Supporting information

Base-catalysed ^{18}F-labelling of trifluoromethyl ketones. Application to the synthesis of ^{18}F-labelled neutrophil elastase inhibitors

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1. General information

Reagents were used as obtained from commercial suppliers without further purification. Trifluoroacetophenones **1g, 1i-o** were used as obtained from commercial suppliers without further purification. Trifluoroacetophenones **1h**,[1] **1r**,[2] and **1p-q**[3] were synthesised following reported literature procedures. Bromodifluoroacetophenone **3r**[4] was synthesised following reported literature procedures. Acetonitrile, diethyl ether, DCM, DMF, and toluene for all reactions were obtained from commercial suppliers and dried using a Vacuum Atmospheres Solvent Purifier system, unless otherwise stated. Dry THF for all reactions was used as received from commercial suppliers, and stored under an inert atmosphere. DCM for the synthesis of **1t**, **4a**, **4t** was redistilled and stored in darkness under an inert atmosphere. All other solvents were used as received from commercial suppliers, with no further purification. IST Phase Separators® were obtained from Biotage. Flash chromatography purifications were carried out using 60 Å (40–65 μm mesh) silica gel from VWR chemicals using *n*-pentane / EtOAc, DCM / Et_2O or DCM / MeOH mixtures as eluent system. Radiochemical units and parameters are used in accordance with the standard of the field.[5]

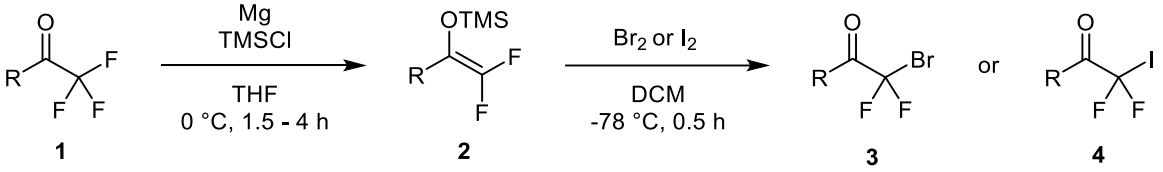
Fluorine-19 experiments. All reactions were carried out in dry, closed glass reaction vessels, using dry solvents under an Ar atmosphere. Analytical TLC was carried out on aluminium-backed plates (1.5 Å, 4 cm) pre-coated (0.25 mm) with silica gel (Merck, Silica Gel 60 F254). Compounds were visualised by exposure to UV light (λ = 254 nm) or by dipping the plates in a solution of 0.75% $KMnO_4$ (w/v) in an aqueous solution of K_2CO_3 (0.36 M) or in a solution of phosphomolybdic acid in EtOH (0.05 M). Melting points were recorded in a metal block and are uncorrected. ^{1}H NMR spectra were recorded at 400 MHz, ^{13}C NMR spectra were recorded at 100 MHz, and ^{19}F NMR spectra were recorded at 377 MHz, with Bruker Ascend™ and Ultra shield™ spectrometers. ^{1}H and ^{13}C NMR chemical shifts (δ) are reported in ppm from tetramethylsilane, using the residual solvent resonance ^{1}H NMR: δ_H = 7.26 ($CDCl_3$); 2.50 ($(CD_3)_2SO$); 4.79 (D_2O), and in ^{13}C NMR: δ_C = 77.2 ($CDCl_3$); 39.52 ($(CD_3)_2SO$), as internal reference. The multiplicity is abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), sept (septet), m (multiplet) and br (broad). Coupling constants (*J*) are given in Hz. High-resolution mass spectra (HRMS) were recorded on a Bruker microTOF ESI-TOF mass spectrometer in positive or negative ion mode.

Fluorine-18 experiments. The labelling reactions were carried out in dry conical glass vials under an atmosphere of dry N_2. Dry DMF for the labelling reactions was obtained from commercial suppliers and stored in an Ar-filled glovebox.

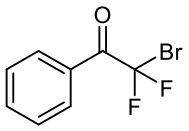
2. Synthesis and characterisation of iodo- and bromodifluoromethyl ketones

General procedure A:

Iodo- and bromodifluoromethyl ketones were prepared following the procedure reported by Hu, Olah and Prakash.[6] First, the difluoro enol silyl ether was synthesised from the corresponding trifluoromethyl ketone and used without further purification.[6,7] The halogenation was performed with either I_2 or Br_2.



2.1. Synthesis of 1-([1,1'-biphenyl]-4-yl)-2-bromo-2,2-difluoroethan-1-one 3g



3g

The title compound **3g** was prepared according to general procedure A above with a reaction time of 3 h starting from 2,2,2-trifluoro-1-phenylethan-1-one (174 mg) using Br_2. Purification by column chromatography (*n*-pentane) afforded the title compound as a colourless oil (50 mg, 57%).

TLC: R_f = 0.60 (*n*-pentane / ethyl acetate 20:1). UV active.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, J_{HH} = 8.6 Hz, 1H), 7.71-7.67 (m, 2H), 7.56-7.52 (m, 2H).

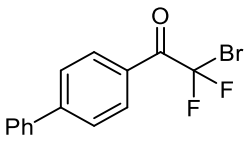
$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 181.5 (t, J_{CF} = 25.9 Hz), 135.2, 130.8 (t, J_{CF} = 2.6 Hz), 129.4, 129.1, 113.8 (t, J_{CF} = 318.6 Hz).

^{19}F NMR (377 MHz, $CDCl_3$): δ = -57.75.

HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_8H_5{}^{79}BrF_2ONa$ 256.9384, found 256.9389.

The obtained NMR data are in agreement with literature values.[6]

2.2. Synthesis of 1-([1,1'-biphenyl]-4-yl)-2-bromo-2,2-difluoroethan-1-one 3h



3h

The title compound **3h** was prepared according to general procedure A above with a reaction time of 3 h starting from 1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethan-1-one (106 mg, 0.5 mmol) using Br_2. Purification by column chromatography (*n*-pentane / ethyl acetate 100:1) afforded the title compound as a colourless oil (78 mg, 93%).

TLC: R_f = 0.15 (*n*-pentane). UV active.

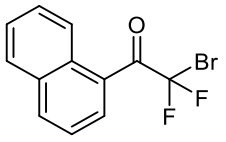
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24-8.22 (m, 2H), 7.77-7.74 (m, 2H), 7.67-7.64 (m, 2H), 7.52-7.48 (m, 2H), 7.47-7.42 (m, 1H).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 181.1 (t, J_{CF} = 25.8 Hz), 148.0, 139.3, 131.5 (t, J_{CF} = 2.8 Hz), 129.3, 129.0, 127.8, 127.6, 127.5, 113.9 (t, J_{CF} = 318.7 Hz).

^{19}F NMR (377 MHz, $CDCl_3$): δ = -57.60.

HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{14}H_9{}^{79}BrF_2ONa$ 332.9697, found 332.9694.

2.3. Synthesis of 2-bromo-2,2-difluoro-1-(naphthalen-1-yl)ethan-1-one 3i



3i

The title compound **3i** was prepared according to general procedure A above with a reaction time of 4 h starting from 2,2,2-trifluoro-1-(naphthalen-1-yl)ethan-1-one (300 mg, 1.4 mmol) using Br_2. Purification by column chromatography (*n*-pentane / ethyl acetate 100:1) afforded the title compound as a light yellow oil (233 mg, 65%).

TLC: R_f = 0.46 (*n*-pentane / ethyl acetate 20:1). UV active.

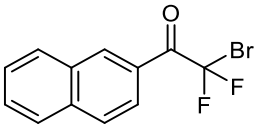
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.56-8.54 (m, 1H), 8.27-8.24 (m, 1H), 8.13 (d, J_{HH} = 8.2 Ha, 1H), 7.94-7.92 (m, 1H), 7.70-7.66 (m, 1H), 7.62-7.54 (m, 2H).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 184.0 (t, J_{CF} = 25.5 Hz), 135.3, 134.1, 131.5, 130.6 (t, J_{CF} = 4.6 Hz), 129.2, 129.0, 127.2, 126.9, 125.3, 124.1, 114.2 (t, J_{CF} = 320.7 Hz).

^{19}F NMR (377 MHz, $CDCl_3$): δ = -51.12 (d, J_{FH} = 2.0 Hz).

HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{12}H_7{}^{79}BrF_2ONa$ 306.9541 [*M*+Na], found 306.9549.

2.4. Synthesis of 2-bromo-2,2-difluoro-1-(naphthalen-2-yl)ethan-1-one 3j



3j

The title compound **3j** was prepared according to general procedure A above with a reaction time of 4 h starting from 2,2,2-trifluoro-1-(naphthalen-2-yl)ethan-1-one (224 mg, 1.0 mmol) using Br_2. Purification by column chromatography (*n*-pentane / ethyl acetate 100:1) afforded the title compound as a light yellow oil (219 mg, 79%).

TLC: R_f = 0.63 (*n*-pentane / ethyl acetate 20:1). UV active.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74 (s, 1H), 8.14-8.12 (m, 1H), 8.03-8.01 (m, 1H), 7.96-7.90 (m, 2H), 7.71-7.67 (m 1H), 7.63-7.59 (m, 1H).

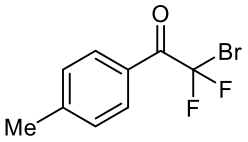
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 181.4 (t, J_{CF} = 25.8 Hz), 136.3, 133.5 (t, J_{CF} = 3.4 Hz), 132.2, 130.2, 129.9, 128.9, 127.9, 127.4, 126.3, 125.0 (t, J_{CF} = 2.0 Hz), 113.9 (t, J_{CF} = 318.6 Hz).

^{19}F NMR (377 MHz, $CDCl_3$): δ = -57.08.

HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{12}H_7{}^{79}BrF_2ONa$ 306.9541, found 306.9541.

The obtained NMR data are in agreement with literature values.[8]

2.5. Synthesis of 2-bromo-2,2-difluoro-1-(*p*-tolyl)ethan-1-one 3k



3k

The title compound **3k** was prepared according to general procedure A above with a reaction time of 1.5 h starting from 2,2,2-trifluoro-1-(*p*-tolyl)ethan-1-one (376 mg, 2 mmol) using Br_2. Purification by column chromatography (*n*-pentane) afforded the title compound as a colourless oil (329 mg, 69%).

TLC: R_f = 0.53 (*n*-pentane / ethyl acetate 20:1). UV active.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, J_{HH} = 8.3 Hz, 2H), 7.33 (d, J_{HH} = 8.1 Hz, 2H), 2.46 (s, 3H).

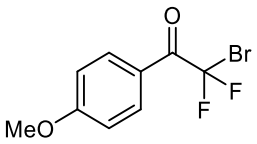
$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ = 181.2 (t, J_{CF} = 25.6 Hz), 146.7, 130.9 (t, J_{CF} = 2.7 Hz), 129.8, 126.6, 113.9 (t, J_{CF} = 318.7 Hz), 22.0.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -57.48.

HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_9H_7{}^{79}BrF_2ONa$ 270.9541, found 270.9538.

The obtained NMR data are in agreement with literature values.[6]

2.6. Synthesis of 2-bromo-2,2-difluoro-1-(4-methoxyphenyl)ethan-1-one 3l



3l

The title compound **3l** was prepared according to general procedure A above with a reaction time of 4 h starting from 2,2,2-trifluoro-1-(4-methoxyphenyl)ethan-1-one (306 mg, 1.5 mmol) using Br_2. Purification by column chromatography (*n*-pentane / ethyl acetate 100:1) afforded the title compound as a pale yellow oil (191 mg, 58%).

TLC: R_f = 0.30 (*n*-pentane / ethyl acetate 20:1). UV active.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15-8.12 (m, 2H), 7.01-6.97 (m, 2H), 3.91 (s, 3H).

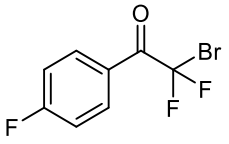
$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ = 180.2 (t, J_{CF} = 25.5 Hz), 165.2, 133.4 (t, J_{CF}= 2.7 Hz), 121.9, 114.4, 113.7 (t, J_{CF} = 318.6 Hz), 55.8.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -56.98.

HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_9H_7{}^{79}BrF_2O_2Na$ 286.9490, found 286.9488.

The obtained NMR data are in agreement with literature values.[8]

2.7. Synthesis of 2-bromo-2,2-difluoro-1-(4-fluorophenyl)ethan-1-one 3m



3m

The title compound **3m** was prepared according to general procedure A above with a reaction time of 1.5 h starting from 1-(4-fluorophenyl)-2,2,2-trifluoroethan-1-one (384 mg, 2.0 mmol) using Br_2. Purification by column chromatography (*n*-pentane / ethyl acetate 100:1) afforded the title compound as a pale yellow oil (282 mg, 53%).

TLC: R_f = 0.63 (*n*-pentane / ethyl acetate 20:1). UV active.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21-8.18 (m, 2H), 7.24-7.18 (m, 2H).

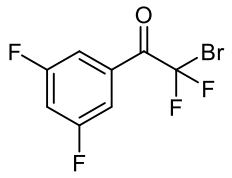
$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 180.1 (t, J_{CF} = 26.2 Hz), 167.0 (d, J_{CF} = 259.5 Hz), 133.8 (dt, J_{CF} = 9.9, 2.8 Hz), 125.6 (d, J_{CF} = 3.1 Hz), 116.5 (d, J_{CF} = 22.1 Hz), 113.6 (t, J_{CF} = 318.08 Hz).

^{19}F NMR (377 MHz, $CDCl_3$): δ = -57.78. -100.26 – -100.33 (m).

HRMS (ESI or APCI): Despite repeated attempts, we were not able to obtain high-resolution mass data for **3m**.

The obtained NMR data are in agreement with literature values.[8]

2.8. Synthesis of 2-bromo-1-(3,5-difluorophenyl)-2,2-difluoroethan-1-one 3n



3n

The title compound **3n** was prepared according to general procedure A above with a reaction time of 1.5 h starting from 1-(3,5-difluorophenyl)-2,2,2-trifluoroethan-1-one (328 mg, 1.5 mmol) using Br_2. Purification by column chromatography (*n*-pentane / ethyl acetate 120:1) afforded the title compound as a light yellow oil (134 mg, 38%).

TLC: R_f = 0.18 (*n*-pentane / ethyl acetate 20:1). UV active.

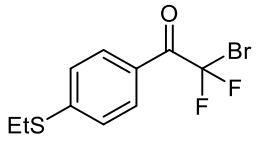
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70-7.63 (m, 2H), 7.16 (tt, J_{HF} = 8.3, J_{HH} = 2.3, 1H).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 179.4 (tt, J_{CF} = 27.1, 3.0 Hz), 164.3 (d, J_{CF} = 11.7 Hz), 161.8 (d J_{CF} = 11.8 Hz), 131.7 (t, J_{CF} = 8.6 Hz), 114.0-113.7 (m), 113.0 (t, J_{CF} = 318.0 Hz), 110.8 (t, J_{CF} = 25.2 Hz).

^{19}F NMR (377 MHz, $CDCl_3$): δ = -58.63, -106.34 – -106.38 (m).

HRMS (ESI or APCI): Despite repeated attempts, we were not able to obtain high-resolution mass data for **3n**.

2.9. Synthesis of 2-bromo-1-(4-(ethylthio)phenyl)-2,2-difluoroethan-1-one 3o



3o

The title compound **3o** was prepared according to general procedure A above with a reaction time of 2 h starting from 1-(4-(ethylthio)phenyl)-2,2,2-trifluoroethan-1-one (234 mg, 1.0 mmol) using Br_2. Purification by column chromatography (*n*-pentane / ethyl acetate 50:1) afforded the title compound as a pale yellow oil (78 mg, 26%).

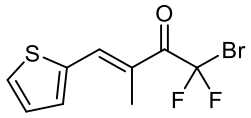
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04-8.01 (m, 2H), 7.33-7.30 (m, 2H), 3.05 (q, J_{HH} = 7.4 Hz, 2H), 1.40 (t, J_{HH} = 7.4 Hz, 3H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 180.6 (t, J_{CF} = 25.7 Hz), 148.7, 131.1 (t, J_{CF} = 2.8 Hz), 125.8, 125.1, 113.8 (t, J_{CF} = 318.5 Hz), 25.7, 13.8.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -57.38.

HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{10}H_9{}^{79}BrF_2OSNa$ 316.9418, found 316.9420.

2.10. Synthesis of (*E*)-1-bromo-1,1-difluoro-3-methyl-4-(thiophen-2-yl)but-3-en-2-one 3p



3p

The title compound **3p** was prepared according to general procedure A above with a reaction time of 4 h starting from (*E*)-1,1,1-trifluoro-3-methyl-4-(thiophen-2-yl)but-3-en-2-one (220 mg, 1.0 mmol) using Br_2. Purification by column chromatography (*n*-pentane / ethyl acetate 100:1) afforded the title compound as a yellow oil (128 mg, 45%).

TLC: R_f = 0.11 (*n*-pentane / ethyl acetate 20:1). UV active.

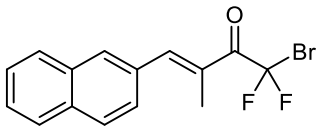
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (s, 1H), 7.69 (d, J_{HH} = 5.1 Hz, 1H), 7.46 (d, J_{HH} = 3.6 Hz, 1H), 7.21 (dd, J_{HH} = 5.0, 3.9 Hz, 1H), 2.28 (s, 3H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 182.7 (t, J_{CF} = 24.3 Hz), 138.5, 138.2 (t, J_{CF} = 4.6 Hz), 135.1, 132.8, 128.1, 125.4, 114.4 (t, J_{CF} = 318.8 Hz), 14.2.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -54.42.

HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_9H_7{}^{79}BrF_2OSNa$ 302.9261, found 302.9259.

2.11. Synthesis of (*E*)-1-bromo-1,1-difluoro-3-methyl-4-(naphthalen-2-yl)but-3-en-2-one 3q



3q

The title compound **3q** was prepared according to general procedure A above with a reaction time of 4 h starting from (*E*)-1,1,1-trifluoro-3-methyl-4-(naphthalen-2-yl)but-3-en-2-one (147 mg, 0.6 mmol) using Br_2. Purification by column chromatography (*n*-pentane / ethyl acetate 100:1) afforded the title compound as a yellow oil (54 mg, 25%).

TLC: R_f = 0.11 (*n*-pentane / ethyl acetate 20:1). UV active.

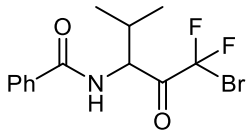
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (s, 1H), 7.96 (s, 1H), 7.92-7.86 (m, 3H), 7.59-7.54 (m, 3H), 2.29 (s, 3H).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 183.5 (t, J_{CF} = 24.4 Hz), 145.8 (t, J_{CF} = 4.2 Hz), 133.7, 133.1, 132.3, 130.9, 129.7, 128.7, 128.5, 127.9, 127.7, 126.9$_7$, 126.9$_6$, 113.8 (t, J_{CF} = 319.1 Hz), 14.3.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -54.76.

HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{15}H_{11}{}^{79}BrF_2ONa$ 346.9854, found 346.9857.

2.12. Synthesis of 5-bromo-5,5-difluoro-3-isopropyl-1-phenylpentane-1,4-dione 3s



3s

The title compound **3s** was prepared according to general procedure A above with a reaction time of 4 h starting from 5,5,5-trifluoro-3-isopropyl-1-phenylpentane-1,4-dione (200 mg, 0.7 mmol) using Br_2. Purification by column chromatography (*n*-pentane / ethyl acetate 13:1) afforded the title compound as a colourless solid (138 mg, 56%).

TLC: R_f = 0.19 (*n*-pentane / ethyl acetate 13:1). UV active.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82-7.80 (m, 2H), 7.57-7.53 (m, 1H), 7.49-7.45 (m, 2H), 6.54 (d, J_{HH} = 9.7 Hz, 1H), 5.41 (dd, J_{HH} = 9.0, 4.4 Hz, 1H), 2.51-2.39 (m, 1H), 1.12 (d, J_{HH} = 6.8 Hz, 3H), 0.97 (d, J_{HH} = 6.9 Hz, 3H).

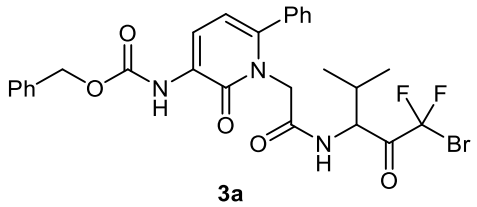
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 191.9 (t, J_{CF} = 27.0 Hz), 167.4, 133.6, 132.3, 128.9, 127.2, 113.6 (t, J_{CF} = 320.0 Hz), 57.8, 30.7, 20.2, 16.7.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -62.53 (d, J_{FF} = 159.8 Hz, 1F), -63.46 (d, J_{FF} = 159.6 Hz, 1F).

HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{13}H_{14}{}^{79}BrF_2NO_2Na$ 356.0068, found: 356.0068.

Melting point: 92.5 – 93.4 °C.

2.13. Synthesis of benzyl (2-(2-((1-bromo-1,1-difluoro-4-methyl-2-oxopentan-3-yl)amino)-2-oxoethyl)-3-oxo-2,3-dihydro-[1,1'-biphenyl]-4-yl)carbamate 3a



3a

The title compound **3a** was prepared according to general procedure A above with a reaction time of 4 h starting from benzyl (3-oxo-2-(2-oxo-2-((1,1,1-trifluoro-4-methyl-2-oxopentan-3-yl)amino)ethyl)-2,3-dihydro-[1,1'-biphenyl]-4-yl)carbamate (324 mg, 0.6 mmol) using Br_2. Purification by column chromatography (DCM / MeOH 600:1) afforded the title compound as a colourless solid (132 mg, 59%).

TLC: R_f = 0.50 (DCM / MeOH 95:5). UV active.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (d, J_{HH} = 8.2 Hz, 1H), 7.94-7.91 (m, 2H), 7.49-7.33 (m, 9H), 7.13 (s, 1H), 6.82 (d, J_{HH} = 9.2 Hz, 1H), 5.26 (s, 2H), 5.20-5.15 (m, 2H), 4.94 (d, J_{HH} = 15.1 Hz, 1H), 2.29-2.18 (m, 1H), 0.87 (d, J_{HH} = 6.8 Hz, 3H), 0.64 (d, J_{HH} = 6.9 Hz, 3H).

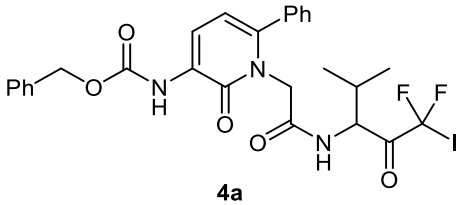
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 191.1 (t, J_{CF} = 26.9 Hz), 168.7, 153.4, 151.0, 148.4, 137.7, 135.8, 128.9, 128.8, 128.7, 128.6, 128.3, 126.4, 121.2, 115.0, 113.2 (t, J_{CF} = 320.1 Hz), 67.7, 65.5, 57.1, 30.4, 19.8, 16.3.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -62.96 (d, J_{FF} = 158.8 Hz, 1F), -63.77 (d, J_{FF} = 158.9, 1F).

HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{27}H_{26}{}^{79}BrF_2N_3O_5Na$ 612.0916, found: 612.0931.

Melting point: 147.4 – 148.2 °C.

2.14. Synthesis of (2-(2-((1-iodo-1,1-difluoro-4-methyl-2-oxopentan-3-yl)amino)-2-oxoethyl)-3-oxo-2,3-dihydro-[1,1'-biphenyl]-4-yl)carbamate 4a



4a

The title compound **4a** was synthesised starting from **1a**[6] using I_2. Magnesium turnings were mechanically activated in an Ar-filled glovebox using magnetic stirring in an Erlenmeyer flask for 18 h.[9] In the glovebox, the activated Mg (38.6 mg, 1.59 mmol, 4.2 equiv.) was added to a vial. Anhydrous THF (1.51 mL) was added to the reaction vial at 0 °C. After 5 min, TMSCl was added drop-wise (0.40 mL, 3.18 mmol, 8.4 equiv.). Then, a solution of **1a** (200.2 mg, 0.38 mmol) in anhydrous THF (1.24 mL) was added. The mixture was stirred at 0 °C for 3 h and, followed by 1 h at room temperature. After this time, the solvent was evaporated. The obtained residue was dispersed in DCM (38 mL) and filtered through a pad of Celite® and washed with DCM (30 mL x 3). The solvent was evaporated to give the desired α,α-difluoro enol silyl ether **2a**. To a solution of **2a** in freshly distilled DCM (1.9 mL) at −78 °C was added I_2 (143.9 mg, 0.567 mmol, 1.5 equiv.). The reaction was stirred at −78 °C for 10 min and then allowed to warm to room temperature stirring for an additional 30 min. After the reaction was complete, the solvent was evaporated and the crude was purified by column chromatography (petroleum ether / ethyl acetate 5:1) to afford the title compound as a colourless solid (186.6 mg, 77%).

TLC: R_f = 0.4 (petroleum ether / ethyl acetate 3:1). UV active.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38 (d, J_{HH} = 8.1 Hz, 1H), 7.94-7.92 (m, 2H), 7.49-7.33 (m, 9H), 7.13 (s, 1H), 6.79 (d, J_{HH} = 9.2 Hz, 1H), 5.26 (s, 2H), 5.22-5.15 (m, 2 H), 4.95 (d, J_{HH} = 15.1 Hz, 1H), 2.22 (dq, J_{HH} = 13.5, 7.0 Hz, 1H), 0.87 (d, J_{HH} = 6.8 Hz, 3H), 0.64 (d, J_{HH} = 6.9 Hz, 3H).

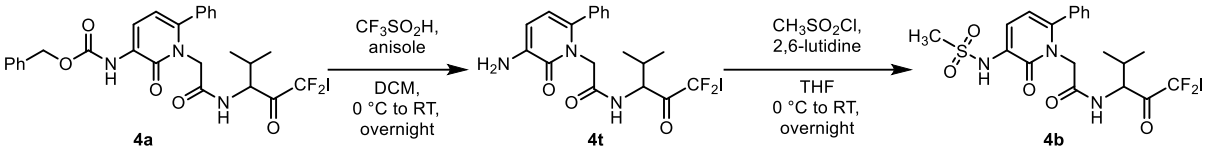
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 192.1 (t, J_{CF} = 24.2 Hz), 168.7, 153.4, 150.9, 148.3, 137.8, 135.8, 128.9$_2$, 128.9$_0$, 128.7, 128.6, 128.2, 126.4, 121.2, 115.0, 95.7 (t, J_{CF} = 327.2 Hz), 67.8, 65.5, 55.9, 30.7, 19.9, 16.4.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -59.93 (d, J_{FF} = 179.6 Hz, 1F), -60.47 (d, J_{FF} = 179.6 Hz, 1F).

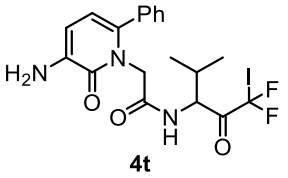
HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{27}H_{26}IF_2N_3O_5Na$ 660.0777, found 660.0783.

Melting point: 148.1 – 149.3 °C.

2.15. Synthetic route to acetamide derivative 4b



2.15.1. Hydrolysis of carbamate 4a to amino compound 4t



The title compound **4t** was synthesized by hydrolysis of the carbamate group of **4a**. To a solution of **4a** (100 mg) and anisole (0.055 mL) in dichloromethane (1.6 mL) at 0 °C was added trifluoromethanesulfonic acid (0.075 mL) while maintaining the temperature below 2 °C. The ice bath was removed, and the reaction mixture was allowed to warm to room temperature and stirred for 1.5 h before saturated aqueous sodium bicarbonate was added slowly to adjust the pH to 7. Ethyl acetate was added, the phases were separated, and the aqueous phase was extracted further with ethyl acetate. The combined organic extract was washed with brine, dried, and evaporated. The crude product was purified by column (DCM / Et_2O = 12:1) to afford the product (61.8 mg, 78%) as a yellow oil.

TLC: R_f = 0.67 (DCM / Et_2O 4:1). UV active.

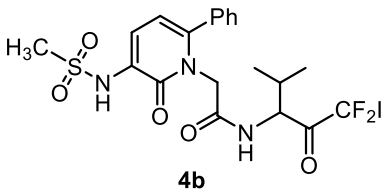
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, J_{HH} = 7.4 Hz, 2H), 7.39 (t, J_{HH} = 7.6 Hz, 2H), 7.35-7.27 (m, 2H), 7.11 (d, J_{HH} = 7.9 Hz, 1H), 6.91 (d, J_{HH} = 9.2 Hz, 1H), 5.28-5.14 (m, 2H), 4.96 (d, J_{HH} = 15.3 Hz, 1H), 4.34 (br s, 1H), 2.24 (dq, J_{HH} = 13.3, 6.7 Hz, 1H), 0.88 (d, J_{HH} = 6.8 Hz, 3H), 0.69 (d, J_{HH} = 6.9 Hz, 3H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 192.2 (t, J_{CF} = 24.2 Hz), 169.2, 150.3, 144.2, 138.5, 128.9, 128.8, 128.0, 125.9, 123.2, 115.2, 95.8 (t, J_{CF} = 327.2 Hz), 65.3, 55.9, 30.8, 19.9, 16.4.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -60.21, -60.20.

HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{19}H_{20}IF_2N_3O_3Na$ 526.0410, found 526.0415.

2.15.2. Synthesis methylsulfonyl derivative 4b



The title compound **4b** was synthesized by mesylation of **4t**. A 10 mL flask under Ar was charged with substrate **4t** (61.8 mg, 0.123 mmol) and DMAP (15.0 mg, 0.123 mmol) dissolved in tetrahydrofuran (1.2 mL). Then, 2,6-lutidine (0.028 mL) was added at 0 °C, followed by methanesulfonyl chloride (0.014 mL). The cloudy, yellow solution was stirred at room temperature overnight; diluted with ethyl acetate (25 mL), washed with hydrochloric acid (1 M), saturated $NaHCO_3$ (aq.), and brine, dried through a phase separator, and evaporated. Then, **4b** was purified by chromatography (DCM / Et_2O 12:1) to afford the product **4b** (21.1 mg, 30%) as a yellow oil.

TLC: R_f = 0.70 (DCM / Et_2O 4:1). UV active.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, J_{HH} = 7.0 Hz, 2H), 7.85 (d, J_{HH} = 8.1 Hz, 1H), 7.50-7.35 (m, 4H), 7.02 (s, 1H), 6.94 (d, J_{HH} = 9.1 Hz, 1H), 5.23-5.13 (m, 2H), 5.05 (d, J_{HH} = 15.1 Hz, 1H), 3.14 (s, 3H), 2.26 (dq, J_{HH} = 13.2, 6.7 Hz, 1H), 0.90 (d, J_{HH} = 6.8 Hz, 3H), 0.73 (d, J_{HH} = 6.9 Hz, 3H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 192.3 (t, J_{CF} = 24.2 Hz), 168.5, 153.4, 151.5, 137.4, 132.1, 129.5, 129.0, 126.7, 119.5, 115.0, 95.8 (t, J_{CF} = 327.3 Hz), 65.3, 56.0, 40.5, 30.7, 19.9, 16.7.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -60.20.

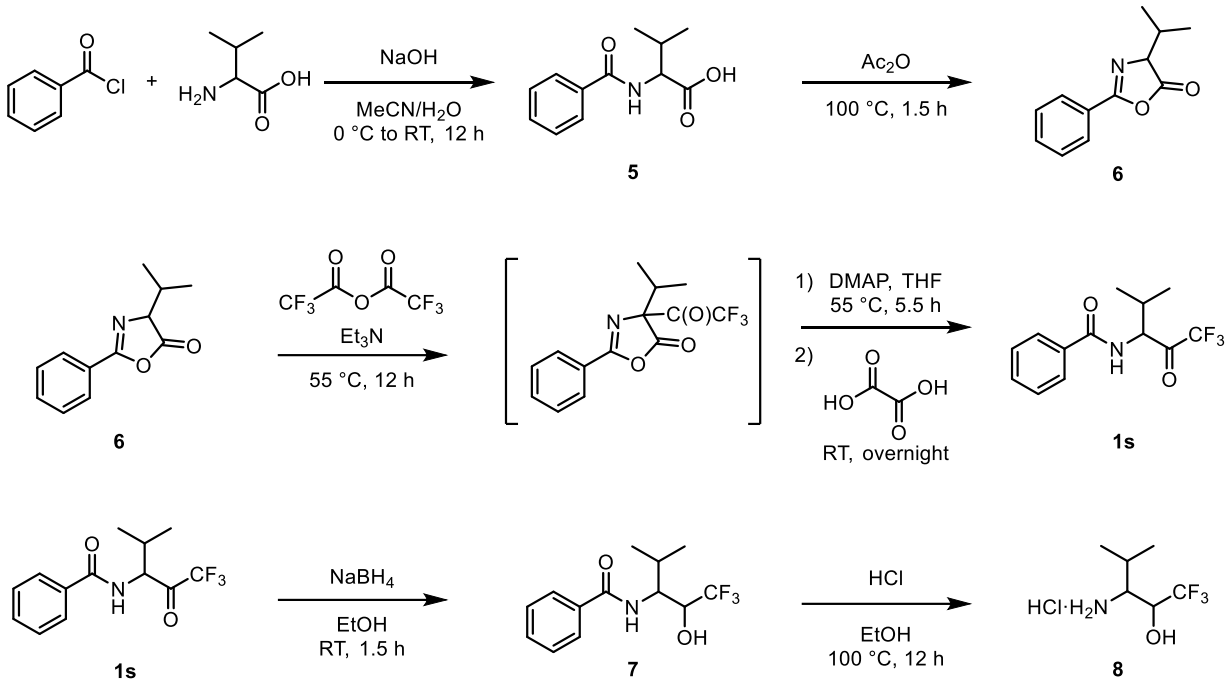
HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{20}H_{21}IF_2N_3O_5SNa$ 580.0220, found 580.0229.

3. Synthesis and characterisation of neutrophil elastase inhibitor 1a

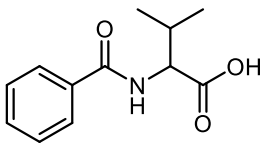
Neutrophil elastase inhibitor **1a** was prepared by a modified literature procedure.[10]

3.1. Synthesis and characterisation of fragment 8

Compound **8** was synthesised according to the following reaction scheme, derived from literature procedures:[10b, c]



3.1.1. Synthesis of *N*-benzoyl-*DL*-valine 5



5

The reaction was performed following a modified literature procedure.[10c] *DL*-Valine (7.4 g, 63 mmol, 1.0 equiv.) and NaOH (2.5 g, 63 mmol, 1.0 equiv.) were dissolved in a mixture of acetonitrile (100 mL) and water (100 mL). The reaction mixture was cooled to 0 °C before benzoyl chloride (8.9 g, 63 mmol, 1.0 equiv.) was added drop-wise. The reaction was stirred at 0 °C for 30 min and then at room temperature for further 16 h. After this time, the acetonitrile was evaporated and concentrated HCl was added to force precipitation of the product. The obtained white solid was filtered, washed with cold Et_2O and dried over P_2O_5 under vacuum to give the desired product as a white solid (12.1 g, 89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.86 (bs, 1H), 7.82-7.80 (m, 2H), 7.56-7.51 (m, 1H), 7.48-7.44 (m, 2H), 6.63 (d, J_{HH} = 8.5 Hz, 1H), 4.81 (dd, J_{HH} = 8.5, 4.8 Hz, 1H), 2.41-2.33 (m, 1H), 1.05 (dd, J_{HH} = 10.7, 6.9 Hz, 6H).

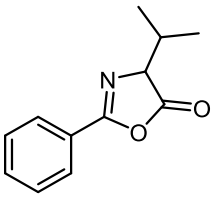
^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 173.1, 166.9, 134.1, 131.3, 128.2, 127.6, 58.4, 29.5, 19.3, 18.8.

HRMS (ESI) *m/z* [M - H]$^-$ calcd for $C_{12}H_{14}NO_3$ 220.0979, found 220.0980.

Melting point: 121.7 – 122.6 °C

The obtained ^{1}H NMR data are in agreement with literature values.[10c]

3.1.2. Synthesis of 4-isopropyl-2-phenyloxazol-5(4*H*)-one 6



6

The reaction was performed following a modified literature procedure.[10b] A solution of *N*-benzoyl-*DL*-valine **5** (6.0 g, 27.1 mmol, 1.0 equiv) was dissolved in acetic anhydride (56 mL, 593 mmol, 21.9 equiv.). The mixture was heated at 100 °C for 2 h. After this time, the mixture was cooled down and the solvent evaporated. Purification by silica gel column chromatography (*n*-pentane / ethyl acetate 20:1 to 10:1) afforded the product as a white solid (5.37 g, 93%).

TLC: R_f = 0.43 (*n*-pentane / ethyl acetate 20:1). UV active.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02-8.00 (m, 2H), 7.59-7.55 (m, 1H), 7.50-7.46 (m, 2H), 4.29 (d, J_{HH} = 4.5 Hz, 1H), 2.44-2.33 (m, 1H), 1.15 (d, J_{HH} = 6.9 Hz, 3H), 1.02 (d, J_{HH} = 6.9 Hz, 3H).

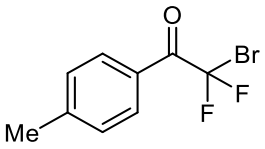
$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ = 177.9, 161.8, 132.8, 128.9, 128.0, 126.1, 70.8, 31.4, 18.9, 17.7.

HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{12}H_{13}NO_2Na$ 226.0838, found 226.0839.

Melting point: 48.0 – 48.5 °C

The obtained NMR data are in agreement with literature values.[10c]

3.1.3. Synthesis of *N*-(1,1,1-trifluoro-4-methyl-2-oxopentan-3-yl)benzamide 1s



3k

The Dakin-West reaction was performed following a modified literature procedure.[10b] To 4-isopropyl-2-phenyloxazol-5(4*H*)-one **6** (4.60 g, 22.6 mmol, 1.0 equiv) was added trifluoroacetic anhydride (8.0 mL, 56.5 mmol, 2.5 equiv) at room temperature. The mixture was cooled to 0 °C and triethylamine (7.9 mL, 56.5 mmol, 2.5 equiv.) was added dropwise over 10 min. The reaction mixture was allowed to warm to room temperature and then heated to 55 °C for 16 h. After this time, the excess of

trifluoroacetic anhydride was evaporated. To the resulting mixture DMAP[11] (1.10 g, 9.0 mmol, 0.4 equiv) was added to the resulting mixture and it was stirred at 55 °C for 5.5 h. The mixture was cooled to room temperature, treated with oxalic acid (7.13 g, 79.1 mmol, 3.5 equiv.) in anhydrous THF (28.5 mL) and stirred for an additional 17 h. Then, the reaction mixture was diluted with EtOAc (80 mL) and washed with 0.5 M saturated $NaHCO_3$ (aq., 80 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (80 mL). The combined organic phases were washed with saturated $NaHCO_3$ (0.5 M, aq., 80 mL), HCl (1 M, aq., 80 mL) and brine (80 mL), then filtered through a phase separator and concentrated. The crude reaction mixture was purified by column chromatography (ethyl acetate / *n*-pentane 1:10 to 1:5) to afford the product as a pale yellow solid (3.759 g, 61%).

TLC: R_f = 0.41 (*n*-pentane / ethyl acetate 20:1). UV active.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82-7.79 (m, 2H), 7.58-7.54 (m, 1H), 7.50-7.46 (m, 2H), 6.50 (d, J_{HH} = 8.4 Hz, 1H), 5.29 (dd, J_{HH} = 8.4, 4.3 Hz, 1H), 2.49-2.41 (m, 1H), 1.14 (d, J_{HH} = 6.8 Hz, 3H), 0.96 (d, J_{HH} = 6.9 Hz, 3H).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 191.3 (q, J_{CF} = 34.8 Hz), 167.7, 133.4 132.3, 128.9, 127.2, 115.6 (q, J_{CF} = 292.3), 59.2, 29.8, 20.0, 16.9.

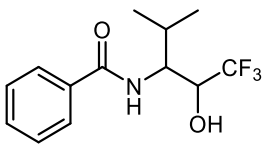
^{19}F NMR (377 MHz, $CDCl_3$): δ = -76.24.

HRMS (ESI) *m/z* $[M - H]^-$ calcd for $C_{13}H_{13}F_3NO_2$ 272.0904, found 272.0897.

Melting point: 92.8 – 93.8 °C.

The obtained ^{1}H NMR data are in agreement with literature values.[10b]

3.1.4. Synthesis of *N*-(1,1,1-trifluoro-2-hydroxy-4-methylpentan-3-yl)benzamide 7



7

The reaction was performed following a modified literature procedure.[10b] *N*-(1,1,1-trifluoro-4-methyl-2-oxopentan-3-yl)benzamide **1s** (1.0 g, 4 mmol, 1.0 equiv.) was dissolved in absolute EtOH (4 mL) and cooled to 0 °C. Then, $NaBH_4$ was added portion-wise over 10 min. The reaction was warmed to room temperature and stirred for 1.5 h. After this time, the reaction was quenched by the addition of water.

The resulting mixture was extracted with DCM. The combined organic phases were filtered through a phase separator and concentrated to give the desired alcohol as a colourless solid (1.0 g, 99%)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77-7.75 (m, 2H), 7.57-7.53 (m, 1H), 7.48-7.44 (m, 2H), 6.15 (d, J_{HH} = 8.4 Hz, 1H), 4.90 (d, J_{HH} = 7.2 Hz, 1H), 4.33-4.25 (m, 1H), 4.24-4.20 (m, 1H), 2.17-2.05 (m, 1H), 1.10 (dd, J_{HH} = 8.0, 6.7 Hz, 6H).

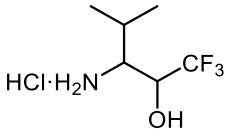
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 170.1, 133.5, 132.4, 129.0, 127.2, 125.2 (q, J_{CF} = 284.1 Hz), 71.4 (q, J_{CF} = 28.9 Hz), 58.5, 29.4, 20.7, 19.9.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -73.97 (d, J_{FH} = 7.0 Hz).

HRMS (ESI) *m/z* [M - H]$^{-}$ calcd for $C_{13}H_{15}F_3NO_2$ 274.1060, found 274.1050.

Melting point: 147.5 – 147.9 °C.

3.1.5. Synthesis of 3-amino-1,1,1-trifluoro-4-methylpentan-2-ol hydrochloride 8



8

The reaction was performed following a modified literature procedure.[10b] In a round-bottom flask fitted with a reflux condenser, *N*-(1,1,1-trifluoro-2-hydroxy-4-methylpentan-3-yl)benzamide **7** (412 mg, 1.5 mmol, 1 equiv.) was dissolved in absolute EtOH (0.9 mL) and concentrated HCl (2.49 mL, 30 mmol, 20 equiv.) was added. The reaction was stirred at 100 °C for 16 h. After this time, the mixture was allowed to cool down and the solvent was evaporated. The crude was dissolved in $CHCl_3$ (0.5 mL) and pentane (10 mL) was slowly added. This caused the formation of a colourless solid, which was filtered off. The oily substance on the bottom of the flask was concentrated to give the desired product as a yellow oil (254 mg, 81%).

^{1}H NMR (400 MHz, D_2O): δ = 4.59-4.52 (m, 1H), 3.39 (t, J_{HH} = 6.6 Hz, 1H), 2.26 (dq, J_{HH} = 13.8, 6.8 Hz, 1H), 1.09 (dd, J_{HH} = 13.4, 6.8 Hz, 6H).

^{13}C{^{1}H} NMR (100 MHz, D_2O): δ = 66.6 (t, J_{CF} = 30.2 Hz), 57.8, 26.7, 18.7, 17.3.

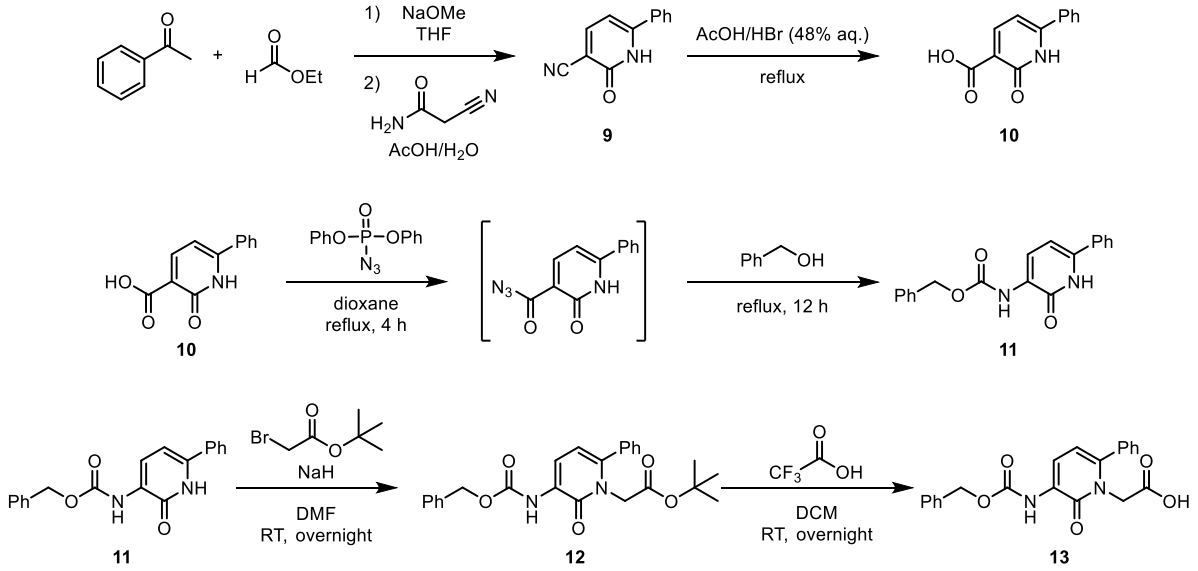
^{19}F NMR (377 MHz, D_2O): δ = -74.45 (d, J_{FH} = 7.2 Hz).

HRMS (ESI) *m/z* [M-HCl + H]$^{+}$ calcd for $C_6H_{13}F_3NO$ 172.0944, found 172.0944.

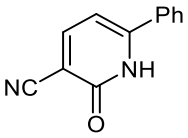
The obtained NMR data are in agreement with literature values.[10b]

3.2. Synthesis and characterisation of fragment 13

Neutrophil elastase inhibitor **1a** was prepared following a reported literature procedure.[10] Fragment **13** was synthesised according to the following reaction scheme:[10a]



3.2.1. Synthesis of 2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile 9



9

The reaction was performed following a modified literature procedure.[10a] In a round-bottom flask fitted with a reflux condenser, NaOMe (8.7 g, 160 mmol, 2.4 equiv.) was suspended in a mixture of THF (60 mL) and Et_2O (60 mL). To this was added ethyl formate (11.4 g, 154 mmol, 2.3 equiv.), followed by a solution of acetophenone (8.5 g, 67 mmol, 1.0 equiv.) in THF (90 mL). The mixture was heated at 40 °C for 3 h. After this time, the mixture was allowed to cool down and the solvents were removed under reduced pressure. The obtained residue was dissolved in water (240 mL) and the pH was adjusted to 9 with concentrated acetic acid before adding cyanoacetamide (10.4 g, 120 mmol, 1.8 equiv.). The mixture was stirred at 90 °C for 16 h. After this time, the solvent was decanted and the gummy residue was washed with HCl (10% aq.) and chloroform to give a colourless solid. The solid was

filtered, washed with Et_2O and dried over P_2O_5 under vacuum to give the desired product as a colourless solid (9.5 g, 73%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.76 (bs, 1H), 8.20 (d, J_{HH} = 7.6 Hz, 1H), 7.81 (d, J_{HH} = 6.3 Hz, 2H), 7.57-7.51 (m, 3H), 6.75 (bs, 1H).

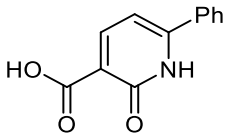
^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 161.2, 152.9, 148.5, 132.2, 131.2, 129.0, 127.6, 116.6, 104.8, 100.7.

HRMS (ESI) *m/z* $[M - H]^-$ calcd for $C_{12}H_7N_2O$ 195.0564, found 195.0557.

Melting point: 289.1 – 289.7 °C

The obtained ^{1}H NMR data is in agreement with literature values.[10a]

3.2.2. Synthesis of 2-oxo-6-phenyl-1,2-dihydropyridine-3-carboxylic acid 10



10

The reaction was performed following a modified literature procedure.[10a] A suspension of 2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile **9** (9.5 g, 50 mmol, 1.0 equiv.) in HBr (48% aq., 32 mL, 286 mmol, 5.8 equiv.) and acetic acid (71 mL, 1245 mmol, 25.1 equiv.) was heated at 120 °C for 16 h. After this time, the mixture was cooled and the pH adjusted to 5 with NaOH (10% aq.), which caused the precipitation of the product. The product was filtered and washed with HCl (10% aq.) and water before drying over P_2O_5 under vacuum to give the desired carboxylic acid as a beige solid (8.3 g, 78%).

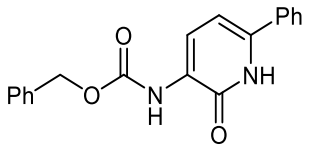
^{1}H NMR (400 MHz, DMSO-d_6): δ = 14.69 (bs, 1H), 13.47 (bs, 1H), 8.42 (d, J_{HH} = 7.6 Hz, 1H), 7.85-7.83 (m, 2H), 7.61-7.54 (m, 3H), 7.02 (d, J_{HH}= 7.6 Hz, 1H).

^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 165.5, 165.1, 152.2, 145.9, 131.7, 131.3, 129.0, 127.9, 114.6, 107.5.

HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{12}H_9NO_3Na$ 238.0475, found 238.0483.

Melting point: 298.5 – 299.3 °C

3.2.3. Synthesis of benzyl (2-oxo-6-phenyl-1,2-dihydropyridin-3-yl)carbamate 11



11

The reaction was performed following a modified literature procedure.[10a] In a three-neck round-bottom flask fitted with a reflux condenser, 2-oxo-6-phenyl-1,2-dihydropyridine-3-carboxylic acid **10** (3.0 g, 14 mmol, 1.0 equiv.) was dissolved in dry dioxane under Ar. Triethylamine (1.9 g, 16 mmol, 1.1 equiv.) and diphenyl phosphoryl azide (4.2 g, 16 mmol, 1.1 equiv.) were added before heating the mixture at 110 °C for 4 h. Then, the mixture was cooled to room temperature and benzyl alcohol (3.0 g, 28 mmol, 2.0 equiv.) was added. The mixture was heated at 110 °C for another 12 h. After this time, the mixture was cooled to room temperature and the solvent was evaporated. The resulting solid was washed with HCl (10% aq.), $NaHCO_3$ (sat. aq.) and water. The crude product was recrystallised from chloroform to give the desired product as a light orange solid (2.2 g, 50%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.20 (bs, 1H), 8.46 (s, 1H), 7.92 (d, J_{HH}= 7.6 Hz, 1H), 7.70 (d, J_{HH} = 7.4 Hz, 2H), 7.48-7.32 (m, 8H), 6.61 (d, J_{HH} = 7.5 Hz, 1H), 5.18 (s, 2H).

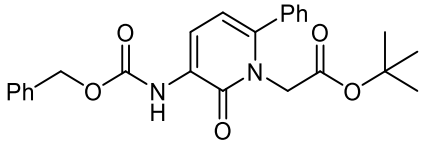
^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 157.9, 153.2, 138.7, 136.4, 133.2, 129.0, 128.8, 128.4, 128.0, 127.7, 126.4, 122.4, 104.0, 66.1.

HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{19}H_{16}N_2O_3Na$ 343.1053, found 343.1054.

Melting point: 211.1 – 211.7 °C

The obtained ^{1}H NMR data are in agreement with literature values.[10a]

3.2.4. Synthesis of tert-butyl 2-(3-(((benzyloxy)carbonyl)amino)-2-oxo-6-phenylpyridin-1(2*H*)-yl)acetate 12



12

The reaction was performed following a modified literature procedure.[10a] Benzyl (2-oxo-6-phenyl-1,2-dihydropyridin-3-yl)carbamate **11** (3.8 g, 12 mmol, 1.0 equiv.) was suspended in dry DMF (50 mL) and

NaH (60% in mineral oil, 0.5 g, 14 mmol, 1.2 equiv.) was added portion-wise. The mixture was stirred for 1.5 h before tert-butyl bromoacetate (2.3 g, 12 mmol, 1.0 equiv.) was added drop-wise. The reaction was stirred at room temperature for 16 h. After this time, the reaction was diluted with water (80 mL) and the mixture was extracted with EtOAc four times. The combined extracts were washed with brine, filtered through a phase separator and concentrated. The crude product was purified by column chromatography (*n*-pentane / ethyl acetate 30:1 to 20:1) to give the desired product as a colourless solid (2.2 g, 44%).

TLC: R_f = 0.38 (*n*-pentane / ethyl acetate 10:1). UV active.

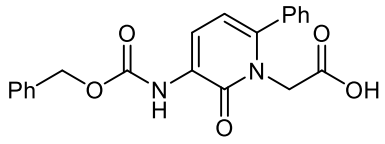
^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.13 (bs, 1H), 8.14 (d, J_{HH} = 8.1 Hz, 1H), 8.02 (d, J_{HH}= 7.4 Hz, 2H), 7.63 (d, J_{HH}= 8.2 Hz, 1H), 7.47-7.34 (m, 8H), 5.19 (s, 2H), 4.85 (s, 2H), 1.37 (2, 9H).

^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 168.3, 154.3, 137.9, 137.0, 129.1, 129.0, 128.9, 128.4, 128.3, 126.3, 121.7, 113.9, 81.5, 66.5, 63.6, 28.2.

HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{25}H_{26}N_2O_5Na$ 457.1734, found 457.1736.

Melting point: 103.5 – 104.2 °C

3.2.5. Synthesis of 2-(3-(((benzyloxy)carbonyl)amino)-2-oxo-6-phenylpyridin-1(2*H*)-yl)acetic acid 13



13

The reaction was performed following a modified literature procedure.[10a] A solution of **12** (3.3 g, 8 mmol, 1.0 equiv.) in DCM (57 mL) was treated with trifluoroacetic acid (13 g, 113 mmol, 15 equiv.). The mixture was stirred at room temperature for 12 h. After this time, the solvents were evaporated to afford the desired product as a colourless solid (2.6 g, 92%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.90 (bs, 1H), 9.12 (s, 1H), 8.16 (d, J_{HH}= 8.1 Hz, 1H), 8.01-7.99 (m, 2H), 7.62 (d, J_{HH} = 8.1 Hz, 1H), 7.47-7.32 (m, 8H), 5.19 (s, 2H), 4.91 (s, 2H).

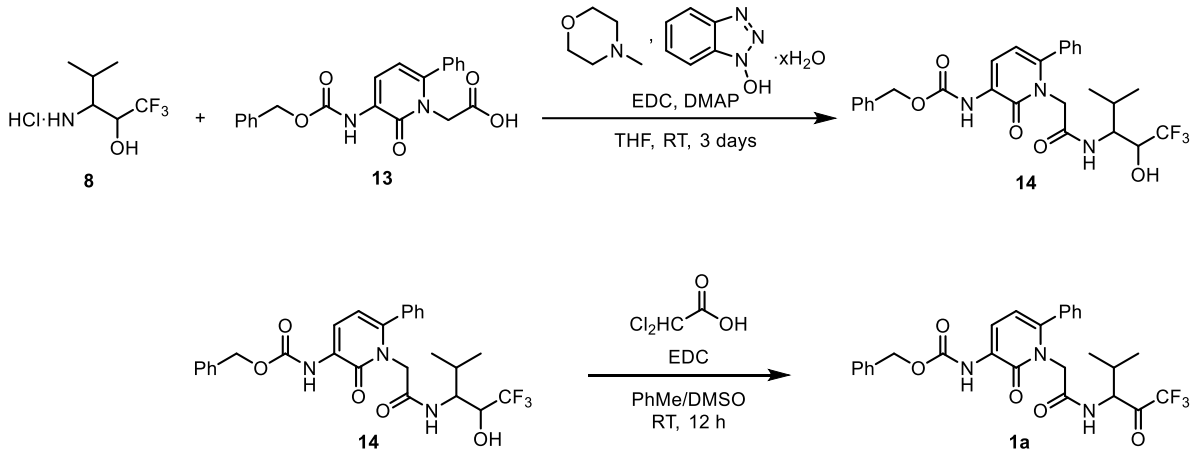
^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 170.2, 153.8, 137.7, 136.5, 128.7, 128.6, 128.4, 128.0, 127.9, 125.9, 121.3, 113.5, 66.1, 62.6.

HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{21}H_{18}N_2O_5Na$ 401.1108, found 401.1104.

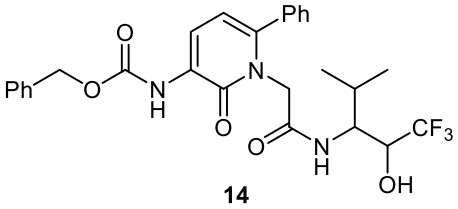
Melting point: 160.7 – 161.2 °C

3.3. Combination of fragments 8 and 13

Fragments **8** and **13** were coupled and oxidised according to the following reaction scheme,[10a] affording neutrophil elastase inhibitor **1a**.



3.3.1. Synthesis of benzyl (6-benzyl-2-oxo-1-(2-oxo-2-((1,1,1-trifluoro-2-hydroxy-4-methylpentan-3-yl)amino)ethyl)-1,2-dihydropyridin-3-yl)carbamate 14



The reaction was performed following a modified literature procedure.[10a] Fragments **8** (233 mg, 1.1 mmol, 1.0 equiv.) and **13** (424 mg, 1.1 mmol, 1.0 equiv.) and hydroxybenzotriazol hydrate (505 mg, 3.2 mmol, 2.9 equiv.) were dissolved in dry THF (14 mL) under Ar. Then, *N*-Methyl morpholine (245 mg, 2.4 mmol, 2.2 equiv.) and EDC (0.24 mL, 1.3 mmol, 1.2 equiv.) were added. The reaction was stirred at room temperature for three days. After this time, EtOAc and HCl (10% aq.) were added. The layers were separated and the organic phase was washed with HCl (10% aq.). The organic phase was filtered through a phase separator and concentrated. Purification by column chromatography (DCM / MeOH 400:1 to 150:1) afforded the desired product as a colourless solid (401 mg, 67%).

TLC: R_f = 0.46 (DCM / MeOH 100:4). UV active.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.27 (s, 1H), 8.04-8.01 (m, 3H), 7.74 (d, J_{HH} = 10.0 Hz, 1H), 7.63 (d, J_{HH} = 8.1 Hz, 1H), 7.46-7.36 (m, 8H), 6.45 (d, J_{HH} = 7.6 Hz, 1H), 5.20 (s, 2H), 4.99 (d, J_{HH} = 14.8 Hz, 1H), 4.83 (d, J_{HH} = 14.9 Hz, 1H), 4.08 (td, J_{HH} = 10.1, 2.9 Hz, 1H), 3.90-3.82 (m, 1H), 2.08 (pd, J_{HH} = 6.8, 2.9 Hz, 1H), 0.61 (d, J_{HH} = 6.8 Hz, 3H), 0.54 (d, J_{HH} = 6.9 Hz, 3H).

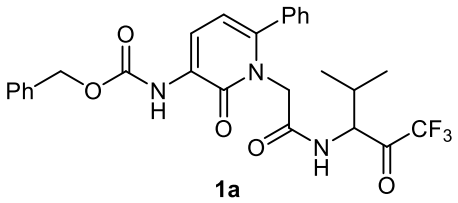
^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 167.8, 154.0, 152.9, 148.0, 137.6, 136.3, 131.1, 128.6$_5$, 125.5$_9$, 128.5, 128.2, 125.8 (q, J_{CF} = 284.8 Hz), 120.9, 113.7, 68 0 (q, J_{CF} = 27.3 Hz), 66.3, 64.0, 50.9, 27.2, 19.4, 14.9.

^{19}F NMR (377 MHz, DMSO-d_6): δ = -74.50 (d, J_{FH} = 7.3 Hz).

HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{27}H_{28}F_3N_3O_5Na$ 554.1873, found 554.1880.

Melting point: 178.2 – 179.1 °C.

3.3.2. Synthesis and characterisation of benzyl (6-benzyl-2-oxo-1-(2-oxo-2-((1,1,1-trifluoro-4-methyl-2-oxopentan-3-yl)amino)ethyl)-1,2-dihydropyridin-3-yl)carbamate 1a



1a

The reaction was performed following a modified literature procedure.[10a, 12] Reaction intermediate **14** (401 mg, 0.7 mmol, 1.0 equiv.) was dissolved in a 1:1 mixture of DMSO and toluene (4 mL) under Ar. To this was added EDC (133 mg, 0.8 mmol, 1.1 equiv.) and dichloroacetic acid (389 mg, 3.0 mmol, 4.0 equiv.). The reaction mixture was stirred at room temperature for 12 h. After this time, the solvent was removed under vacuum. The obtained material was dissolved in EtOAc and washed with HCl (10% aq.), $NaHCO_3$ (sat. aq.) and brine. The organic layer was filtered through a phase separator and concentrated. Purification by column chromatography (DCM / MeOH 300:1) afforded the desired product as a colourless solid (231 mg, 58%).

TLC: R_f = 0.38 (*n*-pentane : EtOAc 3:1). UV-active.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (d, J_{HH} = 8.1 Hz, 1H), 7.94-7.91 (m, 2H), 7.49 (d, J_{HH} = 8.2 Hz, 1H), 7.49-7.35 (m, 8H), 7.09 (s, 1H), 6.86 (d, J_{HH} = 8.7 Hz, 1H), 5.26 (s, 2H), 5.19 (d, J_{HH} = 15.1 Hz, 1H), 5.07 (dd, J_{HH} = 8.7, 4.4 Hz, 1H), 4.93 (d, J_{HH} = 15.1 Hz, 1H), 2.28-2.20 (m, 1H), 0.86 (d, J_{HH} = 6.8 Hz, 3H), 0.60 (d, J_{HH} = 6.9 Hz, 3H).

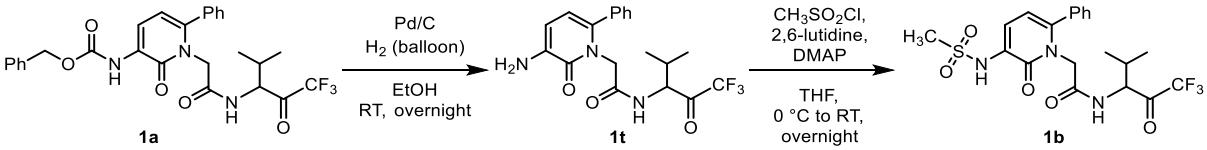
$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ = 190.5 (q, J_{CF} = 35.0 Hz), 169.1, 151.2, 148.5, 137.6, 135.7, 128.8, 128.7_5, 128.7_3, 128.6, 128.5, 126.3, 121.0, 115.2 (q, J_{CF} = 292.4 Hz), 114.8, 67.6, 65.2, 58.5, 29.3, 19.6, 16.4.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -76.32.

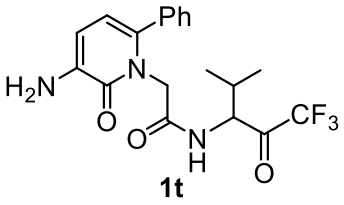
HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{27}H_{26}F_3N_3O_5Na$ 552.1717, found 552.1722.

Melting point: 169.8 – 170.9 °C.

3.4. Synthetic route of 2-(3-(methylsulfonamido)-2-oxo-6-phenylpyridin-1(2*H*)-yl)-*N*-(1,1,1-trifluoro-4-methyl-2-oxopentan-3-yl)acetamide 1b



3.4.1. Synthesis of 2-(3-amino-2-oxo-6-phenylpyridin-1(2*H*)-yl)-*N*-(1,1,1-trifluoro-4-methyl-2-oxopentan-3-yl)acetamide 1t



The reaction was performed following a modified literature procedure.[8] The title compound was synthesized by hydrolysis of the Cbz group of **1a**. To a solution of trifluoro ketone **1a** (50 mg) in ethanol (1.2 mL) was added 10% (w/w) Pd/C (12.5 mg). The mixture was stirred under a hydrogen atmosphere (H_2 balloon) overnight. The catalyst was removed by filtration through a pad of Celite®. The filter pad was washed successively with methanol. Concentration of the filtrate gave the crude product as an off-white solid. This material was dissolved in a minimum volume of methanol. Then, diethyl ether was added, and the mixture was allowed to stand overnight. The precipitate was collected and washed with ether to give a yellow oil (36.3 mg, 97%).

TLC: R_f = 0.13 (*n*-pentane / ethyl acetate 3:1). UV active.

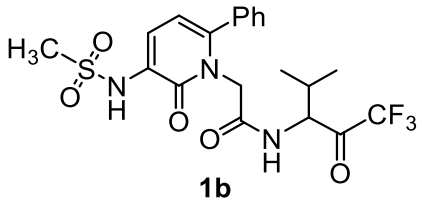
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, J_{HH} = 7.4 Hz, 2H), 7.39 (t, J_{HH} = 7.6 Hz, 2H), 7.35-7.27 (m, 2 H), 7.04 (d, J_{HH} = 7.9 Hz, 1H), 6.93 (d, J_{HH} = 8.4 Hz, 1H), 5.22 (d, J_{HH} = 15.3 Hz, 1H), 5.09 (dd, J_{HH} = 8.7, 4.3 Hz, 1H), 4.93 (d, J_{HH} = 15.3 Hz, 1H), 3.93 (s, 3H), 2.26 (dq, J_{HH} = 13.2, 6.7 Hz, 1H), 0.88 (d, J_{HH} = 6.8 Hz, 3H), 0.64 (d, J_{HH} = 6.9 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ = 190.7 (q, J_{CF} = 34.9 Hz), 169.6, 150.0, 143.6, 138.5, 129.7, 128.7, 127.9, 125.8, 122.7, 115.5 (q, J_{CF} = 292.5 Hz), 115.2, 65.2, 58.5, 29.5, 19.7, 16.3.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -76.32.

HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{19}H_{20}F_3N_3O_3Na$ 418.1349, found 418.1352.

3.4.2. Synthesis of 2-(3-(methylsulfonamido)-2-oxo-6-phenylpyridin-1(2*H*)-yl)-*N*-(1,1,1-trifluoro-4-methyl-2-oxopentan-3-yl)acetamide 1b



1b

The reaction was performed following a modified literature procedure.[8] The title compound was synthesized by mesylation of **1t**. A 10 mL flask under Ar was charged with the substrate (74.7 mg, 0.189 mmol) and DMAP[7] (23.1 mg, 0.189 mmol) dissolved in tetrahydrofuran (1.9 mL). 2,6-Lutidine (0.044 mL) was added at 0 °C, followed by MsCl (0.022 mL). The cloudy, yellow solution was stirred at room temperature overnight; diluted with ethyl acetate (25 mL), washed with hydrochloric acid (1 M), saturated aqueous sodium bicarbonate, and brine. It was then dried and evaporated to give an oil. The oil was purified by chromatography (DCM / Et_2O 6:1) to afford the product (44.7 mg, 50%) as a yellow oil.

TLC: R_f = 0.24 (DCM / Et_2O 4:1). UV active.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, J_{HH} = 7.0 Hz, 2H), 7.82 (d, J_{HH} = 8.0 Hz, 1H), 7.51-7.36 (m, 4H), 7.07 (d, J_{HH} = 8.2 Hz, 1H), 7.02 (s, 1H), 5.21 (d, J_{HH} = 15.1 Hz, 1H), 5.09-4.99 (m, 2H), 3.14 (s, 3H), 2.29 (dq, J_{HH} = 12.7, 6.5 Hz, 1H), 0.90 (d, J_{HH} = 6.7 Hz, 3H), 0.71 (d, J_{HH} = 6.8 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ = 190.7 (q, J_{CF} = 34.8 Hz), 169.0, 153.7, 151.8, 137.4, 132.7, 129.5, 129.0, 126.7, 119.3, 115.5 (q, J_{CF} = 291.9 Hz), 115.0, 65.1, 58.8, 40.5, 29.4, 19.7, 16.8.

^{19}F NMR (377 MHz, $CDCl_3$): δ = -76.30.

HRMS (ESI) *m/z* $[M - H]^-$ calcd for $C_{20}H_{21}F_3N_3O_5S$ 472.1159, found 472.1152.

4. Radiochemical studies

[^{18}F]Fluoride was produced by the nuclear reaction ^{18}O(p,n)^{18}F using [^{18}O]H_2O as target in a Scanditronix MC-17 cyclotron and was separated from [^{18}O]H_2O using a Sep-Pak® Accell Plus QMA Light anion exchange cartridge (Waters, Part No. WAT023525) pretreated with K_2CO_3 (aq. 0.5 M, 10 mL) and later with H_2O (10 mL).

4.1. Preparation of [^{18}F]Bu_4NF

[^{18}F]Fluoride was released from the cartridge as [^{18}F]Bu_4NF using an aqueous solution of Bu_4NHCO_3 (ABX; 0.0375 M) in a 1:1 mixture with acetonitrile (450 μL total volume), every 20 s 150 μL were added through the cartridge. Acetonitrile was added (200 μL) and the [^{18}F]Bu_4NF was dried at 120 °C under a flow of N_2 for 4 min. The drying process was repeated twice using 200 μL of acetonitrile for 3 and 2 min, respectively. The obtained [^{18}F]Bu_4NF was dissolved in dry DMF and used in the next step.

4.2. Preparation of [^{18}F]KF/K_{222}

[^{18}F]Fluoride was released from the cartridge as [^{18}F]KF/K_{222} using a solution of MeCN/water (16 mL : 4 mL; 4:1) of K_2CO_3 (28 mg) and K_{222} (200 mg). 450 μL were taken and pre-mixed with further 150 μL of water (600 μL total volume) and every 20 s 200 μL were added through the cartridge. Acetonitrile was added (200 μL) and the [^{18}F]KF/K_{222} was dried at 120 °C under a flow of $N_2$for 4 min. The drying process was repeated twice using 200 μL of acetonitrile for 3 min and 2 min, respectively. The obtained [^{18}F]Bu_4NF was dissolved in dry DMF and used in the next step.

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

4.3. Synthesis of [^{18}F]trifluoromethyl ketones [^{18}F]1

Radiosynthesis of [^{18}F]1g-o

A dry conical vial was loaded with the corresponding 2-bromo-2,2-difluoro acetophenone (60 μmol) and TBD (60 μmol) and then sealed. The vial was purged with N_2 before adding DMF (150 μL). The DMF solution containing [^{18}F]Bu_4NF (150 μL) was added and the reaction mixture was stirred at 75 °C for

10 min. An aliquote was analysed by radio-HPLC or radio-TLC in order to estimate the radiochemical yield.

Radiosynthesis of [^{18}F]1p-q

These compounds were labelled following the method described above, but heating the reaction mixture to 100 °C instead of 75 °C.

Radiosynthesis of [^{18}F]1r

This compound was labelled following the method described above, but using *N,N*-diisopropylethylamine (DIPEA) instead of TBD as activator.

Radiosynthesis of [^{18}F]1s

Labelling reagent and additive screen:

Entry	Labelling reagent	Additive (60 μmol)	RCY [%]
1	[^{18}F]Bu_4NF	TBD	0
2	[^{18}F]Bu_4NF	MTBD	0
3	[^{18}F]Bu_4NF	–	0
4	[^{18}F]Bu_4NF	DIPEA	6
5	[^{18}F]KF/K_{222}	TBD	44 ± 1 (n = 2)
6	[^{18}F]KF/K_{222}	–	55 ± 4 (n = 2)
7	[^{18}F]KF/K_{222}	DIPEA	46

Optimised procedure:

A dry conical vial was loaded with 5-bromo-5,5-difluoro-3-isopropyl-1-phenylpentane-1,4-dione **3s** (60 μmol, 20 mg) and sealed. The DMF solution containing [^{18}F]KF/K_{222} was added (300 μL) and the reaction mixture was stirred at 75 °C for 10 min. An aliquot was analysed by radio-HPLC in order to estimate the radiochemical yield.

Radiosynthesis of [^{18}F]1a

Precursor, labelling reagent, additive and temperature screen:

Entry	Precursor	Labelling reagent	Additive	Temperature [°C]	RCY [%]
1	**3a** (CF_2Br)	[^{18}F]Bu_4NF	TBD (6 μmol)	75	4
2	**3a** (CF_2Br)	[^{18}F]Bu_4NF	–	75	4
3	**3a** (CF_2Br)	[^{18}F]Bu_4NF	–	50	2
4	**3a** (CF_2Br)	[^{18}F]Bu_4NF	–	100	4
5	**3a** (CF_2Br)	[^{18}F]KF/K_{222}	TBD (60 μmol)	75	0
6	**3a** (CF_2Br)	[^{18}F]KF/K_{222}	–	75	5

7	**3a** (CF_2Br)	[^{18}F]KF/$K_{18\text{-}c\text{-}6}$	–	75	0
8	**4a** (CF_2I)	[^{18}F]Bu_4NF	TBD (6 μmol)	75	0
9	**4a** (CF_2I)	[^{18}F]Bu_4NF	–	75	25 ± 1 (n = 2)
10	**4a** (CF_2I)	[^{18}F]KF/K_{222}	–	75	15

Optimised procedure:

A dry conical vial was loaded with (2-(2-((1-iodo-1,1-difluoro-4-methyl-2-oxopentan-3-yl)amino)-2-oxoethyl)-3-oxo-2,3-dihydro-[1,1'-biphenyl]-4-yl)carbamate **4a** (6 μmol, 3.5 mg) and sealed. The vial was purged with N_2 and the DMF solution containing [^{18}F]Bu_4NF was added (300 μL). The reaction mixture was stirred at 75 °C for 10 min. An aliquot was analysed by radio-HPLC in order to estimate the radiochemical yield.

Radiosynthesis of [^{18}F]1b

Precursor, labelling reagent, additive and temperature screen:

Entry	Precursor	Labelling reagent	Additive (6 μmol)	solvent	Temperature [°C]	Time [min]	RCY [%]
1	**4b** (CF_2I)	[^{18}F]Bu_4NF	TBD	DMF	75	10	3
2	**4b** (CF_2I)	[^{18}F]Bu_4NF	–	DMF	75	10	0 (n = 3)
3	**4b** (CF_2I)	[^{18}F]Bu_4NF	–	DMA	75	10	0 (n = 2)
4	**4b** (CF_2I)	[^{18}F]Bu_4NF	–	MeCN	75	10	2
5	**4b** (CF_2I)	[^{18}F]Bu_4NF	TBD	MeCN	75	10	0 (n = 2)
6	**4b** (CF_2I)	[^{18}F]Bu_4NF	TBD	DMA	75	10	5 ± 0 (n = 2)
7	4b (CF_2I)	[^{18}F]Bu_4NF	TBD	DMA	90	5	0 (n = 2)
8	4b (CF_2I)	[^{18}F]Bu_4NF	TBD	DMA	90	10	15 ± 7 (n = 5)
9	**4b** (CF_2I)	[^{18}F]KF/K_{222}	TBD	DMA	90	10	23
10	**4b** (CF_2I)	[^{18}F]KF/K_{222}	–	DMA	90	10	0

Optimised procedure:

A dry conical vial was loaded with **4b** (6 μmol, 3.5 mg), TBD (6 μmol) and then sealed. The vial was purged with N_2 and the DMA solution containing [^{18}F]Bu_4NF was added (300 μL). The reaction mixture was stirred at 90 °C for 10 min. An aliquot was analysed by radio-HPLC in order to estimate the radiochemical yield.

4.4. Analysis and radiochemical yield (RCY) determination

Radiochemical yields of compounds **[^{18}F]1g-f**, **[^{18}F]1j-k**, **[^{18}F]1m-o**, and **[^{18}F]1r-s** were determined by HPLC analysis of the crude reaction mixtures.

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

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

Method 2. The analyses were performed using an Agilent 1290 Infinity II system with a built-in PDA detector and in series with a Bioscan Flow-Count PMT radioactivity detector using a Phenomenex Gemini NX C18 column (5 μm, 100 x 3.0 mm). The mixtures were eluted with a linear-increase gradient (mobile phase A: acetonitrile, mobile phase B: ammonium formate 50 mM) at a flow of 1.5 mL/min.

Time [min]	Mobile Phase A (MeCN) [%]	Mobile Phase B (AMF) [%]
0	30	70
10	70	30

Method 3. The analyses were performed using an Agilent 1290 Infinity II system with a built-in PDA detector and in series with a Bioscan Flow-Count PMT radioactivity detector using a Phenomenex Kinetex C18 column (2.6 μm, 100 x 2.1 mm). The mixtures were eluted with a linear-increase gradient (mobile phase A: acetonitrile, mobile phase B: water at a flow of 1.5 mL/min.

Time [min]	Mobile Phase A (MeCN) [%]	Mobile Phase B (Water) [%]
0	30	70
10	70	30

Method 4. The analyses were performed using an Agilent 1290 Infinity II system with a built-in PDA detector and in series with a Bioscan Flow-Count PMT radioactivity detector using a Phenomenex Kinietex C18 column (2.6 μm, 100 x 2.1 mm). The mixtures were eluted with a linear-increase gradient (mobile phase A: acetonitrile, mobile phase B: ammonium formate 50 mM) at a flow of 1.5 mL/min.

Time [min]	Mobile Phase A (MeCN) [%]	Mobile Phase B (AMF) [%]
0	30	70
10	70	30

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

Compound	HPLC Method	Retention time UV detector (^{19}F reference) [min]	Compound	Retention time β^+ flow detector (^{18}F-labelled) [min]
1g	1	2.62	**[^{18}F]1g**	2.69
1h	2	4.91	**[^{18}F]1h**	5.01
1j	1	6.73	**[^{18}F]1i**	6.60
1k	1	3.53	**[^{18}F]1k**	3.71
1m	1	3.48	**[^{18}F]1m**	3.33
1n	1	4.08	**[^{18}F]1n**	4.16
1o	1	5.30	**[^{18}F]1o**	5.30
1r	2	3.72	**[^{18}F]1r**	3.86
1s	3	3.48	**[^{18}F]1s**	3.61
1a	4	5.59	**[^{18}F]1a**	6.65

Radiochemical yields of **[^{18}F]1i**, **[^{18}F]1l**, **[^{18}F]1p-q** were determined by TLC analysis of the crude reaction mixtures using an Eckert & Ziegler TLC-MiniScan coupled to a Bioscan Flow-Count PMT radioactivity detector. The TLC plates were eluted using pure EtOAc as mobile phase.

Compound	R_f (^{19}F reference)	Compound	R_f β^+-flow detector (^{18}F-labelled)
[^{18}F]1i	0.64	**[^{18}F]1j**	0.67
[^{18}F]1l	0.65	**[^{18}F]1l**	0.66
[^{18}F]1p	0.66	**[^{18}F]1p**	0.70
[^{18}F]1q	0.66	**[^{18}F]1q**	0.70

4.5. Determination of activity yield (AY) and molar activity (A_m) of [^{18}F]1a

A dry conical vial was loaded with **4a** (6 μmol, 3.8 mg) and sealed. The vial was purged with N_2 and the DMF solution containing [^{18}F]Bu_4NF was added (300 μL, 3.6 GBq). The reaction mixture was stirred at 75 °C for 10 min. An aliquot was analysed by radio-HPLC in order to confirm the formation of the product and estimate the radiochemical yield (RCY = 15%). The labelled compound was purified by semi-preparative HPLC. The isolated activity was 58 MBq (AY = 2% from [^{18}F]Bu_4NF, non-decay corrected) with a radiochemical purity of >99% and a molar activity of 0.41 GBq/μmol 70 min after the end of the bombardment.

The experiment was repeated five times and gave an average RCY of 15 ± 12% and an isolated activity of 30 – 128 MBq (n = 5) (AY = 0.8 – 3.4% from [^{18}F]Bu_4NF, non-decay corrected) with a radiochemical purity of 97 ± 2% and a molar activity of 0.2 – 0.5 GBq/μmol 1 h 1 min after the end of the bombardment.

Purification and analysis:

The crude reaction mixture was purified by semi-preparative HPLC using an Agilent 1260 Infinity II system with an in-series UV-detector (λ = 254 nm), in series with a Bioscan Flow-Count PMT radioactivity detector using a reverse-phase column (Kinetex 5 μm, C18, 100 Å, 10 × 250 mm) eluted with a linear increase gradient (mobile phase A: acetonitrile, mobile phase B: ammonium formate 50 mM) at a flow of 5 mL/min.

Time [min]	Mobile Phase A (MeCN) [%]	Mobile Phase B (AMF) [%]
0	30	70
15	90	10
20	90	10

The product was collected in one fraction over 48 seconds with a retention time of 13.2 min.

Analysis of the purified product was performed using an Agilent 1290 Infinity II system with a built-in PDA detector and in series with a Bioscan Flow-Count PMT radioactivity detector using a Gemini RP-18 end-capped column (2 μm, 100 x 4.6 mm) eluted with a linear-increase gradient (mobile phase A: acetonitrile, mobile phase B: ammonium formate 50 mM) at a flow of 1.5 mL/min.

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

The identity of the labelled compound **[^{18}F]1a** was confirmed by co-injection with a true reference of product **1a** (Figure S1).

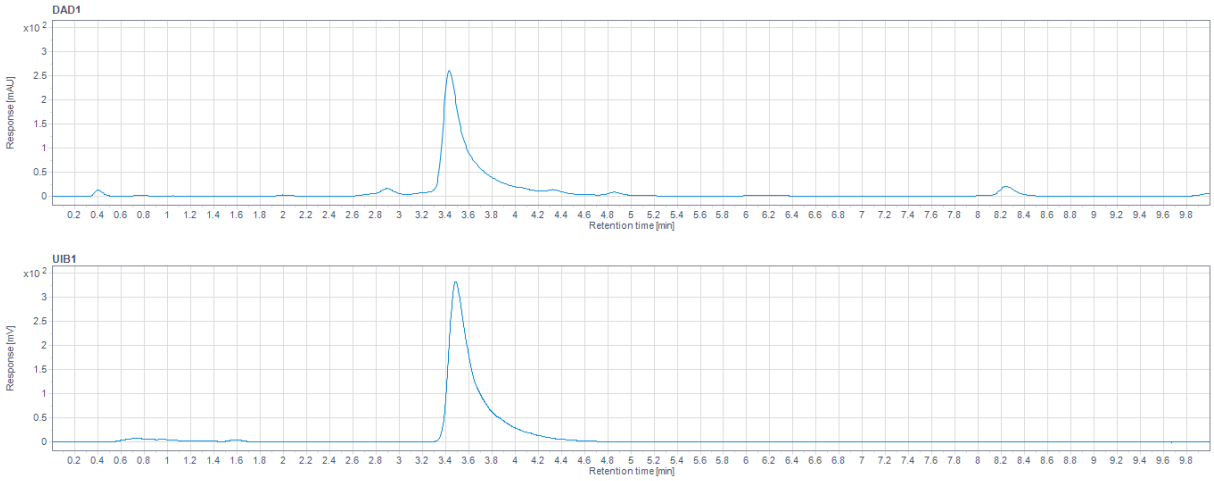


Figure S1. Co-injection of purified product **[^{18}F]1a** and true **1a**.

The molar activity was calculated using a calibration curve (Figure S2). The calibration curve was generated plotting the UV absorption (λ = 260 nm) of known amounts of **1a** against the injected amounts.

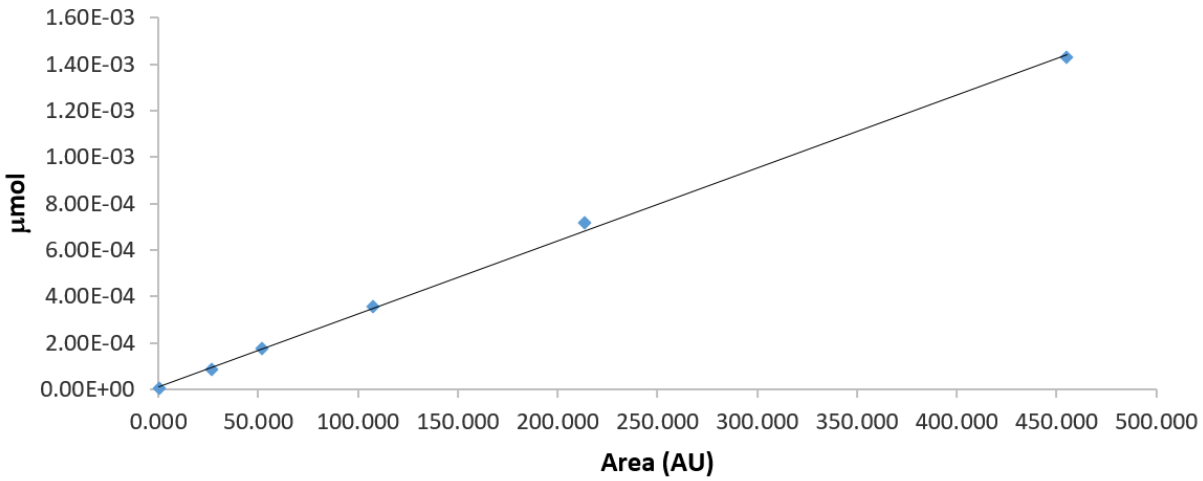


Figure S2. Calibration curve of **1a** for the determination of the molar activity

5. Determination of activity yield (AY) and molar activity (A_m) of [^{18}F]1b

A dry conical vial was loaded with **4b** (6 µmol, 3.5 mg), TBD (6 µmol) and sealed. The vial was purged with N_2 and the DMA solution containing [^{18}F]Bu_4NF was added (300 µL, 4.7 GBq). The reaction mixture was stirred at 90 °C for 10 min. An aliquot was analysed by radio-HPLC in order to confirm the formation of the product and estimate the radiochemical yield (RCY = 30%). The labelled compound was purified by semi-preparative HPLC. The isolated activity was 23 MBq (AY = 0.5% from [^{18}F]Bu_4NF, non-decay corrected) with a radiochemical purity of 57% and a molar activity of 1.27 GBq/µmol 62 min after the end of the bombardment.

Purification and analysis:

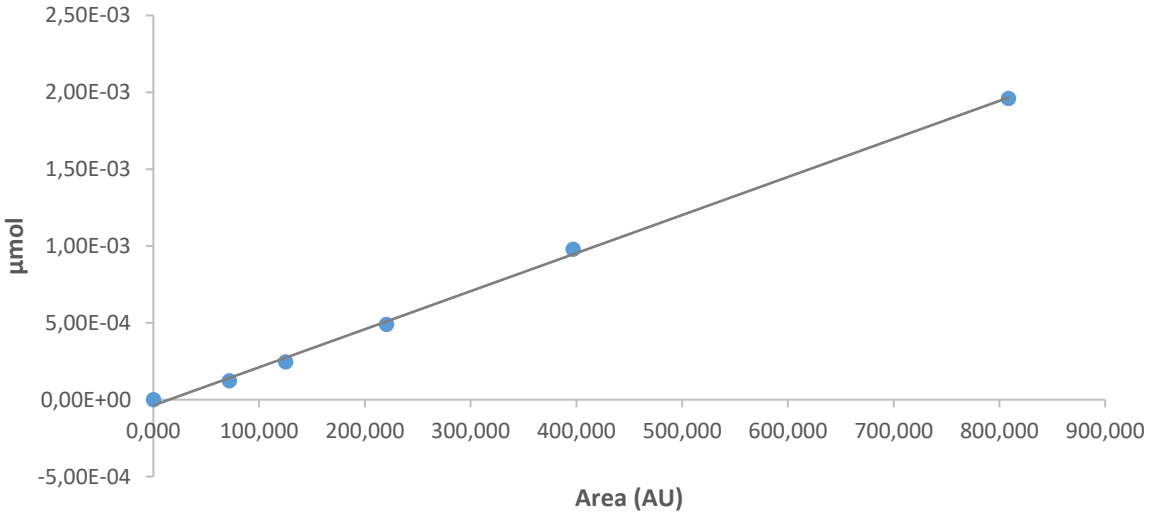
The crude reaction mixture was purified by semi-preparative HPLC using an Agilent 1260 Infinity II system with an in-series UV-detector (λ = 254 nm), in series with a Bioscan Flow-Count PMT radioactivity detector using a reverse-phase column (Gemini NX, 5 µm, C18, 110 Å, 10 × 150 mm) eluted with a linear increase gradient (mobile phase A: acetonitrile, mobile phase B: ammonium formate 50 mM) at a flow of 5 mL/min.

Time [min]	Mobile Phase A (MeCN) [%]	Mobile Phase B (AMF) [%]
0	30	70
15	90	10
20	90	10

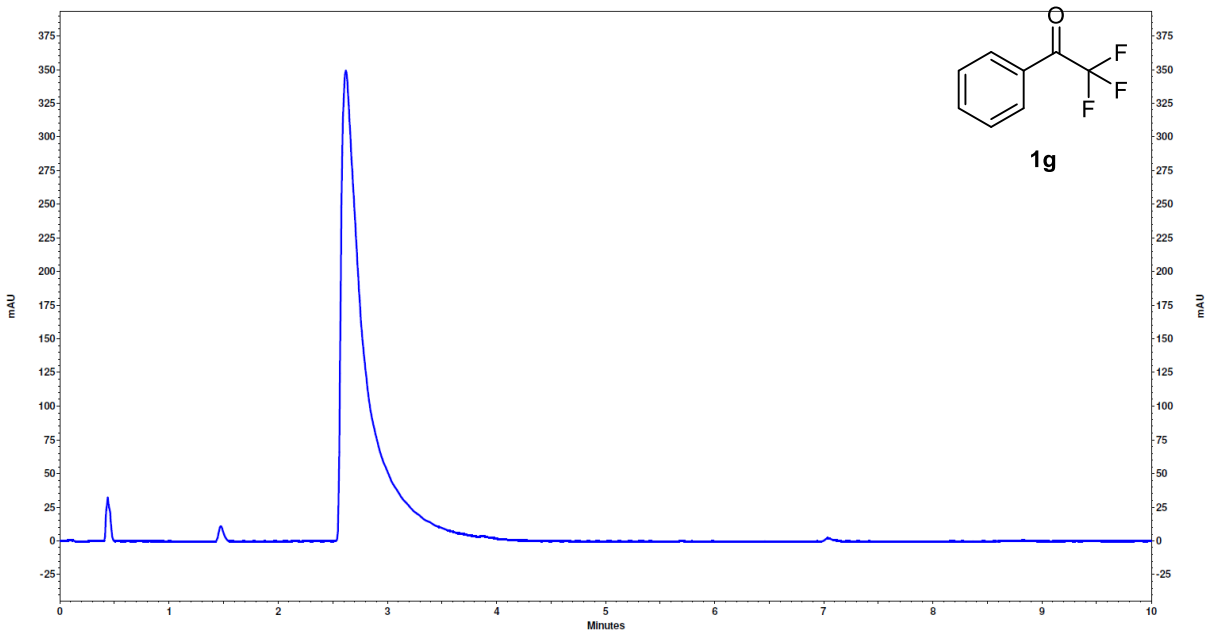
The product was collected in a fraction over 51 seconds with a retention time of 8.5 min.

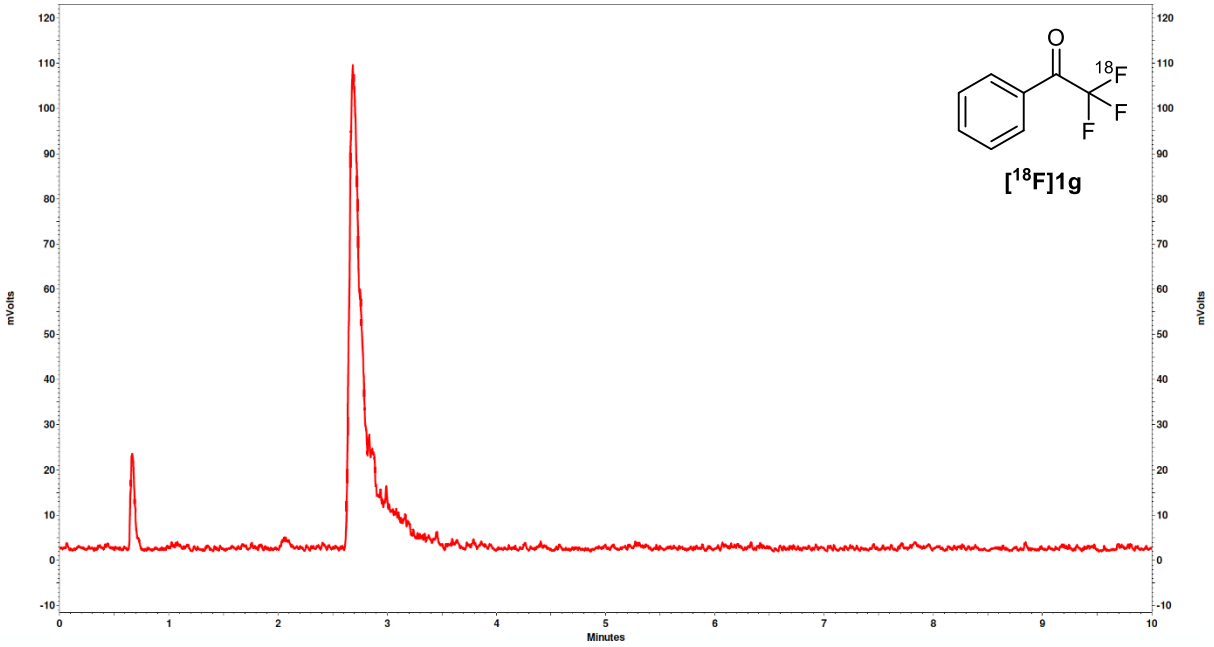
Analysis of the purified product was performed using an Agilent 1290 Infinity II system with a built-in PDA detector and in series with a Bioscan Flow-Count PMT radioactivity detector using a reverse-phase column (Kinetex, 2.6 µm, C18, 100 Å, 4.6 x 100 mm) eluted with a linear-increase gradient (mobile phase A: acetonitrile, mobile phase B: ammonium formate 50 mM) at a flow of 1.5 mL/min.

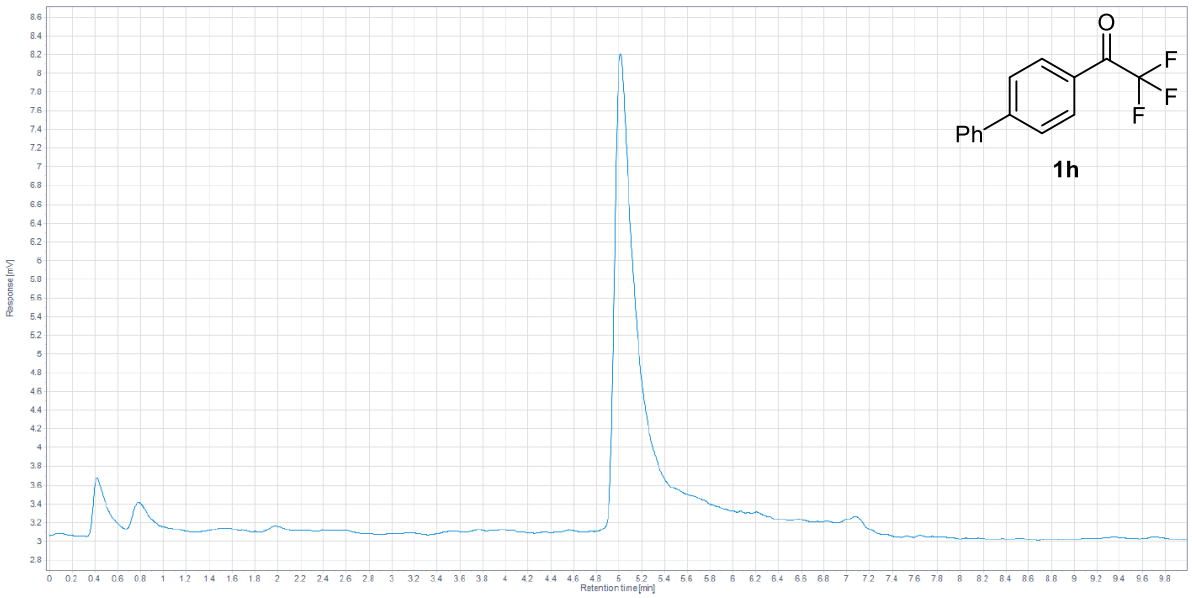
Time [min]	Mobile Phase A (MeCN) [%]	Mobile Phase B (AMF) [%]
0	20	80
10	90	10



6. Radio-HPLC and radio-TLC chromatograms



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Retention time [min]
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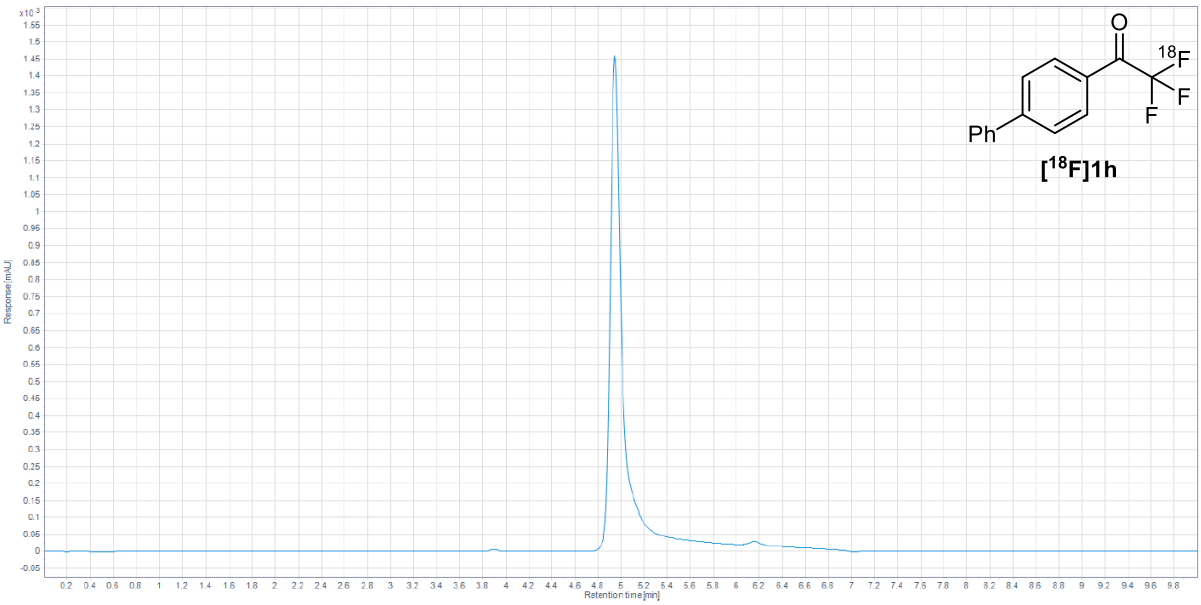
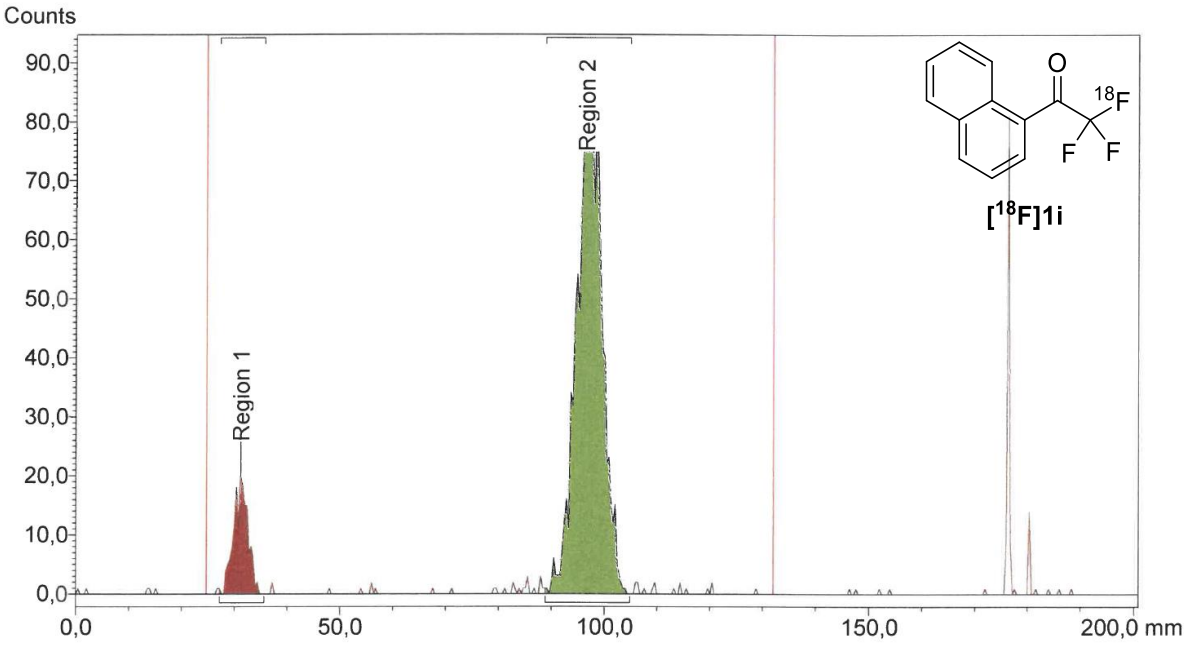
F
F
F
Ph

1h


x10 -3
Response [mAU]
Retention time [min]
O
18F
F
F
Ph

[^{18}F]1h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50,0
40,0
30,0
20,0
10,0
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Region 1
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150,0
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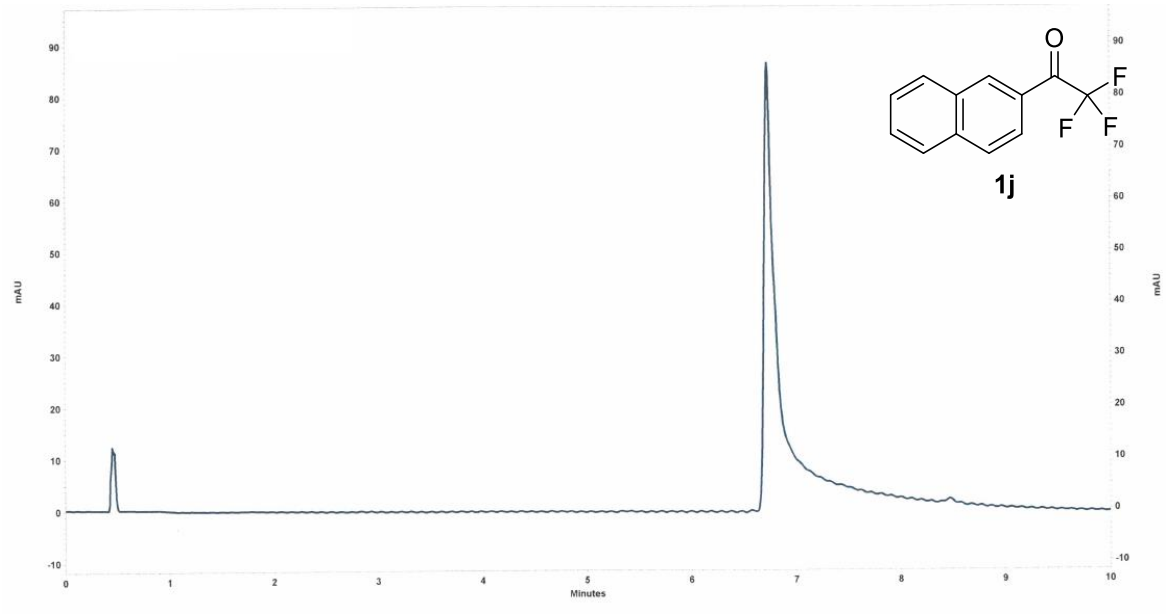
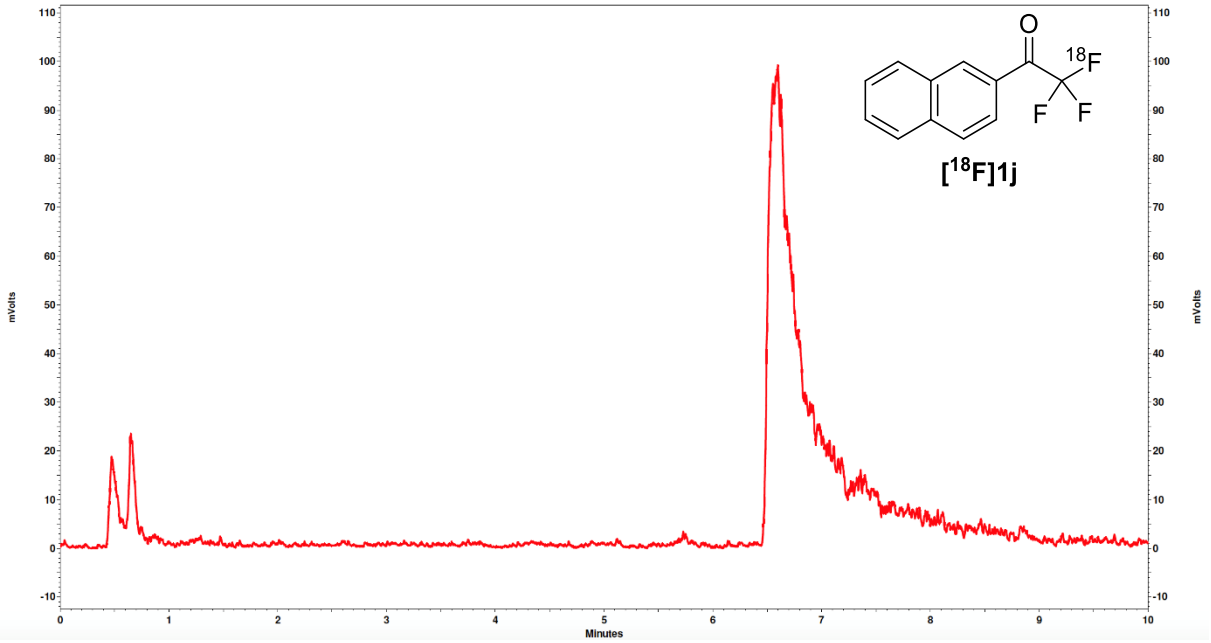

mAU
Minutes
1j


mVolts
Minutes
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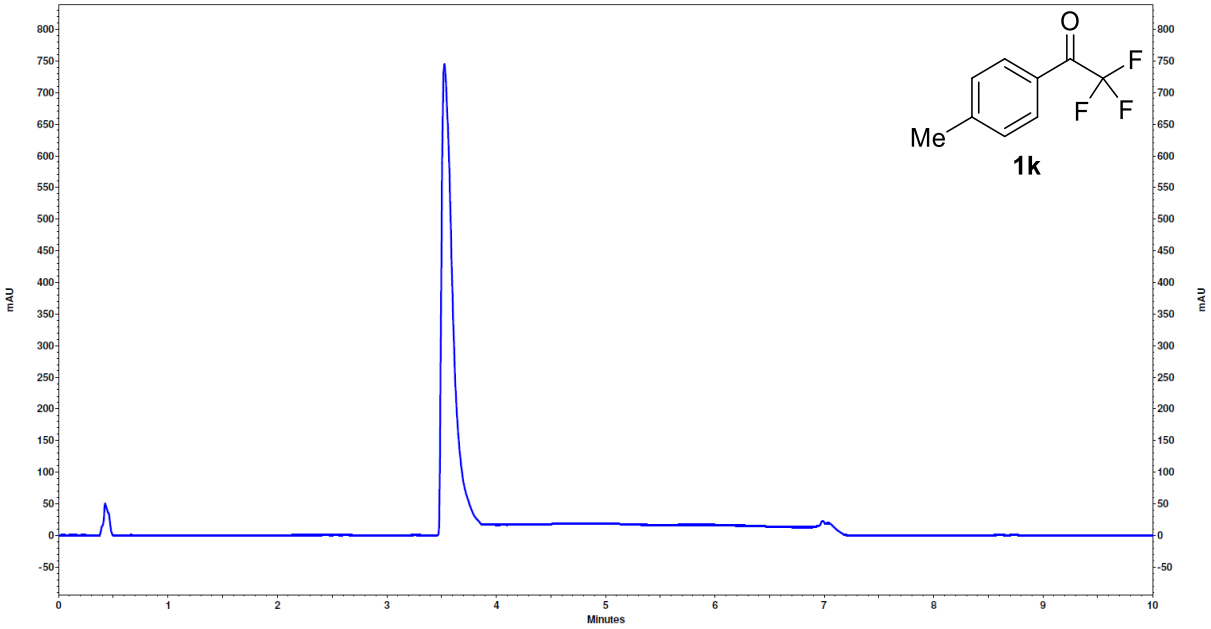
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Minutes
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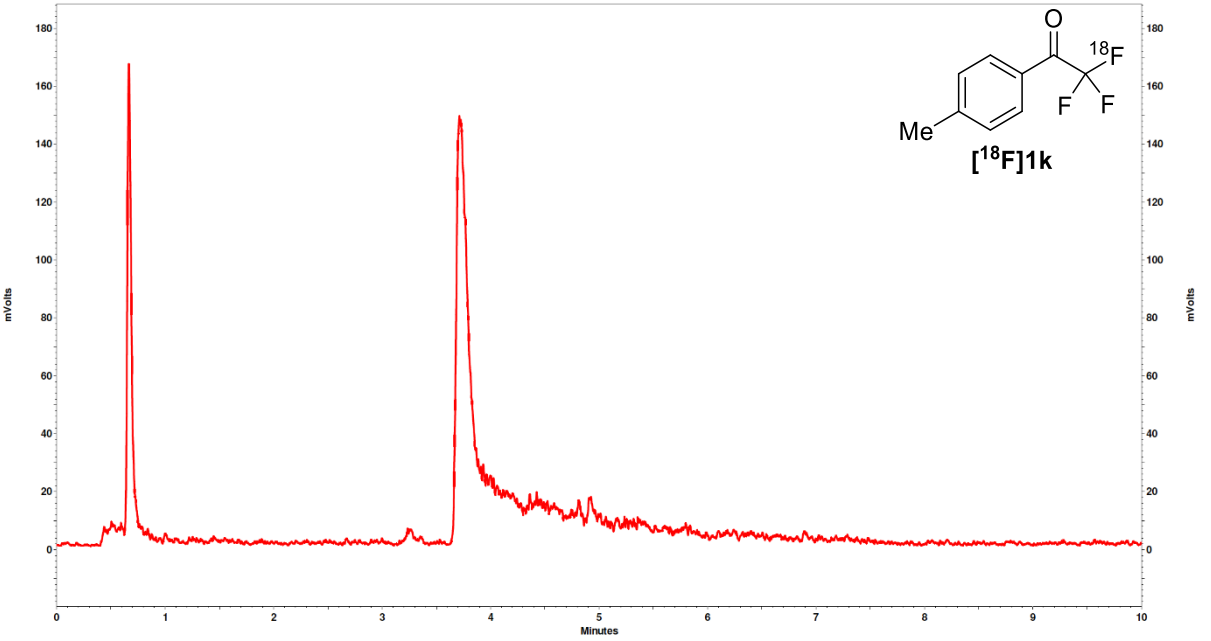
F
F
F
Me
1k


mVolts
Minutes
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18F
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F
Me
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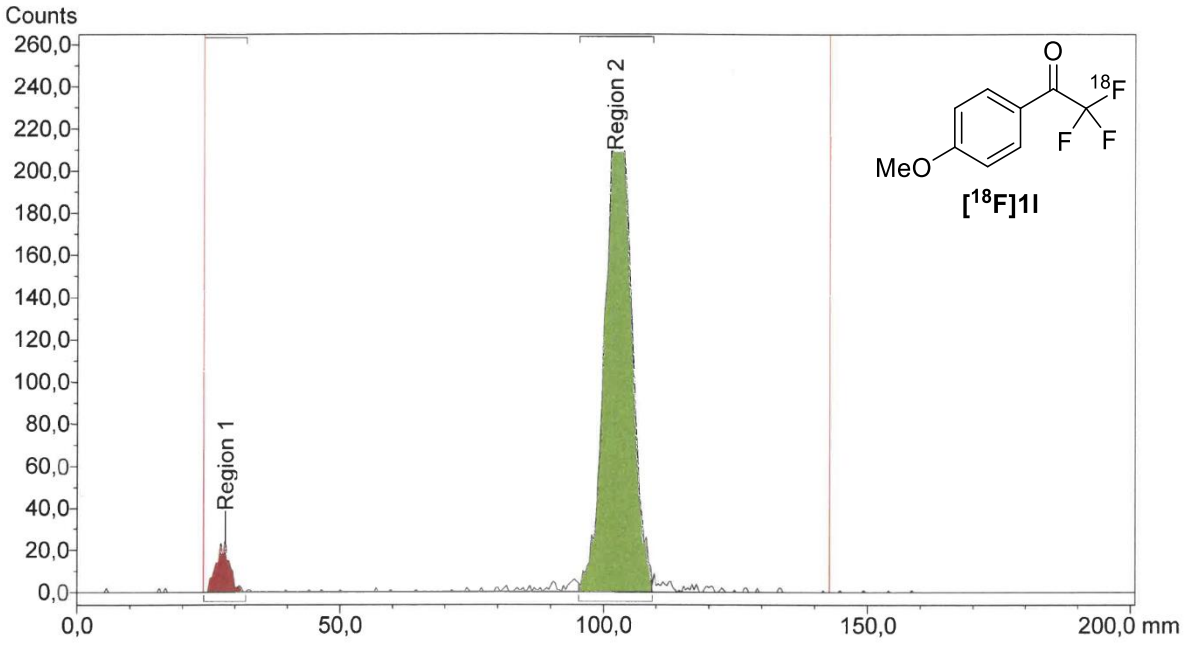
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120,0
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80,0
60,0
40,0
20,0
0,0
Region 1
Region 2
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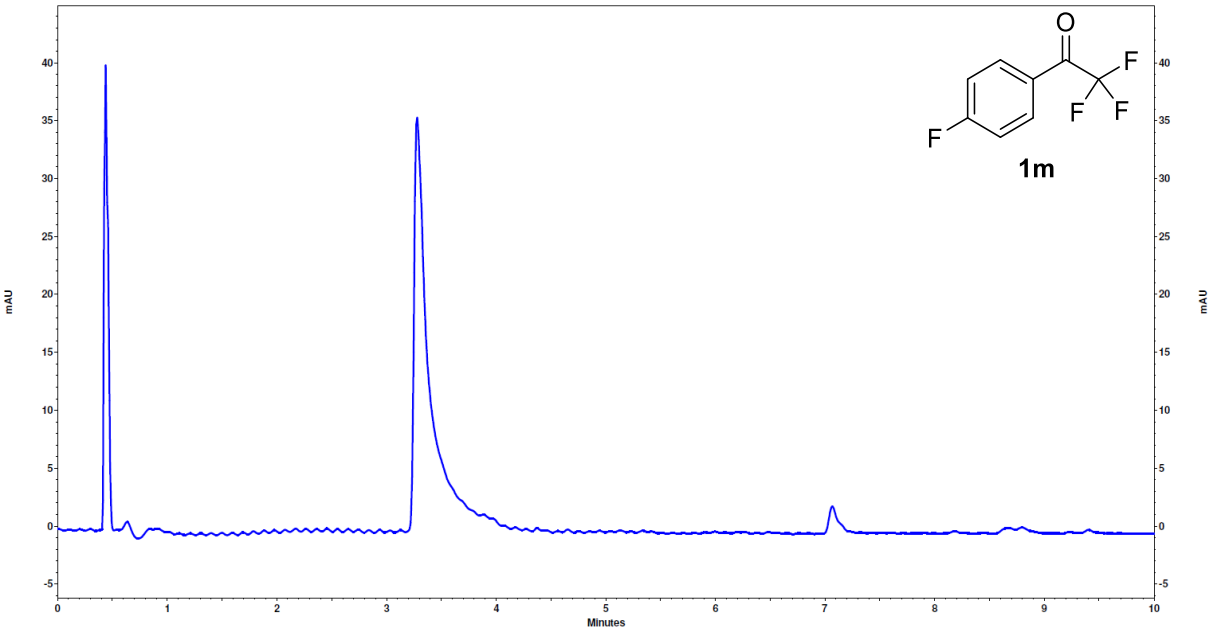
50,0
100,0
150,0
200,0 mm
O
18F
F
F
MeO
[18F]1l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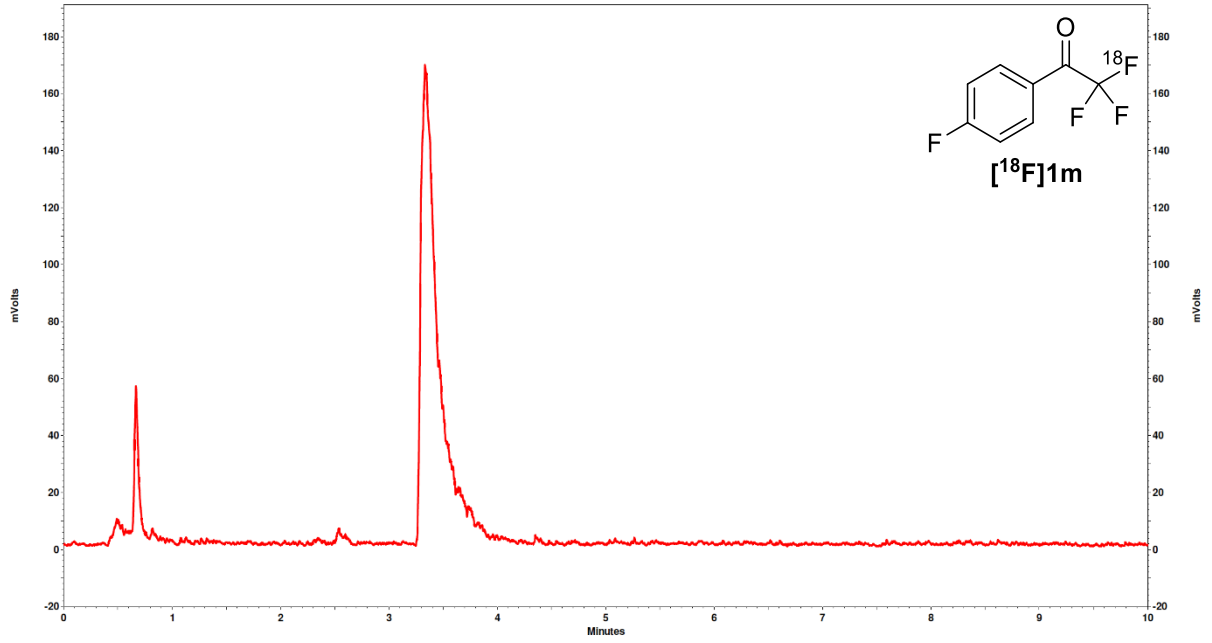
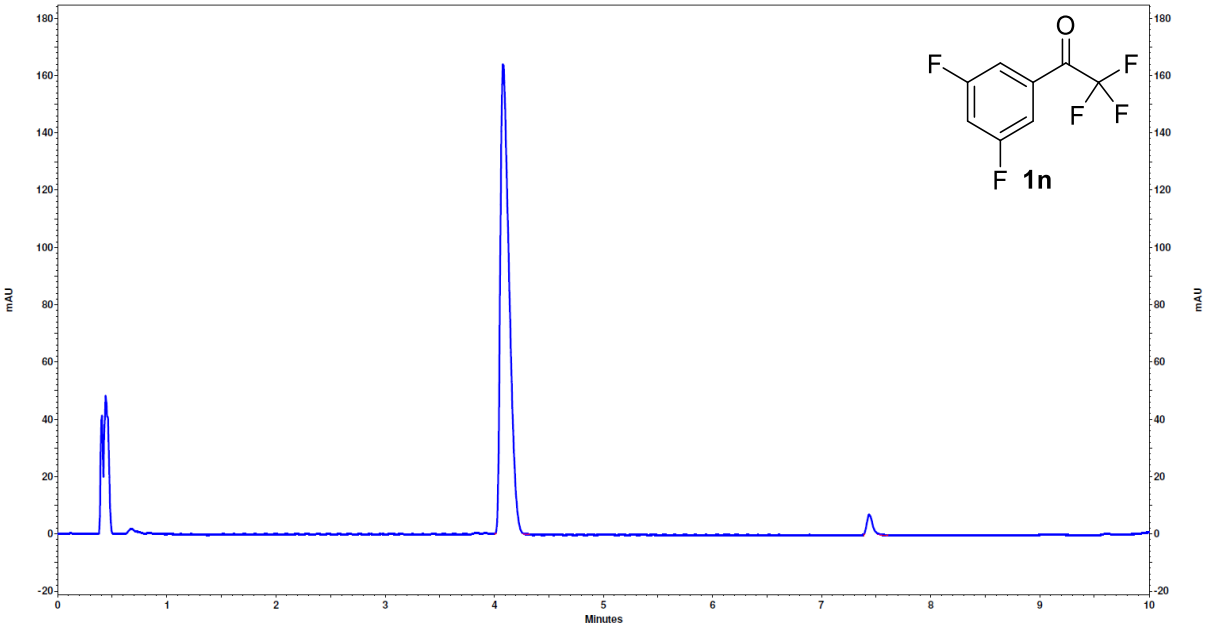
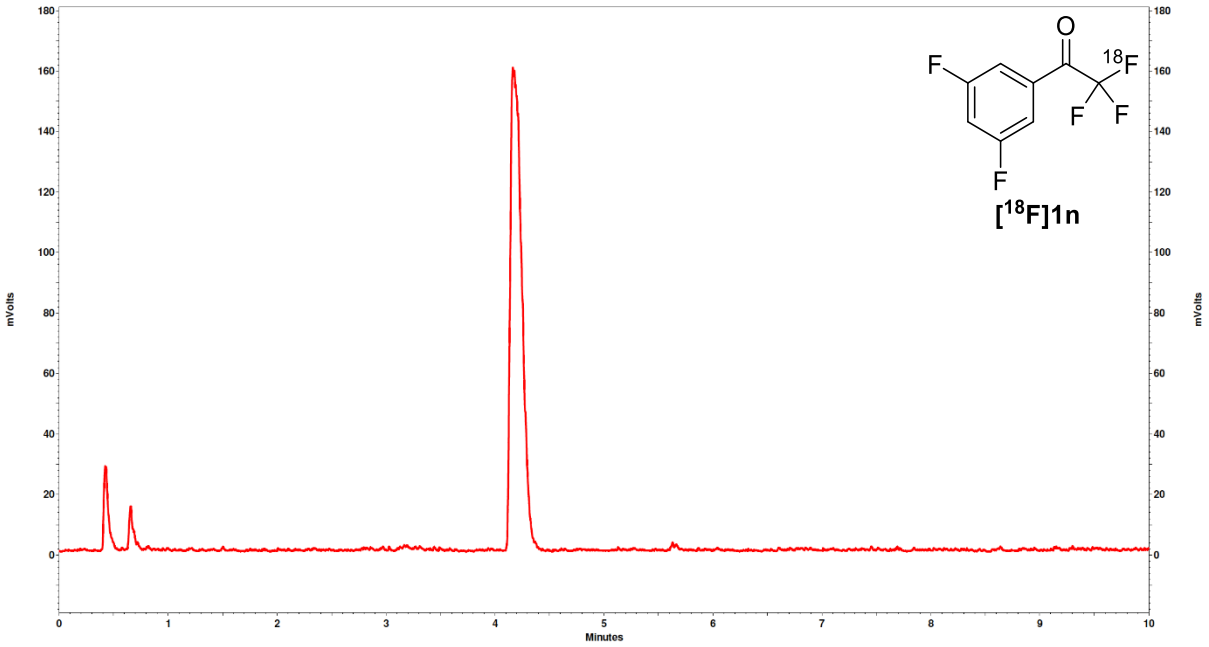
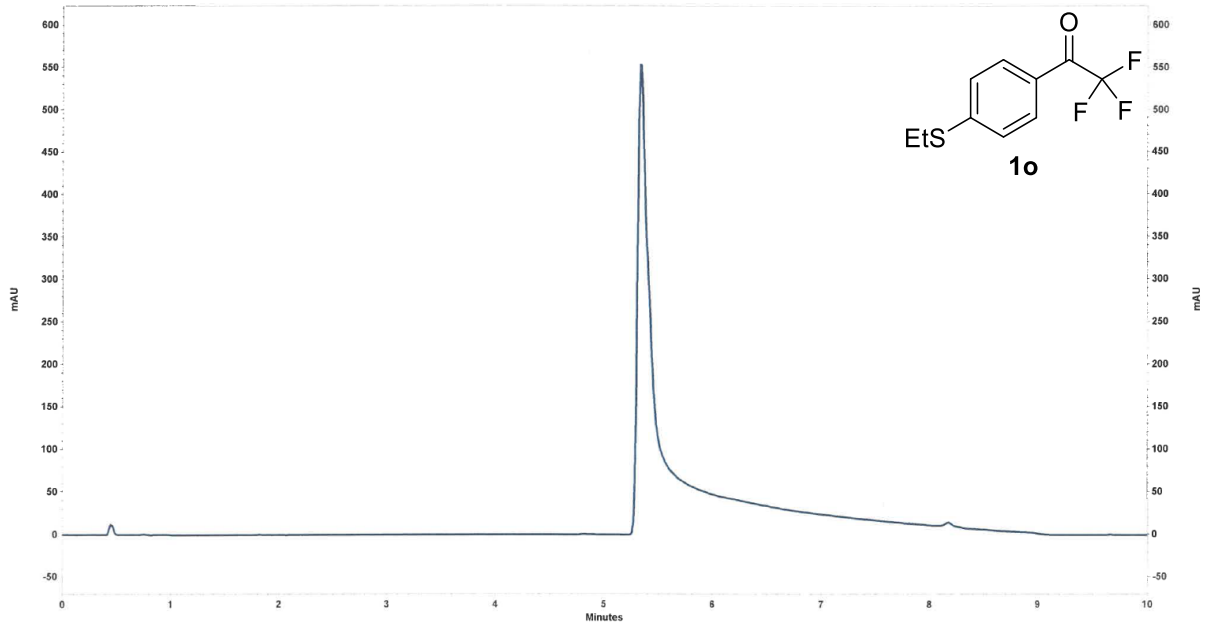
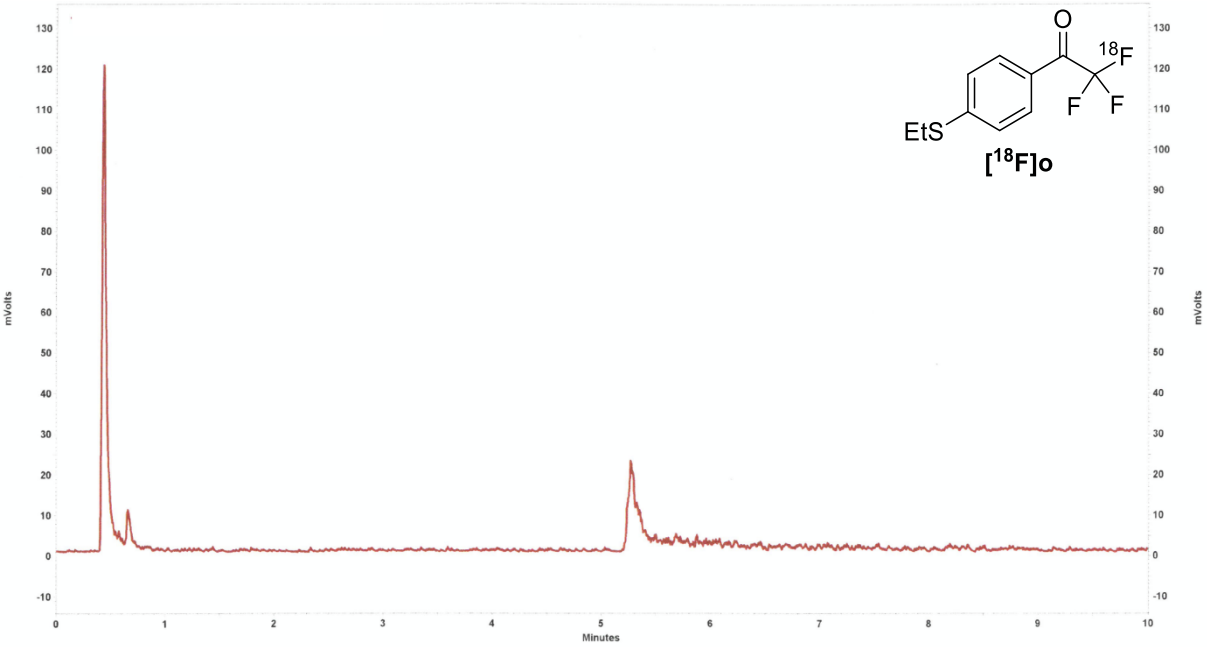
Minutes
1m

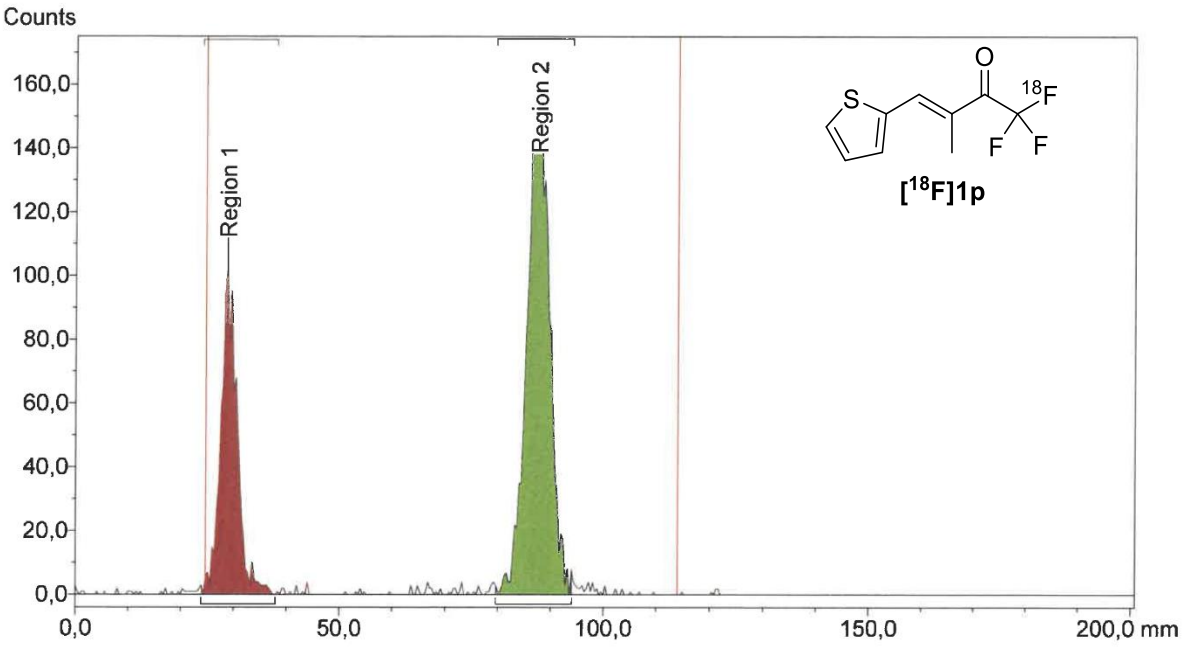

mVolts
Minutes
[18F]1m


mAU
Minutes
1n


mVolts
Minutes
[18F]1n


mAU
Minutes
EtS
O
F
F
F
1o


mVolts
Minutes
EtS
O
18F
F
F
[18F]o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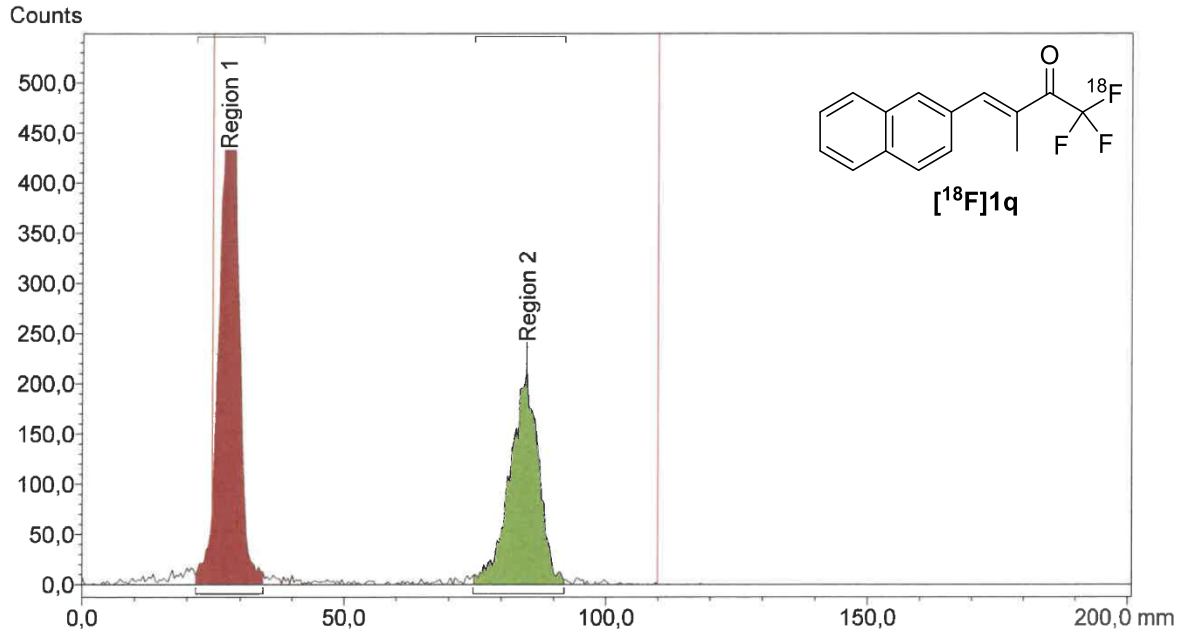
160,0
140,0
120,0
100,0
80,0
60,0
40,0
20,0
0,0
Region 1
Region 2
0,0
50,0
100,0
150,0
200,0 mm
O
S
18F
F
F
[18F]1p


Counts
500,0
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250,0
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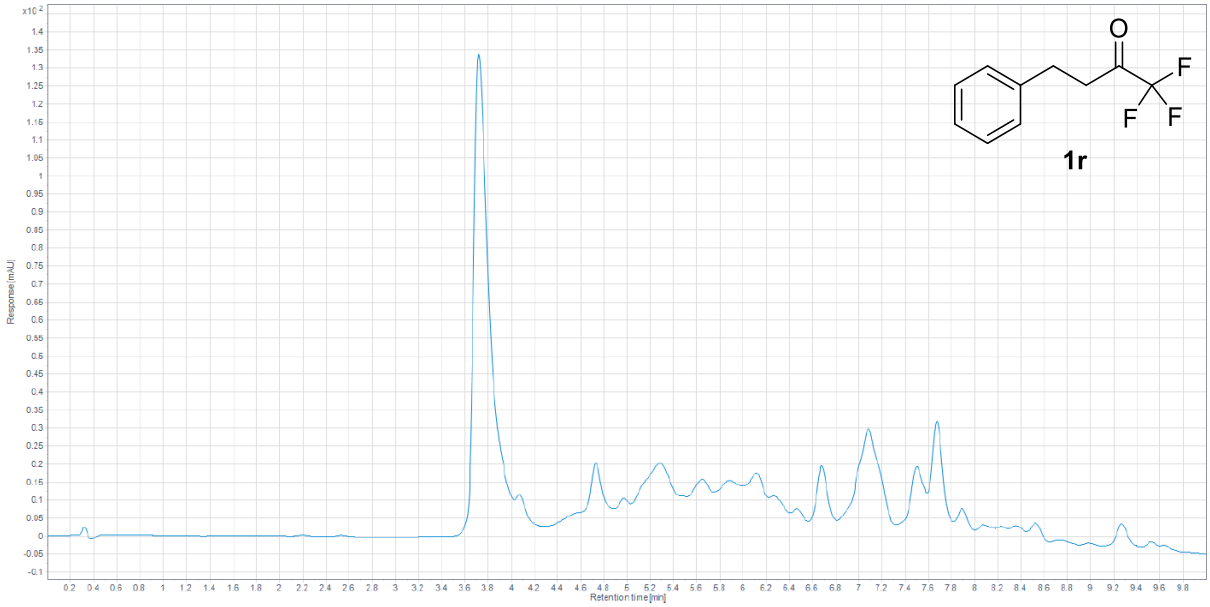
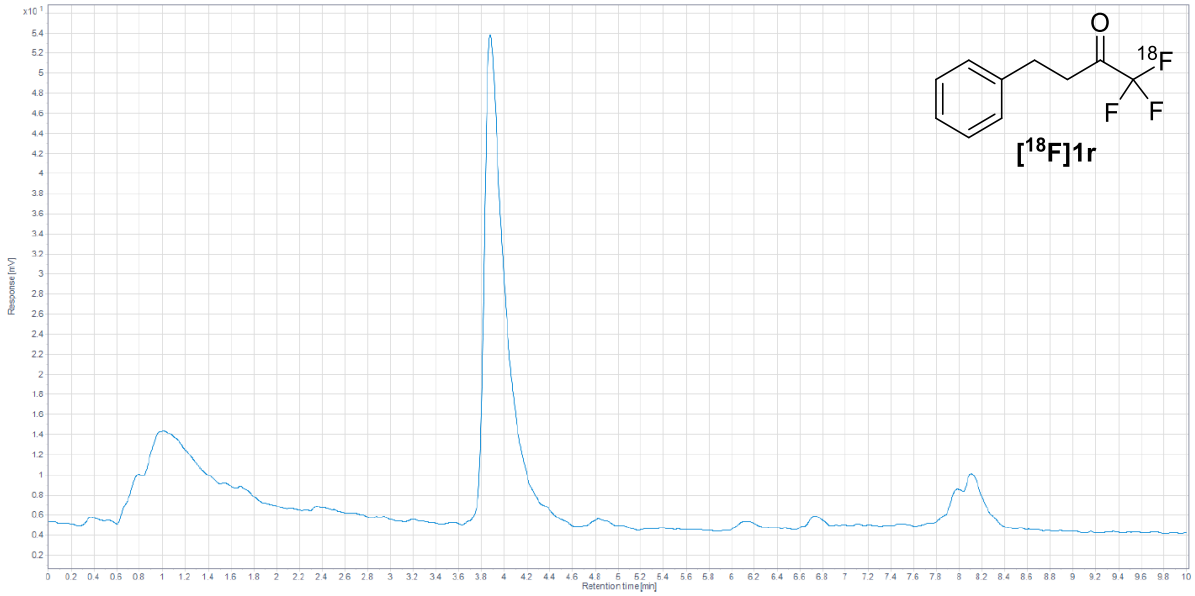
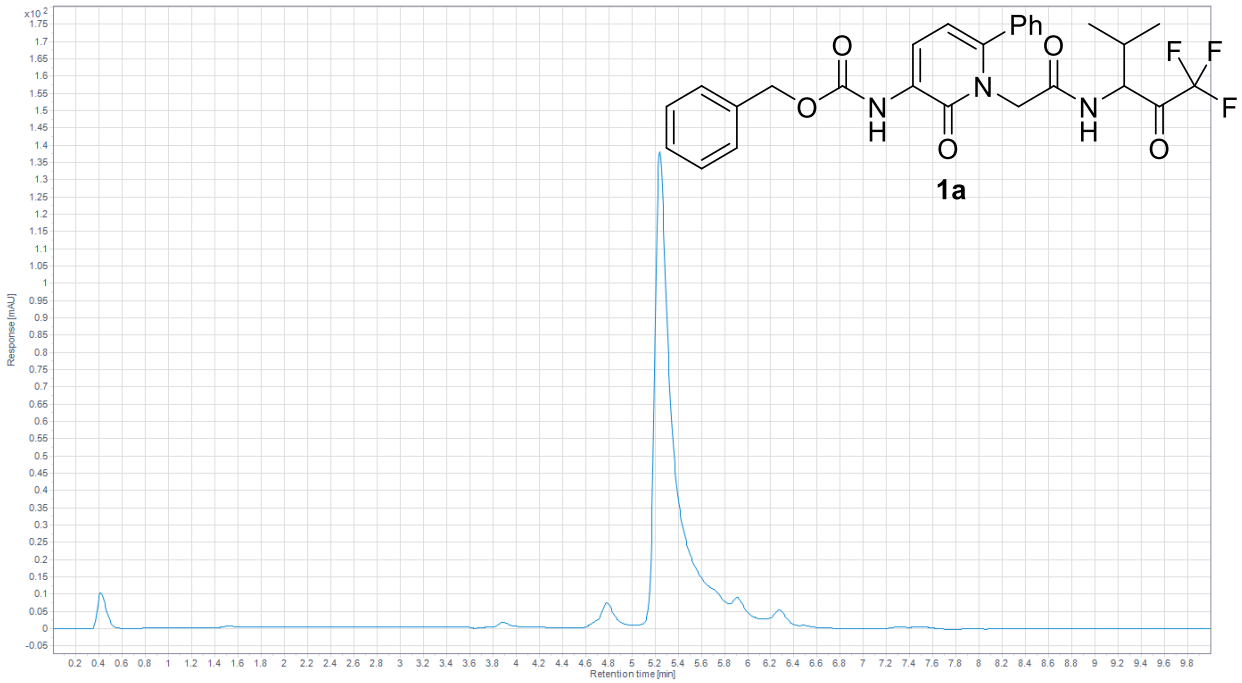
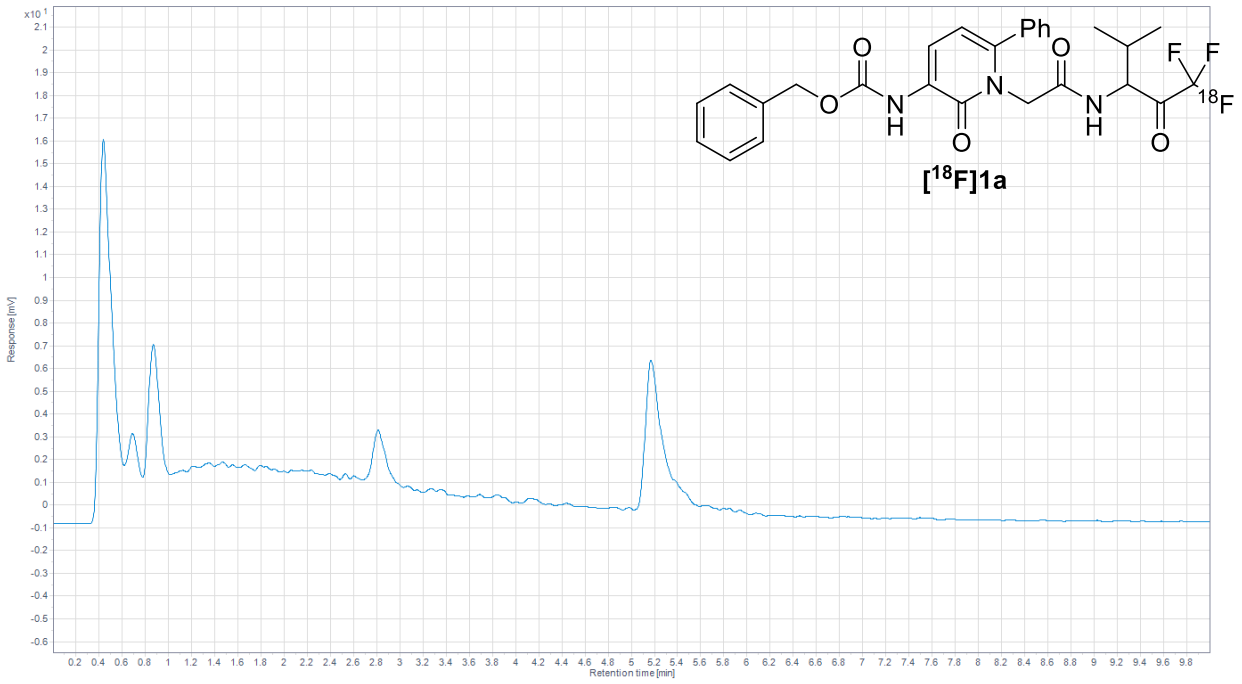
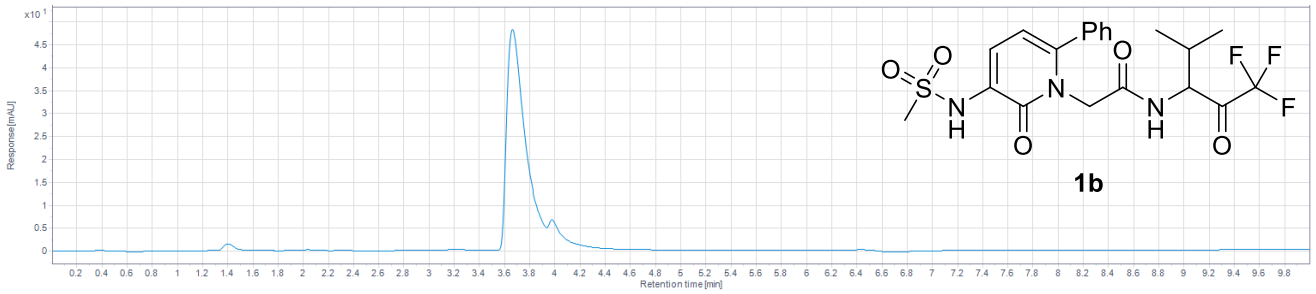
100,0
50,0
0,0
Region 1
Region 2
0,0
50,0
100,0
150,0
200,0 mm
O
18F
F
F
[18F]1q

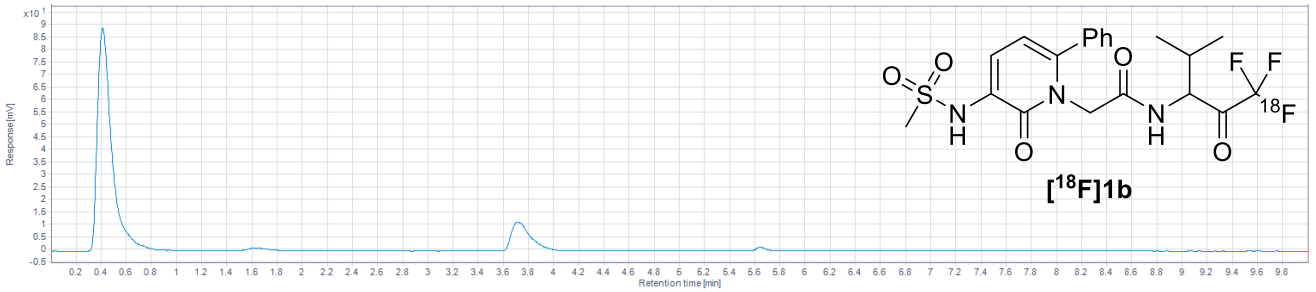

x10 2
Response [mAU]
Retention time [min]
O
F
F
F
1r


x10 1
Response [mV]
Retention time [min]
O
18F
F
F
[18F]1r


x10 2
Response [mAU]
Retention time [min]
Ph
O
N
H
F
F
F
1a

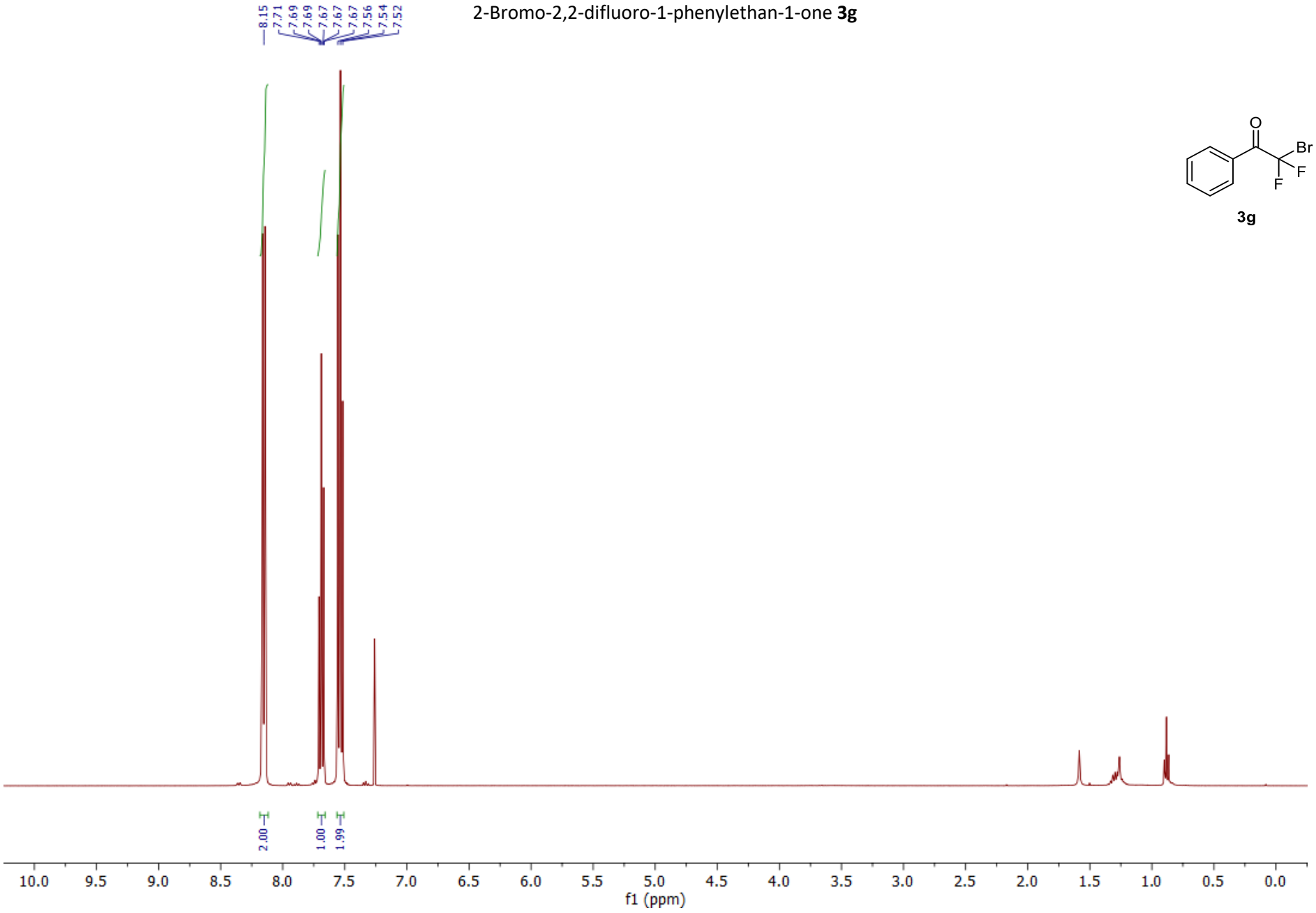

x10 1
Response [mV]
Retention time [min]
Ph
O
N
H
F
F
18F
[18F]1a


x10 1
Response [mAU]
Retention time [min]
Ph
O
O
S
N
H
N
O
O
N
H
F
F
F
O
1b


x10 1
Response [mV]
Retention time [min]
Ph
O
O
S
N
H
N
O
O
N
H
F
F
18F
O
[18F]1b

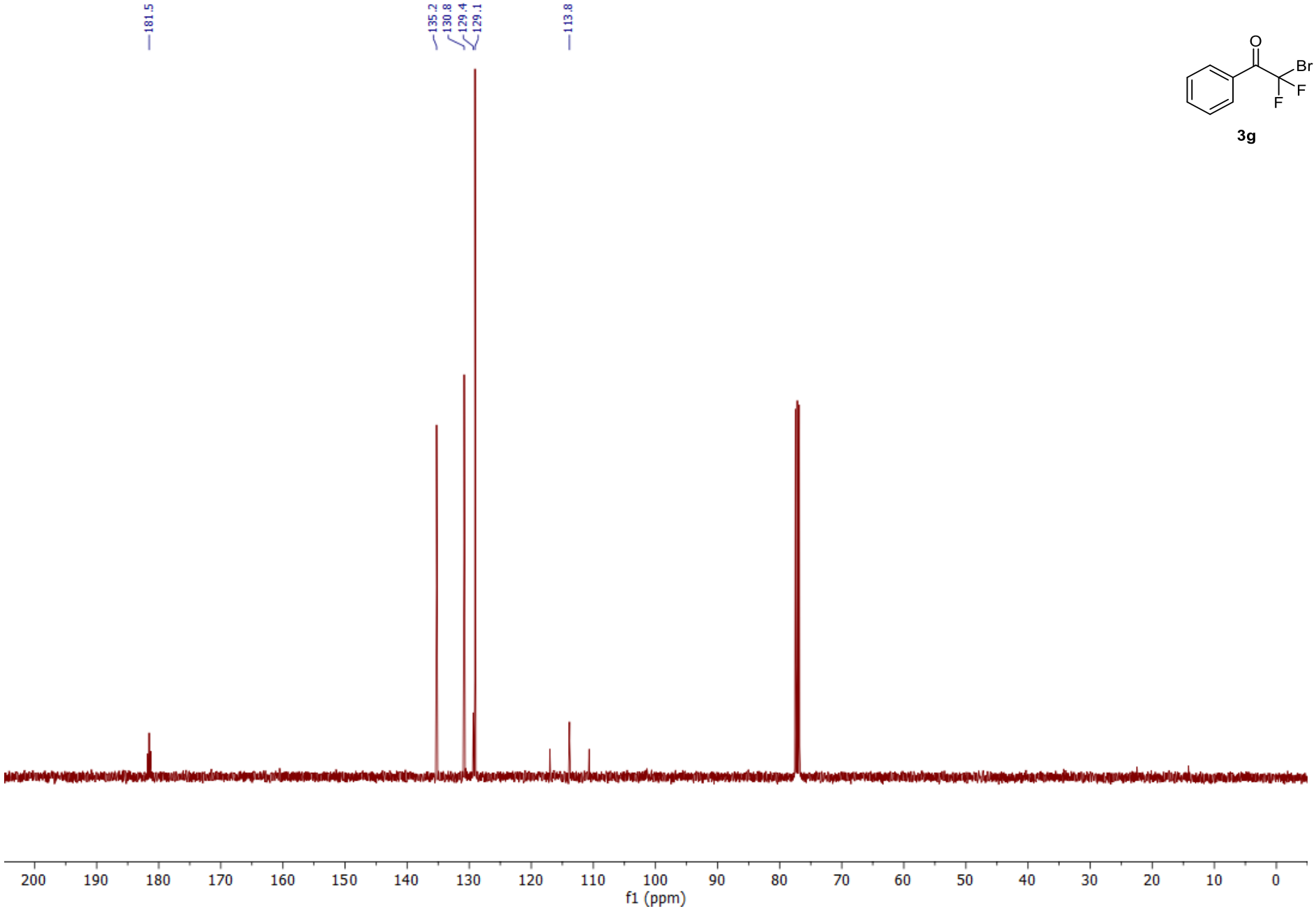
7. ^{1}H-, ^{13}C- and ^{19}F-NMR of compounds

2-Bromo-2,2-difluoro-1-phenylethan-1-one **3g**

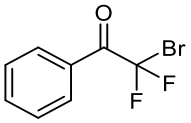


3g

2-Bromo-2,2-difluoro-1-phenylethan-1-one **3g**

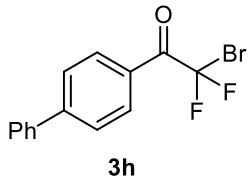


2-Bromo-2,2-difluoro-1-phenylethan-1-one **3g**



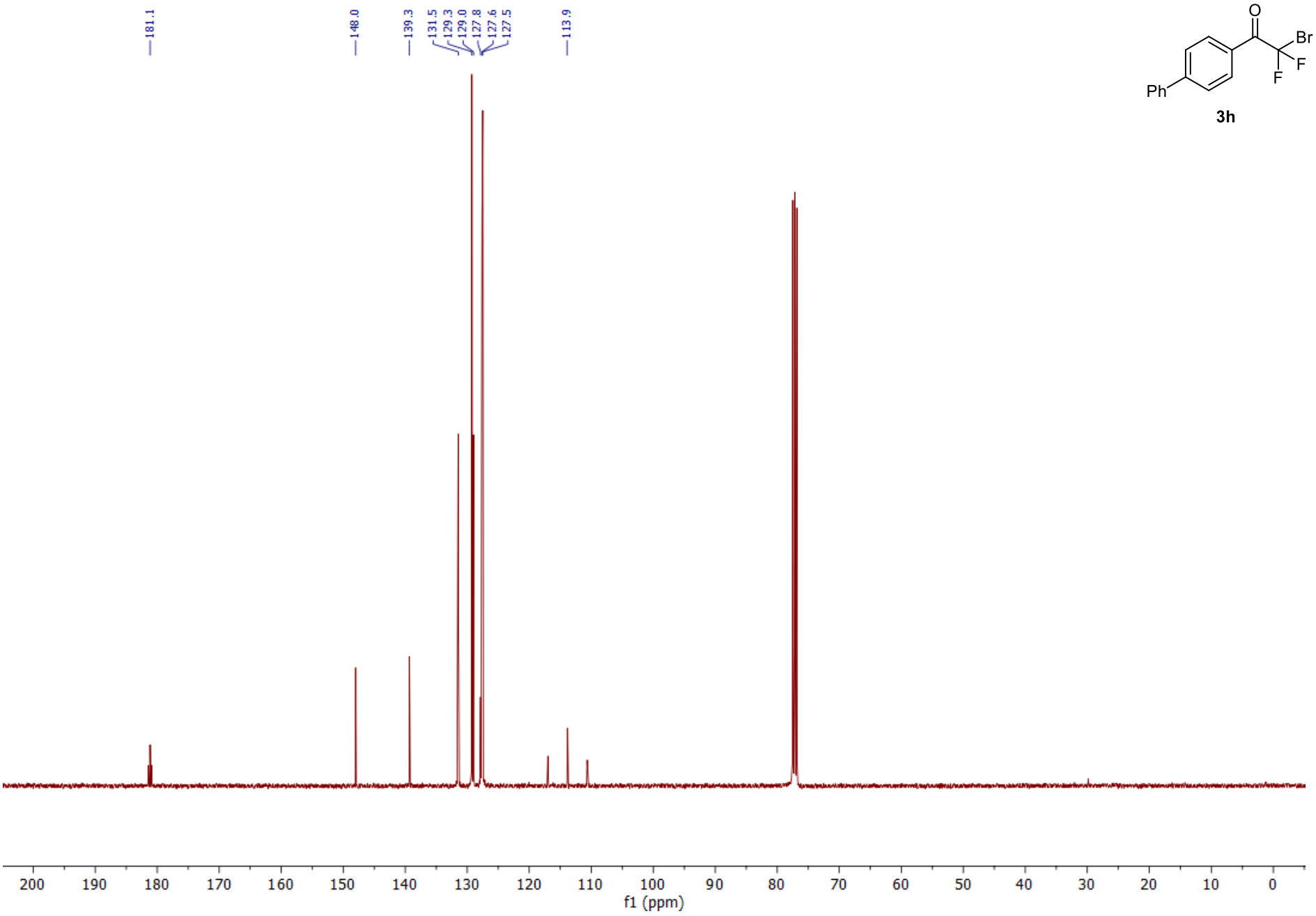
3g

1-([1,1'-Biphenyl]-4-yl)-2-bromo-2,2-difluoroethan-1-one **3h**

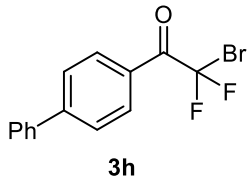


3h

1-([1,1'-Biphenyl]-4-yl)-2-bromo-2,2-difluoroethan-1-one **3h**

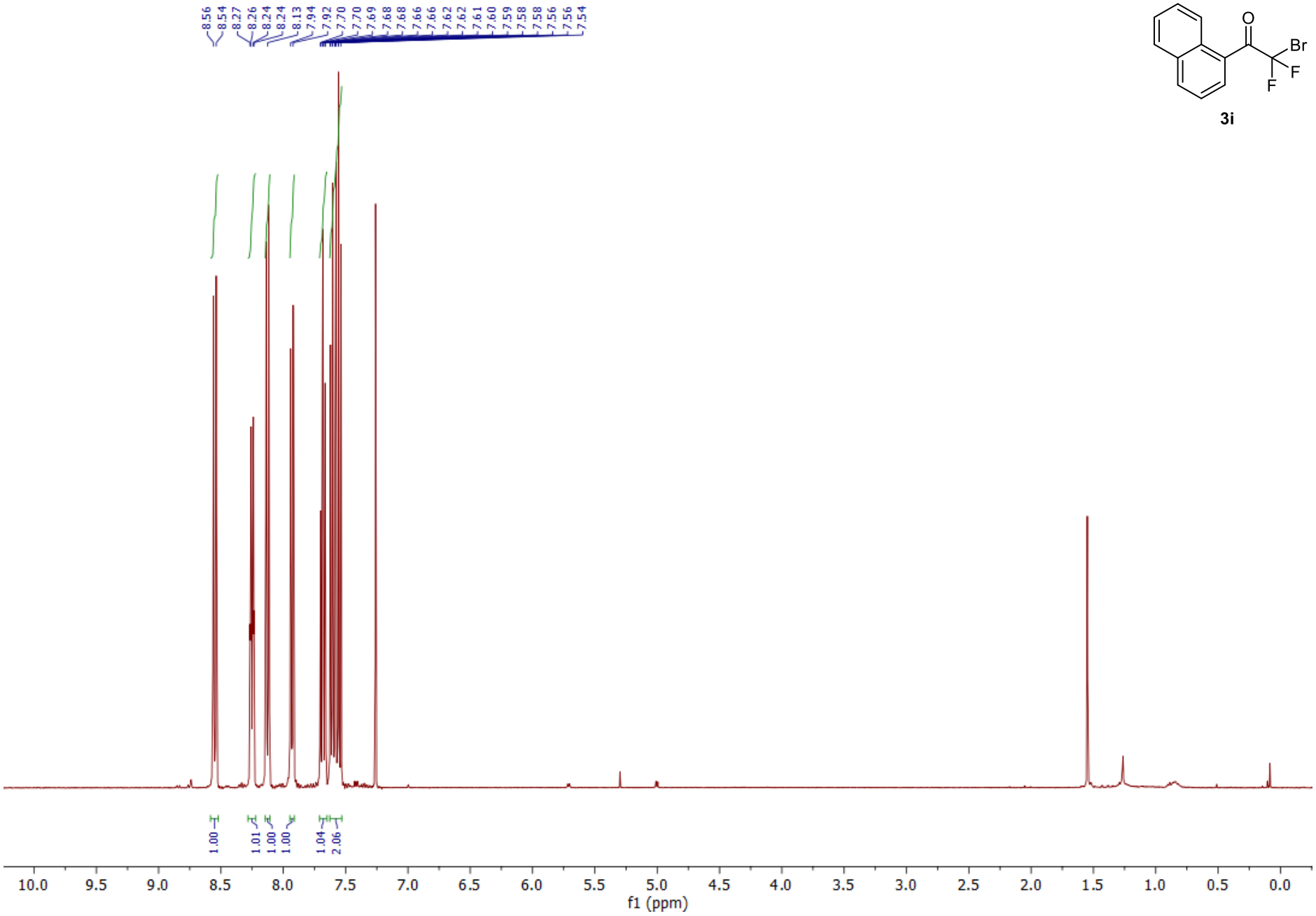


1-([1,1'-Biphenyl]-4-yl)-2-bromo-2,2-difluoroethan-1-one **3h**



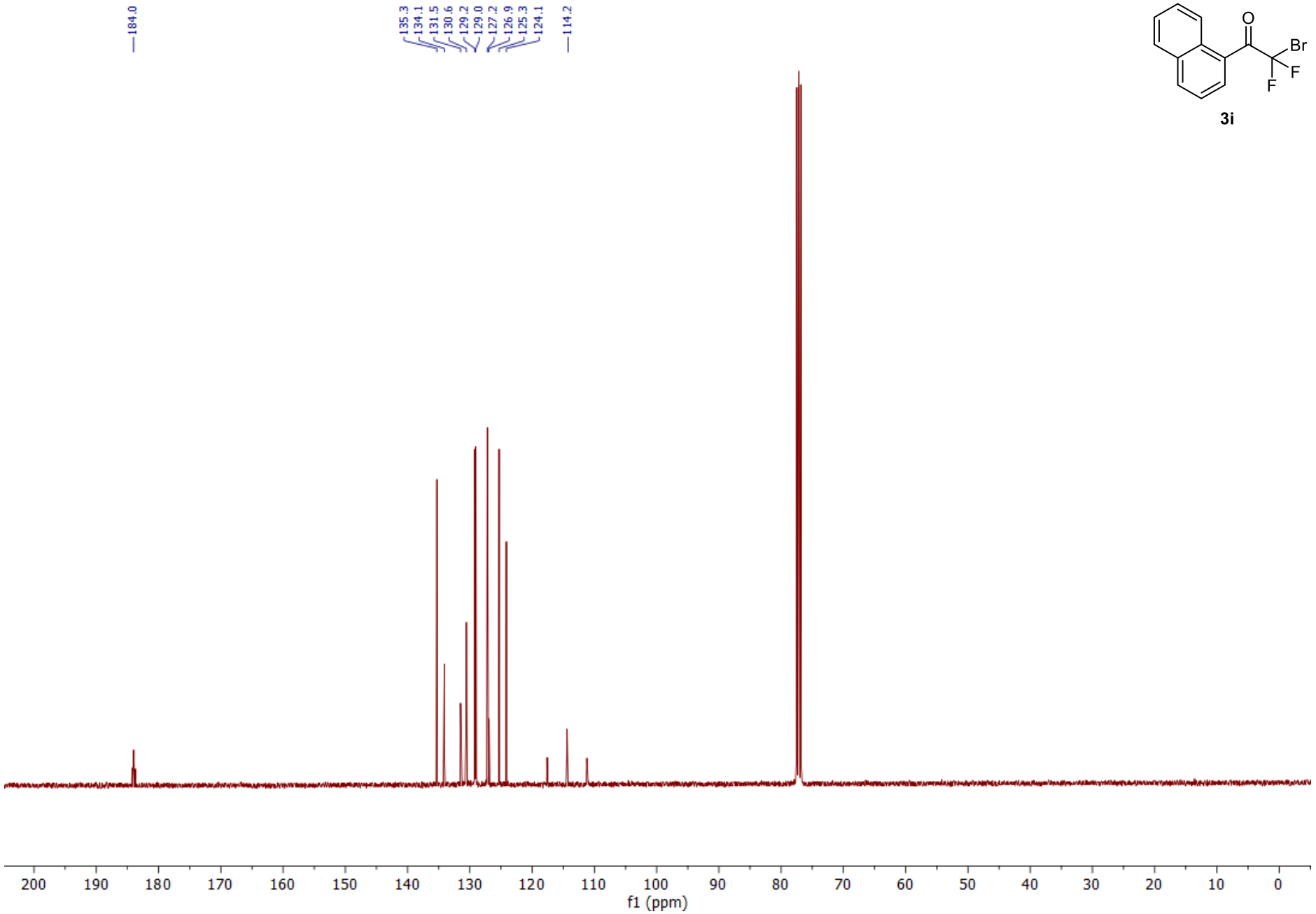
3h

2-Bromo-2,2-difluoro-1-(naphthalen-1-yl)ethan-1-one **3i**

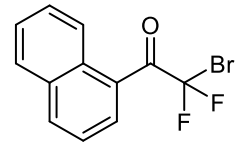


3i

2-Bromo-2,2-difluoro-1-(naphthalen-1-yl)ethan-1-one **3i**

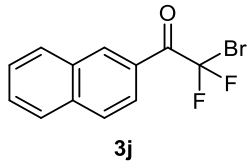


2-Bromo-2,2-difluoro-1-(naphthalen-1-yl)ethan-1-one **3i**



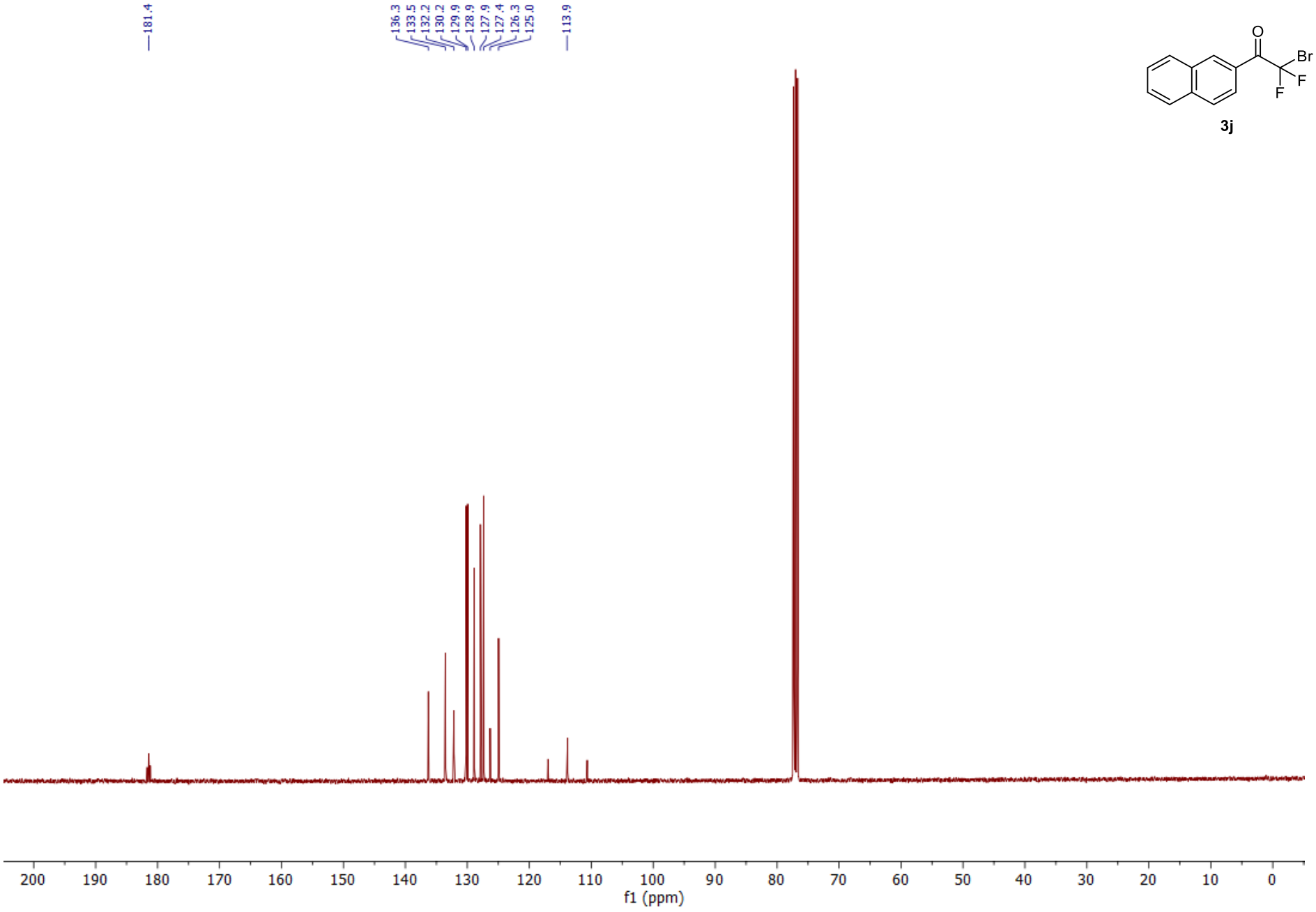
3i

2-Bromo-2,2-difluoro-1-(naphthalen-2-yl)ethan-1-one **3j**

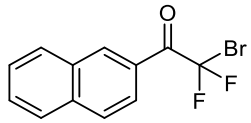


3j

2-Bromo-2,2-difluoro-1-(naphthalen-2-yl)ethan-1-one **3j**

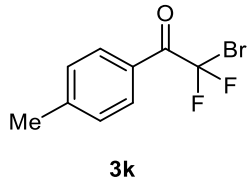


2-Bromo-2,2-difluoro-1-(naphthalen-2-yl)ethan-1-one **3j**



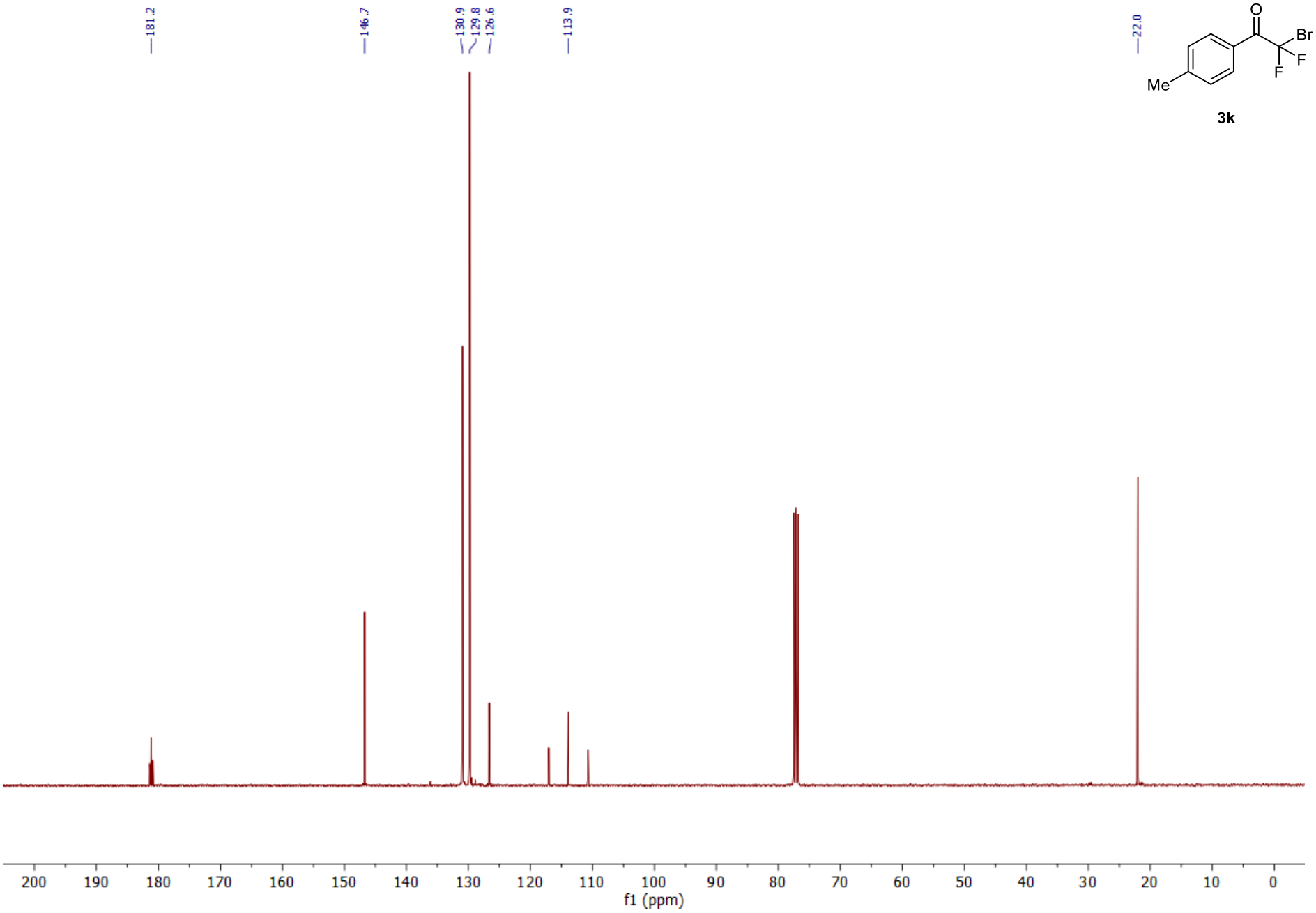
3j

2-Bromo-2,2-difluoro-1-(p-tolyl)ethan-1-one **3k**

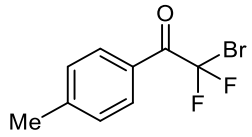


3k

2-Bromo-2,2-difluoro-1-(p-tolyl)ethan-1-one **3k**

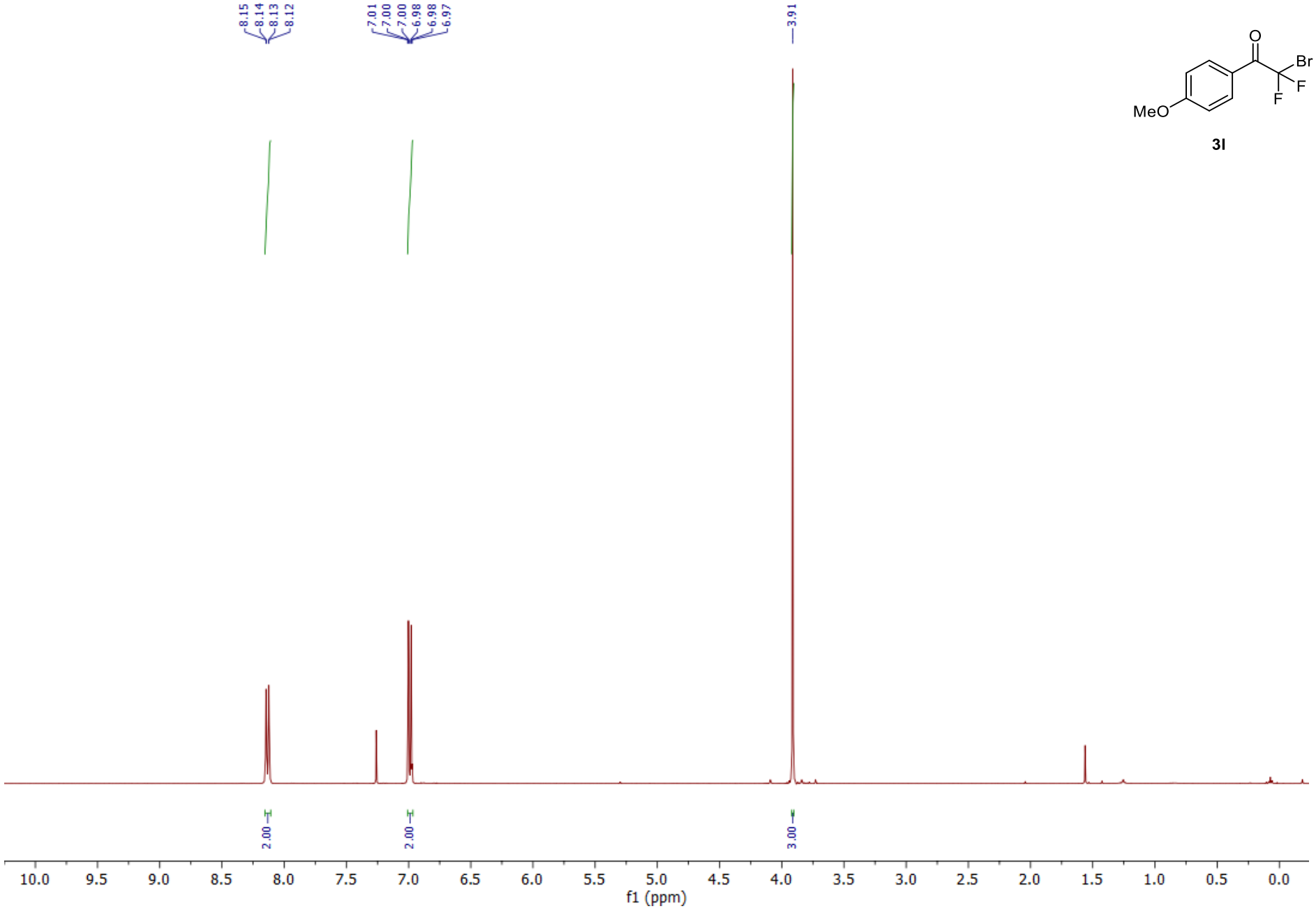


2-Bromo-2,2-difluoro-1-(p-tolyl)ethan-1-one **3k**



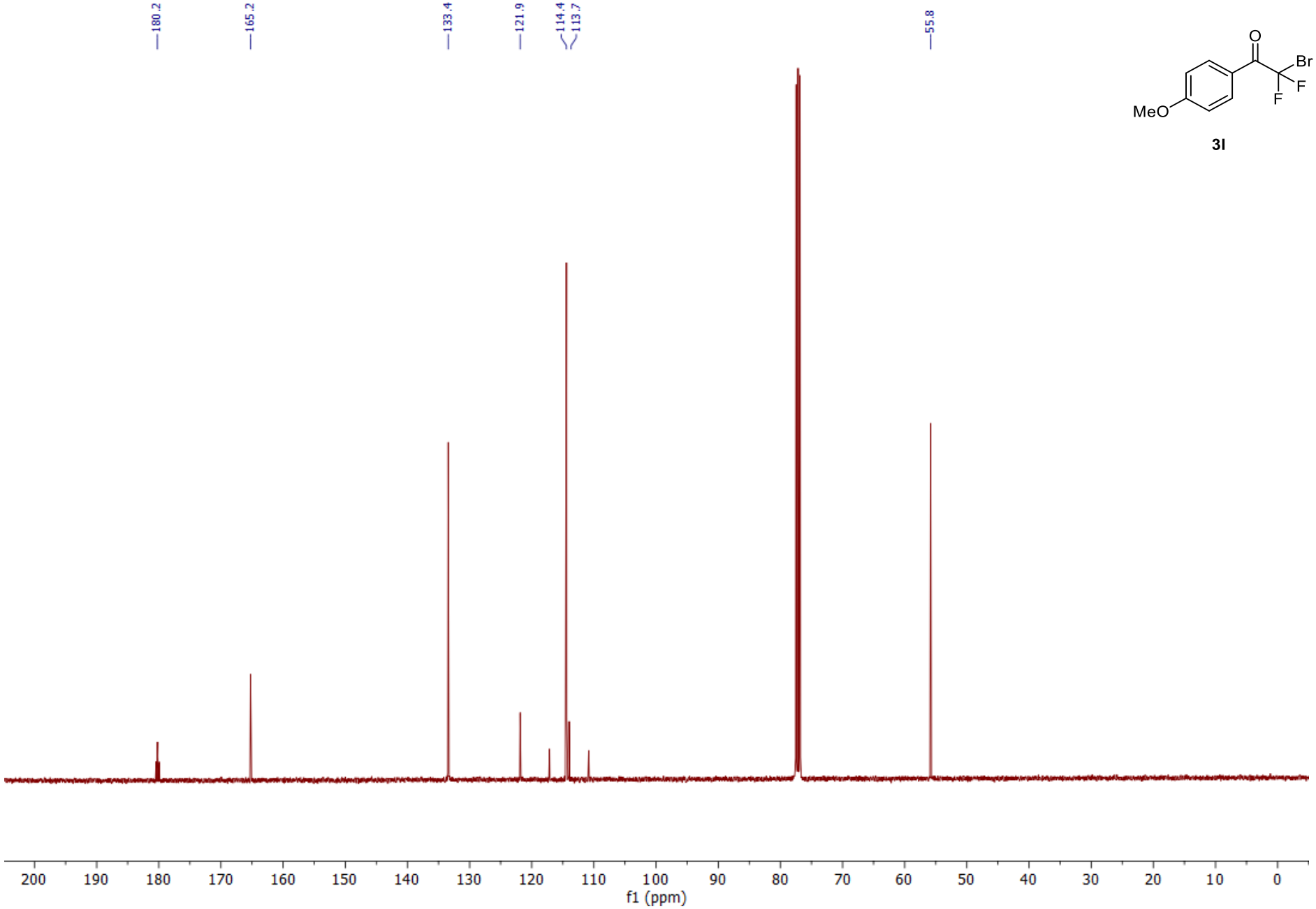
3k

2-Bromo-2,2-difluoro-1-(4-methoxyphenyl)ethan-1-one **3l**



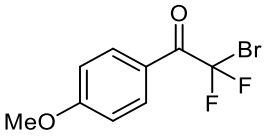
3l

2-Bromo-2,2-difluoro-1-(4-methoxyphenyl)ethan-1-one **3l**



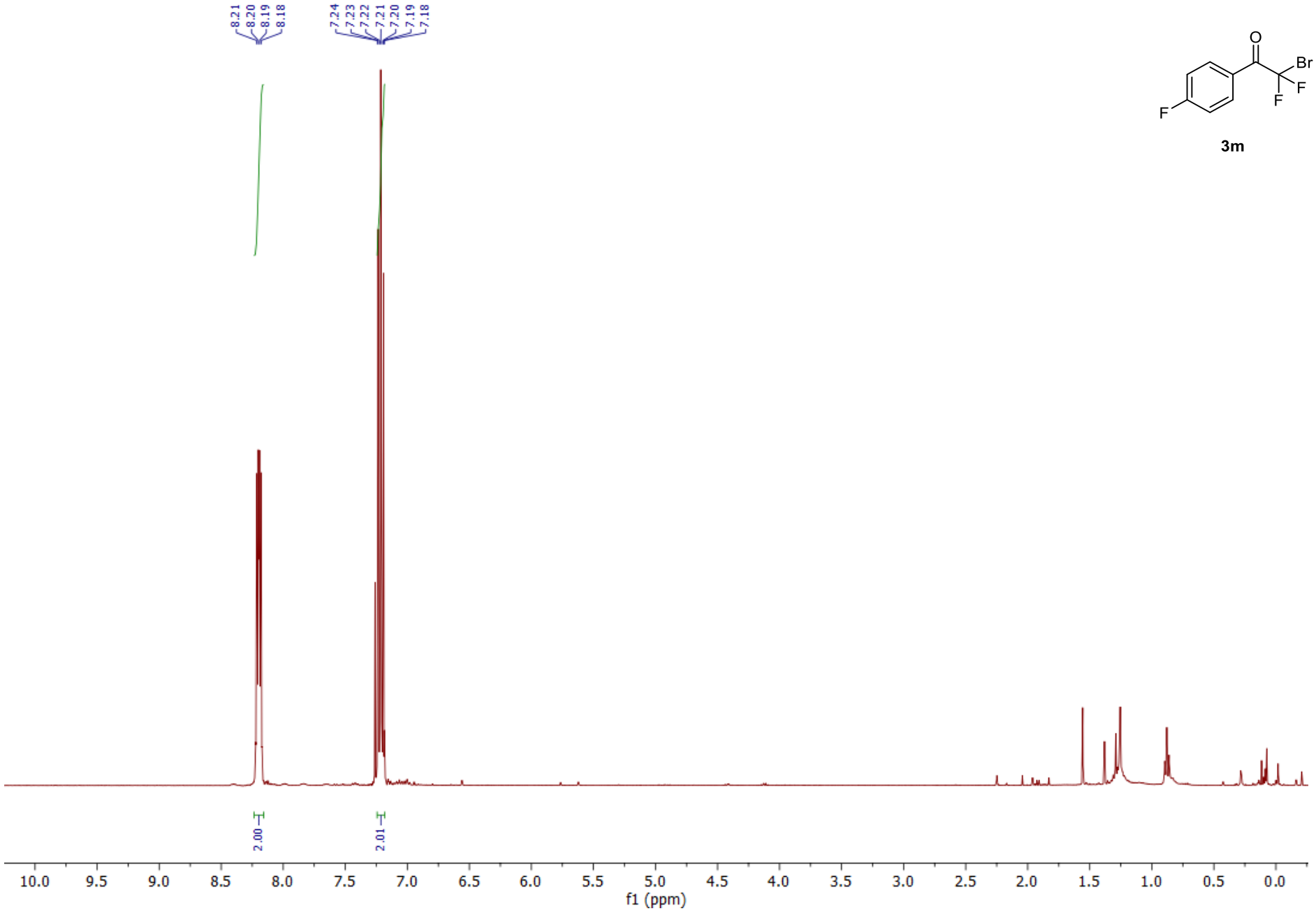
3l

2-Bromo-2,2-difluoro-1-(4-methoxyphenyl)ethan-1-one **3l**



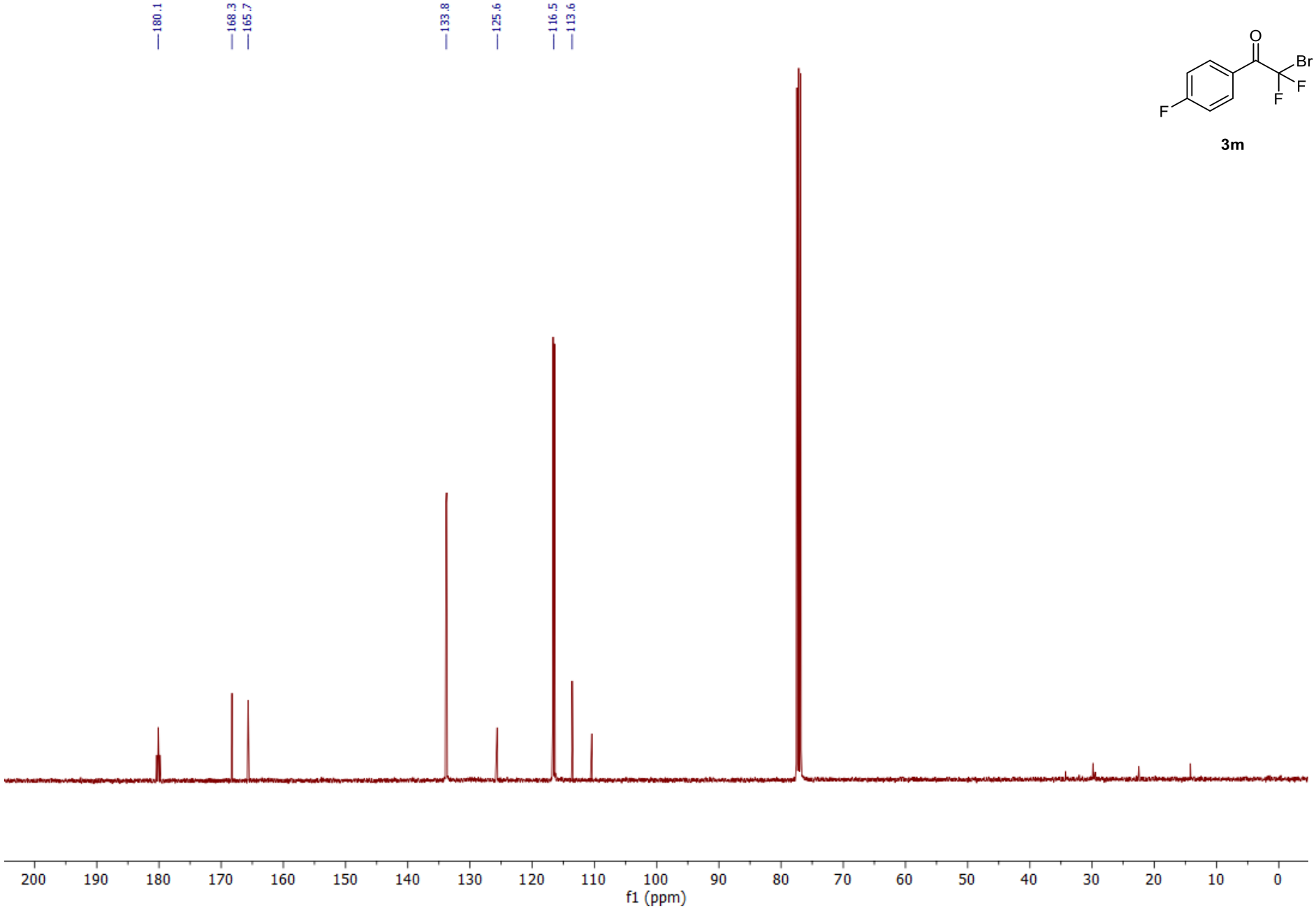
3l

2-Bromo-2,2-difluoro-1-(4-fluorophenyl)ethan-1-one **3m**

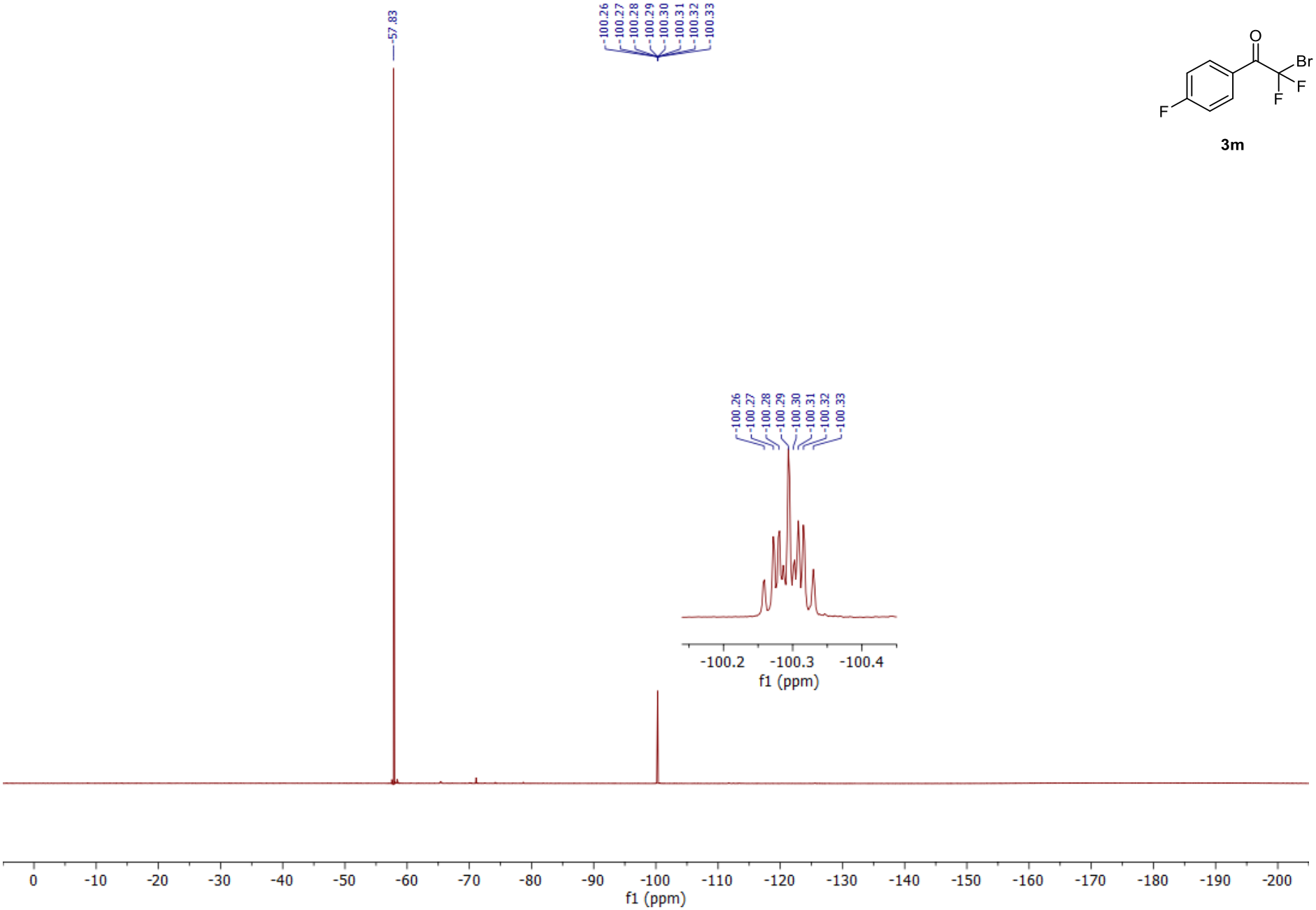


3m

2-Bromo-2,2-difluoro-1-(4-fluorophenyl)ethan-1-one **3m**

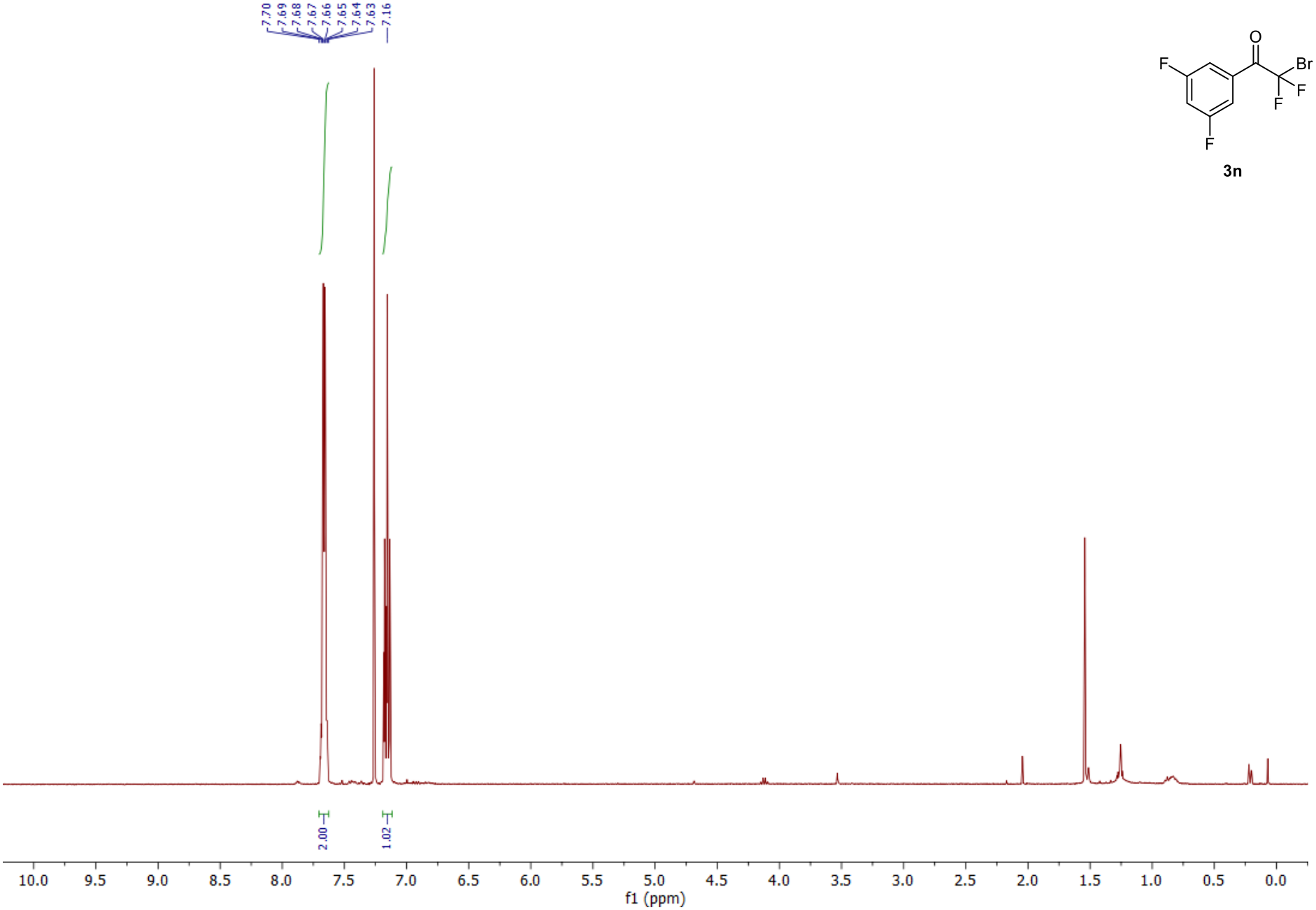


2-Bromo-2,2-difluoro-1-(4-fluorophenyl)ethan-1-one **3m**



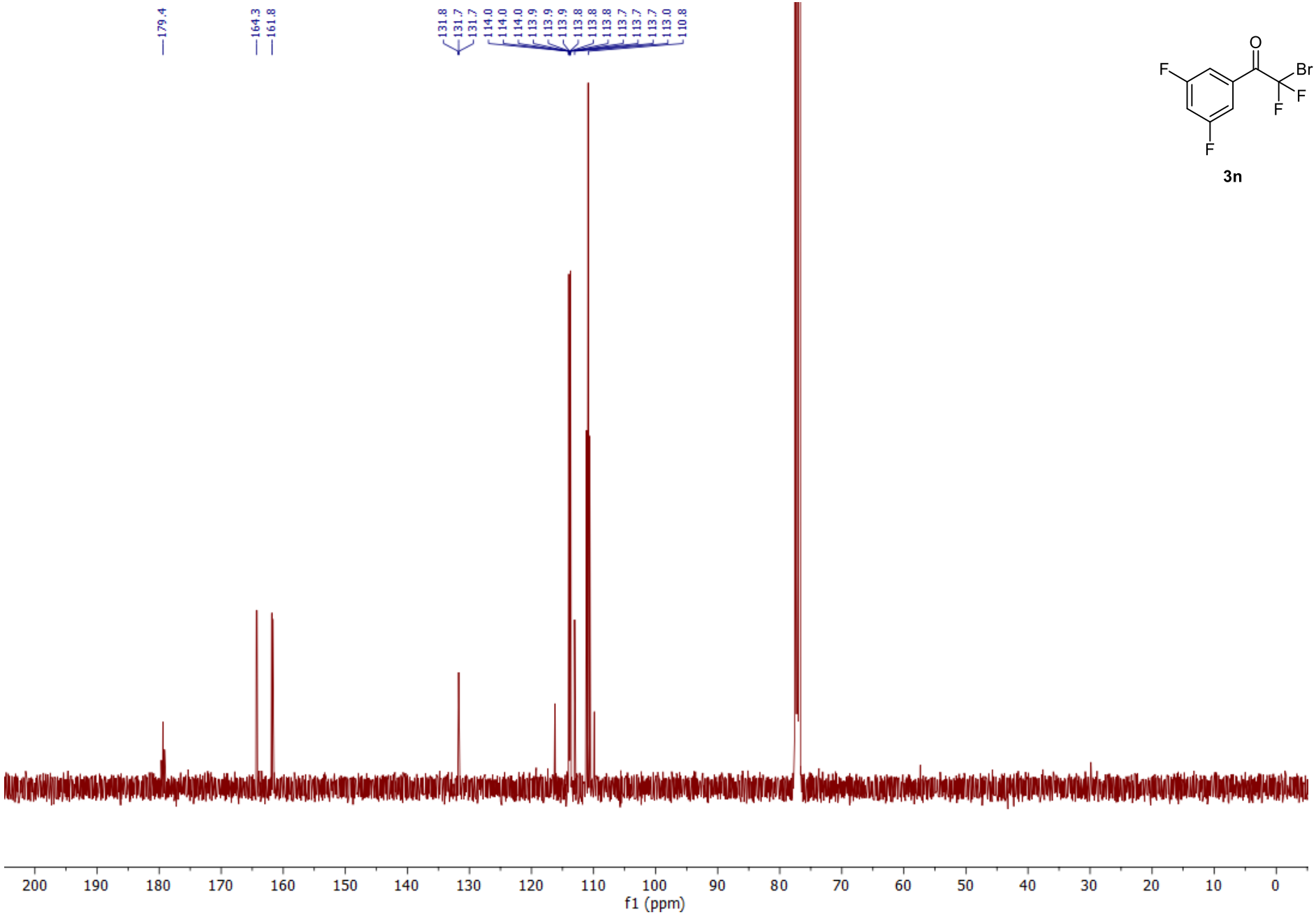
3m

2-Bromo-1-(3,5-difluorophenyl)-2,2-difluoroethan-1-one **3n**



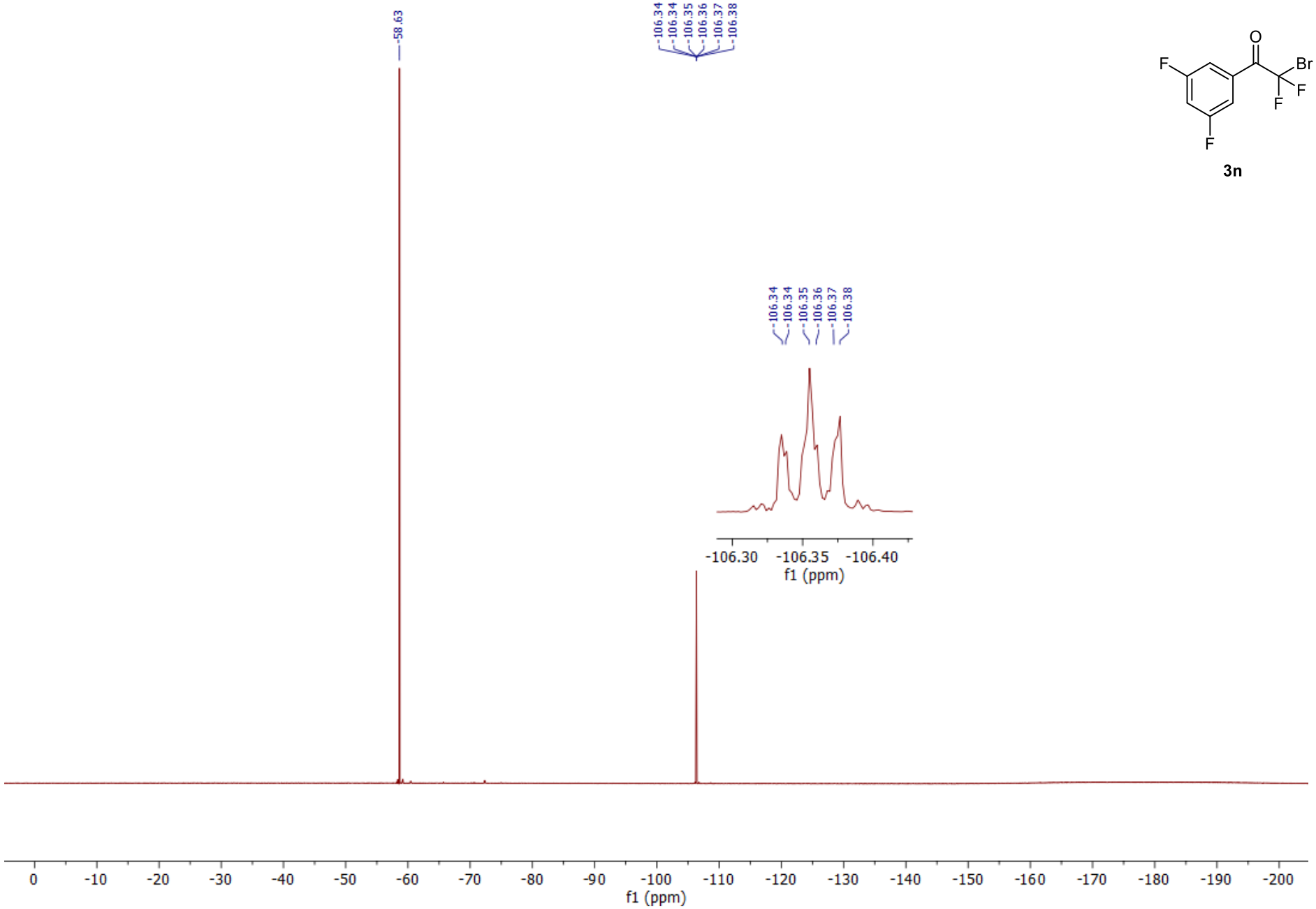
3n

2-Bromo-1-(3,5-difluorophenyl)-2,2-difluoroethan-1-one **3n**



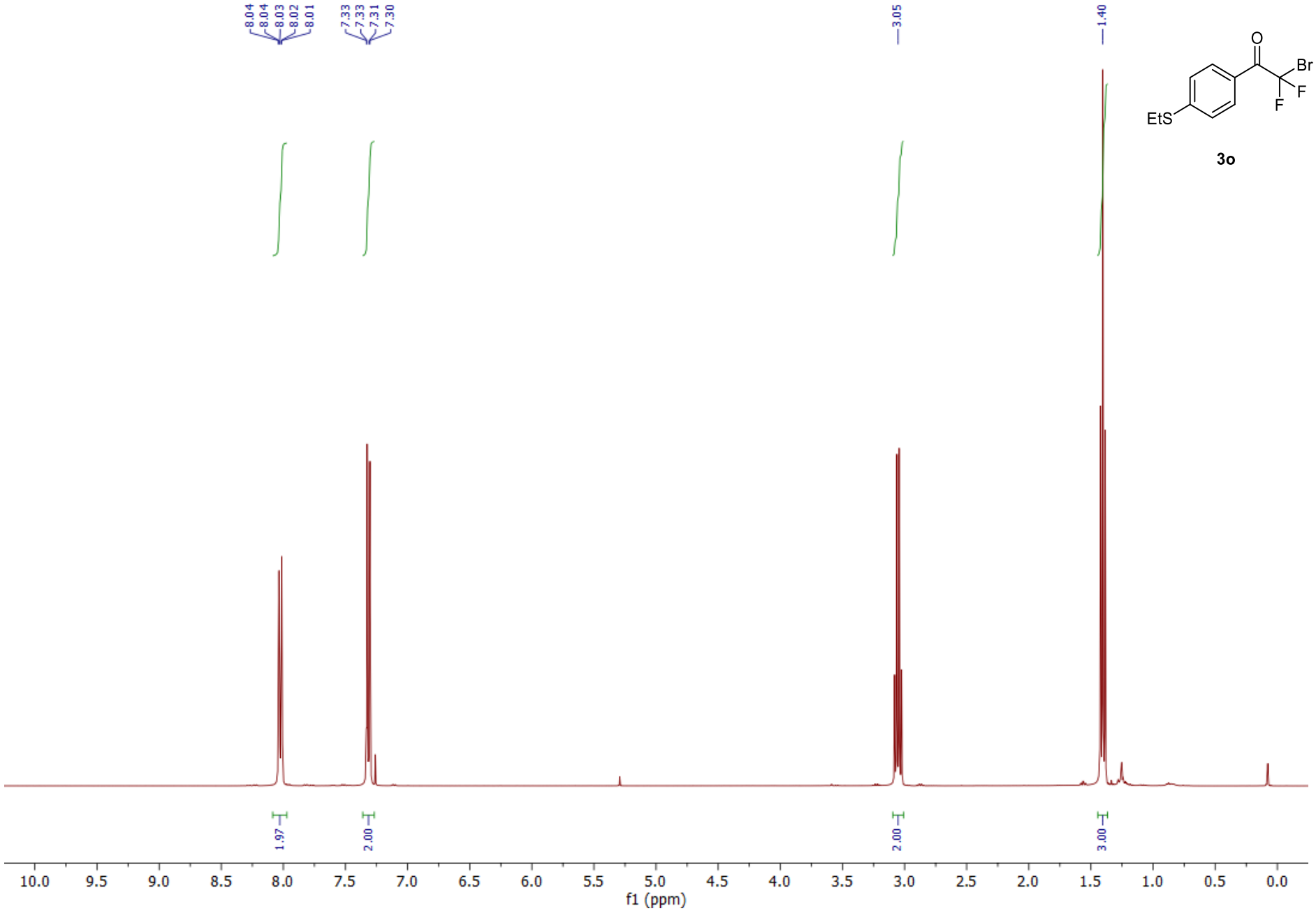
3n

2-Bromo-1-(3,5-difluorophenyl)-2,2-difluoroethan-1-one **3n**

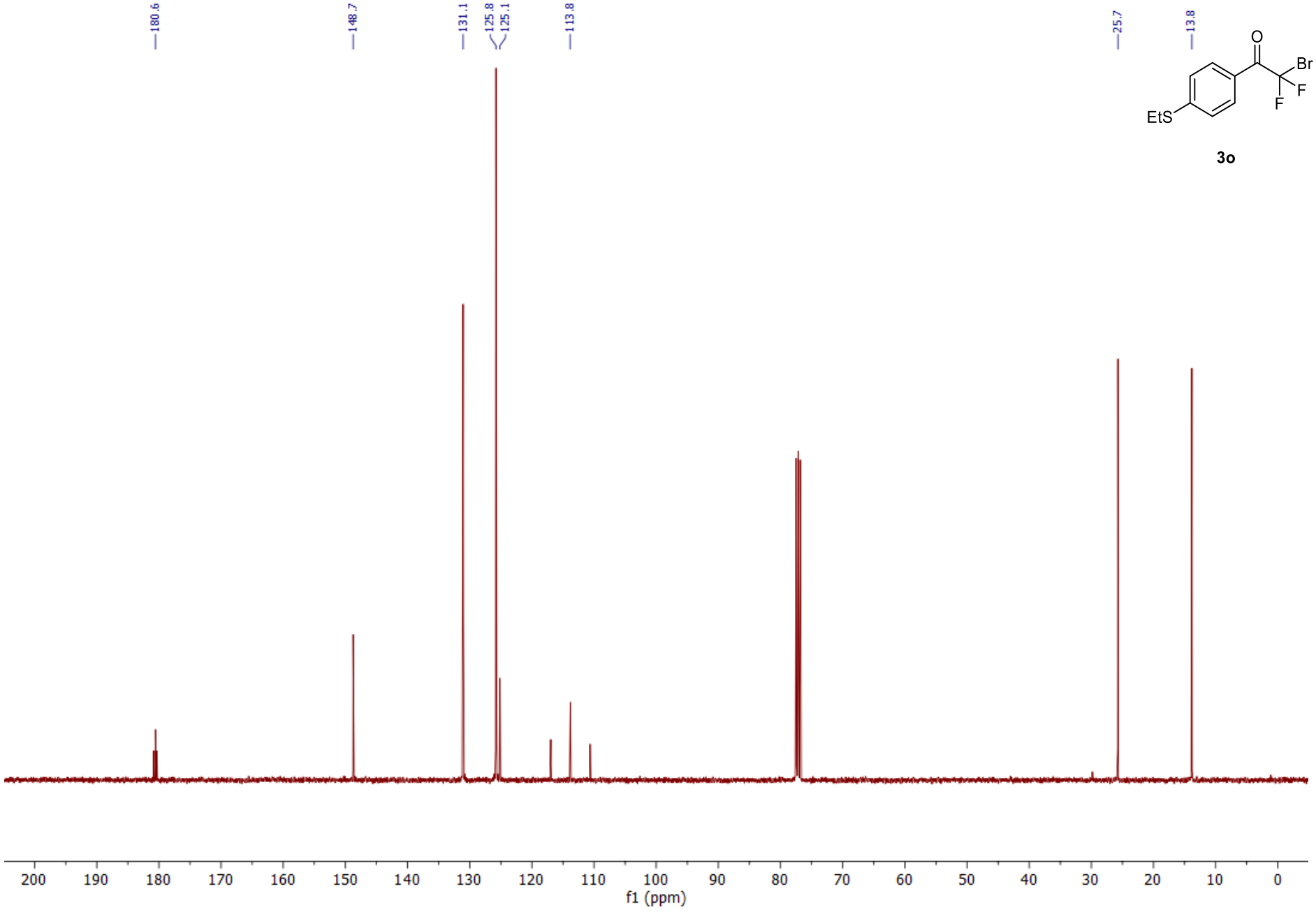


3n

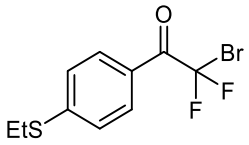
2-Bromo-1-(4-(ethylthio)phenyl)-2,2-difluoroethan-1-one **3o**



2-Bromo-1-(4-(ethylthio)phenyl)-2,2-difluoroethan-1-one **3o**

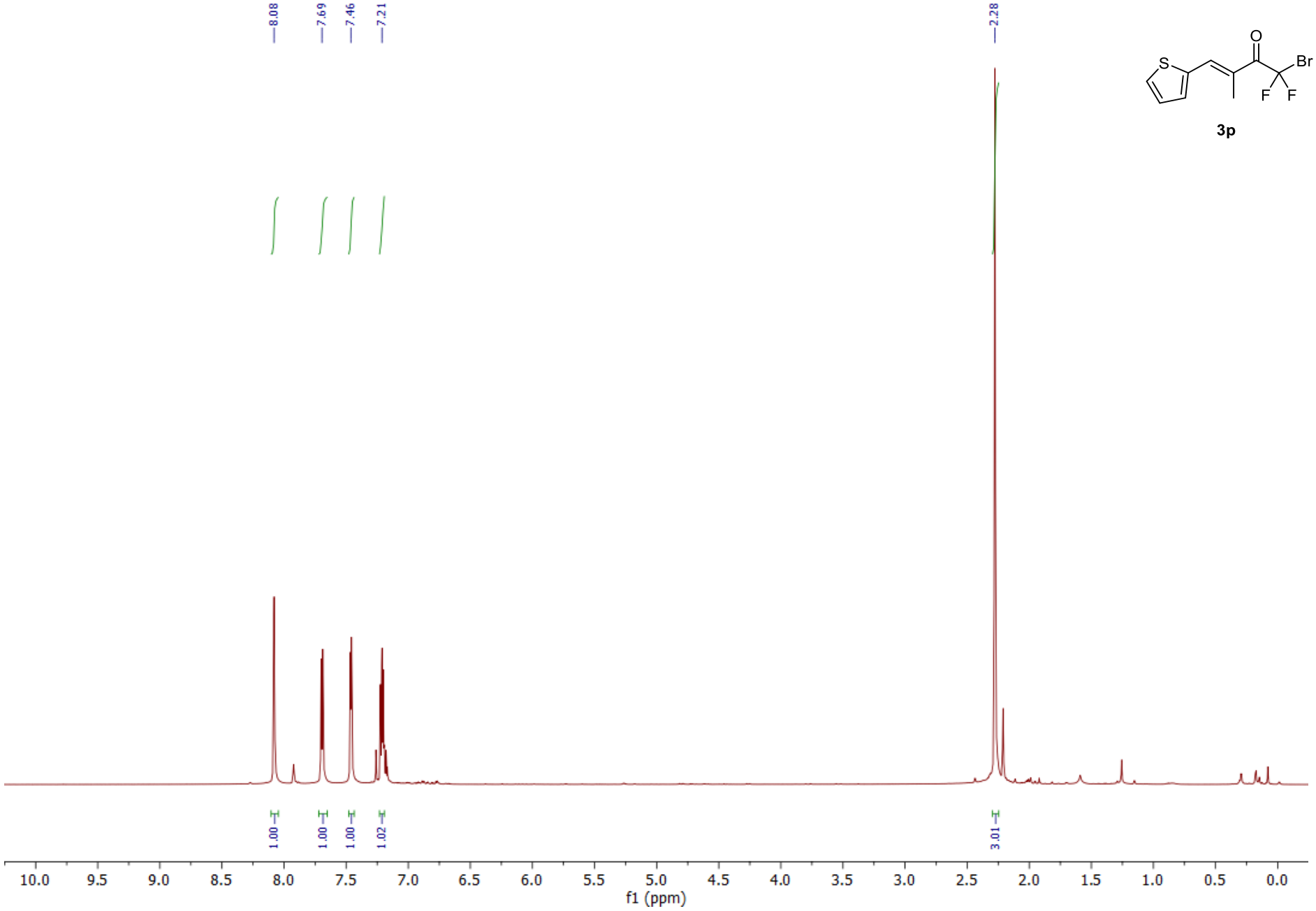


2-Bromo-1-(4-(ethylthio)phenyl)-2,2-difluoroethan-1-one **3o**



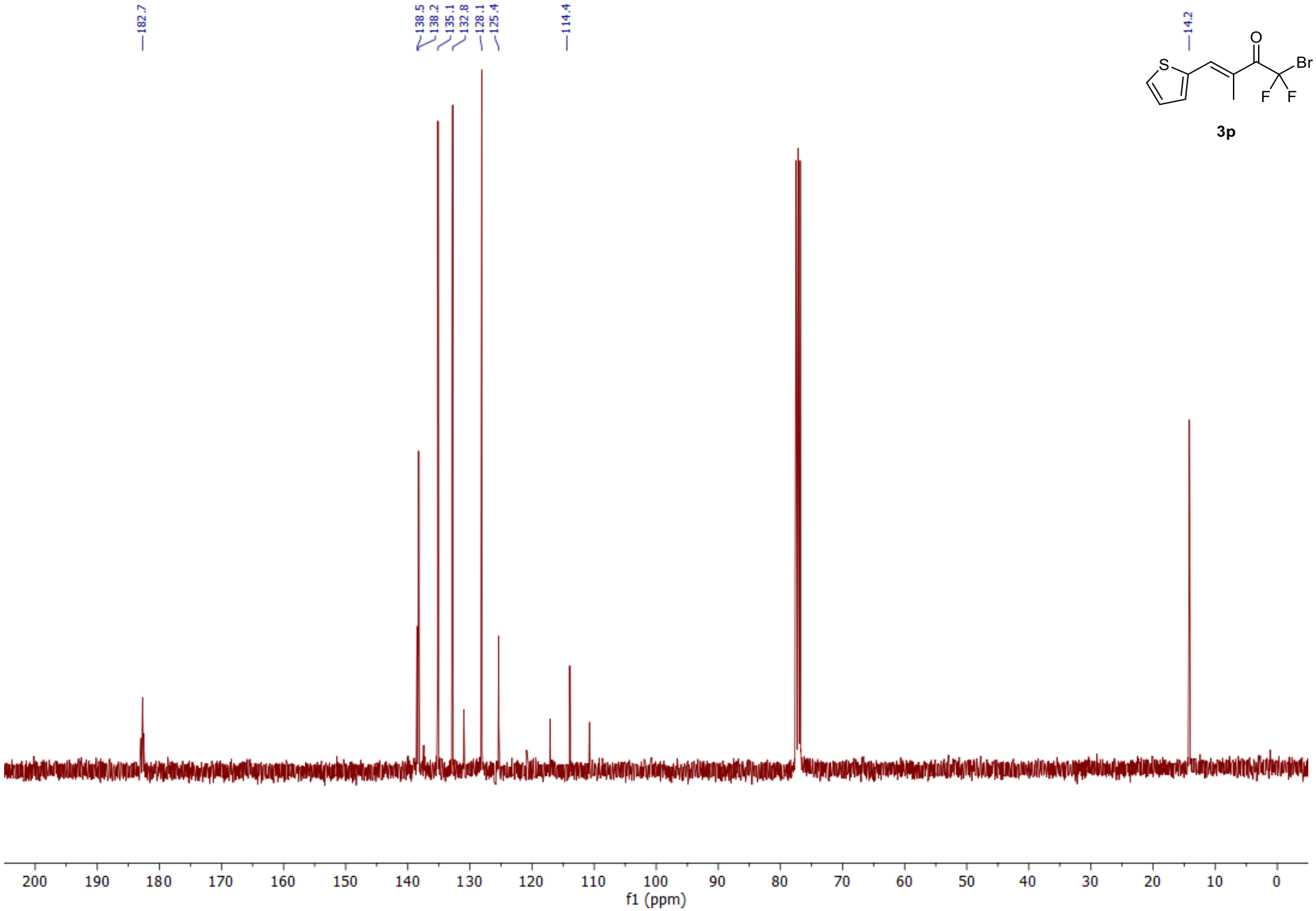
3o

(*E*)-1-Bromo-1,1-difluoro-3-methyl-4-(thiophen-2-yl)but-3-en-2-one **3p**

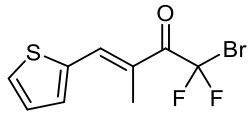


3p

(*E*)-1-Bromo-1,1-difluoro-3-methyl-4-(thiophen-2-yl)but-3-en-2-one **3p**

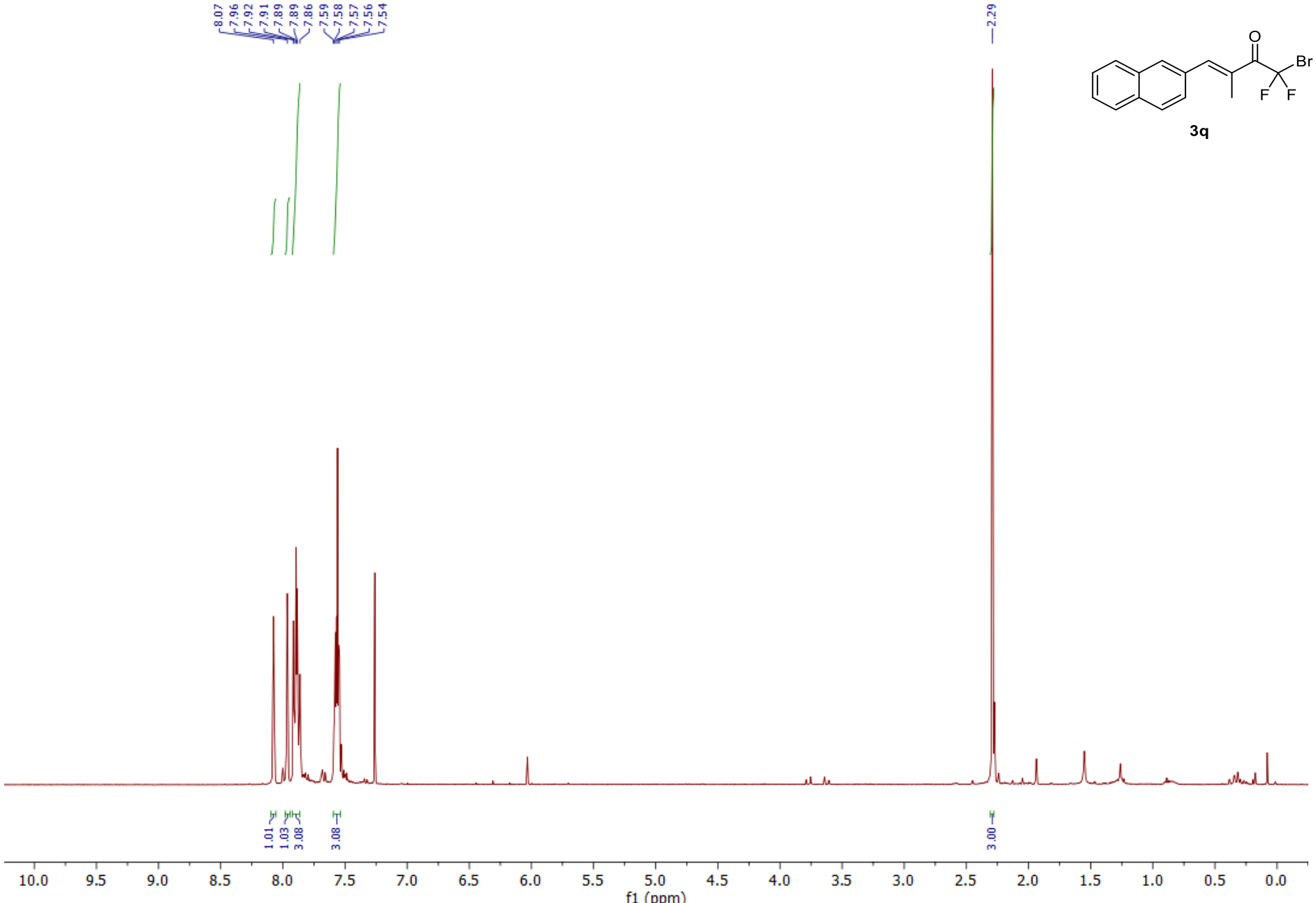


(*E*)-1-Bromo-1,1-difluoro-3-methyl-4-(thiophen-2-yl)but-3-en-2-one **3p**

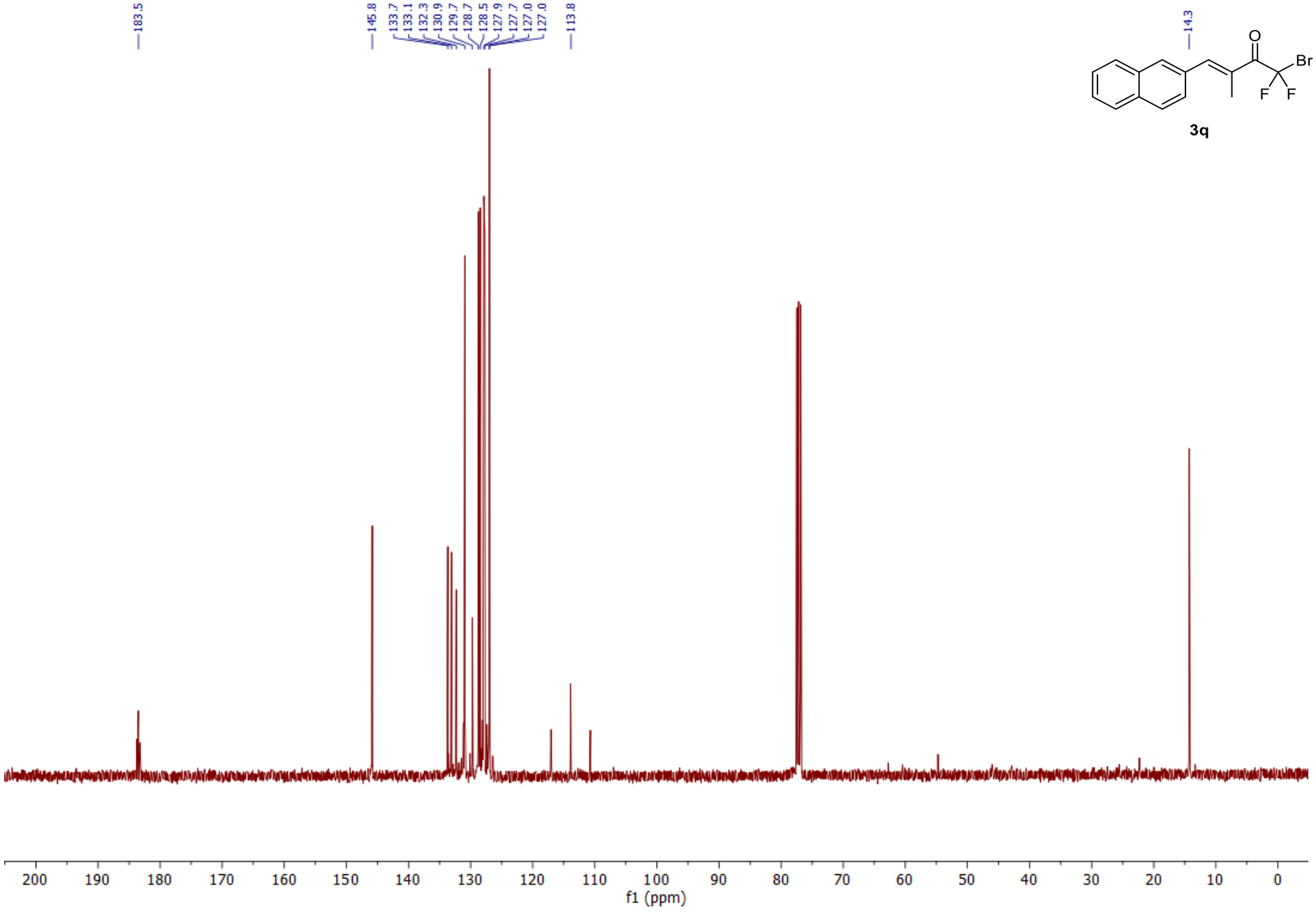


3p

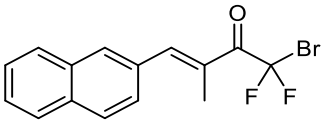
(*E*)-1-Bromo-1,1-difluoro-3-methyl-4-(naphthalen-2-yl)but-3-en-2-one **3q**



(*E*)-1-Bromo-1,1-difluoro-3-methyl-4-(naphthalen-2-yl)but-3-en-2-one **3q**

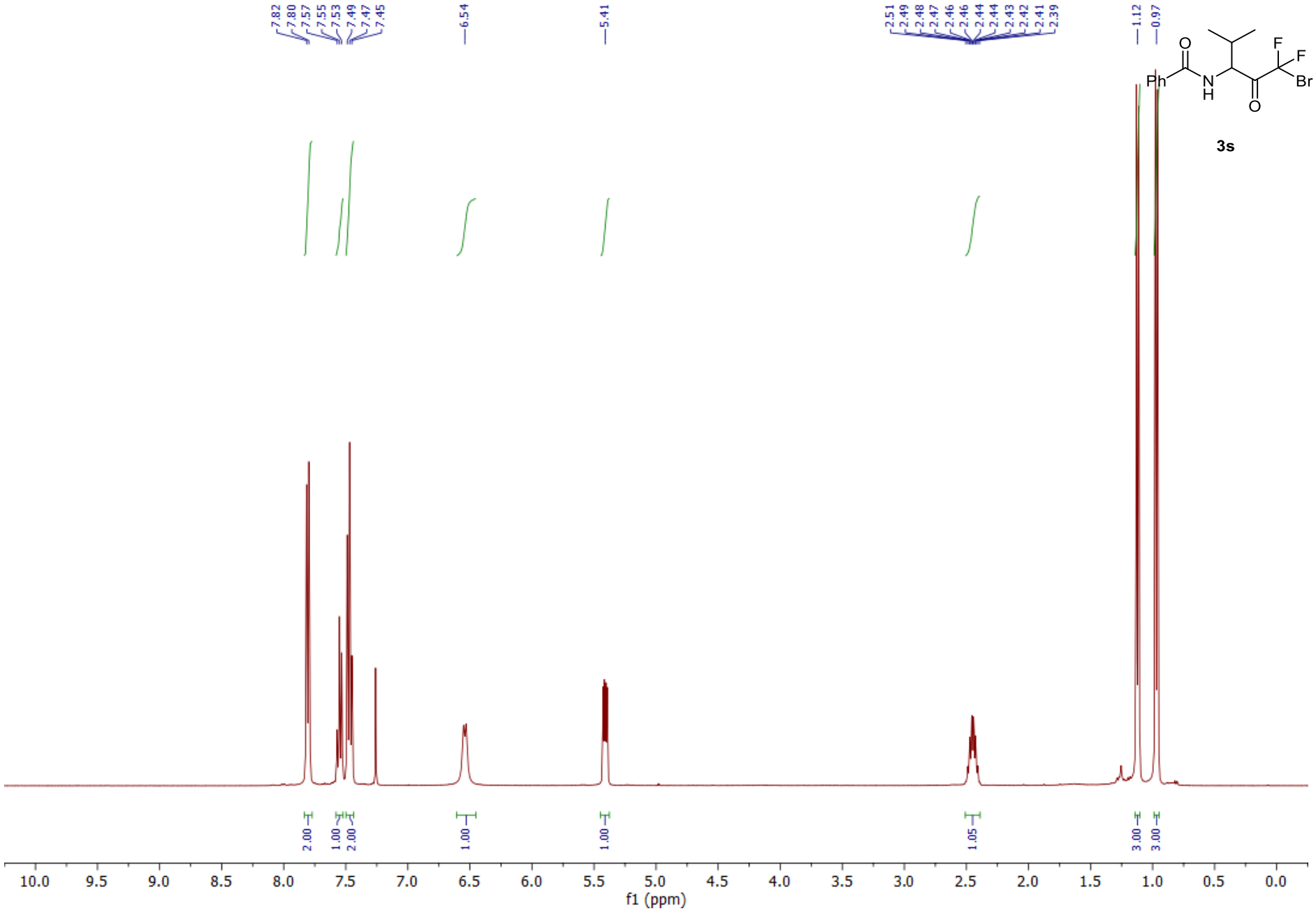


(*E*)-1-Bromo-1,1-difluoro-3-methyl-4-(naphthalen-2-yl)but-3-en-2-one **3q**

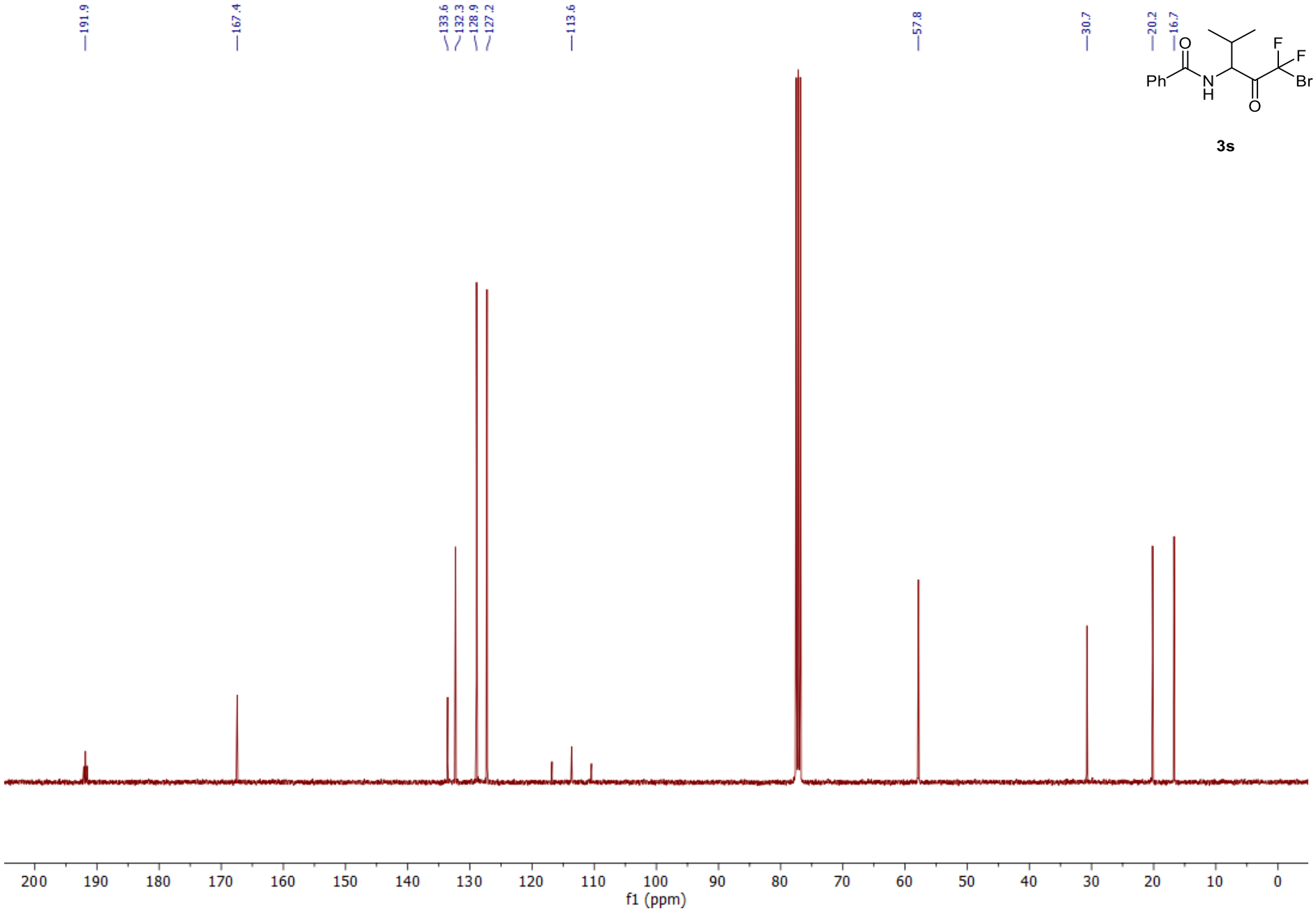


3q

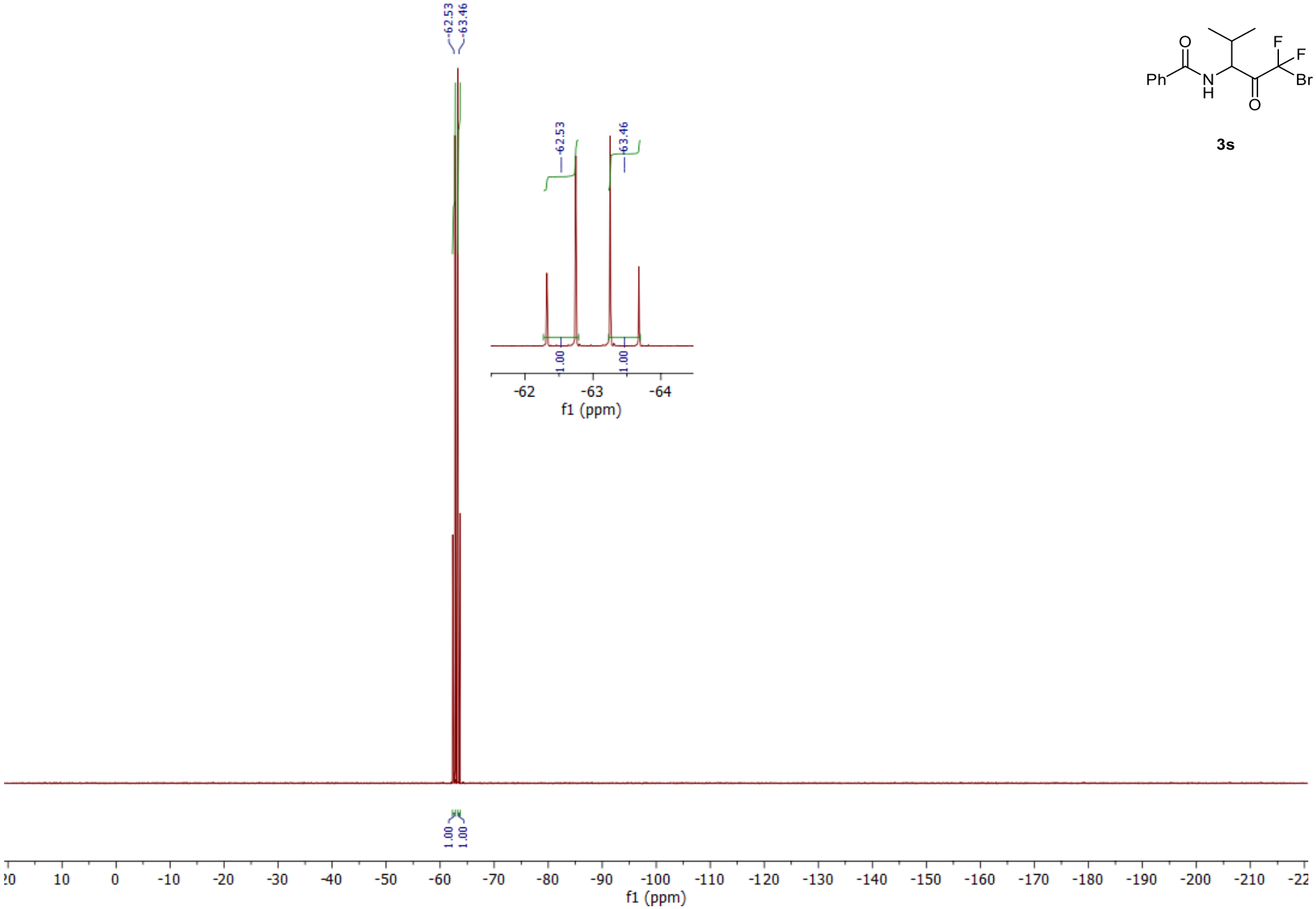
5-Bromo-5,5-difluoro-3-isopropyl-1-phenylpentane-1,4-dione **3s**



5-Bromo-5,5-difluoro-3-isopropyl-1-phenylpentane-1,4-dione **3s**

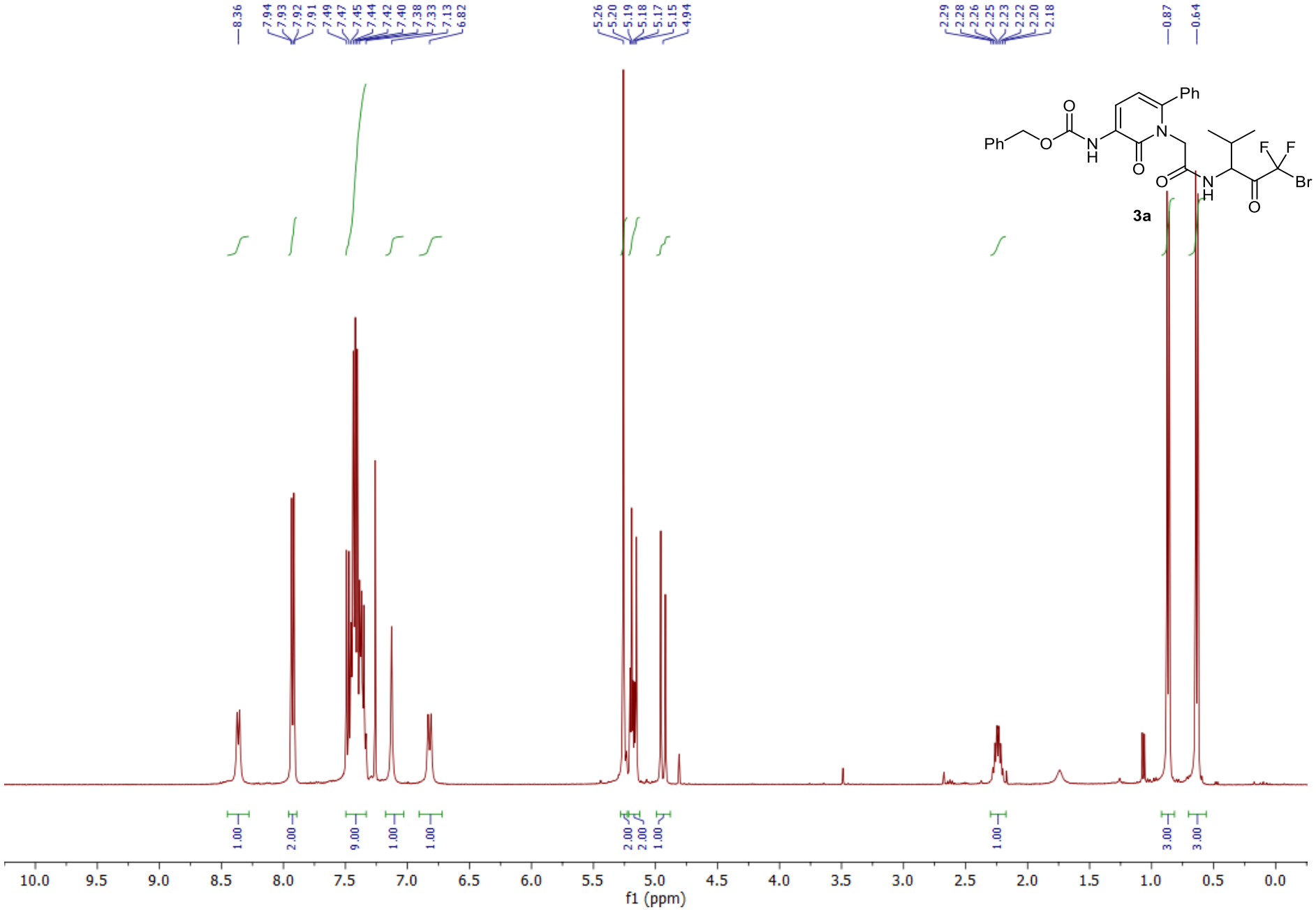


5-Bromo-5,5-difluoro-3-isopropyl-1-phenylpentane-1,4-dione **3s**



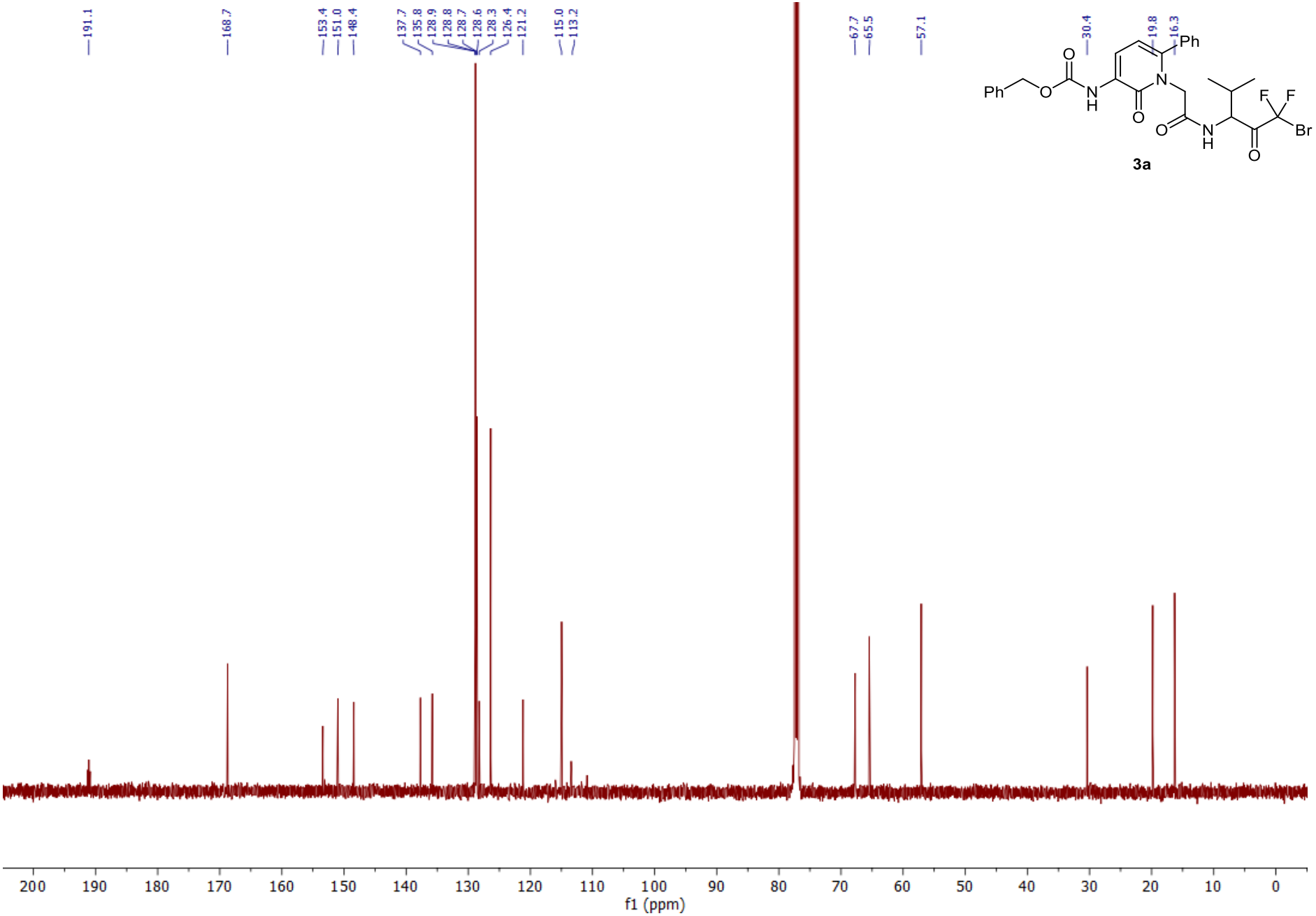
3s

Benzyl (2-(2-((1-bromo-1,1-difluoro-4-methyl-2-oxopentan-3-yl)amino)-2-oxoethyl)-3-oxo-2,3-dihydro-[1,1'-biphenyl]-4-yl)carbamate **3a**

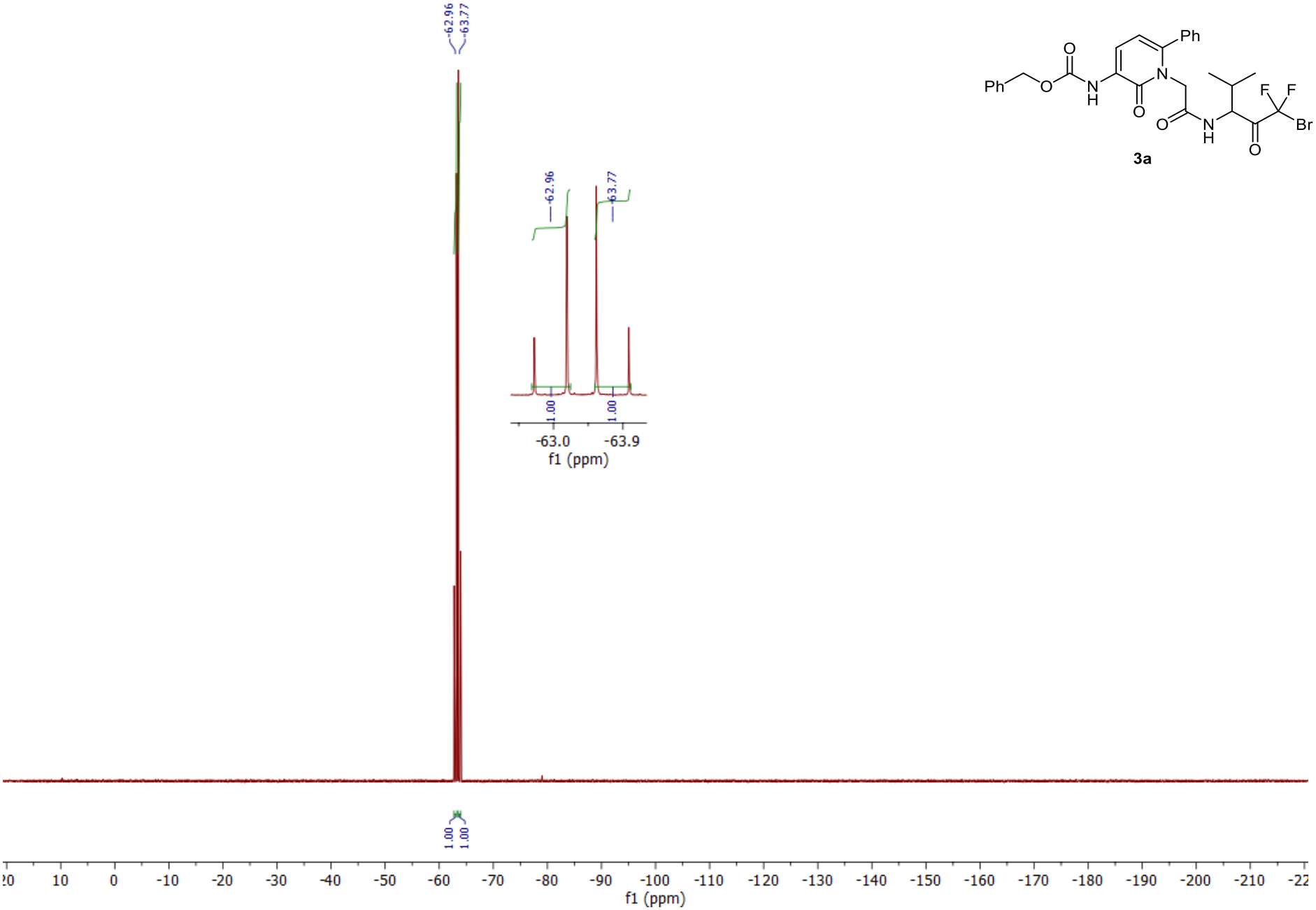


3a

Benzyl (2-(2-((1-bromo-1,1-difluoro-4-methyl-2-oxopentan-3-yl)amino)-2-oxoethyl)-3-oxo-2,3-dihydro-[1,1'-biphenyl]-4-yl)carbamate **3a**

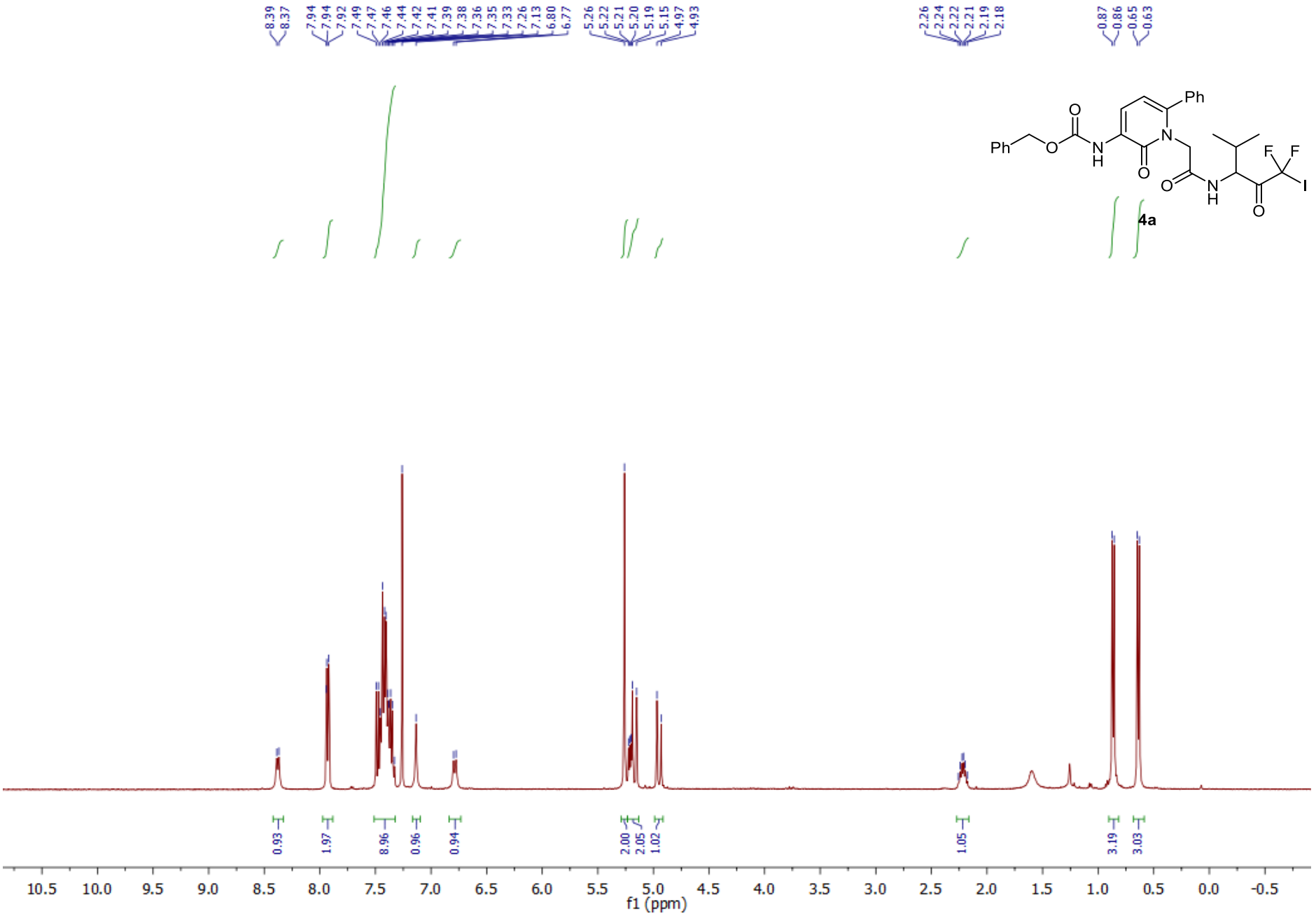


Benzyl (2-(2-((1-bromo-1,1-difluoro-4-methyl-2-oxopentan-3-yl)amino)-2-oxoethyl)-3-oxo-2,3-dihydro-[1,1'-biphenyl]-4-yl)carbamate **3a**

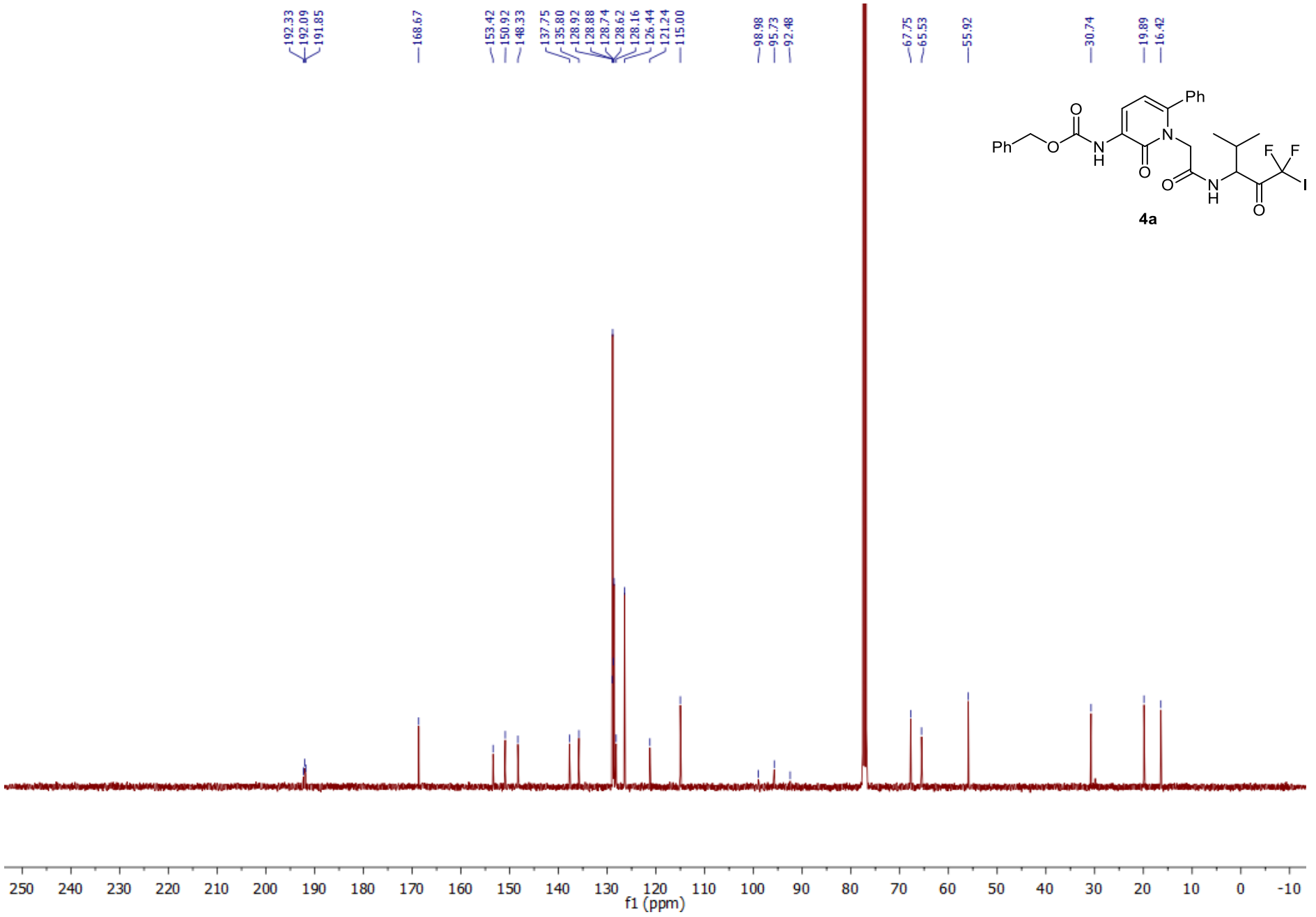


3a

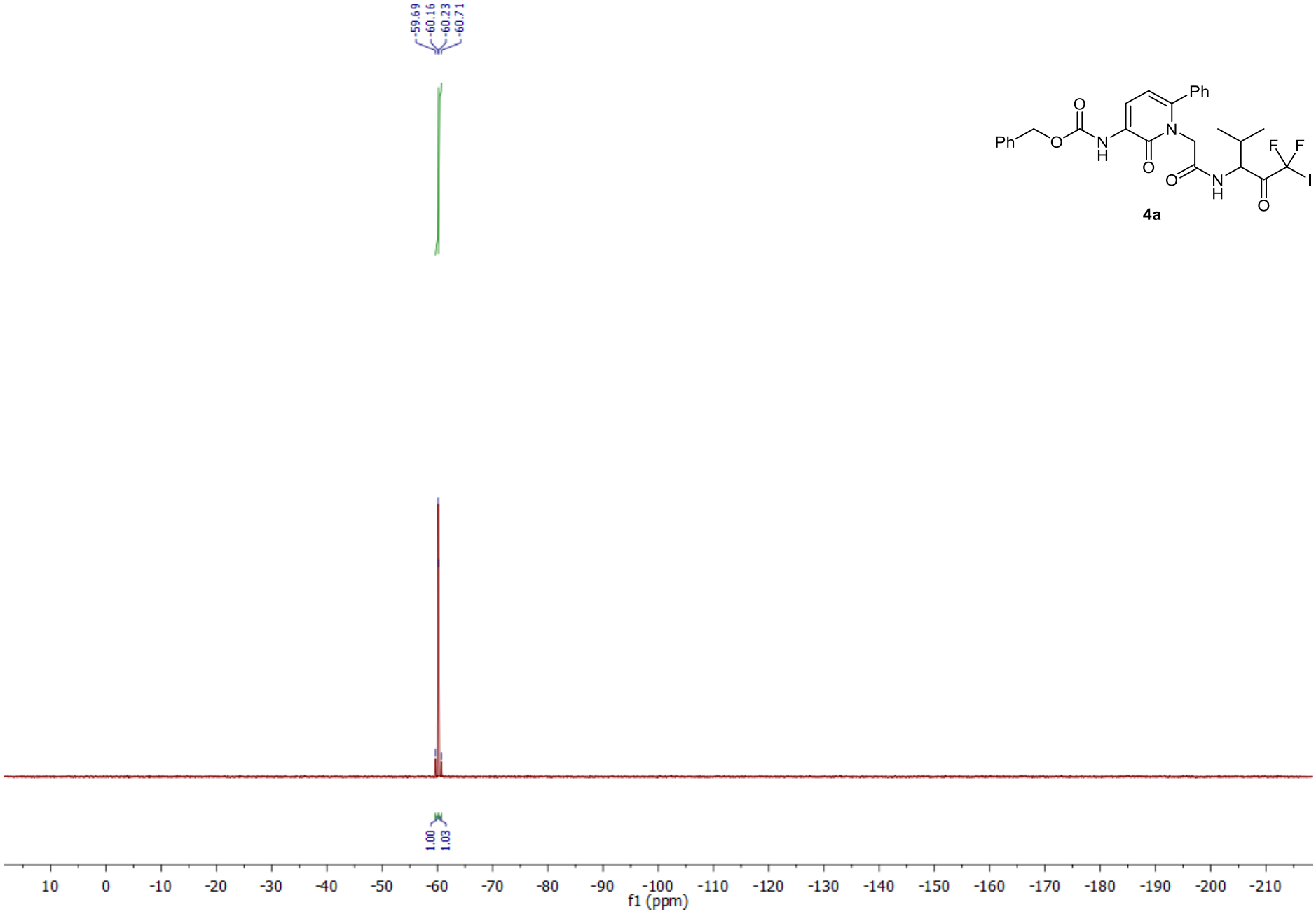
Benzyl (2-(2-((1,1-difluoro-1-iodo-4-methyl-2-oxopentan-3-yl)amino)-2-oxoethyl)-3-oxo-2,3-dihydro-[1,1'-biphenyl]-4-yl)carbamate **4a**



Benzyl (2-(2-((1,1-difluoro-1-iodo-4-methyl-2-oxopentan-3-yl)amino)-2-oxoethyl)-3-oxo-2,3-dihydro-[1,1'-biphenyl]-4-yl)carbamate **4a**

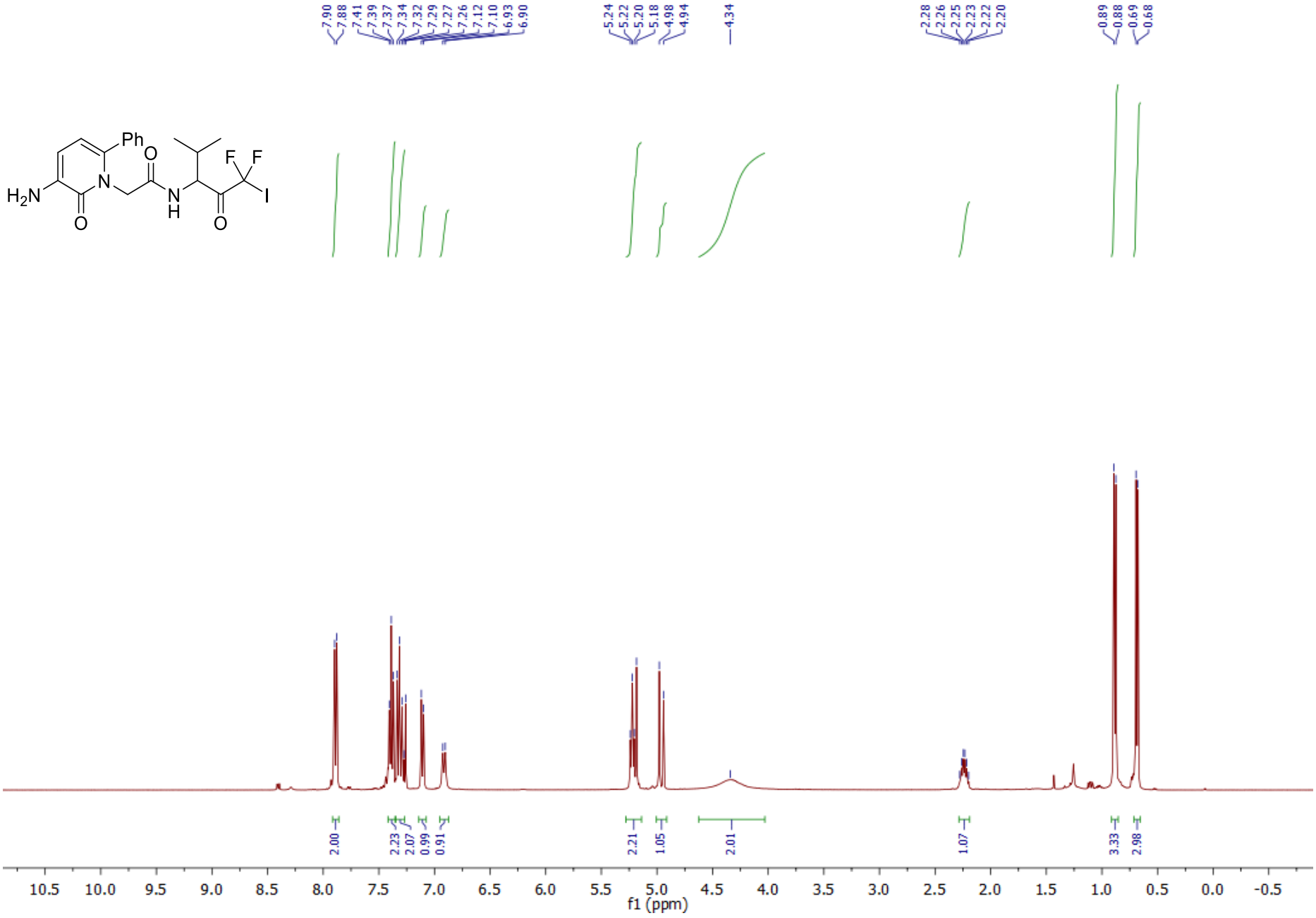


Benzyl (2-(2-((1,1-difluoro-1-iodo-4-methyl-2-oxopentan-3-yl)amino)-2-oxoethyl)-3-oxo-2,3-dihydro-[1,1'-biphenyl]-4-yl)carbamate **4a**

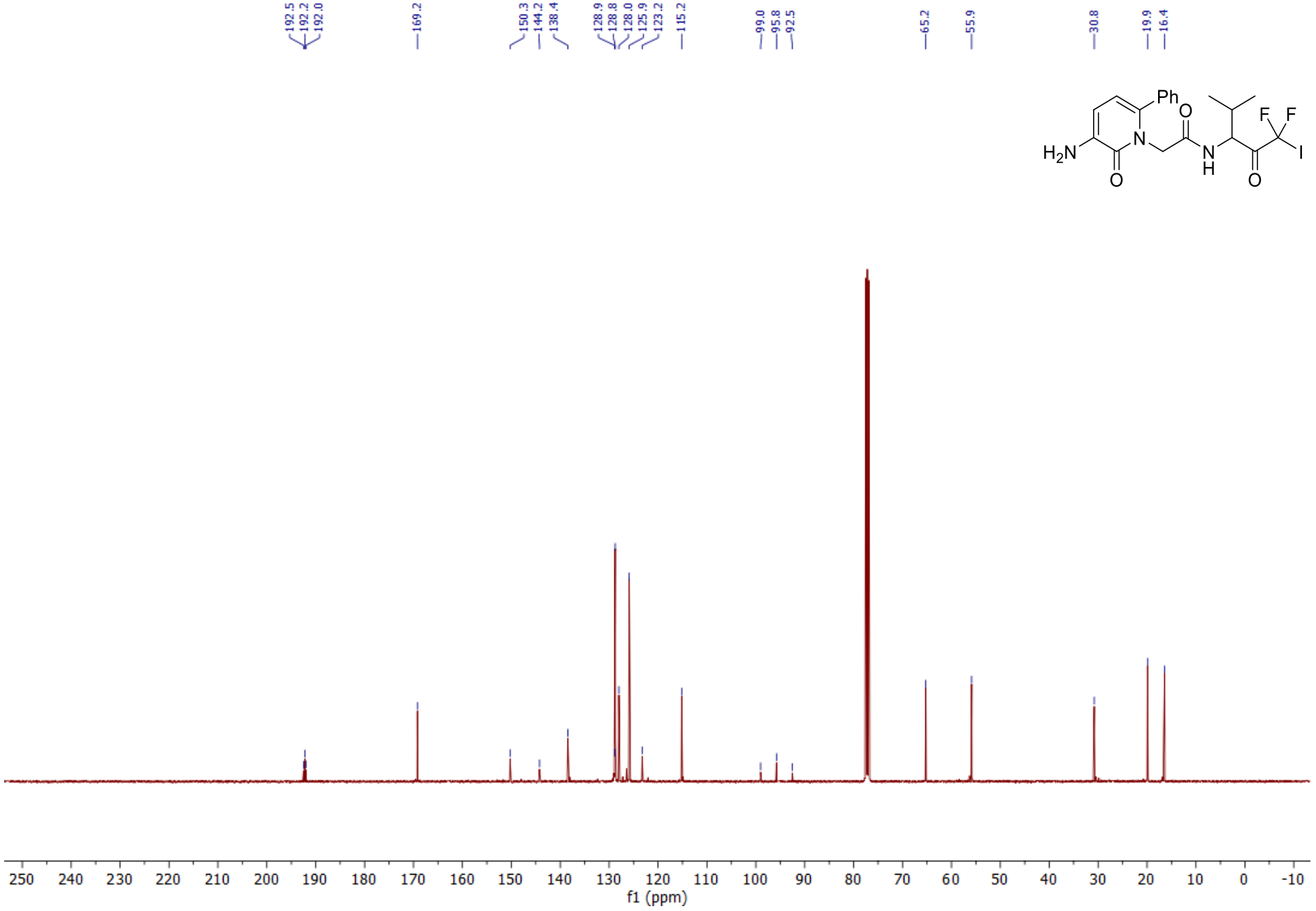


4a

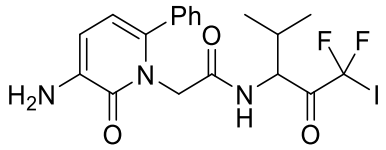
2-(4-amino-3-oxo-2,3-dihydro-[1,1'-biphenyl]-2-yl)-*N*-(1,1-difluoro-1-iodo-4-methyl-2-oxopentan-3-yl)acetamide **4t**



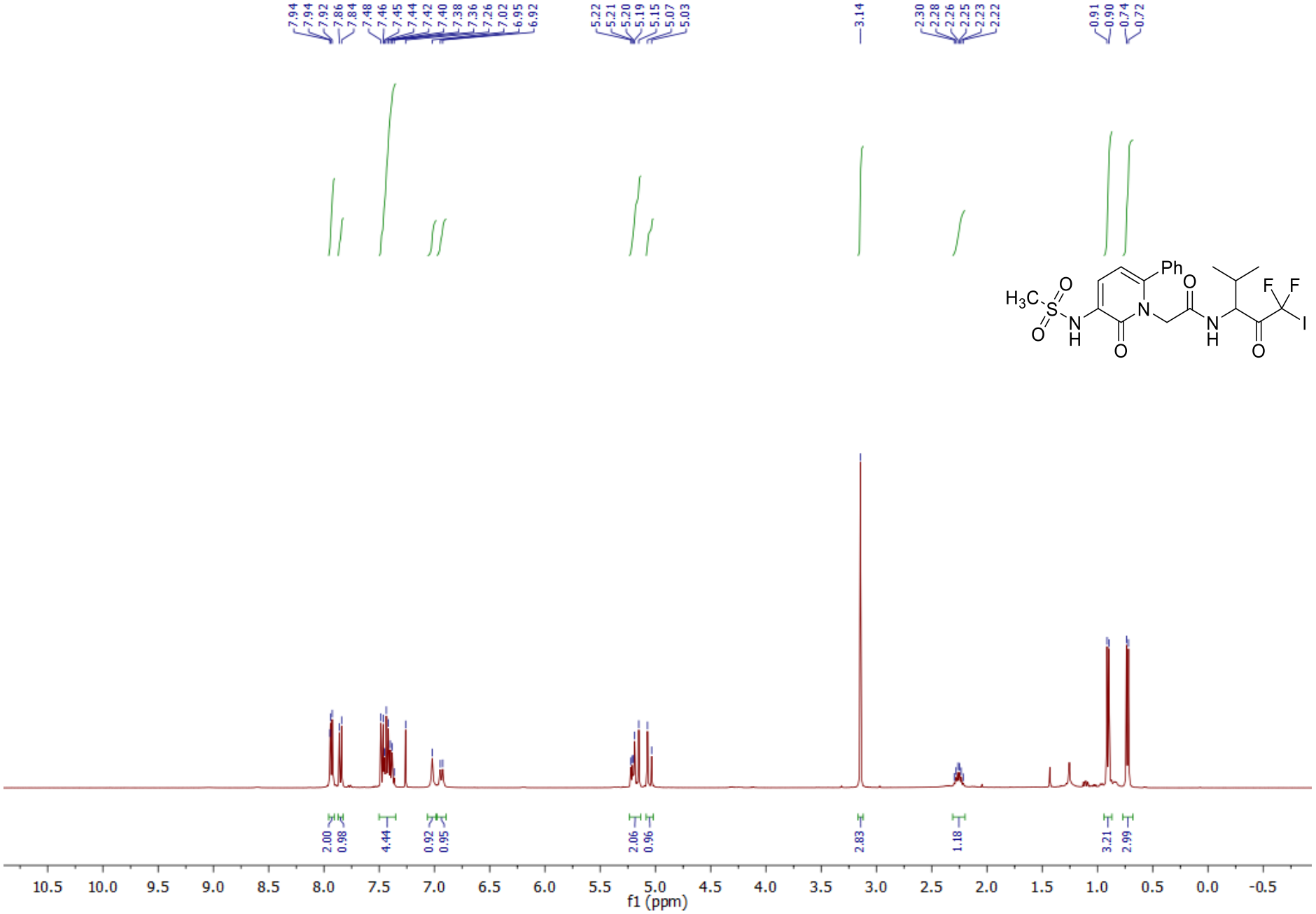
2-(4-amino-3-oxo-2,3-dihydro-[1,1'-biphenyl]-2-yl)-*N*-(1,1-difluoro-1-iodo-4-methyl-2-oxopentan-3-yl)acetamide **4t**



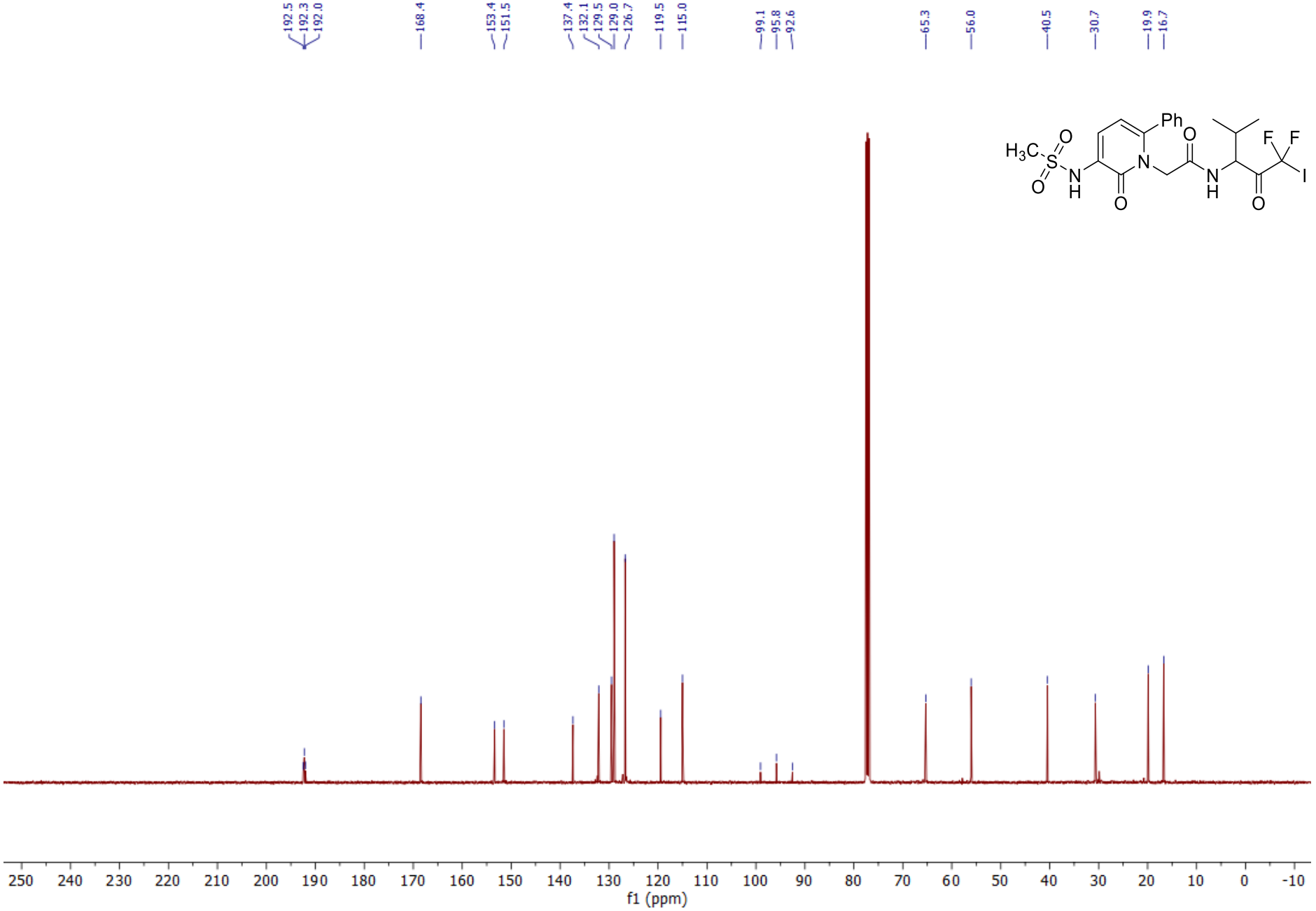
2-(4-amino-3-oxo-2,3-dihydro-[1,1'-biphenyl]-2-yl)-*N*-(1,1-difluoro-1-iodo-4-methyl-2-oxopentan-3-yl)acetamide **4t**



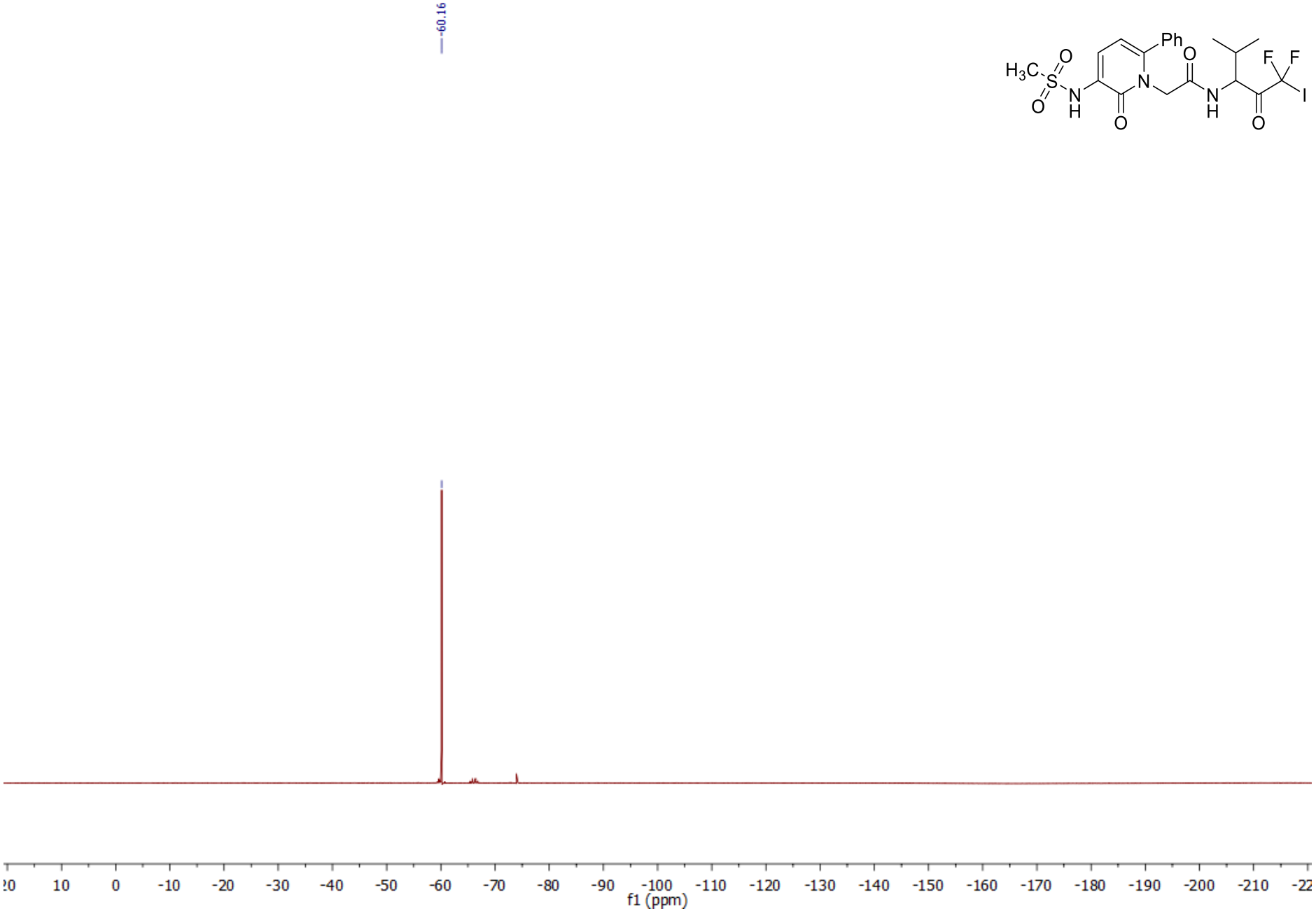
N-(1,1-difluoro-1-iodo-4-methyl-2-oxopentan-3-yl)-2-(3-(methylsulfonamido)-2-oxo-6-phenylpyridin-1(2H)-yl)acetamide **4b**



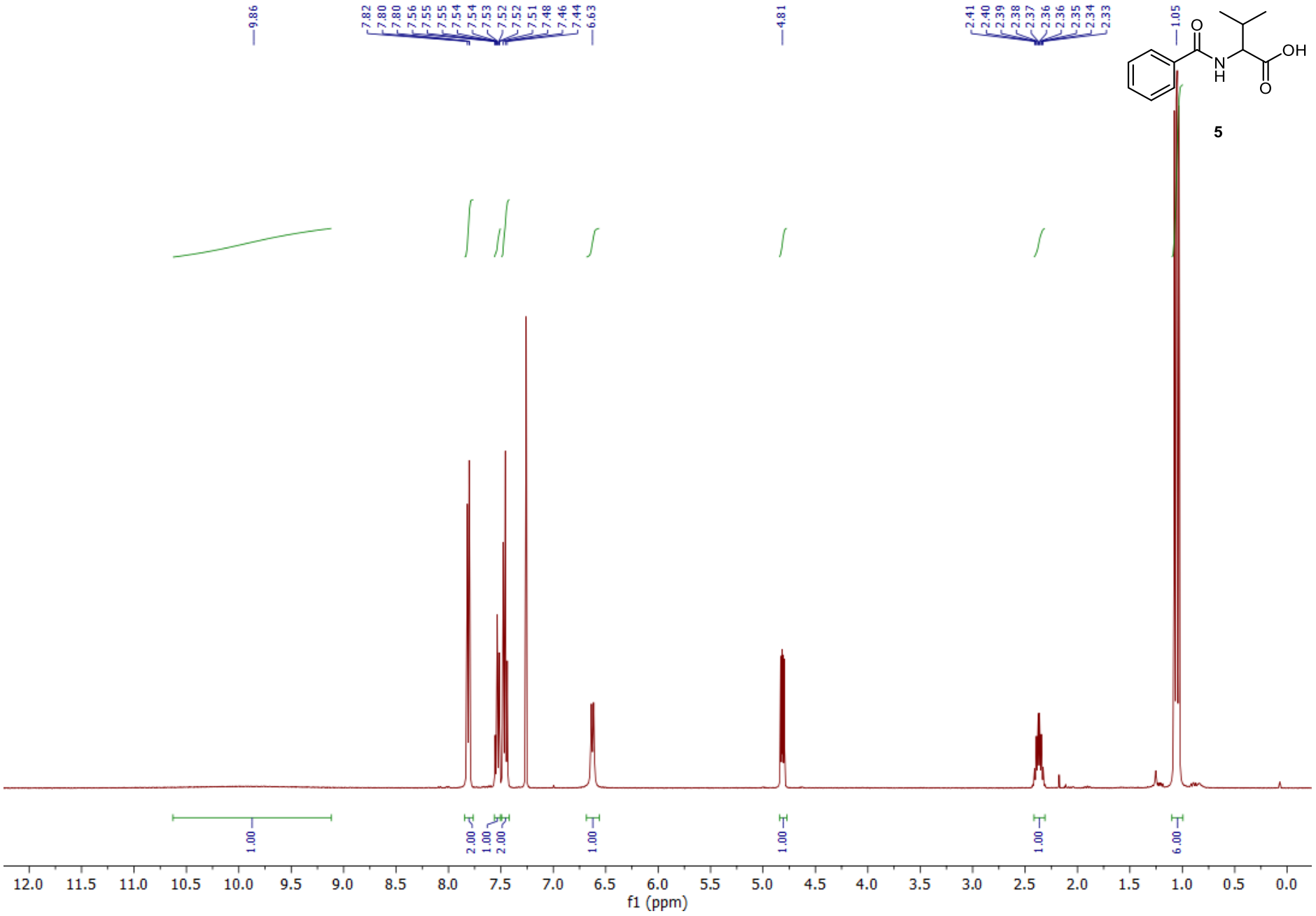
N-(1,1-difluoro-1-iodo-4-methyl-2-oxopentan-3-yl)-2-(3-(methylsulfonamido)-2-oxo-6-phenylpyridin-1(2H)-yl)acetamide **4b**



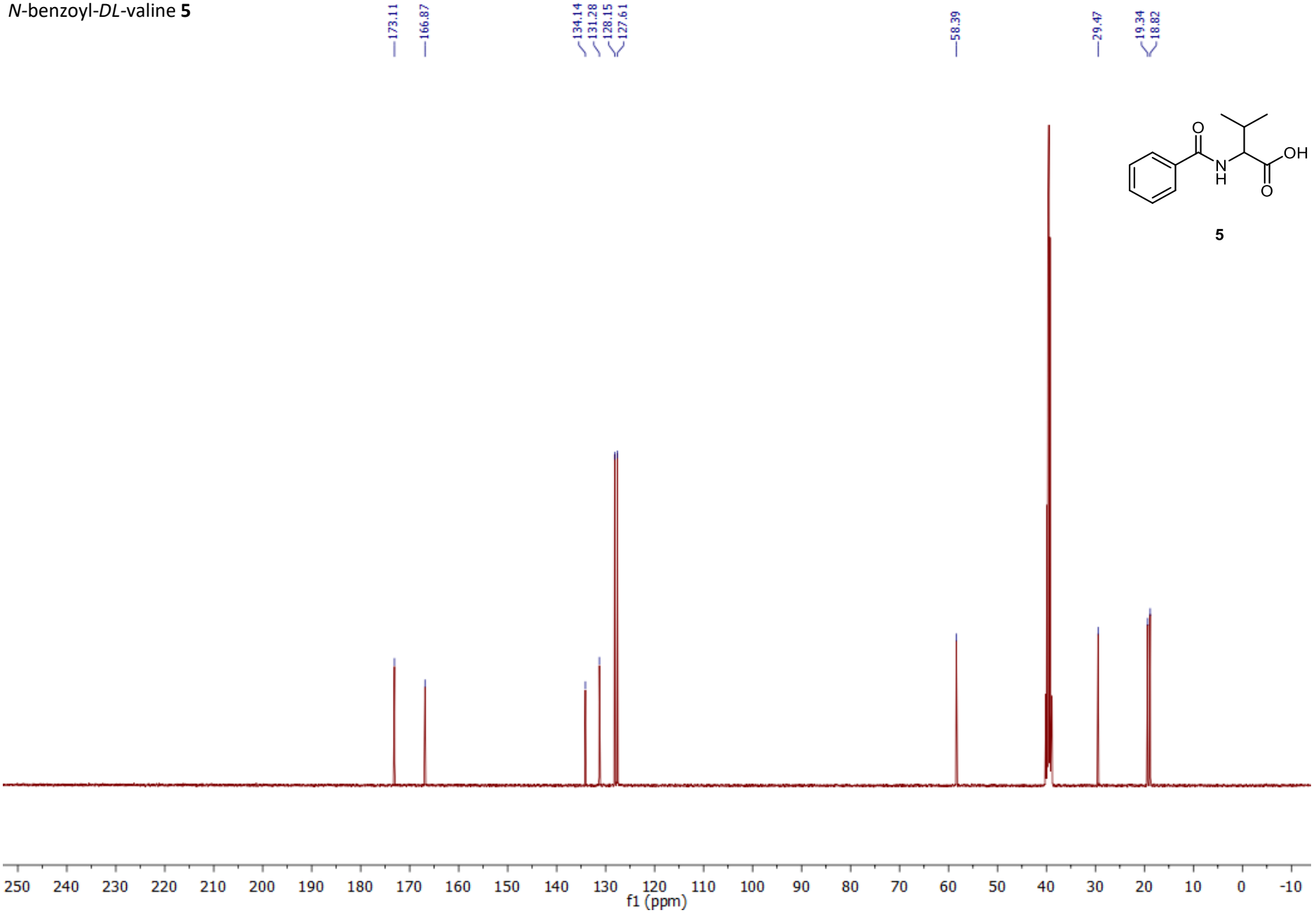
N-(1,1-difluoro-1-iodo-4-methyl-2-oxopentan-3-yl)-2-(3-(methylsulfonamido)-2-oxo-6-phenylpyridin-1(2H)-yl)acetamide **4b**



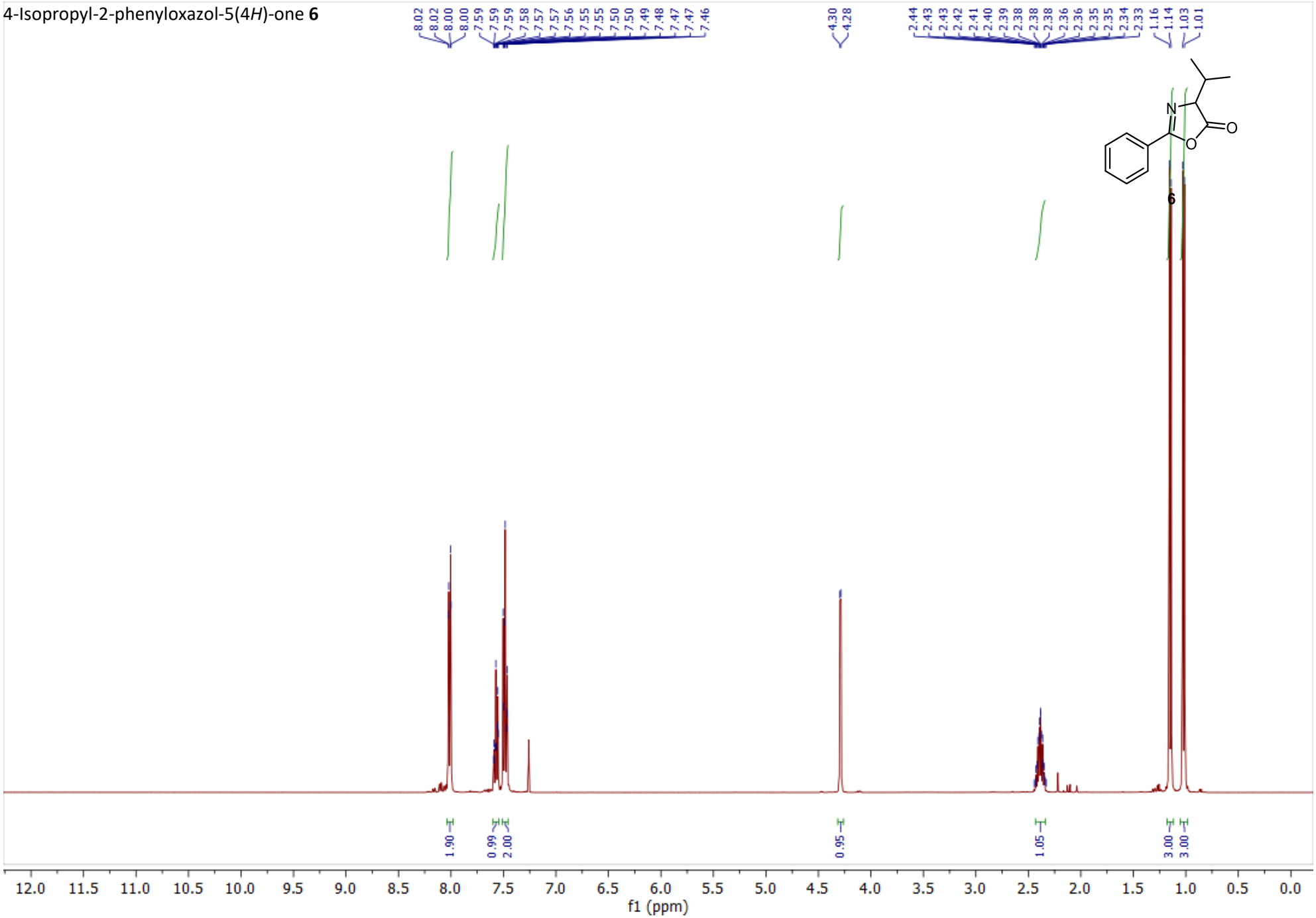
N-benzoyl-*DL*-valine **5**



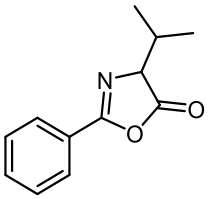
N-benzoyl-*DL*-valine **5**



4-Isopropyl-2-phenyloxazol-5(4*H*)-one **6**

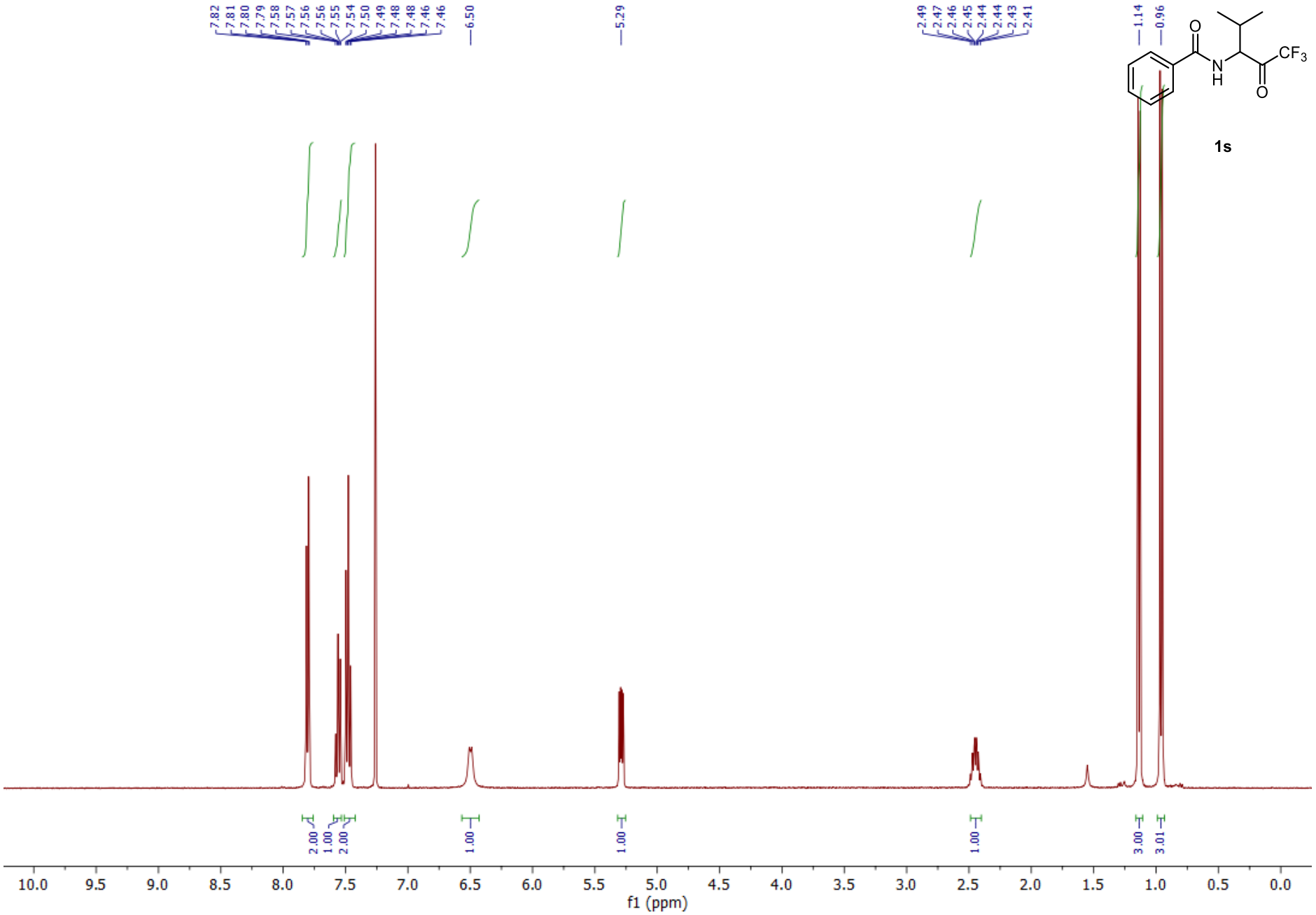


4-Isopropyl-2-phenyloxazol-5(4*H*)-one **6**

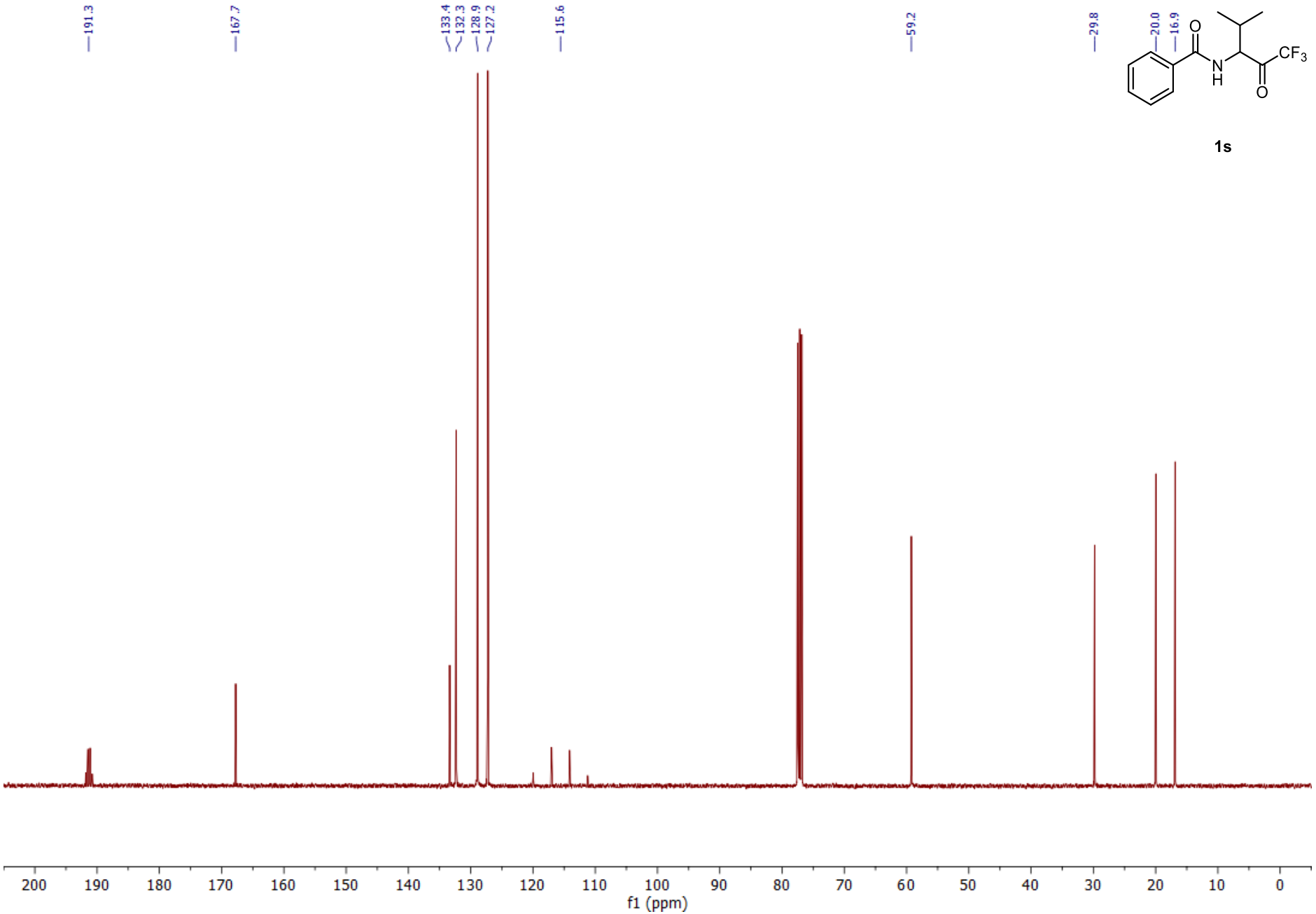


6

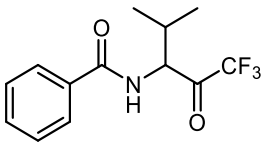
N-(1,1,1-Trifluoro-4-methyl-2-oxopentan-3-yl)benzamide **1s**



N-(1,1,1-Trifluoro-4-methyl-2-oxopentan-3-yl)benzamide **1s**

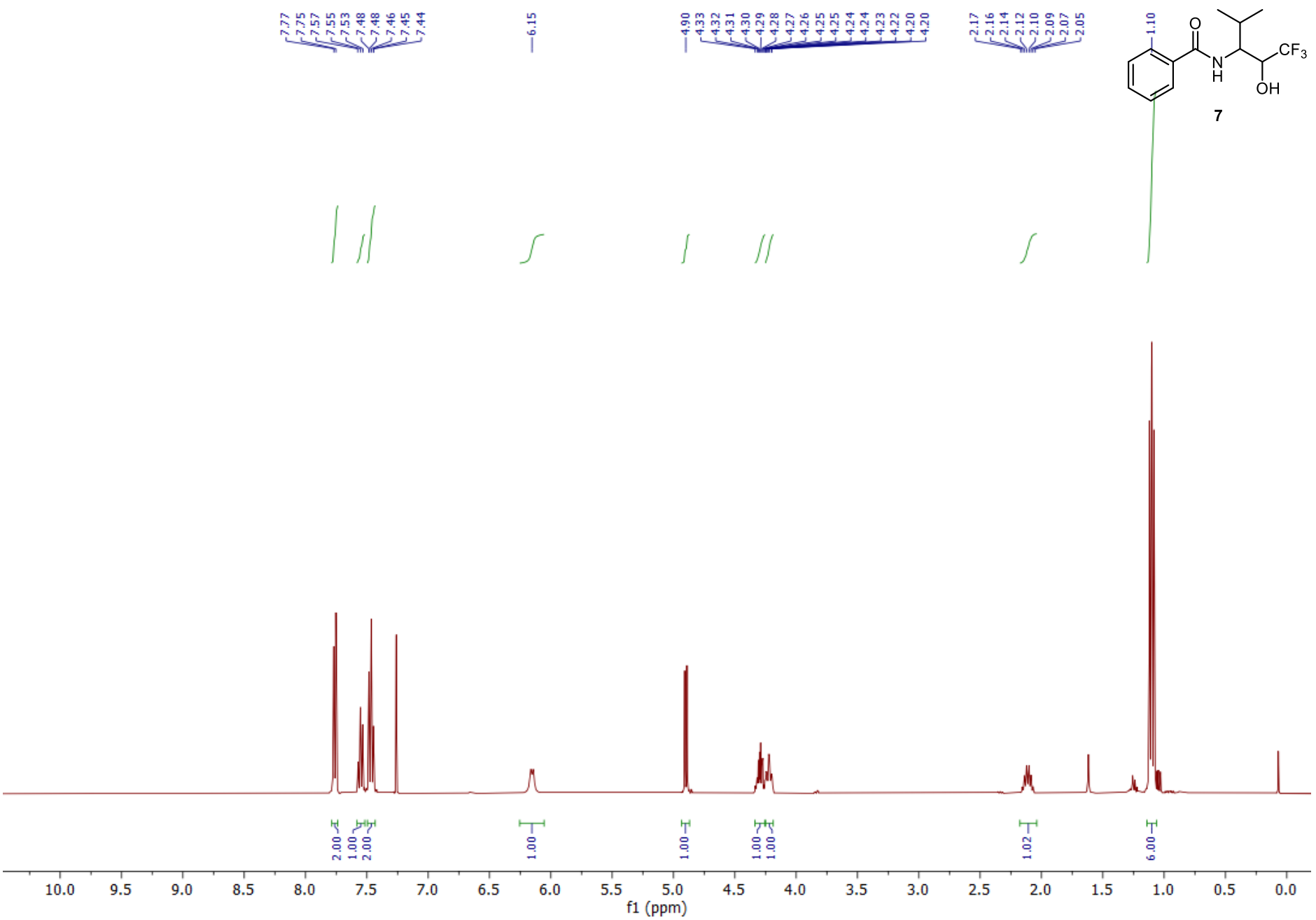


N-(1,1,1-Trifluoro-4-methyl-2-oxopentan-3-yl)benzamide **1s**

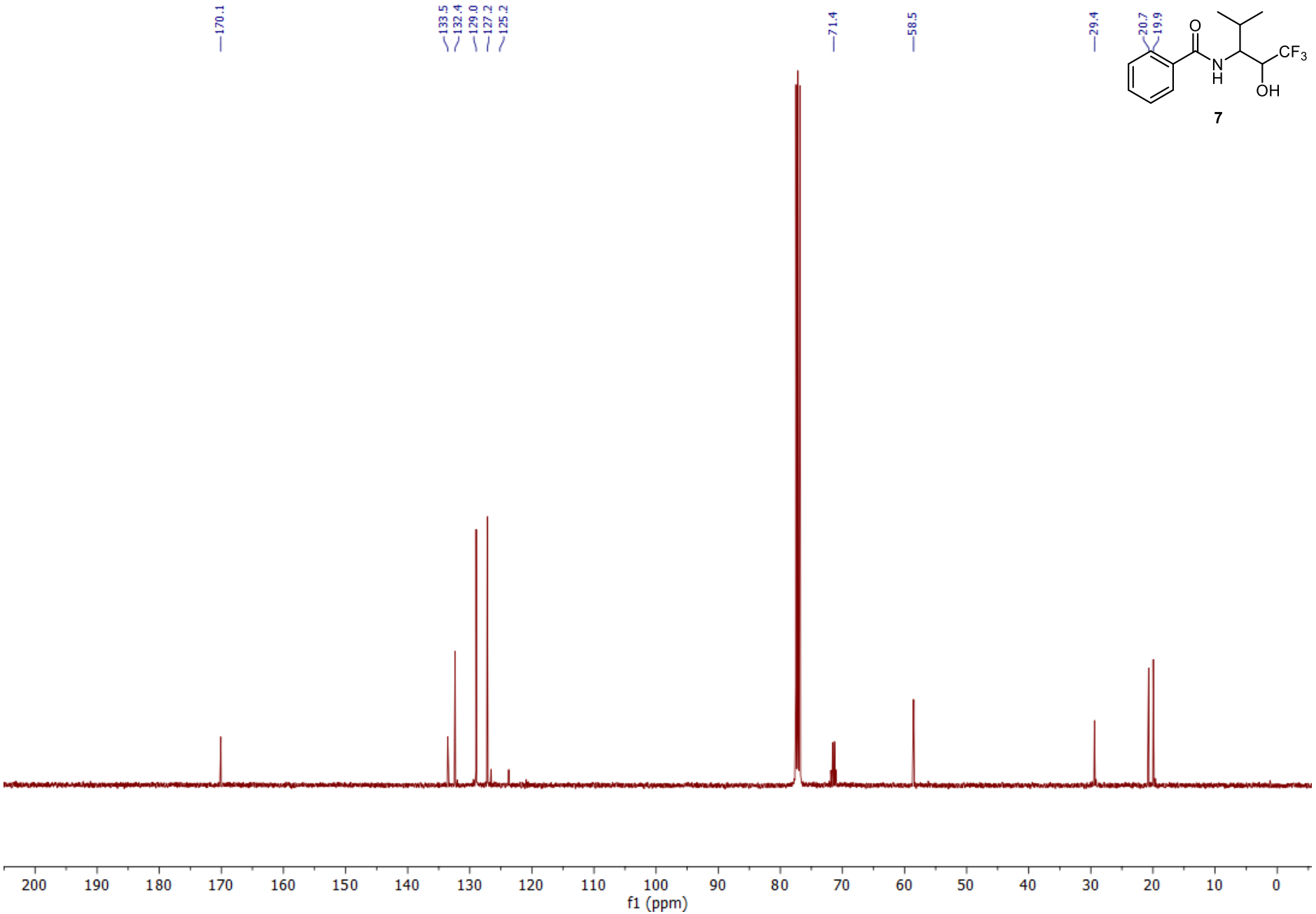


1s

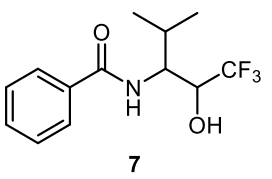
N-(1,1,1-Trifluoro-2-hydroxy-4-methylpentan-3-yl)benzamide **7**



N-(1,1,1-Trifluoro-2-hydroxy-4-methylpentan-3-yl)benzamide **7**

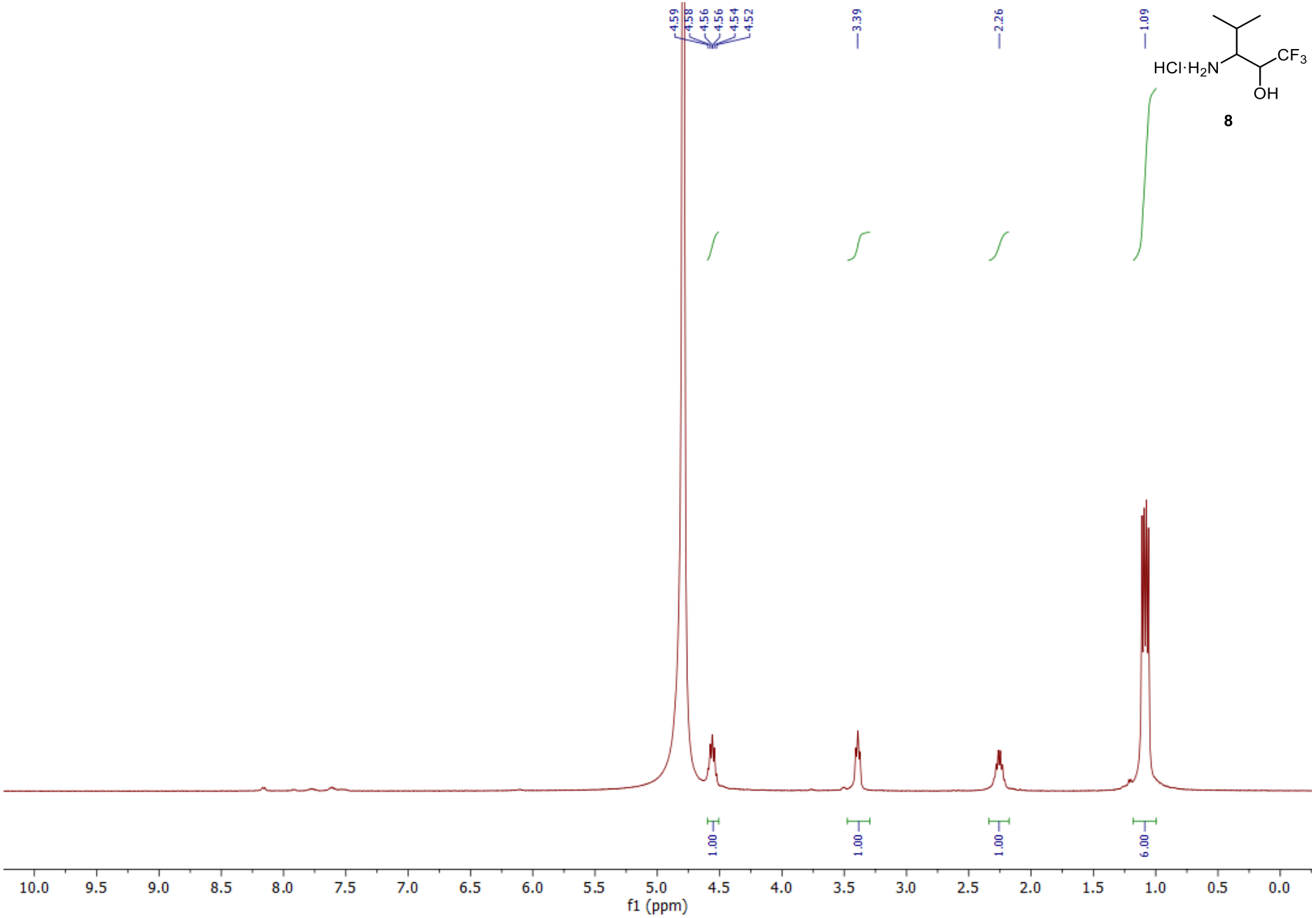


N-(1,1,1-Trifluoro-2-hydroxy-4-methylpentan-3-yl)benzamide **7**

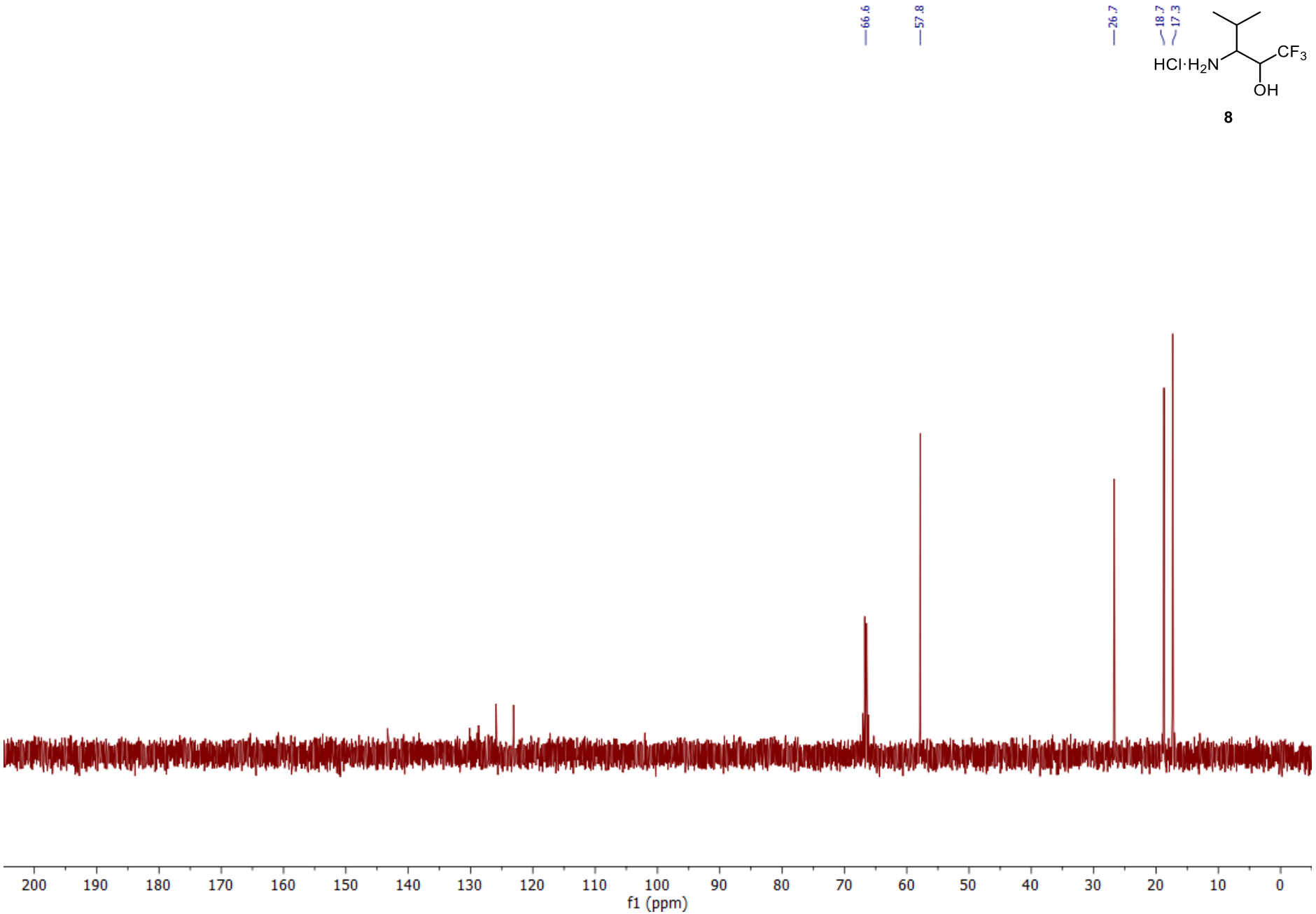


7

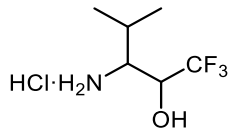
3-Amino-1,1,1-trifluoro-4-methylpentan-2-ol **8**



3-Amino-1,1,1-trifluoro-4-methylpentan-2-ol **8**

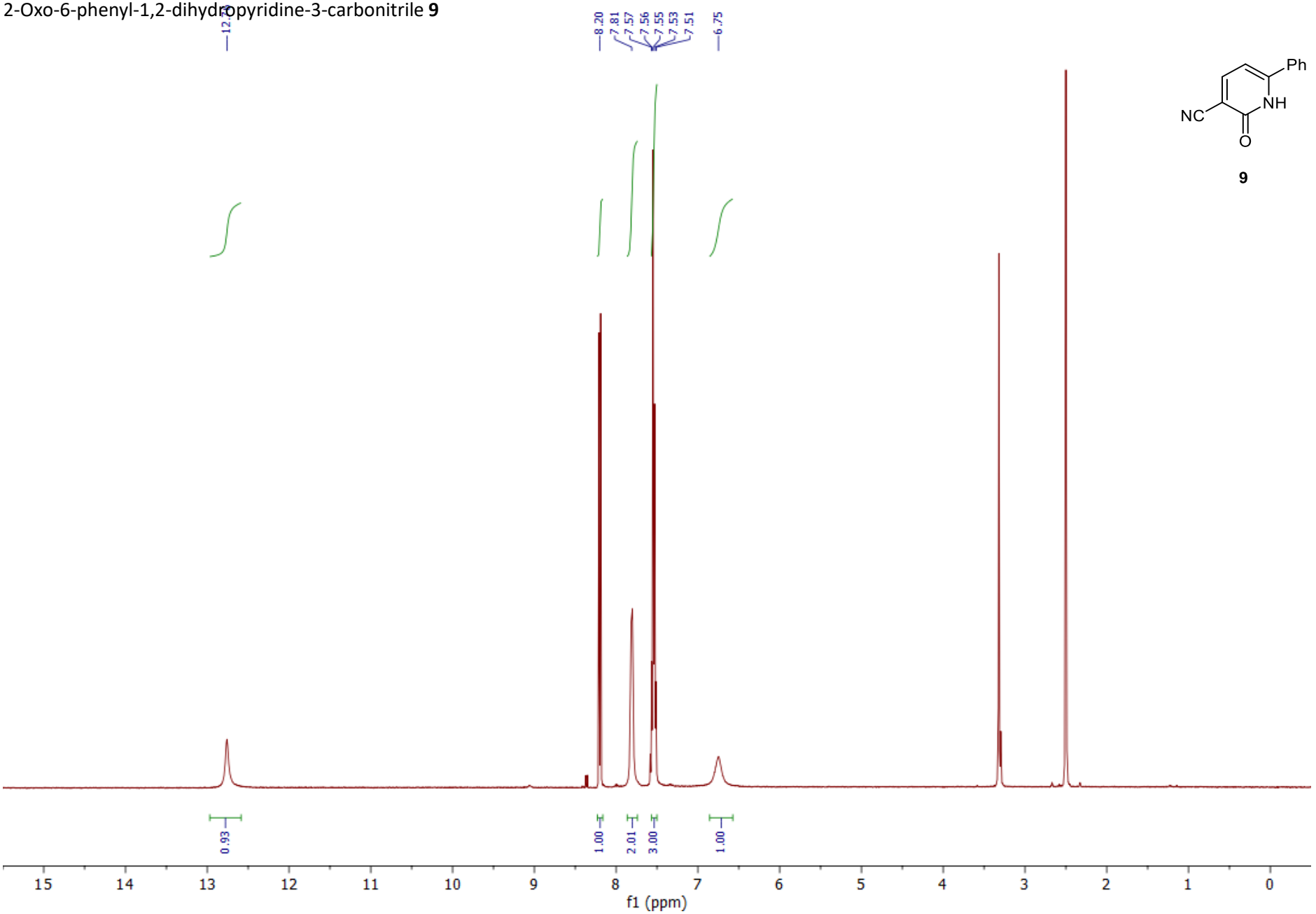


3-Amino-1,1,1-trifluoro-4-methylpentan-2-ol **8**

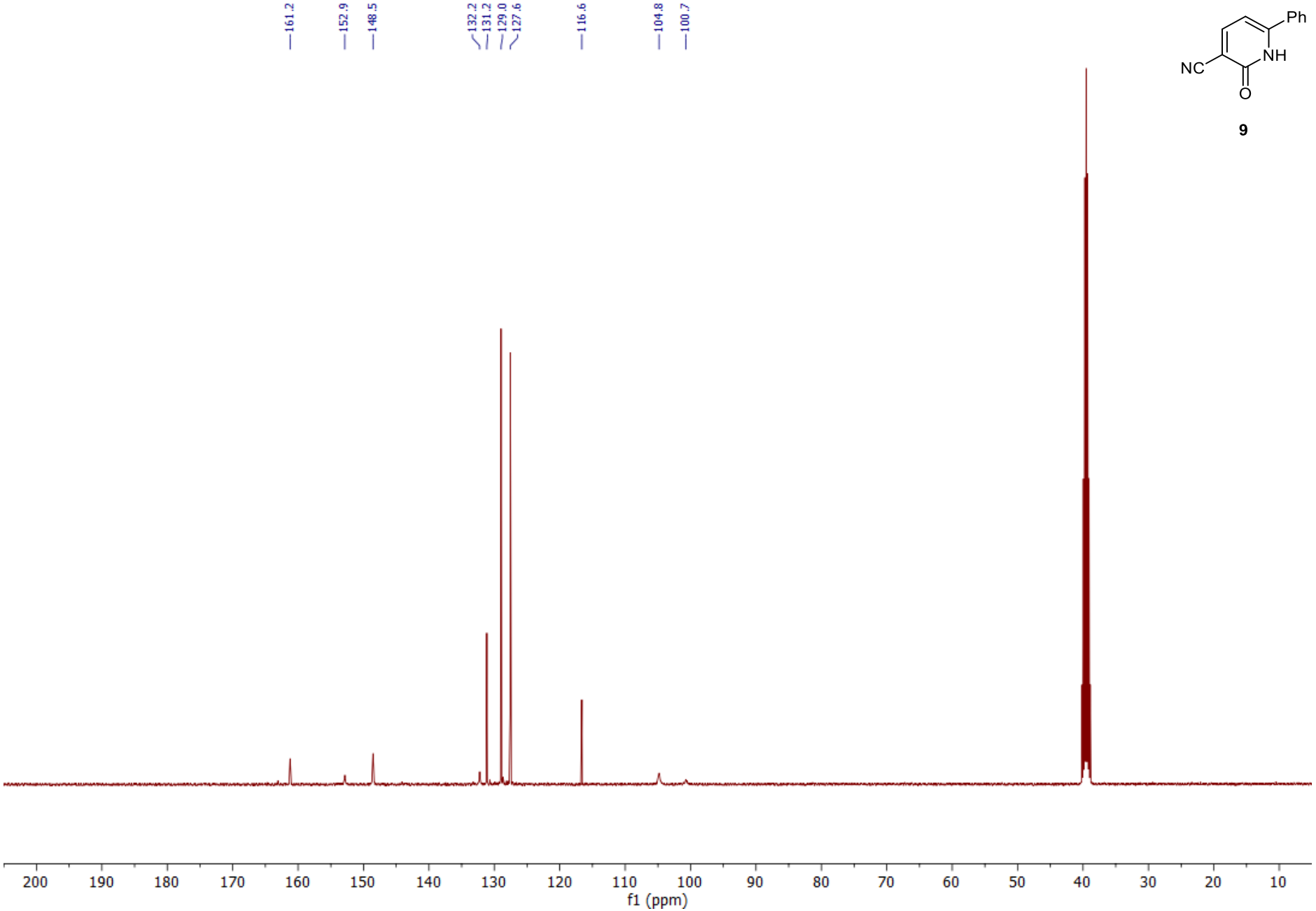


8

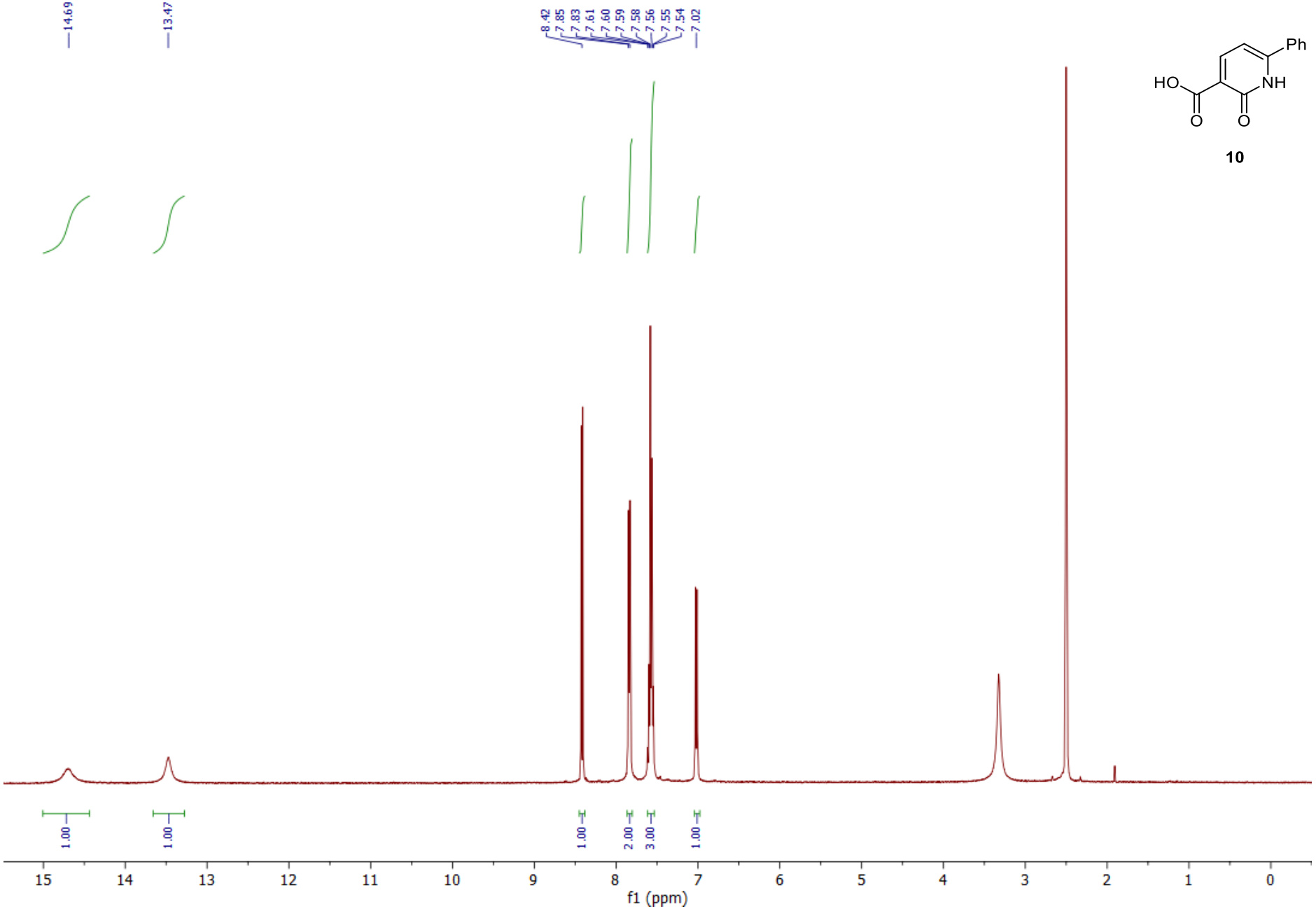
2-Oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile **9**



2-Oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile **9**

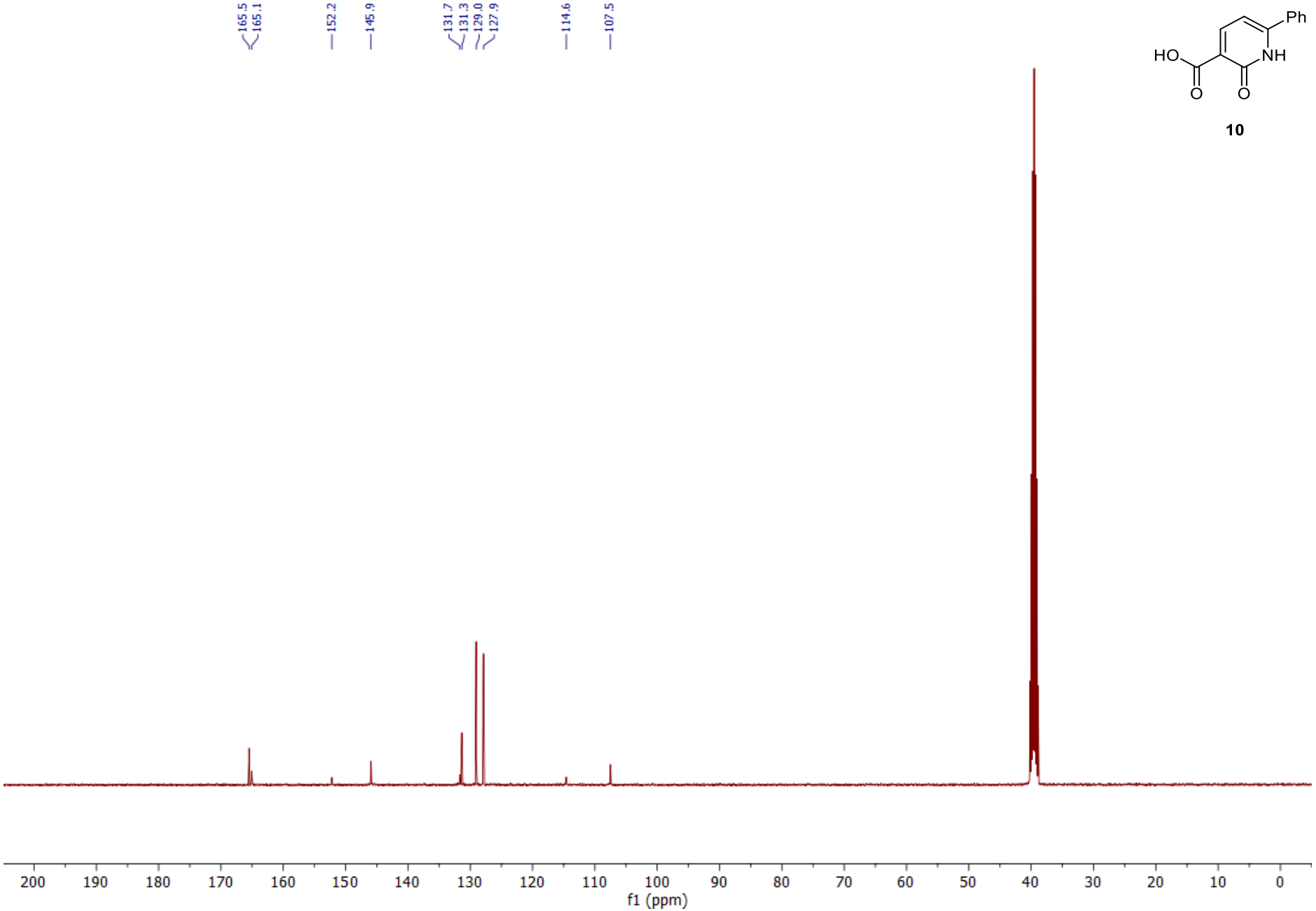


2-Oxo-6-phenyl-1,2-dihydropyridine-3-carboxylic acid **10**

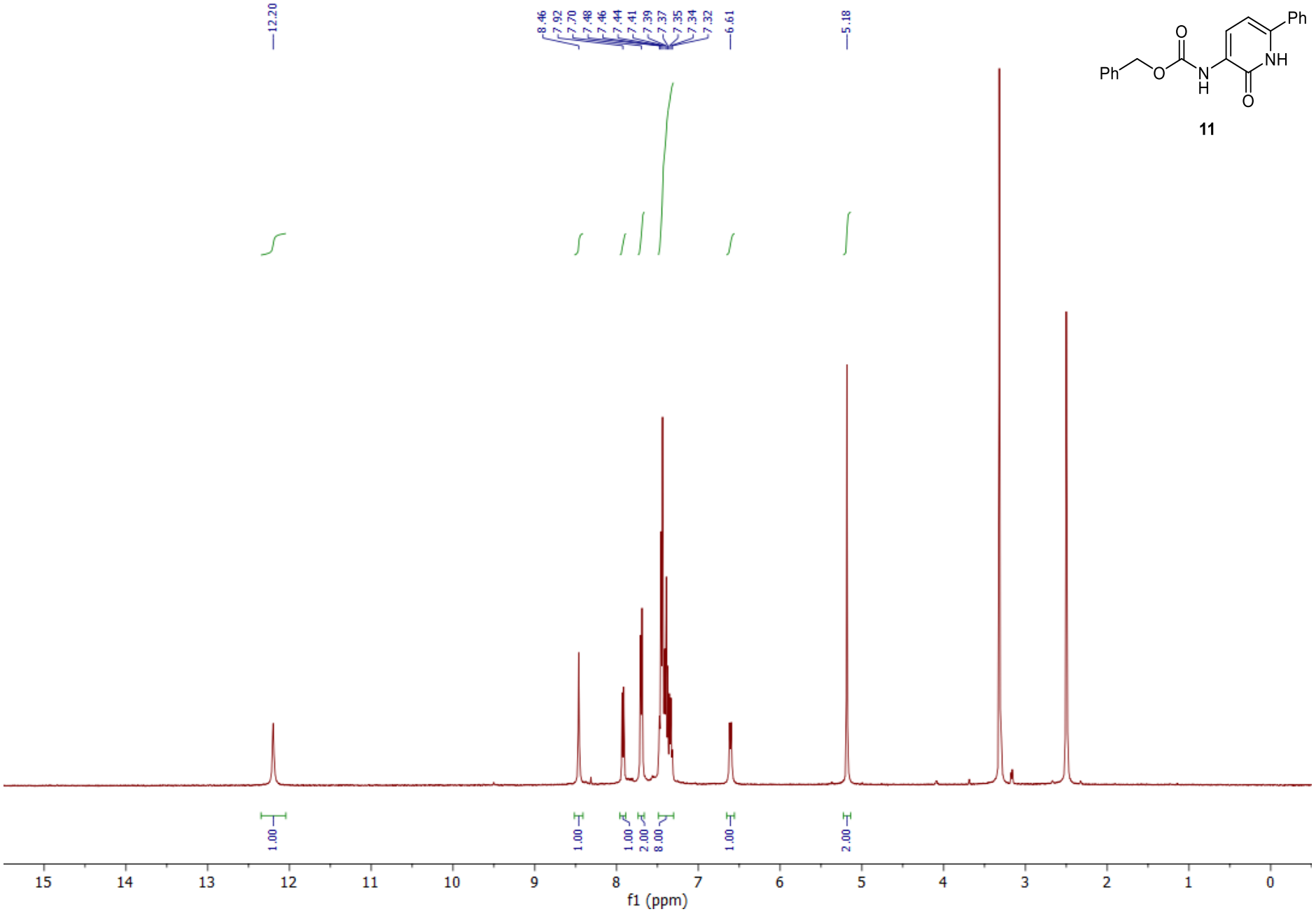


10

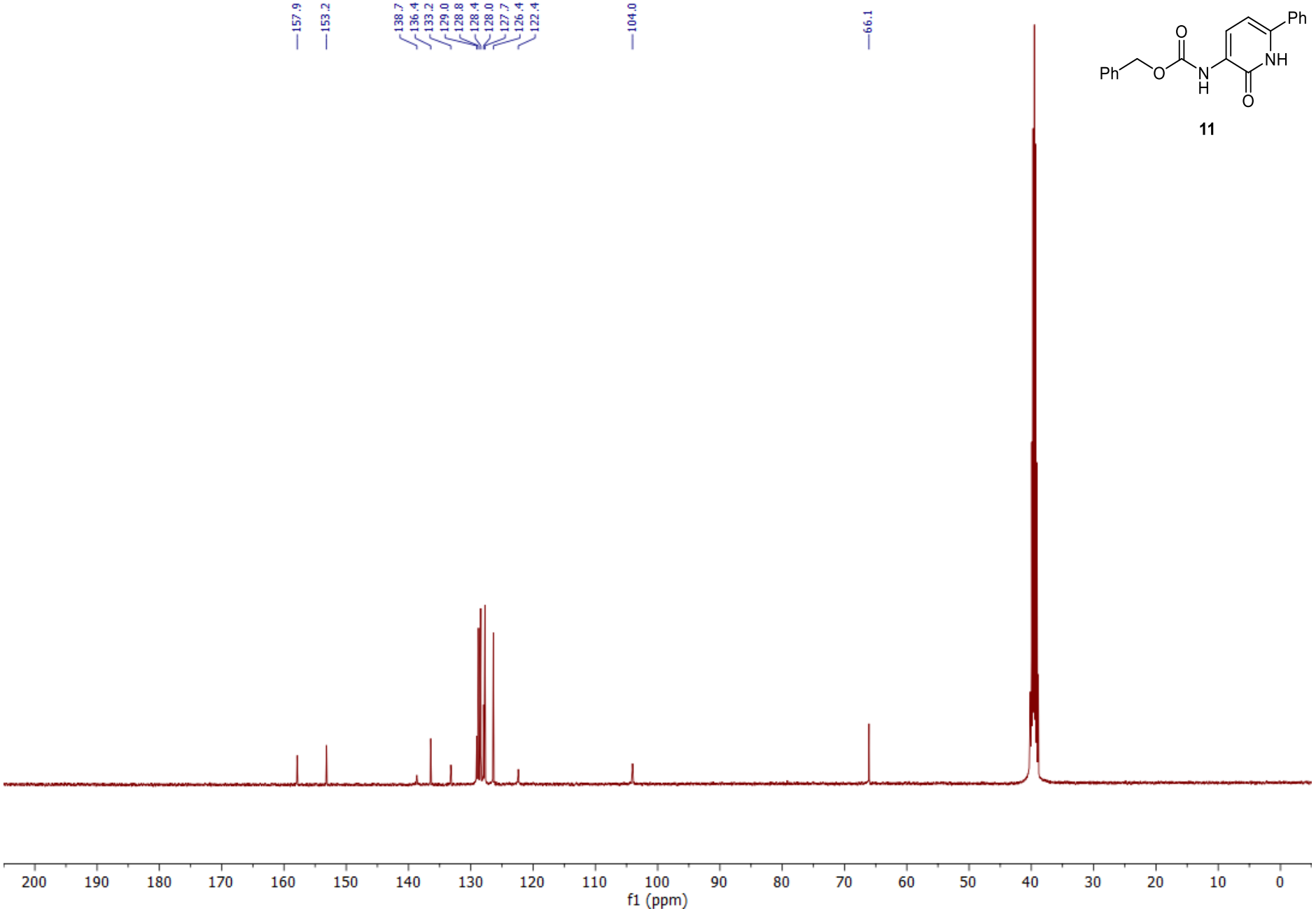
2-Oxo-6-phenyl-1,2-dihydropyridine-3-carboxylic acid **10**



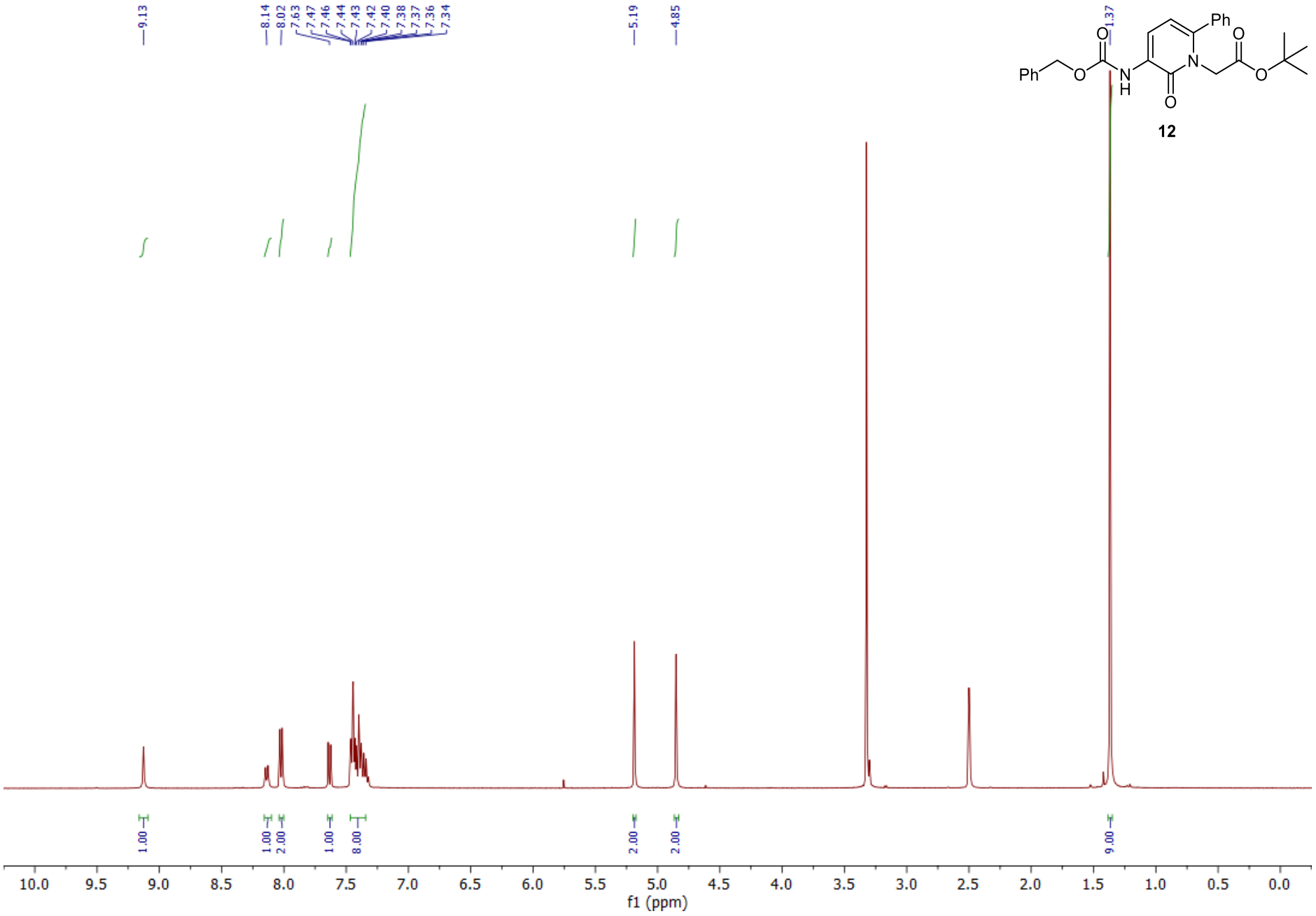
Benzyl (2-oxo-6-phenyl-1,2-dihydropyridin-3-yl)carbamate **11**



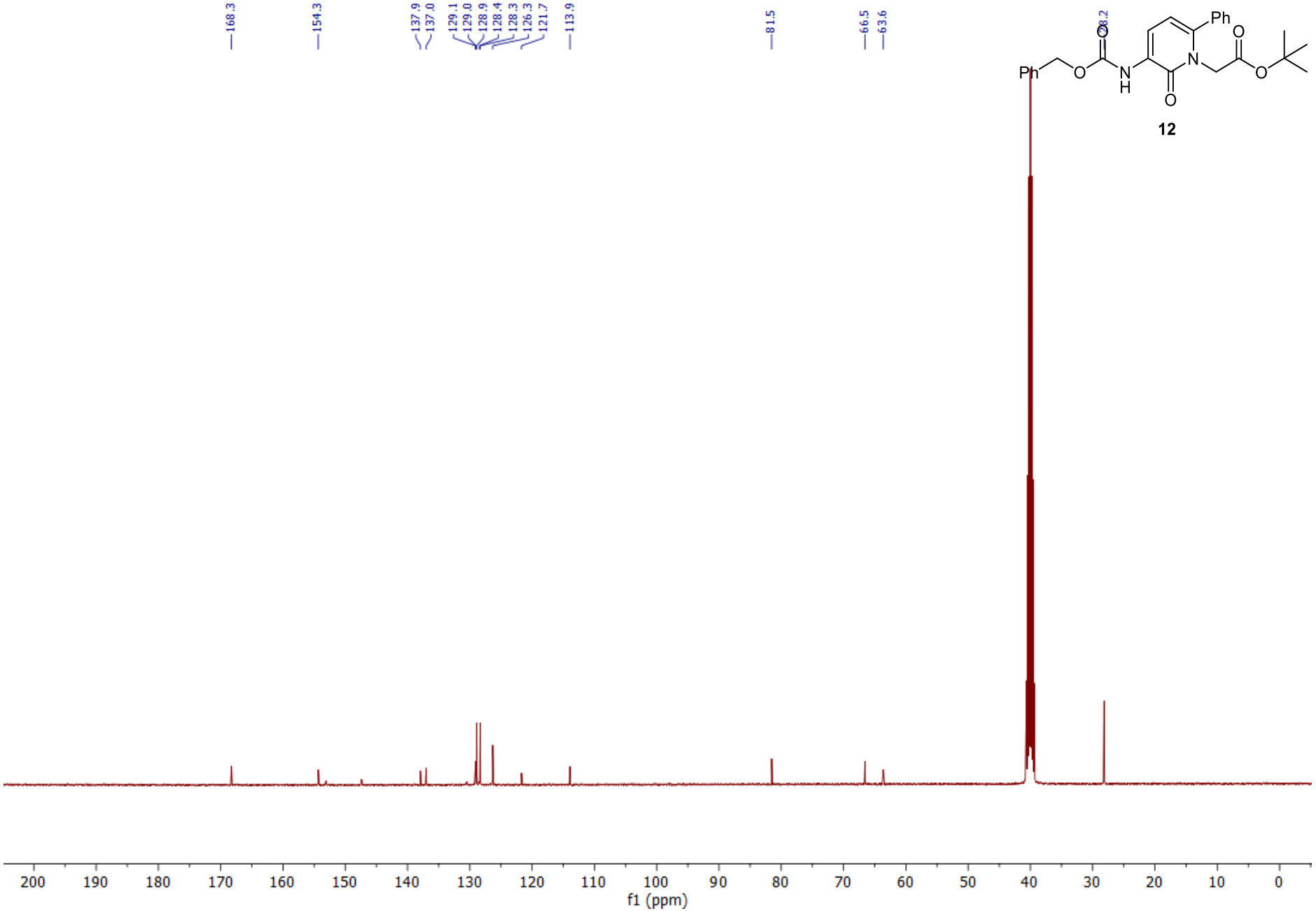
Benzyl (2-oxo-6-phenyl-1,2-dihydropyridin-3-yl)carbamate **11**



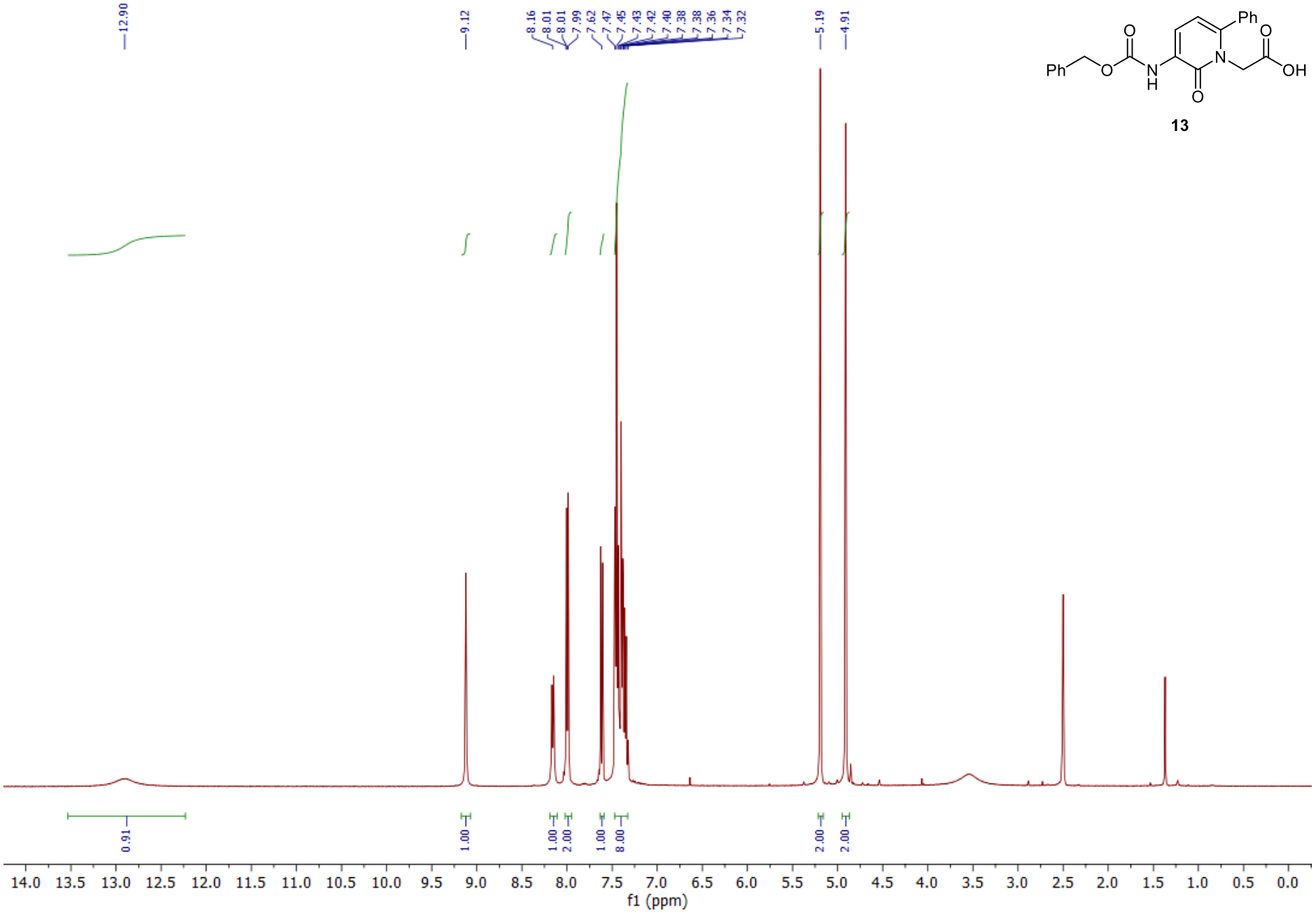
tert-Butyl 2-(3-(((benzyloxy)carbonyl)amino)-2-oxo-6-phenylpyridin-1(2H)-yl)acetate **12**



tert-Butyl 2-(3-(((benzyloxy)carbonyl)amino)-2-oxo-6-phenylpyridin-1(2H)-yl)acetate **12**

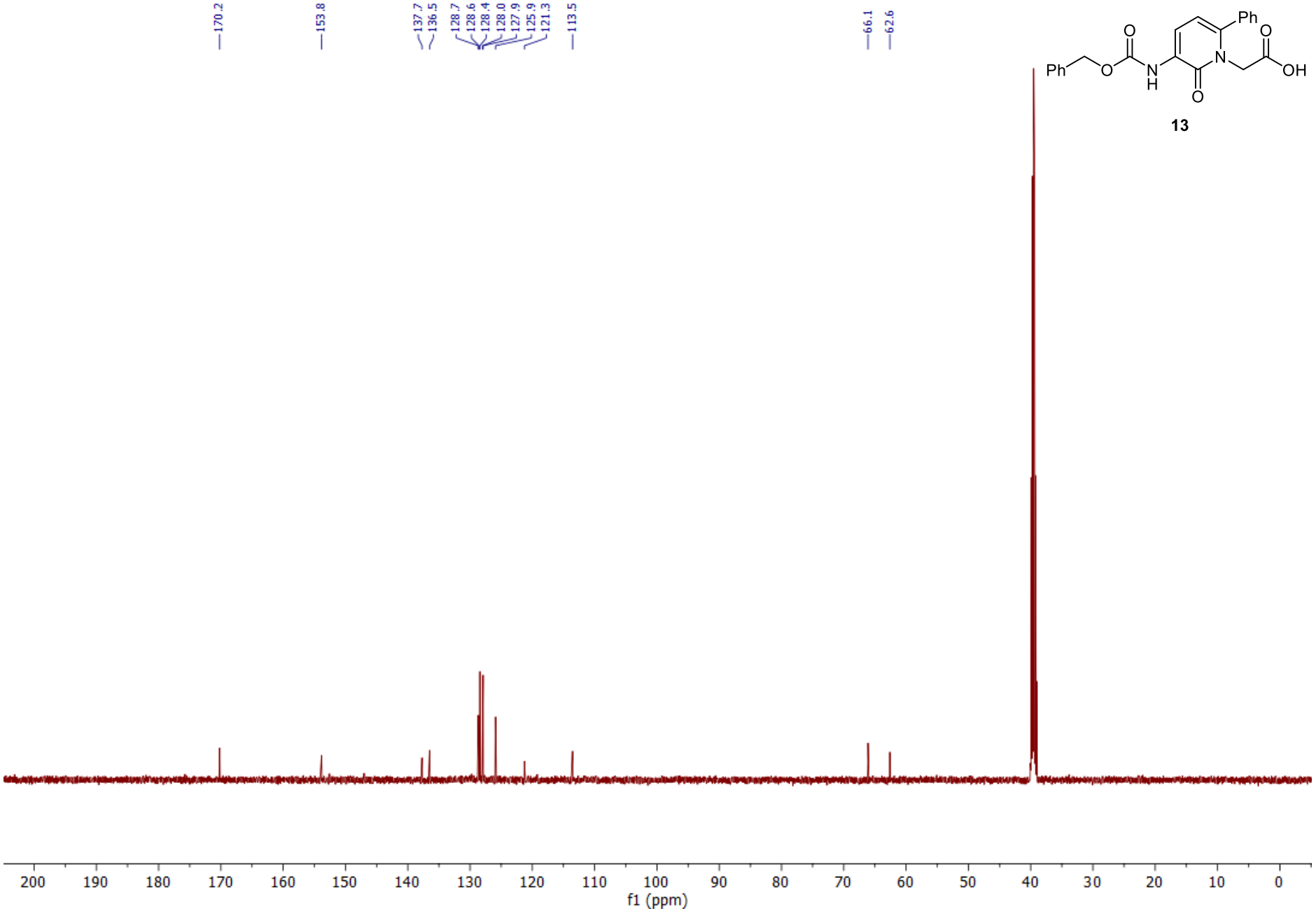


2-(3-(((Benzyloxy)carbonyl)amino)-2-oxo-6-phenylpyridin-1(2H)-yl)acetic acid **13**

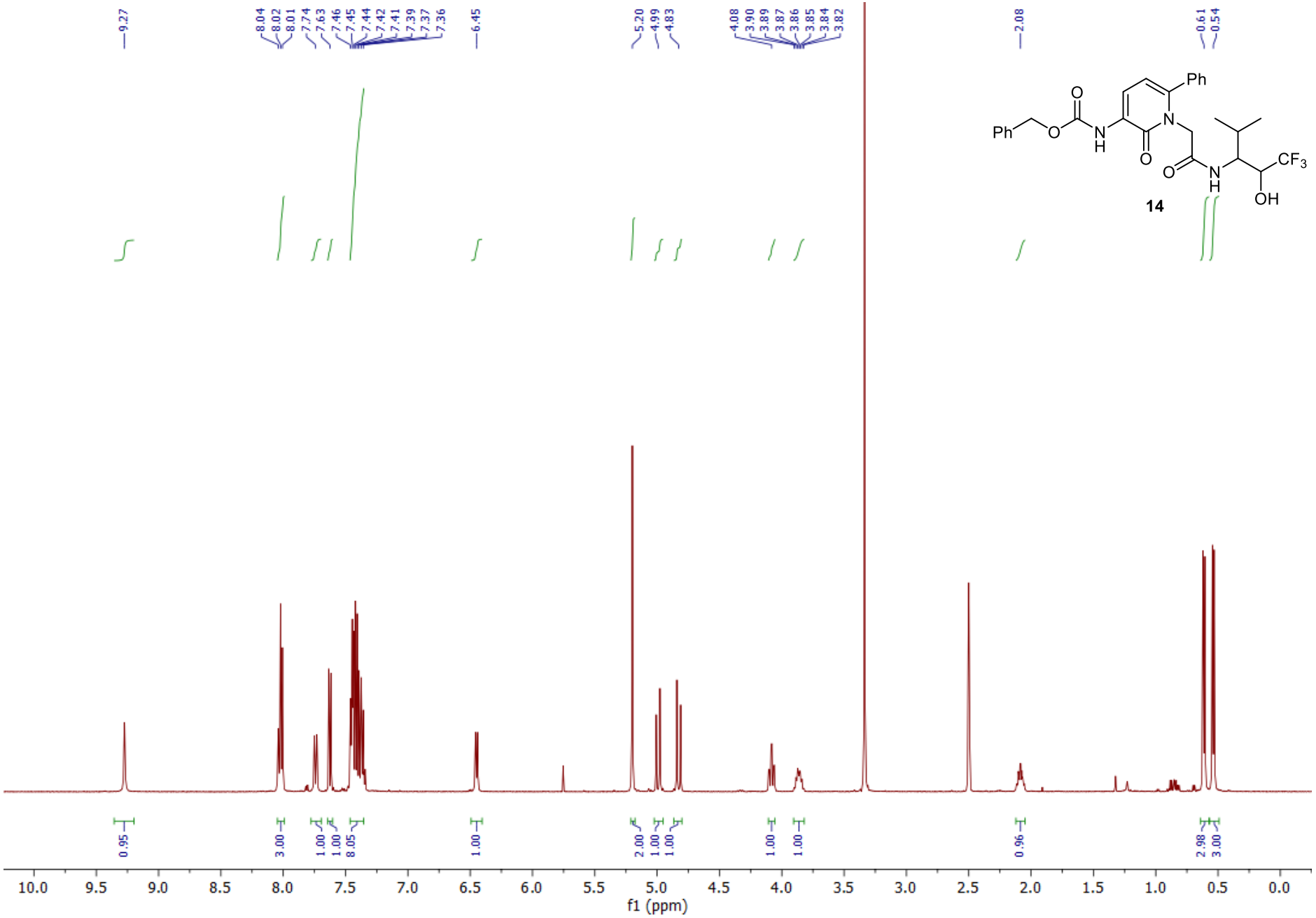


13

2-(3-(((Benzyloxy)carbonyl)amino)-2-oxo-6-phenylpyridin-1(2H)-yl)acetic acid **13**

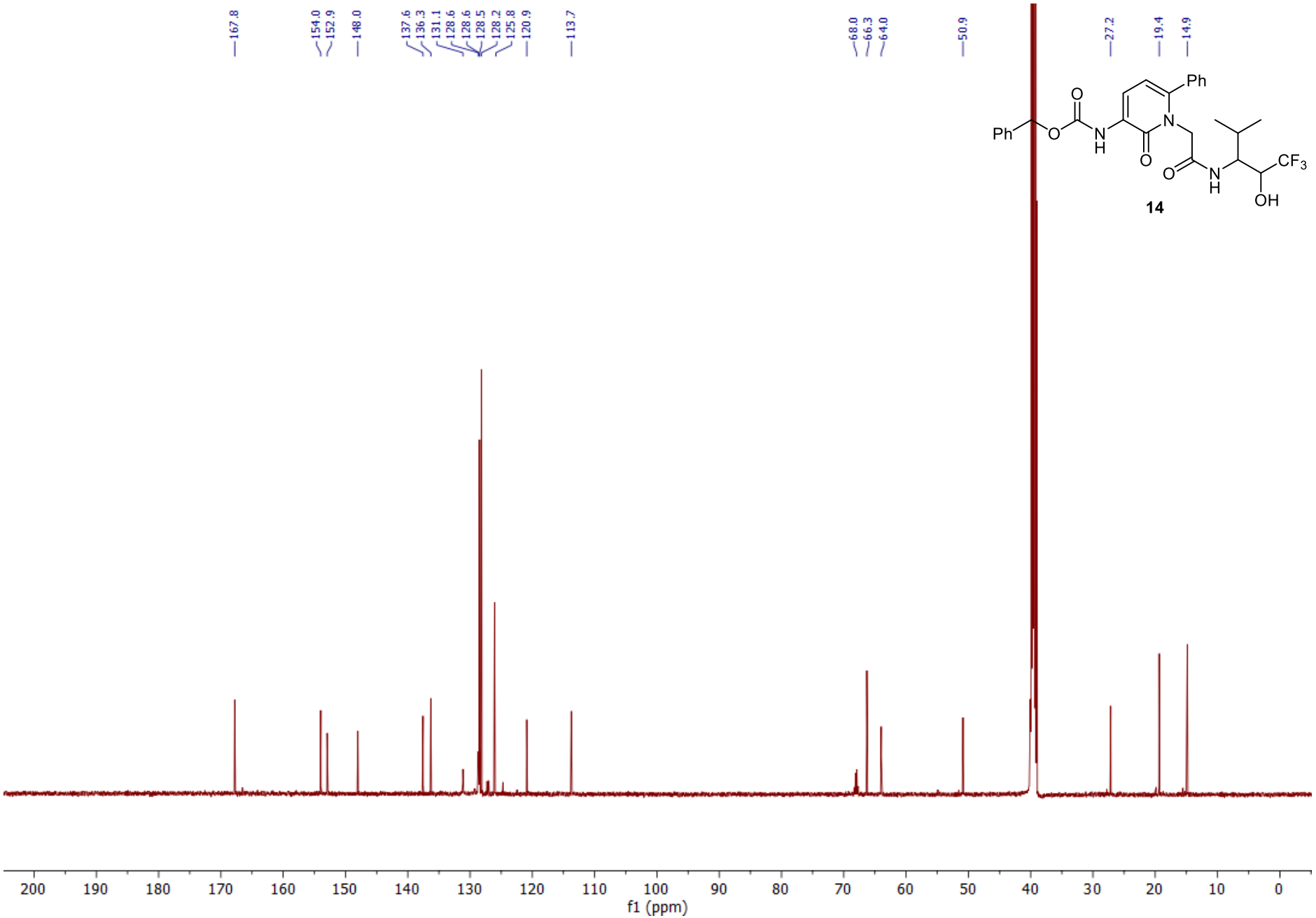


Benzyl (2-oxo-1-(2-oxo-2-((1,1,1-trifluoro-2-hydroxy-4-methylpentan-3-yl)amino)ethyl)-6-phenyl-1,2-dihydropyridin-3-yl)carbamate **14**

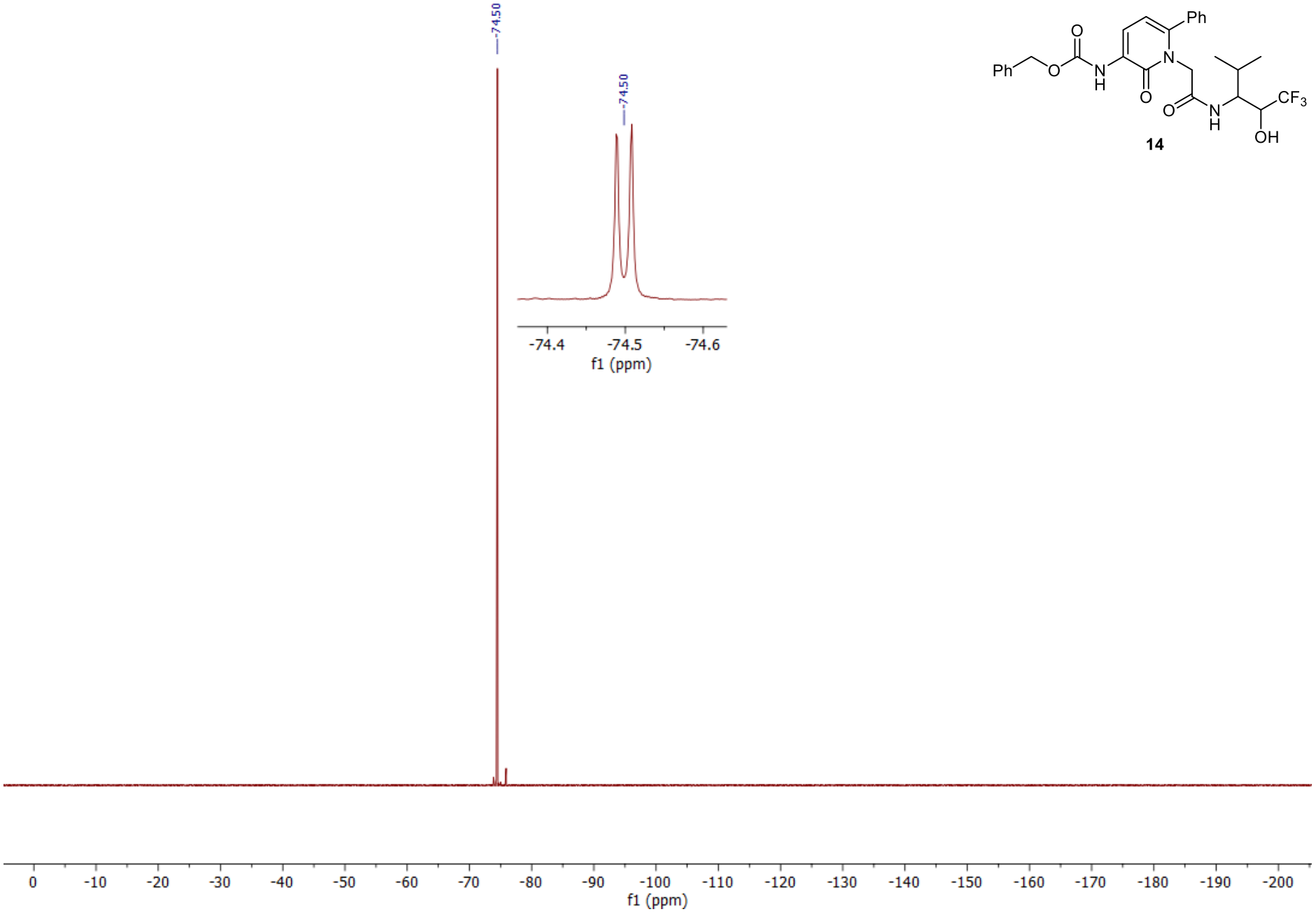


14

Benzyl (2-oxo-1-(2-oxo-2-((1,1,1-trifluoro-2-hydroxy-4-methylpentan-3-yl)amino)ethyl)-6-phenyl-1,2-dihydropyridin-3-yl)carbamate **14**

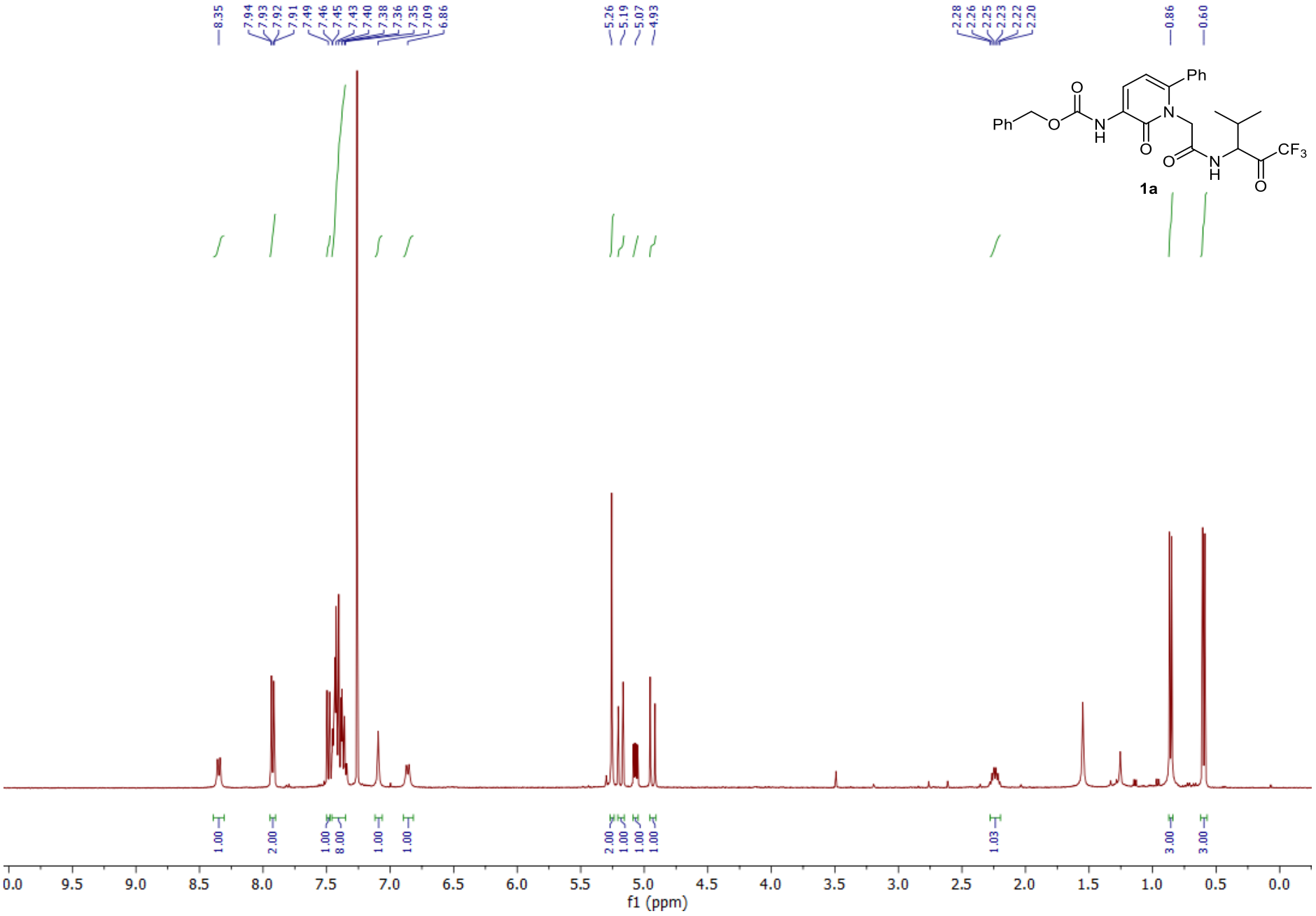


Benzyl (2-oxo-1-(2-oxo-2-((1,1,1-trifluoro-2-hydroxy-4-methylpentan-3-yl)amino)ethyl)-6-phenyl-1,2-dihydropyridin-3-yl)carbamate **14**



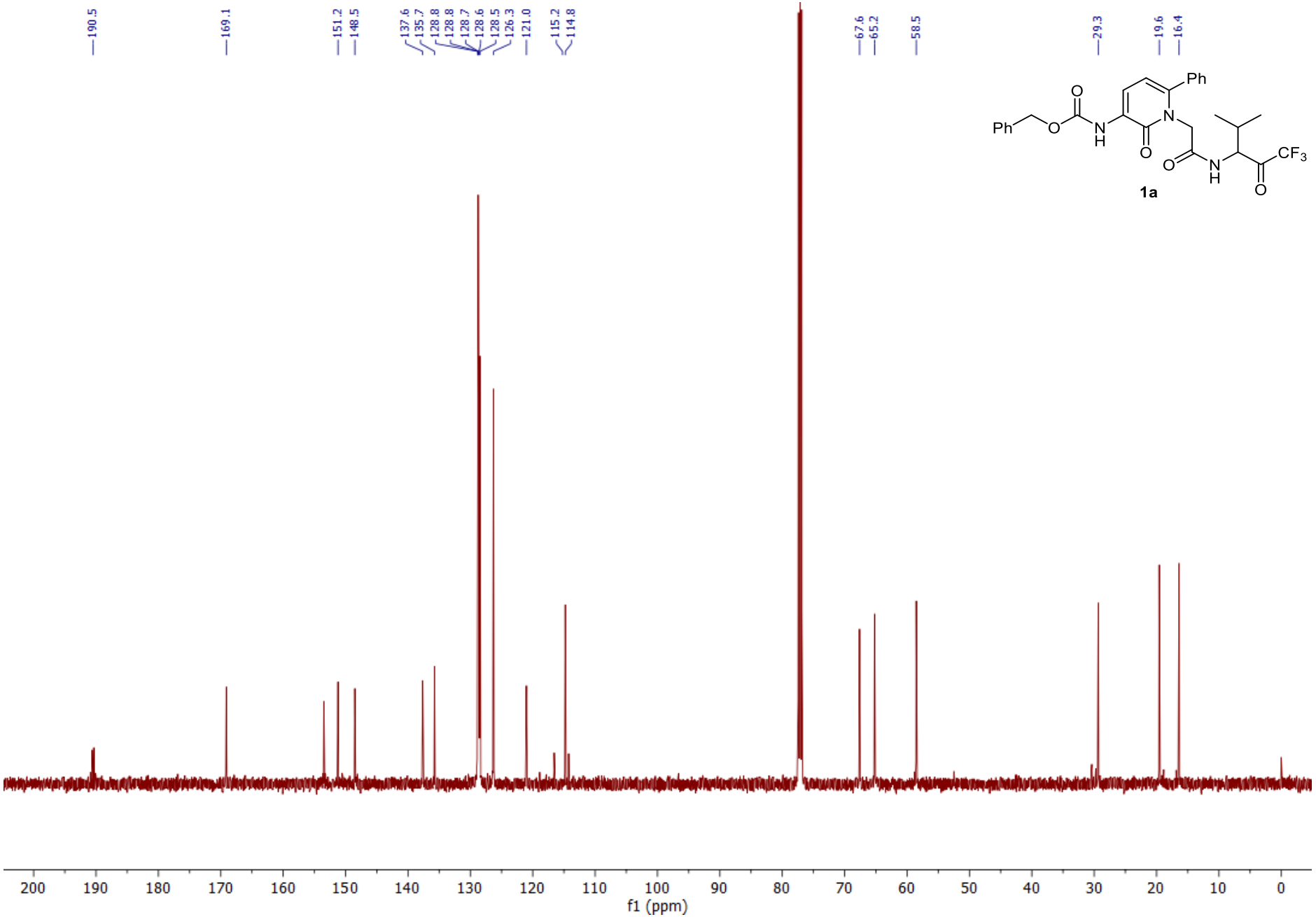
14

Benzyl (2-oxo-1-(2-oxo-2-((1,1,1-trifluoro-4-methyl-2-oxopentan-3-yl)amino)ethyl)-6-phenyl-1,2-dihydropyridin-3-yl)carbamate **1a**

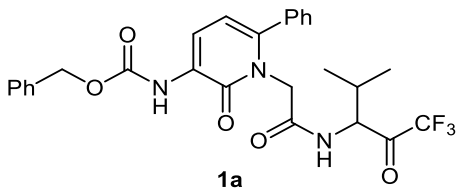


1a

Benzyl (2-oxo-1-(2-oxo-2-((1,1,1-trifluoro-4-methyl-2-oxopentan-3-yl)amino)ethyl)-6-phenyl-1,2-dihydropyridin-3-yl)carbamate **1a**

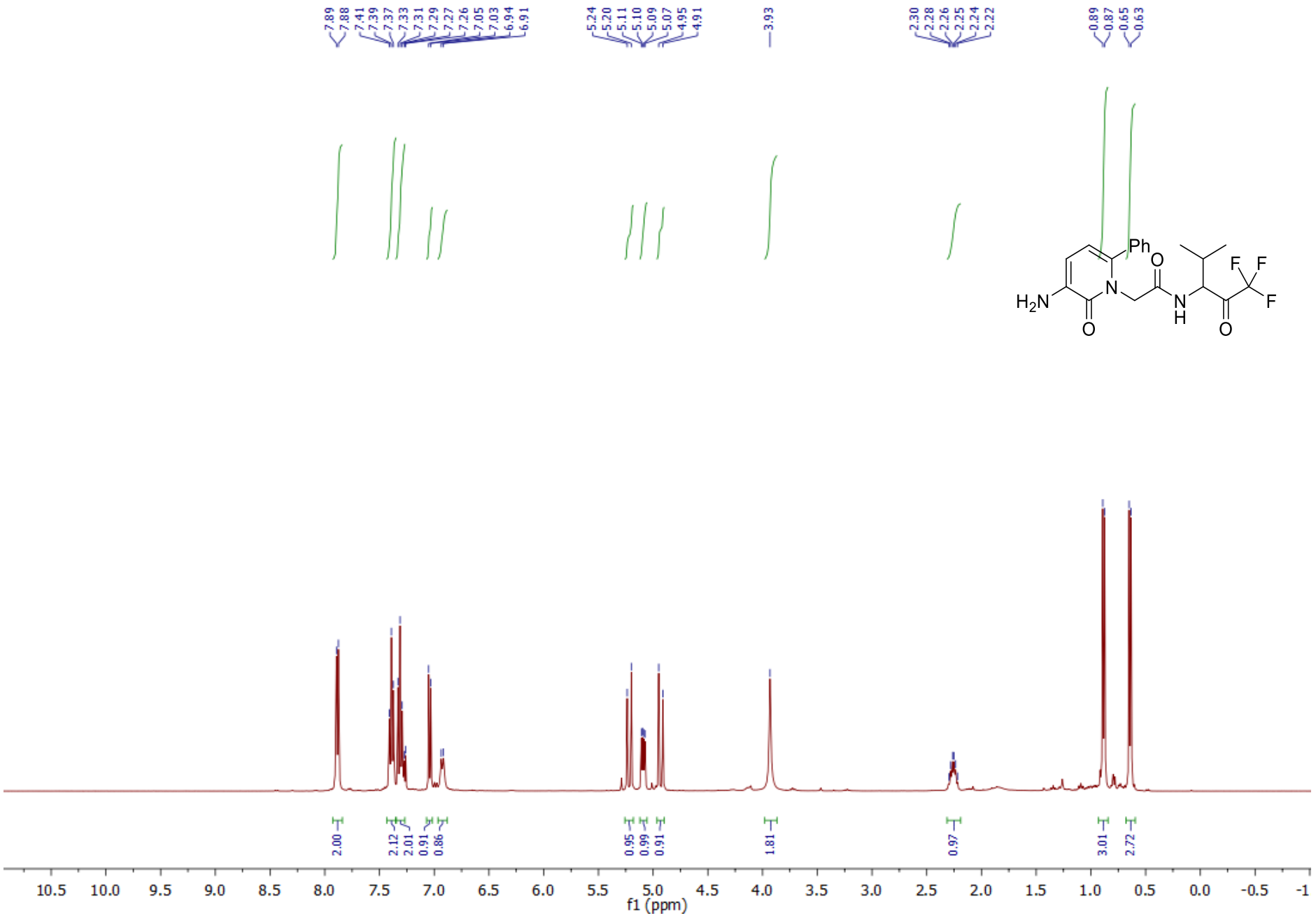


Benzyl (2-oxo-1-(2-oxo-2-((1,1,1-trifluoro-4-methyl-2-oxopentan-3-yl)amino)ethyl)-6-phenyl-1,2-dihydropyridin-3-yl)carbamate **1a**

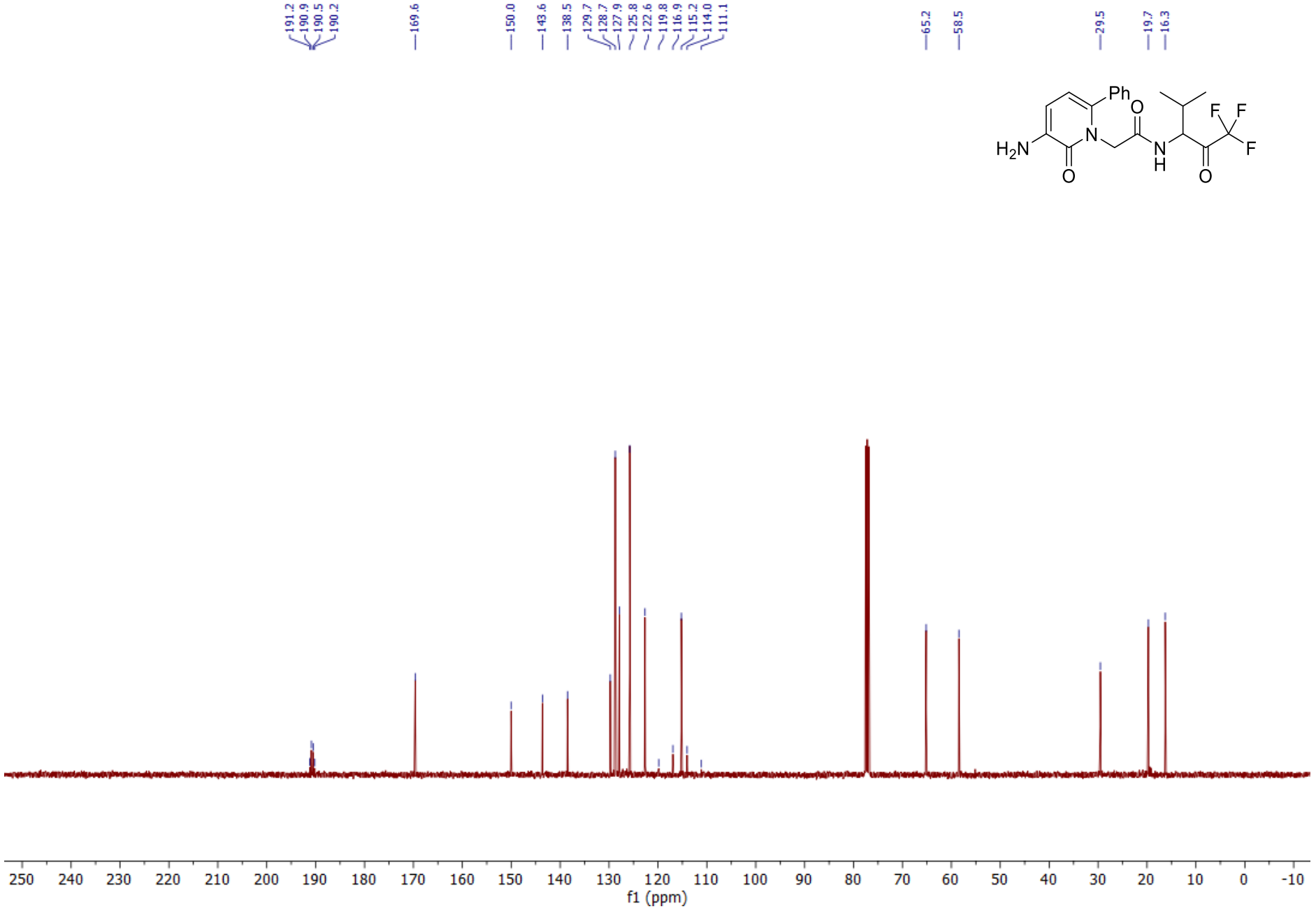


1a

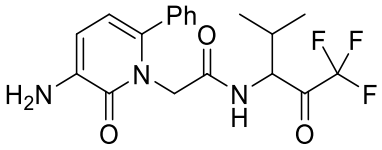
2-(3-amino-2-oxo-6-phenylpyridin-1(2*H*)-yl)-*N*-(1,1,1-trifluoro-4-methyl-2-oxopentan-3-yl)acetamide **1t**

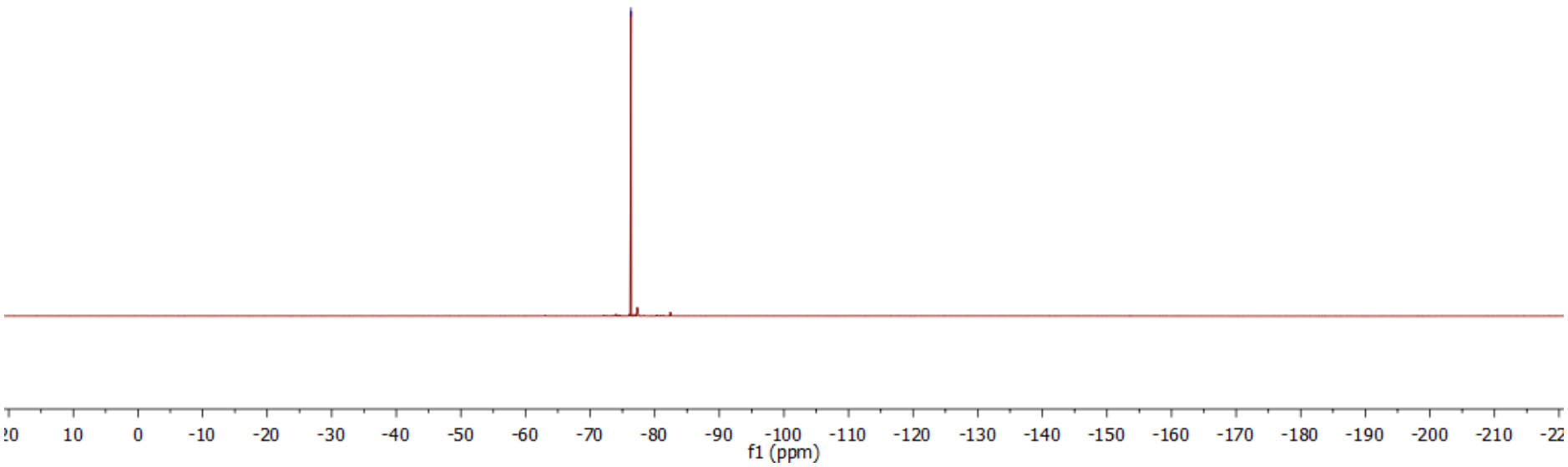


2-(3-amino-2-oxo-6-phenylpyridin-1(2*H*)-yl)-*N*-(1,1,1-trifluoro-4-methyl-2-oxopentan-3-yl)acetamide **1t**

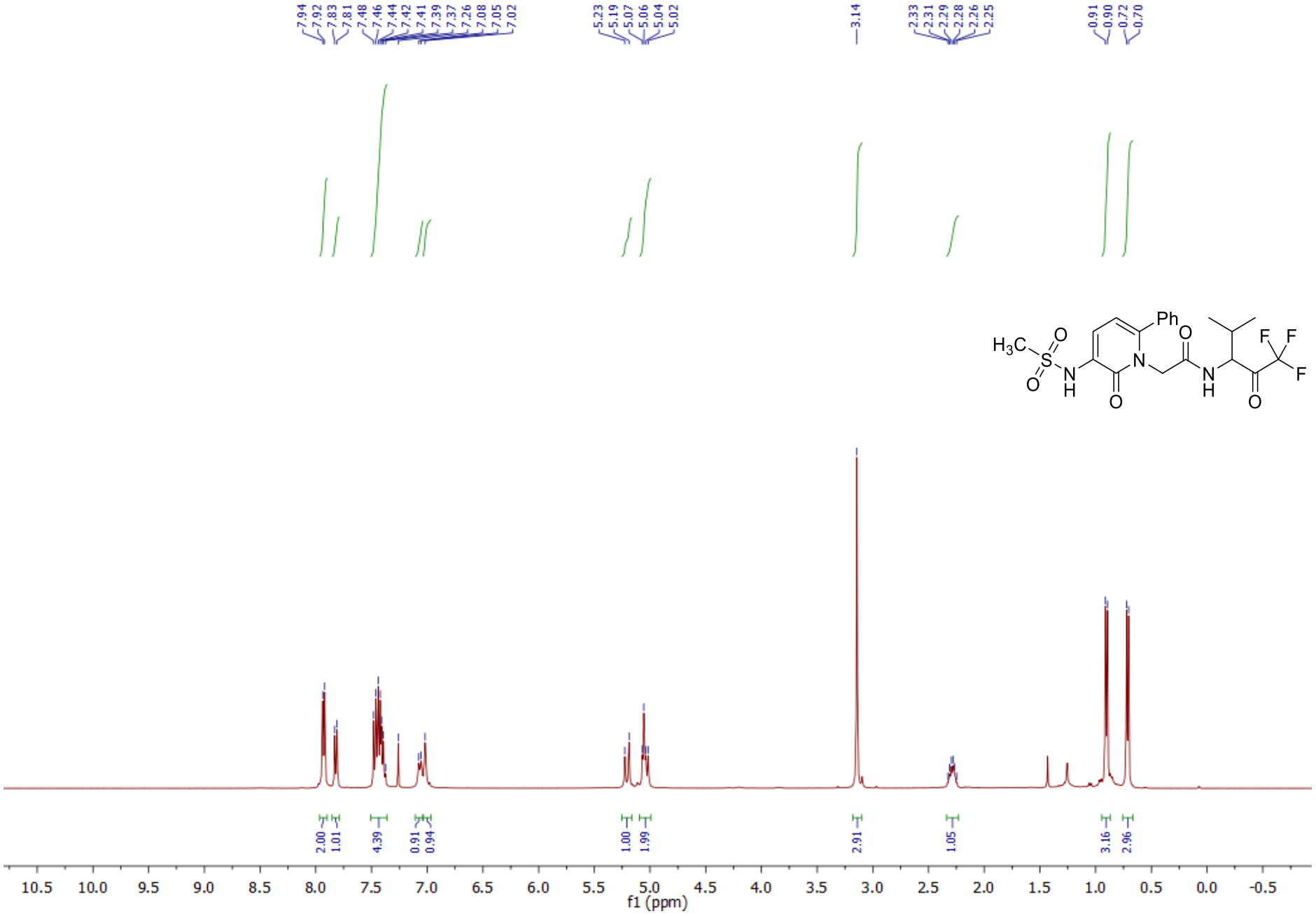


2-(3-amino-2-oxo-6-phenylpyridin-1(2*H*)-yl)-*N*-(1,1,1-trifluoro-4-methyl-2-oxopentan-3-yl)acetamide **1t**

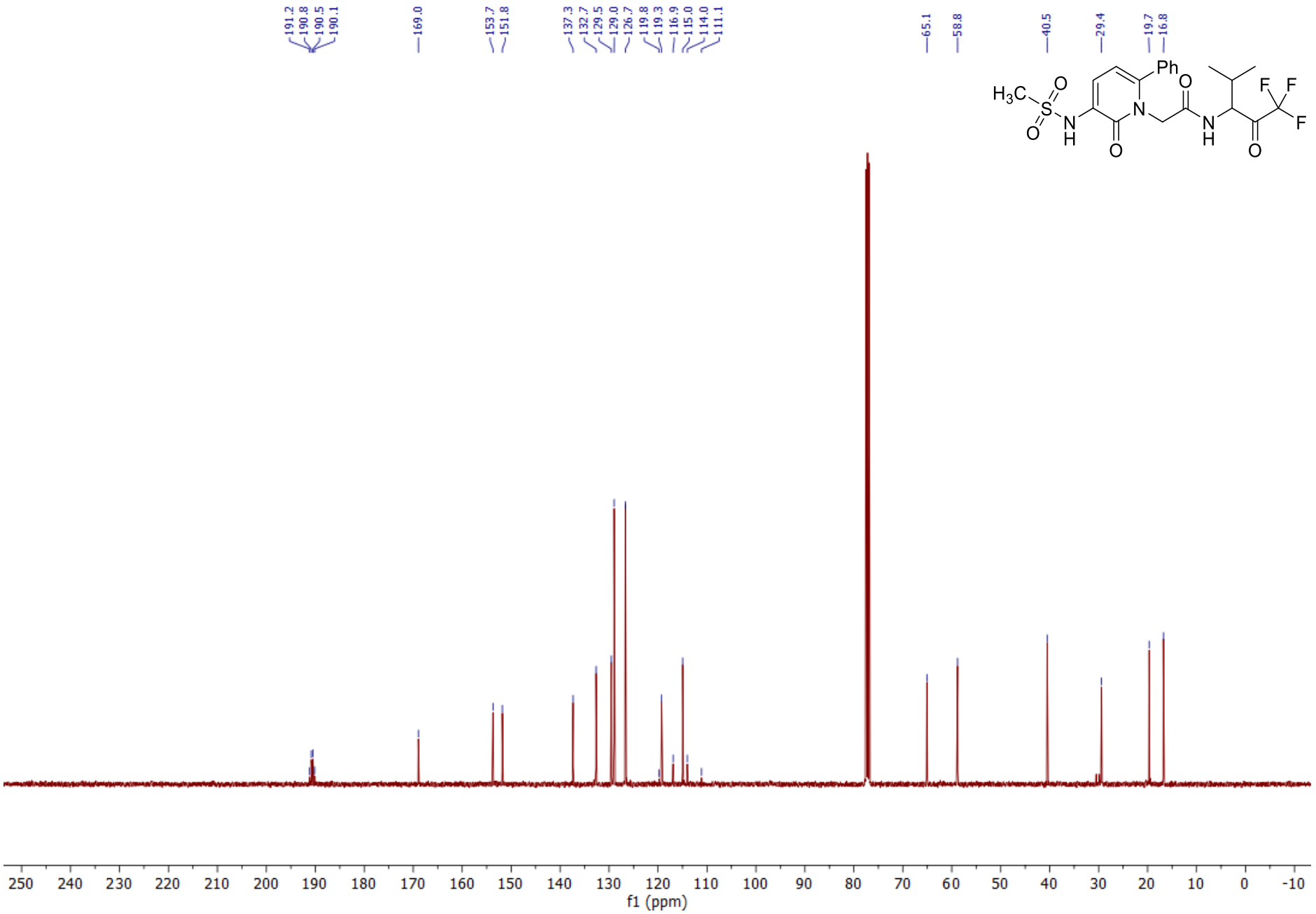




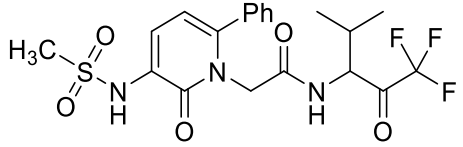
2-(3-(methylsulfonamido)-2-oxo-6-phenylpyridin-1(2*H*)-yl)-*N*-(1,1,1-trifluoro-4-methyl-2-oxopentan-3-yl)acetamide **1b**



2-(3-(methylsulfonamido)-2-oxo-6-phenylpyridin-1(2*H*)-yl)-*N*-(1,1,1-trifluoro-4-methyl-2-oxopentan-3-yl)acetamide **1b**



2-(3-(methylsulfonamido)-2-oxo-6-phenylpyridin-1(2*H*)-yl)-*N*-(1,1,1-trifluoro-4-methyl-2-oxopentan-3-yl)acetamide **1b**



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