Access to 3D Alicyclic Amine-Containing Fragments through Transannular C–H Arylation

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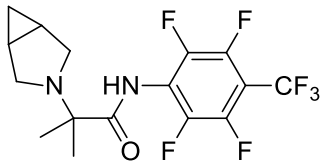
I. Materials and Methods

HPLC grade water, ethyl acetate (EtOAc), heptanes (Hep), methanol (MeOH), dichloromethane (DCM), and acetonitrile (MeCN) for column chromatography were purchased from Aldrich. Deuterated solvents for NMR spectroscopy were purchased from Sigma Aldrich. Reagents were purchased from commercial sources (Sigma Aldrich, Alfa Aeser, Ark Pharm, and ACROS) and used without further purification, unless otherwise noted. Microwave reactions were carried out with Biotage® Initiator+. Thin layer chromatography (TLC) was performed on Merck TLC plates pre-coated with silica gel 60 F_{254}. NMR spectra were recorded on Bruker Avance 500 NMR Spectrometer (500 MHz for ^{1}H; 126 MHz for ^{13}C) and a Varian 400-MR NMR Spectrometer (400 MHz for ^{1}H; 101 MHz for ^{13}C; 376 MHz for ^{19}F) with the residual solvent peak ($CDCl_3$; ^{1}H: δ = 7.26 ppm, ^{13}C: δ = 77.16 ppm), (CDCN; ^{1}H: δ = 1.94 ppm, ^{13}C: δ = 1.32 ppm), and (DMSO-d_6; ^{1}H: δ = 2.50 ppm, ^{13}C: δ = 39.52 ppm) as the internal reference unless otherwise noted. Chemical shifts are reported in parts per million (ppm) (δ) relative to tetramethylsilane. Multiplicities are reported as follows: br (broad signal), s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sex (sextet), m (multiplet), dd (doublet of doublets), ddd (doublet of doublet of doublets), qd (quartet of doublets). Coupling constants (*J*) are reported in Hz. Liquid chromatography mass spectra were recorded on a high performance liquid chromatography with mass spectrometer (LC: Agilent 1200 Series, MS: Thermo Electron Corporation Finnigan Surveyor MSQ Plus). Stock solutions were made using volumetric glassware. Liquid reagents were dispensed by difference from syringes. All reagents were weighed out under ambient conditions.

II. Synthesis of Amine Substrate with Directing Group

Compound (S-1):



Compound **S-1** was synthesized based on a modified literature procedure[1] with the addition of 0.5 equiv NaI. ^{1}H and ^{19}F NMR of the isolated product was consistent with literature values.[1]

III. General Procedures

A. General Procedure for Small Scale Microwave Reactions:

To a medium microwave tube (Biotage®, 2–5 mL) equipped with a stir bar was added $Pd(OAc)_2$ (11.7 mg, 0.052 mmol, 10 mol %), **S-1** (200 mg, 0.52 mmol, 1 equiv), cesium pivalate (365 mg, 1.56 mmol, 3 equiv), aryl iodide (2–3 equiv) and anhydrous *tert*-amyl alcohol (4.8 mL). The cap was crimped and the vessel was flushed with nitrogen. The microwave tube was heated with following parameters: 1 min pre-stirring, followed by a ramp (normal) to 180 °C and held at temperature for 40 min. Hydrazine (250 µL of 35% aqueous) was added to the reaction and allowed to stir at 60 °C for 1 hr. The *tert*-amyl alcohol was removed and the remaining residue was dissolved with EtOAc, filtered through a plug of celite, and concentrated *en vacuo*. The crude reaction was purified via flash column chromatography with EtOAc/Heptanes.

B. General Procedure for Large Scale Microwave Reactions:

To a large microwave tube (Biotage®, 10–20 mL) equipped with a stir bar was added $Pd(OAc)_2$ (23.4 mg, 0.10 mmol, 10 mol %), **S-1** (400 mg, 1.04 mmol, 1 equiv), cesium pivalate (731 mg, 3.12 mmol, 3 equiv), aryl iodide (2–3 equiv) and anhydrous *tert*-amyl alcohol (9.6 mL). The cap was crimped and the vessel was flushed with nitrogen. The microwave tube was heated with following parameters: 1 min pre-stirring, followed by a ramp (normal) to 180 °C and held at temperature for 40 to 50 min. Hydrazine (500 µL of 35% aqueous) was added to the reaction and allowed to stir at 60 °C for 1 hr or at room temperature overnight. The *tert*-amyl alcohol was removed *en vacuo* and the remaining residue dissolved with EtOAc, filtered through a plug of celite, and concentrated *en vacuo*. The crude reaction was purified via flash column chromatography with EtOAc/Heptanes.

C. General Procedure for Removal of Directing Group via SmI_2:

To a round bottom flask under a flow of nitrogen equipped with a stir bar was added the arylated product (1 equiv), 0.1 M SmI_2 (12 equiv), anhydrous triethylamine (80 equiv), anhydrous methanol (40 equiv), and tris(*N,N*-tetramethylene)phosphoricacid triamide (5.5 equiv). The reaction was allowed to stir at room temperature for 3 h. The reaction vessel was then exposed to atmosphere and formation of a white precipitate is observed within 30 minutes. The reaction was quenched with 1 N HCl. To the mixture was added ethyl acetate and the product was extracted into the aqueous acidic layer. The organic layer was set aside and the aqueous layer was basified with solid NaOH until pH 11–12. The aqueous layer was extracted with ethyl acetate (3 x 100 mL) and dried over sodium sulfate. After volatiles were removed a viscous yellow oil remained that was purified by reverse-phase HPLC [Waters XBridge™ C-18 column, 5 µm, 30×100 mm, flow rate 40 mL/minute, 5-100% gradient of acetonitrile in buffer (0.025 M aqueous ammonium bicarbonate, adjusted to pH 10 with ammonium hydroxide or 0.1% TFA)].

D. General Procedure for Removal of Directing Group via SmI_2 and Boc Protection:

To a round bottom flask under a flow of nitrogen equipped with a stir bar was added the arylated product (1 equiv), 0.1 M SmI_2 (12 equiv), anhydrous triethylamine (80 equiv), anhydrous methanol (40 equiv), and tris(*N,N*-tetramethylene)phosphoricacid triamide (5.5 equiv) and allowed to stir at room temperature for 3 h. The reaction vessel was then exposed to atmosphere and formation of a white precipitate is observed within 30 minutes. To the reaction at 0 ºC was added additional trimethylamine (140 equiv) and Boc_2O (80 equiv) and allowed to stir overnight. To the reaction solution was added 1 M citric acid until pH 3–4. The reaction is extracted with DCM (3 x 50 mL).

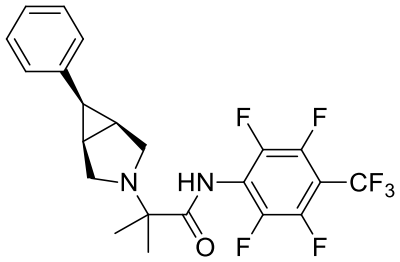
The organic layers were combined, washed with brine and dried over sodium sulfate. The volatiles were removed and the product was purified via flash column chromatography with EtOAc/Heptanes. To the isolated Boc protected amine was added HCl (dioxane, 4 M, 20 equiv) and allowed to stir overnight at room temperature. The product was purified by reverse-phase HPLC as described in General Procedure C.

E. General Procedure for Removal of Directing Group via Acetylation:

To a medium microwave tube (Biotage®, 2–5 mL vial) equipped with a stir bar was added the arylated product (0.217 mmol, 1 equiv) and acetyl chloride (neat, 3.0 mL). The reaction was heated to 150 ºC for 3 hours. The acetyl chloride was removed under reduced pressure and the product diluted in DCM (10 mL). 1 M NaOH (10 mL) was added. The product was extracted with DCM (2 x 10 mL). The volatiles were removed *en vacuo* and the product was purified by reverse-phase HPLC as described in General Procedure C.

IV. Synthesis and Isolation of Products from C–H Functionalization

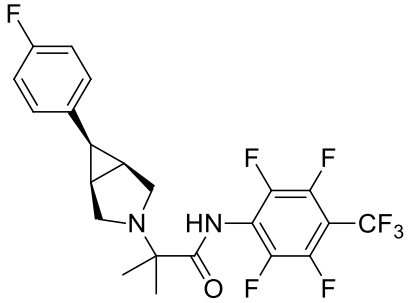
Compound (1):



General procedure **A** was followed using iodobenzene (3 equiv) for 40 min. General procedure **B** was followed using iodobenzene (3 equiv) for 30 min. ^{1}H and ^{19}F NMR of the isolated product was consistent with literature values.[1]

Isolated Yield (small scale 0.13 mmol): 68% (40.7 mg)
Isolated Yield (large scale 1.04 mmol): 83% (average of two runs 412.0 mg, 377.0 mg)

Compound (2):



General procedures **A** and **B** were followed using 4-fluoroiodobenzene (3 equiv) for 40 min and isolated as an off-white solid.

Isolated Yield (small scale 0.52 mmol, general procedure **A**): 50% (125.0 mg)
Isolated Yield (large scale 1.04 mmol, general procedure **B**): 42% (210.2 mg)

R_f: 0.38 (20% EtOAc/80% Hex)

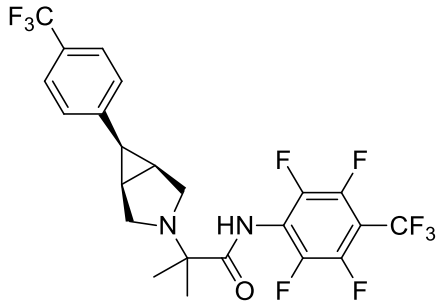
LC-MS: APCI$^+$ (m/z): $[M+H]^+$ calcd for $C_{22}H_{19}F_8N_2O$: 479.129; found: 479.119.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.27 (m, 2H), 6.78 (t, J = 8.5 Hz, 2H), 6.48 (br s, 1H), 2.94 (d, J = 9.0 Hz, 2H), 2.89 (ddd, J = 9.0, 2.0 Hz, 1.0 Hz, 2H), 2.04 (t, J = 8.0 Hz, 1H), 1.87 (m, 2H), 1.14 (s, 6 H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 175.7, 161.1 (d, $J_{C–F}$ = 246 Hz), 133.7, 129.6 (d, $J_{C–F}$ = 7.6 Hz) Hz), 61.1, 45.1, 27.1, 22.2, 20.9. 20.1. The carbon resonances of the directing group (perfluoroarene, C_7F_7) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

^{19}F NMR ($CDCl_3$, 376 MHz): δ –56.1 (t, *J* = 21.8 Hz, 3F), –116.4 (m, 1F), –141.4 (m, 2F), –143.1 (m, 2F).

Compound (3):



General procedure **A** was followed using 4-iodobenzotrifluoride (3 equiv) for 40 min. General procedure **B** was followed using 4-iodobenzotrifluoride (3 equiv) for 30 min and isolated as a light yellow solid.

Isolated Yield (small scale 0.52 mmol, general procedure **A**): 64% (175.3 mg)
Isolated Yield (large scale 1.04 mmol, general procedure **B**): 59% (254 mg)

R_f: 0.26 (20% EtOAc/80% Hex)

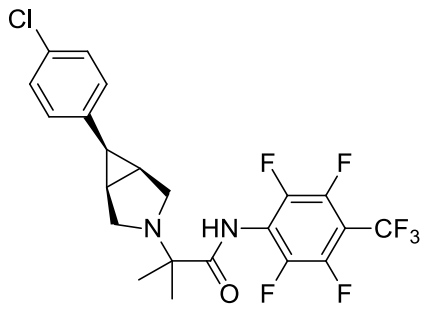
LC-MS: APCI$^+$ (m/z): $[M+H]^+$ calcd for $C_{23}H_{19}F_{10}N_2O$: 529.134; found: 529.071

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.46 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 6.31 (br s, 1H), 3.98 (d, *J* = 9.0 Hz, 2H), 2.90 (d, *J* = 9.0 Hz, 2H), 2.11 (t, *J* = 8.0 Hz, 1H), 1.94 (d, *J* = 8.0 Hz, 2H), 1.14 (s, 6 H).

^{13}C NMR ($CDCl_3$, 126 MHz): 175.7, 142.4, 128.6, 128.3 (q, $J_{C–F}$ = 32.8 Hz), 125.1 (q, $J_{C–F}$ = 3.0 Hz), 123.8 (q, J_{C-F} = 272 Hz), 61.2, 46.1, 22.8, 21.0, 20.2. The carbon resonances of the directing group (perfluoroarene, C_7F_7) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

^{19}F NMR ($CDCl_3$, 376 MHz): δ –56.3 (t, *J* = 22.2 Hz, 3F), –63.3 (s, 3F), –141.3 (m, 2F), –143.5 (m, 2F).

Compound (4):



General procedure **B** was followed using 1-chloro-4-iodobenzene (3 equiv) for 40 min and isolated as a light yellow solid.

Isolated Yield (large scale 1.04 mmol): 34% (183.1 mg)

R_f: 0.44 (20% EtOAc/80% Hex)

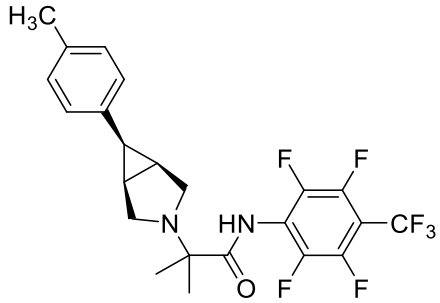
LC-MS: APCI$^+$ (m/z): $[M+H]^+$ calcd for $C_{22}H_{19}ClF_7N_2O$: 495.107; found: 495.167.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.41 (br s, 1H), 2.90 (multiple peaks, 4H), 2.03 (t, *J* = 8.0 Hz, 1H), 1.87 (m, 2H), 1.15 (s, 6 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 175.9, 136.5, 132.0, 129.5, 128.3, 61.1, 45.1, 24.8, 22.3, 21.0. The carbon resonances of the directing group (perfluoroarene, C_7F_7) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

^{19}F NMR ($CDCl_3$, 376 MHz): δ –56.2 (t, *J* = 21.8 Hz, 3F), –141.2 (m, 2F), –143.1 (m, 2F).

Compound (5):



General procedure **A** was followed using 4-iodotoluene (3 equiv) for 40 min. General procedure **B** was followed using 4-iodotoluene (3 equiv) for 30 min and isolated as a light yellow solid.

Isolated Yield (small scale 0.52 mmol, general procedure **A**): 53% (130.0 mg)
Isolated Yield (large scale 1.04 mmol, general procedure **B**): 79% (388.0 mg)

R_f: 0.50 (20% EtOAc/80% Hex)

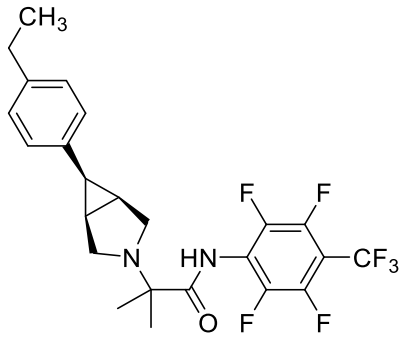
LC-MS: APCI$^+$ (m/z): $[M+H]^+$ calcd for $C_{23}H_{22}F_7N_2O$: 475.162; found: 475.131.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.18 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 6.44 (br s, 1H), 2.97 (d, *J* = 9.2 Hz, 2H), 2.86 (dd, *J* = 9.2, 2.0, 1.2 Hz, 2H), 2.02 (t, *J* = 8.0 Hz, 1H), 1.99 (s, 3H), 1.83 (m, 2H), 1.13 (s, 6 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 176.2, 135.5, 134.9, 128.8, 128.0, 61.0, 45.1, 22.4, 20.9, 20.5, 20.0. The carbon resonances of the directing group (perfluoroarene, C_7F_7) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

^{19}F NMR ($CDCl_3$, 376 MHz): δ –56.2 (t, *J* = 21.8 Hz, 3F), –141.8 (m, 2F), –142.7 (m, 2F).

Compound (6):



General procedure **B** was followed using 4-ethyliodobenzene (3 equiv) for 30 min and isolated as a light brown oil.

Isolated Yield (large scale 1.04 mmol): 71% (360.0 mg)

R_f: 0.52 (20% EtOAc/80% Hex)

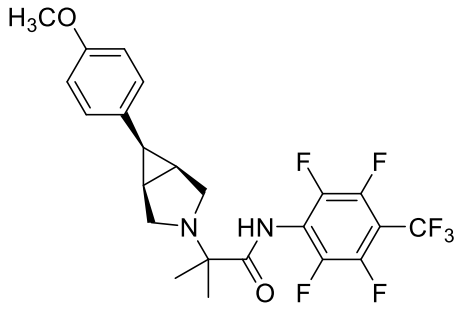
LC-MS: APCI$^+$ (m/z): $[M+H]^+$ calcd for $C_{24}H_{24}F_7N_2O_2$: 489.178 ; found: 489.113.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22 (d, *J* = 8.0 Hz, 2H), 6.91 (d, *J* = 8.0 Hz, 2H), 6.51 (br s, 1H), 2.98 (d, *J* = 9.2 Hz, 2H), 2.85 (m, 2H), 2.27 (q, *J* = 7.6 Hz, 2H), 2.02 (t, *J* = 8.0 Hz, 1H), 1.83 (m, 2H), 1.12 (s, 6 H), 0.95 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 176.3, 141.9, 135.3, 128.2, 127.6, 61.0, 45.2, 28.0, 22.5, 20.9, 20.0, 14.9. The carbon resonances of the directing group (perfluoroarene, C_7F_7) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

^{19}F NMR ($CDCl_3$, 376 MHz): δ –56.2 (t, *J* = 21.8 Hz, 3F), –141.9 (m, 2F), –142.6 (m, 2F).

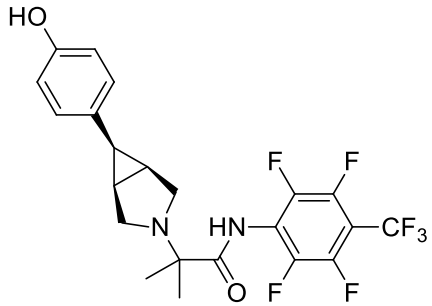
Compound (7):



General procedure **A** was followed using 4-iodoanisole (3 equiv) for 40 min. General procedure **A** was followed using 4-iodoanisole (3 equiv) for 30 min. ^{1}H and ^{19}F NMR of the isolated product was consistent with literature values.[1]

Isolated Yield (small scale 0.52 mmol, general procedure **A**): 60% (32.7 mg)
Isolated Yield (large scale 1.04 mmol, general procedure **B**): 72% (365.4 mg)

Compound (8):



General procedure **A** was followed using 4-iodophenol (3 equiv) for 40 min and isolated as an off-white solid.

Isolated Yield (small scale 0.52 mmol): 12% (30.5 mg)

R_f: 0.66 (50% EtOAc/50% Hex)

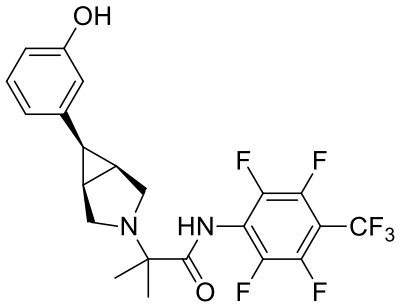
LC-MS: APCI$^+$ (m/z): $[M+H]^+$ calcd for $C_{22}H_{20}F_7N_2O_2$: 477.141; found: 477.141.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.97 (s, 1H), 7.06 (d, J = 8.4 Hz, 2H), 6.56 (br s, 1H), 6.44 (d, J = 8.4 Hz, 2H), 2.84 (m, 4H), 1.92 (t, J = 7.6 Hz, 1H), 1.79 (d, J = 7.6 Hz, 2H), 1.04 (s, 6 H).

^{13}C NMR (DMSO-d_6, 101 MHz): δ 175.4, 155.5, 128.8, 127.5, 114.7, 60.3, 44.6, 21.5, 20.8, 19.6. The carbon resonances of the directing group (perfluoroarene, C_7F_7) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

^{19}F NMR ($CDCl_3$, 376 MHz): δ –55.3 (t, J = 21.4 Hz, 3F), –142.7 (m, 2F), –143.6 (m, 2F).

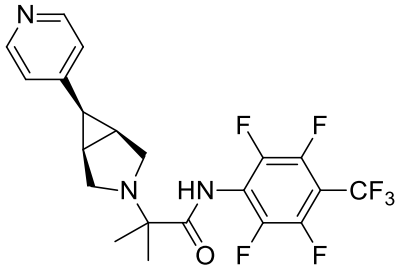
Compound (9):



General procedure **A** was followed using using 3-iodophenol (3 equiv) for 40 min. General procedure **B** was followed using 3-iodophenol (2 equiv) for 30 min. ^{1}H and ^{19}F NMR of the isolated product was consistent with literature values.[1]

Isolated Yield (small scale 0.52 mmol, general procedure **A**): 62% (153.1 mg)
Isolated Yield (large scale 1.04 mmol, general procedure **B**): 56% (278.0 mg)

Compound (10):



General procedure **A** was followed using 4-iodopyridine (3 equiv) for 40 min. General procedure **B** was followed using 4-iodopyridine for 1 h 40 min (1 equiv Het-I at 0 min, then 1 equiv Het-I at 50 min, large scale) and isolated as a white solid.

Isolated Yield (small scale 0.52 mmol, general procedure **A**): 18% (43.5 mg)
Isolated Yield (large scale 1.04 mmol, general procedure **B**): 16% (76.9 mg), recovered 37% **S-1** (144.7 mg)

R_f: 0.40 (50% EtOAc/50% Hex)

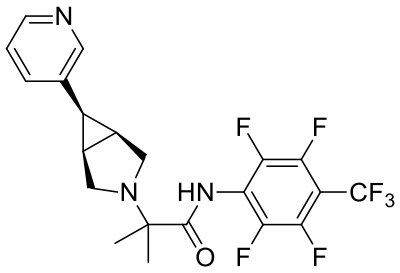
LC-MS: APCI$^+$ (m/z): $[M+H]^+$ calcd for $C_{21}H_{19}F_7N_3O$: 462.142; found: 462.123.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.36 (d, *J* = 5.2 Hz, 2H), 7.28 (d, *J* = 5.2 Hz, 2H), 6.34 (br s, 1H), 2.98 (d, *J* = 9.2 Hz, 2H), 2.88 (d, *J* = 9.2 Hz, 2H), 2.07 (t, *J* = 4.4 Hz, 1H), 1.96 (m, 2H), 1.14 (s, 6 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 175.3, 149.6, 147.2, 123.6, 61.2, 45.1, 22.2, 20.9, 20.0. The carbon resonances of the directing group (perfluoroarene, C_7F_7) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

^{19}F NMR ($CDCl_3$, 376 MHz): δ –56.1 (t, *J* = 21.8 Hz, 3F), –141.0 (m, 2F), –142.9 (m, 2F).

Compound (11):



General procedure **A** followed 3-iodopyridine (3 equiv). General procedure **B** was followed using 3-iodopyridine (2 equiv) for 50 min and isolated as an off-white solid.

Isolated Yield (small scale 0.52 mmol, general procedure **A**): 58% (139.0 mg)
Isolated Yield (large scale 1.04 mmol, general procedure **B**): 49% (234.8 mg)

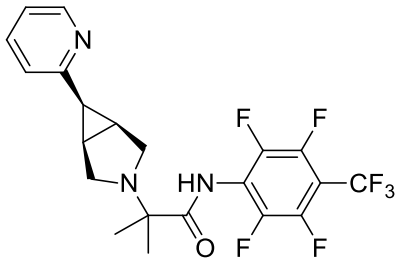
R_f: 0.39 (50% EtOAc/50% Hex)
LC-MS: APCI$^+$ (m/z): $[M+H]^+$ calcd for $C_{21}H_{19}F_7N_3O$: 462.142; found: 462.130.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.58 (m, 1H), 8.28 (d, *J* = 4.4 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.14 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.31 (br s, 1H), 2.95 (d, *J* = 9.2 Hz, 2H), 2.90 (m, 2H), 2.06 (t, *J* = 8.0 Hz, 1H), 1.95 (m, 2H), 1.12 (s, 6 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 175.1, 149.5, 147.5, 135.7, 133.7, 123.1, 61.2, 45.1, 20.8, 20.4, 19.9. The carbon resonances of the directing group (perfluoroarene, C_7F_7) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

^{19}F NMR ($CDCl_3$, 376 MHz): δ –56.1 (t, *J* = 21.8 Hz, 3F), –141.2 (m, 2F), –142.8 (m, 2F).

Compound (12):



General procedure **A** was followed using 2-iodopyridine (2 equiv) for 40 min. General procedure **B** was followed using 2-iodopyridine for 1 h 40 min (1 equiv Het-I at 0 min, then 1 equiv Het-I at 50 min, large scale) and isolated as an off-white solid.

Isolated Yield (small scale 0.52 mmol, general procedure **A**): 28% (66.6 mg)
Isolated Yield (large scale 1.04 mmol, general procedure **B**): 45% (217.4 mg)

R_f: 0.16 (50% EtOAc/50% Hex)

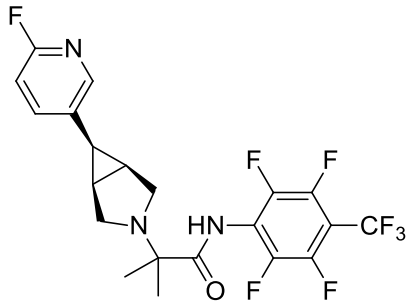
LC-MS: APCI$^+$ (m/z): $[M+H]^+$ calcd for $C_{21}H_{19}F_7N_3O$: 462.142; found: 462.124.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.36 (dd, *J* = 4.8, 0.8 Hz, 1H), 7.47 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.31 (dd, *J* = 7.6, 0.8 Hz, 1H), 6.98 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.76 (br s, 1H), 3.11 (d, *J* = 9.2 Hz, 2H), 2.87 (dd, *J* = 8.8, 1.6 Hz, 2H), 2.20 (t, *J* = 8.0 Hz, 1H), 1.98 (m, 2H), 1.12 (s, 6 H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 175.4, 158.6, 149.1, 135.9, 123.3, 121.2, 61.3, 45.3, 24.5, 20.8, 20.5. The carbon resonances of the directing group (perfluoroarene, C_7F_7) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

^{19}F NMR ($CDCl_3$, 376 MHz): δ –56.1 (t, *J* = 21.8 Hz, 3F), –141.1 (m, 2F), –142.3 (m, 2F).

Compound (13):



General procedure **A** followed 2-fluoro-5-iodopyridine (2 equiv). General procedure **B** was followed using 2-fluoro-5-iodopyridine (2 equiv) for 50 min and isolated as an off-white solid.

Isolated Yield (small scale 0.52 mmol, general procedure **A**): 49% (123.0 mg)
Isolated Yield (large scale 1.04 mmol, general procedure **B**): 42% (211.8 mg)

R_f: 0.51 (50% EtOAc/50% Hex)

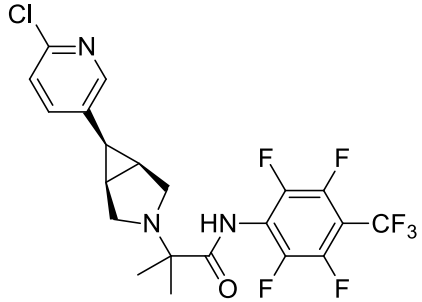
LC-MS: APCI$^+$ (m/z): $[M+H]^+$ calcd for $C_{21}H_{18}F_8N_3O$: 480.132; found: 480.069.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14 (m, 1H), 7.76 (td, *J* = 8.0, 2.4 Hz, 1H), 6.80 (dd, *J* = 8.4 Hz, 2.8 Hz, 1H), 6.49 (br s, 1H), 2.93 (s, 4H), 1.99 (multiple peaks, 3H), 1.15 (s, 6 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 174.9, 162.3 (d, $J_{C–F}$ = 240 Hz), 146.7 (d, $J_{C–F}$ = 13.9 Hz), 140.9 (d, $J_{C–F}$ = 7.4 Hz), 131.2 (d, $J_{C–F}$ = 4.6 Hz), 109.1 (d, $J_{C–F}$ = 37.3 Hz), 61.3, 45.2, 20.9, 20.2, 19.6. The carbon resonances of the directing group (perfluoroarene, C_7F_7) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

^{19}F NMR ($CDCl_3$, 376 MHz): δ –56.1 (t, *J* = 21.8 Hz, 3F), –70.6 (d, *J* = 7.5 Hz, 1F), –141.1 (m, 2F), –143.5 (m, 2F).

Compound (14):



General procedure **B** was followed using 2-chloro-5-iodopyridine (2 equiv) for 50 min and isolated as a yellow solid.

Isolated Yield (large scale 1.04 mmol): 40% (206.6 mg)

R_f: 0.46 (50% EtOAc/50% Hex)

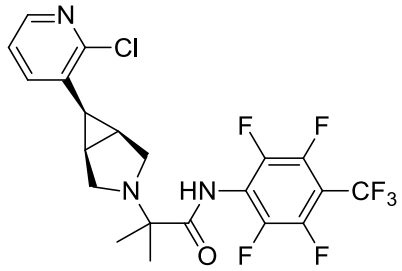
LC-MS: APCI$^+$ (m/z): $[M+H]^+$ calcd for $C_{21}H_{18}Cl_1F_7N_3O$: 496.103 ; found: 496.160.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.33 (m, 1H), 7.63 (ddd, *J* = 8.5 Hz, 2.5 Hz, 1.0 Hz, 1H), 7.17 (d, *J* = 8.5 Hz, 1H), 6.41 (br s, 1H), 2.93 (m, 4H), 1.97 (multiple peaks, 3H), 1.16 (s, 6 H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 175.1, 149.5, 149.2, 138.5, 132.5, 123.8, 61.3, 45.1, 20.9, 20.0, 19.7. The carbon resonances of the directing group (perfluoroarene, C_7F_7) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

^{19}F NMR ($CDCl_3$, 376 MHz): δ –56.2 (t, *J* = 21.8 Hz, 3F), –141.0 (m, 2F), –143.2 (m, 2F).

Compound (15):



General procedure **A** was followed using 2-chloro-3-iodopyridine (2 equiv) for 40 min. General procedure **B** was followed using 2-chloro-3-iodopyridine (2 equiv) for 50 min and isolated as a white solid.

Isolated Yield (small scale 0.52 mmol, general procedure **A**): 25% (63.6 mg)
Isolated Yield (large scale 1.04 mmol, general procedure **B**): 24% (124.0 mg)

R_f: 0.59 (50% EtOAc/50% Hex)

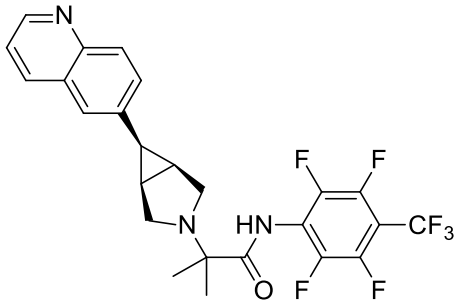
LC-MS: APCI$^+$ (m/z): $[M+H]^+$ calcd for $C_{21}H_{18}Cl_1F_7N_3O$: 496.103 ; found: 496.081.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.11 (dd, *J* = 4.5, 1.5 Hz, 1H), 7.76 (ddd, *J* = 7.5, 2.0, 1.0 Hz, 1H), 7.13 (dd, *J* = 7.5, 4.5 Hz, 1H), 6.46 (br s, 1H), 3.05 (d, *J* = 9.5 Hz, 2H), 2.88 (m, 2H), 2.06 (multiple peaks, 3H), 1.14 (s, 6 H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 175.0, 152.4, 147.6, 138.4, 133.4, 121.8, 61.3, 45.8, 21.6, 21.3, 20.7. The carbon resonances of the directing group (perfluoroarene, C_7F_7) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

^{19}F NMR ($CDCl_3$, 376 MHz): δ –56.1 (t, *J* = 21.8 Hz, 3F), –141.0 (m, 2F), –143.0 (m, 2F).

Compound (16):



General procedure **A** was followed using 6-iodoquinoline (2 equiv) for 40 min and isolated as an off-white solid.

Isolated Yield (small scale 0.52 mmol): 65% (174.0 mg)

R_f: 0.54 (50% EtOAc/50% Hex)

LC-MS: APCI$^+$ (m/z): $[M+H]^+$ calcd for $C_{25}H_{21}F_7N_3O$: 512.157 ; found: 512.098.

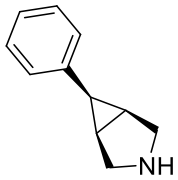
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.66 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.86 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.74 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.68 (m, 1H), 7.09 (dd, *J* = 8.0, 4.0 Hz, 1H), 5.98 (br s, 1H), 3.05 (d, *J* = 9.2 Hz, 2H), 2.93 (dd, *J* = 9.6, 1.2 Hz, 2H), 2.26 (t, *J* = 8.0 Hz, 1H), 1.99 (m, 2H), 1.12 (s, 6 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 175.7, 149.8, 146.7, 136.6, 134.7, 129.5, 127.7, 125.8, 120.8, 60.9, 45.2, 27.2, 22.7, 21.0, 20.3. The carbon resonances of the directing group (perfluoroarene, C_7F_7) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

^{19}F NMR ($CDCl_3$, 376 MHz): δ –56.3 (t, *J* = 21.8 Hz, 3F), –141.5 (m, 2F), –143.3 (m, 2F).

V. Amine Products After Removal of Directing Group

Compound (1-A):



General procedure **C** was followed using **1** (0.272 mmol, 125 mg) and isolated by reverse-phase HPLC as the TFA amine salt (off-white solid).

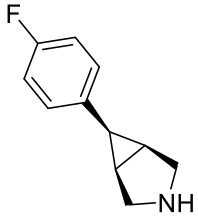
Isolated Yield: 34% yield (25.4 mg)

LC-MS: APCI$^+$ (m/z): $[M+H]^+$ calcd for $C_{11}H_{14}N$: 160.113; found: 160.069.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.48 (br s, 1H), 7.42 (t, *J* = 8.0 Hz, 2H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 4.73 (br s, 1H), 3.64 (d, *J* = 12.4 Hz, 2H), 3.32 (d, *J* = 12.4 Hz, 2H), 2.46 (t, *J* = 8.0 Hz, 1H), 2.22 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 132.0, 130.0, 129.3, 128.5, 45.3, 23.3, 21.4.

Compound (2-A):



General procedure **C** was followed using **2** (0.408 mmol, 195 mg) and isolated by reverse-phase HPLC as the TFA amine salt (off-white solid).

Isolated Yield: 49% yield (57.9 mg)

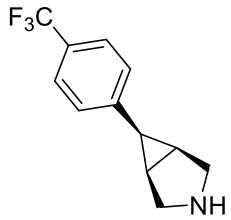
LC-MS: APCI$^+$ (m/z): $[M+H]^+$ calcd for $C_{11}H_{13}FN$: 178.103; found: 178.069.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.85 (br s, 1H), 7.19 (t, *J* = 8.4 Hz, 2H), 7.08 (t, *J* = 8.4 Hz, 2H), 5.94 (br s, 1H), 3.58 (d, *J* = 11.2 Hz, 2H), 3.30 (d, *J* = 11.2 Hz, 2H), 2.39 (t, *J* = 8.0 Hz, 1H), 2.22 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 162.6 (d, J_{C-F} = 249 Hz), 131.2 (d, J_{C-F} = 8.1 Hz), 127.2 (d, J_{C-F} = 3.0 Hz), 116.9 (d, J_{C-F} = 22.2 Hz), 45.0, 23.3. 22.0.

^{19}F NMR ($CDCl_3$, 376 MHz): –75.8 (s, 3F), –113.2 (s, 1F).

Compound (3-A):



General procedure **C** was followed using **3** (0.848 mmol, 448 mg) and isolated by reverse-phase HPLC as the TFA amine salt (off-white solid).

Isolated Yield: 44% (128.4 mg)

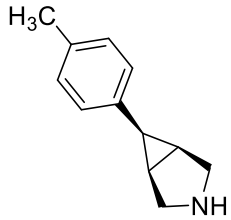
LC-MS: APCI$^+$ (m/z): $[M+H]^+$ calcd for $C_{12}H_{13}F_3N$: 228.100; found: 227.994

^{1}H NMR ($CDCl_3$, 500 MHz): δ 11.07 (br s, 1H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 6.26 (br s, 1H), 3.58 (d, *J* = 12.5 Hz, 2H), 3.29 (d, *J* = 12.5 Hz, 2H), 2.48 (t, *J* = 8.5 Hz, 1H), 2.28 (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 135.8, 130.6 (d, J_{C-F} = 32.8 Hz), 130.1, 126.7 (d, J_{C-F} = 3.7 Hz) Hz), 123.9 (d, J_{C-F} = 273 Hz), 44.8, 24.2, 22.2.

^{19}F NMR ($CDCl_3$, 376 MHz): –63.0 (s, 3F), –75.9 (s, 3F).

Compound (5-A):



General procedure **C** was followed using **5** (0.769 mmol, 365 mg) and isolated by reverse-phase HPLC as the TFA amine salt (light brown solid).

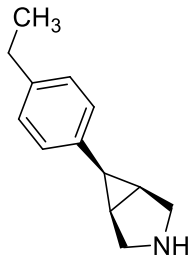
Isolated Yield: 49% (109.0 mg)

LC-MS: APCI$^+$ (m/z): $[M+H]^+$ calcd for $C_{12}H_{16}N$: 174.128; found: 174.194.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.35 (br s, 1H), 7.22 (d, *J* = 7.6 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 4.52 (br s, 1H), 3.63 (m, 2H), 3.32 (dd, *J* = 12.0, 3.2 Hz, 2H), 2.41 (t, *J* = 8.4 Hz, 1H), 2.35 (s, 3H), 2.20 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 138.5, 130.7, 128.9, 128.7, 45.4, 22.7, 21.3, 21.1.

Compound (6-A):



General procedure **C** was followed using **6** (0.588 mmol, 287 mg) and isolated by reverse-phase HPLC as the TFA amine salt (off-white solid).

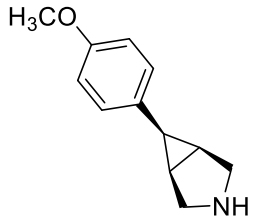
Isolated Yield: 39% (69.0 mg)

LC-MS: APCI$^+$ (m/z): [M+H]$^+$ calcd for $C_{13}H_{18}N$: 188.144; found: 188.312.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.47 (br s, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 5.02 (br s, 1H), 3.60 (m, 2H), 3.32 (dd, *J* = 12.0, 4.4 Hz, 2H), 2.64 (q, *J* = 7.6 Hz, 2H), 2.41 (t, *J* = 8.4 Hz, 1H), 2.20 (m, 2H), 1.22 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 144.7, 129.4, 129.2, 128.8, 45.4, 28.4, 23.1, 21.5, 15.2.

Compound (7-A):



General procedure **C** was followed using **7** (0.367 mmol, 180 mg) and isolated by reverse-phase HPLC as the TFA amine salt (off-white solid).

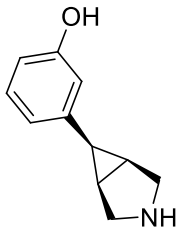
Isolated Yield: 51% yield (56.7 mg)

LC-MS: APCI$^+$ (m/z): [M+H]$^+$ calcd for $C_{12}H_{16}NO$: 190.123; found: 190.153.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.85 (br s, 1H), 7.13 (d, *J* = 8.4 H, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 5.38 (br s, 1H), 3.78 (s, 3H), 3.56 (m, 2H), 3.32 (dd, *J* = 11.6, 3.6 Hz, 2H), 2.36 (t, *J* = 8.4 Hz, 1H), 2.17 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 159.6, 130.4, 123.4, 115.3, 55.2, 45.4, 22.8, 21.6.

Compound (9-A):



General procedure **D** was followed using **9** (0.301 mmol, 143 mg) and isolated by reverse-phase HPLC as the free amine (light brown solid).

Isolated Yield: 38% over two steps (20.1 mg)

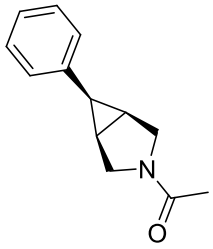
LC-MS: APCI$^+$ (m/z): $[M+H]^+$ calcd for $C_{11}H_{14}NO$: 176.108; found: 176.304.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.12 (t, *J* = 8.0 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 6.56 (multiple peaks, 2H), 2.99 (s, 4H), 2.05 (t, *J* = 8.5 Hz, 1H), 1.82 (d, *J* = 8.5 Hz, 2H). NH and OH peak not present

^{13}C NMR ($CDCl_3$, 126 MHz): δ 157.6, 137.6, 130.0, 119.5, 115.6, 114.3, 46.7, 22.6, 22.0.

VI. Amide Products After Removal of Directing Group

Compound (1-B):



General procedure **E** was followed using **1** (0.217 mmol, 100 mg) and isolated by reverse-phase HPLC as a light brown oil.

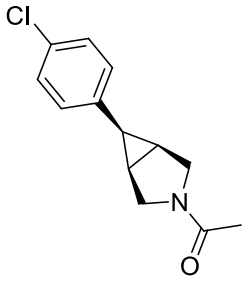
Isolated Yield: 25% yield (11 mg)

LC-MS: APCI$^+$ (m/z): $[M+H]^+$ calcd for $C_{13}H_{16}NO$: 202.123; found: 202.153.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30 (t, *J* = 7.6 Hz, 2H), 7.21 (multiple peaks, 3H), 4.92 (d, *J* = 12.4 Hz, 1H), 3.59 (dd, *J* = 11.0, 4.0 Hz, 1H), 3.32 (d, *J* = 11.0 Hz, 1H), 3.39 (dd, *J* = 12.4, 4.0 Hz, 1H), 2.23 (t, *J* = 8.0 Hz, 1H), 1.97 (m, 2H), 1.47 (s, 3H). Hindered rotation of acetyl group breaks symmetry of molecule

^{13}C NMR ($CDCl_3$, 101 MHz): δ 168.9, 133.8, 128.8, 128.5, 126.9, 46.8, 44.6, 22.5, 21.6, 20.6, 20.1.

Compound (4-B):



General procedure **E** was followed using **4** (0.217 mmol, 107 mg) and isolated by reverse-phase HPLC as a light yellow oil.

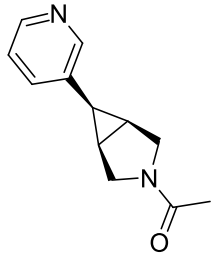
Isolated Yield: 26% yield (13.2 mg)

LC-MS: APCI$^+$ (m/z): $[M+H]^+$ calcd for $C_{13}H_{15}ClNO$: 236.084; found: 236.162.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 3.89 (d, *J* = 12.4 Hz, 1H), 3.62 (dd, *J* = 11.0, 4.0 Hz, 1H), 3.45 (d, *J* = 11.0 Hz, 1H), 3.42 (dd, *J* = 12.4, 4.0 Hz Hz, 1H), 2.17 (t, *J* = 8.0 Hz, 1H), 1.99 (m, 2H), 1.55 (s, 3H). Hindered rotation of acetyl group breaks symmetry of molecule

^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.3, 132.8, 132.2, 130.1, 128.7, 46.7, 44.7, 21.9, 21.6, 20.7, 20.1.

Compound (11-B):



General procedure **E** was followed using **11** (0.217 mmol, 100 mg) and isolated by reverse-phase HPLC as the free pyridine (yellow oil).

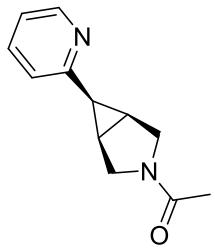
Isolated Yield: 19% yield (8.4 mg)

LC-MS: APCI$^+$ (m/z): $[M+H]^+$ calcd for $C_{12}H_{15}N_2O$: 203.118; found: 203.334.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.51 (s, 1H), 8.46 (d, *J* = 4.8 Hz, 1H), 7.54 (d, *J* = 7.6, 1H), 7.24 (dd, *J* = 7.6, 4.8 Hz, 1H), 3.84 (d, *J* = 12.4 Hz, 1H), 3.63 (dd, *J* = 11.2, 4.0 Hz, 1H), 3.47 (d, *J* = 11.2 Hz, 1H), 3.41 (dd, *J* = 12.4, 4.0 Hz, 1H), 2.18 (t, *J* = 8.0 Hz, 1H), 2.03 (multiple peaks, 2H), 1.50 (s, 3H). Hindered rotation of acetyl group breaks symmetry of molecule

^{13}C NMR ($CDCl_3$, 101 MHz): δ 168.3, 150.1, 148.1, 136.4, 129.9, 123.5, 46.6, 44.3, 22.0, 20.7, 19.9, 19.7.

Compound (12-B):



General procedure **E** was followed using **12** (0.217 mmol, 100 mg) and isolated by reverse-phase HPLC as the pyridine TFA salt (colorless oil).

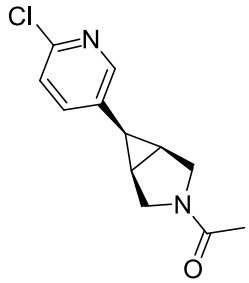
Isolated Yield: 22% yield (15.1 mg)

LC-MS: APCI$^+$ (m/z): $[M+H]^+$ calcd for $C_{12}H_{15}N_2O$: 203.118; found: 203.219.

^{1}H NMR (CD_3CN, 500 MHz): δ 8.75 (dd, *J* = 5.5, 0.5 Hz, 1H), 8.32 (td, *J* = 8.0, 1.5 Hz, 1H), 7.75 (multiple peaks, 2H), 3.99 (br s, 1H), 3.81 (d, *J* = 12.5 Hz, 1H), 3.64 (multiple peaks, 2H), 3.27 (dd, *J* = 12.5, 4.0 Hz, 1H), 2.48 (t, *J* = 8.0 Hz, 1H), 2.20 (m, 1H), 2.15 (m, 1H), 1.44 (s, 3H). Hindered rotation of acetyl group breaks symmetry of molecule

^{13}C NMR (CD_3CN, 126 MHz): δ 169.2, 152.5, 145.8, 143.5, 128.1, 125.7, 46.9, 44.6, 22.9, 22.1, 21.5, 20.8.

Compound (14-B):



General procedure **E** was followed using **14** (0.217 mmol, 108 mg) and isolated by reverse-phase HPLC as the pyridine TFA salt (light yellow oil).

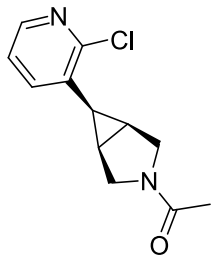
Isolated Yield: 16% yield (11.8 mg)

LC-MS: APCI$^+$ (m/z): $[M+H]^+$ calcd for $C_{12}H_{14}ClN_2O$: 237.079; found: 237.103.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.29 (d, *J* = 1.0 Hz, 1H), 7.52 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 6.33 (br s, 1H), 3.81 (d, *J* = 12.5 Hz, 1H), 3.67 (dd, *J* = 11.0, 4.5 Hz, 1H), 3.46 (d, *J* = 11.0 Hz, 1H), 3.45 (dd, *J* = 12.5, 4.5 Hz, 1H), 2.15 (t, *J* = 8.0, 1H), 2.09 (m, 1H), 2.05 (m, 1H), 1.59 (s, 3H). Hindered rotation of acetyl group breaks symmetry of molecule

^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.0, 149.9, 149.7, 139.3, 128.9, 124.4, 46.6, 44.4, 21.9, 20.8, 19.8, 19.3.

Compound (15-B):



General procedure **E** was followed using **15** (0.217 mmol, 108 mg) and isolated by reverse-phase HPLC as the pyridine TFA salt (colorless oil).

Isolated Yield: 12% yield (9.0 mg)

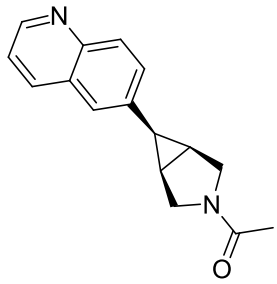
LC-MS: APCI$^+$ (m/z): $[M+H]^+$ calcd for $C_{12}H_{14}ClN_2O$: 237.079; found: 236.918.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.29 (d, *J* = 4.8 Hz, 1H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.19 (dd, *J* = 7.6, 4.8 Hz, 1H), 4.05 (d, *J* = 13.2 Hz, 1H), 3.61 (dd, *J* = 11.2, 4.4 Hz, 1H), 3.44 (m, 2H), 3.23 (br s,

1H), 2.15 (multiple peaks, 3H), 1.52 (s, 3H). Hindered rotation of acetyl group breaks symmetry of molecule

^{13}C NMR ($CDCl_3$, 101 MHz): δ 168.8, 152.3, 148.1, 138.9, 129.8, 122.5, 47.0, 44.8, 22.4, 21.9, 21.2, 20.7.

Compound (16-B):



General procedure **E** was followed using **16** (0.217 mmol, 111 mg) and isolated by reverse-phase HPLC as the pyridine TFA salt (colorless oil).

Isolated Yield: 23% yield (18.1 mg) 168

LC-MS: APCI$^+$ (m/z): $[M+H]^+$ calcd for $C_{16}H_{17}N_2O$: 253.134; found: 253.137.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.67 (br s, 1H), 9.18 (d, *J* = 5.0 Hz, 1H), 8.73 (d, *J* = 8.0 Hz, 1H), 8.53 (d, *J* = 9.0 Hz, 1H), 7.93 (m, 1H), 7.91 (d, *J* = 9.0 Hz, 1H), 8.83 (dd, *J* = 8.0, 5.0 Hz 1H), 4.03 (d, *J* = 12.4 Hz, 1H), 3.71 (dd, *J* = 11.5, 4.5 Hz, 1H), 3.50 (multiple peaks, 2H), 2.46 (m, 1H), 2.20 (m, 2H), 1.40 (s, 3H). Hindered rotation of acetyl group breaks symmetry of molecule

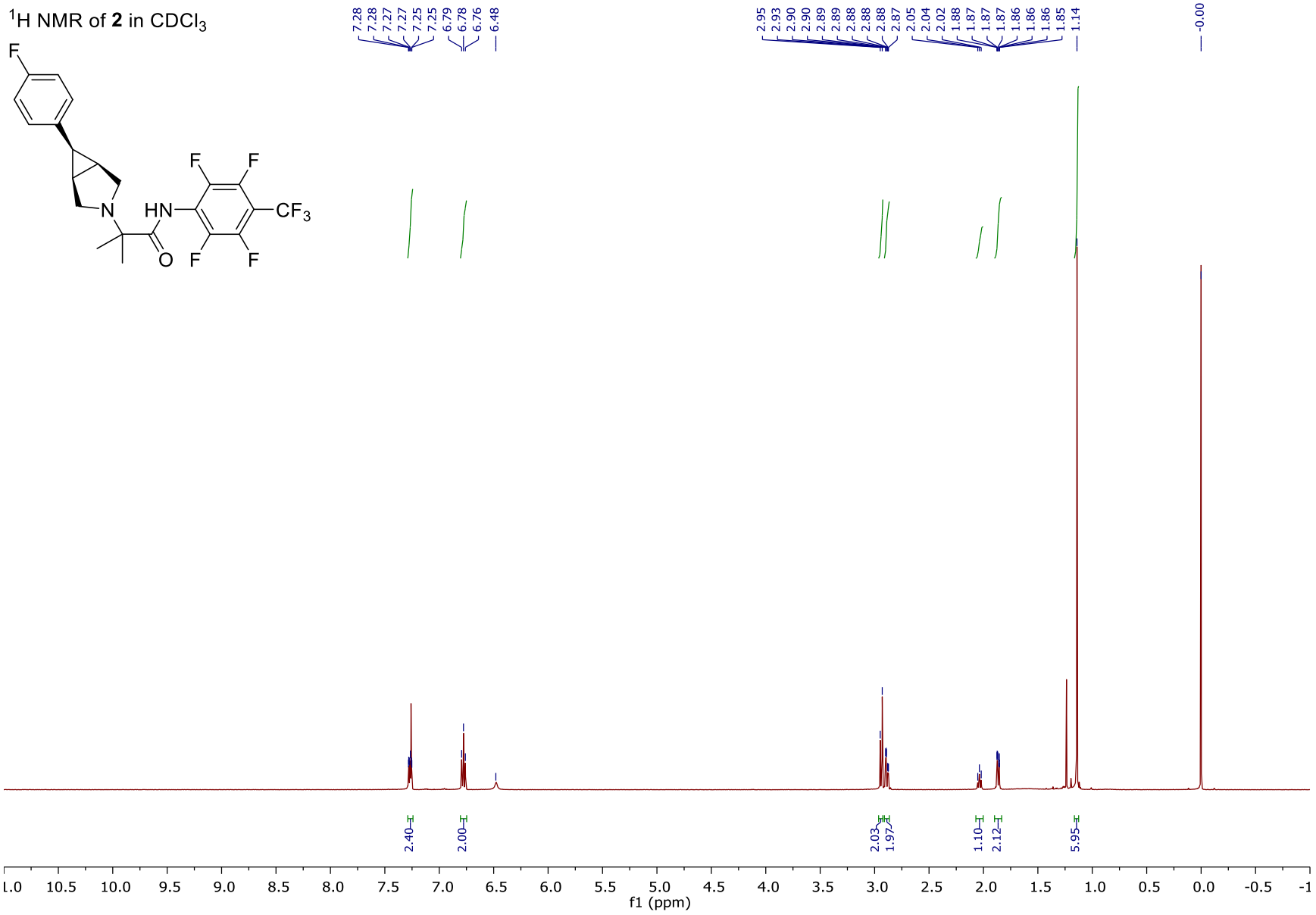
^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.2, 144.5, 144.1, 138.7, 136.9, 135.6, 129.0, 127.6, 122.8, 121.6, 46.7, 44.5, 22.5, 21.7, 21.3, 20.4.

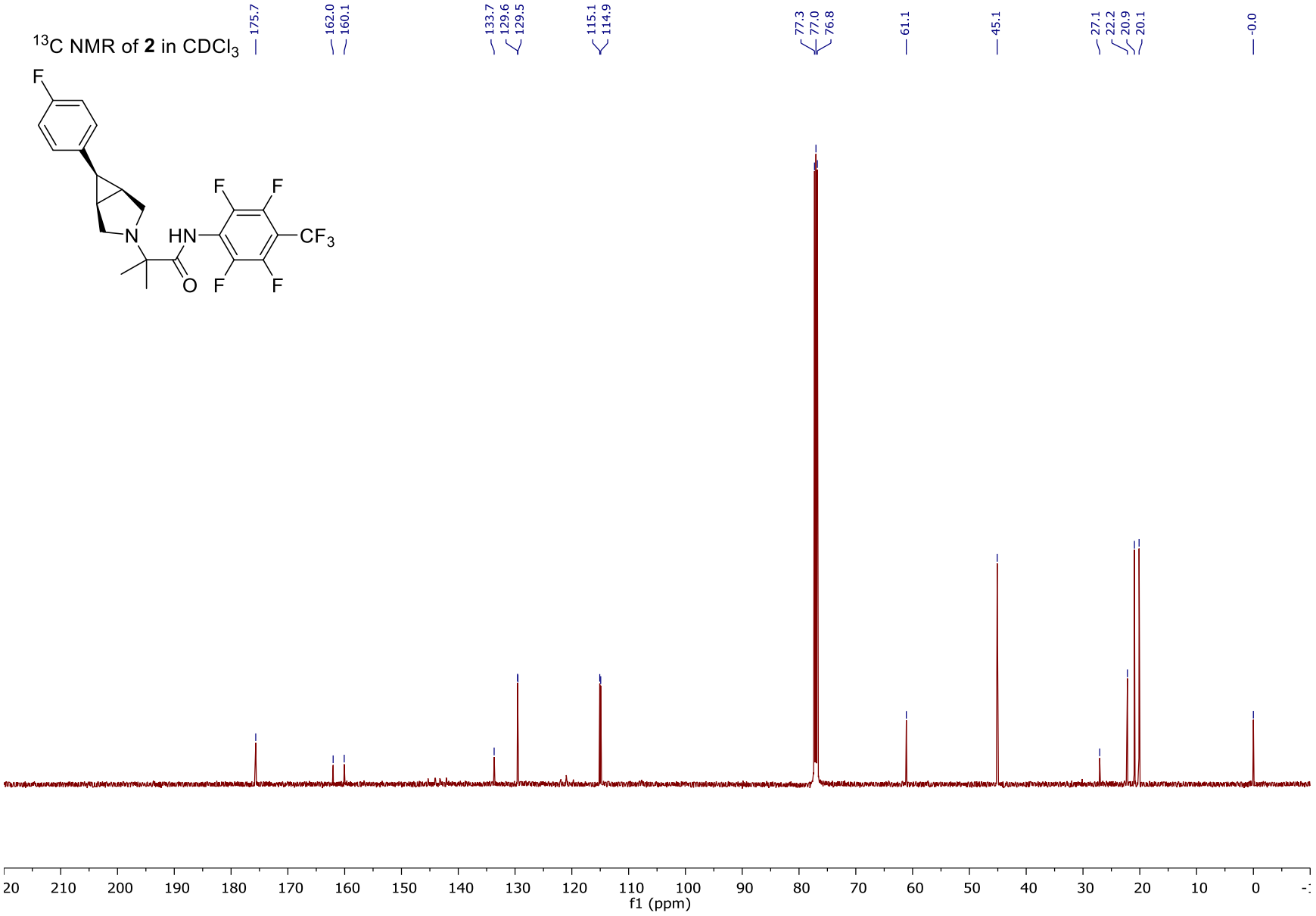
VI. References

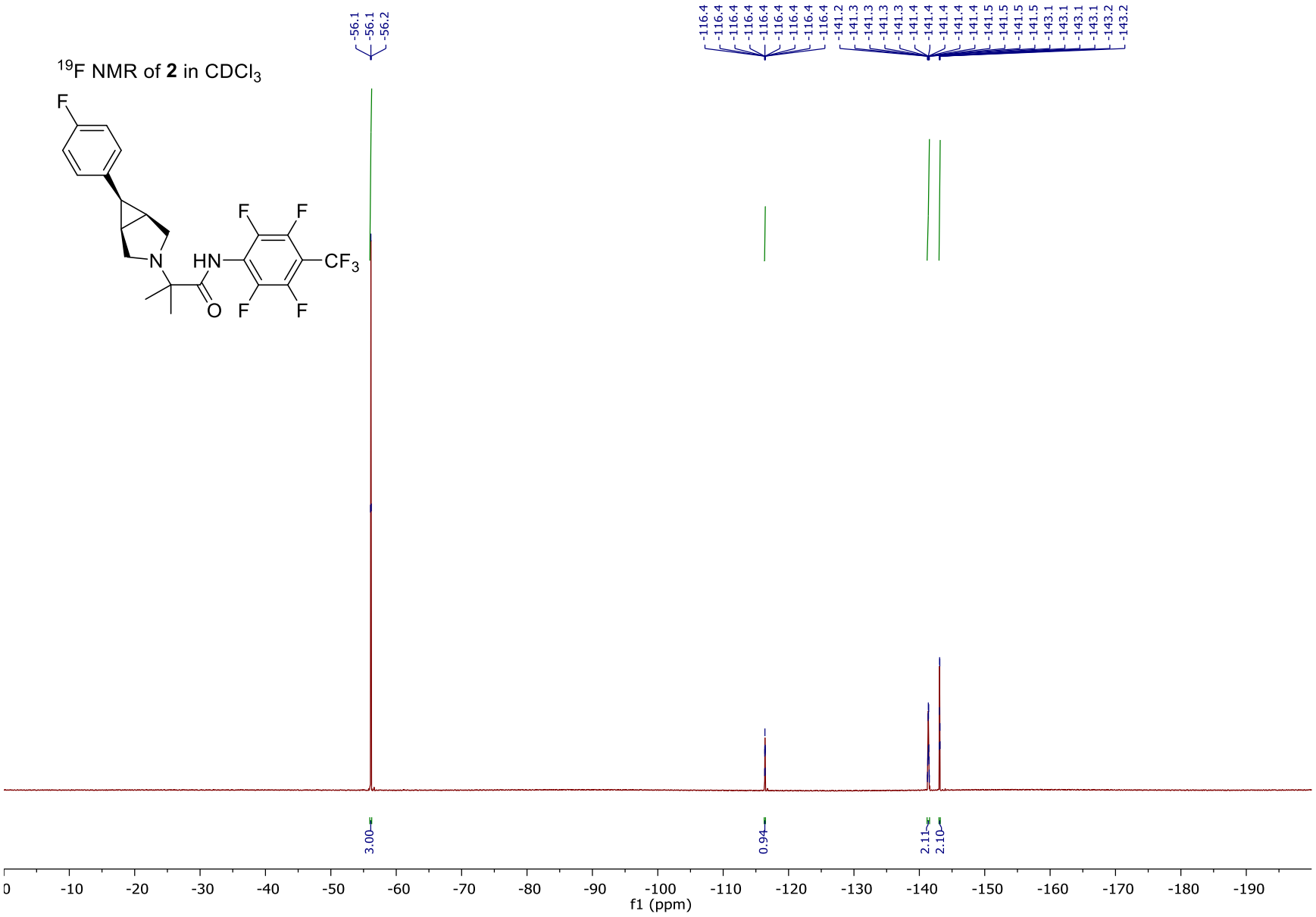
1. Topczewski, J. J.; Cabrera, P. J.; Saper, N. I.; Sanford, M. S. *Nature* **2016**, *531*, 220–224.

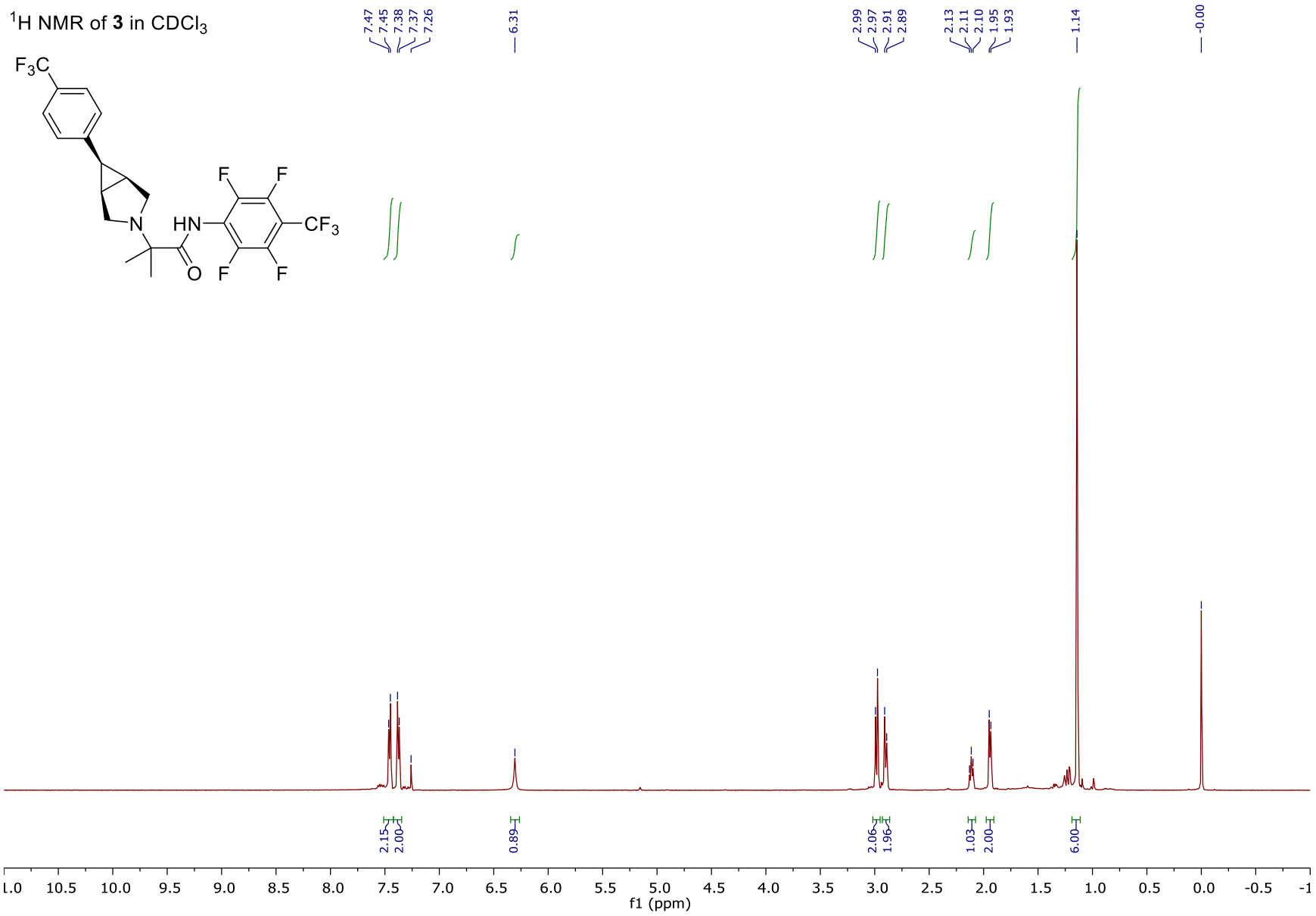
VII. NMR Spectra

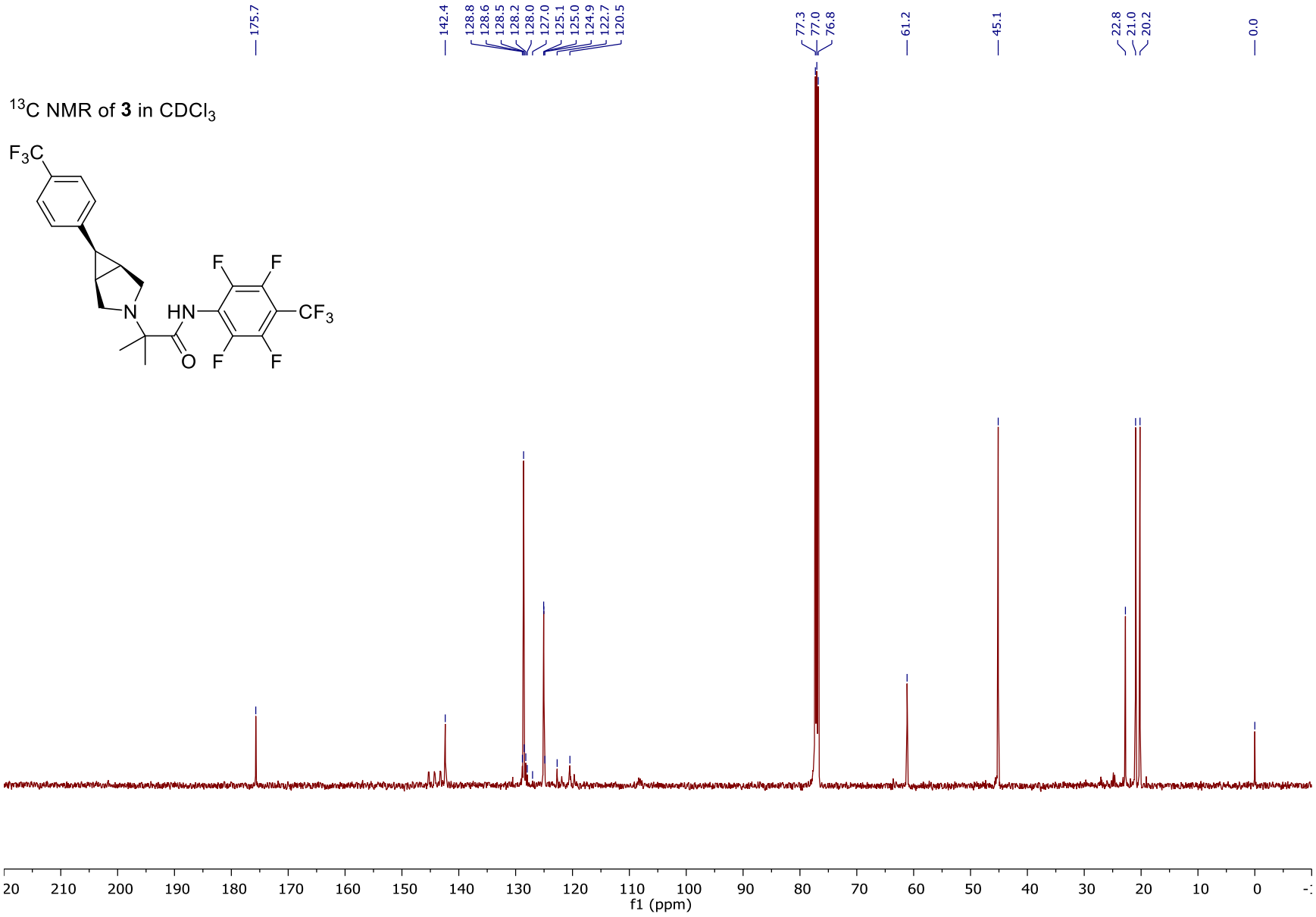
^{1}H NMR of **2** in $CDCl_3$



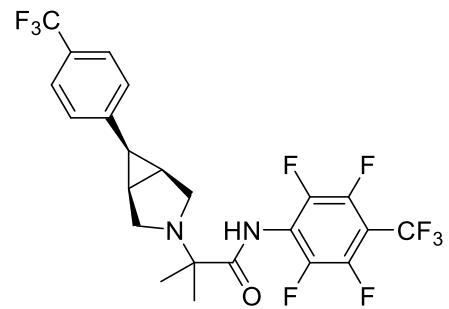

^{13}C NMR of **2** in $CDCl_3$
175.7
162.0
160.1
133.7
129.6
129.5
115.1
114.9
77.3
77.0
76.8
61.1
45.1
27.1
22.2
20.9
20.1
-0.0
F
F
F
HN
N
O
F
F
CF_3
f1 (ppm)


19F NMR of 2 in CDCl3
F
N
HN
O
F
F
F
F
CF3
-56.1
-56.1
-56.2
-116.4
-116.4
-116.4
-116.4
-116.4
-116.4
-116.4
-116.4
-116.4
-141.2
-141.3
-141.3
-141.3
-141.4
-141.4
-141.4
-141.4
-141.4
-141.5
-141.5
-141.5
-143.1
-143.1
-143.1
-143.2
-143.2
3.00
0.94
2.11
2.10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

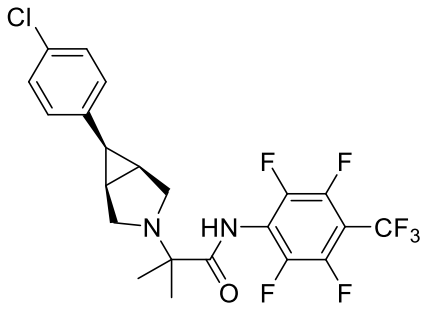

1H NMR of 3 in CDCl3
F3C
F
F
HN
CF3
N
O
F
F
7.47
7.45
7.38
7.37
7.26
6.31
2.99
2.97
2.91
2.89
2.13
2.11
2.10
1.95
1.93
1.14
-0.00
2.15
2.00
0.89
2.06
1.96
1.03
2.00
6.00
f1 (ppm)


175.7
142.4
128.8
128.6
128.5
128.2
128.0
127.0
125.1
125.0
124.9
122.7
120.5
77.3
77.0
76.8
61.2
45.1
22.8
21.0
20.2
0.0
^{13}C NMR of **3** in $CDCl_3$
F_3C
F
F
N
HN
CF_3
O
F
F
f1 (ppm)

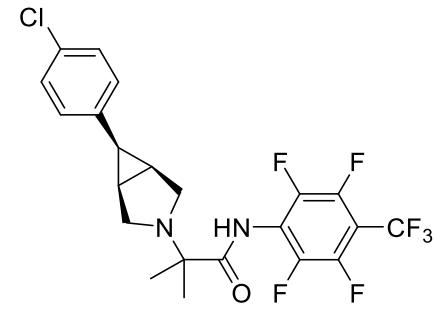
^{19}F NMR of **3** in $CDCl_3$



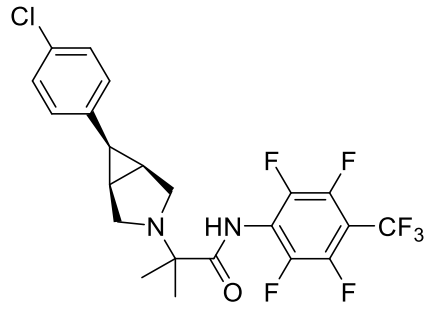
^{1}H NMR of **4** in $CDCl_3$



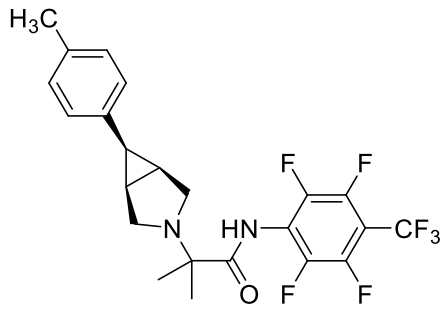
^{13}C NMR of **4** in $CDCl_3$



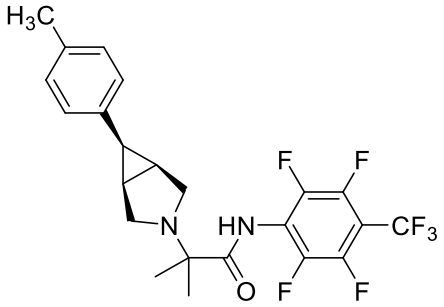
^{19}F NMR of **4** in $CDCl_3$



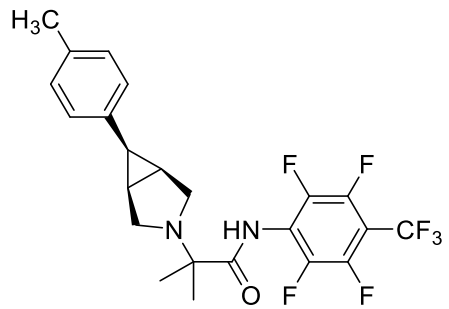
^{1}H NMR of **5** in $CDCl_3$



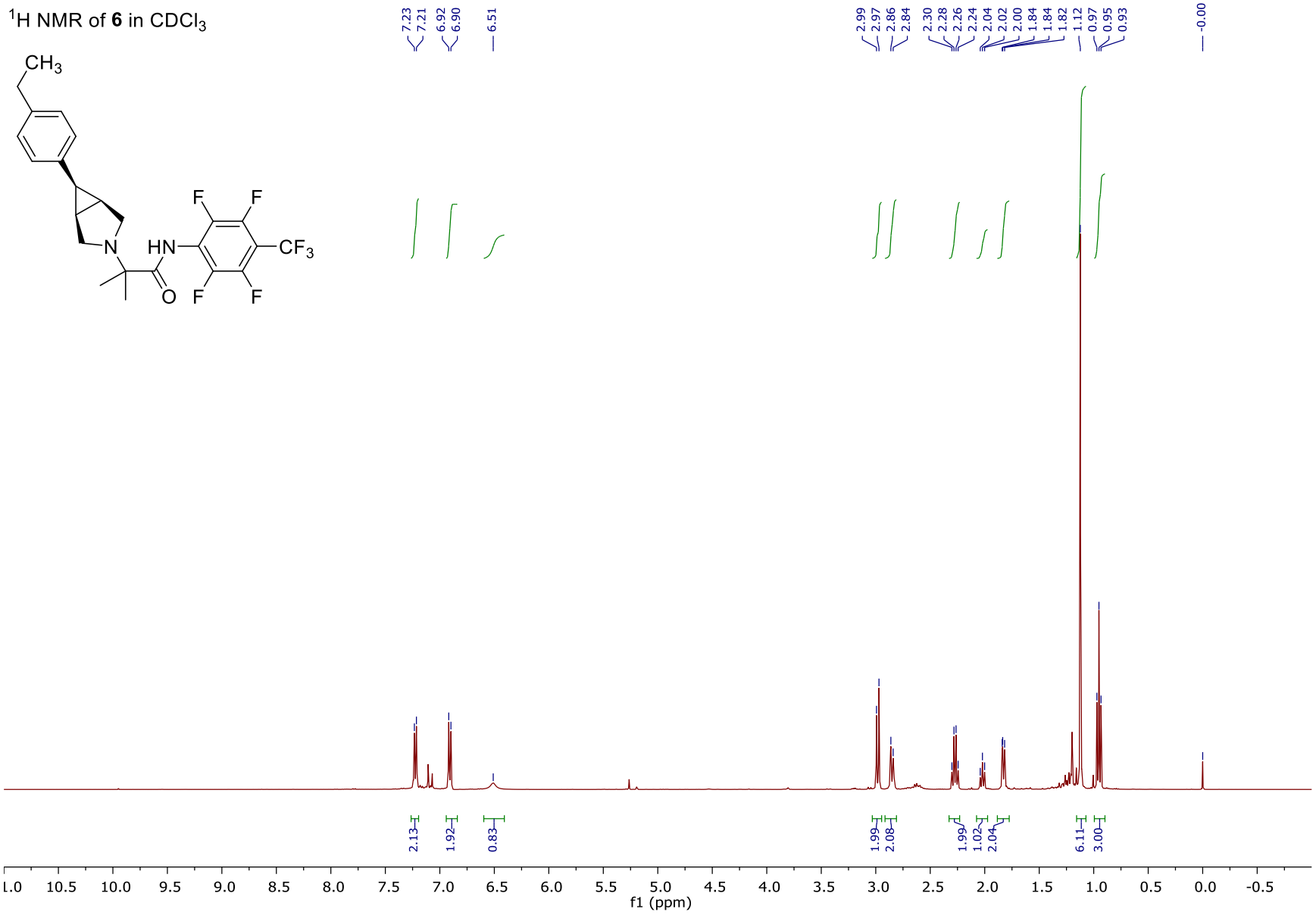
^{13}C NMR of **5** in $CDCl_3$



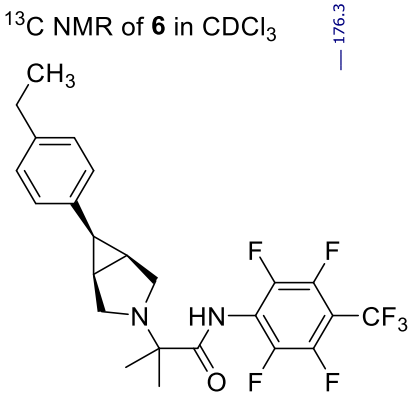
^{19}F NMR of **5** in $CDCl_3$



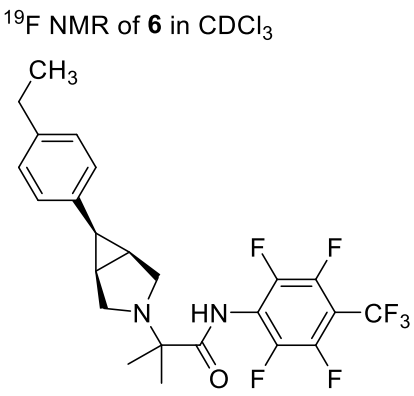
^{1}H NMR of **6** in $CDCl_3$



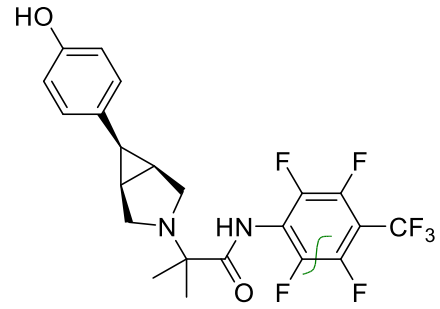
^{13}C NMR of **6** in $CDCl_3$



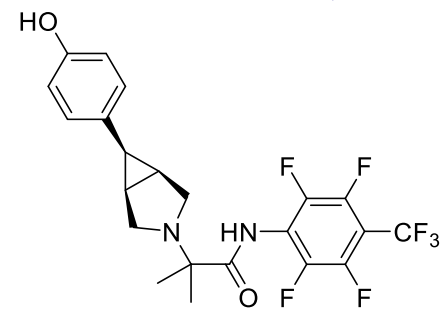
^{19}F NMR of **6** in $CDCl_3$



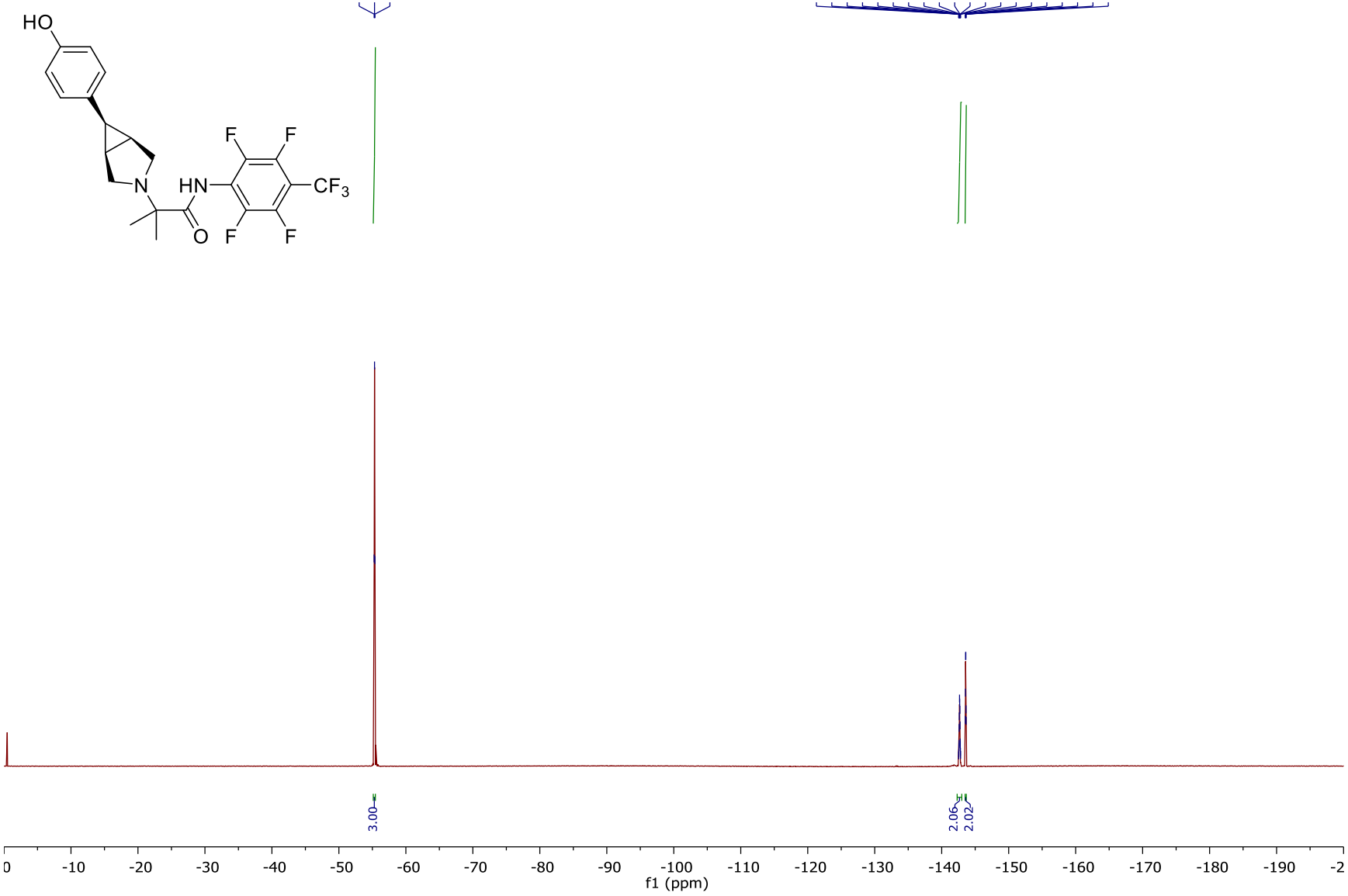
^{1}H NMR of **8** in $CDCl_3$



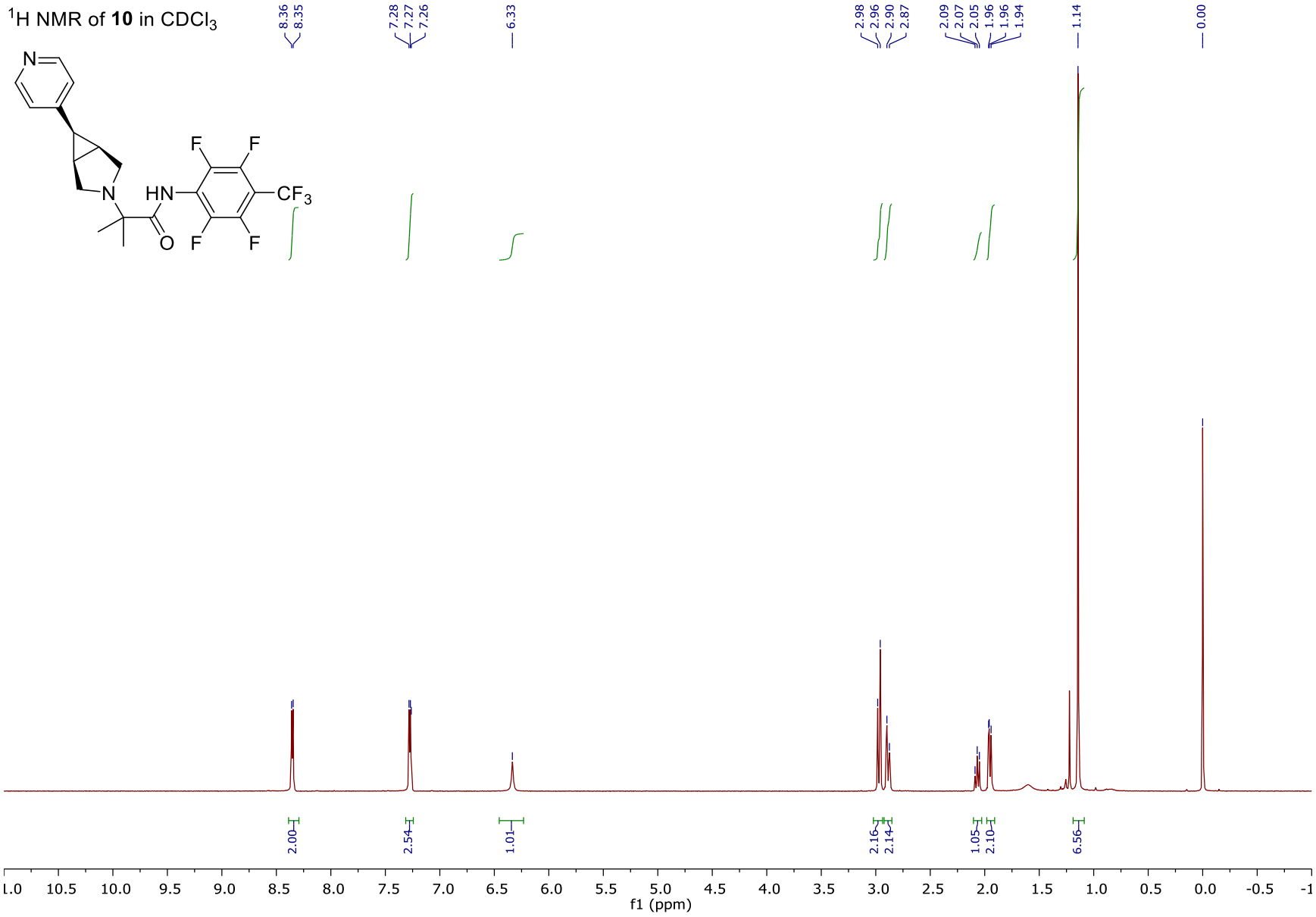
^{13}C NMR of **8** in $CDCl_3$



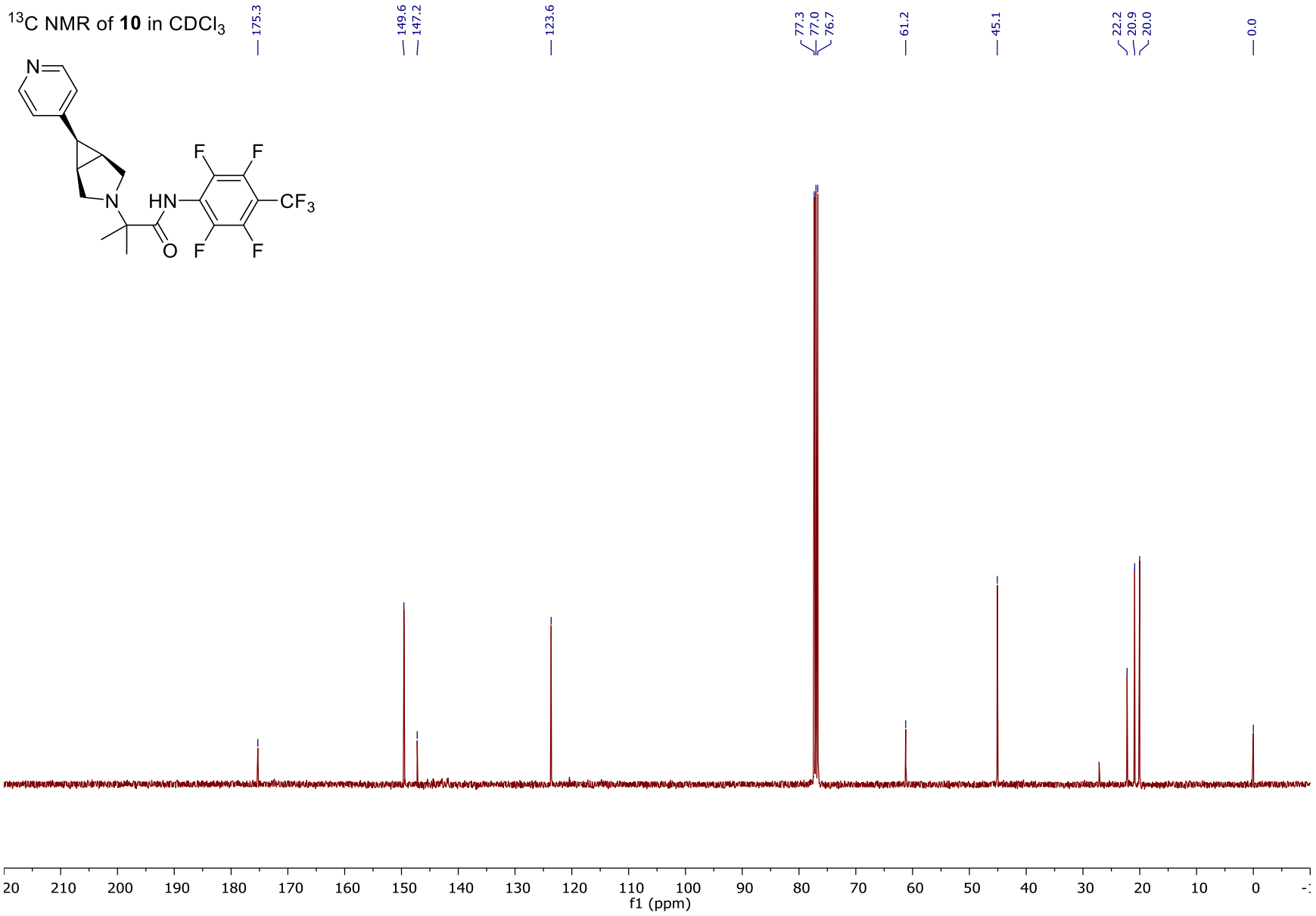
^{19}F NMR of **8** in $CDCl_3$



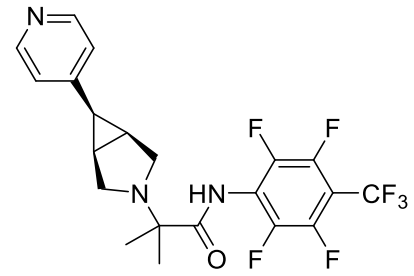
^{1}H NMR of **10** in $CDCl_3$

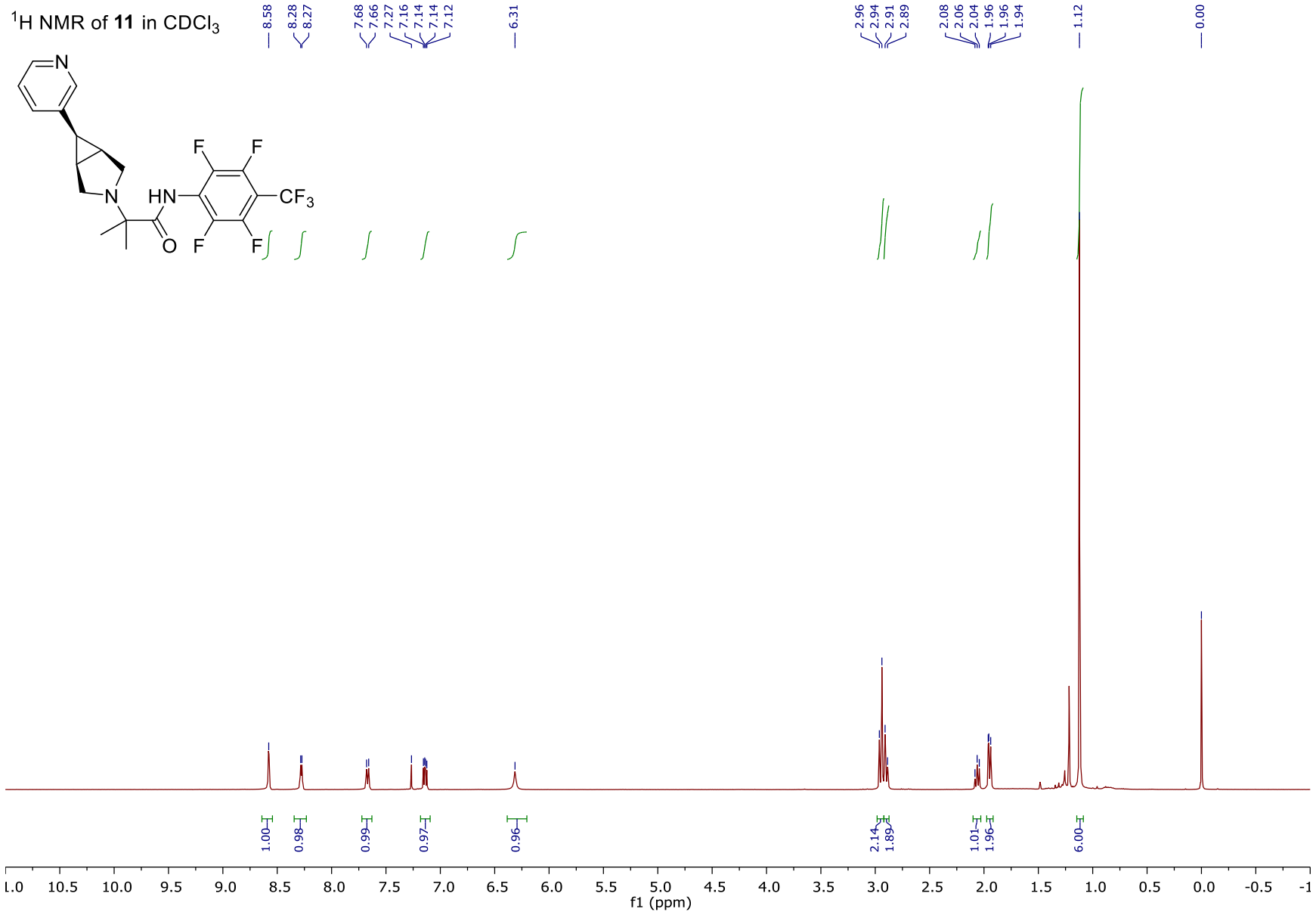


^{13}C NMR of **10** in $CDCl_3$

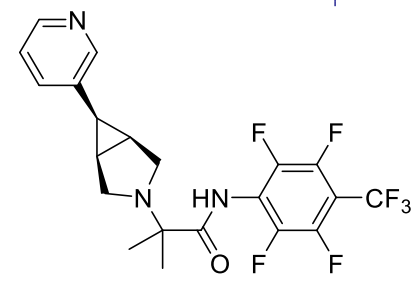


^{19}F NMR of **10** in $CDCl_3$

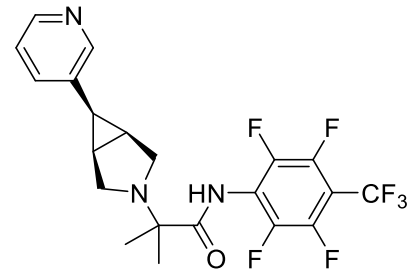


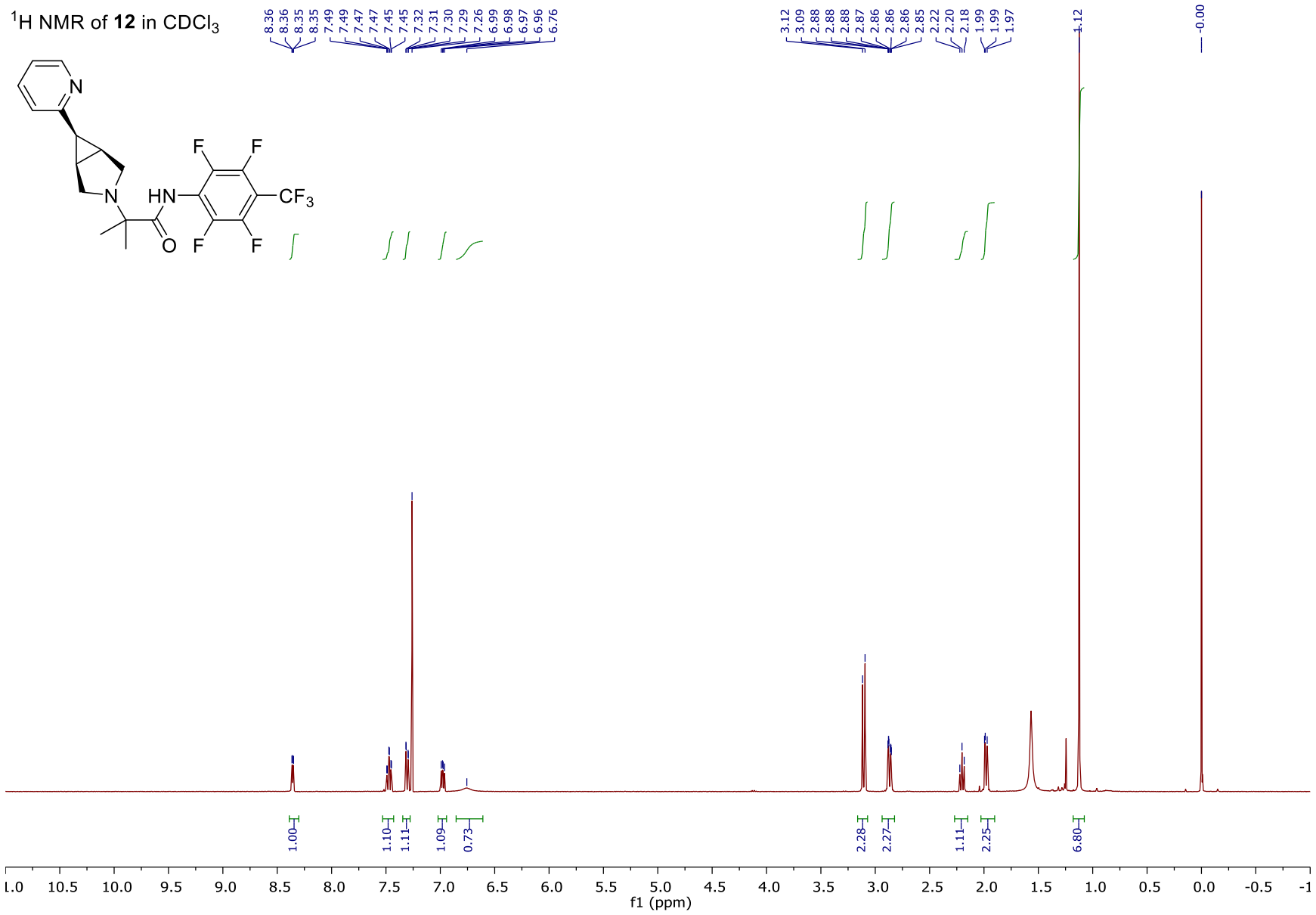

1H NMR of 11 in CDCl3
8.58
8.28
8.27
7.68
7.66
7.27
7.16
7.14
7.14
7.12
6.31
2.96
2.94
2.91
2.89
2.08
2.06
2.04
1.96
1.96
1.94
1.12
0.00
N
N
HN
O
F
F
F
F
CF3
1.00
0.98
0.99
0.97
0.96
2.14
1.89
1.01
1.96
6.00
f1 (ppm)

^{13}C NMR of **11** in $CDCl_3$

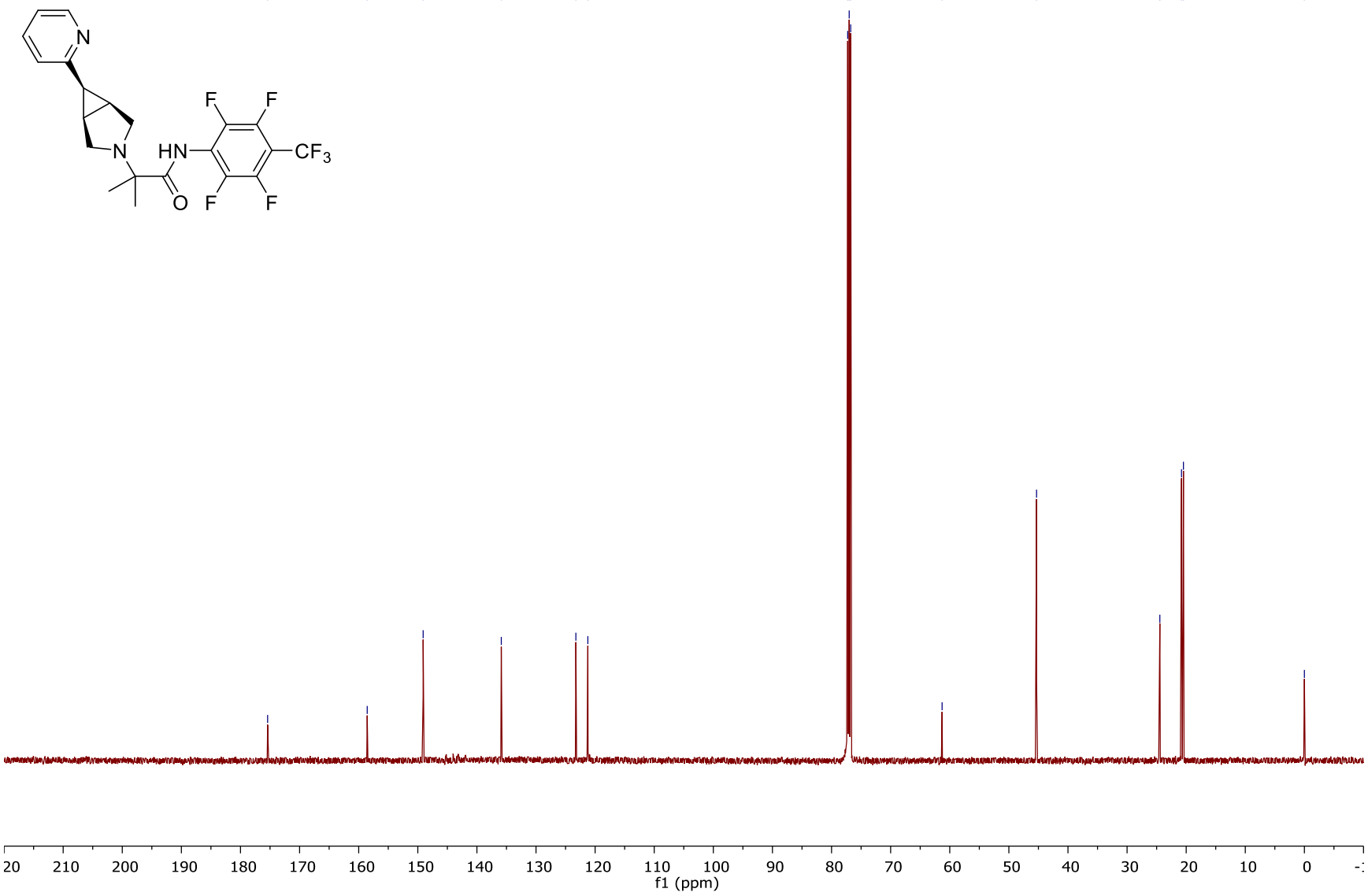


^{19}F NMR of **11** in $CDCl_3$

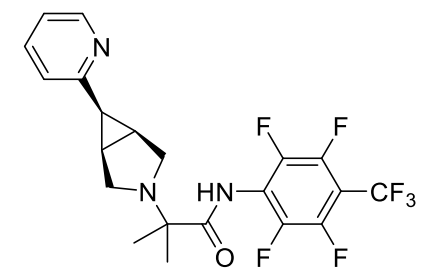


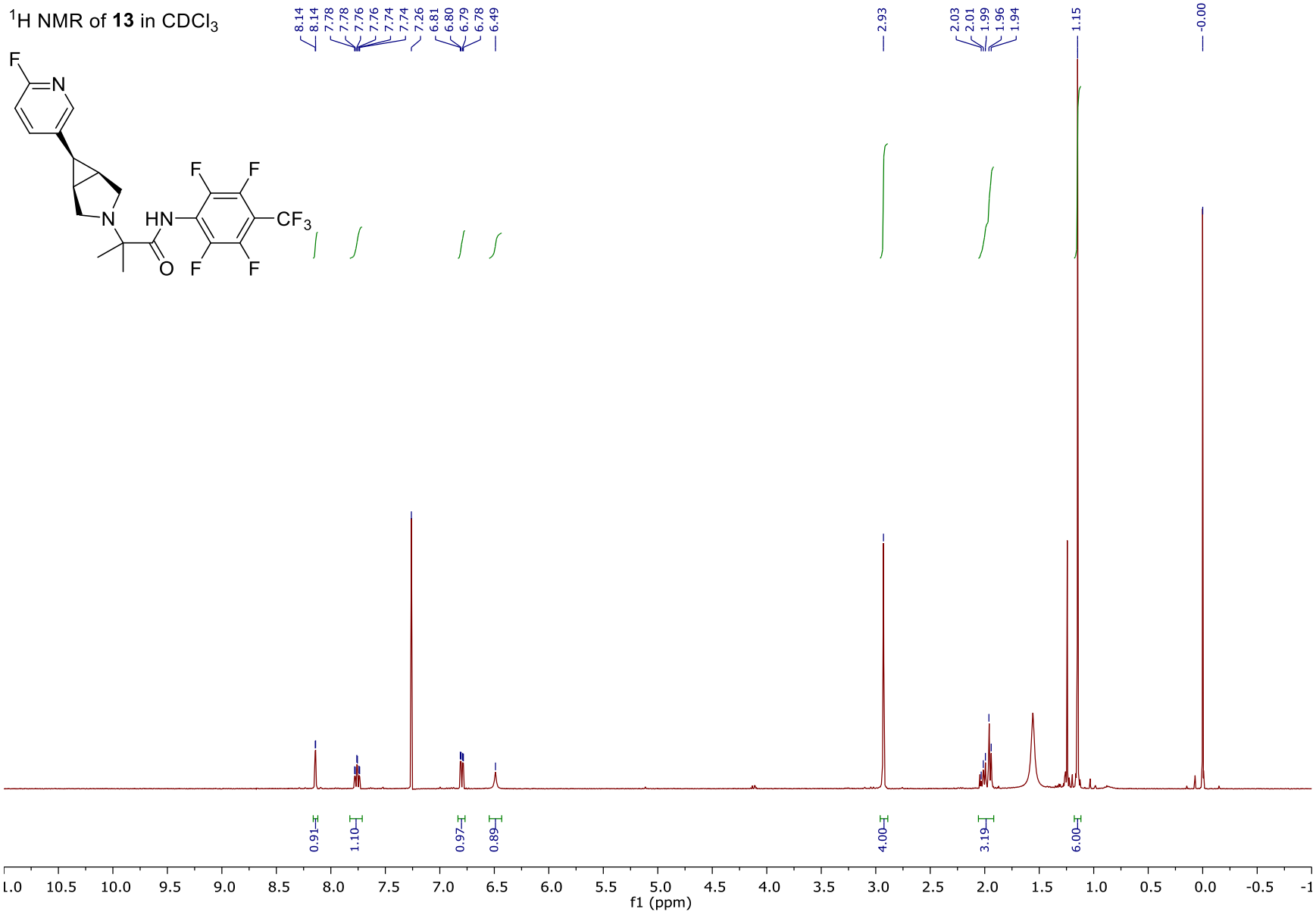

^{1}H NMR of **12** in $CDCl_3$
8.36
8.36
8.35
8.35
7.49
7.49
7.47
7.47
7.45
7.45
7.32
7.31
7.30
7.29
7.26
6.99
6.98
6.97
6.96
6.76
3.12
3.09
2.88
2.88
2.88
2.87
2.86
2.86
2.86
2.85
2.22
2.20
2.18
1.99
1.99
1.97
1.12
-0.00
N
N
HN
F
F
CF3
O
F
F
1.00
1.10
1.11
1.09
0.73
2.28
2.27
1.11
2.25
6.80
f1 (ppm)

^{13}C NMR of **12** in $CDCl_3$

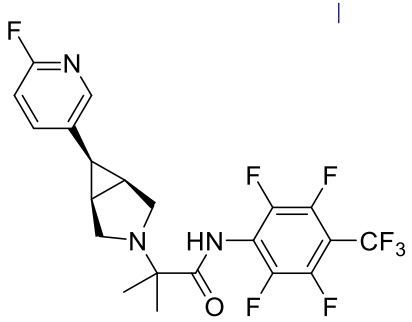


^{19}F NMR of **12** in $CDCl_3$

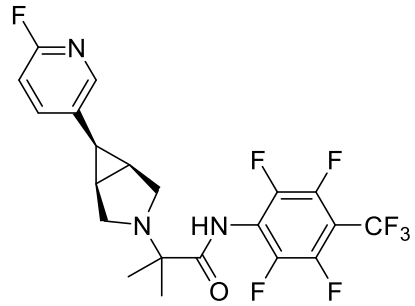


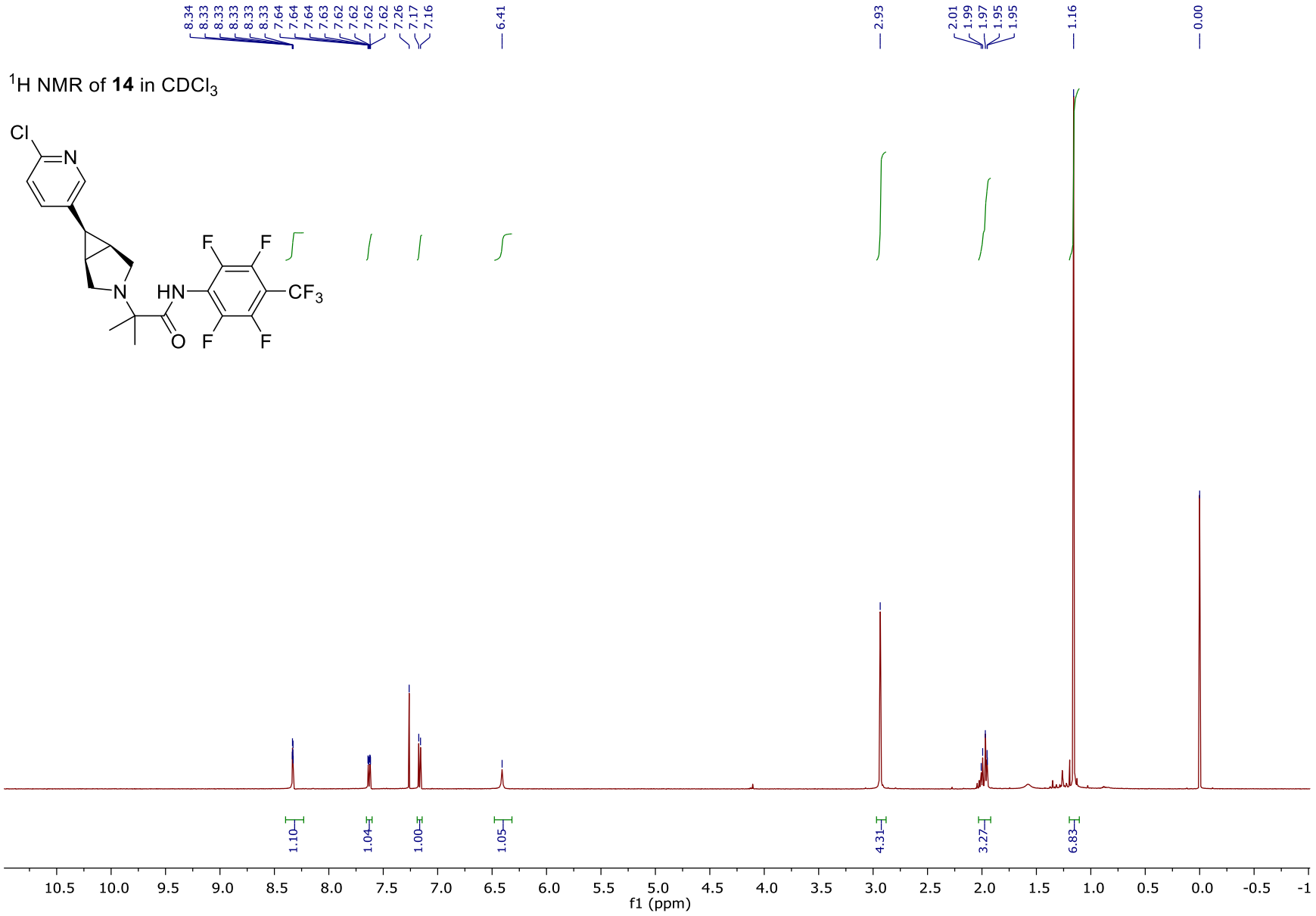

1H NMR of 13 in CDCl3
8.14
8.14
7.78
7.78
7.76
7.76
7.74
7.74
7.26
6.81
6.80
6.79
6.78
6.49
2.93
2.03
2.01
1.99
1.96
1.94
1.15
-0.00
F
N
F
F
N
HN
CF3
O
F
F
0.91
1.10
0.97
0.89
4.00
3.19
6.00
f1 (ppm)

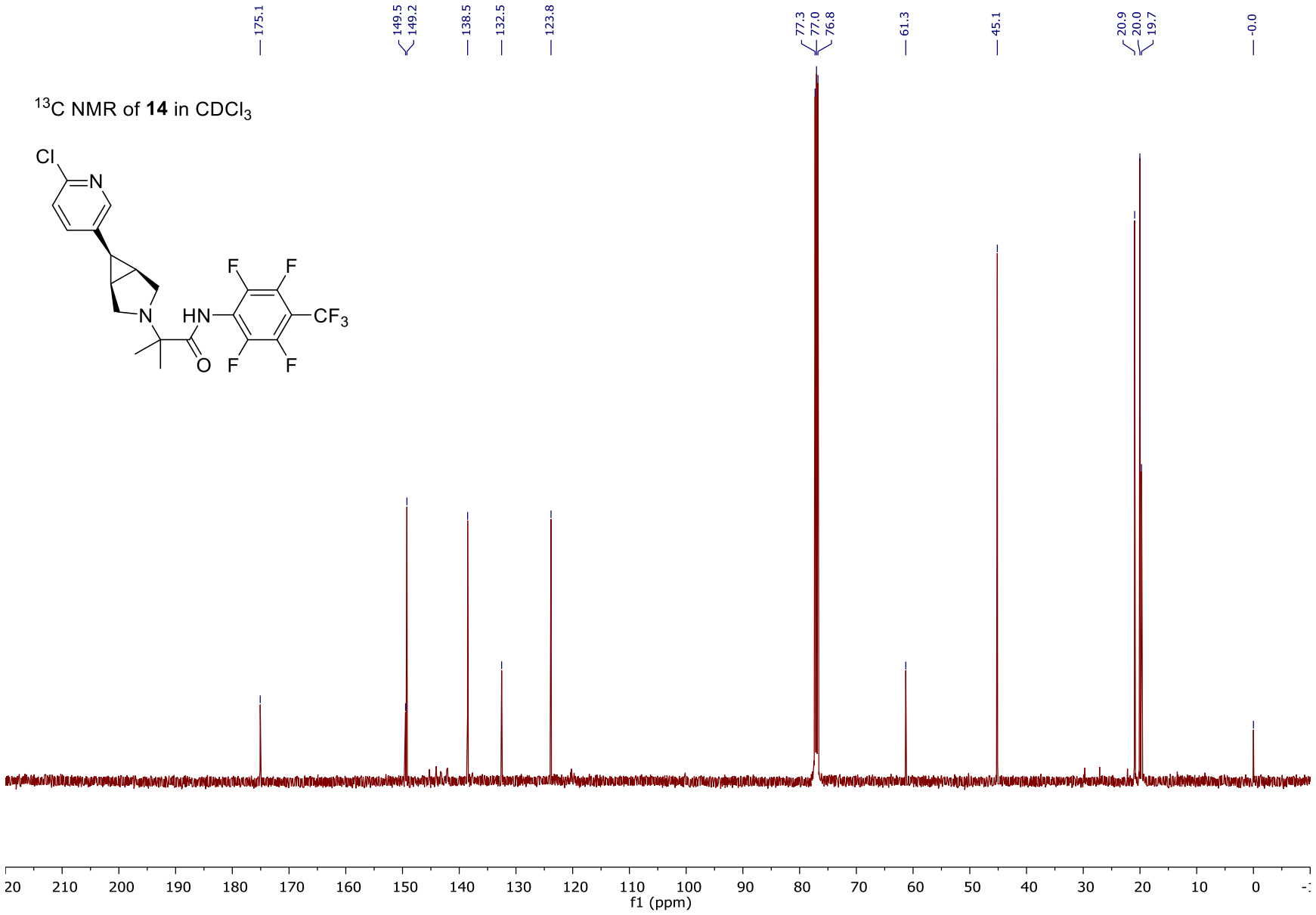
^{13}C NMR of **13** in $CDCl_3$



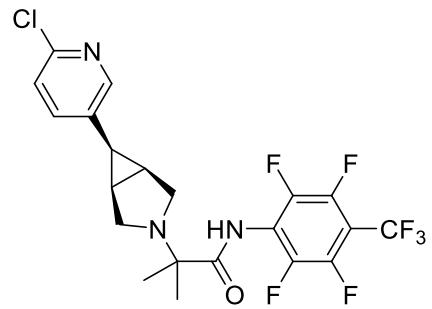
^{19}F NMR of **13** in $CDCl_3$



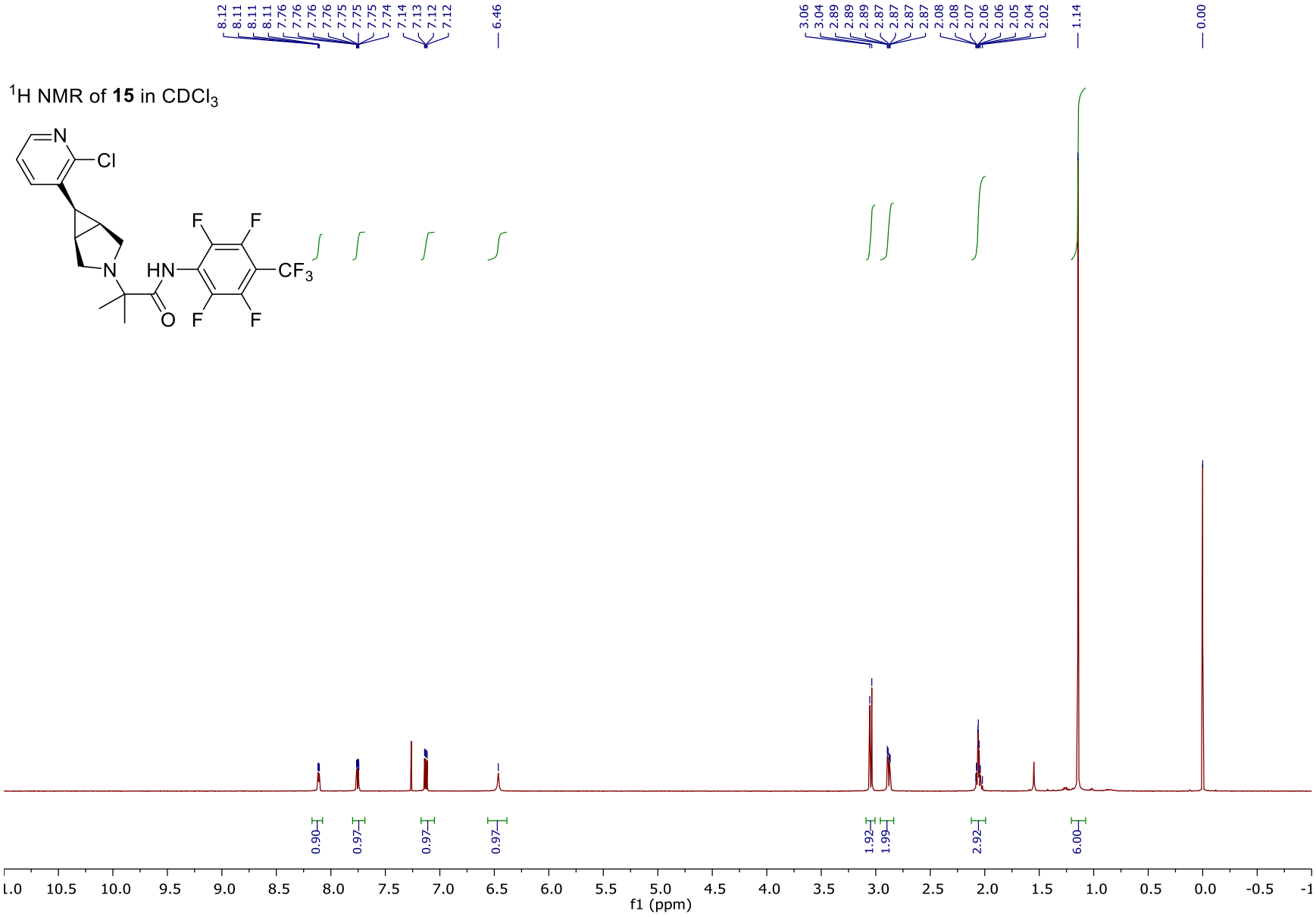

8.34
8.33
8.33
8.33
8.33
8.33
7.64
7.64
7.64
7.63
7.62
7.62
7.62
7.62
7.26
7.17
7.16
6.41
2.93
2.01
1.99
1.97
1.95
1.95
1.16
0.00
1H NMR of 14 in CDCl3
Cl
N
N
HN
O
F
F
F
F
CF3
1.10
1.04
1.00
1.05
4.31
3.27
6.83
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)

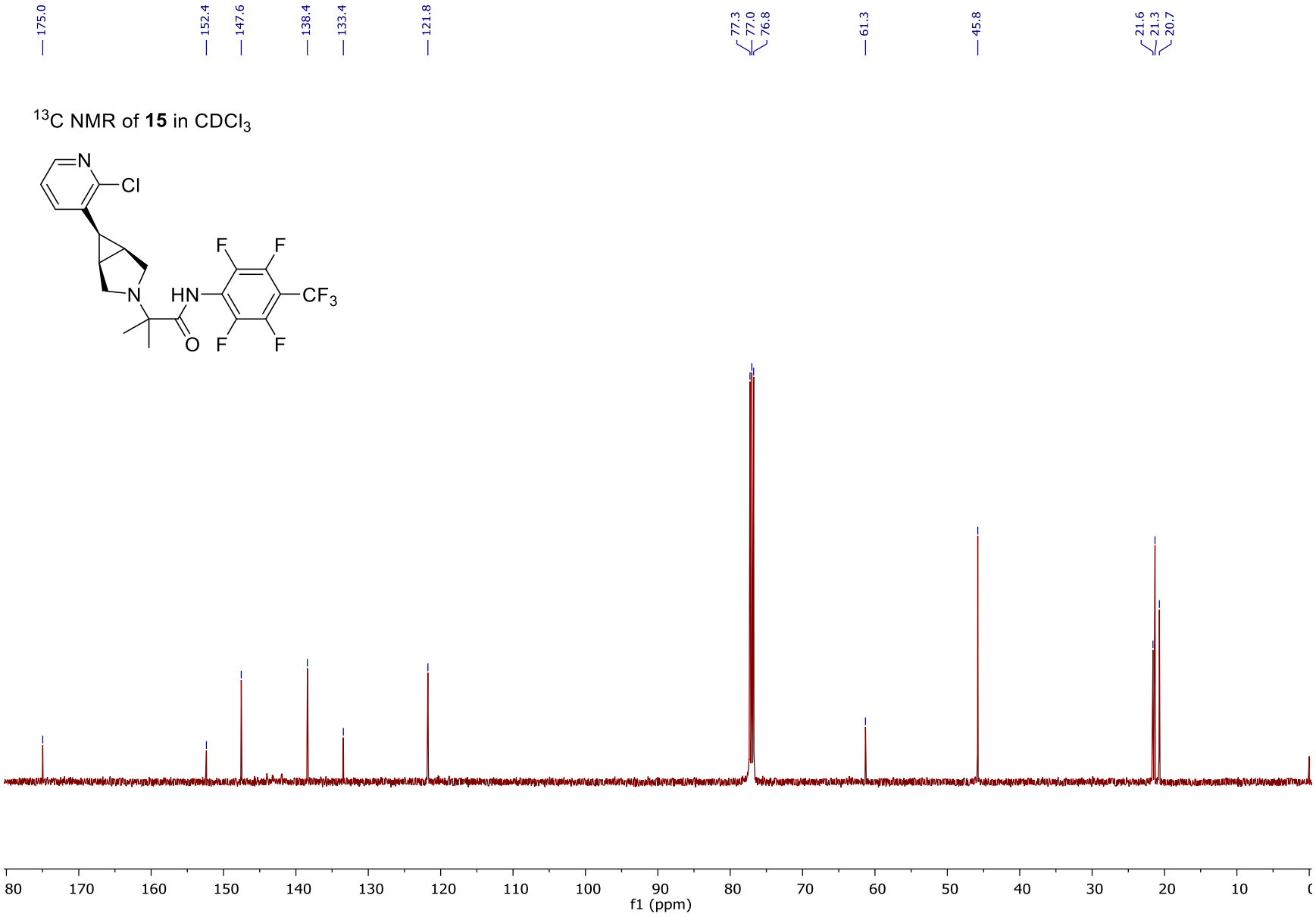

175.1
149.5
149.2
138.5
132.5
123.8
77.3
77.0
76.8
61.3
45.1
20.9
20.0
19.7
-0.0
^{13}C NMR of **14** in $CDCl_3$
Cl
N
N
HN
F
F
CF_3
F
F
O
f1 (ppm)

^{19}F NMR of **14** in $CDCl_3$



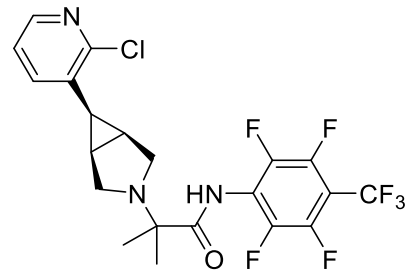
^{1}H NMR of **15** in $CDCl_3$



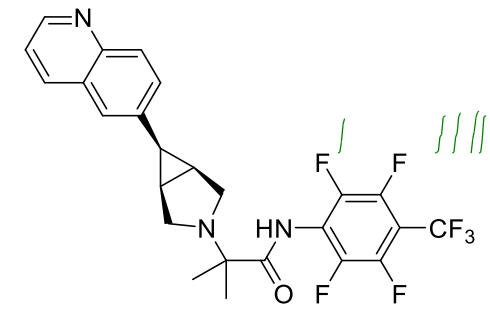


^{13}C NMR of **15** in $CDCl_3$

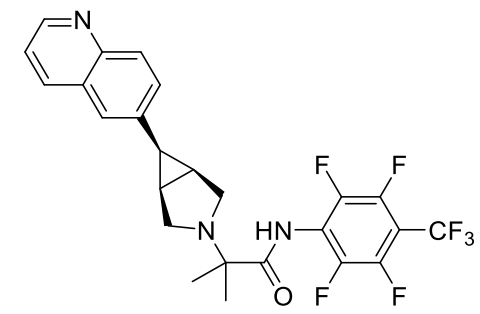
^{19}F NMR of **15** in $CDCl_3$



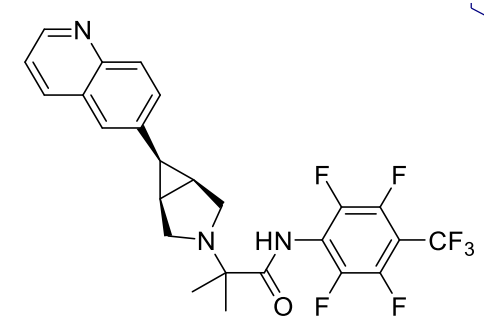
^{1}H NMR of **16** in $CDCl_3$



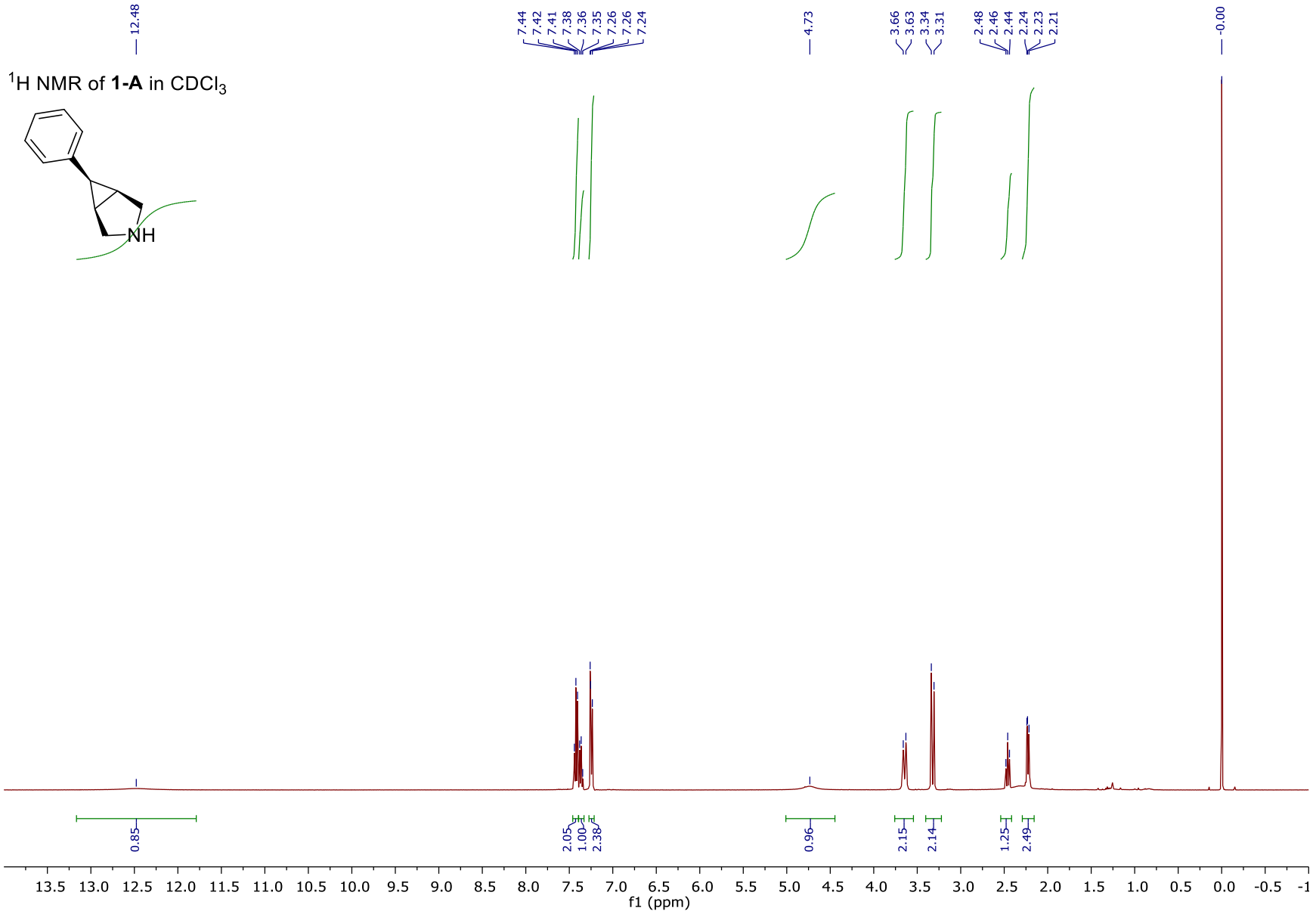
^{13}C NMR of **16** in $CDCl_3$



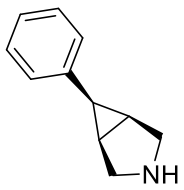
^{19}F NMR of **16** in $CDCl_3$



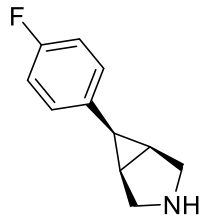
^{1}H NMR of **1-A** in $CDCl_3$



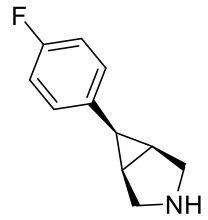
^{13}C NMR of **1-A** in $CDCl_3$



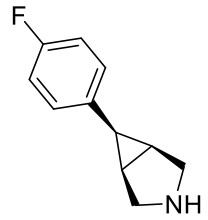
^{1}H NMR of **2-A** in $CDCl_3$

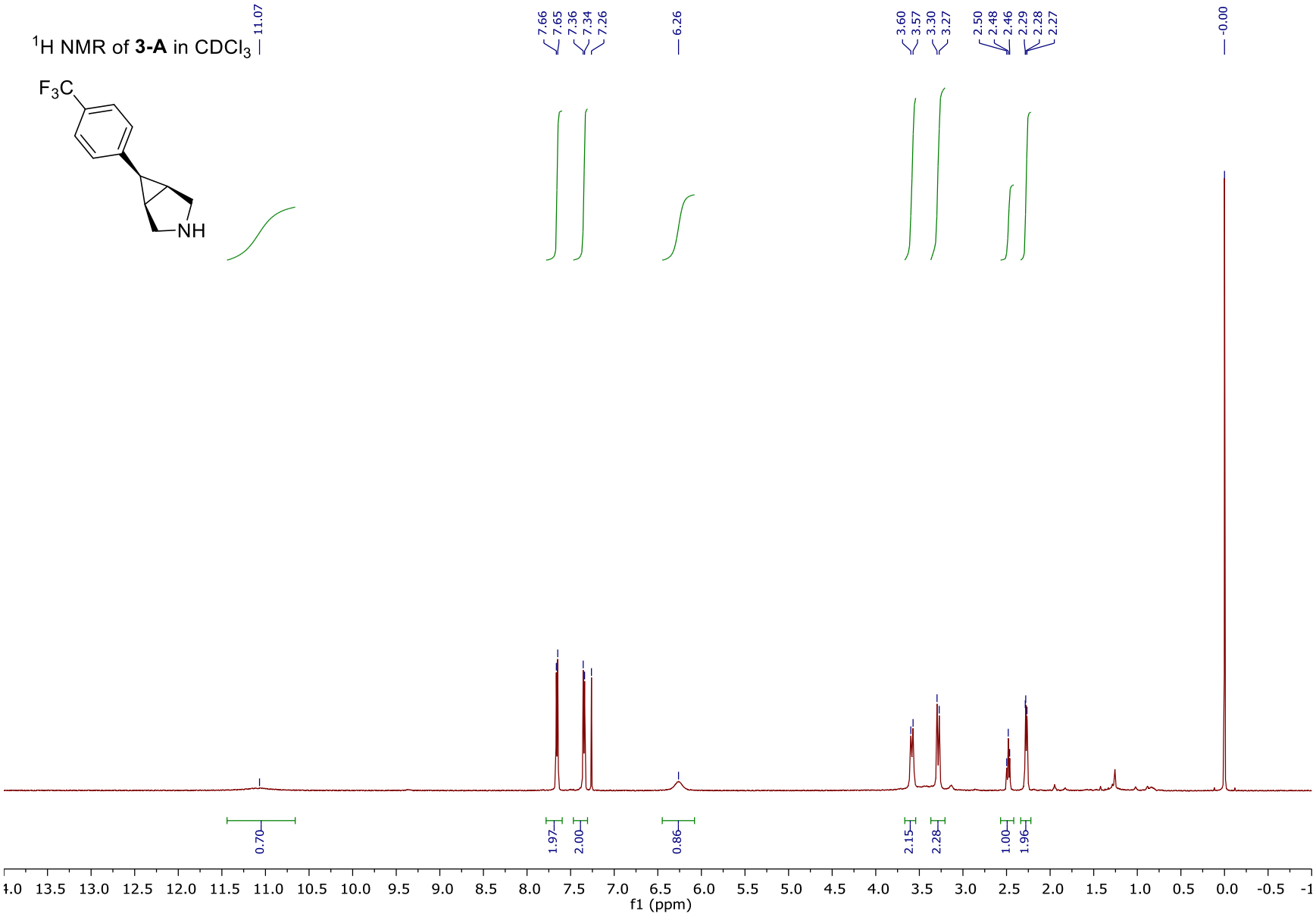


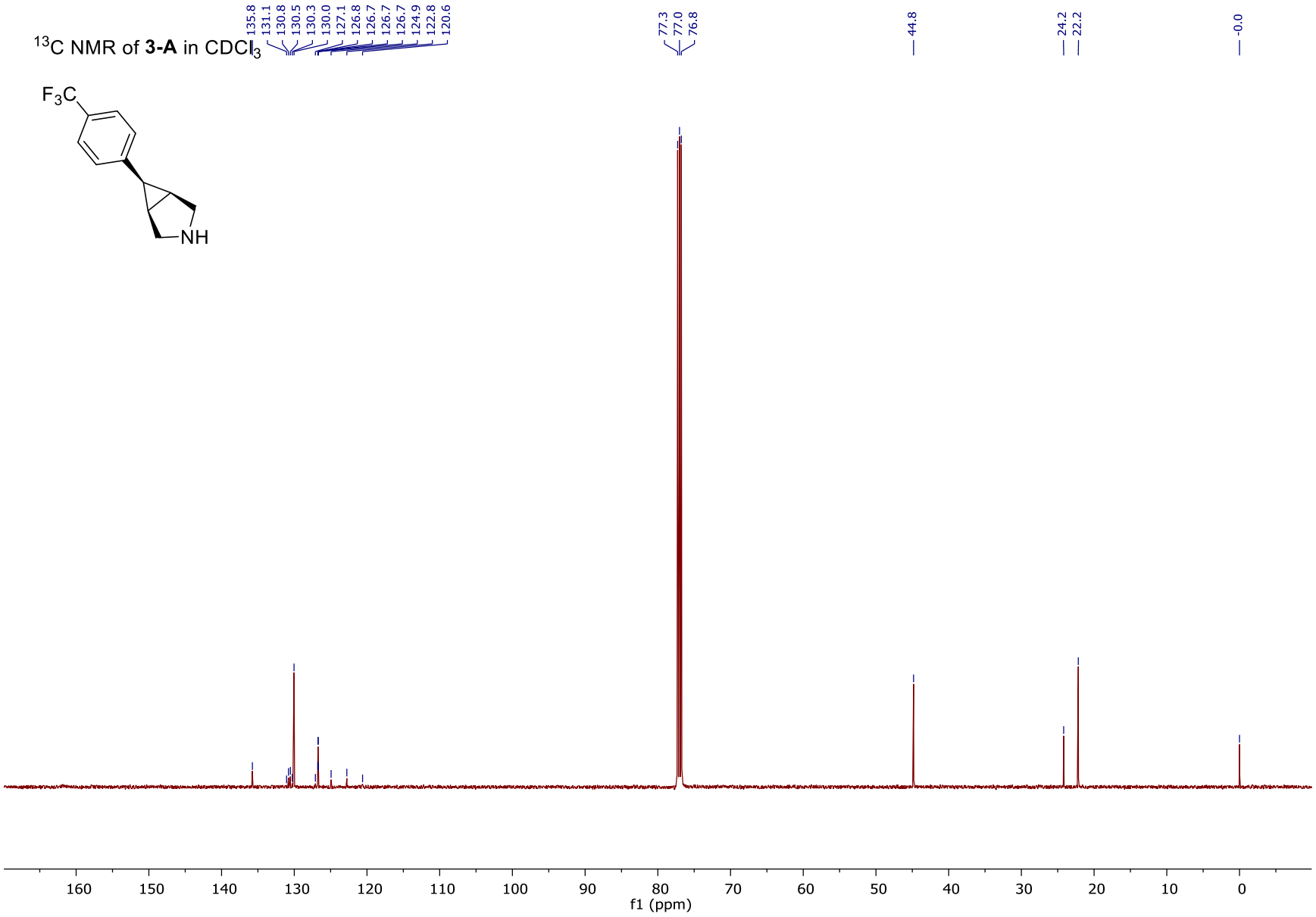
^{13}C NMR of **2-A** in $CDCl_3$



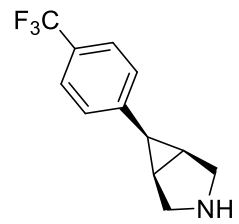
^{19}F NMR of **2-A** in $CDCl_3$



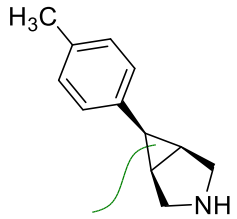

^{1}H NMR of **3-A** in $CDCl_3$
F_3C
NH
11.07
7.66
7.65
7.36
7.34
7.26
6.26
3.60
3.57
3.30
3.27
2.50
2.48
2.46
2.29
2.28
2.27
-0.00
0.70
1.97
2.00
0.86
2.15
2.28
1.00
1.96
f1 (ppm)


^{13}C NMR of **3-A** in $CDCl_3$
135.8
131.1
130.8
130.5
130.3
130.0
127.1
126.8
126.7
126.7
126.7
124.9
122.8
120.6
77.3
77.0
76.8
44.8
24.2
22.2
-0.0
F_3C
NH
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

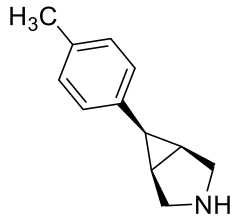
^{19}F NMR of **3-A** in $CDCl_3$



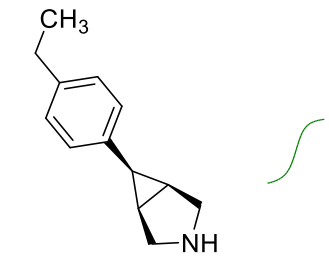
^{1}H NMR of **5-A** in $CDCl_3$



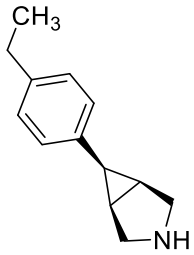
^{13}C NMR of **5-A** in $CDCl_3$



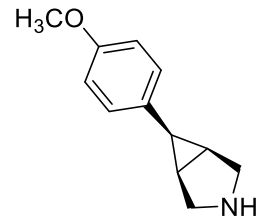
^{1}H NMR of **6-A** in $CDCl_3$



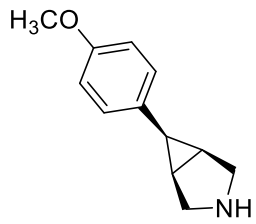
^{13}C NMR of **6-A** in $CDCl_3$



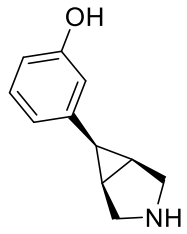
^{1}H NMR of **7-A** in $CDCl_3$



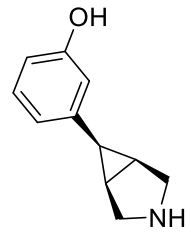
^{13}C NMR of **7-A** in $CDCl_3$



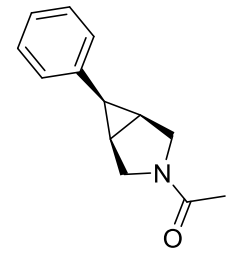
^{1}H NMR of **11-A** in $CDCl_3$



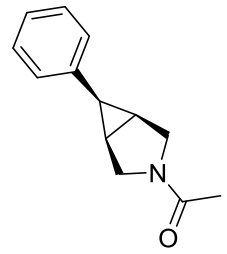
^{13}C NMR of **11-A** in $CDCl_3$



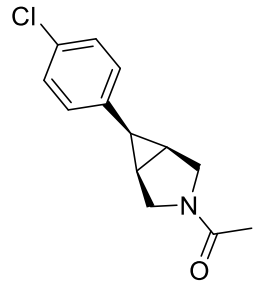
^{1}H NMR of **1-B** in $CDCl_3$



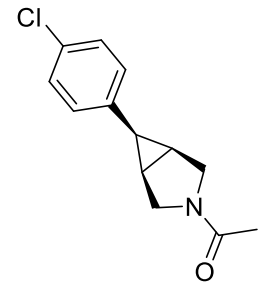
^{13}C NMR of **1-B** in $CDCl_3$



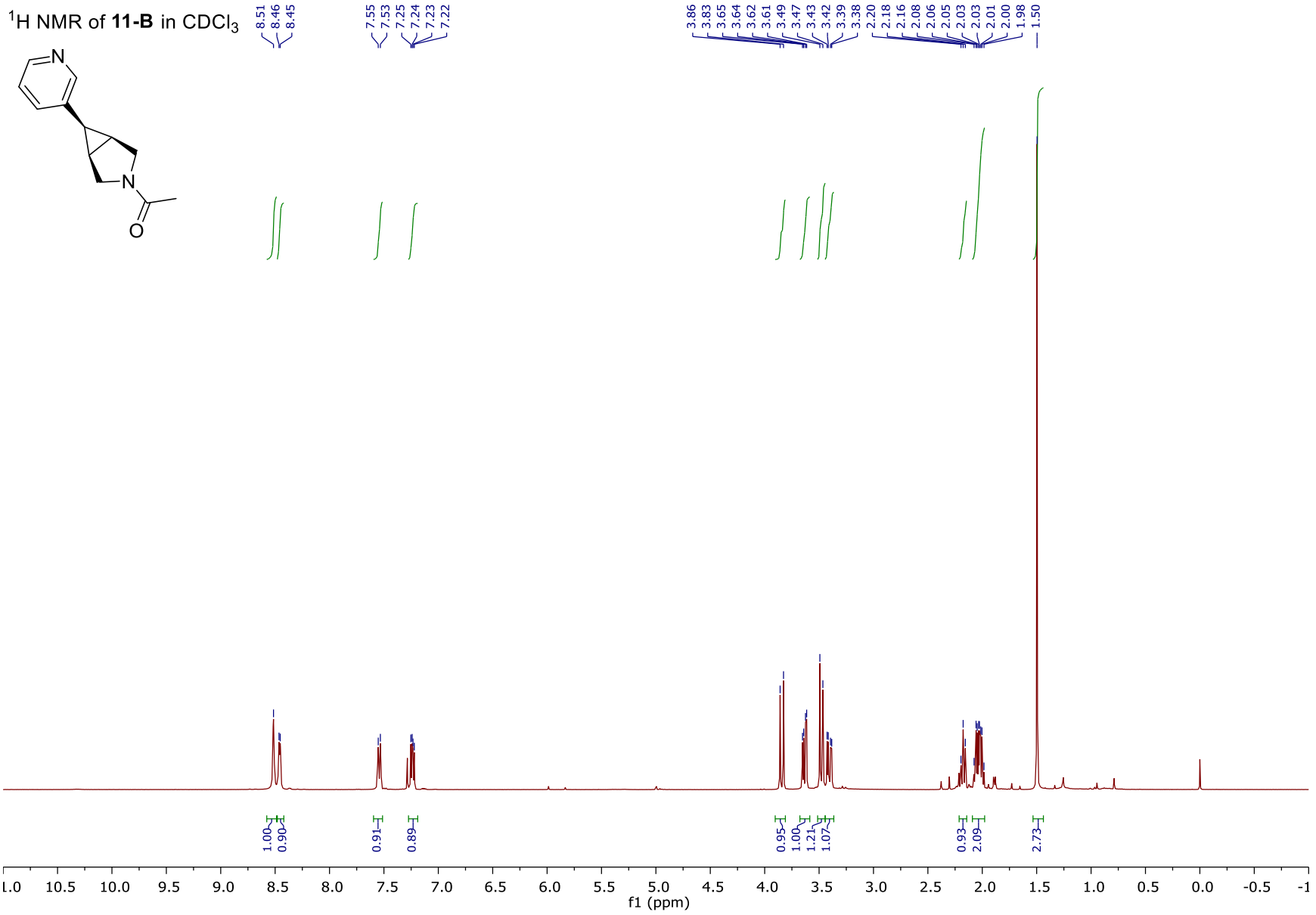
^{1}H NMR of **4-B** in $CDCl_3$



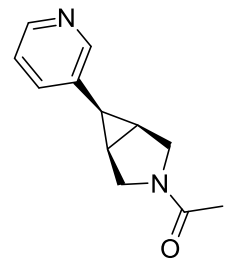
^{13}C NMR of **4-B** in $CDCl_3$



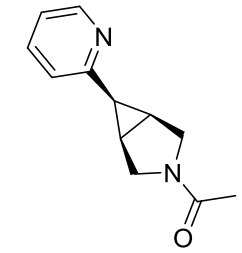
^{1}H NMR of **11-B** in $CDCl_3$



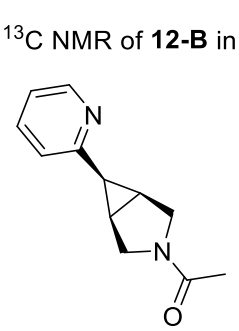
^{13}C NMR of **11-B** in $CDCl_3$



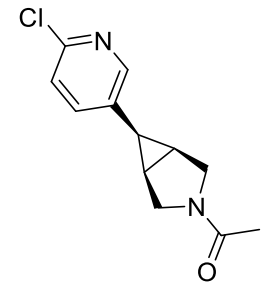
^{1}H NMR of **12-B** in CD_3CN



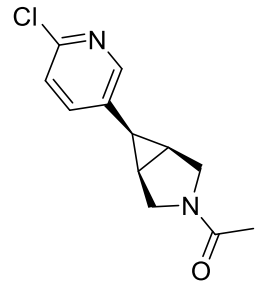
^{13}C NMR of **12-B** in CD_3CN



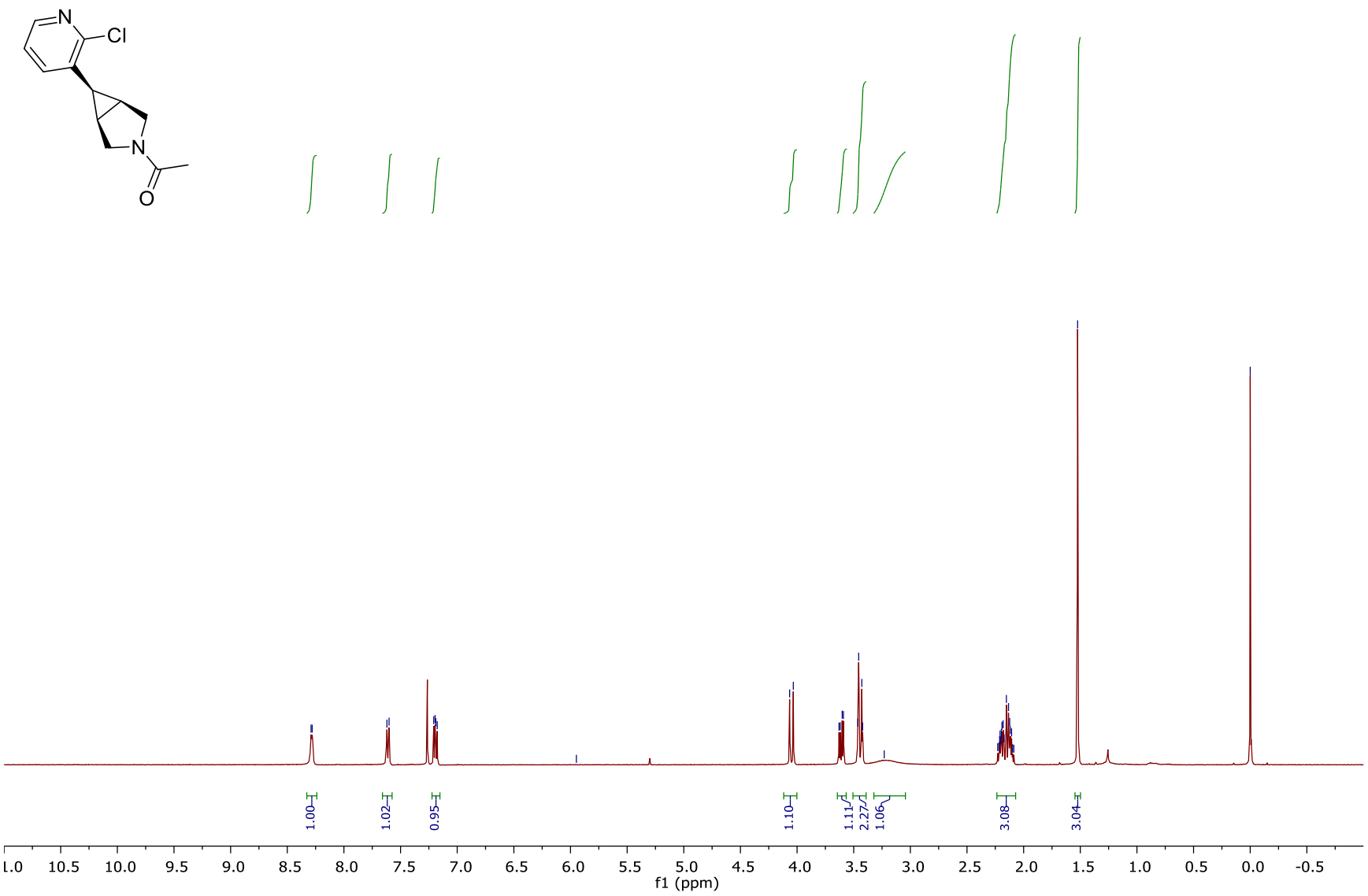
^{1}H NMR of **14-B** in $CDCl_3$



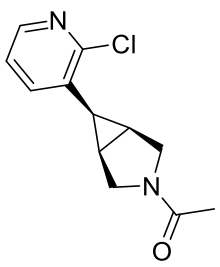
^{13}C NMR of **14-B** in $CDCl_3$

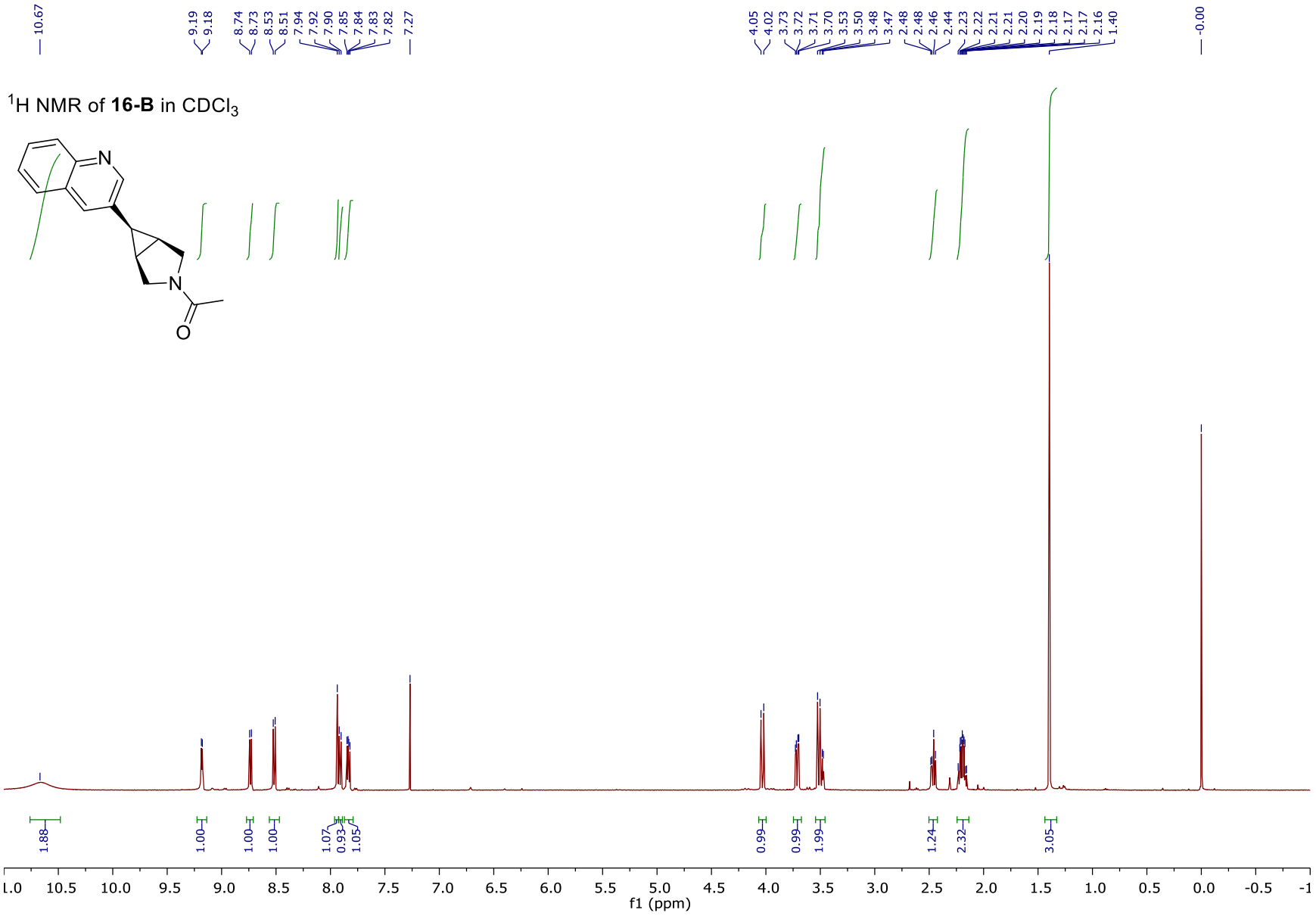


^{1}H NMR of **15-B** in $CDCl_3$



^{13}C NMR of **15-B** in $CDCl_3$




10.67
9.19
9.18
8.74
8.73
8.53
8.51
7.94
7.92
7.90
7.85
7.84
7.83
7.82
7.27
4.05
4.02
3.73
3.72
3.71
3.70
3.53
3.50
3.48
3.47
2.48
2.48
2.46
2.44
2.23
2.22
2.21
2.21
2.20
2.19
2.18
2.17
2.17
2.16
1.40
-0.00
1H NMR of 16-B in CDCl3
N
N
O
1.88
1.00
1.00
1.00
1.07
0.93
1.05
0.99
0.99
1.99
1.24
2.32
3.05
f1 (ppm)

^{13}C NMR of **16-B** in $CDCl_3$