Electronic Supplementary Material (ESI) for ChemComm.

Supporting information

Synthesis of *N*-CF_3 hydrazides through radical trifluoromethylation of azodicarboxylates

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I. Material and method: General information.

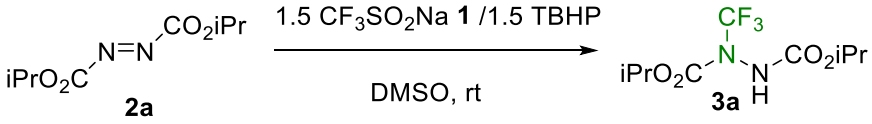
All experiments dealing with air and moisture-sensitive compounds were conducted under an atmosphere of dry argon. The usual solvents were purchased from commercial sources without further purification. Reagents were used without further purification as received from commercial. TLC analyses were performed on silica gel, 60 F250 (0.26 mm thickness) plates. The plates were visualized with UV light (λ = 254 nm) or with a 3.5% solution of phosphomolybdic acid in ethanol or with a solution of $KMnO_4$ in water. Compounds were purified by silica gel chromatography using Merck 60 silica gel (230 – 400 mesh).

NMR spectra were recorded on a Bruker AMX 200 (^{1}H, 200MHz; ^{19}F, 188 MHz), an ultrafield Bruker AVANCE 300 (^{1}H, 300 MHz, ^{13}C, 75 MHz). Chemical shift values (δ) for are reported in ppm downfield from Me_4Si (δ = 0.0 ppm) with the solvent resonance as the internal standard (^{1}H NMR, $CDCl_3$: δ = 7.26 ppm, CD_3OD : δ = 3.31 ppm; ^{13}C NMR, $CDCl_3$: δ = 77.16 ppm, CD_3OD: δ = 49.00 ppm) and internal $CFCl_3$ (0.0 ppm for ^{19}F NMR). Data are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet), coupling constant (Hz), integration, attribution. Melting points were determined on a Kofler melting point apparatus. High-resolution mass spectra (HRMS) were obtained using a TOF LCT Premier apparatus (Waters), with an electrospray ionization source. Melting point was measured on a W+M Heizbank System Kofler WME.

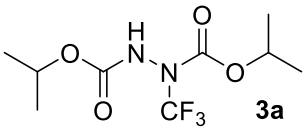
II. Experimental section: Synthesis and characterization of compounds

1. Trifluoromethylation of diazenes

General procedure for the trifluoromethylation of the diisopropyl 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate 3a



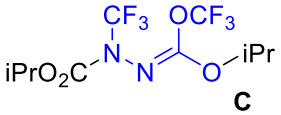
To a stirred solution of diazene **2a** (1.0 mmol) in DMSO (8 mL) and 70 % TBHP in water (1.5 mmol) was added at room temperature drop by drop the triflinate 1 (1.5 mmol) dissolved in water (2 mL). At the end of the addition the yellow disappeared to give a colorless media. After, 15 mL of water was added, and the reaction mixture was extracted with ether (3x15mL). The organic phases dried on Na_2SO_4 was evaporated under reduce pressure. The crude product was purified by column chromatography on silica gel using cyclohexane: ethyl acetate (70/30) as eluent to give *N*-CF_3 hydrazide **3a.**



The title compound was prepared between diazene **2a** (202 mg, 1 mmol) and TBHP (192 mg, 1.5 mmol) and triflinate **1** (2 mL, 1.5 mmol) in DMSO (8 ml) at rt, and purified on silica gel (cyclohexane/EtOAc : 70/30) to afford **3a** (123 mg, 45%).

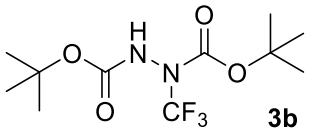
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.95 (s, 1H), 5.02-4.88 (m, 2H), 1.24 (d, *J* = 6.18 Hz, 6H), 1,20 (d, *J* = 6.60 Hz, 6H). **^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)** 154.9, 151.2, 120.1 (q, *J*= 261.9 Hz), 72.7, 70.9, 21.6, 21.5, 21.4. **^{19}F NMR (188 MHz, $CDCl_3$) δ (ppm)** -59.63 (s, CF_3). **HRMS *m/z*** $C_9H_{15}F_3N_2O_4$ $[M+Na]^+$ cal. 295.0882, found. 295.0875. m.p. = 67-68°C.

Isopropyl (Z)-2-(isopropoxy(trifluoromethoxy)methylene)-1-(trifluoromethyl)hydrazine-1-carboxylate C



^{1}H NMR (200 Hz, $CDCl_3$) δ (ppm) 5.08 (m, 2H), 7.25-7.11 (m, 2H), 1.38-1.28 (m, 12H). **^{13}C NMR (75 Hz, $CDCl_3$) δ (ppm)** 153.2, 148.7, 122.8 (q, *J* = 264.6 Hz), 119.3 (q, *J* = 266.7 Hz), 75.0, 74.5, 21.4, 21.3. **^{19}F NMR (188 Hz, $CDCl_3$) δ (ppm)** -59.4 (brs, 1xCF_3), and -65.1 (q, *J*= 4.3 Hz, 1xCF_3).

Di*ter*butyl 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate 3b

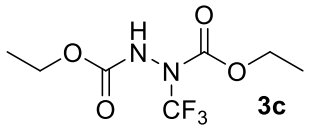


3b

The title compound was prepared between diazene **2b** (690 mg, 3 mmol), TBHP (405 mg, 4.5 mmol) and triflinate **1** (6 mL, 4.5 mmol) in DMSO (24 ml) at rt, and purified on silica gel (cyclohexane/EtOAc : 70/30) to afford **3b** (514 mg, 57%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.59 (br s, 1H), 1.52 (s, 9H), 1.49 (s, 9H). **^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)** 154.2, 150.3, 120.3 (q, *J* = 261.0 Hz), 84.9, 82.5, 27.9, 27.8. **^{19}F NMR (188 MHz, $CDCl_3$) δ (ppm)** -59.43 (s, CF_3). **H RMS *m/z*** $C_{11}H_{19}F_3N_2O_4$ $[M+Na]^+$ cal. 323.1195, found. 323.1195. m.p. = 69-70°C.

Diethyl 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate 3c



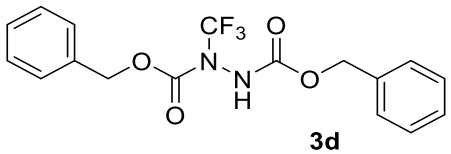
3c

(CF_3SO_2-N(CO_2Et)-NHCO_2Et was contained in it)

The title compound was prepared between diazene **2c** (174 mg, 1 mmol), TBHP (192 mg, 1.5 mmol) and triflinate **1** (2 mL, 1.5 mmol) in DMSO (8 ml) at rt, and purified on silica gel (cyclohexane/EtOAc : 70/30) to afford **3c** (117 mg, 48%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.23 (s, 1H), 4.24 (q, *J* = 7.13 Hz, 2H), 4.16 (q, *J* = 7.05 Hz, 2H), 1.24 (t, *J* = 5.31 Hz, 3H), 1.21 (t, *J* = 5.21 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)** 155.4, 151.7, 120.0 (q, *J* = 262.2 Hz), 64.2, 62.8, 14.1, 13.8. **^{19}F NMR (188 MHz, $CDCl_3$) δ (ppm)** -59.71 (s, CF_3). **HRMS *m/z*** $C_7H_{11}F_3N_2O_4$ $[M+Na]^+$ cal. 267.0569, found. 267.0564.

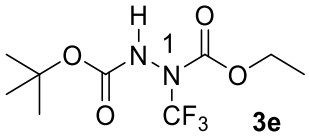
Dibenzyl 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate 3d



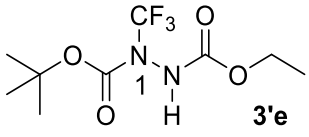
3d

The title compound was prepared between diazene **2d** (298 mg, 1 mmol), TBHP (192 mg, 1.5 mmol) and triflinate **1** (2 mL, 1.5 mmol) in DMSO (8 ml) at rt, and purified on silica gel (cyclohexane/EtOAc : 70/30) to afford **3d/4d** (69 mg, 19%).

2-(tert-butyl) 1-ethyl 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate and 1-(tert-butyl) 2-ethyl 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate 3e/3'e



3e

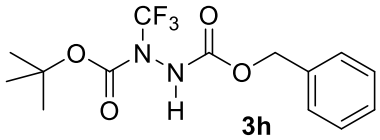


3'e

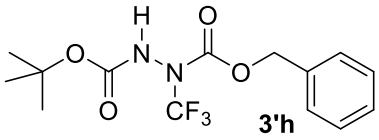
The title compound was prepared by diazene **2e**[1] (202 mg, 1 mmol), NBS (196 mg, 1.1 mmol) and pyridine (87 mg, 1.1 mmol), followed by TBHP (192 mg, 1.5 mmol) and triflinate **1** (2 mL, 1.5 mmol) in DMSO (8 ml) at rt, and purified on silica gel (cyclohexane/EtOAc : 70/30) to afford **3e/3'e** (141 mg, 49%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.82 and 6.70 (s, 1H), 4.25 (q, *J* = 7.01 Hz, 2H), 4.16 (q, *J* = 7.11 Hz, 2H), 1.44 (s, 9H), 1.41 (s, 9H), 1.25 (t, *J* = 5.2 Hz, 3H), 1.22 (t, *J* = 5.1 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)** 155.5, 154.1, 120.3 (q, *J* = 262.0 Hz), 121.1 (q, *J* = 261.9 Hz), 85.3, 82.8, 64.1, 62.7, 27.9, 27.8, 14.2, 14.0. **^{19}F NMR (188 MHz, $CDCl_3$) δ (ppm)** -59.26 (s, CF_3), -59.76 (s, CF_3). **HRMS *m/z*** $C_9H_{15}F_3N_2O_4$ $[M+Na]^+$ cal. 295.0882, found. 295.0883.

2-benzyl 1-(tert-butyl) 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate and 1-benzyl 2-(tert-butyl) 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate 3h/3'h



3h

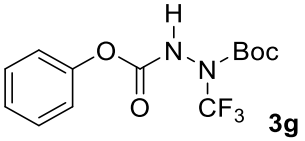


3'h

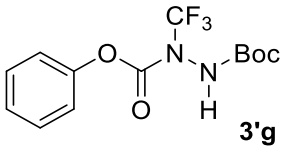
The title compound was prepared between diazene **2f**[2] (264 mg, 1 mmol), TBHP (192 mg, 1.5 mmol) and triflinate **1** (2 mL, 1.5 mmol) in DMSO (8 ml) at rt, and purified on silica gel (cyclohexane/EtOAc : 70/30) to afford **3h/3'h** (138 mg, 41%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.39-7.10 (m, 5H), 6.83 (s, 1H), 6.61 (s, 1H), 5.25-5.11 (m, 2H), 1.37 (s, 9H). **^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)** 155.3, 153.9, 151.7, 150.1, 135.2, 134.4, 128.7, 128.6, 128.3, 120.3 (q, *J* = 261.8 Hz), 120.1 (q, *J* = 262.7 Hz), 85.4, 82.9, 69.5, 68.3, 27.9, 27.5. **^{19}F NMR (188 MHz, $CDCl_3$) δ (ppm)** -59.25 (s, CF_3) and -59.72 (s, CF_3). **H RMS *m/z*** $C_{14}H_{17}F_3N_2O_4$ $[M+Na]^+$ cal. 357.1038, found. 357.1034.

1-(*tert*-butyl) 2-phenyl 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate and 2-(*tert*-butyl) 1-phenyl 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate 3g/3'g



3g

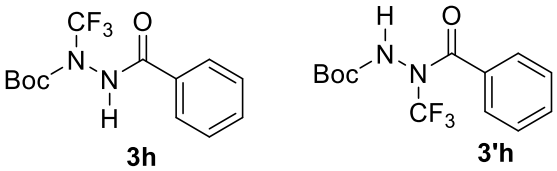


3'g

The title compound was prepared between diazene **2g**[3] (250 mg, 1 mmol), TBHP (192 mg, 1.5 mmol) and triflinate **1** (2 mL, 1.5 mmol) in DMSO (8 ml) at rt, and purified on silica gel (cyclohexane/EtOAc : 70/30) to afford **3g/3'g** (94 mg, 29%).

^{1}H NMR (200 Hz, $CDCl_3$) δ (ppm) 7.54-7.32 (m, 3H), 7.25-7.11 (m, 2H), 6.99 (s, 1H), 6.69 (s, 1H), 1.55 (s, 9H), 1.51 (s, 9H). **^{13}C NMR (75 Hz, $CDCl_3$) δ (ppm)** 153.1, 152.9, 149.4, 149.1, 128.6, 128.4, 125.6, 125.0, 120.1, 119.3 (q, *J* = 263.7 Hz), 119.1 (q, *J* = 265.6 Hz), 84.7, 26.9, 26.8. **^{19}F NMR (188 Hz, $CDCl_3$) δ (ppm)** -59.09 (s, CF_3) and -59.88 (s, CF_3). **HRMS *m/z*** $C_{13}H_{15}F_3N_2O_4$ $[M+Na]^+$ cal. 343.0882, found. 343.0873.

***Tert*-butyl 2-benzoyl-1-(trifluoromethyl)hydrazine-1-carboxylate and *tert*-butyl 2-benzoyl-2-(trifluoromethyl)hydrazine-1-carboxylate 3h/3'h**

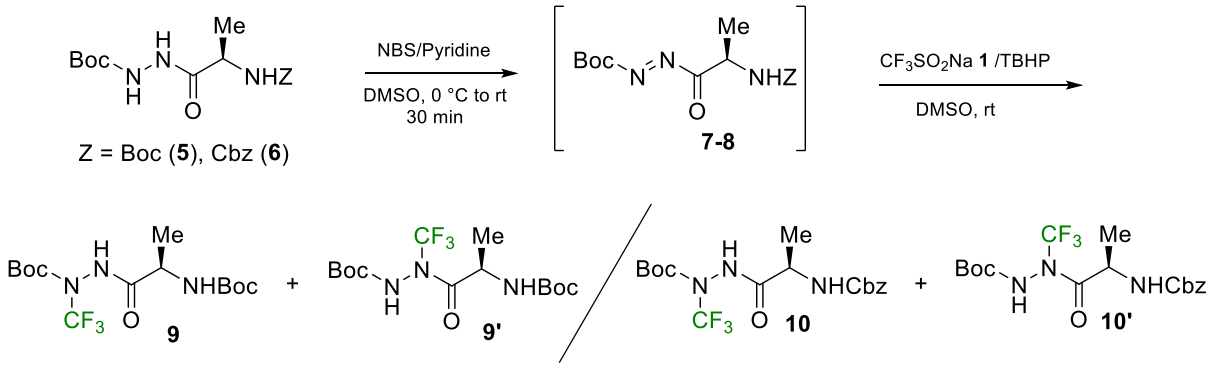


The title compound was prepared between diazene **2h**[1] from hydrazine (236 mg, 1 mmol) treated with NBS (196 mg, 1.1 mmol)/pyridine (87 mg, 1.1 mmol), TBHP (192 mg, 1.5 mmol) and triflinate **1** (2 mL, 1.5 mmol) in DMSO (8 ml) at rt, and purified on silica gel (cyclohexane/EtOAc : 70/30) to afford **3h/3'h** (98 mg, 32%).

(-SO_2CF_3 inside, **^{1}H NMR** and **^{13}C NMR** complex determination)

^{19}F NMR (188 Hz, $CDCl_3$) δ (ppm) -58.88 (s, CF_3) and -61.02 (s, CF_3). **HRMS *m/z*** $C_{13}H_{15}F_3N_2O_3$ $[M+NH_4]^+$ cal. 322.1379, found. 322.1382.

2. Preparation of *N*-CF_3 hydrazides 9-9' and **10-10' from hydrazines 5-6 *via* diazenes 7-8:**

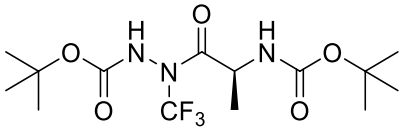


A stirred solution of hydrazines (**5-6**) and pyridine (1.1 eq.), in DMSO at 0 °C was treated with NBS (1.1 eq.) in a single portion. The reaction mixture was allowed to room temperature and stirred 5 min and had changed to a pale yellow to give the diazene **7, 8**. Then at room temperature, TBHP (1.5 eq.) and drop by drop the triflinate **1** (1.5 eq.) dissolved in water were added. At the end of the addition the yellow disappeared to give a colorless media. After, 15 mL of water was added, and the reaction mixture was extracted with ether (3x15mL). The organic phases dried on Na_2SO_4 was evaporated under reduce pressure. The crude product was

purified by column chromatography on silica gel using cyclohexane: ethyl acetate (80/20) as the eluent to give *N*-CF_3 hydrazide **9**, **9'** (51%), **10**, **10'** (26%).

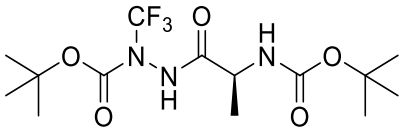
***Tert*-butyl 2-((tert-butoxycarbonyl)-L-alanyl)-2-(trifluoromethyl)hydrazine-1-carboxylate 9' and *Tert*-butyl 2-((tert-butoxycarbonyl)-L-alanyl)-1-(trifluoromethyl)hydrazine-1-carboxylate 9**

The title compounds **9**, **9'** were prepared between hydrazine **5** (303 mg, 1 mmol), NBS (196 mg, 1.1mmol), pyridine (87 mg, 1.1mmol) in DMSO (10 mL), then TBHP (192 mg, 1.5 mmol) and triflinate **1** (234 mg, 1.5 mmol) dissolved in water (2 mL), and purified on silica gel (cyclohexane/EtOAc : 80/20).



9'

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.18 (s, 1H), 5.35 (s, 1H), 4.66 (q, *J* =7.19 Hz, 1H), 1.42 and 1.41 (s, 9H), 1.35 and 1.33 (s, 9H), 1.26 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)** 174.6, 155.6, 154.1, 119.6 (q, *J* = 267.1 Hz), 83.1, 80.5, 47.1, 28.1, 27.9, 17.3. **^{19}F NMR (188 MHz, $CDCl_3$) δ (ppm) (mixture of rotational isomers)** -60.62 (s, CF_3), -60.59 (s, CF_3). **HRMS *m/z*** $C_{14}H_{24}F_3N_3O_5$ $[M+Na]^+$ cal. 394.1566, found. 394.1569. **$[\alpha]_D^{20}$** = +15.0° (*c* 0.0373, CH_3OH).

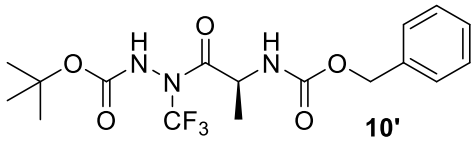


9

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.95 (s, 1H), 5.24-5.21 (brs, 1H), 4.65 (m, 1H), 1.42 (s, 9H), 1.36 (s, 9H), 1.31 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)** 174.5, 155.5, 149.7, 119.7 (q, *J* = 267.3 Hz), 83.0, 80.6, 47.1, 28.2, 27.9, 17.3. **^{19}F NMR (188 MHz, $CDCl_3$) δ (ppm)** -59.14 (s). **HRMS *m/z*** $C_{14}H_{24}F_3N_3O_5$ $[M+Na]^+$ cal. 394.1566, found. 394.1573. **$[\alpha]_D^{20}$** = -27.3° (*c* 0.0386, CH_3OH).

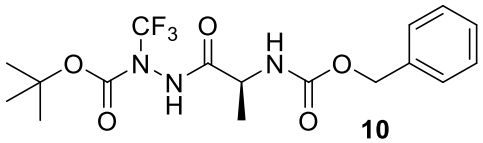
***Tert*-butyl 2-(((benzyloxy)carbonyl)-L-alanyl)-2-(trifluoromethyl)hydrazine-1-carboxylate 10' and *Tert*-butyl 2-(((benzyloxy)carbonyl)-L-alanyl)-1-(trifluoromethyl)hydrazine-1-carboxylate 10**

The title compounds **10**, **10'** were prepared between hydrazine **6** (337 mg, 1 mmol), NBS (196 mg, 1.1mmol), pyridine (87mg, 1.1mmol) in DMSO (10 mL), then TBHP (192 mg, 1.5 mmol) and triflinate **1** (234 mg, 1.5 mmol) dissolved in water (2 mL), and purified on silica gel (cyclohexane/EtOAc : 80/20).



10'

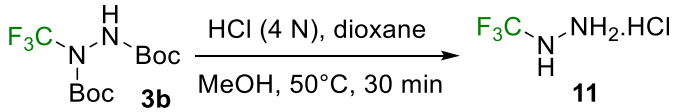
^{1}H NMR (300 MHz, CD_3OD) δ (ppm) 7.36-7.28 (m, 5H), 5.09 (m, 2H), 4.68 (q, *J* = 7.15 Hz, 1H), 1.52 (s, 9H), 1.37 (d, *J* = 7.14 Hz, 3H), 1.32 (d, *J* = 7.05 Hz, 3H). **^{13}C NMR (75 MHz, CD_3OD) δ (ppm)** 175.9, 175.5, 158.2, 138.1, 129.5, 129.0, 128.8, 121.4 (q, *J* = 265.4 Hz), 83.6, 67.8 49.5, 28.4, 16.9. **^{19}F NMR (188 MHz, $CDCl_3$) δ (ppm) (mixture of rotational isomers)** -59.45 (brs, CF_3), -60.30 (s, CF_3), -60.56 (s, CF_3). **HRMS *m/z*** $C_{17}H_{22}F_3N_3O_5$ $[M+Na]^+$ cal. 428.1409, found. 428.1416. **$[\alpha]_D^{20}$** = +23.6° (*c* 0.0233, CH_3OH).



10

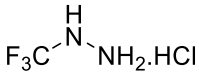
^{1}H NMR (300 MHz, CD_3OD) δ (ppm) 7.25-7.16 (m, 5H), 4.98 (m, 2H), 4.14 (q, *J* = 9.24 Hz, 1H), 1.39 and 1.36 (s, 9H), 1.29 (d, *J* = 4.41 Hz, 3H), 1.26 (d, *J* = 4.35 Hz, 3H). **^{13}C NMR (75 MHz, CD_3OD) δ (ppm)** 174.8, 158.2, 151.2, 138.1, 129.5, 129.0, 128.9, 121.7 (q, *J* = 260.5 Hz), 85.9, 67.7, 50.5, 28.1, 18.1. **^{19}F NMR (188 MHz, $CDCl_3$) δ (ppm) (mixture of rotational isomers)** -59.08 (s, CF_3). **HRMS *m/z*** $C_{17}H_{22}F_3N_3O_5$ $[M+Na]^+$ cal. 428.1409, found. 428.1401. **$[\alpha]_D^{20}$** = -37.6° (*c* 0.0086, CH_3OH).

3. Deprotection of Hydrazide 3b



3b **11**

(trifluoromethyl)hydrazine hydrochloride 11



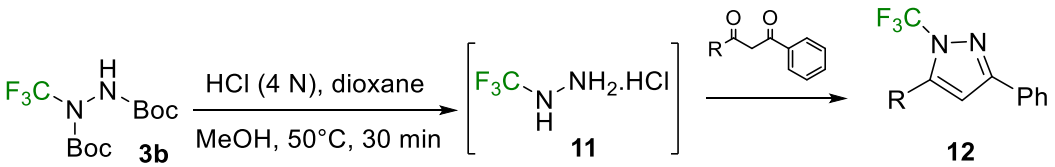
11

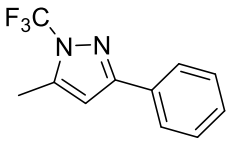
At a solution of *N*-CF_3 hydrazide **3b** (300 mg, 1 mmol) in dichloromethane (10 mL) was added HCl 4N in dioxane (10 eq.) at 0°C. After stirring overnight, the solvents are evaporated to afford crude solid.

^{1}H NMR (300 Hz, $CDCl_3$) δ (ppm) 5.36 (brs, 4H). **^{13}C NMR (75 Hz, CD_3OD) δ (ppm)** 124.0 (q, *J* = 259.9 Hz). **^{19}F NMR (188 Hz, CD_3OD) δ (ppm)** -66.63 (s, CF_3). **HRMS**: compound instable.

4. Synthesis of pyrazoles 12

5-methyl-3-phenyl-1-(trifluoromethyl)-1H-pyrazole 12a



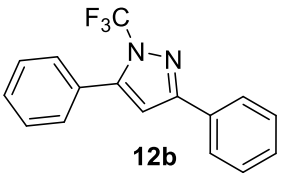


12a

At a solution of *N*-CF_3 hydrazide **3b** (326 mg, 1.1 mmol) and diketone (162 mg, 1 mmol) in MeOH (8 ml) was added HCl 4N in dioxane (4 mL) at 0°C. The mixture was stirred for 10 minutes at room temperature, then placed in a 60°C oil-bath for 30 minutes, the solution of reaction was concentrated, and crude product partitioned between CH_2Cl_2 and $NaHCO_3$ (aq), and the organic phase was separated and washed with NaCl (aq). The organic extract was dried (Na_2SO_4), filtered and concentrated. The compound was purified on silica gel to give pyrazole **12a** as a pale-yellow liquid in 44% yield.

^{1}H NMR (300 Hz, $CDCl_3$) δ (ppm) 7.35-7.24 (m, 5H), 6.09 (s, 1H), 2.23 (s, 3H). **^{13}C NMR (75 Hz, $CDCl_3$) δ (ppm)** 151.8, 145.6, 129.3, 128.9, 128.3, 126.1, 118.7 (q, *J* = 262.1 Hz), 111.1, 13.4. **^{19}F NMR (188 Hz, $CDCl_3$) δ (ppm)** -54.90 (s, CF_3) and -57.61 (s, CF_3, isomer). **HRMS *m/z*** $C_{11}H_9F_3N_2$ $[M+H]^+$ cal. 227.0796, found. 227.0804.

3,5-diphenyl-1-(trifluoromethyl)-1H-pyrazole 12b



12b

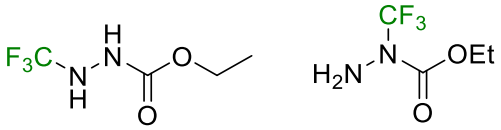
At a solution of *N*-CF_3 hydrazide **3b** (122 mg, 0.41 mmol) and diketone (82 mg, 0.37 mmol) in MeOH (3 mL) was added HCl 4N in dioxane (1.5 mL) at 0°C. The mixture was stirred for 10 minutes at room temperature, then placed in a 60°C oil-bath for 30 minutes, the solution of reaction was concentrated, and crude product partitioned between CH_2Cl_2 and $NaHCO_3$ (aq), and the organic phase was separated and washed with NaCl (aq). The organic extract was dried with Na_2SO_4, filtered and concentrated. The compound was purified on silica gel to give pyrazole **12b** as a colorless liquid in 46% yield.

^{1}H NMR (300 Hz, $CDCl_3$) δ (ppm) 7.78 (m, 2H), 7.37-7.29 (m, 8H), 6.60 (s, 1H). **^{13}C NMR (75 Hz, $CDCl_3$) δ (ppm)** 153.7, 146.0, 131.0, 129.6, 129.1, 129.04, 128.8, 128.4, 128.39, 126.3, 118.9 (q, *J* = 262.9 Hz), 108.2. **^{19}F NMR (188 Hz, $CDCl_3$) δ (ppm)** -54.88 (s, CF_3). **HRMS *m/z*** $C_{16}H_{11}F_3N_2$ $[M+H]^+$ cal. 289.0953, found. 289.0952.

5. General procedure of the Boc group deprotection

At a solution of *N*-CF_3 hydrazide in dichloromethane was added HCl 4N in dioxane (10 eq.) at 0°C. After stirring at room temperature overnight, the solvents are evaporated to afford crude as chlorhydrate salt or neutral compound which are or not purified on silica gel.

Ethyl 2-(trifluoromethyl)hydrazine-1-carboxylate 13 and Ethyl 1-(trifluoromethyl)hydrazine-1-carboxylate 14



13, 38% **14**[a]

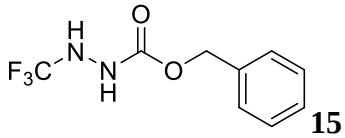
The title compounds **13** and **14** were prepared between hydrazine **3e**/**3'e** (544 mg, 2 mmol), in DCM (20 mL), then HCl 4N (5 ml, 20 mmol), and purified on silica gel (cyclohexane/EtOAc : 80/20).

13: ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 6.20 (brs, 1H), 5.32 (s, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H). **^{19}F NMR (188 MHz, $CDCl_3$) δ (ppm)** -67.20 (d, *J* = 6.2 Hz, CF_3). **^{19}F NMR (188 MHz, CD_3OD) δ (ppm)** -67.70 (s, CF_3). **^{13}C NMR (75 Hz, CD_3OD) δ (ppm)** 159.3, 124.7 (q, *J* = 255.1 Hz), 62.7, 14.8. **HRMS *m/z*** $C_4H_7F_3N_2O_2$ $[M+H]^+$ cal. 173.0521, found. 173.0565. m.p. = 92-93°C.

14: ^{19}F NMR (188 MHz, $CDCl_3$) δ -60.2 (s, CF_3). The product is volatile, spectra of crude in mixture with **13**.

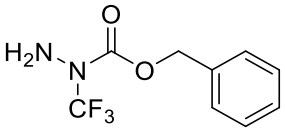
Benzyl 2-(trifluoromethyl)hydrazine-1-carboxylate 15 and benzyl 1-(trifluoromethyl)hydrazine-1-carboxylate 16

The title compounds **15** and **16** were prepared between hydrazine **3f**/**3'f** (334 mg, 1 mmol), in DCM (10 mL), then HCl 4N (2.5 mL, 10 mmol), purified and separated on silica gel (**cyclohexane**/**EtOAc** : 70/30) to afford **15** (35 %) and **16** (38 %) in global 73% yield.



15

Mp : 114-115 °C; **^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm)** 7.45-7.32 (m, 5H), 6.35 (s, 1H), 5.40 (s, 1H), 5.21 (s, 2H). **^{1}H NMR (300 MHz, CD_3OD) δ (ppm)** 7.38-7.2 (m, 5H), 5.15 (s, 2H). **^{13}C NMR (75 MHz, CD_3OD) δ (ppm)** 159.2, 137.7, 129.5, 129.2, 128.9, 124.8 (q, *J* = 255.0 Hz), 68.3. **^{19}F NMR (188 MHz, $CDCl_3$) δ (ppm)** -67.10 (d, *J* = 6.19 Hz, CF_3). **HRMS *m/z*** $C_9H_9F_3N_2O_2$ $[M-H]^-$ cal. 233.0538, found. 233.0536.

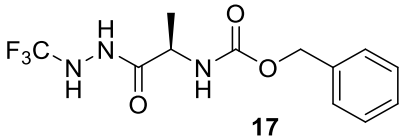


16

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.45-7.35 (m, 5H), 5.30 (s, 2H), 4.17 (brs, 2H). **^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)** 154.2, 134.7, 128.7, 128.4, 128.1, 120.7 (q, *J* = 259.4 Hz), 69.3. **^{19}F NMR (188 MHz, $CDCl_3$) δ (ppm)** -59.99 (s, CF_3). **HRMS *m/z*** $C_9H_9F_3N_2O_2$ $[M+Na]^+$ cal. 257.0514, found. 257.0489.

Benzyl (R)-(1-oxo-1-(2-(trifluoromethyl)hydrazineyl)propan-2-yl)carbamate 17 and benzyl (R)-(1-oxo-1-(1-(trifluoromethyl)hydrazineyl)propan-2-yl)carbamate 18

The title compounds **17** was prepared between hydrazine **10** (138 mg, 0.34 mmol), in DCM (5 mL), then HCl 4N (0.9 ml, 3.4 mmol), and obtained in 77% yield and in good purity without purification (presence of conformers and some traces of side products could not be removed).

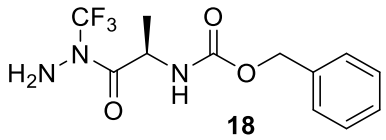


17

^{1}H NMR (300 MHz, CD_3OD) δ (ppm) 7.36-7.29 (m, 5H), 5,1 (s, 2H), 4.19 (q, *J* = 6.9 Hz, 1H), 1.36 (d, *J* = 6.96 Hz, 3H). **^{13}C NMR (75 MHz, CD_3OD) δ (ppm)** 175.5/174.2, 158.2, 138.1, 129.4, 129.0, 128.8, 124.5 (q, *J* = 256.0 Hz), 67.8/67.7, 50.5/50.6, 18.3. **^{19}F NMR (188 MHz, CD_3OD) δ (ppm)** -67.2 (s, CF_3). **HRMS**: *m/z* $C_{12}H_{14}F_3N_3O_3$ $[M+Na]^+$ cal. 328.0885, found. 328.0880. **$[\alpha]_D^{20}$** = -10.6° (*c* 0.036, CH_3OH).

Benzyl (R)-(1-oxo-1-(1-(trifluoromethyl)hydrazineyl)propan-2-yl)carbamate 18

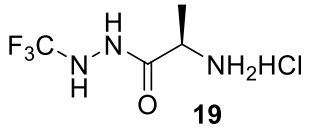
The title compounds **18** was prepared between hydrazine **10'** (200 mg, 0.49 mmol), in DCM (5 mL), then HCl 4N (1.3 ml, 4.9 mmol), and obtained in 79% yield and in good purity without purification.



18

Mp : 89-90 °C; **^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)** 7.50-7.18 (m, 5H), 5.60 (brs, 1H), 5.10 (m, 3H), 4.25 (brs, 2H), 1.39 (d, *J* = 6.84 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)** 175.0, 155.7, 136.3, 128.5, 128.2, 128.0, 120.5 (q, *J* = 264.2 Hz), 66.9, 48.6, 18.4. **^{19}F NMR (188 MHz, $CDCl_3$) δ (ppm)** -61.28 (s, CF_3). **HRMS *m/z*** $C_{12}H_{14}F_3N_3O_3$ $[M+H]^+$ cal. 306.1066, found. 306.1065. **$[\alpha]_D^{20}$** = -5.6° (*c* 0.078, CH_3OH).

(R)-2-amino-N'-(trifluoromethyl)propanehydrazide hydrochloride 19

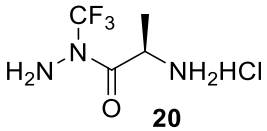


19

The title compounds **19** was prepared between hydrazine **9** (295 mg, 0.79 mmol), in DCM (8 mL), then HCl 4N (2 ml, 7.9 mmol), and obtained in quantitative yield as salt (some side products could not be removed).

^{1}H NMR (300 MHz, CD_3OD) δ (ppm) 4.0 (q, *J* =7.0 Hz), 1H), 1.54 (d, *J* =7.08 Hz, 3H). **^{13}C NMR (75 MHz, CD_3OD) δ (ppm)** 171.3, 124.4 (q, *J* = 256.5 Hz), 49.2, 17.5. **^{19}F NMR (188 MHz, CD_3OD) δ (ppm)** -67.08 (s, CF_3). **HRMS *m/z*** $C_4H_8F_3N_3O$ $[M+H]^+$ cal. 172.0698, found. 172.0690.

(R)-2-amino-N-(trifluoromethyl)propanehydrazide hydrochloride 20



20

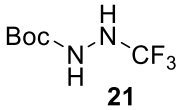
The title compounds **20** was prepared between hydrazine **9'** (392 mg, 1.06 mmol), in DCM (10 mL), then HCl 4N (2.6 ml, 10.6 mmol), and obtained in quantitative yield as salt.

^{1}H NMR (300 MHz, CD_3OD) δ (ppm) 4.8 (m, 1H), 1.64 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR (75 MHz, CD_3OD) δ (ppm)** 173.7, 121.8 (q, *J* = 264.4 Hz), 50.1, 16.3. **^{19}F NMR (188 MHz, CD_3OD) δ (ppm)** -63.11 (s, CF_3). **HRMS *m/z*** $C_4H_8F_3N_3O$ $[M+H]^+$ cal. 172.0698, found. 172.0691.

6. Deprotection of the Cbz group with hydrogen of hydrazides 3g/3'g

At a solution of hydrazides **3g/3'g** (334 mg, 1 mmol) in 10 mL methanol under hydrogen (1 atm) was added Pd/C 10%-15% (33 mg). After 3 h at room temperature, the mixture was filtered on celite and washed with ether. The solvents were evaporated under low pressure. The crude was purified on silica gel (eluent Cyclohexane/ether: 90/10) to afford **21** in 38%. Compound **22** is too volatile to give a yield.

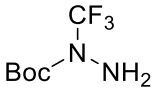
***Tert*-butyl 2-(trifluoromethyl)hydrazine-1-carboxylate 21**



21

Mp: 99-100 °C; **^{1}H NMR (300 Hz, $CDCl_3$) δ (ppm)** 6.14 (s, 1H), 5.39 (s, 1H), 1.50 (s, 9H). **^{13}C NMR (75 Hz, CD_3OD) δ (ppm)** 158.3, 124.8 (q, *J* = 254.8 Hz), 81.8, 28.54. **^{19}F NMR (188 Hz, $CDCl_3$) δ (ppm)** -67.2 (s, CF_3).

***Tert*-butyl 1-(trifluoromethyl)hydrazine-1-carboxylate 22**

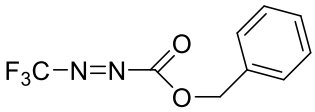


22

Presence of compound **21**. ^{1}H **NMR (300 Hz, $CDCl_3$) δ (ppm)** 4.0 (s, 2H), 1.52 (s, 9H). **^{13}C NMR (75 Hz, $CDCl_3$) δ (ppm)** 153.1, 153.1, 120.9 (q, *J* = 258.8 Hz), 84.8, 27.9. **^{19}F NMR (188 Hz, $CDCl_3$) δ (ppm)** -59.57 (s, CF_3).

7. Reactions with the compound 15

Benzyl 2-(trifluoromethyl)diazene-1-carboxylate 23

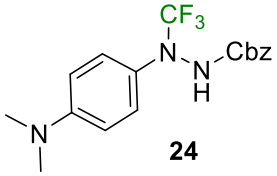


23

In CH_2Cl_2 solvent. **^{19}F NMR (188 Hz, $CDCl_3$) δ (ppm)** -75.34 (s, CF_3).

In a solution of *N*-CF_3 hydrazide **15** (140 mg, 0.66mmol) in dichloromethane (6 mL) were added successively at 0°C, pyridine (52 mg, 0.66mmol) and NBS (117 mg, 0.66 mmol). After 10 minutes, the solution of **23** in dichloromethane was directly used for the next step.

Benzyl 2-(4-(dimethylamino)phenyl)-2-(trifluoromethyl)hydrazine-1-carboxylate 24



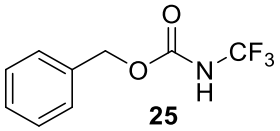
24

At the previous solution of *N*-CF_3 azodicarboxylate **23** in CH_2Cl_2 was added 2 mL of hexafluoroisopropanol (HFIP) then the dimethylaniline (66 mg, 0.55 mmol) at 25°C. The mixture was stirred at this temperature for 5 h. Upon completion of the reaction, the mixture was concentrated under reduce pressure to give a crude product. Then, the crude product was purified by column chromatography (silica gel; cyclohexane/Ethyl acetate, 70/30) to afford **24** in 71% yield in two steps.

Mp : 139-140 °C; **^{1}H NMR (300 Hz, $CDCl_3$) δ (ppm)** 7.23-7.14 (m, 7H), 6.80 (s, 1H), 6.54 (m, 2H), 5.05 (s, 2H), 2.84 (s, 6H). **^{13}C NMR (75 Hz, $CDCl_3$) δ (ppm)** 155.6, 150.4, 135.6, 129.7, 128.6, 128.3, 128.11, 126.9, 122.7 (q, *J* = 256.9 Hz), 112.4, 67.8, 40.4. **^{19}F NMR (188 Hz, $CDCl_3$) δ (ppm)** -64.77 (s, CF_3). **HRMS *m/z*** $C_{17}H_{18}F_3N_3O_2$ $[M+H]^+$ cal. 354.1429, found. 354.1429.

8. Reactions with the compound 16.

Benzyl (trifluoromethyl)carbamate 25[4]

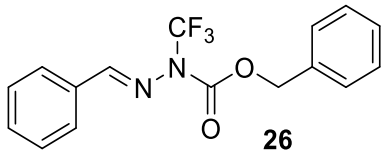


25

To a stirred mixture of **16** (100 mg, 0.43 mmol) in 1.5 mL of acetic acid and 0.5 mL of 1N hydrochloric acid, a solution of sodium nitrite (30 mg, 0.43 mmol) in 0.5 mL of water was added dropwise at 5°C. The reaction mixture was stirred at 5°C for 20 minutes, then warmed to rt for 3 h, solution of reaction was concentrated, the resulting residue was diluted with ether, solid was filtered. After removal of the solvents to give **25** as a pale-yellow solid in 92% yield.

Mp : 66-67 °C; **^{1}H NMR (300 Hz, $CDCl_3$) δ (ppm)** 7.41-7.34 (m, 5H), 6.66 (brs, 1H), 5.22 (s, 2H). **^{13}C NMR (75 Hz, $CDCl_3$) δ (ppm)** 151.2, 134.7, 128.7, 128.6, 128.3, 118.8 (q, *J* = 256.9 Hz), 68.3. **^{19}F NMR (188 Hz, $CDCl_3$) δ (ppm)** -56.89 (s, CF_3). **HRMS *m/z*** $C_9H_8F_3NO_2$ $[M-H]^-$ cal. 218.0429, found. 218.0431.

Benzyl (E)-2-benzylidene-1-(trifluoromethyl)hydrazine-1-carboxylate 26

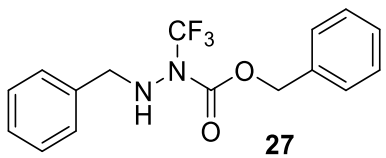


26

Compound **16** (78 mg, 0.15 mmol) was mixed with benzaldehyde (29 mg, 0.12 mmol) in dichloromethane, followed by $MgSO_4$ at rt. After stirring overnight, $MgSO_4$ was filtered, and the solvent was evaporated to give 118 mg of hydrazone **26**.

^{1}H NMR (300 Hz, $CDCl_3$) δ (ppm) 8.48 (s, 1H), 7.65-7.62 (m, 2H), 7.38-7.30 (m, 3H), 7.25-7.22 (m, 5H), 5.20 (s, 2H). **^{13}C NMR (75 Hz, $CDCl_3$) δ (ppm)** 164.3, 151.7, 134.7, 132.7, 131.9, 128.8, 128.7, 128.67, 128.5, 128.0, 120.7 (q, *J* = 262.2 Hz), 69.3. **^{19}F NMR (188 Hz, $CDCl_3$) δ (ppm)** -59.17 (s, CF_3). **HRMS *m/z*** $C_{16}H_{13}F_3N_2O_2$ $[M+Na]^+$ cal. 345.0827, found. 345.0781.

Benzyl 2-benzyl-1-(trifluoromethyl)hydrazine-1-carboxylate 27

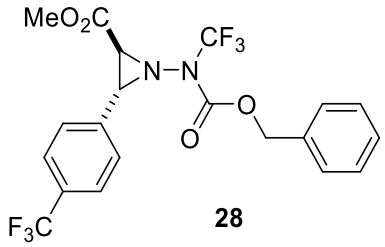


27

The crude compound **26** was directly used and dissolved in THF (4 mL) and acetic acid (0.74 mmol) then $NaBH_3CN$ (35 mg, 0.56 mmol) was added at rt. After 12 hours of stirring, the reaction medium was quenched with a aqueous saturated solution of $NaHCO_3$, the mixture was stirred for 30 minutes. The crude was then extracted with ether and purified by chromatography on silica gel (eluent AcOEt/Cyclohexane ; 70/30) to give the compound **27** in 70% yield.

^{1}H NMR (300 Hz, $CDCl_3$) δ (ppm) 7.33-7.25 (m, 5H), 7.23-7.18 (m, 5H), 5.19 (s, 2H), 4.32 (brs, 1H), 3.93 (d, *J* = 6.03 Hz, 2H). **^{13}C NMR (75 Hz, $CDCl_3$) δ (ppm)** 153.5, 136.0, 134.7, 129.3, 128.7, 128.5, 128.1, 128.0, 125.5, 120.9 (q, *J* = 260.9 Hz), 69.3, 56.1. **^{19}F NMR (188 Hz, $CDCl_3$) δ (ppm)** -59.50 (s, CF_3). **HRMS *m/z*** $C_{16}H_{15}F_3N_2O_2$ $[M+Na]^+$ cal. 347.0983, found. 347.0979.

Methyl *trans*-1-(((benzyloxy) carbonyl) (trifluoromethyl)amino)-3-(4-(trifluoromethyl) phenyl) aziridine-2-carboxylate 28[5]



28

N-CF_3 hydrazine **16** (62 mg, 0.26 mmol, 1 equiv) was added to a solution of alkene (43 mg, 0.26 momol, 1 equiv), iodobenzene diacetate (1.5 equiv) and K_2CO_3 (2.8 equiv) in dichloromethane. The resulting solution was stirred at room temperature until 12 hours. The reaction medium was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was then purified by chromatography on silica gel (eluent AcOEt/Cyclohexane: 80/20) to afford the compound **28** in 83% yield.

^{1}H NMR (300 Hz, $CDCl_3$) δ (ppm) 7.46 (d, *J* = 8.25 Hz, 2H), 7.25-7.15 (m, 7H), 5.16 (d, H_a, *J* = 12.15 Hz, 1H), 5.10 (d, H_b, *J* = 12.12 Hz, 1H), 4.01 (d, *J* = 5.07 Hz, 1H), 3.63 (s, 3H), 3.16 (d, *J* = 5.22 Hz, 1H). **^{13}C NMR (75 Hz, $CDCl_3$) δ (ppm)** 165.6, 152.5, 138.6, 134.2, 130.7 (q, *J* = 32.6 Hz), 128.7, 128.6, 128.2, 127.1, 125.5 (q, *J* = 3.4 Hz), 123.9 (q, *J* = 272.2 Hz), 121.1 (q, *J* = 266.8 Hz), 69.5, 52.8, 51.5, 49.0. **^{19}F NMR (188 Hz, $CDCl_3$) δ (ppm)** -58.77 (s, CF_3), -62.76 (s, CF_3). **H RMS *m/z*** $C_{20}H_{16}F_6N_2O_4$ $[M+Na]^+$ cal. 485.0912, found. 485.0915.

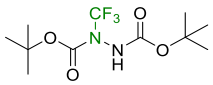
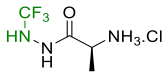
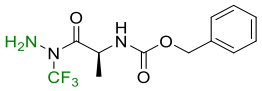
III. Crystallographic details: Crystallographic data collection, structure determination and refinement

Colourless crystals suitable to single crystal X-ray diffraction (SCXRD) analysis were obtained for each compound by slow evaporation of diethylether in solution with cyclohexane for **3b** and **18**, and by mixture of diethylether and methanol for **19**.

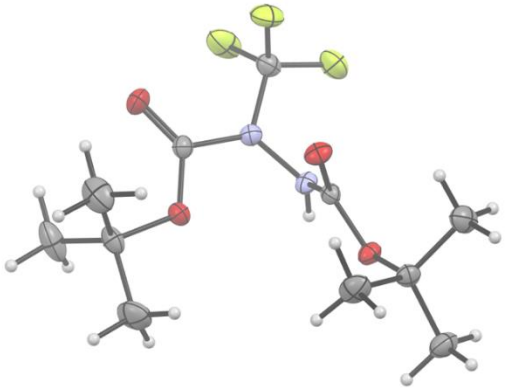
Diffraction data for **3b** and **19** were measured at 173K for the first compound and at room temperature for the second one using a RIGAKU *XtaLabPro* diffractometer equipped with a Mo microfocus sealed tube *MM003* generator coupled to a double-bounce confocal Max-Flux® multilayer optic and a HPAD *PILATUS3R 200K* detector. *CrysAlisPro 1.171.39.46* [6] was employed for the data processing, with *SCALE3 ABSPACK* scaling algorithm implemented for the empirical absorption correction using spherical harmonics. Regarding the third compound, namely **18,** the weakly diffracting crystals were better analyzed also at room temperature using a RIGAKU MM007 HF rotating anode delivering copper radiation through Osmic CMF confocal optics, and a Rapid II curved Image Plate detector. *Fs_process*[7] software comprised in the *CrystalClear 2.0* [8] suite was employed to integrate and scale these data, applying multi-scan *REQAB*[7] for the absorption correction. Nevertheless, no significant signal could be detected at the edge of the large area curved imaging plate and decision was taken to apply a high resolution limit cut-off to 0.96Å. The three structures were all solved by intrinsic phasing methods (*SHELXT* program),[9] then refined by full-matrix least-squares methods on F^2 using *SHELX-L*.[10] All non-hydrogen atoms of the molecules of interest improved by anisotropic refinement. Most of their H atoms were clearly identified in difference maps but were positioned geometrically -or allowed as rigid groups to rotate but not tip regarding the methyl H atoms and those of the $–NH_3^+$ group of the salt **19** structure and refined isotropically with U_{iso} set to $1.2U_{eq}$(C) of the parent carbon or nitrogen atom (or 1.5 for the methyl or the water H atoms). H atom positions were refined in the two N–bound H atoms in **3b** while the N–H distances were restrained to 0.88(1)Å in **18** and the N-bound H atom was freely refined in the case of the low temperature **3b** structure. O–H distances were restrained to 0.83(1)Å, as well as the H-O-H angle, intermolecular H-bond distances for the water molecule trapped in the asymmetric unit (asu) containing three conformers of **18**. For this latter structure, weak data associated with elevated Rint (*ca* 13%) let suggest twinning possibility that *TwinRotMat* routine within *PLATON* [11] did not permit us to discount. SIMU and DELU restraints with default values for the standard deviations were applied to the atoms of the phenyl groups to provide reasonable displacement ellipsoids. Furthermore if the anomalous dispersion mainly provided by the chloride ion confirmed without any ambiguity the *S*-form of the **19** cation via the Flack parameter,[12] x = -0.01(8), this information was hidden in the too noisy data recorded however at the copper wavelength in the case of **18** and the *S*-enantiomer (in triplicate in the asu and known from the starting material), refined as a meaningless two-component inversion twin, was therefore chosen. Crystal data, data collection and structure refinement details are summarized in Table S1.

CCDC 2049521-2049523 (for **3b**, **19**, and **18** respectively) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

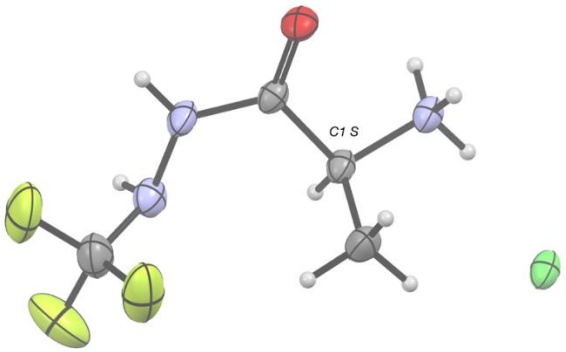
Table S1 Crystal data, data collection and structure refinement details.

Compound	**3b**	**19**	**18**
			
	di-*tert*-butyl 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate	(*S*)-1-oxo-1-(2-(trifluoromethyl)hydrazine)propan-2-aminium chloride	benzyl (*S*)-(1-oxo-1-(1-(trifluoromethyl)hydrazine)propan-2-yl)carbamate
Empirical formula	$C_{11}H_{19}F_3N_2O_4$	$C_4H_9F_3N_3O^+Cl^-$	$C_{12}H_{14}F_3N_3O_3$, *0.33 (H_2O)*
Formula weight	300.28	207.59	311.27
Temperature (K)	173(2)	293(2)	293(2)
Wavelength (Å)	0.71073	0.71073	1.54187
Crystal system, space group	Monoclinic, $P2_1/c$	Monoclinic, $P2_1$	Monoclinic, $P2_1$
Unit cell dimensions | (Å) | (°)	9.7754(3) 16.4149(5) 9.7376(3) 90 102.260(3) 90	4.9770(3) 7.7308(6) 11.6315(12) 90 90.771(7) 90	5.128(3) 27.296(13) 15.794(9) 90 95.556(12) 90
Volume ($Å^3$)	1526.88(8)	447.50(6)	2200.3(19)
Z, Calculated density (Mg/m^3)	4, 1.306	2, 1.541.	6, 1.409.
Absorption coefficient (mm^{-1})	0.121	0.436	1.122
F(000)	632	212	968

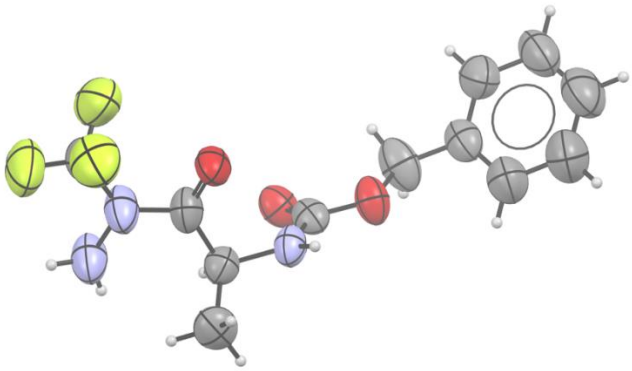
Crystal size (mm)		0.24 x 0.14 x 0.12	0.23 x 0.20 x 0.04	0.32 x 0.11 x 0.09
θ range for data collection (°)		4.535 to 26.731	4.095 to 26.366	2.811 to 53.421
Limiting indices		-12 ≤ h ≤ 12, -20 ≤ k ≤ 20, -12 ≤ l ≤ 12	-6 ≤ h ≤ 6, -9 ≤ k ≤ 9, -13 ≤ l ≤ 14	-5 ≤ h ≤ 3, -28 ≤ k ≤ 28, -16 ≤ l ≤ 16
Reflections collected / unique		15733 / 3226	5704 / 1759	18721 / 5160
R(int)		0.0324	0.0523	0.1440
Completeness to θ_{full} (%)		99.2	99.4	99.8
Absorption correction		Semi-empirical from equivalents		
Max. and min. transmission		1.000 and 0.836	1.000 and 0.360	1.000 and 0.676
Refinement method		Full-matrix least-squares on F^2		
Data / restraints / parameters		3213 / 0 / 191	1753 / 1 / 117	5157 / 196 / 602
Goodness-of-fit on F^2		1.050	1.025	0.923
Final R indices [$I>2\sigma(I)$]	R1, wR2	0.0373, 0.0923	0.0389, 0.0894	0.0891, 0.2072
R indices (all data)	R1, wR2	0.0445, 0.0961	0.0508, 0.0953	0.1368, 0.2454
Absolute structure parameters		n/a	-0.01(8)	0.4(5)
Largest Δ peak and hole (e.Å^{-3})		0.261 and -0.212	0.376 and -0.245	0.272 and -0.215
CCDC deposit number		2049521	2049522	2049523



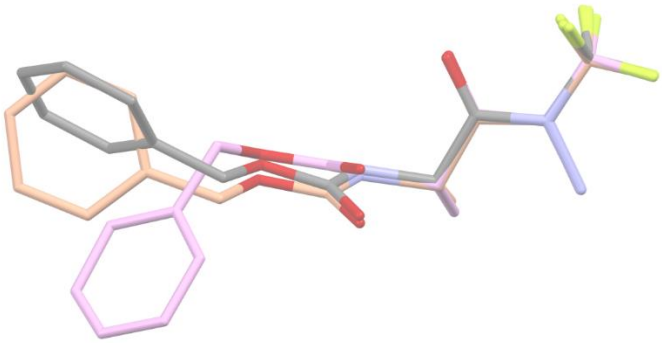
Ortep view of **3b**. Ellipsoids are drawn at 30% of probability.



Ortep view of the chloride salt of the **19** stereoisomer. Ellipsoids are drawn at 30% of probability.



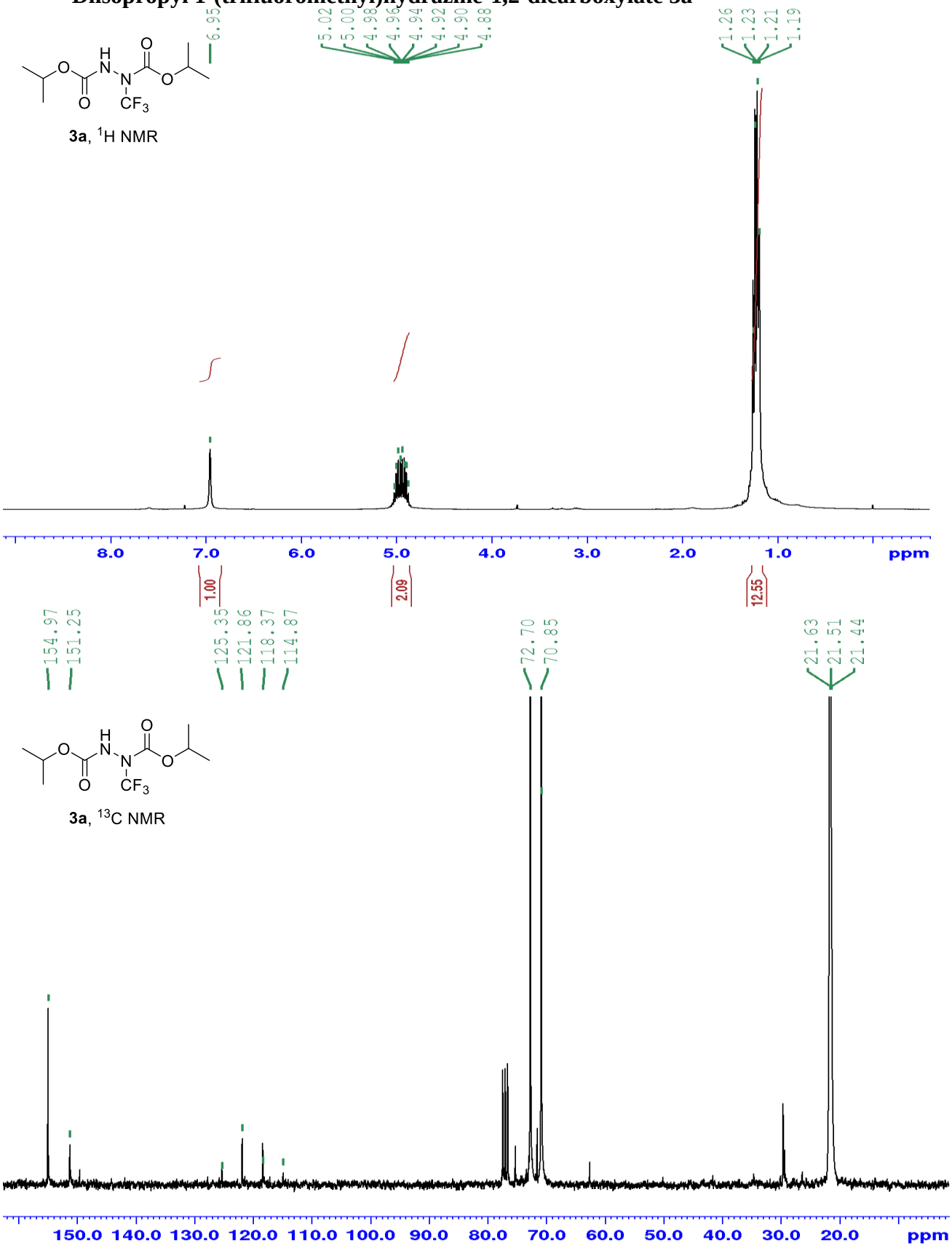
Ortep view of one conformer out of three stereoisomers **18**. Ellipsoids are drawn at 30% of probability.



Overlay view of the three stereoisomers **18** upon the *N*-CF_3 hydrazide part.

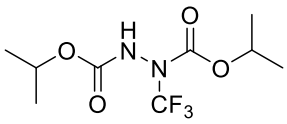
IV. NMR spectra

Diisopropyl 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate 3a

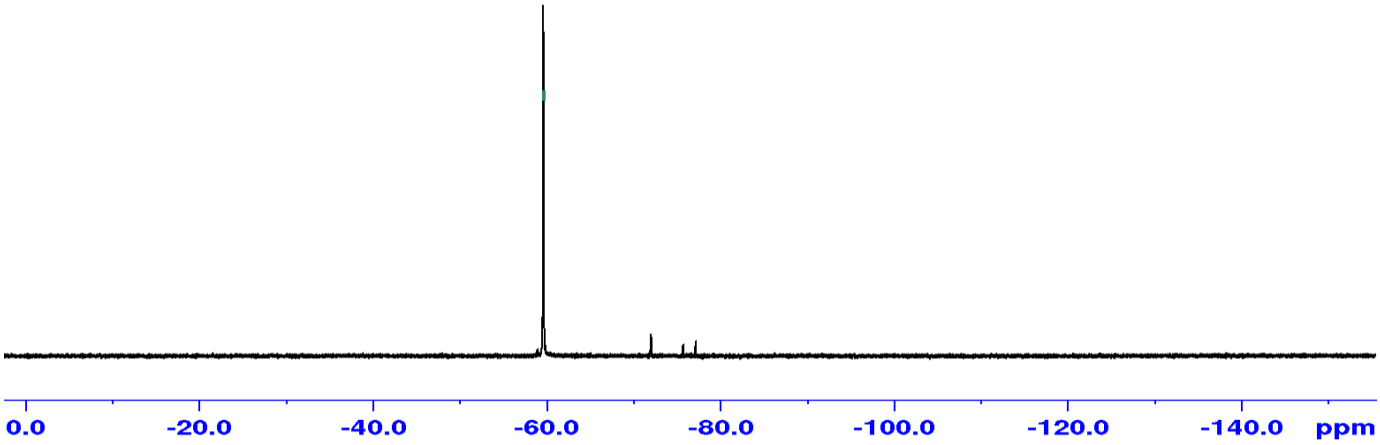


3a, ^{1}H NMR

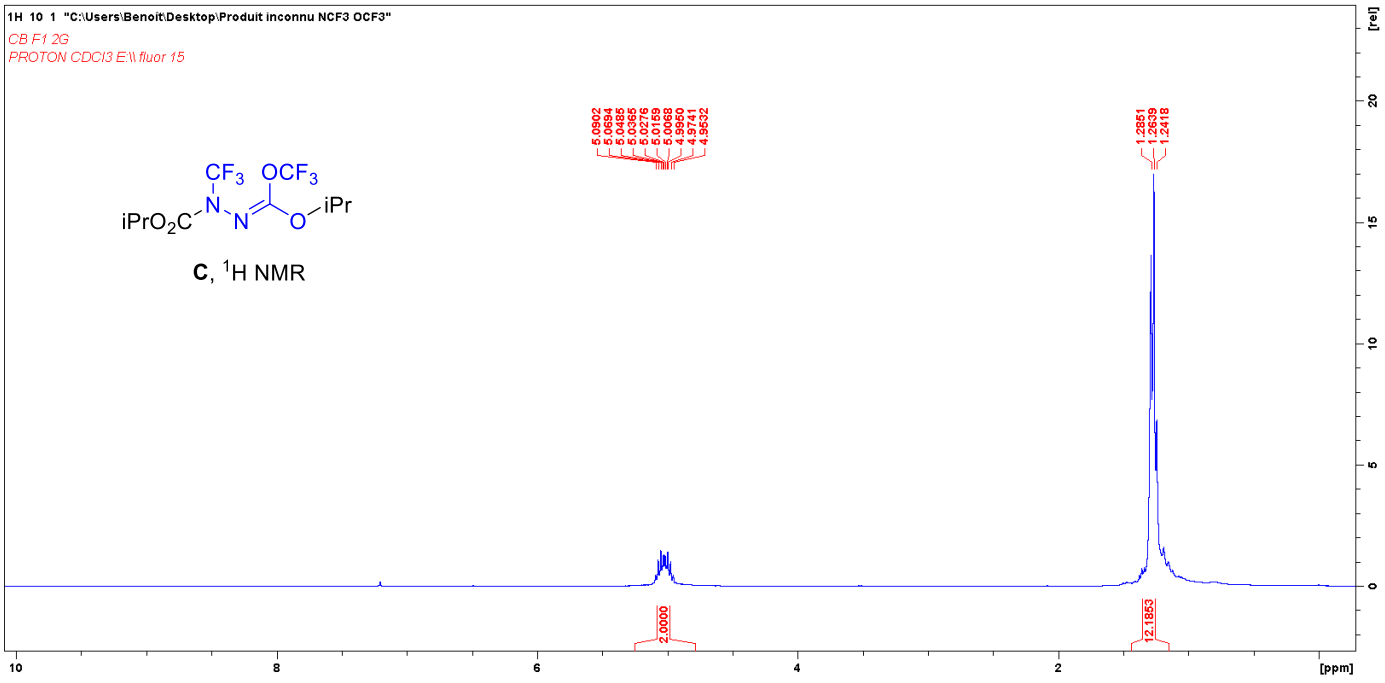
3a, ^{13}C NMR



3a, ^{19}F NMR

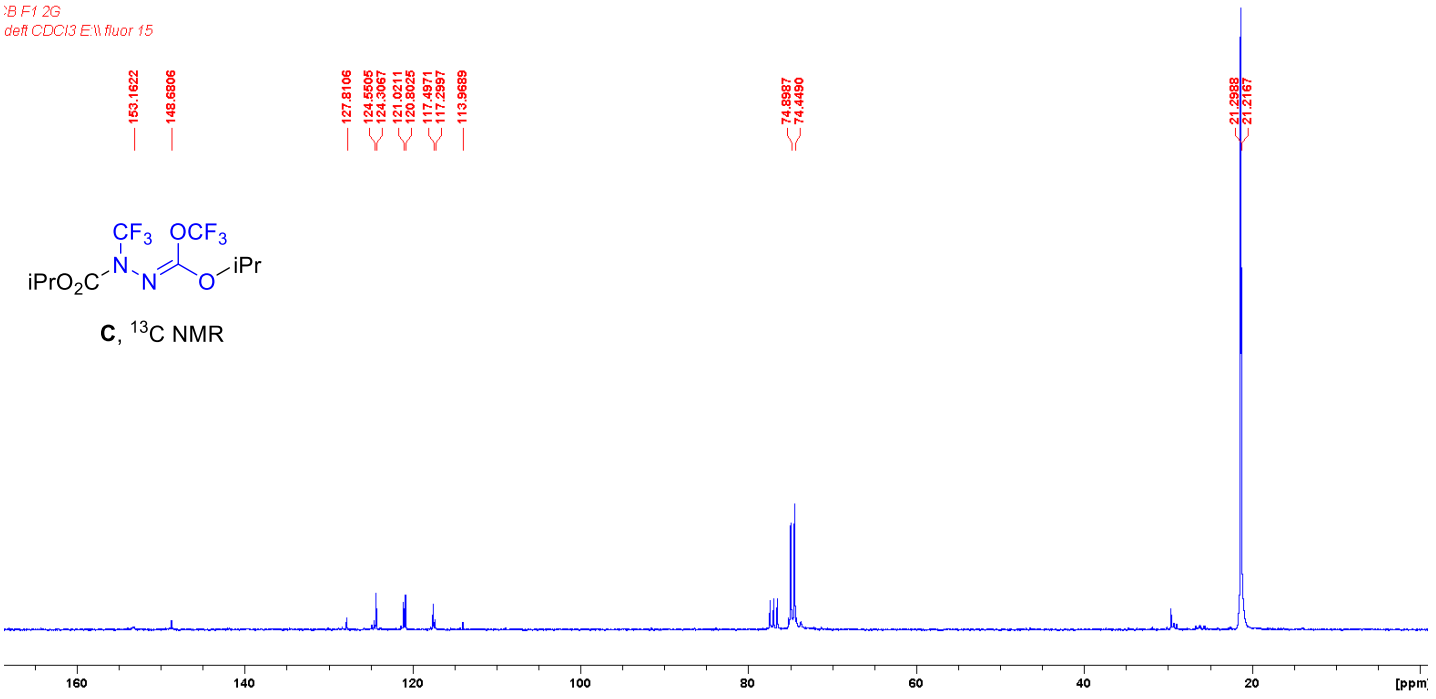


Isopropyl (Z)-2-(isopropoxy(trifluoromethoxy)methylene)-1-(trifluoromethyl)hydrazine-1-carboxylate C



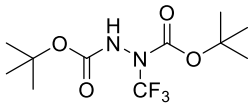
C, ^{1}H NMR

C, ^{19}F NMR

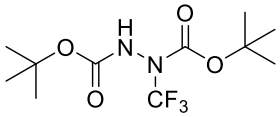


C, ^{13}C NMR

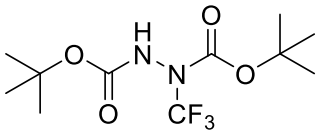
Di*ter*butyl 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate 3b



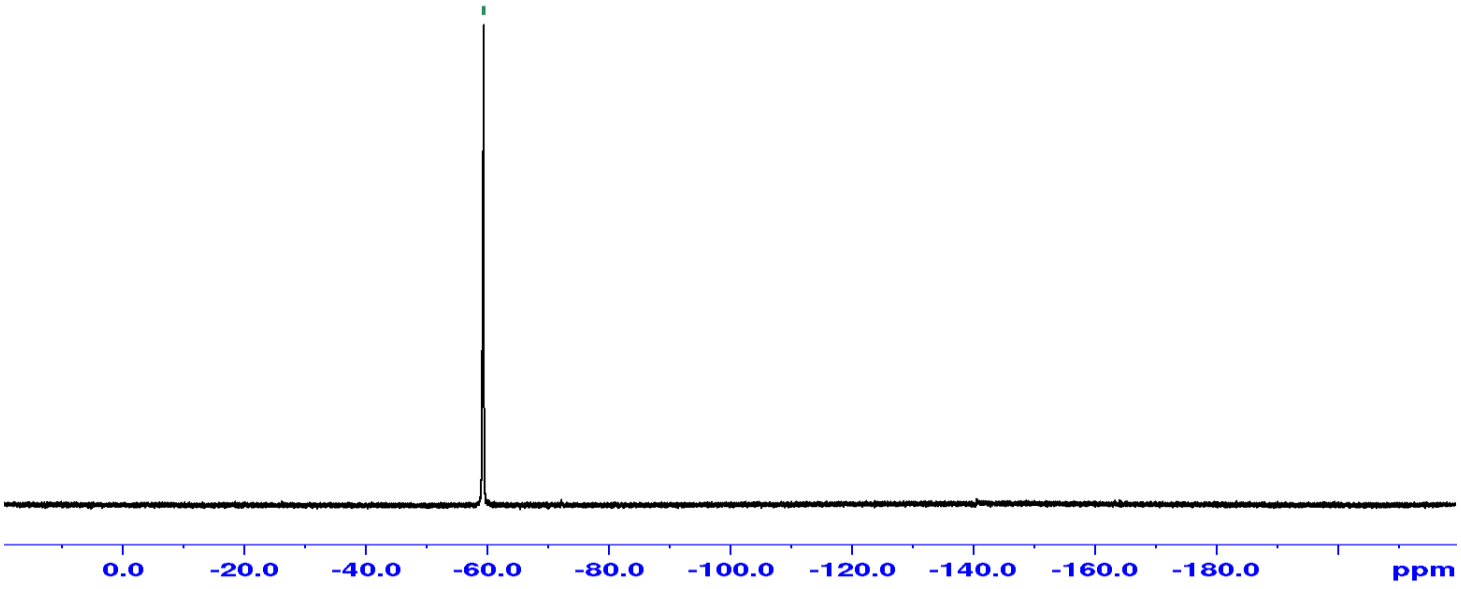
3b, ^{1}H NMR



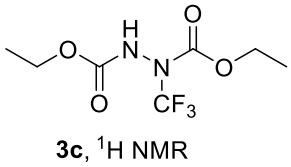
3b, ^{13}C NMR



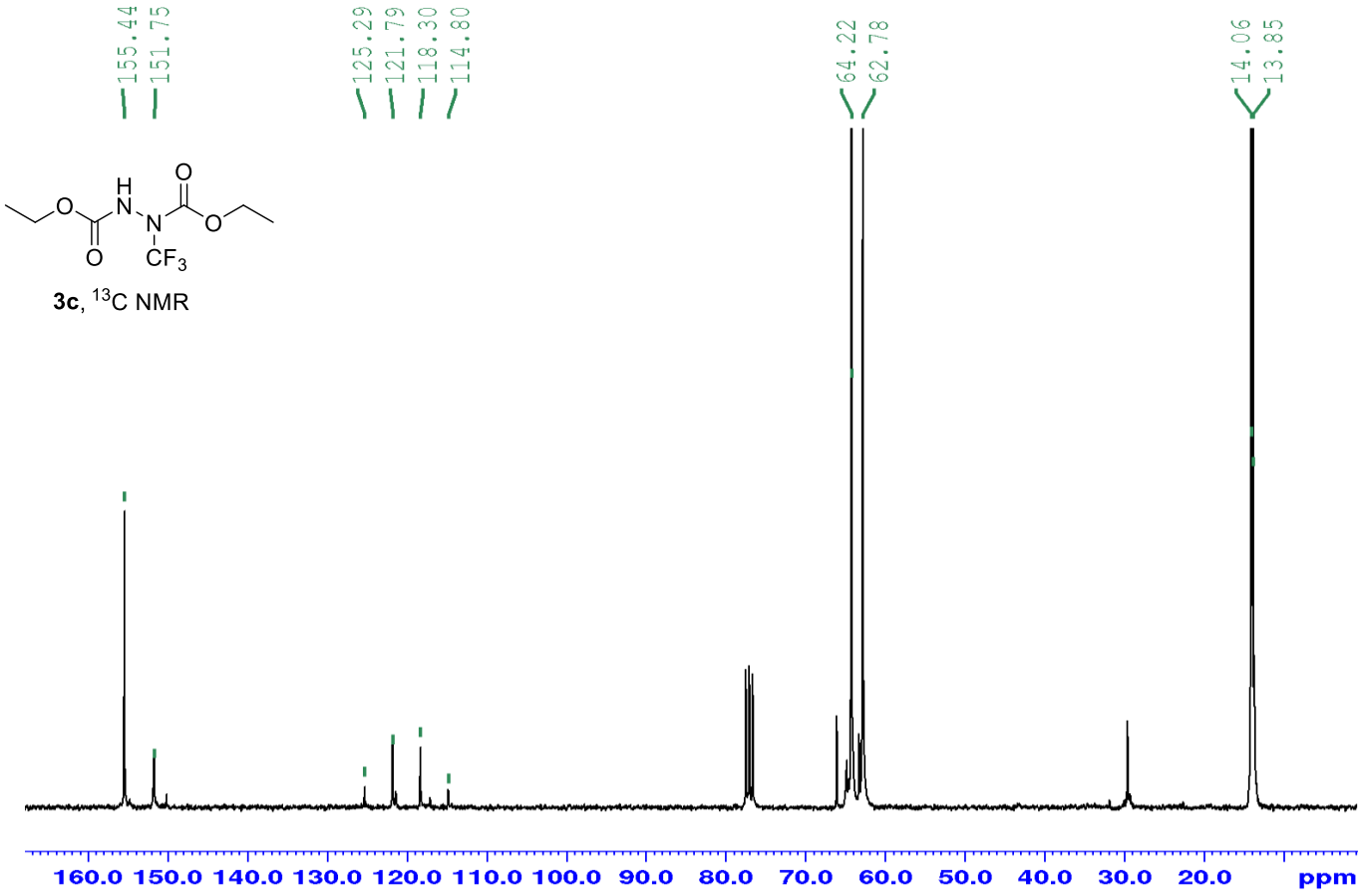
3b, ^{19}F NMR



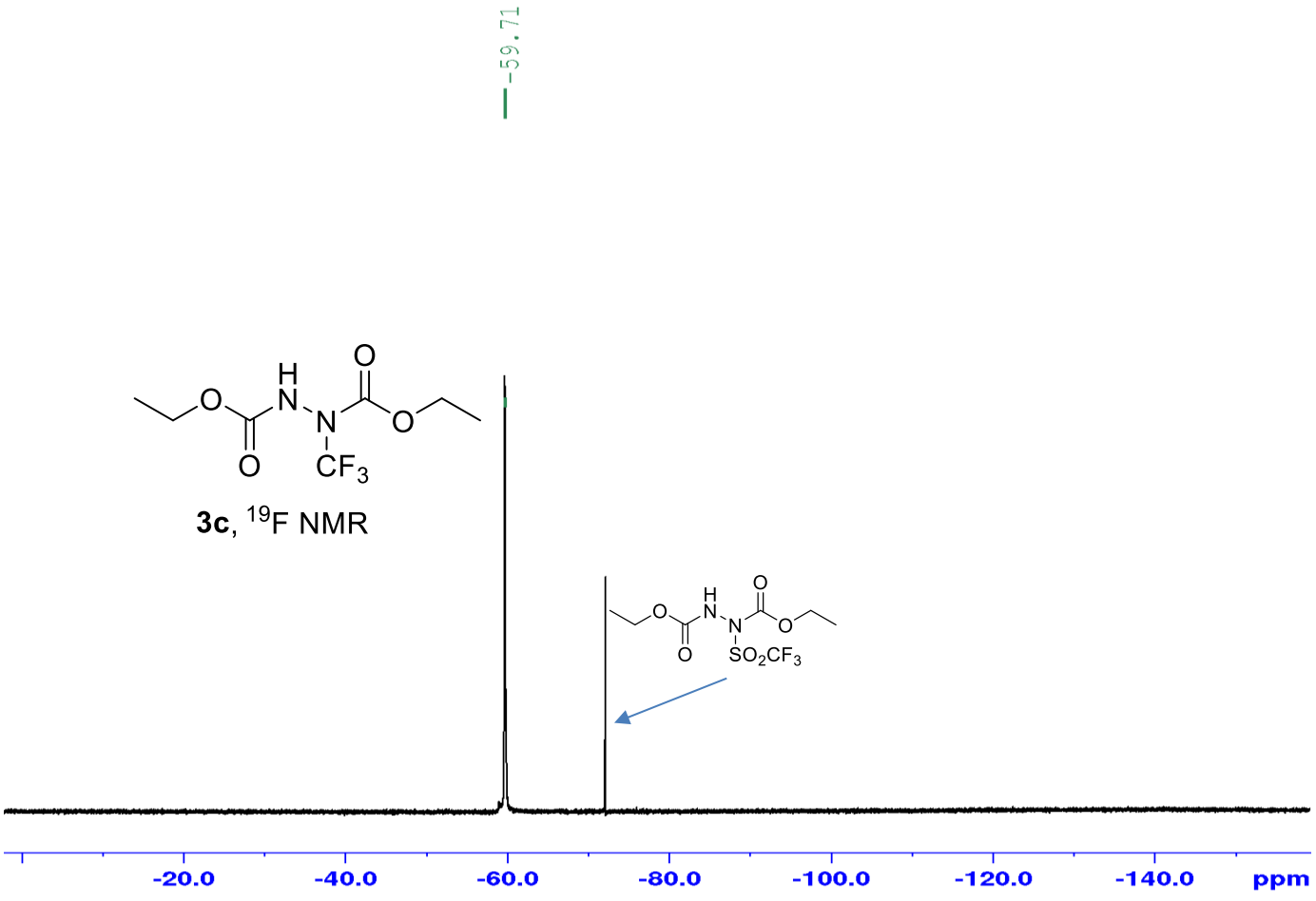
Diethyl 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate 3c



3c, ^{1}H NMR

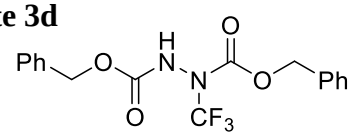


3c, ^{13}C NMR

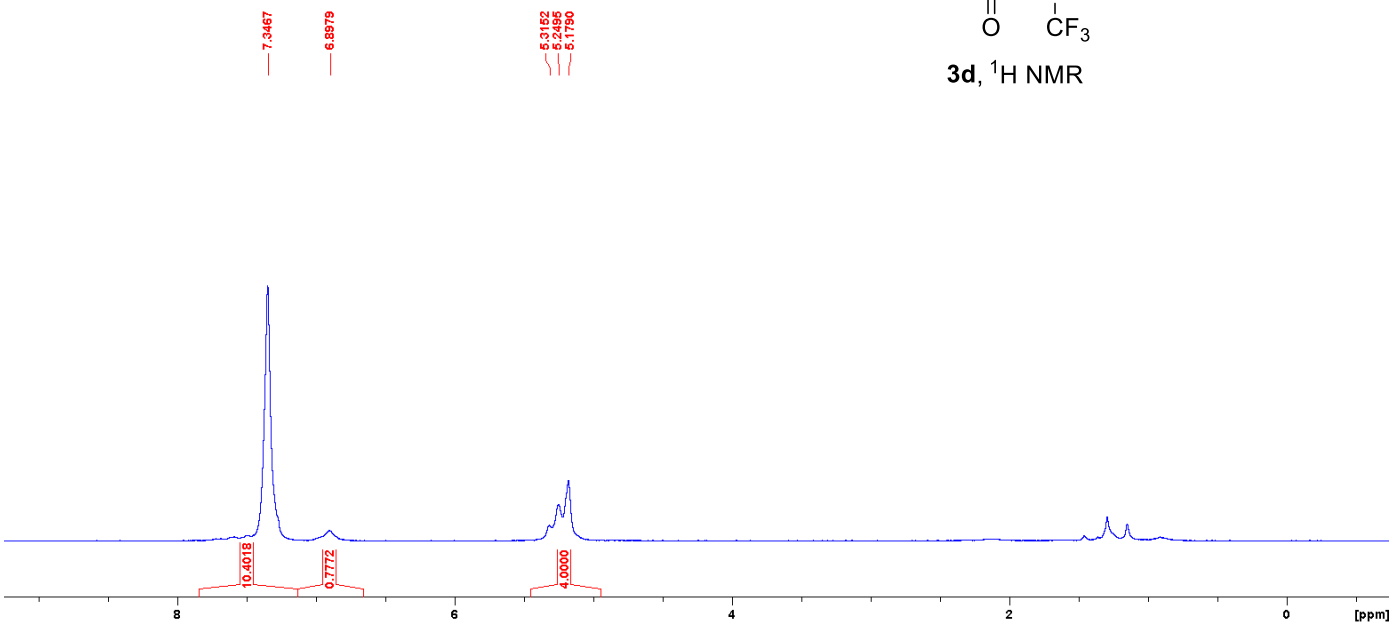


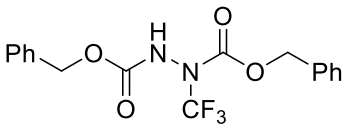
3c, ^{19}F NMR

Dibenzyl 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate 3d

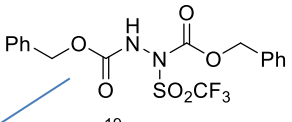


3d, ^{1}H NMR

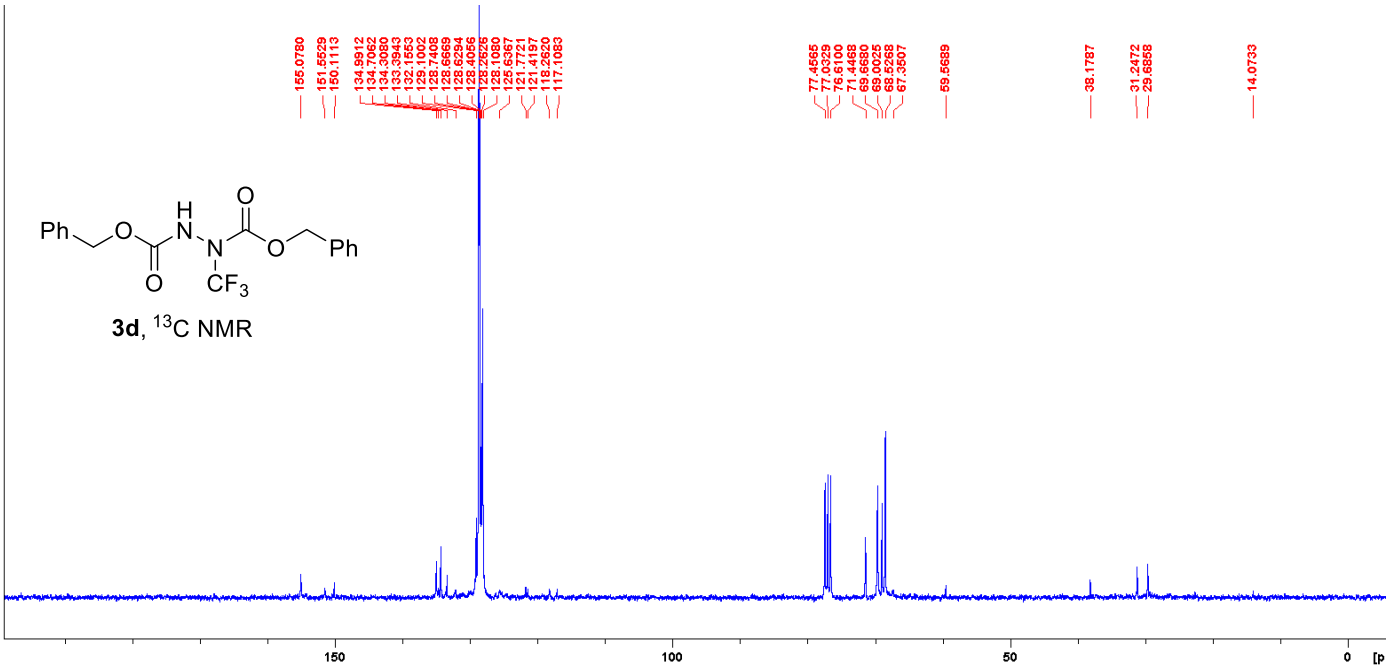




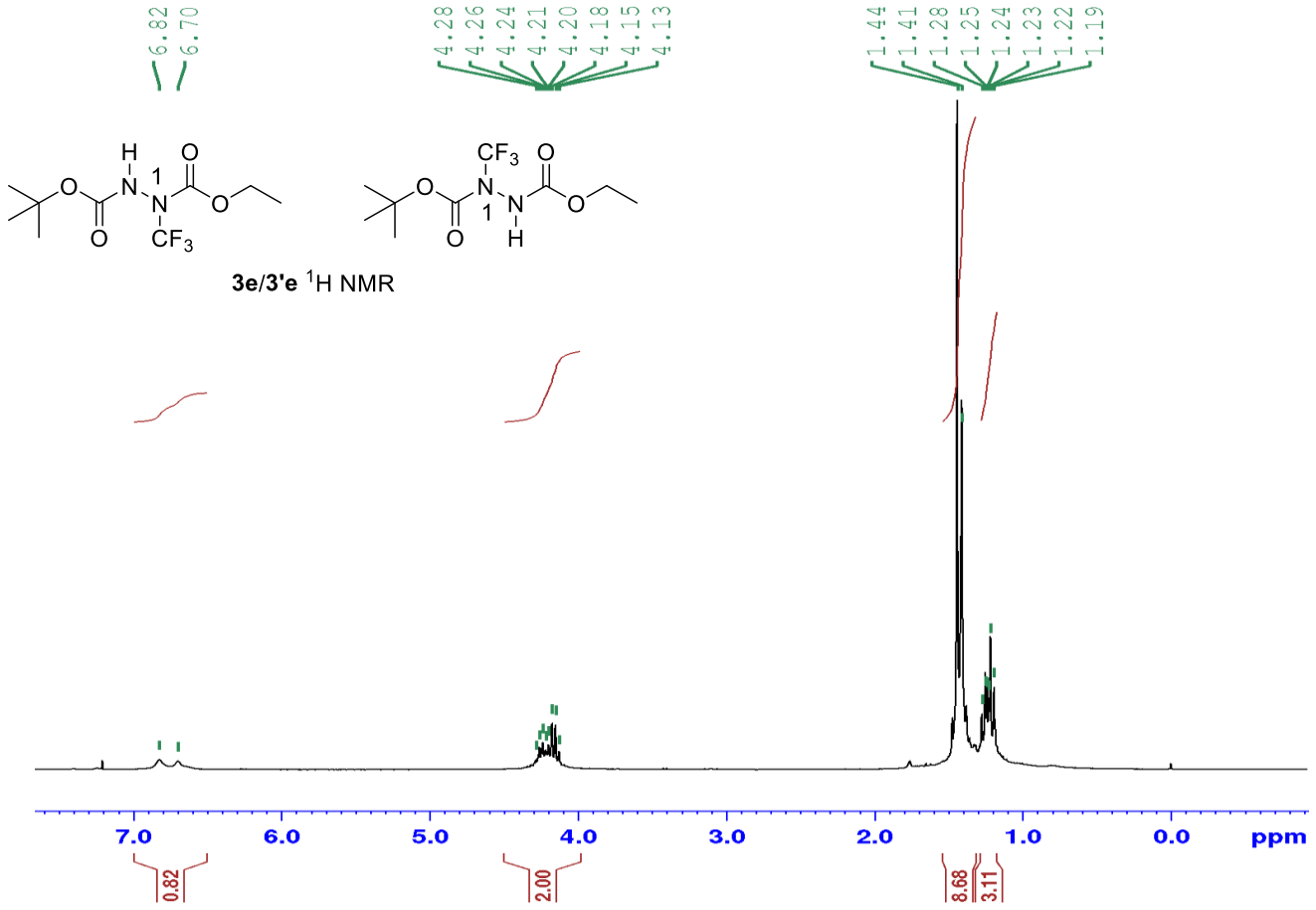
3d, ^{19}F NMR

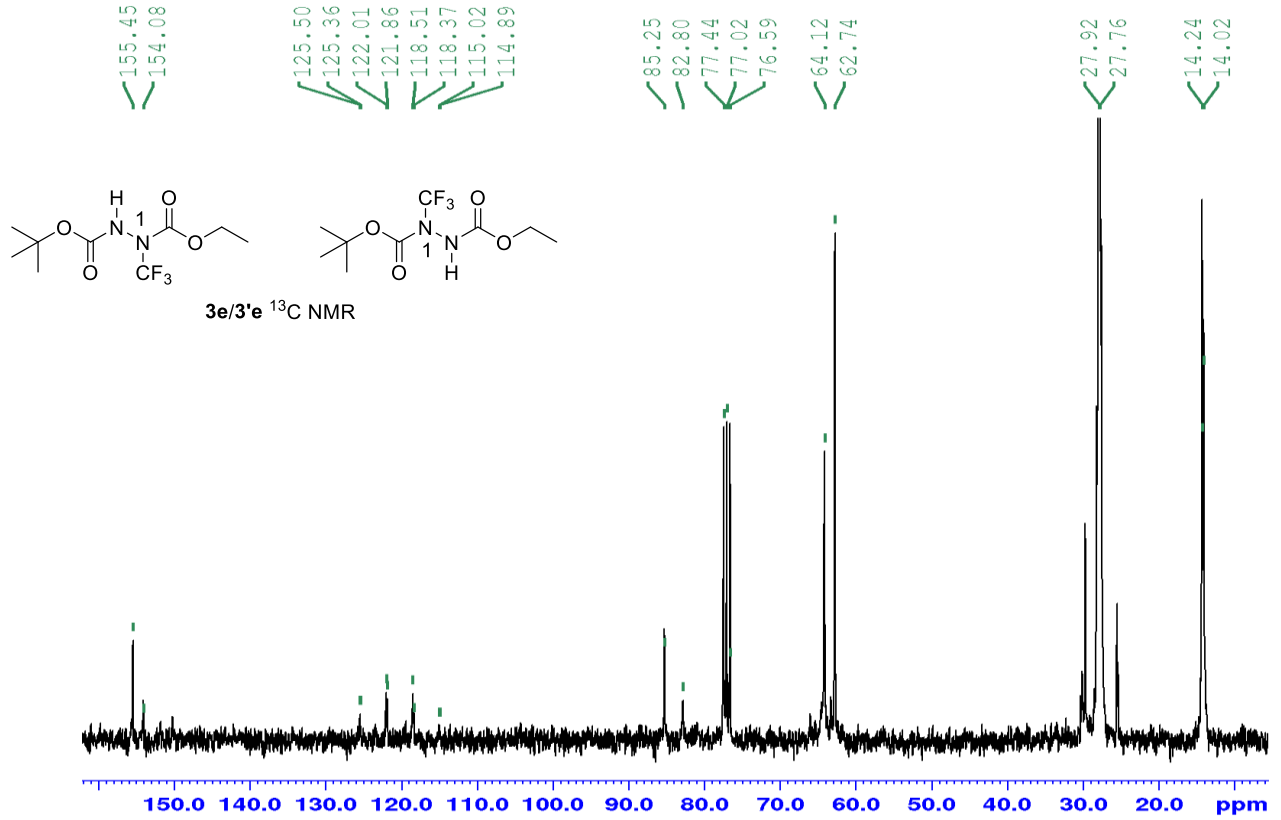


4d, ^{19}F NMR

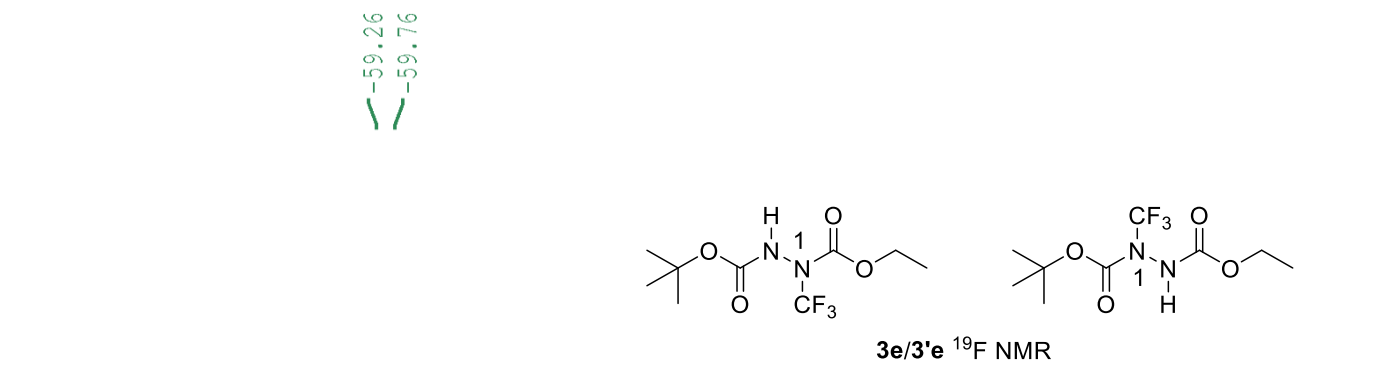


2-(tert-butyl) 1-ethyl 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate and 1-(tert-butyl) 2-ethyl 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate 3e/3'e



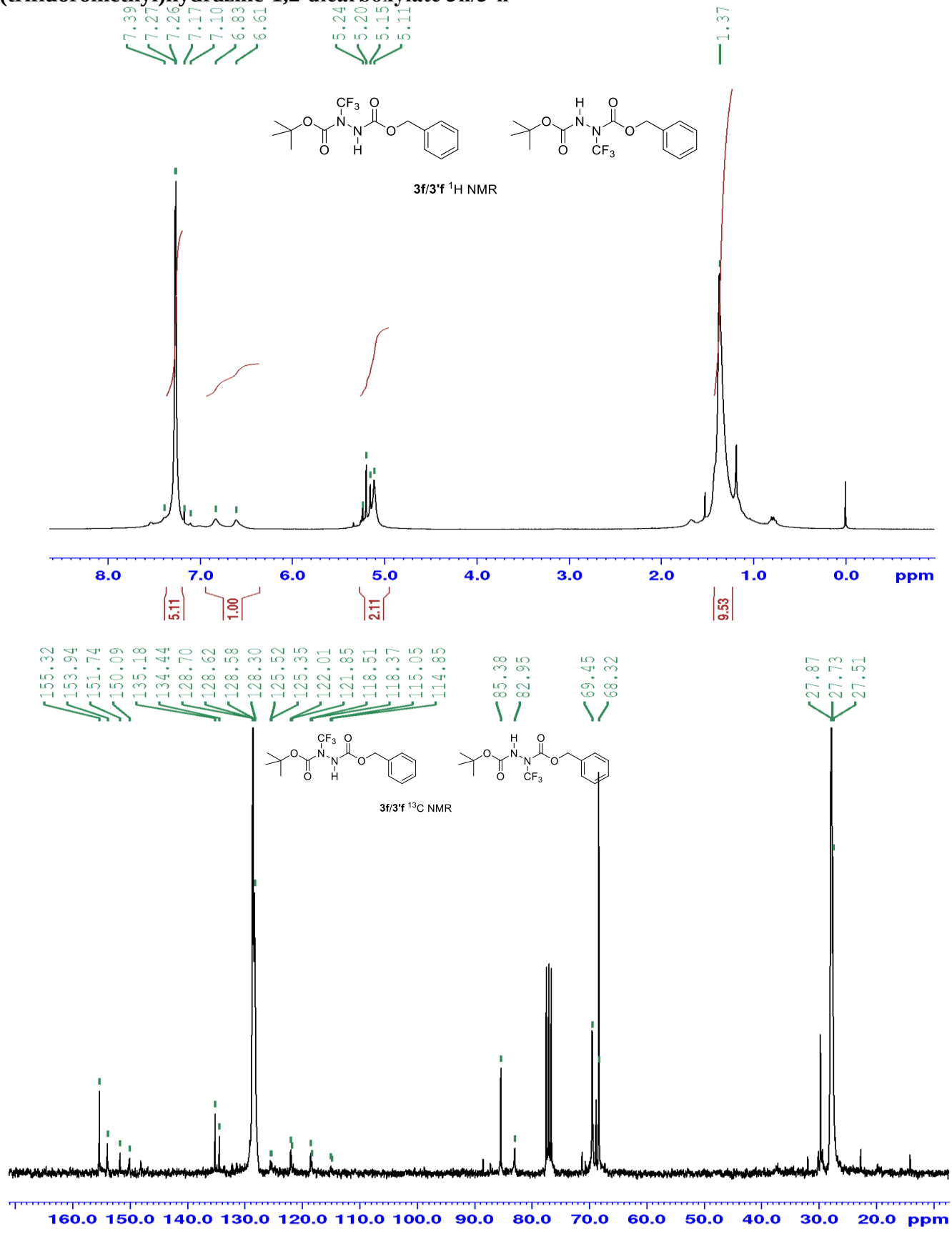


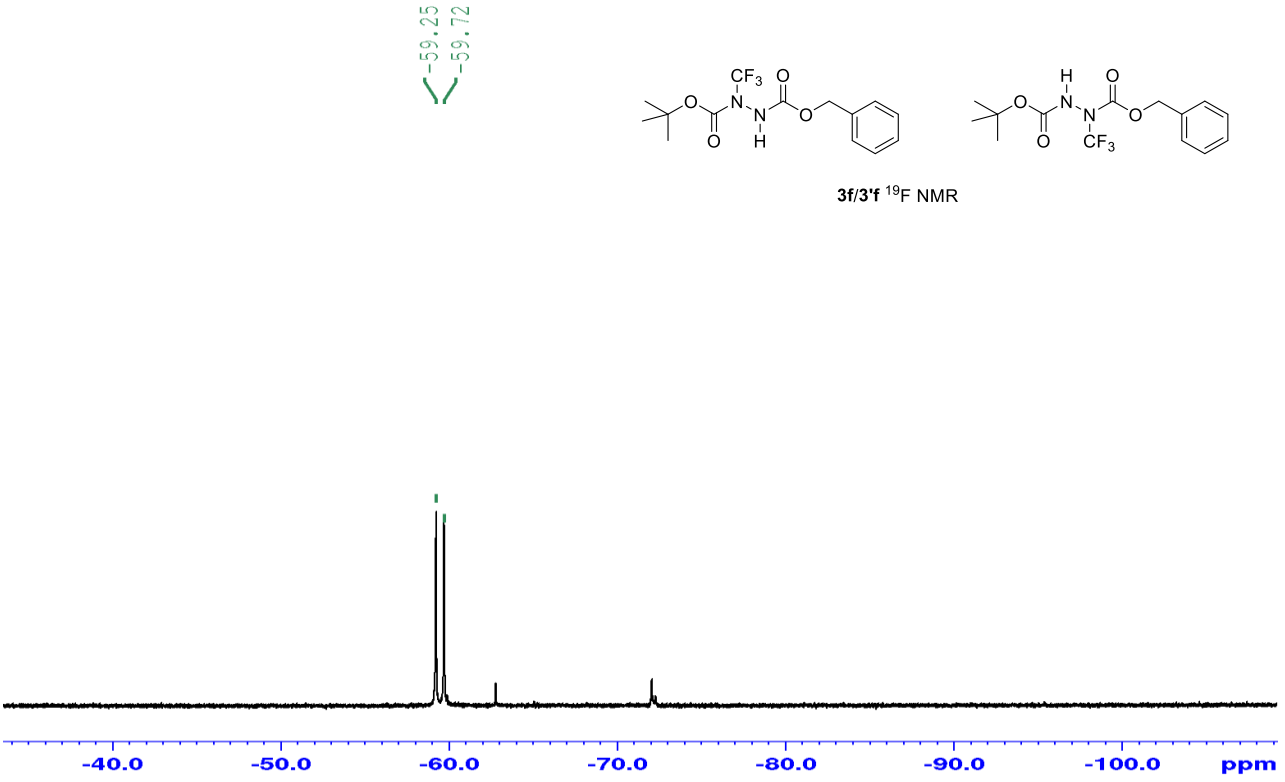
3e/3'e ^{13}C NMR



3e/3'e ^{19}F NMR

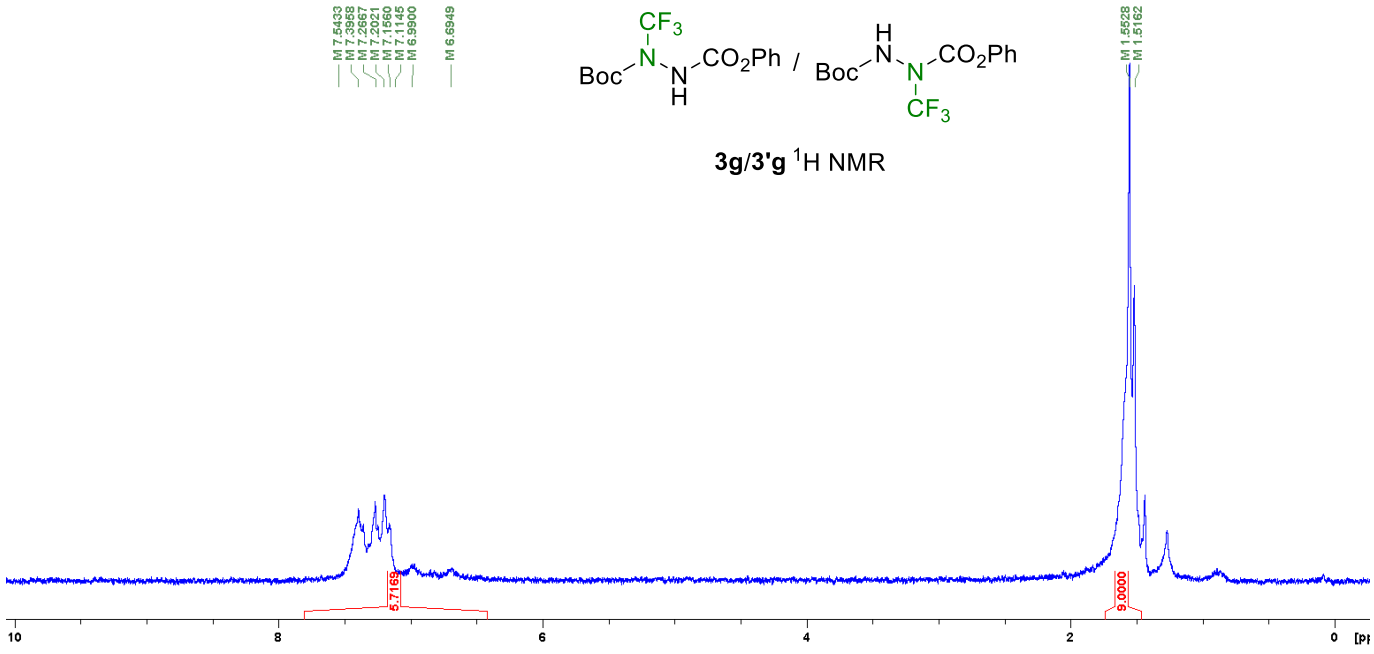
2-benzyl 1-(tert-butyl) 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate and 1-benzyl 2-(tert-butyl) 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate 3h/3'h



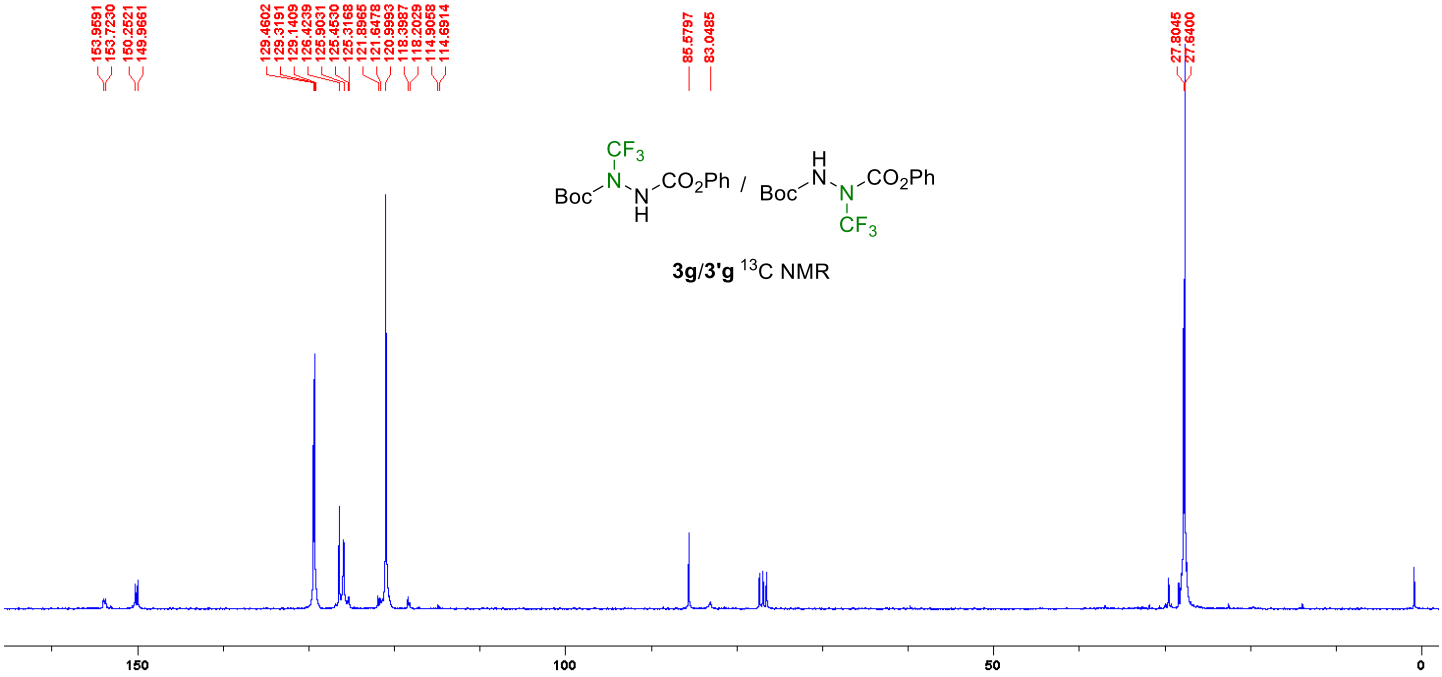


3f/3'f ^{19}F NMR

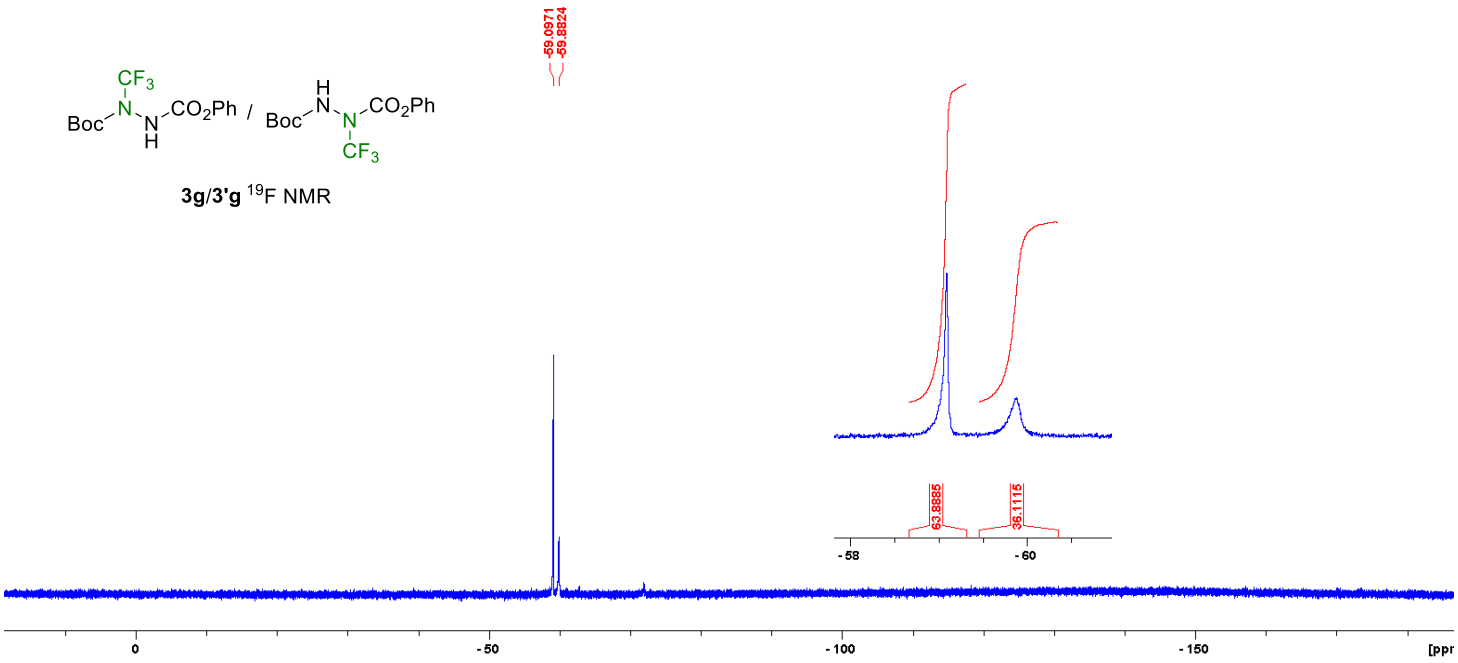
1-(*tert*-butyl) 2-phenyl 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate and 2-(*tert*-butyl) 1-phenyl 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate 3g/3'g



3g/3'g ^{1}H NMR

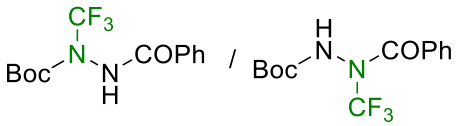


3g/3'g ^{13}C NMR

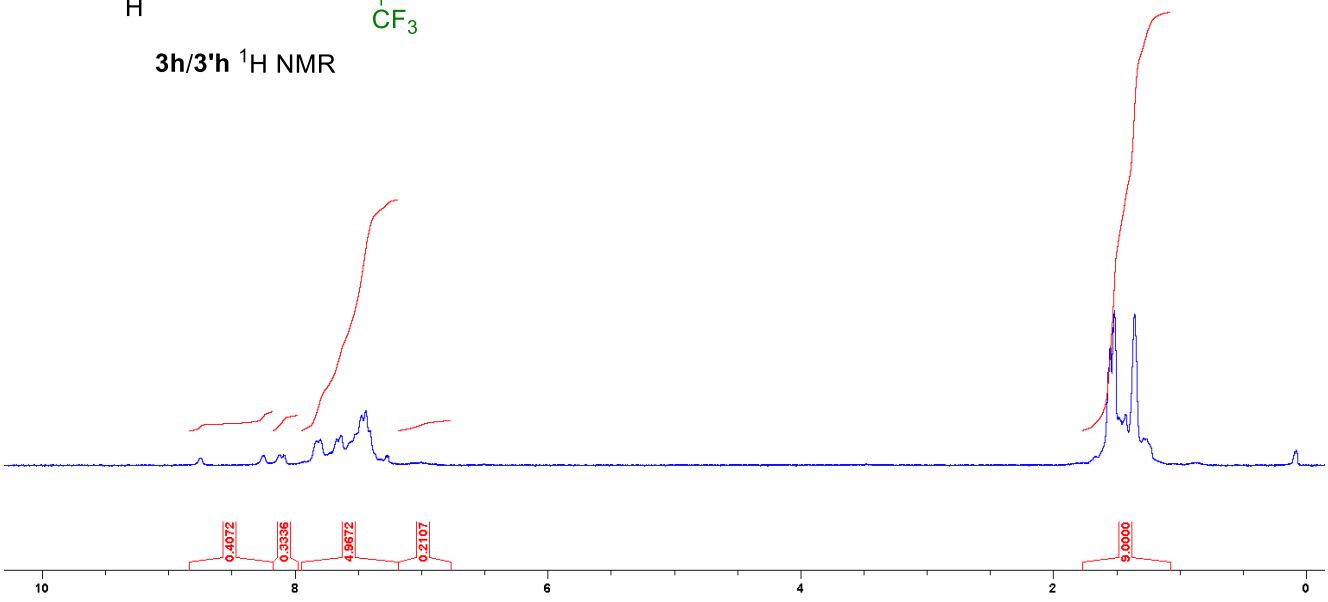


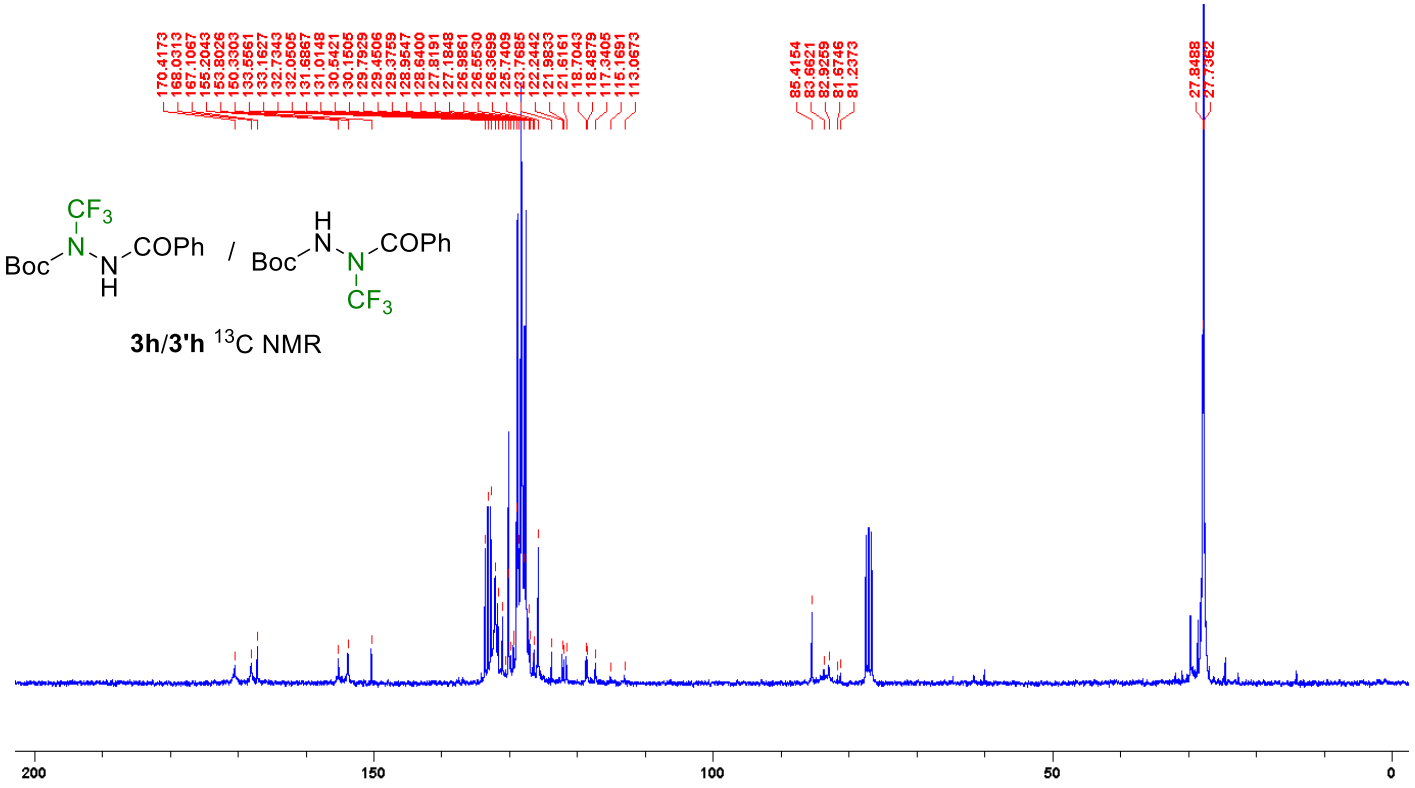
3g/3'g ^{19}F NMR

***Tert*-butyl 2-benzoyl-1-(trifluoromethyl)hydrazine-1-carboxylate and *tert*-butyl 2-benzoyl-2-(trifluoromethyl)hydrazine-1-carboxylate 3h/3'h**

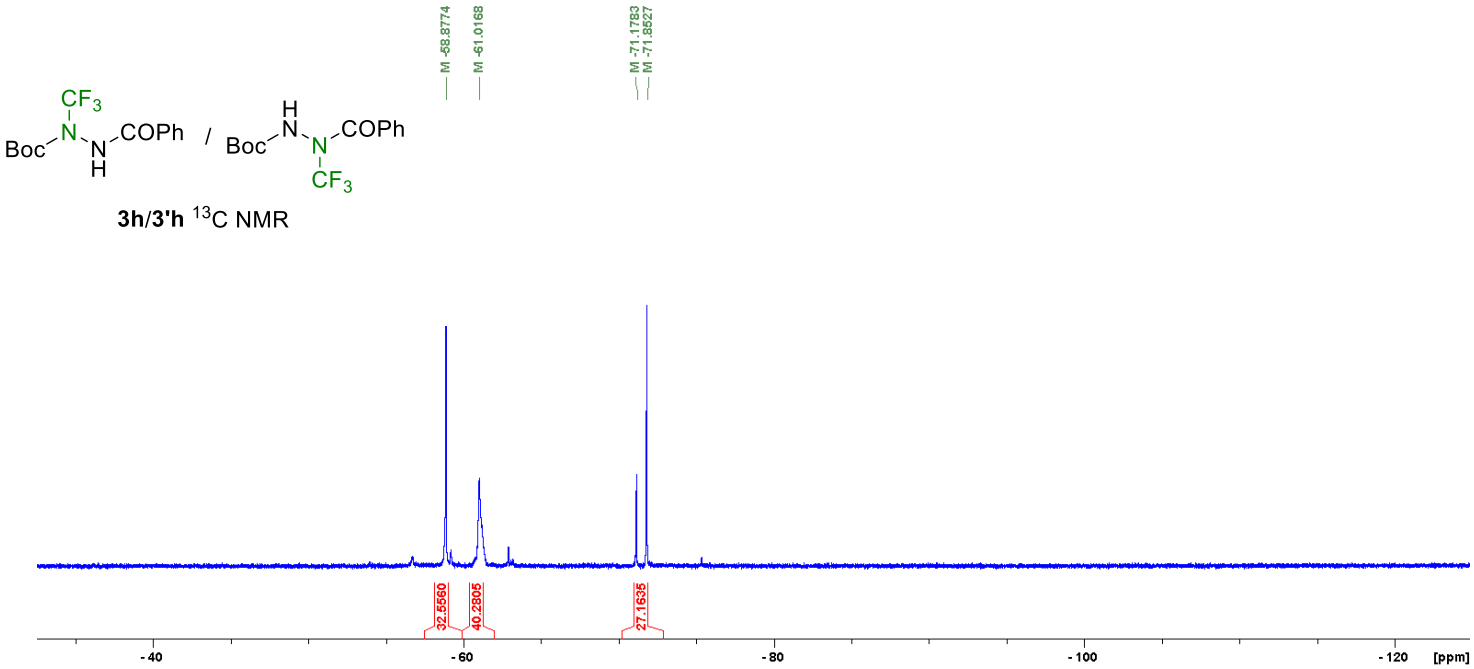


3h/3'h ^{1}H NMR

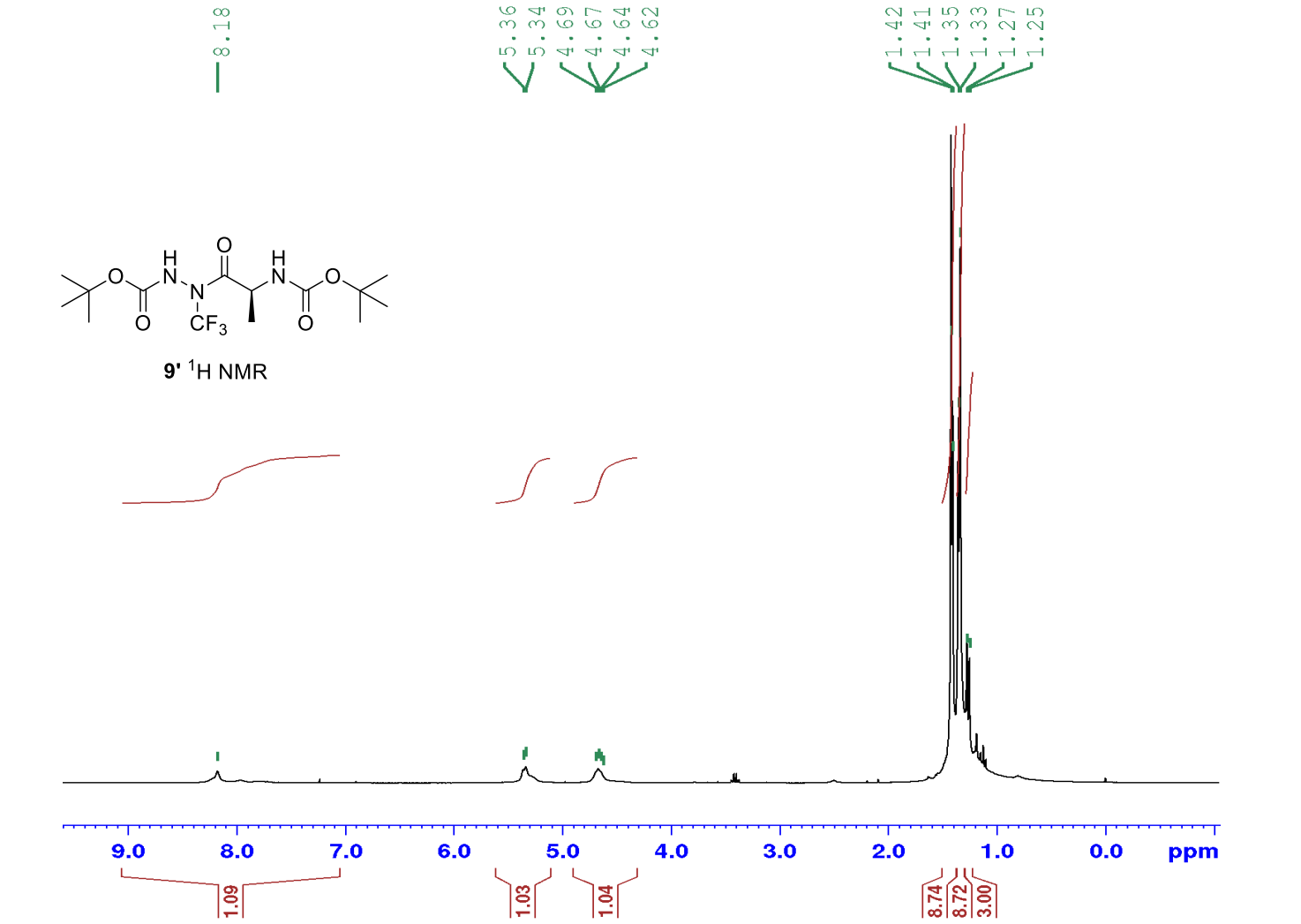


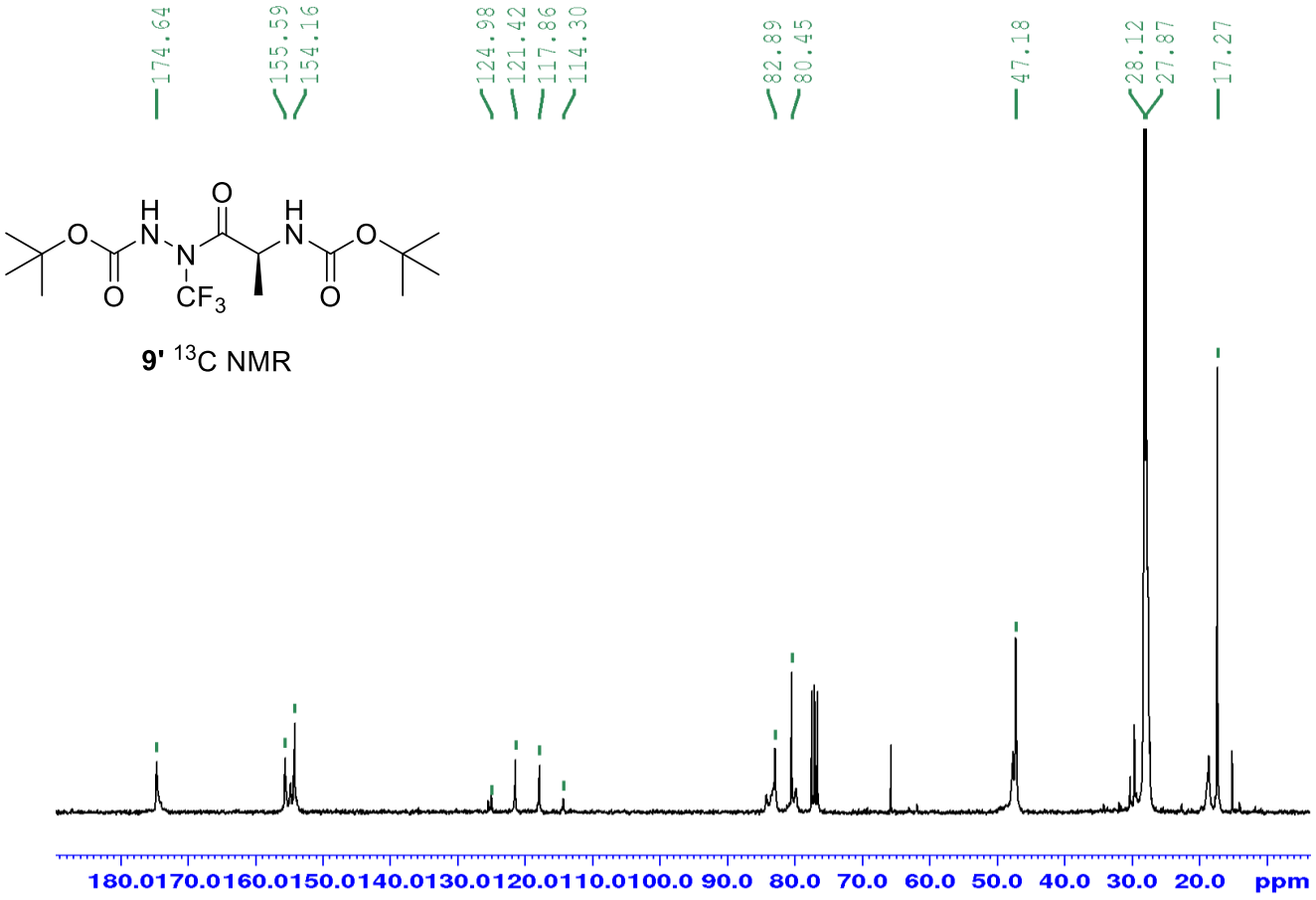


3h/3'h ^{13}C NMR

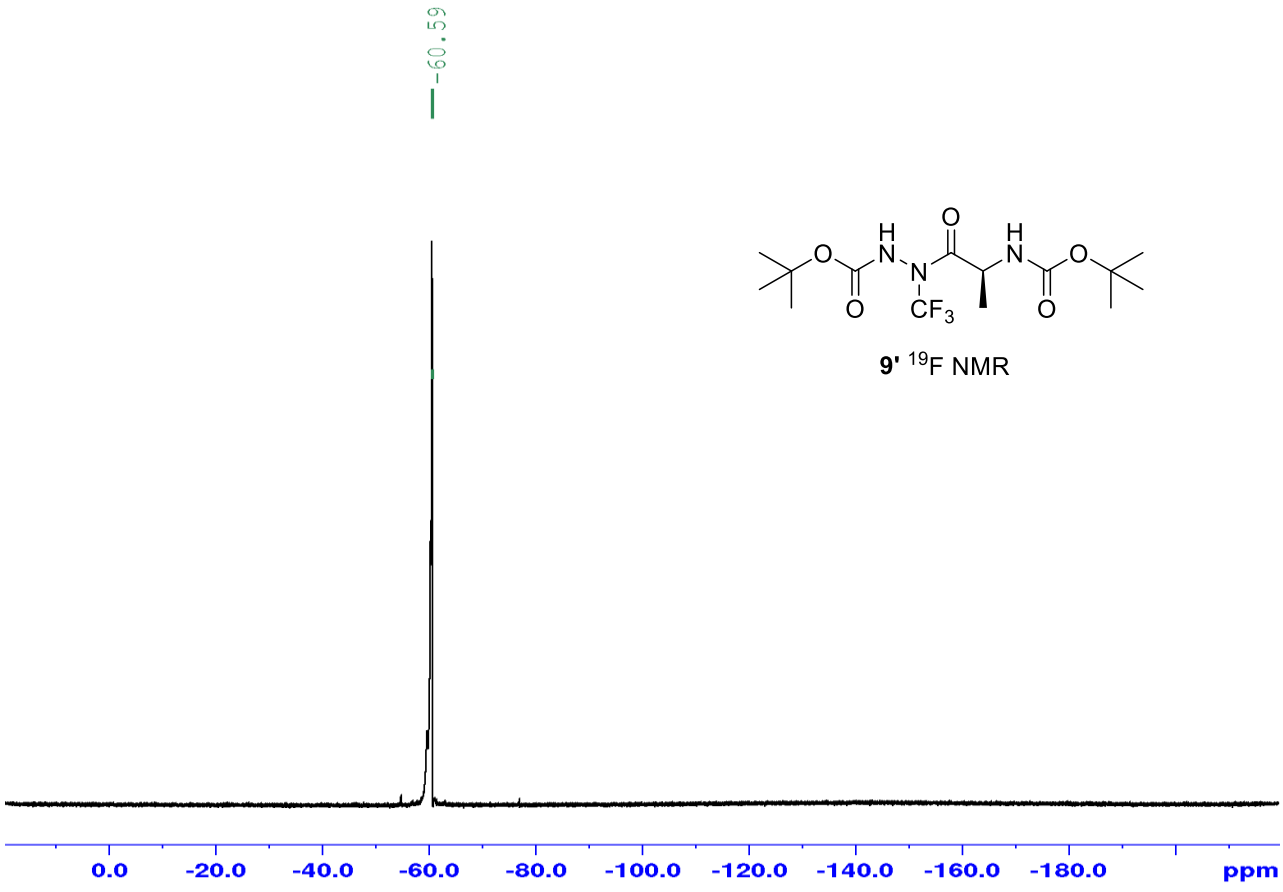


***Tert*-butyl 2-((tert-butoxycarbonyl)-L-alanyl)-2-(trifluoromethyl)hydrazine-1-carboxylate 9'**



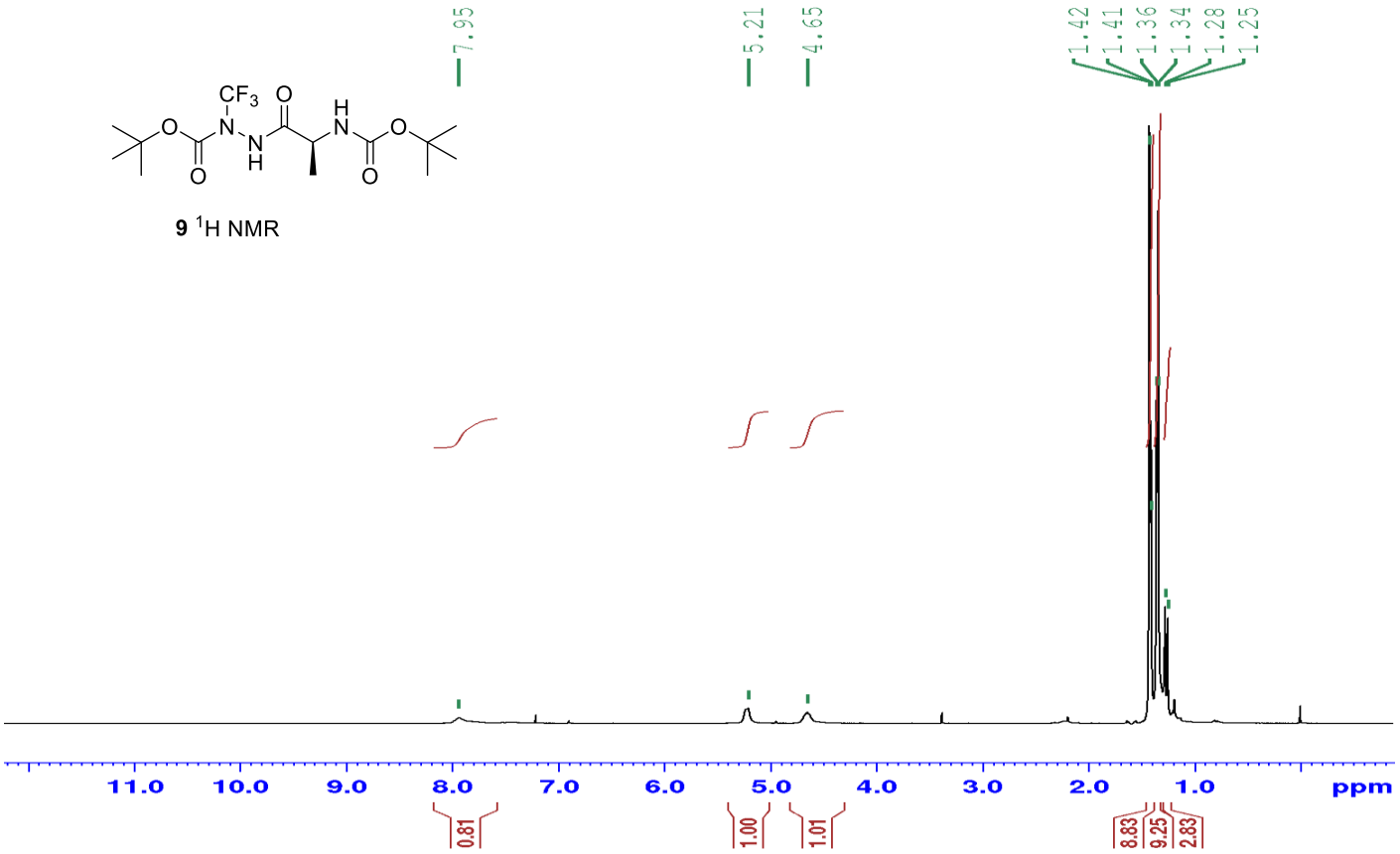


9' ^{13}C NMR

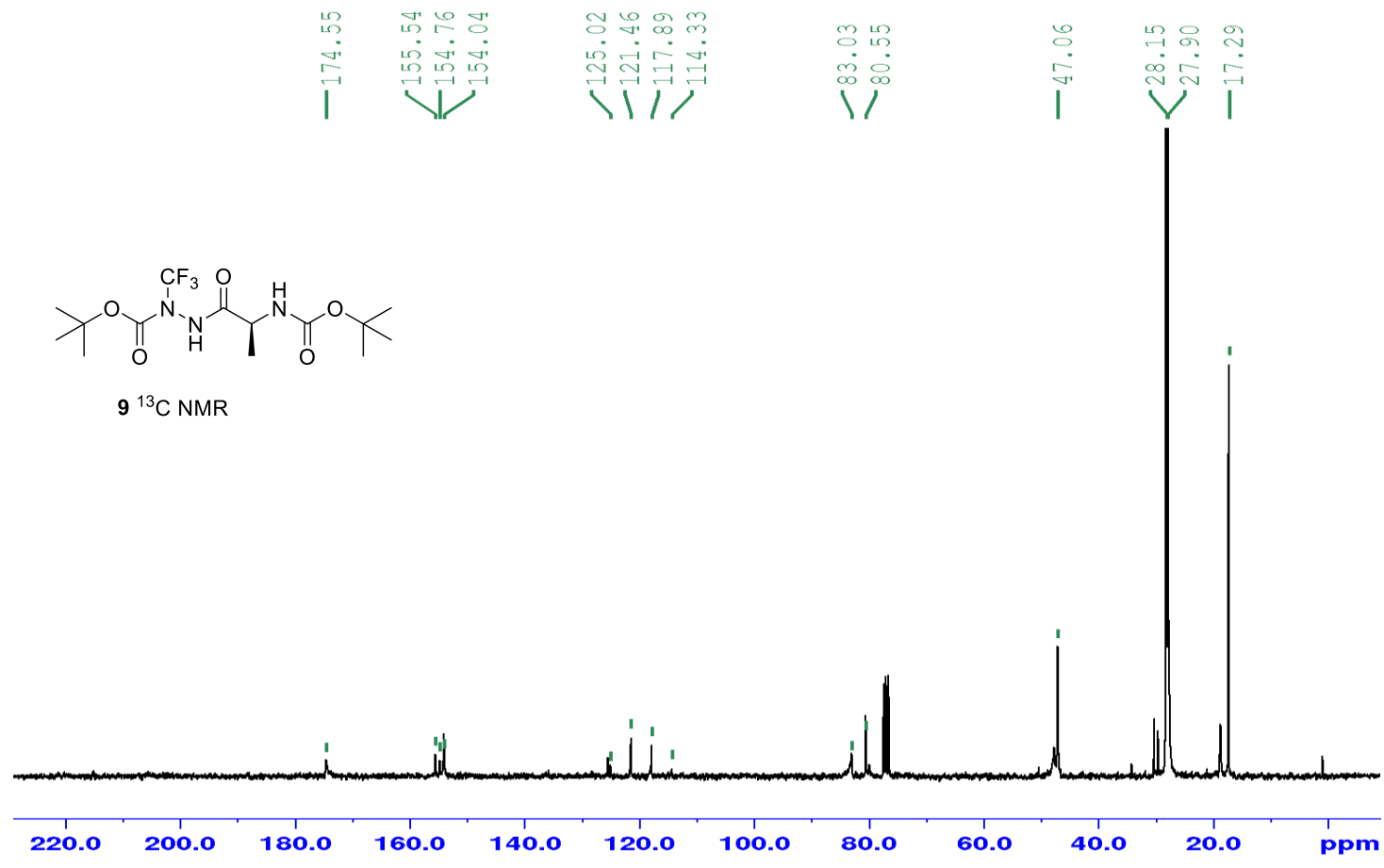


9' ^{19}F NMR

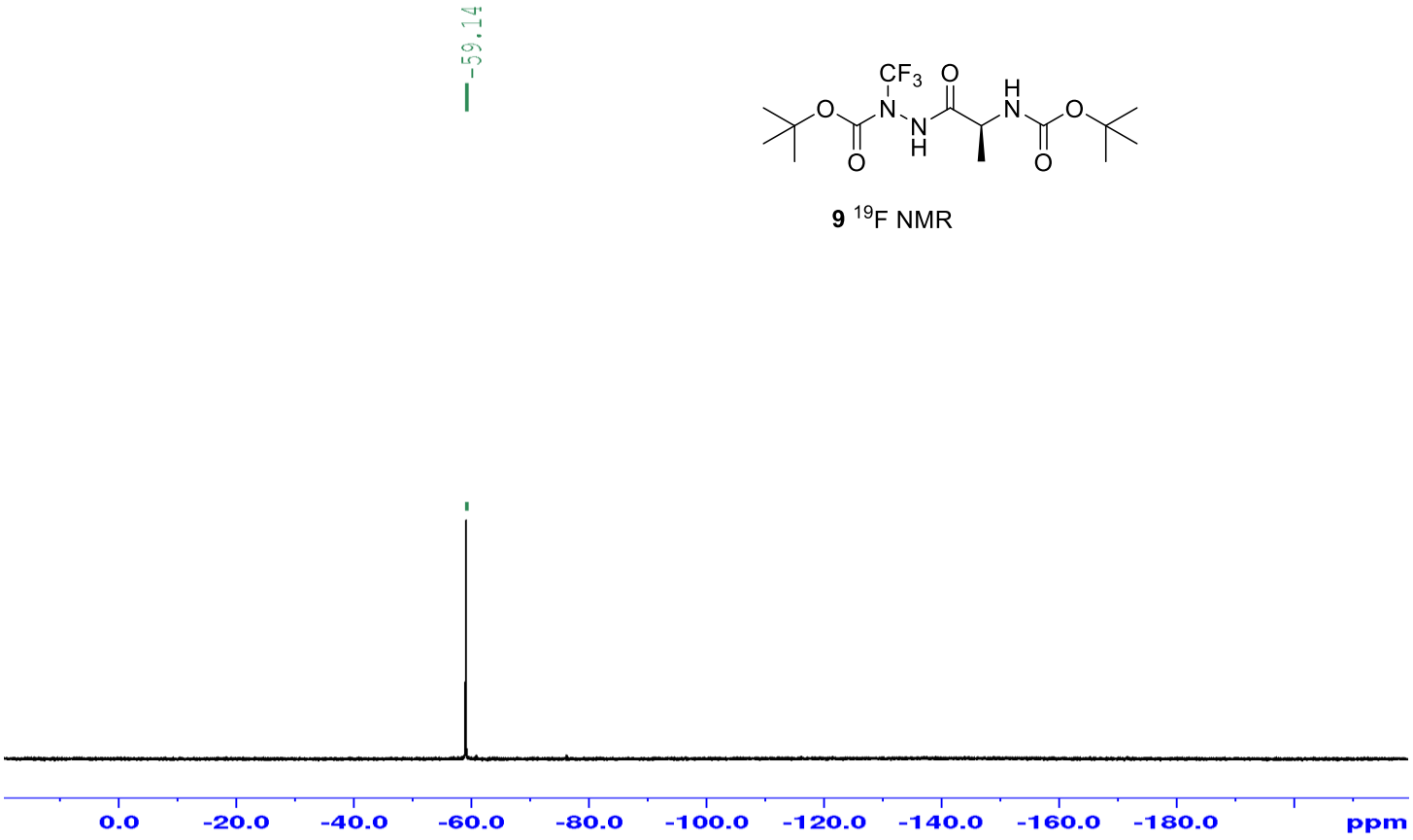
***Tert*-butyl 2-((tert-butoxycarbonyl)-L-alanyl)-1-(trifluoromethyl)hydrazine-1-carboxylate 9**



9 ^{1}H NMR

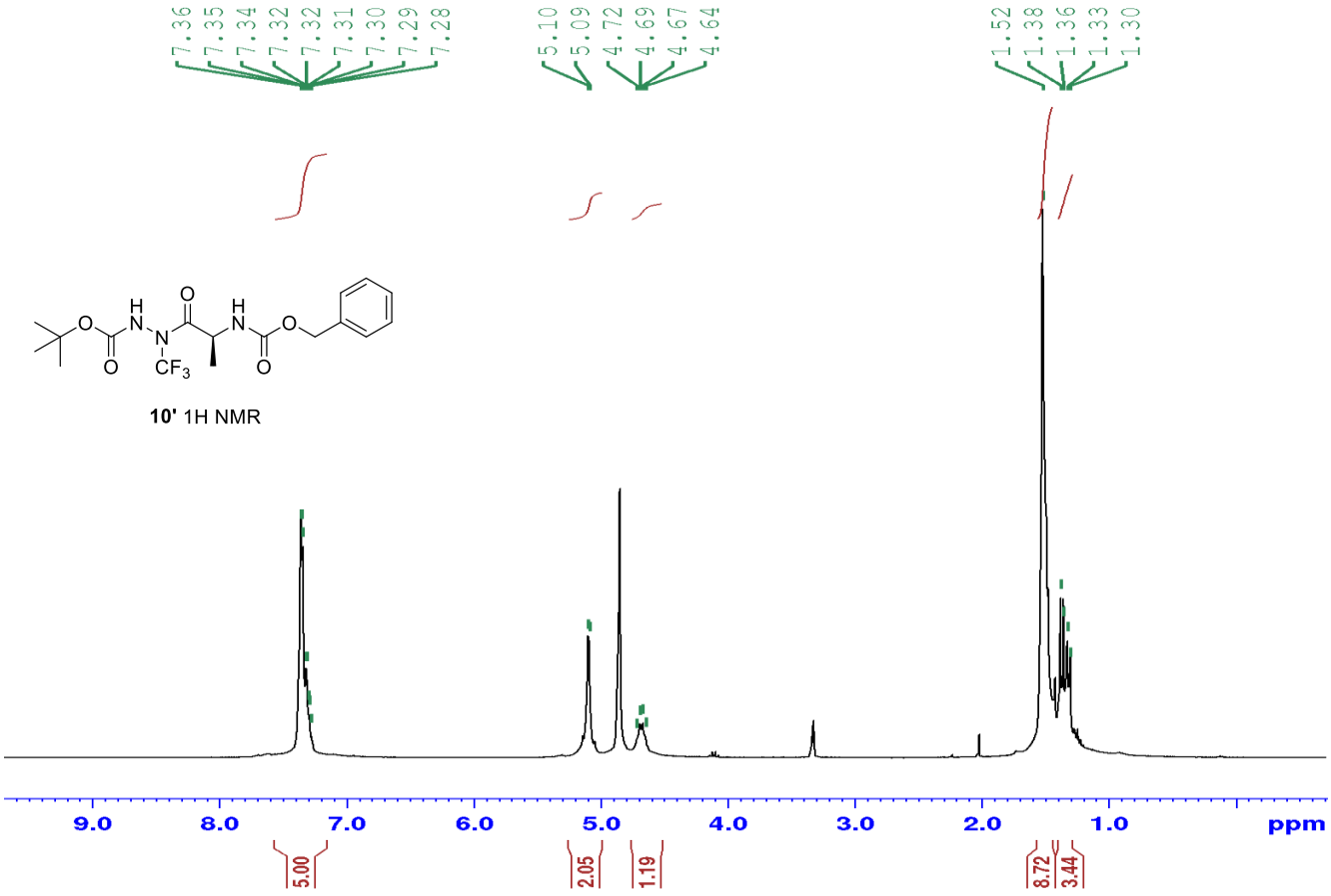


9 ^{13}C NMR

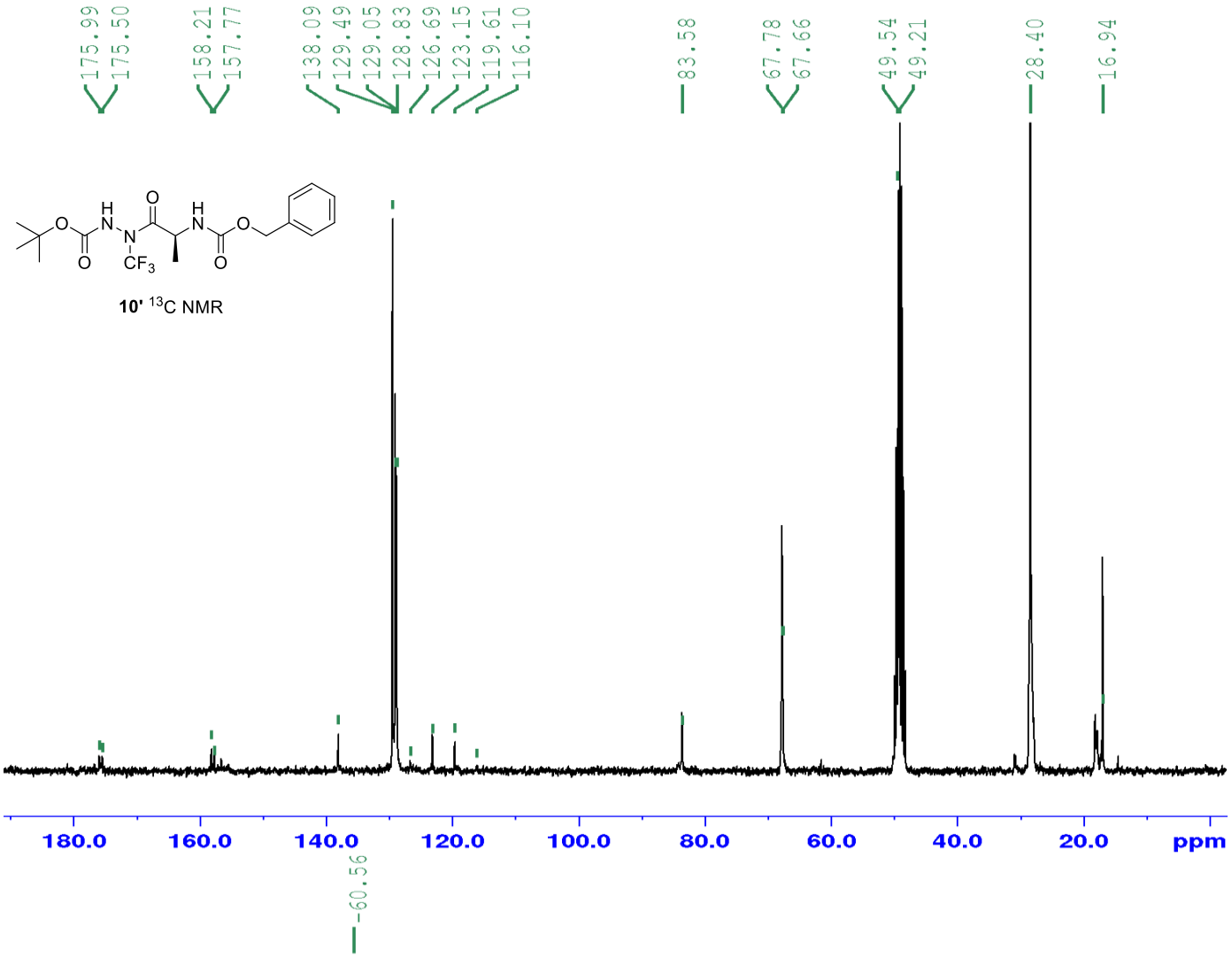


9 ^{19}F NMR

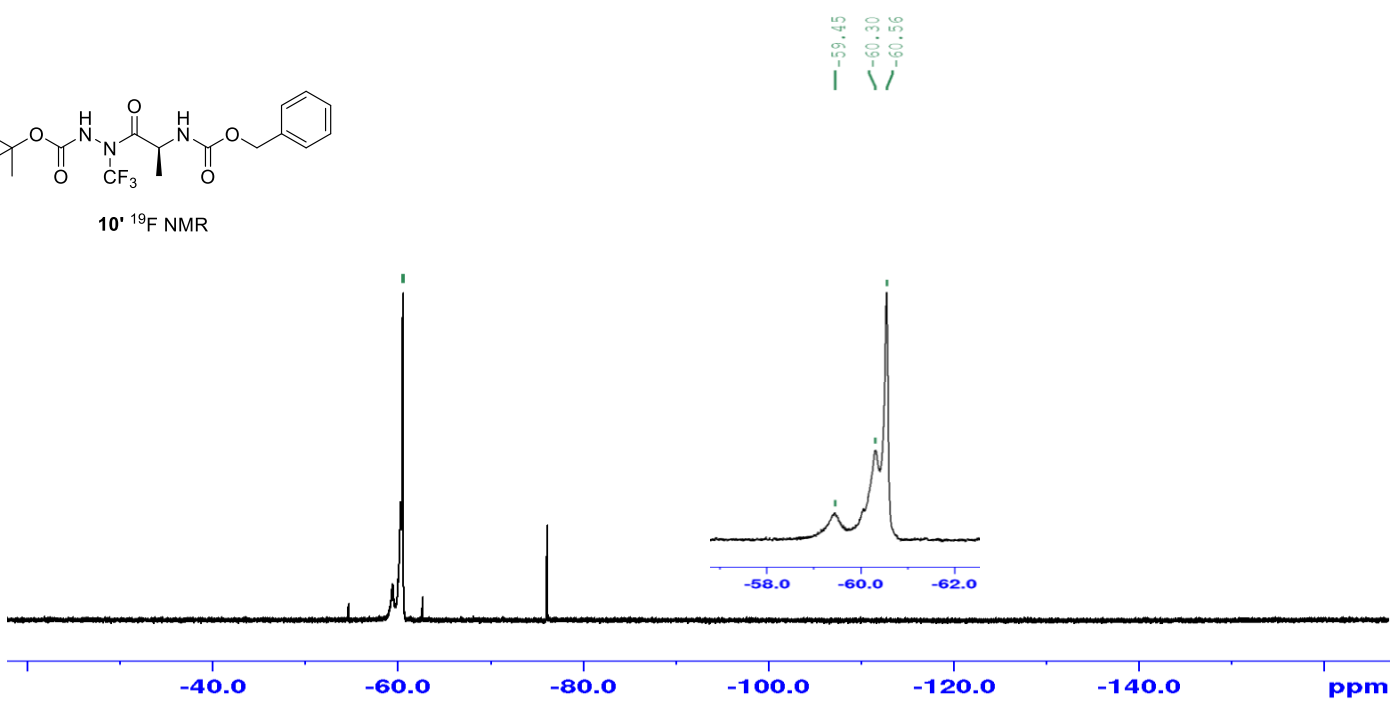
***Tert*-butyl 2-(((benzyloxy)carbonyl)-L-alanyl)-2-(trifluoromethyl)hydrazine-1-carboxylate 10'**



10' 1H NMR

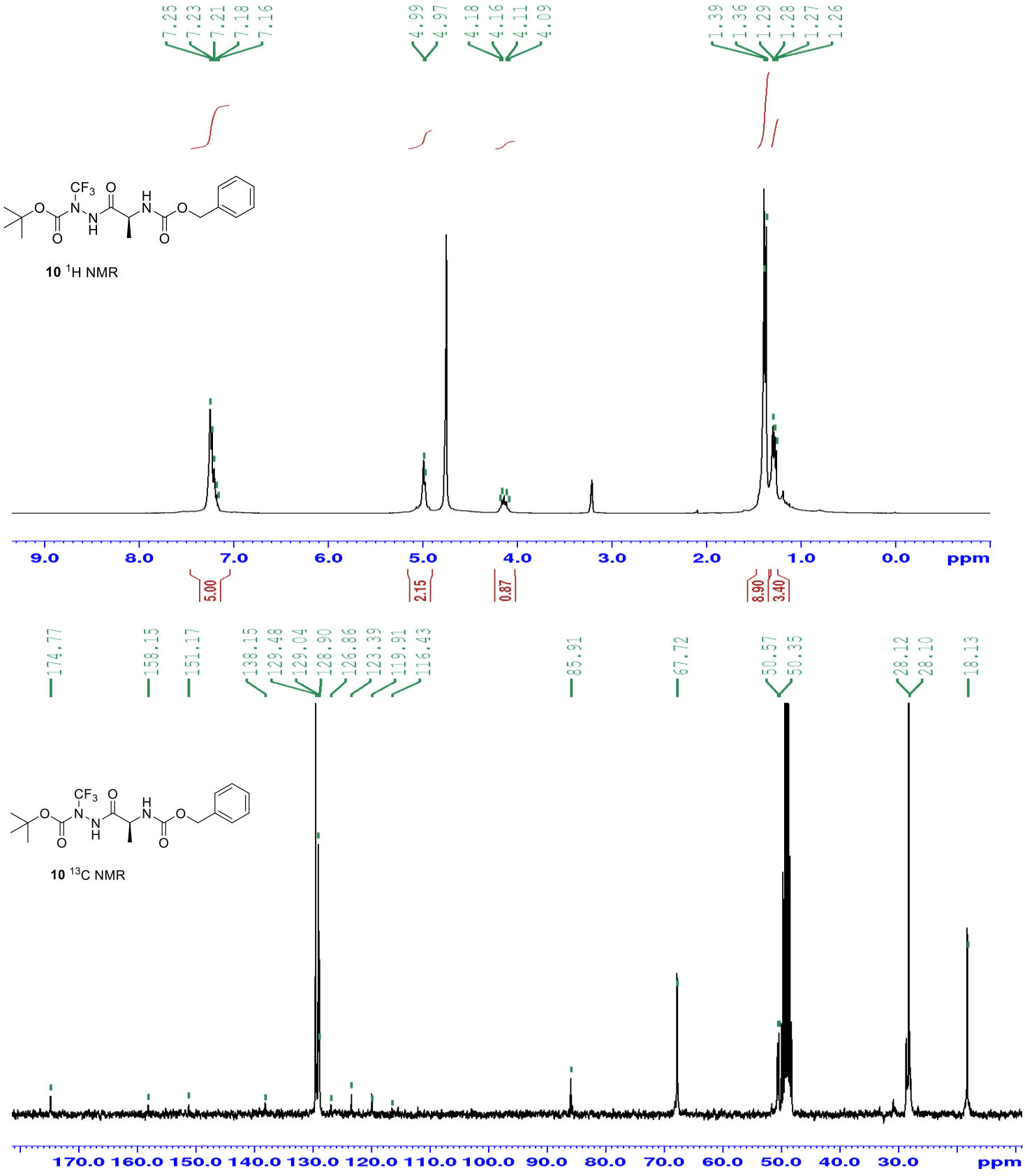


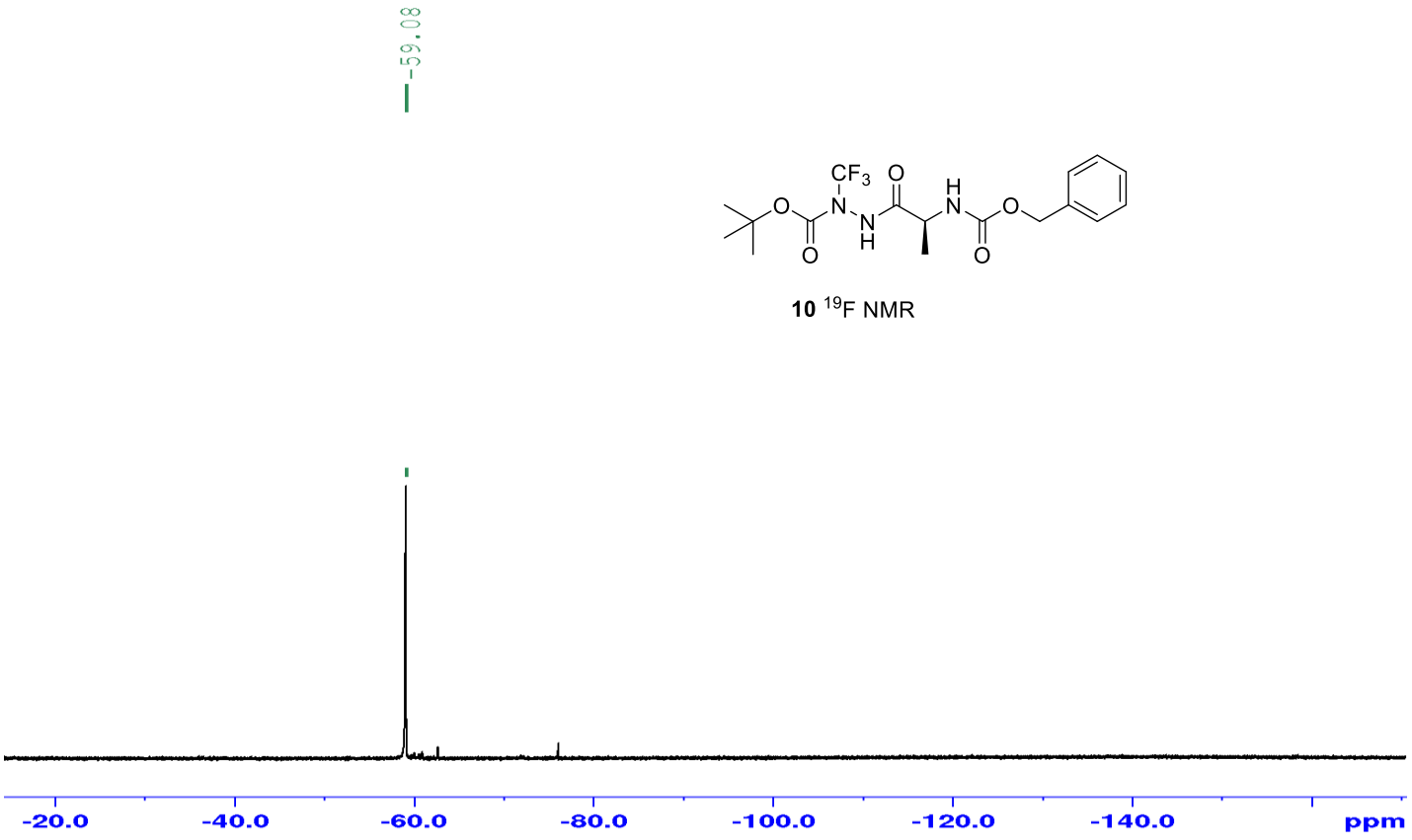
10' ^{13}C NMR



10' ^{19}F NMR

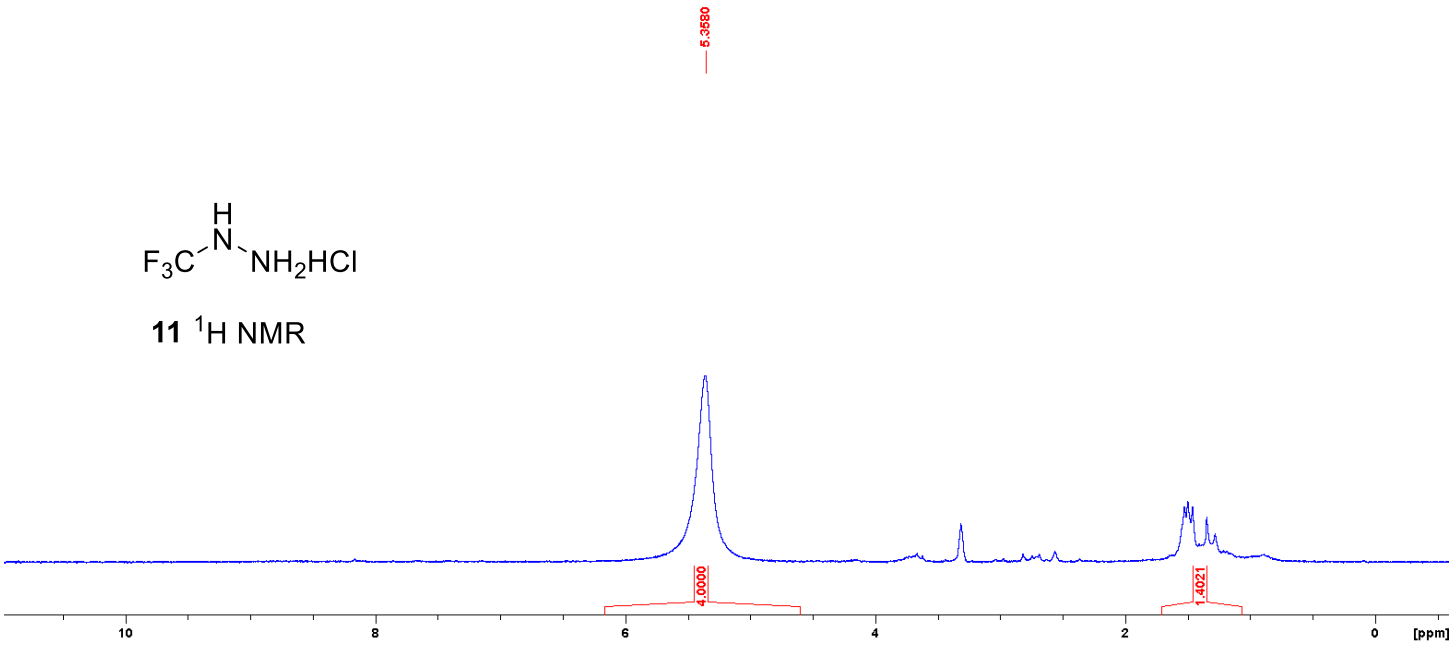
***Tert*-butyl 2-(((benzyloxy)carbonyl)-L-alanyl)-1-(trifluoromethyl)hydrazine-1-carboxylate 10**



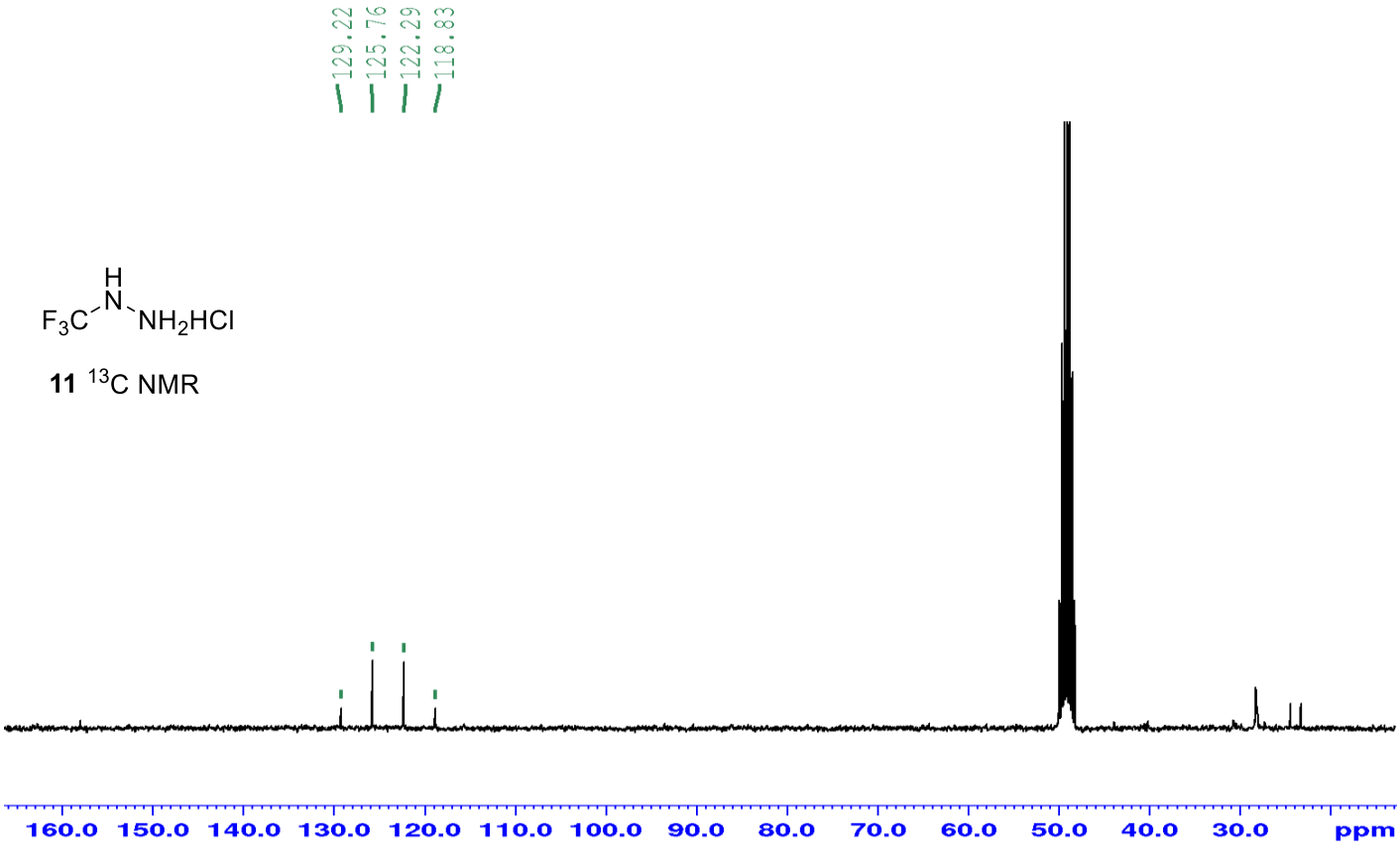


10 ^{19}F NMR

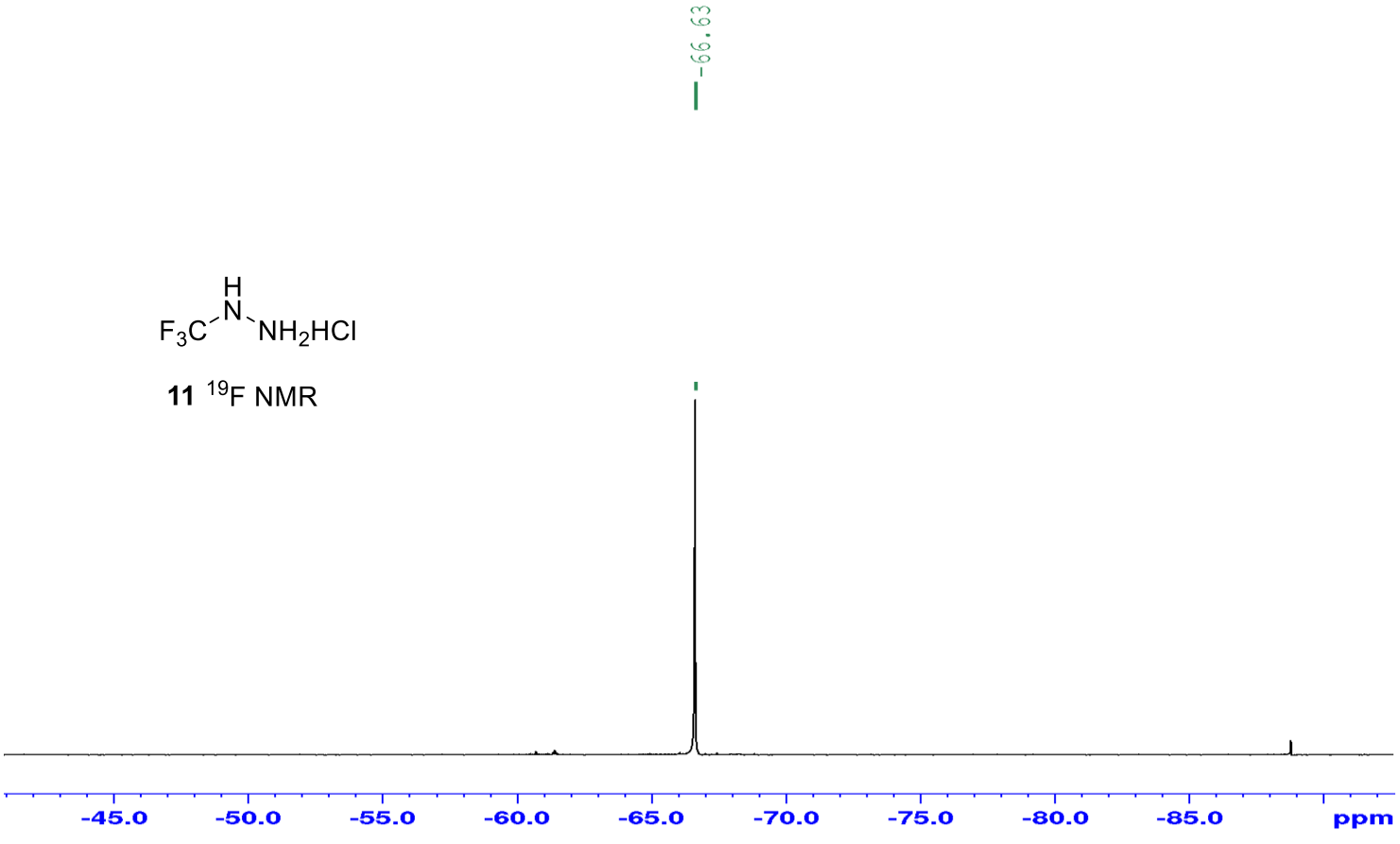
(trifluoromethyl)hydrazine hydrochloride 11



11 ^{1}H NMR

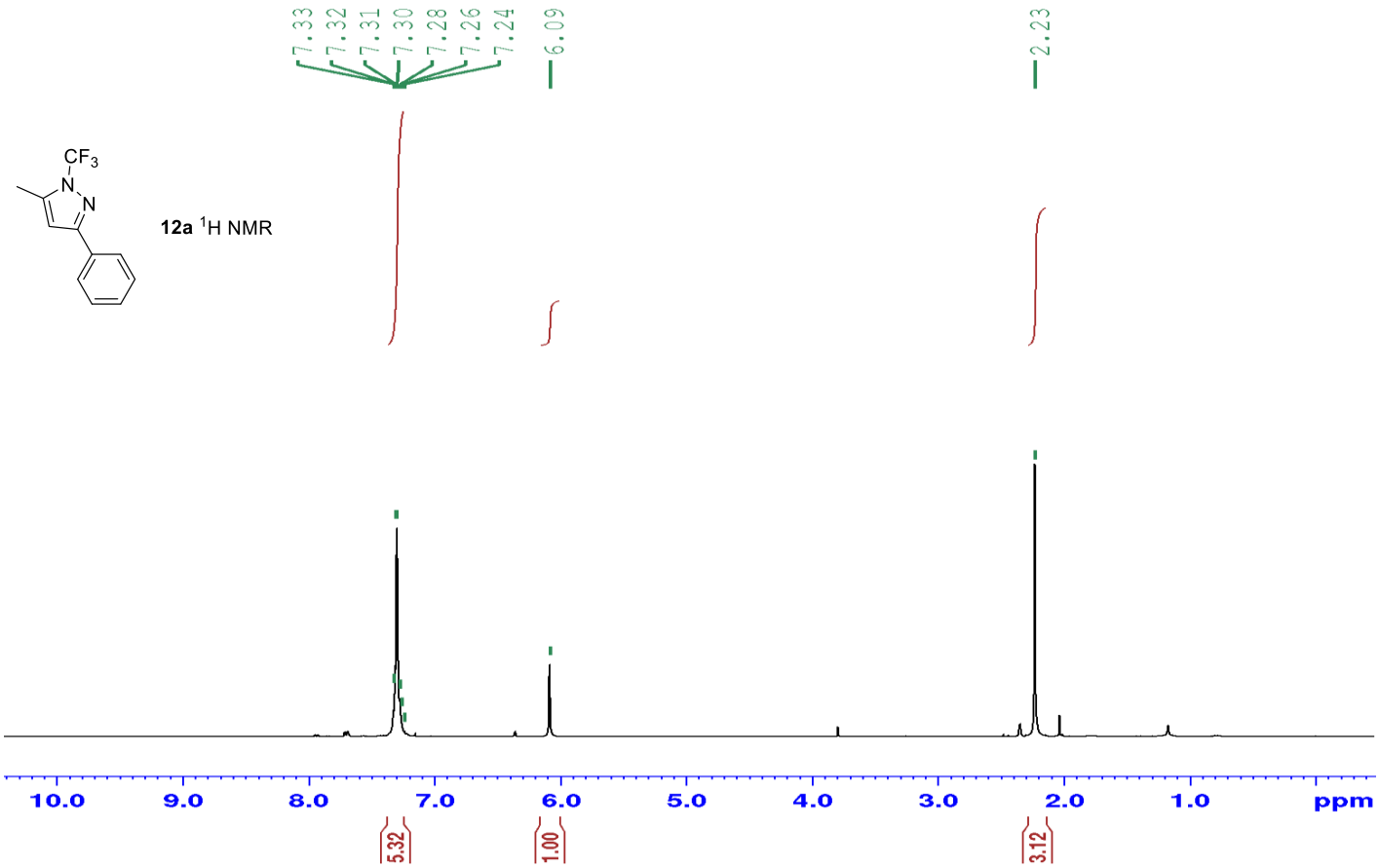


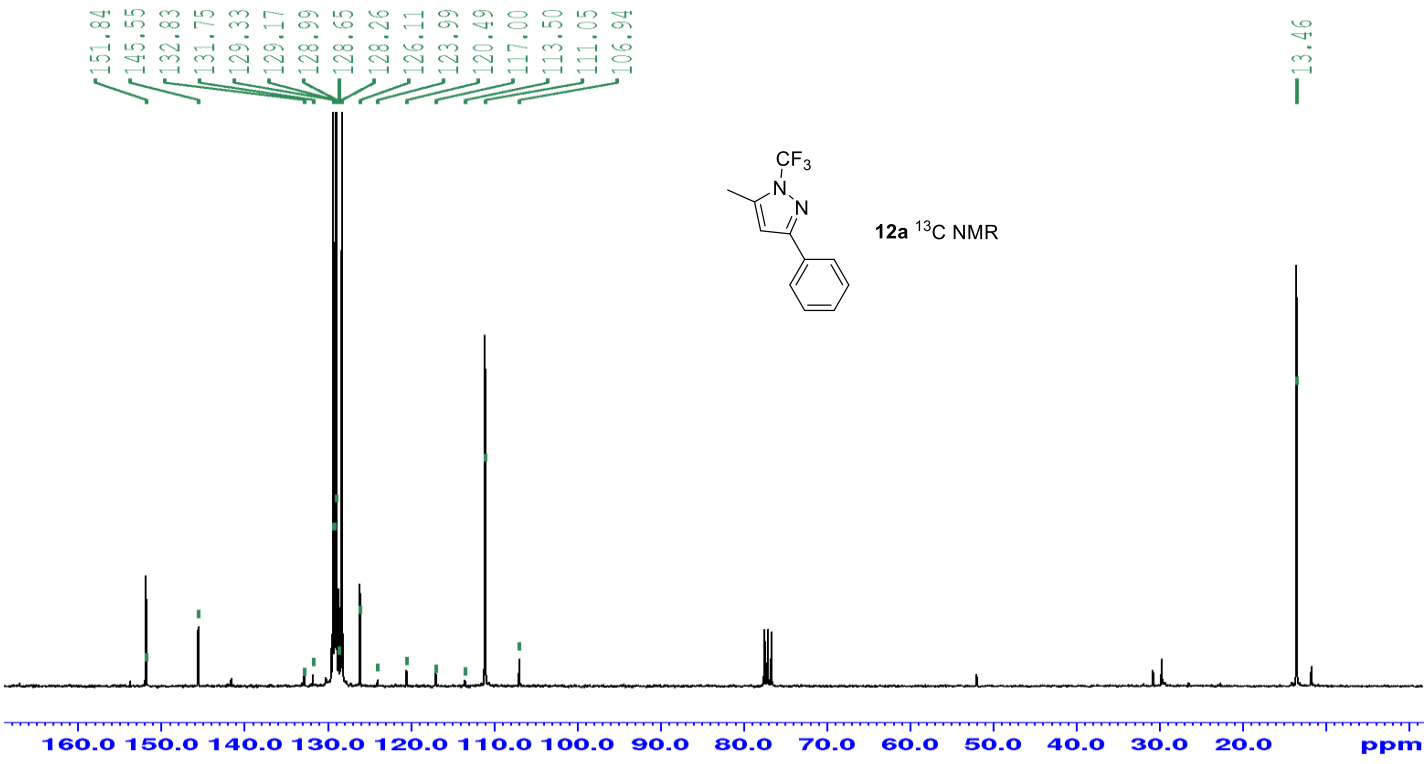
11 ^{13}C NMR

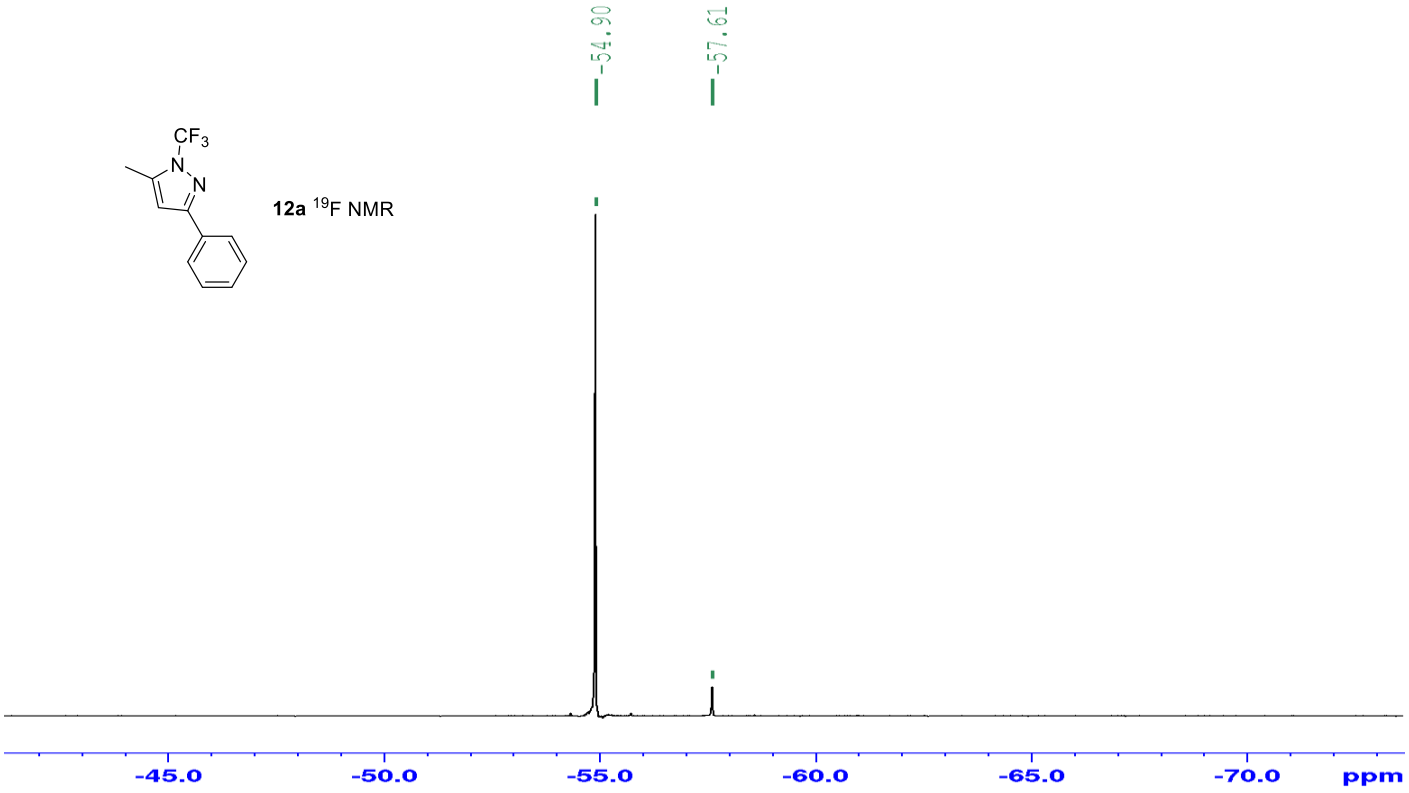


11 ^{19}F NMR

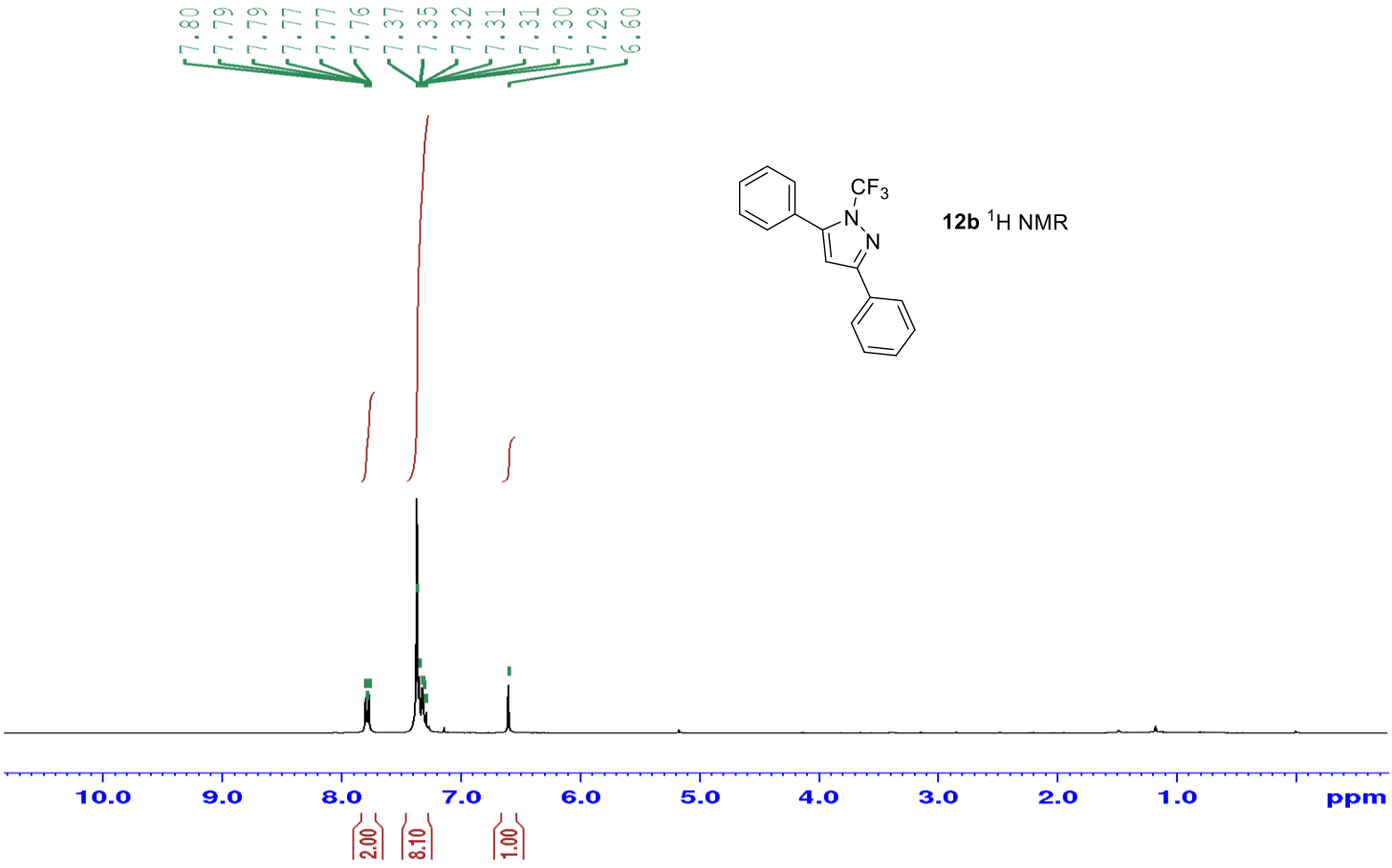
5-methyl-3-phenyl-1-(trifluoromethyl)-1H-pyrazole 12a

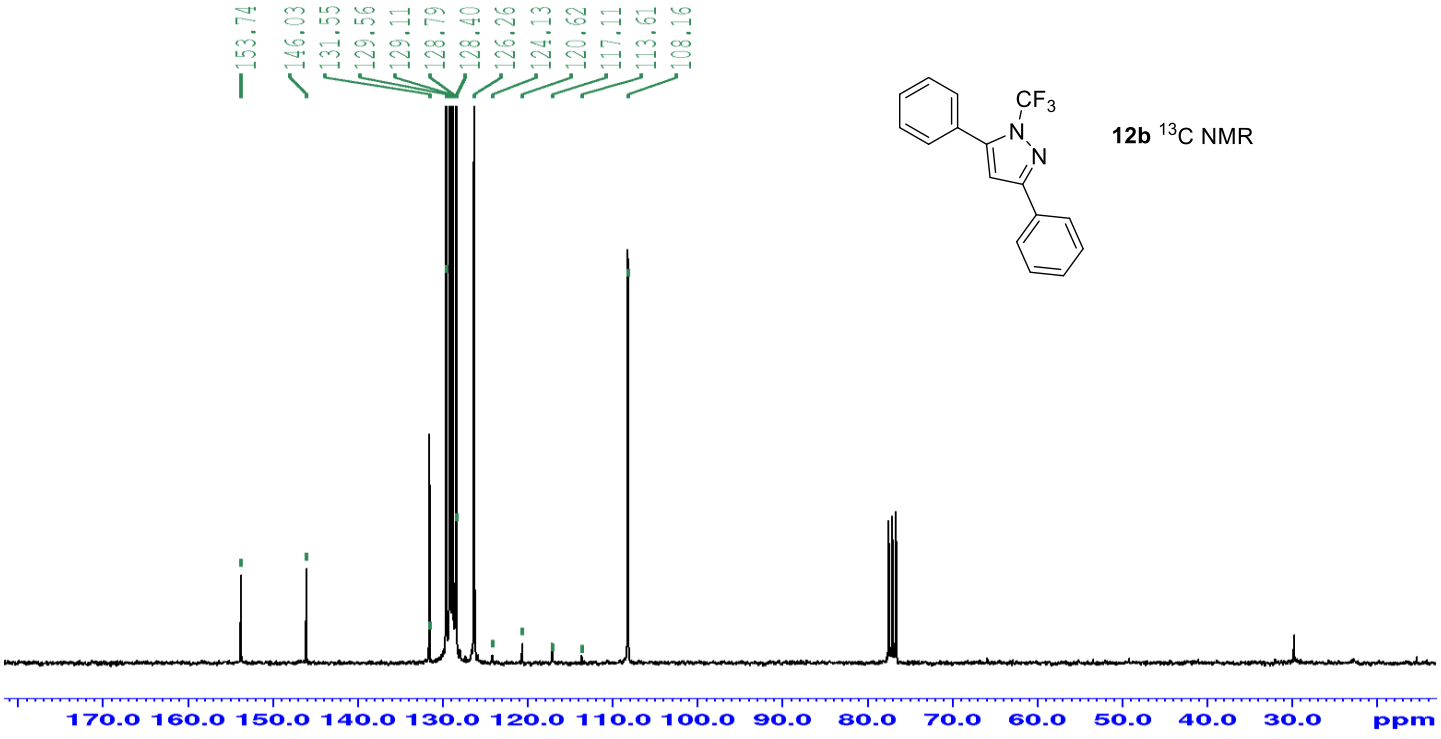




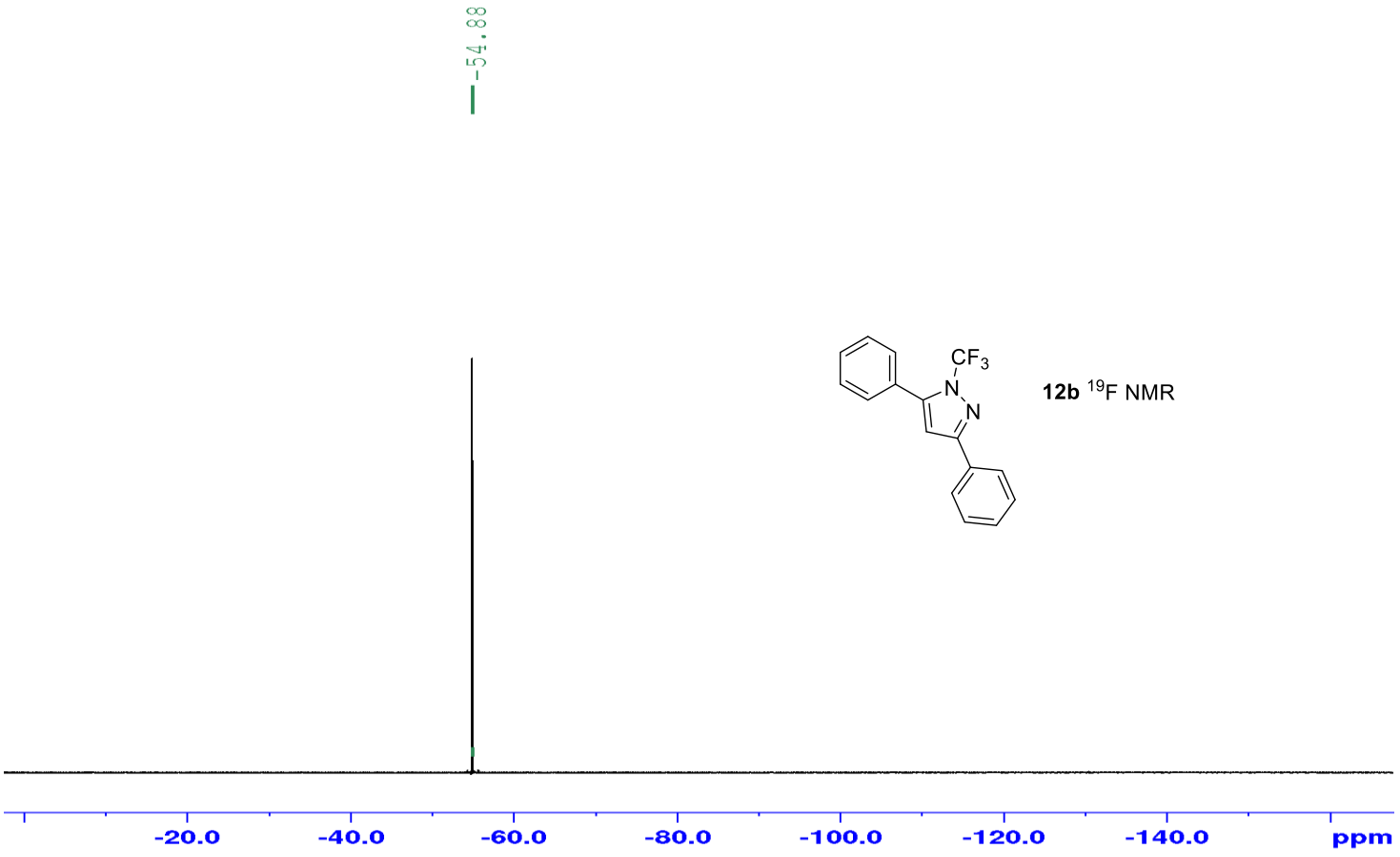


3,5-diphenyl-1-(trifluoromethyl)-1H-pyrazole 12b



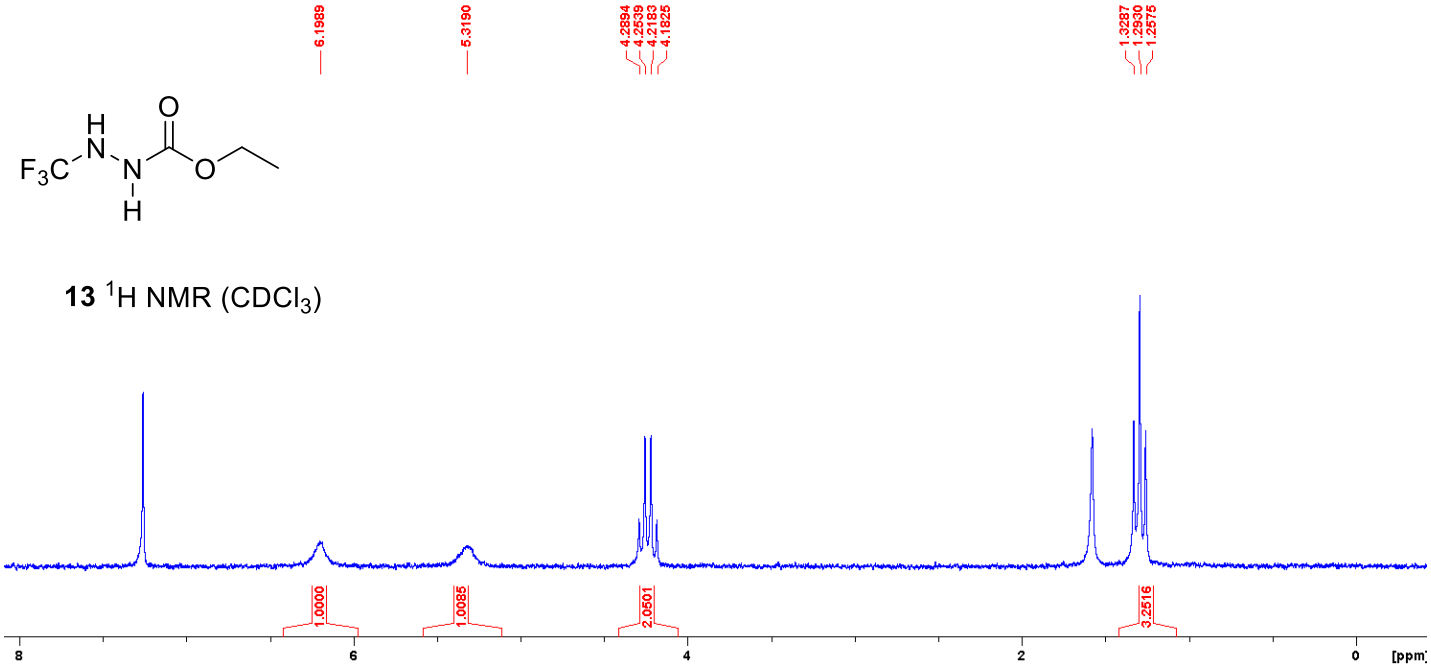


12b ^{13}C NMR

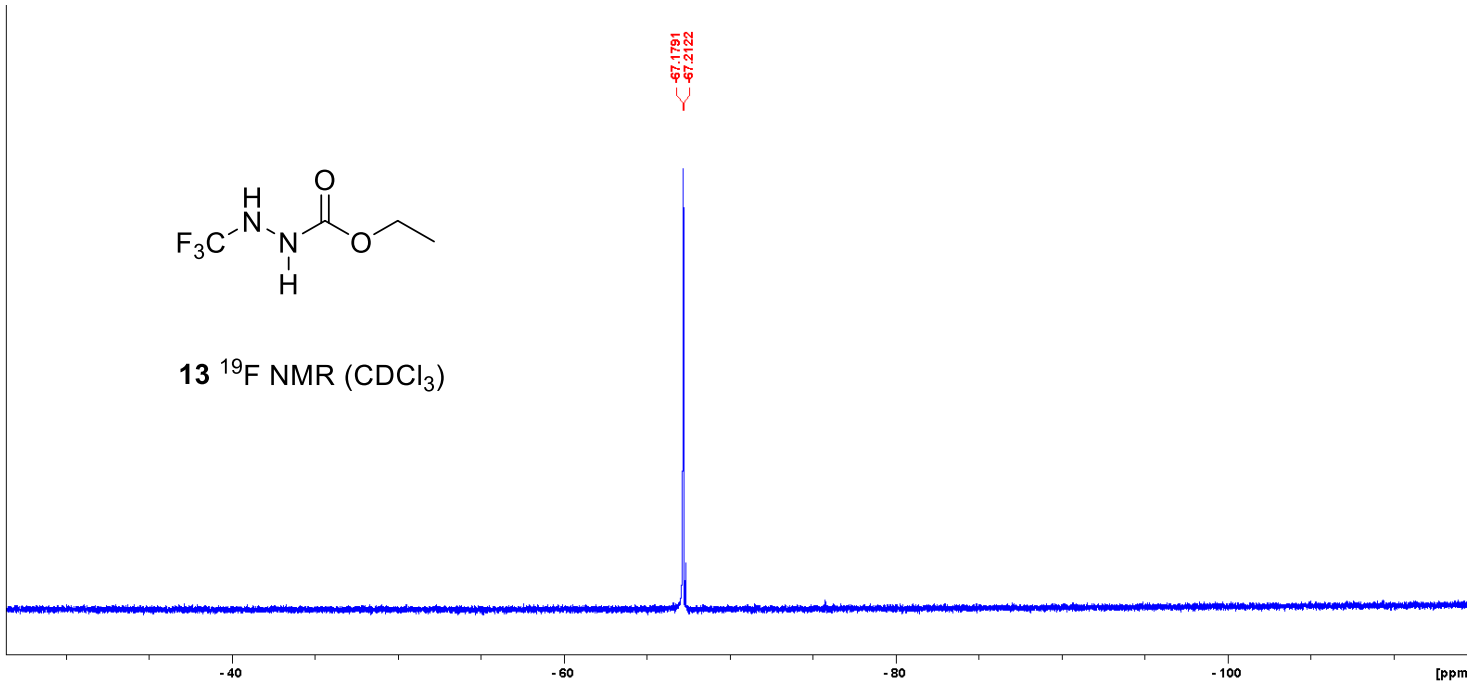


12b ^{19}F NMR

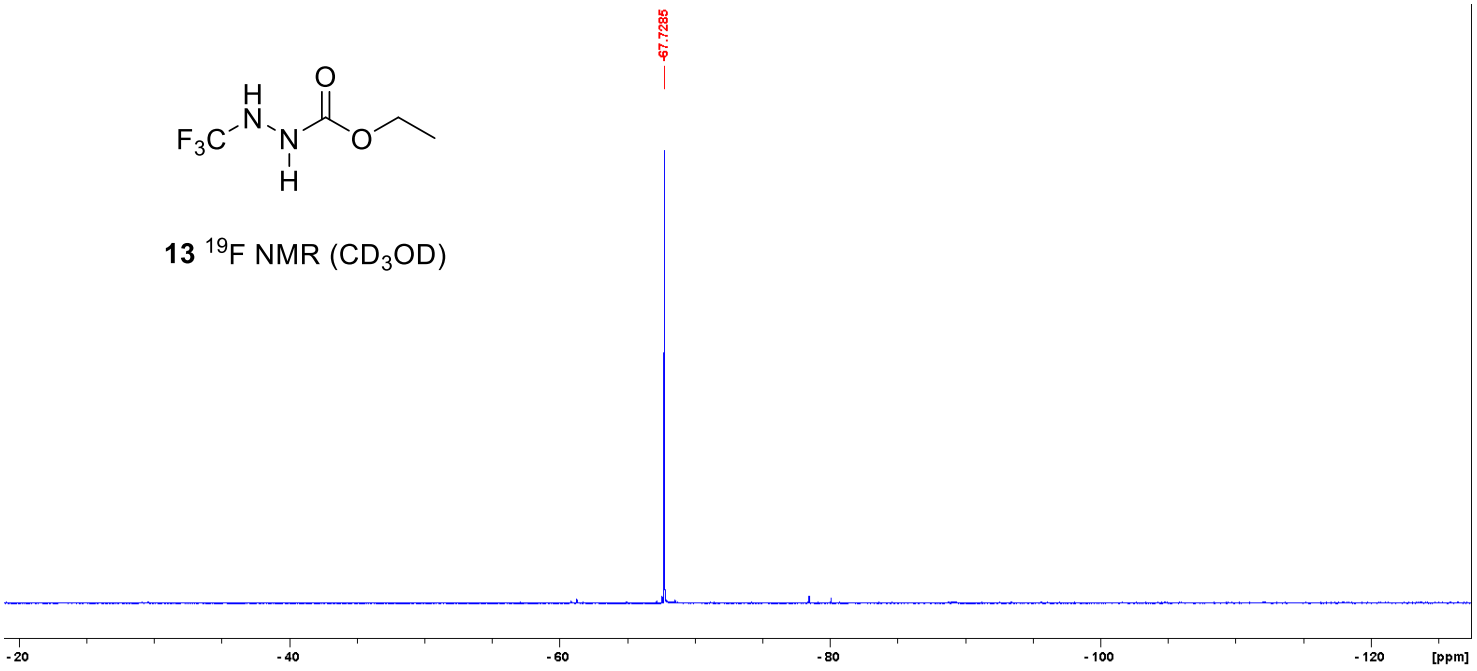
Ethyl 2-(trifluoromethyl)hydrazine-1-carboxylate 13



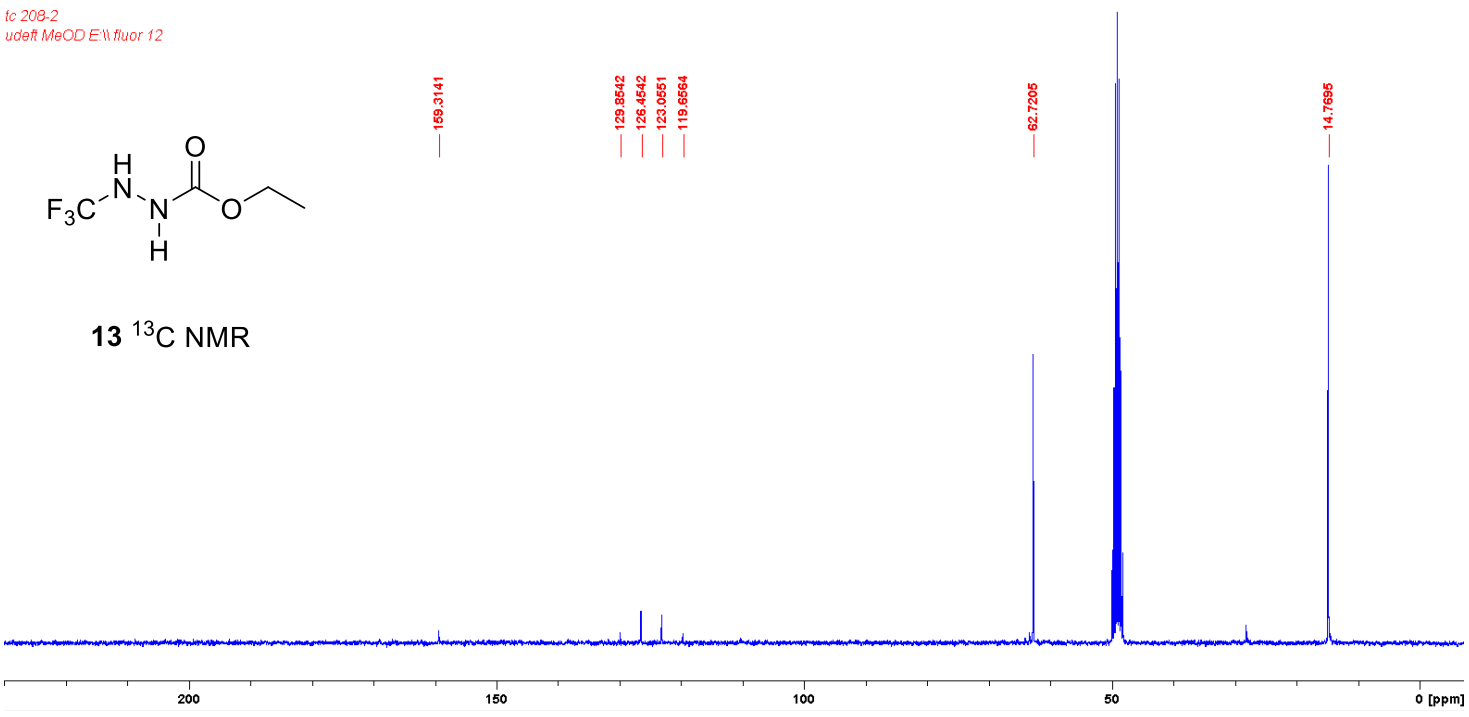
13 ^{1}H NMR ($CDCl_3$)



13 ^{19}F NMR ($CDCl_3$)

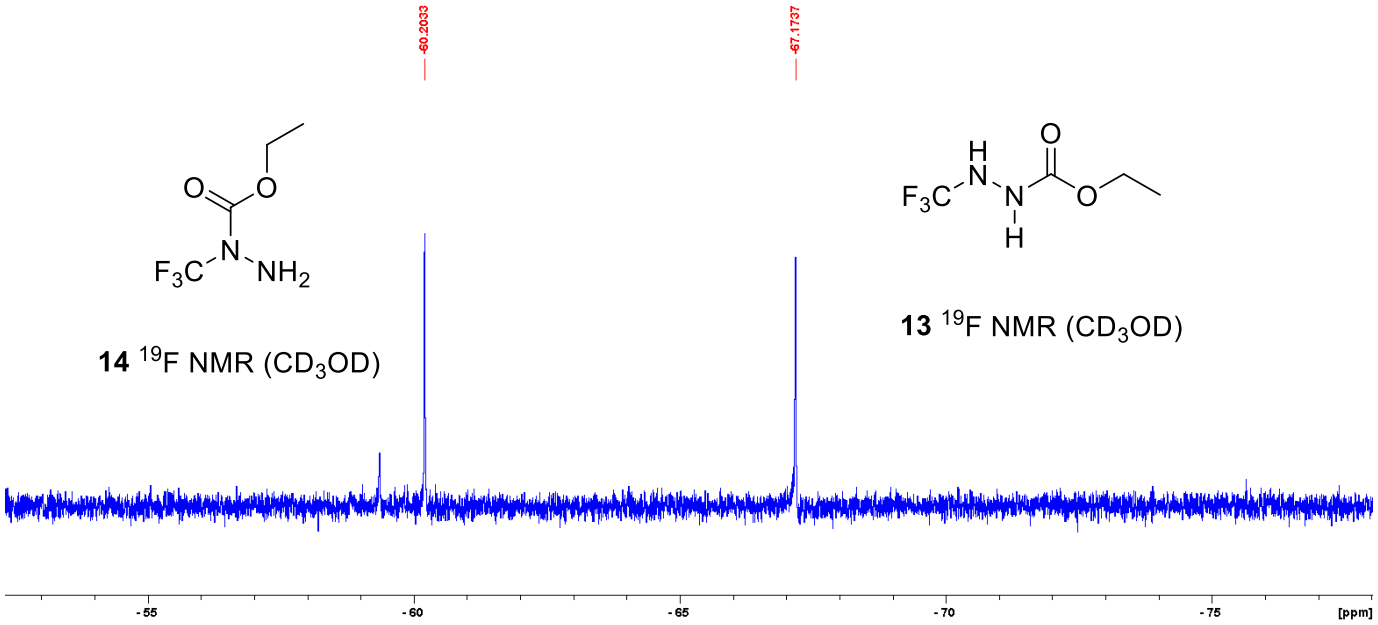


13 ^{19}F NMR (CD_3OD)

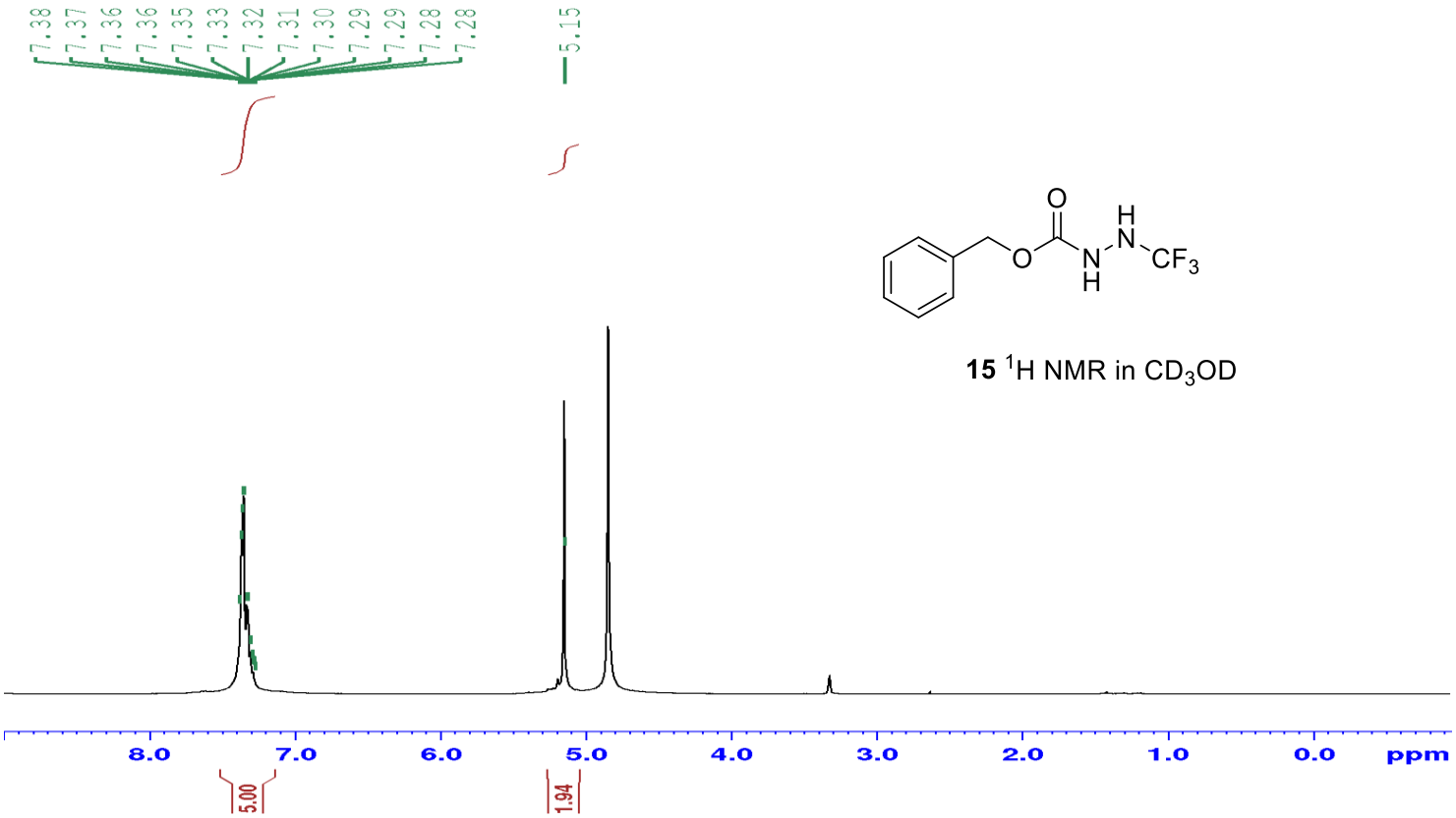


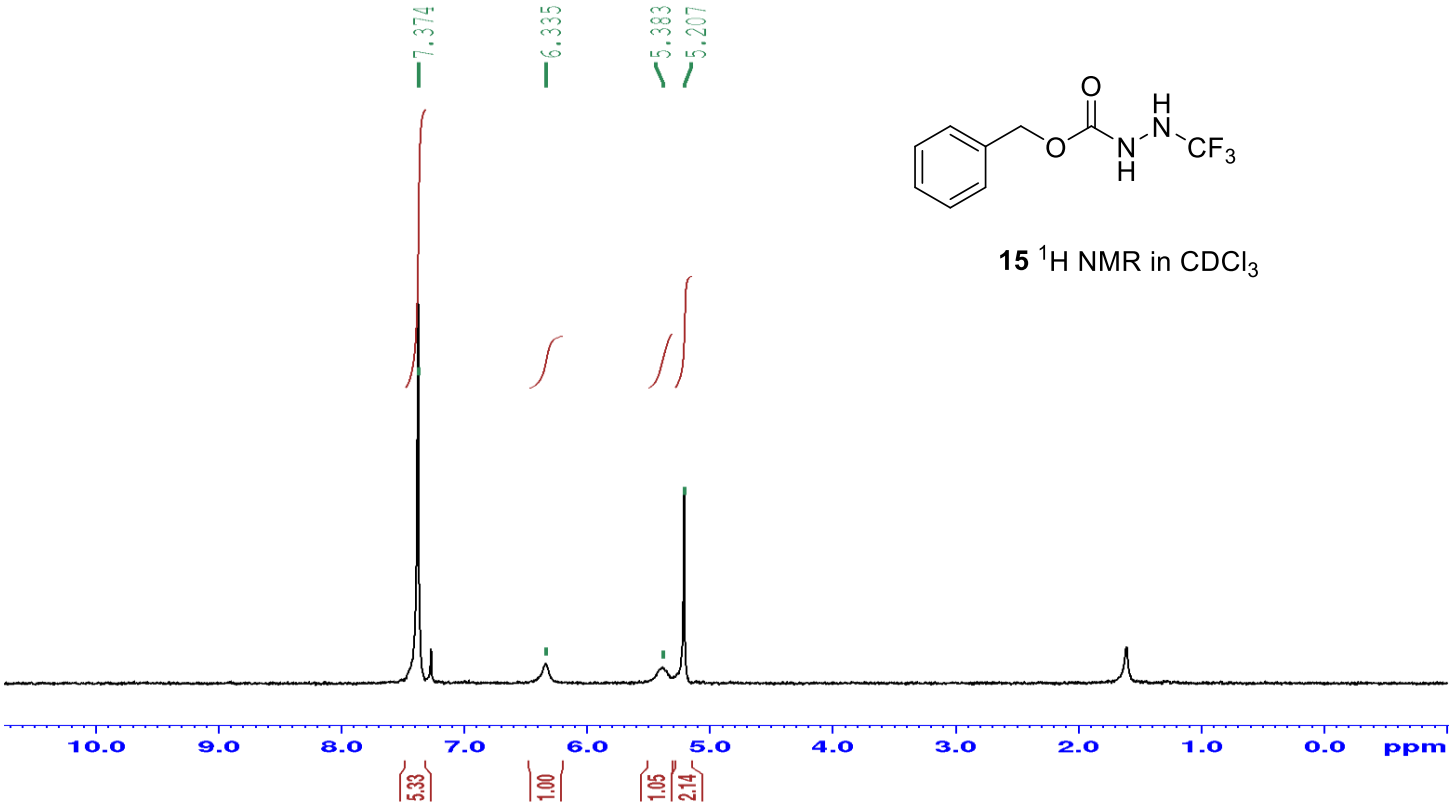
13 ^{13}C NMR

^{19}F NMR of the crude

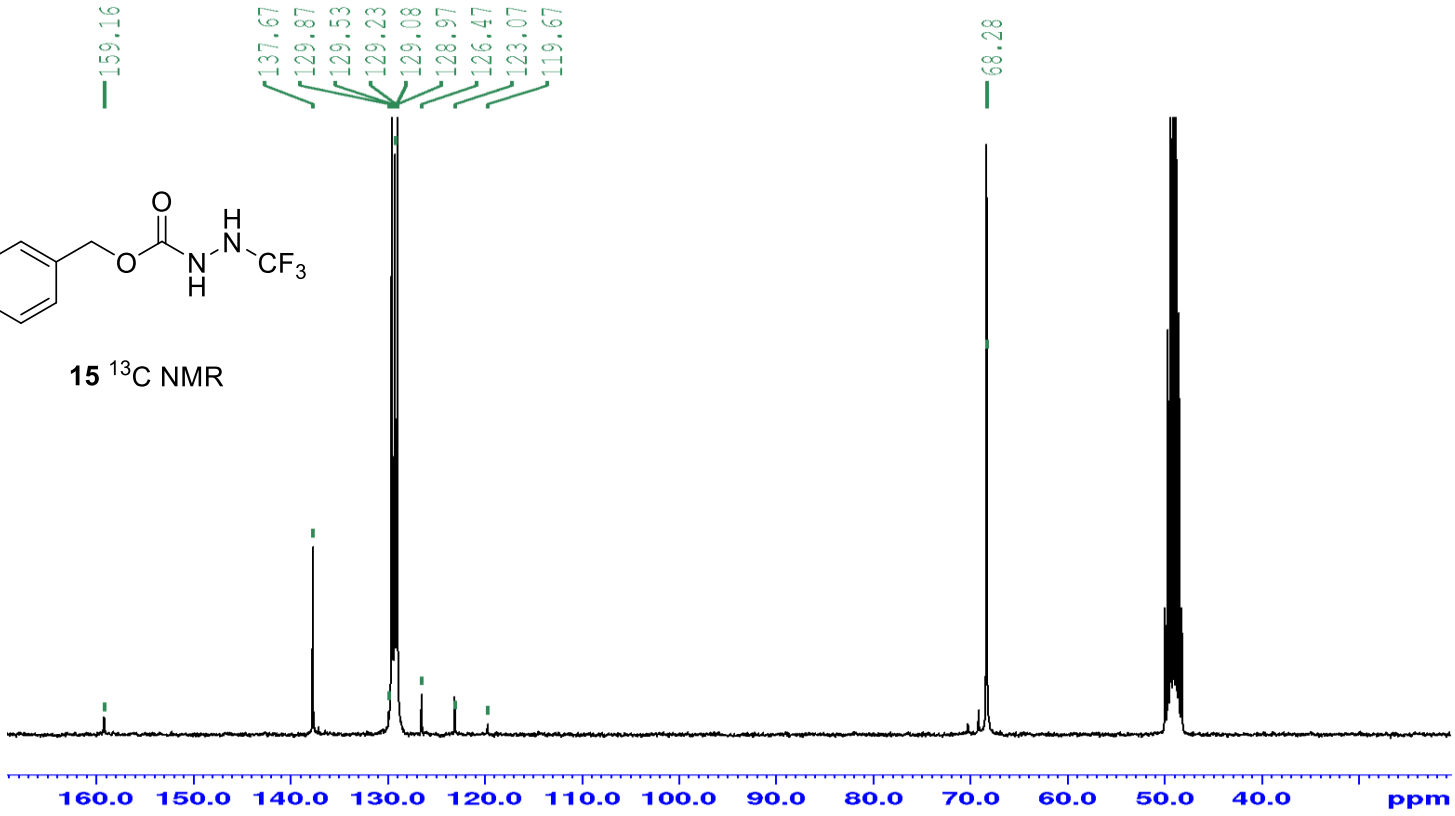


Benzyl 2-(trifluoromethyl)hydrazine-1-carboxylate 15

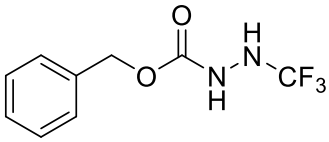




15 ^{1}H NMR in $CDCl_3$

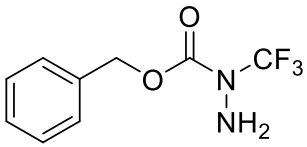


15 ^{13}C NMR

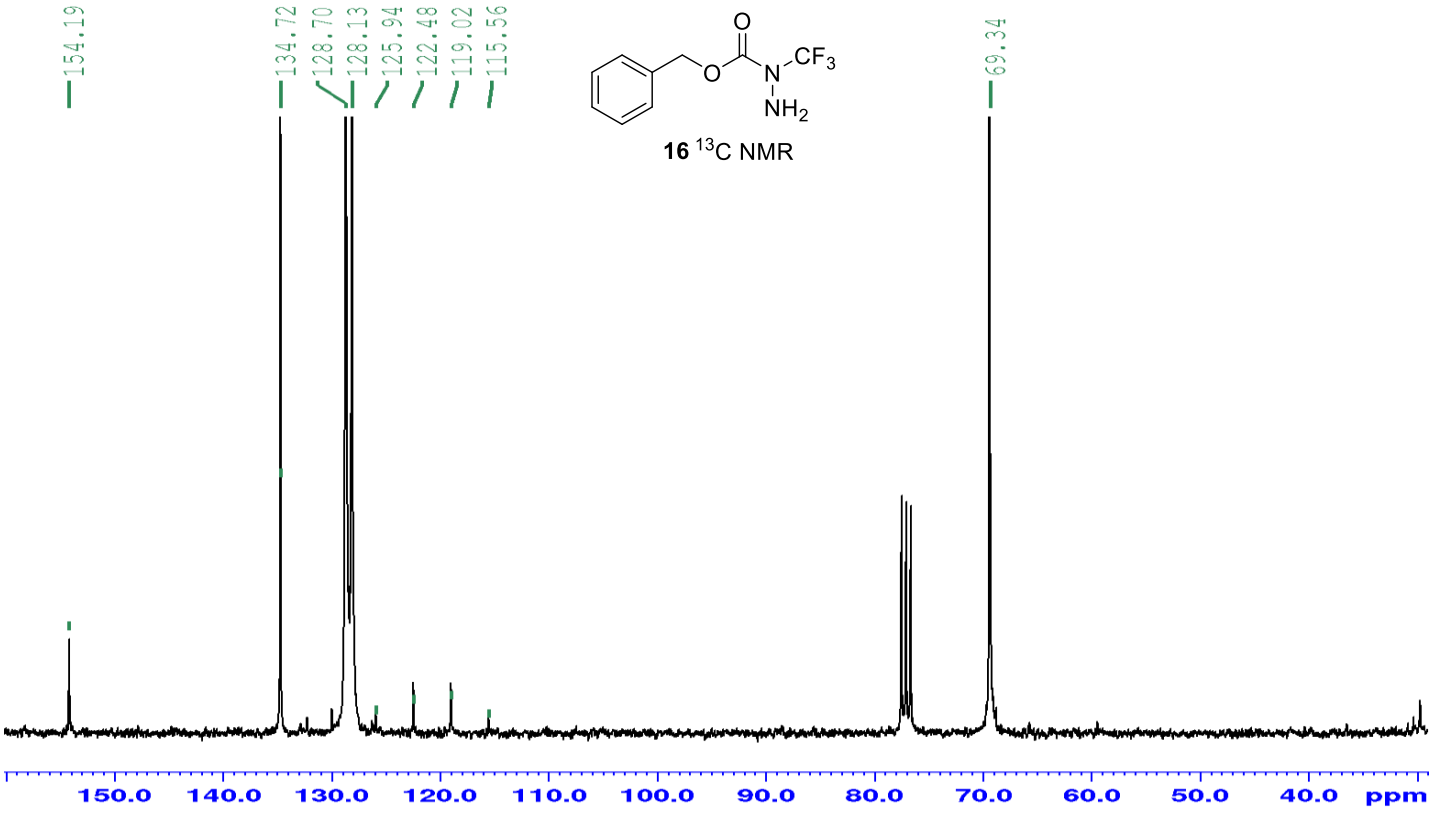


15 ^{19}F NMR ($CDCl_3$)

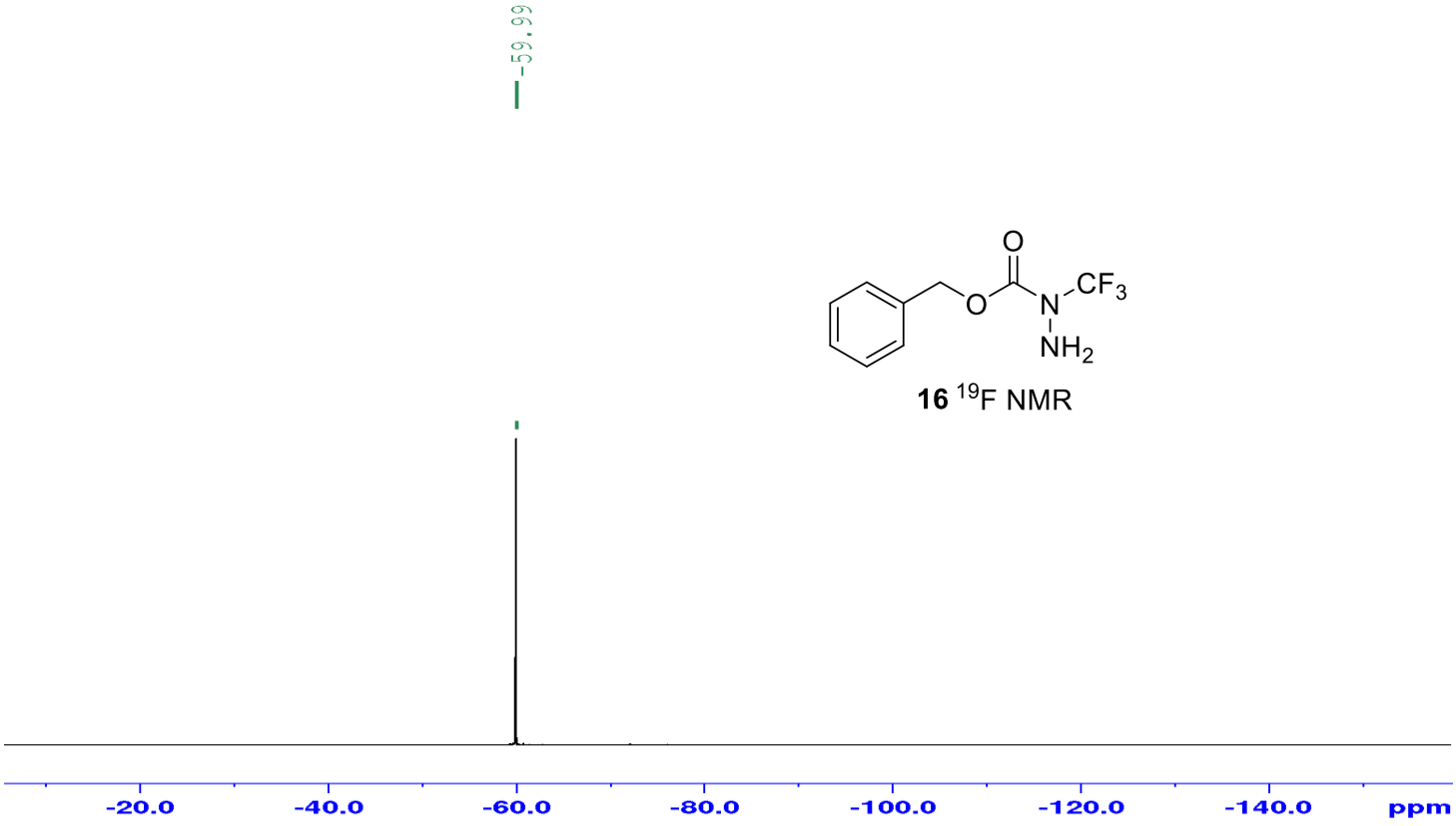
Benzyl 1-(trifluoromethyl)hydrazine-1-carboxylate 16



16 ^{1}H NMR

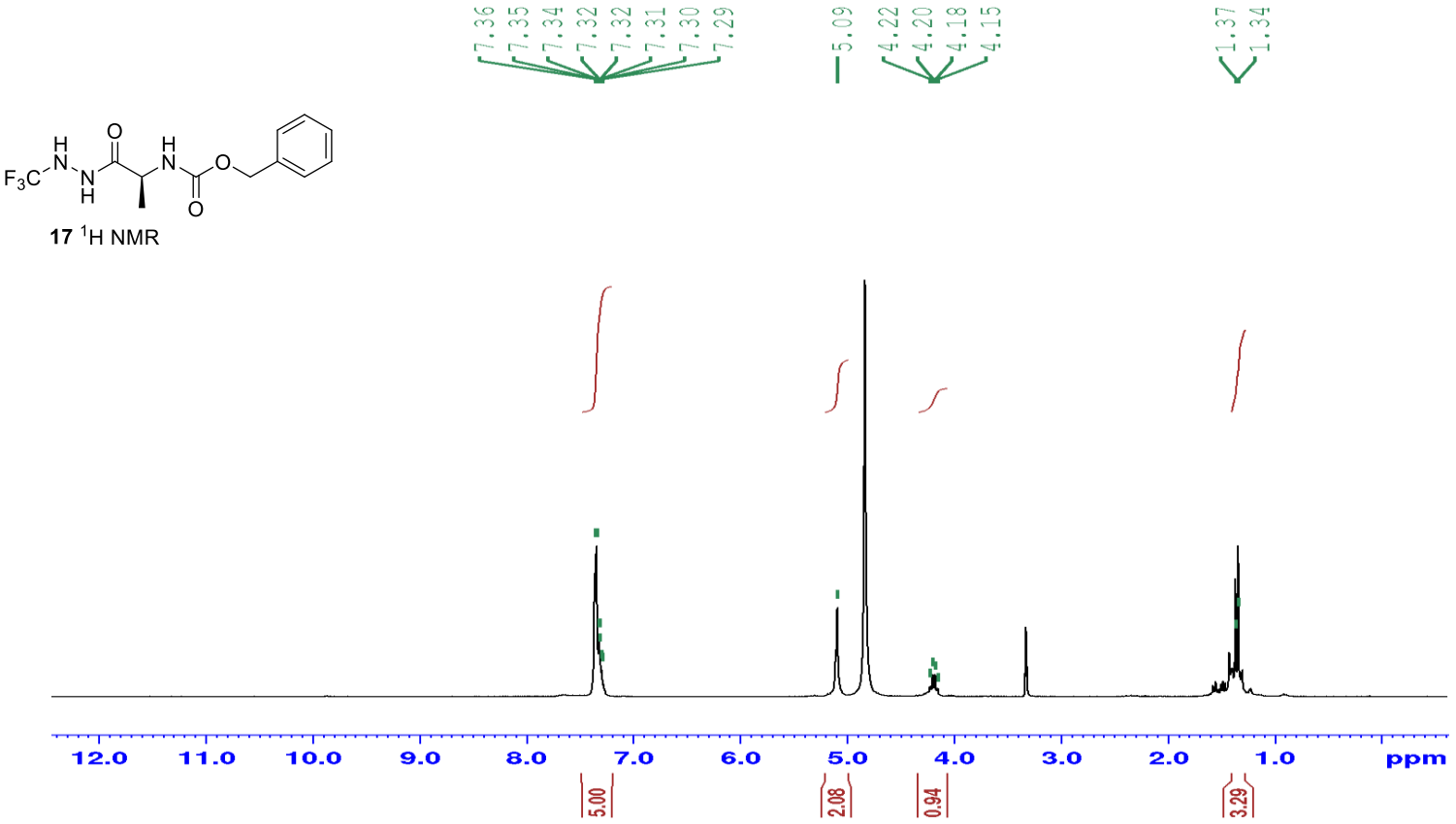


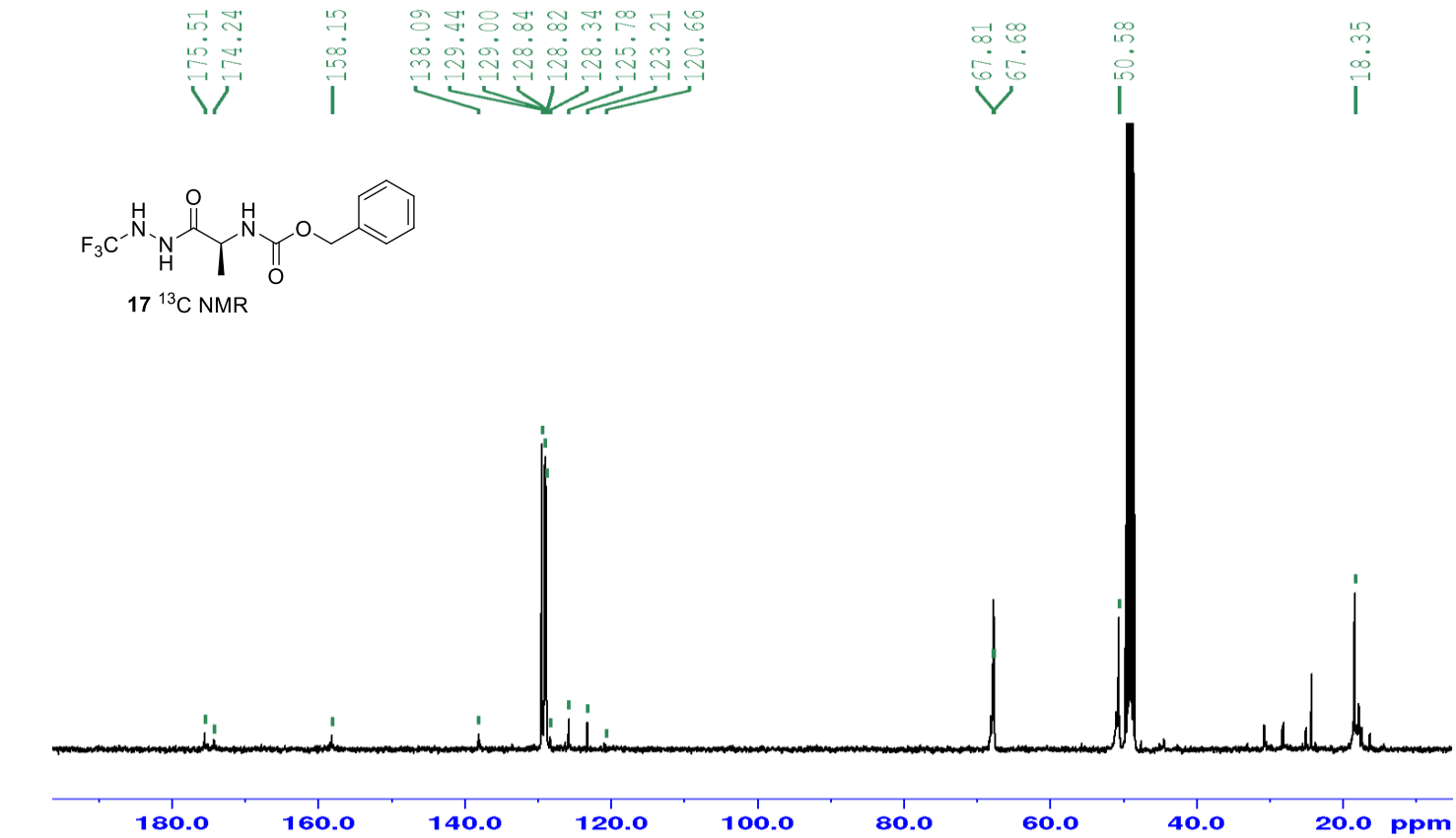
16 ^{13}C NMR

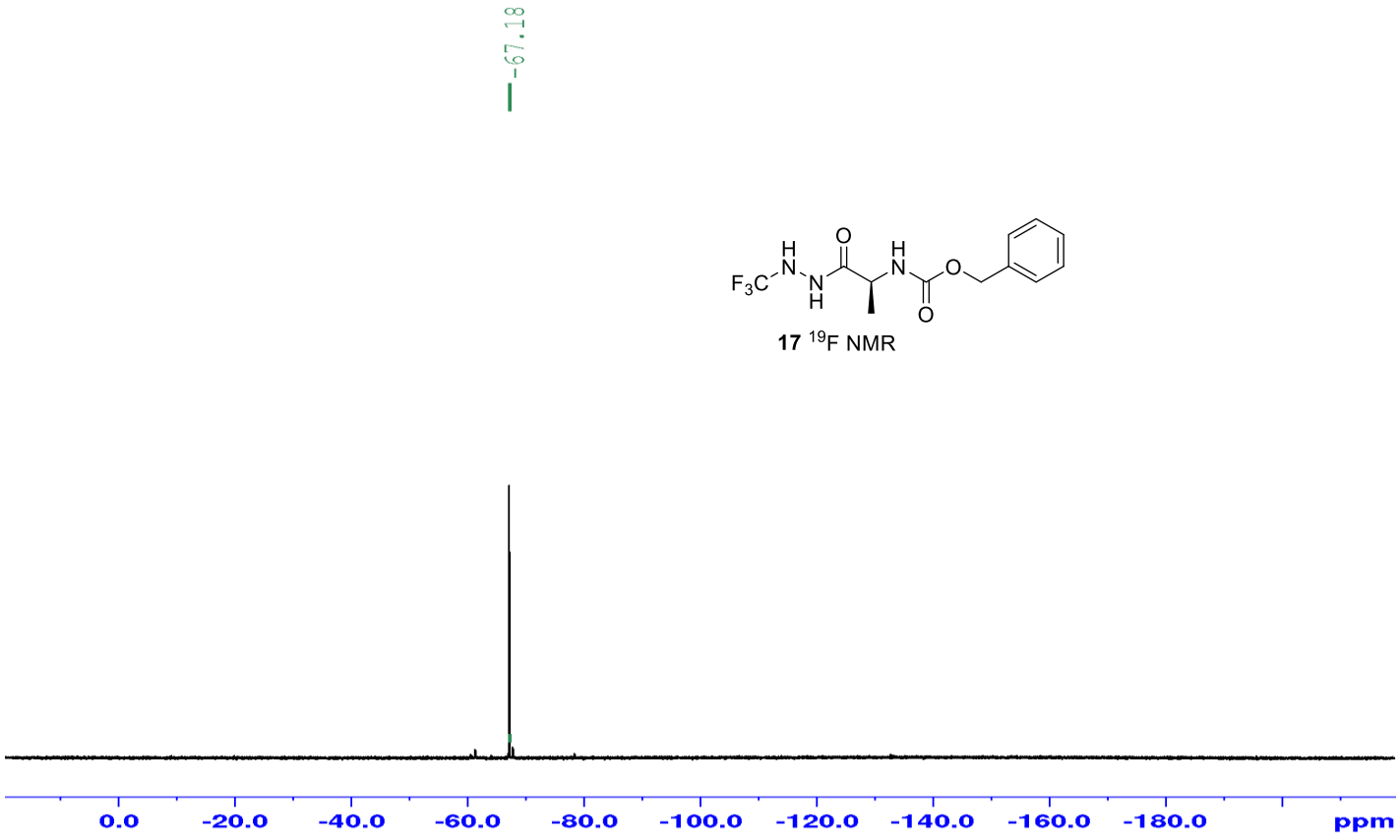


16 ^{19}F NMR

Benzyl (R)-(1-oxo-1-(2-(trifluoromethyl)hydrazineyl)propan-2-yl)carbamate 17

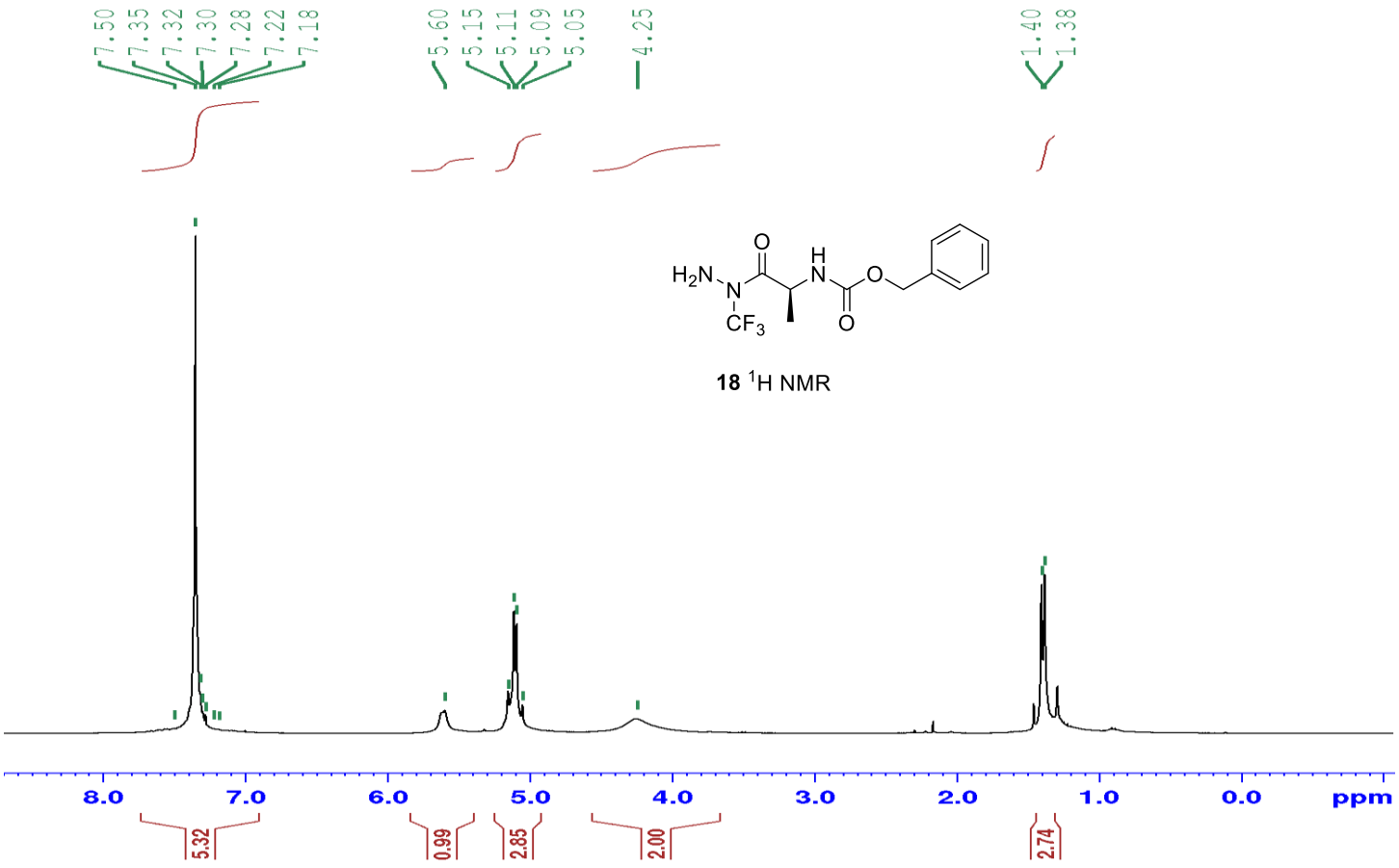




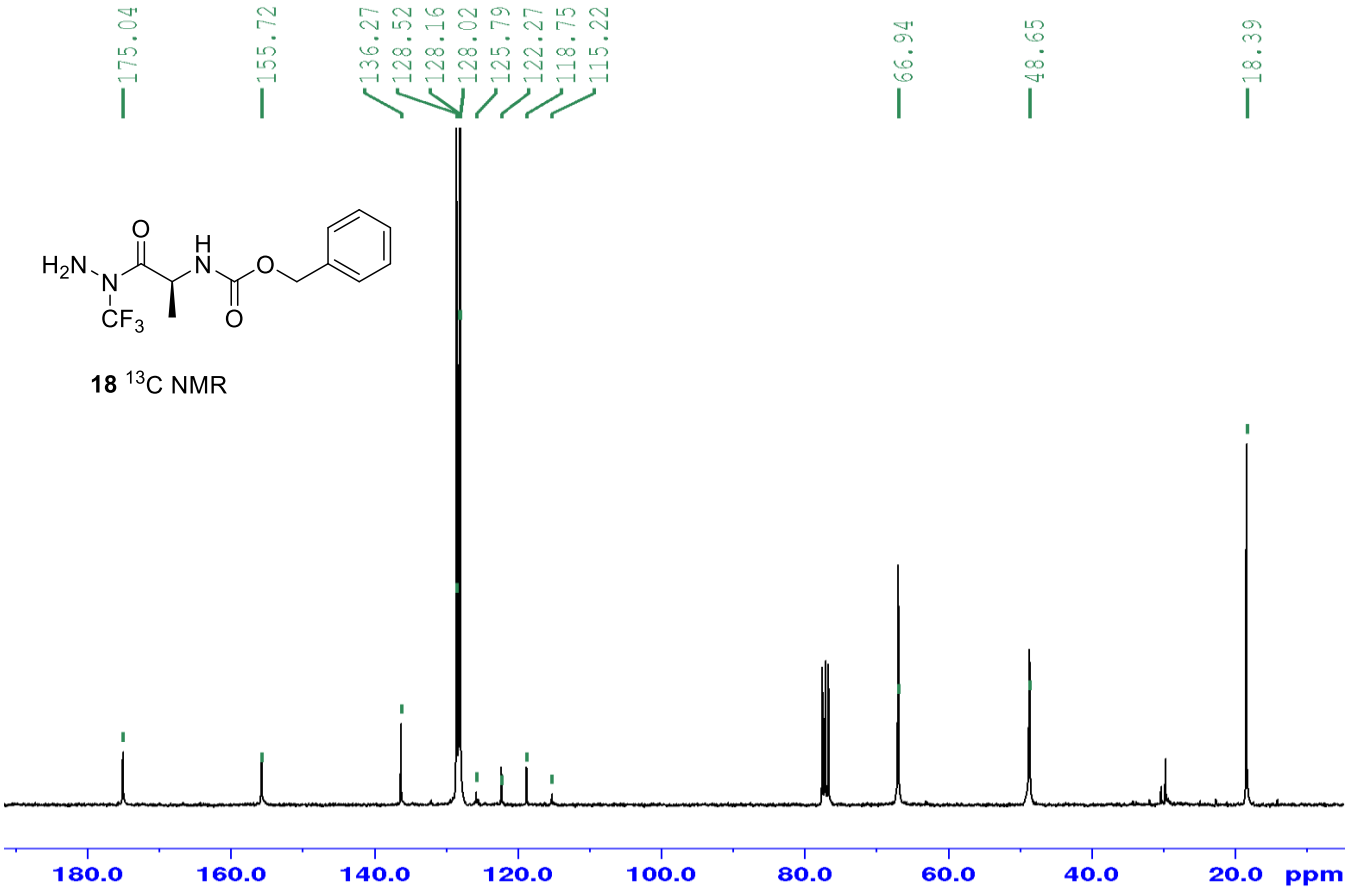


17 ^{19}F NMR

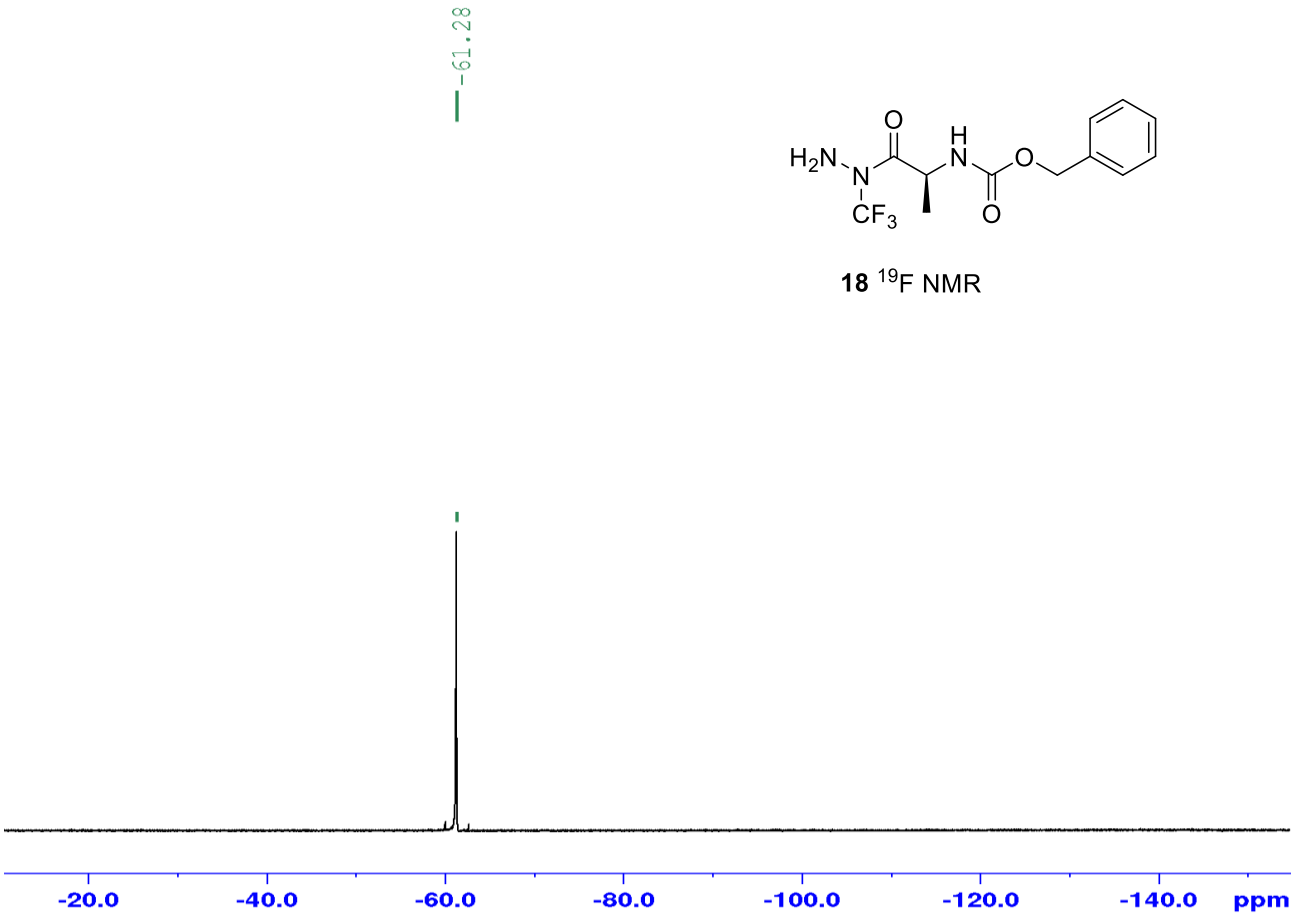
Benzyl (R)-(1-oxo-1-(1-(trifluoromethyl)hydrazineyl)propan-2-yl)carbamate 18



18 ^{1}H NMR

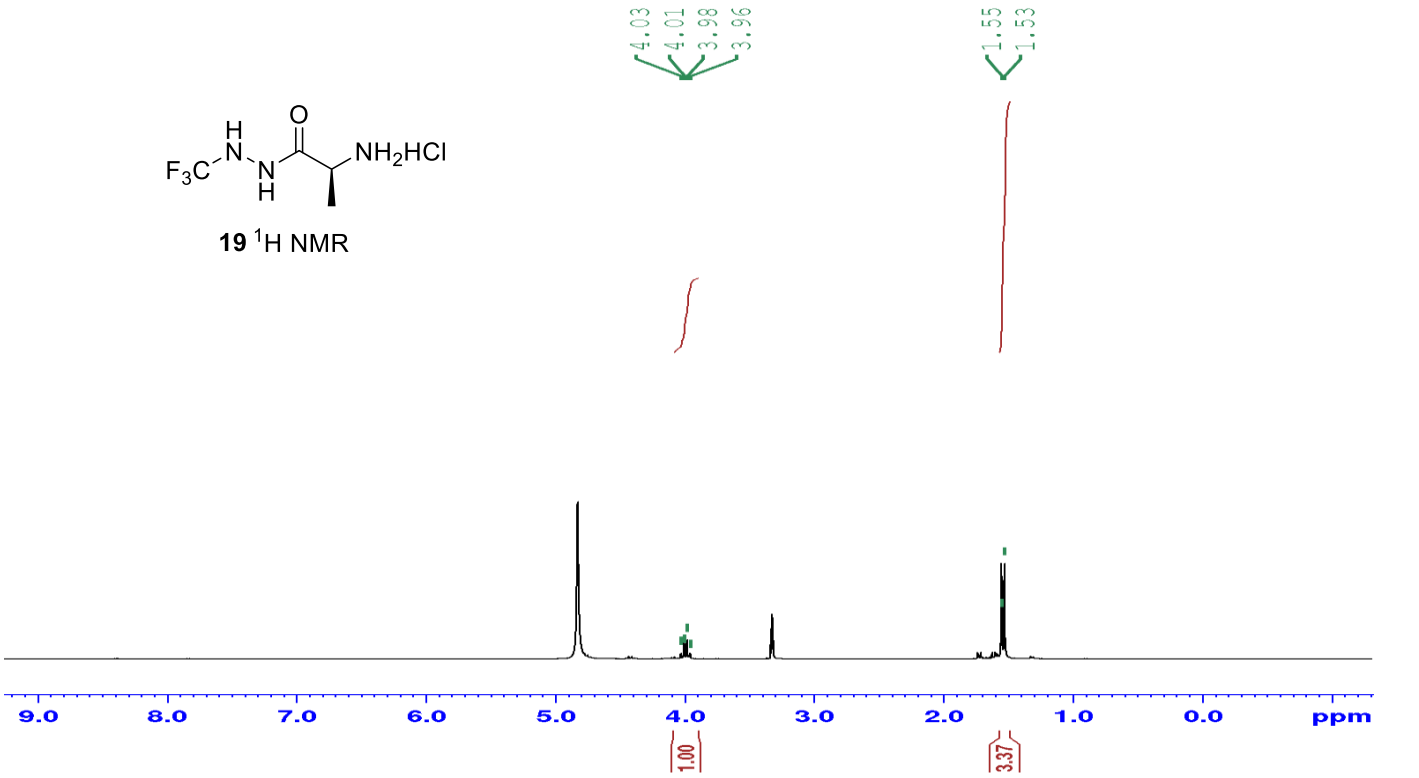


18 ^{13}C NMR

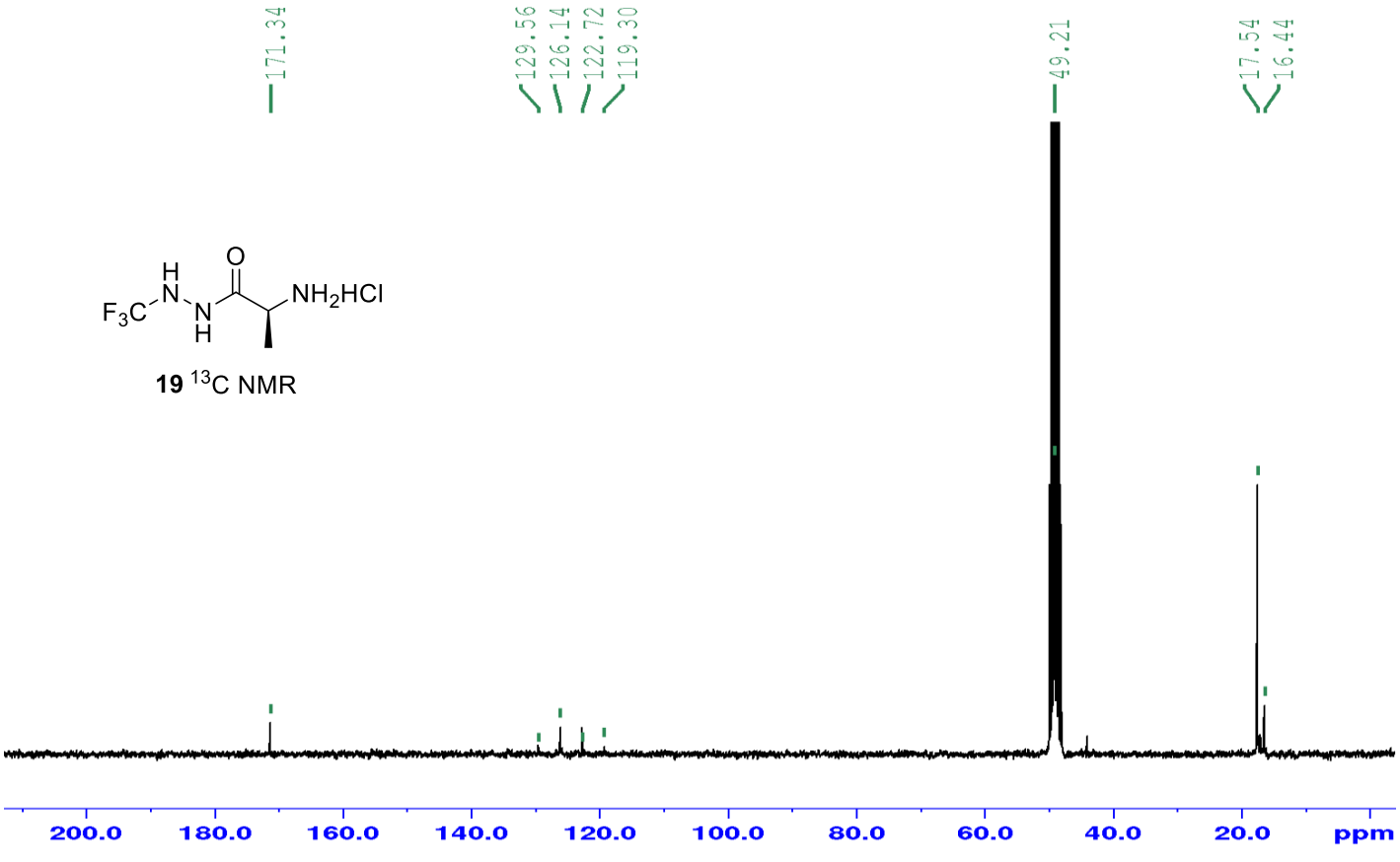


18 ^{19}F NMR

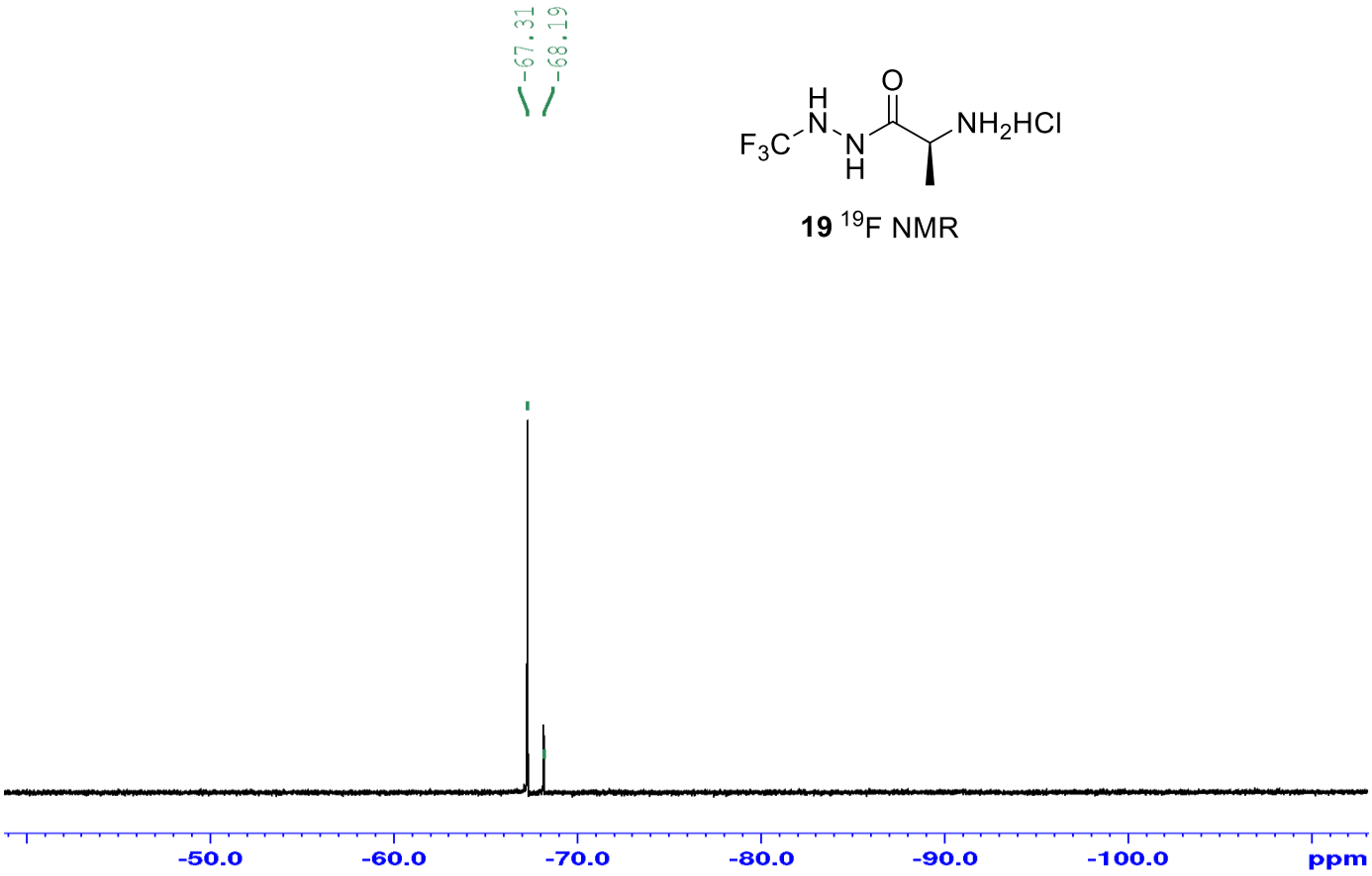
(R)-2-amino-N'-(trifluoromethyl)propanehydrazide hydrochloride 19



19 ^{1}H NMR

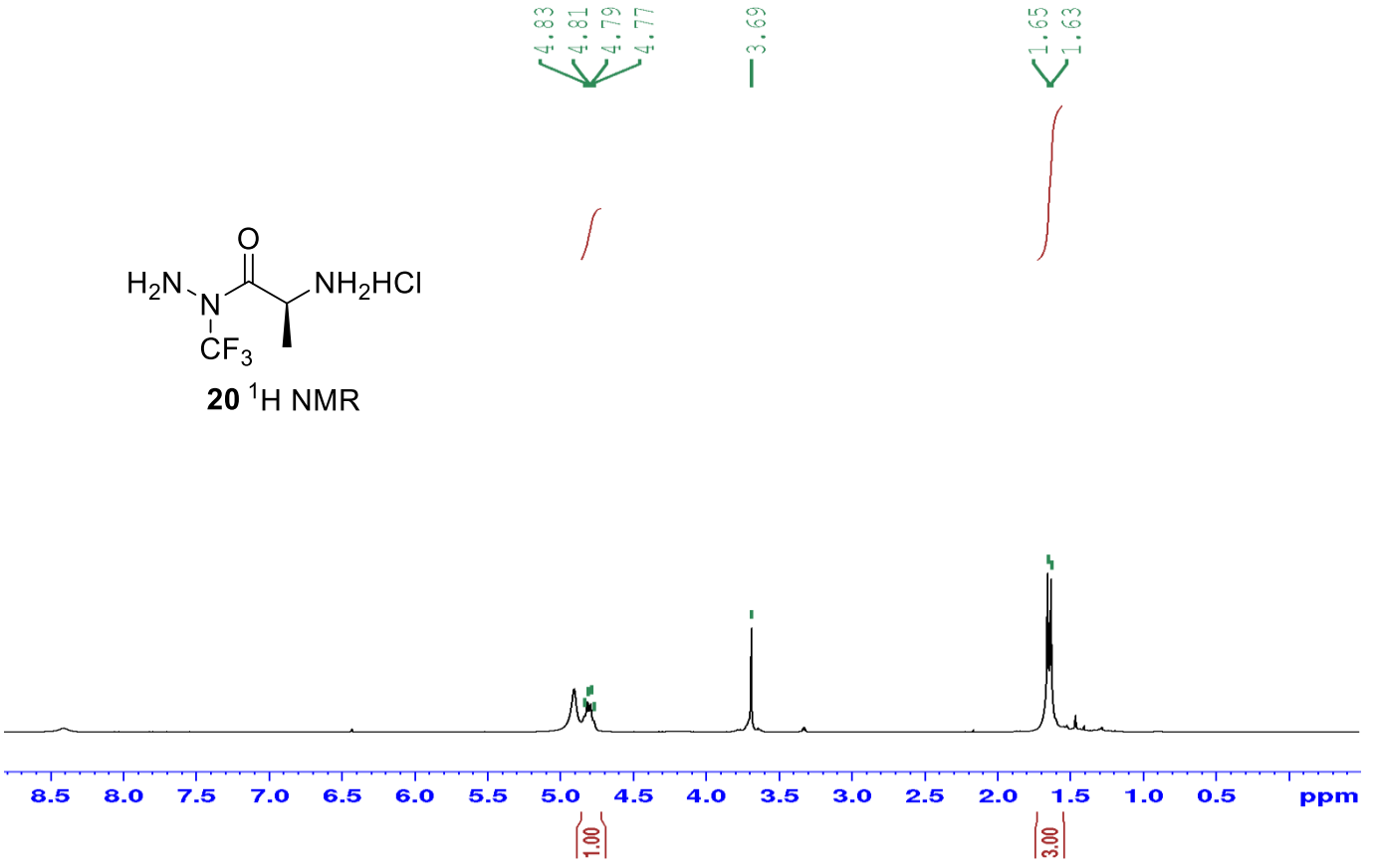


19 ^{13}C NMR

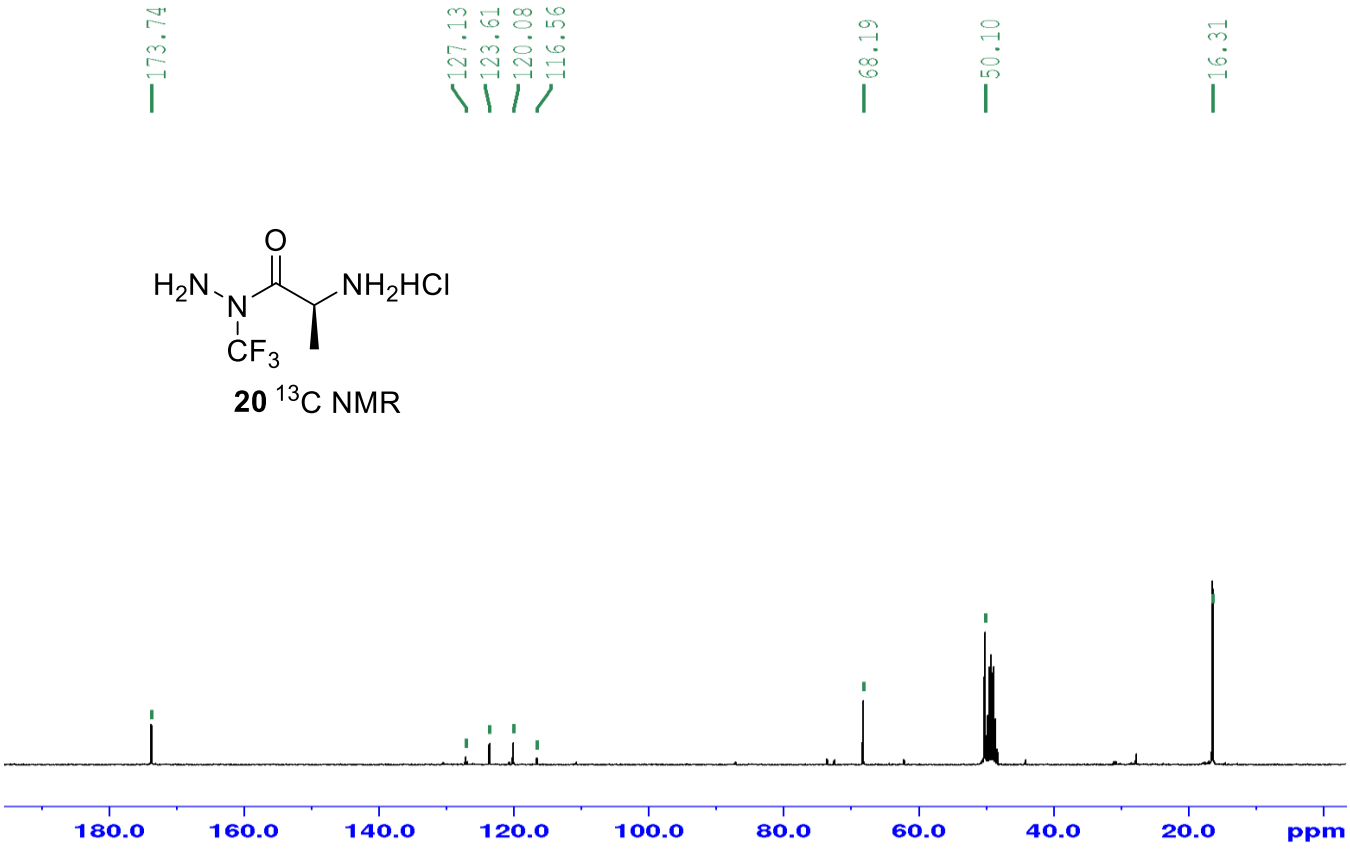


19 ^{19}F NMR

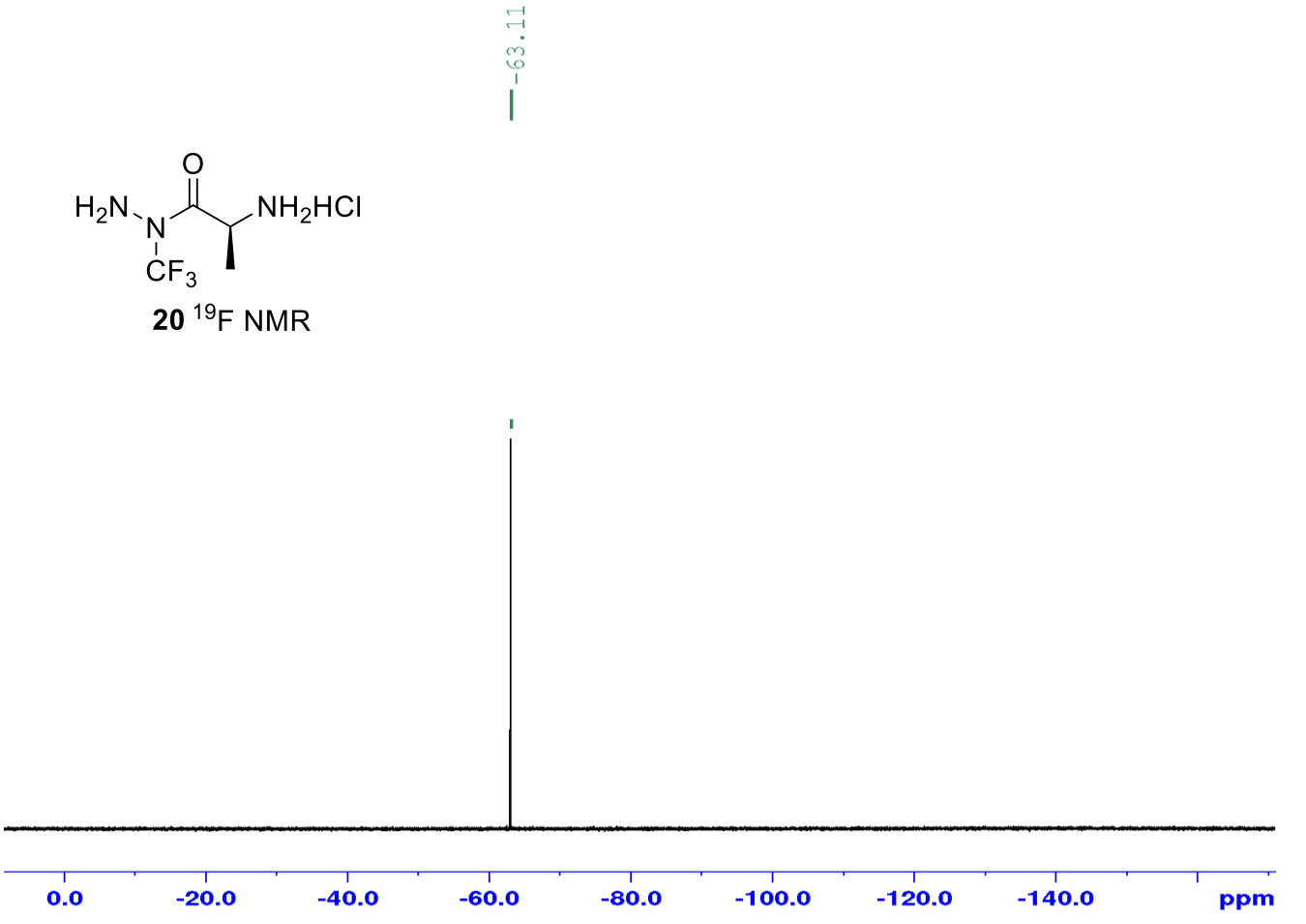
(R)-2-amino-N-(trifluoromethyl)propanehydrazide hydrochloride 20



20 ^{1}H NMR

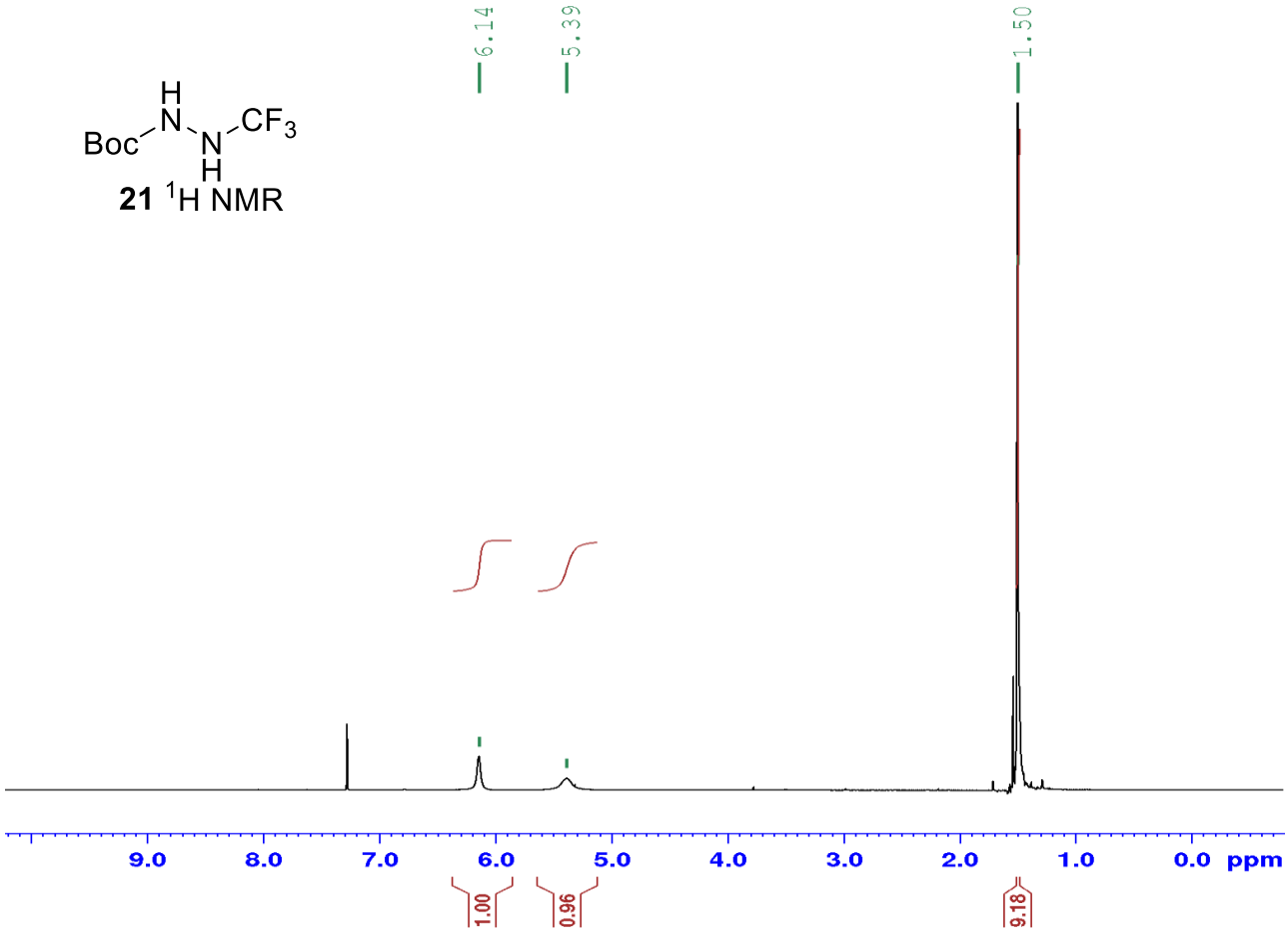


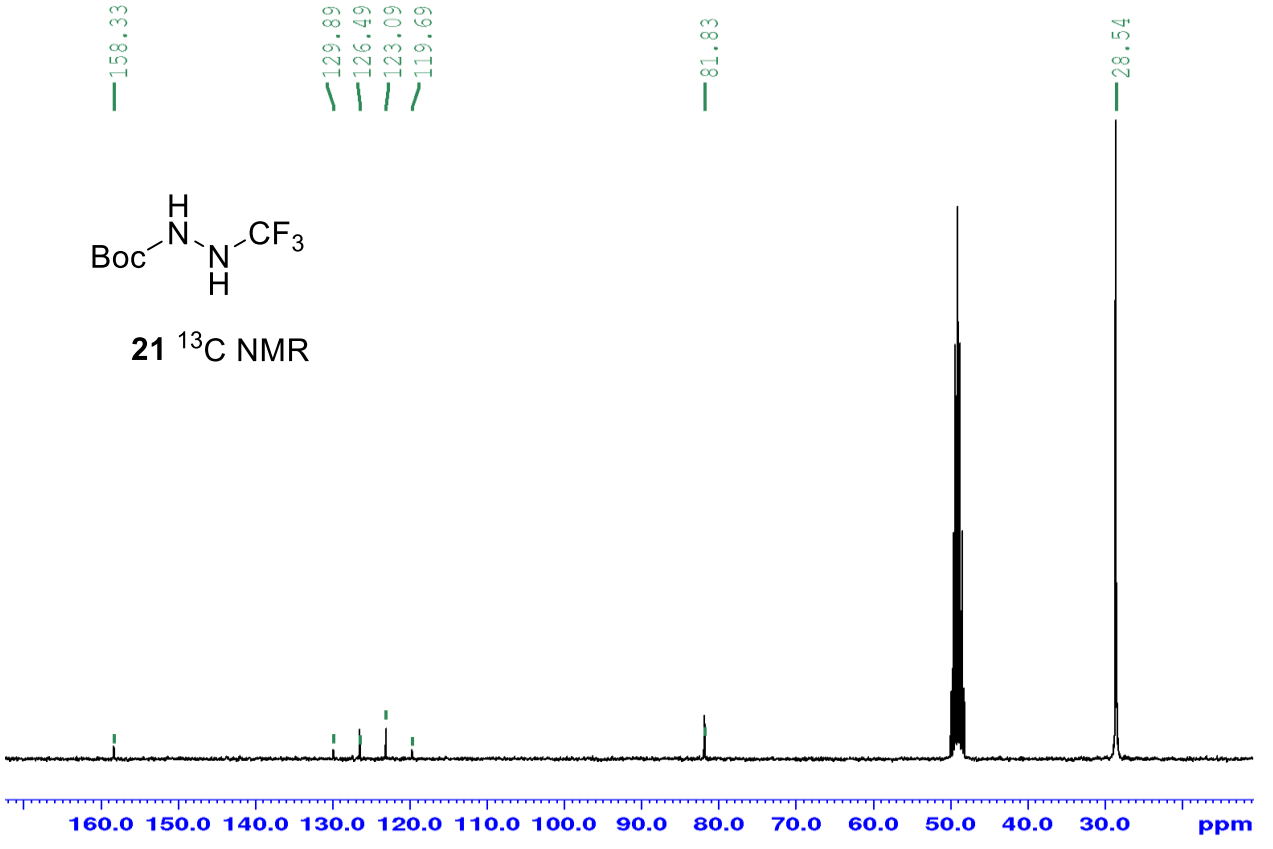
20 ^{13}C NMR

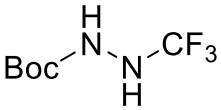


20 ^{19}F NMR

***Tert*-butyl 2-(trifluoromethyl)hydrazine-1-carboxylate 21**



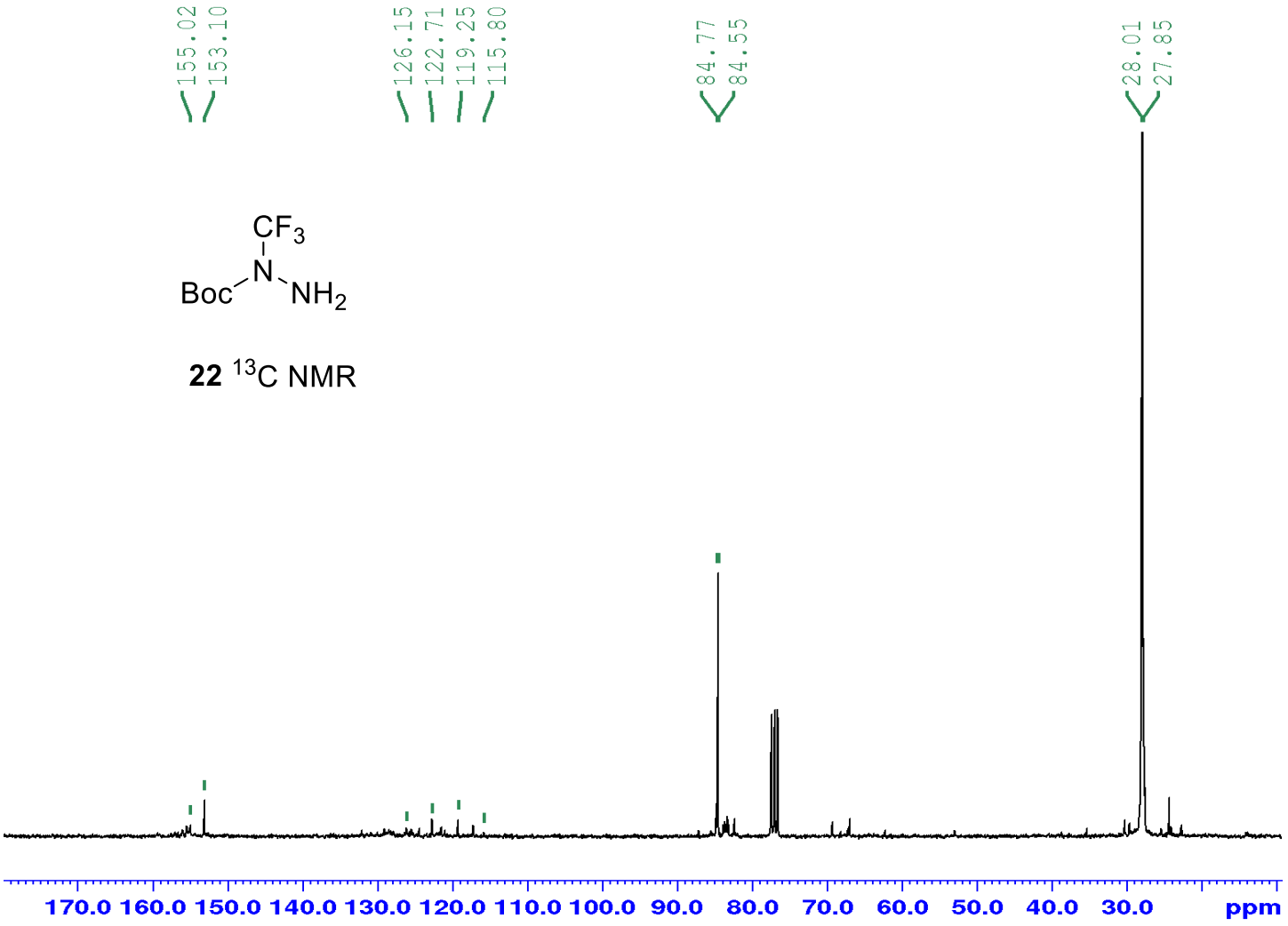




21 ^{19}F NMR

***Tert*-butyl 1-(trifluoromethyl)hydrazine-1-carboxylate 22**

22 ^{1}H NMR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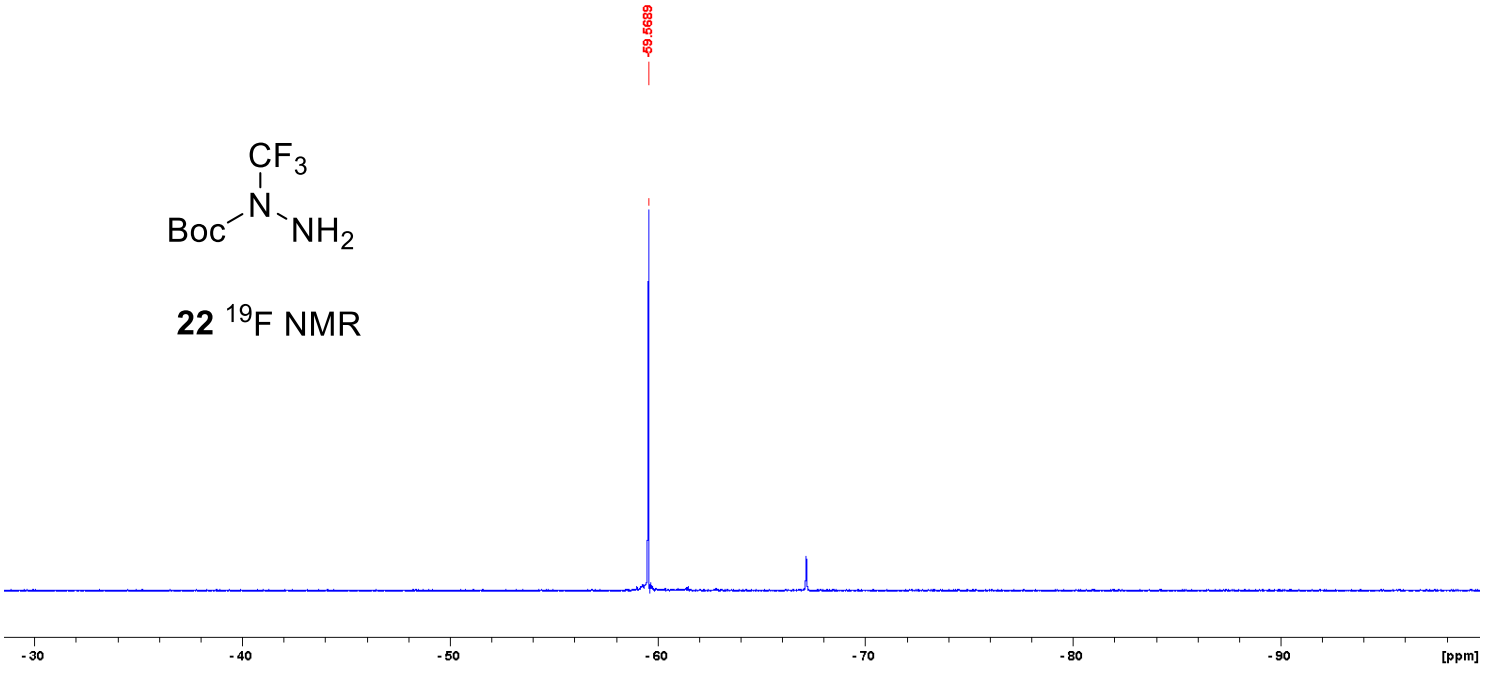
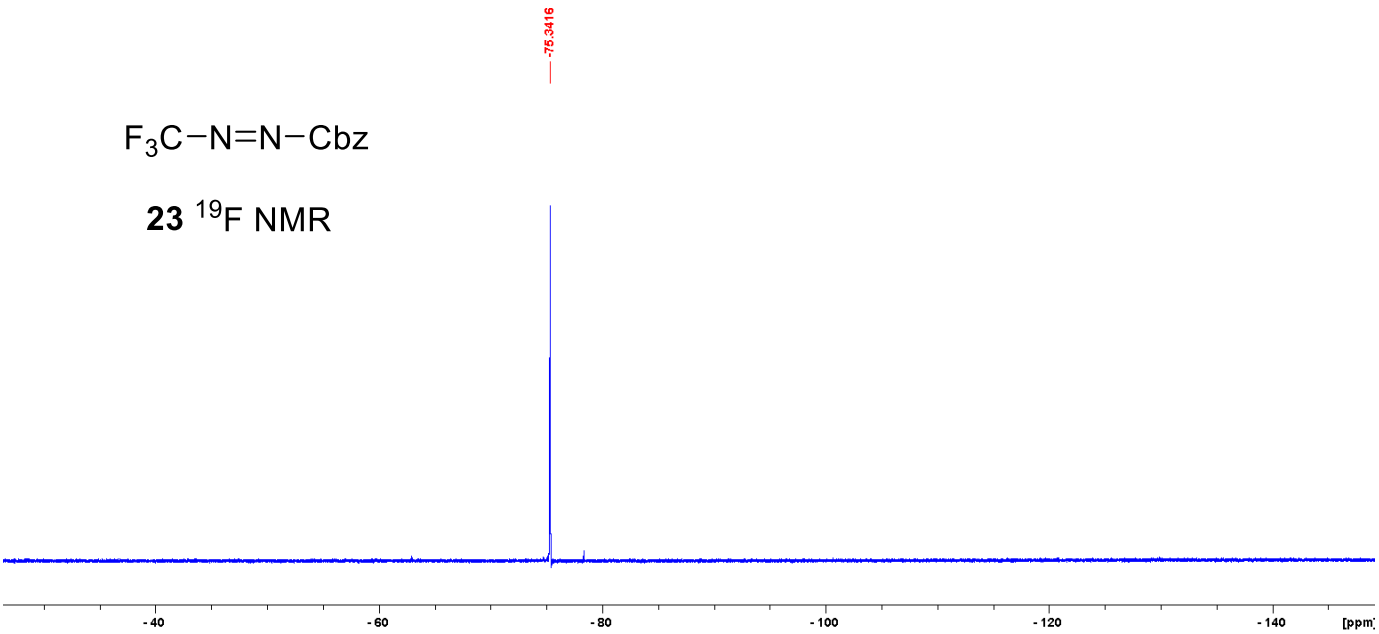
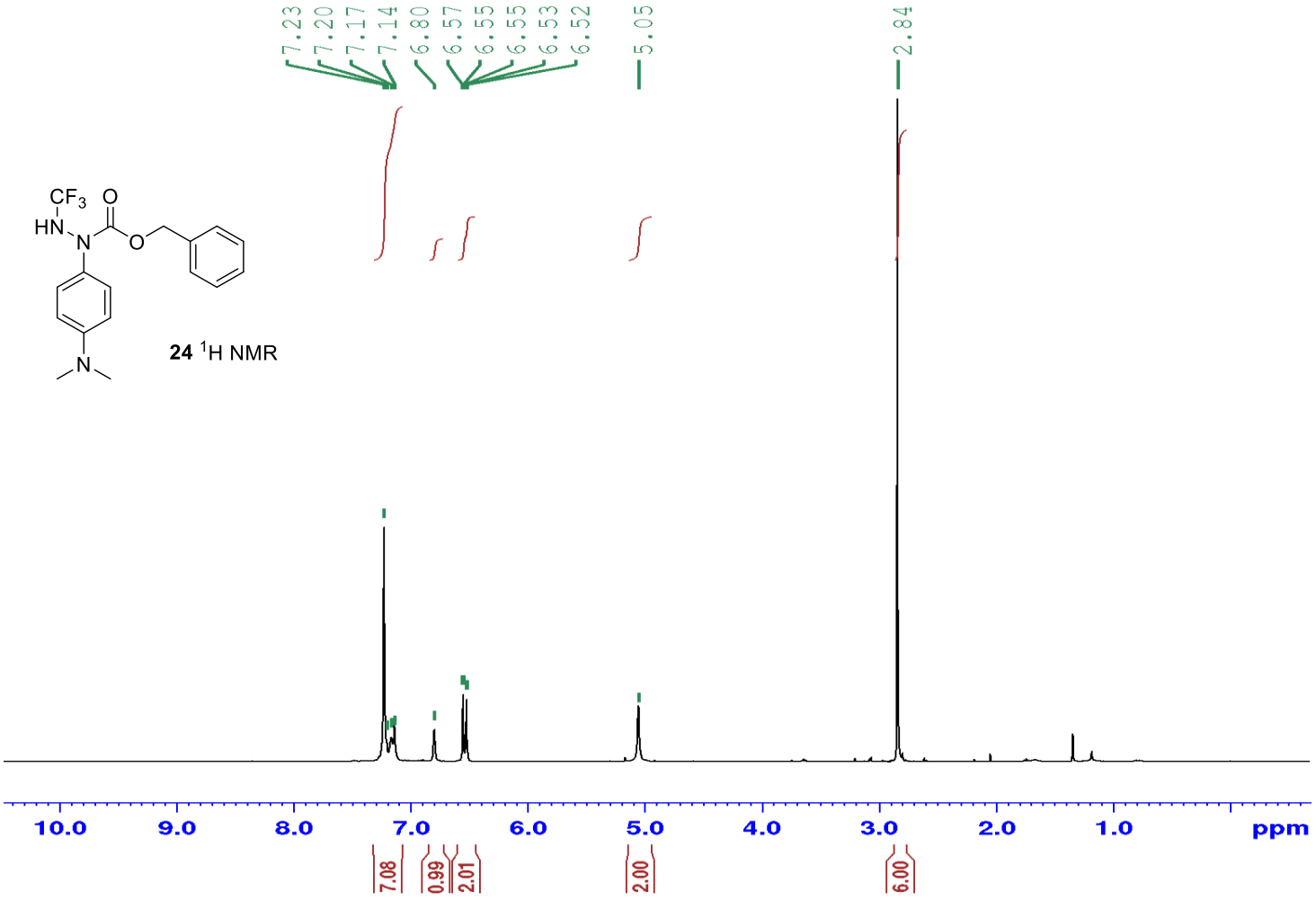
153.10
126.15
122.71
119.25
115.80
84.77
84.55
28.01
27.85
CF3
N
Boc
NH2
22 13C NMR
170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0
ppm

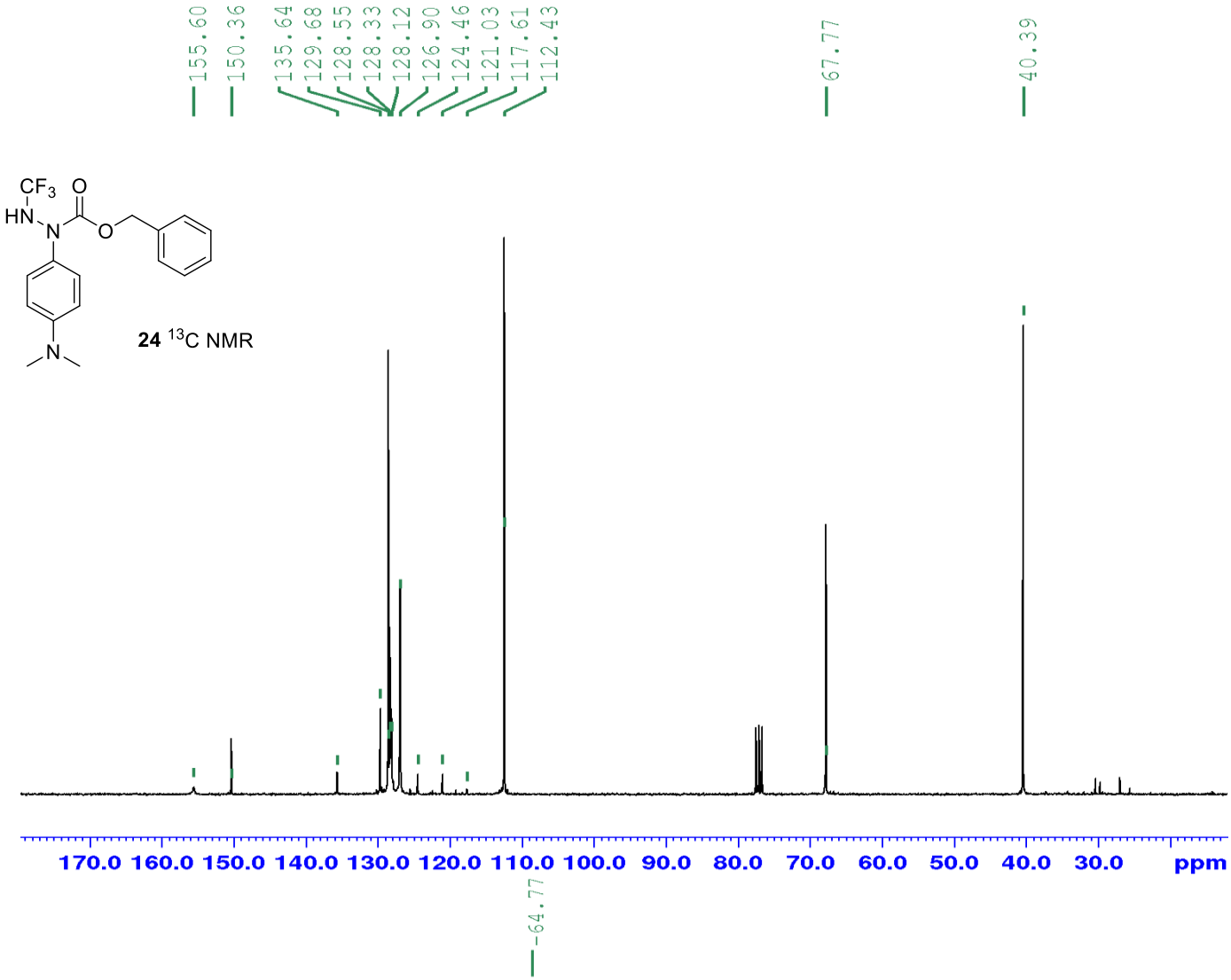

-59.5689
CF3
N
Boc
NH2
22 19F NMR
-30
-40
-50
-60
-70
-80
-90
[ppm]

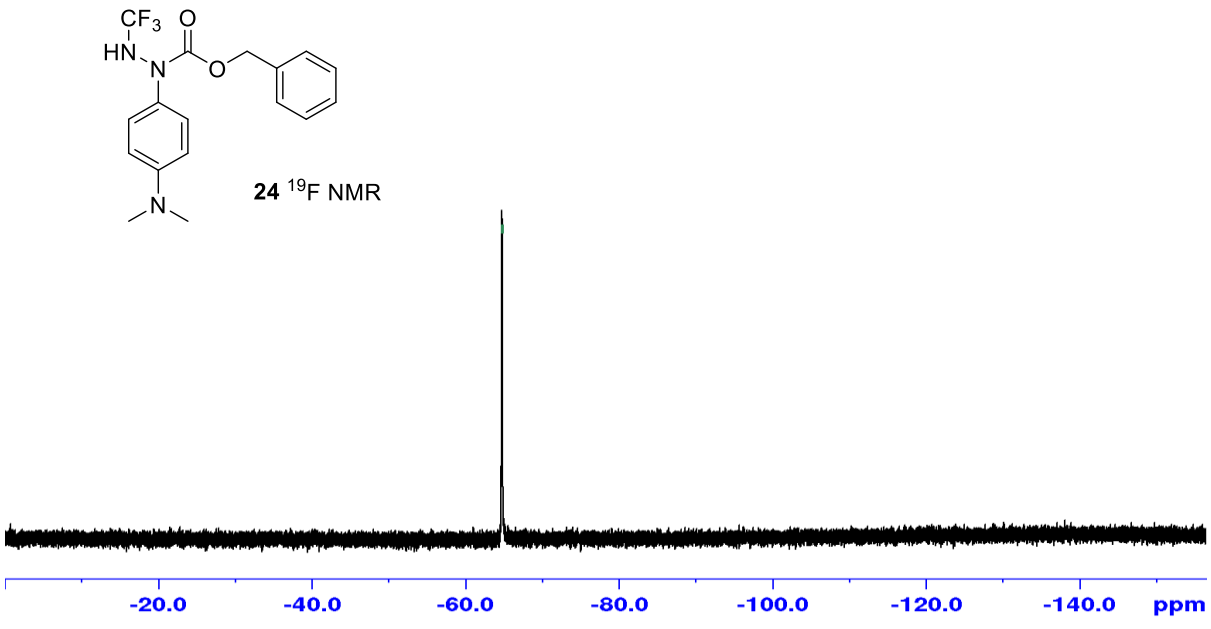
Benzyl 2-(trifluoromethyl)diazene-1-carboxylate 23

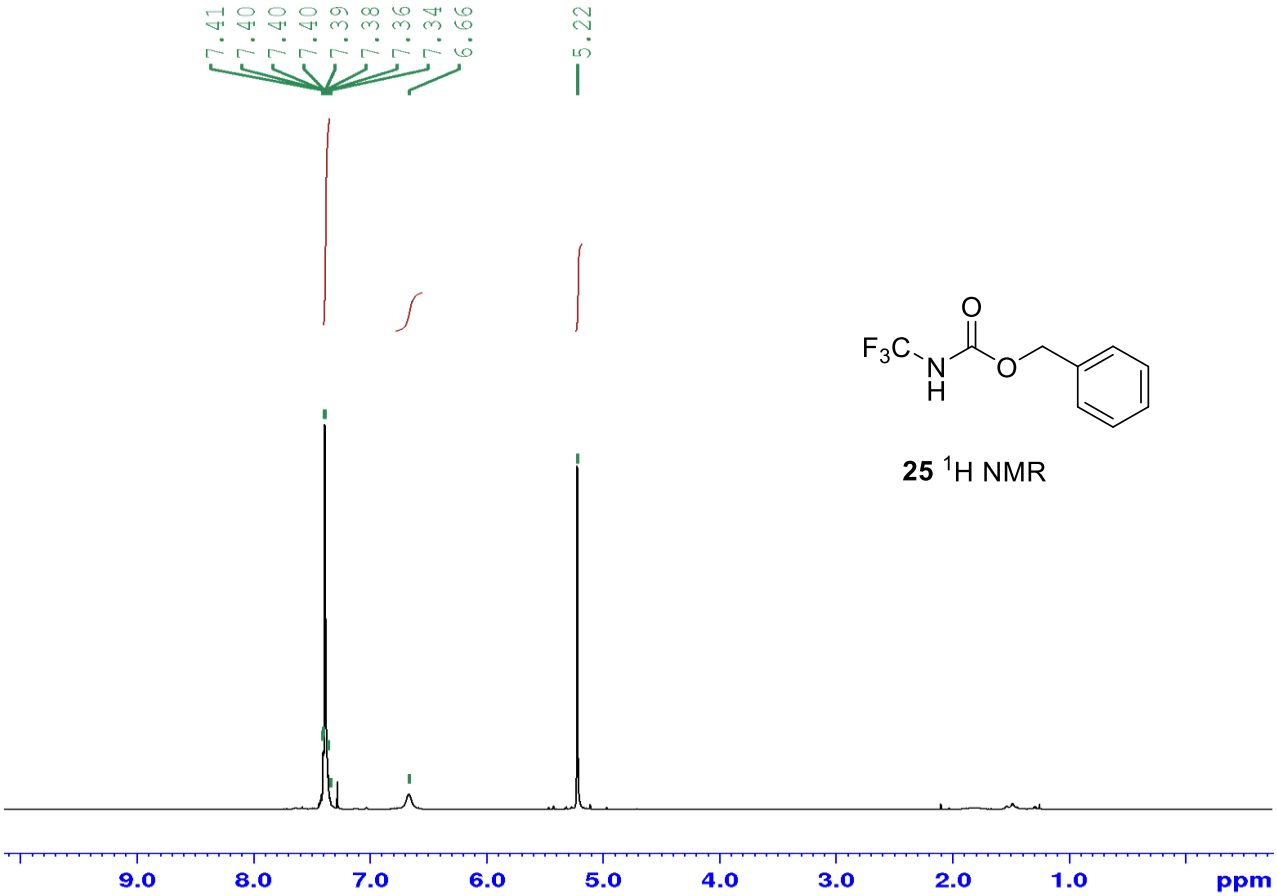


Benzyl 2-(4-(dimethylamino)phenyl)-2-(trifluoromethyl)hydrazine-1-carboxylate 24

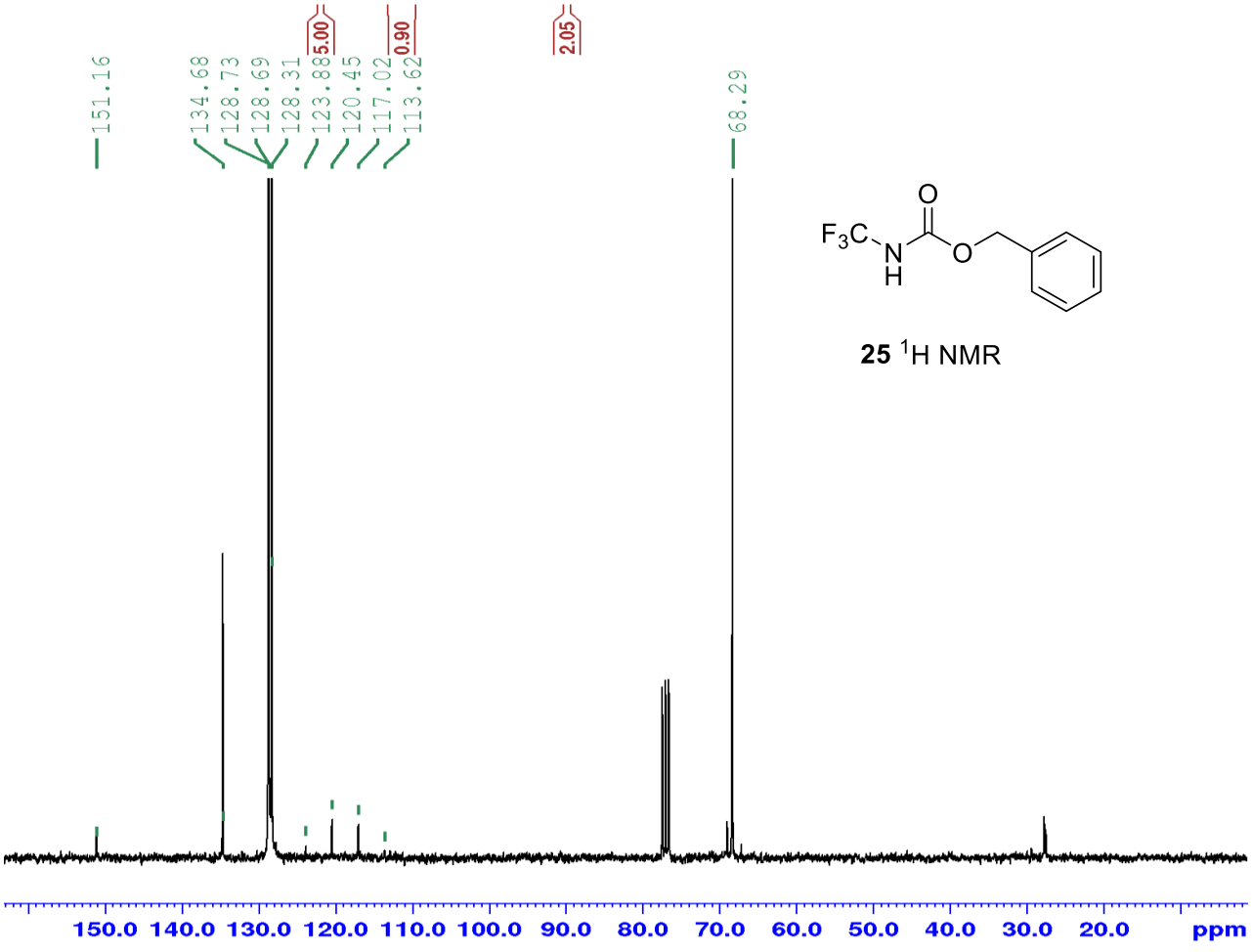



155.60
150.36
135.64
129.68
128.55
128.33
128.12
126.90
124.46
121.03
117.61
112.43
67.77
40.39
CF3
O
HN
N
O
N
24 13C NMR
170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 ppm


-64.77
CF3
O
HN
N
O
N
24 19F NMR
-20.0 -40.0 -60.0 -80.0 -100.0 -120.0 -140.0 ppm

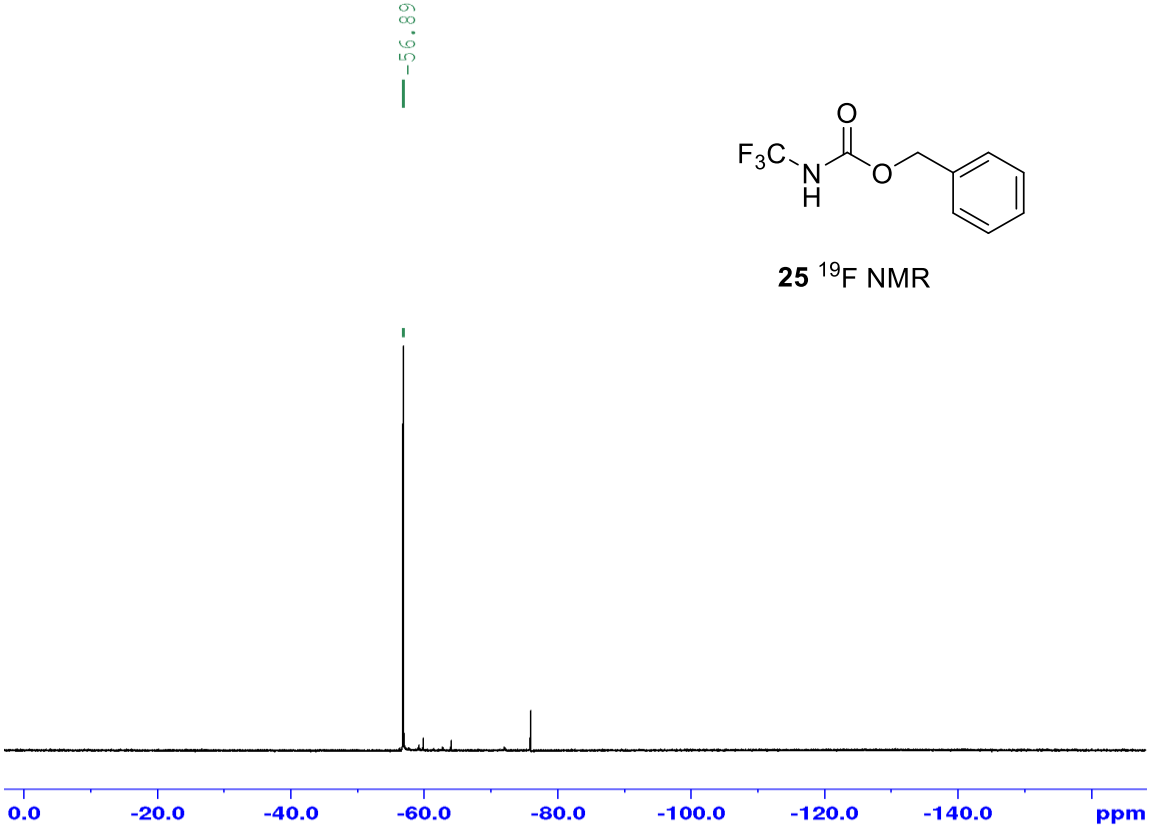


25 ^{1}H NMR

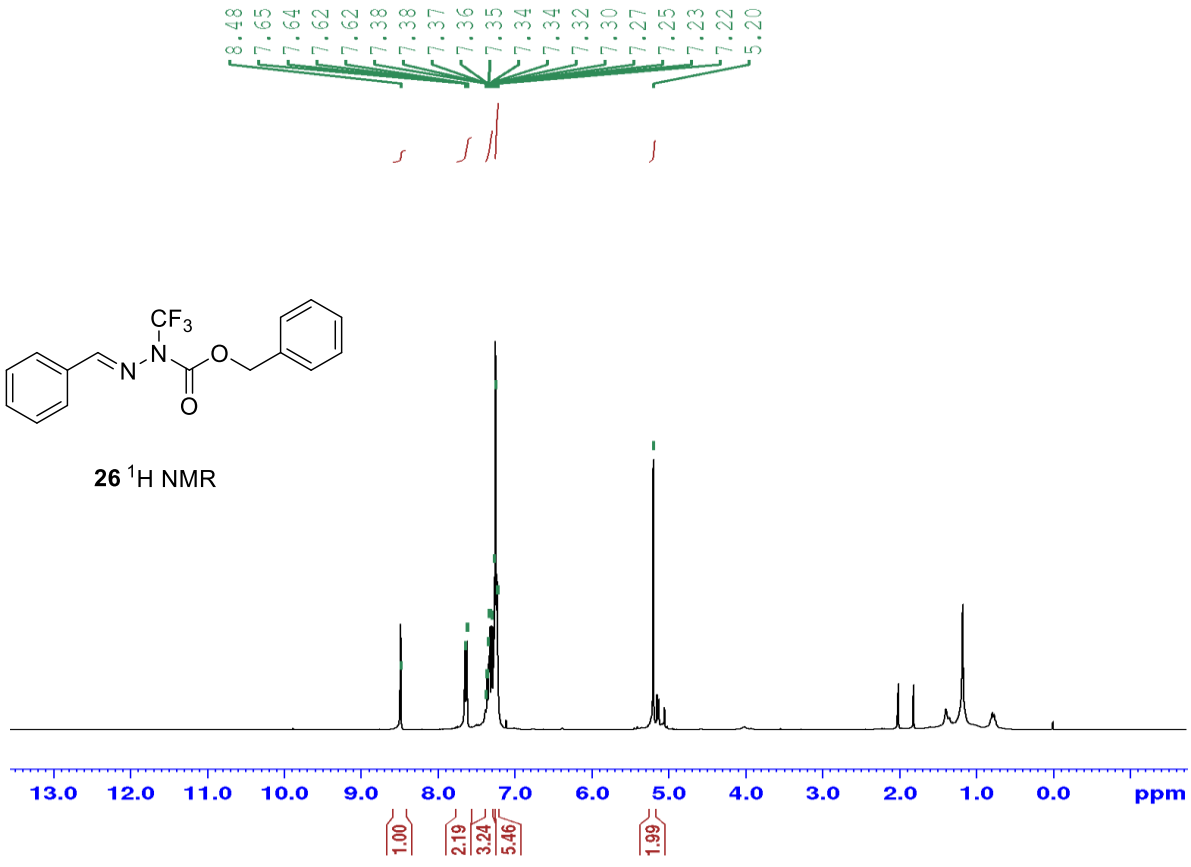


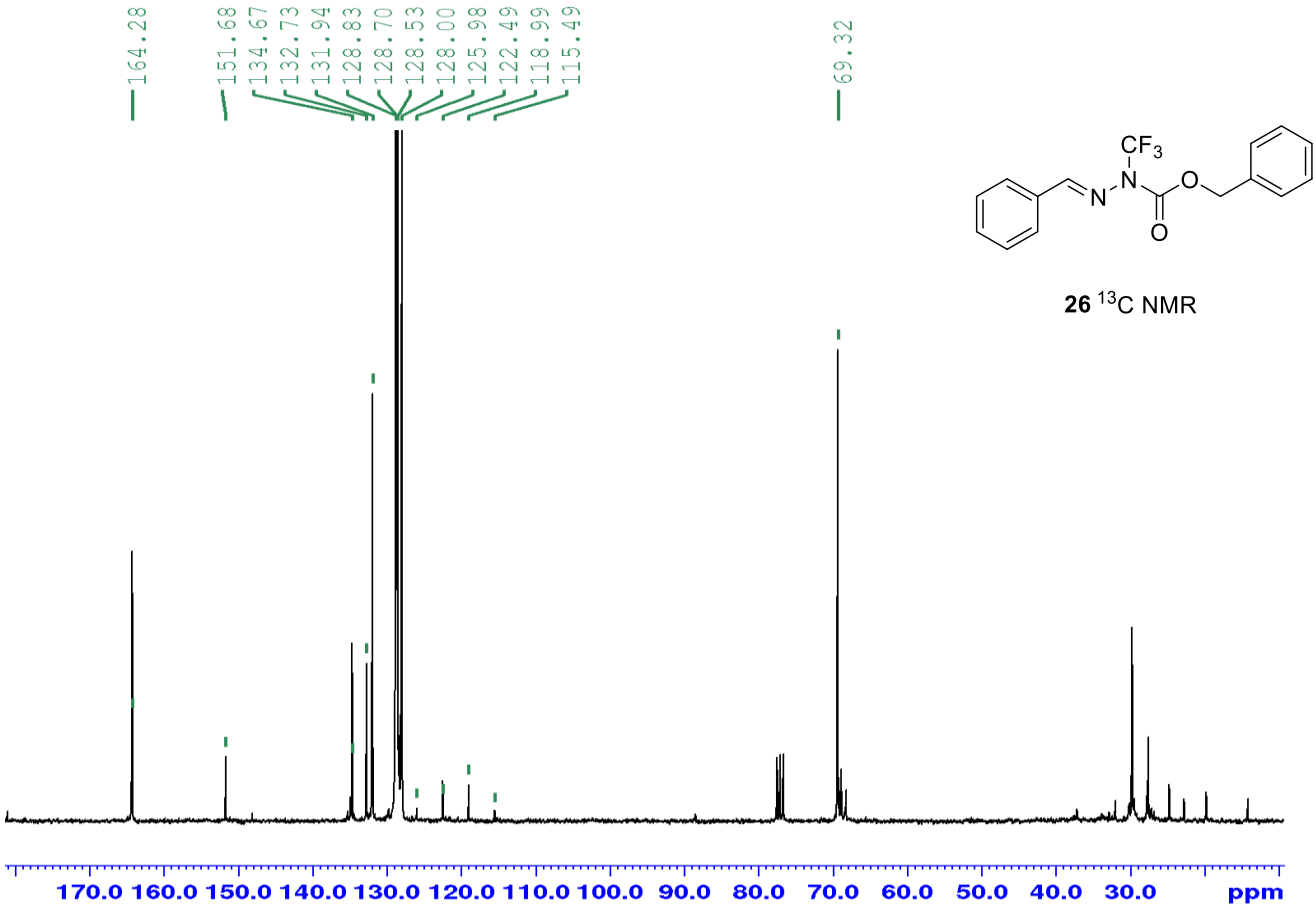
25 ^{1}H NMR

Benzyl (trifluoromethyl)carbamate 25

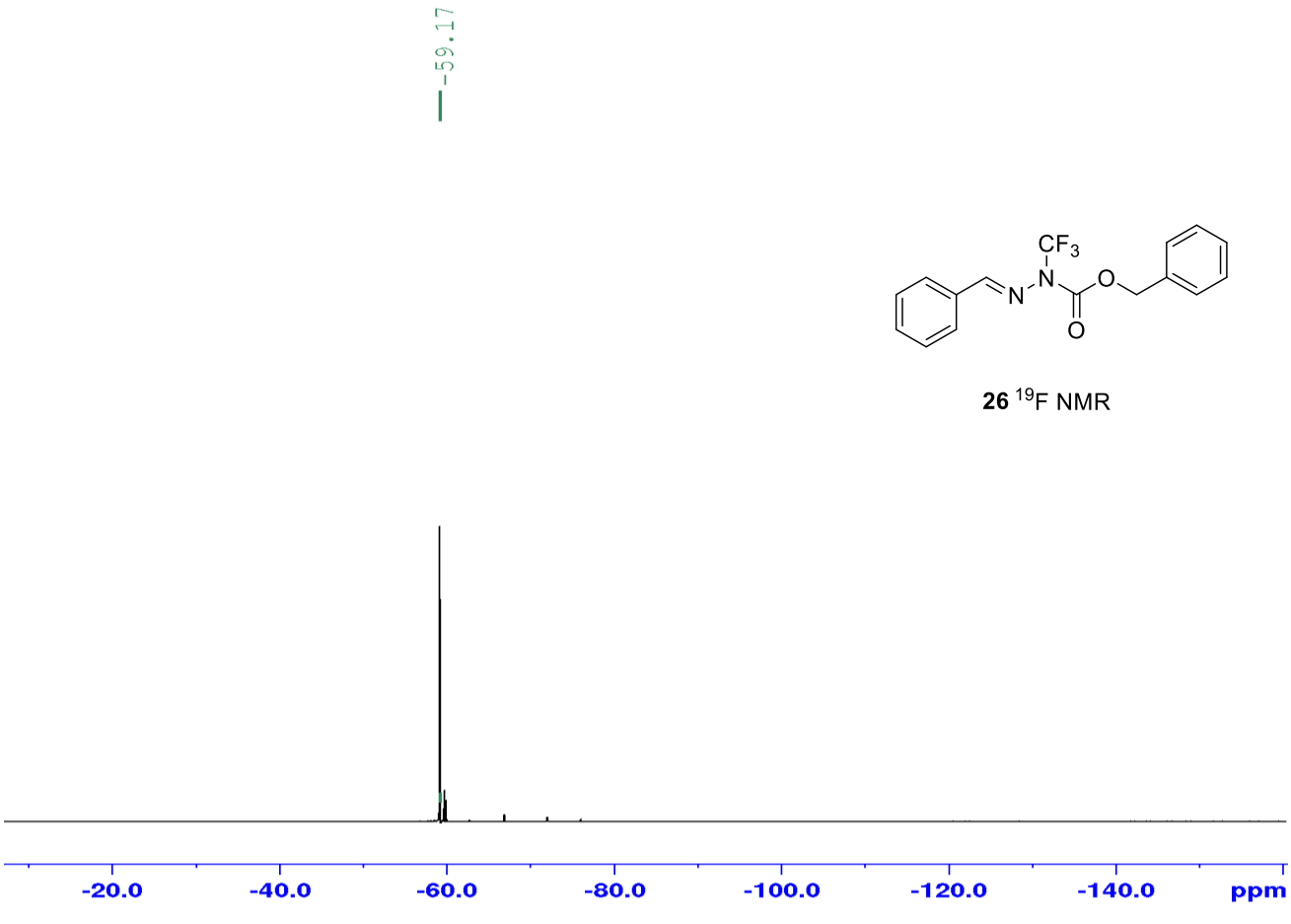


Benzyl (E)-2-benzylidene-1-(trifluoromethyl)hydrazine-1-carboxylate 26



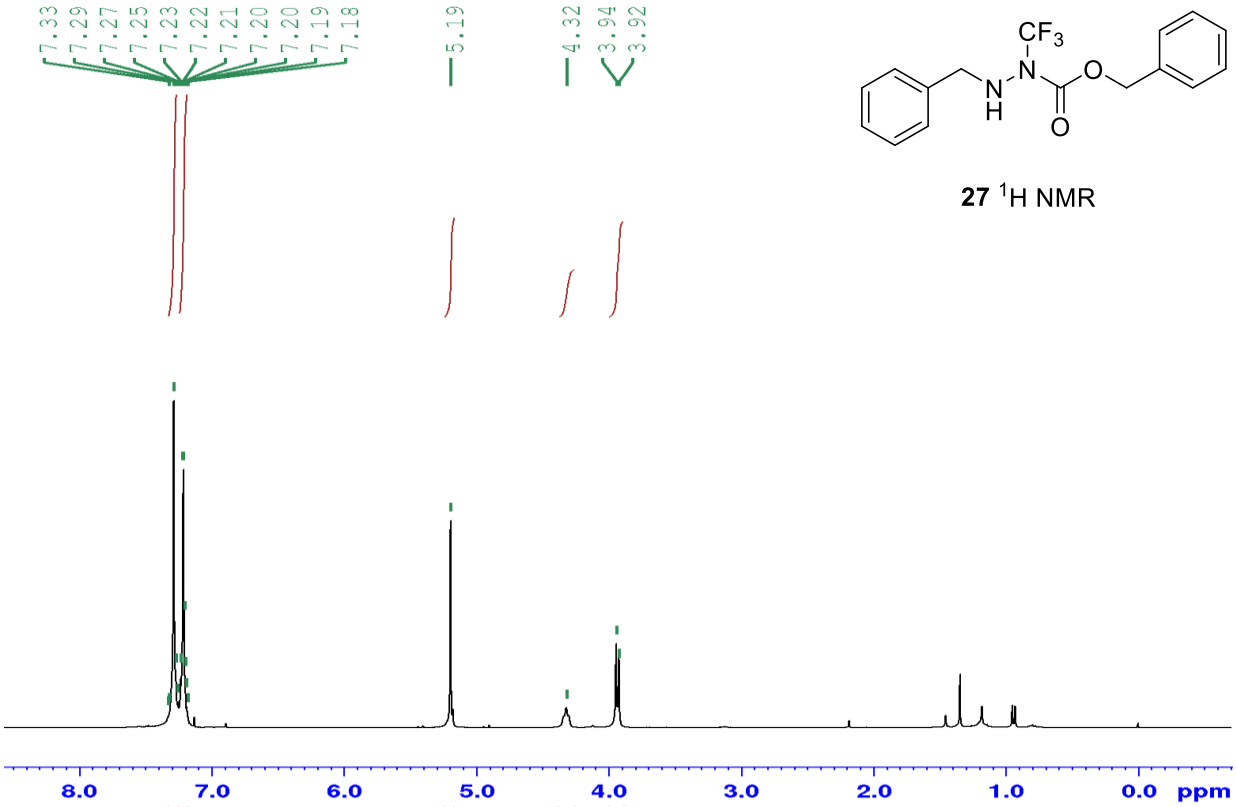


26 ^{13}C NMR

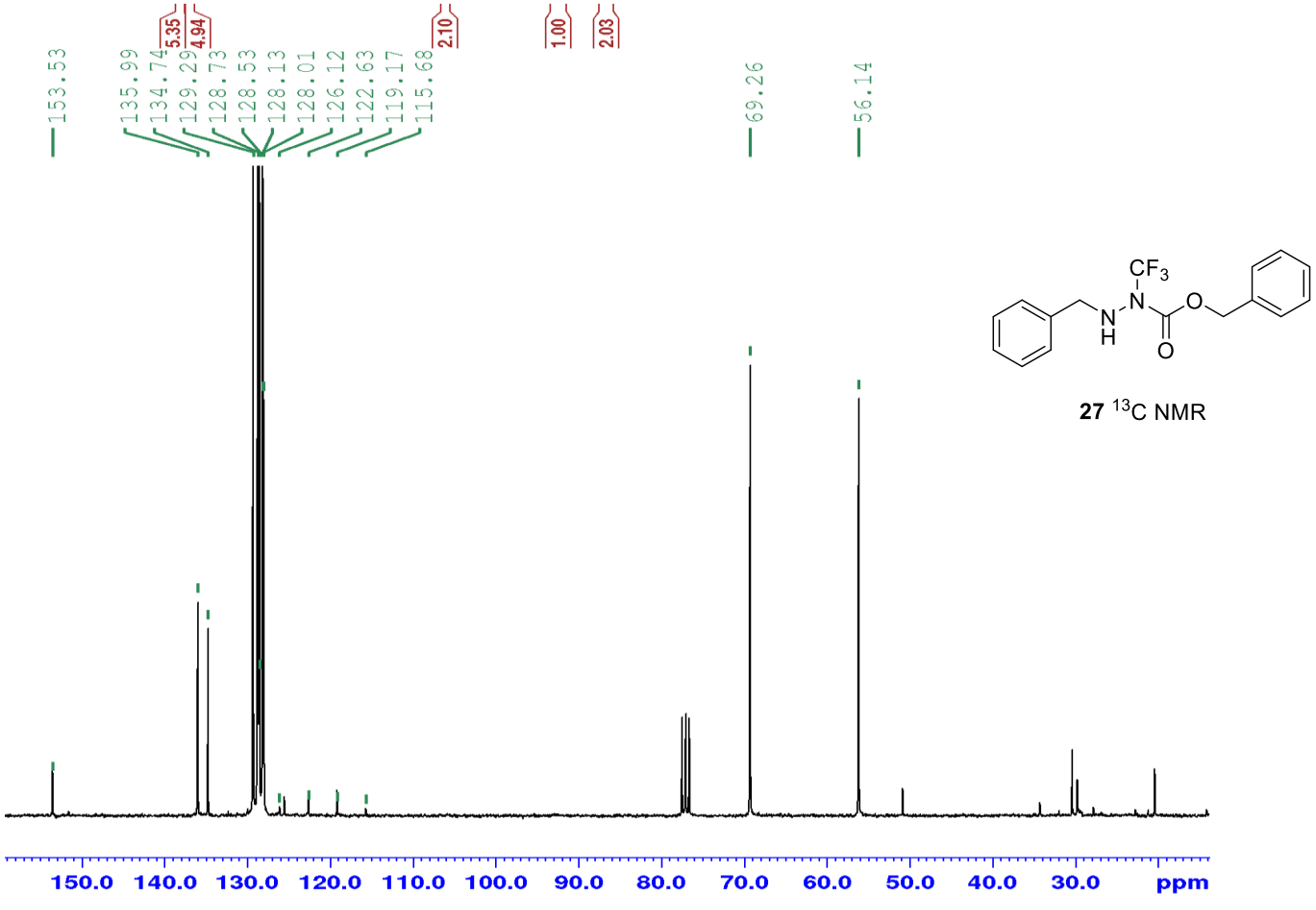


26 ^{19}F NMR

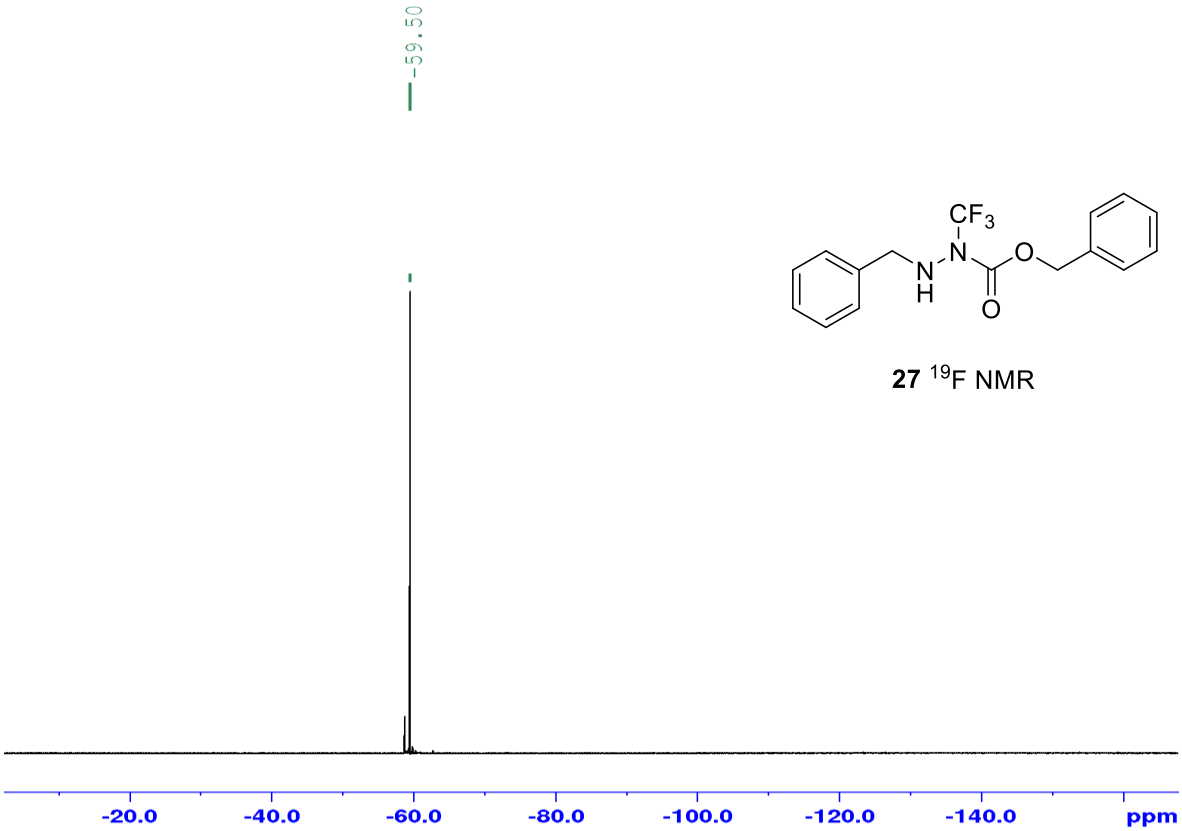
Benzyl 2-benzyl-1-(trifluoromethyl)hydrazine-1-carboxylate 27



27 ^{1}H NMR

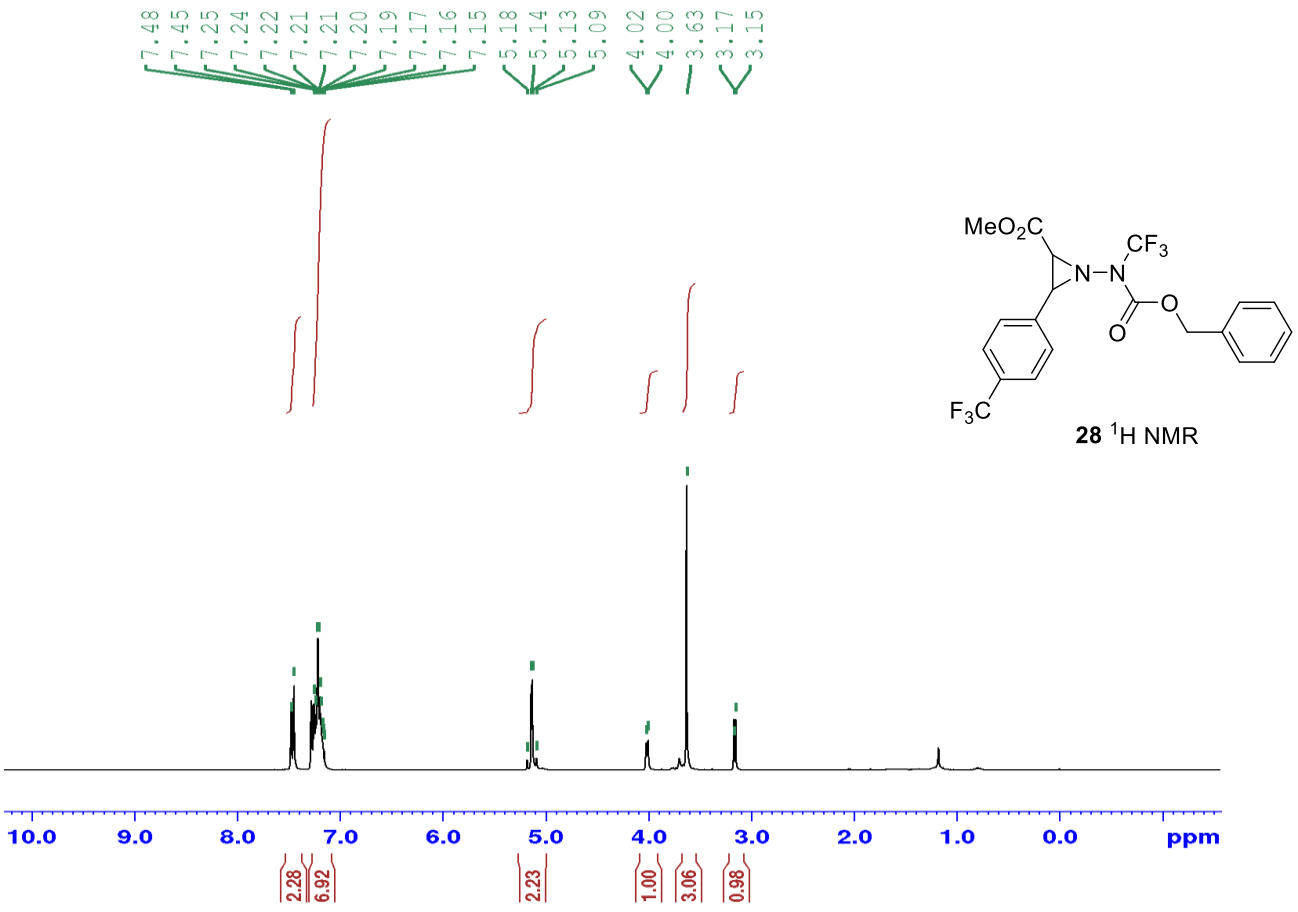


27 ^{13}C NMR

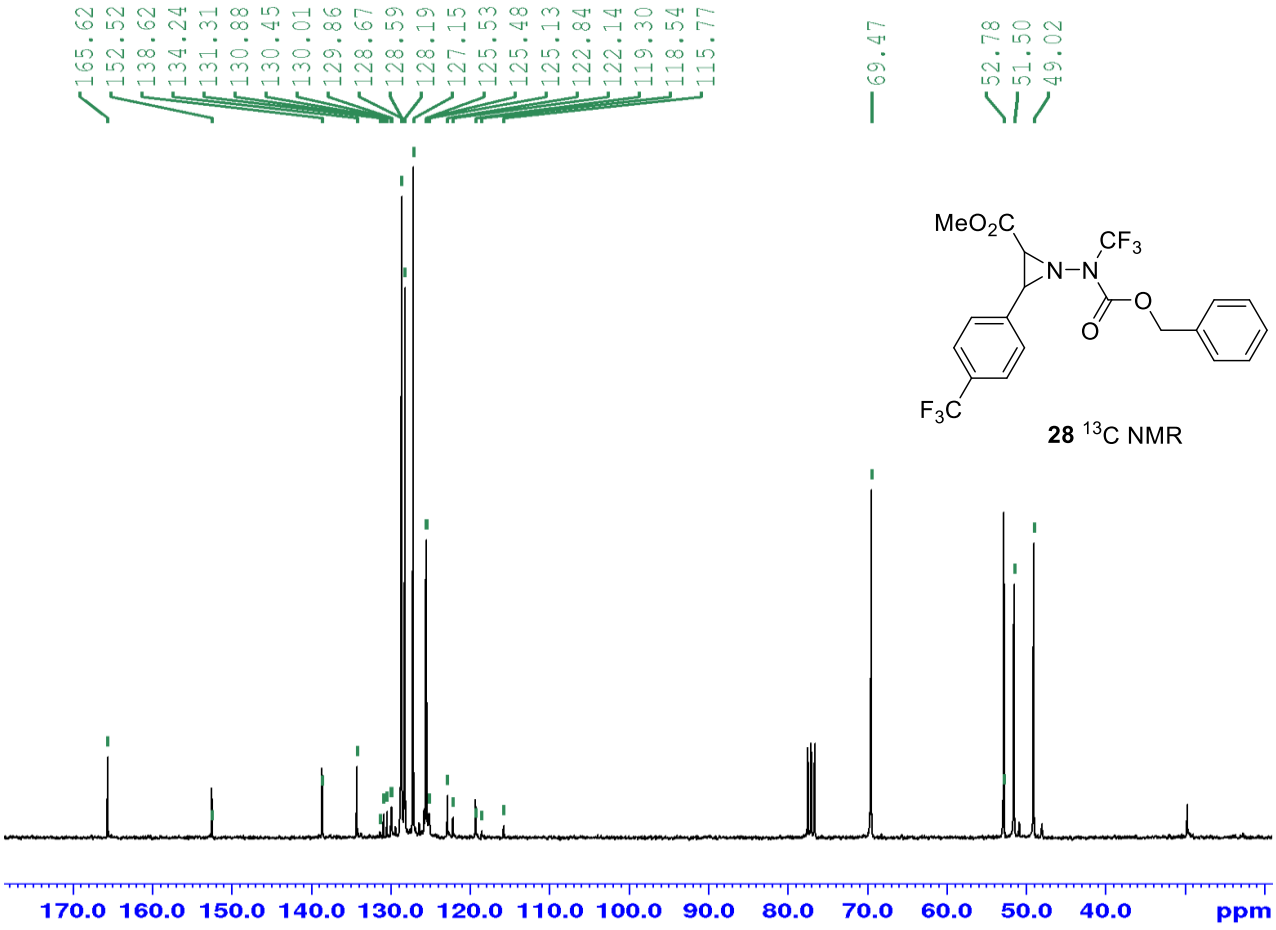


27 ^{19}F NMR

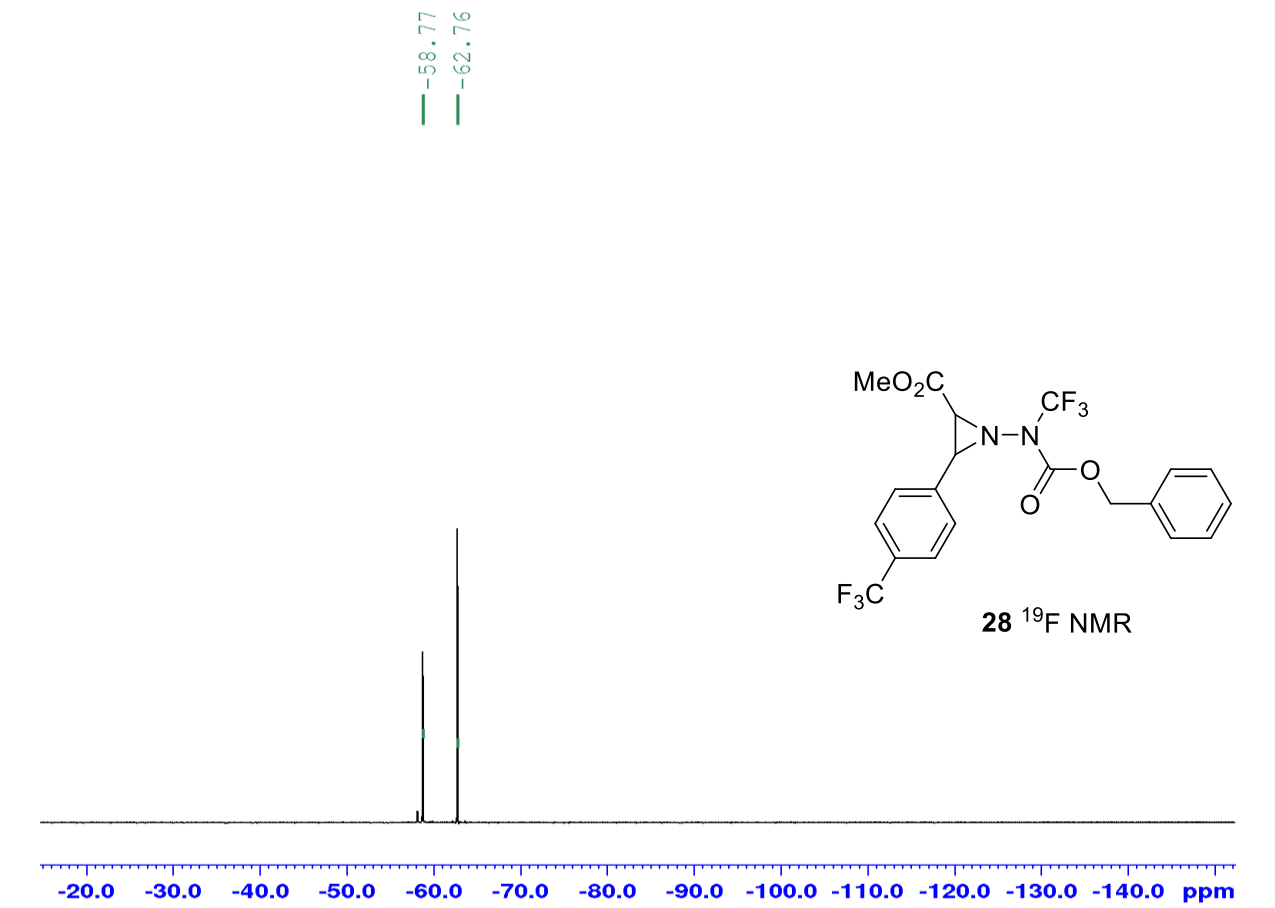
Methyl *trans*-1-(((benzyloxy) carbonyl) (trifluoromethyl)amino)-3-(4-(trifluoromethyl) phenyl) aziridine-2-carboxylate 28



28 ^{1}H NMR



28 ^{13}C NMR

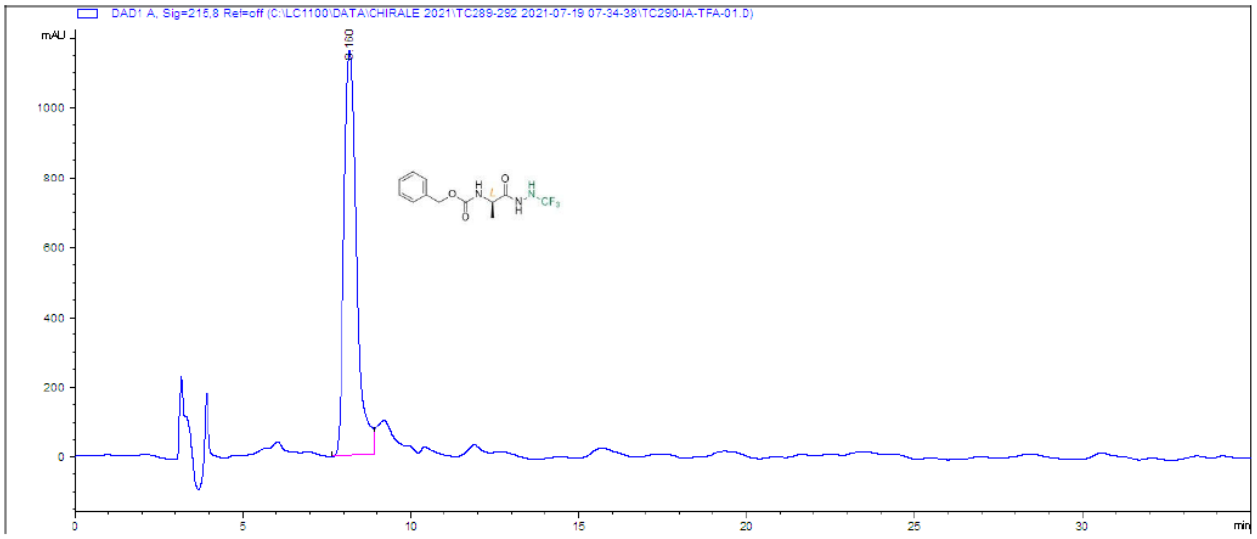


28 ^{19}F NMR

V. Chiral HPLC of compounds 17 and 18

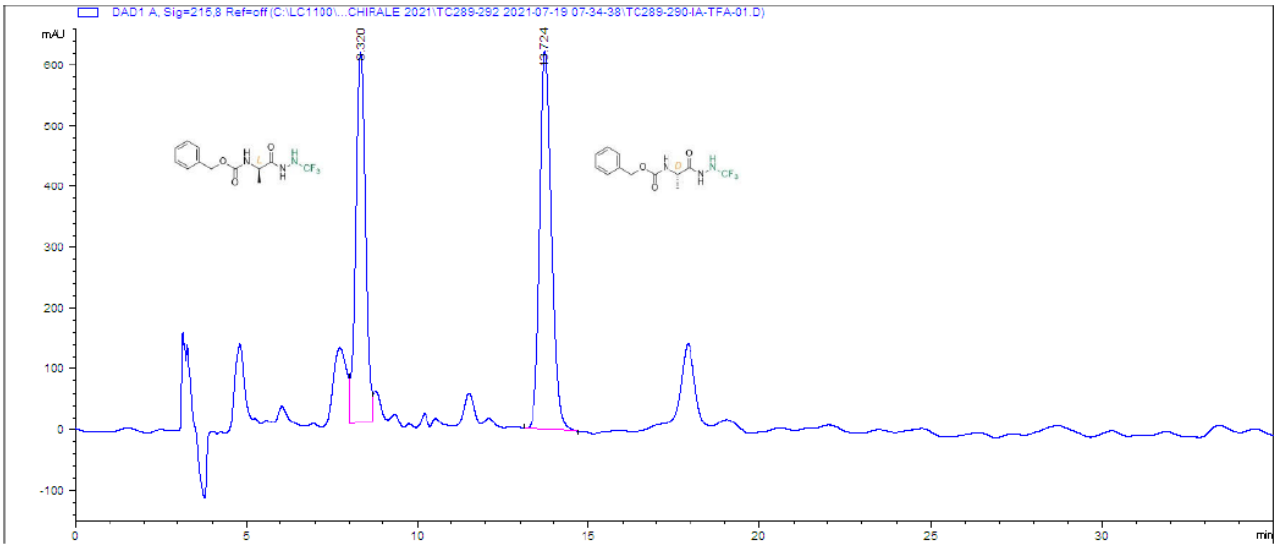
Chiral HPLC of compounds **17** compared with the (*D*)-valine amino acid (Colonne CHIRALCEL IA (Hexane/isopropanol (90:10))

Compound **17**



#	Time	Area	Height	Width	Area%	Symmetry
1	8.16	29955.6	1159	0.3135	100.000	0.78

Compound **17** *N*-CF_3 (*L*)-Val and Compound *N*-CF_3 (*D*)-Val

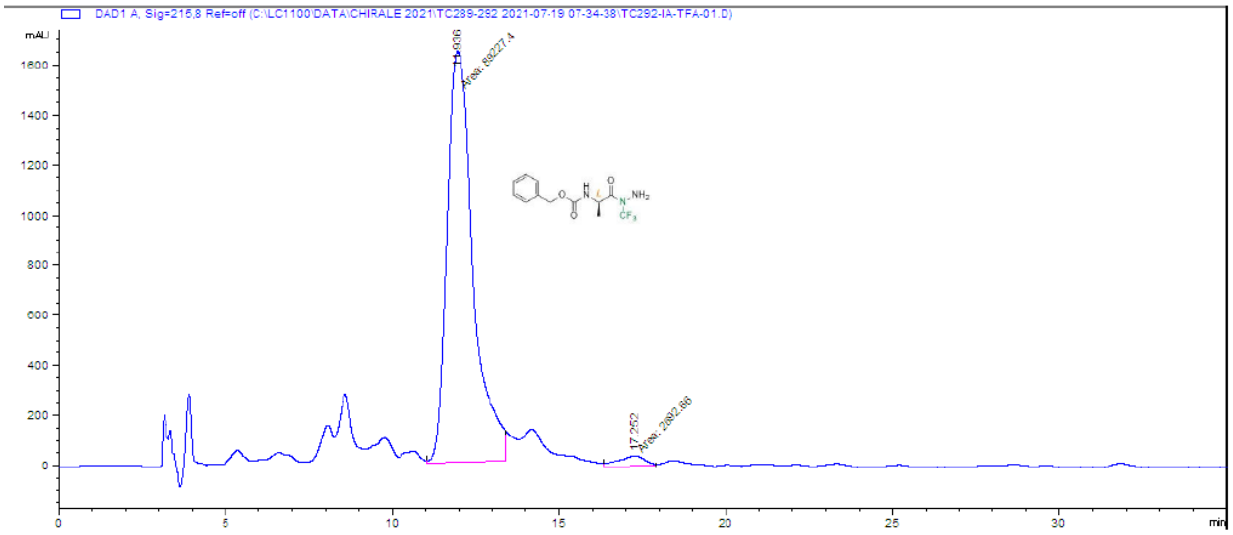


#	Time	Area	Height	Width	Area%	Symmetry
1	8.32	11853.3	610	0.3037	44.381	0.955
2	13.724	14854.7	624.9	0.3543	55.619	0.758

TC 290
215 nm

Chiral HPLC of compounds **18** compared with the *(D)*-valine amino acid (Colonne CHIRALCEL IA (Hexane/isopropanol (90:10))

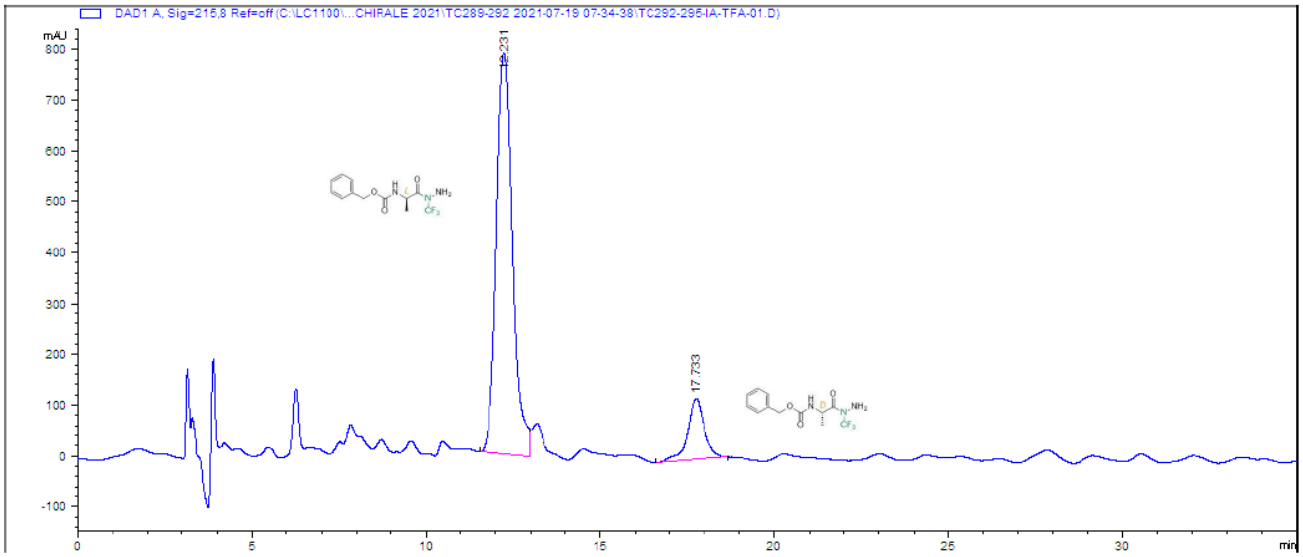
Compounds **18**



#	Time	Area	Height	Width	Area%	Symmetry
1	11.936	89227.4	1646.8	0.903	97.071	0.626
2	17.252	2692.7	45.3	0.9917	2.929	1.568

Compound **18** *N*-CF_3 (*L*)-Val and Compound *N*-CF_3 (*D*)-Val

TC 292-295
215 nm



#	Time	Area	Height	Width	Area%	Symmetry
1	12.231	25385.1	790.9	0.3844	86.187	0.884
2	17.733	4068.5	120.4	0.4303	13.813	0.983

VI. References

1. Compound **2e** and **2h** are prepared according to the conditions reported in Hideyuki Konishi, Tin Yiu Lam, Jeremiah P. Malerich, Viresh H. Rawal, *Org. Lett*. **2010**, *12*, *9*, 2028-2031

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