Supporting Information

Synthesis of Annulated Pyridines as Inhibitors of Aldosterone Synthase (CYP11B2)

Rainer E. Martin,* Johannes Lehmann, Thibaut Alzieu, Mario Lenz, Marjorie A. Carnero Corrales, Johannes D. Aebi, Hans Peter Märki, Bernd Kuhn, Kurt Amrein, Alexander V. Mayweg and Robert Britton*

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1. General Information on Analytical Compound Characterization

^{1}H Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Avance III 600 MHz spectrometer. In the ^{1}H NMR spectra, signal positions (δ) are given in parts per million (ppm) from tetramethylsilane ($\delta = 0$) and were measured relative to the signal of $CDCl_3$ ($\delta =$ 7.26 ppm) or DMSO-d_6 ($\delta = 2.50$ ppm). Resonances in the ^{1}H NMR spectra are reported to the nearest 0.01 ppm. ^{13}C NMR spectra were recorded using the same spectrometer (150 MHz), and signal positions (δ) are given in parts per million (ppm) from tetramethylsilane ($\delta = 0$) and were measured relative to the signal of $CDCl_3$ ($\delta = 77.16$ ppm) or DMSO-d_6 ($\delta =$ 39.52 ppm) and reported to the nearest 0.1 ppm. ^{19}F NMR resonances are reported in ppm and the chemical shift of the lock solvent ($CDCl_3$ or DMSO-d_6) was used as an internal reference. The multiplicities of signals are given as s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broadened and combinations thereof. Coupling constants (J) are reported to the nearest 0.1 Hz.

High resolution mass spectrometry (HRMS) was performed on a Finnigan LTQ FT MS or a Agilent 6520 spectrometer using time of flight (TOF) with positive ESI at 70 eV within a tolerance of ± 5 ppm of the theoretical value.

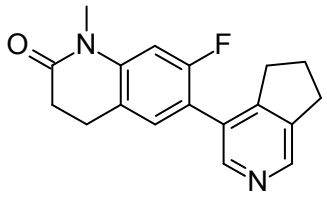
IR spectra were recorded using attenuated total reflectance (ATR) on a Nicolet 6700 from Thermo Scientific.

All compounds in this work have been isolated by MPLC (medium pressure liquid chromatography, CombiFlash Companion, Isco Inc.) or silica column chromatography for the purpose of analytical characterization.

2. Experimental Procedures for Batch and Flow Reactions and Characterization Data

High temperature flow chemistry experiments were conducted on a system very similar to one previously described.[1,2] A Dionex P580 pump was connected to a Supelco stainless steel tube reactor (dimensions: length x OD (ID) = 15.2 m x 3.2 mm (2.1 mm), 53 mL total volume; Supelco premium grade 304 stainless steel tubing, product reference number: 2-0526-U) followed by a small stainless-steel tube (6.6 mm bore and 100 mm length) filled with a short silica plug and glass wool to protect the back-pressure regulator. A HP 6890 Series Gas Chromatography (GC) oven was used as the heating source. Using an appropriate back pressure regulator (BPR), the system was maintained at a total pressure of 750 psi (51.7 bar) in order to keep toluene in the liquid state under the superheated conditions.

6-(6,7-Dihydro-5*H*-cyclopenta[*c*]pyridin-4-yl)-7-fluoro-1-methyl-3,4-dihydroquinolin-2-one (11)

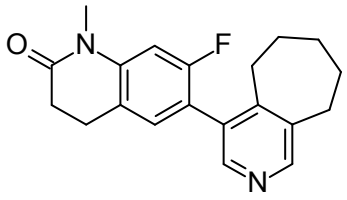


To a solution of 7-fluoro-1-methyl-6-oxazol-5-yl-3,4-dihydroquinolin-2-one (5.0 mg, 20.3 µmol, 1 equiv) in *o*-dichlorobenzene (500 µL) was added cyclopentene (350 mg, 500 µL, 5.14 mmol, 253 equiv) and trifluoroacetic acid (4.63 mg, 3.13 µL, 40.6 µmol, 2 equiv). The reaction mixture was heated by microwave irradiation to 200 °C for 10 h. After being cooled to room temperature, the crude product was purified by medium pressure liquid chromatography eluting with a gradient of *n*-heptane / ethyl acetate (7:3 → 1:1) followed by dichloromethane / methanol (9:1). The title compound was isolated as light brown solid (1.1 mg, 18%) next to starting material (2.0 mg, 40%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.09 (quin, J = 7.5 Hz, 2H), 2.67 – 2.72 (m, 2H), 2.86 (t, J = 7.4 Hz, 2H), 2.92 (t, J = 7.4 Hz, 2H), 3.01 (t, J = 7.4 Hz, 2H), 3.36 (s, 3H), 6.81 (d, J = 11.6 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 8.33 (s, 1H), 8.46 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 24.9, 25.1, 29.8, 30.8, 31.8, 32.38, 32.42, 103.2 (d, J_{CF} = 28.1 Hz), 119.0 (d, J_{CF} = 16.5 Hz), 122.0 (d, J_{CF} = 3.3 Hz), 128.1, 129.9 (d, J_{CF} = 5.0 Hz), 140.1, 142.0 (d, J_{CF} = 10.2 Hz), 145.0,

147.5, 152.9, 159.1 (d, J_{CF} = 245.7 Hz), 170.2 ppm. ^{19}F NMR (375 MHz, $CDCl_3$): δ -115.1 ppm. HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{18}H_{17}FN_2O$ 296.1325, found 296.1332.

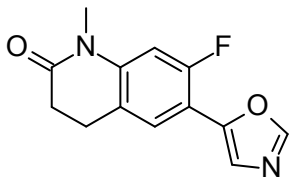
7-Fluoro-1-methyl-6-(6,7,8,9-tetrahydro-5*H*-cyclohepta[*c*]pyridin-4-yl)-3,4-dihydroquinolin-2-one (12)



To 7-fluoro-1-methyl-6-oxazol-5-yl-3,4-dihydroquinolin-2-one (32.0 mg, 130 μmol, 1 equiv) in *o*-dichlorobenzene (500 μL) was added cycloheptene (0.50 g, 0.6 mL, 5.14 mmol, 40 equiv) and the mixture was diluted with toluene to a total volume of 2.5 mL. Trifluoroacetic acid (50.3 mg, 34 μL, 0.44 mmol, 3.4 equiv) was then added and the reaction mixture applied to the flow coil and buffered by 1 mL of a mixture of cycloheptene (0.50 g, 0.6 mL, 5.14 mmol, 40 equiv) and trifluoroacetic acid (50.3 mg, 34 μL, 0.44 mmol, 3.4 equiv) in toluene before and after injection. The residence time of the reaction mixture was adjusted such that it remained in the heated area (230 °C) for 2 hours (factoring in volume expansion of the solvent, the $t_{R,\ eff}$ = 0.35 mL min^{-1}). The crude product was collected into a vial containing triethylamine (5 mL). The flow-coil was cooled to 100 °C and flushed with 1 column volume (53 mL) of MeOH, which was also collected and combined with crude product. Solvents were removed under reduced pressure and the crude product was purified by silica column chromatography eluting with dichloromethane / ethyl acetate (2:1) to provide the title compound as a light brown solid (8.0 mg, 18%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.58 – 1.62 (m, 2H), 1.70 – 1.71 (m, 2H), 1.82 – 1.88 (m, 2H), 2.64 – 2.68 (m, 2H), 2.71 (t, *J* = 7.4 Hz, 2H), 2.84 – 2.88 (m, 2H), 2.92 (t, *J* = 7.4 Hz, 2H), 3.37 (s, 3H), 6.79 (d, *J* = 11.1 Hz, 1H), 7.00 (d, *J* = 7.9 Hz, 1H), 8.24 (s, 1H), 8.33 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 24.9, 26.9, 27.9, 29.8, 31.8 (2 C), 32.6, 33.5, 102.9 (d, J_{CF} = 27.8 Hz), 119.5 (d, J_{CF} = 16.8 Hz), 121.9 (d, J_{CF} = 3.6 Hz), 130.2, 130.5 (d, J_{CF} = 4.7 Hz), 139.0, 142.0 (d, J_{CF} = 9.9 Hz), 148.6, 148.9, 151.3, 159.2 (d, J_{CF} = 244.0 Hz), 170.3 ppm. ^{19}F NMR (375 MHz, $CDCl_3$): δ -114.5 ppm. HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{20}H_{21}FN_2O$ 324.1638, found 324.1646.

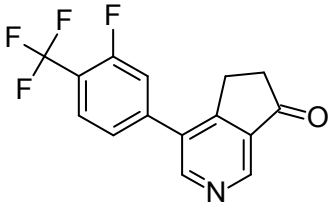
7-Fluoro-1-methyl-6-oxazol-5-yl-3,4-dihydroquinolin-2-one (14)

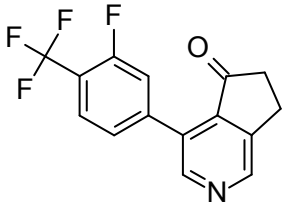


To 6-bromo-7-fluoro-1-methyl-3,4-dihydroquinolin-2-one (0.73 g, 2.84 mmol, 1 equiv) in anhydrous DMA (25 mL) was added pivalic acid (0.32 g, 3.14 mmol, 1.11 equiv), palladium(II) acetate (38.4 mg, 0.17 mmol, 0.06 equiv), 2-di-*tert*-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl (80.3 mg, 0.17 mmol, 0.059 equiv; Me4*t*ButylXPhos; CAS[857356-94-6]), oxazole (0.42 g, 0.40 mL, 6.08 mmol, 2.14 equiv) and potassium carbonate (1.08 g, 9.62 mmol, 3.4 equiv) under an atmosphere of Ar. The reaction mixture was heated by microwave irradiation to 110 °C for 18 h. After being cooled to room temperature, the crude product was purified by by silica column chromatography eluting with a gradient of *n*-heptane / ethyl acetate (9:1 → 1:1) to provide the title compound as a white solid (0.51 g, 73%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.67 – 2.70 (m, 2H), 2.93 – 2.96 (m, 2H), 3.35 (s, 3H), 6.80 (d, J = 12.4 Hz, 1H), 7.43 (d, J = 3.8 Hz, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.93 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 24.9, 29.8, 31.7, 103.3 (d, J_{CF} = 26.4 Hz), 110.2 (d, J_{CF} = 13.8 Hz), 122.3 (d, J_{CF} = 3.3 Hz), 124.98 (d, J_{CF} = 7.4 Hz), 125.03, 141.9 (d, J_{CF} = 10.2 Hz), 145.7 (d, J_{CF} = 3.6 Hz), 150.0, 158.3 (d, J_{CF} = 249.2 Hz), 170.1 ppm. ^{19}F NMR (375 MHz, $CDCl_3$): δ -112.6 ppm. HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{13}H_{11}FN_2O_2$ 246.0805, found 246.0802.

4-[3-Fluoro-4-(trifluoromethyl)phenyl]-5,6-dihydrocyclopenta[*c*]pyridin-7-one (15) and 4-[3-Fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydrocyclopenta[*c*]pyridin-5-one (17)





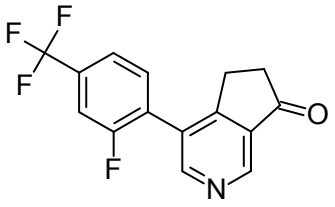
To a solution of 4-[3-fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine (76.0 mg, 0.27 mmol, 1 equiv; **9**) and dirhodium(II, III) tetrakis caprolactamate (1.8 mg, 0.0027 mmol, 0.01 equiv; synthesis described in M. P. Doyle *et al*., *J. Am. Chem. Soc.* 1993,

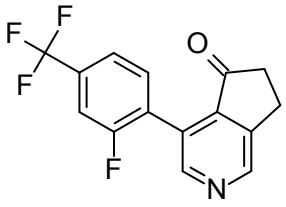
115, 958) in dichloromethane (0.5 mL) was added sodium bicarbonate (22.7 mg, 0.27 mmol, 1 equiv) and *tert*-butyl hydroperoxide (0.25 mL, 1.35 mmol, 5 equiv). The reaction mixture was stirred at room temperature for 48 h. During this time period additional equivalents of *tert*-butyl hydroperoxide (1.25 mL, 6.75 mmol, 25 equiv) were added in small portions. The solvent was removed under reduced pressure and the crude reaction mixture purified by medium pressure liquid chromatography eluting with a gradient of *n*-heptane / ethyl acetate (1:0 → 1:1) to provide 4-[3-fluoro-4-(trifluoromethyl)phenyl]-5,6-dihydrocyclopenta[*c*] pyridin-7-one (17.4 mg, 22%; **15**) and 4-[3-fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-cyclopenta[*c*]pyridin-5-one (15.5 mg, 19%; **17**) both as slightly yellow solids.

Product **15**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.77 – 2.79 (m, 2H), 3.22 – 3.24 (m, 2H), 7.35 (d, J = 10.9 Hz, 1H), 7.38 (d, J = 8.3 Hz, 1H), 7.78 (dd, J = 7.7, 7.7 Hz, 1H), 8.75 (s, 1H), 9.06 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 25.6, 36.2, 117.2 (d, J_{CF} = 21.5 Hz), 124.4 (d, J_{CF} = 3.9 Hz), 128.2 (d, J_{CF} = 6.3 Hz), 133.0, 133.6 (br), 142.0 (d, J_{CF} = 8.5 Hz), 146.6, 152.8, 160.3, 204.8 ppm (3 C not detected). ^{19}F NMR (375 MHz, $CDCl_3$): δ -61.4, -112.6 ppm. HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{15}H_9F_4NO$ 295.0620, found 295.0622.

Product **17**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.77 – 2.81 (m, 2H), 3.25 – 3.29 (m, 2H), 7.34 (d, J = 12.3 Hz, 1H), 7.34 (d, J = 6.3 Hz, 1H), 7.69 (dd, J = 7.7, 7.7 Hz, 1H), 8.57 (s, 1H), 8.96 (s, 1H). HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{15}H_9F_4NO$ 295.0620, found 295.0623.

4-[2-Fluoro-4-(trifluoromethyl)phenyl]-5,6-dihydrocyclopenta[*c*]pyridin-7-one (16) and 4-[2-Fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydrocyclopenta[*c*]pyridin-5-one (18)





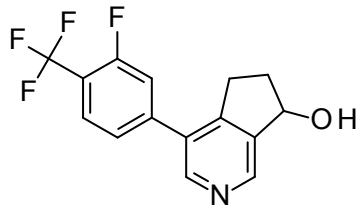
To a solution of 4-[2-fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine (99.8 mg, 0.34 mmol, 1 equiv; **10**) and dirhodium(II, III) tetrakis caprolactamate (2.2 mg, 0.0034 mmol, 0.01 equiv; synthesis described in M. P. Doyle *et al*., *J. Am. Chem. Soc.* 1993, **115**, 958) in dichloromethane (1.5 mL) was added sodium bicarbonate (28.3 mg, 0.34 mmol, 1 equiv) and *tert*-butyl hydroperoxide (0.31 mL, 1.69 mmol, 5 equiv). The reaction mixture was stirred at room temperature for 48 h. During this time period additional equivalents of *tert*-butyl hydroperoxide (1.25 mL, 6.75 mmol, 25 equiv) were added in small portions. The

solvent was removed under reduced pressure and the crude reaction mixture purified by medium pressure liquid chromatography eluting with a gradient of heptane / ethyl acetate (1:0 → 1:1) to provide 4-[2-fluoro-4-(trifluoromethyl)phenyl]-5,6-dihydrocyclopenta[*c*]pyridin-7-one (29.8 mg, 30%; **16**) and 4-[2-fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydrocyclopenta[*c*]-pyridin-5-one (19.9 mg, 20%; **18**) both as off-white solids.

Product **16**: ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.69 – 2.71 (m, 2H), 3.07 – 3.09 (m, 2H), 7.78 (dd, J = 8.0, 1.2 Hz, 1H), 7.84 – 7.87 (m, 1H), 7.95 (dd, J = 10.1, 1.3 Hz, 1H), 8.81 (d, J = 0.9 Hz, 1H), 8.95 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 24.9 (d, J_{CF} = 3.3 Hz), 35.8, 113.8 (qd, J_{CF} = 25.5, 3.9 Hz), 121.9 (dq, J_{CF} = 3.9, 3.9 Hz), 127.2 (qd, J_{CF} = 16.1, 1.1 Hz), 128.8, 132.5, 132.9 (d, J_{CF} = 3.0 Hz), 145.3, 153.4 (br), 159.1 (d, J_{CF} = 248.4), 162.1, 205.2 ppm (2 C not detected). HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{15}H_9F_4NO$ 295.0620, found 295.0626.

Product **18**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.76 – 2.78 (m, 2H), 3.26 – 3.28 (m, 2H), 7.44 – 7.49 (m, 2H), 7.52 – 7.54 (m, 1H), 8.57 (s, 1H), 8.98 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 23.5, 36.5, 113.2 (qd, J_{CF} = 25.5, 4.0 Hz), 121.2 (dq, J_{CF} = 3.9 Hz), 125.8, 126.5 (d, J_{CF} = 18.4 Hz), 131.8 (d, J_{CF} = 3.0 Hz), 140.2, 148.2, 149.0, 150.5, 160.1 (d, J_{CF} = 250.9), 204.9 ppm (2 C not detected). ^{19}F NMR (375 MHz, $CDCl_3$): δ -62.8, -112.1 ppm. HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{15}H_9F_4NO$ 295.0620, found 295.0630.

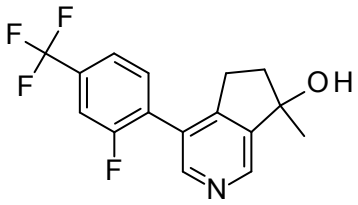
4-[3-Fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-7-ol (19)



To a solution of 4-[3-fluoro-4-(trifluoromethyl)phenyl]-5,6-dihydrocyclopenta[*c*]pyridin-7-one (20 mg, 67.7 µmol, 1 equiv) in methanol (1 mL) was added sodium borohydride (2.56 mg, 67.7 µmol, 1 equiv) at 0 °C under Ar. After 10 min, the reaction was quenched by addition of acetic acid (0.5 mL) and the crude reaction mixture concentrated under reduced pressure. A saturated aqueous solution of sodium bicarbonate (5 mL) was added and the aqueous phase extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and the crude product purified by preparative thin layer chromatography using dichloromethane / methanol (10:1). The title compound was isolated as light yellow oil (16.1 mg, 80%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.05 (dddd, J = 13.5, 8.3, 6.35, 5.2 Hz, 1H), 2.53 (dddd, J = 13.4, 8.2, 6.8, 5.0 Hz, 1H), 2.91 (ddd, J = 17.0, 8.2, 6.5 Hz, 1H), 3.15 (ddd, J = 17.0, 8.4, 5.0 Hz, 1H), 5.44 – 5.46 (m, 1H), 7.29 (d, J = 11.0 Hz, 1H), 7.32 (d, J = 8.1 Hz, 1H), 7.71 (dd, J = 7.7, 7.7 Hz, 1H), 8.52 (s, 1H), 8.70 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 29.7, 36.0, 74.7, 117.0 (d, J_{CF} = 21.2 Hz), 118.0 (dd, J_{CF} = 33.3, 12.7 Hz), 122.7 (q, J_{CF} = 272.9 Hz), 124.3 (d, J_{CF} = 3.6 Hz), 127.8 (q, J_{CF} = 2.1 Hz), 131.9, 141.7, 143.5 (d, J_{CF} = 8.3 Hz), 146.3, 148.4, 150.7, 159.9 (dq, J_{CF} = 257.2, 2.0 Hz) ppm. ^{19}F NMR (375 MHz, $CDCl_3$): δ -61.3, -113.4 ppm. HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{15}H_{11}F_4NO$ 297.0777, found 297.0788.

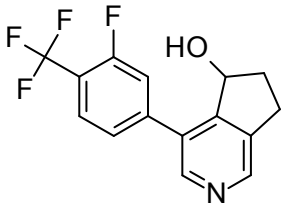
4-[2-Fluoro-4-(trifluoromethyl)phenyl]-7-methyl-5,6-dihydrocyclopenta[*c*]pyridin-7-ol (20)



To a solution of 4-[2-fluoro-4-(trifluoromethyl)phenyl]-5,6-dihydrocyclopenta[*c*]pyridin-7-one (25 mg, 84.7 µmol, 1 equiv) in diethyl ether (3 mL) was added lithium chloride (10.9 mg, 257 µmol, 3 equiv) and methyllithium (63 µl, 101 µmol, 1.2 equiv; 1.6 M solution in diethyl ether) at 0 °C under Ar. After stirring for 1 h, the reaction mixture was left warming up to rt and stirring was continued. After 3 h, the reaction was quenched by addition of a saturated aqueous solution of ammonium chloride (10 mL) and the aqueous phase extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and the crude product purified by preparative thin layer chromatography using dichloromethane / methanol (10:1). The title compound was isolated as light yellow oil (10.0 mg, 38%).

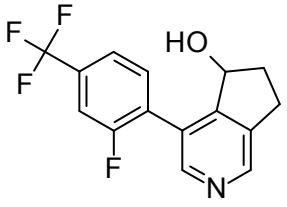
^{1}H NMR (600 MHz, $CDCl_3$): δ 1.67 (br s, 1H), 1.71 (s, 3H), 2.21 – 2.29 (m, 2H), 2.80 (dt, J = 17.1, 7.1 Hz, 1H), 2.97 – 3.02 (m, 1H), 7.47 – 7.48 (m, 2H), 7.53 – 7.55 (m, 1H), 8.49 (s, 1H), 8.68 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 27.7, 29.0, 42.2, 80.7, 113.7 (qd, J_{CF} = 25.9, 3.9 Hz), 121.5 (dq, J_{CF} = 4.1, 4.1 Hz), 127.7 (br), 132.1 (d, J_{CF} = 3.9 Hz), 144.2, 144.9, 149.2, 151.4, 159.6 (d, J_{CF} = 250.3 Hz) ppm (3 C not detected). ^{19}F NMR (375 MHz, $CDCl_3$): δ -61.3, -113.4 ppm. HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{16}H_{13}F_4NO$ 311.0933, found 311.0941.

4-[3-Fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-5-ol (21)



To a solution of 4-[3-fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydrocyclopenta[*c*]pyridin-5-one (15.9 mg, 53.9 µmol, 1 equiv) in methanol (1 mL) was added sodium borohydride (2.04 mg, 53.9 µmol, 1 equiv) at 0 °C under Ar. After 10 min, the reaction was quenched by addition of acetic acid (0.5 mL) and the crude reaction mixture concentrated under reduced pressure. A saturated aqueous solution of sodium bicarbonate (5 mL) was added and the aqueous phase extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and the crude product purified by medium pressure liquid chromatography eluting with a gradient of dichloromethane / isopropanol (1:0 → 1:0.05). The title compound was isolated as white solid (14.1 mg, 88%).
^{1}H NMR (600 MHz, $CDCl_3$): δ 2.12 – 2.17 (m, 1H), 2.39 – 2.45 (m, 1H), 2.97 (ddd, J = 16.7, 8.56, 3.8 Hz, 1H), 3.24 – 3.29 (m, 1H), 5.35 (br s, 1H), 7.51 (d, J = 8.1 Hz, 1H), 7.56 (d, J = 11.3 Hz, 1H), 7.72 (dd, J = 7.7, 7.7 Hz, 1H), 8.51 (s, 1H), 8.62 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 27.9, 35.7, 74.7, 117.6 (d, J_{CF} = 21.6 Hz), 117.6 (d, J_{CF} = 21.6 Hz), 122.7 (q, J_{CF} = 272.9 Hz), 124.7 (d, J_{CF} = 3.5 Hz), 127.6 (qd, J_{CF} = 4.4, 2.1 Hz), 140.0 (qd, J_{CF} = 7.3, 2.8 Hz), 143.5 (dq, J_{CF} = 8.3, 1.3 Hz), 147.0, 147.7, 150.4, 159.9 (dq, J_{CF} = 256.9, 2.1 Hz) ppm (1 C not detected). ^{19}F NMR (375 MHz, $CDCl_3$): δ -61.3, -113.5 ppm. HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{15}H_{11}F_4NO$ 297.0777, found 297.0785.

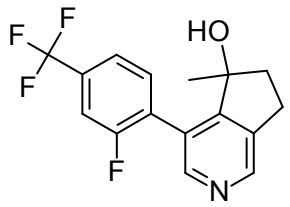
4-[2-Fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-5-ol (22)



To a solution of 4-[2-fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydrocyclopenta[*c*]pyridin-5-one (37.0 mg, 125 µmol, 1 equiv)) in methanol (1 mL) was added sodium borohydride (4.74

mg, 125 µmol, 1 equiv) at 0 °C under Ar. After 10 min, the reaction was quenched by addition of acetic acid (0.5 mL) and the crude reaction mixture concentrated under reduced pressure. A saturated aqueous solution of sodium bicarbonate (5 mL) was added and the aqueous phase extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and the crude product purified by medium pressure liquid chromatography eluting with a gradient of dichloromethane / isopropanol (1:0 → 1:0.05). The title compound was isolated as white solid (24.7 mg, 66%).
^{1}H NMR (600 MHz, $CDCl_3$): δ 2.01 – 2.06 (m, 1H), 2.51 (dddd, J = 13.5, 8.3, 6.8, 5.4 Hz, 1H), 2.92 – 2.98 (m, 1H), 3.19 (ddd, J = 16.2, 8.3, 5.3 Hz, 1H), 5.36 (dd, J = 5.7, 5.7 Hz, 1H), 7.47 (dd, J = 9.7, 1.4 Hz, 1H), 7.54 (dd, J = 8.0, 1.0 Hz, 1H), 7.59 – 7.61 (m, 1H), 8.44 (s, 1H), 8.61 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 27.8, 35.9, 75.6 (d, J = 3.6 Hz), 113.5 (qd, J_{CF} = 25.9, 3.6 Hz), 121.5 (dq, J_{CF} = 4.1, 4.1 Hz), 127.2 (br), 132.2 (d, J_{CF} = 3.6 Hz), 139.2, 147.1, 148.5, 151.9, 159.6 (d, J_{CF} = 249.0 Hz) ppm (3 C not detected). HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{15}H_{11}F_4NO$ 297.0777, found 297.0784.

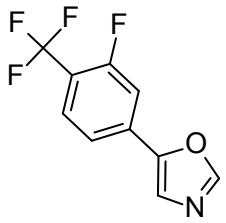
4-[2-Fluoro-4-(trifluoromethyl)phenyl]-5-methyl-6,7-dihydrocyclopenta[*c*]pyridin-5-ol (23)



To a solution of 4-[2-fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydrocyclopenta[*c*]pyridin-5-one (25 mg, 84.7 µmol, 1 equiv) in diethyl ether (3 mL) was added lithium chloride (10.9 mg, 257 µmol, 3 equiv) and methyllithium (63 µl, 101 µmol, 1.2 equiv; 1.6 M solution in diethyl ether) at 0 °C under Ar. After stirring for 1 h, the reaction mixture was left warming up to rt and stirring was continued. After 3 h, the reaction was quenched by addition of saturated aqueous solution of ammonium chloride (10 mL) and the aqueous phase extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and the crude product purified by preparative thin layer chromatography using *n*-heptane / ethyl acetate (10:1). The title compound was isolated as white solid (6.1 mg, 23%).
^{1}H NMR (600 MHz, $CDCl_3$): δ 1.28 (s, 3H), 1.84 (br d, J = 2.0 Hz, 1H), 2.21 – 2.24 (m, 2H), 2.88 – 2.93 (m, 1H), 3.11 (dt, J = 16.3, 6.6 Hz, 1H), 7.45 (d, J = 8.6 Hz, 1H), 7.48 – 7.52 (m,

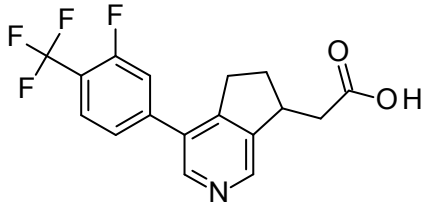
2H), 8.28 (s, 1H), 8.60 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 26.7, 27.0, 29.9, 43.0, 82.2, 113.3 (qd, J_{CF} = 25.6, 3.9 Hz), 121.0 (dq, J_{CF} = 4.1, 4.1 Hz), 126.5 (d, J_{CF} = 1.4 Hz), 128.7 (d, J_{CF} = 16.5 Hz), 133.0 (d, J_{CF} = 3.9 Hz), 147.3, 149.0, 154.0, 155.4, 159.7 (d, J_{CF} = 247.3 Hz) ppm (1 C not detected). ^{19}F NMR (375 MHz, $CDCl_3$): δ -62.8, -110.4 ppm. HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{16}H_{13}F_4NO$ 311.0933, found 311.0940.

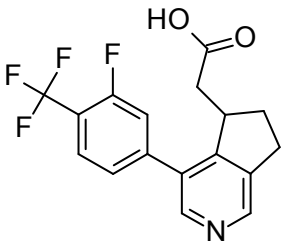
5-[3-Fluoro-4-(trifluoromethyl)phenyl]oxazole (24)



A solution of 3-fluoro-4-(trifluoromethyl)benzaldehyde (1.40 g, 7.07 mmol, 1 equiv) and *p*-toluenesulfonylmethyl isocyanide (1.53 g, 7.68 mmol, 1.1 equiv; TosMIC) in MeOH (100 mL) was treated with potassium carbonate (1.97 g, 14.14 mmol, 2 equiv) and the suspension heated to reflux for 14 h. After being cooled to room temperature, the solvent was removed under reduced pressure and the crude product triturated with water at 0 °C (2 x 25 mL). The slightly orange precipitate was collected by filtration and dried under vaccum (4.46 g, 92%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.49 (d, J = 11.3 Hz, 1H), 7.50 (s, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.67 (dd, J = 7.8, 7.8 Hz, 1H), 7.99 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 112.7 (d, J_{CF} = 23.1 Hz), 118.2 (qd, J_{CF} = 33.4, 12.8 Hz), 119.8 (d, J_{CF} = 3.9 Hz), 122.5 (q, J_{CF} = 272.1 Hz), 124.4, 128.2 (qd, J_{CF} = 4.5, 2.1 Hz), 133.4 (d, J_{CF} = 8.8 Hz), 149.3 (d, J_{CF} = 1.7 Hz), 151.7, 160.3 (dq, J_{CF} = 257.0, 2.2 Hz) ppm. ^{19}F NMR (375 MHz, $CDCl_3$): δ -61.3, -113.0 ppm. MS ES+ (*m/z*): $[M+H]^+$ 232.0.

2-[4-[3-Fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-7-yl]acetic acid (26) and 2-[4-[3-Fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-5-yl]acetic acid (27)

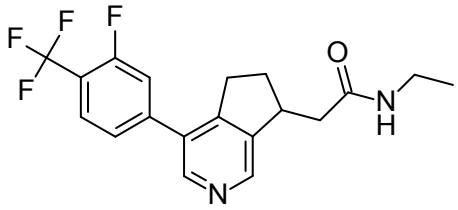




A solution of 5-[3-fluoro-4-(trifluoromethyl)phenyl]oxazole (0.30 g, 1.30 mmol, 1 equiv), 2-cyclopent-2-en-1-ylacetic acid (1.64 g, 13.0 mmol, 10 equiv; CAS[13668-61-6]) and trifluoroacetic acid (0.30 g, 2.60 mmol, 2 equiv) was heated neat under microwave irradiation to 180 °C for 17 h. After purification by medium pressure liquid chromatography eluting with a gradient of heptane / ethyl acetate (1:0 → 0:1) the title compounds were obtained as slightly brown oil (36%; approximate 1:1 mixture). The subsequent reactions were conducted without further separation of the two regioisomers. MS ES+ (*m/z*): $[M+H]^+$ 340.2.

The isomeric carboxylic acids **26** and **27** were difficult to separate by flash coloumn chromatography. Consequently, this purified mixture of acids was converted directly into amides **28-32**, which were separable from the corresponding isomeric amides and were fully characterized.

***N*-Ethyl-2-[4-[3-fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-7-yl]acetamide (28)**

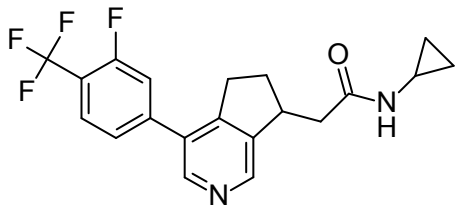


A solution of 2-[4-[3-fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-7-yl]acetic acid and 2-[4-[3-fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]-pyridin-5-yl]acetic acid one (50 mg, 0.15 mmol, 1 equiv) and *N,N*-diisopropylethylamine (0.13 mL, 0.74 mmol, 5 equiv) in DMF (0.4 mL) under Ar was treated with 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluoro-

phosphate (72.9 mg, 0.19 mmol, 1.3 equiv; HATU). To this solution was added ethylamine (0.22 mL, 0.44 mmol, 3 equiv; 2.0 M solution in MeOH) and the reaction mixture stirred at rt for 16 h. Evaporation of the solvent mixture and purification by preparative HPLC on reversed phase eluting with a gradient of acetonitrile - water provided the title compound as white solid (8.1 mg, 30%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.17 (t, J = 7.3 Hz, 3H), 1.80 (dddd, J = 12.8, 7.7, 7.7, 7.7 Hz, 1H), 2.39 (dd, J = 14.5, 8.1 Hz, 1H), 2.46 (dddd, J = 13.0, 7.8, 7.7, 5.3 Hz, 1H), 2.65 (dd, J = 14.5, 6.5 Hz, 1H), 2.91 – 3.01 (m, 2H), 3.33 – 3.37 (m, 2H), 3.82 – 3.87 (m, 1H), 5.53 (br s, 1H), 7.27 – 7.32 (m, 2H), 7.69 (dd, J = 7.6, 7.6 Hz, 1H), 8.48 (br s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 15.1, 31.0, 32.3, 34.7, 40.3, 41.9, 117.0 (d, J_{CF} = 21.2 Hz), 117.8 (qd, J_{CF} = 33.2, 12.5 Hz), 122.7 (q, J_{CF} = 272.1 Hz), 124.3 (d, J_{CF} = 3.6 Hz), 127.6 (qd, J_{CF} = 4.4, 2.1 Hz), 131.9 (br), 143.1 (br), 144.0 (dq, J_{CF} = 8.0, 1.3 Hz), 145.3 (br), 147.2 (br), 151.1, 159.9 (dq, J_{CF} = 256.9, 2.1 Hz), 170.8 ppm. ^{19}F NMR (375 MHz, $CDCl_3$): δ -61.3, -113.7 ppm. HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{19}H_{18}F_4N_2O$ 366.1355, found 366.1378.

_N_-Cyclopropyl-2-[4-[3-fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5_H_-cyclopenta[_c_]pyridin-7-yl]acetamide (29)

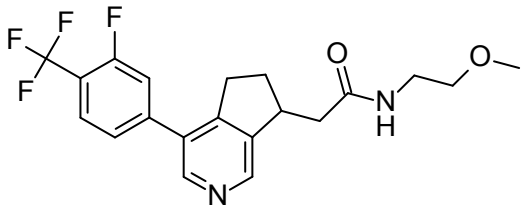


A solution of 2-[4-[3-fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-7-yl]acetic acid and 2-[4-[3-fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]-pyridin-5-yl]acetic acid one (50 mg, 0.15 mmol, 1 equiv) and *N,N*-diisopropylethylamine (0.13 mL, 0.74 mmol, 5 equiv) in DMF (0.4 mL) under Ar was treated with 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluoro-phosphate (72.9 mg, 0.19 mmol, 1.3 equiv; HATU). To this solution was added cyclopropylamine (25.1 mg, 30.5 µL, 0.44 mmol, 3 equiv) and the reaction mixture stirred at rt for 16 h. Evaporation of the solvent mixture and purification by preparative HPLC on reversed phase eluting with a gradient of acetonitrile - water provided the title compound as light brown solid (5.9 mg, 21%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 0.48 – 0.55 (m, 2H), 0.79 – 0.83 (m, 2H), 1.79 (dq, J = 12.8, 7.7, 7.7, 7.7 Hz, 1H), 2.36 (dd, J = 14.5, 8.1 Hz, 1H), 2.46 (dtd, J = 13.0, 7.8, 5.5 Hz, 1H),

2.62 (dd, J = 14.6, 6.5 Hz, 1H), 2.74 – 2.78 (m, 1H), 2.95 – 2.99 (m, 2H), 3.84 (ddd, J = 7.4, 7.4, 7.4 Hz, 1H), 5.61 (br s, 1H), 7.28 (d, J = 11.5 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H), 7.70 (dd, J = 7.7, 7.7 Hz, 1H), 8.45 (s, 1H), 8.48 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 6.9, 22.9, 31.0, 32.3, 40.2, 41.6, 117.0 (d, J_{CF} = 20.9 Hz), 124.3 (d, J_{CF} = 3.6 Hz), 127.7 (qd, J_{CF} = 4.4, 2.1 Hz), 131.7, 142.7, 144.1 (dq, J_{CF} = 8.0, 1.3 Hz), 145.3, 147.2, 151.3, 159.9 (dq, J_{CF} = 256.9, 2.1 Hz), 172.4 ppm (2 C not detected). HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{20}H_{18}F_4N_2O$ 378.1355, found 378.1374.

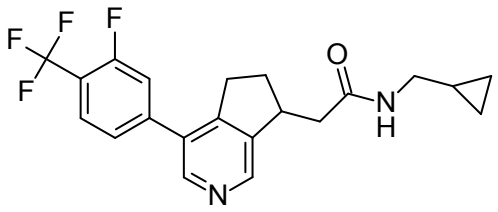
2-[4-[3-Fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-7-yl]-*N*-(2-methoxyethyl)acetamide (30)



A solution of 2-[4-[3-fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-7-yl]acetic acid and 2-[4-[3-fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]-pyridin-5-yl]acetic acid one (50 mg, 0.15 mmol, 1 equiv) and *N,N*-diisopropylethylamine (0.13 mL, 0.74 mmol, 5 equiv) in DMF (0.4 mL) under Ar was treated with 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluoro-phosphate (72.9 mg, 0.19 mmol, 1.3 equiv; HATU). To this solution was added 2-methoxyethanamine (33.1 mg, 38.3 µL, 0.44 mmol, 3 equiv) and the reaction mixture stirred at rt for 16 h. Evaporation of the solvent mixture and purification by preparative HPLC on reversed phase eluting with a gradient of acetonitrile - water provided the title compound as light brown solid (7.4 mg, 25%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.79 – 1.85 (m, 1H), 2.42 – 2.49 (m, 2H), 2.69 (dd, J = 14.7, 6.6 Hz, 1H), 2.94 – 3.04 (m, 2H), 3.36 (s, 3H), 3.46 – 3.52 (m, 4H), 3.84 (dddd, J = 7.4, 7.4, 7.4, 7.4 Hz, 1H), 5.97 (br s, 1H), 7.28 (d, J = 11.1 Hz, 1H), 7.32 (d, J = 8.2 Hz, 1H), 7.70 (dd, J = 7.7, 7.7 Hz, 1H), 8.47 (s, 1H), 8.51 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 31.1, 32.3, 39.4, 40.2, 41.5, 58.9, 71.2, 117.0 (d, J_{CF} = 21.2 Hz), 118.0 (qd, J_{CF} = 33.2, 12.5 Hz), 122.6 (q, J_{CF} = 272.1 Hz), 124.3 (d, J_{CF} = 3.6 Hz), 127.7 (qd, J_{CF} = 4.4, 2.1 Hz), 132.0, 143.2, 143.5 (d, J_{CF} = 8.0 Hz), 144.7, 146.6, 152.4, 159.9 (dq, J_{CF} = 259.4, 2.1 Hz), 171.0 ppm. HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{20}H_{20}F_4N_2O_2$ 396.1461, found 396.1472.

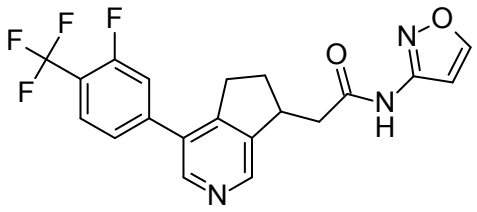
***N*-(Cyclopropylmethyl)-2-[4-[3-fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-7-yl]acetamide (31)**



A solution of 2-[4-[3-fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-7-yl]acetic acid and 2-[4-[3-fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]-pyridin-5-yl]acetic acid one (50 mg, 0.15 mmol, 1 equiv) and *N,N*-diisopropylethylamine (0.13 mL, 0.74 mmol, 5 equiv) in DMF (0.4 mL) under Ar was treated with 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluoro-phosphate (72.9 mg, 0.19 mmol, 1.3 equiv; HATU). To this solution was added cyclopropylmethylamine (31.3 mg, 38.2 µL, 0.44 mmol, 3 equiv) and the reaction mixture stirred at rt for 16 h. Evaporation of the solvent mixture and purification by preparative HPLC on reversed phase eluting with a gradient of acetonitrile - water provided the title compound as light brown solid (10.0 mg, 34%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 0.19 – 0.24 (m, 2H), 0.50 – 0.55 (m, 2H), 0.93 – 1.00 (m, 1H), 1.78 – 1.84 (m, 1H), 2.40 – 2.49 (m, 2H), 2.67 (dd, J = 14.5, 6.6 Hz, 1H), 2.94 – 3.02 (m, 2H), 3.13 – 3.21 (m, 2H), 3.85 (dddd, J = 7.4, 7.4, 7.4, 7.4 Hz, 1H), 5.64 (br s, 1H), 7.28 (d, J = 11.1 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.70 (dd, J = 7.7, 7.7 Hz, 1H), 8.44 (s, 1H), 8.49 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 3.58, 3.64, 10.9, 31.0, 32.3, 40.3, 41.9, 44.7, 117.0 (d, J_{CF} = 21.2 Hz), 117.8 (qd, J_{CF} = 33.2, 12.5 Hz), 122.7 (q, J_{CF} = 272.9 Hz), 124.3 (d, J_{CF} = 3.6 Hz), 127.6 (qd, J_{CF} = 4.4, 2.1 Hz), 131.6, 142.7, 144.0 (d, J_{CF} = 7.7 Hz), 145.4, 147.3, 151.2, 159.9 (dq, J_{CF} = 257.2, 2.0 Hz), 170.9 ppm. HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{21}H_{20}F_4N_2O$ 392.1512, found 392.1529.

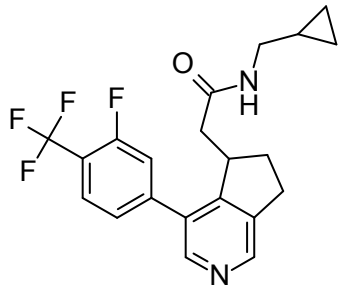
2-[4-[3-Fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-7-yl]-*N*-isoxazol-3-yl-acetamide (32)



A solution of 2-[4-[3-fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-7-yl]acetic acid and 2-[4-[3-fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]-pyridin-5-yl]acetic acid one (50 mg, 0.15 mmol, 1 equiv) and *N,N*-diisopropylethylamine (0.13 mL, 0.74 mmol, 5 equiv) in DMF (0.4 mL) under Ar was treated with 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluoro-phosphate (72.9 mg, 0.19 mmol, 1.3 equiv; HATU). To this solution was added isoxazol-3-amine (37.0 mg, 32.5 µL, 0.44 mmol, 3 equiv) and the reaction mixture stirred at rt for 16 h. Evaporation of the solvent mixture and purification by preparative HPLC on reversed phase eluting with a gradient of acetonitrile - water provided the title compound as light brown solid (5.8 mg, 19%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.87 – 1.93 (m, 1H), 2.50 – 2.56 (m, 1H), 2.70 (dd, J = 15.2, 8.6 Hz, 1H), 2.97 – 3.08 (m, 3H), 3.90 (dddd, J = 7.4, 7.4, 7.4, 7.4 Hz, 1H), 7.15 (d, J = 1.4 Hz, 1H), 7.29 (d, J = 11.1 Hz, 1H), 7.32 (d, J = 8.2 Hz, 1H), 7.71 (dd, J = 7.7, 7.7 Hz, 1H), 8.31 (d, J = 1.4 Hz, 1H), 8.48 (s, 1H), 8.55 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 31.0, 32.4, 39.9, 42.0, 99.6, 117.0 (d, J_{CF} = 21.2 Hz), 117.0 (d, J_{CF} = 21.2 Hz), 122.7 (q, J_{CF} = 272.1 Hz), 124.3 (d, J_{CF} = 3.6 Hz), 127.7 (qd, J_{CF} = 4.5, 1.6 Hz), 131.9 (br), 142.3, 143.7 (d, J_{CF} = 8.3 Hz), 145.2, 147.4, 151.4 (br), 157.6, 159.2, 159.9 (dq, J_{CF} = 257.2, 2.1 Hz), 169.6 ppm. HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{20}H_{15}F_4N_3O_2$ 405.1100, found 405.1115.

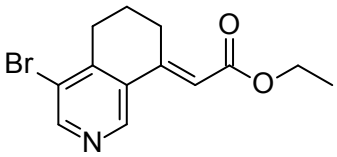
***N*-(Cyclopropylmethyl)-2-[4-[3-fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-5-yl]acetamide (33)**



A solution of 2-[4-[3-fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-7-yl]acetic acid and 2-[4-[3-fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]-pyridin-5-yl]acetic acid one (50 mg, 0.15 mmol, 1 equiv) and *N,N*-diisopropylethylamine (0.13 mL, 0.74 mmol, 5 equiv) in DMF (0.4 mL) under Ar was treated with 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluoro-phosphate (72.9 mg, 0.19 mmol, 1.3 equiv; HATU). To this solution was added cyclopropylmethylamine (31.3 mg, 38.2 µL, 0.44 mmol, 3 equiv) and the reaction mixture stirred at rt for 16 h. Evaporation of the solvent mixture and purification by preparative HPLC on reversed phase eluting with a gradient of acetonitrile - water provided the title compound as light yellow solid (6.0 mg, 20%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 0.11 – 0.16 (m, 2H), 0.43 – 0.50 (m, 2H), 0.81 – 0.87 (m, 1H), 1.87 (dd, J = 14.7, 10.5 Hz, 1H), 1.96 (dddd, J = 8.7, 8.7, 8.7, 4.8 Hz, 1H), 2.10 (dd, J = 14.7, 3.6 Hz, 1H), 2.40 – 2.48 (m, 1H), 2.95 – 3.09 (m, 4H), 4.05 (dddd, J = 10.5, 8.2, 3.9, 3.9 Hz, 1H), 5.24 (br s, 1H), 7.29 (d, J = 10.9 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.71 (dd, J = 7.7, 7.7 Hz, 1H), 8.32 (s, 1H), 8.52 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 3.45, 3.48, 10.7, 28.8, 30.7, 39.9, 40.9, 44.5, 117.1 (d, J_{CF} = 21.2 Hz), 122.6 (q, J_{CF} = 271.5 Hz), 124.4 (d, J_{CF} = 3.9 Hz), 127.9 (qd, J_{CF} = 4.7, 1.7 Hz), 131.8, 140.3, 144.0 (d, J_{CF} = 8.3 Hz), 146.5, 147.6, 152.7, 159.9 (dq, J_{CF} = 260.0, 2.0 Hz), 170.3 ppm (1 C not detected). HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{21}H_{20}F_4N_2O$ 392.1512, found 392.1522.

Ethyl (2*E*)-2-(4-bromo-6,7-dihydro-5*H*-isoquinolin-8-ylidene)acetate (35)

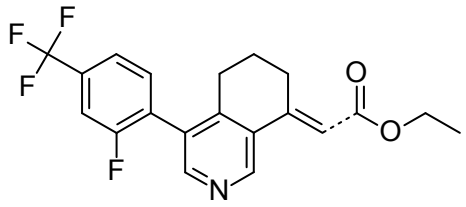


To a solution of sodium bis(trimethylsilyl)amide (33.2 mL, 33.2 mmol, 3 equiv; 1.0 M solution in THF) in THF (80 mL) was added slowly ethyl 2-(diethoxyphosphoryl)acetate (9.92 g, 8.78 mL, 44.2 mmol, 4 equiv; CAS[867-13-0]) at -50 °C and after completed addition the reaction mixture was stirred at 0 °C. After 1 h, 4-bromo-6,7-dihydro-5*H*-isoquinolin-8-one (2.5 g, 11.1 mmol, 1 equiv) was added and stirring continued under heating to reflux for 4 h. The reaction mixture was quenched by addition of a saturated aqueous solution of ammonium chloride (50 mL) and the aqueous phase extracted with ethyl acetate (3 x 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by medium pressure liquid chromatography eluting with a gradient of *n*-heptane / ethyl acetate (1:0 → 1:0.05) provided the product as slightly yellow oil (2.1 g, 65%; approximate ratio (*E*)/(*Z*) = 4:6). The subsequent reaction was conducted without further separation of the two configurational isomers.

(*E*)-Product: ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.33 (t, J = 7.2 Hz, 3H), 1.91 – 1.95 (m, 2H), 2.84 (dd, J = 6.4, 6.4 Hz, 2H), 3.16 – 3.18 (m, 2H), 4.23 (q, J = 7.2 Hz, 2H), 6.38 (t, J = 1.7 Hz, 1H), 8.61 (s, 1H), 8.72 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.5, 22.0, 26.9, 29.9, 60.4, 114.9, 123.6, 133.0, 145.0, 147.3, 151.0, 151.5, 166.4 ppm. HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{13}H_{14}BrNO_2$ 295.0208, found 295.0215.

(*Z*)-Product: ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.25 (t, J = 7.2 Hz, 3H), 2.04 – 2.09 (m, 2H), 2.45 – 2.48 (m, 2H), 2.86 (dd, J = 6.7, 6.7 Hz, 2H), 4.18 (q, J = 7.2 Hz, 2H), 5.90 (t, J = 1.2 Hz, 1H), 8.57 (s, 1H), 8.62 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.2, 23.1, 29.8, 34.5, 60.7, 116.6, 122.9, 131.5, 146.4, 148.8 (2 C), 151.2, 166.5 ppm. HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{13}H_{14}BrNO_2$ 295.0208, found 295.0213.

Ethyl 2-[4-[2-fluoro-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydroisoquinolin-8-yl]acetate

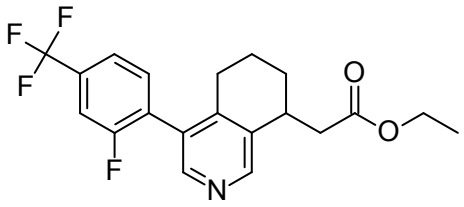


To a solution of ethyl 2-(4-bromo-6,7-dihydro-5*H*-isoquinolin-8-ylidene)acetate (0.70 g, 2.36 mmol, 1 equiv), 2-fluoro-4-(trifluoromethyl)phenylboronic acid (0.59 g, 2.84 mmol, 1.2 equiv) and sodium carbonate (0.28 g, 2.60 mmol, 1.1 equiv) in a mixture of ethanol (13.5 mL) and water (2.5 mL) was added tetrakis(triphenylphosphine)palladium(0) (0.28 g, 0.24 mmol, 0.1 equiv) under Ar. The reaction mixture was heated under microwave irradiation to 85 °C for 6 h. A saturated aqueous solution of sodium chloride (50 mL) was added and the aqueous phase extracted with ethyl acetate (3 x 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by medium pressure liquid chromatography eluting with a gradient of *n*-heptane / ethyl acetate (1:0 → 1:0.1) provided the product as white solid (0.38 g, 42%). MS ES+ (*m/z*): $[M+H]^+$ 380.1. The subsequent reaction was conducted without further separation of the two configurational isomers.

(*E*)-Product: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (t, J = 7.1 Hz, 3H), 1.80 (br s, 2H), 2.57 (br s, 2H), 3.22 (br s, 2H), 4.23 (q, J = 7.1 Hz, 2H), 6.46 (t, J = 1.8 Hz, 1H), 7.39 – 7.47 (m, 2H), 7.54 (d, J = 7.9 Hz, 1H), 8.39 (s, 1H), 8.91 (s, 1H). MS ES+ (*m/z*): $[M+H]^+$ 380.2.

(*Z*)-Product: ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.28 (t, J = 7.2 Hz, 3H), 1.93 (br s, 2H), 2.55 (dd, J = 6.5, 6.5 Hz, 2H), 2.60 (br s, 2H), 4.21 (q, J = 7.2 Hz, 2H), 5.94 (t, J = 1.4 Hz, 1H), 7.41 (dd, J = 7.4, 7.4 Hz, 1H), 7.45 (dd, J = 9.4, 1.4 Hz, 1H), 7.53 (dd, J = 7.9, 1.0 Hz, 1H), 8.34 (s, 1H), 8.79 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.3, 22.3, 26.7 (d, J_{CF} = 2.8 Hz), 34.0, 60.6, 113.5 (dq, J_{CF} = 25.7, 3.7 Hz), 116.8, 121.5 (q, J_{CF} = 3.7 Hz), 123.3 (q, J_{CF} = 274.8 Hz), 129.0 (d, J_{CF} = 17.3 Hz), 129.4, 129.8, 132.5 (d, J_{CF} = 3.6 Hz), 132.7 (dq, J_{CF} = 33.7, 7.2 Hz), 146.2, 149.3, 149.7, 150.5, 159.7 (d, J_{CF} = 249.2 Hz), 166.6 ppm. HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{20}H_{17}F_4NO_2$ 379.1195, found 379.1201.

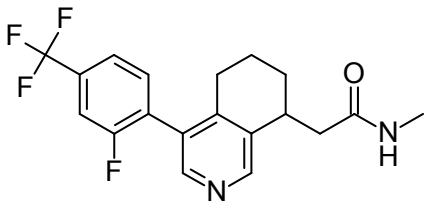
Ethyl 2-[4-[2-fluoro-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydroisoquinolin-8-yl]acetate (37)



To a solution of ethyl 2-[4-[2-fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-isoquinolin-8-ylidene]acetate (0.23 g, 0.60 mmol, 1 equiv) in MeOH (10 mL) was added 10% Pd/C (19 mg, 0.018 mmol, 0.03 equiv) and the reaction mixture stirred under hydrogen (3 bar) for 15 h at rt. The reaction mixture was filtered through Dicalite®, concentrated under reduced pressure and purified by medium pressure liquid chromatography eluting with a gradient of *n*-heptane / ethyl acetate (1:0 → 1:0.2) to provide the title compound as colorless oil (0.21 g, 93%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.29 (t, J = 7.2 Hz, 3H), 1.75 – 1.78 (br m, 3H), 1.92 – 1.98 (m, 1H), 2.52 (br s, 2H), 2.62 (dd, J = 15.4, 9.5 Hz, 1H), 2.75 – 2.77 (m, 1H), 3.51 (dddd, J = 8.8, 4.5, 4.5, 4.5 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 7.38 (dd, J = 7.4, 7.4 Hz, 1H), 7.44 (d, J = 9.3 Hz, 1H), 7.52 (dd, J = 7.9, 0.8 Hz, 1H), 8.22 (s, 1H), 8.49 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.4, 18.7 (br), 26.9, 27.6 (br), 32.4, 41.8, 60.8, 113.5 (dq, J_{CF} = 25.7, 3.7 Hz), 121.4 (dq, J_{CF} = 3.7 Hz), 123.3 (q, J_{CF} = 274.8 Hz), 129.4 (d, J_{CF} = 17.9 Hz), 130.2, 132.4 (d, J_{CF} = 3.9 Hz), 132.6 (d, J_{CF} = 8.0 Hz), 135.3, 145.1, 147.4, 150.4 (br), 159.7 (d, J_{CF} = 248.4 Hz), 172.2 ppm. HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{20}H_{19}F_4NO_2$ 381.1352, found 381.1370.

2-[4-[2-Fluoro-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydroisoquinolin-8-yl]-*N*-methyl-acetamide (38)

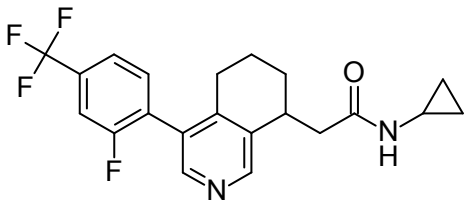


To a solution of ethyl 2-[4-[2-fluoro-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydro-isoquinolin-8-yl]acetate (28.5 mg, 0.075 mmol, 1 equiv) in THF (0.5 mL) was added methylamine (56 µL, 0.11 mmol, 1.5 equiv; 2.0 M solution in THF) and trimethylaluminium (45 µL, 0.090 mmol, 1.2 equiv; 2.0 M solution in toluene) under Ar. The reaction mixture was

heated under microwave irradiation to 120 °C for 1 h. The reaction mixture was quenched by addition of a solution of sodium tartrate (0.2 g) in water (1 mL) and then stirred for 30 min. The aqueous phase was extracted with ethyl acetate (3 x 5 mL), the combined organic phases dried over $MgSO_4$ and concentrated under reduced pressure. Purification by medium pressure liquid chromatography eluting with a gradient of dichloromethane / methanol (1:0 → 1:0.05) provided the title compound as white solid (26.0 mg, 95%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.74 (br s, 3H), 1.92 – 1.97 (m, 1H), 2.40 (dd, J = 14.5, 9.0 Hz, 1H), 2.51 (br s, 2H), 2.62 – 2.64 (m, 1H), 2.85 (d, J = 4.8 Hz, 3H), 3.56 – 3.58 (m, 1H), 5.64 (br s, 1H), 7.36 (dd, J = 7.5, 7.5 Hz, 1H), 7.43 (d, J = 9.5 Hz, 1H), 7.51 (d, J = 7.9 Hz, 1H), 8.20 (s, 1H), 8.48 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 19.0 (br), 26.6, 27.0, 27.7 (br), 32.6, 44.1, 113.4 (dq, J_{CF} = 25.7, 3.7 Hz), 121.4 (qd, J_{CF} = 3.0, 3.0 Hz), 123.3 (qd, J_{CF} = 272.4, 2.5 Hz), 129.3 (d, J_{CF} = 16.8 Hz), 130.3, 132.4 (br), 132.6 (qd, J_{CF} = 33.7, 7.8 Hz), 135.9, 145.3, 146.9, 150.1, 159.7 (dq, J_{CF} = 257.2, 2.0 Hz), 171.8 ppm. HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{19}H_{18}F_4N_2O$ 366.1355, found 366.1382.

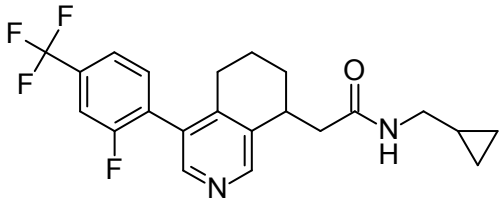
_N_-Cyclopropyl-2-[4-[2-fluoro-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydroisoquinolin-8-yl]acetamide (39)



To a solution of ethyl 2-[4-[2-fluoro-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydro-isoquinolin-8-yl]acetate (28.5 mg, 0.075 mmol, 1 equiv) in THF (0.5 mL) was added cyclopropylamine (6.3 mg, 7.6 µL, 0.11 mmol, 1.5 equiv) and trimethylaluminium (45 µL, 0.090 mmol, 1.2 equiv; 2.0 M solution in toluene) under Ar. The reaction mixture was heated under microwave irradiation to 120 °C for 1 h. The reaction mixture was quenched by addition of a solution of sodium tartrate (0.2 g) in water (1 mL) and then stirred for 30 min. The aqueous phase was extracted with ethyl acetate (3 x 5 mL), the combined organic phases dried over $MgSO_4$ and concentrated under reduced pressure. Purification by medium pressure liquid chromatography eluting with a gradient of dichloromethane / methanol (1:0 → 1:0.05) and preparative TLC on normal phase (ethyl acetate) provided the title compound as white solid (19.5 mg, 67%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 0.47 – 0.53 (m, 2H), 0.78 – 0.80 (m, 2H), 1.73 (br s, 3H), 1.93 – 1.97 (m, 1H), 2.35 (dd, J = 14.5, 8.8 Hz, 1H), 2.40 – 2.52 (br m, 1H), 2.53 – 2.56 (br m, 2H), 2.75 (ddddd, J = 7.0, 7.0, 3.6, 3.6, 3.6 Hz, 1H), 3.55 – 3.58 (m, 1H), 5.71 (br s, 1H), 7.36 (dd, J = 7.5, 7.5 Hz, 1H), 7.43 (dd, J = 9.3, 1.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 8.20 (s, 1H), 8.48 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 6.8, 6.9, 19.1 (br), 22.9, 27.0, 27.7 (br), 32.6, 44.0, 113.4 (dq, J_{CF} = 25.7, 3.7 Hz), 121.4, 123.2 (qd, J_{CF} = 272.4, 2.5 Hz), 129.4 (d, J_{CF} = 17.9 Hz), 130.2, 132.4 – 132.7 (m, 2 C), 135.7, 145.0, 147.2, 150.4, 159.7 (dq, J_{CF} = 257.2, 2.0 Hz), 172.6 ppm. HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{21}H_{20}F_4N_2O$ 392.1512, found 392.1524.

_N_-(Cyclopropylmethyl)-2-[4-[2-fluoro-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydroisoquinolin-8-yl]acetamide (40)

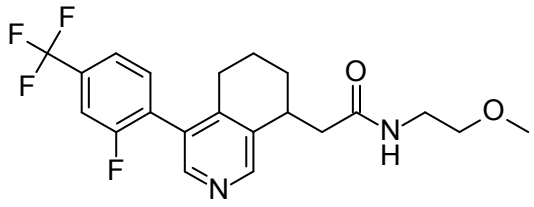


To a solution of ethyl 2-[4-[2-fluoro-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydro-isoquinolin-8-yl]acetate (28.5 mg, 0.075 mmol, 1 equiv) in THF (0.5 mL) was added cyclopropylmethylamine (7.8 mg, 9.5 µL, 0.11 mmol, 1.5 equiv) and trimethylaluminium (45 µL, 0.090 mmol, 1.2 equiv; 2.0 M solution in toluene) under Ar. The reaction mixture was heated under microwave irradiation to 120 °C for 1 h. The reaction mixture was quenched by addition of a solution of sodium tartrate (0.2 g) in water (1 mL) and then stirred for 30 min. The aqueous phase was extracted with ethyl acetate (3 x 5 mL), the combined organic phases dried over $MgSO_4$ and concentrated under reduced pressure. Purification by medium pressure liquid chromatography eluting with a gradient of dichloromethane / methanol (1:0 → 1:0.05) provided the title compound as white solid (26.9 mg, 89%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 0.19 – 0.23 (m, 2H), 0.49 – 0.54 (m, 2H), 0.92 – 0.99 (m, 1H), 1.75 (br s, 3H), 1.94 – 2.00 (m, 1H), 2.41 (dd, J = 14.5, 9.0 Hz, 1H), 2.53 (br s, 2H), 2.64 – 2.66 (m, 1H), 3.16 (dd, J = 7.2, 5.4 Hz, 2H), 3.56 – 3.60 (m, 1H), 5.57 (br s, 1H), 7.37 (dd, J = 7.5, 7.5 Hz, 1H), 7.44 (dd, J = 9.4, 1.2 Hz, 1H), 7.51 (dd, J = 7.9, 1.0 Hz, 1H), 8.21 (s, 1H), 8.50 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 3.57, 3.61, 10.9, 19.1 (br), 27.0, 27.7 (br), 32.6, 44.3, 44.7, 113.4 (dq, J_{CF} = 25.7, 3.7 Hz), 121.4, 123.3 (qd, J_{CF} = 272.4, 2.5 Hz), 129.5 (d, J_{CF}

= 17.1 Hz), 130.2, 132.4 – 132.6 (m, 2 C), 135.7, 145.0, 147.3, 150.5 (br), 159.7 (dq, J_{CF} = 257.2, 2.0 Hz), 171.0 ppm. HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{22}H_{22}F_4N_2O$ 406.1668, found 406.1697.

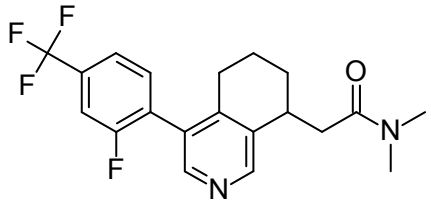
2-[4-[2-Fluoro-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydroisoquinolin-8-yl]-*N*-(2-methoxyethyl)acetamide (41)



To a solution of ethyl 2-[4-[2-fluoro-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydro-isoquinolin-8-yl]acetate (28.5 mg, 0.075 mmol, 1 equiv) in THF (0.5 mL) was added 2-methoxyethanamine (8.3 mg, 9.6 µL, 0.11 mmol, 1.5 equiv) and trimethylaluminium (45 µL, 0.090 mmol, 1.2 equiv; 2.0 M solution in toluene) under Ar. The reaction mixture was heated under microwave irradiation to 120 °C for 1 h. The reaction mixture was quenched by addition of a solution of sodium tartrate (0.2 g) in water (1 mL) and then stirred for 30 min. The aqueous phase was extracted with ethyl acetate (3 x 5 mL), the combined organic phases dried over $MgSO_4$ and concentrated under reduced pressure. Purification by medium pressure liquid chromatography eluting with a gradient of dichloromethane / methanol (1:0 → 1:0.05) provided the title compound as white solid (18.2 mg, 59%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.75 (br s, 3H), 1.93 – 1.99 (m, 1H), 2.41 (dd, J = 14.5, 9.0 Hz, 1H), 2.52 (br s, 2H), 2.64 – 2.66 (m, 1H), 3.36 (s, 3H), 3.46 – 3.52 (m, 4H), 3.56 – 3.60 (m, 1H), 5.84 (br s, 1H), 7.37 (dd, J = 7.5, 7.5 Hz, 1H), 7.44 (dd, J = 9.3, 1.2 Hz, 1H), 7.51 (dd, J = 8.0, 0.9 Hz, 1H), 8.21 (s, 1H), 8.49 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 19.1 (br), 27.0, 27.7 (br), 32.5 (br), 39.4, 44.2, 58.9, 71.3, 113.4 (dq, J_{CF} = 25.9, 3.9 Hz), 121.4 (br), 123.3 (qd, J_{CF} = 272.4, 2.8 Hz), 129.5 (d, J_{CF} = 17.1 Hz), 130.2, 132.4 – 132.6 (m, 2 C), 135.7, 145.0, 147.3, 150.5 (br), 159.7 (d, J_{CF} = 257.2 Hz), 171.2 ppm. HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{21}H_{22}F_4N_2O_2$ 410.1617, found 410.1644.

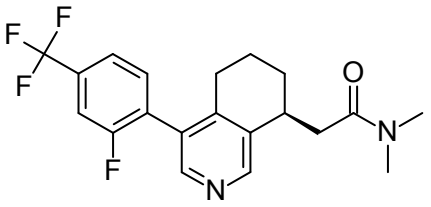
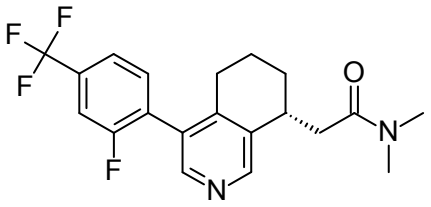
2-[4-[2-Fluoro-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydroisoquinolin-8-yl]-*N*,*N*-dimethyl-acetamide (42)



To a solution of ethyl 2-[4-[2-fluoro-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydro-isoquinolin-8-yl]acetate (28.5 mg, 0.075 mmol, 1 equiv) in THF (0.5 mL) was added dimethylamine (56 µL, 0.11 mmol, 1.5 equiv; 2.0 M solution in THF) and trimethylaluminium (45 µL, 0.090 mmol, 1.2 equiv; 2.0 M solution in toluene) under Ar. The reaction mixture was heated under microwave irradiation to 120 °C for 1 h. The reaction mixture was quenched by addition of a solution of sodium tartrate (0.2 g) in water (1 mL) and then stirred for 30 min. The aqueous phase was extracted with ethyl acetate (3 x 5 mL), the combined organic phases dried over $MgSO_4$ and concentrated under reduced pressure. Purification by medium pressure liquid chromatography eluting with a gradient of dichloromethane / methanol (1:0 → 1:0.05) provided the title compound as white solid (25.3 mg, 89%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.76 (br s, 3H), 1.95 – 2.00 (m, 1H), 2.35 – 2.60 (br m, 2H), 2.65 (dd, J = 15.6, 8.9 Hz, 1H), 2.69 – 2.72 (m, 1H), 2.99 (s, 3H), 3.01 (s, 3H), 3.62 – 3.66 (m, 1H), 7.37 (dd, J = 7.5, 7.5 Hz, 1H), 7.44 (d, J = 9.4 Hz, 1H), 7.51 (d, J = 7.9 Hz, 1H), 8.21 (s, 1H), 8.47 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 19.1 (br), 27.1 (br), 27.8 (br), 32.2 (br), 35.8, 37.5, 40.6, 113.4 (dq, J_{CF} = 25.7, 4.0 Hz), 121.4 (br), 123.3 (qd, J_{CF} = 272.4, 2.8 Hz), 129.5 (dd, J_{CF} = 16.9, 1.0 Hz), 130.1 (br), 132.4 (br m, 2 C), 136.3, 145.1, 147.2, 150.7 (br), 159.7 (dq, J_{CF} = 257.2, 2.0 Hz), 171.3 ppm. HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{20}H_{20}F_4N_2O$ 380.1512, found 380.1532.

(+)-2-[4-[2-Fluoro-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydroisoquinolin-8-yl]-*N*,*N*-dimethyl-acetamide [(+)-42] and (-)-2-[4-[2-Fluoro-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydroisoquinolin-8-yl]-*N*,*N*-dimethyl-acetamide [(-)-42]

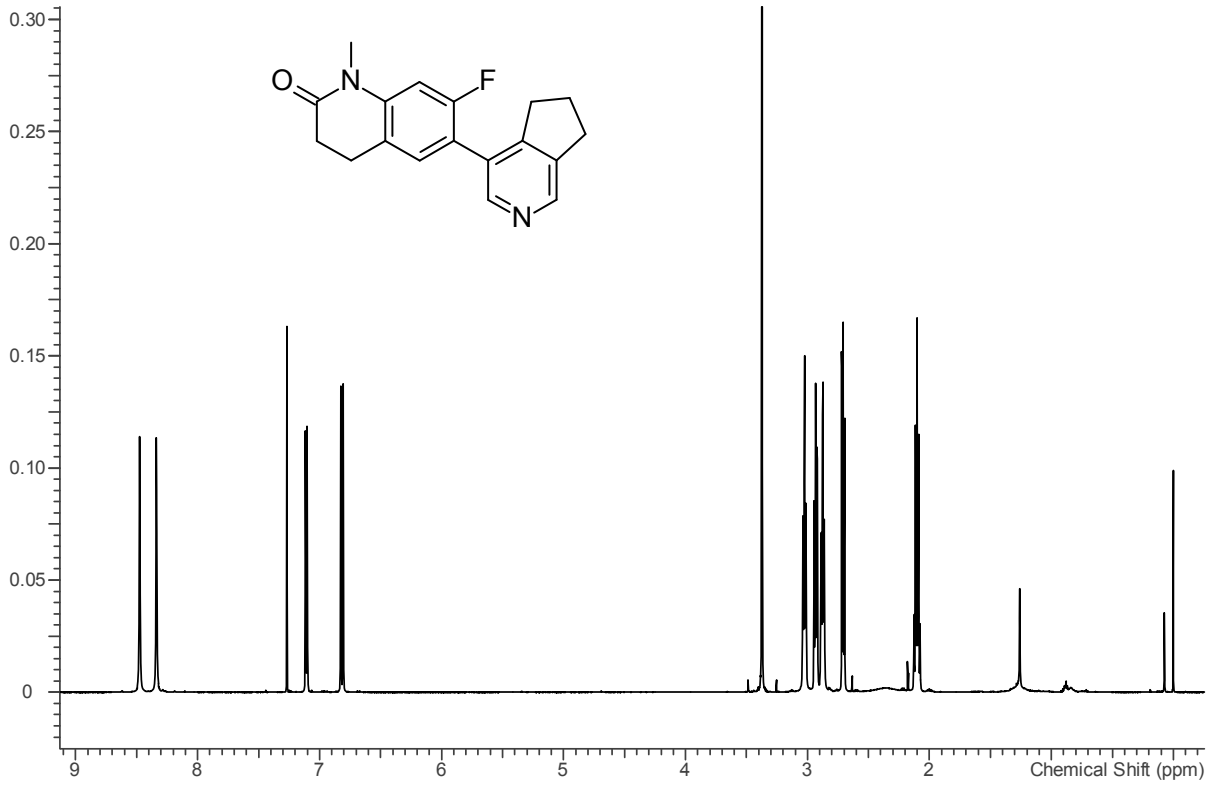
The title compounds were prepared by chiral separation of 2-[4-[2-fluoro-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydroisoquinolin-8-yl]-*N*,*N*-dimethyl-acetamide (80 mg, 0.21 mmol; **42**) on a Reprosil Chiral NR column [*n*-heptane / ethanol (7:3)] to give (+)-2-[4-[2-fluoro-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydroisoquinolin-8-yl]-*N*,*N*-dimethyl-acetamide [22.6 mg, 28% ; (+)-**42**] and (-)-2-[4-[2-fluoro-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydroisoquinolin-8-yl]-*N*,*N*-dimethyl-acetamide [32.4 mg, 41%; (-)-**42**] as colorless oils.

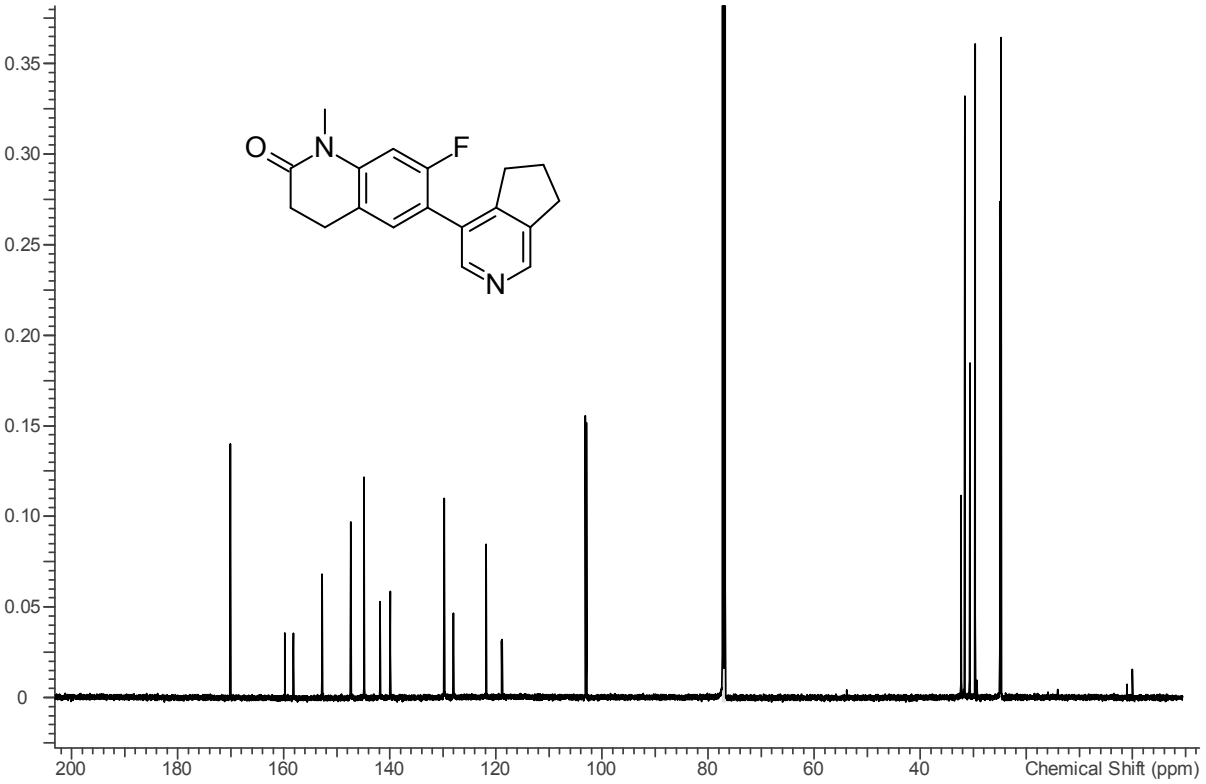
(+)-Product: ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.76 (br s, 3H), 1.95 – 2.00 (m, 1H), 2.35 – 2.60 (br m, 2H), 2.65 (dd, J = 15.6, 8.9 Hz, 1H), 2.69 – 2.72 (m, 1H), 2.99 (s, 3H), 3.01 (s, 3H), 3.62 – 3.66 (m, 1H), 7.37 (dd, J = 7.4, 7.4 Hz, 1H), 7.44 (dd, J = 9.4, 1.3 Hz, 1H), 7.51 (dd, J = 7.9, 0.9 Hz, 1H), 8.21 (s, 1H), 8.47 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 19.1 (br), 27.1 (br), 27.8 (br), 32.2 (br), 35.8, 37.5, 40.6, 113.4 (dq, J_{CF} = 25.7, 3.7 Hz), 121.4 (br), 123.3 (qd, J_{CF} = 272.4, 2.8 Hz), 129.5 (dd, J_{CF} = 16.2, 0.9 Hz), 130.2 (br), 132.4 (br m, 2 C), 136.3, 145.1, 147.1, 150.6 (br), 159.7 (dq, J_{CF} = 257.2, 2.0 Hz), 171.3 ppm. HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{20}H_{20}F_4N_2O$ 380.1512, found 380.1528.

(-)-Product: ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.75 (br s, 3H), 1.94 – 2.00 (m, 1H), 2.35 – 2.60 (br m, 2H), 2.65 (dd, J = 15.6, 8.9 Hz, 1H), 2.69 – 2.73 (m, 1H), 2.99 (s, 3H), 3.01 (s, 3H), 3.62 – 3.66 (m, 1H), 7.37 (dd, J = 7.5, 7.5 Hz, 1H), 7.43 (dd, J = 9.4, 1.4 Hz, 1H), 7.51 (dd, J = 7.9, 1.0 Hz, 1H), 8.21 (s, 1H), 8.47 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 19.0 (br), 27.1 (br), 27.9 (br), 32.2 (br), 35.8, 37.4, 40.6, 113.4 (dq, J_{CF} = 25.7, 3.5 Hz), 121.4 (br), 123.3 (qd, J_{CF} = 272.4, 2.5 Hz), 129.5 (dd, J_{CF} = 16.5, 0.9 Hz), 130.2 (br), 132.4 (br m, 2 C), 136.3, 145.1, 147.1, 150.6 (br), 159.7 (dq, J_{CF} = 257.2, 2.0 Hz), 171.3 ppm. HRMS ESI+ (*m/z*): $[M]^+$ calcd for $C_{20}H_{20}F_4N_2O$ 380.1512, found 380.1528.

3. ^{1}H, ^{13}C and ^{19}F NMR Spectra for New Compounds

6-(6,7-Dihydro-5*H*-cyclopenta[*c*]pyridin-4-yl)-7-fluoro-1-methyl-3,4-dihydroquinolin-2-one (11)

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N
F
N
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0.30
0.25
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200
180
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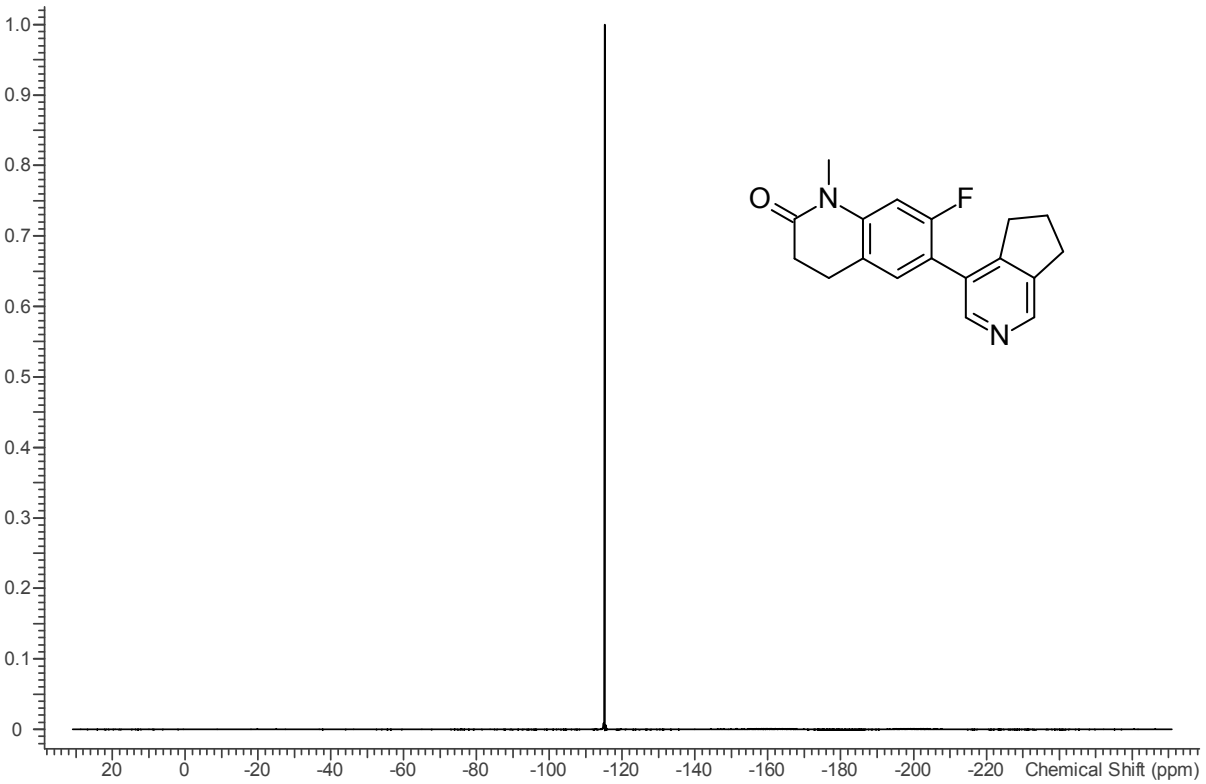
140
120
100
80
60
40
Chemical Shift (ppm)


O
N
F
N
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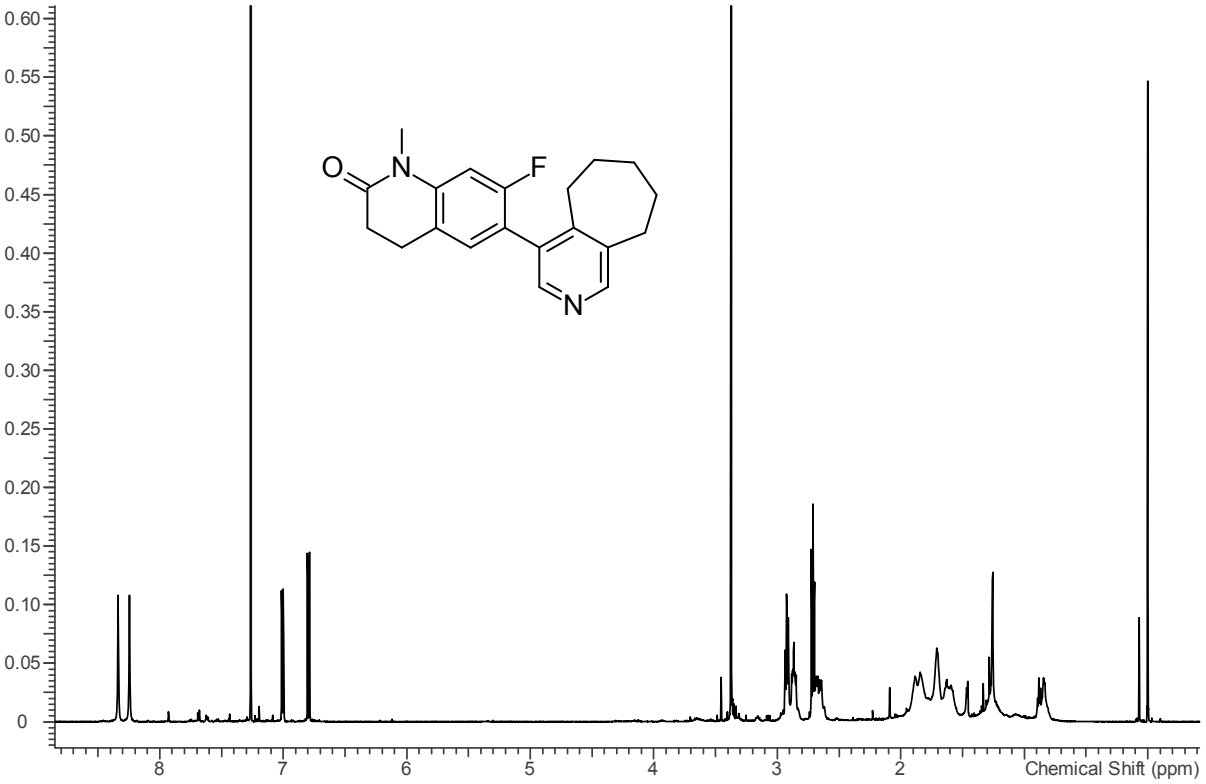
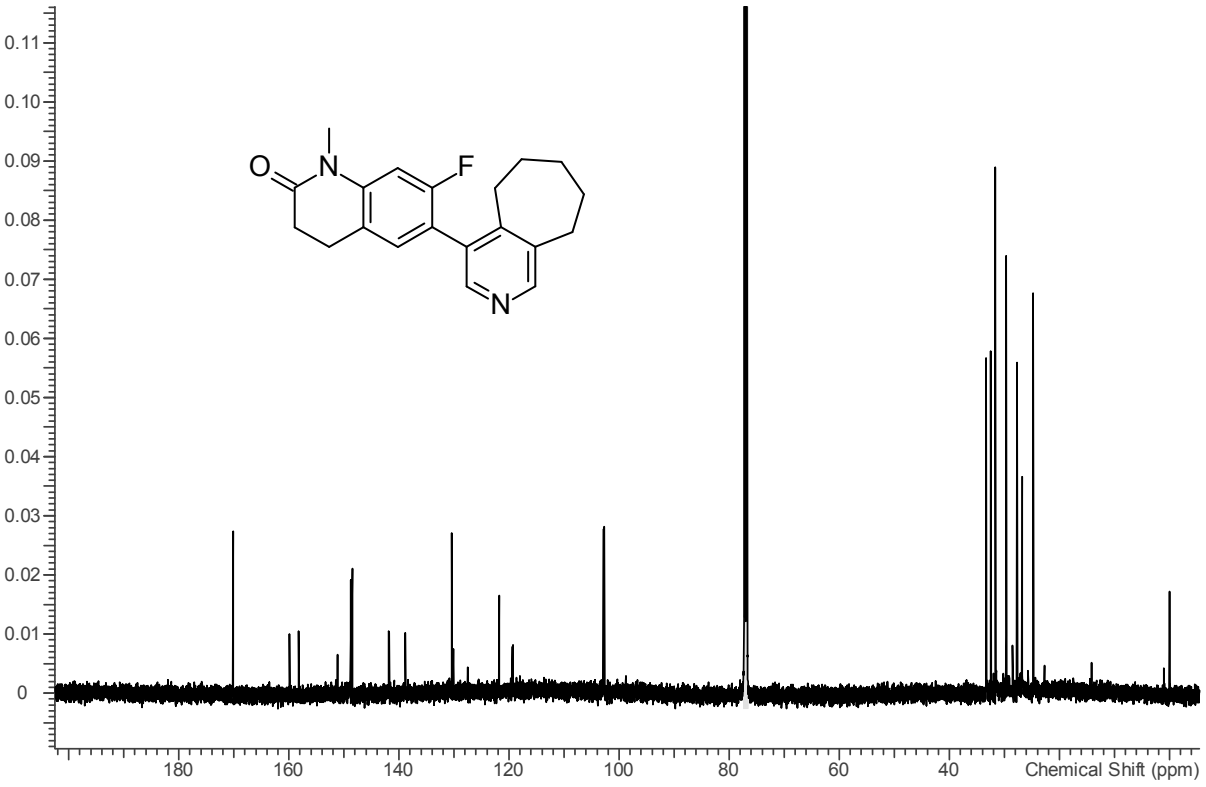
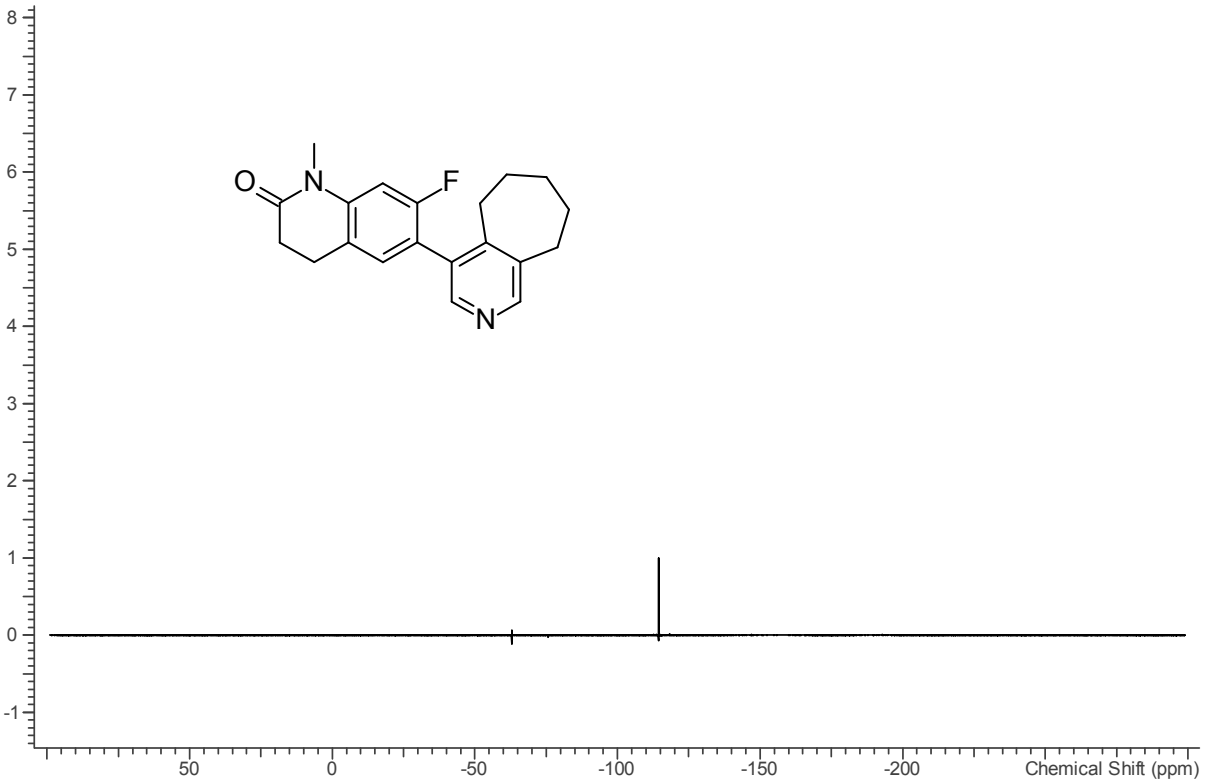
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
Chemical Shift (ppm)

7-Fluoro-1-methyl-6-(6,7,8,9-tetrahydro-5*H*-cyclohepta[*c*]pyridin-4-yl)-3,4-dihydroquinolin-2-one (12)






8
7
6
5
4
3
2
1
0
-1
O
N
F
N
50
0
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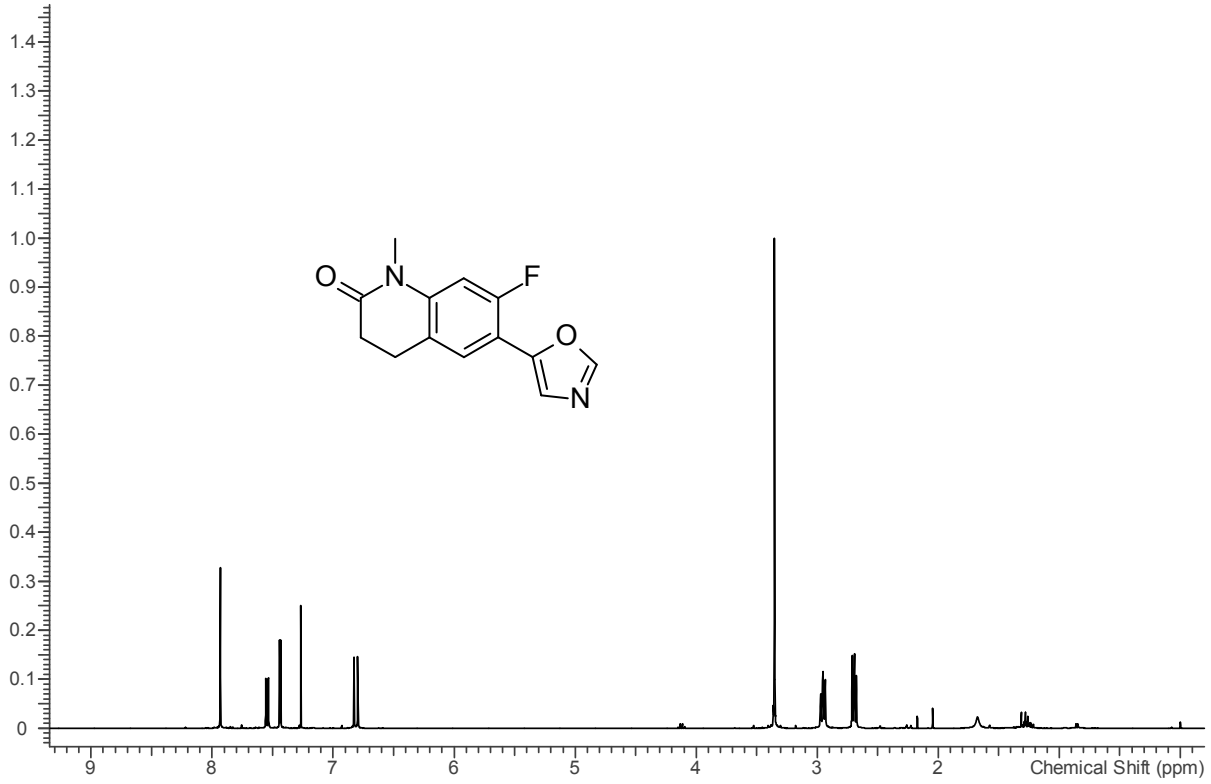
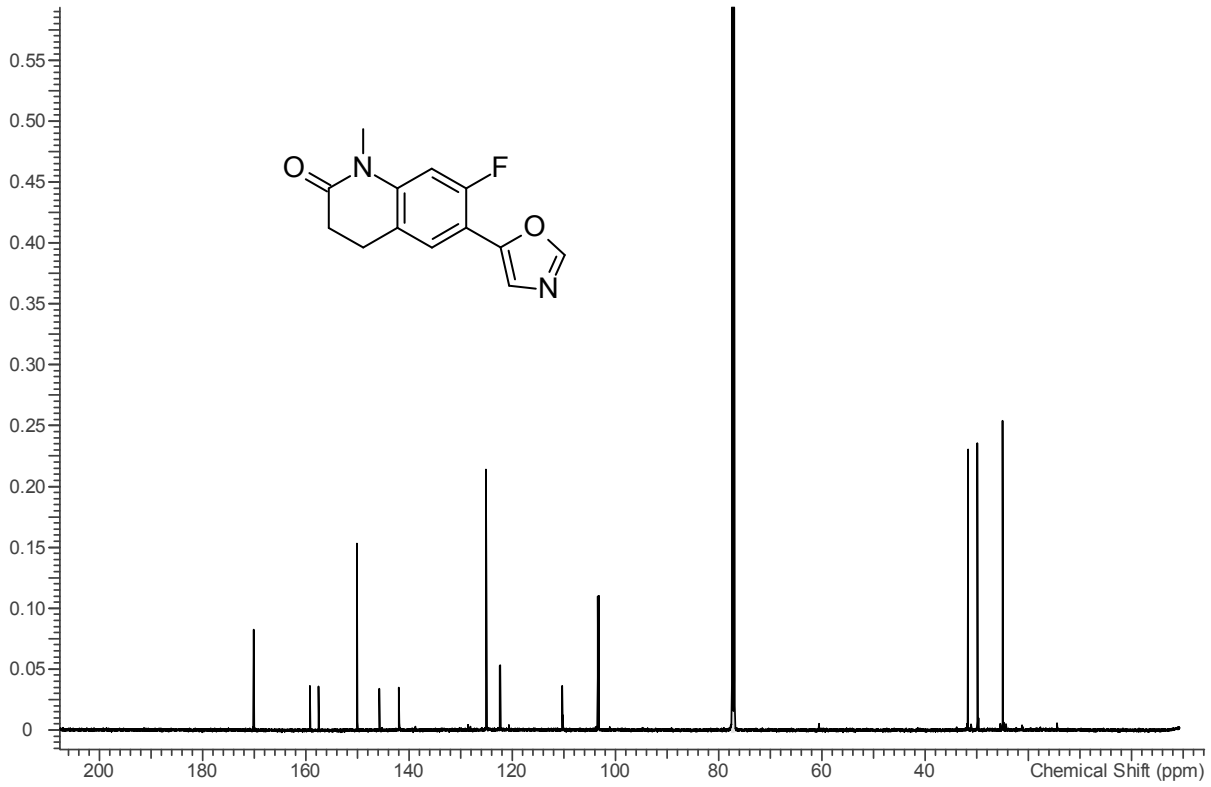
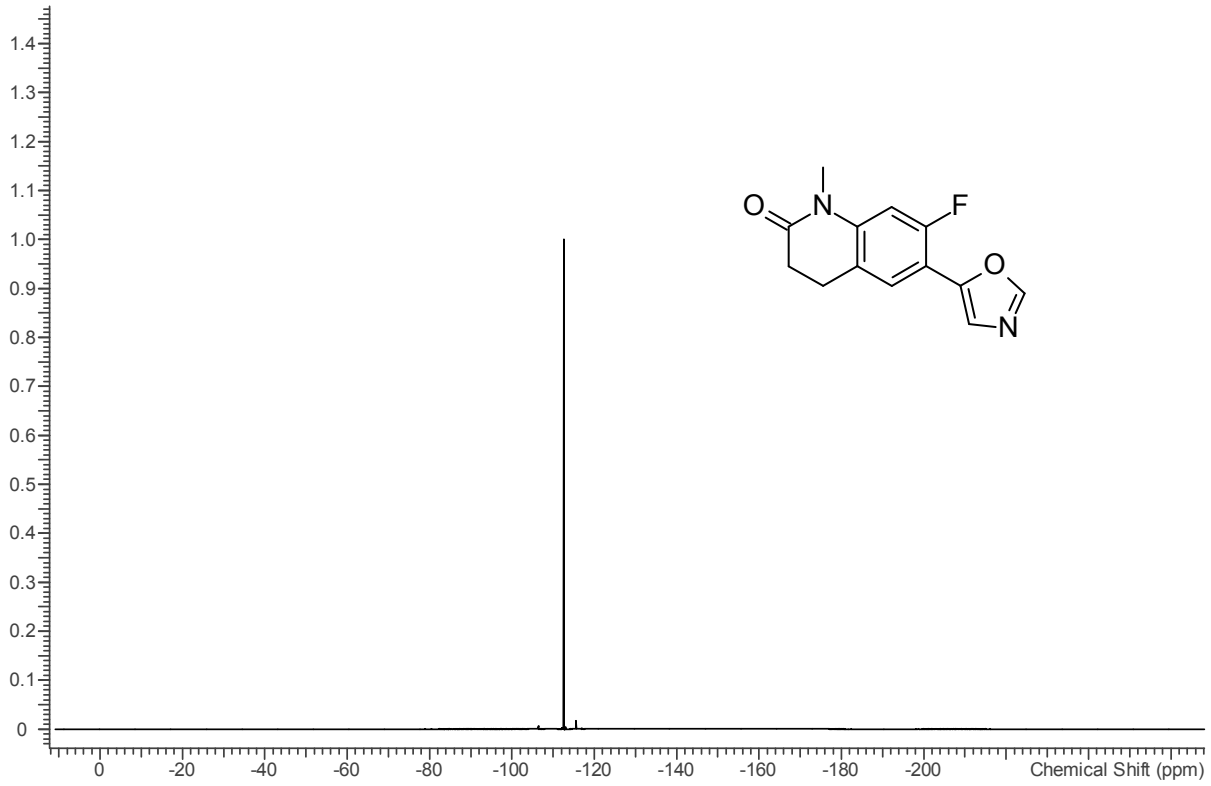
-150
-200
Chemical Shift (ppm)

7-Fluoro-1-methyl-6-oxazol-5-yl-3,4-dihydroquinolin-2-one (14)



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0.1
0
O
N
F
O
N
0
-20
-40
-60
-80
-100
-120
-140
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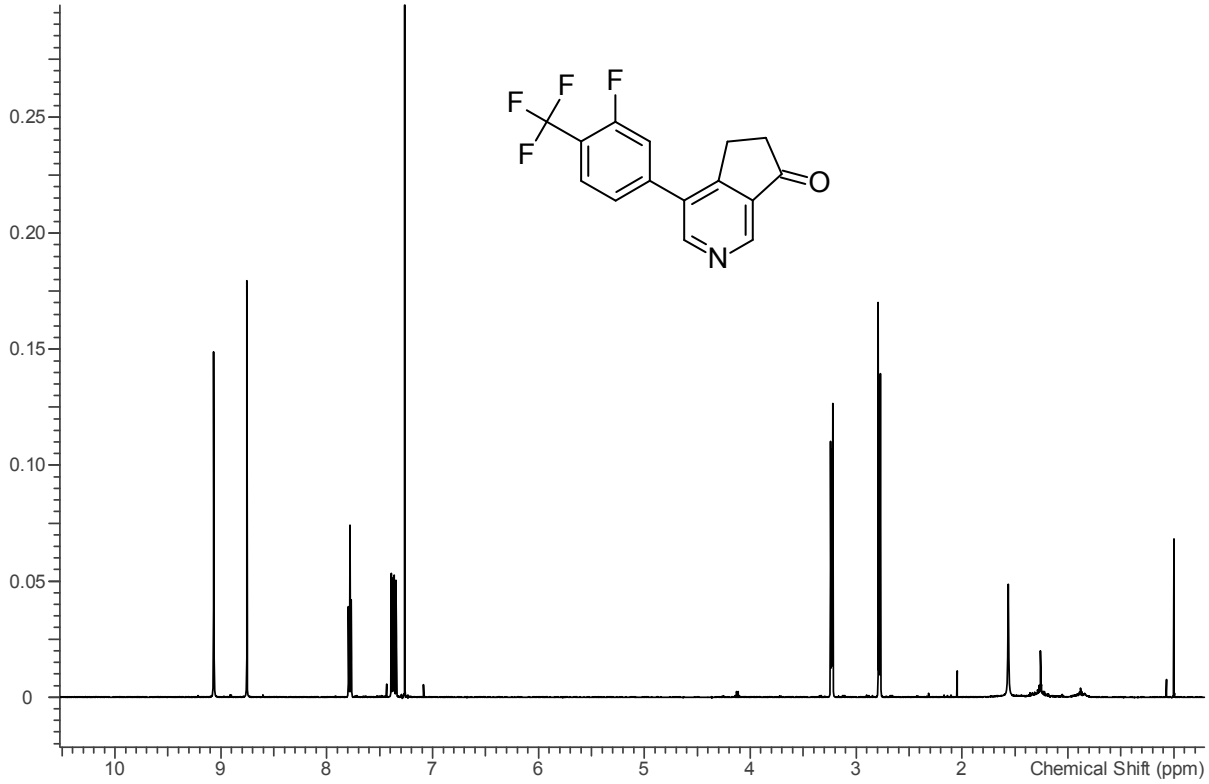
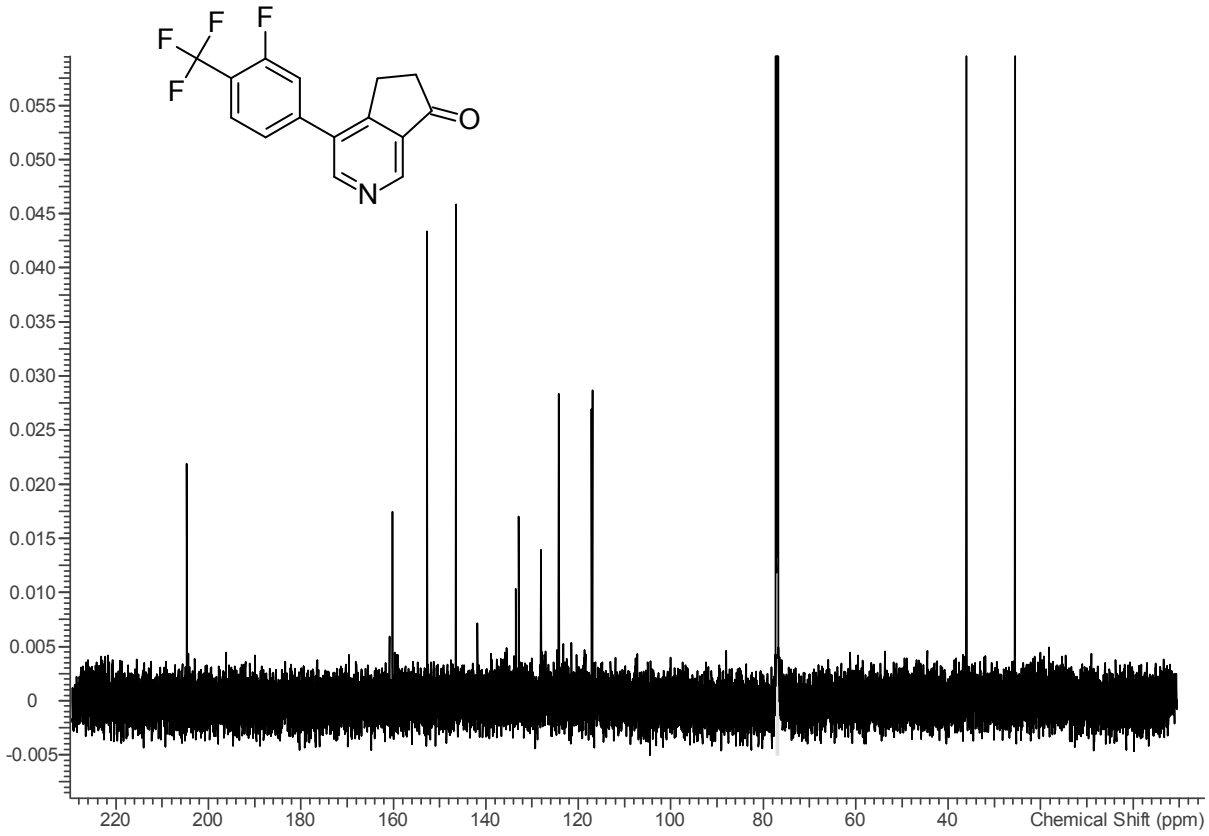
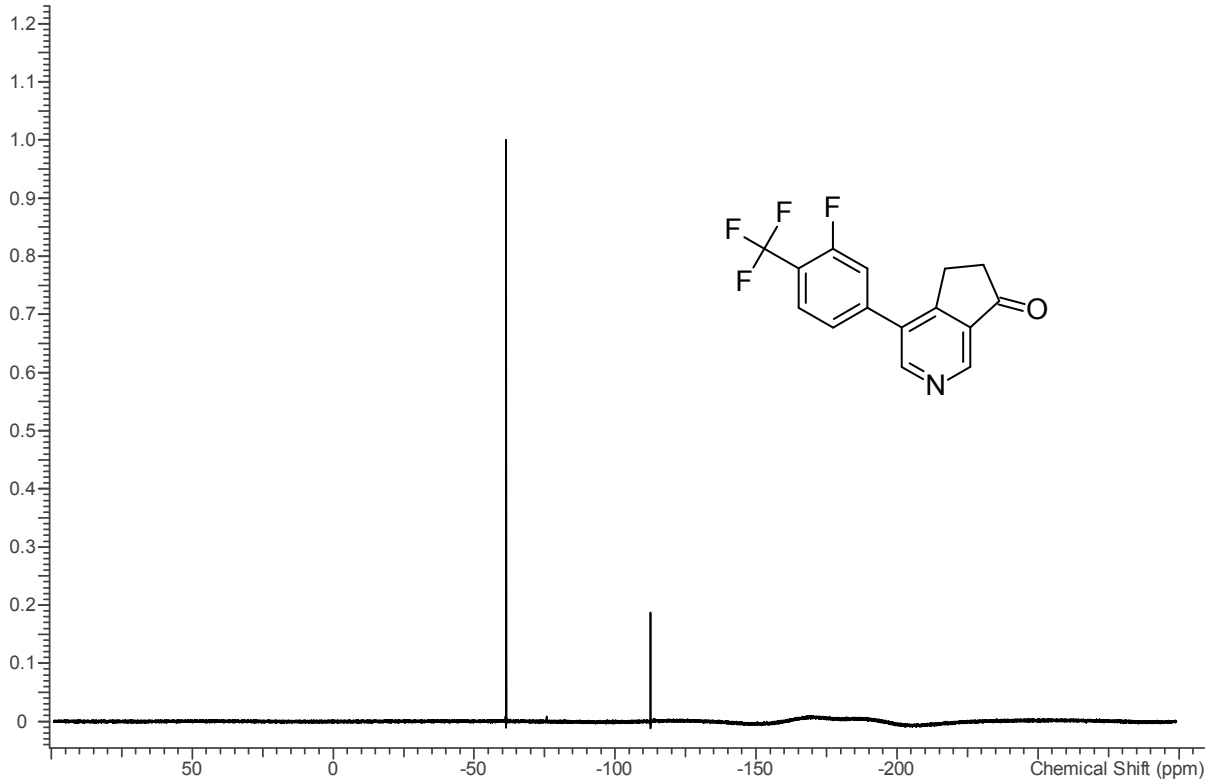
Chemical Shift (ppm)

4-[3-Fluoro-4-(trifluoromethyl)phenyl]-5,6-dihydrocyclopenta[*c*]pyridin-7-one (15)



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0.7
0.6
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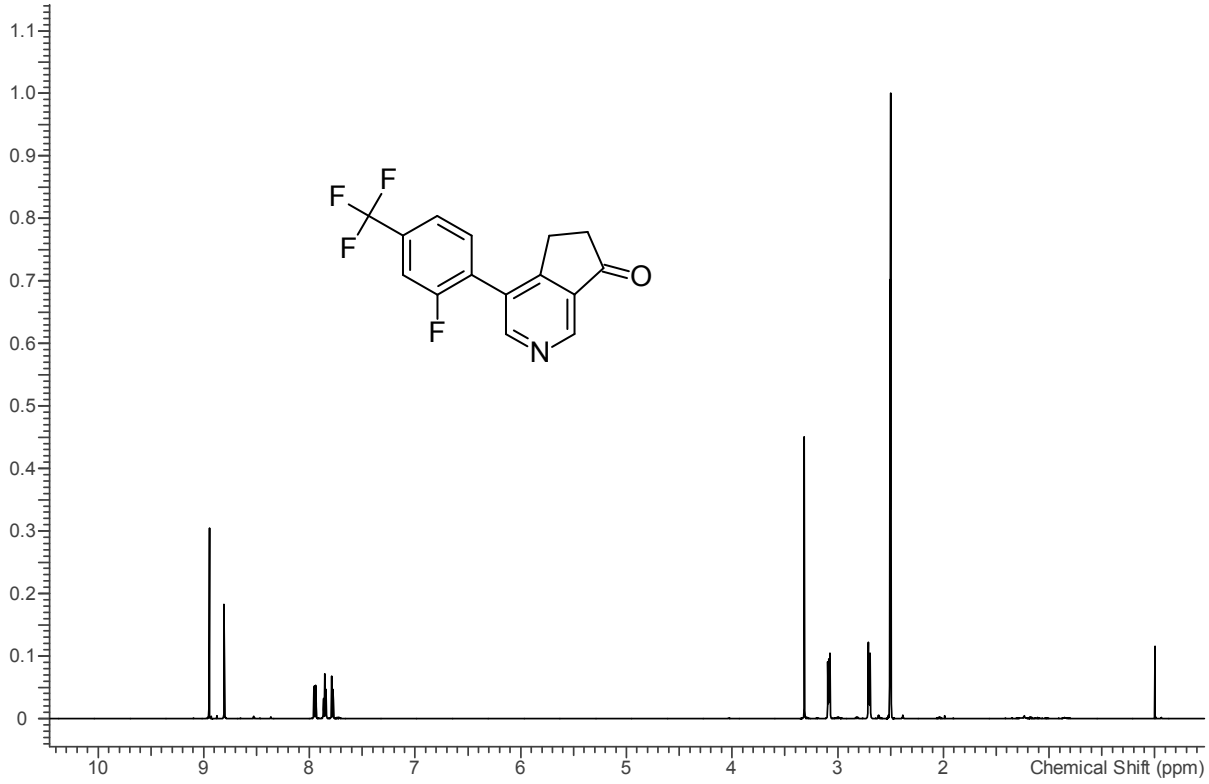
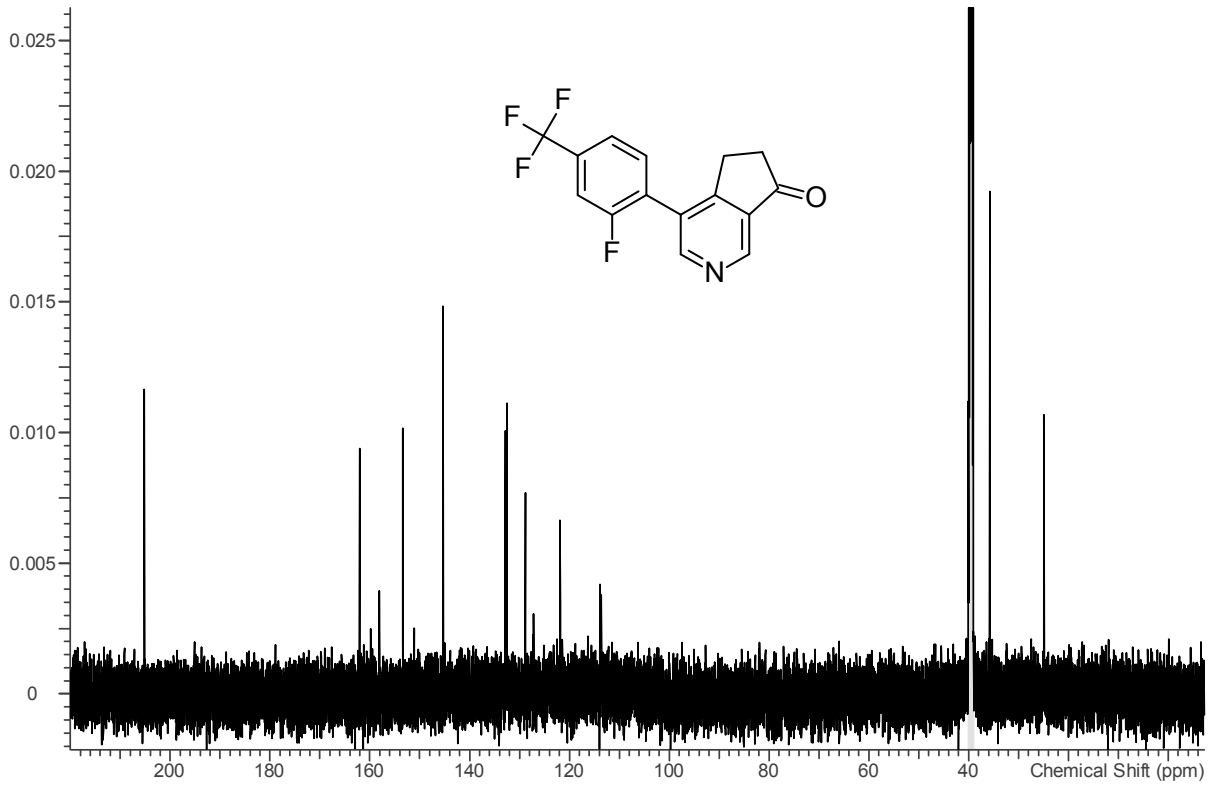
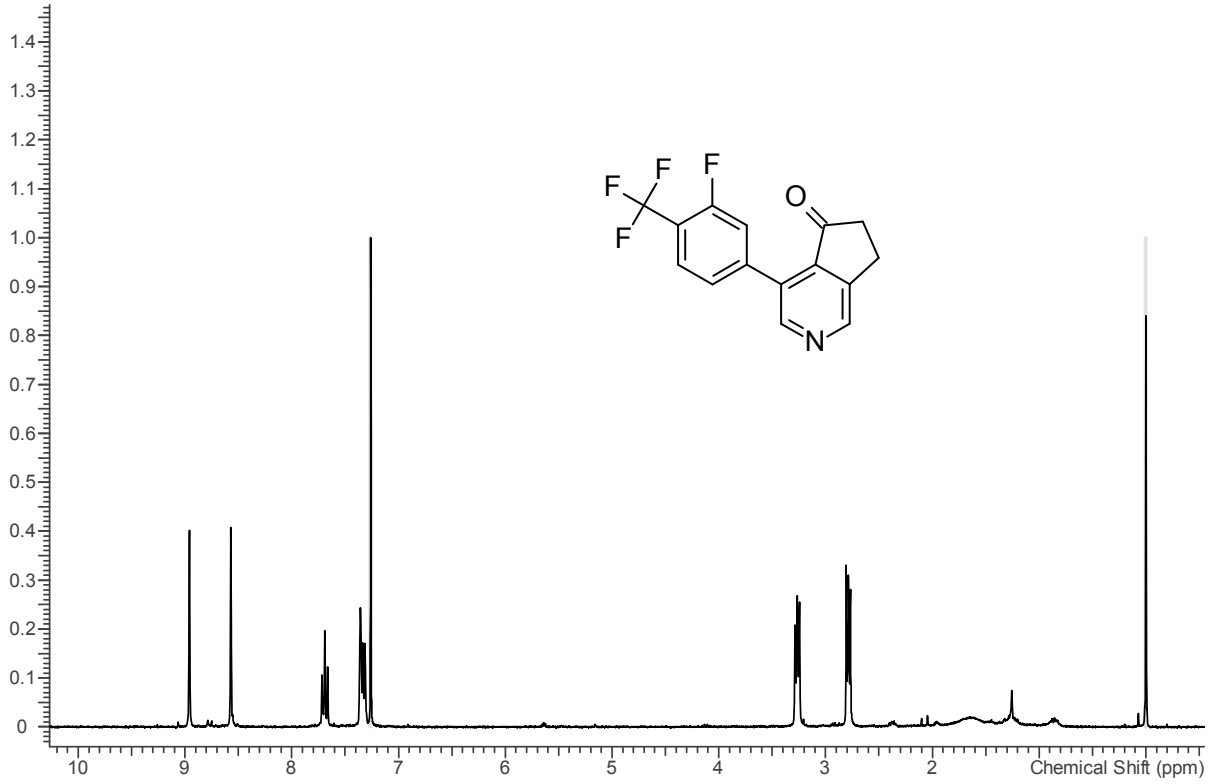
0.4
0.3
0.2
0.1
0
50
0
-50
-100
-150
-200
Chemical Shift (ppm)
F
F
F
F
O
N

4-[2-Fluoro-4-(trifluoromethyl)phenyl]-5,6-dihydrocyclopenta[*c*]pyridin-7-one (16)

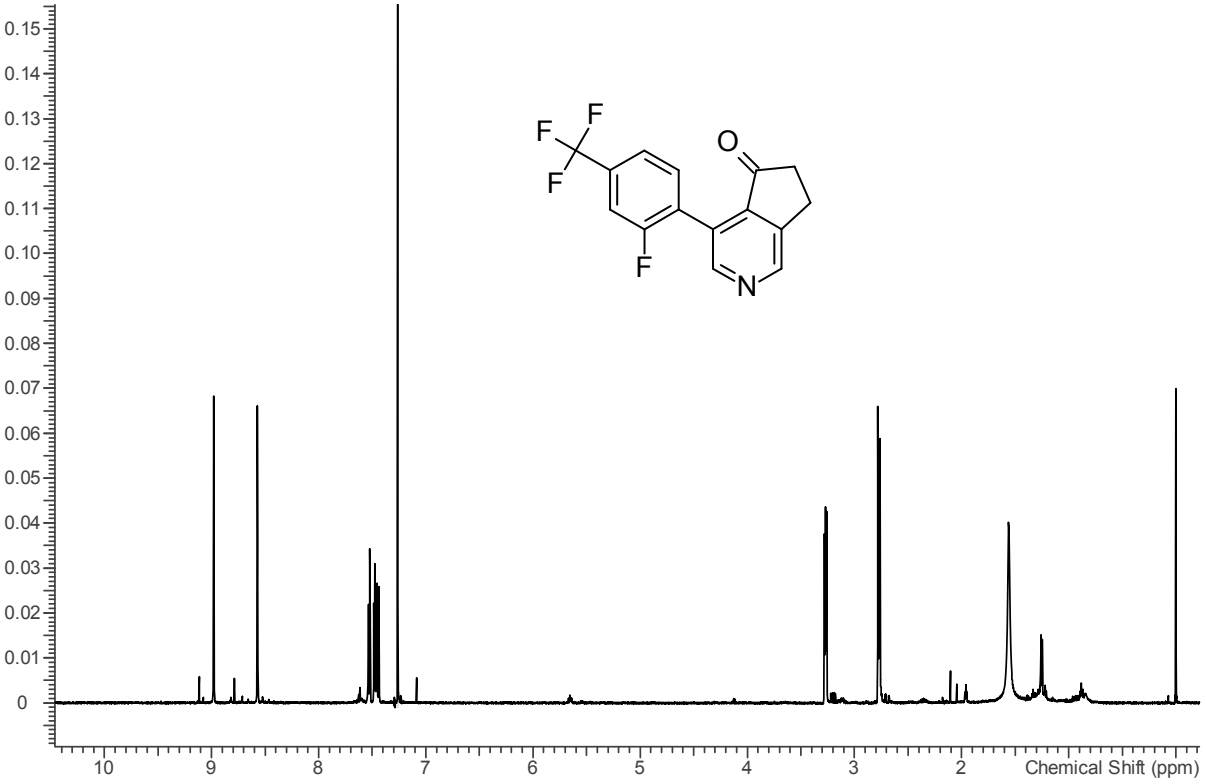


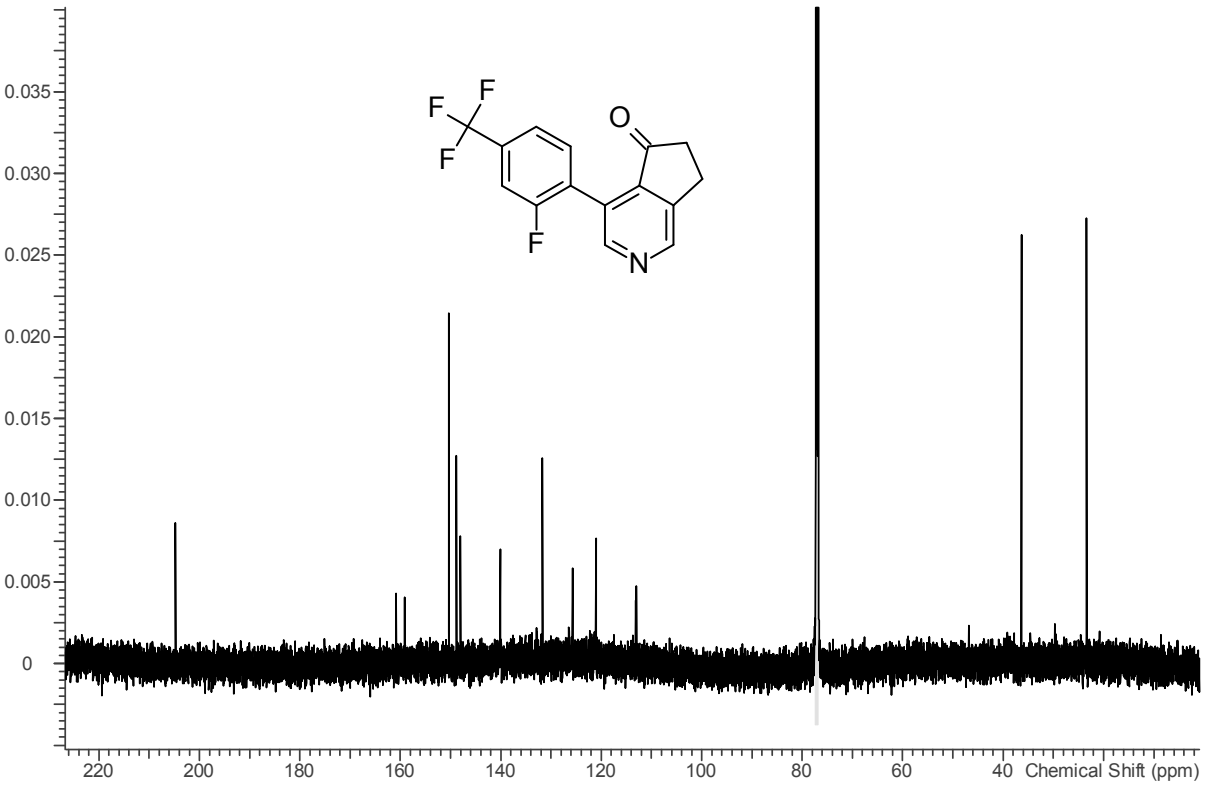


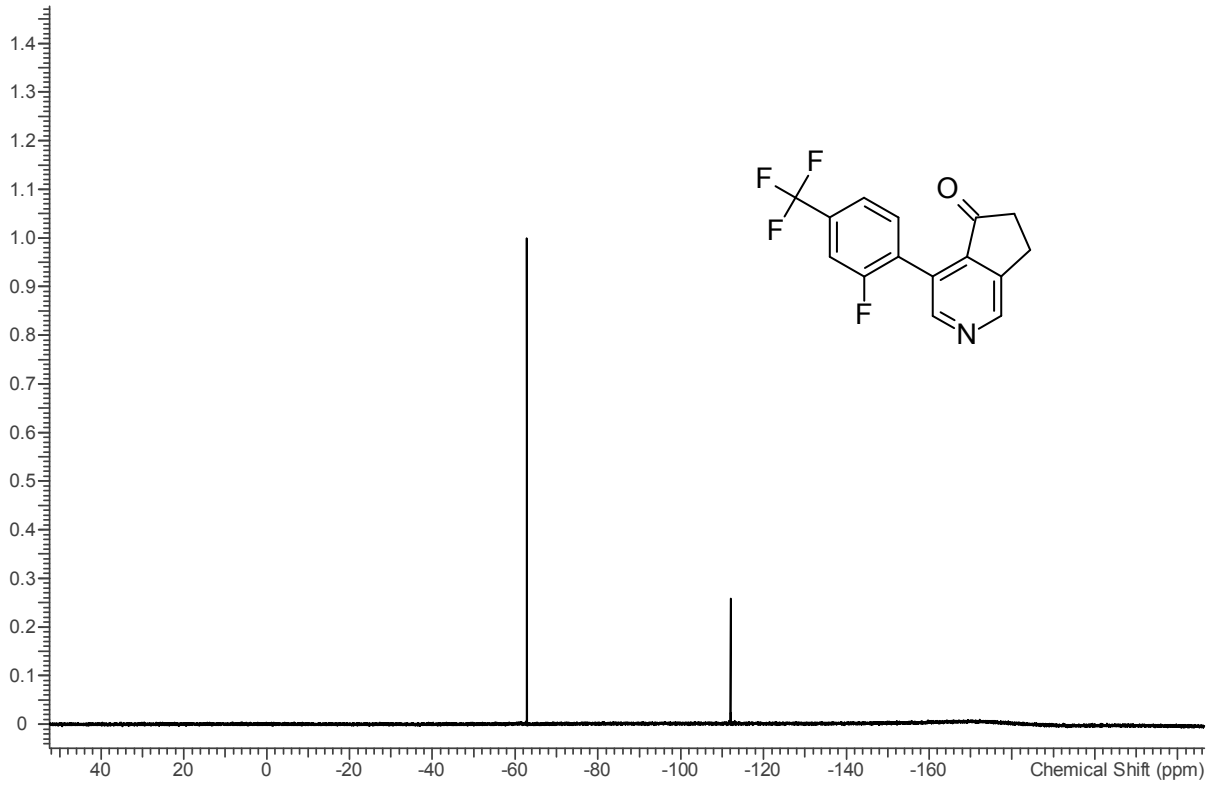
4-[3-Fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydrocyclopenta[*c*]pyridin-5-one (17)



4-[2-Fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydrocyclopenta[*c*]pyridin-5-one (18)



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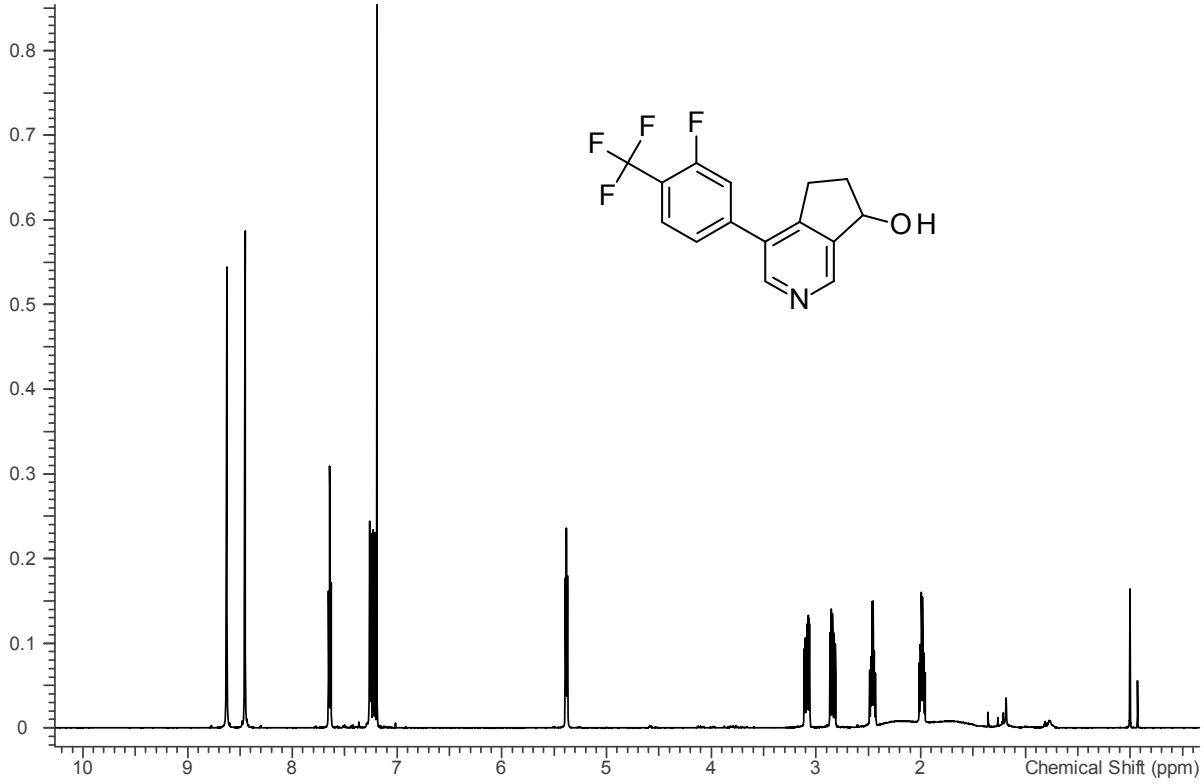
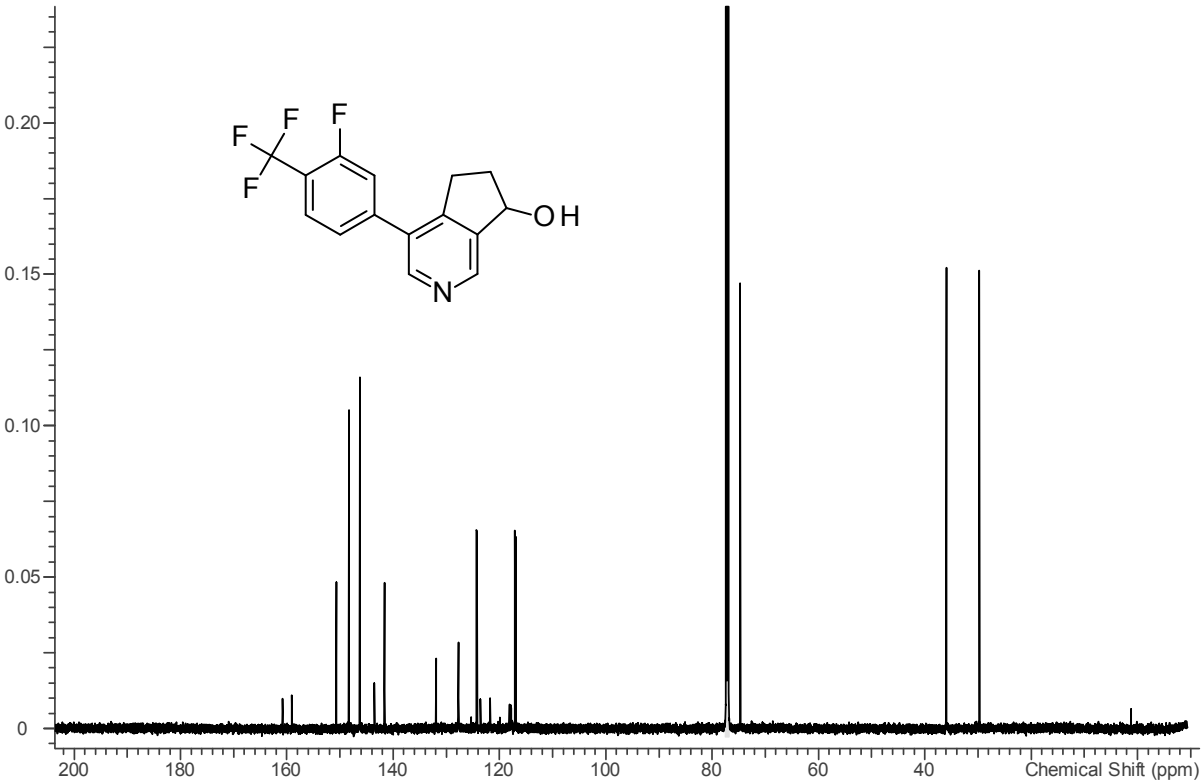
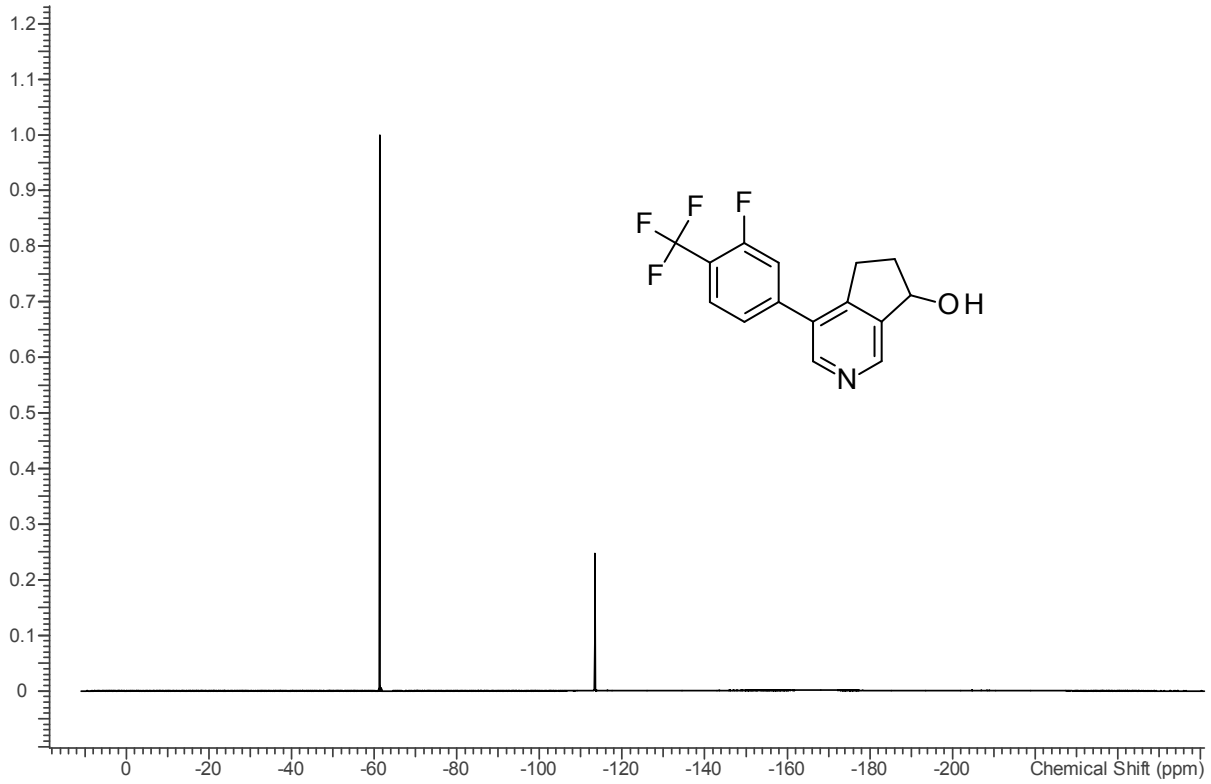
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
Chemical Shift (ppm)
F
F
F
F
O
N

4-[3-Fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-7-ol (19)



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0.6
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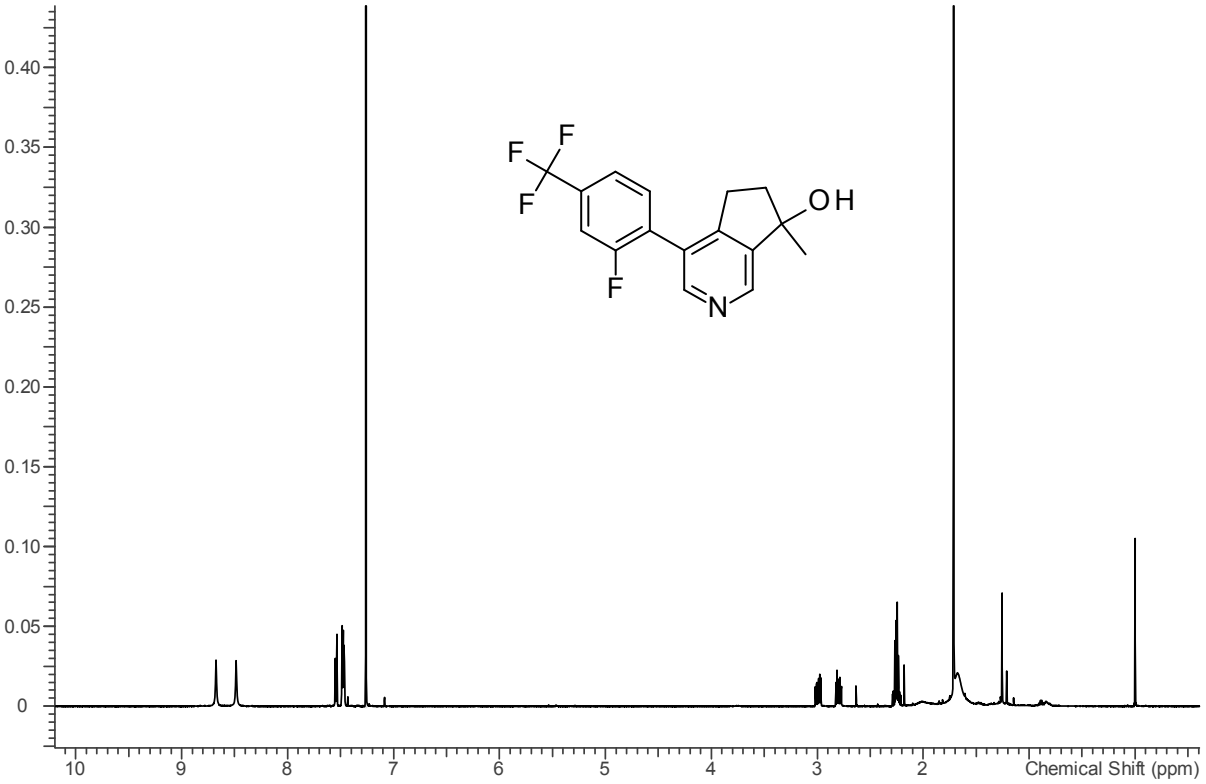
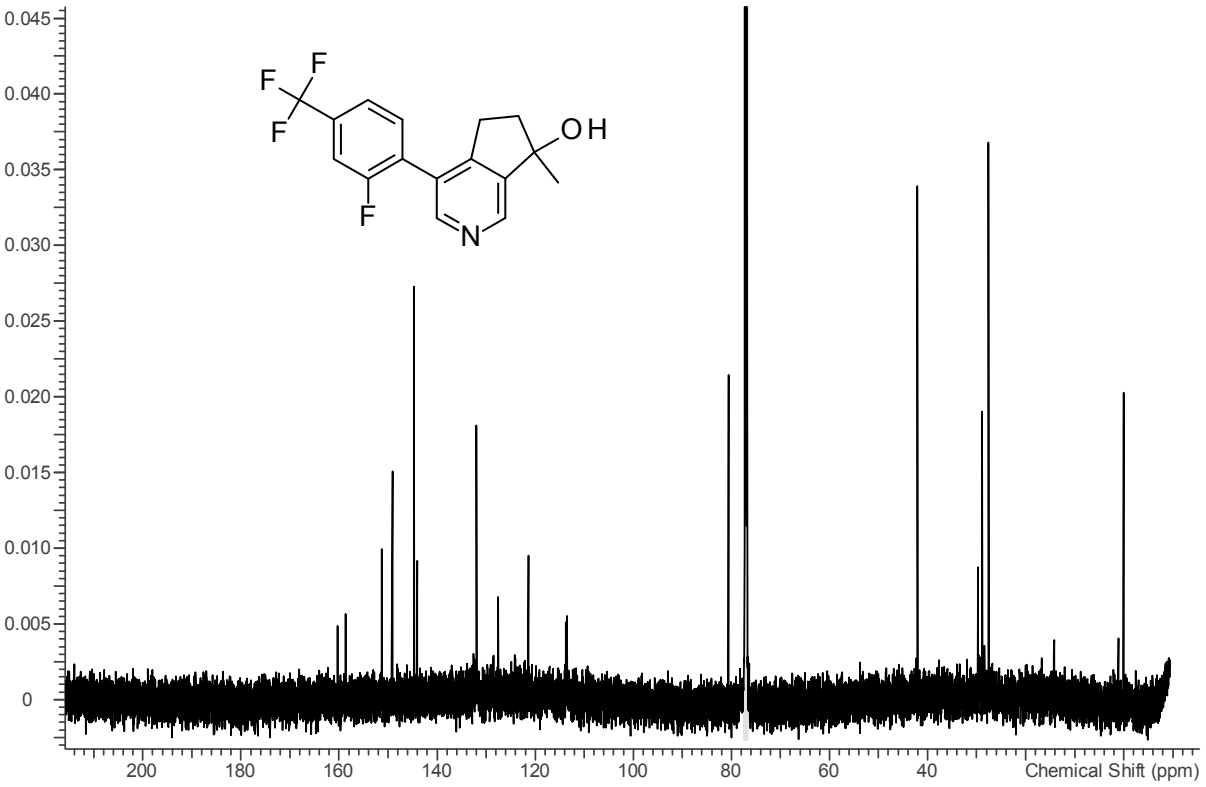
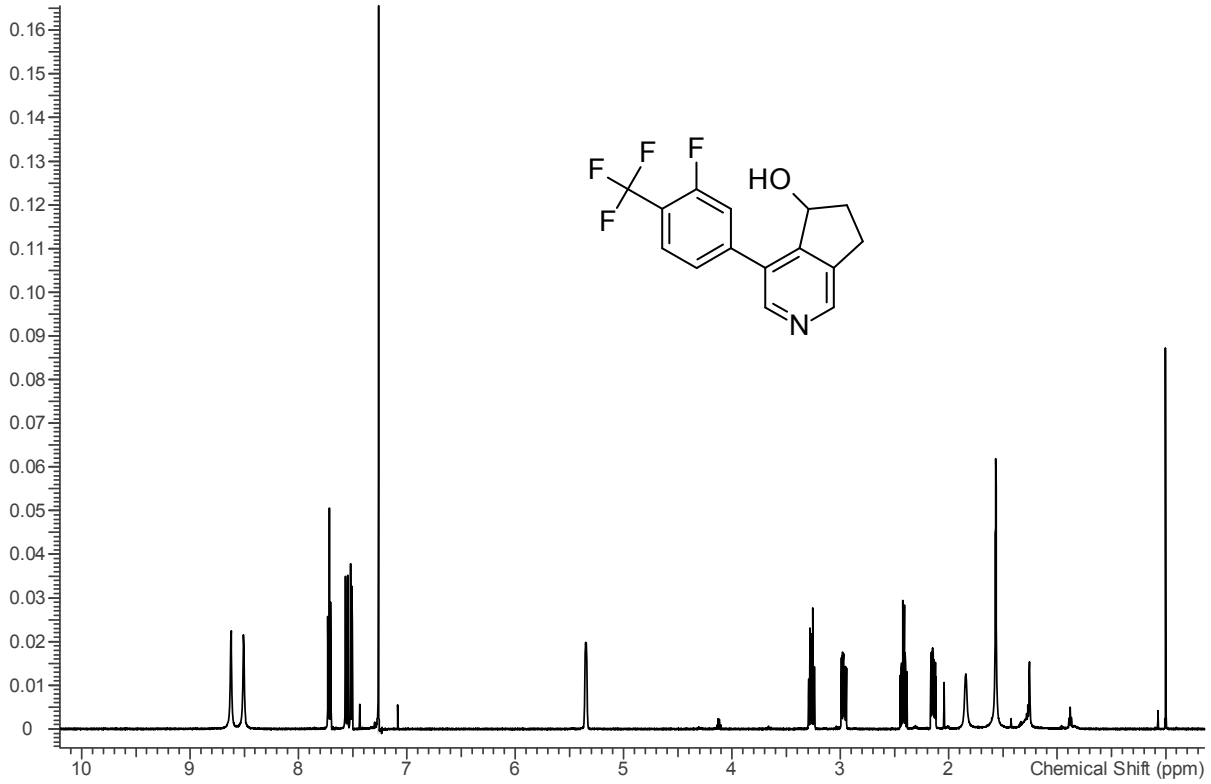
0.2
0.1
0
F
F
F
F
OH
N
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

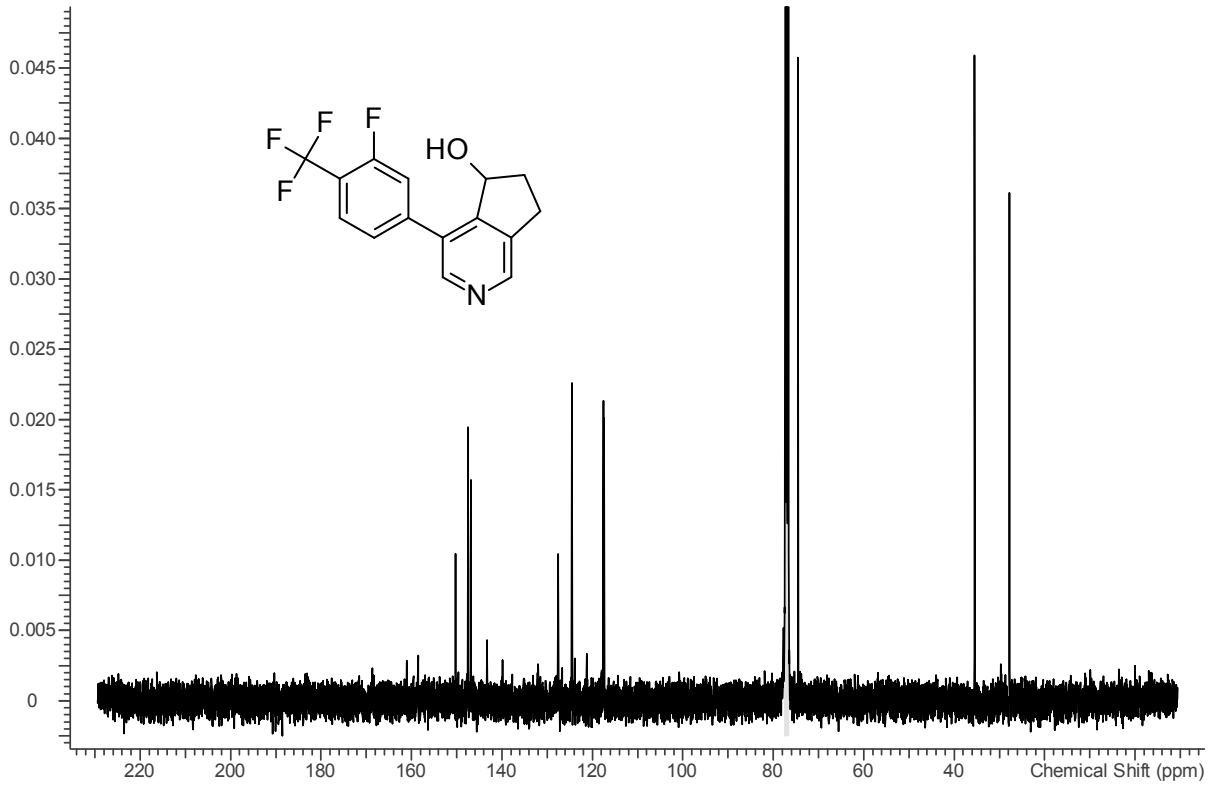
4-[2-Fluoro-4-(trifluoromethyl)phenyl]-7-methyl-5,6-dihydrocyclopenta[*c*]pyridin-7-ol (20)

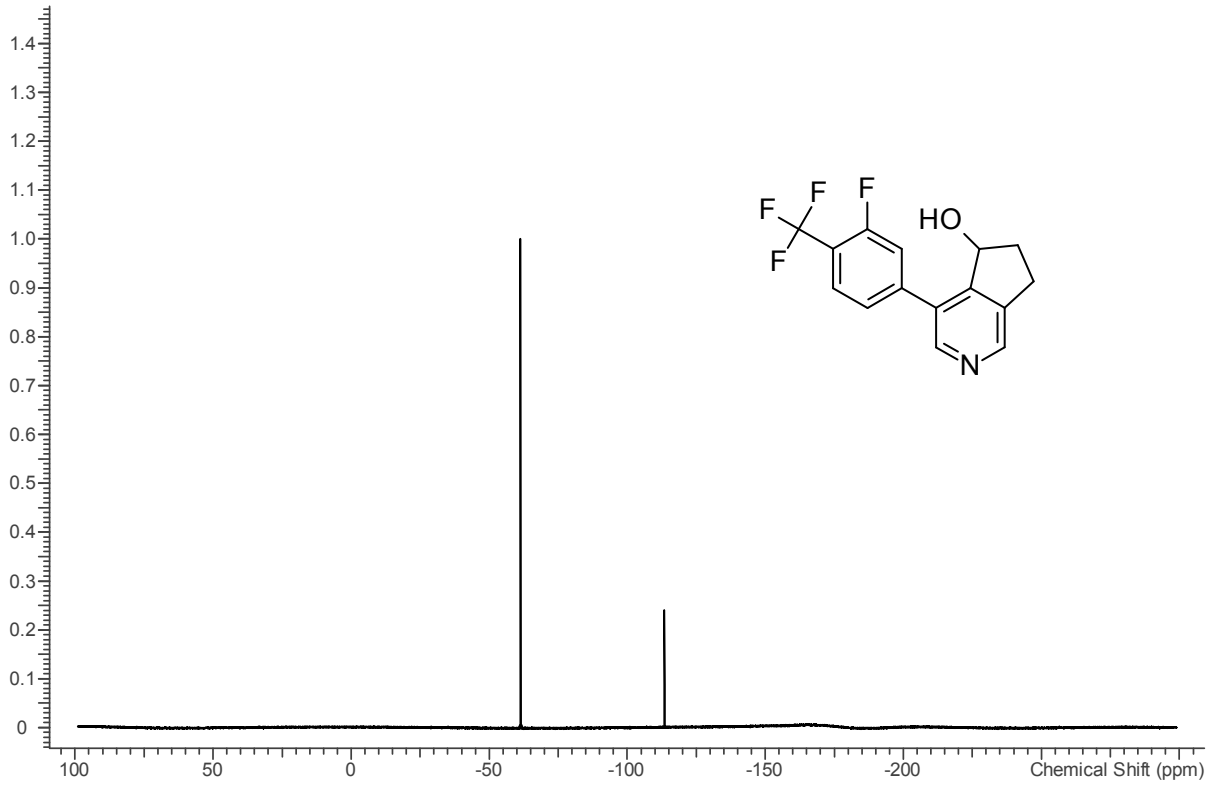




4-[3-Fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-5-ol (21)



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0.8
0.7
0.6
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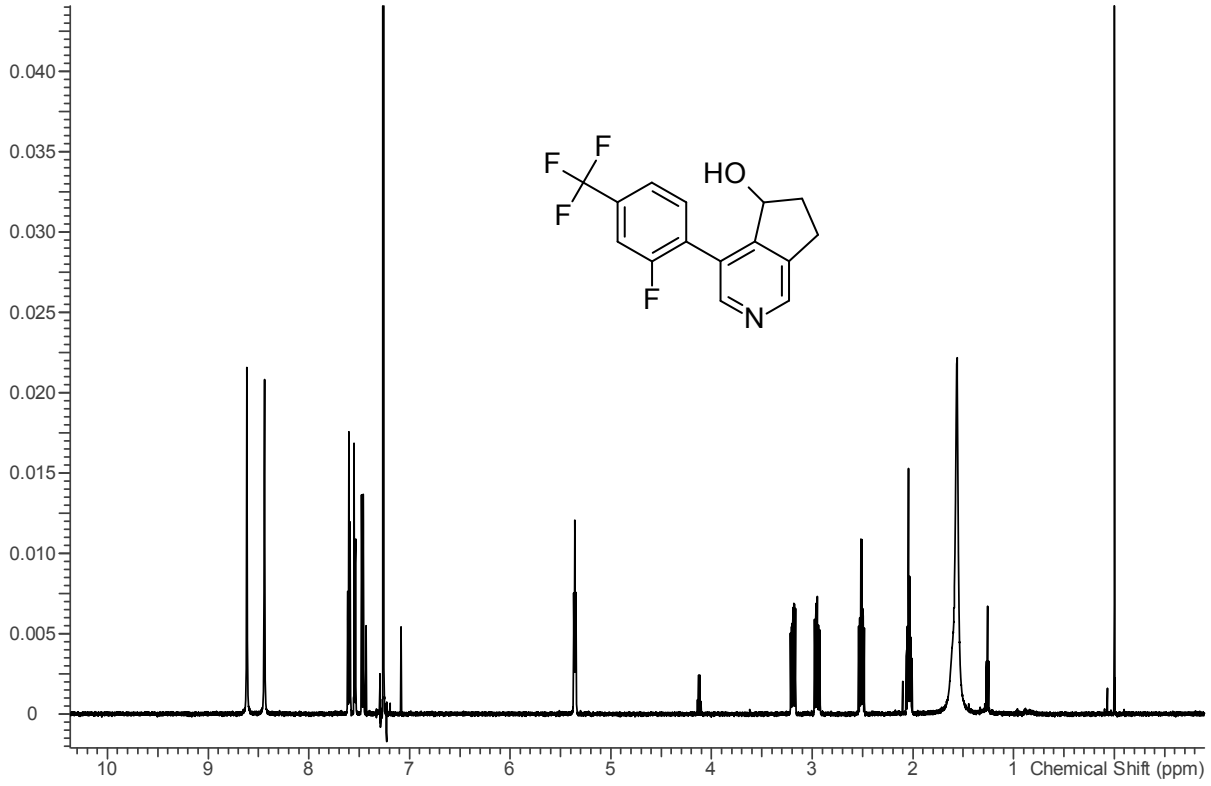
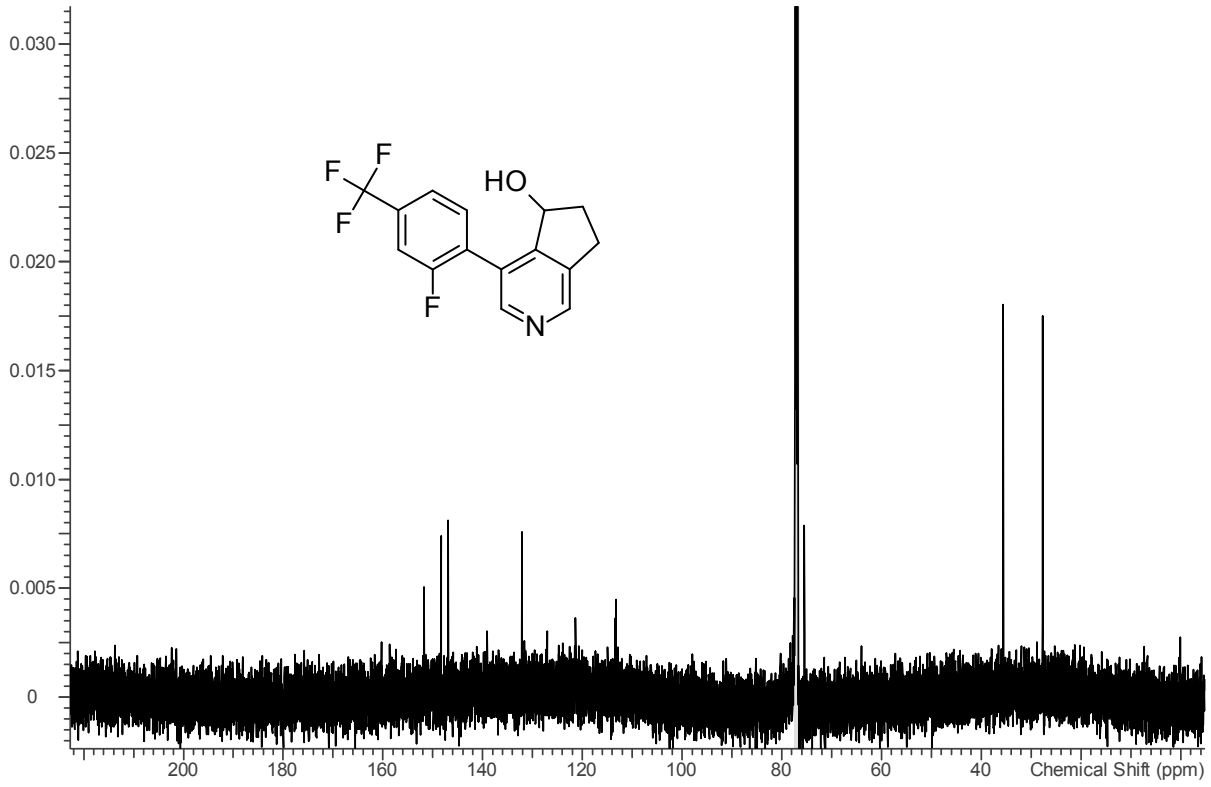
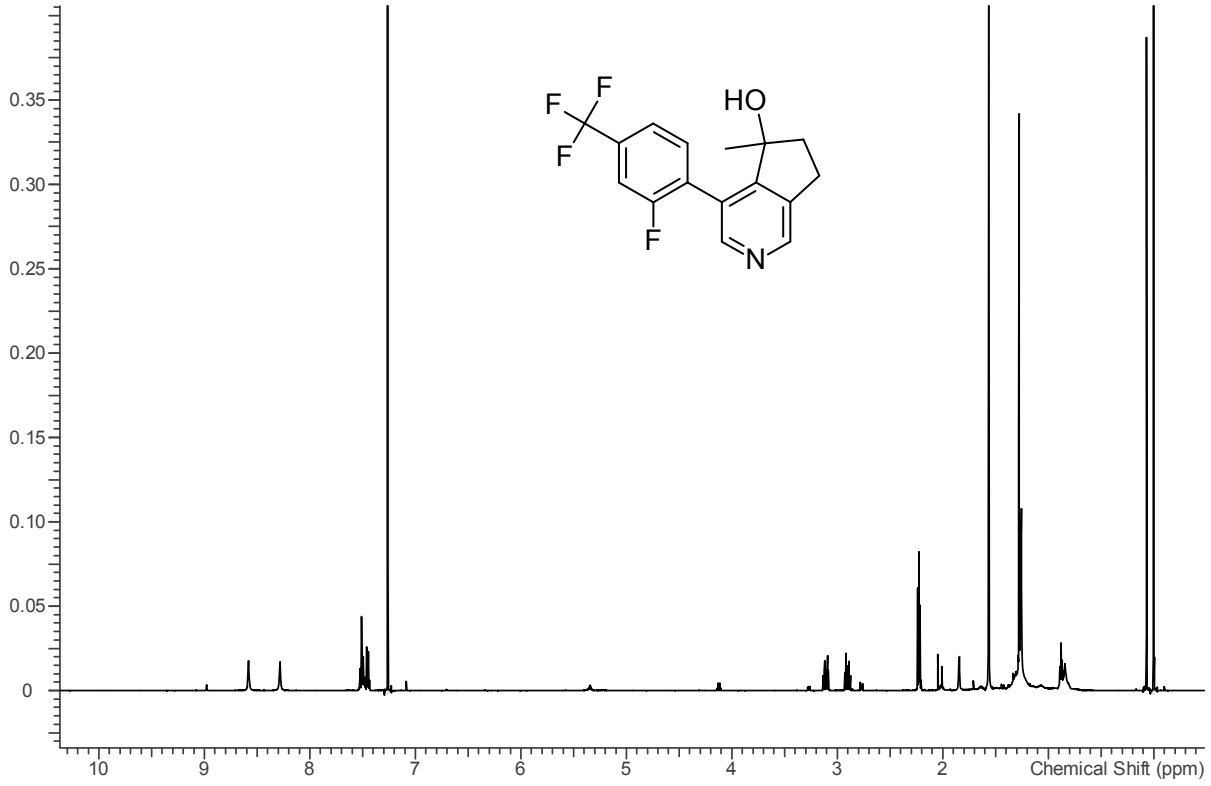
0.3
0.2
0.1
0
100
50
0
-50
-100
-150
-200
Chemical Shift (ppm)
F
F
F
F
HO
N

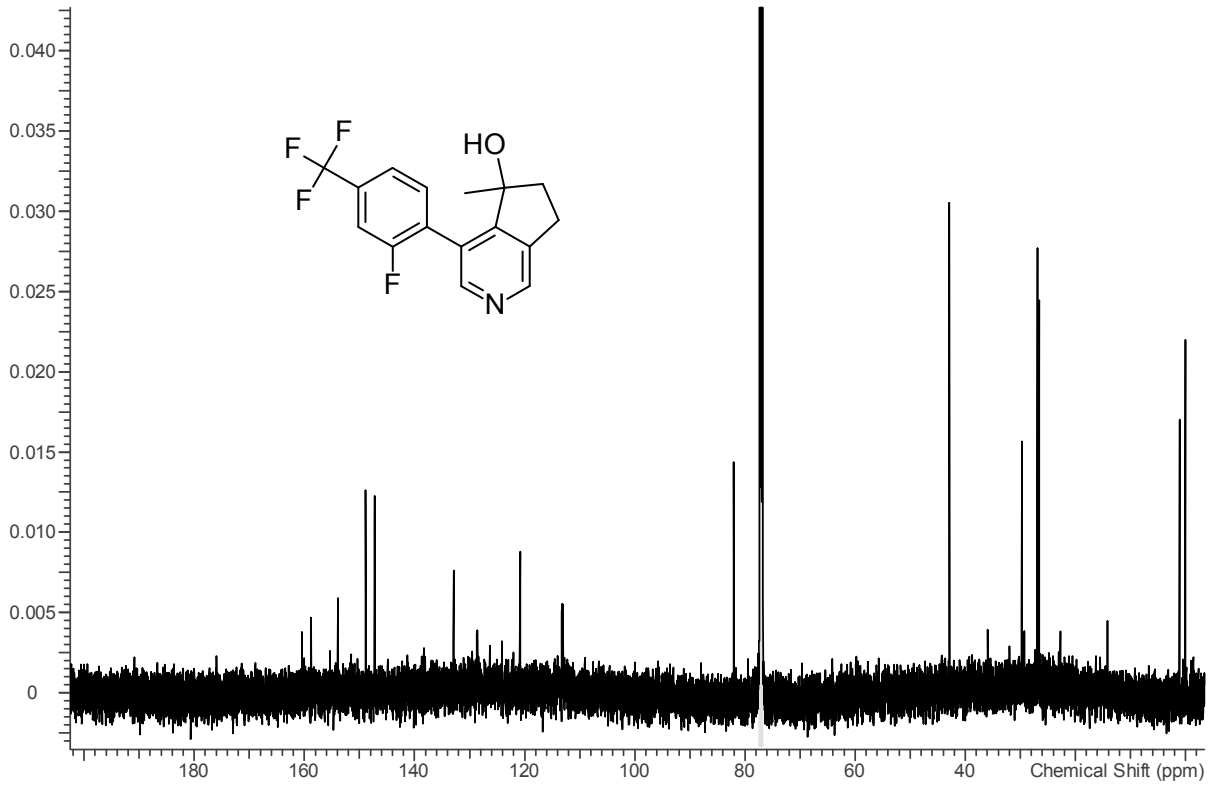
4-[2-Fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-5-ol (22)

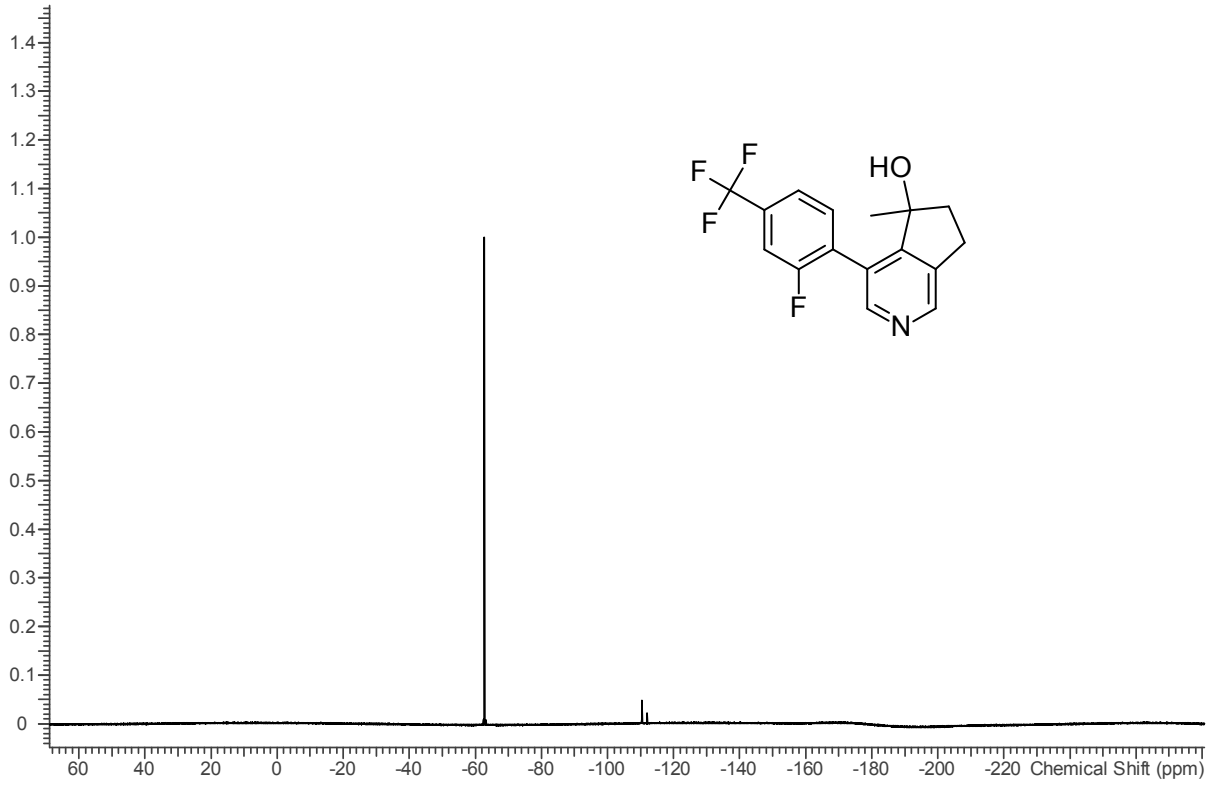




4-[2-Fluoro-4-(trifluoromethyl)phenyl]-5-methyl-6,7-dihydrocyclopenta[*c*]pyridin-5-ol (23)



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1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
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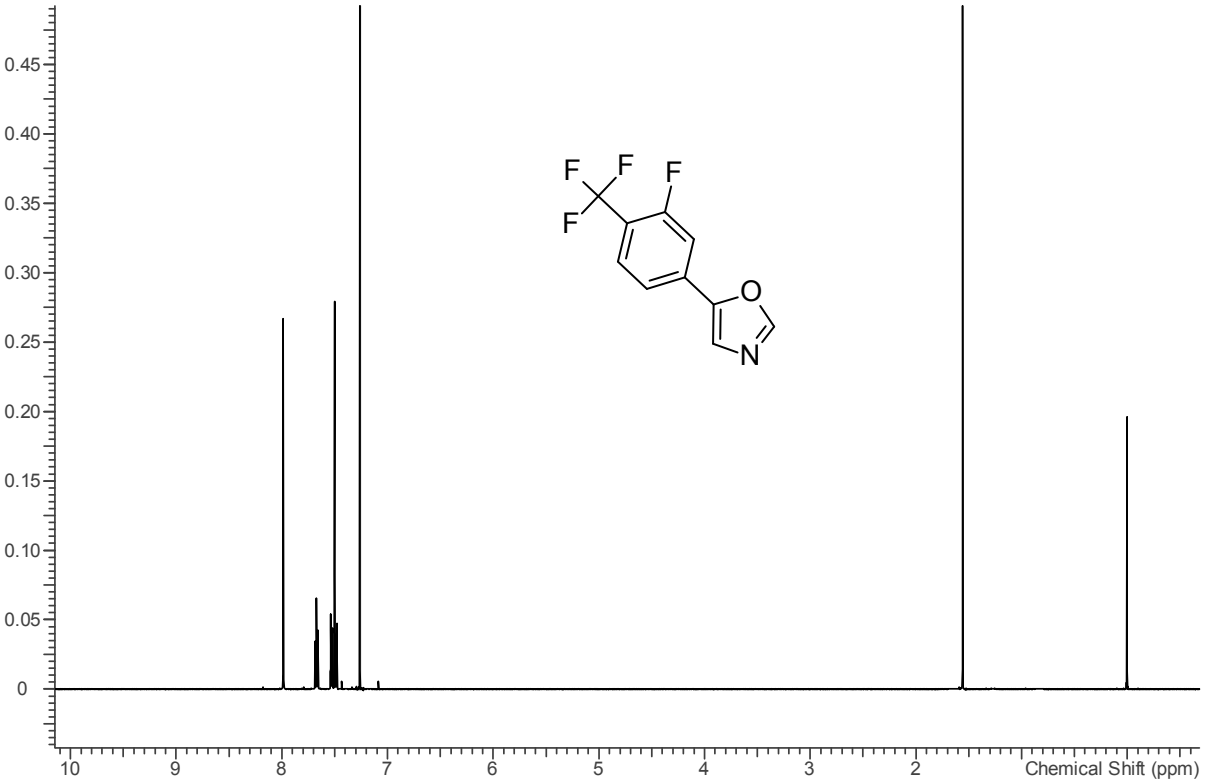
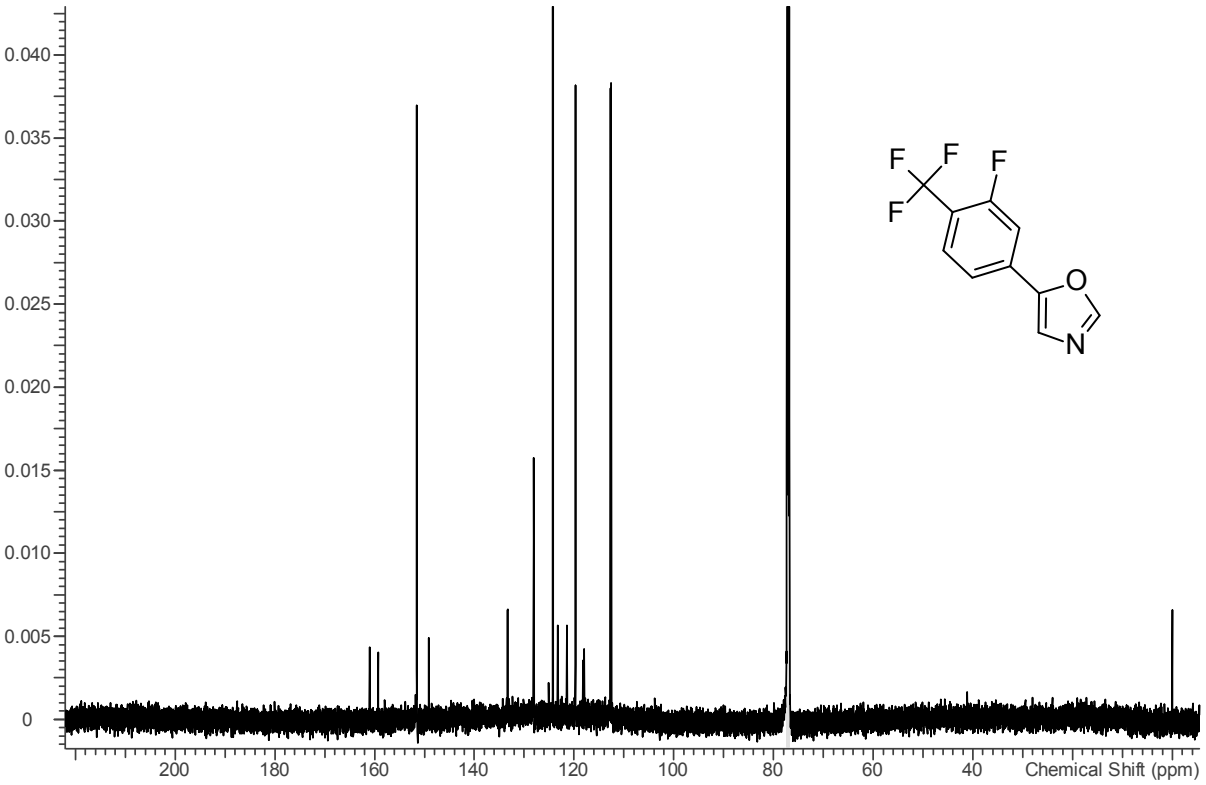
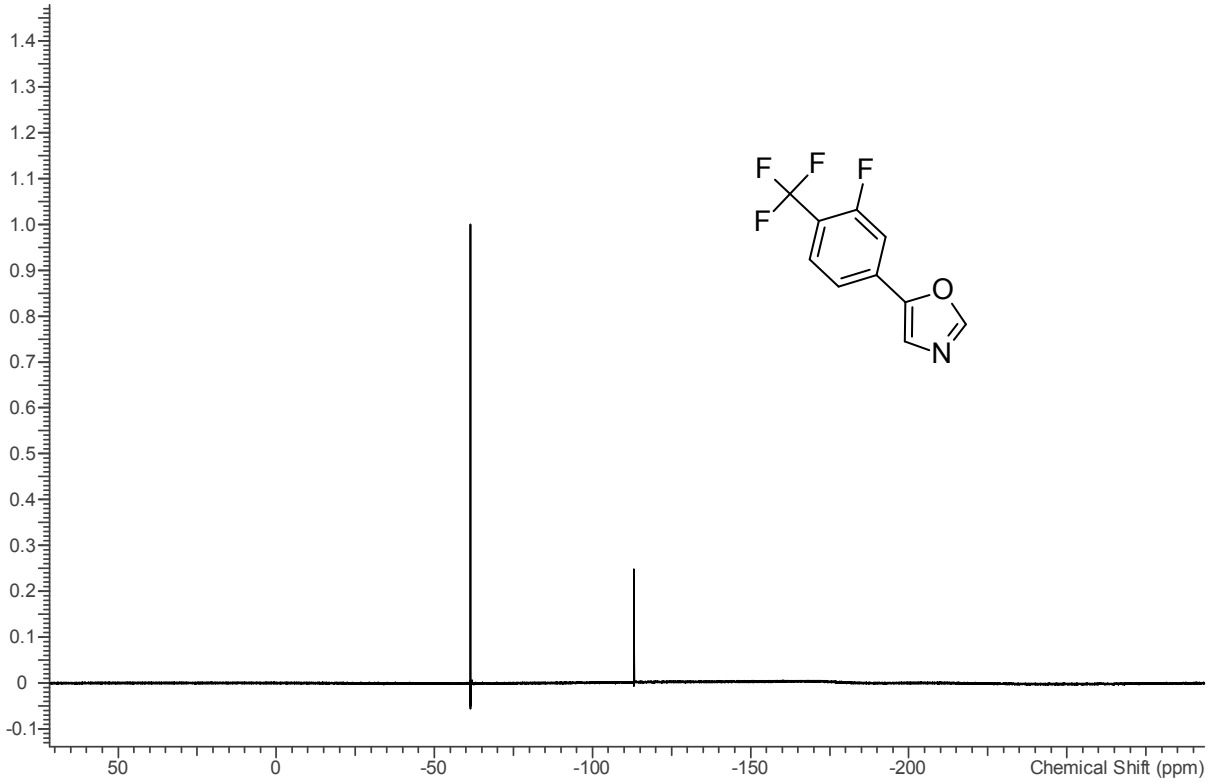
0.1
0
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
Chemical Shift (ppm)
F
F
F
HO
F
N

5-[3-Fluoro-4-(trifluoromethyl)phenyl]oxazole (24)



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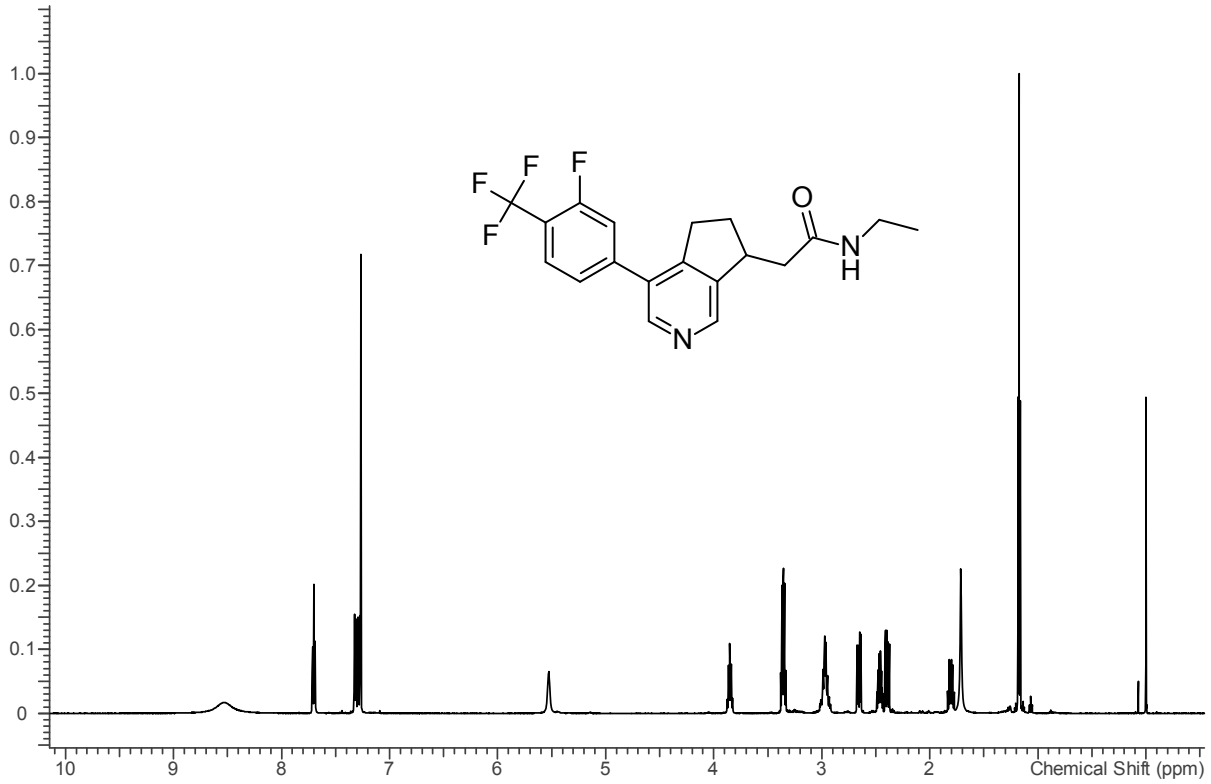
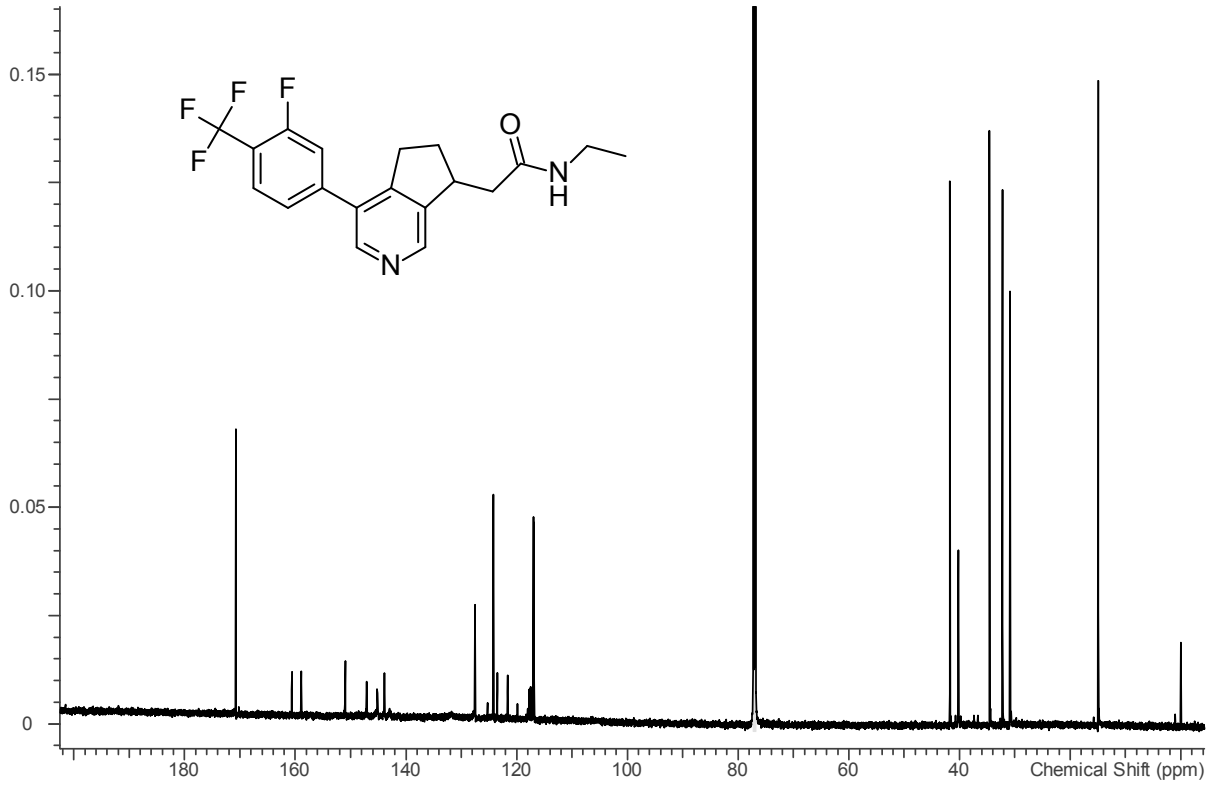
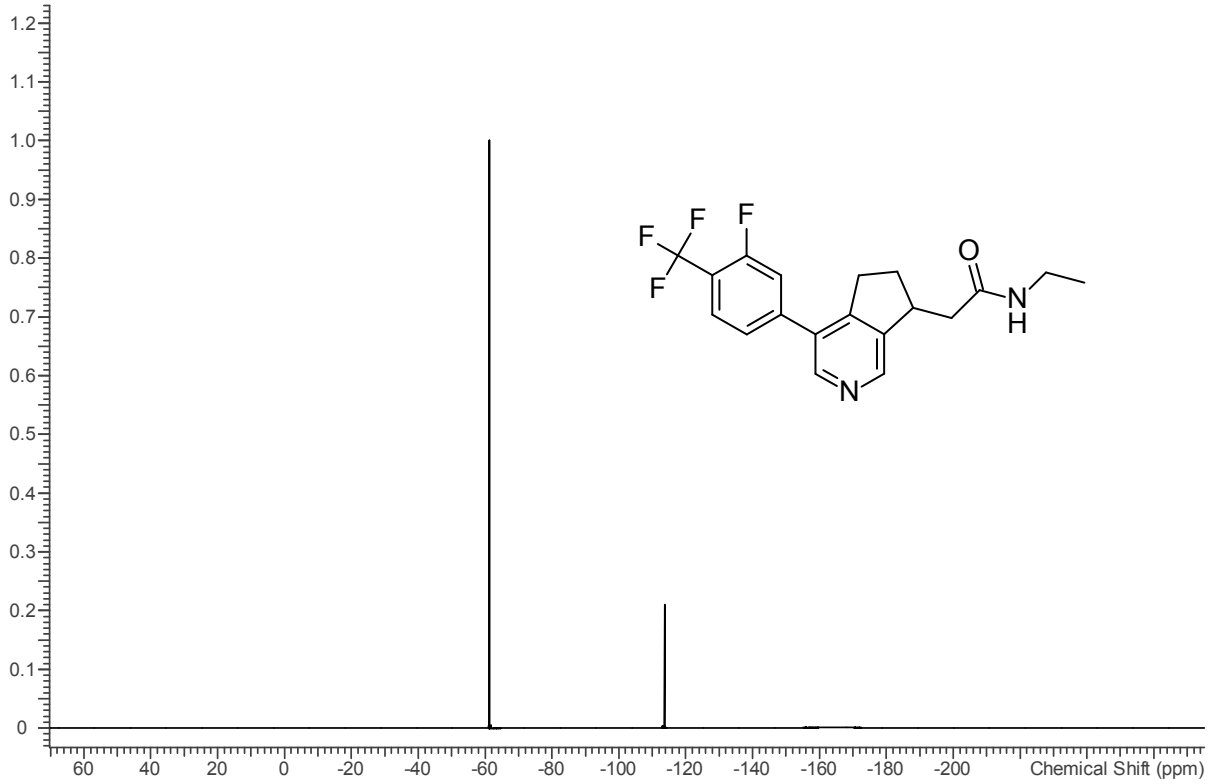
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
50
0
-50
-100
-150
-200
Chemical Shift (ppm)
F
F
F
F
O
N

_N_-Ethyl-2-[4-[3-fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5_H_-cyclopenta[_c_]pyridin-7-yl]acetamide (28)



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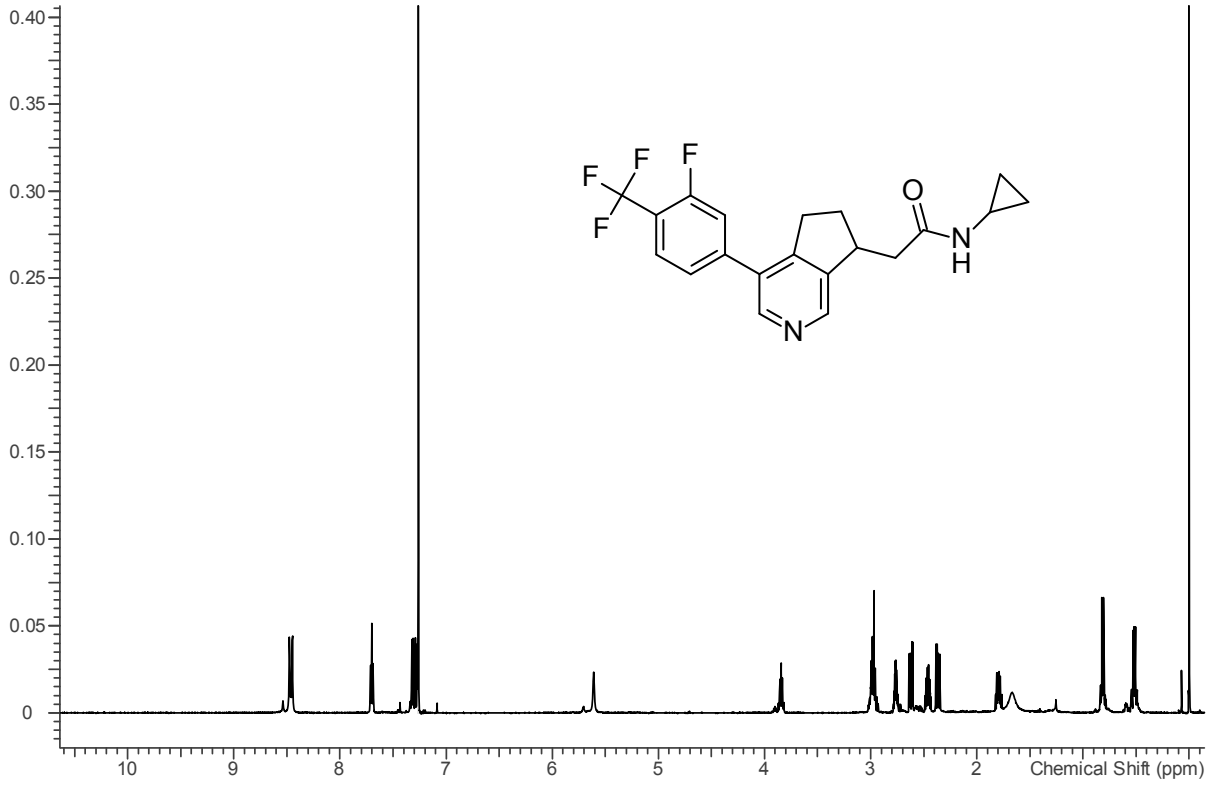
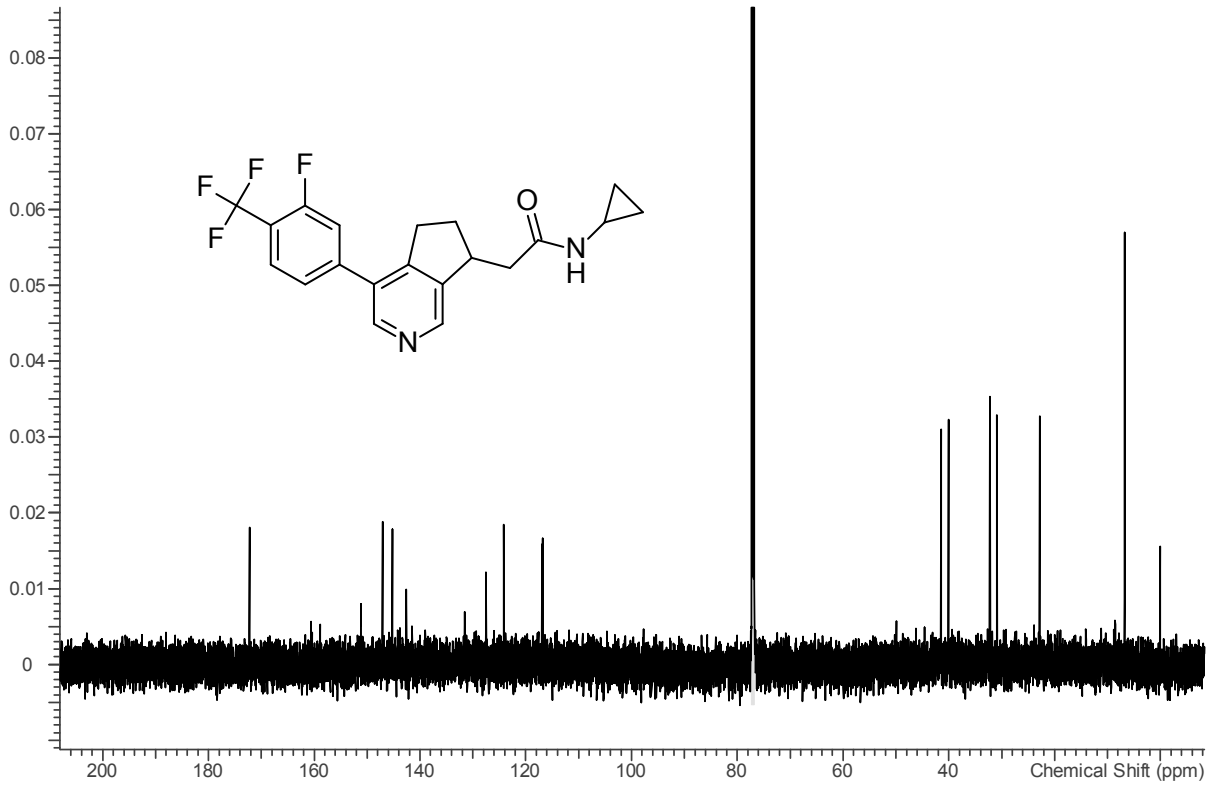
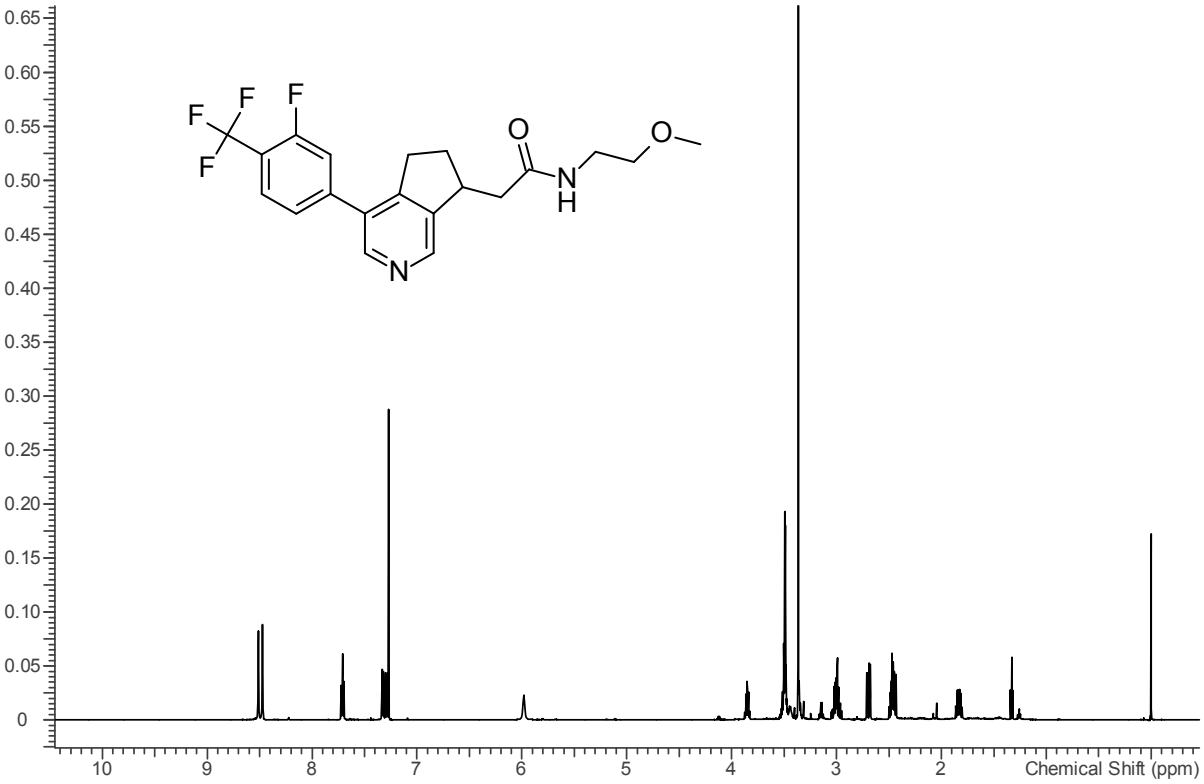
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)
F
F
F
F
O
N
H
N

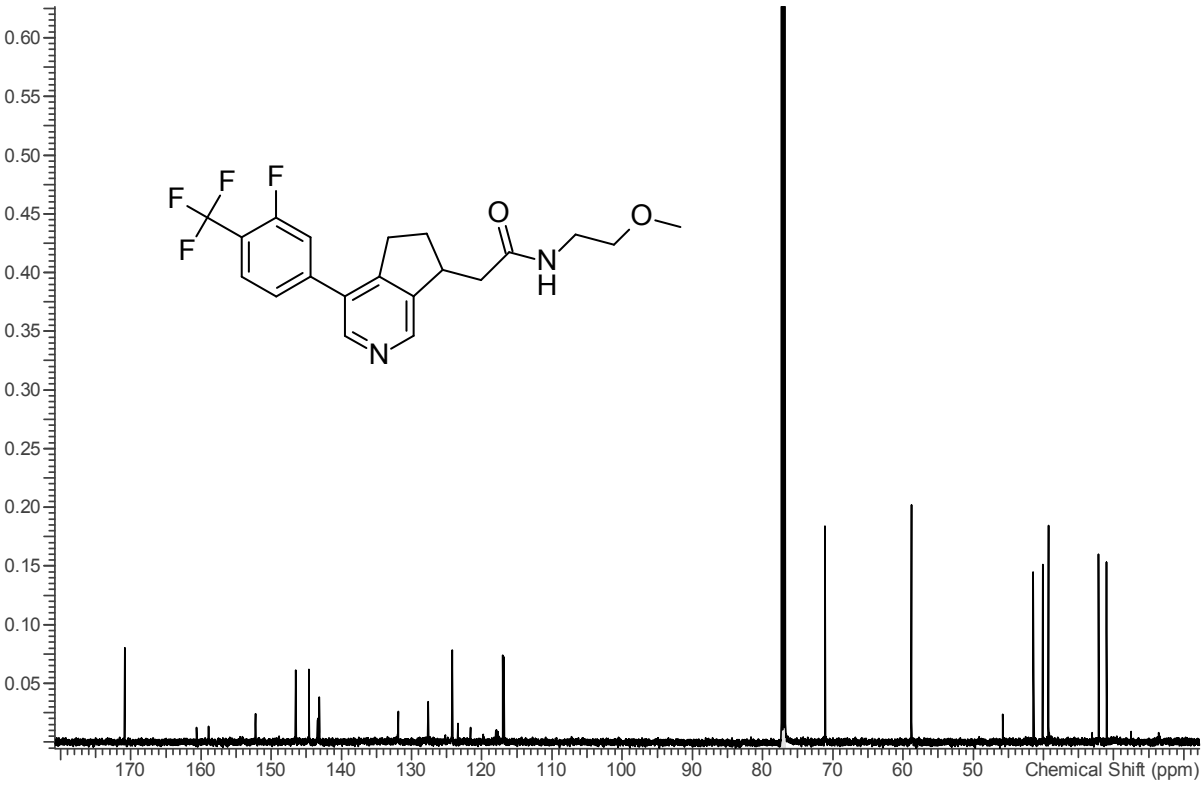
_N_-Cyclopropyl-2-[4-[3-fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5_H_-cyclopenta[_c_]pyridin-7-yl]acetamide (29)



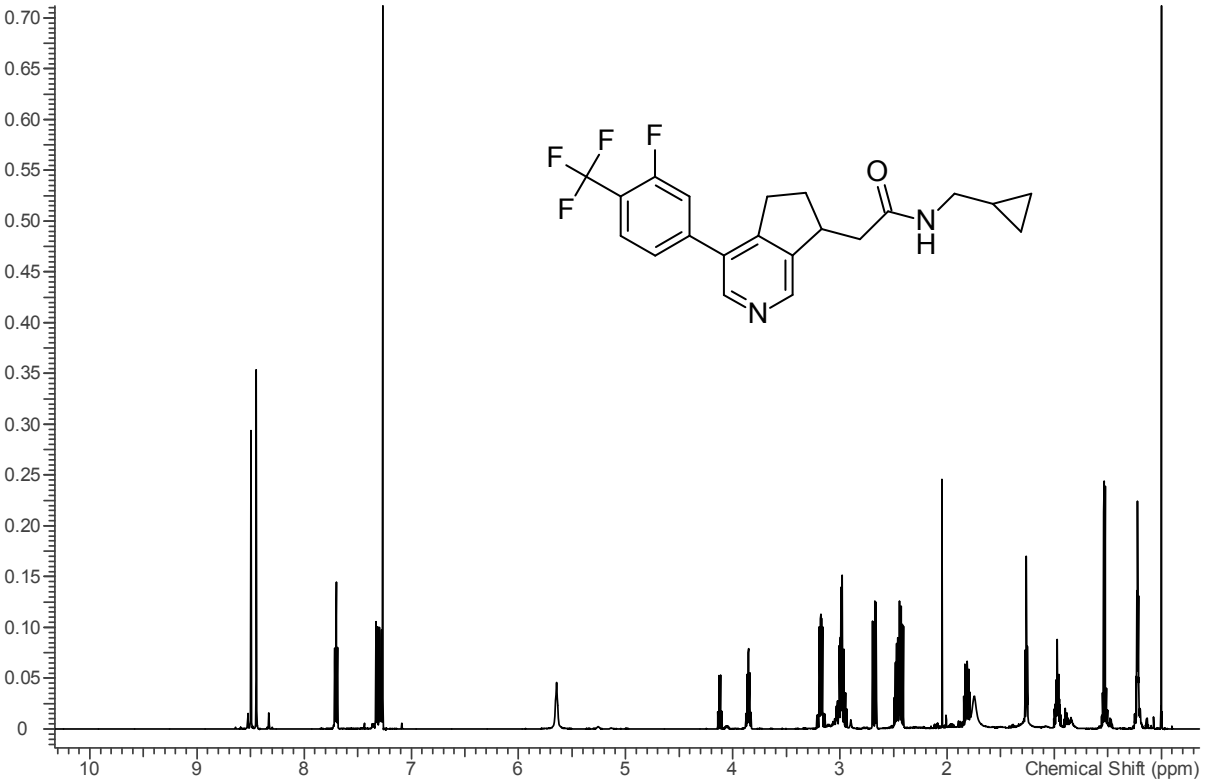


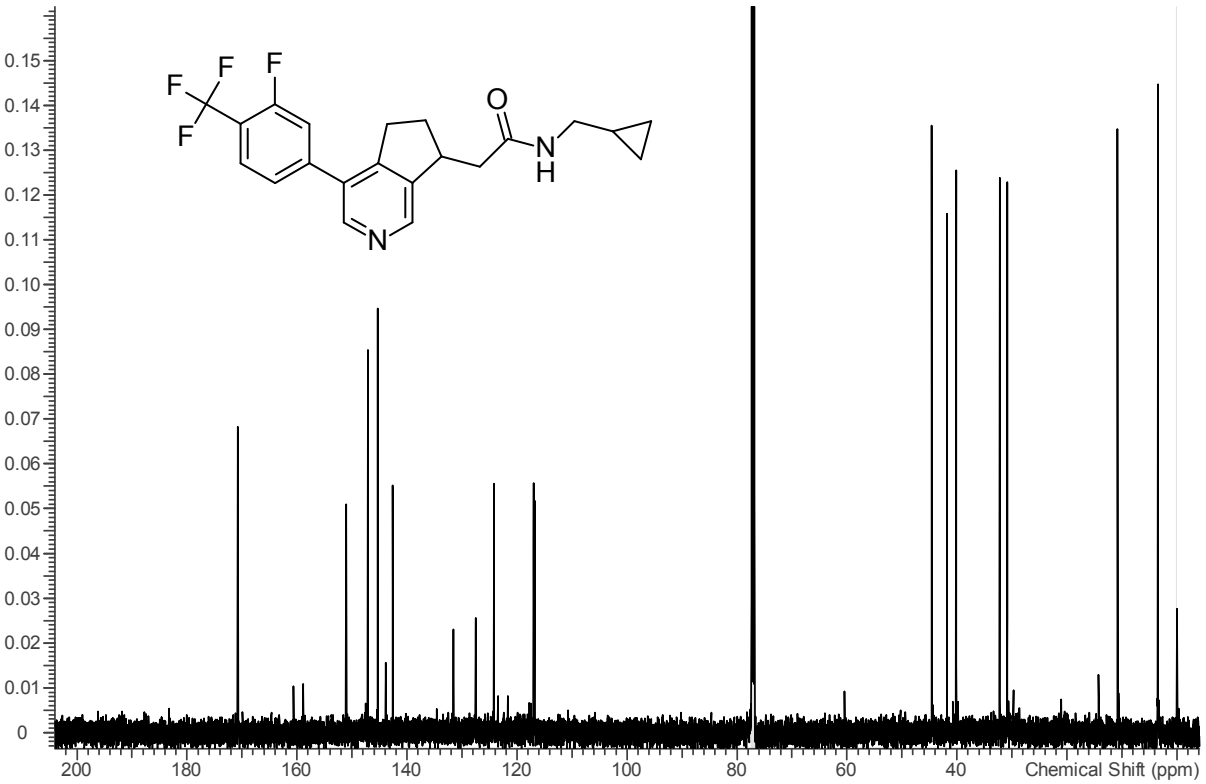
2-[4-[3-Fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-7-yl]-*N*-(2-methoxyethyl)acetamide (30)



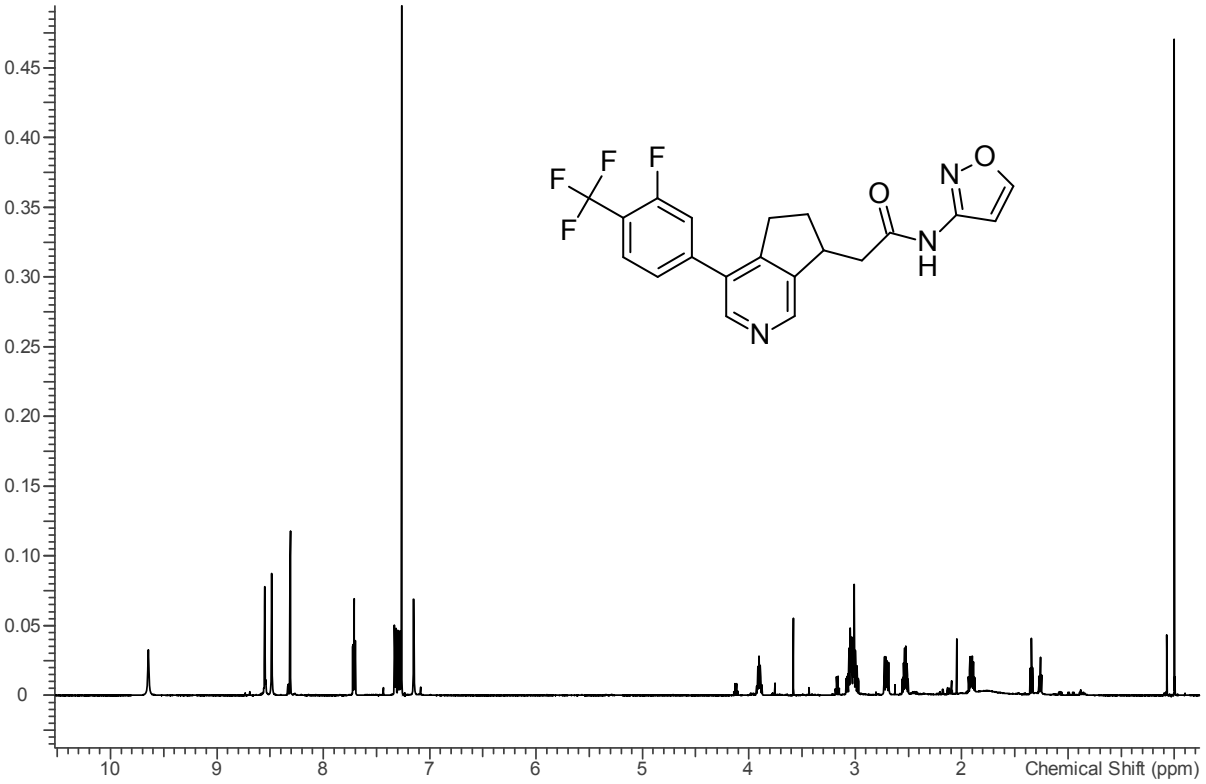


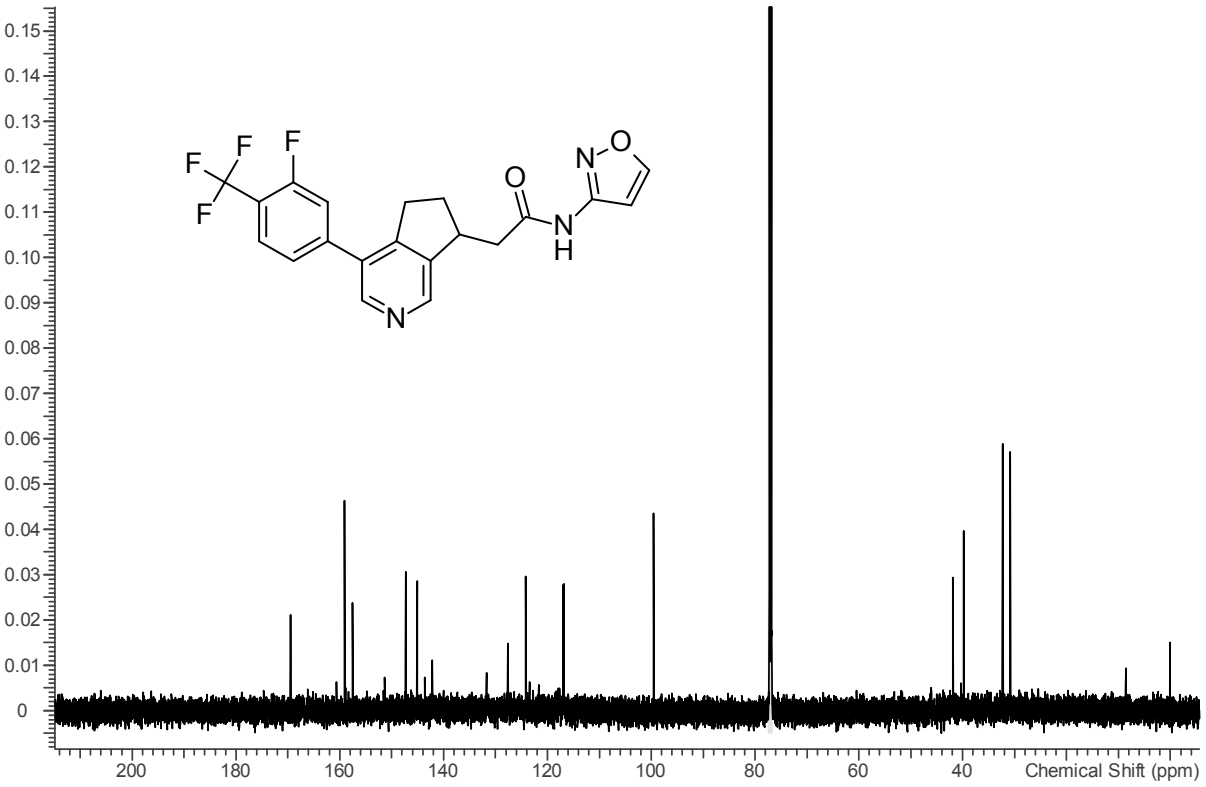
***N*-(Cyclopropylmethyl)-2-[4-[3-fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-7-yl]acetamide (31)**



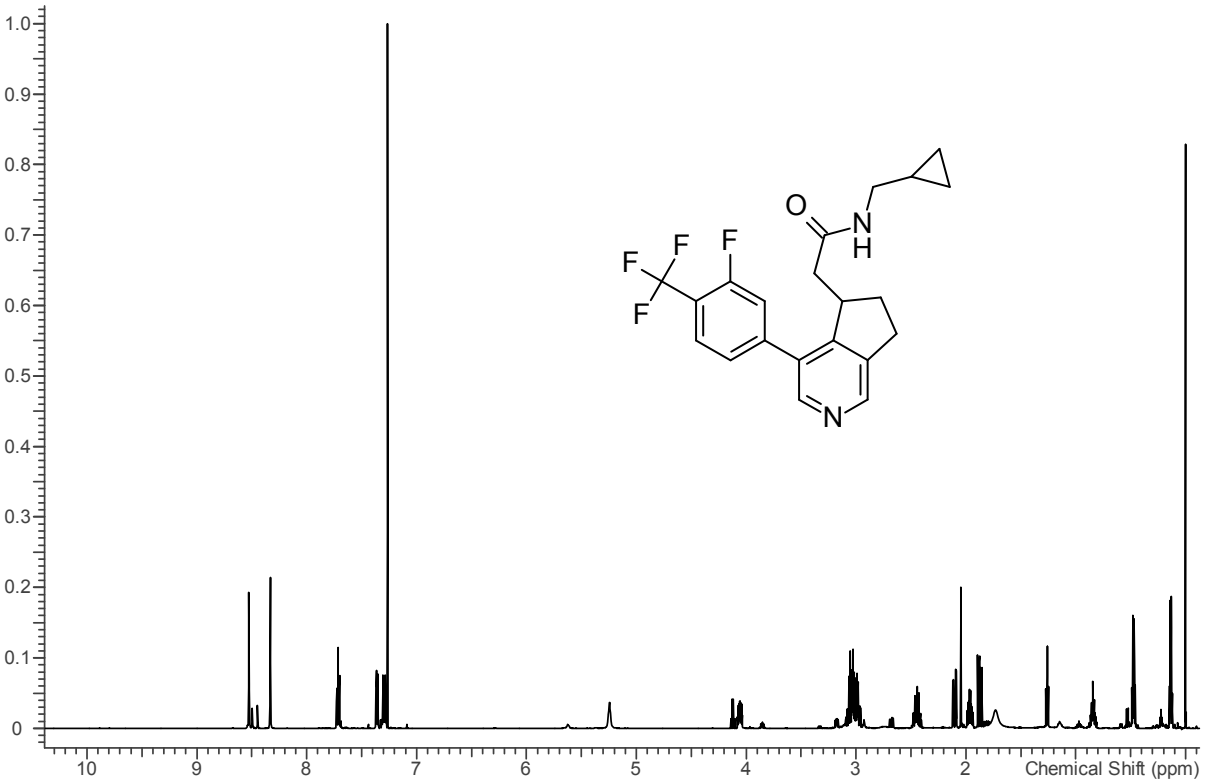


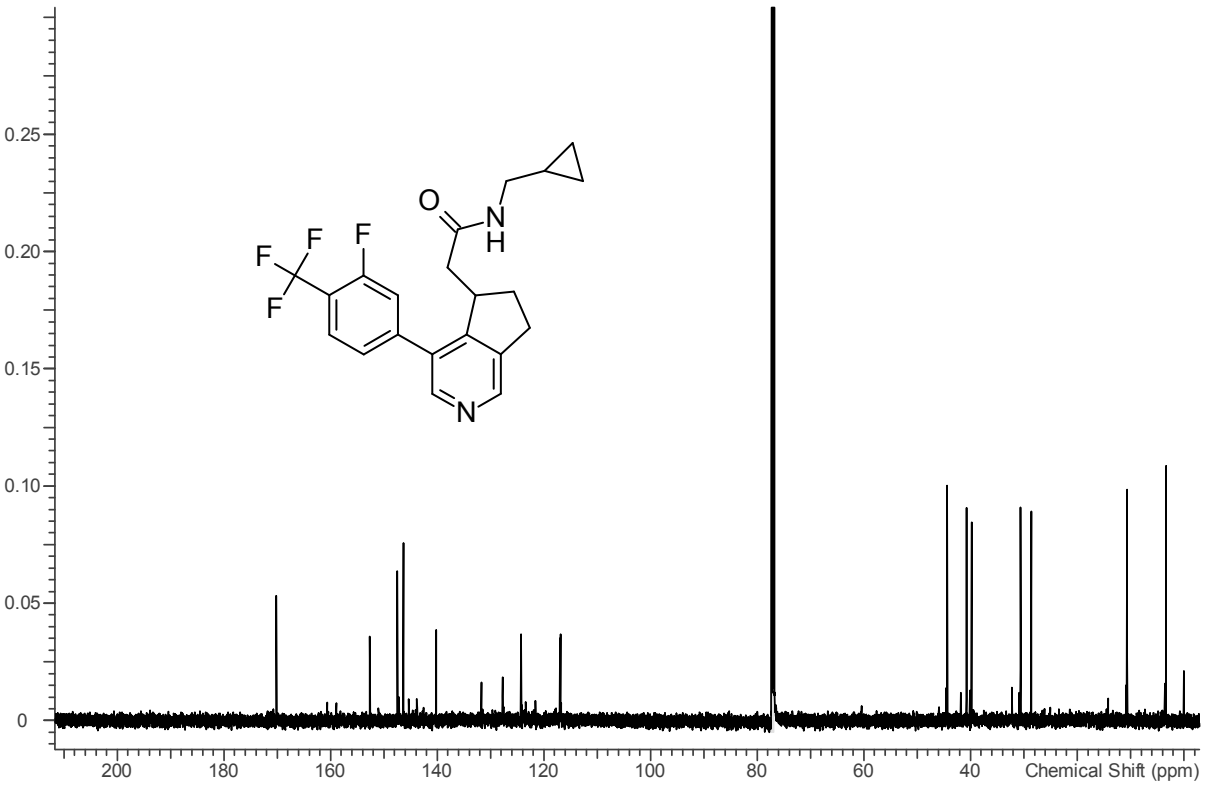
2-[4-[3-Fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-7-yl]-*N*-isoxazol-3-yl-acetamide (32)





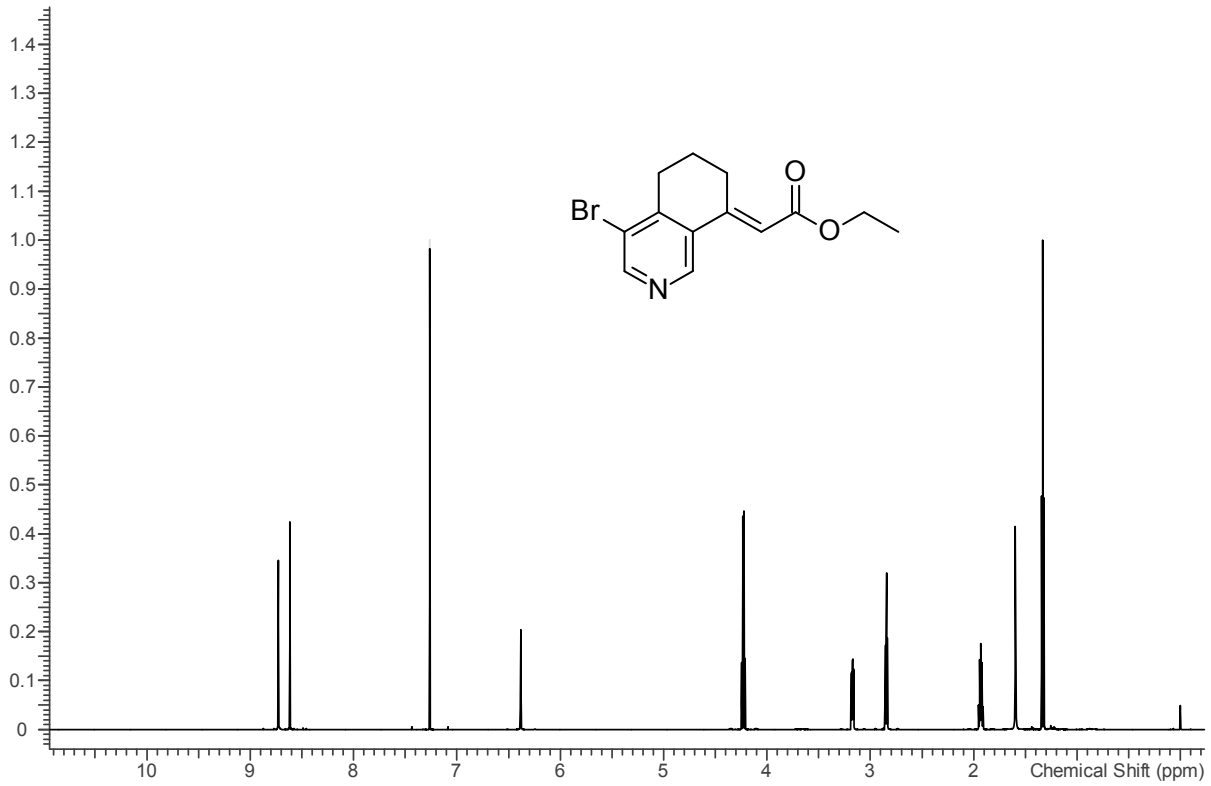
***N*-(Cyclopropylmethyl)-2-[4-[3-fluoro-4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-5-yl]acetamide (33)**

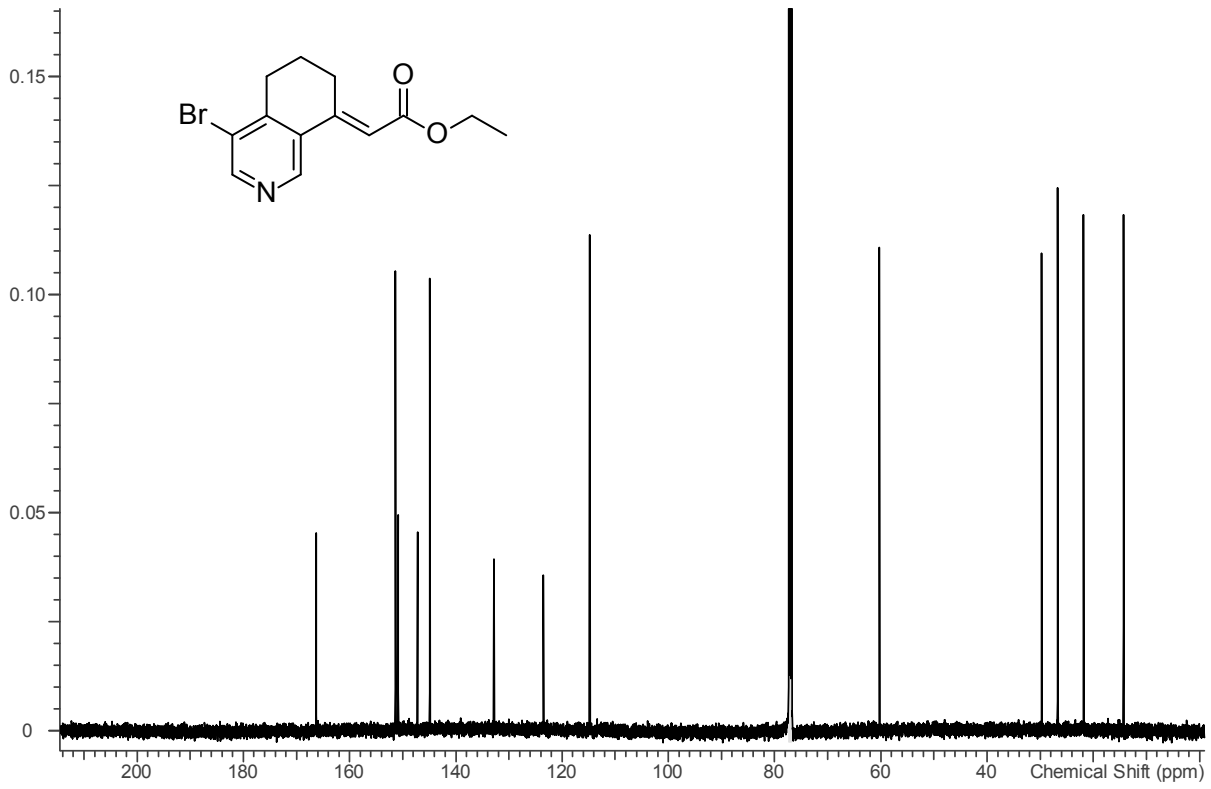




Ethyl (2*E*)-2-(4-bromo-6,7-dihydro-5*H*-isoquinolin-8-ylidene)acetate (35)

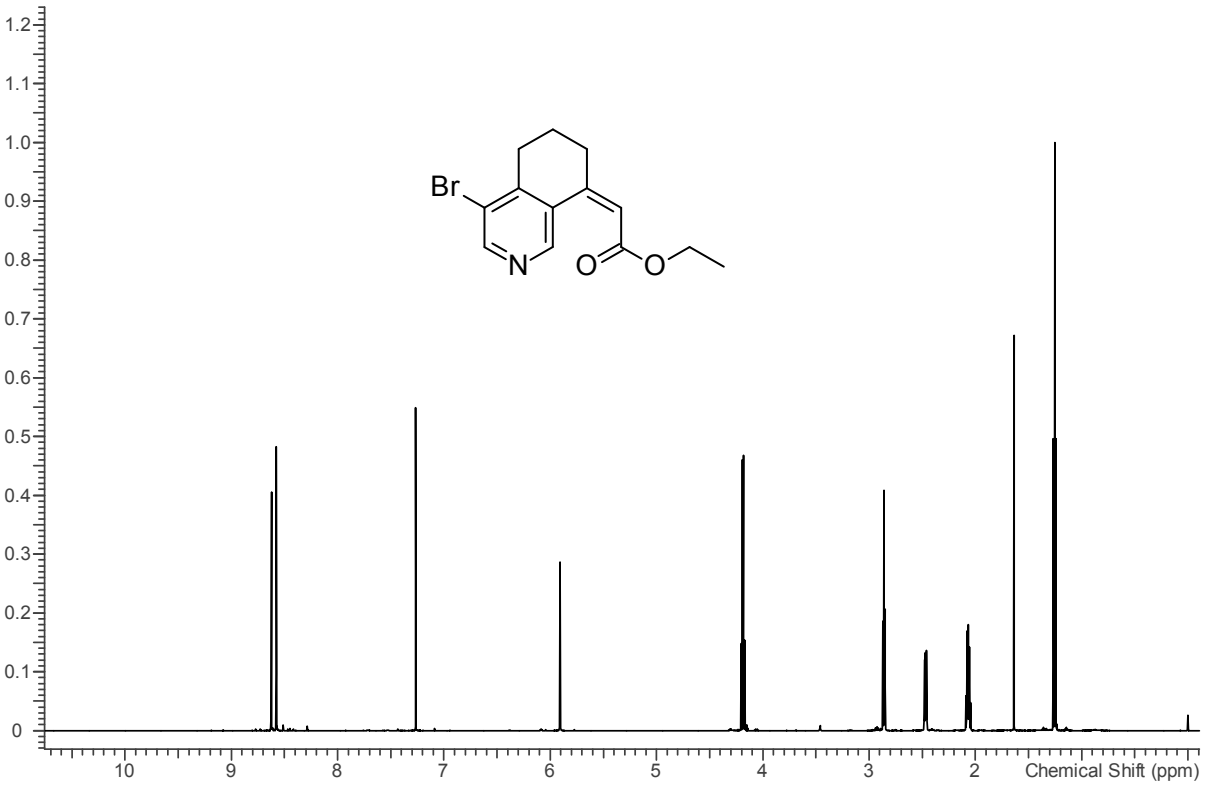
(*E*)-Product:

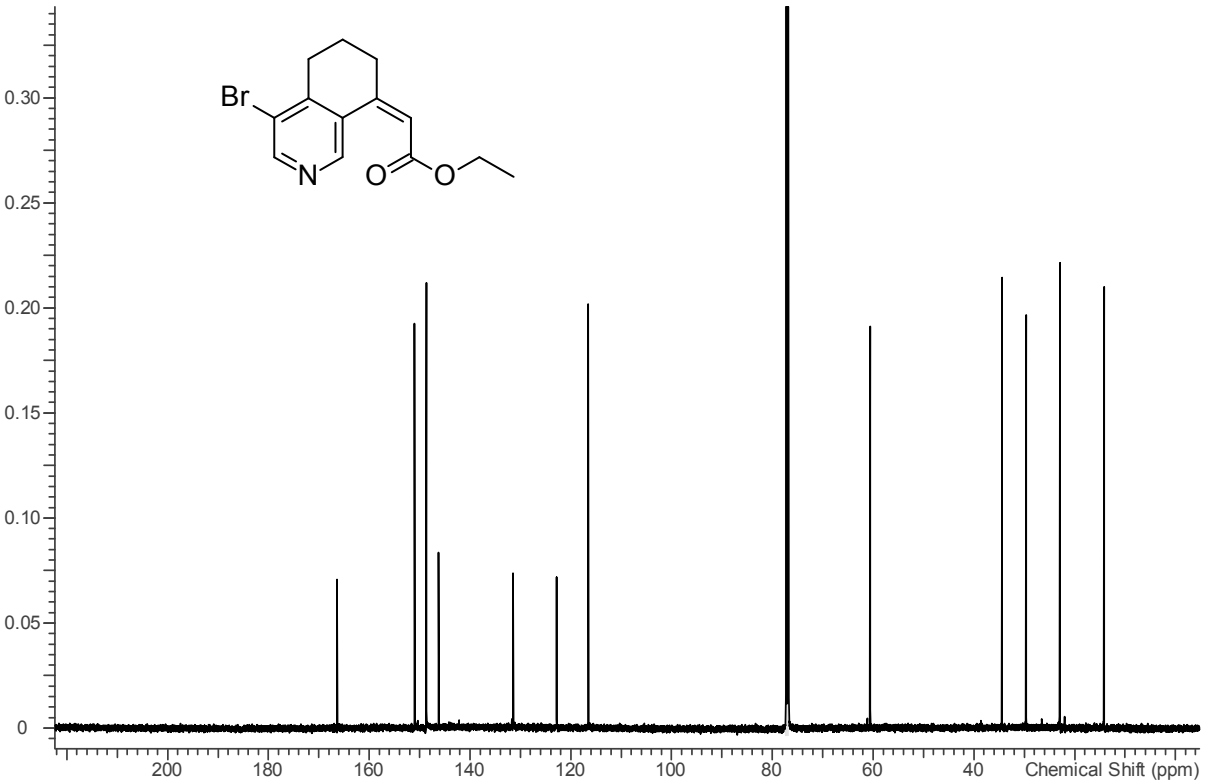




Ethyl (2*E*)-2-(4-bromo-6,7-dihydro-5*H*-isoquinolin-8-ylidene)acetate (35)

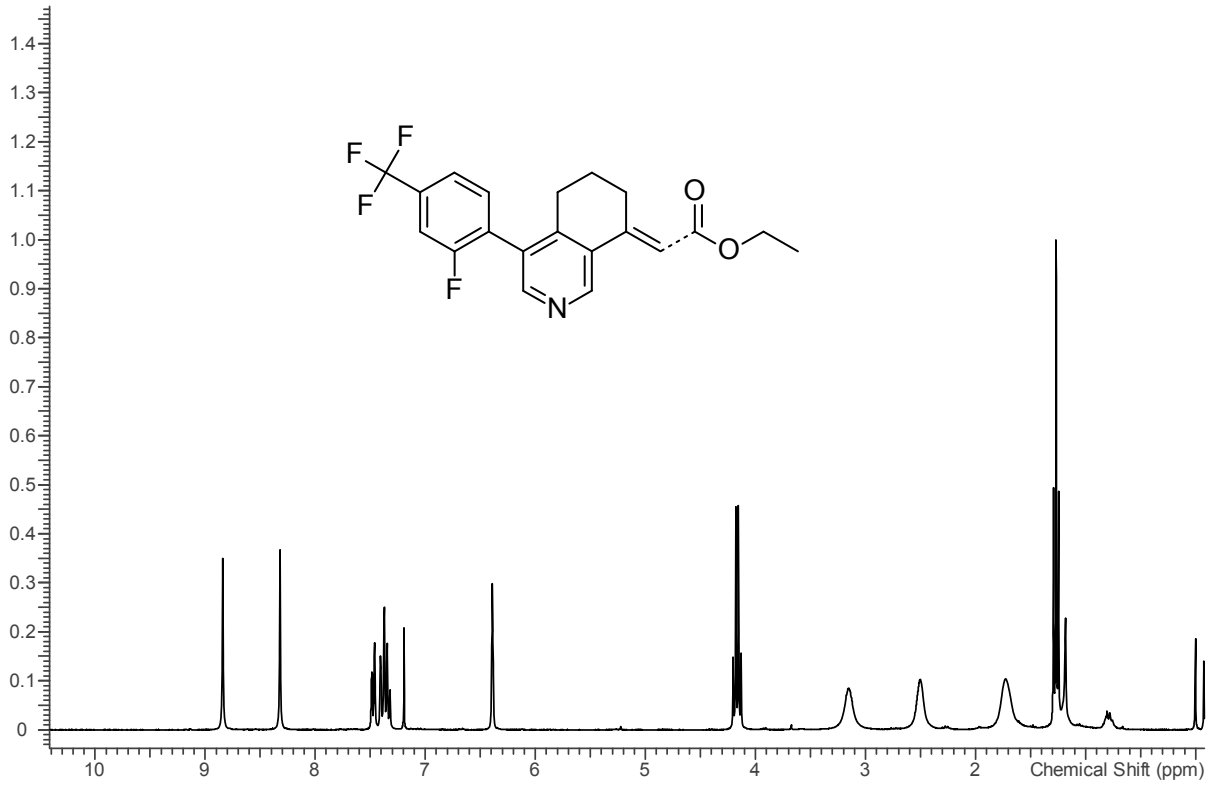
(*Z*)-Product:





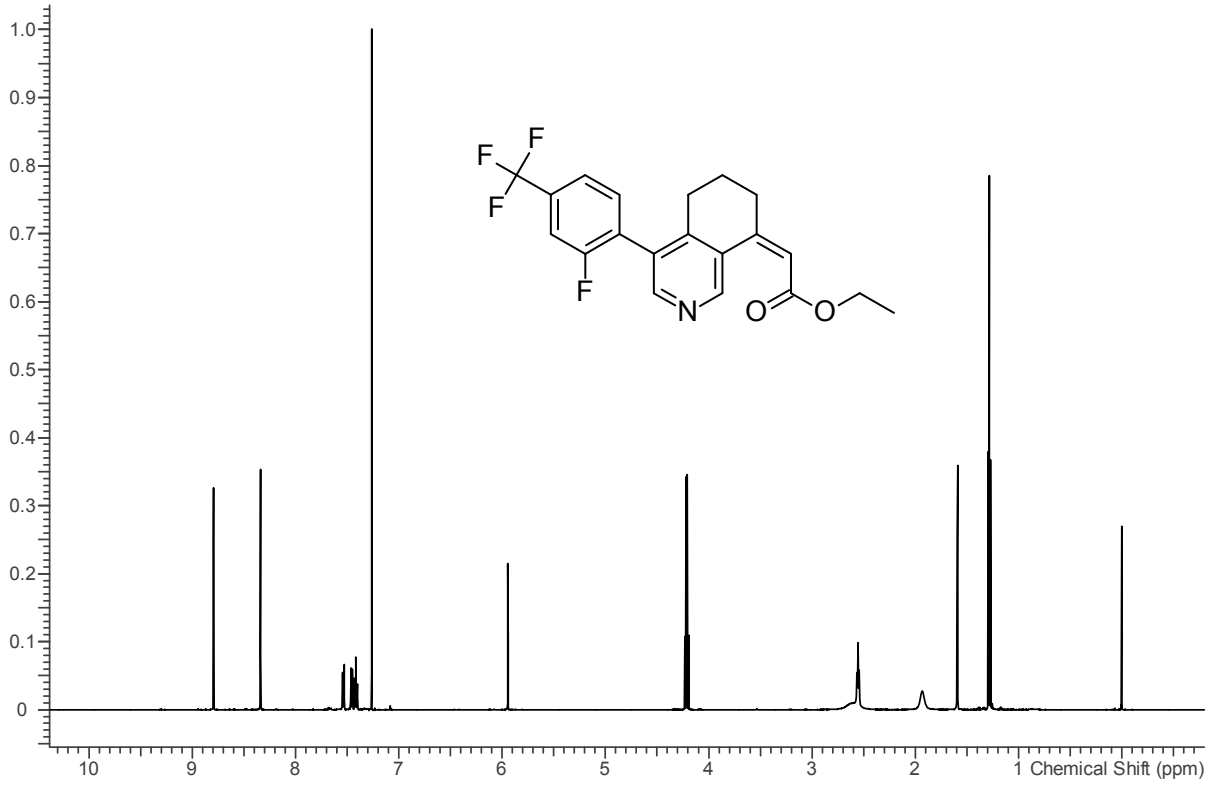
Ethyl 2-[4-[2-fluoro-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydroisoquinolin-8-yl]acetate

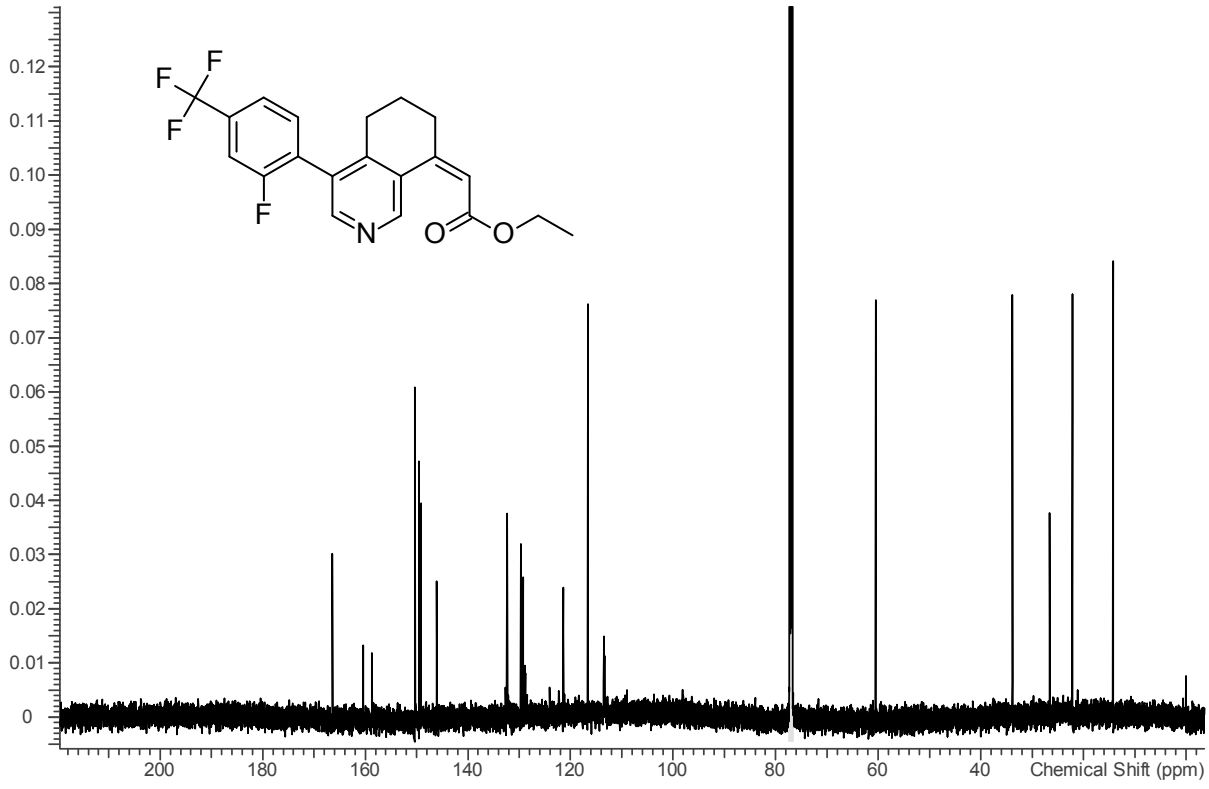
(*E*)-Product:



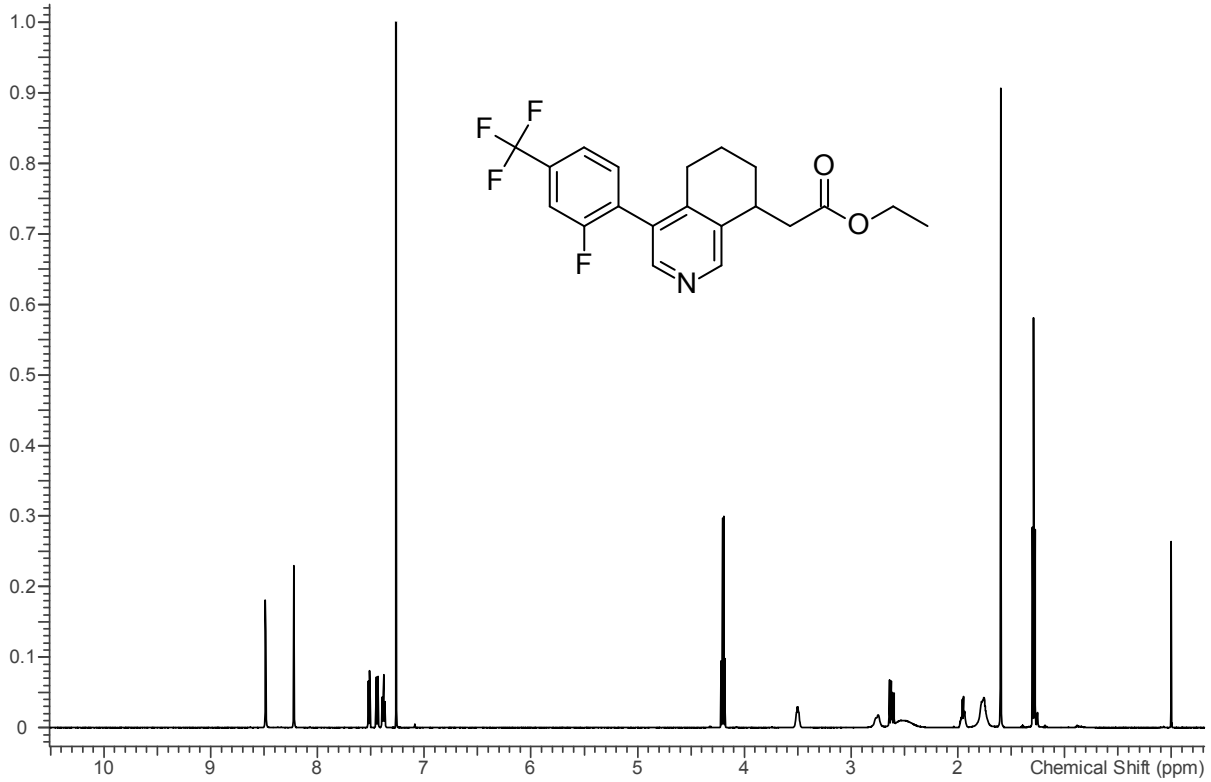
Ethyl 2-[4-[2-fluoro-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydroisoquinolin-8-yl]acetate

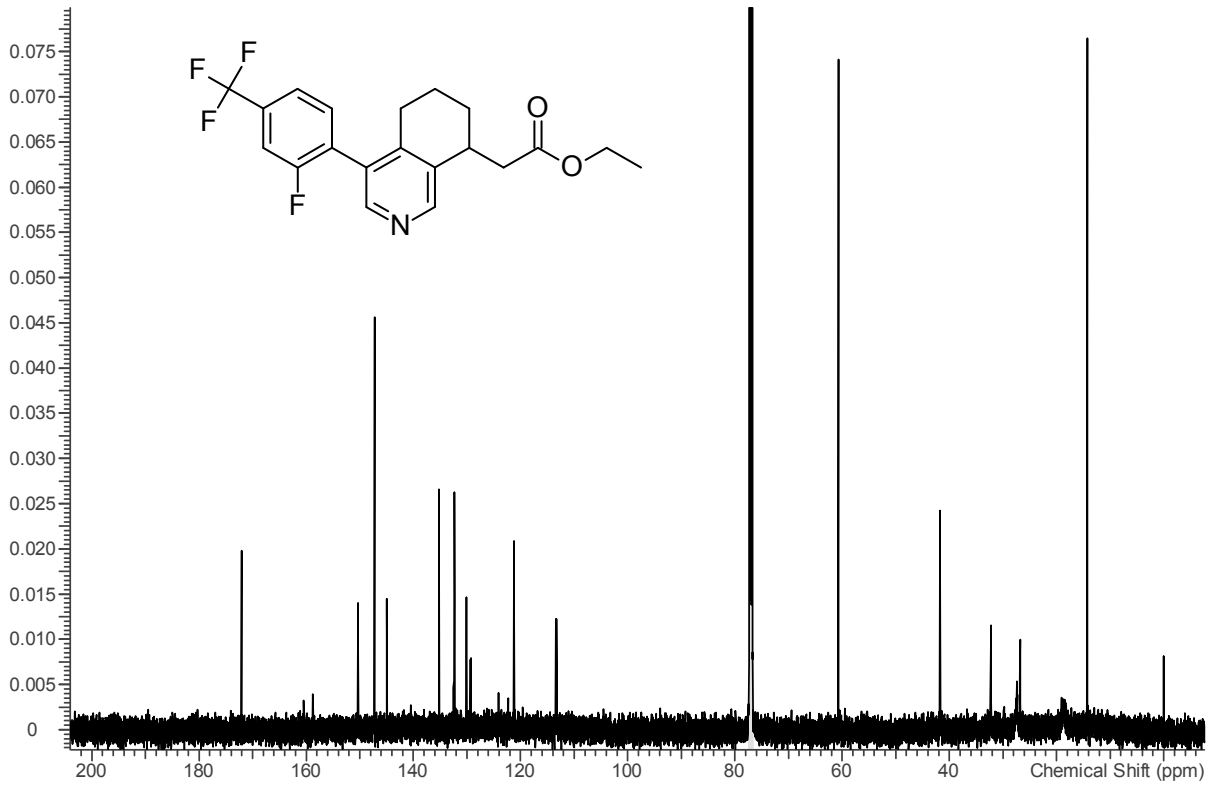
(*Z*)-Product:



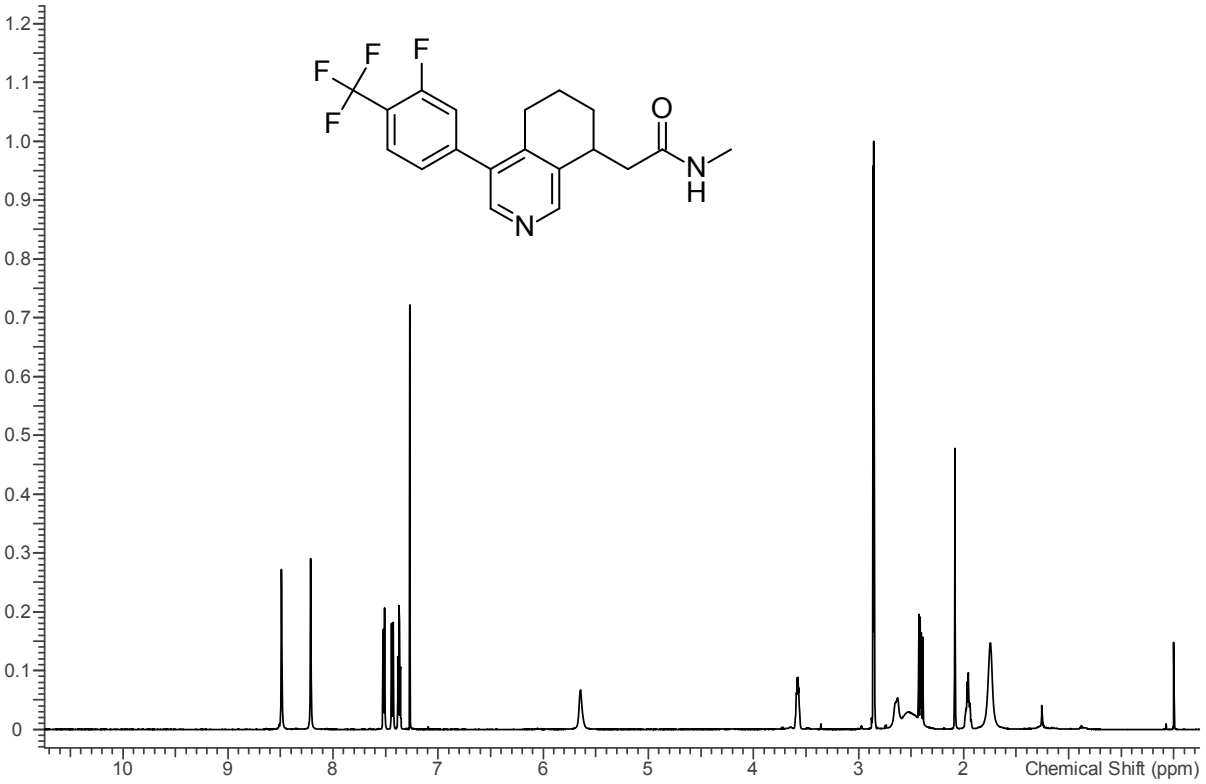


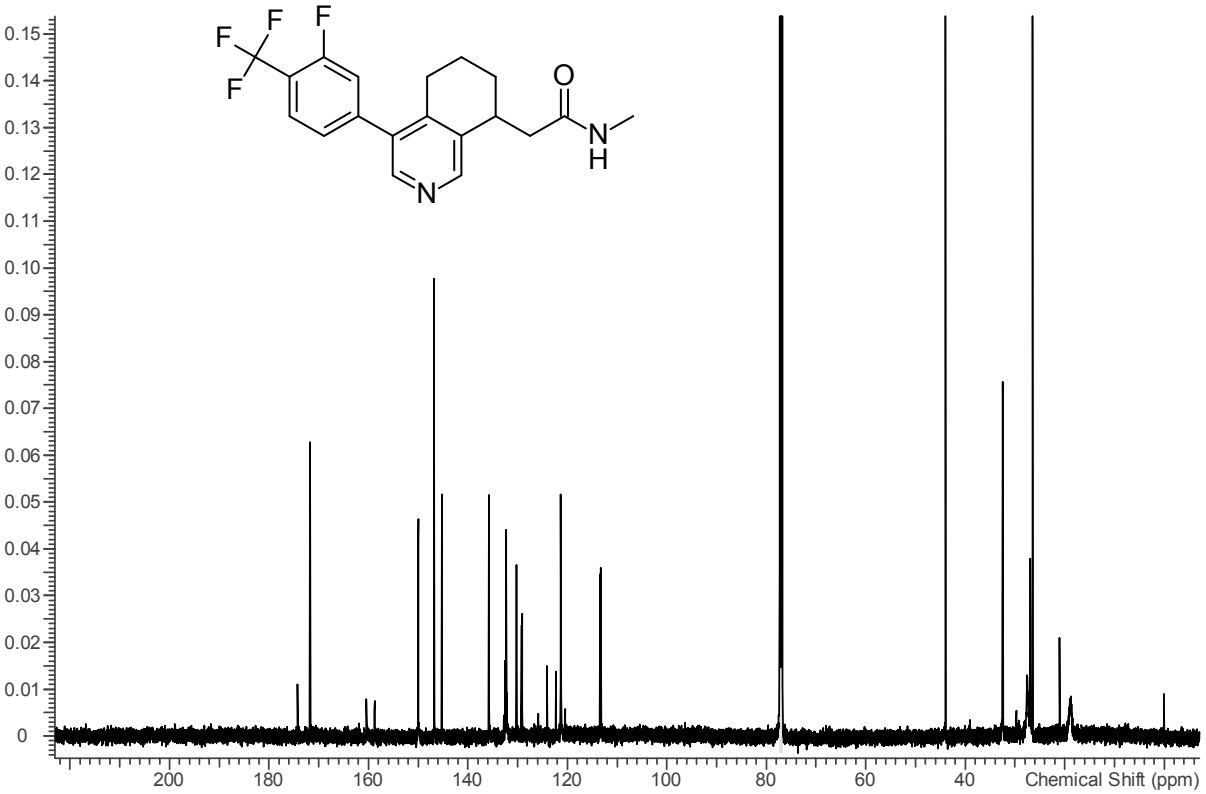
Ethyl 2-[4-[2-fluoro-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydroisoquinolin-8-yl]acetate (37)



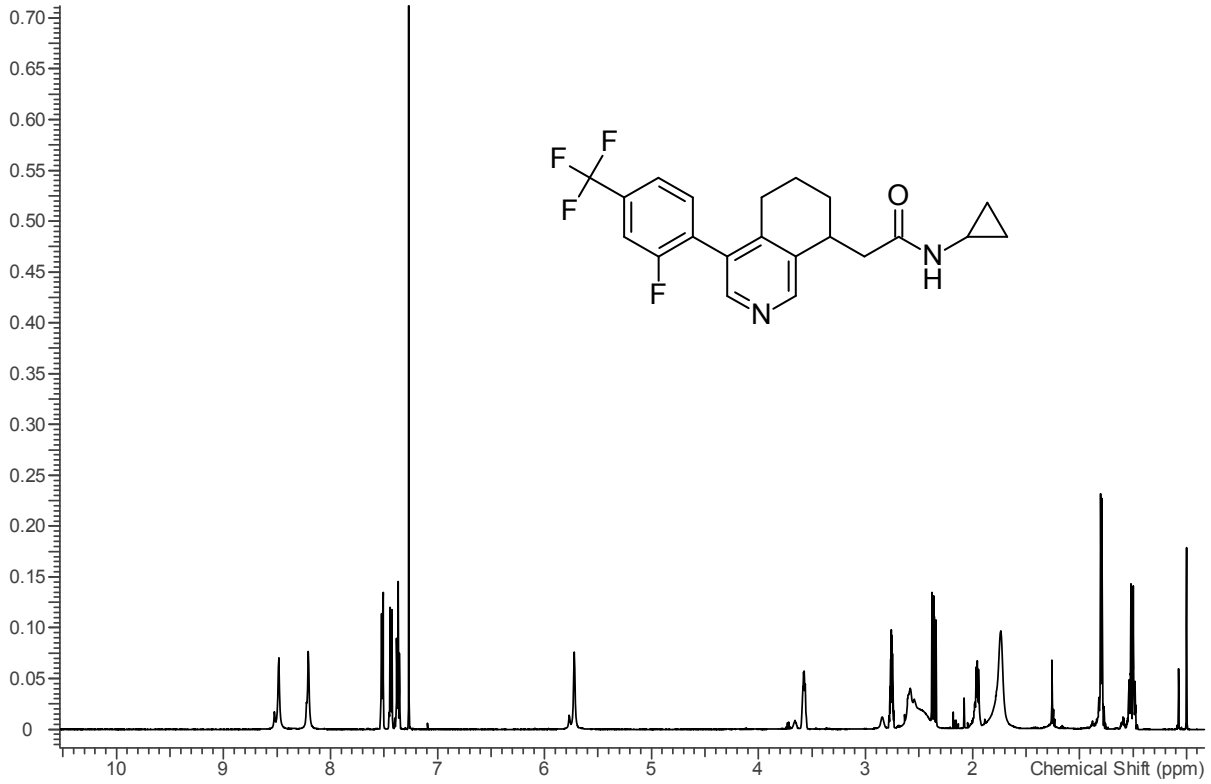


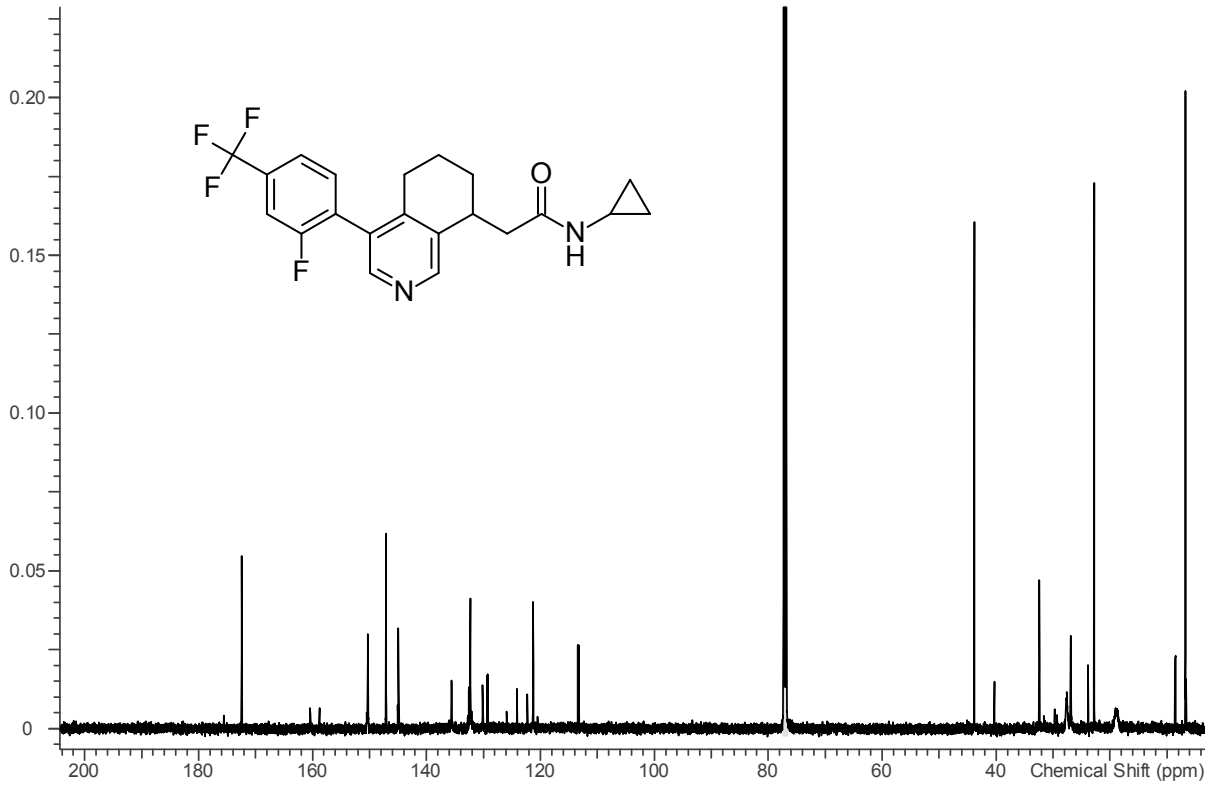
2-[4-[2-Fluoro-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydroisoquinolin-8-yl]-*N*-methyl-acetamide (38)



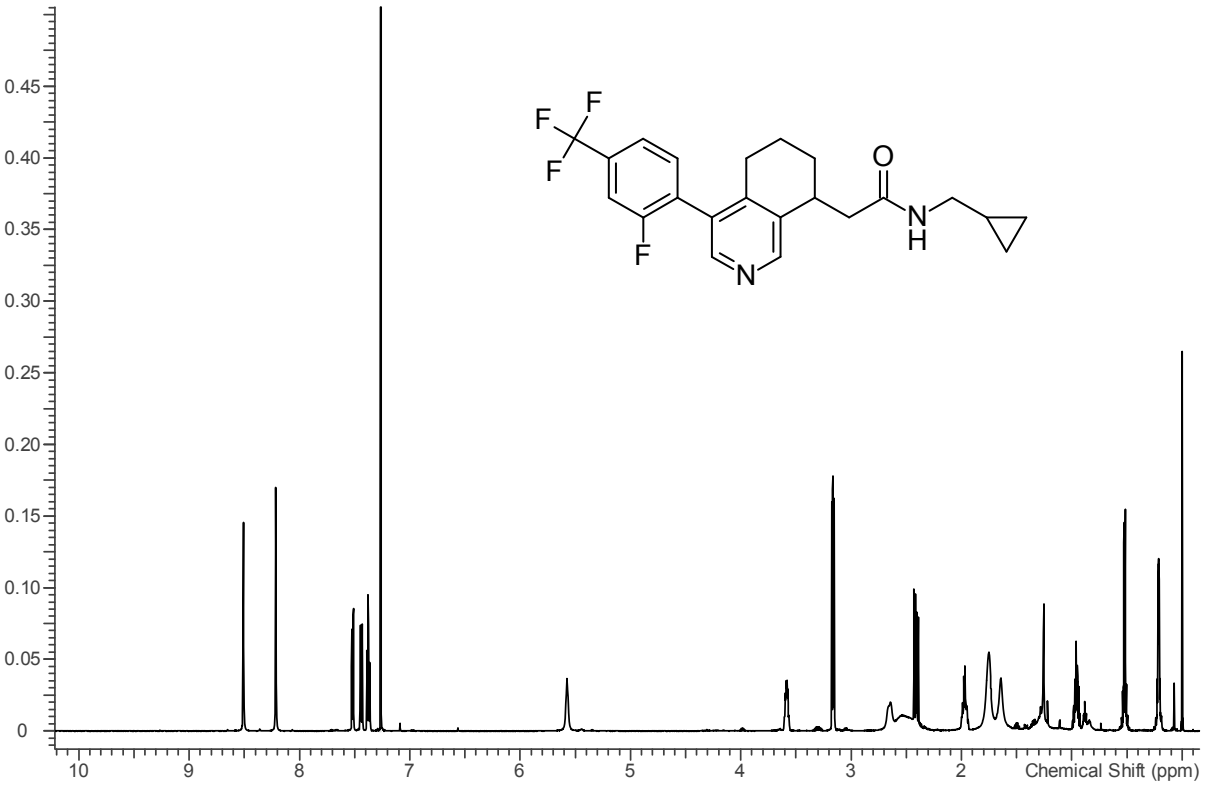


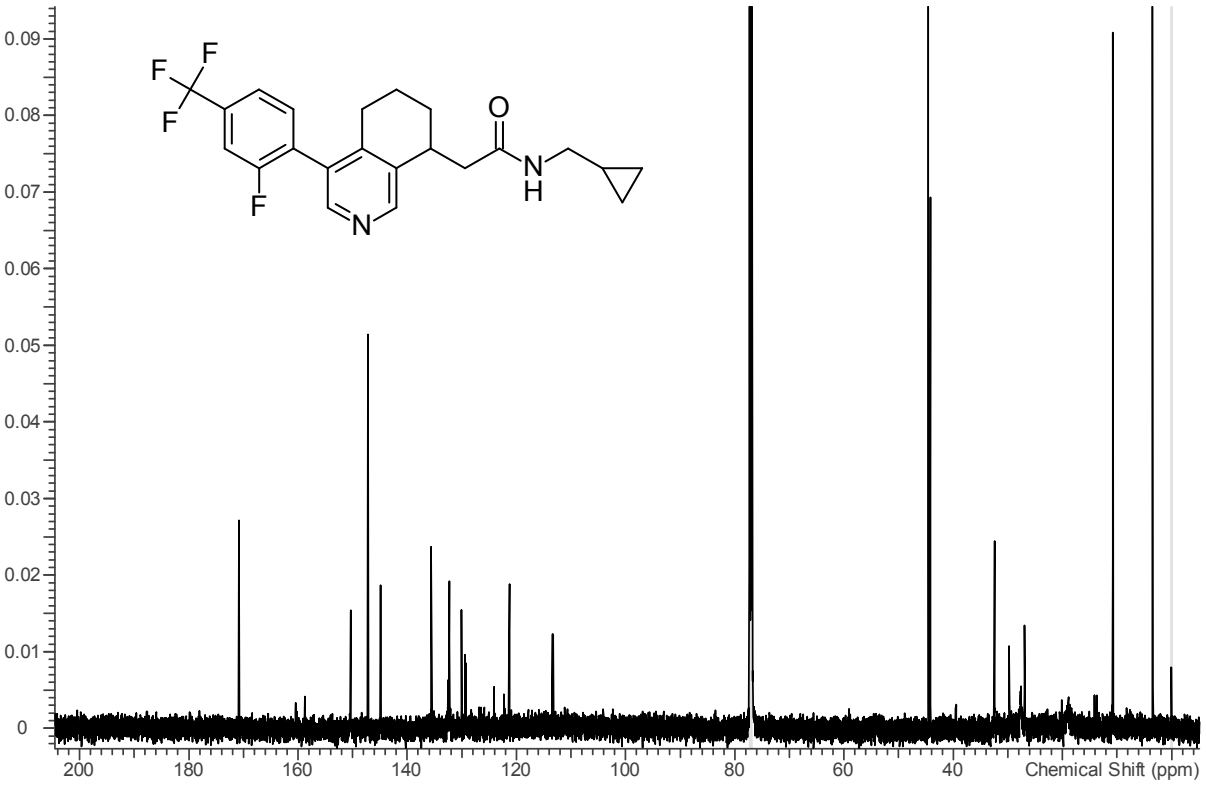
***N*-Cyclopropyl-2-[4-[2-fluoro-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydroisoquinolin-8-yl]acetamide (39)**



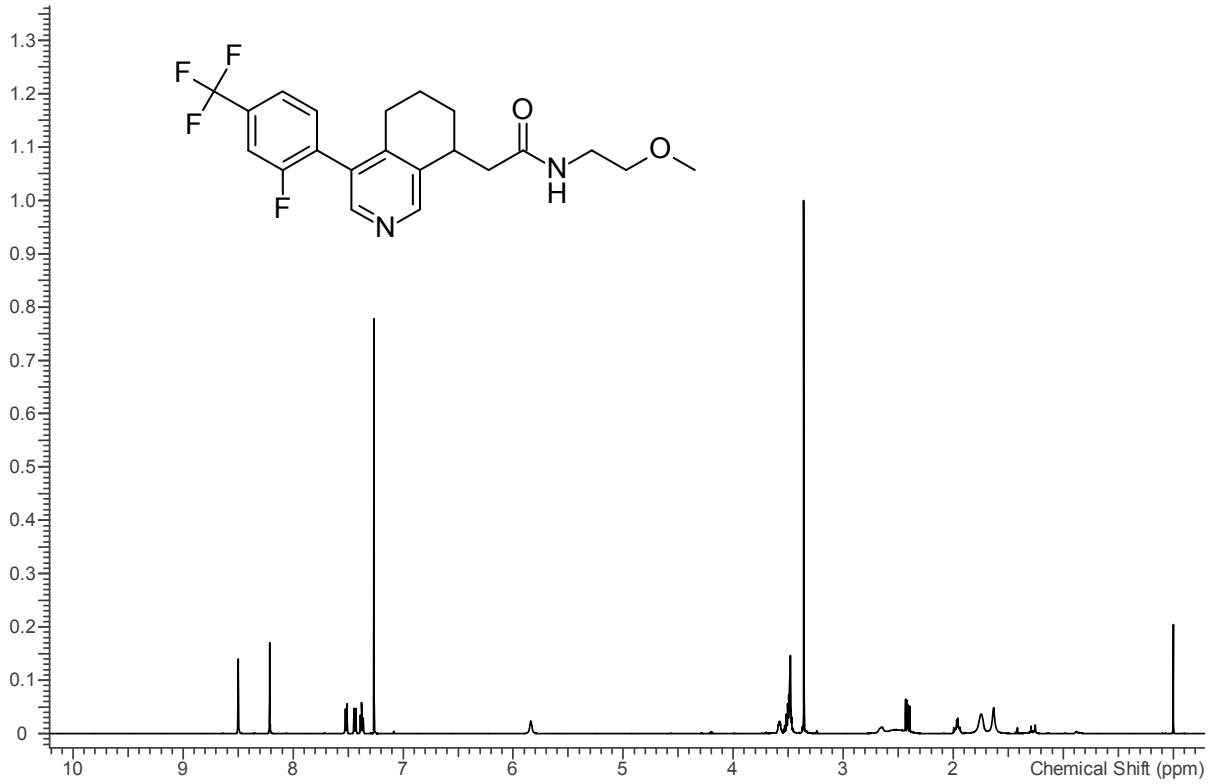


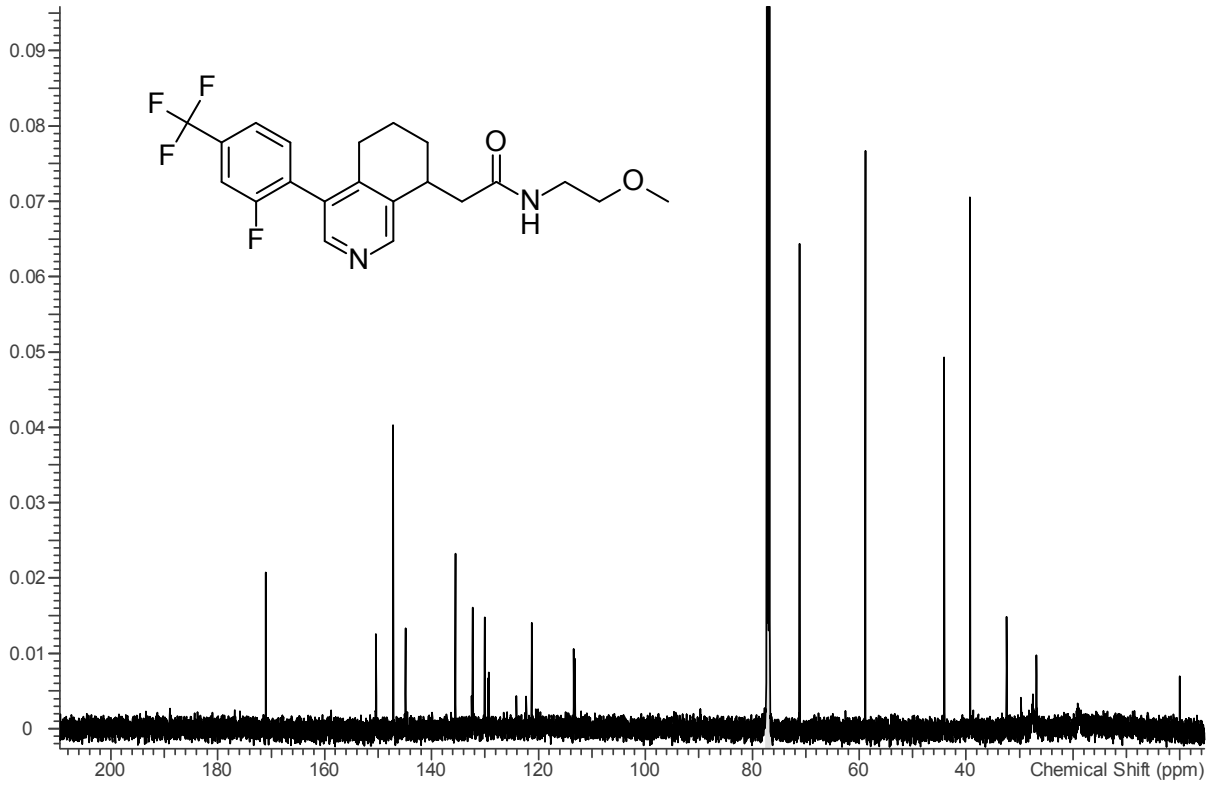
***N*-(Cyclopropylmethyl)-2-[4-[2-fluoro-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydroisoquinolin-8-yl]acetamide (40)**



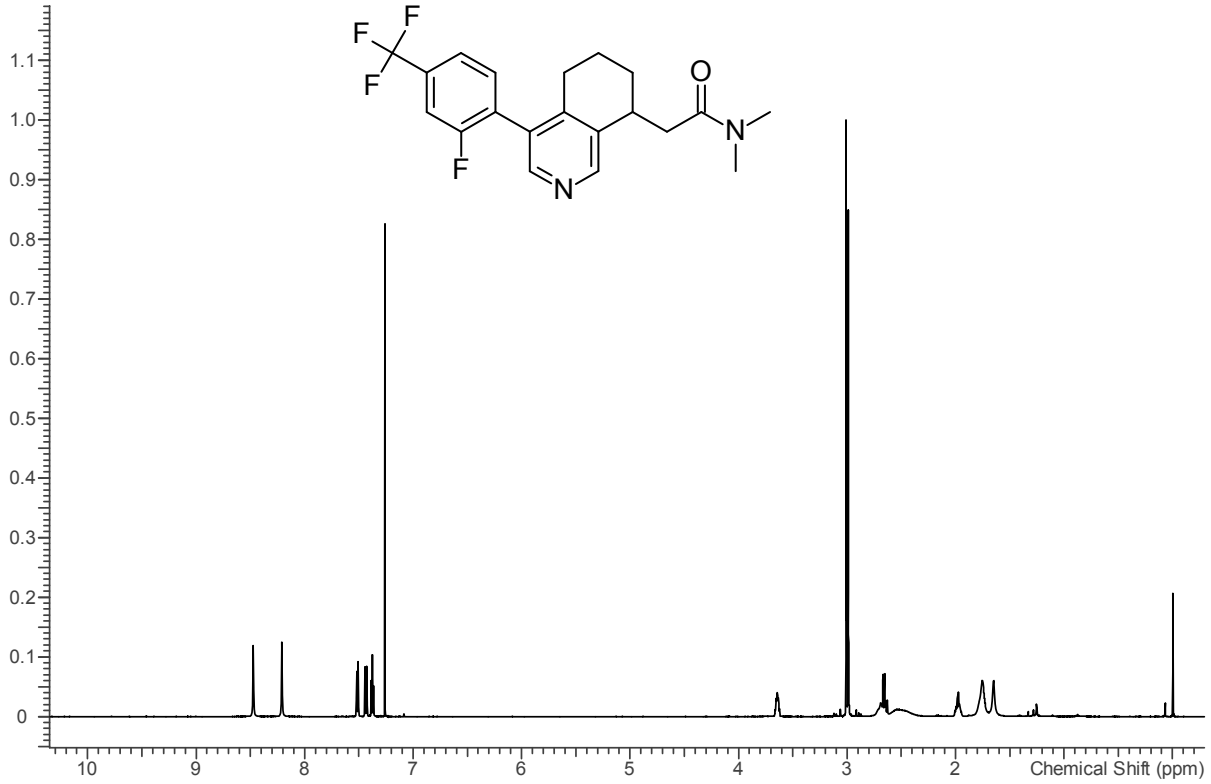


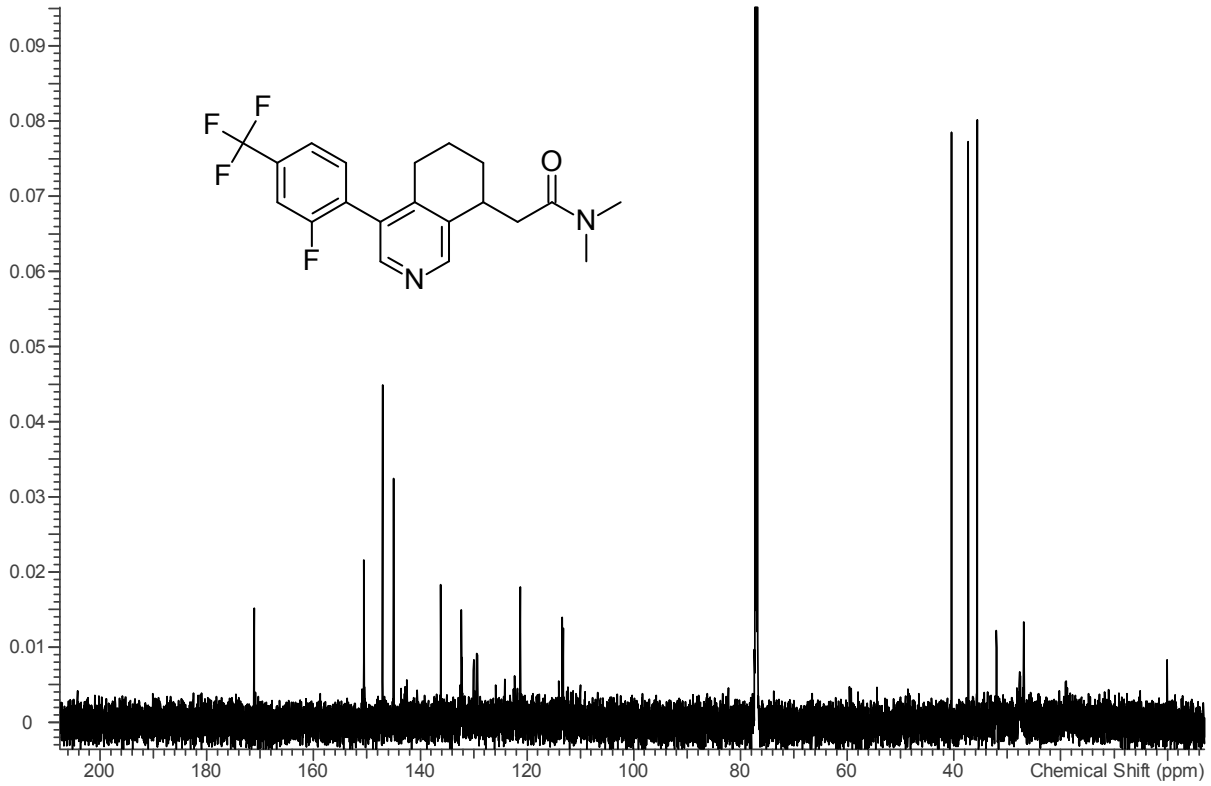
2-[4-[2-Fluoro-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydroisoquinolin-8-yl]-*N*-(2-methoxyethyl)acetamide (41)



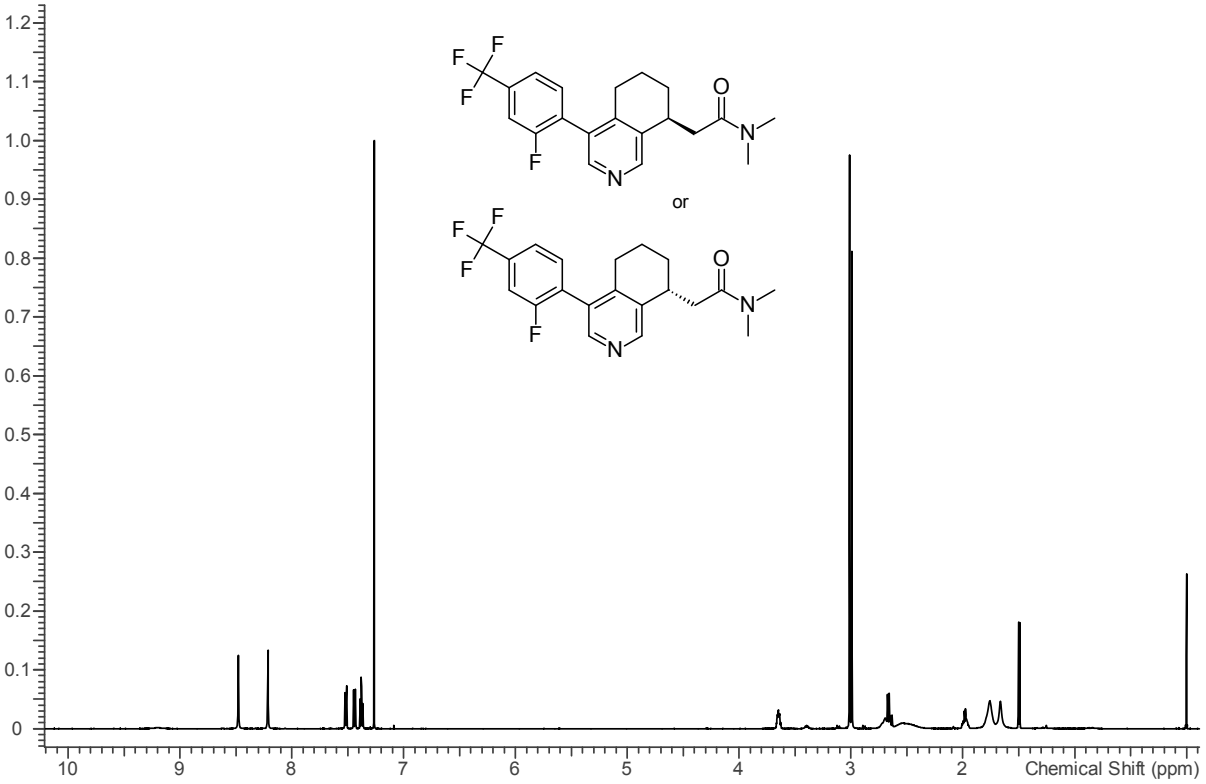


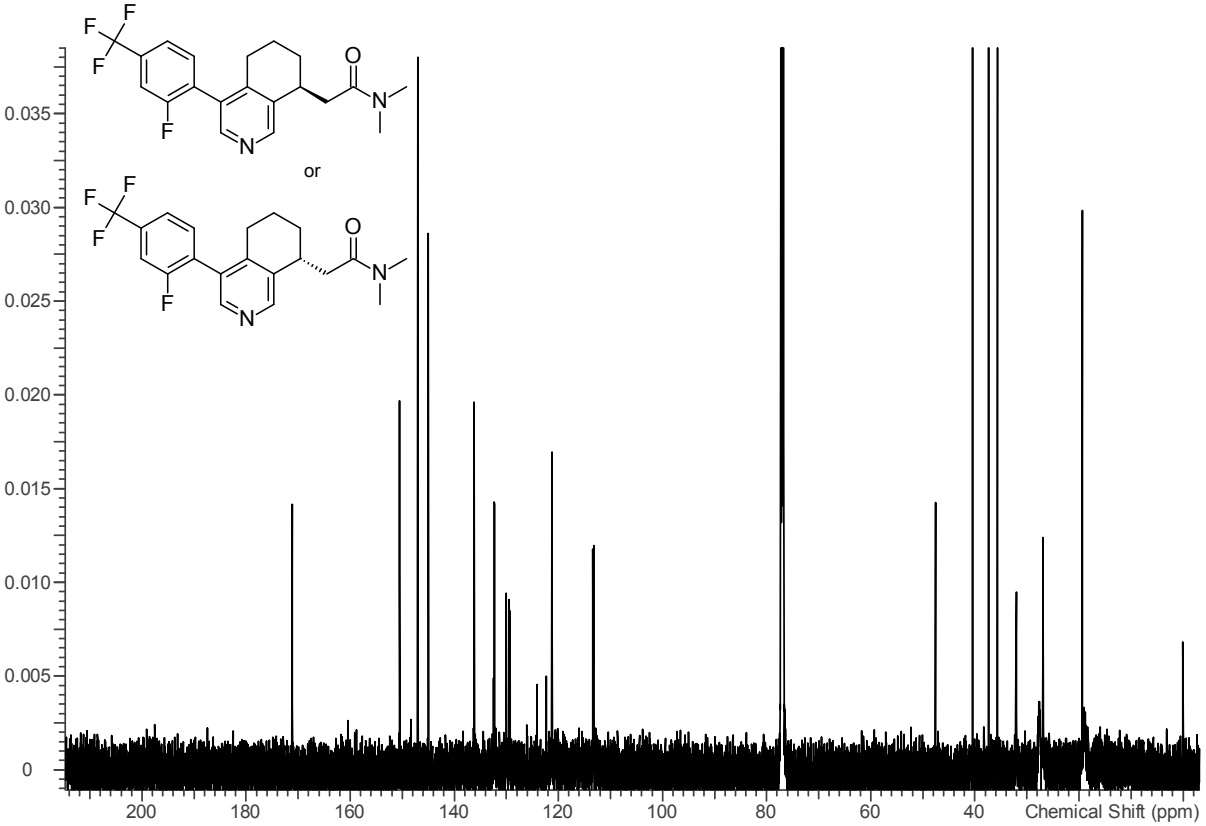
2-[4-[2-Fluoro-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydroisoquinolin-8-yl]-*N*,*N*-dimethyl-acetamide (42)



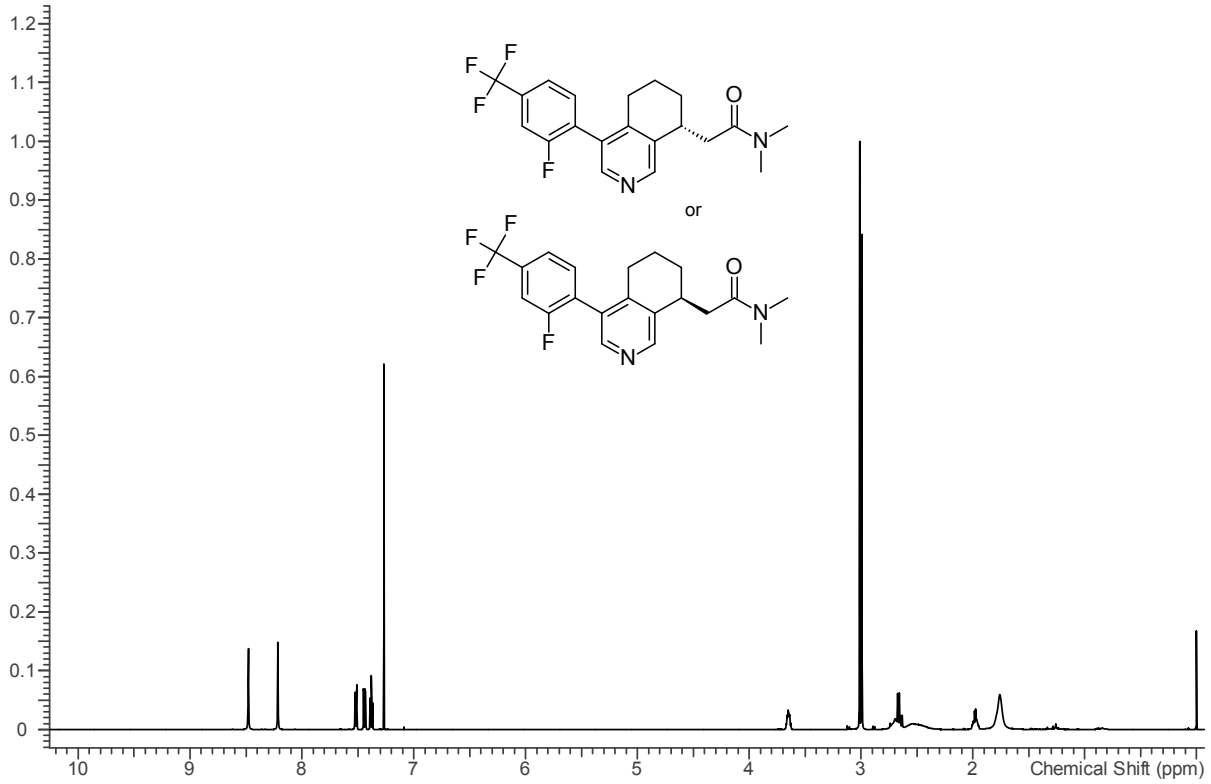


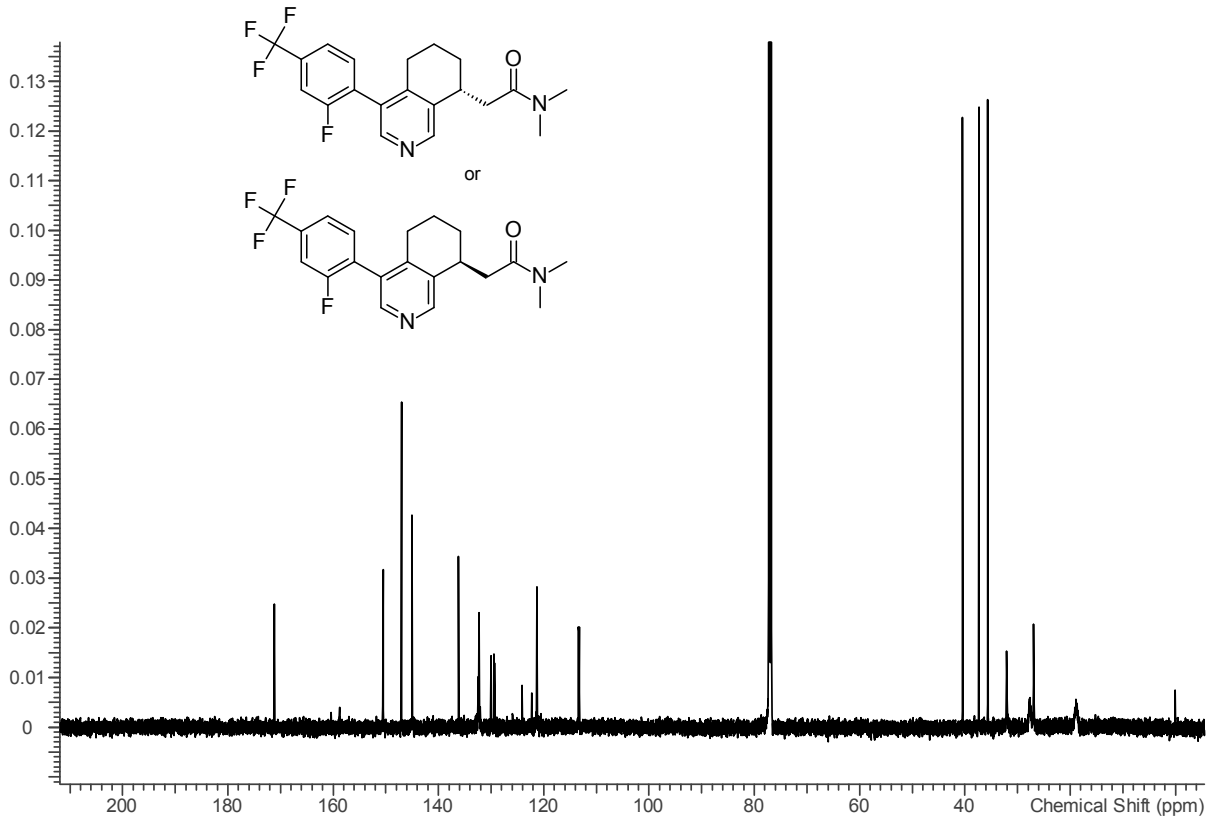
(+)-2-[4-[2-Fluoro-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydroisoquinolin-8-yl]-*N*,*N*-dimethyl-acetamide [(+)-42]





(-)-2-[4-[2-Fluoro-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydroisoquinolin-8-yl]-*N*,*N*-dimethyl-acetamide [(-)-42]





4. References

1. R. E. Martin, F. Morawitz, C. Kuratli, A. M. Alker and A. I. Alanine, *Eur. J. Org. Chem.* 2012, 47.
2. J. Lehmann, T. Alzieu, R. E. Martin and R. Britton, *Org. Lett.* 2013, **15**, 3550.