Electronic Supplementary Material (ESI) for Chemical Communications.

Combined Experimental and Theoretical Study of Long-Range H-F Interactions in α-Fluoro Amides

Elena Cosimi, Nils Trapp, Marc-Olivier Ebert,* and Helma Wennemers*

Laboratory of Organic Chemistry, D-CHAB, ETH Zurich
Vladimir-Prelog-Weg 3
CH-8093 Zurich, Switzerland.

Helma.Wennemers@org.chem.ethz.ch
Marc-Olivier.Ebert@org.chem.ethz.ch

Table of Contents

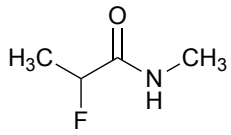
1 General aspects and materials

Reactions requiring anhydrous conditions were performed under dry nitrogen or argon atmospheres in glassware that was dried using either a combination of vacuum and heat-gun or oven. Reaction mixtures were stirred magnetically. Air- and moisture-sensitive liquids and solutions were transferred *via* syringe or cannula into the reaction vessels through rubber septa. All reagents and solvents were purchased at the highest commercial quality available and used as received. Anhydrous solvents were obtained from a purification column composed of activated alumina (A-2). Yields refer to spectroscopically pure compounds unless otherwise stated. Flash chromatography was performed on silica gel (Merck Kieselgel 60 F_{254} 230–400 mesh). Reactions were monitored by thin layer chromatography (TLC) using aluminium-backed silica plates (0.2 mm, 60 F_{254}) from Merck. Visualization was achieved using UV fluorescence (254 and 366 nm), ninhydrine / Δ, phosphomolybdic acid / Δ, potassium permanganate / Δ. **^{1}H-NMR**: chemical shifts (δ_H) are reported in parts per million (ppm) and referenced to the appropriate NMR solvent peak(s). **^{13}C-NMR**: chemical shifts (δ_c) are reported in ppm, referenced to the appropriate solvent peak(s) and are assigned as C, CH, CH_2, CH_3, Ar, ArH. **^{19}F-NMR**: chemical shifts (δ_F) are reported in parts per million (ppm) and are referenced to $CFCl_3$. Appropriate susceptibility corrections were applied if the standard was added using a coaxial insert. In some of the ^{19}F NMR spectra a second set of signals appeared over time. This impurity presumably results from H/D exchange of the NH proton in the presence of residual D_2O.
In ^{1}H, ^{13}C and ^{19}F-NMR spectra, the unsigned coupling constants are reported. For **2** the sign of the $^{4}J_{HF}$ coupling constant was determined to be negative by analysis of a constant-time ^{13}C-HMBC spectrum. We therefore assume that the sign is negative for all $^{4}J_{HF}$ couplings. **HRMS**: high resolution mass spectra were recorded on a Bruker maXis (UHR-TOF) for high-resolution electrospray ionisation (HR-ESI) mass spectrometry, on a Bruker solariX 94 (ESI/MALDI-FT-ICR) and a Bruker Ultra-Flex II (MALDI-TOF) spectrometer for high-resolution MALDI spectra or an EI-Sector-MS. **Elemental analysis**: determination of C, H, and N performed with a LECO TruSpec Micro instrument. Determination of O performed with a LECO 628 O Micro instrument. Determination of halogens in the sample by Schöniger oxidation. Other instruments used: HEKAtechEuroVector. **IR**: recorded on neat compounds using an Agilent Technologies Cary 630 FTIR. Only selected peaks are shown. **NMR** spectra were recorded on a Varian Mercury-VX 300, a Bruker AV III 300 (300 MHz/75 MHz), a Bruker AV III HD 400 (400 MHz/100 MHz), a Bruker AV III 500 (500 MHz/126 MHz) or a Bruker AV III HD 500 (500 MHz/126 MHz). **mp:** measured on a hotstage melting point apparatus (Büchi B-540). **X-Ray:** Full data is listed with the corresponding compounds and as cif files. The F-MTM 2-fluoro-3-((4-methoxyphenyl)thio)-3-oxopropanoate (**8**) was synthesized according to a previously reported procedure.[1] All literature known compounds were characterized by comparison of at least two pieces of spectral data with those reported in the literature.

2 DFT calculations

All DFT calculations were carried out using Gaussian 09 (Rev. C.01 and D.01).[2] Geometry optimizations and frequency calculations were carried out at the B3LYP/AUG-cc-pVTZ level of theory[3, 4] *in vacuo* or in a solvent reaction field using the polarizable continuum model (IEFPCM).[5, 6] Constrained optimization of **1** was carried out *in vacuo* using the "modredundant" option. $^4J_{NHF}$ spin-spin coupling constants were calculated using a two-step procedure: Paramagnetic spin-orbit (PSO), diamagnetic spin-orbit (DSO) and spin-dipole (SD) contributions to the $^4J_{NHF}$ coupling constant were calculated at the B3LYP/AUG-cc-pVTZ level of theory. The Fermi contact term was calculated using the uTZ-w basis set obtained by uncontracting pVTZ and adding tight s-functions.[7] NBO analyses were carried out using NBO 5.9[8] and are based on single-point energy calculations at the B3LYP/AUG-cc-pVTZ level of theory of conformers previously optimized *in vacuo* at the same level of theory.

2.1 2-Fluoro-N-methylpropanamide (1)



1

A series of constrained optimizations was carried out by fixing the F-C-C=O dihedral angle (Θ) in **1. Table 1** and **Figure 1** show the resulting Θ dependence of the relative energy (E) of **1**.

Table 1. B3LYP/AUG-cc-pVTZ energy (E) as a function of the dihedral angle Θ relative to the lowest energy conformation.

Dihedral angle Θ (°)	Rel. E (kcal/mol)
0	6.7
15	7.0
30	7.1
45	7.0
60	6.9
75	6.5
90	6.0
105	5.2
120	4.0
135	2.5
150	1.1
165	0.2
180	0
195	0.5
210	1.5
225	2.6
240	3.6
255	4.2
270	4.6
285	4.8
300	5.0
315	5.3
330	5.7
345	6.2
360	6.7

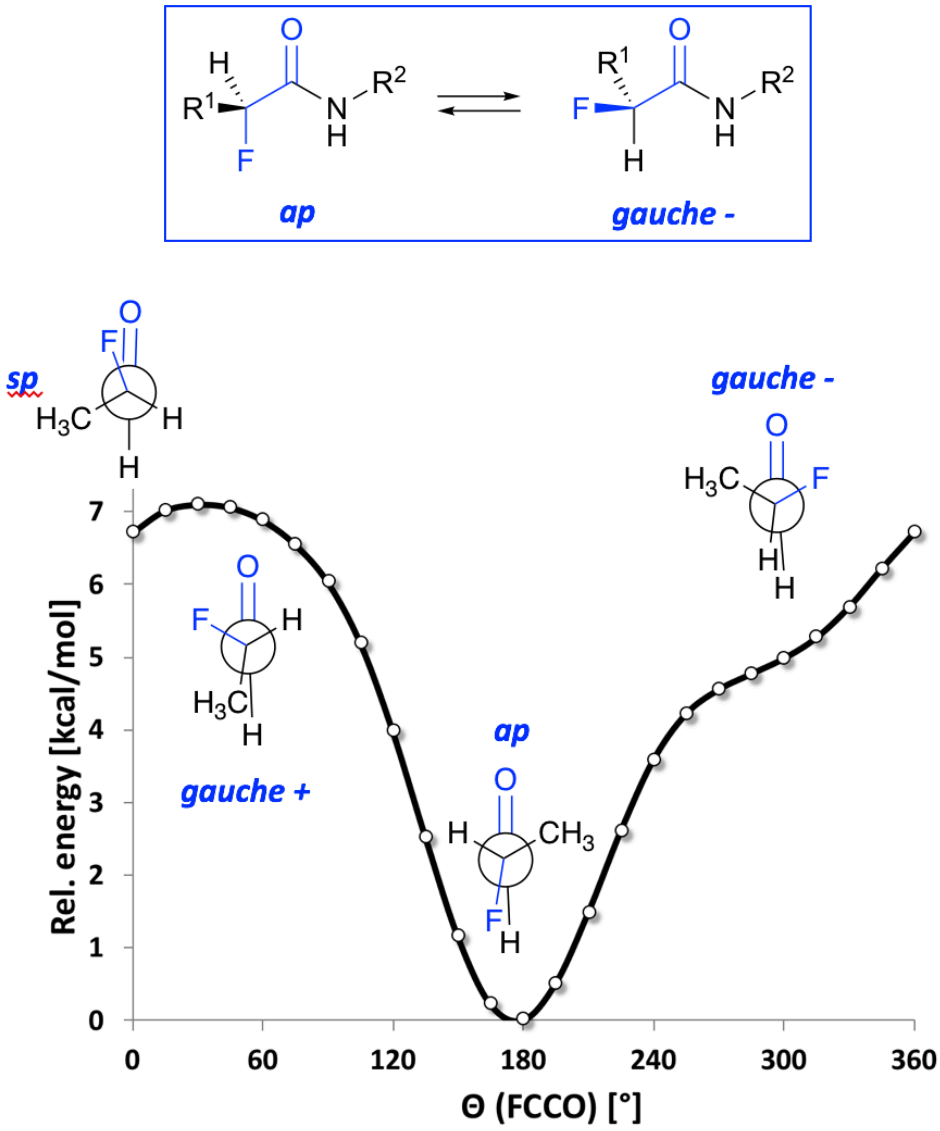


Figure 1. B3LYP/AUG-cc-pVTZ energy (E) in kcal/mol as a function of the dihedral angle Θ (F-C-C=O) in N-methyl α-fluoro propionamide (**1**); *ap* = antiperiplanar, *sp* = synperiplanar.

For each of the conformations listed in **Table 1** the $^4J_{NHF}$ coupling constant was calculated. The resulting total coupling constants as well as the contributions of the four Ramsey terms are listed in **Table 2** and shown in **Fig. 2**.

Table 2. Dihedral angle dependence of $^{4}J_{HF}$ in **1**. The four Ramsey terms are designated as follows. FC: Fermi contact, SD: Spin-dipole. DSO: Diamagnetic spin-orbit, PSO: Paramagnetic spin-orbit.

Dihedral angle Θ (°)	Total J (Hz)	FC (Hz)	SD (Hz)	PSO (Hz)	DSO (Hz)
0	-0.5	0.9	0	-0.1	-1.3
15	-0.8	0.5	0	-0.1	-1.3
30	-0.8	0.4	-0.1	0.1	-1.1
45	-0.5	0.4	-0.1	0.1	-1.1
60	-0.6	0.2	-0.4	0.2	-0.7
75	-0.9	-0.2	-0.6	0.1	-0.3
90	-1.1	-0.5	-0.6	-0.3	0.2
105	-0.9	-0.4	-0.5	-0.8	0.8
120	-0.1	0.5	-0.4	-1.5	1.4
135	-0.4	0.4	-0.3	-2.4	1.9
150	-1.6	-0.5	-0.2	-3.2	2.2
165	-3.4	-2.1	0	-3.7	2.5
180	-4.4	-3	0	-4	2.5
195	-3.8	-2.6	0	-3.7	2.5
210	-2	-1	-0.1	-3.1	2.3
225	-0.8	-0.2	-0.3	-2.2	1.9
240	-0.4	-0.1	-0.4	-1.3	1.4
255	-1.4	-1.2	-0.5	-0.6	0.8
270	-1.6	-1.1	-0.7	-0.2	0.3
285	-1.4	-0.6	-0.7	0	-0.2
300	-0.8	0.2	-0.5	0.1	-0.5
315	-0.3	0.8	-0.3	0	-0.8
330	-0.1	1	-0.1	0	-1
345	-0.2	1	0	-0.1	-1.2
360	-0.5	0.9	0	-0.1	-1.3

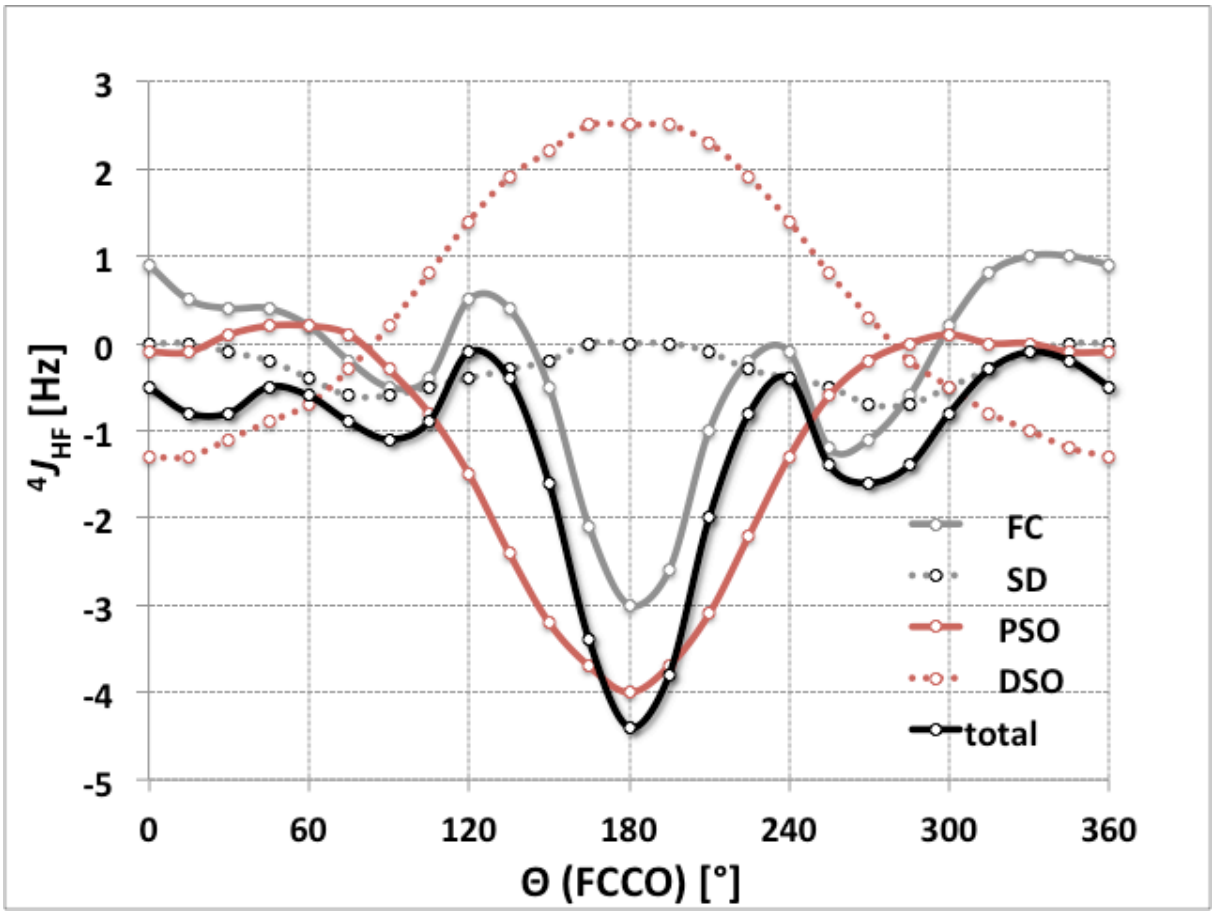
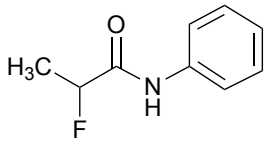


Figure 2. Dihedral angle dependence of $^4J_{HF}$ in **1.** The four Ramsey terms are designated as follows. FC: Fermi contact, SD: Spin-dipole. DSO: Diamagnetic spin-orbit, PSO: Paramagnetic spin-orbit.

The geometry of the conformer with Θ (F-C-C=O)= 180° was further optimized without restraint. As expected this lead only to minor changes (Θ (F-C-C=O)= 176.6°). The $^4J_{HF}$ coupling constant calculated for the resulting conformation is -4.3 Hz. This geometry was also used for the NBO analysis.

2.2 2-Fluoro-N-phenylpropanamide (3)

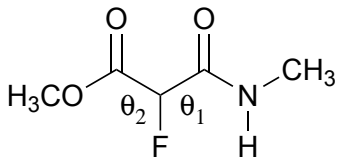
The conformer with Θ (F-C-C=O) = 180° was optimized without restraint as outlined above. This resulted in a final value of Θ of 176°. The calculated coupling constant for this optimized geometry was -7.0 Hz.



3

2.3 Methyl 3-(methylamino)-2-fluoro-3-oxopropanoate (4b)

Experimental data for compound **4** were compared with the results of DFT calculations for the representative model compound **4b** for which the benzyl group is replaced by a methyl group.

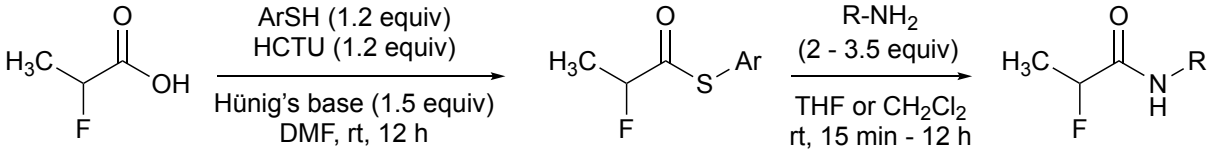


4b

Two low energy conformations were considered for comparison with the experimental $^4J_{NHF}$ coupling constant: Conformation 1 with Θ_1 (F-C-C=O)= -173° and Θ_2 (F-C-C=O)= -38° (global minimum) and conformation 2 with Θ_1 (F-C-C=O)= 179° and Θ_2 (F-C-C=O)= 120°. ΔG (difference of sum of electronic and thermal free energies) between the two conformations is: 0.75 kcal/mol. For both conformations the $^4J_{NHF}$ coupling constant was calculated as described above: Conformation 1: -3.5 Hz Conformation 2: -2.9 Hz. The Boltzmann weighted average value for the calculated $^4J_{NHF}$ coupling constant is thus -3.3 Hz.

3 Synthesis of α-fluoro amides

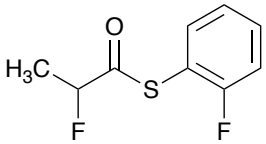
3.1 Synthetic route to α-fluoro propionamides



A Ar = 2F-C_6H_4 (87%)
B Ar = 2-naphthyl (89%)

1 R = Me (40%)
2 R = Bn (77%)
3 R = Ph (65%)

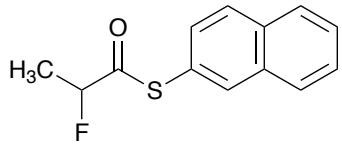
S-(2-fluorophenyl) 2-fluoropropanethioate (A)



To a solution of 2-fluoropropionic acid (0.13 mL, 1.58 mmol, 1 equiv) and HCTU (784 mg, 1.896 mmol, 1.2 equiv) in DMF (1 mL, 1.5 M) was added Hünig's base (0.41 mL, 2.37 mmol, 1.5 equiv) and the reaction mixture was stirred for 10 min at room temperature. To this solution of preactivated acid, 2-fluorothiophenol (0.2 mL, 1.896 mmol, 1.2 equiv) was added and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was directly purified by flash column chromatography (*n*-hexane 100% to *n*-hexane/EtOAc 95:5) and the product was recovered as a white solid (278 mg, 87% yield). Recrystallization from CH_2Cl_2 afforded crystals that were analysed by X-ray crystallography

***R*f** = 0.42 (EtOAc/*n*-hexane, 1:9);
^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ: 7.60-7.32 (m, 2H, ArH), 7.25-7.07 (m, 2H, ArH), 5.14 (dq, $^2J_{HF}$ = 48.5 Hz, $^3J_{HH}$ = 6.8 Hz, 1H, CH), 1.64 (dd, $^3J_{HF}$ = 24.0 Hz, $^3J_{HH}$ = 6.8 Hz, 3H, CH*CH*$_3$).
^{13}C NMR (100 MHz, $CDCl_3$, 25°C) δ: 197.0 (d, $^2J_{CF}$ = 29.4 Hz, C=O), 162.5 (d, $^1J_{CF}$ = 250.2 Hz, Ar), 136.9 (ArH), 132.6 (d, $^3J_{CF}$ = 8.2 Hz, ArH), 124.9 (d, $^4J_{CF}$ = 3.9 Hz, ArH), 116.5 (d, $^2J_{CF}$ = 22.6 Hz, ArH), 113.6 (dd, $^2J_{CF}$ = 18.6 Hz, $^4J_{CF}$ = 6.5 Hz, Ar), 92.8 (d, $^1J_{CF}$ = 185.5 Hz, CH), 18.7 (d, $^2J_{CF}$ = 21.7 Hz, CH_3).
^{19}F NMR (282 MHz, $CDCl_3$, 25°C) δ: −106.33 (m, ArF), −181.14 (dq, $^2J_{HF}$ = 48.5 Hz, $^3J_{HF}$ = 24.0 Hz).
HRMS (EI): Calculated for [$C_9H_8F_2OS$]: 202.0259 m/z; found: 202.0262 m/z.
IR ν_{max}(neat)/cm^{-1}: 2992 (br, CH aliphatic and aromatic), 1706 (C=O).
Mp = 45-46 ºC.

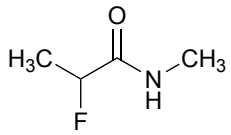
S-(naphthalen-2-yl) 2-fluoropropanethioate (B)



To a solution of 2-fluoropropionic acid (0.42 mL, 5.27 mmol, 1 equiv) and HCTU (2.62 g, 6.32 mmol, 1.2 equiv) in DMF (2.6 mL, 2 M) was added Hünig's base (1.38 mL, 7.9 mmol, 1.5 equiv) and the reaction mixture was stirred for 5 min at room temperature. To this solution of preactivated acid, naphthalene-2-thiol (1.04 g, 6.32 mmol, 1.2 equiv) was added and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was directly purified by flash column chromatography (toluene/*n*-hexane 1:1) and the product was recovered as a white solid (1.098 g, 89% yield).

R_f = 0.31 (toluene/*n*-hexane, 1:1);
^{1}H NMR (400 MHz, CD_2Cl_2, 25°C) δ: 8.04–7.97 (m, 1H, ArH), 7.96-7.79 (m, 3H, ArH), 7.63-7.50 (m, 2H, ArH), 7.46 (dd, $^3J_{HH}$ = 8.6 Hz, $^4J_{HH}$ = 1.8 Hz, 1H, ArH), 5.19 (dq, $^2J_{HF}$ = 48.8 Hz, $^3J_{HH}$ = 6.8 Hz, 1H, CH), 1.65 (dd, $^3J_{HF}$ = 24.1 Hz, $^3J_{HH}$ = 6.8 Hz, 3H, CH_3).
^{13}C NMR (101 MHz, CD_2Cl_2, 25°C) δ: 199.1 (d, $^2J_{CF}$ = 28.5 Hz, C=O), 135.5 (ArH), 134.1 (Ar), 134.0 (Ar), 131.6 (ArH), 129.4 (ArH), 128.41 (ArH), 128.3 (ArH), 128.0 (ArH), 127.3 (ArH), 123.9 (d, $^4J_{CF}$ = 5.8 Hz, Ar), 93.4 (d, $^1J_{CF}$ = 184.8 Hz, CF), 19.1 (d, $^2J_{CF}$ = 21.7 Hz, CH_3).
^{19}F NMR (376 MHz, CD_2Cl_2, 25°C) δ: –181.30 (dq, $^2J_{HF}$ = 48.8 Hz, $^3J_{HH}$ = 24.1 Hz).
HRMS (EI): Calculated for [$C_{13}H_{11}FOS$]: 234.0510 m/z; found: 234.0513 m/z.
Elemental analysis: calculated for [$C_{13}H_{11}FOS$]: [C] 64.64%, [H] 4.73 %, [O] 6.83%, [F] 8.11%, [S] 13.69%; found: [C] 66.89%; [H] 4.83%; [F] 8.10%.
IR ν_{max}(neat)/cm^{-1}: 2992 (br, CH aliphatic and aromatic), 1691 (C=O).
Mp = 51-52 ºC.

2-Fluoro-N-methylpropanamide (1)



In a 10-mL flask charged with **B** (465 mg, 2.3 mmol, 1 equiv), a solution of methyl amine in THF (4 mL, 2 M, 3.5 equiv) was added at 0 ºC. The reaction was stirred for 30 min at room temperature. TLC analysis and NMR spectroscopic analysis of the crude mixture revealed full conversion to the product. The product was purified by distillation at atmospheric pressure (p = 100 mbar, temperature oil bath = 120 ºC) and dried for 30 seconds under high vacuum, to remove traces of THF. The pure product was recovered a clear oil (97 mg, 0.92 mmol, 40% yield). *Note*: the moderate yield was due to partial loss of product by evaporation.

R_f = 0.53 (CH_2Cl_2/MeOH 95:5);
HRMS (ESI)$^+$: Calculated for [C_4H_8FNO+H]: 106.0663 m/z; found: 106.0662 m/z.
IR ν_{max}(neat)/cm^{-1}: 3321 (NH), 2989 (br, CH aliphatic and aromatic), 1656 (C=O).

^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC) δ: 6.32 (br s, 1H, NH), 4.99 (dq, $^{2}J_{HF}$ = 49.5 Hz, $^{3}J_{HH}$ = 6.8 Hz, 1 H, CH), 2.88 (d, $^{3}J_{HH}$ = 5.0 Hz, 3H, NHCH_3), 1.57 (dd, $^{3}J_{HF}$ = 24.8 Hz, $^{3}J_{HH}$ = 6.8 Hz, 3H, CH_3).
^{13}C NMR (126 MHz, $CDCl_3$, 25 ºC) δ: 171.4 (d, $^{2}J_{CF}$ = 18.5 Hz, C=O), 89.1 (d, $^{1}J_{CF}$ = 182.5 Hz, CF), 25.8 (NHCH_3), 18.6 (d, $^{2}J_{CF}$ = 21.5 Hz, CH_3).
^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC) δ: −182.31 (dqd, $^{2}J_{HF}$ = 49.5 Hz, $^{3}J_{HF}$ = 24.8 Hz, $^{4}J_{HF}$ = 4.4 Hz).

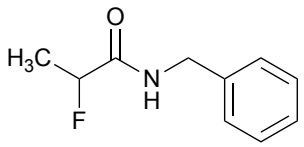
^{1}H NMR (400 MHz, CH_2Cl_2, 25 ºC) δ: 6.36 (br s, 1H, NH), 4.95 (dq, $^{2}J_{HF}$ = 49.5 Hz, $^{3}J_{HH}$ = 6.8 Hz, 1H, CH), 2.81 (d, $^{3}J_{HH}$ = 4.9 Hz, 3H, NHCH_3), 1.53 (dd, $^{3}J_{HF}$ = 24.8 Hz, $^{3}J_{HH}$ = 6.8 Hz, 3H).
^{13}C NMR (101 MHz, CH_2Cl_2, 25 ºC) δ: 171.5 (d, $^{2}J_{CF}$ = 18.9 Hz, C=O), 89.6 (d, $^{1}J_{CF}$ = 182.0 Hz, CF), 25.9 (NHCH_3), 18.8 (d, $^{2}J_{CF}$ = 21.6 Hz, CH_3).
^{19}F NMR (376 MHz, CH_2Cl_2, 25 ºC) δ: −182.75 (dqd, $^{2}J_{HF}$ = 49.5 Hz, $^{3}J_{HF}$ = 24.8 Hz, $^{4}J_{HF}$ = 4.3 Hz).

^{1}H NMR (300 MHz, acetone-d_6, 25 ºC) δ: 7.30 (br s, 1H, NH), 4.94 (dq, $^{2}J_{HF}$ = 49.0 Hz, $^{3}J_{HH}$ = 6.8 Hz, 1H, CH), 2.76 (d, $^{3}J_{HH}$ = 4.8 Hz, 3H, NHCH_3), 1.45 (dd, $^{3}J_{HF}$ = 24.4 Hz, $^{3}J_{HH}$ = 6.7 Hz, 3H, CH_3).
^{13}C NMR (151 MHz, acetone-d_6, 25 ºC) δ: 171.2 (d, $^{2}J_{CF}$ = 19.3 Hz, C=O), 89.5 (d, $^{1}J_{CF}$ = 181.0 Hz, CF), 25.7 (NHCH_3), 18.8 (d, $^{2}J_{CF}$ = 21.9 Hz, CH_3).
^{19}F NMR (282 MHz, acetone-d_6, 25 ºC) δ: −183.35 (dqd, $^{2}J_{HF}$ = 49.0 Hz, $^{3}J_{HF}$ = 24.4 Hz, $^{4}J_{HF}$ = 2.9 Hz). *Processing: Zero filling from FID size = 65536 to spectrum size = 131072; Apodization: Exponential = -0.4, Gaussian = 0.2.*

^{1}H NMR (500 MHz, CD_3OH *with excitation sculpting*, 25 ºC) δ: 8.11 (br s, 1H, NH), 5.2-4.9 (m, 1H, CH), 2.77 (d, $^{3}J_{HH}$ = 4.7 Hz, 3H, NHCH_3), 1.49 (dd, $^{3}J_{HF}$ = 24.3 Hz, $^{3}J_{HH}$ = 6.8 Hz, 3H, CH_3).
^{13}C NMR (126 MHz, CD_3OH, 25 ºC) δ: 173.8 (d, $^{2}J_{CF}$ = 19.8 Hz, C=O), 89.3 (d, $^{1}J_{CF}$ = 181.6 Hz, CF), 25.9 (NHCH_3), 18.7 (d, $^{2}J_{CF}$ = 22.2 Hz, CH_3).
^{19}F NMR (470 MHz, CD_3OH, 25 ºC) δ: –183.33 (dqd, $^{2}J_{HF}$ = 48.6 Hz, $^{3}J_{HF}$ = 24.3 Hz, $^{4}J_{HF}$ = 2.4 Hz). *Processing: Zero filling from FID size = 83326 to spectrum size = 262144; Apodization: Exponential = -0.75, Gaussian = 0.15.*

^{1}H NMR (300 MHz, DMSO-d_6, 25 ºC) δ: 8.06 (br s, 1H, NH), 4.97 (dq, $^{2}J_{HF}$ = 49.0 Hz, $^{3}J_{HH}$ = 6.7 Hz, 1H, CH), 2.62 (d, $^{3}J_{HH}$ = 4.6 Hz, 3H, CH_3), 1.40 (dd, $^{3}J_{HF}$ = 24.5 Hz, $^{3}J_{HH}$ = 6.7 Hz, 1H, 3H, CH_3).
^{13}C NMR (126 MHz, DMSO-d_6, 25 ºC) δ: 170.1 (d, $^{2}J_{CF}$ = 19.8 Hz, C=O), 88.0 (d, $^{1}J_{CF}$ = 179.1 Hz, CF), 25.2 (NHCH_3), 18.4 (d, $^{2}J_{CF}$ = 21.9 Hz, CH_3).
^{19}F NMR (470 MHz, DMSO-d_6, 25 ºC) δ: −181.04 (dqdq, $^{2}J_{HF}$ = 49.0 Hz, $^{3}J_{HF}$ = 24.5 Hz, $^{4}J_{HF}$ = 1.7 Hz, $^{5}J_{HF}$ = 0.7 Hz). *Processing: Zero filling from FID size = 214268 to spectrum size = 524288. $^{5}J_{HF}$ also measurable for Spectrum size = 1048576; Apodization: Exponential = -0.3, Gaussian = 0.2.*

N-benzyl-2-fluoropropanamide (2)



To a solution of **A** (202 mg, 1 mmol, 1 equiv) in CH_2Cl_2 (1 mL), benzylamine (0.22 mL, 2 mmol, 2 equiv) was added dropwise. The reaction mixture was stirred at room temperature for 15 min. TLC analysis (*n*-hexane/ethyl acetate 8:2) revealed full conversion to product. The reaction mixture was directly purified by flash column chromatography (*n*-hexane/EtOAc 9:1 to 8:2) and the product was recovered as a white solid (140 mg, 77% yield). Recrystallization from CH_2Cl_2 afforded crystals that were analysed by X-ray crystallography

R_f = 0.23 (EtOAc/*n*-hexane, 2:8);
HRMS (ESI)$^+$: Calculated for $[C_{10}H_{12}FNO+H]^+$: 182.0976 m/z; found: 182.0972 m/z.
Elemental analysis: calculated for $[C_{10}H_{12}FNO]$: [C] 66.28%, [H] 6.67 %, [O] 8.83%, [F] 10.48%, [N] 7.73%; found: [C] 66.35%; [H] 6.65%; [F] 8.22%.

IR ν_{max}(neat)/cm^{-1}: 3337 (NH), 2939 (br, CH aliphatic and aromatic), 1651 (C=O),1248 (C-N).
Mp = 47-48 ºC.

^{1}H NMR (500 MHz, $CDCl_3$, 25 ºC) δ: 7.50 – 7.26 (m, 5H, ArH), 6.61 (br s, 1H, NH), 5.04 (dq, $^2J_{HF}$ = 49.5 Hz, $^3J_{HH}$ = 6.8 Hz, 1H, CH), 4.57 – 4.40 (m, 2H, CH_2), 1.61 (dd, $^3J_{HF}$ = 24.8 Hz, $^3J_{HH}$ = 6.8 Hz, 3H, CH_3).
^{13}C NMR (126 MHz, $CDCl_3$, 25 ºC) δ: 170.7 (d, $^2J_{CF}$ = 19.1 Hz, C=O), 137.7 (Ar), 129.0 (ArH), 128.0 (ArH), 127.9 (ArH), 89.1 (d, $^1J_{CF}$ = 182.9 Hz, CF), 43.2 (CH_2), 18.7 (d, $^2J_{CF}$ = 21.5 Hz, CH_3).
^{19}F NMR (470 MHz, $CDCl_3$, 25 ºC) δ: −182.08 (dqd, $^2J_{HF}$ = 49.5 Hz, $^3J_{HF}$ = 24.8, $^4J_{HF}$ = 4.6 Hz).

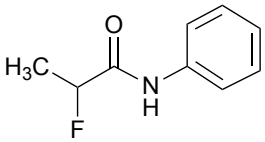
^{1}H NMR (400 MHz, CD_2Cl_2, 25°C) δ: 7.65 – 7.00 (m, 5H, ArH), 6.72 (br s, 1H, NH), 5.03 (dq, $^2J_{HF}$ = 49.5 Hz, $^3J_{HH}$ = 6.8 Hz, 1H), 4.52-4.39 (m, 2H, CH_2), 1.58 (dd, $^3J_{HF}$ = 24.8 Hz, $^3J_{HH}$ = 6.8 Hz, 3H, CH_3).
^{13}C NMR (100 MHz, CD_2Cl_2, 25°C) δ: 170.9 (d, $^2J_{CF}$ = 19.1 Hz, C=O), 138.7 (Ar), 129.2 (ArH), 128.1 (ArH), 128.0 (ArH), 89.6 (d, $^1J_{CF}$ = 182.3 Hz, CH), 43.3 (CH_2), 18.9 (d, $^2J_{CF}$ = 21.5 Hz, CH_3).
^{19}F NMR (376 MHz, CD_2Cl_2, 25°C) δ: −182.68 (dqd, $^2J_{HF}$ = 49.5 Hz, $^3J_{HF}$ = 24.8, $^4J_{HF}$ = 4.3 Hz).

^{1}H NMR (500 MHz, acetone-d_6, 25 ºC) δ: 8.89 (br s, 1H, NH), 8.50 – 8.10 (m, 5H, ArH), 6.06 (dq, $^2J_{HF}$ = 49.0 Hz, $^3J_{HH}$ = 6.7 Hz, 1H, CH), 5.52 – 5.44 (m, 2H, CH_2), 2.54 (dd, $^3J_{HF}$ = 24.4 Hz, $^3J_{HH}$ = 6.7 Hz, 3H, CH_3).
^{13}C NMR (126 MHz, acetone-d_6, 25 ºC) δ: 170.9 (d, $^2J_{CF}$ = 19.7 Hz, C=O), 140.3 (Ar), 129.2 (ArH), 128.3 (ArH), 127.8 (ArH), 89.4 (d, $^1J_{CF}$ = 181.1 Hz, CF), 42.9 (CH_2), 18.8 (d, $^2J_{CF}$ = 22.0 Hz, CH_3).
^{19}F NMR (470 MHz, acetone-d_6, 25 ºC) δ: −183.18 (dqd, $^2J_{HF}$ = 49.0, $^3J_{HF}$ = 24.4, $^4J_{HF}$ = 2.8 Hz).

^{1}H NMR (500 MHz, CD_3OH, *with excitation sculpting*, 25 ºC) δ: 9.42 (br s, 1H, NH), 8.27 – 7.75 (m, 5H, ArH), 5.77 (dq, 1H, $^2J_{HF}$ = 48.8 Hz, $^3J_{HH}$ = 6.8 Hz, 1H), 5.31 – 5.00 (m, 2H, CH_2), 2.29 (dd, $^3J_{HF}$ = 24.2 Hz, $^3J_{HH}$ = 6.8 Hz, 3H, CH_3).
^{13}C NMR (126 MHz, CD_3OH, 25 ºC) δ: 173.2 (d, $^2J_{CF}$ = 20.1 Hz, C=O), 139.6 (Ar), 129.4 (ArH), 128.4 (ArH), 128.1 (ArH), 89.3 (d, $^1J_{CF}$ = 181.7 Hz, CF), 43.5 (CH_2), 18.8 (d, $^2J_{CF}$ = 22.3 Hz, CH_3).
^{19}F NMR (470 MHz, CD_3OH, 25 ºC) δ: −184.05 (dqd, $^2J_{HF}$ = 48.8 Hz, $^3J_{HH}$ = 24.2 Hz, $^4J_{HF}$ < 2.0 Hz).

^{1}H NMR (500 MHz, DMSO-d_6, 25 ºC) δ: 8.69 (br s, 1 H, NH), 7.47 – 7.10 (m, 5H, ArH), 5.06 (dq, $^2J_{HF}$ = 49.0 Hz, $^3J_{HH}$ = 6.7 Hz, 1H, CH), 4.69 – 4.21 (m, 2H, CH_2), 1.45 (dd, $^3J_{HF}$ = 24.5 Hz, $^3J_{HH}$ = 6.7 Hz, 3H, CH_3).
^{13}C NMR (126 MHz, DMSO-d_6, 25 ºC) δ: 169.8 (d, $^2J_{CF}$ = 20.2 Hz, C=O), 139.2 (Ar), 128.3 (ArH), 127.1 (ArH), 126.8 (ArH), 87.9 (d, $^1J_{CF}$ = 178.9 Hz, CF), 41.7 (CH_2), 18.5 (d, $^2J_{CF}$ = 22.0 Hz, CH_3).
^{19}F NMR (470 MHz, DMSO-d_6, 25 ºC) δ: –181.00 (dqd, $^2J_{HF}$ = 49.0 Hz, $^3J_{HF}$ = 24.5 Hz, $^4J_{HF}$ = 1.7 Hz).

2-Fluoro-N-phenylpropanamide (3)



To a solution of **A** (185 mg, 1 mmol, 1 equiv) in CH_2Cl_2 (0.45 mL), aniline (0.17 mL, 2 mmol, 2 equiv) was added dropwise. The reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was directly purified by flash column chromatography (*n*-hexane/EtOAc 9:1 to 8:2) and the product was recovered as a white solid (100 mg, 0.65 mmol, 65% yield). X-ray crystal structure obtained by recrystallization from CH_2Cl_2/*n*-hexane.

***R*$_f$** = 0.27 (EtOAc/*n*-hexane, 2:8);
HRMS (ESI)$^+$: Calculated for $[C_9H_{10}FNO+H]^+$: 168.0819 m/z; found: 168.0820 m/z.
Elemental analysis: calculated for $[C_9H_{10}FNO]$: [C] 64.66%, [H] 6.03 %, [O] 9.57%, [F] 11.36%, [N] 8.38%; found: [C] 64.46%; [H] 6.04%; [F] 11.30%; [N] 8.32%.
IR ν_{max}(neat)/cm^{-1}: 3336 (N-H), 2993 (br, CH aliphatic and aromatic), 1666 (C=O), 1249 (C-N).
Mp = 59-60 ºC.

^{1}H NMR (500 MHz, $CDCl_3$, 25 ºC) δ: 8.00 (br s, 1H, NH), 7.70 – 7.50 (m, 2H, ArH), 7.45 – 7.31 (m, 2H, ArH), 7.25 – 7.10 (m, 1H, ArH), 5.15 (dq, $^2J_{HF}$ = 49.5 Hz, $^3J_{HH}$ = 7.0 Hz, 1H, CH), 1.70 (dd, $^3J_{HF}$ = 24.8 Hz, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3).
^{13}C NMR (126 MHz, $CDCl_3$, 25 ºC) δ: 168.7 (d, $^2J_{CF}$ = 18.0 Hz, C=O), 136.8 (Ar), 129.3 (ArH), 125.1 (ArH), 120.1 (ArH), 89.1 (d, $^1J_{CF}$ = 184.6 Hz, CF), 18.6 (d, $^2J_{CF}$ = 21.4 Hz, CH_3).
^{19}F NMR (470 MHz, $CDCl_3$, 25 ºC) δ: –179.84 (dqd, $^2J_{HF}$ = 49.5 Hz, $^3J_{HF}$ = 24.8 Hz, $^4J_{HF}$ = 6.8 Hz).

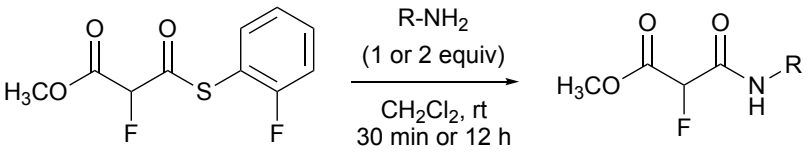
^{1}H NMR (400 MHz, CD_2Cl_2, 25 ºC) δ: 8.05 (br s, 1H, NH), 7.65-7.50 (m, 2H, ArH), 7.40-7.30 (m, 2H, ArH), 7.25-7.05 (m, 1H, ArH), 5.11 (dq, $^{2}J_{HF}$ = 49.4 Hz, $^{3}J_{HH}$ = 6.8 Hz, 1H, CH), 1.65 (dd, $^{3}J_{HF}$ = 24.9 Hz, $^{3}J_{HH}$ = 6.8 Hz, 3H, CH_3).
^{13}C NMR (101 MHz, CD_2Cl_2, 25 ºC) δ: 169.1 (d, $^{2}J_{CF}$ = 18.1 Hz, C=O), 137.6 (Ar), 129.6 (ArH), 125.3 (ArH), 120.5 (ArH), 89.6 (d, $^{1}J_{CF}$ = 184.1 Hz, CF), 18.7 (d, $^{2}J_{CF}$ = 21.5 Hz, CH_3).
^{19}F NMR (376 MHz, CD_2Cl_2, 25 ºC) δ: -180.58 (dqd, $^{2}J_{HF}$ = 49.8 Hz, $^{3}J_{HF}$ = 24.8 Hz, $^{4}J_{HF}$ = 6.5 Hz).

^{1}H NMR (500 MHz, acetone-d_6, 25 ºC) δ: 10.18 (br s, 1H, NH), 8.44 – 8.73 (m, 2H, ArH), 8.40 – 8.28 (m, 2H, ArH), 8.17 – 8.08 (m, 1H, ArH), 6.15 (dq, $^{2}J_{HF}$ = 49.0 Hz, $^{3}J_{HH}$ = 6.8 Hz, 1H, CH), 2.60 (dd, $^{3}J_{HF}$ = 24.4 Hz, $^{3}J_{HH}$ = 6.8 Hz, 3H, CH_3).
^{13}C NMR (126 MHz, acetone-d_6, 25 ºC) δ: 169.4 (d, $^{2}J_{CF}$ = 19.3 Hz, C=O), 139.2 (Ar), 129.5 (ArH), 124.9 (ArH), 120.9 (ArH), 89.3 (d, $^{1}J_{CF}$ = 182.4 Hz, CF), 18.7 (d, $^{2}J_{CF}$ = 22.0 Hz, CH_3).
^{19}F NMR (470 MHz, acetone-d_6, 25 ºC) δ: −181.40 (dqd, $^{2}J_{HF}$ = 49.0 Hz, $^{3}J_{HH}$ = 24.4 Hz, $^{4}J_{HF}$ = 3.9 Hz).

^{1}H NMR (500 MHz, CD_3OH, *with excitation sculpting*, 25 ºC) δ: 10.53 (br s, 1H, NH), 8.55 – 8.20 (m, 2H, ArH), 8.17 – 7.98 (m, 2H, ArH), 7.95 – 7.84 (m, 1H, ArH), 5.86 (dq, $^{1}J_{HF}$ = 48.5 Hz, $^{3}J_{HH}$ = 6.8 Hz, 1H, CH), 2.36 (dd, $^{3}J_{HF}$ = 24.2 Hz, $^{3}J_{HH}$ = 6.8 Hz, 3H, CH_3).
^{13}C NMR (126 MHz, CD_3OH, 25 ºC) δ: 171.4 (d, $^{2}J_{CF}$ = 19.9 Hz, C=O), 138.7 (Ar), 129.7 (ArH), 125.8 (ArH), 122.0 (ArH), 89.3 (d, $^{1}J_{CF}$ = 182.4 Hz, CF), 18.7 (d, $^{2}J_{CF}$ = 22.4 Hz).
^{19}F NMR (470 MHz, CD_3OH, 25 ºC) δ: −182.64 (dq, $^{2}J_{HF}$ = 48.5 Hz, $^{3}J_{HF}$ = 24.2 Hz). NH undergoes rapid H/D exchange, therefore $^{4}J_{HF}$ not measurable.

^{1}H NMR (500 MHz, DMSO-d_6, 25 ºC) δ: 10.61 (br s, 1H, NH), 8.32 – 8.17 (m, 2H, ArH), 7.97 – 7.77 (m, 2H, ArH), 7.72 – 7.53 (m, 1H, ArH), 5.73 (dq, $^{2}J_{HF}$ = 48.7 Hz, $^{3}J_{HH}$ = 6.7 Hz, 1H, CH), 2.08 (dd, $^{2}J_{HF}$ = 24.5 Hz, $^{3}J_{HH}$ = 6.7 Hz, 3H).
^{13}C NMR (126 MHz, DMSO-d_6, 25ºC) δ: 168.4 (d, $^{2}J_{CF}$ = 20.4 Hz, C=O), 138.1 (Ar), 128.7 (ArH), 123.9 (ArH), 120.0 (ArH), 87.8 (d, $^{1}J_{CF}$ = 178.9 Hz, CF), 18.3 (d, $^{2}J_{CF}$ = 22.2 Hz, CH_3).
^{19}F NMR (470 MHz, DMSO-d_6, 25 ºC) δ: −179.39 (dqd, $^{2}J_{HF}$ = 49.0 Hz, $^{3}J_{HF}$ = 4.6 Hz, $^{4}J_{HF}$ = 1.8 Hz).

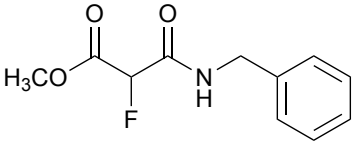
3.2 Synthetic route to α-fluoro malonamides



F-MTM

4 R = Bn (87%)
5 R = Ph (98%)

Methyl 3-(benzylamino)-2-fluoro-3-oxopropanoate (4)



To a solution of methyl 2-fluoro-3-((4-methoxyphenyl)thio)-3-oxopropanoate (**F-MTM**)[1] (71.4 mg, 0.29 mmol) in CH_2Cl_2 (0.3 mL, 1 M), benzylamine (0.032 mL, 0.29 mmol, 1 eq) was added dropwise and the mixture was stirred at room temperature for 30 min (the solution turned into a white suspension). The crude mixture was purified by flash chromatography on silica, eluting with EtOAc/*n*-hexane to afford the above product as a white solid (57 mg, 0.2531 mmol, 87% yield). Recrystallization from CH_2Cl_2/*n*-hexane afforded crystals that were analysed by X-ray crystallography.

***R*$_f$** = 0.21 (EtOAc/*n*-hexane, 3:7);
HRMS (ESI)$^+$: calculated for $[C_{11}H_{12}FNO_3+Na]^+$: 248.0693 m/z; found: 248.0698 m/z.
Elemental analysis: calculated for $[C_{11}H_{12}FNO_3]$: [C] 58.66%, [H] 5.37 %, [O] 21.31%, [F] 8.44%, [N] 6.22%; found: [C] 58.89%; [H] 5.46%; [F] 8.50%; [N] 6.24%.
IR ν_{max}(neat)/cm^{-1}: 3306 (N-H), 2950 (br, C-H arom. and aliph.), 1754 (C=O), 1670 (C=O), 1260 (C-N).
Mp = 84-85 ºC.

^{1}H NMR (500 MHz, $CDCl_3$, 25 ºC) δ: 7.39 – 7.26 (5H, ArH), 6.66 (br s, 1H, NH), 5.33 (d, $^2J_{HF}$ = 48.9 Hz, 1H, CH), 4.55, 4.47 (2 x dd, $^2J_{HH}$ = 14.7 Hz, $^3J_{HH}$ = 5.7 Hz, 2H, CH_2), 3.88 (s, 3H, OCH_3).
^{13}C NMR (126 MHz, $CDCl_3$, 25 ºC) δ: 165.3 (d, $^2J_{CF}$ = 23.9 Hz, C=O), 163.2 (d, $^2J_{CF}$ = 20.1 Hz, C=O), 136.9 (Ar), 129.0 (ArH), 128.1 (ArH), 128.0 (ArH), 87.1 (d, $^1J_{CF}$ = 199.0 Hz, CF), 53.5 (d, $^4J_{CF}$ = 1.0 Hz, OCH_3), 43.6 (CH_2).
^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC) δ: –192.65 (dd, $^2J_{HF}$ = 48.9 Hz, $^4J_{HF}$ = 3.3 Hz).

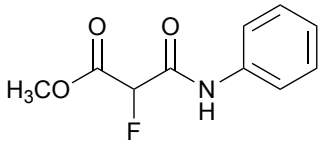
^{1}H NMR (500 MHz, CD_2Cl_2, 25 ºC) δ: 7.44 – 7.19 (m, 5H ArH), 6.71 (br s, 1H, NH), 5.31 (d, $^2J_{HF}$ = 48.7 Hz, 1H, CH), 4.51, 4.46 (2H, 2 x dd, $^2J_{HH}$ = 14.9 Hz, $^3J_{HH}$ = 6.0 Hz, 2H, CH_2), 3.85 (s, 3H, OCH_3).
^{13}C NMR (101 MHz, CD_2Cl_2, 25 ºC) δ: 165.8 (d, $^2J_{CF}$ = 23.7 Hz, C=O), 163.5 (d, $^2J_{CF}$ = 20.2 Hz, C=O), 137.9 (Ar), 129.3 (ArH), 128.3 (ArH), 128.2 (ArH), 87.7 (d, $^1J_{CF}$ = 198.5 Hz, CF), 53.8 (d, $^4J_{CF}$ = 1.0 Hz, OCH_3), 43.8 (CH_2).
^{19}F NMR (470 MHz, CD_2Cl_2, 25 ºC) δ: –193.36 (dd, $^2J_{HF}$ = 48.7 Hz, $^4J_{HF}$ = 2.7 Hz).

^{1}H NMR (300 MHz, acetone-d_6, 25 ºC) δ: 8.20 (br s, 1H, NH), 7.37-7.19 (m, 5H ArH), 5.48 (d, $^2J_{HF}$ = 48.2 Hz, 1H, CH), 4.51, 4.45 (2 x dd, $^2J_{HH}$ = 17.0 Hz, $^3J_{HH}$ = 6.0 Hz, 2H, CH_2), 3.80 (s, 3H, OCH_3).
^{13}C NMR (100 MHz, acetone-d_6, 25 ºC) δ: 166.4 (d, $^2J_{CF}$ = 24.1 Hz, C=O), 164.3 (d, $^2J_{CF}$ = 20.9 Hz, C=O), 139.6 (Ar), 129.2 (ArH), 128.3 (ArH), 127.9 (ArH), 88.0 (d, $^1J_{CF}$ = 194.6 Hz, CF), 53.1 (d, $^4J_{CF}$ = 1.0 Hz, OCH_3), 43.4 (CH_2).
^{19}F NMR (470 MHz, acetone-d_6, 25 ºC) δ: –194.29 (ddt, $^2J_{HF}$ = 48.3 Hz, $^4J_{HF}$ = 1.5 Hz, $^5J_{HF}$ = 0.8 Hz). *Spectrum measured with selective decoupling from methyl ester group.*

^{1}H NMR (500 MHz, CD_3OH, *with excitation sculpting*, 25 ºC) δ: 9.02 (br s, 1H, NH), 7.47 – 7.10 (m, 5H, ArH), 5.42 (d, $^2J_{HF}$ = 48.2 Hz, 1H, CH), 4.50 – 4.34 (m, 2H, CH_2), 3.81 (s, 3H, CH_3).
^{13}C NMR (100 MHz, CD_3OH, 25 ºC) δ: 166.9 (d, $^2J_{CF}$ = 24.3 Hz, C=O), 166.0 (d, $^2J_{CF}$ = 21.0 Hz, C=O), 139.1 (Ar), 129.4 (ArH), 128.4 (ArH), 128.2 (ArH), 87.9 (d, $^1J_{CF}$ = 194.9 Hz, CF), 53.3 (d, $^4J_{CF}$ = 1.0 Hz, OCH_3), 43.9 (CH_2);
^{19}F NMR (470 MHz, CD_3OH, 25 ºC) δ: –195.65 (d, $^2J_{HF}$ = 48.2 Hz); $^4J_{HF}$ < 2 Hz.

^{1}H NMR (400 MHz, DMSO-d_6, 25 ºC) δ: 9.12 (t, $^3J_{HH}$ = 6.0 Hz, 1H, NH), 5.59 (d, $^2J_{HF}$ = 47.6 Hz, 1H, CH), 4.36, 4.31 (2 x dd, $^2J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 6.0 Hz, 2H, CH_2), 3.76 (s, 3H, OCH_3).
^{13}C NMR (100 MHz, DMSO-d_6, 25 ºC) δ: 165.7 (d, $^2J_{CF}$ = 24.5 Hz, C=O), 163.2 (d, $^2J_{CF}$ = 20.9 Hz, C=O), 138.5 (Ar), 128.3 (ArH), 127.2 (ArH), 127.0 (ArH), 86.5 (d, $^1J_{CF}$ = 190.9 Hz, CF), 52.7 ($^4J_{CF}$ = 1 Hz, OCH_3), 42.1 (CH_2).
^{19}F NMR (470 MHz, DMSO-d_6, 25 ºC) δ: –192.98 (d, $^2J_{HF}$ = 47.6 Hz, $^4J_{HF}$ = 0.7 Hz). *Spectrum measured with selective decoupling from methyl ester group.*

Methyl 2-fluoro-3-oxo-3-(phenylamino)propanoate (5)



To a solution of methyl 2-fluoro-3-((4-methoxyphenyl)thio)-3-oxopropanoate (**8**) (71.4 mg, 0.29 mmol, 1 equiv) in CH_2Cl_2 (0.3 mL, 1 M), aniline (0.053 mL, 0.58 mmol, 2 equiv) was added and the mixture was stirred at room temperature for 12 hours. The crude mixture was purified by flash chromatography on silica, eluting with EtOAc/*n*-hexane to afford the above product as a clear oil (60 mg, 0.2841 mmol, 98%).

R_f = 0.27 (EtOAc/*n*-hexane, 3:7);
HRMS (ESI): calculated for $[C_{10}H_{10}FNO_3+H]^+$: 212.0717 m/z; found: 212.0722 m/z.
Elemental analysis: calculated for $[C_{10}H_{10}FNO_3]$: [C] 56.87%, [H] 4.77%, [O] 22.73%, [F] 9.00%, [N] 6.63%; found: [C] 56.88%; [H] 4.81%; [F] 9.00%; [N] 6.62%.
IR ν_{max}(neat)/cm^{-1}: 3293 (N-H), 2950 (br, C-H arom. and aliph.), 1755 (C=O), 1676 (C=O), 1248 (C-N);
Mp = 62-63 ºC.

^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC) δ: 8.04 (br s, 1H, NH), 7.63 – 7.49 (m, 2H, ArH), 7.44 – 7.30 (m, 2H, ArH), 7.23–7.12 (m, 1H, ArH), 5.41 (d, $^{2}J_{HF}$ = 48.8 Hz, 1H, CH), 3.90 (s, 3H, OCH_3);
^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC) δ: 165.1 (d, $^{2}J_{CF}$ = 24.1 Hz, C=O), 161.0 (d, $^{2}J_{CF}$ = 19.2 Hz, C=O), 136.3 (Ar), 129.3 (ArH), 125.6 (ArH), 120.2 (ArH), 87.1 (d, $^{3}J_{CF}$ = 200.7 Hz, CF), 53.7 (d, $^{4}J_{CF}$ = 1.0 Hz);
^{19} F NMR (282 MHz, $CDCl_3$, 25 ºC) δ: –190.52 (dd, $^{2}J_{HF}$ = 48.8, $^{4}J_{HF}$ = 4.5 Hz).

^{1}H NMR (400 MHz, CD_2Cl_2, 25 ºC) δ: 8.10 (br s, 1H, NH), 7.60-7.56 (m, 2H, ArH), 7.42-7.32 (m, 2H, ArH), 7.22-7.14 (m, 1H, ArH), 5.41 (d, $^{2}J_{HF}$ = 48.8 Hz, 1H, CH), 3.87 (s, 3H, OCH_3).
^{13}C NMR (100 MHz, CD_2Cl_2, 25 ºC) δ: 165.5 (d, $^{2}J_{CF}$ = 23.8 Hz, C=O), 161.5 (d, $^{2}J_{CF}$ = 19.6 Hz, C=O), 137.0 (Ar), 129.7 (ArH), 125.9 (ArH), 120.7 (ArH), 87.6 (d, $^{1}J_{CF}$ = 200.3 Hz, CF), 54.0 (d, $^{4}J_{CF}$ = 1.0 Hz, OCH_3).
^{19}F NMR (377 MHz, CD_2Cl_2, 25 ºC) δ: –191.49 (dd, $^{2}J_{HF}$ = 48.8 Hz, $^{4}J_{HF}$ = 4.2 Hz).

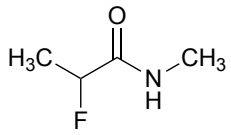
^{1}H NMR (400 MHz, acetone-d_6, 25 ºC) δ: 9.56 (br s, 1H, NH), 7.79-7.77 (m, 2H, ArH), 7.41-7.30 (m, 2H, ArH), 7.20-7.11 (m, 1H, ArH), 5.58 (d, $^{2}J_{HF}$ = 48.0 Hz, 1H, CH), 3.83 (s, 3H, OCH_3).
^{13}C NMR (100 MHz, acetone-d_6, 25 ºC) δ: 166.2 (d, $^{2}J_{CF}$ = 24.2 Hz, C=O), 162.6 (d, $^{2}J_{CF}$ = 20.9 Hz, C=O), 138.7 (Ar), 129.7 (ArH), 125.5 (ArH), 120.9 (ArH), 88.0 (d, $^{1}J_{CF}$ = 195.5 Hz, CF), 53.2 (d, $^{4}J_{CF}$= 1.1 Hz, OCH_3).
^{19}F NMR (470 MHz, acetone-d_6, 25 ºC) δ: –192.86 (d, $^{2}J_{HF}$ = 48.0 Hz, $^{4}J_{HF}$ = 1.8 Hz).

^{1}H NMR (500 MHz, CD_3OH, 25 ºC) δ: 10.26 (br s, NH), 7.65 – 7.53 (m, 2H, ArH), 7.43 – 7.26 (m, 2H, ArH), 7.26–7.06 (m, 1H, ArH), 5.55 (d, $^{2}J_{HF}$ = 47.9 Hz, 1H, CH), 3.87 (s, 3H, CH_3).
^{1}H NMR (500 MHz, CD_3OH, *with excitation sculpting*, 25 ºC) δ: 10.26 (br s, NH), 7.65 – 7.53 (m, 2H, ArH), 7.43 – 7.26 (m, 2H, ArH), 7.26–7.06 (m, 1H, ArH), 5.55 (d, $^{2}J_{HF}$ = 47.9 Hz, 1H, CH), 3.87 (s, 3H, CH_3).
^{13}C NMR (100 MHz, CD_3OH, 25 ºC) δ: 166.8 (d, $^{2}J_{CF}$ = 24.3 Hz, C=O), 164.1 (d, $^{2}J_{CF}$ = 21.3 Hz, C=O), 138.5 (Ar), 129.8 (ArH), 126.1 (ArH), 121.7 (ArH), 88.0 (d, $^{1}J_{CF}$ = 194.8 Hz), 53.4 (d, $^{4}J_{CF}$ = 1.0 Hz);
^{19}F NMR (470 MHz, CD_3OH, 25 ºC) δ: –194.54 (d, $^{2}J_{HF}$ = 47.9 Hz). NH undergoes rapid H/D exchange, therefore $^{4}J_{HF}$ not measurable.

^{1}H NMR (400 MHz, DMSO-d_6, 25 ºC) δ: 10.60 (br s, 1H, NH), 7.68 – 7.57 (m, 2H, ArH), 7.40 – 7.30 (m, 2H, ArH), 7.18–7.10 (m, 1H, ArH), 5.70 (d, $^{2}J_{HF}$ = 47.4 Hz, 1H, CH), 3.78 (s, 3H, OCH_3).
^{13}C NMR (100 MHz, DMSO-d_6, 25 ºC) δ: 165.5 (d, $^{2}J_{CF}$ = 24.8 Hz, C=O), 161.7 (d, $^{2}J_{CF}$ = 21.4 Hz, C=O), 137.6 (Ar), 128.9 (ArH), 124.5 (ArH), 119.9 (ArH), 86.6 (d, $^{1}J_{CF}$ = 190.8 Hz, CF), 52.9 (OCH_3, $^{2}J_{CF}$ = 0.5 Hz).
^{19}F NMR (470 MHz, DMSO-d_6, 25 ºC) δ: –191.86 (d, $^{2}J_{HF}$ = 47.4 Hz). $^{4}J_{HF}$ < 1 Hz.

4 Dilution experiments and K_d value determination

Solutions of **1-5** at 0.8-200 mM concentrations in CD_2Cl_2 were analyzed by ^1H NMR and ^{19}F NMR spectroscopic analysis at –80 ºC. Values of δ_{NH} were utilized to determine the K_d of dimerization. The values of $^4J_{HF}$ were also measured.



1

Initial concentration = 200 mM

^{1}H NMR (500 MHz, CD_2Cl_2, –80 ºC) δ: 6.94 (br s, 1H, NH), 5.06 (dq, $^2J_{HF}$ = 50.0 Hz, $^3J_{HH}$ = 6.8 Hz, 1H, CH), 2.84 (d, $^3J_{HH}$ = 4.9 Hz, 3H, NHCH_3), 1.57 (dd, $^3J_{HF}$ = 25.0 Hz, $^3J_{HH}$ = 6.8 Hz, 3H, CH_3).
^{19}F NMR (471 MHz, CD_2Cl_2, –80 ºC) δ: -182.50 (dqd, $^2J_{HF}$ = 50.0 Hz, $^3J_{HF}$ = 25.0 Hz, $^4J_{HF}$ = 3.8 Hz). **^{19}F NMR** (471 MHz, CD_2Cl_2, –80 ºC) not decoupled δ: -182.50.

***Concentration = 50 mM* (¼ initial concentration)**

^{1}H NMR (500 MHz, CD_2Cl_2, –80 ºC) δ: 6.71 (br s, 1H, NH), 5.06 (dq, $^2J_{HF}$ = 50.0 Hz, $^3J_{HH}$ = 6.8 Hz, 1H, CH), 2.84 (d, $^3J_{HH}$ = 4.8 Hz, 3H, NHCH_3), 1.57 (dd, $^3J_{HF}$ = 25.0 Hz, $^3J_{HH}$ = 6.8 Hz, 3H, CH_3).
^{19}F NMR (471 MHz, CD_2Cl_2, –80 ºC) δ: -182.49 (dqd, $^2J_{HF}$ = 50.0 Hz, $^3J_{HF}$ = 25.0 Hz, $^4J_{HF}$ = 4.1 Hz). **^{19}F NMR** (471 MHz, CD_2Cl_2, –80 ºC) not decoupled δ: -182.49.

***Concentration = 12.5 mM* (1/16 initial concentration)**

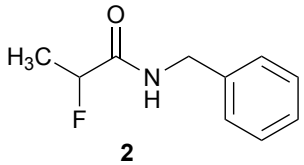
^{1}H NMR (500 MHz, CD_2Cl_2, –80 ºC) δ: 6.60 (br s, 1H, NH), 5.06 (dq, $^2J_{HF}$ = 50.0 Hz, $^3J_{HH}$ = 6.8 Hz, 1H, CH), 2.84 (d, $^3J_{HH}$ = 5.1 Hz, 3H, NHCH_3), 1.57 (dd, $^3J_{HF}$ = 25.2 Hz, $^3J_{HH}$ = 6.8 Hz, 3H, CH_3).
^{19}F NMR (471 MHz, CD_2Cl_2, –80 ºC) δ: -182.47 (dqd, $^2J_{HF}$ = 50.0 Hz, $^3J_{HF}$ = 25.2 Hz, $^4J_{HF}$ = 4.2 Hz). **^{19}F NMR** (471 MHz, CD_2Cl_2) not decoupled δ: -182.47.

***Concentration = 3.1 mM* (1/64 initial concentration)**

^{1}H NMR (500 MHz, CD_2Cl_2, –80 ºC) δ: 6.56 (br s, 1H, NH), 5.06 (dq, $^2J_{HF}$ = 50.0 Hz, $^3J_{HH}$ = 6.8 Hz, 1H, CH), 2.84 (d, $^3J_{HH}$ = 4.8 Hz, 3H, NHCH_3), 1.57 (dd, $^3J_{HF}$ = 25.0 Hz, $^3J_{HH}$ = 6.8 Hz, 3H, CH_3).
^{19}F NMR (471 MHz, CD_2Cl_2, –80 ºC) δ: -182.47 (dqd, $^2J_{HF}$ = 50.0 Hz, $^3J_{HF}$ = 25.0 Hz, $^4J_{HF}$ = 4.3 Hz).

***Concentration = 0.8 mM* (1/256 initial concentration)**

^{1}H NMR (500 MHz, CD_2Cl_2, –80 ºC) δ: 6.56 (br s, 1H, NH), 5.06 (dq, $^2J_{HF}$ = 50.0 Hz, $^3J_{HH}$ = 6.8 Hz, 1H, CH), 2.84 (d, $^3J_{HH}$ = 4.8 Hz, 3H, NHCH_3), 1.57 (dd, $^3J_{HF}$ = 25.2 Hz, $^3J_{HH}$ = 6.8 Hz, 3H, CH_3).
^{19}F NMR (471 MHz, CD_2Cl_2, –80 ºC) δ: -182.47 (dqd, $^2J_{HF}$ = 50.0 Hz, $^3J_{HF}$ = 25.2, $^4J_{HF}$ = 4.3 Hz). **^{19}F NMR** (471 MHz, CD_2Cl_2, –80 ºC) not decoupled δ: -182.47.



2

Initial concentration = 200 mM

^{1}H NMR (500 MHz, CD_2Cl_2, –80 ºC) δ: 7.47-7.20 (m, 5H, ArH), 7.12 (td, $^{3}J_{HH}$ = 6.2 Hz, $^{4}J_{HF}$ = 3.9 Hz, 1H, NH), 5.08 (dq, $^{2}J_{HF}$ = 50.0 Hz, $^{3}J_{HH}$ = 6.8 Hz, 1H, CH), 4.47, 4.43 (2 x dd, $^{2}J_{HH}$ = 15.0 Hz, $^{3}J_{HH}$ = 6.2 Hz, 2H, CH_2), 1.58 (dd, $^{3}J_{HF}$ = 25.0 Hz, $^{3}J_{HH}$ = 6.8 Hz, 3H, CH_3).
^{19}F NMR (471 MHz, CD_2Cl_2, –80 ºC) δ: -182.52 (dqd, $^{2}J_{HF}$ = 50.0 Hz, $^{3}J_{HF}$ = 25.0 Hz, $^{4}J_{HF}$ = 3.9 Hz). **^{19}F NMR** (471 MHz, CD_2Cl_2, –80 ºC) not decoupled δ: -182.52.

Concentration = 50 mM **(¼ initial concentration)**

^{1}H NMR (500 MHz, CD_2Cl_2, –80 ºC) δ: 7.60 – 7.15 (m, 5H, ArH), 7.01 (td, $^{3}J_{HH}$ = 6.1 Hz, $^{4}J_{HF}$ = 4.2 Hz, 1H, NH), 5.11 (dq, $^{2}J_{HF}$ = 49.5 Hz, $^{3}J_{HH}$ = 6.8 Hz, 1H, CH), 4.65 – 4.30 (m, 2H, CH_2), 1.60 (dd, $^{3}J_{HF}$ = 25.1 Hz, $^{3}J_{HH}$ = 6.8 Hz, 3H, CH_3).
^{19}F NMR (471 MHz, CD_2Cl_2, –80 ºC) δ: -182.52 (dqd, $^{2}J_{HF}$ = 49.5 Hz, $^{3}J_{HF}$ = 25.1 Hz, $^{4}J_{HF}$ = 4.2 Hz). **^{19}F NMR** (471 MHz, CD_2Cl_2, –80 ºC) not decoupled δ: -182.52.

Concentration = 12.5 mM **(1/16 initial concentration)**

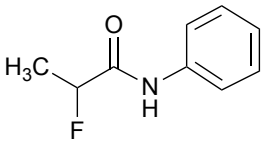
^{1}H NMR (500 MHz, CD_2Cl_2, –80 ºC) δ: 7.50 – 7.24 (m, 5H, ArH), 6.95 (td, $^{3}J_{HH}$ = 6.1 Hz, $^{4}J_{HF}$ = 4.2 Hz, 1H, NH), 5.13 (dq, $^{2}J_{HF}$ = 50.0 Hz, $^{3}J_{HH}$ = 6.8 Hz, 1H, CH), 4.59 – 4.40 (m, 2H, CH_2), 1.61 (dd, $^{3}J_{HF}$ = 25.2 Hz, $^{3}J_{HH}$ = 6.8 Hz, 3H, CH_3).
^{19}F NMR (471 MHz, CD_2Cl_2, –80 ºC) δ: -182.51 (dqd, $^{2}J_{HF}$ = 50.0 Hz, $^{3}J_{HF}$ = 25.2 Hz, $^{4}J_{HF}$ = 4.2 Hz). **^{19}F NMR** (471 MHz, CD_2Cl_2, –80 ºC) not decoupled δ: -182.51.

Concentration = 3.1 mM **(1/64 initial concentration)**

^{1}H NMR (500 MHz, CD_2Cl_2, –80 ºC) δ: 7.42 – 7.06 (m, 5H), 6.93 (td, $^{3}J_{HH}$ = 6.0 Hz, $^{4}J_{HF}$ = 4.3 Hz, 1H, NH), 5.05 (dq, $^{2}J_{HF}$ = 50.0 Hz, $^{3}J_{HH}$ = 6.8 Hz, 1H, CH), 4.55 – 4.31 (m, 2H, CH_2), 1.53 (dd, $^{3}J_{HF}$ = 25.1 Hz, 6.8 Hz, 3H, CH_3).
^{19}F NMR (471 MHz, CD_2Cl_2, –80 ºC) δ: -182.51 (dqd, $^{2}J_{HF}$ = 50.0 Hz, $^{3}J_{HF}$ = 25.1 Hz, $^{4}J_{HF}$ = 4.3 Hz). **^{19}F NMR** (471 MHz, CD_2Cl_2, –80 ºC) not decoupled δ: -182.51.

Concentration = 0.8 mM **(1/256 initial concentration)**

^{1}H NMR (500 MHz, CD_2Cl_2, –80 ºC) δ: 7.44 – 7.05 (m, 5H, ArH), 6.92 (br s, 1H, NH), 5.05 (dd, $^{2}J_{HF}$ = 50.0 Hz, $^{3}J_{HH}$ = 6.8 Hz, 1H, CH), 4.52 – 4.33 (m, 2H, CH_2), 1.53 (dd, $^{3}J_{HF}$ = 25.2 Hz, $^{3}J_{HH}$ = 6.8 Hz, 3H, CH_3).
^{19}F NMR (471 MHz, CD_2Cl_2, –80 ºC) δ: -182.51 (dqd, $^{2}J_{HF}$ = 50.0 Hz, 25.2, $^{4}J_{HF}$ = 4.3 Hz). **^{19}F NMR** (471 MHz, CD_2Cl_2, –80 ºC) not decoupled δ: -182.51.



3

Initial concentration = 200 mM

^{1}H NMR (500 MHz, CD_2Cl_2, –80 ºC) δ: 8.34 (br s, 1H, NH), 7.75 – 7.54 (m, 2H, ArH), 7.48 – 7.28 (m, 2H, ArH), 7.27 – 7.05 (m, 1H, ArH), 5.19 (dq, $^{2}J_{HF}$ = 50.0 Hz, $^{3}J_{HH}$ = 6.8 Hz, 1H, CH), 1.66 (dd, $^{3}J_{HF}$ = 25.2 Hz, $^{3}J_{HH}$ = 6.8 Hz, 3H, CH_3).
^{19}F NMR (471 MHz, CD_2Cl_2, –80 ºC) δ: -180.36 (dqd, $^{2}J_{HF}$ = 50.0 Hz, $^{3}J_{HF}$ = 25.2 Hz, $^{4}J_{HF}$ = 6.2 Hz).

Concentration = 50 mM **(¼ initial concentration)**

^{1}H NMR (500 MHz, CD_2Cl_2, –80 ºC) δ: 8.26 (d, $^{4}J_{HF}$ = 6.5 Hz, 1H, NH), 7.70 – 7.54 (m, 2H, ArH), 7.48 – 7.31 (m, 2H, ArH), 7.26 – 7.12 (m, 1H, ArH), 5.19 (dq, $^{2}J_{HF}$ = 50.0 Hz, $^{3}J_{HH}$ = 6.9 Hz, 1H, CH), 1.66 (dd, $^{3}J_{HF}$ = 25.2 Hz, $^{3}J_{HH}$ = 6.9 Hz, 3H, CH_3).
^{19}F NMR (471 MHz, CD_2Cl_2, –80 ºC) δ: -180.36 (dqd, $^{2}J_{HF}$ = 50.0 Hz, $^{3}J_{HF}$ = 25.2 Hz, $^{4}J_{HF}$ = 6.5 Hz).

Concentration = 12.5 mM **(1/16 initial concentration)**

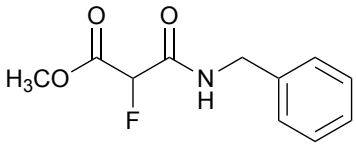
^{1}H NMR (500 MHz, CD_2Cl_2, –80 ºC) δ: 8.23 (d, $^{4}J_{HF}$ = 6.5 Hz, 1H, NH), 7.71 – 7.54 (m, 2H, ArH), 7.40 (td, $^{3}J_{HH}$ = 7.5 Hz, $^{4}J_{HH}$ = 1.5 Hz, 2H, ArH), 7.20 (tt, $^{3}J_{HH}$ = 7.5 Hz, $^{4}J_{HH}$ = 1.5 Hz, 1H, ArH), 5.19 (dq, $^{2}J_{HF}$ = 50.0 Hz, $^{3}J_{HH}$ = 6.9 Hz, 1H, CH), 1.67 (dd, $^{3}J_{HF}$ = 25.2 Hz, $^{3}J_{HH}$ = 6.9 Hz, 3H, CH_3).
^{19}F NMR (471 MHz, CD_2Cl_2, –80 ºC) δ: -180.35 (dqd, $^{2}J_{HF}$ = 50.0 Hz, $^{3}J_{HF}$ = 25.2 Hz, $^{4}J_{HF}$ = 6.5 Hz).

Concentration = 3.1 mM **(1/64 initial concentration)**

^{1}H NMR (500 MHz, CD_2Cl_2, –80 ºC) δ: 8.22 (d, $^{4}J_{HF}$ = 6.5 Hz, 1H, NH), 7.64 (dd, $^{3}J_{HH}$ = 8.0 Hz, $^{4}J_{HH}$ = 1.0 Hz, 2H, ArH), 7.48-7.30 (m, 2H, ArH), 7.20 (tt, $^{3}J_{HH}$ = 8.0 Hz, $^{4}J_{HH}$ = 1.0 Hz, 1H, ArH), 5.19 (dq, $^{2}J_{HF}$ = 50.0 Hz, $^{3}J_{HH}$ = 6.9 Hz, 1H, CH), 1.67 (dd, $^{3}J_{HF}$ = 25.2 Hz, $^{3}J_{HH}$ = 6.9 Hz, 3H, CH_3).
^{19}F NMR (471 MHz, CD_2Cl_2, –80 ºC) δ: -180.35 (dqd, $^{2}J_{HF}$ = 50.0 Hz, $^{3}J_{HF}$ = 25.2 Hz, $^{4}J_{HF}$ = 6.5 Hz).

Concentration = 0.8 mM **(1/256 initial concentration)**

^{1}H NMR (500 MHz, CD_2Cl_2, –80 ºC) δ: 8.22 (d, $^{4}J_{HF}$ = 6.5 Hz, 1H, NH), 7.75 – 7.55 (m, 2H, ArH), 7.48 – 7.32 (m, 2H, ArH), 7.27 – 7.12 (m, 1H, ArH), 5.19 (dq, $^{2}J_{HF}$ = 50.0 Hz, $^{3}J_{HH}$ = 6.9 Hz, 1H, CH), 1.67 (dd, $^{3}J_{HF}$ = 25.2 Hz, $^{3}J_{HH}$ = 6.9 Hz, 3H, CH_3).
^{19}F NMR (471 MHz, CD_2Cl_2, –80 ºC) δ: -180.34 (dqd, $^{2}J_{HF}$ = 50.0 Hz, $^{3}J_{HF}$ = 25.2 Hz, $^{4}J_{HF}$ = 6.5 Hz).



4

Initial concentration = 200 mM

^{1}H NMR (500 MHz, CD_2Cl_2, –80 ºC) δ: 7.34-7.18 (m, 5H, ArH), 7.20 (br s, 1H, NH), 5.36 (d, $^{2}J_{HF}$ = 48.3 Hz, 1H, CH), 4.46, 4.33 (2 x dd, $^{2}J_{HH}$ = 14.9 Hz, $^{3}J_{HH}$ = 6.0 Hz, 2H, CH_2), 3.78 (s, 3H, OCH_3).

^{19}F NMR (471 MHz, CD_2Cl_2, –80 ºC) δ: –193.71 (dd, $^{2}J_{HF}$ = 48.3 Hz, $^{4}J_{HF}$ = 2.5 Hz).

***Concentration = 50 mM* (¼ initial concentration)**

^{1}H NMR (500 MHz, CD_2Cl_2, –80 ºC) δ: 7.34-7.20 (m, 5H ArH), 7.08 (td, $^{3}J_{HF}$ = 6.0 Hz, $^{4}J_{HF}$ = 2.6 Hz, 1H, NH), 5.37 (d, $^{2}J_{HF}$ = 48.3 Hz, 1H, CH), 4.47, 4.34 (2 x dd, $^{2}J_{HH}$ = 14.9 Hz, $^{3}J_{HH}$ = 6.0 Hz, 2H, CH_2), 3.80 (s, 3H, OCH_3).

***Concentration = 12.5 mM* (1/16 initial concentration)**

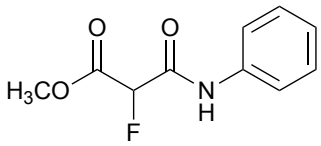
^{1}H NMR (500 MHz, CD_2Cl_2, –80 ºC) δ: 7.35-7.20 (m, 5H ArH), 6.96 (td, $^{3}J_{HH}$ = 6.0 Hz, $^{4}J_{HF}$ = 2.7 Hz, 1H), 5.38 (d, $^{2}J_{HF}$ = 48.3 Hz, 1H, CH), 4.48, 4.35 (2 x dd, $^{2}J_{HH}$ = 14.9 Hz, $^{3}J_{HH}$ = 6.0 Hz, 2H, CH_2), 3.81 (s, 3H, OCH_3).

***Concentration = 3.1 mM* (1/64 initial concentration)**

^{1}H NMR (500 MHz, CD_2Cl_2, –80 ºC) δ: 7.35-7.23 (5H ArH), 6.90 (td, $^{3}J_{HH}$ = 5.9 Hz, $^{4}J_{HF}$ = 2.7 Hz, 1H, NH), 5.39 (d, $^{2}J_{HF}$ = 48.3 Hz, 1H, CH), 4.49, 4.35 (2 x dd, $^{2}J_{HH}$ = 14.9 Hz, $^{3}J_{HH}$ = 6.0 Hz, 2H, CH_2), 3.81 (s, 3H, OCH_3).

***Concentration = 0.8 mM* (1/256 initial concentration)**

^{1}H NMR (500 MHz, CD_2Cl_2, –80 ºC) δ: 7.37-7.20 (m, 5H ArH), 6.88 (td, $^{3}J_{HH}$ = 5.9 Hz, $^{4}J_{HF}$ = 2.7 Hz, 1H, NH), 5.39 (d, $^{2}J_{HF}$ = 48.4 Hz, 1H, CH), 4.49, 4.36 (2 x dd, $^{2}J_{HH}$ = 15.0 Hz, $^{3}J_{HH}$ = 5.5 Hz, 2H, CH_2), 3.82 (s, 3H, OCH_3).



5

Initial concentration = 200 mM

^{1}H NMR (500 MHz, CD_2Cl_2, –80 ºC) δ: 8.64 (d, $^4J_{HF}$ = 3.9 Hz, 1H, NH), 7.64-7.47 (m, 2H, ArH), 7.33 (dd, $^3J_{HH}$ = 8.5 Hz, $^3J_{HH}$ = 7.3 Hz, 2H, ArH), 7.22-7.11 (m, 1H, ArH), 5.51 (d, $^2J_{HF}$ = 48.5 Hz, 1H), 3.81 (s, 3H, OCH_3).

***Concentration = 50 mM* (¼ initial concentration)**

^{1}H NMR (500 MHz, CD_2Cl_2, –80 ºC) δ: 8.42 (d, $^4J_{HF}$ = 4.2 Hz, 1H, NH), 7.60-7.50 (m, 2H, ArH), 7.40-7.28 (m, 2H, ArH), 7.20-7.10 (m, 1H, ArH), 5.49 (d, $^2J_{HF}$ = 48.2 Hz, 1H, CH), 3.82 (s, 3H, OCH_3).

***Concentration = 12.5 mM* (1/16 initial concentration)**

^{1}H NMR (500 MHz, CD_2Cl_2, –80 ºC) δ: 8.28 (d, $^4J_{HF}$ = 4.2 Hz, 1H, NH), 7.74-7.49 (m, 2H), 7.34 (dd, $^3J_{HH}$ = 8.5, $^3J_{HH}$ = 7.3 Hz, 2H), 7.23-7.07 (m, 1H), 5.48 (d, $^2J_{HF}$ = 48.2 Hz, 1H), 3.83 (s, 3H, OCH_3).

***Concentration = 3.1 mM* (1/64 initial concentration)**

^{1}H NMR (500 MHz, CD_2Cl_2, –80 ºC) δ: 8.21 (d, $^4J_{HF}$ = 4.3 Hz, 1H, NH), 7.60-7.48 (m, 2H, ArH), 7.40-7.28 (m, 2H, ArH), 7.20-7.10 (m, 1H, ArH), 5.47 (d, $^2J_{HF}$ = 48.2 Hz, 1H, CH), 3.83 (s, 3H, OCH_3).

***Concentration = 0.8 mM* (1/256 initial concentration)**

^{1}H NMR (500 MHz, CD_2Cl_2, –80 ºC) δ: 8.18 (d, $^4J_{HF}$ = 4.3 Hz, 1H, NH), 7.65-7.41 (m, 2H, ArH), 7.41-7.25 (m, 2H, ArH), 7.21-7.11 (m, 1H, ArH), 5.47 (d, $^2J_{HF}$ = 48.3 Hz, 1H), 3.83 (s, 3H, OCH_3).

Determination of the K_d of dimerization

The values of the chemical shifts of the NH amide proton (δ_{NH}) at concentrations of 0.8-200 mM were utilized for the determination of the dissociation constant.

Entry	1 (Me)	2 (Bn)	3 (Ph)	4 (Bn/ester)	5 (Ph/ester)
[ ] / mM	δ_{NH}	δ_{NH}	δ_{NH}	δ_{NH}	δ_{NH}
0.8	6.56	6.92	8.22	6.88	8.18
3.1	6.56	6.93	8.22	6.90	8.21
12.5	6.60	6.95	8.23	6.96	8.28
50	6.71	7.01	8.26	7.08	8.42
200	6.94	7.12	8.34	7.20	8.64

The equation used to calculate the dissociation constant (K_D) for the monomer/dimer equilibrium of **1**–**5** was derived as follows:[9]

A self-associating system where a molecule dimerizes can be described as:

$$\mathrm{M} + \mathrm{M} \rightleftarrows \mathrm{D}$$

M = monomer
D = dimer

(1) $$\mathrm{K_D} = \frac{[\mathrm{M}]^2}{[\mathrm{D}]}$$

[M] = concentration of the monomer in mol/L
[D] = concentration of the monomer in mol/L

From the mass balance, the total concentration of the monomer, $[M]_0$, can be expressed as:

(2) $$[M]_0 = [\mathrm{M}] + 2[\mathrm{D}]$$

The combination of (1) and (2) leads to:

(3) $$\mathrm{K_D} = \frac{[\mathrm{M}]^2}{[\mathrm{D}]} = \frac{([\mathrm{M}]_0 - 2[\mathrm{D}])^2}{[\mathrm{D}]}$$

Rearrangement yields the following quadratic equation:

(4) $$4[\mathrm{D}]^2 - (4[\mathrm{M}]_0 + \mathrm{K_D})[\mathrm{D}] + [\mathrm{M}]_0{}^2 = 0$$

Solving the quadratic equation for [D] yields:

(5) $$[D] = \frac{4[M]_0 + K_D - \sqrt{K_D{}^2 + 8[M]_0 K_D}}{8}$$

The observed chemical shift can be expressed as:

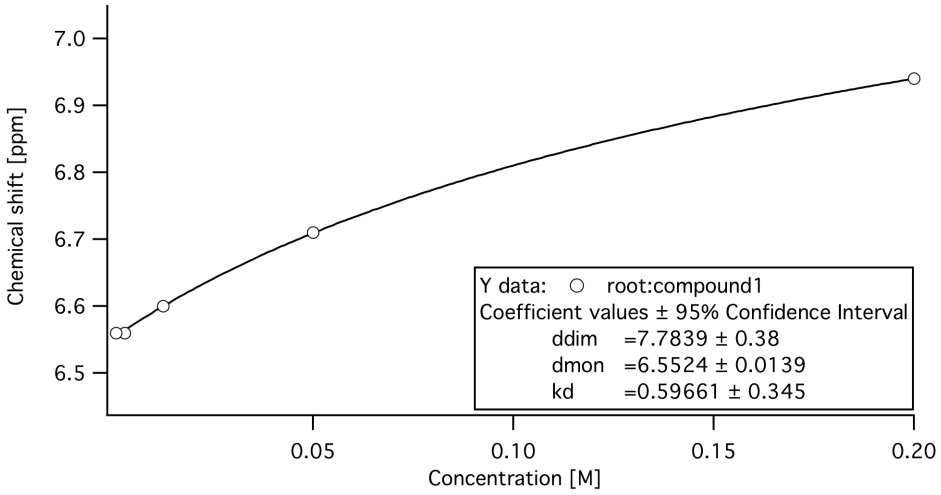
(6) $$\delta_{obs} = \delta_M + 2(\delta_D - \delta_M)\frac{[D]}{[M]_0}$$

Combinination of (5) and (6) yields:

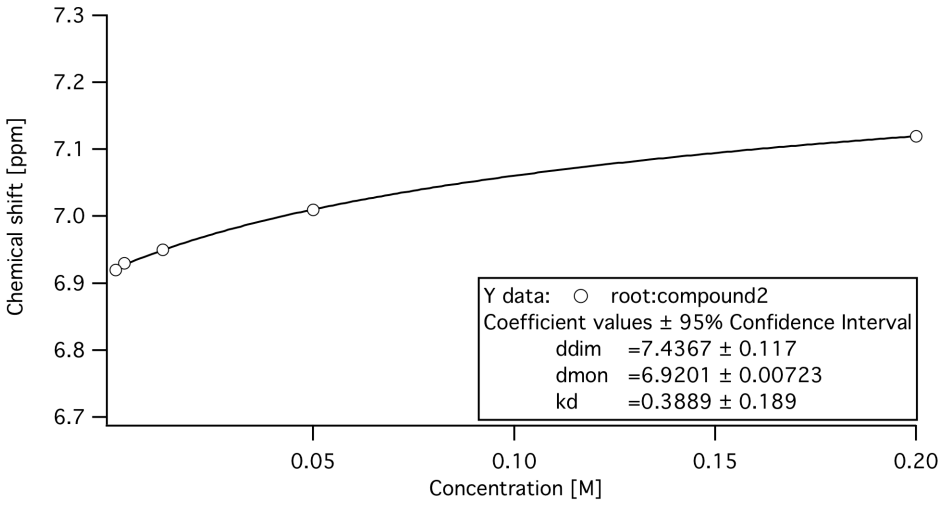
(7) $$\delta_{obs} = \delta_M + \frac{\delta_D - \delta_M}{[M]_0} \cdot \frac{4[M]_0 + K_D - \sqrt{K_D{}^2 + 8[M]_0 K_D}}{4}$$

Equation (7) was used to fit the data using the program Igor Pro (version 6.37).

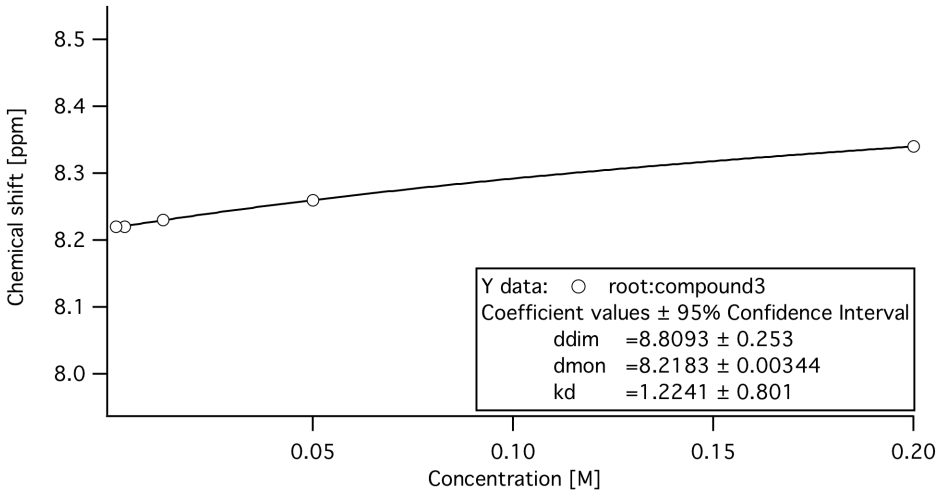
Compound 1



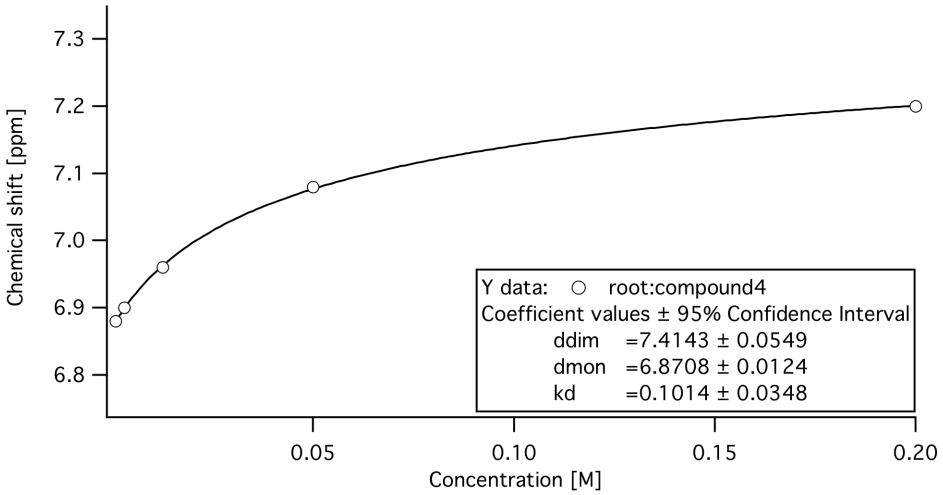
Compound 2



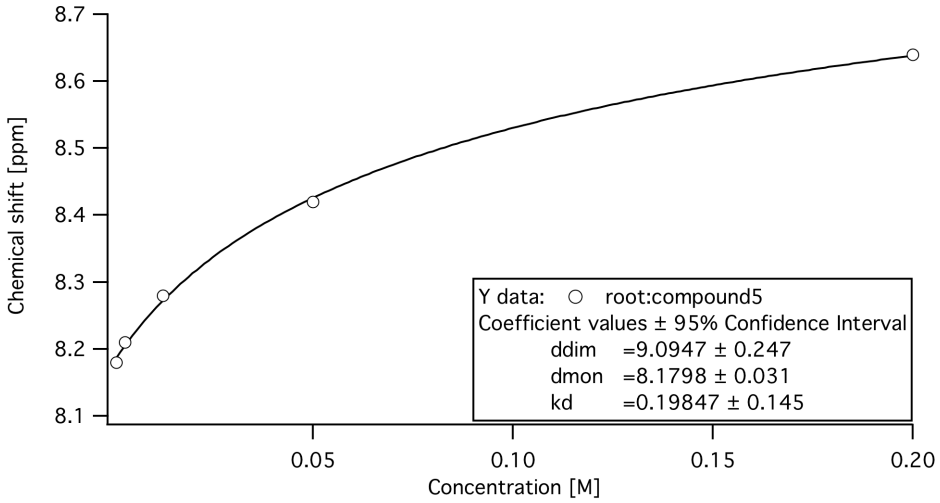
Compound 3



Compound 4



Compound 5



Data fitting was also performed using the online fitting program BindFit v.0.5[10, 11] using the model called "NMR Dimer Aggregation". The K_D values obtained using equation (3) were reproduced using BindFit.

Table 3. K_D values (mM) obtained with Igor (+/- 95% confidence interval) and Bindfit.

K_D / mM	1 (Me)	2 (Bn)	3 (Ph)	4 (Bn/ester)	5 (Ph/ester)
Igor	597 +/- 345	389 +/- 189	1224 +/- 801	101 +/- 35	199 +/- 145
BindFit	597 +/- 36	387 +/- 22	1222 +/- 47	106 +/- 12	197 +/- 28

Fitting results from Bindfit – Dimerization model (Nealder-Mead algorithm)

K_a = association (dimerization) constant; K_d = dissociation constant

Compound 1: http://app.supramolecular.org/bindfit/view/245fc448-cdef-4e0f-b5b5-3ab8590b8925

K_e	K_e error (%)	K_a / M	K_a error (%)	K_d / M	K_d / mM	K_d error / mM
3.3512	11.9948	1.6756	5.9974	0.5968	596.8	35.79

Compound 2: http://app.supramolecular.org/bindfit/view/ce86392c-603c-4878-a8b2-905b19cb2645

K_e	K_e error (%)	K_a / M	K_a error (%)	K_d / M	K_d / mM	K_d error / mM
5.1629	11.1617	2.5814	5.5809	0.3874	387.4	21.62

Compound 3: http://app.supramolecular.org/bindfit/view/3a1d738e-410e-4d54-a261-9dea740f4e59

K_e	K_e error (%)	K_a / M	K_a error (%)	K_d / M	K_d / mM	K_d error / mM
1.6362	7.7434	0.8181	3.8717	1.2224	1222.4	47.33

Compound 4: http://app.supramolecular.org/bindfit/view/37df6e8f-2591-49f0-ad5a-a4febe0e0a42

K_e	K_e error (%)	K_a / M	K_a error (%)	K_d / M	K_d / mM	K_d error / mM
19.4919	23.84	9.746	11.92	0.1026	102.6	12.23

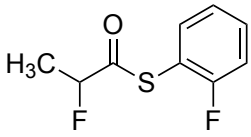
Compound 5: http://app.supramolecular.org/bindfit/view/bf378e34-cdf9-40c1-93af-f3a1a4d37e05

K_e	K_e error (%)	K_a / M	K_a error (%)	K_d / M	K_d / mM	K_d error / mM
10.1694	28.1889	5.0847	14.0944	0.1967	196.7	27.72

5 X-ray crystal structures

Single crystalline samples were measured on a Rigaku Oxford Diffraction XtaLAB Synergy-S Dualflex kappa diffractometer equipped with a Dectris Pilatus 300 HPAD detector and using microfocus sealed tube Cu-Kα radiation with mirror optics (λ = 1.54178 Å).
All measurements were carried out at 100K using an Oxford Cryosystems Cryostream 800 sample cryostat. Data were integrated using CrysAlisPro and corrected for absorption effects using a combination of empirical (ABSPACK) and numerical corrections.[12] The structures were solved using SHELXT[13] and refined by full-matrix least-squares analysis (SHELXL)[14,15] using the program package OLEX2.[16] Unless otherwise indicated below, all non-hydrogen atoms were refined anisotropically and hydrogen atoms were constrained to ideal geometries and refined with fixed isotropic displacement parameters (in terms of a riding model). All following ellipsoid plots are drawn at 50% probability.
CCDC 1884976 (**A**), 1884973 (**2**), 1884975 (**3**) and 1884974 (**4**) contain the supplementary crystallographic data for this paper, including structure factors and refinement instructions. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(1223)-336-033; e-mail: deposit@ccdc.cam.ac.uk), or via https://www.ccdc.cam.ac.uk/getstructures.
Compounds **A** and **2**-**4** crystallized from CH_2Cl_2 or CH_2Cl_2/*n*-hexane mixtures.
It is well known that X-ray crystal structures often cannot provide realistic X-H distances, and indeed free refinement yields too short bonds in all described structures. To obtain better geometrical parameters involving the proton positions, N-H bond lengths were restrained to an averaged reference value, based on neutron diffraction data, i.e. 1.019(1) Å in the temperature range 60 K < T < 140 K.[17] The resulting models were refined to convergence before determining contact distances and angles (Tables **4**-**6** at pp. S32, S34, and S36).

S-(2-Fluorophenyl) 2-fluoropropanethioate (A)



Bond precision: C-C = 0.0031 A Wavelength=1.54184

Cell: a=5.7309(1) b=15.2234(2) c=10.3215(1)
alpha=90 beta=94.292(1) gamma=90

Temperature: 100 K

	Calculated	Reported
Volume	897.96(2)	897.96(2)
Space group	P 21/c	P 1 21/c 1
Hall group	-P 2ybc	-P 2ybc
Moiety formula	C9 H8 F2 O S	C9 H8 F2 O S
Sum formula	C9 H8 F2 O S	C9 H8 F2 O S
Mr	202.21	202.21
Dx,g cm^{-3}	1.496	1.496
Z	4	4
Mu (mm-1)	3.156	3.156
F000	416.0	416.0
F000'	418.73	
h,k,lmax	7,19,13	7,19,13
Nref	1959	1915
Tmin,Tmax	0.716,0.825	0.620,1.000
Tmin'	0.559	

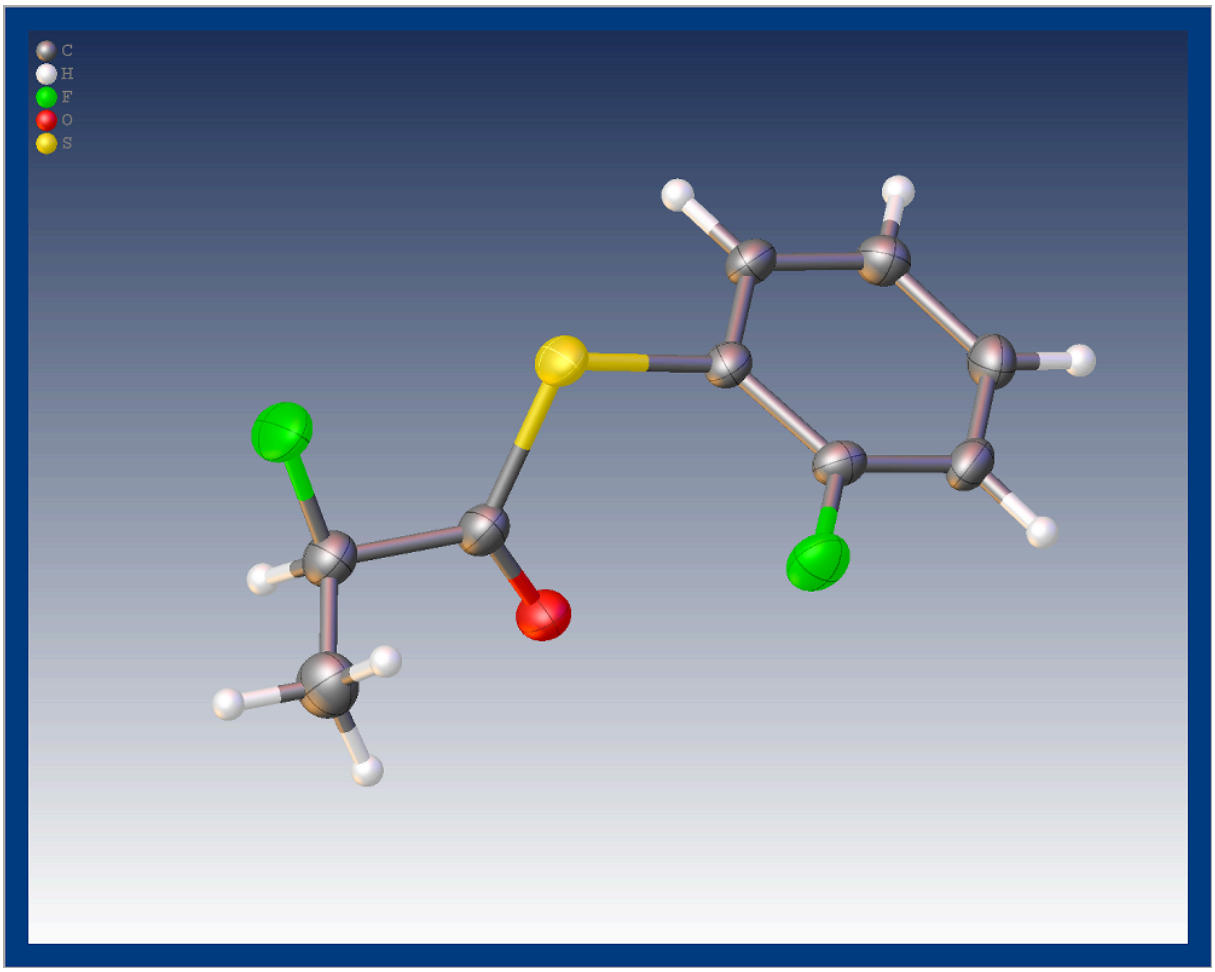
Correction method= # Reported T Limits: Tmin=0.620 Tmax=1.000

AbsCorr = MULTI-SCAN

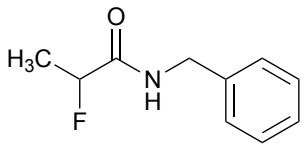
Data completeness= 0.978 Theta(max)= 79.623

R(reflections)= 0.0448(1843) wR2(reflections)= 0.1203(1915)

S = 1.098 Npar= 11


C
H
F
O
S

N-Benzyl-2-fluoropropanamide (2)



Bond precision: C-C = 0.0043 A Wavelength=1.54184

Cell:	a=5.7997(2)	b=7.8020(3)	c=10.7127(4)
	alpha=101.380(3)	beta=93.123(3)	gamma=94.168(3)

Temperature: 100 K

	Calculated	Reported
Volume	472.78(3)	472.78(3)
Space group	P 1	P 1
Hall group	P 1	P 1
Moiety formula	C10 H11 F N O	C10 H12 F N O
Sum formula	C10 H12 F N O	C10 H12 F N O
Mr	181.21	181.21
Dx,g cm^{-3}	1.273	1.273
Z	2	2
Mu (mm-1)	0.796	0.796
F000	192.0	192.0
F000'	192.64	
h,k,lmax	7,9,13	7,9,13
Nref	4128[2064]	3651
Tmin,Tmax	0.924,0.987	0.782,1.000
Tmin'	0.878	

Correction method= # Reported T Limits: Tmin=0.782 Tmax=1.000
AbsCorr = MULTI-SCAN

Data completeness= 1.77/0.88 Theta(max)= 79.974

R(reflections)= 0.0406(3115) wR2(reflections)= 0.1196(3651)

S = 1.060 Npar= 243

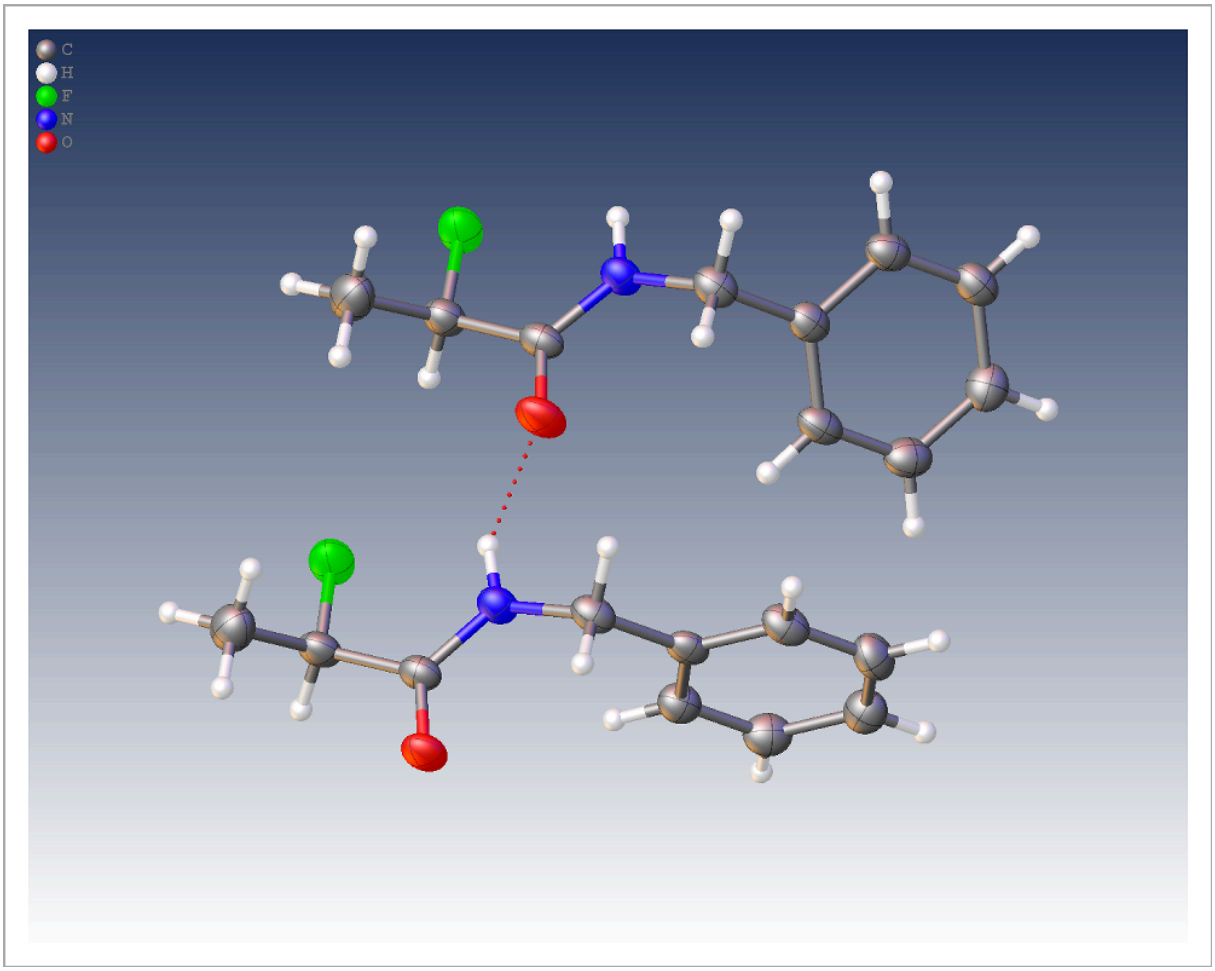
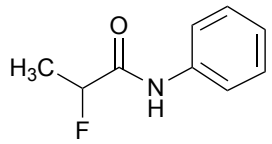


Table 4. Distances and angles for molecules **A** and **B** in the unit cell of the X-ray crystal structure of **2**.

Entry	**A**	**B**
H…F	2.21591(9)	2.23224(9)
N-H[a]	1.019	1.019
N…O(interm.)	2.78319(10)	2.779958(10)
H…O(interm.)	1.84759(7)	1.87379(7)
C-F	1.40686(5)	1.40402(5)
C=O	1.23504(5)	1.23513(5)
F…N	2.62229(12)	2.61224(12)
F-H-N	101.860(3)	101.164(3)
F-C-C=O amide (Θ)	-174.728(1)	-178.1521(1)
H-N-C=O	-177.955(1)	-176.832(1)

[a]The N-H distance is constrained to 1.019 Å according to neutron diffraction data in the temperature range 60 K < T < 140 K.[17]

2-Fluoro-N-phenylpropanamide (3)



Bond precision: C-C = 0.0032 A Wavelength=1.54184

Cell:	a=5.3093(1)	b=15.1016(2)	c=10.2968(2)
	alpha=90	beta=95.575(1)	gamma=90

Temperature: 100 K

	Calculated	Reported
Volume	821.68(2)	821.68(2)
Space group	P c	P 1 c 1
Hall group	-P 2yc	-P 2yc
Moiety formula	C9 H10 F N O	C9 H10 F N O
Sum formula	C9 H10 F N O	C9 H10 F N O
Mr	167.18	167.18
Dx,g cm^{-3}	1.351	1.351
Z	4	4
Mu (mm-1)	0.872	0.872
F000	352.0	352.0
F000'	353.21	
h,k,lmax	6,19,13	6,19,13
Nref	3561[1790]	3424
Tmin,Tmax	0.967,0.974	0.852,1.000
Tmin'	0.898	

Correction method= # Reported T Limits: Tmin=0.852 Tmax=1.000
AbsCorr = MULTI-SCAN

Data completeness= 1.91/0.96 Theta(max)= 79.498

R(reflections)= 0.0350(3172) wR2(reflections)= 0.0946(3424)

S = 1.094 Npar= 282

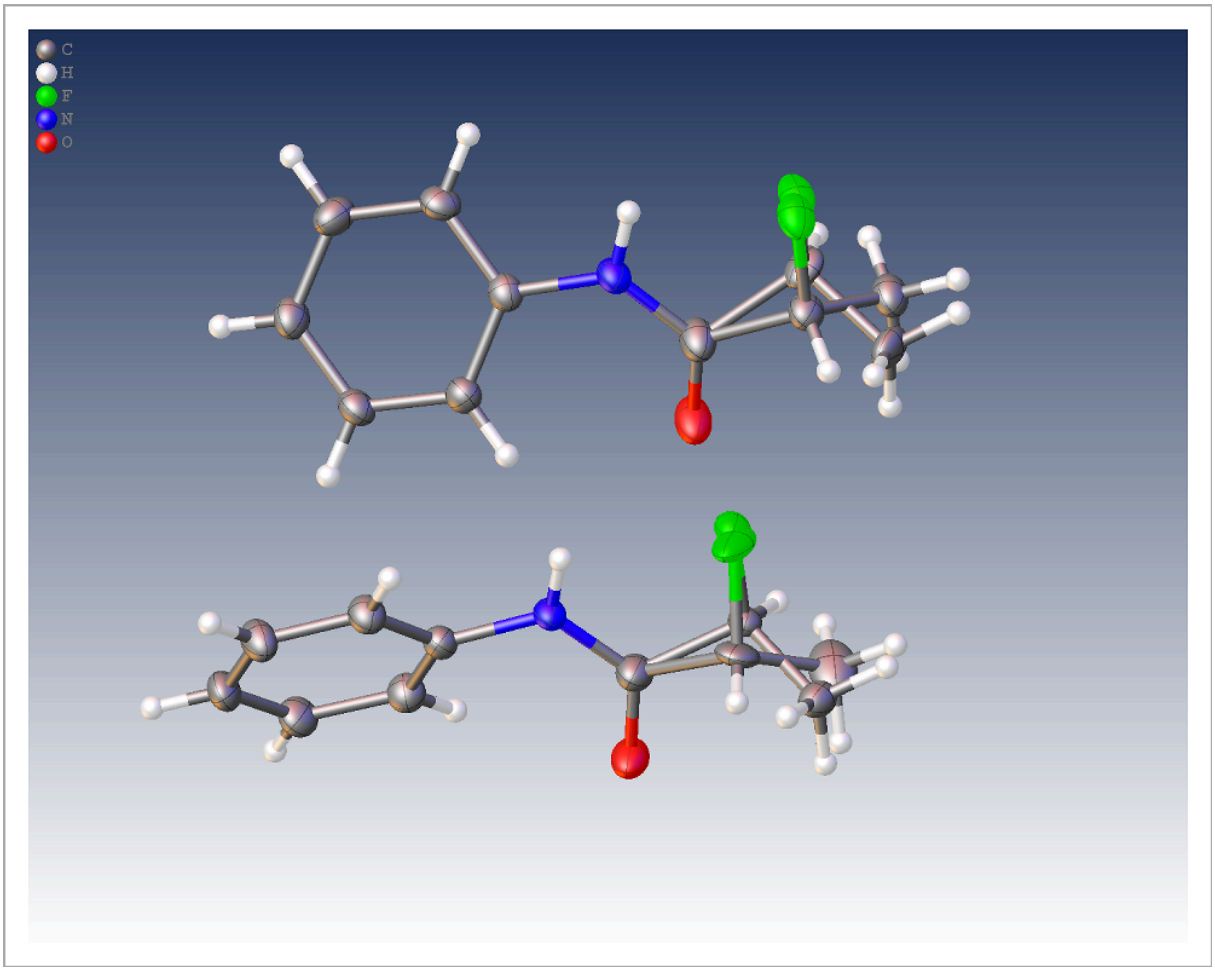


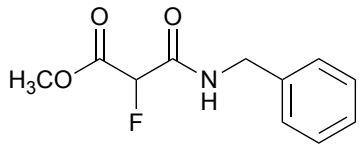
Table 5. Distances and angles for molecules **A** and **C** in the unit cell of the X-ray crystal structure of **3**. Values **B** and **D** taken from the less occupied part of the disorder within the CH_3CF moiety.

Entry	**A**	**B**	**C**	**D**
H…F	2.13329(4)[b]	2.16592(4)[b]	2.17476(4)[b]	2.09147(4)[b]
N-H[a]	1.019	1.019	1.019	1.019
N…O(interm.)	3.09035(6)		3.08714(6)	
H…O(interm.)	2.12911(4)		2.15147(4)	
C-F	1.41576(3)[b]	1.41161(2)[b]	1.41761(3)[b]	1.38348(2)[b]
C=O	1.21984(2)		1.22785(2)	
F…N	2.58482(5)[b]	2.62061(5)[b]	2.62377(5)[b]	2.57275(5)[b]
F-H-N	104.562(2)[b]	104.954(2)[b]	104.598(2)[b]	106.453(2)[b]
F-C-C=O amide (Θ)	-175.137(1)[b]	169.263(1)[b]	179.613(1)[b]	-169.369(1)[b]
H-N-C=O	172.476(1)		-169.071(1)	

[a]The N-H distance is constrained to 1.019 Å according to neutron diffraction data in the temperature range 60 K < T < 140 K.[17]

[b]Biased by soft restraints used in disorder refinement (SADI, RIGU).

Methyl 3-(benzylamino)-2-fluoro-3-oxopropanoate (4)



Bond precision: C-C = 0.0018 A Wavelength=1.54184

Cell: a=8.5328(1) b=10.2996(1) c=23.8575(3)
alpha=90 beta=95.575(1) gamma=90

Temperature: 100 K

	Calculated	Reported
Volume	2096.70(4)	2096.70(4)
Space group	P b c a	P b c a
Hall group	-P 2ac 2ab	-P 2ac 2ab
Moiety formula	C11 H12 F N O3	C11 H12 F N O3
Sum formula	C11 H12 F N O3	C11 H12 F N O3
Mr	225.22	225.22
Dx,g cm^{-3}	1.427	1.427
Z	8	8
Mu (mm-1)	0.984	0. 984
F000	944.0	944.0
F000’	947.47	
h,k,lmax	10,13,30	10,13,30
Nref	2292	2274
Tmin,Tmax	0.883,0.952	0.798,1.000
Tmin’	0.876	

Correction method= # Reported T Limits: Tmin=0.798 Tmax=1.000
AbsCorr = MULTI-SCAN

Data completeness= 0.992 Theta(max)= 80.370

R(reflections)= 0.0401(2123) wR2(reflections)= 0.1176(2274)

S = 1.069 Npar= 149

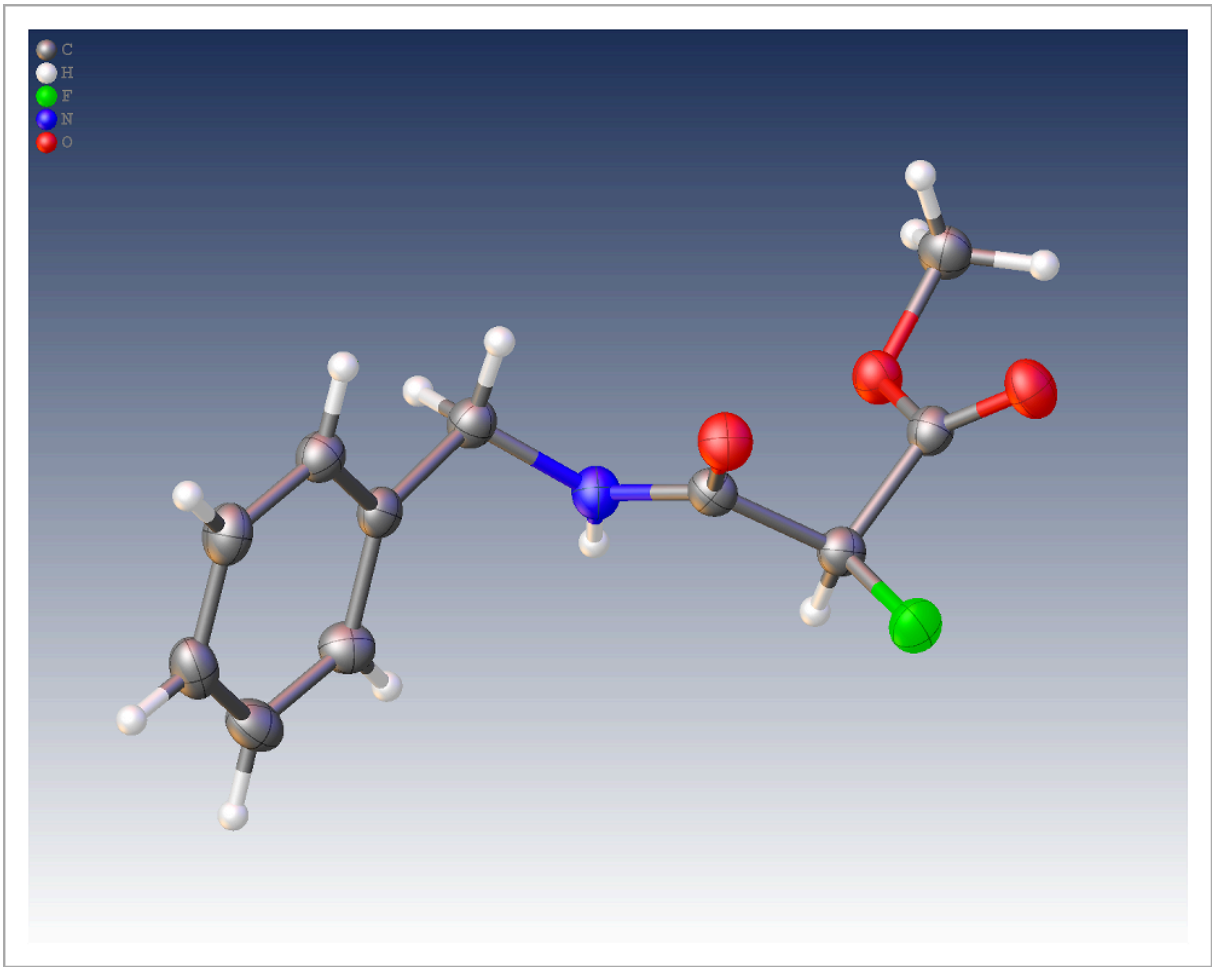


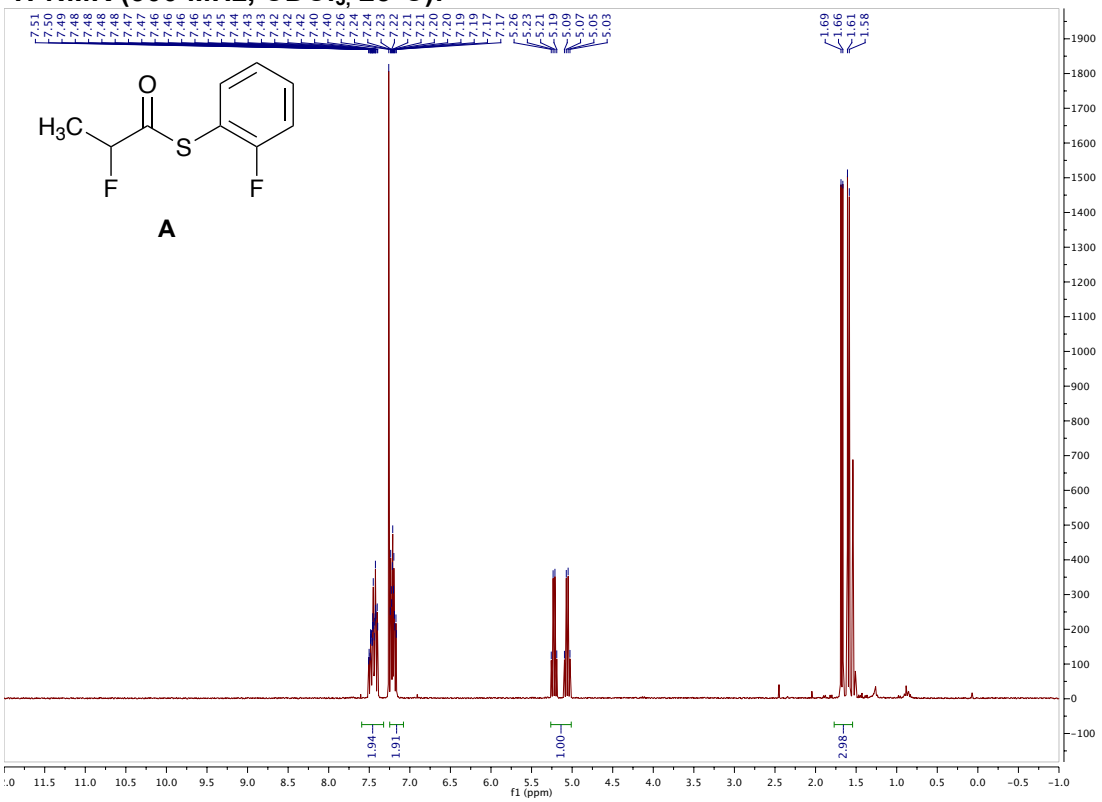
Table 6. Distances and angles of the X-ray crystal structure of **4**.

Entry	**Compound 4**
N-H[a]	1.019
N…O(interm.)	2.90343(2)
H…O(interm.)	1.95936(2)
C-F	1.38595(1)
C=O	1.23588(1)
F…N	-
F-H-N	-
F-C-C=O amide	42.259(1)
F-C-C=O ester	-16.618(1)
F-C-C-O ester	165.613(1)
H-N-C=O	-171.264(1)

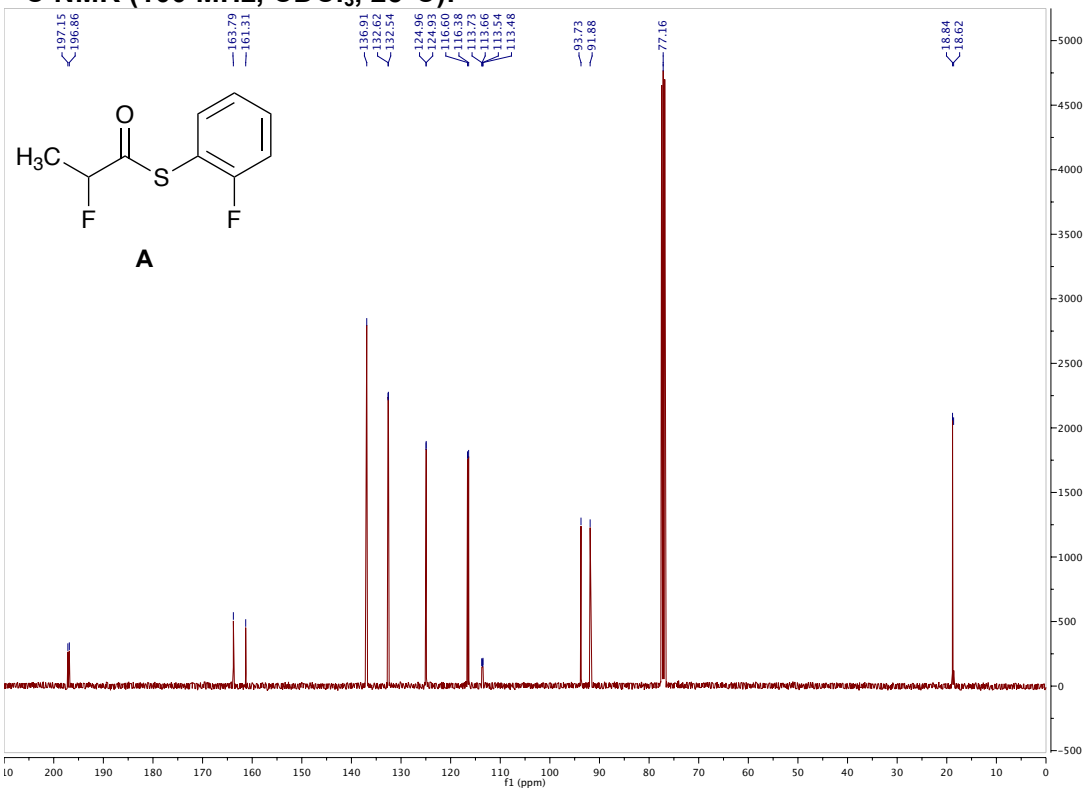
[a]The N-H distance is constrained to 1.019 Å according to neutron diffraction data in the temperature range 60 K < T < 140 K.[17]

6 NMR spectra

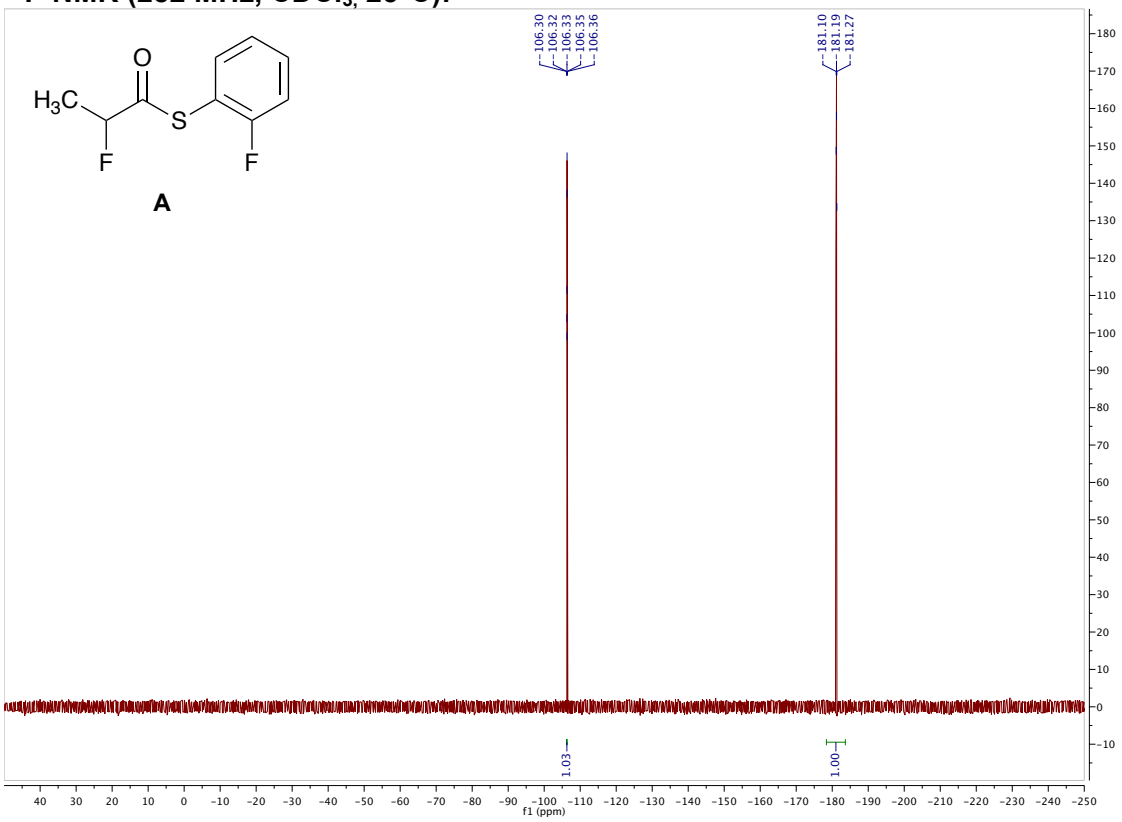
^{1}H-NMR (300 MHz, $CDCl_3$, 25°C):



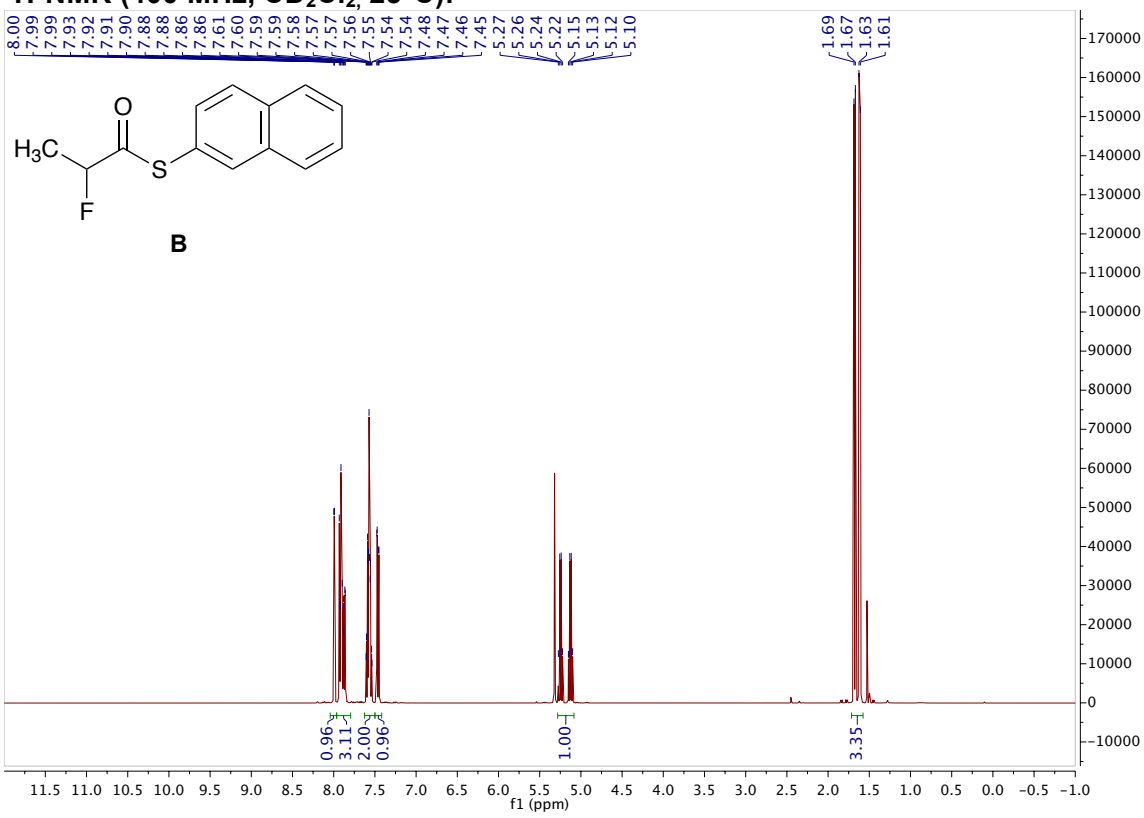
^{13}C NMR (100 MHz, $CDCl_3$, 25°C):



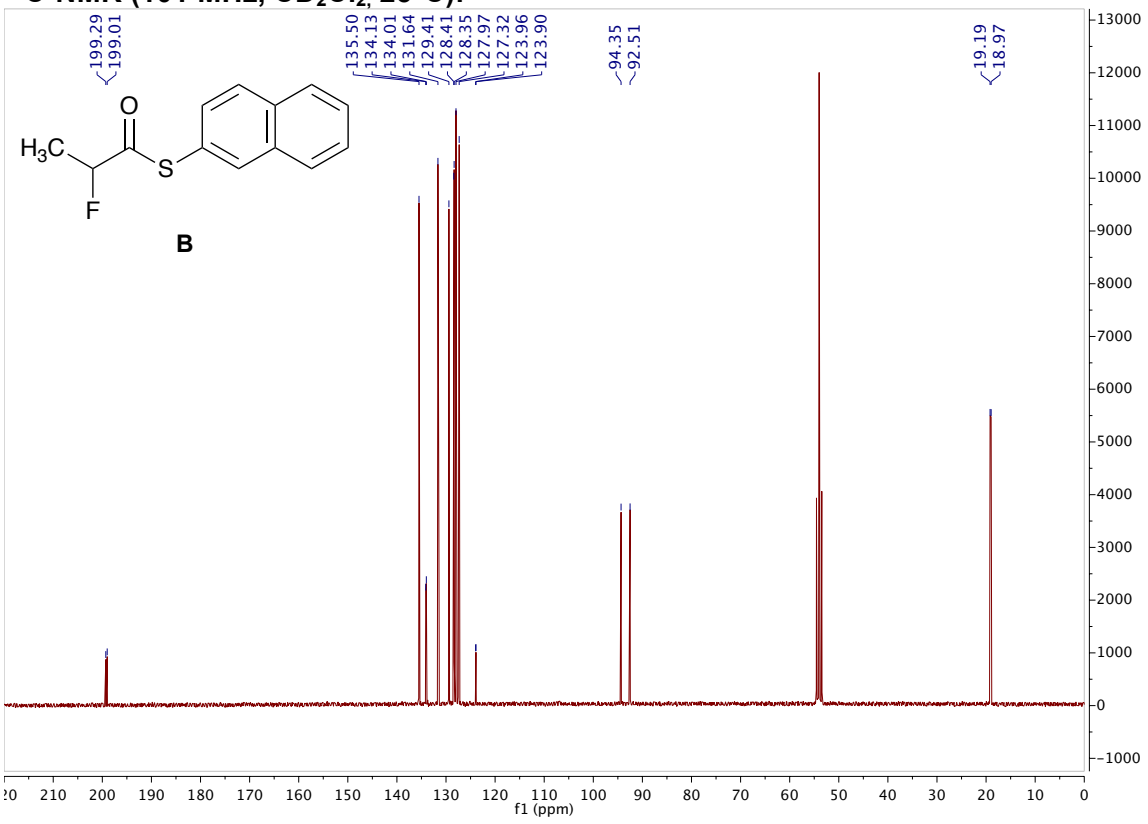
^{19}F-NMR (282 MHz, $CDCl_3$, 25°C):



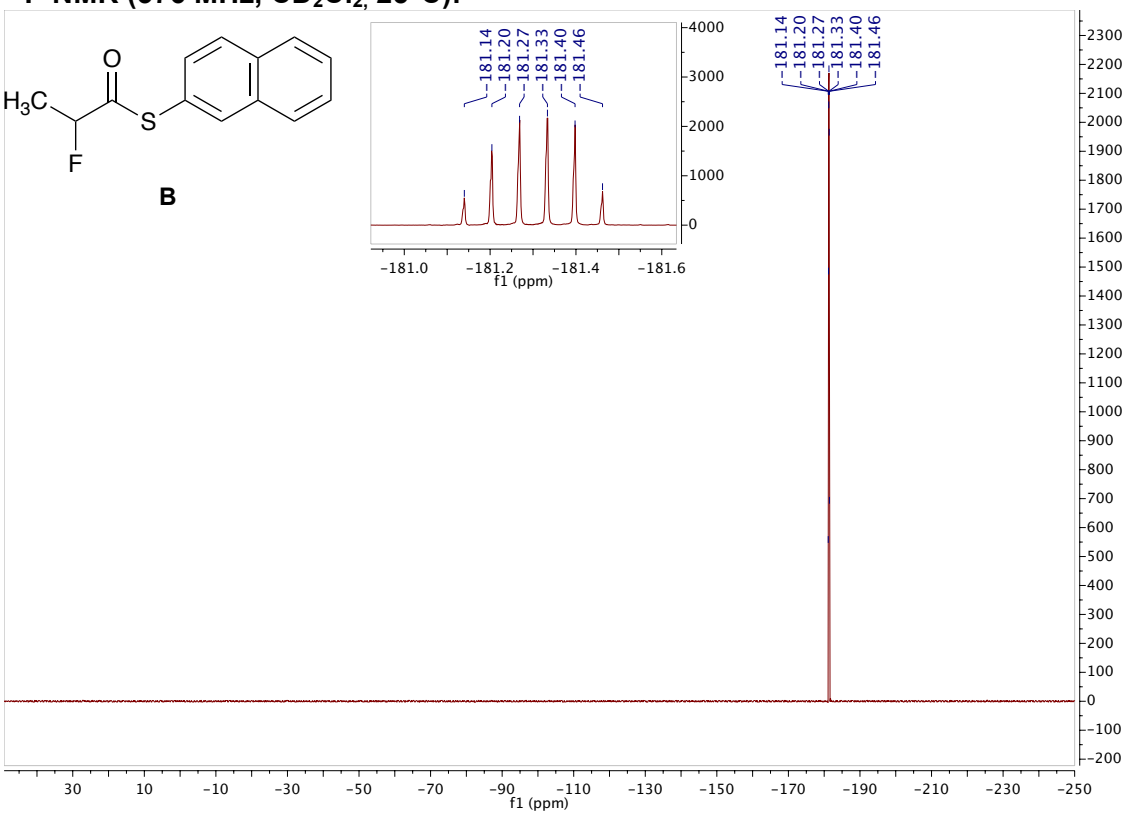
^{1}H-NMR (400 MHz, CD_2Cl_2, 25°C):



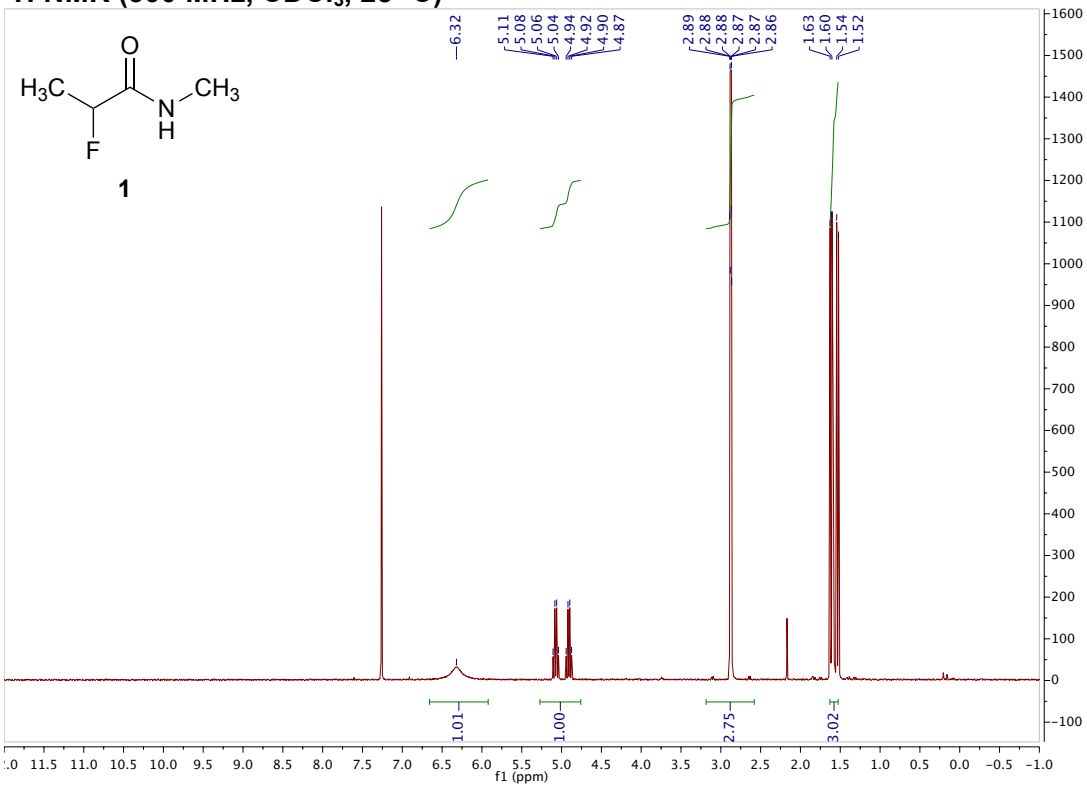
^{13}C-NMR (101 MHz, CD_2Cl_2, 25°C):



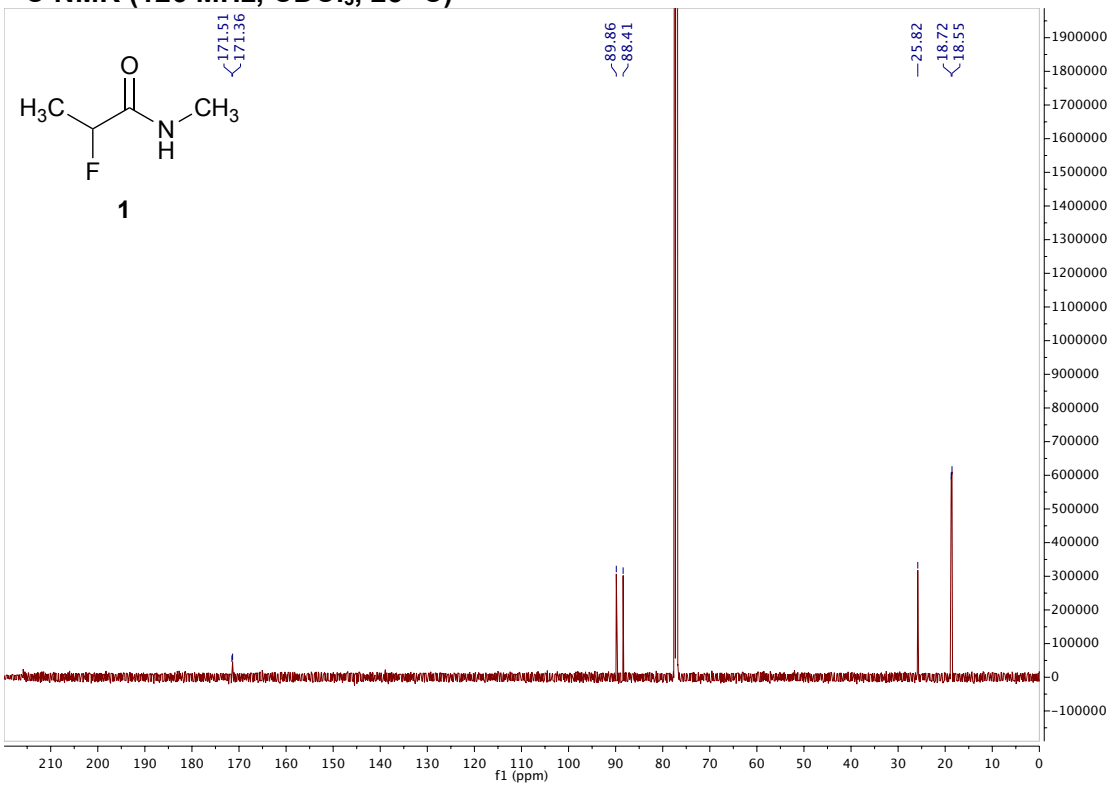
^{19}F-NMR (376 MHz, CD_2Cl_2, 25°C):



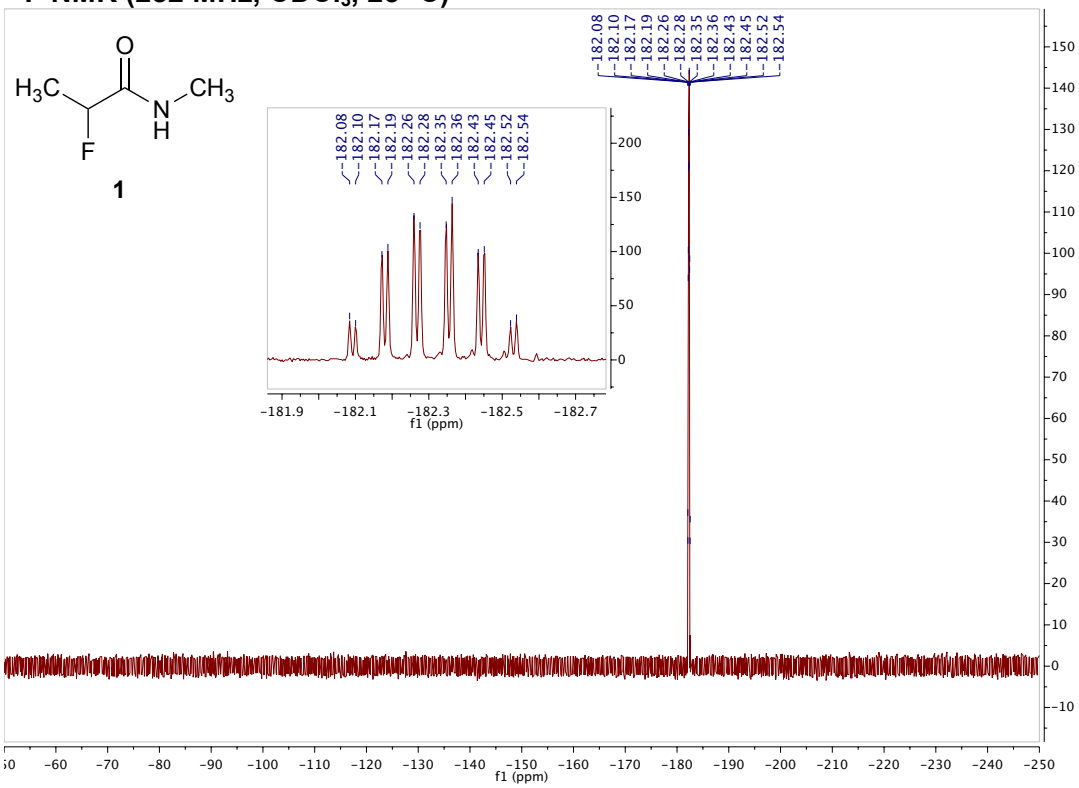
^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC)



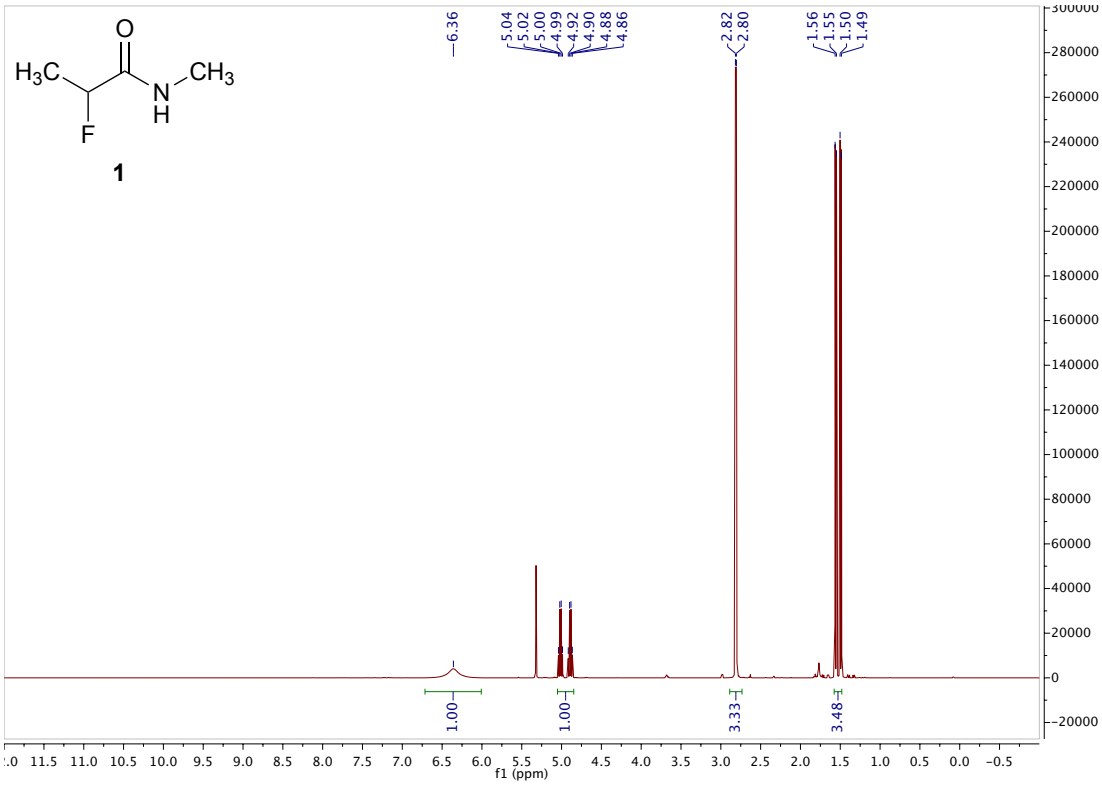
^{13}C NMR (126 MHz, $CDCl_3$, 25 ºC)



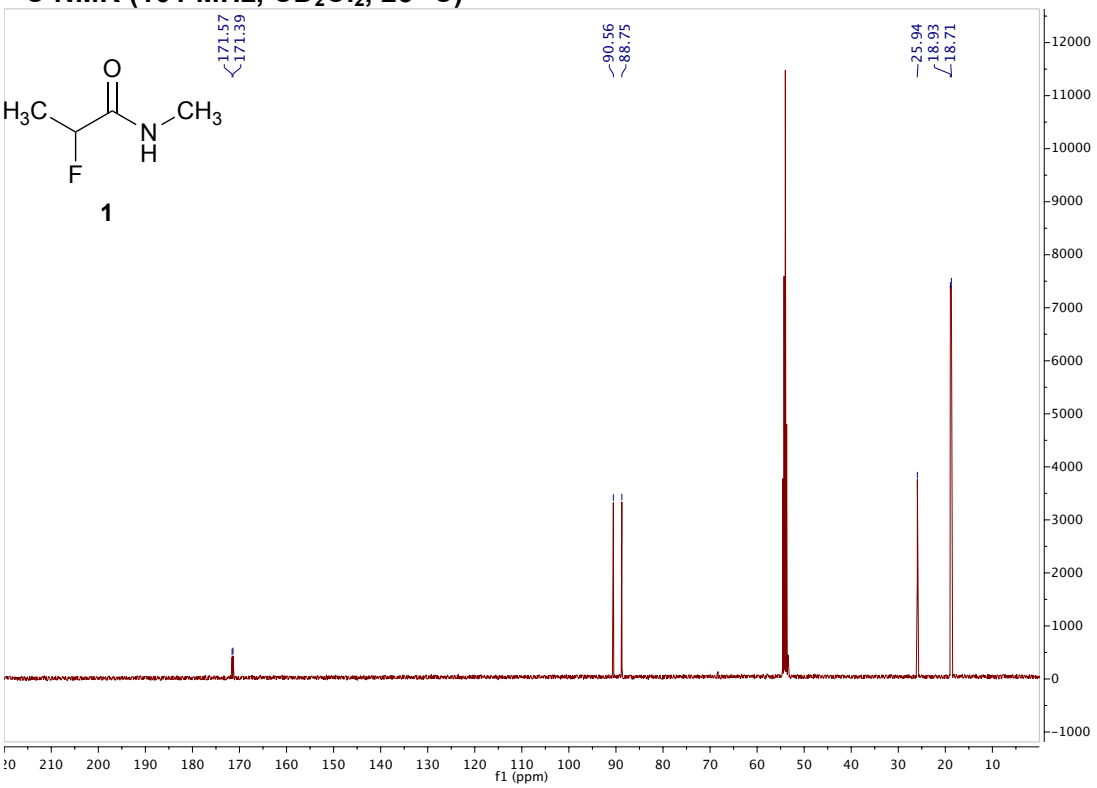
^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC)



^{1}H NMR (400 MHz, CD_2Cl_2, 25 ºC)

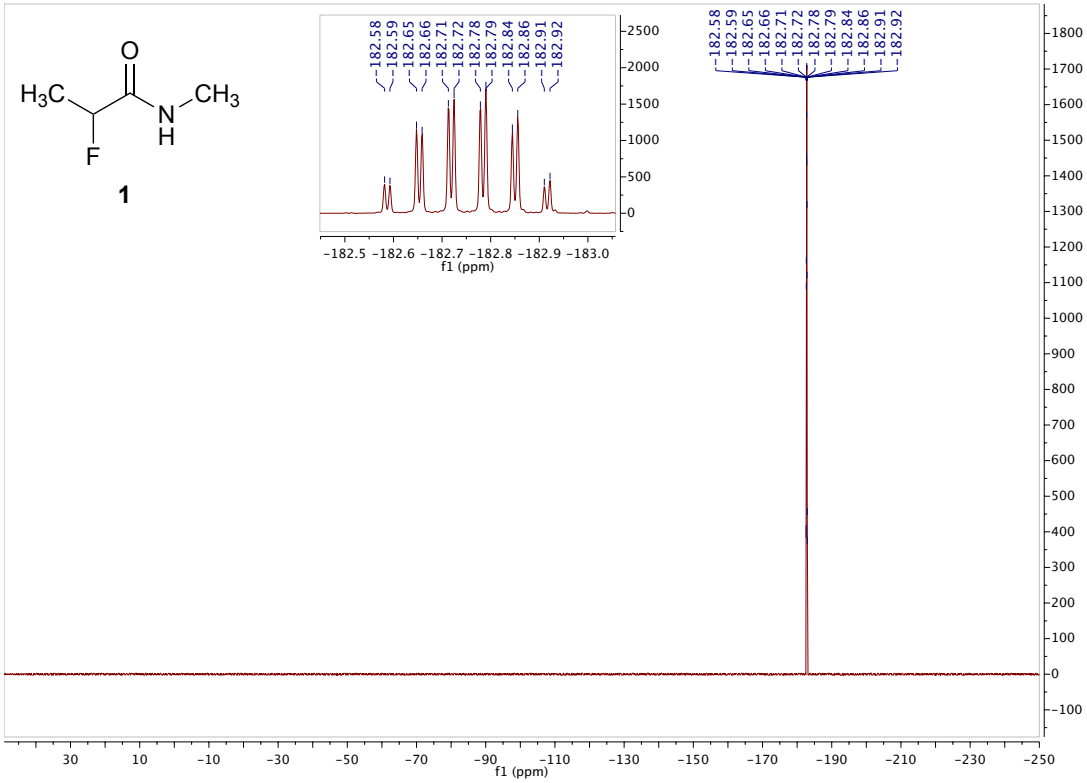


^{13}C NMR (101 MHz, CD_2Cl_2, 25 ºC)



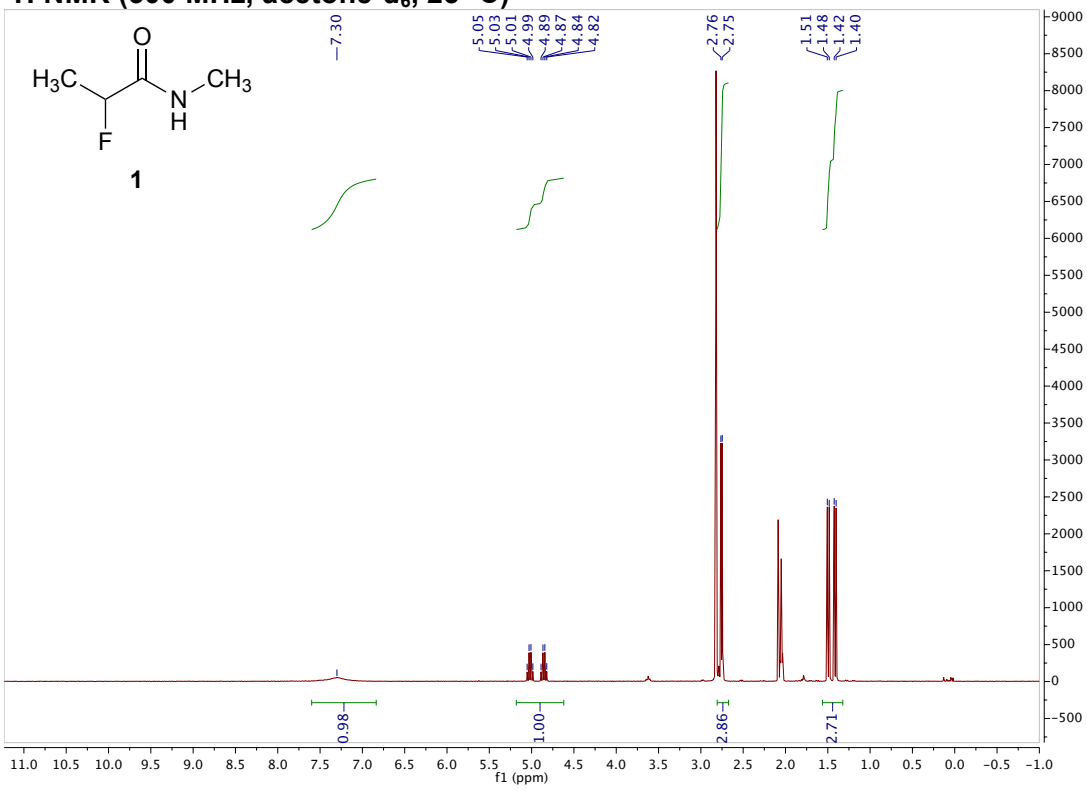
1

^{19}F NMR (376 MHz, CD_2Cl_2, 25 ºC)

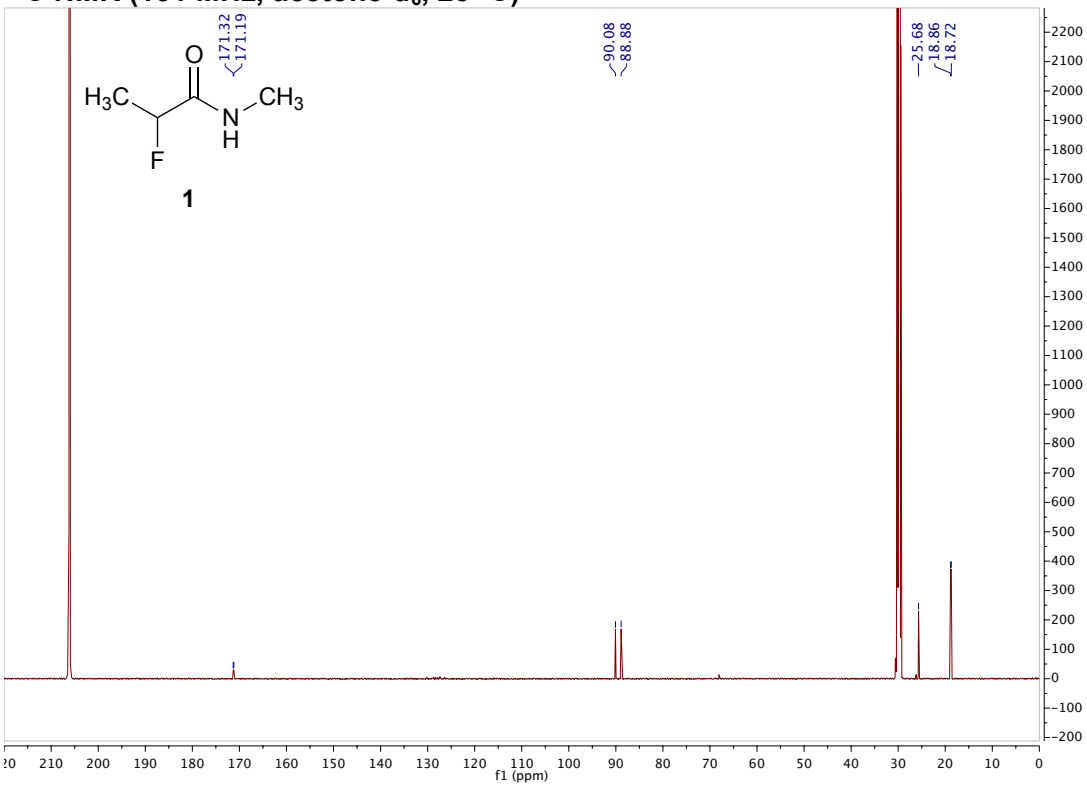


1

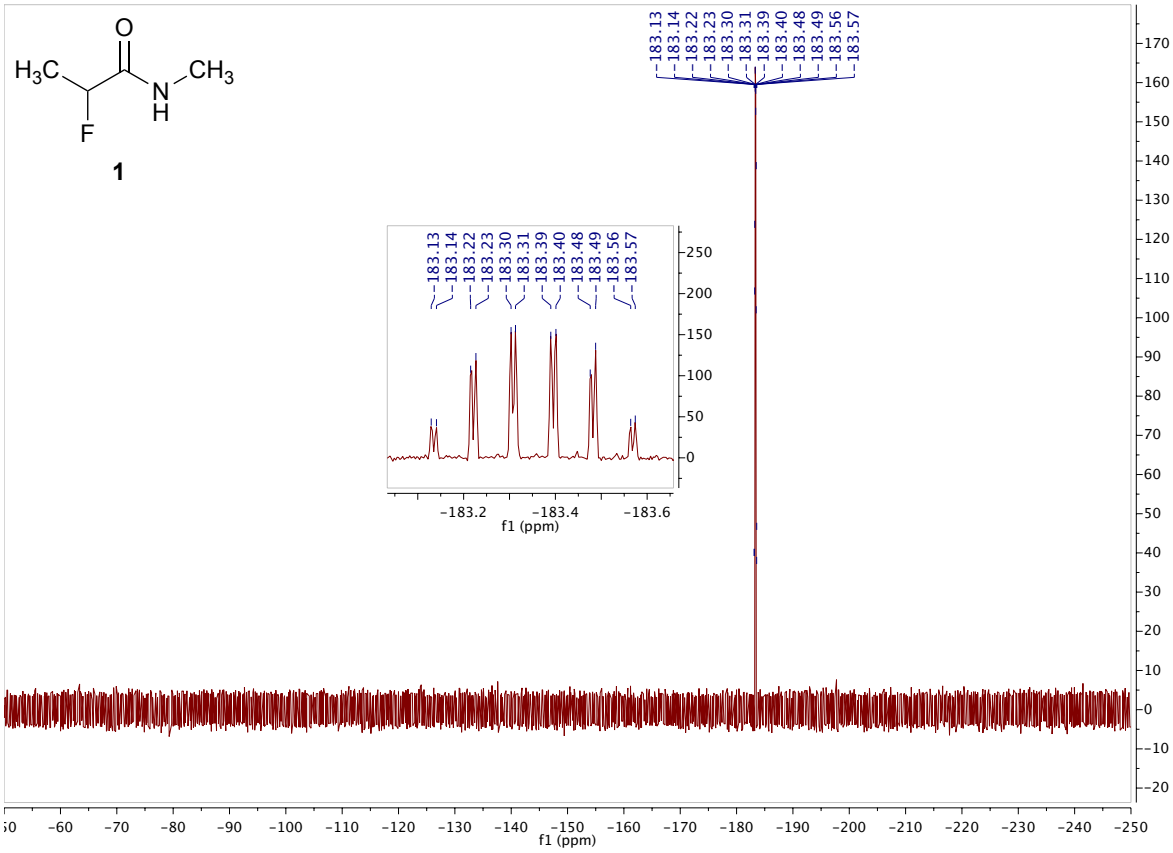
^{1}H NMR (300 MHz, acetone-d_6, 25 ºC)



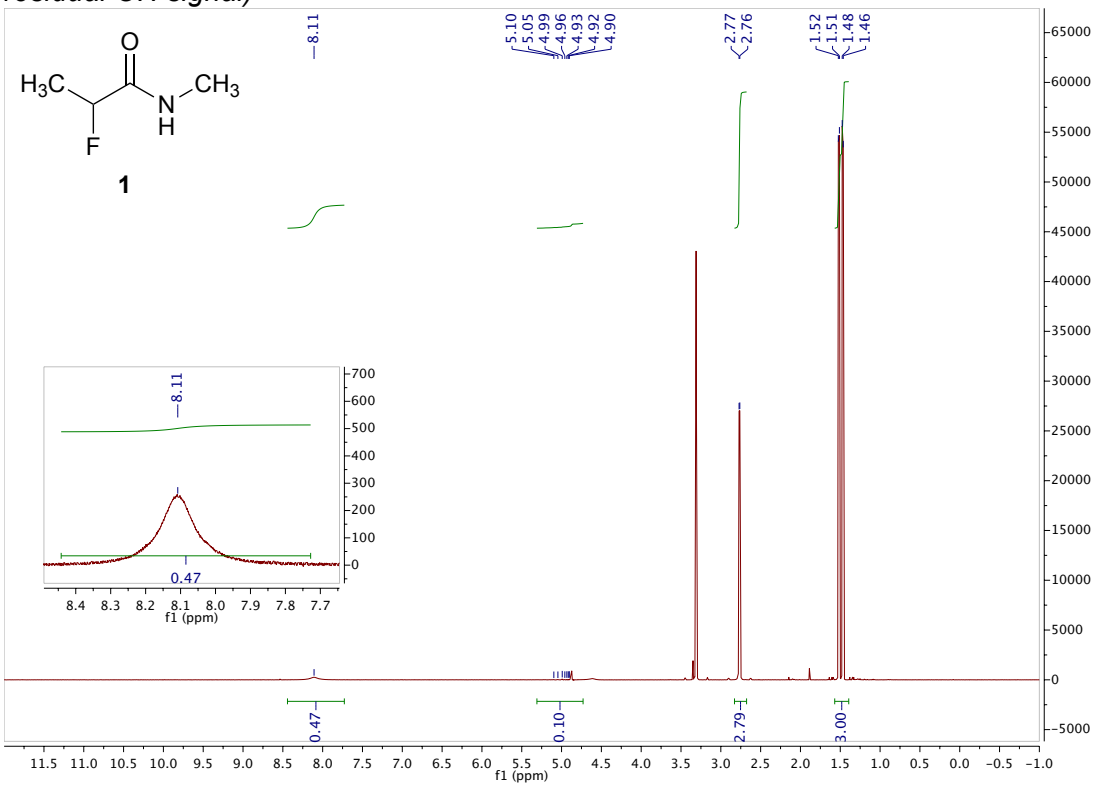
^{13}C NMR (151 MHz, acetone-d_6, 25 ºC)



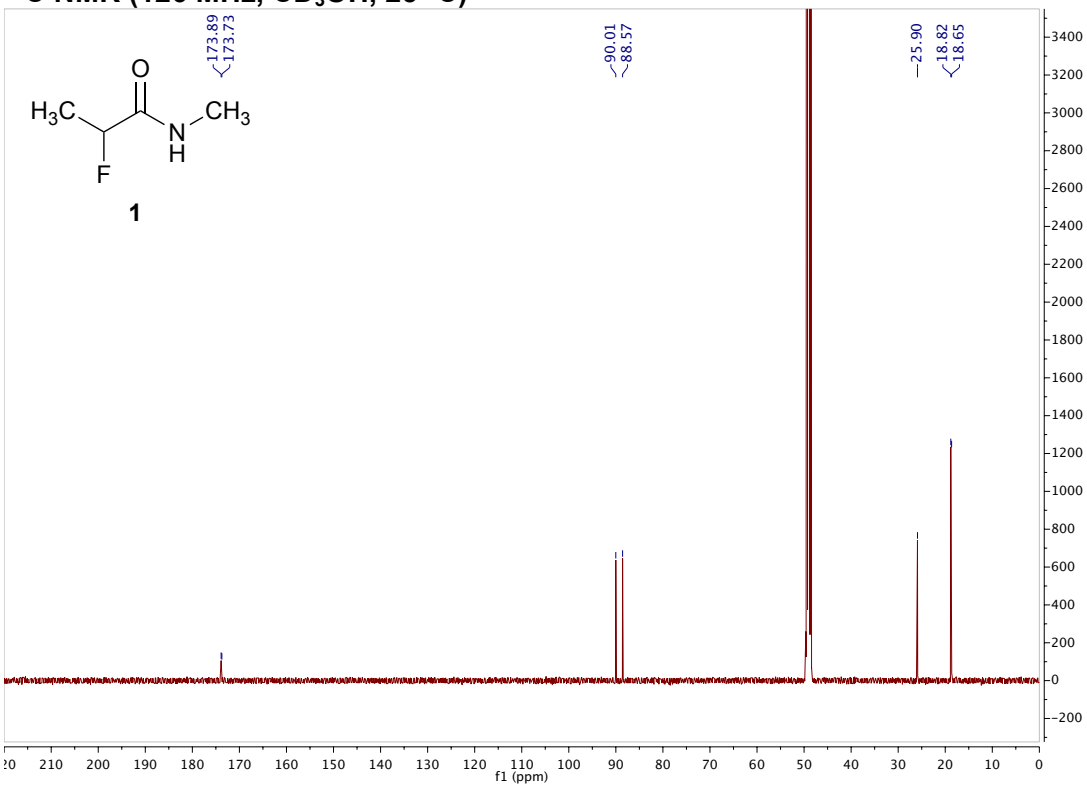
^{19}F NMR (282 MHz, acetone-d_6, 25 ºC)



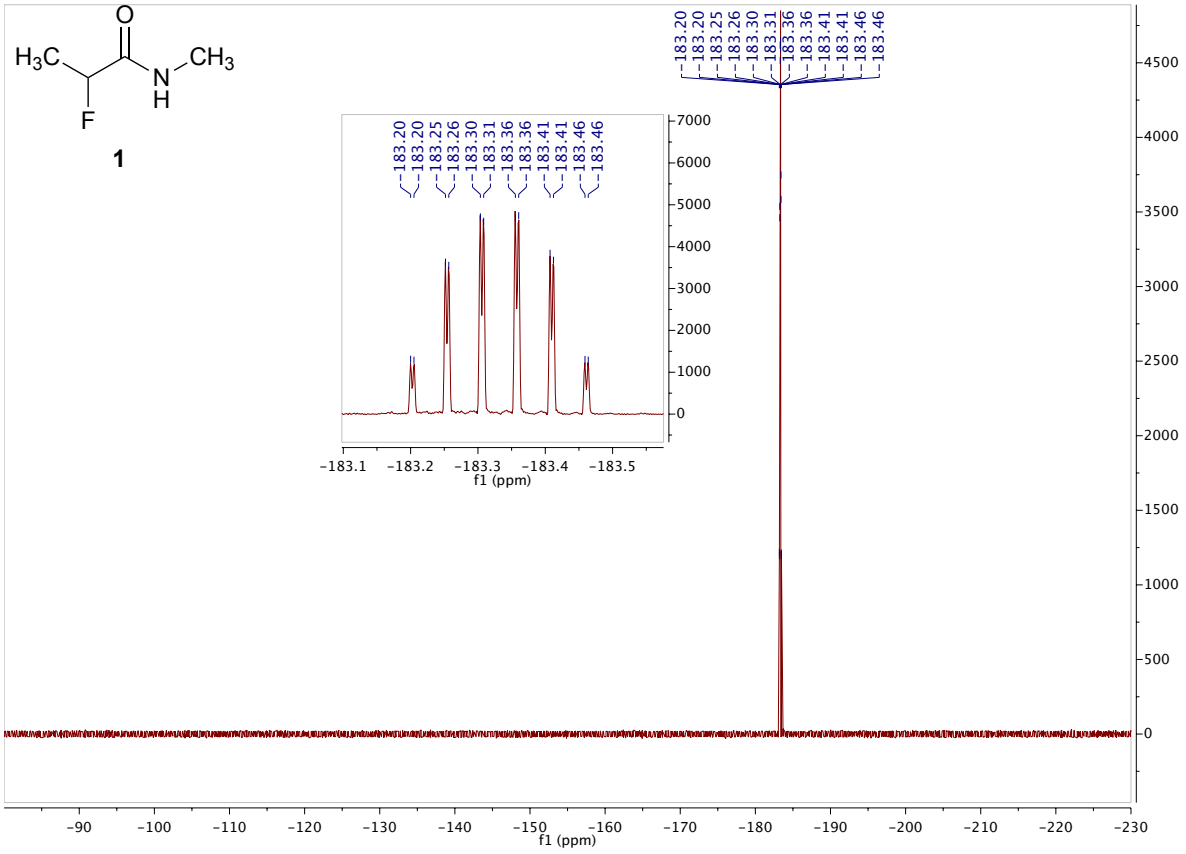
^{1}H NMR (500 MHz, CD_3OH, 25 ºC) *with excitation sculpting (integration issues close to residual OH signal)*



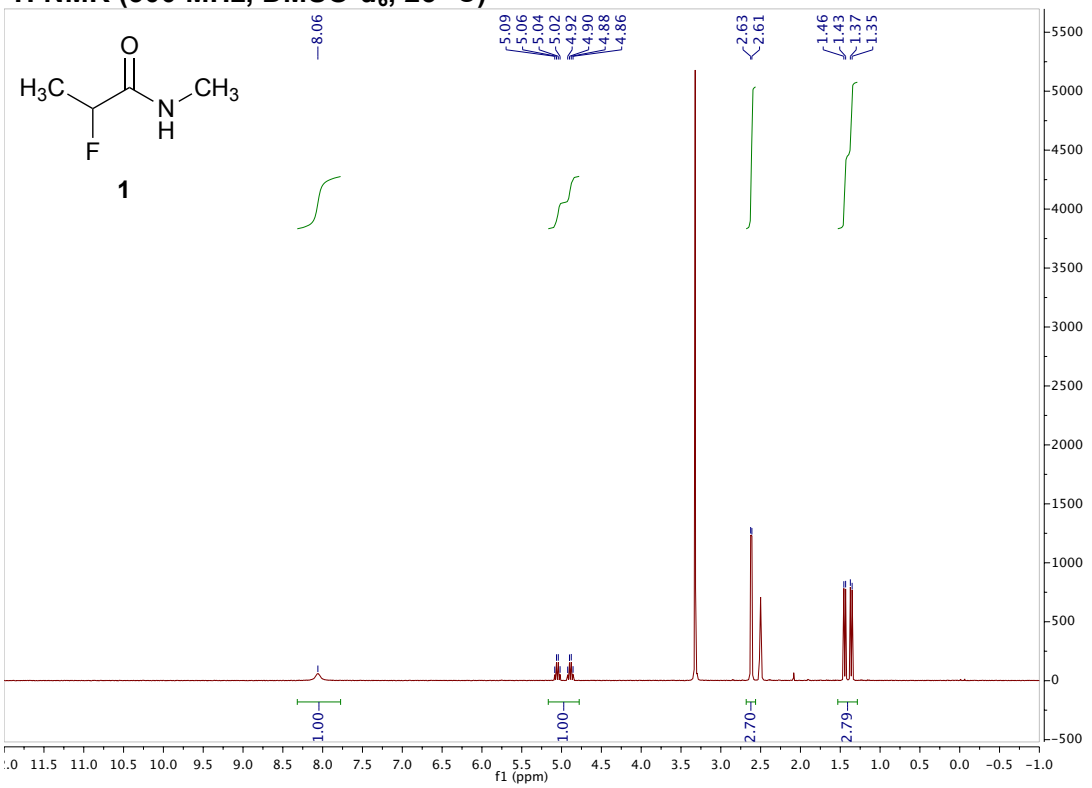
^{13}C NMR (126 MHz, CD_3OH, 25 ºC)



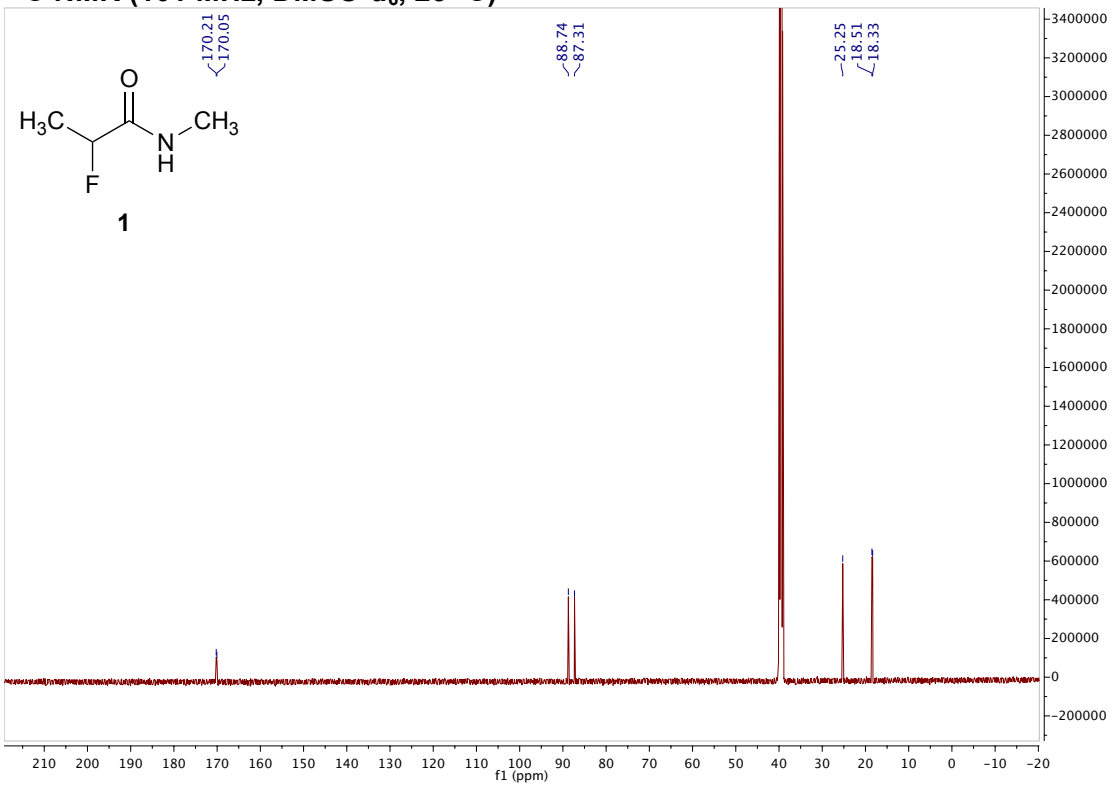
^{19}F NMR (470 MHz, CD_3OH, 25 ºC)



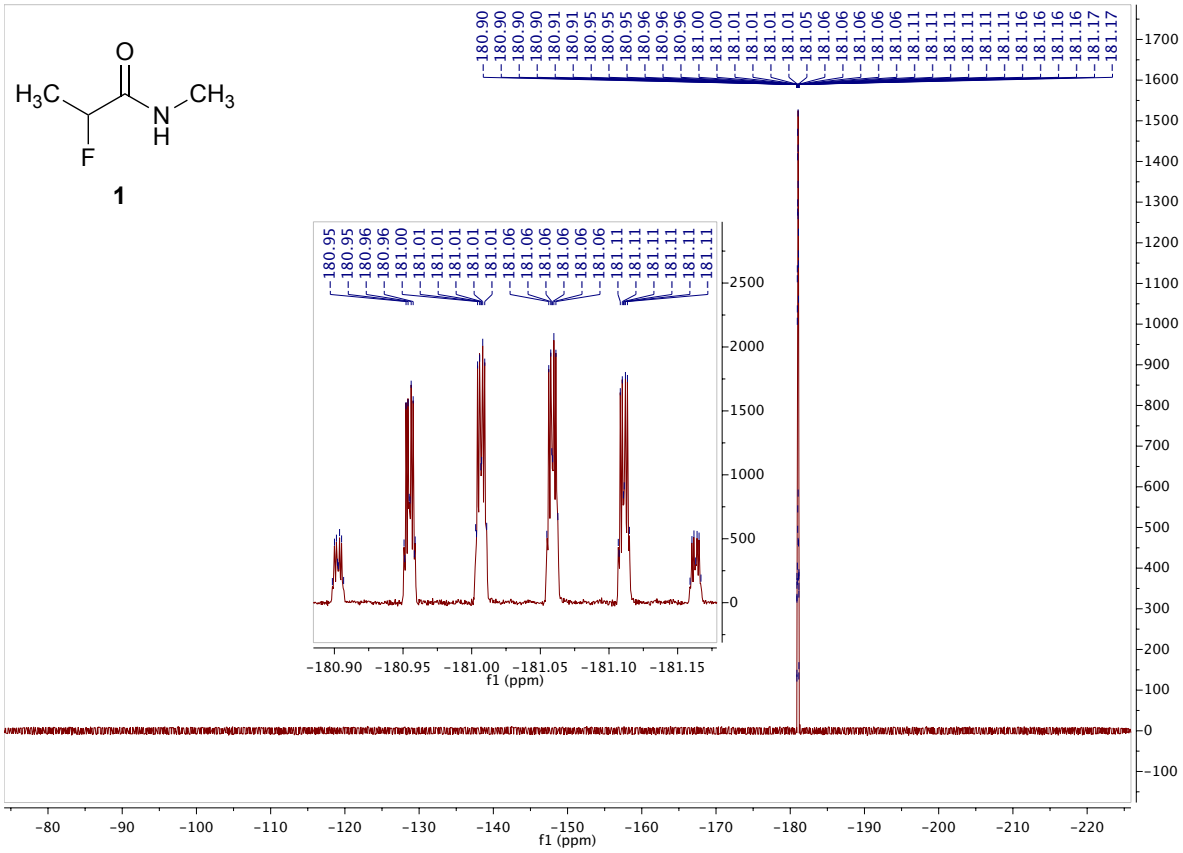
^{1}H NMR (300 MHz, DMSO-d_6, 25 ºC)



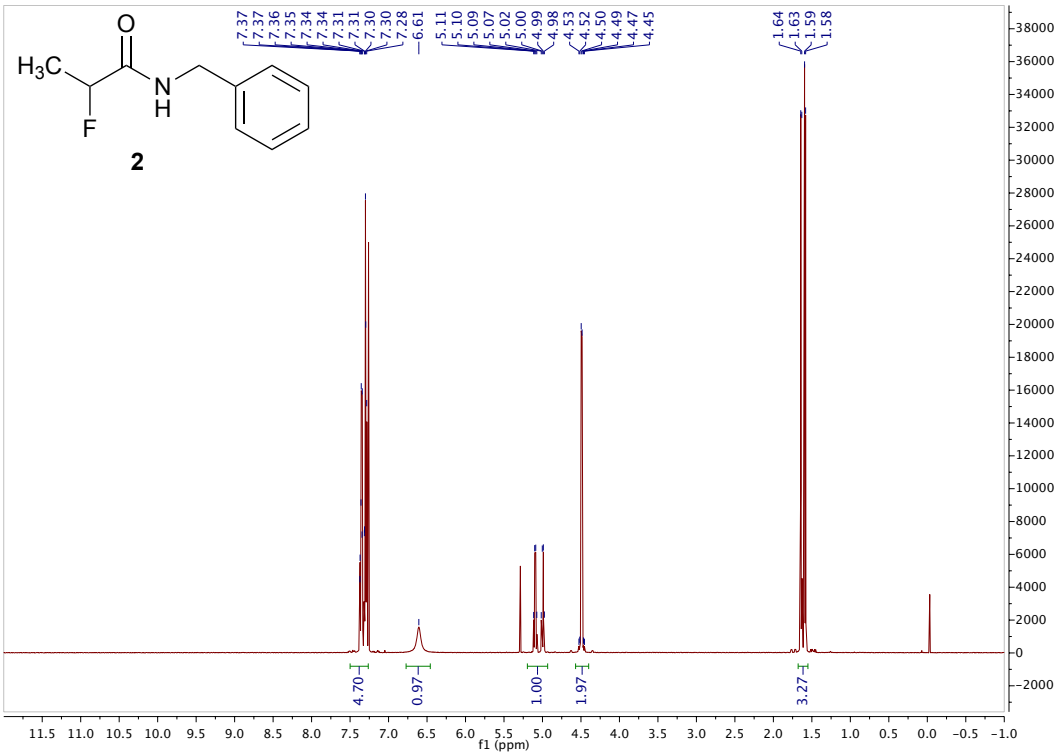
^{13}C NMR (101 MHz, DMSO-d_6, 25 ºC)



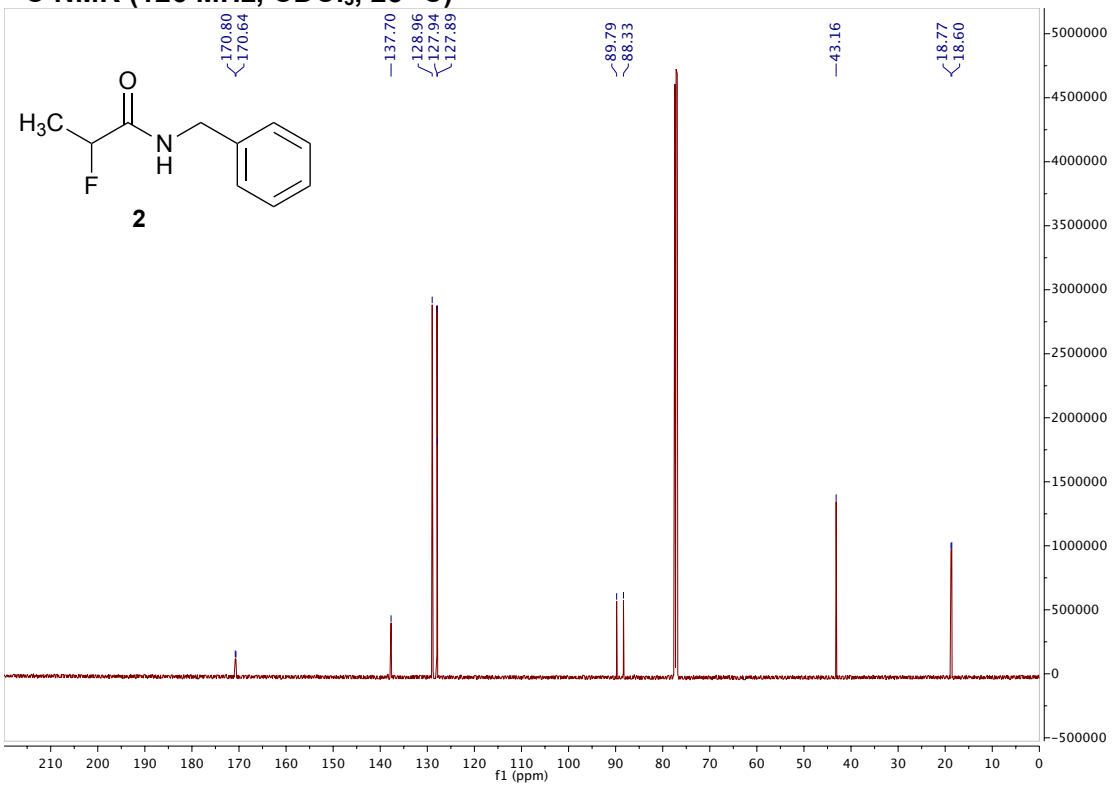
^{19}F NMR (470 MHz, DMSO-d_6, 25 ºC)



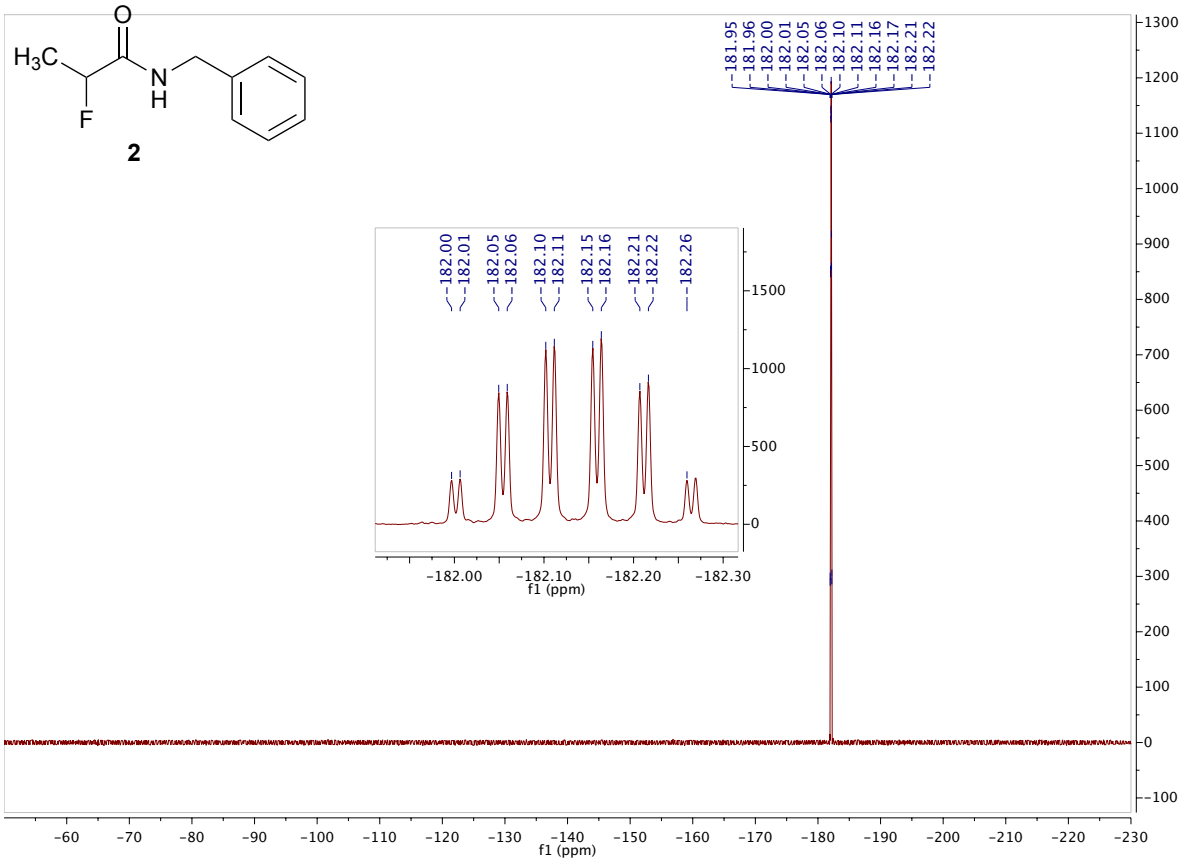
^{1}H NMR (500 MHz, $CDCl_3$, 25 °C)



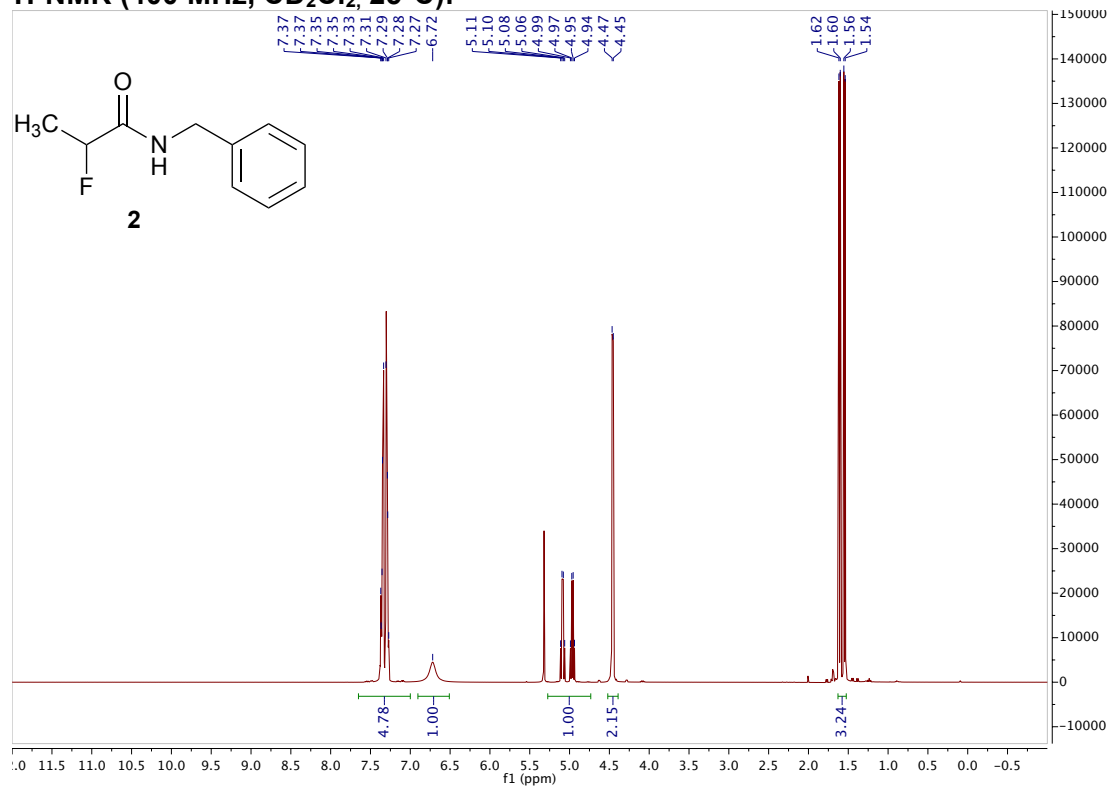
^{13}C NMR (126 MHz, $CDCl_3$, 25 °C)



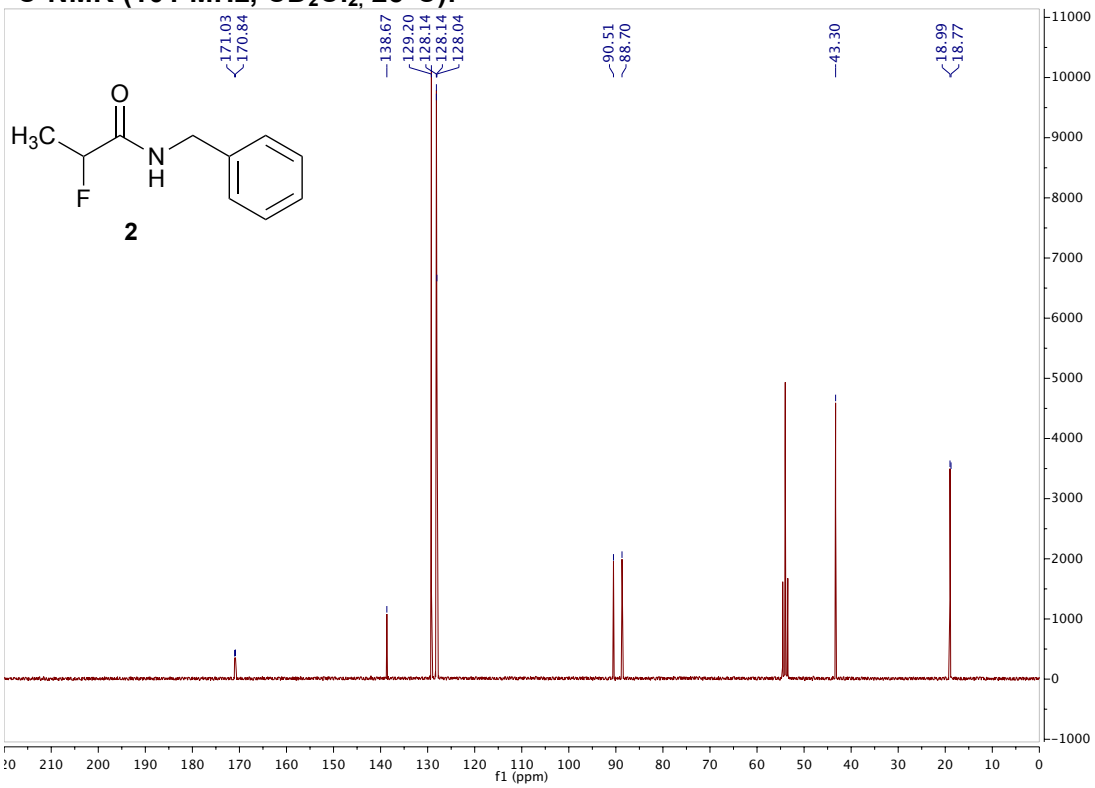
^{19}F NMR (470 MHz, $CDCl_3$, 25 ºC):



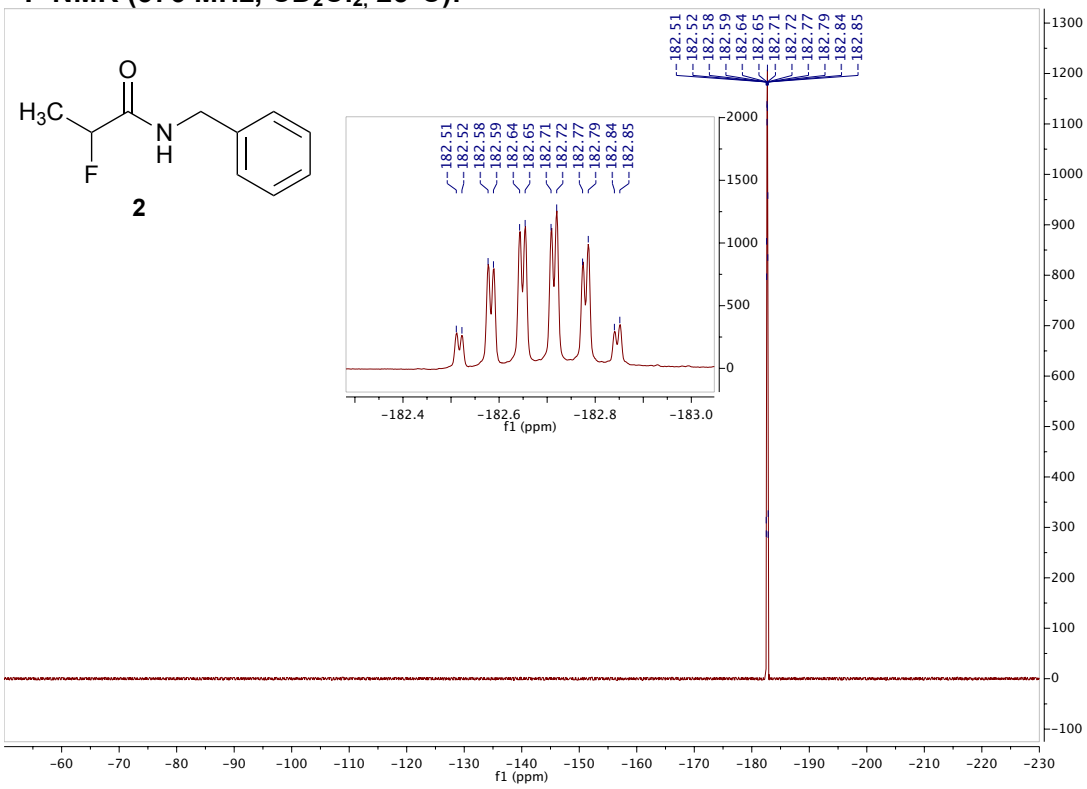
^{1}H-NMR (400 MHz, CD_2Cl_2, 25°C):



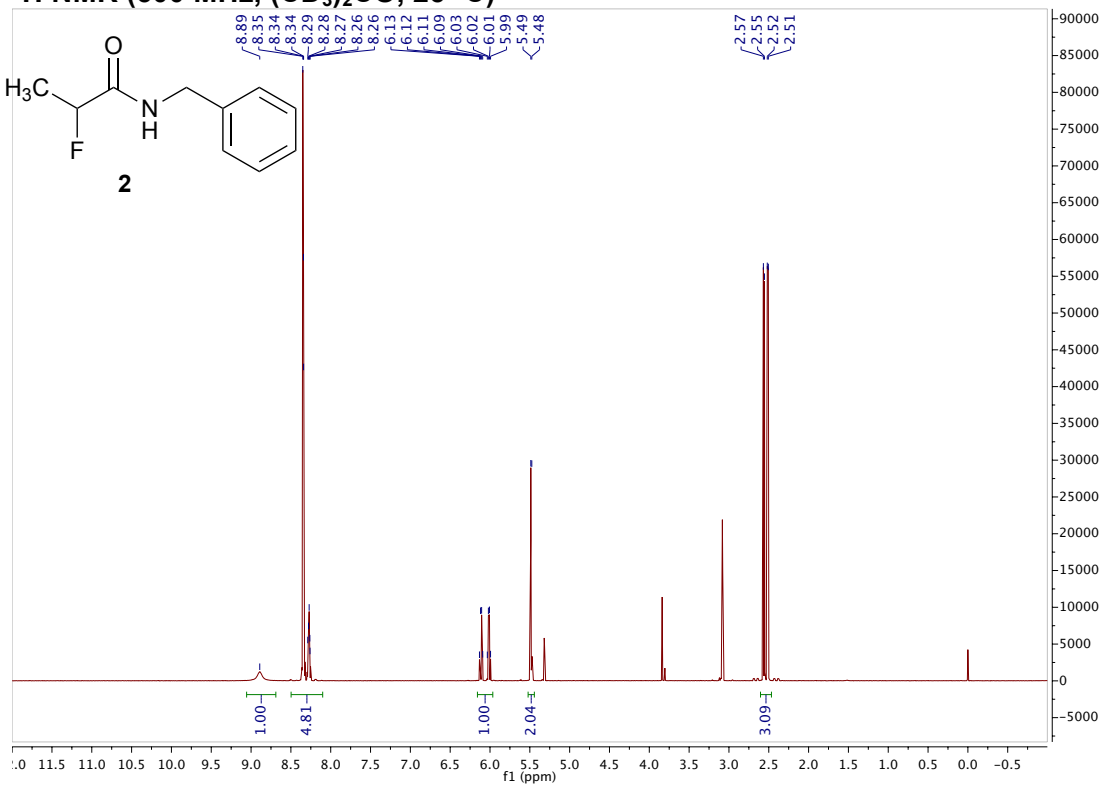
^{13}C-NMR (101 MHz, CD_2Cl_2, 25°C):



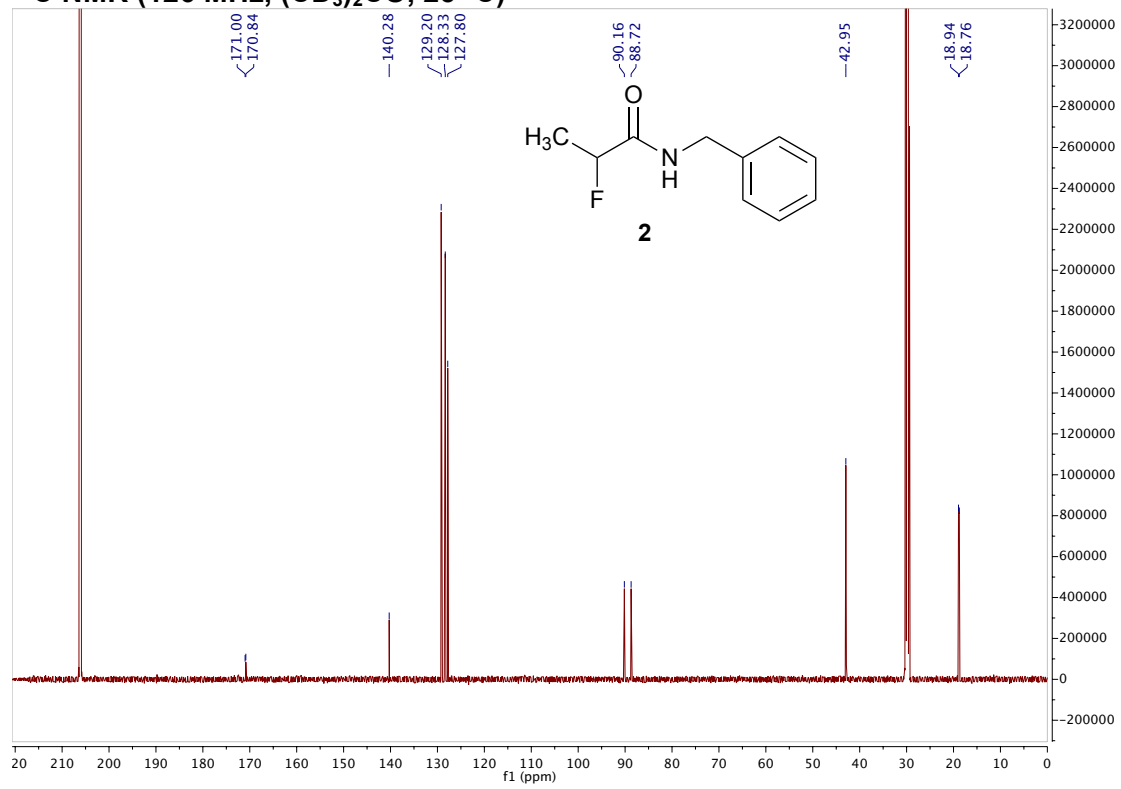
^{19}F-NMR (376 MHz, CD_2Cl_2, 25°C):



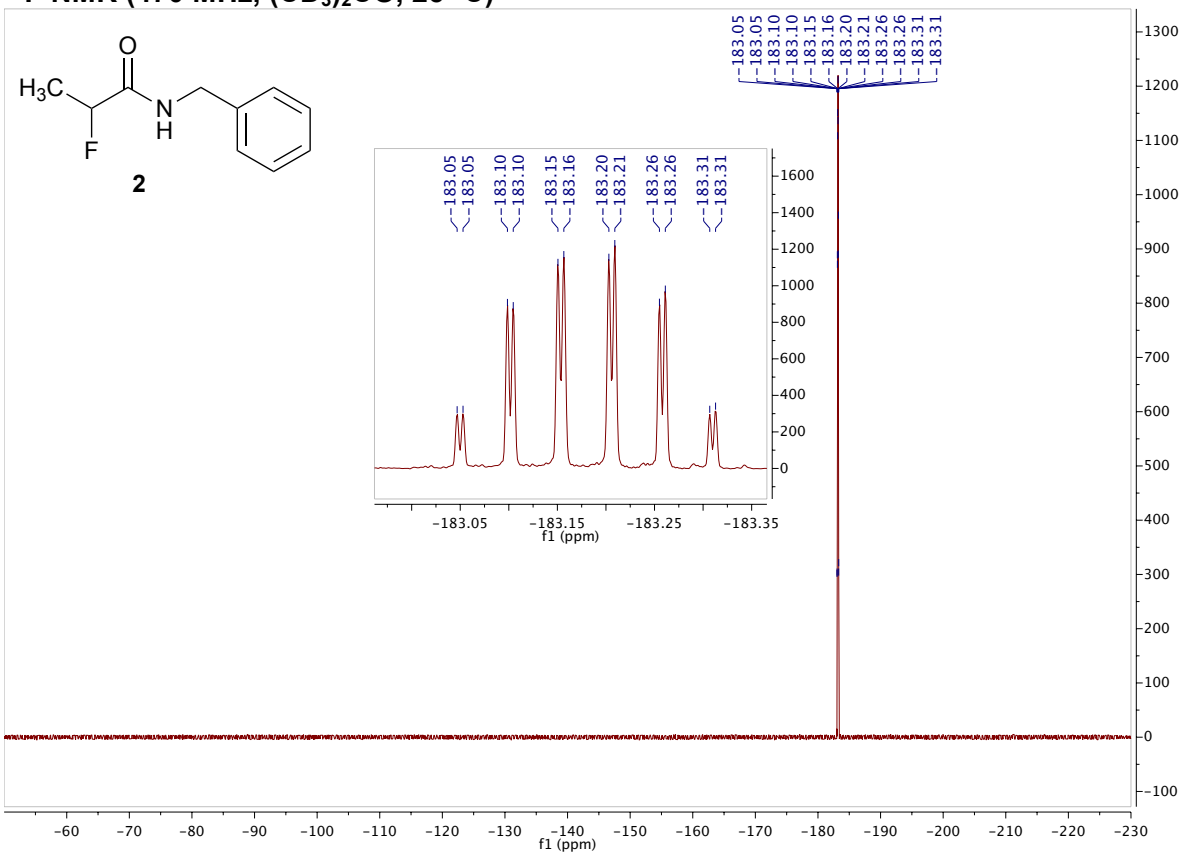
^{1}H NMR (500 MHz, $(CD_3)_2CO$, 25 ºC)



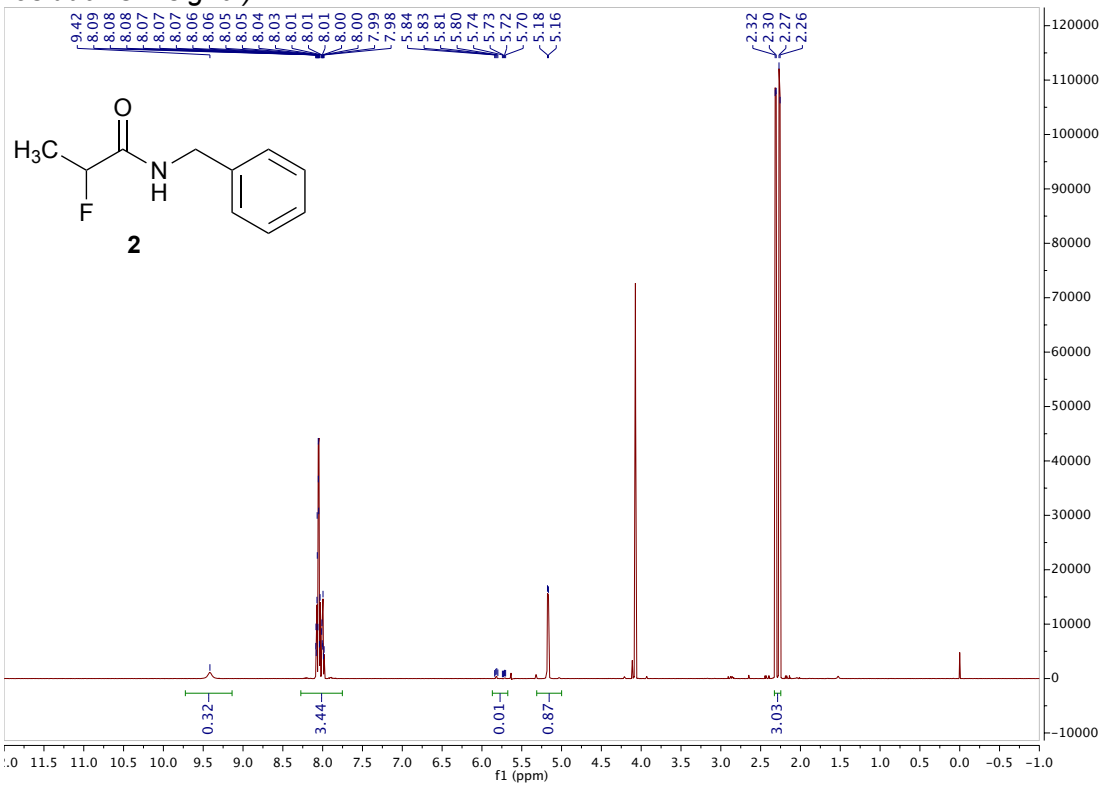
^{13}C NMR (126 MHz, $(CD_3)_2CO$, 25 ºC)



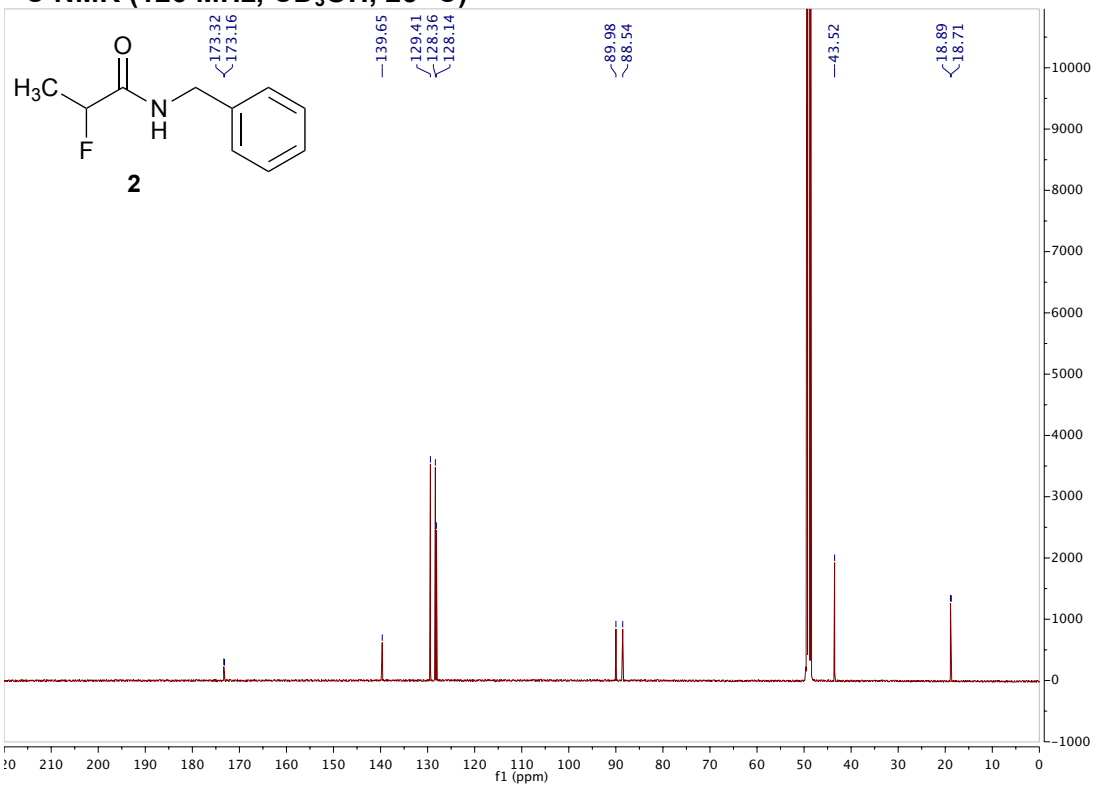
^{19}F NMR (470 MHz, $(CD_3)_2CO$, 25 ºC)



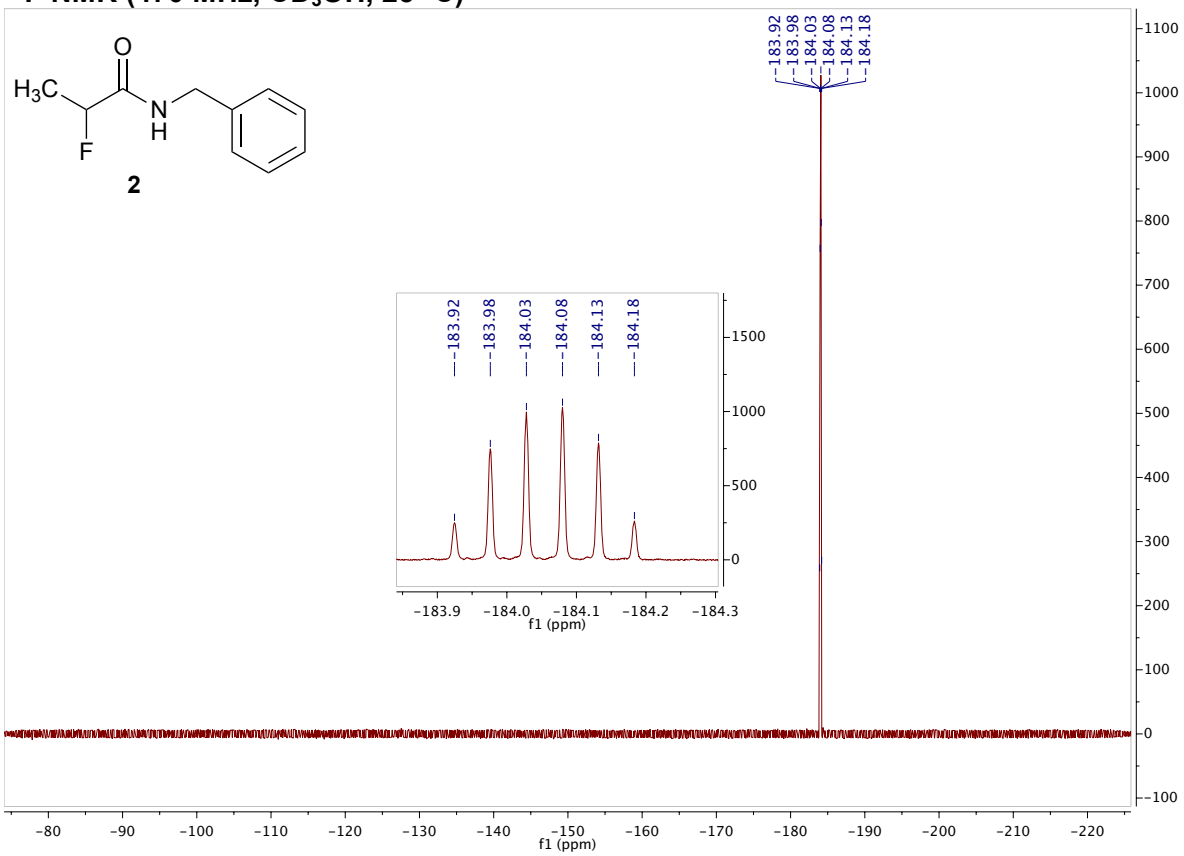
^{1}H NMR (500 MHz, CD_3OH, 25 ºC) with excitation sculpting *(integration issues close to residual OH signal)*



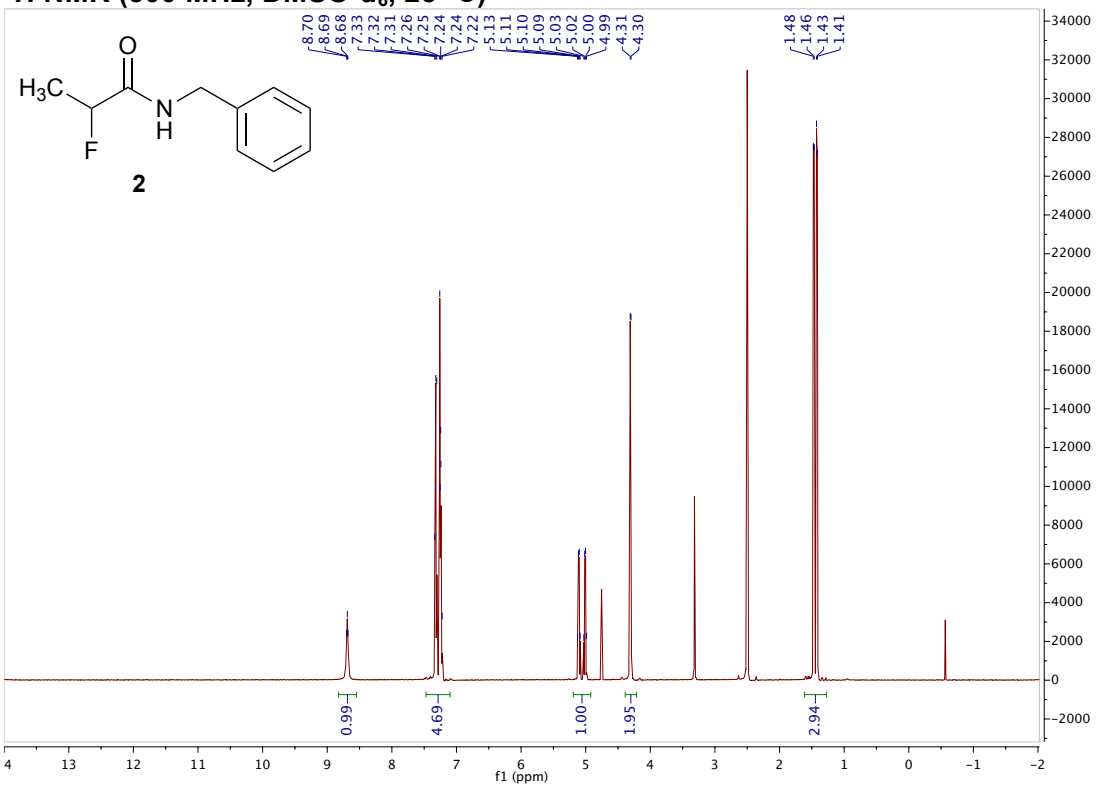
^{13}C NMR (126 MHz, CD_3OH, 25 ºC)



^{19}F NMR (470 MHz, CD_3OH, 25 ºC)

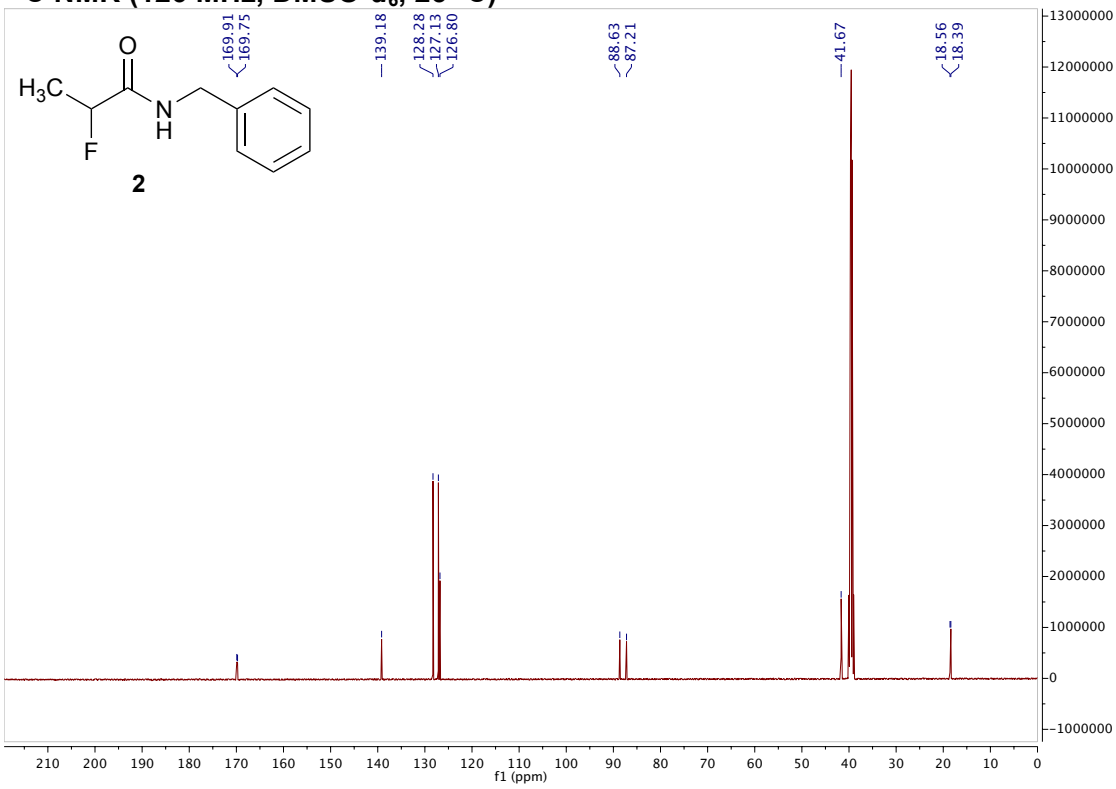


^{1}H NMR (500 MHz, DMSO-d_6, 25 ºC)



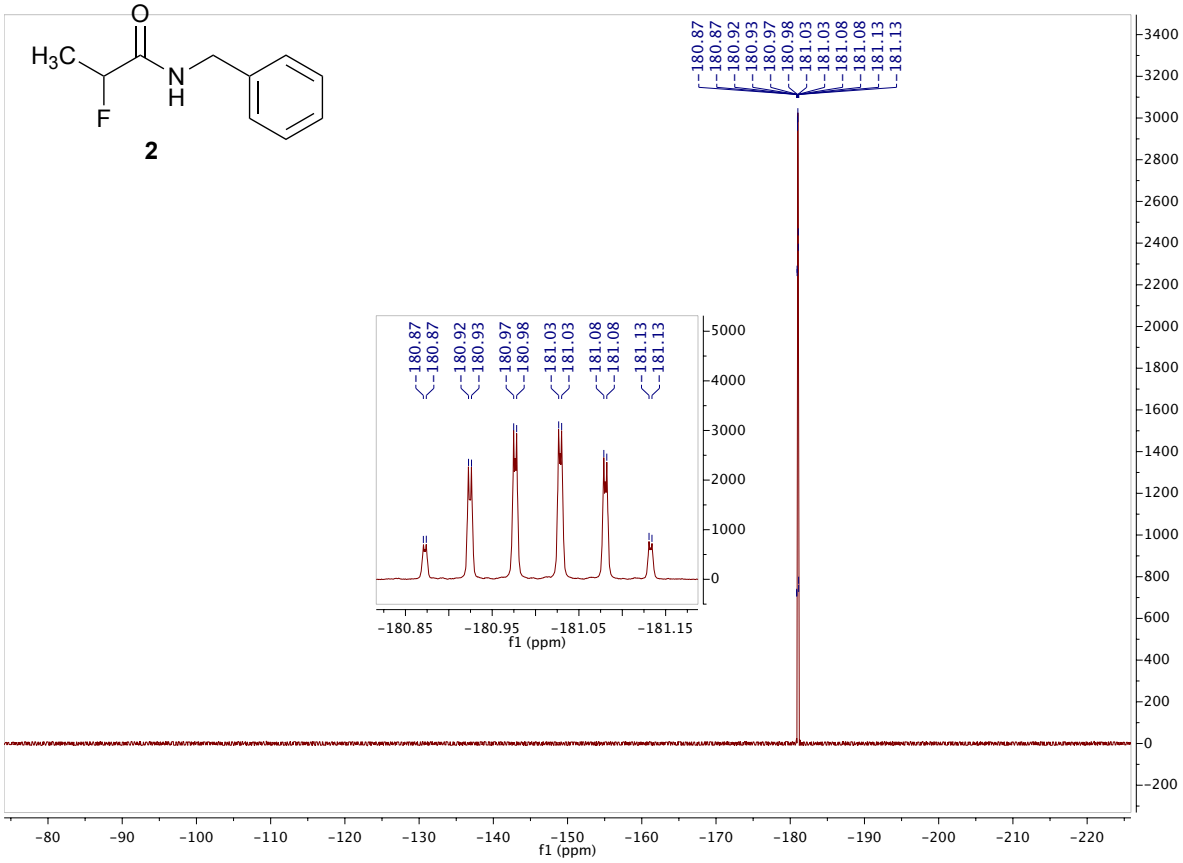
2

^{13}C NMR (126 MHz, DMSO-d_6, 25 ºC)

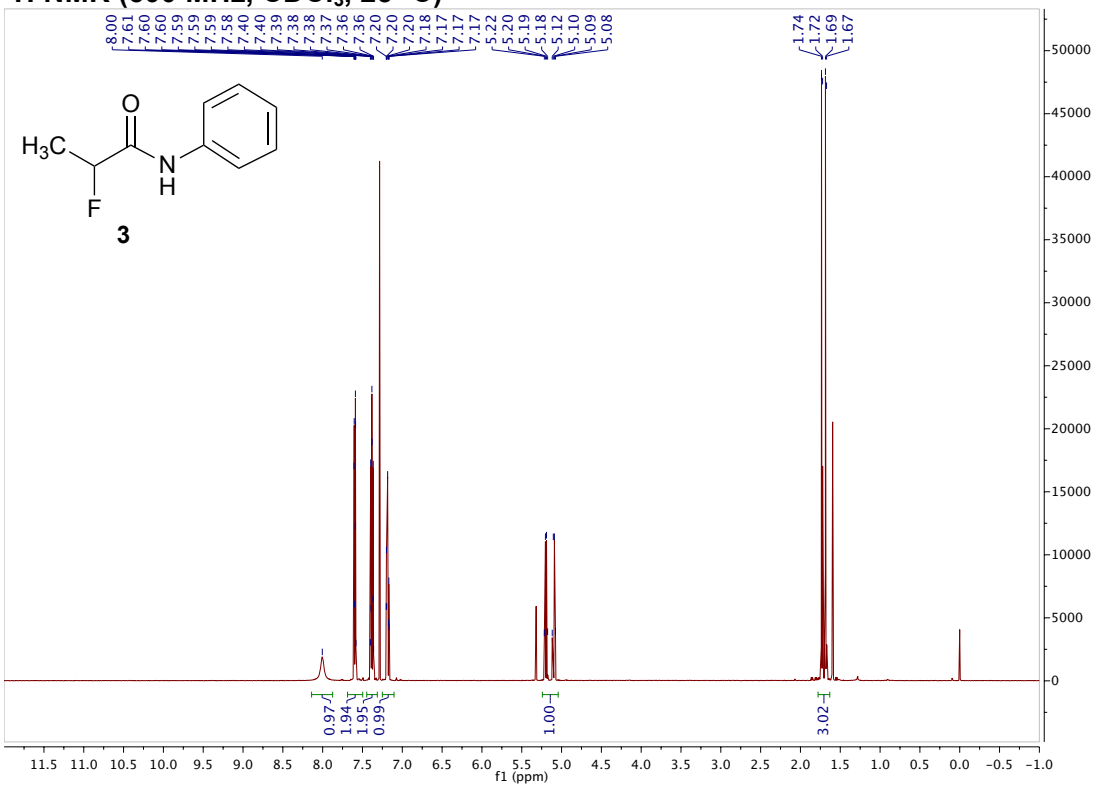


2

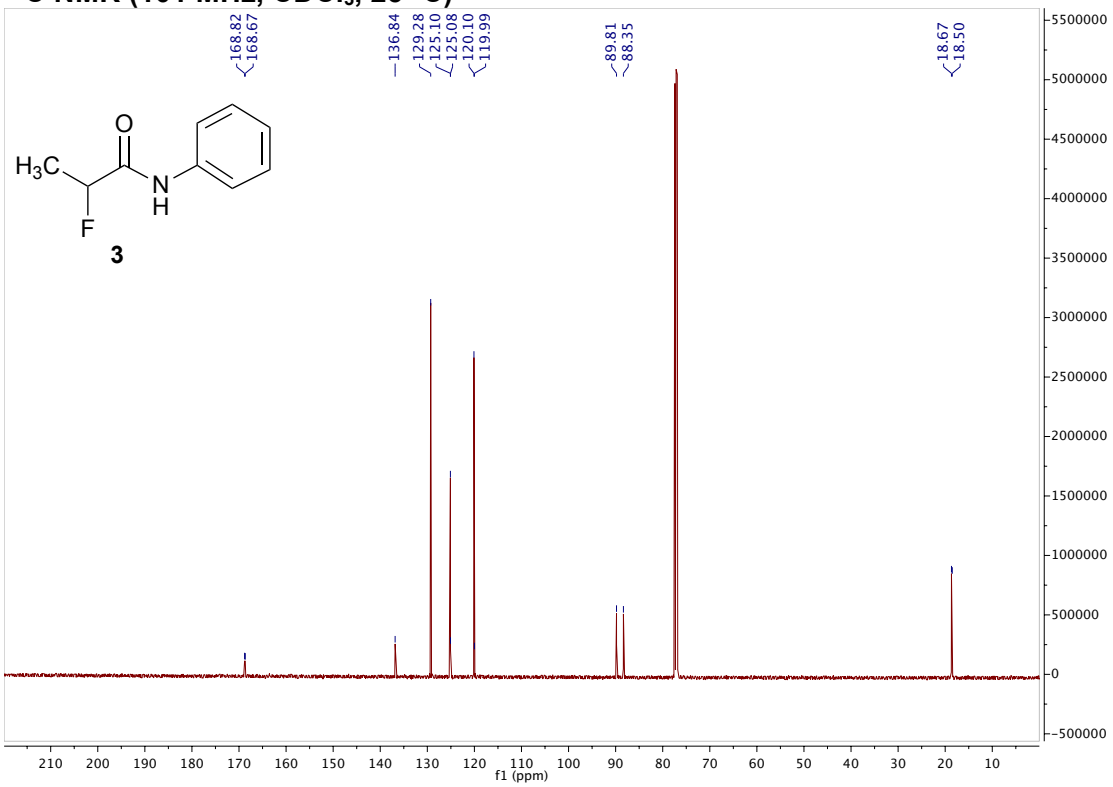
^{19}F NMR (470 MHz, DMSO-d_6, 25 ºC)



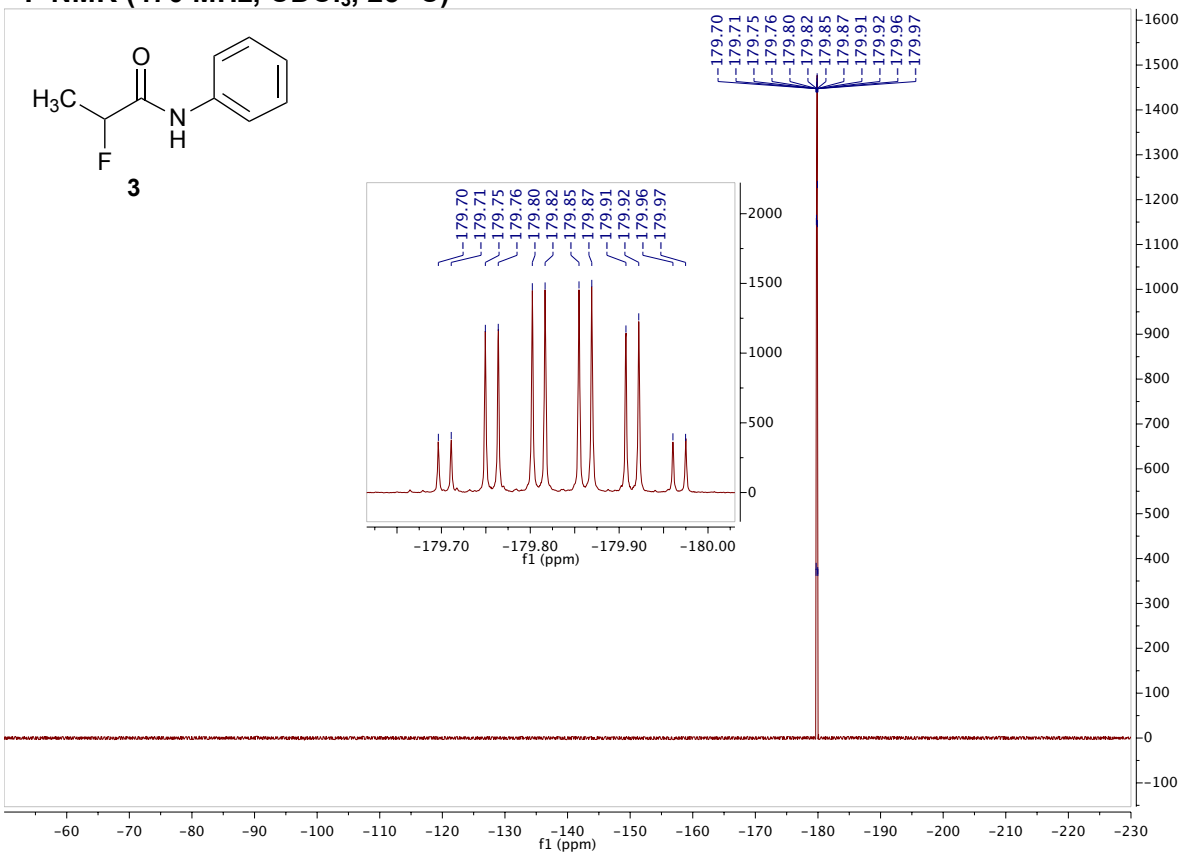
^{1}H NMR (500 MHz, $CDCl_3$, 25 °C)



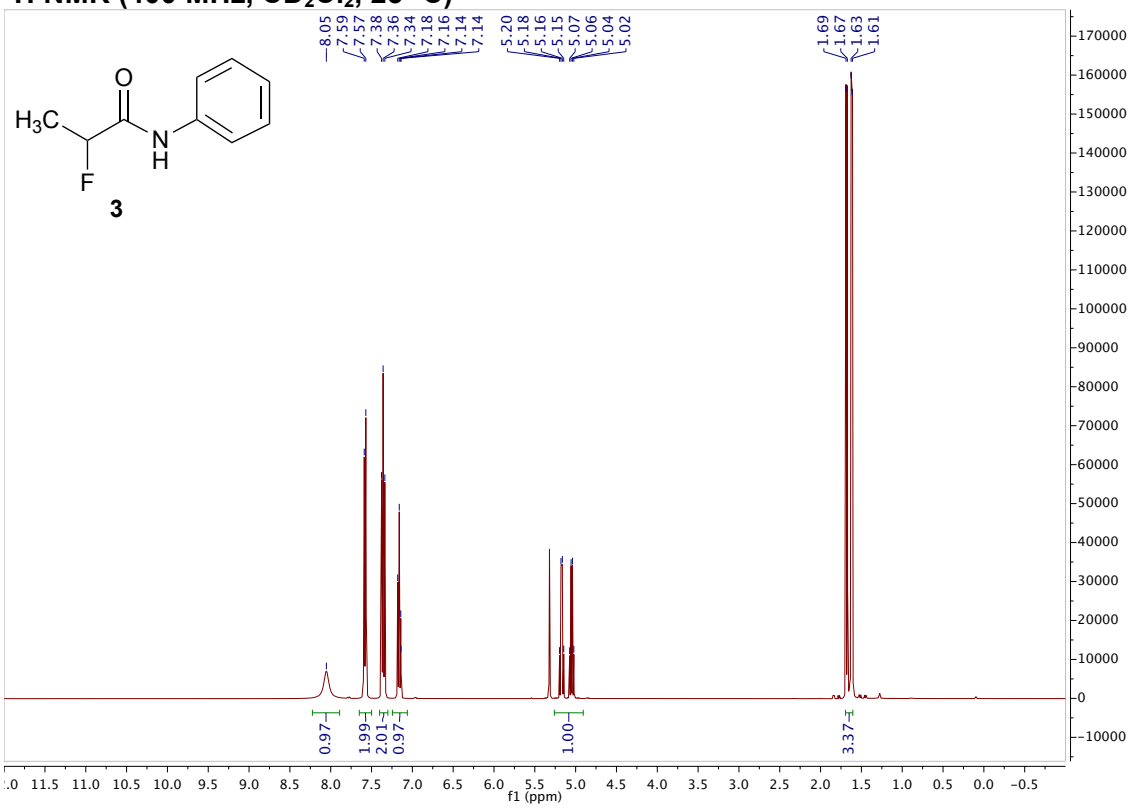
^{13}C NMR (101 MHz, $CDCl_3$, 25 °C)



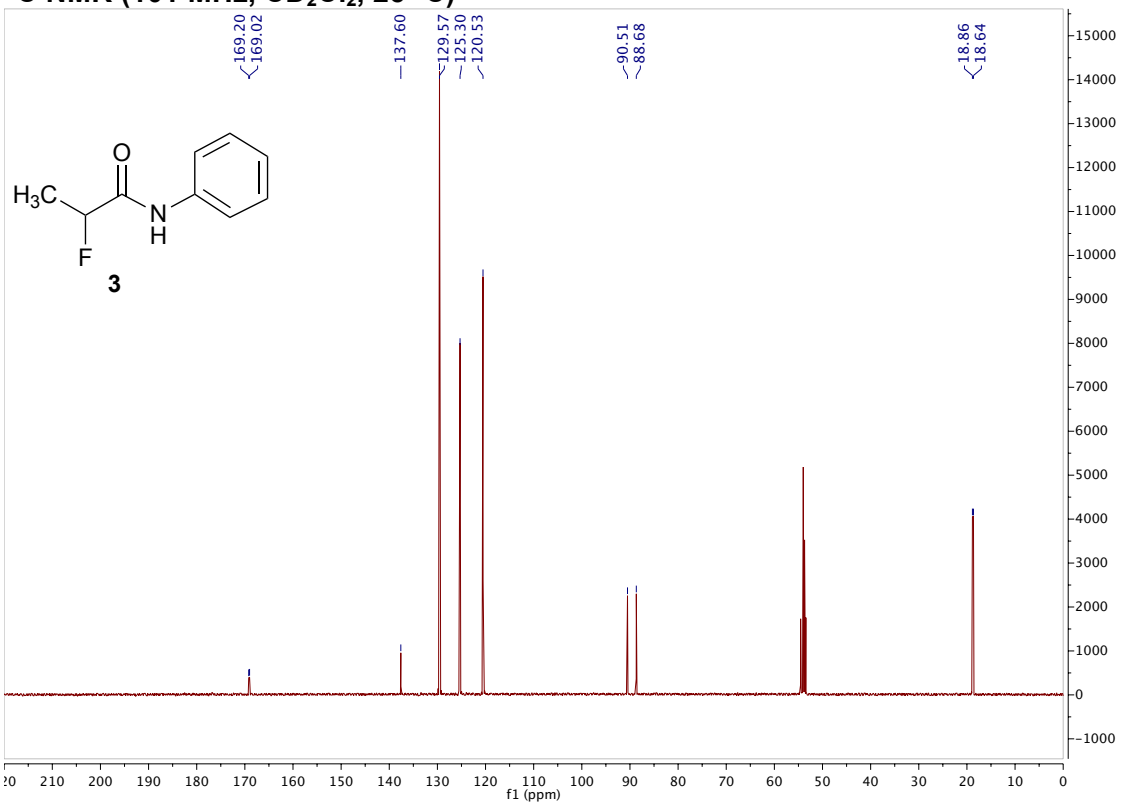
^{19}F NMR (470 MHz, $CDCl_3$, 25 ºC)



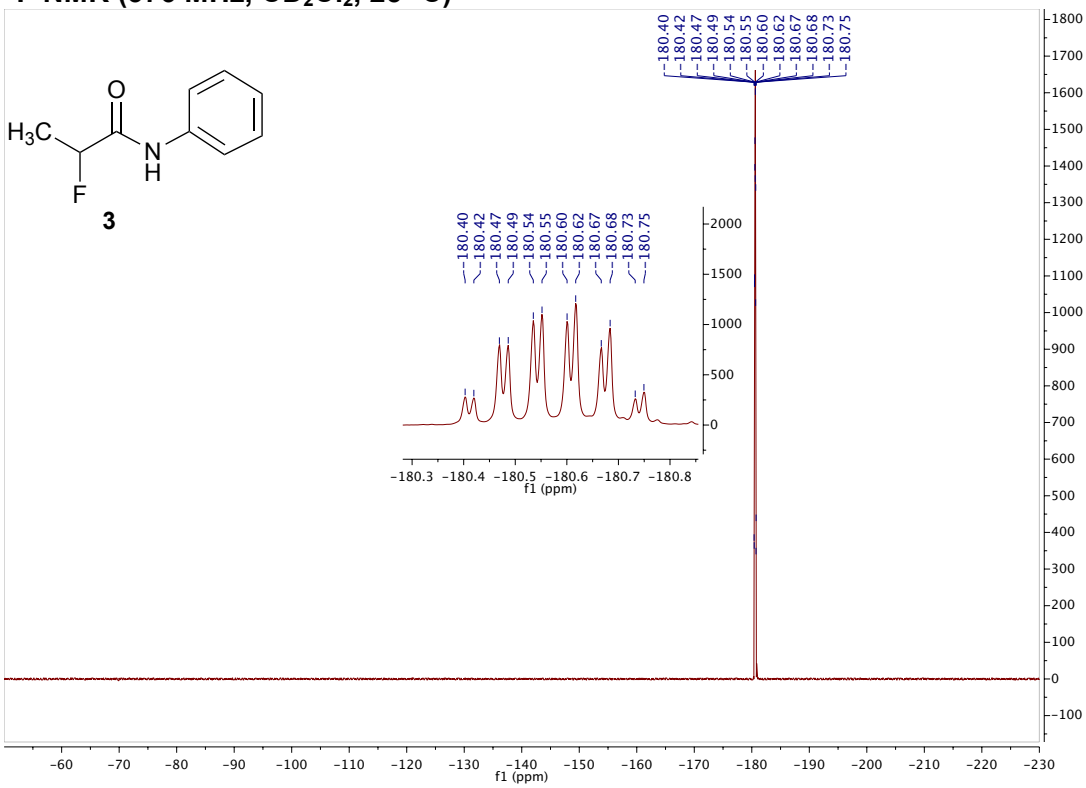
^{1}H NMR (400 MHz, CD_2Cl_2, 25 ºC)



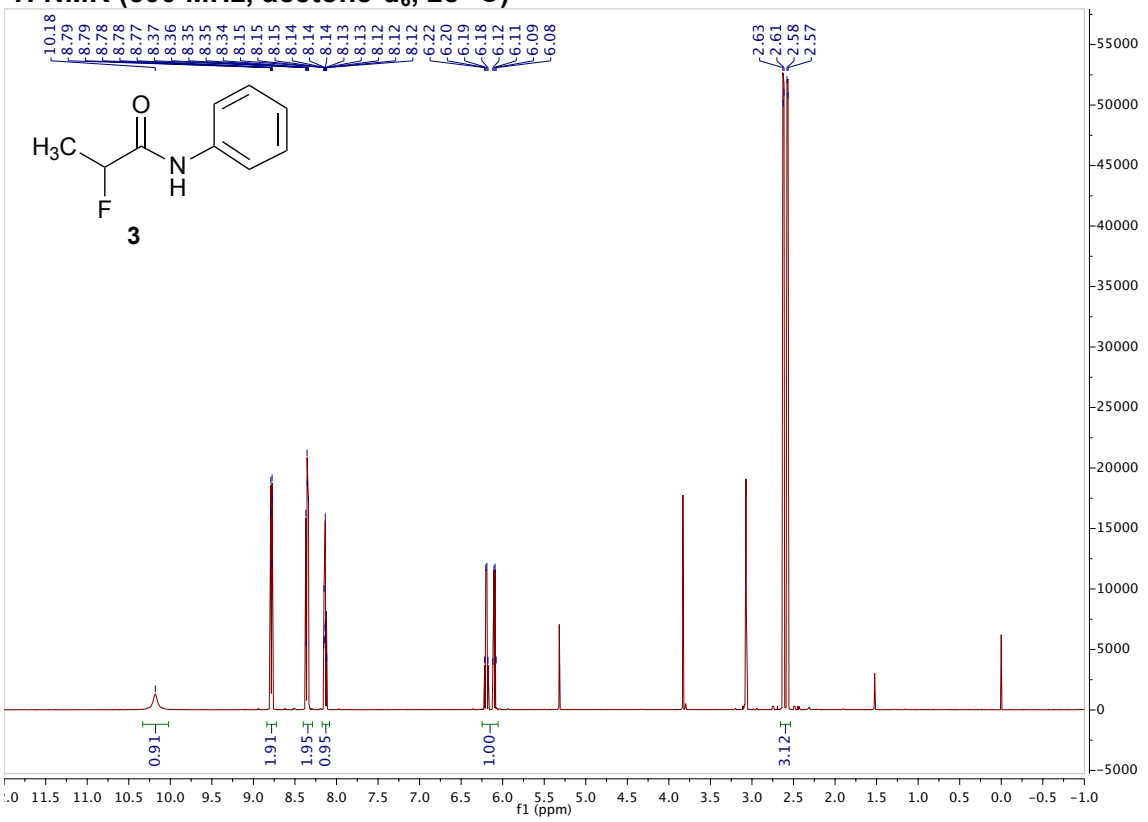
^{13}C NMR (101 MHz, CD_2Cl_2, 25 ºC)



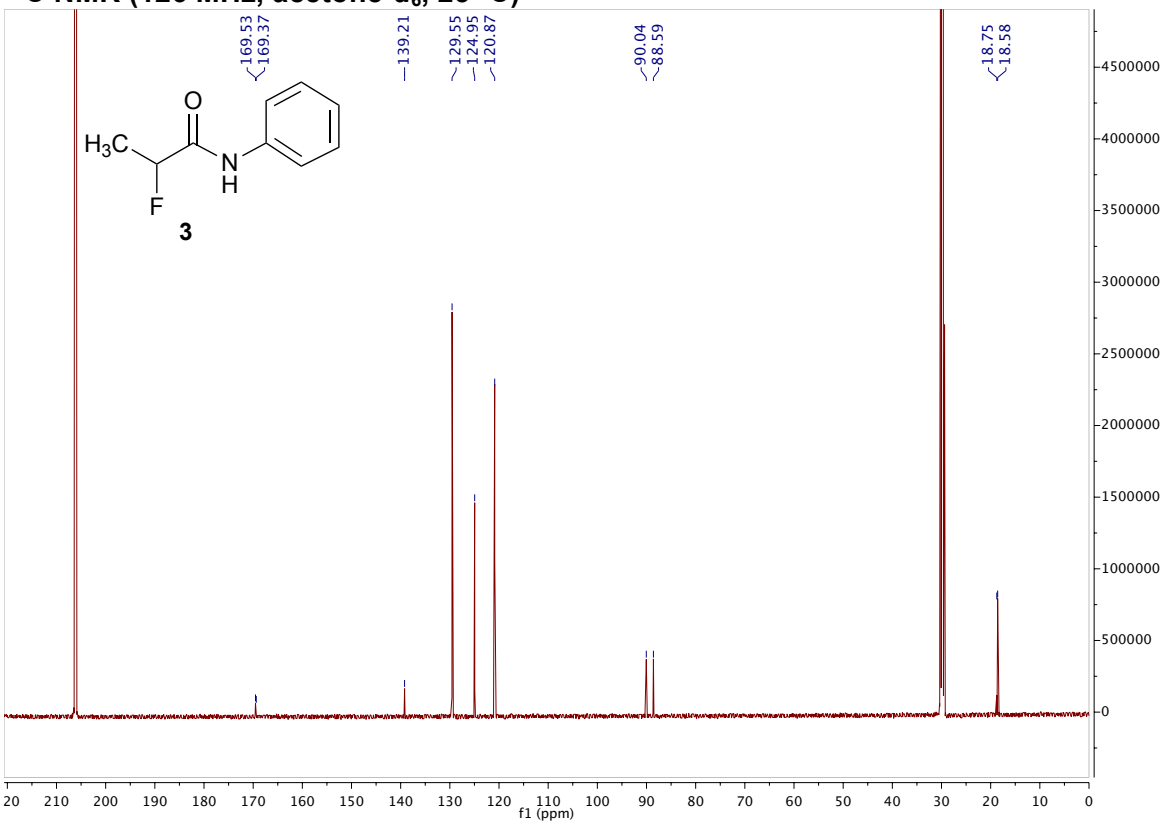
^{19}F NMR (376 MHz, CD_2Cl_2, 25 ºC)



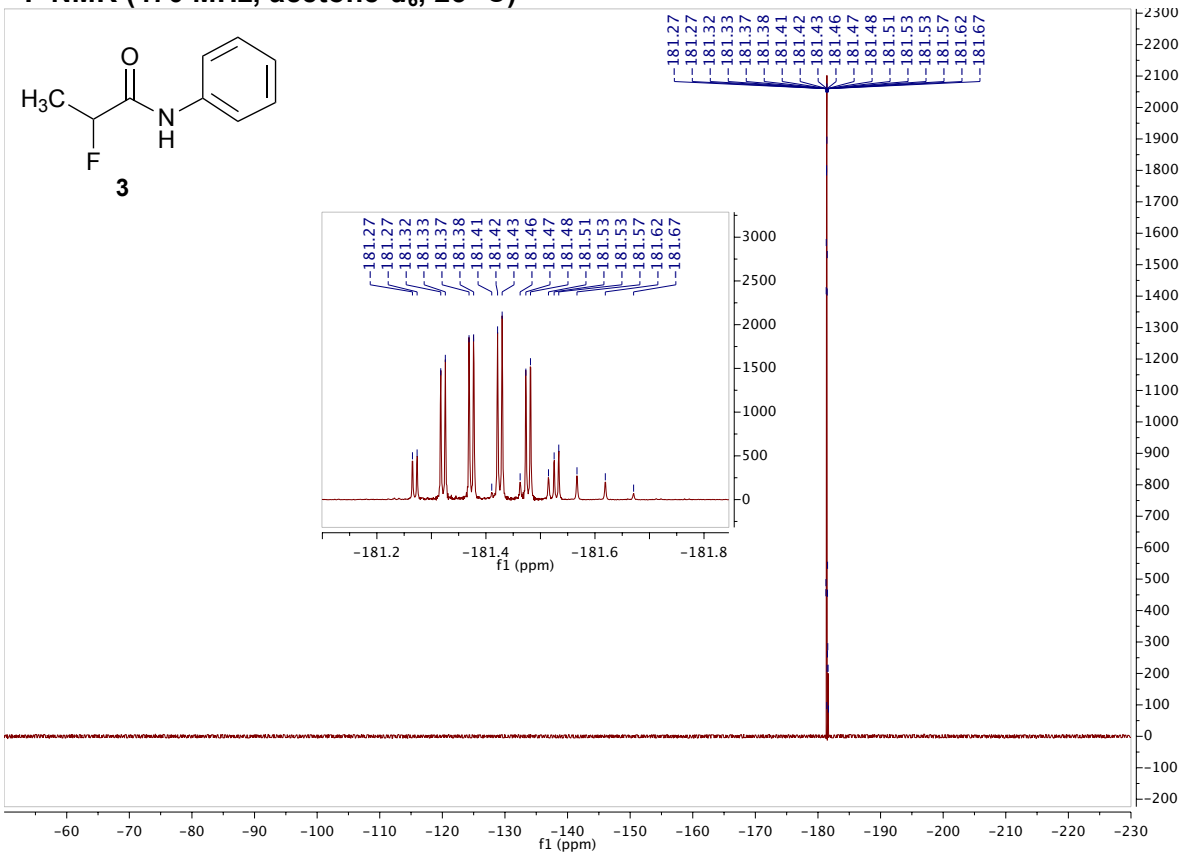
^{1}H NMR (500 MHz, acetone-d_6, 25 ºC)



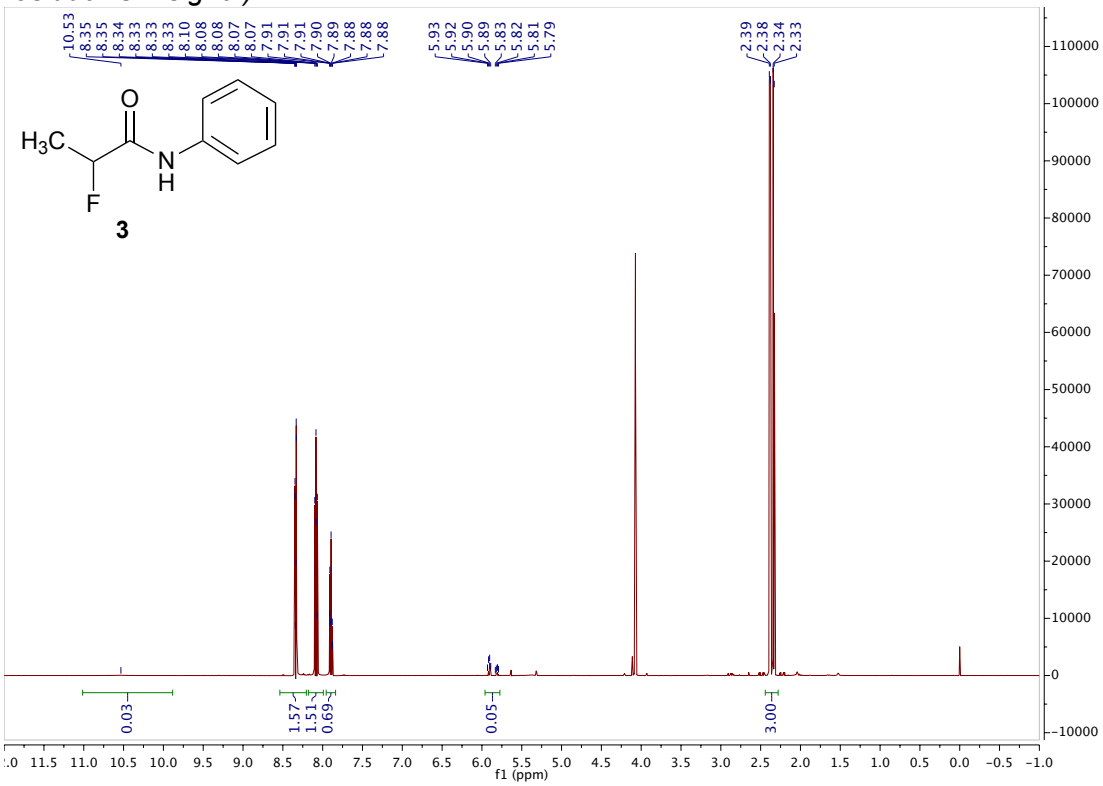
^{13}C NMR (126 MHz, acetone-d_6, 25 ºC)



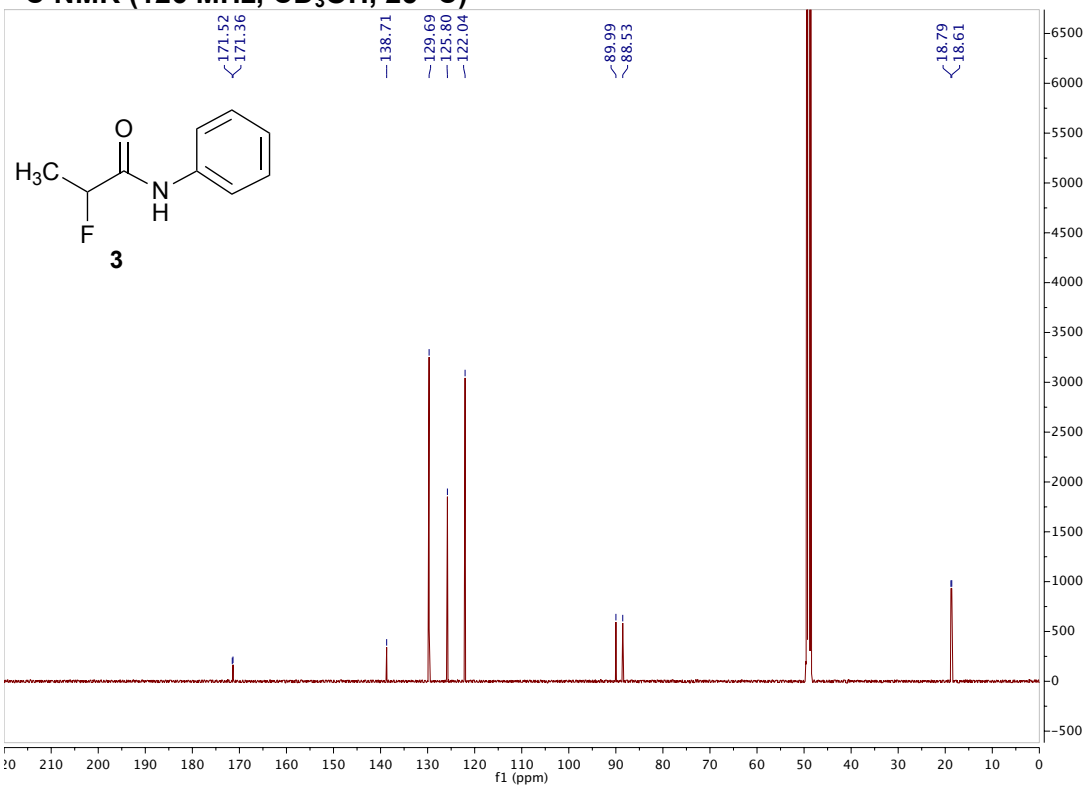
^{19}F NMR (470 MHz, acetone-d_6, 25 ºC)



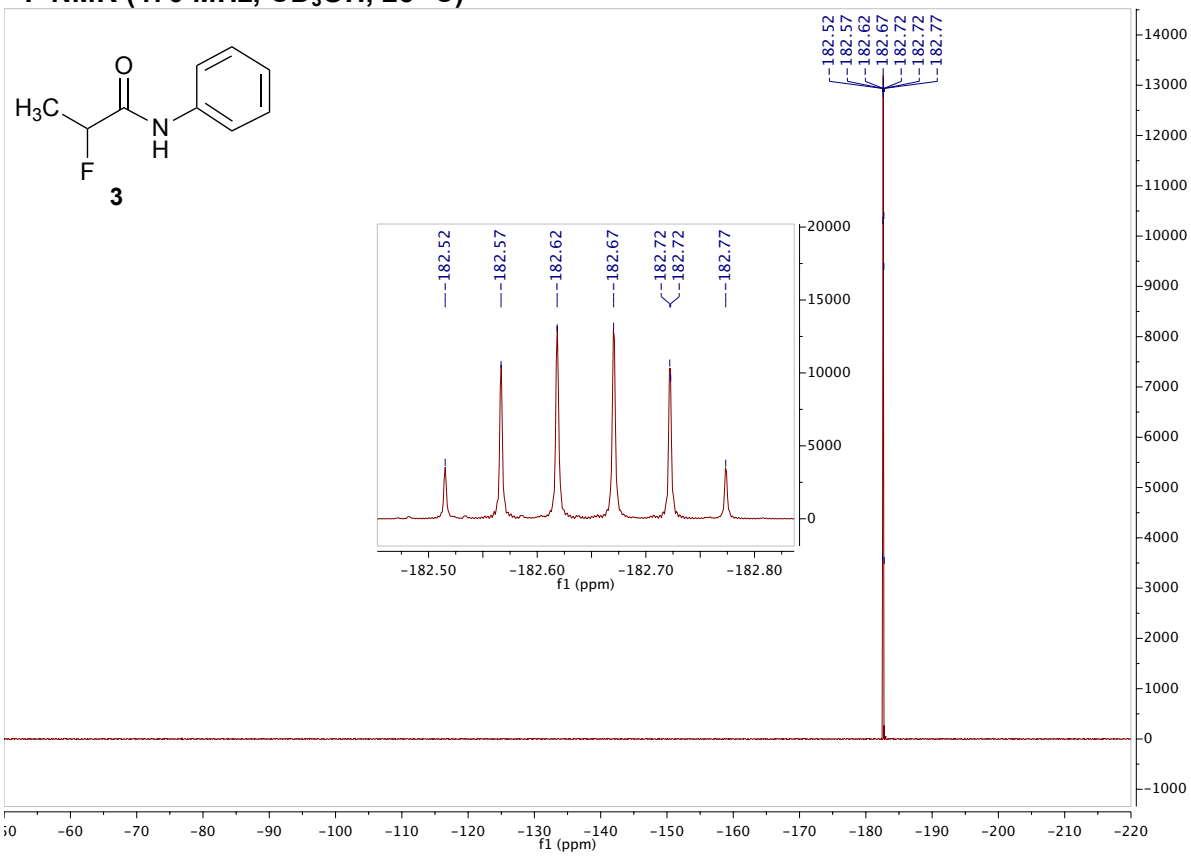
^{1}H NMR (500 MHz, CD_3OH, 25 ºC) with excitation sculpting *(integration issues close to residual OH signal)*



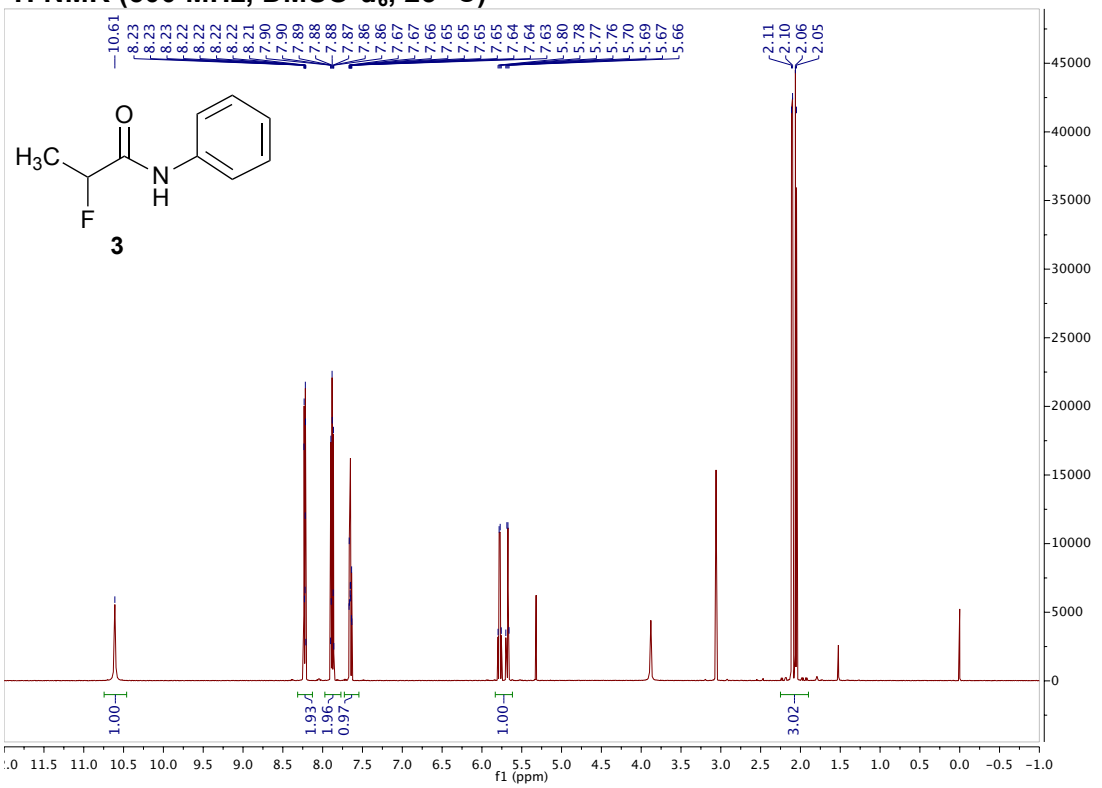
^{13}C NMR (126 MHz, CD_3OH, 25 ºC)



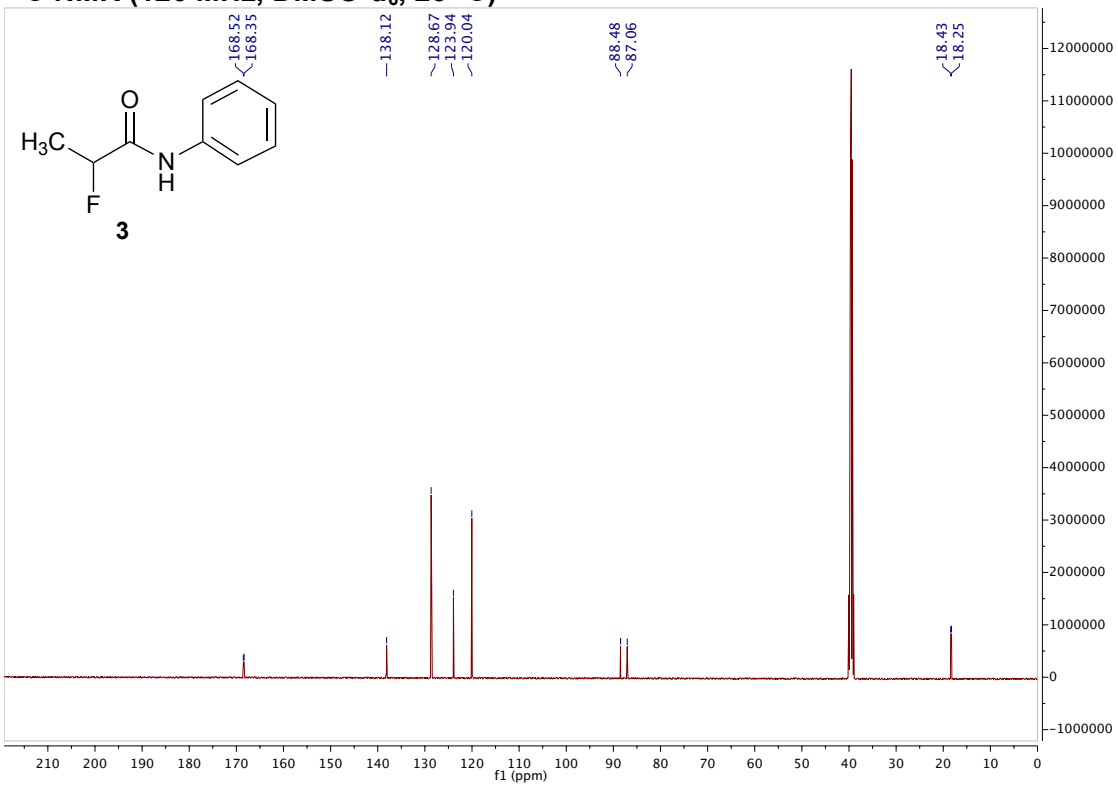
^{19}F NMR (470 MHz, CD_3OH, 25 ºC)



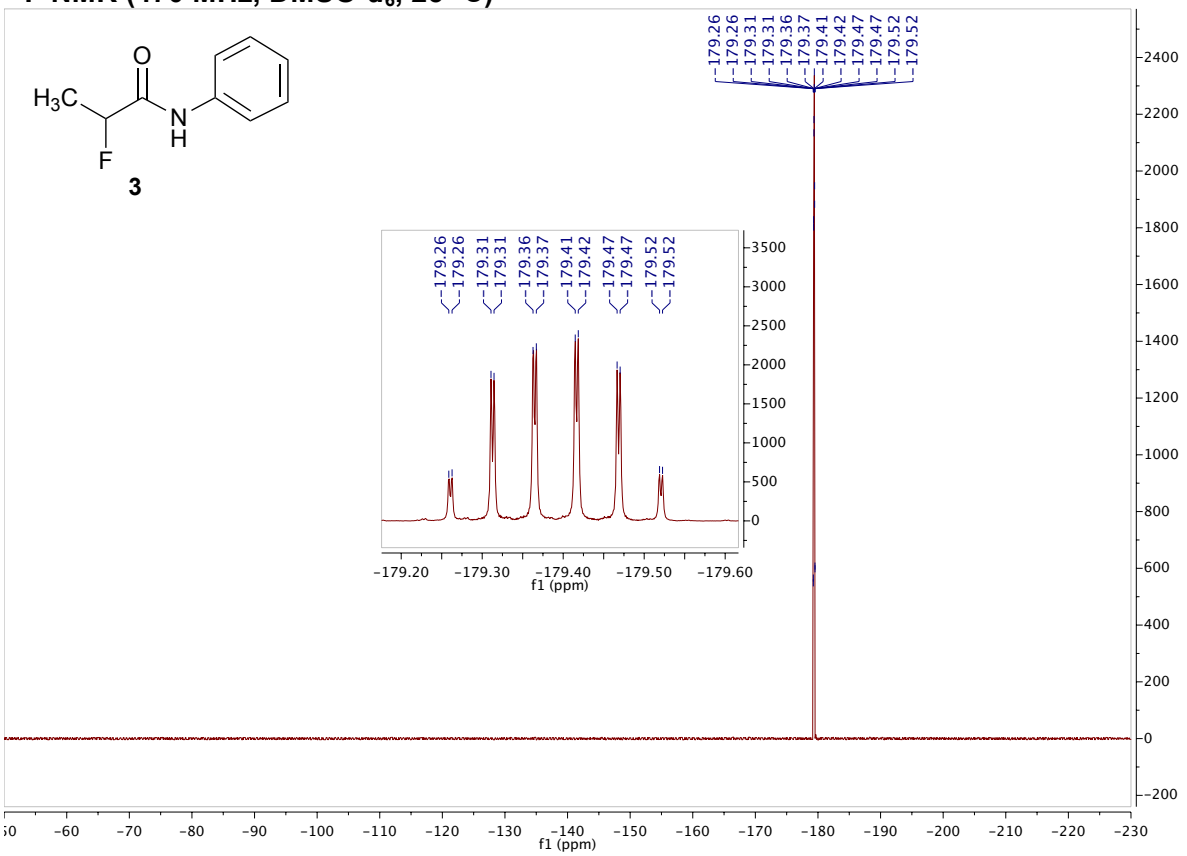
^{1}H NMR (500 MHz, DMSO-d_6, 25 ºC)



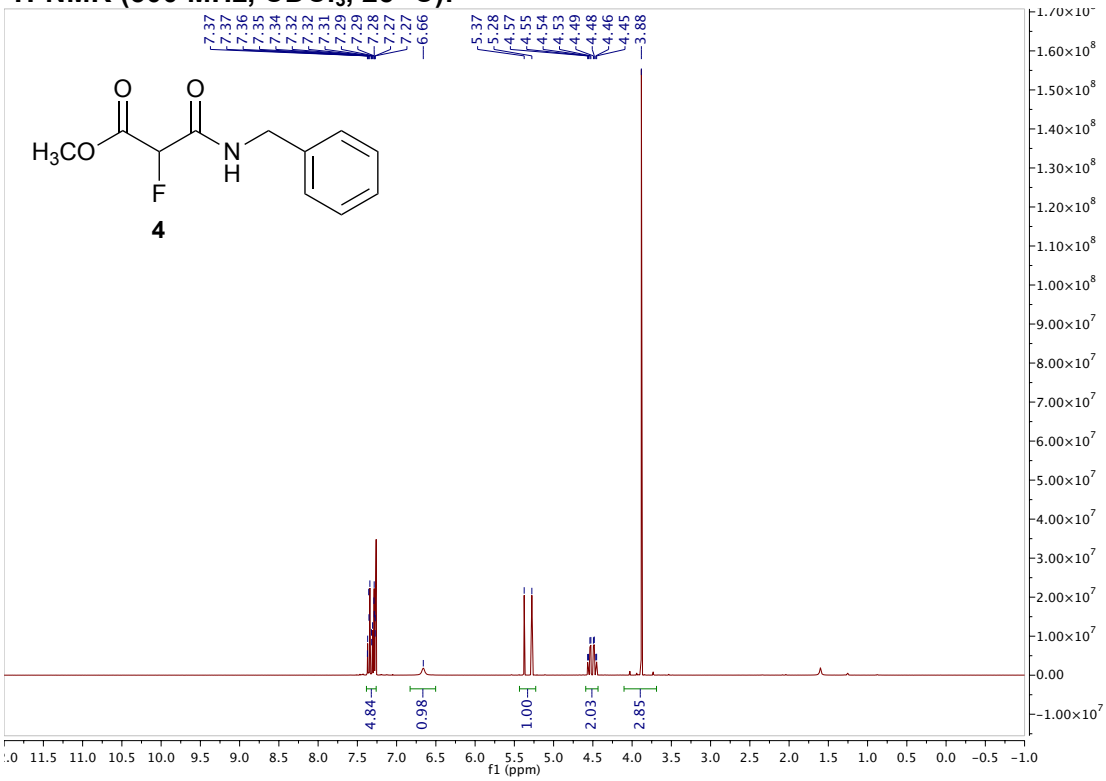
^{13}C NMR (126 MHz, DMSO-d_6, 25 ºC)



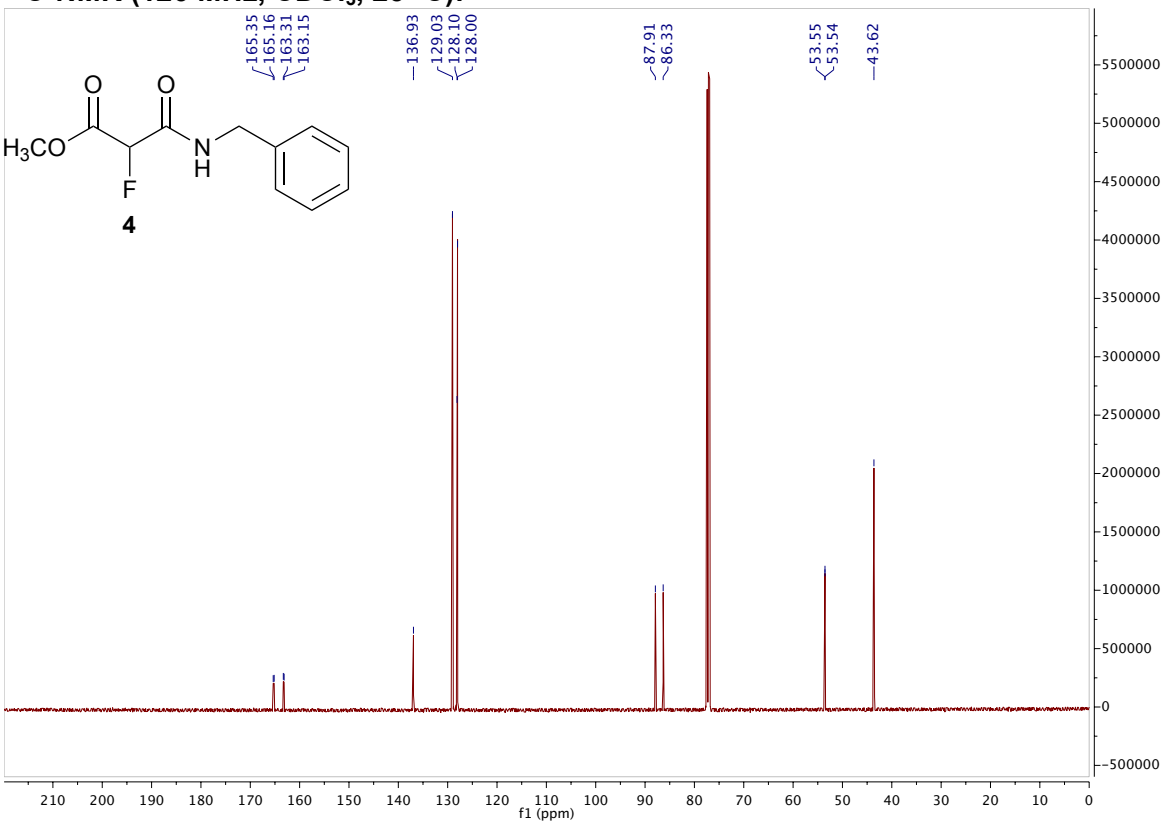
^{19}F NMR (470 MHz, DMSO-d_6, 25 ºC)



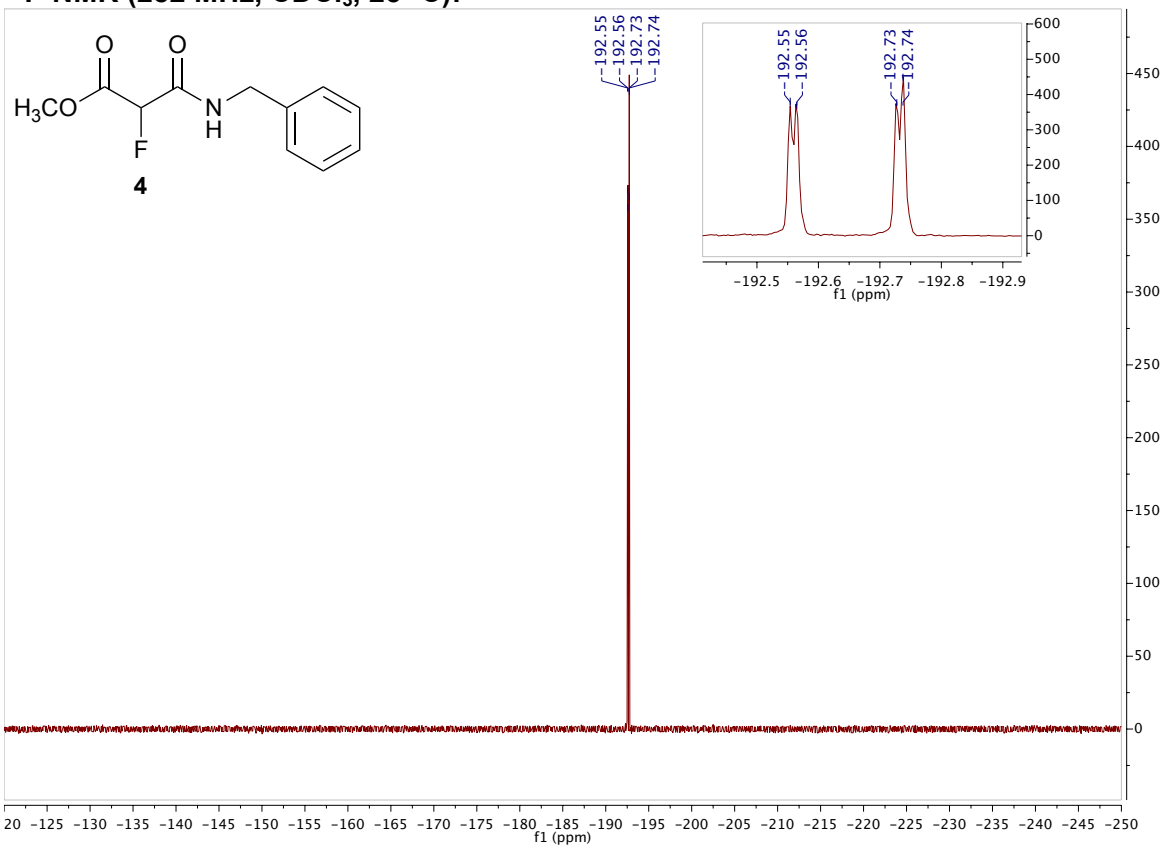
^{1}H-NMR (500 MHz, $CDCl_3$, 25 ºC):



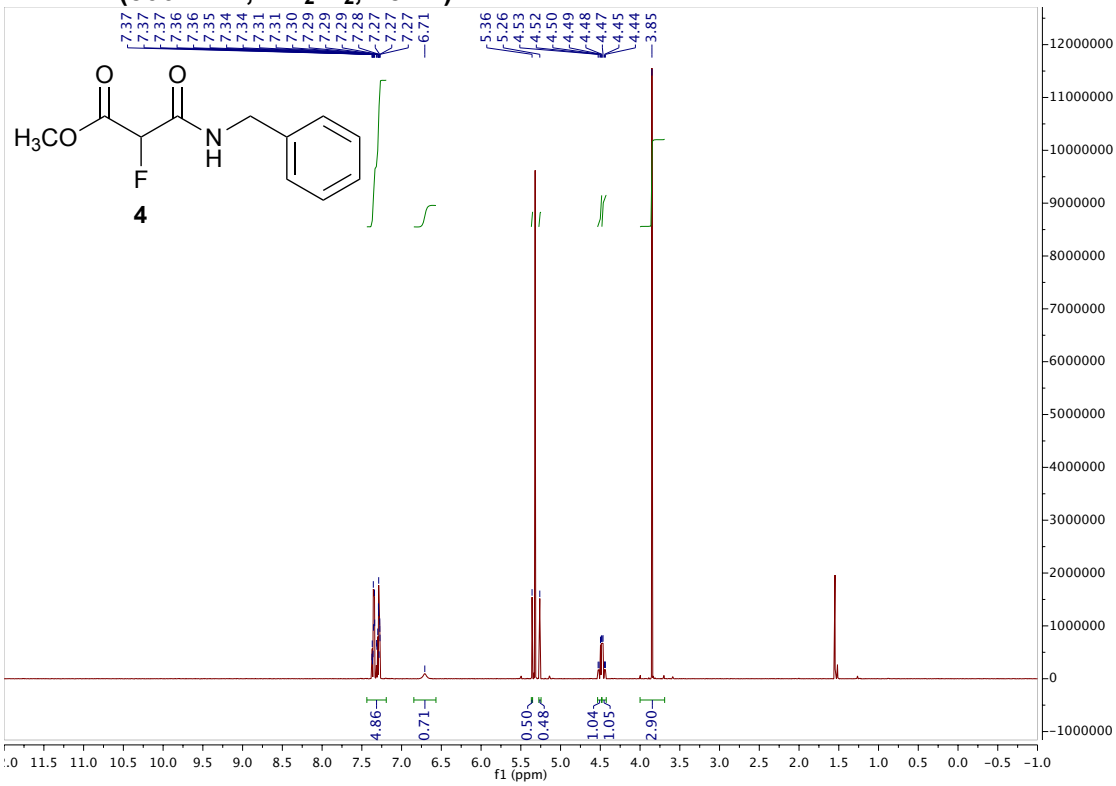
^{13}C-NMR (126 MHz, $CDCl_3$, 25 ºC):



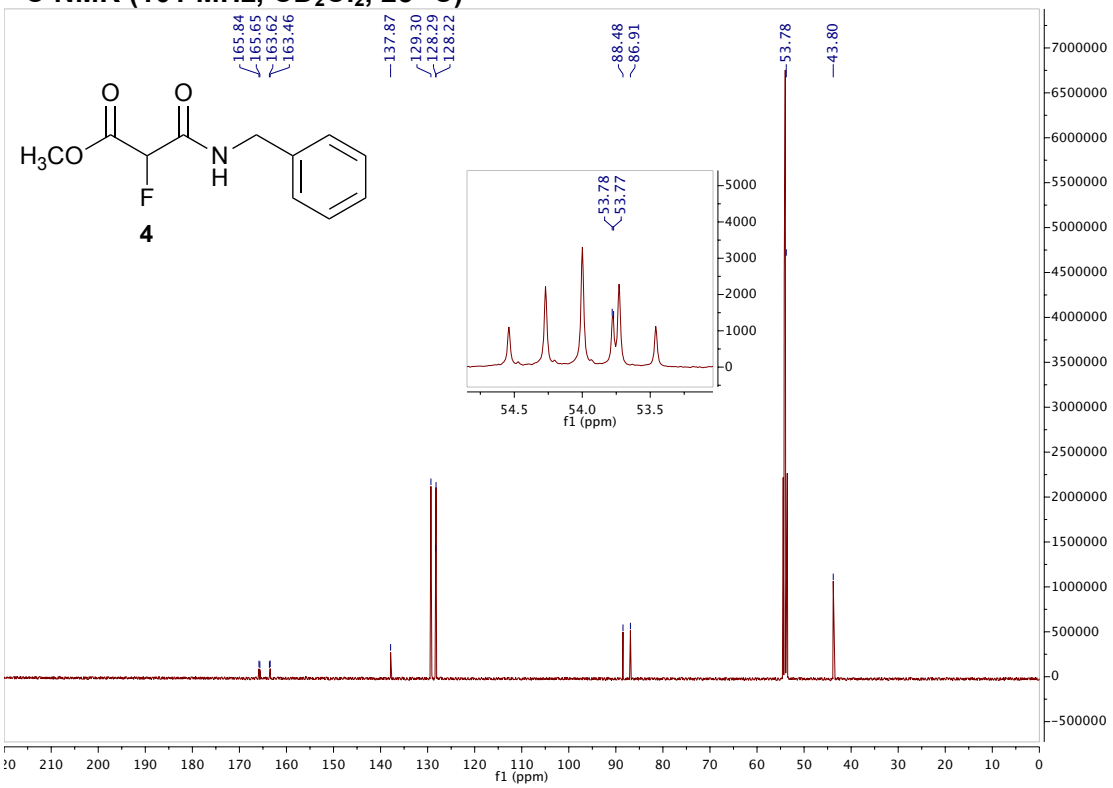
^{19}F-NMR (282 MHz, $CDCl_3$, 25 ºC):



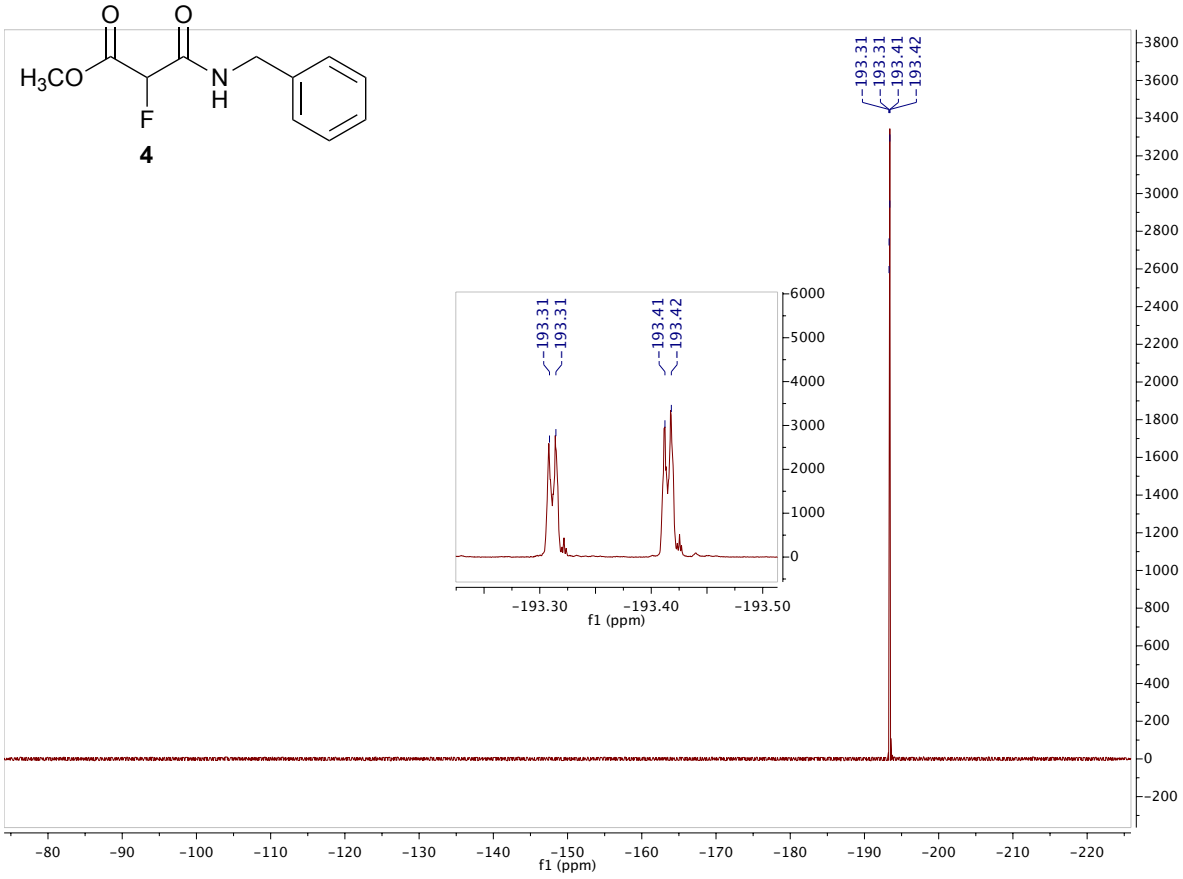
^{1}H NMR (500 MHz, CD_2Cl_2, 25 ºC)



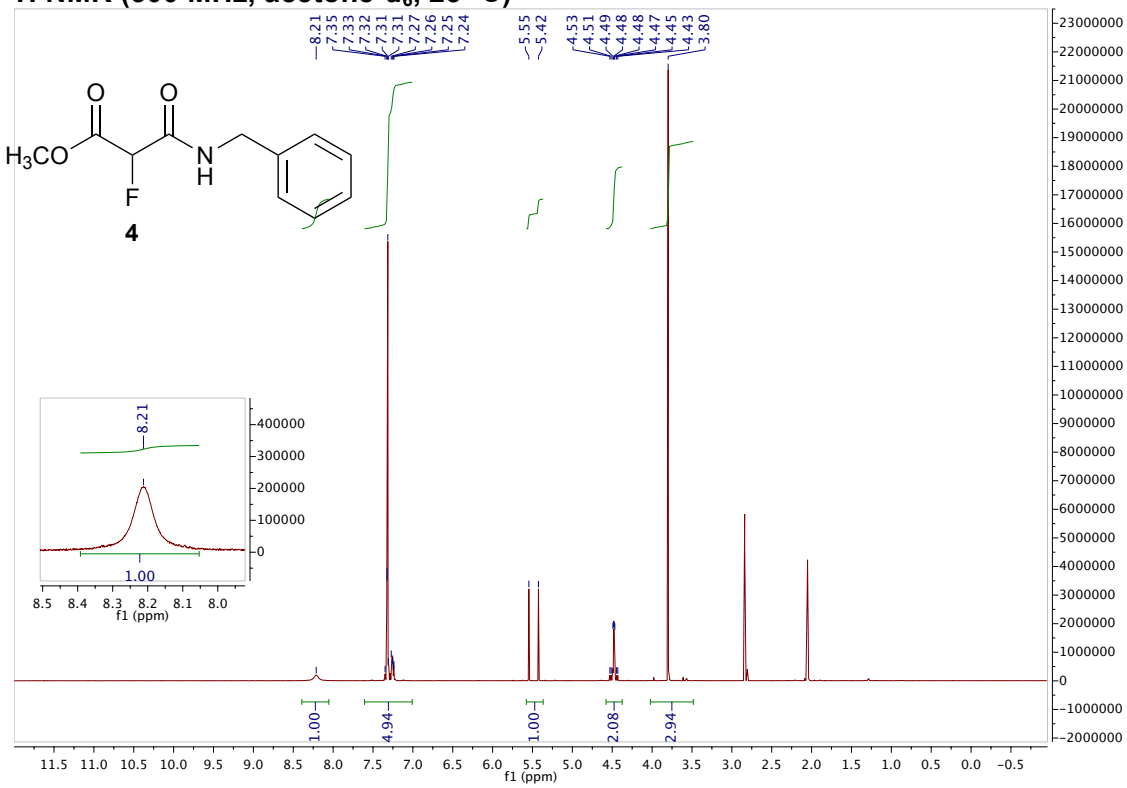
^{13}C NMR (101 MHz, CD_2Cl_2, 25 ºC)



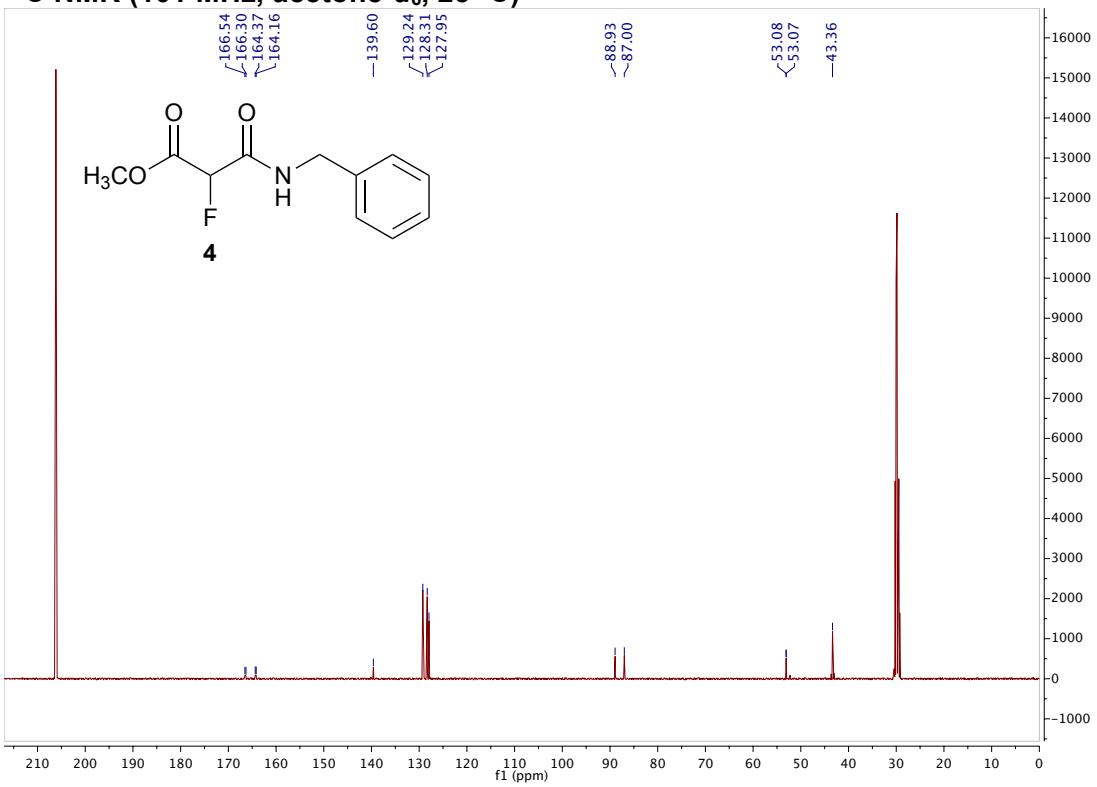
^{19}F NMR (470 MHz, CD_2Cl_2, 25 ºC)



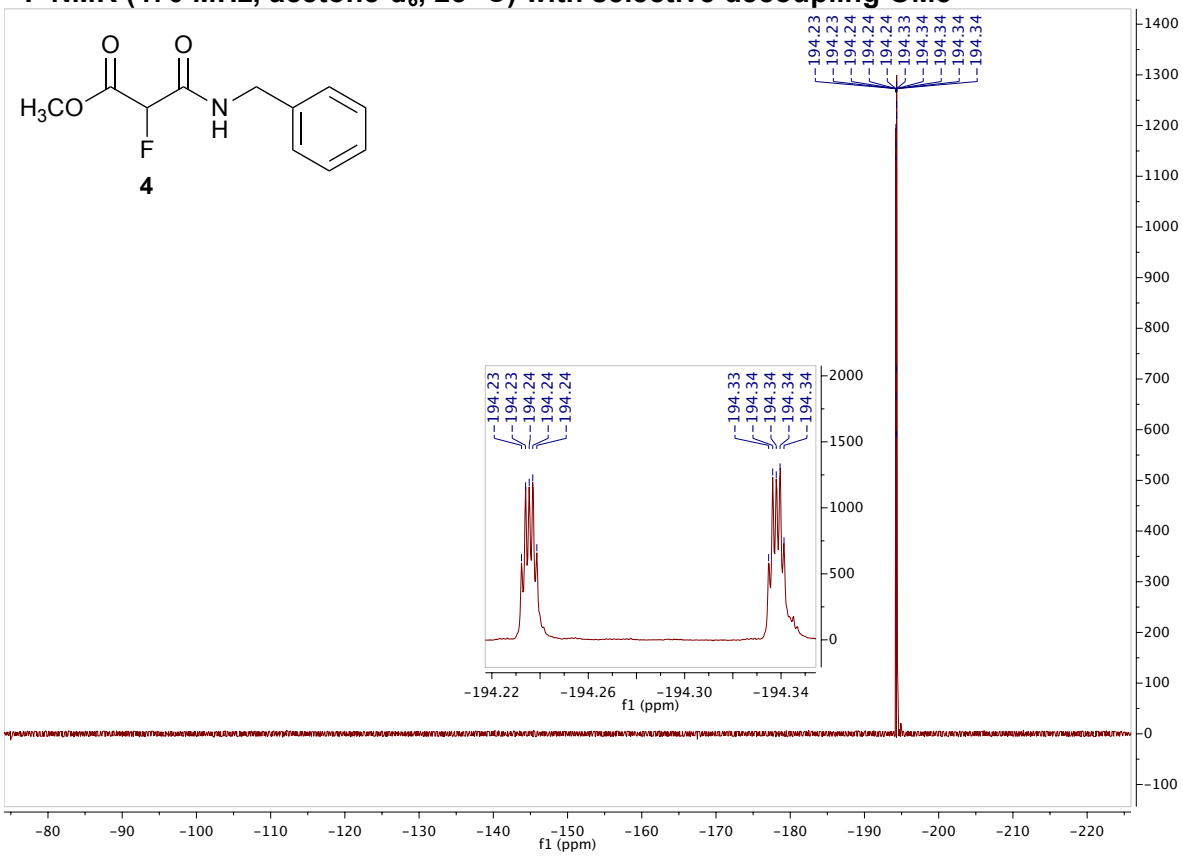
^{1}H NMR (300 MHz, acetone-d_6, 25 ºC)



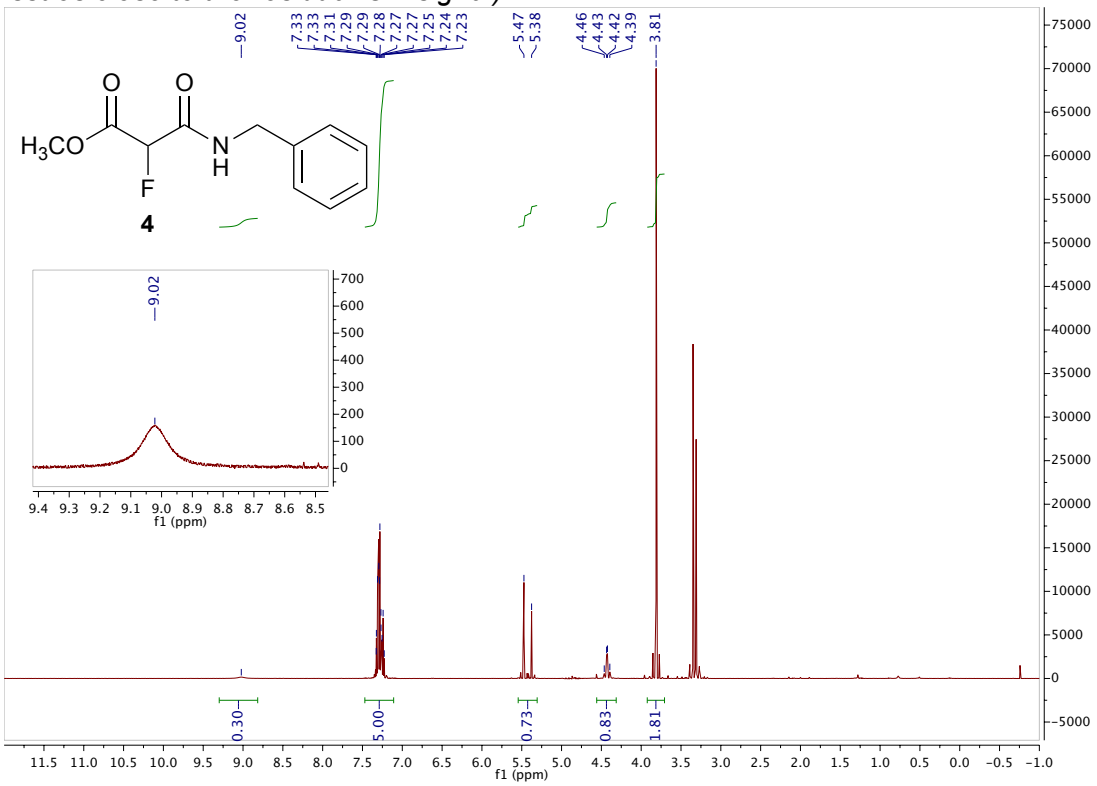
^{13}C NMR (101 MHz, acetone-d_6, 25 ºC)



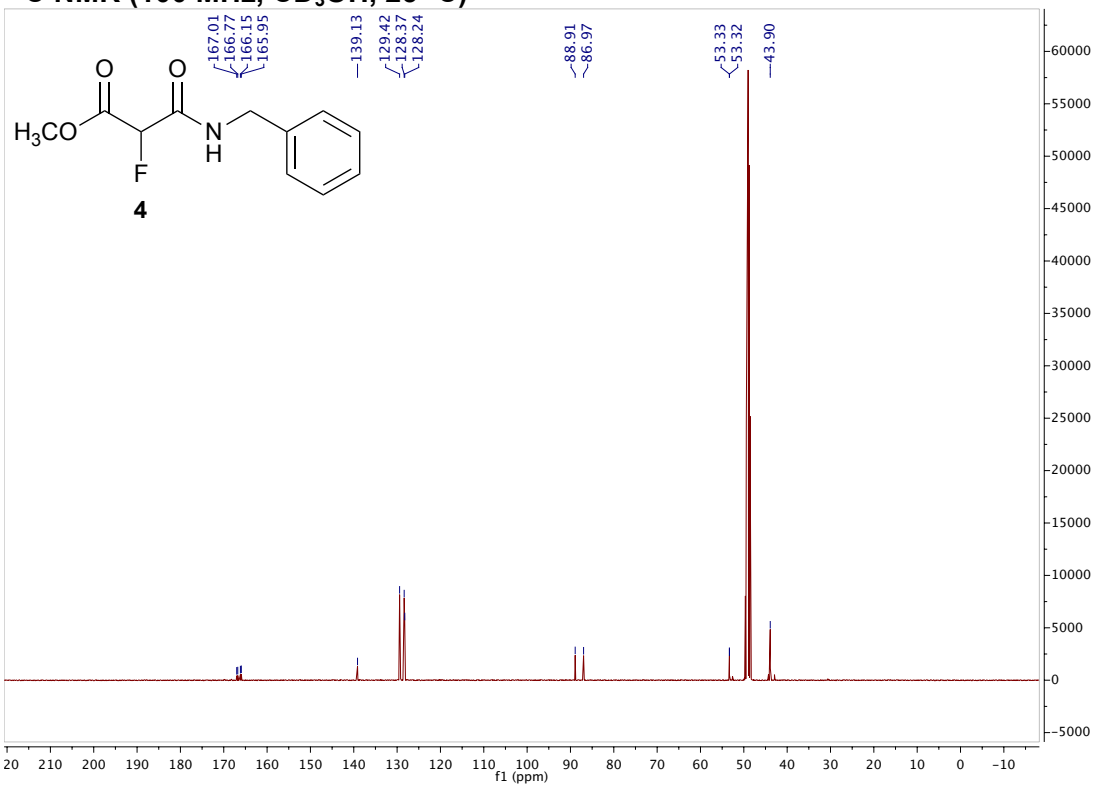
^{19}F NMR (470 MHz, acetone-d_6, 25 ºC) with selective decoupling OMe



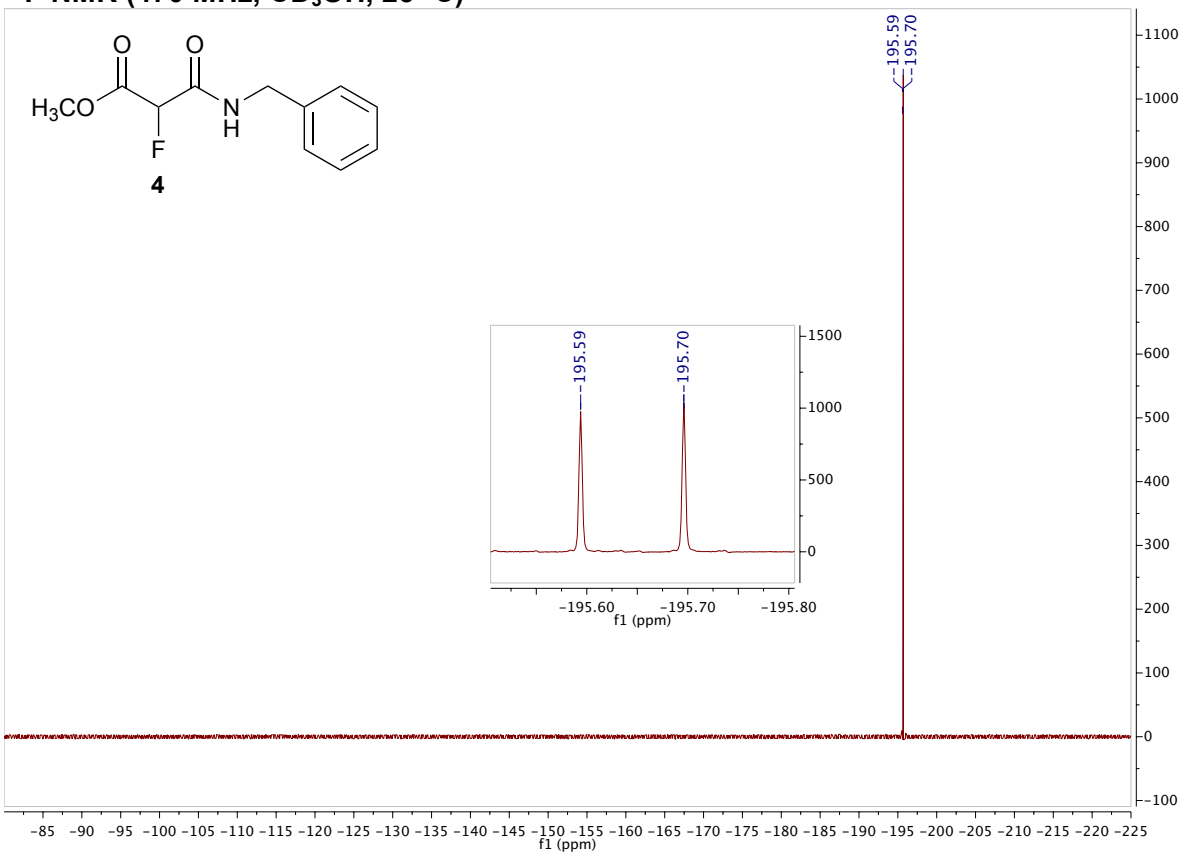
^{1}H NMR (500 MHz, CD_3OH, 25 ºC) with excitation sculpting *(shimming issues and integration issues close to the residual OH signal)*



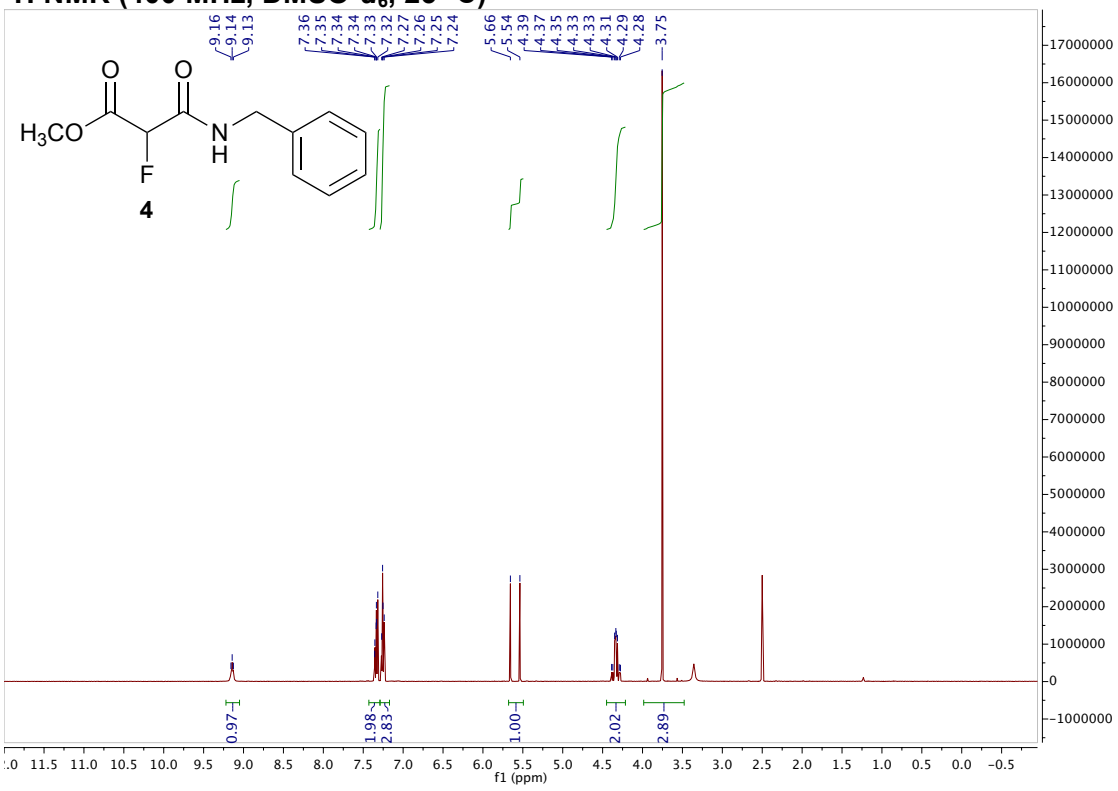
^{13}C NMR (100 MHz, CD_3OH, 25 ºC)



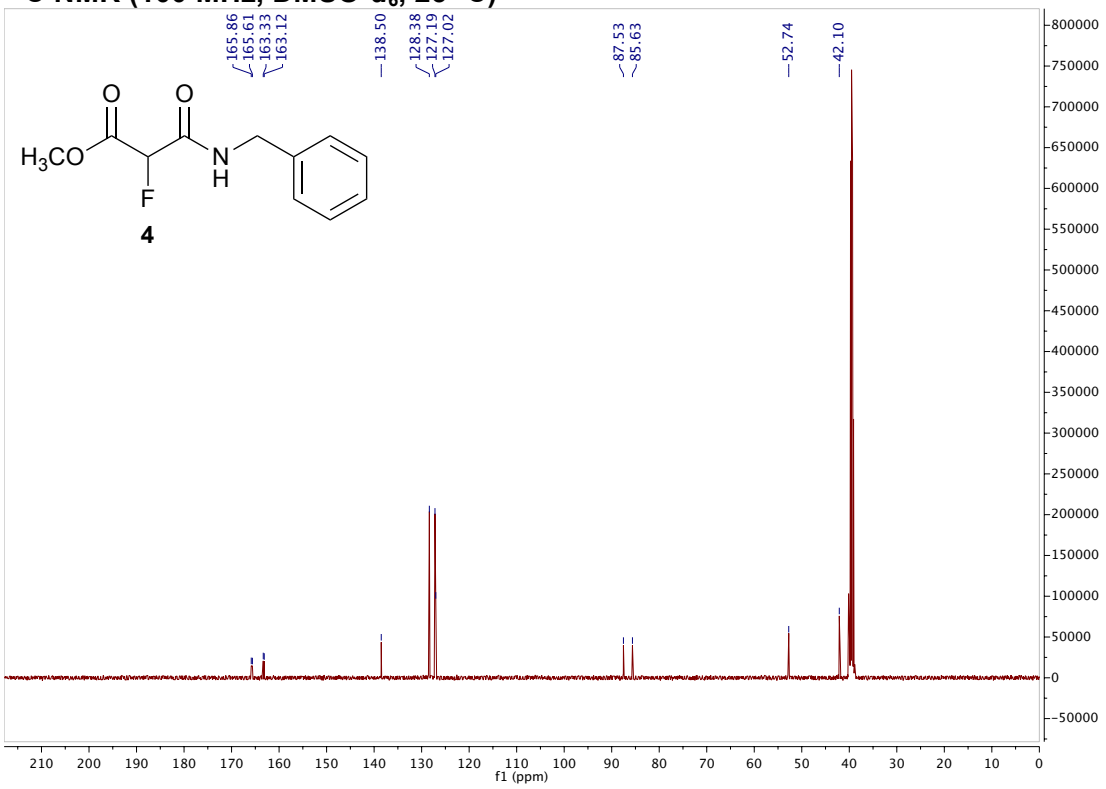
^{19}F NMR (470 MHz, CD_3OH, 25 ºC)



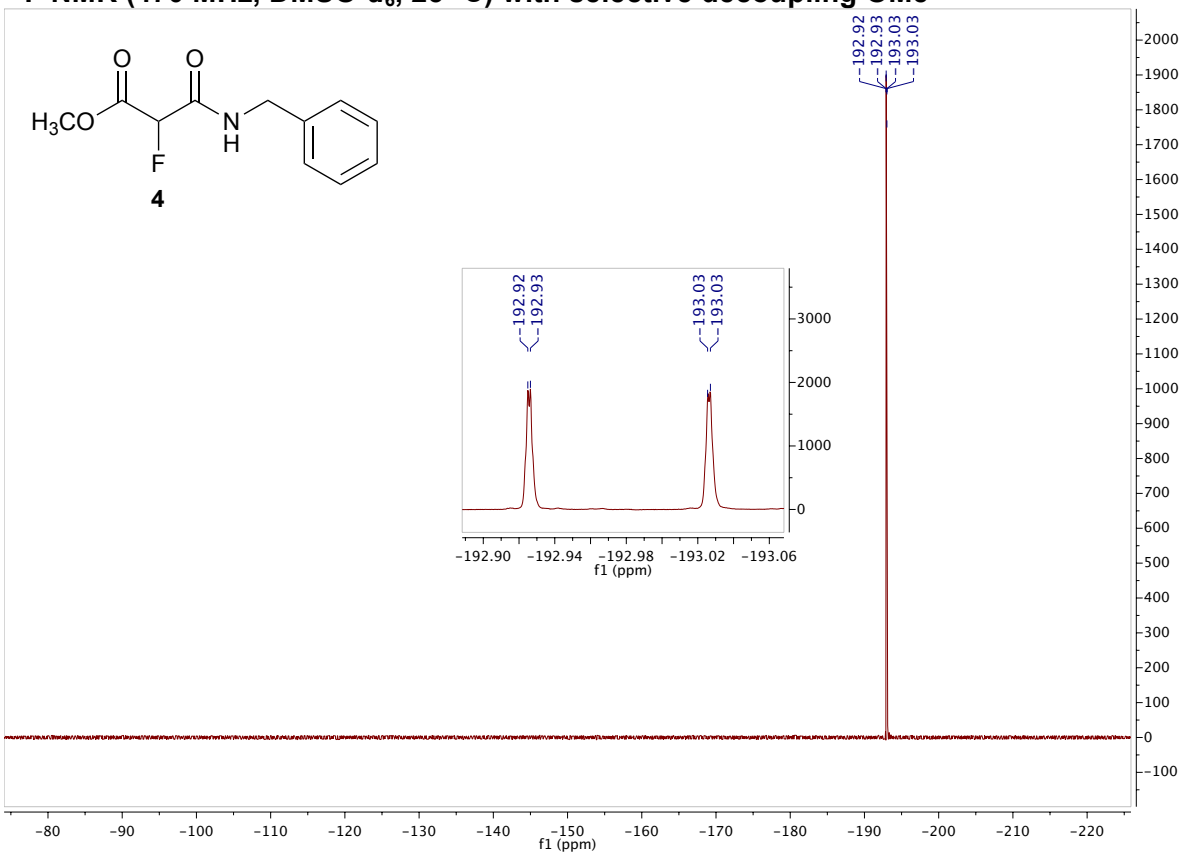
^{1}H NMR (400 MHz, DMSO-d_6, 25 ºC)



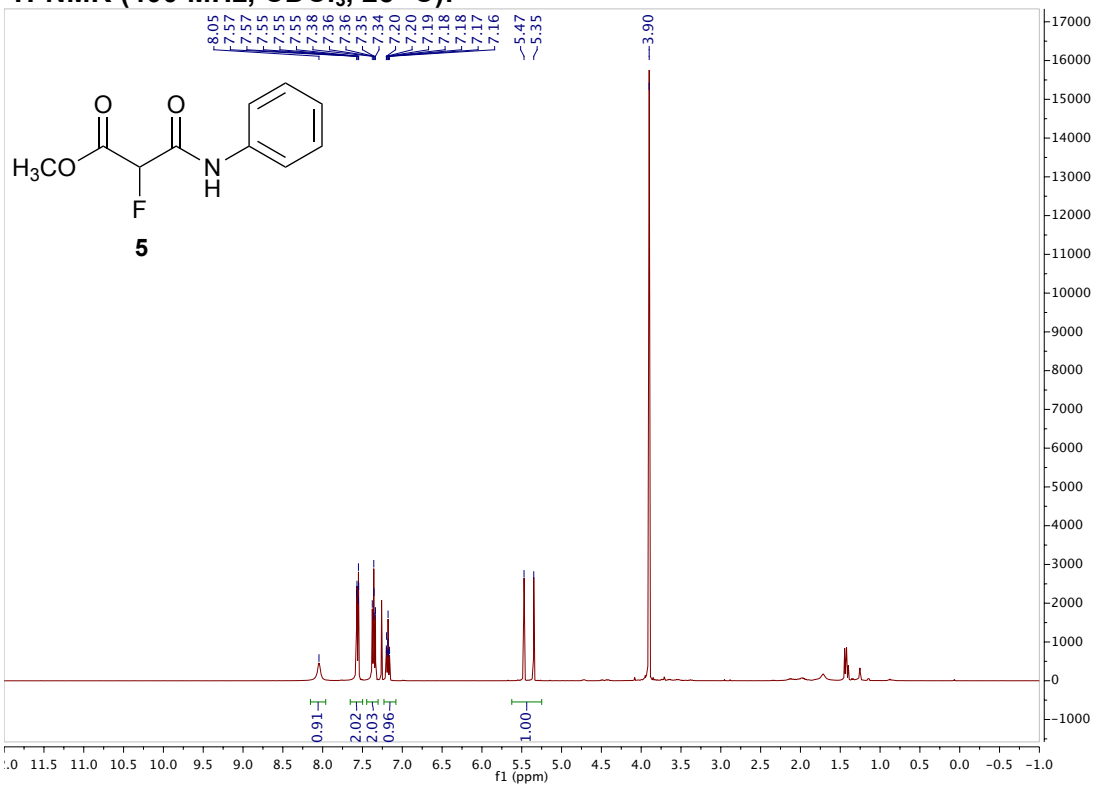
^{13}C NMR (100 MHz, DMSO-d_6, 25 ºC)



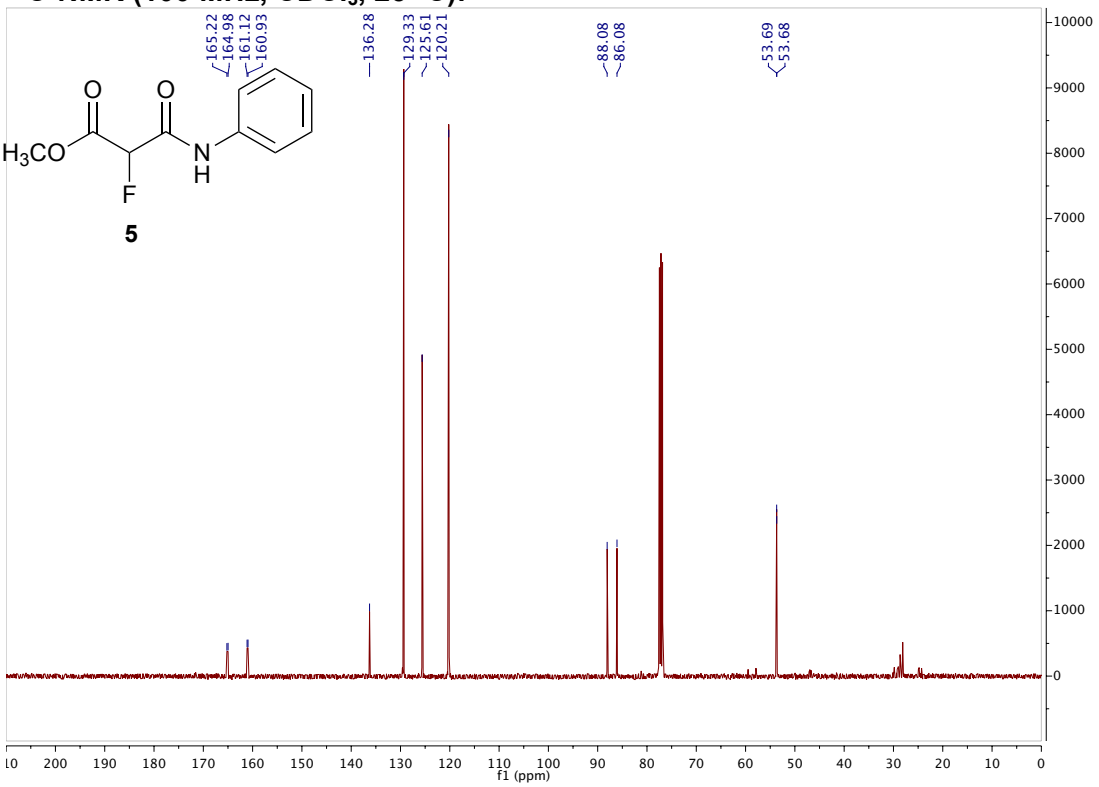
^{19}F NMR (470 MHz, DMSO-d_6, 25 ºC) with selective decoupling OMe



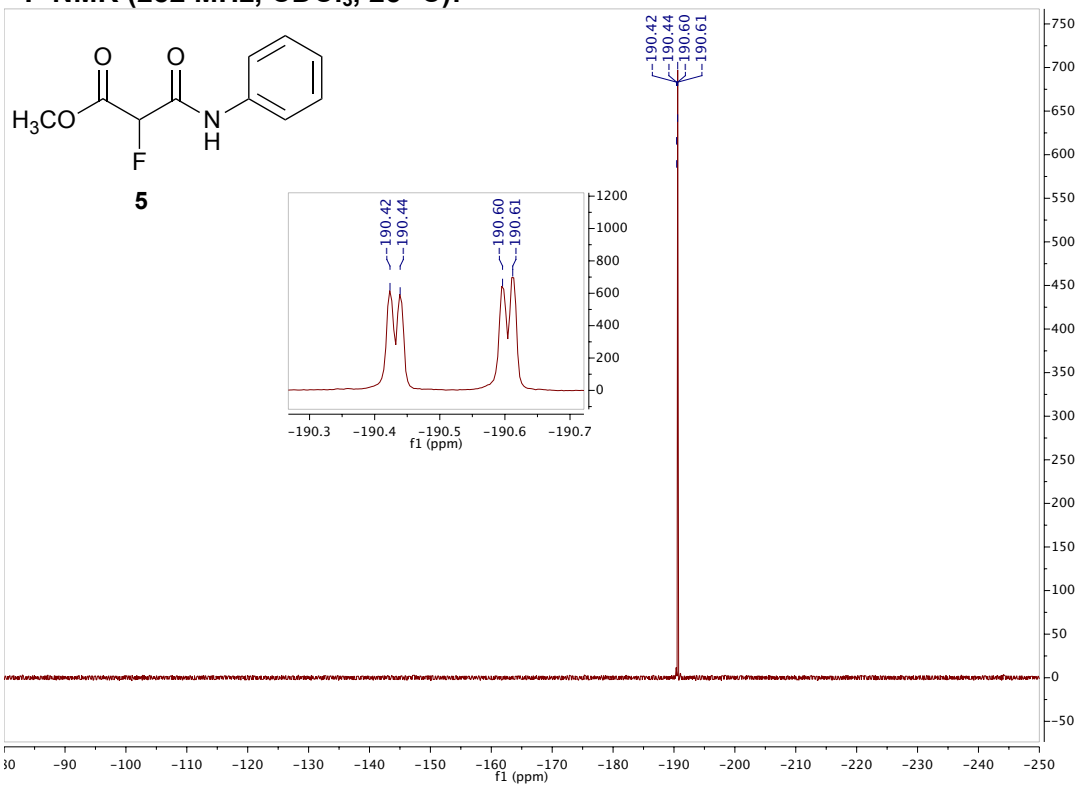
^{1}H-NMR (400 MHz, $CDCl_3$, 25 ºC):



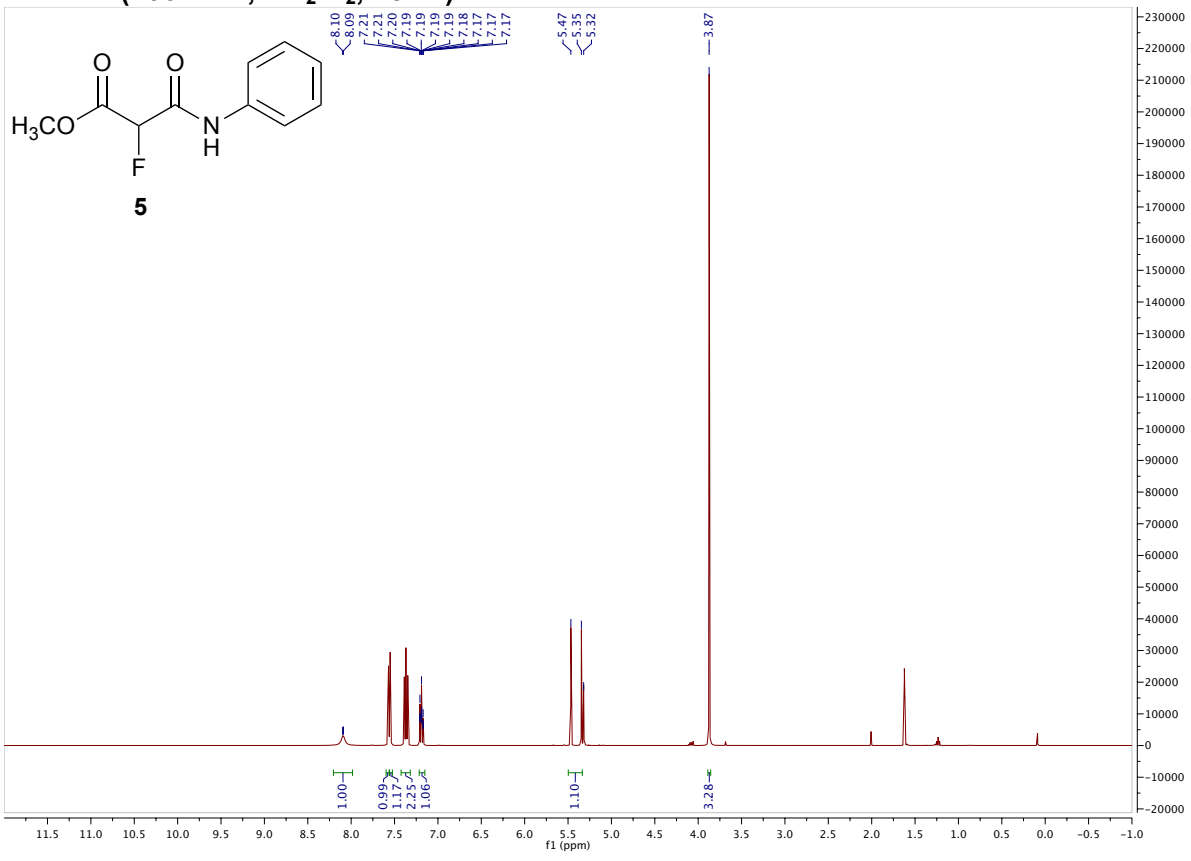
^{13}C-NMR (100 MHz, $CDCl_3$, 25 ºC):



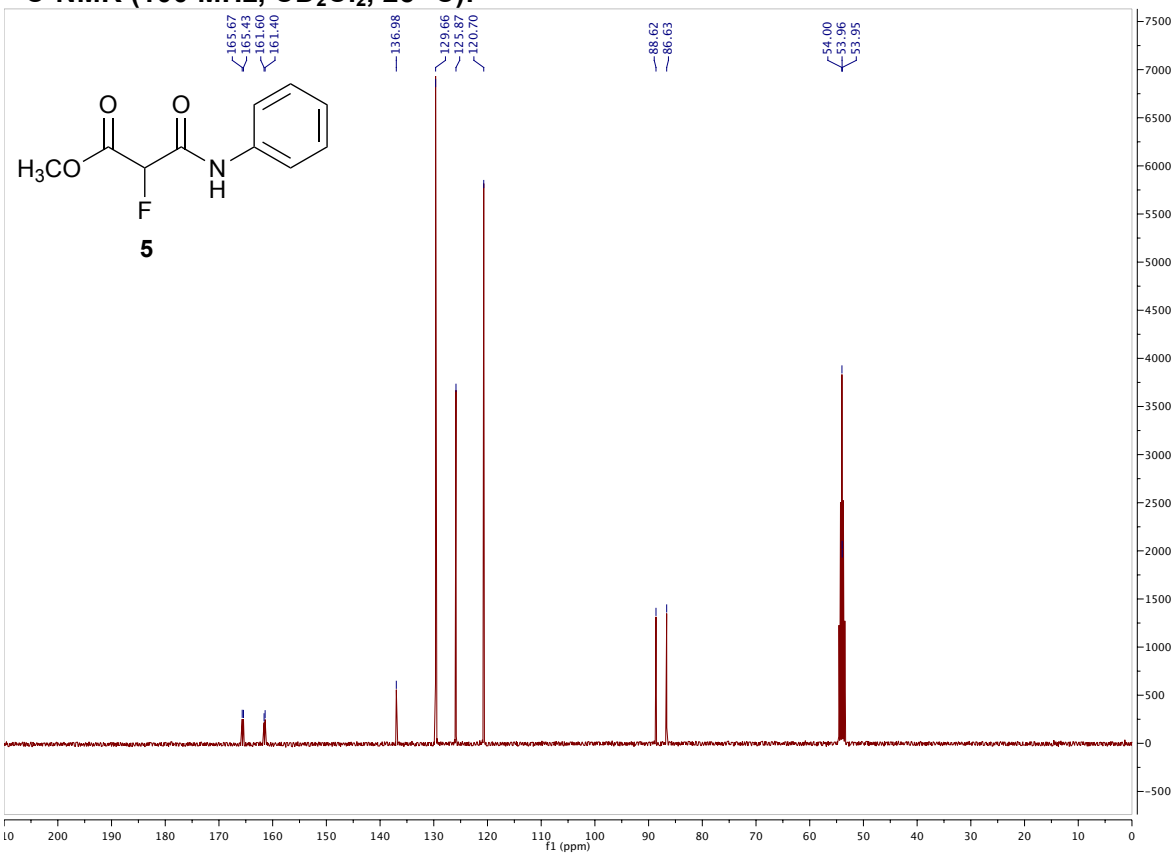
^{19}F-NMR (282 MHz, $CDCl_3$, 25 ºC):



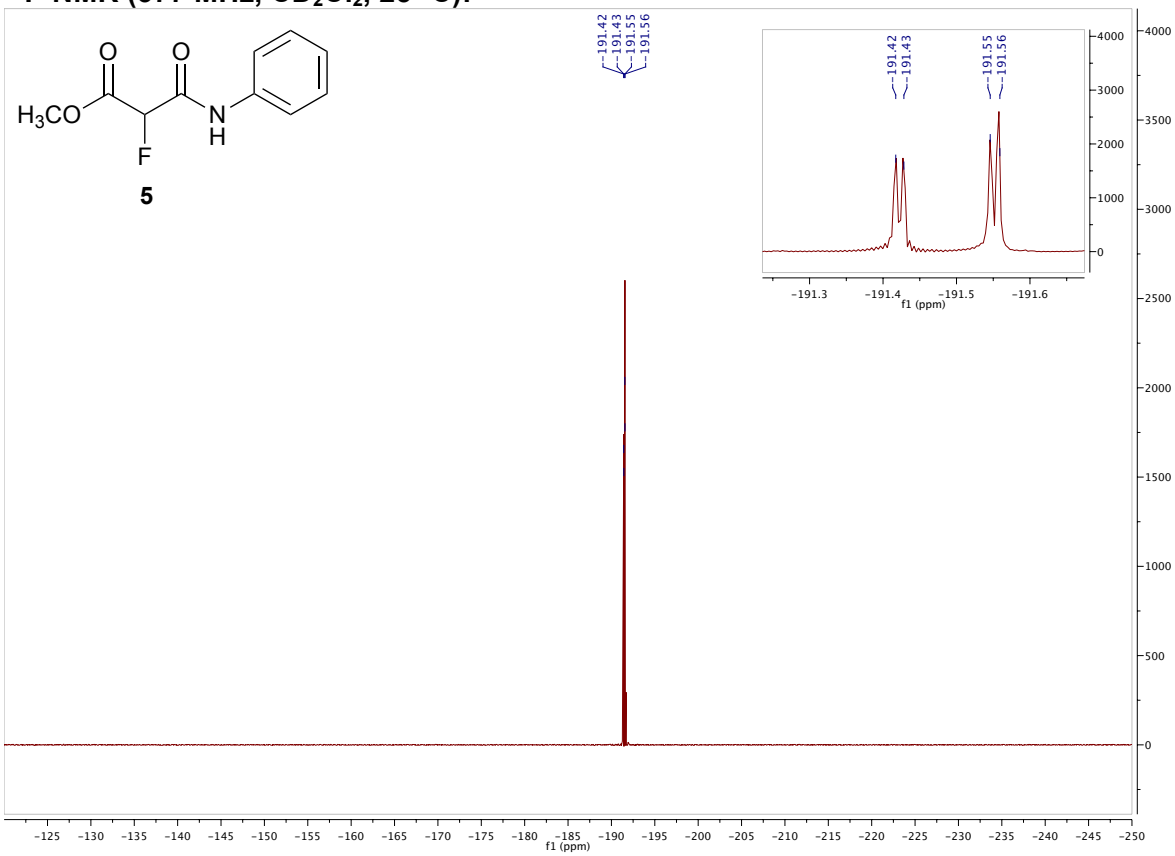
^{1}H-NMR (400 MHz, CD_2Cl_2, 25 ºC):



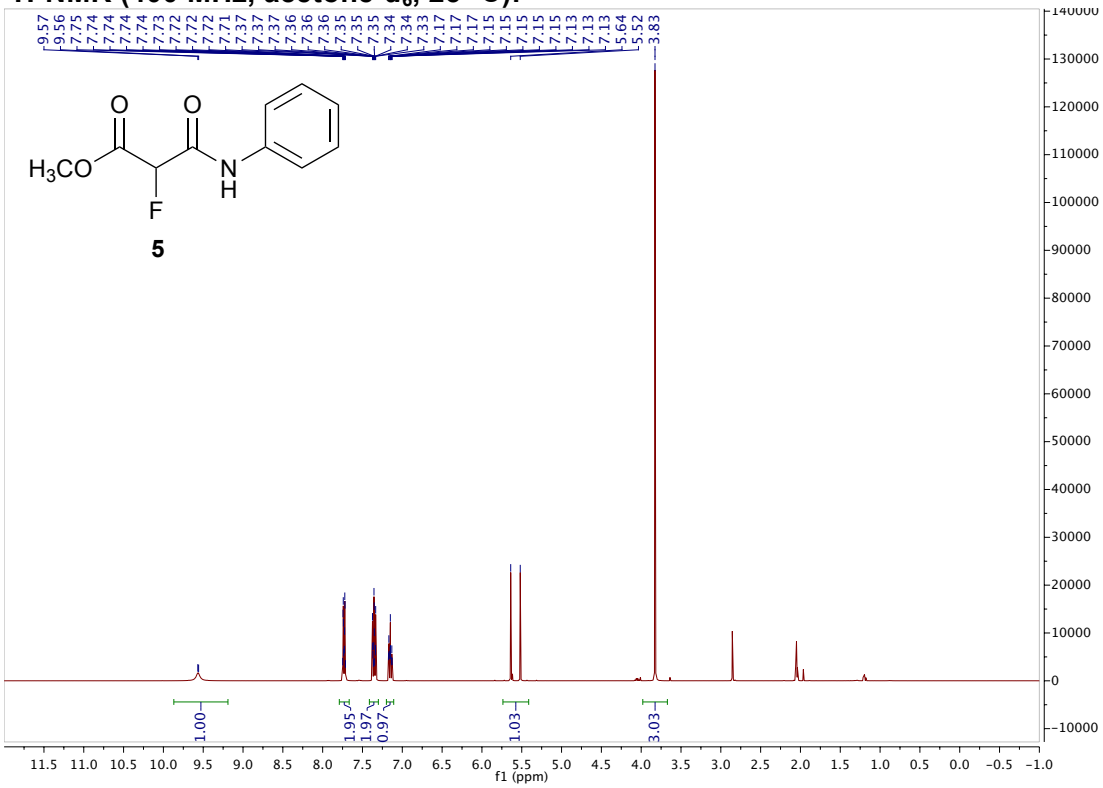
^{13}C-NMR (100 MHz, CD_2Cl_2, 25 ºC):



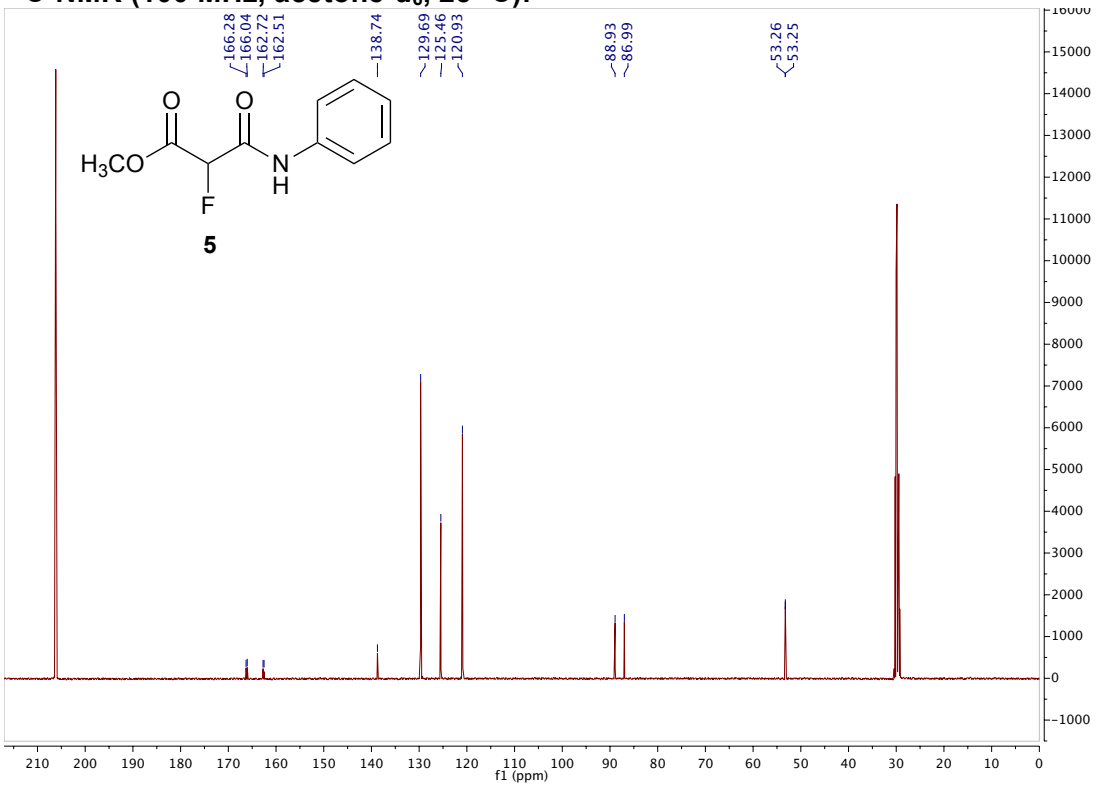
^{19}F-NMR (377 MHz, CD_2Cl_2, 25 ºC):



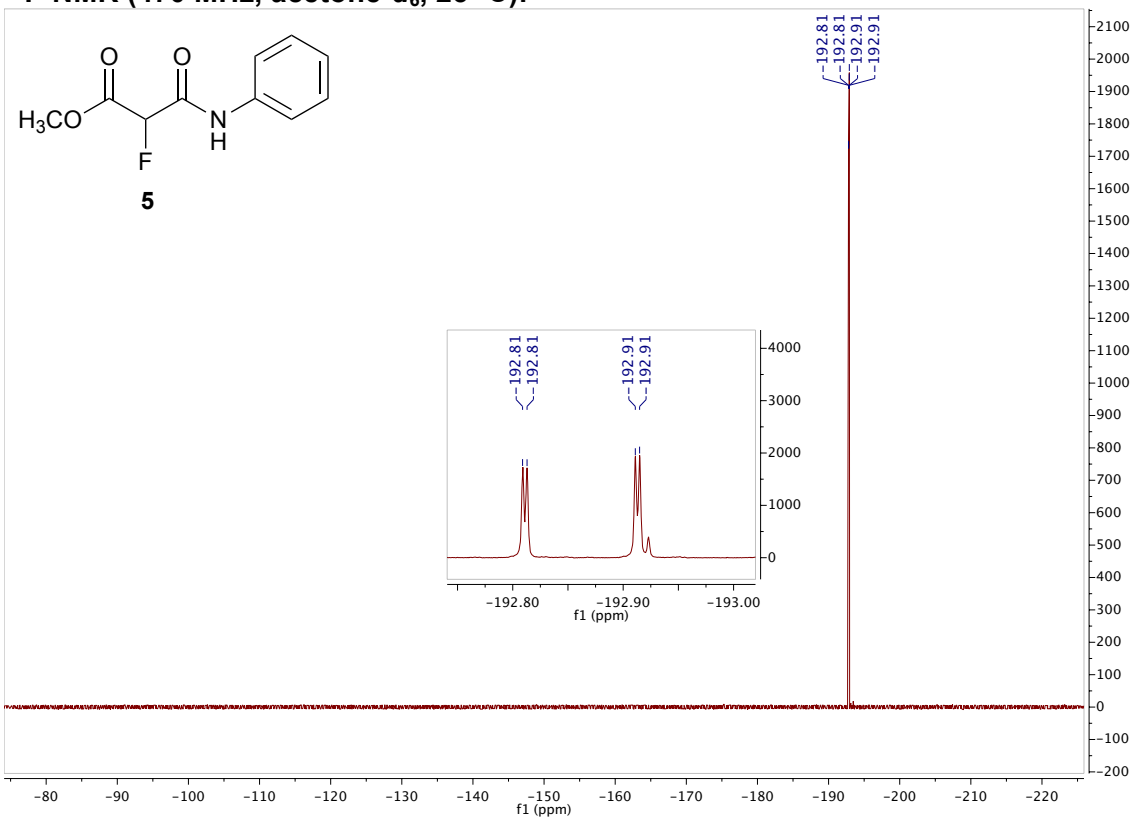
^{1}H-NMR (400 MHz, acetone-d_6, 25 ºC):



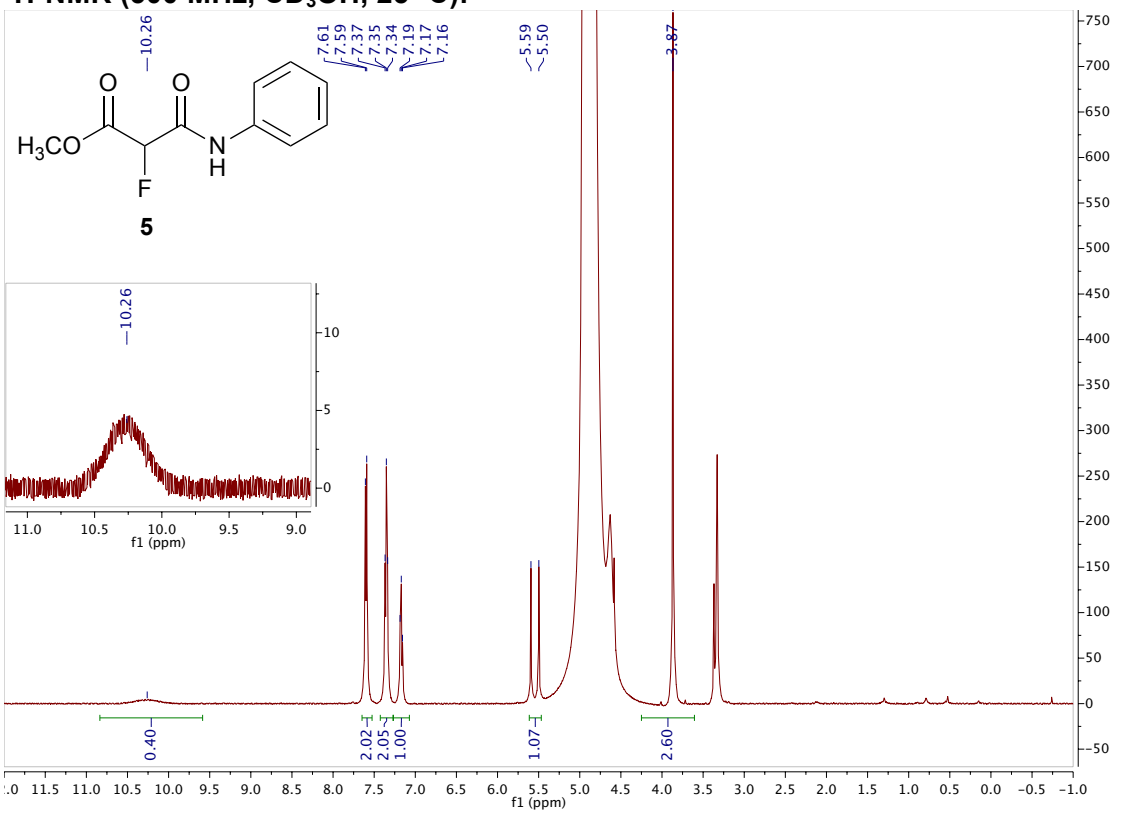
^{13}C-NMR (100 MHz, acetone-d_6, 25 ºC):



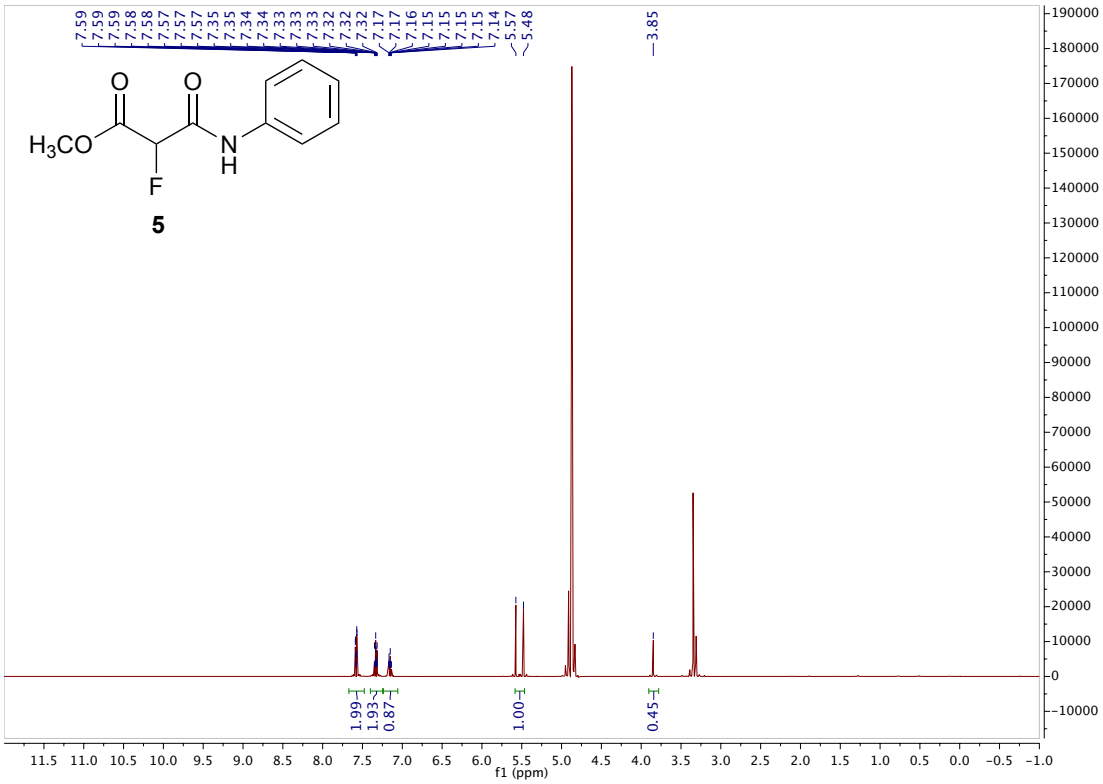
^{19}F-NMR (470 MHz, acetone-d_6, 25 ºC):



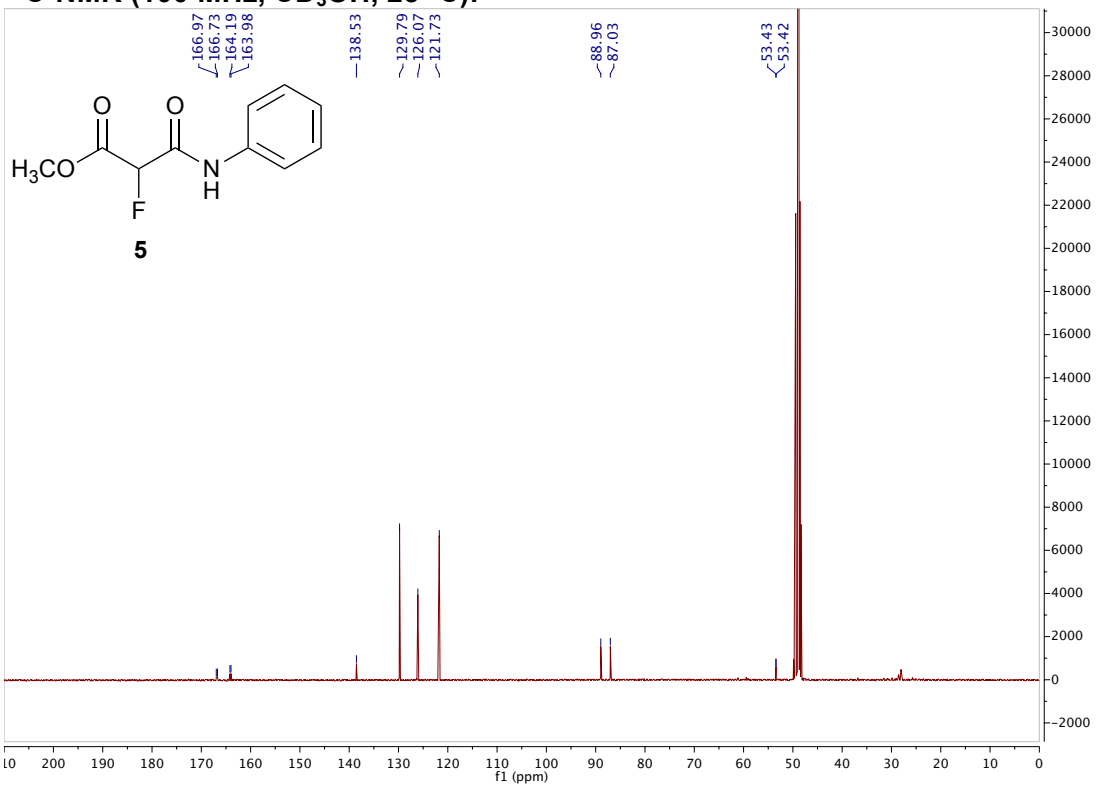
^{1}H-NMR (500 MHz, CD_3OH, 25 ºC):



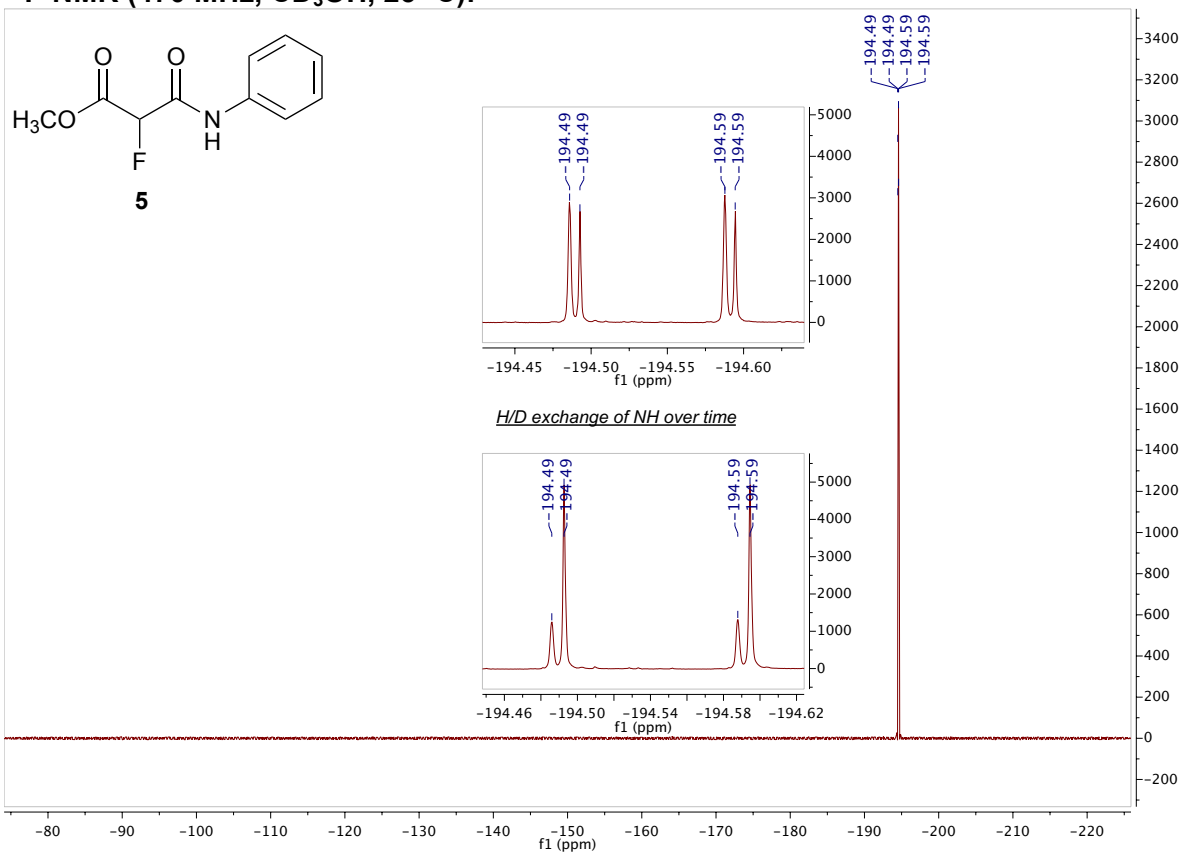
^{1}H-NMR (500 MHz, CD_3OH, 25 ºC) with excitation sculpting *(integration issues close to residual OH signal)*



^{13}C-NMR (100 MHz, CD_3OH, 25 ºC):

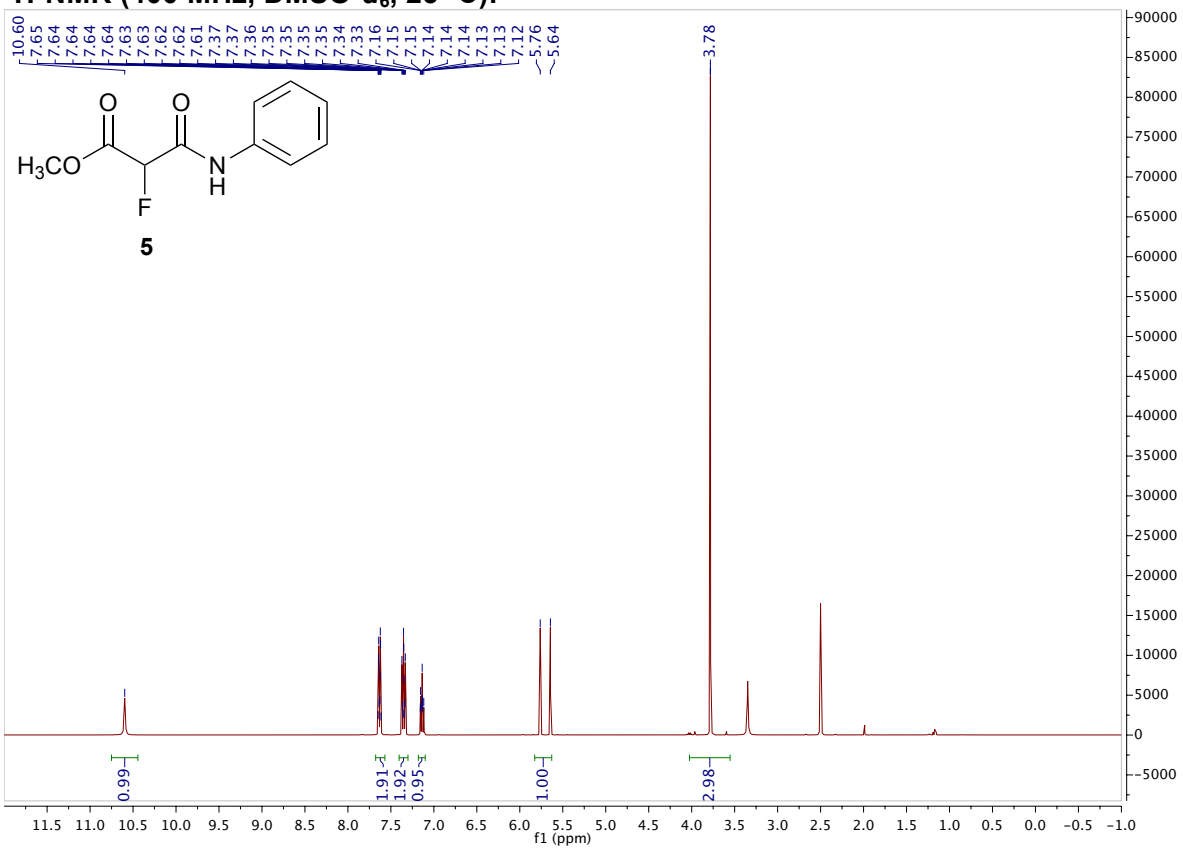


^{19}F-NMR (470 MHz, CD_3OH, 25 ºC):



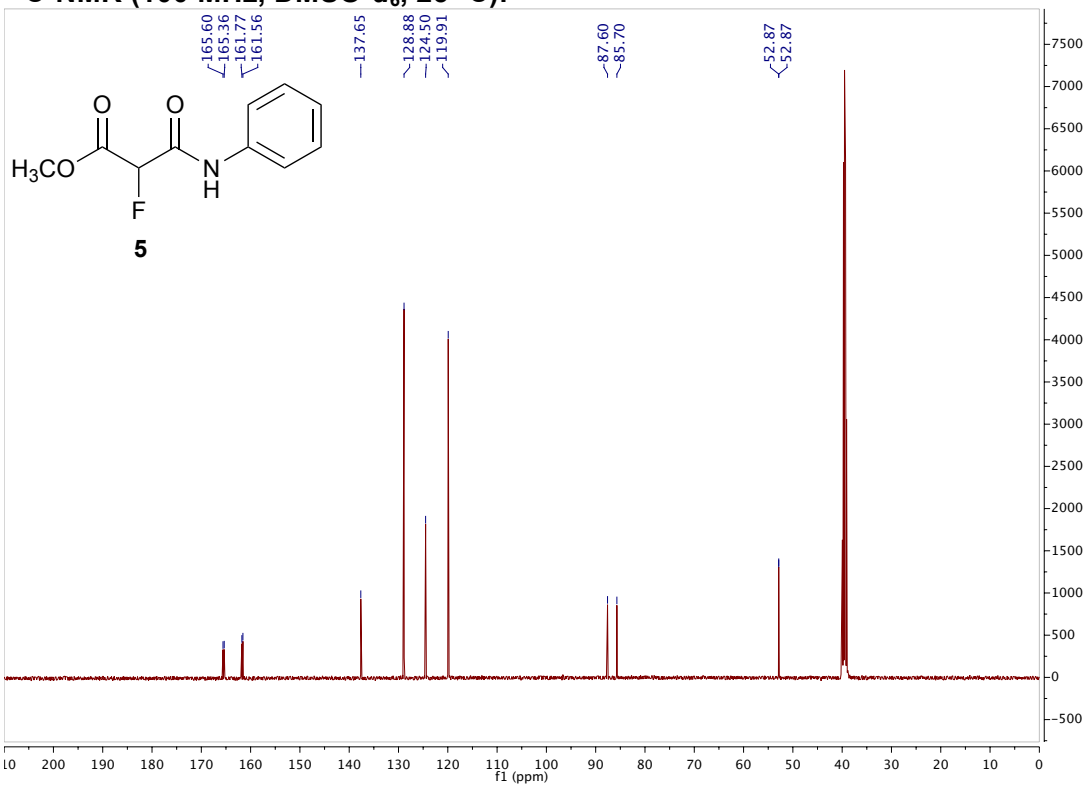
5

^{1}H-NMR (400 MHz, DMSO-d_6, 25 ºC):

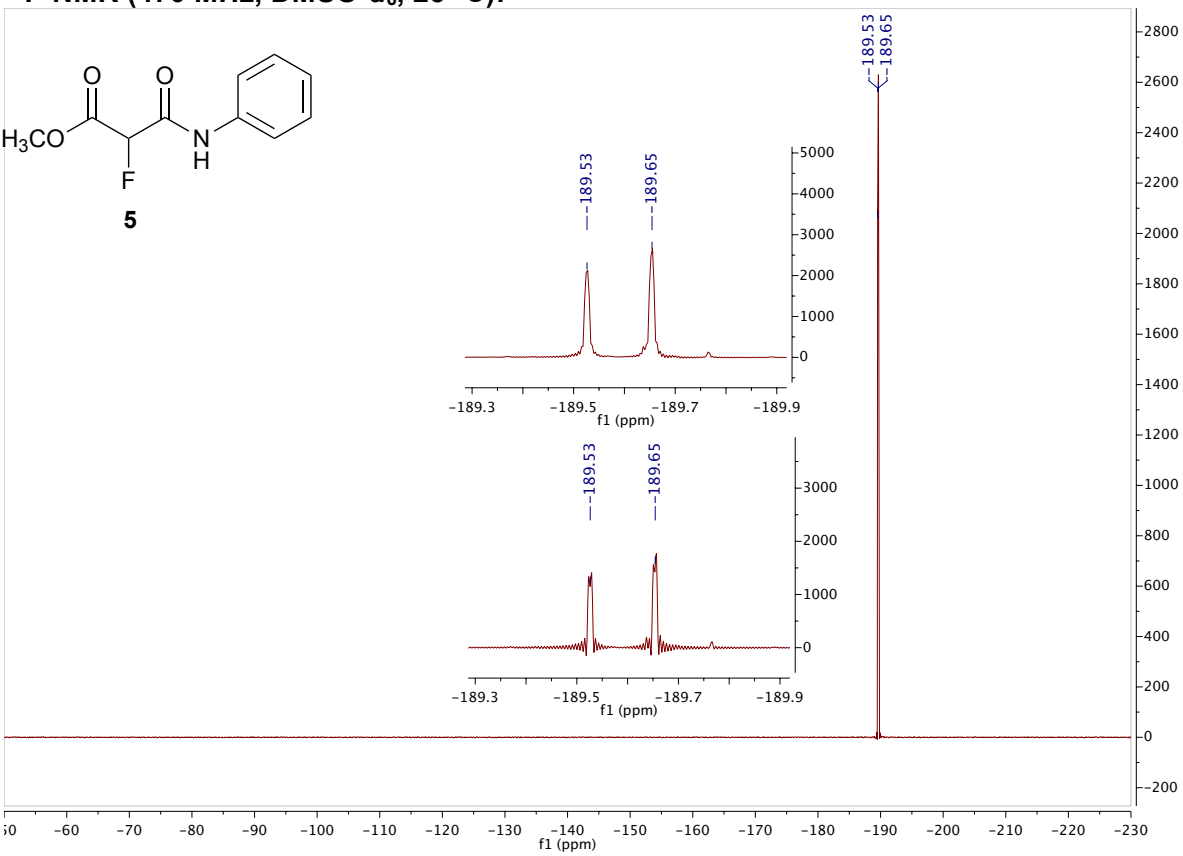


5

^{13}C-NMR (100 MHz, DMSO-d_6, 25 ºC):

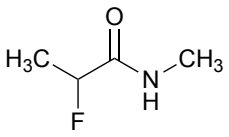


^{19}F-NMR (470 MHz, DMSO-d_6, 25 ºC):

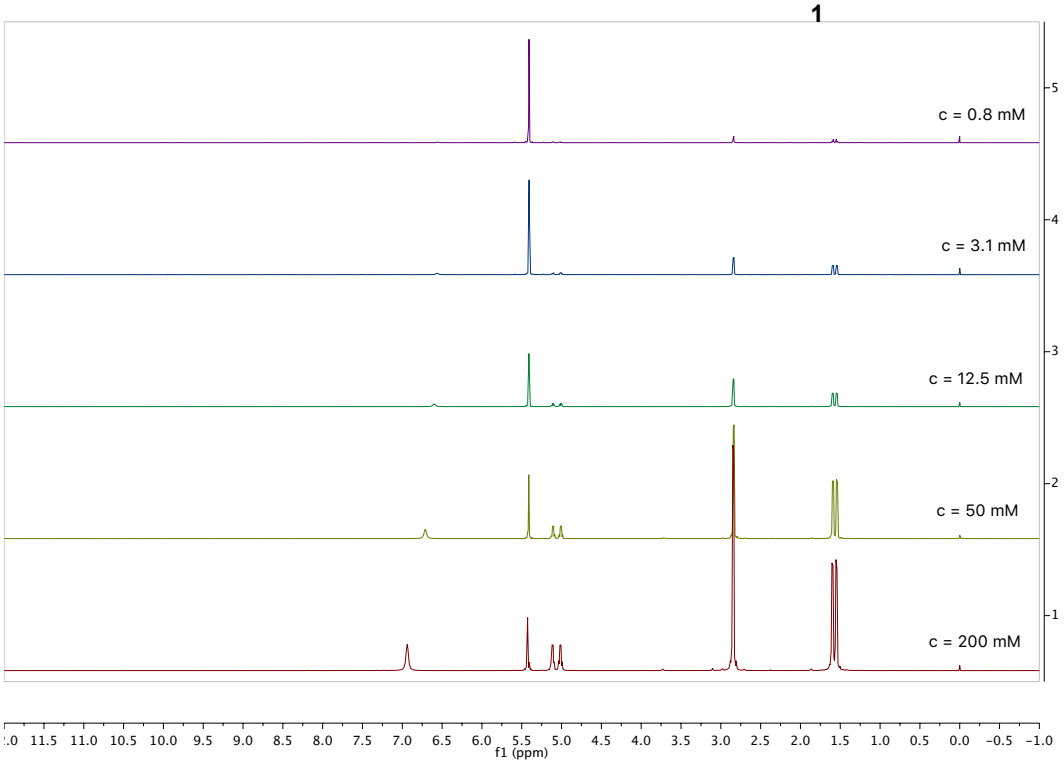


NMR spectra of dilution experiments

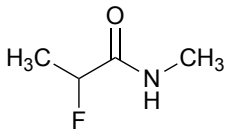
^{1}H-NMR (500 MHz, CD_2Cl_2, –80 ºC):



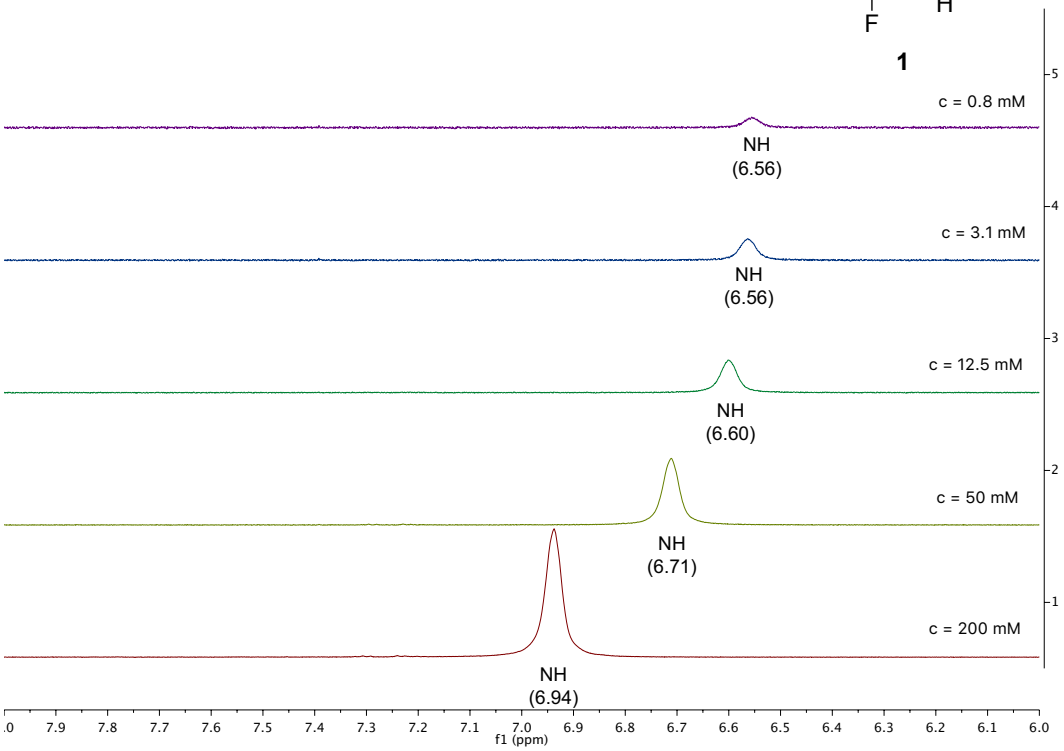
1



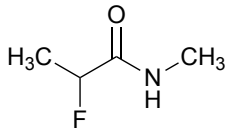
^{1}H-NMR (500 MHz, CD_2Cl_2, –80 ºC), detail:



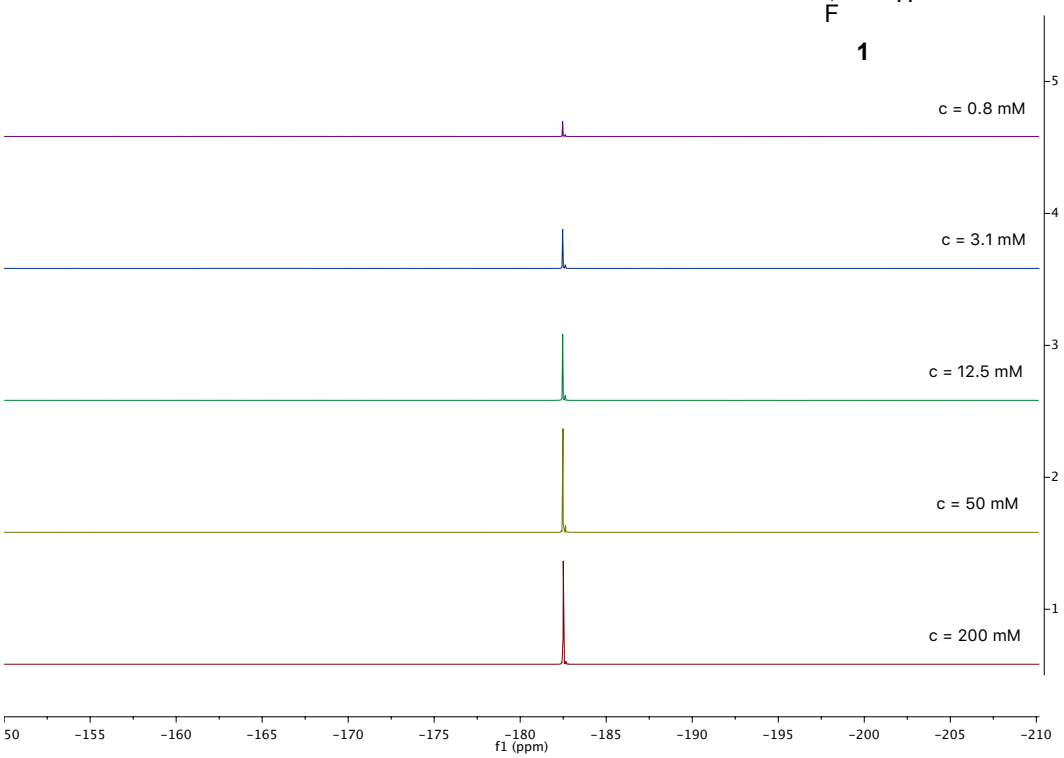
1



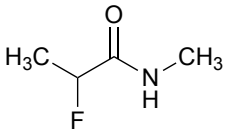
^{19}F-NMR (471 MHz, CD_2Cl_2, –80 °C):



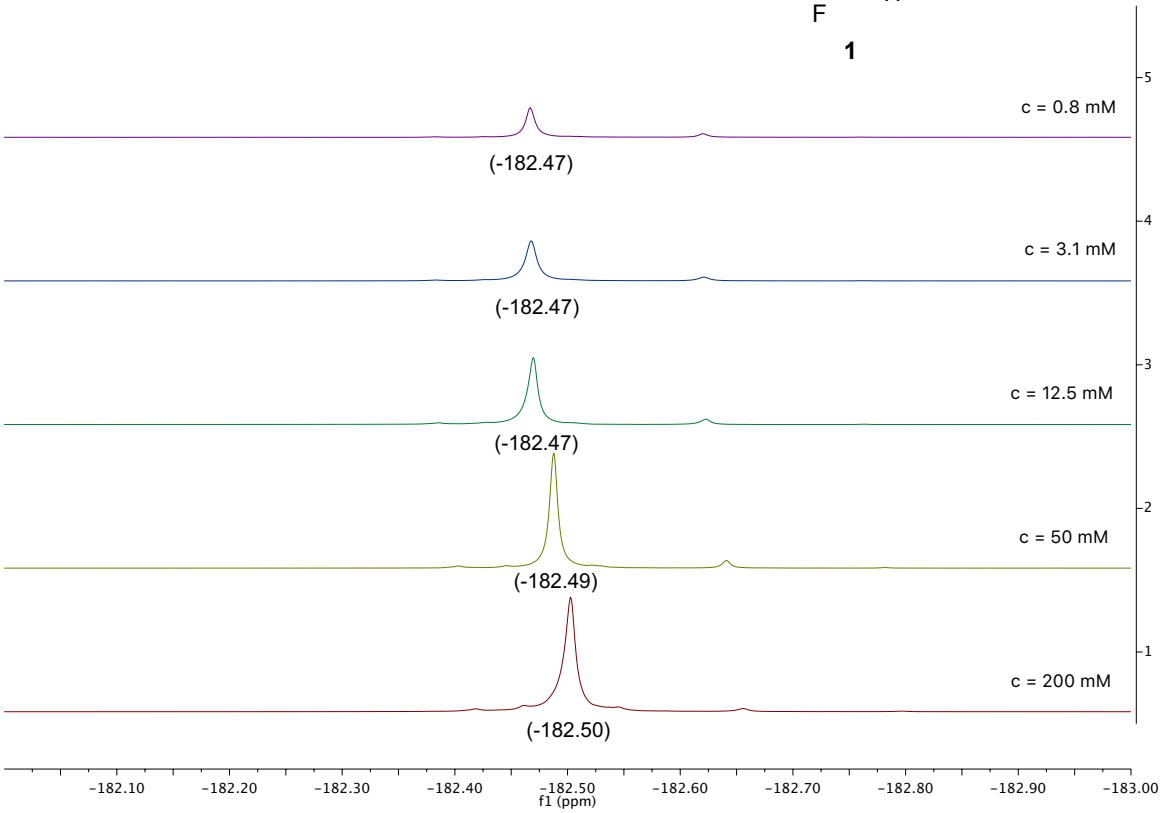
1



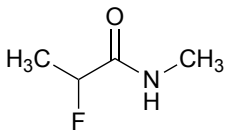
^{19}F-NMR (471 MHz, CD_2Cl_2, –80 °C), detail:



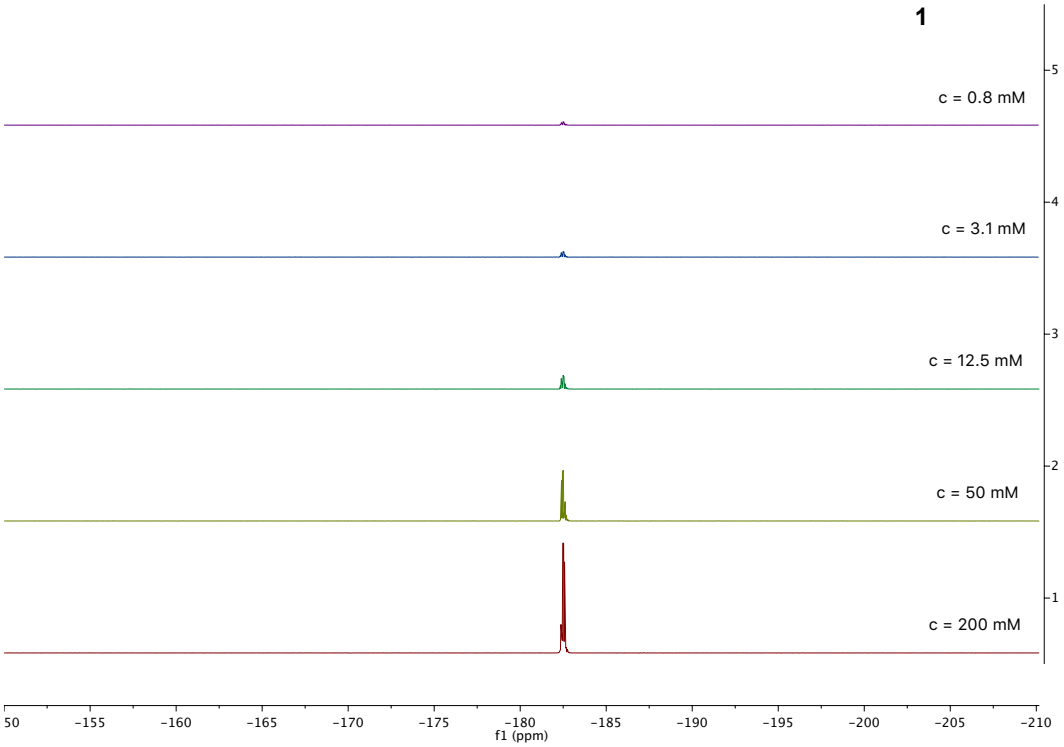
1



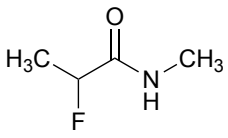
^{19}F-NMR (471 MHz, CD_2Cl_2, –80 ºC) not decoupled:



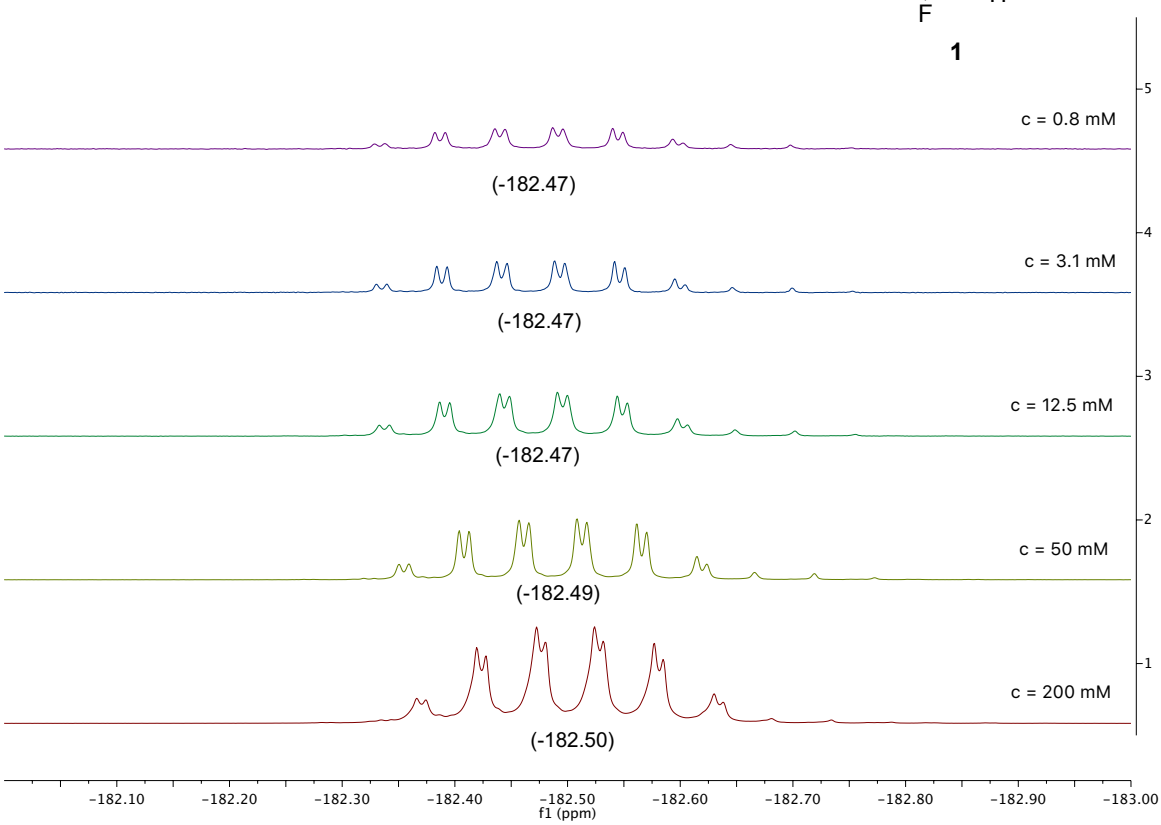
1



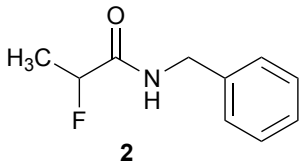
^{19}F-NMR (471 MHz, CD_2Cl_2, –80 ºC) not decoupled, detail:



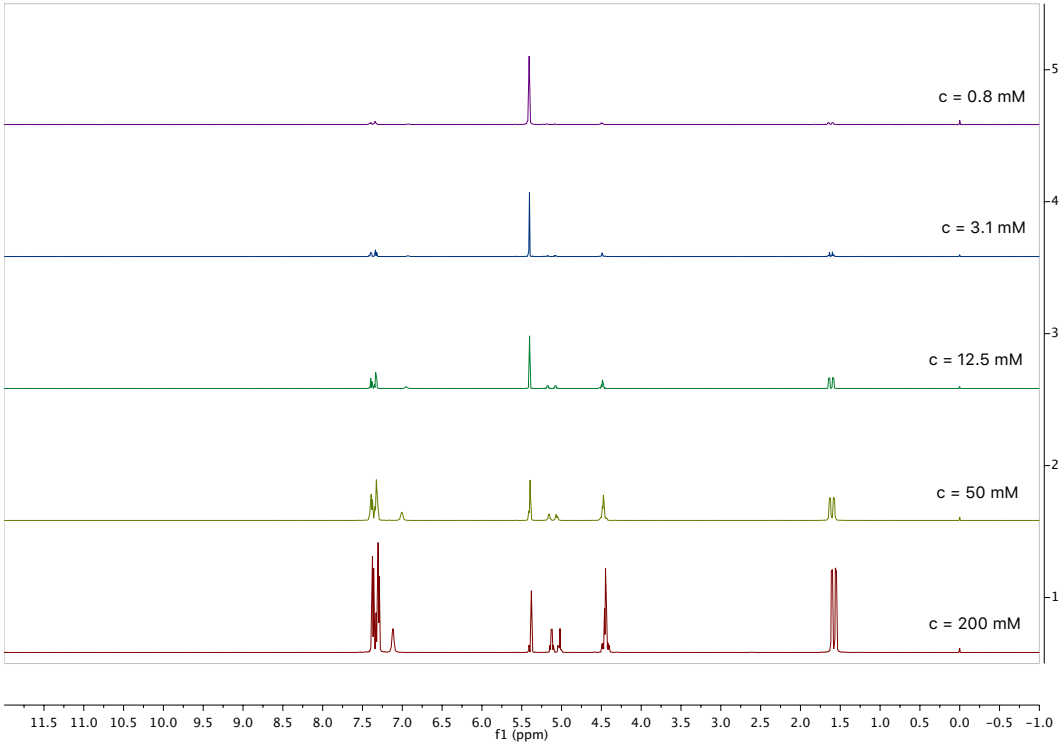
1



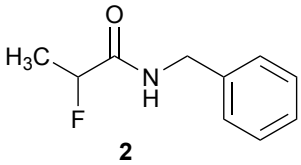
^{1}H-NMR (500 MHz, CD_2Cl_2, –80 ºC):



2

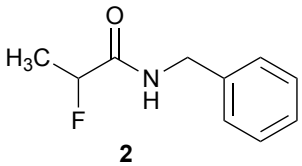


^{1}H-NMR (500 MHz, CD_2Cl_2, –80 ºC), detail:

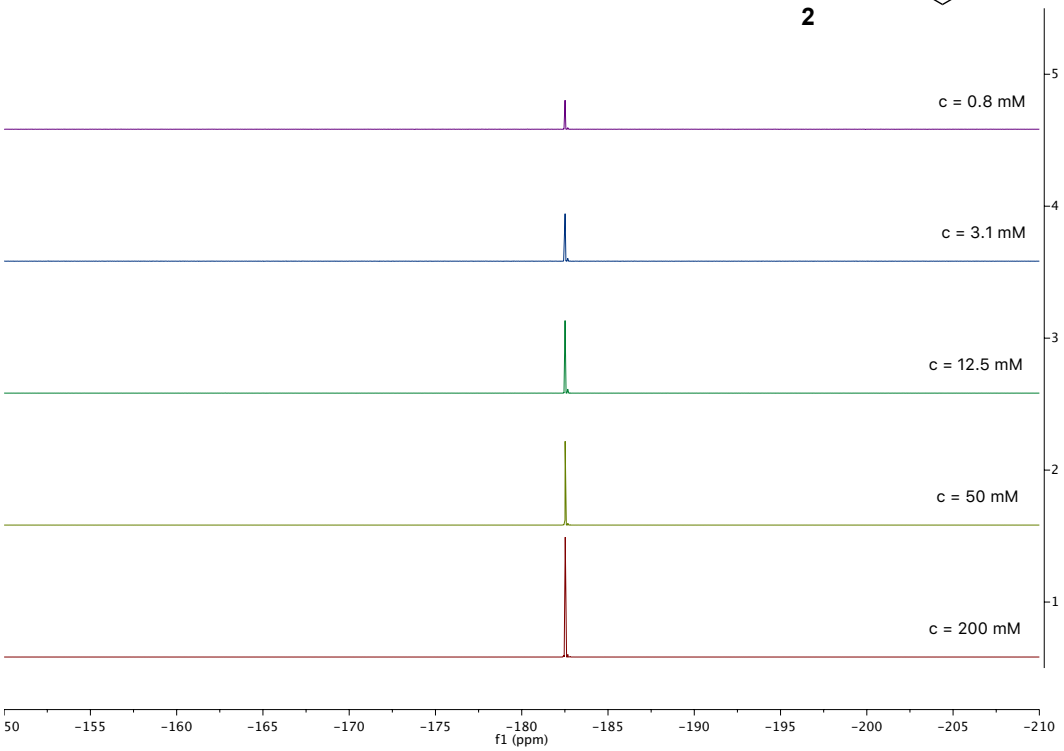


2

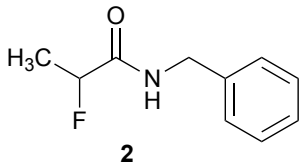
^{19}F-NMR (471 MHz, CD_2Cl_2, –80 ºC):



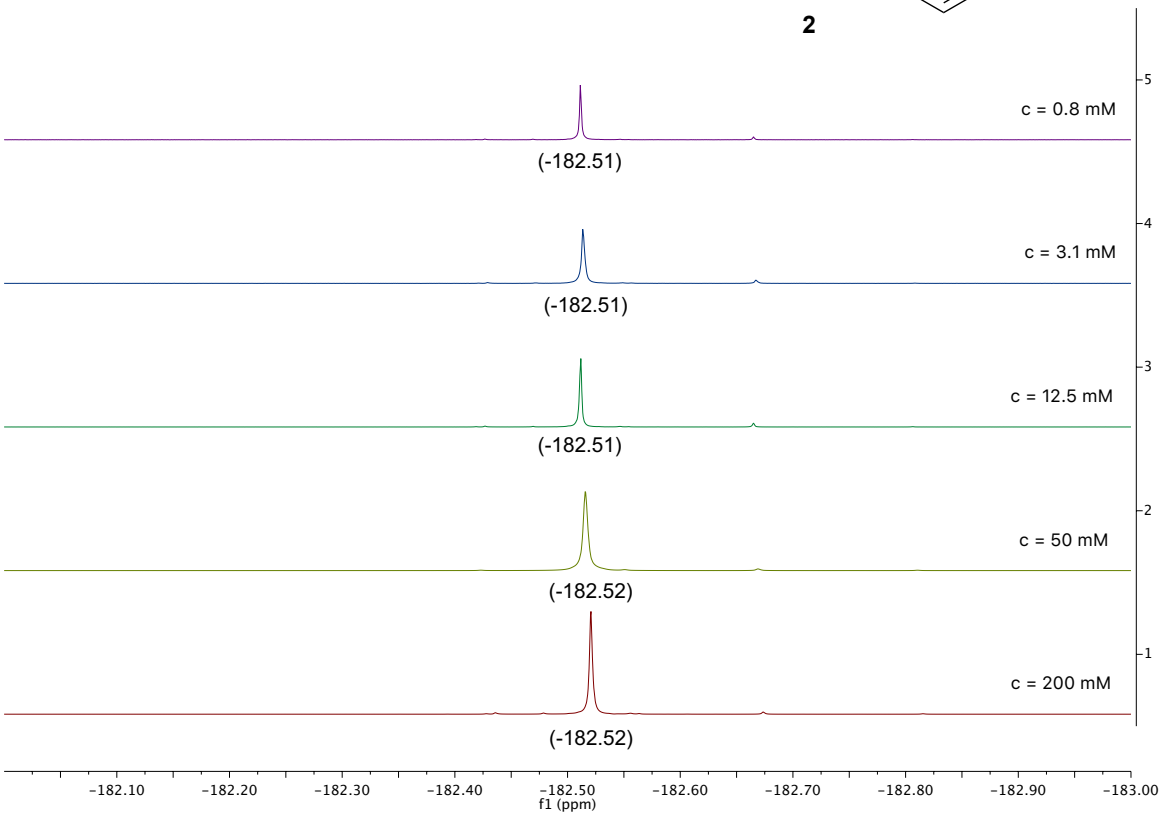
2



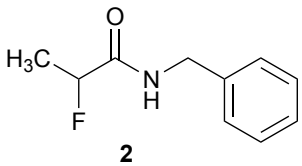
^{19}F-NMR (471 MHz, CD_2Cl_2, –80 ºC), detail:



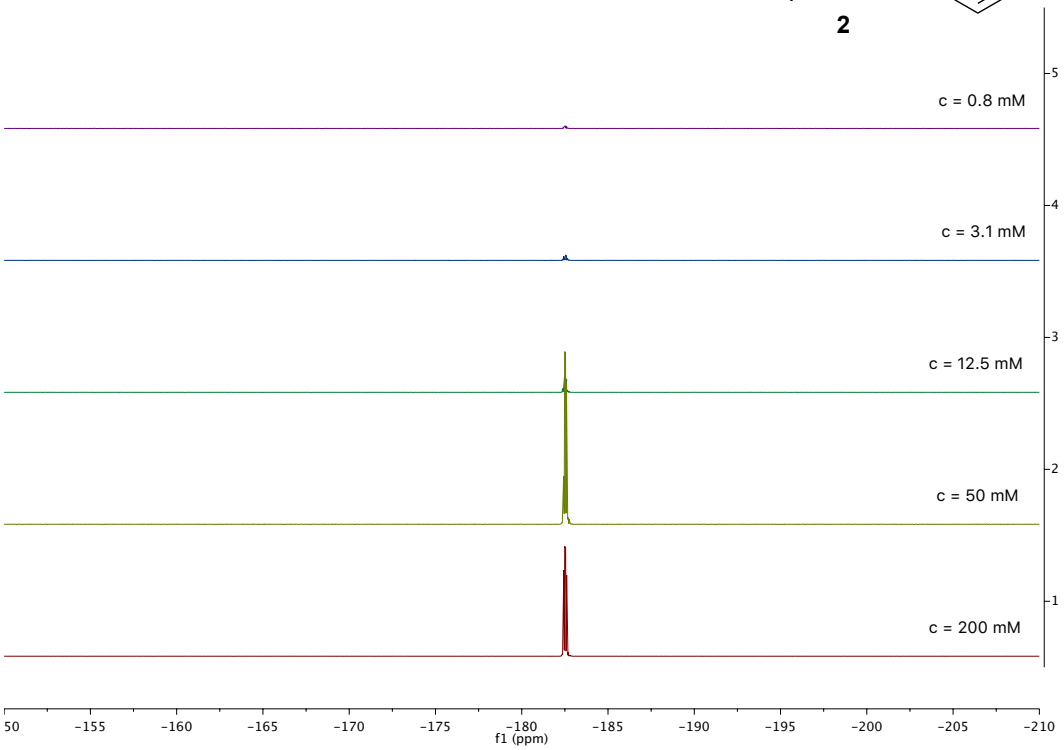
2



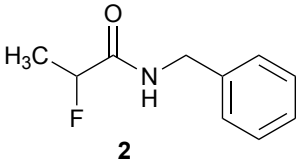
^{19}F-NMR (471 MHz, CD_2Cl_2, –80 ºC) not decoupled:



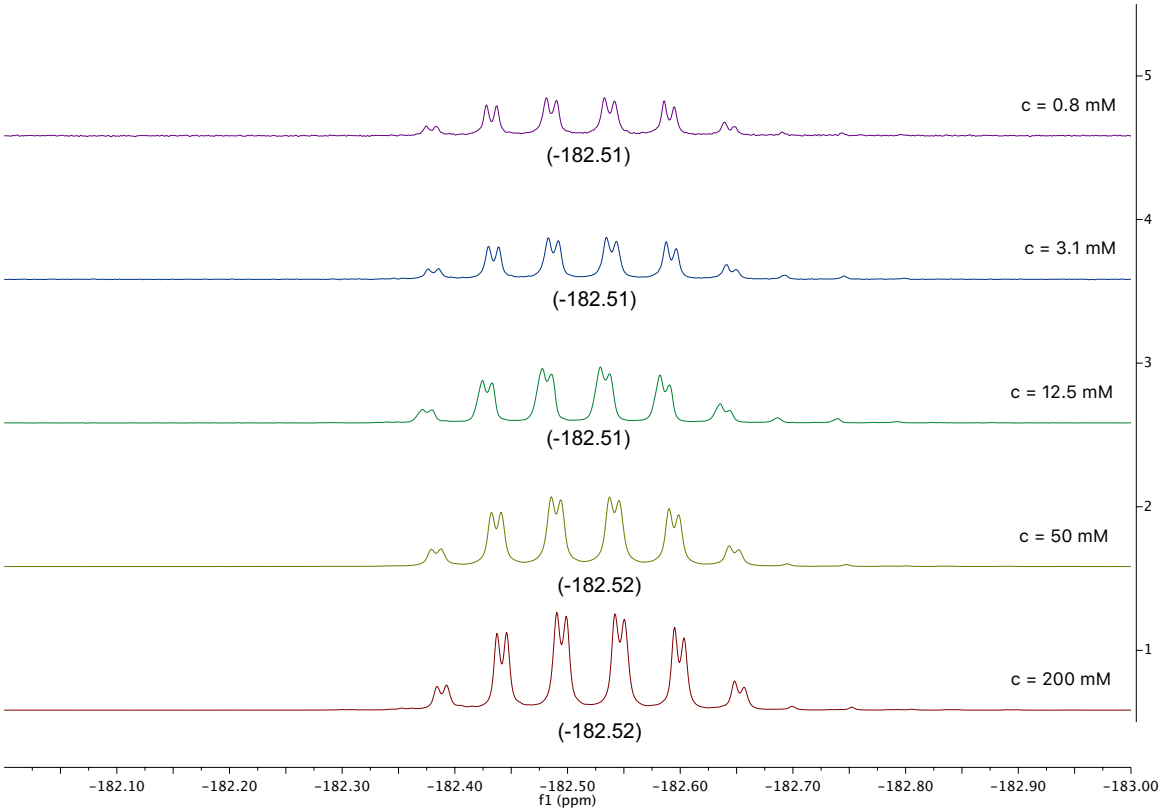
2



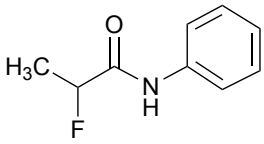
^{19}F-NMR (471 MHz, CD_2Cl_2, –80 ºC) not decoupled, detail:



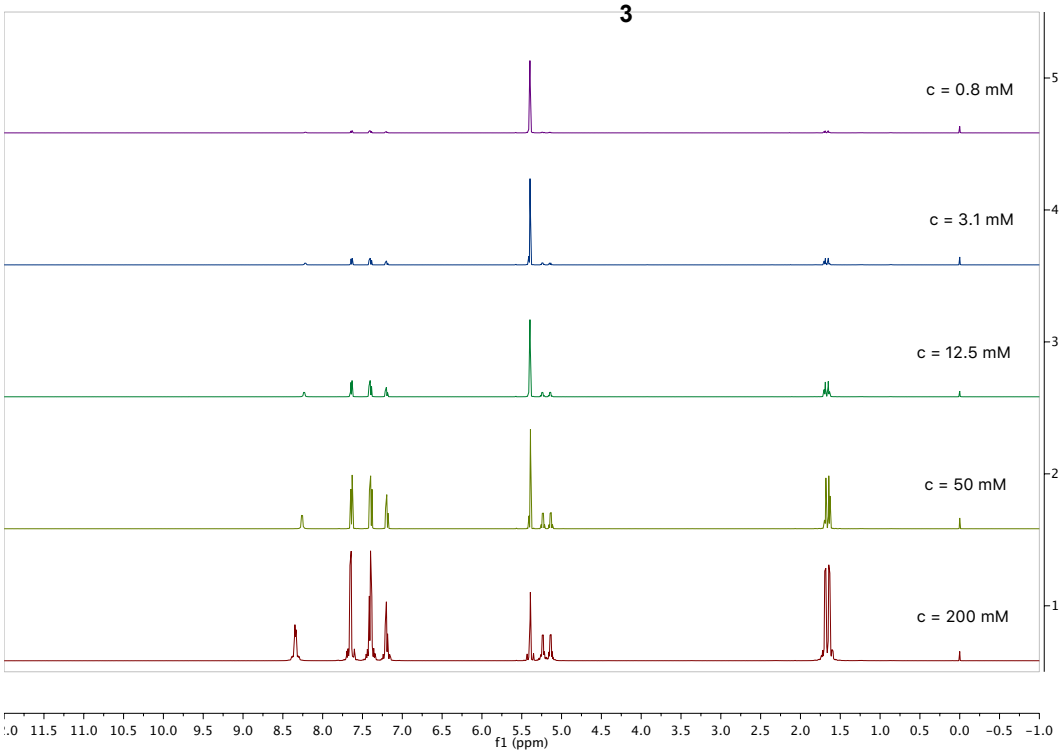
2



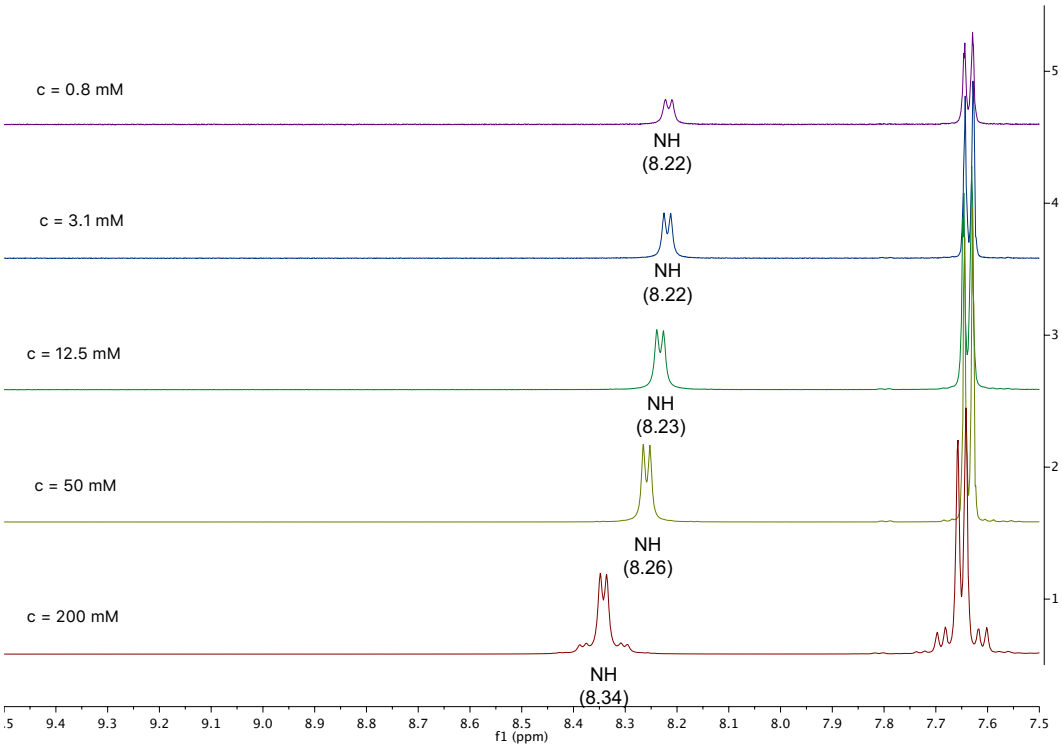
^{1}H-NMR (500 MHz, CD_2Cl_2, –80 ºC):



3

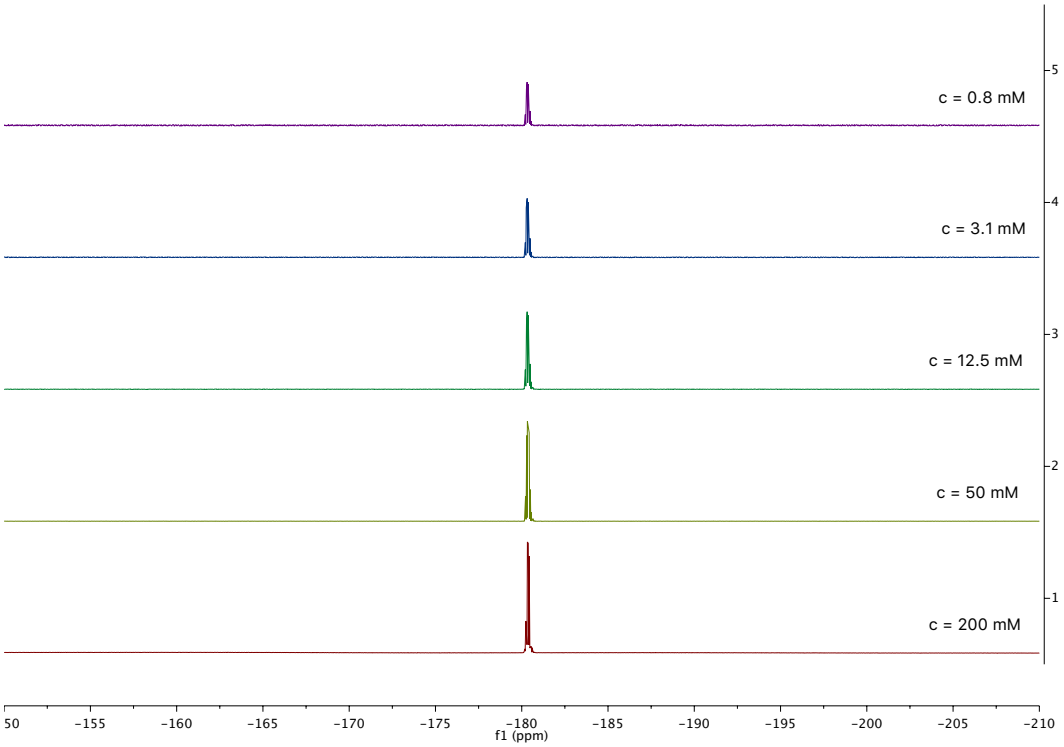


^{1}H-NMR (500 MHz, CD_2Cl_2, –80 ºC), detail:

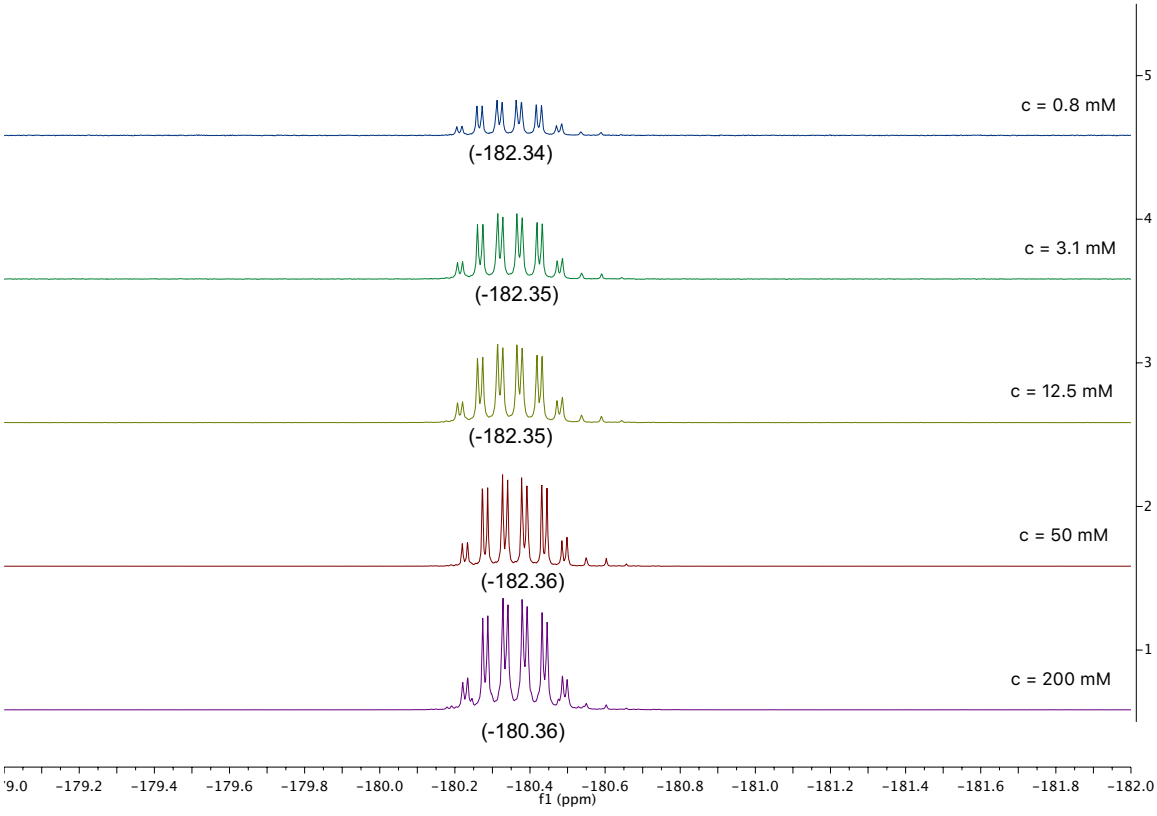


Note: shimming issues were encountered with the sample at 200 mM concentration.

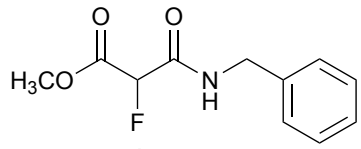
^{19}F-NMR (471 MHz, CD_2Cl_2, –80 ºC) not decoupled:



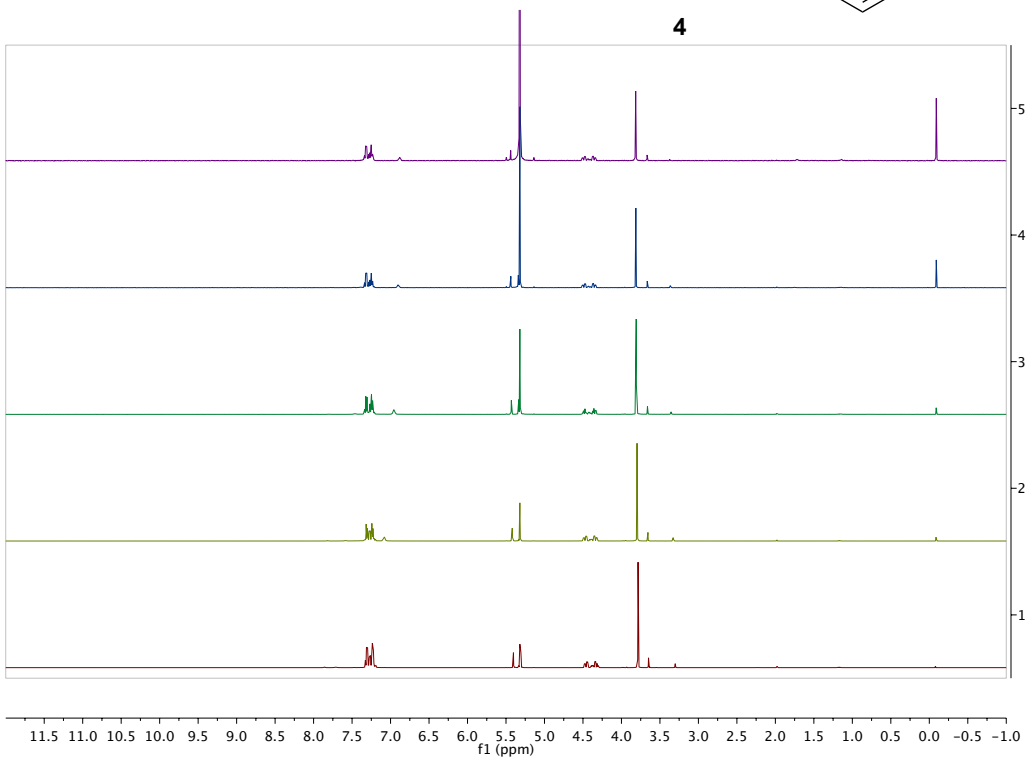
^{19}F-NMR (471 MHz, CD_2Cl_2, –80 ºC) not decoupled, detail:



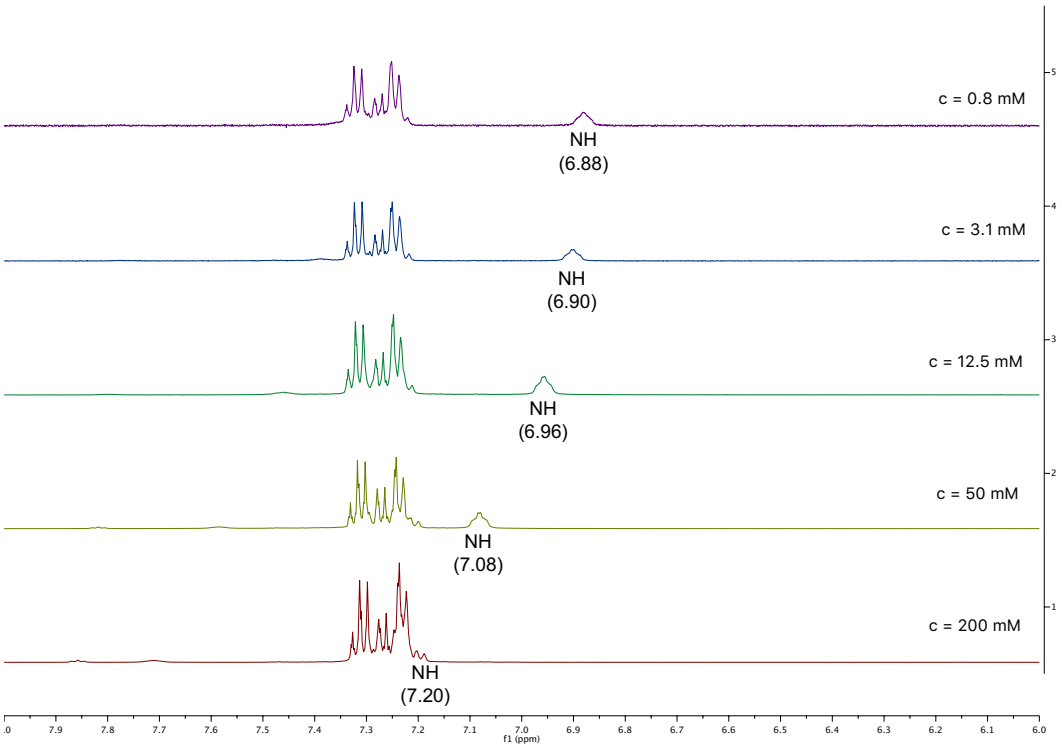
^{1}H-NMR (500 MHz, CD_2Cl_2, –80 ºC):



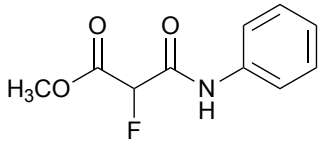
4



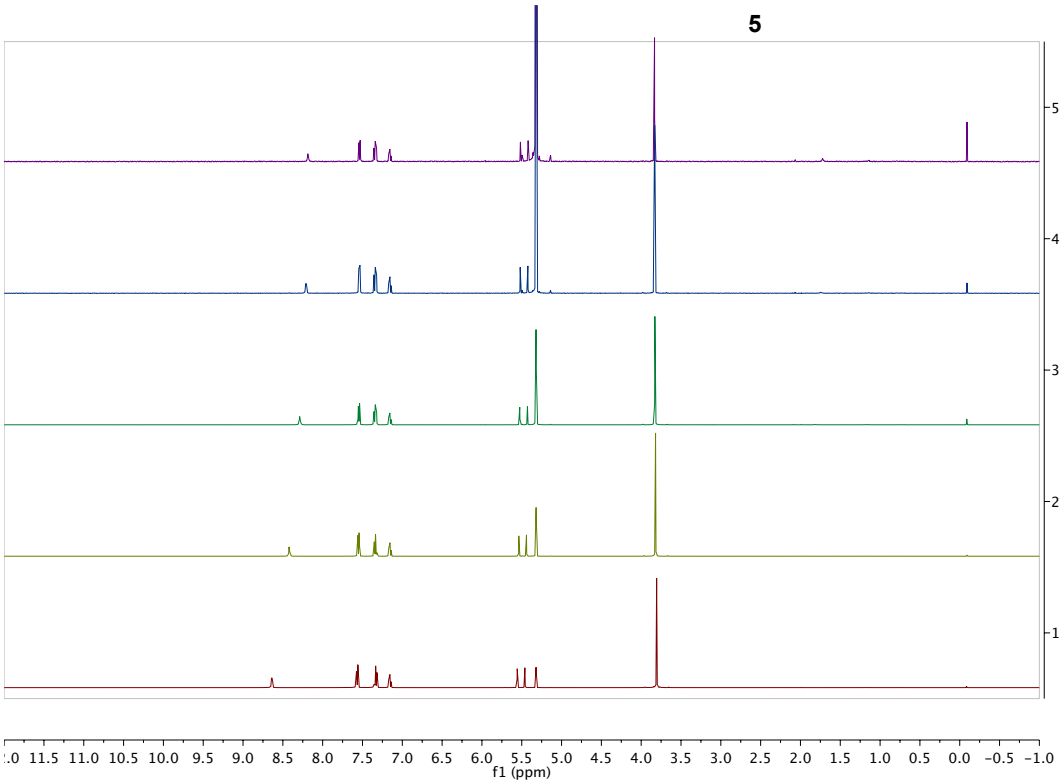
Detail (8 ppm – 6 ppm):



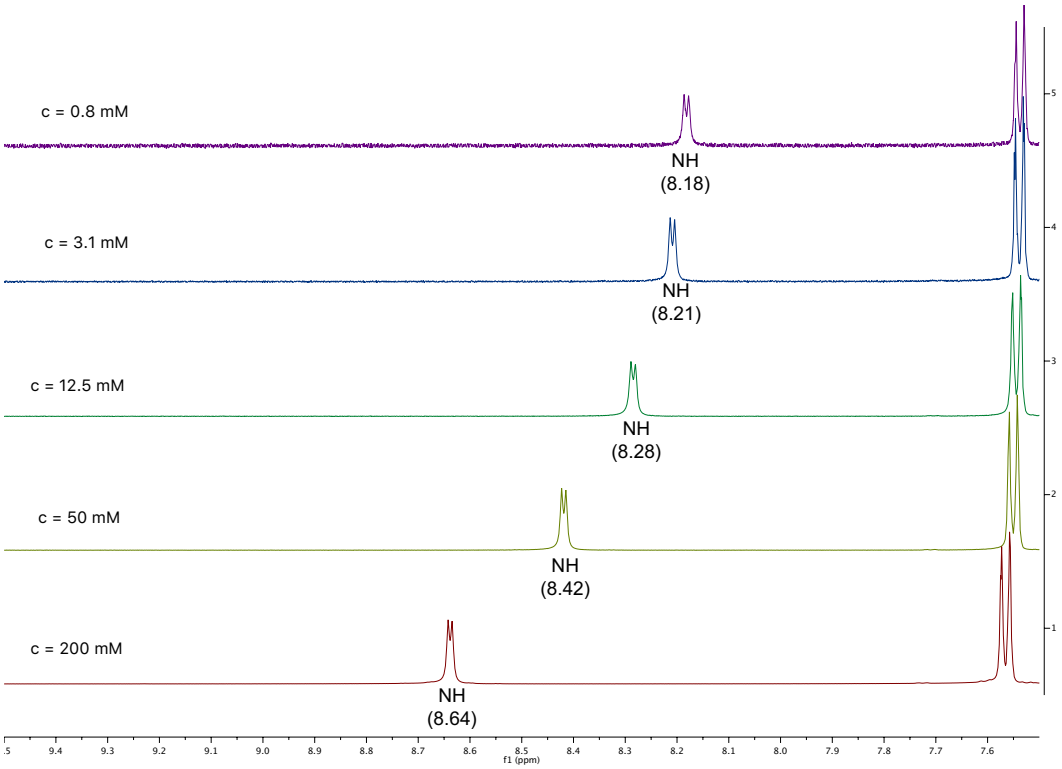
^{1}H-NMR (500 MHz, CD_2Cl_2, –80 ºC):



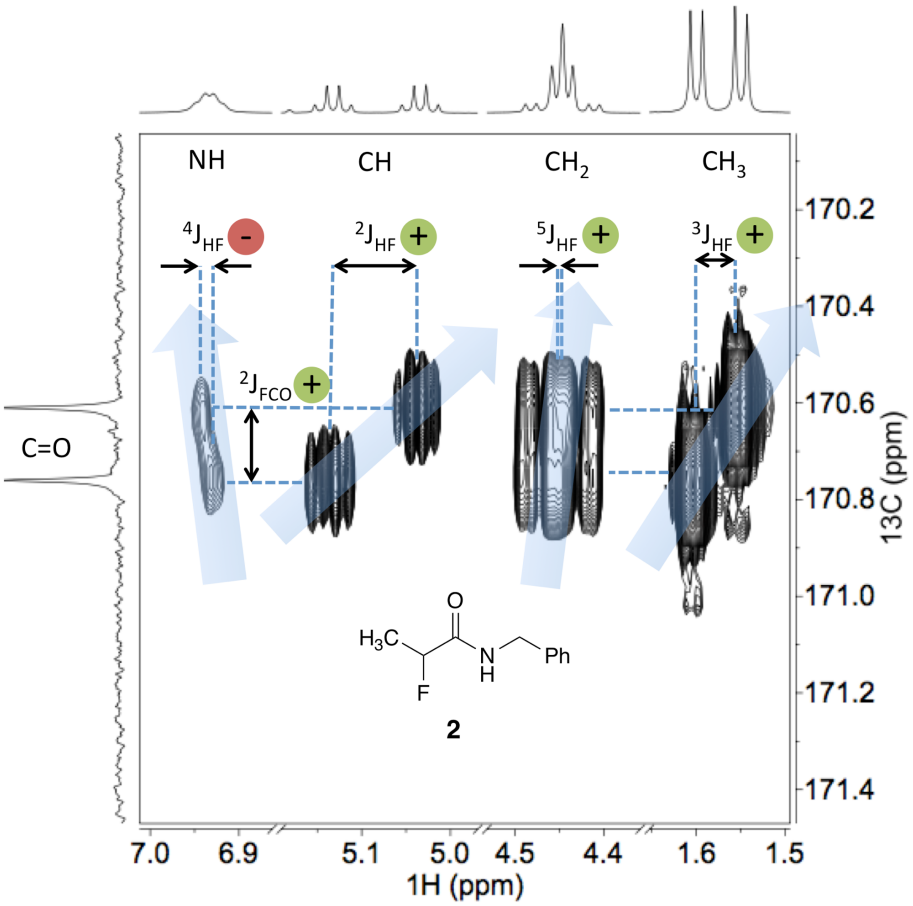
5



Detail (9.5 ppm – 7.5 ppm):



Selective constant time ^{13}C-HMBC (500 MHz, CD_2Cl_2, –80 ºC):



Pulse sequence: hmbcctetgpnd (v 1.6 2012/01/31) from Bruker standard library with 1ms reburp pulse for selective refocusing. Spectral widths were 16 ppm in the direct dimension and 21 ppm in the indirect dimension. The transmitters were set to 6 ppm and 175 ppm, respectively. A total of 4k x 256 data points was recorded. The time domain in both dimensions was extended to twice its size by zero-filling. A sine bell shifted by 90° was used for apodization in the indirect dimension. The spectrum is presented in magnitude mode.

Cross-peaks appear as reduced multiplets due to the influence of the passive HF and CF couplings. The characteristic tilt in the cross-peak structure (shown as transparent blue arrow) is indicative for the relative sign of the passive couplings: A tilt to the right results from passive couplings of identical sign, a tilt to the left results from passive couplings of opposite sign. Since $^{3}J_{HF}$ is expected to be positive $^{2}J_{FCO}$ must also be positive (cf. rightmost cross-peak) and $^{4}J_{HF}$ in turn is negative (cf. leftmost cross-peak).

7 References

1. E. Cosimi, O. D. Engl, J. Saadi, M. O. Ebert and H. Wennemers, *Angew. Chem. Int. Ed.*, 2016, **55**, 13127-13131.
2. Gaussian 09, revision C0.1 and D.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, N. R. J. Gao, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. J. A. Montgomery, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, J. A. Rendell, C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.
3. A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648-5652.
4. T. H. Dunning, *J. Chem. Phys.*, 1989, **90**, 1007-1023.
5. E. Cancès, B. Mennucci and J. Tomasi, *J. Chem. Phys.*, 1997, **107**, 3032-3041.
6. B. Mennucci, R. Cammi and J. Tomasi, *J. Chem. Phys.*, 1998, **109**, 2798-2807.
7. W. Deng, J. R. Cheeseman and M. J. Frisch, *J. Chem. Theory Comput.*, 2006, **2**, 1028-1037.
8. NBO 5.9, E. D. Glendening, J. K. Badenhoop, A. E. Reed, J. E. Carpenter, J. A. Bohmann, C. M. Morales and F. Weinhold, Theoretical Chemistry Institute, University of Wisconsin, Madison WI, 2012.
9. P. Thordarson, in *Supramolecular Chemistry: From Molecules to Nanomaterials*, eds. P. A. Gale and J. W. Steed, John Wiley & Sons, Chichester, 2012, vol. 2, pp. 239-274.
10. D. B. Hibbert and P. Thordarson, *Chem. Commun.*, 2016, **52**, 12792-12805.
11. Bindfit, http://supramolecular.org, (accessed June, 2018).
12. *CrysAlisPro and ABSPACK.* Rigaku Oxford Diffraction, **2016**.
13. Sheldrick, G. M. *Acta Cryst*. 2015, **A71**, 3–8.
14. Sheldrick, G. M. *Acta Cryst*. 2008, **A64**, 112–122.
15. Sheldrick, G. M. *Acta Cryst*. 2015, **C71**, 3–8.
16. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. *J. Appl. Cryst*. 2009, **42**, 339–341.
17. F. H. Allen and I. J. Bruno, *Acta Cryst.*, 2010, **B66**, 380-386.