Access to unprotected β-fluoroalkyl β-amino acids and their α-hydroxy derivatives

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Supporting Information

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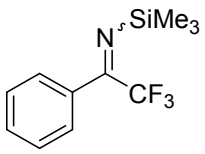
General information

Unless otherwise noted, all reagents and solvents were purchased from commercial sources and used as received. The reactions were monitored by ^{19}F NMR spectra of the reaction mixture samples or thin-layer chromatography (TLC) using silica gel gel (60 F254) plates (compounds were visualized using a UV lamp (254 nm) and/or by potassium permanganate stain). Flash column chromatography was carried out on silica gel 60 (230-400 mesh, 0.040-0.063 mm). Melting points (mp [°C]) were taken on samples in open capillary tubes and are uncorrected. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a spectrometer at 250 MHz (^{19}F: 235 MHz), 400 MHz (^{13}C: 101 MHz; ^{19}F: 376 MHz) or 500 MHz (^{13}C: 126 MHz; ^{19}F: 470 MHz). Chemical shifts are given in parts per million from tetramethylsilane (^{1}H NMR) or CCl_3F (^{19}F NMR) as internal standard. The following abbreviations are used for the proton spectra multiplicities: s: singulet, d: doublet, t: triplet, q: quartet, qt: quintuplet, m: multiplet, br.: broad, dd: double doublet, dt: double triplet. High-resolution accurate mass measurements (HRMS) were recorded with a Maxis Bruker 4G instrument and were performed in positive mode with an ESI source on a Q-TOF mass spectrometer with an accuracy tolerance of 2 ppm by the "Fédération de Recherche" ICOA/CBM (FR2708) platform. Microwaves-assisted reactions were carried out in a Biotage Initiator microwave synthesis instrument and temperatures were measured by IR-sensor (Biotage, Uppsala, Sweden). Infrared (IR) spectra were recorded on a Bruker Vertex 70 (ATR) or FT-IR spectrometer. The samples were prepared as neat films or as fine powders and the wave numbers are reported in cm^{-1}. Compounds **1a-z** were provided by Sigma-Alrich, Fluorochem or Enamine LTD and used as received.

1. Synthesis of 3-amino-4,4,4-trifluoro-3-phenyl-butanoic acid (4a) by Methods A, B and C

Synthesis of 1,1,1-trimethyl-N-(2,2,2-trifluoro-1-phenylethylidene)silanamine (2a).

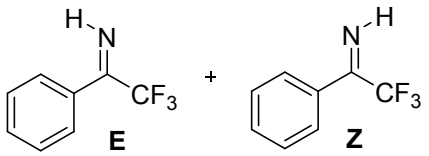


A solution of 1-phenyl-2,2,2-trifluoroethanone **1a** (0.87 g, 5.0 mmol, 1 equiv) in anhydrous hexane (15 mL) was cooled to 0-5 °C in ice water bath and lithium hexamethyldisilazide solution (1.0 M in hexanes, Sigma-Aldrich, 5.50 mL, 1.1 equiv) was added at stirring *via* syringe over 10 min under argon atmosphere. The reaction mixture was stirred for 20 min at 0-5 °C and additionally for 2 h at room temperature. After that the mixture was cooled to 0-5 °C in ice water bath and cold water (15 mL) was added at vigorous stirring *via* dropping funnel. The resulted mixture was stirred for 5 min. The organic layer was separated, washed with brine (2×10 mL), dried over anhydrous magnesium sulfate and filtered. Solvents were removed under reduced pressure. Yellow liquid (1.17 g, 95 % yield). The spectral data of **2a** are consisted with that already reported.[1] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.58 (d, J = 7.5

[1] Gosselin, F.; O'Shea, P. D.; Roy, S.; Reamer, R. A.; Chen, C.-Y.; Volante, R. P. *Org. Lett.* **2005**, *7*, 355–358.

Hz, 2H), 7.48 – 7.42 (m, 3H), 0.20 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 158.8 (q, J = 33 Hz), 135.7, 130.4, 128.3, 127.7, 117.9 (q, J = 289 Hz), 0.3. **^{19}F NMR** (376 MHz, $CDCl_3$): δ –69.4 (s).

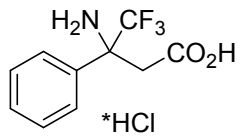
Synthesis of 2,2,2-trifluoro-1-phenylethanimine (3a).

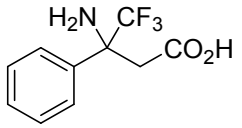


1,1,1-Trimethyl-N-(2,2,2-trifluoro-1-phenylethylidene)-silanamine **2a** (736 mg, 3 mmol, 1 equiv) was dissolved in THF (10 mL) and a solution of ammonium chloride (481 mg, 9 mmol, 3 equiv) in water (10 mL) was added at room temperature. The resulted emulsion was stirred for 1 h at room temperature and then extracted with dichloromethane (2×10 mL). The organic layers were combined, dried over anhydrous magnesium sulfate, filtered and solvents were evaporated under vacuum. The slightly yellow liquid was distilled under vacuum (20-30 mmHg) using Kugelrohr apparatus to give **3a** as a colorless liquid (291 mg, 56 % yield, mixture of the *E/Z* isomers, 0.4:1). The spectral data of **3a** are consisted with that already reported.[2] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.70 (br s, 0.4H), 10.80 (br s, 1H), 7.98 (d, J = 7.3 Hz, 2H), 7.60 – 7.30 (m, 5.2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.7 (q, J = 23 Hz), 163.60 (q, J = 31 Hz), 132.3, 132.2, 131.8, 131.0, 129.1, 128.7, 128.1, 126.5, 120.3 (q, J = 281 Hz), 118.5 (q, J = 283 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): δ –69.2 (s, 0.4F), –70.2 (s, 1F).

Synthesis of 3-amino-4,4,4-trifluoro-3-phenyl-butanoic acid (4a).

Method A and B (4a hydrochloride salt). Compound **3a** (260 mg, 1.50 mmol, 1 equiv, Method A) or **2a** (368 mg, 1.50 mmol, 1 equiv, Method B) was dissolved in anhydrous acetonitrile (1 mL), then malonic acid (468 mg, 4.50 mmol, 3 equiv) was added and the mixture was stirred at room temperature for 24 h. The white precipitate was collected by filtration, washed with acetonitrile (2×2 mL) and dried on air. The filtrate was evaporated to dryness under vacuum. The remained residue and the solid were combined and dissolved in aqueous hydrochloric acid (5 % w/w, 6 mL). The clear solution was evaporated to dryness. The residue was treated with ethyl acetate (5 mL). The white solid was collected by filtration, washed with ethyl acetate (3×5 mL) and dried under vacuum to give hydrochloride salt of **4a** as a white solid (352 mg, 87 % yield, method A; 348 mg, 86 % yield, Method B). Mp 230–232 °C. IR (neat): ν_{max} 3013, 1723, 1522, 1426, 1212, 1164, 902, 693. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.63 (d, J = 7.0 Hz, 2H), 7.46–7.53 (m, 3H), 3.80 (d, J = 17.5 Hz, 1H), 3.47 (d, J = 17.5 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 169.7, 132.0, 130.1, 129.2, 127.2, 124.3 (q, J = 287 Hz), 61.8 (q, J = 26 Hz), 35.9. **^{19}F NMR** (376 MHz, DMSO-d_6): δ –75.3 (s). **HRMS** (ESI+): calcd for $C_{10}H_{11}F_3NO_2$ $[M+H]^+$: 234.0736, found 234.0733.



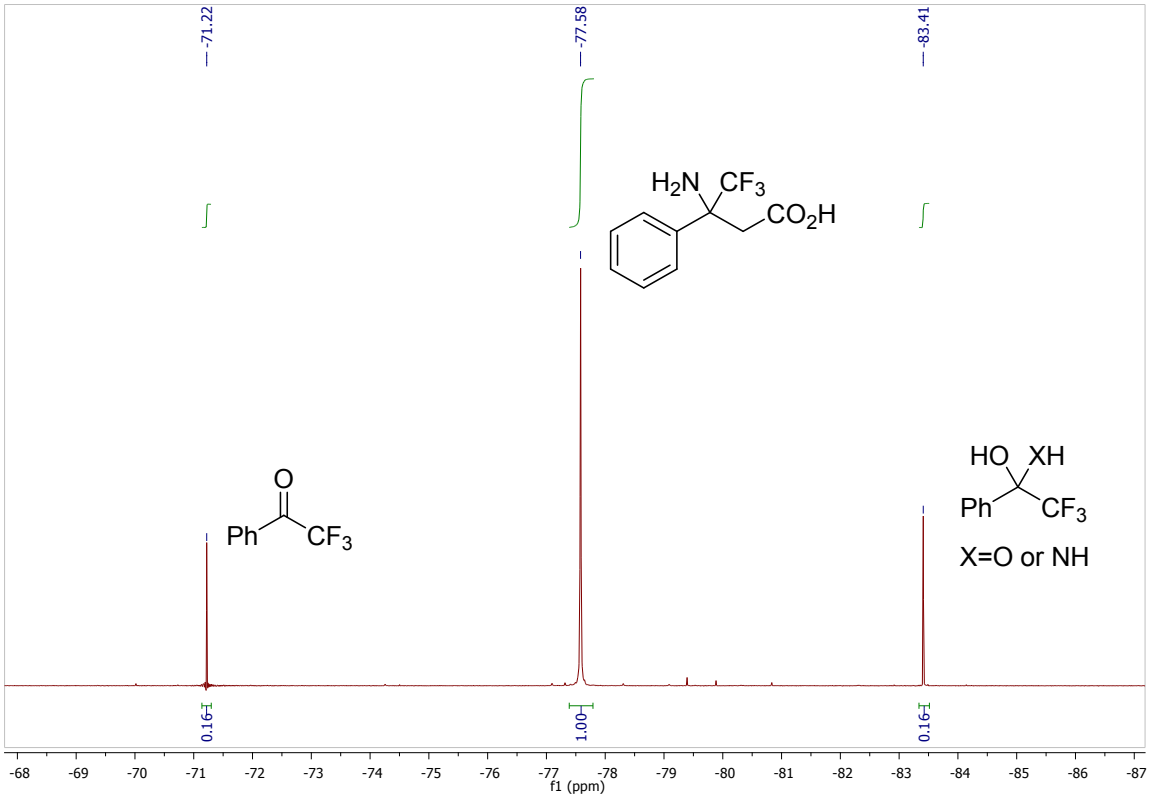


Method C (free 4a).[3] A solution of 1-phenyl-2,2,2-trifluoroethanone **1a** (261 mg, 1.50 mmol, 1 equiv) in anhydrous THF (5 mL) was cooled to 0-5 °C in ice water bath and lithium hexamethyldisilazide solution (1.0 M in THF, Sigma-Aldrich, 1.50 mL, 1 equiv) was added at stirring *via* syringe in 5 min under argon atmosphere. The reaction mixture was stirred 20 min at 0-5 °C and 2 h at room temperature. After that the mixture was cooled to 0-5 °C in ice water bath and a solution of trimethylchlorosilane

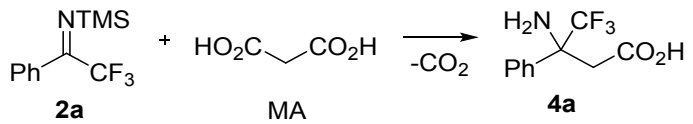
[2] Morisaki, K.; Morimoto, H.; Ohshima, T. *Chem. Comm.* **2017**, *53*, 6319–6322. We assigned the major isomer as *Z* on the basis of downshielded aromatic *ortho* protons signal at 7.66 ppm in the ^{1}H NMR spectra.

(163 mg, 1.50 mmol, 1 equiv) in THF (2 mL) was added *via* syringe in single portion. The resulted mixture was stirred for 2 h at room temperature. Then malonic acid (468 mg, 4.50 mmol, 3 equiv) was added and the mixture was stirred at 66 °C for 3 h. The reaction mixture was cooled to 5 °C and left at this temperature overnight. The precipitate formed was collected by filtration and washed with THF (3×3 mL), distilled water (3×3 mL) and dried under vacuum to give free **4a** as a white solid (161 mg, 46 %). Mp 175–177 °C (lit. 177–178 °C).[3] IR (neat): ν_{max} 2993, 2786, 1650, 1558, 1182, 694. **^{1}H NMR** (400 MHz, DMSO-d_6): 7.66 (d, J = 7.4 Hz, 2H), 7.4 – 7.35 (m, 3H), 5.02 (br s, 3H), 3.26 (d, J = 16.0 Hz, 1H), 2.95 (d, J = 16.0 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 171.1, 138.1, 128.55, 128.51, 127.52, 126.7 (q, J = 287 Hz), 60.5 (q, J = 26 Hz), 39.6. **^{19}F NMR** (376 MHz, DMSO-d_6): δ –77.7 (s).

^{19}F NMR spectra of the reaction mixture after heating in THF (0.2 mL aliquot). The sample was mixed with DMSO-d_6 (0.5 mL) directly in an NMR tube:



2. Optimization and conditions screening for the addition of MA to 1,1,1-trimethyl-N-(2,2,2-trifluoro-1-phenylethylidene)silanamine 2a[a] (Table 1S).



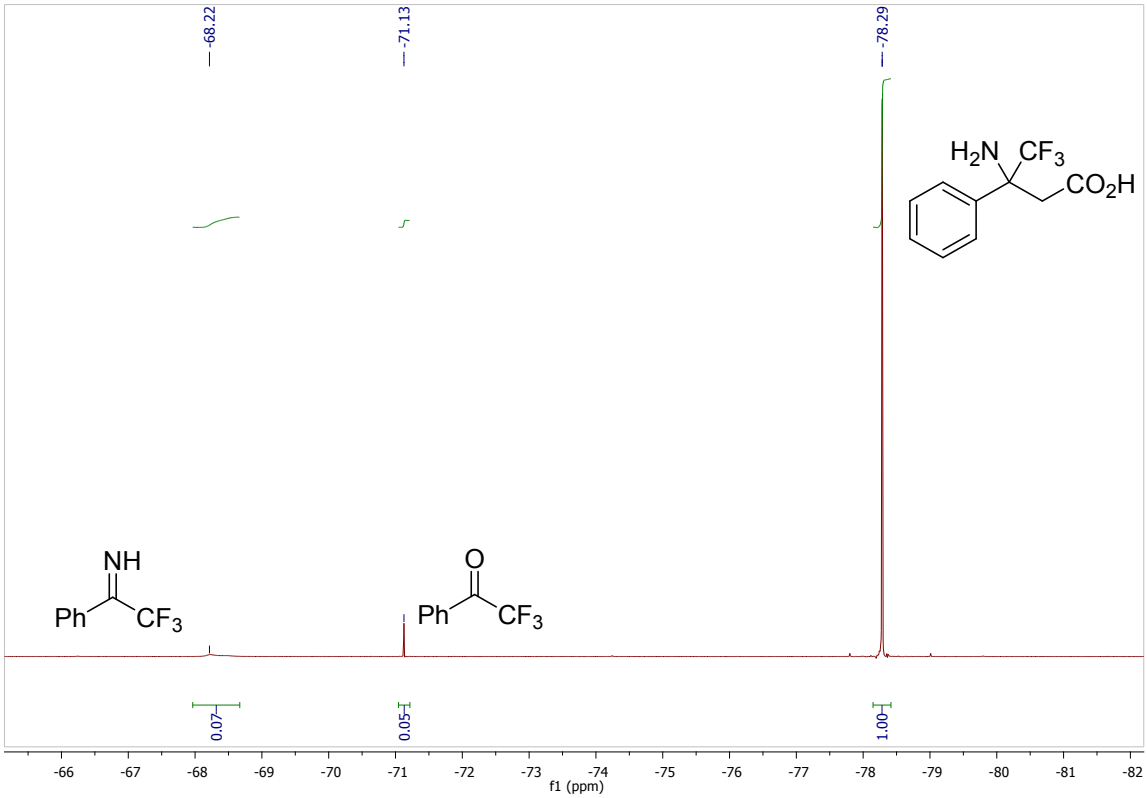
[3] Kolycheva, M.T.; Gerus, I.I.; Yagupol'ski, Yu.L.; Kukhar, V. P. *J. Org. Chem. USSR (Eng. Transl.)* **1991**, *27*, 101–104.

Entry	Solvent[b]	MA equiv	Temp, °C	Time, h	Conversion (%)[c]	Yield (%)[c,d]
1	toluene	3	80	1	99	97
2	dioxane	3	80	1	99	96
3	$CHCl_3$	3	61	1	93	89
4	THF	3	66	1	95	93
5	ethyl acetate	3	77	1	99	97
6	acetone	3	56	1	99[e]	<25[e]
7	dimethyl carbonate	3	80	1	99	97
8	MTBE	3	55	1	94	90
9	MeOH	3	65	1	99	13
10	CH_3CN	3	80	1	99	98
11	CH_3CN	3	rt	24	99	97
12	CH_3CN	3	80 MW[f]	1	99	98
13	CH_3CN	2	80	1	94	89
14	**CH_3CN**	**2**	**80**	**2**	**99**	**98**
15	CH_3CN	1.2	80	2	66	64
16	solvent free	2	80	2	99	98

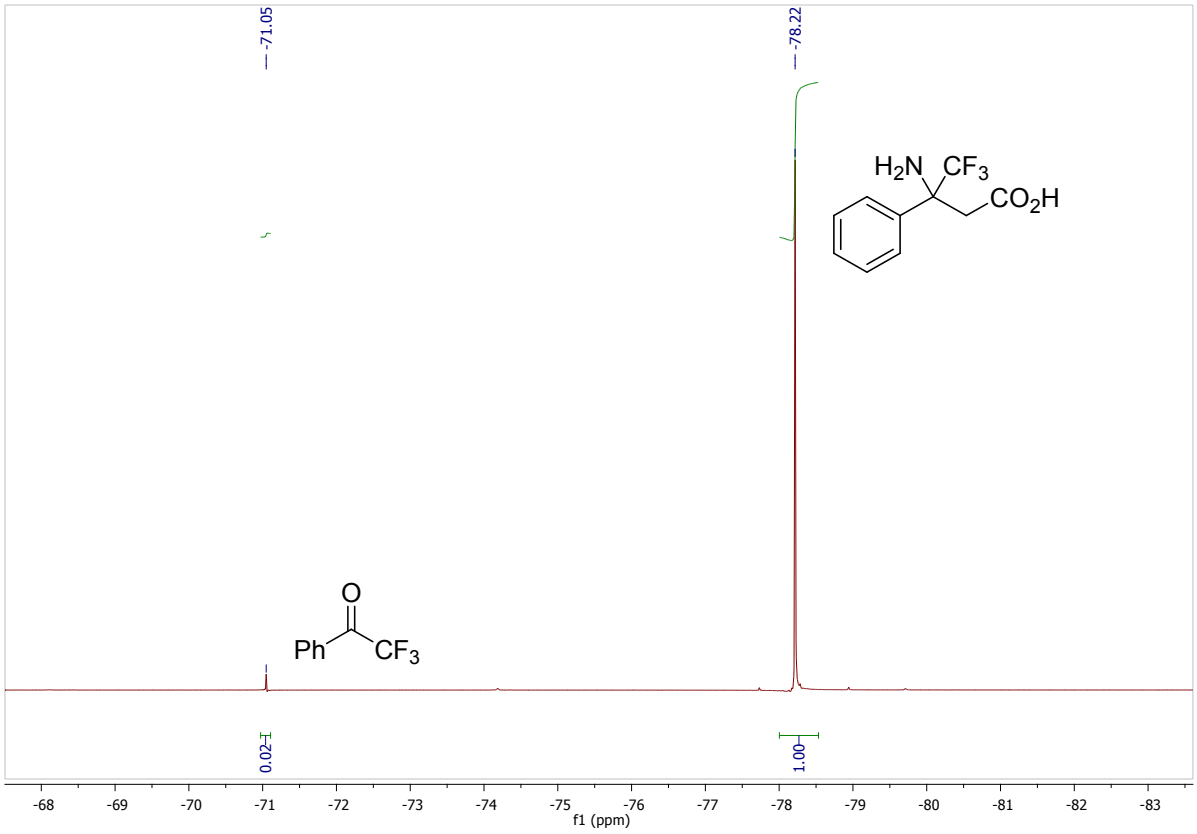
[a] The reaction was performed using **2a** (50 mg, 0.2 mmol) and 0.2 mL of solvent in a sealed vessel. [b]Anhydrous solvents were used. [c] ^{19}F NMR monitoring of the crude reaction mixture after cooling and dilution with DMSO-d_6 (0.5 mL). [d] ^{19}F NMR yield. [e] Complex mixture was formed. [f] Microwave activation was used.

Representative examples of the reaction monitoring by ^{19}F NMR (Table 1S):

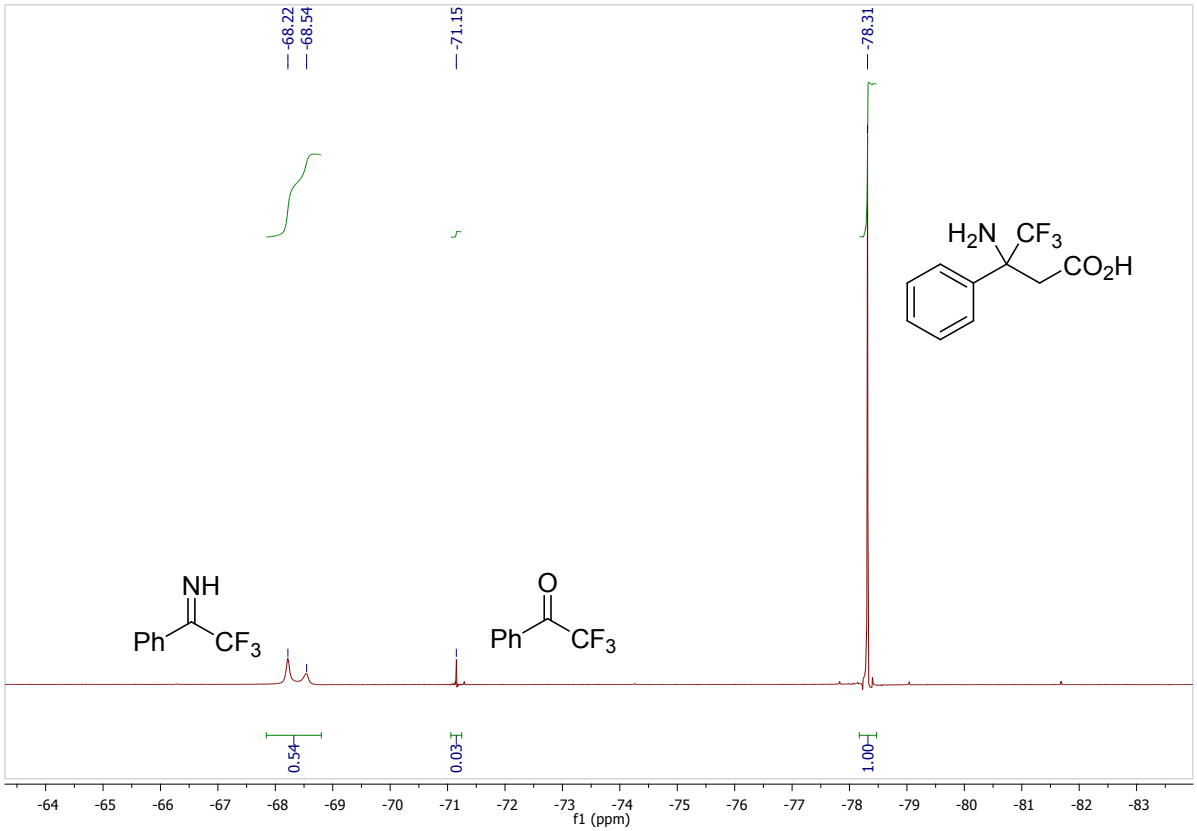
Entry 13:


-68.22
-71.13
-78.29
H2N CF3
CO2H
NH
Ph CF3
O
Ph CF3
0.07
0.05
1.00
-66 -67 -68 -69 -70 -71 -72 -73 -74 -75 -76 -77 -78 -79 -80 -81 -82
f1 (ppm)

Entry 14:



Entry 15:

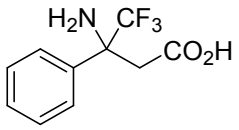


3. Synthesis of compounds 4a-y. General procedure (GP).

Step 1. Reaction of ketones 1a-y with lithium hexamethyldisilazide. Preparation of crude compounds 2a-y. To a solution of ketone **1a-y** (1.50 mmol, 1 equiv) in anhydrous hexane (10 mL) cooled to 0-5 °C using an ice water bath, lithium hexamethyldisilazide solution (1.0 M in hexanes, 1.65 mL, 1.1 equiv) was added *via* a syringe over 5 min under argon atmosphere. The reaction mixture was stirred for 20 min at 0-5 °C and for 2 h at room temperature. After the mixture was cooled down to 0-5 °C, cold water (5 mL) was added under vigorous stirring. The resulted mixture was stirred for 5 min at 0-5 °C. Organic layer was separated, washed with brine (2×10 mL), dried over anhydrous magnesium sulfate, filtered and solvents were removed under vacuum. The residual liquid or oil was dried at 35-40 °C and 15 Torr for 1 h. The crude compound **2a-y** thus obtained was used immediately in the next step without further purification.

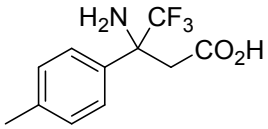
Step 2. Reaction of crude compounds 2a-y with malonic acid. Synthesis of compounds 4a-y. The crude compound **2a-y** was dissolved in anhydrous acetonitrile (1 mL), then malonic acid (312 mg, 3.0 mmol, 2 equiv) was added and the mixture was stirred at 80 °C for 2 h. After cooling, the reaction mixture was treated as specified for each example. The yields are calculated based on corresponding starting ketone **1a-y**.

3-Amino-4,4,4-trifluoro-3-phenylbutanoic acid (4a).



Following the **GP**, using 1-phenyl-2,2,2-trifluoroethanone **1a** (261 mg, 1.5 mmol, 1 equiv). The reaction mixture obtained according to **GP** was evaporated to dryness and the residue was dissolved in aqueous hydrochloric acid (10 % w/w, 3 mL). The solution was evaporated to dryness. The residue was treated with ethyl acetate (3 mL). The white solid was collected by filtration, washed with ethyl acetate (3×3 mL), dried under vacuum and dissolved in distilled water (3 mL). A solution of sodium hydrocarbonate (115 mg, 1.37 mmol, 0.91 equiv) in distilled water (3 mL) was added to this solution. The mixture was stirred at room temperature for 1 h. The precipitate was collected by filtration, washed with distilled water (3×3 mL) and dried in vacuum to give free **4a** as a white solid (263 mg, 71 % starting from **1a**). This material was identical to the free **4a** obtained by Method C (see section 1). The synthesis was repeated on 10 mM scale with 75 % yield of **4a**.

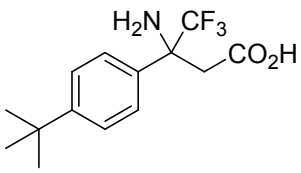
3-Amino-4,4,4-trifluoro-3-*p*-tolylbutanoic acid (4b).



Following the **GP** using 1-(4-methylphenyl)-2,2,2-trifluoroethanone **1b** (282 mg, 1.5 mmol, 1 equiv). The reaction mixture obtained according to **GP** was treated as described for preparation of free **4a**. White solid (267 mg, 72 %). Mp 157–159 °C. IR (neat): ν_{max} 2774, 1643, 1567, 1397, 1319, 1162, 806, 660. **^{1}H NMR** (400 MHz, DMSO-d_6): 7.51 (d, J = 7.7 Hz, 2H), 7.20 (d, J = 7.8 Hz, 2H), 3.20 (d, J = 15.9 Hz, 1H), 2.90 (d, J = 15.9 Hz, 1H), 2.30 (s, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 171.0, 137.9, 135.0, 129.1, 127.4, 126.7 (q, J = 287 Hz), 60.3, 39.5, 21.0. **^{19}F NMR** (376 MHz, DMSO-d_6): δ –77.9 (s). **HRMS** (ESI+): calcd for $C_{11}H_{13}F_3NO_2$ $[M+H]^+$: 248.0892, found 248.0894.

This compound was also prepared by Method C using 1-(4-methylphenyl)-2,2,2-trifluoroethanone **1a** (282 mg, 1.50 mmol, 1 equiv) as described for the preparation of free **4a**. White solid (148 mg, 40 %).

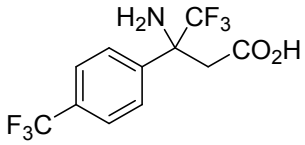
3-Amino-3-(4-*tert*-butylphenyl)-4,4,4-trifluorobutanoic acid (4c).



Following the **GP** using 1-(4-*tert*-butylphenyl)-2,2,2-trifluoroethanone **1c** (345 mg, 1.50 mmol, 1 equiv). The reaction mixture obtained

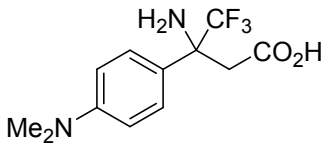
according to **GP** was filtered. The solid material was washed with acetonitrile (3×2 mL), water (3×2 mL) and dried at 50 °C for 3 h. White solid (330 mg, 76 %). Mp 211–213 °C. IR (neat): ν_{max} 2966, 2871, 1644, 1580, 1474, 1393, 1272, 1172, 991, 822, 663. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.56 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 4.92 (br s, 3H), 3.21 (d, J = 15.5 Hz, 1H), 2.93 (d, J = 15.9 Hz, 1H), 1.29 (s, 9H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 171.1, 150.9, 135.0, 126.7 (q, J = 286 Hz), 125.4, 60.2 (q, J = 26 Hz), 39.5, 34.6, 31.5. **^{19}F NMR** (376 MHz, DMSO-d_6): δ –77.8 (s). **HRMS** (ESI+): calcd for $C_{14}H_{19}F_3NO_2$ $[M+H]^+$: 290.1362, found 290.1362.

3-Amino-4,4,4-trifluoro-3-(4-(trifluoromethyl)phenyl)butanoic acid (4d).



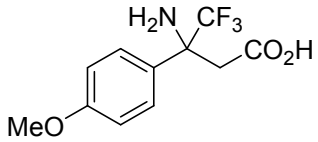
Following the **GP** using 1-(4-trifluoromethylphenyl)-2,2,2-trifluoroethanone **1d** (363 mg, 1.50 mmol, 1 equiv). The reaction mixture obtained according to **GP** was treated as described for preparation of free **4a**. White solid (307 mg, 68 %). Mp 145–147 °C. IR (neat): ν_{max} 2853, 1643, 1569, 1483, 1398, 1324, 1269, 1166, 1117, 1073, 660. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.90 (d, J = 7.9 Hz, 2H), 7.77 (d, J = 8.0 Hz, 2H), 6.00 (br s, 3H), 3.36 (d, J = 16.2 Hz, 1H), 2.97 (d, J = 16.2 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 170.9, 143.2, 129.1 (q, J = 31 Hz), 128.7, 126.5 (q, J = 286 Hz), 125.3 (q, J = 4 Hz), 124.4 (q, J = 270 Hz), 60.7 (q, J = 26 Hz), 40.6. **^{19}F NMR** (376 MHz, DMSO-d_6): δ –61.13 (s, 3F), –77.57 (s, 3F). **HRMS** (ESI+): calcd for $C_{11}H_{10}F_6NO_2$ $[M+H]^+$: 302.0610, found 302.0609.

3-Amino-3-(4-(dimethylamino)phenyl)-4,4,4-trifluorobutanoic acid (4e).



Following the **GP** using 1-(4-(dimethylamino)phenyl)-2,2,2-trifluoroethanone **1e** (326 mg, 1.50 mmol, 1 equiv). The reaction mixture obtained according to **GP** was treated as described for preparation of free **4a** (2 equiv instead of 1 equiv of sodium hydrocarbonate were used). Light beige solid (273 mg, 66 %). Mp 141–143 °C. IR (neat): ν_{max} 2889, 1618, 1574, 1477, 1327, 1162, 812, 660. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.40 (d, J = 8.6 Hz, 2H), 6.70 (d, J = 8.8 Hz, 2H), 3.12 (d, J = 15.7 Hz, 2H), 2.90 (m, 7H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 171.1, 150.4, 128.1, 126.9 (q, J = 289 Hz), 124.4, 112.11, 59.7 (q, J = 26 Hz), 39.4. **^{19}F NMR** (376 MHz, DMSO-d_6): δ –78.13 (s). **HRMS** (ESI+): calcd for $C_{12}H_{16}F_3N_2O_2$ $[M+H]^+$: 277.1158, found 277.1158.

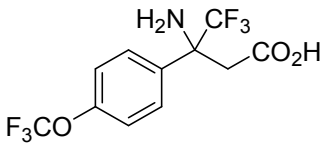
3-Amino-3-(4-methoxyphenyl)-4,4,4-trifluorobutanoic acid (4f).



Following the **GP** using 1-(4-methoxyphenyl)-2,2,2-trifluoroethanone **1f** (306 mg, 1.50 mmol, 1 equiv). The reaction mixture obtained according to **GP** was treated as described for preparation of free **4a**. White solid (292 mg, 74 %). Mp 151–153 °C. IR (neat): ν_{max} 3079, 2844, 2781, 1642, 1539, 1516, 1397, 1320, 1257, 1158, 1087, 1000, 820, 661. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.55 (d, J = 8.4 Hz, 2H), 6.94 (d, J = 8.6 Hz, 2H), 5.15 (br s, 3H), 3.76 (s, 3H), 3.19 (d, J = 15.9 Hz, 1H), 2.90 (d, J = 15.9 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 171.1,

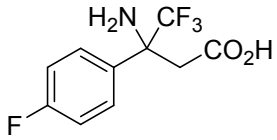
159.4, 129.75, 128.8, 126.7 (q, J = 280 Hz), 113.9, 60.0 (q, J = 26 Hz), 55.5, 39.6. **^{19}F NMR** (376 MHz, DMSO-d_6): δ –78.05 (s). **HRMS** (ESI+): calcd for $C_{11}H_{13}F_3NO_3$ $[M+H]^+$: 264.0842, found 264.0841.

3-Amino-4,4,4-trifluoro-3-(4-(trifluoromethoxy)phenyl)butanoic acid (4g).



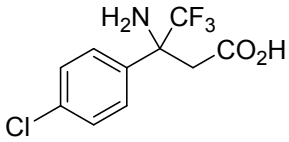
Following the **GP** using 1-(4-trifluoromethoxyphenyl)-2,2,2-trifluoroethanone **1g** (387 mg, 1.50 mmol, 1 equiv). The reaction mixture obtained according to **GP** was treated as described for preparation of free **4a**. White solid (328 mg, 69 %). Mp 167–169 °C. IR (neat): ν_{max} 2783, 1644, 1547, 1402, 1267, 1203, 1169, 956, 842, 660. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.79 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 3.32 (d, J = 16.1 Hz, 1H), 2.96 (d, J = 16.1 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 170.9, 148.6, 129.8, 126.4 (q, J = 293 Hz), 120.8, 120.5 (q, J = 255 Hz), 60.4 (q, J = 26 Hz), 39.9. **^{19}F NMR** (376 MHz, DMSO-d_6): δ –56.80 (s, 3F), –77.73 (s, 3F). **HRMS** (ESI+): calcd for $C_{11}H_{10}F_6NO_3$ $[M+H]^+$: 318.0559, found 318.0560.

3-Amino-4,4,4-trifluoro-3-(4-fluorophenyl)butanoic acid (4h).



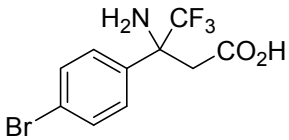
Following the **GP** using 1-(4-fluorophenyl)-2,2,2-trifluoroethanone **1h** (288 mg, 1.50 mmol, 1 equiv). The reaction mixture obtained according to **GP** was evaporated to dryness and water (3 mL) was added to the residue. The white precipitate formed was collected by filtration, washed with distilled water (3×3 mL), petroleum ether (2×5 mL) and dried in vacuum to give free **4d**. White solid (279 mg, 74 %). Mp 179–181 °C. IR (neat): ν_{max} 2999, 2876, 2766, 1621, 1570, 1401, 1248, 1173, 825, 662. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 7.69 (s, 2H), 7.21 (t, J = 8.2 Hz, 2H), 6.08 (br s, 3H), 3.26 (d, J = 16.0 Hz, 1H), 2.92 (d, J = 16.0 Hz, 1H). **^{13}C NMR** (126 MHz, DMSO-d_6): δ 171.0, 162.3 (d, J = 246 Hz), 126.6 (q, J = 286 Hz), 115.2 (d, J = 21 Hz), 60.57 (q, J = 26 Hz), 39.92. **^{19}F NMR** (470 MHz, DMSO-d_6): δ –78.5 (s, 3F), –115.3 (s, 1F). **HRMS** (ESI+): calcd for $C_{10}H_{10}F_4NO_2$ $[M+H]^+$: 252.0642, found 252.0641.

3-Amino-3-(4-chlorophenyl)-4,4,4-trifluorobutanoic acid (4i).



Following the **GP** using 1-(4-chlorophenyl)-2,2,2-trifluoroethanone **1i** (313 mg, 1.50 mmol, 1 equiv). The reaction mixture obtained according to **GP** was treated as described for preparation of free **4h**. White solid (281 mg, 70 %). Mp 156–158 °C. IR (neat): ν_{max} 2873, 2714, 1626, 1565, 1418, 1257, 1158, 1009, 820, 664. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.66 (d, J = 6.5 Hz, 2H), 7.45 (d, J = 6.5 Hz, 2H), 3.26 (d, J = 15.8 Hz, 2H), 2.91 (d, J = 15.8 Hz, 2H). **^{13}C NMR** (126 MHz, DMSO-d_6): δ 170.8, 137.4, 133.5, 129.6, 128.4, 126.5 (q, J = 286 Hz), 60.4 (q, J = 26 Hz), 39.6. **^{19}F NMR** (376 MHz, DMSO-d_6): δ –78.3 (s). **HRMS** (ESI+): calcd for $C_{10}H_{10}ClF_3NO_2$ $[M+H]^+$: 268.0346, found 268.0342.

3-Amino-3-(4-bromophenyl)-4,4,4-trifluorobutanoic acid (4j).

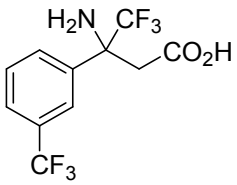


Following the **GP** using 1-(4-bromophenyl)-2,2,2-trifluoroethanone **1j** (379 mg, 1.50 mmol, 1 equiv). The reaction mixture obtained according to

GP was treated as described for preparation of free **4h**. White solid (337 mg, 72 %). Mp 135–137 °C. IR (neat): ν_{max} 2870, 1625, 1556, 1402, 1244, 1139, 1021, 807, 661. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 7.59 (s, 4H), 3.26 (d, J = 16.1 Hz, 1H), 2.91 (d, J = 16.1 Hz, 1H). **^{13}C NMR** (126 MHz, DMSO-d_6): δ 171.0, 137.9, 131.4, 130.0, 126.5 (q, J = 286 Hz), 122.2, 60.5 (q, J = 26 Hz), 39.6. **^{19}F NMR** (376 MHz, DMSO-d_6): δ –78.3 (s). **HRMS** (ESI+): calcd for $C_{10}H_{10}BrF_3NO_2$ $[M+H]^+$: 311.9841, found 311.9840.

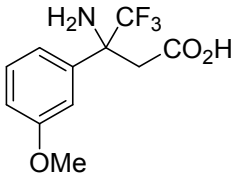
This compound was also prepared by Method C using 1-(4-bromophenyl)-2,2,2-trifluoroethanone **1j** (379 mg, 1.50 mmol, 1 equiv) as described for preparation of free **4a**. The reaction mixture obtained according to this procedure was cooled to 0-5 °C in ice bath and then water (1 mL) was added. The mixture was stirred for 10 min and evaporated to dryness. The residue was treated with water (5 mL). The precipitate was collected by filtration, washed with distilled water (3×3 mL), petroleum ether (2×5 mL) and dried in vacuum at 50 °C to give free **4j** as a white solid (183 mg, 39 %).

3-Amino-4,4,4-trifluoro-3-(3-(trifluoromethyl)phenyl)butanoic acid (4k).



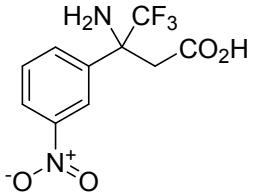
Following the **GP** using 1-(3-trifluoromethylphenyl)-2,2,2-trifluoroethanone **1k** (363 mg, 1.50 mmol, 1 equiv). The reaction mixture obtained according to **GP** was treated as described for preparation of free **4h**. White solid (348 mg, 77 %). Mp 162–164 °C. IR (neat): ν_{max} 3356, 3277, 1716, 1522, 1426, 1329, 1221, 1126, 1045, 803, 699. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 8.03 (s, 1H), 7.95 (d, J = 6.9 Hz, 1H), 7.71 (d, J = 6.7 Hz, 1H), 7.63 (t, J = 7.2 Hz, 1H), 6.22 (br s, 3H), 3.38 (d, J = 16.1 Hz, 1H), 2.96 (d, J = 16.1 Hz, 1H). **^{13}C NMR** (126 MHz, DMSO-d_6): δ 170.9, 140.0, 131.9, 129.5, 129.4 (q, J = 33 Hz), 126.5 (q, J = 286 Hz), 125.3 (q, J = 4 Hz), 124.7 (q, J = 272 Hz), 124.4 (q, J = 4 Hz), 60.7 (q, J = 26 Hz), 39.6. **^{19}F NMR** (470 MHz, DMSO-d_6): δ –61.0 (s, 3F), –77.8 (s, 3F). **HRMS** (ESI+): calcd for $C_{11}H_{10}F_6NO_2$ $[M+H]^+$: 302.0610, found 302.0610.

3-Amino-4,4,4-trifluoro-3-(3-methoxyphenyl)butanoic acid (4l).



Following the **GP** using 1-(3-methoxyphenyl)-2,2,2-trifluoroethanone **1l** (306 mg, 1.50 mmol, 1 equiv). The reaction mixture obtained according to **GP** was treated as described for preparation of free **4a**. White solid (288 mg, 73 %). Mp 147–149 °C. IR (neat): ν_{max} 3104, 2808, 2767, 1641, 1545, 1520, 1386, 1325, 1273, 1160, 1077, 813, 663. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.31 (t, J = 7.7 Hz, 1H), 7.25 – 7.12 (m, 2H), 6.94 (d, J = 7.7 Hz, 1H), 6.11 (br s, 3H), 3.77 (s, 3H), 3.23 (d, J = 16.0 Hz, 1H), 2.92 (d, J = 16.0 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 171.1, 159.5, 139.8, 129.6, 126.6 (q, J = 286 Hz), 119.7, 114.2, 113.5, 60.5 (q, J = 27 Hz), 55.6, 39.7. **^{19}F NMR** (376 MHz, DMSO-d_6): δ –76.8 (s). **HRMS** (ESI+): calcd for $C_{11}H_{13}F_3NO_3$ $[M+H]^+$: 264.0842, found 264.0839.

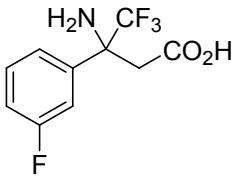
3-Amino-4,4,4-trifluoro-3-(3-nitrophenyl)butanoic acid (4m).



Following the **GP** using 1-(3-nitrophenyl)-2,2,2-trifluoroethanone **1m** (329 mg, 1.50 mmol, 1 equiv). The reaction mixture obtained according to **GP** was

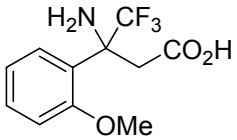
treated as described for preparation of free **4a**. White solid (284 mg, 68 %). Mp 141–143 °C. IR (neat): ν_{max} 2830, 2712, 1642, 1533, 1524, 1362, 1306, 1217, 1155, 1071, 828, 662. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 8.55 (s, 1H), 8.22 (d, J = 7.0 Hz, 2H), 8.10 (d, J = 7.0 Hz, 2H), 7.69 (t, J = 6.9 Hz, 1H), 3.41 (d, J = 16.0 Hz, 1H), 2.97 (d, J = 16.0 Hz, 1H). **^{13}C NMR** (126 MHz, DMSO-d_6): δ 170.8, 148.3, 141.0, 134.5, 130.1, 126.4 (q, J = 286 Hz), 123.6, 122.7, 60.7 (q, J = 26 Hz), 39.8. **^{19}F NMR** (376 MHz, DMSO-d_6): δ –78.1 (s). **HRMS** (ESI+): calcd for $C_{10}H_{10}F_3N_2O_4$ $[M+H]^+$: 279.0587, found 279.0588.

3-Amino-4,4,4-trifluoro-3-(3-fluorophenyl)butanoic acid (4n).



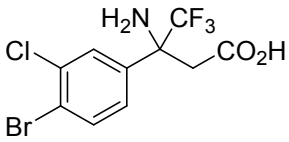
Following the **GP** using 1-(3-fluorophenyl)-2,2,2-trifluoroethanone **1n** (288 mg, 1.50 mmol, 1 equiv). The reaction mixture obtained according to **GP** was treated as described for preparation of free **4h**. White solid (283 mg, 75 %). Mp 170–172 °C. IR (neat): ν_{max} 3065, 2781, 1645, 1546, 1443, 1398, 1268, 1179, 783, 692. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.65 – 7.35 (m, 3H), 7.19 (t, J = 7.5 Hz, 1H), 3.30 (d, J = 16.1 Hz, 1H), 2.93 (d, J = 16.1 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 181.0, 162.4 (d, J = 243 Hz), 141.4 (d, J = 8 Hz), 130.3 (d, J = 9 Hz), 125.8 (q, J = 286 Hz), 123.8, 115.4 (d, J = 20 Hz), 115.0 (d, J = 23 Hz), 60.5 (q, J = 26 Hz), 39.6. **^{19}F NMR** (376 MHz, DMSO-d_6): δ –77.74 (s, 3F), –113.28 (s, 1F). **HRMS** (ESI+): calcd for $C_{10}H_{10}F_4NO_2$ $[M+H]^+$: 252.0642, found 252.0641.

3-Amino-4,4,4-trifluoro-3-(2-methoxyphenyl)butanoic acid (4o).



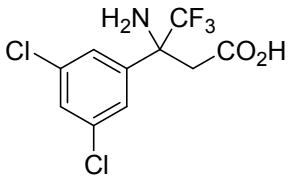
Following the **GP** using 1-(2-methoxyphenyl)-2,2,2-trifluoroethanone **1o** (306 mg, 1.50 mmol, 1 equiv). The reaction mixture obtained according to **GP** was treated as described for preparation of free **4a**. White solid (280 mg, 71 %). Mp 159–161 °C. IR (neat): ν_{max} 3039, 2841, 1642, 1537, 1426, 1256, 1177, 1077, 1030, 749, 662. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.67 (d, J = 7.6 Hz, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.05 (d, J = 8.1 Hz, 1H), 6.99 (t, J = 7.4 Hz, 1H), 5.88 (br s, 3H), 3.77 (s, 3H), 3.62 (d, J = 16.2 Hz, 1H), 2.85 (d, J = 16.2 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 171.5, 158.4, 130.5, 130.3, 126.8 (q, J = 287 Hz), 125.1, 120.8, 113.0, 60.7 (q, J = 27 Hz), 56.2, 39.7. **^{19}F NMR** (376 MHz, DMSO-d_6): δ –77.6 (s). **HRMS** (ESI+): calcd for C11H13F3NO3 $[M+H]^+$: 264.0842, found 264.0841.

3-Amino-3-(4-bromo-3-chlorophenyl)-4,4,4-trifluorobutanoic acid (4p).



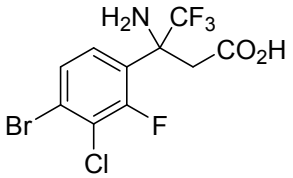
Following the **GP** using 1-(4-bromo-3-chlorophenyl)-2,2,2-trifluoroethanone **1p** (431 mg, 1.50 mmol, 1 equiv). The reaction mixture obtained according to **GP** was treated as described for preparation of free **4h**. White solid (364 mg, 70 %). Mp 158–160 °C. IR (neat): ν_{max} 3342, 3250, 2871, 1650, 1559, 1388, 1343, 1172, 1036, 847, 804, 680. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 7.93 (s, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 3.34 (d, J = 16.2 Hz, 1H), 2.89 (d, J = 16.2 Hz, 1H). **^{13}C NMR** (126 MHz, DMSO-d_6): δ 170.9, 140.5, 133.8, 133.5, 130.0, 128.4, 126.3 (q, J = 286 Hz), 121.9, 60.5 (q, J = 26 Hz), 39.5. **^{19}F NMR** (376 MHz, DMSO-d_6): –78.2 (s). **HRMS** (ESI+): calcd for $C_{10}H_9BrClF_3NO_2$ $[M+H]^+$: 345.9451, found 345.9451.

3-Amino-3-(3,5-dichlorophenyl)-4,4,4-trifluorobutanoic acid (4q).



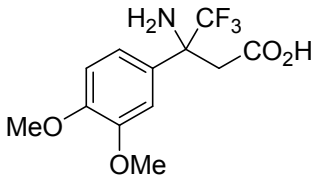
Following the **GP** using 1-(3,5-dichlorophenyl)-2,2,2-trifluoroethanone **1q** (365 mg, 1.50 mmol, 1 equiv). The reaction mixture obtained according to **GP** was treated as described for preparation of free **4h**. White solid (331 mg, 73 %). Mp 169–171 °C. IR (neat): ν_{max} 3357, 3276, 2877, 1636, 1569, 1427, 1325, 1163, 1059, 850, 805, 682. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.74 (s, 2H), 7.62 (s, 1H), 6.31 (br s, 3H), 3.45 (d, J = 16.3 Hz, 1H), 2.90 (d, J = 16.3 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 170.8, 142.8, 134.3, 128.3, 126.9, 126.2 (q, J = 287 Hz), 60.7 (q, J = 26 Hz), 39.6. **^{19}F NMR** (376 MHz, DMSO-d_6): δ –77.6 (s). **HRMS** (ESI+): calcd for $C_{10}H_9Cl_2F_3NO_2$ $[M+H]^+$: 301.9956, found 301.9956.

3-Amino-3-(4-bromo-3-chloro-2-fluorophenyl)-4,4,4-trifluorobutanoic acid (4r).



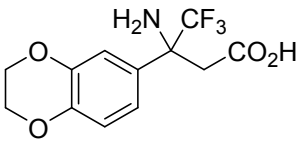
Following the **GP** using 1-(3,4-dimethoxyphenyl)-2,2,2-trifluoroethanone **1r** (458 mg, 1.50 mmol, 1 equiv). The reaction mixture obtained according to **GP** was treated as described for preparation of free **4h**. White solid (388 mg, 71 %). Mp 182–184 °C. IR (neat): ν_{max} 2887, 1630, 1592, 1548, 1395, 1186, 1088, 865, 664. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 7.77 (t, J = 8.1 Hz, 1H), 7.71 (d, J = 8.8 Hz, 1H), 6.22 (br s, 3H), 3.42 (d, J = 16.4 Hz, 1H), 2.92 (d, J = 16.3 Hz, 1H). **^{13}C NMR** (126 MHz, DMSO-d_6): δ 170.8, 156.3 (d, J = 253 Hz), 130.7 (d, J = 4 Hz), 129.0 (d, J = 3 Hz), 126.5 (d, J = 13 Hz), 126.2 (q, J = 287 Hz), 123.7, 122.1 (d, J = 23 Hz), 60.4 (q, J = 28 Hz), 39.2 (d, J = 9 Hz). **^{19}F NMR** (470 MHz, DMSO-d_6): –78.3 (d, J = 14 Hz, 3F), –104.4 (m, 1F). **HRMS** (ESI+): calcd for $C_{10}H_8BrClF_4NO_2$ $[M+H]^+$: 363.9357, found 363.9355.

3-Amino-3-(3,4-dimethoxyphenyl)-4,4,4-trifluorobutanoic acid (4s).



Following the **GP** using 1-(3,4-dimethoxyphenyl)-2,2,2-trifluoroethanone **1s** (351 mg, 1.50 mmol, 1 equiv). The reaction mixture obtained according to **GP** was treated as described for preparation of free **4a**. White solid (312 mg, 71 %). Mp 136–138 °C. IR (neat): ν_{max} 3129, 2799, 2760, 1642, 1538, 1515, 1380, 1331, 1292, 1176, 1005, 823, 667. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 7.21 (s, 1H), 7.11 (d, J = 8.4 Hz, 1H), 6.94 (d, J = 8.5 Hz, 1H), 6.29 (br s, 3H), 3.75 (s, 6H), 3.18 (d, J = 15.8 Hz, 1H), 2.88 (d, J = 15.9 Hz, 1H). **^{13}C NMR** (126 MHz, DMSO-d_6): δ 171.1, 149.1, 148.6, 130.2, 126.7 (q, J = 285 Hz), 120.1, 111.8, 111.6, 60.2 (q, J = 26 Hz), 56.1, 55.9, 39.6. **^{19}F NMR** (470 MHz, DMSO-d_6): –77.9 (s). **HRMS** (ESI+): calcd for $C_{12}H_{15}F_3NO_4$ $[M+H]^+$: 294.0947, found 294.0946.

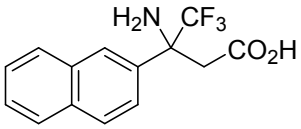
3-Amino-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-4,4,4-trifluorobutanoic acid (4t).



Following the **GP** using 1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2,2,2-trifluoroethanone **1t** (348 mg, 1.50 mmol, 1 equiv). The reaction mixture obtained according to **GP** was treated as described for preparation of free **4a**. White solid (293 mg, 67 %). Mp 152–154 °C. IR (neat): ν_{max} 3053, 2874, 1648, 1567, 1513, 1436, 1399, 1305, 1178, 1068, 672. **^{1}H NMR** (400 MHz, DMSO-d_6): δ

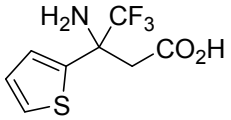
7.15 (s, 1H), 7.06 (d, J = 8.3 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 4.24 (s, 4H), 3.15 (d, J = 15.9 Hz, 1H), 2.87 (d, J = 15.9 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 171.0, 143.7, 143.6, 130.9, 126.6 (q, J = 286 Hz), 120.4, 117.0, 116.7, 64.5, 60.0 (q, J = 26 Hz), 39.5. **^{19}F NMR** (376 MHz, DMSO-d_6): δ –77.9 (s). **HRMS** (ESI+): calcd for $C_{12}H_{13}F_3NO_4$ $[M+H]^+$: 292.0791, found 292.0793.

3-Amino-4,4,4-trifluoro-3-(naphthalen-2-yl)butanoic acid (4u).



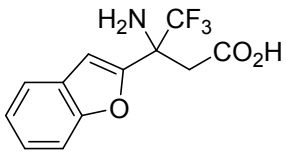
Following the **GP** using 2,2,2-trifluoro-1-(naphthalen-2-yl)ethanone **1u** (336 mg, 1.50 mmol, 1 equiv). The reaction mixture obtained according to **GP** was treated as described for preparation of free **4h**. White solid (302 mg, 71 %). Mp 117–119 °C. IR (neat): ν_{max} 2872, 1633, 1581, 1467, 1385, 1271, 1172, 812, 746, 678. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 8.24 (s, 1H), 7.90-7.93 (m, 3H), 7.77-7.80 (m, 1H), 7.54 (s, 2H), 3.41 (d, J = 15.5 Hz, 1H), 3.03 (d, J = 15.5 Hz, 1H). **^{13}C NMR** (126 MHz, DMSO-d_6): δ 171.1, 135.8, 132.9, 132.8, 128.7, 127.9, 127.71, 127.1, 126.8, 126.8 (q, J = 286 Hz), 125.2, 60.7 (q, J = 25 Hz), 39.8. **^{19}F NMR** (376 MHz, DMSO-d_6): –77.9 (s). **HRMS** (ESI+): calcd for $C_{14}H_{13}F_3NO_2$ $[M+H]^+$: 284.0892, found 284.0891.

3-Amino-4,4,4-trifluoro-3-(thiophen-2-yl)butanoic acid (4v).



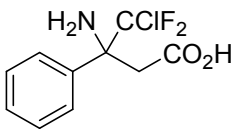
Following the **GP** using 2,2,2-trifluoro-1-(thiophen-2-yl)ethanone **1v** (270 mg, 1.50 mmol, 1 equiv). The reaction mixture obtained according to **GP** was treated as described for preparation of free **4a**. White solid (248 mg, 69 %). Mp 127–129 °C. IR (neat): ν_{max} 3081, 2911, 2786, 1640, 1538, 1426, 1324, 1274, 1185, 1151, 696, 666. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.53 (d, J = 4.7 Hz, 1H), 7.22 (s, 1H), 7.04 (t, J = 4.0 Hz, 1H), 6.14 (br s, 3H), 3.08 (d, J = 15.7 Hz, 1H), 2.93 (d, J = 15.7 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 170.9, 143.2, 127.5, 127.1, 126.9, 126.1 (q, J = 286 Hz), 59.7 (q, J = 28 Hz), 40.8. **^{19}F NMR** (376 MHz, DMSO-d_6): δ –78.5 (s). **HRMS** (ESI+): calcd for $C_8H_9F_3NO_2S$ $[M+H]^+$: 240.0300, found 240.0298.

3-Amino-3-(benzofuran-2-yl)-4,4,4-trifluorobutanoic acid (4w).



Following the **GP** using 1-(benzofuran-2-yl)-2,2,2-trifluoroethanone **1w** (321 mg, 1.50 mmol, 1 equiv). The reaction mixture obtained according to **GP** was treated as described for preparation of free **4h**. Beige solid (266 mg, 65 %). Mp 169–171 °C. IR (neat): ν_{max} 3362, 3300, 2993, 1702, 1584, 1452, 1295, 1181, 1040, 987, 752, 666. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.66 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 8.1 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.25 (d, J = 7.6 Hz, 1H), 7.16 (s, 1H), 6.21 (br s, 3H), 3.20 (d, J = 15.7 Hz, 1H), 2.91 (d, J = 15.7 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 170.6, 155.0, 154.8, 128.05, 125.8 (q, J = 286 Hz), 125.2, 123.6, 121.8, 111.7, 106.6, 58.9 (q, J = 28 Hz), 37.9. **^{19}F NMR** (376 MHz, DMSO-d_6): δ –78.1 (s). **HRMS** (ESI+): calcd for $C_{12}H_{11}F_3NO_3$ $[M+H]^+$: 274.0685, found 274.0686.

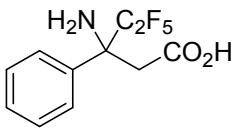
3-Amino-4-chloro-4,4-difluoro-3-phenylbutanoic acid (4x).



Following the **GP** using 2-chloro-2,2-difluoro1-phenylethanone **1y** (286 mg, 1.50 mmol, 1 equiv). The reaction mixture obtained according to **GP** was

treated as described for preparation of free **4a**. White solid (262 mg, 70 %). Mp 154–156 °C. IR (neat): ν_{max} 3082, 2796, 1644, 1537, 1394, 1308, 1218, 1095, 982, 928, 691. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.65 (d, J = 7.2 Hz, 2H), 7.51 – 7.24 (m, 3H), 3.31 (d, J = 15.8 Hz, 1H), 2.96 (d, J = 15.8 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 171.0, 138.3, 132.8 (t, J = 302 Hz), 128.6, 128.4, 128.0, 64.8 (t, J = 22 Hz), 40.2. **^{19}F NMR** (376 MHz, DMSO-d_6): δ –61.5 (d, J = 158 Hz, 1F), –61.9 (d, J = 158 Hz, 1F). **HRMS** (ESI+): calcd for $C_{10}H_{11}ClF_2NO_2$ $[M+H]^+$: 250.0440, found 250.0439.

3-Amino-4,4,5,5,5-pentafluoro-3-phenylpentanoic acid (4y).

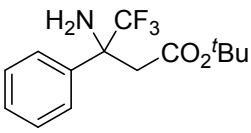


Following the **GP** using 2,2,3,3,3-pentafluoro-1-phenylpropan-1-one **1y** (336 mg, 1.50 mmol, 1 equiv). The reaction mixture obtained according to **GP** was treated as described for preparation of free **4h**. White solid (297 mg, 70 %). Mp 152–154 °C. IR (neat): ν_{max} 3104, 2834, 1644, 1563, 1396, 1320, 1218, 1189, 1119, 1024, 693. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.64 (d, J = 7.4 Hz, 2H), 7.45 – 7.30 (m, 3H), 6.18 (br s, 2H), 3.31 (d, J = 15.9 Hz, 1H), 2.98 (d, J = 15.9 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 171.1, 137.9, 128.5, 128.4, 127.7, 118.3 (m), 60.8 (t, J = 22 Hz), 39.9. **^{19}F NMR** (376 MHz, DMSO-d_6): δ –76.8 (s, 3F), –118.8 (d, J = 271 Hz, 1F), –119.6 (d, J = 271 Hz, 1F). **HRMS** (ESI+): calcd for $C_{11}H_{11}F_5NO_2$ $[M+H]^+$: 284.0704, found 284.0701.

4. Synthesis of compounds 6a-c.

Crude compound **2a** obtained from ketone **1a** (261 mg, 1.5 mmol, 1 equiv) was dissolved in anhydrous acetonitrile (1 mL), then compound **5a-c** (4.5 mmol, 3 equiv) was added and the mixture was stirred at 80 °C for 2 h. After cooling, the solvent was evaporated, the residue was dissolved in petroleum ether (10 mL) and the obtained solution was washed with a sodium hydrocarbonate solution (0.5 M, 3×10 mL) and brine (10 mL). Organic layer was separated, dried over anhydrous magnesium sulfate, filtered and the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel with chloroform/methanol (98:2) as eluent. The yields are calculated based on starting ketone **1a**.

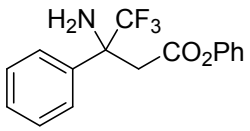
tert-Butyl 3-amino-4,4,4-trifluoro-3-phenylbutanoate (6a).



Using 3-tert-butoxy-3-oxopropanoic acid **5a**[4] (721 mg, 4.5 mmol, 3 equiv). Colorless oil (334 mg, 77 %). IR (neat): ν_{max} 3400, 3361, 2979, 2935, 1722, 1606, 1449, 1368, 1249, 1145, 836, 698. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62 (d, J = 7.5 Hz, 2H), 7.42–7.34 (m, 3H), 3.19 (d, J = 15.2 Hz, 1H), 2.87 (d, J = 15.2 Hz, 1H), 2.36 (br s, 2H), 1.26 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 168.7, 137.5, 128.3, 128.2, 126.9, 126.1 (q, J = 285 Hz), 81.6, 60.8 (q, J = 27 Hz), 42.0, 27.7. **^{19}F NMR** (376 MHz, $CDCl_3$): δ –79.1 (s). **HRMS** (ESI+): calcd for $C_{14}H_{19}F_3NO_2$ $[M+H]^+$: 290.1362, found 290.1363.

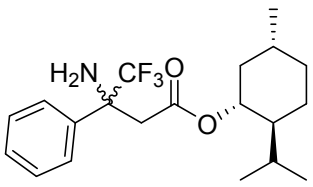
Phenyl 3-amino-4,4,4-trifluoro-3-phenylbutanoate (6b).

[4] Kanemitsu, T.; Furukoshi, S.; Miyazaki, M.; Nagata, K.; Itoh T. *Tetrahedron: Asymmetry.* **2015**, *26(4)*, 214–218.



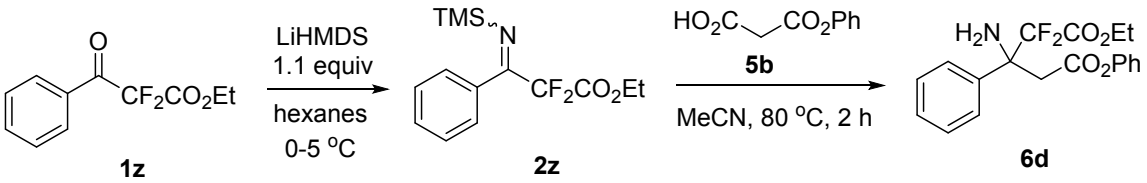
Using 3-oxo-3-phenoxypropanoic acid **5b**[5] (811 mg, 4.5 mmol, 3 equiv). White solid (362 mg, 78 %). Mp 62–64 °C. IR (neat): ν_{max} 3408, 3338, 2922, 1749, 1488, 1320, 1151, 1003, 814, 665. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 7.5 Hz, 2H), 7.50–7.39 (m, 3H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 2H), 3.54 (d, *J* = 15.3 Hz, 1H), 3.23 (d, *J* = 15.3 Hz, 1H), 2.43 (br s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 168.2, 150.0, 137.0, 129.4, 128.7, 128.5, 126.9, 126.1, 126.1 (q, *J* = 285 Hz), 121.3, 60.9 (q, *J* = 27 Hz), 41.1. **^{19}F NMR** (376 MHz, $CDCl_3$): δ –78.9 (s). **HRMS** (ESI+): calcd for $C_{16}H_{14}F_3NO_2$ $[M+H]^+$: 310.1049, found 310.1052.

(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 3-amino-4,4,4-trifluoro-3-phenylbutanoate (6c, d.r. 65:35).



Using 3-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-3-oxopropanoic acid **5c**[6] (1.09 g, 4.5 mmol, 3 equiv). Colorless viscous oil (435 mg, 78 %). IR (neat): ν_{max} 3401, 2955, 2928, 2870, 1725, 1606, 1449, 1148, 983, 697. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 7.5 Hz, 2H), 7.46–7.32 (m, 3H), 4.58 (qd, *J* = 10.7, 4.3 Hz, 1H), 3.29 (d, *J* = 15.5 Hz, 1H), 2.96 (d, *J* = 15.5 Hz, 1H), 2.40 (br s, 2H), 1.82 (d, *J* = 11.6 Hz, 0.35H), 1.69–1.49 (m, 3.65H), 1.38 (s, 1H), 1.27 (s, 1H), 0.97 (s, 1H), 0.88–0.72 (m, 8H), 0.66 (d, *J* = 6.9 Hz, 2H), 0.53 (d, *J* = 6.9 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 169.2, 137.3, 128.42, 128.39, 128.3, 126.9, 126.8, 126.0 (q, *J* = 285 Hz), 75.0, 74.9, 60.8 (q, *J* = 27 Hz), 46.8, 46.7, 41.0, 40.9, 40.5, 34.1, 31.3, 31.3, 25.93, 25.85, 23.2, 23.1, 21.91, 21.86, 20.8, 16.0, 15.8. **^{19}F NMR** (376 MHz, $CDCl_3$): δ –79.1 (s, 0.33F), –79.2 (s, 0.67F). **HRMS** (ESI+): calcd for $C_{20}H_{29}F_3NO_2$ $[M+H]^+$: 372.2144, found 372.2148.

5. Synthesis of 1-ethyl 5-phenyl 3-amino-2,2-difluoro-3-phenylpentanedioate (6d).



A solution of ethyl 2,2-difluoro-3-oxo-3-phenylpropanoate **1z** (342 mg, 1.50 mmol, 1 equiv) in anhydrous hexane (10 mL) was cooled to 0-5 °C using an ice water bath, and lithium bis(trimethylsilyl)amide solution (1.0 M in hexanes, Sigma-Aldrich, 1.80 mL, 1.2 equiv) was added *via* a dropping funnel over 10 min under an argon atmosphere. The reaction mixture was stirred for 20 min at 0-5 °C and then for 2 h at room temperature. The mixture was then cooled to 0-5 °C and was poured into a stirred cold solution of ammonium chloride (160 mg, 3 mmol, 2 equiv) in water (5 mL). The resulted mixture was stirred for 5 min at 0-5 °C. The organic layer was separated, washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under vacuum. The residual brown oil was dried at 35-40 °C and 15 Torr for 1 h. The crude compound **2z** thus obtained was used for preparation of **6d** as described for **6b**. Brown amorphous solid (196 mg, 36 %). IR (neat): ν_{max} 3401, 3357, 2911, 1749, 1739, 1454, 1335, 1158, 996, 819, 663. **^{1}H NMR** (400 MHz, $CDCl_3$): δ

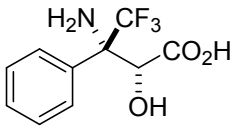
[5] Ryu, Y.; Scott, A. I. *Tetrahedron Lett.* **2003**, *44*, 7499–7502.
[6] Junek, H.; Ziegler, E.; Herzog, U.; Kroboth, H. *Synthesis*, **1976**, 332–334.

7.66 (d, J = 7.5 Hz, 2H), 7.48–7.35 (m, 3H), 7.29 (t, J = 7.8 Hz, 2H), 7.18 (t, J = 7.4 Hz, 1H), 6.74 (d, J = 7.6 Hz, 2H), 4.19 (q, J = 7.1 Hz, 2H), 3.61 (d, J = 15.3 Hz, 1H), 3.31 (d, J = 15.3 Hz, 1H), 2.47 (br s, 2H), 1.16 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 168.9, 163.0 (t, J = 32 Hz), 150.1, 137.9, 129.3, 128.4, 128.3, 127.0, 126.0, 121.3, 115.94 (t, J = 262 Hz), 62.8, 61.59 (t, J = 23 Hz), 40.8. **^{19}F NMR** (376 MHz, $CDCl_3$): δ –112.5 (d, J = 252 Hz, 1F), –114.0 (d, J = 252 Hz, 1F). **HRMS** (ESI+): calcd for $C_{19}H_{20}F_2NO_4$ $[M+H]^+$: 364.1354, found 364.1358.

6. Synthesis of compounds 7a-h.

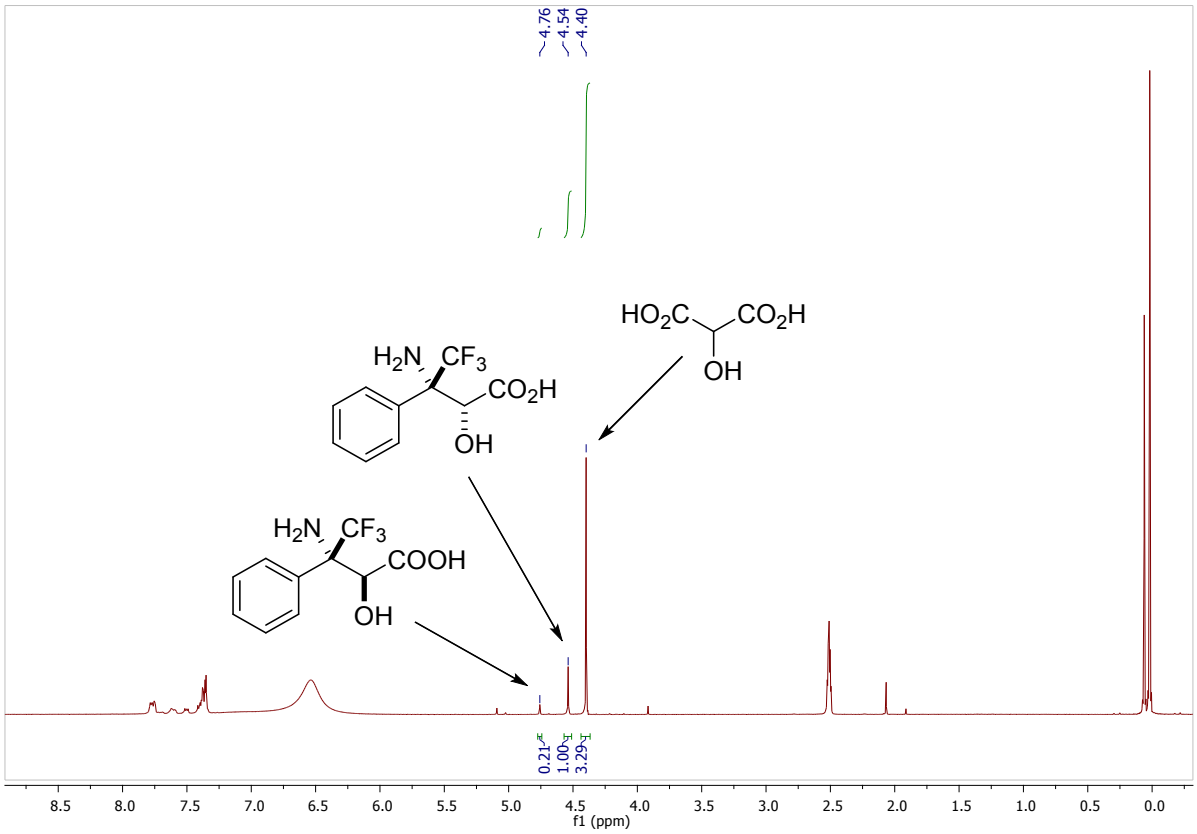
Synthesized following **GP** (2-hydroxymalonic acid, 540 mg, 4.5 mmol, 3 equiv was used instead of malonic acid) as described for preparation of compound **4h**. For purification, the obtained products were recrystallized from acetonitrile. Yields are calculated starting from corresponding ketones **1**.

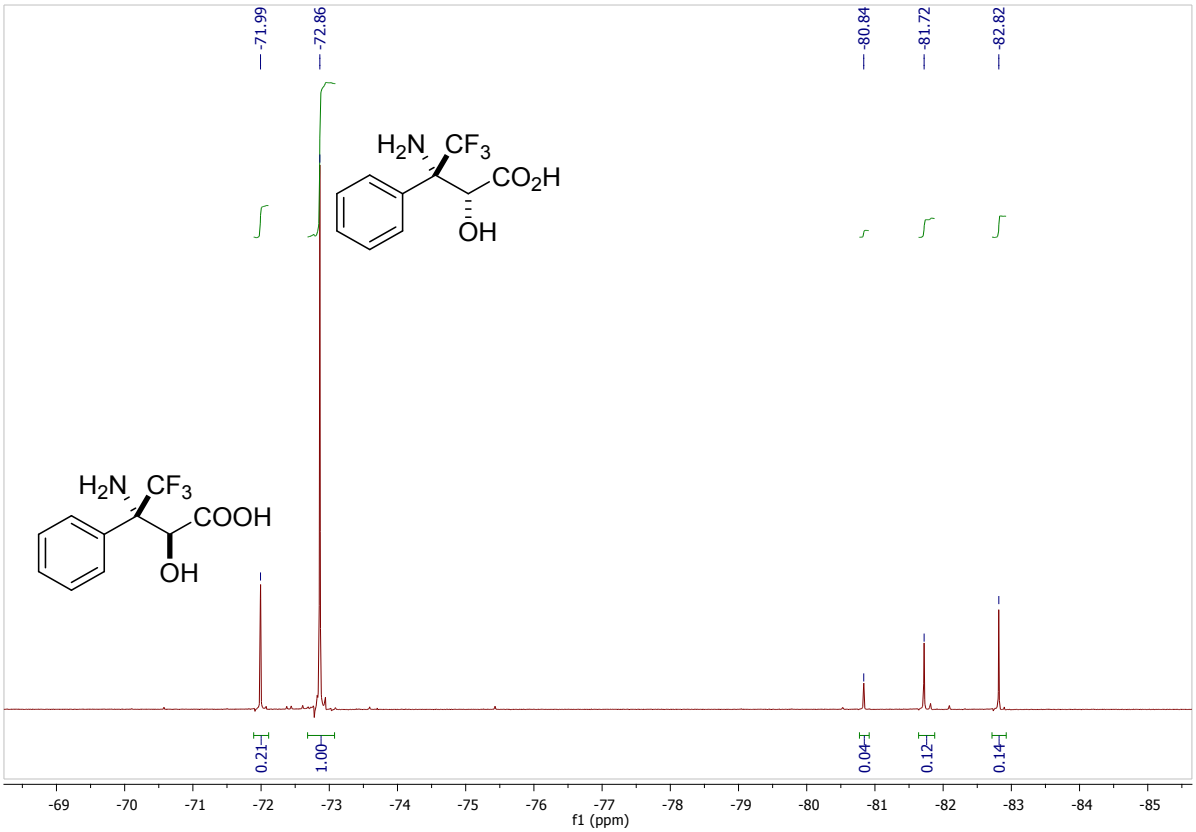
(2*R,3*S**)-3-Amino-4,4,4-trifluoro-2-hydroxy-3-phenylbutanoic acid (7a).**



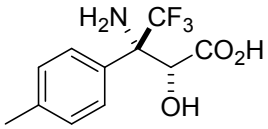
Prepared from **1a** (261 mg, 1.5 mmol, 1 equiv). White solid (146 mg, 39 %). Mp 248–250 °C. IR (neat): ν_{max} 3075, 1621, 1450, 1301, 1181, 1144, 1038, 993, 760, 693. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.78 (s, 2H), 7.37 (s, 3H), 5.67 (br s, 4H), 4.57 (s, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 173.1, 136.0, 128.8, 128.3, 128.0, 126.2 (q, J = 289 Hz), 73.1, 63.7 (q, J = 25 Hz). **^{19}F NMR** (376 MHz, DMSO-d_6): δ –72.9 (s). **HRMS** (ESI+): calcd for $C_{10}H_{11}F_3NO_3$ $[M+H]^+$: 250.0685, found 250.0685.

^{1}H and ^{19}F NMR spectra (DMSO-d_6) of the residue (50 mg) after evaporation of the reaction mixture:



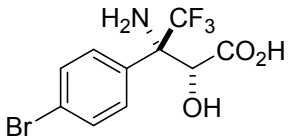


(2*R,3*S**)-3-Amino-4,4,4-trifluoro-2-hydroxy-3-p-tolylbutanoic acid (7b).**



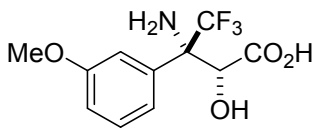
Prepared from **1b** (282 mg, 1.5 mmol, 1 equiv). White solid (150 mg, 38 %). Mp 248–250 °C. IR (neat): ν_{max} 3063, 1632, 1594, 1468, 1381, 1300, 1206, 1178, 1156, 1039, 811, 683. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.65 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.1 Hz, 2H), 6.15 (br s, 4H), 4.53 (s, 1H), 2.30 (s, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 173.1, 138.2, 132.8, 128.9, 127.9, 126.2 (q, J = 289 Hz), 73.1, 63.3 (q, J = 25 Hz), 20.98. **^{19}F NMR** (376 MHz, DMSO-d_6): δ –73.0 (s). **HRMS** (ESI+): calcd for $C_{11}H_{13}F_3NO_3$ $[M+H]^+$: 264.0842, found 264.0842.

(2*R,3*S**)-3-Amino-3-(4-bromophenyl)-4,4,4-trifluoro-2-hydroxybutanoic acid (7c).**



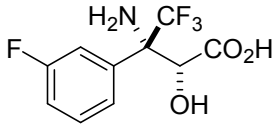
Prepared from **1j** (380 mg, 1.5 mmol, 1 equiv). White solid (167 mg, 34 %). Mp 217–219 °C. IR (neat): ν_{max} 3045, 2873, 1615, 1591, 1437, 1310, 1206, 1172, 1033, 767. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.72 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.6 Hz, 2H), 6.24 (br s, 4H), 4.54 (s, H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 172.9, 135.8, 131.2, 130.5, 126.1 (q, J = 287 Hz), 122.5, 73.3, 63.6 (q, J = 25 Hz). **^{19}F NMR** (376 MHz, DMSO-d_6): δ –73.0 (s). **HRMS** (ESI+): calcd for $C_{10}H_{10}BrF_3NO_3$ $[M+H]^+$: 327.9790, found 327.9791.

(2*R,3*S**)-3-Amino-4,4,4-trifluoro-2-hydroxy-3-(3-methoxyphenyl)butanoic acid (7d).**



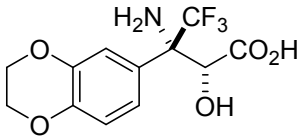
Prepared from **1l** (306 mg, 1.5 mmol, 1 equiv). White solid (151 mg, 36 %). Mp 208–210 °C. IR (neat): ν_{max} 3057, 2844, 1610, 1585, 1450, 1307, 1180, 1147, 1044, 780, 734. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.35 (s, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.29 (t, J = 7.9 Hz, 1H), 6.94 (d, J = 7.2 Hz, 1H), 6.02 (s, 4H), 4.54 (s, 1H), 3.76 (s, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 173.0, 159.2, 137.5, 129.3, 126.2 (q, J = 287 Hz), 120.2, 114.6, 113.8, 73.2, 63.6 (q, J = 24 Hz), 55.5. **^{19}F NMR** (376 MHz, DMSO-d_6): δ –72.8 (s). **HRMS** (ESI+): calcd for $C_{11}H_{13}F_3NO_4$ $[M+H]^+$: 280.0791, found 280.0788.

(2*R,3*S**)-3-Amino-4,4,4-trifluoro-3-(3-fluorophenyl)-2-hydroxybutanoic acid (7e).**



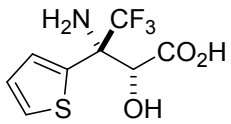
Prepared from **1n** (288 mg, 1.5 mmol, 1 equiv). White solid (132 mg, 33 %). Mp 227–229 °C. IR (neat): ν_{max} 3067, 1620, 1596, 1445, 1383, 1307, 1213, 1179, 1142, 788, 703. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.62 (d, J = 6.9 Hz, 2H), 7.43 (dd, J = 14.5, 7.6 Hz, 1H), 7.20 (t, J = 7.7 Hz, 1H), 5.76 (br s, 4H), 4.56 (s, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 172.9, 162.1 (d, J = 243 Hz), 139.3 (d, J = 8 Hz), 130.1 (d, J = 8 Hz), 126.1 (q, J = 287 Hz), 124.3, 115.7 (d, J = 21 Hz), 115.4 (d, J = 24 Hz), 73.3, 63.7 (q, J = 24 Hz). **^{19}F NMR** (376 MHz, DMSO-d_6): δ –72.9 (s, 3F), (–113.3) – (–113.4) (m, 1F). **HRMS** (ESI+): calcd for $C_{10}H_{10}F_4NO_3$ $[M+H]^+$: 268.0591, found 268.0590.

(2*R,3*S**)-3-amino-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-4,4,4-trifluoro-2-hydroxybutanoic acid (7f).**



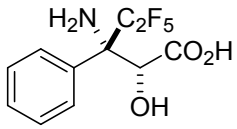
Prepared from **1t** (348 mg, 1.5 mmol, 1 equiv). White solid (161 mg, 35 %). Mp 220–222 °C. IR (neat): ν_{max} 3084, 1651, 1591, 1516, 1455, 1429, 1295, 1204, 1180, 1156, 1063, 896, 693. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.29 (s, 1H), 7.21 (d, J = 8.1 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 6.13 (s, 4H), 4.47 (s, 1H), 4.24 (s, 4H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 173.0, 144.0, 143.0, 128.5, 126.2 (q, J = 287 Hz), 121.0, 117.3, 116.7, 73.1, 64.6, 64.5, 62.9 (q, J = 24 Hz). **^{19}F NMR** (376 MHz, DMSO-d_6): δ –73.1 (s). **HRMS** (ESI+): calcd for $C_{12}H_{13}F_3NO_5$ $[M+H]^+$: 308.0740, found 308.0740.

(2*R,3*S**)-3-Amino-4,4,4-trifluoro-2-hydroxy-3-(thiophen-2-yl)butanoic acid (7g).**



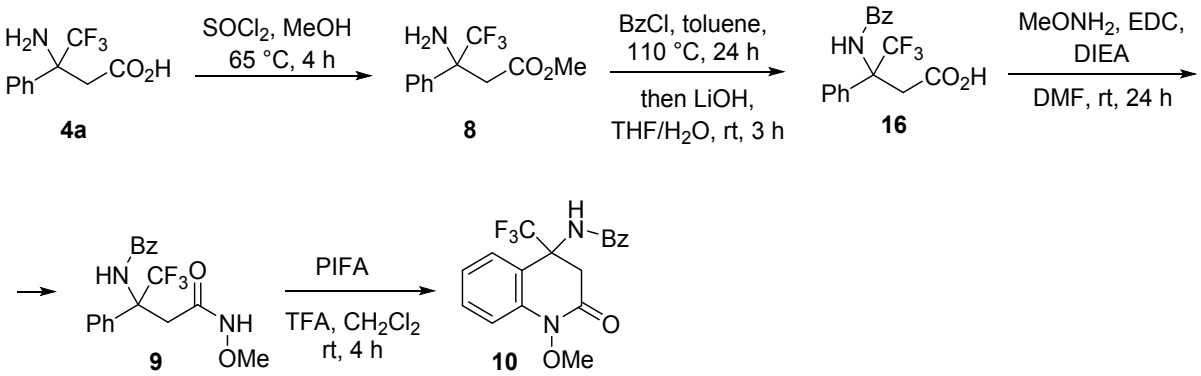
Prepared from **1v** (270 mg, 1.5 mmol, 1 equiv). White solid (138 mg, 36 %). Mp 213–215 °C. IR (neat): ν_{max} 3058, 1639, 1436, 1378, 1297, 1212, 1180, 1143, 738, 687. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.53 (d, J = 5.0 Hz, 1H), 7.35 (d, J = 3.3 Hz, 1H), 7.04 (t, J = 4.0 Hz, 1H), 6.13 (br s, 4H), 4.45 (s, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 172.6, 139.5, 127.6, 127.4, 126.9, 125.73 (q, J = 287 Hz), 73.2, 63.3 (q, J = 26 Hz). **^{19}F NMR** (376 MHz, DMSO-d_6): δ –74.1 (s). **HRMS** (ESI+): calcd for $C_8H_9F_3NO_3S$ $[M+H]^+$: 256.0249, found 256.0247.

(2*R,3*S**)-3-Amino-4,4,5,5,5-pentafluoro-2-hydroxy-3-phenylpentanoic acid (7h).**

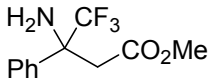


Prepared from **1y** (336 mg, 1.5 mmol, 1 equiv). White solid (171 mg, 38 %). Mp 202–204 °C. IR (neat): ν_{max} 3073, 1620, 1448, 1378, 1326, 1240, 1123, 1070, 993, 697. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.75 (d, J = 7.0 Hz, 2H), 7.40 – 7.32 (m, 3H), 6.07 (s, 4H), 4.66 (s, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 173.4, 136.2, 128.7, 128.2, 128.1, 118.03 (m), 73.6, 63.8 (t, J = 20 Hz). **^{19}F NMR** (376 MHz, DMSO-d_6): δ –76.3 (s, 3F), –115.4 (d, J = 275 Hz, 1F), –117.2 (d, J = 275 Hz, 1F). **HRMS** (ESI+): calcd for $C_{11}H_{11}F_5NO_3$ $[M+H]^+$: 300.0653, found 300.0656.

7. Synthesis of compounds 8-10.

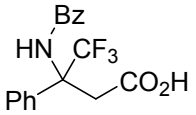


Methyl 3-amino-4,4,4-trifluoro-3-phenylbutanoate (8).



To a stirred suspension of compound **4a** (1 g, 4.29 mmol, 1.0 equiv) in methanol (20 mL) at 0-5 °C was added thionyl chloride (1.53 g, 12.87 mmol, 3.0 equiv) and the resulting mixture was stirred at 65 °C for 4 h. After cooling, the reaction mixture was evaporated. The residue was quenched with a saturated aqueous solution of sodium hydrocarbonate (20 mL) and extracted with dichloromethane (2×20 mL). The combined organic phases were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The product **8** was obtained in >95 % purity and used in the next step without additional purification. Colorless oil (944 mg, 89 %). IR (neat): ν_{max} 3414, 3352, 2930, 1733, 1609, 1438, 1276, 1147, 1000, 764, 698, 660. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62 (d, J = 7.5 Hz, 2H), 7.46 – 7.30 (m, 3H), 3.60 (s, 3H), 3.27 (d, J = 15.7 Hz, 1H), 3.00 (d, J = 15.7 Hz, 1H), 2.37 (br s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 170.0, 137.3, 128.5, 128.4, 126.7, 126.1 (q, J = 286 Hz), 60.7 (q, J = 26 Hz), 51.9, 40.6. **^{19}F NMR** (376 MHz, DMSO-d_6): δ –79.0 (s). **HRMS** (ESI+): calcd for $C_{11}H_{13}F_3NO_2$ $[M+H]^+$: 248.0892, found 248.0888.

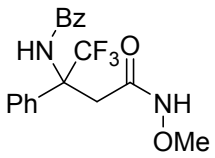
3-Benzamido-4,4,4-trifluoro-3-phenylbutanoic acid (16).



A mixture of compound **8** (900 mg, 3.64 mmol, 1 equiv) and benzoyl chloride (512 mg, 3.64 mmol, 1 equiv) was stirred at 110 °C for 24 h. After cooling the reaction mixture was evaporated. The residue was dissolved in diethyl ether (30 mL) and washed with a hydrochloric acid (1 M, 2×10 mL), water (mL) and a

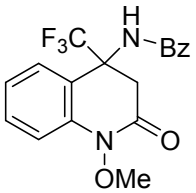
saturated sodium hydrocarbonate solution (2×20 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was dissolved in THF (10 mL) and a solution of lithium hydroxide monohydrate (183 mg, 4.37 mmol, 1.2 equiv) in water (20 mL) was added. The mixture was stirred at room temperature for 3 h and then THF was evaporated under reduced pressure. The remained solution was treated with hydrochloric acid (1 M, 10 mL) and extracted with diethyl ether (2×20 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was recrystallized from cyclohexane and isopropanol (10:1). White solid (909 mg, 74 %). Mp 125–127 °C. IR (neat): ν_{max} 3434, 3251, 3066, 2870, 1729, 1707, 1682, 1636, 1557, 1516, 1313, 1169, 1045, 696. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 12.48 (s, 1H), 8.96 (s, 1H), 7.85 (d, J = 7.3 Hz, 2H), 7.68 – 7.30 (m, 8H), 3.61 (d, J = 15.2 Hz, 1H), 3.52 (d, J = 15.2 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 170.4, 167.5, 137.0, 135.4, 131.9, 128.7, 128.6, 128.3, 127.0, 125.7 (q, J = 288 Hz), 63.6 (q, J = 27 Hz), 37.0. **^{19}F NMR** (376 MHz, DMSO-d_6): δ –71.7 (s). **HRMS** (ESI+): calcd for $C_{17}H_{15}F_3NO_3$ $[M+H]^+$: 338.0998, found 338.1000.

N-(1,1,1-Trifluoro-4-(methoxyamino)-4-oxo-2-phenylbutan-2-yl)benzamide (9).



To a stirred solution of compound **16** (500 mg, 1.48 mmol, 1.0 equiv), diisopropylethylamine (612 mg, 4.74 mmol, 3.2 equiv) and methoxyamine hydrochloride (247 mg, 2.96 mmol, 2 equiv) in anhydrous dimethylformamide (10 mL) at 0-5 °C was added N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (340 mg, 1.77 mmol, 1.2 equiv). The resulting mixture was stirred at room temperature for 18 h and then water (20 mL) and ethyl acetate (30 mL) were added. The organic phase was washed with brine (3×20 mL), a hydrochloric acid solution (0.5 M, 3×20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was recrystallized from acetonitrile and diethyl ether (1:20). White solid (385 mg, 71 %). Mp 148–150 °C. IR (neat): ν_{max} 3178, 3003, 1682, 1657, 1517, 1489, 1319, 1168, 1144, 1060, 961. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 11.42 (s, 1H), 9.42 (s, 1H), 7.89 (d, J = 7.4 Hz, 2H), 7.61 – 7.53 (m, 3H), 7.46 – 7.35 (m, 5H), 3.52 (s, 3H), 3.02 (d, J = 14.7 Hz, 1H), 2.93 (d, J = 14.7 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 165.9, 165.3, 136.7, 134.8, 132.2, 129.0, 128.8, 128.4, 127.8, 126.3, 125.9 (q, J = 289 Hz), 64.3 (q, J = 28 Hz), 63.6, 37.5. **^{19}F NMR** (376 MHz, DMSO-d_6): δ –68.3 (s). **HRMS** (ESI+): calcd for $C_{18}H_{18}F_3N_2O_3$ $[M+H]^+$: 367.1264, found 367.1262.

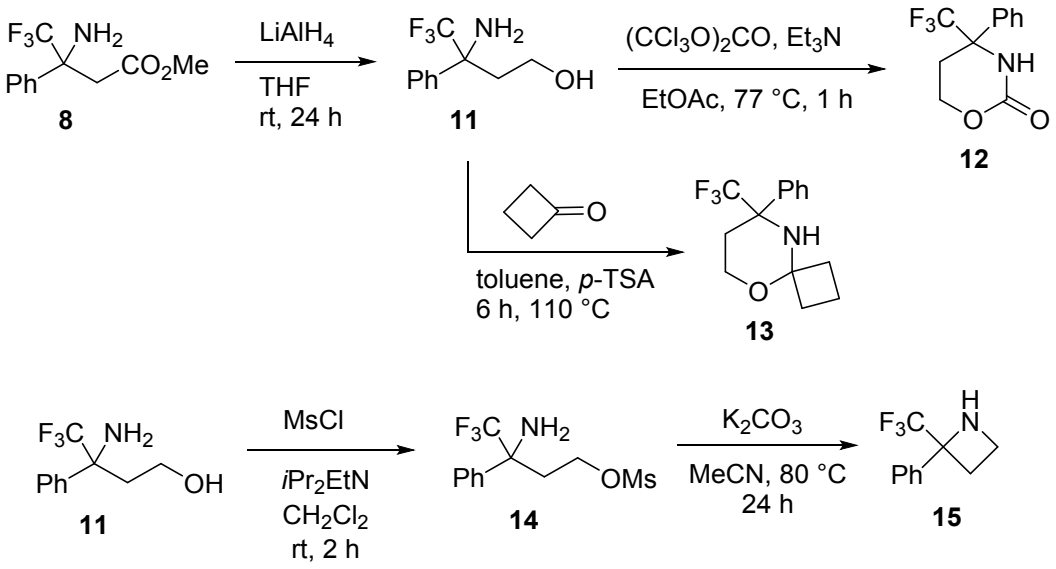
N-(1-Methoxy-2-oxo-4-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-4-yl)benzamide (10).



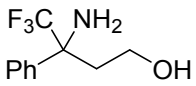
To a stirred solution of compound **9** (300 mg, 0.82 mmol, 1.0 equiv) and trifluoroacetic acid (187 mg, 1.64 mmol, 2 equiv) in anhydrous dichloromethane (10 mL) at room temperature was added phenyliodine bis(trifluoroacetate) (353 mg, 0.9 mmol, 1.1 equiv). The resulting mixture was stirred at room temperature for 4 h and then mixed with a saturated sodium hydrocarbonate solution (20 mL). The organic phase was separated, washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was recrystallized from acetonitrile and diethyl ether (1:20). White solid (218 mg, 73 %). Mp 205–207 °C. IR (neat): ν_{max} 3308, 3008, 2943, 1666, 1602, 1523, 1456, 1359, 1278, 1164, 1069, 714. **^{1}H NMR** (400 MHz, $CDCl_3$):

δ 7.81 (d, J = 7.7 Hz, 2H), 7.61 (t, J = 7.3 Hz, 1H), 7.55 – 7.44 (m, 3H), 7.41 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 6.69 (s, 1H), 4.37 (d, J = 16.8 Hz, 1H), 3.93 (s, 3H), 3.08 (d, J = 16.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.3, 160.8, 137.5, 133.3, 132.7, 131.0, 129.0, 127.1, 127.0, 125.2 (q, J = 287 Hz), 124.0, 117.8, 113.6, 60.9 (q, J = 28 Hz), 35.4. **^{19}F NMR** (376 MHz, $CDCl_3$): δ –80.2 (s). **HRMS** (ESI+): calcd for $C_{18}H_{16}F_3N_2O_3$ $[M+H]^+$: 365.1107, found 365.1107.

8. Synthesis compounds 11-15.



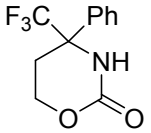
3-Amino-4,4,4-trifluoro-3-phenylbutan-1-ol (11).



To a stirred solution of compound **8** (800 mg, 3.24 mmol, 1.0 equiv) in anhydrous tetrahydrofurane (20 mL) at 0-5 °C was added lithium aluminum hydride (184 mg, 4.86 mmol, 3 equiv). The resulting mixture was stirred at room temperature for 24 h and then successively quenched at 0-5 °C with methanol (5 mL) and a sodium hydroxide solution (1 M, 30 mL) and stirred at room temperature for 1 h. The solid was filtered off and the clear filtrate was extracted with dichloromethane (2×20 mL). The organic phase was washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was mixed with a hydrochloric acid solution (0.5 M, 20 mL) and the aqueous phase was washed with diethyl ether (2×10 mL). Then a saturated sodium hydrocarbonate solution (20 mL) was added and the mixture was extracted with dichloromethane (2×20 mL). The organic phases were combined, washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was recrystallized from cyclohexane. White solid (575 mg, 81 %). Mp 65–67 °C. IR (neat): ν_{max} 3355, 3287, 3186, 2948, 2874, 1595, 1338, 1151, 1066, 953, 697. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.51 – 7.35 (m, 5H), 3.76 – 3.47 (m, 2H), 3.43 – 3.40 (m, 1H), 2.29 – 1.91 (m, 4H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 135.7, 128.6, 128.4, 126.6 (q, J = 286 Hz), 126.39, 62.4 (q, J = 26 Hz),

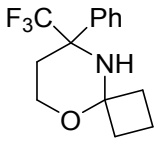
58.8, 36.45. **^{19}F NMR** (470 MHz, $CDCl_3$): δ –79.5 (s). **HRMS** (ESI+): calcd for $C_{10}H_{13}F_3NO$ $[M+H]^+$: 220.0943, found 220.0942.

4-Phenyl-4-(trifluoromethyl)-1,3-oxazinan-2-one (12).



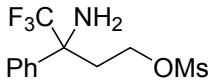
A solution of triphosgene (298 mg, 1.0 mmol, 1.1 equiv) in ethyl acetate (5 mL) was added dropwise over 10 min to a solution of compound **11** (200 mg, 0.91 mmol, 1.0 equiv) in ethyl acetate (10 mL) at 0-5 °C. The resulting mixture was refluxed for 1 h, cooled to room temperature and filtered. The filtrate was washed with brine (2×10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was recrystallized from cyclohexane and isopropanol (20:1). White solid (172 mg, 77 %). Mp 103–105 °C. IR (neat): ν_{max} 3231, 3133, 2956, 1704, 1423, 1279, 1249, 1162, 724. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.57 – 7.30 (m, 5H), 4.30 (dt, *J* = 11.0, 3.9 Hz, 1H), 3.94 (td, *J* = 11.1, 2.3 Hz, 1H), 2.66 – 2.56 (m, 1H), 2.46 (d, *J* = 14.3 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 153.6, 135.7, 129.3, 129.05, 126.6, 124.8 (q, *J* = 286 Hz), 62.8, 62.5 (q, *J* = 28 Hz), 28.4. **^{19}F NMR** (470 MHz, $CDCl_3$): δ –77.85 (s). **HRMS** (ESI+): calcd for $C_{11}H_{11}F_3NO_2$ $[M+H]^+$: 246.0736, found 246.0734.

8-Phenyl-8-(trifluoromethyl)-5-oxa-9-azaspiro[3.5]nonane (13).



A solution of compound **11** (200 mg, 0.91 mmol, 1.0 equiv), cyclobutanone (128 mg, 1.82 mmol, 2 equiv) and *p*-toluenesulfonic acid (16 mg, 0.09 mmol, 0.1 equiv) in toluene (5 mL) was refluxed for 24 h. After cooling to room temperature the reaction mixture was evaporated, treated with petroleum ether (5 mL) and filtered. The filtrate was cooled to –20 °C and left at this temperature for 24 h. The precipitate was filtered, washed with cold (–20 °C) pentane and dried on air. White solid (202 mg, 82 %). Mp 31–33 °C. IR (neat): ν_{max} 3332, 2975, 2868, 1452, 1289, 1145, 1009, 704. **^{1}H NMR** (500 MHz, $CDCl_3$): 7.72 (d, *J* = 7.2 Hz, 2H), 7.48 – 7.32 (m, 3H), 3.93 (d, *J* = 11.7 Hz, 1H), 3.78 (t, *J* = 11.2 Hz, 1H), 2.40 (d, *J* = 14.0 Hz, 1H), 2.32 – 2.23 (m, 1H), 2.22 – 2.06 (m, 3H), 1.73 – 1.61 (m, 4H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 135.2, 129.2, 128.6, 128.0, 125.6 (q, *J* = 285 Hz), 87.55, 60.15 (q, *J* = 26 Hz), 57.5, 36.1, 32.4, 27.0, 13.2. **^{19}F NMR** (470 MHz, $CDCl_3$): δ –80.0 (s). **HRMS** (ESI+): calcd for $C_{14}H_{17}F_3NO$ $[M+H]^+$: 272.1257, found 272.1256.

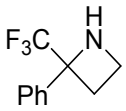
3-Amino-4,4,4-trifluoro-3-phenylbutyl methanesulfonate (14).



A solution of methanesulfonyl chloride (82 mg, 0.72 mmol, 1.05 equiv) in dichloromethane (5 mL) was added dropwise over 5 min to a solution of compound **11** (150 mg, 0.68 mmol, 1.0 equiv) and diisopropylethylamine (93 mg, 0.72 mmol, 1.05 equiv) in dichloromethane (10 mL) at 0-5 °C. The resulting mixture was stirred at room temperature for 2 h. Then water (10 mL) was added with stirring. The organic phase was separated and washed with brine (2×10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The obtained product was used in the next step without further purification (>95 % purity by ^{1}H NMR). White solid (187 mg, 92 %). Mp 68-70 °C. IR (neat): ν_{max} 3379, 3319, 3234, 3027, 1623, 1346, 1166, 987, 702, 528. **^{1}H NMR** (400 MHz, $CDCl_3$): 7.53 (d, *J* = 7.4 Hz, 2H),

7.35 – 7.41 (m, 3H), 4.22 – 4.28 (m, 1H), 3.94 – 4.00 (m, 1H), 2.79 (s, 3H), 2.66 – 2.55 (m, 1H), 2.35 – 2.24 (m, 1H), 1.81 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 135.7, 128.7, 128.6, 126.7 (q, J = 287 Hz), 65.4, 60.5 (q, J = 26 Hz), 37.15, 34.8. **^{19}F NMR** (376 MHz, $CDCl_3$): δ –79.9 (s). **HRMS** (ESI+): calcd for $C_{11}H_{15}F_3NO_3S$ $[M+H]^+$: 298.0719, found 298.0718.

2-Phenyl-2-(trifluoromethyl)azetidine (15).



To a solution of compound **14** (100 mg, 0.34 mmol, 1.0 equiv) in acetonitrile (5 mL) was added potassium carbonate (94 mg, 0.68 mmol, 2.0 equiv) and the mixture was heated with stirring at 80 °C for 24 h. After cooling the mixture was filtered. The filtrate was evaporated. The residue was dissolved in pentane (10 mL) and washed with brine (2×10 mL). The organic phase was separated, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Colorless oil (63 mg, 93 %). IR (neat): ν_{max} 3318, 2971, 2866, 1457, 1280, 1135, 1010, 692. The product was purified by column chromatography on silica gel with dichloromethane/methanol (98:2) as eluent. Colorless oil (63 mg, 93 %). IR (neat): ν_{max} 3318, 2971, 2866, 1457, 1280, 1135, 1010, 692. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.44 – 7.28 (m, 5H), 3.79 (q, J = 7.5 Hz, 1H), 3.53 – 3.43 (m, 1H), 3.05 – 2.94 (m, 1H), 2.77 (q, J = 7.5 Hz, 1H), 2.65 (br s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 139.8, 128.0, 127.7, 126.6 (q, J = 284 Hz), 126.25, 67.5 (q, J = 29 Hz), 42.3, 28.7. **^{19}F NMR** (376 MHz, $CDCl_3$): δ –81.7 (s). **HRMS** (ESI+): calcd for $C_{10}H_{11}F_3N$ $[M+H]^+$: 202.0838, found 202.0835.

9. X-ray structure determination for compound 7b.

Crystallographic data collection, structure determination and refinement.

Massive colourless crystals were obtained for hydrate of 3-carboxy-1,1,1-trifluoro-3-hydroxy-2-(*p*-tolyl)propan-2-aminium chloride, **7b** hydrochloride, from ethanol. One 0.37 x 0.35 x 0.09 mm crystal was selected dipped in Paratone® oil, picked up in the rayon loop and then quickly cryo-cooled in a stream of cold nitrogen gas at the kappa-axis goniostat of a RIGAKU XtaLabPro diffractometer comprised of a Mo microfocus sealed tube generator coupled to a double-bounce confocal Max-Flux® multilayer optic. X-ray diffraction images were collected with use of an HPAD PILATUS3 R 200K detector at a temperature set up to 100K under the control of the CrysAlisPro software.[7]

All 17383 intensities measured in four ω-scans (total of 618 frames of 0.5°width) were integrated, scaled and merged by *CrysalisPro*, which also applies a multi-scan absorption correction (SCALE3 ABSPACK scaling algorithm), into the set of 3648 unique reflections with the overall R_{int} factor of 0.049. The crystal structure was solved by intrinsic phasing methods (*SHELXT* program)[8] in the monoclinic space group $P2_1/c$, then refined by full-matrix least-squares methods on F^2 using *SHELX-L*[9] upon 199 parameters against 3642 reflections. All non-hydrogen atoms improved by anisotropic refinement. Most of the H atoms were identified in difference maps. Methyl H atoms were idealized and included as rigid groups allowed to rotate but not tip (AFIX 137) and refined with U_{iso} set to $1.5U_{eq}$(C) of the parent carbon atom. Similarly the same thing was done with hydroxyl and carboxylic H atoms using AFIX 147. Conversely, positions of those in the NH_3^+ were freely refined. All other H atoms bound to carbon atoms were positioned geometrically and refined with U_{iso} set to $1.2U_{eq}$(C) of the parent carbon atom. A water molecule is lying almost on a centre of inversion, implying alternate orientation every a.u. (its occupancy factor is set to 0.5). Hydrogen atoms were positioned with distance restraints (DFIX, DANG instructions) to favor hydrogen bonding with hydroxy O at general position and chlorine ion at -x+1,y-1/2,-z+1/2. Refinement converged to R1 = 4% (all data) with the use of the following weighted refinement scheme: $w = 1/[\sigma^2(F_o^2) + (0.0357P)^2 + 0.6243P]$ with $P = [\max(F_o^2,0) + 2F_o^2]/3$. X-ray crystallography data collection parameters and

[7] Rigaku, O. D. *CrysAlisPRO*. Rigaku Oxford Diffraction, Yarnton, Oxfordshire, England, 2015.
[8] Sheldrick, G. M. *Acta Crystallogr.* **2015**, *A71*, 3-8.
[9] Sheldrick, G. M. *Acta Crystallogr.* **2015**, *C71*, 3-8

structure refinement statistics are reported in Table S2. An Ortep[10] view of the asymmetric unit is shown in Figure S1.

CCDC 1864064 contains the supplementary crystallographic data for the **7b** compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

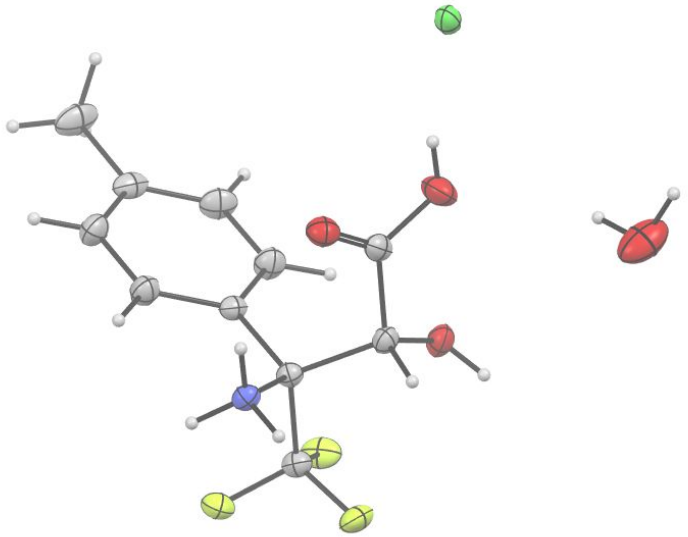


Figure S1. Ortep plot of **7b**. Ellipsoids are drawn at 50% of probability and hydrogen atoms, with sphere radius of arbitrary size.

Table S2 Crystal data and structure refinement for **7b**.

Identification code	VS171	
Empirical formula	C_{11} H_{13} F_3 N O_3, Cl, 0.5 (H_2 O)	
Formula weight	308.68	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 2_1/c	
Unit cell dimensions	a = 12.7048(5) Å	α= 90°.
	b = 7.9136(3) Å	β= 100.806(4)°.
	c = 13.7019(5) Å	γ = 90°.
Volume	1353.16(9) Å^3	
Z	4	
Density (calculated)	1.515 Mg/m^3	
Absorption coefficient	0.325 mm^{-1}	
F(000)	636	
Crystal size	0.37 x 0.35 x 0.09 mm^3	
□ range for data collection	3.97 to 30.24°.	

[10] (a) Burnett, M. N. & Johnson, C. K. *ORTEPIII*. Report ORNL-6895. Oak Ridge National Laboratory, Tennessee, USA, 1996. (b) Macrae, C. F., Edgington, P. R., McCabe, P., Pidcock, E., Shields, G. P., Taylor, R., Towler, M. & van de Streek, J. *J. Appl. Cryst.* **2006**, *39*, 453-457.

Index ranges	$-17 \leq h \leq 17$, $-11 \leq k \leq 9$, $-19 \leq l \leq 19$
Reflections collected	17383
Independent reflections	3648 [R(int) = 0.049]
Completeness to □ = 25.24°	99.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.000 and 0.267
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3642 / 7 / 199
Goodness-of-fit on F^2	1.048
Final R indices [I>2□(I)]	R1 = 0.0343, wR2 = 0.0876
R indices (all data)	R1 = 0.0403, wR2 = 0.0913
Largest diff. peak and hole	0.478 and -0.266 e.Å^{-3}

Table S3. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **7b** deposit. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	2527(1)	3634(1)	5811(1)	23(1)
Cl(1)	4070(1)	3678(1)	2207(1)	21(1)
N(1)	3945(1)	7695(1)	6296(1)	17(1)
F(1)	2546(1)	7971(1)	7515(1)	22(1)
C(1)	2954(1)	6624(2)	6087(1)	15(1)
O(2)	4098(1)	6179(1)	4490(1)	23(1)
F(2)	3273(1)	5502(1)	7733(1)	26(1)
C(2)	2089(1)	7477(2)	5325(1)	16(1)
C(3)	1197(1)	6552(2)	4869(1)	23(1)
O(3)	3216(1)	3737(1)	4128(1)	31(1)
F(3)	1618(1)	5764(1)	7008(1)	27(1)
C(4)	395(1)	7320(2)	4185(1)	25(1)
C(5)	458(1)	9007(2)	3926(1)	23(1)
C(6)	1347(1)	9921(2)	4382(1)	25(1)
C(7)	2154(1)	9170(2)	5074(1)	22(1)
C(8)	-414(1)	9812(2)	3173(1)	33(1)
C(9)	3308(1)	4858(2)	5754(1)	18(1)
C(10)	3574(1)	5016(2)	4714(1)	20(1)
C(11)	2586(1)	6448(2)	7095(1)	19(1)
O(1W)	4703(2)	213(4)	4787(2)	47(1)

Table S3. Bond lengths [Å] and angles [°] for **7b**.

O(1)-C(9)	1.3995(15)
N(1)-C(1)	1.4999(15)
F(1)-C(11)	1.3404(15)
C(1)-C(2)	1.5242(16)
C(1)-C(11)	1.5454(17)
C(1)-C(9)	1.5621(17)
O(2)-C(10)	1.2086(17)
F(2)-C(11)	1.3414(15)
C(2)-C(7)	1.3897(18)
C(2)-C(3)	1.3950(18)
C(3)-C(4)	1.3886(19)
O(3)-C(10)	1.3184(16)
F(3)-C(11)	1.3283(15)
C(4)-C(5)	1.387(2)
C(5)-C(6)	1.387(2)
C(5)-C(8)	1.5073(18)
C(6)-C(7)	1.3934(18)
C(9)-C(10)	1.5304(18)
O(1W)-O(1W)#1	0.928(5)

N(1)-C(1)-C(2)	110.61(10)
N(1)-C(1)-C(11)	105.34(10)
C(2)-C(1)-C(11)	110.62(10)
N(1)-C(1)-C(9)	106.49(9)
C(2)-C(1)-C(9)	113.92(10)
C(11)-C(1)-C(9)	109.44(10)
C(7)-C(2)-C(3)	118.41(12)
C(7)-C(2)-C(1)	121.86(11)
C(3)-C(2)-C(1)	119.72(11)
C(4)-C(3)-C(2)	120.31(13)
C(5)-C(4)-C(3)	121.55(13)
C(6)-C(5)-C(4)	117.95(12)
C(6)-C(5)-C(8)	121.29(14)
C(4)-C(5)-C(8)	120.75(14)
C(5)-C(6)-C(7)	121.13(13)
C(2)-C(7)-C(6)	120.64(13)
O(1)-C(9)-C(10)	113.01(11)
O(1)-C(9)-C(1)	110.93(10)
C(10)-C(9)-C(1)	109.00(10)
O(2)-C(10)-O(3)	125.00(12)
O(2)-C(10)-C(9)	121.73(12)
O(3)-C(10)-C(9)	113.20(11)
F(3)-C(11)-F(1)	107.24(10)
F(3)-C(11)-F(2)	108.03(10)
F(1)-C(11)-F(2)	107.16(10)
F(3)-C(11)-C(1)	112.73(10)
F(1)-C(11)-C(1)	110.14(10)
F(2)-C(11)-C(1)	111.31(10)

Symmetry transformations used to generate equivalent atoms:
#1 -x+1,-y,-z+1

Table S4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for vs171_deposit. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	25(1)	17(1)	26(1)	4(1)	0(1)	-2(1)
Cl(1)	24(1)	17(1)	21(1)	-2(1)	-3(1)	3(1)
N(1)	14(1)	19(1)	17(1)	1(1)	1(1)	0(1)
F(1)	24(1)	26(1)	18(1)	-4(1)	5(1)	0(1)
C(1)	14(1)	17(1)	15(1)	0(1)	2(1)	0(1)
O(2)	22(1)	27(1)	22(1)	-1(1)	7(1)	1(1)
F(2)	29(1)	30(1)	17(1)	8(1)	3(1)	4(1)
C(2)	14(1)	20(1)	13(1)	0(1)	3(1)	3(1)
C(3)	20(1)	23(1)	24(1)	1(1)	-2(1)	-1(1)
O(3)	41(1)	30(1)	23(1)	-8(1)	8(1)	-5(1)
F(3)	22(1)	37(1)	23(1)	-1(1)	8(1)	-10(1)
C(4)	17(1)	34(1)	23(1)	0(1)	-2(1)	1(1)
C(5)	18(1)	34(1)	16(1)	2(1)	4(1)	11(1)
C(6)	28(1)	23(1)	23(1)	5(1)	2(1)	6(1)
C(7)	22(1)	21(1)	22(1)	2(1)	-1(1)	1(1)
C(8)	24(1)	49(1)	25(1)	9(1)	2(1)	16(1)
C(9)	18(1)	17(1)	18(1)	2(1)	1(1)	2(1)
C(10)	18(1)	22(1)	18(1)	-2(1)	1(1)	7(1)
C(11)	18(1)	22(1)	16(1)	1(1)	2(1)	-2(1)
O(1W)	37(2)	64(2)	45(2)	22(1)	19(1)	9(1)

Table S5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **7b**.

	x	y	z	U(eq)
H(1O)	2789	2877	6214	28
HN1	4460(14)	7210(20)	6738(13)	20
HN2	3833(12)	8720(20)	6547(11)	20
HN3	4195(13)	7830(20)	5743(13)	20
H(3)	1137	5392	5028	28
HO3	3390	3875	3571	46
H(4)	-211	6675	3886	30
H(6)	1406	11080	4219	30
H(7)	2755	9822	5378	27
H(8A)	-356	9426	2505	49
H(8B)	-338	11044	3209	49
H(8C)	-1115	9490	3314	49
H(9)	3978	4523	6221	22
H(1OW)	4780(40)	-380(50)	4270(20)	71
H(2OW)	4230(30)	940(50)	4510(30)	71

Table S6. Torsion angles [°] for **7b**.

N(1)-C(1)-C(2)-C(7)	-14.43(16)
C(11)-C(1)-C(2)-C(7)	101.89(13)
C(9)-C(1)-C(2)-C(7)	-134.34(12)
N(1)-C(1)-C(2)-C(3)	166.38(11)
C(11)-C(1)-C(2)-C(3)	-77.30(14)
C(9)-C(1)-C(2)-C(3)	46.47(15)
C(7)-C(2)-C(3)-C(4)	-0.2(2)
C(1)-C(2)-C(3)-C(4)	179.03(12)
C(2)-C(3)-C(4)-C(5)	0.6(2)
C(3)-C(4)-C(5)-C(6)	-0.7(2)
C(3)-C(4)-C(5)-C(8)	179.30(13)
C(4)-C(5)-C(6)-C(7)	0.3(2)
C(8)-C(5)-C(6)-C(7)	-179.68(13)
C(3)-C(2)-C(7)-C(6)	-0.19(19)
C(1)-C(2)-C(7)-C(6)	-179.39(12)
C(5)-C(6)-C(7)-C(2)	0.1(2)
N(1)-C(1)-C(9)-O(1)	163.25(10)
C(2)-C(1)-C(9)-O(1)	-74.55(13)
C(11)-C(1)-C(9)-O(1)	49.86(13)
N(1)-C(1)-C(9)-C(10)	-71.71(12)
C(2)-C(1)-C(9)-C(10)	50.50(13)
C(11)-C(1)-C(9)-C(10)	174.91(10)
O(1)-C(9)-C(10)-O(2)	168.09(11)
C(1)-C(9)-C(10)-O(2)	44.26(15)
O(1)-C(9)-C(10)-O(3)	-14.69(15)
C(1)-C(9)-C(10)-O(3)	-138.52(11)
N(1)-C(1)-C(11)-F(3)	169.64(10)
C(2)-C(1)-C(11)-F(3)	50.09(14)
C(9)-C(1)-C(11)-F(3)	-76.23(13)
N(1)-C(1)-C(11)-F(1)	49.91(12)
C(2)-C(1)-C(11)-F(1)	-69.64(13)
C(9)-C(1)-C(11)-F(1)	164.05(10)
N(1)-C(1)-C(11)-F(2)	-68.79(12)
C(2)-C(1)-C(11)-F(2)	171.65(10)
C(9)-C(1)-C(11)-F(2)	45.34(13)

Symmetry transformations used to generate equivalent atoms: #1 -x+1,-y,-z+1

Table S7. Hydrogen bonds for vs171_deposit [Å and °].

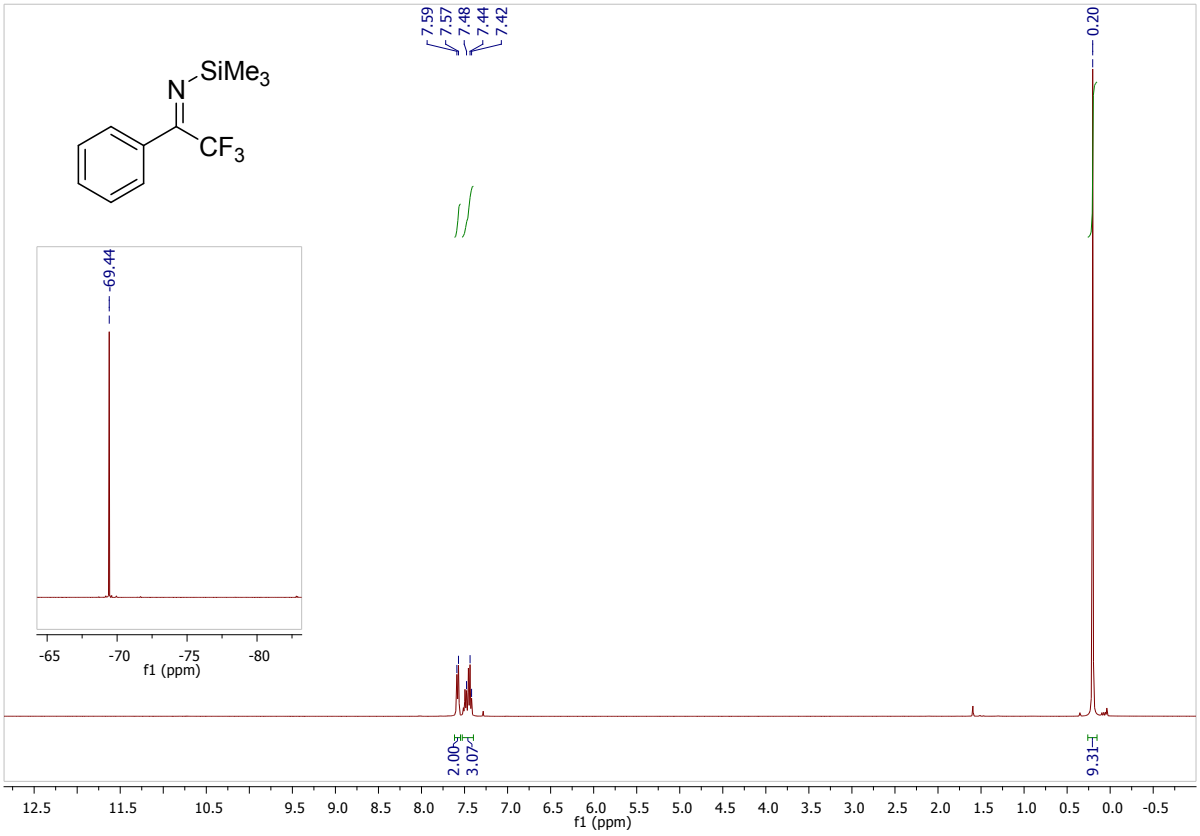
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1O)...Cl(1)#2	0.84	2.28	3.0725(10)	158.2
N(1)-HN1...Cl(1)#3	0.890(18)	2.251(18)	3.1322(11)	170.8(15)
N(1)-HN2...Cl(1)#4	0.903(18)	2.246(18)	3.1217(12)	163.3(14)
N(1)-HN3...O(2)	0.881(18)	2.143(17)	2.7893(15)	129.7(14)
N(1)-HN3...O(1W)#5	0.881(18)	2.451(17)	3.150(3)	136.6(14)
N(1)-HN3...O(1W)#3	0.881(18)	2.295(17)	2.975(3)	133.9(14)
O(3)-HO3...Cl(1)	0.84	2.21	3.0292(11)	166.3
C(9)-H(9)...Cl(1)#2	1.00	2.86	3.4656(13)	119.4
O(1W)-H(1OW)...Cl(1)#6	0.869(19)	2.81(3)	3.601(3)	152(5)
O(1W)-H(1OW)...F(2)#7	0.869(19)	2.57(4)	3.102(3)	121(3)
O(1W)-H(2OW)...O(3)	0.869(18)	2.562(19)	3.394(3)	161(4)

Symmetry transformations used to generate equivalent atoms:
#1 -x+1,-y,-z+1 #2 x,-y+1/2,z+1/2 #3 -x+1,-y+1,-z+1
#4 x,-y+3/2,z+1/2 #5 x,y+1,z #6 -x+1,y-1/2,-z+1/2
#7 x,-y+1/2,z-1/2

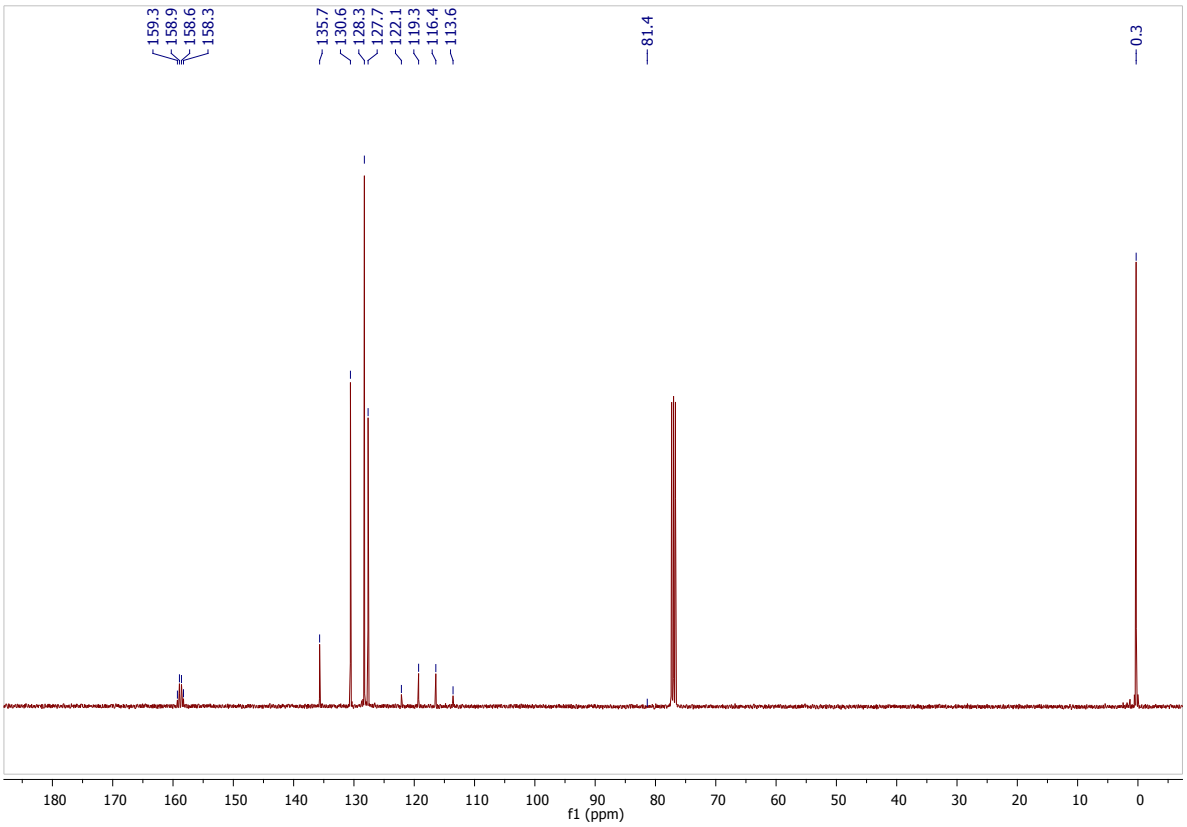
10. ^{1}H, ^{19}F and ^{13}C NMR spectra

1,1,1-Trimethyl-N-(2,2,2-trifluoro-1-phenylethylidene)silanamine (2a)

^{1}H NMR (400 MHz, $CDCl_3$), **^{19}F NMR** (376 MHz, $CDCl_3$):

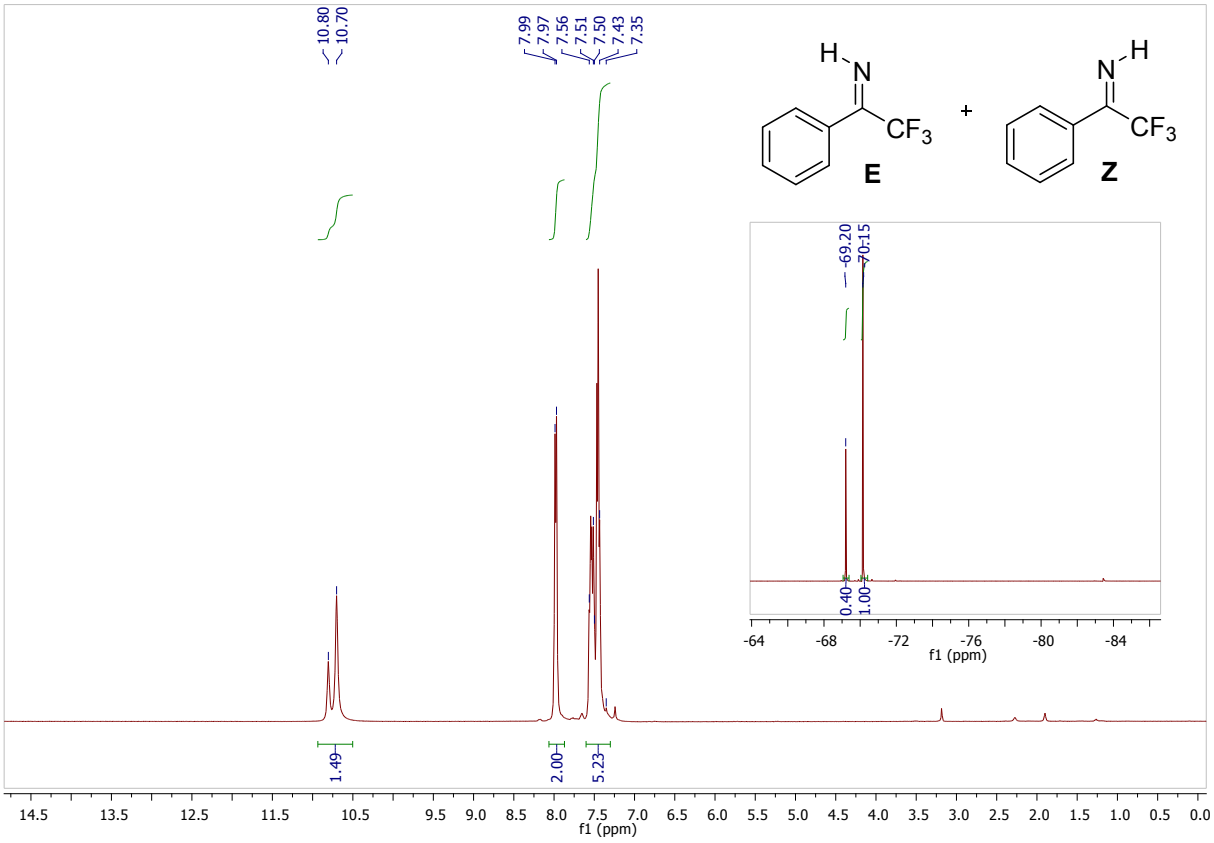


^{13}C NMR (101 MHz, $CDCl_3$):

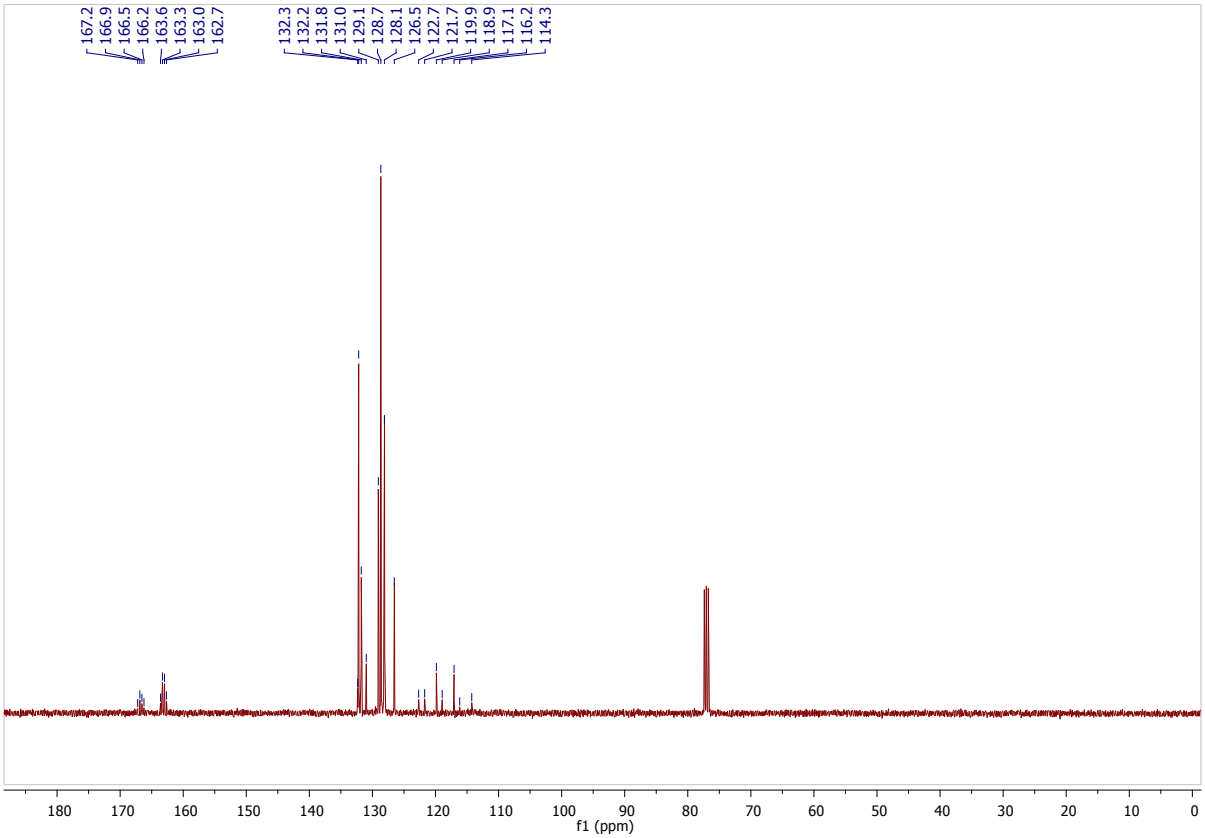


2,2,2-Trifluoro-1-phenylethanimine (3a, E/Z isomers 0.4:1)

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

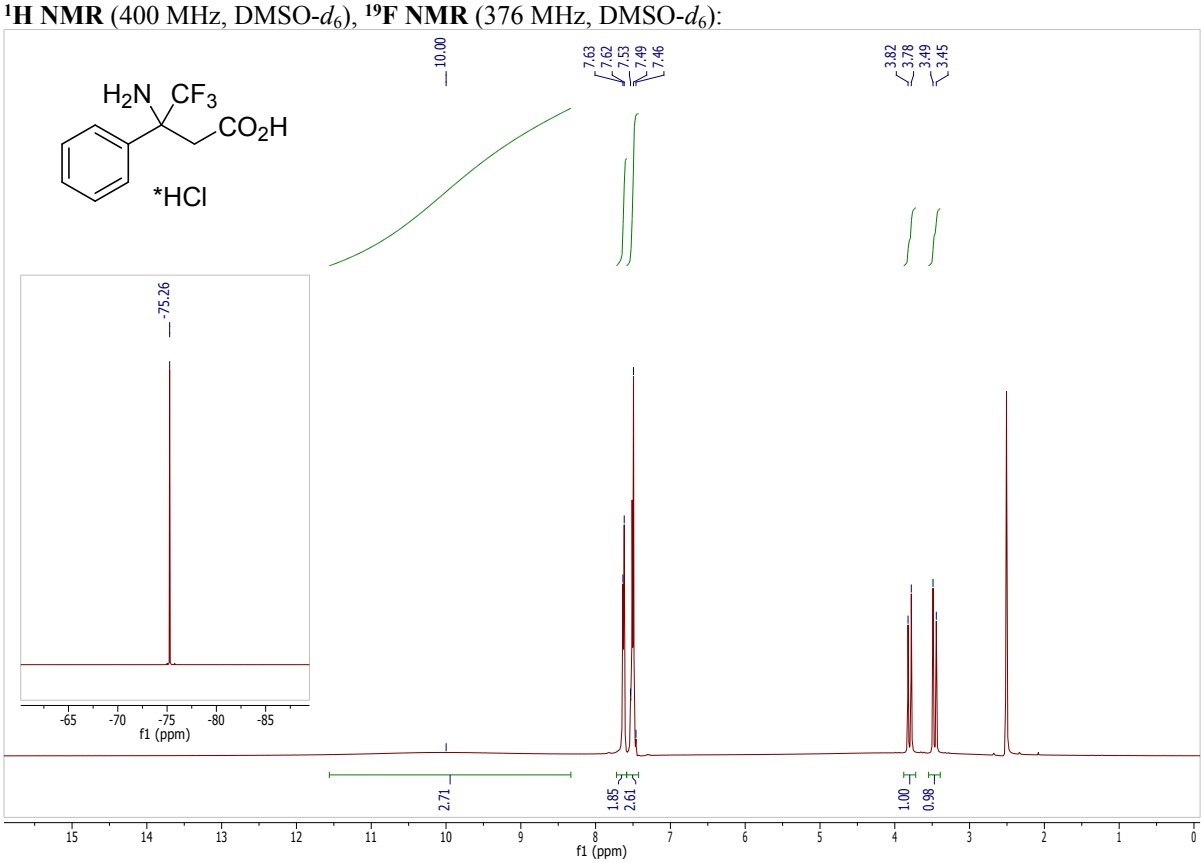


^{19}F NMR (376 MHz, $CDCl_3$):

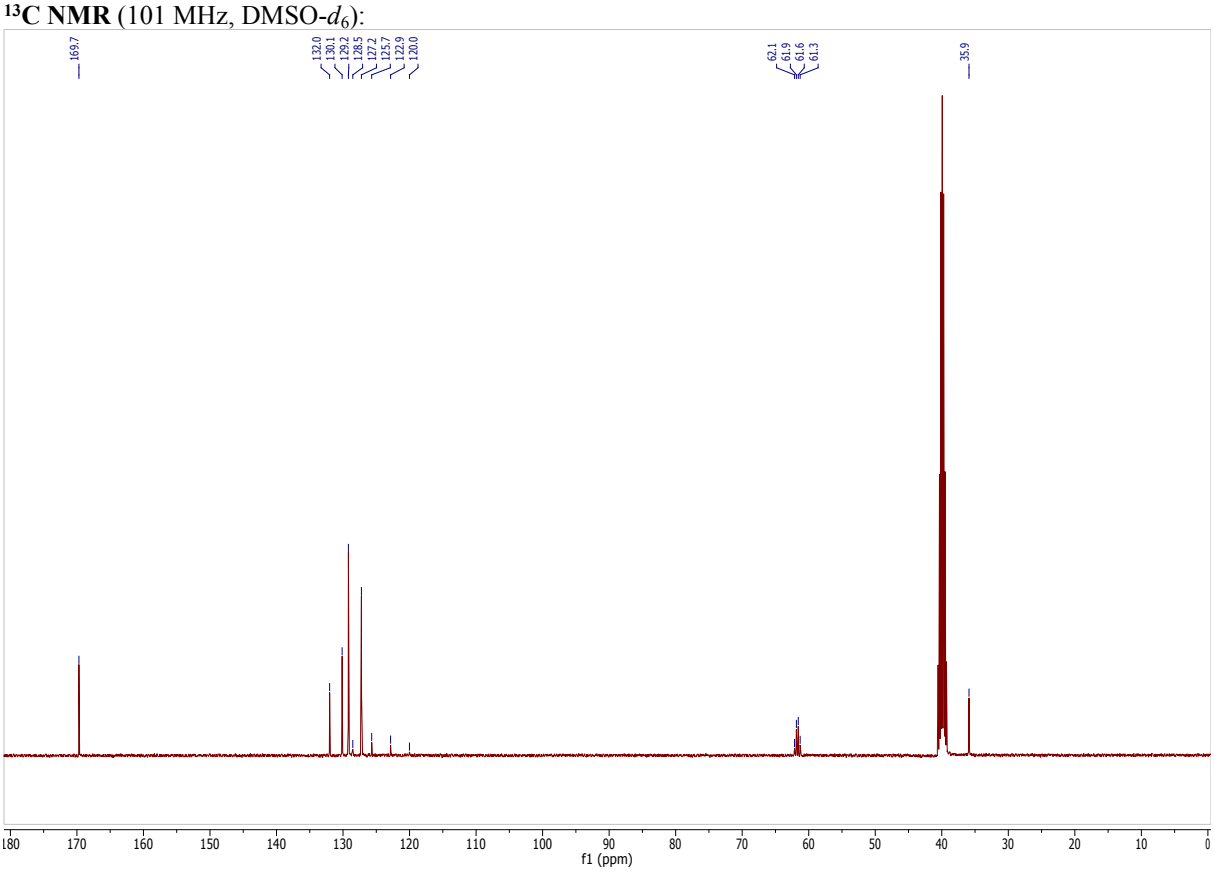


3-Amino-4,4,4-trifluoro-3-phenylbutanoic acid (4a, hydrochloride salt)

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

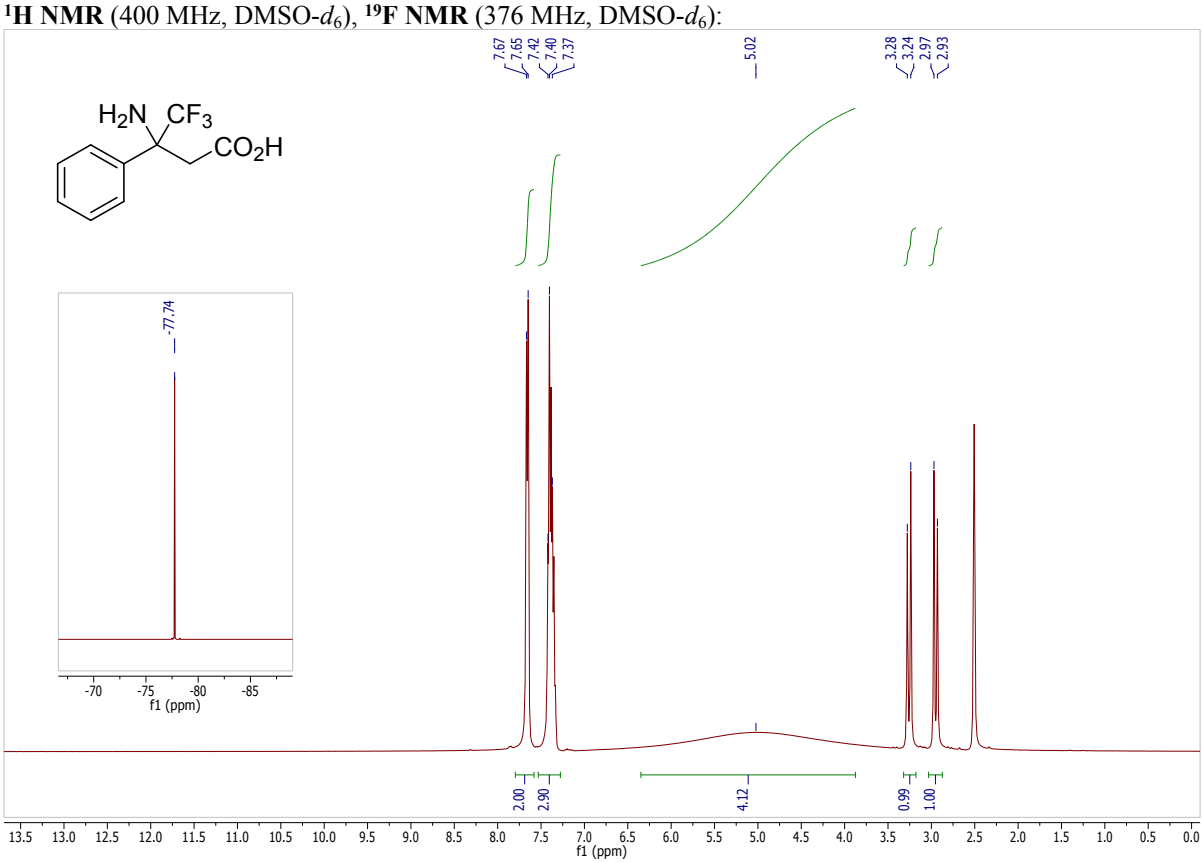


^{13}C NMR (101 MHz, DMSO-d_6):

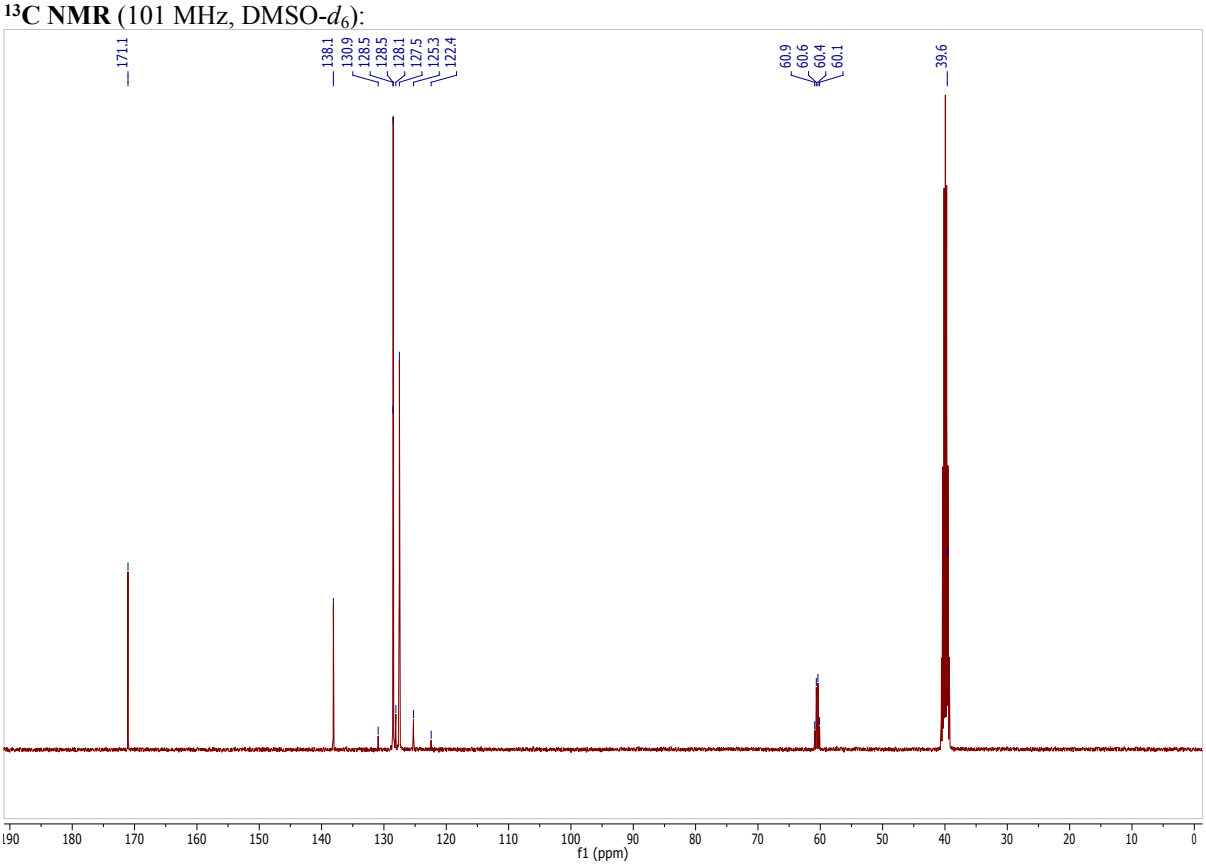


3-Amino-4,4,4-trifluoro-3-phenylbutanoic acid (4a, free)

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

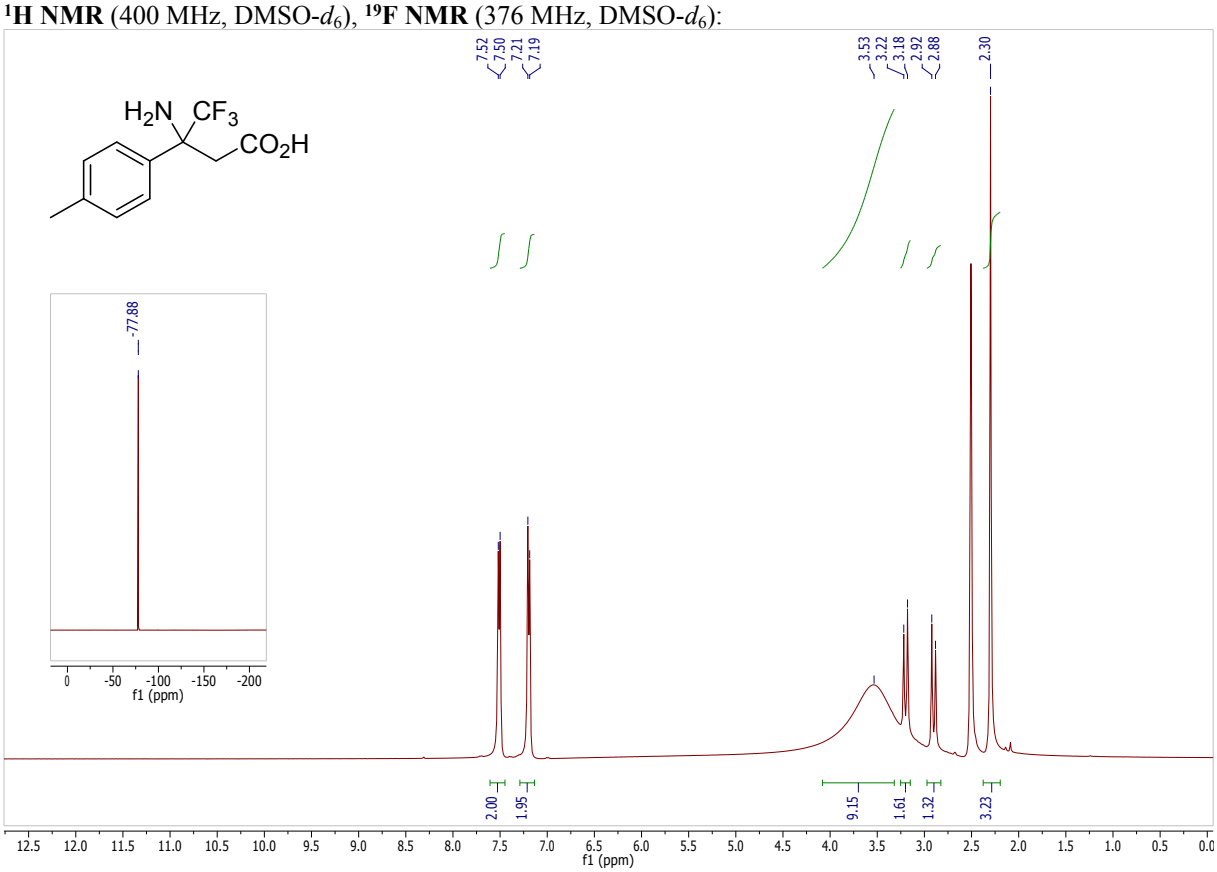


^{13}C NMR (101 MHz, DMSO-d_6):

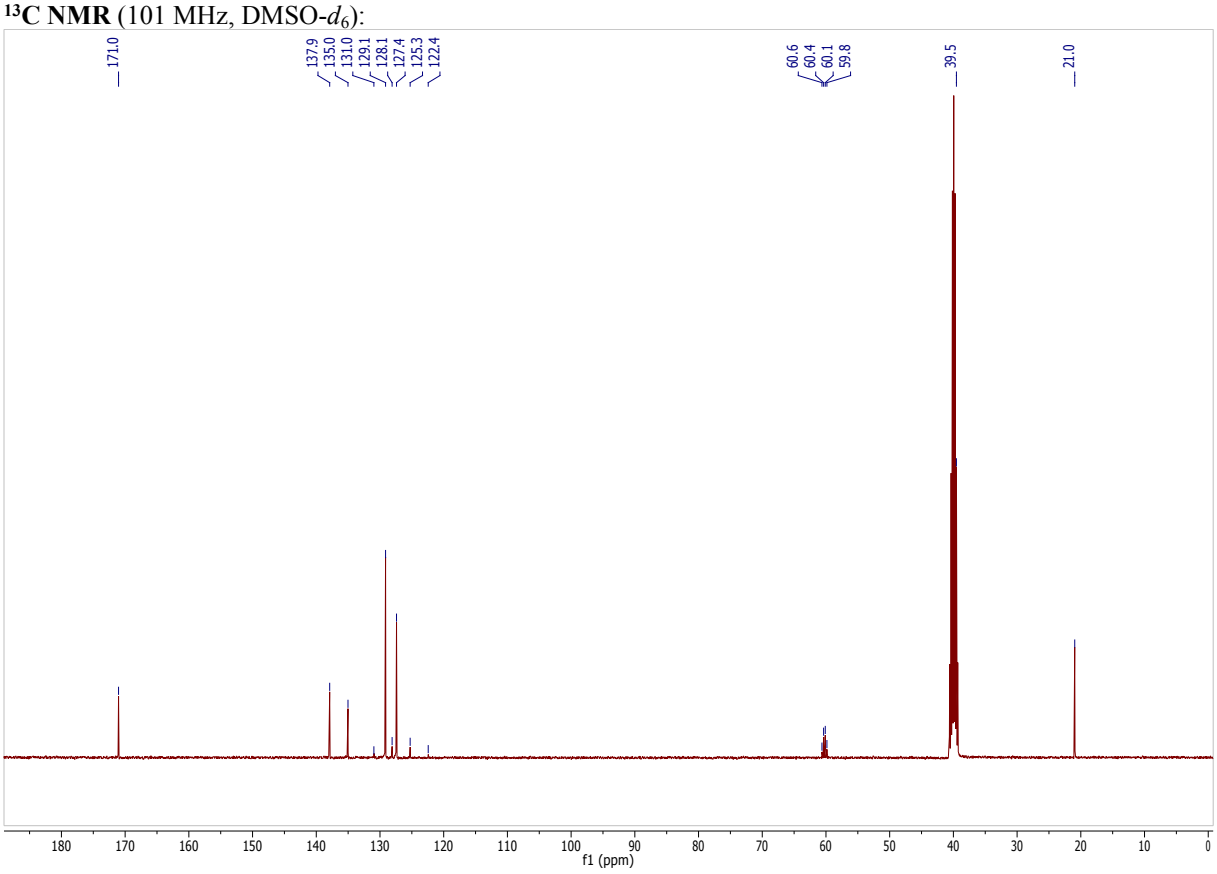


3-Amino-4,4,4-trifluoro-3-p-tolylbutanoic acid (4b)

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

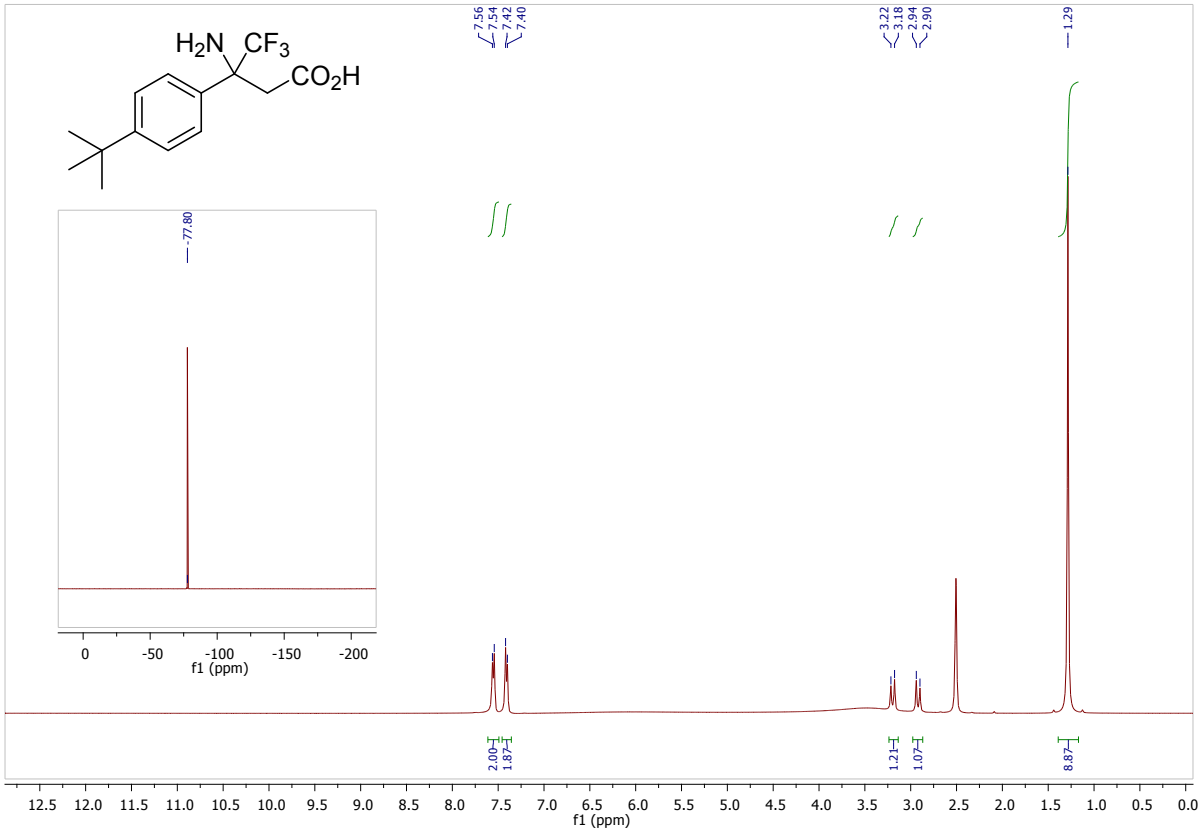


^{13}C NMR (101 MHz, DMSO-d_6):

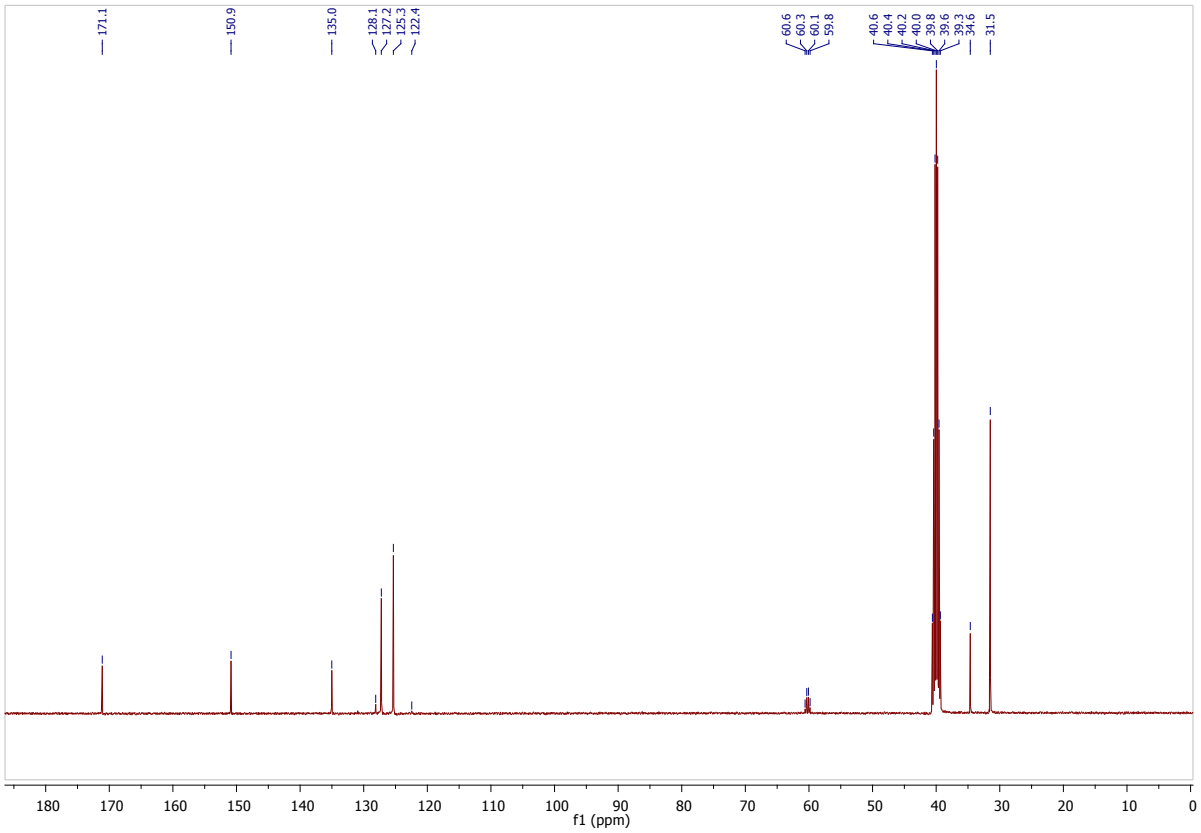


3-Amino-3-(4-*tert*-butylphenyl)-4,4,4-trifluorobutanoic acid (4c)

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

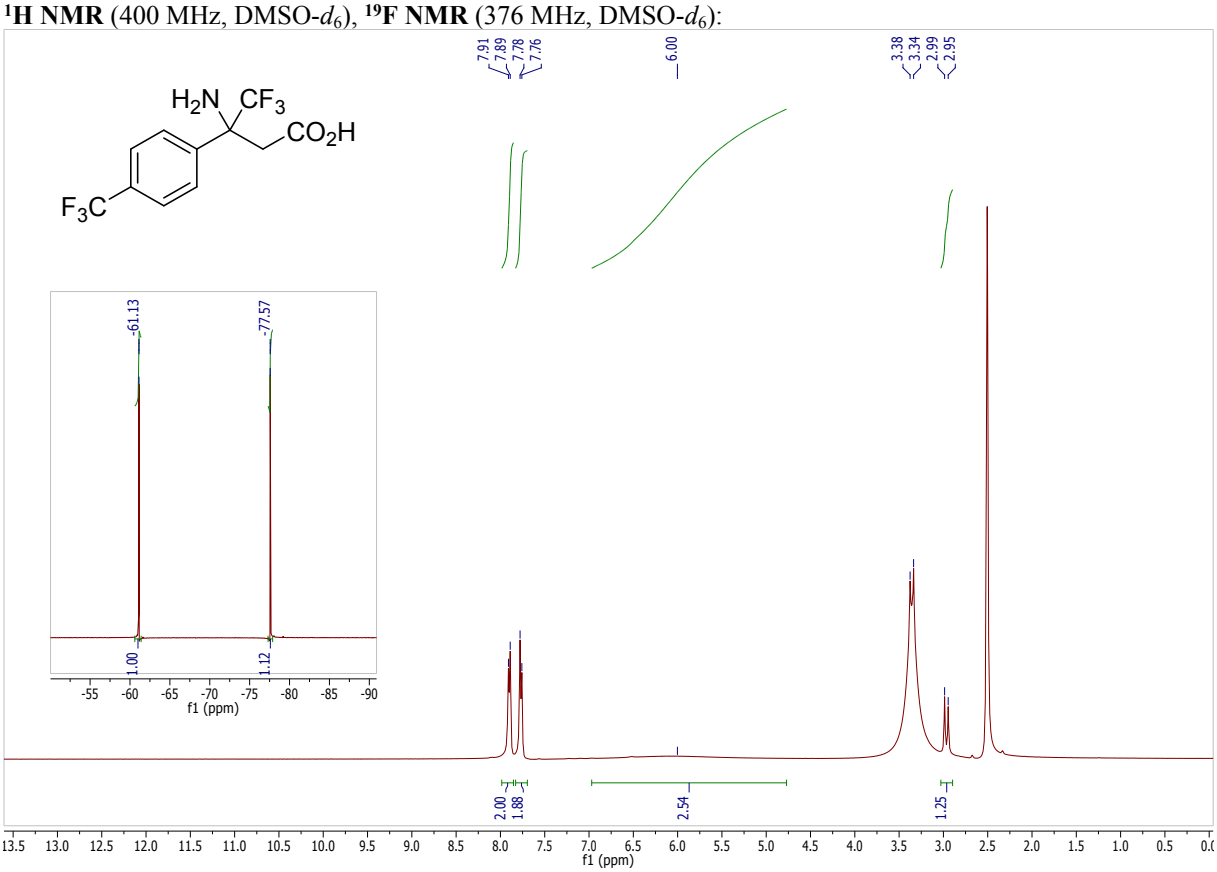


^{13}C NMR (101 MHz, DMSO-d_6):

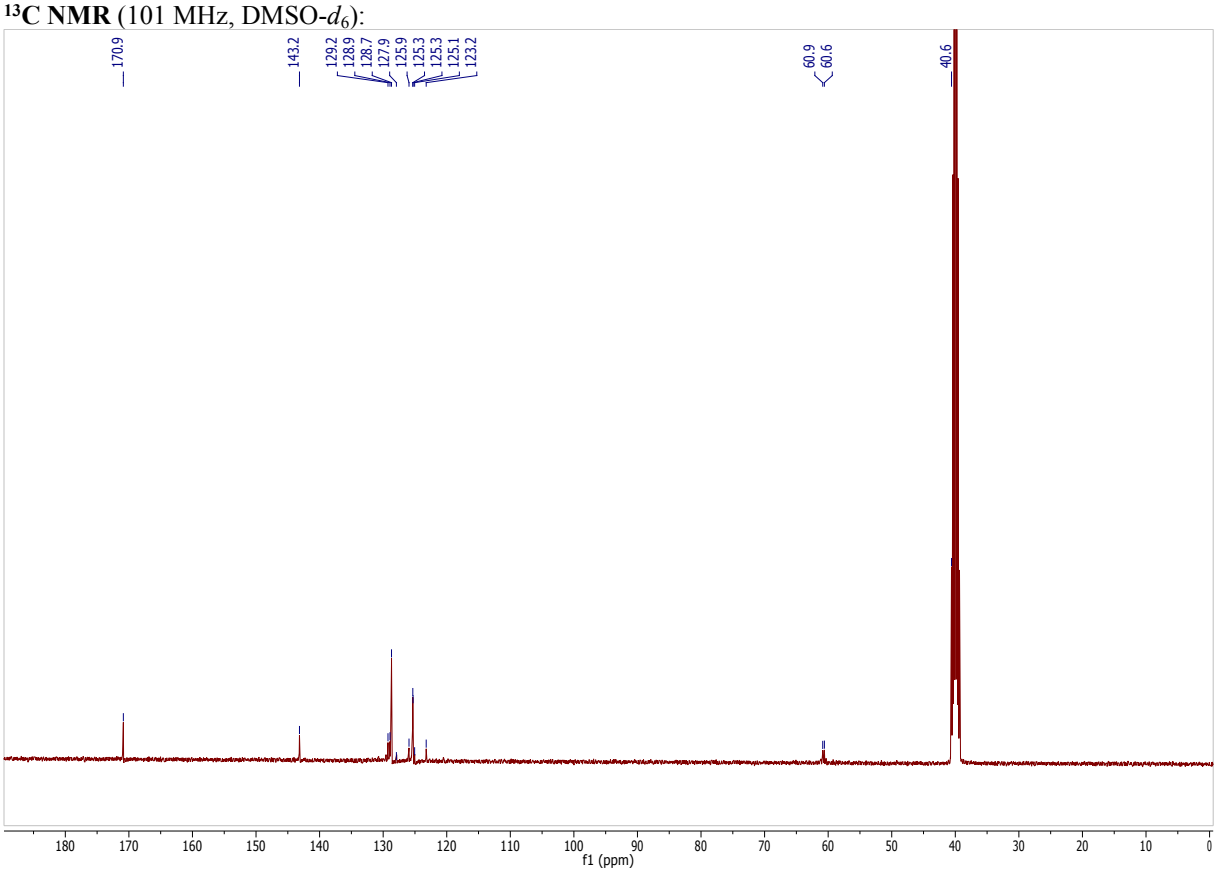


3-Amino-4,4,4-trifluoro-3-(4-(trifluoromethyl)phenyl)butanoic acid (4d)

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

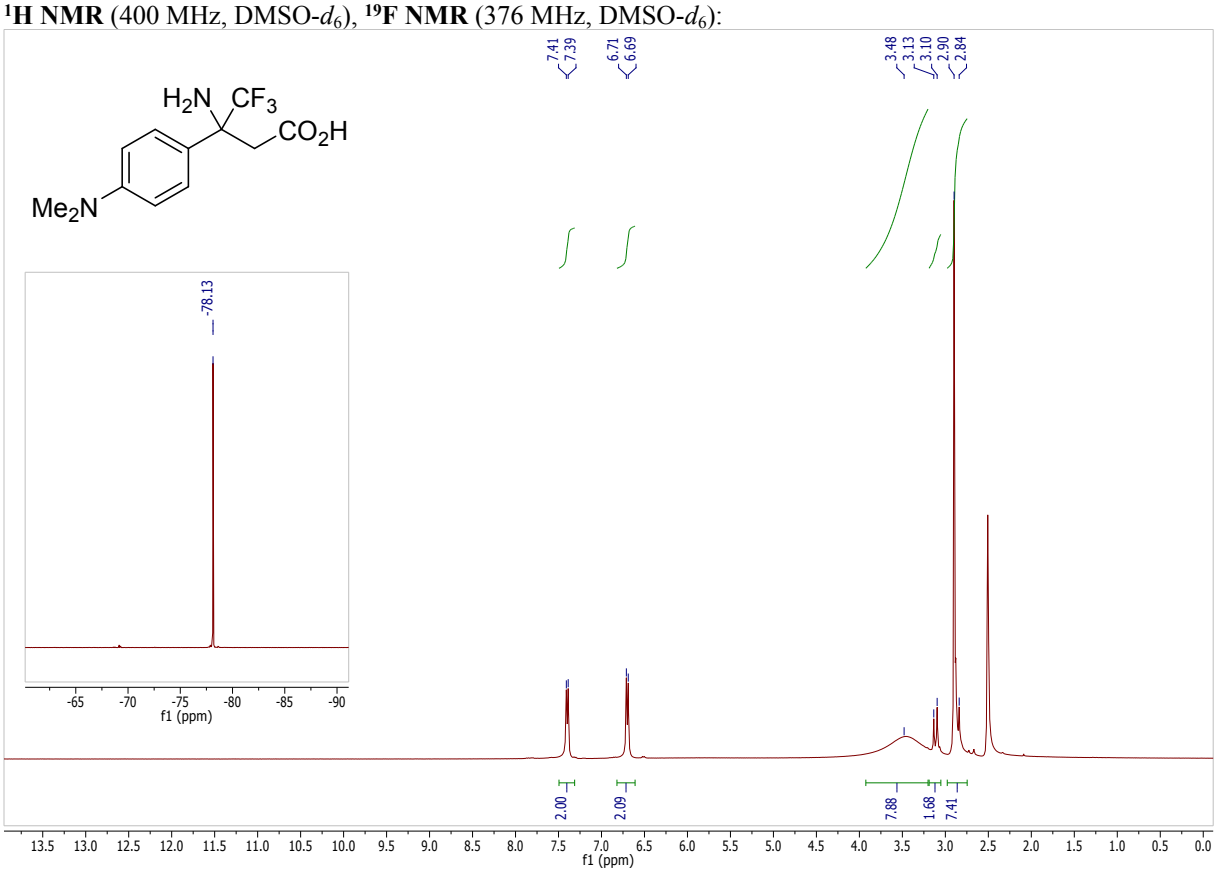


^{13}C NMR (101 MHz, DMSO-d_6):

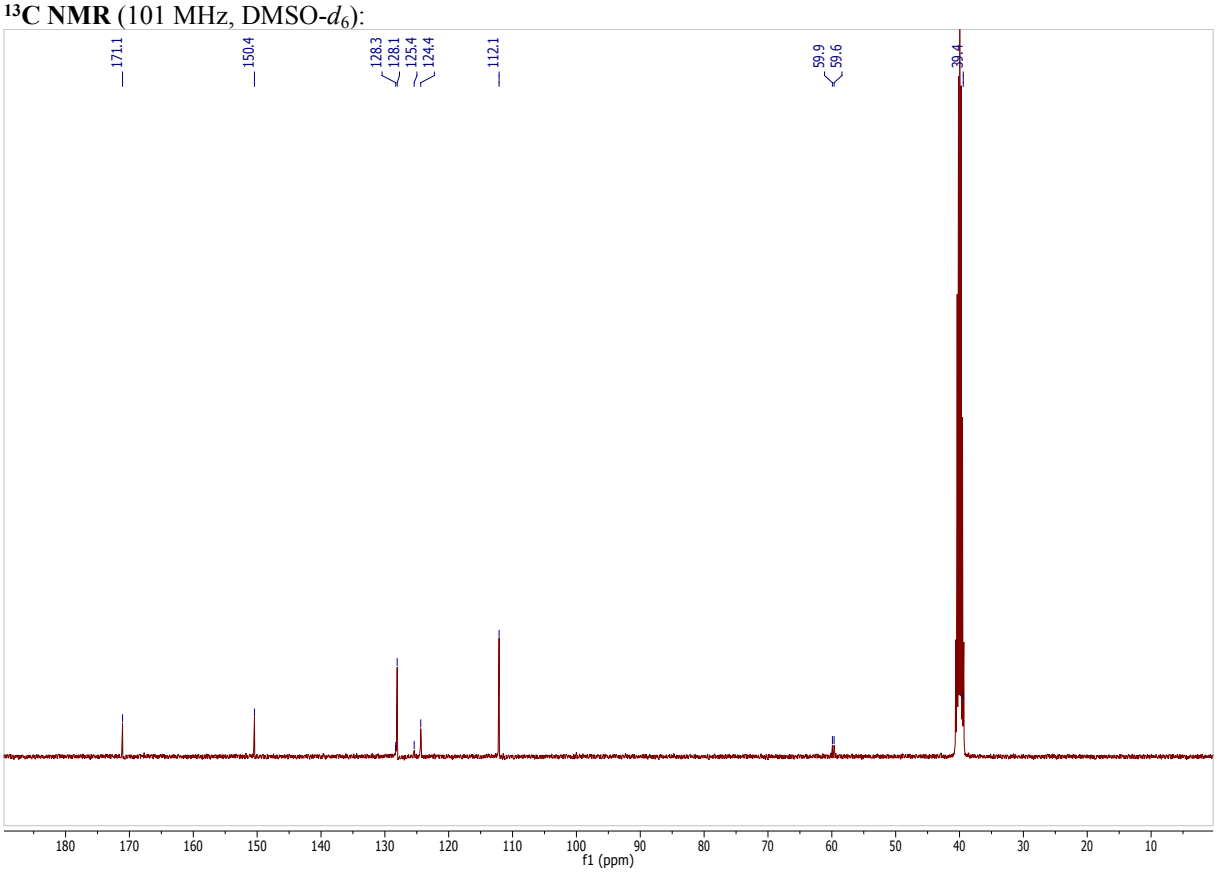


3-Amino-3-(4-(dimethylamino)phenyl)-4,4,4-trifluorobutanoic acid (4e)

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

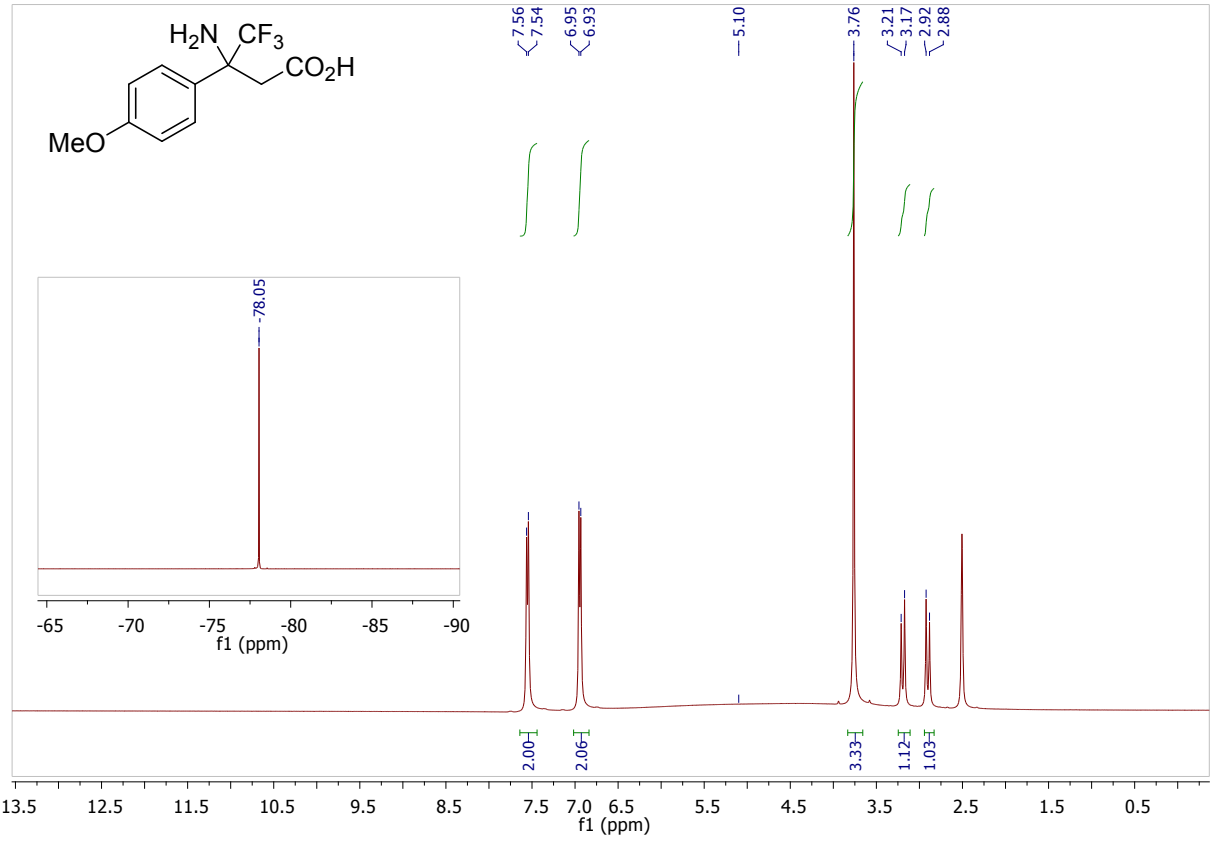


^{13}C NMR (101 MHz, DMSO-d_6):

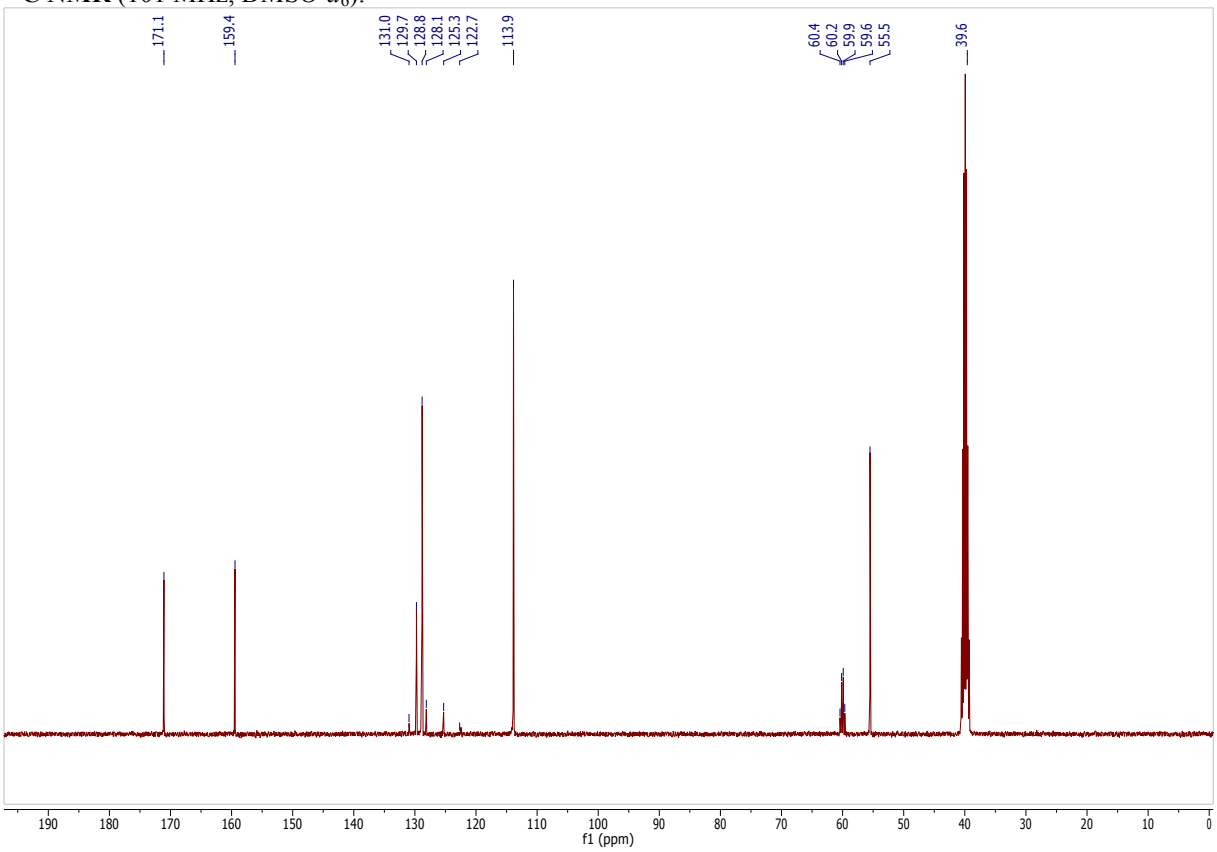


3-Amino-3-(4-methoxyphenyl)-4,4,4-trifluorobutanoic acid (4f)

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

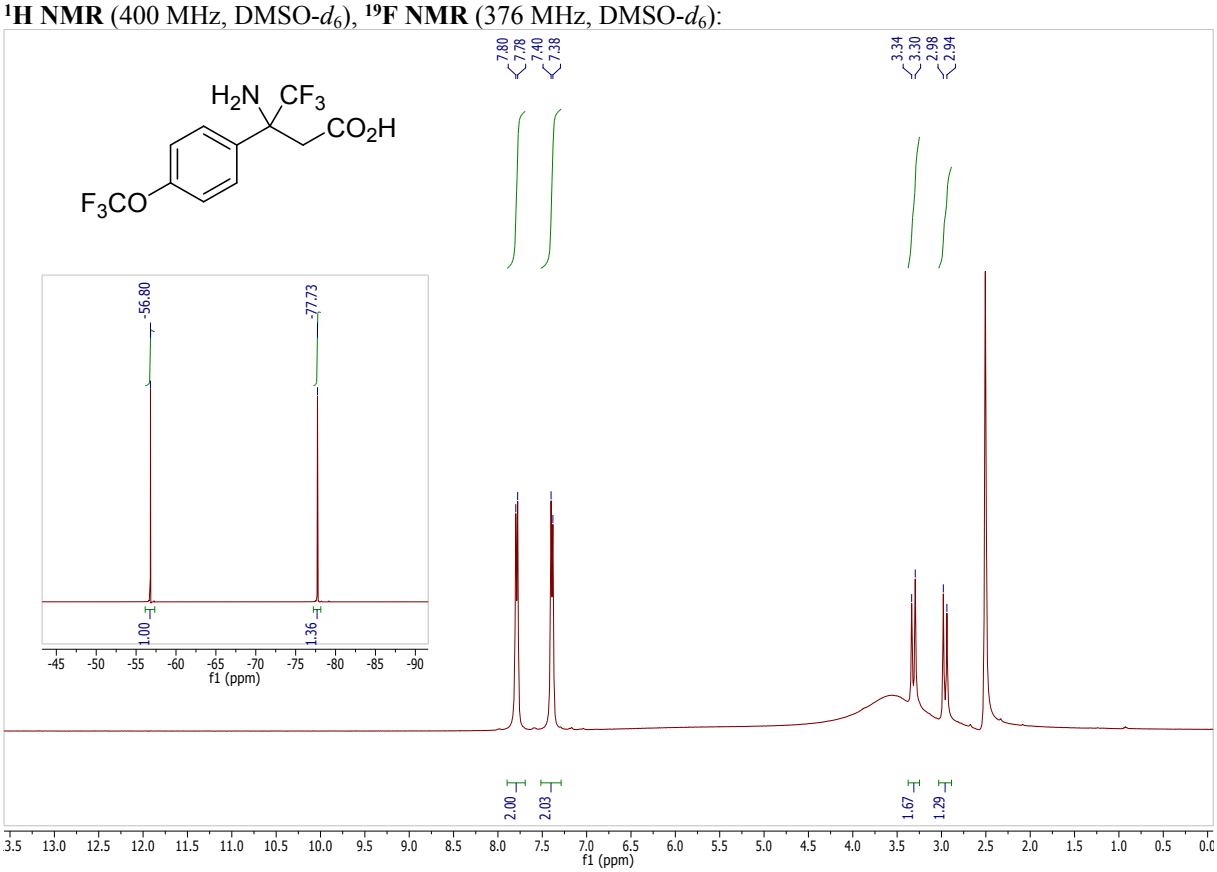


^{13}C NMR (101 MHz, DMSO-d_6):

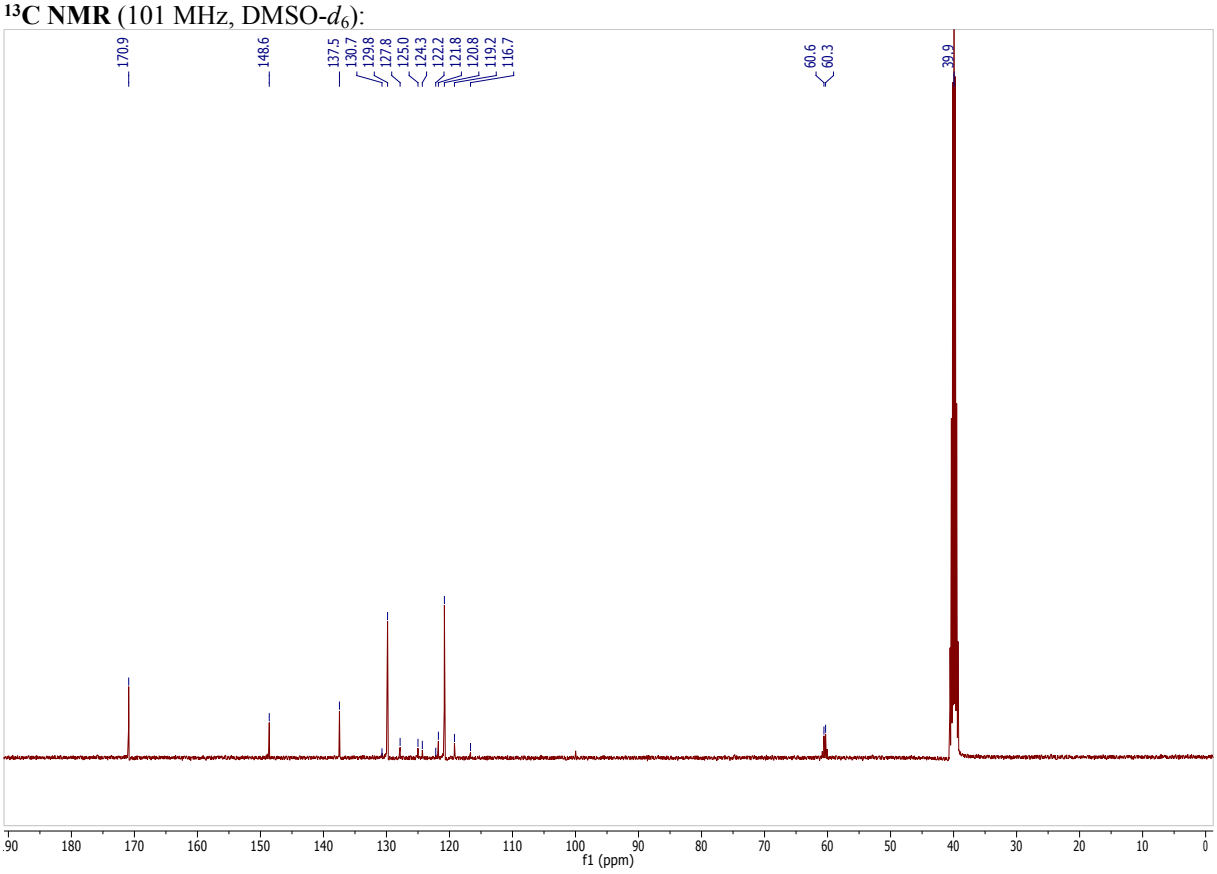


3-Amino-4,4,4-trifluoro-3-(4-(trifluoromethoxy)phenyl)butanoic acid (4g)

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

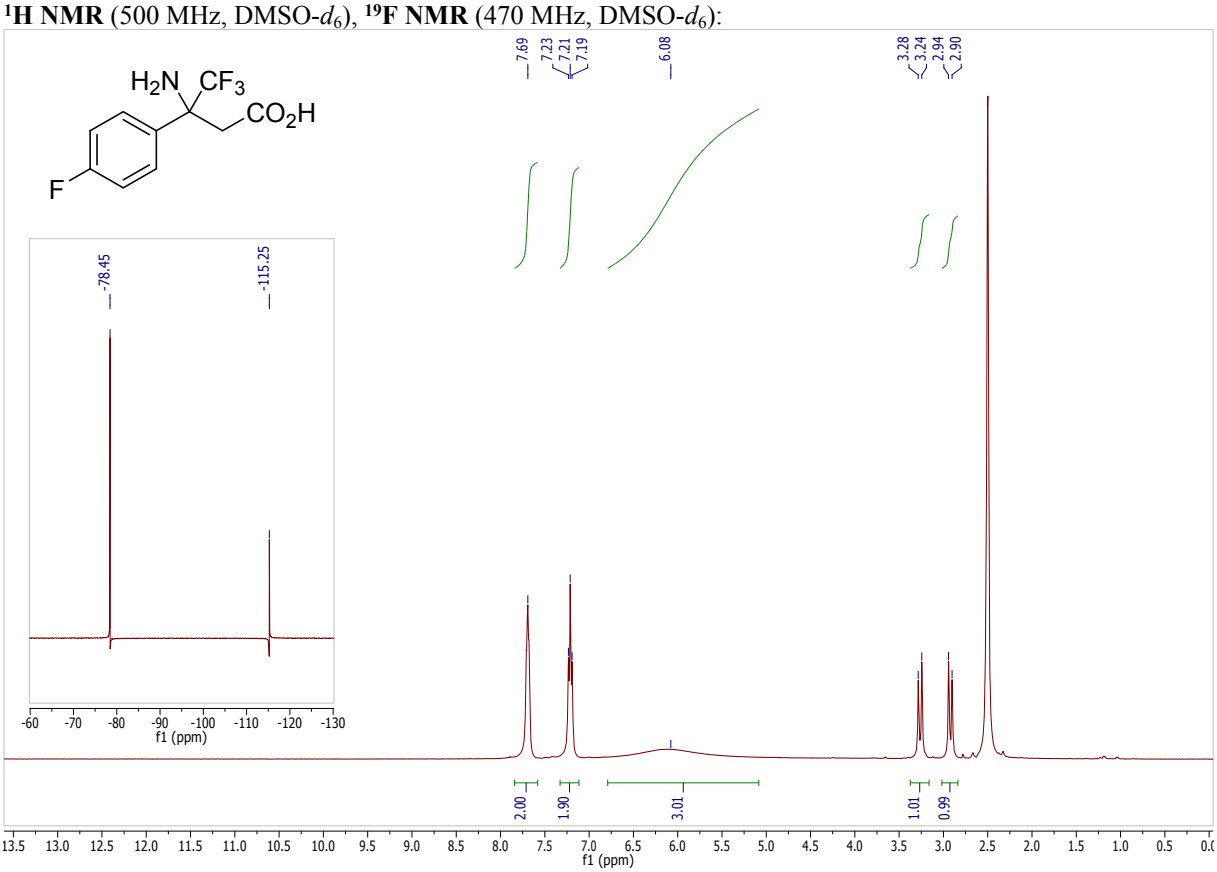


^{13}C NMR (101 MHz, DMSO-d_6):

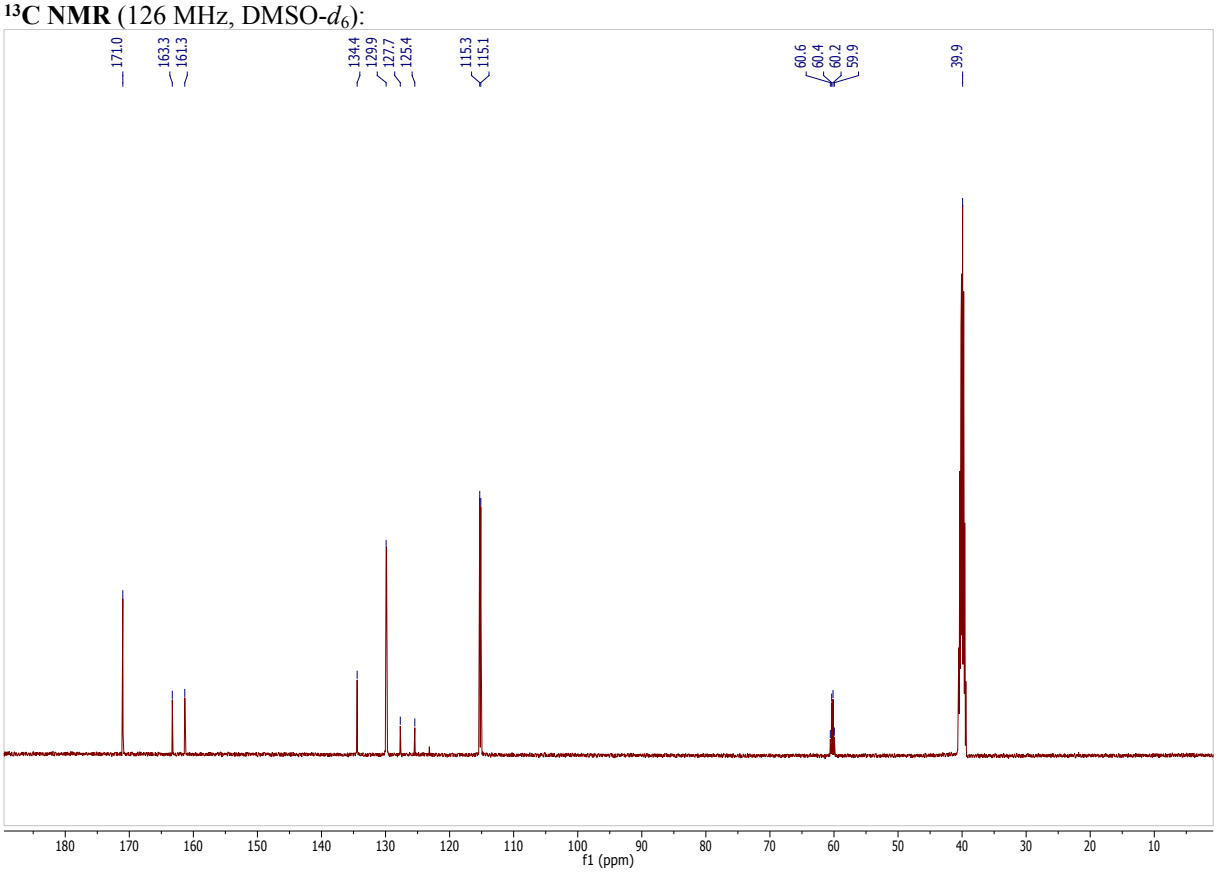


3-Amino-4,4,4-trifluoro-3-(4-fluorophenyl)butanoic acid (4h)

^{1}H NMR (500 MHz, DMSO-d_6), **^{19}F NMR** (470 MHz, DMSO-d_6):

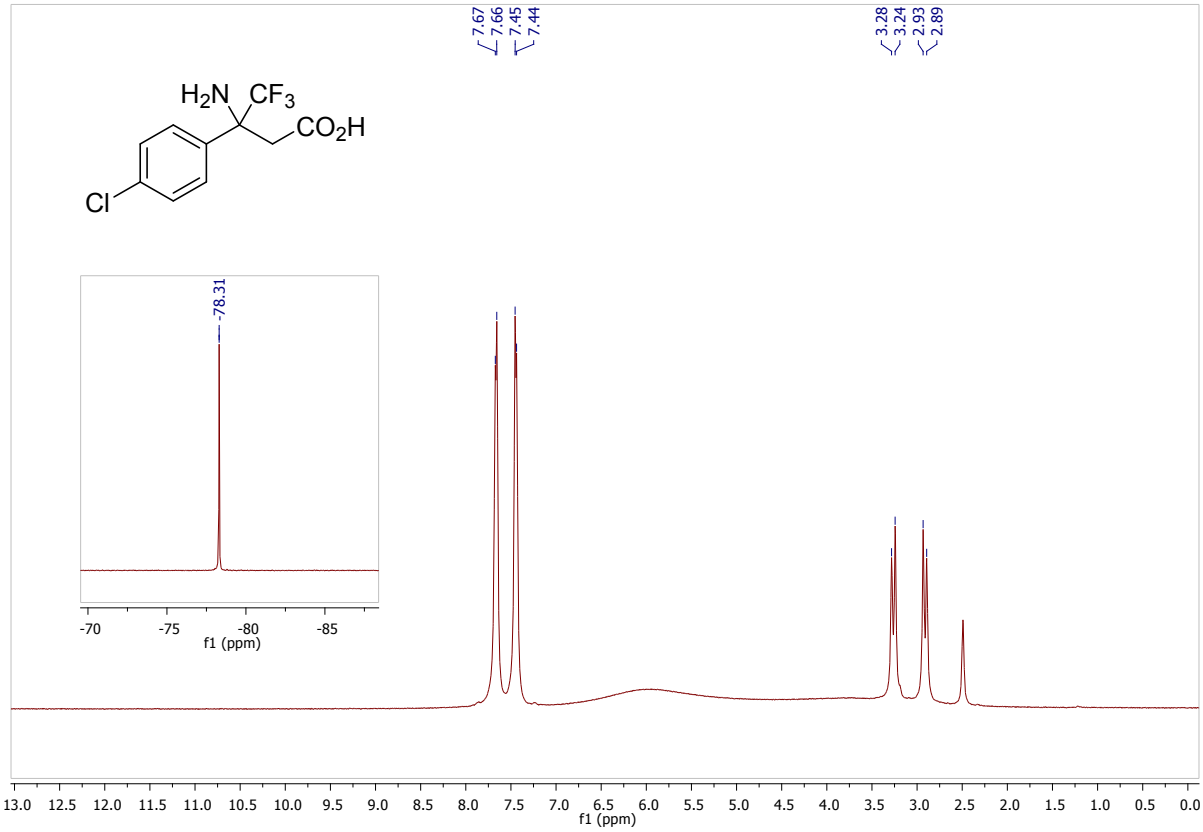


^{13}C NMR (126 MHz, DMSO-d_6):

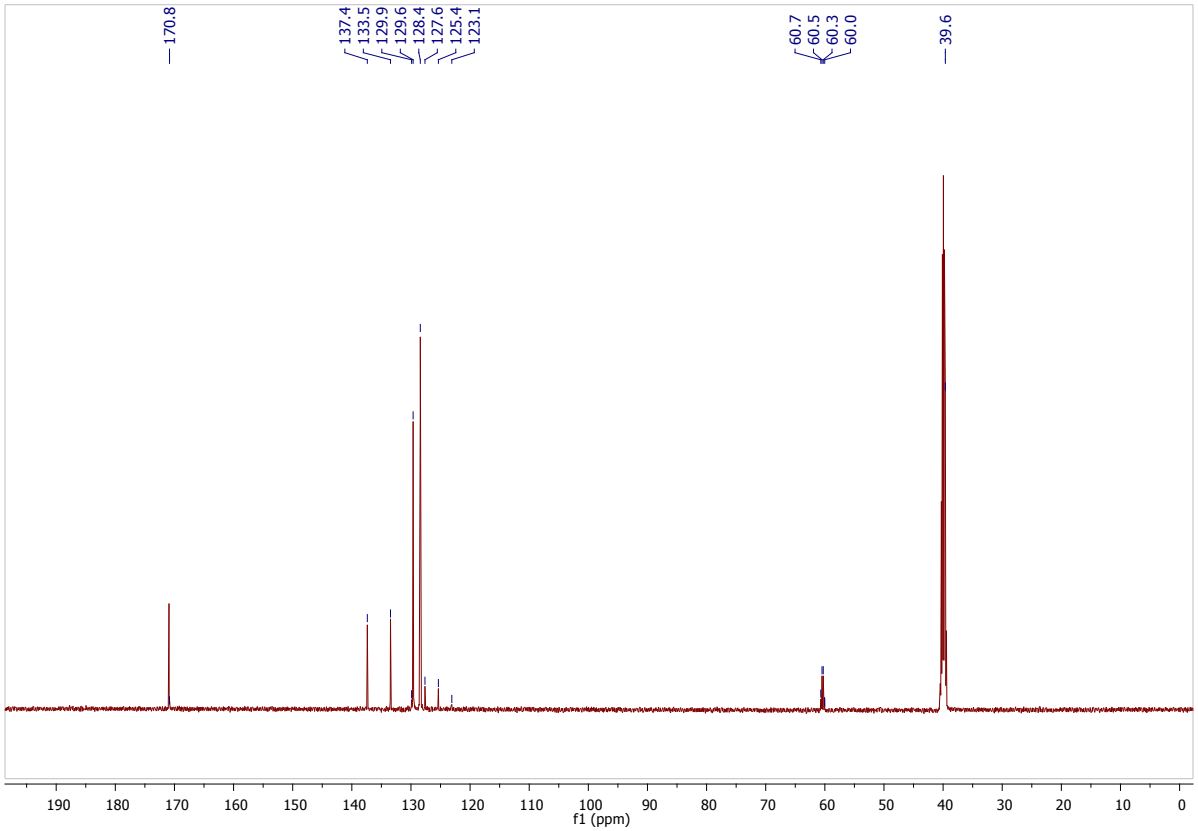


3-Amino-3-(4-chlorophenyl)-4,4,4-trifluorobutanoic acid (4i)

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

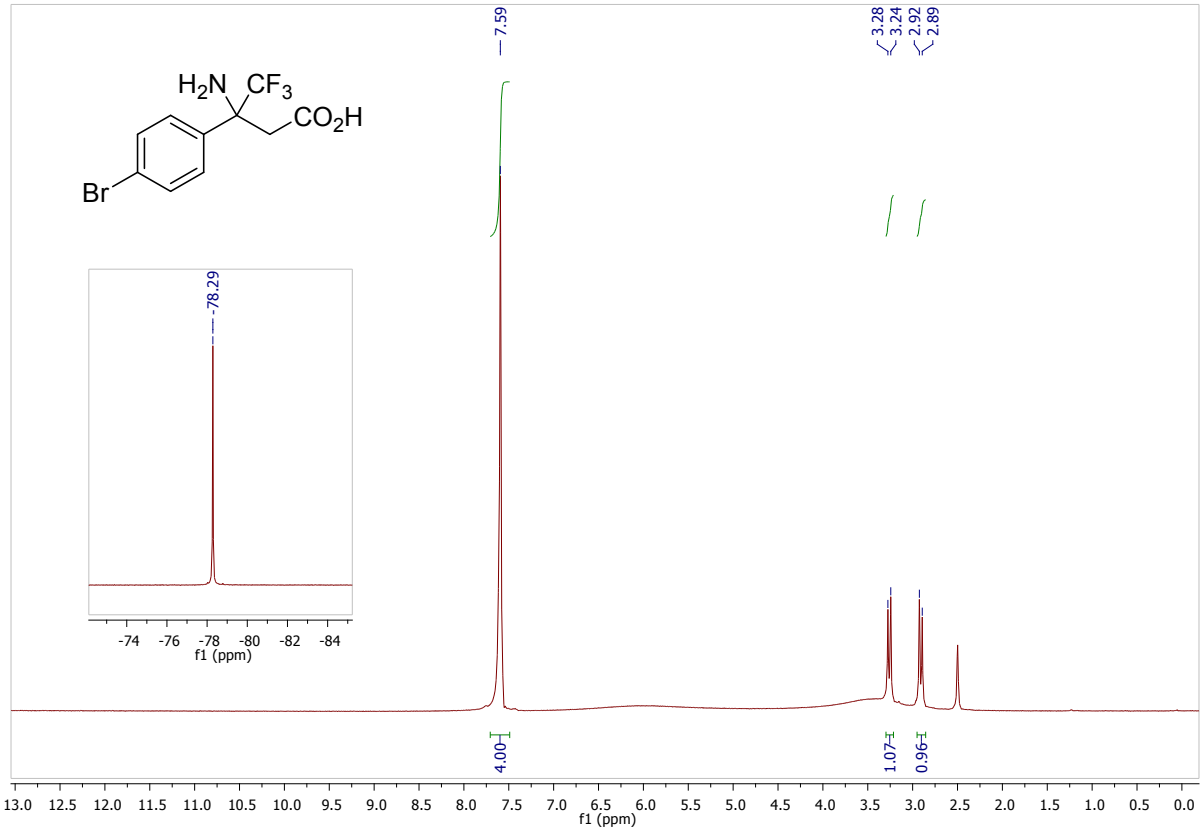


^{13}C NMR (126 MHz, DMSO-d_6):

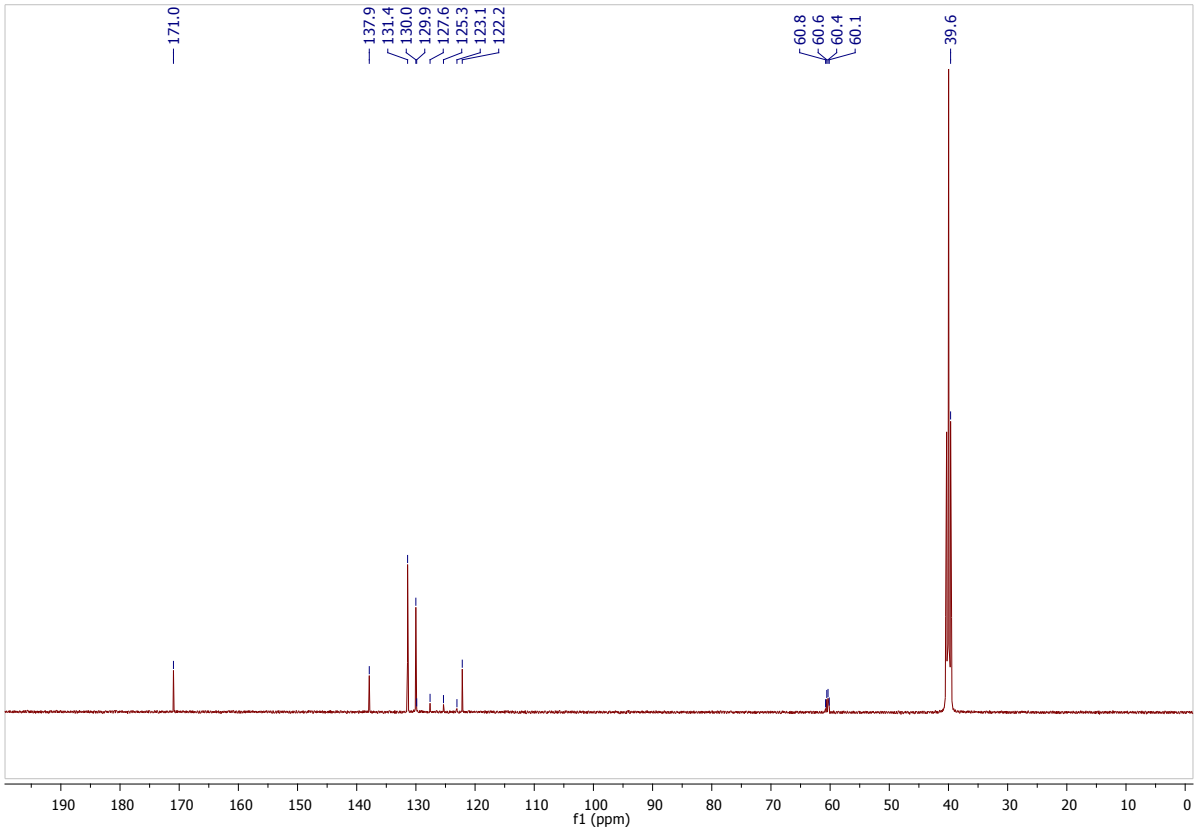


3-Amino-3-(4-bromophenyl)-4,4,4-trifluorobutanoic acid (4j)

^{1}H NMR (500 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

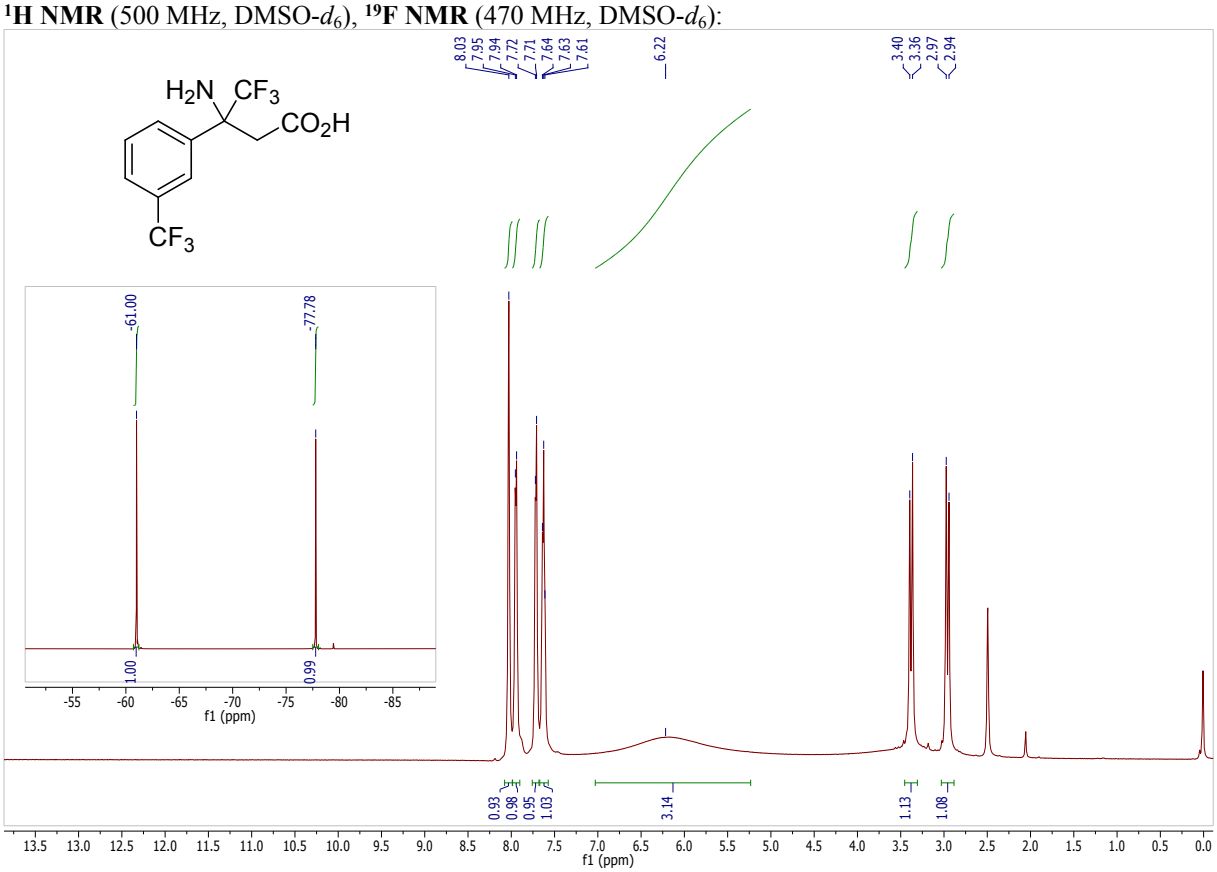


^{13}C NMR (126 MHz, DMSO-d_6):

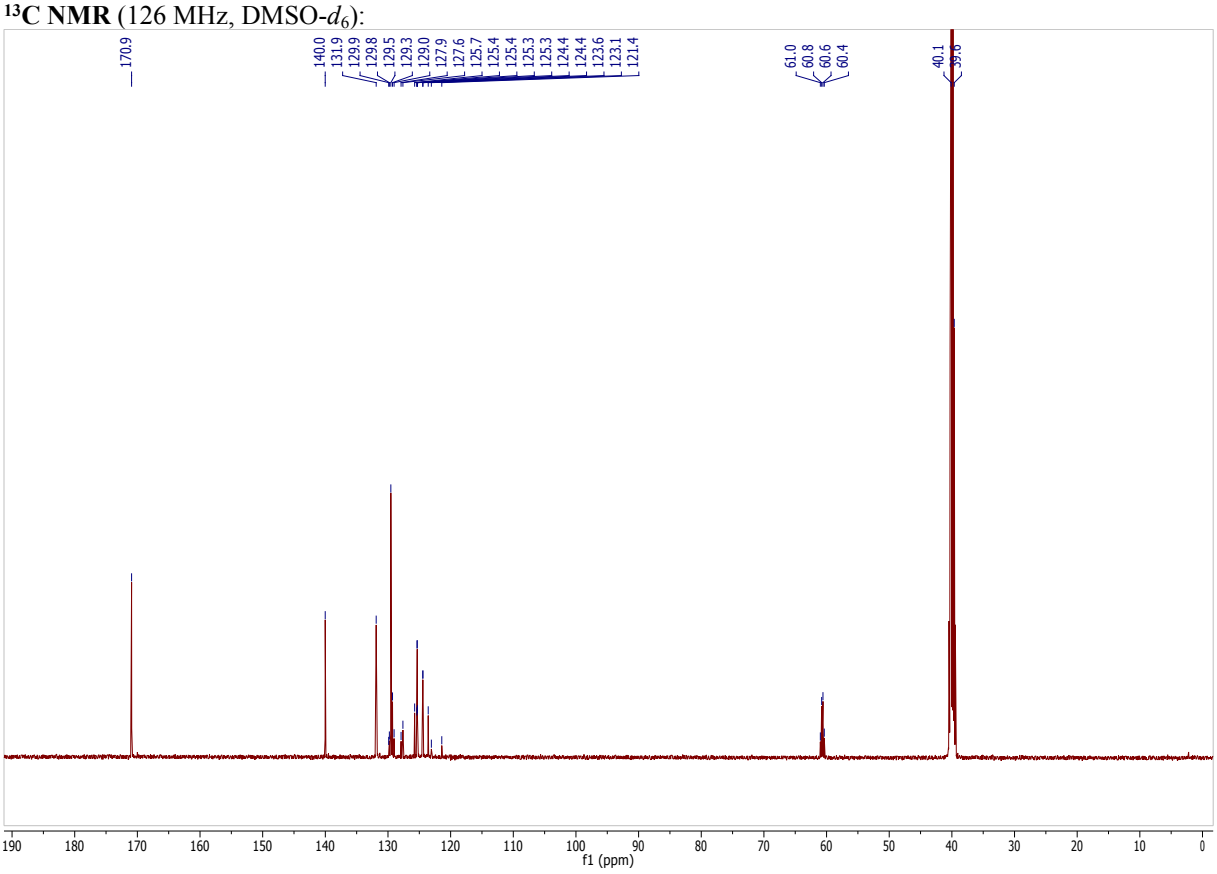


3-Amino-4,4,4-trifluoro-3-(3-(trifluoromethyl)phenyl)butanoic acid (4k)

^{1}H NMR (500 MHz, DMSO-d_6), **^{19}F NMR** (470 MHz, DMSO-d_6):

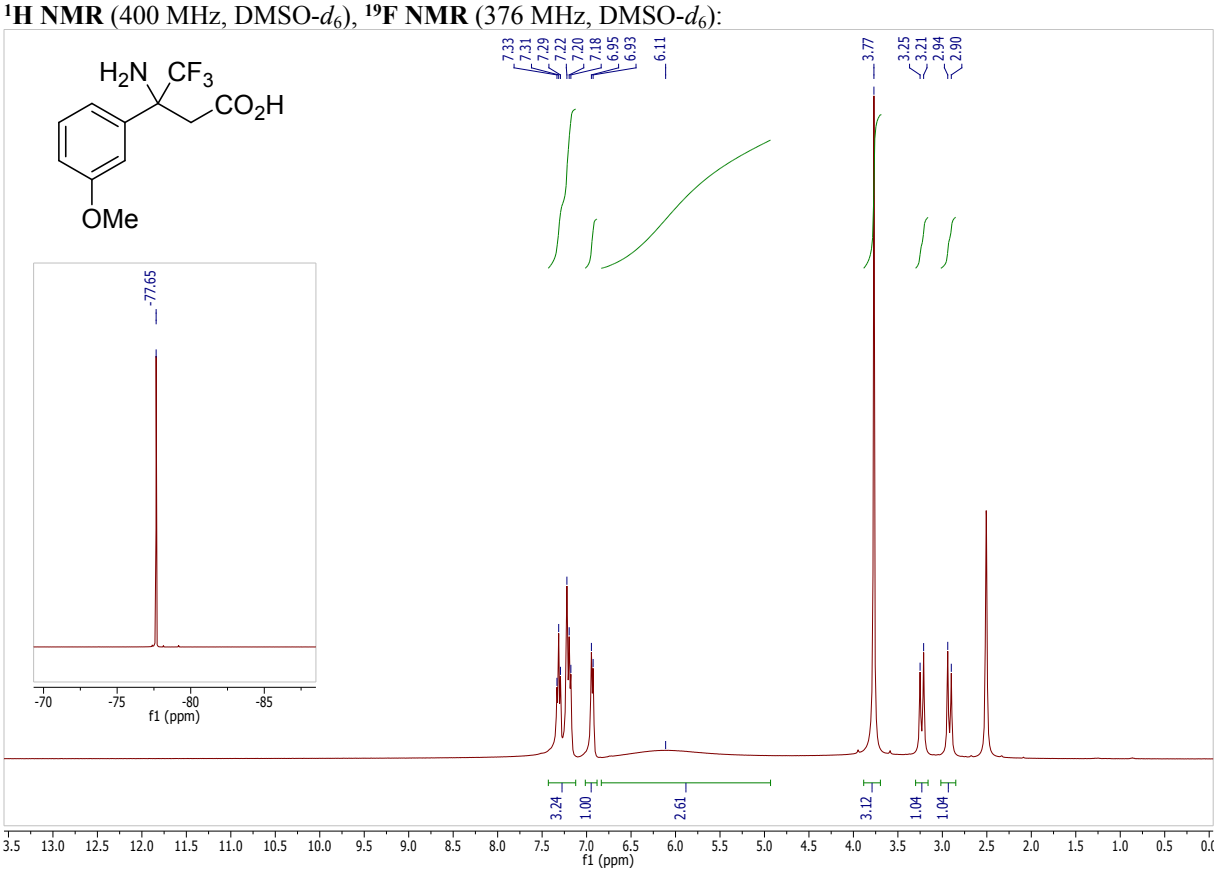


^{13}C NMR (126 MHz, DMSO-d_6):

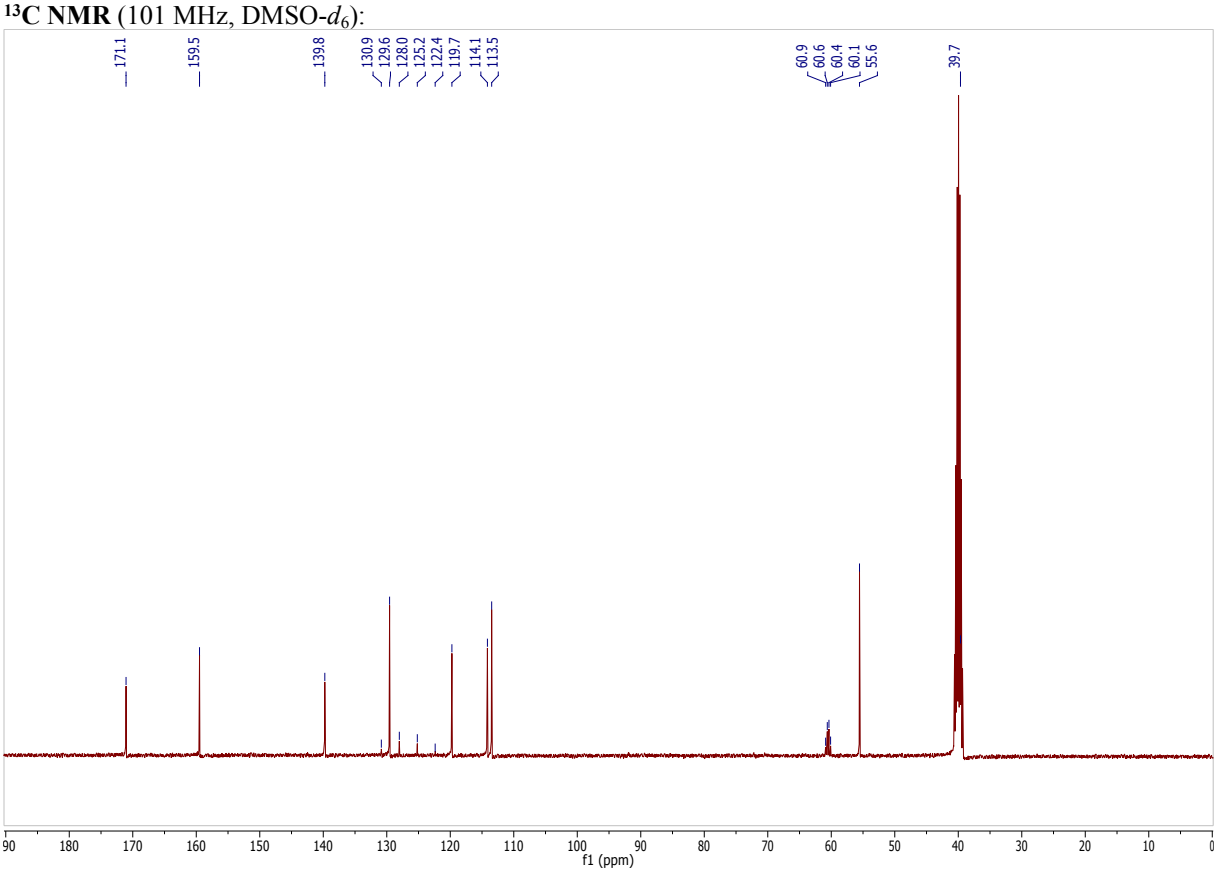


3-Amino-4,4,4-trifluoro-3-(3-methoxyphenyl)butanoic acid (4l)

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

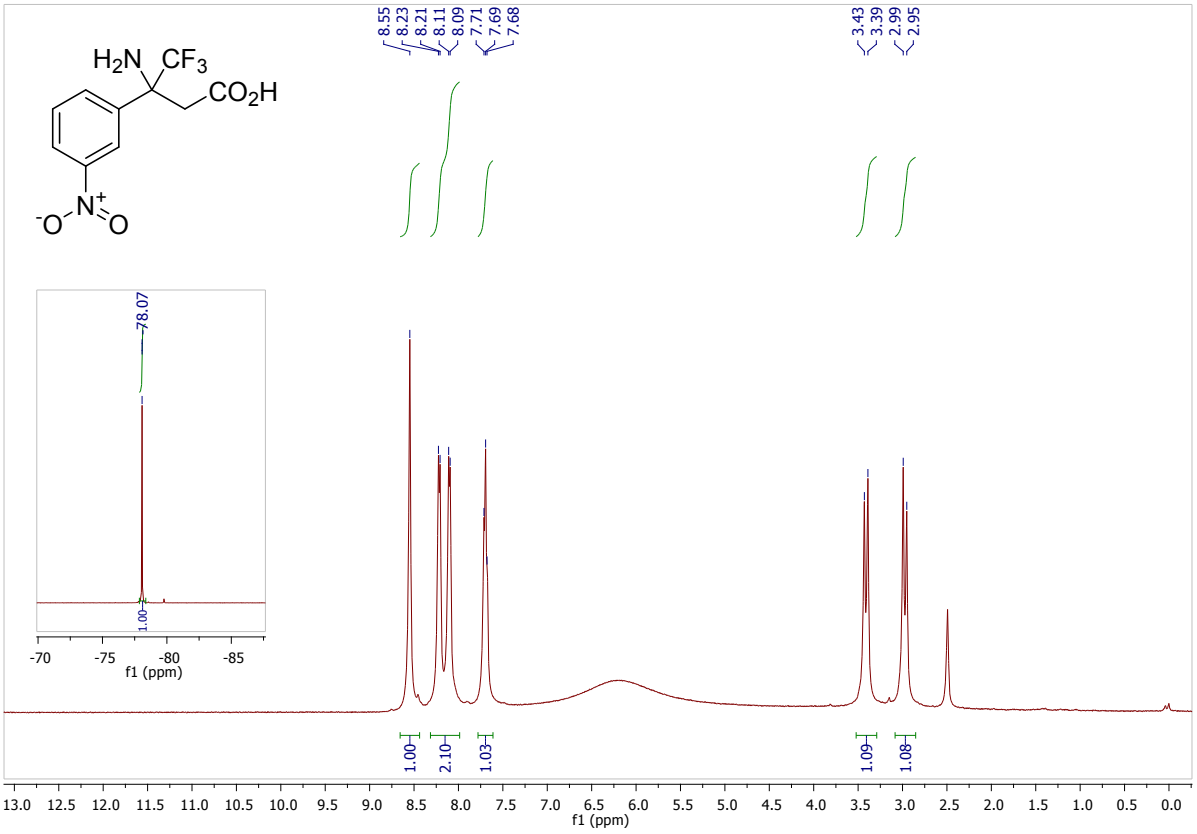


^{13}C NMR (101 MHz, DMSO-d_6):

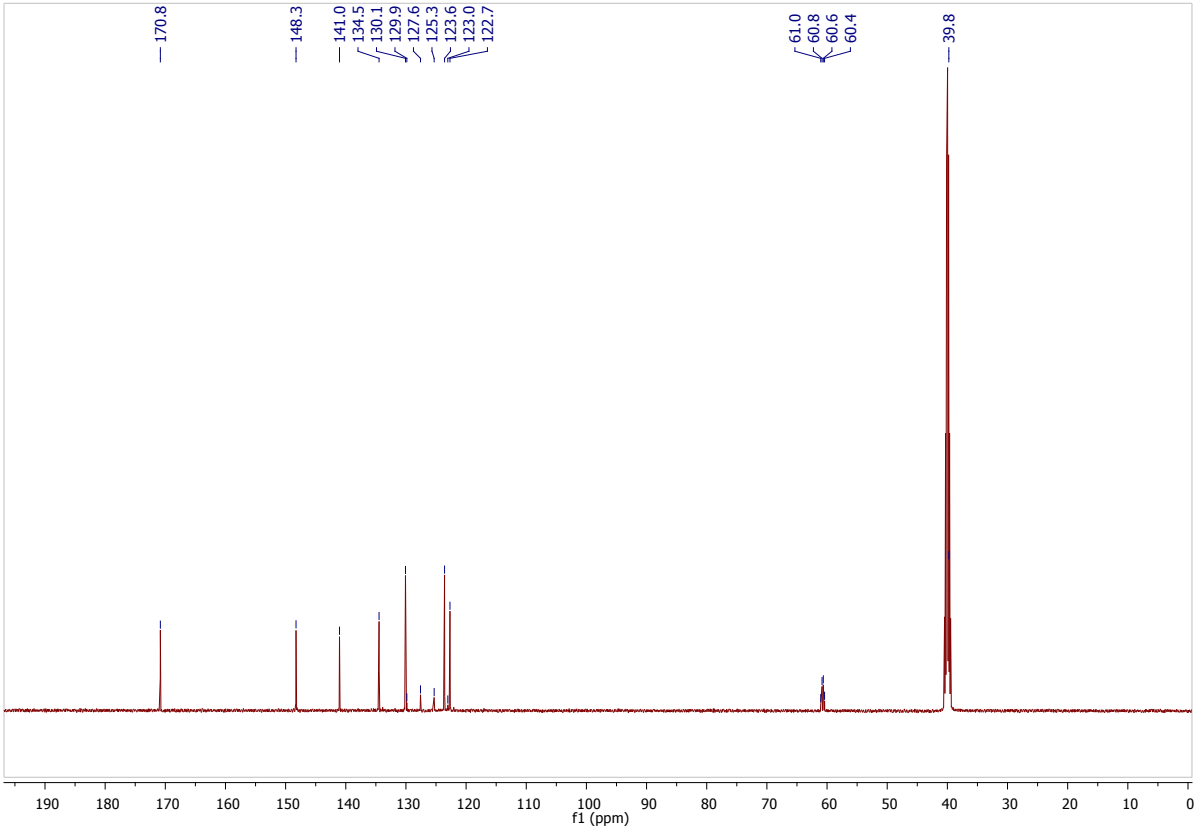


3-Amino-4,4,4-trifluoro-3-(3-nitrophenyl)butanoic acid (4m)

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

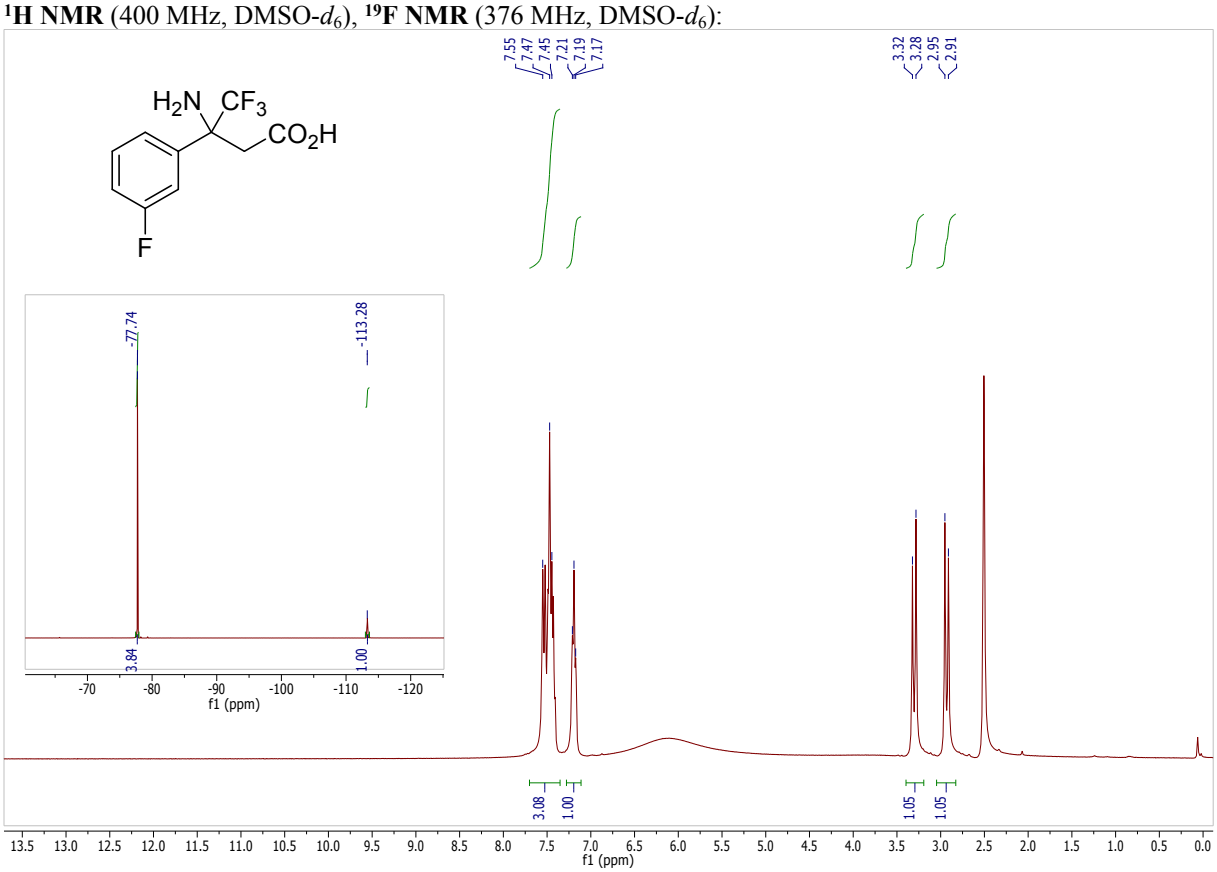


^{13}C NMR (126 MHz, DMSO-d_6):

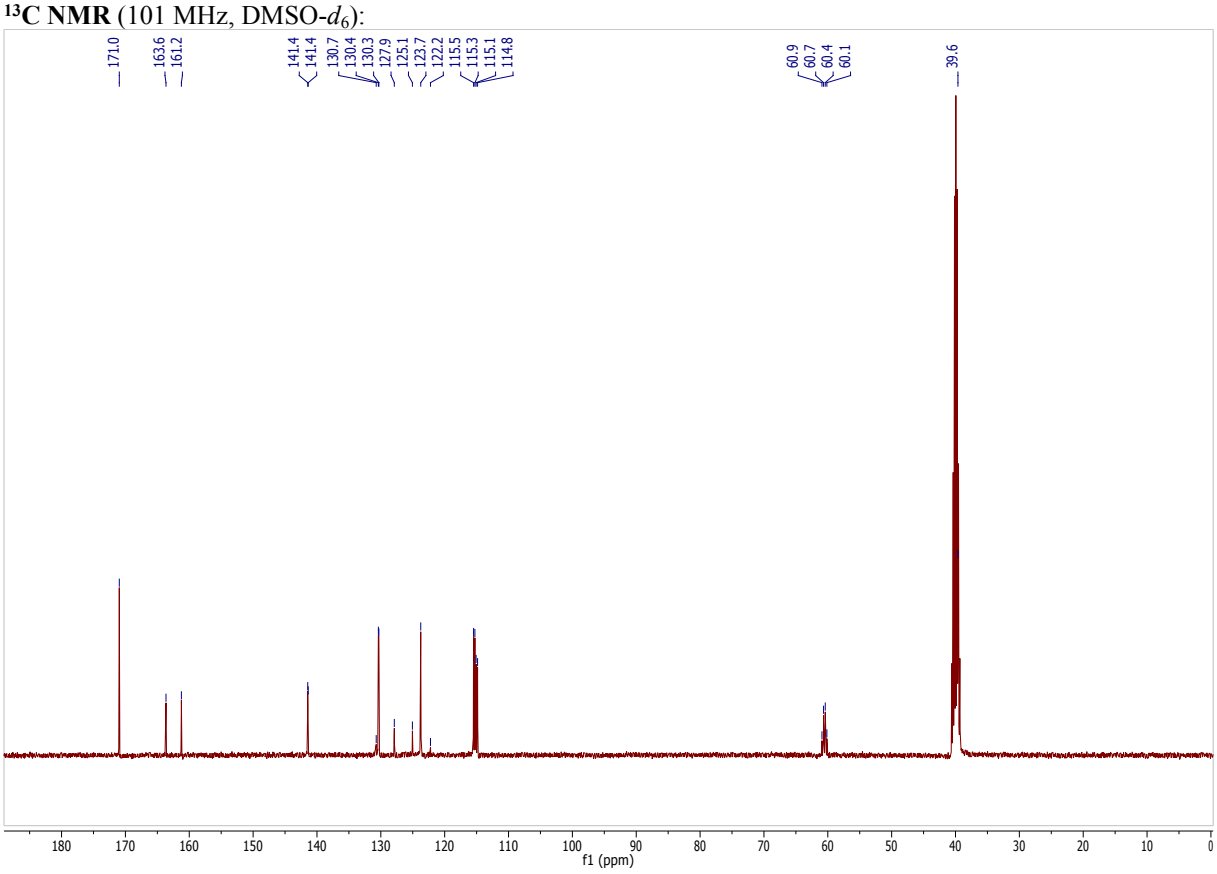


3-Amino-4,4,4-trifluoro-3-(3-fluorophenyl)butanoic acid (4n)

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

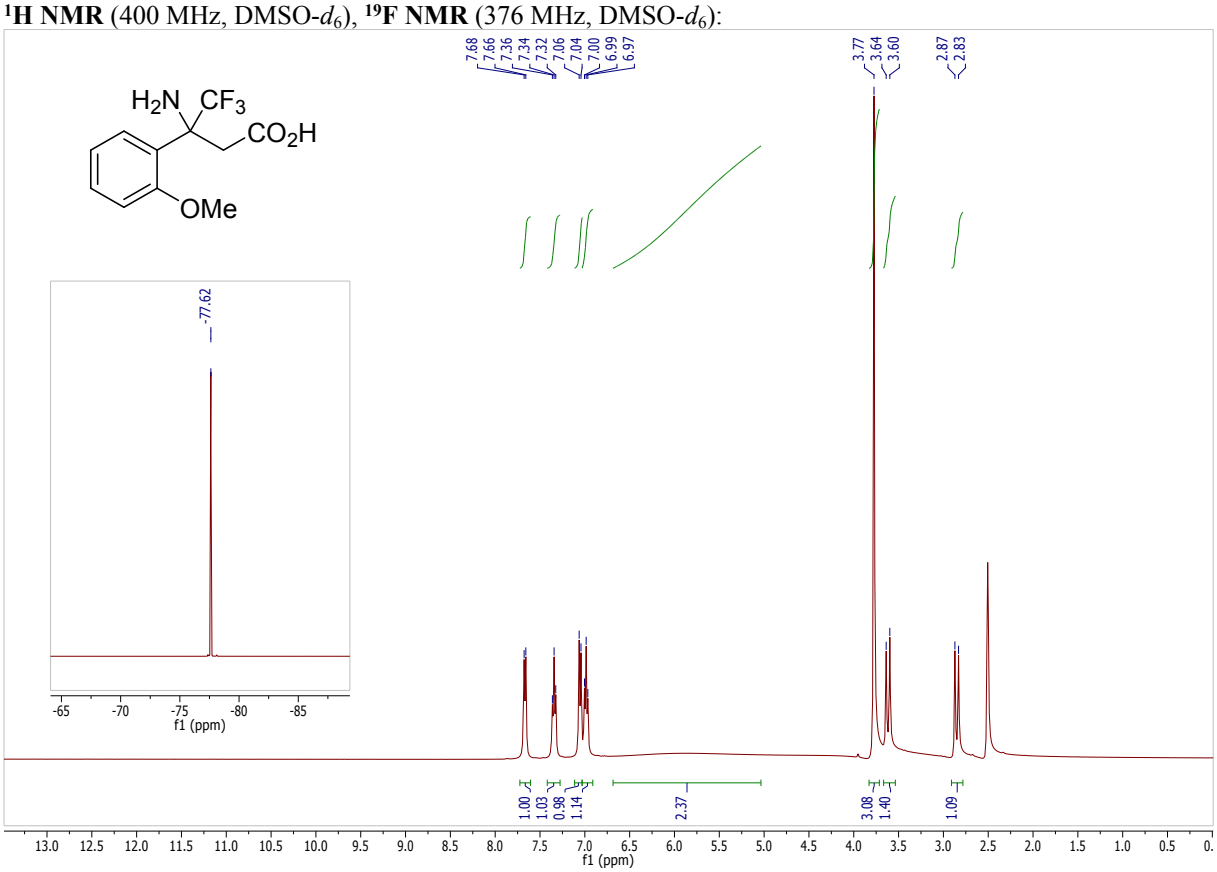


^{13}C NMR (101 MHz, DMSO-d_6):

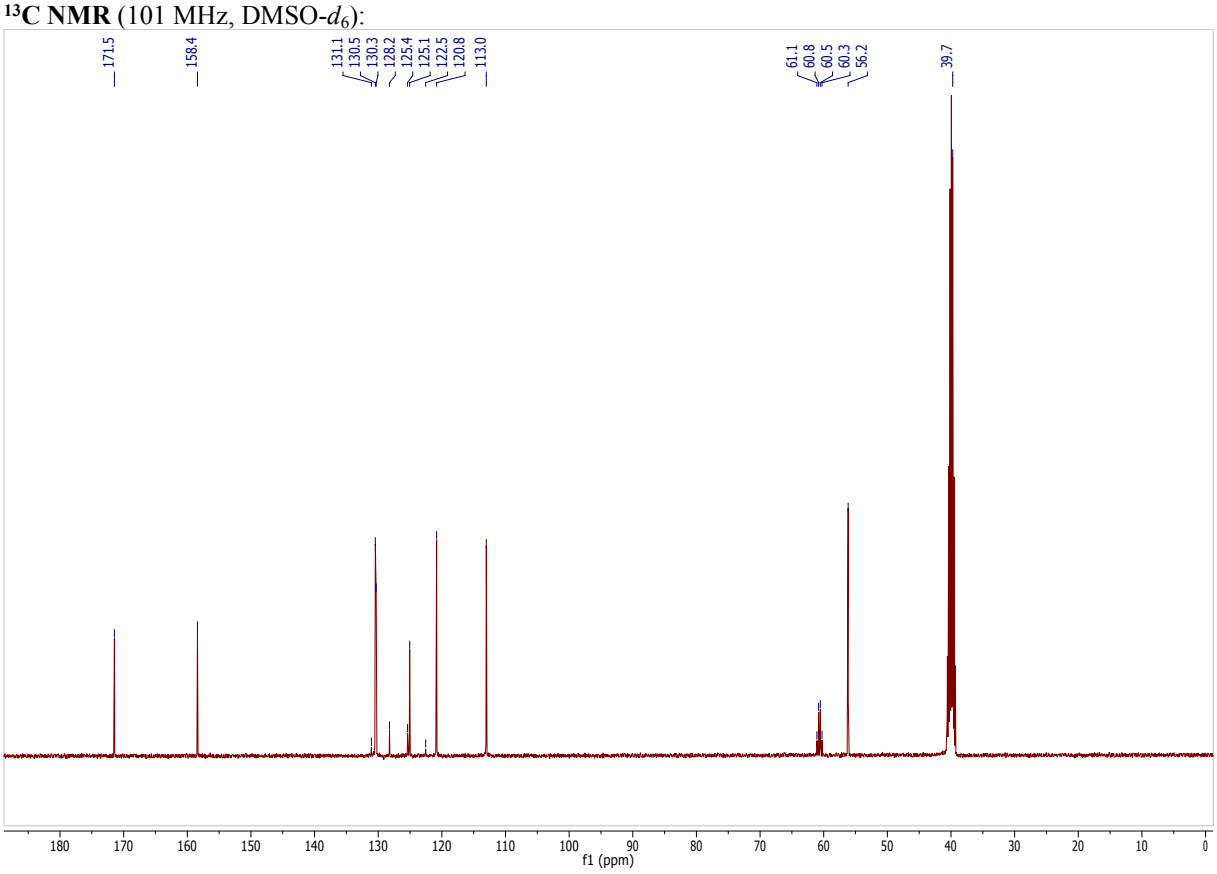


3-Amino-4,4,4-trifluoro-3-(2-methoxyphenyl)butanoic acid (4o)

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

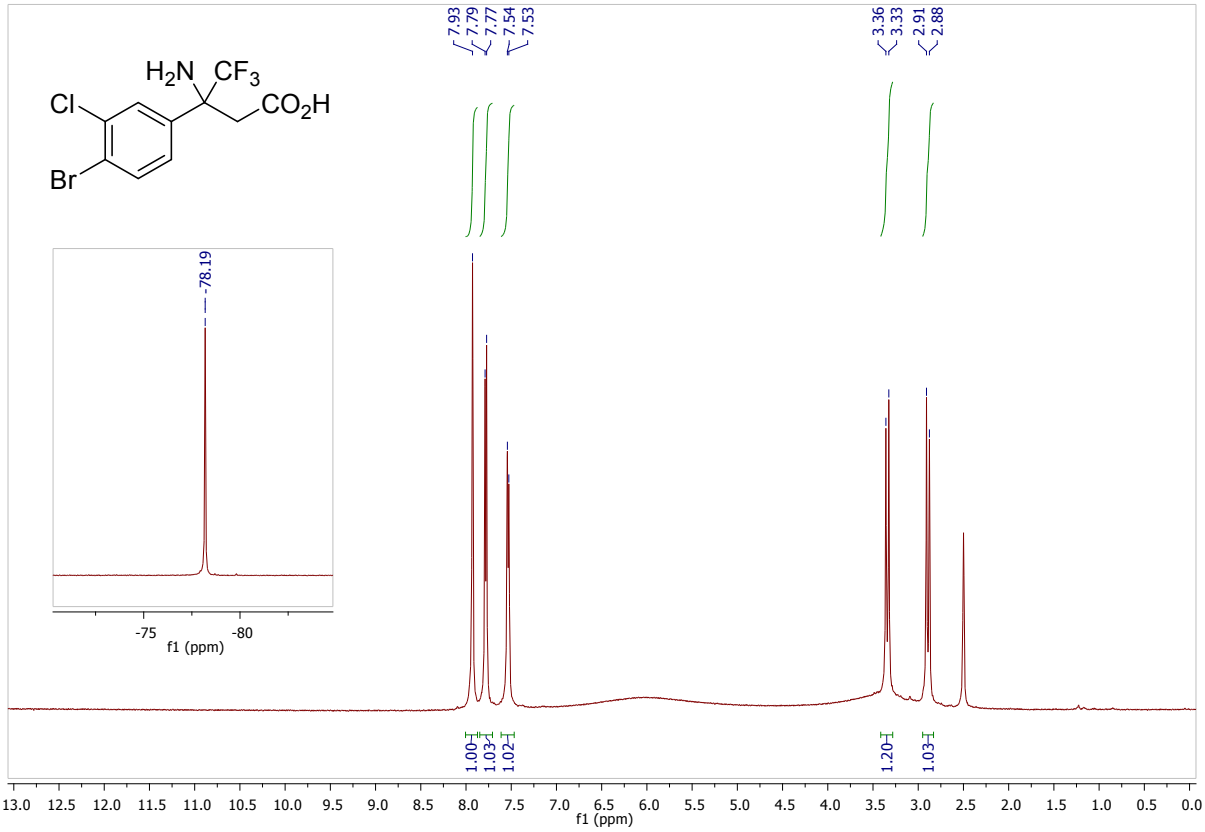


^{13}C NMR (101 MHz, DMSO-d_6):

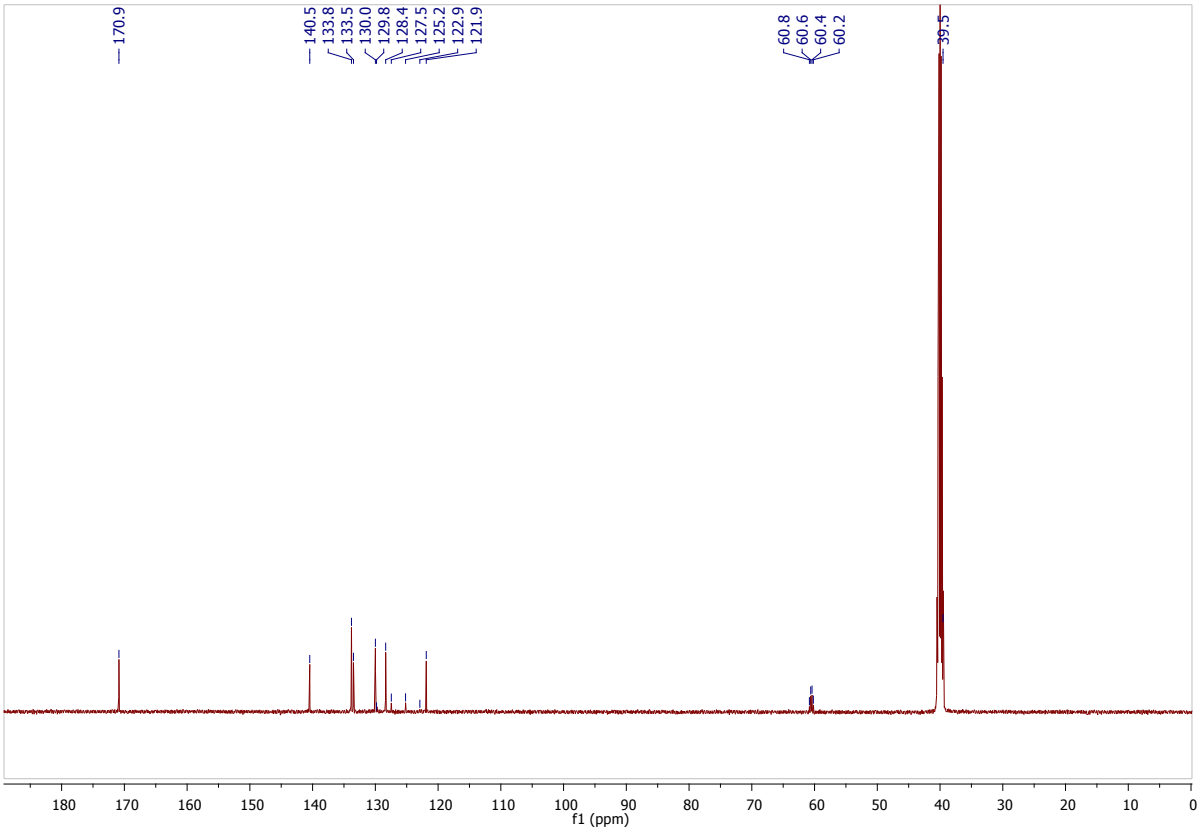


3-Amino-3-(4-bromo-3-chlorophenyl)-4,4,4-trifluorobutanoic acid (4p)

^{1}H NMR (500 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

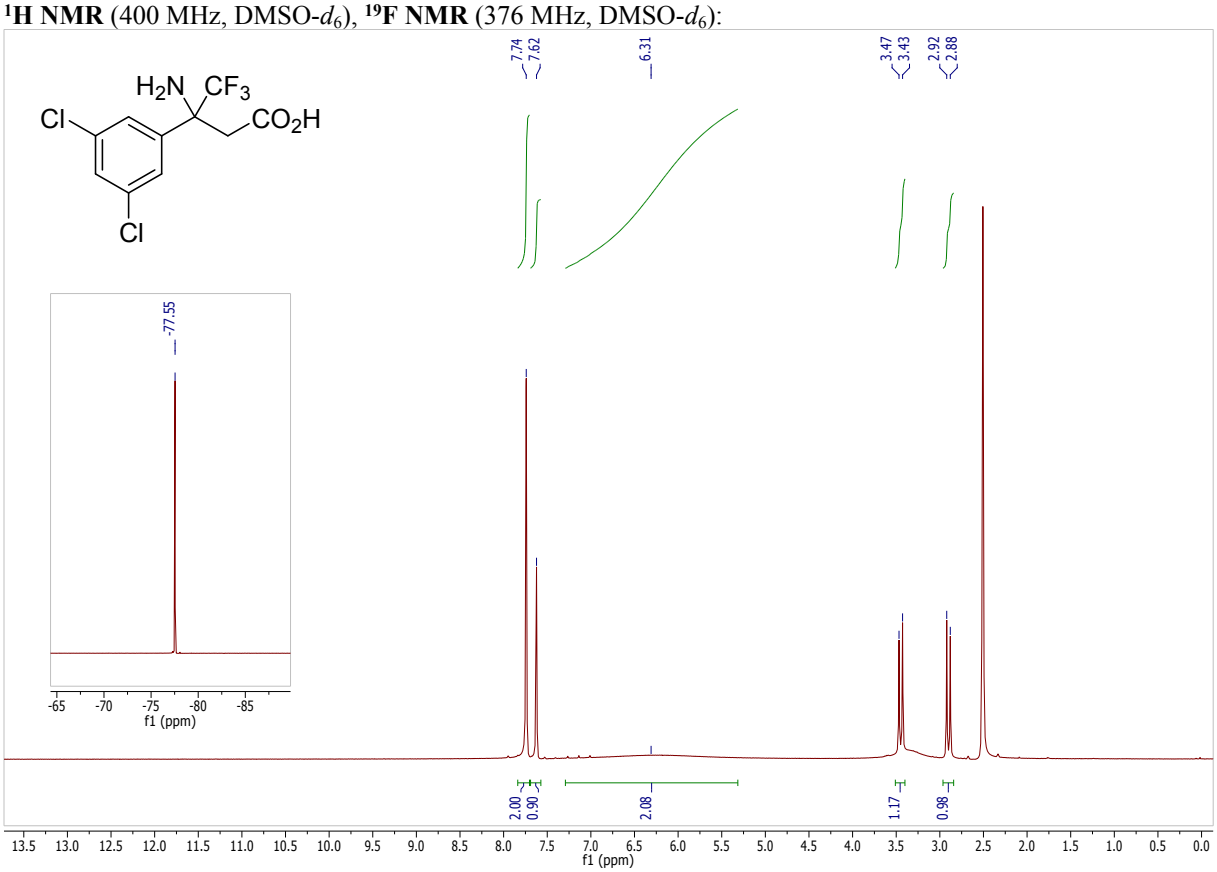


^{13}C NMR (126 MHz, DMSO-d_6):

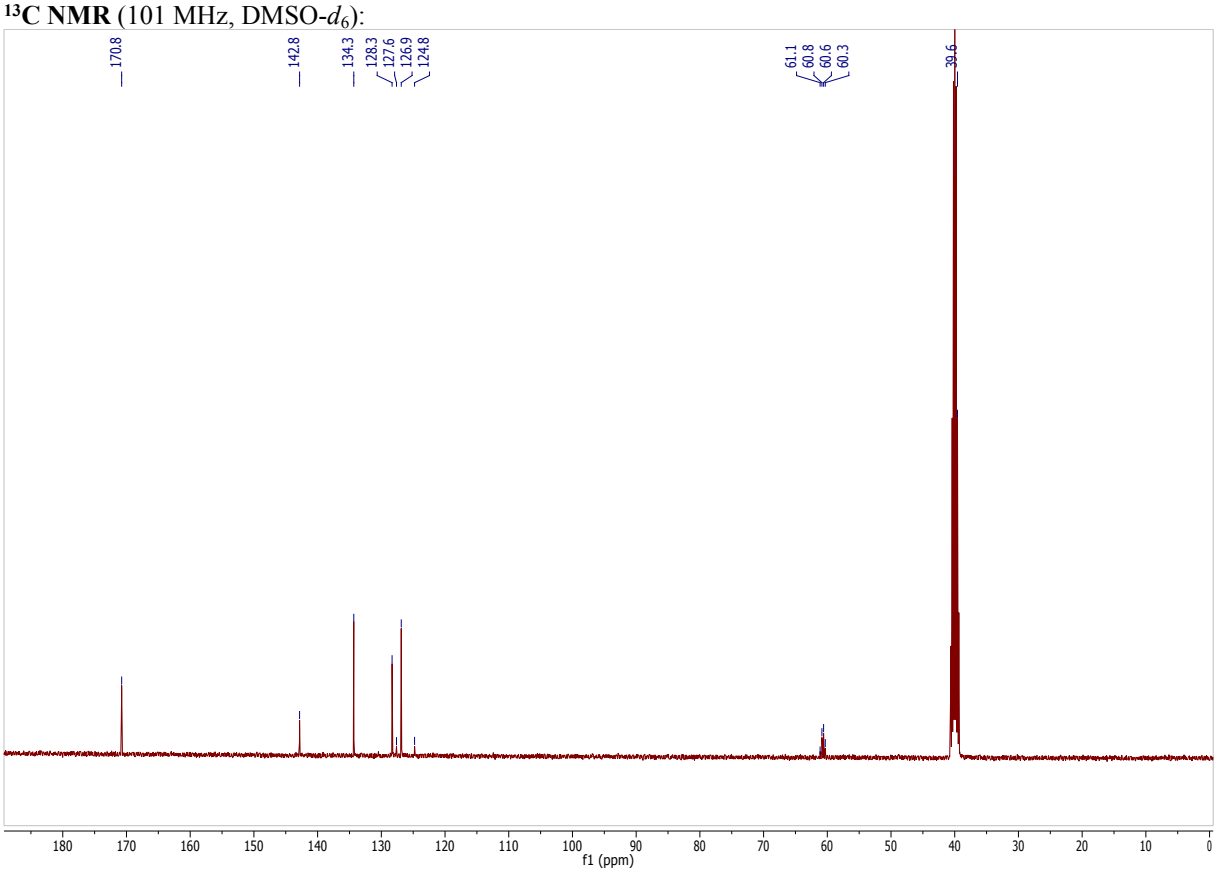


3-Amino-3-(3,5-dichlorophenyl)-4,4,4-trifluorobutanoic acid (4q)

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

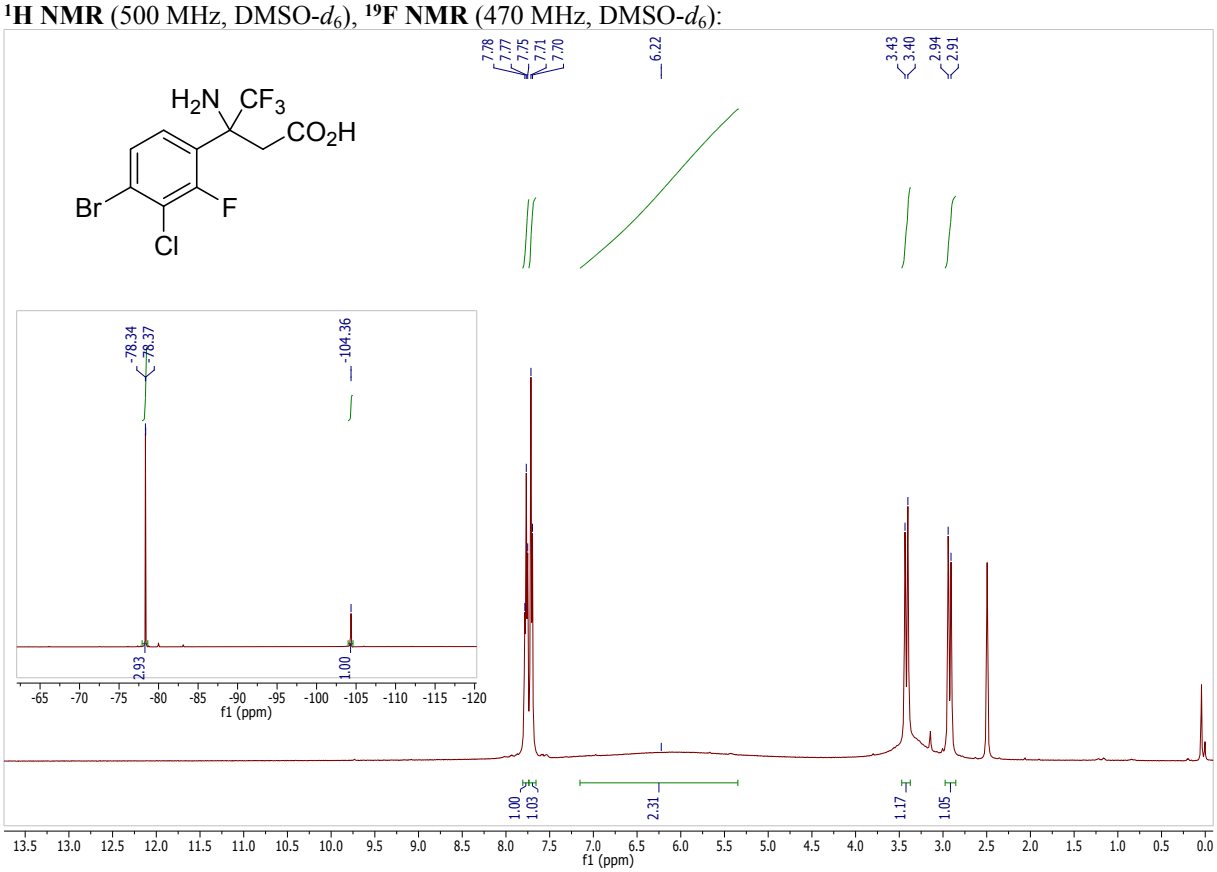


^{13}C NMR (101 MHz, DMSO-d_6):

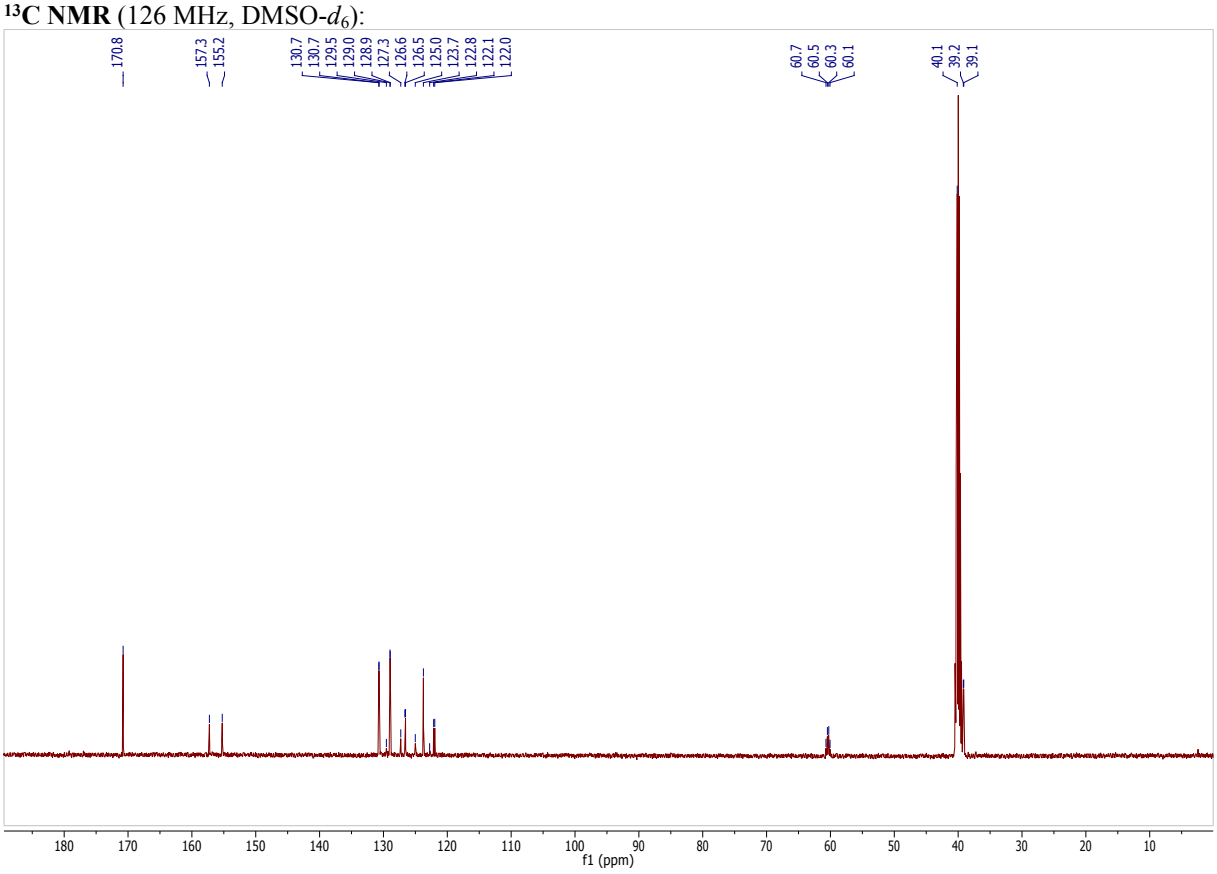


3-Amino-3-(4-bromo-3-chloro-2-fluorophenyl)-4,4,4-trifluorobutanoic acid (4r)

^{1}H NMR (500 MHz, DMSO-d_6), **^{19}F NMR** (470 MHz, DMSO-d_6):

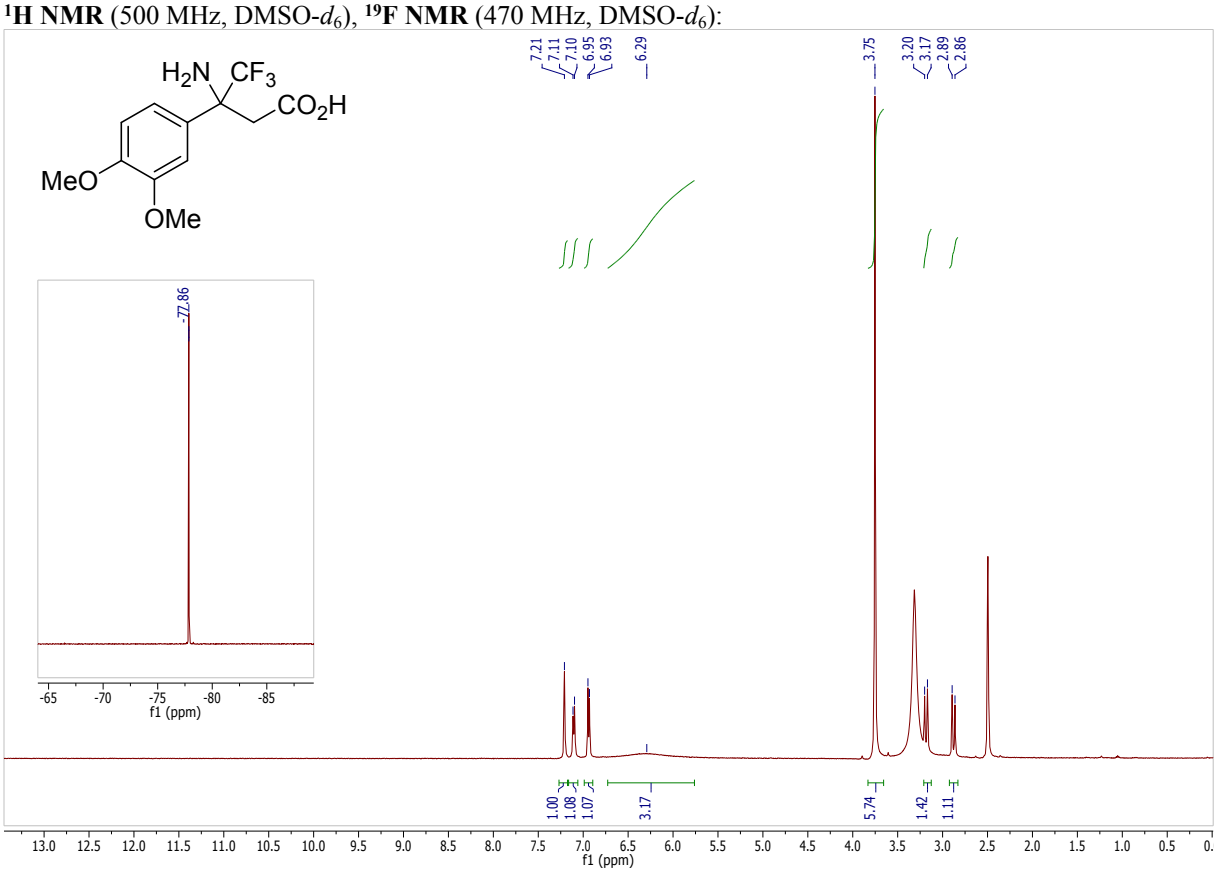


^{13}C NMR (126 MHz, DMSO-d_6):

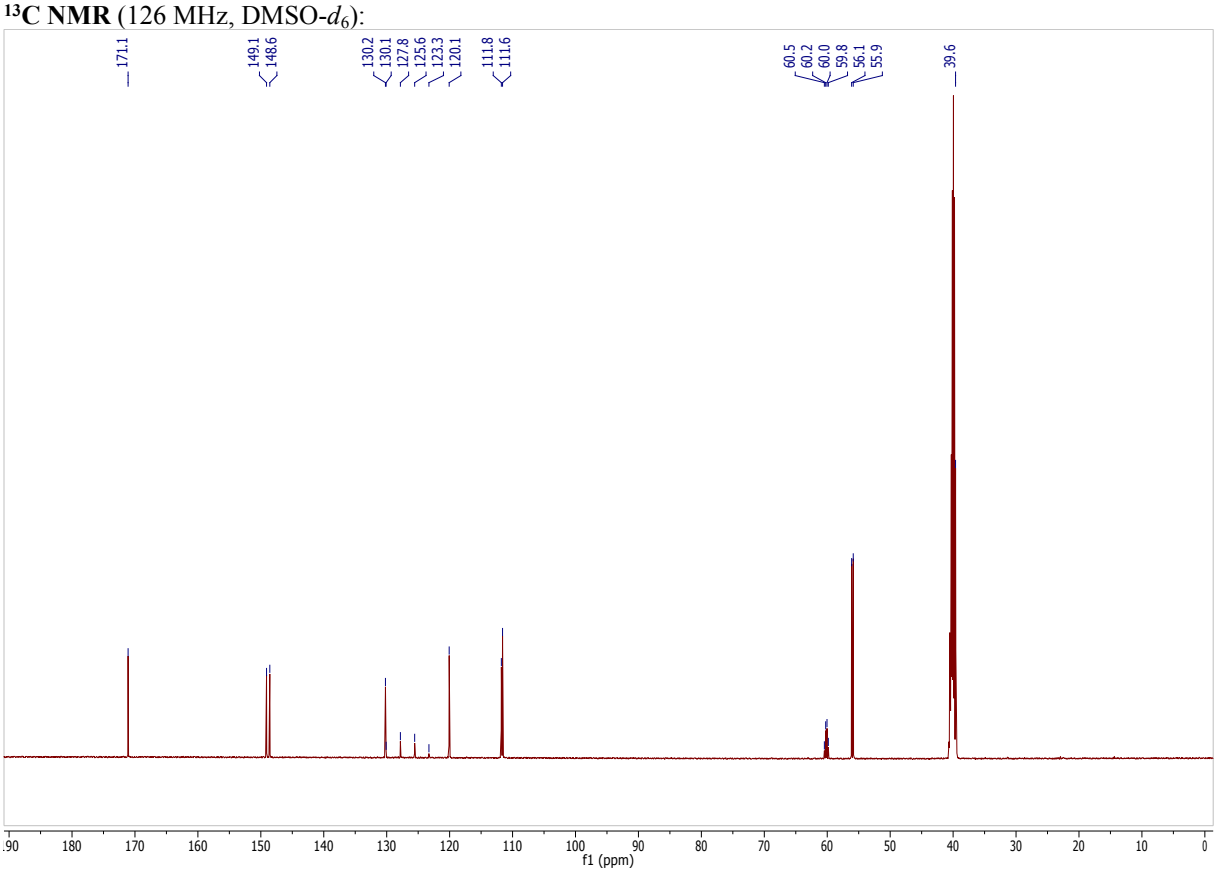


3-Amino-3-(3,4-dimethoxyphenyl)-4,4,4-trifluorobutanoic acid (4s)

^{1}H NMR (500 MHz, DMSO-d_6), **^{19}F NMR** (470 MHz, DMSO-d_6):

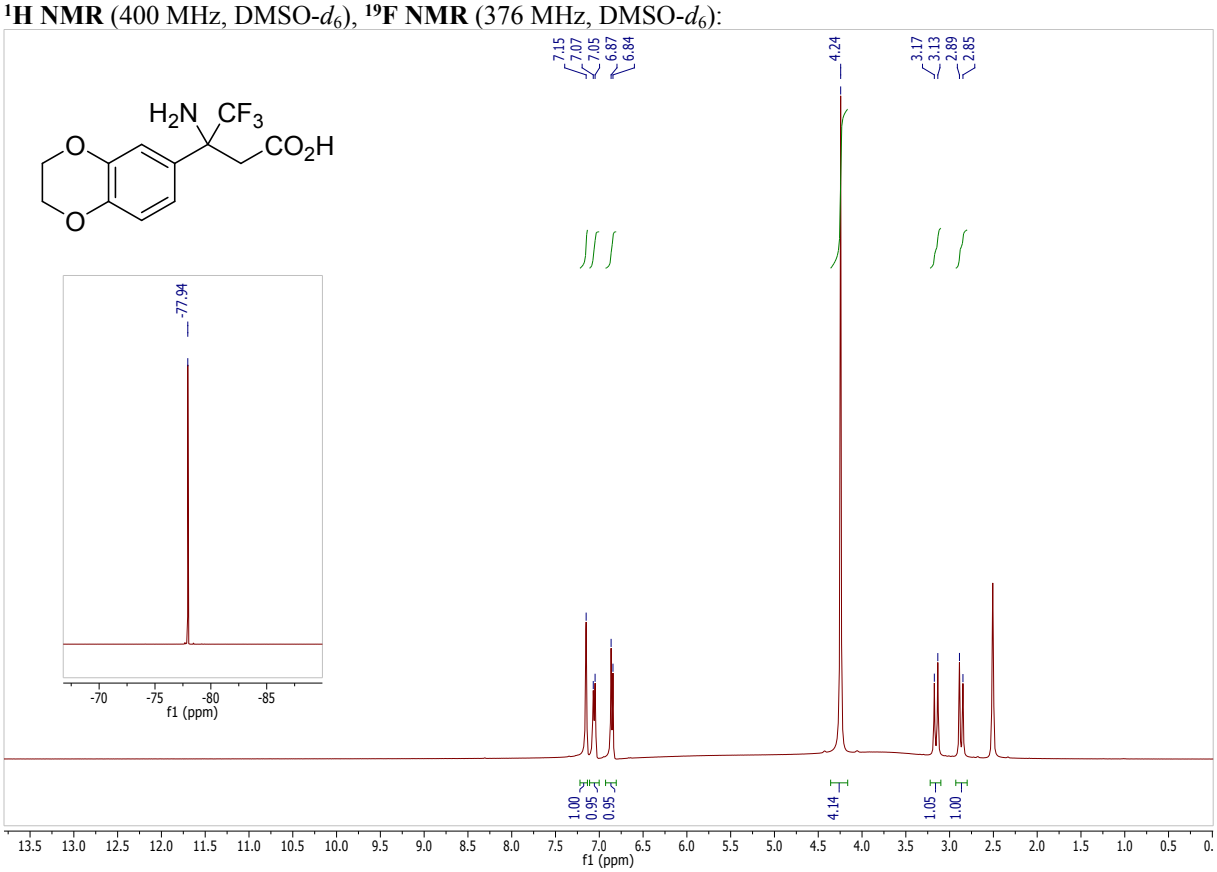


^{13}C NMR (126 MHz, DMSO-d_6):

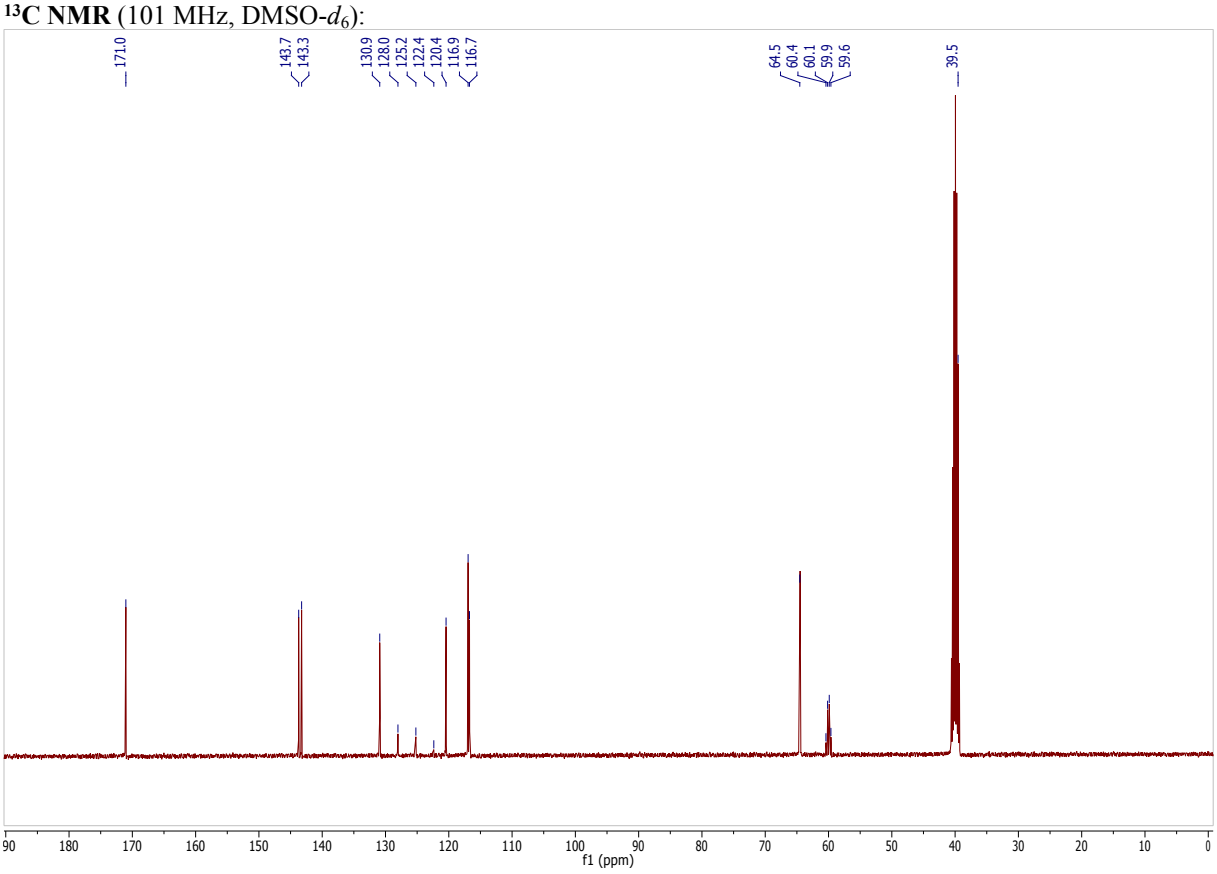


3-Amino-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-4,4,4-trifluorobutanoic acid (4t)

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

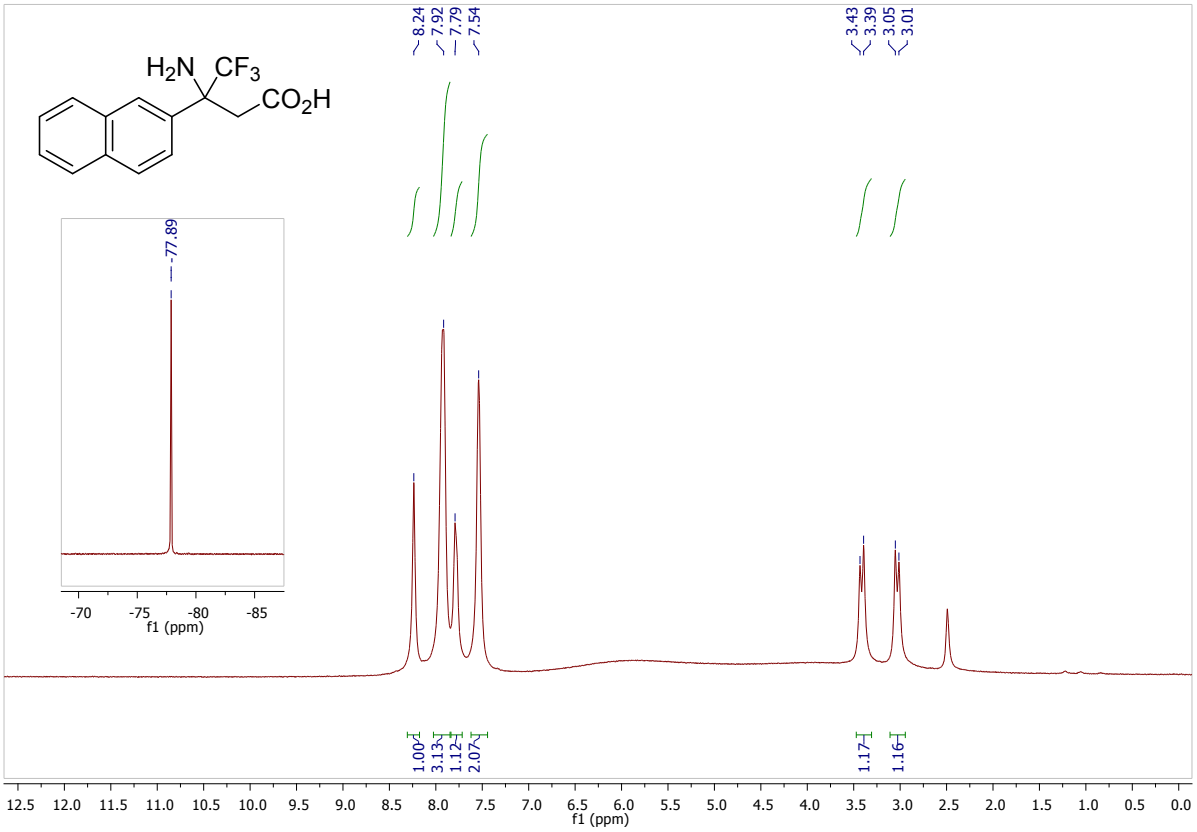


^{13}C NMR (101 MHz, DMSO-d_6):

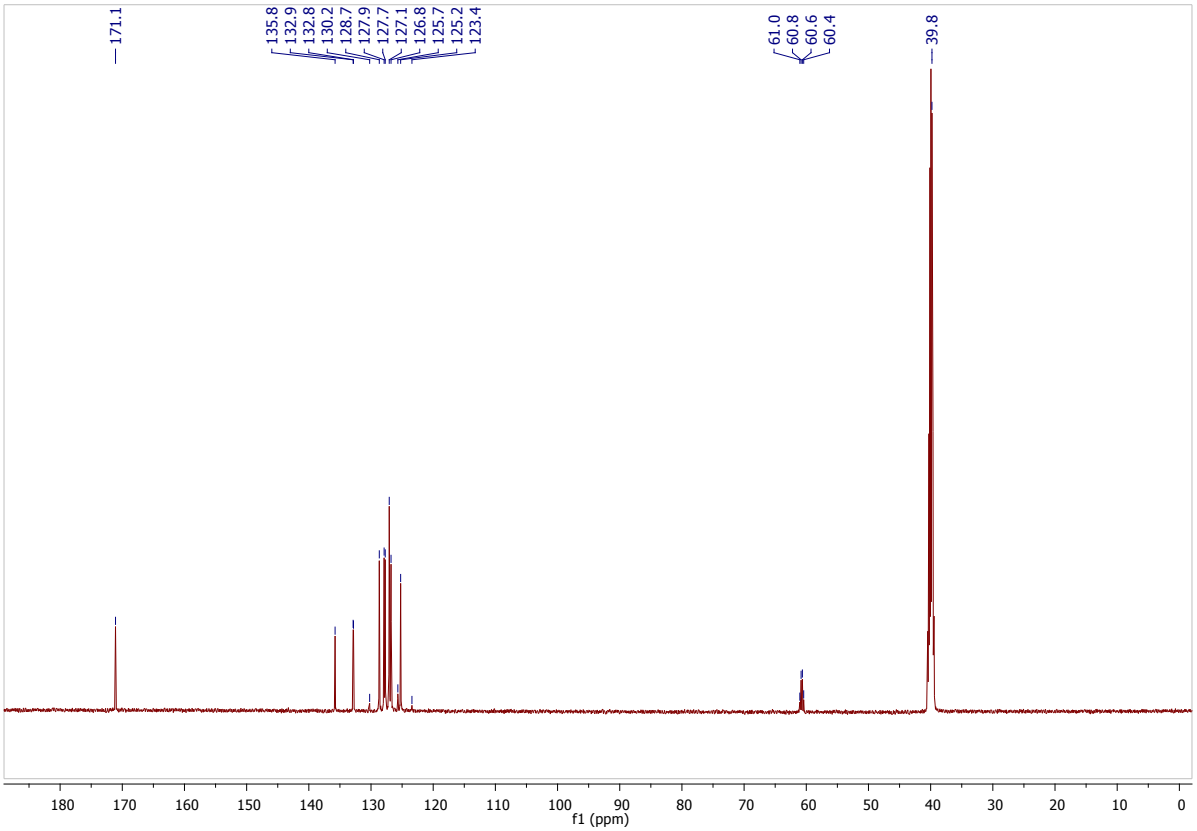


3-Amino-4,4,4-trifluoro-3-(naphthalen-2-yl)butanoic acid (4u)

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

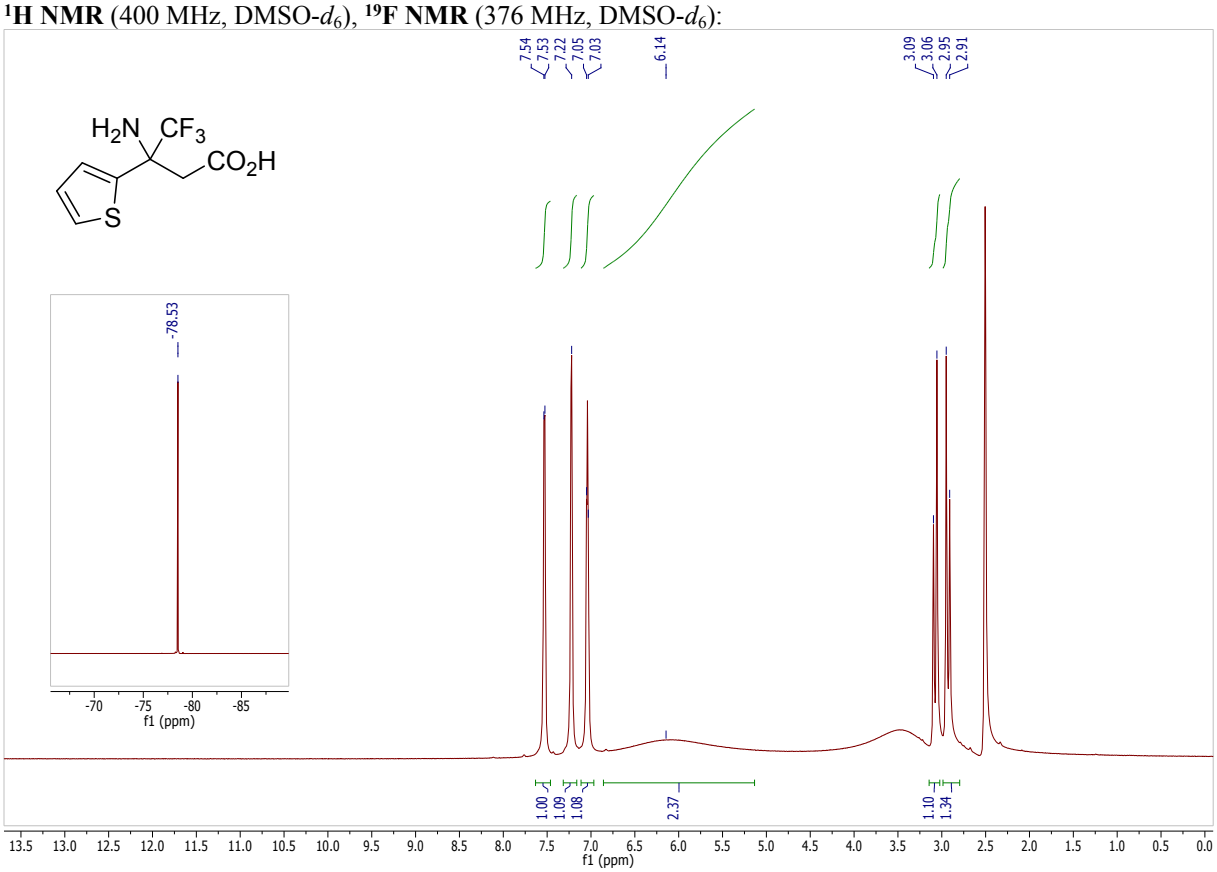


^{13}C NMR (126 MHz, DMSO-d_6):

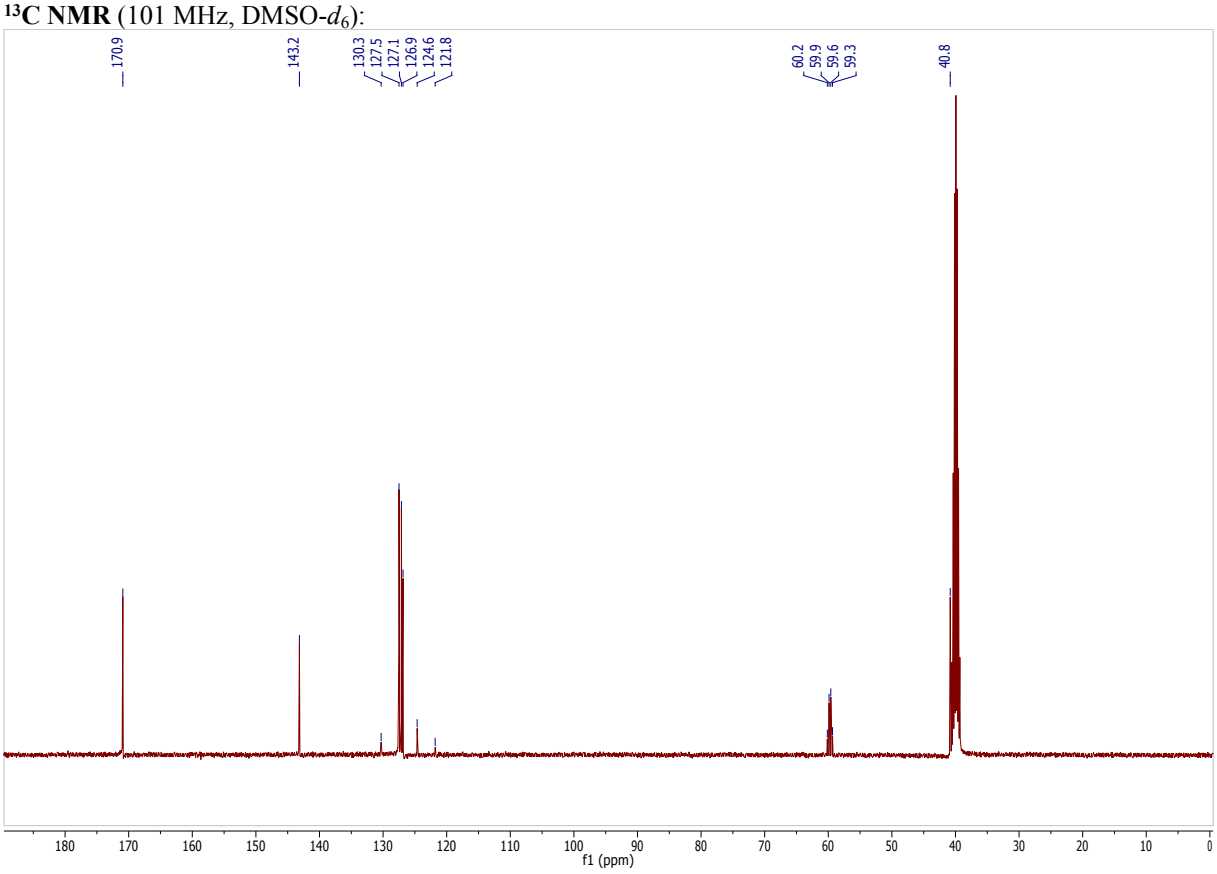


3-Amino-4,4,4-trifluoro-3-(thiophen-2-yl)butanoic acid (4v)

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

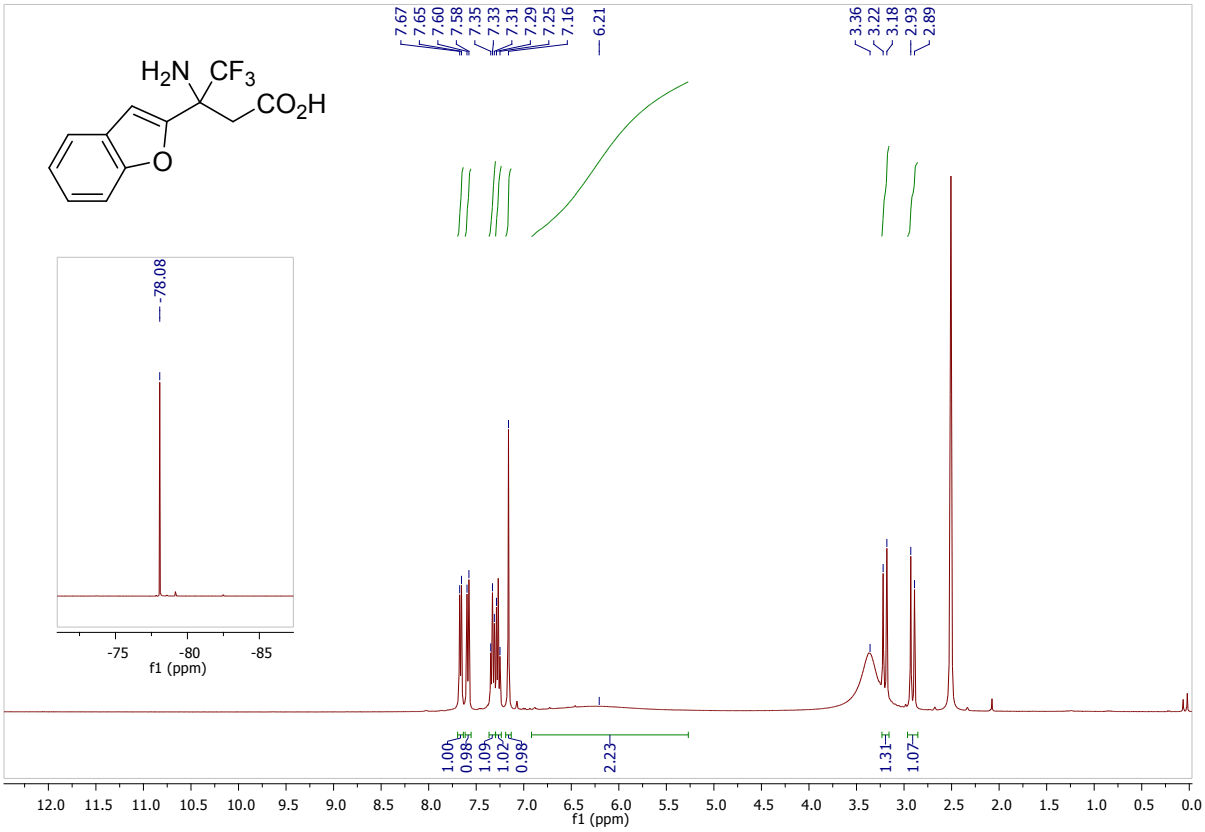


^{13}C NMR (101 MHz, DMSO-d_6):

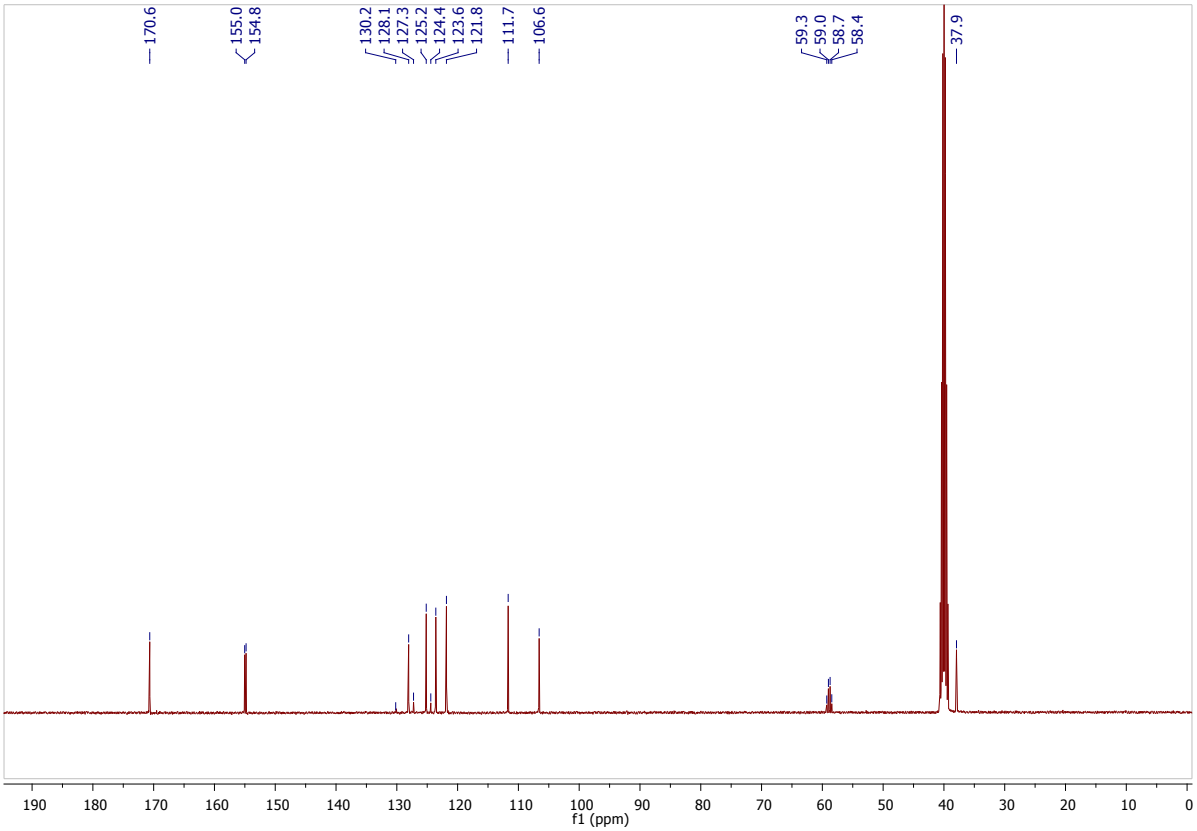


3-Amino-3-(benzofuran-2-yl)-4,4,4-trifluorobutanoic acid (4w)

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

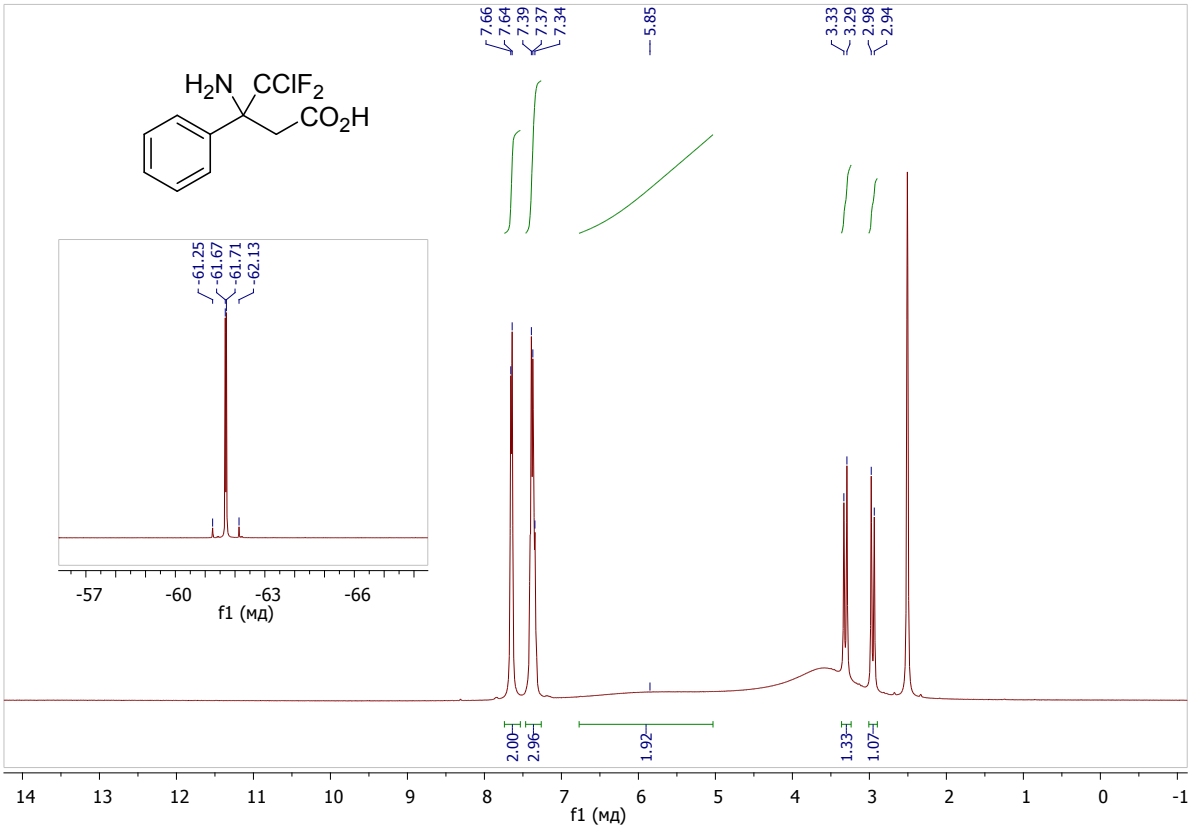


^{13}C NMR (101 MHz, DMSO-d_6):

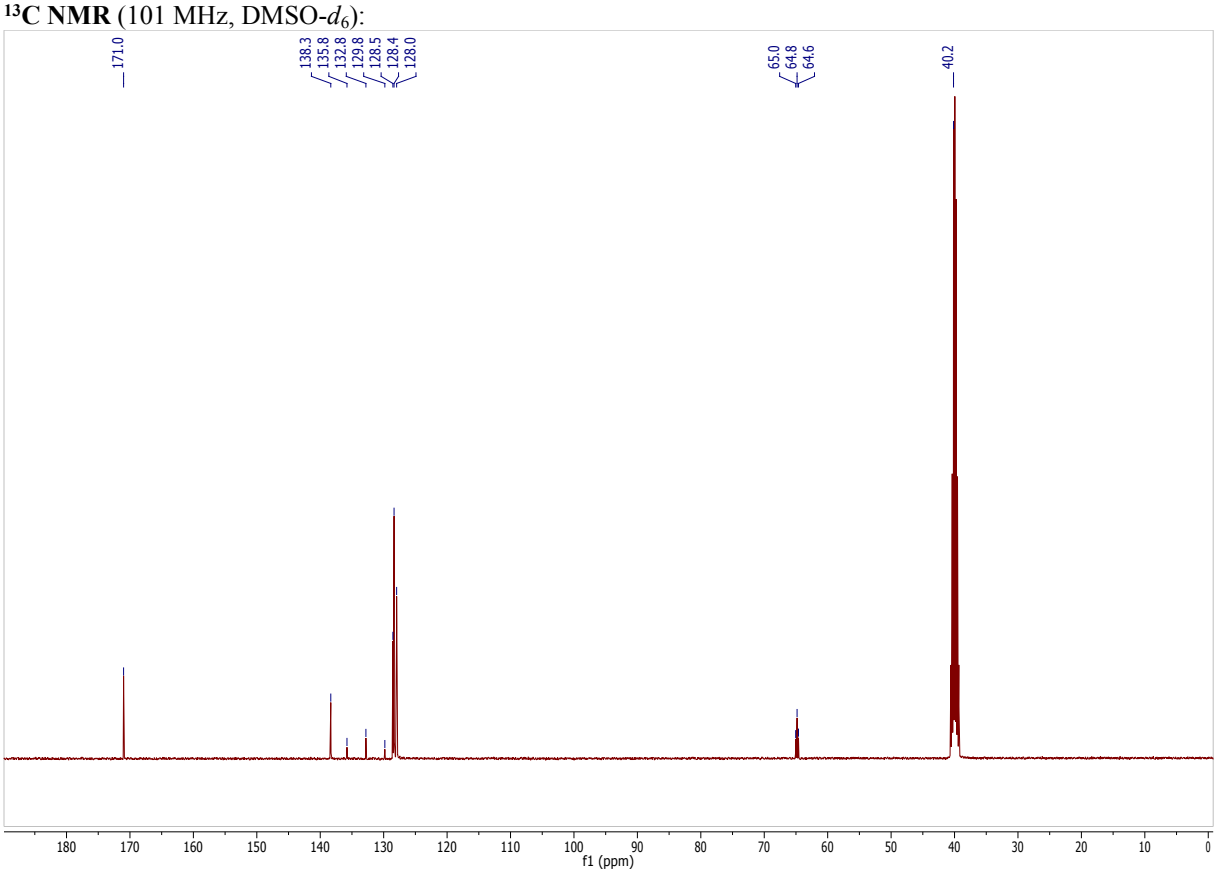


3-Amino-4-chloro-4,4-difluoro-3-phenylbutanoic acid (4x)

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

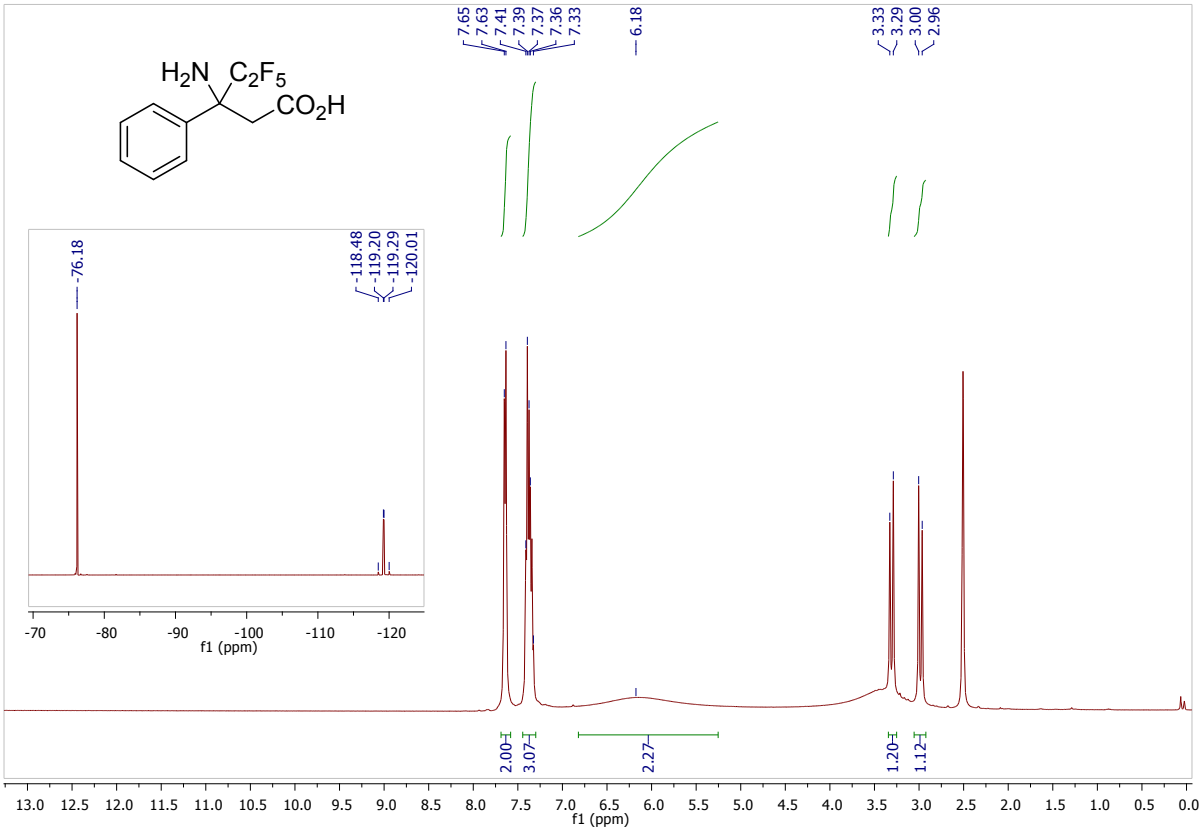


^{13}C NMR (101 MHz, DMSO-d_6):

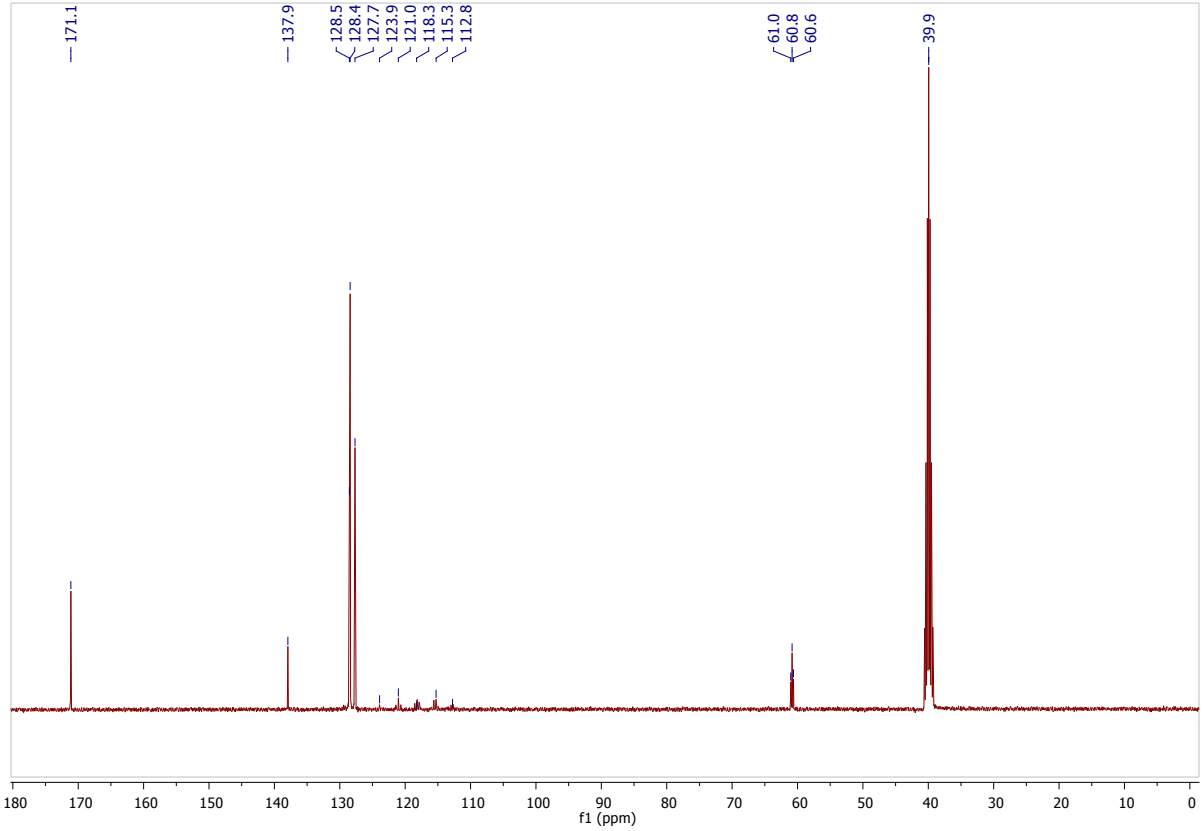


3-Amino-4,4,5,5,5-pentafluoro-3-phenylpentanoic acid (4y)

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

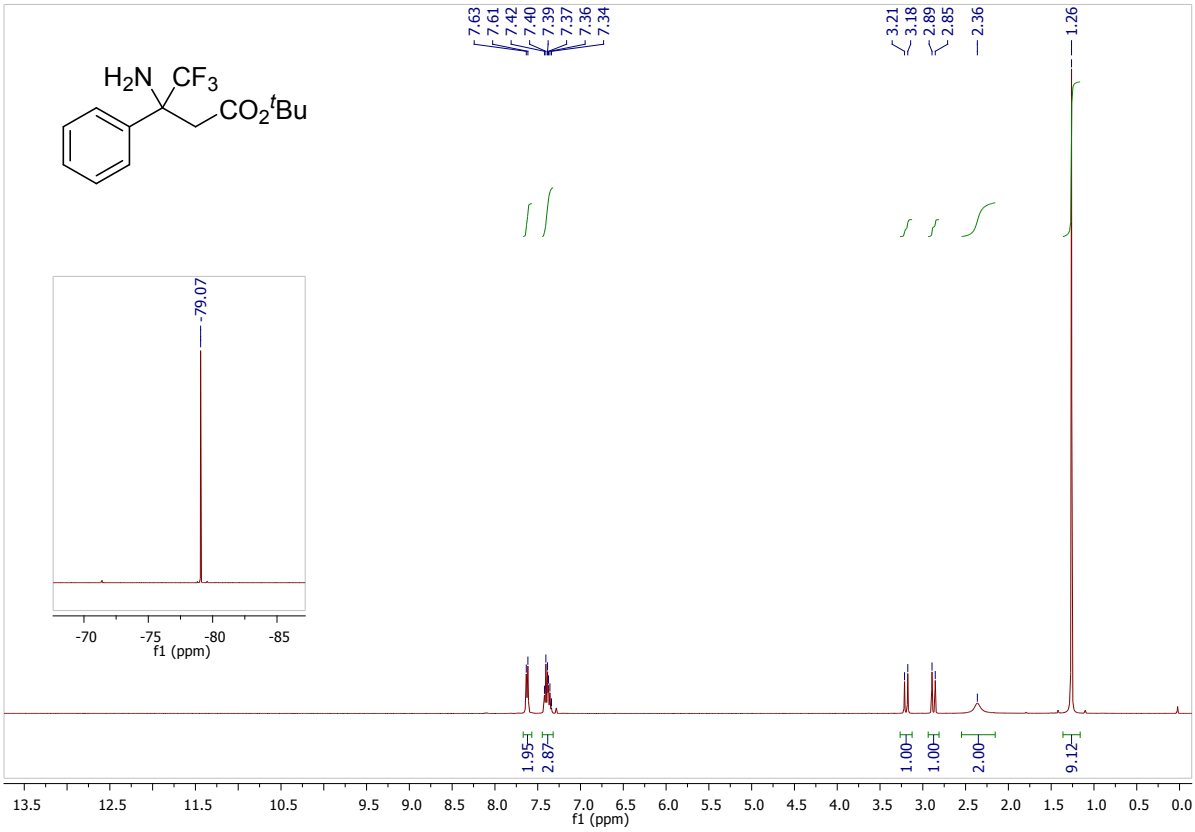


^{13}C NMR (101 MHz, DMSO-d_6):

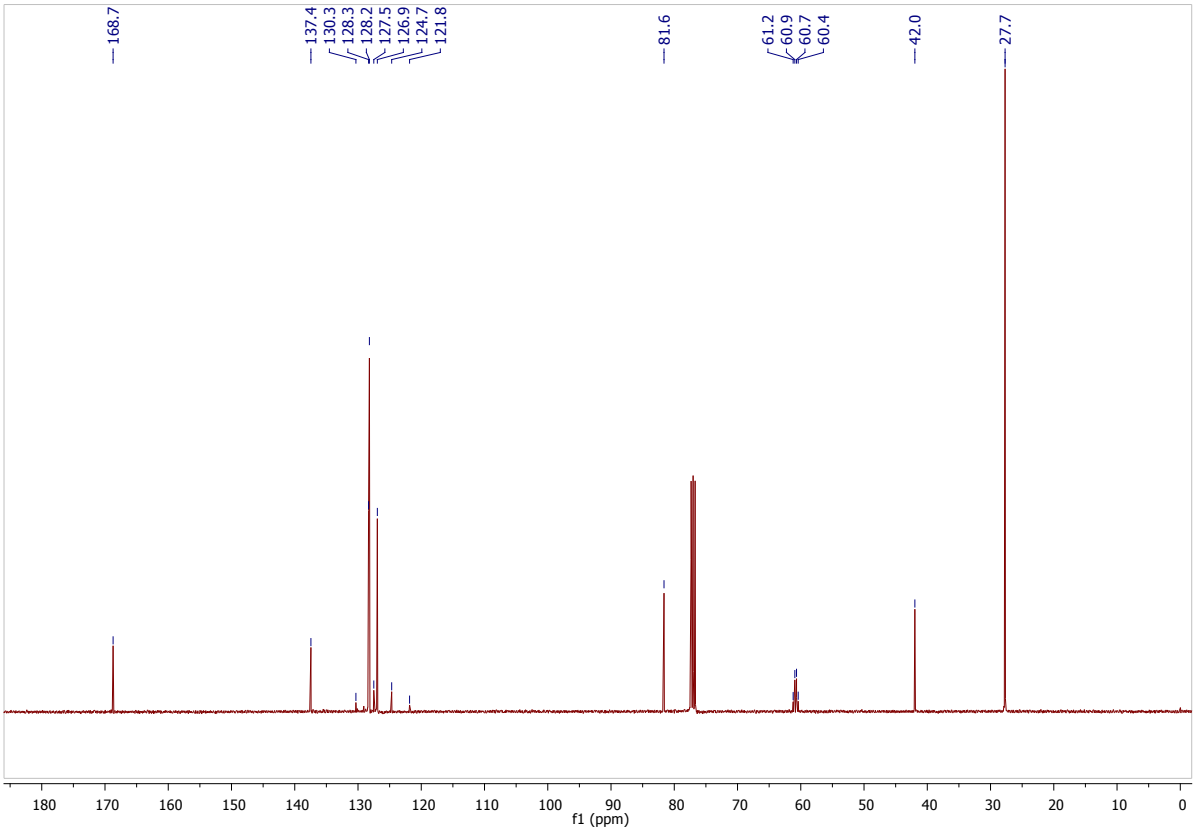


tert-Butyl 3-amino-4,4,4-trifluoro-3-phenylbutanoate (6a)

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

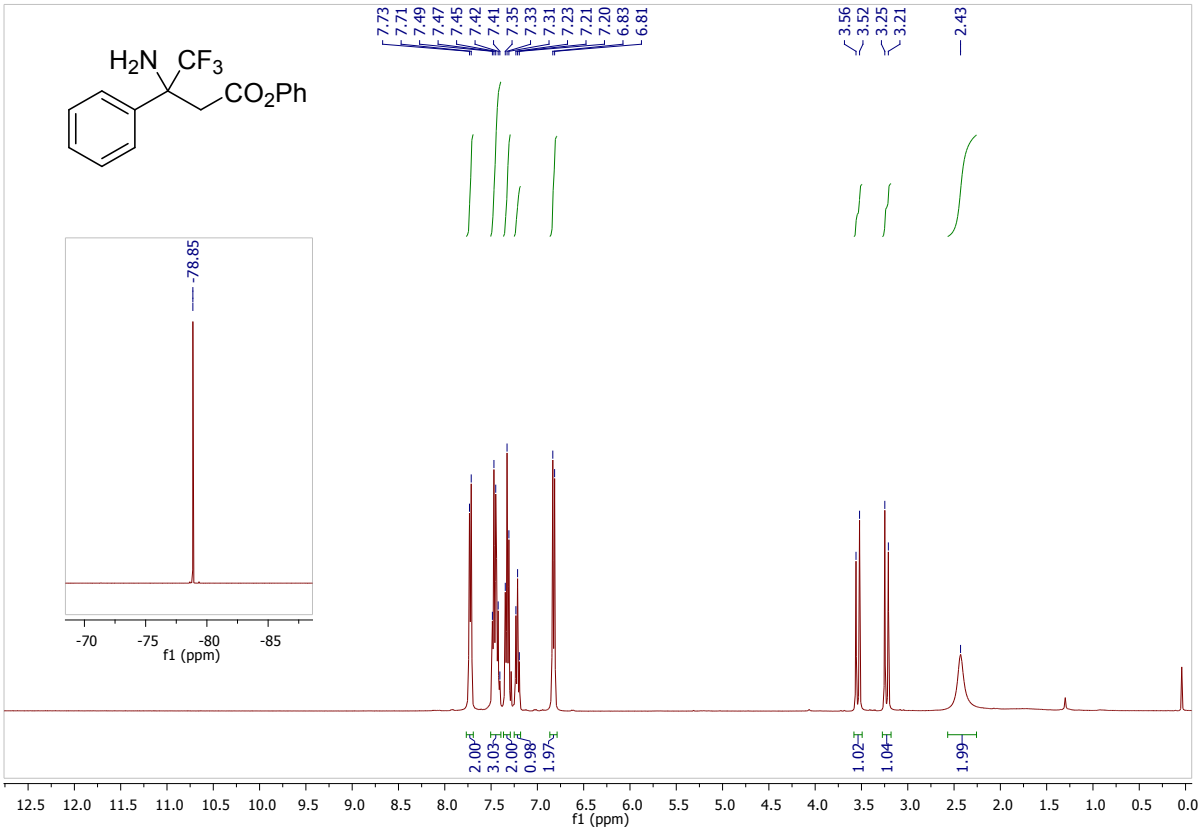


^{13}C NMR (101 MHz, DMSO-d_6):

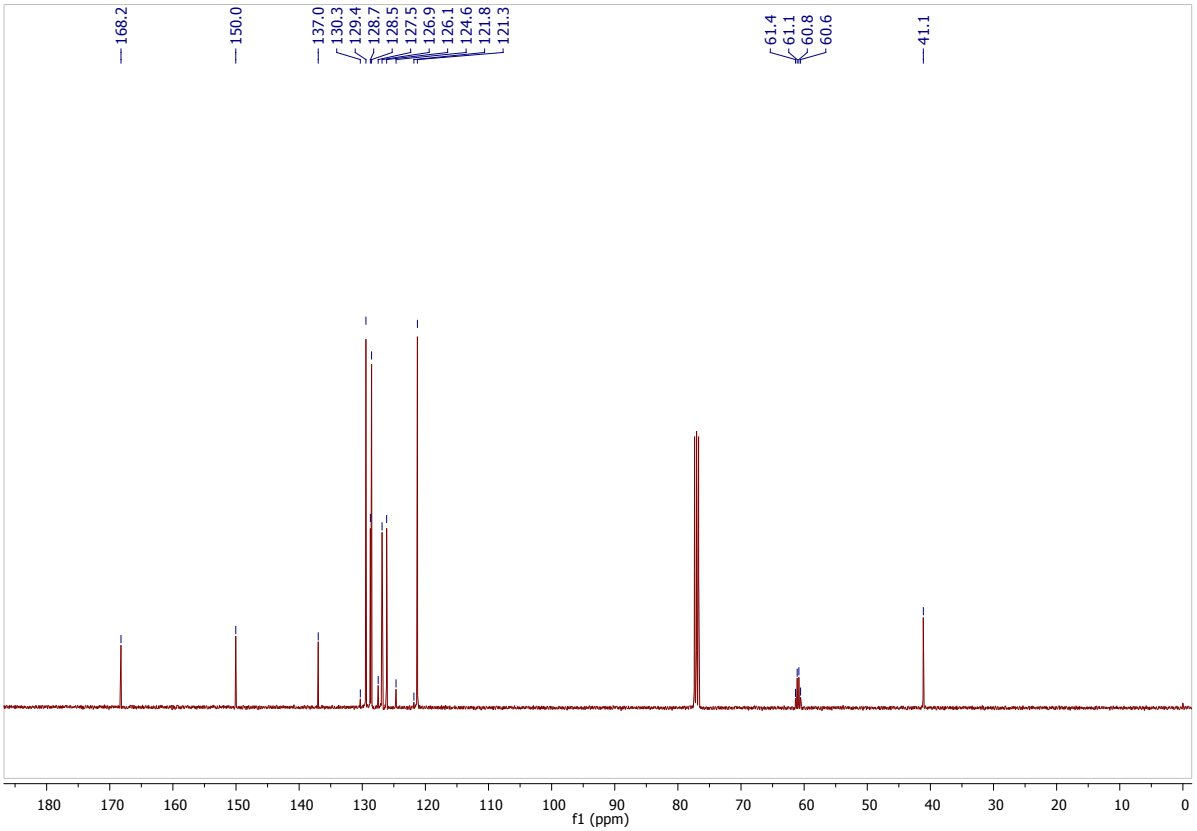


Phenyl 3-amino-4,4,4-trifluoro-3-phenylbutanoate (6b)

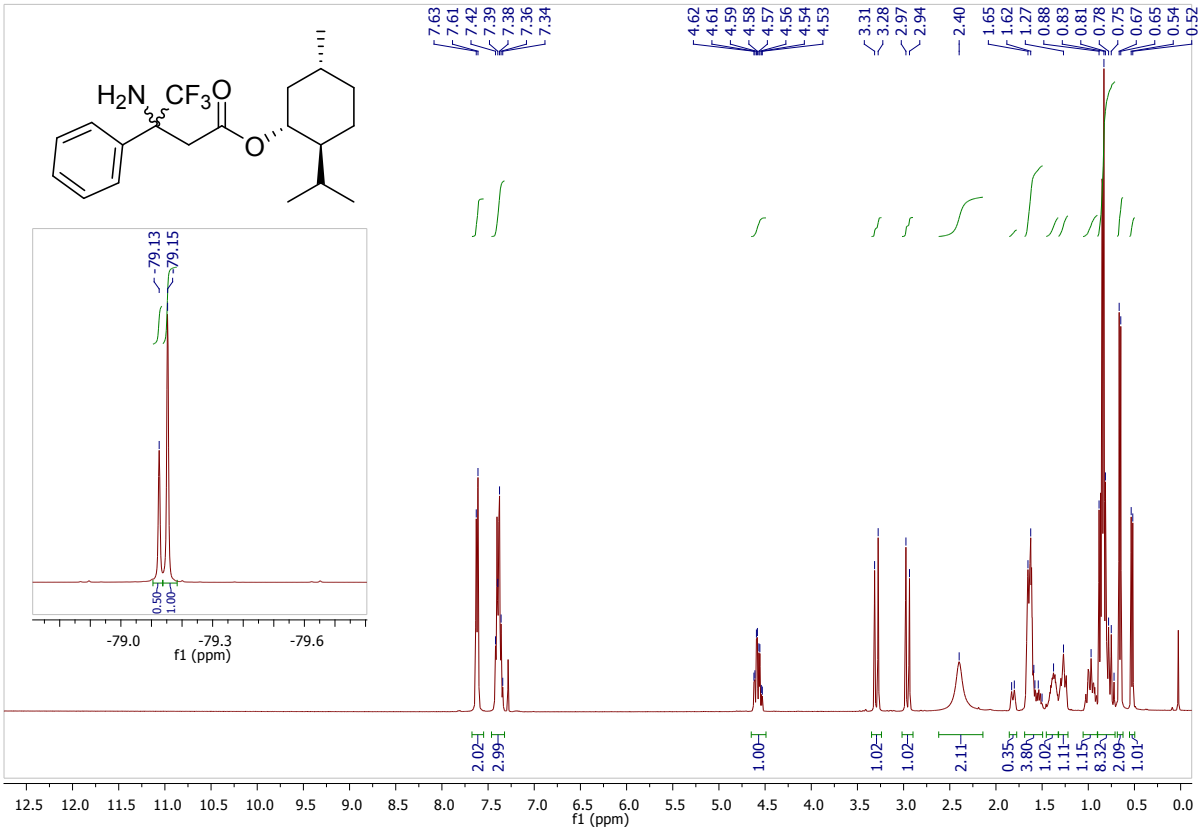
^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):



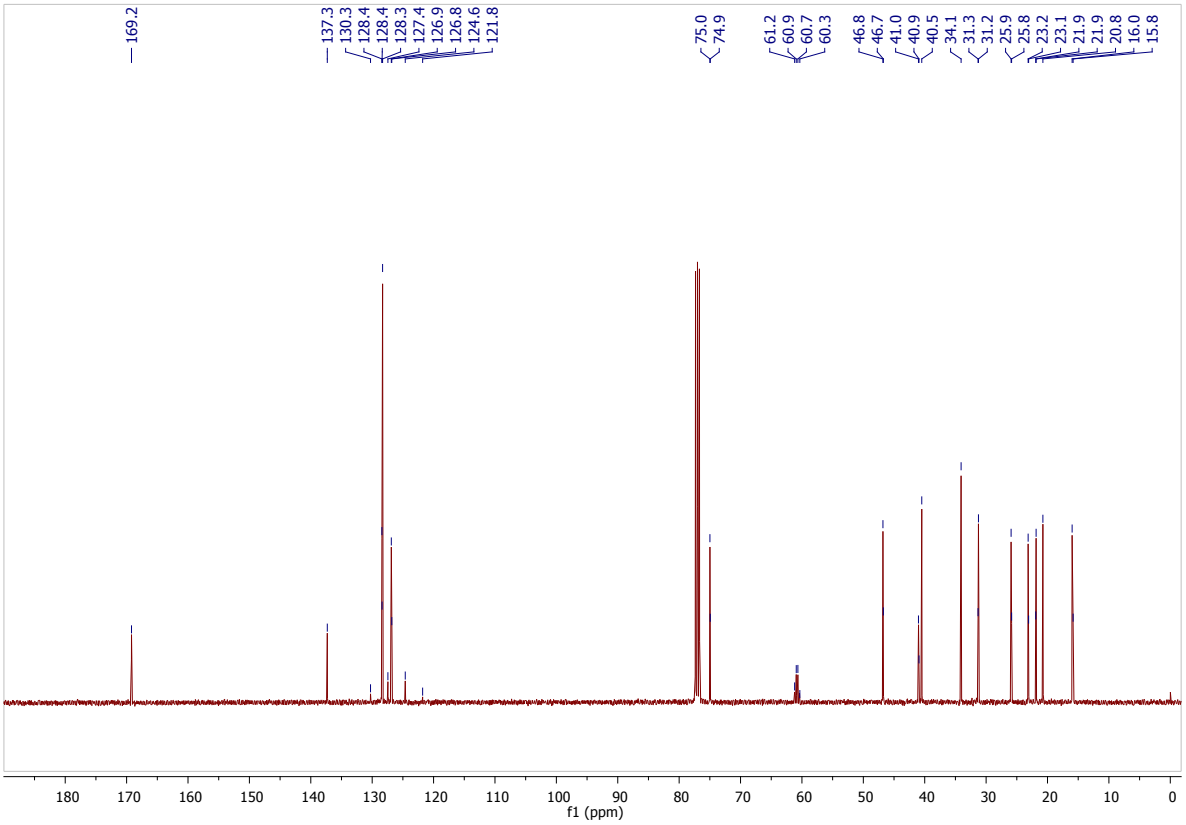
^{13}C NMR (101 MHz, DMSO-d_6):



(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 3-amino-4,4,4-trifluoro-3-phenylbutanoate (6c, d.r. 65:35)
^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

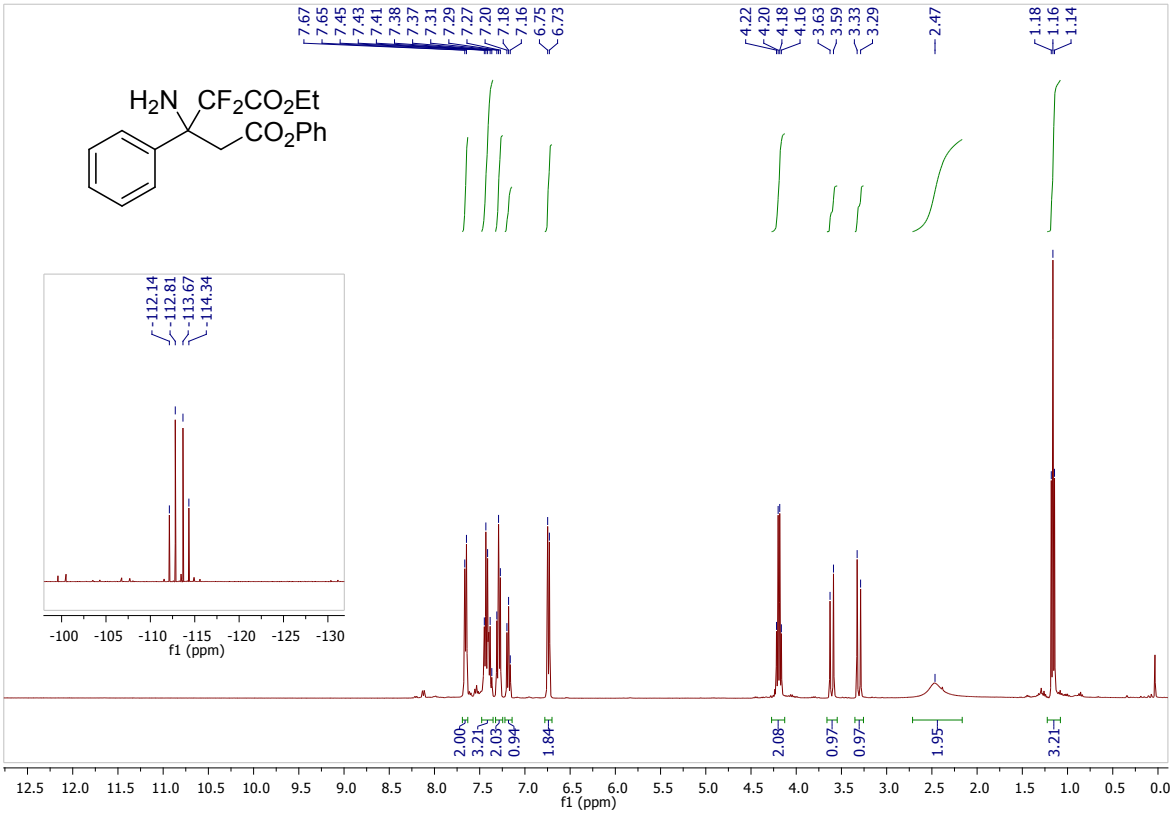


^{13}C NMR (101 MHz, DMSO-d_6):

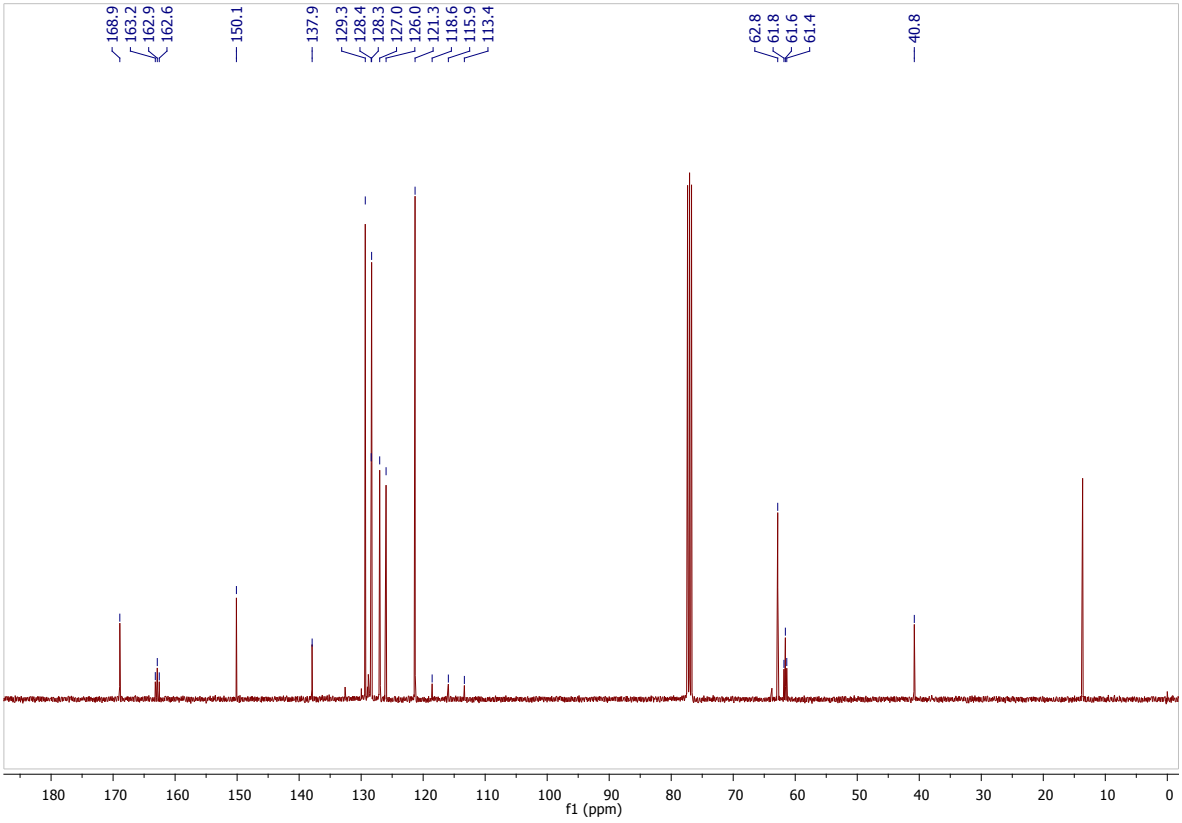


1-Ethyl 5-phenyl 3-amino-2,2-difluoro-3-phenylpentanedioate (6d with some impurities)

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

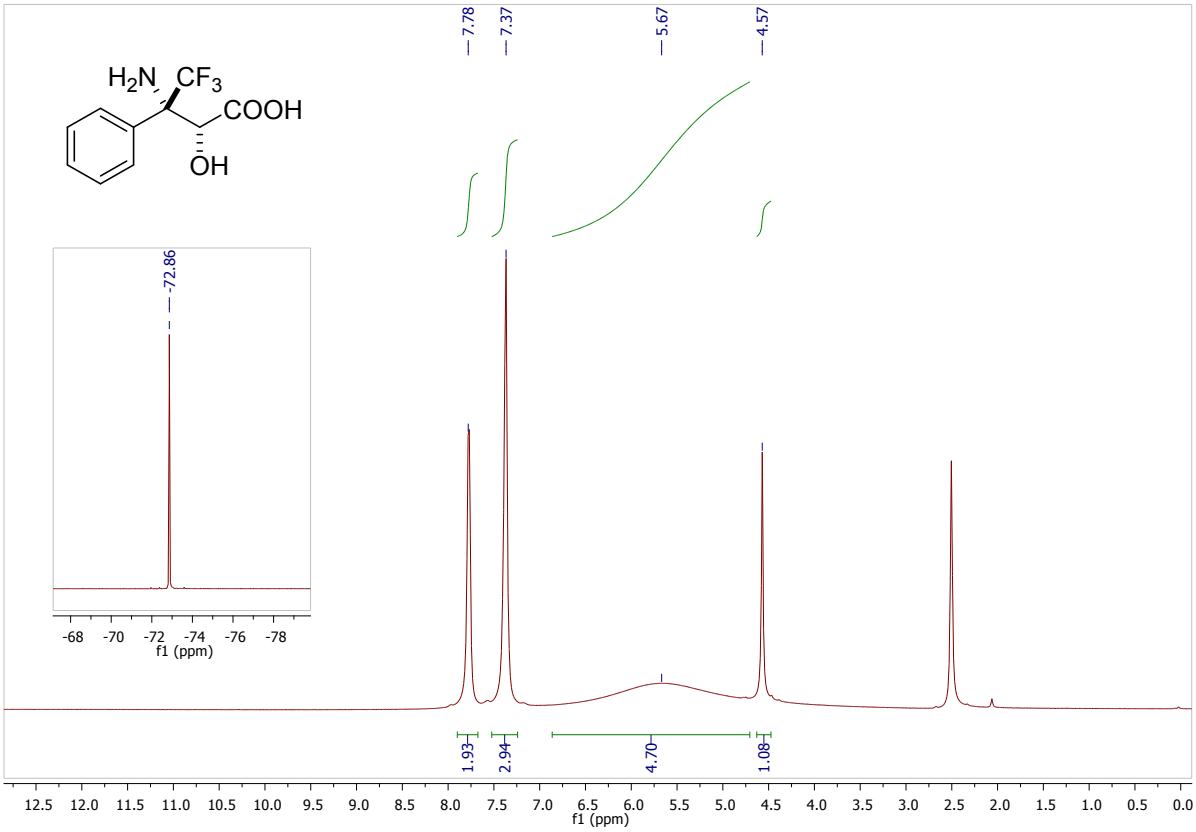


^{13}C NMR (101 MHz, DMSO-d_6):

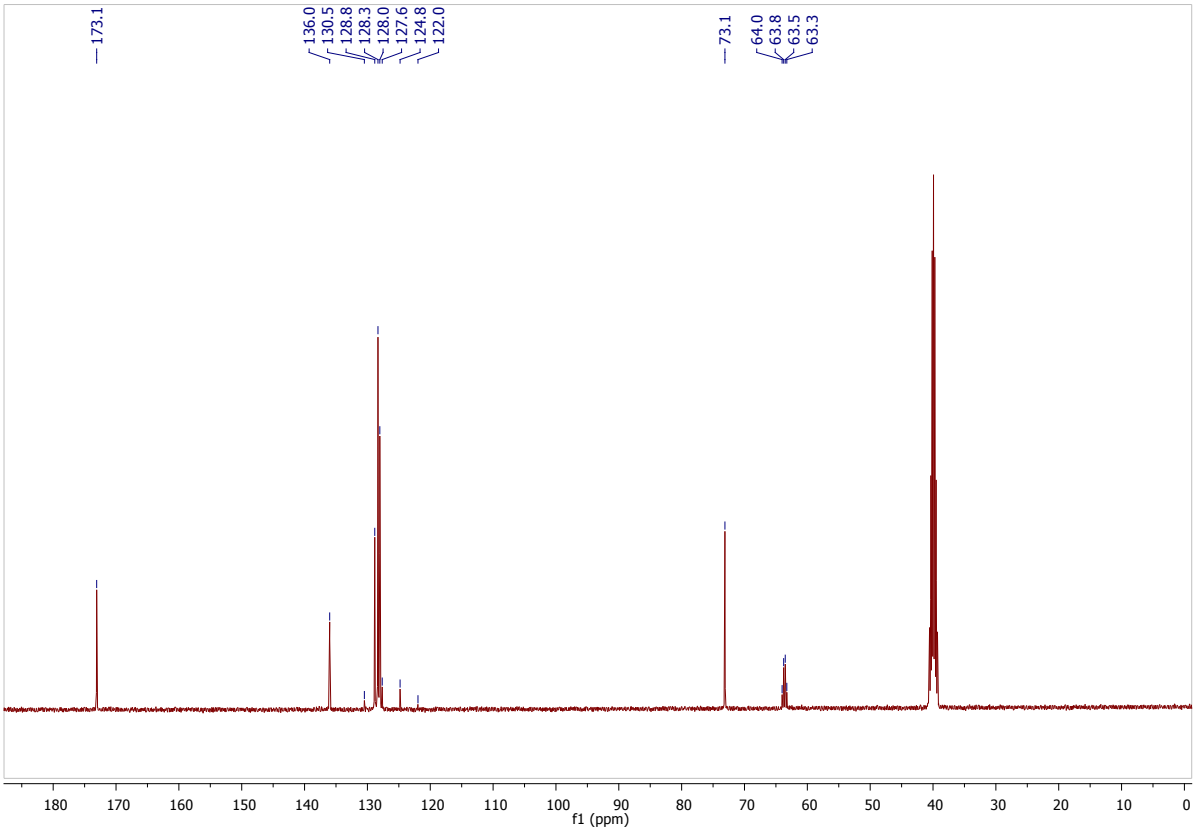


(2*R,3*S**)-3-Amino-4,4,4-trifluoro-2-hydroxy-3-phenylbutanoic acid (7a)**

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

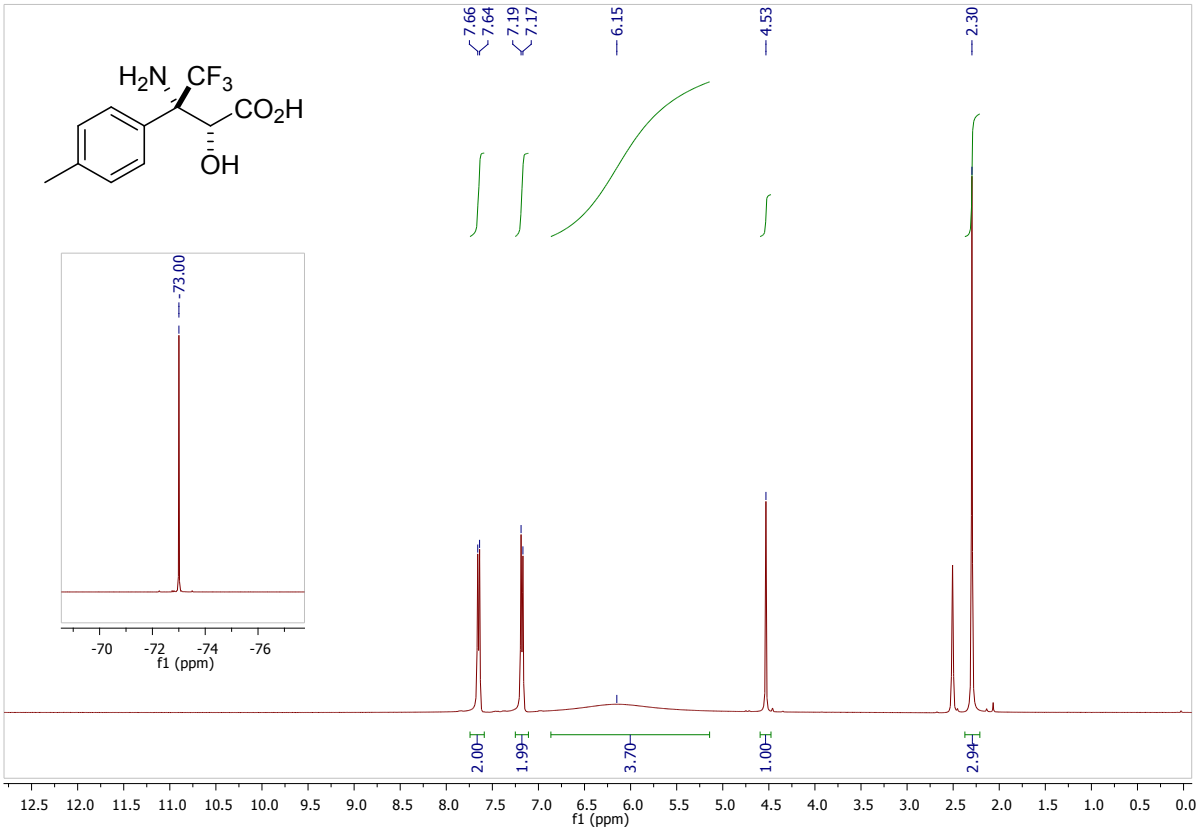


^{13}C NMR (101 MHz, DMSO-d_6):

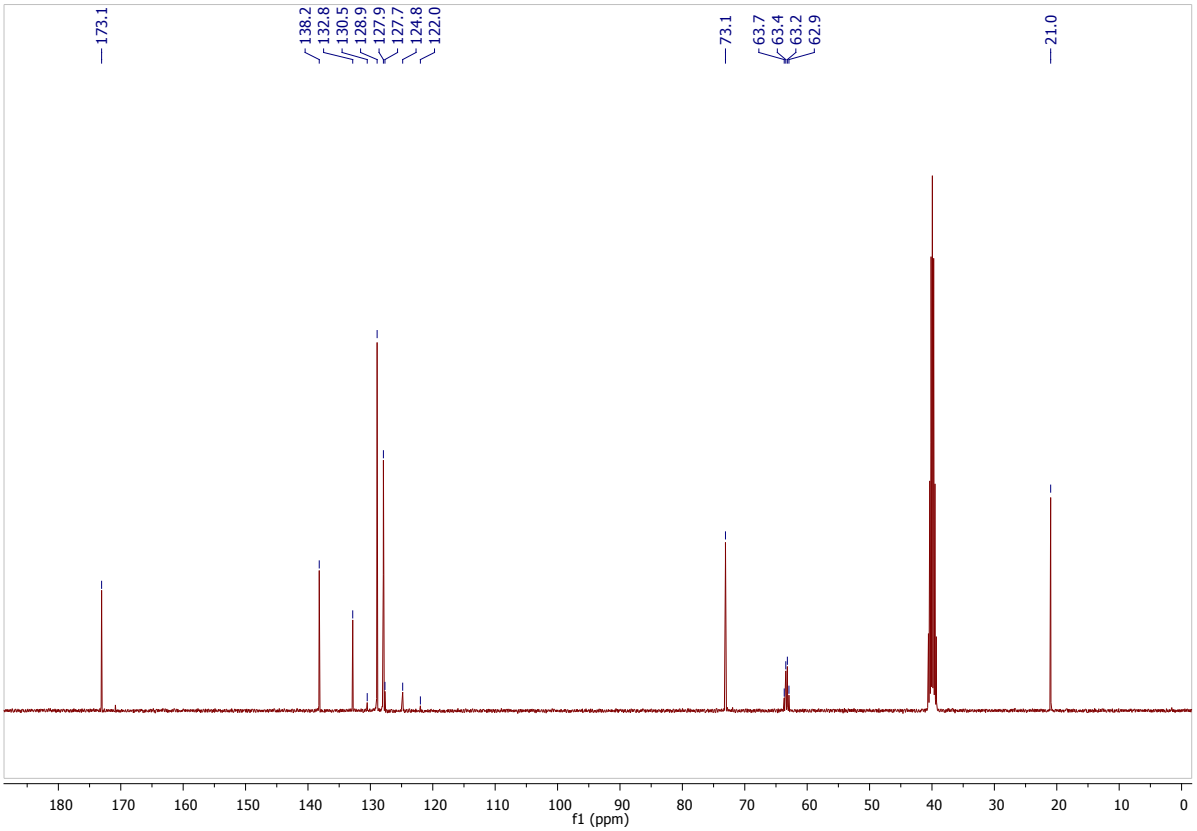


(2*R,3*S**)-3-amino-4,4,4-trifluoro-2-hydroxy-3-p-tolylbutanoic acid (7b)**

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

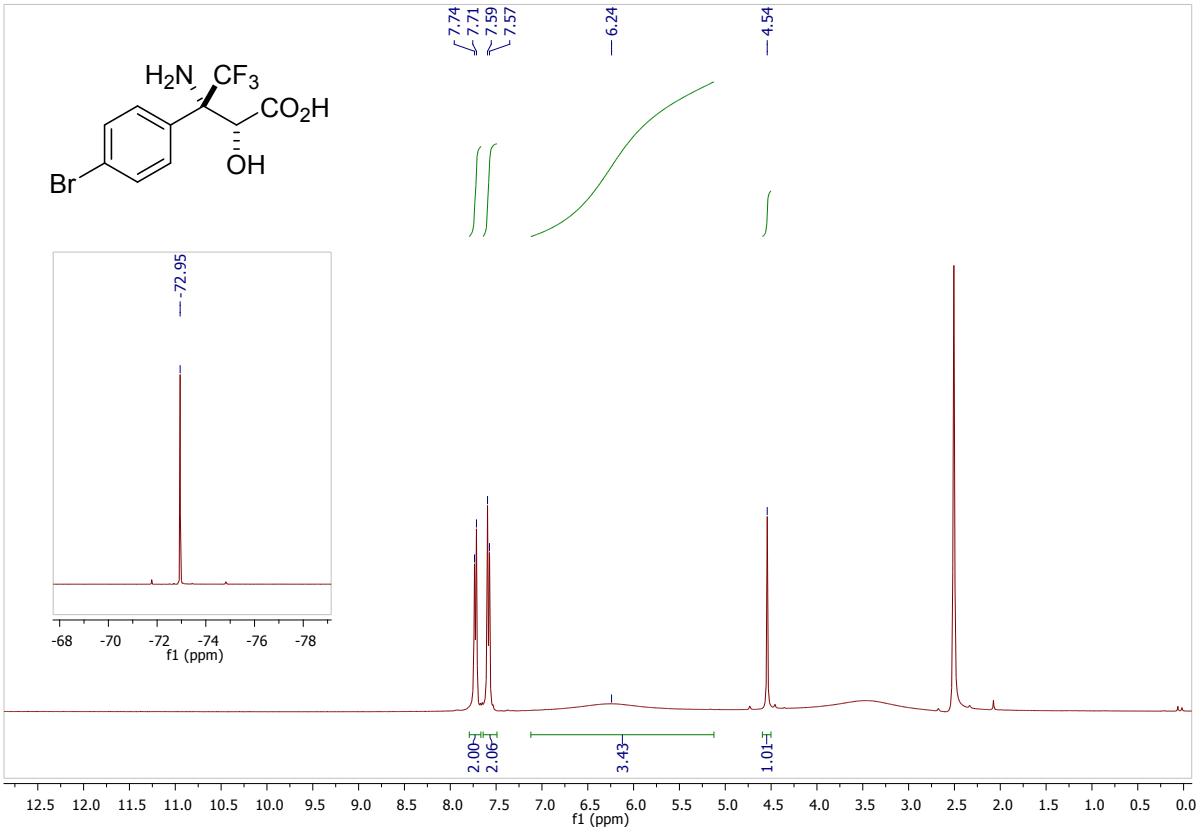


^{13}C NMR (101 MHz, DMSO-d_6):

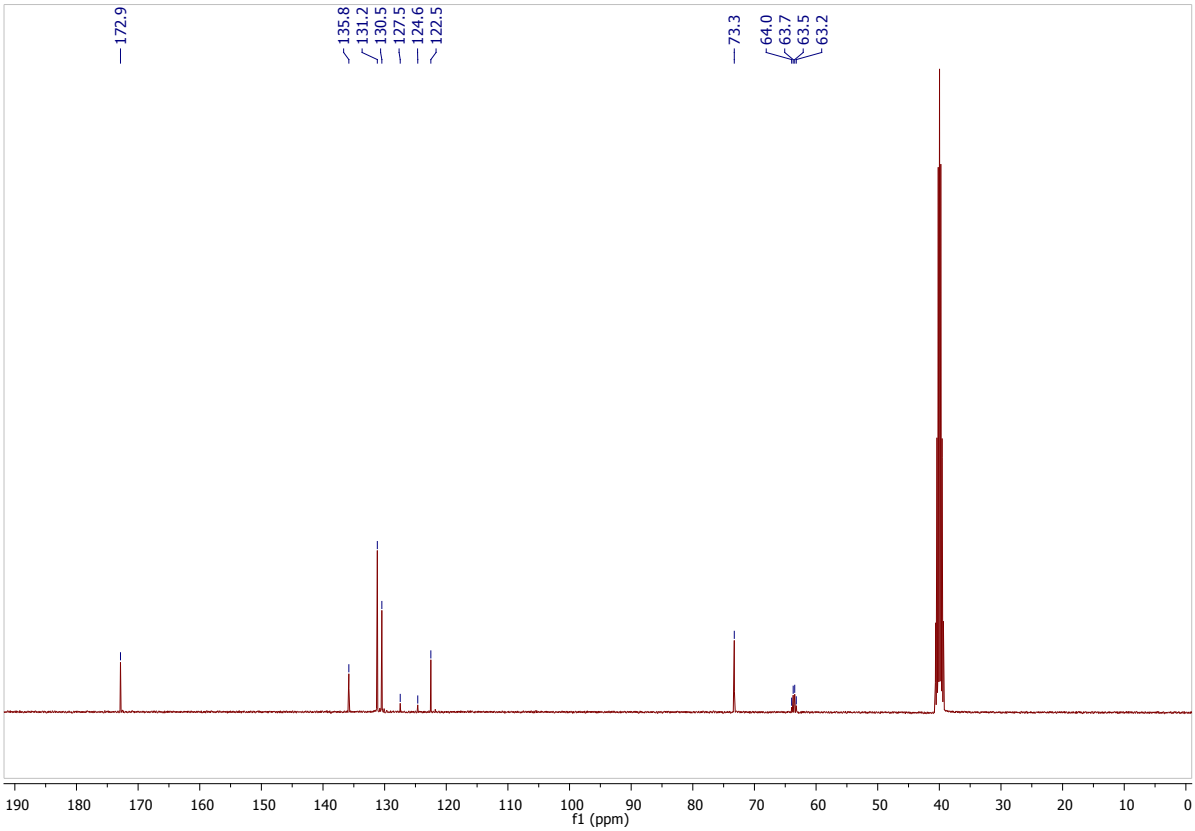


(2R*,3S*)-3-Amino-3-(4-bromophenyl)-4,4,4-trifluoro-2-hydroxybutanoic acid (7c)

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

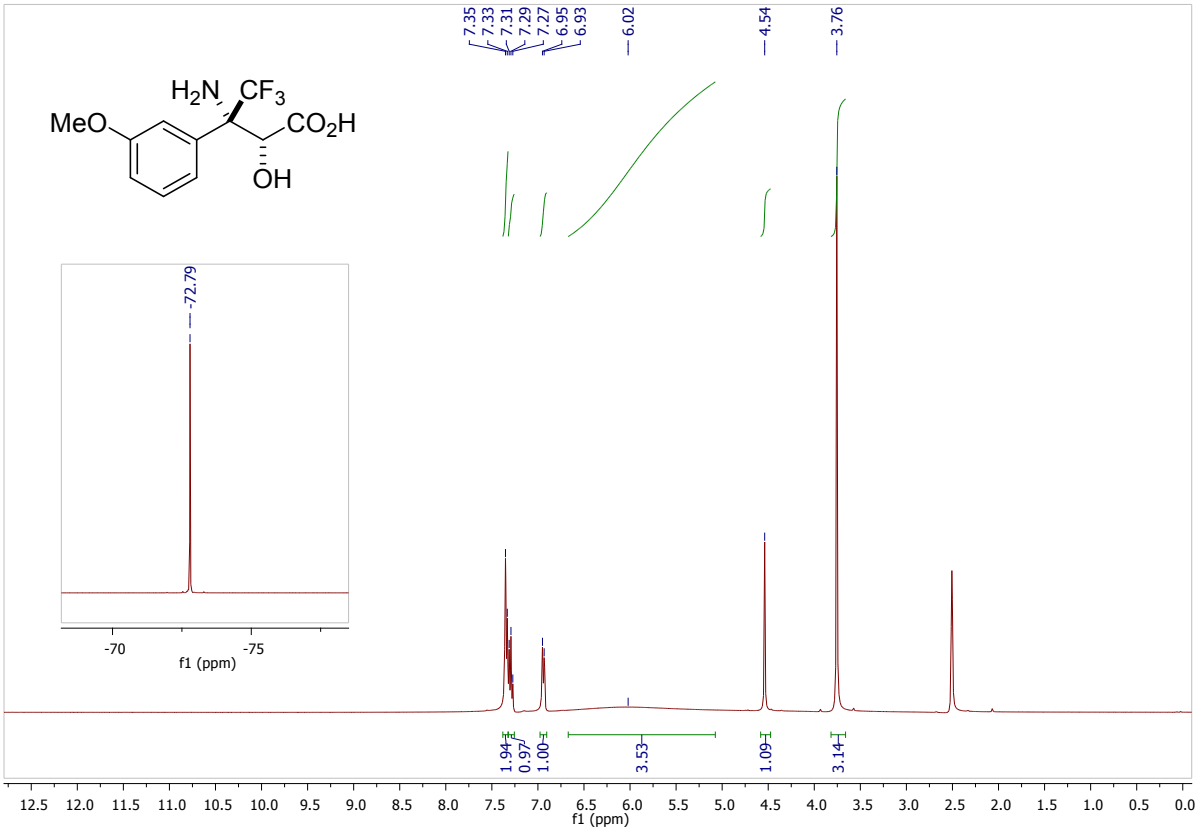


^{13}C NMR (101 MHz, DMSO-d_6):

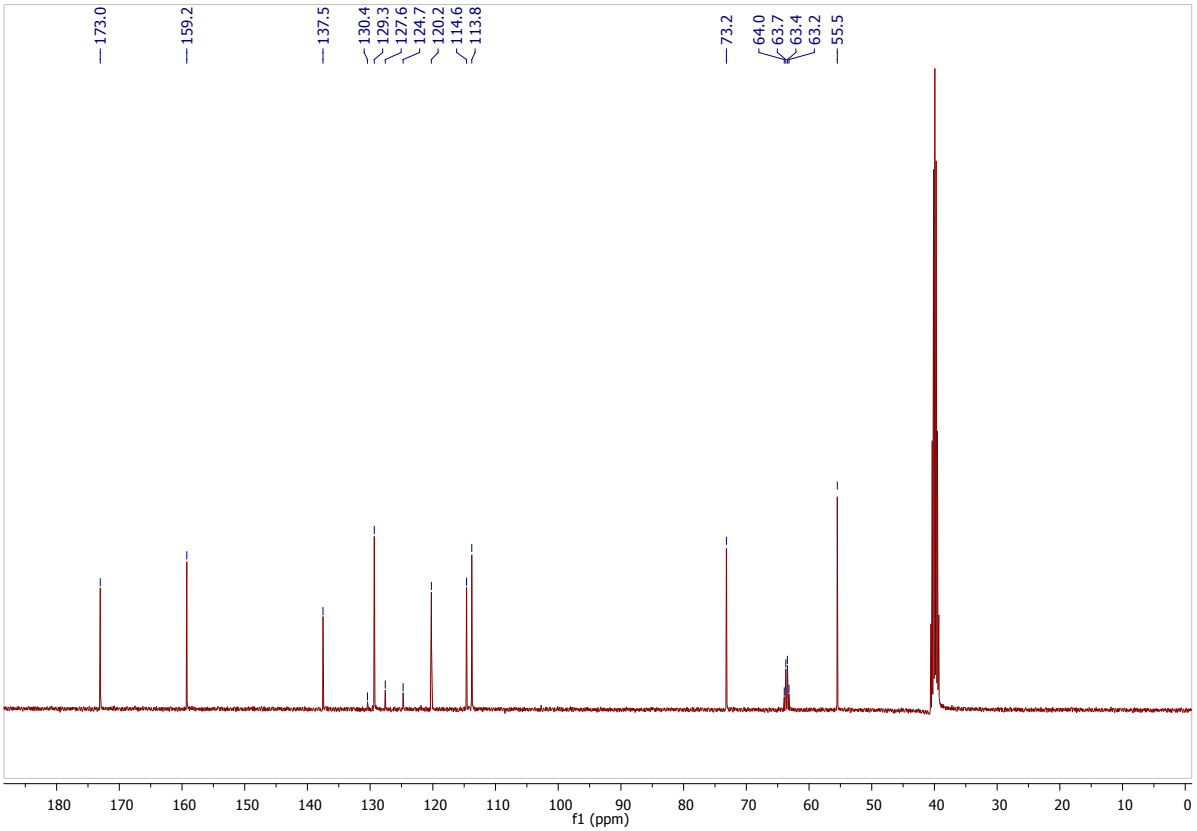


(2*R,3*S**)-3-Amino-4,4,4-trifluoro-2-hydroxy-3-(3-methoxyphenyl)butanoic acid (7d)**

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

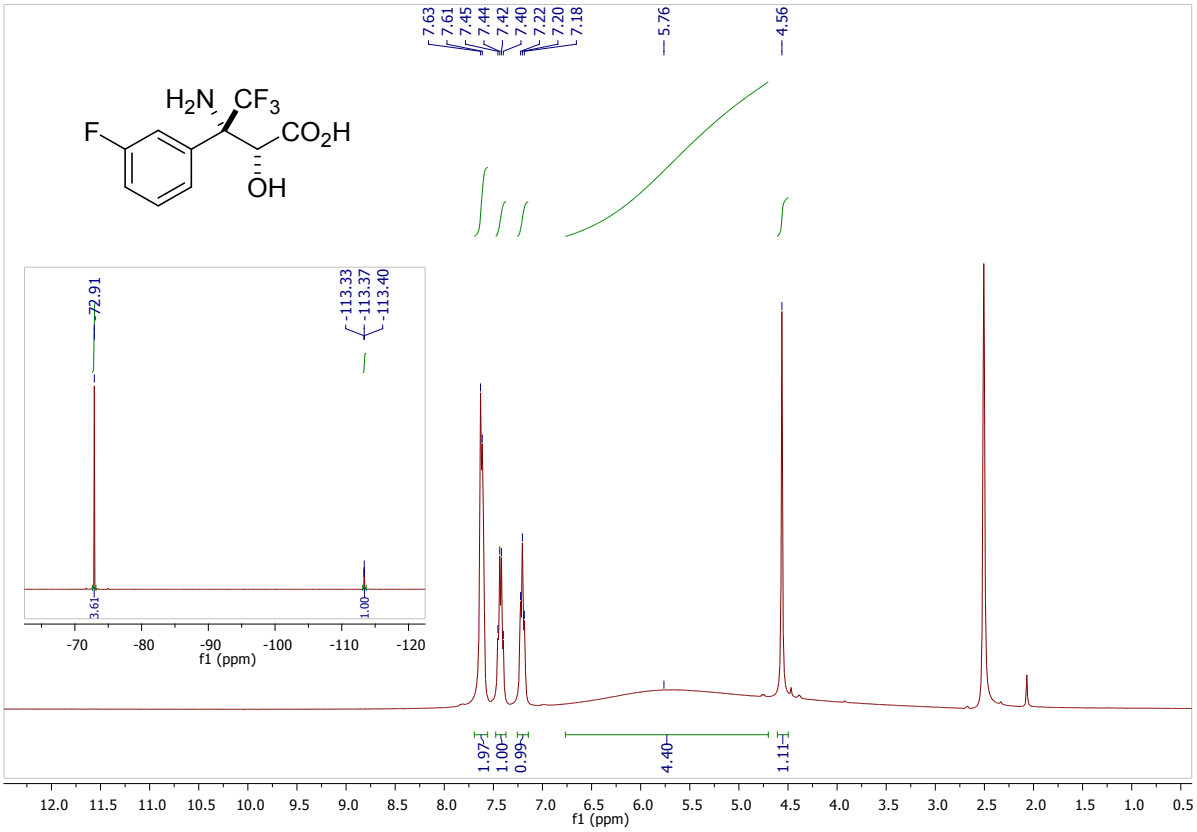


^{13}C NMR (101 MHz, DMSO-d_6):

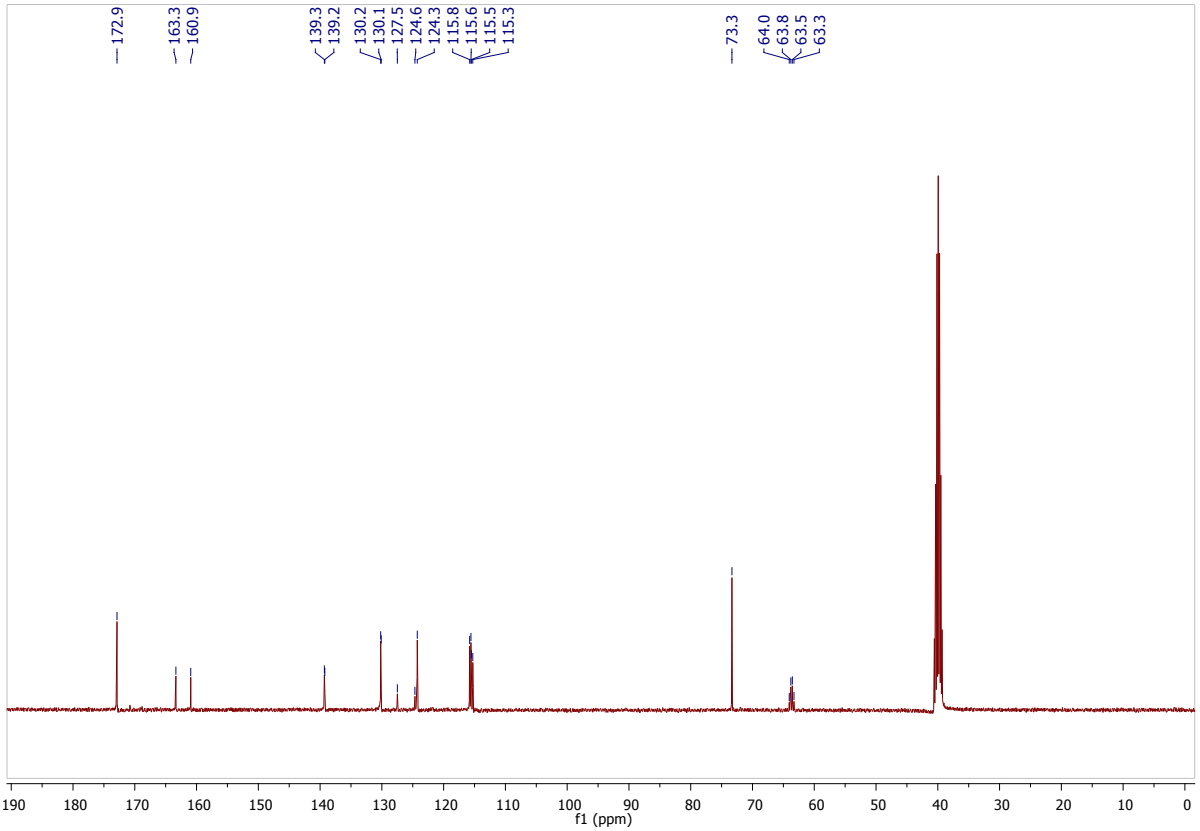


(2*R,3*S**)-3-Amino-4,4,4-trifluoro-3-(3-fluorophenyl)-2-hydroxybutanoic acid (7e)**

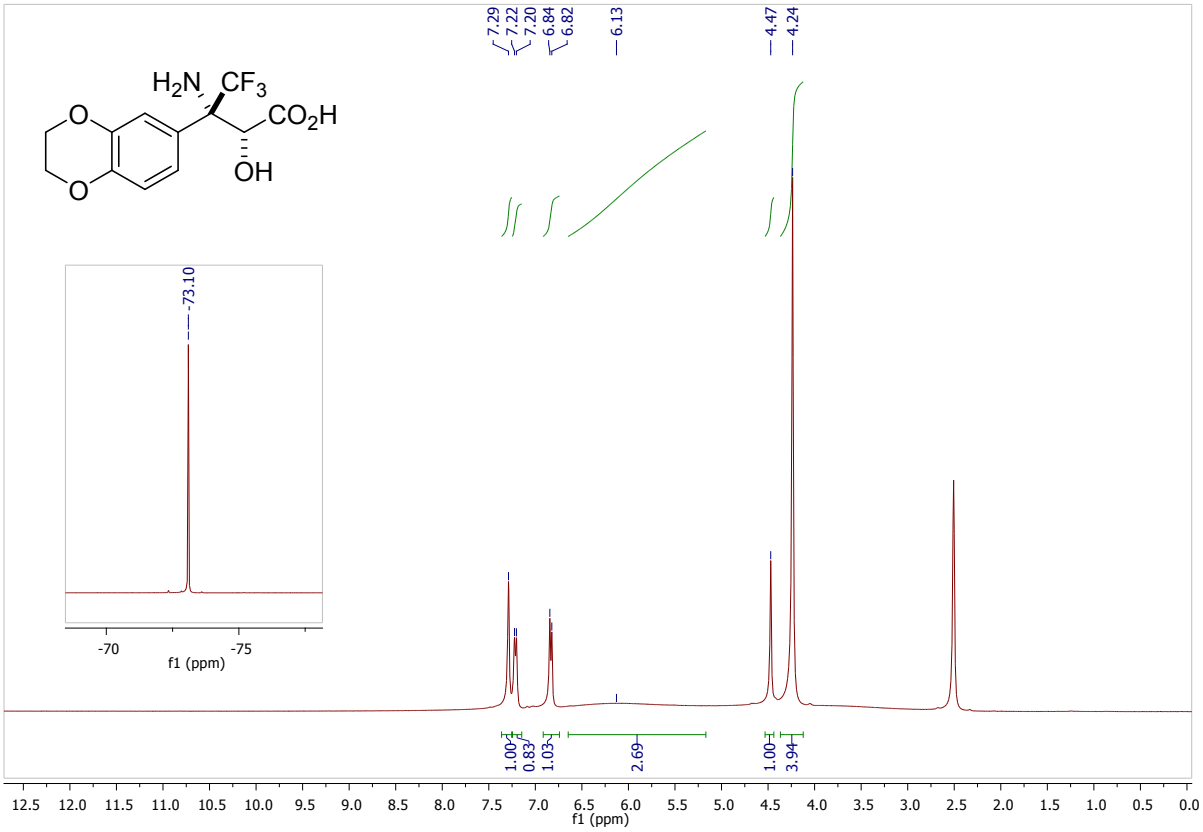
^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):



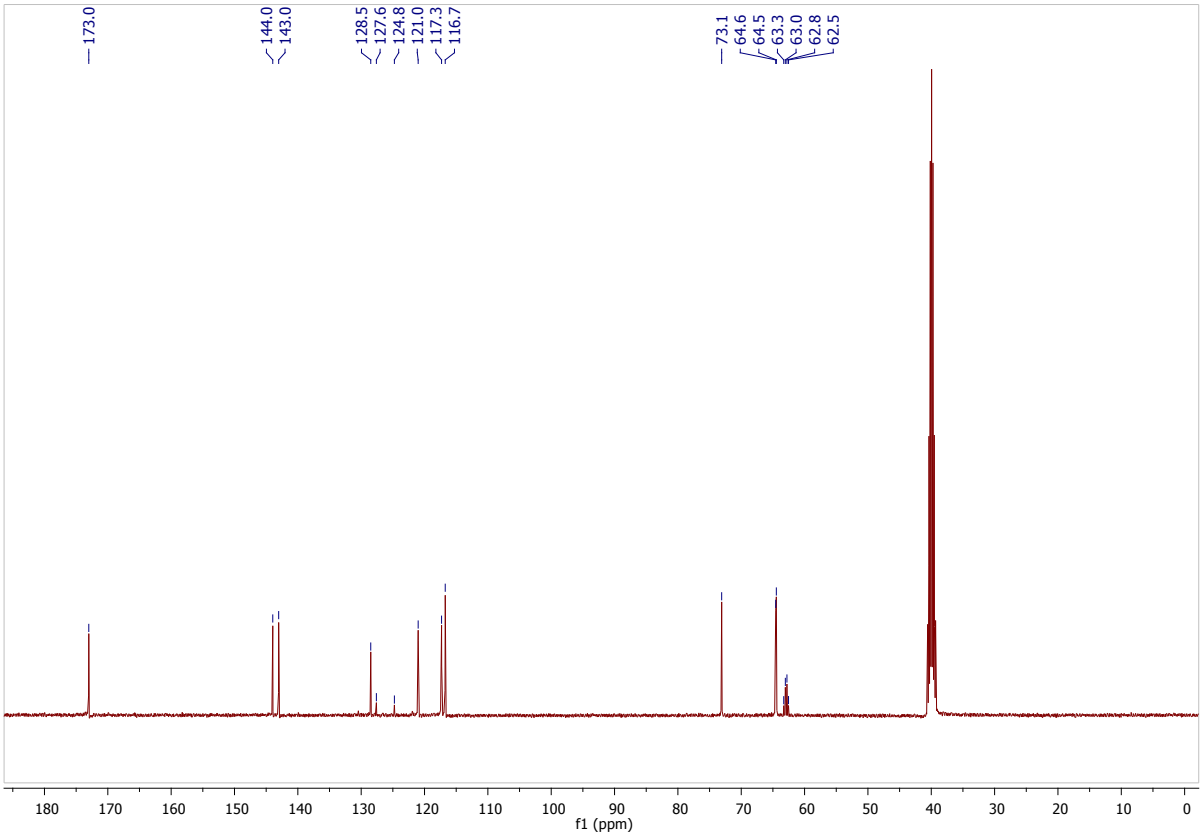
^{13}C NMR (101 MHz, DMSO-d_6):



(2*R,3*S**)-3-amino-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-4,4,4-trifluoro-2-hydroxybutanoic acid (7f)**
^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

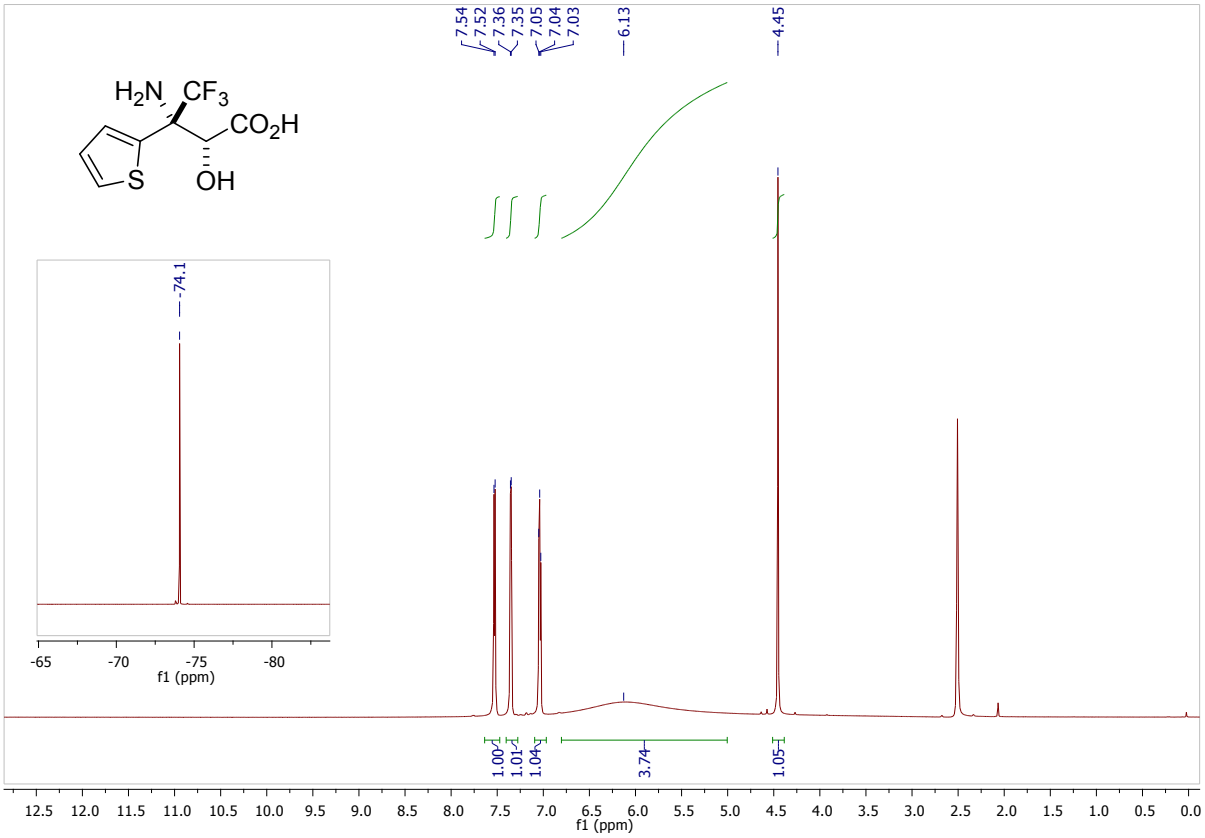


^{13}C NMR (101 MHz, DMSO-d_6):

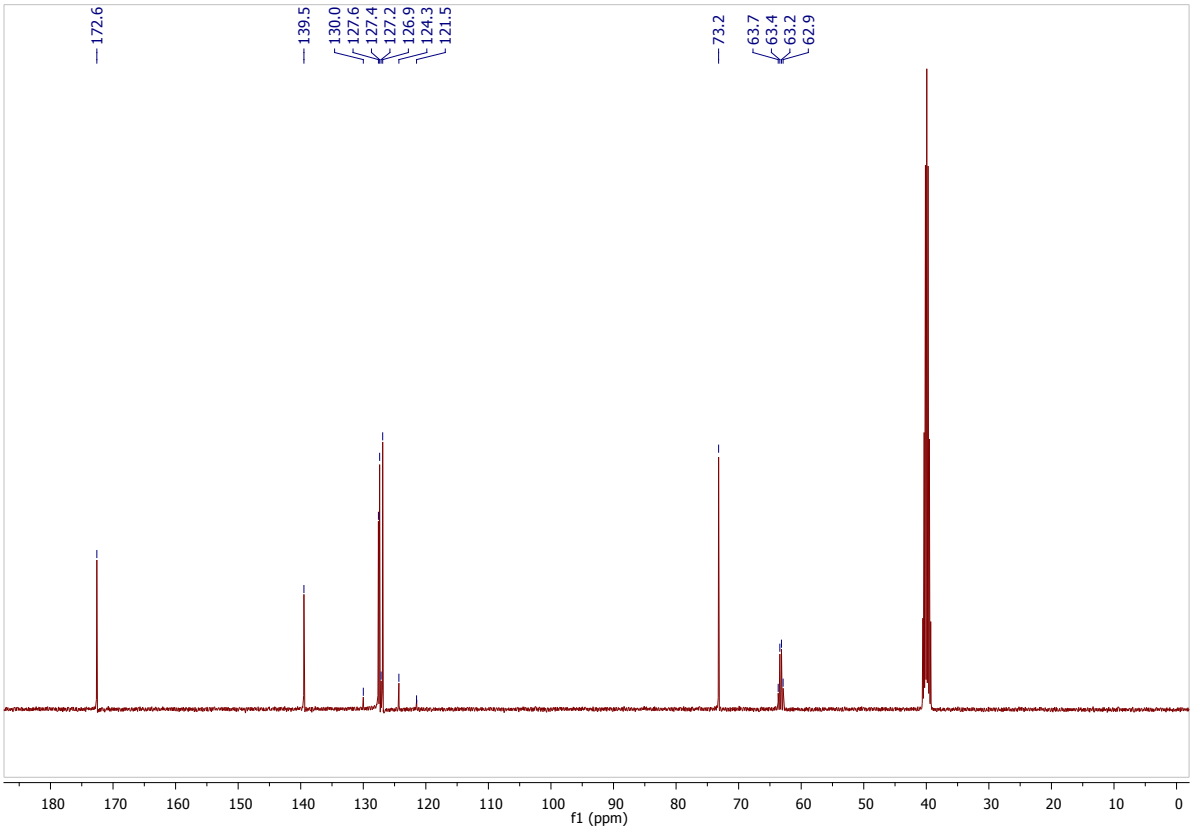


(2*R,3*S**)-3-amino-4,4,4-trifluoro-2-hydroxy-3-(thiophen-2-yl)butanoic acid (7g)**

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

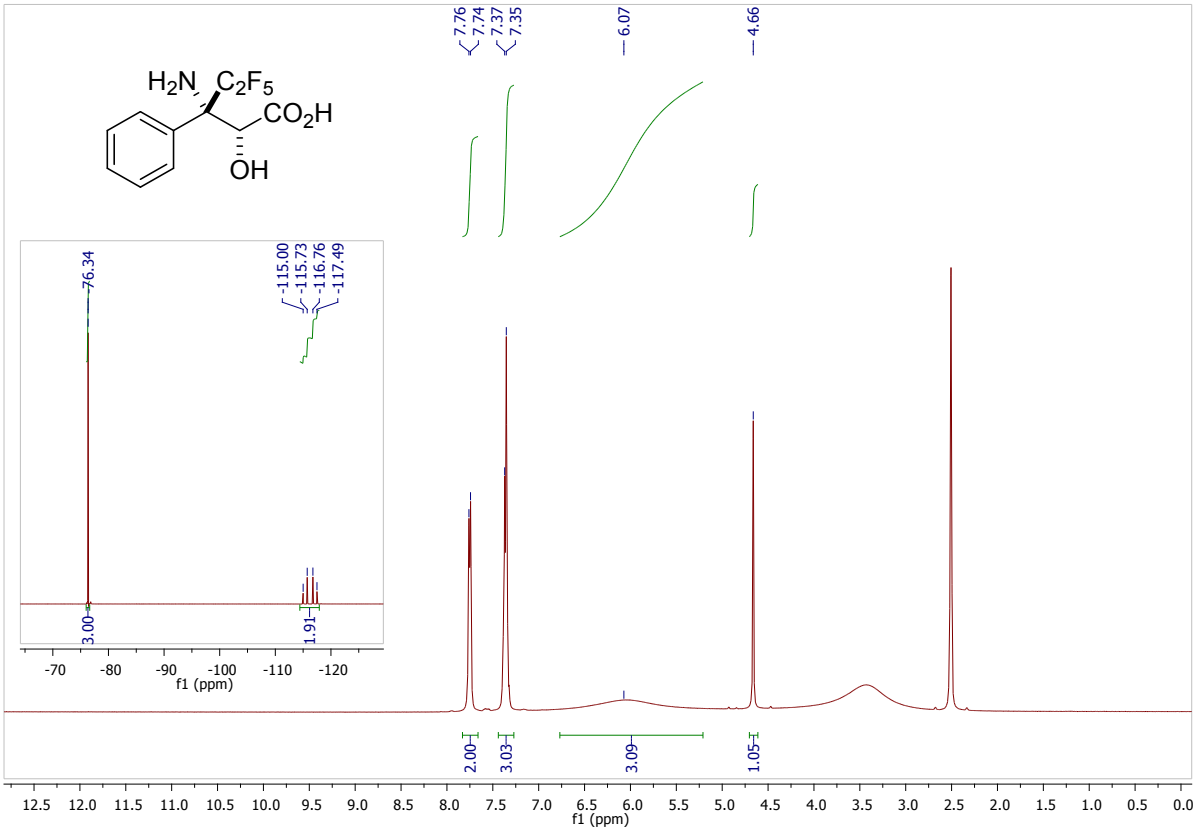


^{13}C NMR (101 MHz, DMSO-d_6):

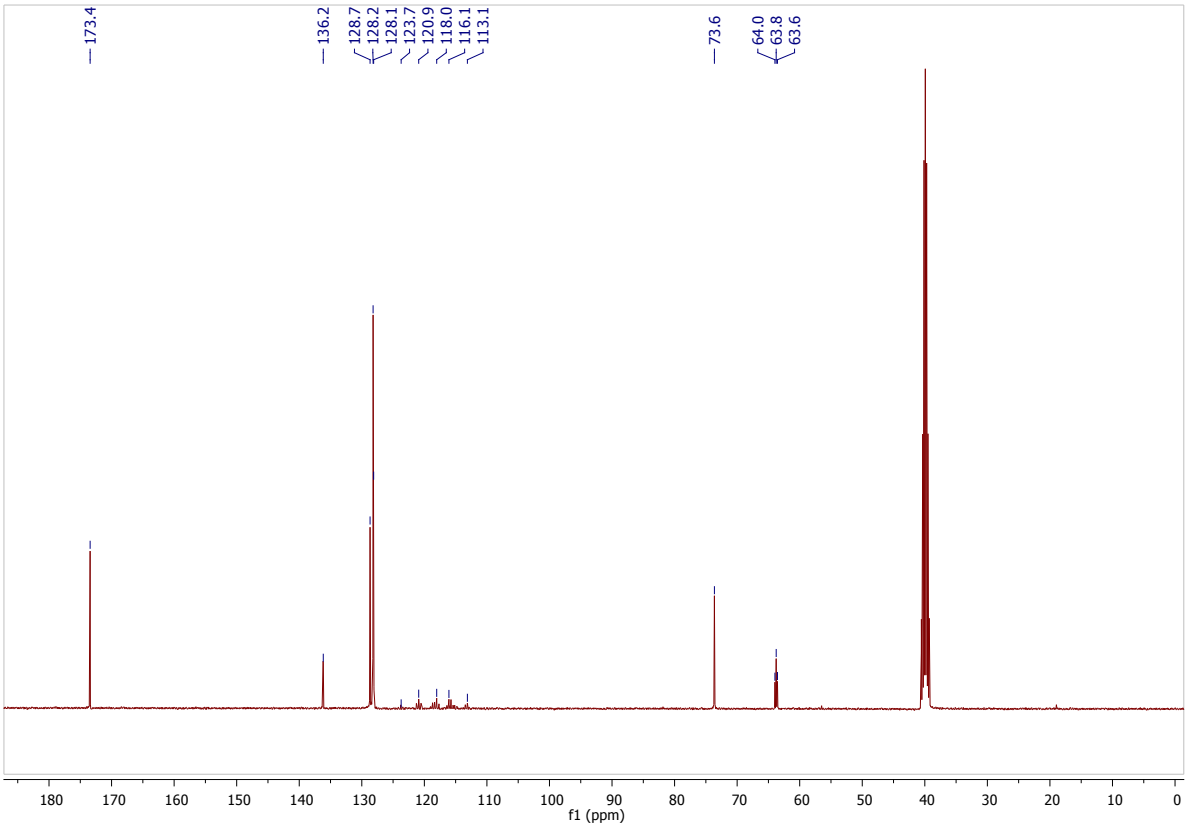


(2*R,3*S**)-3-Amino-4,4,5,5,5-pentafluoro-2-hydroxy-3-phenylpentanoic acid (7h)**

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

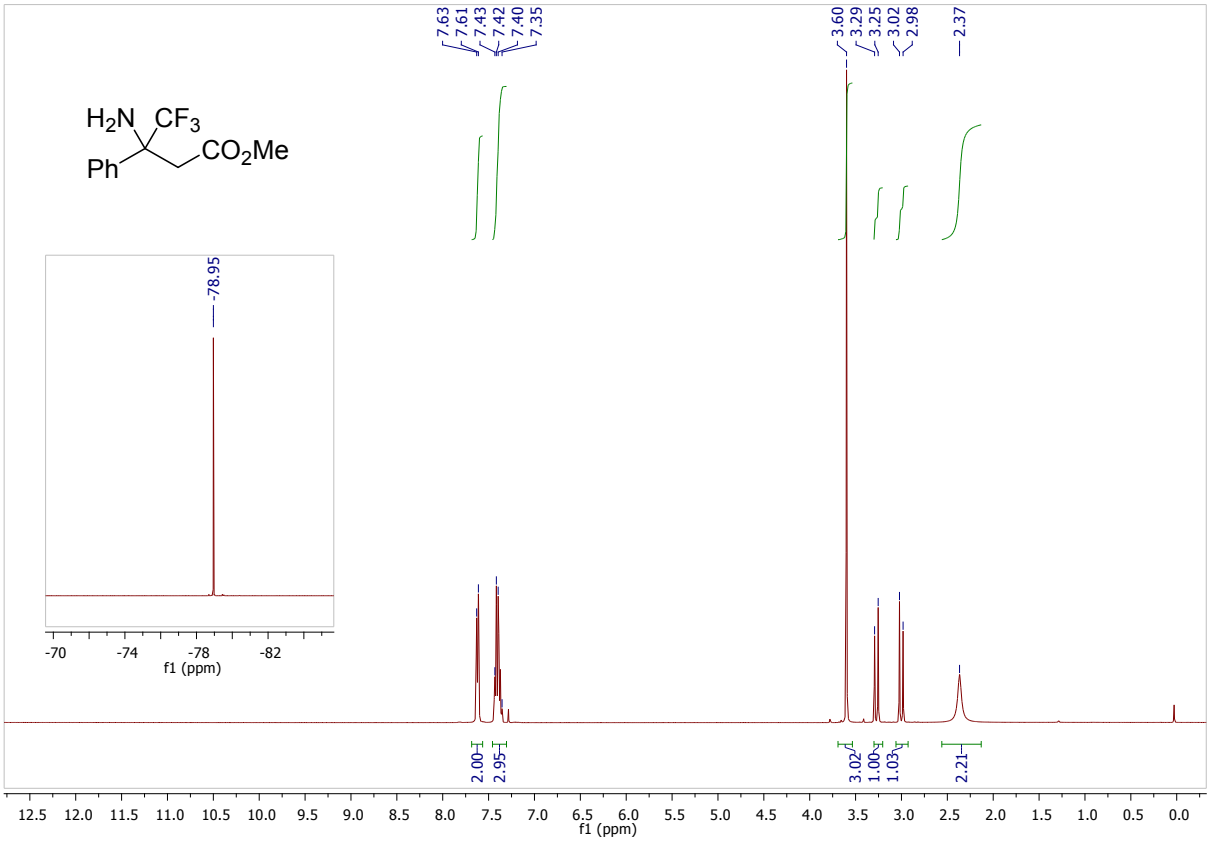


^{13}C NMR (101 MHz, DMSO-d_6):

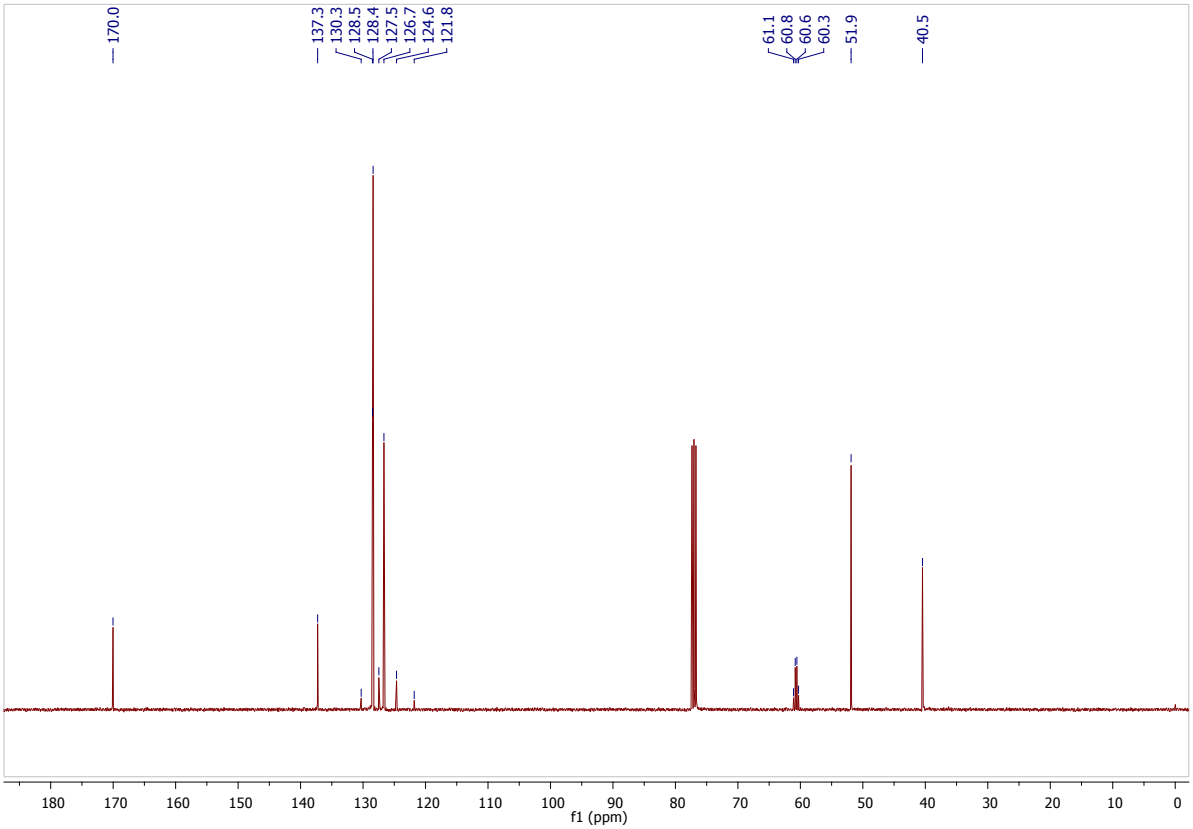


Methyl 3-amino-4,4,4-trifluoro-3-phenylbutanoate (8)

^{1}H NMR (400 MHz, $CDCl_3$), **^{19}F NMR** (376 MHz, $CDCl_3$):

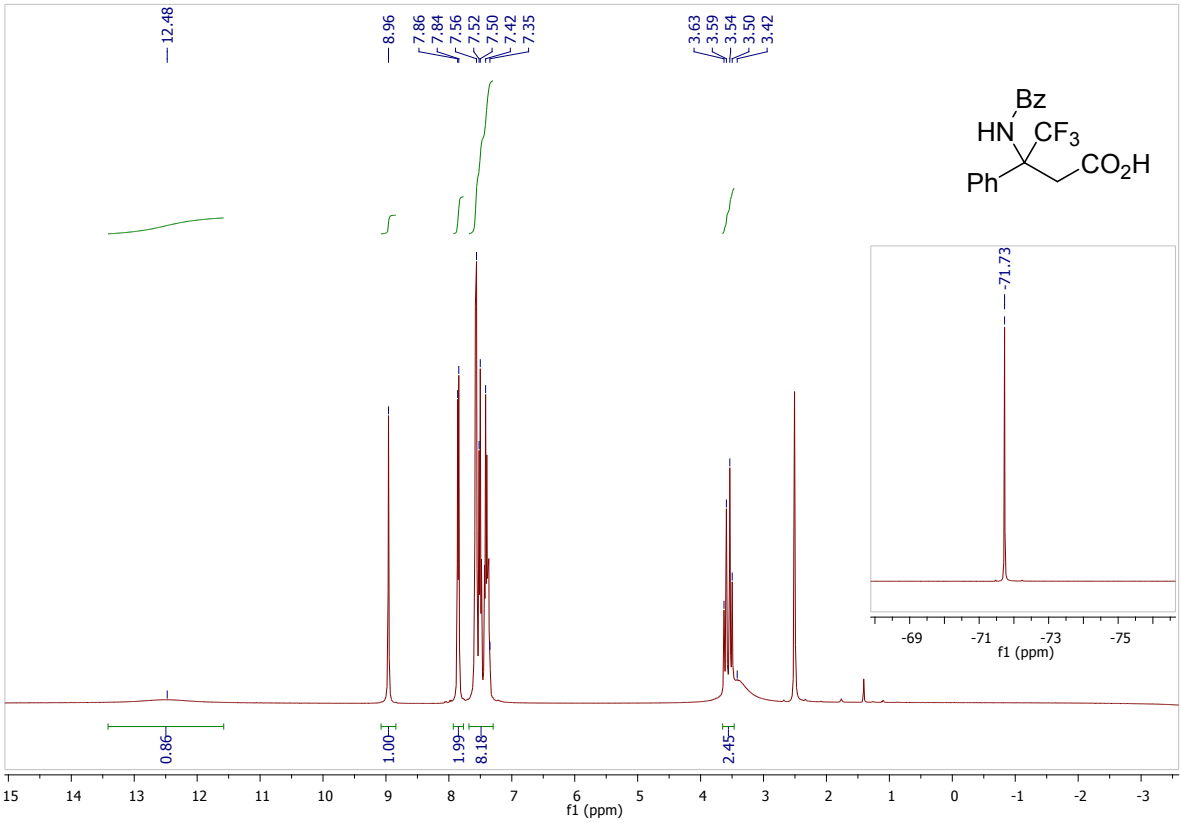


^{13}C NMR (101 MHz, $CDCl_3$):

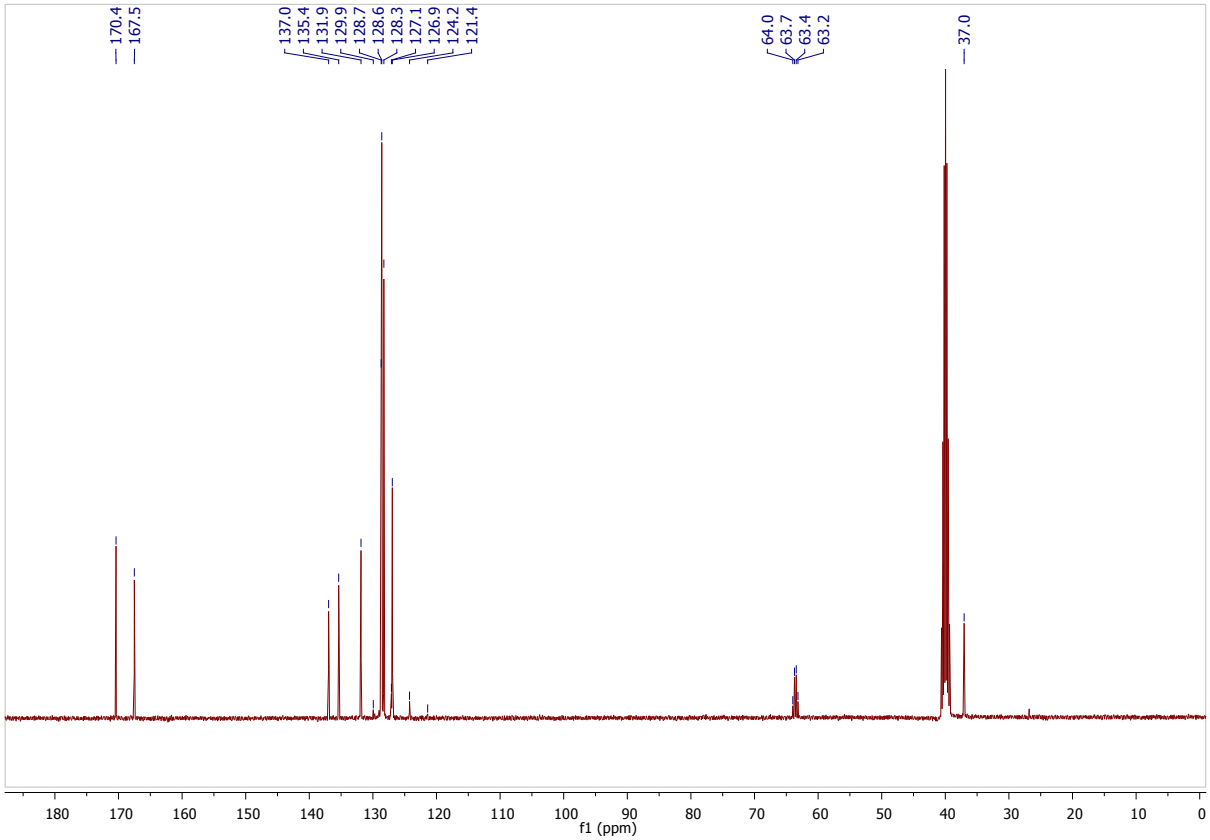


3-Benzamido-4,4,4-trifluoro-3-phenylbutanoic acid (16)

^{1}H NMR (400 MHz, $CDCl_3$), **^{19}F NMR** (376 MHz, $CDCl_3$):

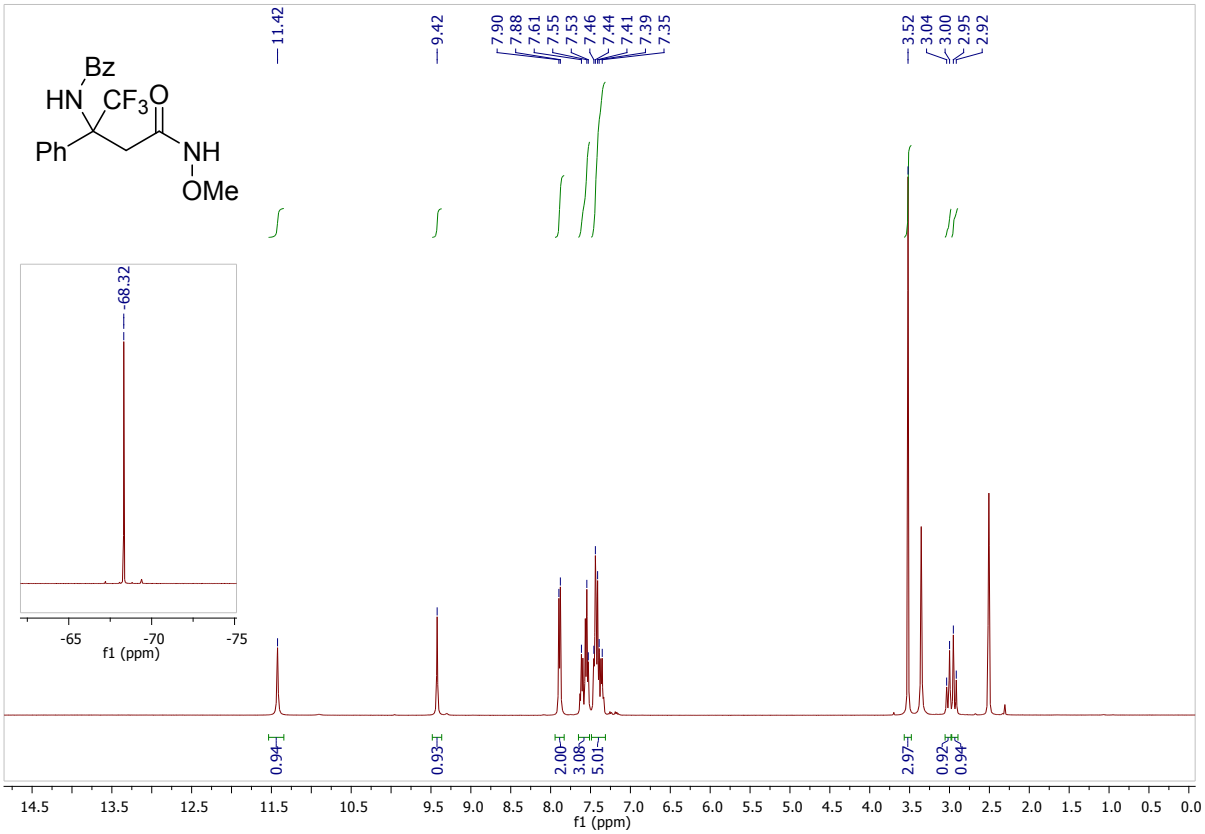


^{13}C NMR (101 MHz, $CDCl_3$):

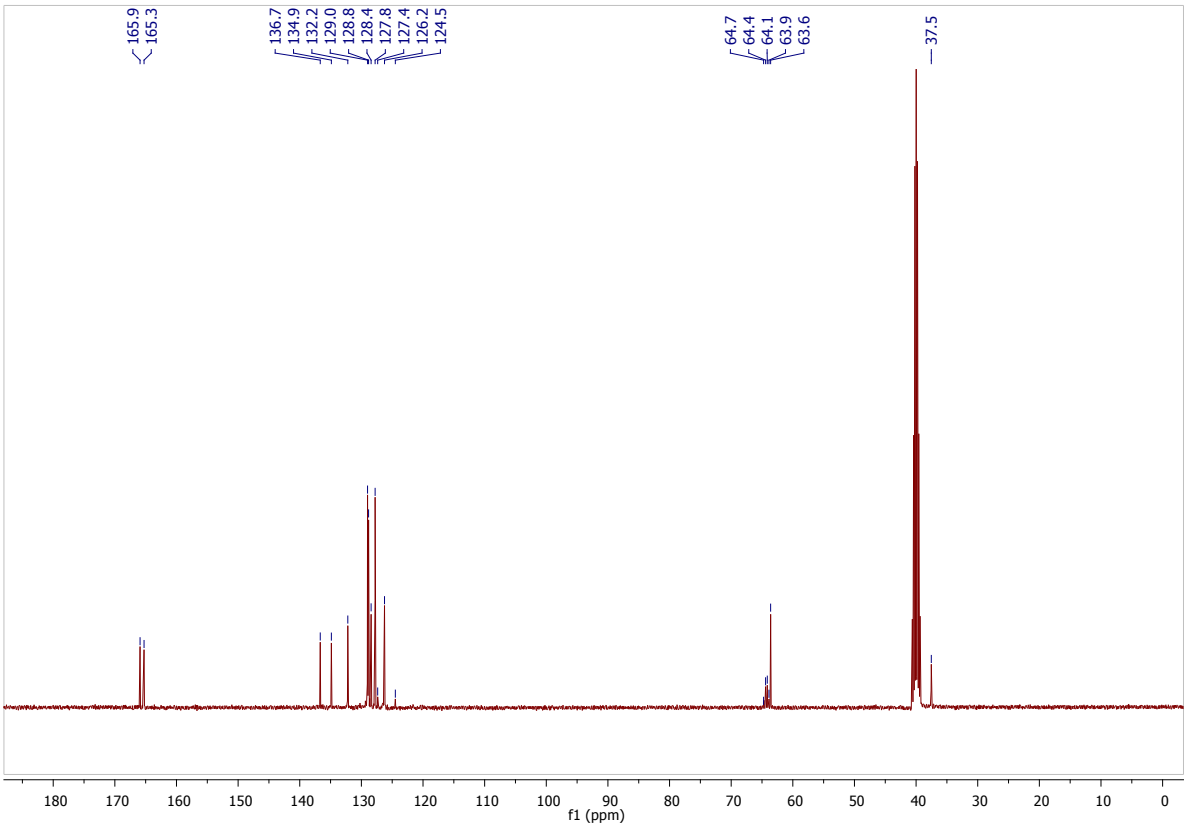


N-(1,1,1-Trifluoro-4-(methoxyamino)-4-oxo-2-phenylbutan-2-yl)benzamide (9)

^{1}H NMR (400 MHz, DMSO-d_6), **^{19}F NMR** (376 MHz, DMSO-d_6):

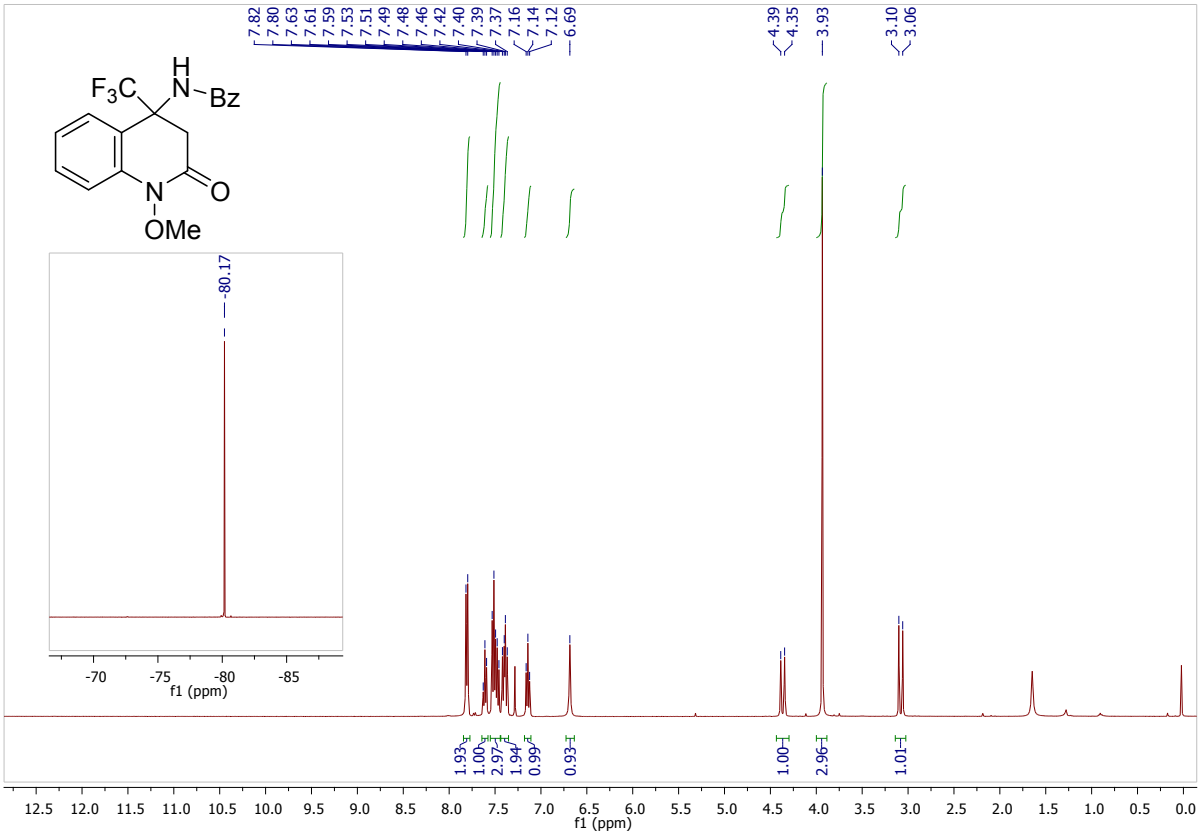


^{13}C NMR (101 MHz, DMSO-d_6):

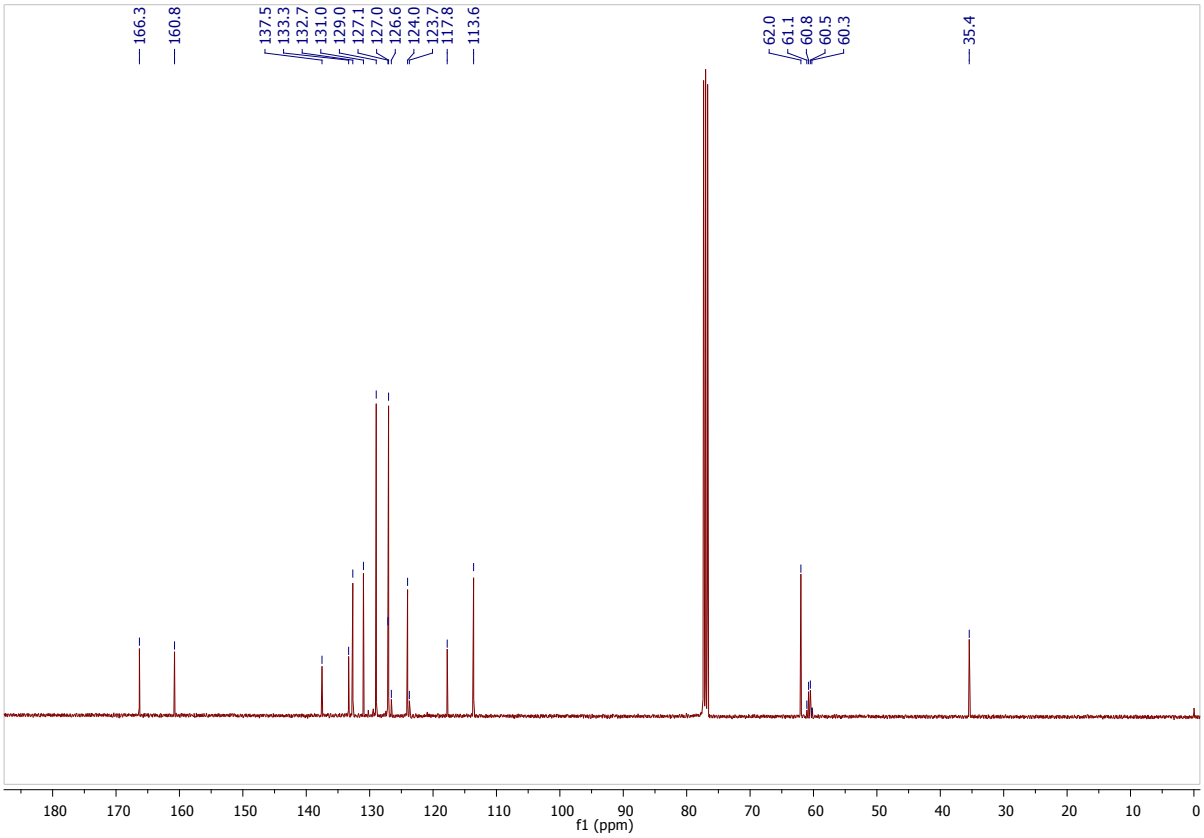


N-(1-Methoxy-2-oxo-4-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-4-yl)benzamide (10)

^{1}H NMR (400 MHz, $CDCl_3$), **^{19}F NMR** (376 MHz, $CDCl_3$):

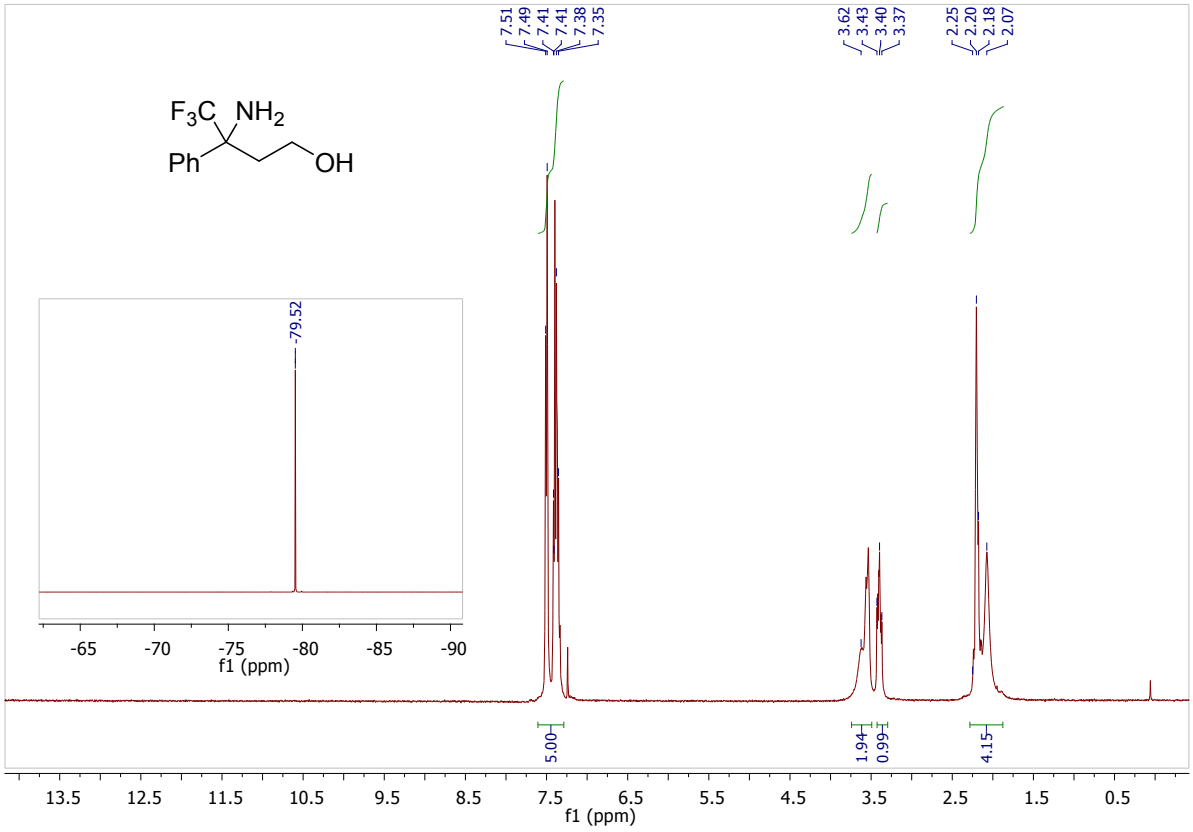


^{13}C NMR (101 MHz, $CDCl_3$):

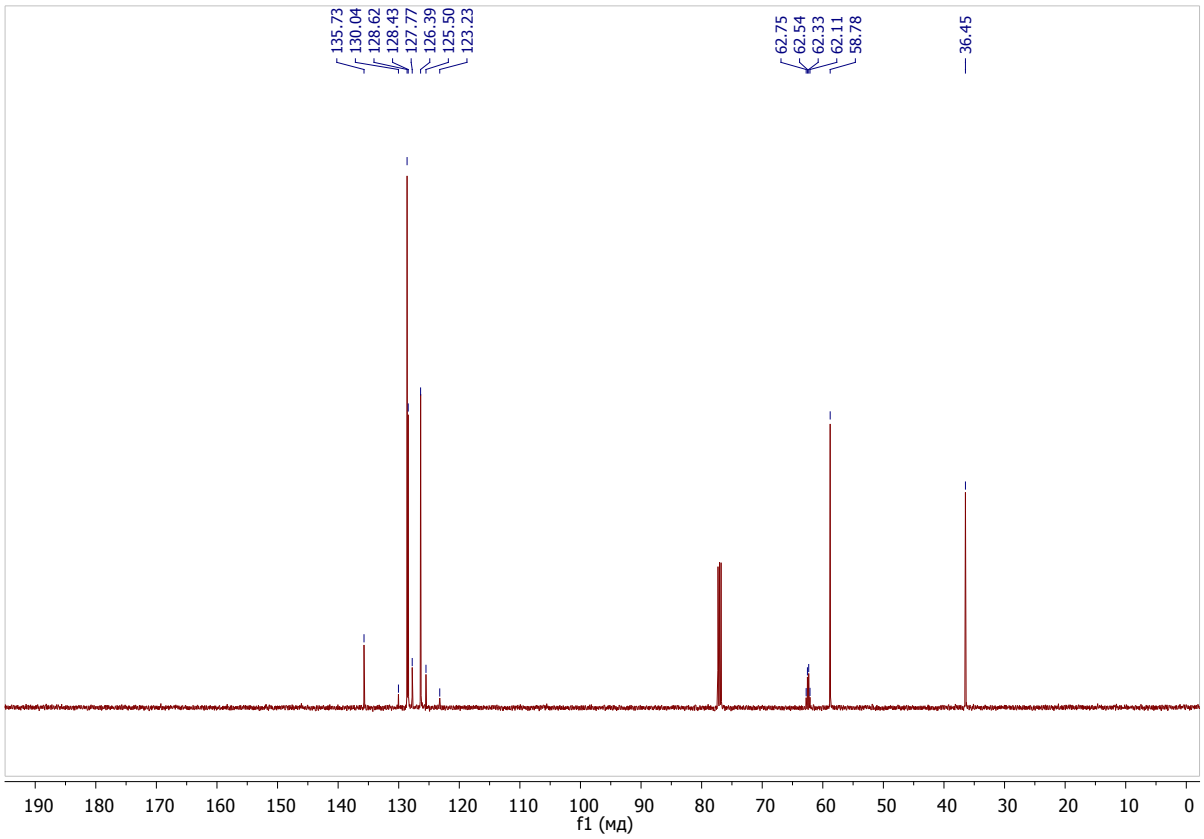


3-Amino-4,4,4-trifluoro-3-phenylbutan-1-ol (11)

^{1}H NMR (400 MHz, $CDCl_3$), **^{19}F NMR** (470 MHz, $CDCl_3$):

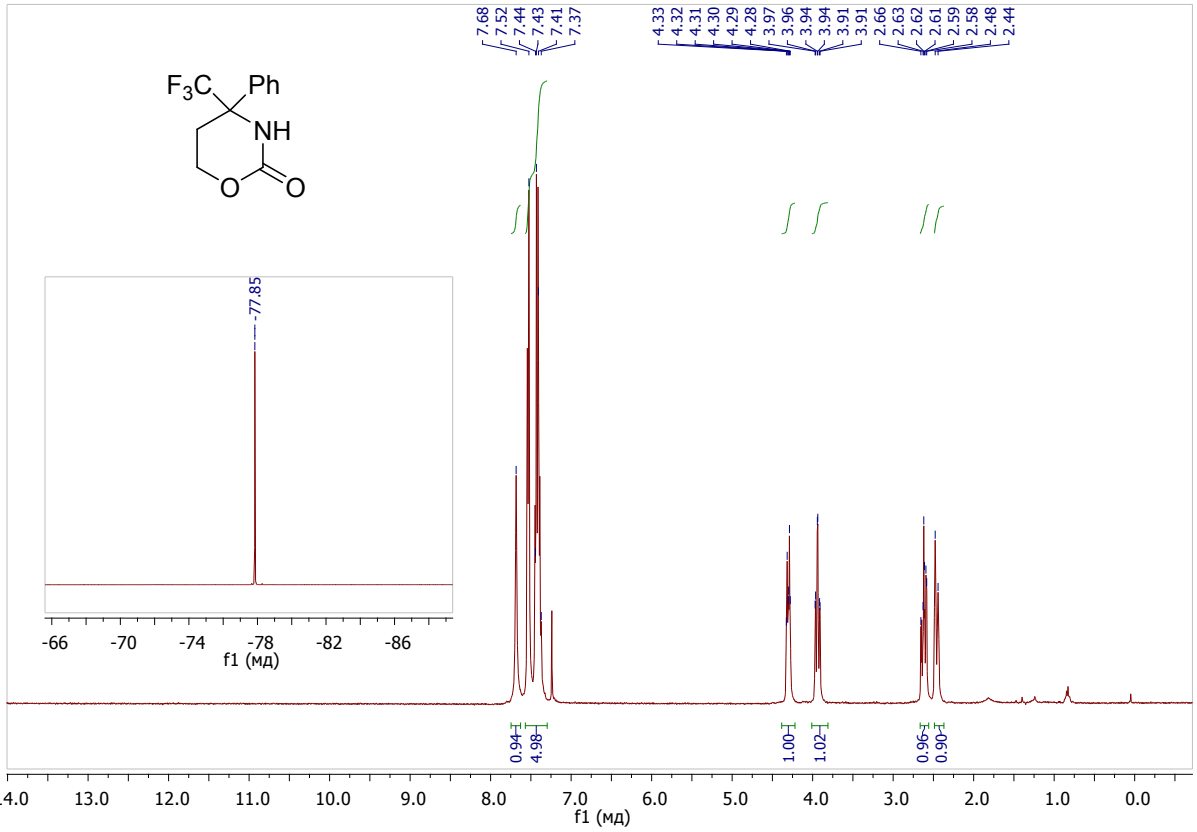


^{13}C NMR (126 MHz, $CDCl_3$):

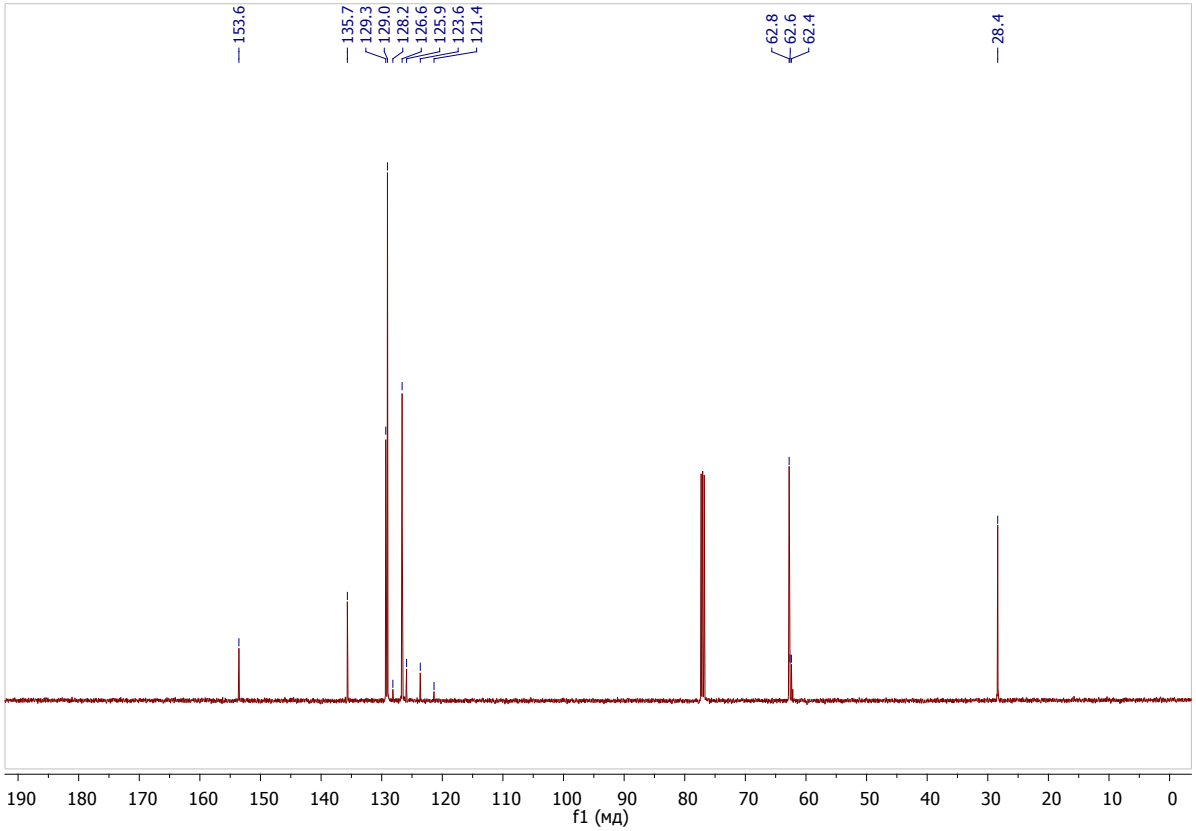


4-Phenyl-4-(trifluoromethyl)-1,3-oxazinan-2-one 12

^{1}H NMR (400 MHz, $CDCl_3$), **^{19}F NMR** (470 MHz, $CDCl_3$):

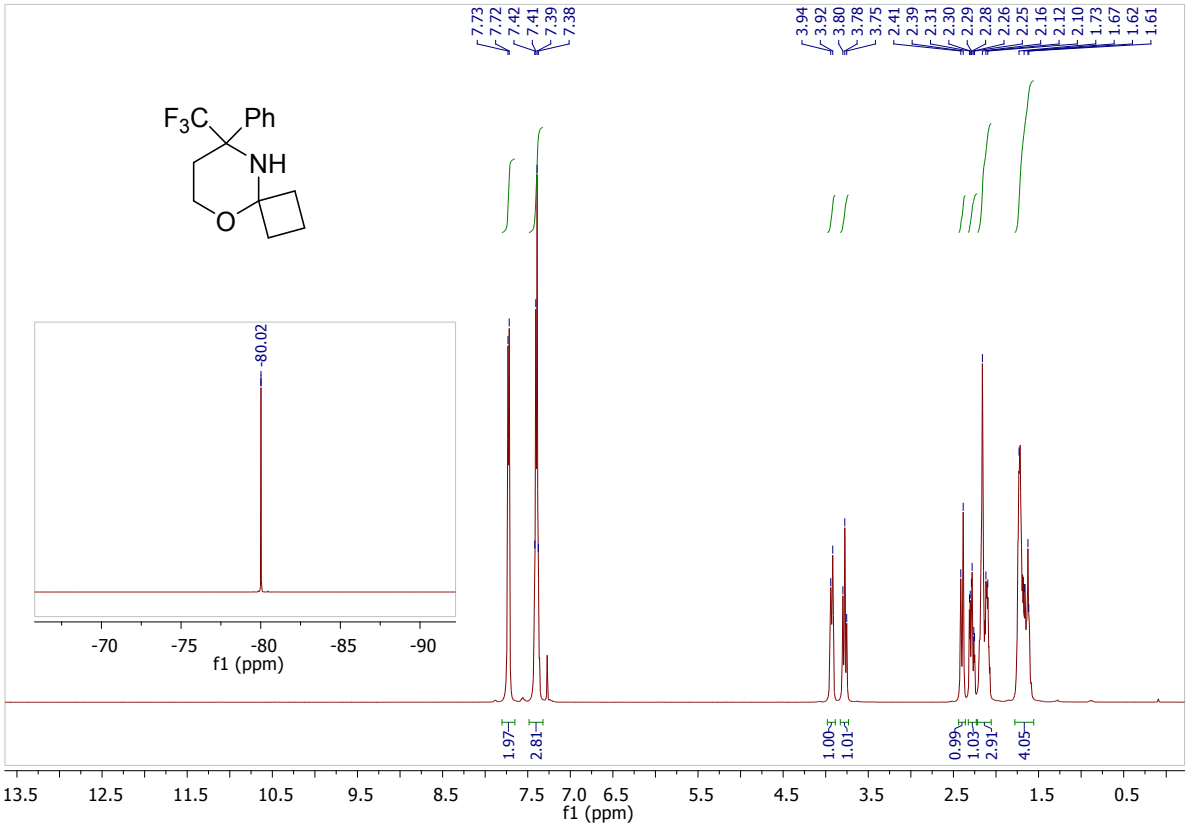


^{13}C NMR (126 MHz, $CDCl_3$):

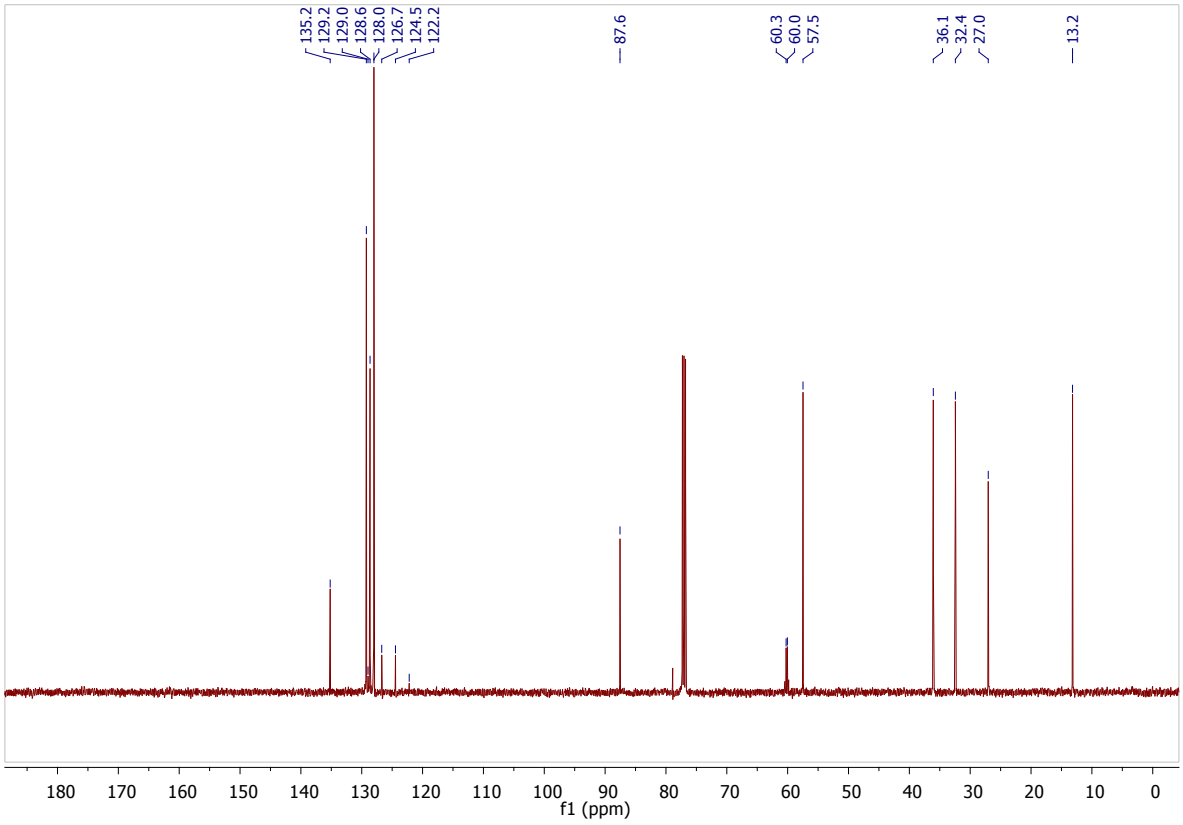


8-Phenyl-8-(trifluoromethyl)-5-oxa-9-azaspiro[3.5]nonane (13)

^{1}H NMR (500 MHz, DMSO-d_6), **^{19}F NMR** (470 MHz, $CDCl_3$):

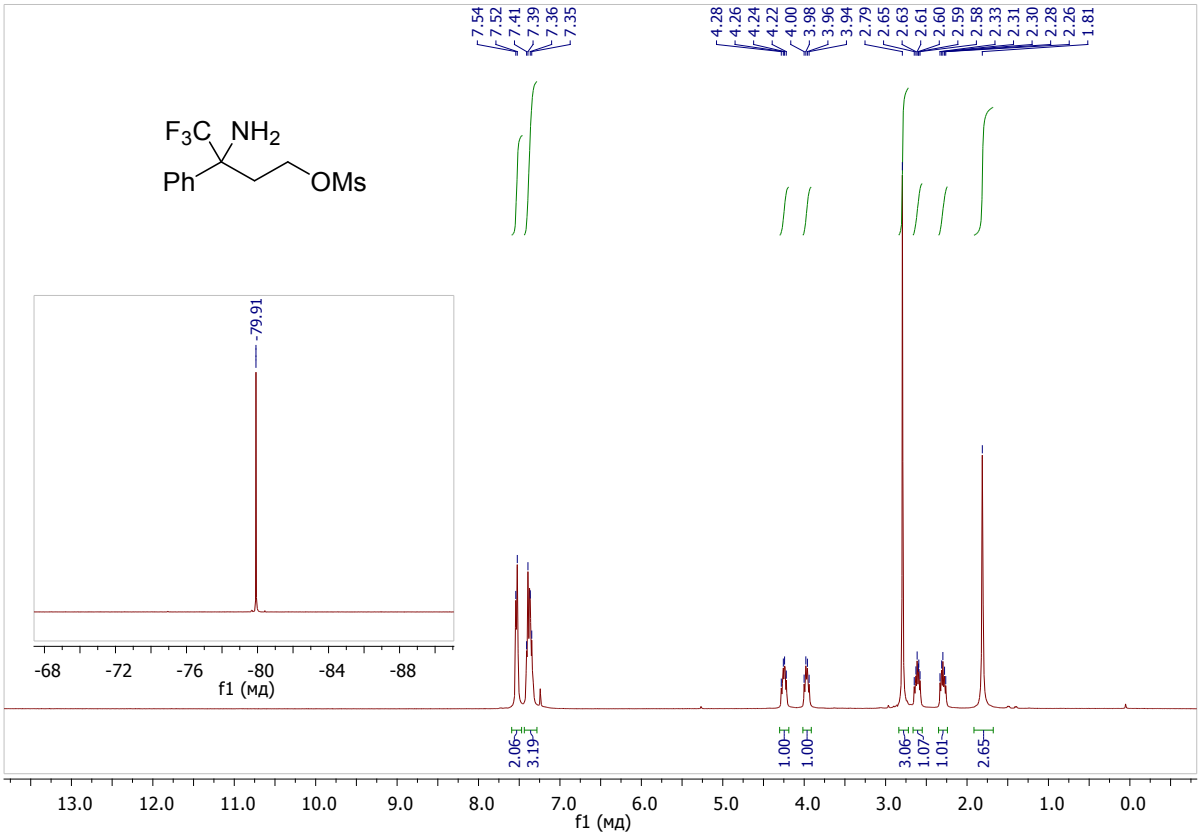


^{13}C NMR (126 MHz, $CDCl_3$):

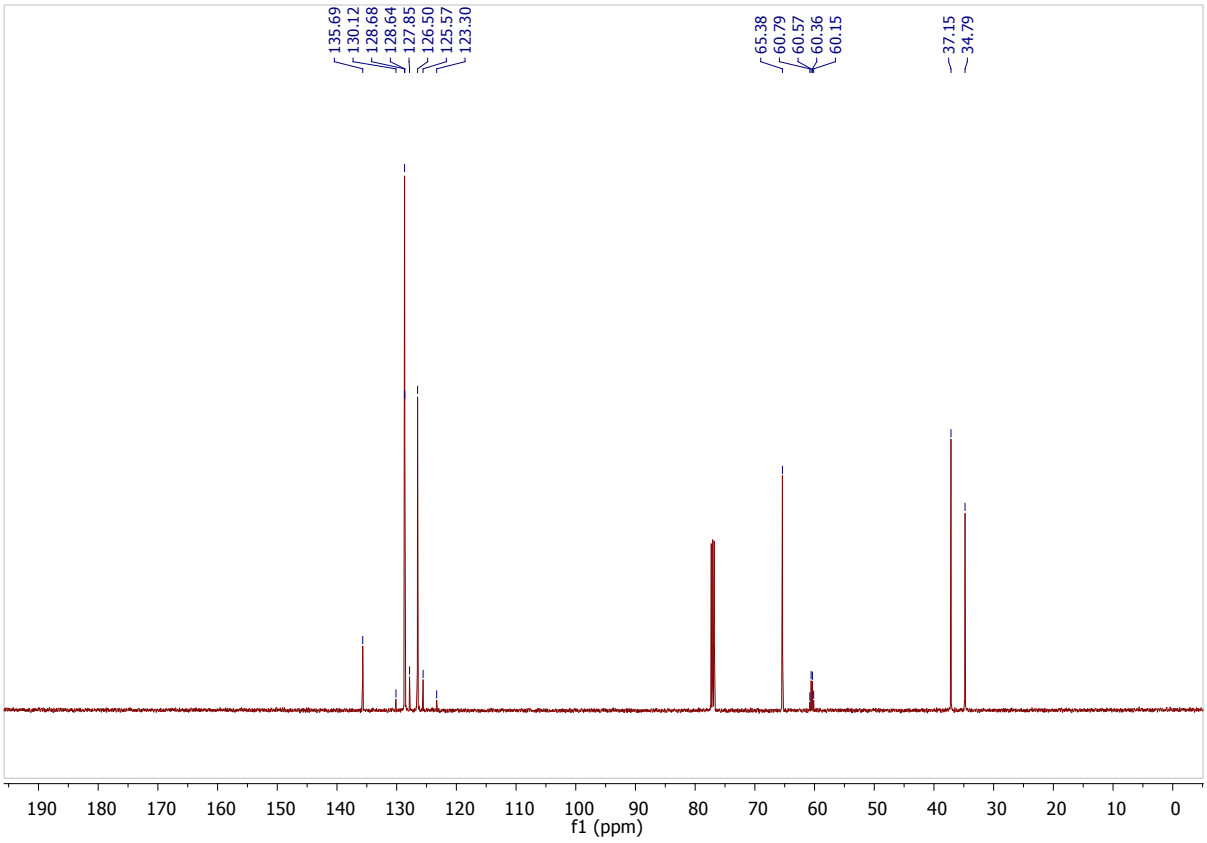


3-Amino-4,4,4-trifluoro-3-phenylbutyl methanesulfonate (14)

^{1}H NMR (400 MHz, $CDCl_3$), **^{19}F NMR** (376 MHz, $CDCl_3$):

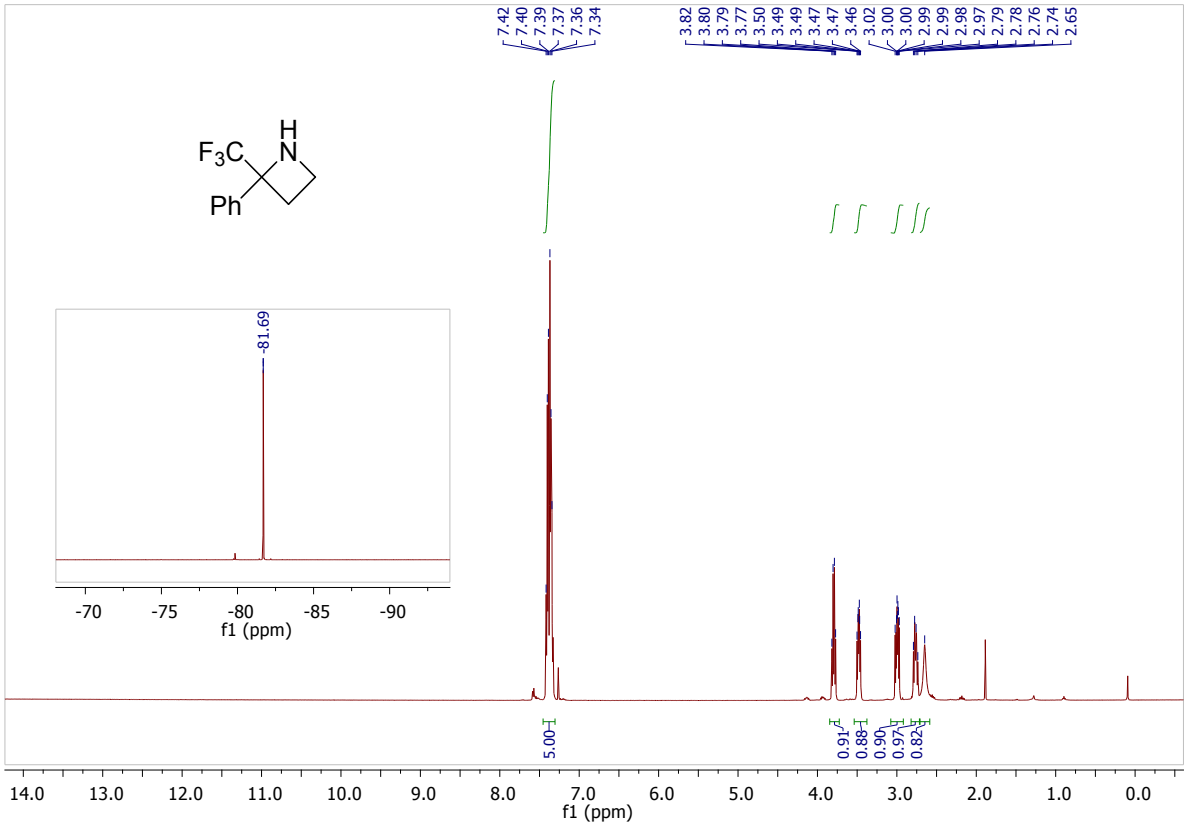


^{13}C NMR (126 MHz, $CDCl_3$):



2-Phenyl-2-(trifluoromethyl)azetidine (15)

^{1}H NMR (500 MHz, $CDCl_3$), **^{19}F NMR** (376 MHz, $CDCl_3$):



^{13}C NMR (126 MHz, $CDCl_3$):