Diastereoselective Synthesis and Conformational Analysis of 4,5-Difluoropipecolic Acids

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SUPPORTING INFORMATION

Contents:

1. Reagents and instrumentation

All purchased reagents were used without further purification unless otherwise noted. All solvents were dried over 4Å molecular sieves before used unless stated otherwise. Reactions were stirred using Teflon-coated magnetic stirrers. Analytical TLC was performed with 0.20 mm silica gel 60F plates with a 254 nm fluorescent indicator. TLC plates were visualized by ultraviolet light or by treatment with a spray of Pancaldi reagent [$(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O] or a solution of 0.5% ninhydrin in *n*-butanol. Chromatographic purification of products was carried out by flash column chromatography on silica gel (230-400 mesh). Melting points were determined using a WRX-4 visual melting point apparatus. Both melting points and boiling points are uncorrected. NMR spectra were measured in $CDCl_3$ (with TMS as internal standard) or DMSO-d_6 or CD_3OD or D_2O on a Bruker AV400 (1H at 400 MHz, ^{13}C at 100 MHz) magnetic resonance spectrometer. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hz. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High-resolution mass spectra (HRMS) were recorded on a SYNAPT G2Si High Definition MS System operating in ESI mode.

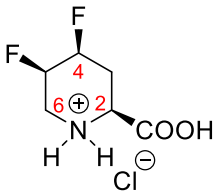
2. Synthetic procedures and characterization data

General procedure for the synthesis of fluorinated pipecolic acid analogs (11)

Ruthenium (III) chloride trihydrate (0.024 mmol, 0.06 equiv) was added to a mixture of **15** (0.40 mmol, 1 equiv), sodium metaperiodate (7.2 mmol, 18 equiv), carbon tetrachloride (4 mL), acetonitrile (4 mL) and deionized water (5 mL), and the mixture was stirred at 25 °C until total consumption of the starting material. Isopropyl alcohol (5 mL) was added, and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl, then dried with anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was subjected to flash chromatography eluting with 200:1:1 dichloromethane/methanol/ acetic acid to give the corresponding Boc-protected carboxylic acid.

The Boc-protected carboxylic acid synthesized above was dissolved in THF (3.0 mL), and to this solution was added dropwise 3N hydrogen chloride solution. The mixture was stirred at room temperature overnight. After TLC indicated the disappearance of the starting material, the solvent was removed to give the title compound.

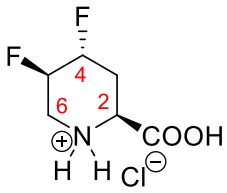
(2*R*,4*R*,5*S*)-4,5-Difluoropiperidine-2-carboxylic acid hydrochloride (11a)



The title compound was synthesized following the General Procedure above. Data for **11a**: colorless solid (67%); **^{1}H NMR** (400 MHz, D_2O) δ 5.12 (ddddd, *J* = 48.0, 9.0, 4.0, 2.0, 1.0 Hz, 1H, H_5), 4.89 (ddddd, 44.0, 27.0, 11.0, 4.0, 2.0 Hz, H, H_4), 4.01 (dd, *J* = 12.5, 1.0 Hz, 1H, H_2), 3.69 (dddd, *J* = 14.6, 10.0, 5.0, 4.0 Hz, 1H, H_{6a}), 3.26 (dd, *J* = 37.3, 14.6, 1.0 Hz, 1H, H_{6e}), 2.54 (ddddd, *J* = 15.0, 5.0, 4.0, 1.0, 1.0 Hz, 1H, H_{3a}), 2.16 (ddddd, *J* = 15.0, 12.5, 11.0, 8.0, 2.0 Hz, 1H, H_{3e}); **^{13}C{^{1}H} NMR** (100 MHz, D_2O) δ 172.2 (COOH), 88.6 (dd, *J* = 183.0, 17.7 Hz, C_5), 86.7 (dd, *J* = 178.5, 18.6 Hz,

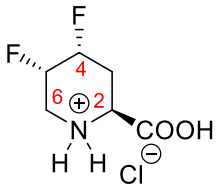
C_4), 57.3 (d, J = 11.6 Hz, C_2), 46.8 (dd, J = 20.2, 7.2 Hz, C_6), 28.4 (dd, J = 24.3, 3.8 Hz, C_3); **^{19}F NMR** (376 MHz, D_2O) δ –190.1 (d, J = 43.8 Hz, F_5), –207.4 (tdt, J = 38.0, 25.8, 13.1 Hz, F_4); **^{19}F{^{1}H} NMR** (376 MHz, D_2O) δ –190.1 (d, J = 14.3 Hz, F_5), –207.4 (d, J = 14.3 Hz, F_4).

(2*R*,4*S*,5*S*)-4,5-Difluoropiperidine-2-carboxylic acid hydrochloride (11b)



The title compound was synthesized following the General Procedure above. Data for **11b**: colorless solid (72%); **^{1}H NMR** (400 MHz, D_2O) δ 5.04 (ddddd, J = 43.0, 3.8, 1.5, 1.5, 1.3 Hz, 1H, H_5), 4.98 (ddddd, J = 43.5, 4.0, 3.3, 2.0, 1.5 Hz, 1H, H_4), 4.15 (dd, J = 13.3, 3.3 Hz, 1H, H_2), 3.66 (dddd, J = 14.8, 12.0, 2.3, 1.5 Hz, 1H, H_{6a}), 3.45 (dddd, J = 41.0, 14.8, 2.8, 1.3 Hz, 1H, H_{6e}), 2.57 (ddddd, J = 15.0, 12.5, 3.3, 3.26, 1.0 Hz, 1H, H_{3a}), 2.18 (ddddd, J = 43.0, 15.0, 13.3, 4.0, 2.0 Hz, 1H, H_{3a}); **^{13}C{^{1}H} NMR** (100 MHz, D_2O) δ 170.4 (COOH), 82.6 (d, J = 172.4, 32.0 Hz, C_5), 81.8 (d, J = 173.8, 33.8 Hz, C_4), 51.3 (C_2), 42.6 (d, J = 19.9 Hz, C_6), 26.0 (d, J = 20.0 Hz, C_3); **^{19}F NMR** (376 MHz, D_2O) δ –196.5 (m, F_5), –197.4 (m, F_4); **^{19}F{^{1}H} NMR** (376 MHz, D_2O) δ –196.5 (d, J = 14.5 Hz, F_5), –197.4 (d, J = 14.5 Hz, F_4).

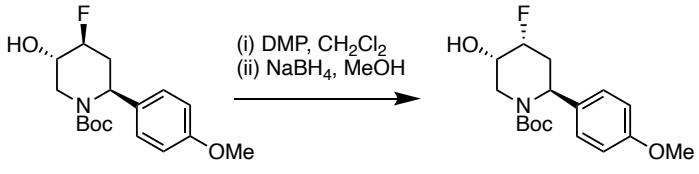
(2*R*,4*S*,5*R*)-4,5-Difluoropiperidine-2-carboxylic acid hydrochloride (11d)



The title compound was synthesized following the General Procedure above. Data for **11d**: colorless solid (68%); **^{1}H NMR** (400 MHz, D_2O) δ 4.99 (ddddd, J = 46.0, 18.0, 7.0, 3.0, 1.5 Hz, 1H, H_5), 4.93 (ddddd, J = 43.0, 23.0, 6.0, 3.0, 3.0 Hz, 1H, H_4), 4.21 (dd, J =8.9, 4.5 Hz, 1H, H_2), 3.50 (dddd, J = 14.0, 7.5, 7.0, 2.5 Hz, 1H, H_{6a}), 3.42 (dddd, J = 15.0, 14.0, 4.0, 1.5 Hz, 1H, H_{6e}), 2.51 (ddddd, J = 15.0, 12.0, 6.0, 4.5, 3.0 Hz, 1H, H_{3a}), 2.20 (dddd, J = 27.0, 15.0, 8.9, 3.0, 1.0 Hz, 1H, H_{3e}); **^{13}C{^{1}H} NMR** (100 MHz, D_2O) δ 172.6 (COOH), 87.1 (dd, J = 179.7, 17.4 Hz, C_5), 86.5 (dd, J =

180.1, 18.0 Hz, C_4), 54.8 (d, J = 6.4 Hz, C_2), 43.5 (dd, J = 28.5, 5.7 Hz, C_6), 29.4 (dd, J = 21.7, 5.9 Hz, C_3); **^{19}F NMR** (376 MHz, D_2O) δ –200.5 (m, F_5), –203.5 (m, F_4); **^{19}F{^{1}H} NMR** (376 MHz, D_2O) δ –200.5 (F_5), –203.5 (F_4).

***tert*-Butyl (2*S*,4*R*,5*S*)-4-fluoro-5-hydroxy-2-(4-methoxyphenyl)piperidine-1-carboxylate (12d)**



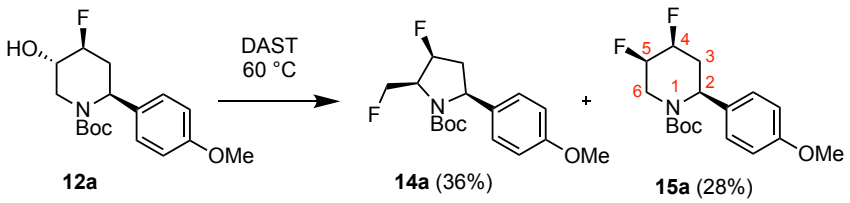
12a **12d** (32%) + **12a** (35%)

Dess-Martin periodinane (580 mg, 1.37 mmol) was added to a solution of alcohol **12a** (142 mg, 0.44 mmol) in CH_2Cl_2 (10 mL). After the disappearance of starting material, saturated aqueous $NaHCO_3$ and excess $Na_2S_2O_3$ were added to the reaction mixture. After the solids were dissolved, the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried with $MgSO_4$, and filtered. After removal of the solvent under vacuo at 30 °C, the residue was purified by flash chromatography on silica gel using petroleum ether/EtOAc = 1:10 as the eluent, to afford an intermediate ketone which was used directedly due to its instability.

The crude ketone obtained above was dissolved in MeOH (5 mL), to which was added $NaBH_4$ (50 mg, 1.32 mmol) at 0 °C. After reaction at this temperature for 1 h, the reaction was quenched with sat. aqueous NH_4Cl. Then, the mixture was extracted with EtOAc. The combined organic layers were washed with water, dried with anhydrous Na_2SO_4, and filtered. After removal of the solvent *in vacuo*, the residue was purified by flash chromatography on silica gel using petroleum ether/EtOAc = 1:10 as the eluent, to afford **12d** (45 mg, 32%), with the recovery of the starting alcohol (49 mg, 35%).

Data for **12d**: colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.17 (d, J = 8.5 Hz, 2H, Ar), 6.86 (d, J = 8.8 Hz, 2H, Ar), 5.38 (d, J = 6.9 Hz, 1H, H_2), 4.91 (dt, J = 50.8, 2.9 Hz, 1H, H_4), 4.14 (dd, J = 13.1, 5.4 Hz, 1H, H_6), 3.78 (s, 3H, Ar-O-C$\underline{H}_3$), 3.66 (dddd, J = 26.9, 11.3, 5.5, 2.5 Hz, 1H, H_5), 2.94–2.79 (m, 2H, H_3, H_6), 2.25 (bs, 1H, O$\underline{H}$), 2.09 (dddd, J = 47.0, 15.5, 7.1, 2.3 Hz, 1H, H_3), 1.47 (s, 9H, C(C$\underline{H}_3$)$_3$); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 158.4 ($\underline{C}$OO), 155.2 (Ar), 132.0 (Ar), 127.2 (d, J = 2.4 Hz, Ar), 113.8 (Ar), 89.9 (d, J = 174.2 Hz, C_4), 80.6 (O-$\underline{C}$(CH$_3$)), 67.5 (d, J = 18.9 Hz, C_5), 55.3 (Ar-O-$\underline{C}$H$_3$), 49.7 (C_2), 40.8 (d, J = 3.7 Hz, C_6), 31.6 (d, J = 18.6 Hz, C_3), 28.5 (C($\underline{C}$H$_3$)$_3$); **^{19}F NMR** (376 MHz, $CDCl_3$) δ –202.7 (tdd, J = 49.0, 26.8, 9.5 Hz); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ –202.7.

***tert*-Butyl (2*S*,3*S*,5*S*)-3-fluoro-2-(fluoromethyl)-5-(4-methoxyphenyl)pyrrolidine-1-carboxylate (14a); and *tert*-butyl (2S,4R,5R)-4,5-difluoro-2-(4-methoxyphenyl)piperidine-1-carboxylate (15a)**



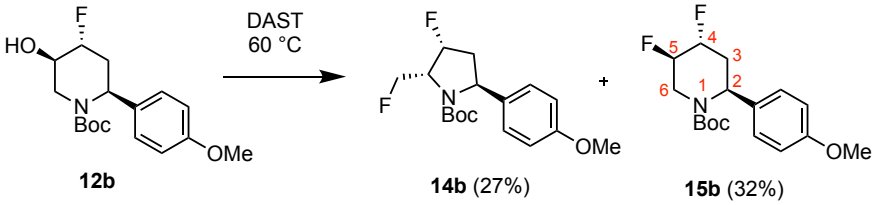
12a **14a** (36%) **15a** (28%)

A mixture of fluorohydrin **12a**[1] (65 mg, 0.2 mmol) and neat DAST (322 mg, 2.0 mmol, 0.33 mL) was stirred at 60 ºC in a plastic reaction vessel overnight. The mixture was cooled to 0 ºC, diluted with dichloromethane, and quenched slowly with $NaHCO_3$ at 0 ºC. The crude product was subjected to flash chromatography eluting with 1:50→1:20 petroleum ether/ethyl acetate to give a product that was tentatively identified as **14a** (22 mg, 36%) and product **15a** (18 mg, 28%).

Data for **14a′** (after deprotection of Boc group): colorless oil; **^{1}H NMR** (400 MHz, D_2O) δ 7.52 (d, *J* = 8.7 Hz, 2H, Ar), 7.10 (d, J = 8.8 Hz, 2H, Ar), 5.61 (ddt, *J* = 52.0, 5.9, 2.9 Hz, 1H), 5.03 (t, *J* = 8.7 Hz, 1H), 4.97 (t, *J* = 4.0 Hz, 1H), 4.85 (t, *J* = 3.7 Hz, 1H), 4.52 – 4.30 (m, 1H), 3.87 (s, 3H), 3.11–2.91 (m, 1H), 2.69 (dddd, *J* = 27.5, 15.1, 8.5, 3.4 Hz, 1H); **^{13}C NMR** (100 MHz, D_2O) δ 162.5 (Ar), 132.2 (Ar), 128.4 (Ar), 117.3 (Ar), 95.6 (dd, *J* = 179.3, 5.7 Hz, FCH_2), 82.5 (dd, *J* = 169.9, 8.2 Hz, CHF-CH_2), 66.5 (dd, *J* = 26.2, 18.0 Hz, N-CH-CH_2F), 64.0 (Ar-O-CH_3), 58.0 (Ar-CH-N), 39.0 (d, *J* = 21.7 Hz, CHF-CH_2); **^{19}F NMR** (376 MHz, D_2O) δ –175.3 (dtd, *J* = 52.9, 26.9, 19.5 Hz), –229.8 (td, *J* = 46.2, 27.5 Hz); **^{19}F{^{1}H} NMR** (376 MHz, D_2O) δ –175.3, –229.8; **HRMS** (ESI) calcd. for $C_{12}H_{16}F_2NO^+$ $[M+H]^+$ 228.1194, found 228.1197.

Data for **15a**: colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.6 Hz, 2H, Ar), 6.87 (d, *J* = 8.8 Hz, 2H, Ar), 5.38 (d, *J* = 7.1 Hz, 1H, H_2), 5.06 (dd, *J* = 51.5, 6.3 Hz, 1H, H_5), 4.73–4.39 (m, 1H, H_6), 4.36–4.21 (m, 1H, H_6), 3.80 (s, 3H, Ar-O-C$\underline{H}_3$), 3.24 (ddd, *J* = 13.4, 11.2, 2.7 Hz, 1H, H_3), 2.84 (ddt, *J* = 14.7, 9.3, 4.7 Hz, 1H, H_4), 2.11 (dddd, *J* = 44.1, 15.7, 7.3, 2.1 Hz, 1H, H_3), 1.47 (s, 9H, C(C$\underline{H}_3$)$_3$); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 158.5 (COO), 155.1 (Ar), 131.8 (Ar), 127.2 (d, *J* = 2.4 Hz, Ar), 113.9 (Ar), 87.0 (dd, *J* = 180.8, 16.6 Hz, C_5), 86.4 (dd, *J* = 187.0, 17.5 Hz, C_4), 81.0 (O-$\underline{C}$(CH_3)), 55.4 (Ar-O-$\underline{C}H_3$), 50.1 (C_2), 38.2 (dd, *J* = 30.8, 4.4 Hz, C_6), 31.6 (dd, *J* = 18.6, 4.7 Hz, C_3), 28.5 (C($\underline{C}H_3$)$_3$); **^{19}F NMR** (376 MHz, $CDCl_3$) δ –194.9 (d, *J* = 45.7 Hz), –202.0 (dddd, *J* = 53.3, 35.9, 21.0, 10.6 Hz); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ –194.9 (d, *J* = 11.6 Hz), –202.0 (d, *J* = 11.6 Hz); **HRMS** (ESI) calcd. for $C_{17}H_{23}F_2NNaO_3^+$ $[M+Na]^+$ 350.1538, found 350.1542.

***tert*-Butyl (2*R*,3*R*,5*S*)-3-fluoro-2-(fluoromethyl)-5-(4-methoxyphenyl)pyrrolidine-1-carboxylate (14b); and *tert*-butyl (2*S*,4*S*,5*S*)-4,5-difluoro-2-(4-methoxyphenyl)piperidine-1-carboxylate (15b)**

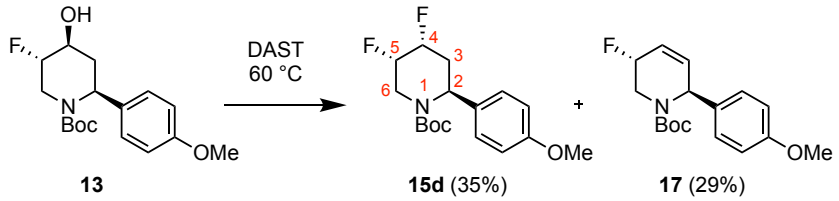


A mixture of fluorohydrin **12b**[1] (81 mg, 0.25 mmol) and neat DAST (405 mg, 2.5 mmol, 0.33 mL) was stirred at 60 ºC in a plastic reaction vessel overnight. The mixture was cooled to 0 ºC, diluted with dichloromethane, and quenched slowly with $NaHCO_3$ at 0 ºC. The crude product was subjected to flash chromatography eluting with 1:50→1:20 petroleum ether/ethyl acetate to give two isolated products: a compound tentatively identified as **14b** (24 mg, 27%); and **15b** (26 mg, 32%).

Data for **14b**: colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.7 Hz, 2H, Ar), 6.85 (d, *J* = 8.7 Hz, 2H, Ar), 5.19 (dd, *J* = 51.7, 3.6 Hz, 1H, N-C<u>H</u>-CH_2), 4.87–4.75 (m, 2H, FC<u>H</u>$_2$-CH), 4.65 (d, *J* = 8.8 Hz, 1H, CH-C<u>H</u>$_2$-CHF), 4.30 (t, *J* = 27.0 Hz, 1H, Ar-C<u>H</u>-N), 3.79 (s, 3H, Ar-O-C<u>H</u>$_3$), 2.54 (ddd, *J* = 19.6, 14.8, 6.6 Hz, 1H, CH-C<u>H</u>$_2$-CHF), 2.08 (dt, *J* = 45.5, 12.8 Hz, 1H, C<u>H</u>F), 1.15 (s, 9H, C(C<u>H</u>$_3$)$_3$); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 158.8 (<u>C</u>OO), 155.1 (Ar), 135.8 (Ar), 127.2 (Ar), 113.8 (Ar), 93.9 (d, *J* = 177.8 Hz, F<u>C</u>H_2), 82.6 (dd, *J* = 172.4, 11.9 Hz, <u>C</u>HF-CH_2), 80.5 (O-<u>C</u>(CH$_3$)), 67.3 – 63.9 (m, N-<u>C</u>H-CH_2F), 60.7 (CHF-<u>C</u>H_2), 55.4 (d, *J* = 3.8 Hz, Ar-O-<u>C</u>H_3), 42.6 (Ar-<u>C</u>H-N), 28.2 (C(<u>C</u>H_3)$_3$); **HRMS** (ESI) calcd. for $C_{17}H_{24}F_2NNO_3^+$ $[M+H]^+$ 328.1719, found 328.1720.

Data for **15b**: colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 7.8 Hz, 2H, Ar), 6.90 (d, *J* = 8.8 Hz, 2H, Ar), 5.53 (bs, 1H, H_2), 4.84–4.71 (m, 0.5 H, H_6), 4.64 (ddt, *J* = 13.8, 6.5, 4.8 Hz, 1H, H_5), 4.57–4.46 (m, 0.5 H, H_6), 4.45–4.32 (m, 1H, H_6), 3.80 (s, 3H, Ar-O-C<u>H</u>$_3$), 2.86–2.75 (m, 1H, H_3), 2.70 (ddd, *J* = 13.3, 10.8, 5.0 Hz, 1H, H_4), 2.14–1.93 (m, 1H, H_3), 1.49 (s, 9H, C(C<u>H</u>$_3$)$_3$); **^{13}CNMR** (100 MHz, $CDCl_3$) δ 158.7 (<u>C</u>OO), 155.8 (Ar), 130.2 (Ar), 127.3 (Ar), 114.4 (Ar), 89.7 (C_5), 87.9 (C_4), 80.7 (O-<u>C</u>(CH$_3$)), 66.0 (dd, J = 20.5, 3.2 Hz, C_6), 55.4 (d, *J* = 4.1 Hz, C_2), 52.4 (Ar-O-<u>C</u>H_3), 43.1 (d, *J* = 20.8 Hz, C_3), 28.5 (C(<u>C</u>H_3)$_3$); **^{19}F NMR** (376 MHz, $CDCl_3$) δ –187.4 (bs), –191.6 (dt, *J* = 50.9, 14.2 Hz); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ –187.4, –191.6 (d, *J* = 13.6 Hz); **HRMS** (ESI) calcd. for $C_{17}H_{23}F_2NNaO_3^+$ $[M+Na]^+$ 350.1538, found 350.1542.

***tert*-Butyl (2*S*,4*S*,5*R*)-4,5-difluoro-2-(4-methoxyphenyl)piperidine-1-carboxylate (15d); and tert-butyl (3S,6S)-3-fluoro-6-(4-methoxyphenyl)-3,6-dihydropyridine-1(2H)-carboxylate (17)**



13 **15d** (35%) **17** (29%)

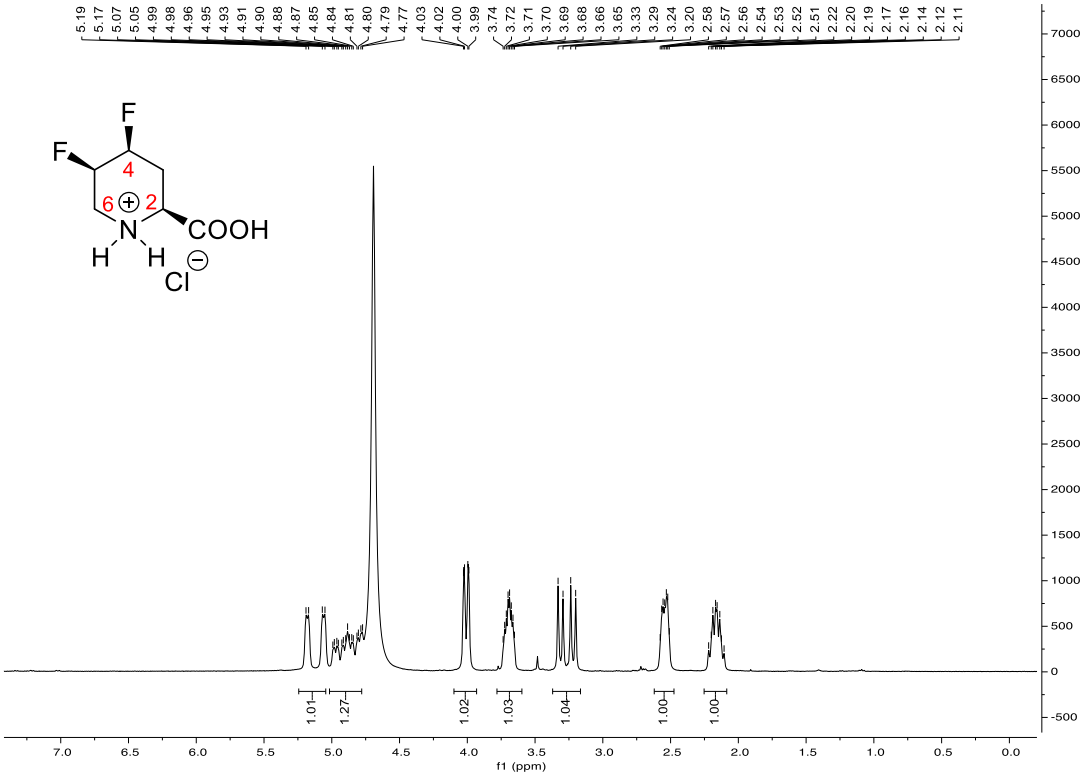
A mixture of fluorohydrin **13** (132 mg, 0.4 mmol) and neat DAST (644 mg, 4 mmol, 0.52 mL) was stirred at 60 ºC in a plastic reaction vessel overnight. The mixture was cooled to 0 ºC, diluted with dichloromethane, and quenched slowly with $NaHCO_3$ at 0 ºC. The crude product was subjected to flash chromatography eluting with 1:50→1:20 petroleum ether/ethyl acetate to give the two isolated products **15d** (45 mg, 35%) and **17** (35 mg, 29%).

Data for **15d**: colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.20–7.10 (m, 2H, Ar), 6.89 (d, J = 8.8 Hz, 2H, Ar), 5.66 (bs, 1H, H_2), 4.74 (dt, J = 50.9, 3.9 Hz, 1H, H_5), 4.63–4.39 (m, 2H, H_6), 3.79 (s, 3H, Ar-O-CH_3), 2.85 (ddt, J = 38.3, 15.3, 1.4 Hz, 1H, H_4), 2.62–2.50 (m, 1H, H_3), 2.50–2.39 (m, 1H, H_3), 1.49 (s, 9H, C(CH_3)$_3$); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 158.9 (COO), 155.7 (Ar), 129.7 (Ar), 127.1 (Ar), 114.5 (Ar), 86.8 (dd, J = 183.5, 18.7 Hz, C_5), 85.9 (dd, J = 183.5, 16.7 Hz, C_4), 80.9 (O-C(CH$_3$)), 55.4 (Ar-O-CH_3), 52.2 (d, J = 12.9 Hz, C_2), 42.9 (dd, J = 20.4, 7.3 Hz, C_6), 28.4 (C(CH_3)$_3$), 27.5 (dd, J = 19.2, 2.4 Hz, C_3); **^{19}F NMR** (376 MHz, $CDCl_3$) δ –190.4 (d, J = 45.7 Hz), –207.7 (dddt, J = 52.1, 38.4, 26.9, 13.4 Hz); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ –190.4 (bs), –207.7 (d, J = 15.7 Hz); **HRMS** (ESI) calcd. for $C_{17}H_{23}F_2NNaO_3^+$ $[M+Na]^+$ 350.1538, found 350.1541.

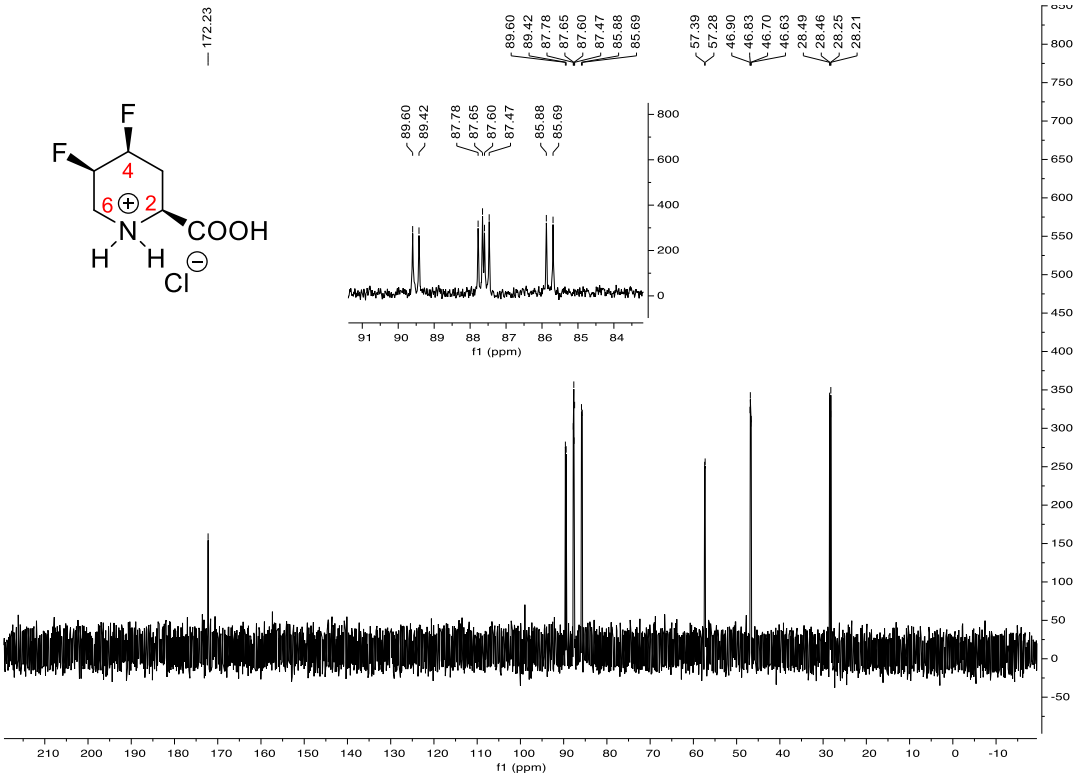
Data for **17**: colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.20 (m, 2H, Ar), 6.92–6.78 (m, 2H, Ar), 6.27 (s, 1H, CHF-CH=CH), 6.16 (ddt, J = 10.1, 5.3, 1.6 Hz, 1H, CHF-CH=CH), 5.90–5.55 (m, 1H, Ar-CH), 5.00–4.76 (m, 1H, N-CH_2), 4.57–4.27 (m, 1H, N-CH_2), 3.79 (s, 3H, Ar-O-CH_3), 3.06 (ddd, J = 38.1, 15.3, 2.4 Hz, 1H, CHF-CH_2), 1.48 (s, 9H, C(CH_3)$_3$); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 159.4 (COO), 154.8 (Ar), 135.7 (Ar), 130.6 (d, J = 4.8 Hz, CHF-CH=CH), 129.0 (Ar), 122.6 (Ar), 114.0 (CHF-CH=CH), 82.0 (d, J = 171.0 Hz, CHF), 80.4 (O-C(CH$_3$)), 55.4 (Ar-O-CH_3), 53.2 (N-CH_2), 42.5 (Ar-CH-N), 28.5 (C(CH_3)$_3$); **^{19}F NMR** (376 MHz, $CDCl_3$) δ –169.7 (m, 0.5F), –170.1 (m, 0.5F) [two rotamers]; **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ –169.7 (s, 0.5F), –170.1 (s, 0.5F) [two rotamers].

3. Selected NMR spectra

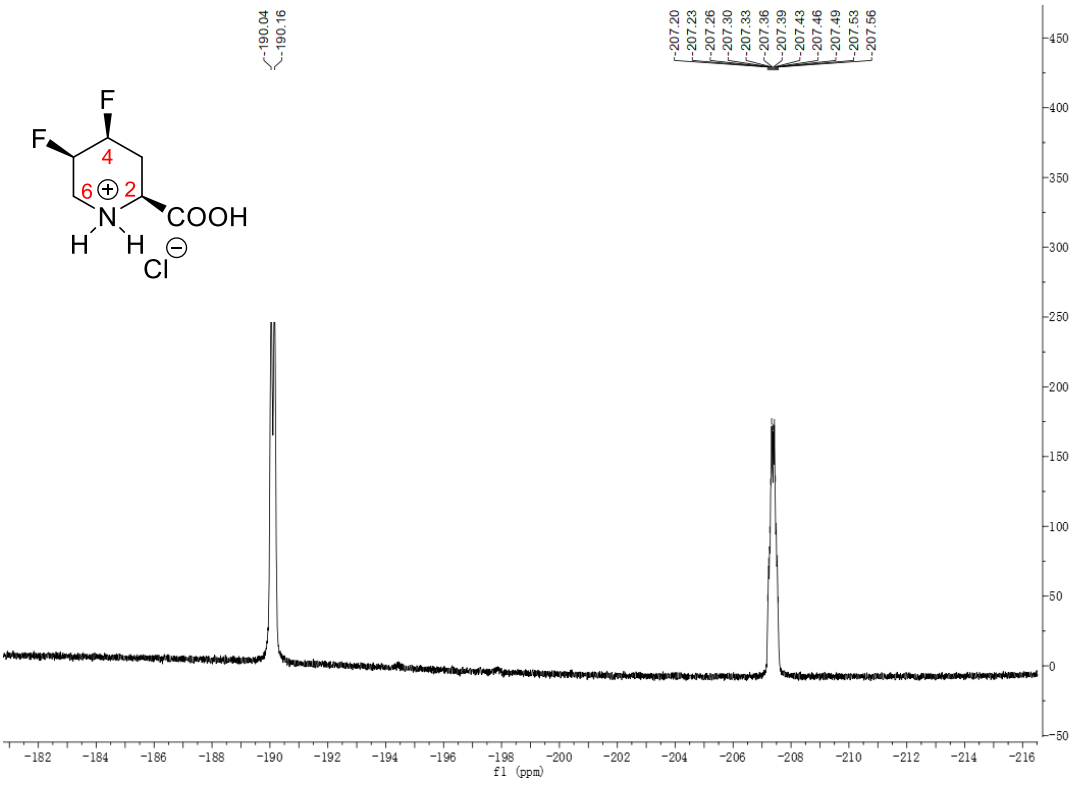
^{1}H NMR (400 MHz, D_2O) of **11a**



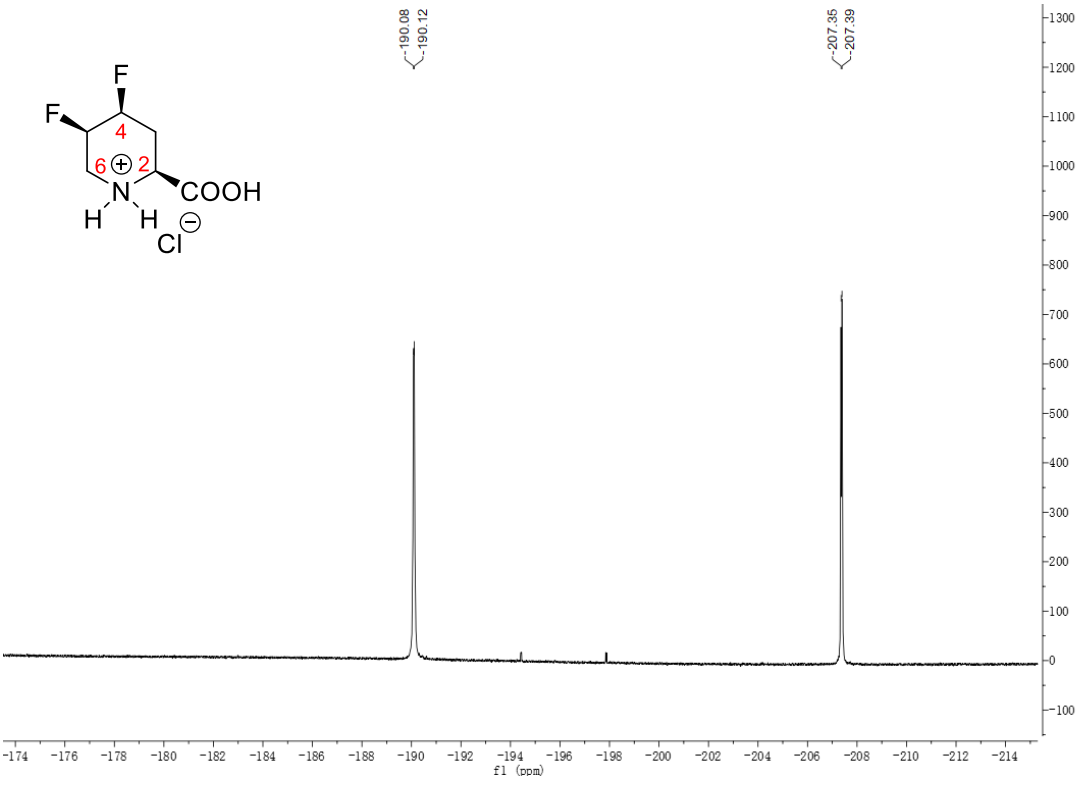
^{13}C{^{1}H} NMR (100 MHz, D_2O) of **11a**



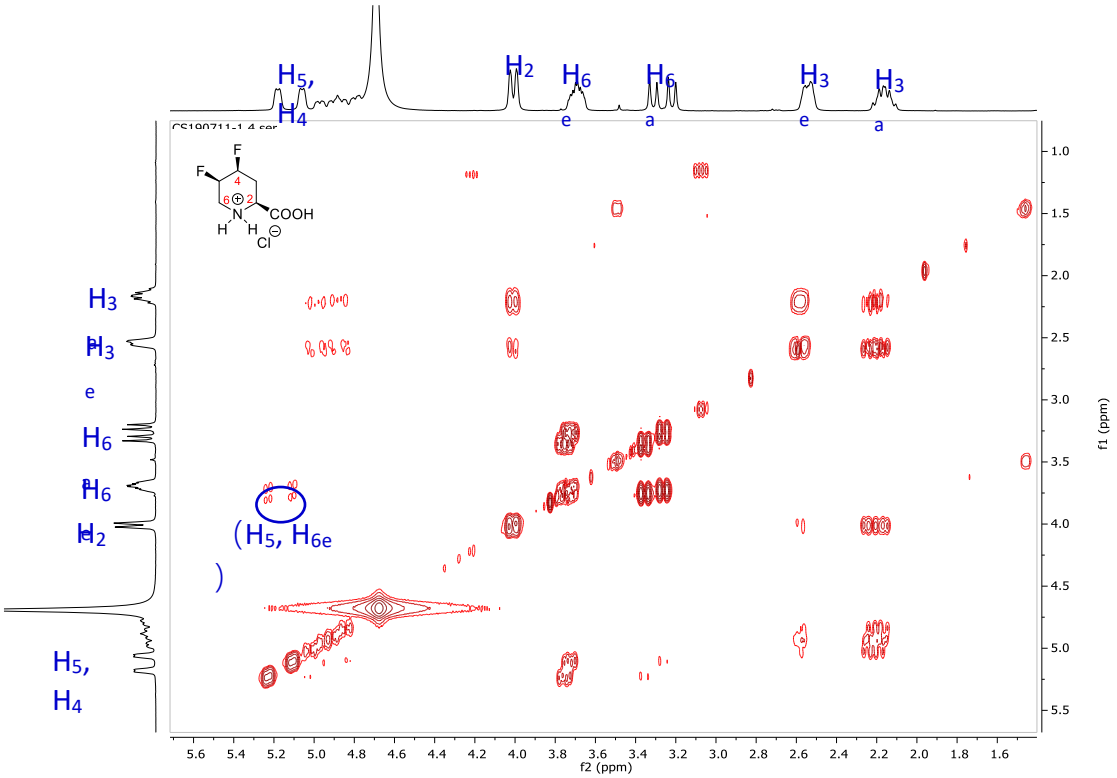
^{19}F NMR (376 MHz, D_2O) of **11a**



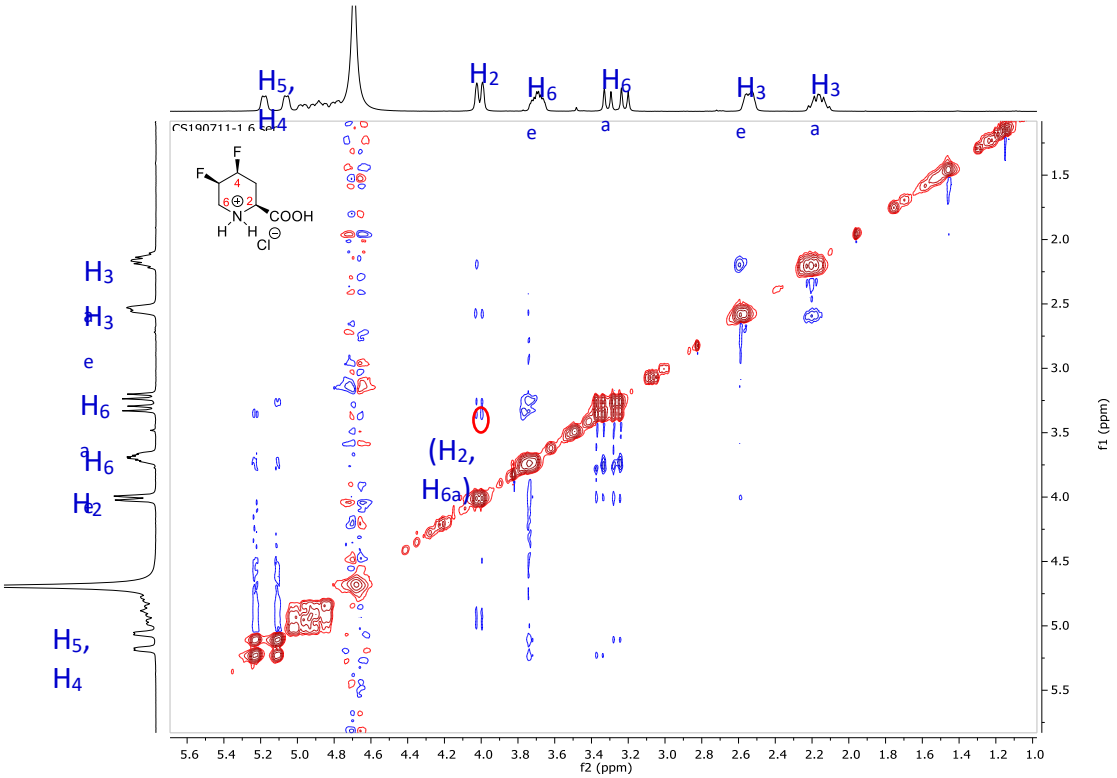
^{19}F{^{1}H} NMR (376 MHz, D_2O) of **11a**



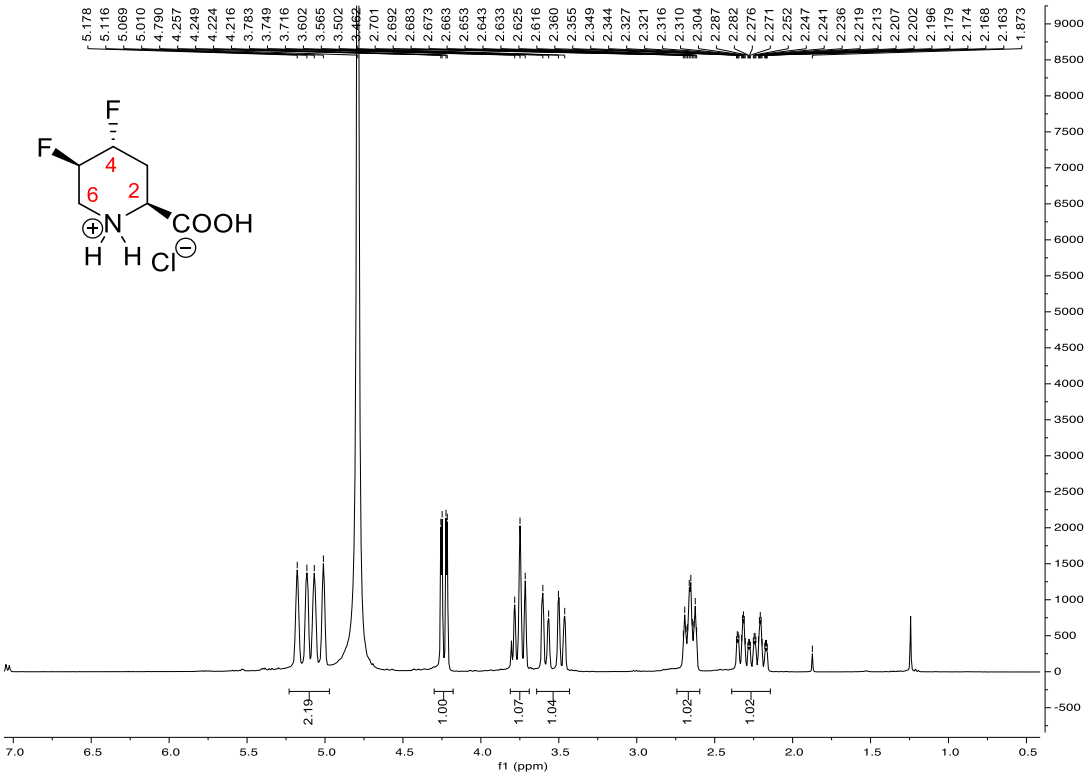
^{1}H-^{1}H COSY of compound **11a**



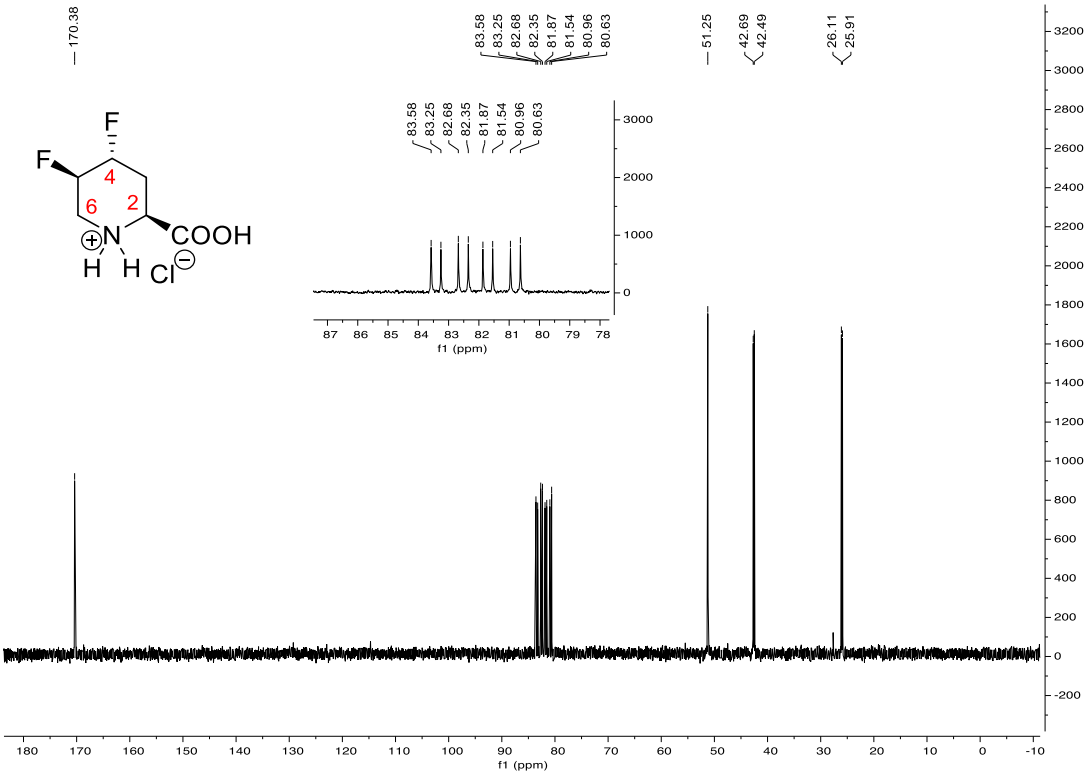
^{1}H-^{1}H NOESY of compound **11a**



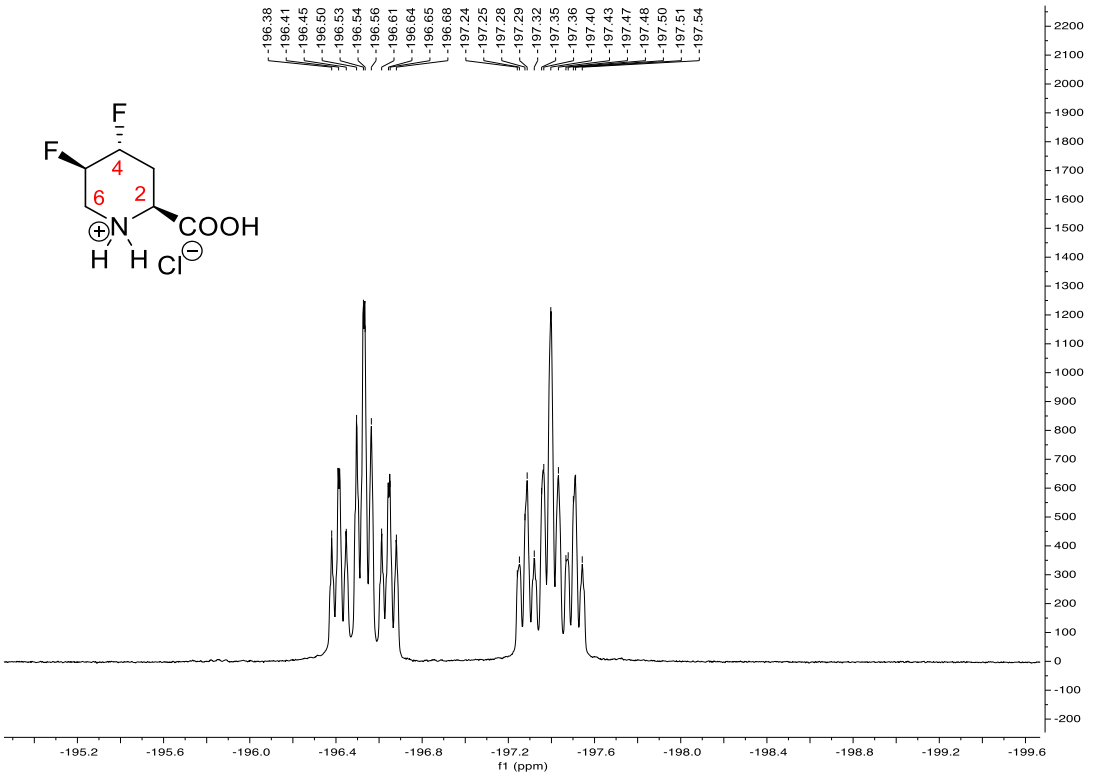
^{1}H NMR (400 MHz, D_2O) of **11b**



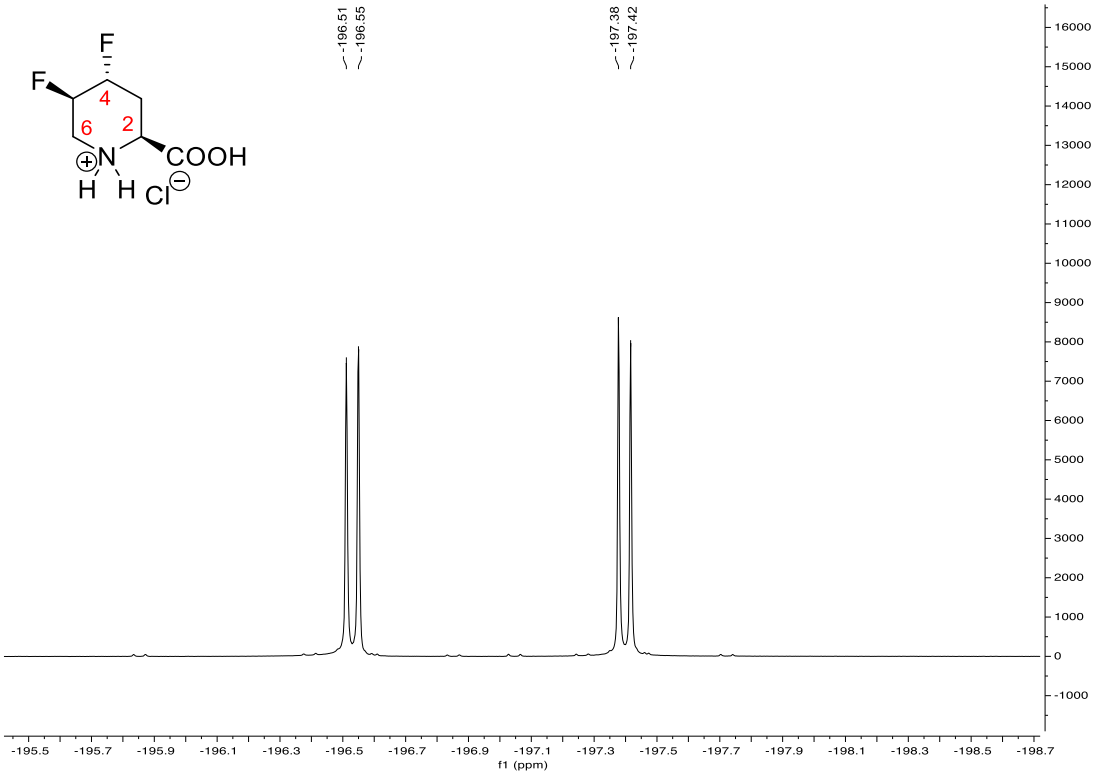
^{13}C{^{1}H} NMR (100 MHz, D_2O) of **11b**



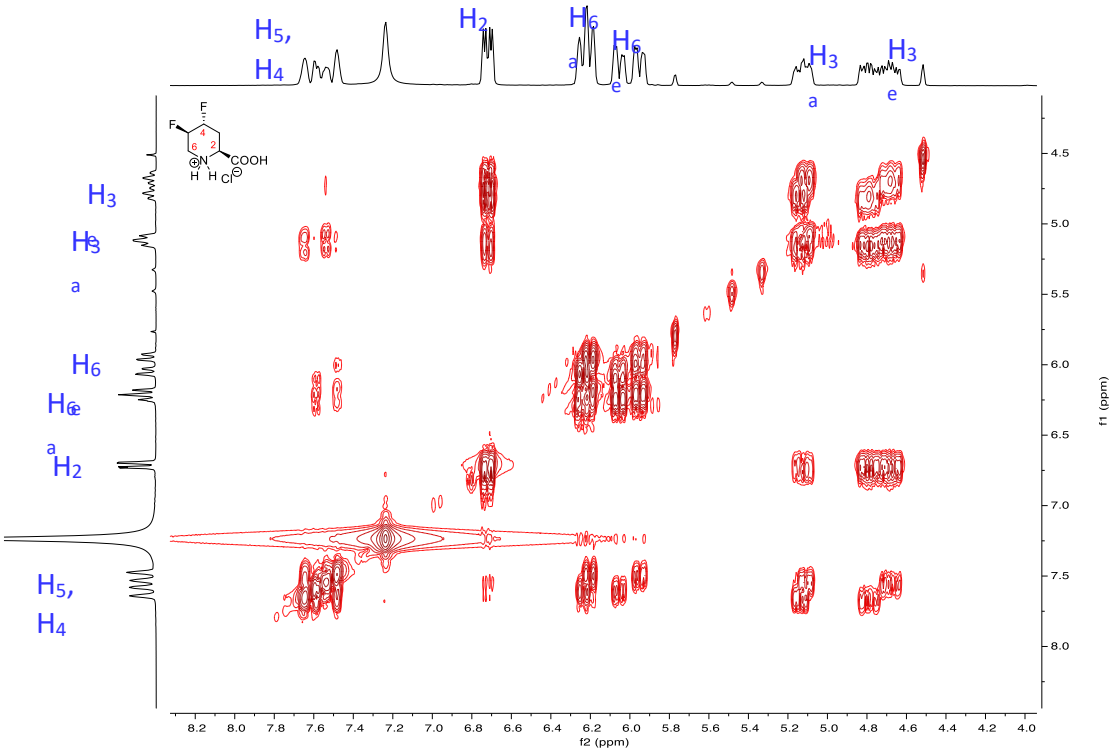
^{19}F NMR (376 MHz, D_2O) of **11b**



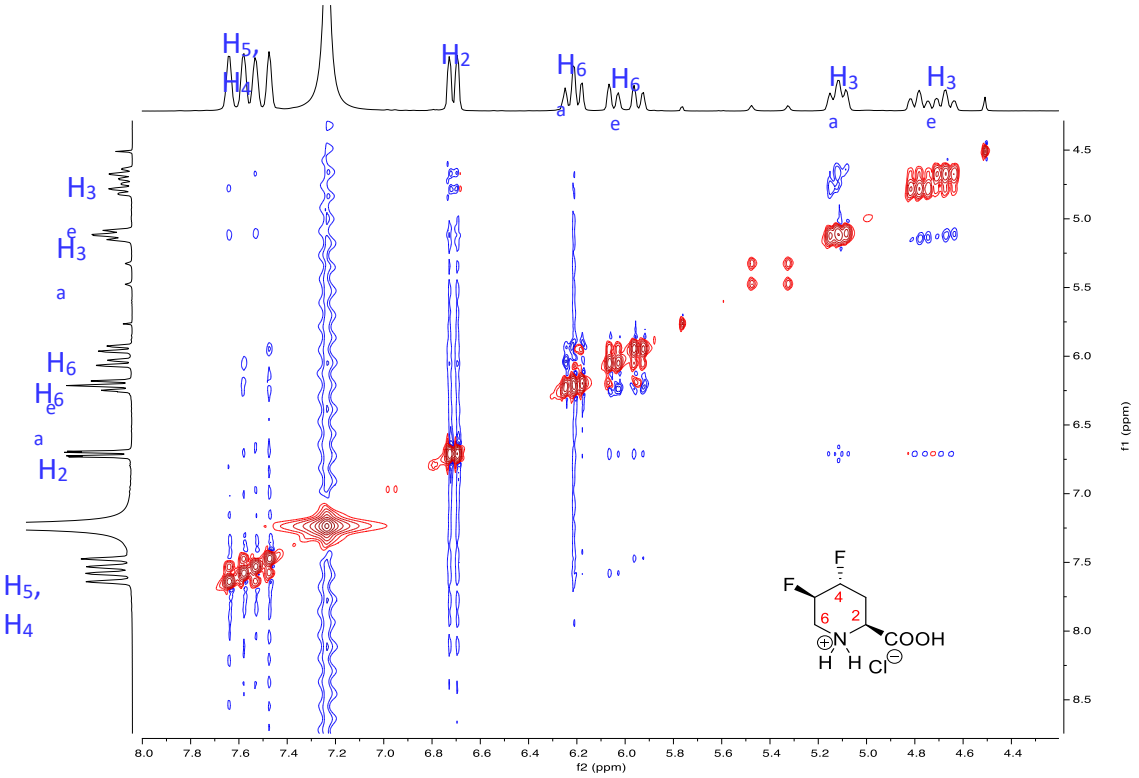
^{19}F{^{1}H} NMR (376 MHz, D_2O) of **11b**



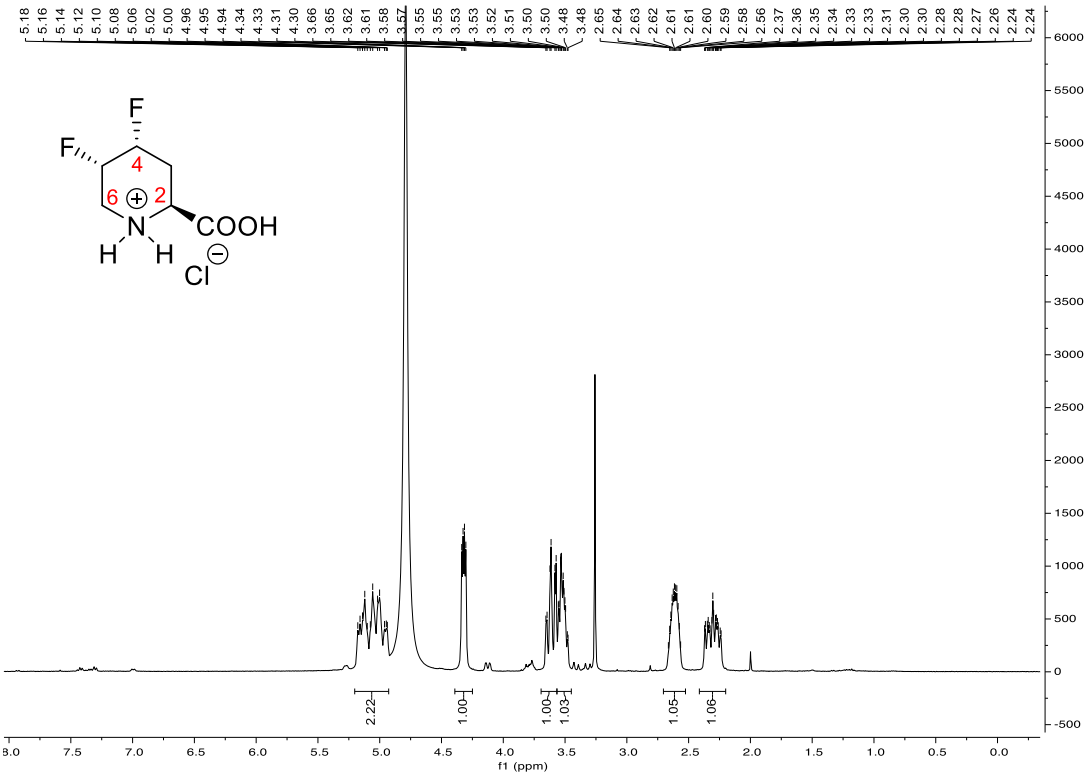
^{1}H-^{1}H COSY of compound **11b**



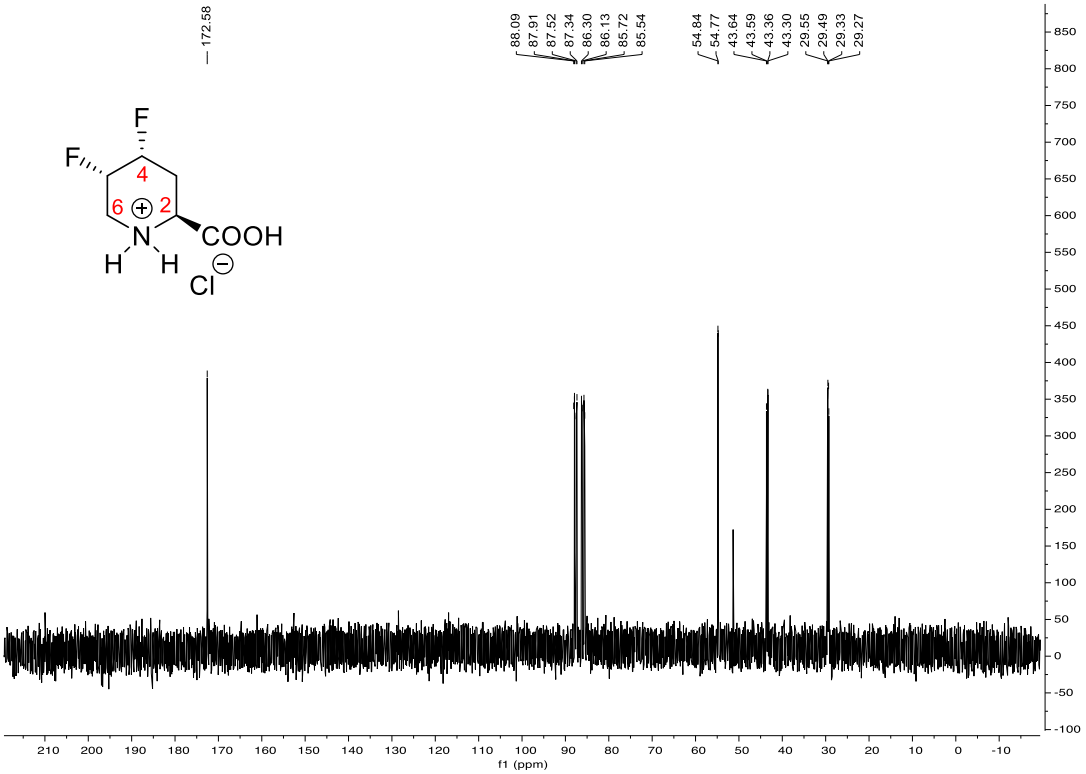
^{1}H-^{1}H NOESY of compound **11b**



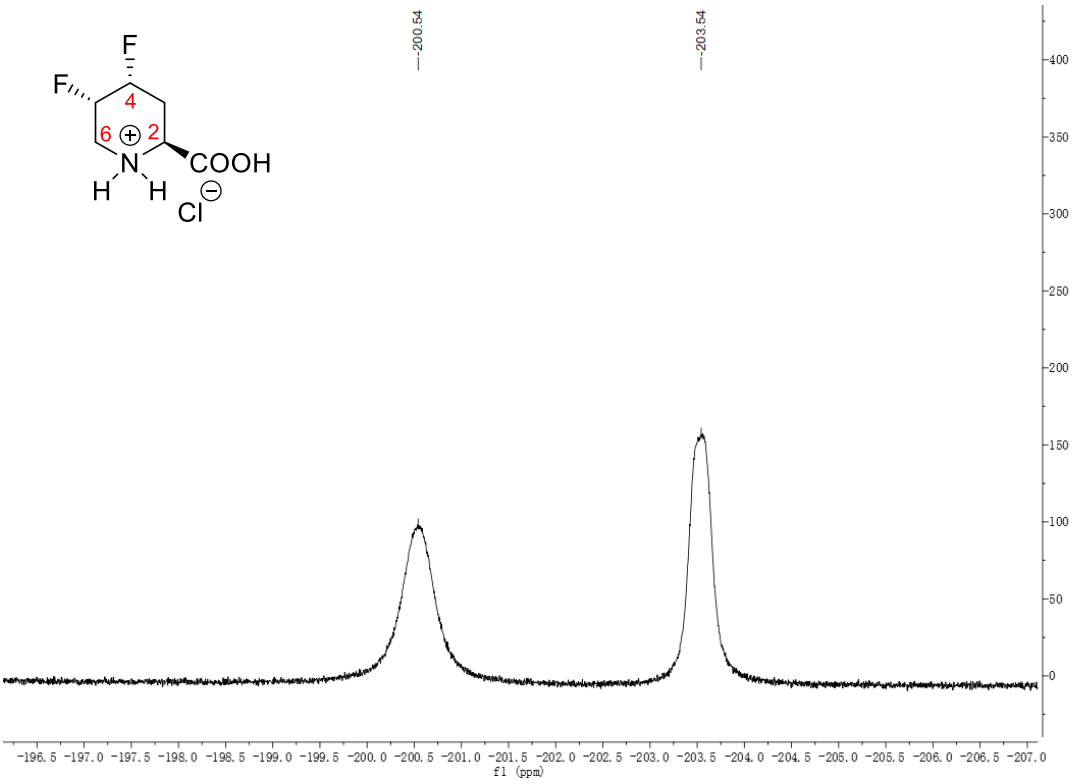
^{1}H NMR (400 MHz, D_2O) of **11d**



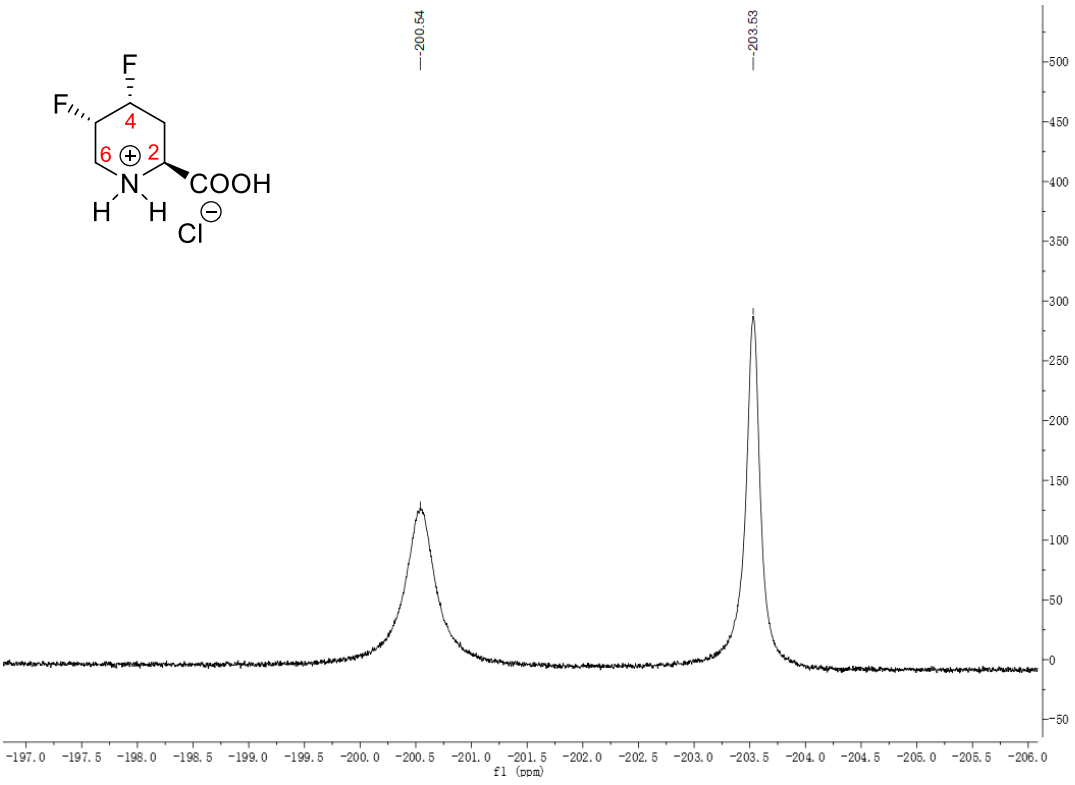
^{13}C{^{1}H} NMR (100 MHz, D_2O) of **11d**



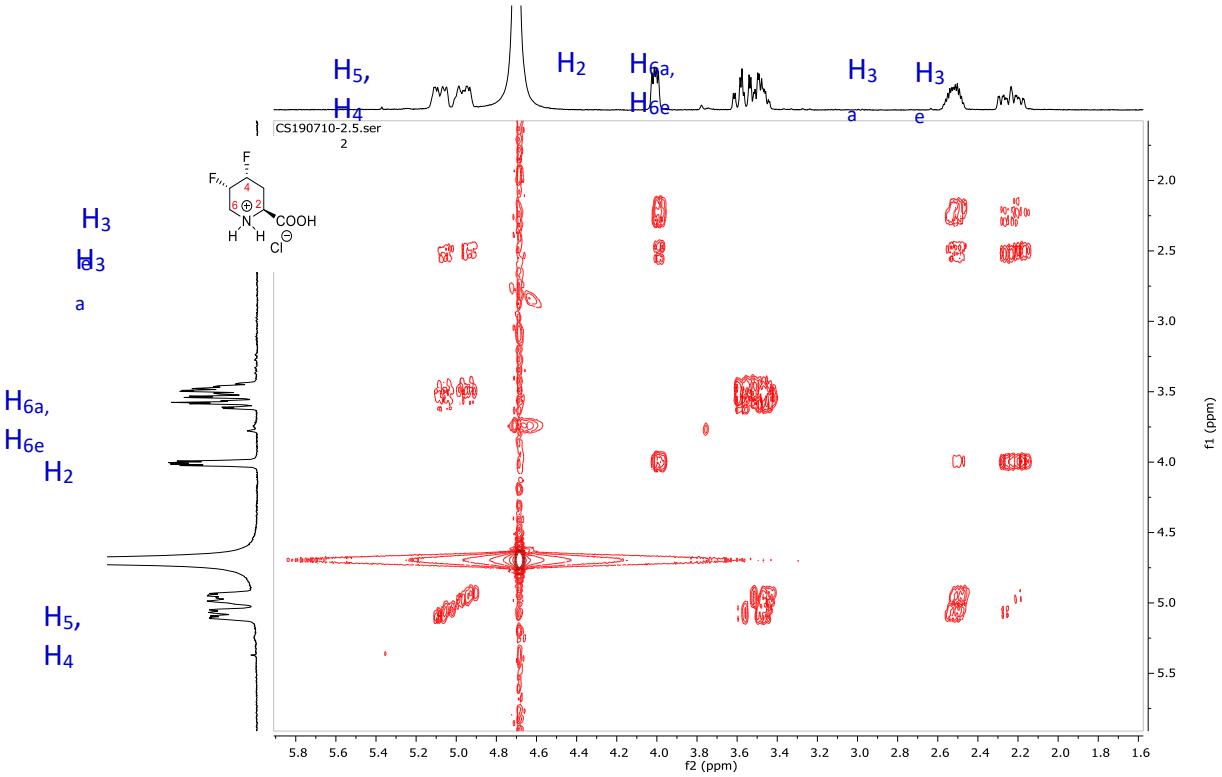
^{19}F NMR (376 MHz, D_2O) of **11d**



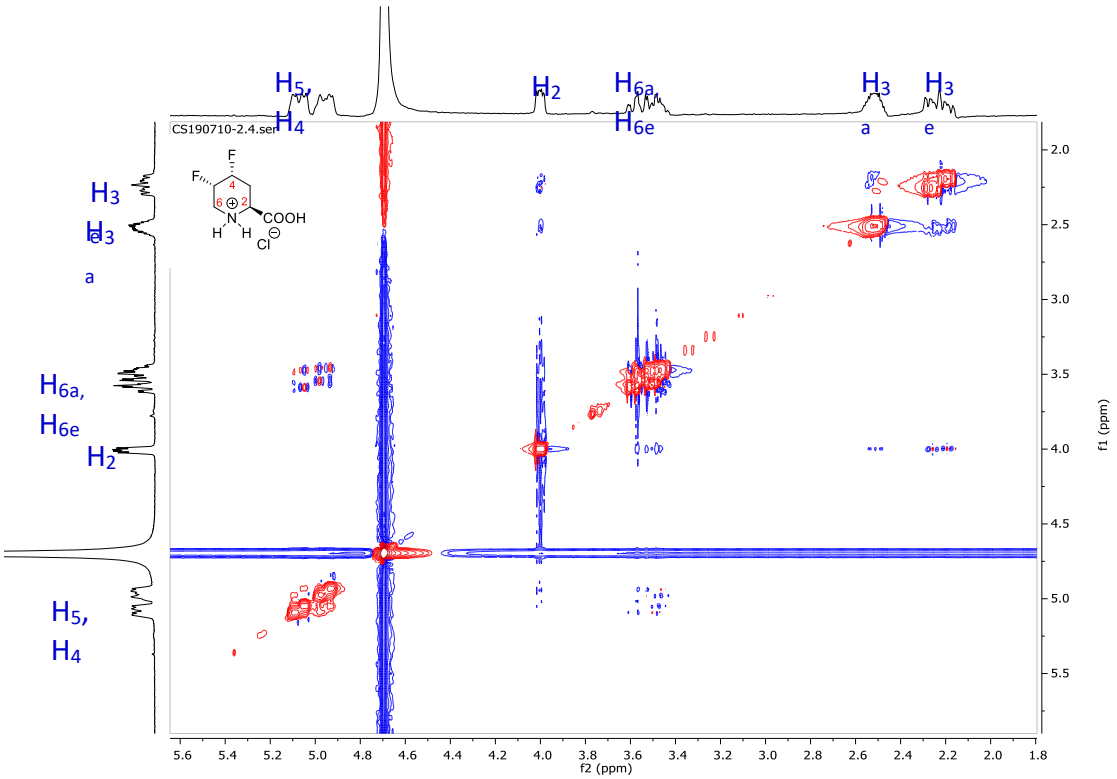
^{19}F{^{1}H} NMR (376 MHz, D_2O) of **11d**



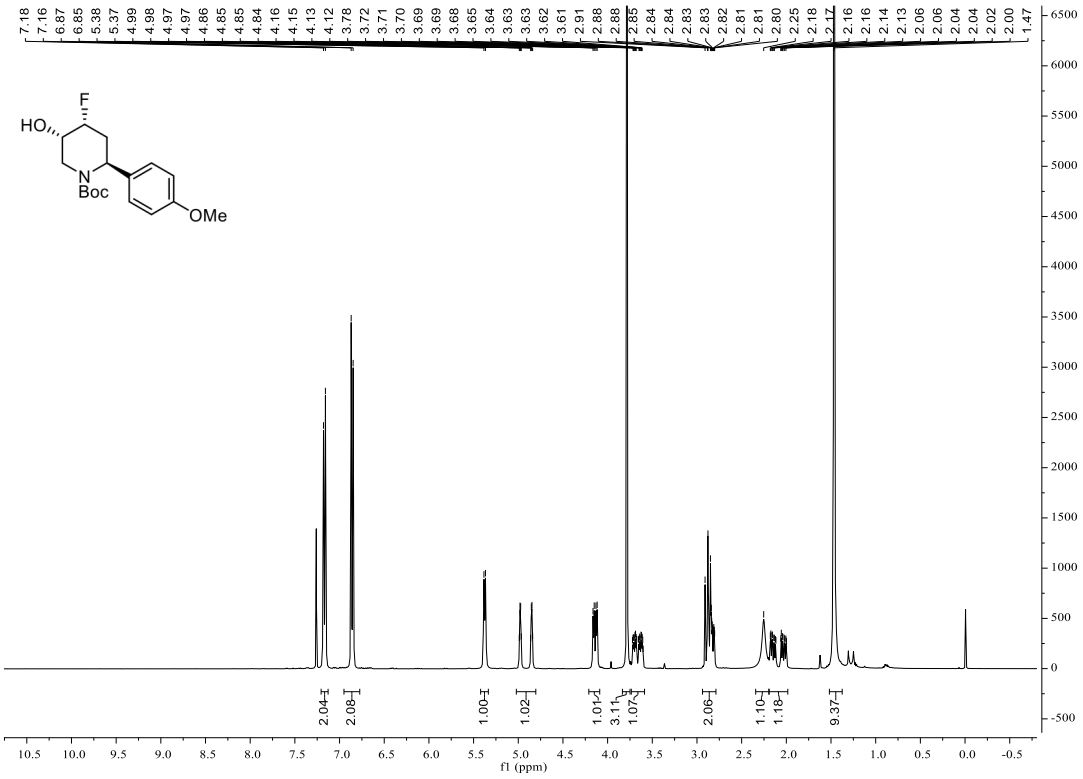
^{1}H-^{1}H COSY of compound **11d**



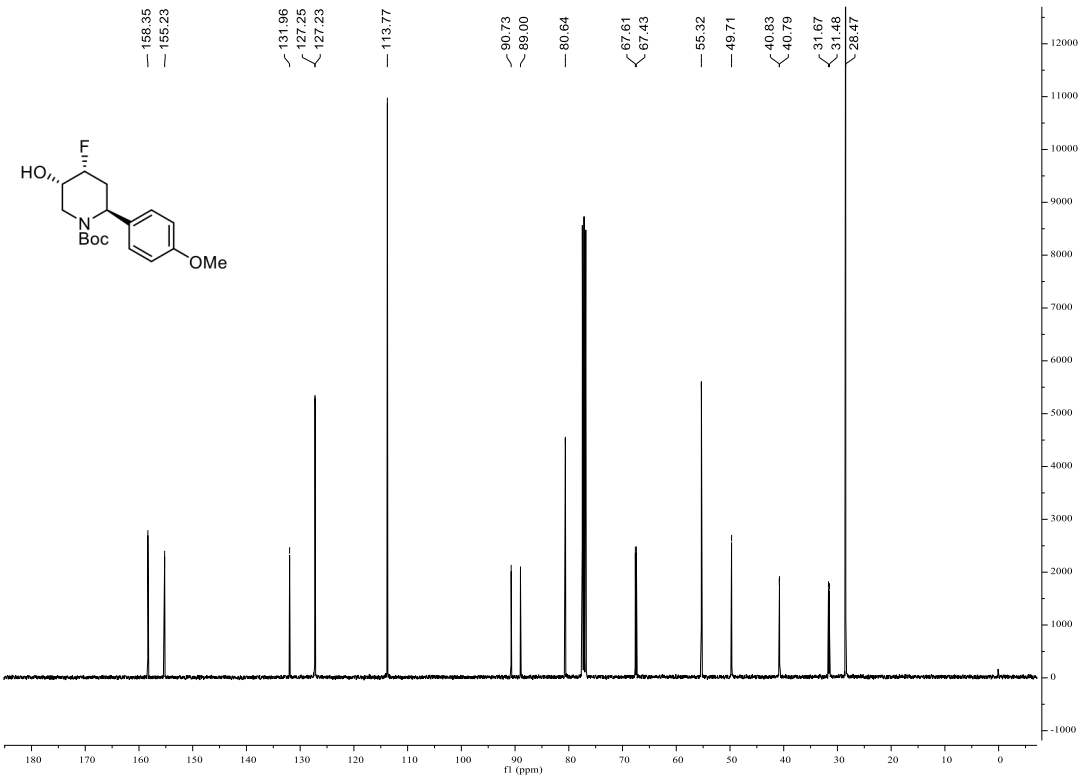
^{1}H-^{1}H NOESY of compound **11d**



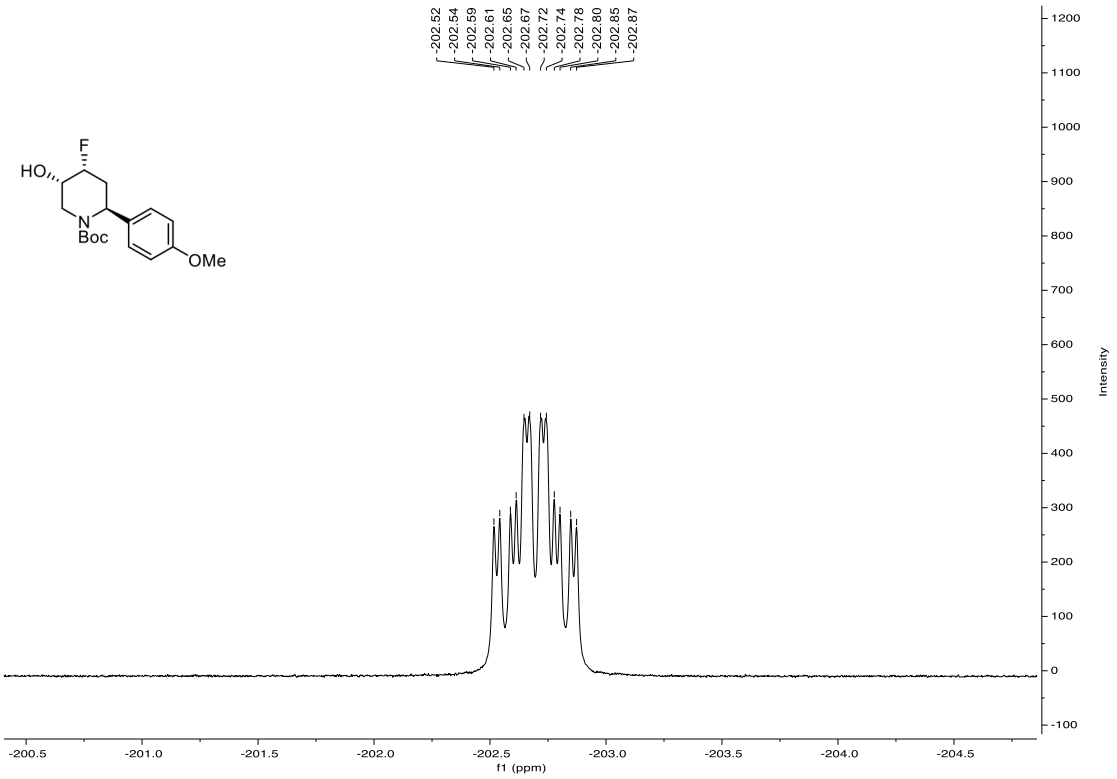
^{1}H NMR (400 MHz, $CDCl_3$) of **12d**



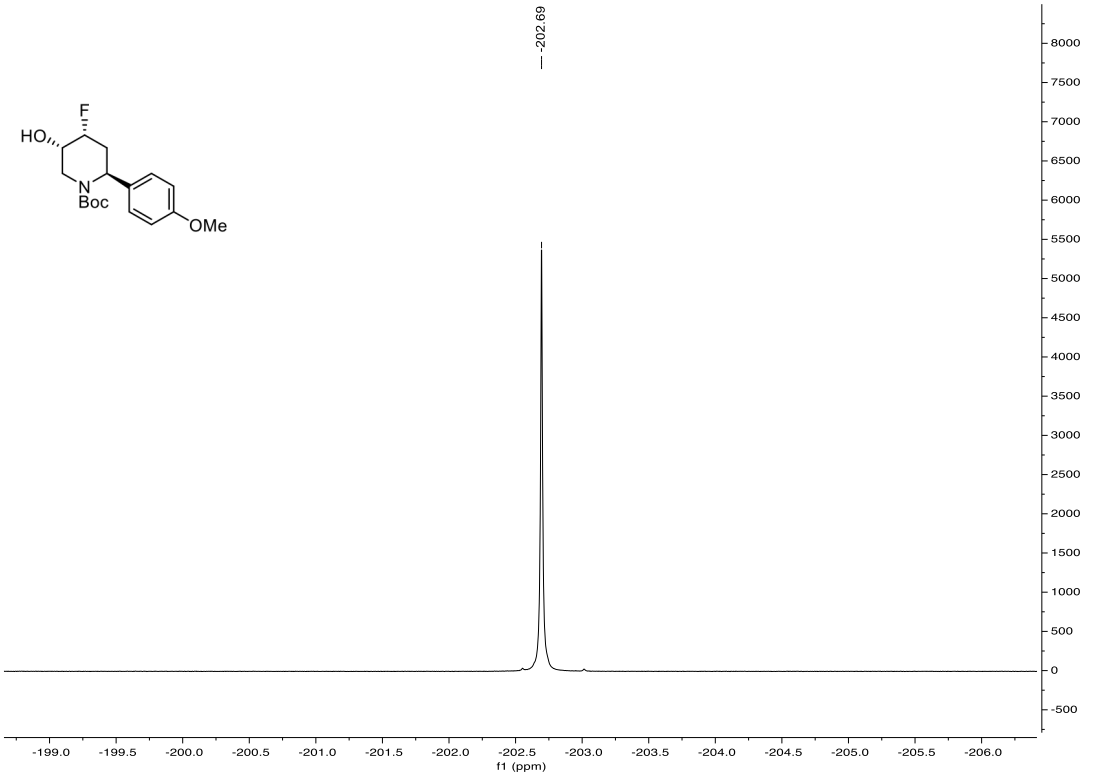
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) of **12d**



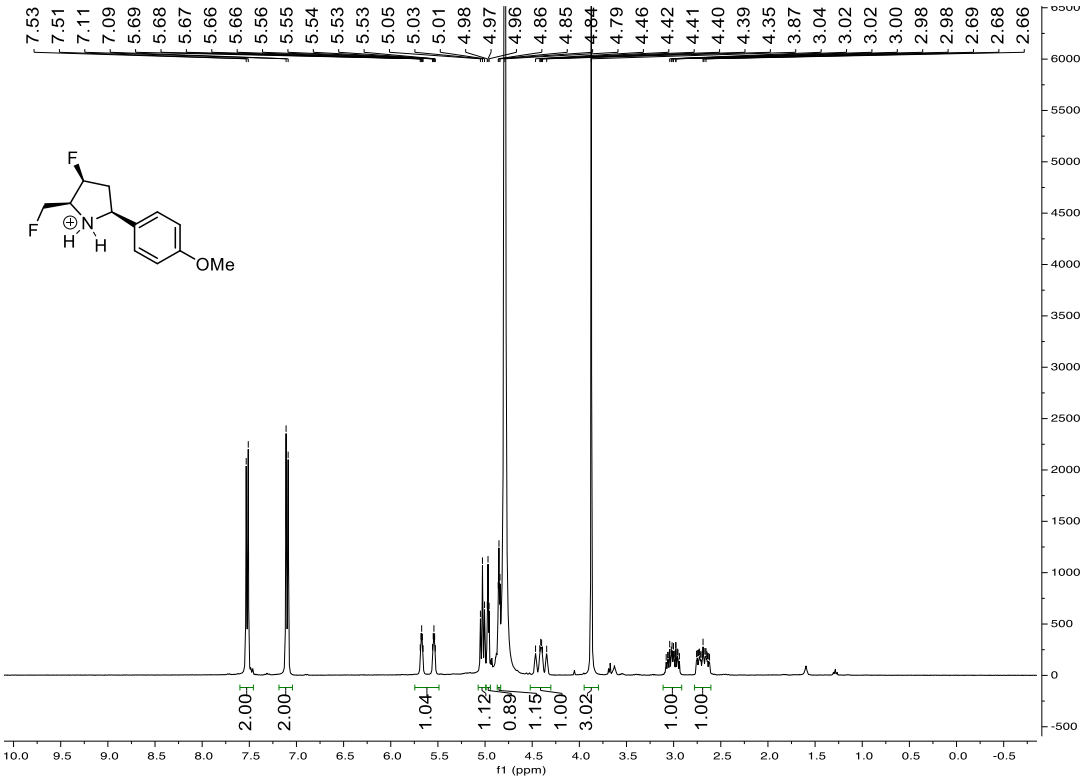
^{19}F NMR (376 MHz, $CDCl_3$) of **12d**



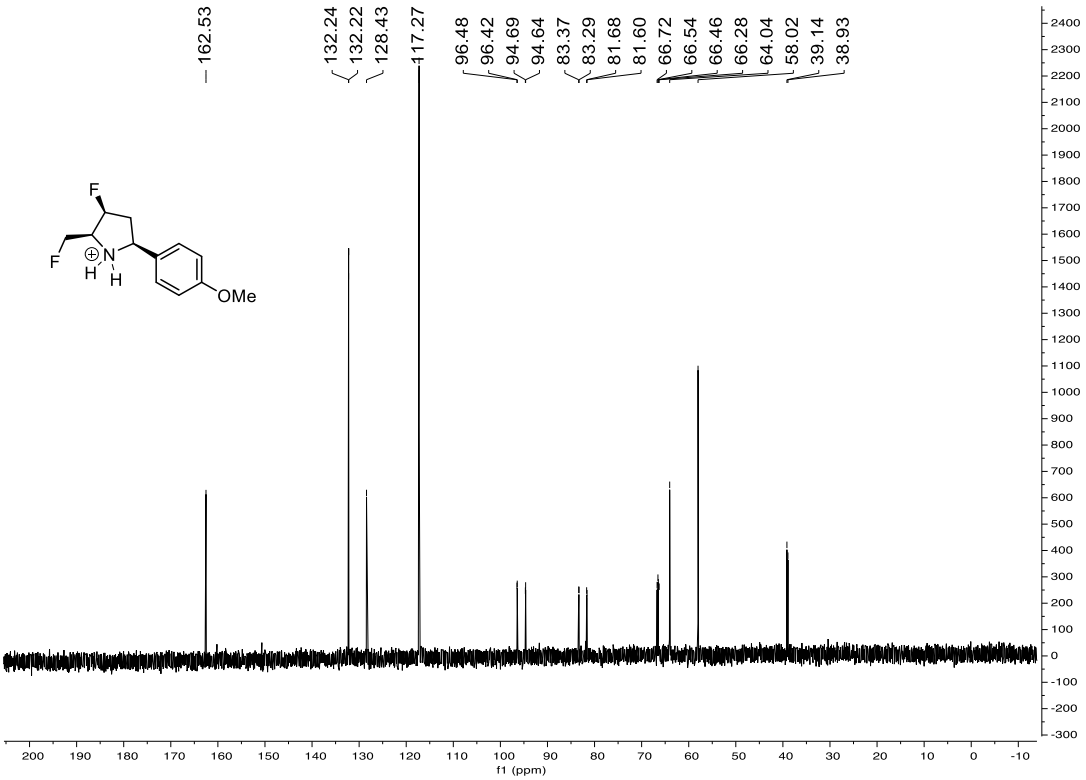
^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) of **12d**



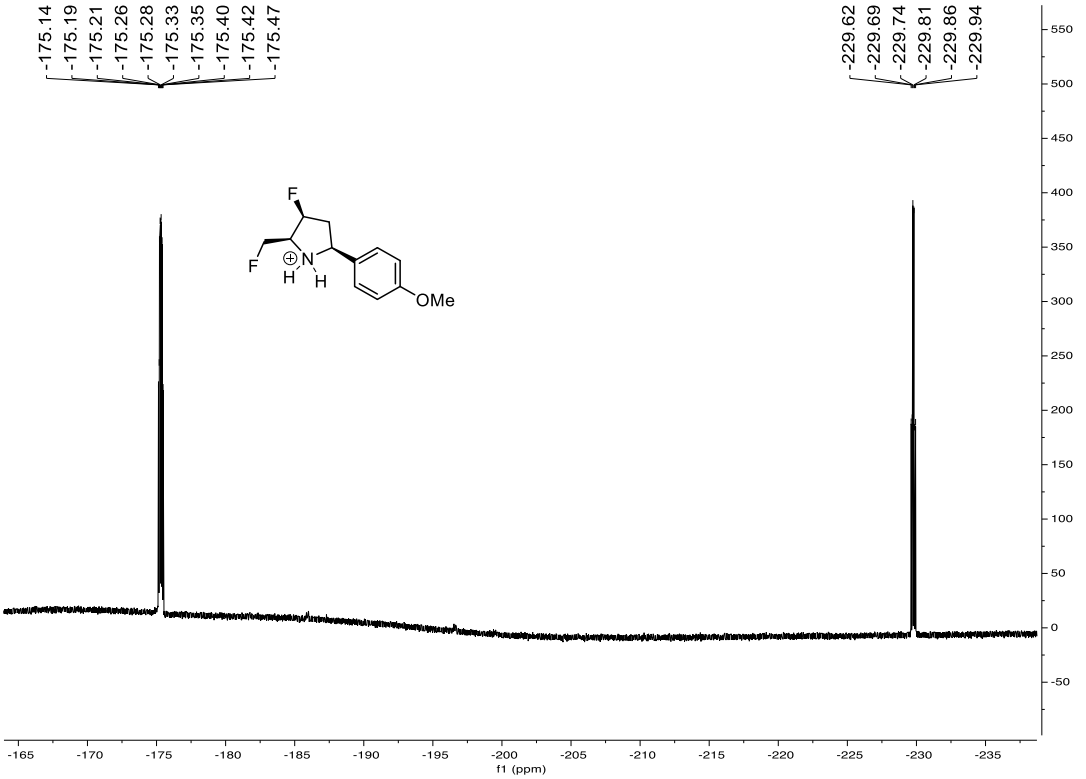
^{1}H NMR (400 MHz, D_2O) of **14a′**



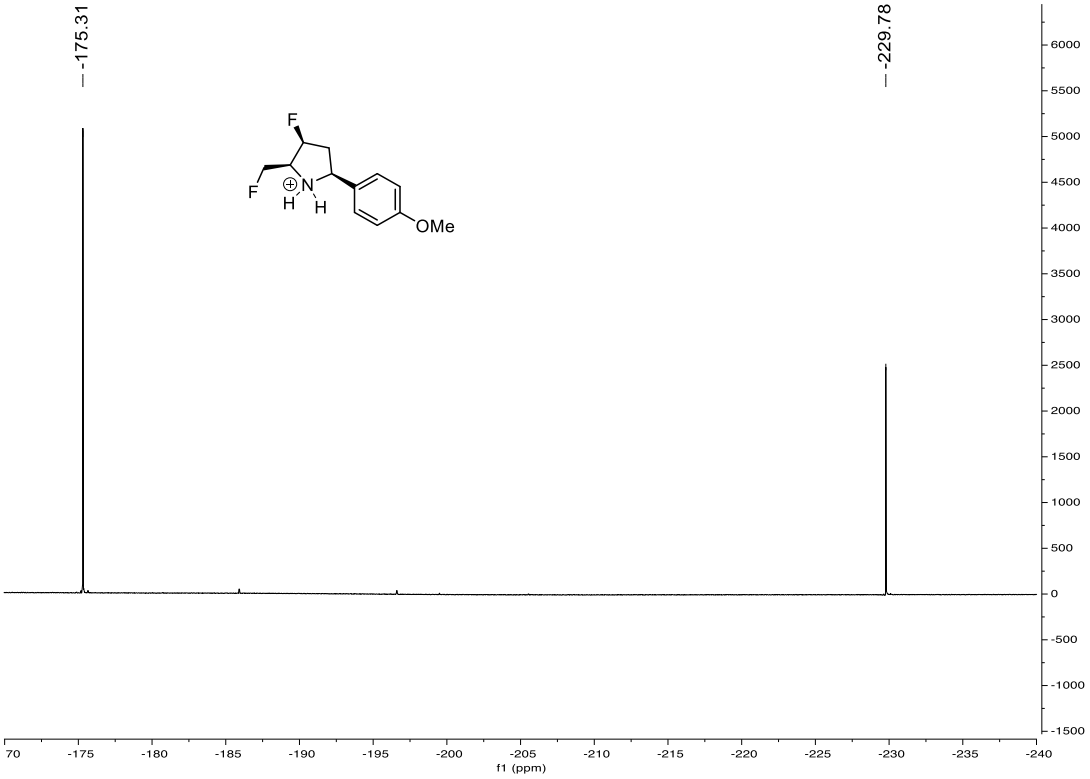
^{13}C{^{1}H} NMR (100 MHz, D_2O) of **14a′**



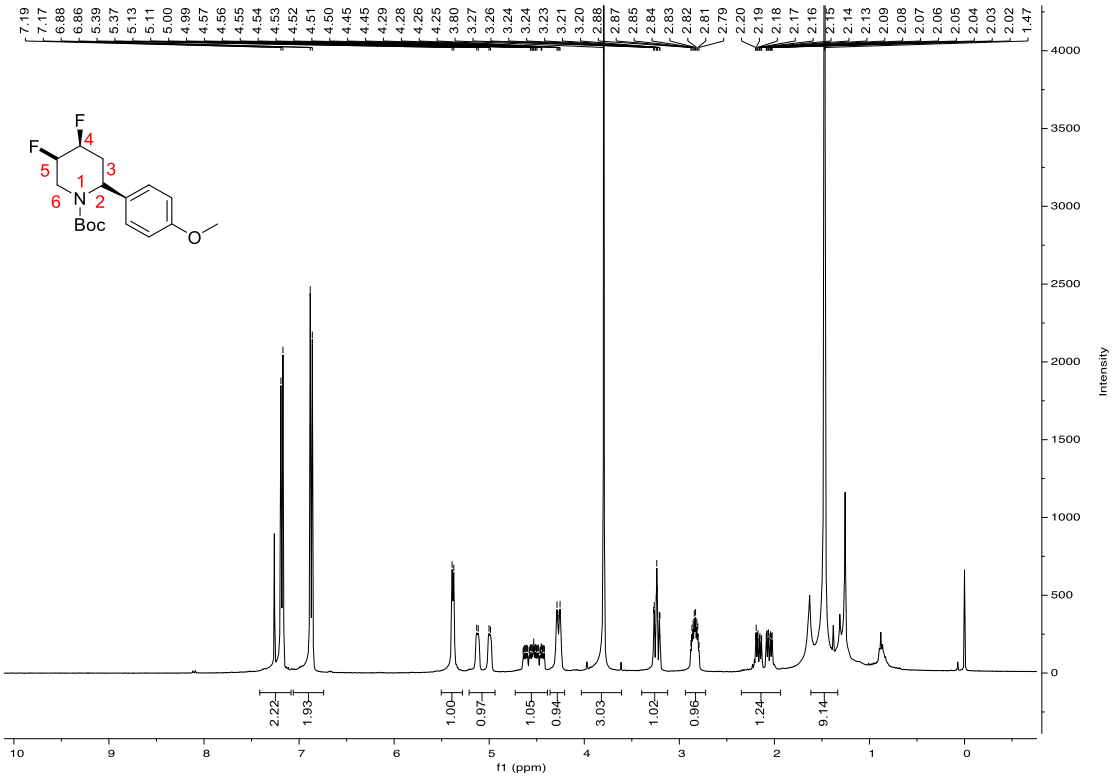
^{19}F NMR (376 MHz, D_2O) of **14a′**



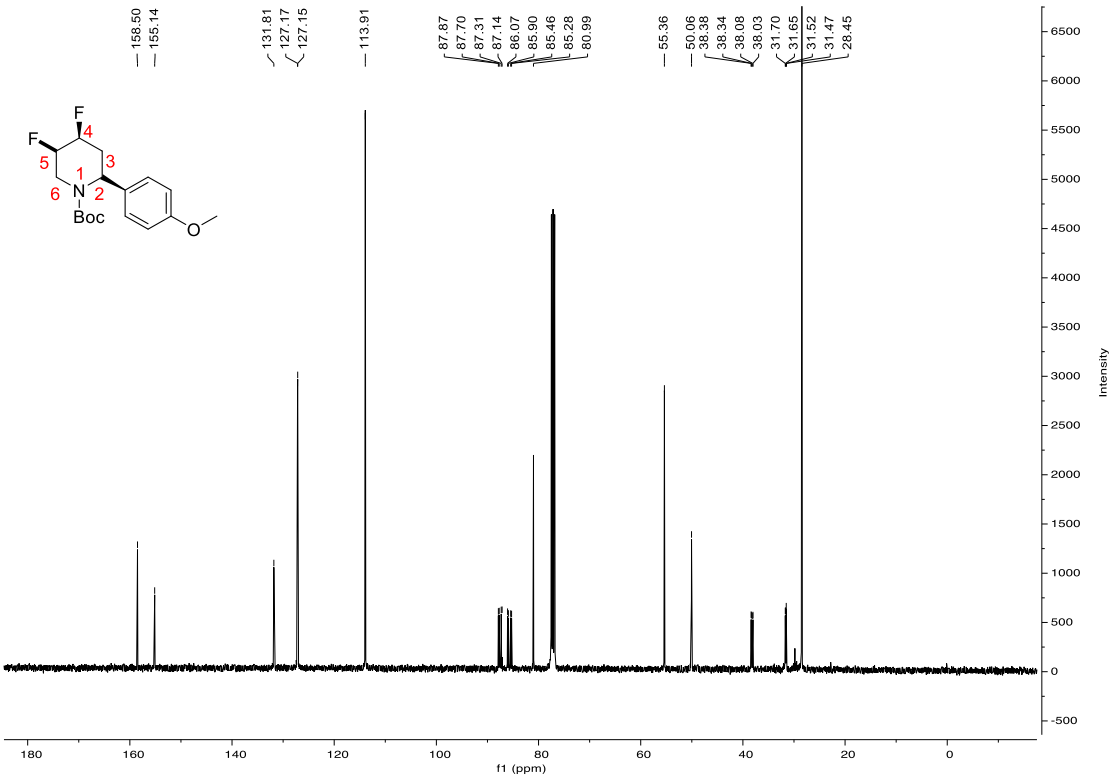
^{19}F {^{1}H} NMR (376 MHz, D_2O) of **14a′**



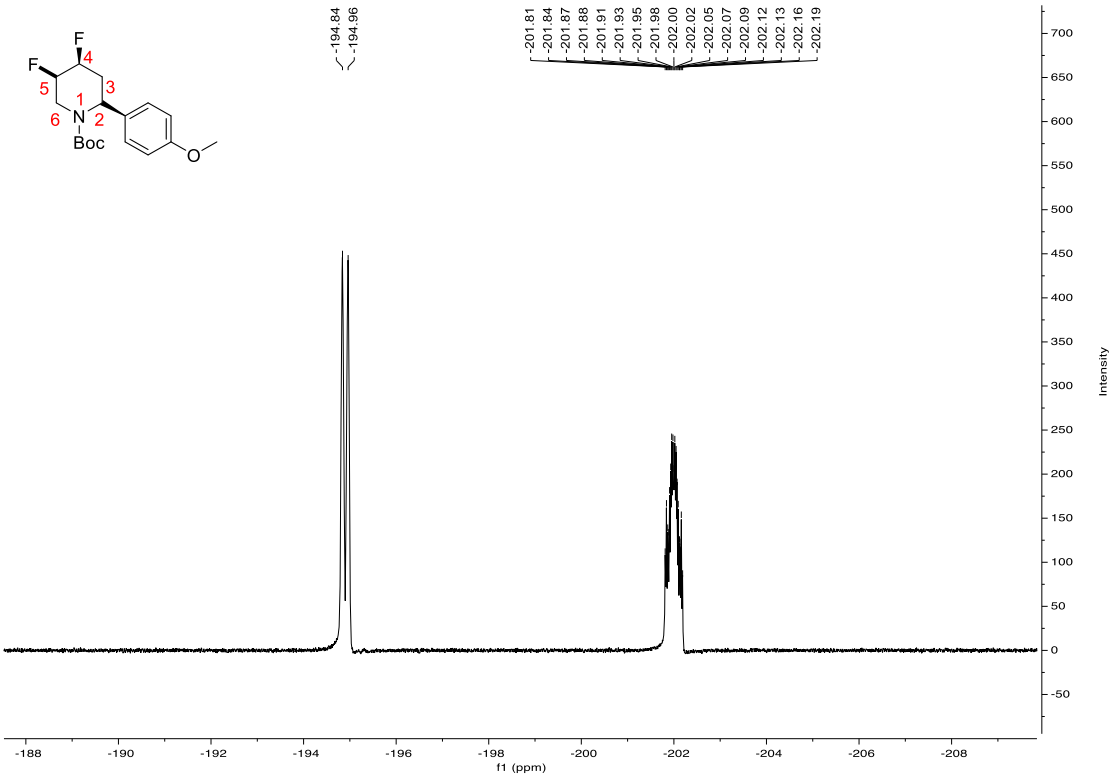
^{1}H NMR (400 MHz, $CDCl_3$) of **15a**



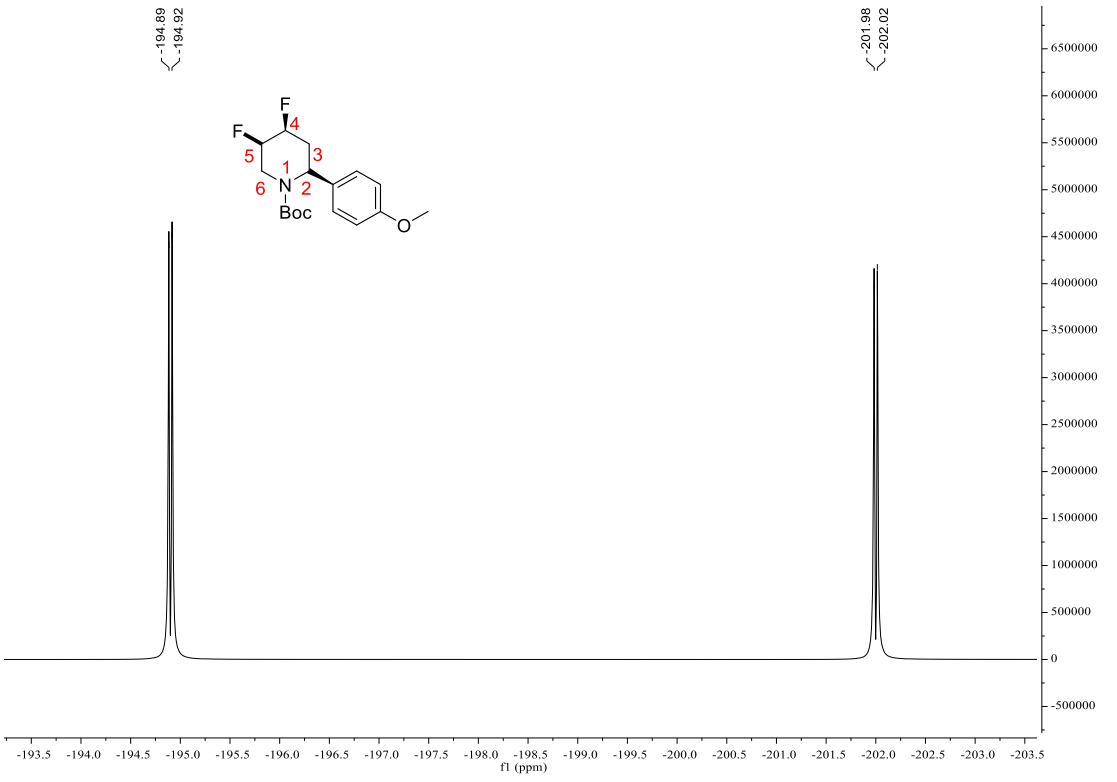
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) of **15a**



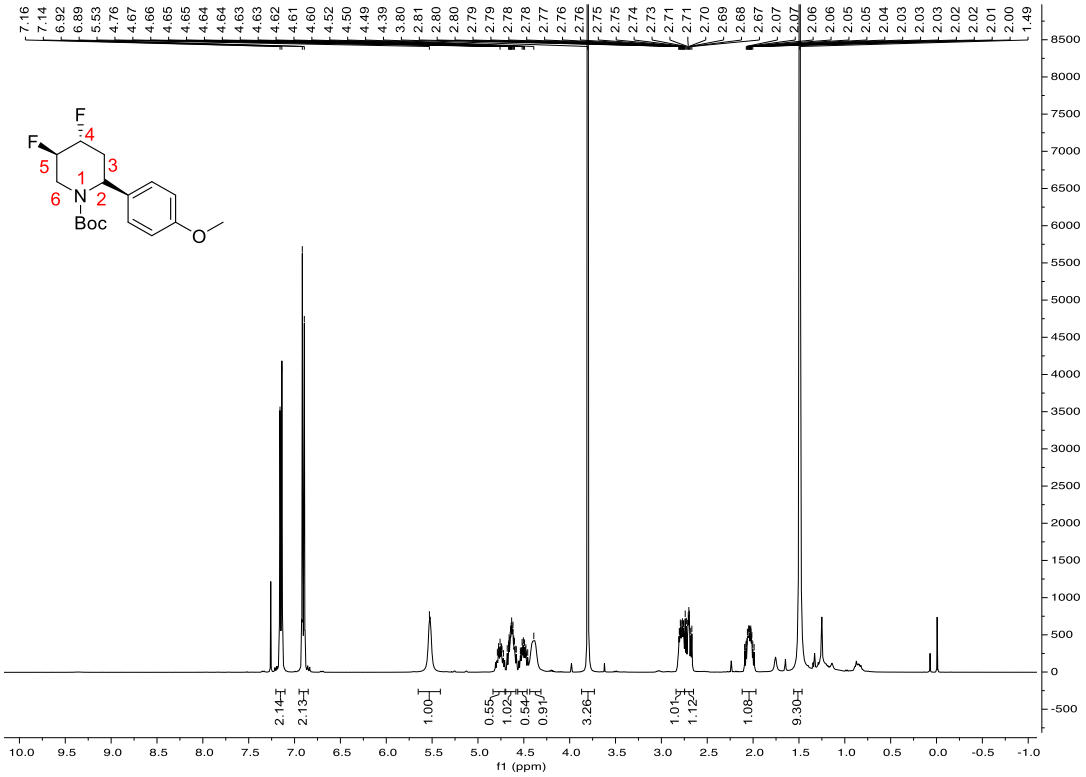
^{19}F NMR (376 MHz, $CDCl_3$) of **15a**



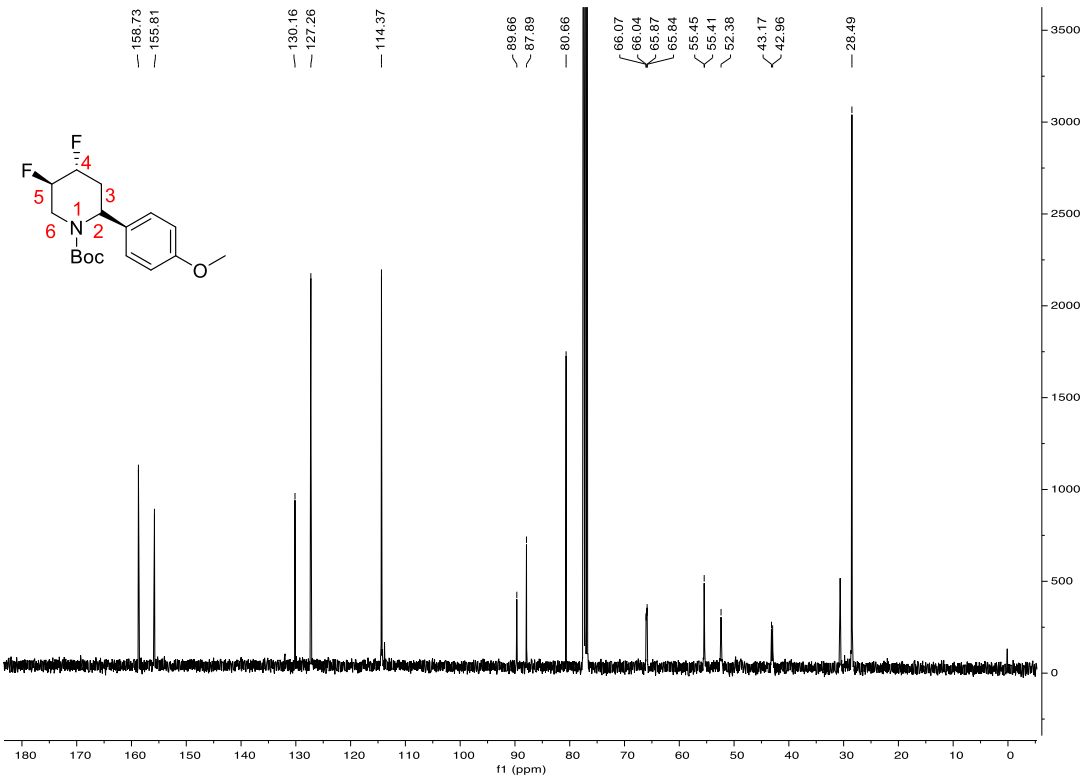
^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) of **15a**



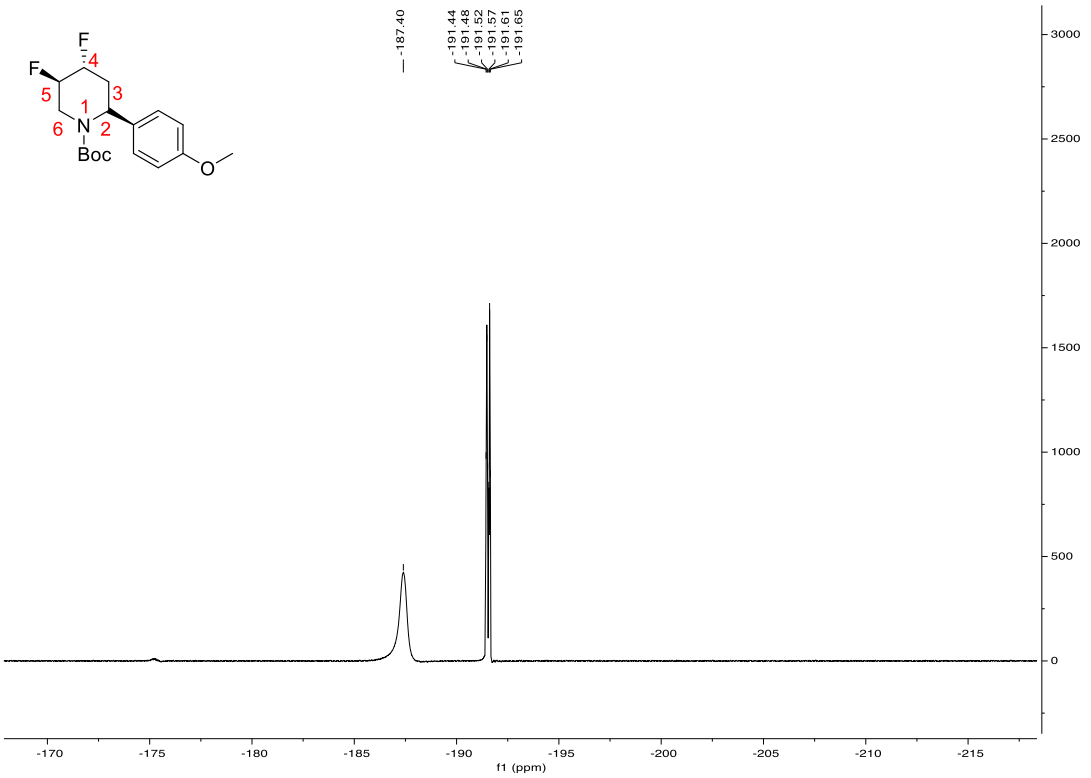
^{1}H NMR (400 MHz, $CDCl_3$) of **15b**



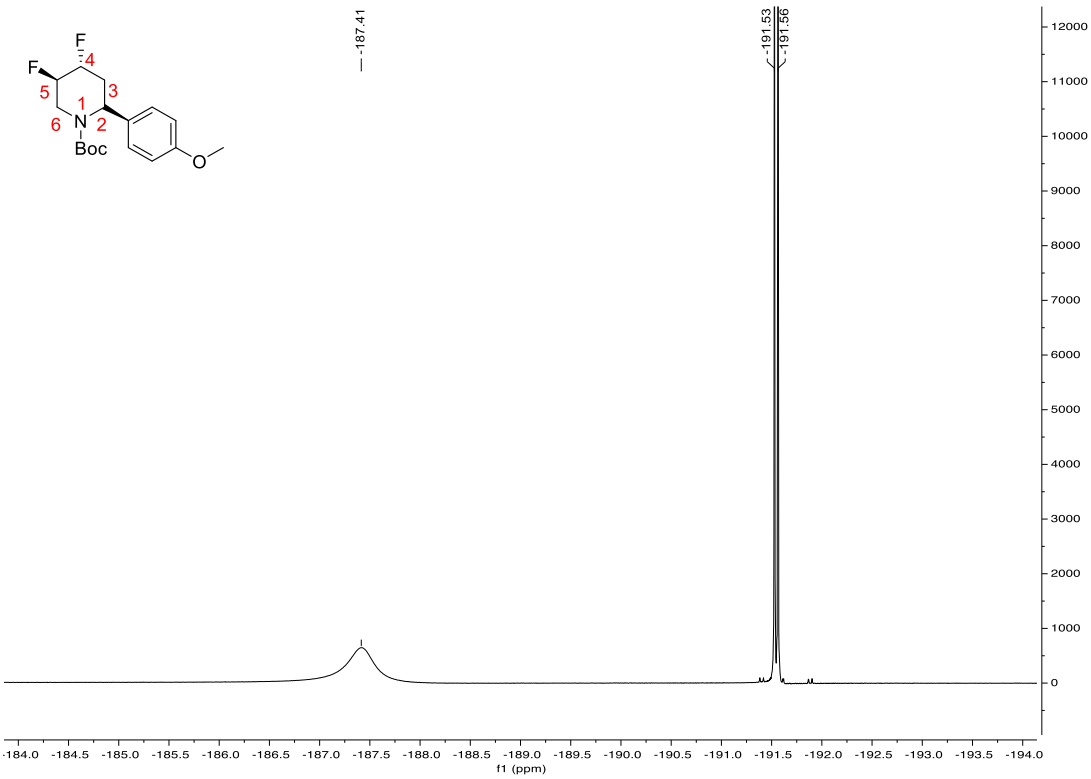
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) of **15b**



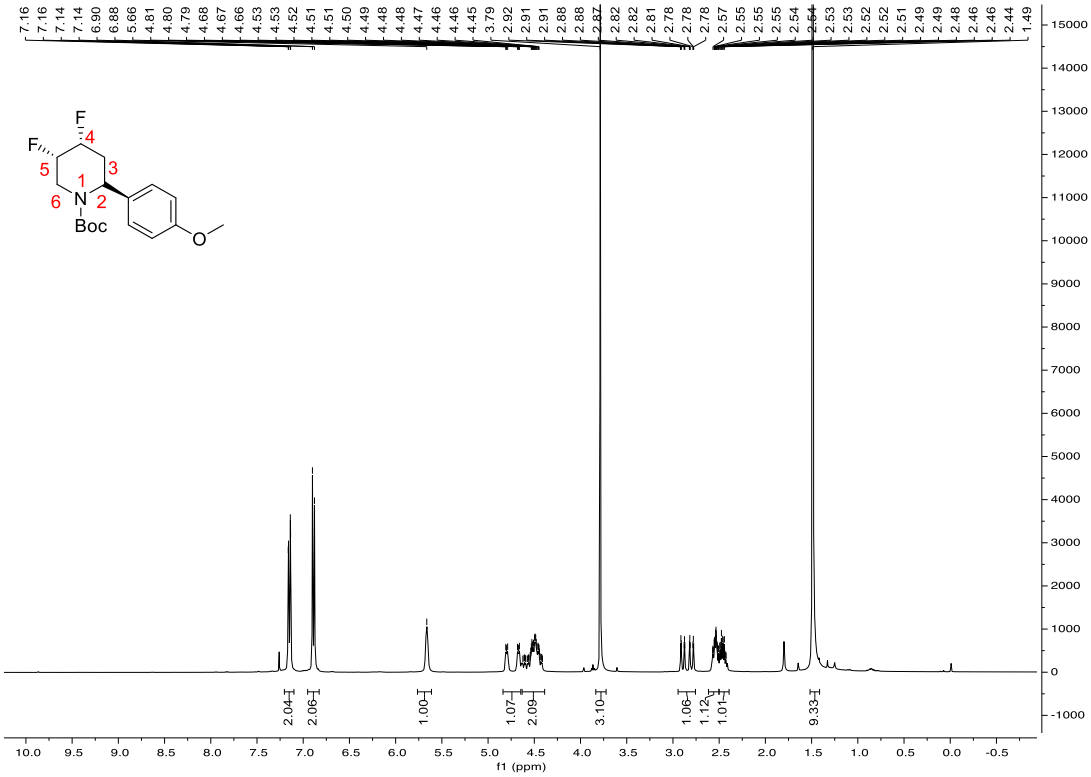
^{19}F NMR (376 MHz, $CDCl_3$) of **15b**



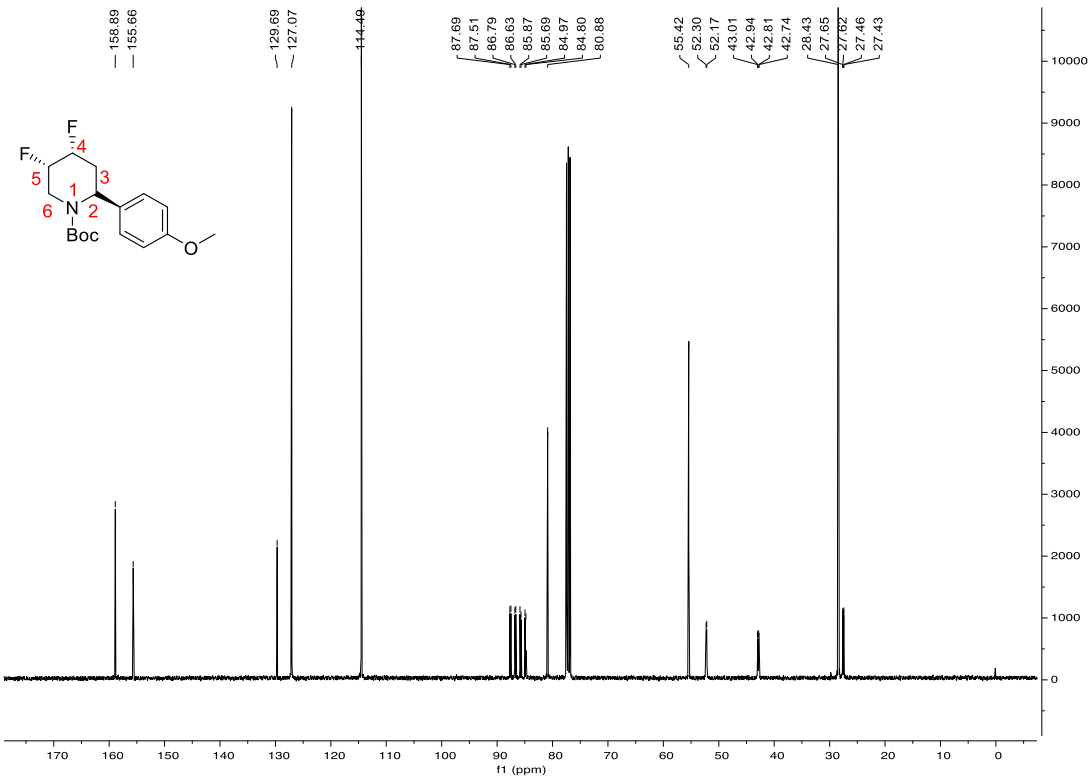
^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) of **15b**



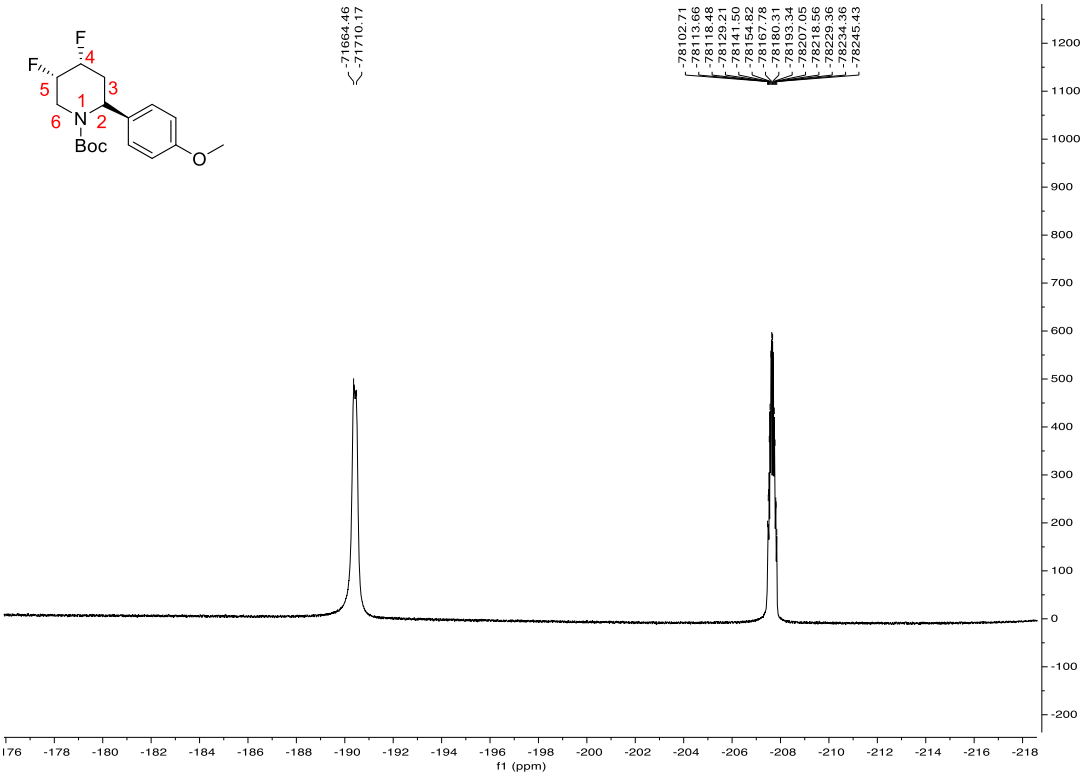
^{1}H NMR (400 MHz, $CDCl_3$) of **15d**



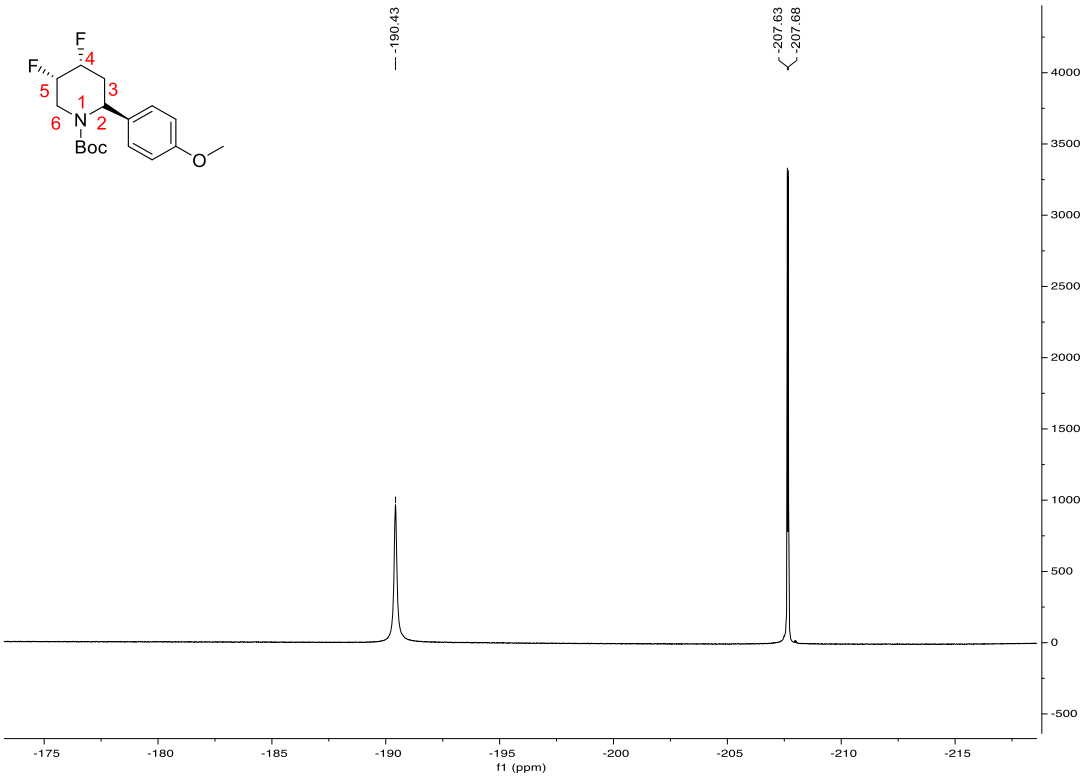
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) of **15d**



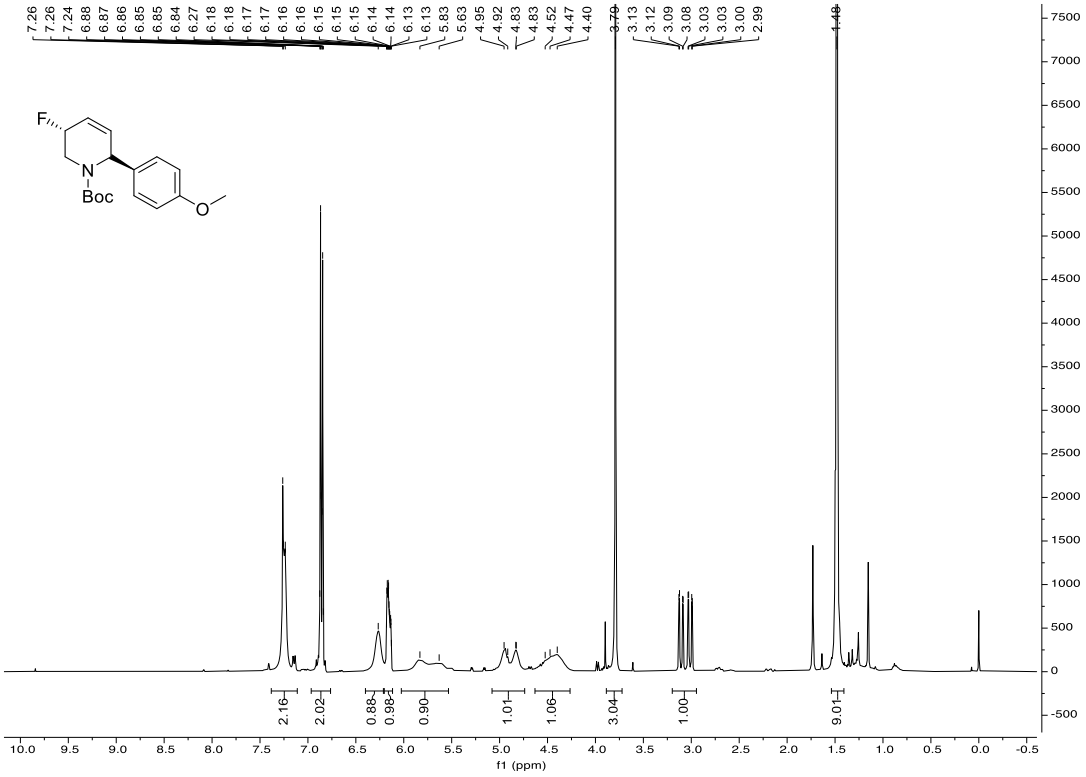
^{19}F NMR (376 MHz, $CDCl_3$) of **15d**



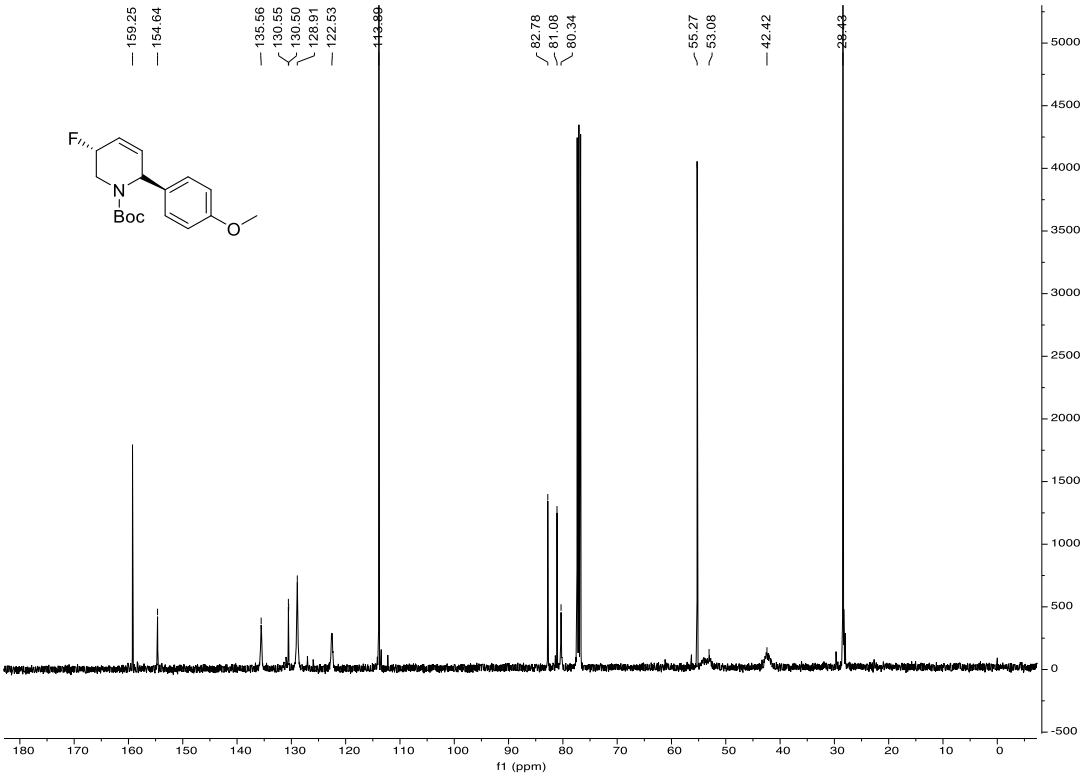
^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) of **15d**



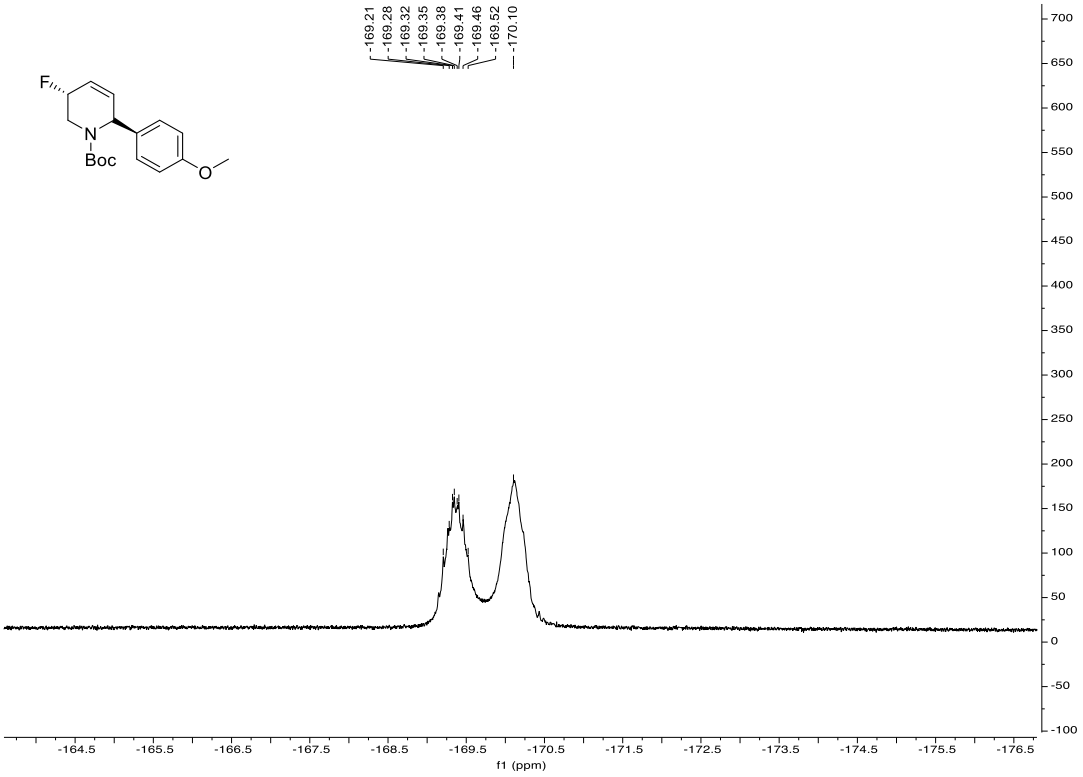
^{1}H NMR (400 MHz, $CDCl_3$) of **17**



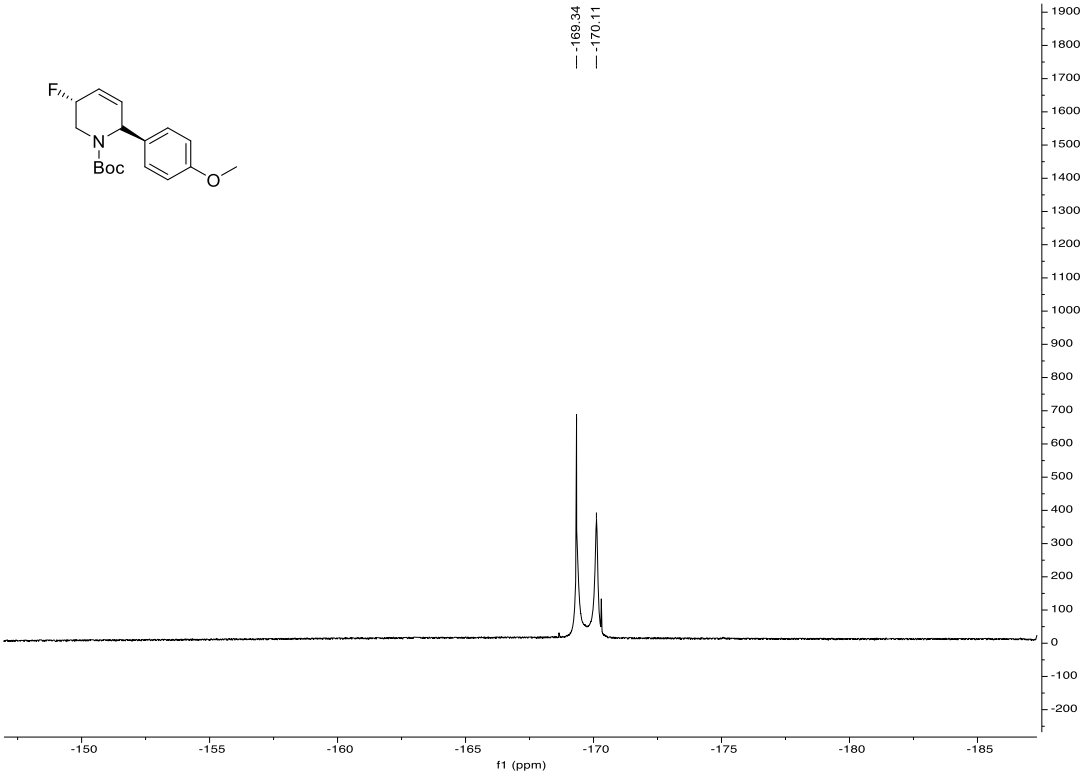
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) of **17**



^{19}F NMR (376 MHz, $CDCl_3$) of **17**

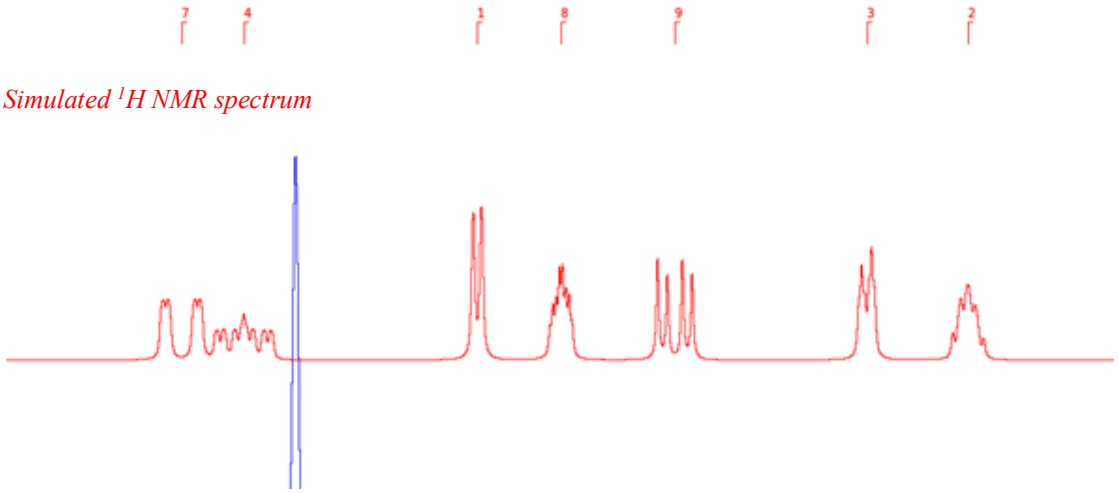


^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) of **17**



4. Conformational analysis details

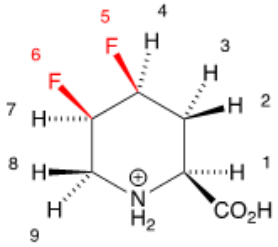
Accurate *J*-values of compound 11a



Simulated ^{1}H NMR spectrum

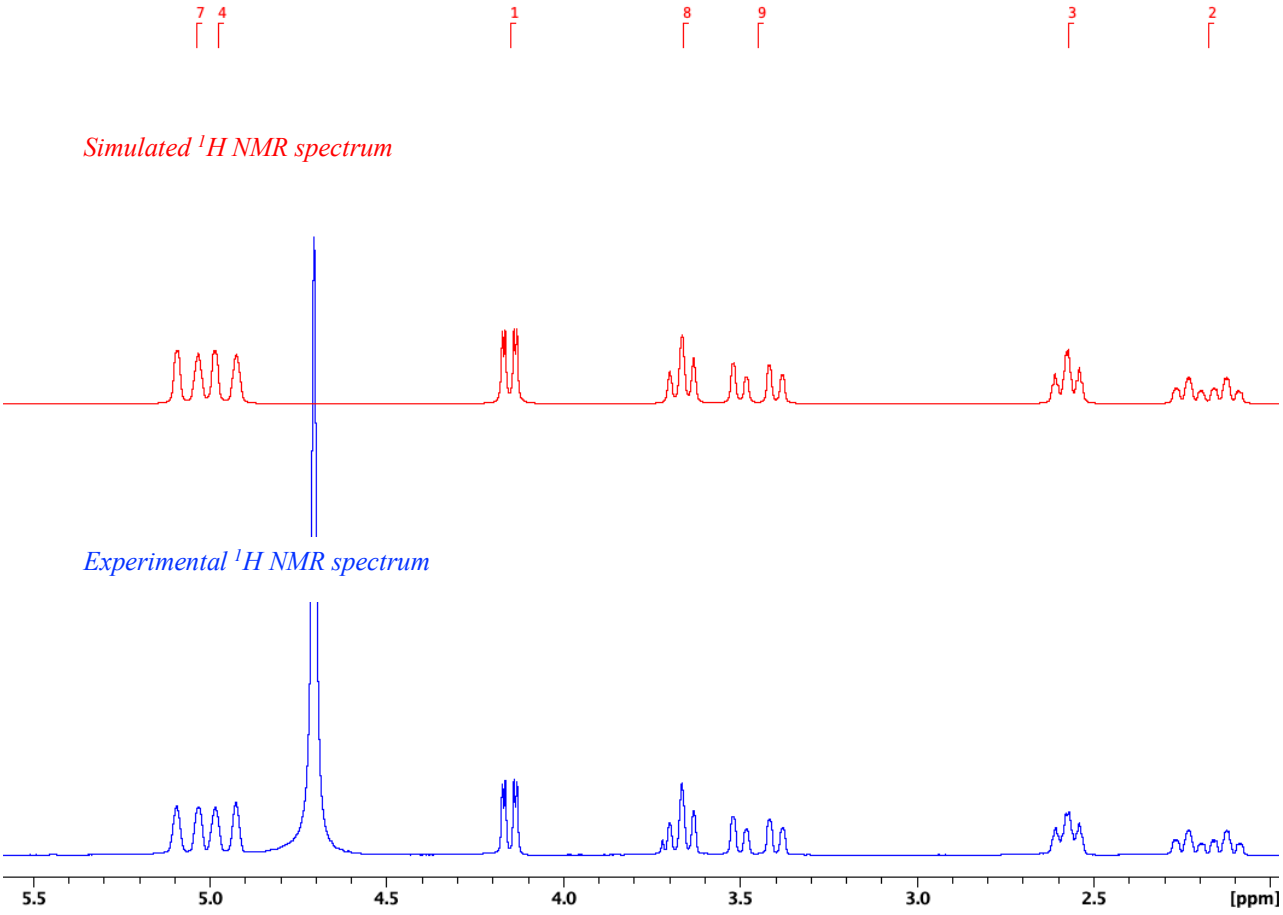
Experimental ^{1}H NMR spectrum

J-values (Hz):

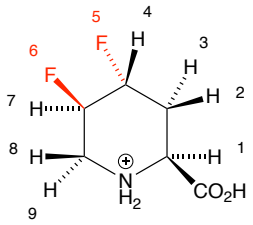


	2	3	4	5	6	7	8	9
1	1:2 12.5000 (–)	1:3 1.0000 (–)	1:4 0.0000 (–)	1:5 2.3000 (–)	1:6 0.0000 (–)	1:7 0.0000 (–)	1:8 0.0000 (–)	1:9 0.0000 (–)
2		2:3 15.0000 (–)	2:4 11.0000 (–)	2:5 8.0000 (–)	2:6 2.0000 (–)	2:7 0.0000 (–)	2:8 0.0000 (–)	2:9 0.0000 (–)
3			3:4 4.0000 (–)	3:5 5.0000 (–)	3:6 1.0000 (–)	3:7 0.0000 (–)	3:8 0.0000 (–)	3:9 0.0000 (–)
4				4:5 44.0000 (–)	4:6 27.0000 (–)	4:7 2.0000 (–)	4:8 0.0000 (–)	4:9 0.0000 (–)
5					5:6 0.0000 (–)	5:7 9.0000 (–)	5:8 5.0000 (–)	5:9 0.0000 (–)
6						6:7 47.9600 (–)	6:8 10.0000 (–)	6:9 37.3000 (–)
7							7:8 4.0000 (–)	7:9 1.0000 (–)
8								8:9 14.6000 (–)

Accurate *J*-values of compound 11b

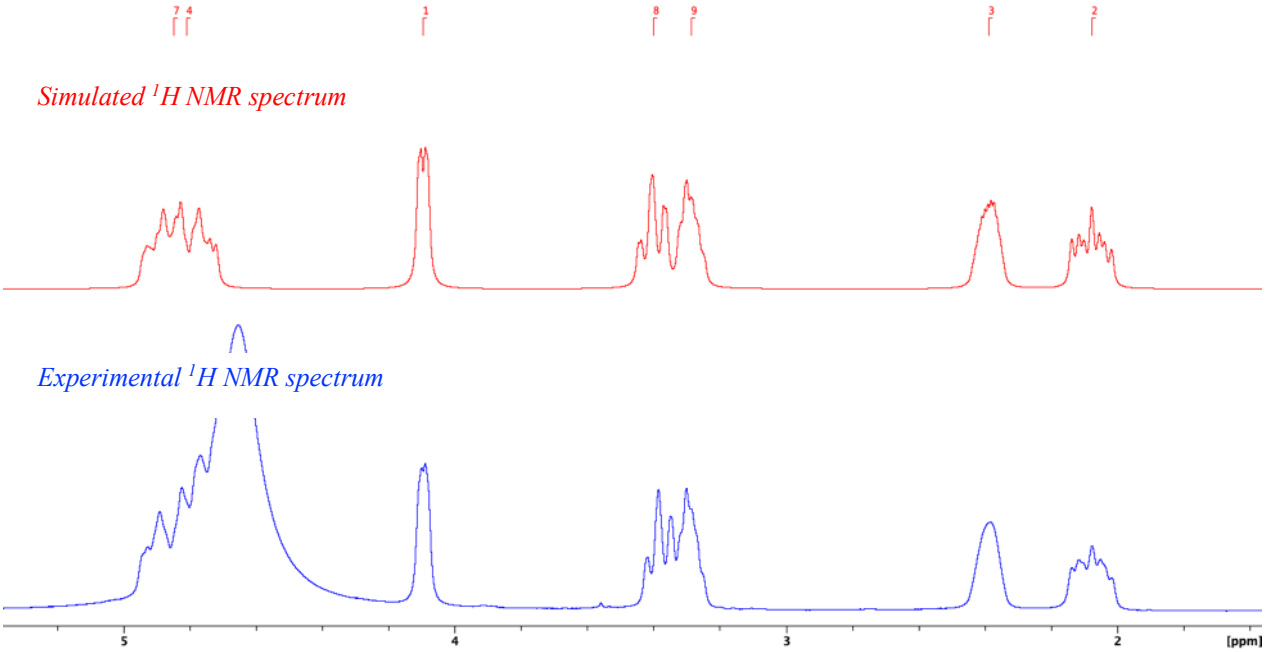


J-values (Hz):

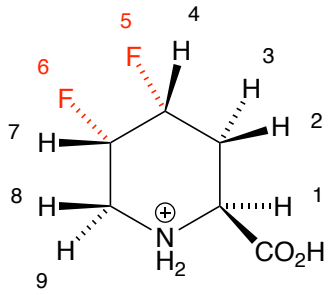


	2	3	4	5	6	7	8	9
1	1:2 13.3000 (–)	1:3 3.2600 (–)	1:4 0.0000 (–)	1:5 0.0000 (–)	1:6 0.0000 (–)	1:7 0.0000 (–)	1:8 0.0000 (–)	1:9 0.0000 (–)
2		2:3 15.0000 (–)	2:4 2.0000 (–)	2:5 43.0000 (–)	2:6 4.0000 (–)	2:7 0.0000 (–)	2:8 0.0000 (–)	2:9 0.0000 (–)
3			3:4 3.3000 (–)	3:5 12.5000 (–)	3:6 1.0000 (–)	3:7 0.0000 (–)	3:8 0.0000 (–)	3:9 0.0000 (–)
4				4:5 43.5000 (–)	4:6 4.0000 (–)	4:7 1.5000 (–)	4:8 0.0000 (–)	4:9 0.0000 (–)
5					5:6 14.9000 (–)	5:7 3.8000 (–)	5:8 2.3000 (–)	5:9 2.8000 (–)
6						6:7 43.0000 (–)	6:8 12.0000 (–)	6:9 41.0000 (–)
7							7:8 1.5000 (–)	7:9 1.3000 (–)
8								8:9 14.8000 (–)

Accurate *J*-values of compound 11d



J-values (Hz):



	2	3	4	5	6	7	8	9
1	1:2 8.5000 (–)	1:3 3.5000 (–)	1:4 0.0000 (–)	1:5 1.0000 (–)	1:6 0.0000 (–)	1:7 0.0000 (–)	1:8 0.0000 (–)	1:9 0.0000 (–)
2		2:3 15.0000 (–)	2:4 2.0000 (–)	2:5 25.0000 (–)	2:6 0.9000 (–)	2:7 0.0000 (–)	2:8 0.0000 (–)	2:9 0.0000 (–)
3			3:4 7.4000 (–)	3:5 7.4000 (–)	3:6 3.7000 (–)	3:7 0.0000 (–)	3:8 0.0000 (–)	3:9 0.0000 (–)
4				4:5 43.0000 (–)	4:6 21.0000 (–)	4:7 2.0000 (–)	4:8 0.0000 (–)	4:9 0.0000 (–)
5					5:6 0.0000 (–)	5:7 23.0000 (–)	5:8 1.0000 (–)	5:9 3.0000 (–)
6						6:7 42.0000 (–)	6:8 16.5000 (–)	6:9 7.5000 (–)
7							7:8 4.0000 (–)	7:9 7.5000 (–)
8								8:9 14.0000 (–)