SUPPORTING INFORMATION

Synthesis of 6-azaindoles via electrophilic [4+1]-cyclization of 3-amino-4-methyl pyridines: new frontiers of the diversity

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General information

All solvents were purified according to the standard procedures. All starting materials were obtained from Enamine Ltd. and used without additional purification. Melting points were measured on an automated melting point system. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H and 126 MHz for ^{13}C), Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H, 101 MHz for ^{13}C, and 376 MHz for ^{19}F), Agilent ProPulse 600 spectrometer (at 151 MHz for ^{13}C NMR), Varian Gemini 200 (at 188 MHz for ^{19}F), or Bruker Avance III (at 302 MHz for ^{1}H NMR and 76 MHz for ^{13}C NMR) in a DMSO-d_6, $CDCl_3$ or D_2O solution. NMR chemical shifts are reported in ppm units with the use of the δ scale and referenced using the solvent peaks at 7.26 and 77.1 ppm ($CDCl_3$) for ^{1}H and ^{13}C nuclei, respectively, and 2.48 and 39.5 ppm (DMSO-d_6) for ^{1}H and ^{13}C nuclei, respectively; hexafluorobenzene was uses as the internal standard for ^{19}F NMR. The following descriptions were used for the signal shapes in ^{1}H NMR spectra: s – for a singlet, d – a doublet, t – a triplet, q – a quartet, m – a multiplet. Elemental analyses were performed at the Laboratory of Organic Analysis, Institute of Organic Chemistry, National Academy of Sciences of Ukraine, their results were found to be in good agreement (±0.4%) with the calculated values. Mass spectra were recorded on Agilent 1100 LCMSD SL instrument (chemical ionization (APCI)). High-resolution mass spectra (HRMS) were obtained on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer. Full crystallographic details have been deposited at Cambridge Crystallographic Data Centre (CCDC). Any request to the CCDC for these materials should quote the full literature citation and reference number CCDC 2277541- 2277546. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Synthetic procedures for the compounds

General protocol for TFAA-assisted reactions (compounds 5a-i, 6j-m, 7 and 8)

To a solution of corresponding pyridine **1** (1 mmol) in Pyridine (5 mL) trifluoroacetic anhydride (3.3 equiv) was added at 0ºC. Cooling bath was then removed and the reaction mixture was left to stir for 48h. After that the mixture was diluted with water and extracted with $CHCl_3$. Organic layer was washed with brine, dried over Na_2SO_4 and evaporated to dryness. The residue was purified by silica gel column chromatography using EtOAC – Hex (0-5%) as eluent to give a title product.

The described procedure was also used for multi-gram synthesis of compound **5a**.

Compounds **17-20** were obtained by the same protocol using acetic anhydride, difluoroacetic anhydride or trichloroacetic anhydride instead of TFAA, respectively.

Compounds **6a**, **17** and **21** were synthesized according to above-mentioned procedure, but using 1.3 equiv of a corresponding anhydride.

Synthesis of compound 10

A mixture of compound **5c** (0.314 g, 0.001 mol) and Na_2CO_3 (2.0 equiv) in water (3 mL) was heated at 50ºC for 2 days. After that, the content was cooled to room temperature and acidified with $NaHSO_4$ to pH 5. A precipitate formed was collected by filtration, washed with water and dried in air affording acid **10**.

Synthesis of compound 11

A solution of compound **5a** (0.282 g, 0.001 mol) and MeI (1.0 equiv) in DCM (5 mL) was allowed to react for 3 days at room temperature. After the time elapsed the reaction mixture was evaporated to dryness and the residue was treated with aq. Na_2CO_3. A precipitate formed was collected by filtration, washed with water and dried in air affording acid **11**.

Synthesis of compound 12

A mixture of compound **11** (0.296 g, 0.001 mol) and Na_2CO_3 (2.0 equiv) in water (3 mL) was heated at 50ºC for 2 days. After that, the content was cooled to room temperature and acidified with $NaHSO_4$ to pH 5. Precipitate formed was collected by filtration, washed with water and dried in air affording acid **12**.

Synthesis of compound 13

A mixture of compound **5a** (0.282 g, 0.001 mol) and Na_2CO_3 (3.0 equiv) in water (5 mL) was heated at 80ºC for 16 hours. After that, the content was cooled to room temperature, a solid formed was collected by filtration, washed with water and dried in air affording trifluoromethyl derivative **13**.

Synthesis of compound 14

A mixture of compound **13** (0.186 g, 0.001 mol) and Na_2CO_3 (2.0 equiv) in water (3 mL) was set to reflux and the reaction was monitored by TLC (EtOAC – Hex (10:1)). After the starting compound was exhausted, the content was cooled to room temperature and acidified with $NaHSO_4$ to pH 5. A precipitate formed was collected by filtration, washed with water and dried in air affording acid **14**.

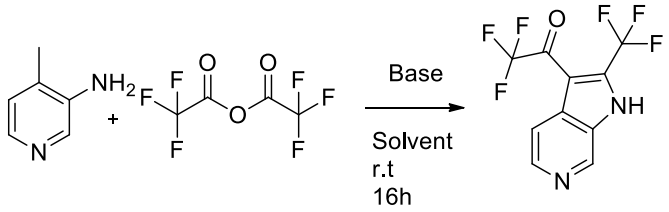
Synthesis of compound 15

A mixture of compound **5b** (0.301 g, 0.001 mol) and Na_2CO_3 (2.0 equiv) in water (3 mL) was heated at 50ºC for 2 days. After that, the content was cooled to room temperature and acidified with $NaHSO_4$ to pH 5. A precipitate formed was collected by filtration, washed with water and dried in air affording acid **15**.

Synthesis of compound 16

Solution of compound **1a** in DMF (0.6 M, 5.0 g in 77 mL) was cooled to 0ºC and $POCl_3$ (3.3 equiv) was added dropwise maintaining the temperature below 10ºC. After addition was completed, the mixture was stirred for 48 hours at room temperature. Then a precipitate formed was filtered off and treated with aq. NaOH. A solid was filtered off, washed with water giving formyl derivative **16**.

VALIDATION EXPERIMENT

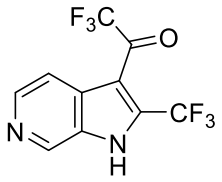


TFAA (3.3 eq) was added at room temperature to a solution of **4-methylpyridin-3-amine** (100 mg) and **BASE** (6.6 eq) in **SOLVENT** (4 ml) and left to stirred overnight. After the reaction mixture was analyzed by LCMS

Solvent	Base	Conversion by LCMS, %
THF	DMAP	0
THF	Py	75
THF	TEA	25.3
THF	DIPEA	15
dioxane	DMAP	0
dioxane	Py	87
dioxane	TEA	26
dioxane	DIPEA	11
DCM	DMAP	0
DCM	Py	92
DCM	TEA	44
DCM	DIPEA	21
toluene	DMAP	0
toluene	Py	27
toluene	TEA	29.5
toluene	DIPEA	24

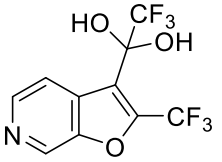
Characterization of the compounds synthesized

2,2,2-Trifluoro-1-(2-(trifluoromethyl)-1*H*-pyrrolo[2,3-*c*]pyridin-3-yl)ethan-1-one (5a)



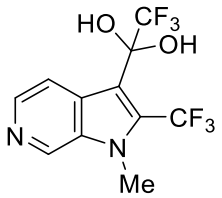
Light brown powder, yield 231 mg (82%), mp 253-254 °C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 14.44 (s, 1H), 9.25 (s, 1H), 8.27 (d, J = 6.7 Hz, 1H), 8.00 (d, J = 6.7 Hz, 1H). ^{19}F NMR (188 MHz, $CDCl_3$) δ -64.58 (s), -75.26 (s). ^{13}C NMR (76 MHz, DMSO-d_6) δ 171.62 (q, J = 35.8 Hz), 152.72 (q, J = 35.9 Hz), 141.61, 138.52, 134.92, 130.19, 122.01 (q, J = 271.3 Hz), 117.45 (q, J = 291.1 Hz), 115.94 (q, J = 5.7 Hz), 106.43. MS (ES-API) (*m/z*): 283 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_{10}H_5F_6N_2O^+$ $[M + H]^+$: 283.0306; found 283.0305. Anal. Calcd for $C_{10}H_4F_6N_2O$: C 42.57; H 1.43; N 9.93. Found, %: C 41.93; H 1.46; N 10.04.

2,2,2-Trifluoro-1-(2-(trifluoromethyl)furo[2,3-*c*]pyridin-3-yl)ethane-1,1-diol (5b)



White crystals, yield 105 mg (35%), mp 122-123 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (s, 1H), 8.55 (s, 1H), 8.43 (s, 2H), 7.91 (s, 1H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -59.17 (s), -83.91 (s). ^{13}C NMR (126 MHz, DMSO-d_6) δ 150.19, 143.93, 143.16 (q, J = 41.6 Hz), 135.72, 132.55, 126.82, 124.53, 122.08, 120.26, 118.78, 118.10, 91.76 (q, J = 34.0 Hz). MS (ES-API) (*m/z*): 302 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_{10}H_6F_6NO_3^+$ $[M+H]^+$: 302.0246; found 302.0245. Anal. Calcd for $C_{10}H_5F_6NO_3$: C 39.88; H 1.67; N 4.65. Found, %: C 40.01; H 1.66; N 4.72.

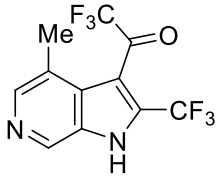
2,2,2-Trifluoro-1-(1-methyl-2-(trifluoromethyl)-1*H*-pyrrolo[2,3-*c*]pyridin-3-yl)ethane-1,1-diol (5c)



White crystals, yield 210 mg (67%), mp 93-94 °C. ^{1}H NMR (400 MHz, Deuterium Oxide) δ 9.20 (s, 1H), 8.41 (d, J = 6.6 Hz, 1H), 8.16 (d, J = 6.7 Hz, 1H), 4.65 (s, 5H), 4.12 – 3.88 (m, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -55.48 (q, J = 6.2 Hz),

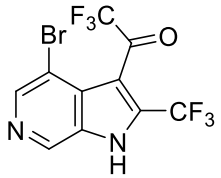
-85.31 (q, *J* = 6.3 Hz). ^{13}C NMR (76 MHz, D_2O) δ 135.18 (q, *J* = 39 Hz), 135.29, 132.90, 128.86, 128.60, 122.57 (q, *J* = 288 Hz), 120.62, 119.40 (q, *J* = 273 Hz), 115.45 (q, *J* = 2.3 Hz), 92.32 (q, *J* = 41.8 Hz), 33.85 (q, *J* = 4.6 Hz). MS (ES-API) (*m/z*): 315 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_{11}H_9F_6N_2O_2^+$ $[M+H]^+$: 315.0568; found 315.0562. Anal. Calcd for $C_{11}H_8F_6N_2O_2$: C 42.05; H 2.57; N 8.92. Found,%: C 41.98; H 2.56; N 9.01.

2,2,2-Trifluoro-1-(4-methyl-2-(trifluoromethyl)-1*H*-pyrrolo[2,3-*c*]pyridin-3-yl)ethan-1-one (5d)



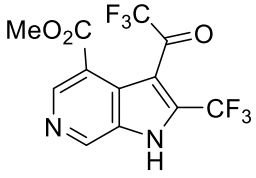
White crystals, yield 231 mg (78%), mp 195-197 °C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 9.09 (s, 1H), 7.99 (s, 1H), 2.33 (s, 3H). ^{19}F NMR (188 MHz, Chloroform-*d*) δ -61.13 (q, *J* = 7.7 Hz), -75.79 (q, *J* = 7.7 Hz). ^{13}C NMR (76 MHz, DMSO-d_6) δ 182.10 (q, *J* = 40.3 Hz), 147.69 (q, *J* = 34.2 Hz), 140.75, 138.49, 132.60, 127.34, 126.90, 122.21 (q, *J* = 272 Hz), 116.13 (q, *J* = 292 Hz), 107.10, 17.33. MS (ES-API) (*m/z*): 297 $[M + H]^+$. HRMS (ESI-TOF) for **5d·H_2O** calcd for $C_{11}H_9F_6N_2O_2^+$ $[M+H]^+$: 315.0568; found 315.0561. Anal. Calcd for $C_{11}H_6F_6N_2O$: C 44.61; H 2.04; N 9.46. Found,%: C 44.92; H 2.01; N 9.29.

1-(4-Bromo-2-(trifluoromethyl)-1*H*-pyrrolo[2,3-*c*]pyridin-3-yl)-2,2,2-trifluoroethan-1-one (5e)



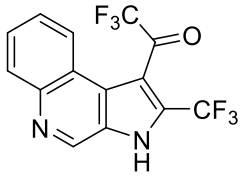
White crystals, yield 165 mg (46%), mp 205-207 °C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 9.24 (s, 1H), 8.46 (s, 1H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -59.92 (q, *J* = 4.7 Hz), -75.27 (q, *J* = 4.7 Hz). ^{13}C NMR (76 MHz, DMSO-d_6) δ 182.91 (q, *J* = 37.2 Hz), 139.45, 135.97, 134.63, 130.98, 121.68 (q, *J* = 272 Hz), 115.93 (q, *J* = 292 Hz), 113.59, 109.62, 107.08. MS (ES-API) (*m/z*): 361 $[M + H]^+$. HRMS (ESI-TOF) for **5e·H_2O** calcd for $C_{10}H_6BrF_6N_2O_2^+$ $[M+H]^+$: 378.9517; found 378.9510. Anal. Calcd for $C_{10}H_3BrF_6N_2O$: C 33.27; H 0.84; N 7.76. Found, %:C 33.14; H 0.87; N 7.52.

Methyl 3-(2,2,2-trifluoroacetyl)-2-(trifluoromethyl)-1*H*-pyrrolo[2,3-*c*]pyridine-4-carboxylate (5f)



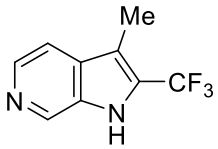
White crystals, yield 291 mg (85%), mp 193-194 °C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 9.31, 8.68, 3.87, 2.48. ^{19}F NMR ($CDCl_3$, 188 MHz) δ -78.77 (s), -61.90 (s). ^{13}C NMR (76 MHz, DMSO-d_6) δ 181.28 (q, J = 35.7 Hz), 165.96, 150.93, 140.18, 137.60, 133.20, 132.67, 121.62 (q, J = 273 Hz), 117.36, 116.59 (q, J = 292 Hz), 106.91, 53.17. MS (ES-API) (*m/z*): 341 $[M+H]^+$. HRMS (ESI-TOF) calcd for $C_{12}H_7F_6N_2O_3^+$ $[M+H]^+$: 341.0361; found 341.0354. Anal. Calcd for $C_{12}H_6F_6N_2O_3$: C 33.27; H 0.84; N 7.76. Found, %: C 33.14; H 0.87; N 7.52.

2,2,2-Trifluoro-1-(2-(trifluoromethyl)-3*H*-pyrrolo[2,3-*c*]quinolin-1-yl)ethan-1-one (5g)



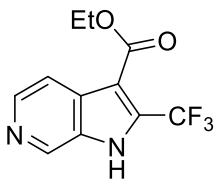
Light brown powder, yield 289 mg (86%), mp 245-247 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.15 (dd, J = 8.5, 1.4 Hz, 1H), 8.12 (dd, J = 8.5, 1.5 Hz, 1H), 7.78 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H), 7.72 (ddd, J = 8.3, 7.0, 1.4 Hz, 1H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -58.96 (q, J = 7.2 Hz), -74.59 (q, J = 7.2 Hz). ^{13}C NMR (101 MHz, DMSO) δ 183.81 (q, J = 35.4 Hz), 139.38, 137.08, 133.62, 133.07, 129.19, 127.89, 123.82, 123.54, 122.45, 122.30, 120.85, 117.71, 114.81, 108.95. MS (ES-API) (*m/z*): 333 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_{14}H_7F_6N_2O^+$ $[M+H]^+$: 333.0463; found 333.0456. Anal. Calcd for $C_{14}H_6F_6N_2O$: C 50.62; H 1.82; N 8.43. Found, %: C 50.44; H 1.87; N 8.52.

3-Methyl-2-(trifluoromethyl)-1*H*-pyrrolo[2,3-*c*]pyridine (5h)



Brown powder, yield 166 mg (83%), mp >250 °C (sublimates at 230°C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (s, 1H), 8.20 (d, J = 6.0 Hz, 1H), 7.63 (d, J = 5.6 Hz, 1H), 2.37 (s, 3H). ^{19}F NMR (DMSO, 376 MHz) δ -58.09 (s). ^{13}C NMR (101 MHz, DMSO) δ 138.16, 136.21, 133.36, 131.95, 125.88 (q, J = 36.4 Hz), 122.46 (q, J = 269.7 Hz), 114.68, 111.90, 8.37. MS (ES-API) (*m/z*): 201 $[M+H]^+$. HRMS (ESI-TOF) calcd for $C_9H_8F_3N_2^+$ $[M+H]^+$: 201.0640; found 201.0633. Anal. Calcd for $C_9H_7F_3N_2$: C 54.01; H 3.53; N 14.00. Found, %: C 53.92; H 3.48; N 14.13.

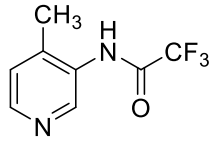
Ethyl 2-(trifluoromethyl)-1*H*-pyrrolo[2,3-*c*]pyridine-3-carboxylate (5i)



Brown powder, yield 235 mg (91%), mp 212-216 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.18 (s, 1H), 9.13 (s, 1H), 8.27 – 8.11 (m, 2H), 4.25 (q, J = 7.1 Hz, 2H), 1.28

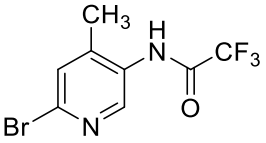
(t, *J* = 7.0 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.78 (s). ^{13}C NMR (126 MHz, DMSO) δ 161.90, 144.65 (q, *J* = 36.5 Hz), 137.39, 136.17, 132.87, 129.39, 121.03 (q, *J* = 272.1 Hz), 116.93, 104.82, 59.70, 13.96. MS (ES-API) (*m/z*): 259 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_{11}H_{10}F_3N_2O_2^+$ $[M+H]^+$: 259.0694; found 259.0686. Anal. Calcd for $C_{11}H_9F_3N_2O_2$: C 51.17; H 3.51; N 10.85. Found, %: C 51.30; H 3.39; N 11.01.

2,2,2-Trifluoro-N-(4-methylpyridin-3-yl)acetamide (6a)



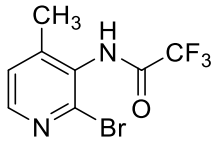
Oil, yield 159 mg (78%). ^{1}H NMR (302 MHz, DMSO-d_6) δ 11.23 (s, 1H), 8.57 – 8.31 (m, 2H), 7.34 (d, *J* = 5.2 Hz, 1H), 2.20 (s, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -74.48 (s). ^{13}C NMR (151 MHz, dmso) δ 155.93 (q, *J* = 37.8 Hz), 148.67, 147.79, 143.84, 130.90, 126.02, 116.38 (q, *J* = 288.4 Hz), 17.25. MS (ES-API) (*m/z*): 333 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_8H_8F_3N_2O^+$ $[M+H]^+$: 205.0583; found 205.0579. Anal. Calcd for $C_8H_7F_3N_2O$: C 47.07; H 3.46; N 13.72. Found, %: C 47.28; H 3.45; N 13.12.

N-(6-Bromo-4-methylpyridin-3-yl)-2,2,2-trifluoroacetamide (6j)



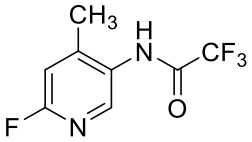
Oil, yield 127 mg (45%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.23 (s, 1H), 8.30 (s, 1H), 7.69 (s, 1H), 2.21 (s, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -74.41 (s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.58 (q, *J* = 37.8 Hz), 147.87, 147.29, 139.52, 130.77, 129.30, 115.85 (q, *J* = 288.5 Hz), 16.71. MS (ES-API) (*m/z*): 283 $[M+H]^+$. HRMS (ESI-TOF) calcd for $C_8H_7BrF_3N_2O^+$ $[M+H]^+$: 282.9694; found 282.9686. Anal. Calcd for $C_8H_6BrF_3N_2O$: C 33.95; H 2.14; N 9.90. Found, %: C 33.92; H 2.17; N 9.89.

N-(2-Bromo-4-methylpyridin-3-yl)-2,2,2-trifluoroacetamide (6k)



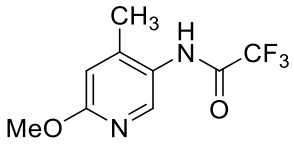
Oil, yield 147 mg (52%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.47 (s, 1H), 8.28 (d, *J* = 4.9 Hz, 1H), 7.45 (d, *J* = 4.9 Hz, 1H), 2.25 (s, 3H). ^{19}F NMR (DMSO-*d6*, 376 MHz) δ -74.75 (s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.15 (q, *J* = 37.8 Hz), 149.11, 148.38, 142.05, 130.21, 125.69, 115.85 (q, *J* = 288.5 Hz), 17.54. MS (ES-API) (*m/z*): 283 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_8H_7BrF_3N_2O^+$ $[M+H]^+$: 282.9694; found 282.9687. Anal. Calcd for $C_8H_6BrF_3N_2O$: C 33.95; H 2.14; N 9.90. Found, %: C 33.99; H 2.15; N 9.85.

2,2,2-Trifluoro-N-(6-fluoro-4-methylpyridin-3-yl)acetamide (6l)



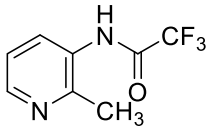
Oil, yield 107 mg (48%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.14 (s, 1H), 8.14 (s, 1H), 7.20 (s, 1H), 2.25 (s, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -72.08 (s), -74.52 (s). ^{13}C NMR (101 MHz, DMSO) δ 162.20 (d, *J* = 237.4 Hz), 156.26 (q, *J* = 37.4 Hz), 150.68 (d, *J* = 10.1 Hz), 145.65 (d, *J* = 17.2 Hz), 129.56, 116.40 (q, *J* = 289.9 Hz), 111.00 (d, *J* = 39.4 Hz), 17.65. MS (ES-API) (*m/z*): 223 [M + H]$^{+}$. HRMS (ESI-TOF) calcd for $C_8H_7F_4N_2O^{+}$ [M+H]$^{+}$: 223.0495; found 223.0485. Anal. Calcd for $C_8H_6F_4N_2O$: C 43.26; H 2.72; N 12.61. Found, %: C 43.37; H 2.67; N 12.77.

2,2,2-Trifluoro-N-(6-methoxy-4-methylpyridin-3-yl)acetamide (6m)



Oil, yield 124 mg (53%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 8.04 (s, 1H), 6.80 (s, 1H), 3.85 (s, 3H), 2.16 (s, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -74.51 (s). ^{13}C NMR (101 MHz, DMSO) δ 163.25, 156.36 (q, *J* = 36.4 Hz), 147.41, 145.03, 125.36, 116.52 (q, *J* = 282.9 Hz), 111.58, 53.75, 17.38. MS (ES-API) (*m/z*): 235 [M + H]$^{+}$. HRMS (ESI-TOF) calcd for $C_9H_{10}F_3N_2O_2^{+}$ [M+H]$^{+}$: 235.0689; found 235.0688. Anal. Calcd for $C_9H_9F_3N_2O_2$: C 46.16; H 3.87; N 11.96. Found, %: C 46.01; H 3.98; N 12.03.

2,2,2-Trifluoro-N-(2-methylpyridin-3-yl)acetamide (7)



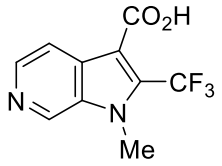
Oil, yield 126 mg (62%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.17 (s, 1H), 8.42 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.70 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.31 (dd, *J* = 8.0, 4.8 Hz, 1H), 2.39 (s, 3H). ^{19}F NMR ($CDCl_3$, 376 MHz) δ -74.09 (s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.30 (q, *J*= 37.8 Hz), 154.00, 147.83, 134.38, 129.53, 121.70, 115.92 (q, *J* = 289.8 Hz), 20.54. MS (ES-API) (*m/z*): 205 [M + H]$^{+}$. HRMS (ESI-TOF) calcd for $C_8H_8F_3N_2O^{+}$ [M+H]$^{+}$: 205.0589; found 205.0581. Anal. Calcd for $C_8H_7F_3N_2O$: C 47.07; H 3.46; N 13.72. Found, %: C 47.43; H 3.42; N 13.51.

2,2,2-Trifluoro-N-(4-methylpyrimidin-5-yl)acetamide (8)

Oil, yield 65 mg (32%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.02 (s, 1H), 8.97 (s, 1H), 8.84 (s, 1H), 2.51 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.79 (s). ^{13}C NMR

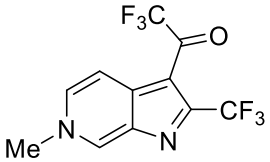
(101 MHz, $CDCl_3$) δ 161.40, 156.33, 155.93 (q, *J* = 38.4 Hz), 152.12, 128.78, 115.55 (q, *J* = 288.7 Hz), 20.39. MS (ES-API) (*m/z*): 206 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_7H_7F_3N_3O^+$ $[M+H]^+$: 206.0536; found 206.0531. Anal. Calcd for $C_7H_6F_3N_3O$: C 40.99; H 2.95; N 20.48. Found, %: C 41.08; H 3.04; N 20.25.

1-methyl-2-(trifluoromethyl)-1*H*-pyrrolo[2,3-*c*]pyridine-3-carboxylic acid (10)



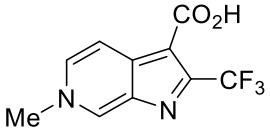
White crystals, yield 159 mg (65%), mp 257-259 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 9.59 (s, 1H), 8.49 (d, *J* = 6.1 Hz, 1H), 8.25 (d, *J* = 6.0 Hz, 1H), 4.15 (s, 3H). ^{19}F NMR (cdcl3, 188 MHz) δ -53.77 (s). 13C NMR (126 MHz, DMSO) δ 162.57, 135.11, 133.73 (q, *J* = 37.8 Hz), 133.12, 132.85, 132.05, 119.84 (q, *J* = 273.4 Hz), 117.66, 110.48, 33.89. MS (ES-API) (*m/z*): 245 $[M+H]^+$. HRMS (ESI-TOF) calcd for $C_{10}H_8F_3N_2O_2^+$ $[M+H]^+$: 245.0538; found 245.0530. Anal. Calcd for $C_{10}H_7F_3N_2O_2$: C 49.19; H 2.83; N 11.47. Found, %: C 49.43; H 2.86; N 11.51.

2,2,2-Trifluoro-1-(6-methyl-2-(trifluoromethyl)-6*H*-pyrrolo[2,3-c]pyridin-3-yl)ethan-1-one (11)



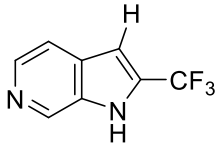
White crystals, yield 257 mg (87%), mp 261-262 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 9.29 (s, 1H), 8.26 (d, *J* = 6.9 Hz, 1H), 7.93 (d, *J* = 6.9 Hz, 1H), 4.26 (s, 3H). ^{19}F NMR (DMSO, 376 MHz) δ -74.15 (s), -63.42 (s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.53 (q, *J* = 35.3 Hz), 152.97 (q, *J* = 36.5 Hz), 142.10, 138.69, 136.85, 134.41, 121.97 (q, *J* = 270.9 Hz), 119.77 (q, *J* = 289.8 Hz), 116.19 (q, *J* = 6.3 Hz), 106.35, 46.70. MS (ES-API) (*m/z*): 297 $[M + H]^+$. HRMS (ESI-TOF) for **11·H_2O** calcd for $C_{11}H_9F_6N_2O_2^+$ $[M+H]^+$: 315.0568; found 315.0561. Anal. Calcd for $C_{11}H_6F_6N_2O$: C 44.61; H 2.04; N 9.46. Found, %: C 44.43; H 2.06; N 9.51.

6-Methyl-2-(trifluoromethyl)-6*H*-pyrrolo[2,3-*c*]pyridine-3-carboxylic acid (12)



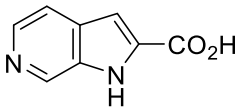
White crystals, yield 168 mg (69%), mp 282-283 °C. ^1H NMR (302 MHz, DMSO-d_6) δ 9.08 (s, 1H), 8.10 (d, *J* = 6.7 Hz, 1H), 8.02 (d, *J* = 6.8 Hz, 1H), 4.22 (s, 3H). ^{19}F NMR (376 MHz, DMSO-*d6*) δ -60.97 (s). ^{13}C NMR (76 MHz, D2O) δ 166.78,152.69 (q, J = 35.0 Hz), 142.58, 140.64, 139.36, 133.58, 124.76 (q, J = 271.3 Hz), 119.20, 107.13, 48.47. MS (ES-API) (m/z): 245 $[M+H]^+$. HRMS (ESI-TOF) calcd for $C_{10}H_8F_3N_2O_2^+$ $[M+H]^+$: 245.0532; found 245.0525. Anal. Calcd for $C_{10}H_7F_3N_2O_2$: C 49.19; H 2.89; N 11.47. Found, %: C 49.43; H 2.96; N 11.51.

2-(Trifluoromethyl)-1*H*-pyrrolo[2,3-*c*]pyridine (13)



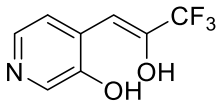
This compound was obtained in 88% yield. Analytical and spectroscopic data are in accordance with those reported in literature.[1] ^{1}H NMR (400 MHz, DMSO-d6) δ 12.83 (s, 1H), 8.89 (s, 1H), 8.20 (d, J = 5.6 Hz, 1H), 7.67 (d, *J* = 5.6 Hz, 1H), 7.07 (s, 1H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.03 (s). ^{13}C NMR (76 MHz, dmso) δ 136.48 (q, *J* = 52.5 Hz), 136.25, 132.12, 130.58, 129.65, 120.23 (q, *J* = 269.8 Hz), 119.60, 104.32 (q, *J* = 3.0 Hz). HRMS (ESI-TOF) calcd for $C_8H_6F_3N_2^+$ $[M+H]^+$: 187.0483; found 187.0474. Anal. Calcd for $C_8H_5F_3N_2$: C 51.62; H 2.71; N 15.05. Found, %: C 51.45; H 2.83; N 15.15.

1*H*-Pyrrolo[2,3-*c*]pyridine-2-carboxylic acid (14)



This compound was obtained in 73% yield. Analytical and spectroscopic data are in accordance with those reported in literature.[2] ^{1}H NMR (500 MHz, DMSO-d6) δ 8.79 (s, 1H), 8.13 (d, J = 5.5 Hz, 1H), 7.60 (d, J = 5.5 Hz, 1H), 7.07 (s, 1H). ^{13}C NMR (126 MHz, DMSO) δ 163.14, 137.52, 137.37, 131.43, 128.45, 127.71, 119.55, 108.86. HRMS (ESI-TOF) calcd for $C_8H_7N_2O_2^+$ $[M+H]^+$: 163.0508; found 163.0498. Anal. Calcd for $C_8H_6N_2O_2$: C 59.26; H 3.73; N 17.28. Found, %: C 59.38; H 3.77; N 17.16.

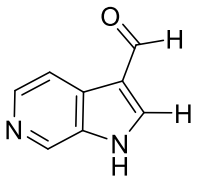
4-(3,3,3-Trifluoro-2-hydroxyprop-1-en-1-yl)pyridin-3-ol (15)



White crystals, yield 78 mg (38%), mp 97-98 °C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 16.17 (s, 1H), 7.77 (d, *J* = 6.1 Hz, 1H), 7.71 (s, 1H), 7.29 (s, 1H), 5.47 (s, 1H).

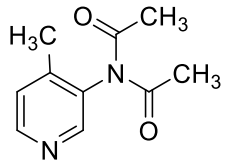
^{13}C NMR (76 MHz, dmso) δ 160.33, 155.07, 145.25, 129.88, 126.41, 124.81 (q, *J* = 298.3Hz), 122.67, 91.75. MS (ES-API) (*m/z*): 206 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_8H_7F_3NO_2^+$ $[M+H]^+$: 206.0423; found 206.0416. Anal. Calcd for $C_8H_6F_3NO_2$: C 46.84; H 2.95; N 6.83. Found, %: C 46.95; H 3.02; N 6.72.

1*H*-Pyrrolo[2,3-*c*]pyridine-3-carbaldehyde (16)



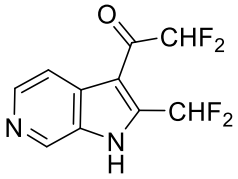
Yellow powder, yield 90 mg (62%), mp 145-147 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.99 (s, 1H), 8.87 (s, 1H), 8.49 (s, 1H), 8.31 (d, *J* = 5.4 Hz, 1H), 7.98 (d, *J* = 5.4 Hz, 1H). ^{13}C NMR (126 MHz, dmso-d_6) δ 185.72, 141.48, 136.00, 134.96, 129.54, 117.82, 115.62. MS (ES-API) (*m/z*): 147 [M + H]$^{+}$. HRMS (ESI-TOF) calcd for $C_8H_7N_2O^+$ [M+H]$^{+}$: 147.0558; found 147.0550. Anal. Calcd for $C_8H_6N_2O$: C 65.75; H 4.14; N 19.17. Found, %: C 65.58; H 4.21; N 19.27.

N-Acetyl-N-(4-methylpyridin-3-yl)acetamide (18)



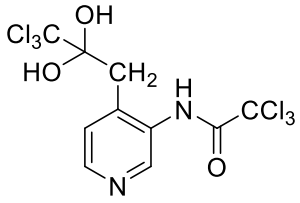
Oil, yield 40 mg (20%), mp 78-83 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.46 (d, *J* = 4.9 Hz, 1H), 8.39 (s, 1H), 7.39 (d, *J* = 5.0 Hz, 1H), 2.18 (s, 6H), 2.11 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.50, 150.16, 149.97, 145.74, 136.05, 126.25, 26.85, 16.85. MS (ES-API) (*m/z*): 193 [M + H]$^{+}$. HRMS (ESI-TOF) calcd for $C_{10}H_{13}N_2O_2^+$ [M+H]$^{+}$ 193.0972; found 193.0970. Anal. Calcd for $C_{10}H_{12}N_2O_2$: C 62.49; H 6.29; N14.57. Found, %: C 62.61; H 6.23; N 14.50.

1-(2-(Difluoromethyl)-1*H*-pyrrolo[2,3-*c*]pyridin-3-yl)-2,2-difluoroethan-1-one (19)



White crystals, yield 213 mg (86%), mp 227-228 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.05 (s, 1H), 8.28 (d, *J* = 6.3 Hz, 1H), 7.99 (d, *J* = 6.3 Hz, 1H), 7.50 (t, *J* = 53.7 Hz, 1H), 7.05 (t, *J* = 53.0 Hz, 1H). ^{19}F NMR (188 MHz, Chloroform-*d*) δ -115.67 (d, *J* = 53.8 Hz), -127.25 (d, *J* = 52.8 Hz). ^{13}C NMR (76 MHz, dmso) δ 181.66 (t, J = 24.3 Hz), 149.97, 138.84, 135.16, 134.71, 133.71, 116.13, 110.96 (t, *J* = 237.1 Hz), 110.54, 110.24 (t, *J* = 247.0 Hz). MS (ES-API) (*m/z*): 247 [M + H]$^{+}$. HRMS (ESI-TOF) for **19·H$_2$O** calcd for $C_{10}H_9F_4N_2O_2^+$ [M+H]$^{+}$: 265.0600; found 265.0594. Anal. Calcd for $C_{10}H_6F_2N_2O$: C 48.79; H 2.46; N 11.38. Found, %: C 48.81; H 2.38; N 11.68.

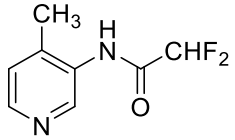
2,2,2-Trichloro-N-(4-(3,3,3-trichloro-2,2-dihydroxypropyl)pyridin-3-yl)acetamide (20)



Yellow powder, yield 178 mg (43%), mp 138-142 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.17 (s, 1H), 8.90 (s, 1H), 8.57 (d, *J* = 5.0 Hz, 1H), 7.34 (d, *J* = 5.0 Hz, 1H), 7.28 (d, *J* = 1.2 Hz, 1H), 4.39 (s, 2H). MS (ES-API) (*m/z*): 415 [M + H]$^{+}$.

HRMS (ESI-TOF) calcd for $C_{10}H_9Cl_6N_2O_3^+$ $[M+H]^+$: 414.8739; found 414.8736. Anal. Calcd for $C_{10}H_8Cl_6N_2O_3$: C 28.81; H 1.93; N 6.72. Found, %: C 28.55; H 1.98; N 6.88. ^{13}C NMR is not informative due to hindered rotation.

2,2-Difluoro-N-(4-methylpyridin-3-yl)acetamide (21)



Oil, yield 141 mg (76%). ^1H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 1H), 8.33 (d, *J* = 5.3 Hz, 1H), 7.32 (d, *J* = 4.9 Hz, 1H), 6.46 (tt, *J* = 53.6, 1.9 Hz, 1H), 2.21 (s, 3H). ^{19}F NMR (376 MHz, DMSO-*d6*) δ -126.13 (d, J = 53.4 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.98 (t, J = 25.2 Hz), 147.72, 147.25, 143.00, 132.24, 125.93, 109.05 (t, J = 248.2 Hz), 17.46. MS (ES-API) (m/z): 187 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_8H_9F_2N_2O^+$ $[M+H]^+$: 187.0677; found 187.0672. Anal. Calcd for $C_8H_8F_2N_2O$: C 51.56; H 4.33; N 15.05 Found, %: C 51.28; H 4.45; N 15.12.

References

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2 M. H. Fisher and A. R. Matzuk, *J. Heterocycl. Chem.*, 1969, **6**, 775–776

X-Ray diffraction data

All crystallographic measurements were performed on a Bruker Smart Apex II diffractometer operating in the ω and θ scans mode with graphite-monochromated Mo-K_α radiation (λ = 0.71078 Å). The data were corrected for Lorentz-polarization effects and for the effects of absorption (multi-scans method was applied for all compounds). The structures were solved by direct methods and refined by the full-matrix least-squares technique in the anisotropic approximation for non-hydrogen atoms using the Bruker SHELXTL program package.[1] All CH hydrogen atoms were placed at calculated positions and refined as 'riding' model. The OH and NH hydrogen atoms were found in DF synthesis of electron density and refined isotropically. The crystal data for all compounds studied by X-ray single crystal diffraction experiments are in Tables S1-S2.

Full crystallographic details have been deposited at Cambridge Crystallographic Data Centre (CCDC). Any request to the CCDC for these materials should quote the full literature citation and reference number CCDC 2277541-2277546.

Alert 420 (Level B) detected by checkcif procedure for structure **20** (CCDC 2277541) is related to the absence of the acceptor for the H-Bond O4 -H4B---A. The hydrogen atoms by N and O atoms are located from DF synthesis of the electron density and their position is refined with restrained at 0.85Å bond distances. The O4 atom of the solwate water molecule work as an acceptor for H3-O3. The H4a atom has the O1 atom as an acceptor and the second acceptor for H4b atom is absent, but possibly this H atom is disordered over two positions.

Refinement of **5c*TFA** (CCDC 2277545). Most problems with the structure refinement were associated with the disordered fluorine atoms of the CF_3 groups and also hardly disordered over several positions of solvate MTBE molecule, thus the standard procedure SQUEEZE in the PLATON where used for the correction of the dataset. The total potential void available to the solvent in the unit cell is 1481$Å^3$ (or 32.6% of volume) and the number of electrons is 413 e, which agrees well with the number of electrons in the MTBE molecule.

Alert 420 (Level B) detected by checkcif procedure for structure **5c*TFA** (CCDC 2277545) is related to the absence of the acceptor for the H-Bond OH---A, because the data were processed using a SQUEEZE procedure for a barely disordered in cavity solvated MTBE molecule. Thus, the H atom is directed into the cavities, but the MTBE acceptor molecule is absent.

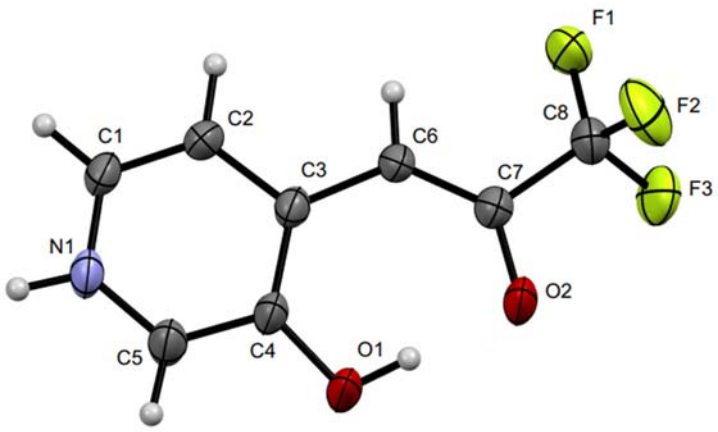


Figure S1. Structure of **15** (CCDC 2277545). The atoms are shown in anisotropic approximation with 50% of probability

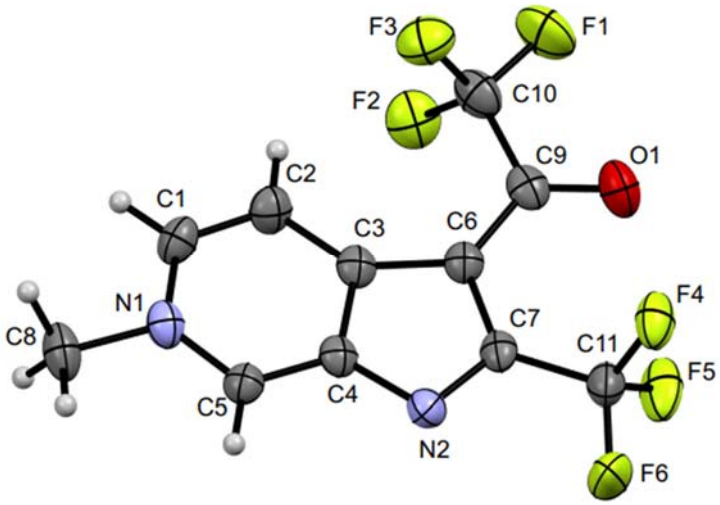


Figure S2. Structure of **11** (CCDC 2277542). The atoms are shown in anisotropic approximation with 50% of probability

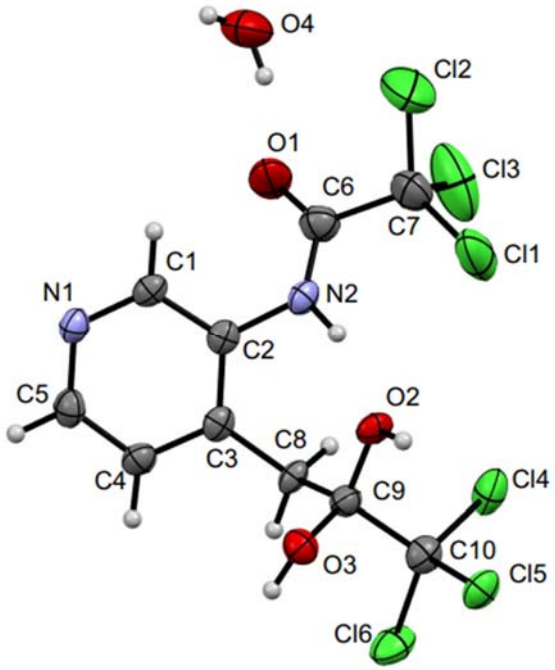


Figure S3. Structure of **20** (CCDC 2277543). The atoms are shown in anisotropic approximation with 50% of probability

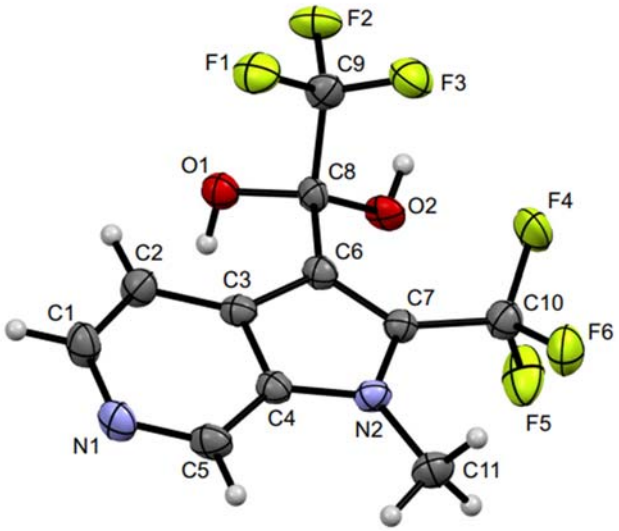


Figure S4. Structure of **5c** (CCDC 2277544). The atoms are shown in anisotropic approximation with 50% of probability

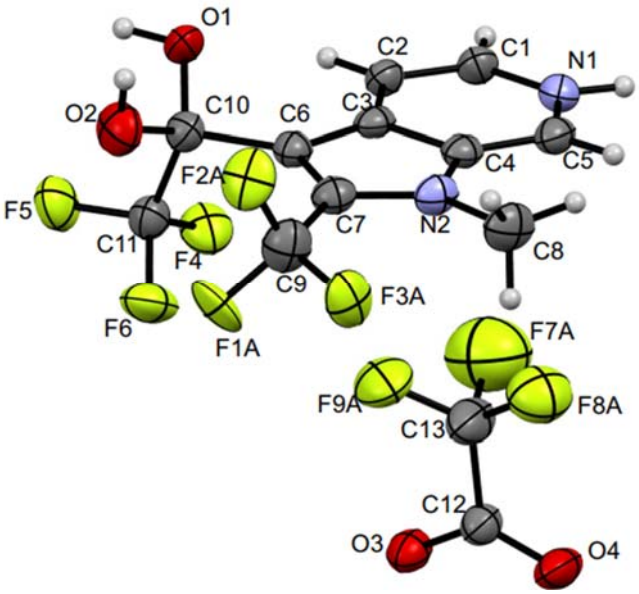


Figure S5. Structure of **5c-TFA** MTBE solv. (CCDC 2277545). The atoms are shown in anisotropic approximation with 50% of probability. For disordered fluorine atoms, only one position is shown

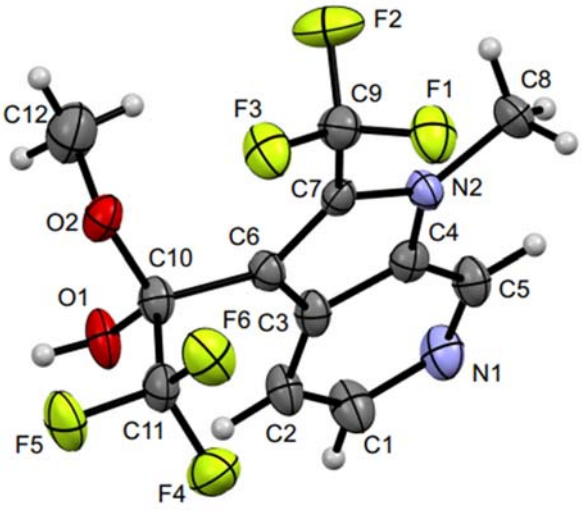


Figure S6. Structure of **9** (CCDC 2277546). The atoms are shown in anisotropic approximation with 50% of probability

Table S1. Crystal data for compounds **15** (CCDC 2277541), **11** (CCDC 2277542) and **20** (CCDC 2277543)

	15	**11**	**20**
Formula	$C_8H_6F_3NO_2$	$C_{11}H_6F_6N_2O$	$C_{10}H_8Cl_6N_2O_3 \cdot H_2O$
T/ K	173	173	173
M	205.14	296.18	434.90
Crystal system	Monoclinic	Orthorhombic	Monoclinic
Space group, Z	*C2*/c, 8	$P2_12_12_1$, 4	$P2_1$/c, 4
a / Å	14.9715(7)	4.6838(3)	10.9295(7)
b/ Å	7.8801(4)	15.0703(8)	12.7056(8)
c/ Å	15.8936(8)	15.9130(8)	13.4470(9)
α/ °	90	90	90
β/ °	116.348(2)	90	112.199(4)
γ/ °	90	90	90
V/ $Å^3$	1680.28(15)	1123.24(11)	1728.9(2)
μ(Mo-K_α)/mm^{-1}	0.159	0.182	1.008
D_c/g·cm^{-3}	1.622	1.751	1.671
Θ max (°)	26.7	26.4	25.7
Meas/Unique reflns	5085/1745	6354/2291	14514/3290
Parameters refined	151	182	215
R1, wR2 [I > 2σ(I)]	0.0490, 0.1019	0.0476, 0.0843	0.0768, 0.1688
R1, wR2 (all data)	0.0851, 0.1165	0.0692, 0.0923	0.1382, 0.1960
Goof on F^2	1.008	1.015	1.027
Max, min / peak e·$Å^{-3}$	0.22/-0.21	0.18/-0.19	0.86/-0.45

Table S2. Crystal data for compounds **5c** (CCDC 2277544), **5c*TFA** (CCDC 2277545) and **9** (CCDC 2277546)

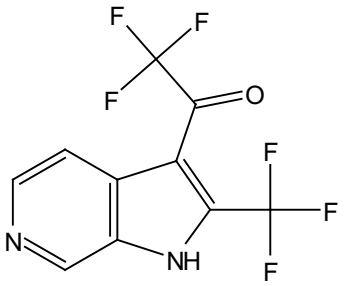
	5c	**5c*TFA**	**9**
Formula	$C_{11}H_8F_6N_2O_2$	$C_{11}H_9F_6N_2O_2*C_2F_3O_2*C_5H_{12}O$	$C_{12}H_{10}F_6N_2O_2$
T/ K	173	173	173
M	383.46	516.37	328.22
Crystal system	Triclinic	Monoclinic	Monoclinic
Space group, Z	*P-1*, 2	*C2/c*, 8	$P2_1$/c, 4
a / Å	7.8422(5)	35.604(2)	10.4771(8)
b/ Å	8.9422(6)	6.8088(4)	15.0099(13)

c/ Å	9.9332(7)	21.8140(13)	8.5190(7)
α/ °	68.876(5)	90	90
β/ °	83.817(5)	120.757(3)	99.894(5)
γ/ °	65.104(5)	90	90
V/ $Å^3$	588.59(7)	4544.4(5)	1319.77(19)
$\mu(Mo\text{-}K_\alpha)/mm^{-1}$	0.185	0.156	0.169
$D_c/g\cdot cm^{-3}$	1.773	1.509	1.652
Θ max (°)	25.6	25.0	25.0
Meas/Unique reflns	17341/3508	13257/3947	10450/2294
Parameters refined	199	321	201
R1, wR2 [I > 2σ(I)]	0.0494, 0.1020	0.0627, 0.1987	0.0712, 0.1674
R1, wR2 (all data)	0.0872, 0.1173	0.0843, 0.2280	0.1232, 0.1880
Goof on F^2	1.012	1.093	1.059
Max, min / peak $e\cdot Å^{-3}$	0.26/-0.25	0.65/-0.52	0.24/-0.24

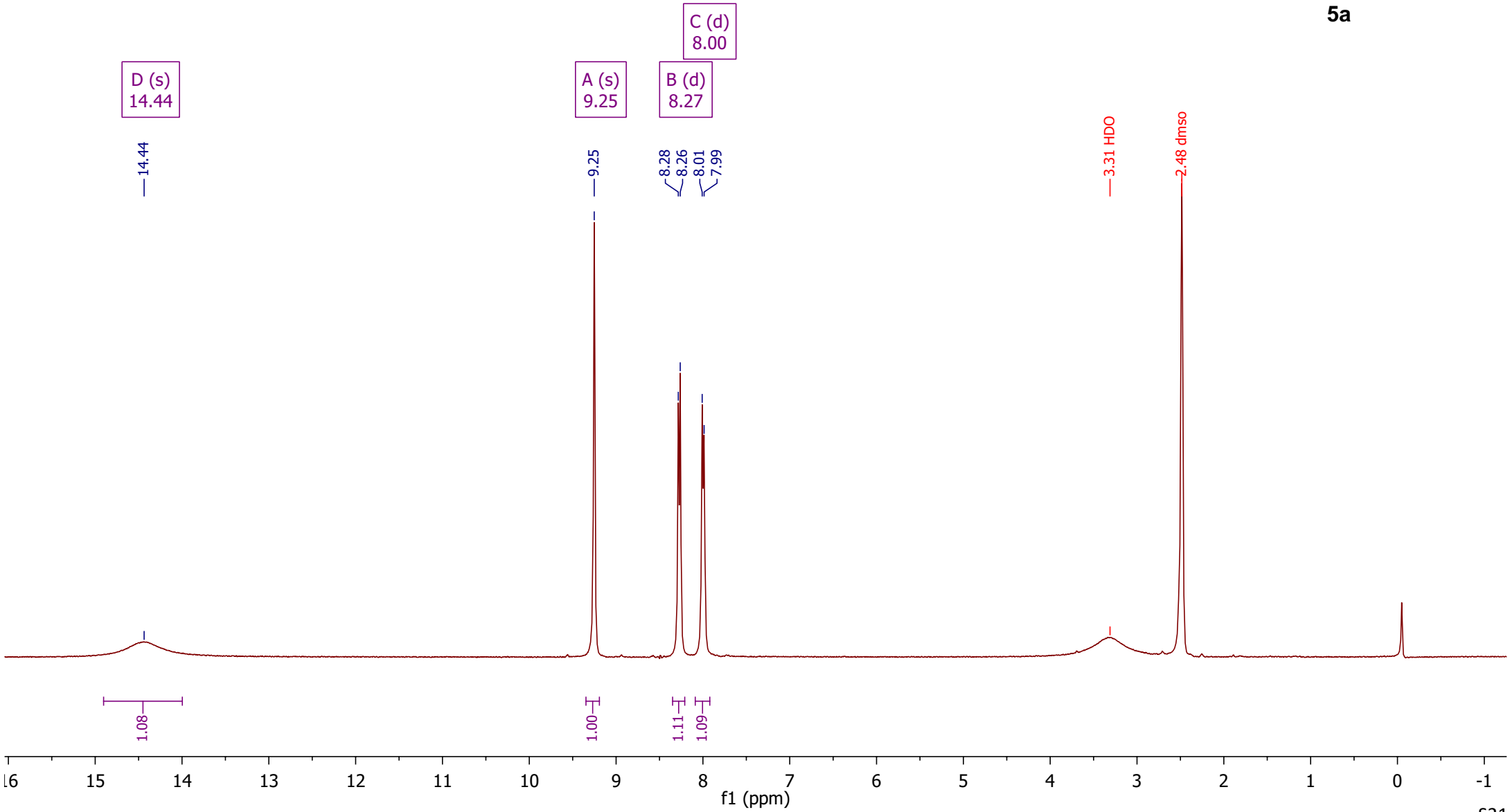
[1] Sheldrick, G. *ActaCryst., Sect. A,* **2008**, *64*, 112

^{1}H NMR of Compound **5a**

^{1}H NMR (302 MHz, DMSO-d_6) δ 14.44 (s, 1H), 9.25 (s, 1H), 8.27 (d, J = 6.7 Hz, 1H), 8.00 (d, J = 6.7 Hz, 1H).

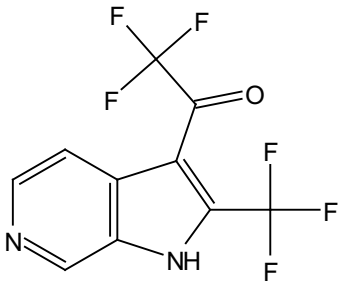


5a



^{13}C NMR of Compound **5a**

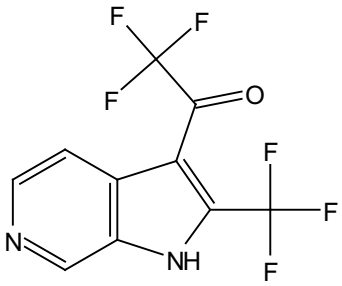
^{13}C NMR (76 MHz, dmso) δ 171.62 (q, *J* = 35.8), 152.72 (q, *J* = 35.9 Hz), 141.61, 138.52, 134.92, 130.19, 122.01 (q, *J* = 271.3 Hz), 117.45 (q, *J* = 291.1 Hz), 115.94 (q, *J* = 5.7 Hz), 106.43



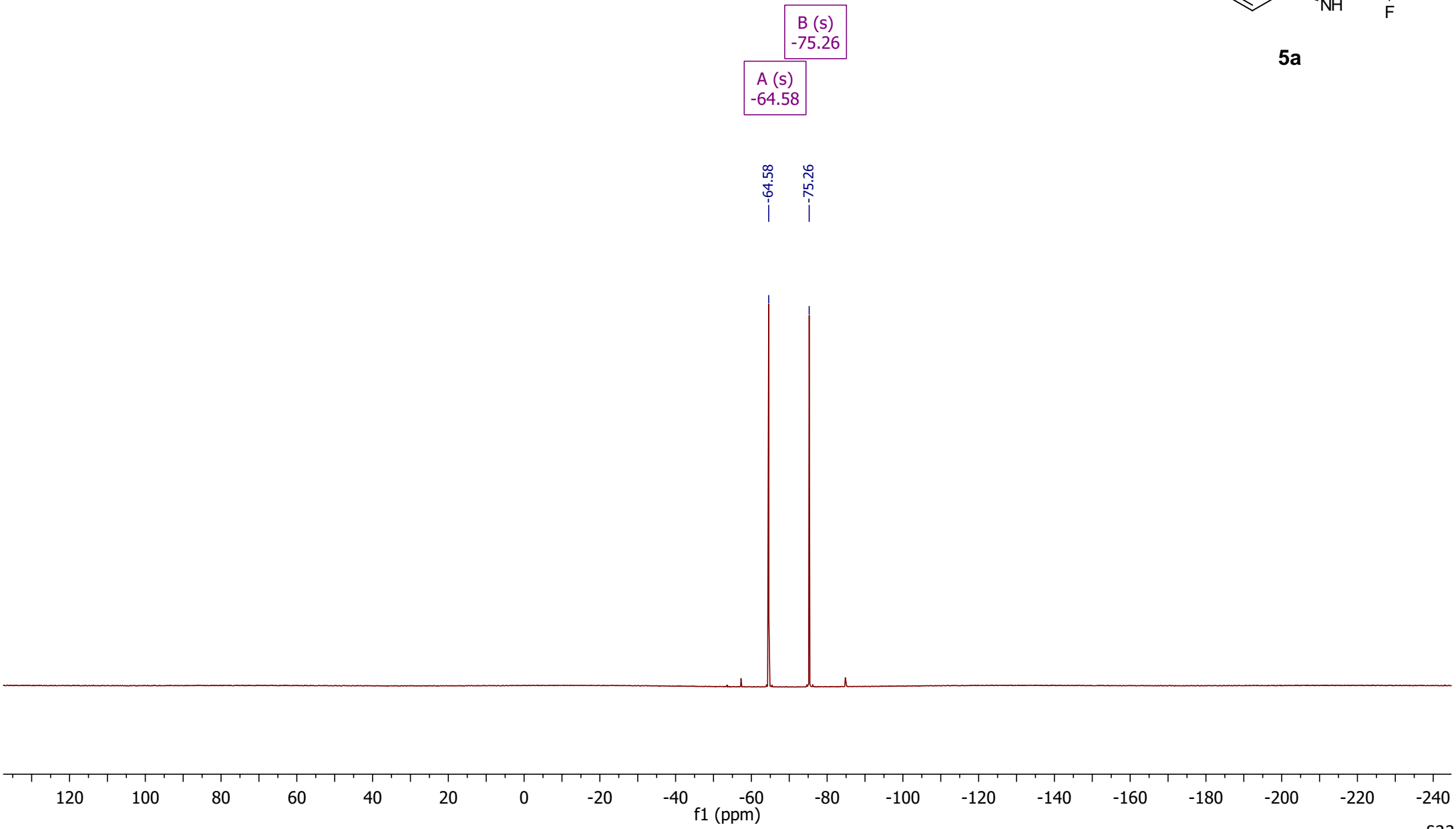
5a

^{19}F NMR of Compound **5a**

^{19}F NMR (188 MHz, cdcl$_3$) δ -64.58, -75.26.

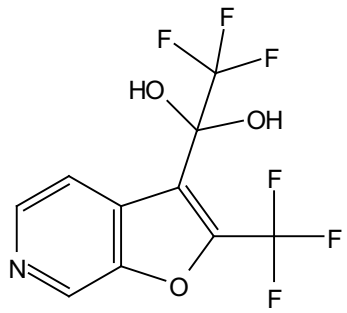


5a

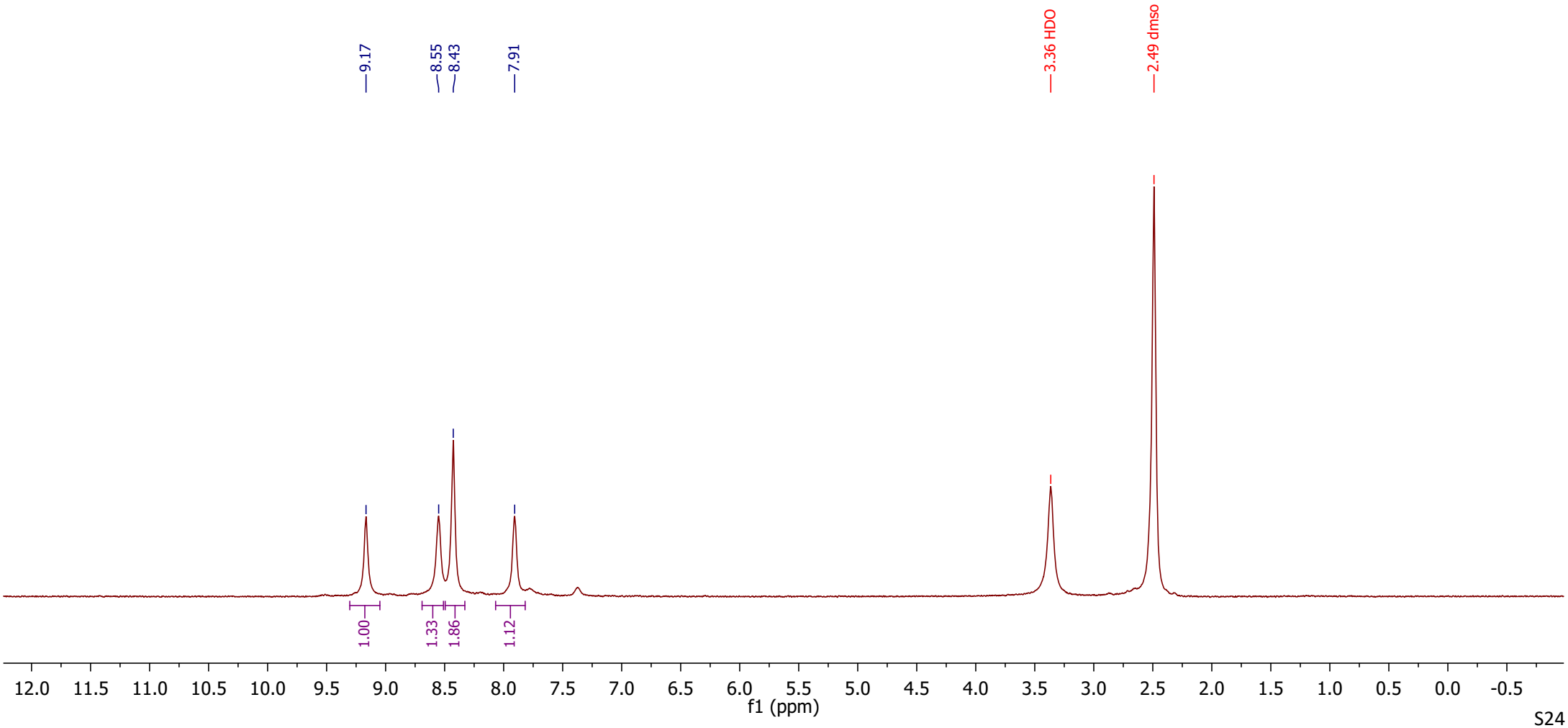


^{1}H NMR of Compound **5b**

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (s, 1H), 8.55 (s, 1H), 8.43 (s, 2H), 7.91 (s, 1H).

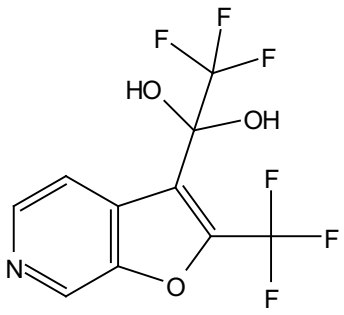


5b



^{13}C NMR of Compound **5b**

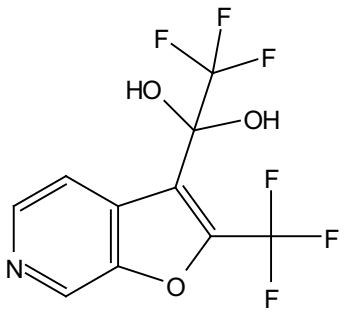
^{13}C NMR (126 MHz, dmso-d_6) δ 150.19, 143.93, 143.16 (q, J = 41.6 Hz), 135.72, 132.55, 126.82, 124.53, 122.08, 120.26, 118.78, 118.10, 91.76 (q, J = 34.0 Hz).



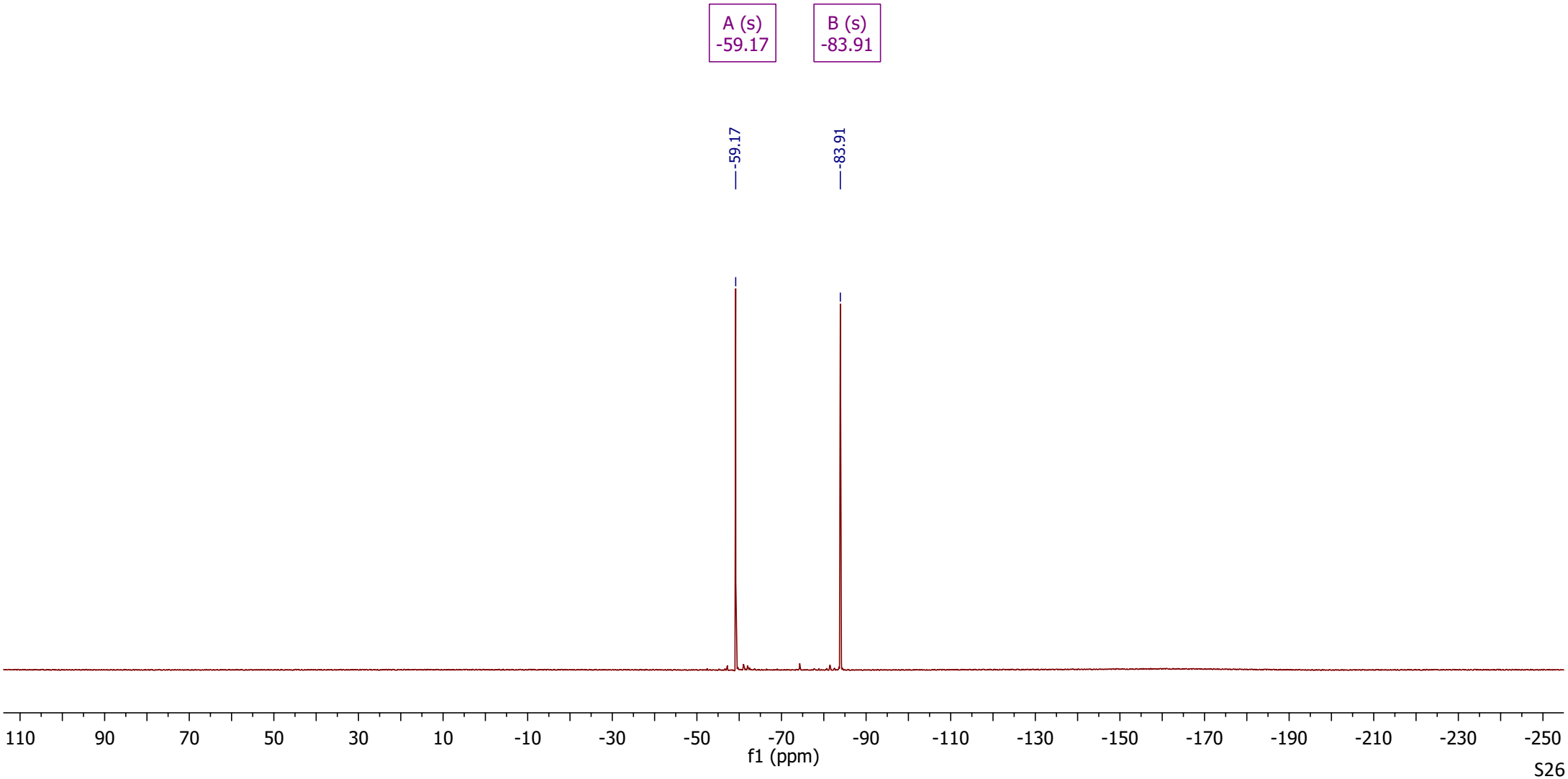
5b

^{19}F NMR of Compound **5b**

^{19}F NMR (376 MHz, DMSO-d_6) δ -59.17, -83.91.

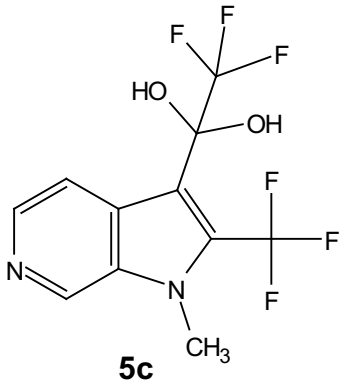


5b

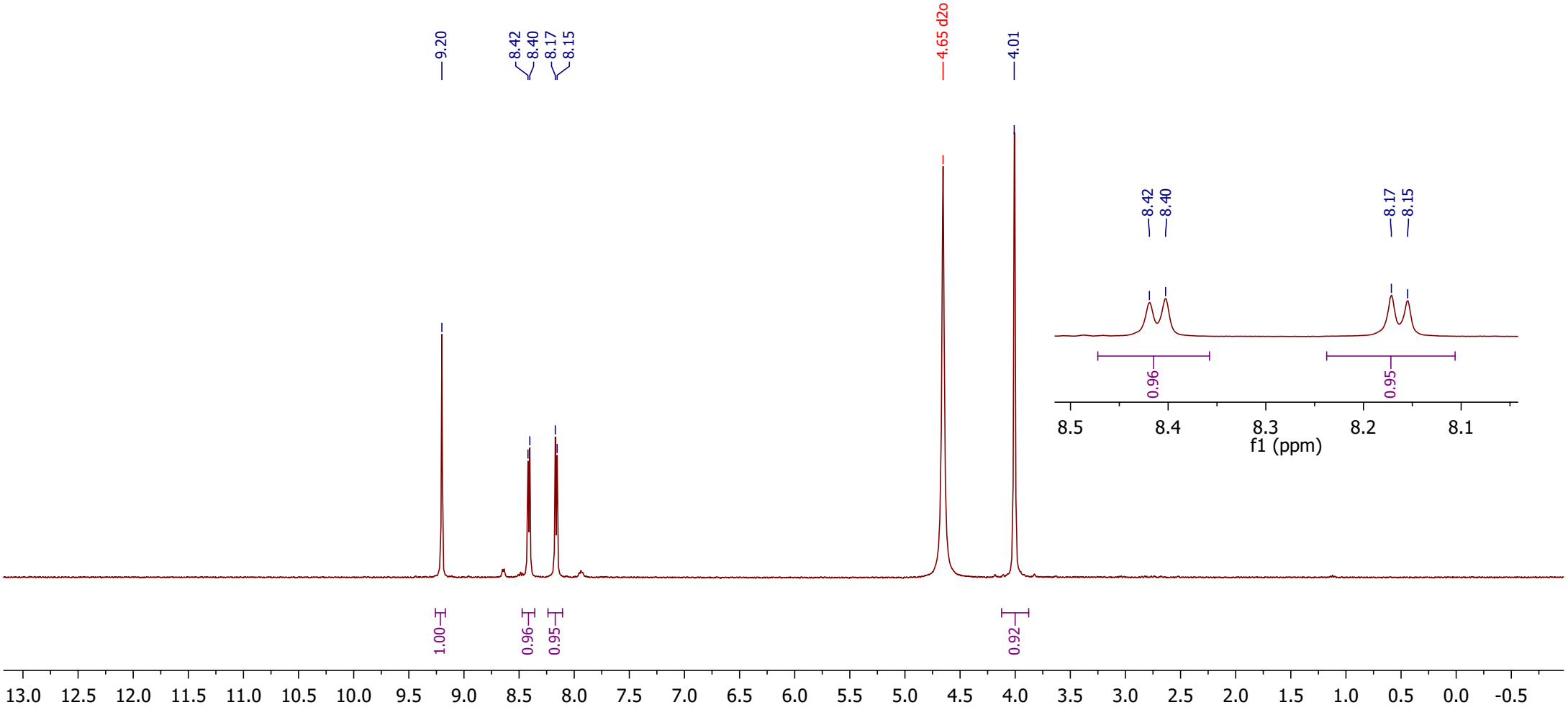


^{1}H NMR of Compound **5c**

^{1}H NMR (400 MHz, Deuterium Oxide) δ 9.20 (s, 1H), 8.41 (d, J = 6.6 Hz, 1H), 8.16 (d, J = 6.7 Hz, 1H), 4.65 (s, 5H), 4.12 – 3.88 (m, 3H).

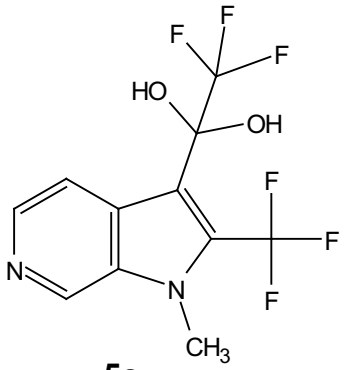


5c

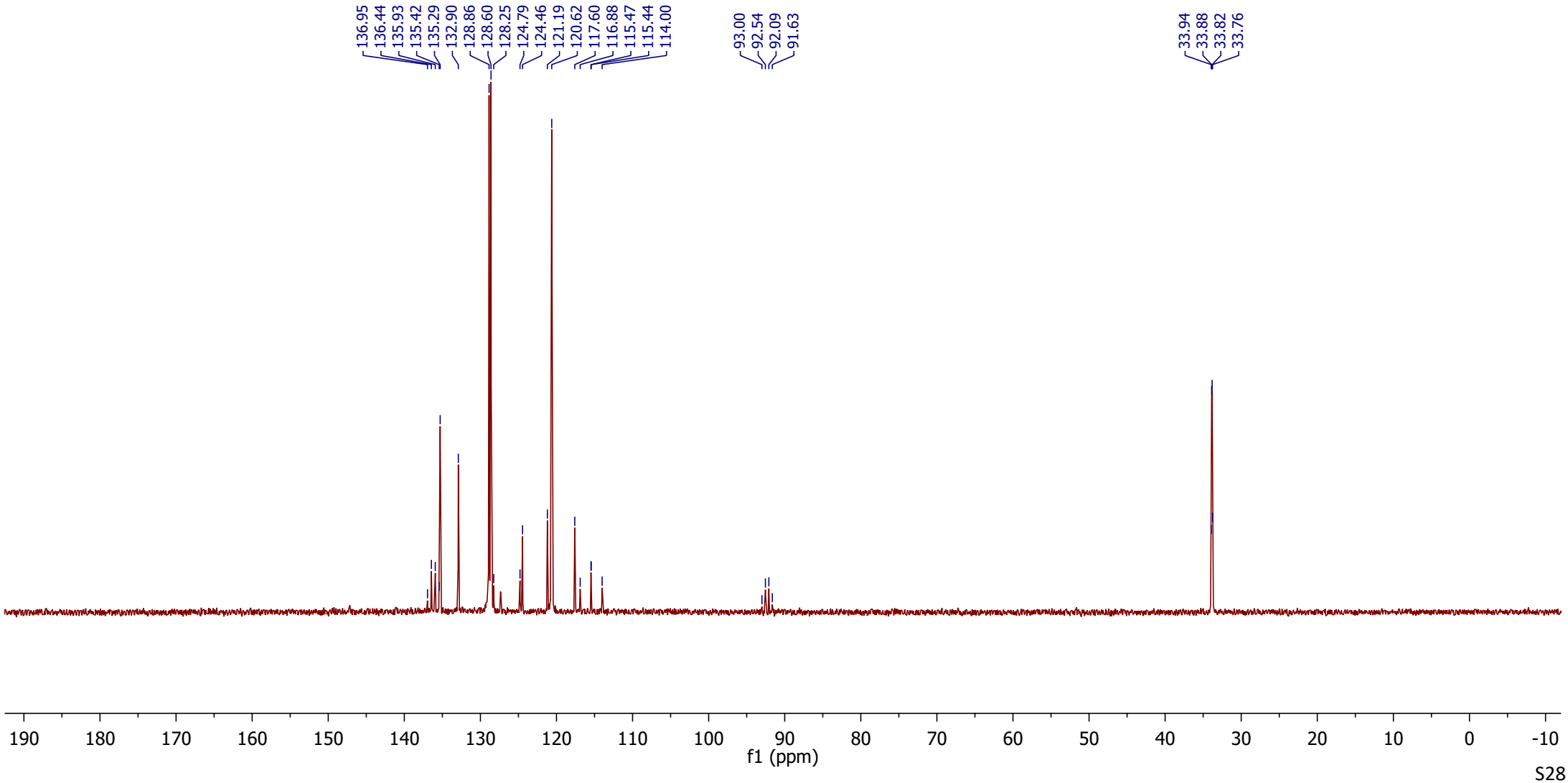


^{13}C NMR of Compound **5c**

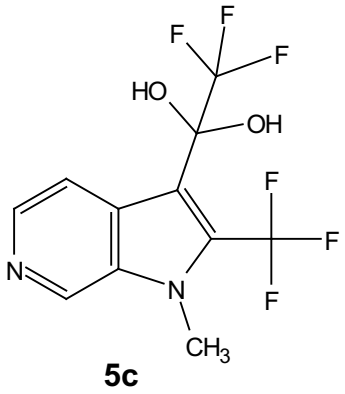
^{13}C NMR (76 MHz, d_2o) δ 135.18 (q, *J* = 39 Hz), 135.29, 132.90, 128.86, 128.60, 122.57 (q, *J* = 288 Hz), 120.62, 119.40 (q, *J* = 273 Hz), 115.45 (q, J = 2.3 Hz), 92.32 (q, *J* = 41.8 Hz), 33.85 (q, *J* = 4.6 Hz).



5c

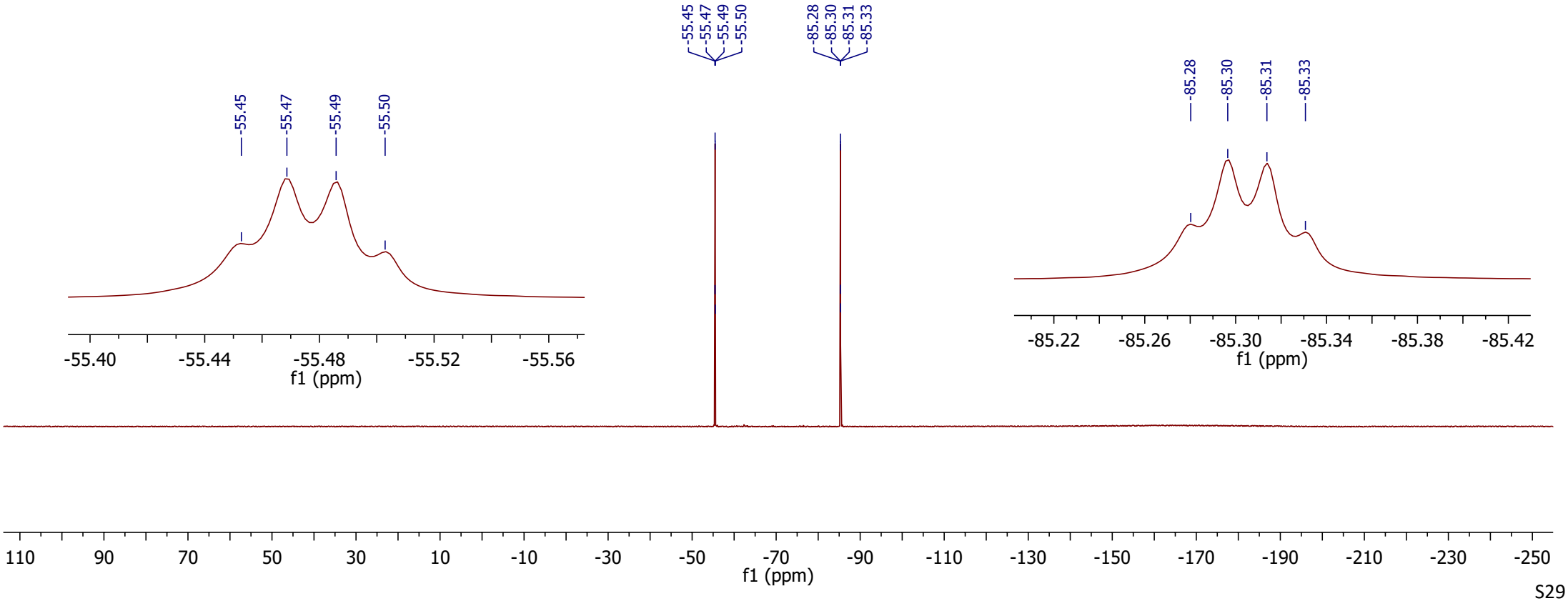


^{19}F NMR of Compound **5c**



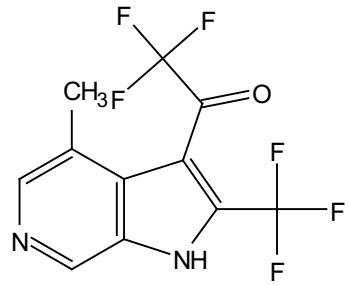
5c

^{19}F NMR (376 MHz, DMSO-d_6) δ -55.48 (q, J = 6.2 Hz), -85.31 (q, J = 6.3 Hz).

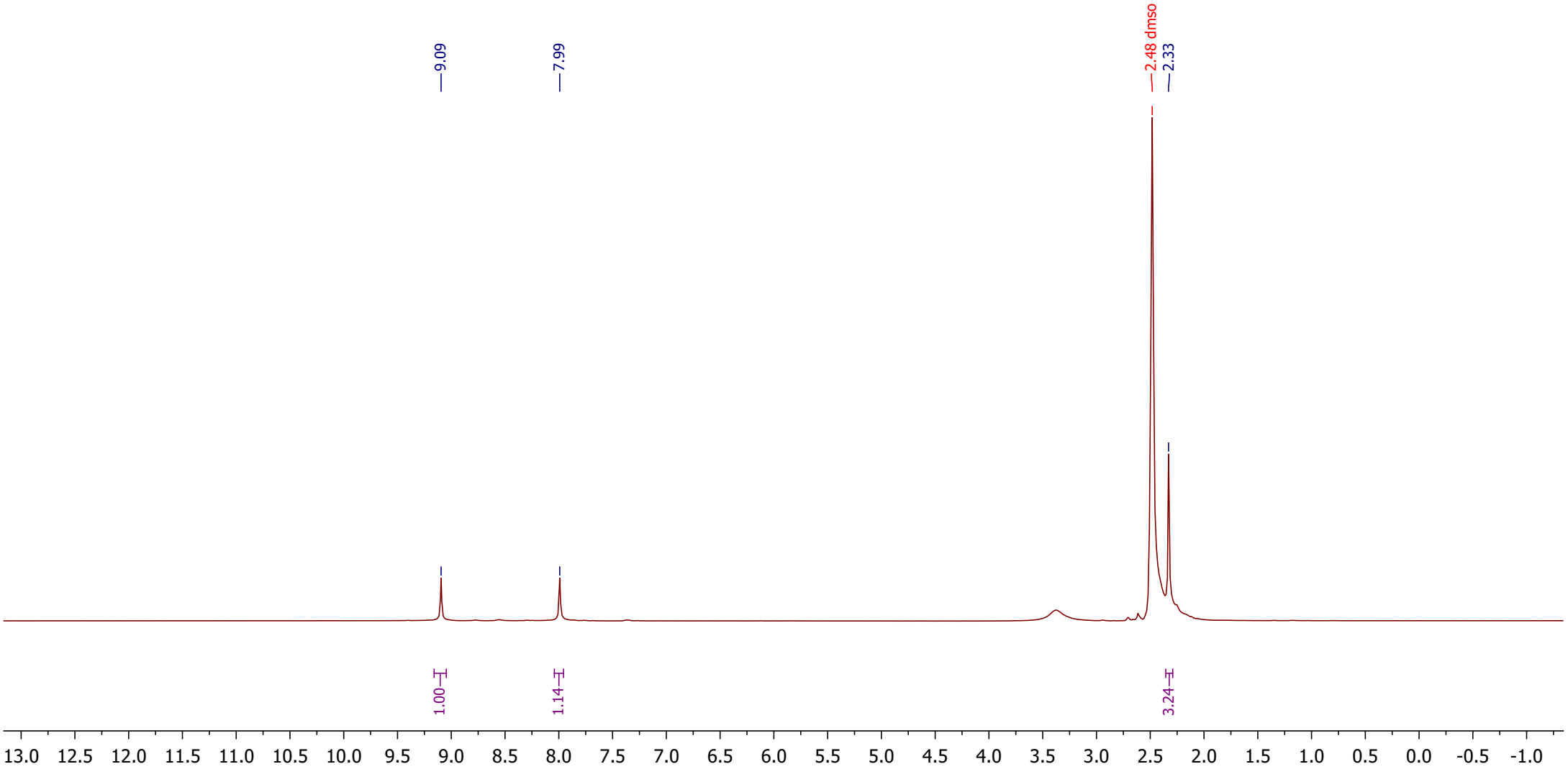


^{1}H NMR of Compound **5d**

^{1}H NMR (302 MHz, DMSO-d_6) δ 9.09 (s, 1H), 7.99 (s, 1H), 2.33 (s, 3H).

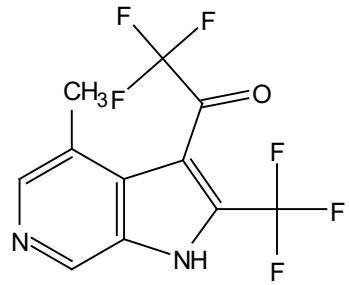


5d



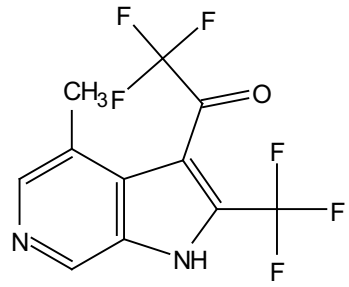
^{13}C NMR of Compound **5d**

^{13}C NMR (76 MHz, dmso) δ 182.10 (q, J = 40.3 Hz), 147.69 (q, J = 34.2 Hz), 140.75, 138.49, 132.60, 127.34, 126.90, 122.21 (q, J = 272 Hz), 116.13 (q, J = 292 Hz), 107.10, 17.33.



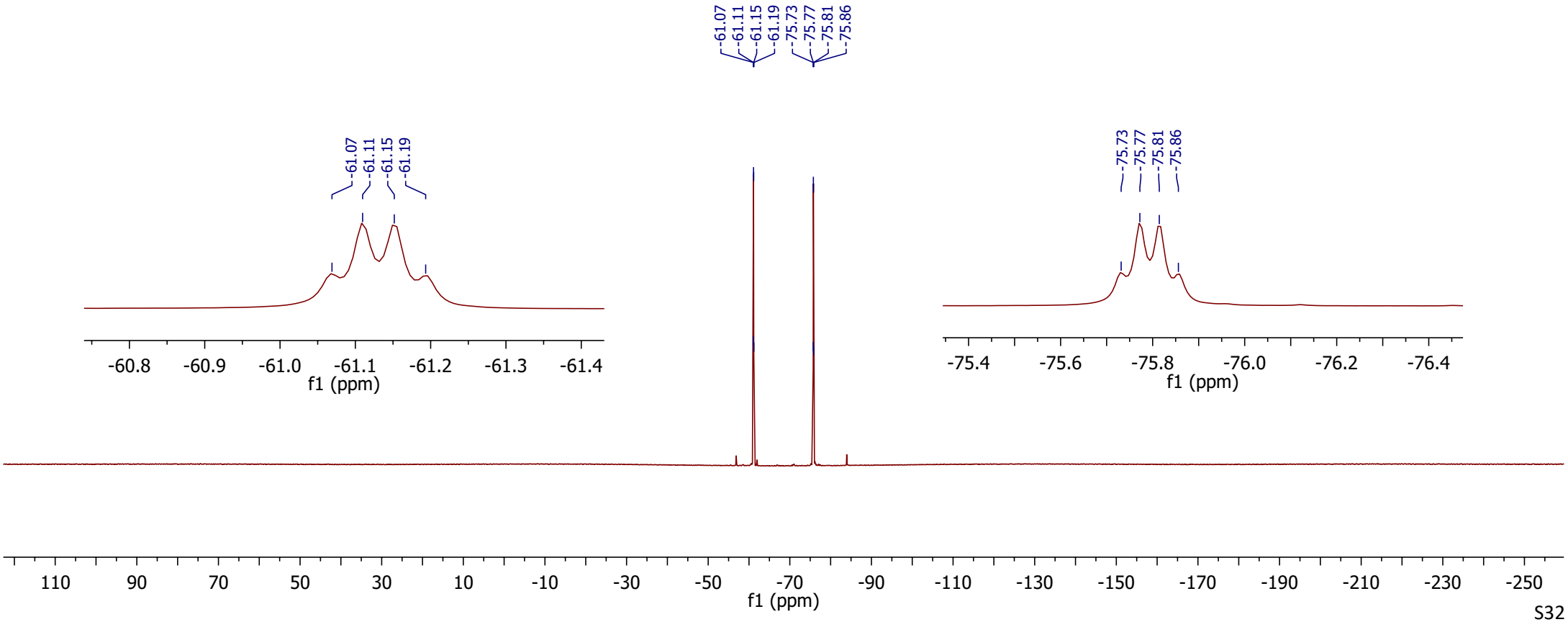
5d

^{19}F NMR of Compound **5d**



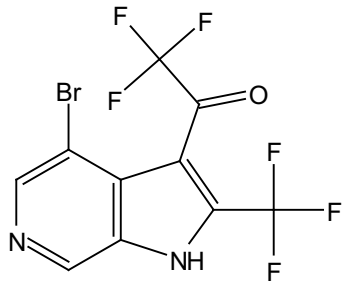
5d

^{19}F NMR (188 MHz, Chloroform-*d*) δ -61.13 (q, *J* = 7.7 Hz), -75.79 (q, *J* = 7.7 Hz).

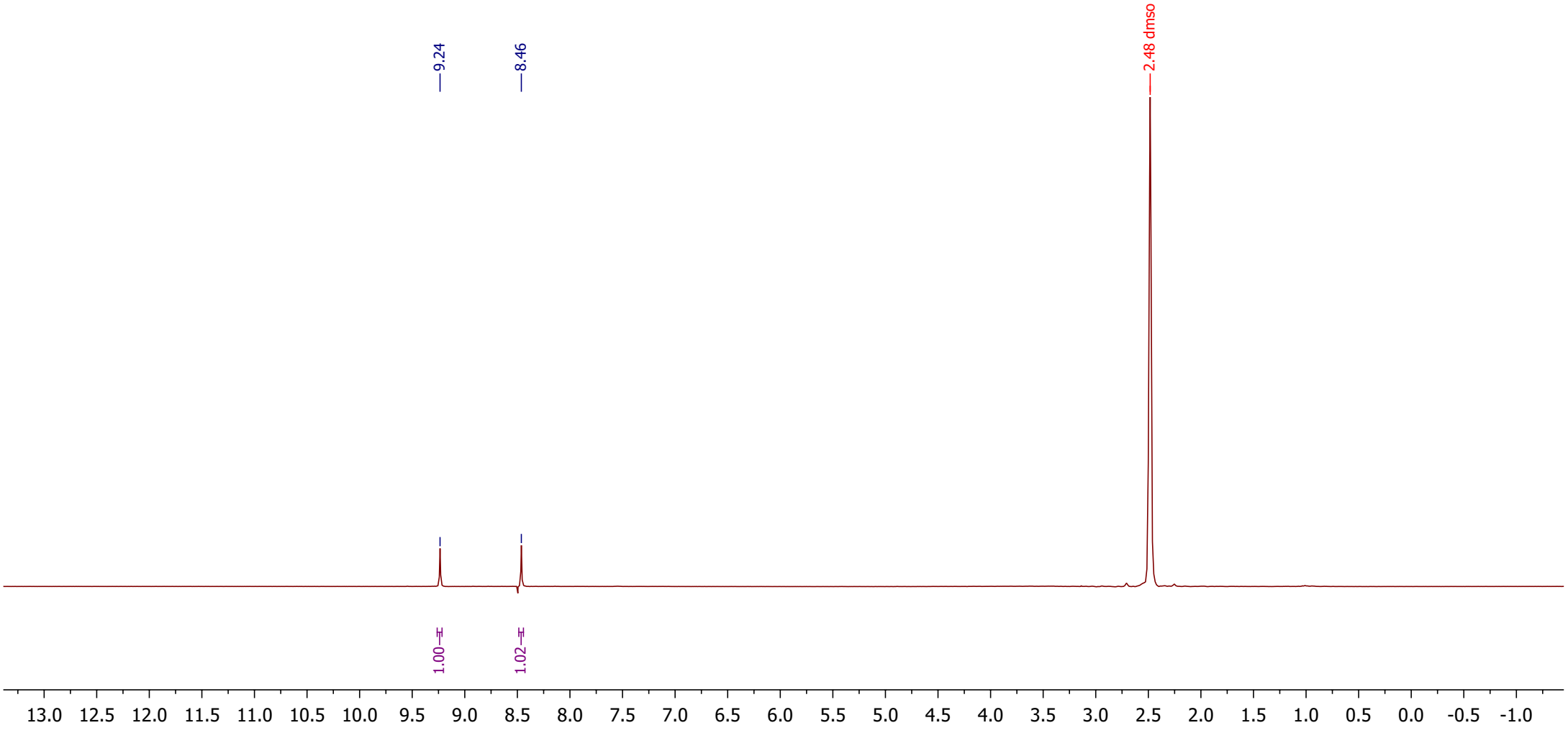


^{1}H NMR of Compound **5e**

^{1}H NMR (302 MHz, DMSO-d_6) δ 9.24 (s, 1H), 8.46 (s, 1H).

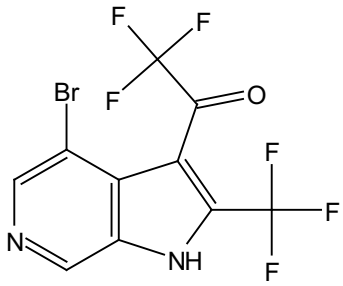


5e



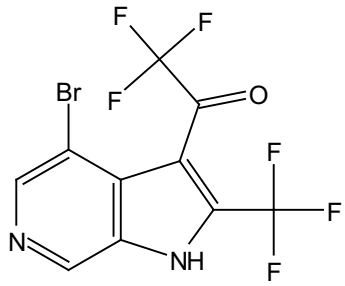
^{13}C NMR of Compound **5e**

^{13}C NMR (76 MHz, dmso) δ 182.91 (q, J = 37.2 Hz), 139.45, 135.97, 134.63, 130.98, 121.68 (q, J = 272 Hz), 115.93 (q, J = 292 Hz), 113.59, 109.62, 107.08.



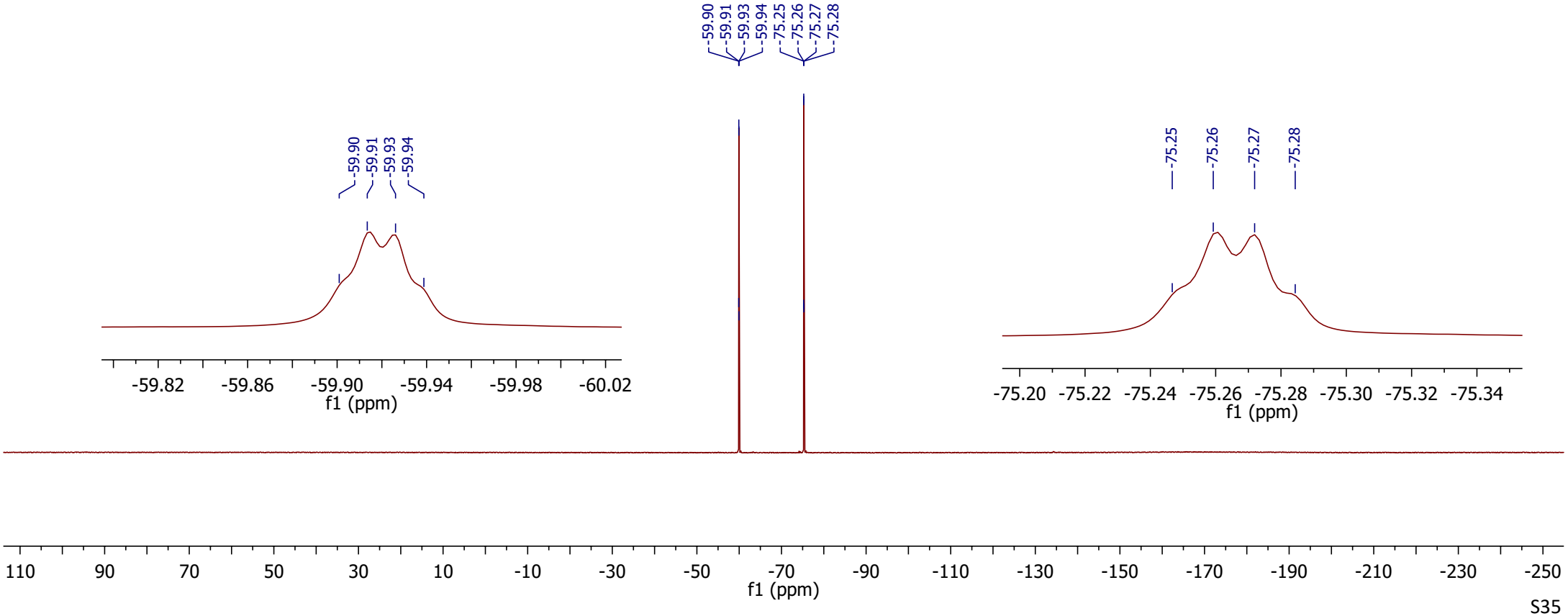
5e

^{19}F NMR of Compound **5e**

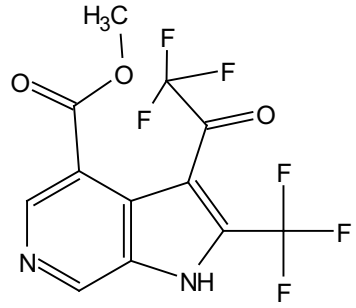


5e

^{19}F NMR (376 MHz, DMSO-d_6) δ -59.92 (q, J = 4.7 Hz), -75.27 (q, J = 4.7 Hz).



^{1}H NMR of Compound **5f**

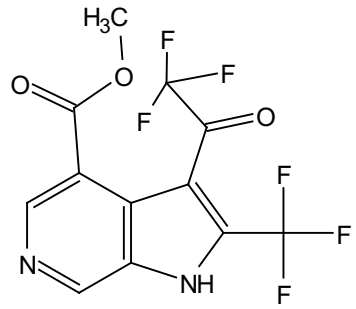


5f

^{1}H NMR (302 MHz, dmso) δ 9.31, 8.68, 3.87, 2.48.

^{13}C NMR of Compound **5f**

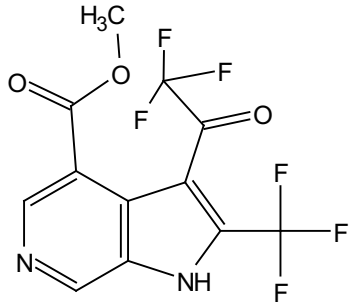
^{13}C NMR (76 MHz, dmso) δ 181.28 (q, J = 35.7 Hz), 165.96, 150.93, 140.18, 137.60, 133.20, 132.67, 121.62 (q, J = 273 Hz), 117.36, 116.59 (q, J = 292 Hz), 106.91, 53.17.



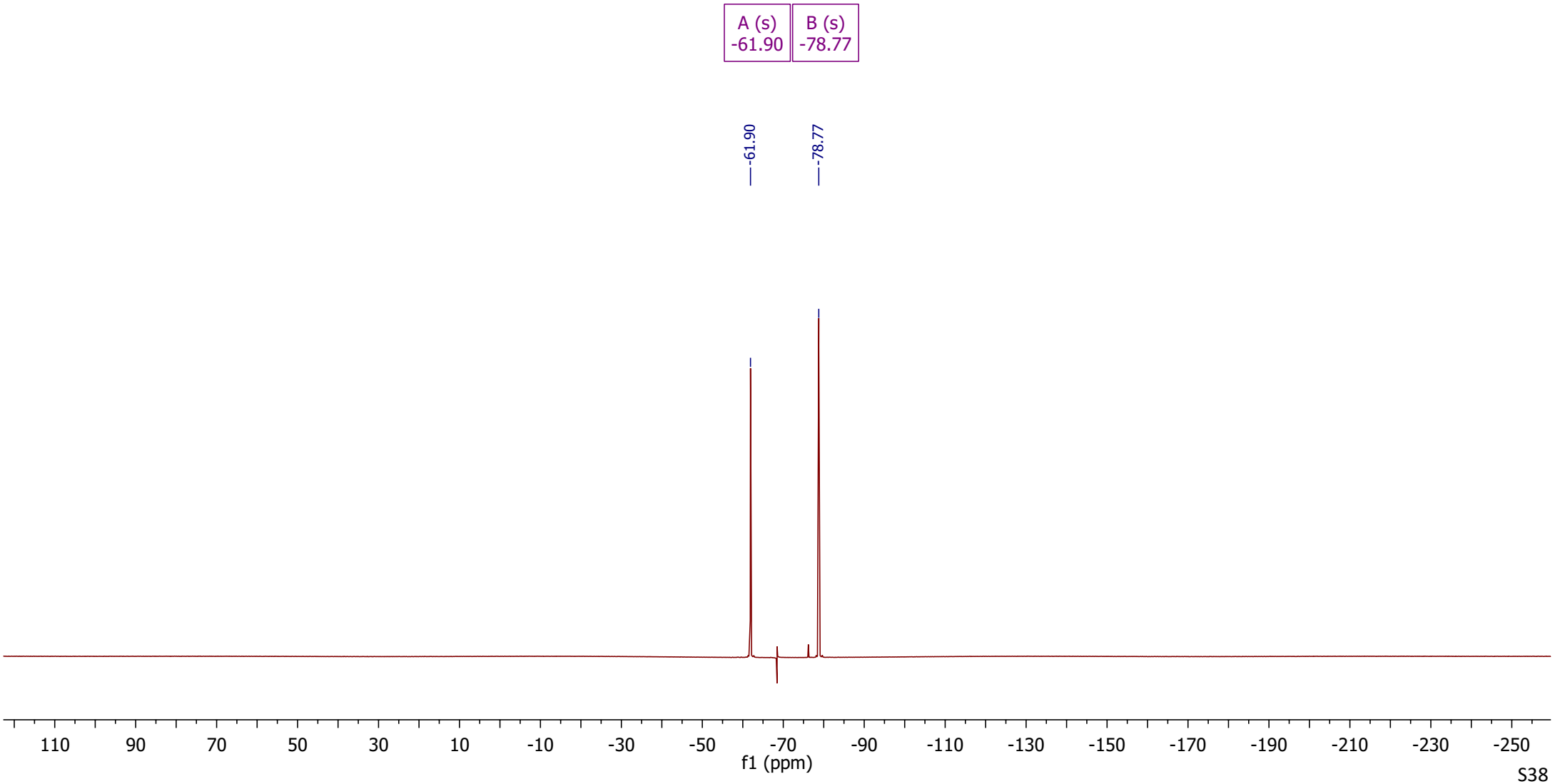
5f

^{19}F NMR of Compound **5f**

^{19}F NMR ($cdcl_3$, 188 MHz) δ -78.77, -61.90.

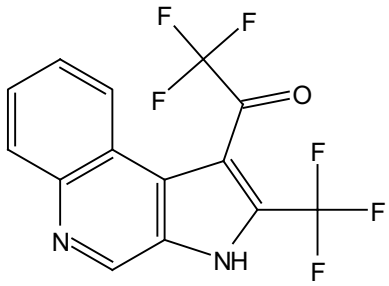


5f

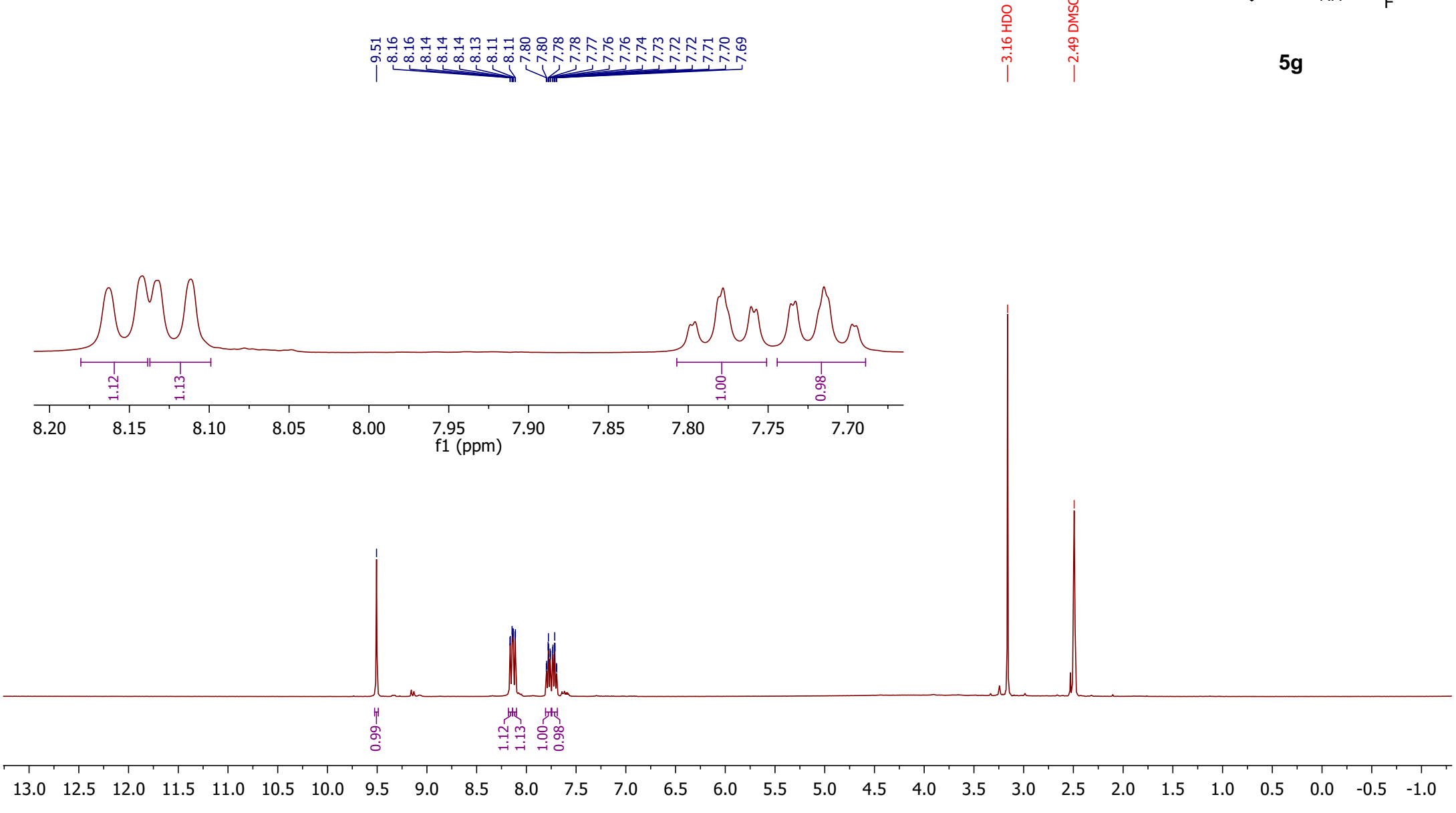


^{1}H NMR of Compound **5g**

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.15 (dd, J = 8.5, 1.4 Hz, 1H), 8.12 (dd, J = 8.5, 1.5 Hz, 1H), 7.78 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H), 7.72 (ddd, J = 8.3, 7.0, 1.4 Hz, 1H).

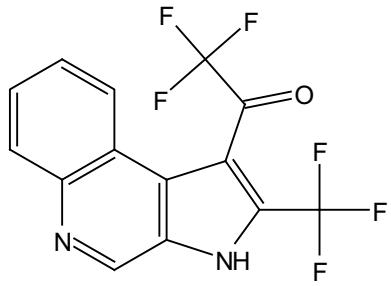


5g

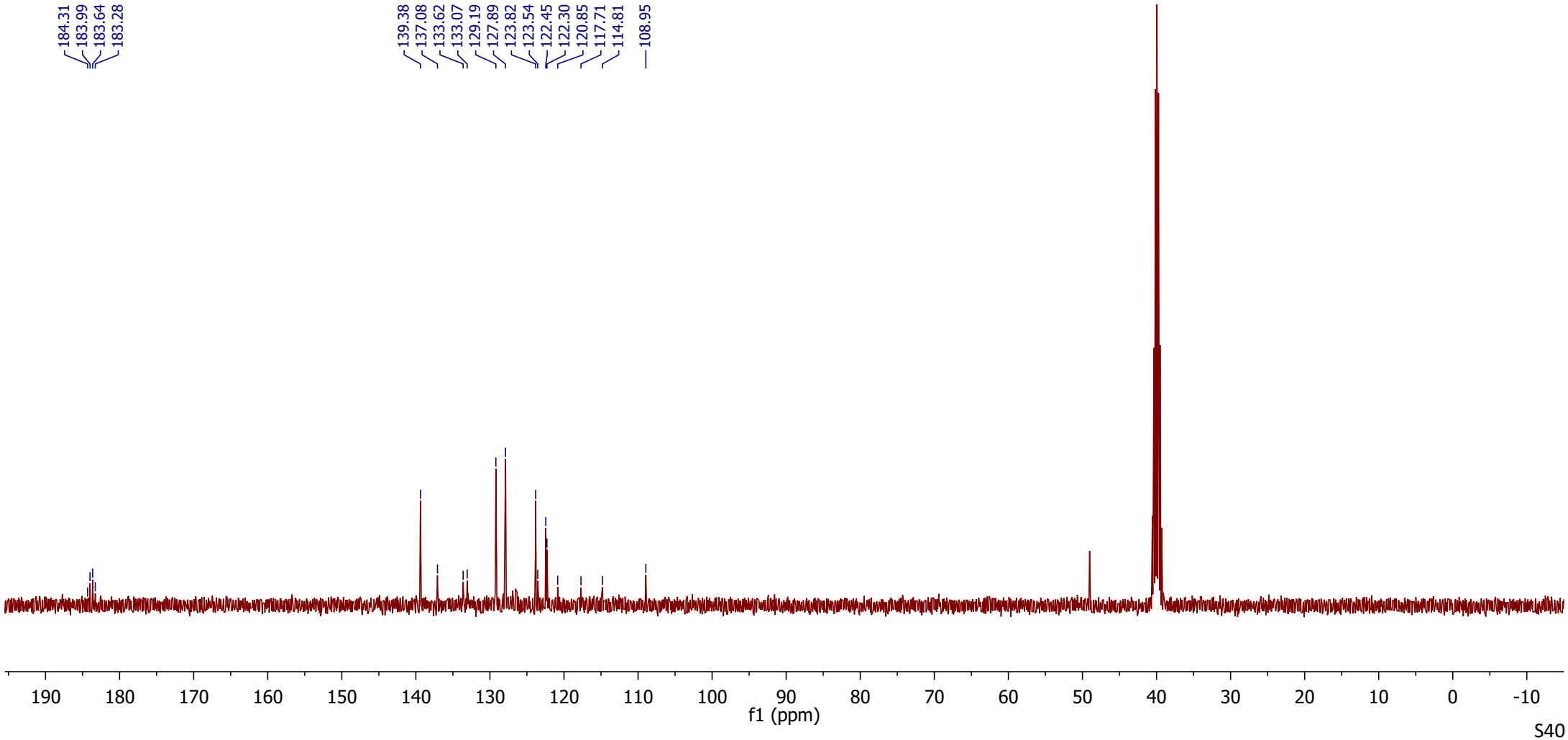


^{13}C NMR of Compound **5g**

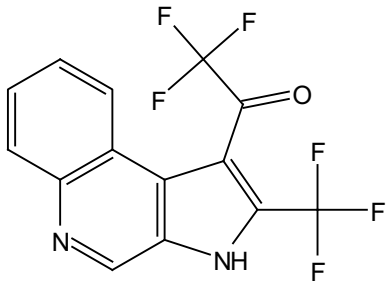
^{13}C NMR (101 MHz, DMSO) δ 183.81 (q, J = 35.4 Hz), 139.38, 137.08, 133.62, 133.07, 129.19, 127.89, 123.82, 123.54, 122.45, 122.30, 120.85, 117.71, 114.81, 108.95.



5g

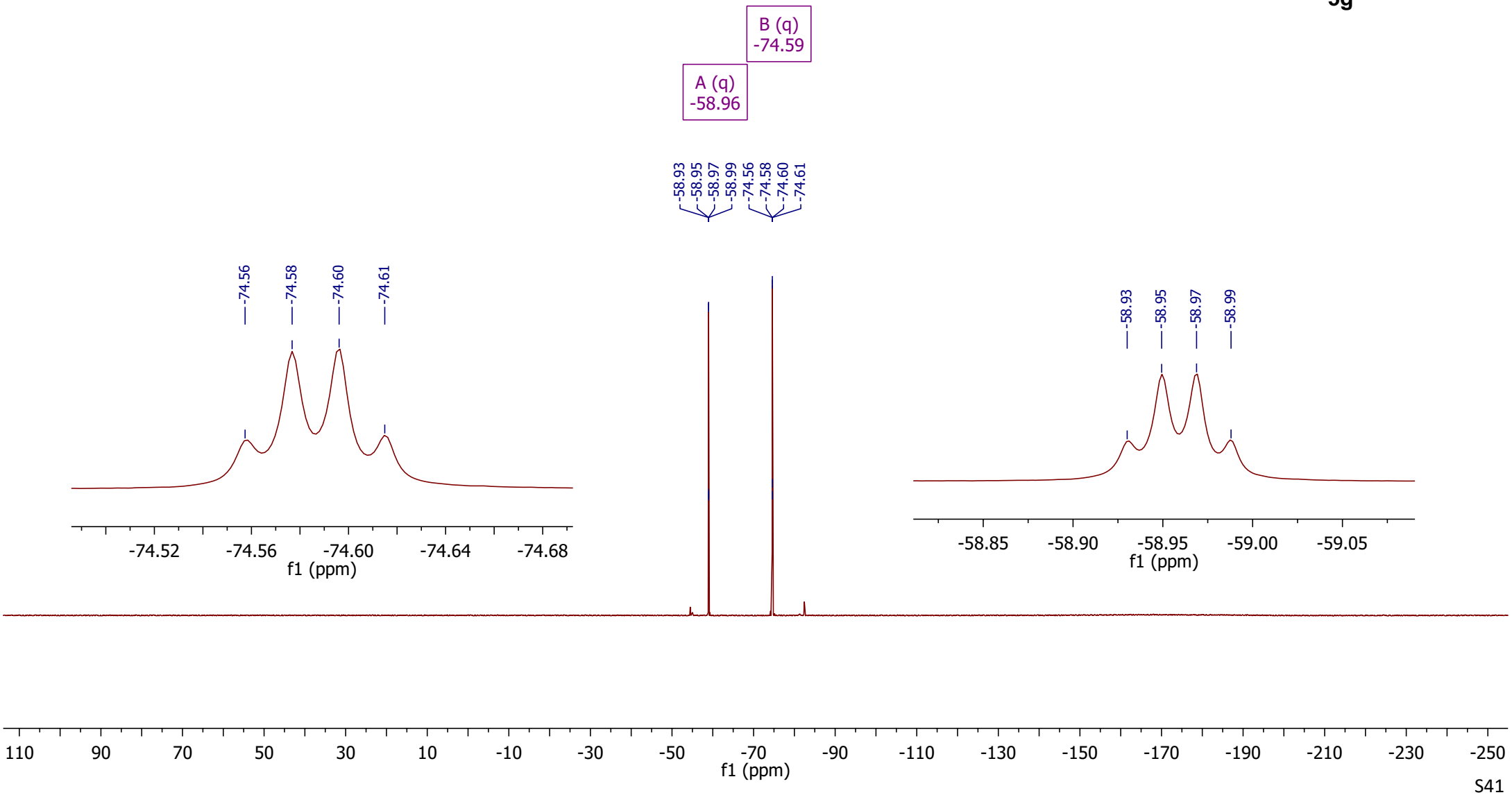


^{19}F NMR of Compound **5g**

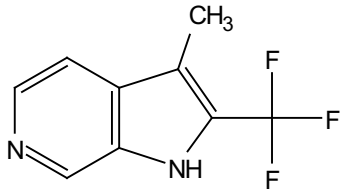


5g

^{19}F NMR (376 MHz, DMSO-d_6) δ -58.96 (q, J = 7.2 Hz), -74.59 (q, J = 7.2 Hz).



^{1}H NMR of Compound **5h**

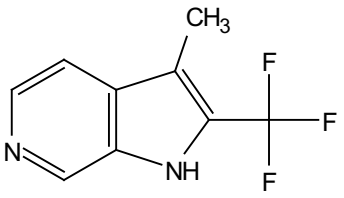


5h

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (s, 1H), 8.20 (d, J = 6.0 Hz, 1H), 7.63 (d, J = 5.6 Hz, 1H), 2.37 (s, 3H).

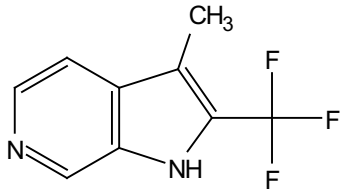
^{13}C NMR of Compound **5h**

^{13}C NMR (101 MHz, DMSO) δ 138.16, 136.21, 133.36, 131.95, 125.88 (q, J = 36.4 Hz), 122.46 (q, J = 269.7 Hz), 114.68, 111.90, 8.37.



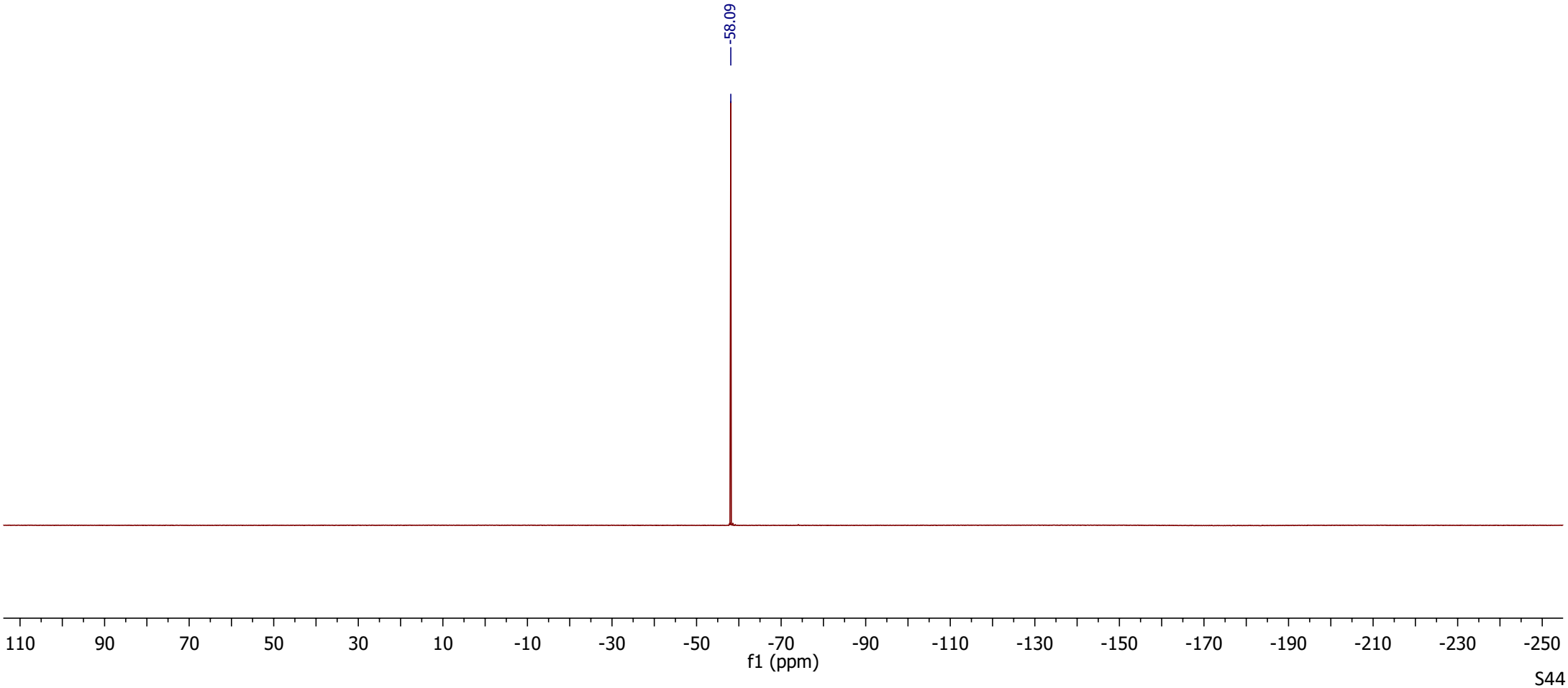
5h

^{19}F NMR of Compound **5h**



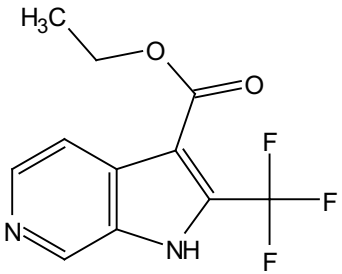
5h

^{19}F NMR (DMSO, 376 MHz) δ -58.09.

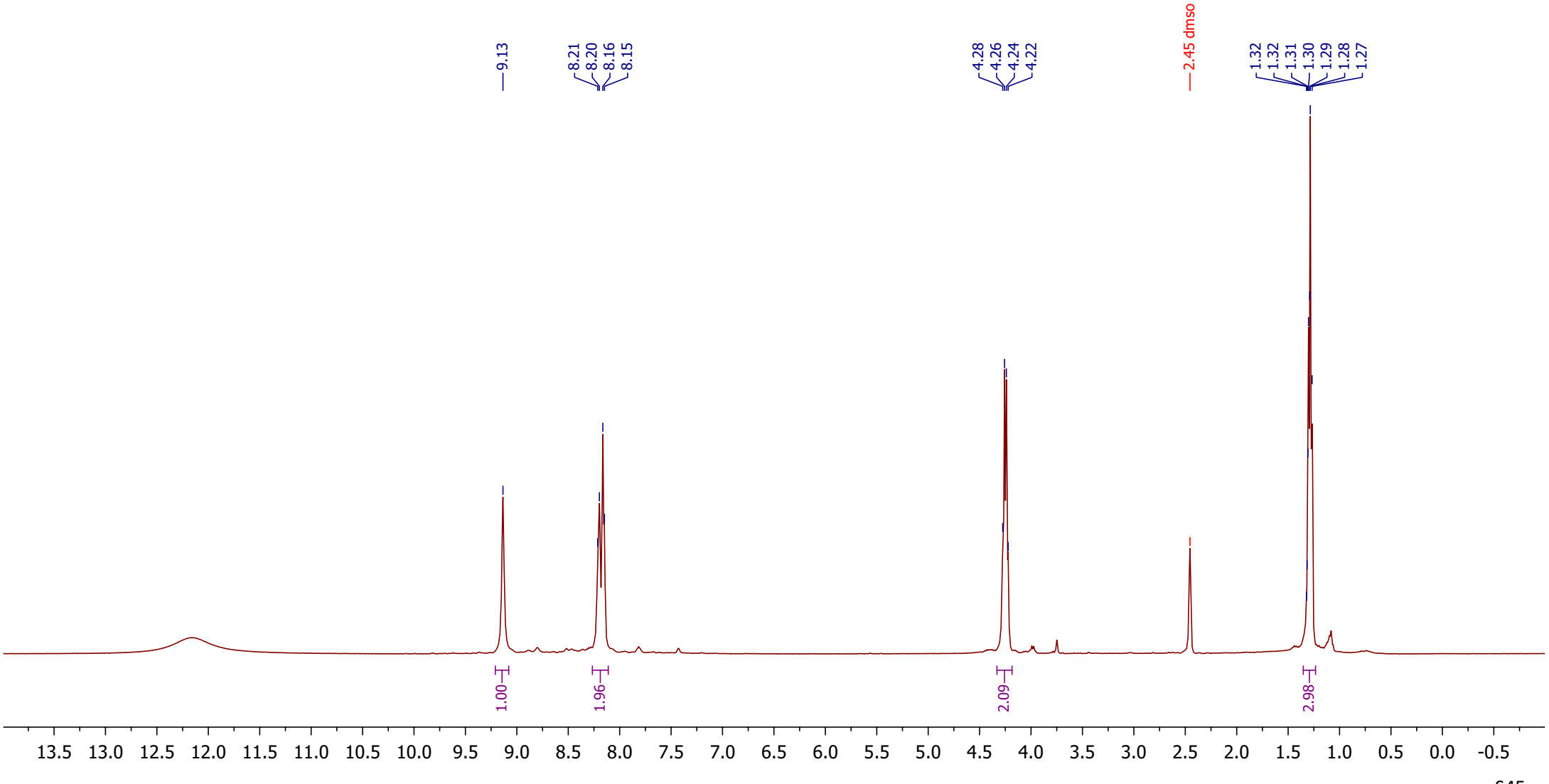


^{1}H NMR of Compound **5i**

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.18 (s, 1H), 9.13 (s, 1H), 8.27 – 8.11 (m, 2H), 4.25 (q, J = 7.1 Hz, 2H), 1.28 (t, J = 7.0 Hz, 3H).

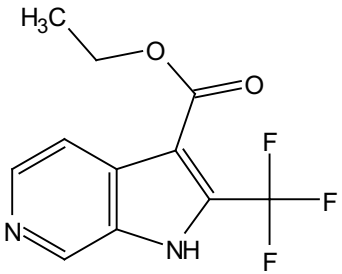


5i

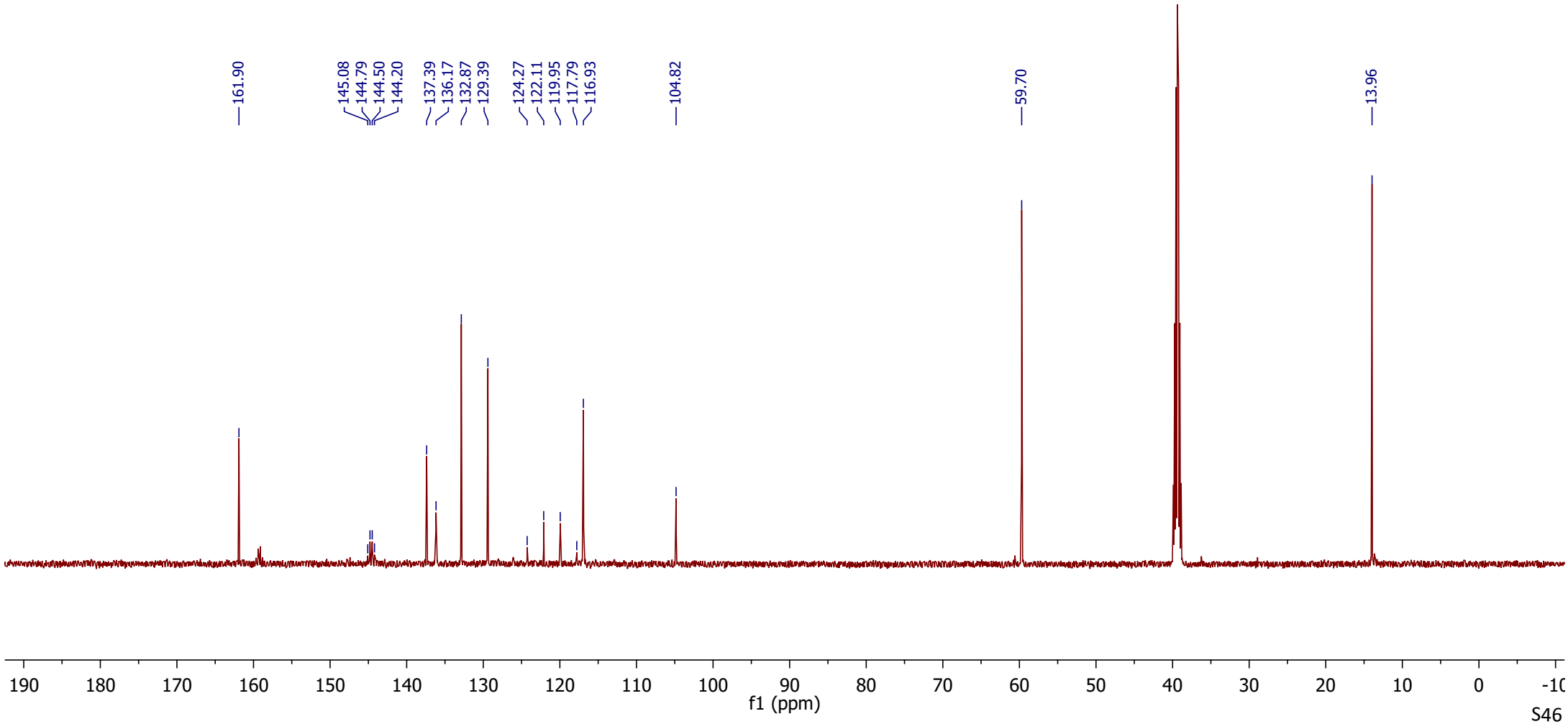


^{13}C NMR of Compound **5i**

^{13}C NMR (126 MHz, DMSO) δ 161.90, 144.65 (q, J = 36.5 Hz), 137.39, 136.17, 132.87, 129.39, 121.03 (q, J = 272.1 Hz), 116.93, 104.82, 59.70, 13.96.

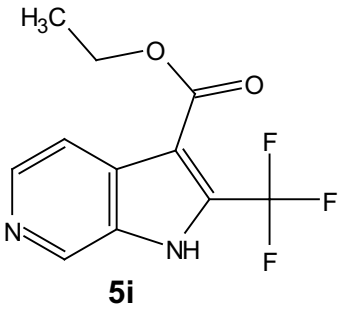


5i



^{19}F NMR of Compound **5i**

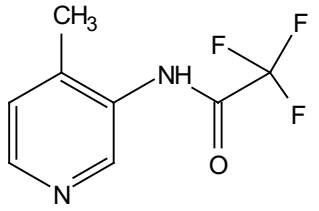
^{19}F NMR (376 MHz, DMSO-d_6) δ -60.78



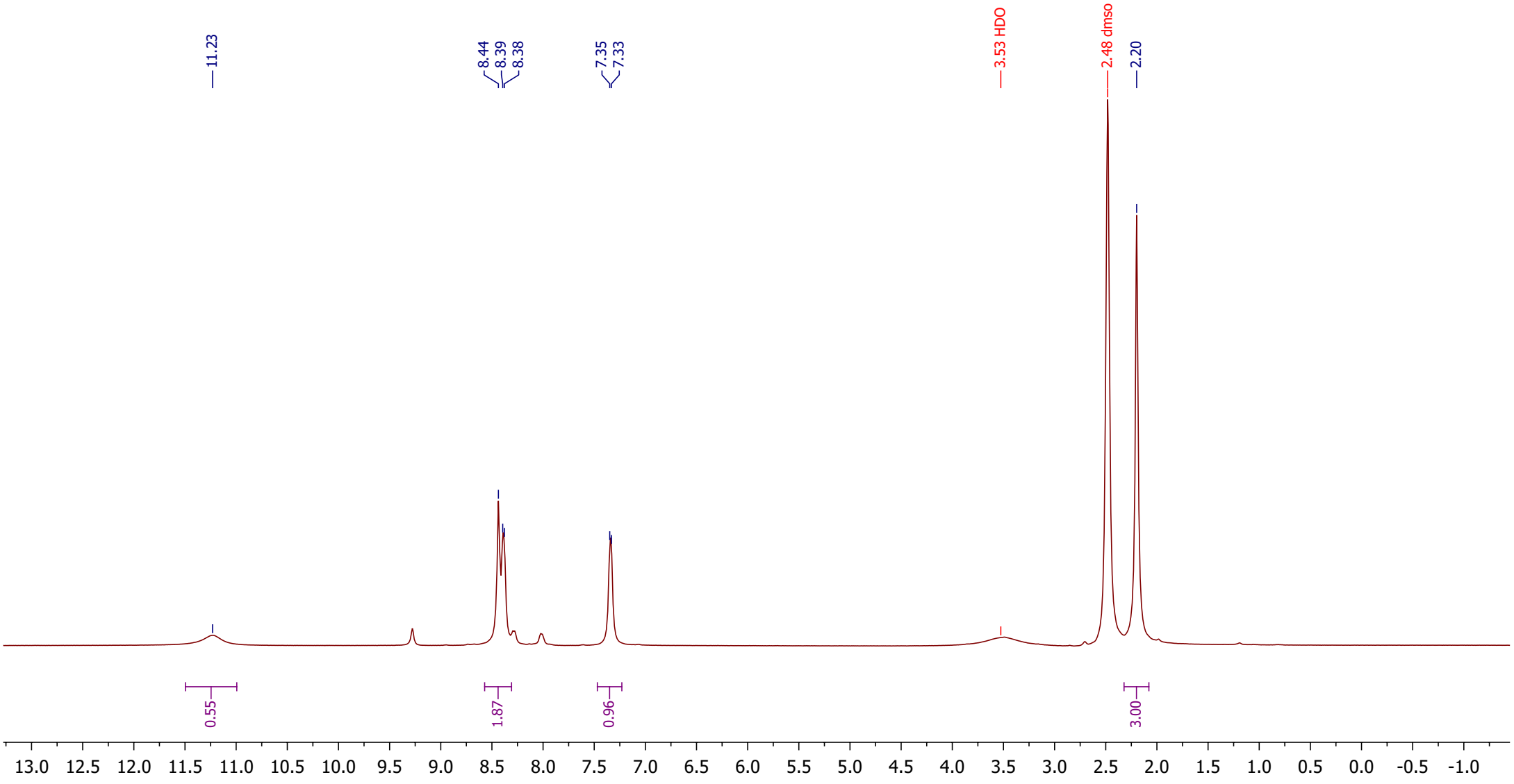
5i

^{1}H NMR of Compound **6a**

^{1}H NMR (302 MHz, DMSO-d_6) δ 11.23 (s, 1H), 8.57 – 8.31 (m, 2H), 7.34 (d, J = 5.2 Hz, 1H), 2.20 (s, 3H).

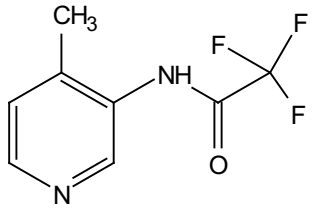


6a



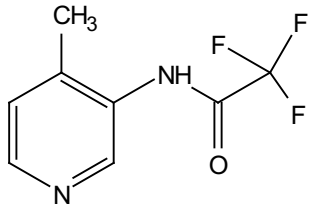
^{13}C NMR of Compound **6a**

^{13}C NMR (151 MHz, dmso) δ 155.93 (q, J = 37.8 Hz), 148.67, 147.79, 143.84, 130.90, 126.02, 116.38 (q, J = 288.4 Hz), 17.25.



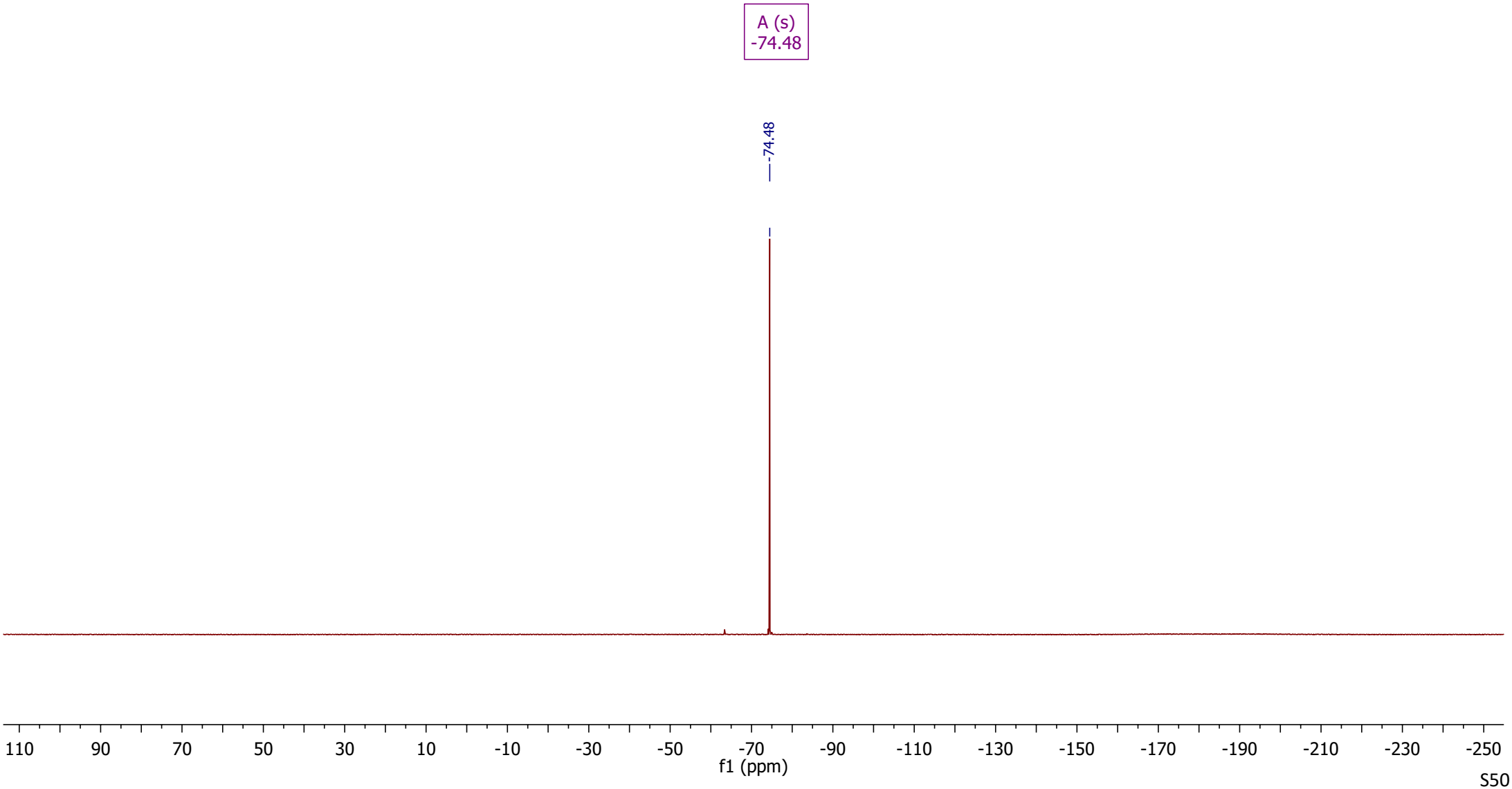
6a

^{19}F NMR of Compound **6a**



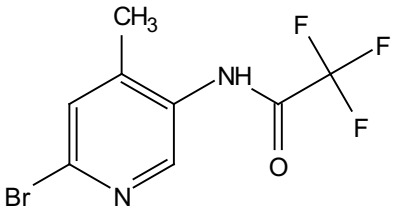
6a

^{19}F NMR (376 MHz, DMSO-d_6) δ -74.48.

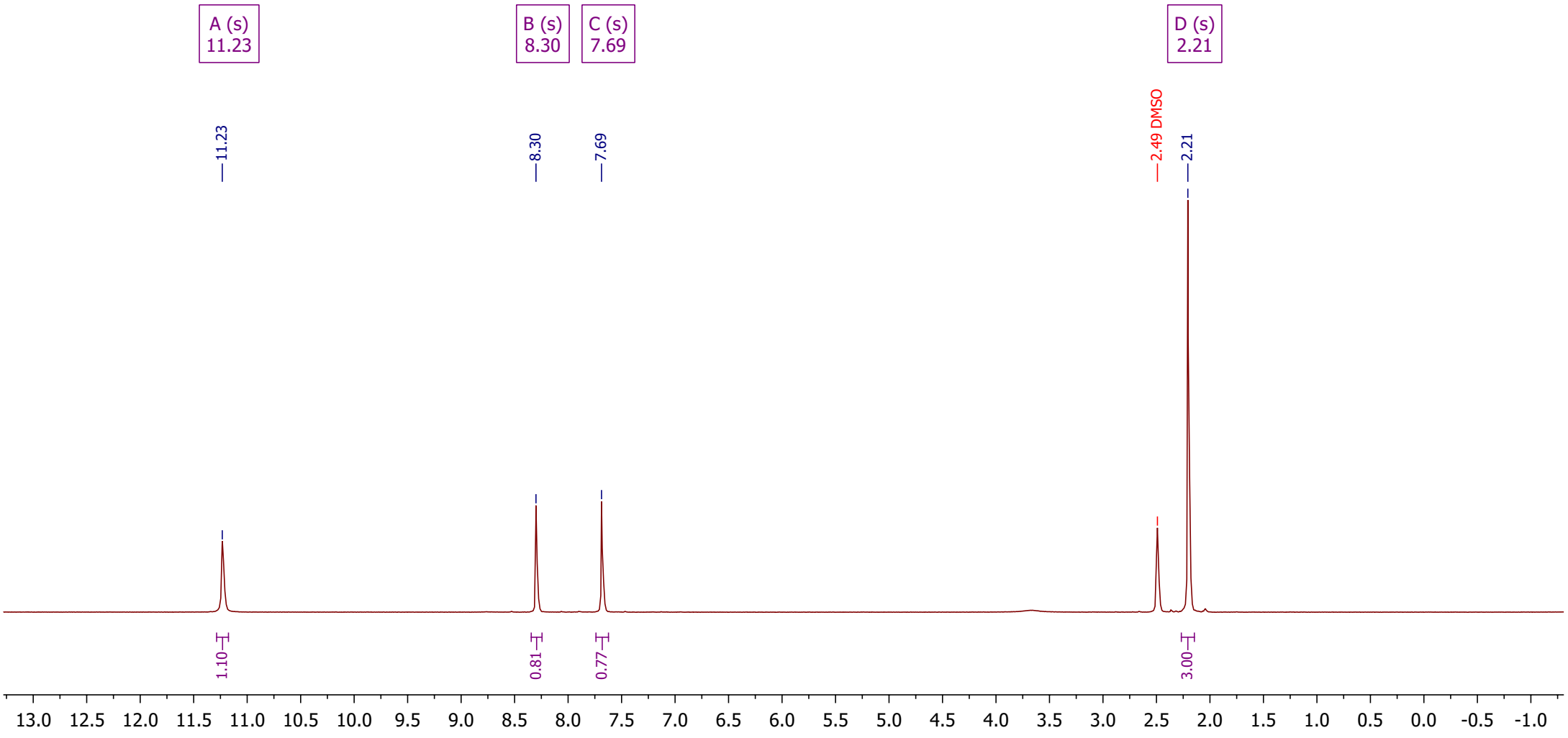


^{1}H NMR of Compound **6j**

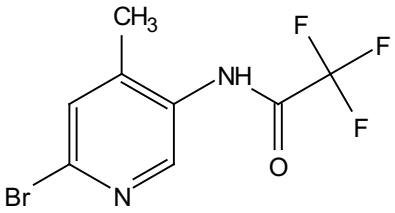
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.23 (s, 1H), 8.30 (s, 1H), 7.69 (s, 1H), 2.21 (s, 3H).



6j

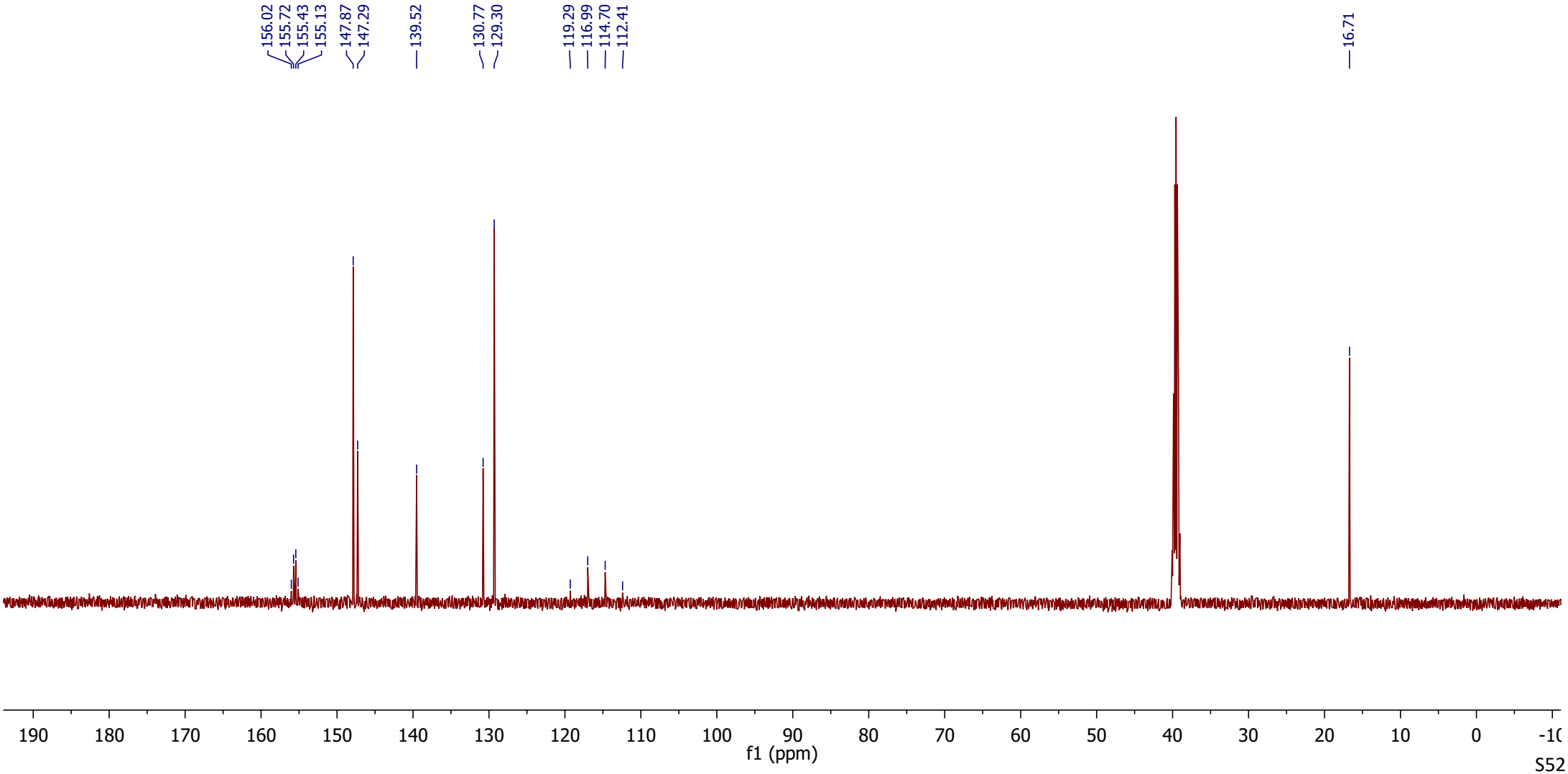


^{13}C NMR of Compound **6j**



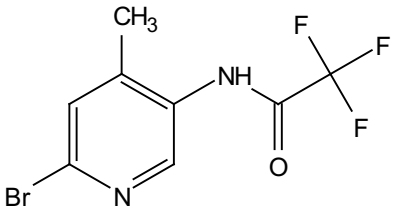
6j

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.58 (q, J = 37.8 Hz), 147.87, 147.29, 139.52, 130.77, 129.30, 115.85 (q, J = 288.5 Hz), 16.71.

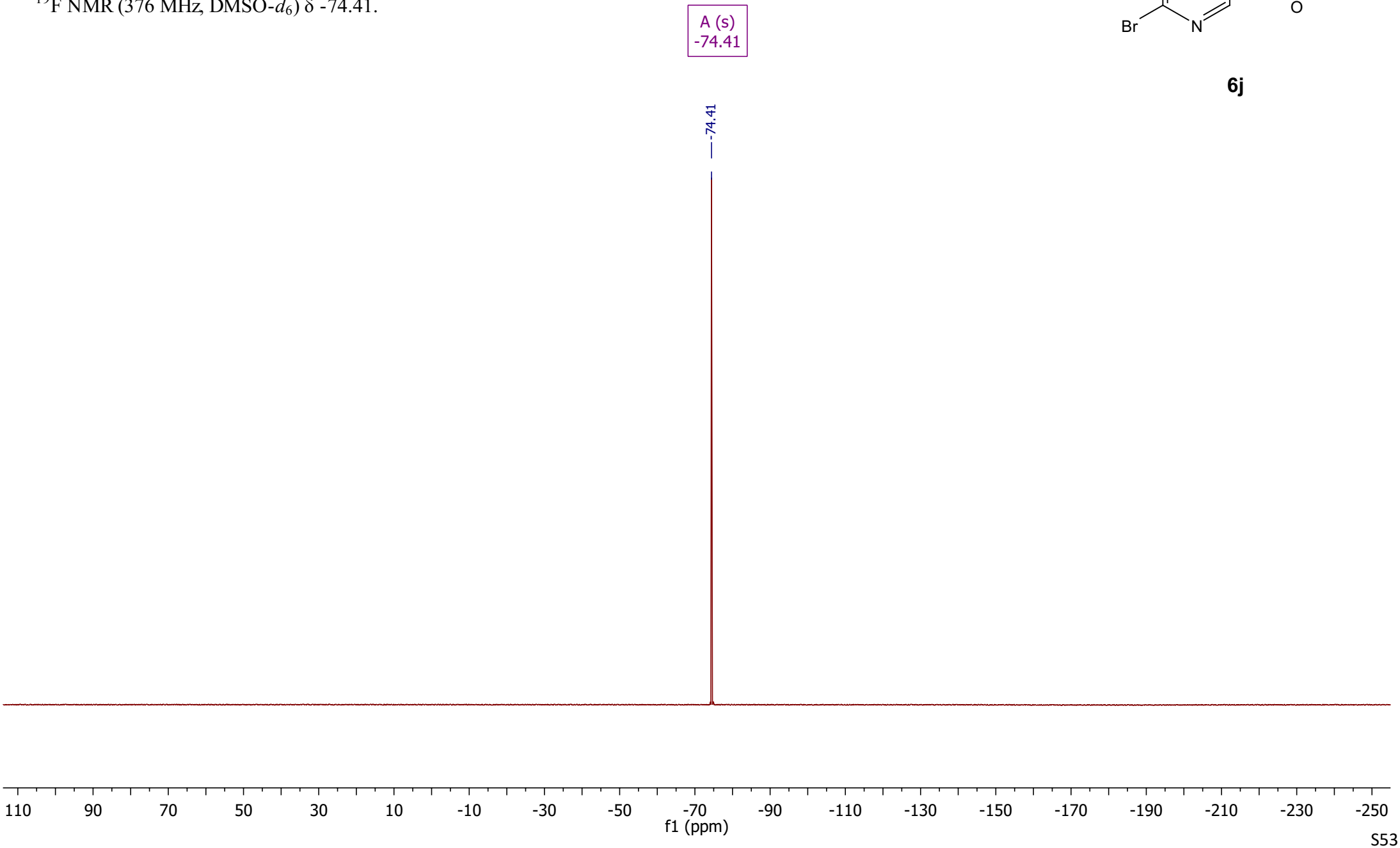


^{19}F NMR of Compound **6j**

^{19}F NMR (376 MHz, DMSO-d_6) δ -74.41.

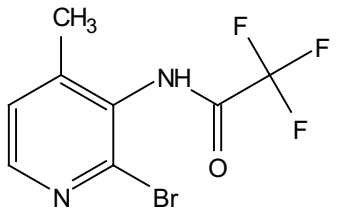


6j

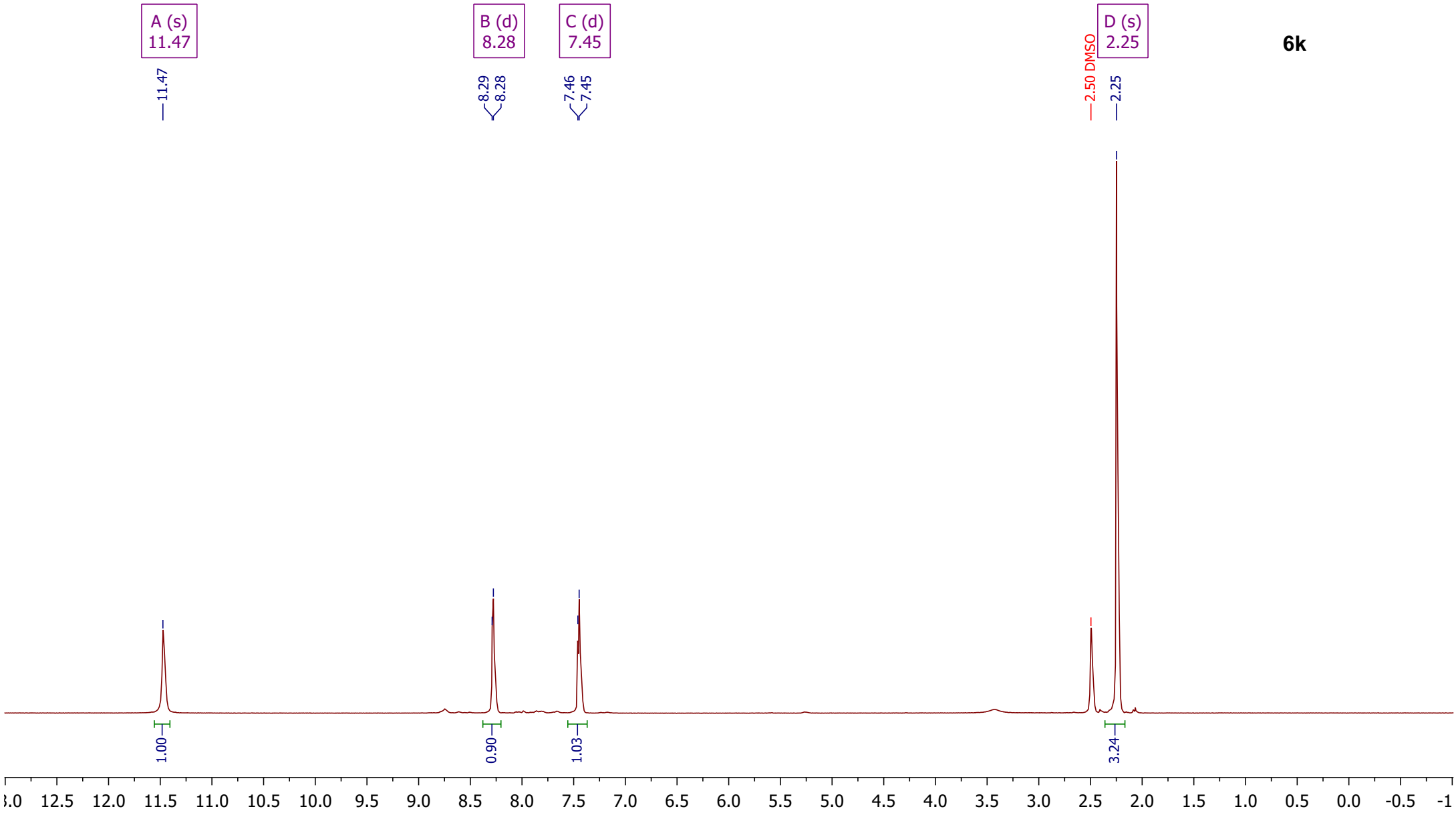


^{1}H NMR of Compound **6k**

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.47 (s, 1H), 8.28 (d, J = 4.9 Hz, 1H), 7.45 (d, J = 4.9 Hz, 1H), 2.25 (s, 3H).

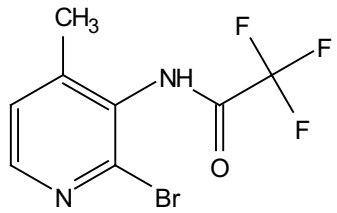


6k

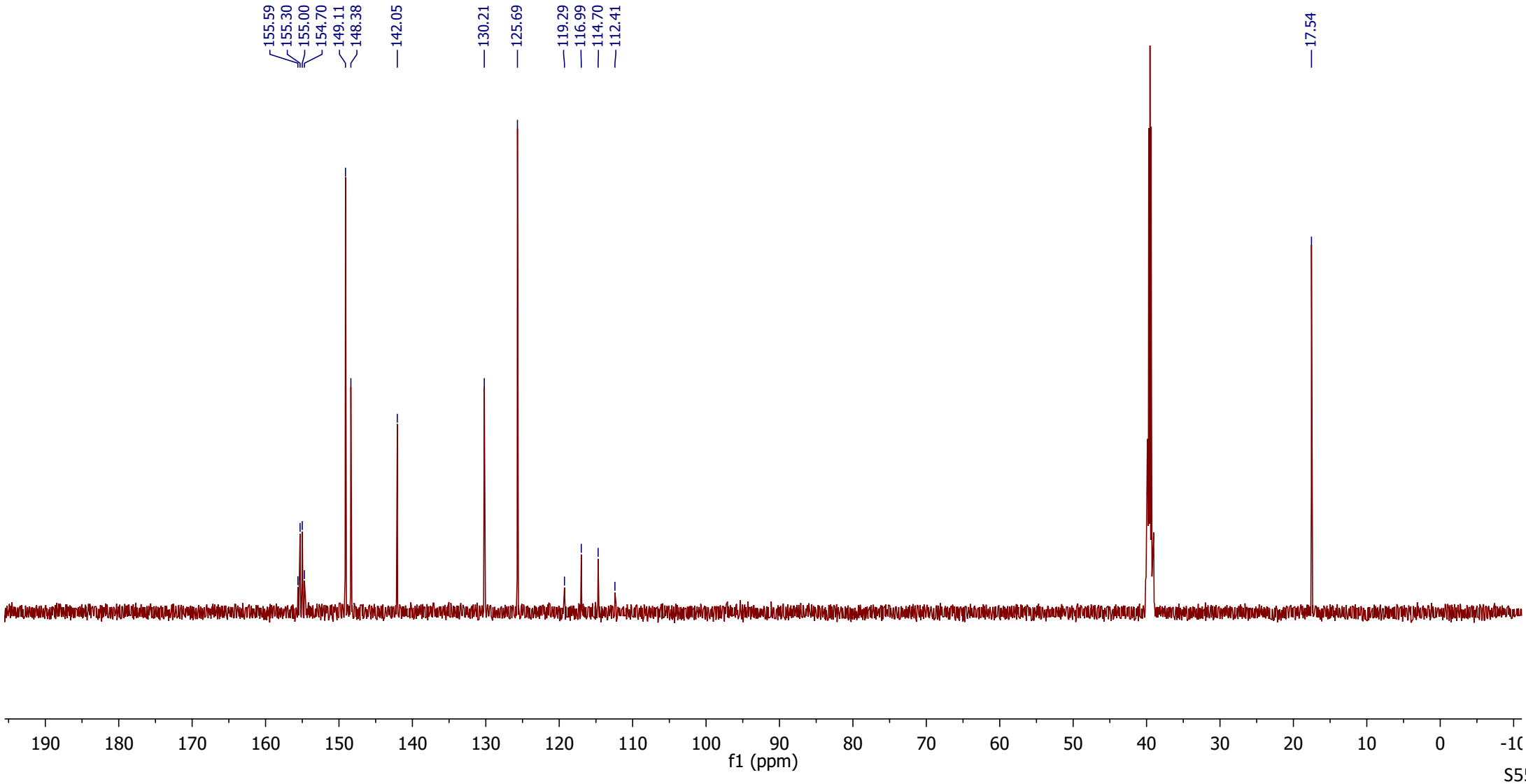


^{13}C NMR of Compound **6k**

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.15 (q, J = 37.8 Hz), 149.11, 148.38, 142.05, 130.21, 125.69, 115.85 (q, J = 288.5 Hz), 17.54.

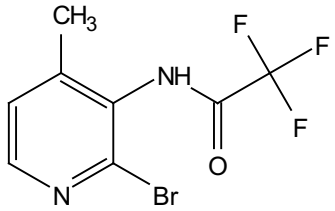


6k

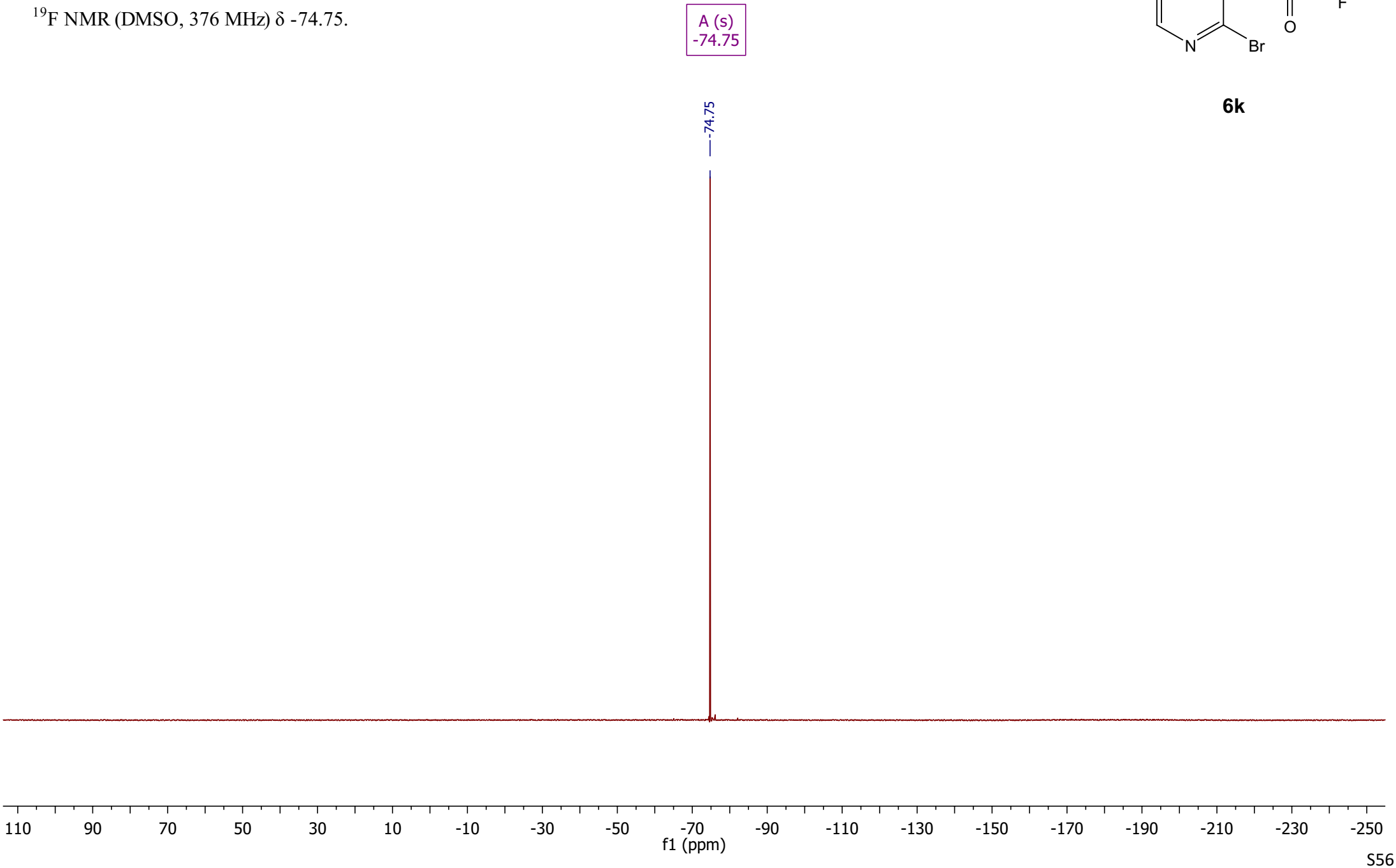


^{19}F NMR of Compound **6k**

^{19}F NMR (DMSO, 376 MHz) δ -74.75.

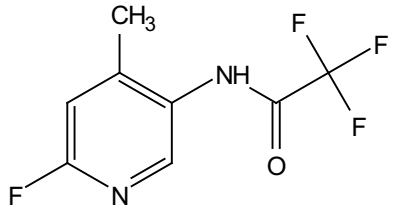


6k

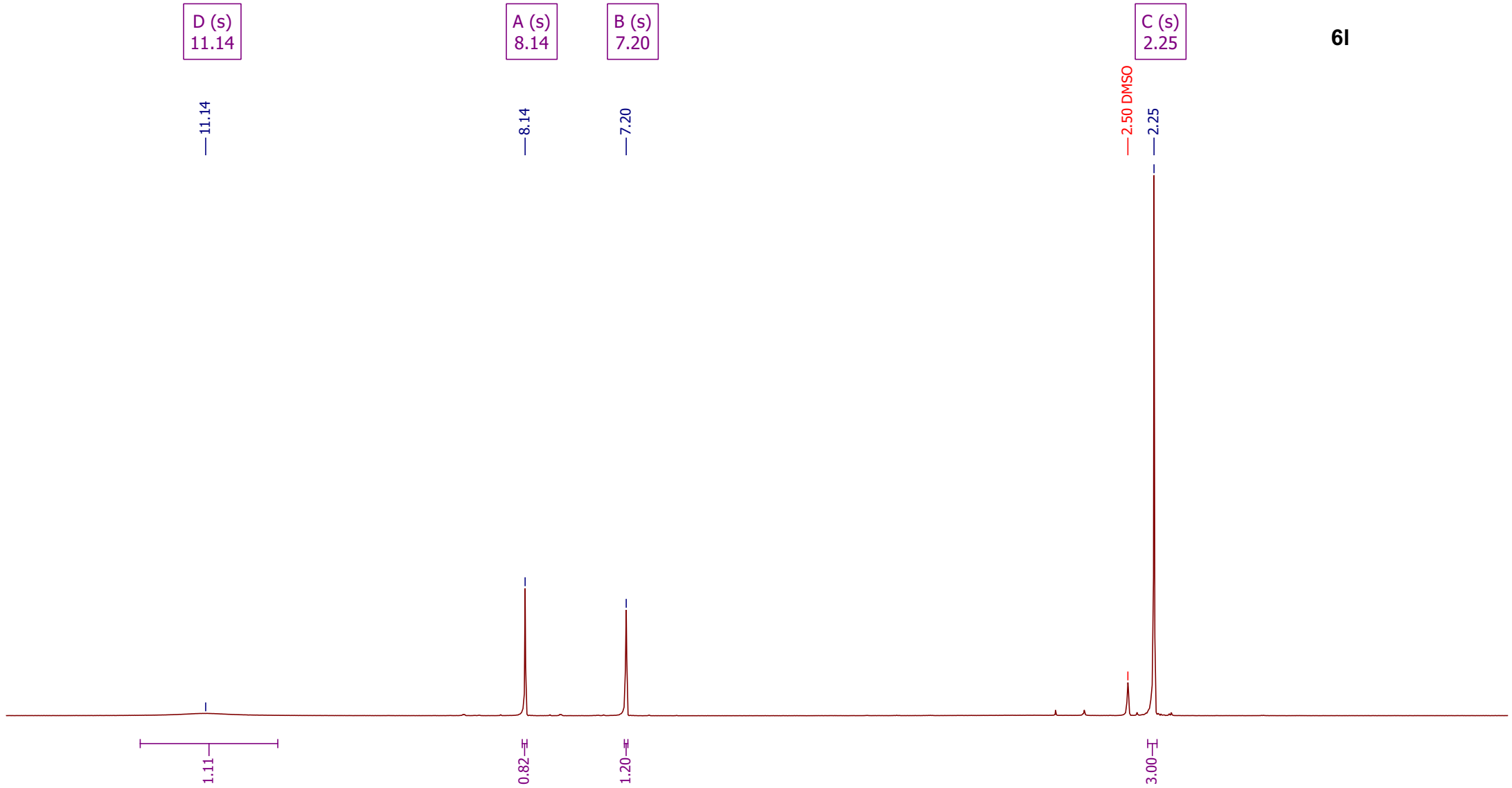


^{1}H NMR of Compound **6l**

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.14 (s, 1H), 8.14 (s, 1H), 7.20 (s, 1H), 2.25 (s, 3H).

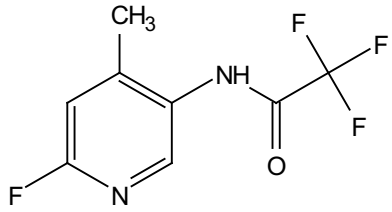


6l



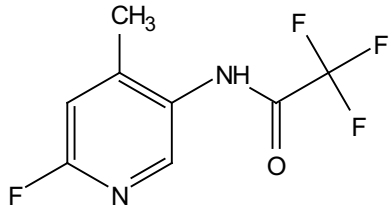
^{13}C NMR of Compound **6l**

^{13}C NMR (101 MHz, DMSO) δ 162.20 (d, J = 237.4 Hz), 156.26 (q, J = 37.4 Hz), 150.68 (d, J = 10.1 Hz),145.65 (d, J = 17.2 Hz), 129.56, 116.40 (q, J = 289.9 Hz), 111.00 (d, J = 39.4 Hz), 17.65.



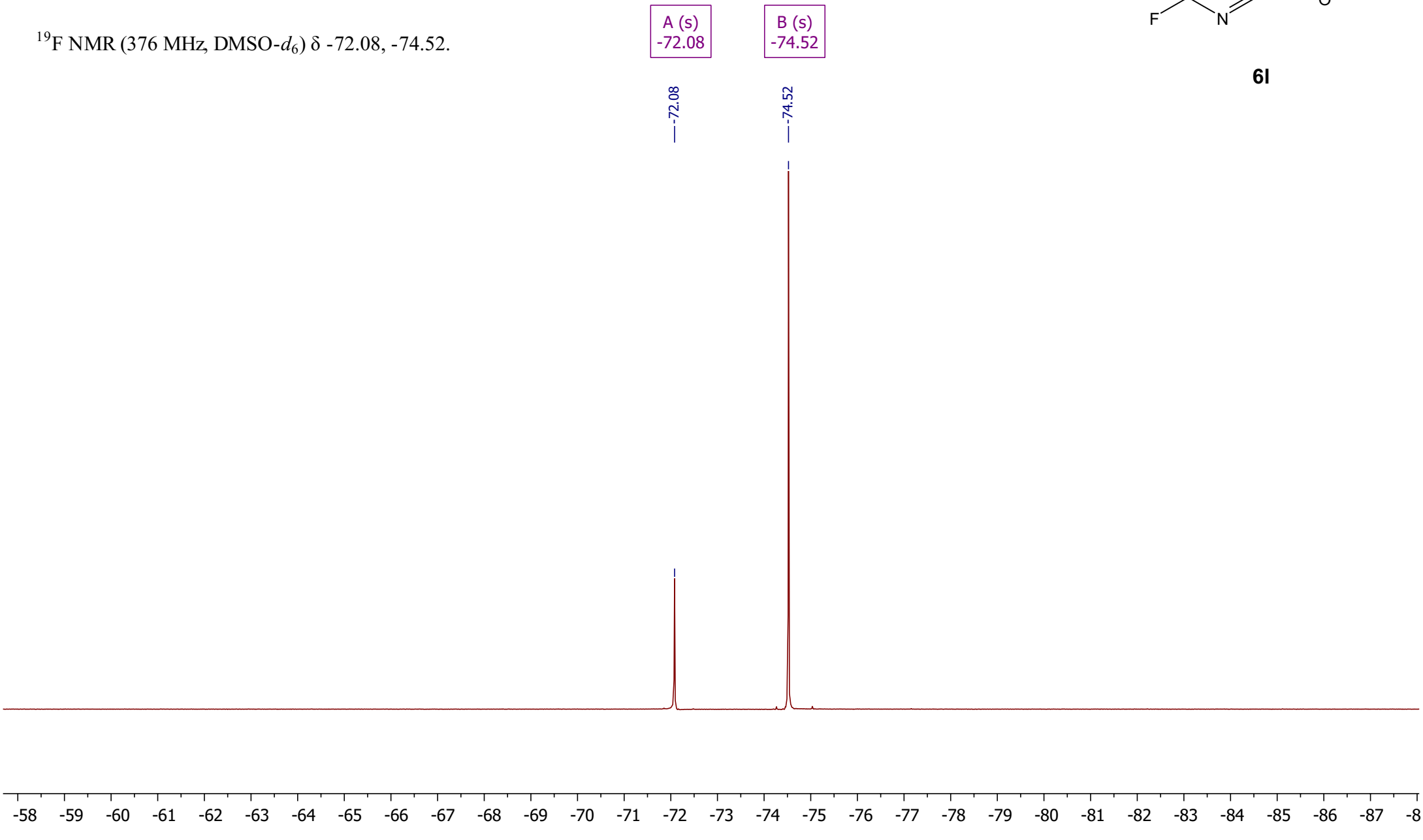
6l

^{19}F NMR of Compound **6l**



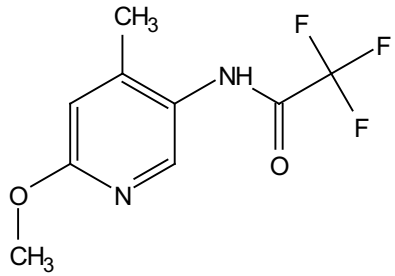
6l

^{19}F NMR (376 MHz, DMSO-d_6) δ -72.08, -74.52.

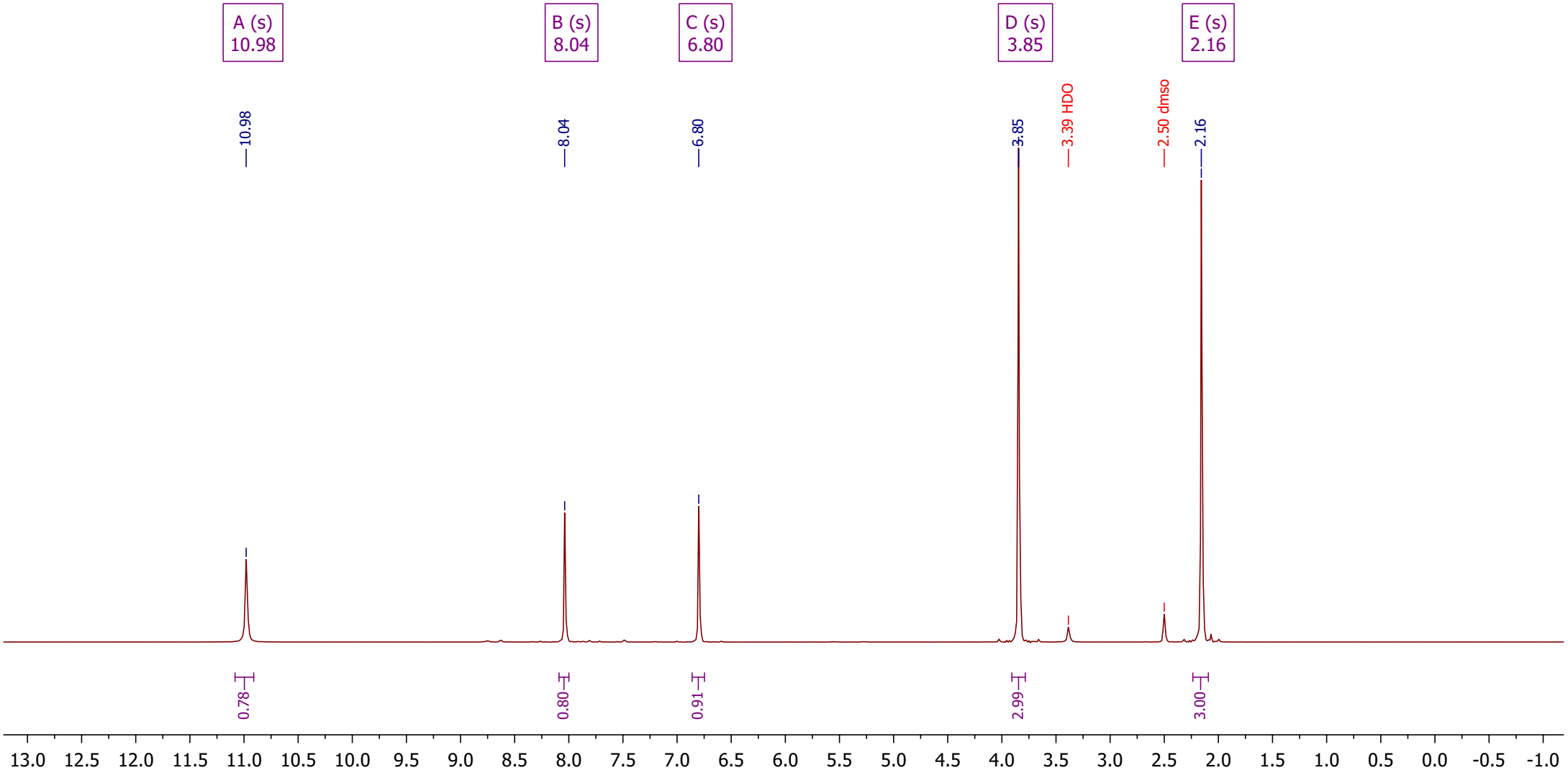


^{1}H NMR of Compound **6m**

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 8.04 (s, 1H), 6.80 (s, 1H), 3.85 (s, 3H), 2.16 (s, 3H).

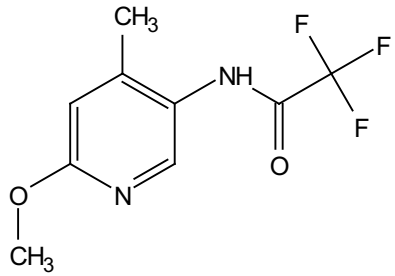


6m

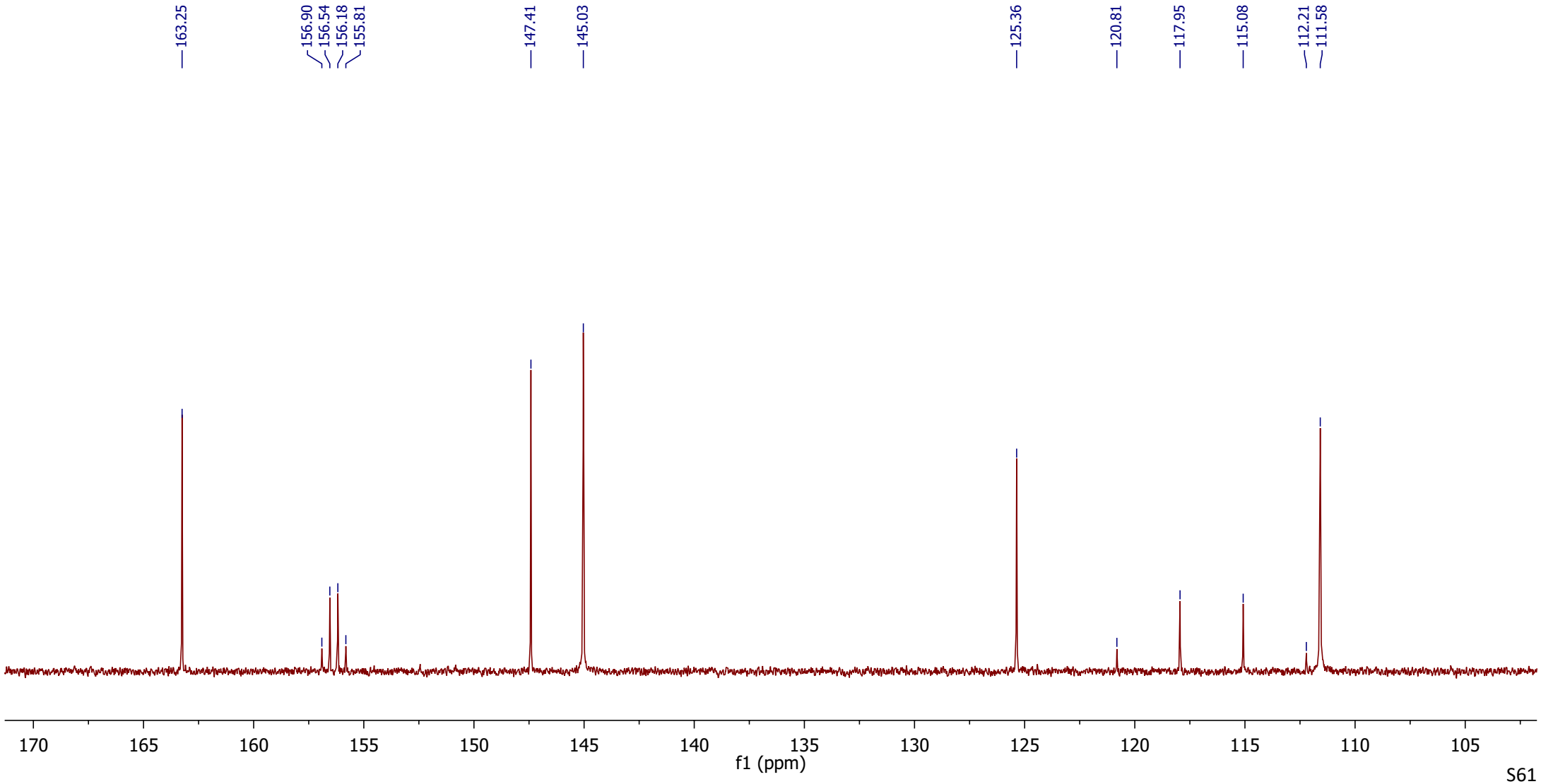


^{13}C NMR of Compound **6m**

^{13}C NMR (101 MHz, DMSO) δ 163.25, 156.36 (q, J = 36.4 Hz), 147.41, 145.03, 125.36, 116.52 (q, J = 282.9 Hz), 111.58, 53.75, 17.38.

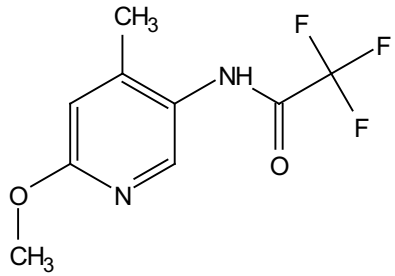


6m

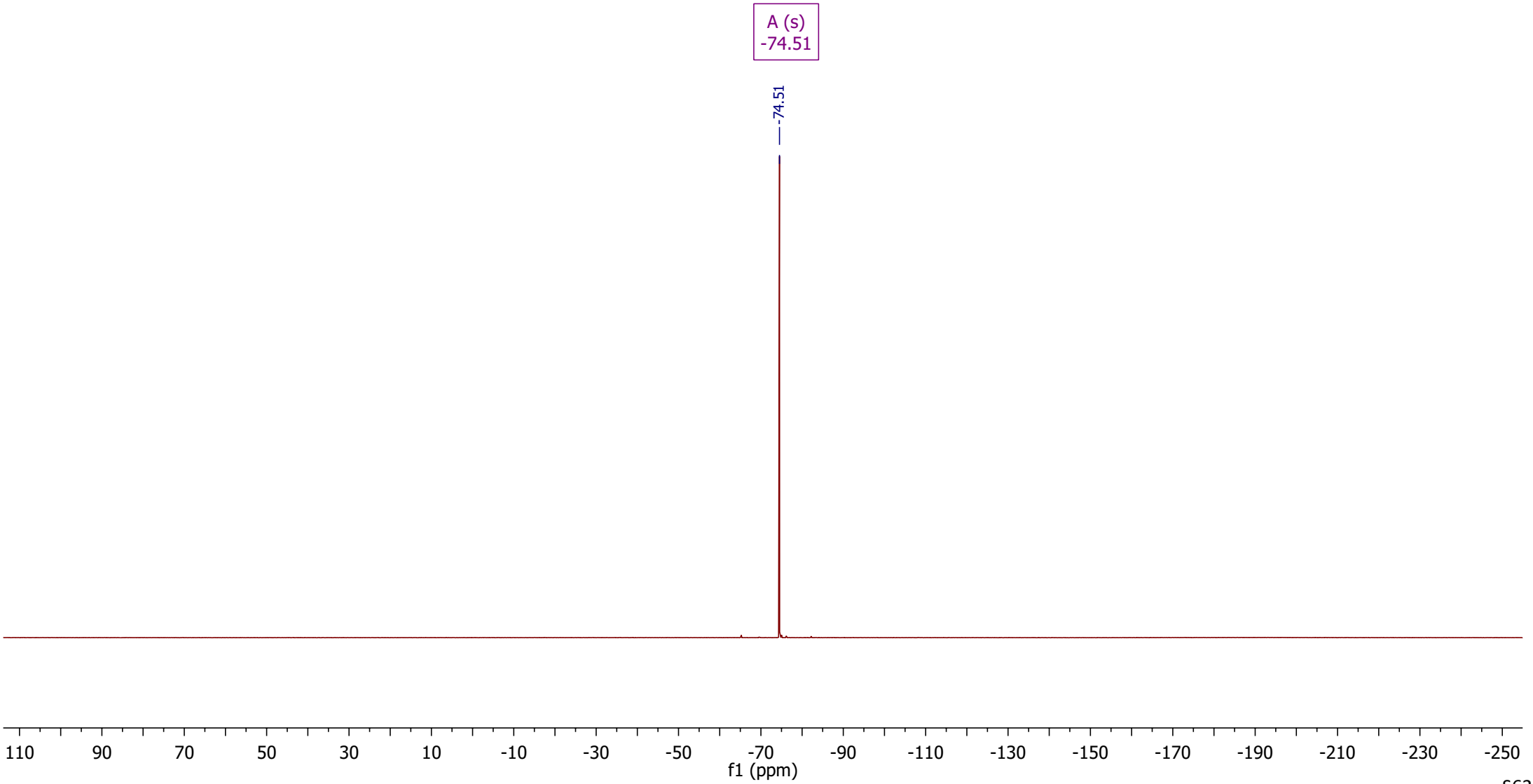


^{19}F NMR of Compound **6m**

^{19}F NMR (376 MHz, DMSO-d_6) δ -74.51.

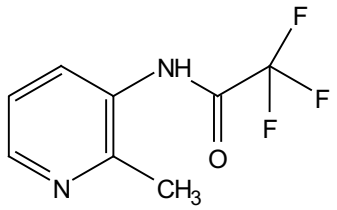


6m

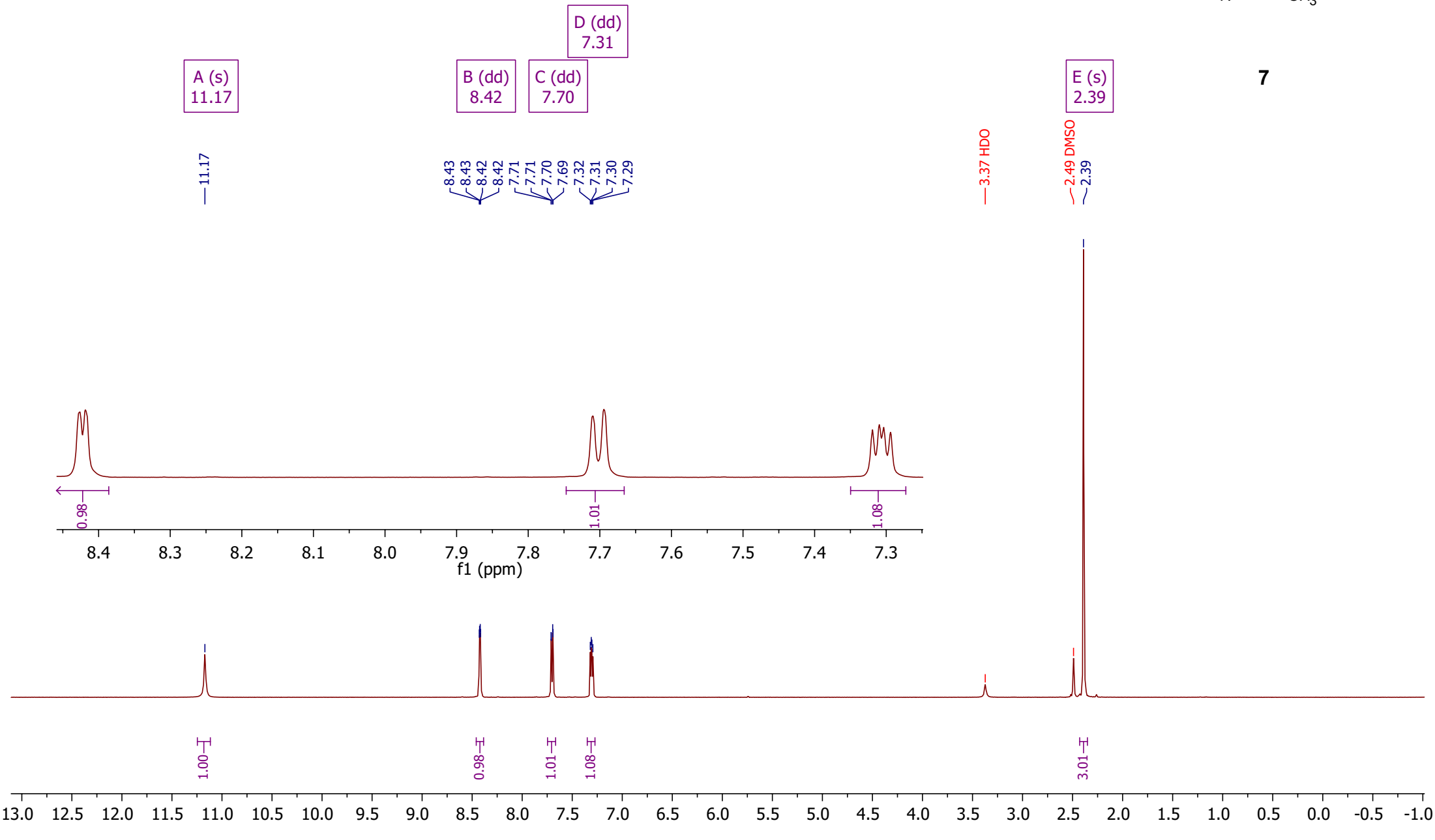


^{1}H NMR of Compound **7**

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.17 (s, 1H), 8.42 (dd, J = 4.8, 1.6 Hz, 1H), 7.70 (dd, J = 8.0, 1.7 Hz, 1H), 7.31 (dd, J = 8.0, 4.8 Hz, 1H), 2.39 (s, 3H).

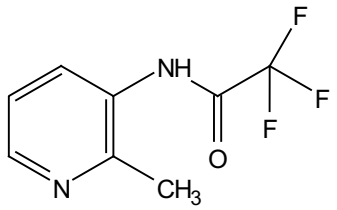


7

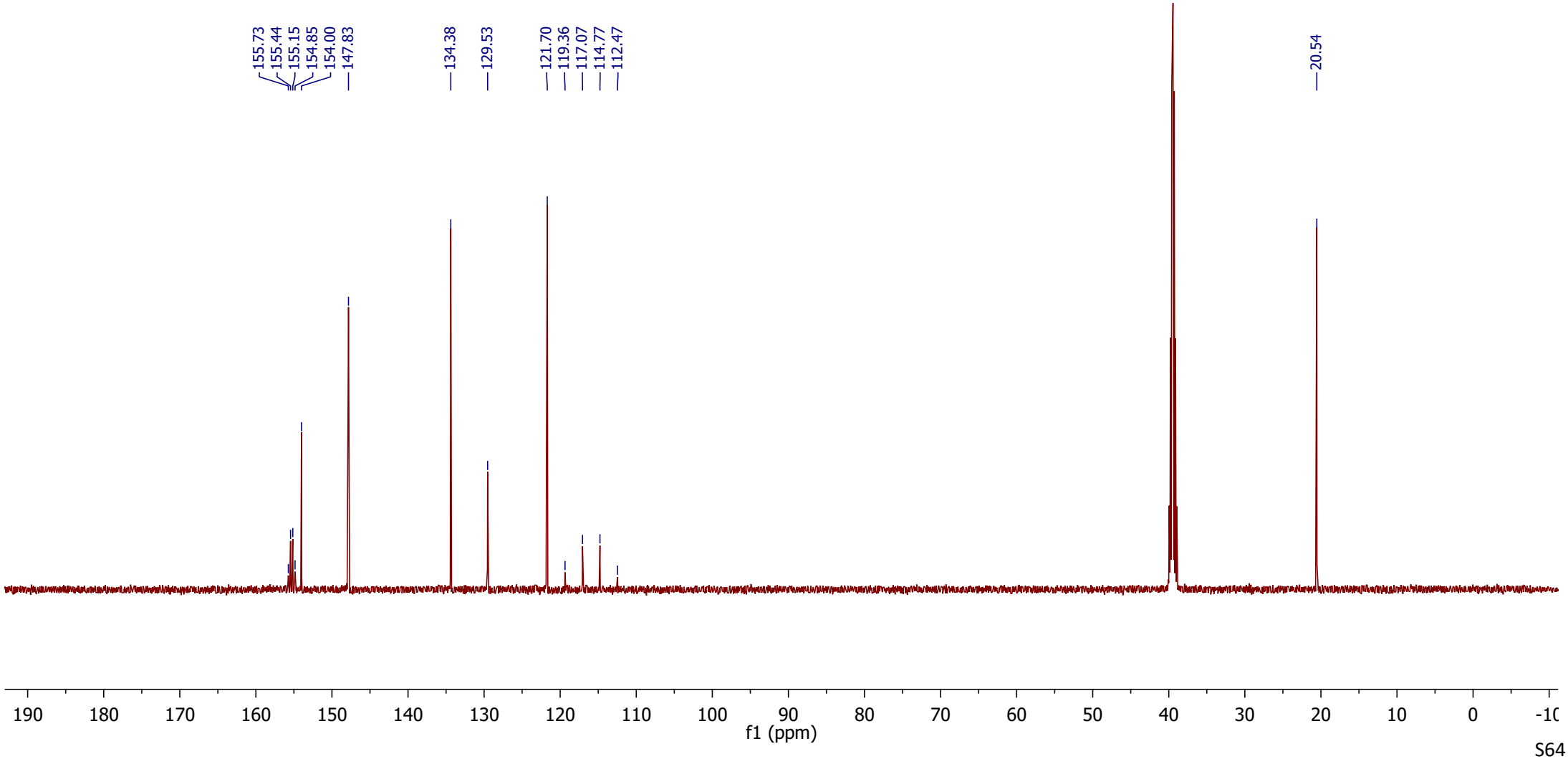


^{13}C NMR of Compound **7**

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.30 (q, J = 37.8 Hz), 154.00, 147.83, 134.38, 129.53, 121.70, 115.92 (q, J = 289.8 Hz), 20.54.

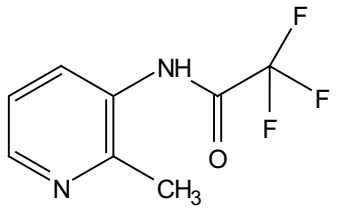


7

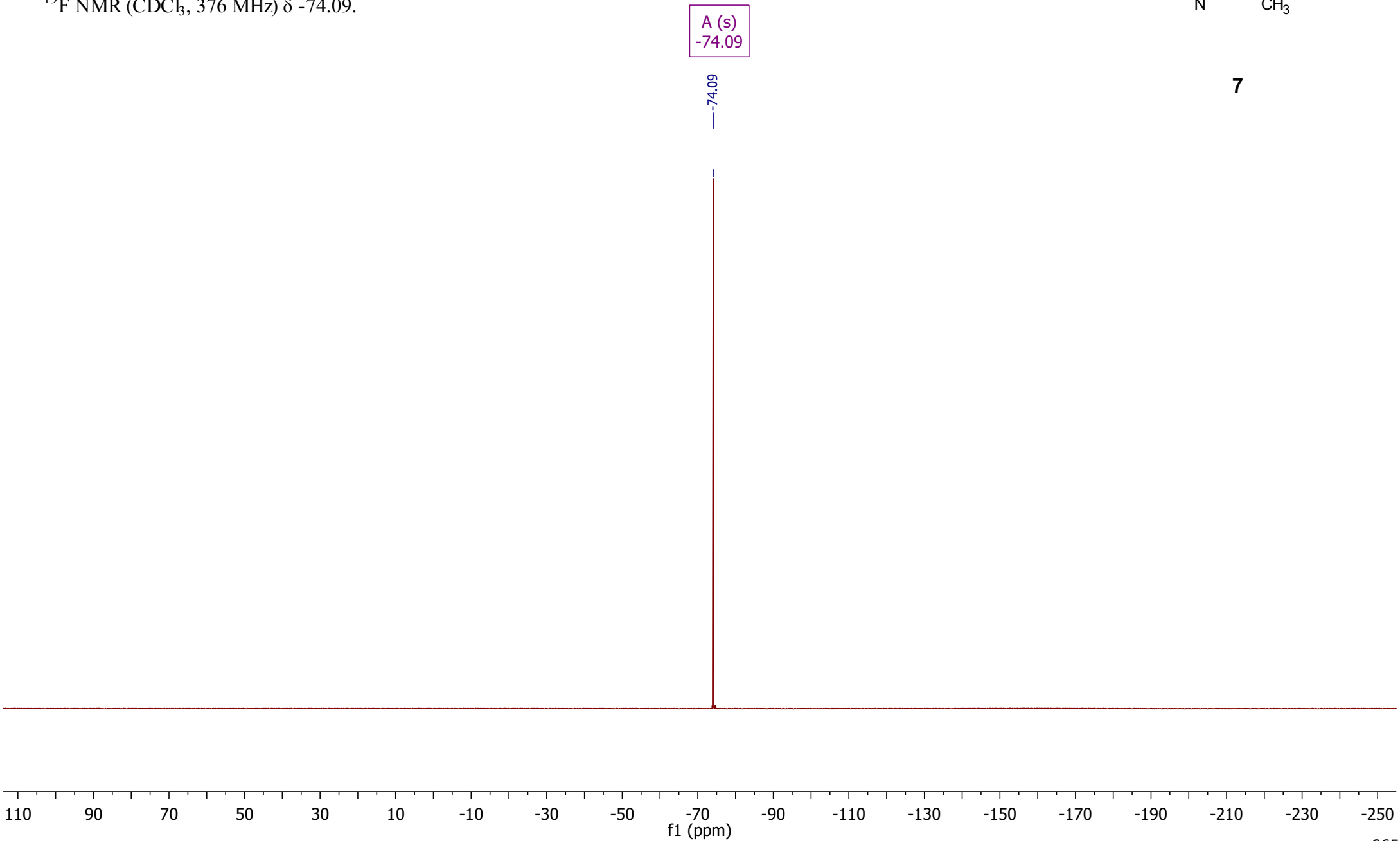


^{19}F NMR of Compound **7**

^{19}F NMR ($CDCl_3$, 376 MHz) δ -74.09.

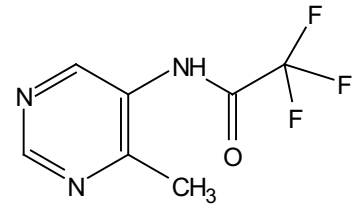


7

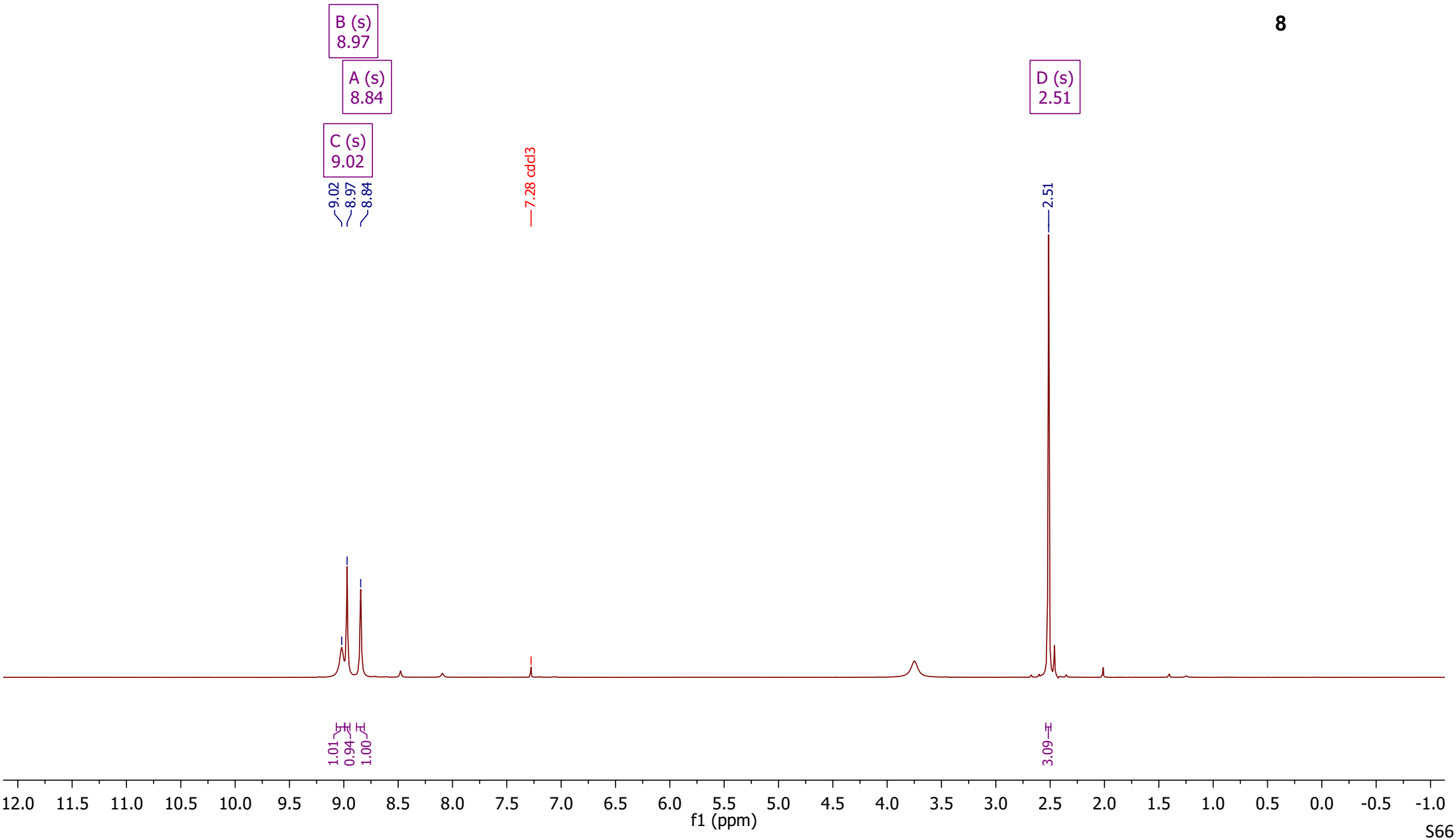


^{1}H NMR of Compound **8**

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.02 (s, 1H), 8.97 (s, 1H), 8.84 (s, 1H), 2.51 (s, 3H).

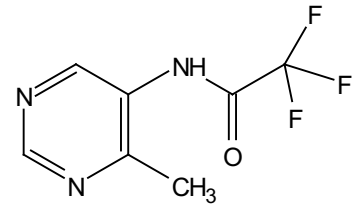


8

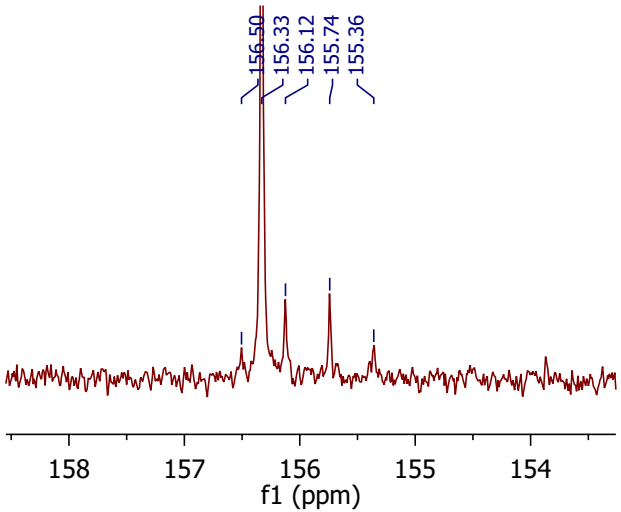


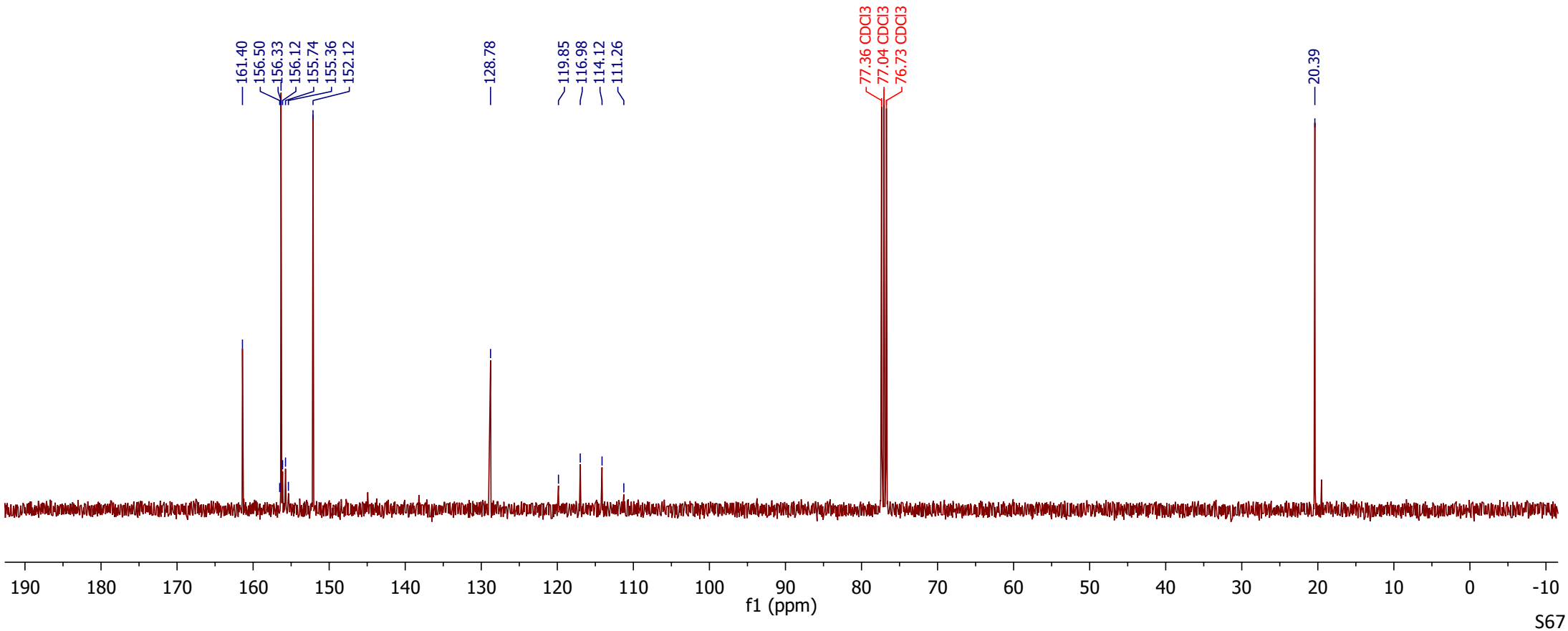
^{13}C NMR of Compound **8**

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.40, 156.33, 155.93 (q, J = 38.4 Hz), 152.12, 128.78, 115.55 (q, J = 288.7 Hz), 20.39.



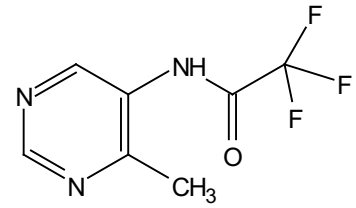
8





^{19}F NMR of Compound **8**

^{19}F NMR (376 MHz, $CDCl_3$) δ -75.79.



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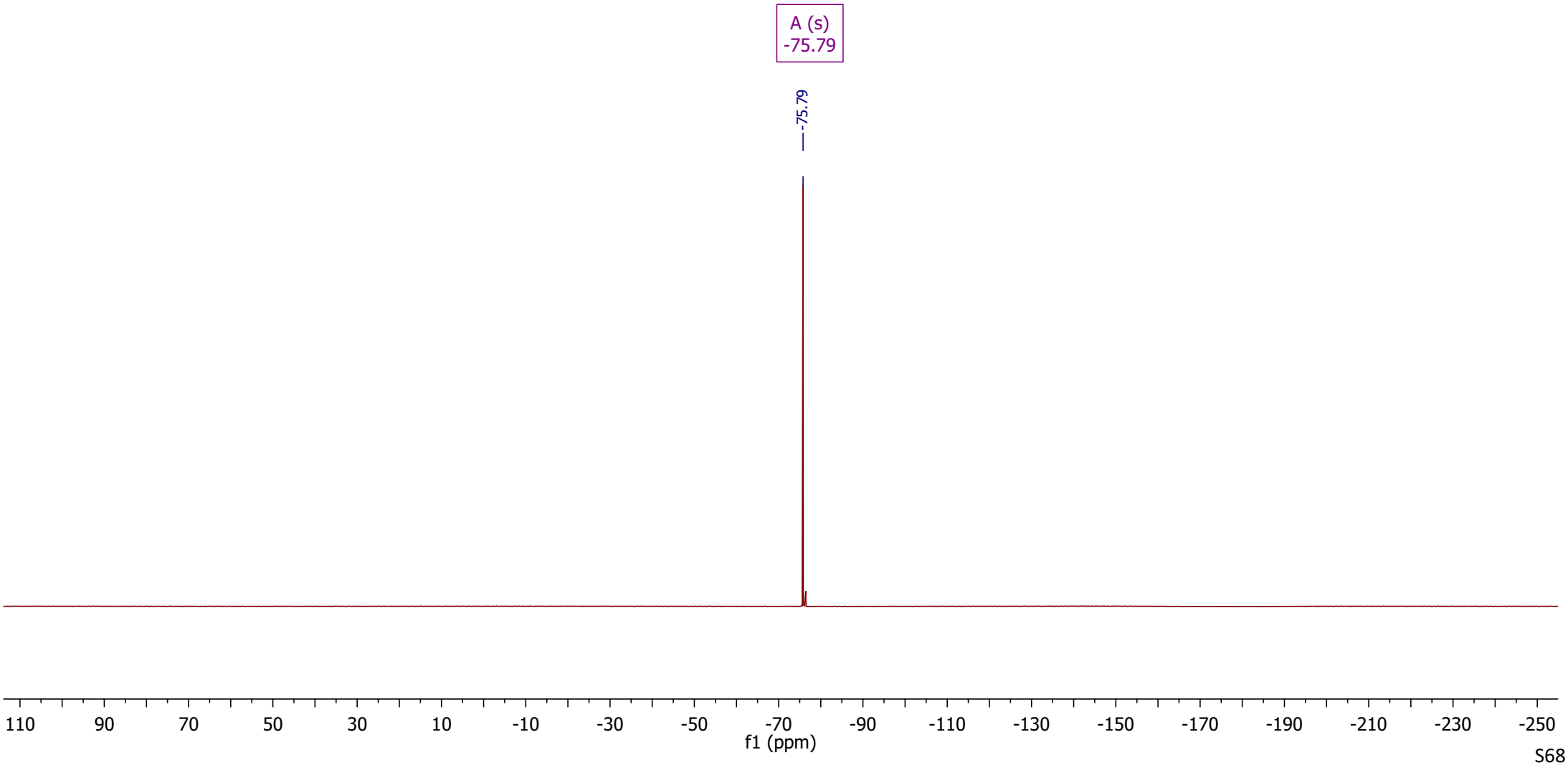
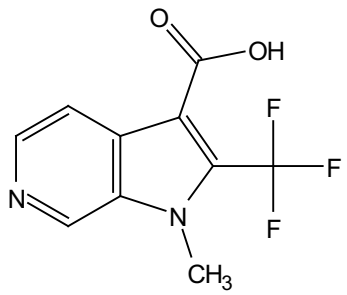


^{1}H NMR of Compound **10**

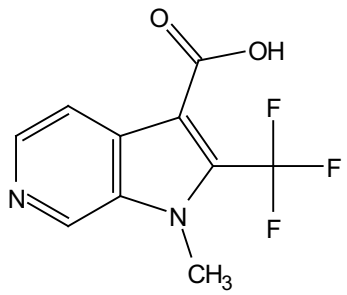
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.59 (s, 1H), 8.49 (d, J = 6.1 Hz, 1H), 8.25 (d, J = 6.0 Hz, 1H), 4.15 (s, 3H).



10

^{13}C NMR of Compound **10**

^{13}C NMR (126 MHz, DMSO) δ 162.57, 135.11, 133.73 (q, J = 37.8 Hz), 133.12, 132.85, 132.05, 119.84 (q, J = 273.4 Hz), 117.66, 110.48, 33.89.



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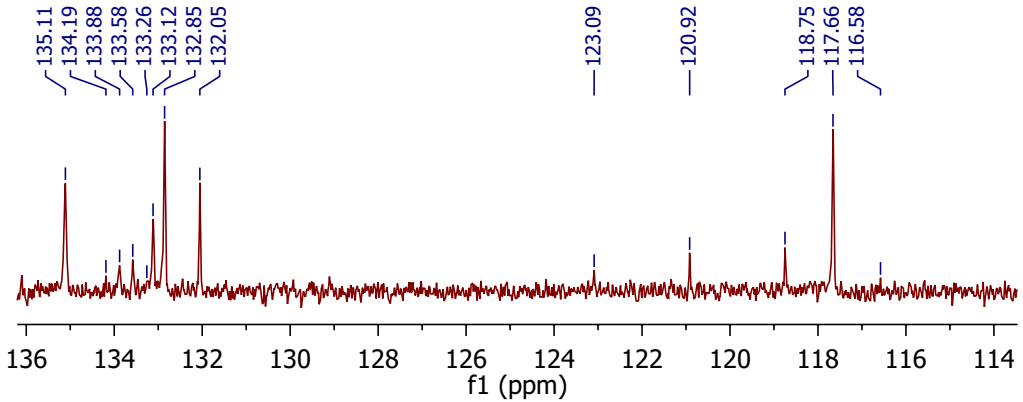
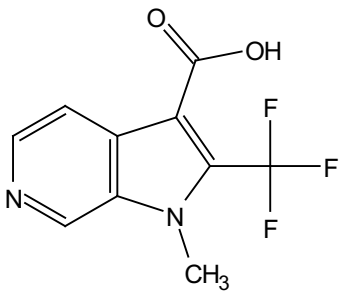
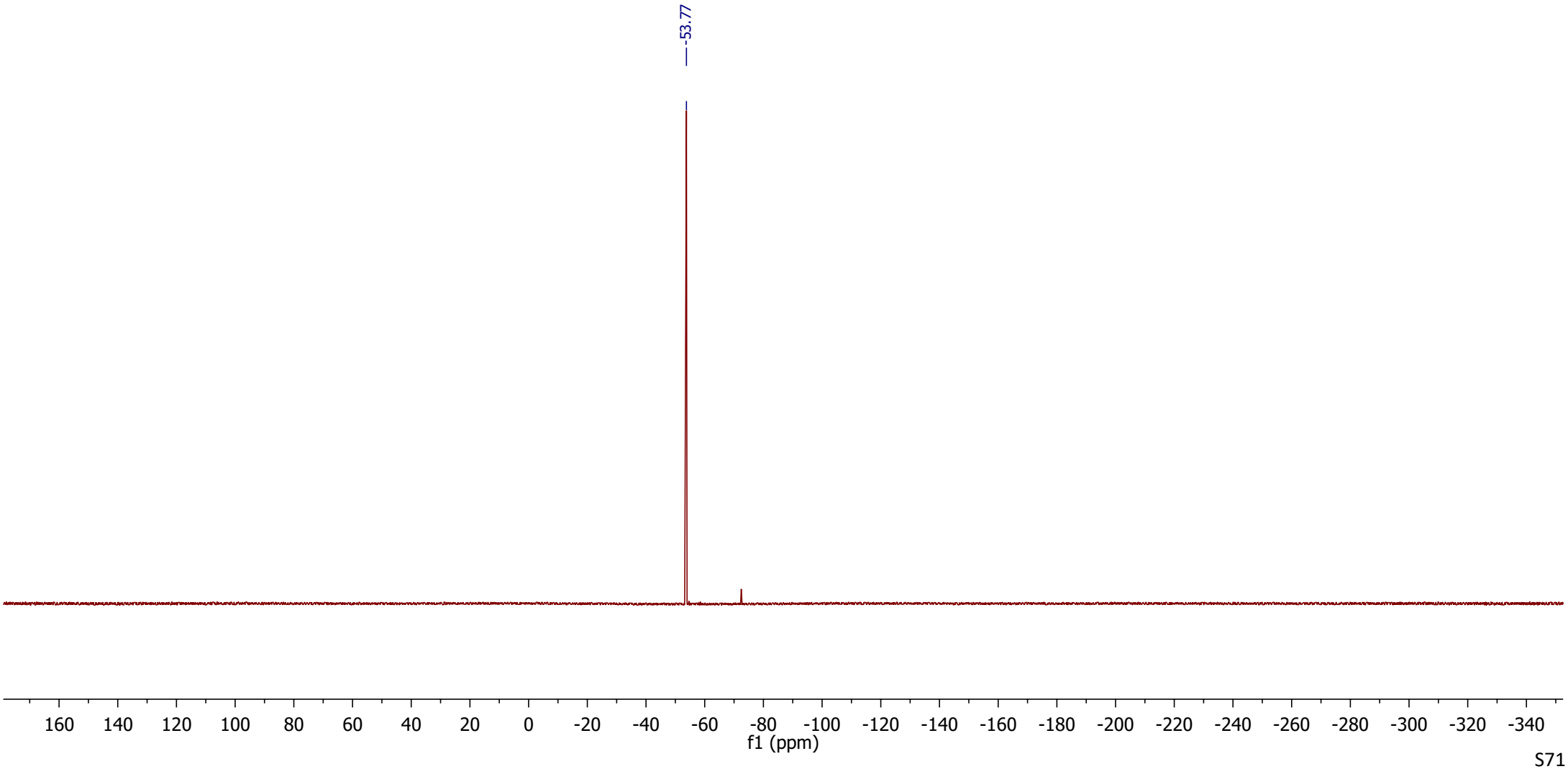


^{19}F NMR of Compound **10**

^{19}F NMR ($cdcl_3$, 188 MHz) δ -53.77.

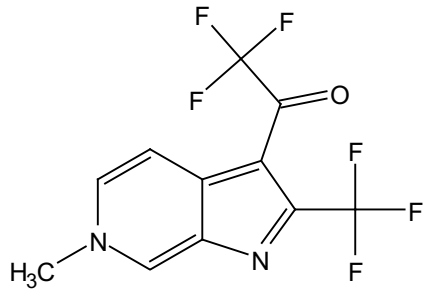


10

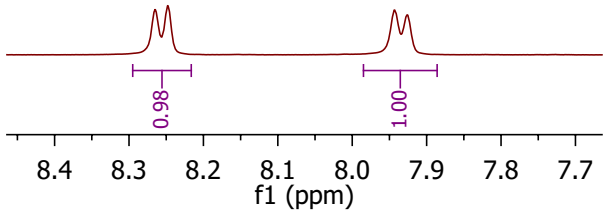


^{1}H NMR of Compound **11**

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.29 (s, 1H), 8.26 (d, J = 6.9 Hz, 1H), 7.93 (d, J = 6.9 Hz, 1H), 4.26 (s, 3H).

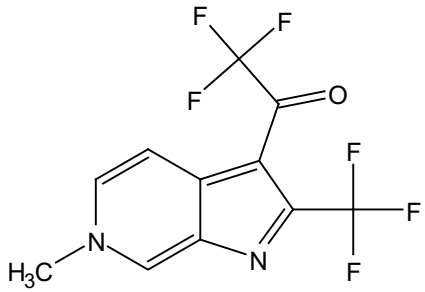


11



^{13}C NMR of Compound **11**

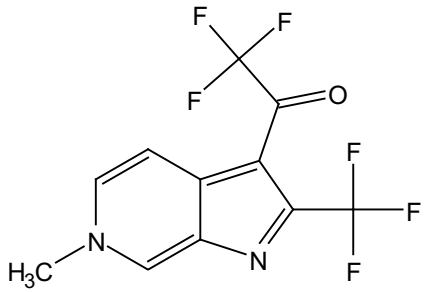
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.53 (q, J = 35.3 Hz), 152.97 (q, J = 36.5 Hz), 142.10, 138.69, 136.85, 134.41, 121.97 (q, J = 270.9 Hz), 119.77 (q, J = 289.8 Hz), 116.19 (q, J = 6.3 Hz), 106.35, 46.70.



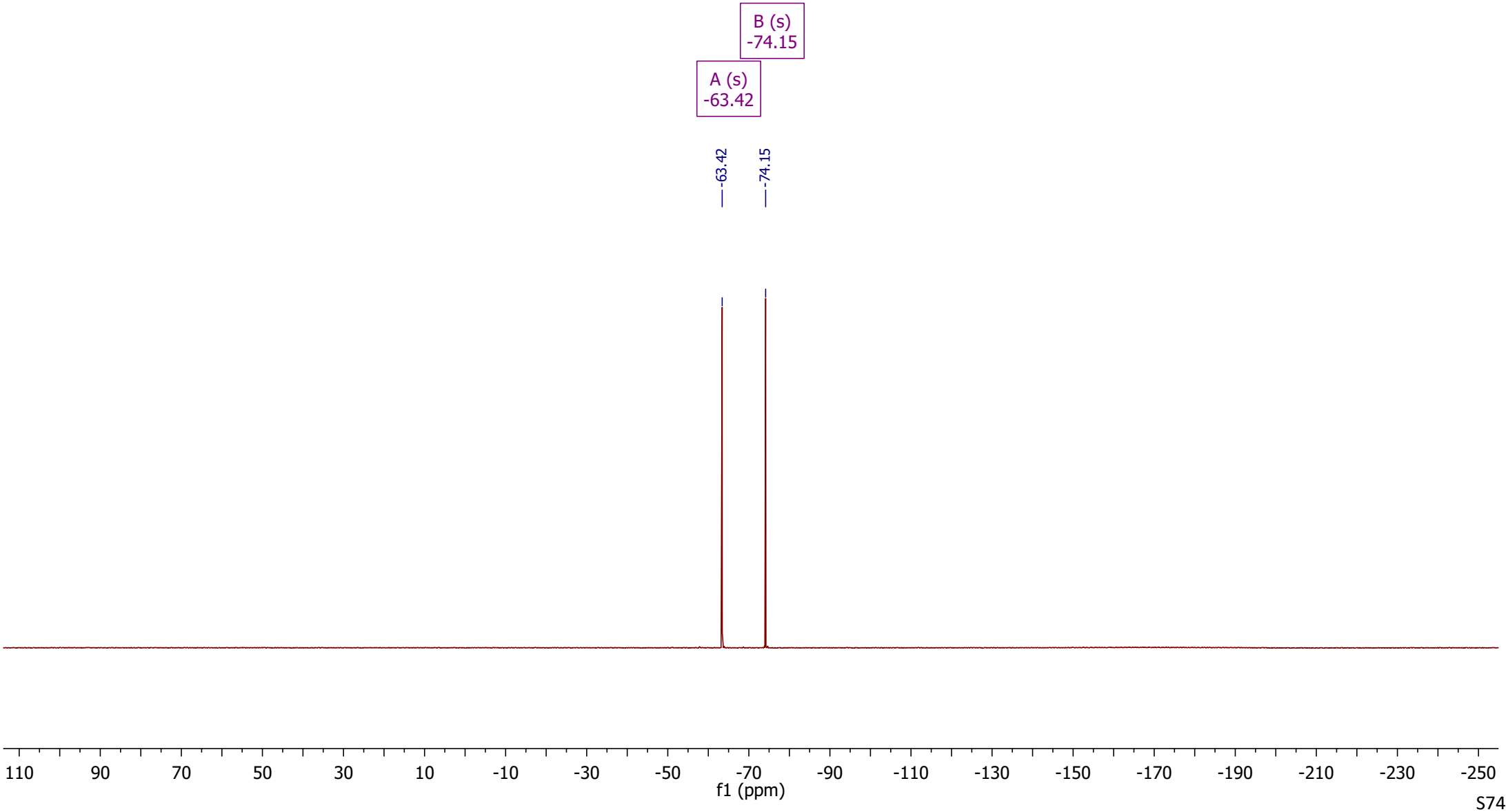
11

^{19}F NMR of Compound **11**

^{19}F NMR (DMSO, 376 MHz) δ -74.15, -63.42.

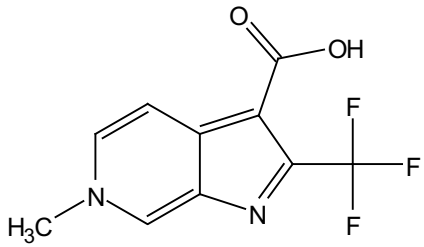


11

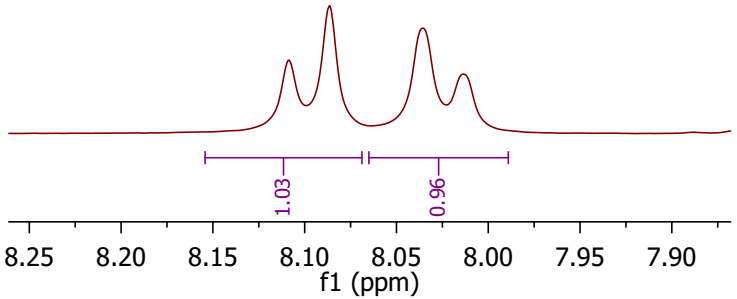


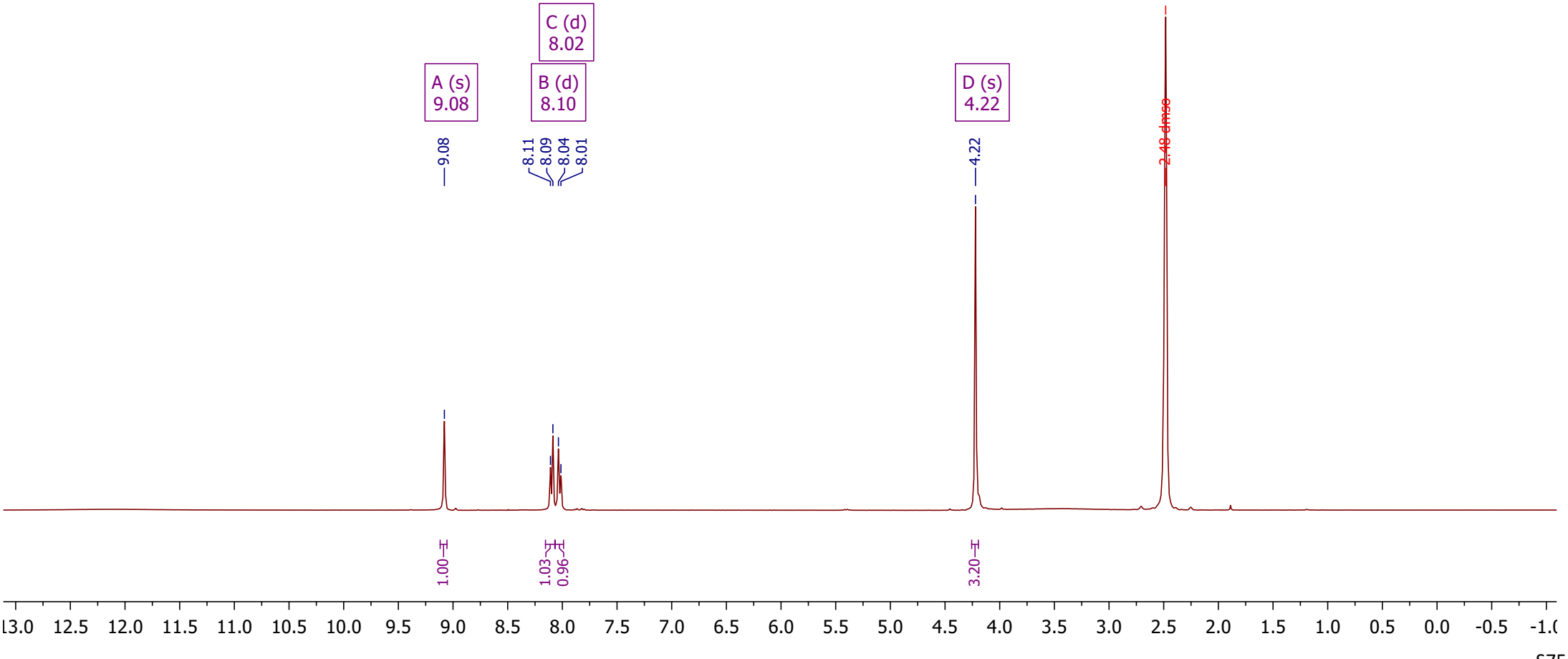
^{1}H NMR of Compound **12**

^{1}H NMR (302 MHz, DMSO-d_6) δ 9.08 (s, 1H), 8.10 (d, J = 6.7 Hz, 1H), 8.02 (d, J = 6.8 Hz, 1H), 4.22 (s, 3H).



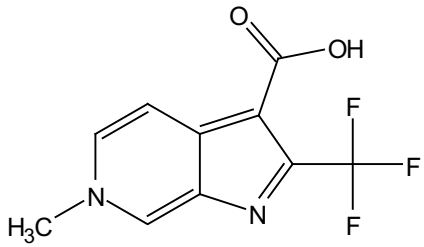
12



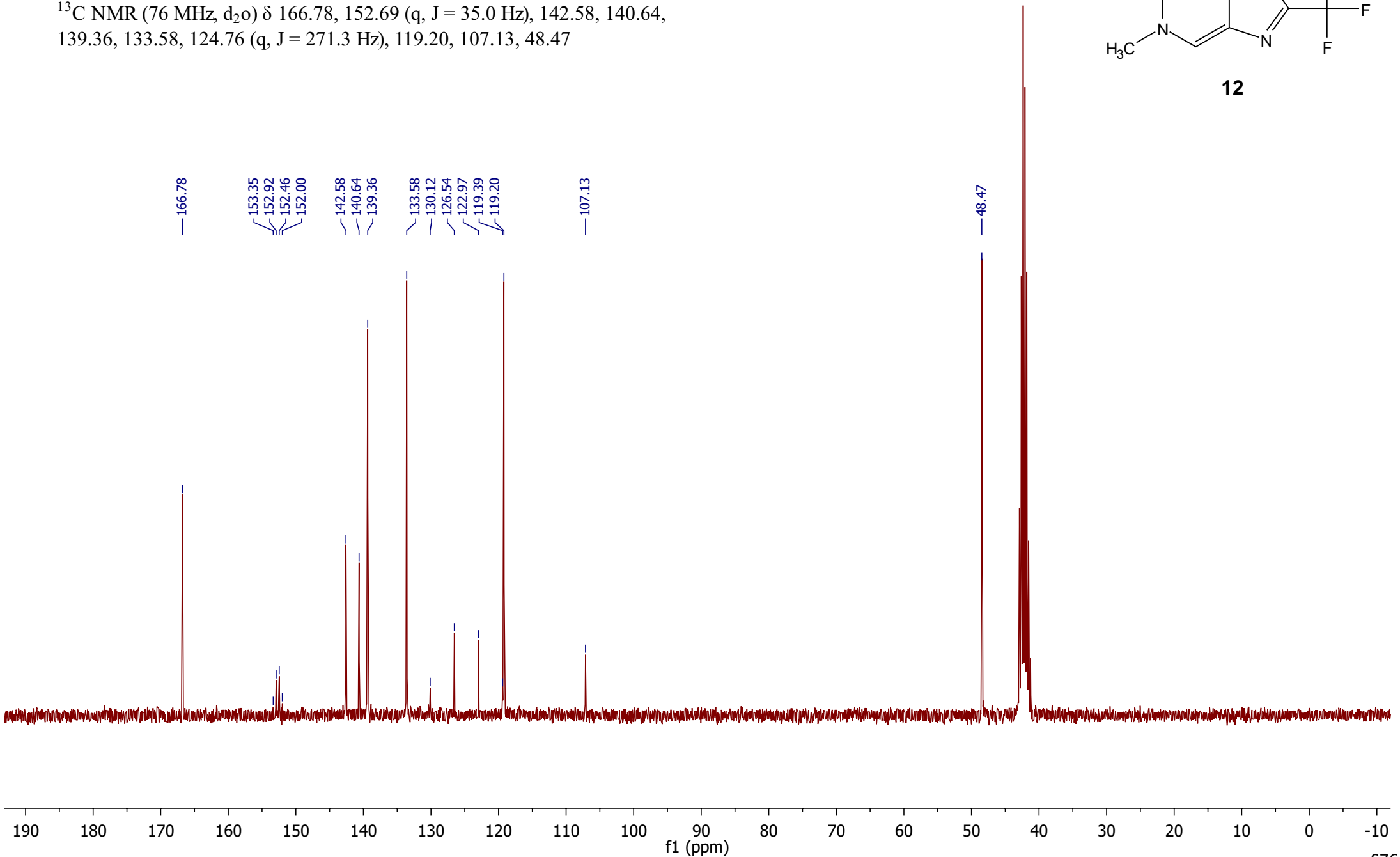


^{13}C NMR of Compound **12**

^{13}C NMR (76 MHz, d_2o) δ 166.78, 152.69 (q, J = 35.0 Hz), 142.58, 140.64, 139.36, 133.58, 124.76 (q, J = 271.3 Hz), 119.20, 107.13, 48.47

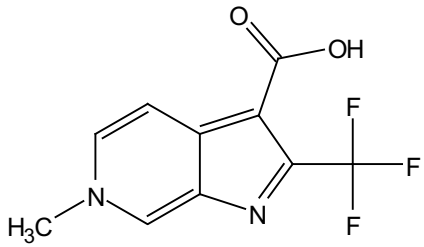


12

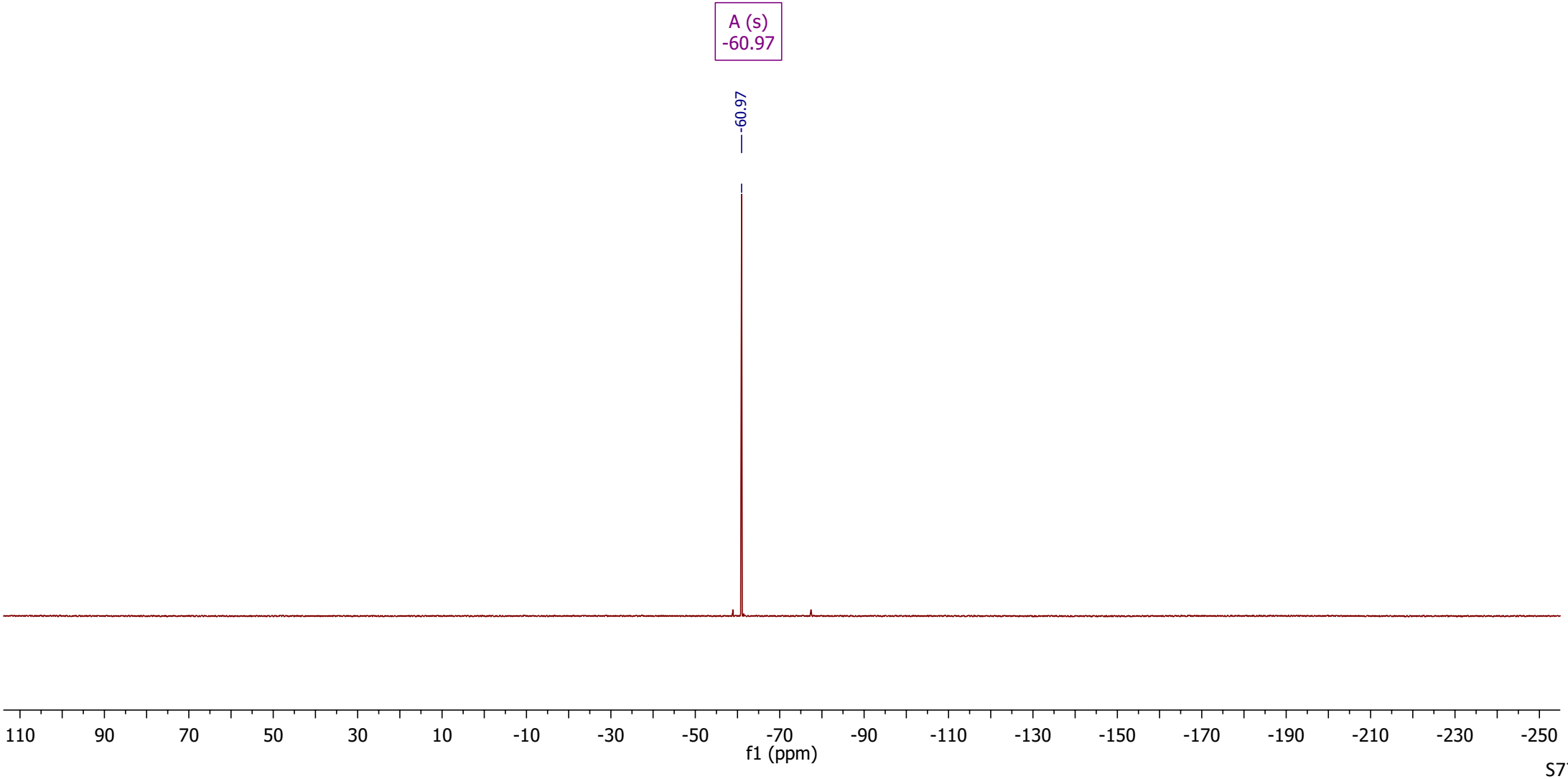


^{19}F NMR of Compound **12**

^{19}F NMR (376 MHz, DMSO-d_6) δ -60.97.

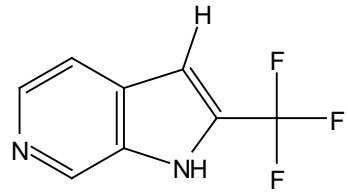


12



^{1}H NMR of Compound **13**

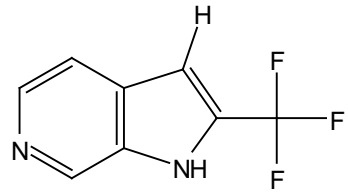
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.83 (s, 1H), 8.89 (s, 1H), 8.20 (d, J = 5.6 Hz, 1H), 7.67 (d, J = 5.6 Hz, 1H), 7.07 (s, 1H).



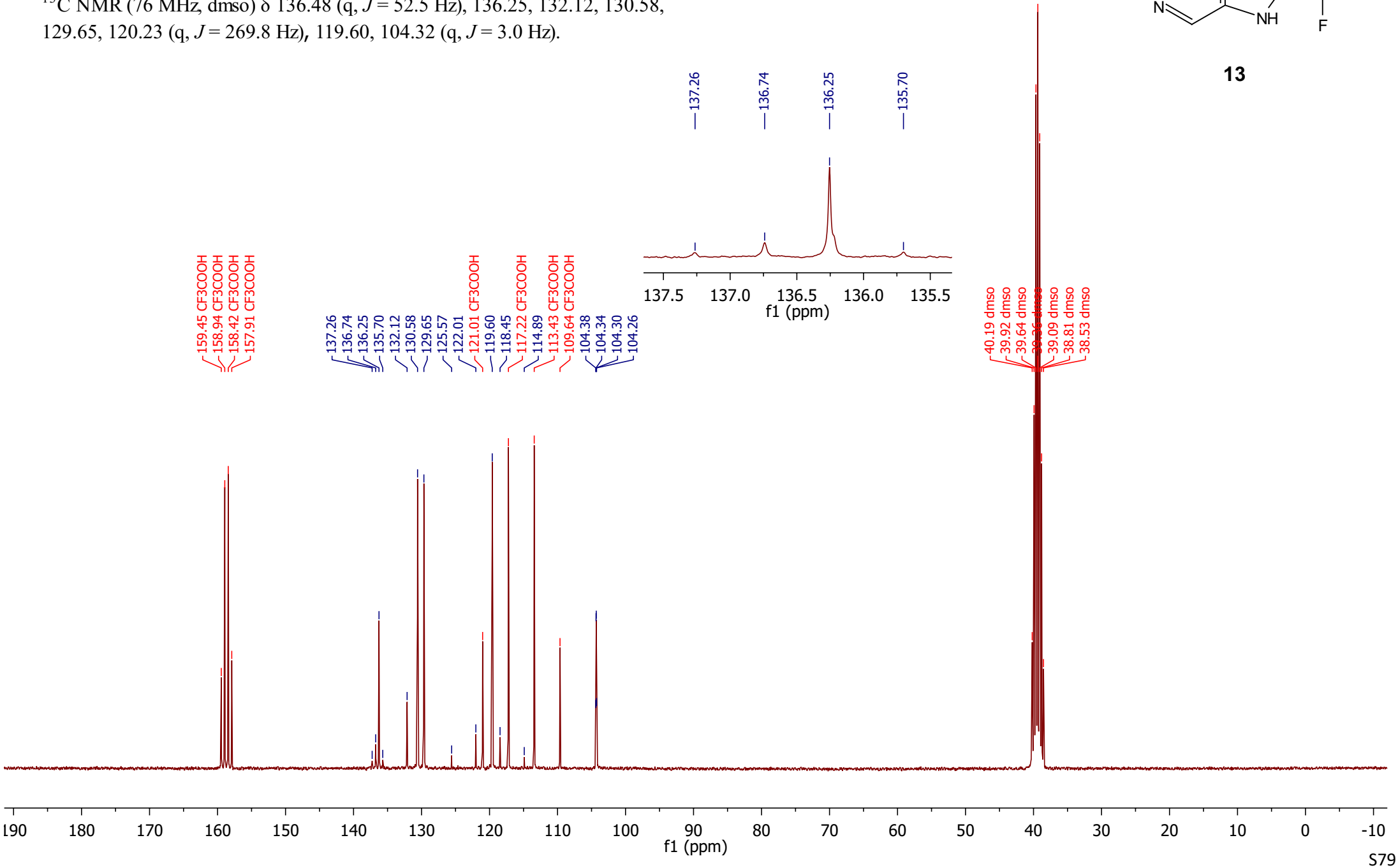
13

^{13}C NMR of Compound **13**

^{13}C NMR (76 MHz, dmso) δ 136.48 (q, *J* = 52.5 Hz), 136.25, 132.12, 130.58, 129.65, 120.23 (q, *J* = 269.8 Hz), 119.60, 104.32 (q, *J* = 3.0 Hz).

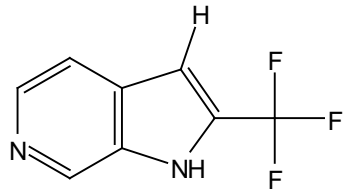


13

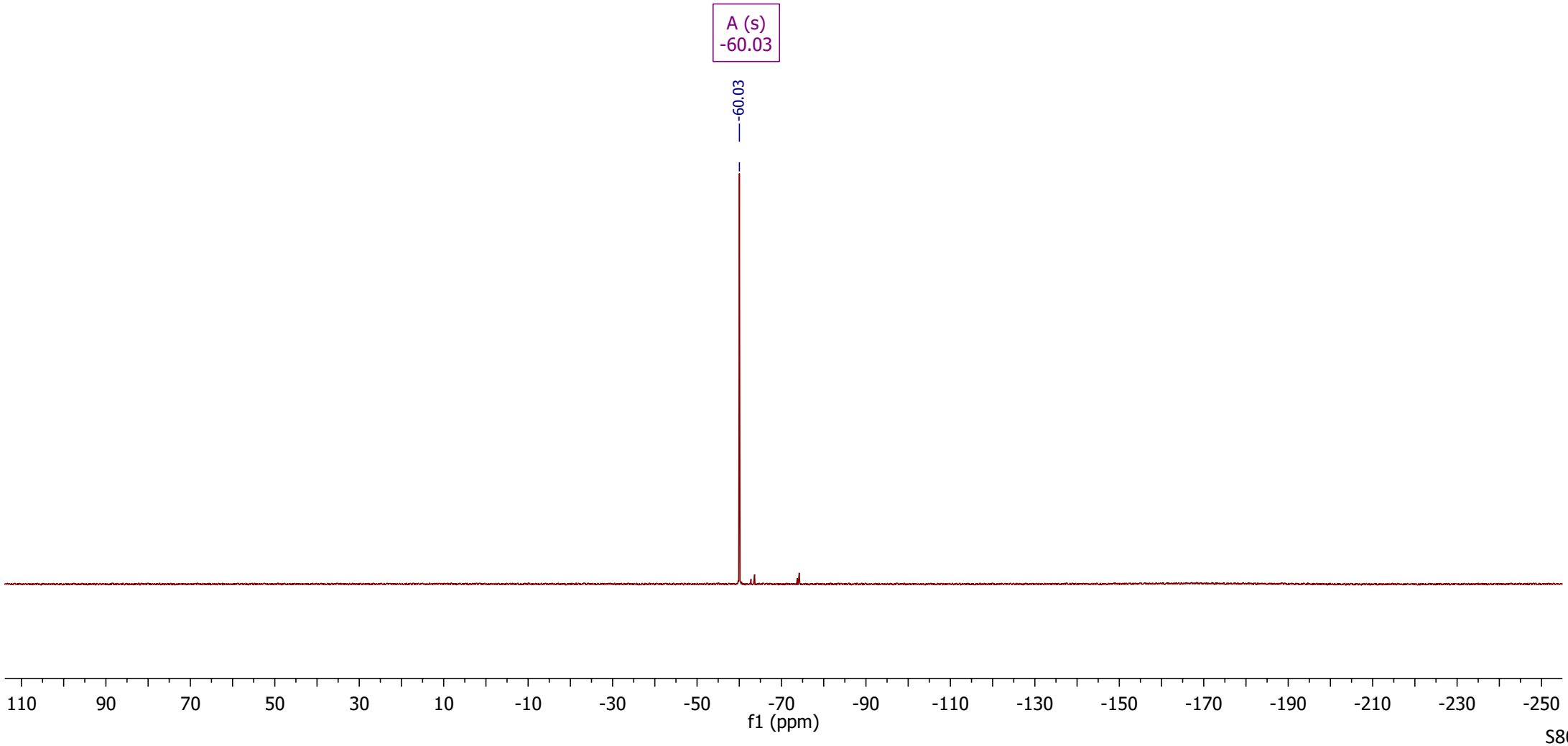


^{19}F NMR of Compound **13**

^{19}F NMR (376 MHz, DMSO-d_6) δ -60.03.

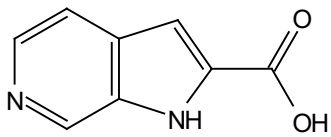


13



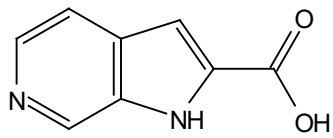
^{1}H NMR of Compound **14**

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.13 (d, J = 5.5 Hz, 1H), 7.60 (d, J = 5.5 Hz, 1H), 7.07 (s, 1H).



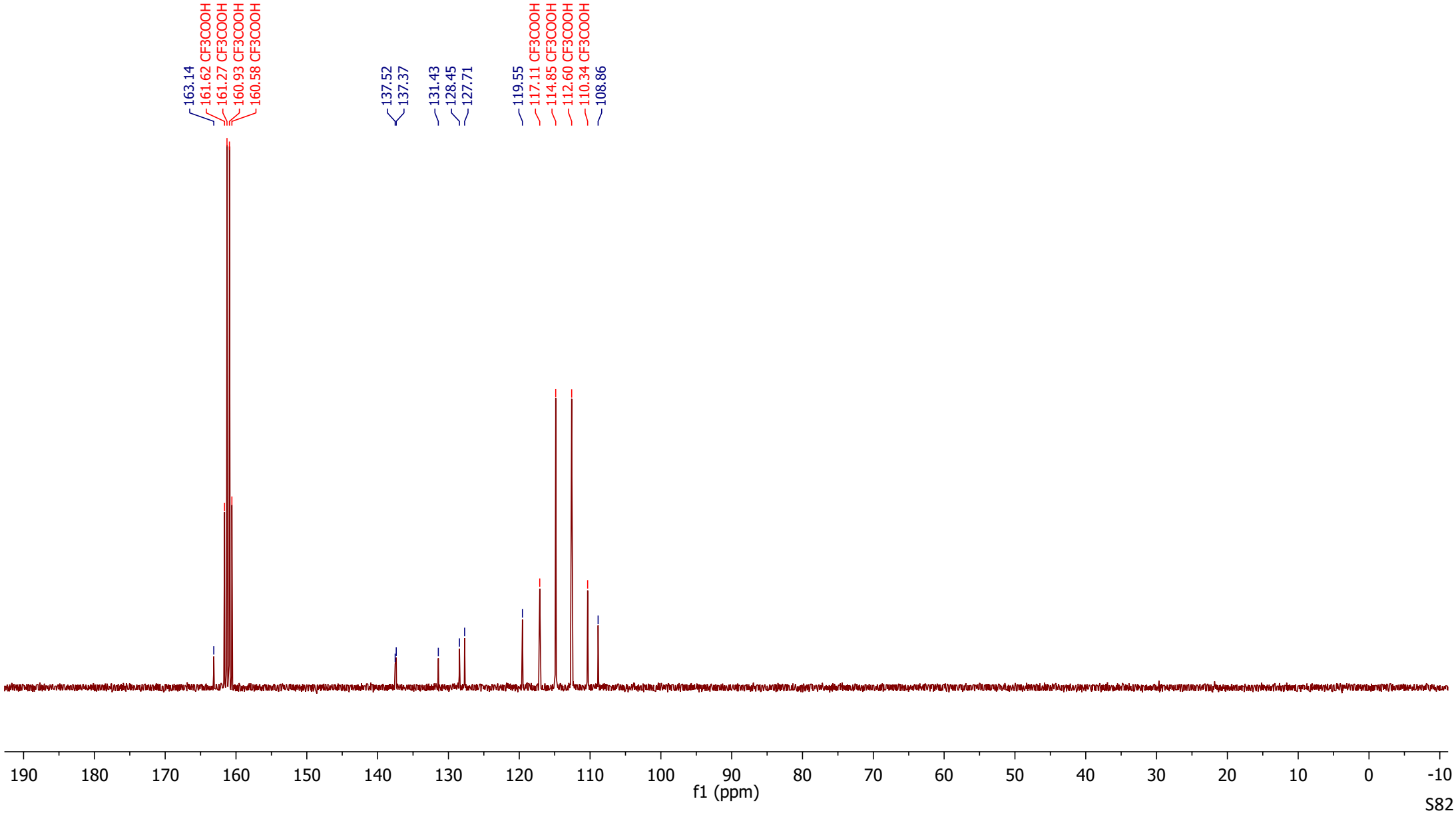
14

^{13}C NMR of Compound **14**



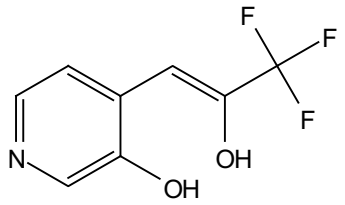
14

^{13}C NMR (126 MHz, DMSO) δ 163.14, 137.52, 137.37, 131.43, 128.45, 127.71, 119.55, 108.86



^{1}H NMR of Compound **15**

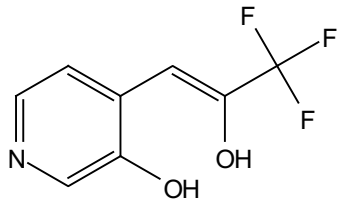
^{1}H NMR (302 MHz, DMSO-d_6) δ 16.17 (s, 1H), 7.77 (d, J = 6.1 Hz, 1H), 7.71 (s, 1H), 7.29 (s, 1H), 5.47 (s, 1H).



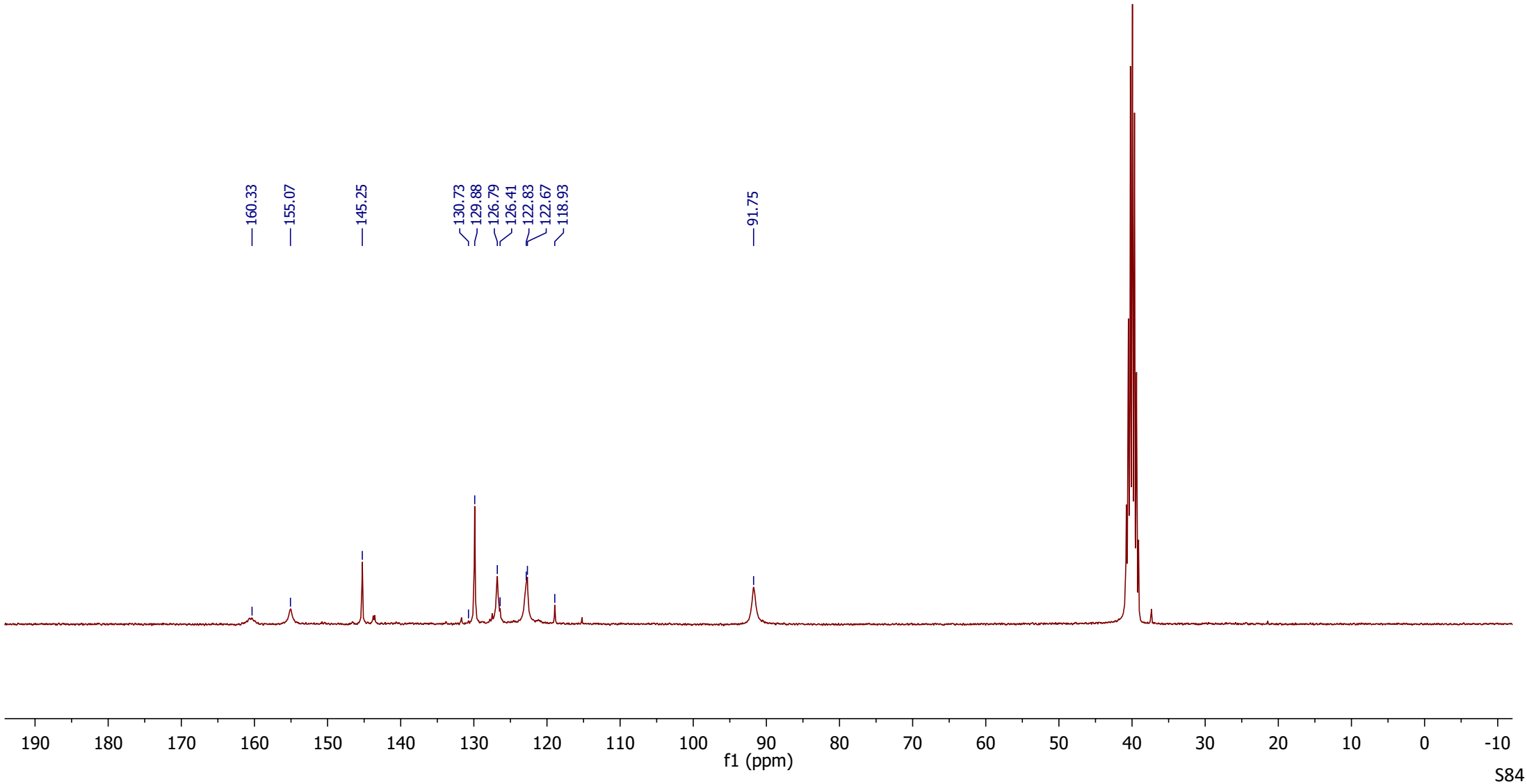
15

^{13}C NMR of Compound **15**

^{13}C NMR (76 MHz, dmso) δ 160.33, 155.07, 145.25, 129.88, 126.41, 124.81 (q, J = 298.3Hz), 122.67, 91.75.

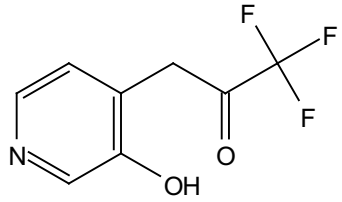


15

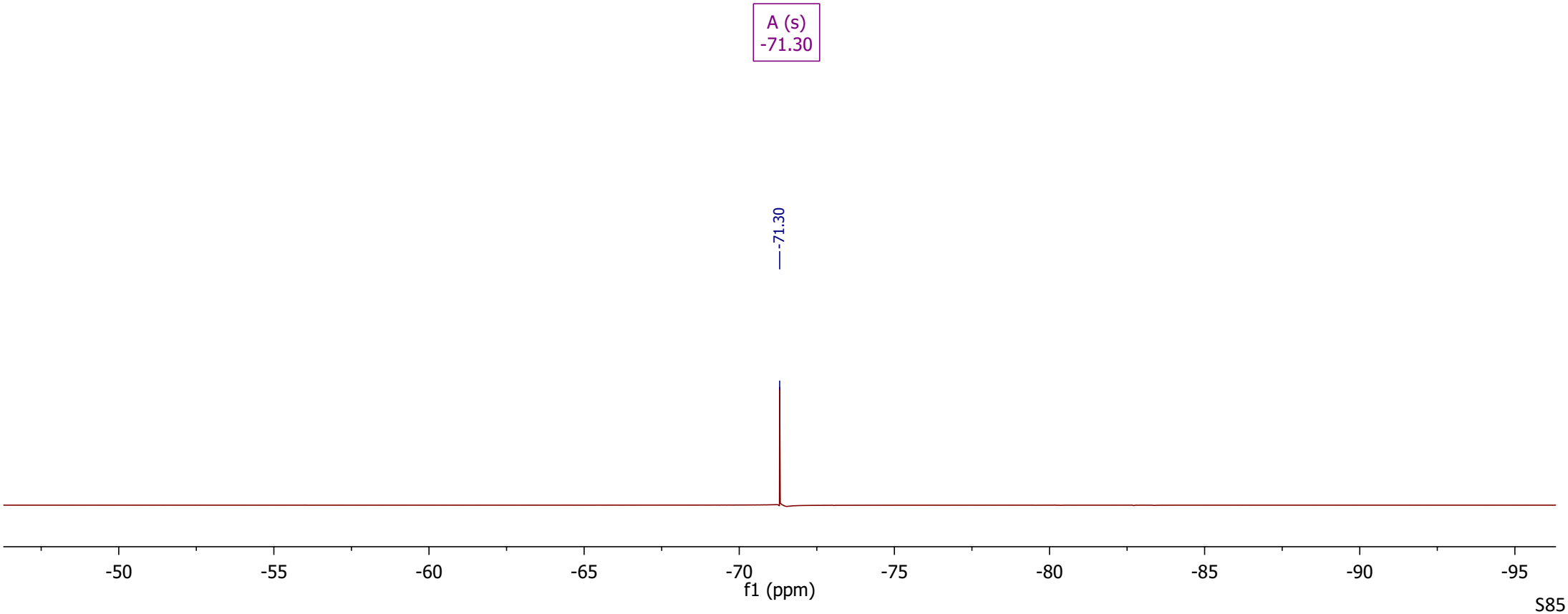


^{19}F NMR of Compound **15**

^{19}F NMR (188 MHz, DMSO-d_6) δ -71.30.

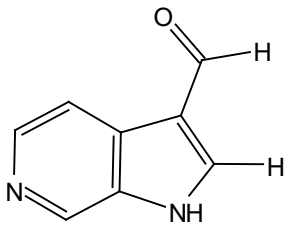


15



^{1}H NMR of Compound **16**

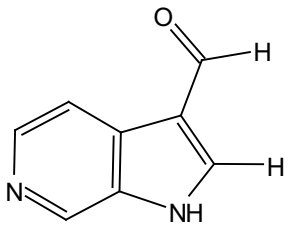
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.99 (s, 1H), 8.87 (s, 1H), 8.49 (s, 1H), 8.31 (d, J = 5.4 Hz, 1H), 7.98 (d, J = 5.4 Hz, 1H).



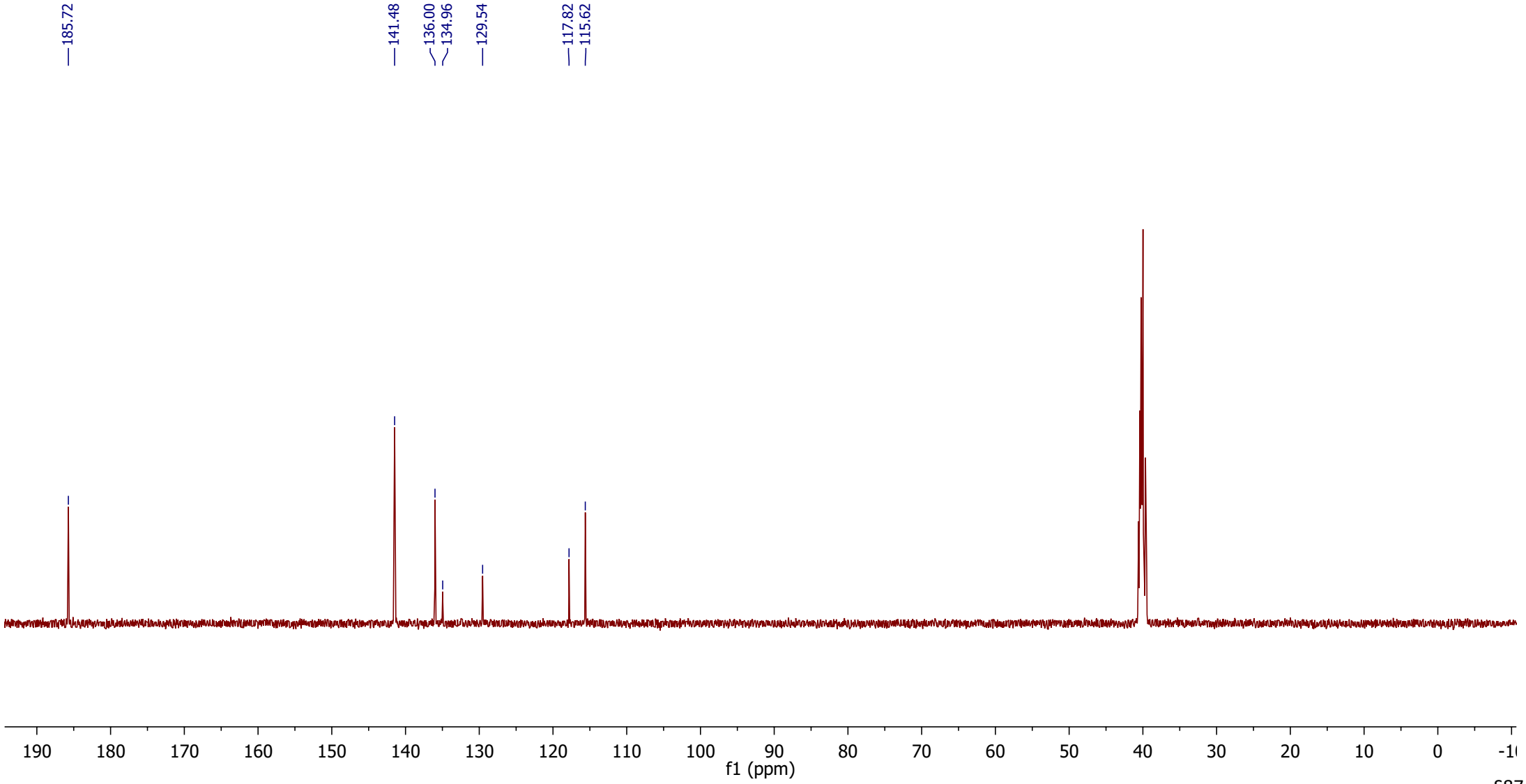
16

^{13}C NMR of Compound **16**

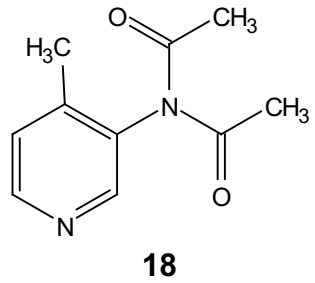
^{13}C NMR (126 MHz, dmso-d_6) δ 185.72, 141.48, 136.00, 134.96, 129.54, 117.82, 115.62.



16

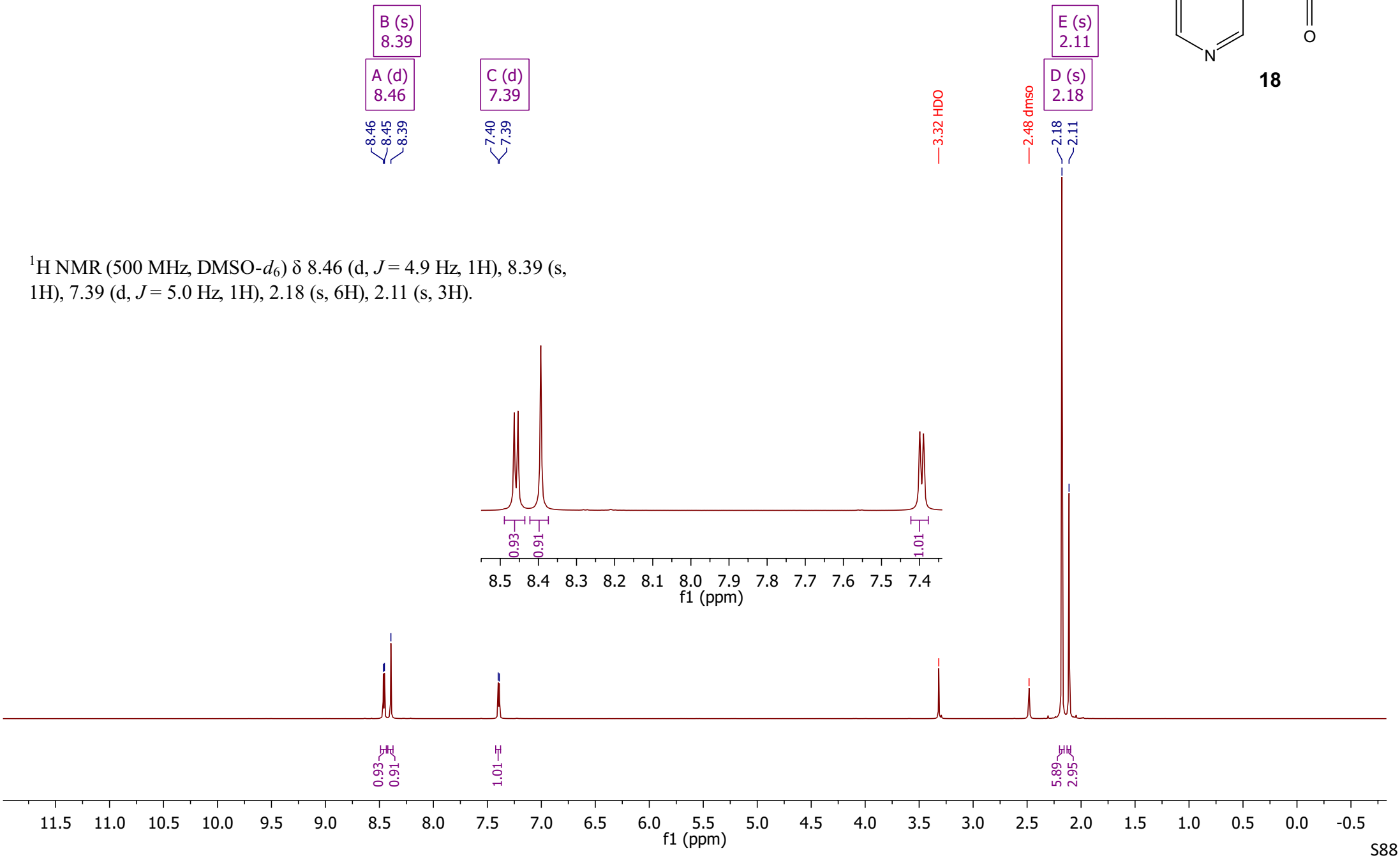


^{1}H NMR of Compound **18**



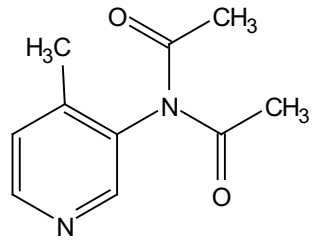
18

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.46 (d, J = 4.9 Hz, 1H), 8.39 (s, 1H), 7.39 (d, J = 5.0 Hz, 1H), 2.18 (s, 6H), 2.11 (s, 3H).

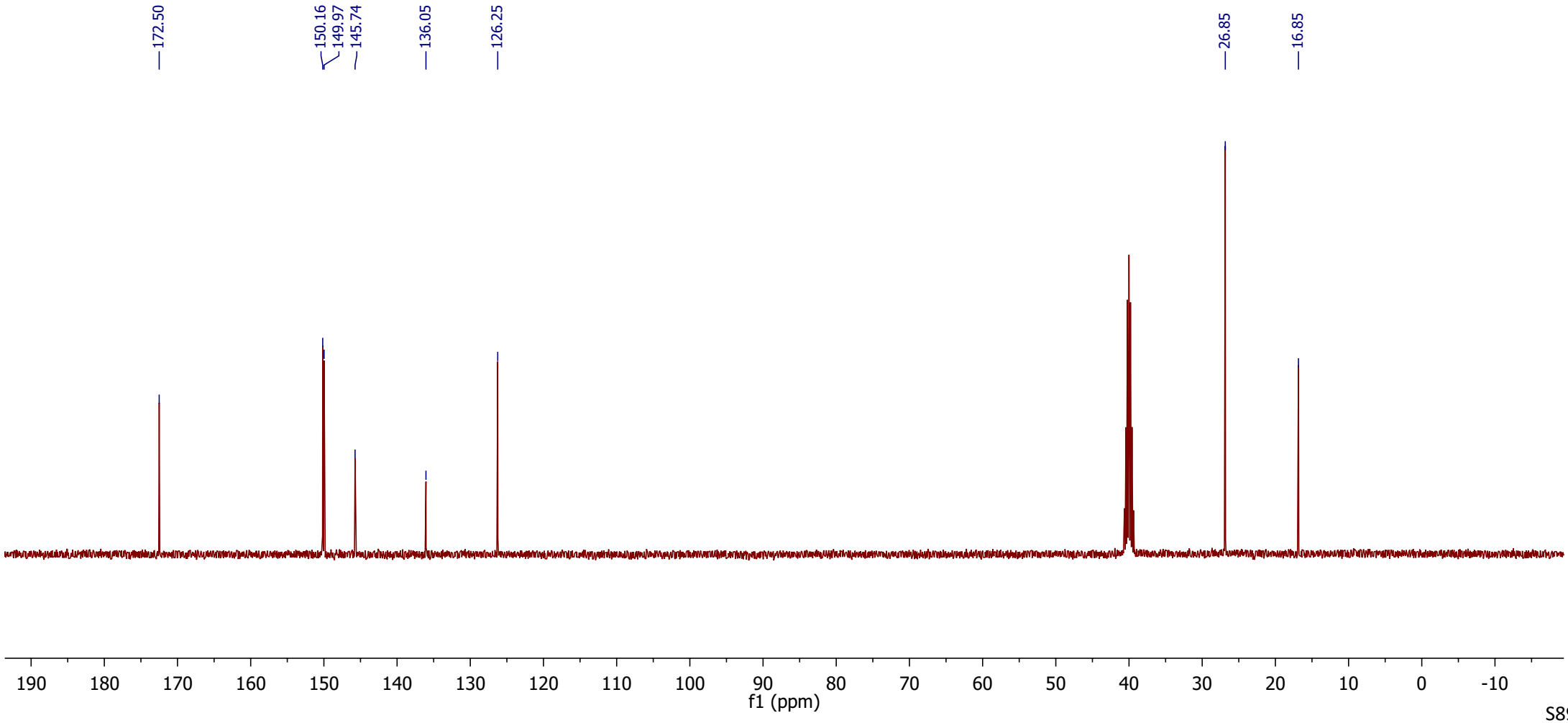


^{13}C NMR of Compound **18**

^{13}C NMR (101 MHz, DMSO) δ 172.50, 150.16, 149.97, 145.74, 136.05, 126.25, 26.85, 16.85.

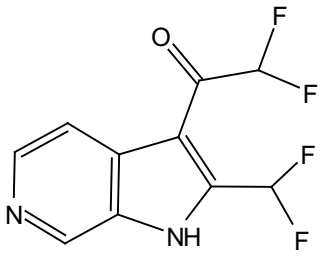


18



^{1}H NMR of Compound **19**

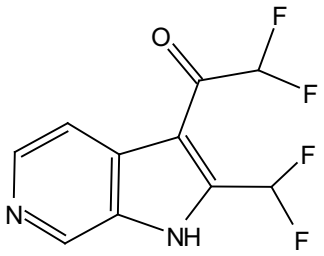
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.05 (s, 1H), 8.28 (d, J = 6.3 Hz, 1H), 7.99 (d, J = 6.3 Hz, 1H), 7.50 (t, J = 53.7 Hz, 1H), 7.05 (t, J = 53.0 Hz, 1H).



19

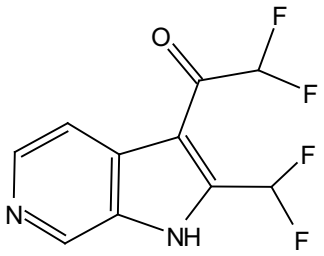
^{13}C NMR of Compound **19**

^{13}C NMR (76 MHz, dmso) δ 181.66 (t, J = 24.3 Hz), 149.97, 138.84, 135.16, 134.71, 133.71, 116.13, 110.96 (t, J = 237.1 Hz), 110.54, 110.24 (t, J = 247.0 Hz)



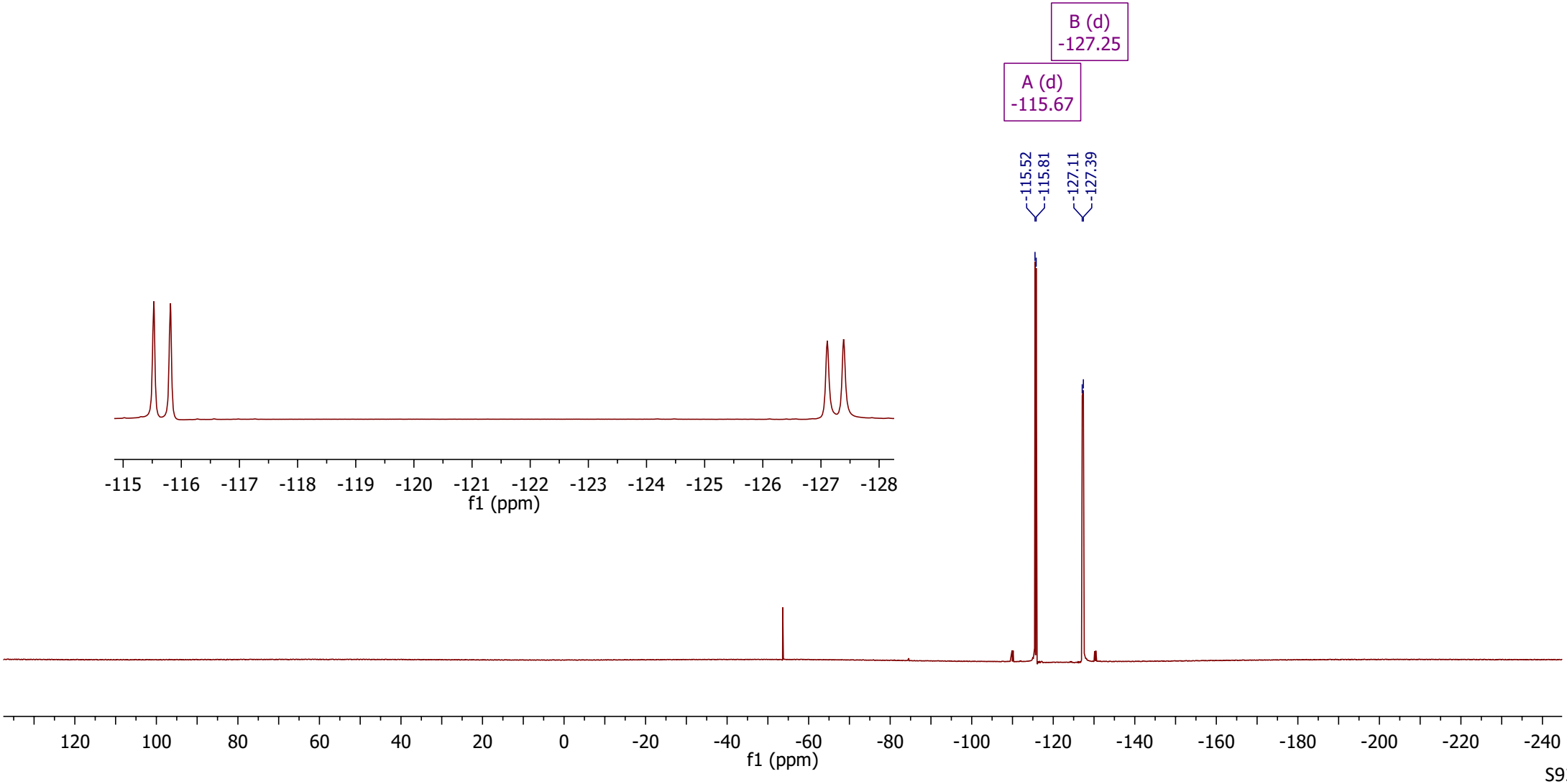
19

^{19}F NMR of Compound **19**

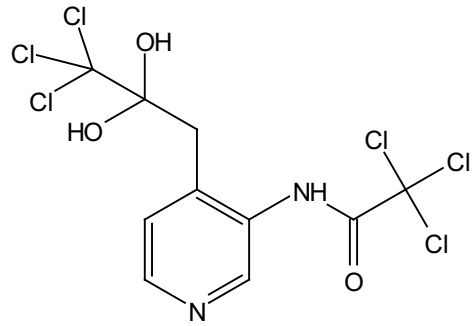


19

^{19}F NMR (188 MHz, Chloroform-*d*) δ -115.67 (d, *J* = 53.8 Hz), -127.25 (d, *J* = 52.8 Hz).

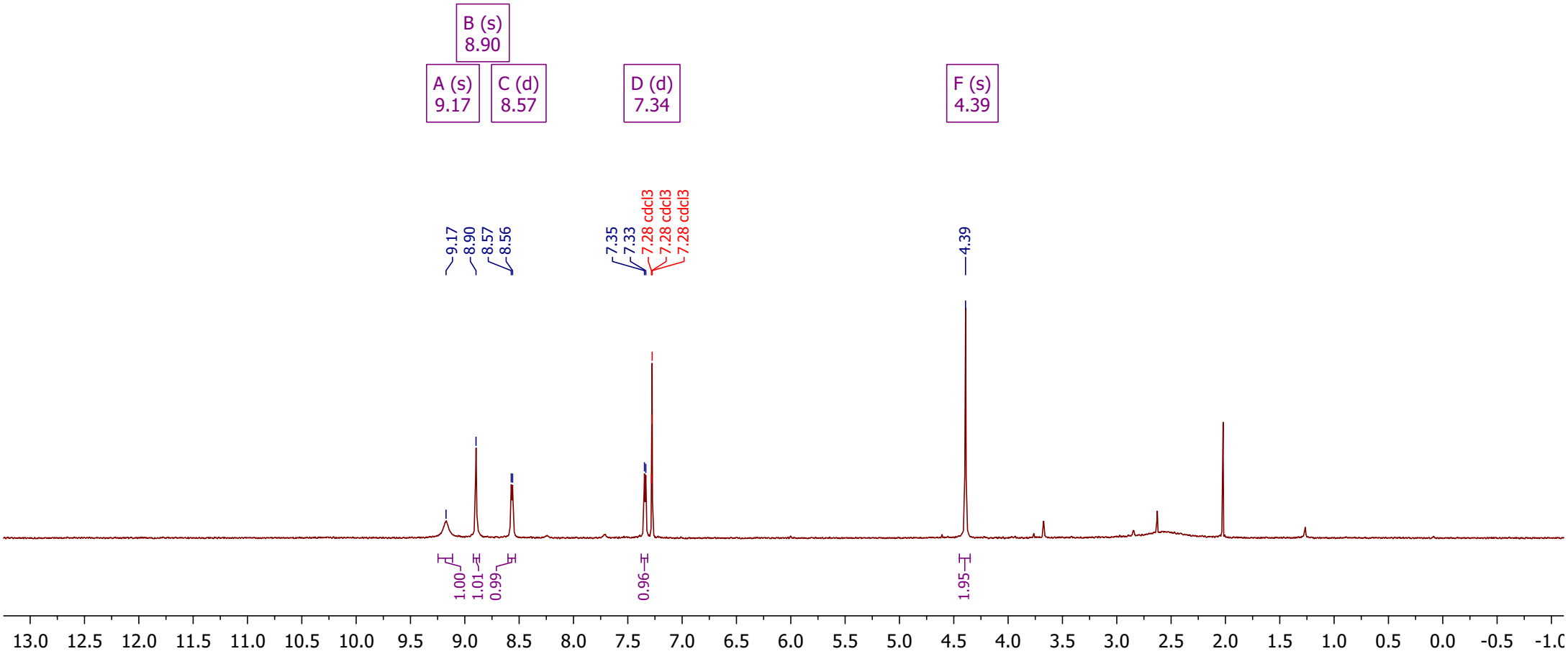


^{1}H NMR of Compound **20**

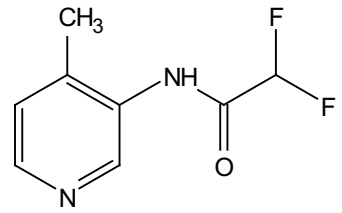


20

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.17 (s, 1H), 8.90 (s, 1H), 8.57 (d, *J* = 5.0 Hz, 1H), 7.34 (d, *J* = 5.0 Hz, 1H), 7.28 (d, *J* = 1.2 Hz, 1H), 4.39 (s, 2H).



^{1}H NMR of Compound **21**

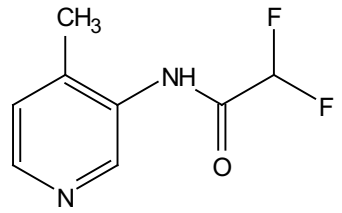


21

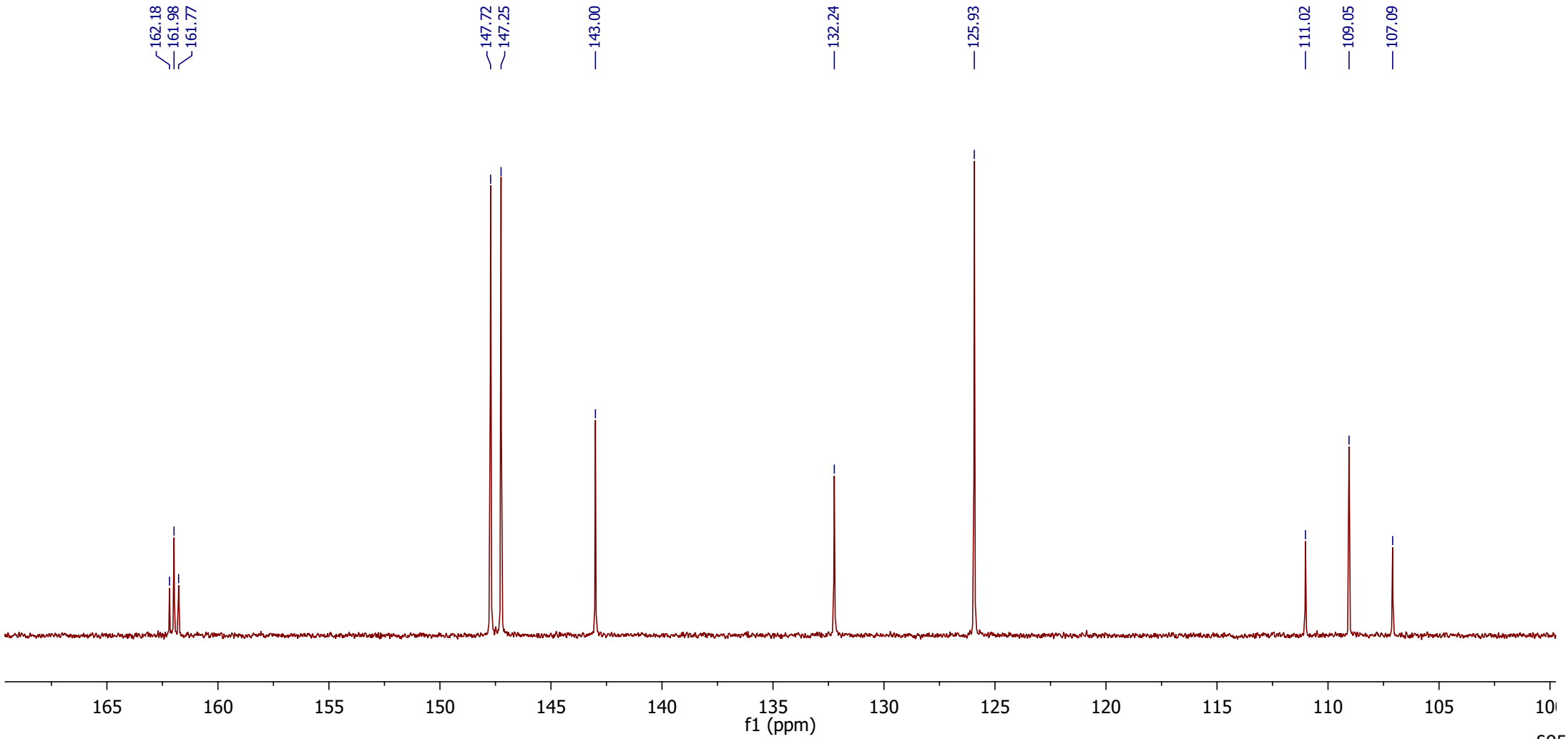
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 1H), 8.33 (d, J = 5.3 Hz, 1H), 7.32 (d, J = 4.9 Hz, 1H), 6.46 (tt, J = 53.6, 1.9 Hz, 1H), 2.21 (s, 3H).

^{13}C NMR of Compound **21**

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.98 (t, J = 25.2 Hz), 147.72, 147.25, 143.00, 132.24, 125.93, 109.05 (t, J = 248.2 Hz), 17.46

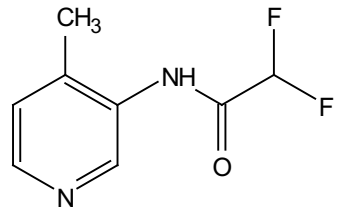


21

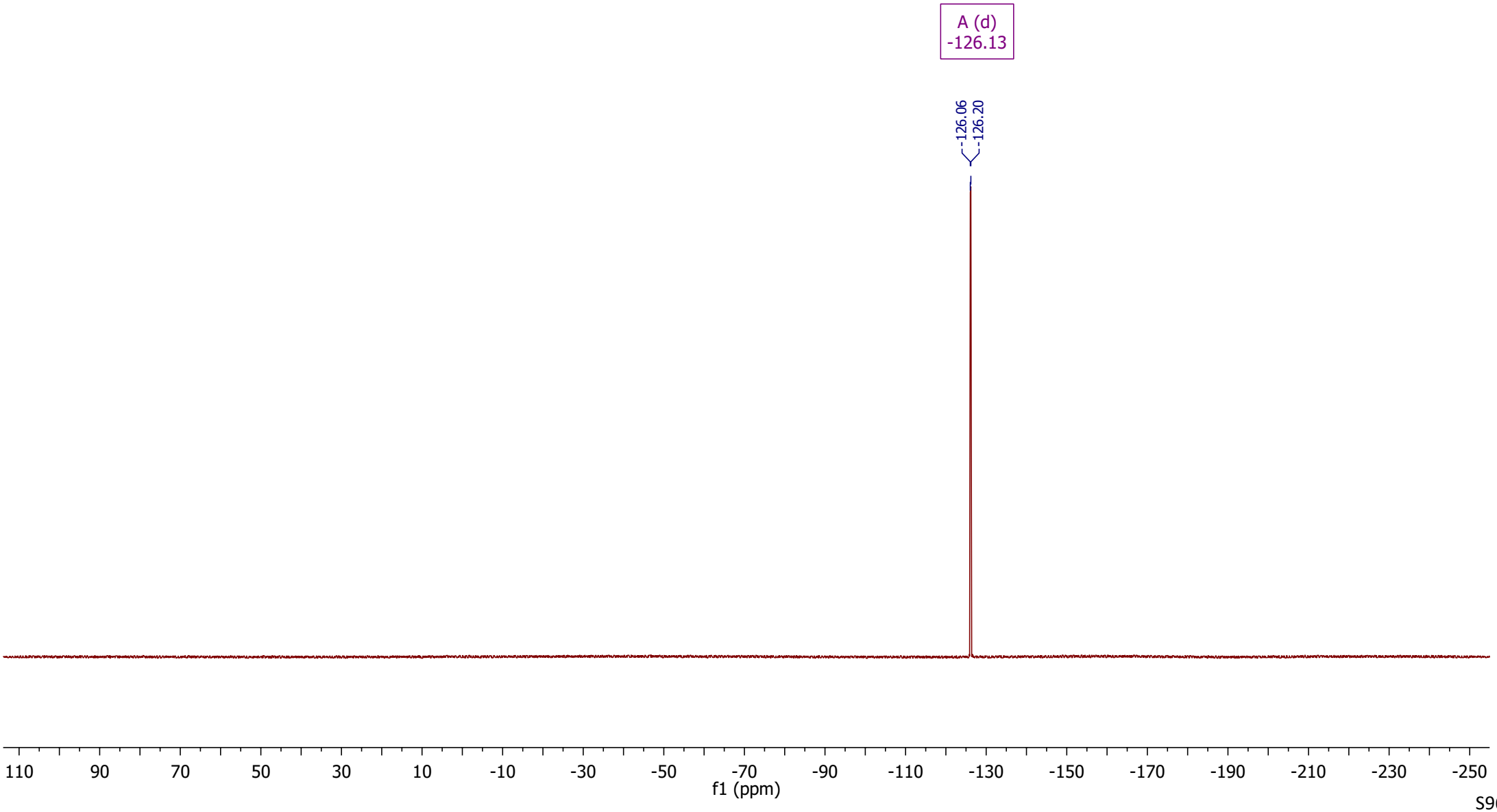


^{19}F NMR of Compound **21**

^{19}F NMR (376 MHz, DMSO-d_6) δ -126.13 (d, J = 53.4 Hz).

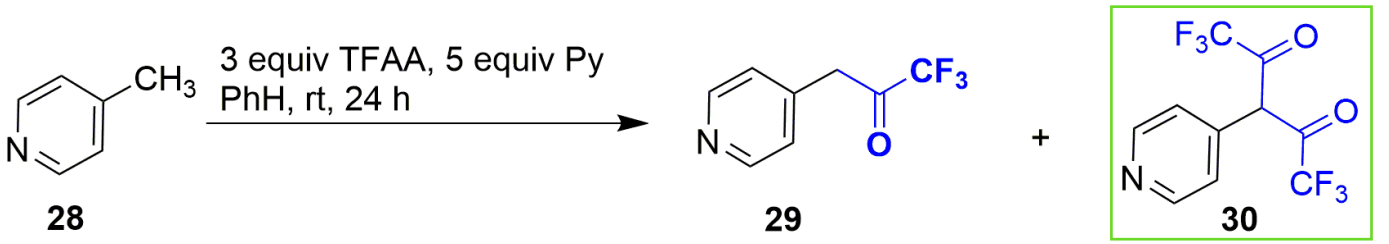


21



The reaction was reproduced from:

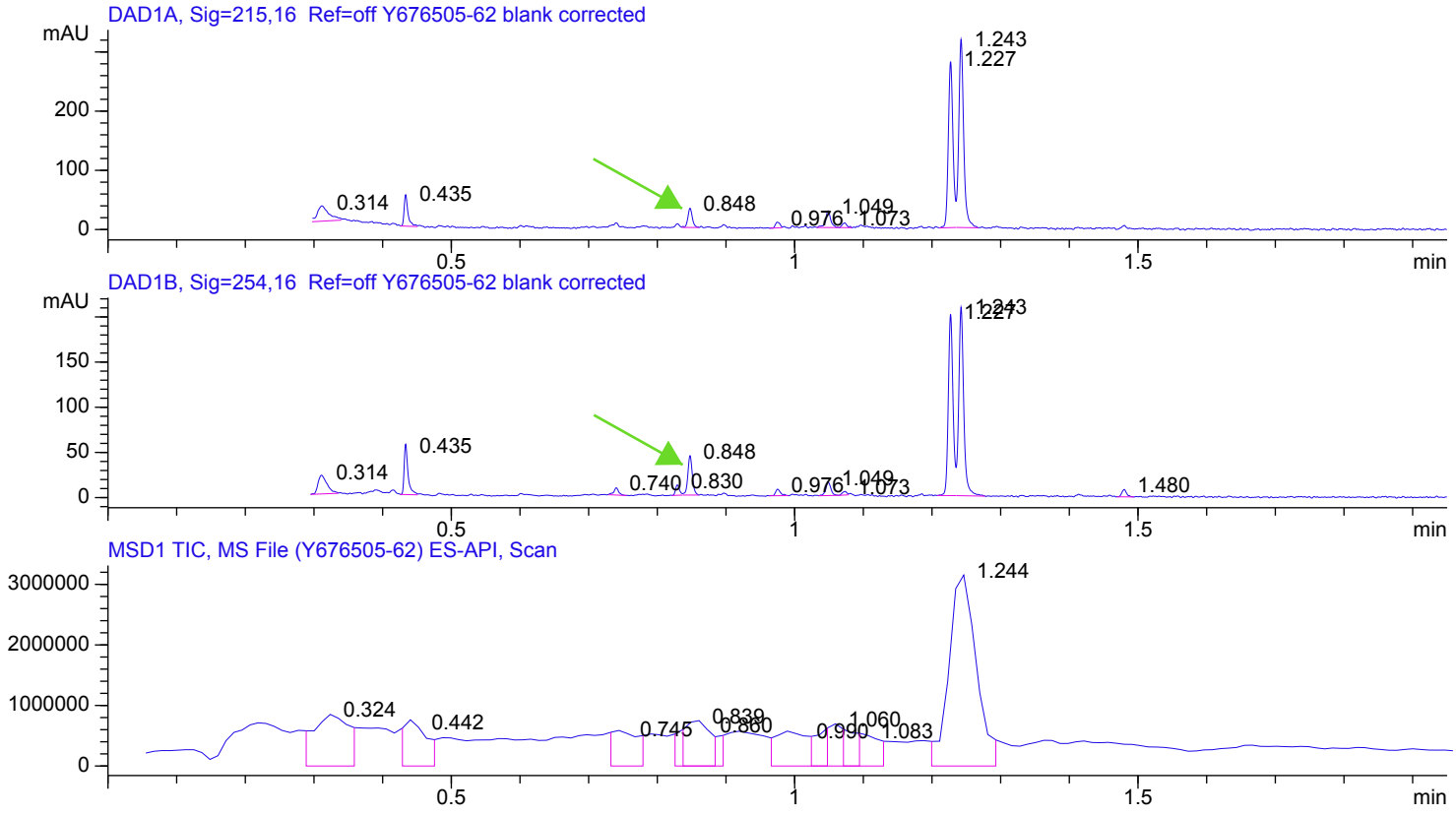
Kawase, M. et al. *Heterocycles* **1998**, *48* (10), 2103-2109.

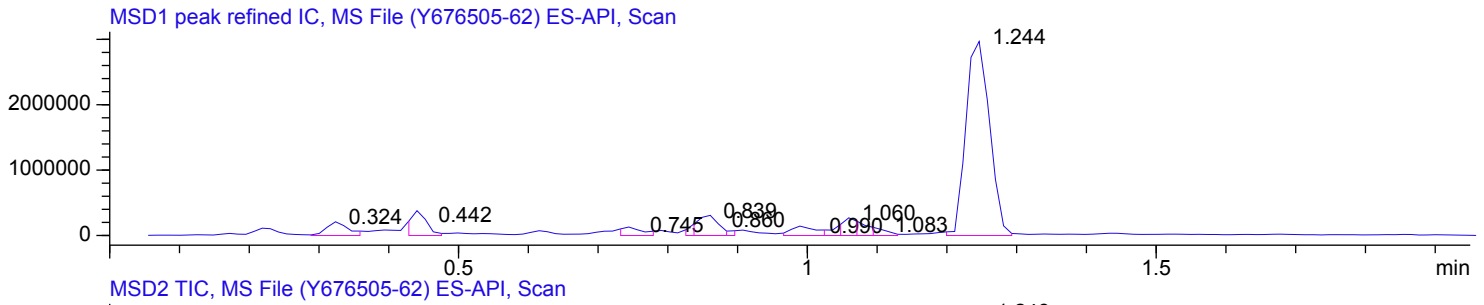


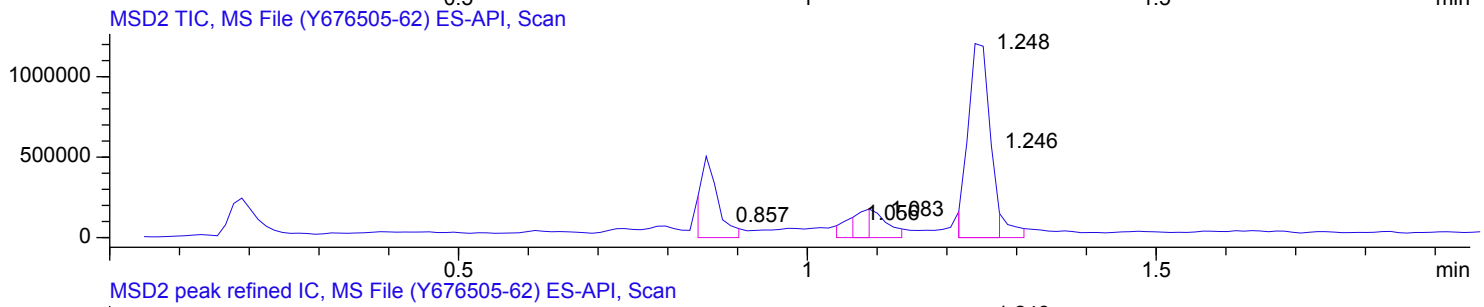
28 **29** **30**

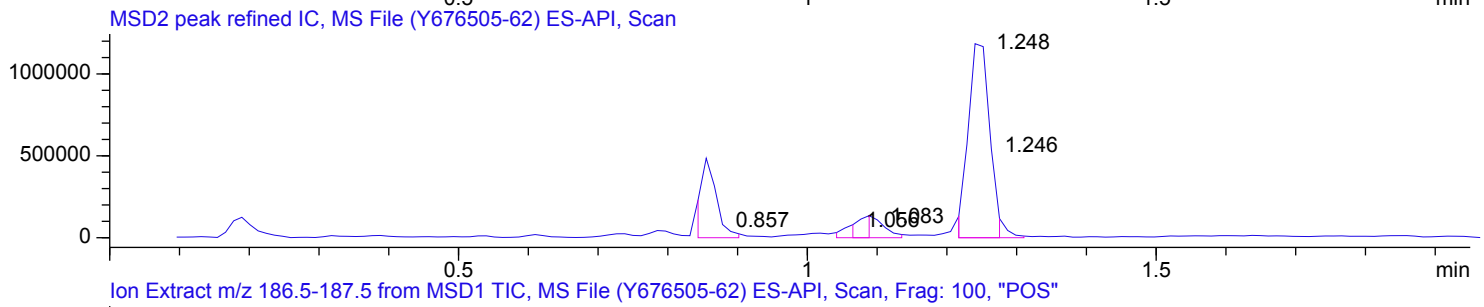
Exact Mass: 189.04 Exact Mass: 285.02

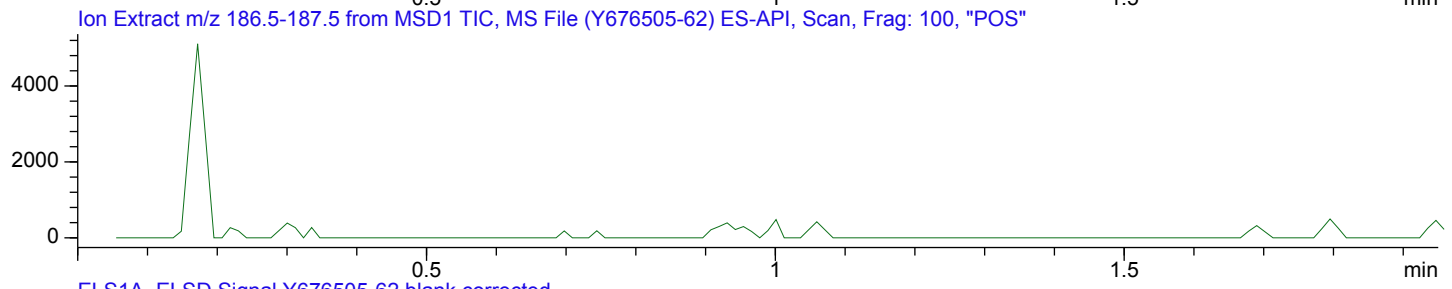
#	RT	DAD1A	DAD1B	MSD1	MSD2	ELSD	MSD1 ions	MSD1 rt	MSD2 ions	MSD2 rt	Info
1	0.314	8.1%	6.5%	4.4%	---	---	251.2(100)	0.324	---	---	
2	0.435	5.5%	7.6%	5.7%	---	---	251.2(100)	0.442	---	---	
3	0.740	---	1.4%	0.7%	---	---	359.2(100)	0.745	---	---	
4	0.830	---	1.6%	2.0%	---	---	436.2(100)	0.839	---	---	
5	0.848	3.9%	7.0%	4.2%	22.7%	3.3%	286.0(100)	0.860	284.0(100)	0.857	
6	0.976	1.2%	1.3%	2.6%	---	---	534.0(100)	0.990	---	---	
7	1.049	3.9%	2.7%	4.2%	1.6%	---	496.2(61),421.0(39)	1.060	530.2(100)	1.056	
8	1.073	1.0%	0.7%	1.7%	4.1%	---	346.0(100)	1.083	380.0(64),382.0(36)	1.083	
9	1.227	34.8%	33.0%	74.6%	---	---	457.0(94),545.2(2),515.2(2)	1.244	---	---	
10	1.237	---	---	---	63.1%	96.7%	---	---	491.0(96),569.0(4)	1.246	
11	1.243	41.7%	36.9%	---	8.5%	---	---	---	284.0(100)	1.248	
12	1.480	---	1.4%	---	---	---	---	---	---	---	

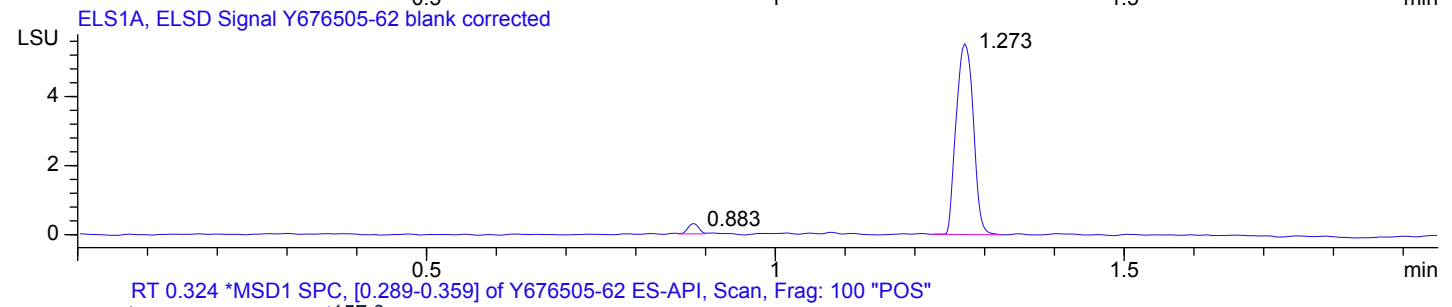



MSD1 peak refined IC, MS File (Y676505-62) ES-API, Scan
2000000
1000000
0
1.244
0.324
0.442
0.745
0.839
0.860
0.990
1.060
1.083
0.5
1
1.5
min

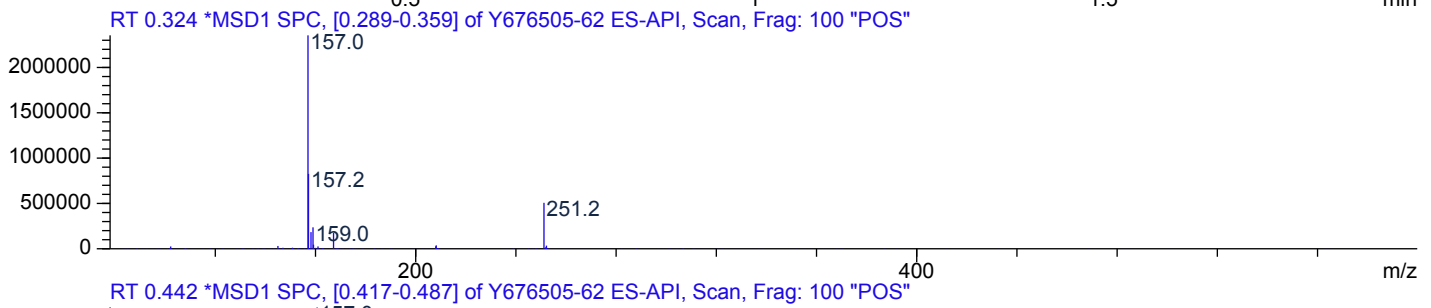

MSD2 TIC, MS File (Y676505-62) ES-API, Scan
1000000
500000
0
1.248
1.246
0.857
1.060
1.083
0.5
1
1.5
min


MSD2 peak refined IC, MS File (Y676505-62) ES-API, Scan
1000000
500000
0
1.248
1.246
0.857
1.060
1.083
0.5
1
1.5
min

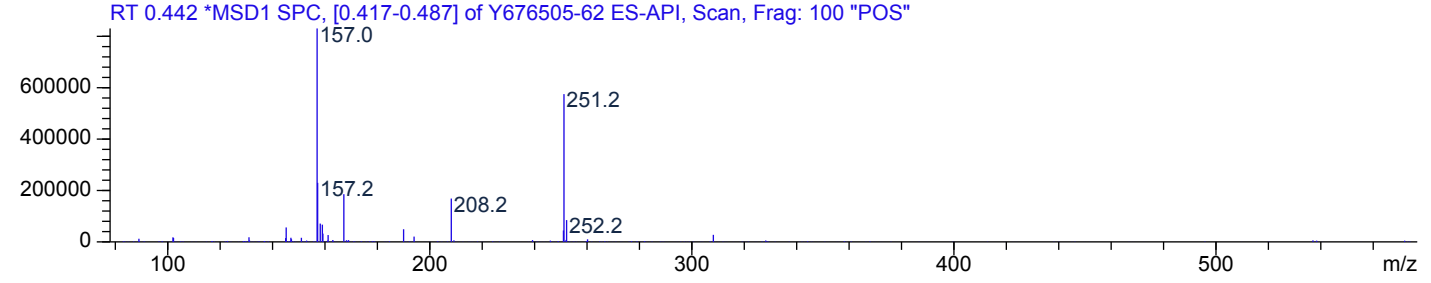

Ion Extract m/z 186.5-187.5 from MSD1 TIC, MS File (Y676505-62) ES-API, Scan, Frag: 100, "POS"
4000
2000
0
0.5
1
1.5
min


ELS1A, ELSD Signal Y676505-62 blank corrected
LSU
4
2
0
1.273
0.883
0.5
1
1.5
min

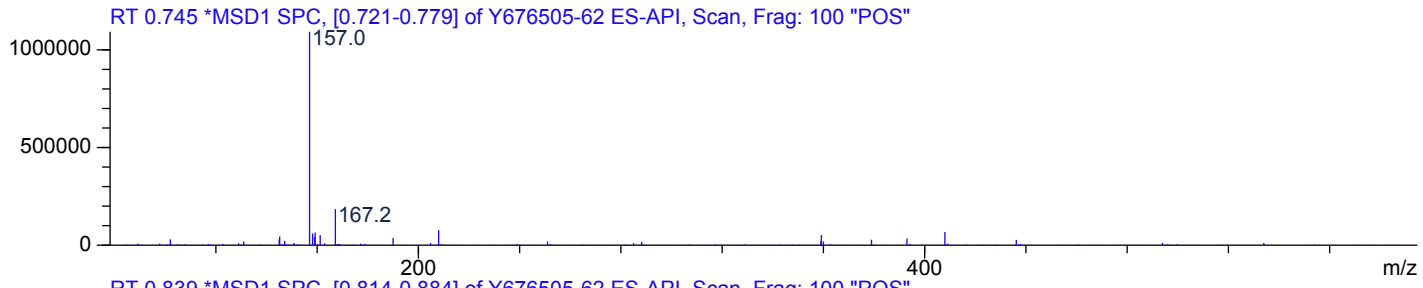
0.324


RT 0.324 *MSD1 SPC, [0.289-0.359] of Y676505-62 ES-API, Scan, Frag: 100 "POS"
2000000
1500000
1000000
500000
0
157.0
157.2
159.0
251.2
200
400
m/z

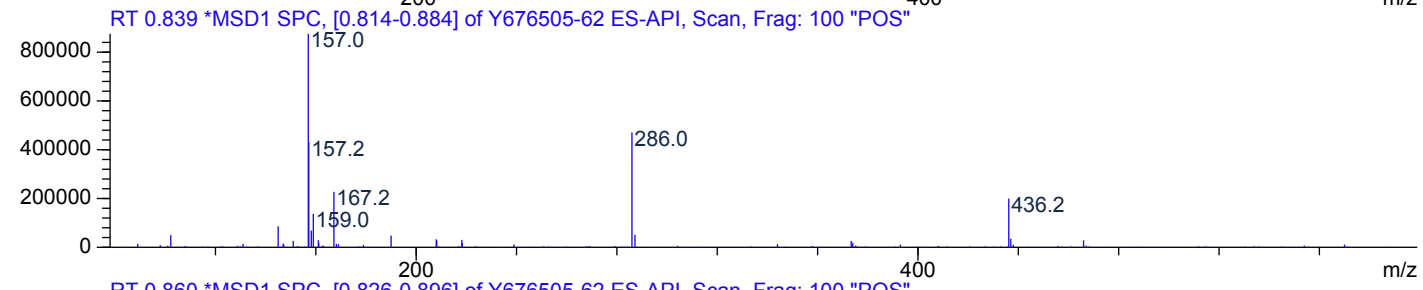
0.442


RT 0.442 *MSD1 SPC, [0.417-0.487] of Y676505-62 ES-API, Scan, Frag: 100 "POS"
600000
400000
200000
0
157.0
157.2
208.2
251.2
252.2
100
200
300
400
500
m/z

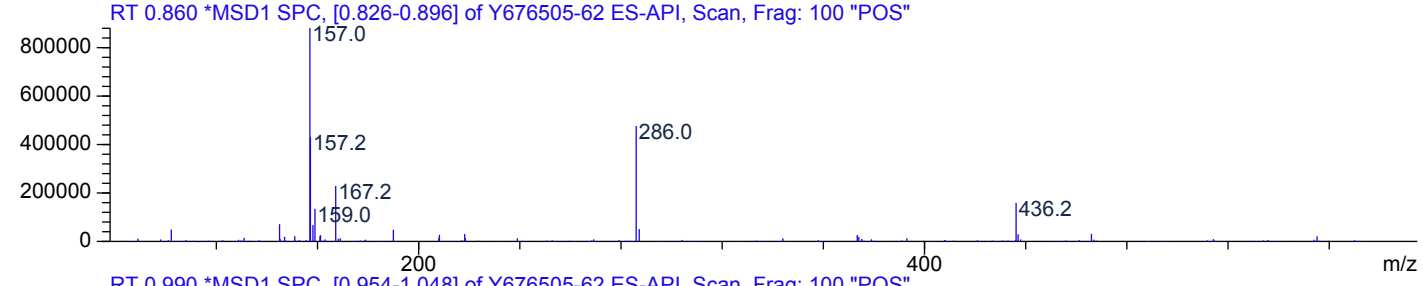
0.745



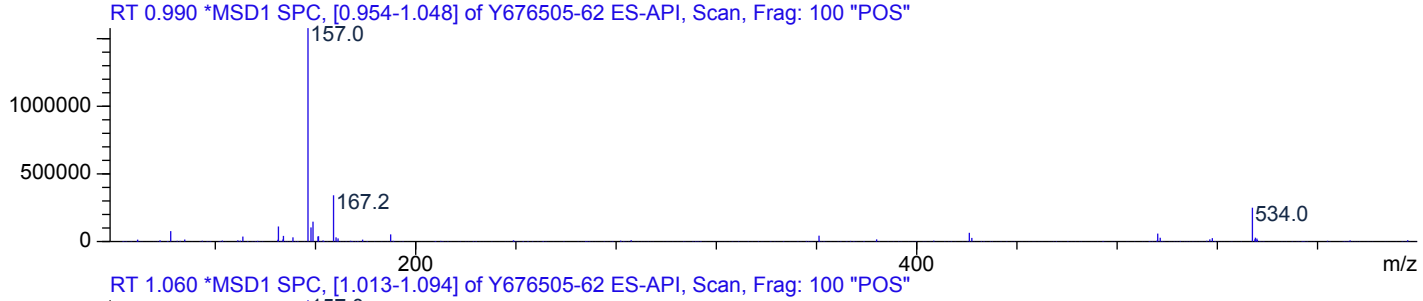
0.839



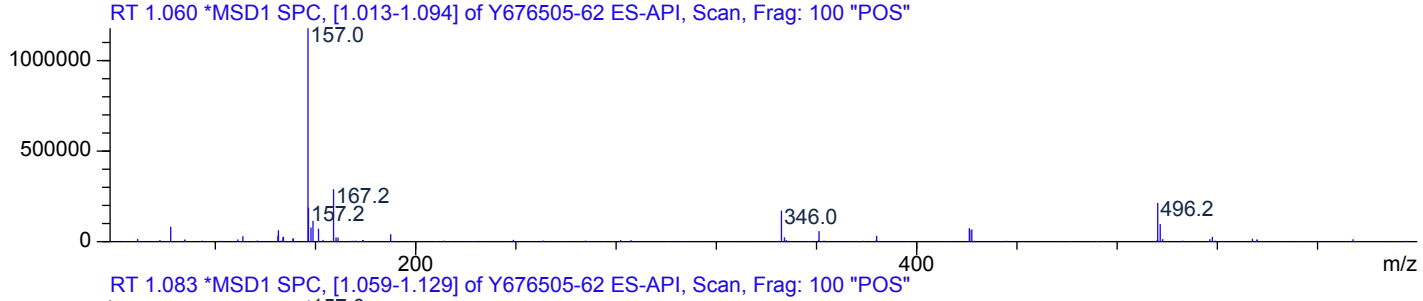
0.860



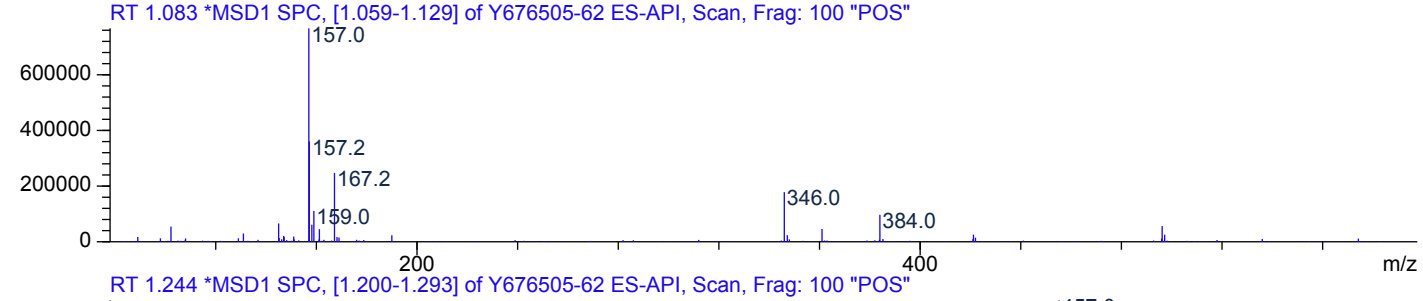
0.990



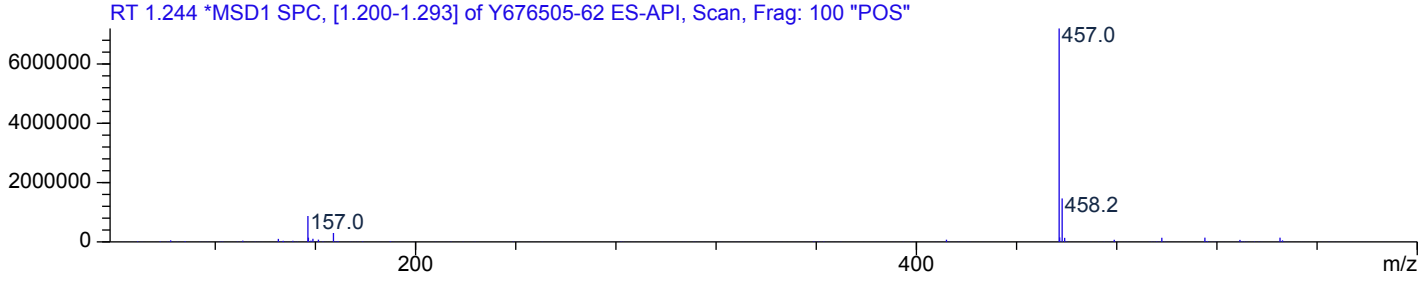
1.060



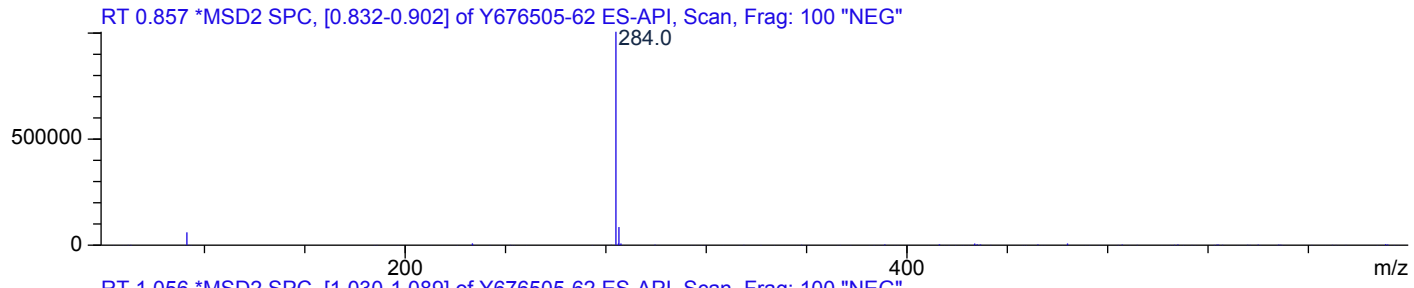
1.083



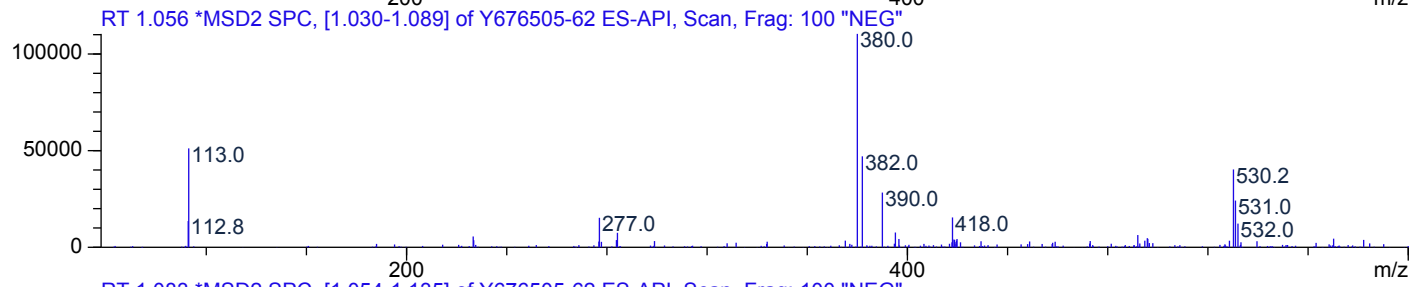
1.244



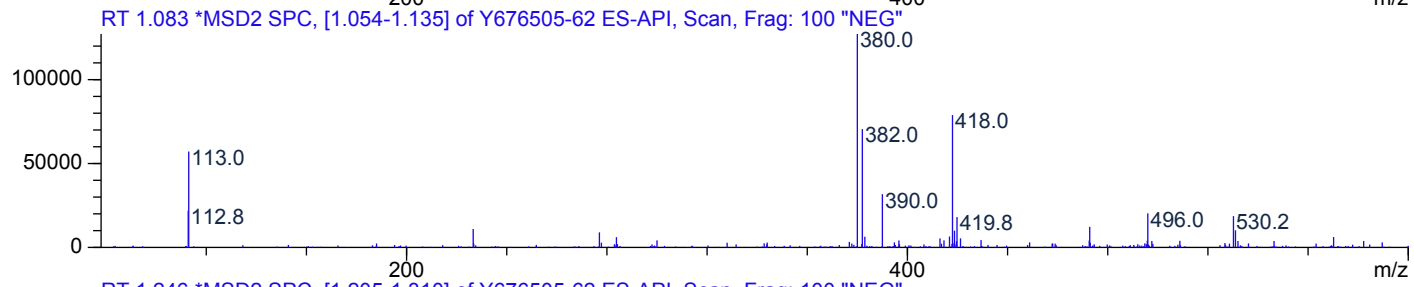
0.857



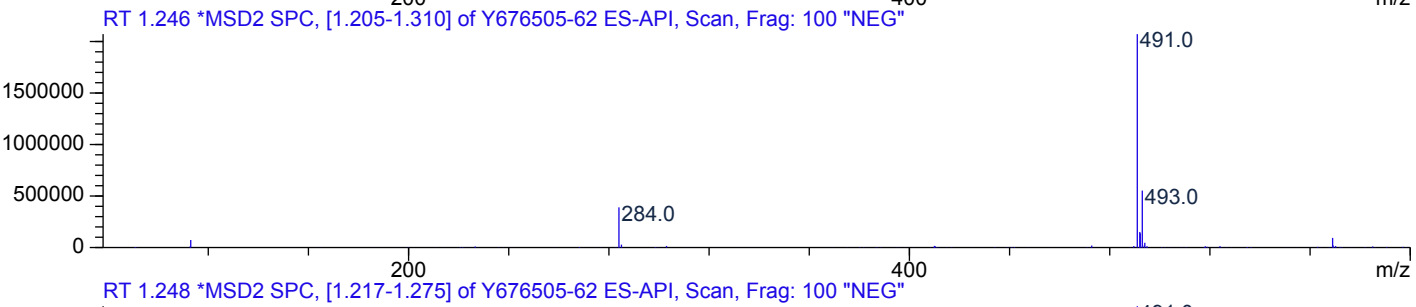
1.056



1.083



1.246



1.248