), 4.47 (dqd, *J* = 10.0, 6.9, 3.2 Hz, 1H), 3.79 (s, 3H), 1.26 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 161.2 (d, *J* = 246.6 Hz), 160.2, 159.5 (t, *J* = 27.5 Hz), 152.9, 138.6, 136.4 (d, *J* = 3.0 Hz), 135.1, 135.0, 130.2, 125.6, 124.4 (d, *J* = 8.4 Hz), 119.6, 118.8, 116.5 (d, *J* = 22.9 Hz), 113.7, 112.2, 111.9 (t, *J* = 314.2 Hz), 111.3, 104.5, 81.4, 55.4, 51.3, 13.9.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -60.50 (d, *J*(F,F) = 161.5 Hz, 1F), -61.01 (d, *J*(F,F) = 161.5 Hz, 1F), -115.12 - -115.18 (m, 1F).

HRMS (ESI): m/z calcd for $C_{25}H_{21}N_3O_3{}^{79}BrF_3$+$Na^+$: 570.0611 [*M*+Na]$^+$; found: 570.0625.

Synthesis and characterization of *N*-benzyl-2-bromo-2,2-difluoro-*N*-phenylacetamide 1e:



In a 50 mL bottom flask *N*-benzylaniline (3.0 mmol, 1 equiv., 550 mg) was dissolved in THF (15 mL) under an atmosphere of argon. The reaction was cooled at -78 ºC and ^{n}BuLi (2.5 M in hexane, 3.0 mmol, 1.0 equiv., 1.2 mL) was added dropwise and the reaction was stirred at -78 ºC for 2 h. 2-Bromo-2,2-difluoroacetyl chloride (3.0 mmol, 1.0 equiv., 580 mg) was added dropwise and the reaction was stirred at - 78 ºC for 2 h following by 1 h at room temperature. The reaction was quenched with NH_4Cl (sat. aq, 10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 1:30) afforded the title compound as a white solid (527 mg, 52%). M.p. = 72-73 ºC.

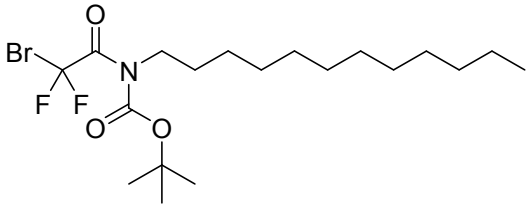
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.37-7.26 (m, 6H), 7.19-7.18 (m, 2H), 7.05-7.03 (m, 2H), 4.91 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 159.3 (t, *J*(C,F) = 25.9 Hz), 139.4, 135.5, 129.3, 129.2, 129.1, 129.0, 128.7, 128.2, 111.8 (t, *J*(C,F) = 317.6 Hz), 56.4.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -51.79.

HRMS (ESI): m/z calcd for $C_{15}H_{12}NO^{79}BrF_2$+Na^+: 361.9963 [*M*+Na]$^+$; found: 361.9974.

Synthesis and characterization of *tert*-butyl 2-bromo-2,2-difluoroacetyl(dodecyl)carbamate (1q)



To a solution of 2-Bromo-*N*-dodecyl-2,2-difluoroacetamide (1.20 mmol, 420 mg) in dry acetonitrile (12 mL) were added DMAP (2.40 mmol, 293 mg) and Boc_2O (3.60 mmol, 786 mg) in one portion. The mixture was stirred at room temperature for 19 hours. The crude reaction mixture was concentrated and purified by column chromatography (SiO_2, EtOAc / *n*-pentane 1:9) to afford the title compound as a colorless oil (373 mg, 69%).

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 3.70 – 3.65 (m, 2H), 1.63 – 1.56 (m, 2H), 1.54 (s,

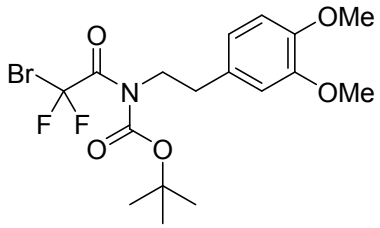
9H), 1.33 – 1.23 (m, 18H), 0.91 – 0.85 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 162.2 (t, *J*(C,F) = 29.1 Hz), 151.5, 111.8 (t, *J*(C,F) = 315.9 Hz), 85.7, 47.9, 32.0, 29.8, 29.7, 29.6, 29.5, 29.3, 28.3, 27.8, 26.7, 22.8, 14.2.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -54.11.

HRMS (ESI): m/z calcd for $C_{19}H_{34}NO_3{}^{79}BrF_2$+Na$^+$: 464.1582 [*M*+Na]$^+$; found: 464.1598.

Synthesis and characterization of tert-butyl (2-bromo-2,2-difluoroacetyl)(3,4-dimethoxyphenethyl)carbamate (1s)



To a solution of 2-Bromo-*N*-(3,4-dimethoxyphenethyl)-2,2-difluoroacetamide (0.296 mmol, 100 mg) in dry acetonitrile (4 mL) were added DMAP (0.591 mmol, 72 mg) and Boc_2O (0.887 mmol, 194 mg) in one portion. The mixture was stirred at room temperature for 4 hours. The crude reaction mixture was concentrated and purified by column chromatography (SiO2, EtOAc / *n*-pentane 1:6) to afford the title compound as a yellow oil (90 mg, 69%).

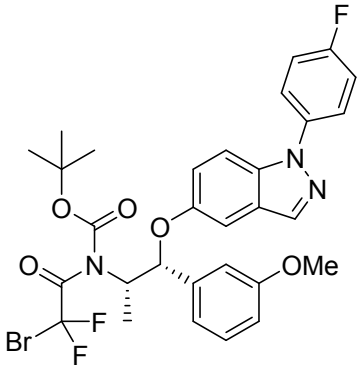
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 6.81-6.78 (m, 1H), 6.75-6.72 (m, 1H), 6.71-6.70 (m, 1H), 3.92-3.89 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.88-2.84 (m, 2H), 1.47 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 162.1 (t, *J*(C,F) = 29.4 Hz), 151.2, 149.1, 148.0, 130.2, 121.2, 112.3, 111.6 (t, *J*(C,F) = 315.7 Hz), 111.5, 85.9, 56.1, 55.9, 49.2, 34.1, 27.7.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -54.21.

HRMS (ESI): m/z calcd for $C_{17}H_{22}NO_5{}^{79}BrF_2$+Na$^+$: 460.0542 [*M*+Na]$^+$; found: 460.0562.

Synthesis and characterization of *tert*-butyl 2-bromo-2,2-difluoroacetyl((1*R*,2*S*)-1-(1-(4-fluorophenyl)-1*H*-indazol-5-yloxy)-1-(3-methoxyphenyl)propan-2-yl)carbamate (1u)



To a solution of 2-Bromo-*N*-(3,4-dimethoxyphenethyl)-2,2-difluoroacetamide (0.383 mmol, 210 mg) in dry acetonitrile (4 mL) were added DMAP (0.766 mmol, 94 mg) and Boc_2O (1.15 mmol, 251 mg) in one portion. The mixture was stirred at room temperature for 2 d. The crude reaction mixture was concentrated and purified by column chromatography (SiO_2, Et_2O / *n*-pentane 1:4) to afford the title compound as a yellowish foam (84 mg, 34%).

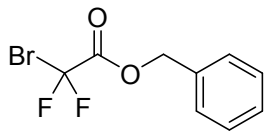
^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ = 7.98 (s, 1H), 7.63 – 7.58 (m, 2H), 7.50 (d, *J* = 9.1 Hz, 1H), 7.25 – 7.15 (m, 3H), 7.11 (dd, *J* = 9.1, 2.3 Hz, 1H), 7.06 (d, *J* = 2.2 Hz, 1H), 7.03 (d, *J* = 7.7 Hz, 1H), 6.99 – 6.96 (m, 1H), 6.80 (dd, *J* = 8.2, 2.5 Hz, 1H), 5.57 (d, *J* = 9.1 Hz, 1H), 4.75 (dq, *J* = 9.0, 6.7 Hz, 1H), 3.77 (s, 3H), 1.62 (d, *J* = 6.7 Hz, 3H), 1.39 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 163.0 (t, *J* = 29.0 Hz), 161.2 (d, *J* = 246.3 Hz), 159.9, 153.2, 151.2, 139.6, 136.5 (d, *J* = 3.0 Hz), 135.0, 134.9, 129.8, 125.7, 124.3 (d, *J* = 8.4 Hz), 120.1, 119.7, 116.4 (d, *J* = 22.8 Hz), 114.6, 112.4, 112.3 (t, *J* = 318.2 Hz), 111.0, 104.8, 86.2, 82.4, 59.2, 55.3, 27.6, 14.8.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -51.65 (d, *J*(F,F) = 162.7 Hz, 1F), -57.03 (d, *J*(F,F) = 162.7 Hz, 1F), -115.31 - -115.39 (m, 1F).

HRMS (ESI): m/z calcd for $C_{30}H_{29}N_3O_5{}^{79}BrF_3$+$Na^+$: 670.1135 [*M*+Na]$^+$; found: 670.1115.

Synthesis and characterization of benzyl 2-bromo-2,2-difluoroacetate (3a)



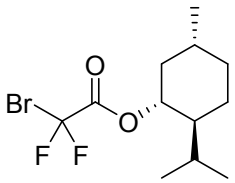
In a 20 mL glass vial benzyl alcohol (3.08 mmol, 1 equiv., 333 mg) was dissolved in *n*-hexane (5 mL) under an atmosphere of air. Ethyl 2-bromo-2,2-difluoroacetate (12.3 mmol, 4 equiv., 2.5 g) was added followed by 2 drops of concentrated H_2SO_4 and the reaction was stirred at room temperature for 16 h. The reaction was quenched with Na_2CO_3 (sat. aq, 10 mL), extracted with EtOAc (3 x 10 mL) and washed with Na_2CO_3 (sat. aq). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 1:40) afforded the title compound as a colorless oil (367 mg, 45%).

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.42-7.38 (m, 5H), 5.36 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 159.6 (t, J(C,F) = 31.5 Hz), 133.6, 129.3, 129.0, 128.7, 108.9 (t, J(C,F) = 314.4 Hz), 69.9.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -60.70.

Synthesis and characterization of (-)-Menthyl 2-bromo-2,2-difluoroacetate (3b)



In a 20 mL glass vial (-)-menthol (3.08 mmol, 1 equiv., 554 mg) was dissolved in *n*-hexane (5 mL) under an atmosphere of air. Ethyl 2-bromo-2,2-difluoroacetate (12.3 mmol, 4 equiv., 2.5 g) was added followed by 2 drops of concentrated H_2SO_4 and the reaction was stirred at room temperature for 16 h. The reaction was quenched with Na_2CO_3 (sat. aq, 10 mL), extracted with EtOAc (3 x 10 mL) and washed with Na_2CO_3 (sat. aq). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 1:10) afforded the title compound as a light yellow oil (186 mg, 19%).

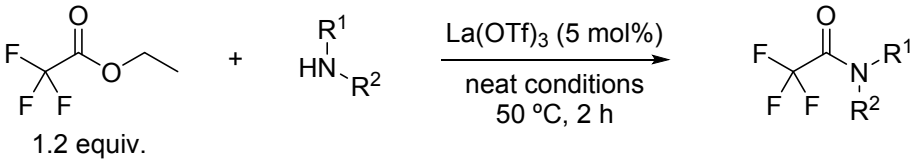
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 4.84 (td, J(H,H) = 11.0, 4.5 Hz, 1H), 2.09-2.04 (m, 1H), 1.97-1.87 (m, 1H), 1.77-1.69 (m, 2H), 1.58-1.47 (m, 2H), 1.18-1.07 (m, 2H), 0.97-0.85 (m, 1H), 0.95 (d, J(H,H) = 6.6 Hz, 3H), 0.92 (d, J(H,H) = 7.0 Hz, 3H), 0.79 (d, J(H,H) = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 159.4 (t, J(C,F) = 30.8 Hz), 109.1 (t, J(C,F) = 314.8 Hz), 79.7, 46.9, 40.0, 34.1, 31.6, 26.3, 23.5, 22.0, 20.7, 16.3.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -60.63 (d, J(F,F) = 162.7 Hz, 1F), -61.04 (d, J(F,F) = 162.8 Hz, 1F).

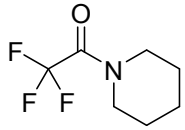
HRMS (ESI): m/z calcd for $C_{12}H_{19}O_2{}^{79}BrF_2$+$Na^+$: 335.0429 $[M+Na]^+$; found: 335.0429.

Synthesis and characterization of trifluoroacetamides 2a-u:



Following the procedure described in the literature.[3,4] In a 5 mL sealed glass vial the corresponding amine (2.5 mmol, 1 equiv.), ethyl 2,2,2-trifluoroacetate (3.0 mmol, 1.2 equiv., 426 mg) and $La(OTf)_3$ (0.125 mmol, 0.05 equiv., 73 mg) were stirred under an atmosphere of argon at 50 ºC for 2 h. Purification by column chromatography afforded the desired amide.

2,2,2-Trifluoro-1-(piperidin-1-yl)ethan-1-one (2a)



From piperidine (463 mg). Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 1:9) afforded the title compound as a colorless oil (367 mg, 81%).

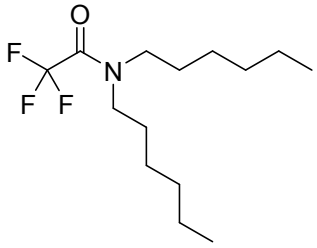
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 3.63-3.60 (m, 2H), 3.54-3.52 (m, 2H), 1.73-1.61 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 155.4 (q, *J*(C,F) = 35.3 Hz), 116.7 (q, *J*(C,F) = 288.0 Hz), 46.9 (q, *J*(C,F) = 3.5 Hz), 44.7, 26.4, 25.5, 24.2.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -68.90.

HRMS (ESI): m/z calcd for $C_7H_{10}F_3NO+Na^+$: 204.0607 [*M*+Na]$^+$; found: 204.0606.

2,2,2-Trifluoro-*N*,*N*-dihexylacetamide (2b)



From *N*,*N*-dihexylamine (431 mg). Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 1:9) afforded the title compound as a slightly yellow oil (499 mg, 70%).

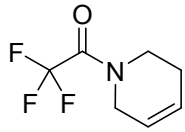
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 3.36-3.28 (m, 4H), 1.62-1.51 (m, 4H), 1.33-1.24 (m, 12H), 0.90-0.84 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 156.7 (q, *J*(C,F) = 35.4 Hz), 116.8 (t, *J*(C,F) = 287.9 Hz), 47.7 (q, *J*(C,F) = 3.3 Hz), 47.1, 31.6, 31.4, 28.8, 26.9, 26.6, 26.4, 22.6, 14.1, 14.0.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -69.00.

(EI) *m/z* (rel intens) 281.96 (*M*$^+$,12), 237.98 (3), 212.12 (M$^+$-CF_3, 74), 210.10 (58), 181.03 (4), 140.14 (100), 128.20 (11).

1-(5,6-Dihydropyridin-1(2*H*)-yl)-2,2,2-trifluoroethanone (2c)



From 1,2,3,6-tetrahydropyridine (208 mg). Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 1:10) afforded the title compound as a colorless oil (325 mg, 73%).

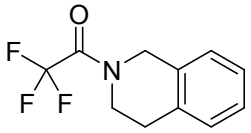
^{1}H NMR (400 MHz, $CDCl_3$, TMS, mixture of two rotamers): δ = 5.94-5.84 (m, 1H), 5.73-5.63 (m, 1H), 4.12-4.07 (m, 2H), 3.77-3.66 (m, 2H), 2.28-2.21 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS, mixture of two rotamers): δ(major) = 156.0 (q, *J*(C,F) = 35.2 Hz), 125.2, 123.4, 116.6 (q, *J*(C,F) = 285.8 Hz), 43.3, 42.9 (q, *J*(C,F) = 3.6 Hz), 25.7. δ(minor) = 156.0 (q, *J*(C,F) = 35.2 Hz), 126.3, 122.6, 116.7 (q, *J*(C,F) = 283.2 Hz), 44.7 (q, *J*(C,F) = 4.0 Hz), 40.5, 24.6.

^{19}F NMR (377 MHz, $CDCl_3$, mixture of two rotamers): δ(major) = -69.34. δ(minor) = -69.60.

HRMS (ESI): m/z calcd for $C_7H_8F_3NO+Na^+$: 202.0450 [*M*+Na]$^+$; found: 202.0447.

1-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-2,2,2-trifluoroethan-1-one (2d)



From 1,2,3,4-tetrahydroisoquinoline (462 mg). Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 1:9) afforded the title compound as a colorless oil (430 mg, 74%).

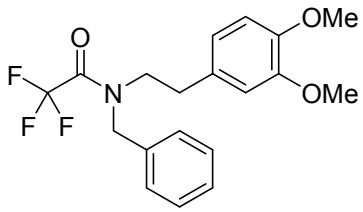
^{1}H NMR (400 MHz, $CDCl_3$, TMS, mixture of two rotamers): δ(major) = 7.26-7.09 (m, 4H), 4.80 (s, 2H), 3.87-3.82 (m, 2H), 2.99-2.93 (m, 2H). δ(minor) = 7.26-7.09 (m, 4H), 4.75 (s, 2H), 3.92-3.87 (m, 2H), 2.99-2.93 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS, mixture of two rotamers): δ(major) = 156.0 (q, *J*(C,F) = 35.9 Hz), 133.3, 131.5, 128.7, 127.1, 127.0, 126.6, 116.9 (q, *J*(C,F) = 287.8 Hz), 45.6, 43.4 (q, *J*(C,F) = 3.6 Hz), 29.3. δ(minor) = 155.9 (q, *J*(C,F) = 35.9 Hz), 134.1, 131.5, 128.9, 127.6, 126.9, 126.1, 116.9 (q, *J*(C,F) = 287.8 Hz), 47.0 (q, *J*(C,F) = 4.0 Hz), 41.9, 27.9.

^{19}F NMR (377 MHz, $CDCl_3$, mixture of two rotamers): δ(major) = -69.41. δ(minor) = -69.37.

(EI) *m/z* (rel intens) 229.12 (*M*$^+$, 100), 214.31 (28), 160,31 (M-CF_3, 11), 115.50 (78), 104.33 (33), 78.57 (46).

_N_-Benzyl-_N_-(3,4-dimethoxyphenethyl)-2,22,-trifluoroacetamide (2f)



From *N*-benzyl-2-(3,4-dimethoxyphenyl)ethan-1-amine (678 mg). Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 1:2) afforded the title compound as a yellow oil (240 mg, 28%).

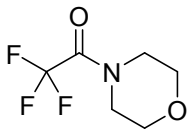
^{1}H NMR (400 MHz, $CDCl_3$, TMS, mixture of two rotamers): δ(major) 7.37 – 7.27 (m, 3H), 7.24 – 7.21 (m, 1H), 7.15 – 7.11 (m, 1H), 6.79 (dd, *J*(H,H) = 8.1, 2.5 Hz, 1H), 6.68 – 6.60 (m, 2H), 4.38 (s, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.51-3.46 (m, 2H), 2.80-2.74 (m, 2H). δ(minor) 7.37 – 7.27 (m, 3H), 7.24 – 7.21 (m, 1H), 7.15 – 7.11 (m, 1H), 6.79 (dd, *J*(H,H) = 8.1, 2.5 Hz, 1H), 6.68 – 6.60 (m, 2H), 4.65 (s, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.54 – 3.50 (m, 2H), 2.85 – 2.81 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS, mixture of two rotamers): δ(major) = 156.9 (q, *J*(C,F) = 35.7 Hz), 149.0, 147.8, 134.8, 130.7, 128.9, 128.0, 127.4, 120.7, 116.6 (q, *J*(C,F) = 288.0 Hz) 111.9, 111.4, 55.8, 55.7, 51.6 (q, *J*(C,F) = 3.2 Hz), 48.5, 32.4. δ(minor) = 157.1 (q, *J* = 35.6 Hz), 149.1, 148.0, 135.4, 129.8, 128.9, 128.2, 127.4, 120.6, 116..8 (q, *J* = 288.0 Hz), 111.8, 111.5, 55.9, 55.8, 48.4 (q, *J* = 3.1 Hz), 34.8.

^{19}F NMR (377 MHz, $CDCl_3$, mixture of two rotamers): δ(major) = -68.20. δ(minor) = -68.65.

HRMS (ESI): m/z calcd for $C_{19}H_{20}F_3NO_3$+Na^+: 390.1287 [*M*+Na]$^+$; found: 390.1278.

2,2,2-Trifluoro-1-morpholinoethan-1-one (2g)



From morpholine (218 mg). Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 1:9) afforded the title compound as a colorless oil (444 mg, 97%).

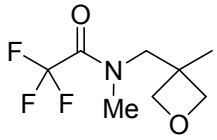
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 3.77-3.68 (m, 6H), 3.63-3.61 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 155.6 (q, *J*(C,F) = 35.8 Hz), 116.4 (q, *J*(C,F) = 287.9 Hz), 66.5, 66.5, 46.4 (q, *J*(C,F) = 3.2 Hz), 43.6.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -68.97.

HRMS (ESI): m/z calcd for $C_6H_8F_3NO_2$+Na^+: 206.0399 [*M*+Na]$^+$; found: 206.0402.

2,2,2-trifluoro-*N*-methyl-*N*-((3-methyloxetan-3-yl)methyl)acetamide (2h)



From *N*-methyl-1-(oxetan-yl)-methanamine (288 mg). Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 3:2) afforded the title compound as a colorless oil (361 mg, 73%).

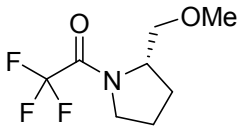
^{1}H NMR (400 MHz, $CDCl_3$, TMS, mixture of two rotamers): δ(major) = 4.61 (d, *J*(H,H) = 6.1 Hz, 2H), 4.34 (d, *J*(H,H) = 6.2 Hz, 2H), 3.68 (s, 2H), 3.10 (q, *J*(H,F) = 61.6 Hz, 3H), 1.33 (s, 3H). δ(minor) = 4.59 (d, *J*(H,H) = 6.3 Hz, 2H), 4.37 (d, *J*(H,H) = 6.2 Hz, 2H), 3.63 (s, 2H), 2.89 (s, 3H), 1.34 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS, mixture of two rotamers): δ(major) = 157.6 (q, *J*(C,F) = 35.8 Hz), 116.5 (q, *J*(C,F) = 287.9 Hz), 81.4, 55.8, 40.1, 36.3 (q, *J*(C,F) = 4.0 Hz), 21.3. δ(minor) = 157.6 (q, *J*(C,F) = 35.8 Hz), 116.4 (q, *J*(C,F) = 288.0 Hz), 81.3, 55.0 (q, *J*(C,F) = 3.2 Hz), 39.4, 33.7, 20.8.

^{19}F NMR (377 MHz, $CDCl_3$, mixture of two rotamers): δ(major) = -69.59. δ(minor) = -67.23.

HRMS (ESI): m/z calcd for C_8H_{12} F_3NO_2+Na^+: 234.0712 [*M*+Na]$^+$; found: 234.0717..

(*S*)-2,2,2-trifluoro-1-(2-(methoxymethyl)pyrrolidin-1-yl)ethanone (2i)



From (*S*)-2-(methoxymethyl)pyrrolidine (288 mg). Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 1:5) afforded the title compound as a colorless oil (491 mg, 93%).

^{1}H NMR (400 MHz, $CDCl_3$, TMS, mixture of two rotamers): δ = 4.30-4.24 (m, 1H), 3.66-3.59 (m, 2H), 3.55-3.47 (m, 2H), 3.31 (s, 3H), 2.11-1.85 (m, 4H).

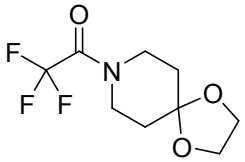
^{13}C NMR (100 MHz, $CDCl_3$, TMS, mixture of two rotamers): δ(major) = 155.6 (q, *J*(C,F) = 36.6 Hz), 116.3 (q, *J*(C,F) = 287.8 Hz), 71.3, 59.0, 58.6, 47.2 (q, *J*(C,F) = 3.5 Hz), 26.8, 24.5. δ(minor) = 155.7 (q, *J*(C,F) = 36.4 Hz), 116.4 (q, *J*(C,F) = 285.3 Hz), 73.2, 57.3 (q, *J*(C,F) =

2.3 Hz), 47.5, 28.8, 20.6.

^{19}F NMR (377 MHz, $CDCl_3$, mixture of two rotamers): δ(major) = -72.54. δ(minor) = -70.59.

HRMS (ESI): m/z calcd for $C_8H_{12}F_3NO_2$+Na^+: 234.0712 [*M*+Na]$^+$; found:234.0723.

2,2,2-Trifluoro-1-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)ethan-1-one (2j)



From 1,4-dioxa-8-azaspiro[4.5]decane (358 mg). Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 1:3) afforded the title compound as colorless oil (488 mg, 82%).

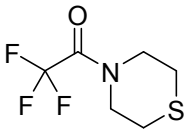
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 4.01-3.97 (m, 4H), 3.78-3.75 (m, 2H), 3.68-3.65 (m, 2H), 1.77-1.75 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 155.5 (q, *J*(C,F) = 35.7 Hz), 116.6 (q, *J*(C,F) = 288.0 Hz), 106.3, 64.7, 43.8 (q, *J*(C,F) = 3.6 Hz), 41.9, 35.6, 34.7.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -68.92.

HRMS (ESI): m/z calcd for $C_9H_{12}F_3NO_3$+Na^+: 262.0661 [*M*+Na]$^+$; found: 262.0664.

2,2,2-Trifluoro-1-thiomorpholinoethan-1-one (2k)



From thiomorpholine (258 mg). Purificaiton by column chromatograpy (SiO_2; EtOAc / *n*-pentane 1:2) afforded the title compound as a colorless oil (463 mg, 93%).

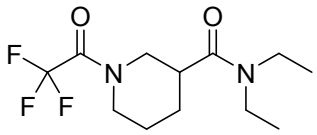
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 3.93-3.91 (m, 2H), 3.85-3.83 (m 2H), 2.70-2.67 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 155.7 (q, *J*(C,F) = 39.5 Hz), 116.6 (q, *J*(C,F) = 287.9 Hz), 48.7 (q, *J*(C,F) = 3.3 Hz), 46.3, 28.1, 27.3.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -68.86.

HRMS (ESI): m/z calcd for $C_6H_8F_3NOS$+Na^+: 222.0171 [*M*+Na]$^+$; found: 222.0167.

_N_,_N_-diethyl-1-(2,2,2-trifluoroacetyl)piperidine-3-carboxamide (2l)



From _N_,_N_-diethylpiperidine-3-carboxamide (222 mg). Purification by column chromatography (SiO_2; EtOAc / _n_-pentane 1:2) afforded the title compound as a colorless oil (337 mg, 81%).

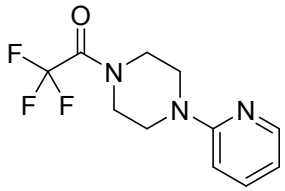
^{1}H NMR (400 MHz, $CDCl_3$, TMS, mixture of two rotameres): δ(major) = 4.61-4.47 (m, 1H), 4.06-3.91 (m, 1H), 3.56-3.21 (m, 4H), 3.20-2.70 (m, 2H), 2.70-2.59 (m, 1H), 1.99-1.79 (m, 3H), 1.65-1.50 (m, 1H), 1.22 (t, _J_(H,H) = 7.2 Hz, 3H), 1.12 (t, _J_(H,H) = 7.0 Hz, 3H). δ(minor) = 4.61-4.47 (m, 1H), 4.06-3.91 (m, 1H), 3.56-3.21 (m, 4H), 3.20-2.70 (m, 2H), 2.70-2.59 (m, 1H), 1.99-1.79 (m, 3H), 1.65-1.50 (m, 1H), 1.21 (t, _J_(H,H) = 7.2 Hz, 3H), 1.12 (t, _J_(H,H) = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS, mixture of two rotameres): δ(major) = 171.6, 155.5 (q, _J_(C,F) = 35.5 Hz), 116.5 (q, _J_(C,F) = 288.0 Hz), 46.4, 46.3, (q, _J_(C,F) = 3.0 Hz), 42.1, 40.2, 39.0, 27.6, 25.5, 14.8, 13.0. δ(minor) = 171.6, 155.2 (q, _J_(C,F) = 35.5 Hz), 116.5 (q, _J_(C,F) = 288.0 Hz), 48.4 (q, _J_(C,F) = 3.0 Hz), 44.0, 41.9, 40.2, 40.1, 28.1, 24.4, 14.8, 13.0.

^{19}F NMR (377 MHz, $CDCl_3$, mixture of two rotamers): δ(major) = -68.98 (s, 3F). δ(minor) = -68.83 (s, 3F).

HRMS (ESI): m/z calcd for $C_{12}H_{19}F_3N_2O_2$+Na^+: 303.1291 [_M_+Na]$^+$; found: 303.1286.

2,2,2-Trifluoro-1-(4-(pyridin-2-yl)piperazin-1-yl)ethan-1-one (2m)



From 1-(pyridin-2-yl)piperazine (408 mg). Purification by column chromatography (SiO_2; EtOAc / _n_-pentane 1:2) afforded the title compound as a colorless oil (541 mg, 83%).

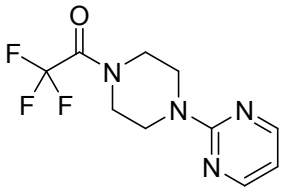
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.21 (ddd, _J_(H,H) = 4.9, 1.9, 0.8 Hz, 1H), 7.53 (ddd, _J_(H,H) = 8.6, 7.2, 2.0 Hz, 1H), 6.71 (ddd, _J_(H,H) = 7.2, 4.9, 0.8 Hz, 1H), 6.68 – 6.66 (m, 1H), 3.82 – 3.79 (m, 2H), 3.74 – 3.71 (m, 2H), 3.66 – 3.60 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 158.9, 155.8 (q, _J_(C,F) = 36.0 Hz), 148.2, 138.0, 116.6 (q, _J_(C,F) = 287.9 Hz), 114.6, 107.5, 45.6 (q, _J_(C,F) = 3.4 Hz), 45.5, 45.1, 43.2.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -68.87.

HRMS (ESI): m/z calcd for $C_{11}H_{12}F_3N_3O$+H^+: 260.1005 [_M_+H]$^+$; found: 260.1004.

2,2,2-Trifluoro-1-(4-(pyrimidin-2-yl)piperazin-1-yl)ethan-1-one (2n)



From 2-(piperazin-1-yl)pyrimidine (411 mg). Purification by column chromatography (SiO_2; EtOAc / *n* -pentane 1:1) afforded the title compound as a white solid (557 mg, 86%). M.p. = 80-83 ºC.

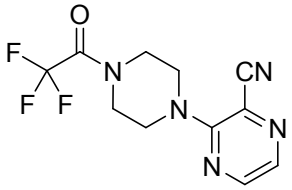
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.33 (d, *J*(H,H) =4.8 Hz, 2H), 6.57 (t, *J*(H,H) =4.8 Hz, 1H), 3.92-3.89 (m, 4H), 3.76-3.74 (m, 2H), 3.67-3.65 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 161.5, 158.0, 155.8 (q, *J*(C,F) = 36.1 Hz), 116.6 (q, *J*(C,F) = 288.1 Hz), 111.1, 45.8 (q, *J*(C,F) = 3.3 Hz), 43.9, 43.4, 43.3.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -68.84.

HRMS (ESI): m/z calcd for $C_{10}H_{11}F_3N_4O$+Na^+: 283.0777 [*M*+Na]$^+$; found: 283.0774.

3-(4-(2,2,2-Trifluoroacetyl)piperazin-1-yl)pyrazine-2-carbonitrile (2o)



From 3-(piperazin-1-yl)pyrazine-2-carbonitrile (70 mg). Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 1:4) afforded the title compound as a yellow foam (53 mg, 51%).

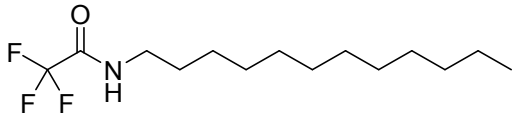
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.33 (d, *J*(H,H) =2.2 Hz, 1H), 8.15 (d, *J*(H,H) =2.2 Hz, 1H), 3.90-3.79 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 157.1, 155.9 (q, *J*(C,F) = 36.1 Hz), 145.1, 136.4, 117.0, 116.5, 116.4 (q, *J*(C,F) = 287.8 Hz), 47.6, 47.0, 45.4 (q, *J*(C,F) = 3.5 Hz), 43.0.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -68.91.

HRMS (ESI): m/z calcd for $C_{11}H_{10}F_3N_5O$+Na^+: 308.0735 [*M*+Na]$^+$; found: 308.0735.

***N*-Dodecyl-2,2,2-trifluoroacetamide (2p)**



From *N*-dodecylamine (449 mg). Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 1:9) afforded the title compound as a white solid (741 mg, 83%). M.p. = 53-55 ºC.

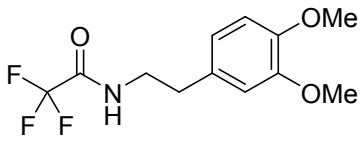
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 6.52 (bs, 1H), 3.37-3.31 (m, 2H), 1.61-1.53 (m, 2H), 1.35-1.20 (m, 18H), 0.90-0.84 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 157.4 (q, *J*(C,F) = 36.8 Hz), 116.0 (q, *J*(C,F) = 287.8 Hz), 40.2, 32.0, 29.8, 29.7, 29.6, 29.5, 29.3, 29.0, 26.8, 22.8, 14.2.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -76.05.

HRMS (ESI): m/z calcd for $C_{14}H_{26}F_3NO+Na^+$: 304.1859 [*M*+Na]$^+$; found: 304.1856.

_N_-(3,4-Dimethoxyphenethyl)-2,2,2-trifluoroacetamide (2r)



From 2-(3,4-dimethoxyphenyl)ethan-1-amine (453 mg). Purification by column chromatography (SiO_2, EtOAc / *n*-pentane 1:2) afforded the title compound as a white solid (430 mg, 62%). M.p. = 87.1-88.0 ^{o}C.

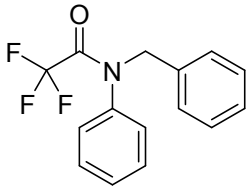
^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ = 6.83-6.81 (m, 1H), 6.73-6.70 (m, 1H), 6.69-6.67 (m, 1H), 6.41 (bs, 1H), 3.86 (s, 6H), 3.61-3.56 (q, *J*(HH) = 4.7 Hz, 2H), 2.84-2.81 (t, *J*(HH) = 7.0 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 157.3 (q, *J* = 38.8 Hz), 149.4, 148.2, 130.1, 120.7, 115.9 (q, *J* = 287.8 Hz), 111.9, 111.7, 56.0, 55.9 , 41.3 , 34.6 .

^{19}F NMR (377 MHz, $CDCl_3$): δ = -76.01.

HRMS (ESI): m/z calcd for $C_{12}H_{14}F_3NO_3+Na^+$: 300.0823 [*M*+Na]$^+$; found: 300.0818.

Synthesis and characterization of _N_-benzyl-2,2,2-trifluoro-_N_-phenylacetamide 2e:



In a 50 mL bottom flask *N*-benzylaniline (3.0 mmol, 1 equiv., 550 mg) was dissolved in THF (15 mL) under an atmosphere of argon. The reaction was cooled at -78 ºC and ^{n}BuLi (2.5 M in hexane, 3.0 mmol, 1.0 equiv., 1.2 mL) was added dropwise and the reaction was

stirred at -78 ºC for 2 h. Trifluoroacetic anhydride (3.6 mmol, 1.2 equiv., 756 mg) was added dropwise and the reaction was stirred at - 78 ºC for 1 h following by 0.5 h at room temperature. The reaction was quenched with NH_4Cl (sat. aq, 10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 1:40) afforded the title compound as a yellow solid (744 mg, 89%). M.p. = 40.5-43.2 ºC.

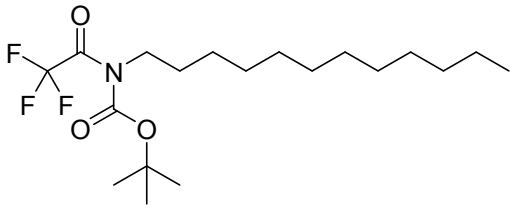
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.39-7.28 (m, 6H), 7.19-7.16 (m, 2H), 7.01-6.99 (m, 2H), 4.91 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 157.1 (q, *J*(C,F) = 35.6 Hz), 138.8, 135.4, 129.4, 129.3, 129.2, 128.8, 128.7, 128.3, 116.6 (q, *J*(C,F) = 288.4 Hz), 55.6.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -67.01.

HRMS (ESI): m/z calcd for $C_{15}H_{12}F_3NO+Na^+$: 302.0763 [*M*+Na]$^+$; found: 302.0758.

Synthesis and characterization of *tert*-butyl dodecyl(2,2,2-trifluoroacetyl)carbamate 2q



To a solution of *N*-dodecyl-2,2,2-trifluoroacetamide (1.76 mmol, 496 mg) in dry acetonitrile (17 mL) were added DMAP (3.53 mmol, 431 mg) and Boc_2O (5.29 mmol, 1.15 g) in one portion. The mixture was stirred at room temperature for 18 hours. The crude reaction mixture was concentrated and purified by column chromatography (SiO_2, Et_2O / *n*-pentane 1:60 to 1:20) to afford the title compound as a colorless oil (453 mg, 64%).

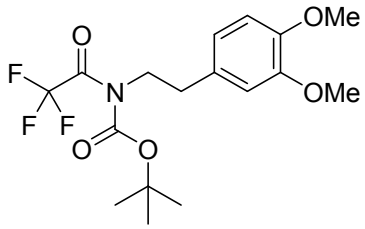
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 3.72 – 3.66 (m, 2H), 1.63 – 1.55 (m, 2H), 1.53 (s, 9H), 1.33 – 1.23 (m, 18H), 0.90 – 0.85 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 159.8 (q, *J*(C,F) = 39.4 Hz), 151.2, 116.0 (q, *J*(C,F) = 286.6 Hz), 85.7, 47.1, 32.1, 29.8, 29.7, 29.6, 29.5, 29.3, 28.2, 27.7, 26.7, 22.8, 14.2.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -69.30.

HRMS (ESI): m/z calcd for $C_{19}H_{34}F_3NO_3+Na^+$: 404.2383 [*M*+Na]$^+$; found: 404.2394.

Synthesis and characterization of tert-butyl (3,4-dimethoxyphenethyl)(2,2,2-trifluoroacetyl)carbamate 2s



To a solution of *N*-(3,4-Dimethoxyphenethyl)-2,2,2-trifluoroacetamide (0.361 mmol, 100 mg) in dry acetonitrile (4 mL) were added DMAP (0.721 mmol, 88 mg) and Boc_2O (1.082 mmol, 236 mg) in one portion. The mixture was stirred at room temperature for 4 hours. The crude reaction mixture was concentrated and purified by column chromatography (SiO_2, EtOAc / *n*-pentane 1:15) to afford the title compound as a yellow oil (90 mg, 69%).

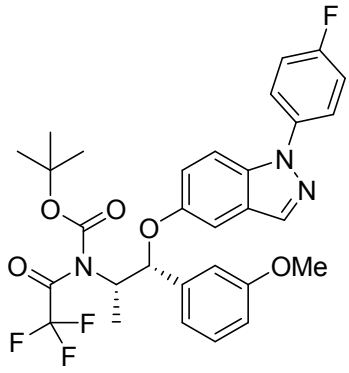
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 6.80-6.78 (m, 1H), 6.74-6.72 (m, 1H), 6.70-6.69 (m, 1H), 3.93-6.89 (m, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 2.87-2.83(m, 2H), 1.46 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 159.8 (q, *J*(C,F) = 39.7 Hz), 150.9, 149.1, 148.0, 130.2, 121.2, 116.5 (t, *J*(C,F) = 286.5 Hz), 112.3, 111.5, 85.9, 56.0, 55.9, 48.4, 34.0, 27.6.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -69.26.

HRMS (ESI): m/z calcd for $C_{17}H_{22}F_3NO_5$+Na^+: 400.1342 [*M*+Na]$^+$; found: 400.1356.

Synthesis and characterization of *tert*-butyl 2,2,2-trifluoroacetyl((1*R*,2*S*)-1-(1-(4-fluorophenyl)-1*H*-indazol-5-yloxy)-1-(3-methoxyphenyl)propan-2-yl)carbamate 2u



To a solution of 2,2,2-trifluoro-*N*-((1*R*,2*S*)-1-((1-(4-fluorophenyl)-1*H*-indazol-5-yl)oxy)-1-(3-methoxyphenyl)propan-2-yl)acetamide (0.240 mmol, 117 mg) in dry acetonitrile (2 mL) were added DMAP (0.480 mmol, 59 mg) and Boc_2O (0.720 mmol, 157 mg) in one portion. The mixture was stirred at room temperature for 3 days. The crude reaction mixture was concentrated and purified by column chromatography (SiO_2, Et_2O / *n*-pentane 1:3) to afford the title compound as a white foam (100 mg, 71%).

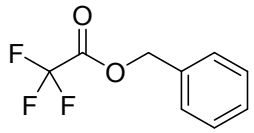
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.98 (s, 1H), 7.63 – 7.58 (m, 2H), 7.51 – 7.48 (m, 1H), 7.25 – 7.16 (m, 3H), 7.12 (dd, *J* = 9.1, 2.3 Hz, 1H), 7.07 (d, *J* = 2.3 Hz, 1H), 7.03 – 6.99 (m, 1H), 6.97 – 6.95 (m, 1H), 5.57 (d, *J* = 9.2 Hz, 1H), 4.83 (dq, *J* = 9.0, 6.7 Hz, 1H), 3.76 (s, 3H), 1.64 (d, *J* = 6.7 Hz, 3H), 1.39 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 161.1 (d, *J* = 246.3 Hz), 160.6 (q, *J* = 39.3 Hz), 159.9, 153.2, 150.9, 139.6, 136.4 (d, *J* = 2.9 Hz), 135.0, 134.9, 129.8, 125.6, 124.3 (d, *J* = 8.3 Hz), 120.1, 119.6, 116.4 (d, *J* = 22.9 Hz), 115.5 (q, *J* = 287.5 Hz), 114.6, 112.3, 111.0, 104.8, 86.2, 82.3, 58.7, 55.2, 27.4, 14.8.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -69.98 (s, 3F), -115.32 – -115.39 (m, 1F).

HRMS (ESI): m/z calcd for $C_{30}H_{29}F_4N_3O_5$+Na^+: 610.1936 [*M*+Na]$^+$; found: 610.1927.

Synthesis and characterization of benzyl 2,2,2-trifluoroacetate (4a)



In a 20 mL glass vial benzyl alcohol (3.08 mmol, 1 equiv., 333 mg) was dissolved in *n*-hexane (5 mL) under an atmosphere of air. Ethyl 2,2,2-trifluoroacetate (12.3 mmol, 4 equiv., 1.7 g) was added followed by 2 drops of concentrated H_2SO_4 and the reaction was stirred at room temperature for 16 h. The reaction was quenched with Na_2CO_3 (sat. aq, 10 mL), extracted with EtOAc (3 x 10 mL) and washed with Na_2CO_3 (sat. aq). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (*n*-pentane) afforded the title compound as a colorless oil (310 mg, 51%).

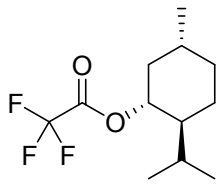
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.43-7.36 (m, 5H), 5.36 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 157.5 (q, J(C,F) = 42.5 Hz), 133.4, 129.4, 129.0, 128.8, 114.7 (q, J(C,F) = 285.7 Hz), 69.7.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -74.96.

(EI) m/z (rel intens) 203.93 (M^+, 45), 135.18 (12), 107.23 (30), 91.41 (100).

Synthesis and characterization of (-)-Menthyl 2,2,2-trifluoroacetate (4b)



In a 20 mL glass vial (-)-menthol (3.08 mmol, 1 equiv., 554 mg) was dissolved in *n*-hexane (5 mL) under an atmosphere of air. Ethyl 2,2,2-trifluoroacetate (12.3 mmol, 4 equiv., 1.7 g) was added followed by 2 drops of concentrated H_2SO_4 and the reaction was stirred at room temperature for 16 h. The reaction was quenched with Na_2CO_3 (sat. aq, 10 mL), extracted with EtOAc (3 x 10 mL) and washed with Na_2CO_3 (sat. aq). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 1:20) afforded the title compound as a light yellow oil (249 mg, 35%).

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 4.87 (td, J(H,H) = 11.0, 4.5 Hz, 1H), 2.09-2.01 (m, 1H), 1.91-1.78 (m, 1H), 1.77-1.67 (m, 2H), 1.59-1.45 (m, 2H), 1.19-1.03 (m, 2H), 0.97-0.88 (m, 1H), 0.94 (d, J(H,H) = 6.6 Hz, 3H), 0.91 (d, J(H,H) = 7.0 Hz, 3H), 0.78 (d, J(H,H) = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 157.3 (q, J(C,F) = 41.6 Hz), 114.8 (q, J(C,F) = 285.7 Hz), 79.5, 46.9, 40.2, 34.1, 31.6, 26.4, 23.6, 21.9, 20.6, 16.3.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -75.30.

(EI) m/z (rel intens) 139.02 (M^+-CO_2CF_3, 17), 123.11 (9), 95.13 (44), 81.24 (100), 79.36 (52), 67.41 (54).

Radiochemistry

Preparation of [^{18}F]Bu_4NF:

[^{18}F]Fluoride was produced using a GE PETtrace 800 cyclotron and was separated from [^{18}O]water using anion exchange Sep-Pak® Accell Plus QMA Light cartridges (Waters Corporation, Milford, Massachusetts USA) pretreated with K_2CO_3 (aq. 0.5 M, 10 mL) and later with H_2O (10 mL). [^{18}F]Fluoride was next released from the cartridge with a solution of Bu_4NHCO_3 (0.0375 M, 600 μL) in a mixture acetonitrile / H_2O (1:1). Azeotropic drying was performed on a NanoTek® automated microfluidic device (Advion). Acetonitrile (600 μL) was added and the [^{18}F]fluoride was dried at 102 °C with a flow of nitrogen for 400 s. The drying process was repeated (x2) using 1000 μL of dry acetonitrile. The dried [^{18}F]Bu_4NF was dissolved in dry DMF and used in the next step.

Radiolabelling of 2a-u:

A 3.5 mL vial containing a magnetic stirrer was charged with the corresponding bromodifluoroacetamide **1a-u** (1 equiv., 0.06 mmol), DBU (1 equiv., 0.06 mmol, 9 mg) and dry DMF (300 μL). The [^{18}F]Bu_4NF solution in dry DMF was added (100 μL, 40-60 MBq aprox.) and the reaction was stirred at 100 °C in an oil bath for 10 min. The reaction was quenched by addition of acetonitrile at room temperature.

Radiolabelling of 2p, 2r and 2t:

A 2 mL vial containing a magnetic stirrer was charged with (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-bromo-2,2-difluoroacetate **3b** (1 equiv., 0.06 mmol, 19 mg), DBU (1 equiv., 0.06 mmol, 9 mg) and dry DMF (300 μL). The [^{18}F]Bu_4NF solution in dry DMF was added (100 μL, 40-60 MBq aprox.) and the reaction was stirred at 100 °C in an oil bath for 10 min. The reaction was cooled at room temperature and a solution of the corresponding amine (1.5 equiv., 0.09 mmol) and $Ln(OTf)_3$ (0.5 equiv., 0.03 mmol, 17 mg) in dry DMF (0.4 mL) was added. The reaction was stirred for 20 min at room temperature and quenched by addition of acetonitrile.

Analysis and radiochemical conversion (RCC) determination:

Radiochemical conversions (RCCs) were determined by radio-HPLC (the values were comparable to those obtained by radio-TLC). High pressure liquid chromatographic (HPLC) analyses were performed using an Agilent 1220 Infinity LC system with a built-in photodiode array (PDA) UV-detector, in series with a Eckert & Ziegler β^+-flow detector. The flow rate was of 3 mL / min using a HPLC reverse phase column XBridge® Waters (C18, 5 μm, 4.6 x 150 mm, column oven at 40 °C) and eluted with a linear increase gradient (mobile phase A:

acetonitrile, mobile phase B: $HCOONH_4$, 0.1 M). The ^{18}F-labeled compounds (**2a-u** and-**3a-b**) were identified by comparison of the retention time with the corresponding references.

HPLC Gradient 1		
Time (min)	Phase A (%)	Phase B (%)
0	60	40
5	95	5
10	98	2

HPLC Gradient 2		
Time (min)	Phase A (%)	Phase B (%)
0	20	80
7	95	5
10	98	2

HPLC Gradient 3		
Time (min)	Phase A (%)	Phase B (%)
0	10	90
8	80	20
10	98	2

Compound	HPLC Method	Retention time (CF_3-Reference) UV-detector (min)	Retention time (^{18}F-labelled) β^+-flow detector (min)
2a	Gradient 2	3.182	3.250
2b	Gradient 1	4.207	4.267
2c	Gradient 3	4.227	4.283
2d	Gradient 1	1.200	1.250
2e	Gradient 1	1.740	1.783
2f	Gradient 2	4.967	5.067
2g	Gradient 3	2.473	2.550
2h	Gradient 3	3.087	3.167
2i	Gradient 3	4.040	4.117
2j	Gradient 3	3.780	3.833
2k	Gradient 3	3.927	4.000
2l	Gradient 2	2.980	3.033
2m	Gradient 3	4.633	4.700
2n	Gradient 3	4.153	4.250
2o	Gradient 2	3.113	3.167
2p	Gradient 1	4.033	4.133
2q	Gradient 1	6.287	6.383
2r	Gradient 2	2.873	2.983
2s	Gradient 2	5.327	5.450
2t	Gradient 2	5.467	5.567
2u	Gradient 1	4.407	-
4a	Gradient 1	1.598	-
4b	Gradient 1	3.833	3.933

Semi-preparative-HPLC purification and calculation of the specific activity (S.A.):

Semi-preparative high pressure liquid chromatographic (HPLC) was performed using a TRACERlab FX C Pro chemistry synthesizer with a built-in β^+-flow detector in series with a photodiode array (PDA) UV detector. The flow rate was of 6 mL / min using a HPLC reverse phase column ACE (C18-HL, 5 μm, 410 x 250 mm) and eluted with an isocratic gradient (mobile phase acetonitrile / $HCOONH_4$ 0.1 M, 50:50).

Example 1:

A 3.5 mL vial containing a magnetic stirrer was charged with 2-bromo-2,2-difluoro-1-(piperidin-1-yl)ethanone **1a** (15 mg, 1 equiv., 0.06 mmol), DBU (1 equiv., 0.06 mmol, 9 mg). The [^{18}F]Bu_4NF solution in dry DMF was added (400 μL) and the reaction was stirred at 100 ^oC in an oil bath for 10 min. The reaction was quenched by diluting it with 4 mL of a mixture acetonitrile / $HCOONH_4$ 0.1 M (50:50) at room temperature and the ^{18}F-labelled compound **2a** was purified by semi-preparative-HPLC (44% RCY, 0.336 GBq, starting with 0.762 GBq in the reaction).

The specific activity (S.A.) of the purified product **2a** was calculated using the calibration curve in Figure S1; giving a value of 0.10 GBq/μmol.

Example 2:

A 3.5 mL vial containing a magnetic stirrer was charged with 2-bromo-2,2-difluoro-1-(piperidin-1-yl)ethanone **1a** (0.15 mg in dry DMF (100 μL), 0.01 equiv., 0.06 mmol), DBU (1 equiv., 0.06 mmol, 9 mg). The [^{18}F]Bu_4NF solution in dry DMF was added (300 μL) and the reaction was stirred at 100 ^oC in an oil bath for 10 min. The reaction was quenched by diluting it with 4 mL of a mixture acetonitrile / $HCOONH_4$ 0.1 M (50:50) at room temperature and the ^{18}F-labelled compound **2a** was purified by semi-preparative-HPLC (4% RCY, 0.284 GBq, starting with 7.16 GBq in the reaction).

The specific activity (S.A.) of the purified product **2a** was calculated using the calibration curve in Figure S1; giving a value of 8.4 GBq/μmol.

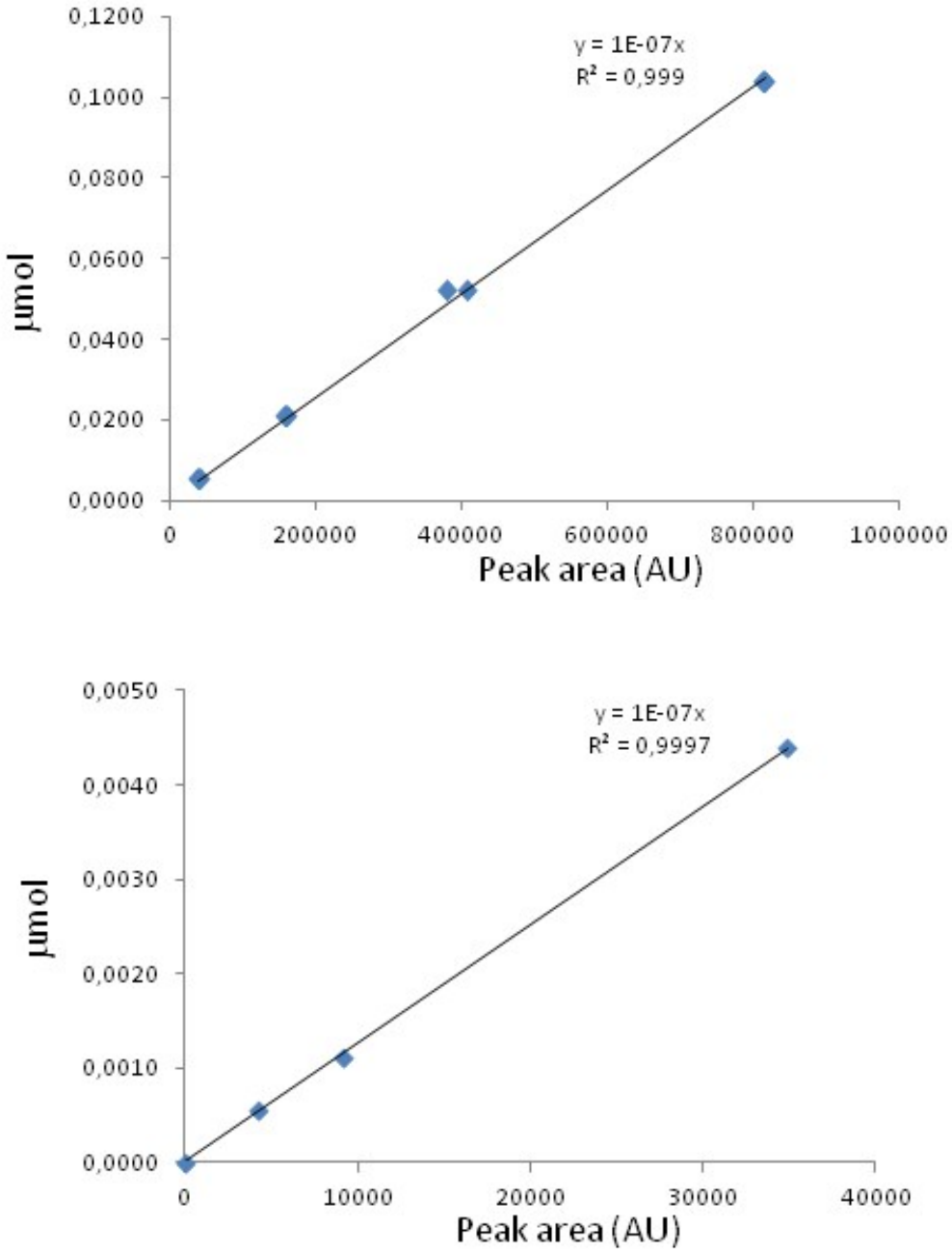
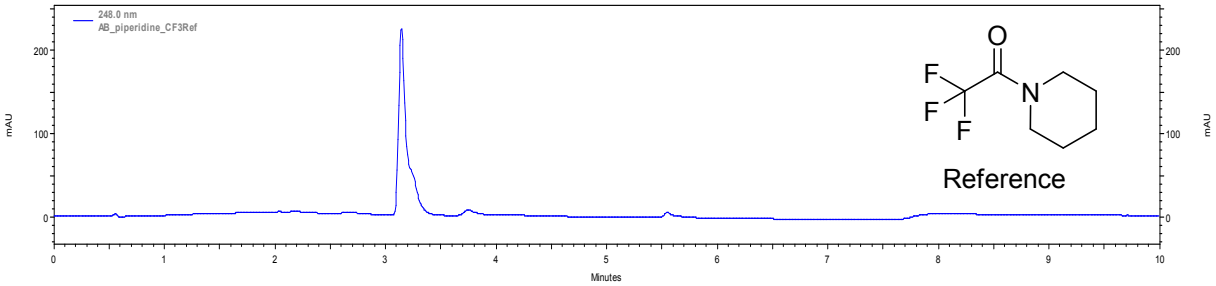
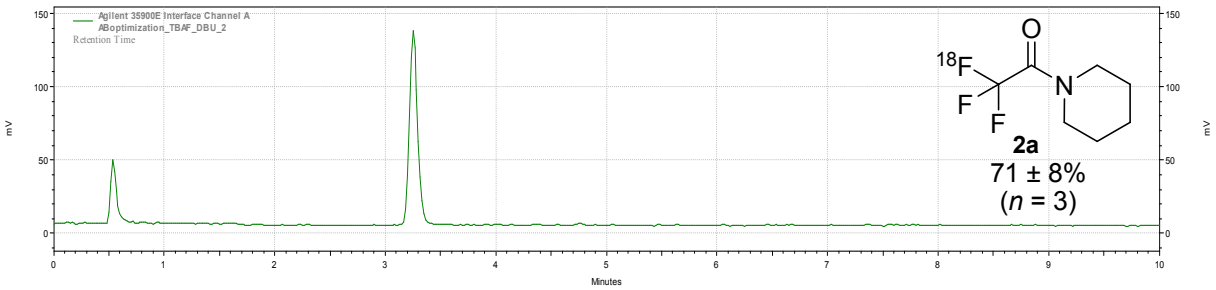
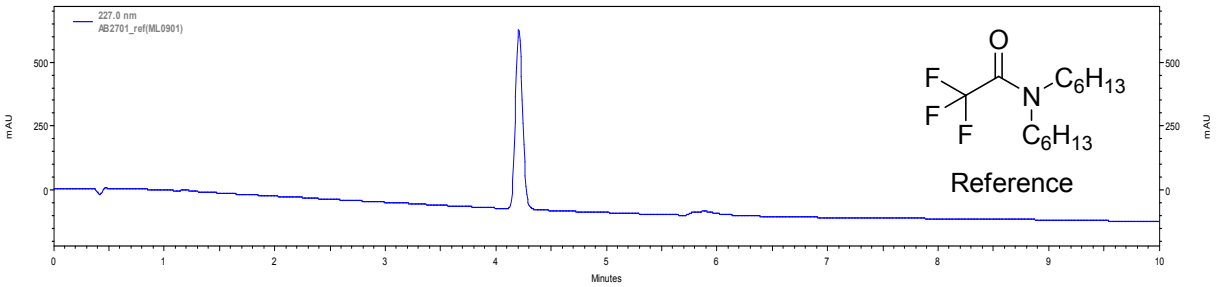


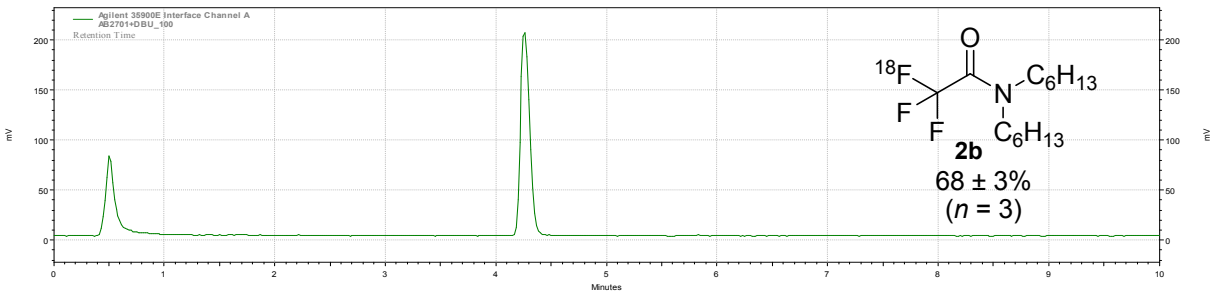
Figure S1. Calibration curves for the determination of the specific activity (S.A.) of compound **2a**.Top: high concentration. Bottom: low concentration.

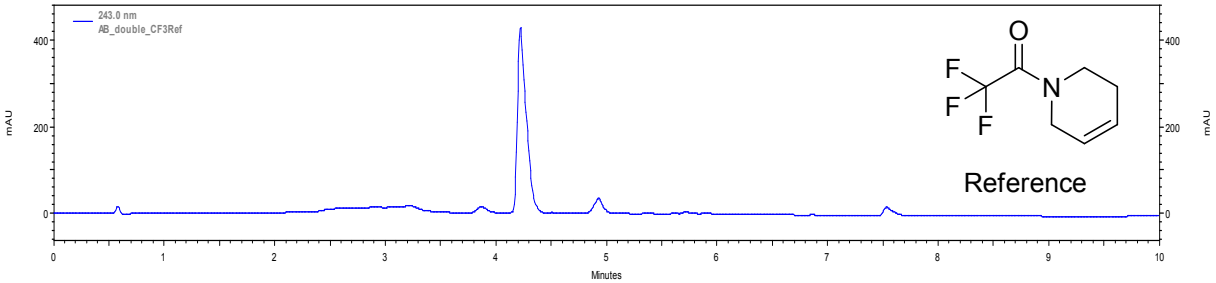
Radio-HPLC chromatograms

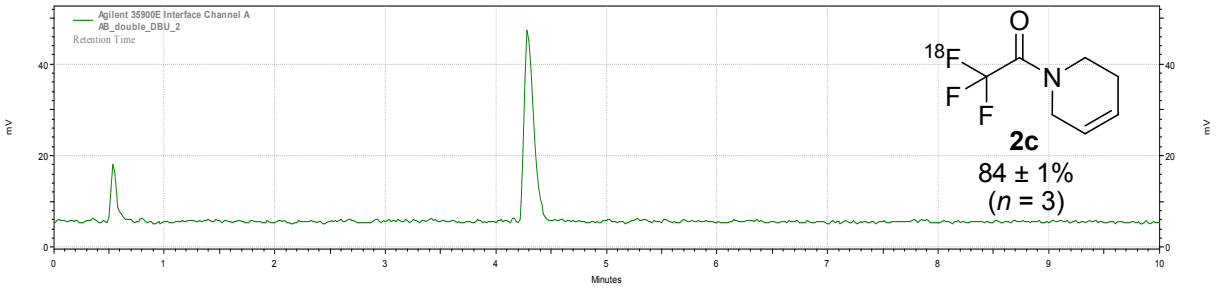


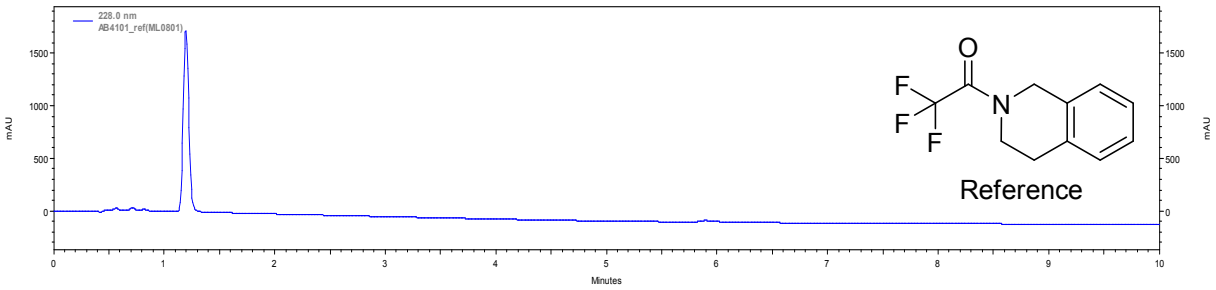


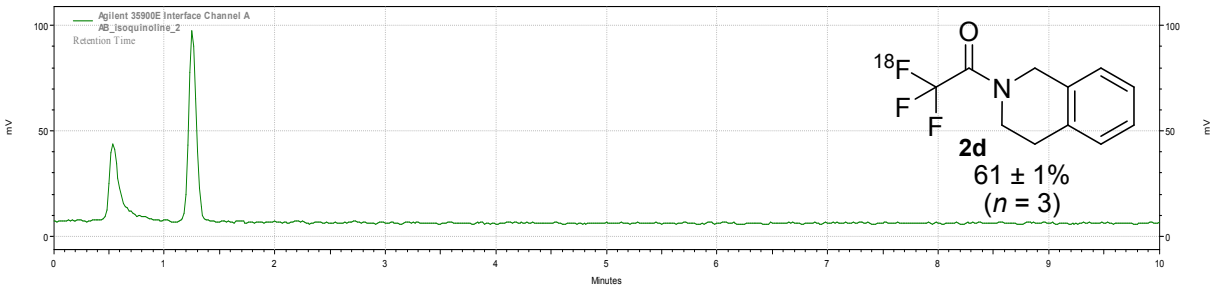


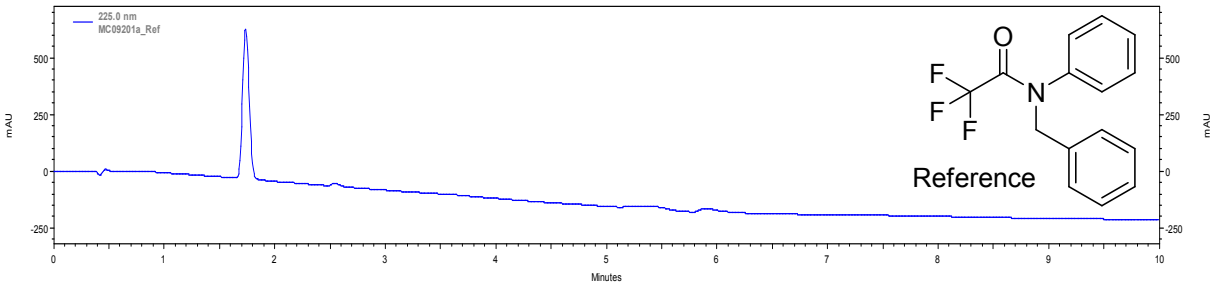


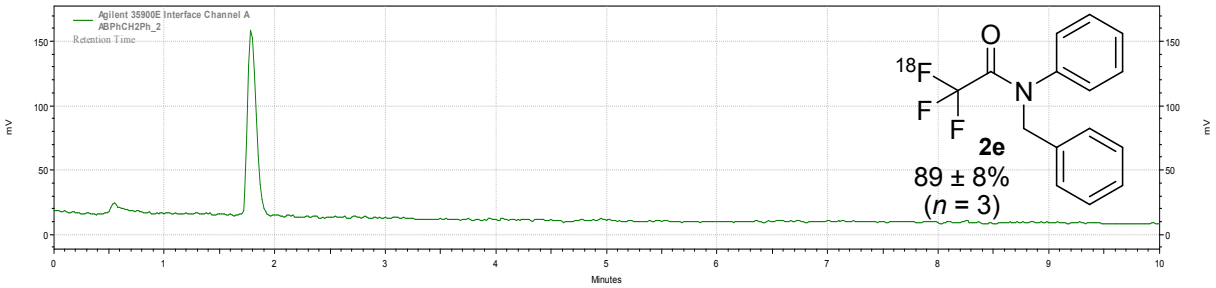

243.0 nm
AB_double_CF3Ref
mAU
Minutes
Reference

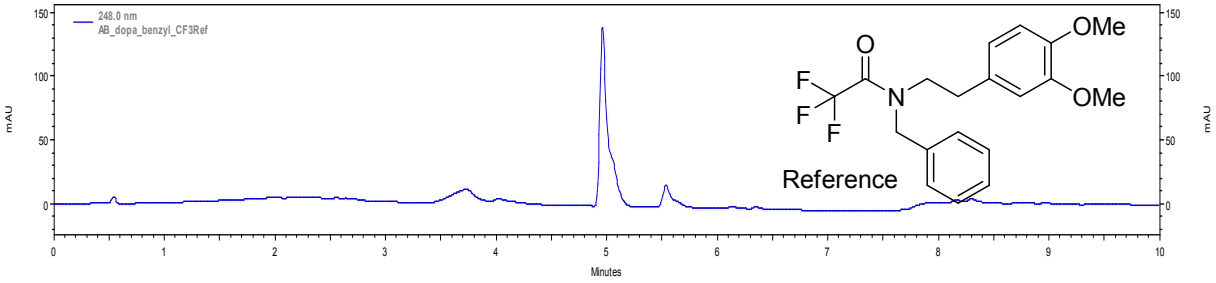

Agilent 35900E Interface Channel A
AB_double_DBU_2
Retention Time
mV
Minutes
2c
84 ± 1%
(n = 3)

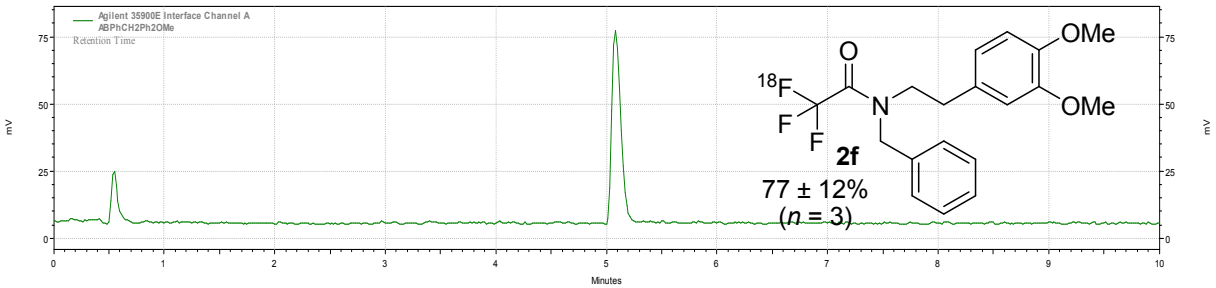

228.0 nm
AB4101_ref(ML0801)
mAU
Minutes
Reference

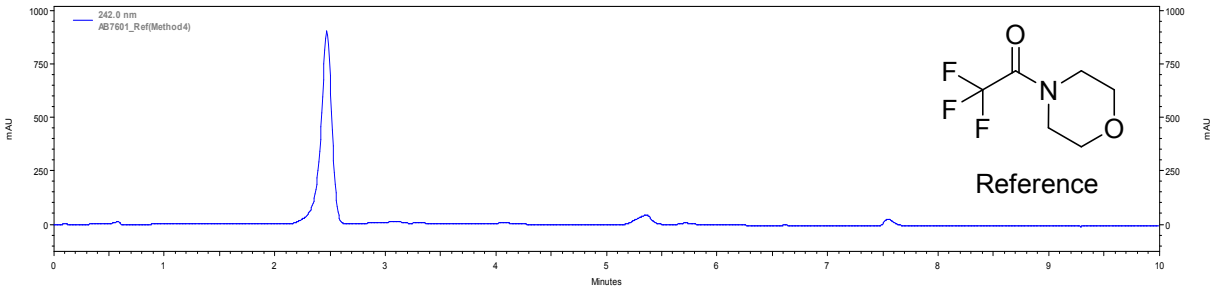

Agilent 35900E Interface Channel A
AB_isoquinoline_2
Retention Time
mV
Minutes
2d
61 ± 1%
(n = 3)

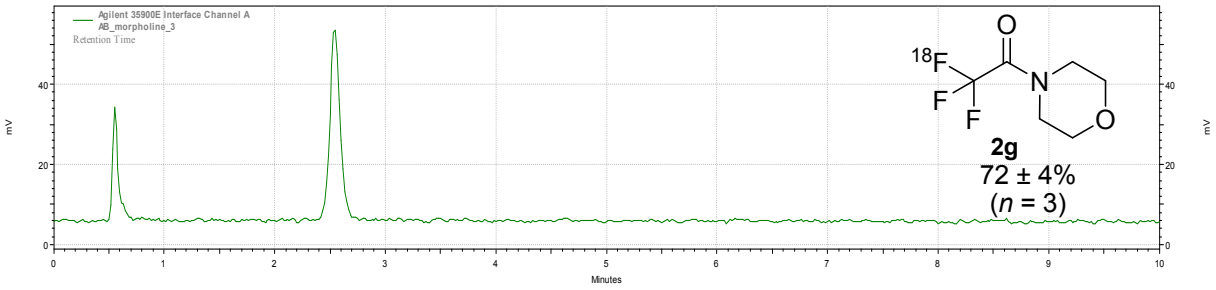

225.0 nm
MC09201a_Ref
mAU
Minutes
Reference

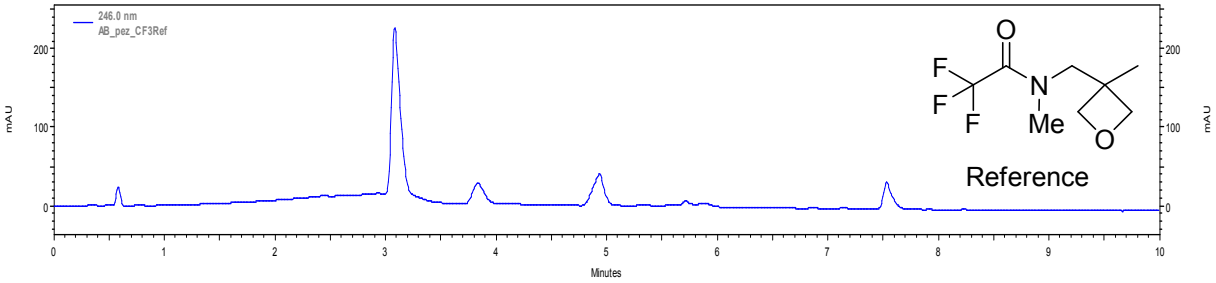

Agilent 35900E Interface Channel A
ABPhCH2Ph_2
Retention Time
mV
Minutes
2e
89 ± 8%
(n = 3)

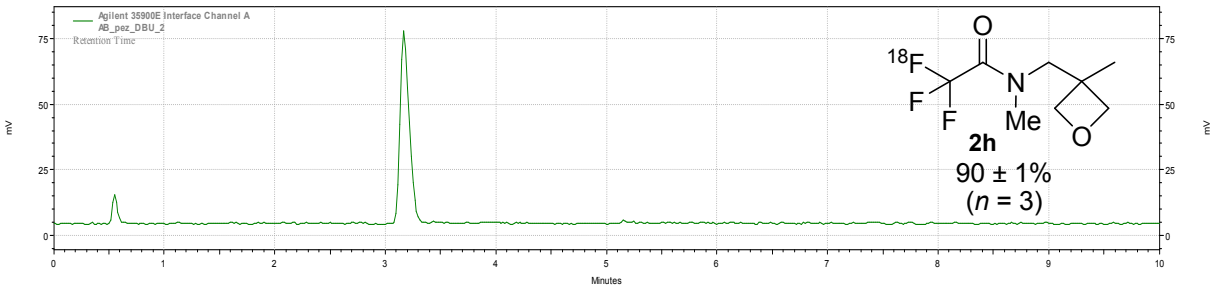

248.0 nm
AB_dopa_benzyl_CF3Ref
mAU
Minutes
Reference

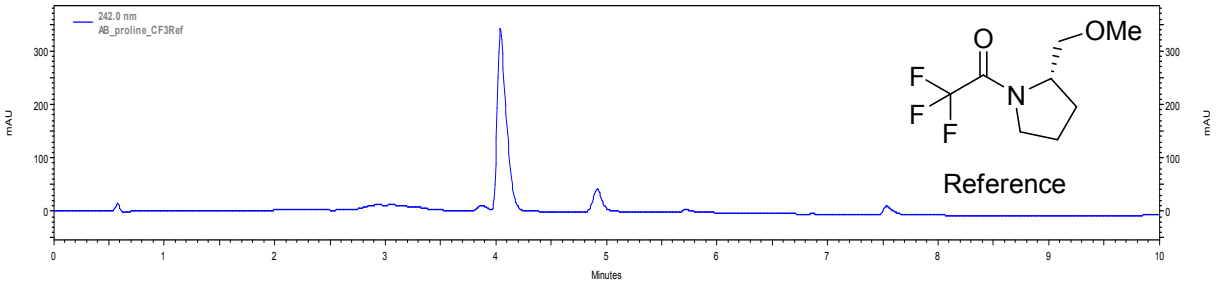

Agilent 35900E Interface Channel A
ABPhCH2Ph2OMe
Retention Time
mV
Minutes
2f
77 ± 12%
(n = 3)

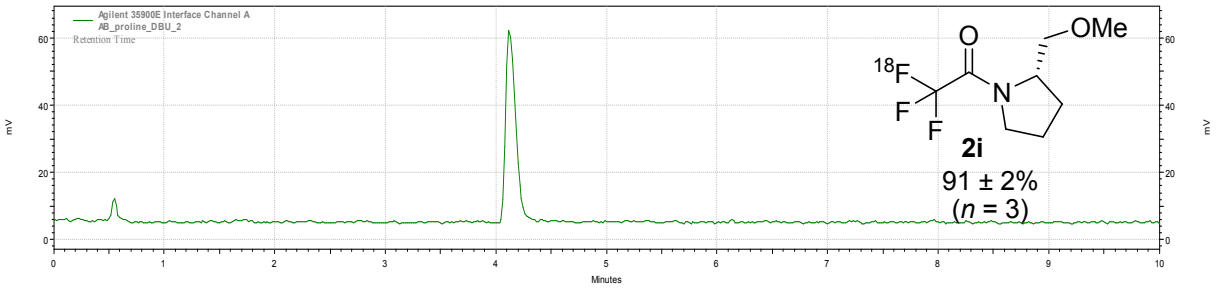

242.0 nm
AB7601_Ref(Method4)
mAU
Minutes
Reference

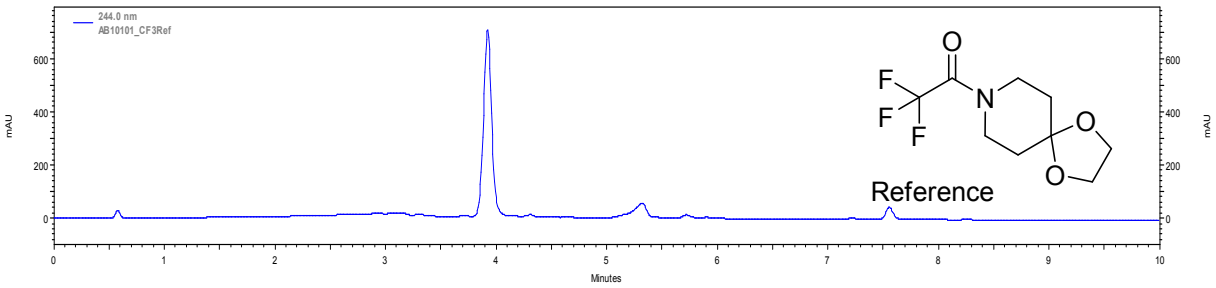

Agilent 35900E Interface Channel A
AB_morpholine_3
Retention Time
mV
Minutes
2g
72 ± 4%
(n = 3)

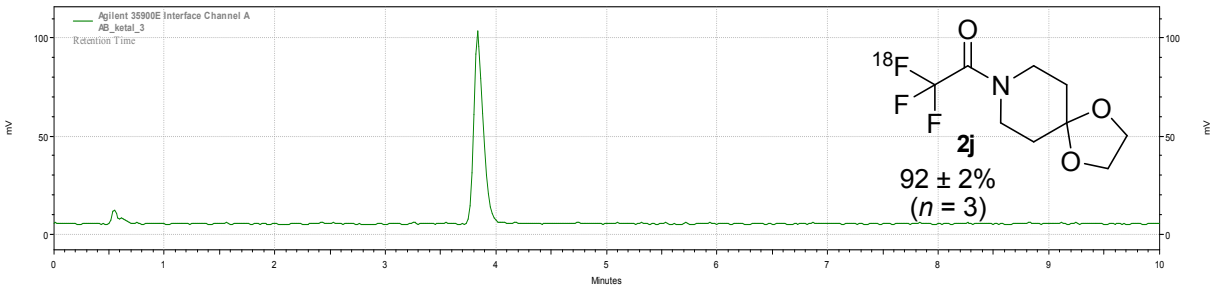

246.0 nm
AB_pez_CF3Ref
mAU
Minutes
Reference

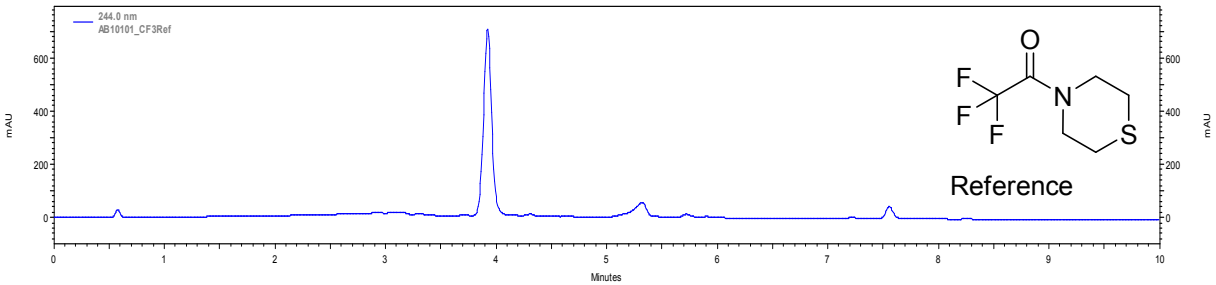

Agilent 35900E Interface Channel A
AB_pez_DBU_2
Retention Time
mV
Minutes
2h
90 ± 1%
(n = 3)

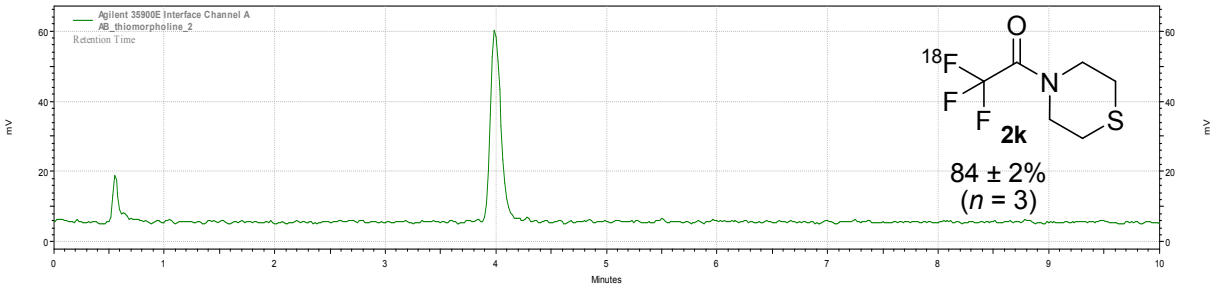

242.0 nm
AB_proline_CF3Ref
mAU
Minutes
Reference

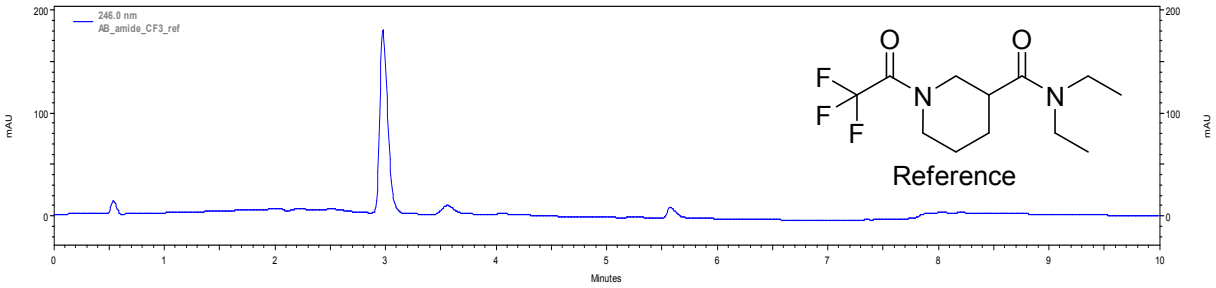

Agilent 35900E Interface Channel A
AB_proline_DBU_2
Retention Time
mV
Minutes
2i
91 ± 2%
(n = 3)

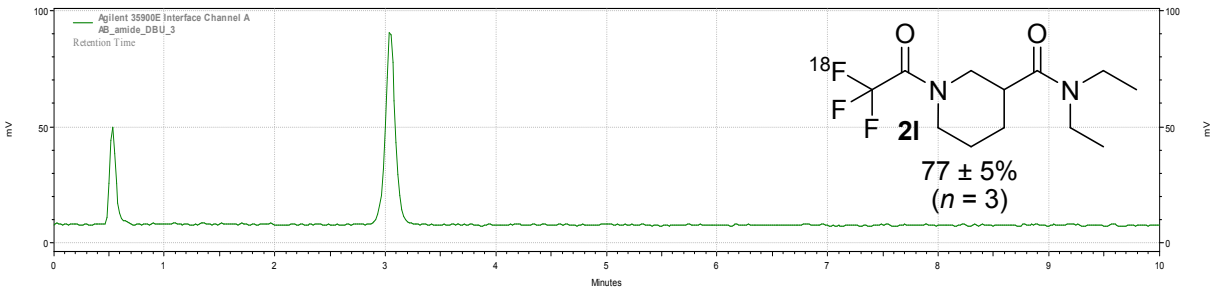

244.0 nm
AB10101_CF3Ref
mAU
Minutes
Reference

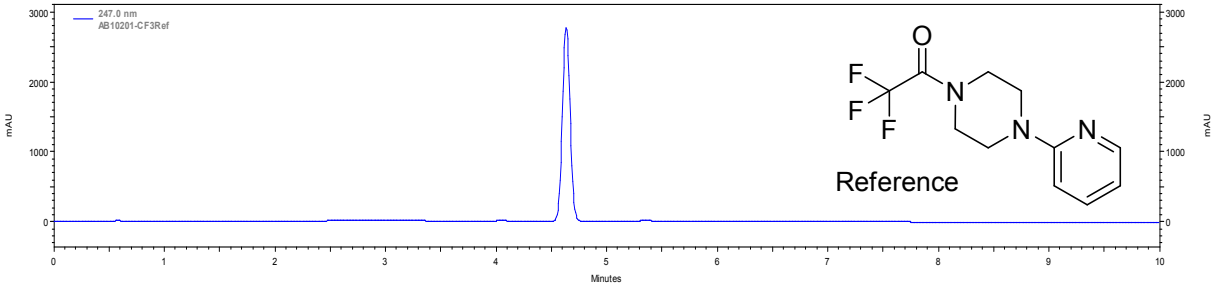

Agilent 35900E Interface Channel A
AB_ketal_3
Retention Time
mV
Minutes
2j
92 ± 2%
(n = 3)

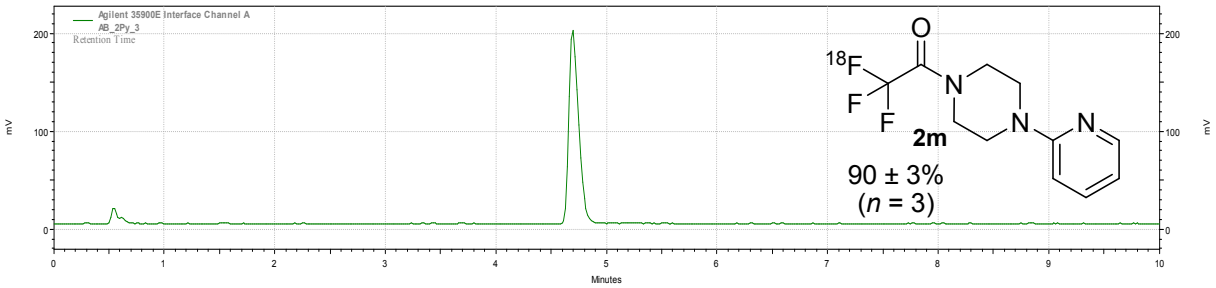

244.0 nm
AB10101_CF3Ref
mAU
Minutes
Reference

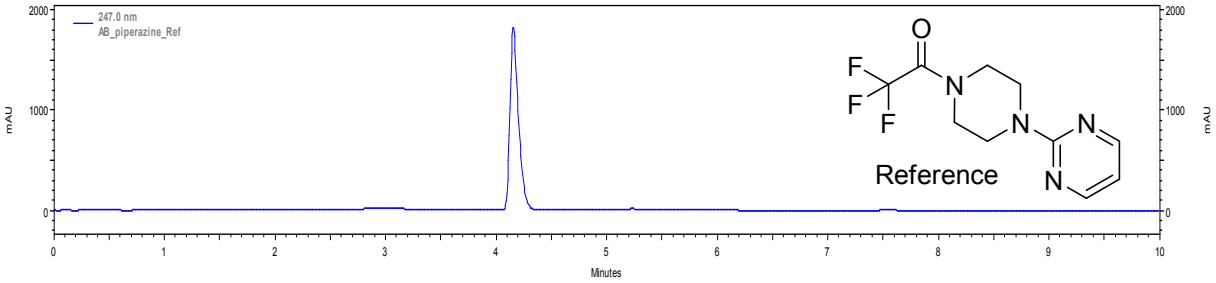

Agilent 35900E Interface Channel A
AB_thiomorpholine_2
Retention Time
mV
Minutes
2k
84 ± 2%
(n = 3)

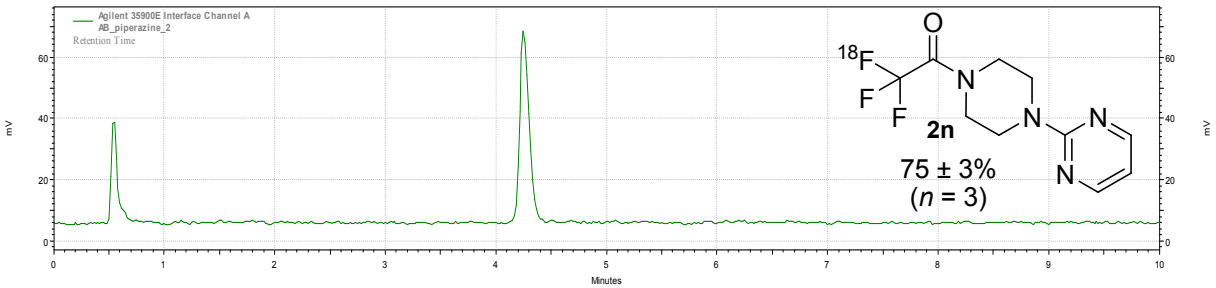

246.0 nm
AB_amide_CF3_ref
mAU
Minutes
Reference

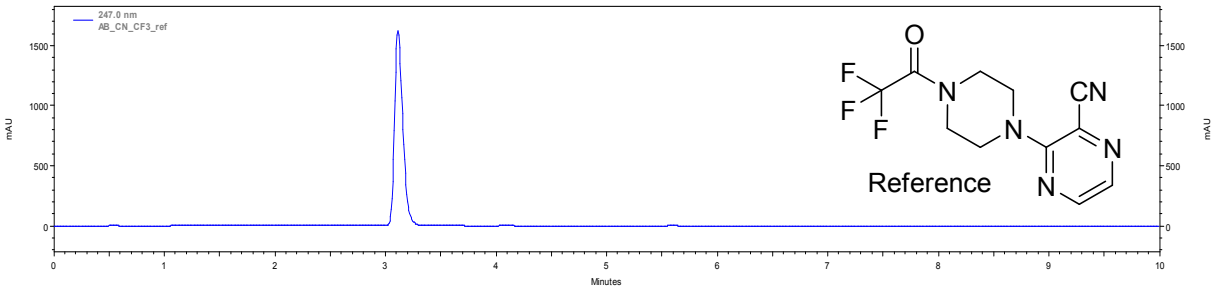

Agilent 35900E Interface Channel A
AB_amide_DBU_3
Retention Time
mV
Minutes
2l
77 ± 5%
(n = 3)

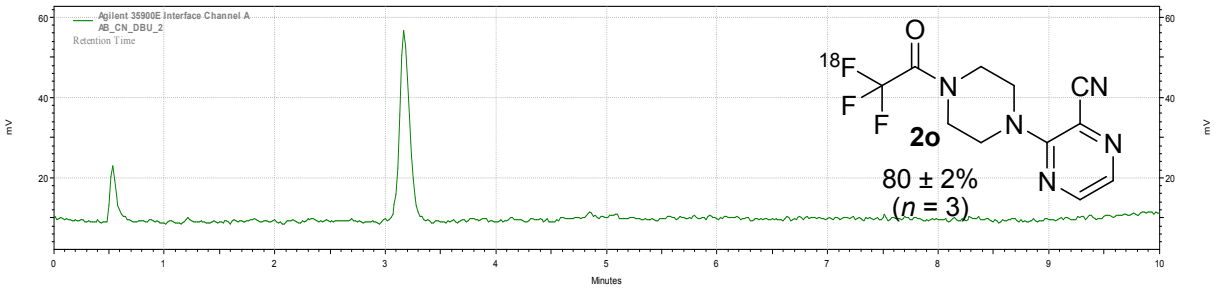

247.0 nm
AB10201-CF3Ref
mAU
Minutes
Reference

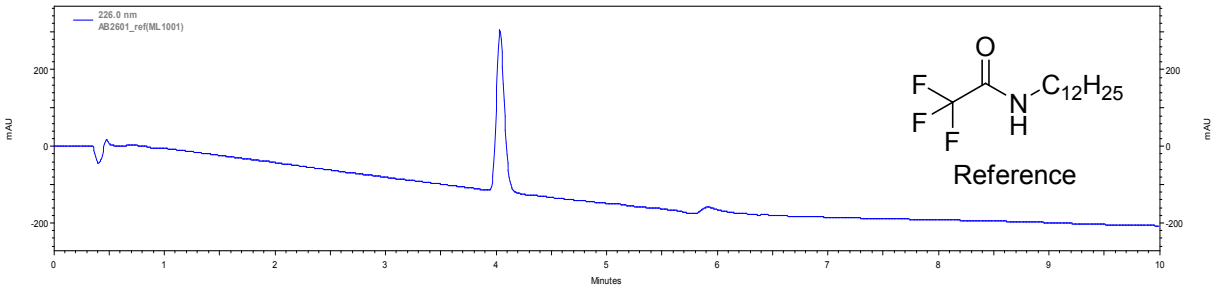

Agilent 35900E Interface Channel A
AB_2Py_3
Retention Time
mV
Minutes
2m
90 ± 3%
(n = 3)

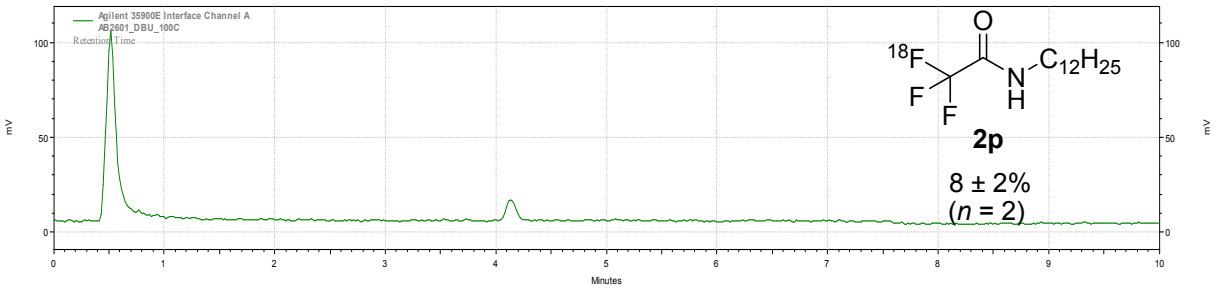

247.0 nm
AB_piperazine_Ref
mAU
Minutes
Reference

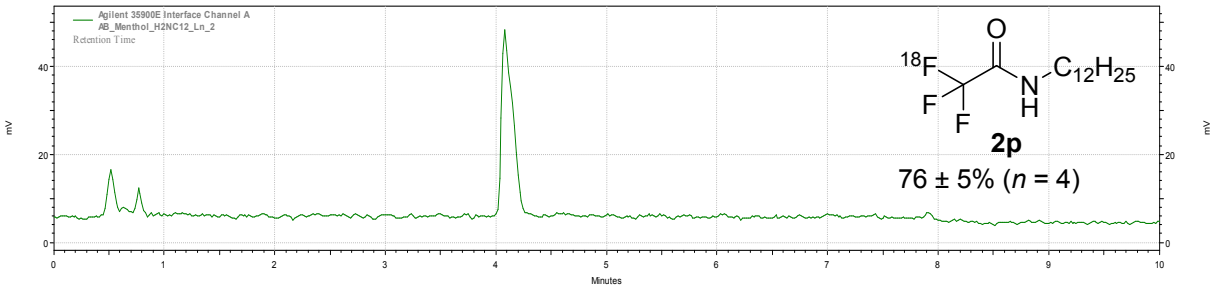

Agilent 35900E Interface Channel A
AB_piperazine_2
Retention Time
mV
Minutes
2n
75 ± 3%
(n = 3)

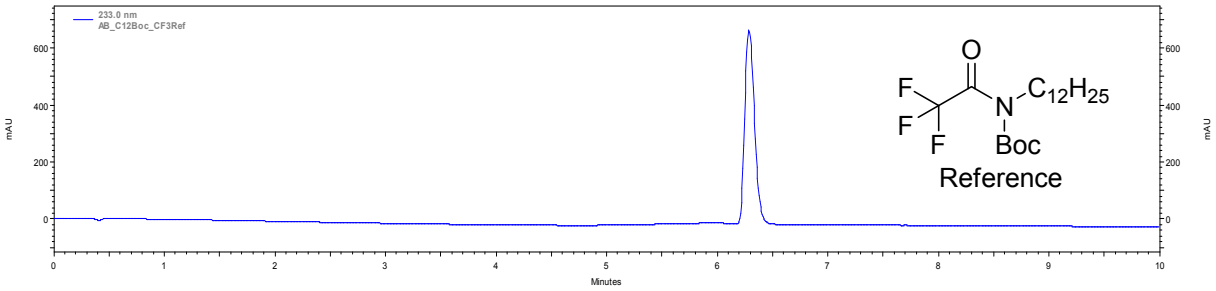

247.0 nm
AB_CN_CF3_ref
mAU
Minutes
Reference

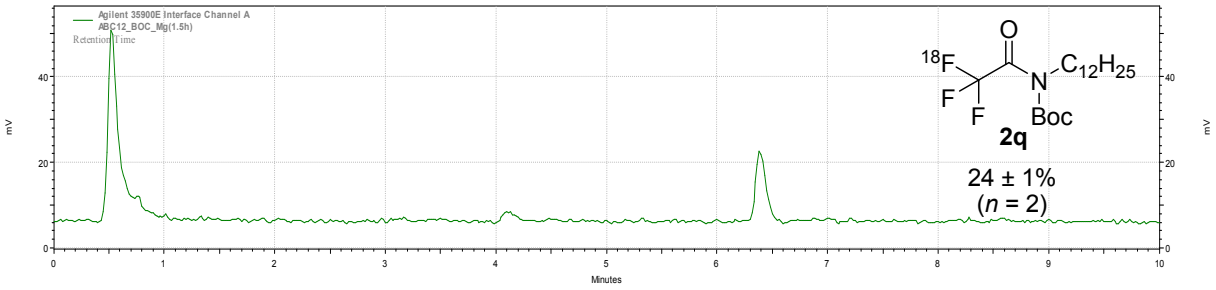

Agilent 35900E Interface Channel A
AB_CN_DBU_2
Retention Time
mV
Minutes
2o
80 ± 2%
(n = 3)

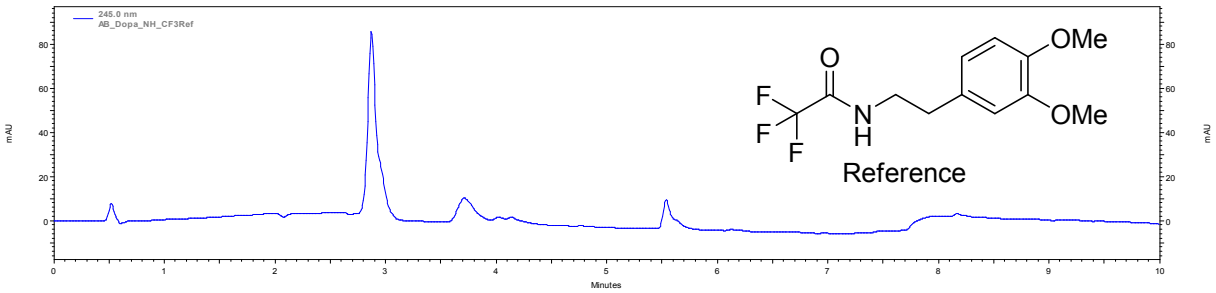

226.0 nm
AB2601_ref(ML1001)
mAU
Minutes
Reference

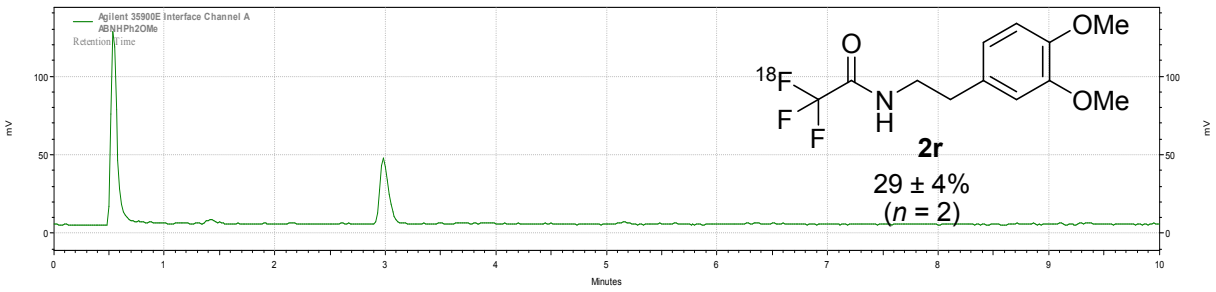

Agilent 35900E Interface Channel A
AB2601_DBU_100C
Retention Time
mV
Minutes
2p
8 ± 2%
(n = 2)

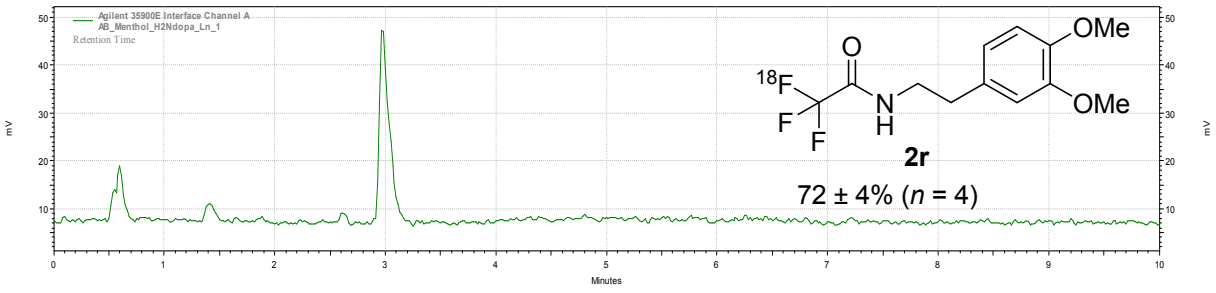

Agilent 35900E Interface Channel A
AB_Menthol_H2NC12_Ln_2
Retention Time
mV
Minutes
2p
76 ± 5% (n = 4)

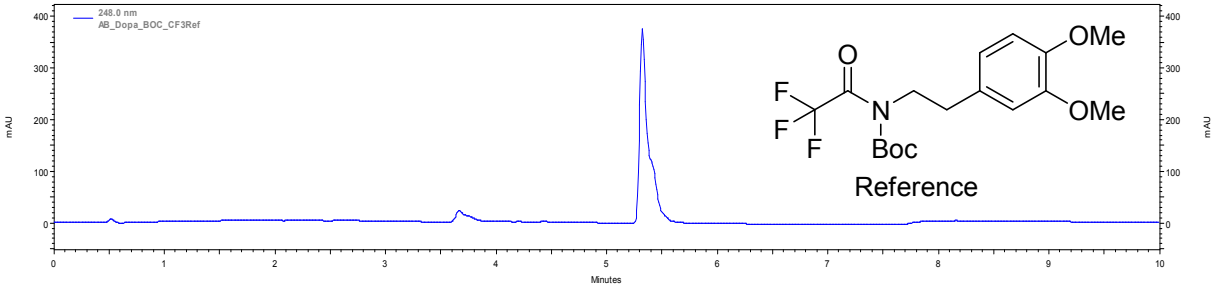

233.0 nm
AB_C12Boc_CF3Ref
mAU
Minutes
Reference

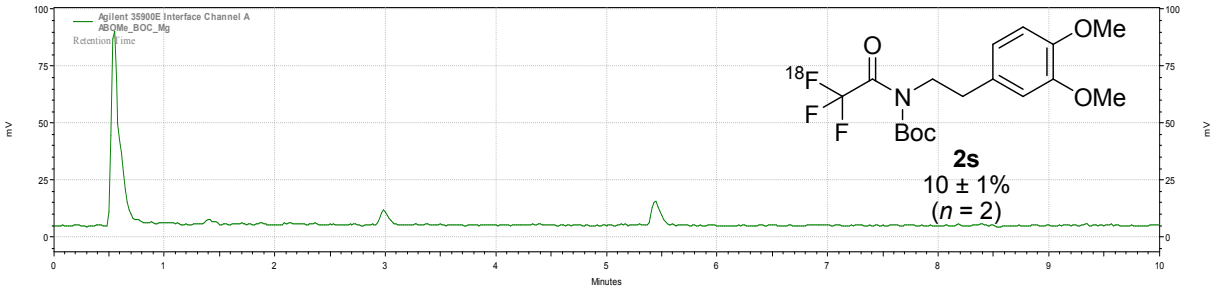

Agilent 35900E Interface Channel A
AB_C12_BOC_Mg(1.5h)
Retention Time
mV
Minutes
2q
24 ± 1%
(n = 2)

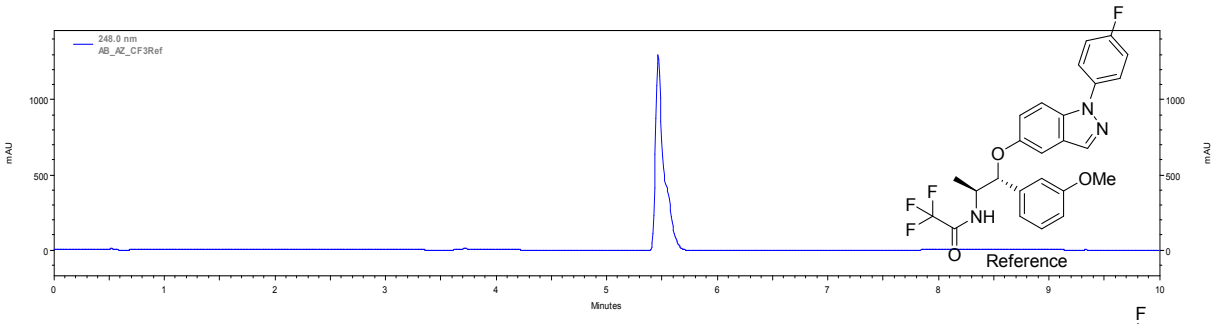

246.0 nm
AB_Dopa_NH_CF3Ref
mAU
Minutes
Reference

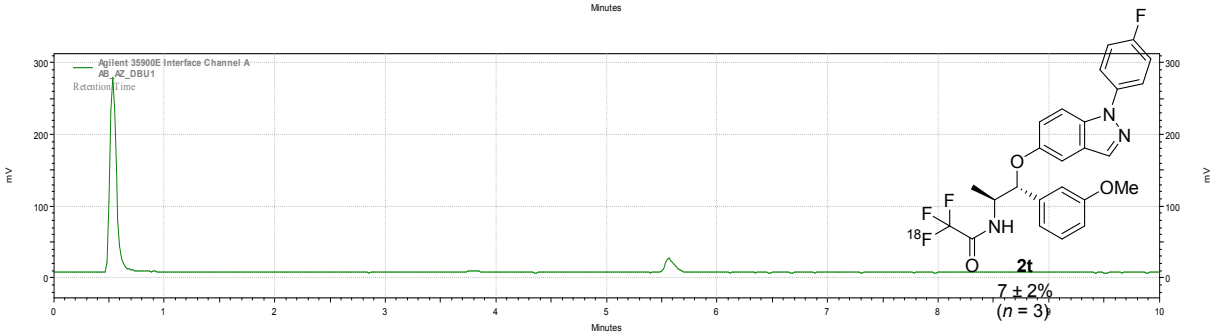

Agilent 35900E Interface Channel A
ABNHPh2OMe
Retention Time
mV
Minutes
2r
29 ± 4%
(n = 2)

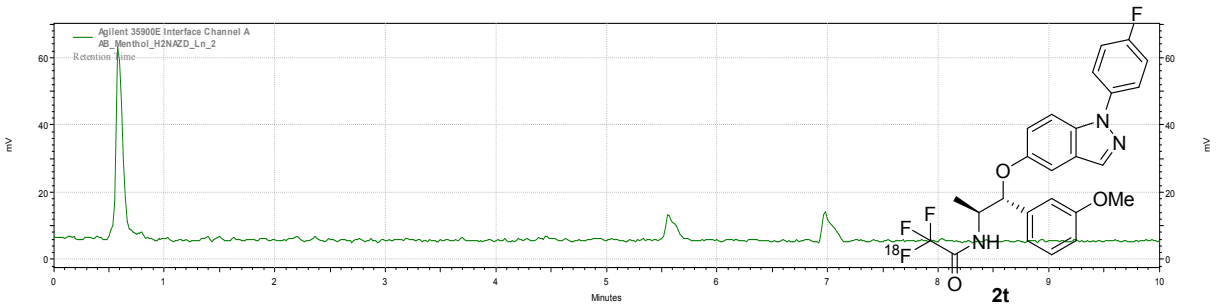

Agilent 35900E Interface Channel A
AB_Menthol_H2Ndopa_Ln_1
Retention Time
mV
Minutes
2r
72 ± 4% (n = 4)

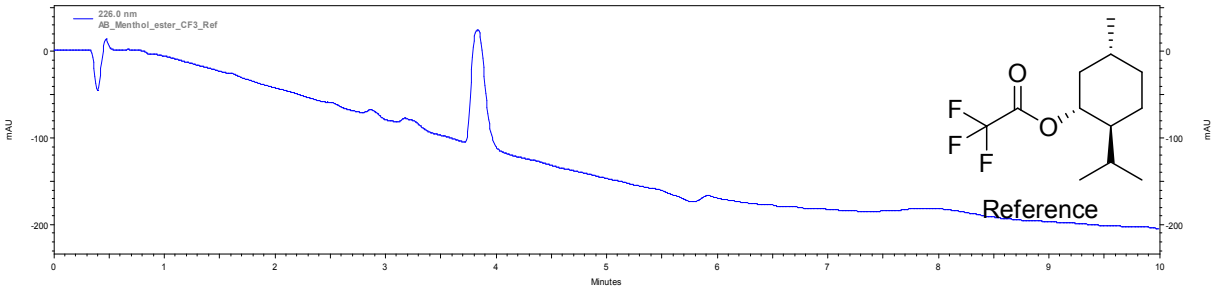

248.0 nm
AB_Dopa_BOC_CF3Ref
mAU
Minutes
OMe
OMe
O
F
F
F
N
Boc
Reference

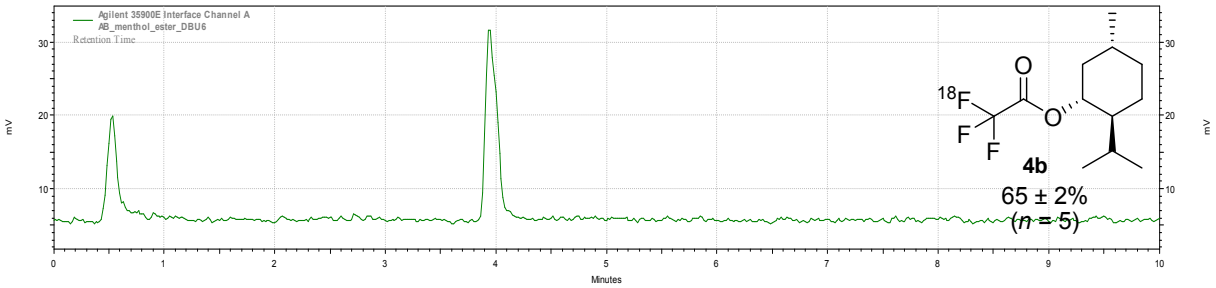

Agilent 35900E Interface Channel A
ABOMe_BOC_Mg
Retention Time
mV
Minutes
OMe
OMe
O
18F
F
F
N
Boc
2s
10 ± 1%
(n = 2)


248.0 nm
AB_AZ_CF3Ref
mAU
Minutes
F
N
N
O
OMe
F
F
NH
O
Reference

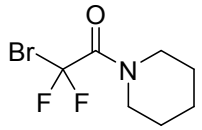

Agilent 35900E Interface Channel A
AB_AZ_DBU1
Retention Time
mV
Minutes
F
N
N
O
OMe
F
18F
NH
O
2t
7 ± 2%
(n = 3)

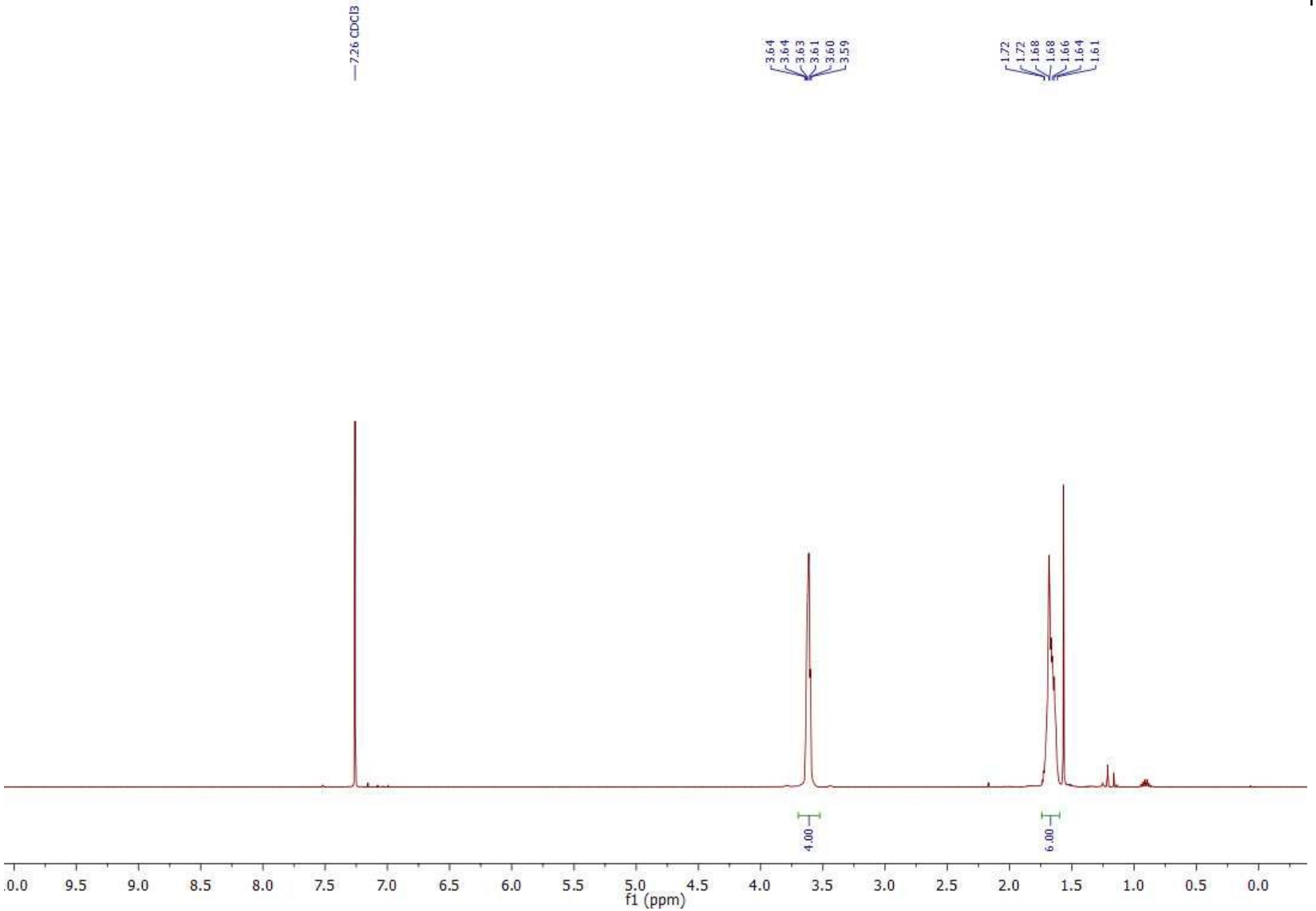

Agilent 35900E Interface Channel A
AB_Menthol_H2NAZD_Ln_2
Retention Time
mV
Minutes
F
N
N
O
OMe
F
18F
NH
O
2t
12 ± 2% (n = 2)


226.0 nm
AB_Menthol_ester_CF3_Ref
mAU
Minutes
Reference

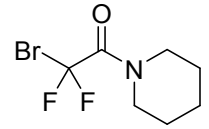

Agilent 35900E Interface Channel A
AB_menthol_ester_DBU6
Retention Time
mV
Minutes
4b
65 ± 2%
(n = 5)

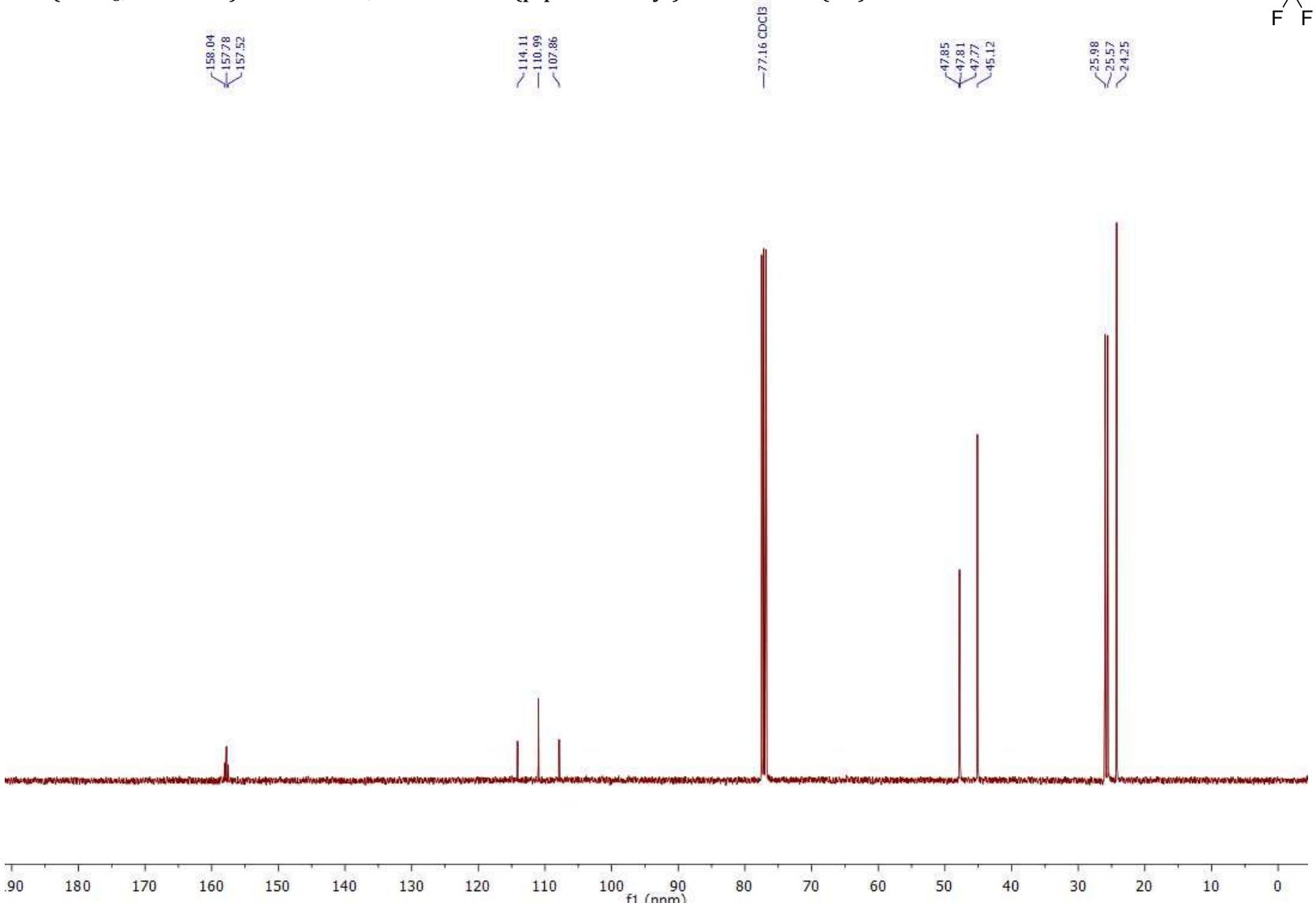
^{1}H NMR ($CDCl_3$, 400 MHz). 2-Bromo-2,2-difluoro-1-(piperidin-1-yl)ethan-1-one (**1a**)



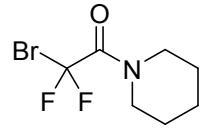


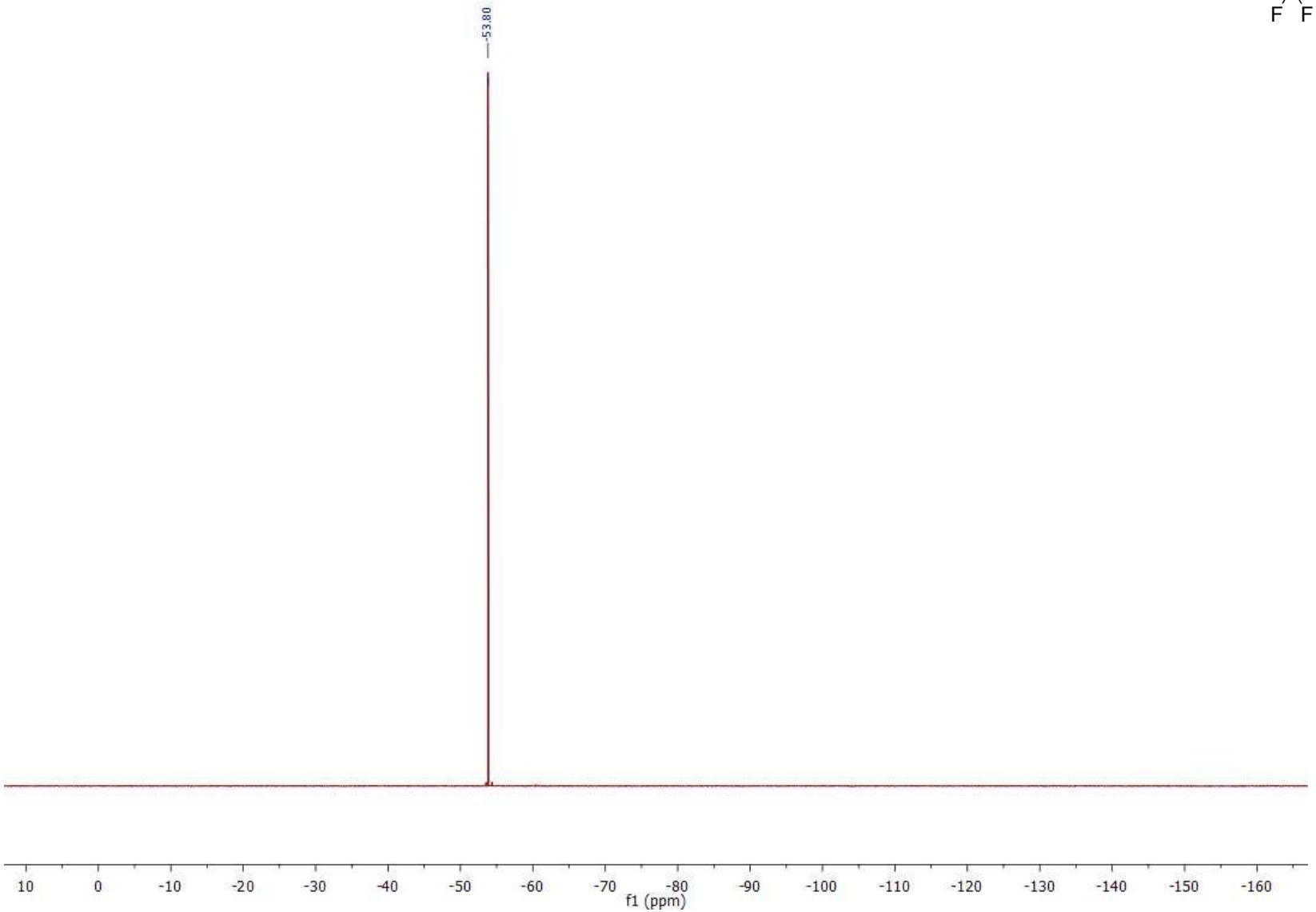
^{13}C NMR ($CDCl_3$, 100 MHz). 2-Bromo-2,2-difluoro-1-(piperidin-1-yl)ethan-1-one (**1a**)



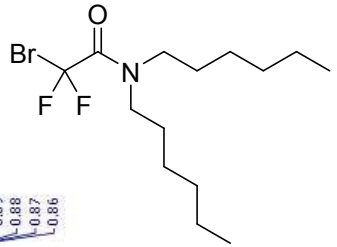


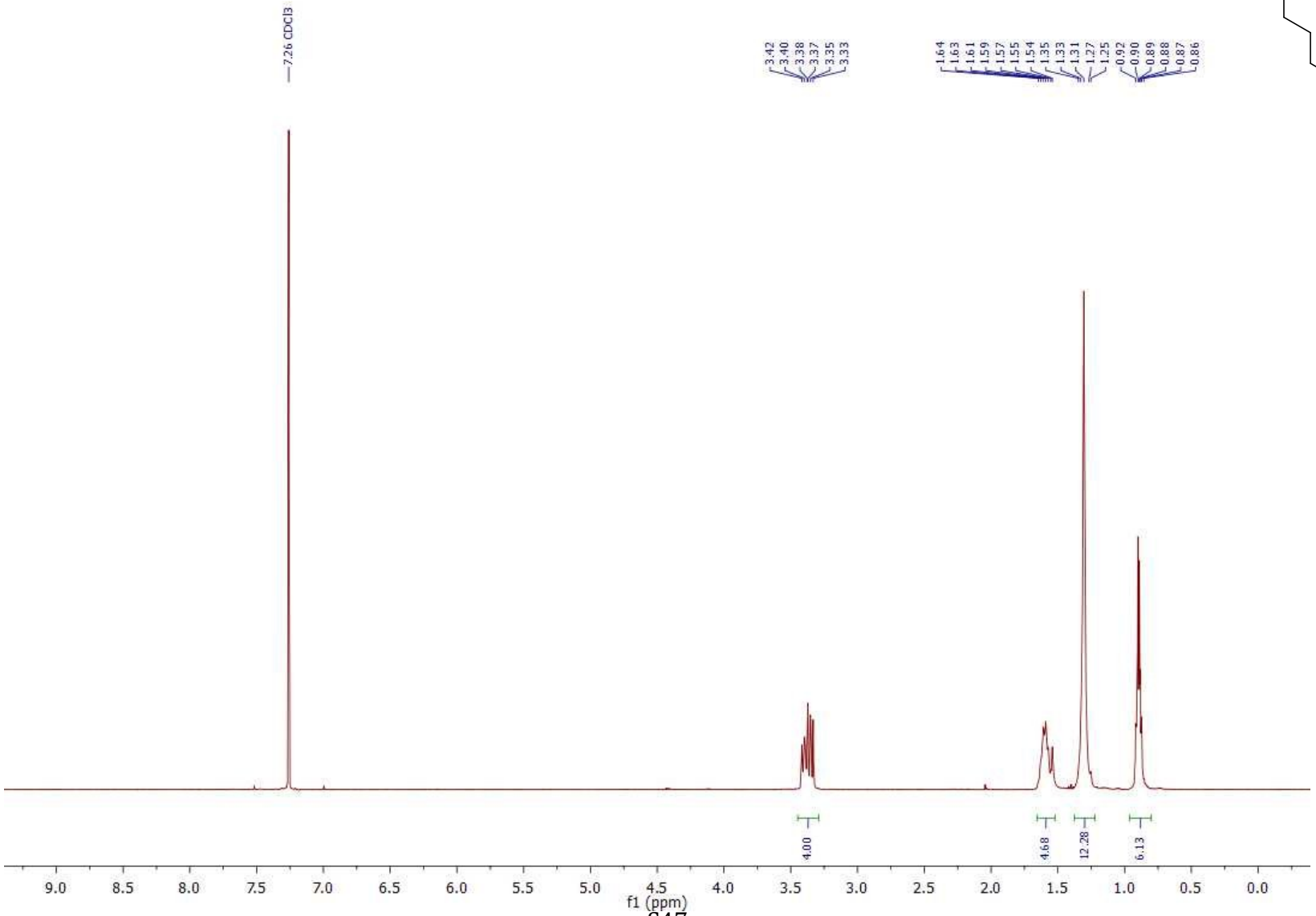
^{19}F NMR ($CDCl_3$, 377 MHz). 2-Bromo-2,2-difluoro-1-(piperidin-1-yl)ethan-1-one (**1a**)



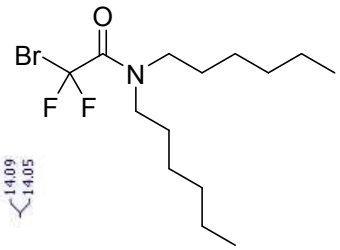


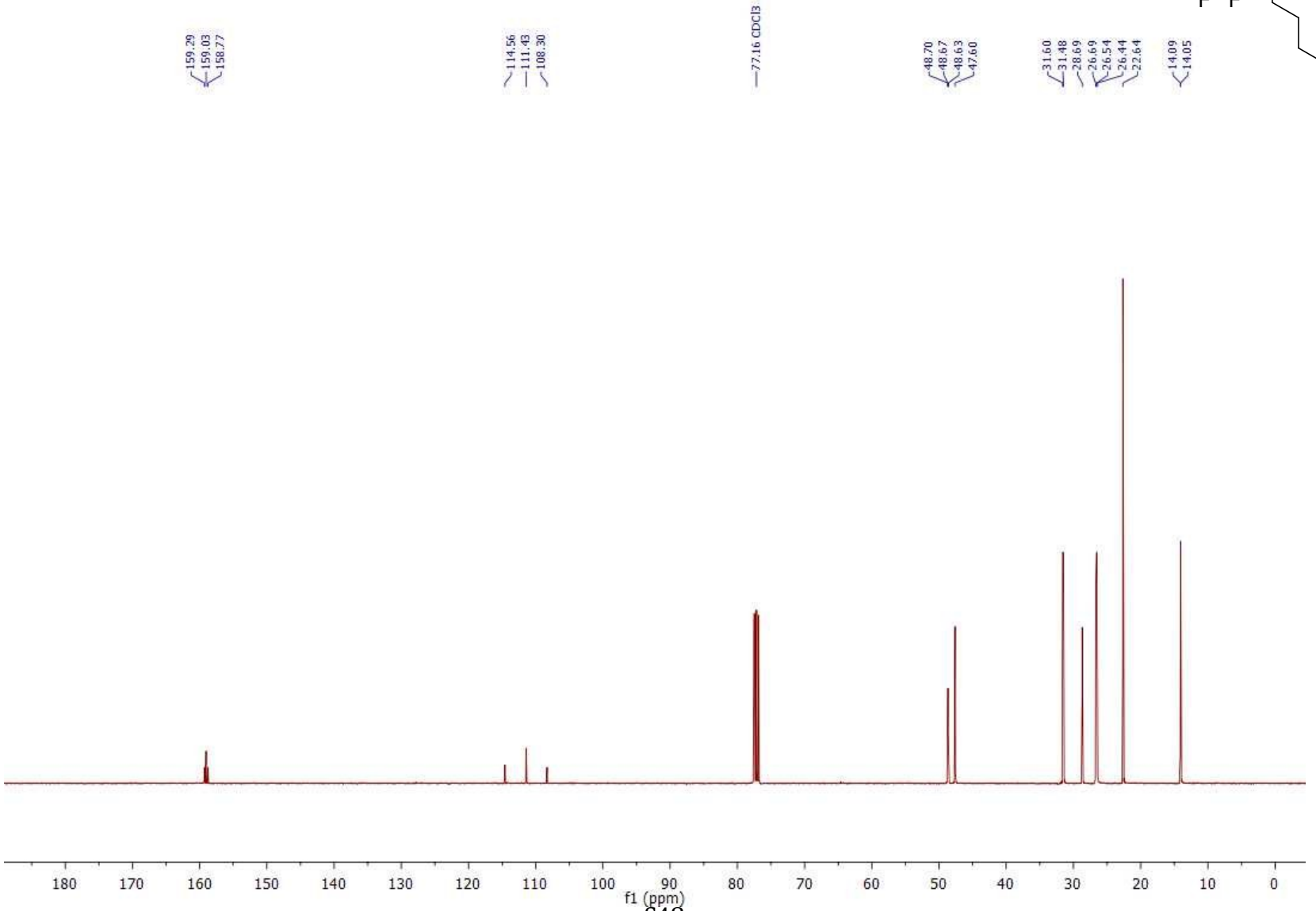
^{1}H NMR ($CDCl_3$, 400 MHz). 2-Bromo-2,2-difluoro-*N*,*N*-dihexylacetamide (**1b**)



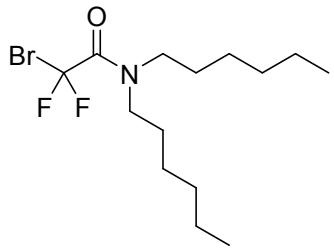


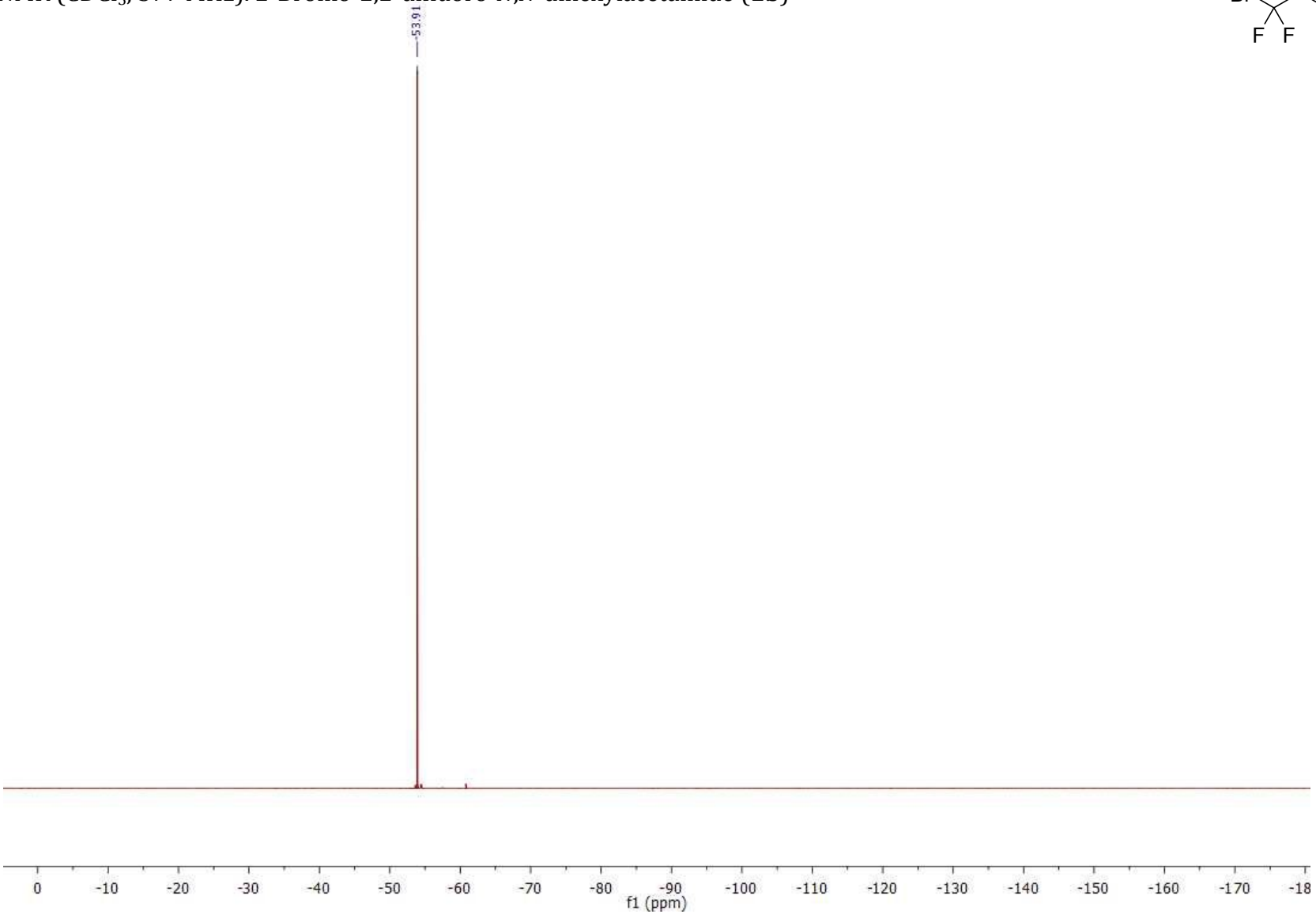
^{13}C NMR ($CDCl_3$, 100 MHz). 2-Bromo-2,2-difluoro-*N*,*N*-dihexylacetamide (**1b**)



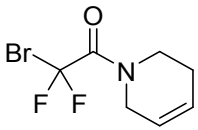


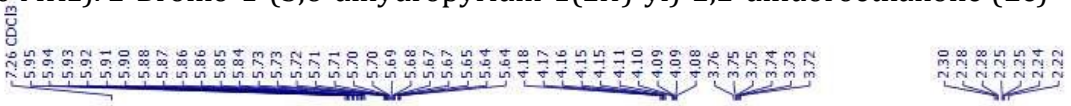
^{19}F NMR ($CDCl_3$, 377 MHz). 2-Bromo-2,2-difluoro-*N*,*N*-dihexylacetamide (**1b**)

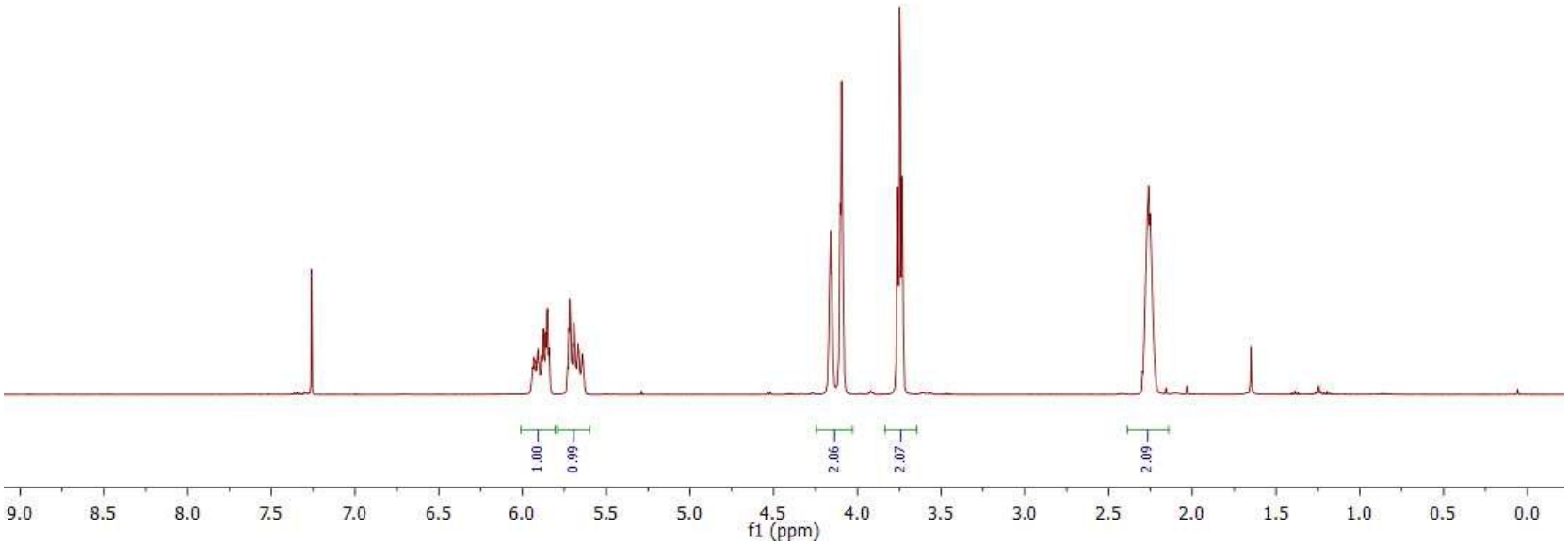




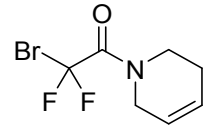
^{1}H NMR ($CDCl_3$, 400 MHz). 2-Bromo-1-(5,6-dihydropyridin-1(2*H*)-yl)-2,2-difluoroethanone (**1c**)

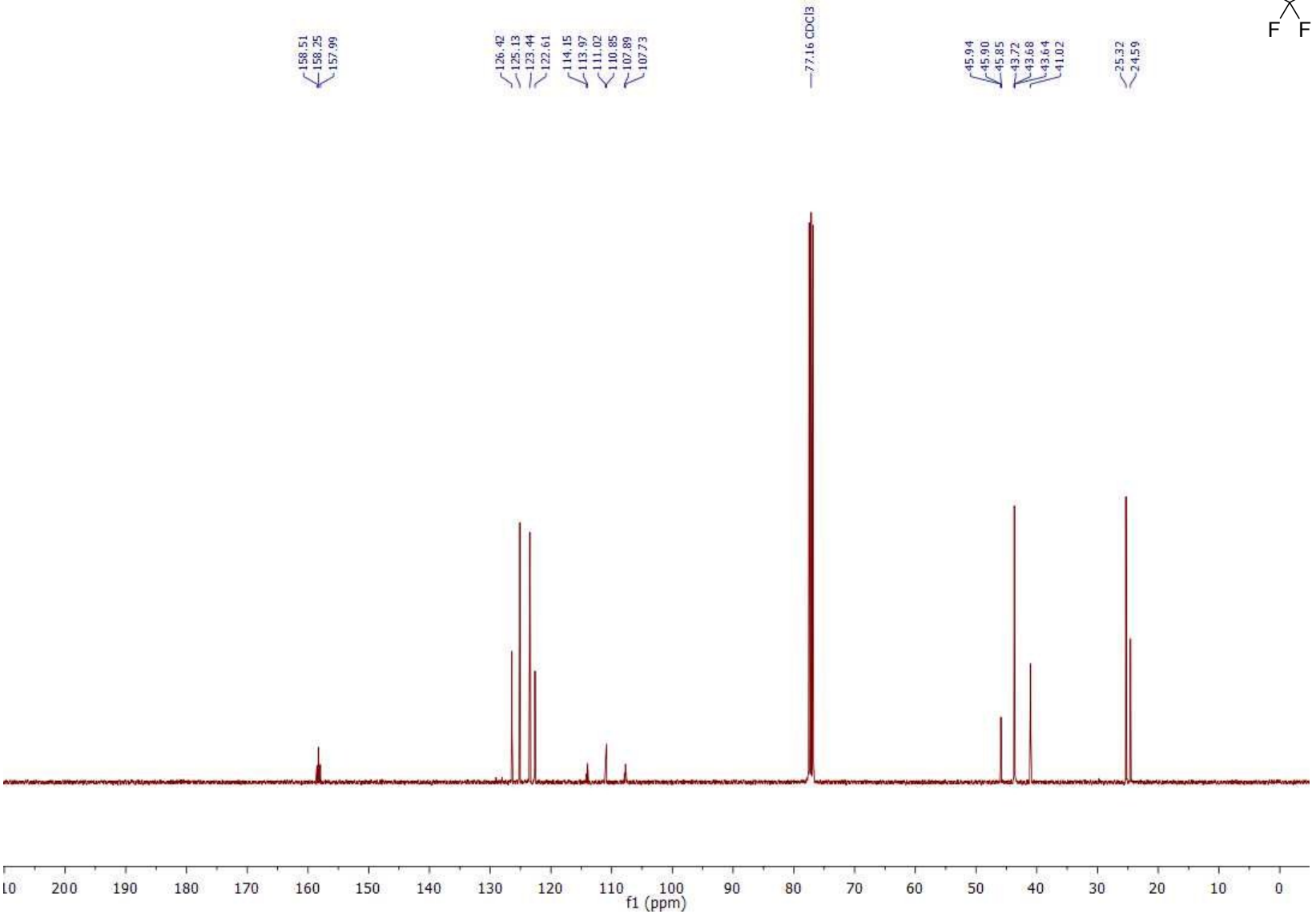




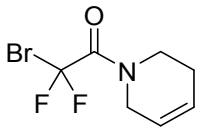


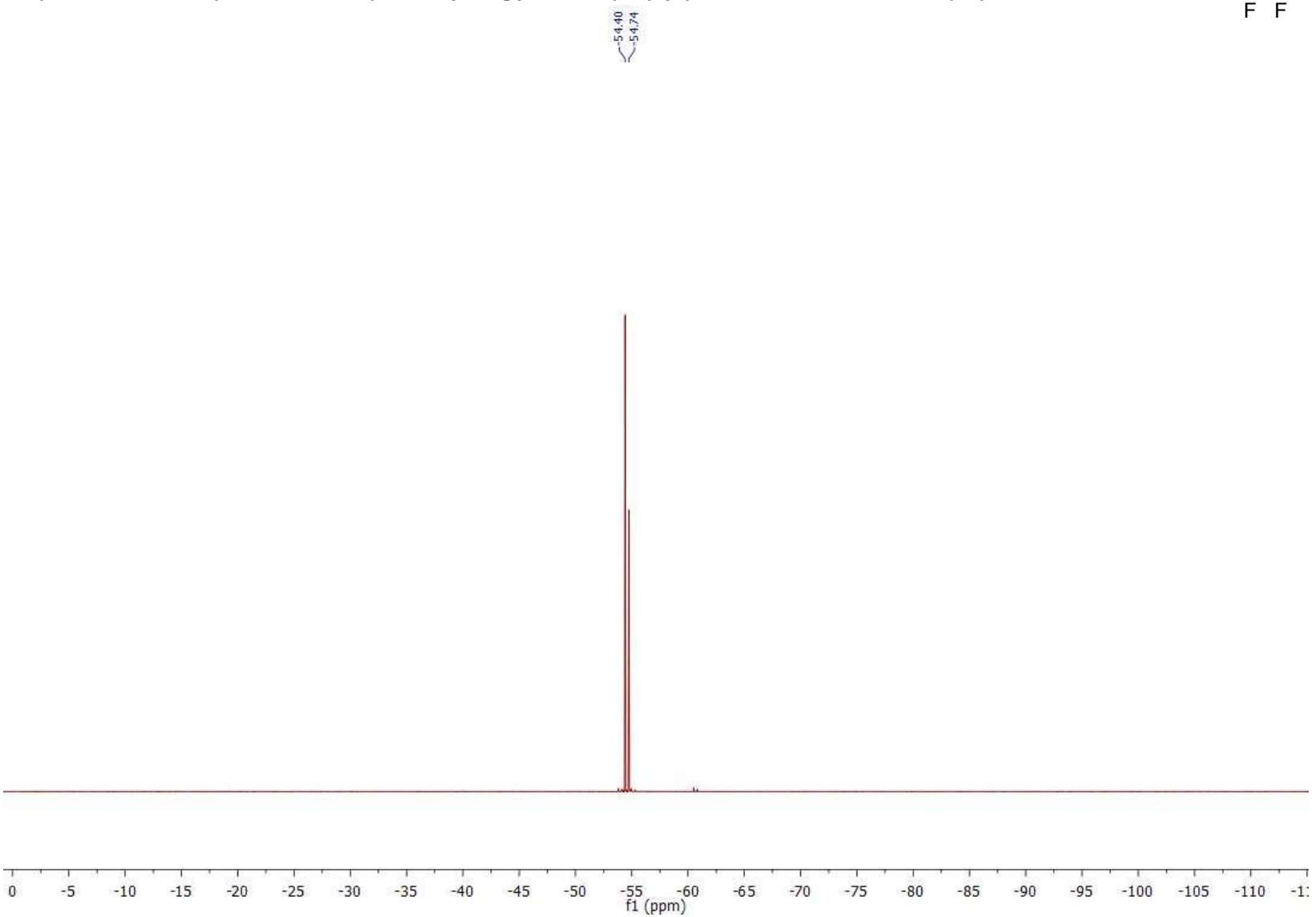
^{13}C NMR ($CDCl_3$, 100 MHz). 2-Bromo-1-(5,6-dihydropyridin-1(2*H*)-yl)-2,2-difluoroethanone (**1c**)



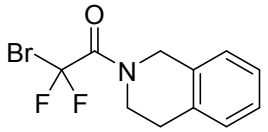


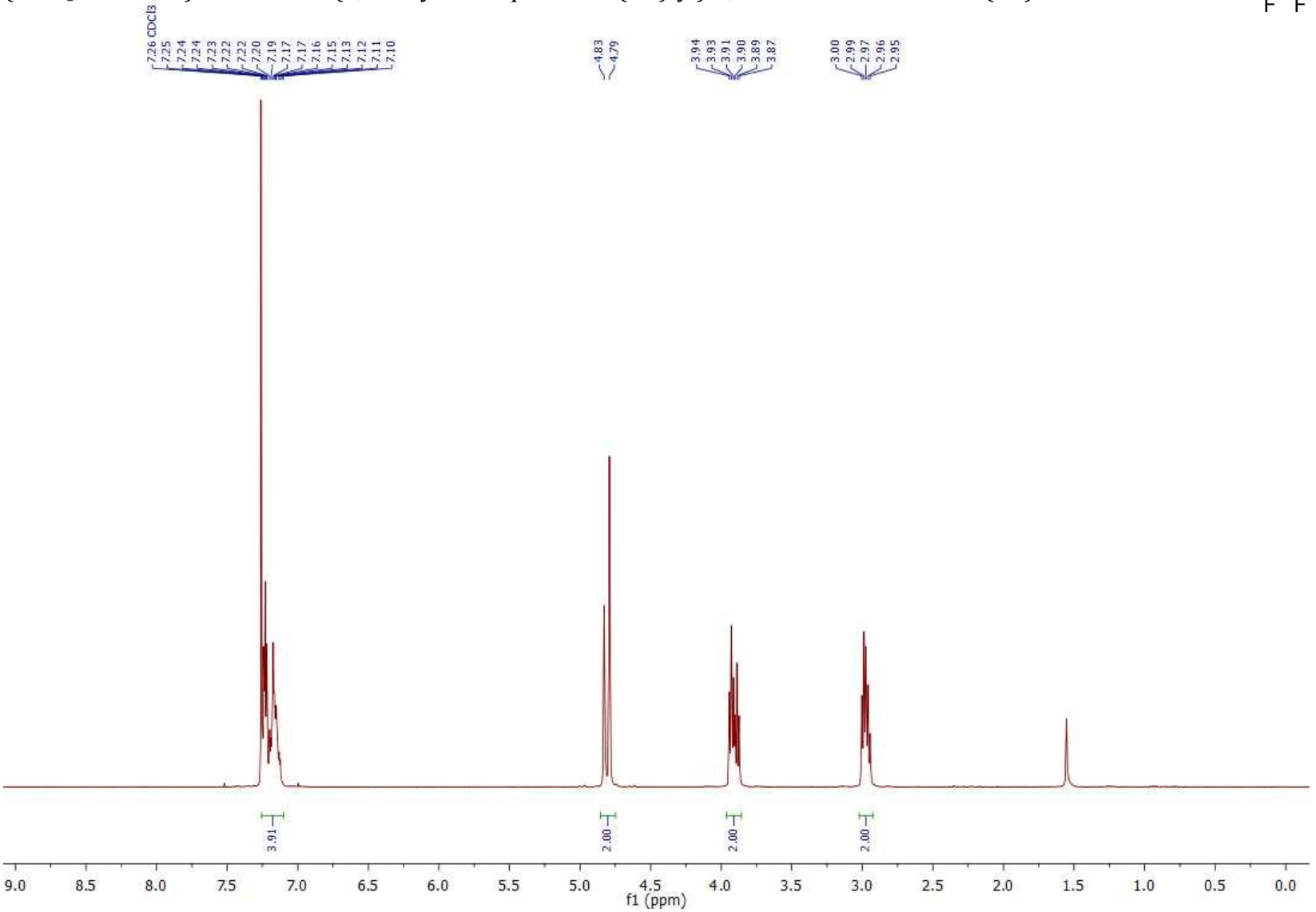
^{19}F NMR ($CDCl_3$, 377 MHz). 2-Bromo-1-(5,6-dihydropyridin-1(2*H*)-yl)-2,2-difluoroethanone (**1c**)



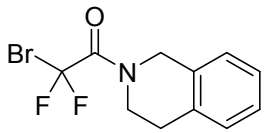


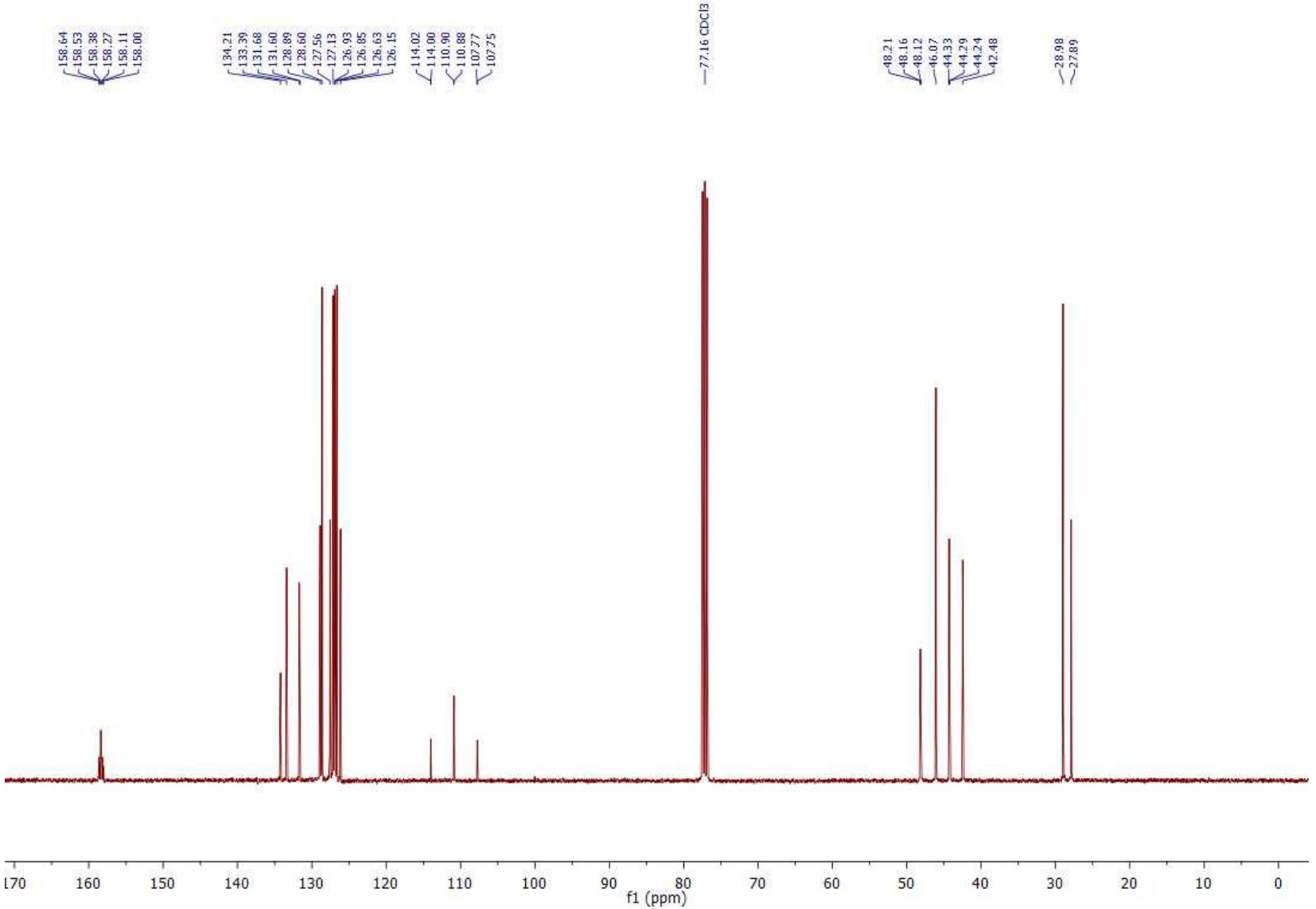
^{1}H NMR ($CDCl_3$, 400 MHz). 2-Bromo-1-(3,4-dihydroisoquinolin-2(1*H*)-yl)-2,2-difluoroethan-1-one (**1d**)



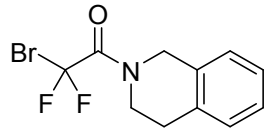


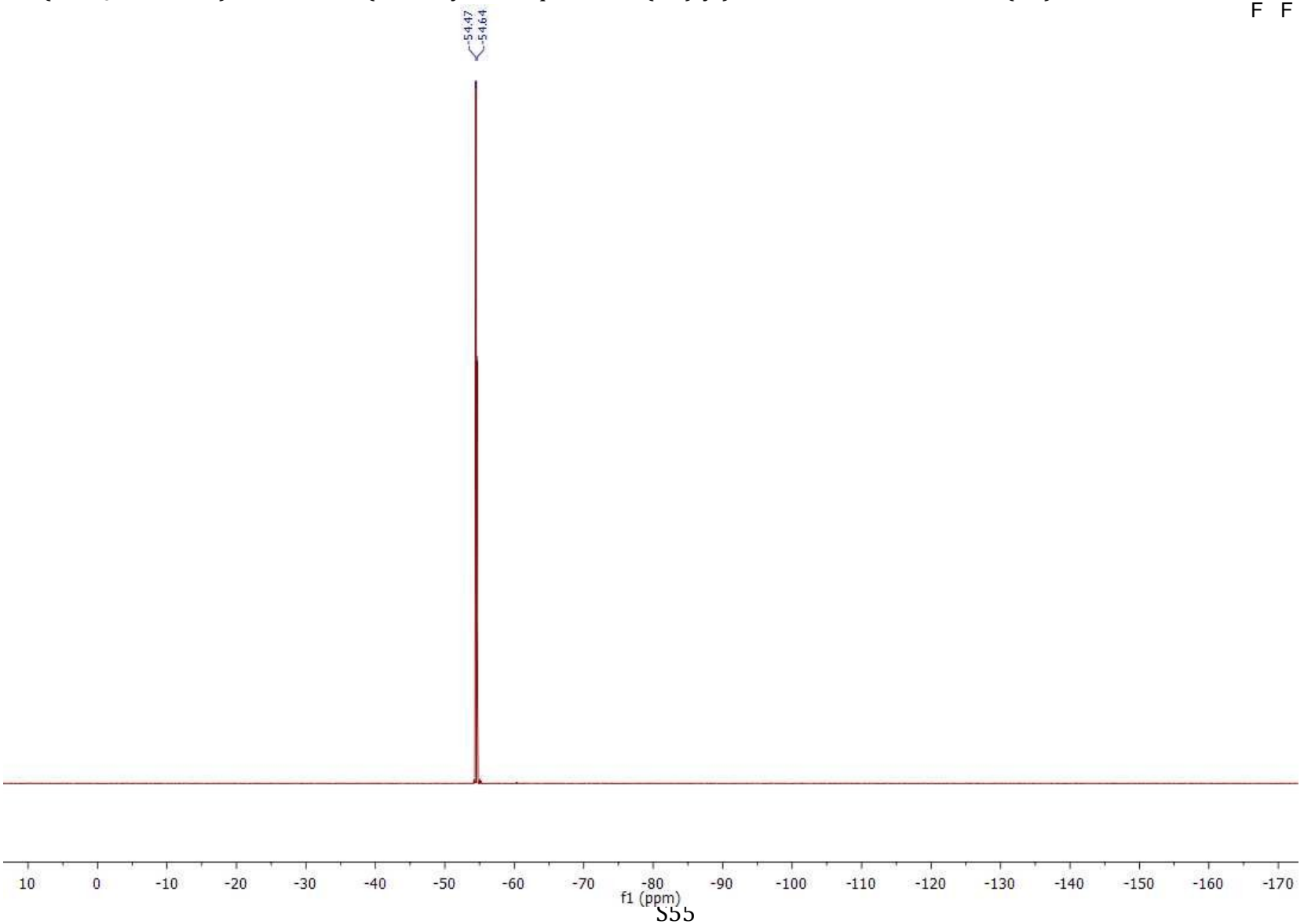
^{13}C NMR ($CDCl_3$, 100 MHz). 2-Bromo-1-(3,4-dihydroisoquinolin-2(1*H*)-yl)-2,2-difluoroethan-1-one (**1d**)



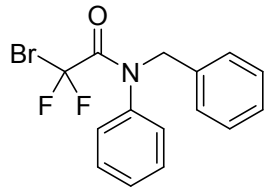


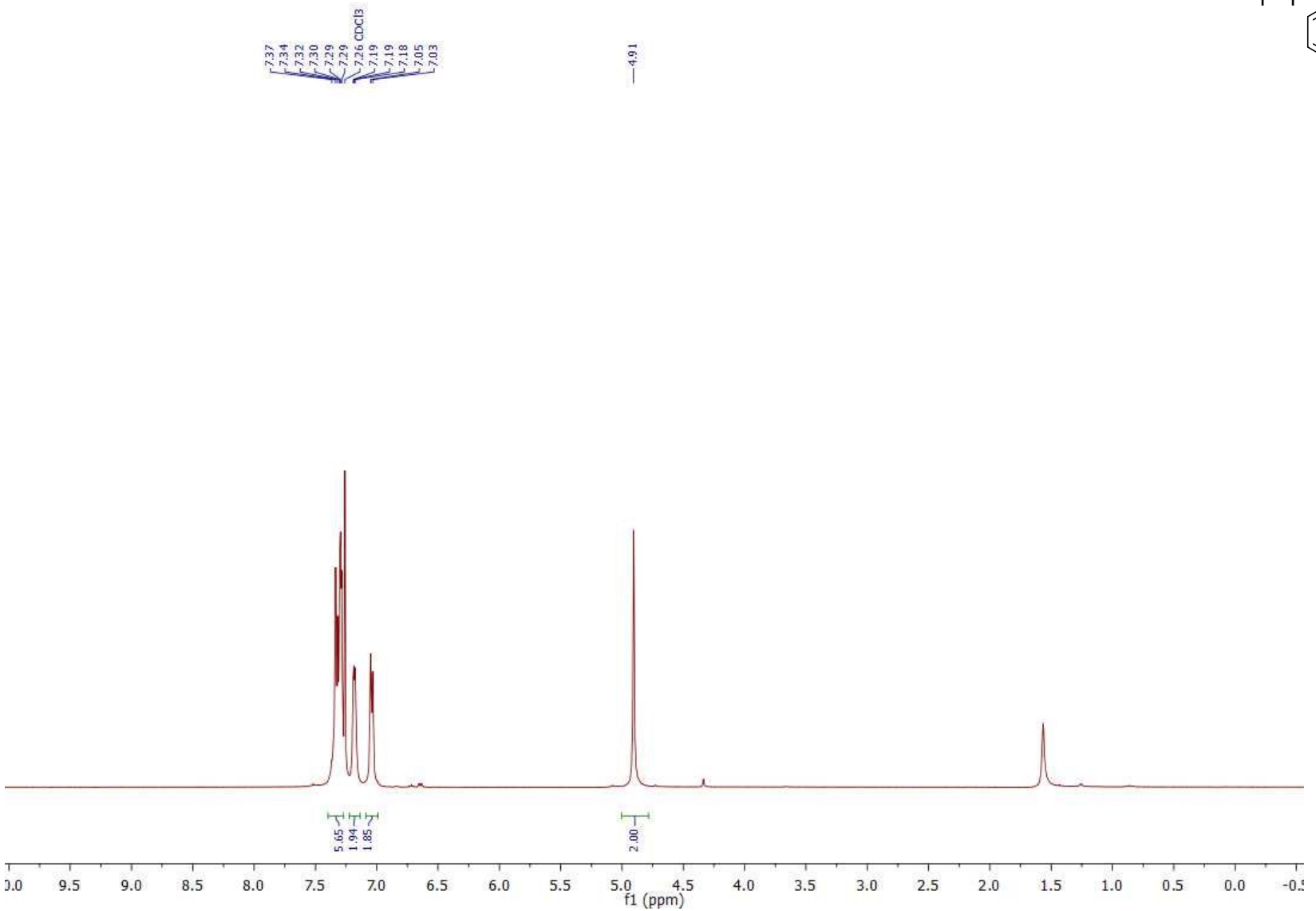
^{19}F NMR ($CDCl_3$, 377 MHz). 2-Bromo-1-(3,4-dihydroisoquinolin-2(1*H*)-yl)-2,2-difluoroethan-1-one (**1d**)



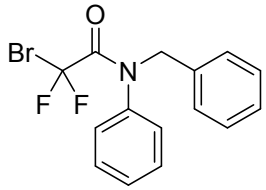


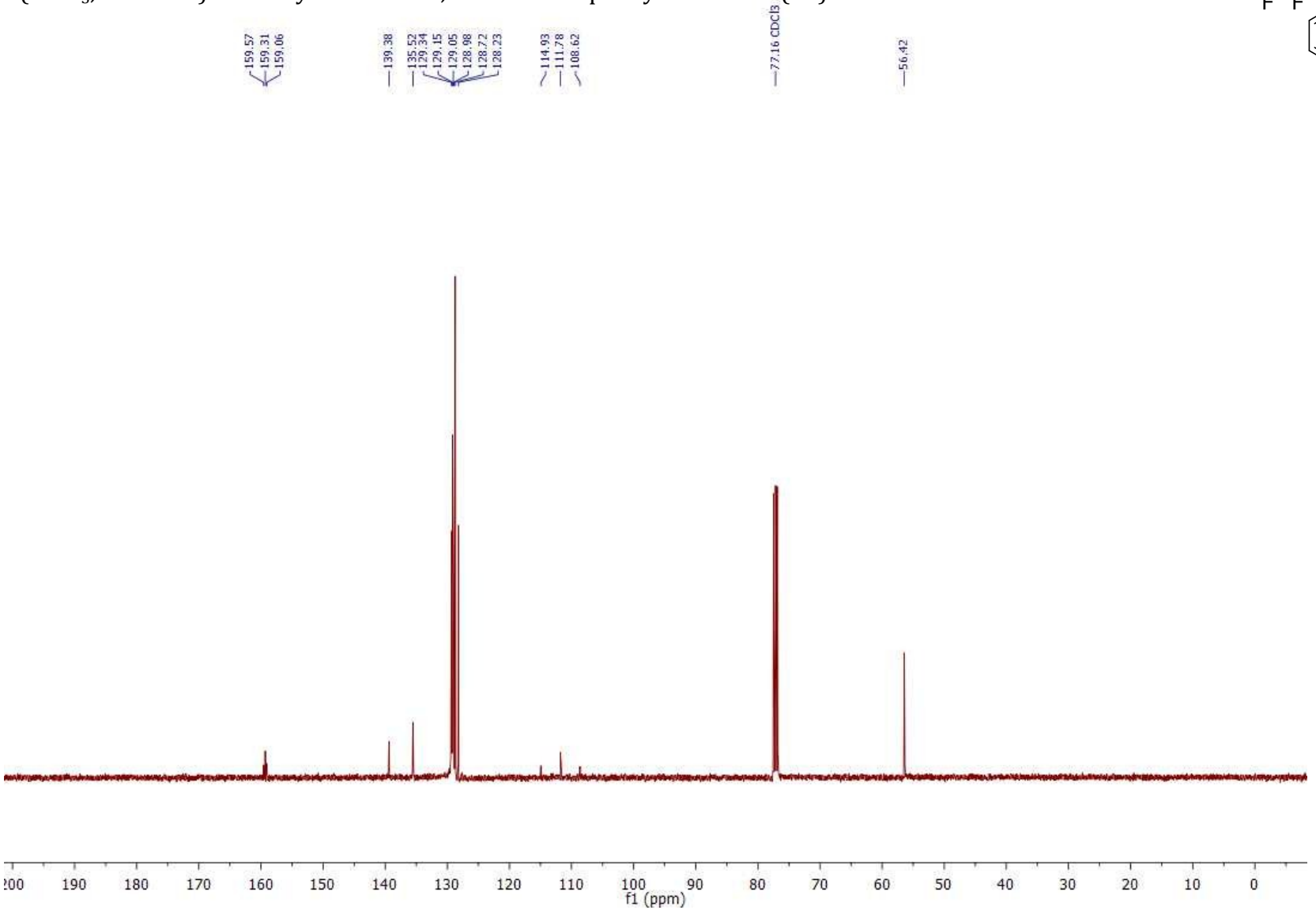
^{1}H NMR ($CDCl_3$, 400 MHz). *N*-benzyl-2-bromo-2,2-difluoro-*N*-phenylacetamide (**1e**)



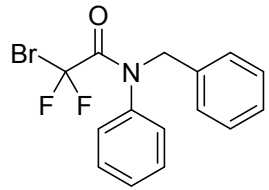


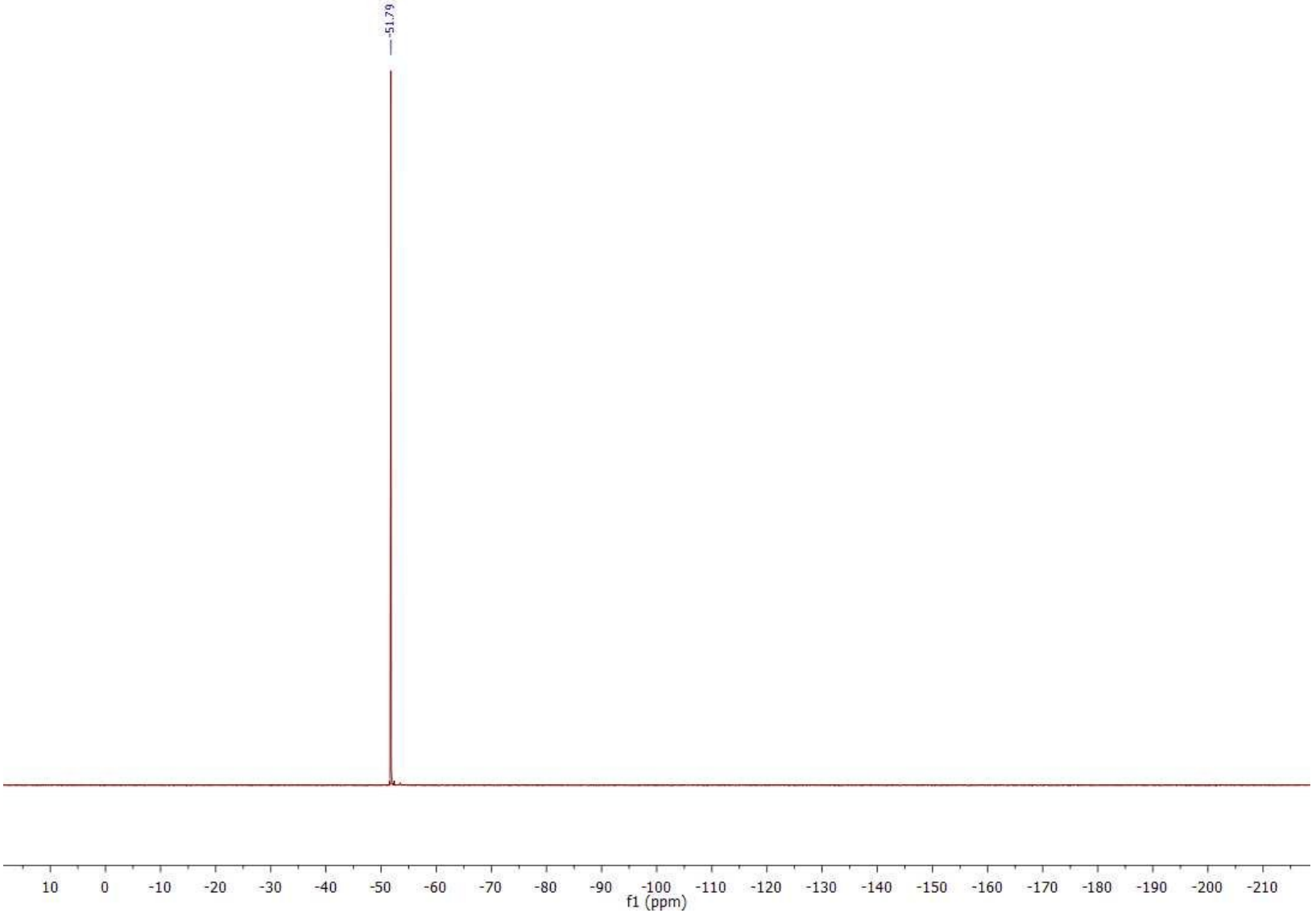
^{13}C NMR ($CDCl_3$, 100 MHz). *N*-benzyl-2-bromo-2,2-difluoro-*N*-phenylacetamide (**1e**)



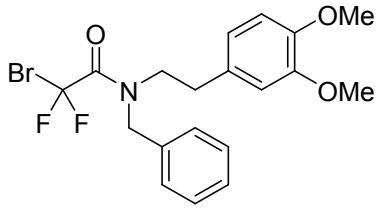


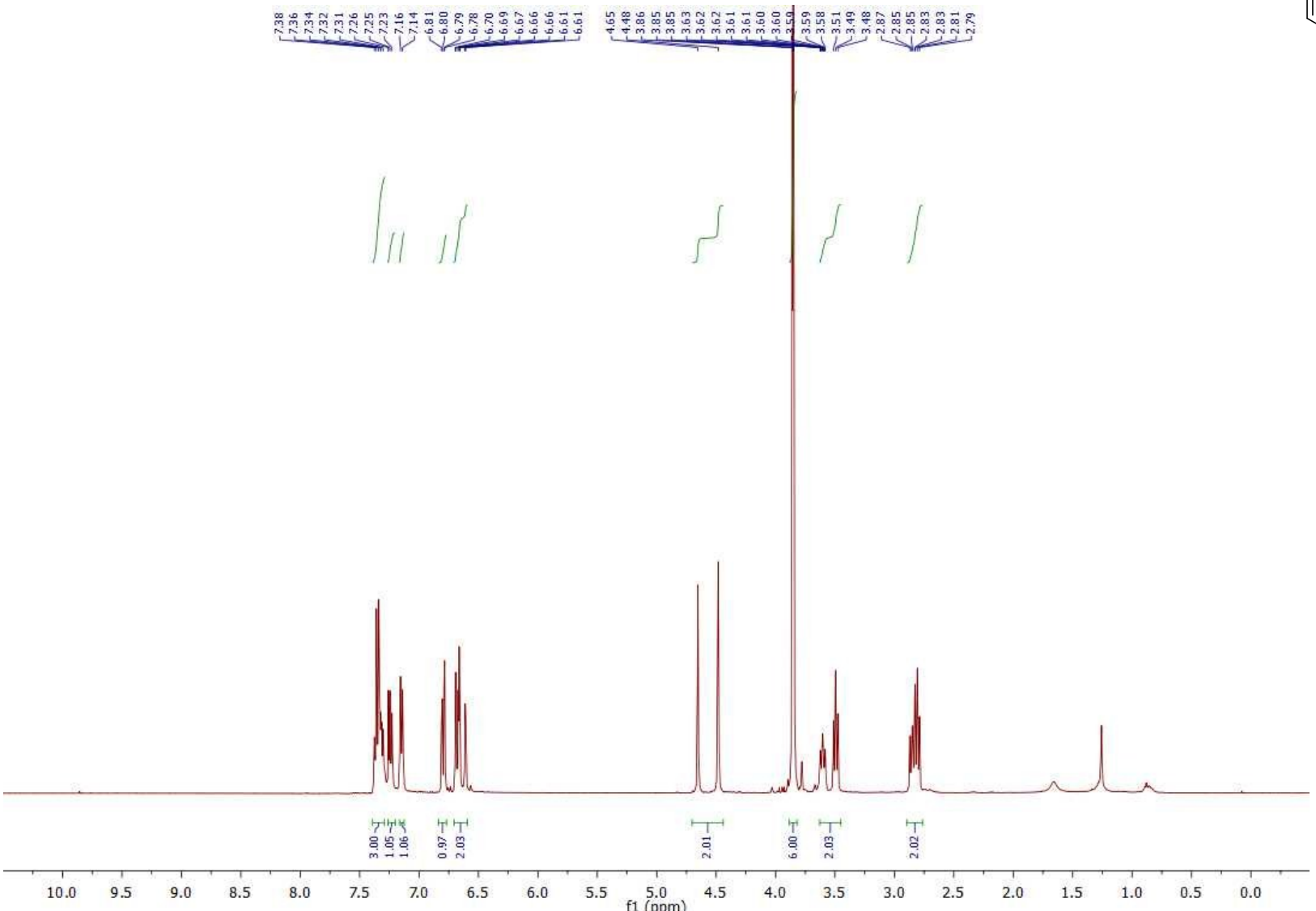
^{19}F NMR ($CDCl_3$, 377 MHz). *N*-benzyl-2-bromo-2,2-difluoro-*N*-phenylacetamide (**1e**)



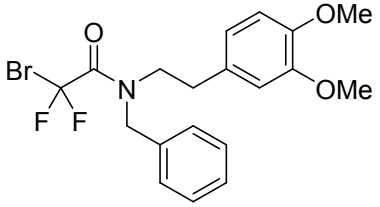


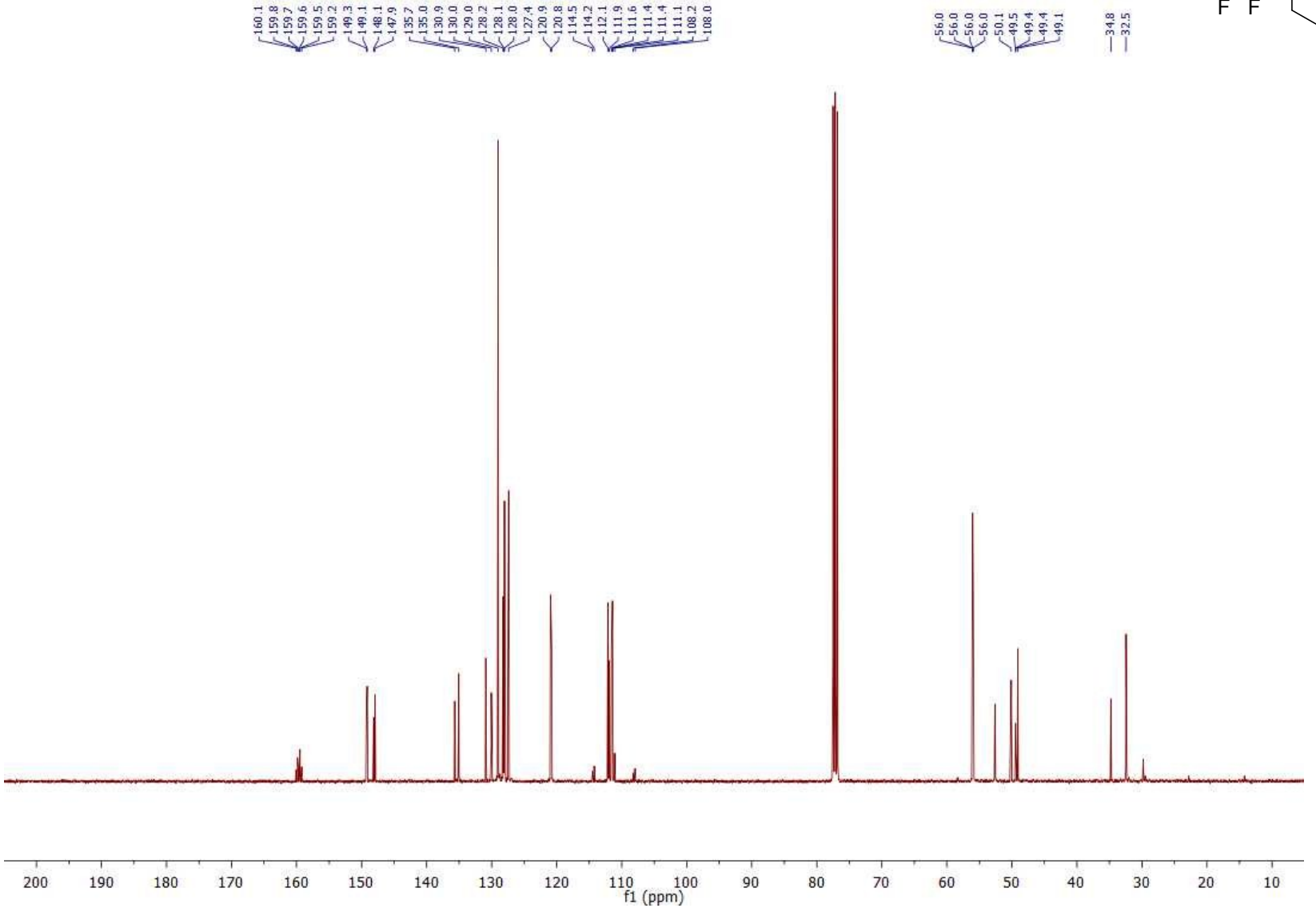
^{1}H NMR ($CDCl_3$, 400 MHz). *N*-Benzyl-2-bromo-*N*-(3,4-dimethoxyphenethyl)-2,2-difluoroacetamide (**1f**)



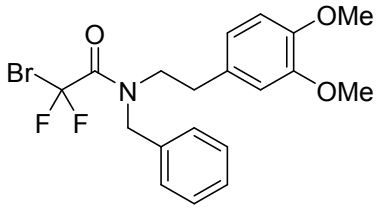


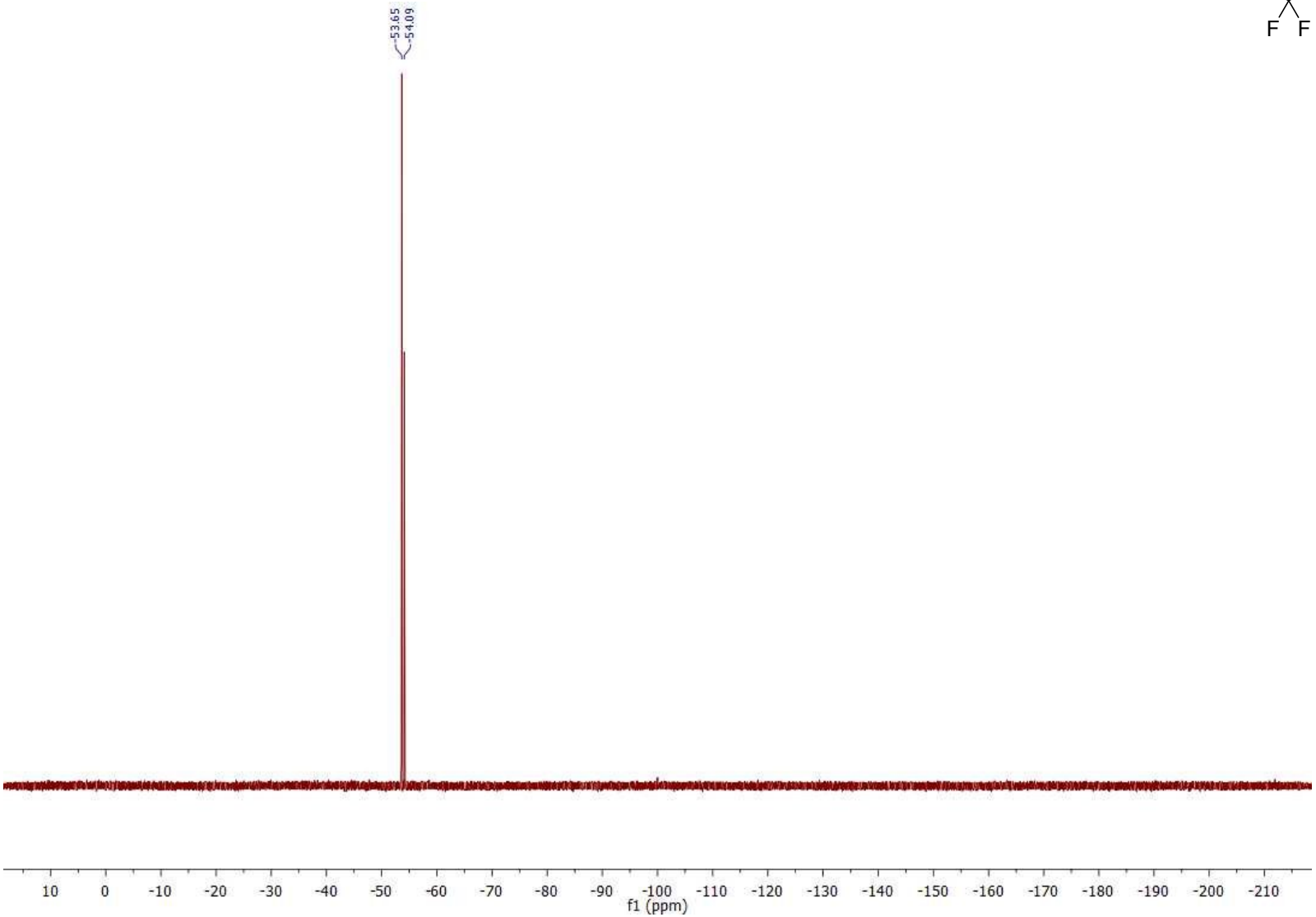
^{13}C NMR ($CDCl_3$, 100 MHz). *N*-Benzyl-2-bromo-*N*-(3,4-dimethoxyphenethyl)-2,2-difluoroacetamide (**1f**)



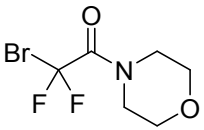


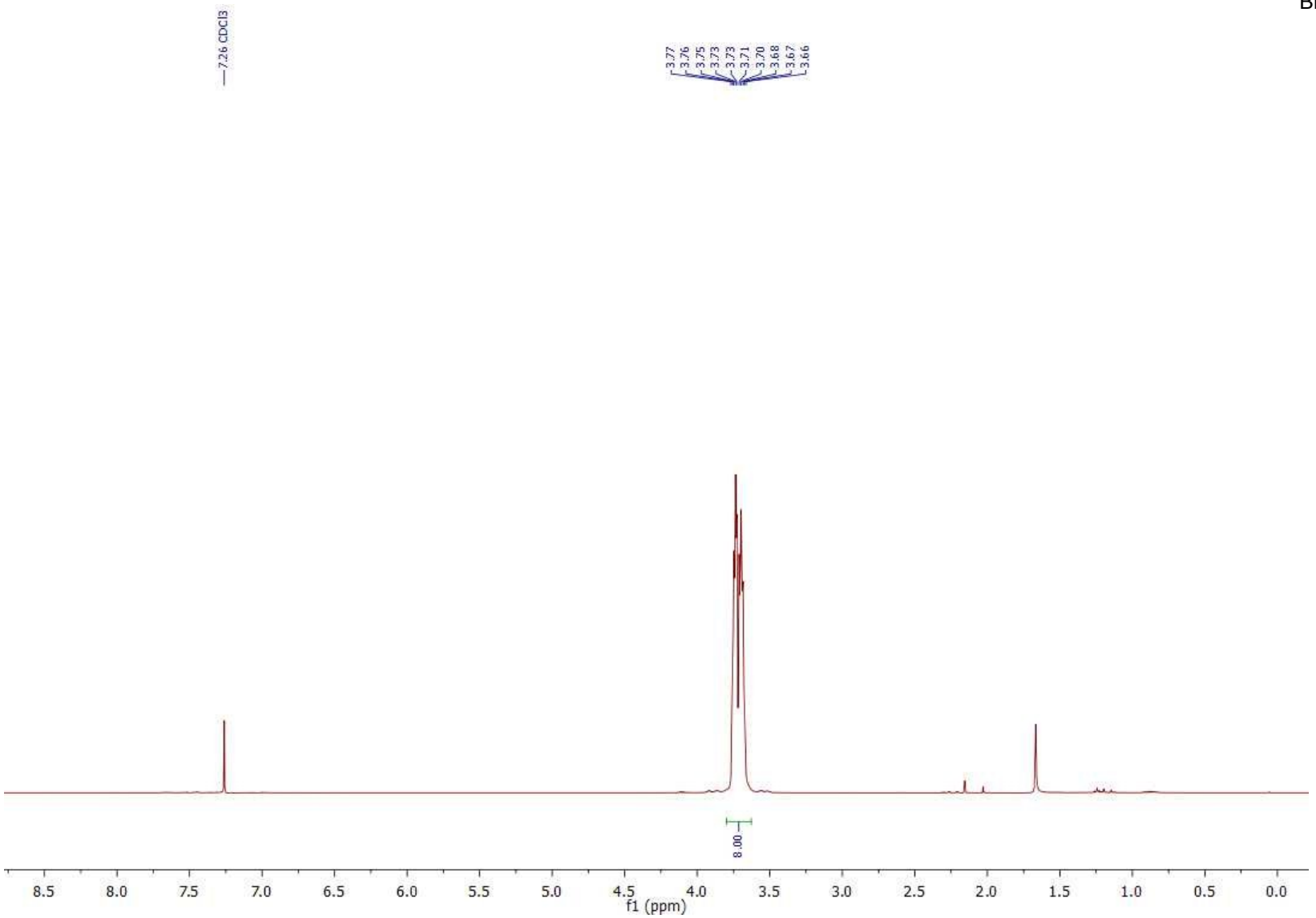
^{19}F NMR ($CDCl_3$, 377 MHz). *N*-Benzyl-2-bromo-*N*-(3,4-dimethoxyphenethyl)-2,2-difluoroacetamide (**1f**)



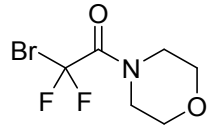


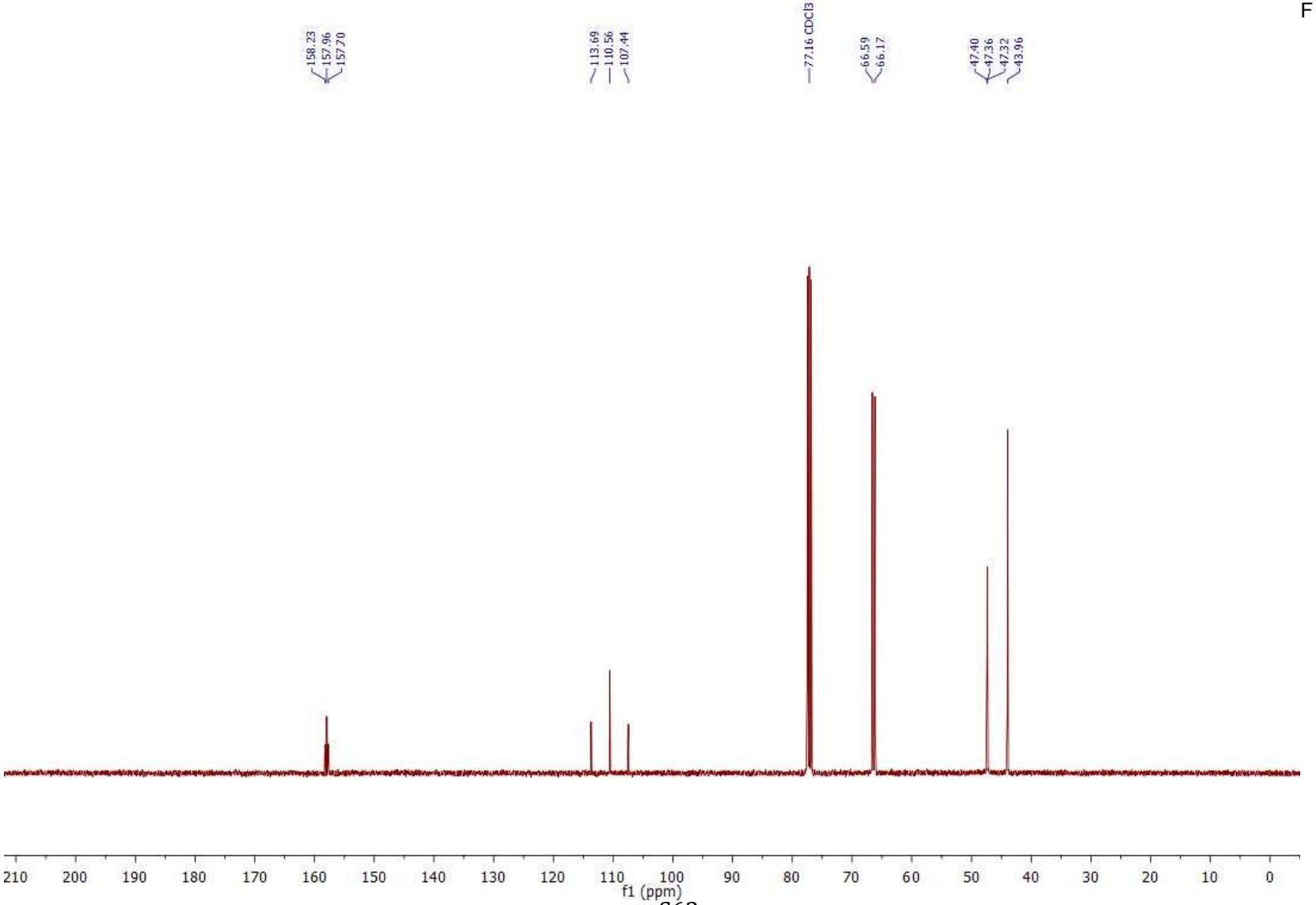
^{1}H NMR ($CDCl_3$, 400 MHz). 2-Bromo-2,2-difluoro-1-morpholinoethan-1-one (**1g**)



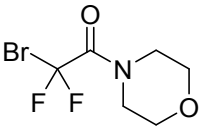


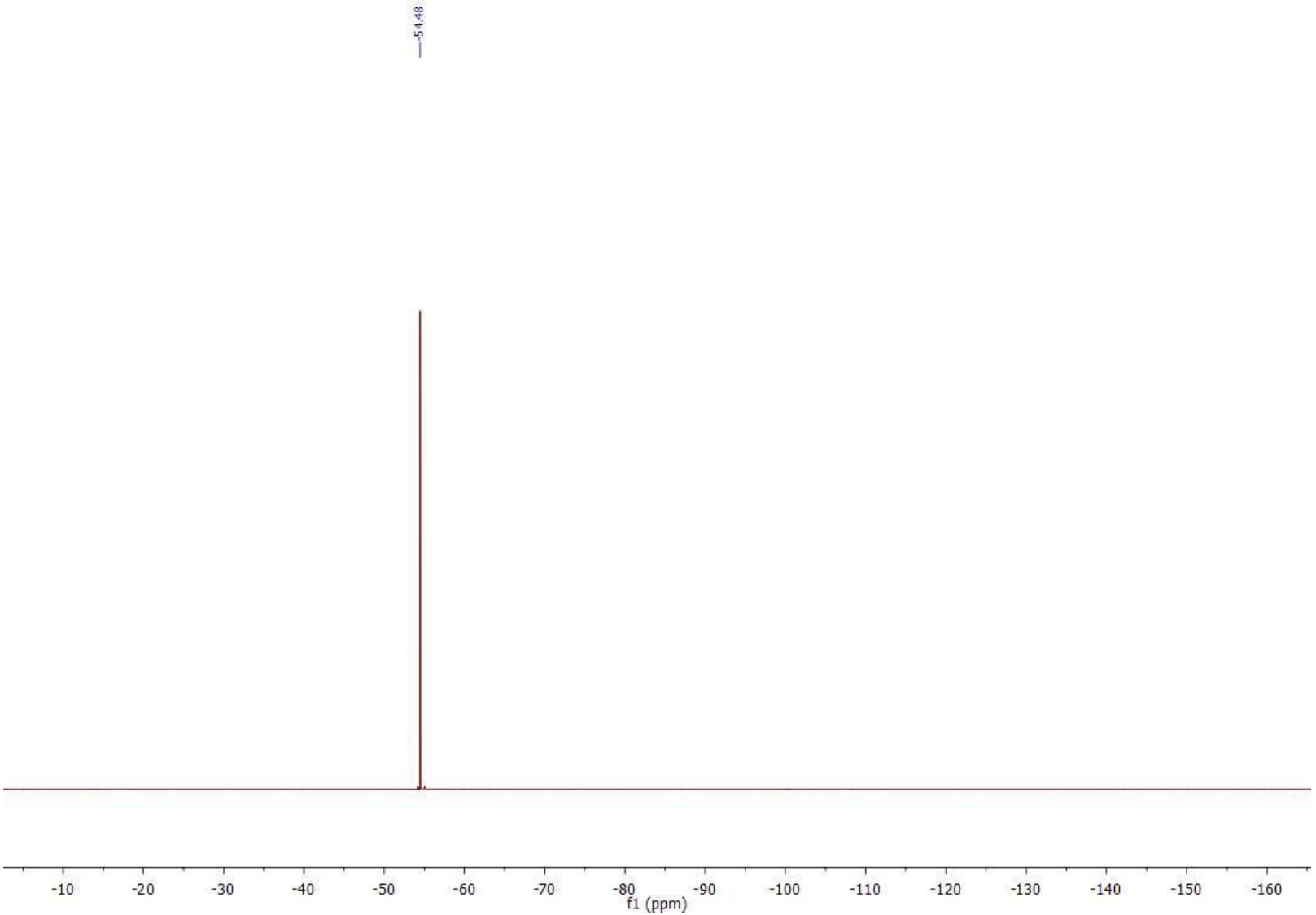
^{13}C NMR ($CDCl_3$, 100 MHz). 2-Bromo-2,2-difluoro-1-morpholinoethan-1-one (**1g**)



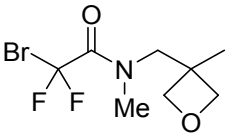


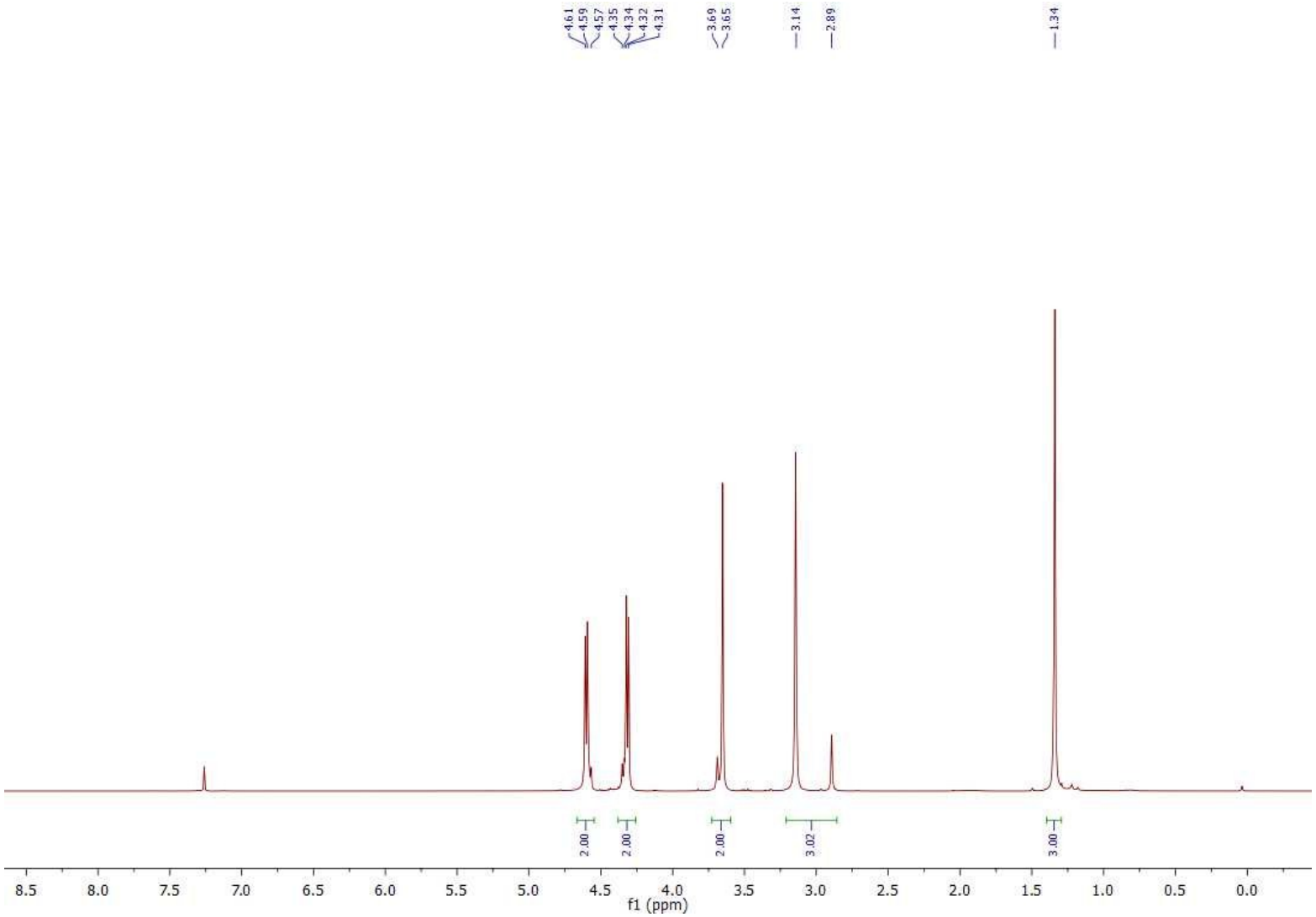
^{19}F NMR ($CDCl_3$, 377 MHz). 2-Bromo-2,2-difluoro-1-morpholinoethan-1-one (**1g**)



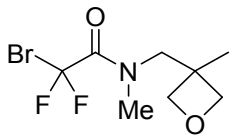


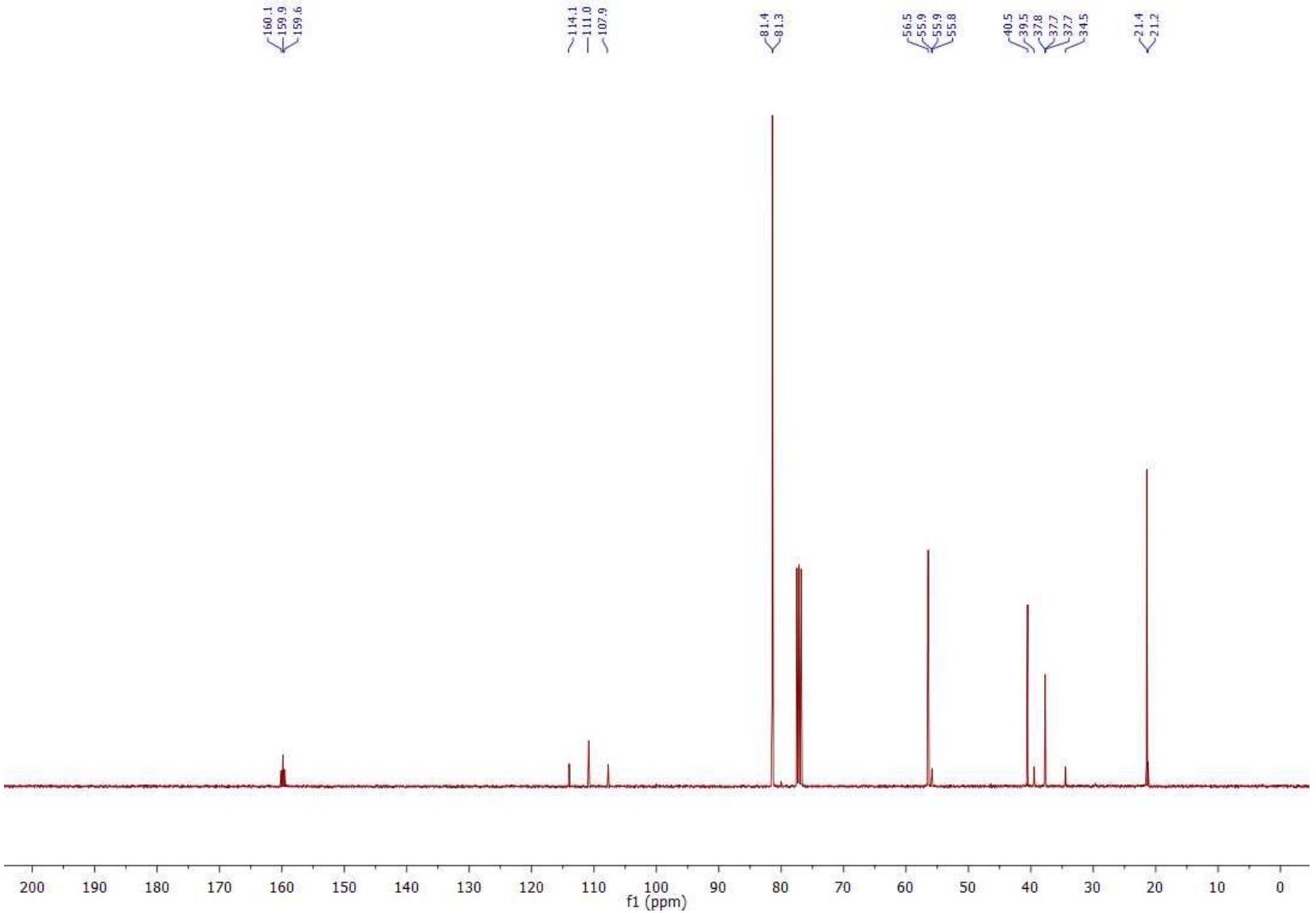
^{1}H NMR ($CDCl_3$, 400 MHz). 2-Bromo-2,2-difluoro-*N*-methyl-*N*-((3-methyloxetan-3-yl)methyl)acetamide (**1h**)



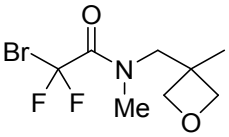


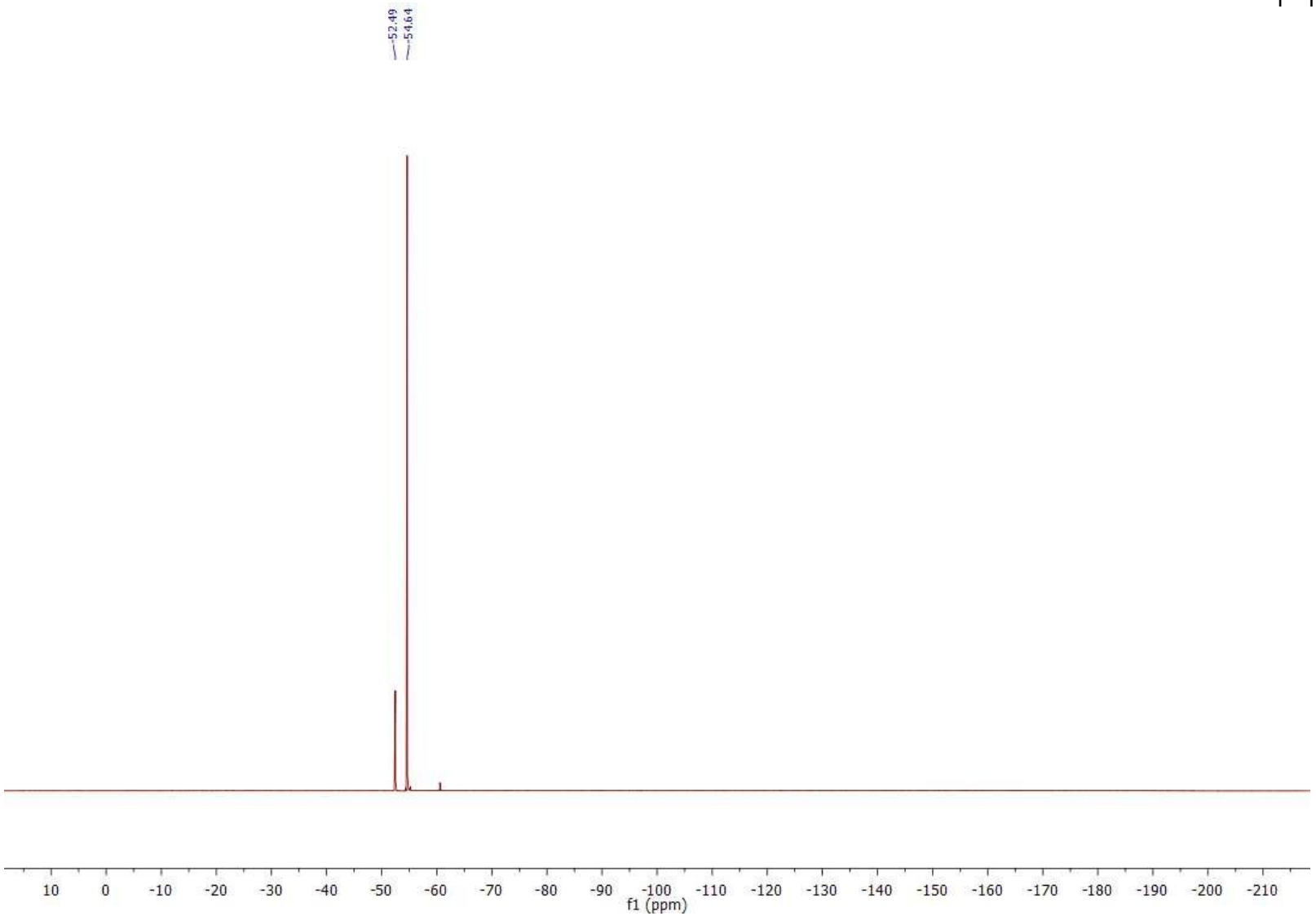
^{13}C NMR ($CDCl_3$, 100 MHz). 2-Bromo-2,2-difluoro-*N*-methyl-*N*-((3-methyloxetan-3-yl)methyl)acetamide (**1h**)



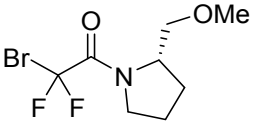


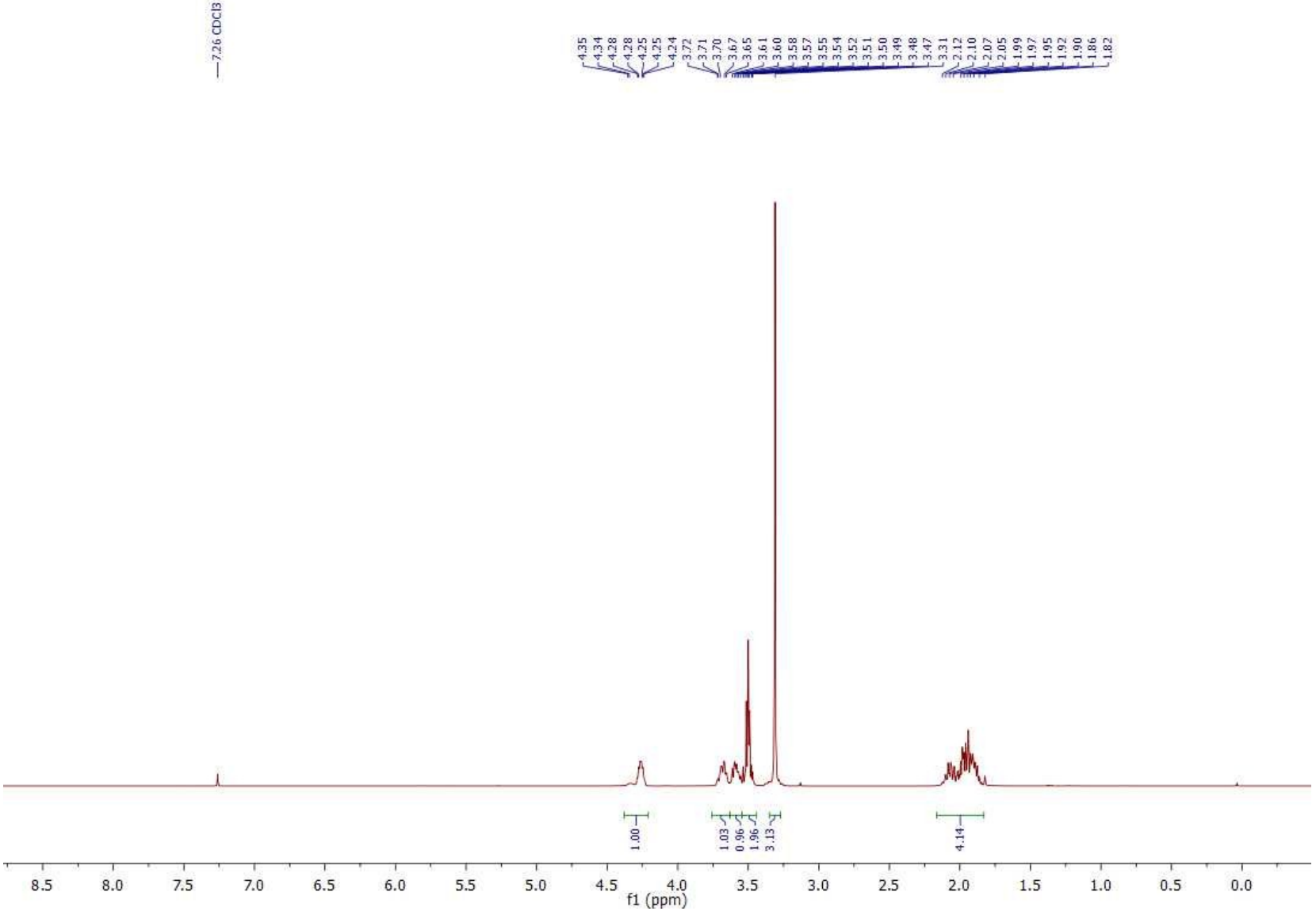
^{19}F NMR ($CDCl_3$, 377 MHz). 2-Bromo-2,2-difluoro-*N*-methyl-*N*-((3-methyloxetan-3-yl)methyl)acetamide (**1h**)



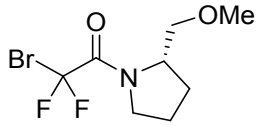


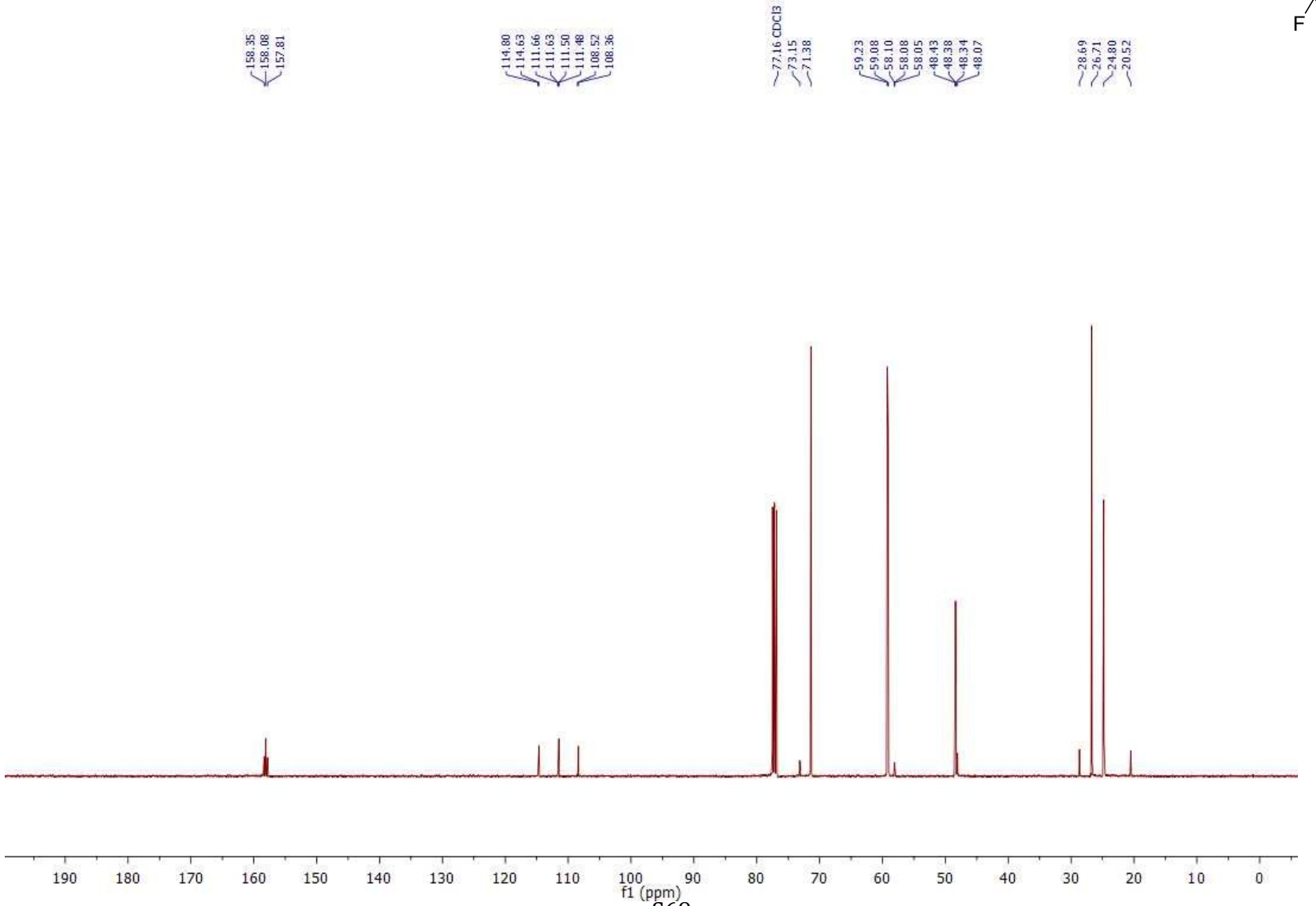
^{1}H NMR ($CDCl_3$, 400 MHz). (*S*)-2-Bromo-2,2-difluoro-1-(2-(methoxymethyl)pyrrolidin-1-yl)ethanone (**1i**)



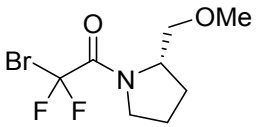


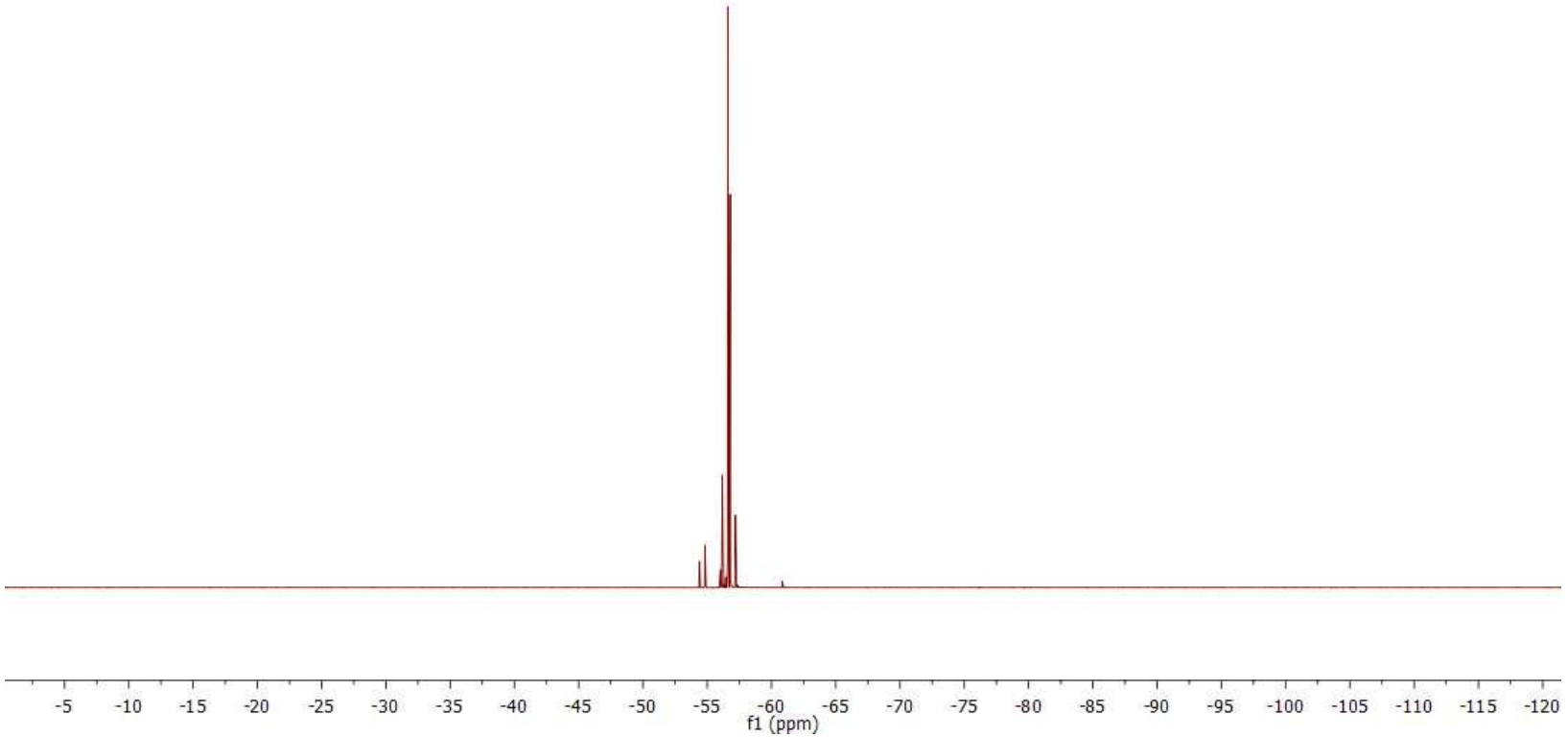
^{13}C NMR ($CDCl_3$, 100 MHz). (*S*)-2-Bromo-2,2-difluoro-1-(2-(methoxymethyl)pyrrolidin-1-yl)ethanone (**1i**)



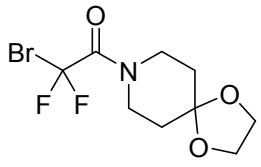


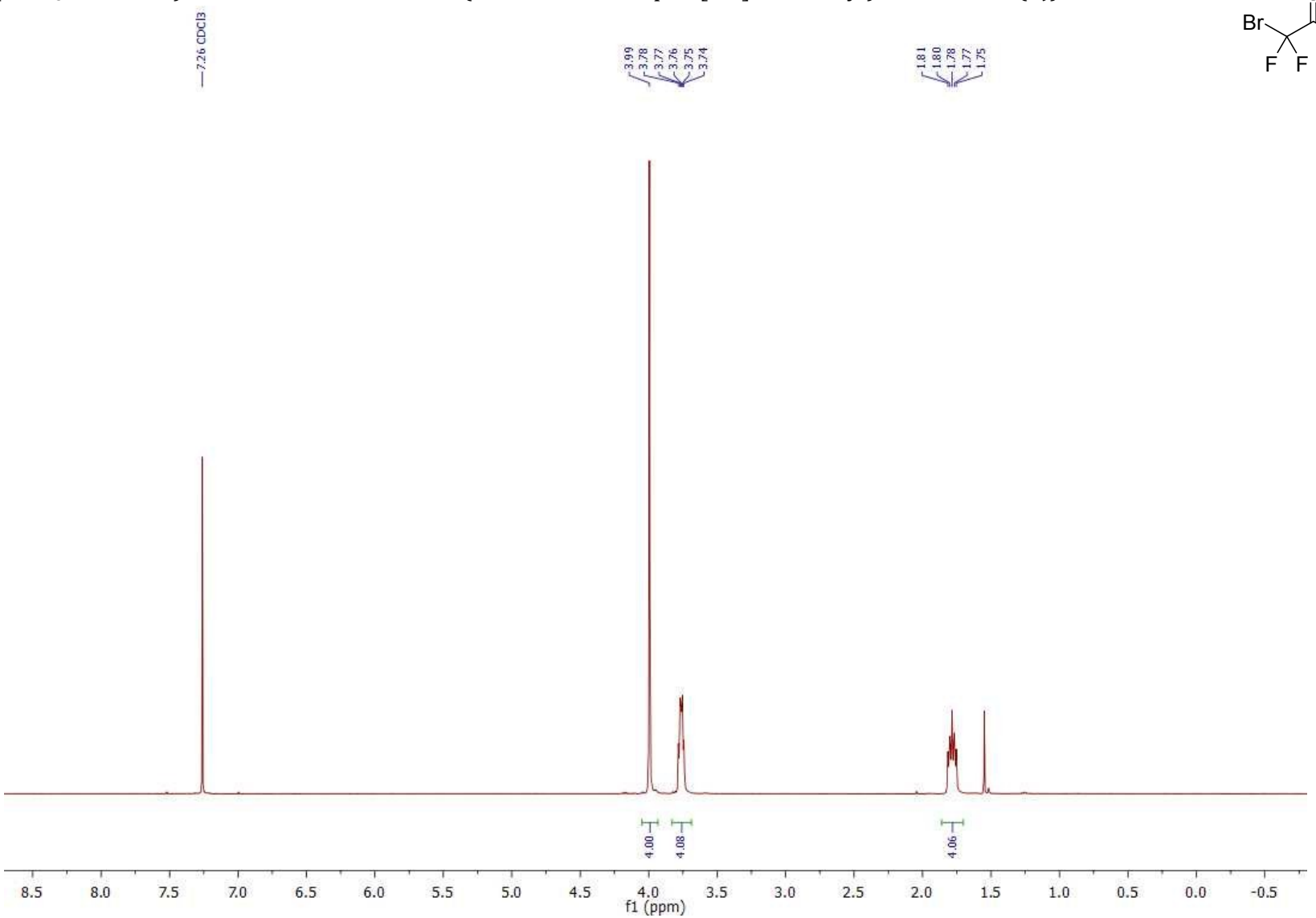
^{19}F NMR ($CDCl_3$, 377 MHz). (*S*)-2-Bromo-2,2-difluoro-1-(2-(methoxymethyl)pyrrolidin-1-yl)ethanone (**1i**)



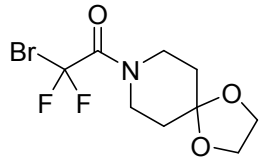


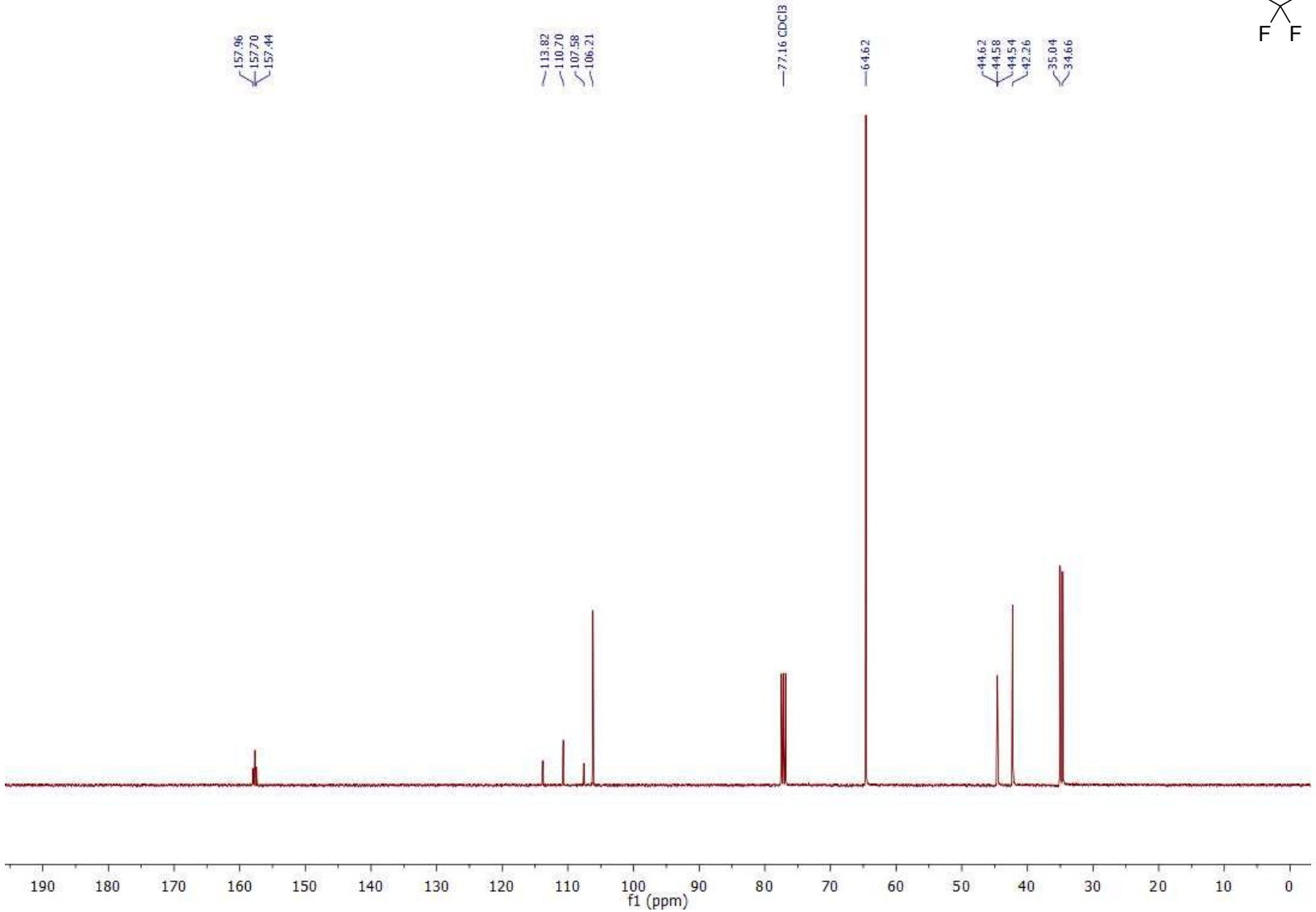
^{1}H NMR ($CDCl_3$, 400 MHz). 2-Bromo-2,2-difluoro-1-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)ethan-1-one (**1j**)



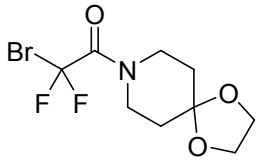


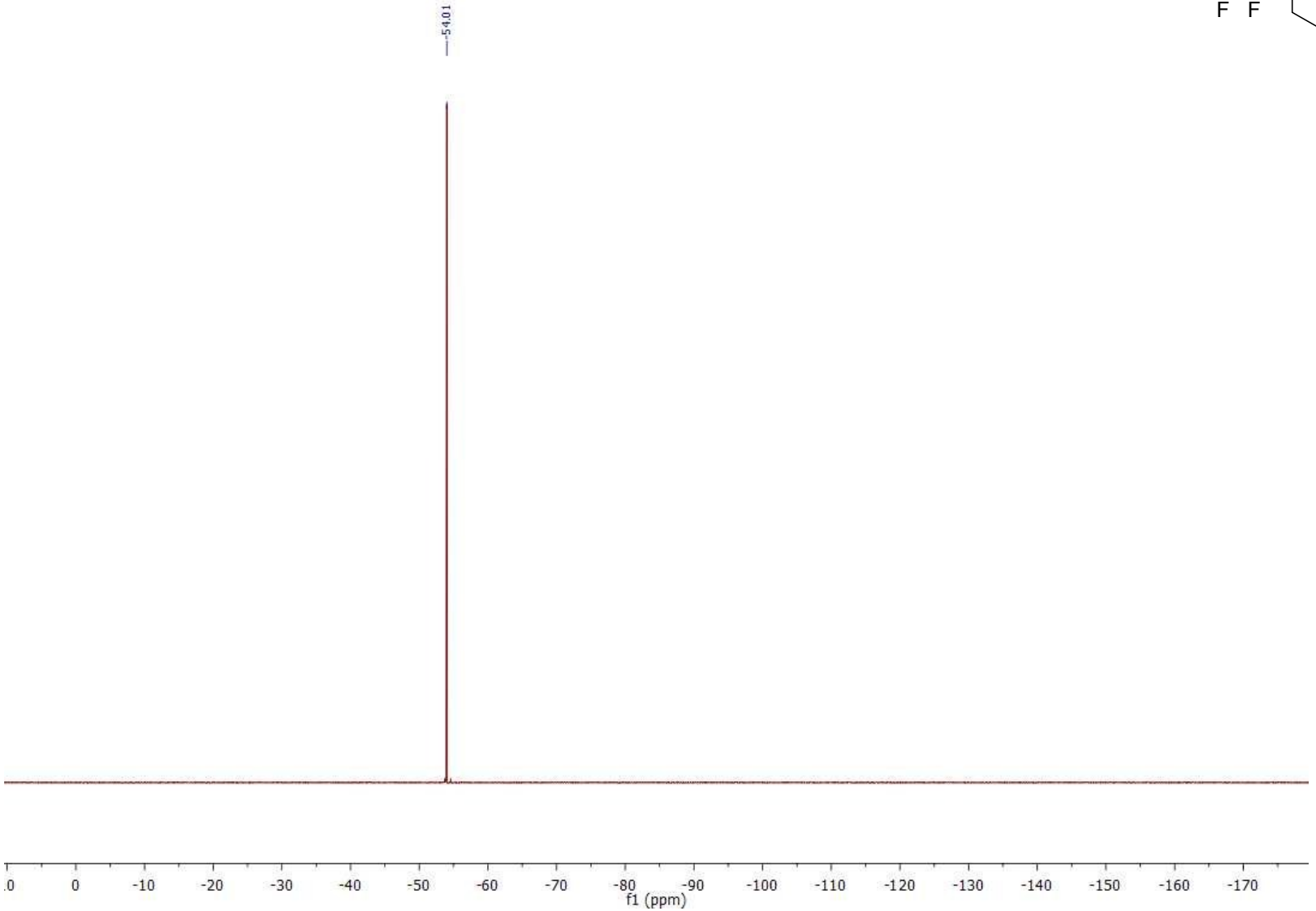
^{13}C NMR ($CDCl_3$, 100 MHz). 2-Bromo-2,2-difluoro-1-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)ethan-1-one (**1j**)



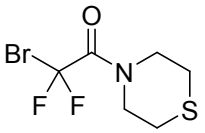


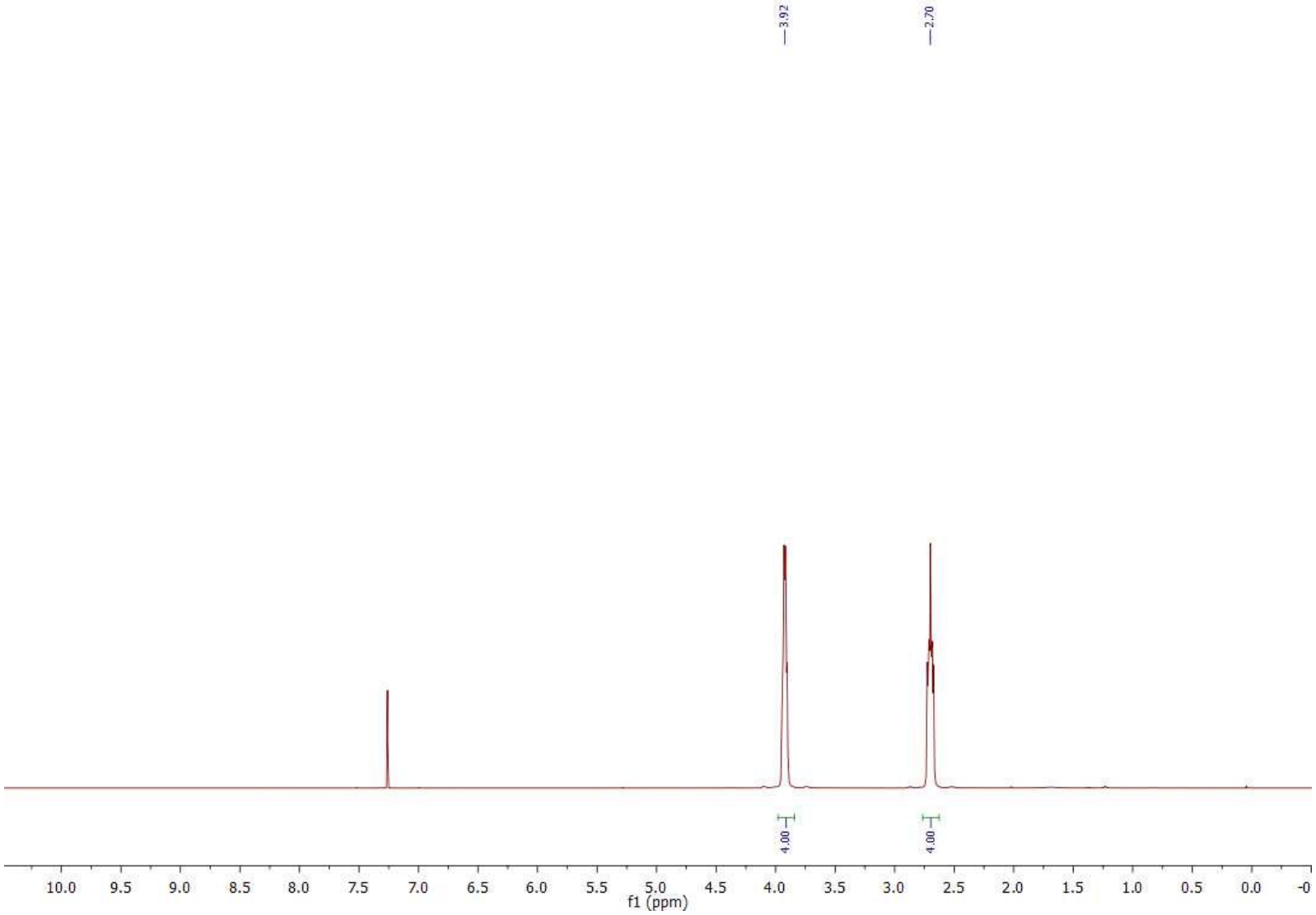
^{19}F NMR ($CDCl_3$, 377 MHz). 2-Bromo-2,2-difluoro-1-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)ethan-1-one (**1j**)



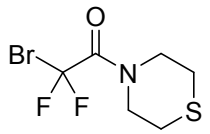


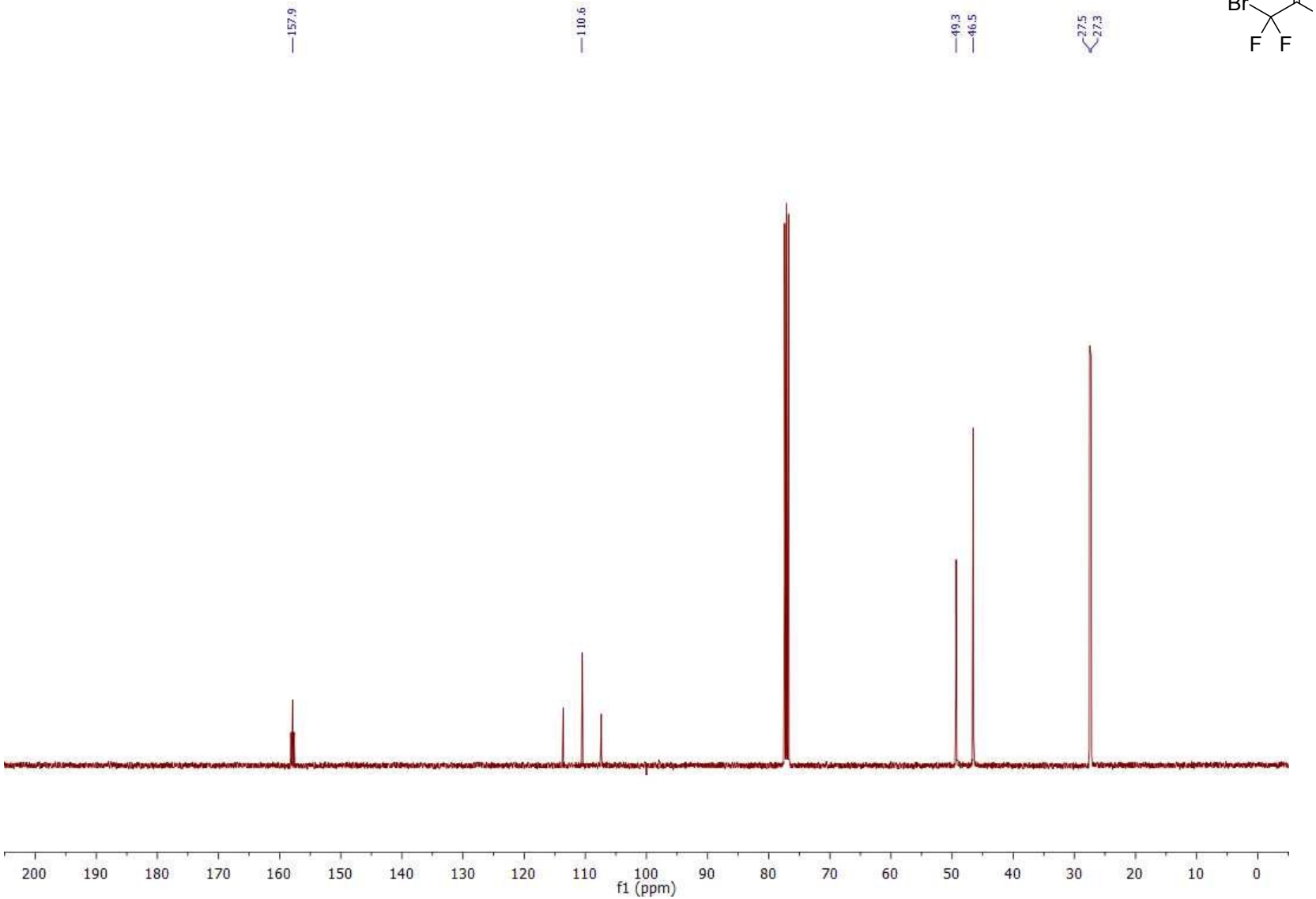
^{1}H NMR ($CDCl_3$, 400 MHz). 2-Bromo-2,2-difluoro-1-thiomorpholinoethan-1-one (**1k**)



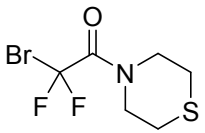


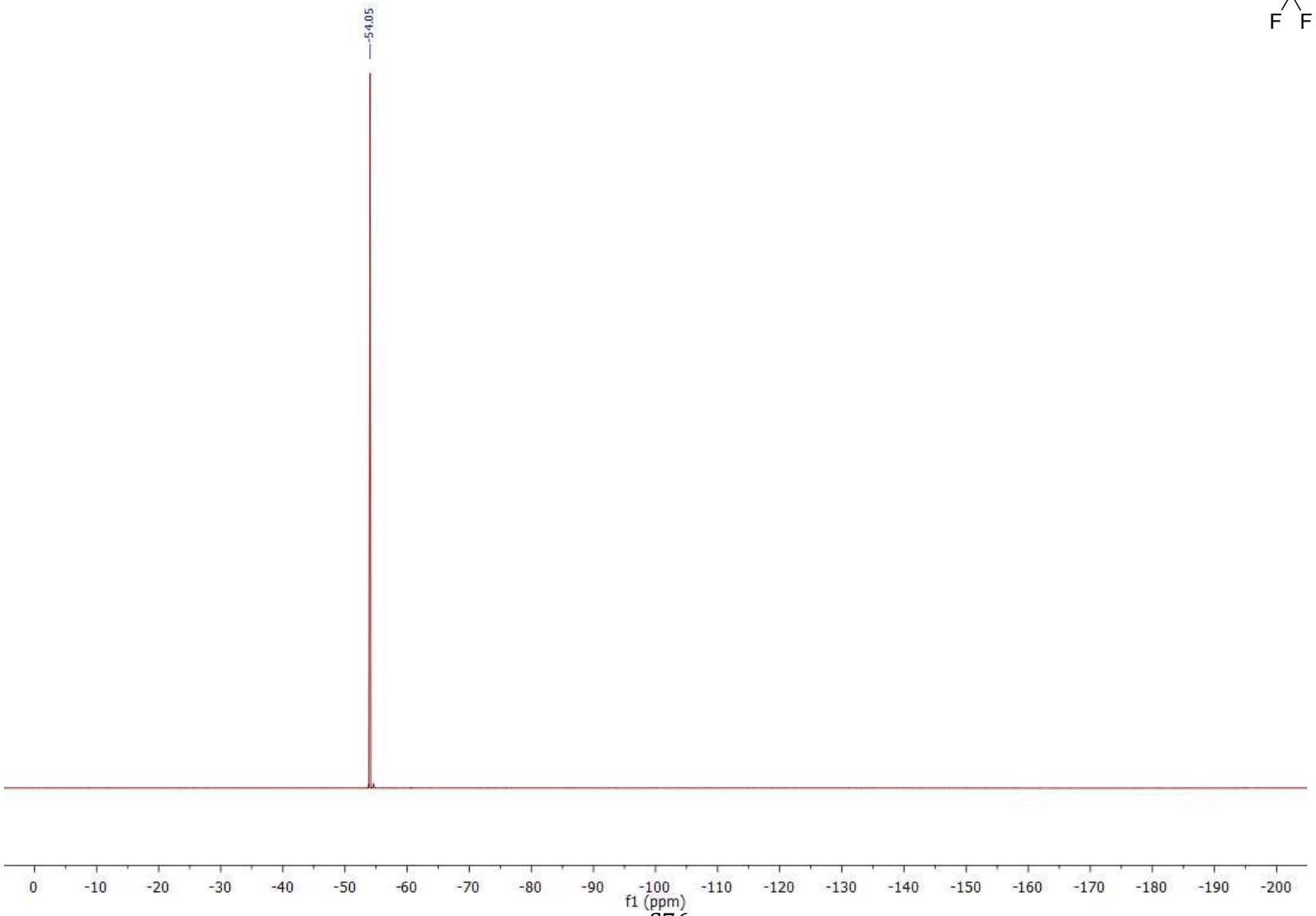
^{13}C NMR ($CDCl_3$, 100 MHz). 2-Bromo-2,2-difluoro-1-thiomorpholinoethan-1-one (**1k**)



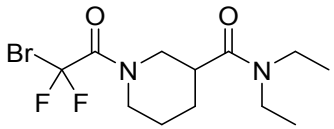


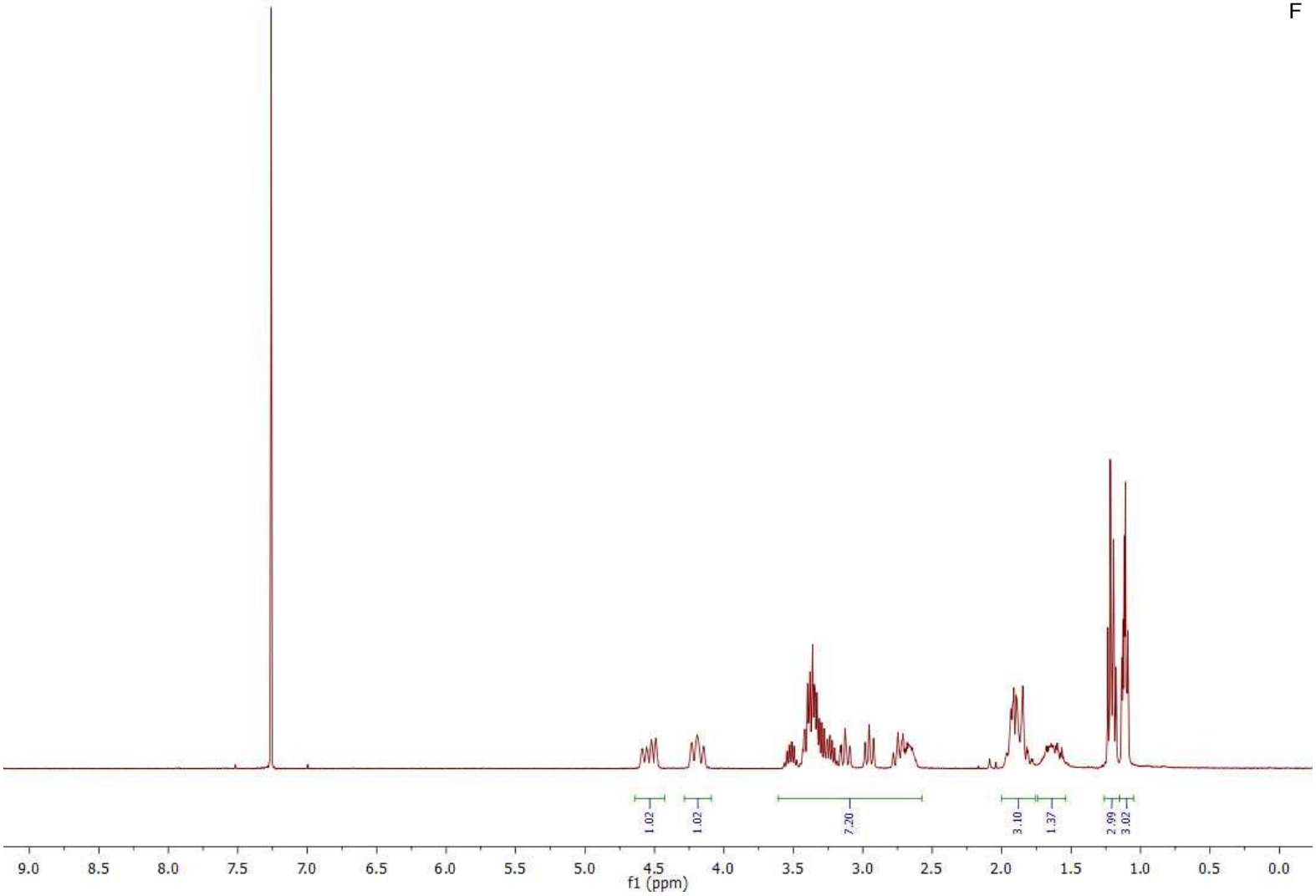
^{19}F NMR ($CDCl_3$, 377 MHz). 2-Bromo-2,2-difluoro-1-thiomorpholinoethan-1-one (**1k**)



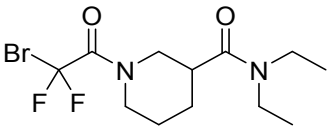


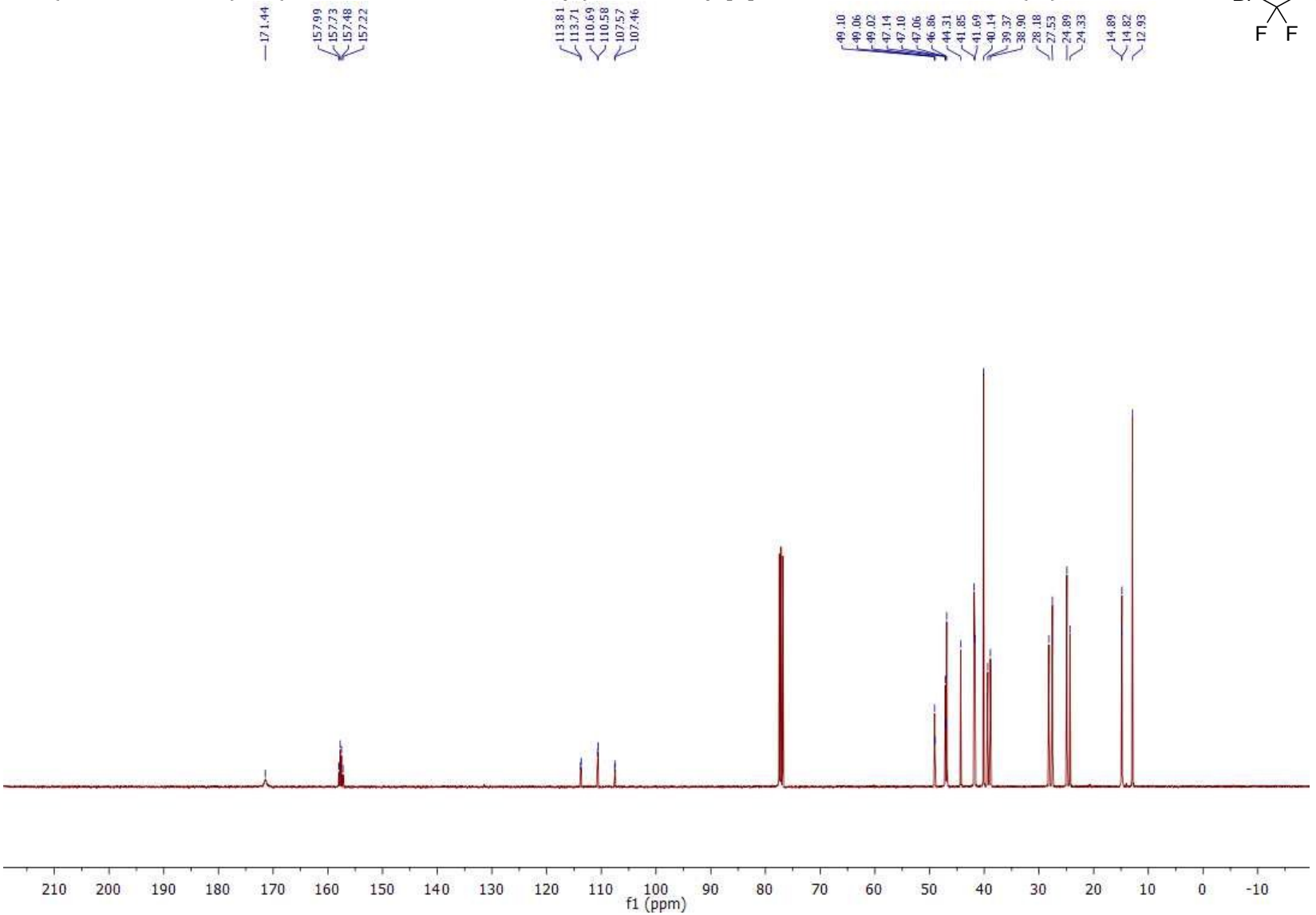
^{1}H NMR ($CDCl_3$, 400 MHz). 1-(2-Bromo-2,2-difluoroacetyl)-*N*,*N*-diethylpiperidine-3-carboxamide (**1l**)



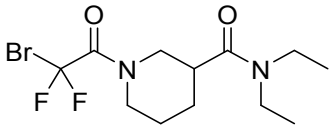


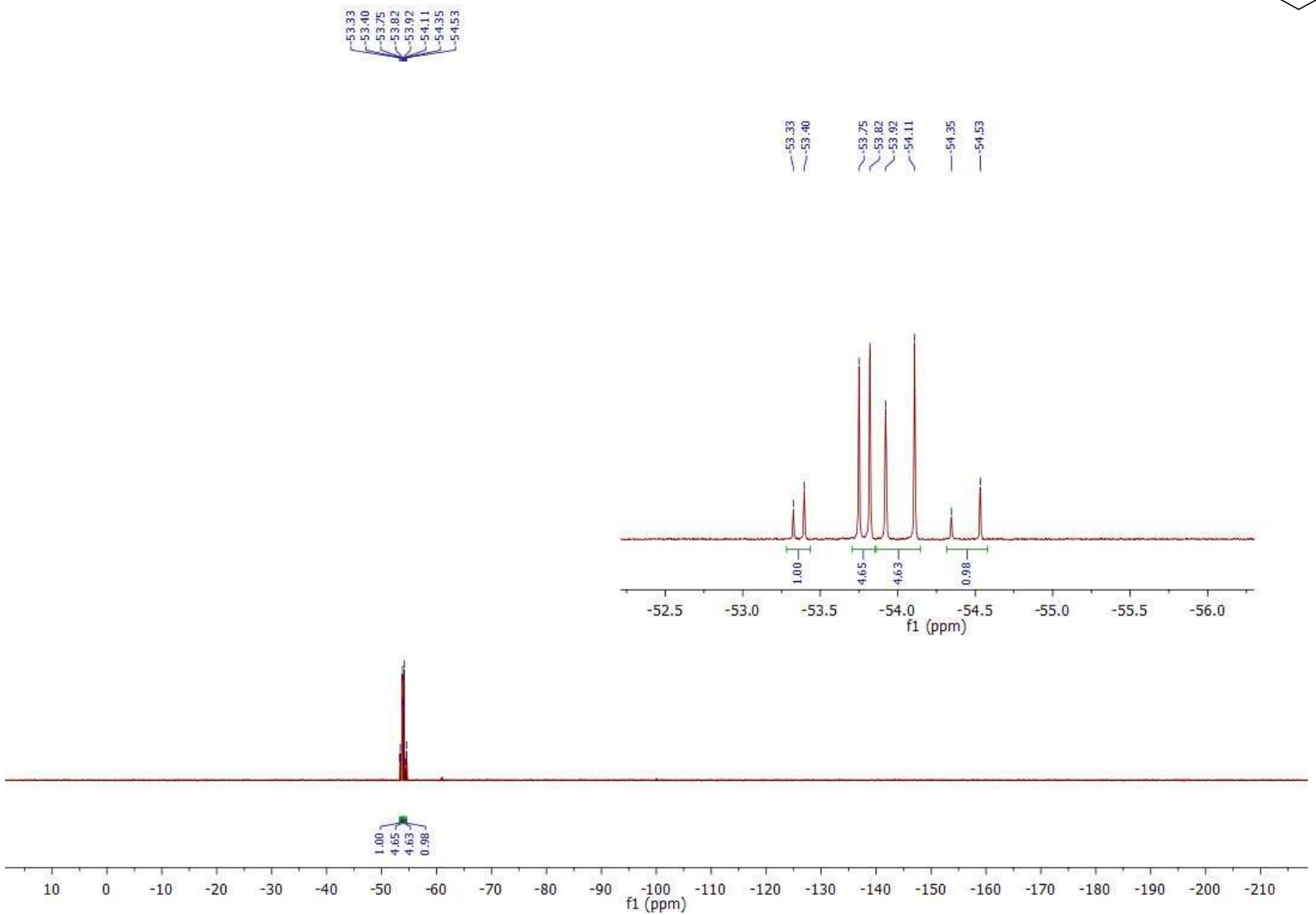
^{13}C NMR ($CDCl_3$, 100 MHz). 1-(2-Bromo-2,2-difluoroacetyl)-*N*,*N*-diethylpiperidine-3-carboxamide (**1l**)



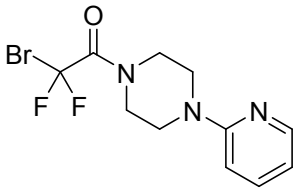


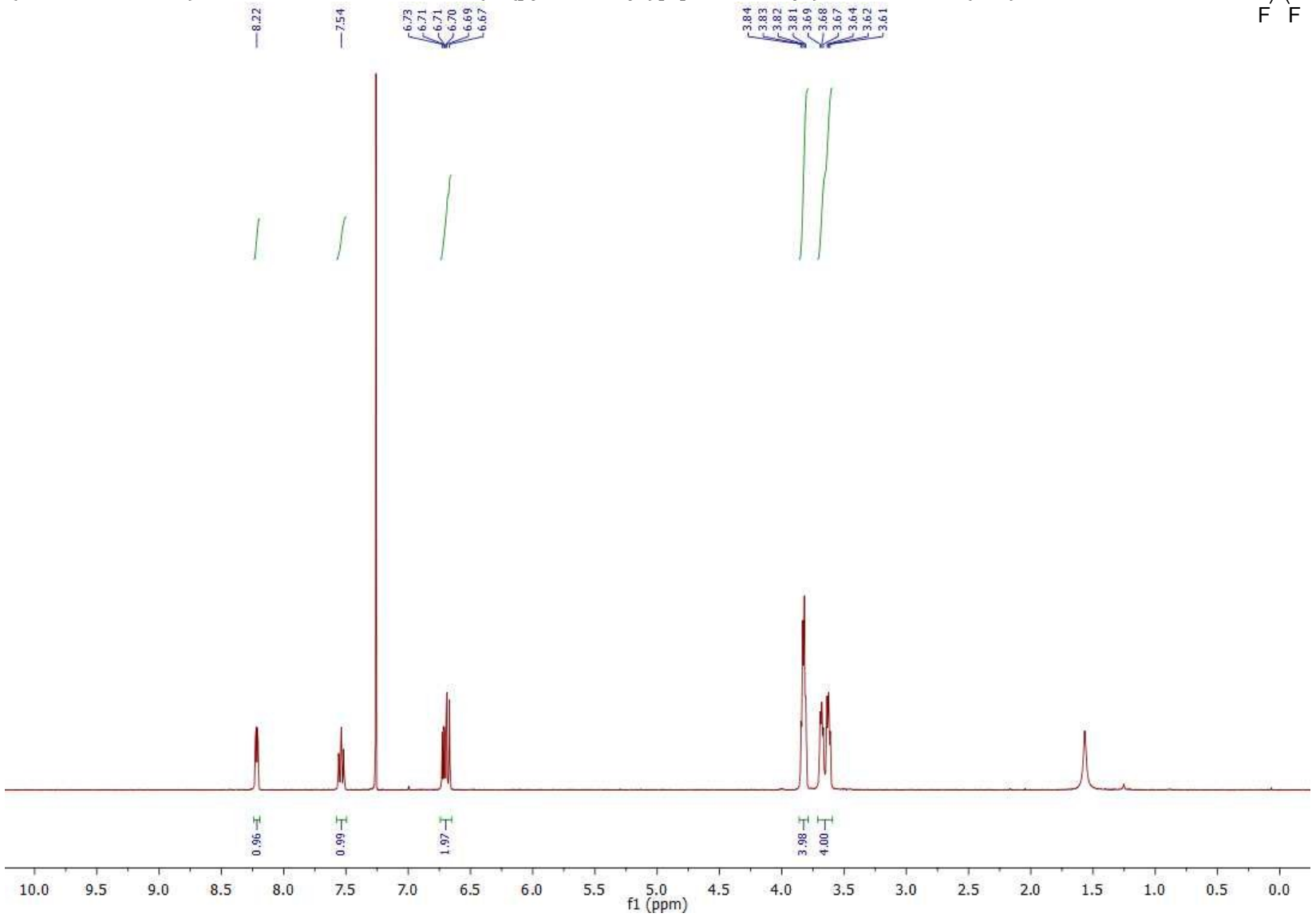
^{19}F NMR ($CDCl_3$, 377 MHz). 1-(2-Bromo-2,2-difluoroacetyl)-*N*,*N*-diethylpiperidine-3-carboxamide (**1l**)



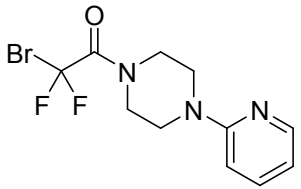


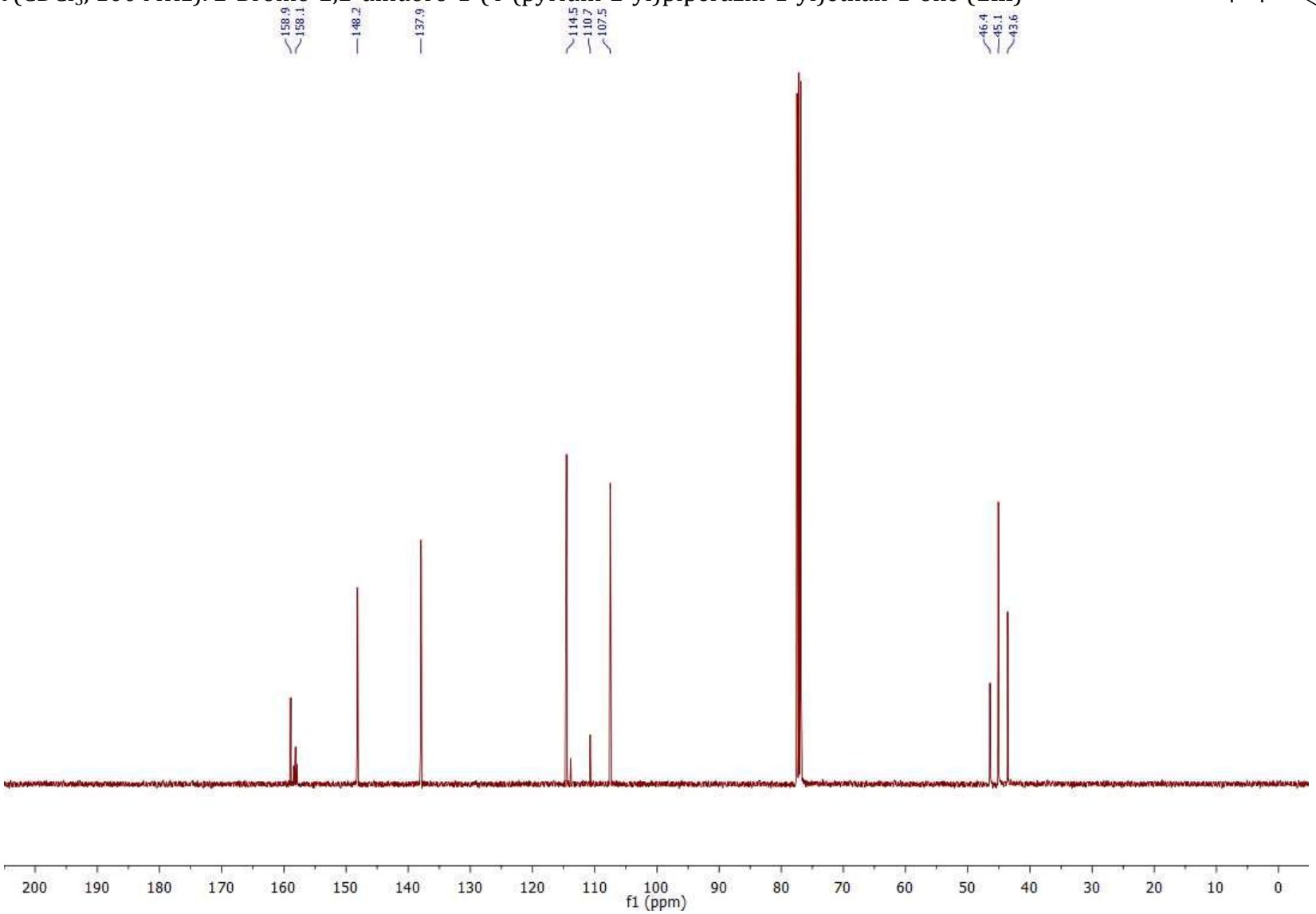
^{1}H NMR ($CDCl_3$, 400 MHz). 2-Bromo-2,2-difluoro-1-(4-(pyridin-2-yl)piperazin-1-yl)ethan-1-one (**1m**)

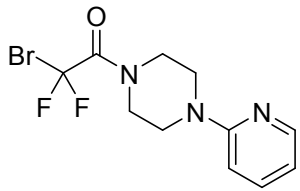




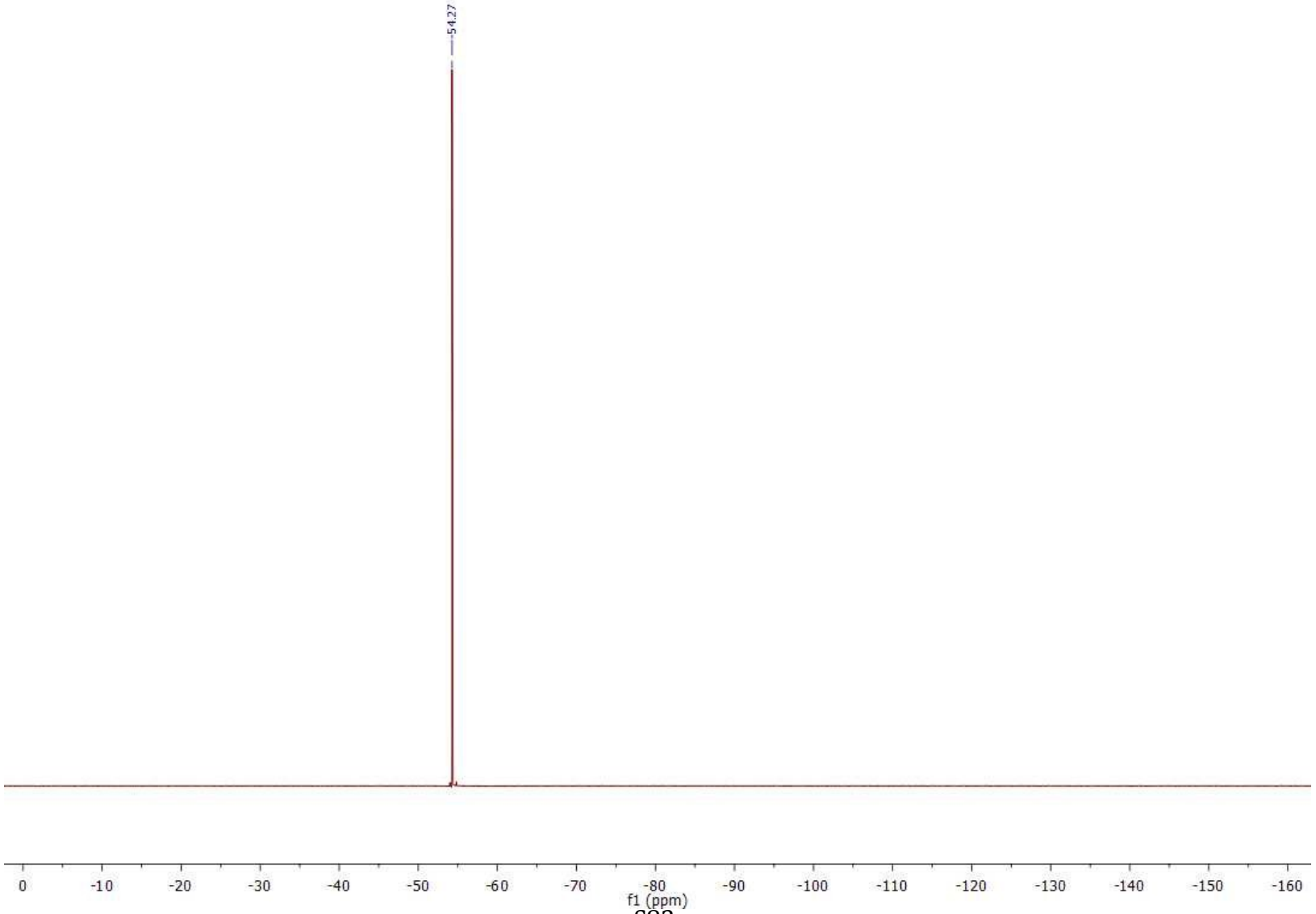
^{13}C NMR ($CDCl_3$, 100 MHz). 2-Bromo-2,2-difluoro-1-(4-(pyridin-2-yl)piperazin-1-yl)ethan-1-one (**1m**)



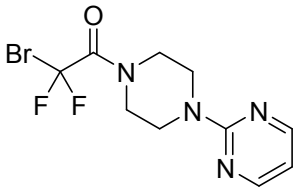


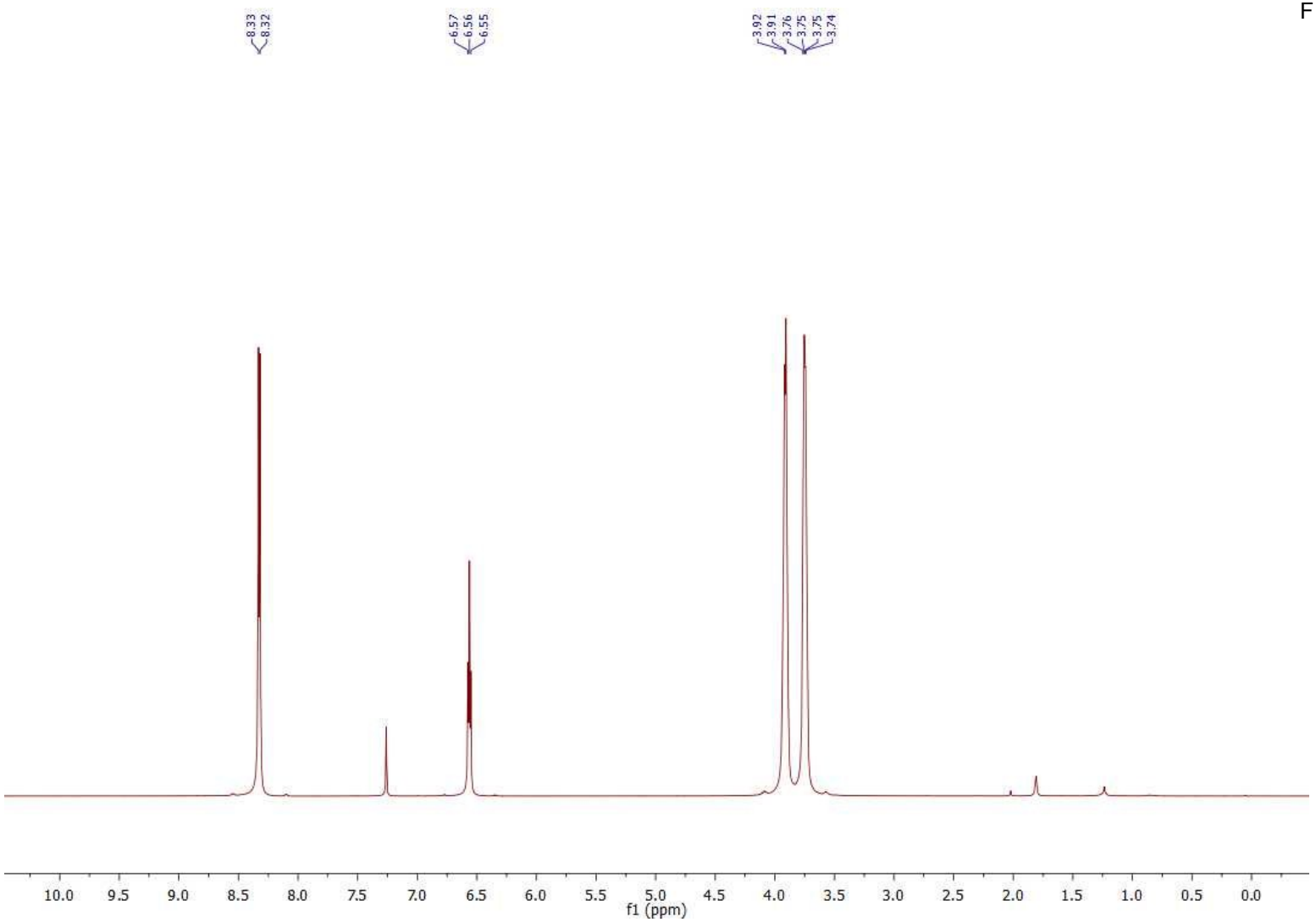


^{19}F NMR ($CDCl_3$, 377 MHz). 2-Bromo-2,2-difluoro-1-(4-(pyridin-2-yl)piperazin-1-yl)ethan-1-one (**1m**)

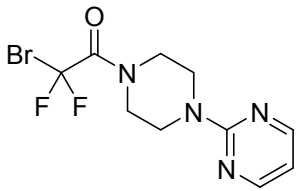


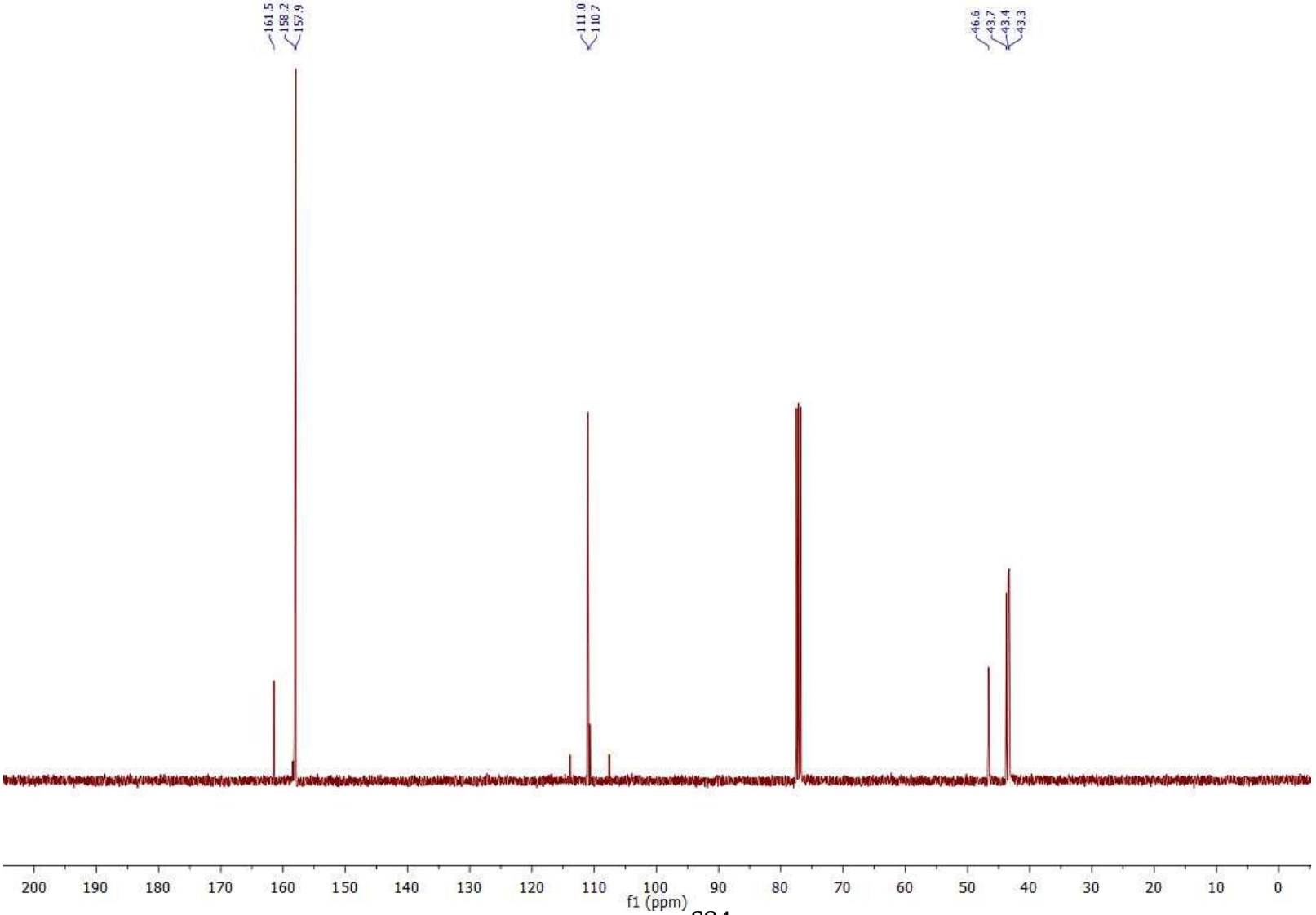
^{1}H NMR ($CDCl_3$, 400 MHz). 2-Bromo-2,2-difluoro-1-(4-(pyrimidin-2-yl)piperazin-1-yl)ethan-1-one (**1n**)



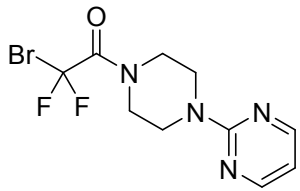


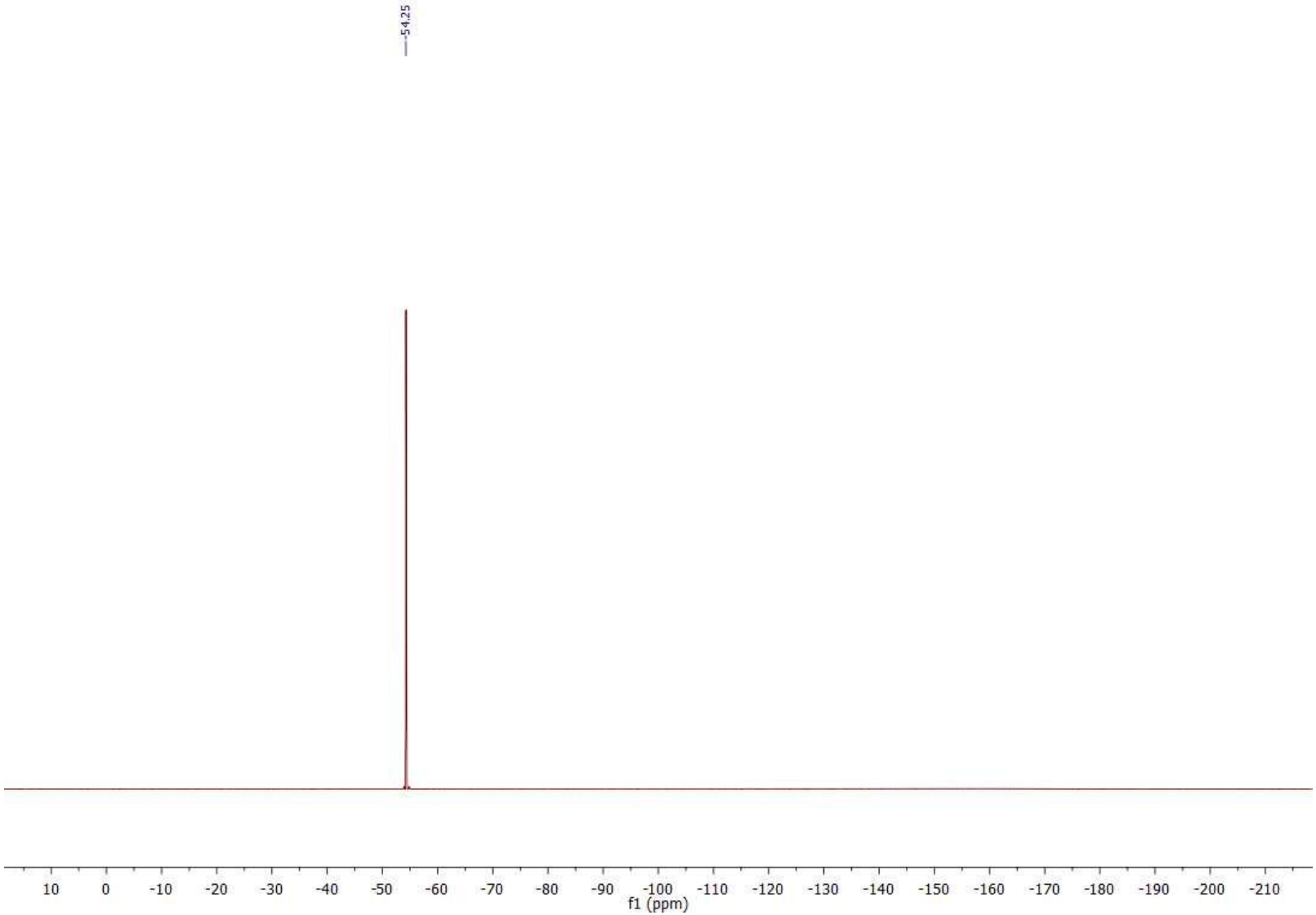
^{13}C NMR ($CDCl_3$, 100 MHz). 2-Bromo-2,2-difluoro-1-(4-(pyrimidin-2-yl)piperazin-1-yl)ethan-1-one (**1n**)



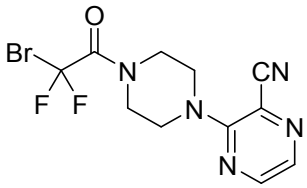


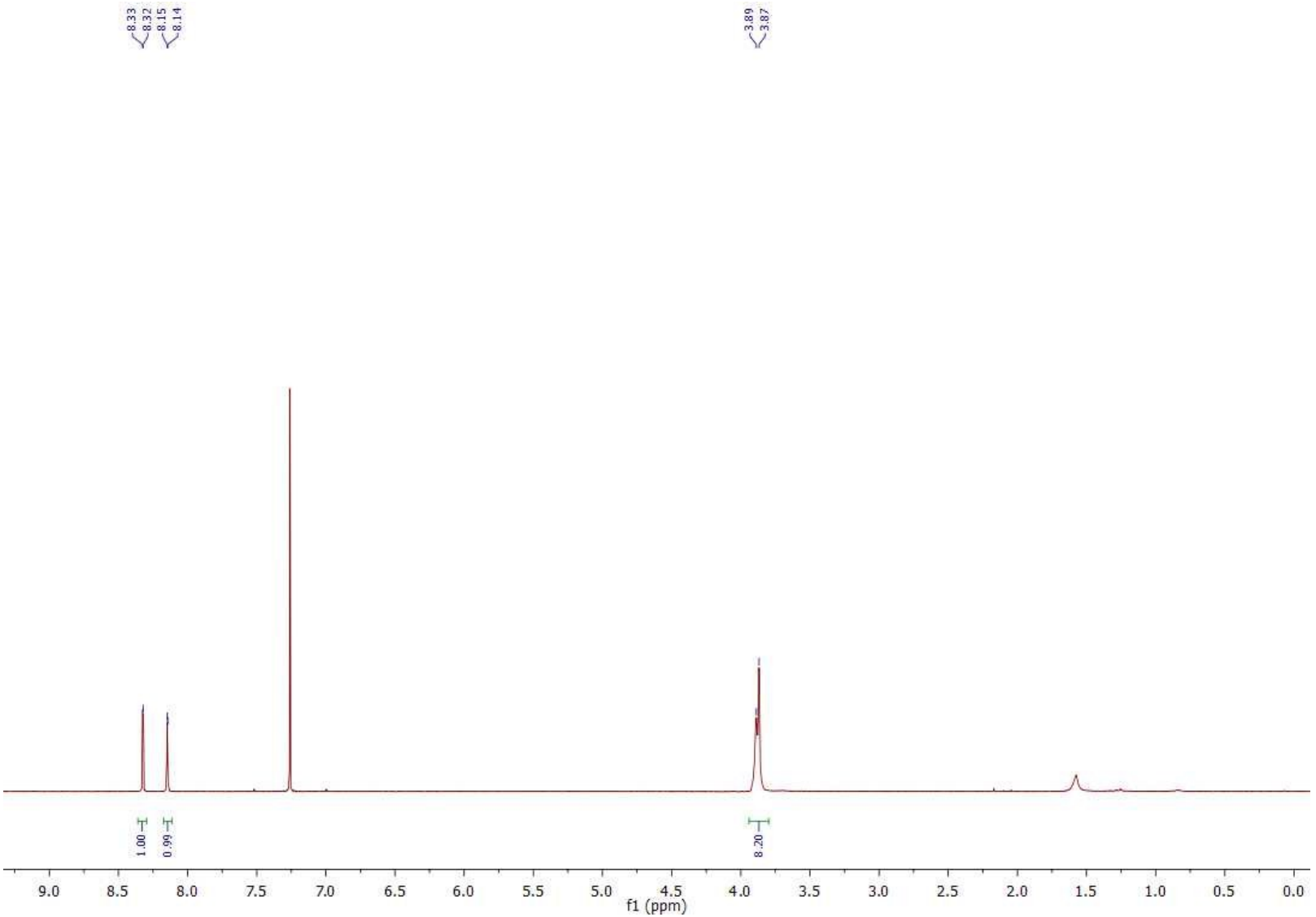
^{19}F NMR ($CDCl_3$, 377 MHz). 2-Bromo-2,2-difluoro-1-(4-(pyrimidin-2-yl)piperazin-1-yl)ethan-1-one (**1n**)



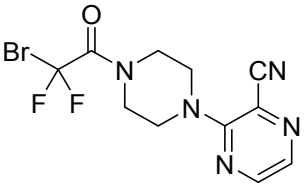


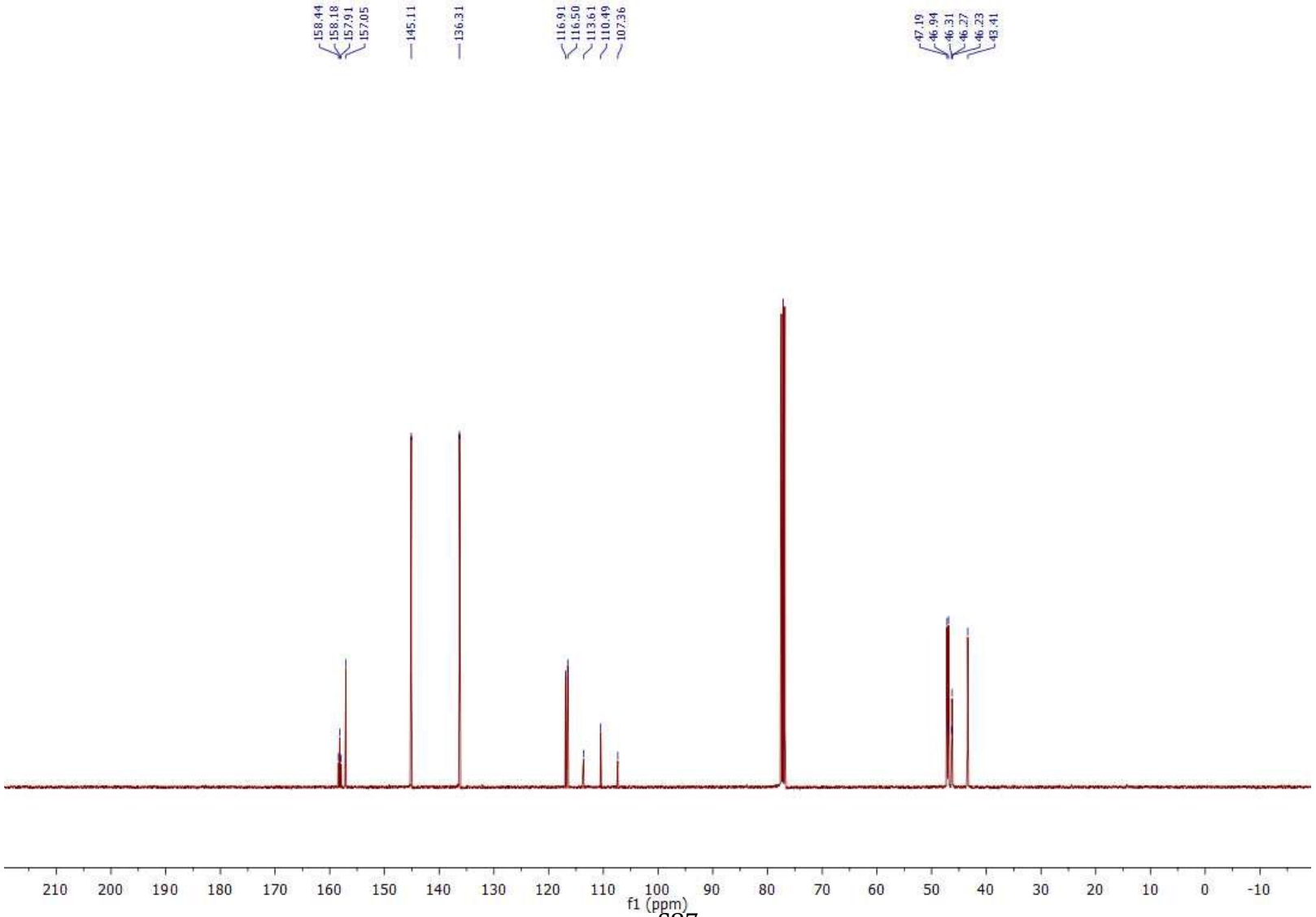
^{1}H NMR ($CDCl_3$, 400 MHz). 3-(4-(2-Bromo-2,2-difluoroacetyl)piperazin-1-yl)pyrazine-2-carbonitrile (**1o**)



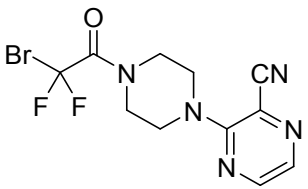


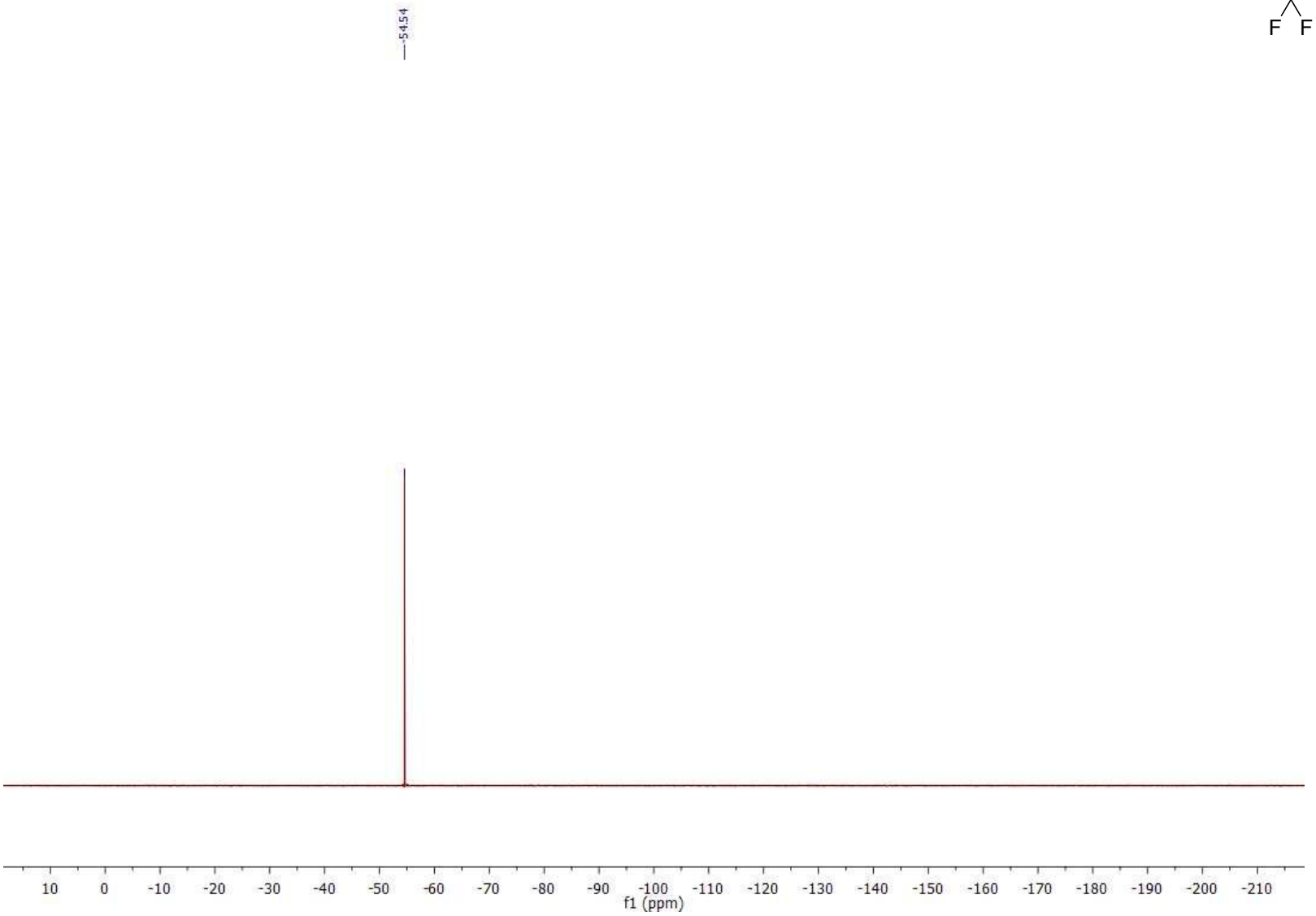
^{13}C NMR ($CDCl_3$, 100 MHz). 3-(4-(2-Bromo-2,2-difluoroacetyl)piperazin-1-yl)pyrazine-2-carbonitrile (**1o**)



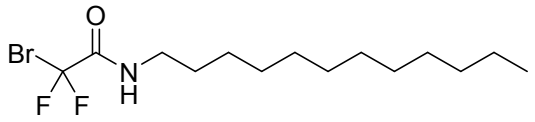


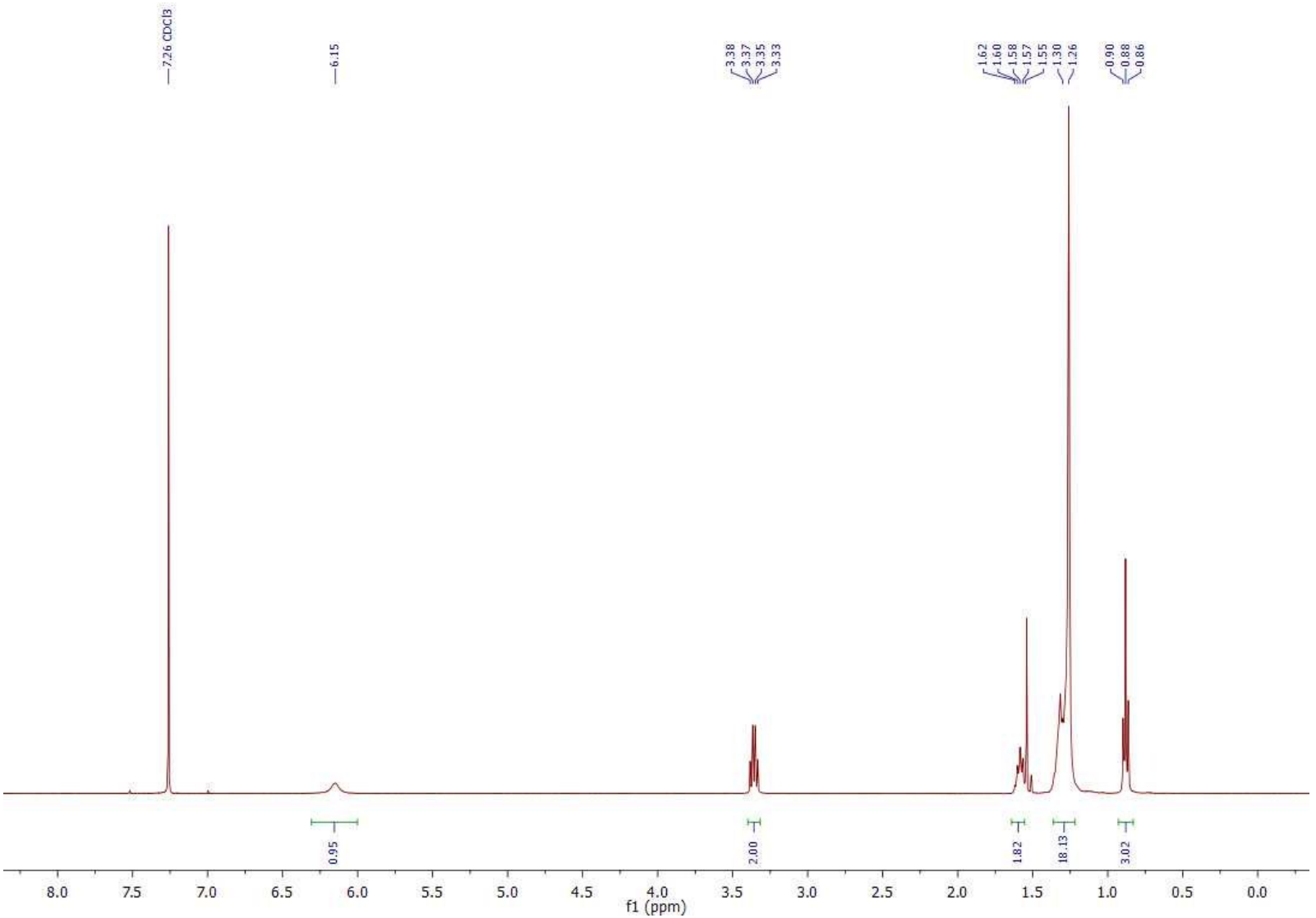
^{19}F NMR ($CDCl_3$, 377 MHz). 3-(4-(2-Bromo-2,2-difluoroacetyl)piperazin-1-yl)pyrazine-2-carbonitrile (**1o**)



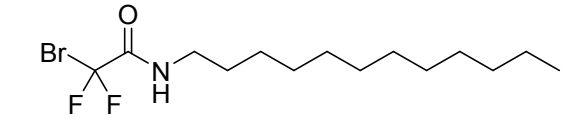


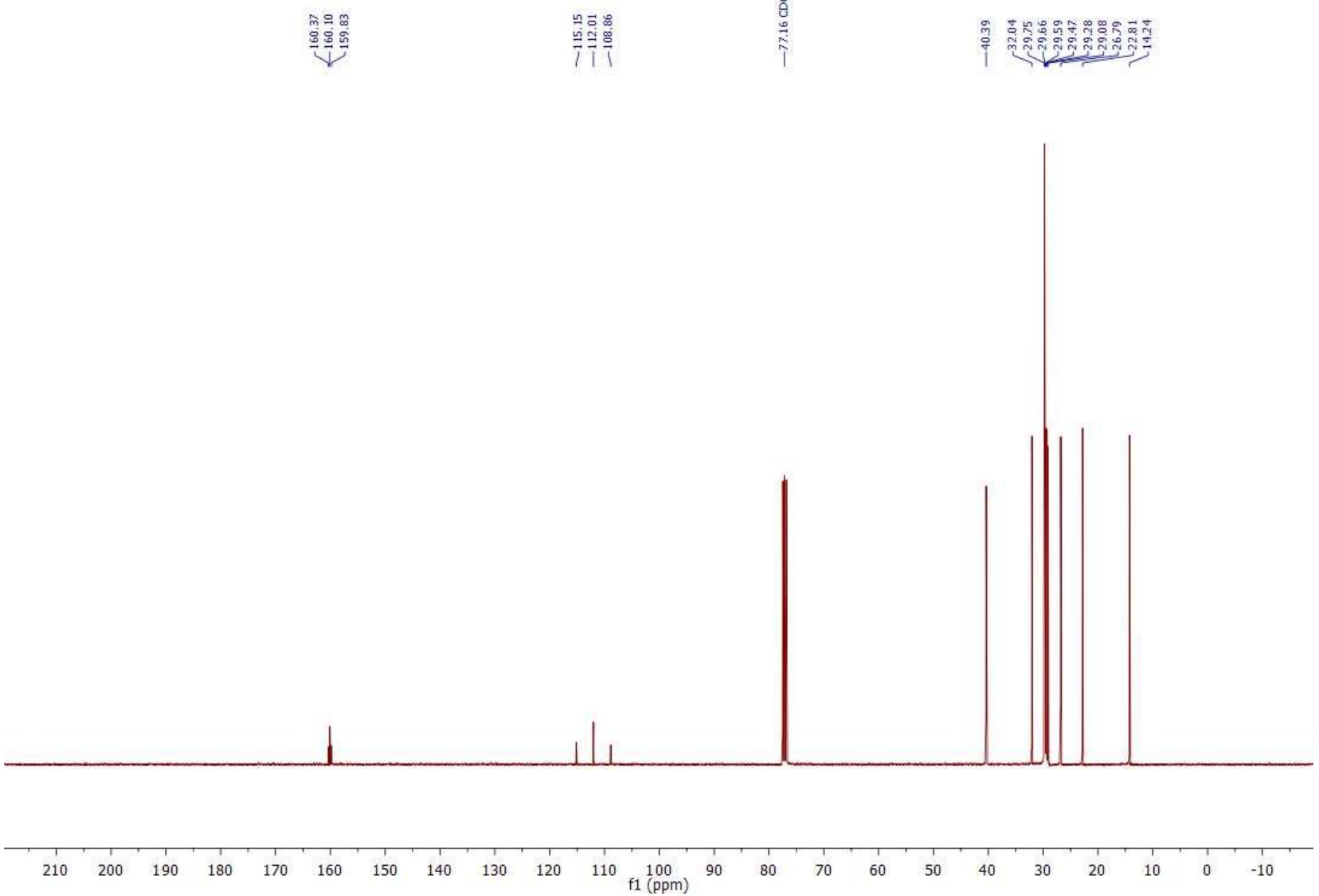
^{1}H NMR ($CDCl_3$, 400 MHz). 2-Bromo-*N*-dodecyl-2,2-difluoroacetamide (**1p**)



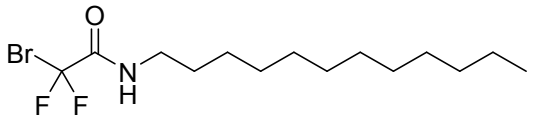


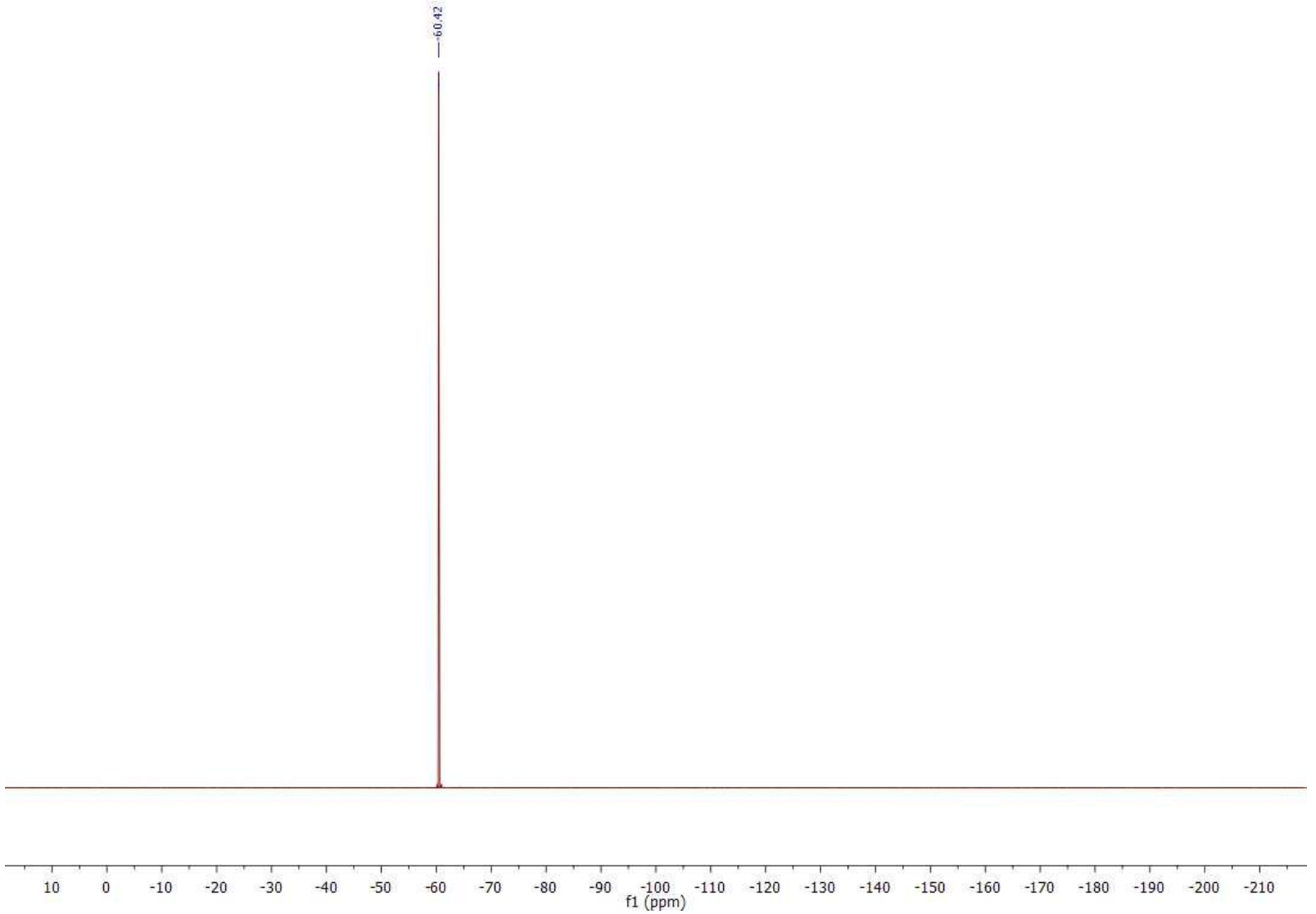
^{13}C NMR ($CDCl_3$, 100 MHz). 2-Bromo-*N*-dodecyl-2,2-difluoroacetamide (**1p**)



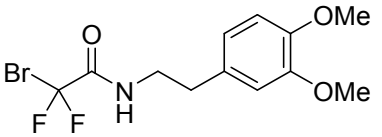


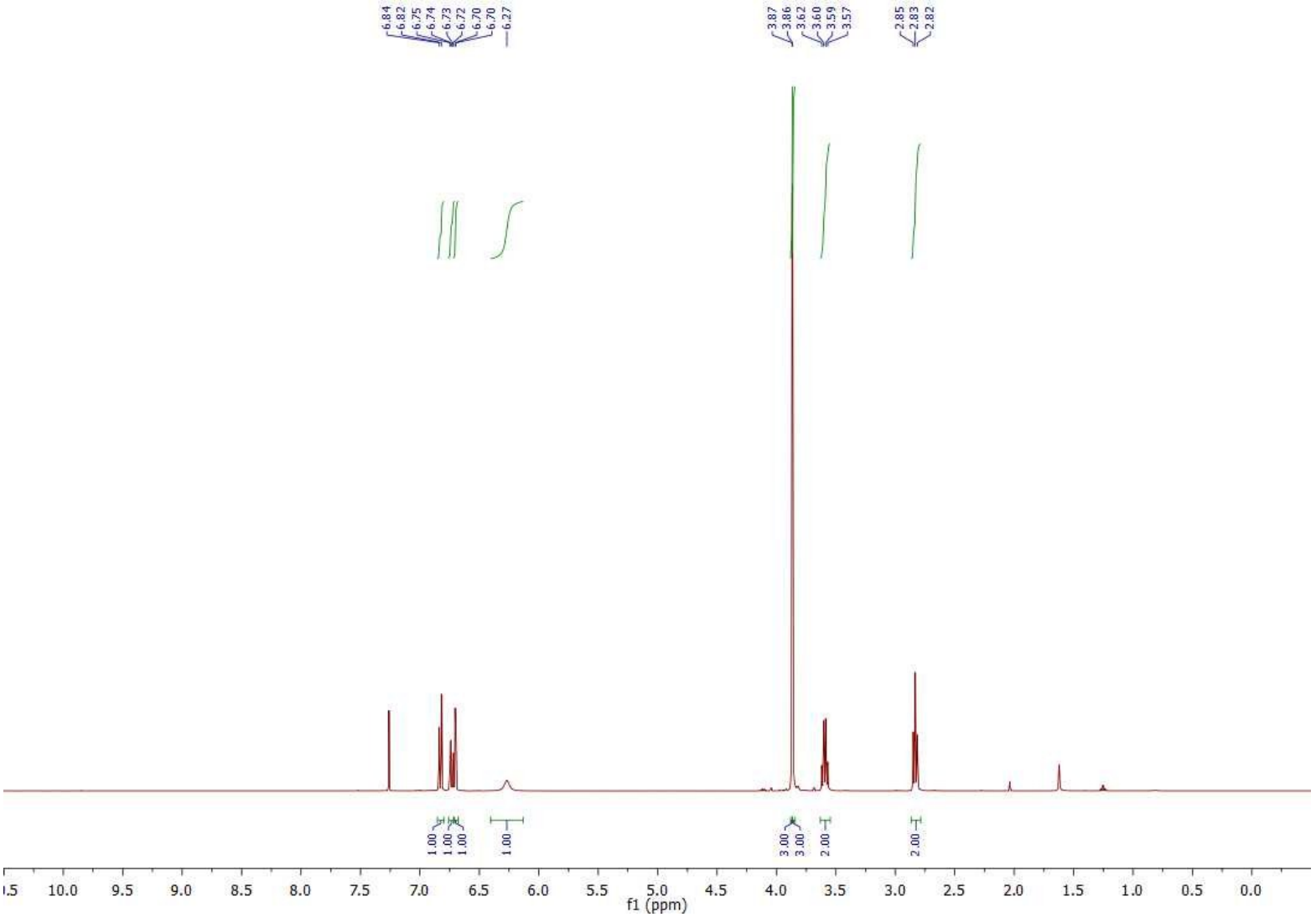
^{19}F NMR ($CDCl_3$, 377 MHz). 2-Bromo-*N*-dodecyl-2,2-difluoroacetamide (**1p**)



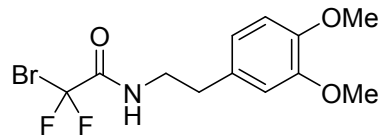


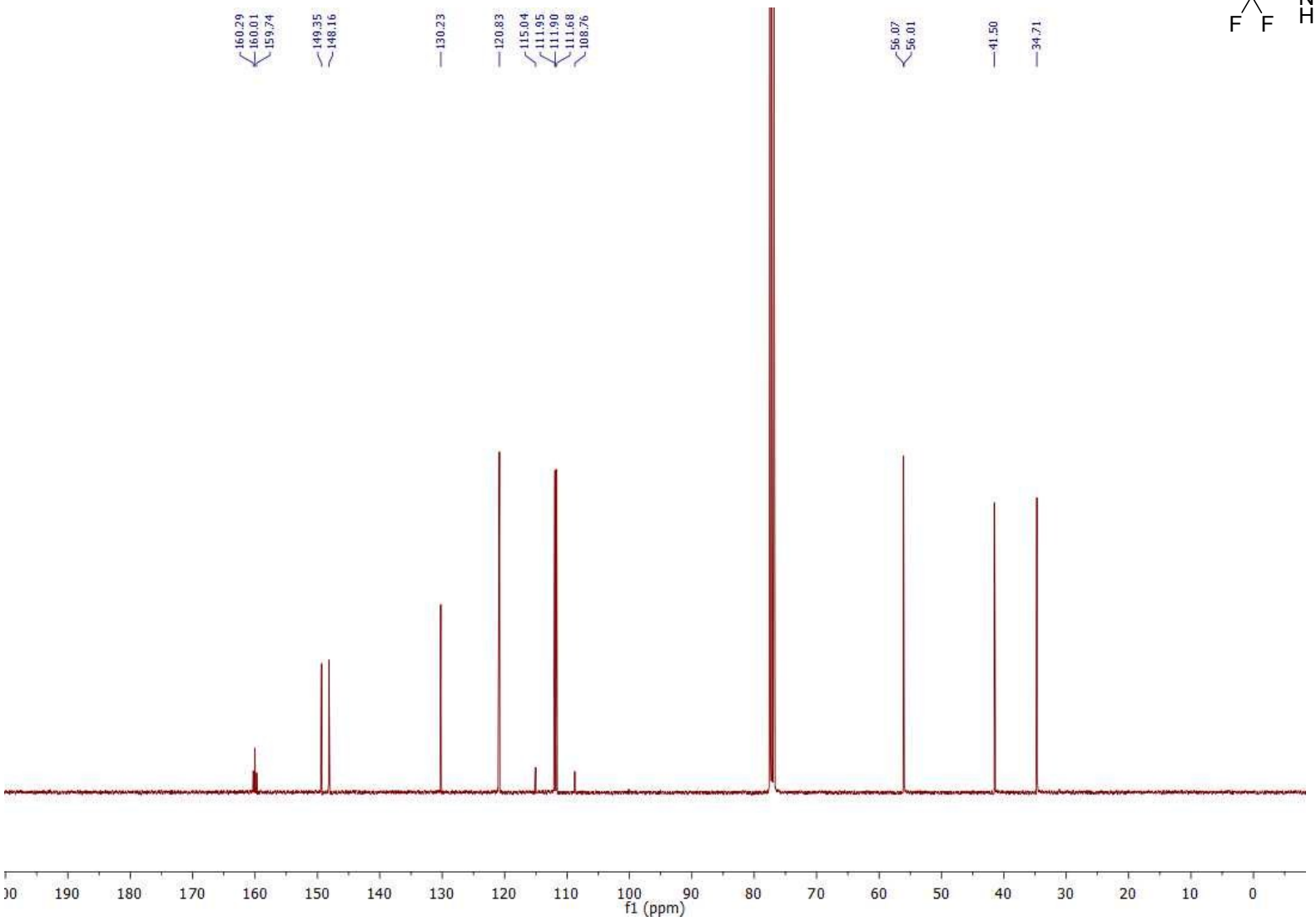
^{1}H NMR ($CDCl_3$, 400 MHz). 2-Bromo-*N*-(3,4-dimethoxyphenethyl)-2,2-difluoroacetamide (**1r**)



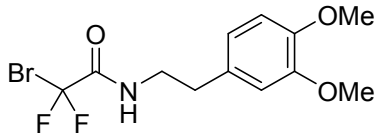


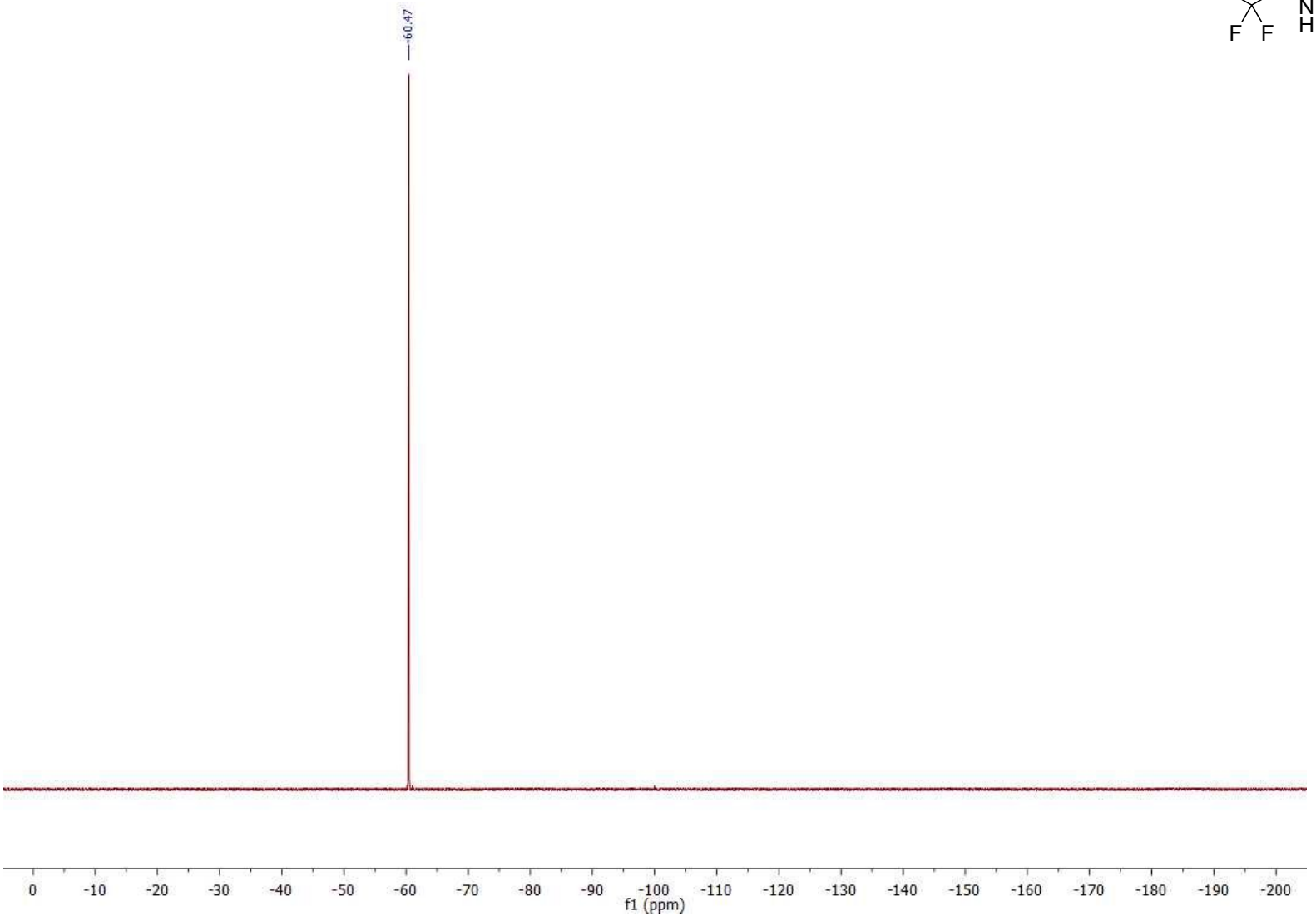
^{13}C NMR ($CDCl_3$, 100 MHz). 2-Bromo-*N*-(3,4-dimethoxyphenethyl)-2,2-difluoroacetamide (**1r**)





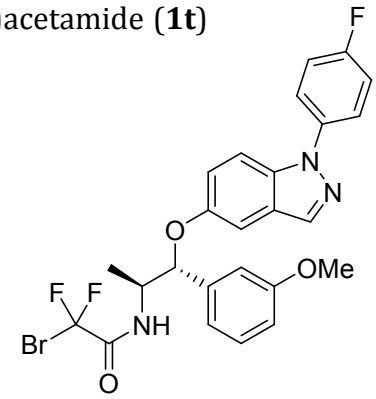
^{19}F NMR ($CDCl_3$, 377 MHz). 2-Bromo-*N*-(3,4-dimethoxyphenethyl)-2,2-difluoroacetamide (**1r**)

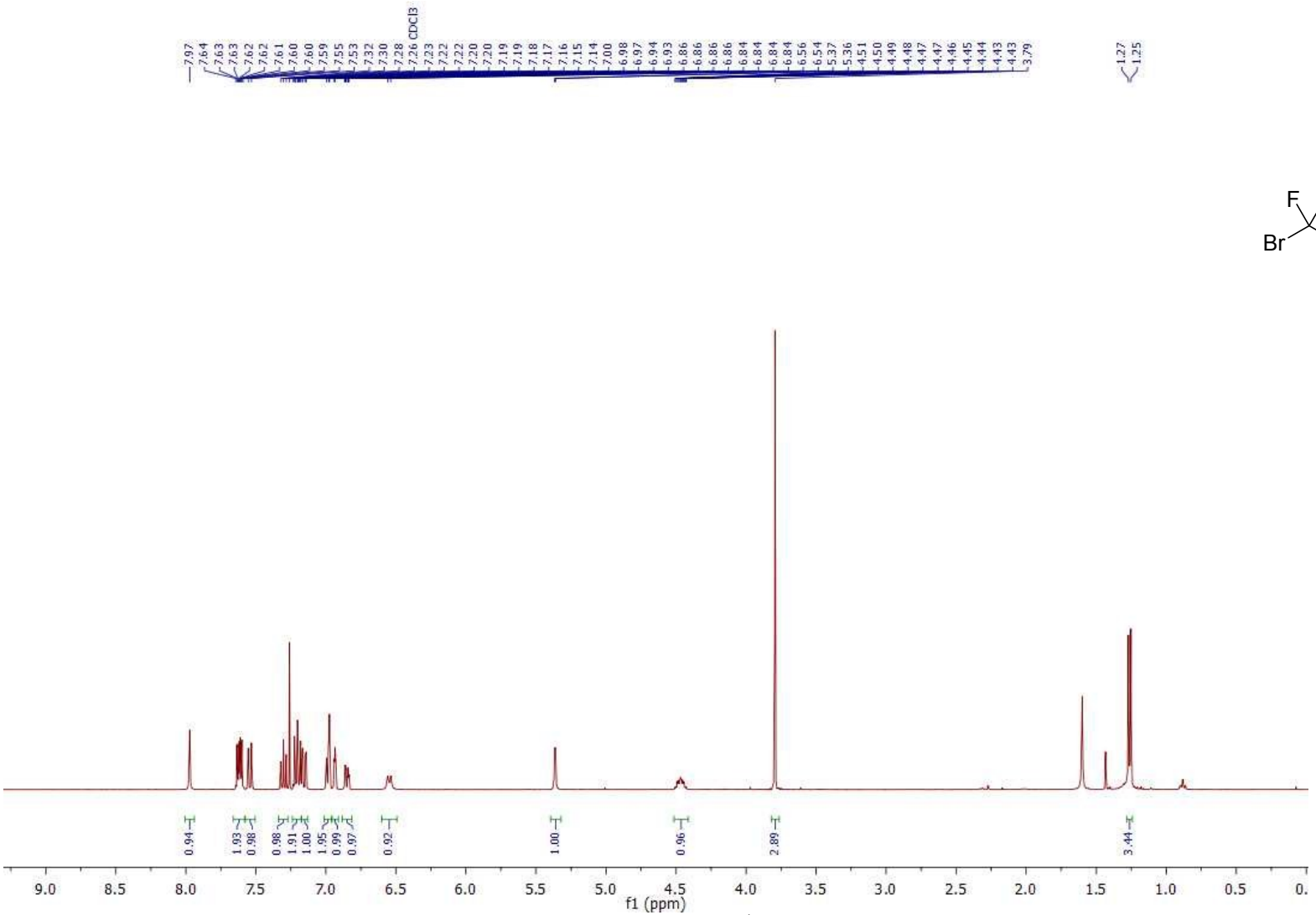




^{1}H NMR ($CDCl_3$, 400 MHz).

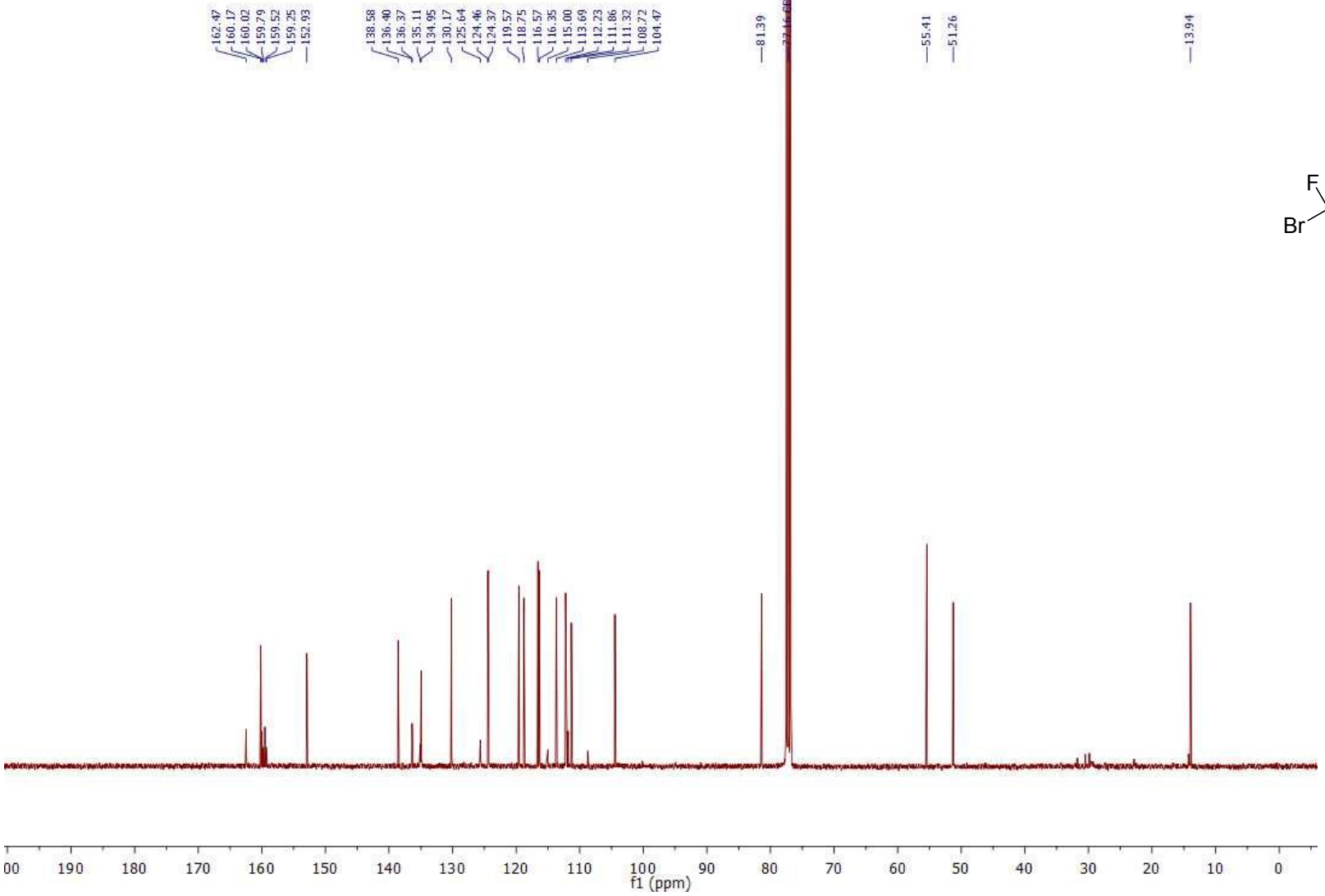
2-Bromo-2,2-difluoro-*N*-((1*R*,2*S*)-1-((1-(4-fluorophenyl)-1*H*-indazol-5-yl)oxy)-1-(3-methoxyphenyl)propan-2-yl)acetamide (**1t**)

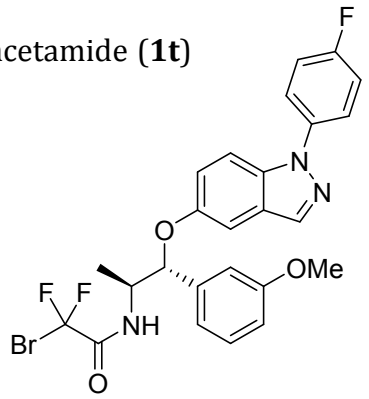




^{13}C NMR ($CDCl_3$, 100 MHz).

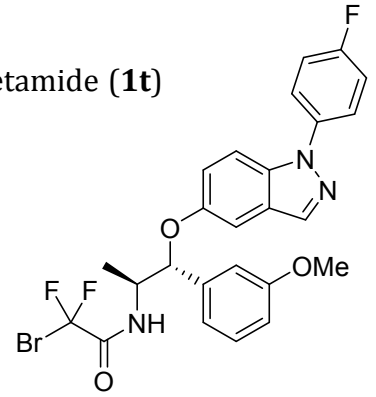
2-Bromo-2,2-difluoro-*N*-((1*R*,2*S*)-1-((1-(4-fluorophenyl)-1*H*-indazol-5-yl)oxy)-1-(3-methoxyphenyl)propan-2-yl)acetamide (**1t**)

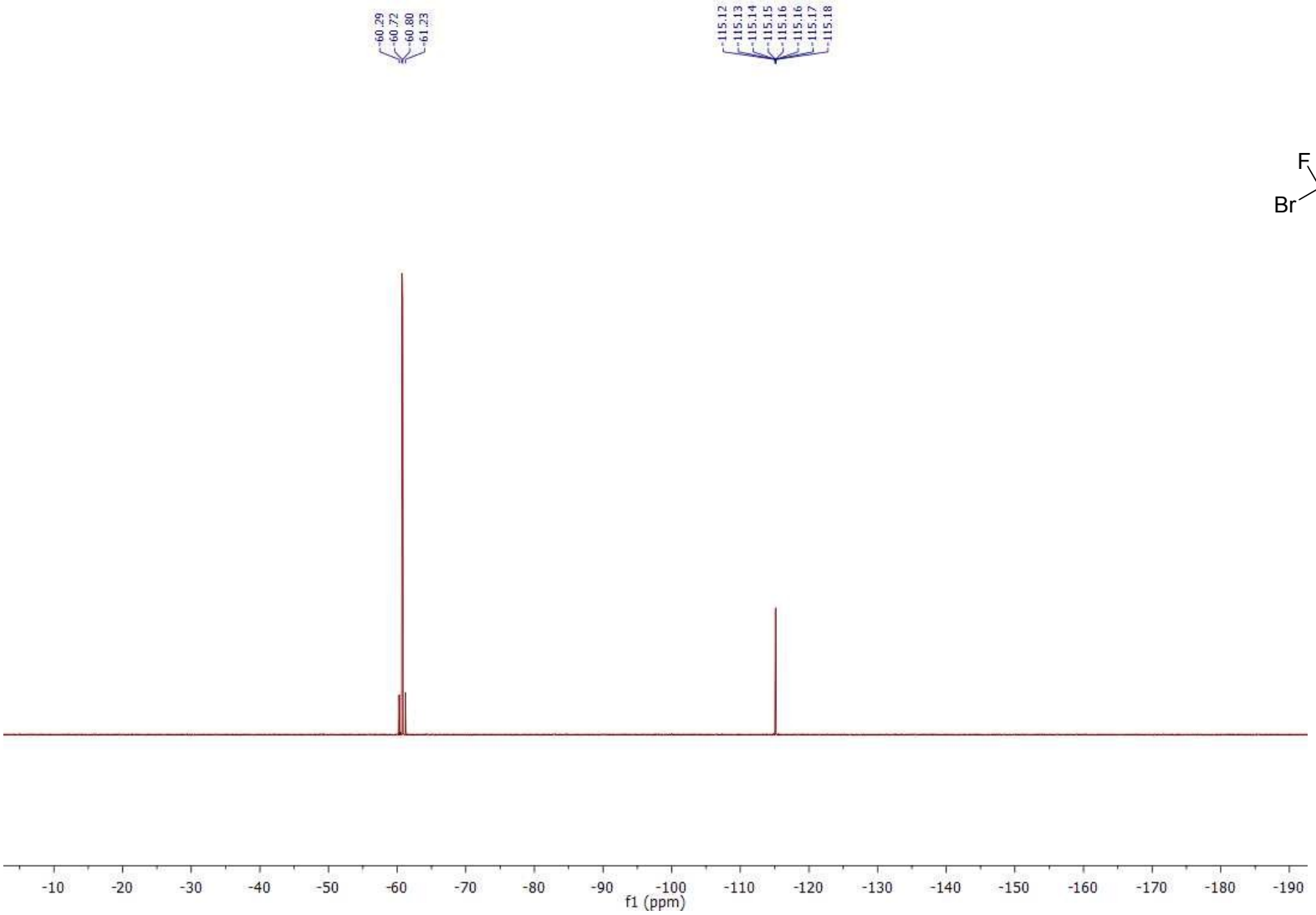




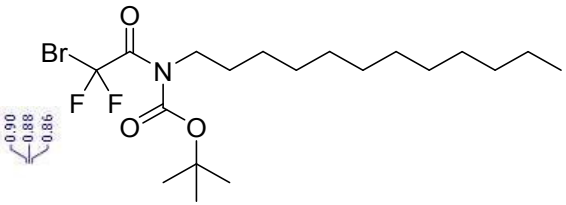
^{19}F NMR ($CDCl_3$, 377 MHz).

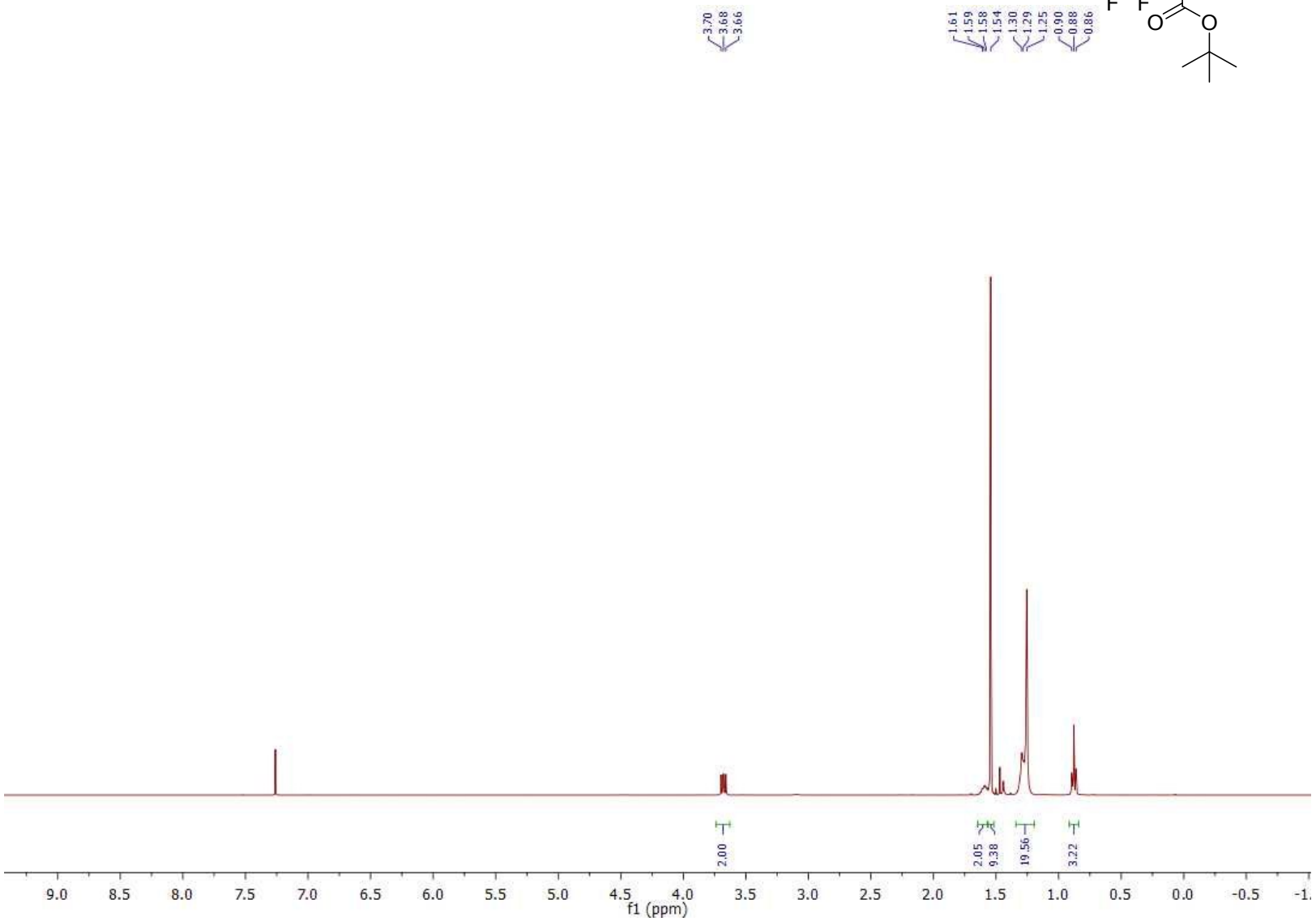
2-Bromo-2,2-difluoro-*N*-((1*R*,2*S*)-1-((1-(4-fluorophenyl)-1*H*-indazol-5-yl)oxy)-1-(3-methoxyphenyl)propan-2-yl)acetamide (**1t**)



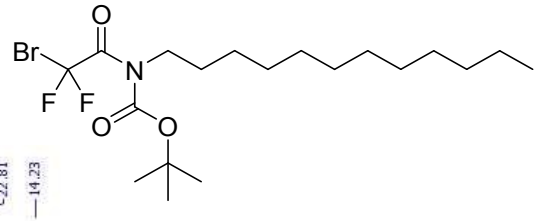


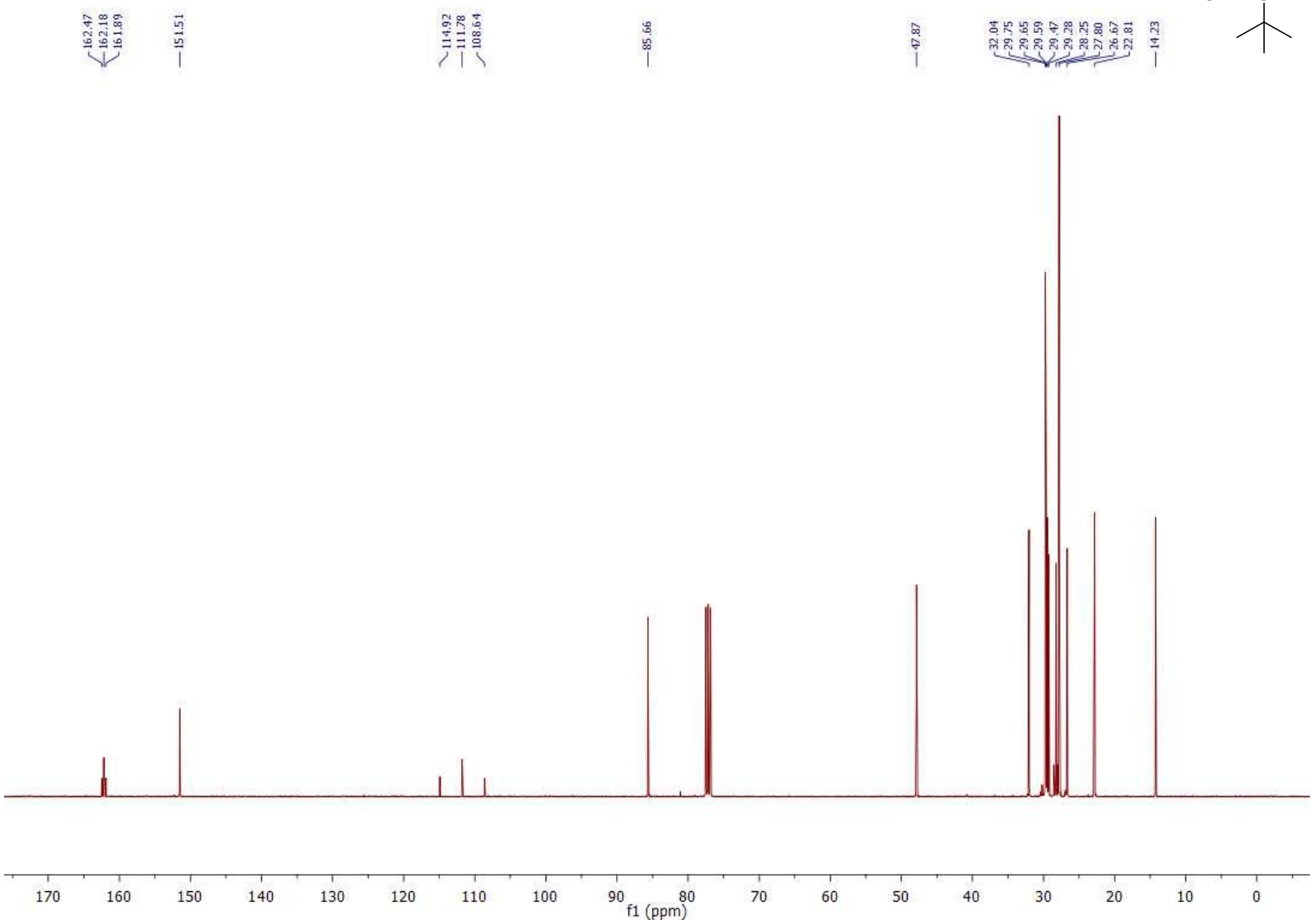
^{1}H NMR ($CDCl_3$, 400 MHz). *tert*-Butyl 2-bromo-2,2-difluoroacetyl(dodecyl)carbamate (**1q**)



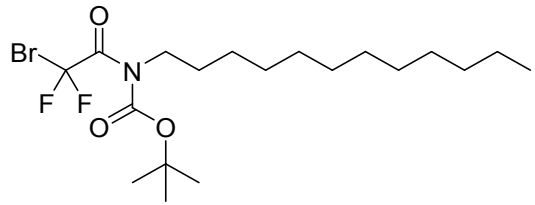


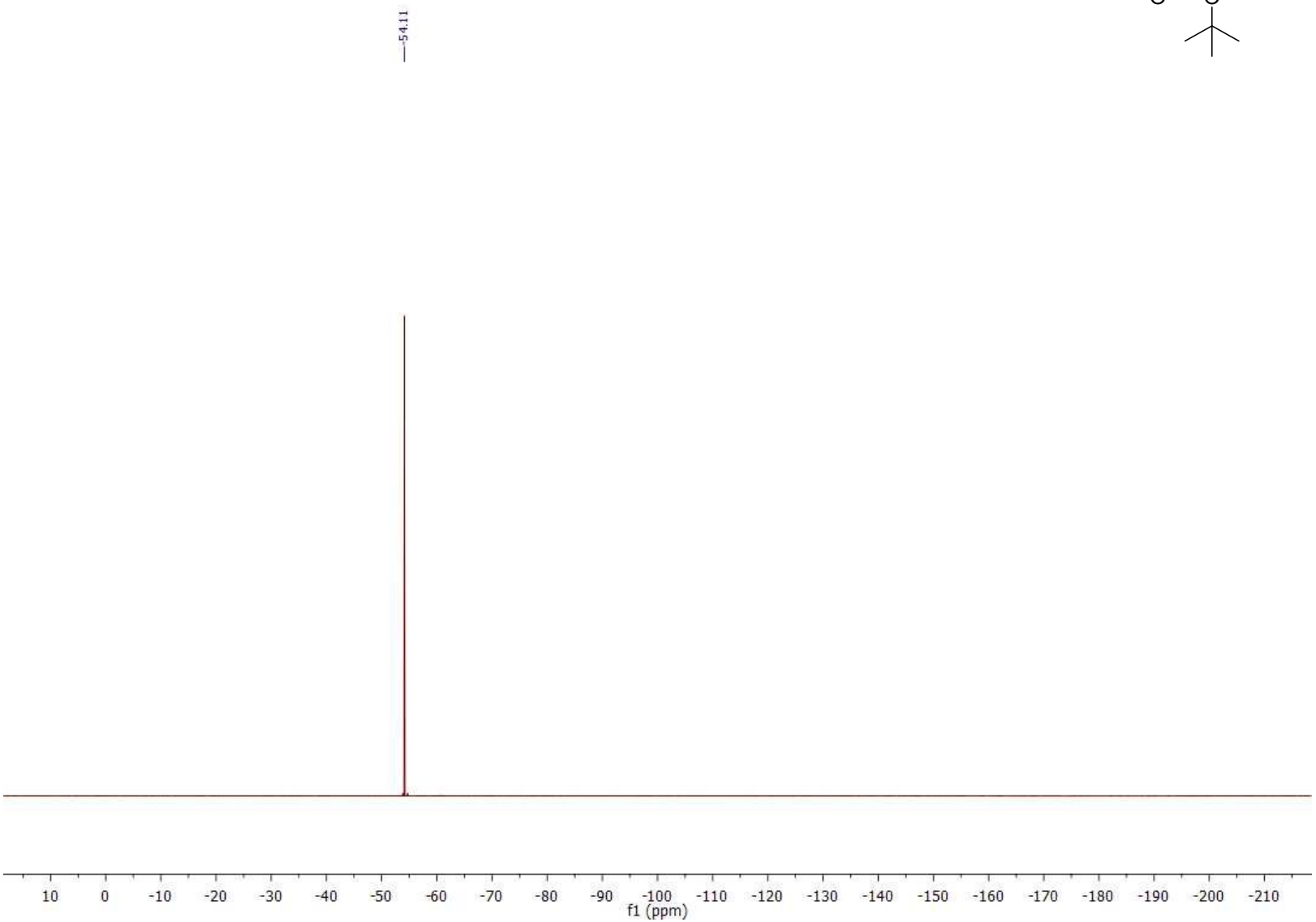
^{13}C NMR ($CDCl_3$, 100 MHz). *tert*-Butyl 2-bromo-2,2-difluoroacetyl(dodecyl)carbamate (**1q**)



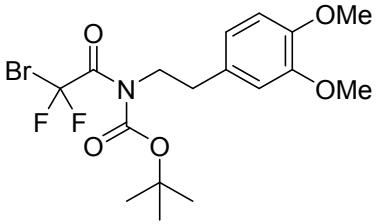


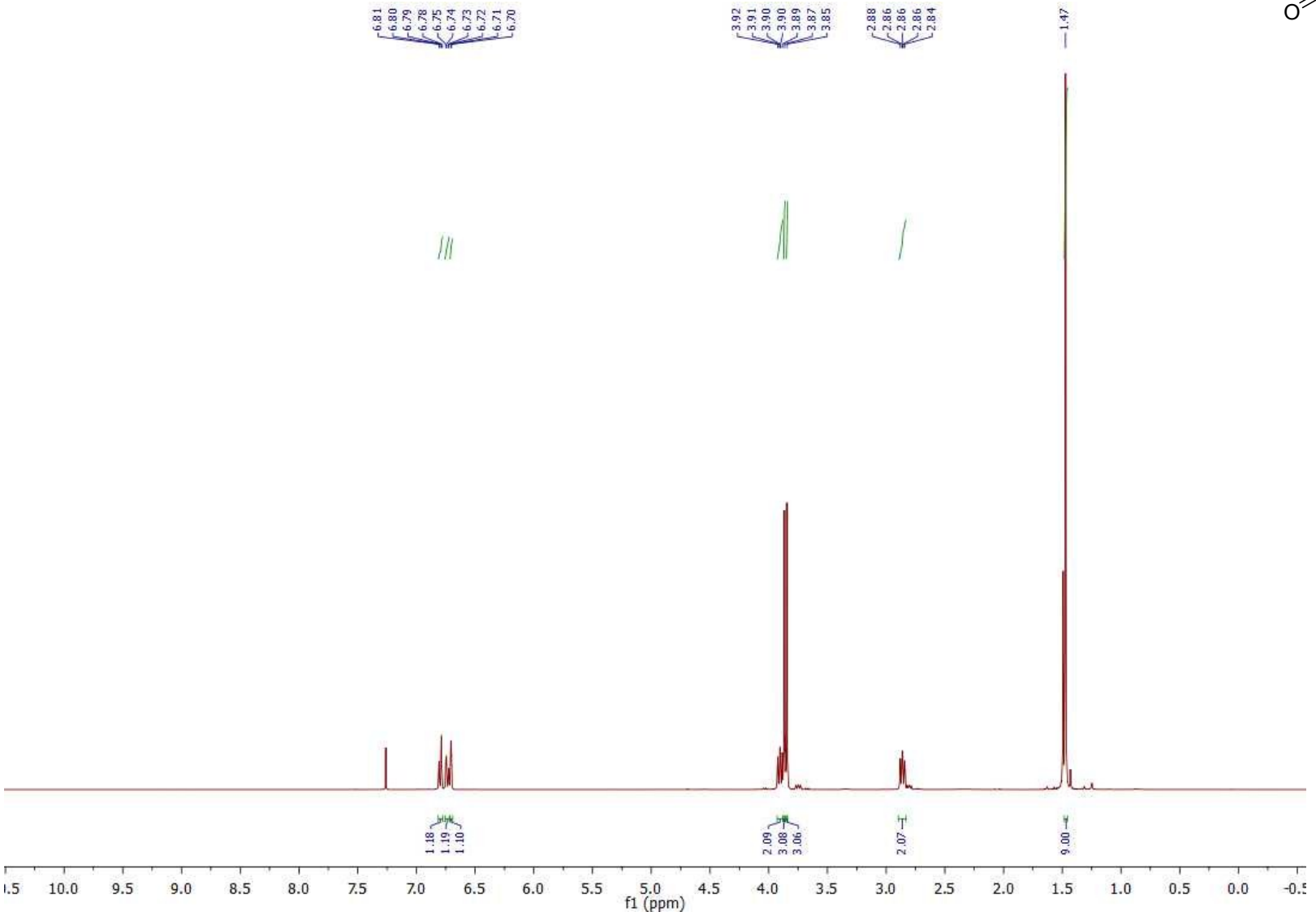
^{19}F NMR ($CDCl_3$, 377 MHz). *tert*-Butyl 2-bromo-2,2-difluoroacetyl(dodecyl)carbamate (**1q**)



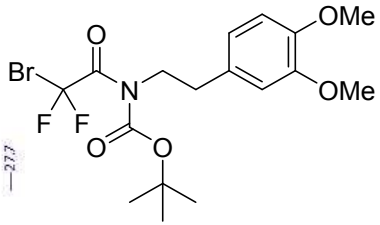


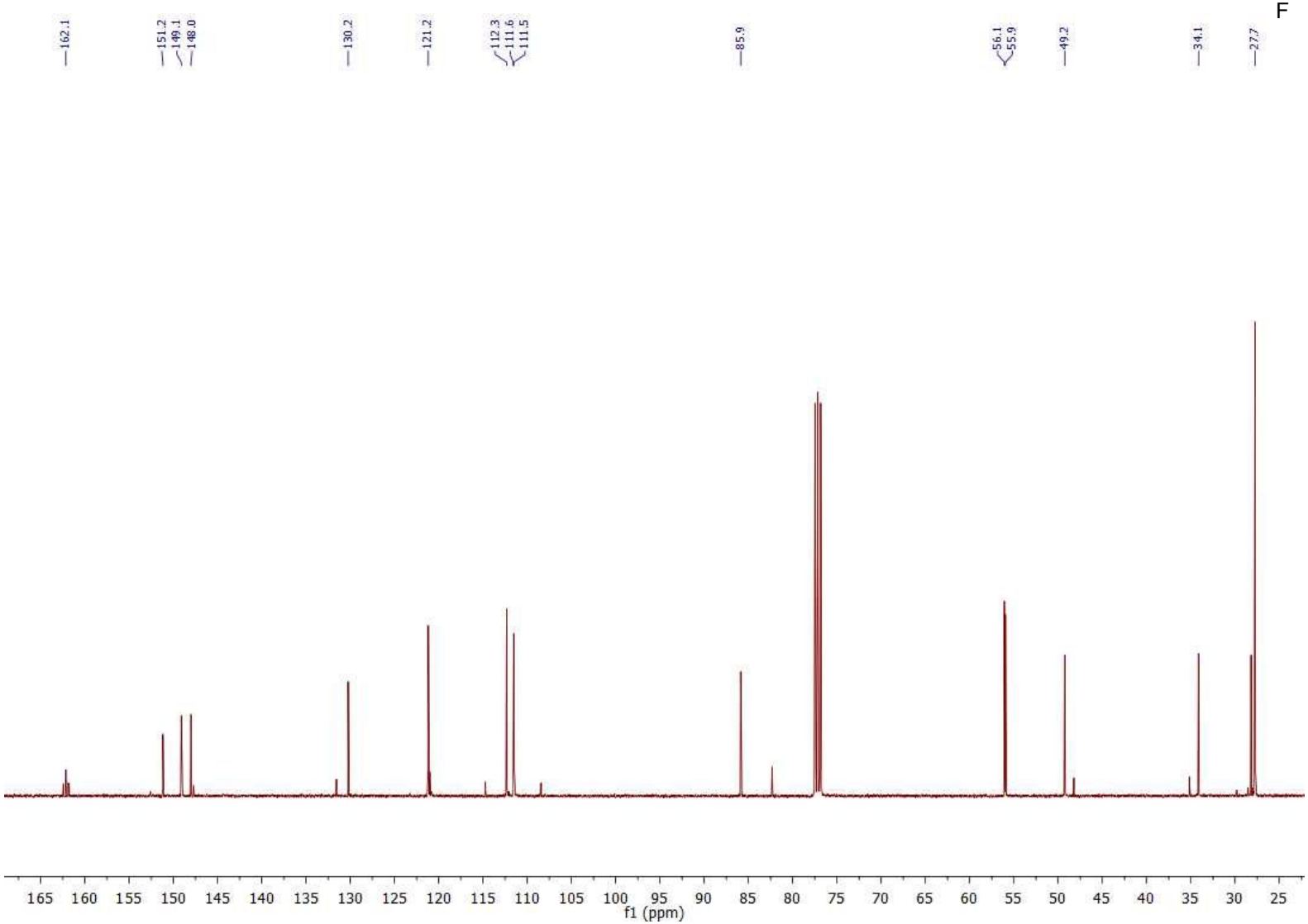
^{1}H NMR ($CDCl_3$, 400 MHz). *tert*-Butyl (2-bromo-2,2-difluoroacetyl)(3,4-dimethoxyphenethyl)carbamate (**1s**)



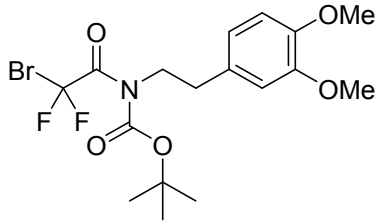


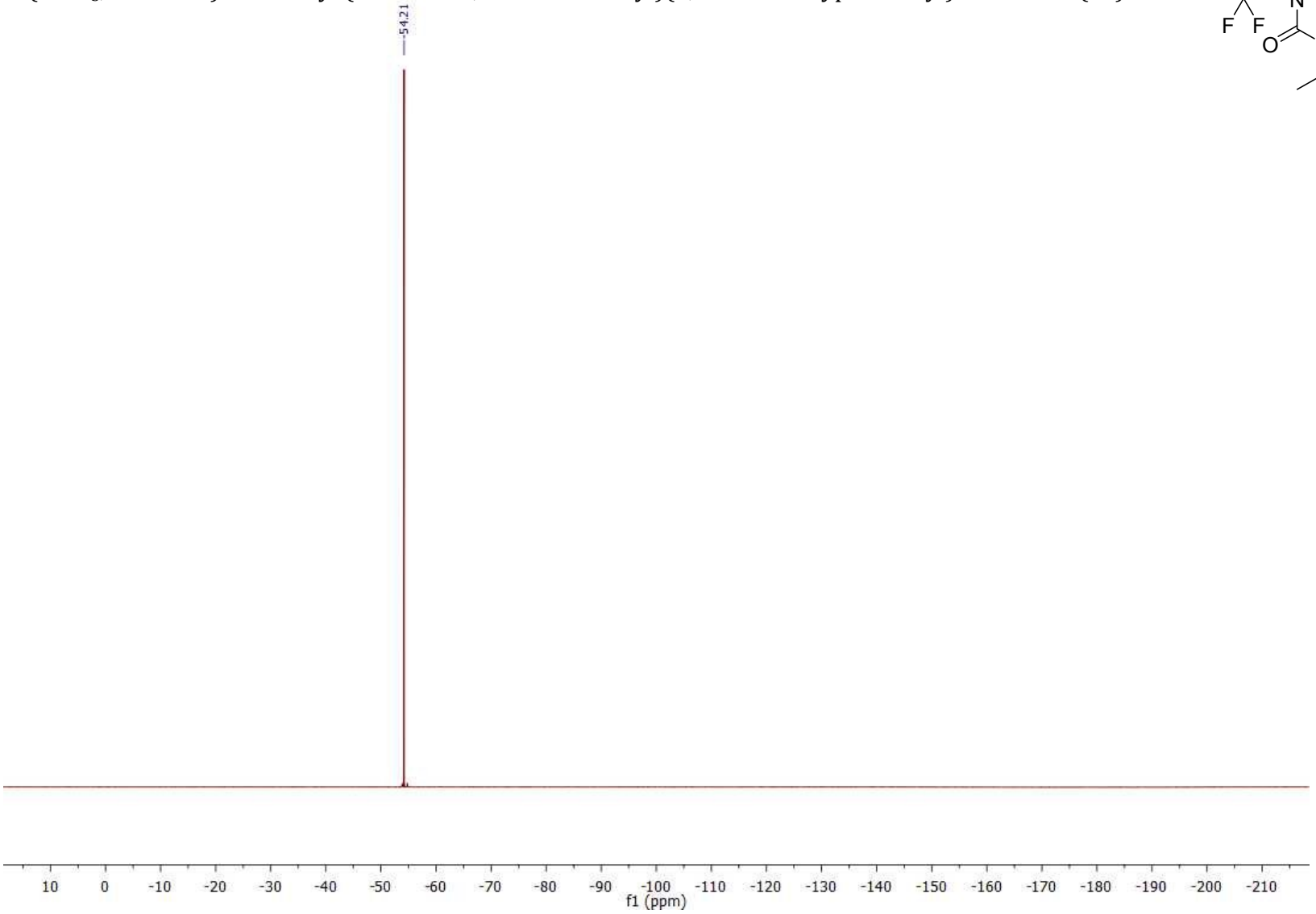
^{13}C NMR ($CDCl_3$, 100 MHz). *tert*-Butyl (2-bromo-2,2-difluoroacetyl)(3,4-dimethoxyphenethyl)carbamate (**1s**)





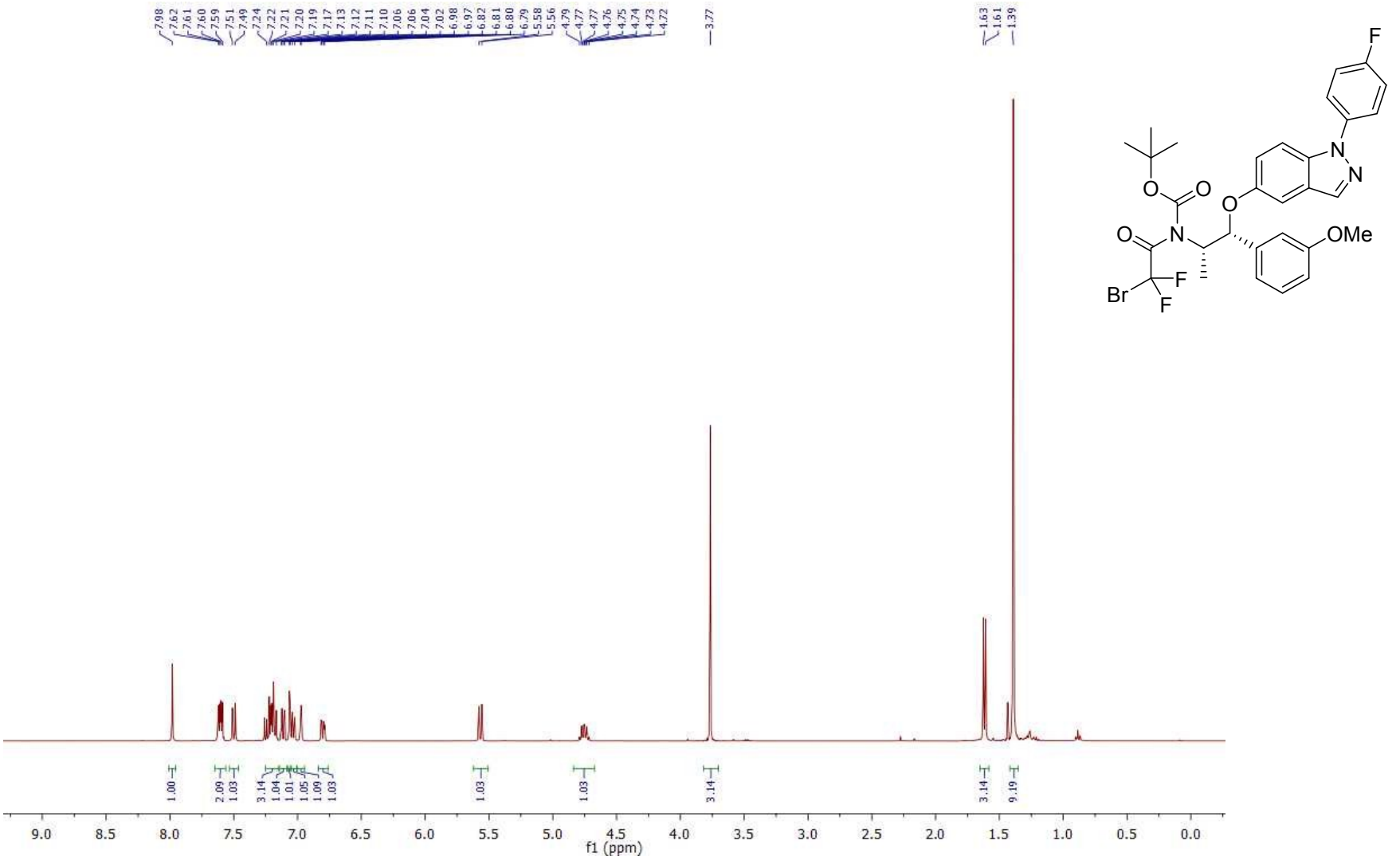
^{19}F NMR ($CDCl_3$, 377 MHz). *tert*-Butyl (2-bromo-2,2-difluoroacetyl)(3,4-dimethoxyphenethyl)carbamate (**1s**)





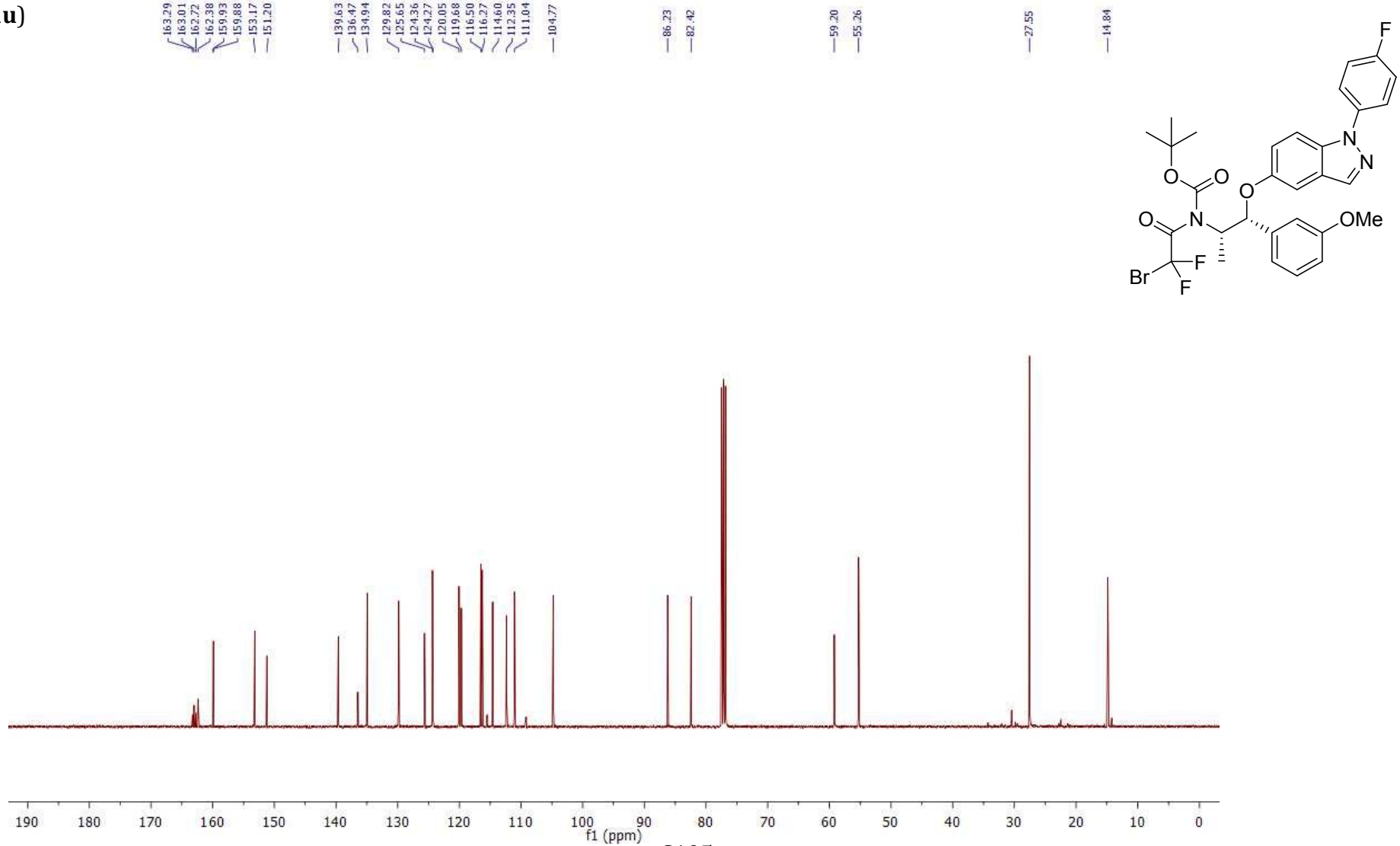
^{1}H NMR ($CDCl_3$, 400 MHz).

tert-Butyl 2-bromo-2,2-difluoroacetyl((1*R*,2*S*)-1-(1-(4-fluorophenyl)-1*H*-indazol-5-yloxy)-1-(3-methoxyphenyl)propan-2-yl)carbamate (**1u**)



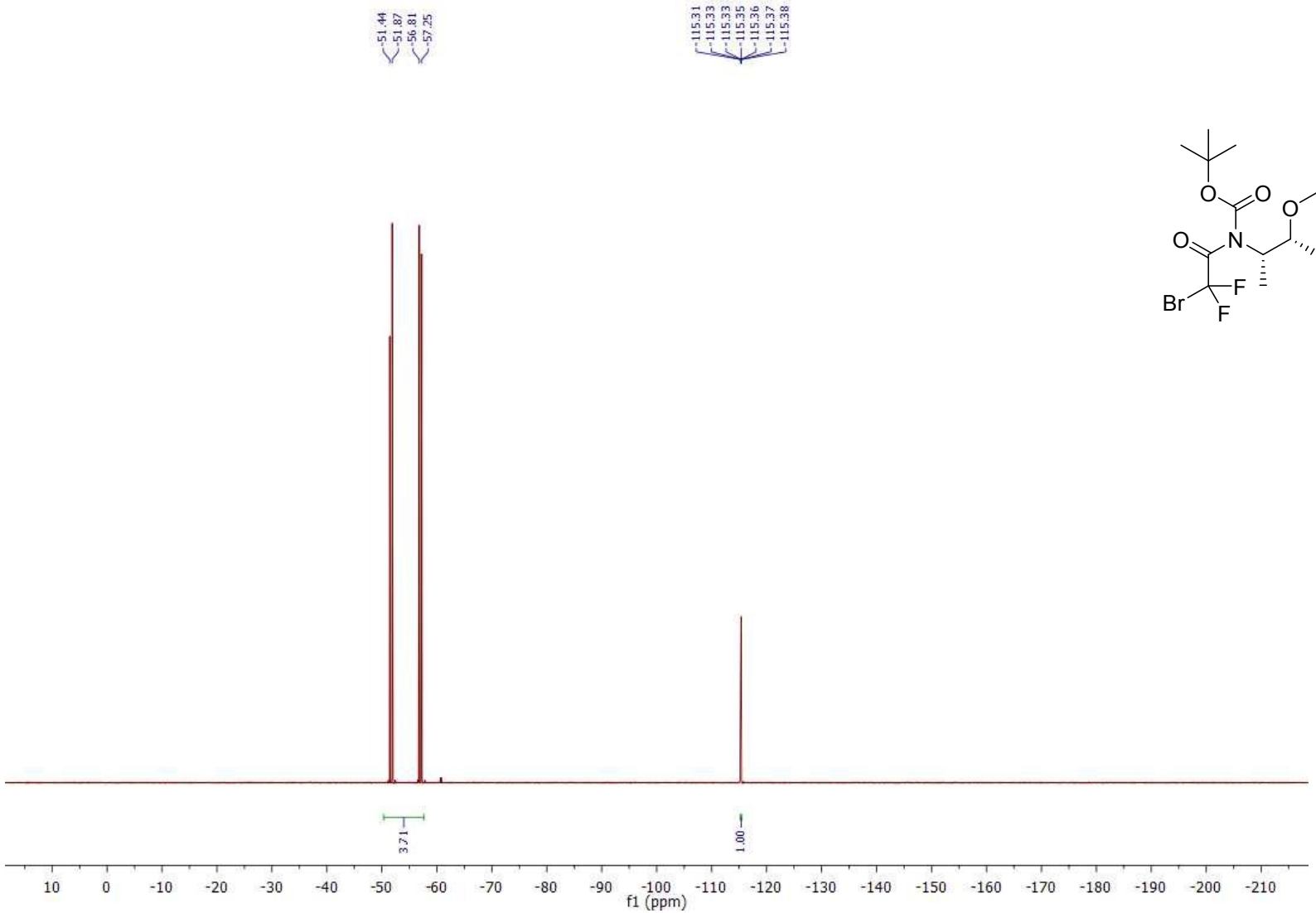
^{13}C NMR ($CDCl_3$, 100 MHz).

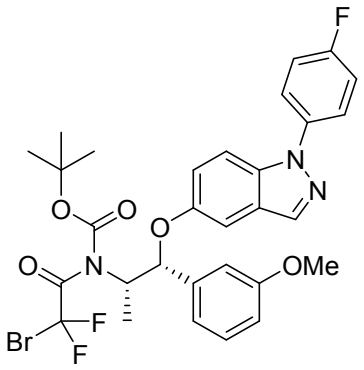
tert-Butyl 2-bromo-2,2-difluoroacetyl((1*R*,2*S*)-1-(1-(4-fluorophenyl)-1*H*-indazol-5-yloxy)-1-(3-methoxyphenyl)propan-2-yl)carbamate (**1u**)



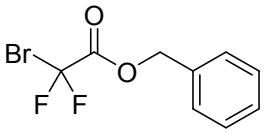
^{19}F NMR ($CDCl_3$, 377 MHz).

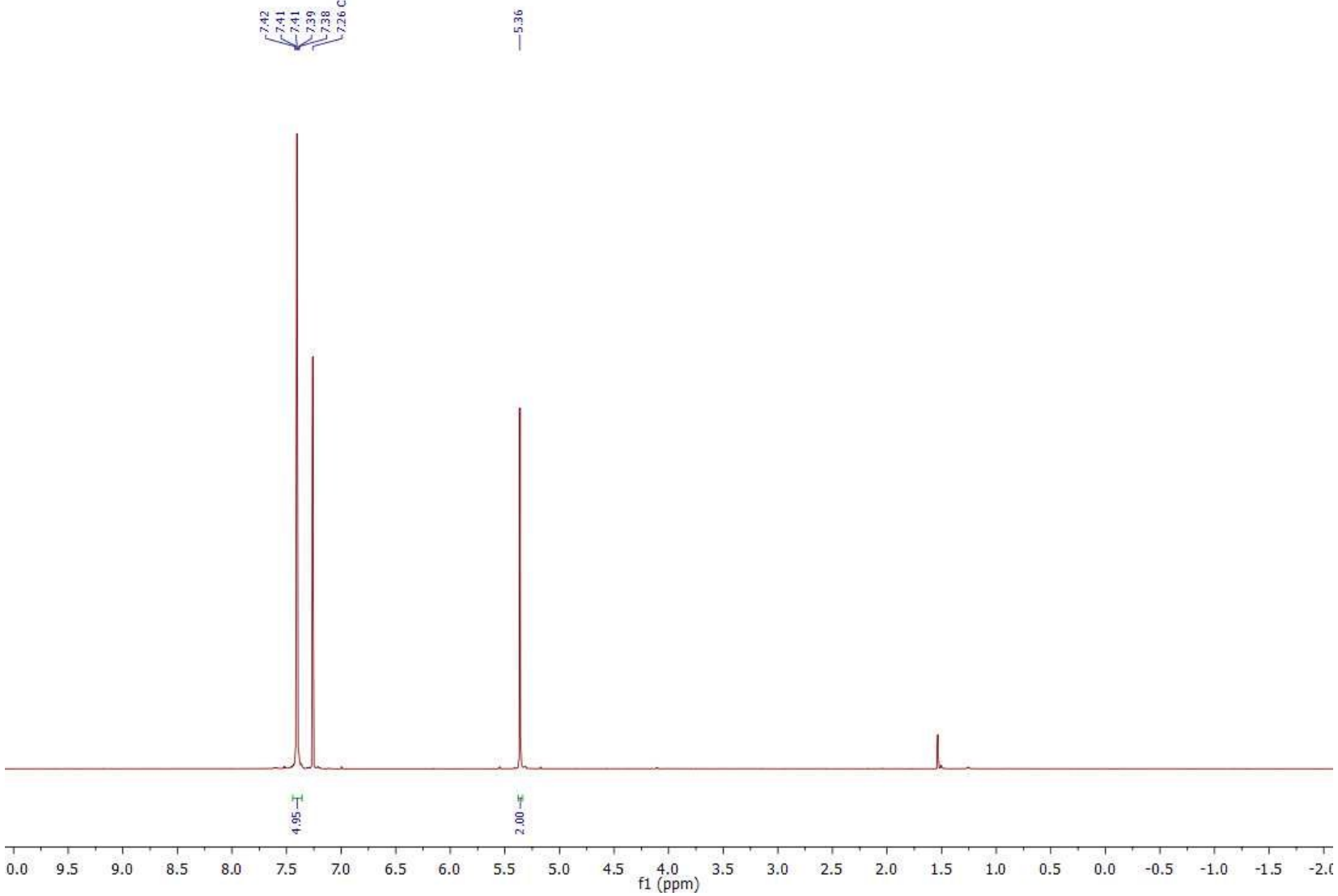
tert-Butyl 2-bromo-2,2-difluoroacetyl((1*R*,2*S*)-1-(1-(4-fluorophenyl)-1*H*-indazol-5-yloxy)-1-(3-methoxyphenyl)propan-2-yl)carbamate (**1u**)



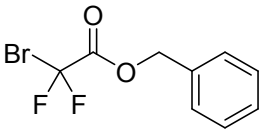


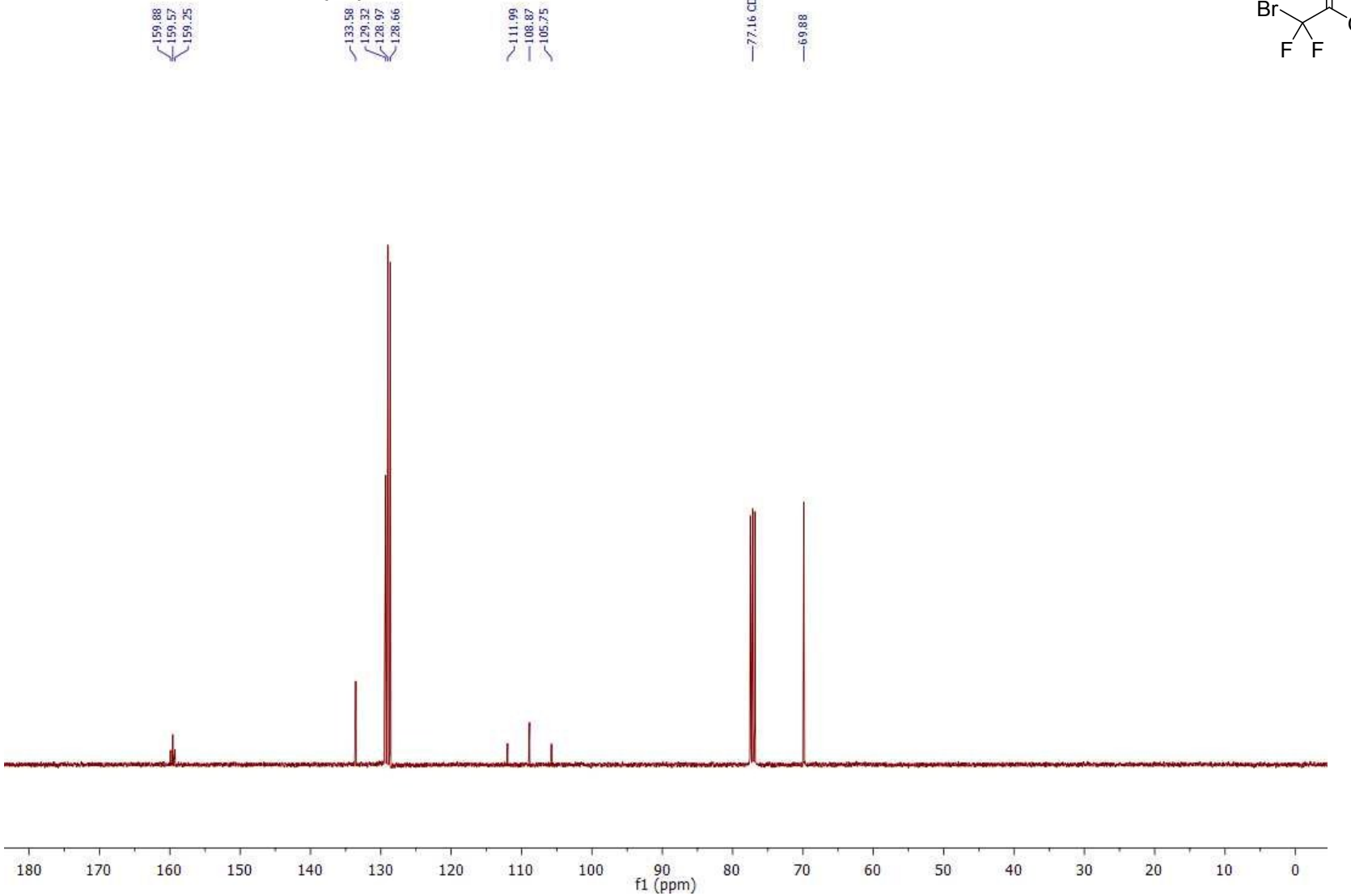
^{1}H NMR ($CDCl_3$, 400 MHz).
Benzyl 2-bromo-2,2-difluoroacetate (**3a**)



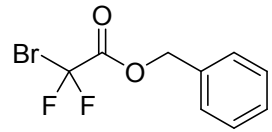


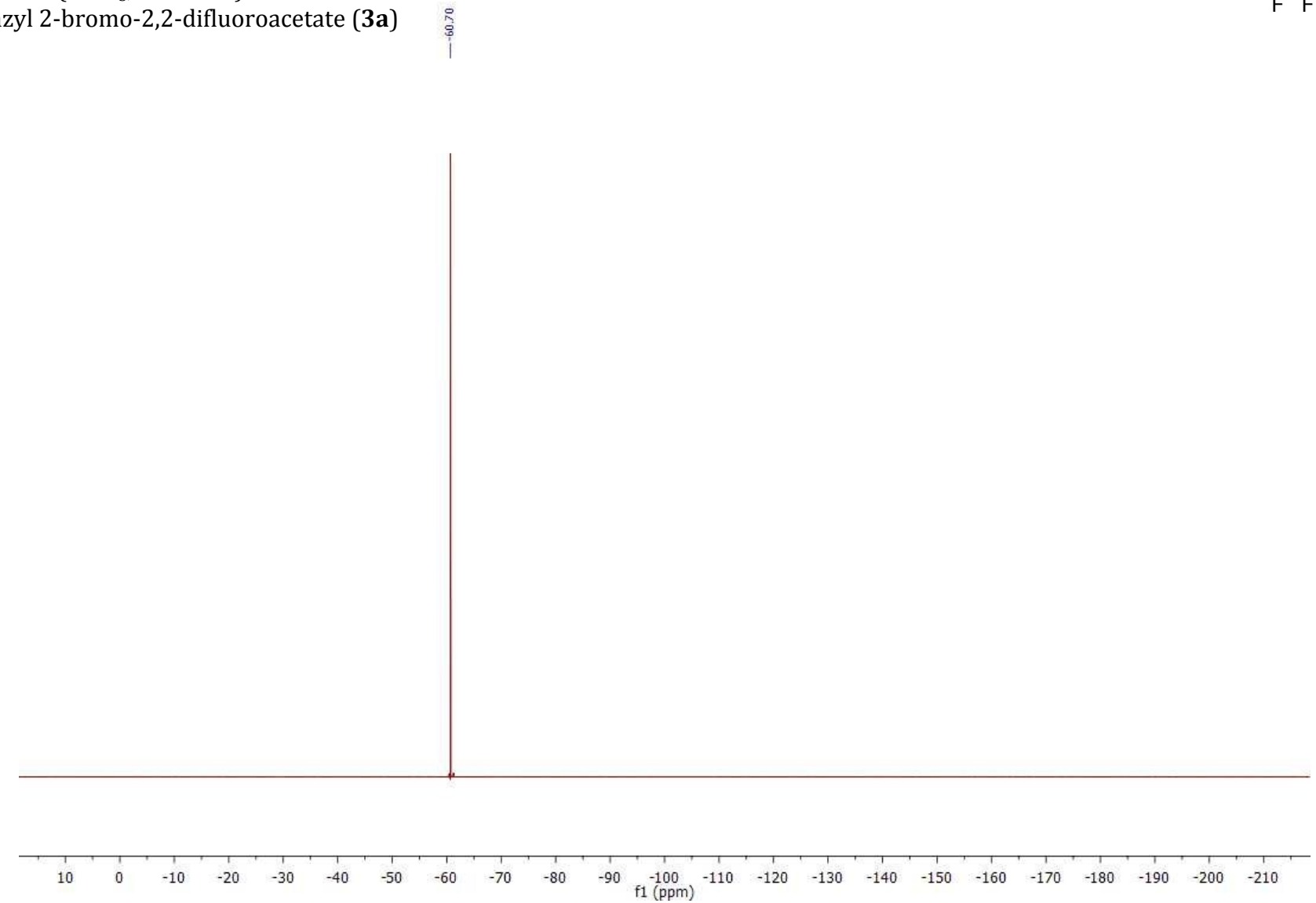
^{13}C NMR ($CDCl_3$, 100 MHz).
Benzyl 2-bromo-2,2-difluoroacetate (**3a**)



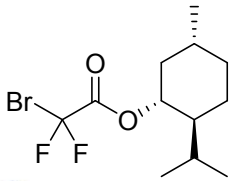


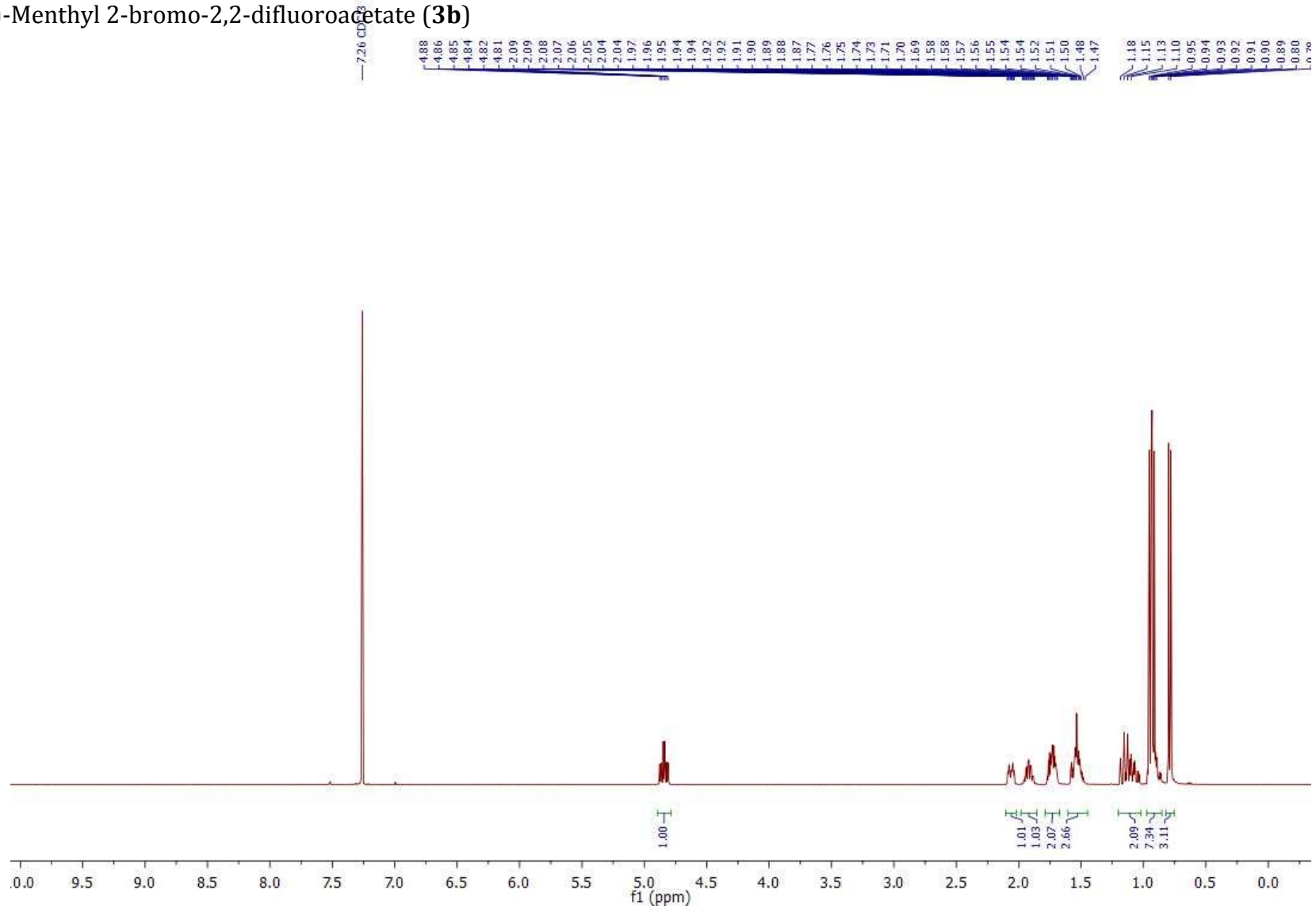
^{19}F NMR ($CDCl_3$, 377 MHz).
Benzyl 2-bromo-2,2-difluoroacetate (**3a**)



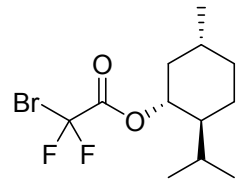


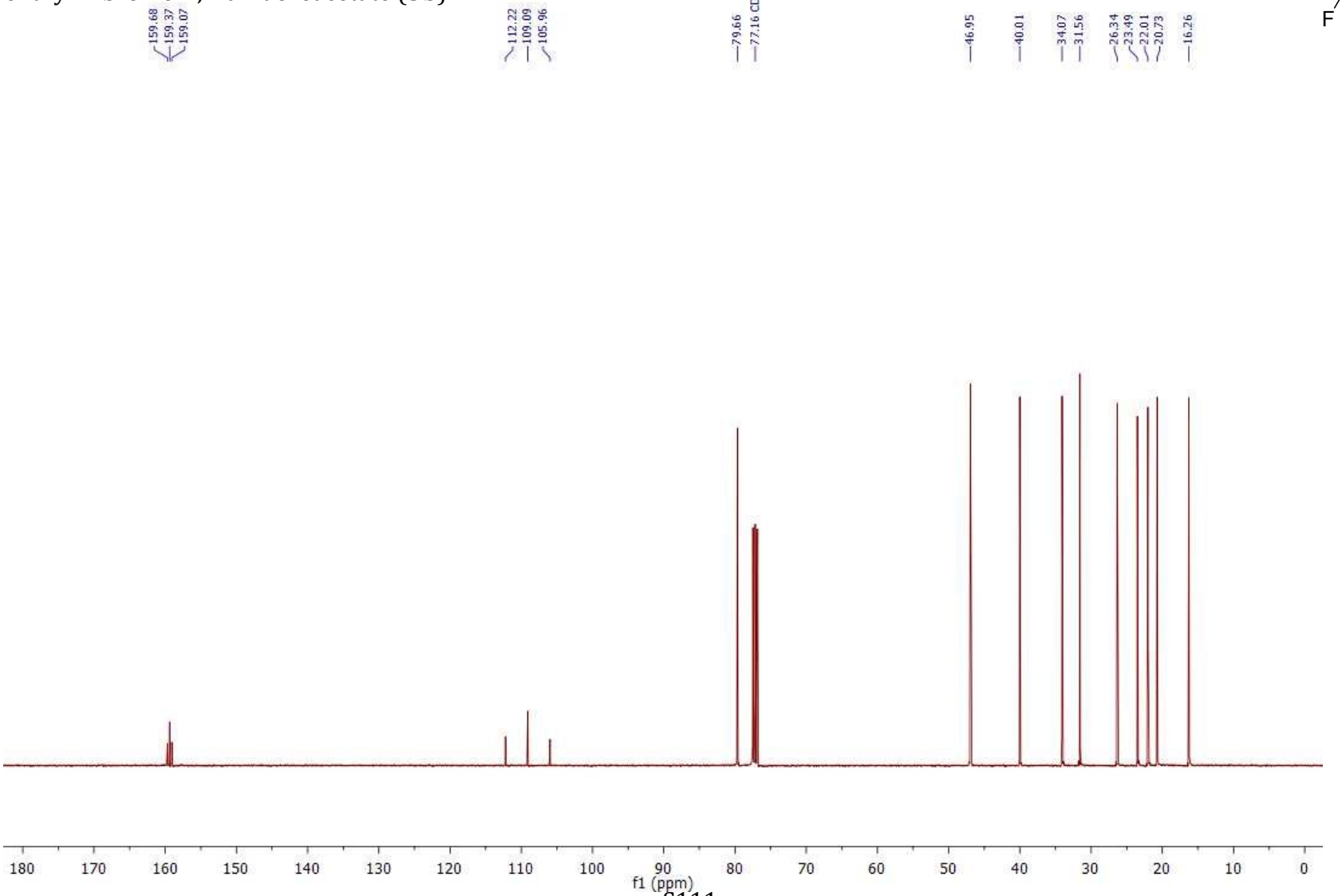
^{1}H NMR ($CDCl_3$, 400 MHz).
(-)-Menthyl 2-bromo-2,2-difluoroacetate (**3b**)



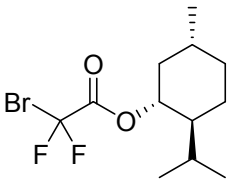


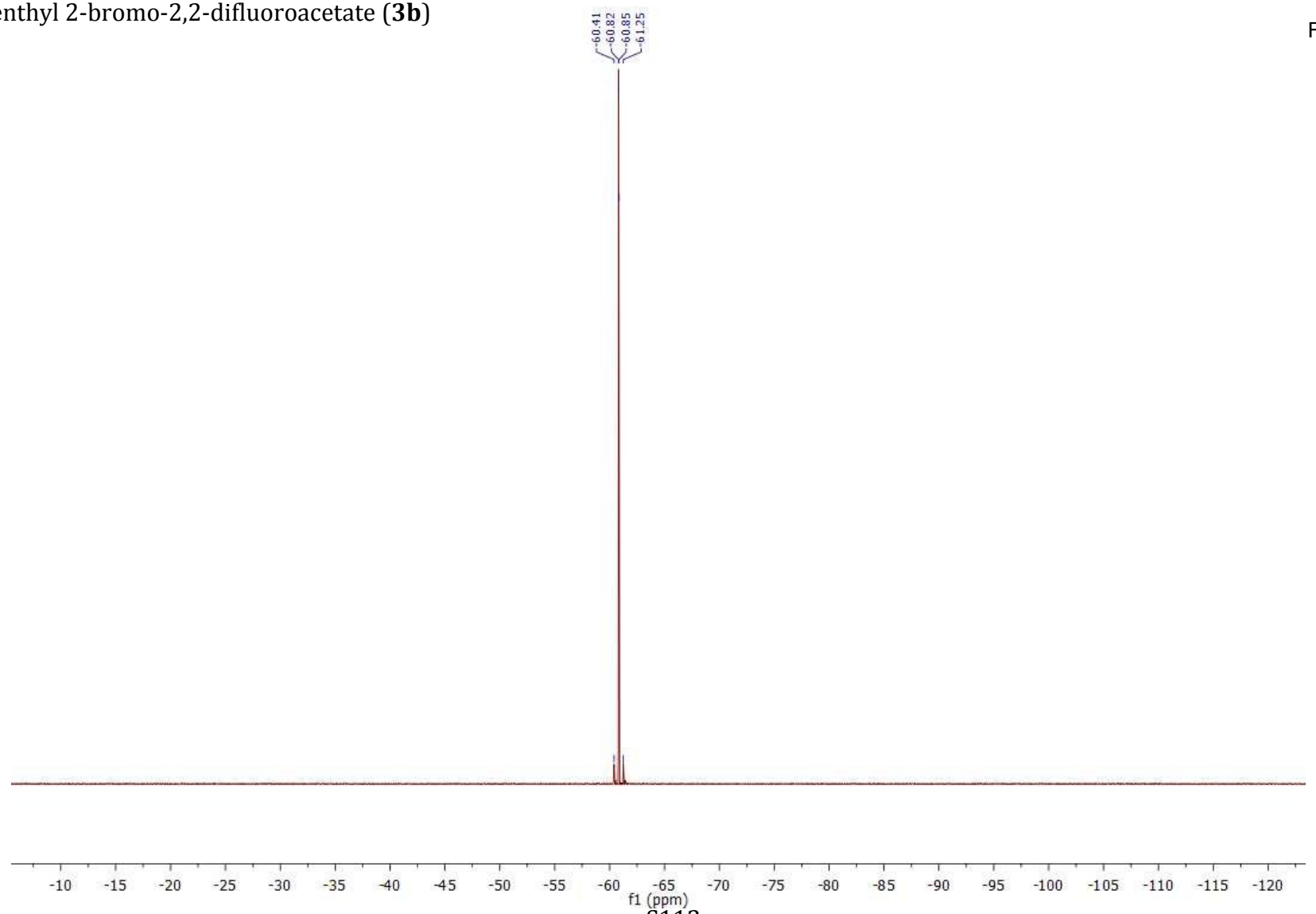
^{13}C NMR ($CDCl_3$, 100 MHz).
(-)-Menthyl 2-bromo-2,2-difluoroacetate (**3b**)



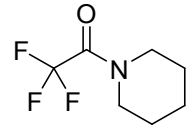


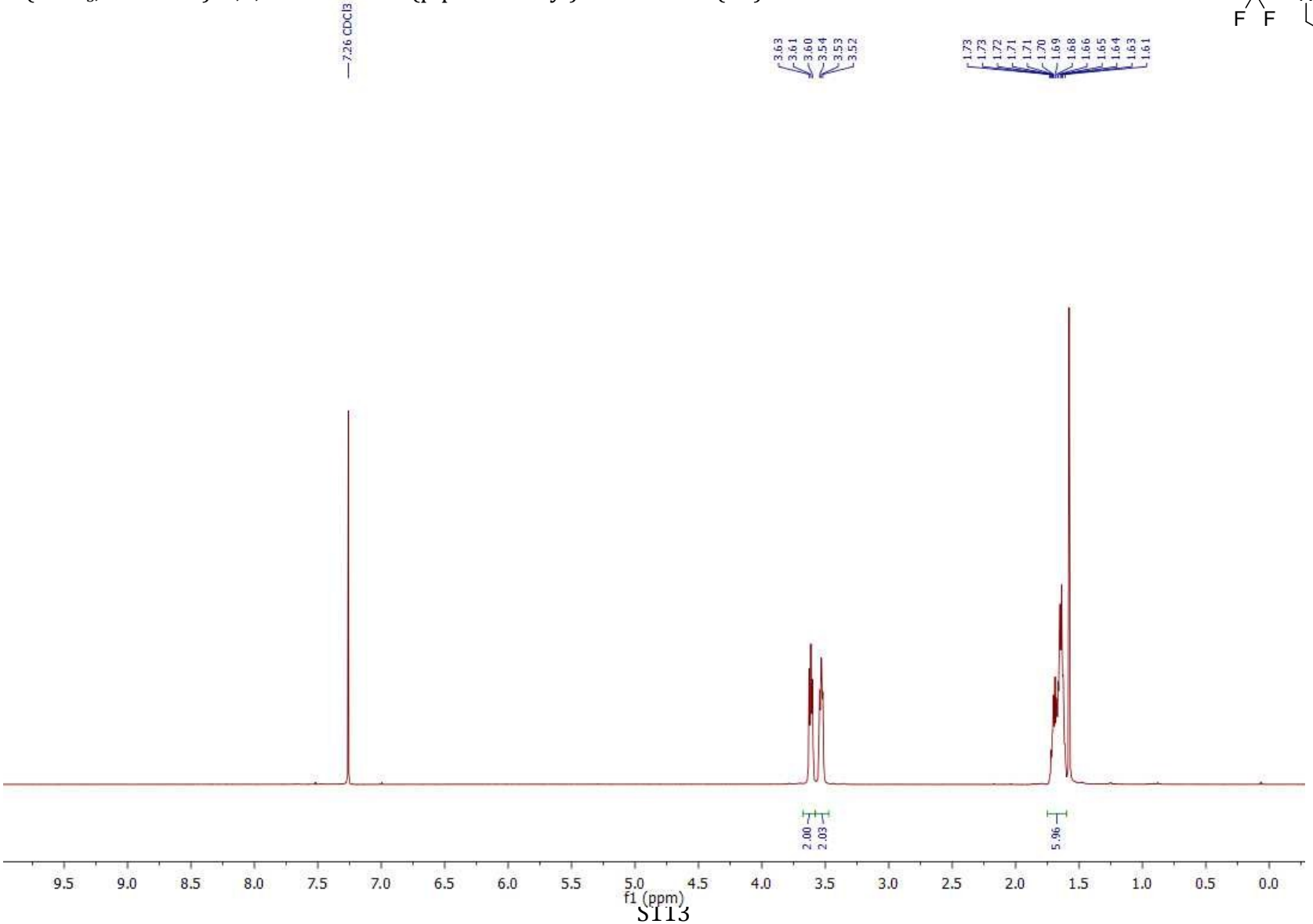
^{19}F NMR ($CDCl_3$, 377 MHz).
(-)-Menthyl 2-bromo-2,2-difluoroacetate (**3b**)



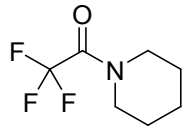


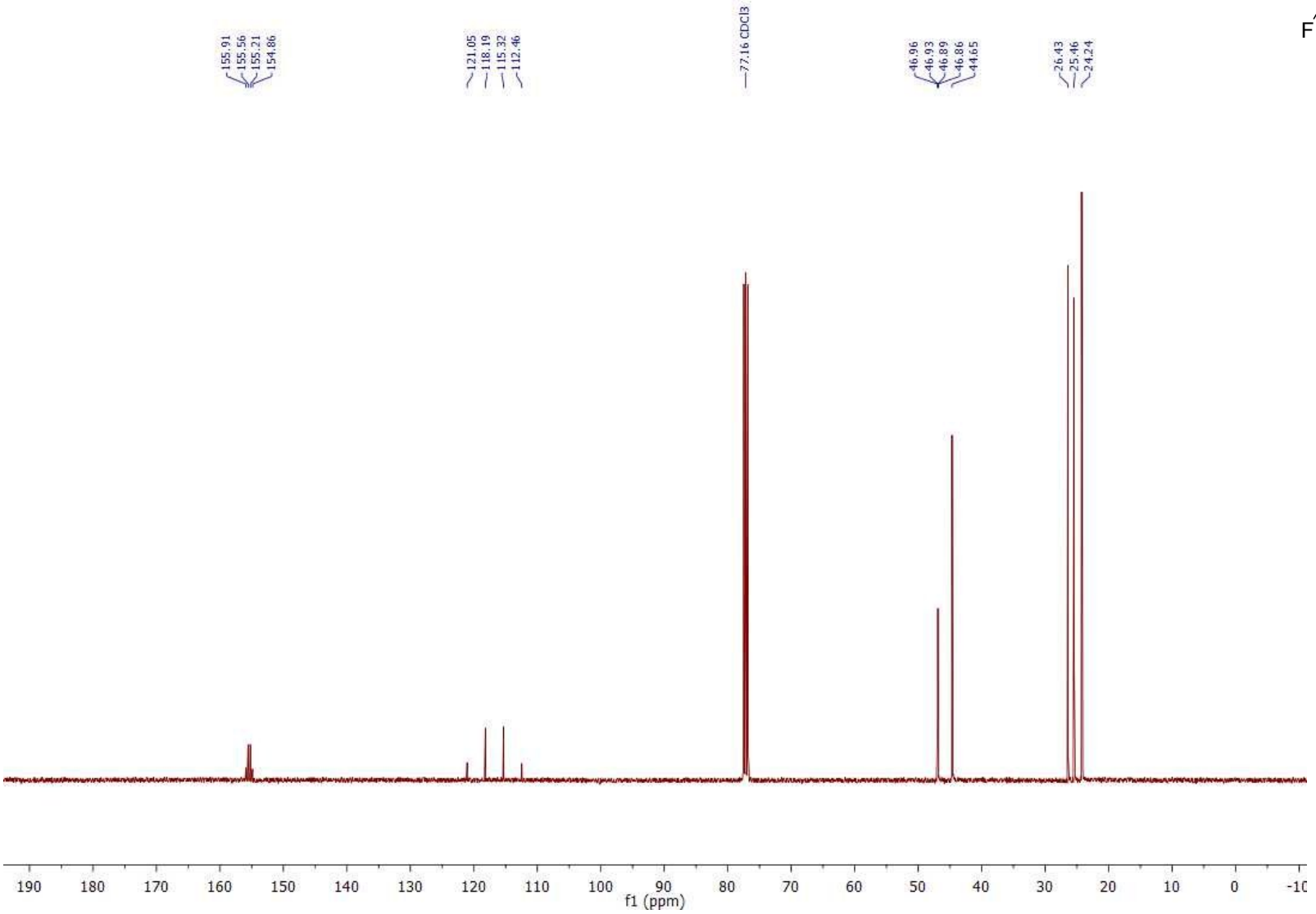
^{1}H NMR ($CDCl_3$, 400 MHz). 2,2,2-Trifluoro-1-(piperidin-1-yl)ethan-1-one (**2a**)



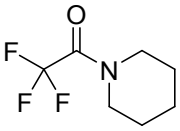


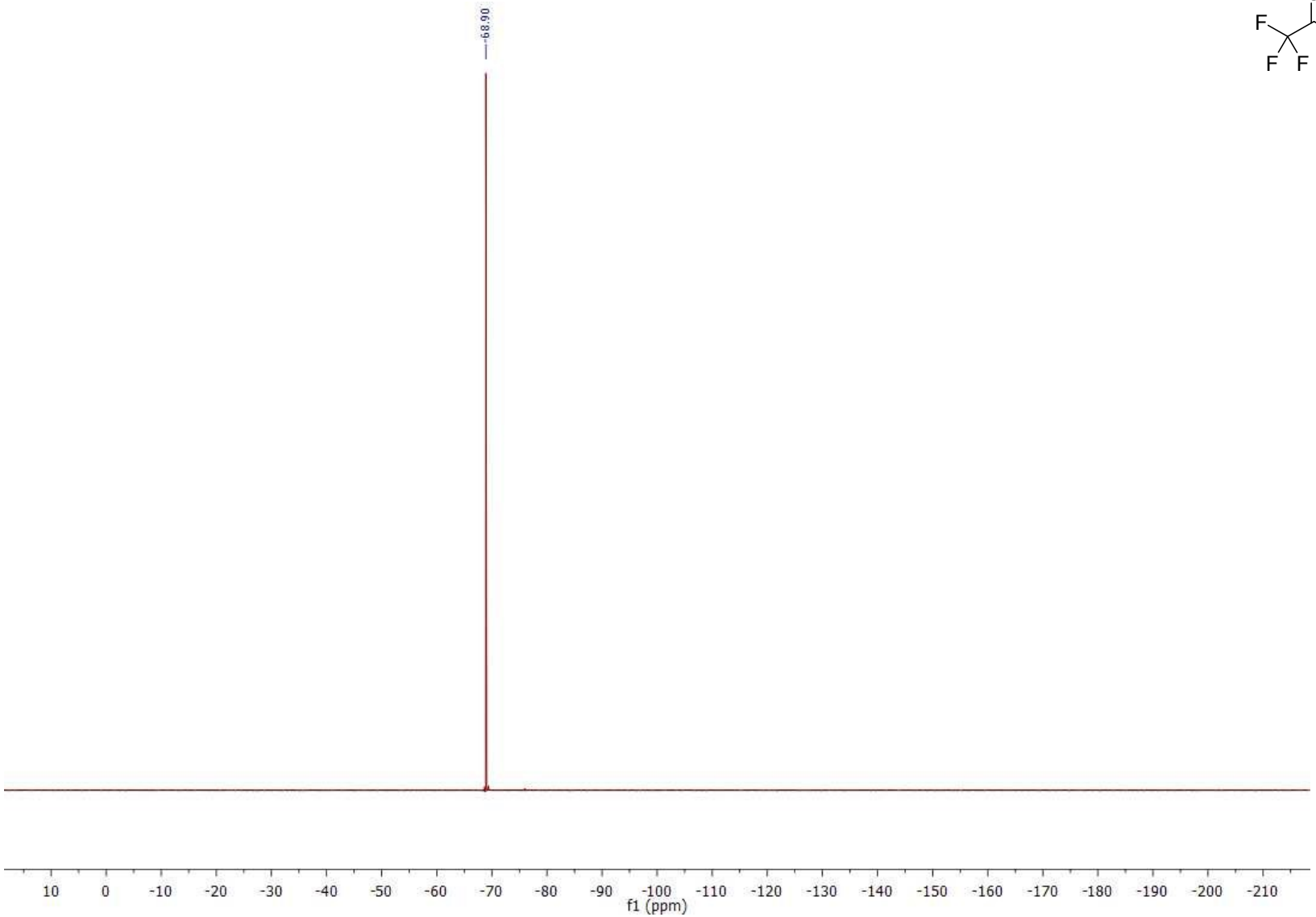
^{13}C NMR ($CDCl_3$, 100 MHz). 2,2,2-Trifluoro-1-(piperidin-1-yl)ethan-1-one (**2a**)



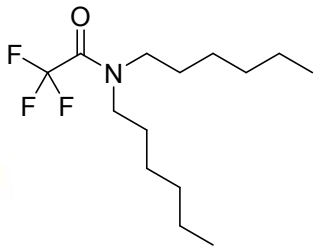


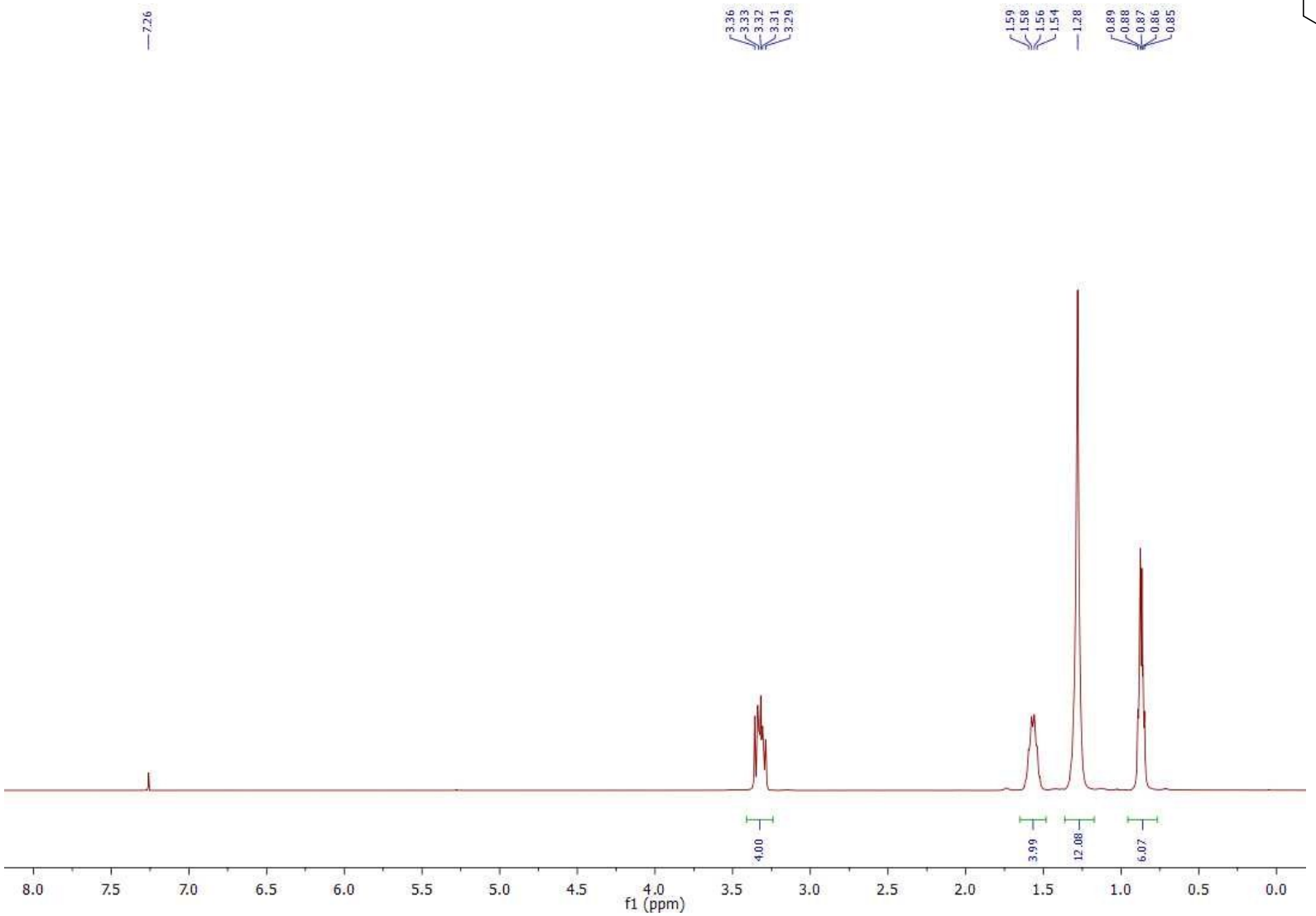
^{19}F NMR ($CDCl_3$, 377 MHz). 2,2,2-Trifluoro-1-(piperidin-1-yl)ethan-1-one (**2a**)



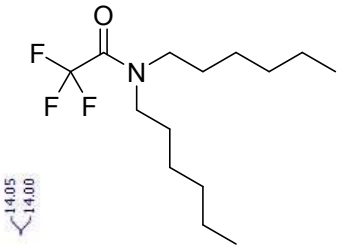


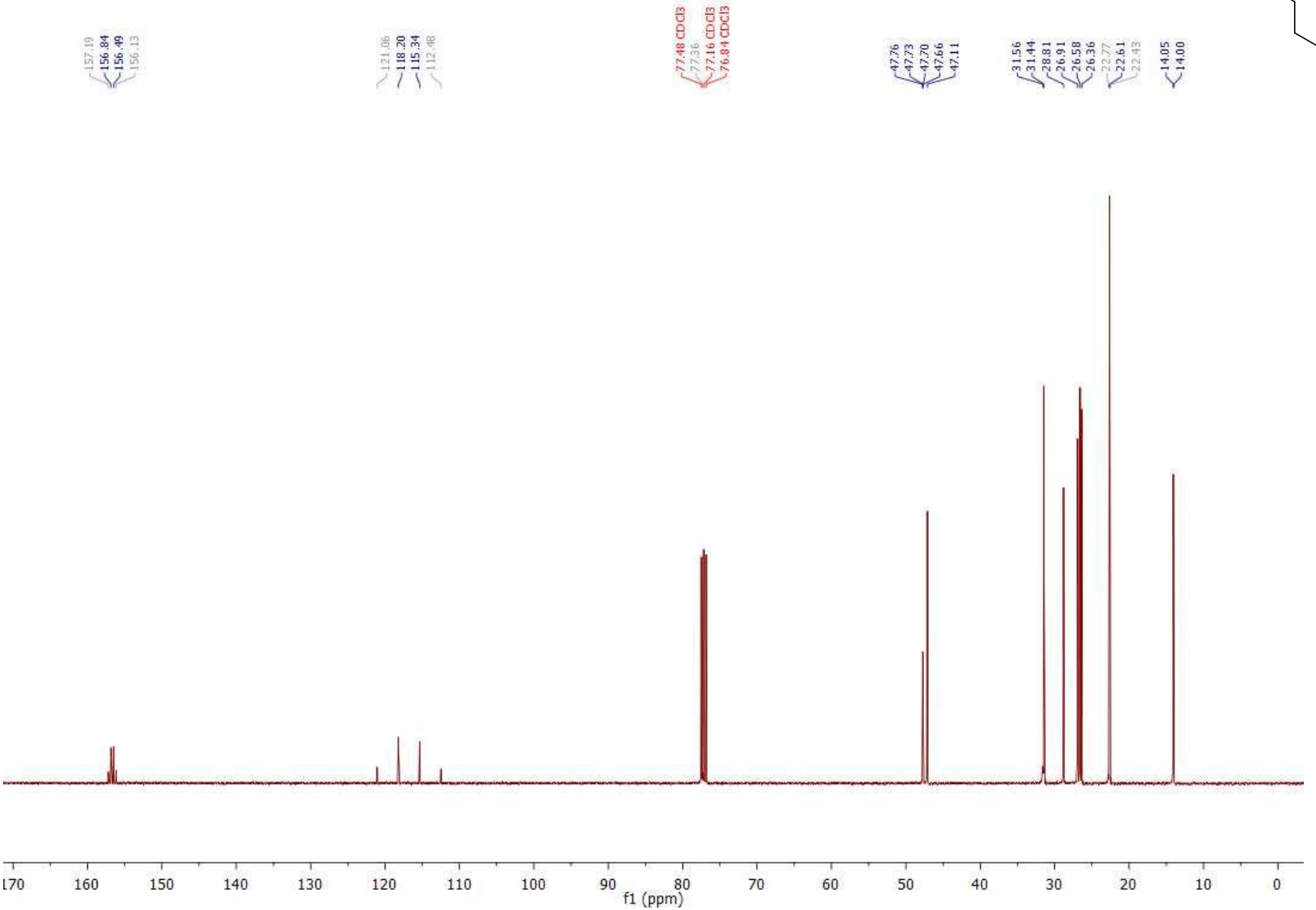
^{1}H NMR ($CDCl_3$, 400 MHz). 2,2,2-Trifluoro-*N*,*N*-dihexylacetamide (**2b**)



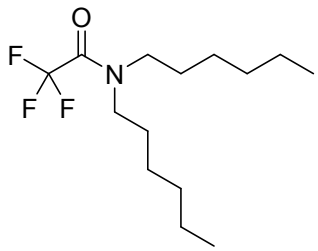


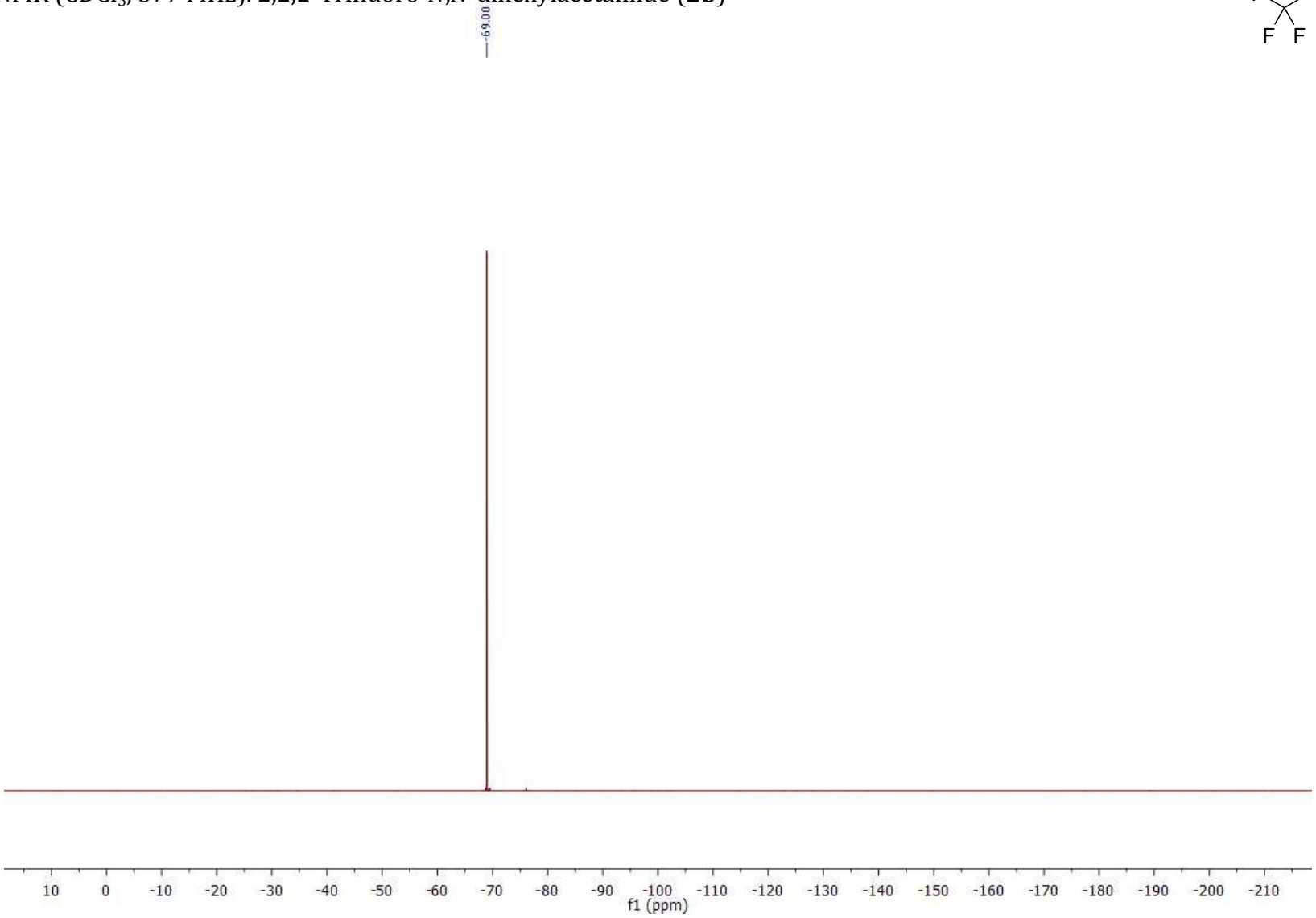
^{13}C NMR ($CDCl_3$, 100 MHz). 2,2,2-Trifluoro-*N*,*N*-dihexylacetamide (**2b**)



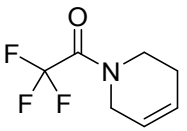


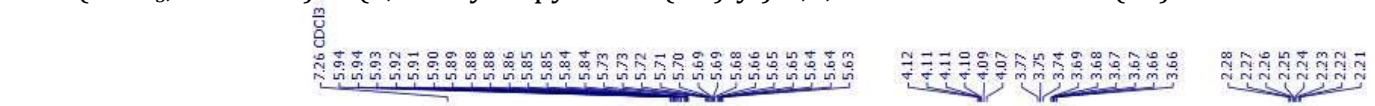
^{19}F NMR ($CDCl_3$, 377 MHz). 2,2,2-Trifluoro-*N*,*N*-dihexylacetamide (**2b**)

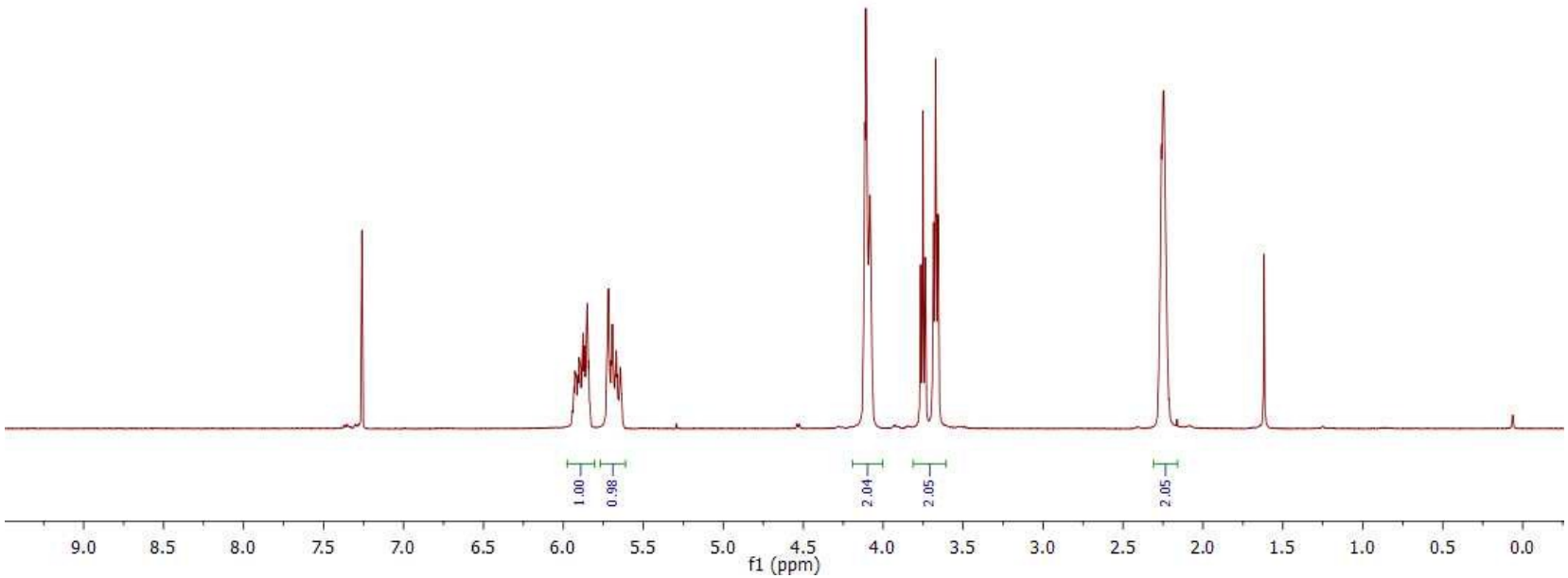




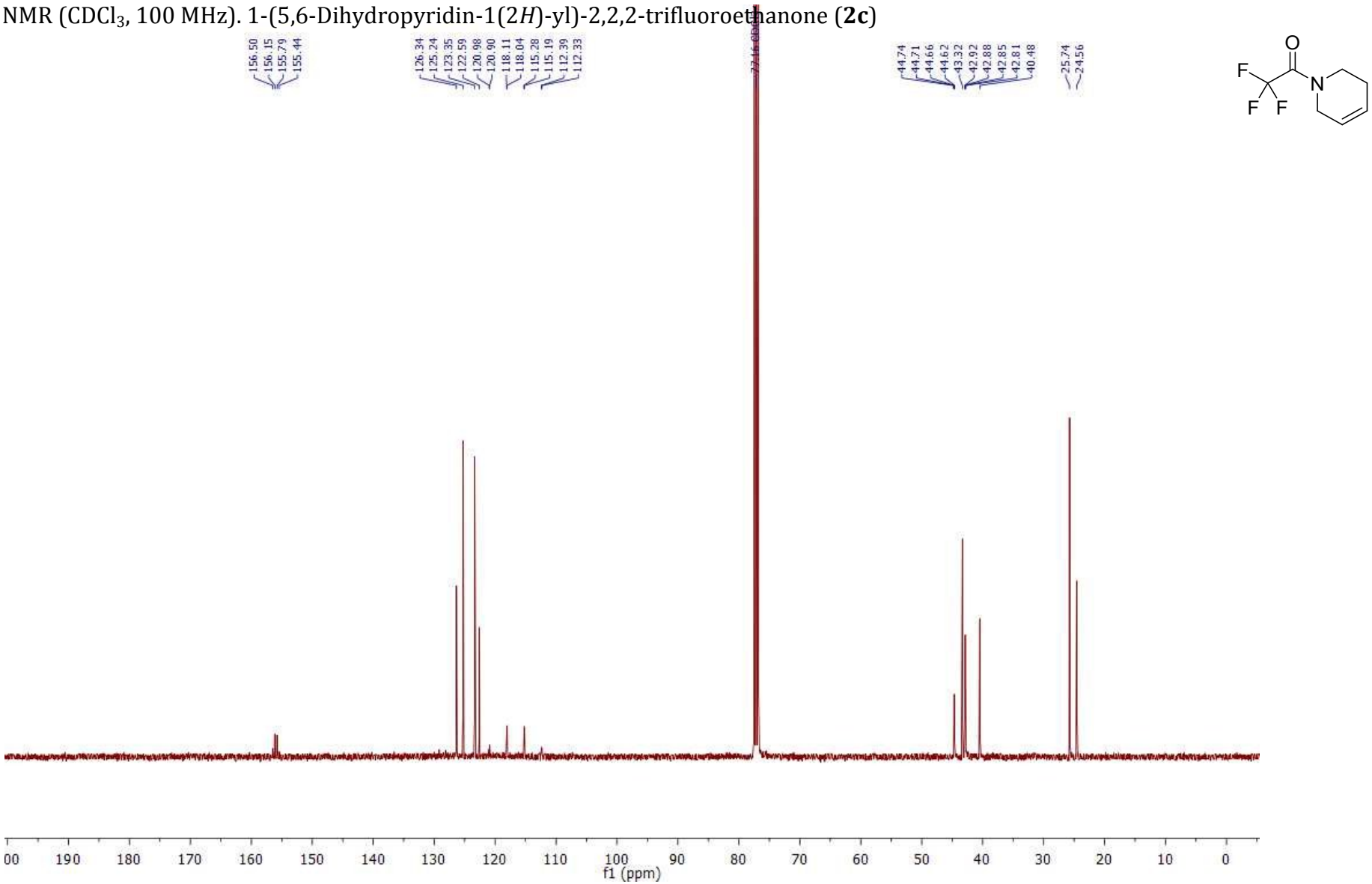
^{1}H NMR ($CDCl_3$, 400 MHz). 1-(5,6-Dihydropyridin-1(2*H*)-yl)-2,2,2-trifluoroethanone (**2c**)



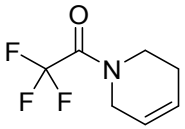


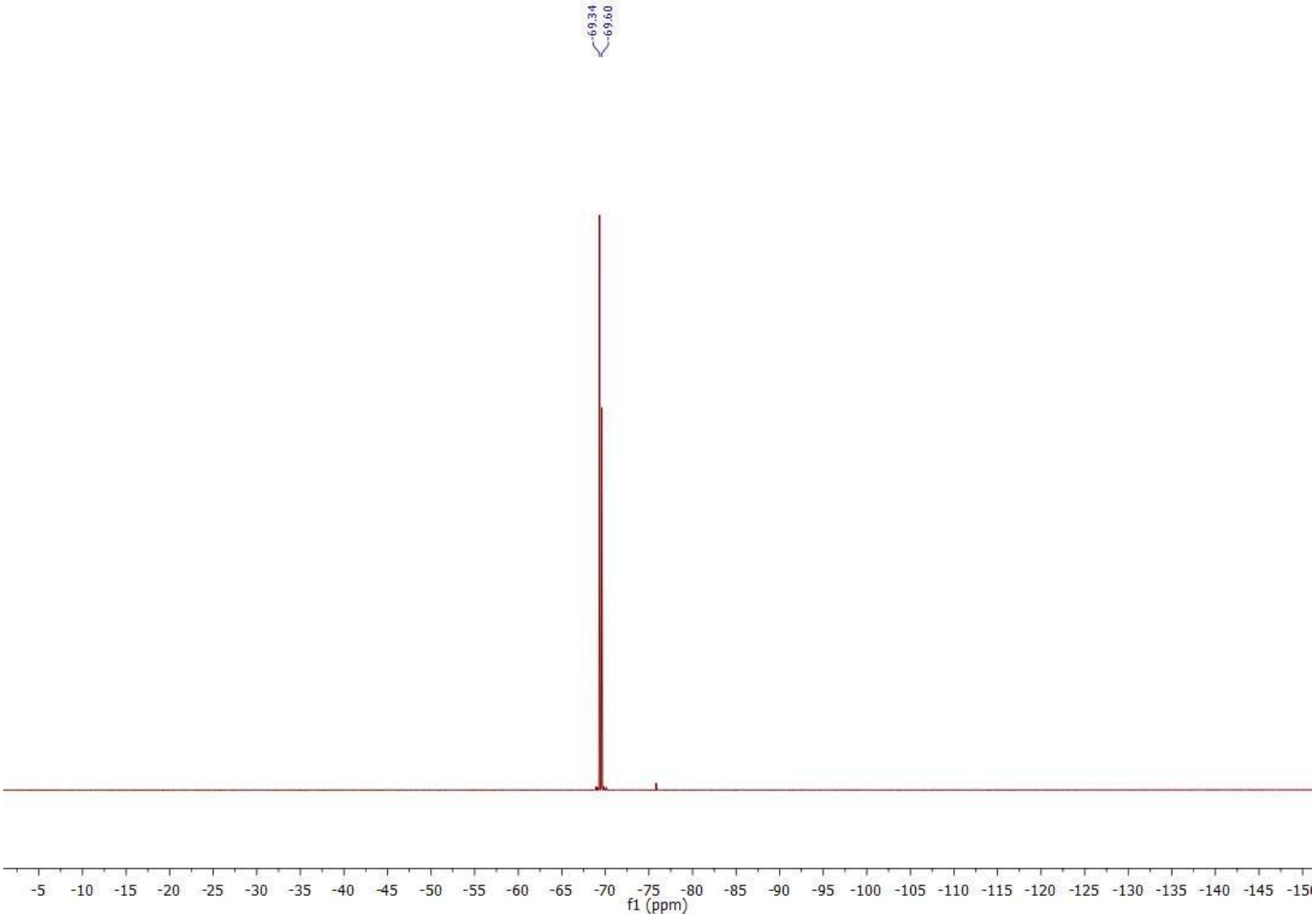


^{13}C NMR ($CDCl_3$, 100 MHz). 1-(5,6-Dihydropyridin-1(2*H*)-yl)-2,2,2-trifluoroethanone (**2c**)

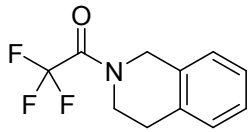


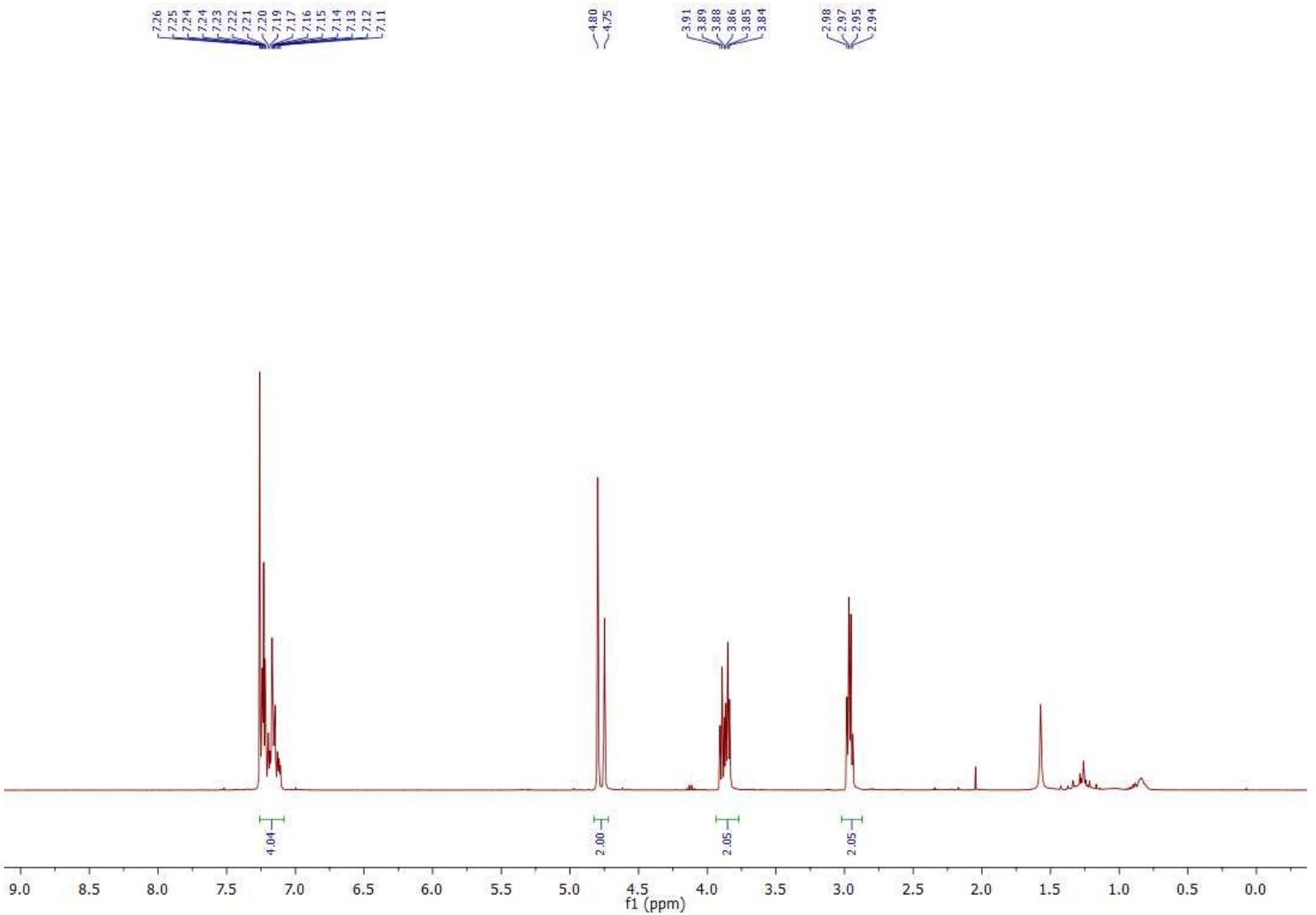
^{19}F NMR ($CDCl_3$, 377 MHz). 1-(5,6-Dihydropyridin-1(2*H*)-yl)-2,2,2-trifluoroethanone (**2c**)



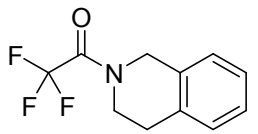


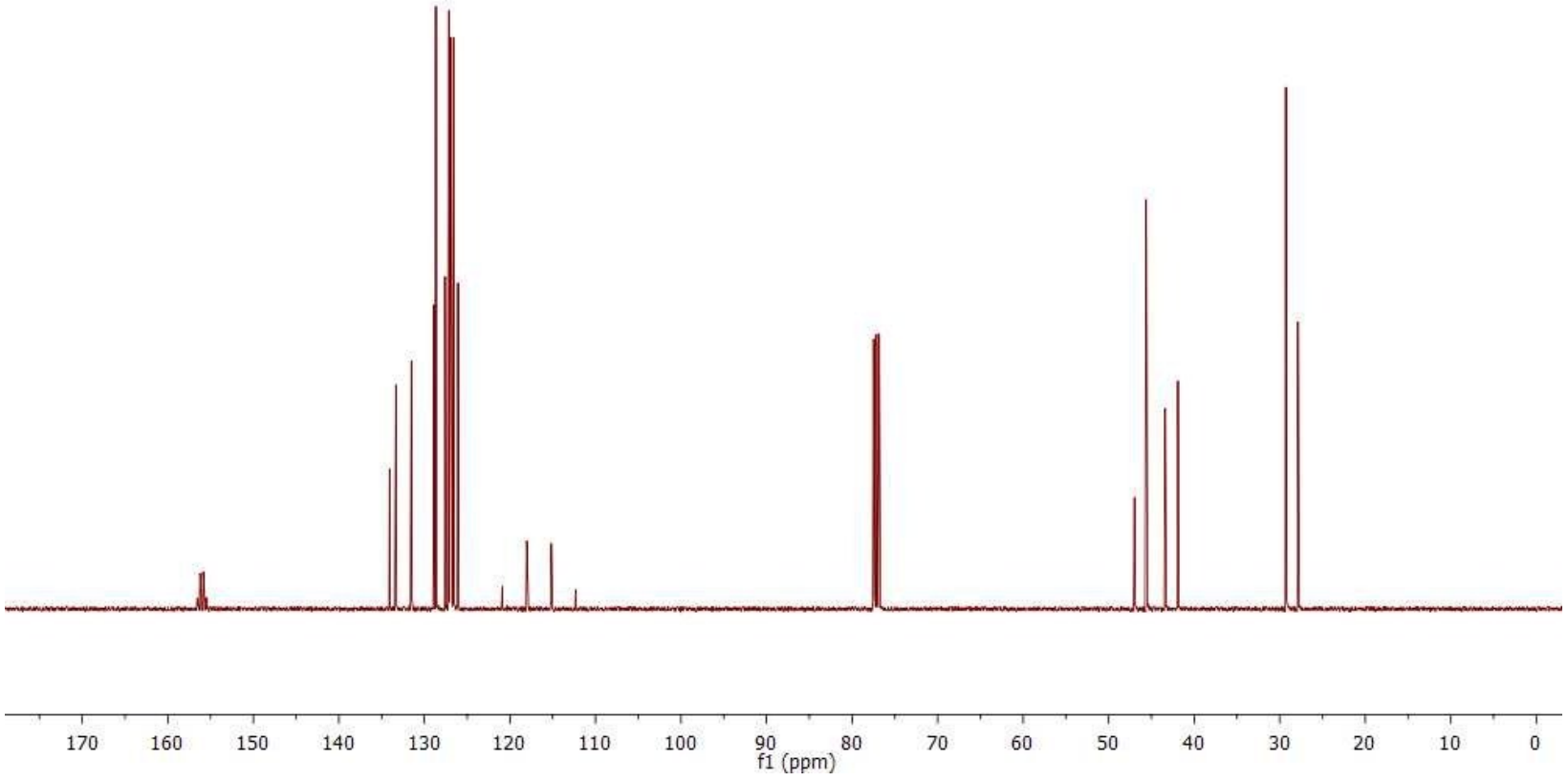
^{1}H NMR ($CDCl_3$, 400 MHz). 1-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-2,2,2-trifluoroethan-1-one (**2d**)



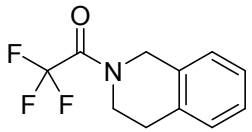


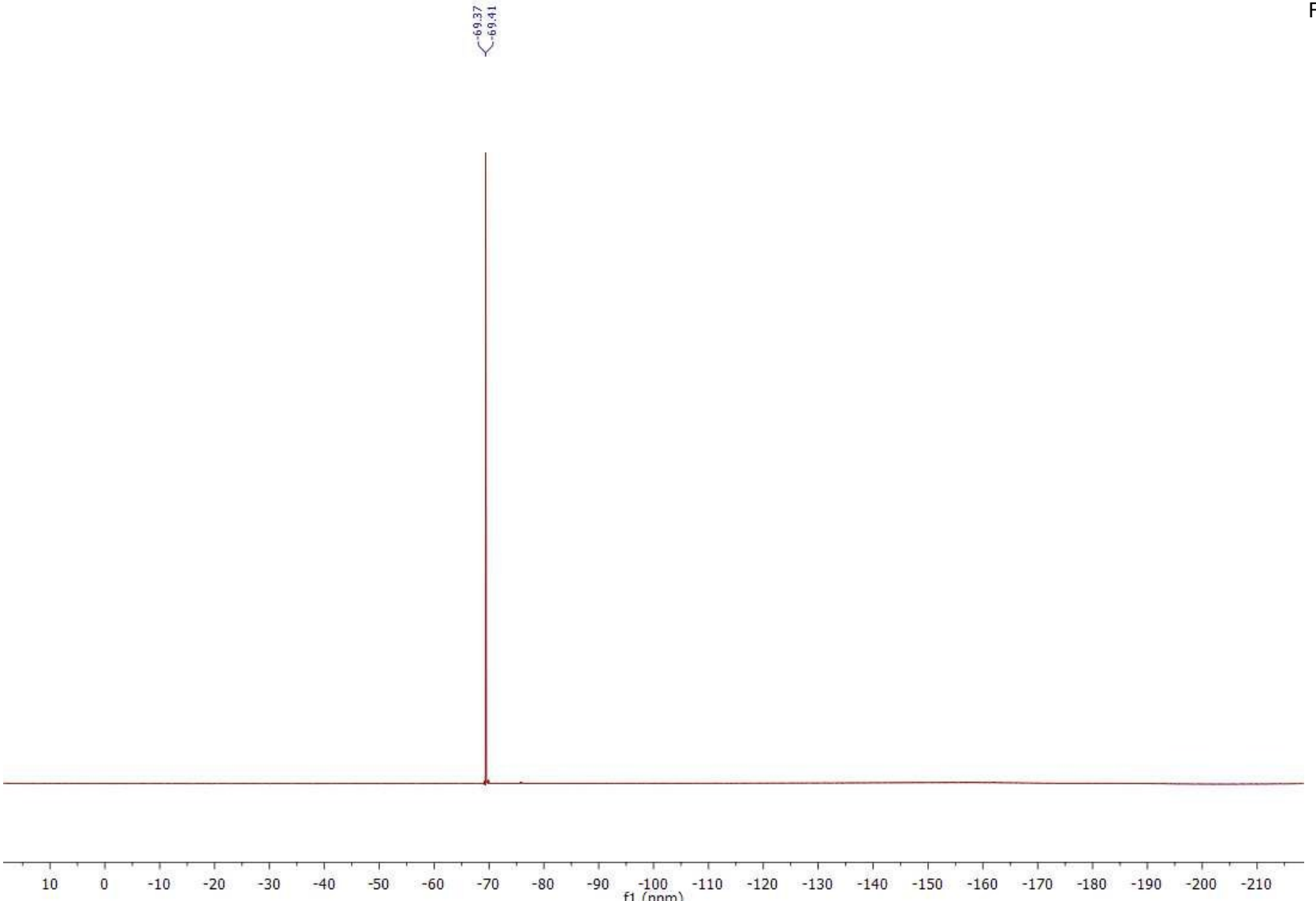
^{13}C NMR ($CDCl_3$, 100 MHz). 1-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-2,2,2-trifluoroethan-1-one (**2d**)



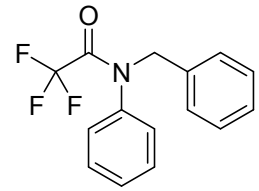


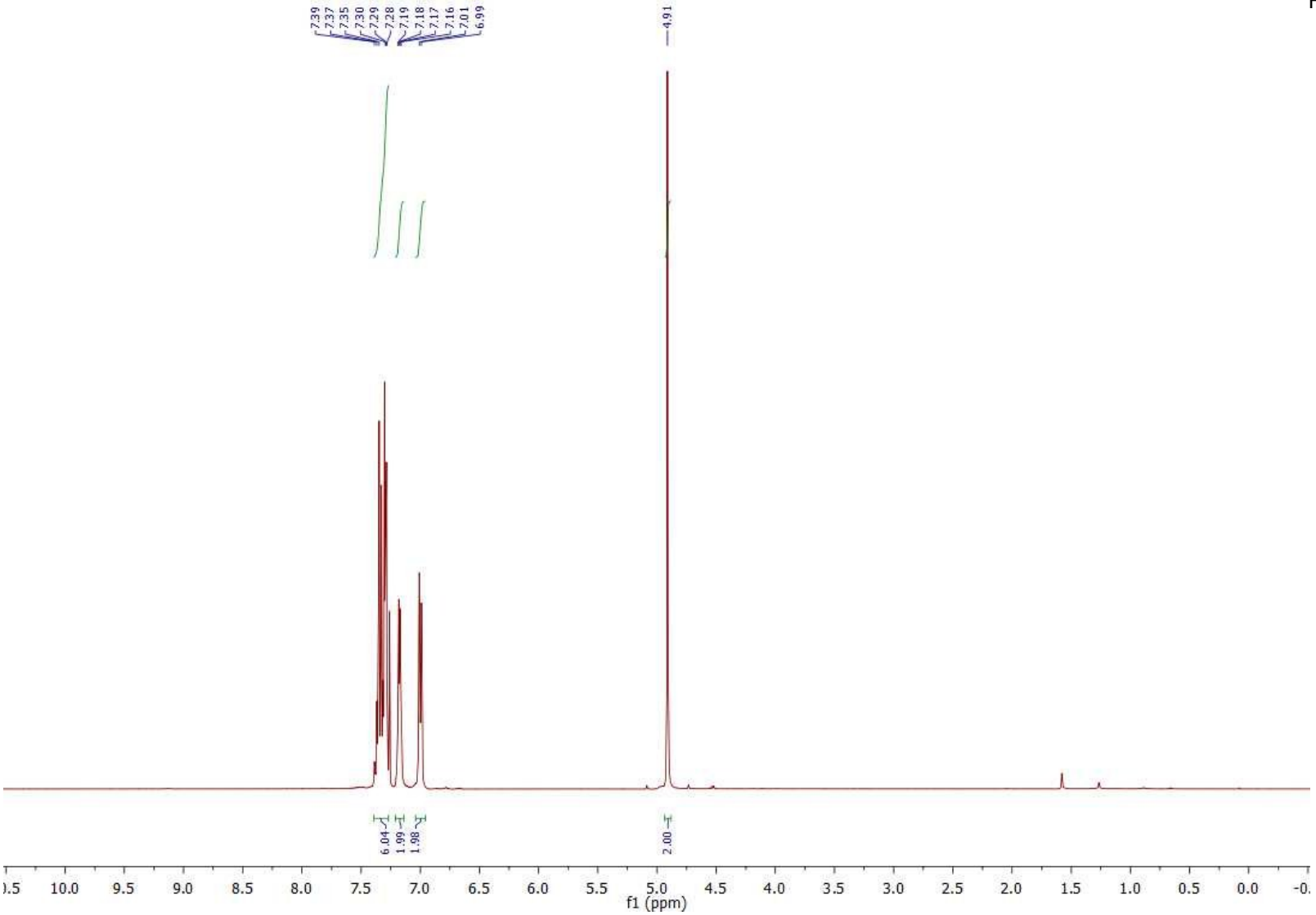
^{19}F NMR ($CDCl_3$, 377 MHz). 1-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-2,2,2-trifluoroethan-1-one (**2d**)



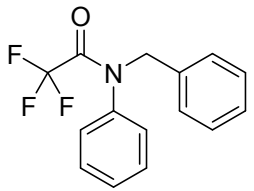


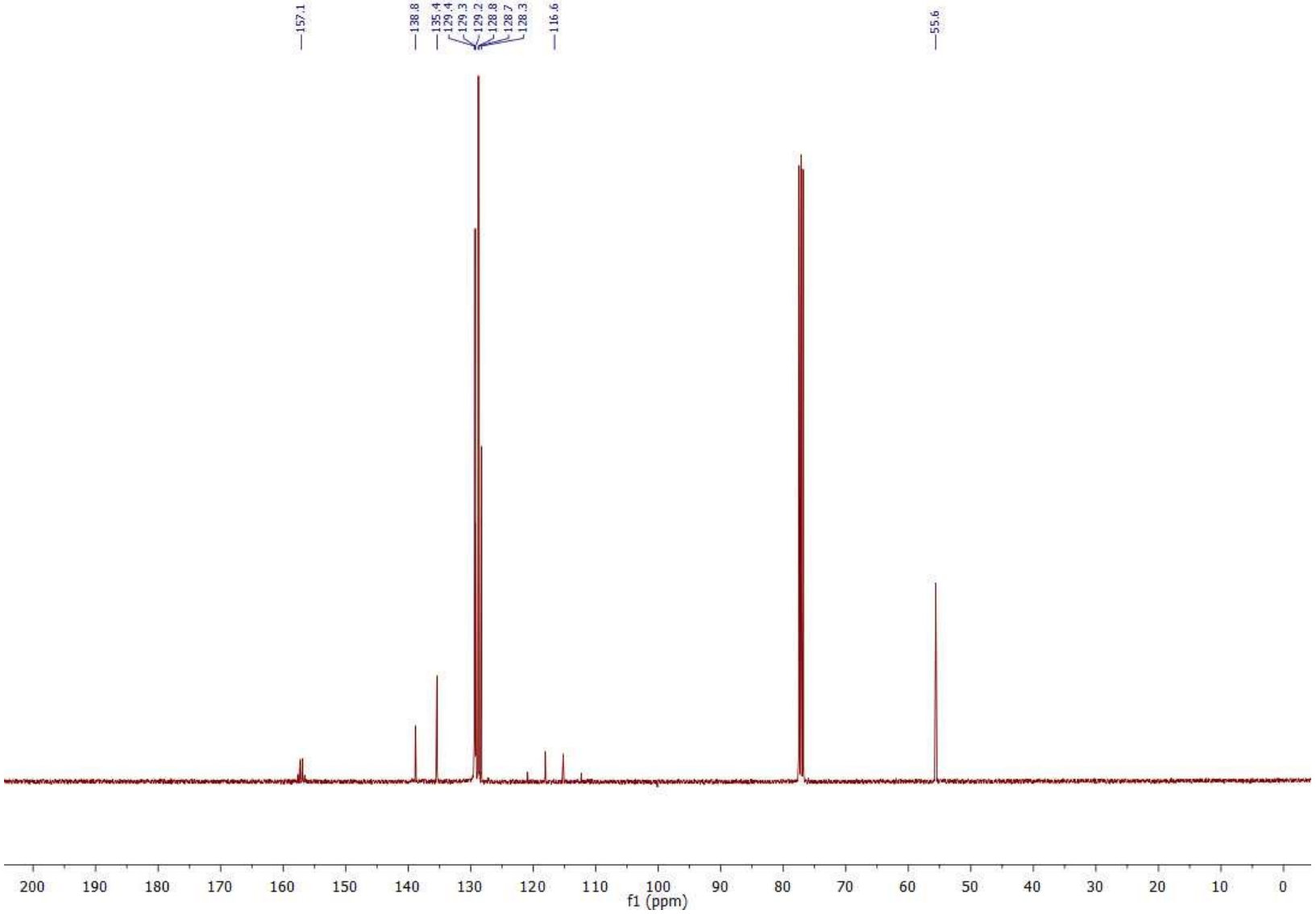
^{1}H NMR ($CDCl_3$, 400 MHz). *N*-benzyl-2,2,2-trifluoro-*N*-phenylacetamide (**2e**)



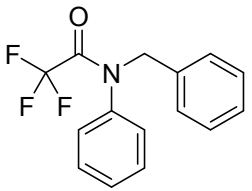


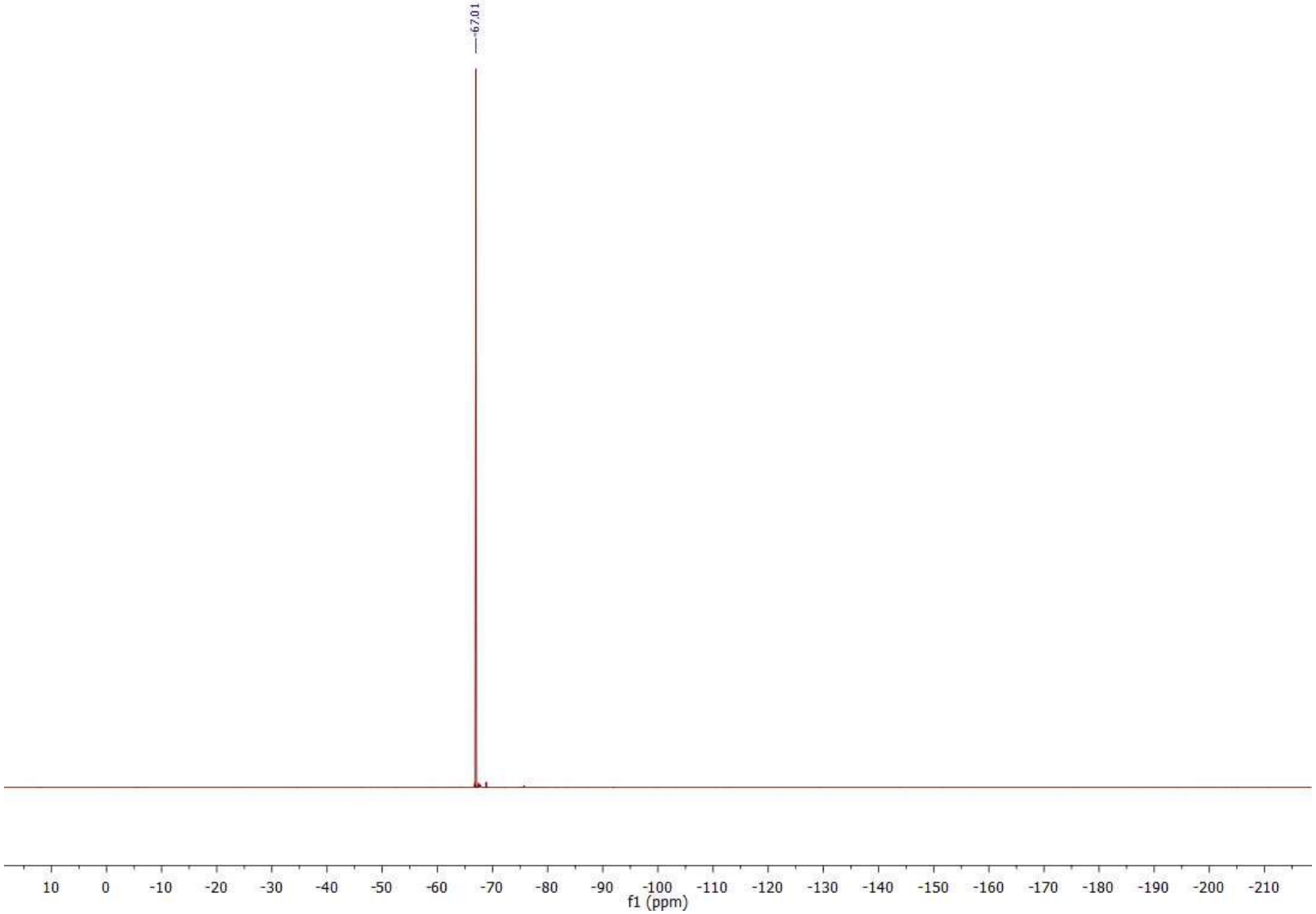
^{13}C NMR ($CDCl_3$, 100 MHz). *N*-benzyl-2,2,2-trifluoro-*N*-phenylacetamide (**2e**)



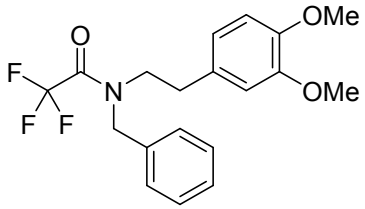


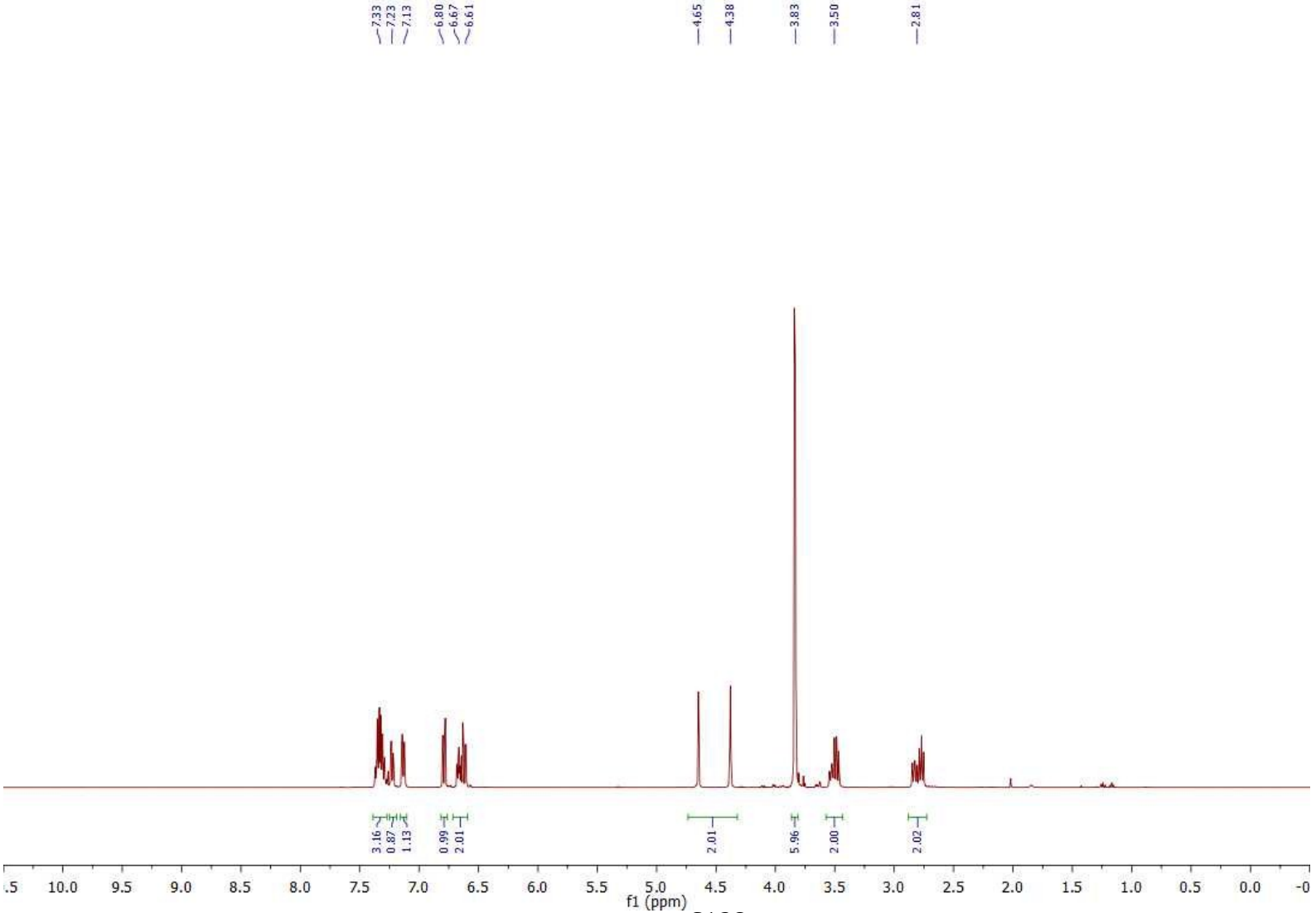
^{19}F NMR ($CDCl_3$, 377 MHz). *N*-benzyl-2,2,2-difluoro-*N*-phenylacetamide (**2e**)



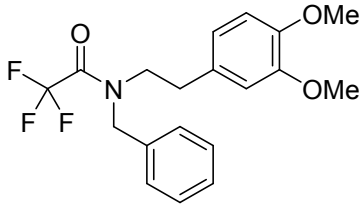


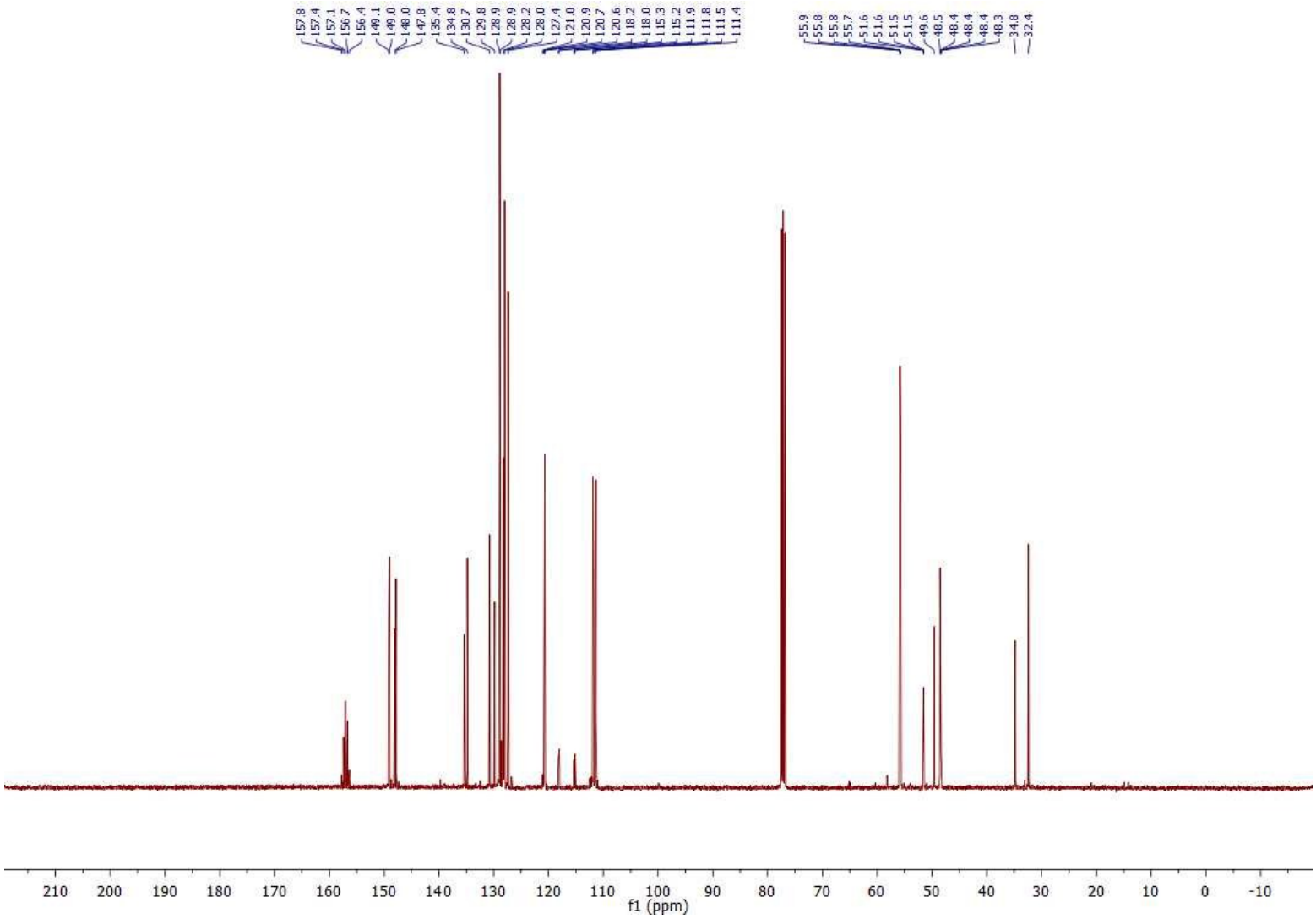
^{1}H NMR ($CDCl_3$, 400 MHz). *N*-Benzyl-*N*-(3,4-dimethoxyphenethyl)-2,2,2-trifluoroacetamide (**2f**)



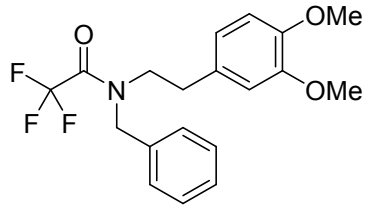


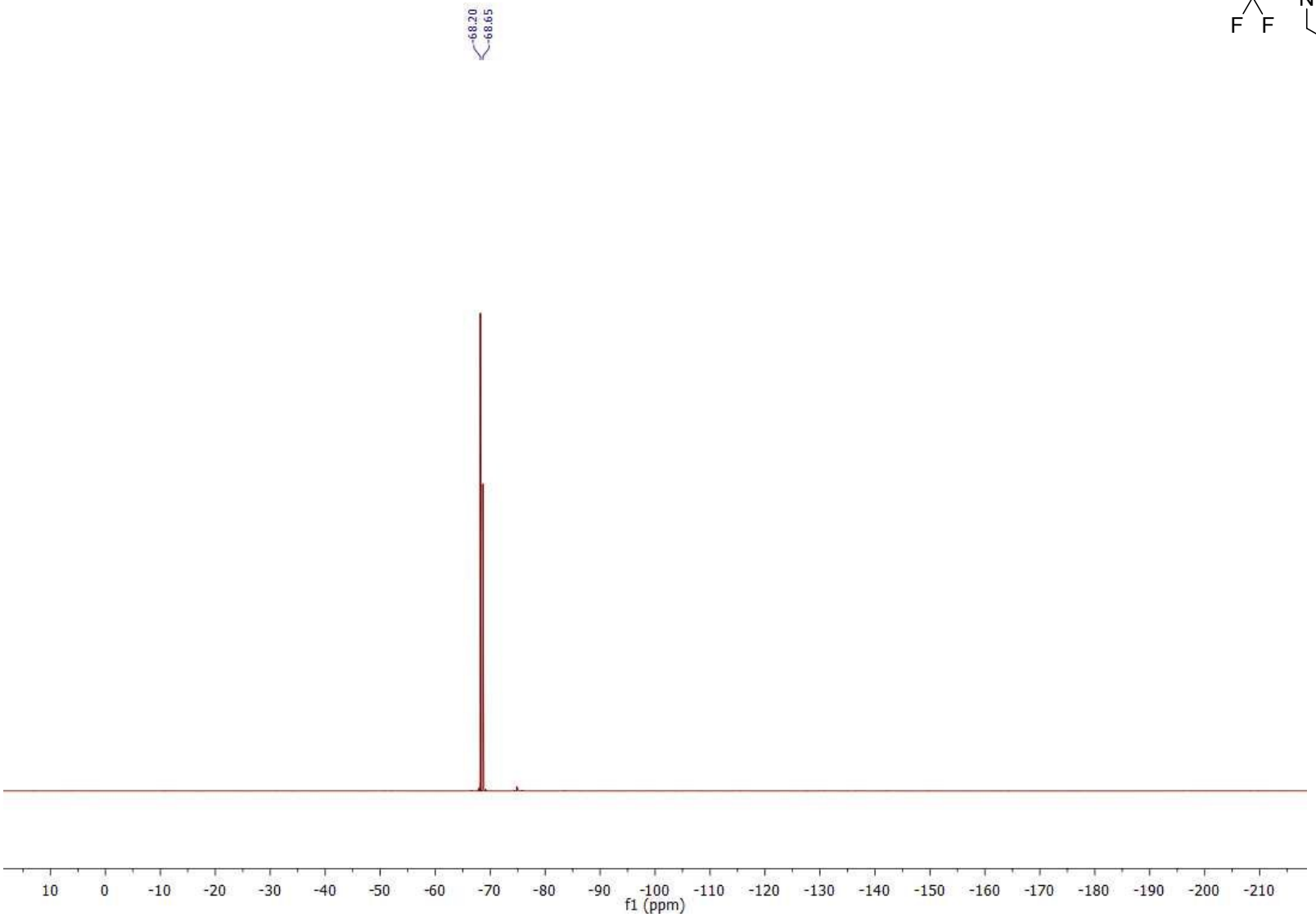
^{13}C NMR ($CDCl_3$, 100 MHz). *N*-Benzyl-*N*-(3,4-dimethoxyphenethyl)-2,2,2-trifluoroacetamide (**2f**)



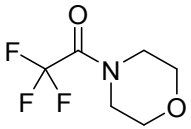


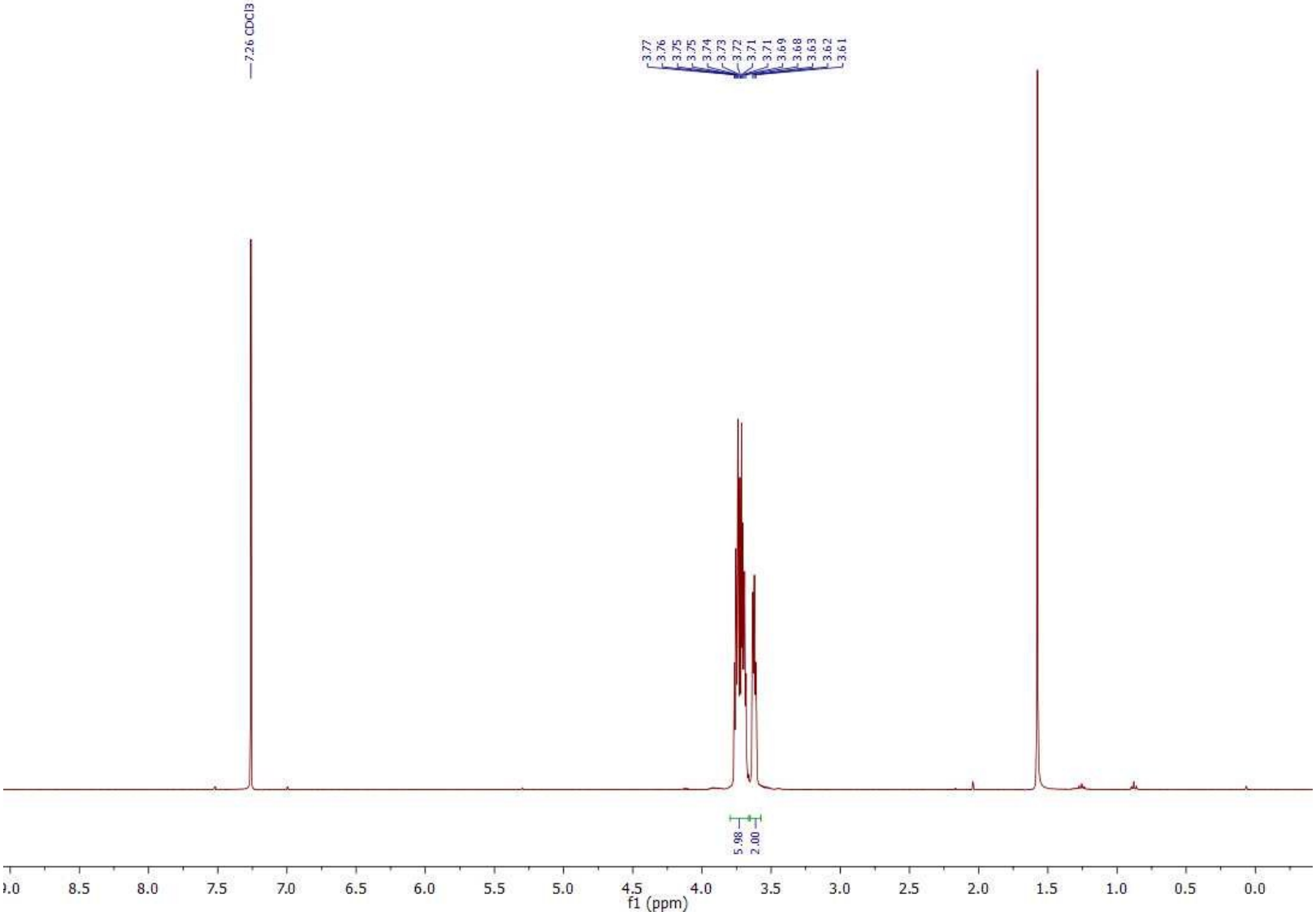
^{19}F NMR ($CDCl_3$, 377 MHz). *N*-Benzyl-*N*-(3,4-dimethoxyphenethyl)-2,2,2-trifluoroacetamide (**2f**)



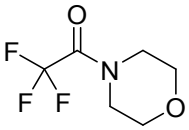


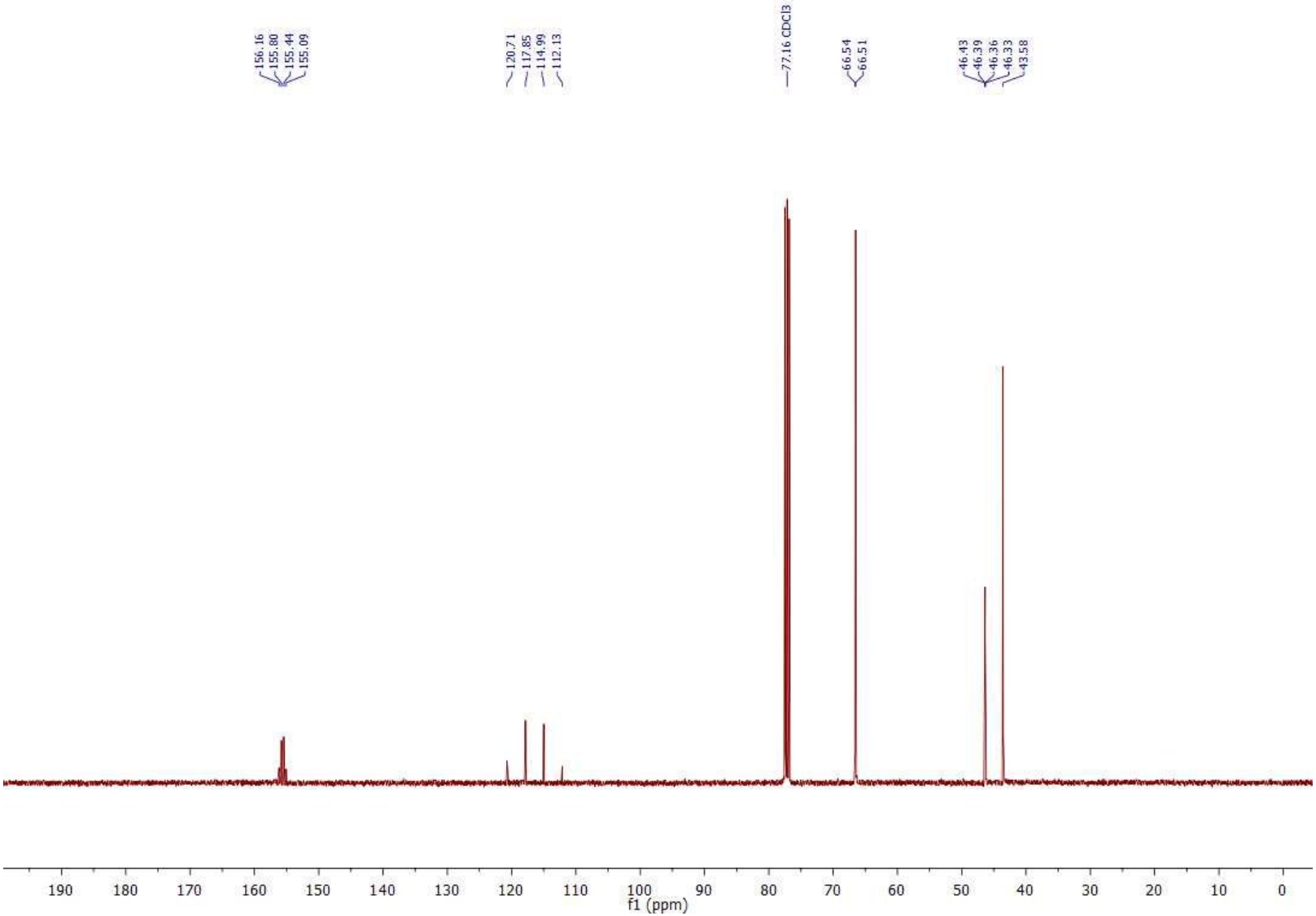
^{1}H NMR ($CDCl_3$, 400 MHz). 2,2,2-Trifluoro-1-morpholinoethan-1-one (**2g**)



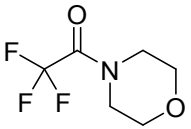


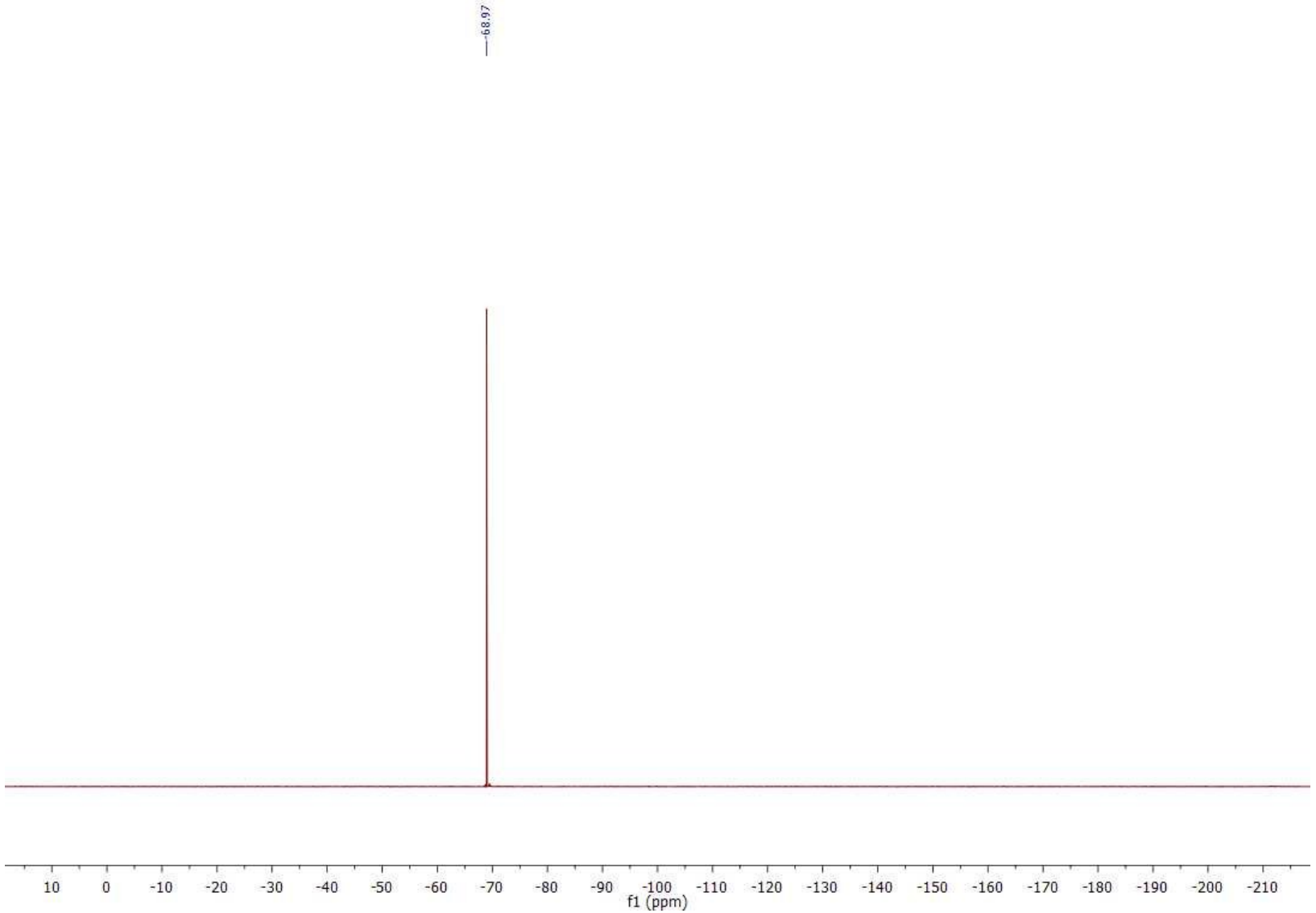
^{13}C NMR ($CDCl_3$, 100 MHz). 2,2,2-Trifluoro-1-morpholinoethan-1-one (**2g**)



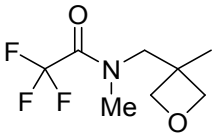


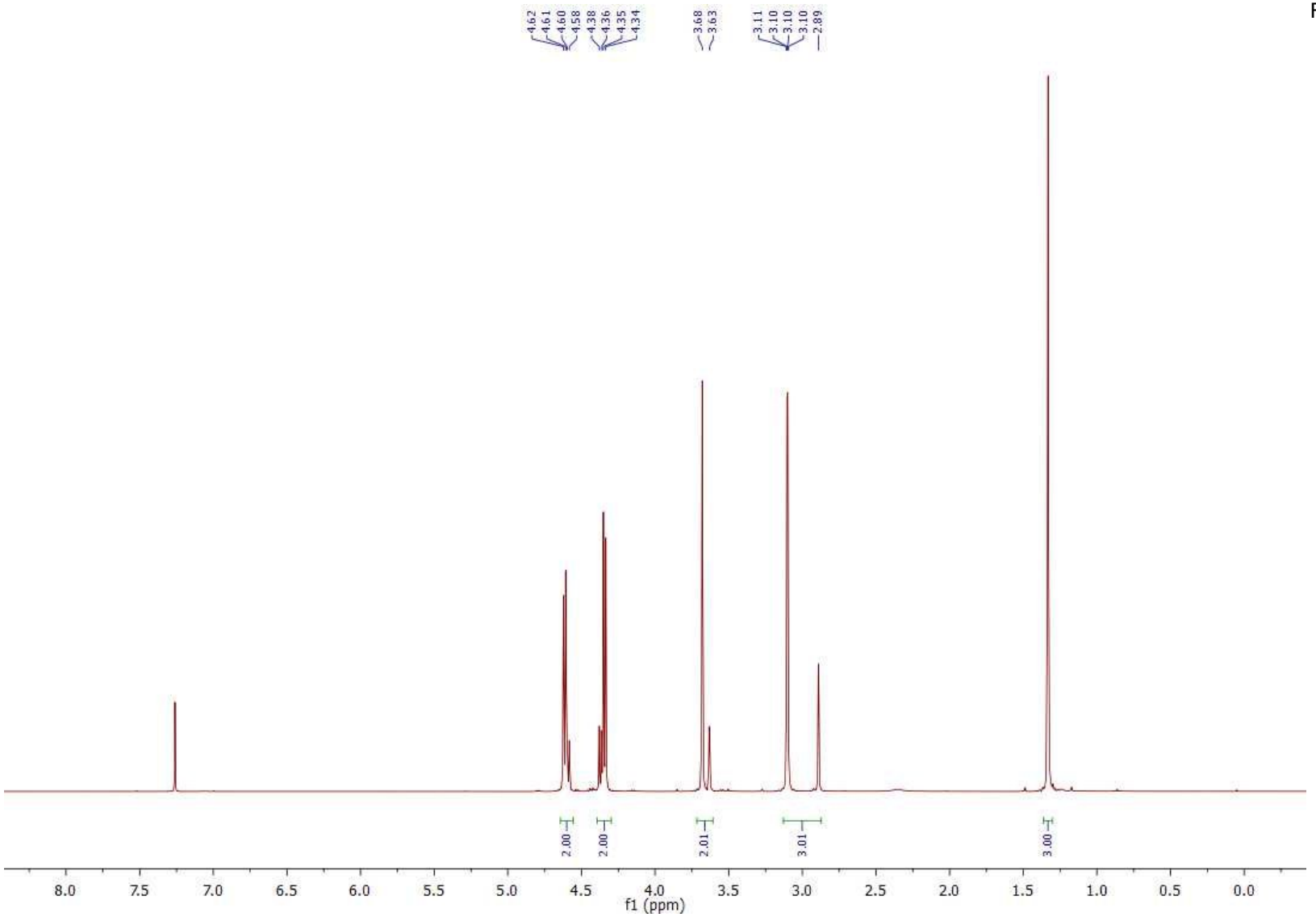
^{19}F NMR ($CDCl_3$, 377 MHz). 2,2,2-Trifluoro-1-morpholinoethan-1-one (**2g**)



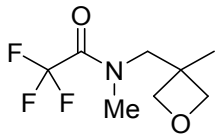


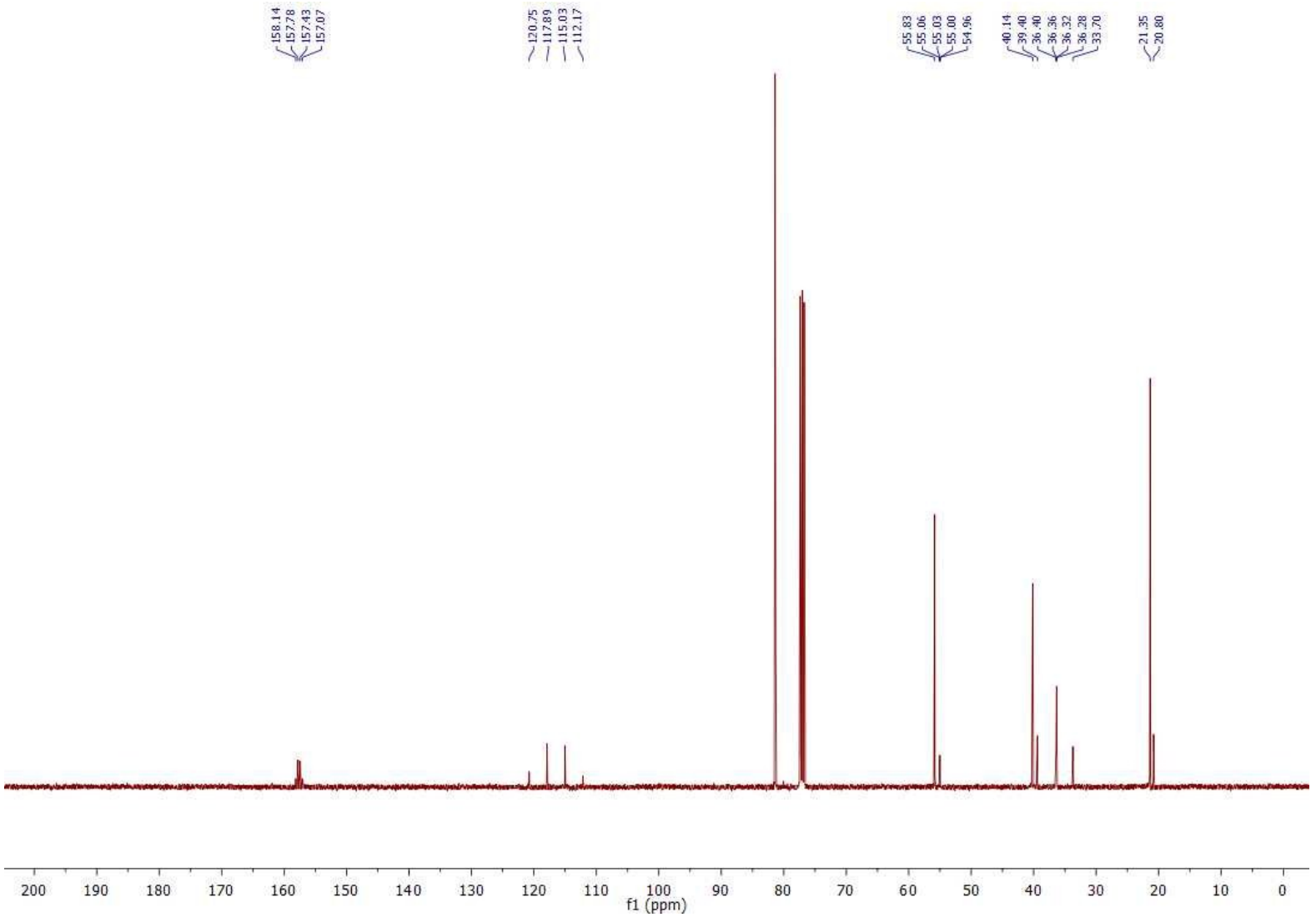
^{1}H NMR ($CDCl_3$, 400 MHz). 2,2,2-Trifluoro-*N*-methyl-*N*-((3-methyloxetan-3-yl)methyl)acetamide (**2h**)



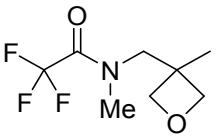


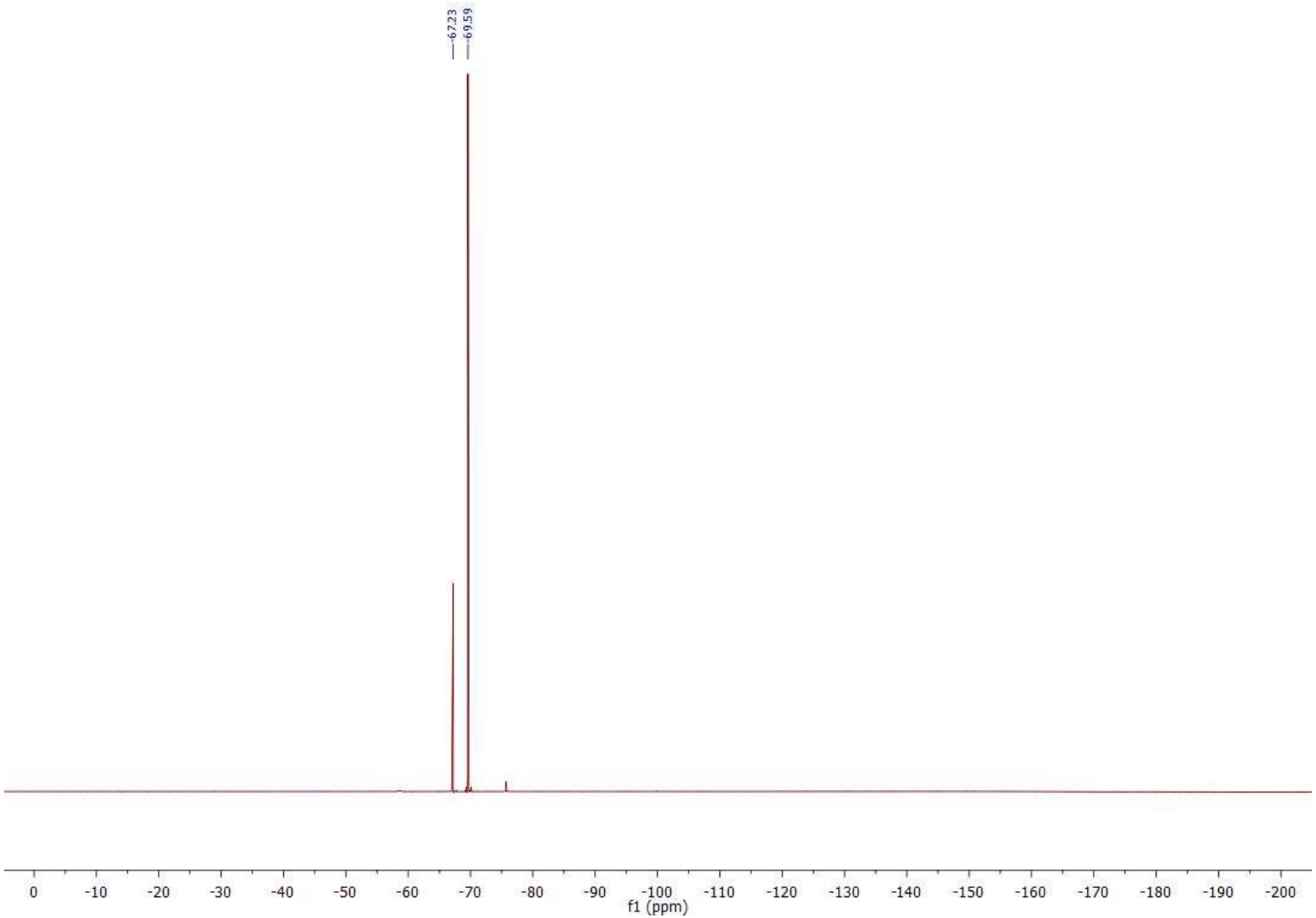
^{13}C NMR ($CDCl_3$, 100 MHz). 2,2,2-Trifluoro-*N*-methyl-*N*-((3-methyloxetan-3-yl)methyl)acetamide (**2h**)



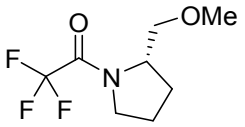


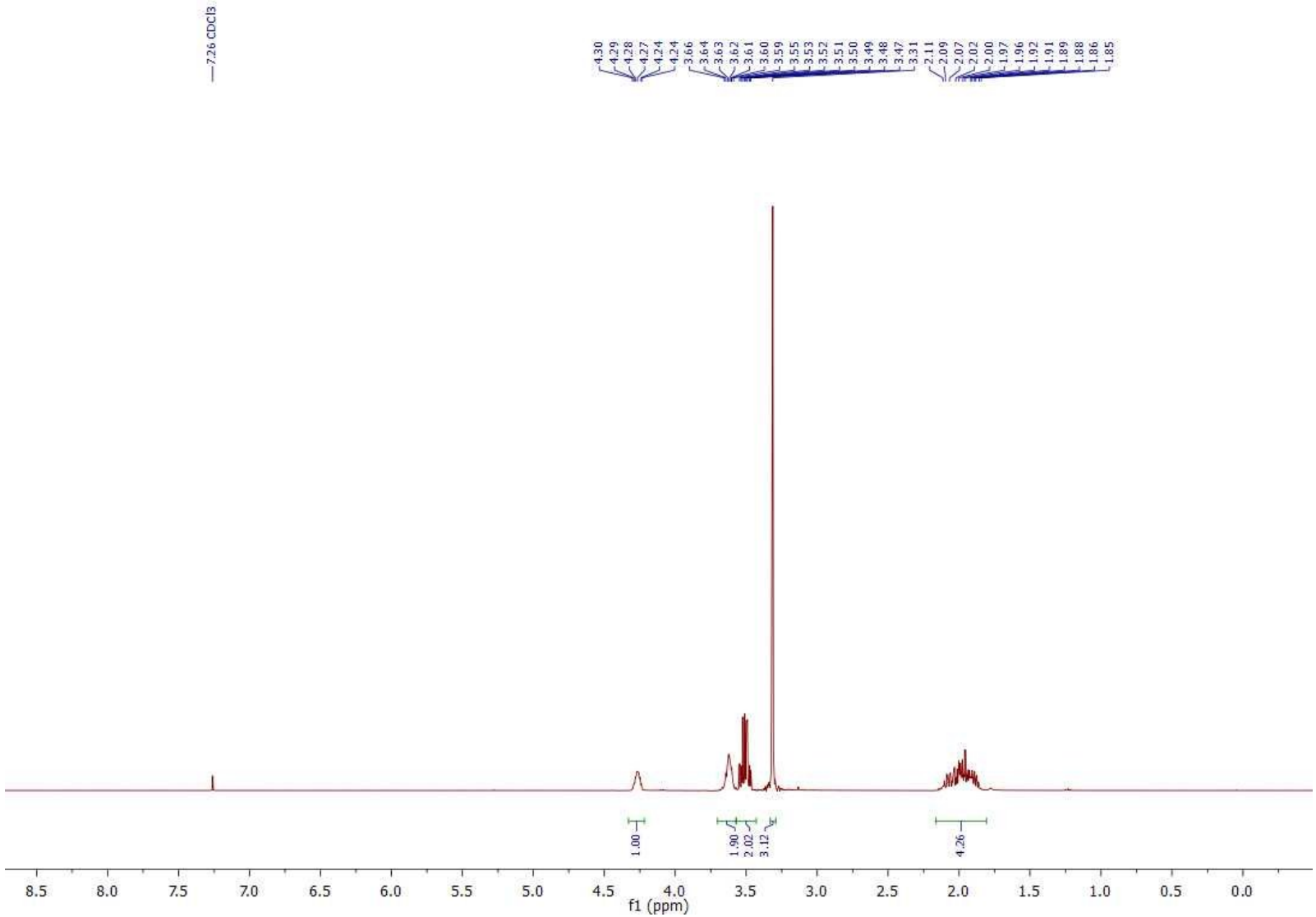
^{19}F NMR ($CDCl_3$, 377 MHz). 2,2,2-Trifluoro-*N*-methyl-*N*-((3-methyloxetan-3-yl)methyl)acetamide (**2h**)



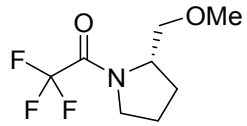


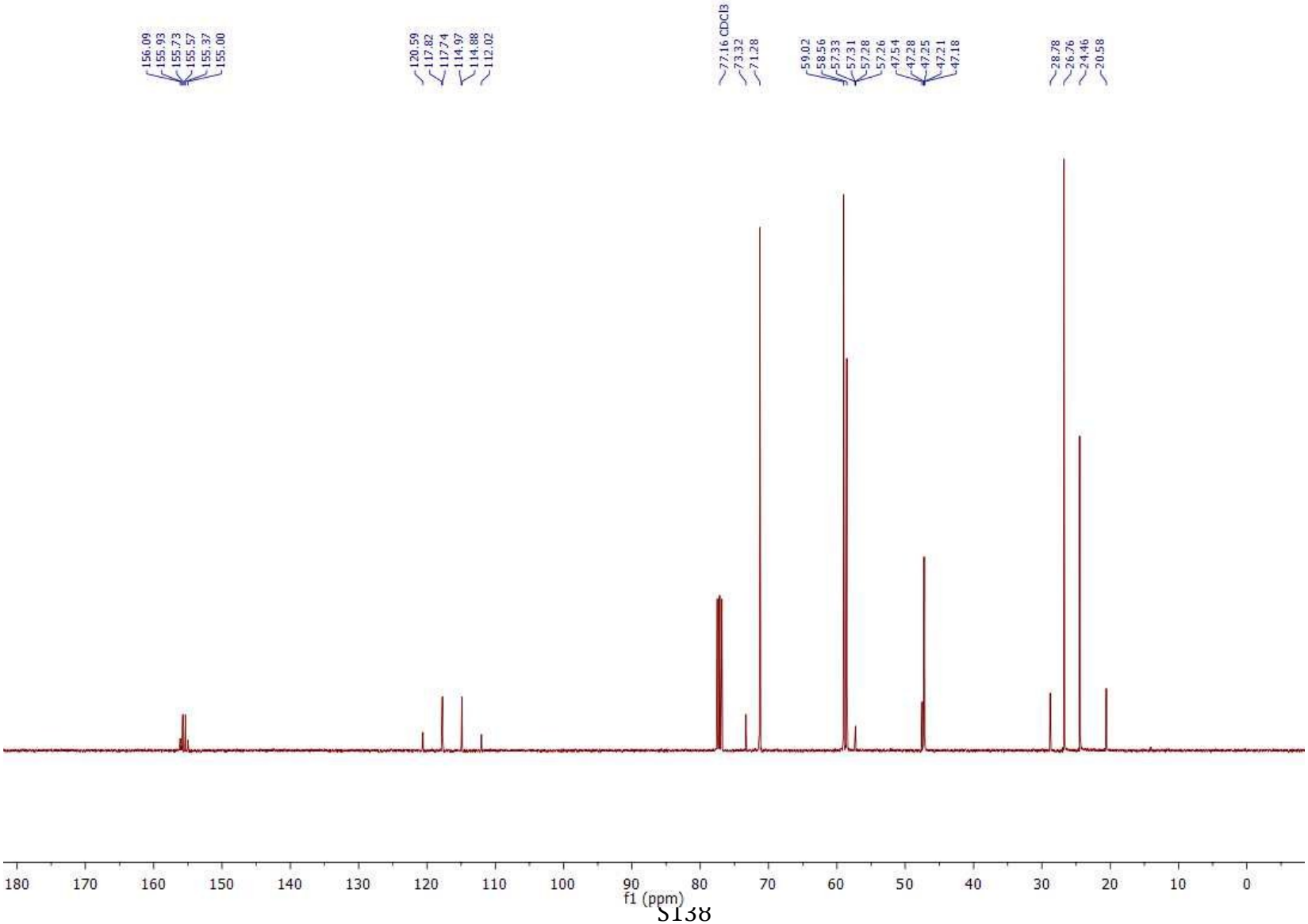
^{1}H NMR ($CDCl_3$, 400 MHz). (*S*)-2,2,2-Trifluoro-1-(2-(methoxymethyl)pyrrolidin-1-yl)ethanone (**2i**)



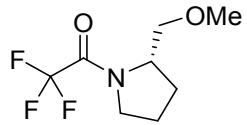


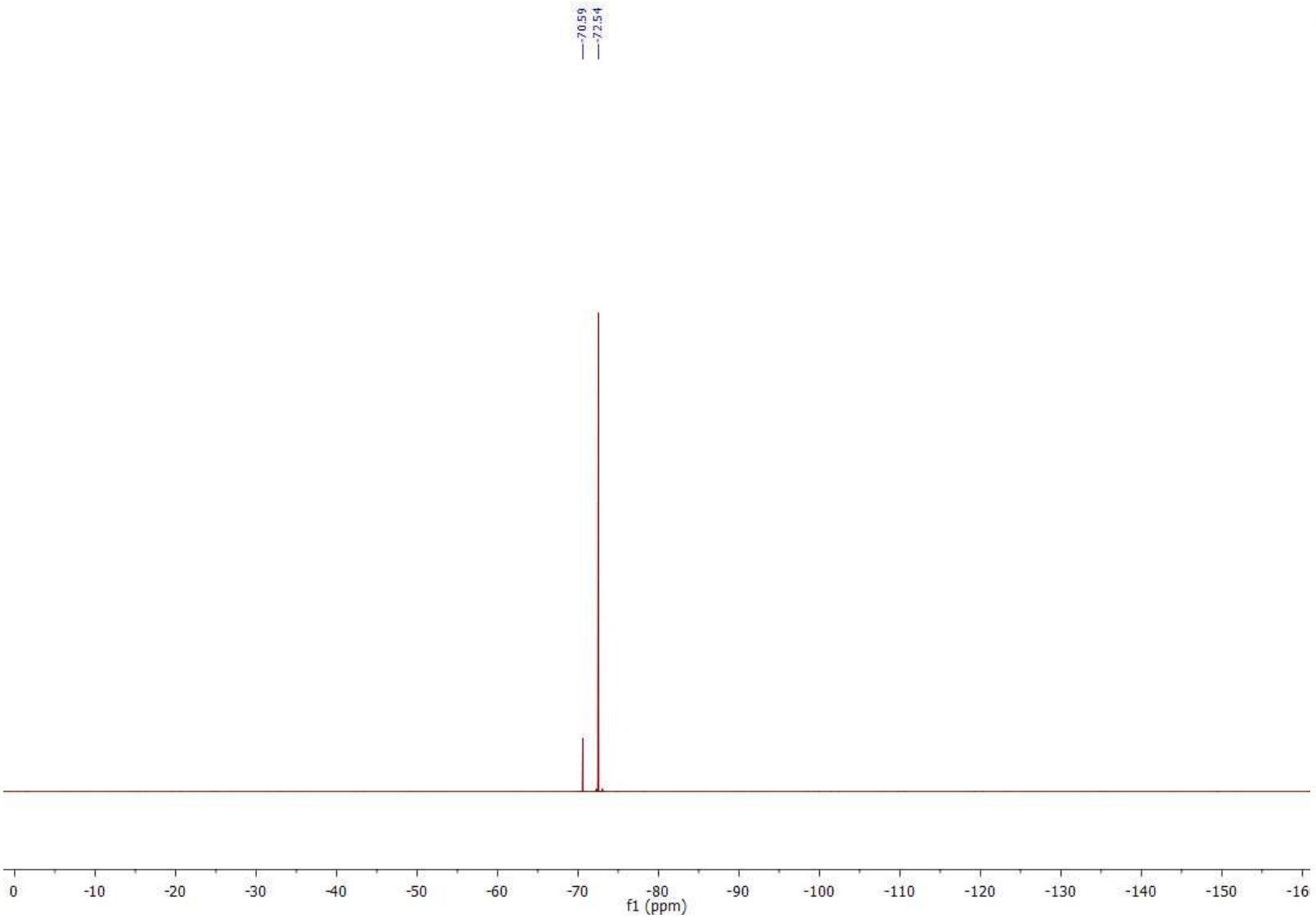
^{13}C NMR ($CDCl_3$, 100 MHz). (*S*)-2,2,2-Trifluoro-1-(2-(methoxymethyl)pyrrolidin-1-yl)ethanone (**2i**)



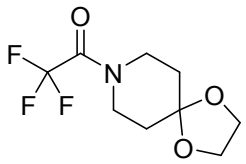


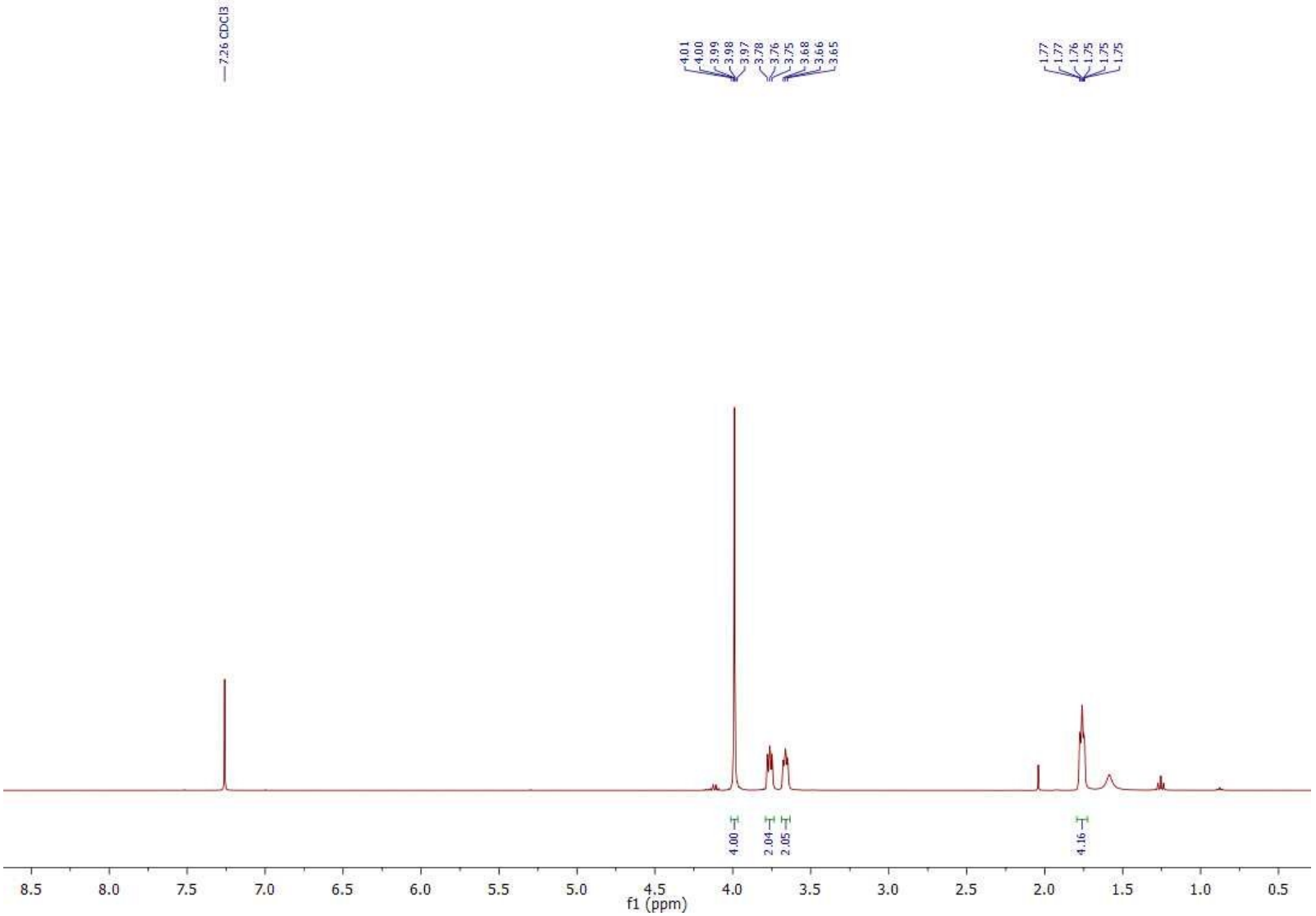
^{19}F NMR ($CDCl_3$, 377 MHz). (*S*)-2,2,2-Trifluoro-1-(2-(methoxymethyl)pyrrolidin-1-yl)ethanone (**2i**)



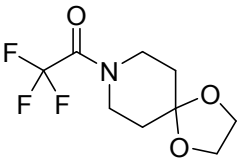


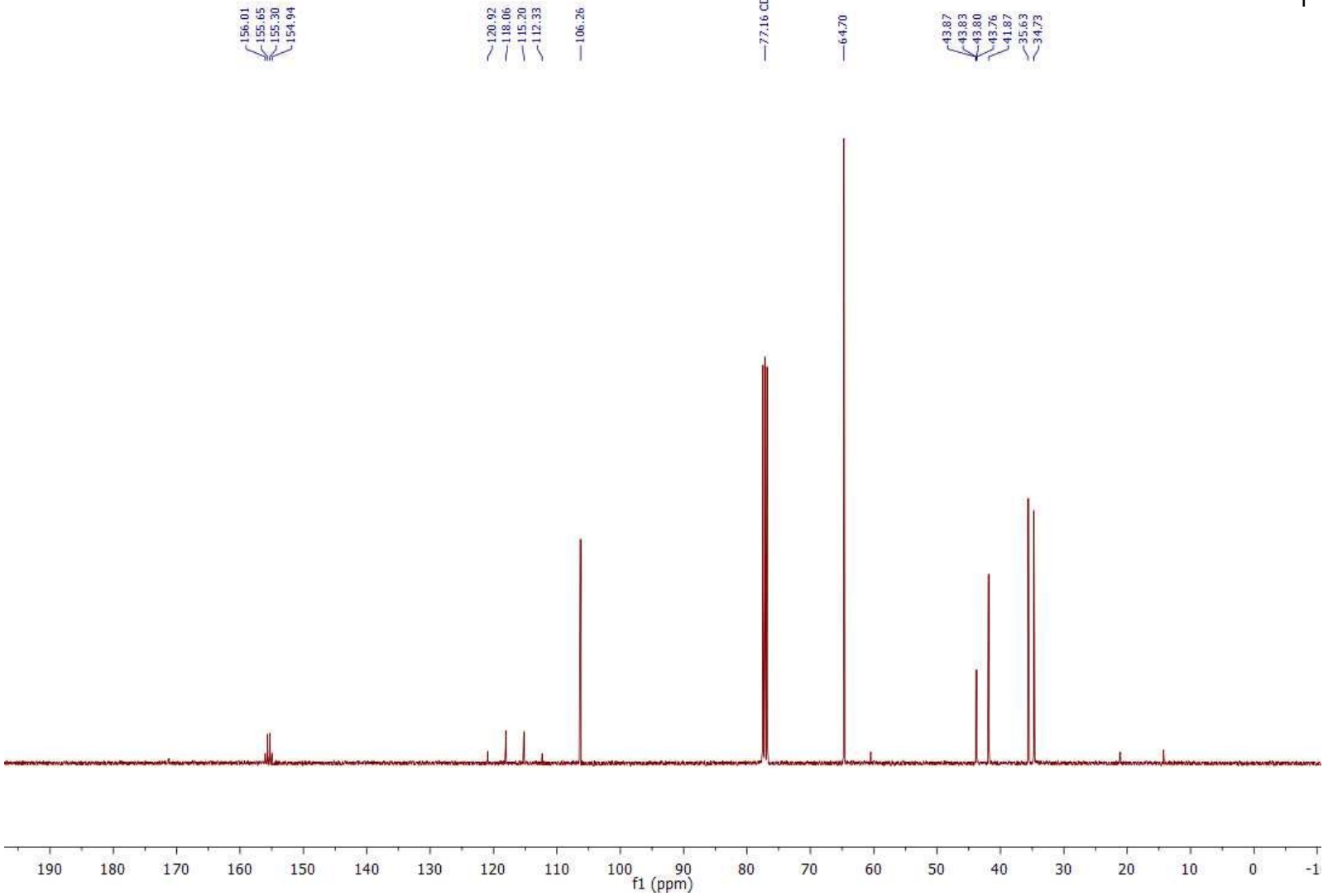
^{1}H NMR ($CDCl_3$, 400 MHz). 2,2,2-Trifluoro-1-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)ethan-1-one (**2j**)



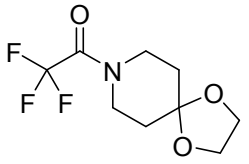


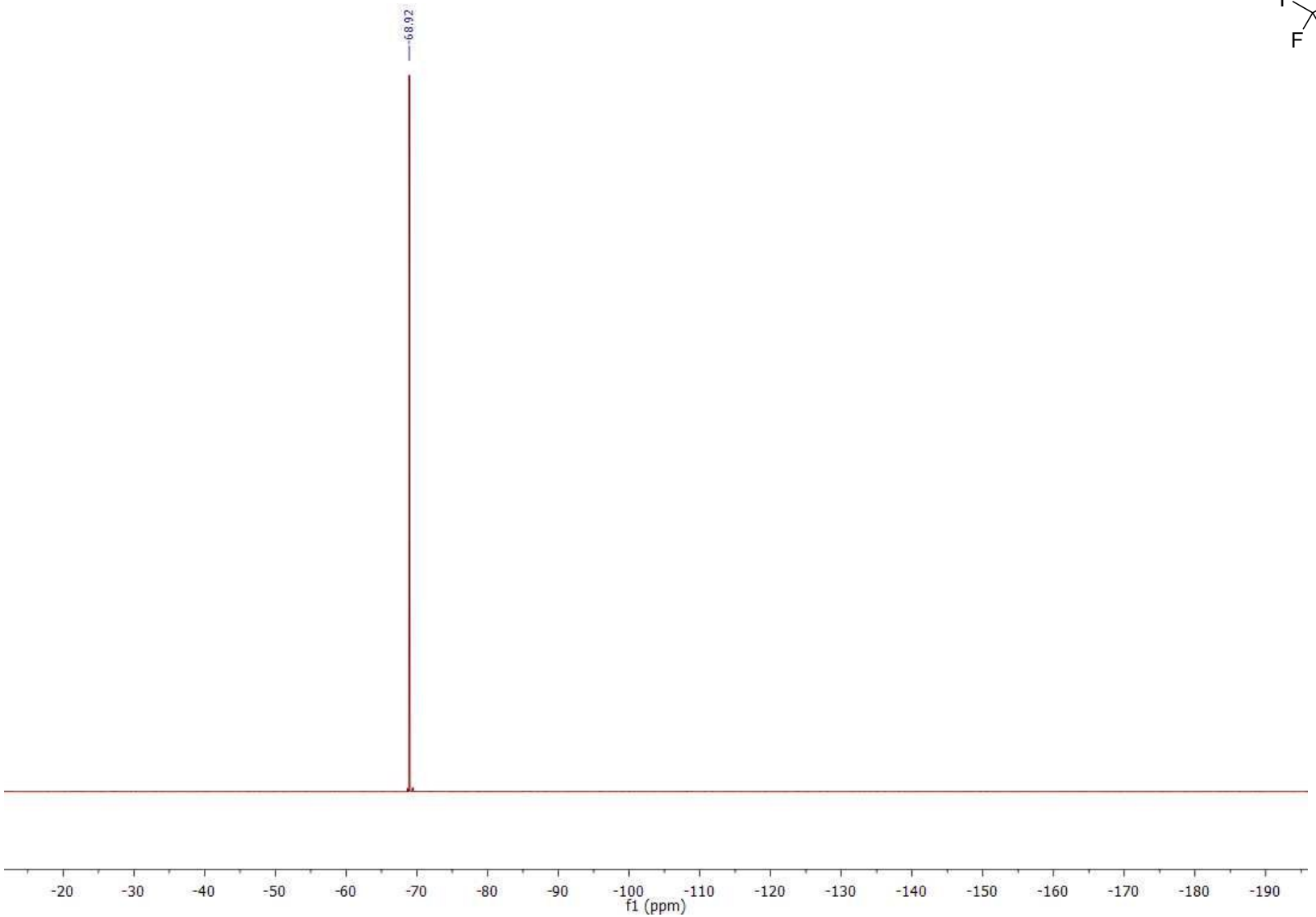
^{13}C NMR ($CDCl_3$, 100 MHz). 2,2,2-Trifluoro-1-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)ethan-1-one (**2j**)



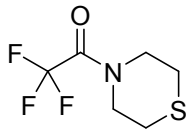


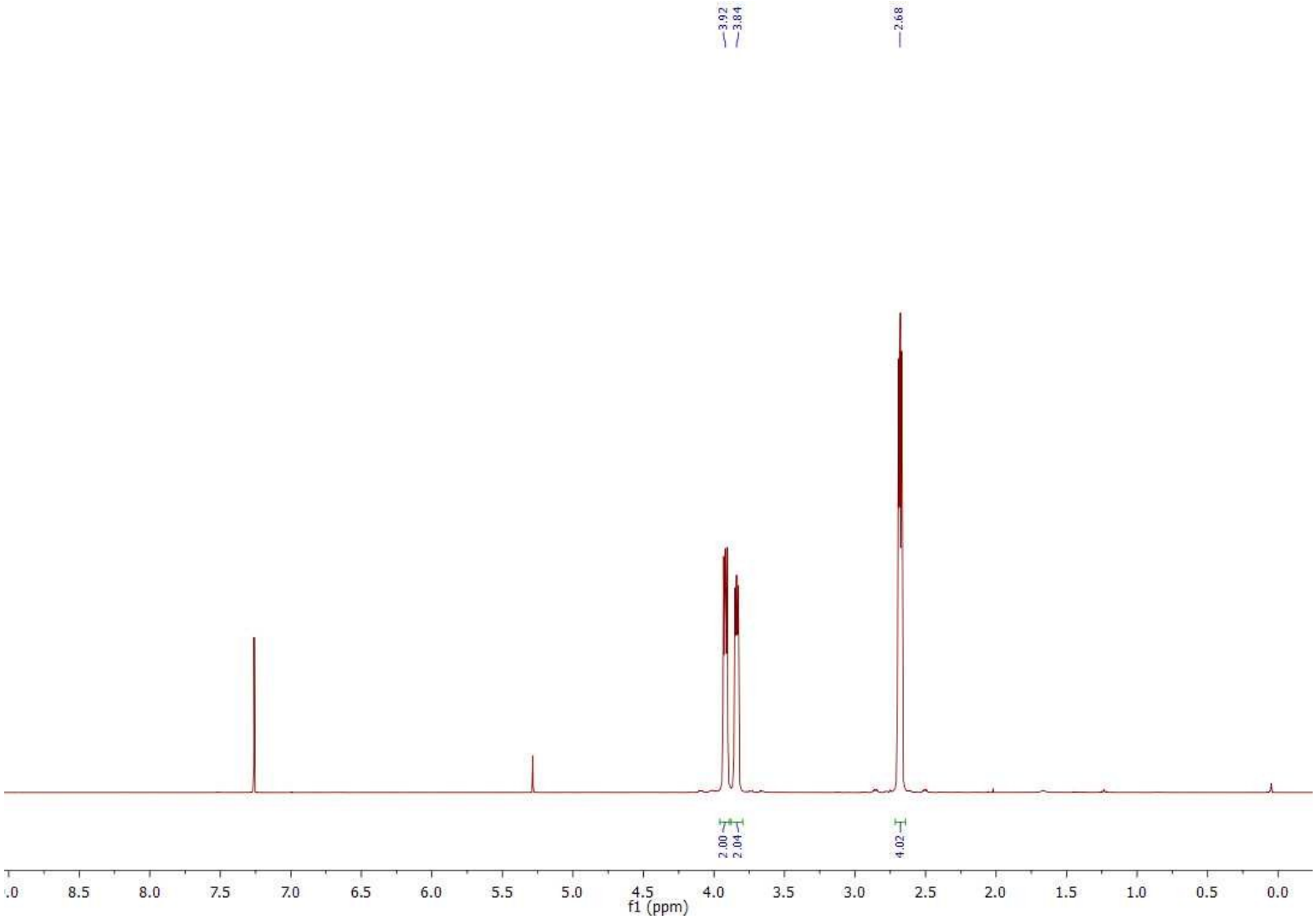
^{19}F NMR ($CDCl_3$, 377 MHz). 2,2,2-Trifluoro-1-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)ethan-1-one (**2j**)



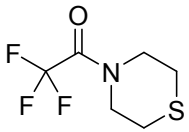


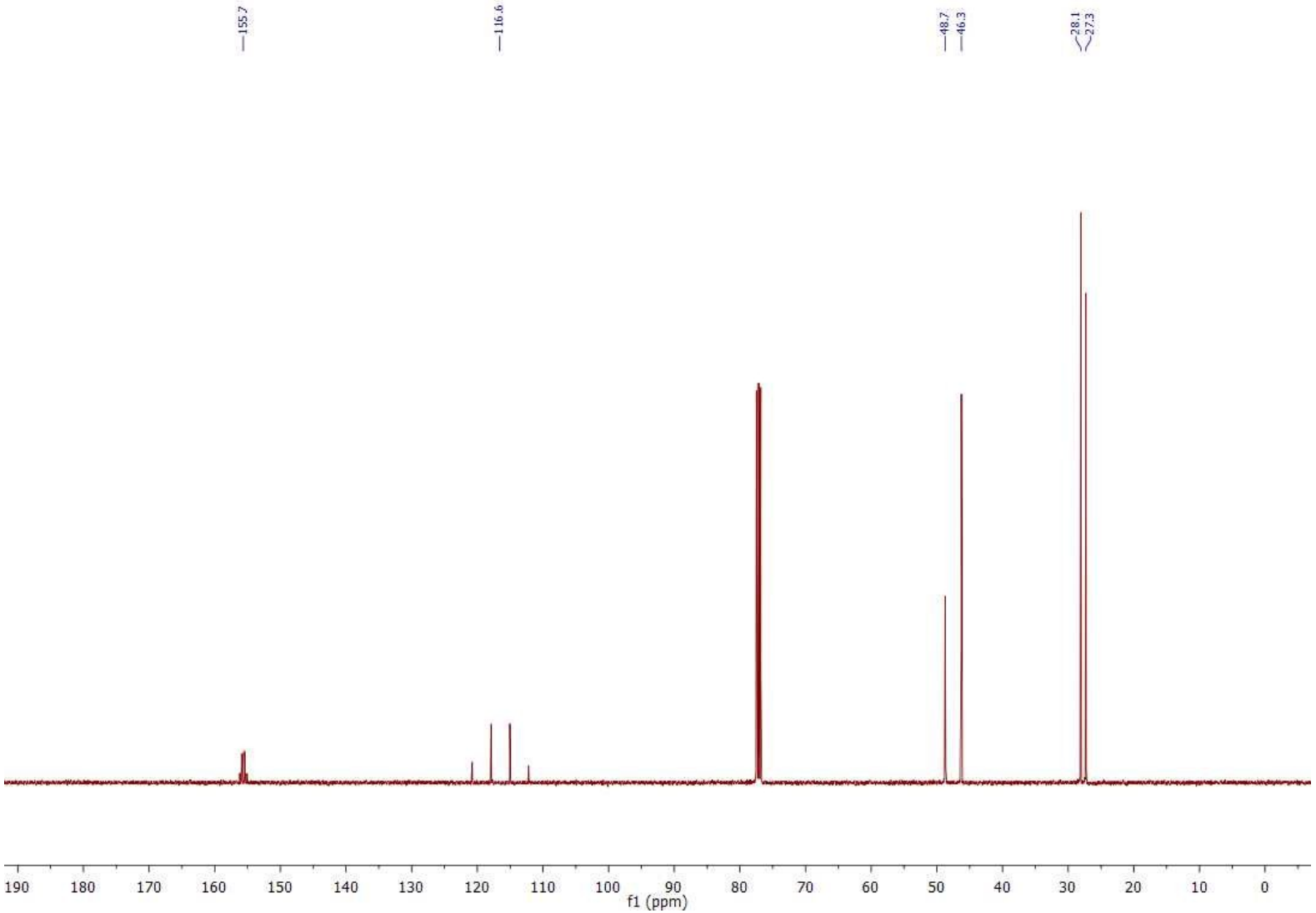
^{1}H NMR ($CDCl_3$, 400 MHz). 2,2,2-Trifluoro-1-thiomorpholinoethan-1-one (**2k**)



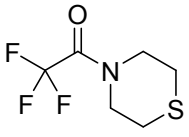


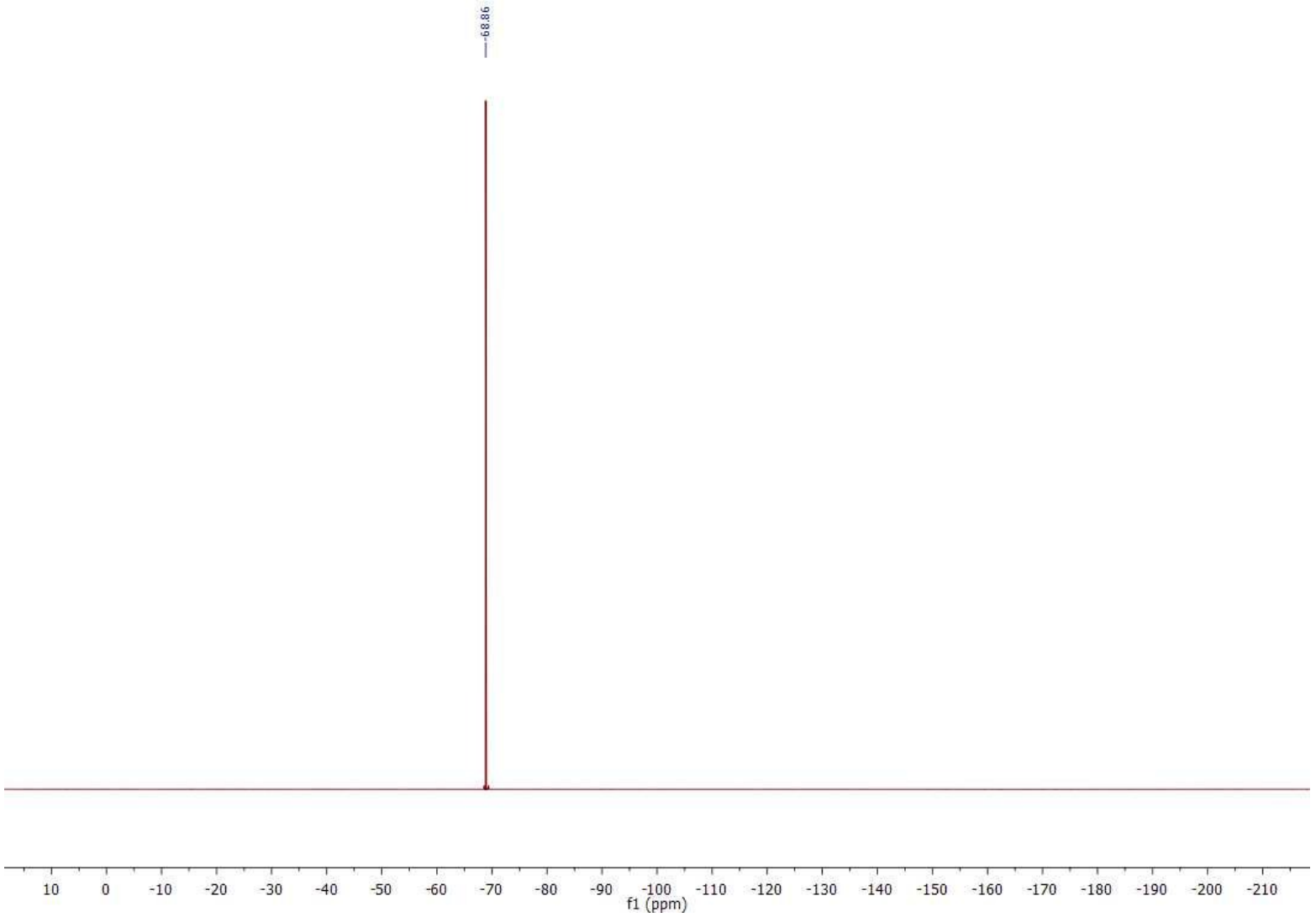
^{13}C NMR ($CDCl_3$, 100 MHz). 2,2,2-Trifluoro-1-thiomorpholinoethan-1-one (**2k**)



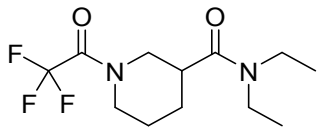


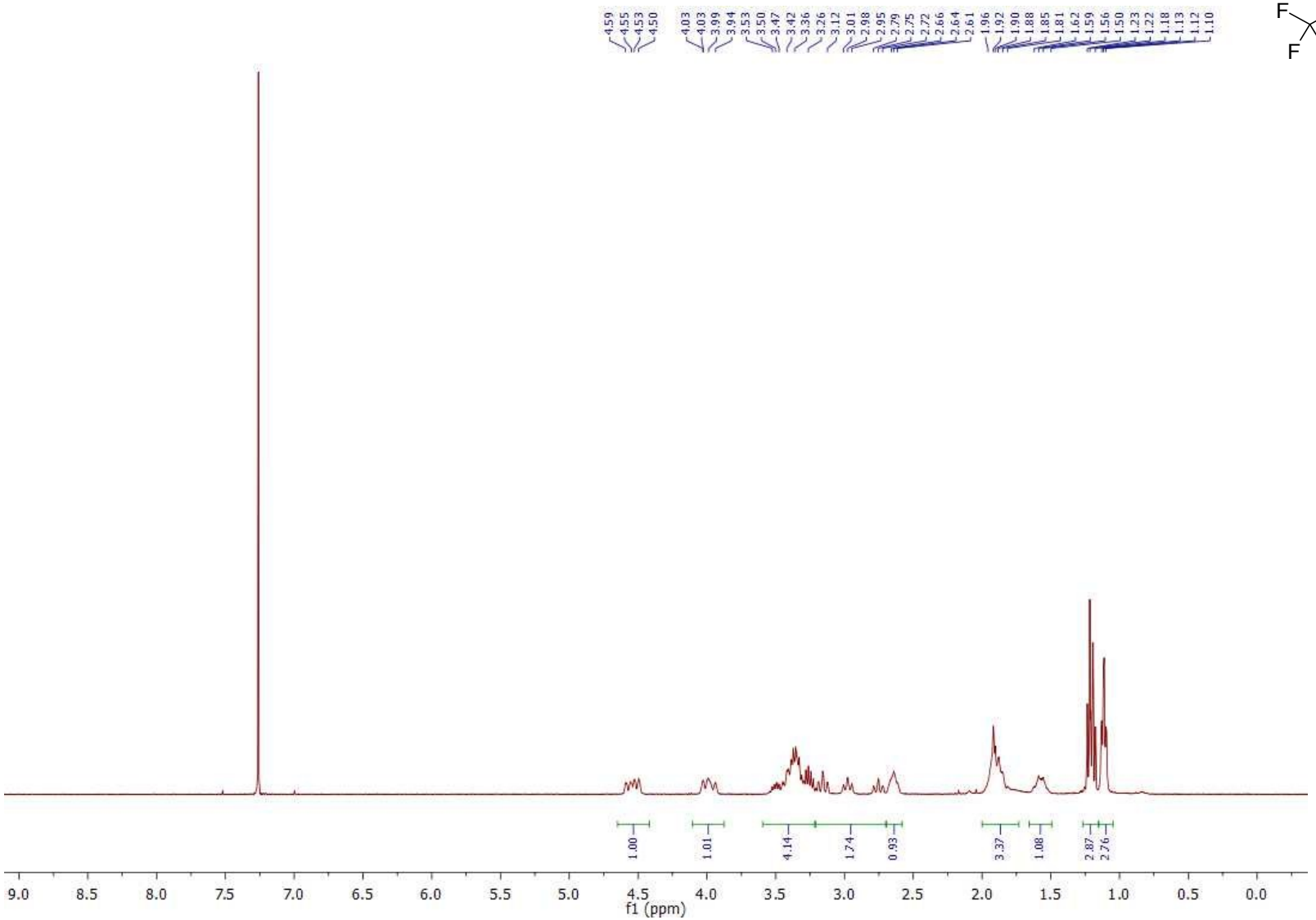
^{19}F NMR ($CDCl_3$, 377 MHz). 2,2,2-Trifluoro-1-thiomorpholinoethan-1-one (**2k**)



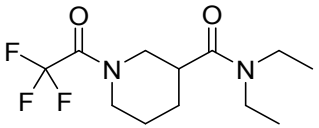


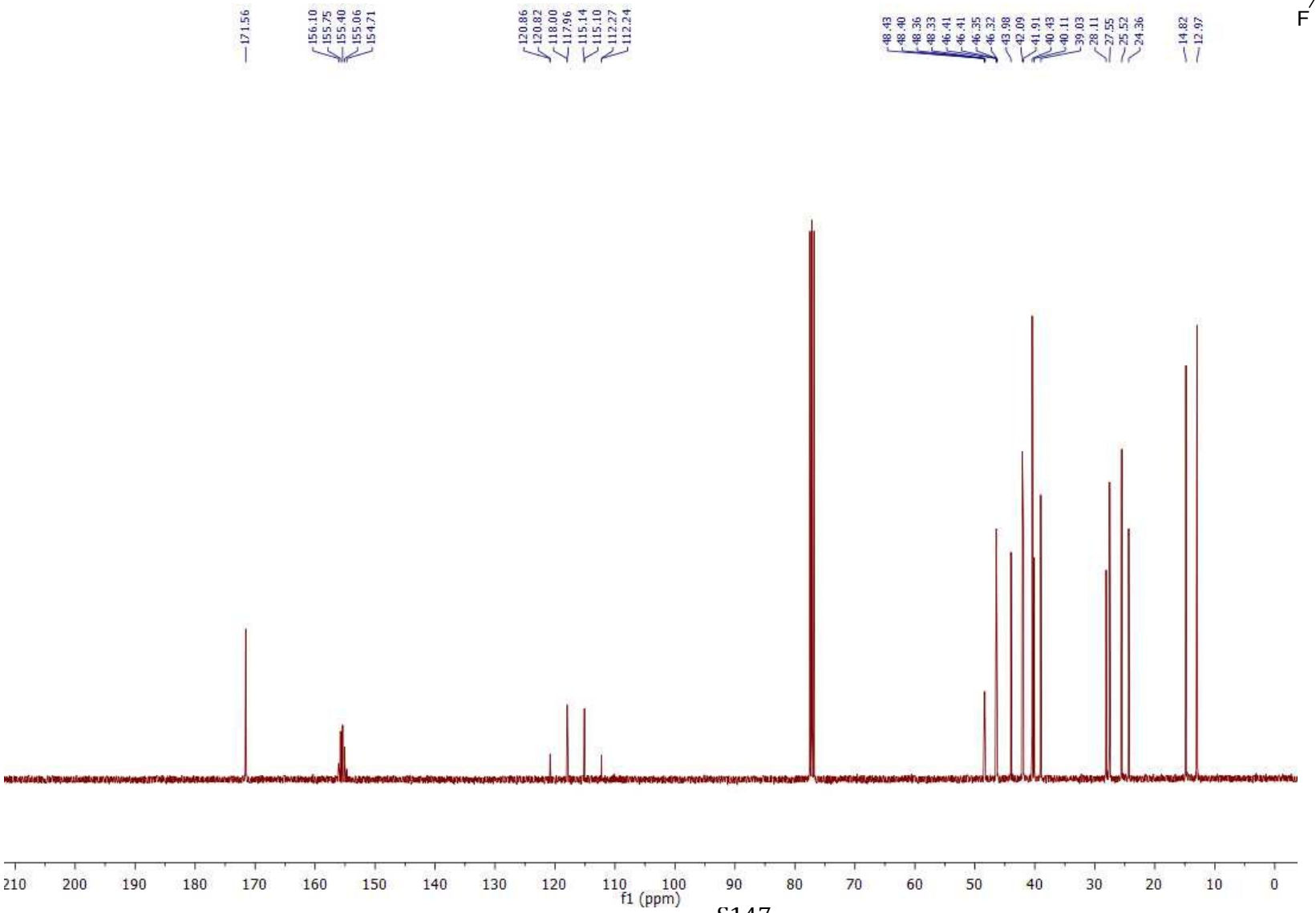
^{1}H NMR ($CDCl_3$, 400 MHz). *N*,*N*-diethyl-1-(2,2,2-trifluoroacetyl)piperidine-3-carboxamide (**2l**)



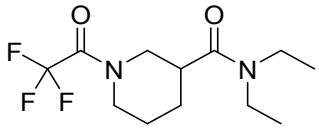


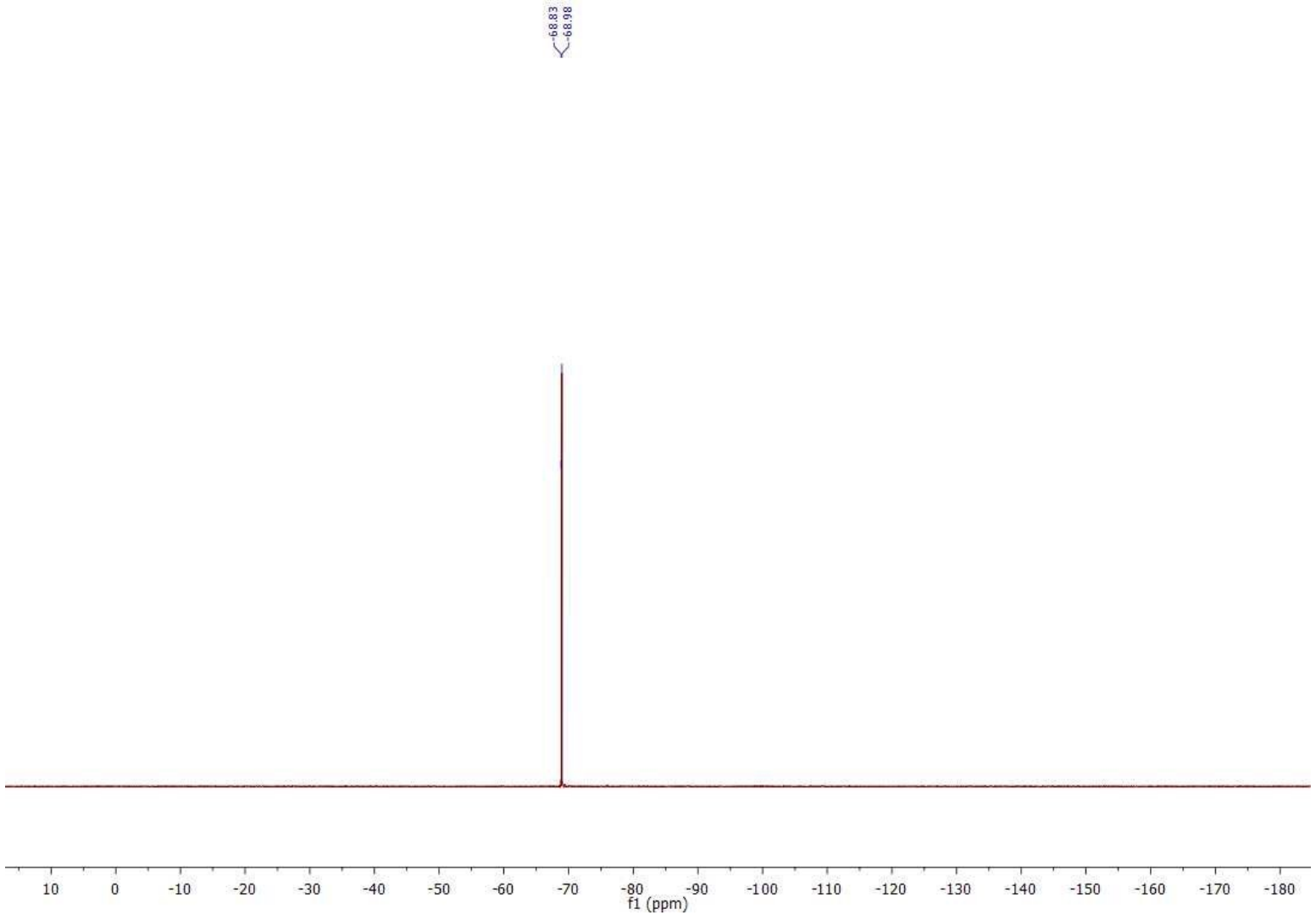
^{13}C NMR ($CDCl_3$, 100 MHz). *N*,*N*-diethyl-1-(2,2,2-trifluoroacetyl)piperidine-3-carboxamide (**2l**)



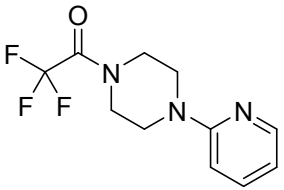


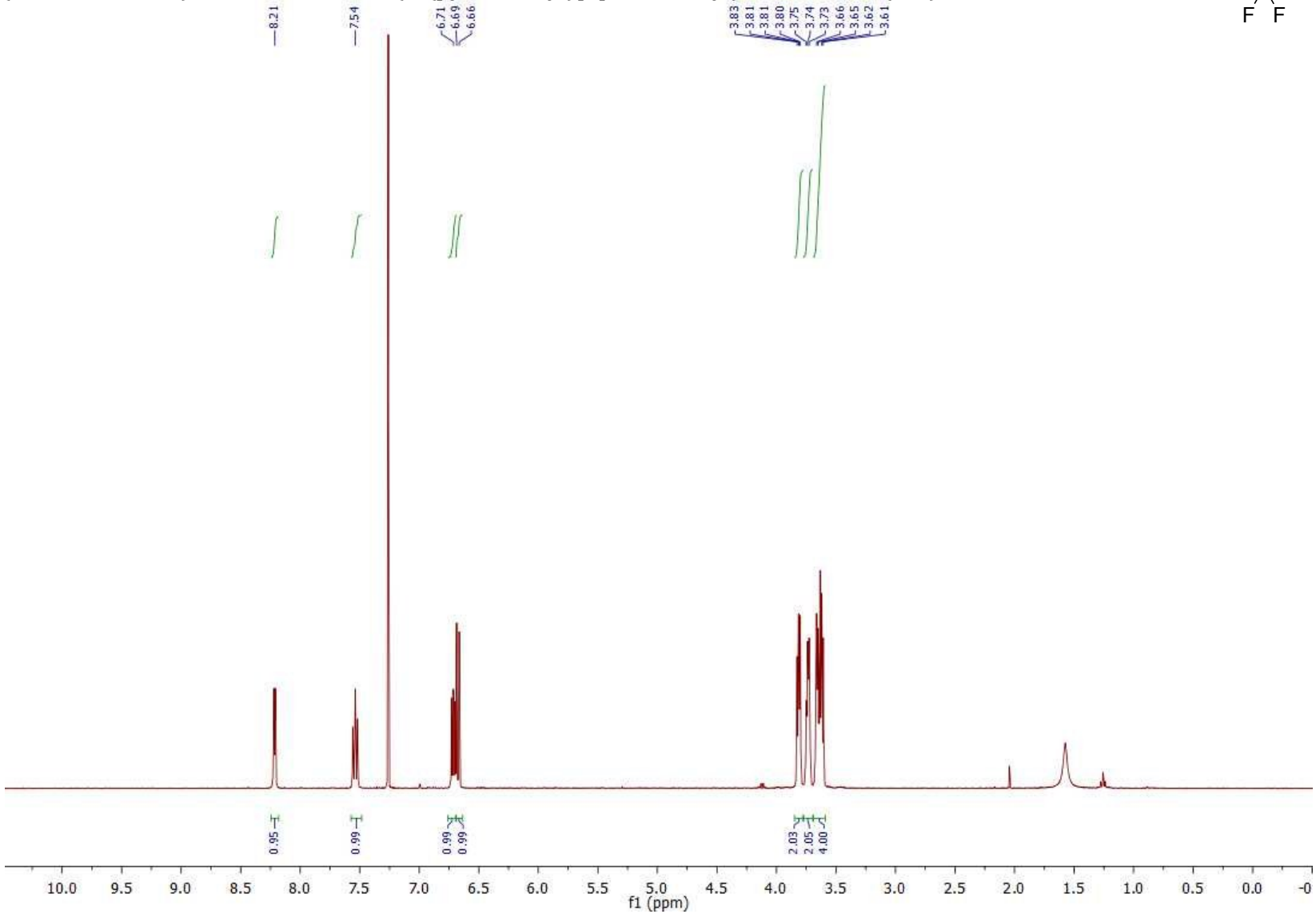
^{19}F NMR ($CDCl_3$, 377 MHz). *N*,*N*-diethyl-1-(2,2,2-trifluoroacetyl)piperidine-3-carboxamide (**2l**)



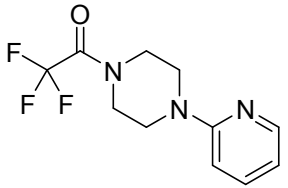


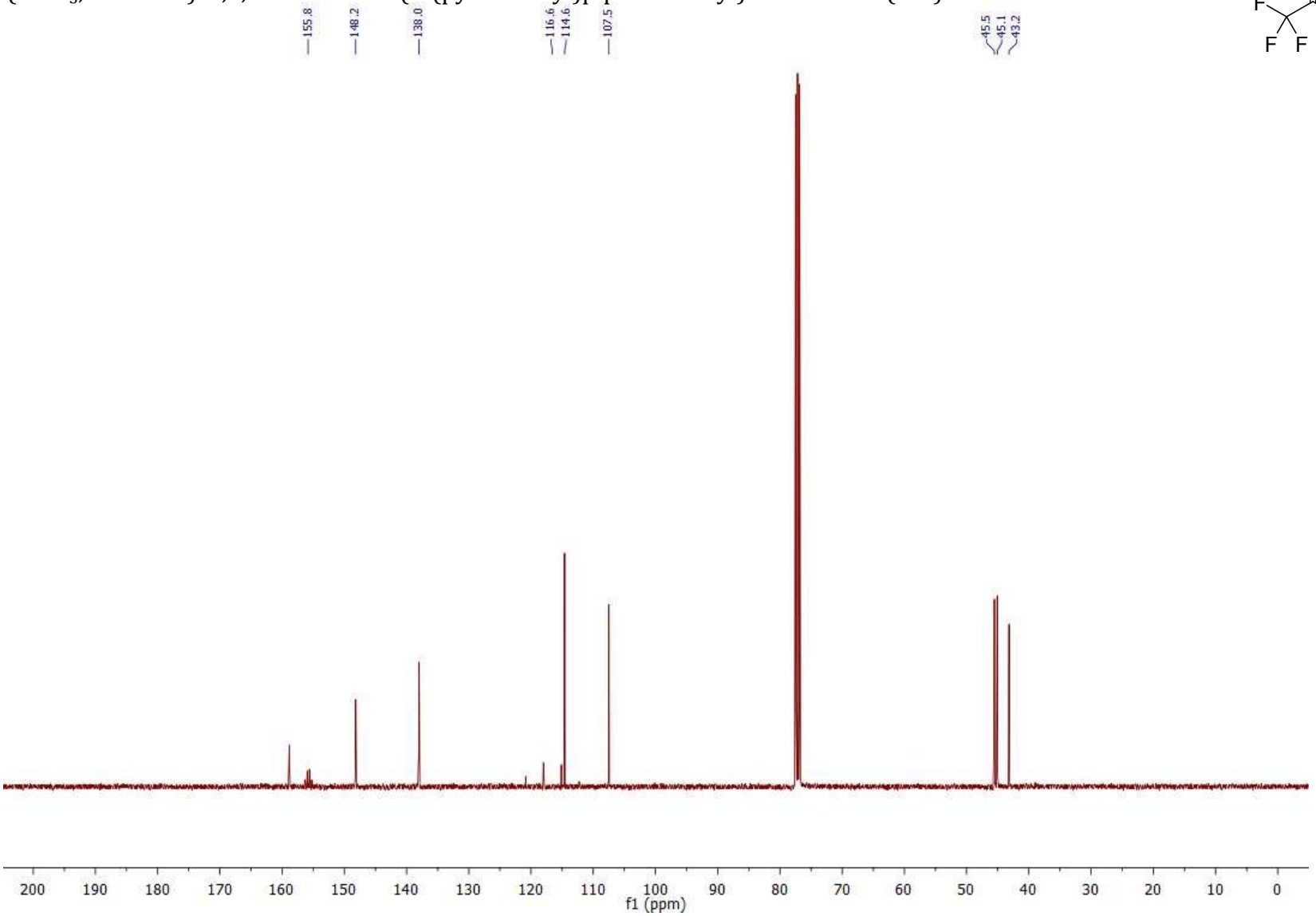
^{1}H NMR ($CDCl_3$, 400 MHz). 2,2,2-Trifluoro-1-(4-(pyridin-2-yl)piperazin-1-yl)ethan-1-one (**2m**)



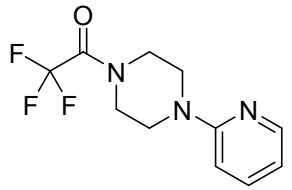


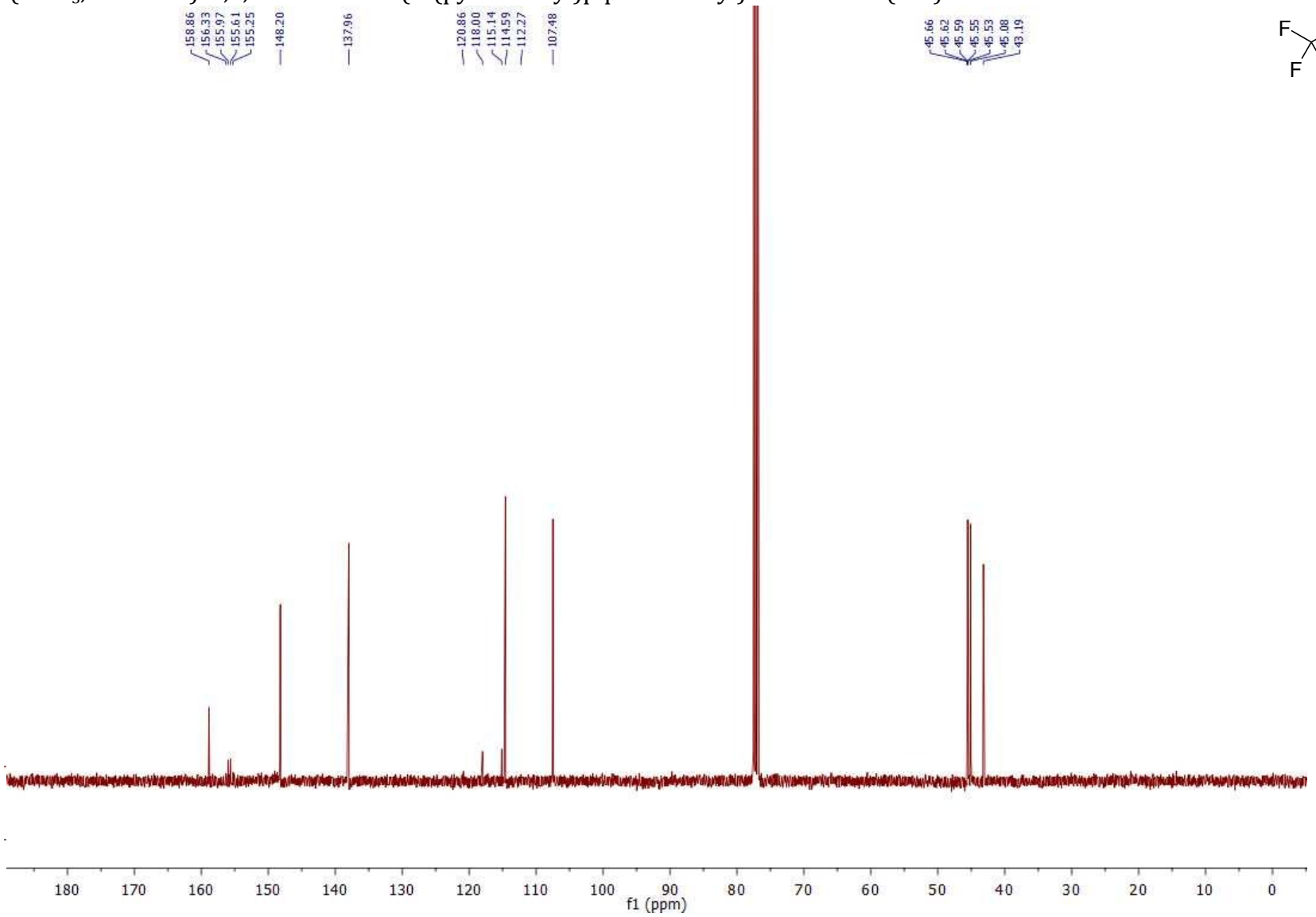
^{13}C NMR ($CDCl_3$, 100 MHz). 2,2,2-Trifluoro-1-(4-(pyridin-2-yl)piperazin-1-yl)ethan-1-one (**2m**)



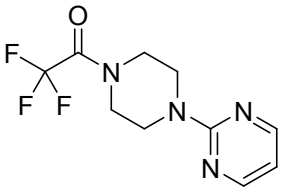


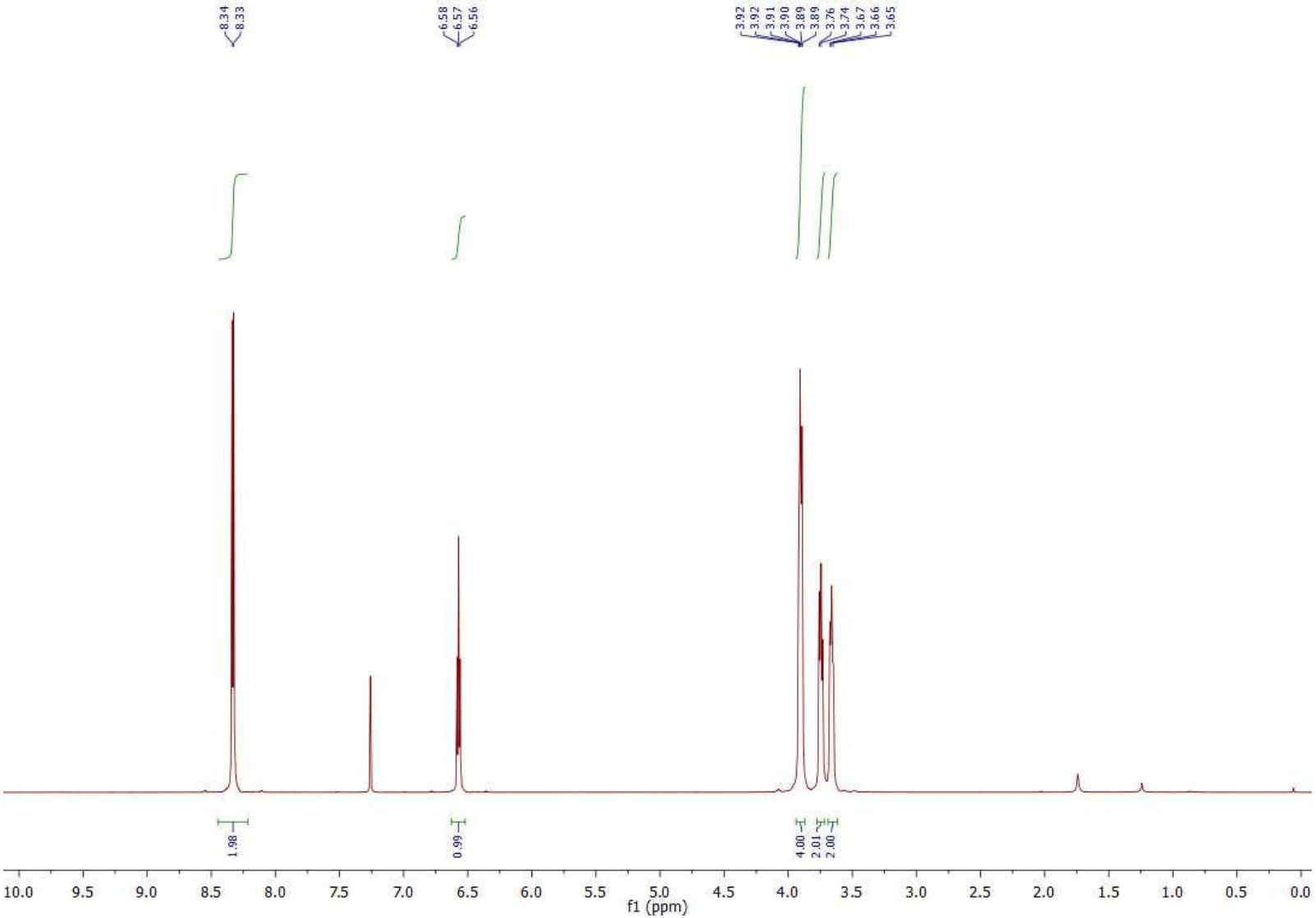
^{19}F NMR ($CDCl_3$, 377 MHz). 2,2,2-Trifluoro-1-(4-(pyridin-2-yl)piperazin-1-yl)ethan-1-one (**2m**)



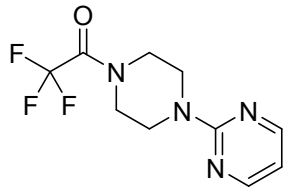


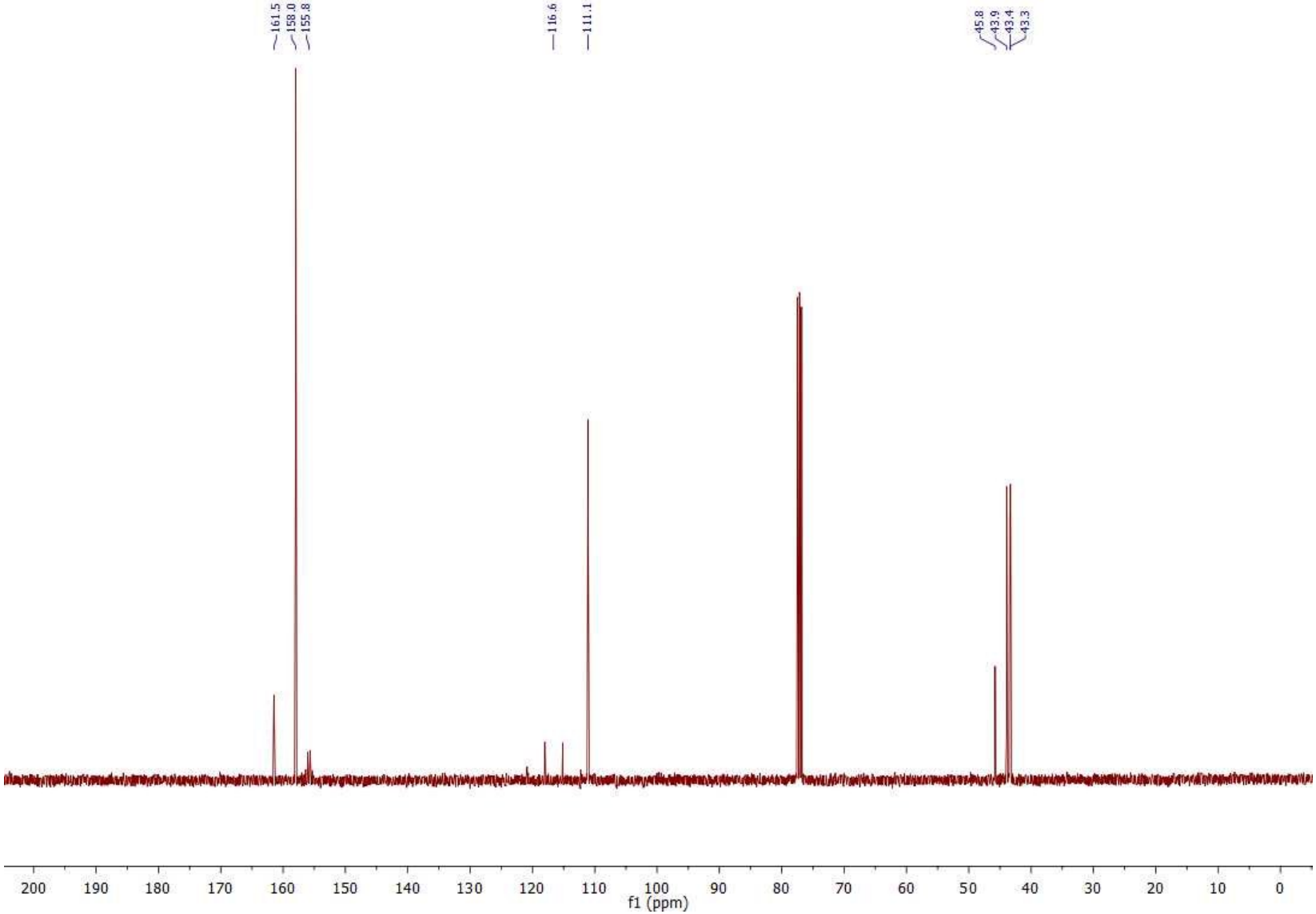
^{1}H NMR ($CDCl_3$, 400 MHz). 2,2,2-Trifluoro-1-(4-(pyrimidin-2-yl)piperazin-1-yl)ethan-1-one (**2n**)



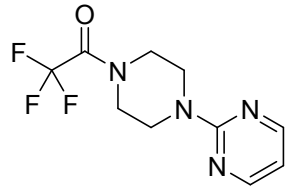


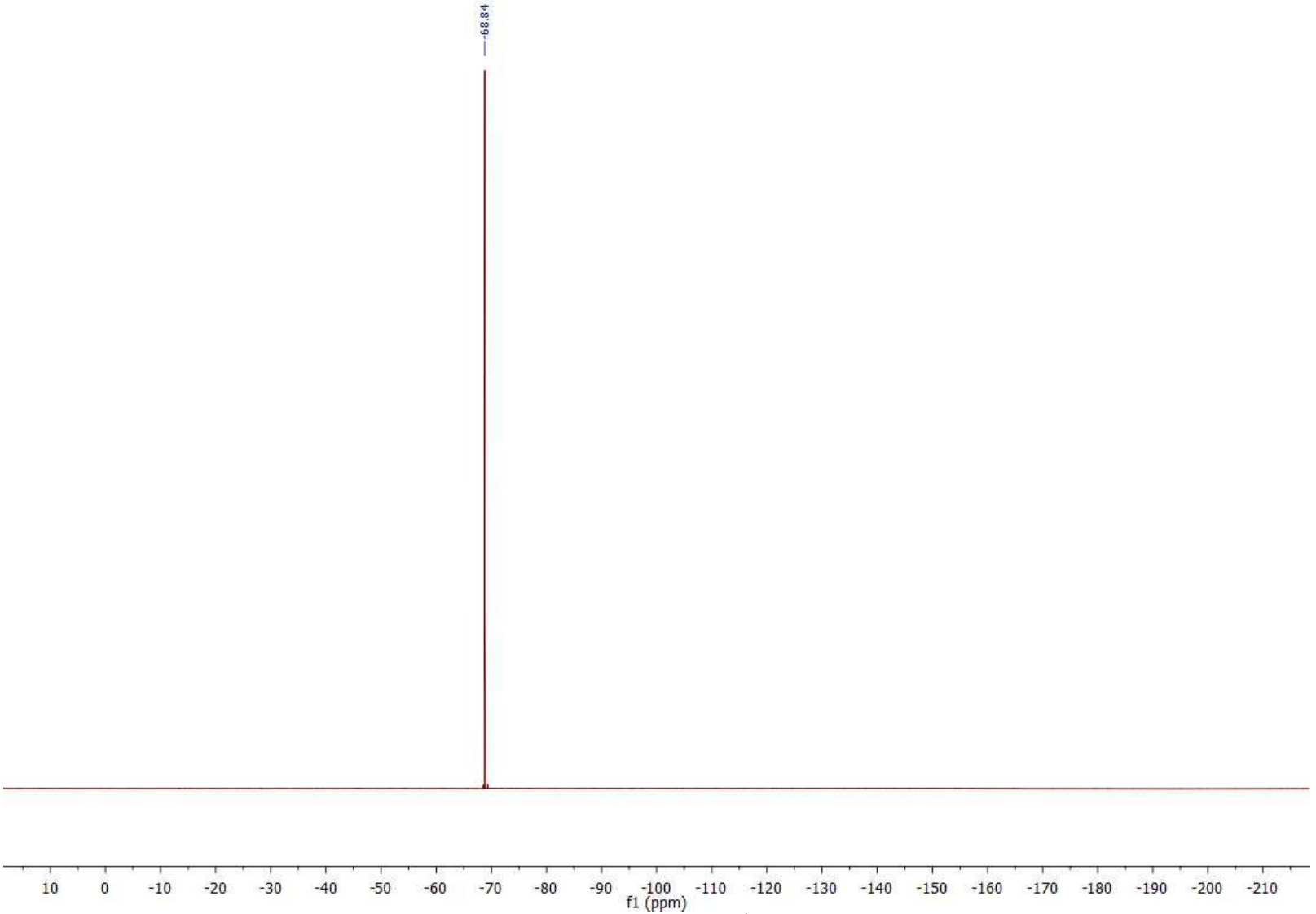
^{13}C NMR ($CDCl_3$, 100 MHz). 2,2,2-Trifluoro-1-(4-(pyrimidin-2-yl)piperazin-1-yl)ethan-1-one (**2n**)



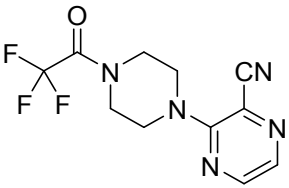


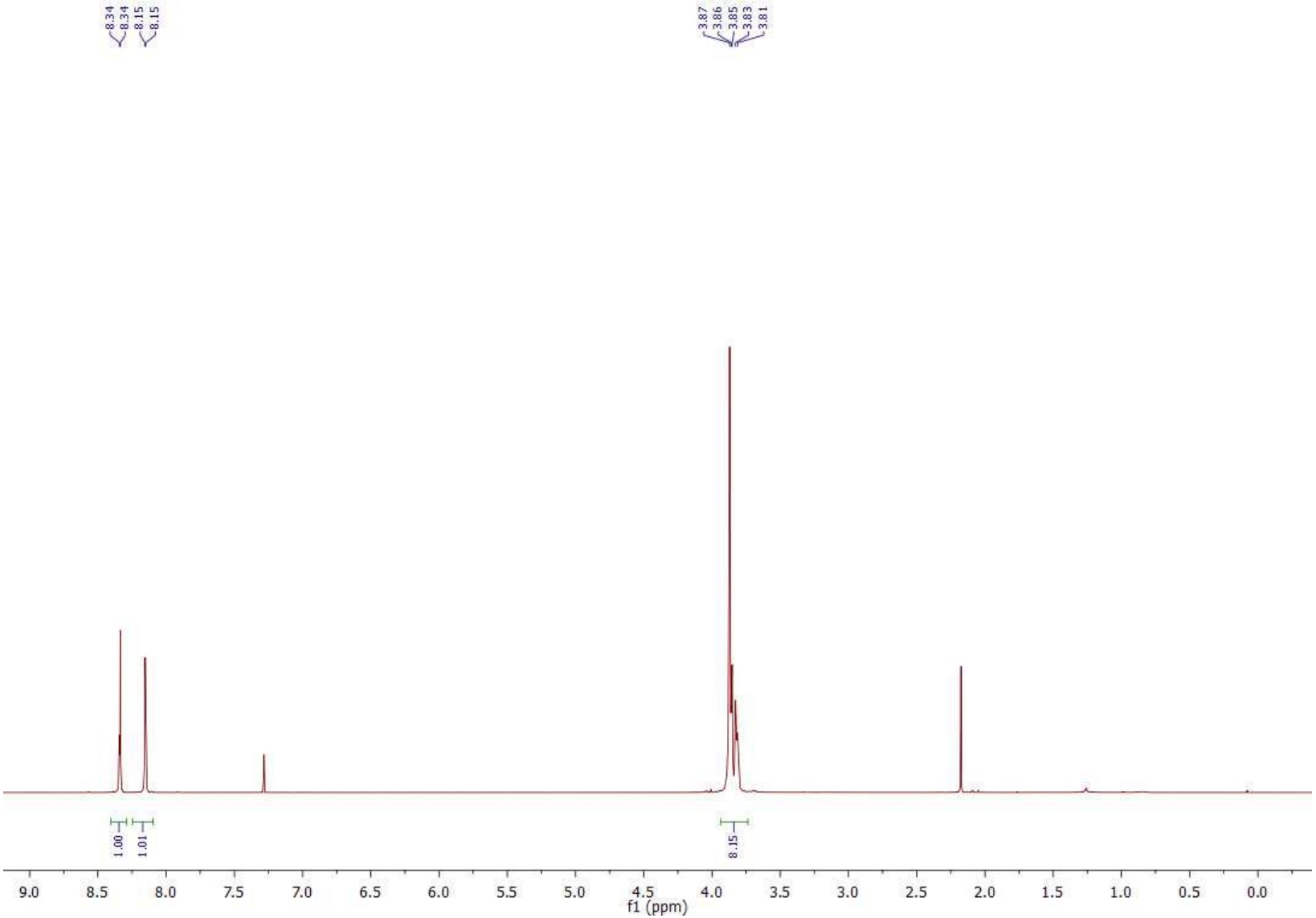
^{19}F NMR ($CDCl_3$, 377 MHz). 2,2,2-Trifluoro-1-(4-(pyrimidin-2-yl)piperazin-1-yl)ethan-1-one (**2n**)



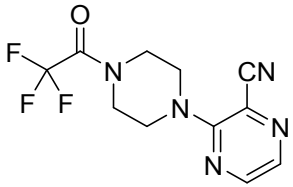


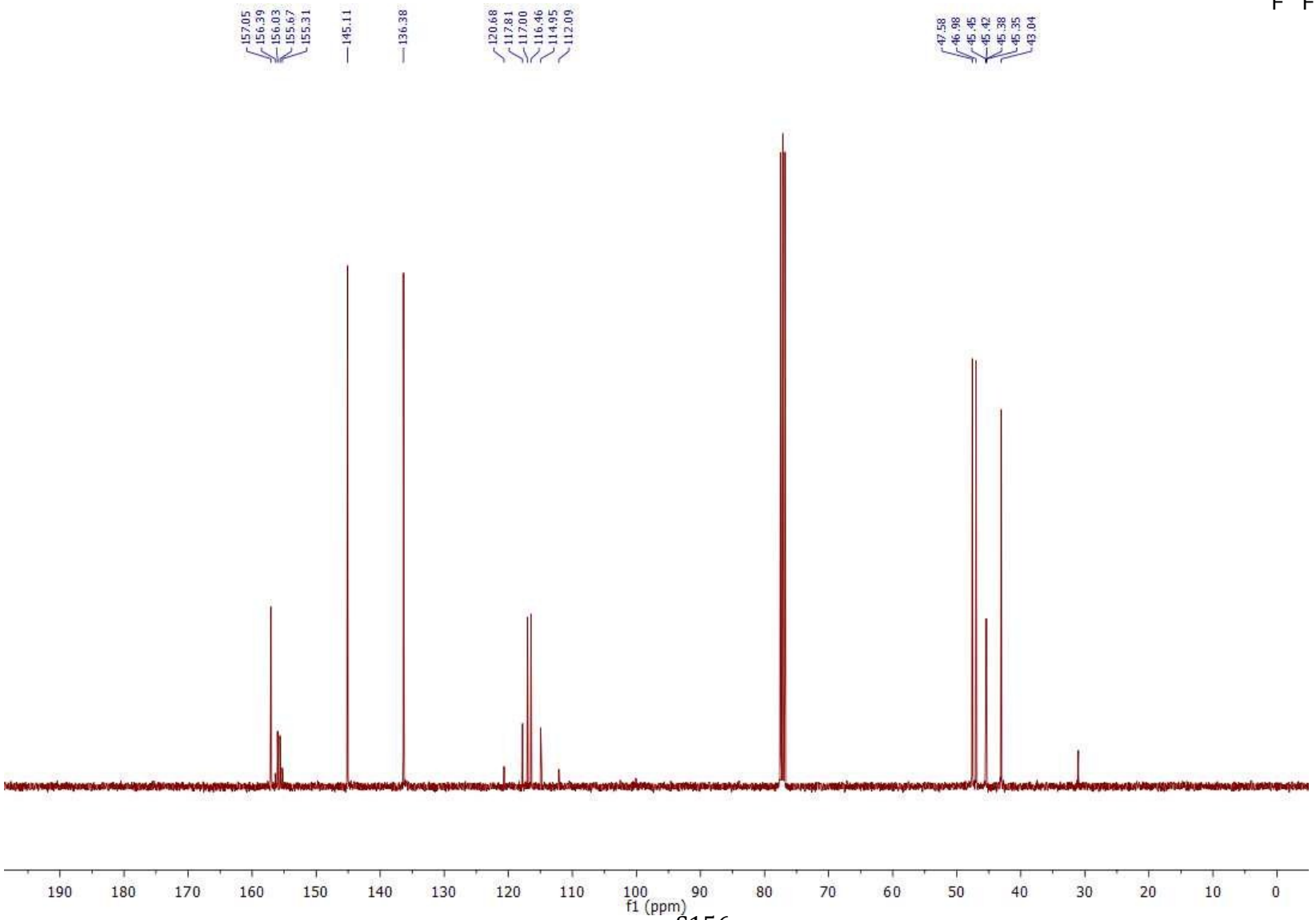
^{1}H NMR ($CDCl_3$, 400 MHz). 3-(4-(2,2,2-Trifluoroacetyl)piperazin-1-yl)pyrazine-2-carbonitrile (**2o**)



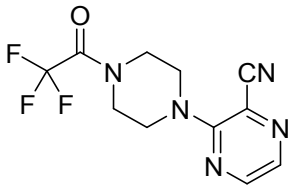


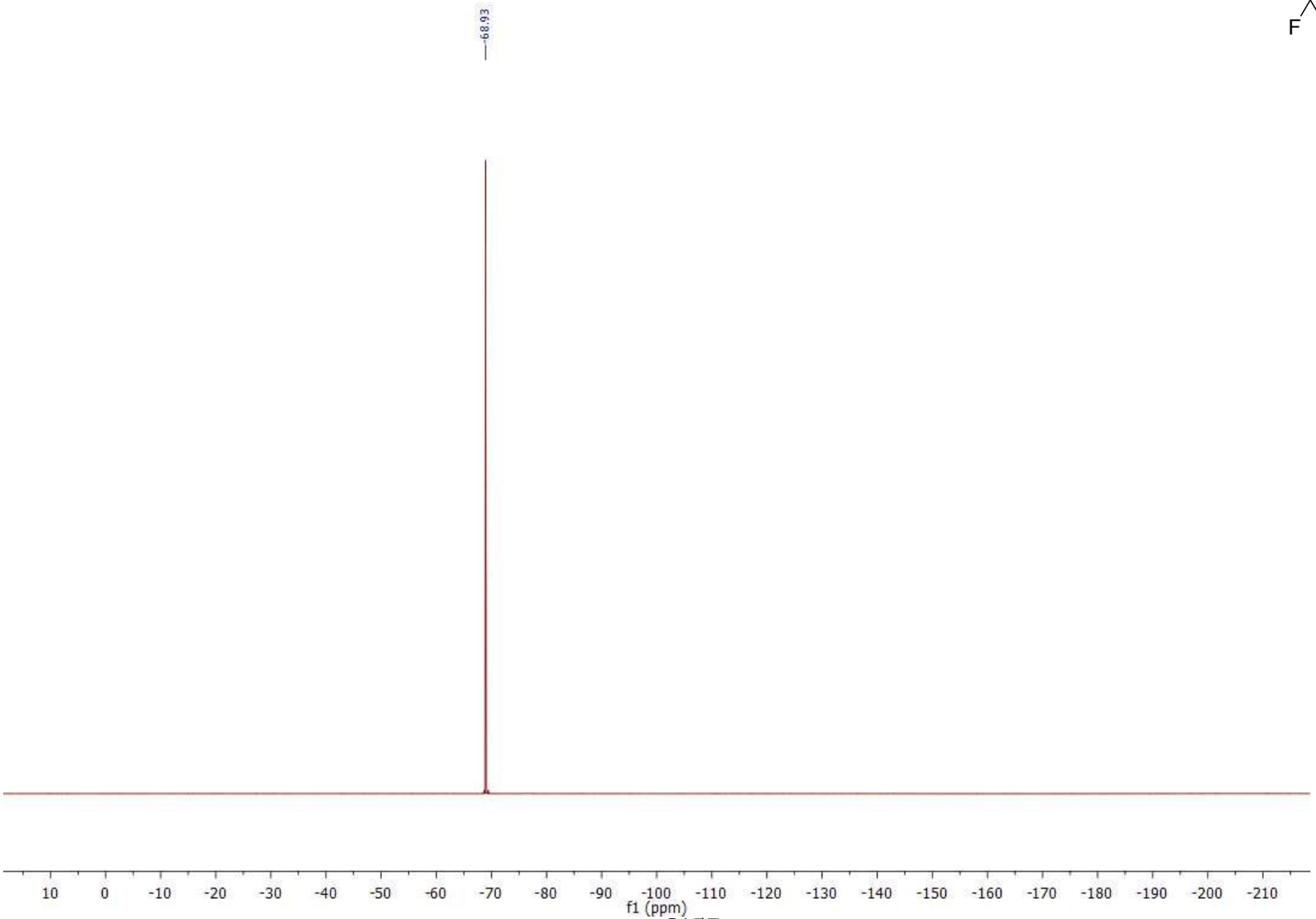
^{13}C NMR ($CDCl_3$, 100 MHz). 3-(4-(2,2,2-Trifluoroacetyl)piperazin-1-yl)pyrazine-2-carbonitrile (**2o**)

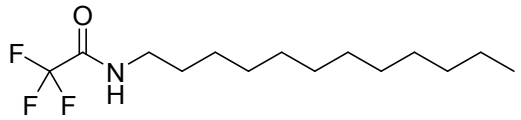




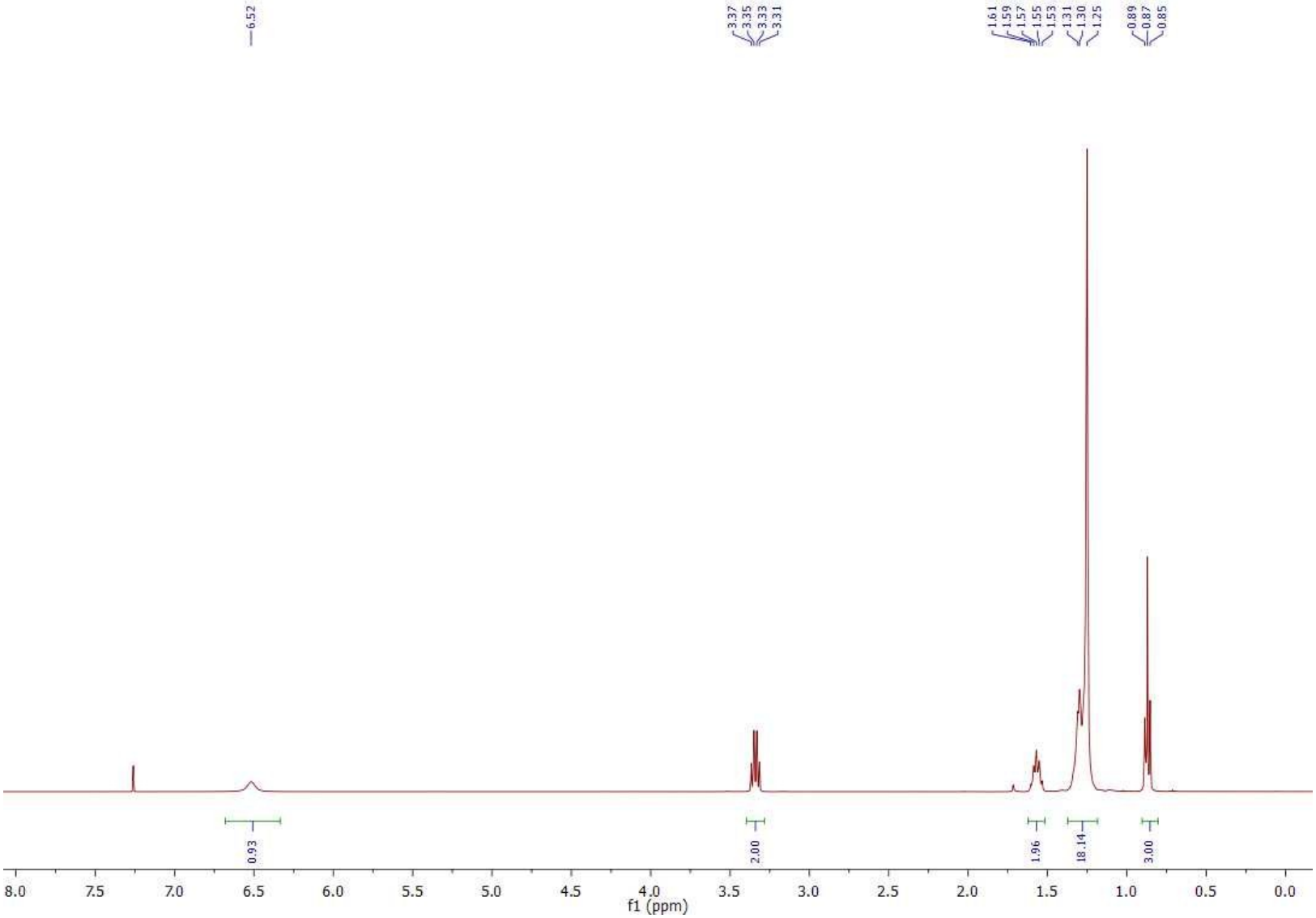
^{19}F NMR ($CDCl_3$, 377 MHz). 3-(4-(2,2,2-Trifluoroacetyl)piperazin-1-yl)pyrazine-2-carbonitrile (**2o**)



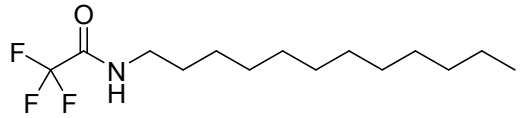


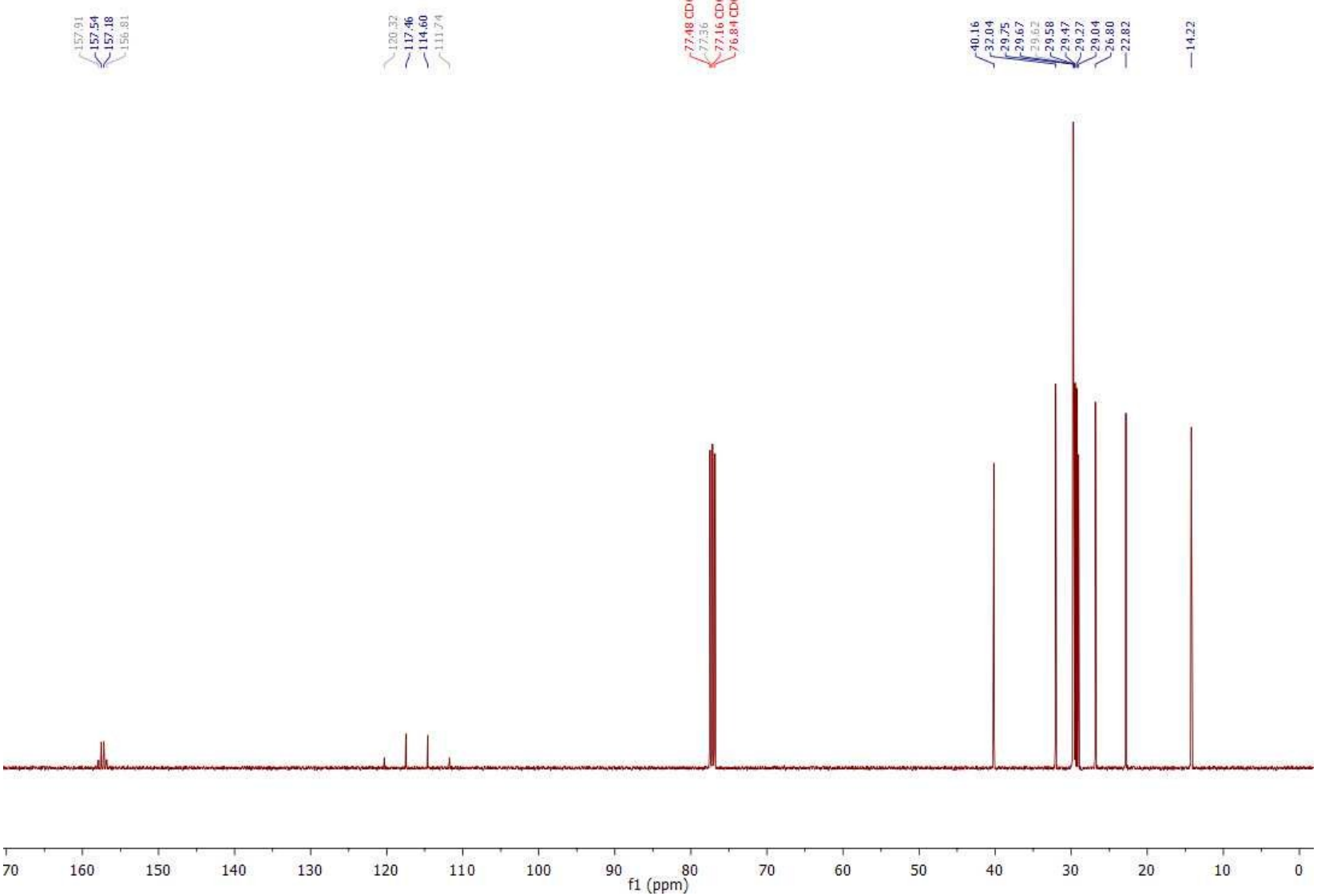


^{1}H NMR ($CDCl_3$, 400 MHz). *N*-Dodecyl-2,2,2-trifluoroacetamide (**2p**)

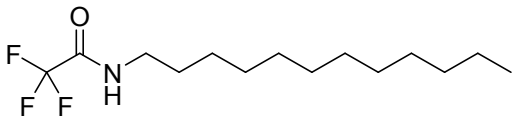


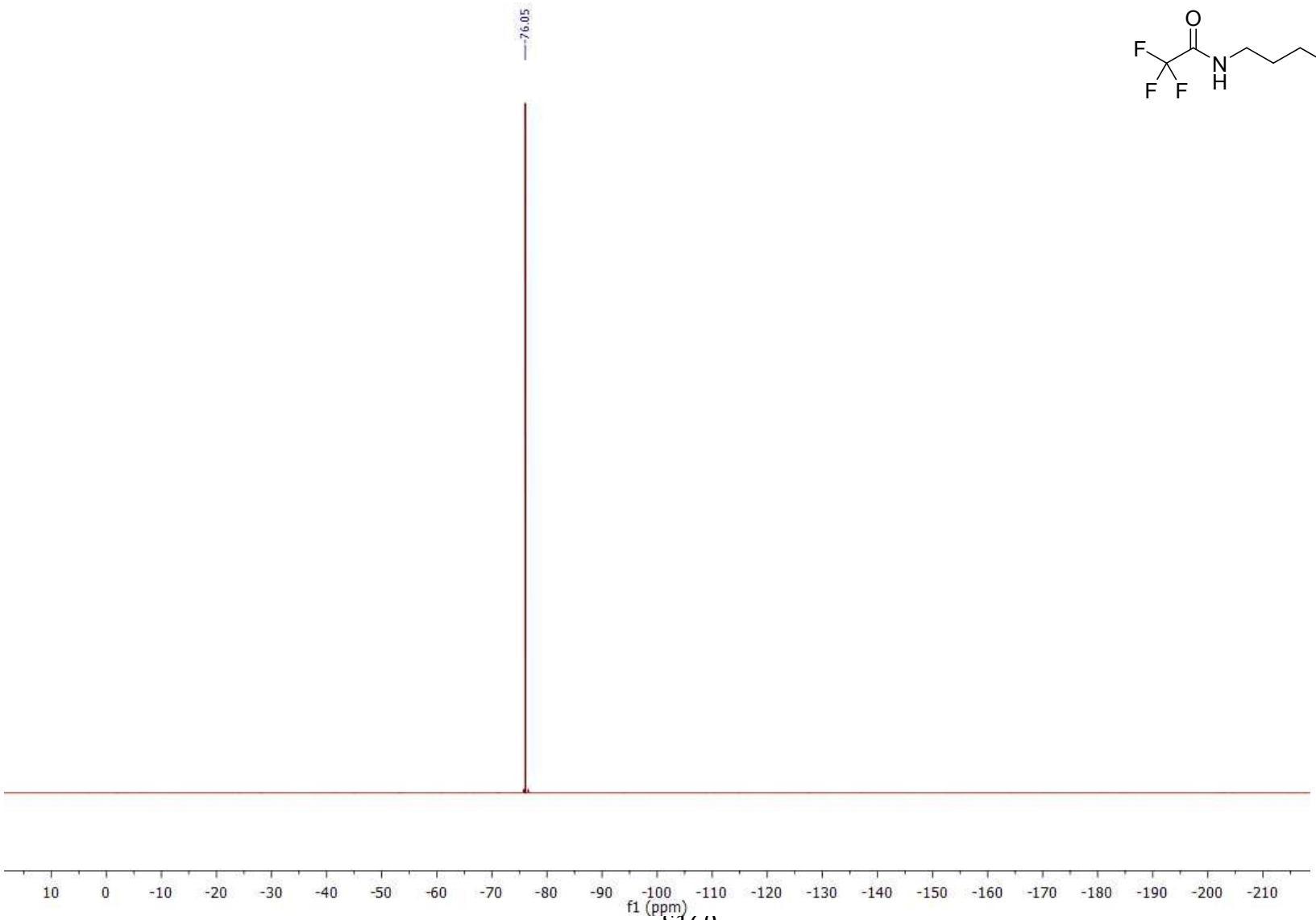
^{13}C NMR ($CDCl_3$, 100 MHz). *N*-Dodecyl-2,2,2-trifluoroacetamide (**2p**)



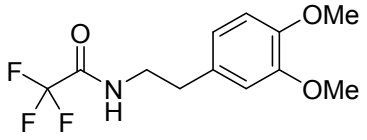


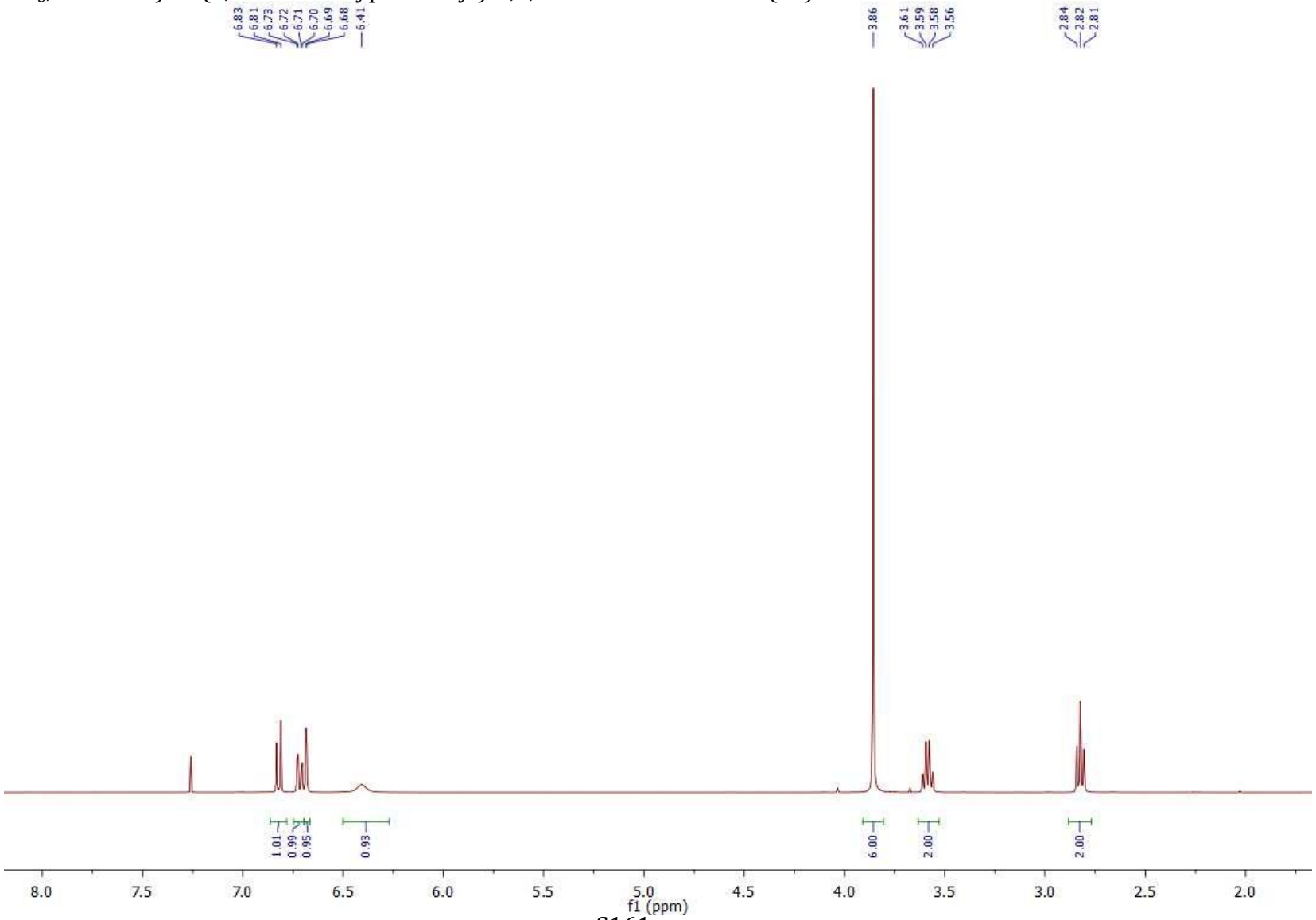
^{19}F NMR ($CDCl_3$, 377 MHz). *N*-Dodecyl-2,2,2-trifluoroacetamide (**2p**)

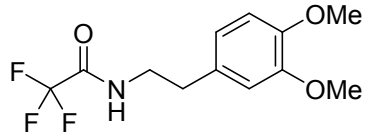




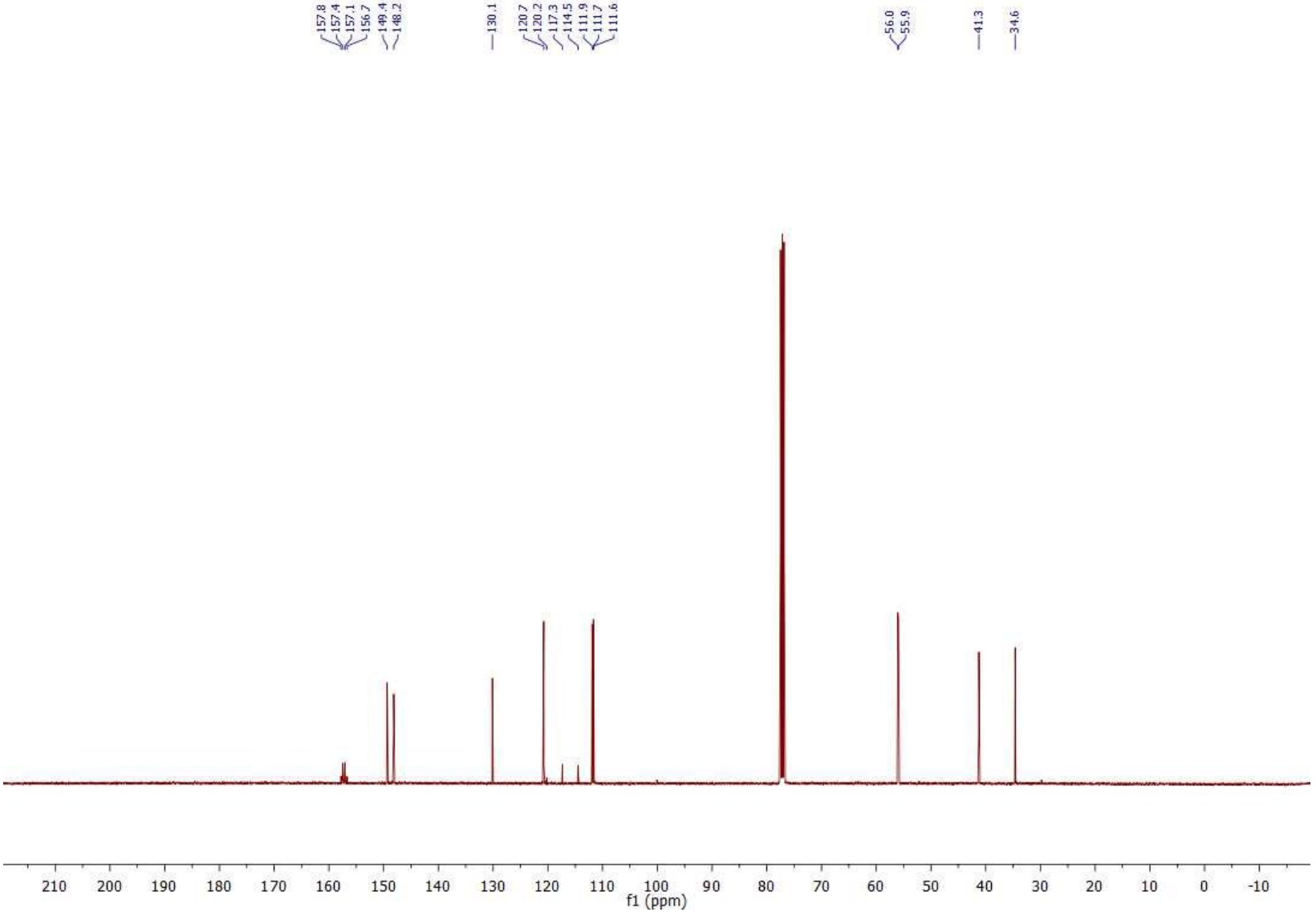
^{1}H NMR ($CDCl_3$, 400 MHz). *N*-(3,4-dimethoxyphenethyl)-2,2,2-trifluoroacetamide (**2r**)



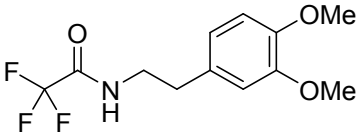


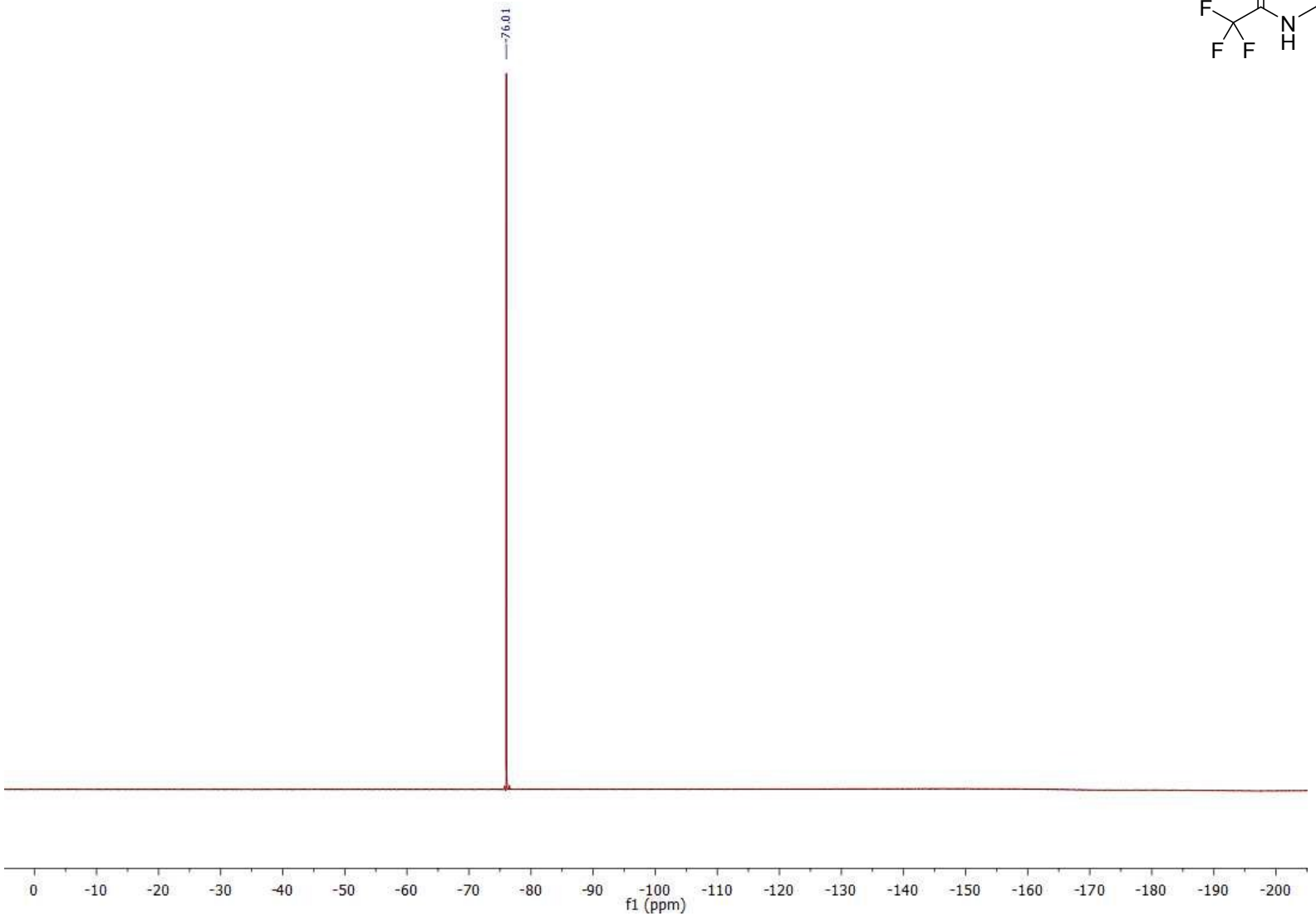


^{13}C NMR ($CDCl_3$, 100 MHz). *N*-(3,4-dimethoxyphenethyl)-2,2,2-trifluoroacetamide (**2r**)

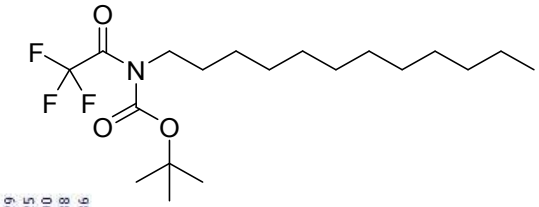


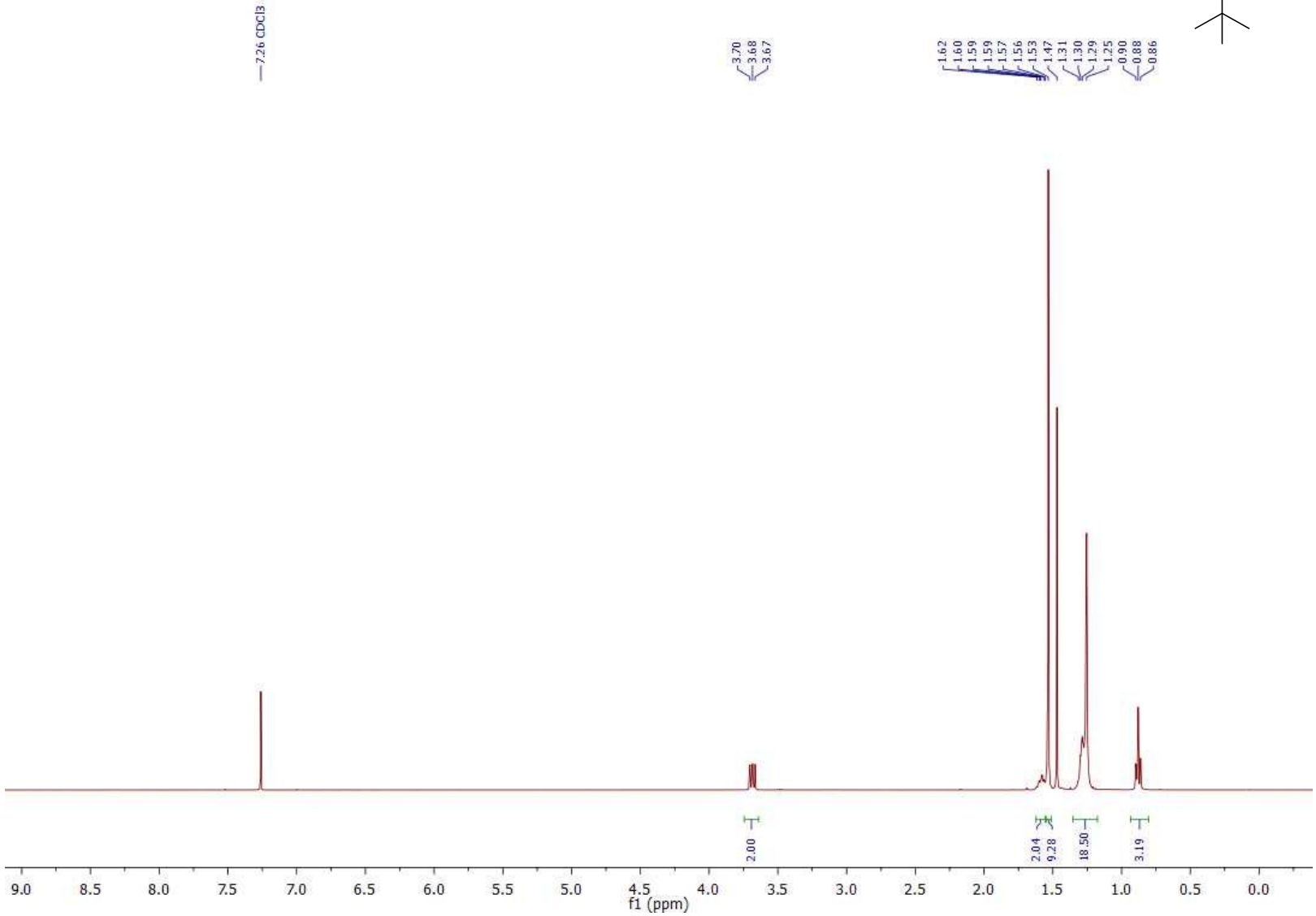
^{19}F NMR ($CDCl_3$, 377 MHz). *N*-(3,4-dimethoxyphenethyl)-2,2,2-trifluoroacetamide (**2r**)



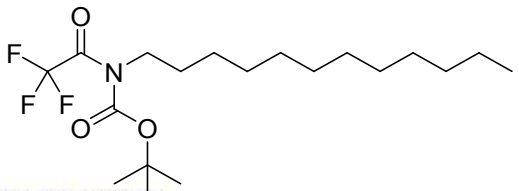


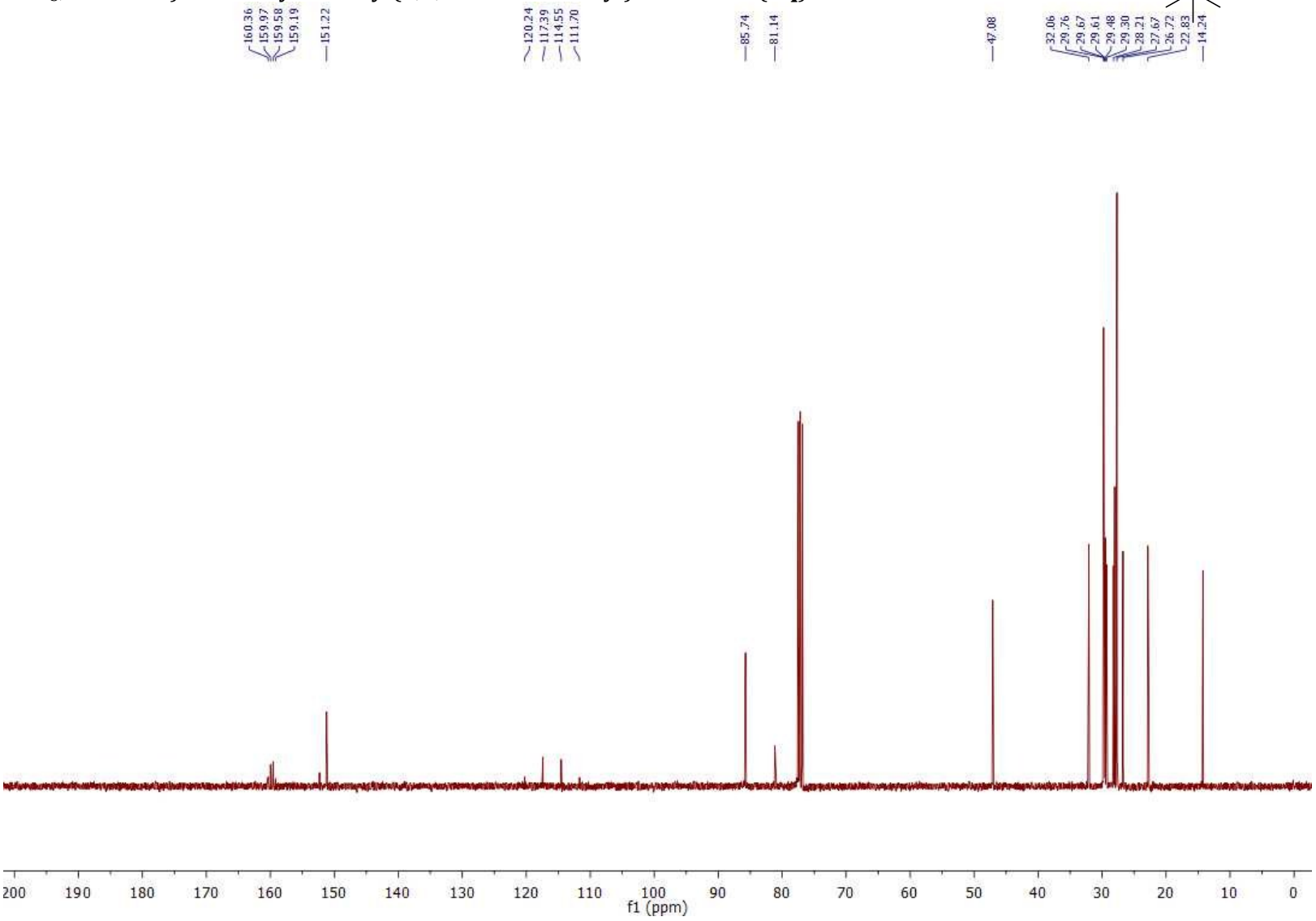
^{1}H NMR ($CDCl_3$, 400 MHz). *tert*-Butyl dodecyl(2,2,2-trifluoroacetyl)carbamate (**2q**)



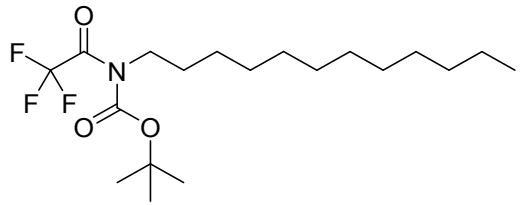


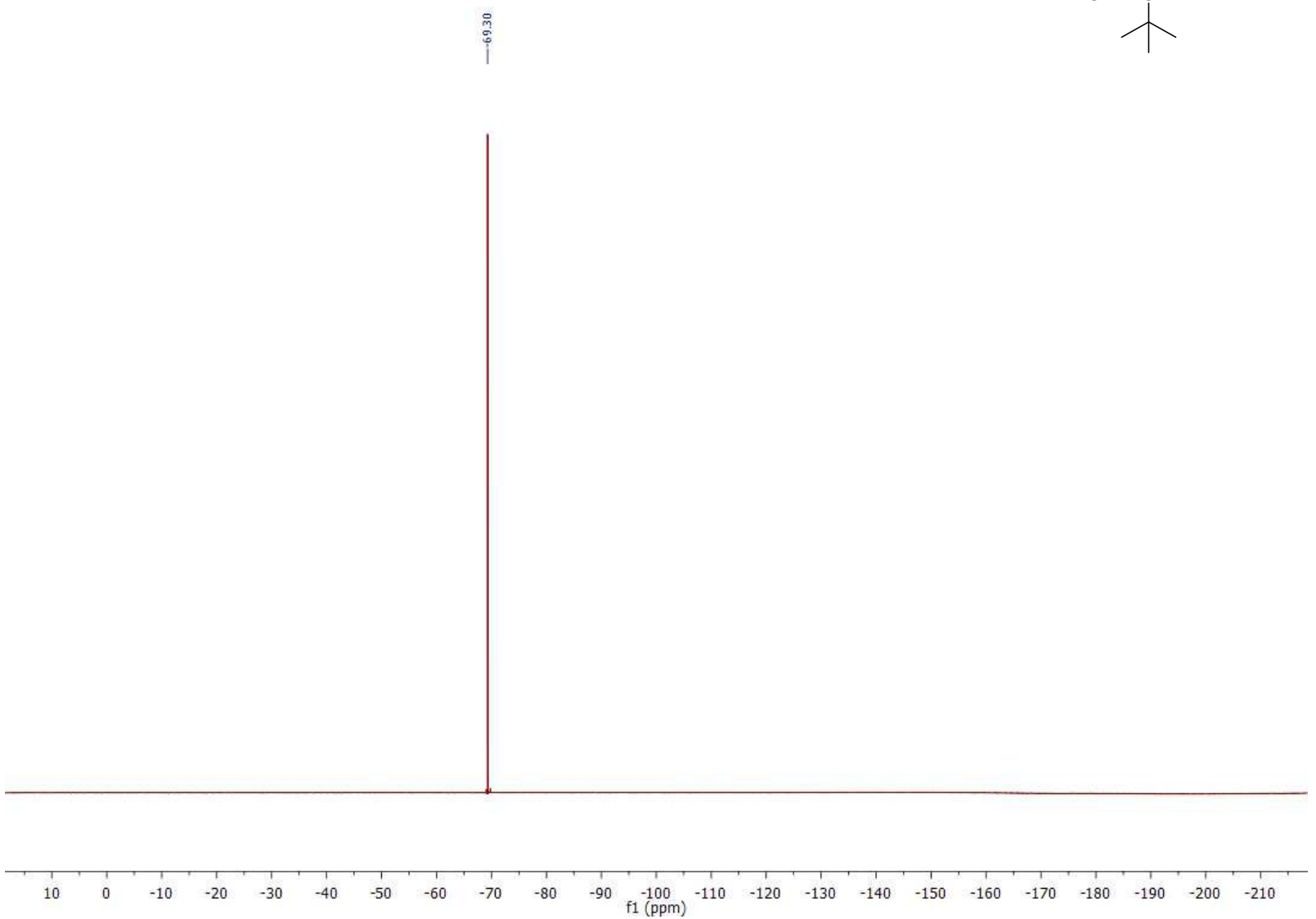
^{13}C NMR ($CDCl_3$, 100 MHz). *tert*-Butyl dodecyl(2,2,2-trifluoroacetyl)carbamate (**2q**)



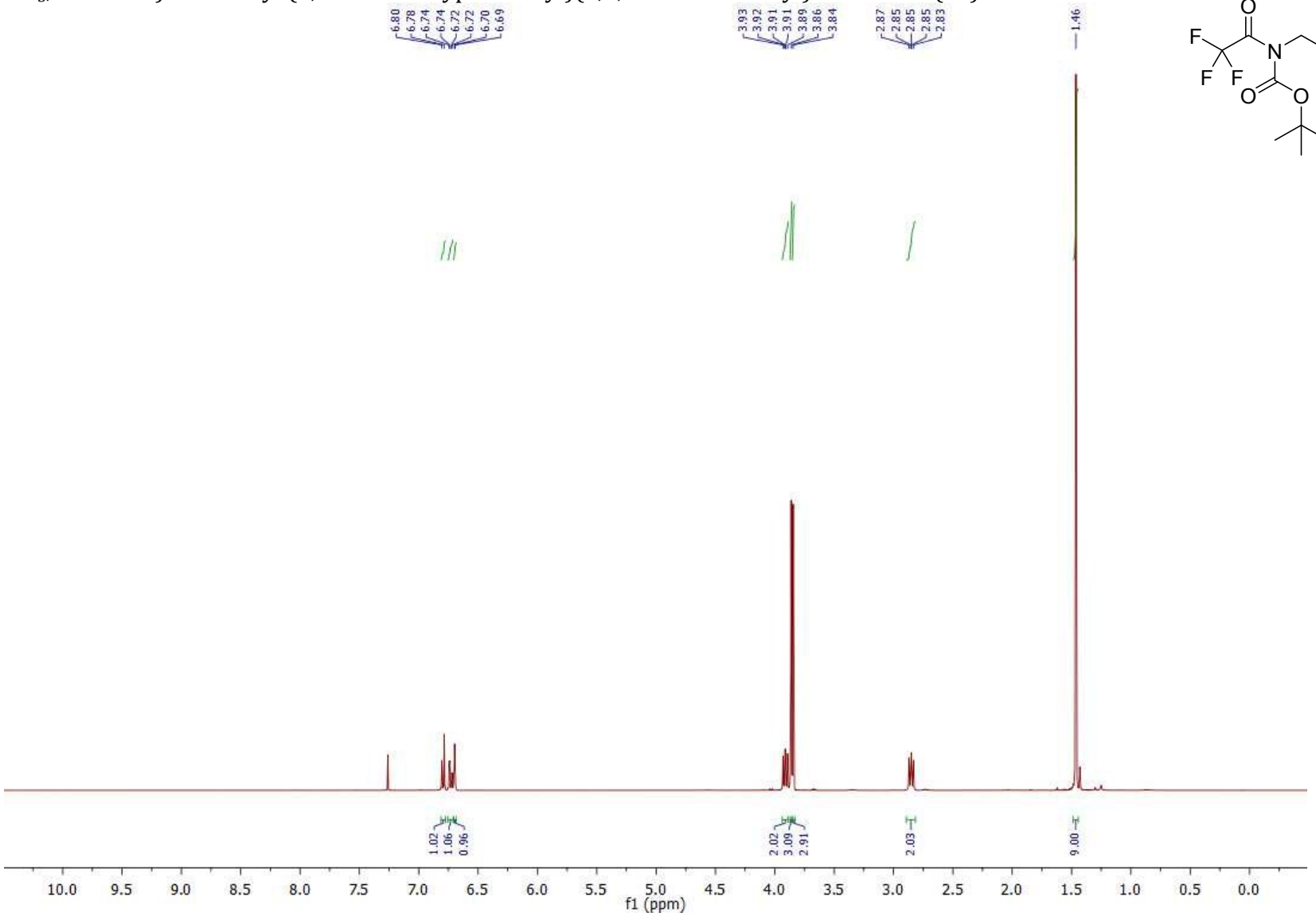


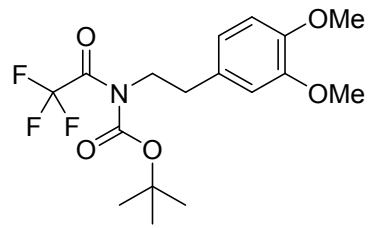
^{19}F NMR ($CDCl_3$, 377 MHz). *tert*-Butyl dodecyl(2,2,2-trifluoroacetyl)carbamate (**2q**)



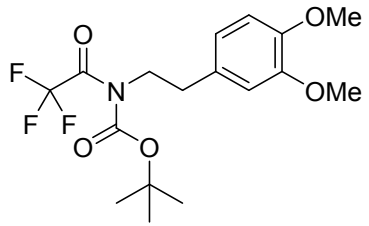


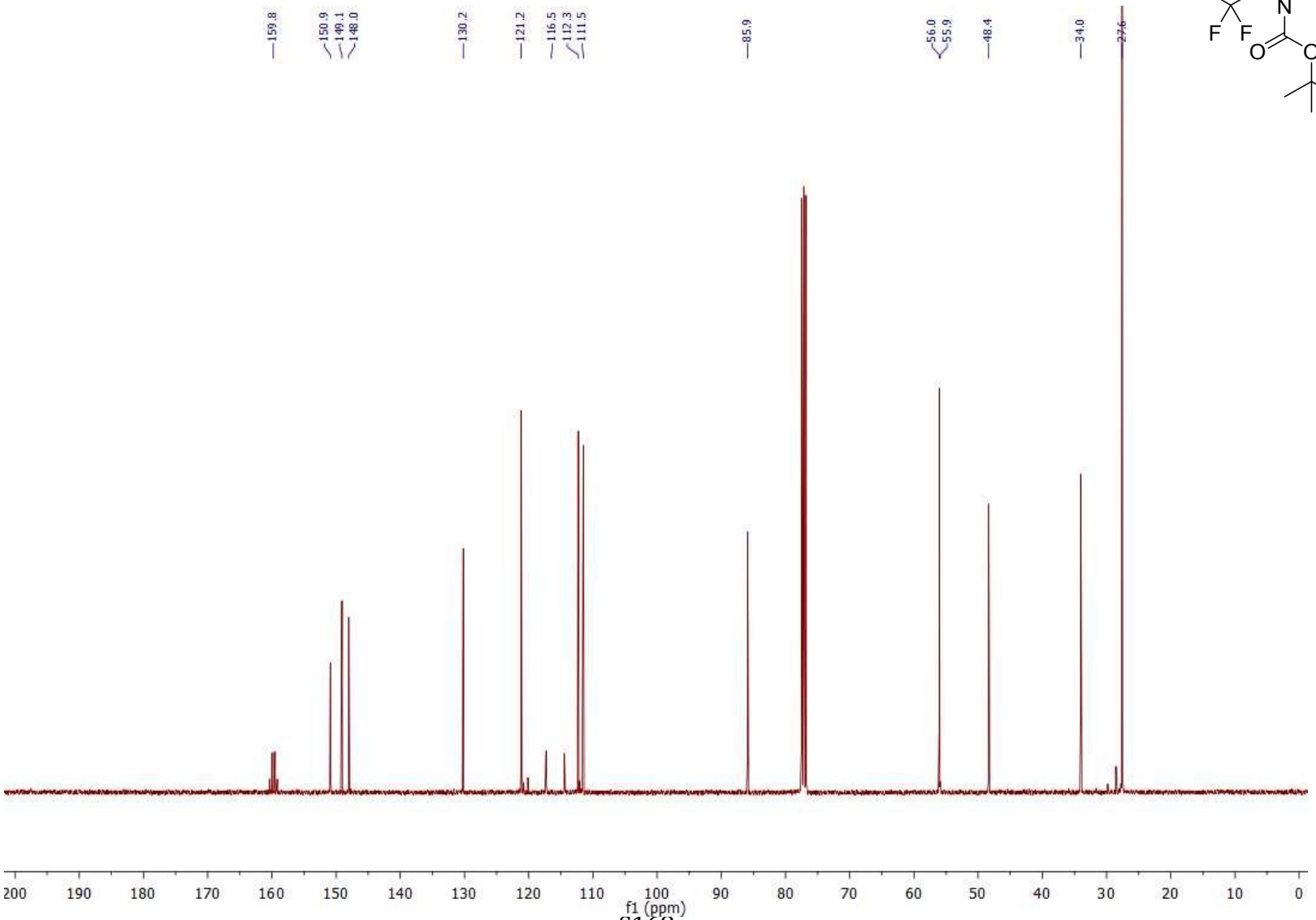
^{1}H NMR ($CDCl_3$, 400 MHz). *tert*-Butyl (3,4-dimethoxyphenethyl)(2,2,2-trifluoroacetyl)carbamate (**2s**)



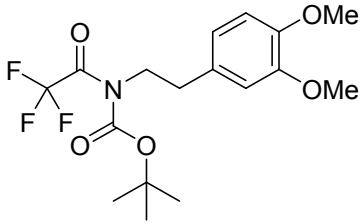


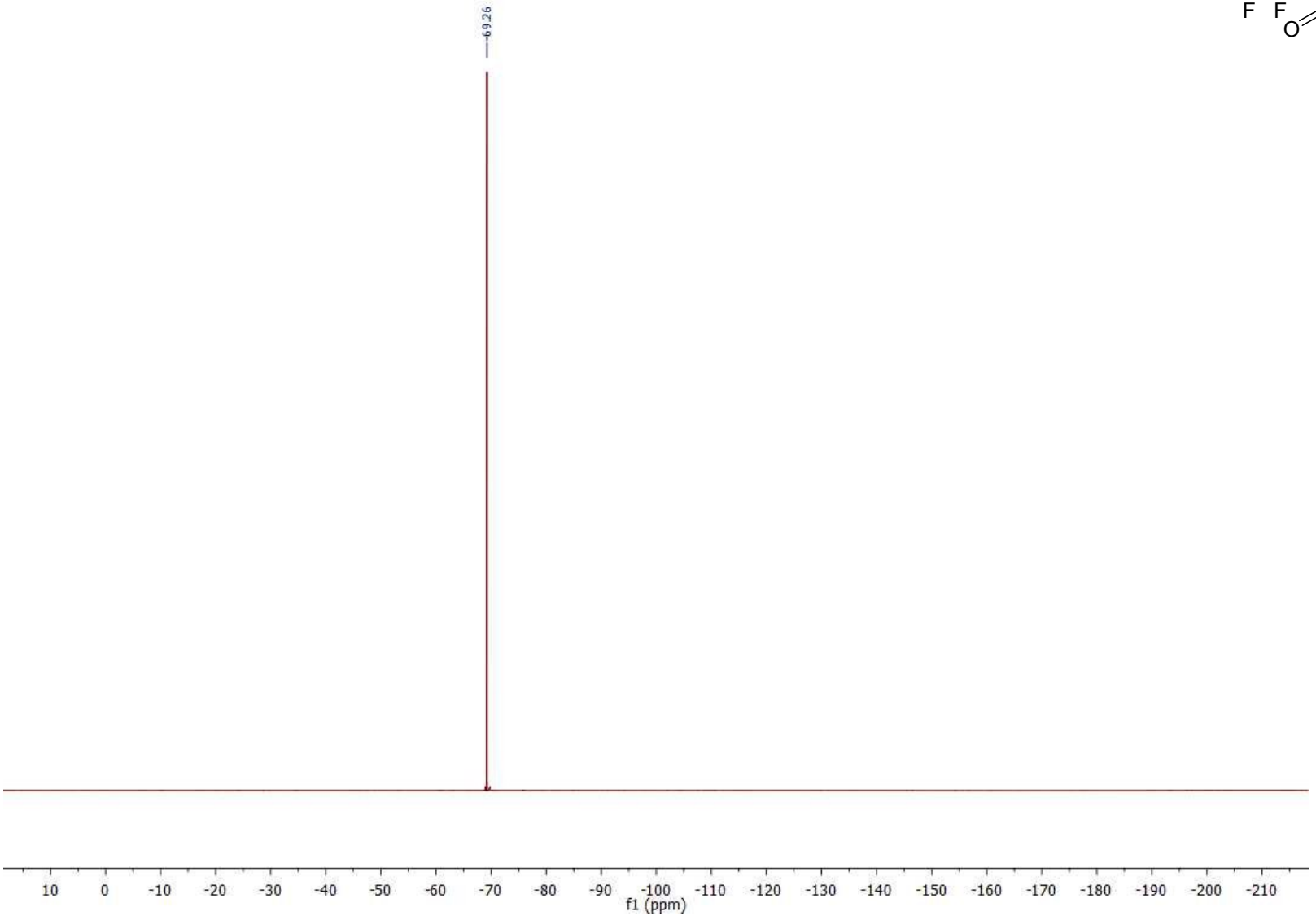
^{13}C NMR ($CDCl_3$, 100 MHz). *tert*-Butyl (3,4-dimethoxyphenethyl)(2,2,2-trifluoroacetyl)carbamate (**2s**)





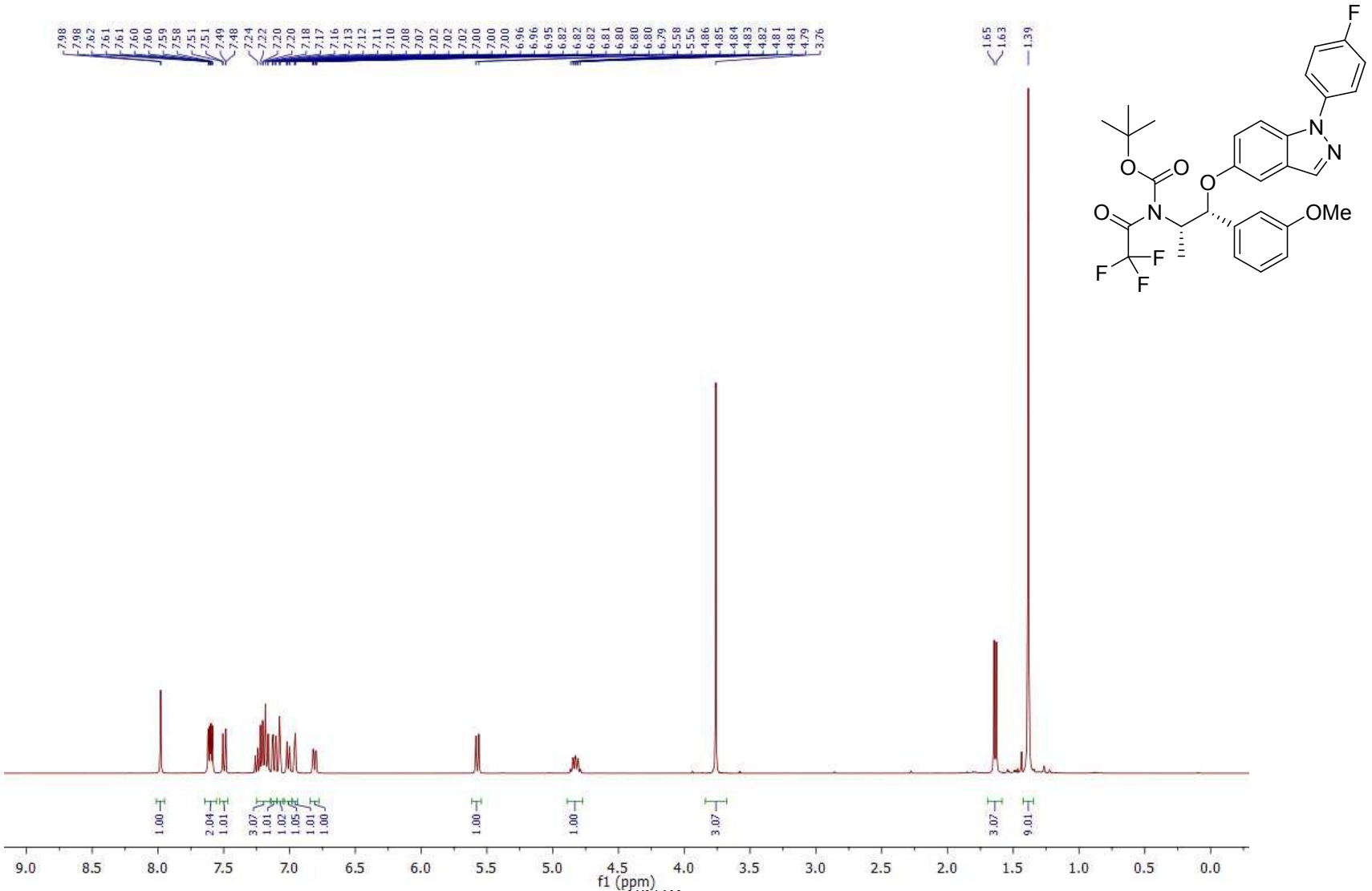
^{19}F NMR ($CDCl_3$, 377 MHz). *tert*-Butyl (3,4-dimethoxyphenethyl)(2,2,2-trifluoroacetyl)carbamate (**2s**)





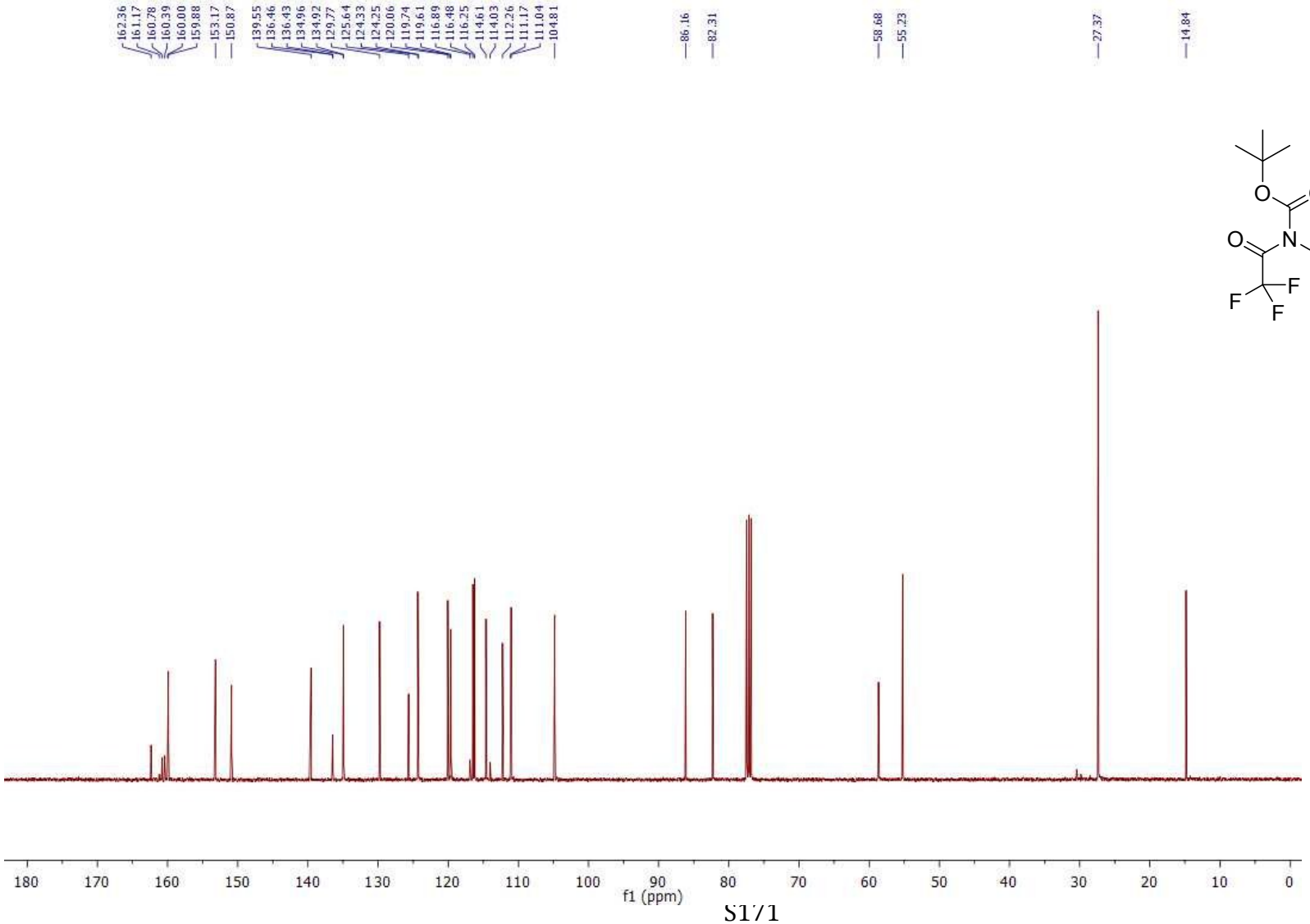
^{1}H NMR ($CDCl_3$, 400 MHz).

tert-Butyl 2,2,2-trifluoroacetyl((1*R*,2*S*)-1-(1-(4-fluorophenyl)-1*H*-indazol-5-yloxy)-1-(3-methoxyphenyl)propan-2-yl)carbamate (**2u**)



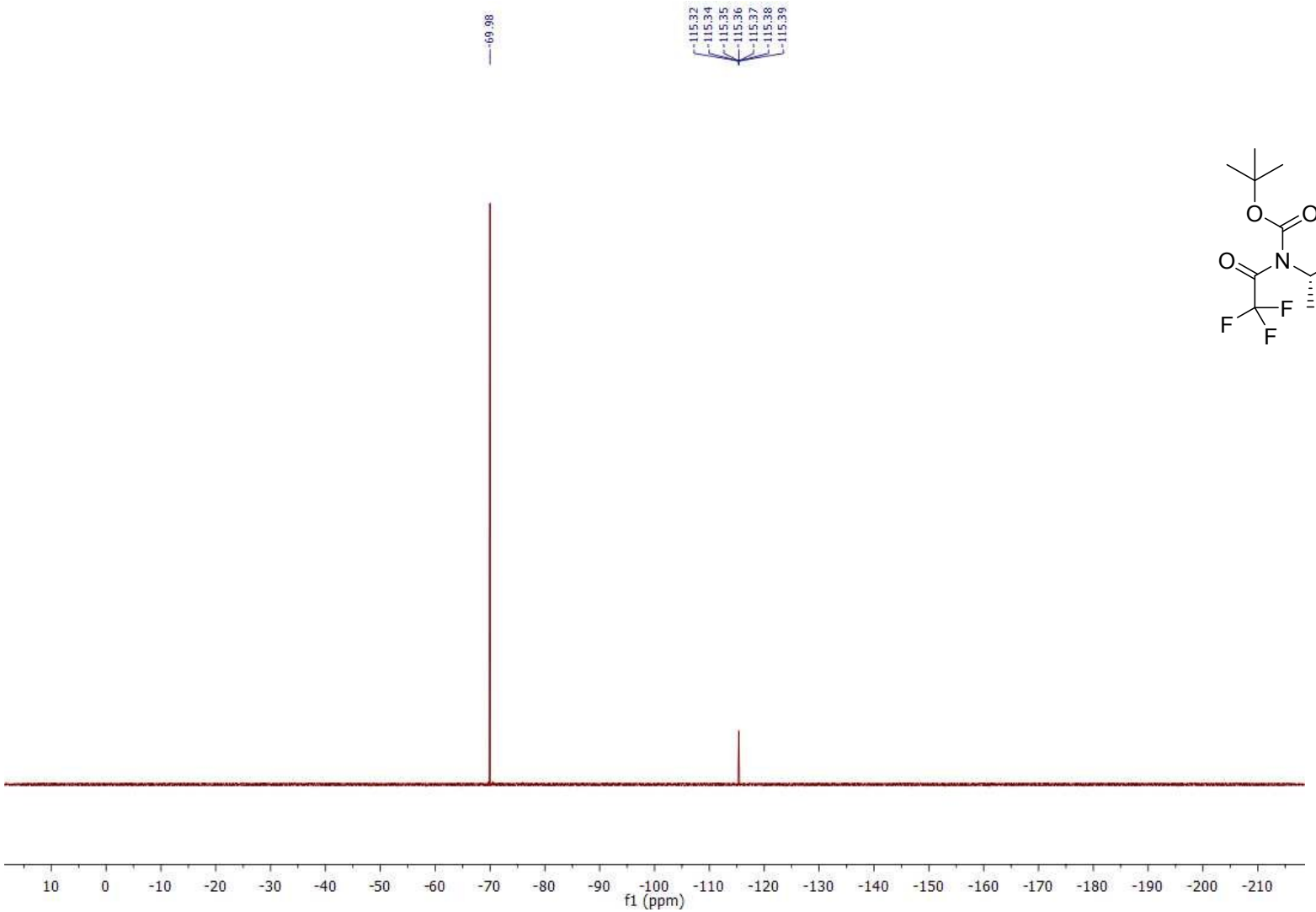
^{13}C NMR ($CDCl_3$, 100 MHz).

tert-Butyl 2,2,2-trifluoroacetyl((1*R*,2*S*)-1-(1-(4-fluorophenyl)-1*H*-indazol-5-yloxy)-1-(3-methoxyphenyl)propan-2-yl)carbamate (**2u**)

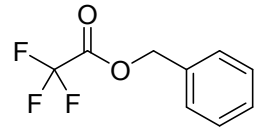


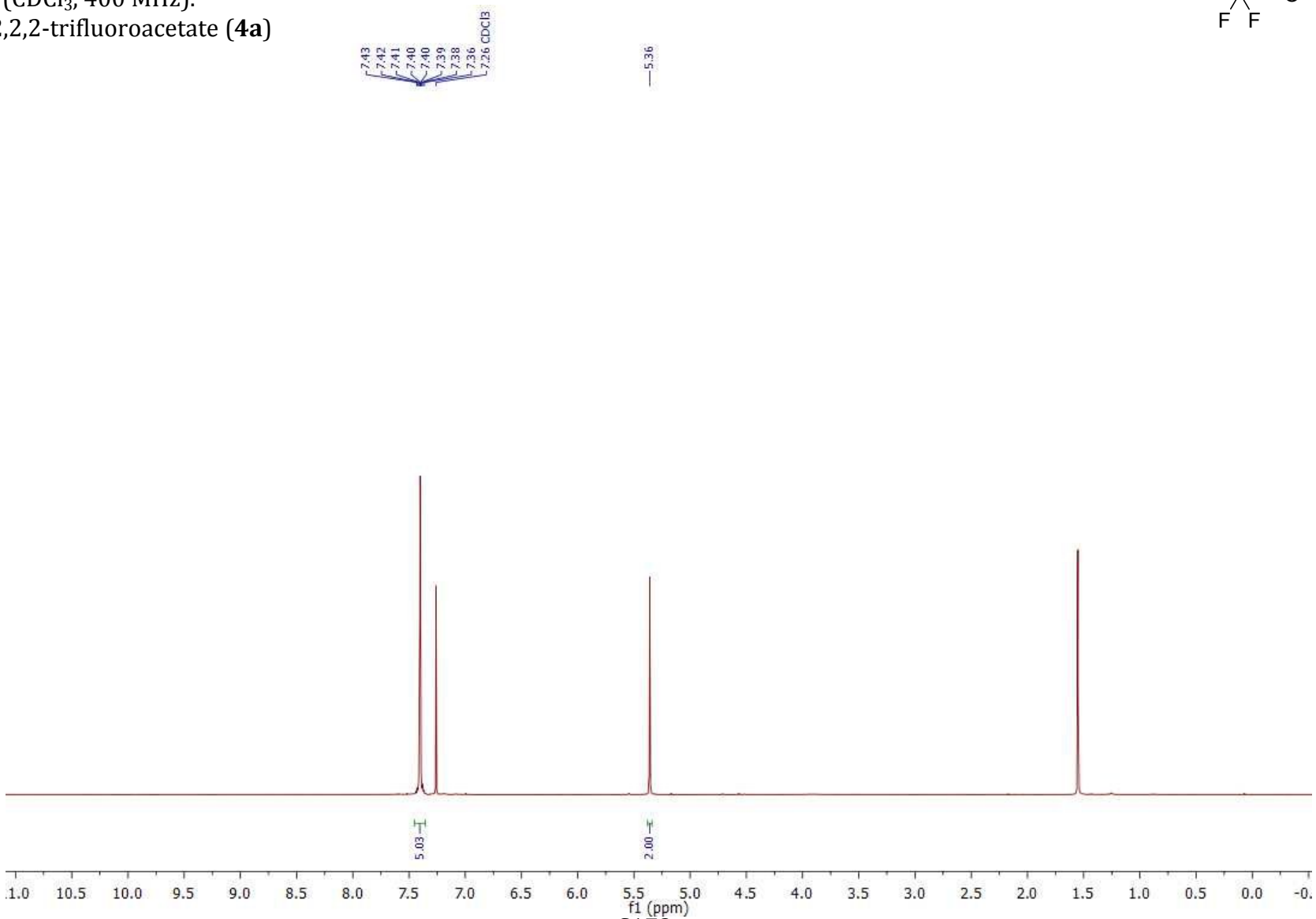
^{19}F NMR ($CDCl_3$, 377 MHz).

tert-Butyl 2,2,2-trifluoroacetyl((1*R*,2*S*)-1-(1-(4-fluorophenyl)-1*H*-indazol-5-yloxy)-1-(3-methoxyphenyl)propan-2-yl)carbamate (**2u**)

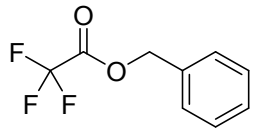


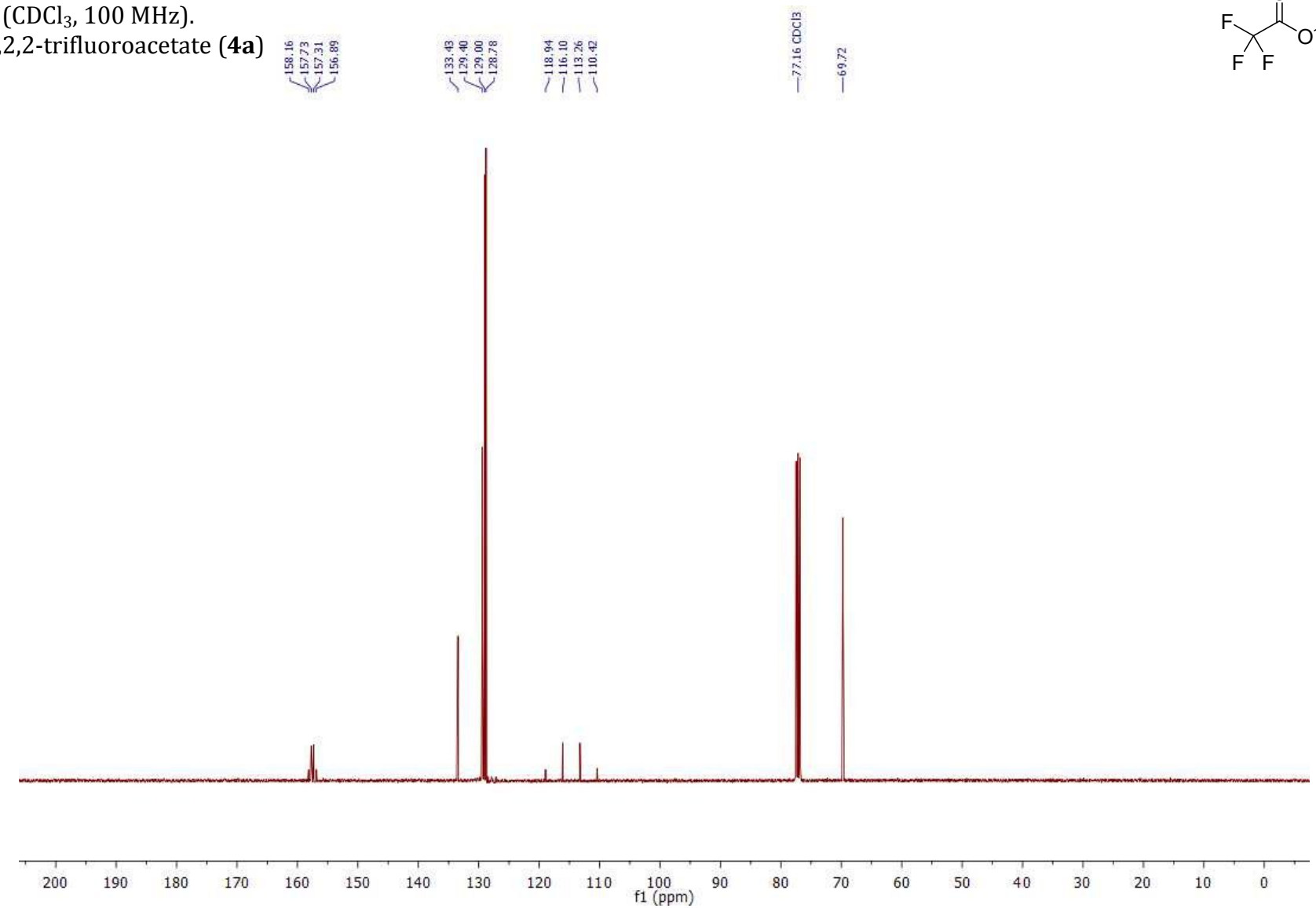
^{1}H NMR ($CDCl_3$, 400 MHz).
Benzyl 2,2,2-trifluoroacetate (**4a**)



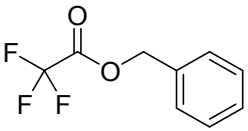


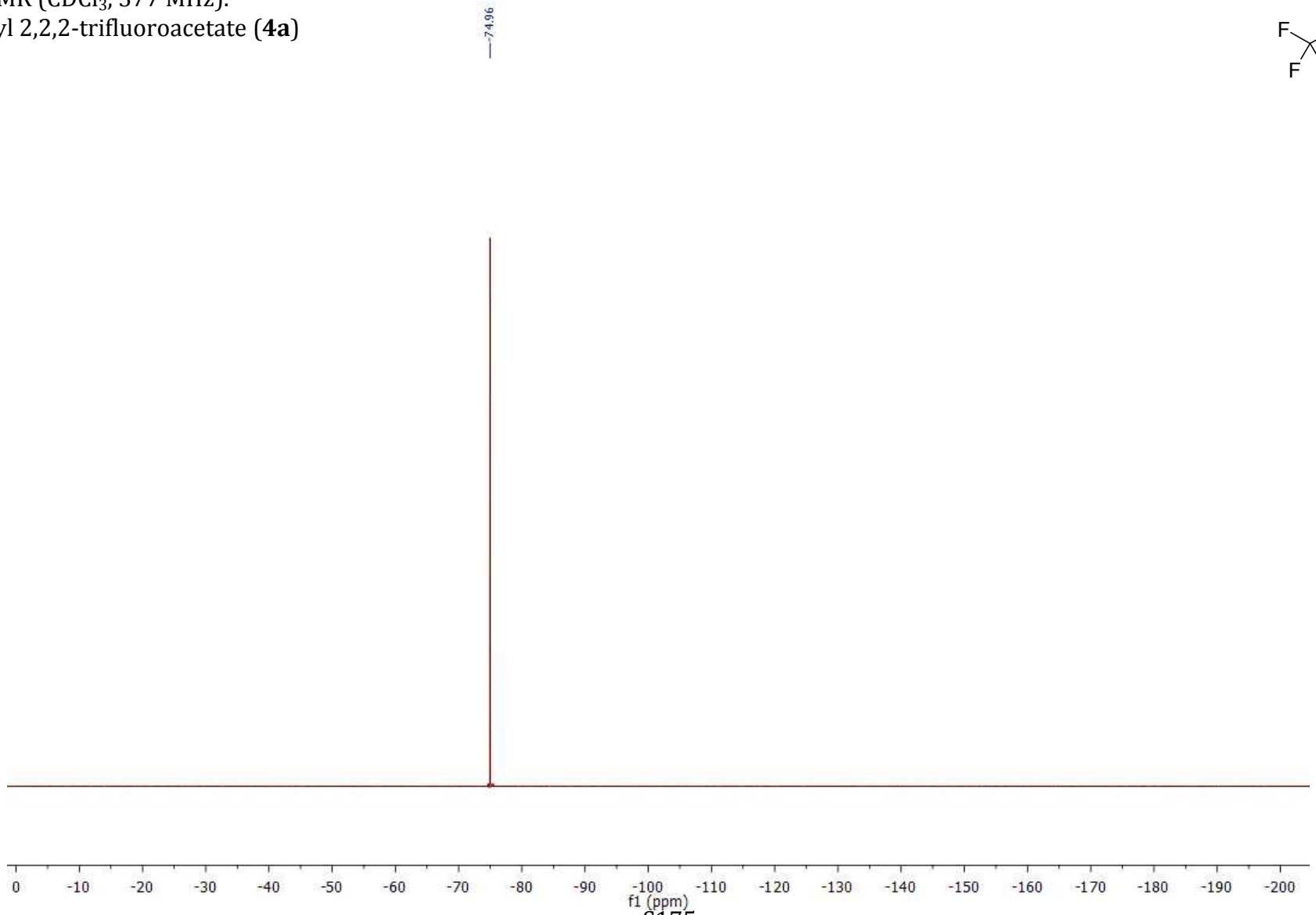
^{13}C NMR ($CDCl_3$, 100 MHz).
Benzyl 2,2,2-trifluoroacetate (**4a**)



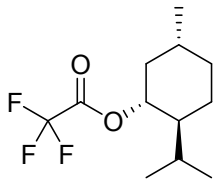


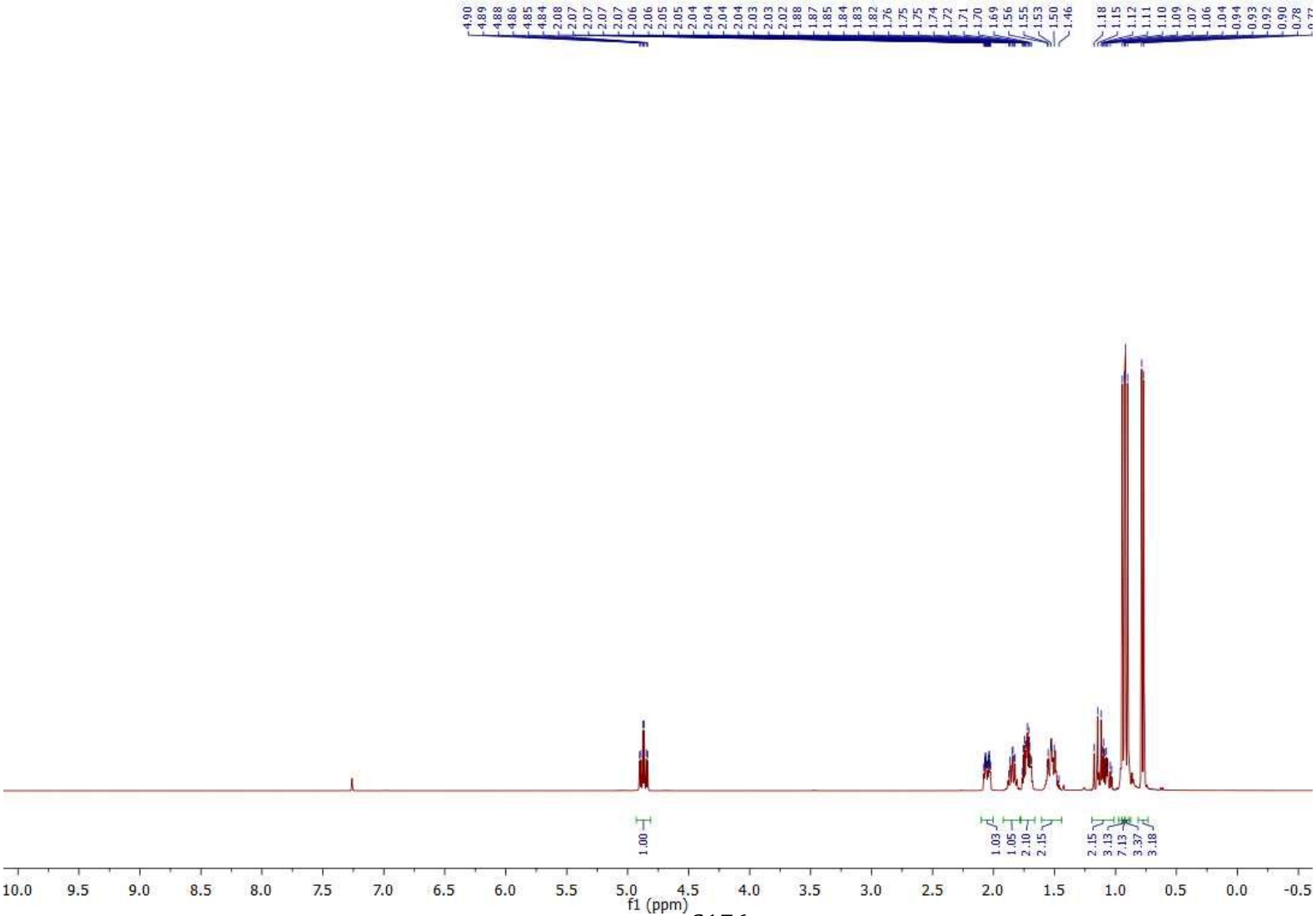
^{19}F NMR ($CDCl_3$, 377 MHz).
Benzyl 2,2,2-trifluoroacetate (**4a**)



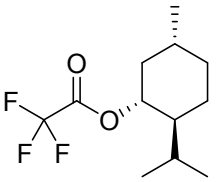


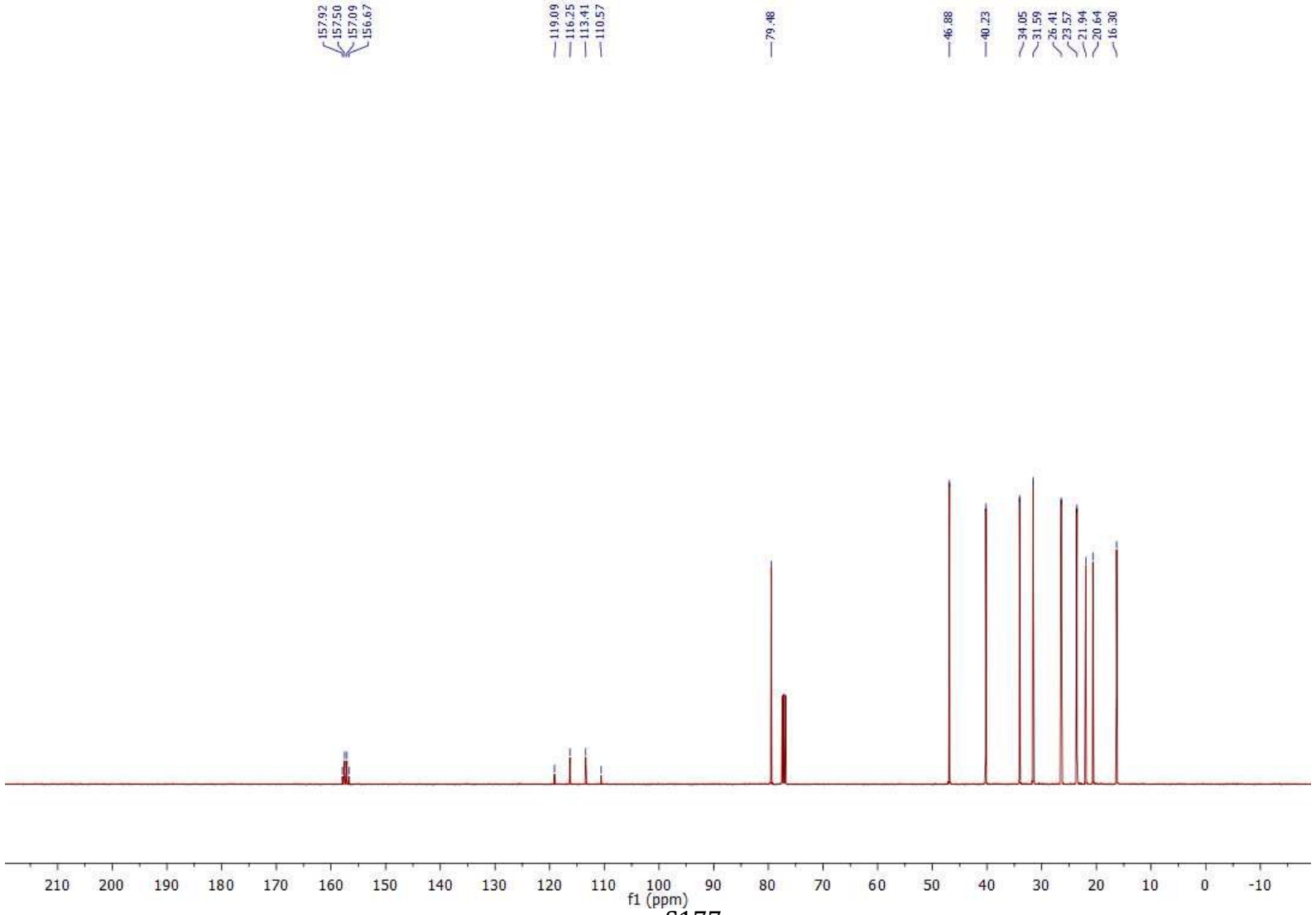
^{1}H NMR ($CDCl_3$, 400 MHz).
(-)-Menthyl 2,2,2-trifluoroacetate (**4b**)



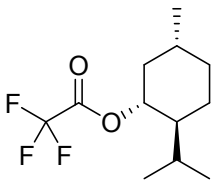


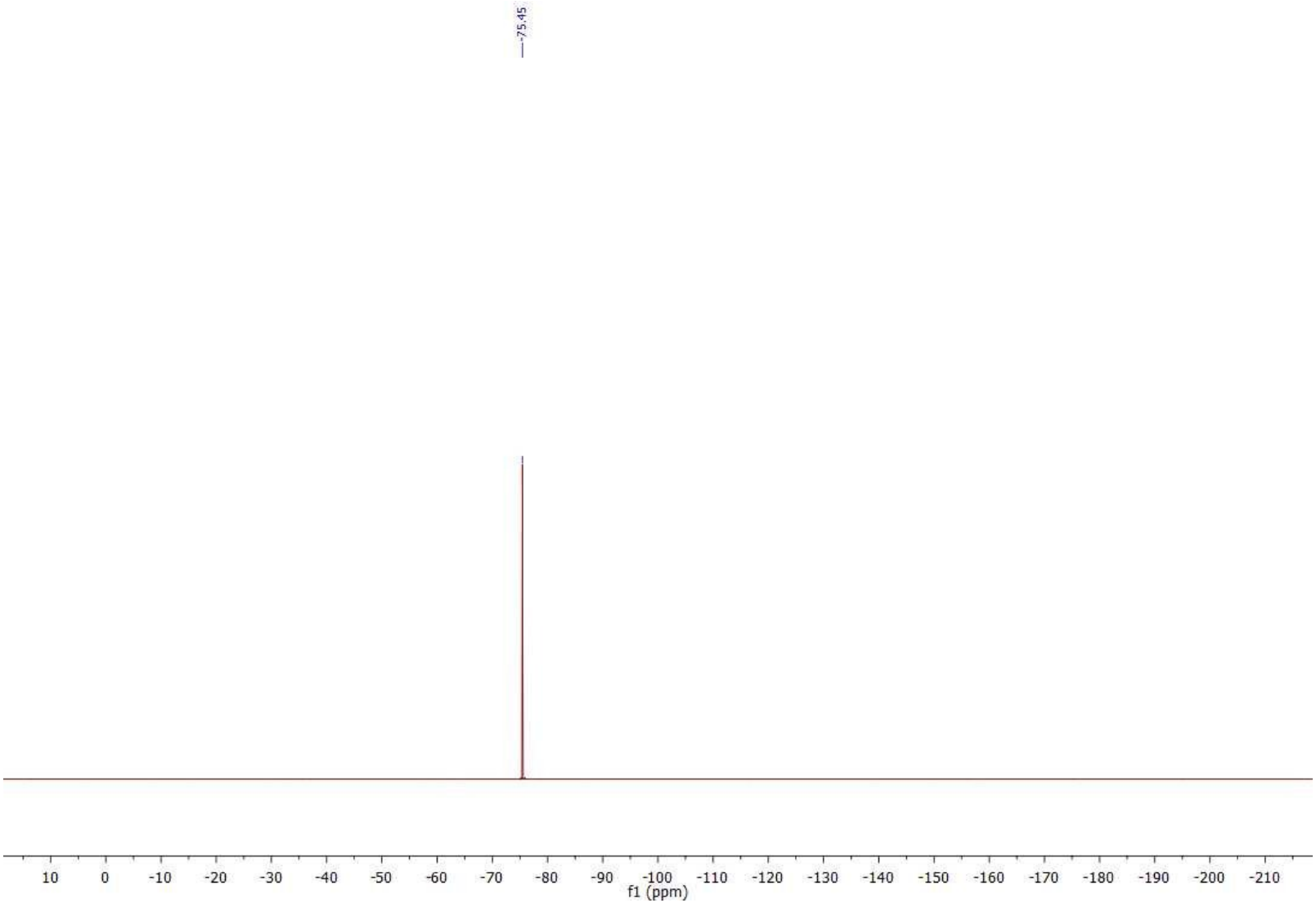
^{13}C NMR ($CDCl_3$, 100 MHz).
(-)-Menthyl 2,2,2-trifluoroacetate (**4b**)





^{19}F NMR ($CDCl_3$, 377 MHz).
(-)-Menthyl 2,2,2-trifluoroacetate (**4b**)





(1) Wang, L.; Wei, X.-J.; Jia, W.-L.; Zhong, J.-J.; Wu, L.-Z.; Liu, Q. *Org. Lett.* **2014**, *16*, 5842-5845.
(2) Morimoto, H.; Fujiwara, R.; Shimizu, Y.; Morisaki, K.; Ohshima, T. *Org. Lett.* **2014**, *16*, 2018-2021.