Supporting Information

Enantioselective synthesis of *cis*-hexahydro-*γ*-carboline derivatives via Ir-catalysed asymmetric hydrogenation

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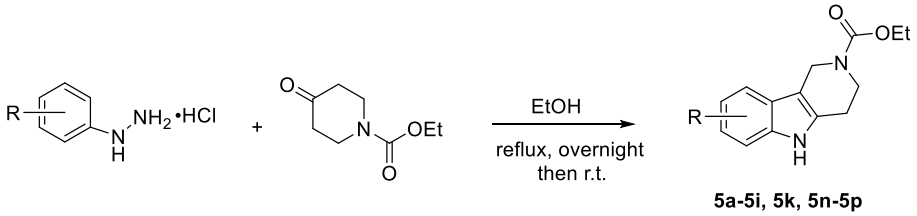
I. General Information

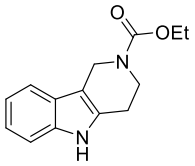
Unless otherwise mentioned, all experiments were carried out under an atmosphere of argon in a glovebox or using standard Schlenk techniques. Solvents were dried with standard procedures and degassed with argon gas. Flash column chromatography was performed using Tsingdao silica gel (particle size 300-400 mesh). NMR spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR, 376 MHz for ^{19}F NMR or a Bruker DPX 600 spectrometer at 600 MHz for ^{1}H NMR, 151 MHz for ^{13}C NMR, 565 MHz for ^{19}F NMR in $CDCl_3$ or d^6-DMSO with tetramethyl silane (TMS) as internal standard. Chemical shifts are reported in ppm and coupling constants are given in Hz. Chemical shifts were reported relative to TMS (0.00 ppm), d^6-DMSO (2.50 ppm) or $CDCl_3$ (7.26 ppm) for ^{1}H NMR and relative to $CDCl_3$ (77.16 ppm) or d^6-DMSO (39.52 ppm) for ^{13}C NMR. LC-MS analysis was carried out on Agilent 1200 Series instrument using a reversed phase column (Athena C18, 120 Å, 4.6 *150 mm, 5 μm). The starting materials aryl hydrazine and 1-carbethoxy-4-piperidone were purchased from commercial suppliers and used without further purification. High resolution mass spectra (HRMS) were obtained on Thermo Scientific Q Exactive hybrid quadrupole-Orbitrap mass spectrometer. PE refers to petroleum ether, DCE refers to 1,2-dichloroethane, DCM refers to dichloromethane.

II. General Procedure for Preparation of Substrates 5a-5i, 5k, 5n-5p

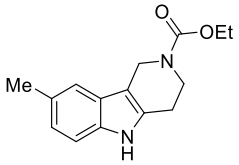


5a-5i, 5k, 5n-5p

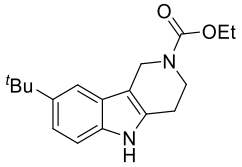
Following a literature procedure[1], aryl hydrazine hydrochloride (3.6 mmol) and 1-carbethoxy-4-piperidone (3 mmol) were suspended in EtOH (5 mL) and heated to reflux for overnight, then cooled down to room temperature. The resulting mixture was concentrated, filtered and washed with 50% aqueous EtOH to afford the desired product. The residue was purified by flash column.



Ethyl 1,3,4,5-tetrahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (**5a**)[2]: white solid, 659 mg, 90% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 7.8 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 7.11 (t, J = 7.4 Hz, 1H), 4.70 (s, 2H), 4.22 (q, J = 7.1 Hz, 2H), 3.88 (s, 2H), 2.84 (s, 2H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.3, 134.7, 133.0, 126.8, 124.1, 120.9, 116.8, 108.5, 104.4, 61.8, 41.3, 23.5, 14.9. The resulting data is according to the reported literature.

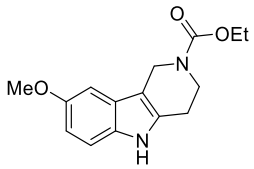


Ethyl 8-methyl-1,3,4,5-tetrahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (**5b**)[3] : white solid, 666 mg, 86% yield. ^{1}H NMR (600 MHz, *d*^{6}-DMSO) δ 10.76 (s, 1H), 7.20 – 7.18 (m, 2H), 6.89 – 6.84 (m, 1H), 4.57 (s, 2H), 4.11 (q, J = 7.1 Hz, 2H), 3.75 (t, J = 5.5 Hz, 2H), 2.78 (t, J = 5.5 Hz, 2H), 2.36 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, *d*^{6}-DMSO) δ 155.6, 134.7, 133.0, 127.4, 125.8, 122.6, 117.4, 111.1, 105.4, 61.3, 41.4, 23.4, 21.6, 15.1. ^{13}C NMR (151 MHz, *d*^{6}-DMSO) δ 155.2, 134.2, 132.5, 127.0, 125.4, 122.1, 116.9, 110.6, 105.0, 60.8, 41.00, 22.9, 21.2, 14.7. HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{19}N_2O_2^+$: 259.1441, found: 259.1441. The resulting data is according to the reported literature.

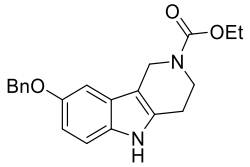


Ethyl 8-(tert-butyl)-1,3,4,5-tetrahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (**5c**): white solid,

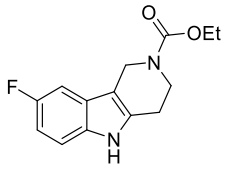
630 mg, 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.44 (s, 1H), 7.25 (s, 2H), 4.70 (s, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 2H), 2.83 (s, 2H), 1.39 (s, 9H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, *d*^{6}-DMSO) δ 155.2, 140.8, 134.0, 132.4, 124.9, 118.7, 112.9, 110.4, 105.4, 60.8, 41.1, 34.2, 31.9, 23.0, 14.7. HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{25}N_2O_2^+$:301.1911, found:301.1912.



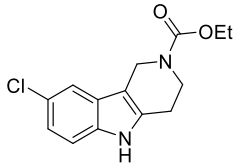
Ethyl 8-methoxy-1,3,4,5-tetrahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (5d)[4] : white solid, 477 mg, 58% yield. ^{1}H NMR (600 MHz, *d*^{6}-DMSO) δ 10.72 (s, 1H), 7.17 (d, *J* = 8.6 Hz, 1H), 6.93 (s, 1H), 6.67 (d, *J* = 8.6 Hz, 1H), 4.55 (s, 2H), 4.10 (q, *J* = 7.0 Hz, 2H), 3.80 – 3.70 (m, 5H), 2.77 (s, 2H), 1.22 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, *d*^{6}-DMSO) δ 155.2, 153.1, 133.2, 130.8, 125.4, 111.5, 110.3, 105.3, 99.5, 60.8, 55.3, 41.1, 23.3, 23.0, 14.7. HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{19}N_2O_3^+$: 275.1390, found: 275.1391. The resulting data is according to the reported literature.



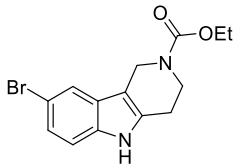
Ethyl 8-(benzyloxy)-1,3,4,5-tetrahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (5e)[5] : white solid, 714 mg, 68% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 – 8.07 (brs, 1H), 7.78 (d, *J* = 7.4 Hz, 2H), 7.69 (t, *J* = 7.5 Hz, 2H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.30 (d, *J* = 1.5 Hz, 1H), 7.19 (d, *J* = 8.6 Hz, 1H), 5.40 (s, 2H), 4.95 (s, 2H), 4.51 (q, *J* = 7.1 Hz, 2H), 4.17 (s, 2H), 3.12 (s, 2H), 1.61 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2, 152.2, 137.9, 133.3, 131.1, 128.3, 127.6, 127.6, 125.5, 111.6, 111.0, 105.5, 101.1, 69.8, 60.9, 41.1, 23.3, 14.7. HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{23}N_2O_3^+$: 351.1703, found: 351.1705.



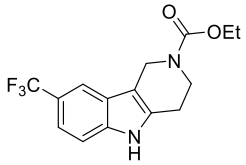
Ethyl 8-fluoro-1,3,4,5-tetrahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (5f)[6] : white solid, 652 mg, 83% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.20 (s, 1H), 7.09 (d, *J* = 8.7 Hz, 1H), 6.89 (t, *J* = 8.2 Hz, 1H), 4.64 (s, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 2H), 2.83 (s, 2H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, *d*^{6}-DMSO) δ 156.8 (d, *J* = 231.0 Hz), 155.1, 134.8, 125.3 (d, *J* = 10.1 Hz), 111.7 (d, *J* = 9.8 Hz), 108.4 (d, *J* = 25.9 Hz), 106.0, 102.3 (d, *J* = 23.4 Hz), 60.9, 40.9, 23.0, 14.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ -124.4. HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{14}N_2O_2^-$: 261.1039, found: 261.1044.



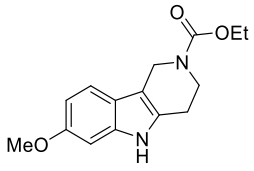
Ethyl 8-chloro-1,3,4,5-tetrahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (**5g**)[5] : white solid, 678 mg, 81% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.41 (s, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.14 – 7.06 (m, 1H), 4.64 (s, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 2H), 2.84 (s, 2H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, *d*^{6}-DMSO) δ 155.1, 134.5, 134.3, 126.2, 123.2, 120.5, 116.7, 112.3, 105.6, 60.9, 40.8, 22.9, 14.6. HRMS (ESI/ion trap) *m/z*: $[M - H]^-$ calcd for $C_{14}H_{14}ClN_2O_2^-$: 277.0744, found: 277.0747.



Ethyl 8-bromo-1,3,4,5-tetrahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (**5h**)[5] : white solid, 844 mg, 87% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.57 (s, 1H), 7.23 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 4.64 (s, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 2H), 2.84 (s, 2H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, *d*^{6}-DMSO) δ 155.1, 134.5, 126.9, 123.0, 119.7, 112.8, 111.1, 105.6, 60.9, 40.8, 22.9, 14.6. HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{16}BrN_2O_2^-$: 323.0390, found: 323.0392.



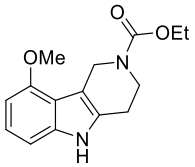
Ethyl 8-(trifluoromethyl)-1,3,4,5-tetrahydro-2H-pyrido[4,3-b]indole-2-carboxylate (**5i**): white solid, 805 mg, 86% yield. ^{1}H NMR (600 MHz, *d*^{6}-DMSO) δ 11.42 (d, *J* = 6.7 Hz, 1H), 7.85 (d, *J* = 7.1 Hz, 1H), 7.59 – 7.39 (m, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 4.64 (s, 2H), 4.22 – 4.04 (m, 2H), 3.90 – 3.68 (m, 2H), 2.83 (s, 2H), 1.36 – 1.05 (m, 3H). ^{13}C NMR (151 MHz, *d*^{6}-DMSO) δ 155.6, 137.9, 135.6, 126.2 (q, *J* = 271.1 Hz), 124.9, 119.9 (q, *J* = 31.3 Hz), 117.6, 115.5, 111.9, 107.2 (m), 61.4, 41.24, 23.3, 15.1. ^{19}F NMR (565 MHz, *d*^{6}-DMSO) δ -58.3. HRMS (ESI/ion trap) m/z: $[M + H]^+$ calcd for $C_{15}H_{16}F_3N_2O_2^+$: 313.1158, found: 313.1154.



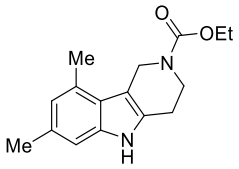
1k

Ethyl 7-methoxy-1,3,4,5-tetrahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (**5k**): following the general procedure, the crude product was purified by flash column (EtOAc : hexane, 2:1), afforded

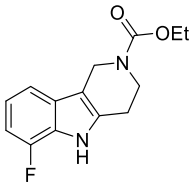
the desired product (30% yield, 247 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.32 (d, J = 8.5 Hz, 1H), 6.82 (s, 1H), 6.77 (dd, J = 8.5, 2.0 Hz, 1H), 4.65 (s, 2H), 4.20 (q, J = 7.1 Hz, 2H), 3.84 (d, J = 10.7 Hz, 5H), 2.80 (s, 2H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, d^6-DMSO) δ 155.1, 153.1, 137.1, 130.5, 121.5, 115.4, 105.1, 104.5, 99.0, 60.8, 55.1, 42.4, 40.8, 22.8, 14.7.
HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{19}N_2O_3^+$: 275.1390, found: 275.1391.



Ethyl 9-methoxy-1,3,4,5-tetrahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (**5n**) : following the general procedure, the crude product was purified by flash column (EtOAc : hexane, 2:1), afforded the desired product (16% yield,132 mg). ^{1}H NMR (600 MHz, d^6-DMSO) δ 10.86 (s, 1H), 6.92 (t, J = 7.8 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.44 (d, J = 7.6 Hz, 1H), 4.70 (s, 2H), 4.10 (d, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.71 (t, J = 5.6 Hz, 2H), 2.74 (d, J = 5.0 Hz, 2H), 1.21 (t, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, d^6-DMSO) δ 155.1, 153.1, 137.1, 130.5, 121.5, 115.4, 105.3, 104.5, 99.0, 60.8, 55.1, 42.3, 23.1, 22.8, 14.7. HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{19}N_2O_3^+$: 275.1390, found: 275.1391.



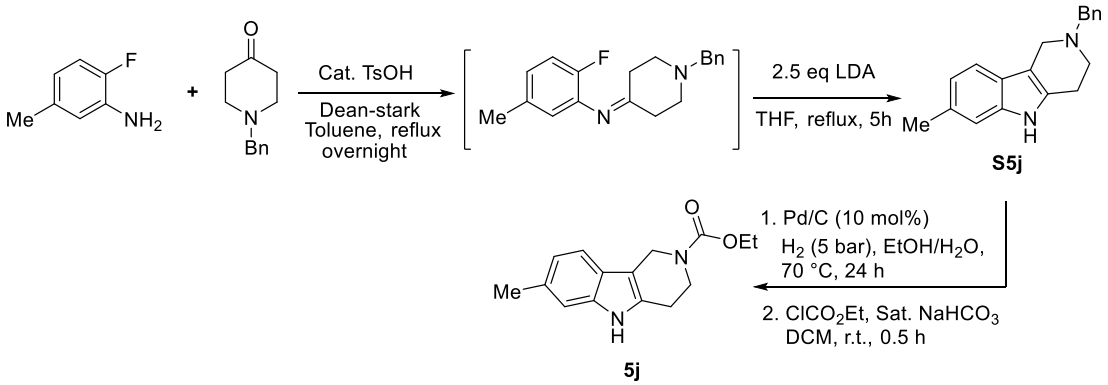
Ethyl 7,9-dimethyl-1,3,4,5-tetrahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (**5o**) [7] : white solid, 685 mg, 84% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (s, 1H), 6.91 (s, 1H), 6.68 (s, 1H), 4.90 (s, 2H), 4.21 (q, J = 7.1 Hz, 2H), 3.83 (s, 2H), 2.80 (s, 2H), 2.58 (s, 3H), 2.39 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, d^6-DMSO) δ 155.1, 136.3, 130.9, 129.6, 127.9, 122.6, 121.3, 108.7, 105.8, 60.8, 42.5, 40.8, 40.2, 23.2, 21.2, 19.4, 14.7. HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{21}N_2O_2^+$: 273.1598, found: 273.1599.



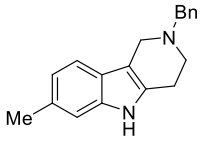
Ethyl 6-fluoro-1,3,4,5-tetrahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (**5p**) : white solid, 597 mg, 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.21 (d, J = 7.8 Hz, 1H), 7.01 (td, J = 7.9, 4.8 Hz, 1H), 6.87 (dd, J = 11.1, 8.0 Hz, 1H), 4.69 (s, 2H), 4.22 (q, J = 7.1 Hz, 2H), 3.87 (s, 2H), 2.86 (s, 2H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, d^6-DMSO) δ 155.1, 148.9 (d, J = 241.9 Hz), 134.9, 129.0 (d, J = 3.4 Hz), 123.4 (d, J = 13.0 Hz), 119.0 (d, J = 6.3 Hz), 113.5 (d, J = 2.5 Hz),

106.6, 105.8 (d, J = 16.3 Hz), 60.9, 40.9, 22.9, 14.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -135.1. HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{16}FN_2O_2^+$: 263.1190, found: 263.1191.

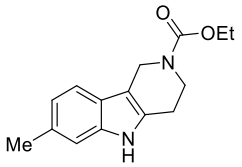
III. Procedure for Preparation of Substrate 5j



Following the general procedure,[8] *N*-Benzyl-4-piperidone (2.9 g, 17 mmol), 2-fluoro-5-methylaniline (1.88 g, 15 mmol) and catalytic *p*-TsOH (50 mg) were combined in toluene (80 mL) and heated at reflux with removal of H_2O using a Dean–Stark trap. After 15 h the reaction was cooled to r.t. washed with sat. $NaHCO_3$ and concentrated in vacuo. The crude reaction mixture was then purified under vacuum under heating to remove unreacted starting materials, to give the imine as a bright yellow oil (1.69 g, 90%). This material was sufficiently pure to be used without further purification.



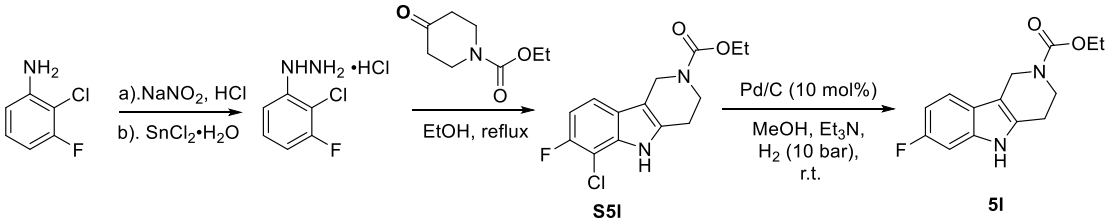
2-Benzyl-7-methyl-2,3,4,5-tetrahydro-*1H*-pyrido[4,3-*b*]indole (**S5j**) : The imine (1.39 g, 5 mmol) was dissolved in anhydrous THF (15 mL) under Ar in an oven dried flask equipped with a reflux condenser. The solution was cooled to –78 °C and a fresh prepared LDA (0.69 M, 12.5 mmol) in THF (18 mL) was added via syringe. The reaction was stirred at –78 °C for 15 min, then warmed to r.t. and heated to reflux under an atmosphere of argon gas. TLC analysis showed a quantitative conversion to a new product after 5 h at reflux and the reaction was cooled to rt, quenched with H_2O (2 mL) and filtrated through celite, washed with CH_2Cl_2 (20 mL). The mixture was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by flash chromatography (EtOAc : hexane, 1:1) to give **S5j** as a yellow solid (1.27 g, 92% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.41 (d, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.27 (t, *J* = 7.1 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 6.94 (s, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 3.78 (s, 2H), 3.70 (s, 2H), 2.85 (t, *J* = 5.7 Hz, 2H), 2.71 (t, *J* = 5.5 Hz, 2H), 2.40 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.6, 136.5, 131.3, 130.7, 129.2, 128.3, 127.1, 124.0, 120.8, 117.1, 110.7, 108.5, 62.4, 50.2, 49.8, 23.7, 21.7. HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{20}N_2^-$: 277.1699, found: 277.1689.



1j

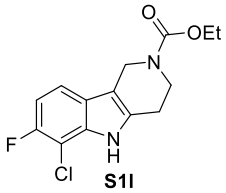
Ethyl 7-methyl-1,3,4,5-tetrahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (5j) : Following the literature procedure, **S5j** (1.0 g, 3.6 mmol) and 10 mol% Pd/C (5 wt%) (766 mg) were suspended in a 70% EtOH/ H_2O solution (20 mL) and placed under hydrogen at atmospheric pressure. The reaction was heated to 70 °C and stirred for 24 h, after which the reaction was filtered through filter paper before cooling to remove Pd/C. The filter cake was washed with 70% EtOH/H_2O (3 × 50 mL) and the combined washes and filtrate were concentrated in vacuo. The crude product was recrystallized from a 70% EtOH/H_2O solution, and the precipitate was isolated by filtration, washed with cold MeOH, and dried in vacuo. The resulted product was used directly in next step. The crude product was dissolved in DCM (20 mL), and saturated $NaHCO_3$ (10 mL) was added, then the resulted mixture was cold at ice-water bath. Ethyl chloroformate (1.3 eq.) was added dropwise to the mixture. After completion, the organic phase was separated and dried over anhydrous Na_2SO_4, concentrated under vacuum. The resulted residue was purified by flash column (EtOAc : hexane, 2:1), afford product **5j** (817 mg, 88% yield). ^{1}H NMR (400 MHz, d^6-DMSO) δ 10.73 (s, 1H), 7.26 (d, J = 7.9 Hz, 1H), 7.08 (s, 1H), 6.79 (d, J = 8.0 Hz, 1H), 4.54 (s, 2H), 4.09 (q, J = 7.1 Hz, 2H), 3.74 (t, J = 5.6 Hz, 2H), 2.76 (t, J = 5.1 Hz, 2H), 2.37 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, d^6-DMSO) δ 155.1, 136.3, 131.7, 129.6, 123.0, 120.1, 116.9, 110.9, 105.2, 60.8, 41.0, 40.1, 22.9, 21.4, 14.7. HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{19}N_2O_2^-$: 259.1441, found: 259.1440.

IV. Procedure for Preparation of Substrate 5l and 5m



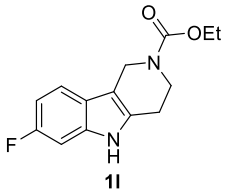
S5l **5l**

To a suspension of 2-chloro-3-fluoroaniline (5.0 g, 33.3 mmol) in water (8.4 mL) and concentrated HCl (8.4 mL) at 0 °C, a solution of sodium nitrite (3.68 g, 53.3 mmol) in water (8 mL) was added dropwise. After the mixture was stirred at the same temperature for 0.5 h, a solution of tin(II) chloride hydrate (13.6 g, 60 mmol) in concentrated hydrochloric acid (15 mL) was added dropwise at 0 °C, and the mixture was stirred at ambient temperature overnight. The reaction mixture was filtered, and the filtrate was extracted with EA, the organic phase was discarded and the water phase was neutralized by NaOH (12 M) solution, extracted with DCM, and dried under reduced pressure, the residue was formed as hydrochloride salt in 1,4-dioxane to give the (2-chloro-3-fluorophenyl) hydrazine hydrochloride as a white powder (2.7 g, yield 42%). ^{1}H NMR (600 MHz, d^6-DMSO) δ 10.52 (brs, 3H), 8.41 (s, 1H), 7.35 (dd, J = 14.5, 8.3 Hz, 1H), 6.98 (t, J = 7.3 Hz, 2H). ^{13}C NMR (151 MHz, d^6-DMSO) δ 157.8 (d, J = 244.8 Hz), 143.4, 128.5 (d, J = 9.5 Hz), 110.1, 108.8 (d, J = 21.3 Hz), 106.5 (d, J = 20.9 Hz). ^{19}F NMR (565 MHz, d^6-DMSO) δ -115.6.



S1l

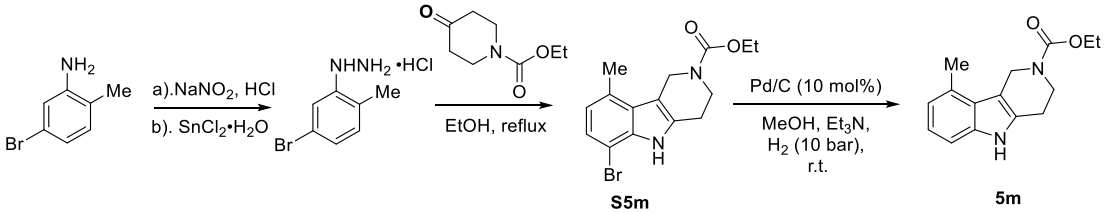
Ethyl 6-chloro-7-fluoro-1,3,4,5-tetrahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (**S5l**): (2-chloro-3-fluorophenyl)hydrazine hydrochloride (1.96 g, 10 mmol) and 1-carbethoxy-4-piperidone (1.54 g, 9 mmol) were suspended in EtOH (15 mL) and heated to reflux for overnight, then cooled down to room temperature. The resulting mixture was concentrated, filtered and washed with 50% aqueous EtOH to afford the desired product **S5l** (1.5 g, 56% yield). ^{1}H NMR (600 MHz, *d*^{6}-DMSO) δ 11.43 (s, 1H), 7.39 (dd, *J* = 8.0, 4.5 Hz, 1H), 7.04 – 6.94 (m, 1H), 4.56 (s, 2H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.74 (t, *J* = 5.7 Hz, 2H), 2.80 (t, *J* = 5.5 Hz, 2H), 1.21 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, *d*^{6}-DMSO) δ 155.1, 153.5 (d, *J* = 236.5 Hz), 134.7, 133.2, 123.1, 116.7 (d, *J* = 9.1 Hz), 107.7 (d, *J* = 23.5 Hz), 106.9, 101.9 (d, *J* = 21.9 Hz), 60.9, 40.7, 40.1, 23.2, 14.6. ^{19}F NMR (565 MHz, *d*^{6}-DMSO) δ -128.8. HRMS (ESI/ion trap) *m/z*: [M – H]$^{-}$ calcd for $C_{14}H_{13}ClFN_2O_2^-$: 295.0655, found: 295.0652.



1l

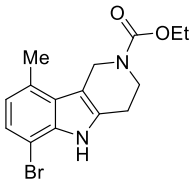
Ethyl 7-fluoro-1,3,4,5-tetrahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (**5l**): A mixture of **S1l** (1.2 g, 4.0 mmol), 5 mol% Pd/C (824 mg, 10 mol%) and Et_3N (1.44 g, 12.1 mmol) in MeOH (10 mL) and THF (3 mL) was stirred under hydrogen atmosphere (10 bar) at room temperature overnight. The mixture was filtered and the filtrate was concentrated to afford the crude product. After removing the ammonium salt through extraction, product **5l** (0.99 g, 95%yield) was afforded. ^{1}H NMR (600 MHz, *d*^{6}-DMSO) δ 11.01 (s, 1H), 7.39 (s, 1H), 7.08 (d, *J* = 10.1 Hz, 1H), 6.81 (t, *J* = 9.2 Hz, 1H), 4.57 (s, 2H), 4.10 (q, *J* = 7.0 Hz, 2H), 3.74 (t, *J* = 5.4 Hz, 2H), 2.77 (s, 2H), 1.21 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, *d*^{6}-DMSO) δ 158.6 (d, *J* = 233.3 Hz), 155.1, 135.8 (d, *J* = 12.1 Hz), 133.2, 121.2, 118.0 (d, *J* = 10.1 Hz), 106.7 (d, *J* = 24.1 Hz), 105.8, 97.2 (d, *J* = 25.5 Hz), 60.9, 40.9, 40.1, 23.1, 14.6. ^{19}F NMR (565 MHz, *d*^{6}-DMSO) δ -122.5. HRMS (ESI/ion trap) *m/z*: [M – H]$^{-}$ calcd for $C_{14}H_{14}FN_2O_2^-$: 261.1045, found: 261.1042.

Following the procedure for preparation of **5l**, substrate **5m** was prepared as follows:

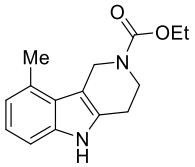


S5m **5m**

Followed by the procedure of synthesis of **5l**, using 2-bromo-5-methylaniline (5 g, 25 mmol) as starting material, (2-bromo-5-methyl)hydrazine hydrochloride (2.8 g, 48% yield) was afford.

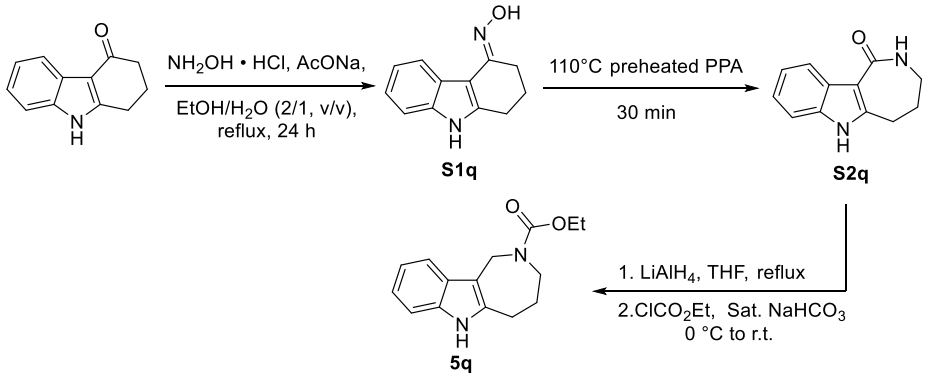


Ethyl 6-bromo-9-methyl-1,3,4,5-tetrahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (**S5m**) : prepared using (2-bromo-5-methyl)hydrazine hydrochloride (2.0 g, 8.4 mmol) and 1-carbethoxy-4-piperidone (1.28 g, 7.5 mmol), afford 1.82 g, 72% yield. ^{1}H NMR (600 MHz, *d*^{6}-DMSO) δ 11.04 (s, 1H), 7.10 (d, *J* = 7.7 Hz, 1H), 6.66 (d, *J* = 7.8 Hz, 1H), 4.81 (s, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.72 (t, *J* = 5.7 Hz, 2H), 2.81 (t, *J* = 5.5 Hz, 2H), 2.50 (s, 3H), 1.22 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, *d*^{6}-DMSO) δ 155.1, 133.9, 133.4, 128.2, 126.2, 123.0, 121.0, 107.5, 101.2, 60.9, 42.2, 40.6, 23.3, 19.1, 14.6. HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{18}BrN_2O_2^+$: 337.0546, found: 337.0544.



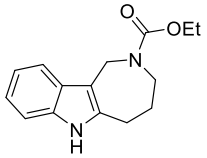
Ethyl 9-methyl-1,3,4,5-tetrahydro-*2H*-pyrido[4,3-b]indole-2-carboxylate (**5m**) : prepared by using **S5m** (1.35 g, 4.0 mmol), afford **5m** with 1.01 g, 98% yield. ^{1}H NMR (600 MHz, *d*^{6}-DMSO) δ 10.84 (s, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 6.92 – 6.85 (m, 1H), 6.69 (d, *J* = 7.1 Hz, 1H), 4.82 (s, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.72 (t, *J* = 5.8 Hz, 2H), 2.77 (t, *J* = 5.7 Hz, 2H), 2.52 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, *d*^{6}-DMSO) δ 155.1, 135.8, 131.8, 128.3, 124.6, 120.7, 119.5, 108.7, 106.0, 60.8, 54.9(CH_2Cl_2), 42.5, 40.7, 23.2, 19.6, 14.6. HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{19}N_2O_2^-$: 259.1441, found: 259.1441.

V. Procedure for Preparation of Substrate 5q



Following the procedure of literature[9], sodium acetate (1.98 g, 24.2 mmol) and hydroxylamine hydrochloride (1.68 g, 24.2 mmol) were added to commercially available 1,2,3,9-tetrahydro-*4H*-carbazol-4-one (2.98 g, 16.1 mmol), in 40 mL of EtOH/water 2/1 v/v, and the mixture was refluxed 24 h under nitrogen atmosphere. After cooling, the solvent was removed and the residue was suspended in 150 mL of water and triturated, until precipitation of the desired oxime product as brown solid (**S1q**), which was collected by filtration and recrystallized from EtOH and water (2.74 g, yield 85%). Analytical and spectral data were in agreement with those of literature. ^{1}H NMR (600 MHz, *d*^{6}-DMSO) δ 11.41 (s, 1H), 8.17 (d, *J* = 7.9 Hz, 1H), 7.38 (t, *J* = 5.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.09 – 7.03 (m, 1H), 7.04 – 6.96 (m, 1H), 3.33 (s, 1H), 3.20 (dd, *J* = 9.6, 5.0 Hz, 2H), 3.10 (t, *J* = 6.7 Hz, 2H), 1.99 (dt, *J* = 11.0, 7.4 Hz, 2H).

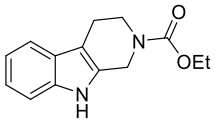
Compound **S1q** (2.6 g, 13 mmol) of was added portionwise to 97 g of preheated (110 °C) PPA under vigorous stirring, and the mixture was stirred at this temperature for 30 min. Then, 200 g of ice were carefully poured into the mixture and triturated until complete dissolution of PPA and formation of a grey precipitate, which was collected by filtration under reduced pressure, washed with 100 mL of water, 10 mL of 5% diluted ammonia and further 100 mL of water. The solid was then suspended into 50 mL of MeOH and, after addition of 1.0 g of vegetal carbon, refluxed for 1 h. After cooling, the suspension was filtered on a Celite pad and the solvent removed to furnish **S2q** as pale brown solid (1.1 g) without further purification.



Ethyl 3,4,5,6-tetrahydroazepino[4,3-*b*]indole-2(*1H*)-carboxylate (**5q**) :

$LiAlH_4$ (1.25 g, 33 mmol) was added to a solution of **S2q** (0.6 g, 3 mmol) in 100 mL of dry 1,4-dioxane, and the mixture was refluxed until disappearance of the starting material (TLC). After cooling, the reaction was quenched by adding 10 mL of a saturated solution of sodium sulfate (Na_2SO_4) and stirred at rt for 30 min. The mixture was then filtered and the precipitate was washed with 20 mL of 1,4-dioxane. The collected filtrates were concentrated and the residue, suspended in 80 mL of distilled water, was extracted with 3 × 50 mL of CH_2Cl_2. The organic fractions were dried (Na_2SO_4), filtered and concentrated under reduced pressure, afforded an oil residue (0.5 g) without further purification. Then the residue was dissolved in CH_2Cl_2 (20 mL) and 10 mL saturated

$NaHCO_3$ at an ice bath, ethyl chloroformate (1.3 eq.) was added dropwise, then warmed the reaction to room temperature, after 0.5 h traced by TLC until disappearance of the starting material. Separation of the organic phase and the water phase was extracted with CH_2Cl_2 (20 mL x3), combined the organic phase and washed with saturated brine, dried over anhydrous Na_2SO_4, concentrated under evaporator, afforded the crude residue. Then crude product was purified through flash column (EtOAc/PE, 1:2), afforded compound **5q** as white solid. (558 mg, 72% yield). ^{1}H NMR (600 MHz, CD_2Cl_2) δ 8.54 – 8.07 (m, 1H), 7.52 (d, *J* = 7.2 Hz, 1H), 7.41 – 7.17 (m, 1H), 7.18 – 6.96 (m, 2H), 4.87 – 4.62 (m, 2H), 4.24 – 3.95 (m, 2H), 3.96 – 3.67 (m, 2H), 2.93 (s, 2H), 2.03 – 1.80 (m, 2H), 1.32 – 0.95 (m, 3H). ^{13}C NMR (151 MHz, CD_2Cl_2) δ 156.3, 137.1, 134.8, 128.1, 121.3, 119.7, 117.8, 111.6, 110.9, 61.6, 49.7, 43.2, 27.8, 27.2, 14.9. **rotamer** ^{13}C NMR (151 MHz, CD_2Cl_2) δ 156.3, 137.7, 134.8, 128.0, 121.1, 119.7, 117.6, 111.8, 110.8, 61.6, 50.4, 45.0, 44.2, 42.9, 27.8, 26.8, 14.8. HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{19}N_2O_2^+$: 259.1441, found: 259.1440.



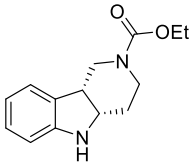
Ethyl 1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole-2-carboxylate (**5r**) [10] : Following the reported literature, to a solution of 1,2,3,4-Tetrahydro-β-carboline (344 mg, 2 mmol) in CH_2Cl_2 (6 mL) was added slowly ethyl carbonochloridate (245 mg, 2.3 mmol) and Et_3N (607 mg, 6 mmol) at 0 °C. After the addition was completed, the reaction mixture was allowed to reach room temperature and stirred for 3 h. And then the solvent was evaporated to get the crude product, which was crystallized from water to give the desired product (450 mg, 92%) as a white solid.

^{1}H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.10 – 7.02 (m, 1H), 7.00 – 6.91 (m, 1H), 4.61 (s, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.72 (t, *J* = 5.7 Hz, 2H), 2.70 (t, *J* = 5.6 Hz, 2H), 1.22 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 155.1, 135.9, 131.1, 126.5, 120.8, 118.5, 117.5, 111.0, 106.7, 61.0, 41.8, 21.0, 14.6.

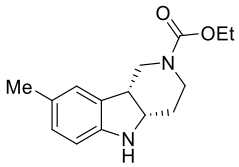
HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{17}N_2O_2^+$: 245.1285, found: 245.1286.

VI. General Procedure for the Asymmetric Hydrogenation Reaction

In the argon-filled glovebox, a solution of $[Ir(COD)Cl]_2$ (6.72 mg, 0.01 mmol) and ZhaoPhos (18.2 mg, 0.021 mmol) in 2.0 mL anhydrous solvent was stirred at room temperature for 20 min. A specified volume of the resulting solution (100 μL, 1 mol% Ir-Zhaophos catalyst) was transferred by syringe to a score-break ampule charged with substrate (0.1 mmol in 1.0 mL dichloromethane) and TsOH (1.2 eq.) as acid additive. The ampule was placed into an autoclave, which was then charged with desired pressure of hydrogen gas. The autoclave was stirred at desired temperature for the indicated period of time. After release of H_2, saturated sodium bicarbonate solution and dichloromethane was added and the mixture was stirred for 10 min. The organic layer was dried with anhydrous Na_2SO_4. After removal of solvent, the crude product was analyzed by ^1H NMR to determine the conversion. Purification was performed by silica gel column chromatography, eluted with Petrol ether / EtOAc, to give the desired product. The enantiomeric excess was determined by HPLC analysis.

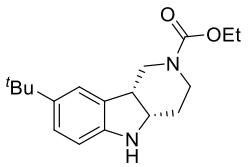


Ethyl (4a*S*,9b*R*)- 1,3,4,4a,5,9b-hexahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (**6a**): purified by flash chromatography (silica, petroleum ether/ethyl acetate = 2/1, v/v), oily solid, 24.2 mg, 98% yield, 93% ee, $[\alpha]_D^{23}$ + 75.5 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 7.2 Hz, 1H), 7.05 (td, *J* = 7.6, 1.2 Hz, 1H), 6.73 (td, *J* = 7.4, 0.8 Hz, 1H), 6.66 (d, *J* = 7.8 Hz, 1H), 4.20 – 4.06 (m, 2H), 3.97 (dt, *J* = 6.8, 4.9 Hz, 1H), 3.96 – 3.64 (m, 2H), 3.63 – 3.53 (m, 1H), 3.49 – 3.11 (m, 3H), 1.90 (ddt, *J* = 14.1, 9.3, 4.6 Hz, 1H), 1.76 (ddd, *J* = 14.4, 9.3, 5.3 Hz, 1H), 1.26 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.7, 150.9, 130.1, 128.1, 124.3, 119.1, 110.0, 61.3, 57.5, 43.9, 41.0, 39.8, 28.1, 14.8. The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak OD-3 column (0.46 x 25 cm), Hexane/^{i}PrOH = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, t_R: 11.140 min (*R, S*) (minor), 12.028 min (*S, R*) (major). HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{19}N_2O_2^+$: 247.1441, found: 247.1442.

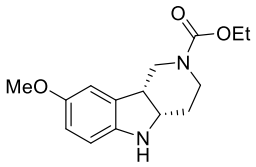


Ethyl (4a*S*,9b*R*)-8-methyl-1,3,4,4a,5,9b-hexahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (**6b**): purified by flash chromatography (silica, petroleum ether/ethyl acetate = 2/1, v/v), oily solid, 25.2 mg, 97% yield, 94% ee, $[\alpha]_D^{25}$ + 53.9 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 6.95 (s, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 6.58 (d, *J* = 7.8 Hz, 1H), 4.13 (dtt, *J* = 10.6, 7.1, 3.6 Hz, 2H), 3.97 – 3.92 (m, 1H), 3.91 – 3.50 (m, 3H), 3.49 – 3.04 (m, 3H), 2.25 (s, 3H), 1.89 (ddt, *J* = 14.1, 9.4, 4.7 Hz, 1H), 1.76 (td, *J* = 9.2, 4.7 Hz, 1H), 1.27 (t, *J* = 6.3 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.8, 148.5, 130.9, 130.5, 128.4, 125.1, 110.1, 61.3, 57.8, 44.0, 41.2, 39.9, 28.2, 20.9, 14.8. The enantiomeric excess was

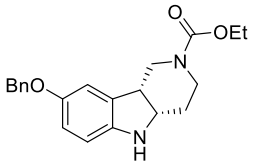
determined by HPLC analysis on Daicel Chiralpak OD-3 column (0.46 x 25 cm), Hexane/^{i}PrOH = 80:20, flow rate = 1.0 mL/min, λ = 210 nm, t_R: 7.090 min (*R, S*) (minor), 9.004 min (*S, R*) (major). HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{21}N_2O_2^+$: 261.1598, found: 261.1599.



Ethyl (4a*S*,9b*R*)-8-(*tert*-butyl)-1,3,4,4a,5,9b-hexahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (**6c**): purified by flash chromatography (silica, petroleum ether/ethyl acetate = 2/1, v/v), oily solid, 29.5 mg, 97% yield, 91% ee, $[\alpha]_D^{25}$ + 35.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (s, 1H), 7.11 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.64 (d, *J* = 8.1 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.03 – 3.95 (m, 2H), 3.93 – 2.93 (m, 5H), 1.93 (ddt, *J* = 14.2, 9.4, 4.6 Hz, 1H), 1.80 (dd, *J* = 9.6, 4.7 Hz, 1H), 1.31 (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 148.4, 142.4, 130.1, 124.8, 121.2, 109.6, 61.4, 57.8, 44.2, 41.2, 39.9, 34.3, 31.8, 28.2, 14.9. The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak AD-3 column (0.46 x 25 cm), Hexane/^{i}PrOH = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, t_R: 5.955 min (*S, R*) (major), 6.906 min (*R, S*) (minor). HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{27}N_2O_2^+$: 303.2067, found: 303.2070.

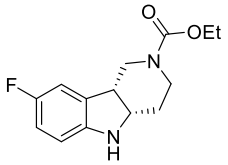


Ethyl (4a*S*,9b*R*)-8-methoxy-1,3,4,4a,5,9b-hexahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (**6d**): purified by flash chromatography (silica, petroleum ether/ethyl acetate = 2/1, v/v), oily solid, 25.7 mg, 93% yield, 92% ee, $[\alpha]_D^{25}$ + 42.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.76 (s, 1H), 6.62 (dt, *J* = 14.0, 5.3 Hz, 2H), 4.20 – 4.07 (m, 2H), 3.99 – 3.94 (m, 1H), 3.93 – 3.76 (m, 1H), 3.74 (s, 3H), 3.66 – 3.09 (m, 5H), 1.88 (ddd, *J* = 18.6, 9.3, 4.5 Hz, 1H), 1.75 (brs, 1H), 1.26 (brs, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.8, 153.8, 144.6, 131.8, 113.0, 111.2, 110.8, 61.4, 58.0, 56.1, 44.0, 41.4, 40.0, 28.2, 14.9. The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak OD-3 column (0.46 x 25 cm), Hexane/^{i}PrOH = 80:20, flow rate = 1.0 mL/min, λ = 210 nm, t_R: 8.012 min (*R, S*) (minor), 21.165 min (*S, R*) (major). HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{21}N_2O_3^+$: 277.1547, found: 277.1548.

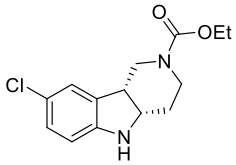


Ethyl (4a*S*,9b*R*)-8-(benzyloxy)-1,3,4,4a,5,9b-hexahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (**6e**): purified by flash chromatography (silica, petroleum ether/ethyl acetate = 2/1, v/v), oily solid, 34.8 mg, 99% yield, 94% ee, $[\alpha]_D^{25}$ + 28.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ

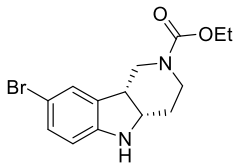
7.42 (d, J = 7.3 Hz, 2H), 7.37 (t, J = 7.5 Hz, 2H), 7.31 (t, J = 7.3 Hz, 1H), 6.84 (d, J = 2.3 Hz, 1H), 6.70 (dd, J = 8.4, 2.5 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H), 4.98 (s, 2H), 4.18 – 4.09 (m, 2H), 3.98 – 3.94 (m, 1H), 3.84 (d, J = 94.5 Hz, 1H), 3.67 – 3.10 (m, 5H), 1.88 (ddd, J = 13.8, 9.3, 4.6 Hz, 1H), 1.76 (dd, J = 9.2, 4.2 Hz, 1H), 1.31 – 1.25 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7, 152.9, 144.9, 137.6, 131.9, 128.6, 127.9, 127.6, 114.2, 112.3, 110.7, 71.1, 61.4, 58.0, 44.0, 41.4, 39.9, 28.1, 14.8. The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak OD-3 column (0.46 x 25 cm), Hexane/^{i}PrOH = 80:20, flow rate = 1.0 mL/min, λ = 210 nm, t_R: 8.050 min (*R, S*) (minor), 19.245 min (*S, R*) (major). HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{25}N_2O_3^+$: 353.1860, found: 353.1860.



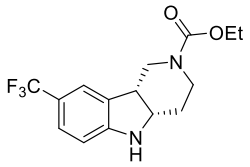
Ethyl (4a*S*,9b*R*)-8-fluoro-1,3,4,4a,5,9b-hexahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (**6f**): purified by flash chromatography (silica, petroleum ether/ethyl acetate = 2/1, v/v), oily solid, 25.8 mg, 97% yield, 90% ee, $[\alpha]_D^{25}$ + 61.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (dd, J = 8.2, 2.5 Hz, 1H), 6.74 (td, J = 8.9, 2.6 Hz, 1H), 6.56 (dd, J = 8.4, 4.3 Hz, 1H), 4.18 – 4.09 (m, 2H), 3.98 (dt, J = 10.1, 5.0 Hz, 1H), 3.80 (brd, J = 63.1 Hz, 1H), 3.69 – 3.13 (m, 5H), 1.88 (ddd, J = 13.8, 6.8, 4.8 Hz, 1H), 1.80 – 1.66 (m, 1H), 1.27 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0 (d, J = 235.7 Hz), 155.6, 146.8, 131.7 (d, J = 34.0 Hz), 114.0 (d, J = 23.2 Hz), 111.6 (d, J = 23.7 Hz), 110.2 (d, J = 7.5 Hz), 61.3, 58.0, 43.6, 41.2, 39.8, 27.9, 14.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ -125.8. The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak OD-3 column (0.46 x 25 cm), Hexane/^{i}PrOH = 80:20, flow rate = 1.0 mL/min, λ = 210 nm, t_R: 6.487 min (*R, S*) (minor), 9.634 min (*S, R*) (major). HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{18}FN_2O_2^+$: 265.1347, found: 265.1349.



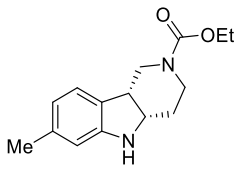
Ethyl (4a*S*,9b*R*)-8-chloro-1,3,4,4a,5,9b-hexahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (**6g**): purified by flash chromatography (silica, petroleum ether/ethyl acetate = 2/1, v/v), oily solid, 27.4 mg, 98% yield, 86% ee, $[\alpha]_D^{25}$ + 30.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (s, 1H), 6.99 (dd, J = 8.2, 2.1 Hz, 1H), 6.55 (d, J = 8.3 Hz, 1H), 4.20 – 4.06 (m, 2H), 3.98 (dt, J = 10.1, 5.0 Hz, 1H), 3.94 – 3.65 (m, 2H), 3.62 – 3.07 (m, 4H), 1.94 – 1.83 (m, 1H), 1.72 (brs, 1H), 1.26 (t, J = 6.3 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.7, 149.5, 131.8, 127.9, 124.6, 123.6, 110.8, 61.5, 57.9, 43.6, 41.2, 39.8, 28.0, 14.8. The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak OD-3 column (0.46 x 25 cm), Hexane/^{i}PrOH = 80:20, flow rate = 1.0 mL/min, λ = 210 nm, t_R: 6.739 min (*R, S*) (minor), 12.626 min (*S, R*) (major). HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{18}ClN_2O_2^+$: 281.1051, found: 281.1053.



Ethyl (4a*S*,9b*R*)-8-bromo-1,3,4,4a,5,9b-hexahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (**6h**): purified by flash chromatography (silica, petroleum ether/ethyl acetate = 2/1, v/v), oily solid, 31.4 mg, 98% yield, 84% ee, $[\alpha]_D^{25}$ + 19.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 1.8 Hz, 1H), 7.13 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.52 (d, *J* = 8.2 Hz, 1H), 4.19 – 4.07 (m, 2H), 3.97 (dt, *J* = 10.1, 5.0 Hz, 1H), 3.92 – 3.65 (m, 2H), 3.62 – 3.13 (m, 4H), 1.88 (td, *J* = 13.9, 4.8 Hz, 1H), 1.70 (s, 1H), 1.27 (brs, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7, 149.9, 132.3, 130.7, 127.3, 111.3, 110.5, 61.5, 57.8, 43.6, 41.1, 39.8, 28.0, 14.8. The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak OD-3 column (0.46 x 25 cm), Hexane/^{i}PrOH = 80:20, flow rate = 1.0 mL/min, λ = 210 nm, t_R: 6.989 min (*R, S*) (minor), 13.105 min (*S, R*) (major). HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{18}BrN_2O_2^+$: 325.0546, found: 325.0548.

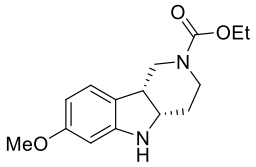


Ethyl (4a*S*,9b*R*)-8-trifluoromethyl-1,3,4,4a,5,9b-hexahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (**6i**): purified by flash chromatography (silica, petroleum ether/ethyl acetate = 2/1, v/v), oily solid, 30.4 mg, 97% yield, 66% ee, $[\alpha]_D^{25}$ + 18.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 6.64 (d, *J* = 8.1 Hz, 1H), 4.16 – 4.08 (m, 2H), 4.08 – 4.00 (m, 2H), 3.98 – 3.11 (m, 5H), 1.92 (ddt, *J* = 13.9, 9.2, 4.7 Hz, 1H), 1.74 (s, 1H), 1.31 – 1.19 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.6, 153.7, 129.9, 126.0 (q, *J* = 3.4 Hz), 123.1 (q, *J* = 270.6 Hz), 121.4, 120.65 (d, *J* = 32.2 Hz), 108.8, 61.4, 57.6, 43.2, 40.7, 39.7, 27.8, 14.6. ^{19}F NMR (565 MHz, $CDCl_3$) δ -60.8. The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak OD-3 column (0.46 x 25 cm), Hexane/^{i}PrOH = 85:15, flow rate = 0.8 mL/min, λ = 254 nm, t_R: 8.52 min (*R, S*) (minor), 10.46 min (*S, R*) (major). HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{18}F_3N_2O_2^+$: 315.1315, found: 315.1311.

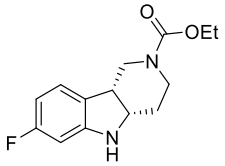


Ethyl (4a*S*,9b*R*)-7-methyl-1,3,4,4a,5,9b-hexahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (**6j**): purified by flash chromatography (silica, petroleum ether/ethyl acetate = 2/1, v/v), oily solid, 25.6 mg, 98% yield, 92% ee, $[\alpha]_D^{23}$ + 56.9 (*c* 1.0, $CHCl_3$).^{1}H NMR (600 MHz, $CDCl_3$) δ 7.00 (d, *J* = 7.4 Hz, 1H), 6.55 (d, *J* = 7.4 Hz, 1H), 6.50 (s, 1H), 4.13 (p, *J* = 7.2 Hz, 2H), 4.07 – 3.63 (m, 3H), 3.57 (dt, *J* = 11.4, 5.1 Hz, 1H), 3.42 (d, *J* = 12.7 Hz, 1H), 3.25 (t, *J* = 33.4 Hz, 2H), 2.26 (s, 3H), 1.89 (ddt, *J* = 14.4, 9.6, 4.6 Hz, 1H), 1.76 (dt, *J* = 14.4, 5.2 Hz, 1H), 1.31 – 1.23 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ

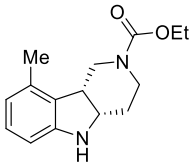
155.8, 151.1, 138.1, 127.4, 124.0, 119.9, 111.0, 61.3, 57.7, 44.1, 39.9, 28.1, 21.7, 14.9. The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak OD-3 column (0.46 x 25 cm), Hexane/^{i}PrOH = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, t_R: 7.836 min (*S, R*) (major), 9.540 min (*R, S*) (minor). HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{21}N_2O_2^+$: 261.1598, found: 261.1596.



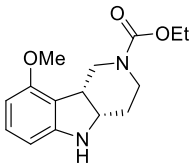
Ethyl (4a*S*,9b*R*)-7-methoxy-1,3,4,4a,5,9b-hexahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (**6k**): purified by flash chromatography (silica, petroleum ether/ethyl acetate = 2/1, v/v), oily solid, 26.2 mg, 95% yield, 90% ee, $[\alpha]_D^{25}$ + 79.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, *J* = 7.7 Hz, 1H), 6.34 – 6.17 (m, 2H), 4.12 (dtd, *J* = 10.3, 7.0, 3.6 Hz, 2H), 3.98 (dd, *J* = 11.5, 4.9 Hz, 1H), 3.93 – 3.65 (m, 2H), 3.65 – 3.51 (m, 1H), 3.47 – 3.35 (m, 1H), 3.31 – 3.10 (m, 2H), 1.94 – 1.84 (m, 1H), 1.75 (ddd, *J* = 14.3, 9.4, 5.2 Hz, 1H), 1.26 (t, *J* = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.4, 155.7, 152.2, 124.5, 122.7, 103.7, 96.9, 61.3, 57.9, 55.4, 44.1, 40.2, 39.8, 28.1, 14.8. The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak OD-3 column (0.46 x 25 cm), Hexane/^{i}PrOH = 80:20, flow rate = 1.0 mL/min, λ = 210 nm, t_R: 8.288 min (*S, R*) (major), 19.862 min (*R, S*) (minor). HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{21}N_2O_3^+$: 277.1547, found: 277.1548.



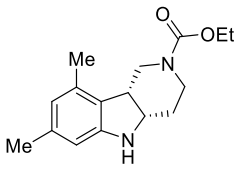
Ethyl (4a*S*,9b*R*)-7-fluoro-1,3,4,4a,5,9b-hexahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (**6l**): purified by flash chromatography (silica, petroleum ether/ethyl acetate = 2/1, v/v), oily solid, 25.9 mg, 98% yield, 82% ee, $[\alpha]_D^{25}$ + 3.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.03 – 6.97 (m, 1H), 6.40 – 6.36 (m, 1H), 6.33 (dd, *J* = 9.7, 2.2 Hz, 1H), 4.16 – 4.08 (m, 2H), 4.01 (dd, *J* = 11.9, 4.9 Hz, 1H), 3.89 – 3.68 (m, 2H), 3.58 – 3.52 (m, 1H), 3.44 – 3.18 (m, 3H), 1.89 (ddt, *J* = 13.8, 9.1, 4.3 Hz, 1H), 1.74 (ddd, *J* = 14.4, 9.3, 5.3 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.6 (d, *J* = 241.9 Hz), 155.8, 152.4 (d, *J* = 11.6 Hz), 125.7 (d, *J* = 34.2 Hz), 124.8, 105.1 (d, *J* = 16.3 Hz), 97.7 (d, *J* = 26.4 Hz), 61.4, 58.1, 43.9, 40.2, 39.7, 28.0, 14.8. ^{19}F NMR (565 MHz, $CDCl_3$) δ -114.9. The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak OD-3 column (0.46 x 25 cm), Hexane/^{i}PrOH = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, t_R: 7.574 min (*S, R*) (major), 9.122 min (*R, S*) (minor). HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{18}FN_2O_2^+$: 265.1347, found: 265.1345.



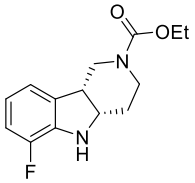
Ethyl (4a*S*,9b*R*)-9-methyl-1,3,4,4a,5,9b-hexahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (**6m**): purified by flash chromatography (silica, petroleum ether/ethyl acetate = 2/1, v/v), oily solid, 25.5 mg, 98% yield, 91% ee, $[\alpha]_D^{22}$ + 54.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.96 (t, *J* = 7.7 Hz, 1H), 6.55 (d, *J* = 7.6 Hz, 1H), 6.52 (d, *J* = 7.7 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.09 – 3.62 (m, 4H), 3.26 (d, *J* = 13.9 Hz, 1H), 2.73 (brs, 1H), 2.28 (s, 3H), 1.96 (s, 1H), 1.91 – 1.80 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.7, 150.9, 134.4, 129.7, 128.0, 120.6, 107.6, 61.3, 57.7, 43.7, 39.6, 27.9, 18.4, 14.8. The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak OD-3 column (0.46 x 25 cm), Hexane/^{i}PrOH = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, t_R: 9.997 min (*S, R*) (major), 11.021 min (*R, S*) (minor). HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{21}N_2O_2^+$: 261.1598, found: 261.1596.



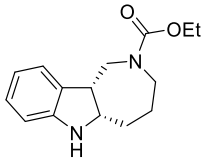
Ethyl (4a*S*,9b*R*)-9-methoxy-1,3,4,4a,5,9b-hexahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (**6n**): purified by flash chromatography (silica, petroleum ether/ethyl acetate = 2/1, v/v), oily solid, 27.3 mg, 99% yield, 95% ee, $[\alpha]_D^{25}$ + 29.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (t, *J* = 8.0 Hz, 1H), 6.30 (t, *J* = 8.0 Hz, 2H), 4.27 – 3.96 (m, 4H), 3.79 (s, 3H), 3.78 – 3.66 (m, 2H), 3.40 (s, 1H), 3.37 – 3.27 (m, 1H), 3.18 – 2.76 (m, 1H), 1.95 (dd, *J* = 14.7, 9.6 Hz, 1H), 1.88 – 1.80 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0, 155.9, 152.6, 129.4, 117.3, 103.4, 101.9, 61.2, 57.4, 55.3, 43.1, 39.6, 38.8, 27.8, 14.9. The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak OD-3 column (0.46 x 25 cm), Hexane/^{i}PrOH = 80:20, flow rate = 1.0 mL/min, λ = 210 nm, t_R: 10.693 min (*R, S*) (minor), 12.109 min (*S, R*) (major). HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{21}N_2O_3^+$: 277.1547, found: 277.1548.



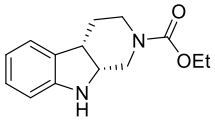
Ethyl (4a*S*,9b*R*)-7,9-dimethyl-1,3,4,4a,5,9b-hexahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (**6o**): purified by flash chromatography (silica, petroleum ether/ethyl acetate = 2/1, v/v), oily solid, 26.1 mg, 95% yield, 89% ee, $[\alpha]_D^{25}$ + 73.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (s, 1H), 6.36 (s, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 4.10 (brs, 1H), 3.96 (dt, *J* = 7.0, 3.6 Hz, 1H), 3.93 – 3.60 (m, 2H), 3.24 (dd, *J* = 25.8, 11.8 Hz, 2H), 2.72 (brs, 1H), 2.23 (d, *J* = 1.4 Hz, 6H), 2.02 – 1.89 (m, 1H), 1.89 – 1.78 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.6, 151.1, 137.9, 134.0, 126.9, 121.3, 108.3, 61.2, 57.8, 43.8, 39.5, 39.0, 27.9, 21.5, 18.2, 14.8. The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak OD-3 column (0.46 x 25 cm), Hexane/^{i}PrOH = 80:20, flow rate = 1.0 mL/min, λ = 210 nm, t_R: 5.654 min (*S, R*) (major), 6.425 min (*R, S*) (minor). HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{23}N_2O_2^+$: 275.1754, found: 275.1755.



Ethyl (4a*S*,9b*R*)-6-fluoro-1,3,4,4a,5,9b-hexahydro-*2H*-pyrido[4,3-*b*]indole-2-carboxylate (**6p**): purified by flash chromatography (silica, petroleum ether/ethyl acetate = 2/1, v/v), oily solid, 25.6 mg, 97% yield, 77% ee, $[\alpha]_D^{25}$ + 53.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (d, *J* = 7.3 Hz, 1H), 6.82 (dd, *J* = 9.7, 8.4 Hz, 1H), 6.65 (ddd, *J* = 8.1, 7.5, 4.6 Hz, 1H), 4.11 (ddq, *J* = 14.3, 7.2, 3.5 Hz, 2H), 4.01 (dt, *J* = 6.8, 4.9 Hz, 1H), 3.97 – 3.66 (m, 2H), 3.60 – 3.52 (m, 1H), 3.48 – 3.38 (m, 1H), 3.36 – 3.13 (m, 2H), 1.90 (ddt, *J* = 14.1, 9.3, 4.6 Hz, 1H), 1.77 (dt, *J* = 14.2, 4.6 Hz, 1H), 1.24 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6, 149.4 (d, *J* = 240.4 Hz), 137.7 (d, *J* = 12.9 Hz), 133.9 (d, *J* = 7.5 Hz), 119.6 (d, *J* = 23.1 Hz), 114.7 (d, *J* = 17.5 Hz), 61.3, 58.2, 43.7, 41.3, 39.7, 27.9, 14.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -135.5. The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak AD-3 column (0.46 x 25 cm), Hexane/^{i}PrOH = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, t_R: 6.800 min (*R, S*) (minor), 7.666 min (*S, R*) (major). HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{18}FN_2O_2^+$: 265.1347, found: 265.1349.



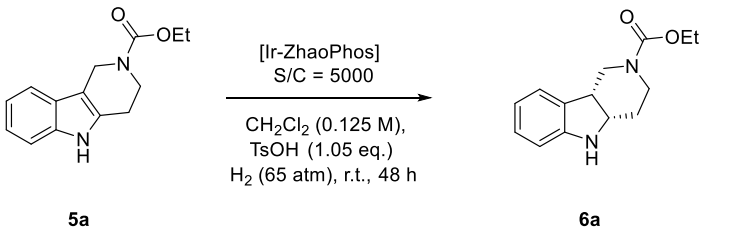
Ethyl (5a*S*,10b*R*)-3,4,5,5a,6,10b-hexahydroazepino[4,3-*b*]indole-2(*1H*)-carboxylate (**6q**): purified by flash chromatography (silica, petroleum ether/ethyl acetate = 2/1, v/v), oily solid, 16.9 mg, 65% yield, 98% ee, $[\alpha]_D^{25}$ + 81.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 6.97 (m, 2H), 6.70 (t, *J* = 7.4 Hz, 1H), 6.57 (d, *J* = 7.9 Hz, 1H), 4.18 (dt, *J* = 22.1, 11.0 Hz, 3H), 4.02 (tt, *J* = 9.8, 4.8 Hz, 2H), 3.88 – 3.51 (m, 2H), 3.16 – 2.98 (m, 1H), 2.96 – 2.80 (m, 1H), 2.02 – 1.90 (m, 2H), 1.87 – 1.78 (m, 1H), 1.70 – 1.58 (m, 1H), 1.33 – 1.26 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.9, 150.7, 129.4, 128.1, 124.3, 118.4, 108.9, 61.3, 49.1, 48.1, 45.5, 31.7, 25.4, 14.8. **rotamer :** ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.9, 150.7, 129.6, 127.9, 124.6, 118.5, 108.8, 62.5, 49.0, 48.4, 44.7, 31.9, 25.5, 14.8. The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak AD-3 column (0.46 x 25 cm), Hexane/^{i}PrOH = 80:20, flow rate = 1.0 mL/min, λ = 210 nm, t_R: 6.599 min (*R, S*) (minor), 12.318 min (*S, R*) (major). HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{21}N_2O_2^+$: 261.1598, found: 261.1597.



Ethyl (4aS,9aR)-1,3,4,4a,9,9a-hexahydro-2H-pyrido[3,4-b]indole-2-carboxylate (**6r**): purified by flash chromatography (silica, petroleum ether/ethyl acetate = 2/1, v/v), oily solid, 23.6 mg, 96% yield, 75% ee, $[\alpha]_D^{25}$ -60.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (dd, *J* = 14.8, 7.4 Hz, 2H), 6.73 (t, *J* = 7.3 Hz, 1H), 6.63 (d, *J* = 7.7 Hz, 1H), 4.12 (dd, *J* = 13.8, 6.8 Hz, 2H), 4.00 – 3.81 (m, 1H), 3.66 – 3.47 (m, 1H), 2.00 (td, *J* = 12.3, 5.9 Hz, 1H), 1.85 (s, 1H), 1.32 – 1.13 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 150.3, 130.9, 127.6, 123.5, 118.7, 109.6, 61.1, 57.2, 44.0, 40.8,

39.1, 26.0, 14.5. The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak OD-3 column (0.46 x 25 cm), Hexane/iPrOH = 80 : 20, flow rate = 1.0 mL/min, λ = 254 nm, t_R: 10.68 min (*R, S*) (minor), 11.92 min (*S, R*) (major).
HRMS (ESI/ion trap) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{19}N_2O_2^+$: 247.1411, found: 247.1412.

VII. Gram Scale Reaction and High Turnover Reaction



5a

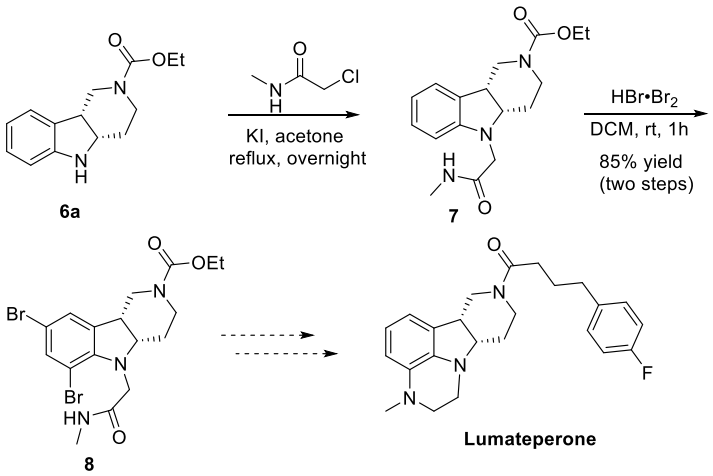
5 mmol, 1.22 g

6a

95% conv. 91% ee, 90% yield

In the argon-filled glovebox, a solution of $[Ir(COD)Cl]_2$ (6.7 mg, 0.01 mmol) and ZhaoPhos (18.2 mg, 0.021 mmol) in 2.0 mL anhydrous solvent was stirred at room temperature for 20 min. A specified volume of the resulting solution (100 μL, 1 mol% Ir-Zhaophos catalyst) was transferred by syringe to a score-break ampule charged with substrate (5 mmol, 1.22 g) in 40 mL dichloromethane and TsOH (904 mg, 5.25 mmol, 1.05 eq.) as acid additive. The ampule was placed into an autoclave, which was then charged with hydrogen gas (65 atm). The autoclave was stirred at room temperature for 48 h. After release of H_2, saturated sodium bicarbonate solution and dichloromethane was added and the mixture was stirred for 10 min. The organic layer was dried with anhydrous Na_2SO_4. After removal of solvent, the crude product was analysed by ^1H NMR to determine the conversion. Purification was performed by silica gel column chromatography, eluted with Petrol ether / EtOAc, to give the desired product **6a** (90% yield, 91% ee).

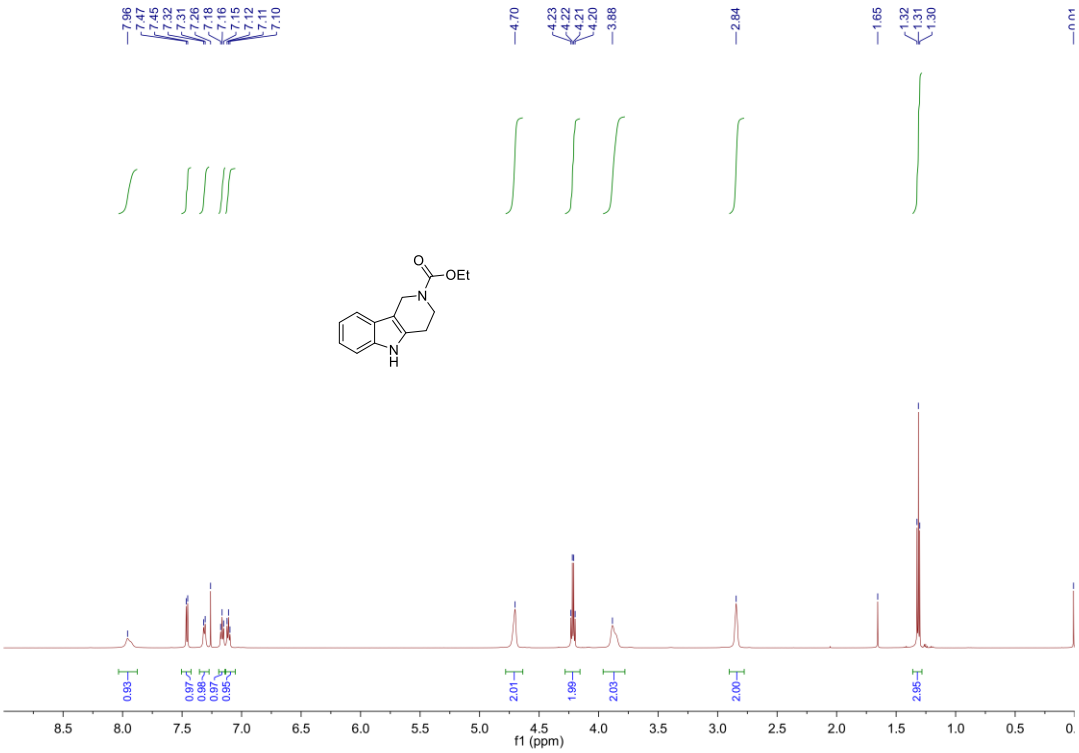
VIII. Synthetic Application from 6a to Lumateperone Intermediate



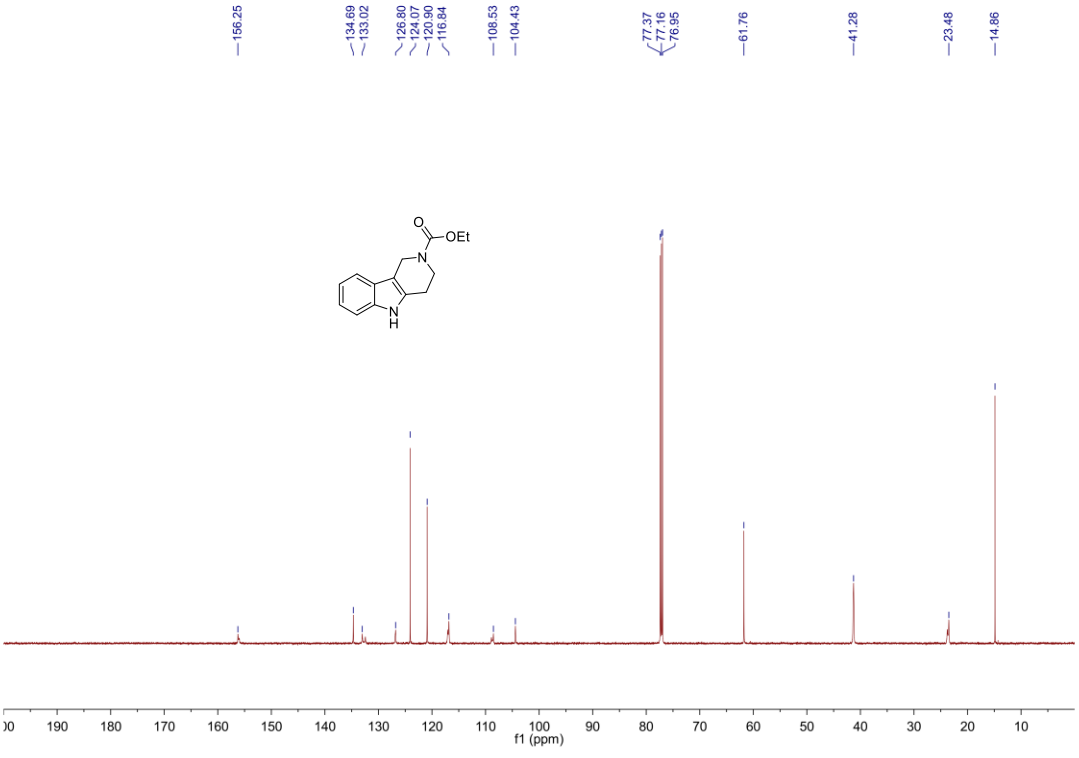
Synthesis of compound **8**: In argon atmosphere, to a solution of **2a** (739 mg, 3 mmol) in acetone (15 mL) were added 2-chloro-*N*-methylacetamide (387 mg, 3.6 mmol), KI (250 mg, 1.5 mmol), and K_2CO_3 (620 mg, 4.5 mmol). The reaction mixture was heated at 70 °C for 24 h, cooled to room temperature, and then the solid was removed by filtration through celite, and the filtrate was concentrated under vacuum. The residue was dissolved in CH_2Cl_2, washed by saturated NaCl, and then was dried over anhydrous Na_2SO_4, and the filtrate was concentrated under vacuum to give crude product **7**. Then to a solution the crude product **7** in CH_2Cl_2 (15 mL), monopyridin-1-ium tribromide (2.11 g, 6.6 mmol) was added in portions, and the reaction was completed after 1h traced by TLC. Then the reaction mixture was diluted with CH_2Cl_2 (20 mL), quenched by aq. Na_2CO_3, separated the organic phase, washed with aq. Na_2SO_3, dried over anhydrous Na_2SO_4, then the filtrate was concentrated under vacuum to give crude residue. The residue was purified by silica gel flash column chromatography eluting with a gradient of 30−50% ethyl acetate in petrol ether to give the title compound **8** (1.21 g, 85% yield after two steps, 93% ee). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.16 (s, 1H), 6.81 (brs, 1H), 4.32 – 4.18 (m, 1H), 4.14 – 3.96 (m, 2H), 3.89 – 3.12 (m, 7H), 2.87 (d, J = 4.9 Hz, 3H), 1.96 – 1.85 (m, 1H), 1.83 – 1.72 (m, 1H), 1.21 (t, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.1, 155.7, 147.8, 136.1, 135.4, 126.7, 113.0, 105.1, 65.6, 61.7, 54.6, 43.5, 41.1, 39.9, 26.2, 25.0, 14.7. The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak OD-3 column (0.46 x 25 cm), Hexane/^{i}PrOH = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, t_R: 7.88 min (*R, S*) (minor), 8.49 min (*S, R*) (major). HRMS (ESI/ion trap) m/z: $[M + H]^+$ calcd for $C_{17}H_{22}Br_2N_3O_3^+$: 474.0022, found: 474.0020.

IX. NMR Spectra of Compounds 5a-5r, 6a-6r, 8

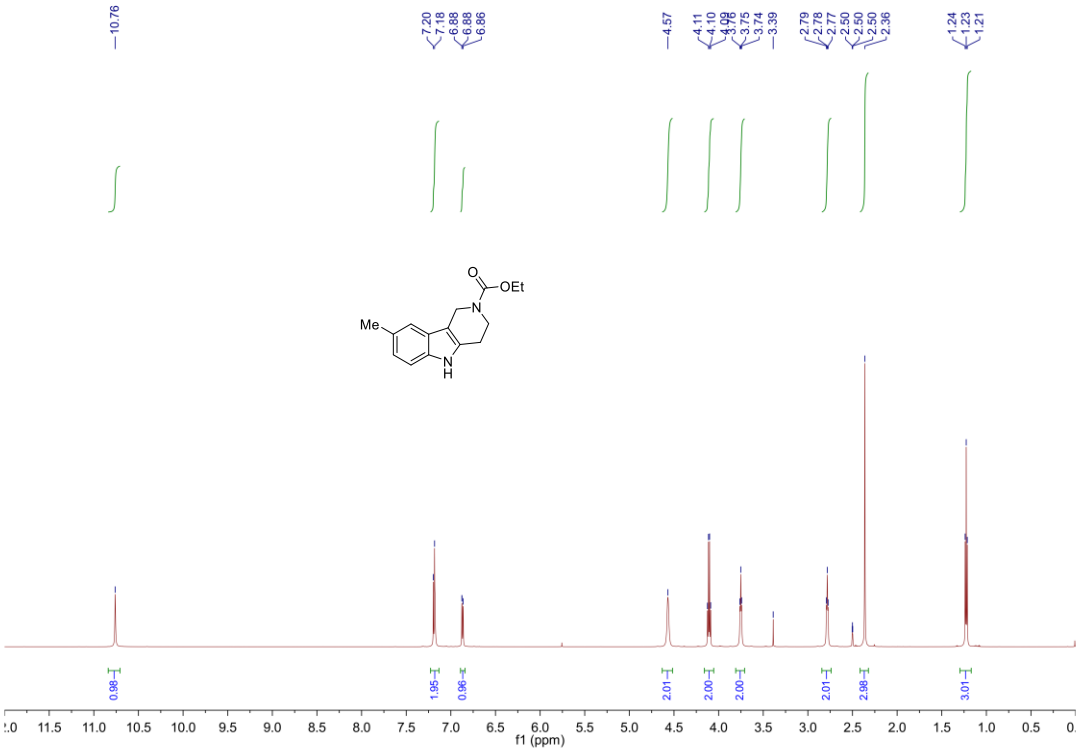
^{1}H NMR (600 MHz, $CDCl_3$) of compound **5a**



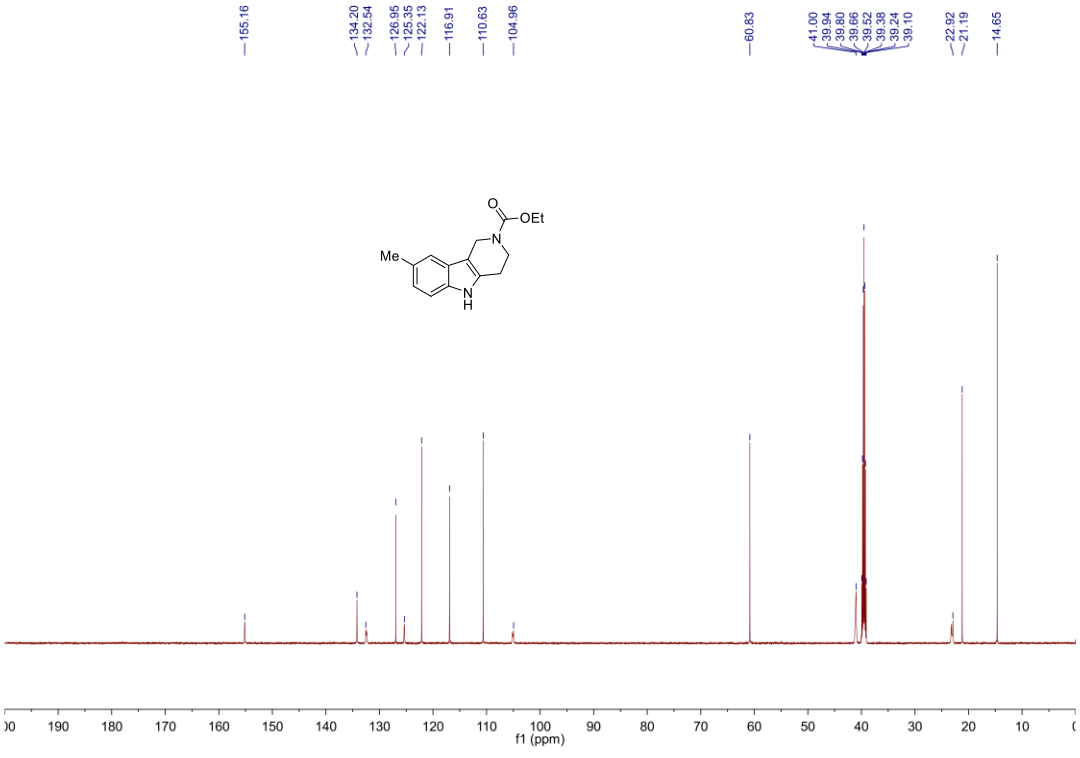
^{13}C NMR (151 MHz, $CDCl_3$) of compound **5a**



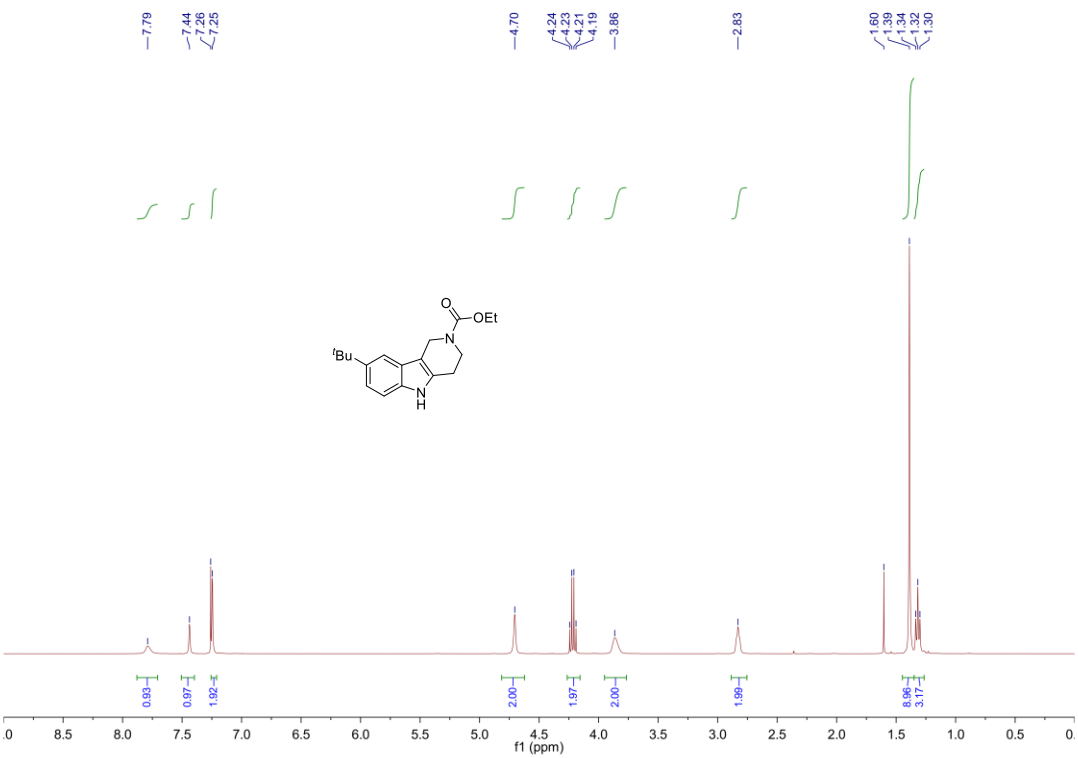
^{1}H NMR (600 MHz, d^6-DMSO) of compound **5b**



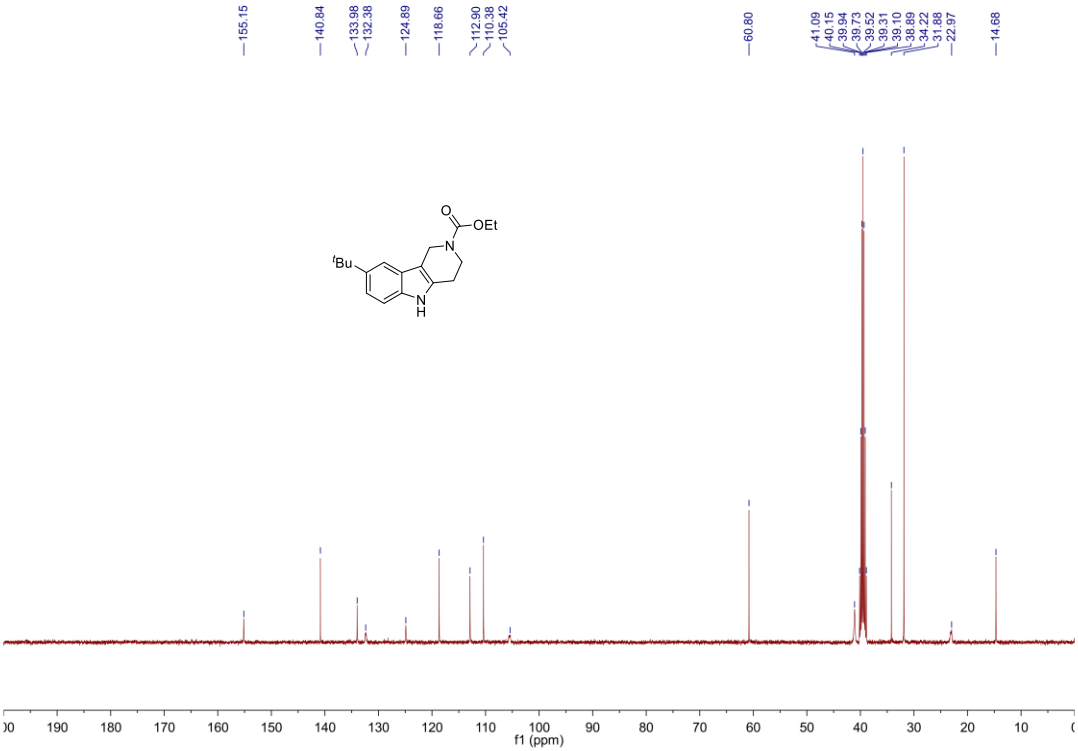
^{1}H NMR (151 MHz, d^6-DMSO) of compound **5b**



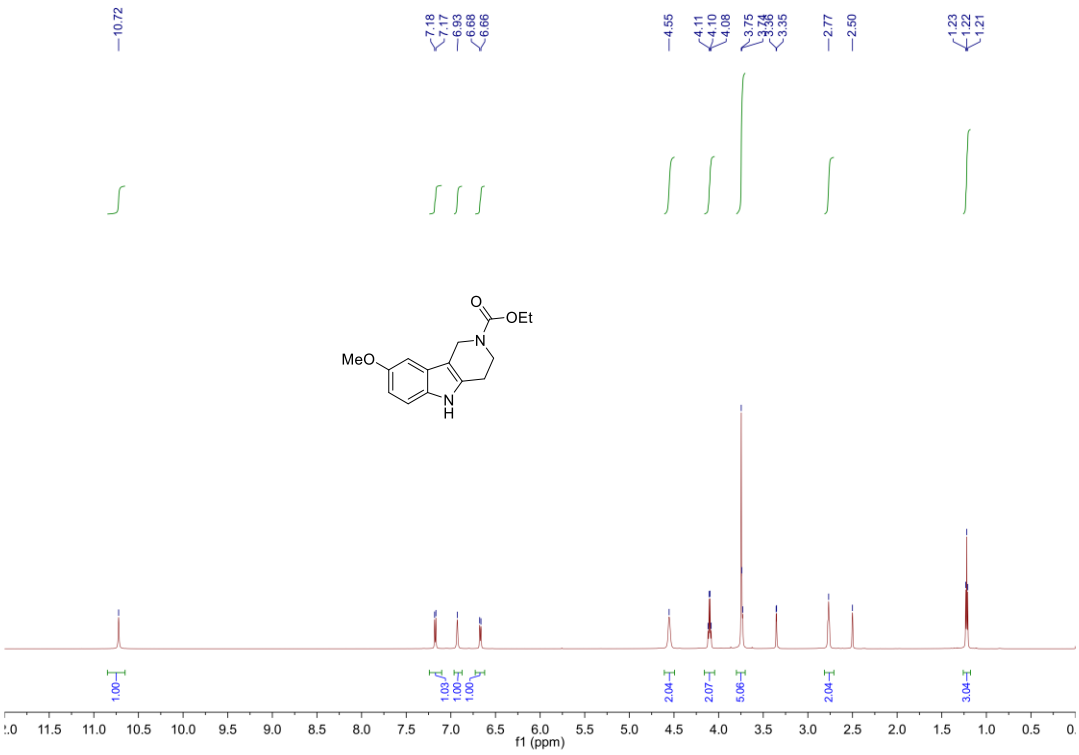
^{1}H NMR (400 MHz, $CDCl_3$) of compound **5c**



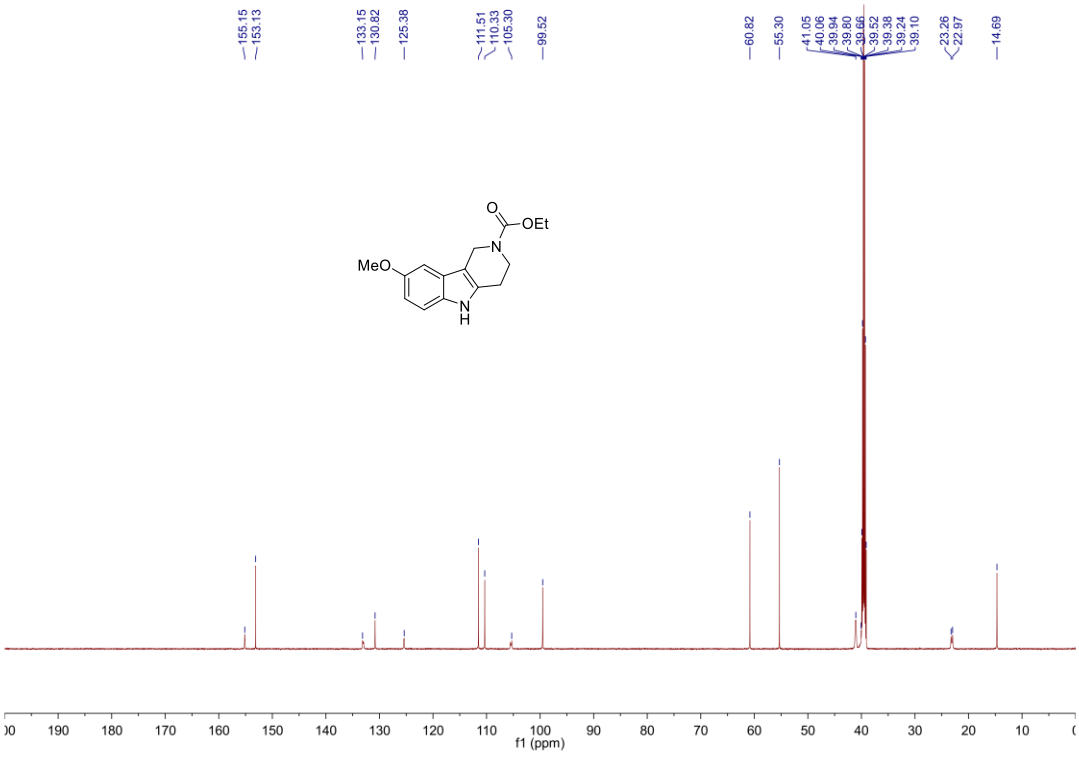
^{13}C NMR (101 MHz, d^6-DMSO) of compound **5c**



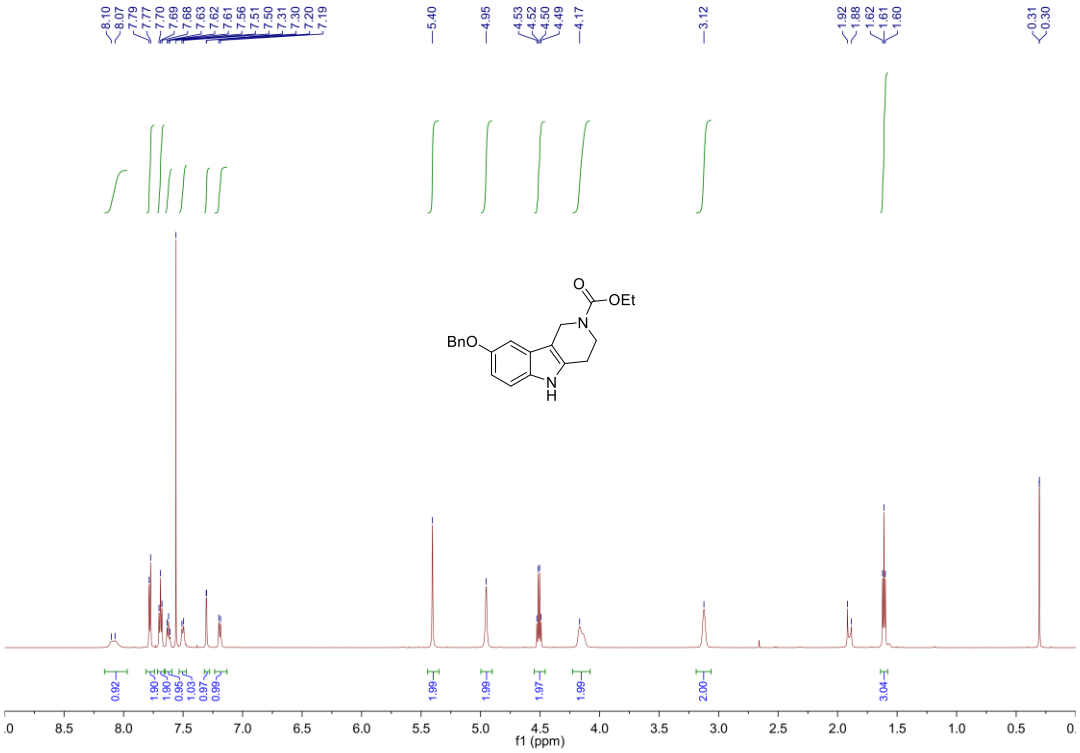
^{1}H NMR (600 MHz, d^6-DMSO) of compound **5d**



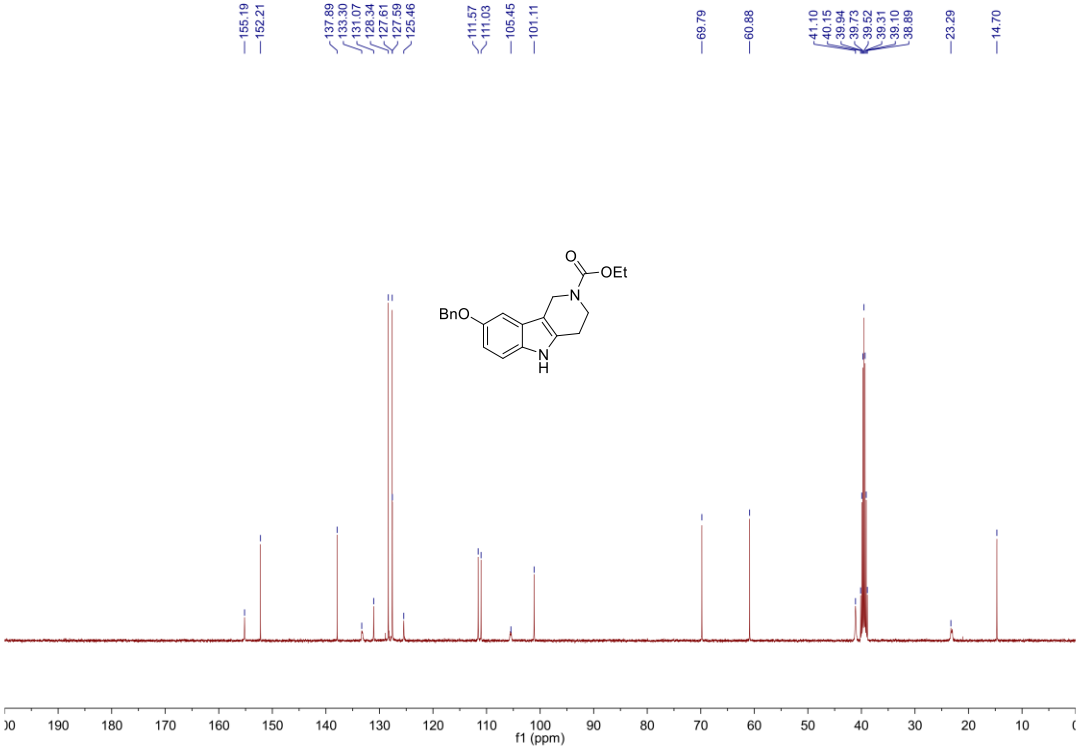
^{1}H NMR (151 MHz, d^6-DMSO) of compound **5d**



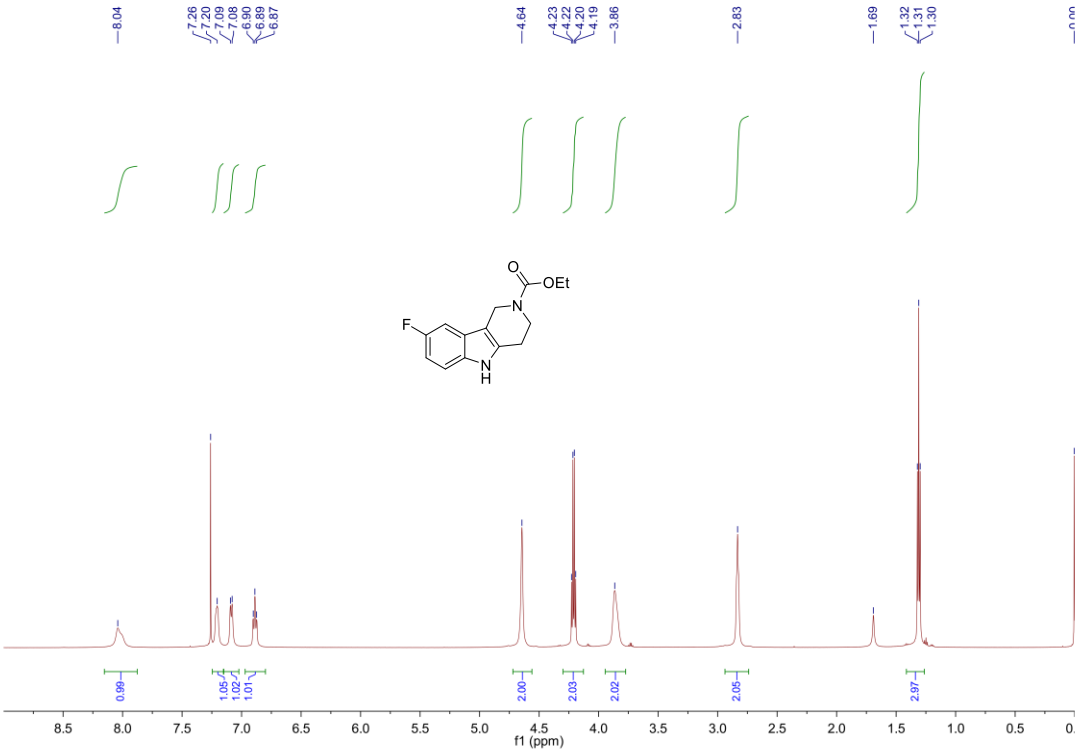
^{1}H NMR (600 MHz, $CDCl_3$) of compound **5e**



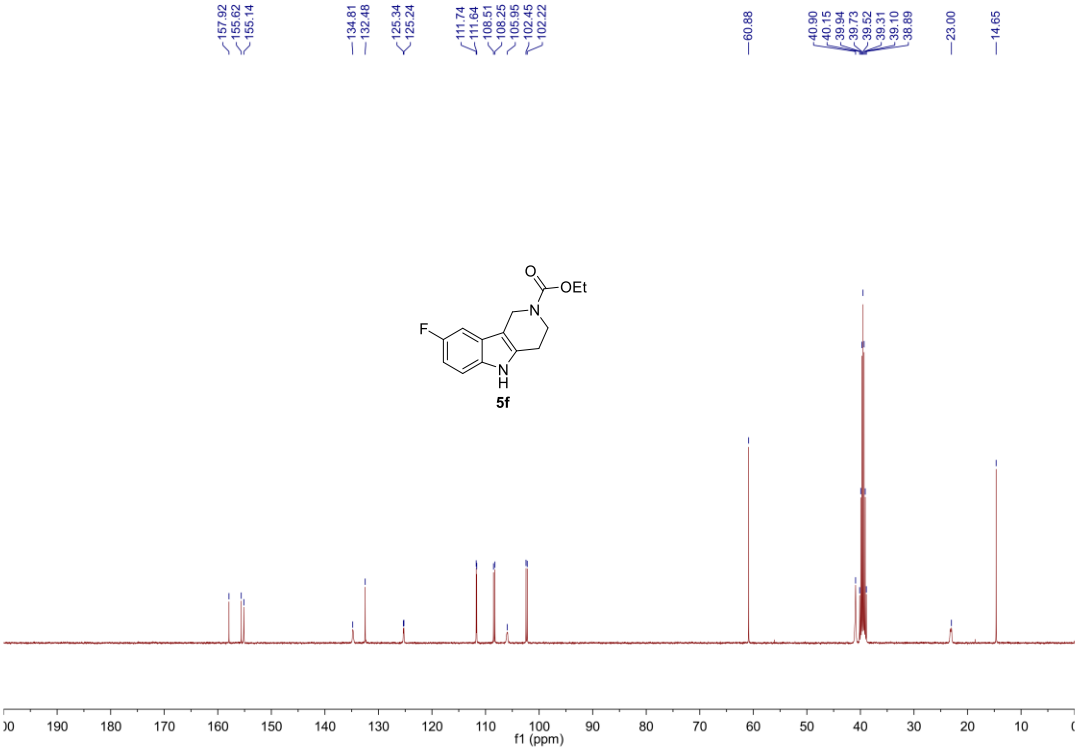
^{13}C NMR (101 MHz, $CDCl_3$) of compound **5e**



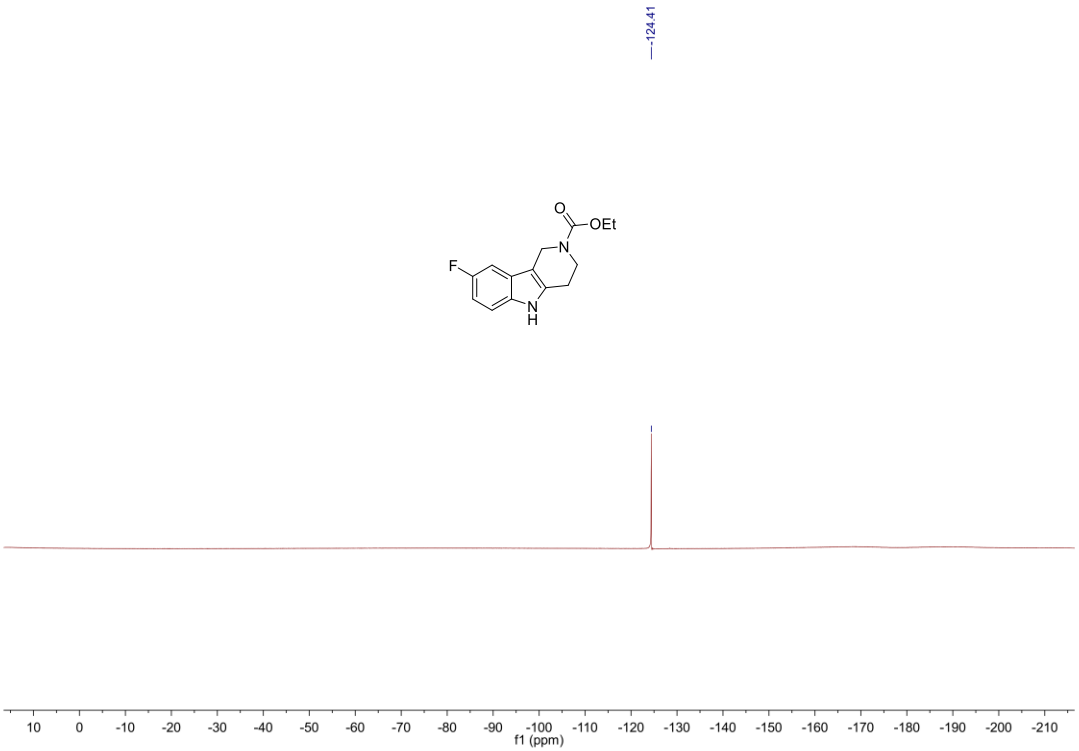
^{1}H NMR (600 MHz, $CDCl_3$) of compound **5f**



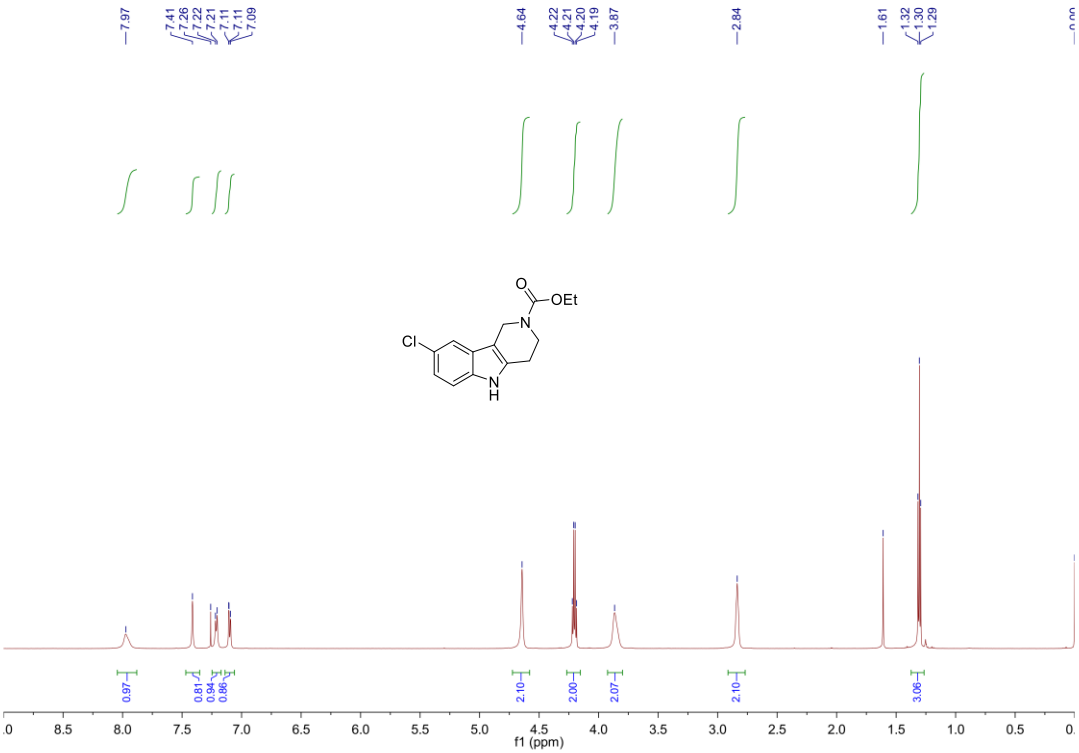
^{13}C NMR (101 MHz, d^6-DMSO) of compound **5f**



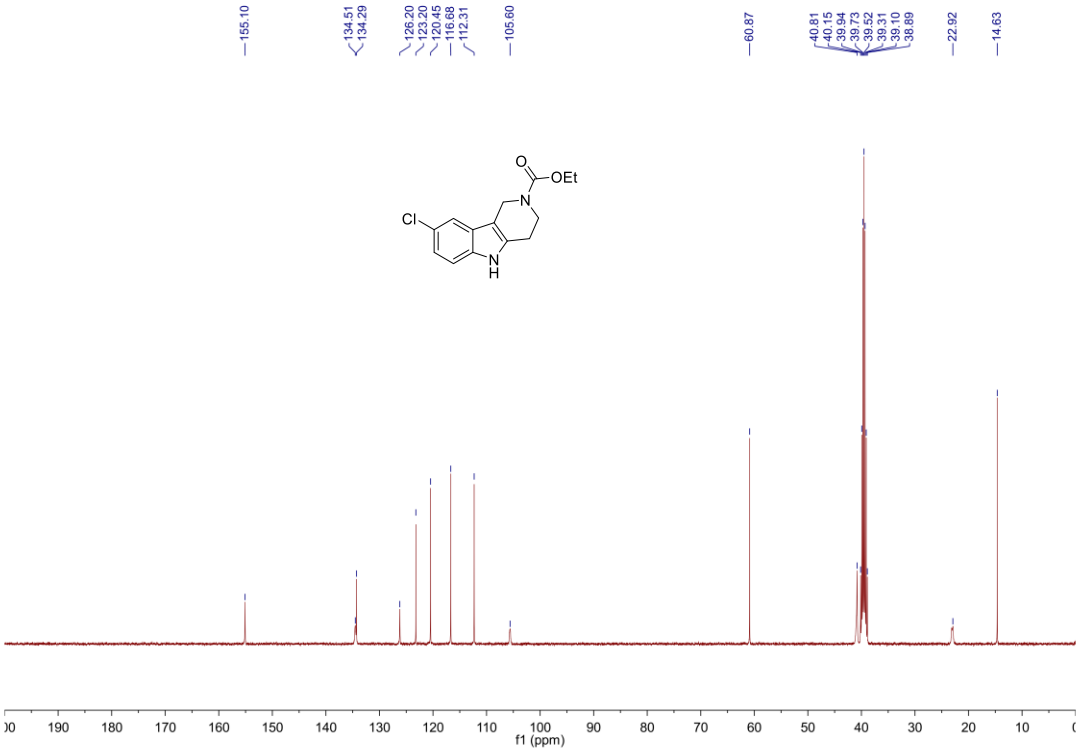
^{19}F NMR (376 MHz, $CDCl_3$) of compound **5f**



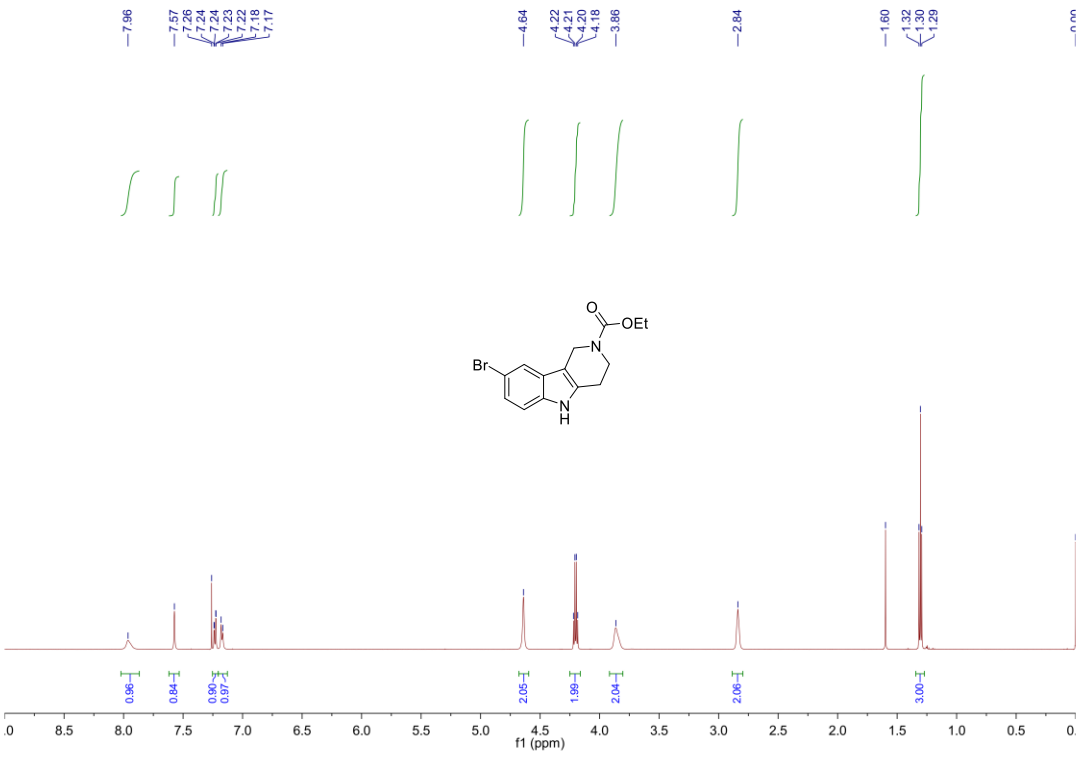
^{1}H NMR (600 MHz, $CDCl_3$) of compound **5g**



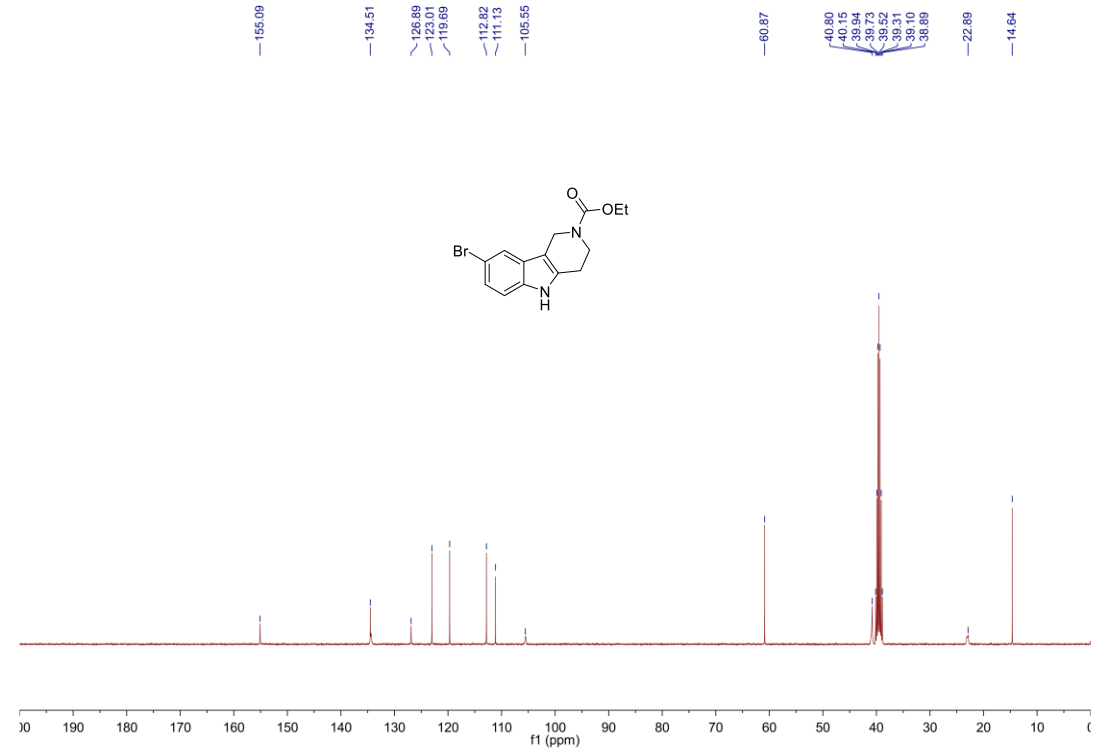
^{13}C NMR (101 MHz, d^6-DMSO) of compound **5g**



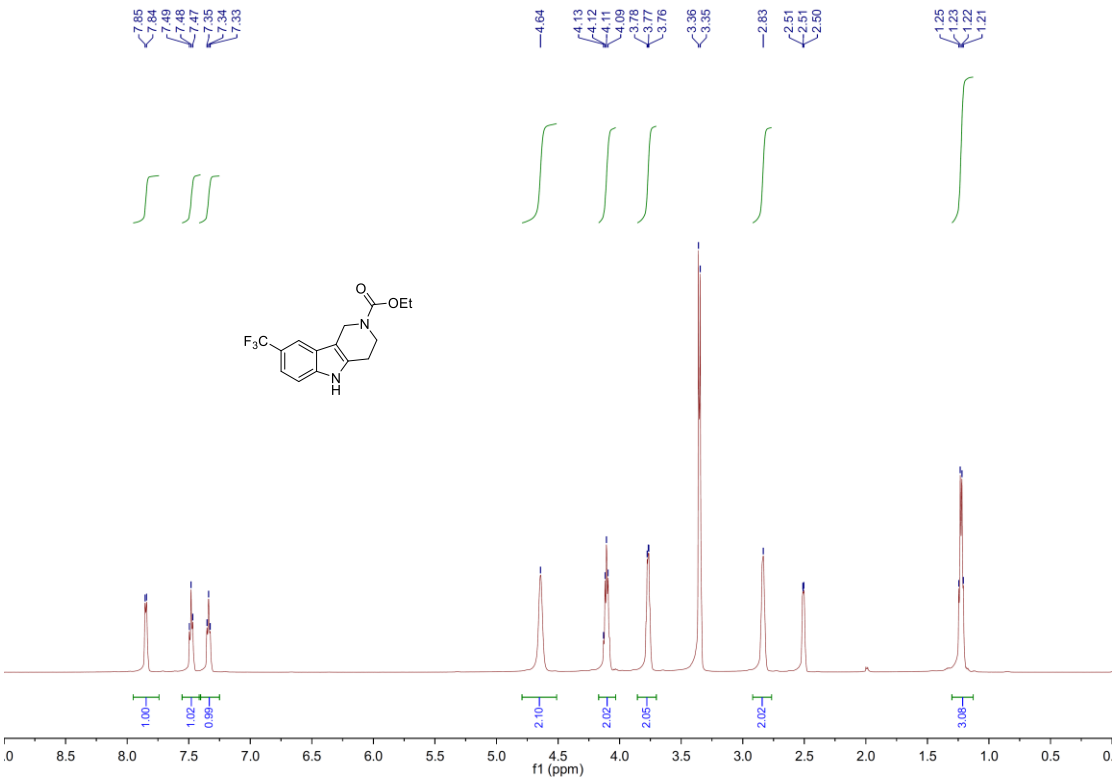
^{1}H NMR (600 MHz, $CDCl_3$) of compound **5h**



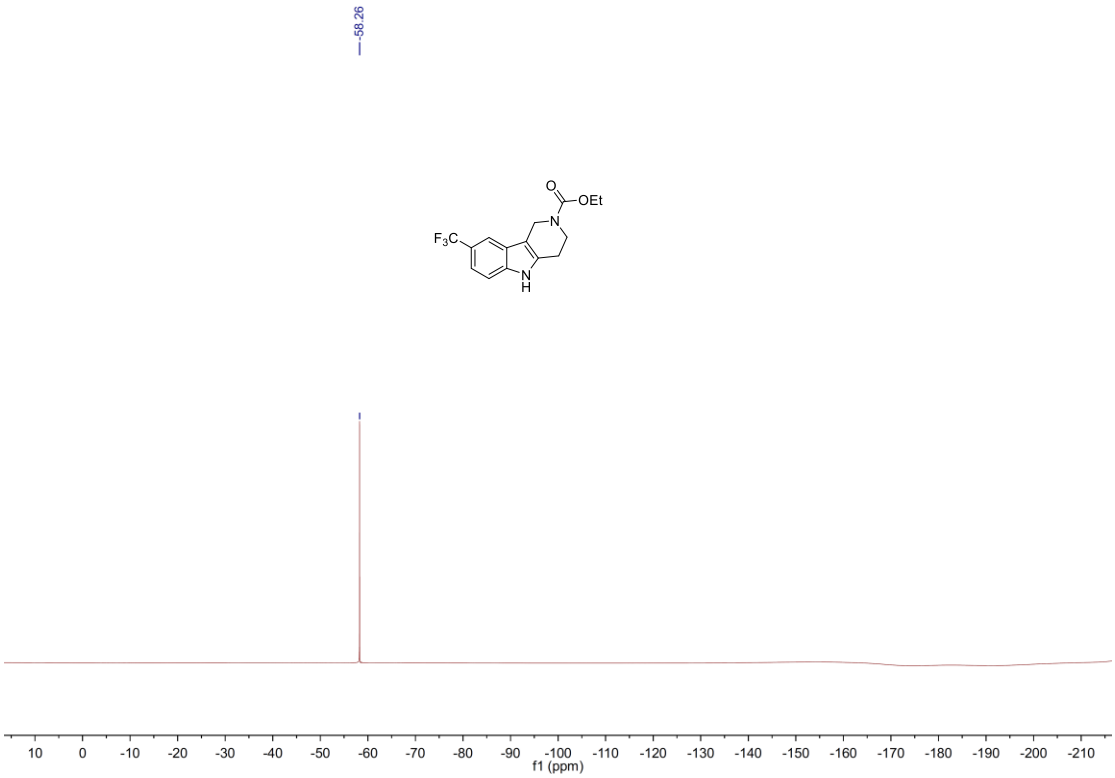
^{13}C NMR (101 MHz, d^6-DMSO) of compound **5h**



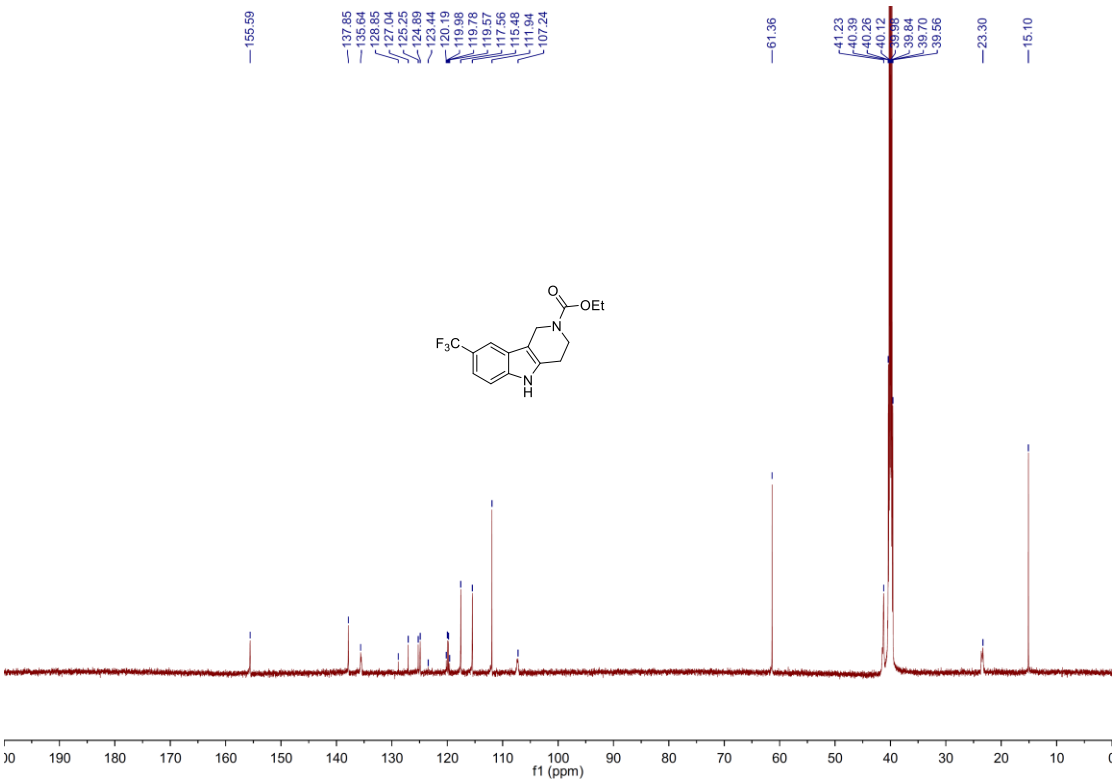
^{1}H NMR (600 MHz, d^6-DMSO) of compound **5i**



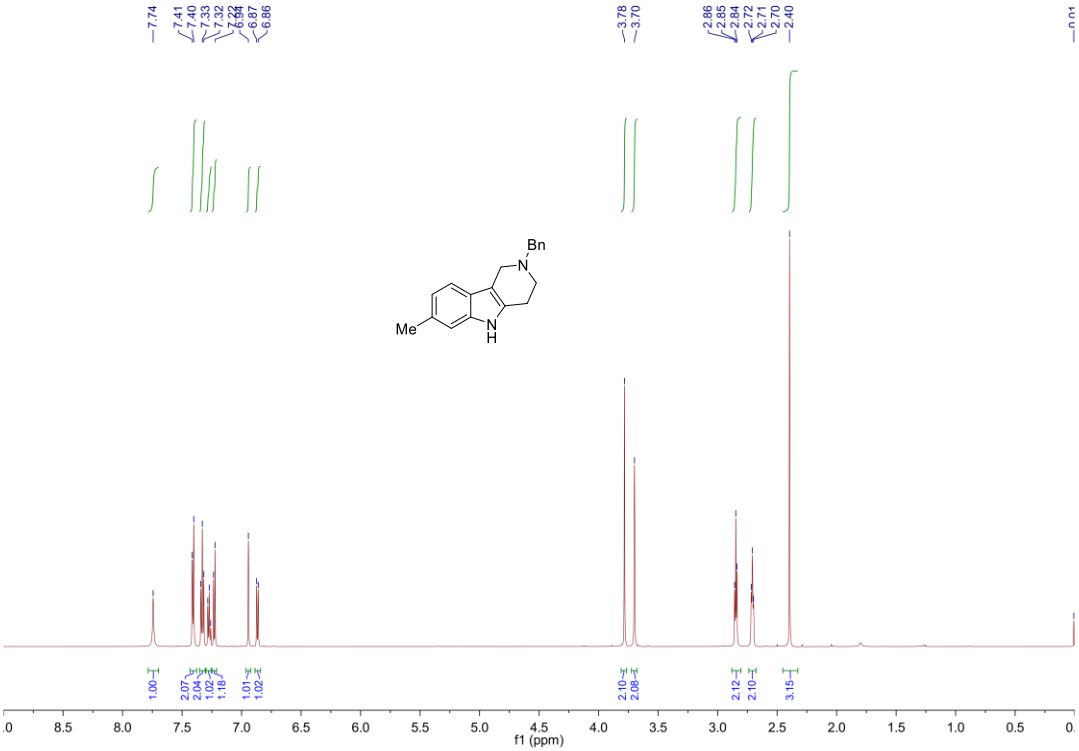
^{19}F NMR (565 MHz, d^6-DMSO) of compound **5i**



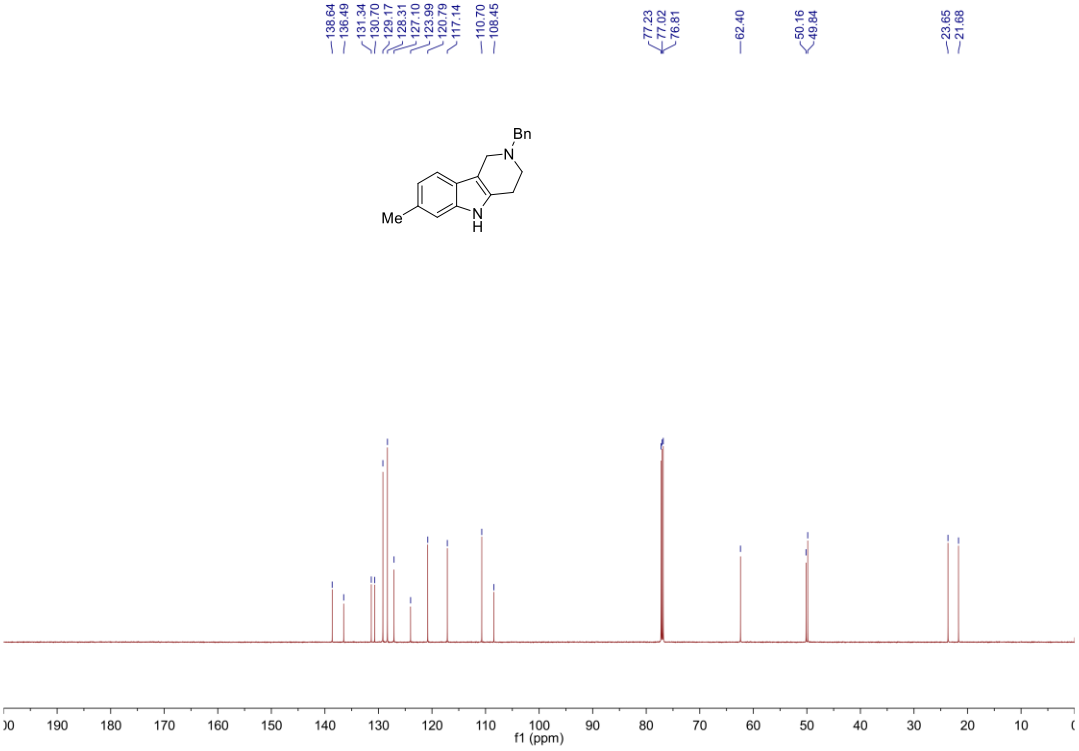
^{13}C NMR (151 MHz, d^6-DMSO) of compound **5i**



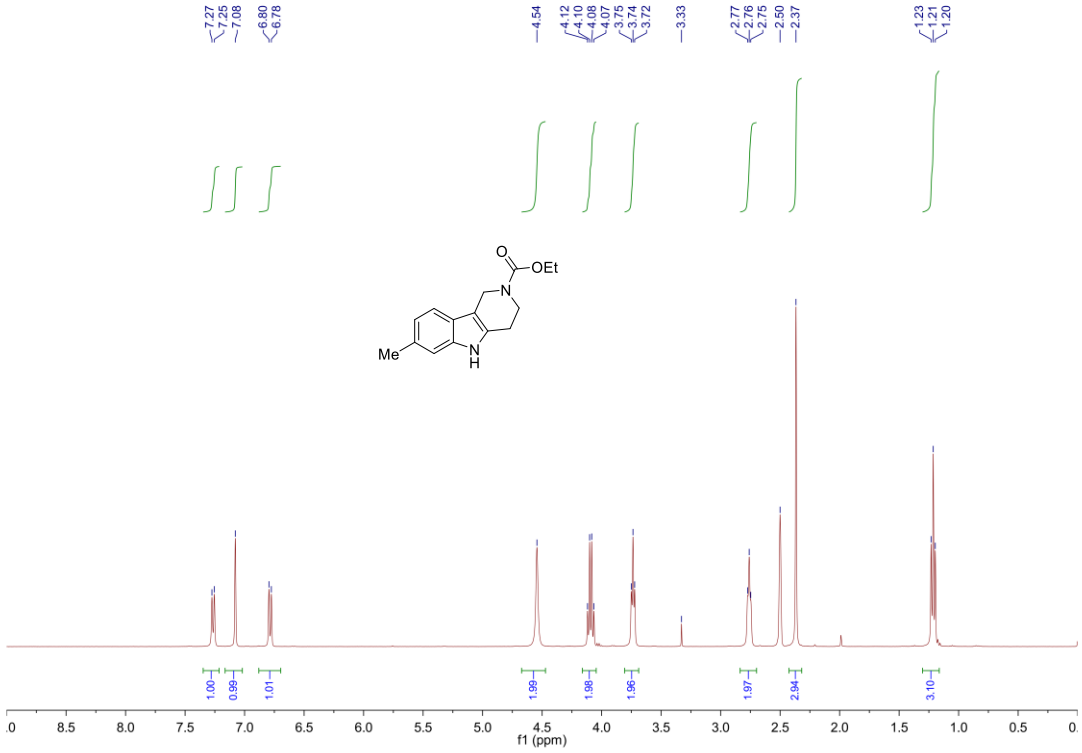
^{1}H NMR (600 MHz, $CDCl_3$) of compound **S5j**



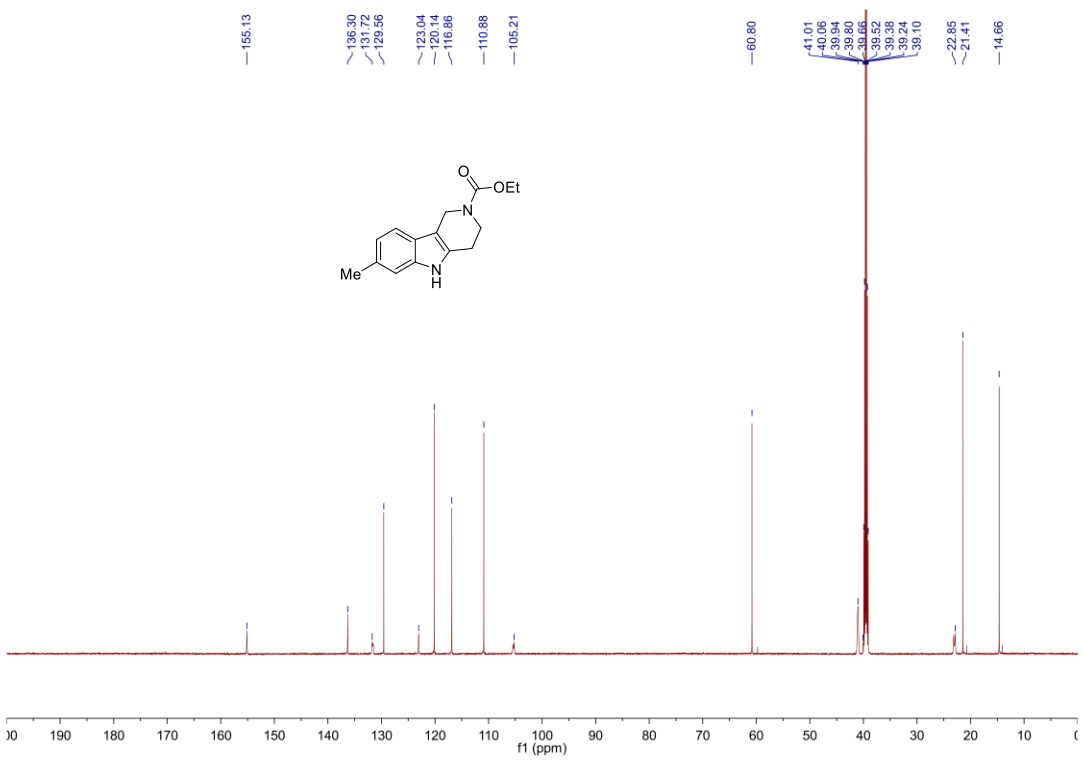
^{13}C NMR (151 MHz, $CDCl_3$) of compound **S5j**



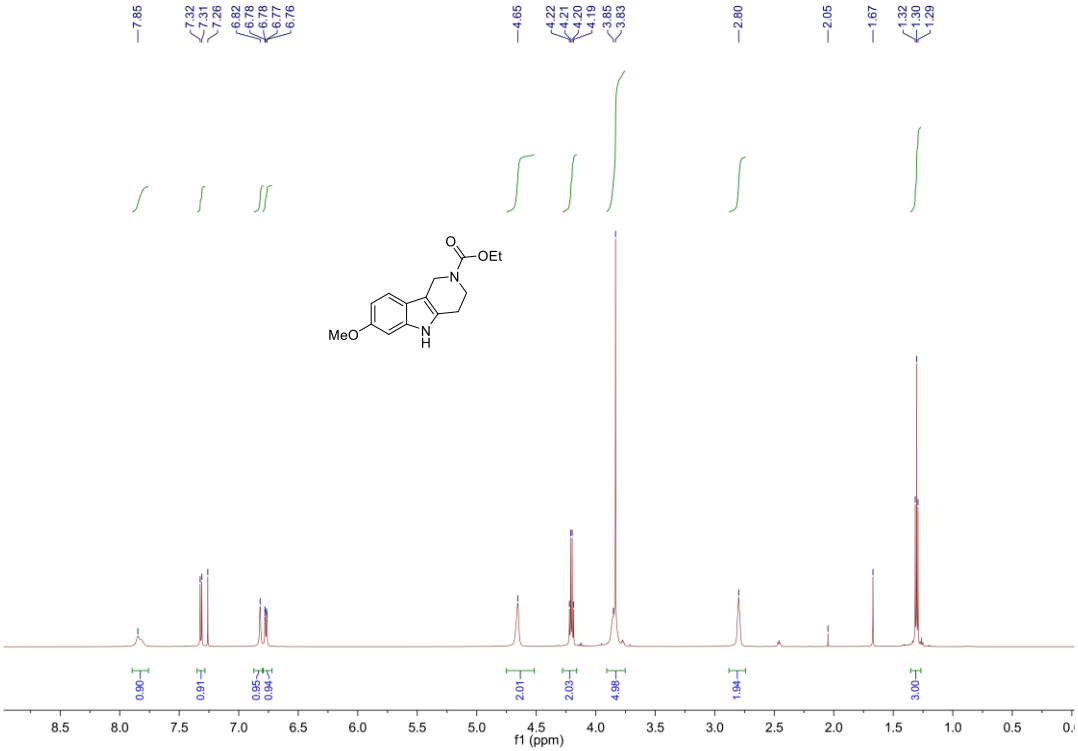
^{1}H NMR (400 MHz, d^{6}-DMSO) of compound **5j**



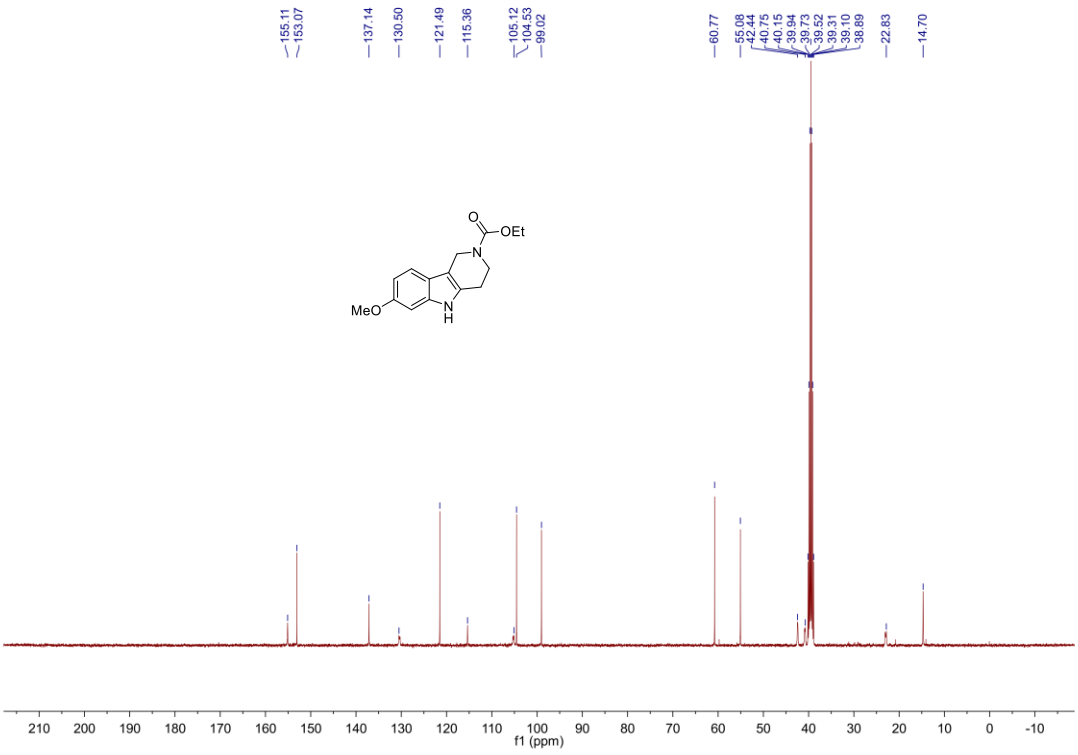
^{13}C NMR (151 MHz, d^{6}-DMSO) of compound **5j**



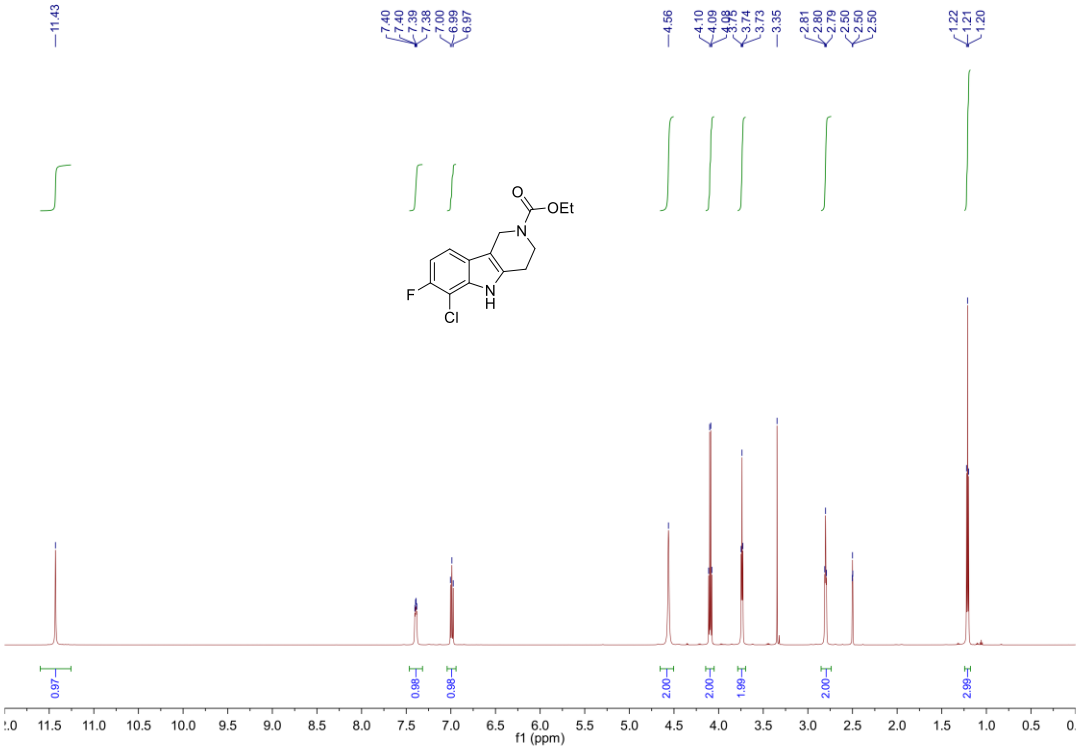
^{1}H NMR (600 MHz, $CDCl_3$) of compound **5k**



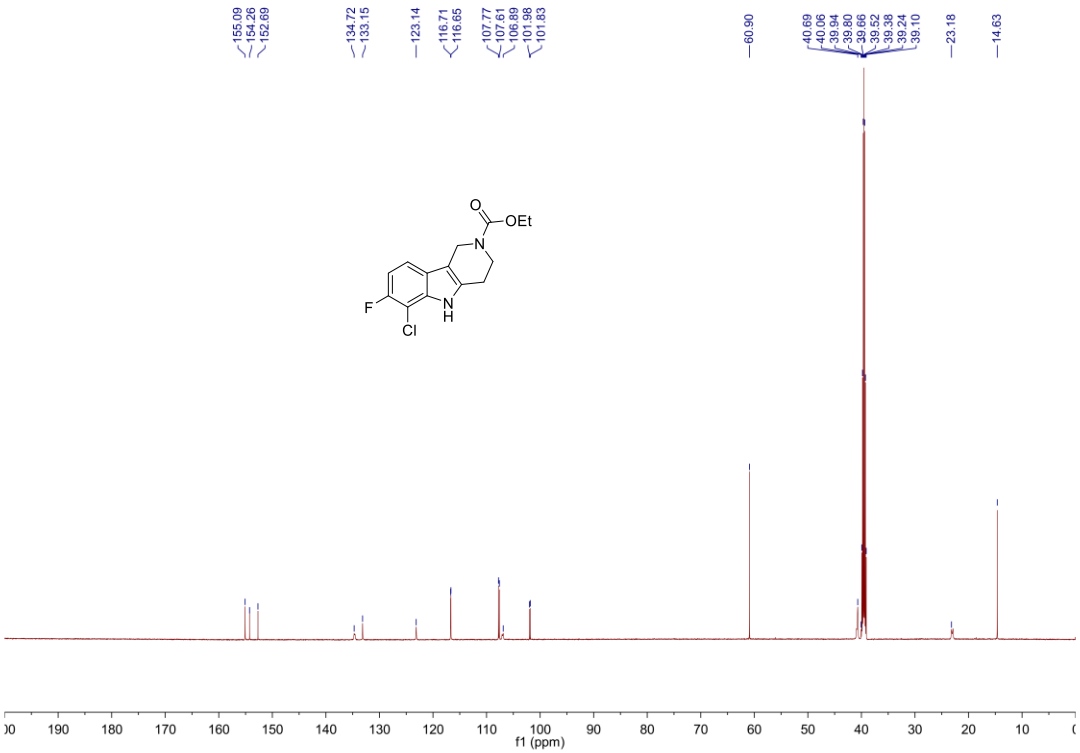
^{13}C NMR (101 MHz, d^6-DMSO) of compound **5k**



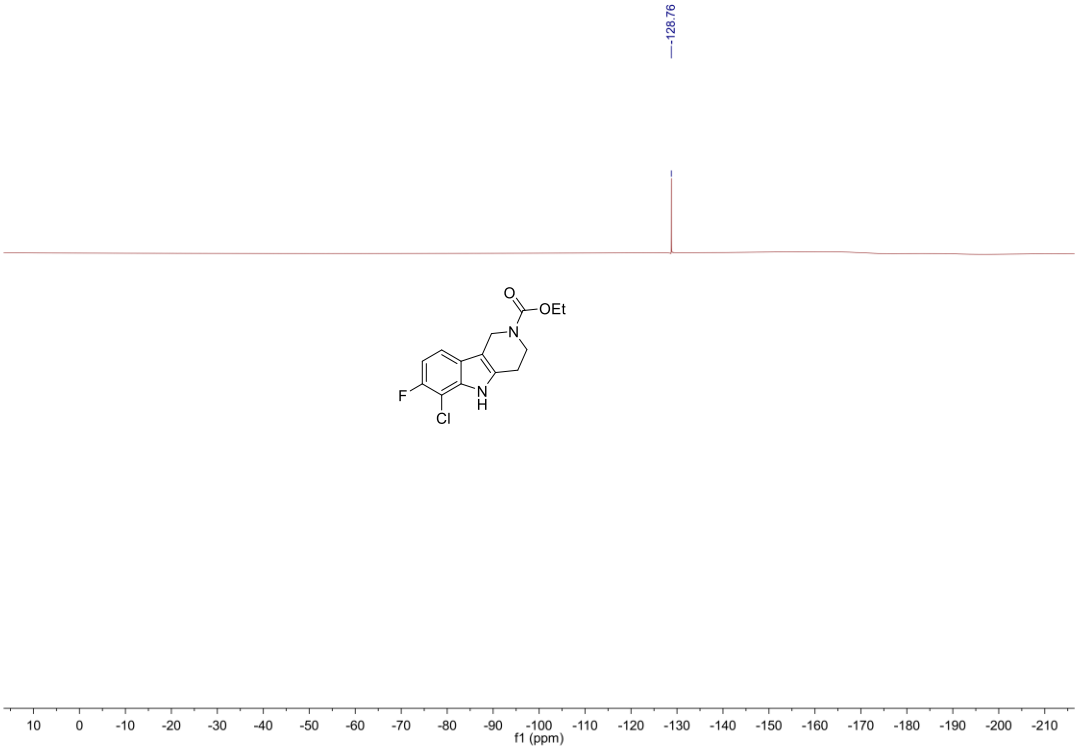
^{1}H NMR (600 MHz, d^{6}-DMSO) of compound **S5l**



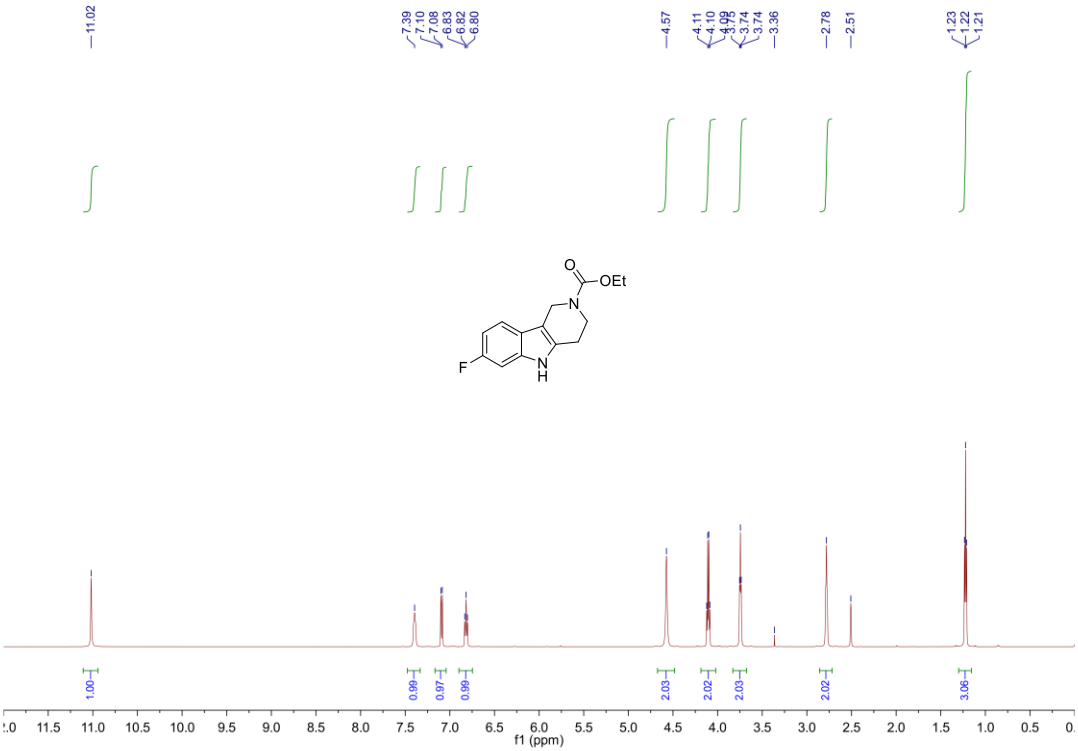
^{13}C NMR (151 MHz, d^{6}-DMSO) of compound **S5l**



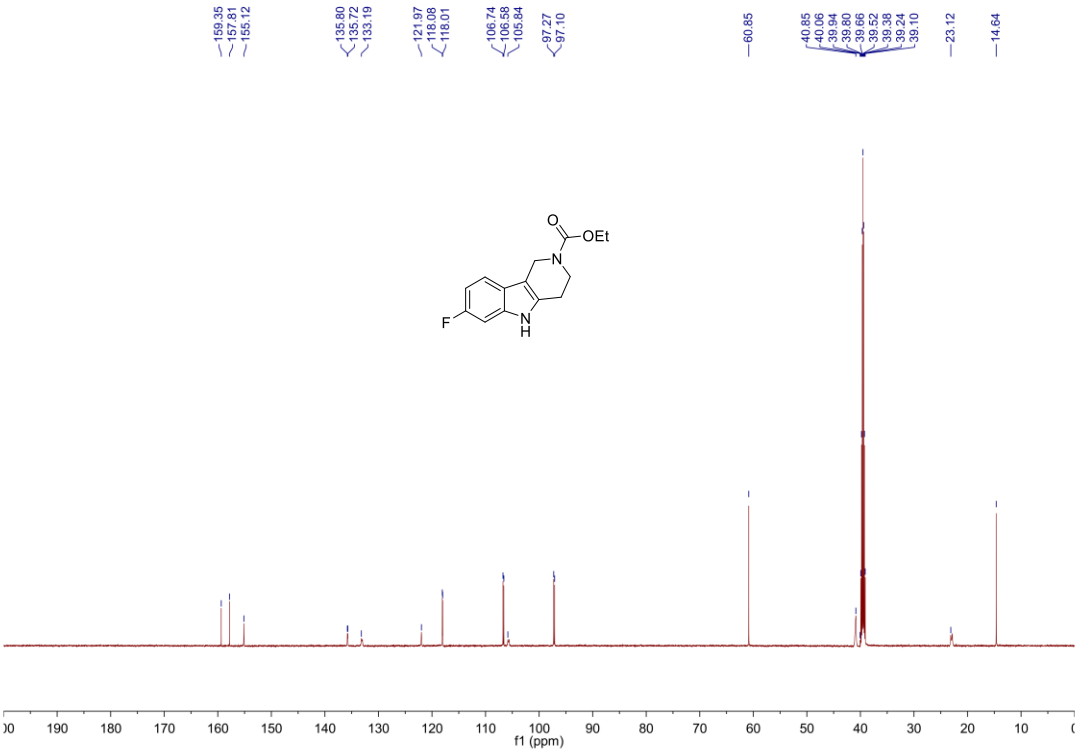
^{19}F NMR (565 MHz, d^6-DMSO) of compound **S5l**



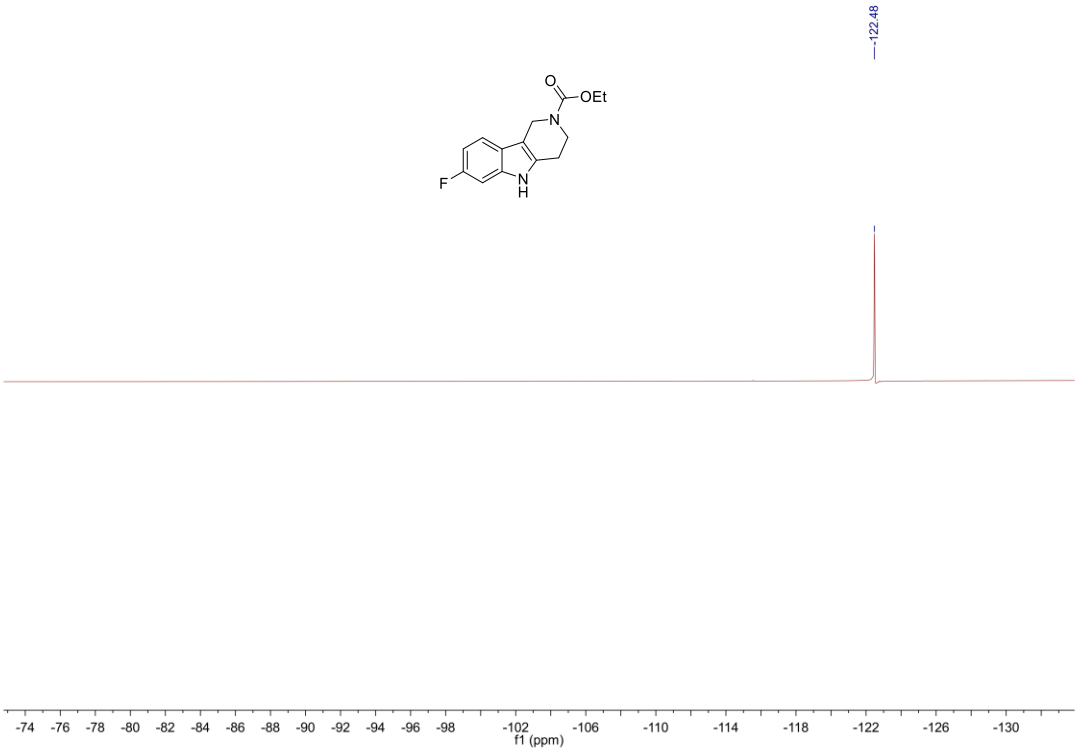
^{1}H NMR (600 MHz, d^6-DMSO) of compound **5l**



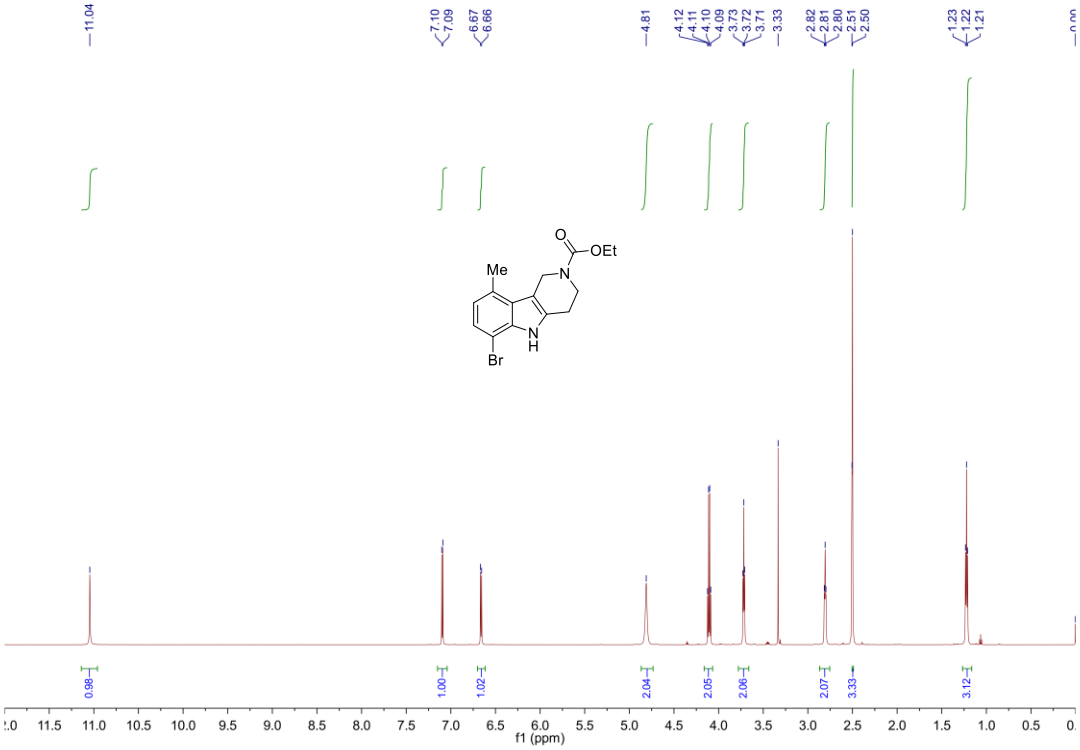
^{13}C NMR (151 MHz, d^6-DMSO) of compound **5l**



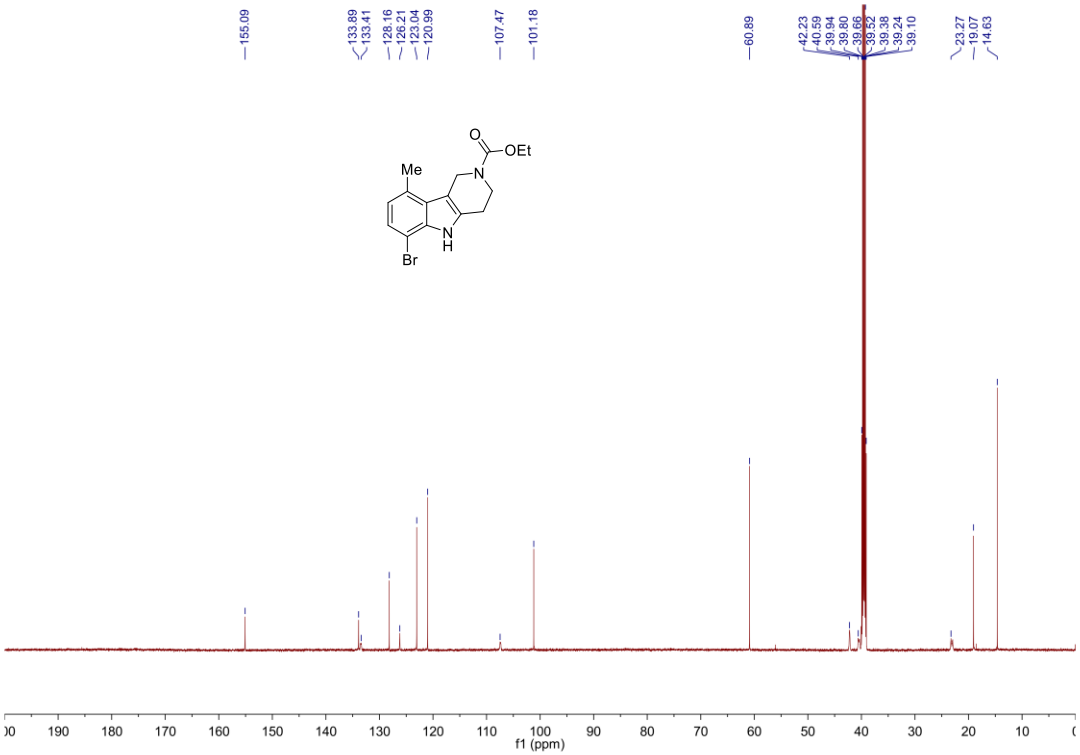
^{19}F NMR (565 MHz, d^6-DMSO) of compound **5l**



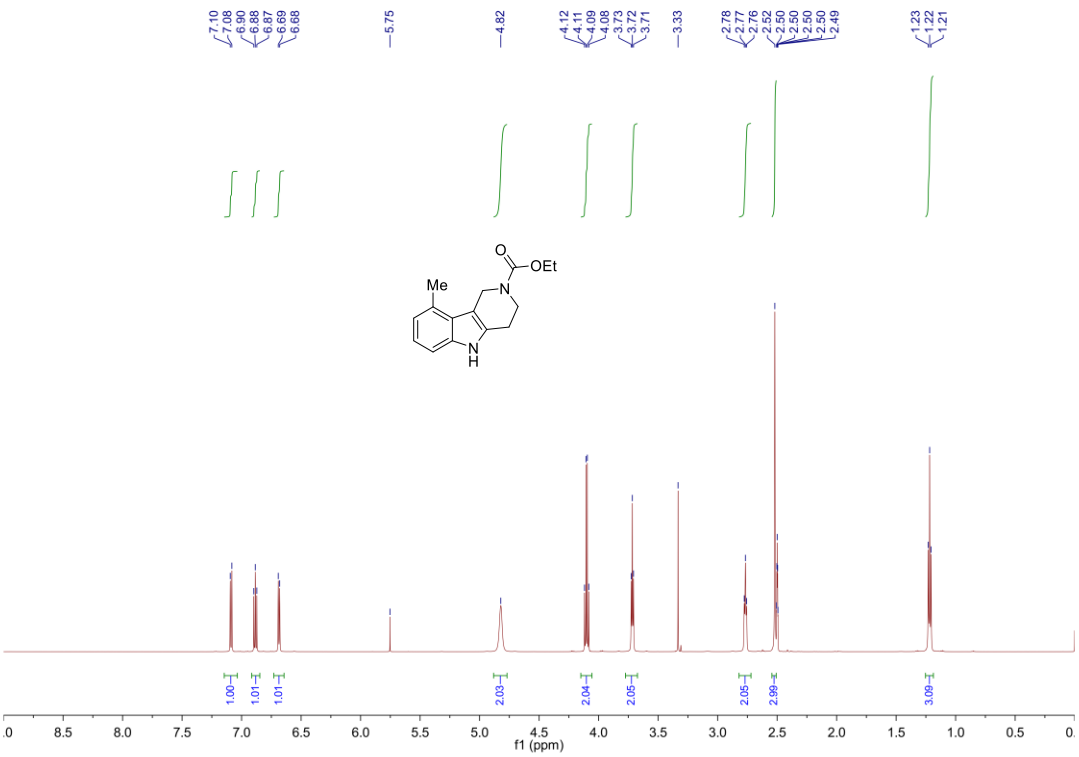
^{1}H NMR (600 MHz, d^{6}-DMSO) of compound **S5m**



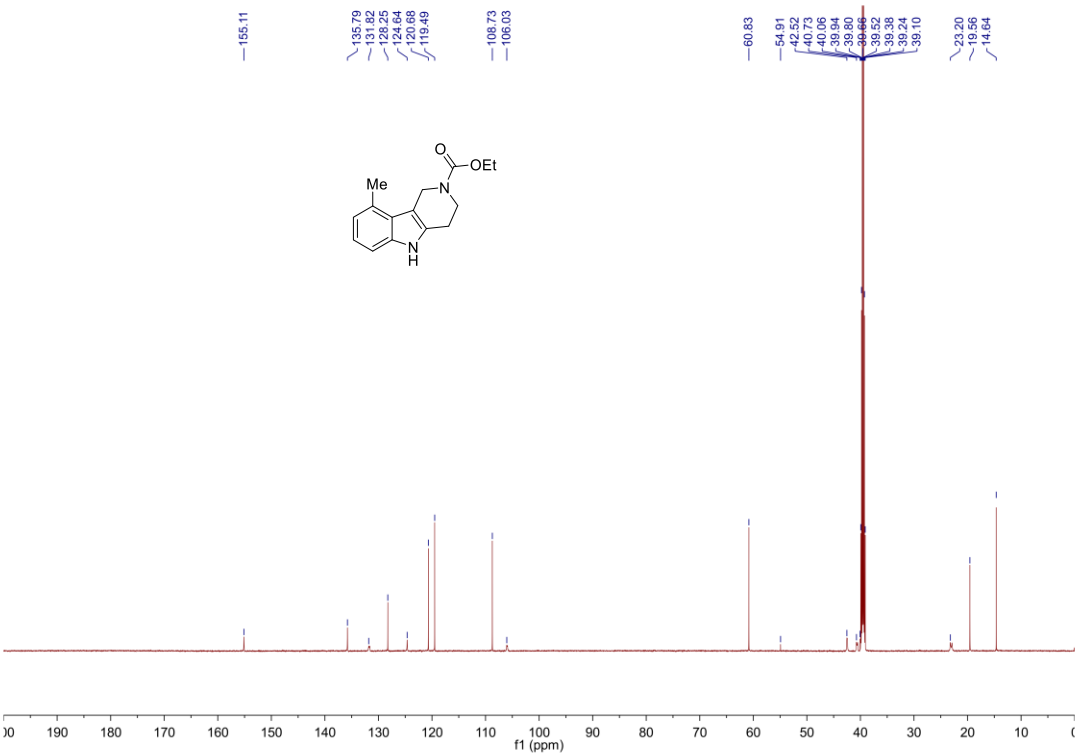
^{13}C NMR (151 MHz, d^{6}-DMSO) of compound **S5m**



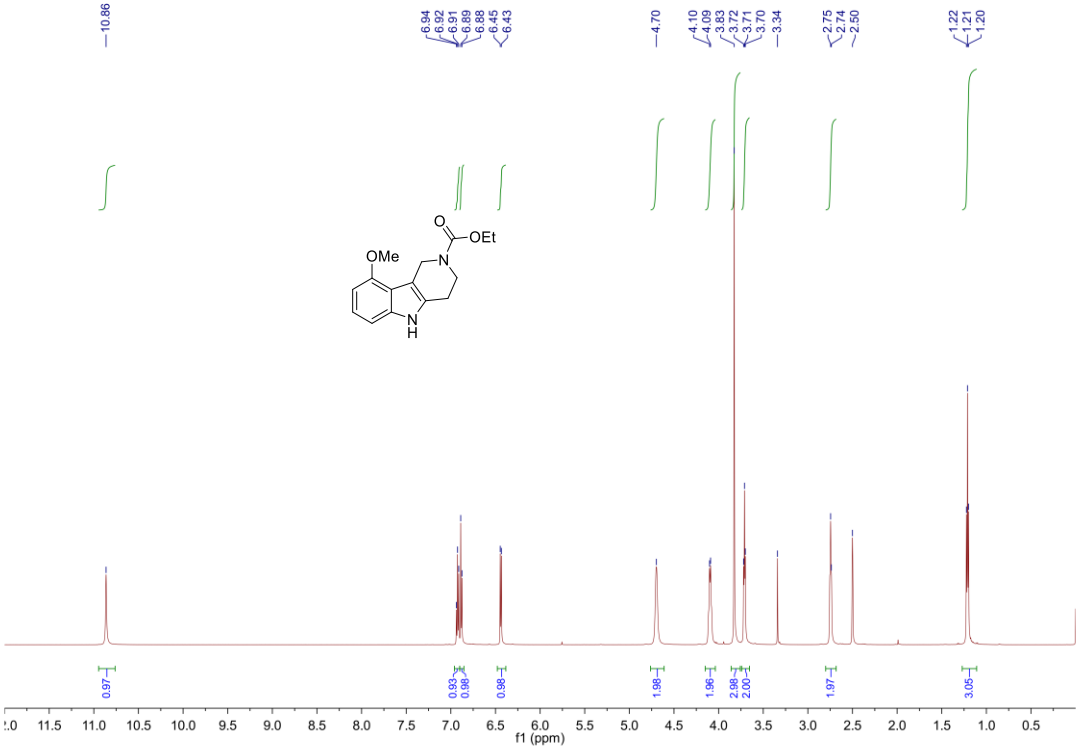
^{1}H NMR (600 MHz, d^{6}-DMSO) of compound **5m**



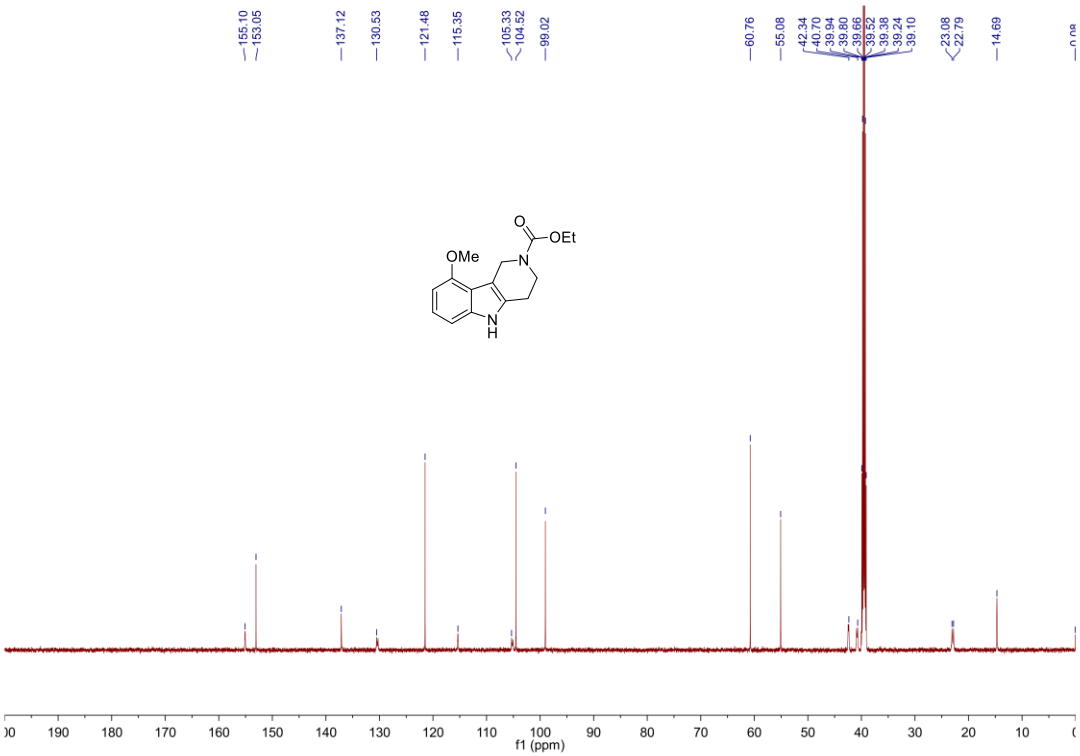
^{13}C NMR (151 MHz, d^{6}-DMSO) of compound **5m**



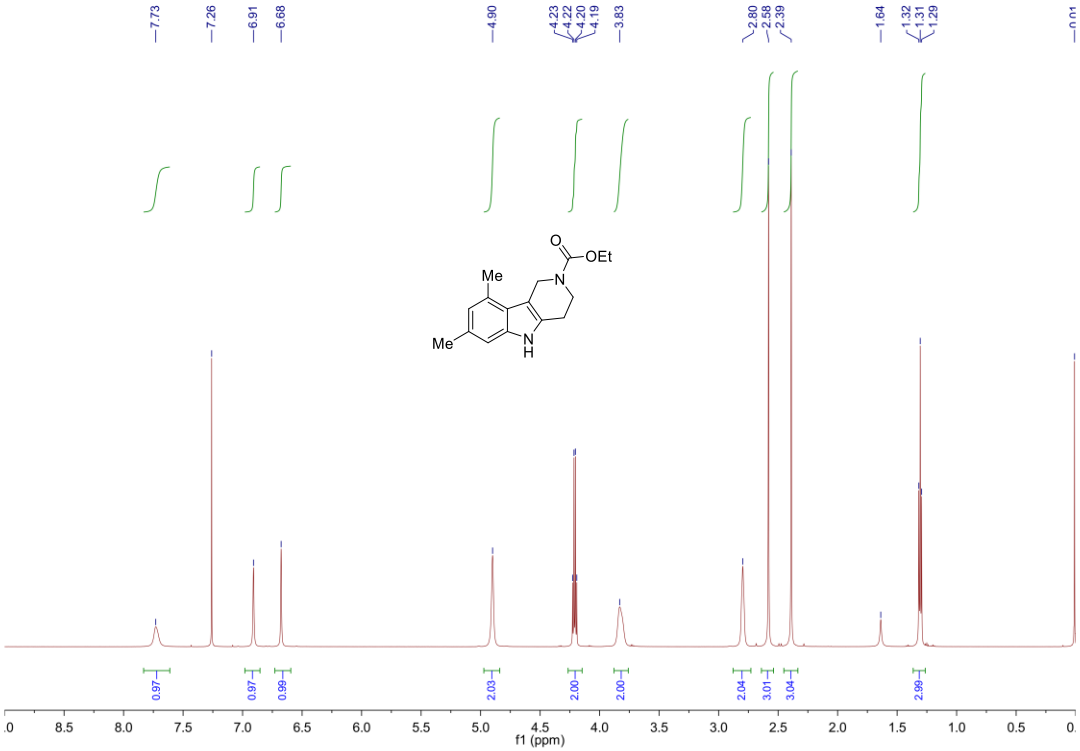
^{1}H NMR (600 MHz, d^{6}-DMSO) of compound **5n**



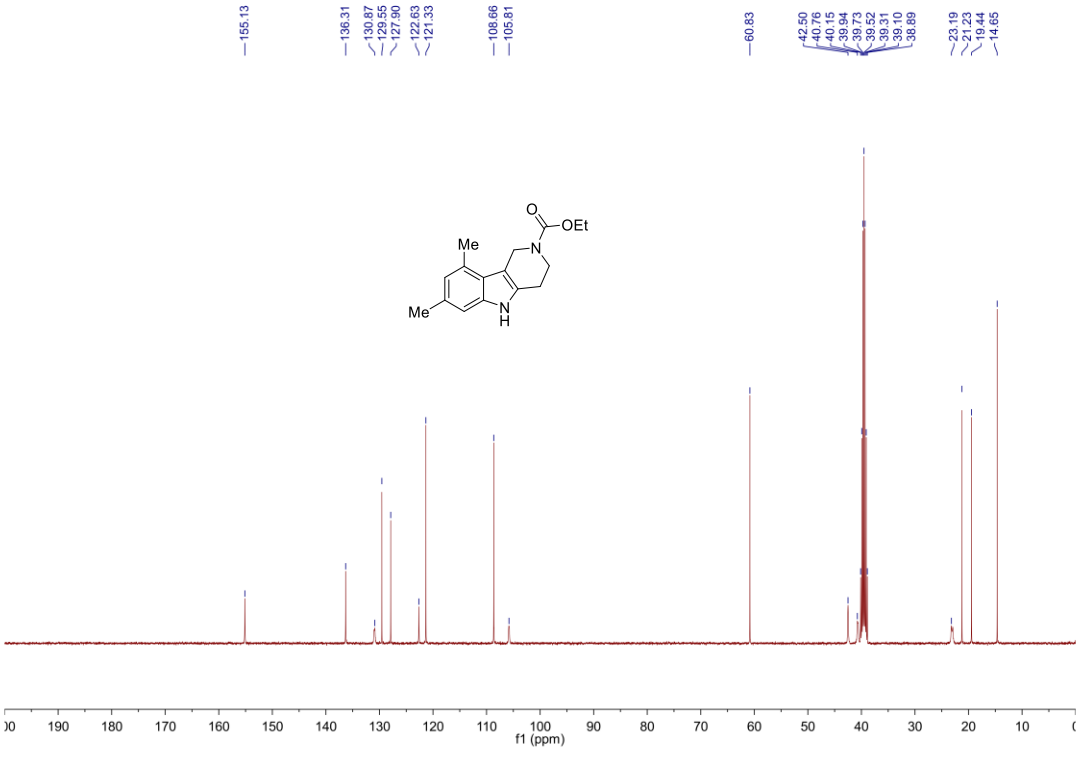
^{13}C NMR (151 MHz, d^{6}-DMSO) of compound **5n**



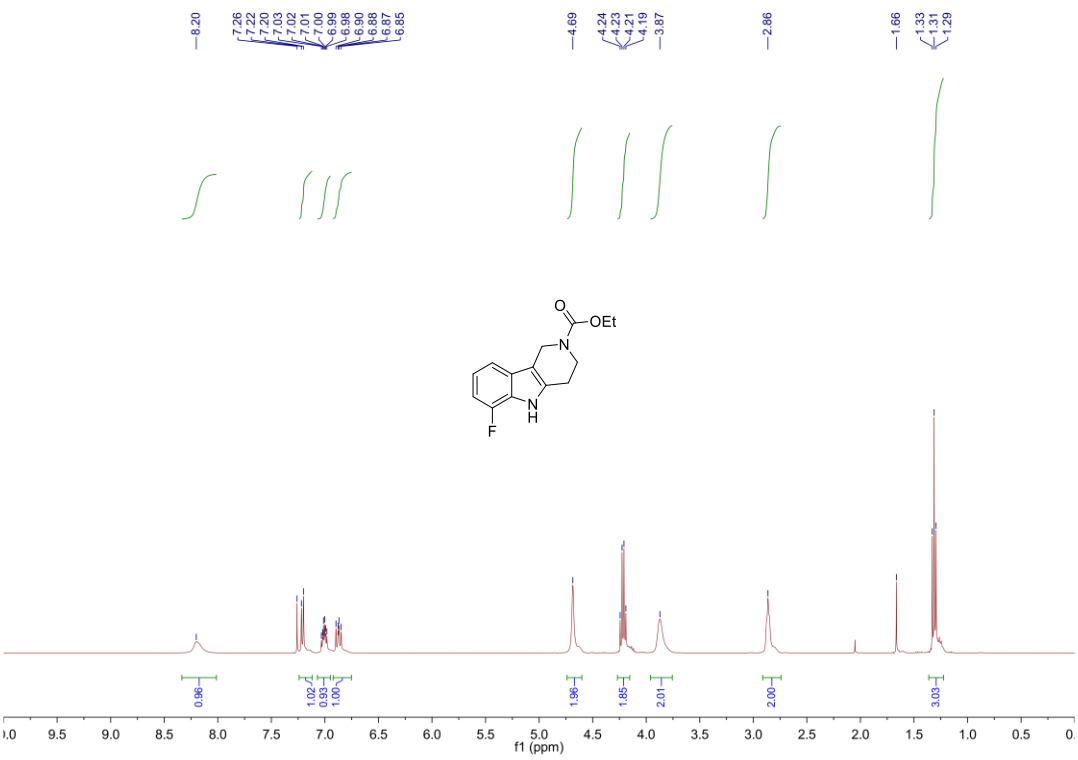
^{1}H NMR (600 MHz, $CDCl_3$) of compound **5o**



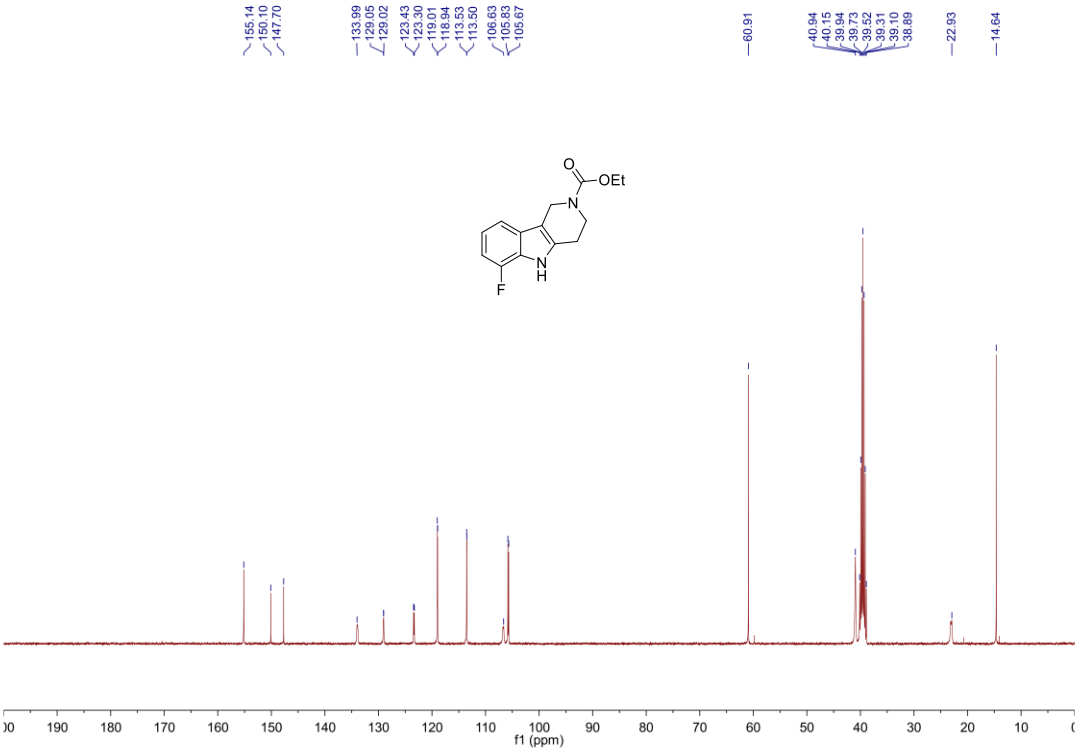
^{13}C NMR (101 MHz, d^6-DMSO) of compound **5o**



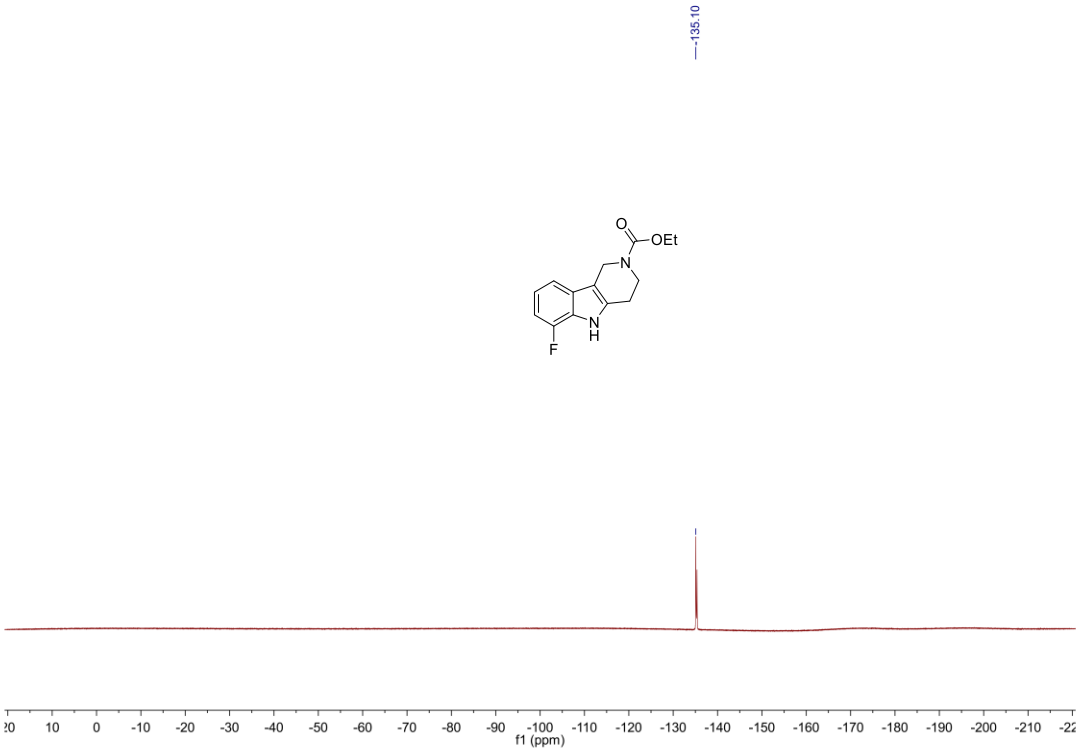
^{1}H NMR (600 MHz, $CDCl_3$) of compound **5p**



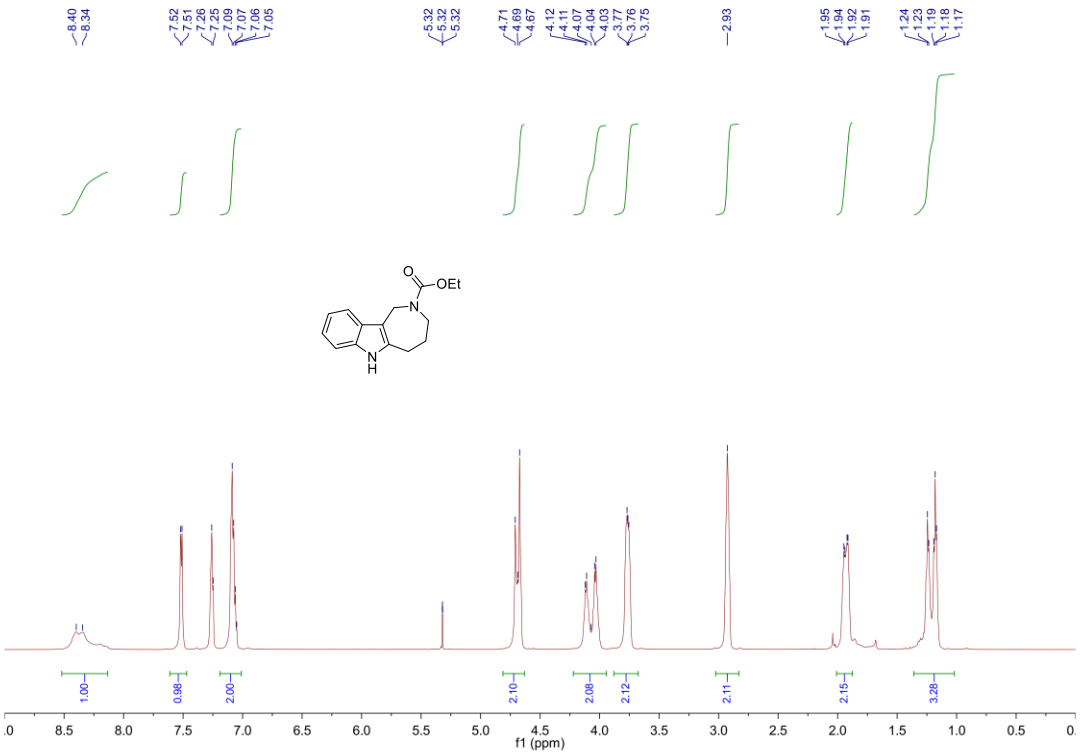
^{13}C NMR (101 MHz, d^6-DMSO) of compound **5p**



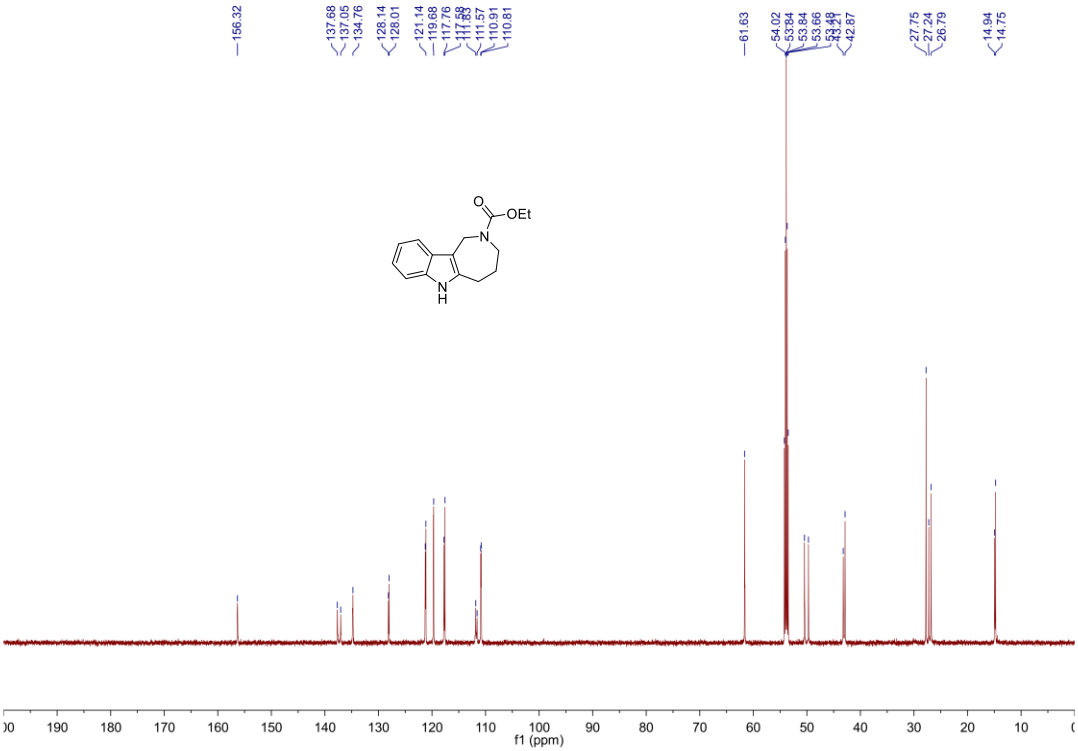
^{19}F NMR (376 MHz, $CDCl_3$) of compound **5p**



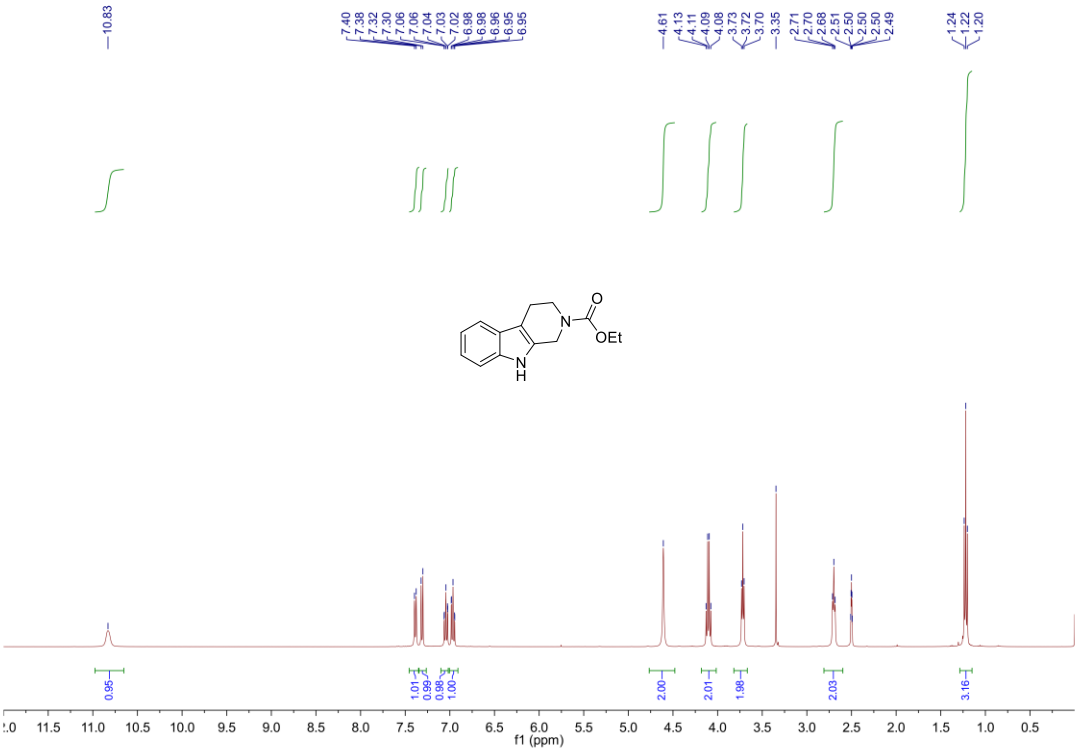
^{1}H NMR (600 MHz, CD_2Cl_2) of compound **5q**



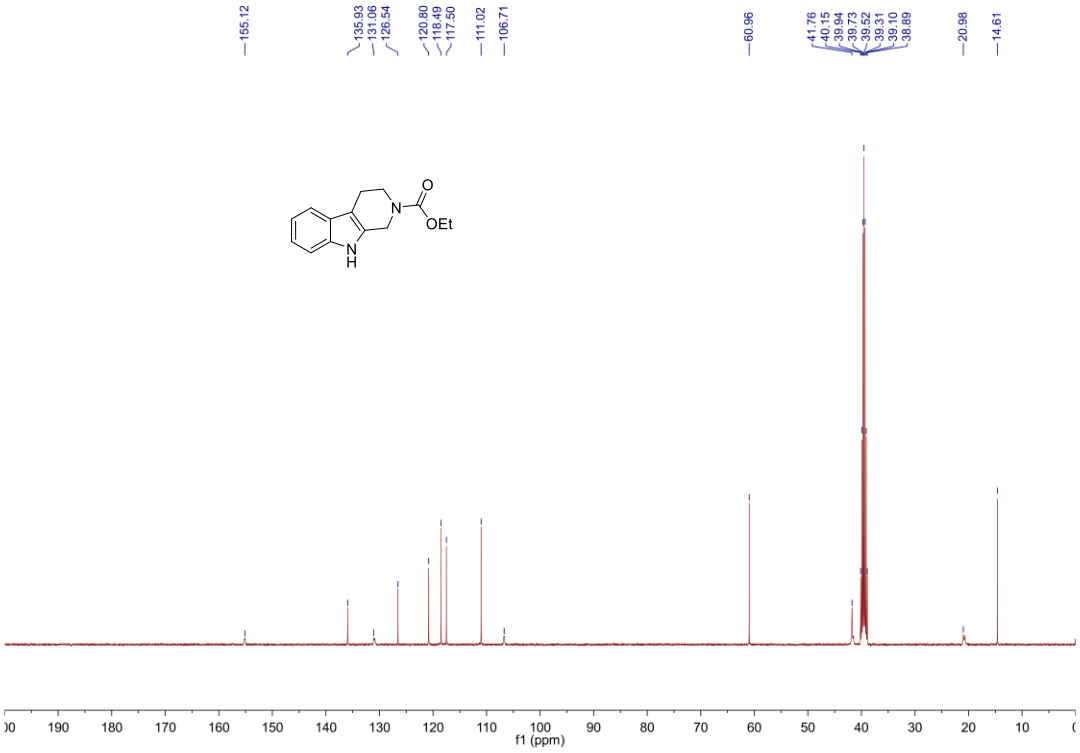
^{13}C NMR (151 MHz, CD_2Cl_2) of compound **5q**



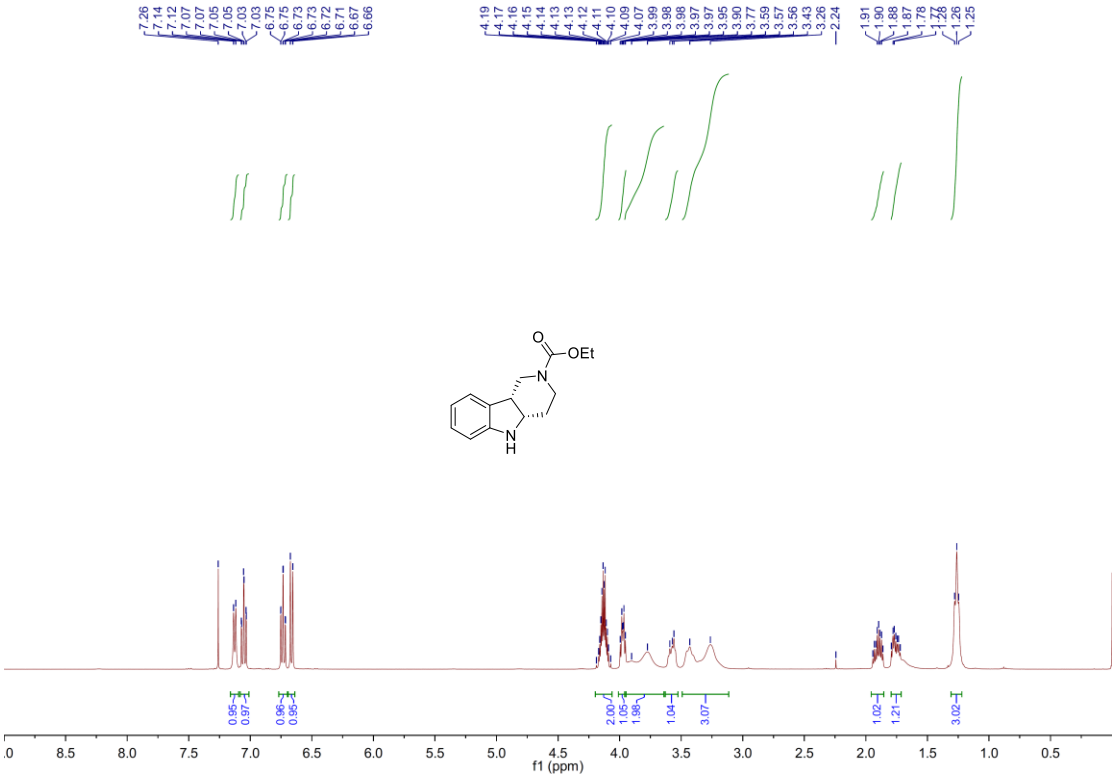
^{1}H NMR (400 MHz, $CDCl_3$) of compound **5r**



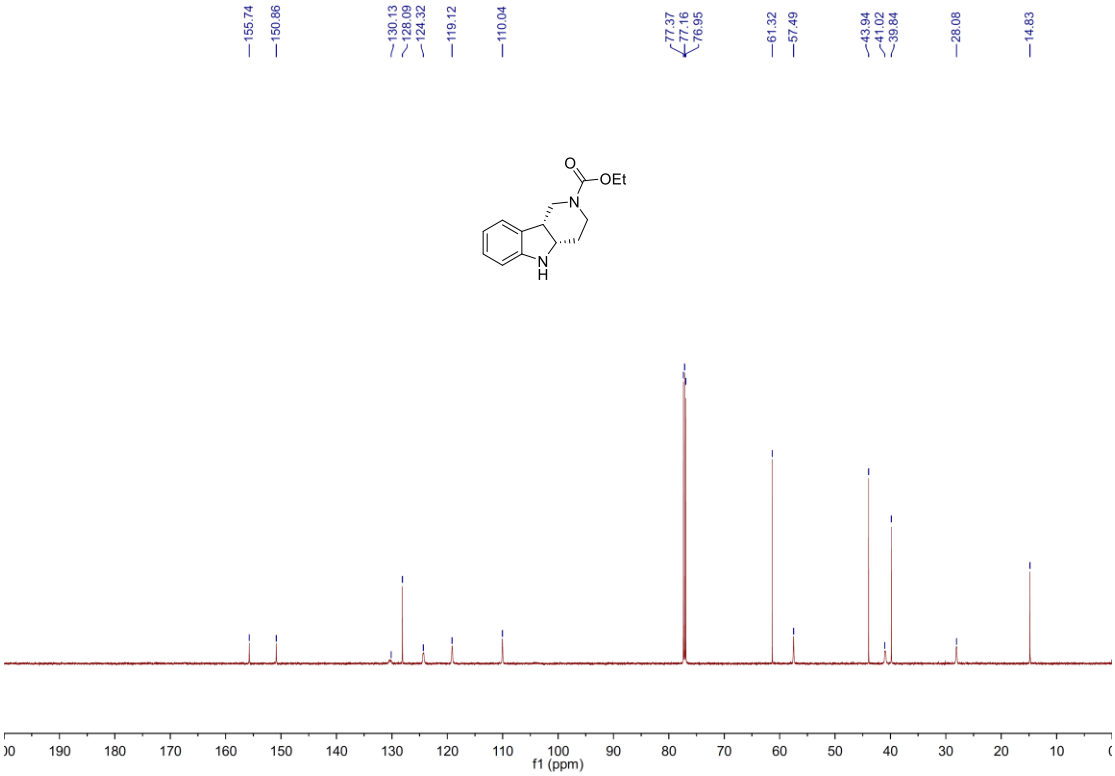
^{13}C NMR (151 MHz, $CDCl_3$) of compound **5r**



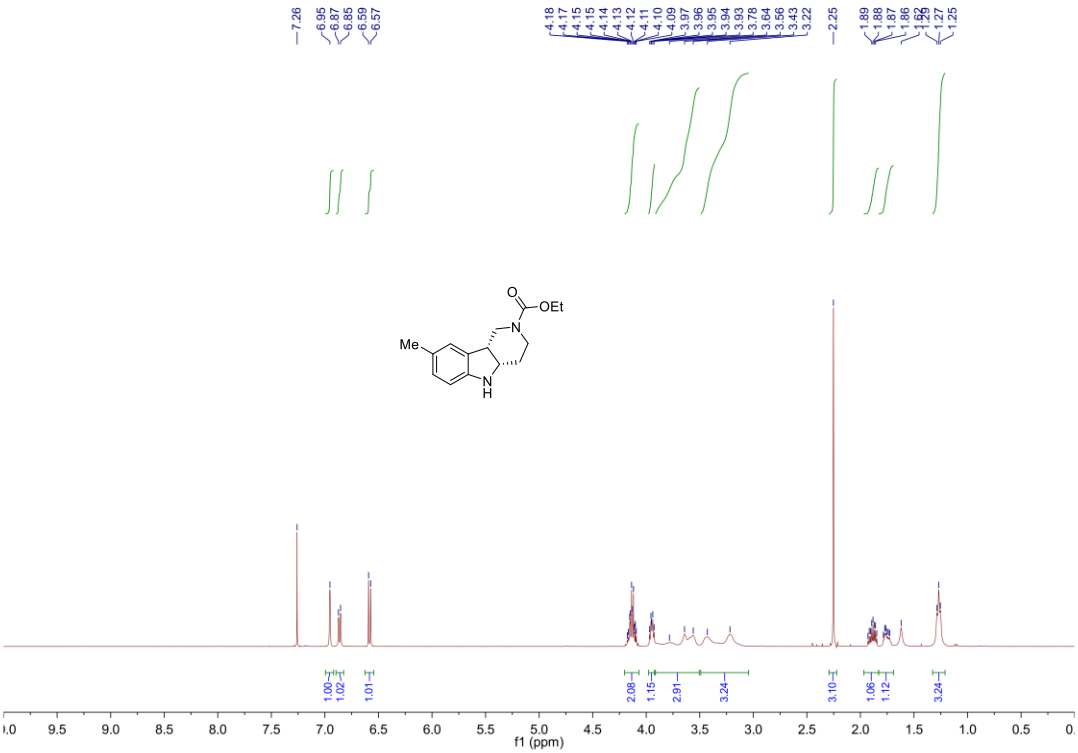
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6a**



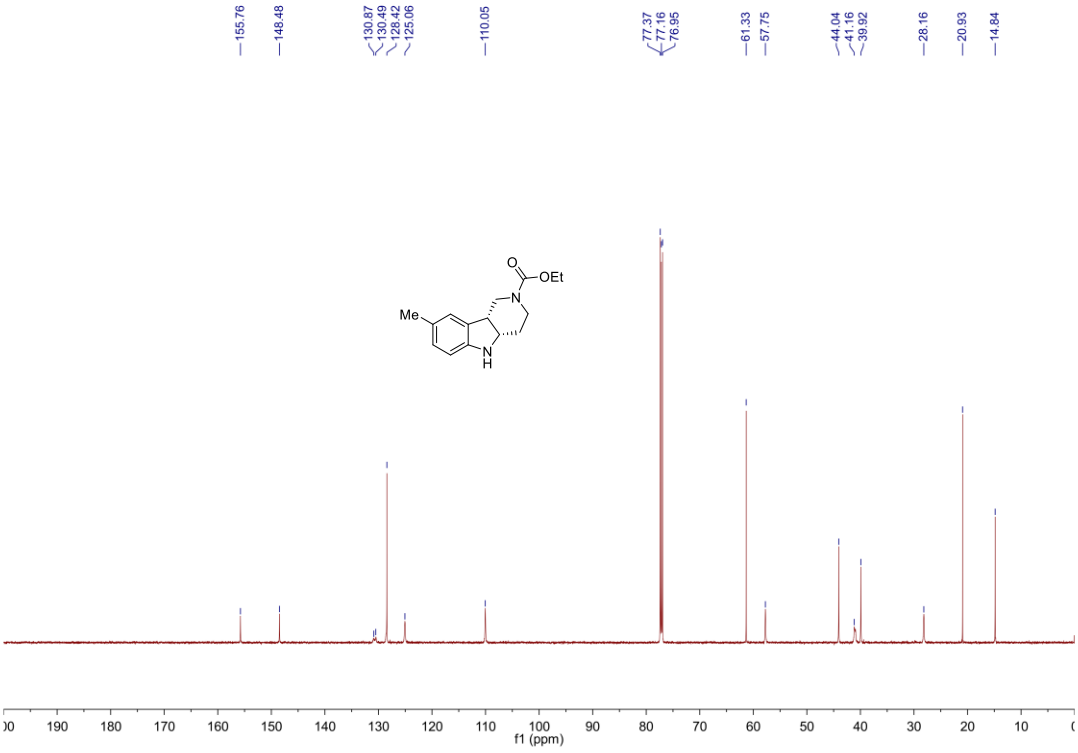
^{13}C NMR (151 MHz, $CDCl_3$) of compound **6a**



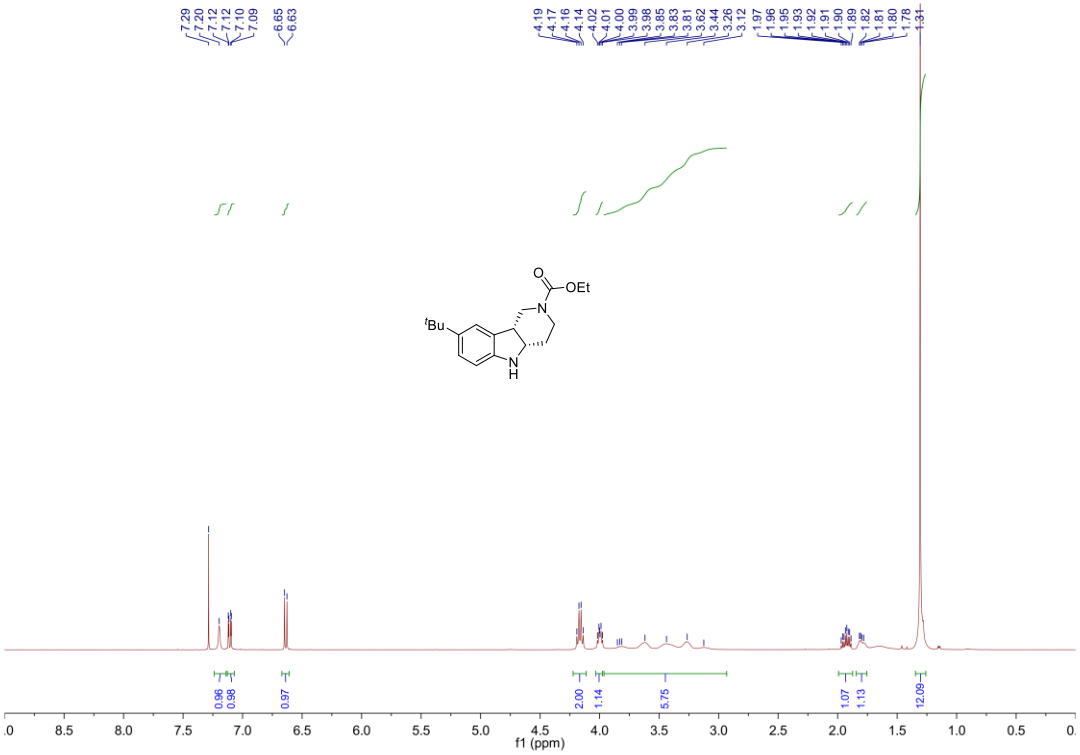
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6b**



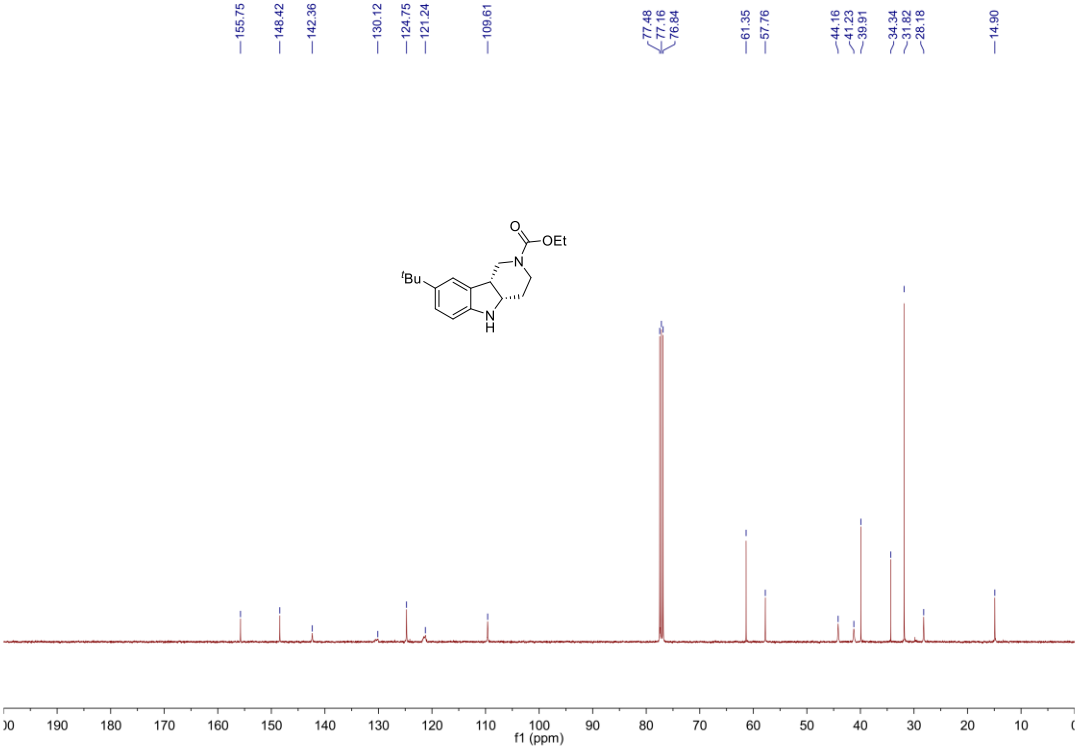
^{13}C NMR (151 MHz, $CDCl_3$) of compound **6b**



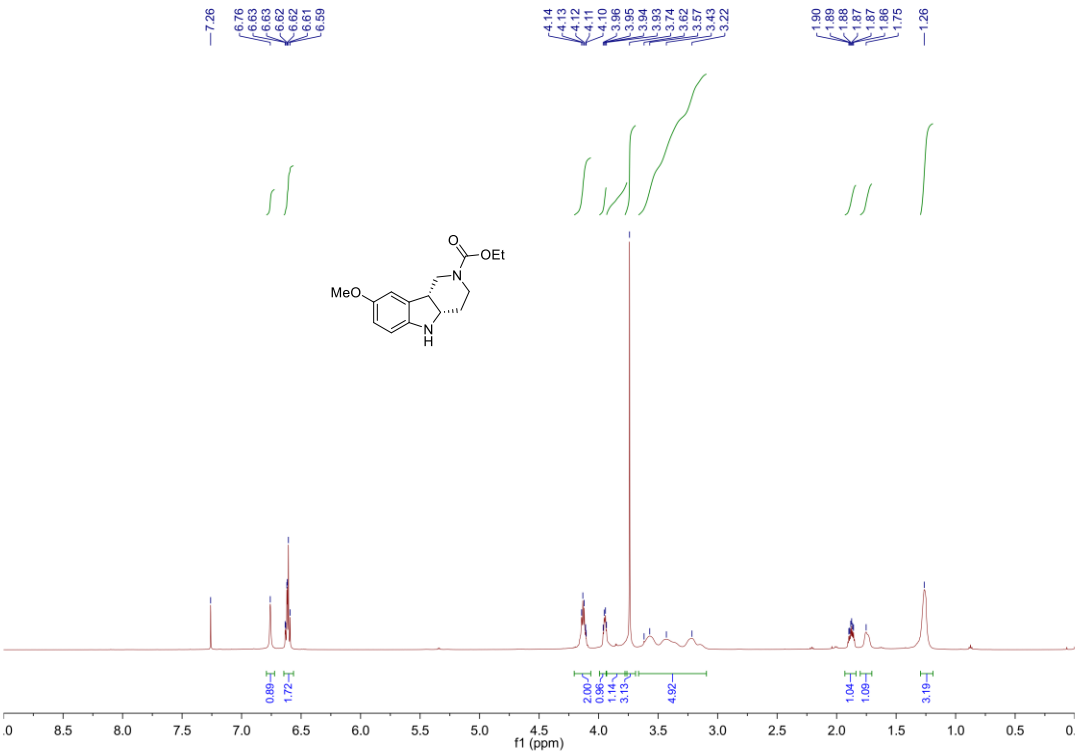
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6c**



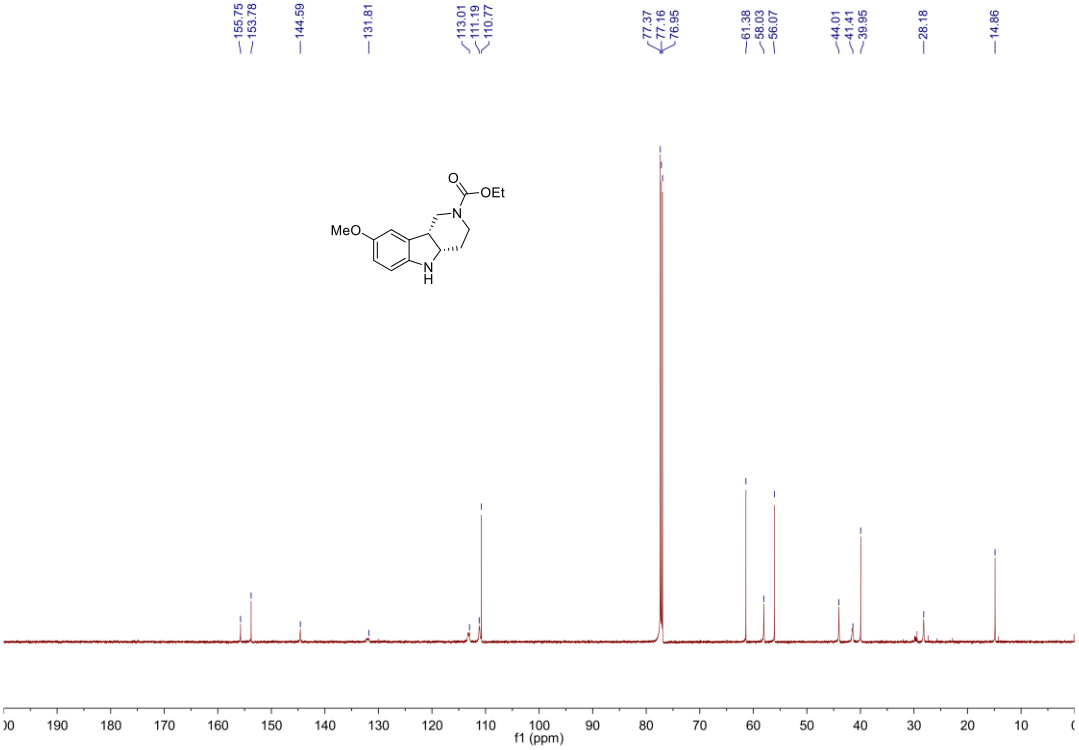
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6c**



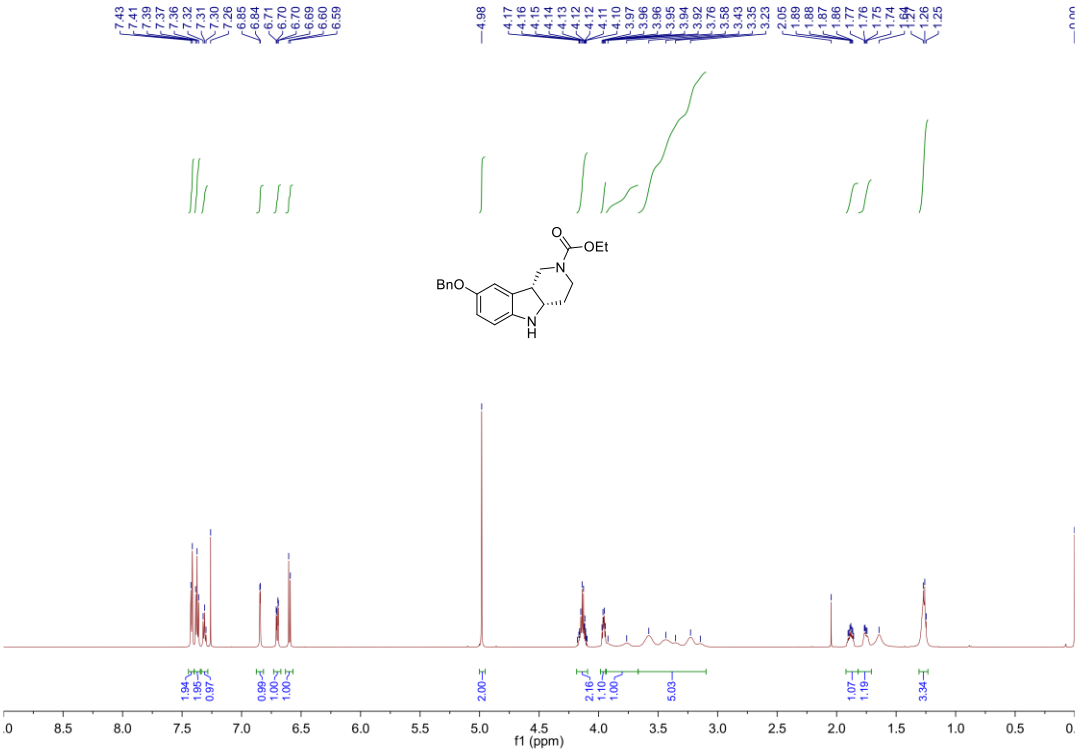
^{1}H NMR (600 MHz, $CDCl_3$) of compound **6d**



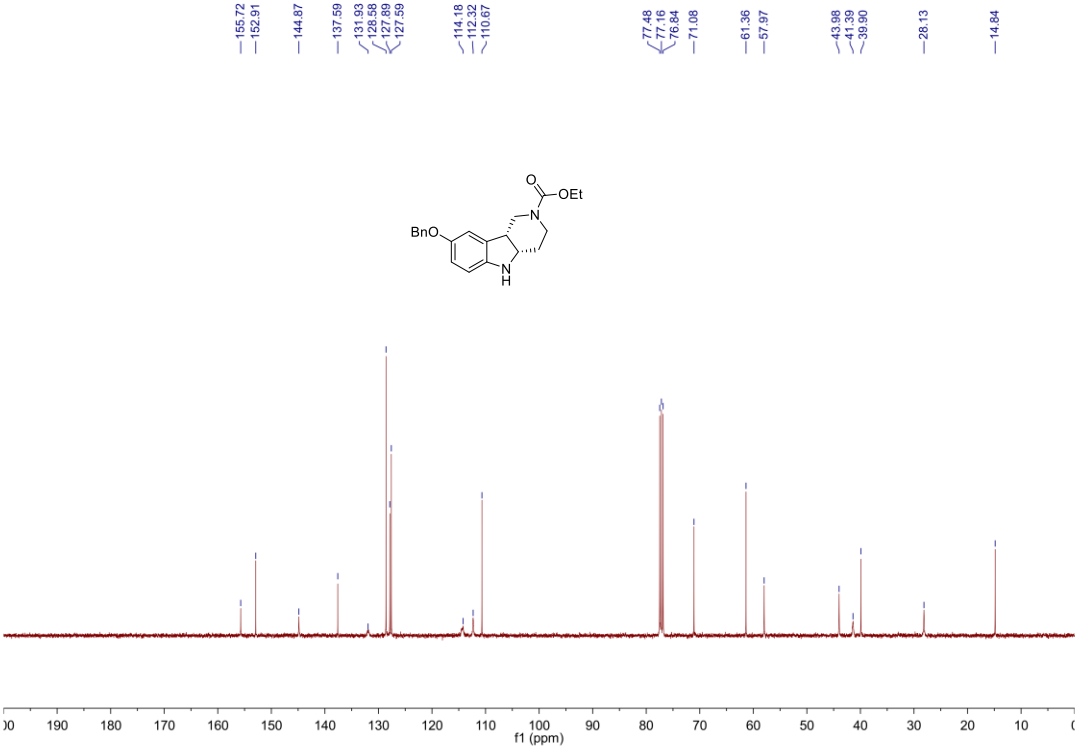
^{13}C NMR (151 MHz, $CDCl_3$) of compound **6d**



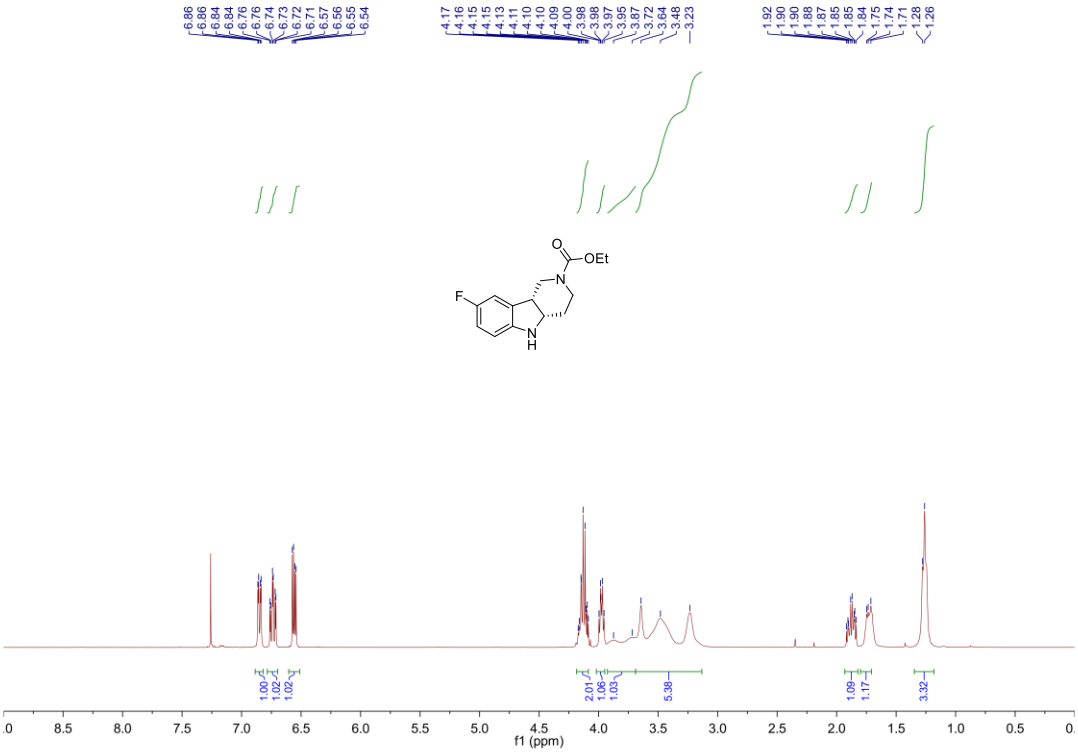
^{1}H NMR (600 MHz, $CDCl_3$) of compound **6e**



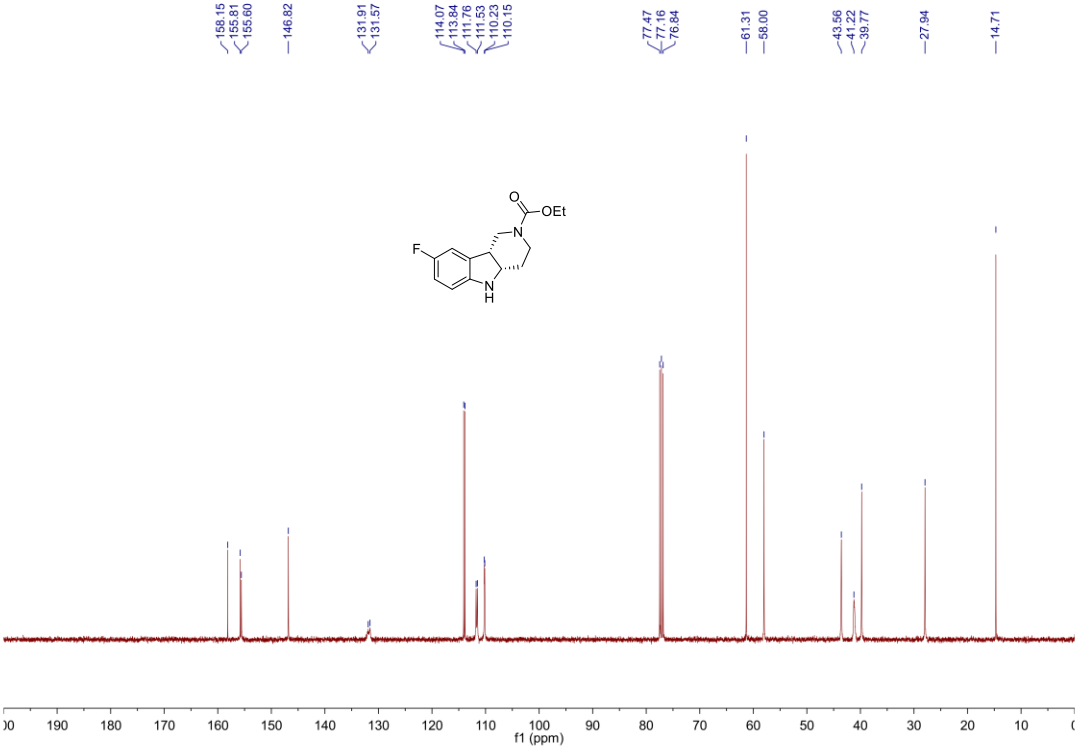
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6e**



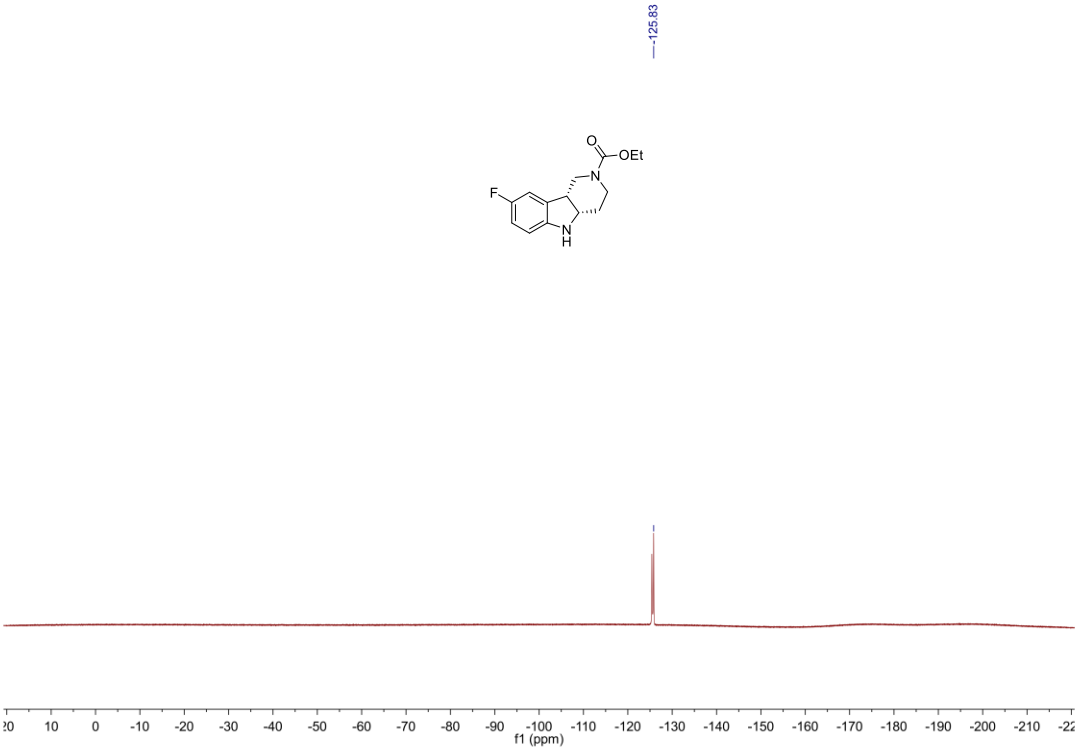
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6f**



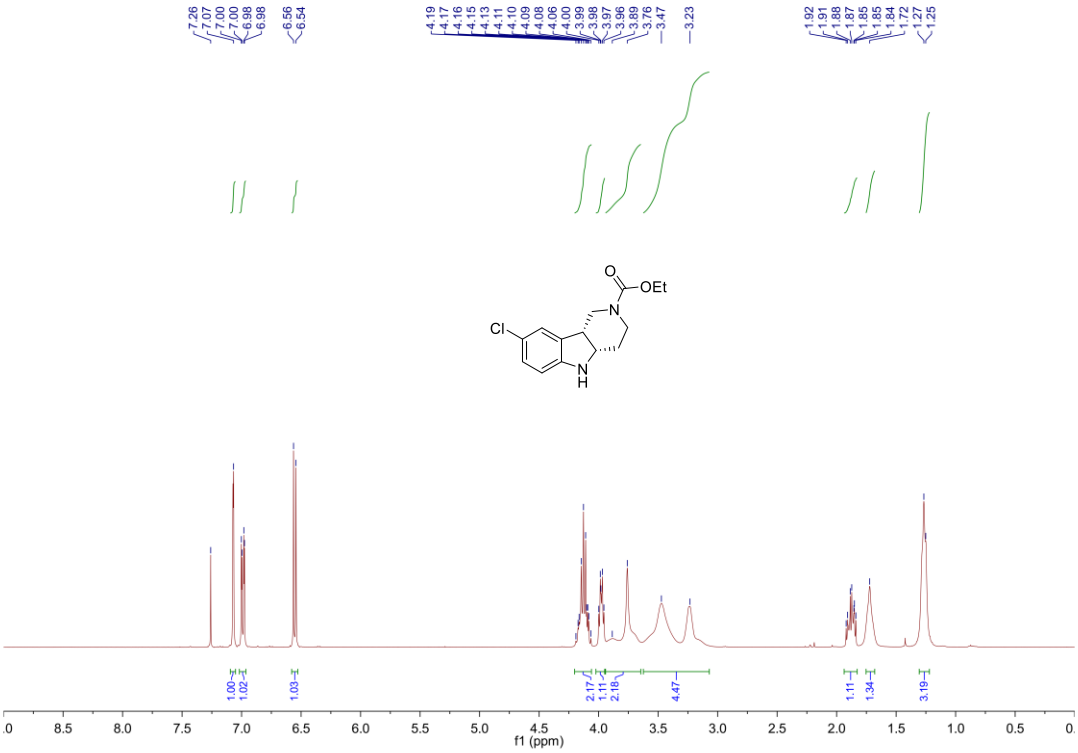
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6f**



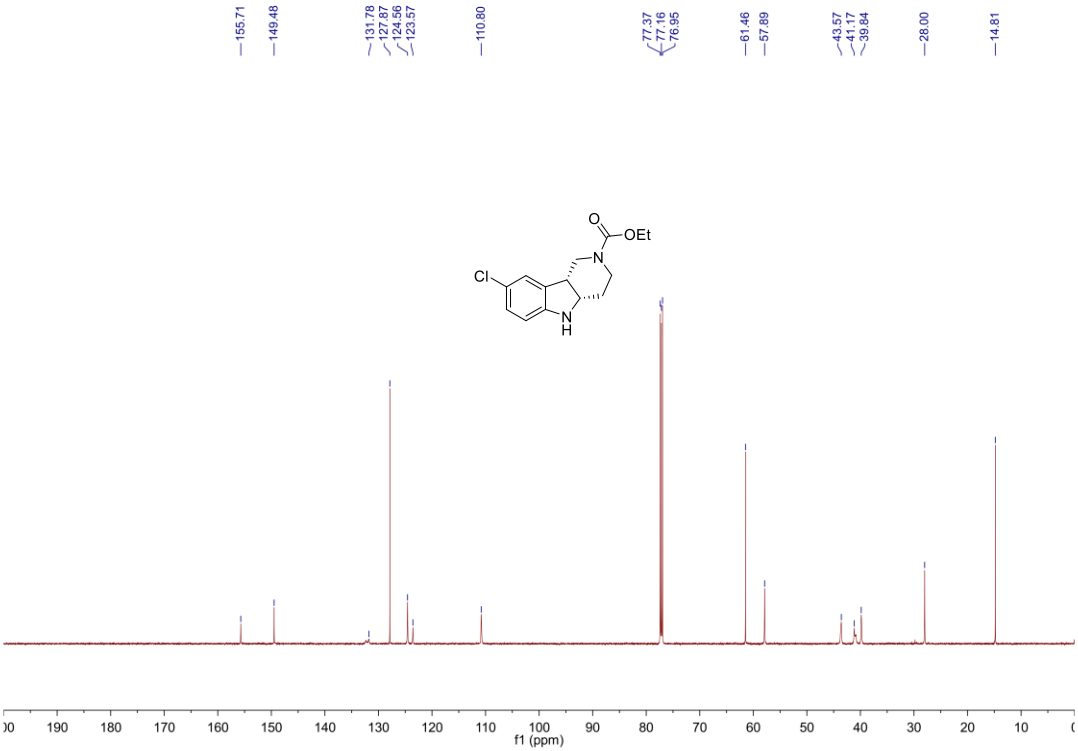
^{19}F NMR (376 MHz, $CDCl_3$) of compound **6f**



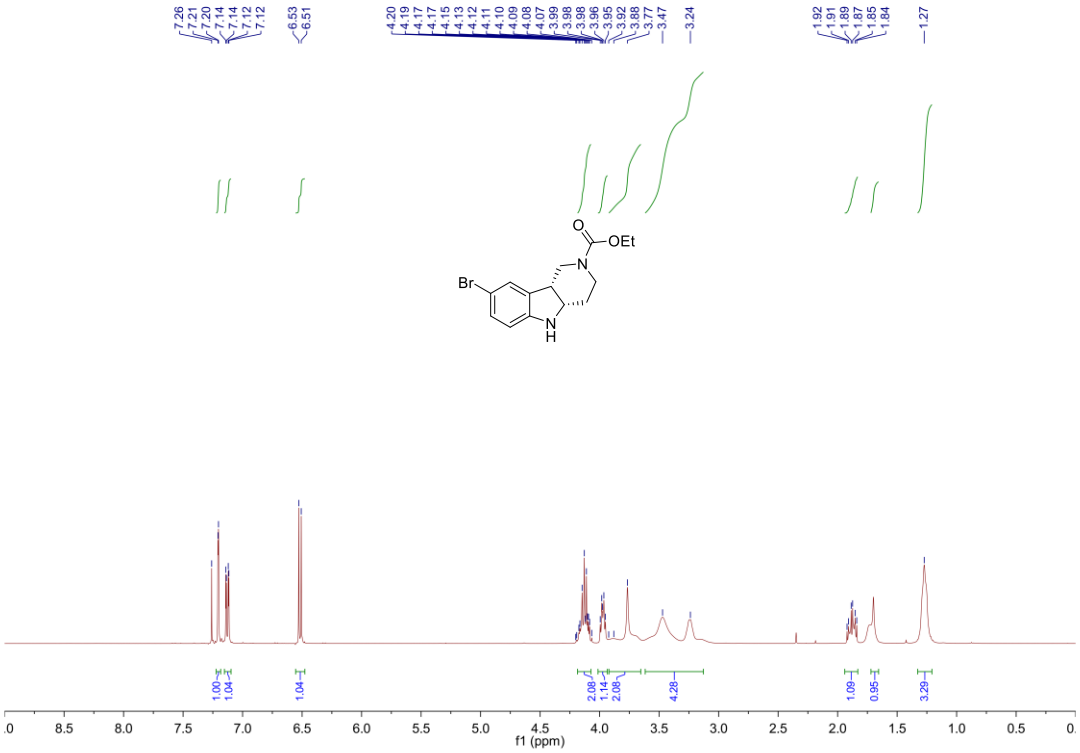
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6g**



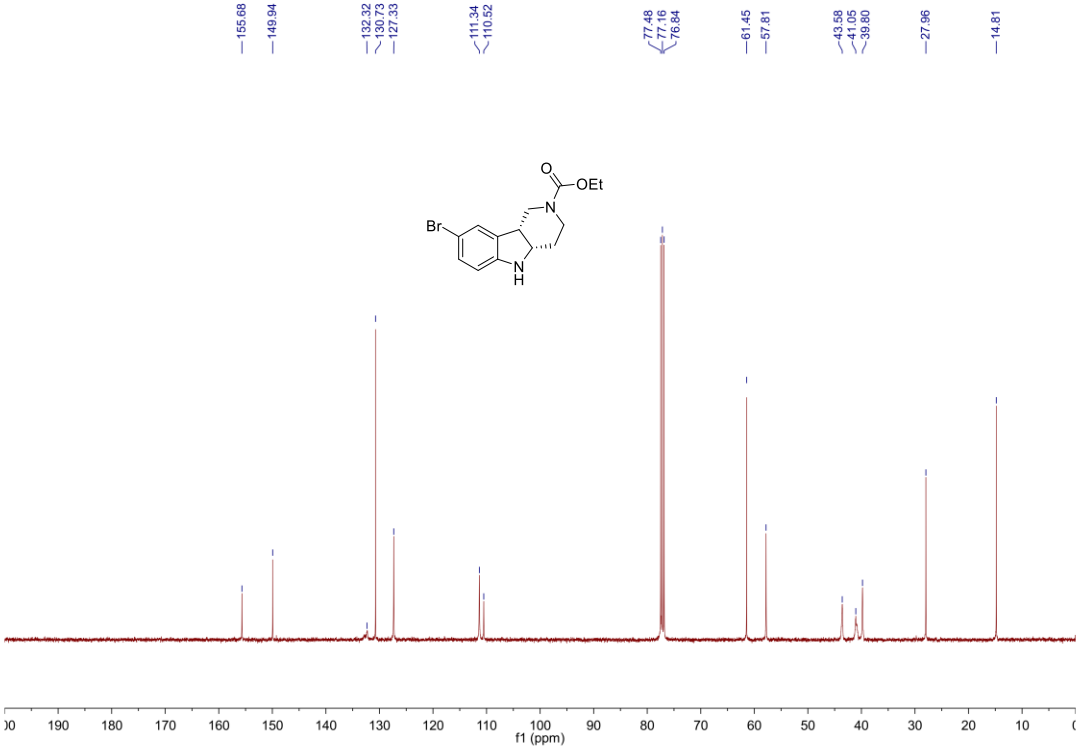
^{13}C NMR (151 MHz, $CDCl_3$) of compound **6g**



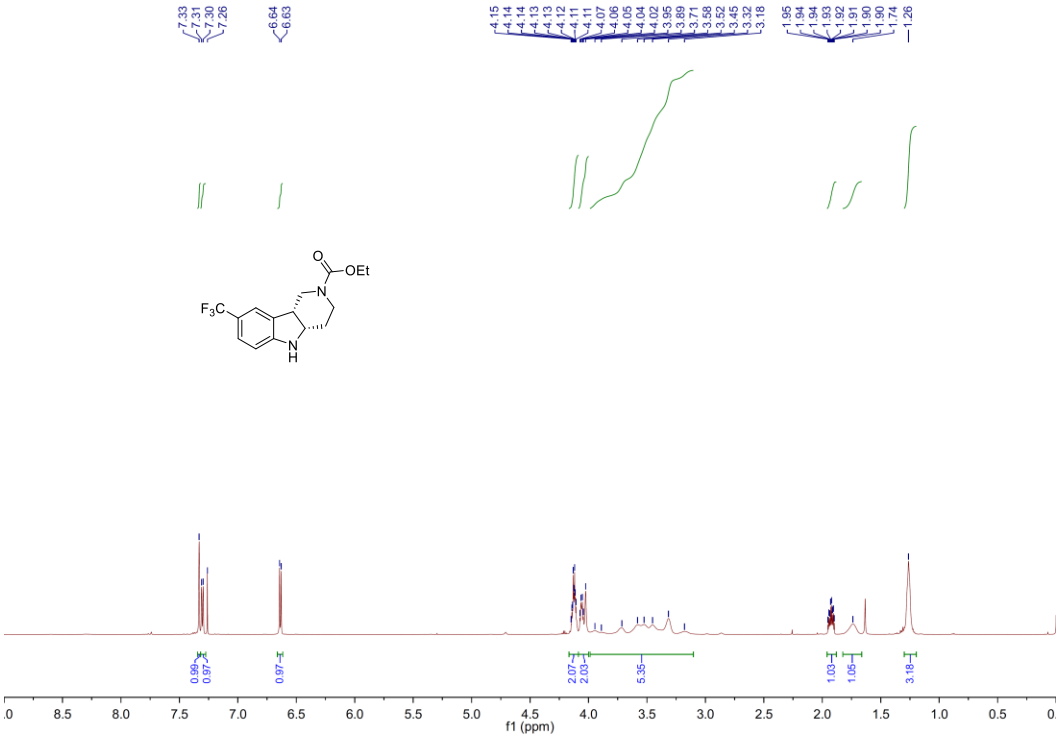
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6h**



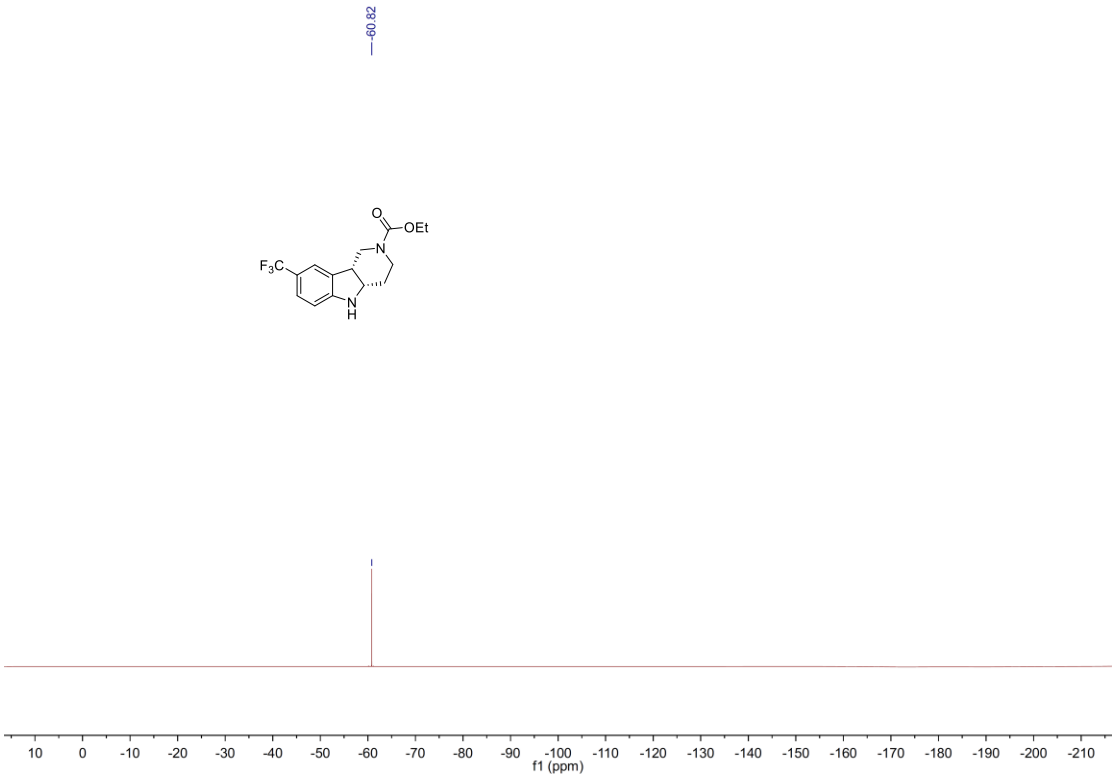
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6h**



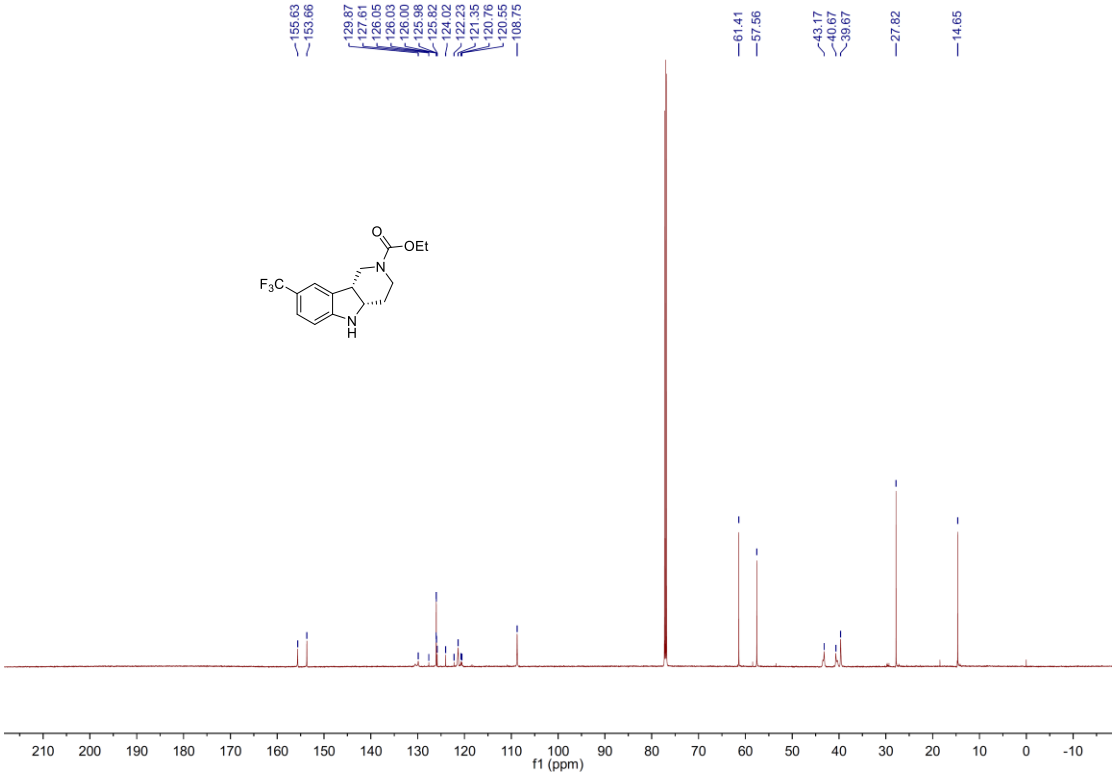
^{1}H NMR (600 MHz, $CDCl_3$) of compound **6i**



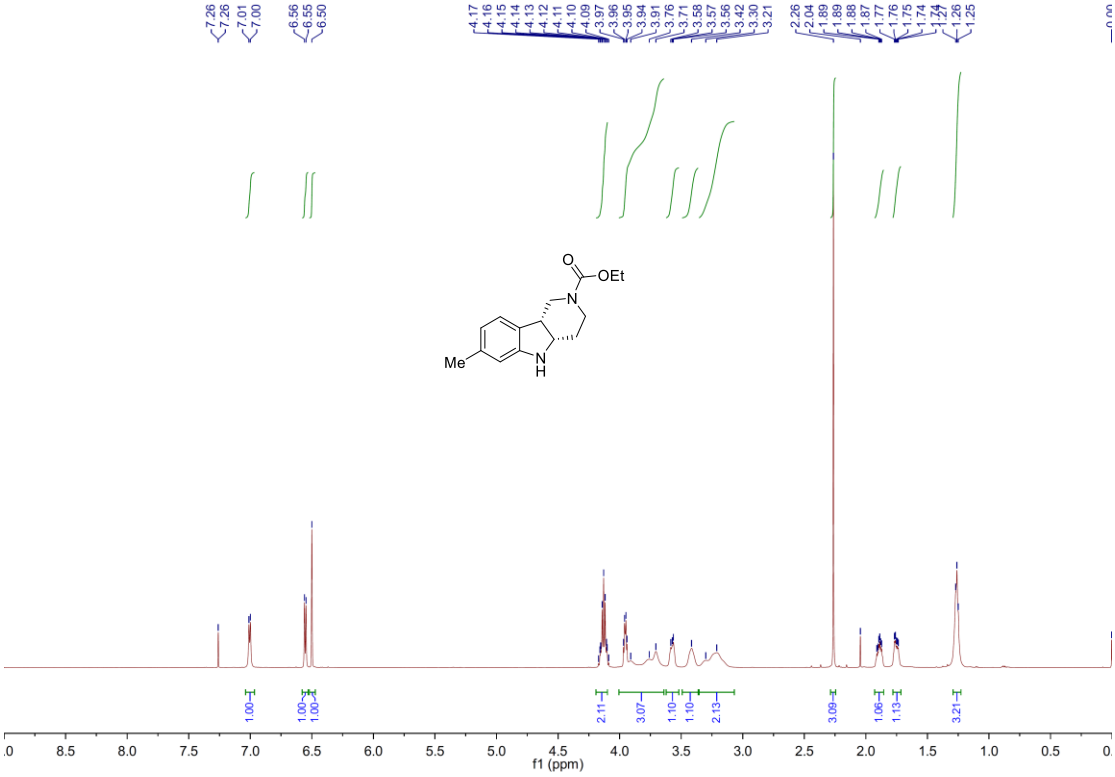
^{19}F NMR (565 MHz, $CDCl_3$) of compound **6i**



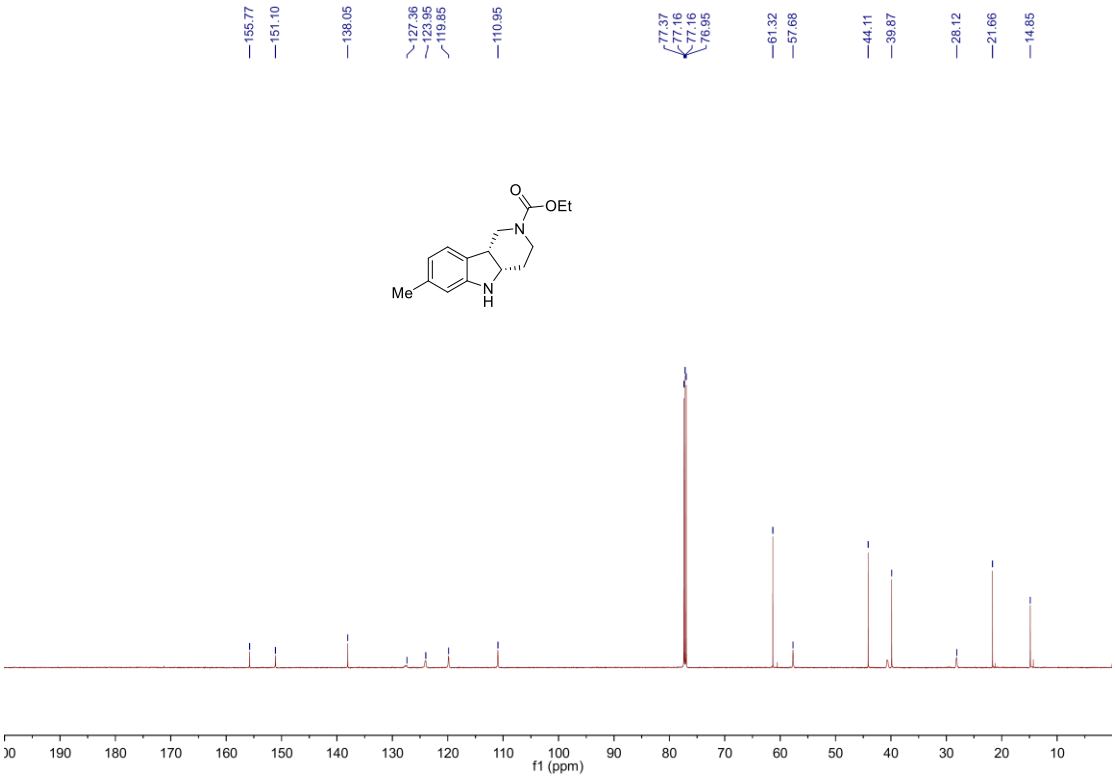
^{13}C NMR (151 MHz, $CDCl_3$) of compound **6i**



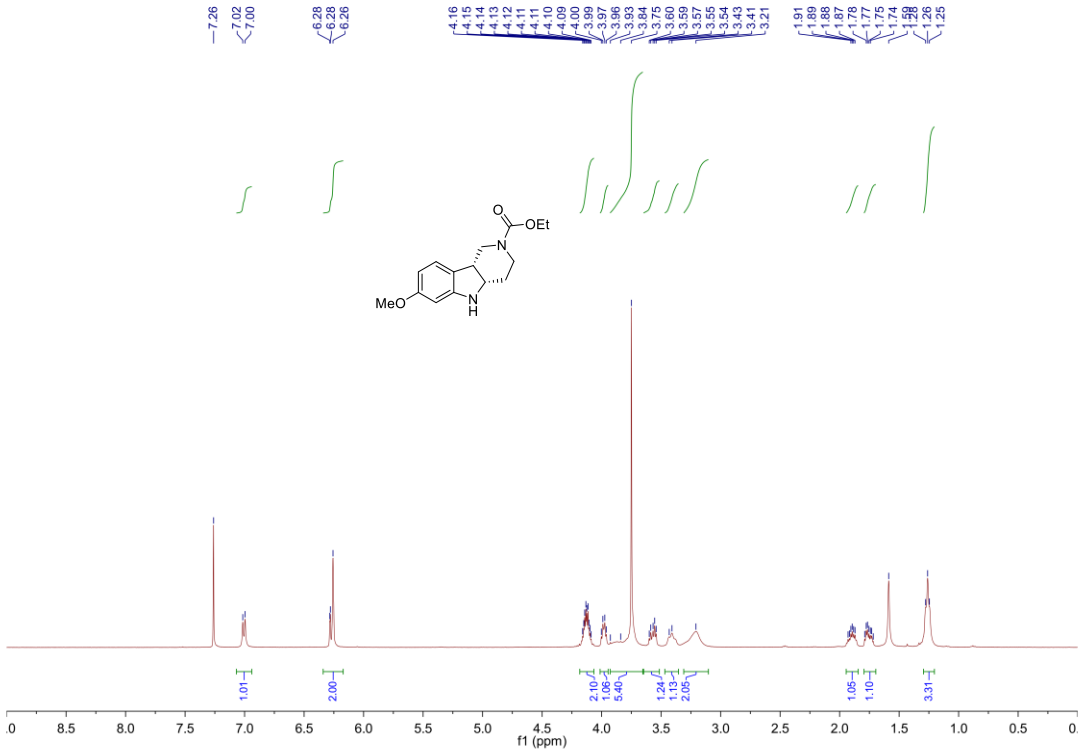
^{1}H NMR (600 MHz, $CDCl_3$) of compound **6j**



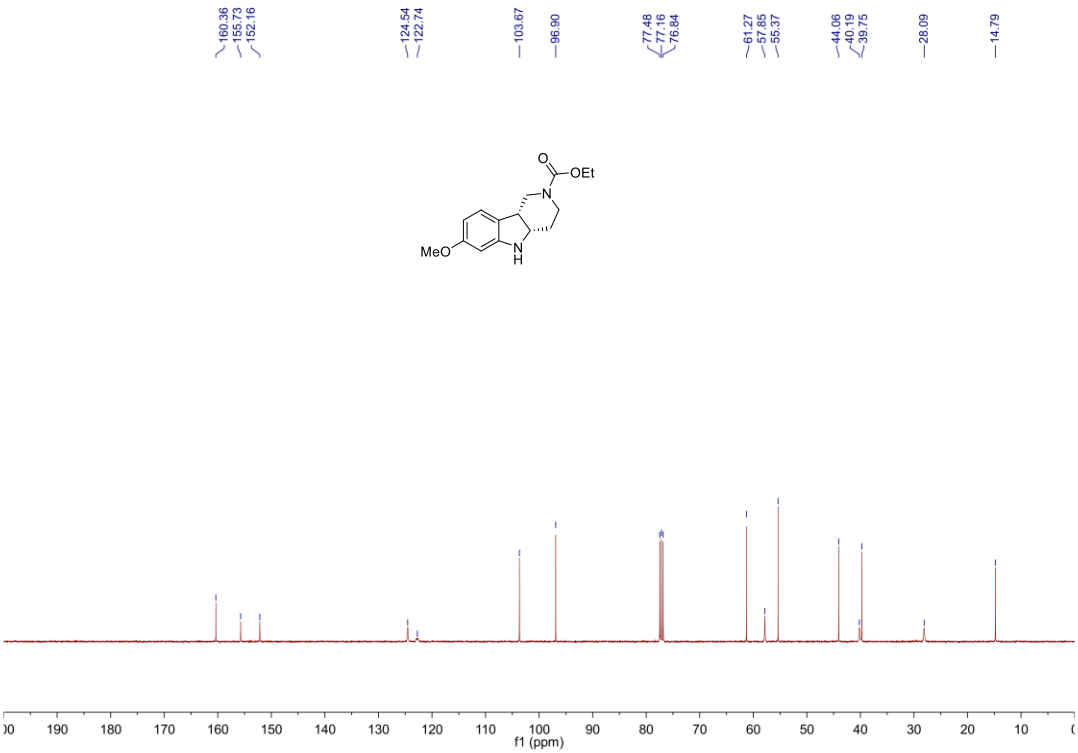
^{13}C NMR (151 MHz, $CDCl_3$) of compound **6j**



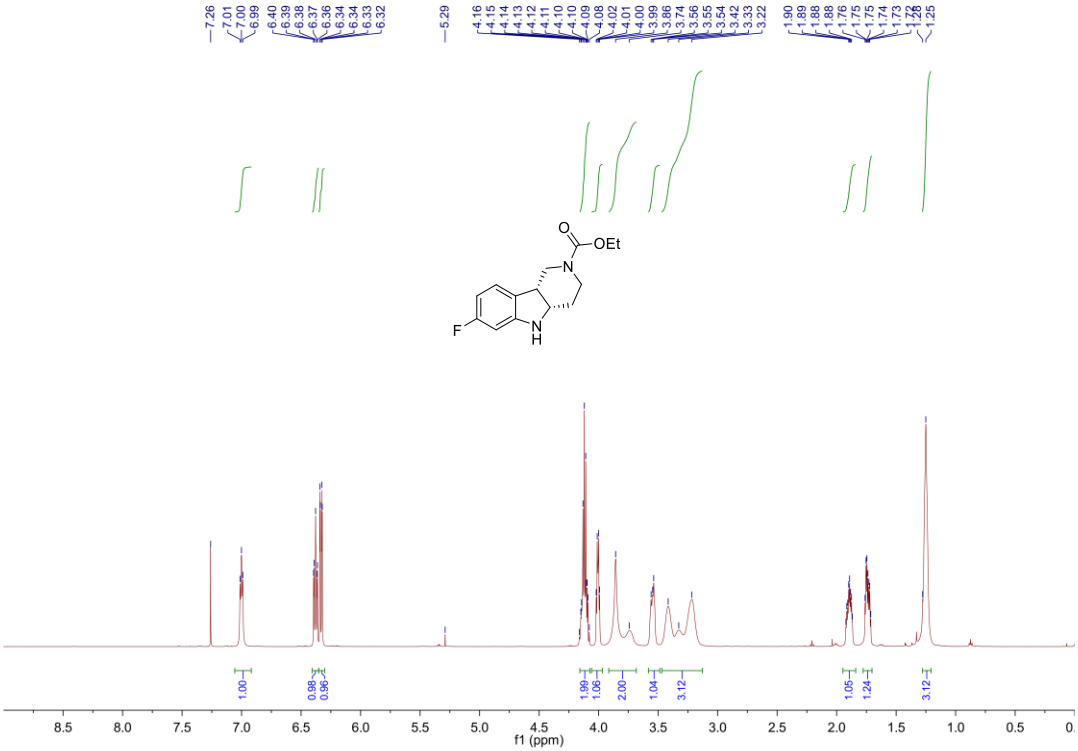
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6k**



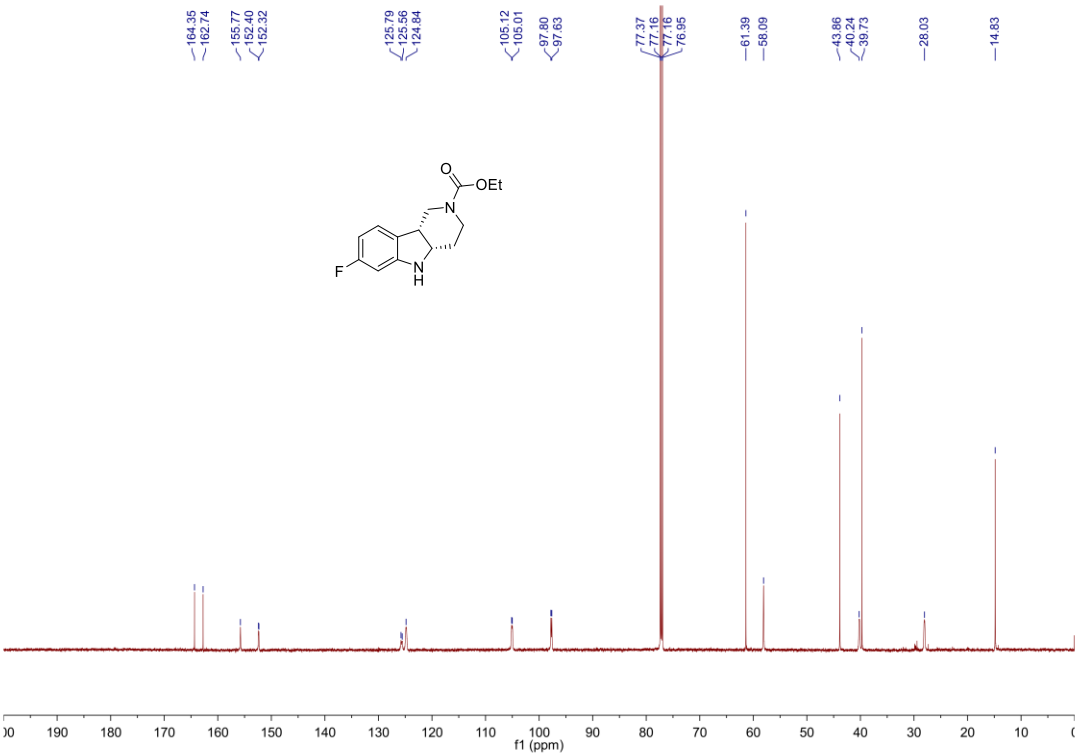
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6k**



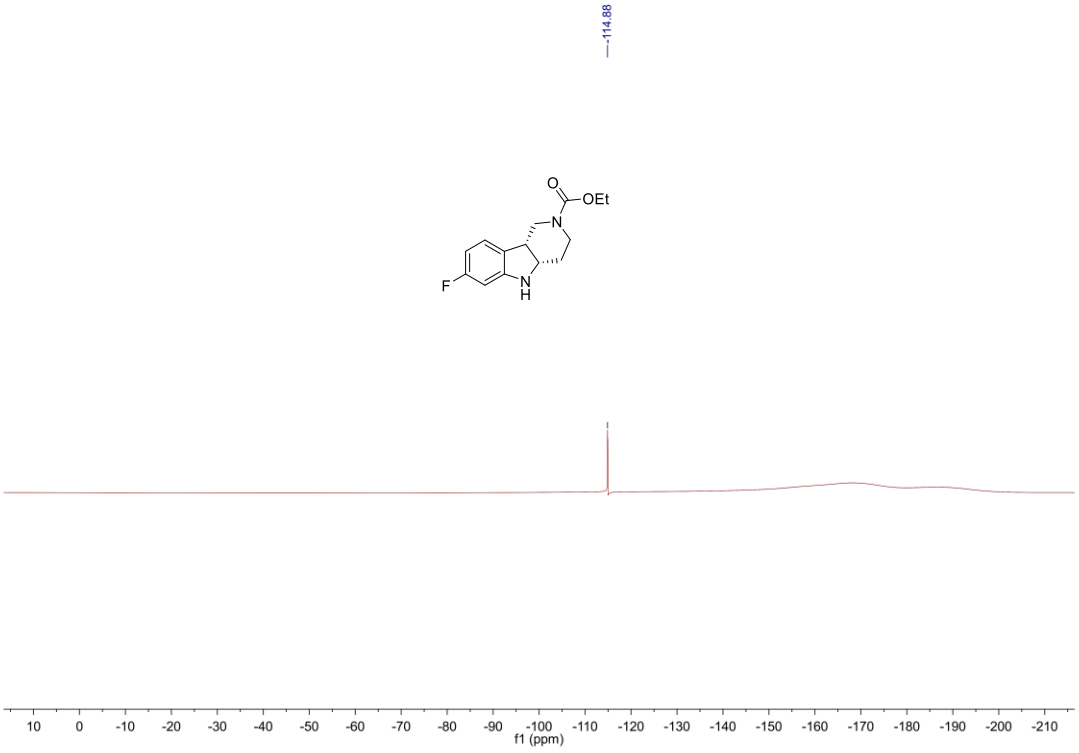
^{1}H NMR (600 MHz, $CDCl_3$) of compound **6l**



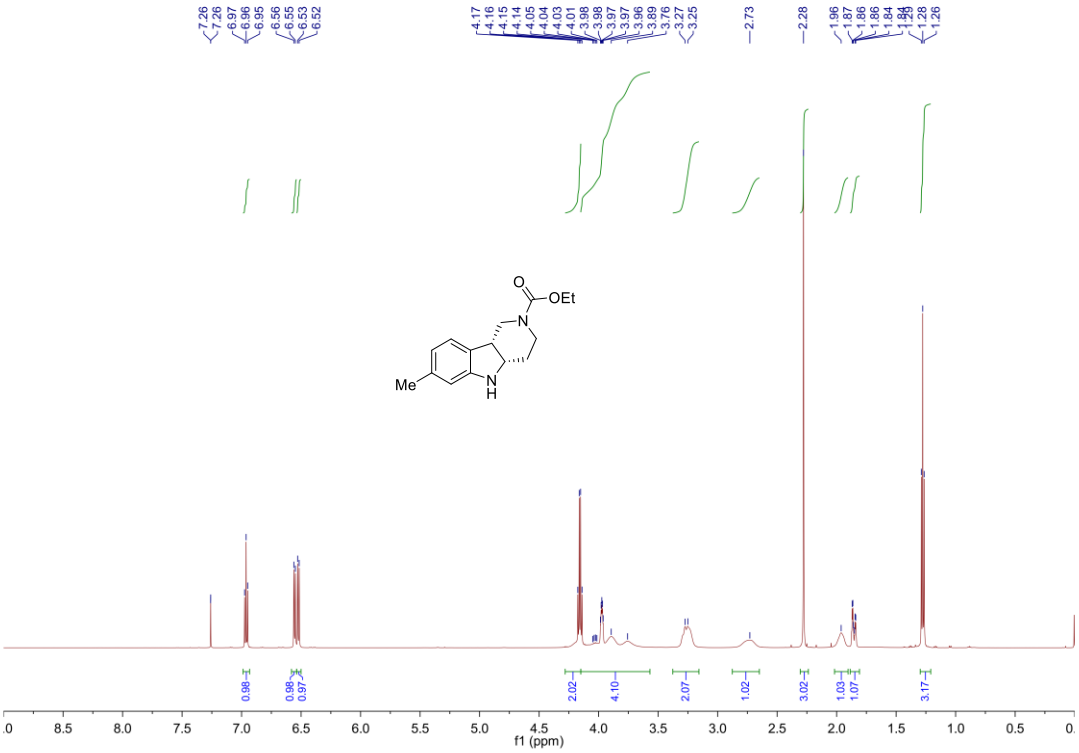
^{13}C NMR (151 MHz, $CDCl_3$) of compound **6l**



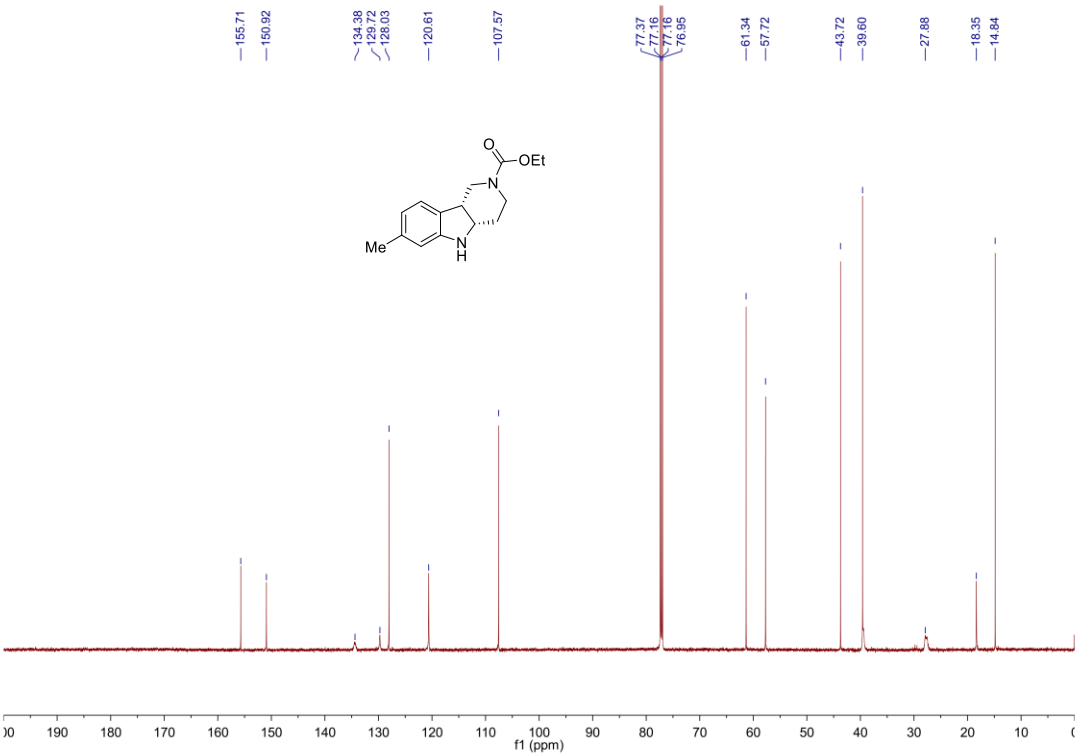
^{19}F NMR (565 MHz, $CDCl_3$) of compound **6l**



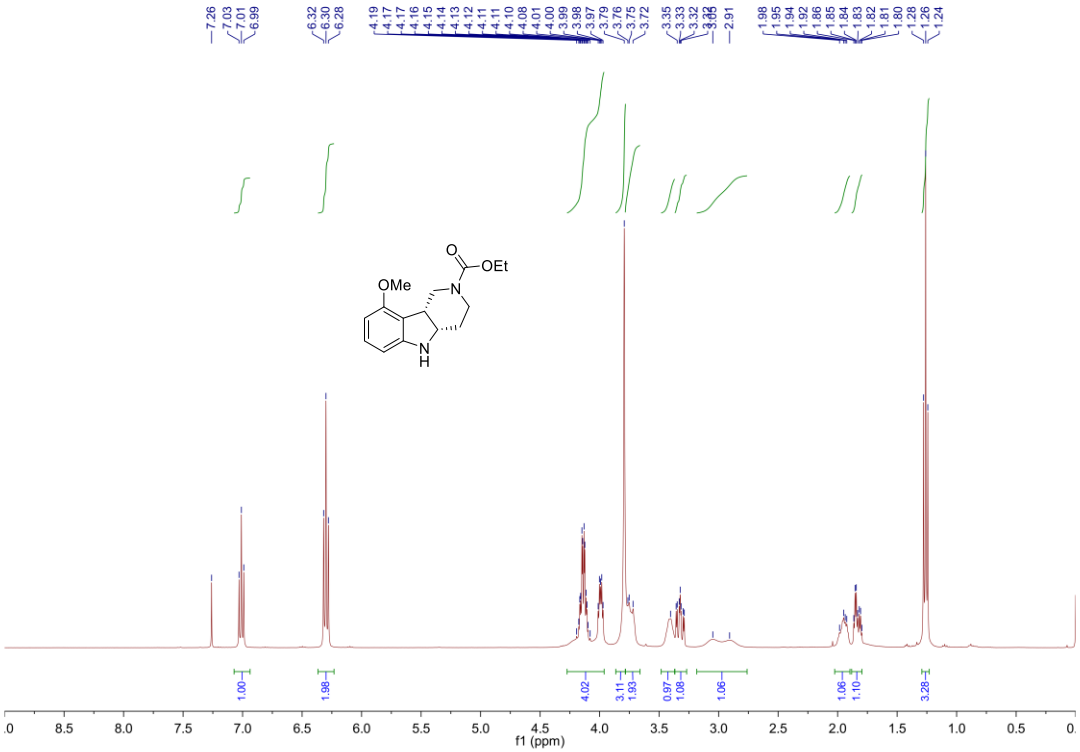
^{1}H NMR (600 MHz, $CDCl_3$) of compound **6m**



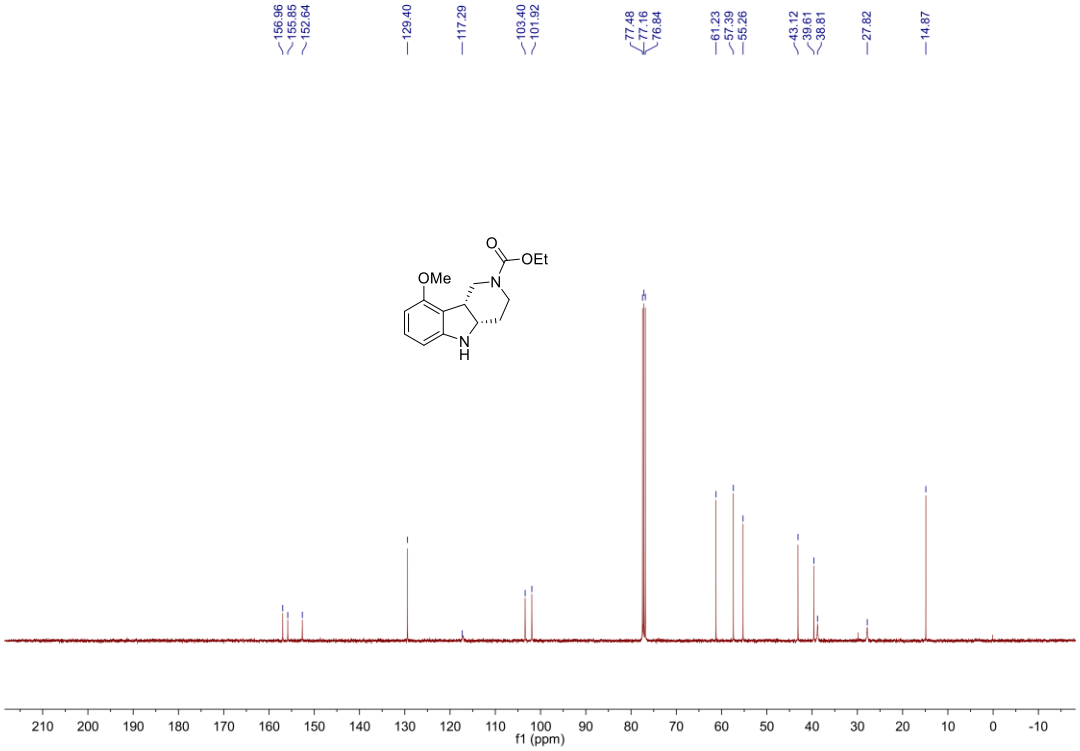
^{13}C NMR (151 MHz, $CDCl_3$) of compound **6m**



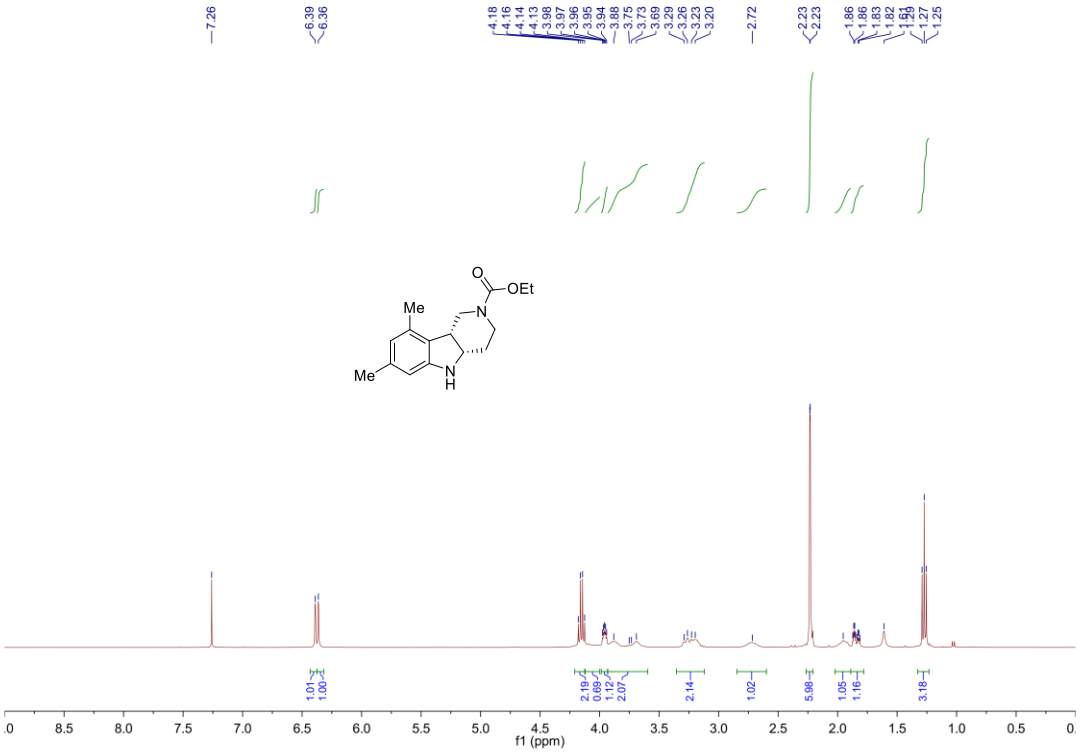
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6n**



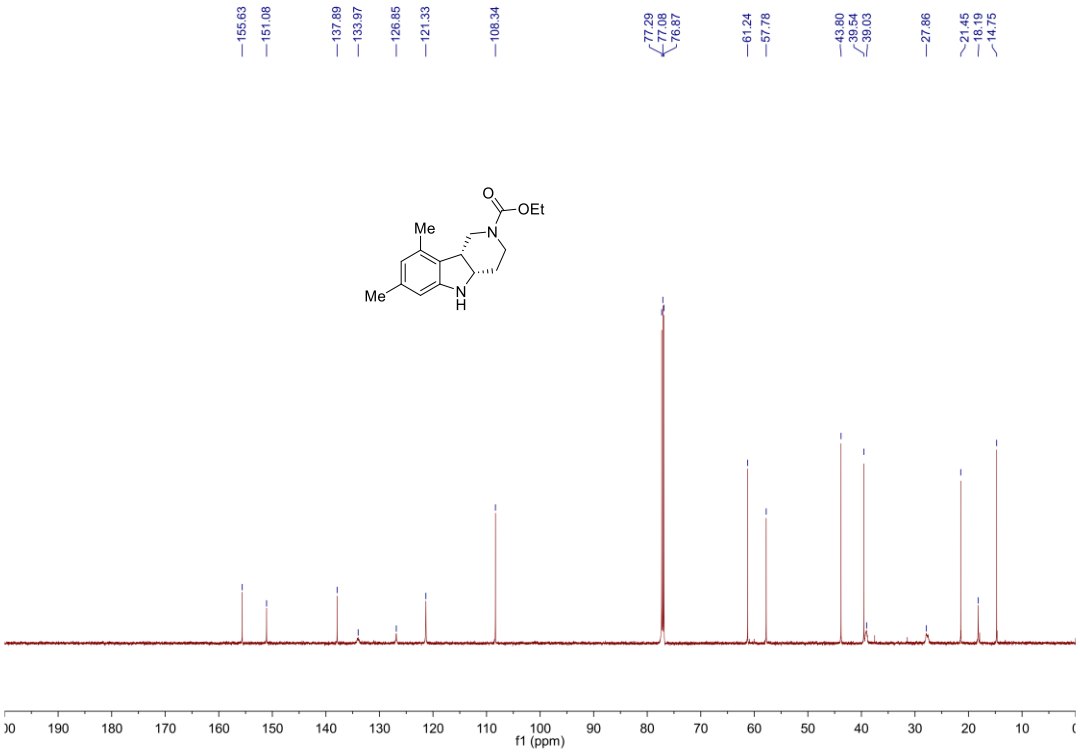
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6n**



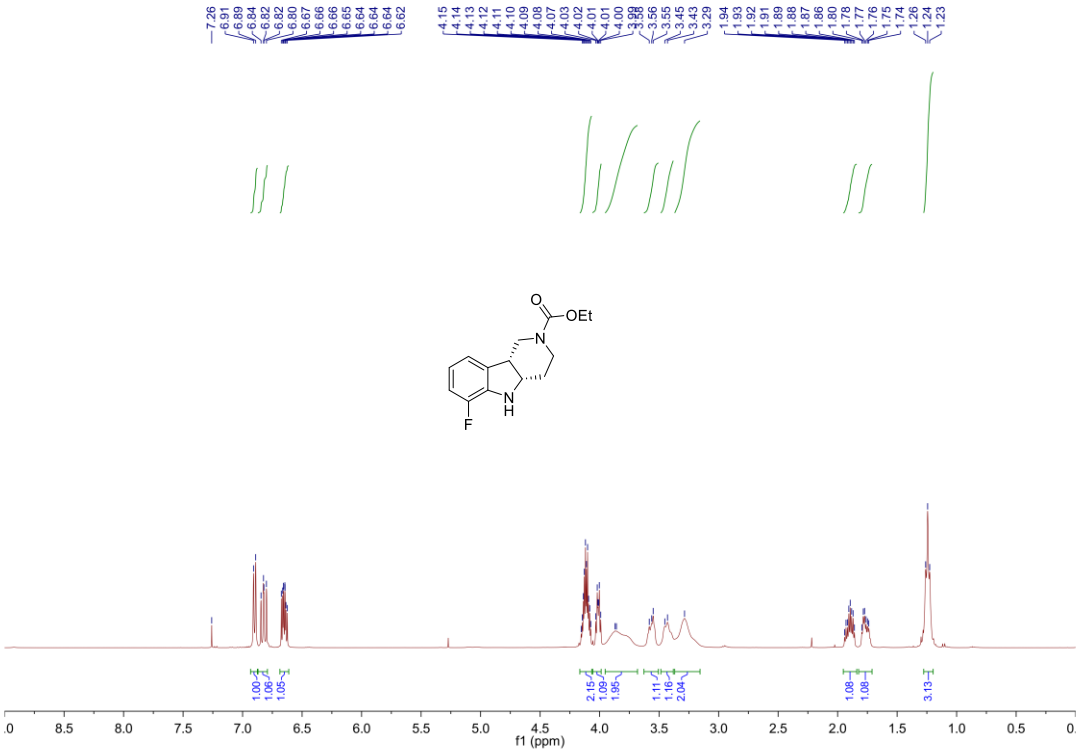
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6o**



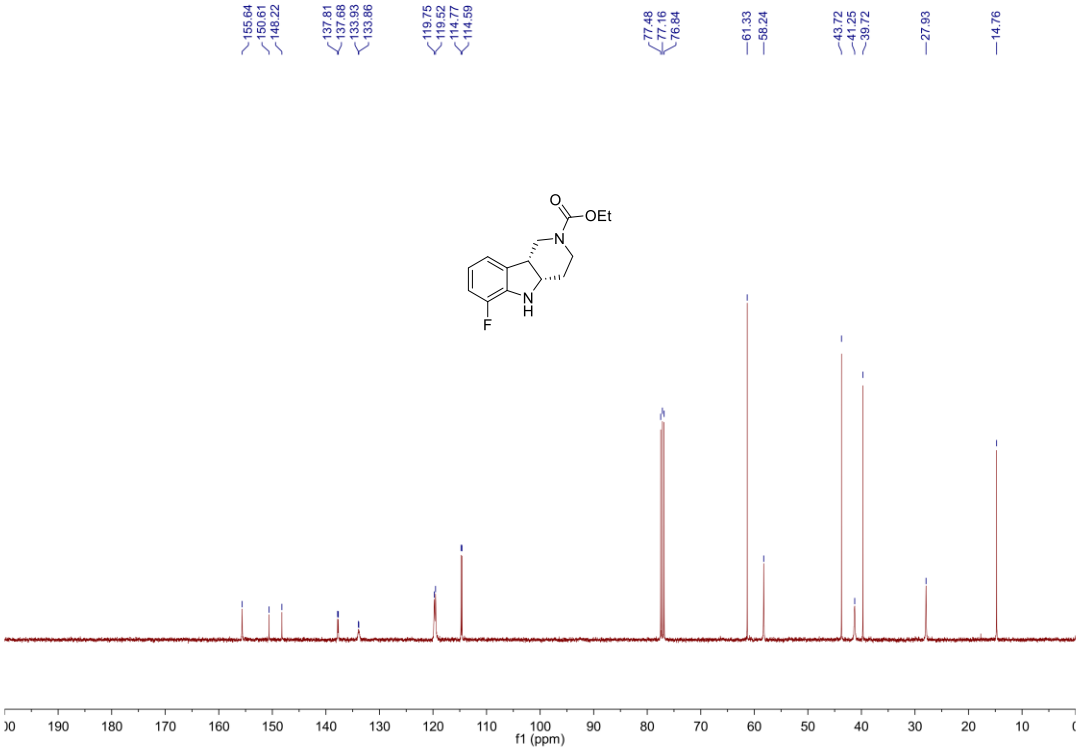
^{13}C NMR (151 MHz, $CDCl_3$) of compound **6o**



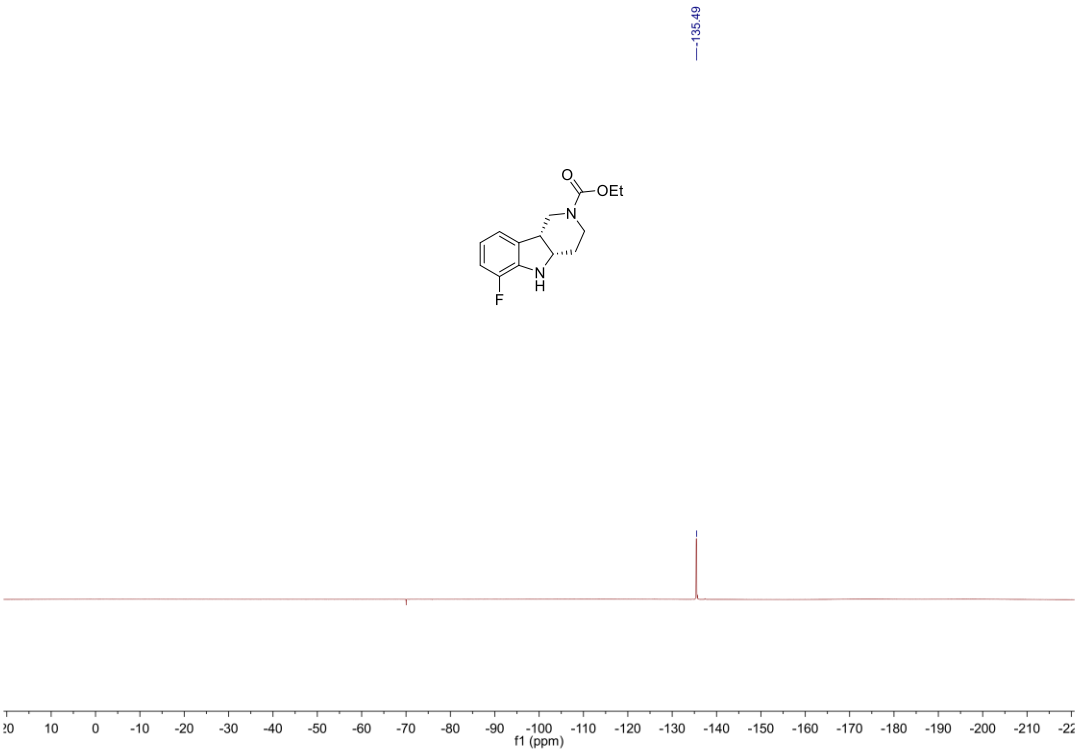
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6p**



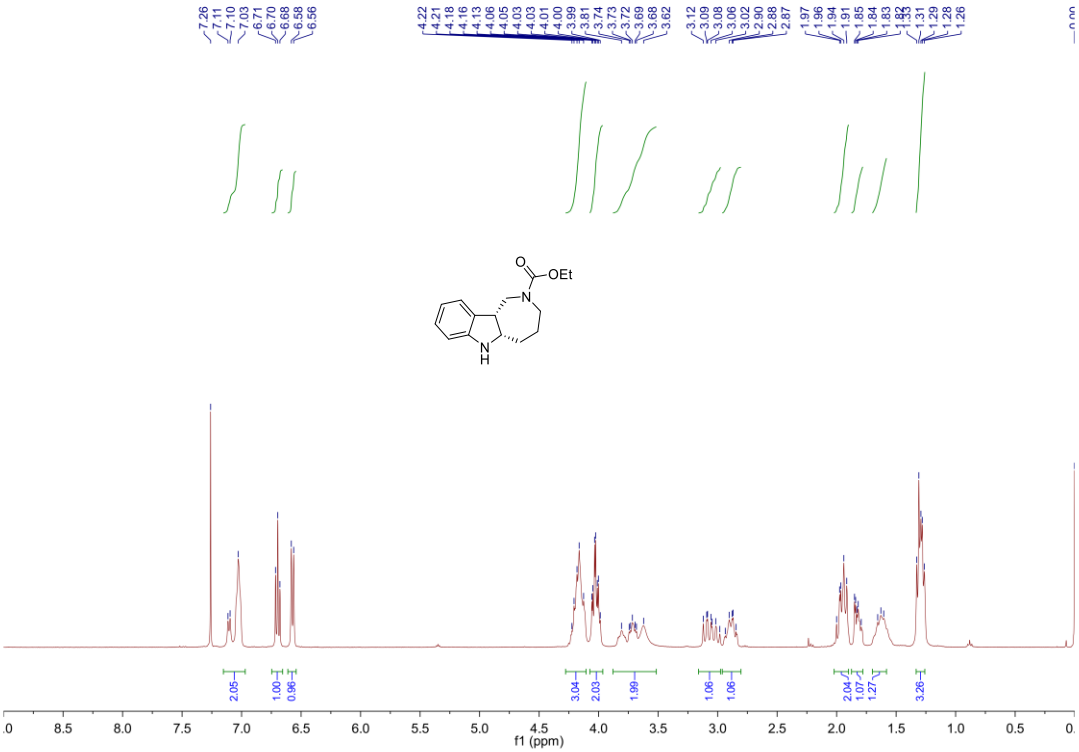
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6p**



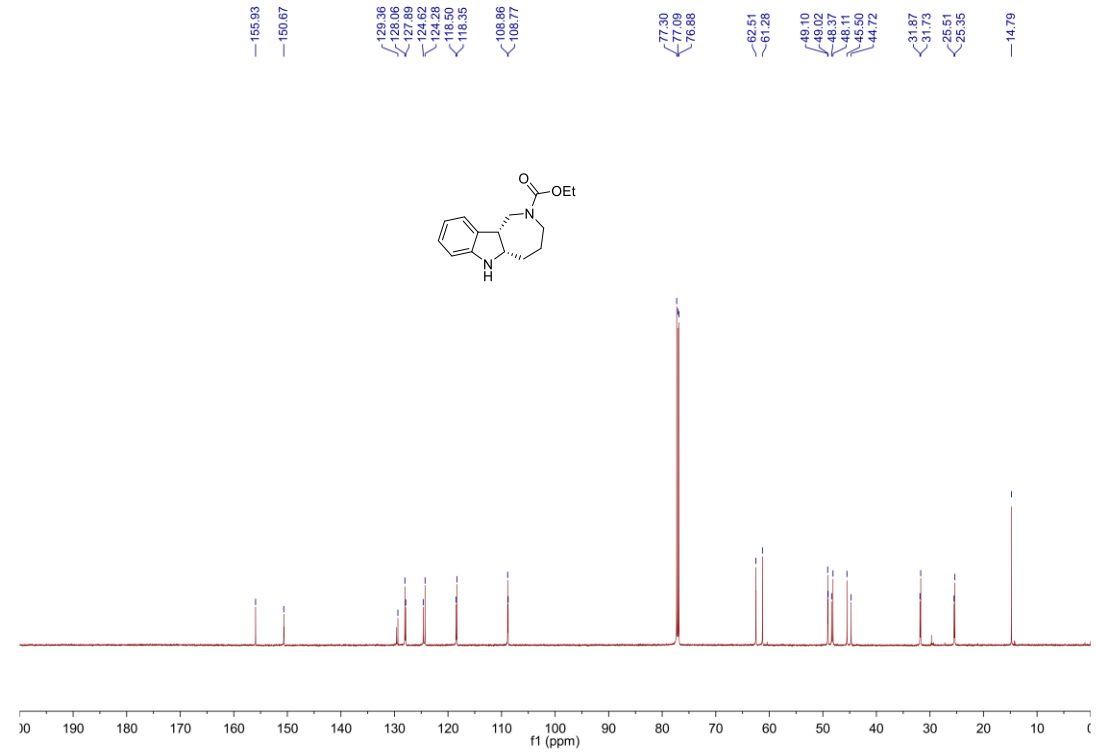
^{19}F NMR (376 MHz, $CDCl_3$) of compound **6p**



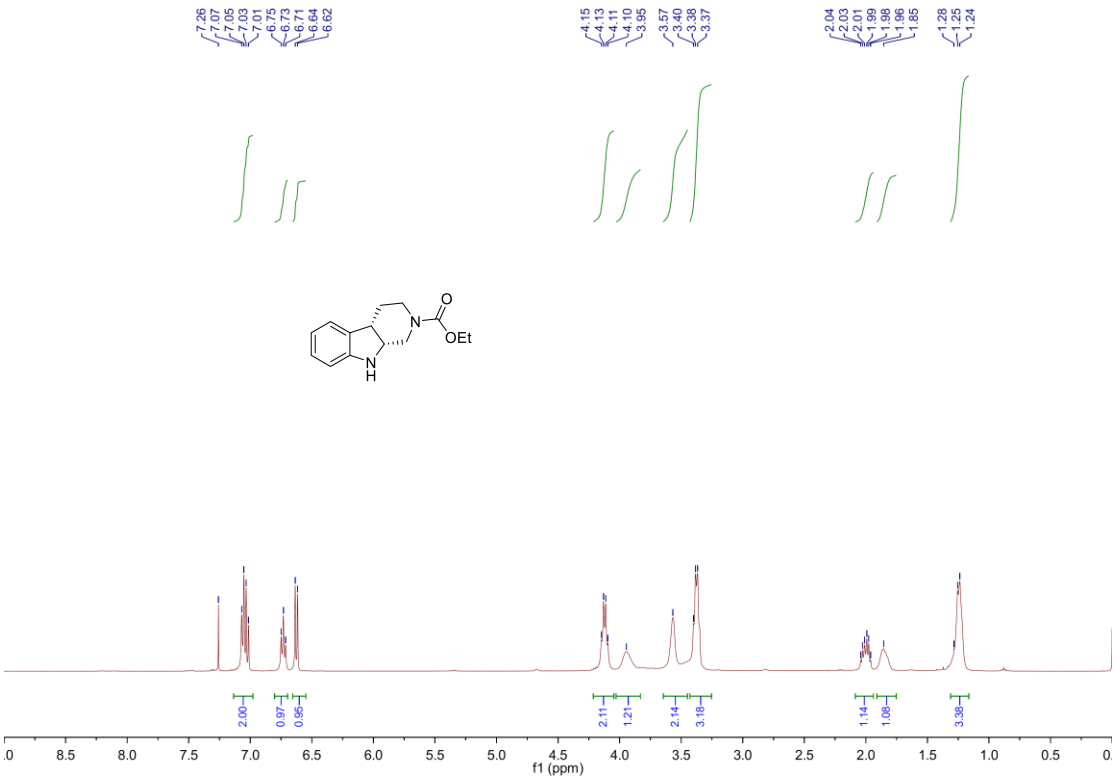
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6q**



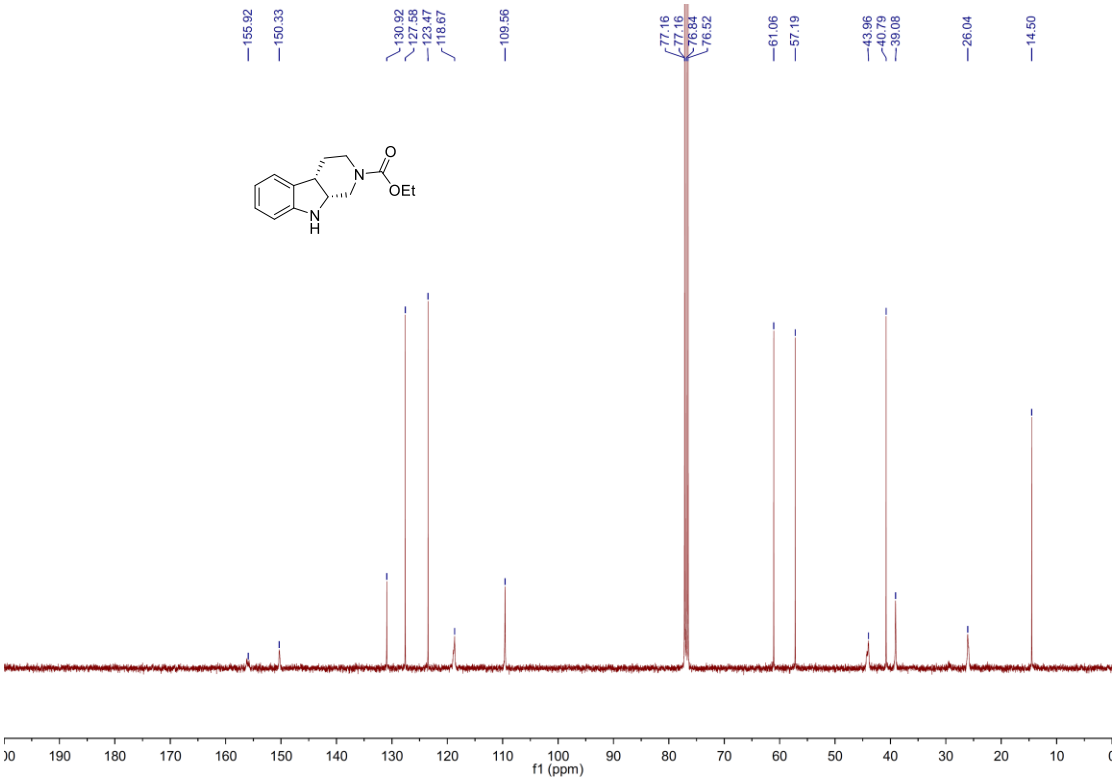
^{13}C NMR (151 MHz, $CDCl_3$) of compound **6q**



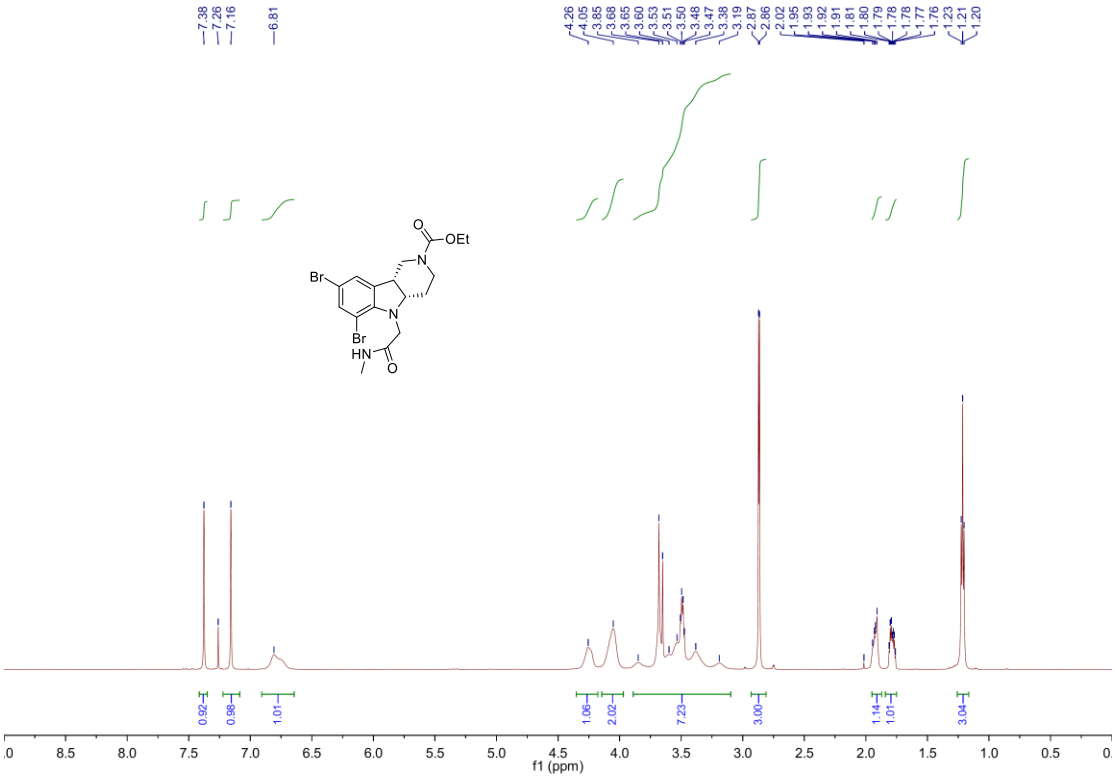
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6r**



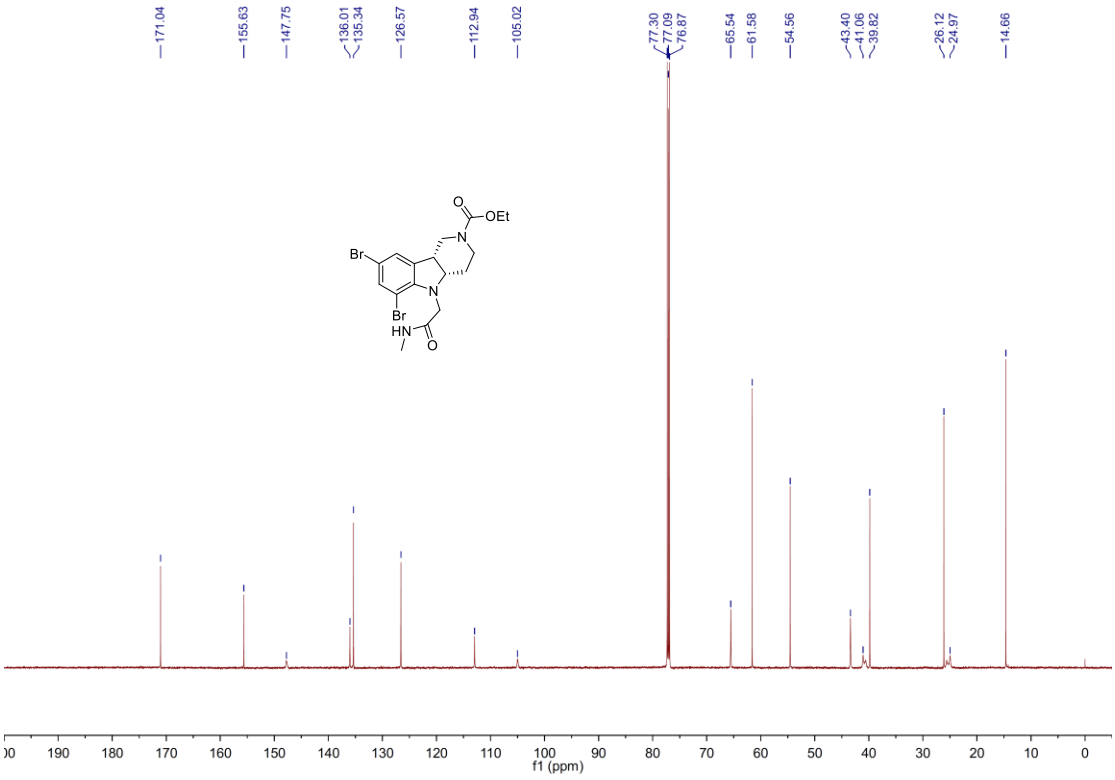
^{13}C NMR (151 MHz, $CDCl_3$) of compound **6r**



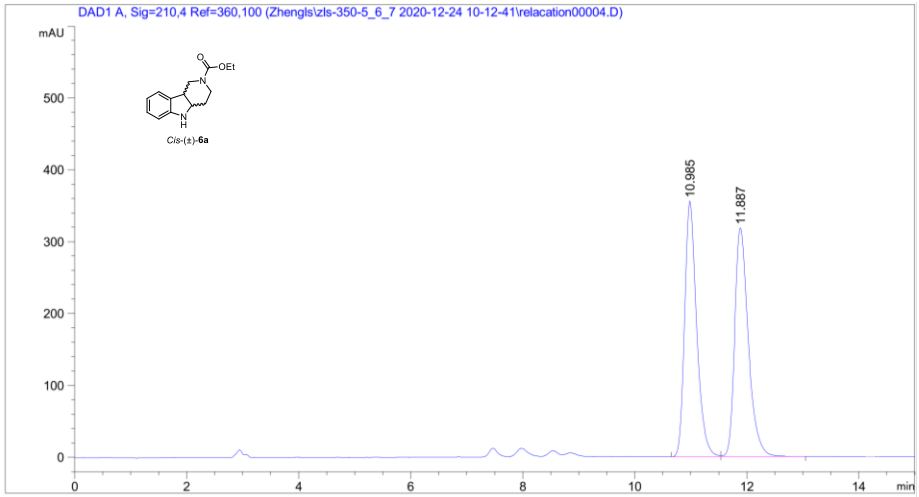
^{1}H NMR (600 MHz, $CDCl_3$) of compound **8**



^{13}C NMR (151 MHz, $CDCl_3$) of compound **8**



X. HPLC Spectra of *cis*-(±)-6a-6r, (±)-8 and Chiral Compounds 6a-6r, 8

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                      Area Percent Report
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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.985 BV    0.2282 5315.38330  355.95148  49.7995
   2  11.887 VB    0.2542 5358.18604  318.58466  50.2005
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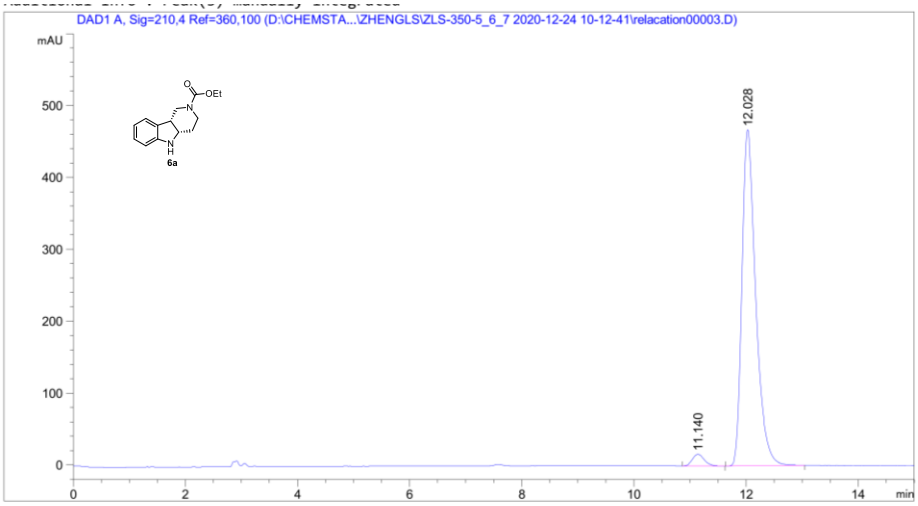


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  11.140 BB    0.2227  243.16959   16.43012   2.9586
   2  12.028 BB    0.2589 7975.86230  467.74191  97.0414
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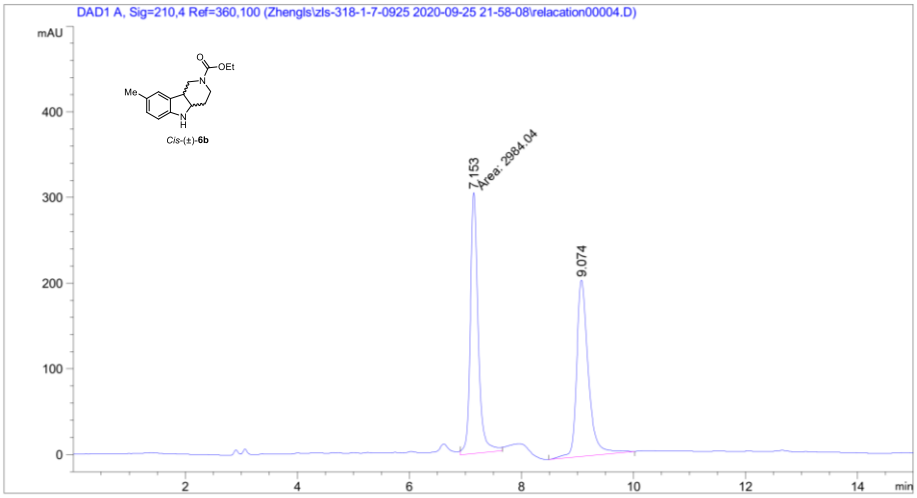


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                      Area Percent Report
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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.153 MM    0.1630 2984.04346  305.06253  50.0901
   2   9.074 BB    0.2164 2973.30664  205.95201  49.9099
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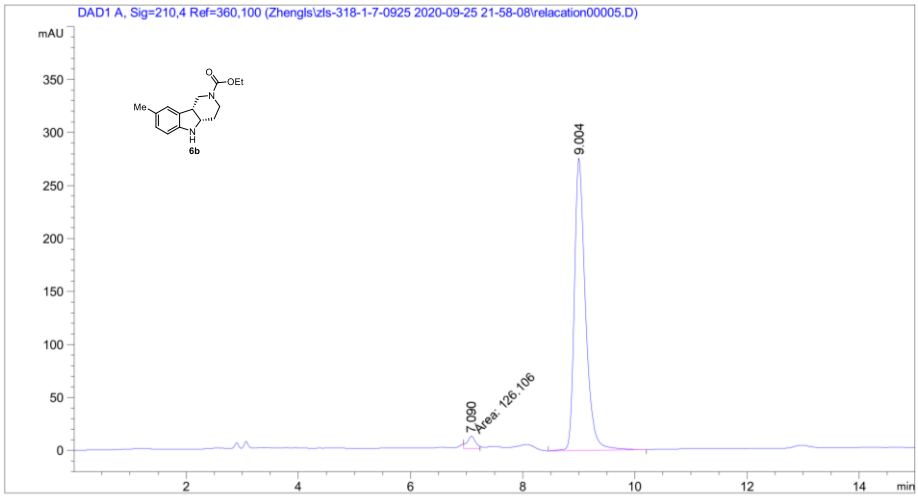


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.090 MM    0.1749  126.10619   12.01711   3.2044
   2   9.004 BB    0.2091 3809.24194  275.90793  96.7956
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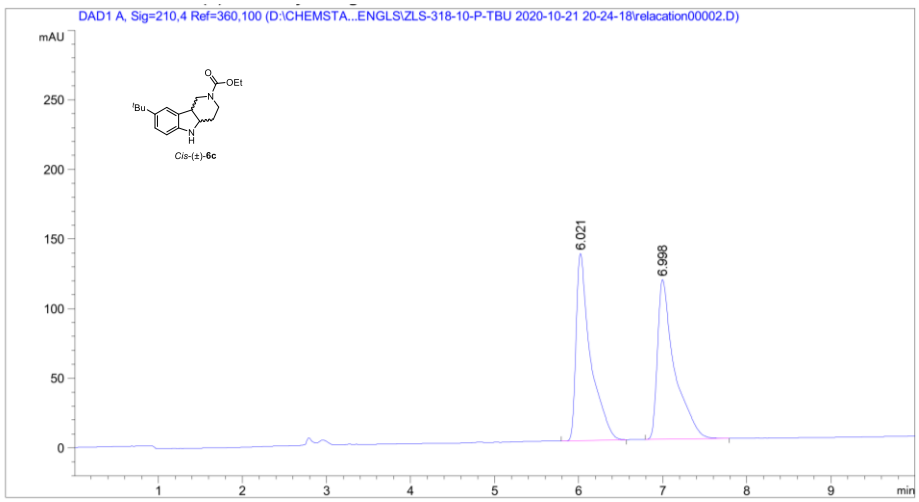


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.021 BB    0.1665 1597.44946  134.53699  49.7772
   2   6.998 BB    0.1979 1611.74719  114.72469  50.2228
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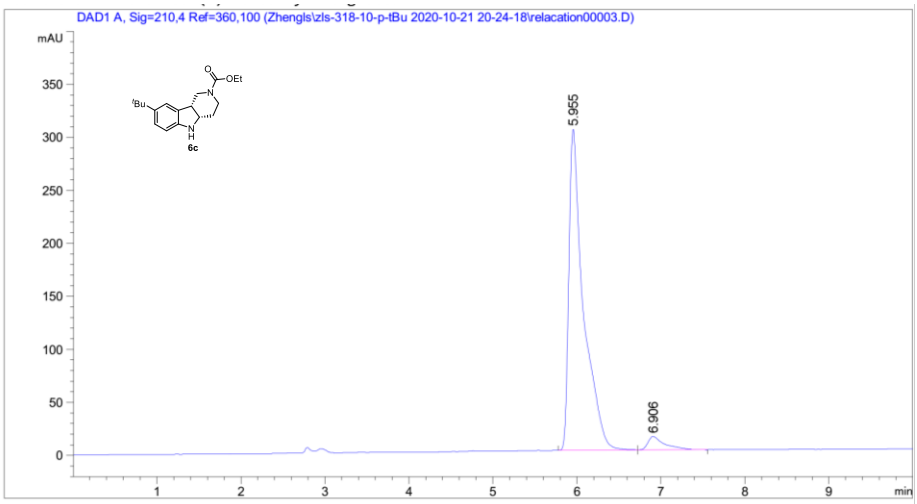


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   5.955 BV    0.1707 3652.96997  302.90927  95.3470
   2   6.906 VB    0.1956  178.26561   12.71069   4.6530
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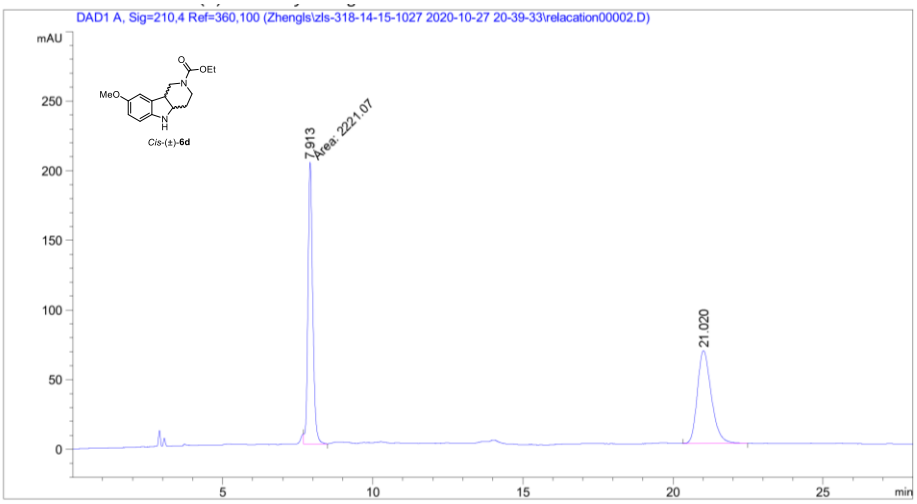


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.913 FM    0.1832 2221.07446  202.02271  50.8606
   2  21.020 BB    0.4983 2145.91406   66.52642  49.1394
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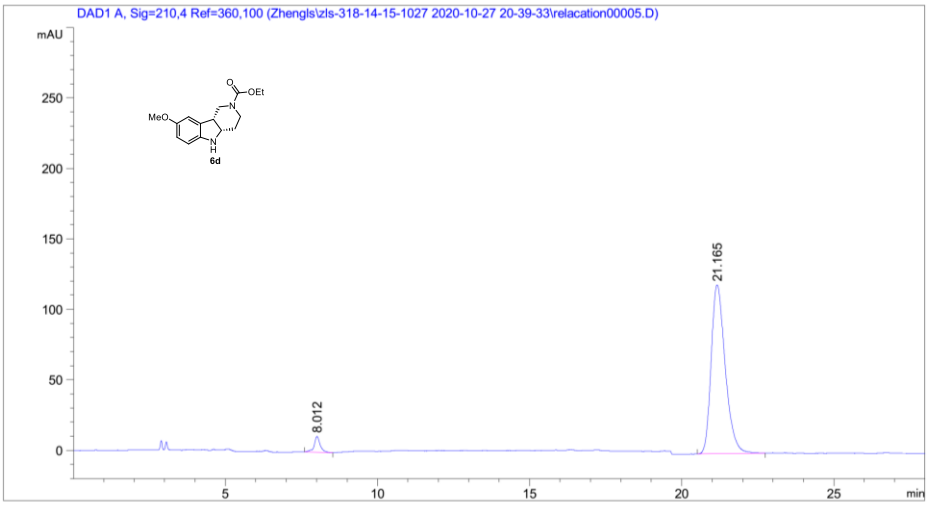


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.012 BB    0.2029  153.82138   11.15668   3.8424
   2  21.165 BB    0.4908 3849.46509  119.82839  96.1576
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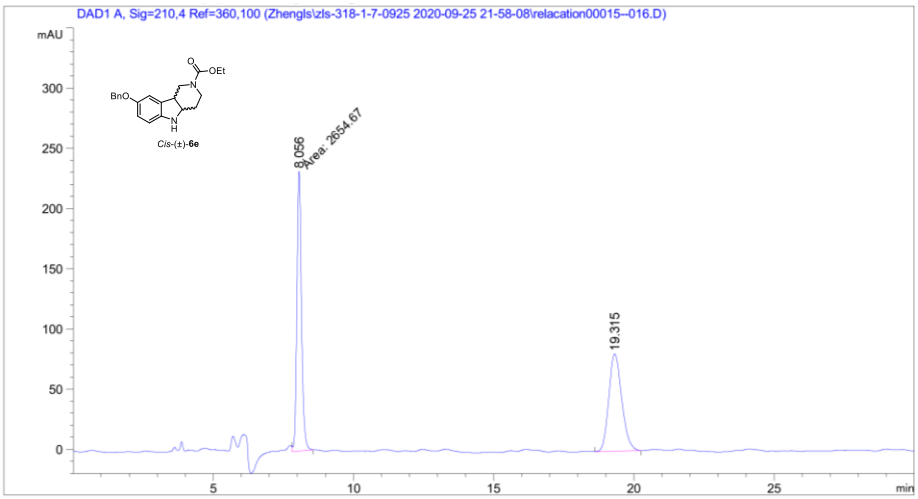


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.056 MM    0.1903 2654.66602  232.48933  50.6264
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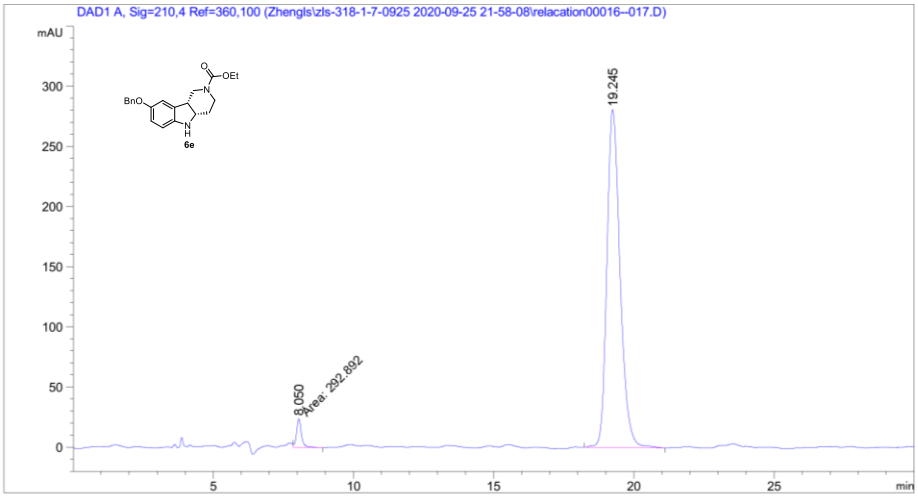


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                      Area Percent Report
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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.050 FM    0.2072  292.89197   23.56196   3.0967
   2  19.245 BB    0.4986 9165.36328  280.94107  96.9033
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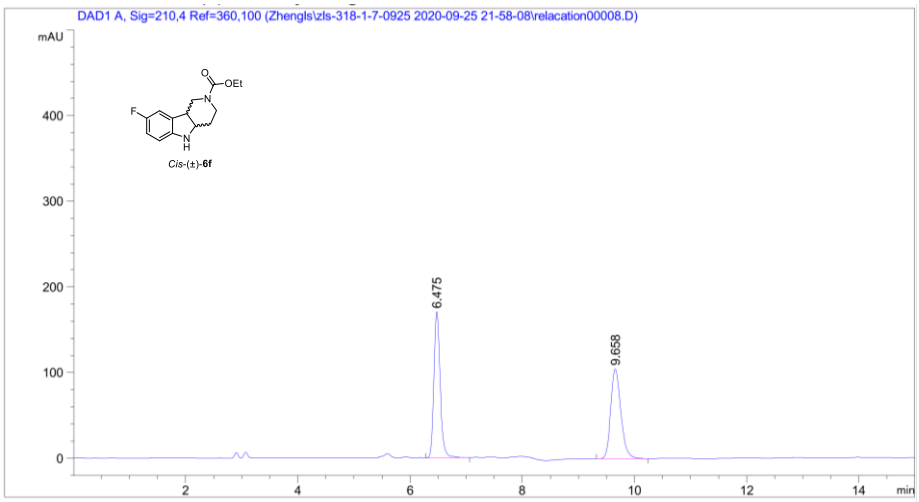


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.475 BB    0.1177 1310.66931  170.44864  49.9947
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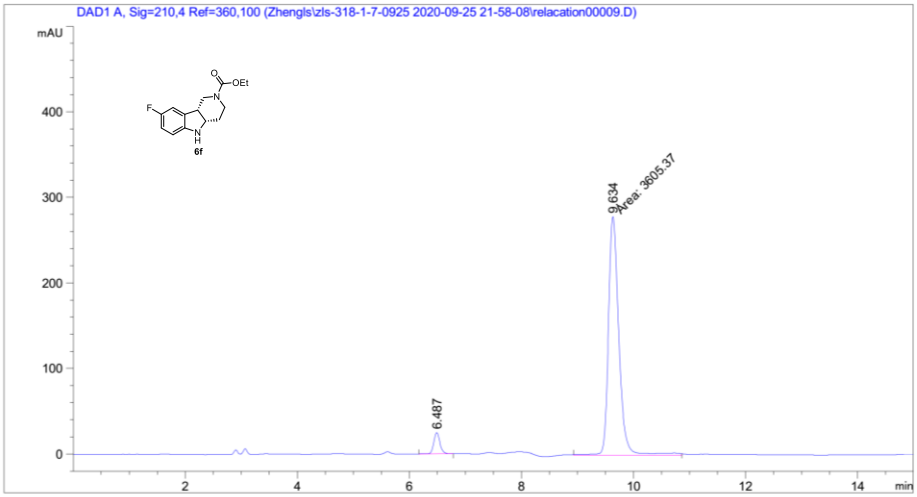


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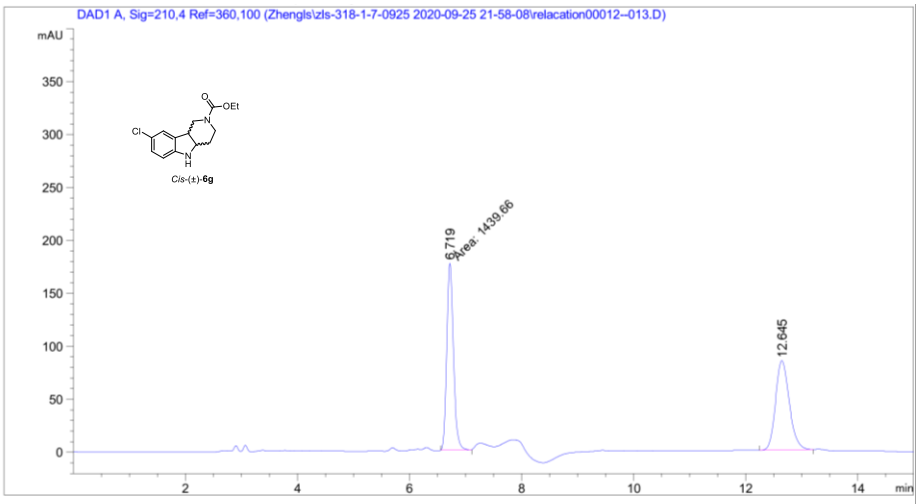
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.487 BB    0.1176  190.54088   24.80309   5.0196
   2   9.634 MM    0.2156 3605.37231  278.73877  94.9804
```

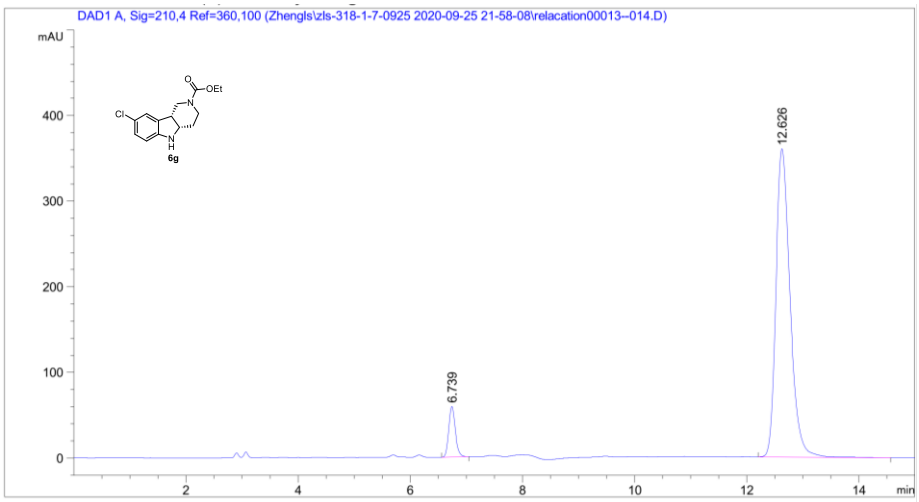



```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.719 MM    0.1361 1439.65698  176.36047  50.1169
   2  12.645 BB    0.2624 1432.94031   84.26061  49.8831
```

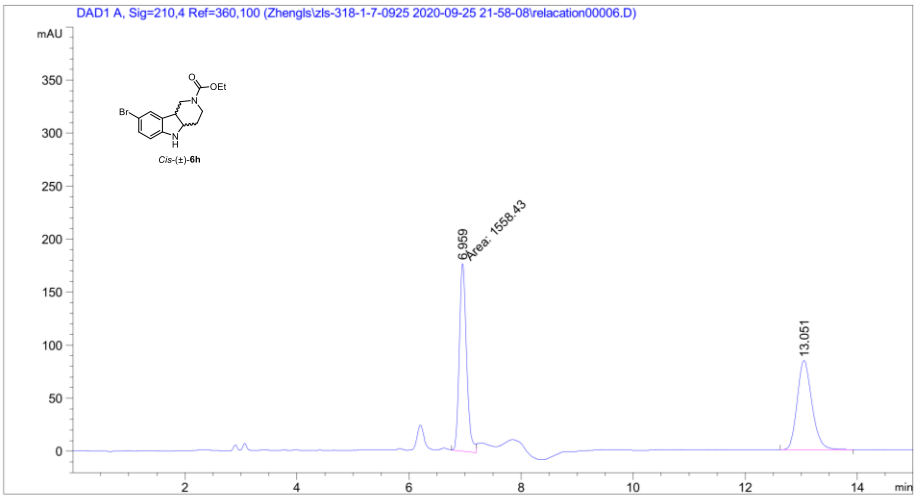



```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.739 BB    0.1247  480.41342   59.17236   7.0951
   2  12.626 BB    0.2660 6290.67041  359.75702  92.9049
```

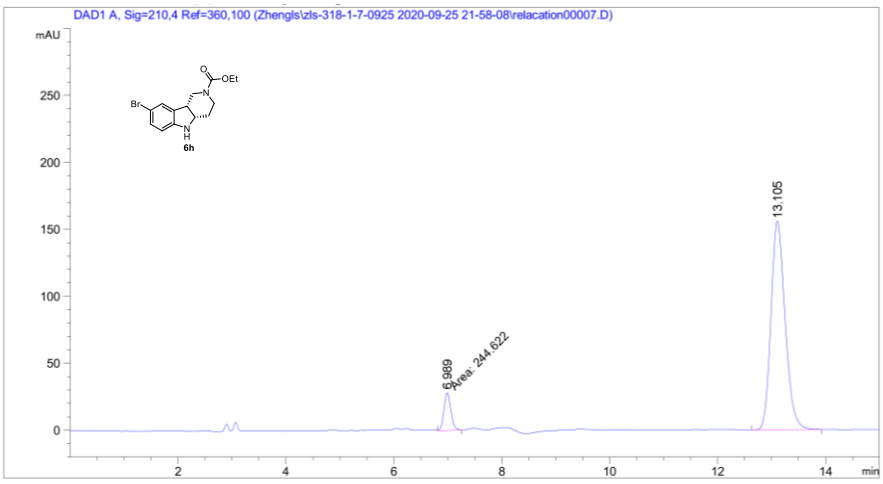



```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.959 MF    0.1467 1558.42932  176.99638  50.3561
   2  13.051 BB    0.2811 1536.38818   84.12392  49.6439
```

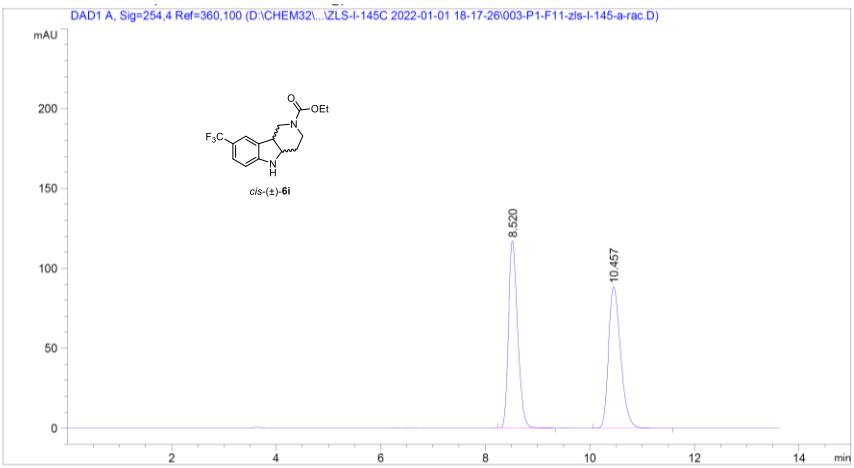



```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.989 MM    0.1448  244.62207   28.15826   7.9510
   2  13.105 BB    0.2801 2832.00342  155.73909  92.0490
```

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=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.520 BB    0.1853 1418.84399  117.17514  49.9853
   2  10.457 BB    0.2450 1419.67676   88.58092  50.0147
```

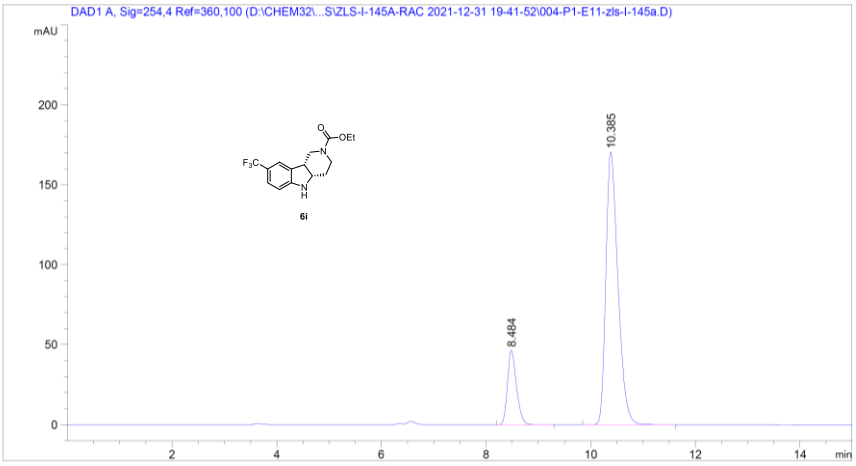


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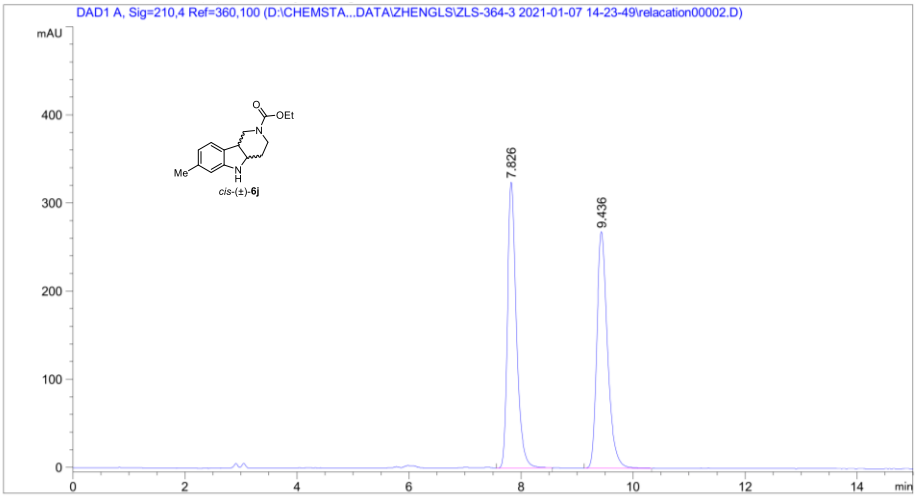
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.484 BB    0.1844  560.01794   46.54556  17.0085
   2  10.385 BB    0.2450 2732.56836  170.49403  82.9915
```

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=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.826 BB    0.1667 3579.00610  324.40195  49.9409
   2   9.436 BB    0.2028 3561.82275  268.36957  49.7011
   3  18.483 BB    0.2397   25.65842    1.38788   0.3580
```

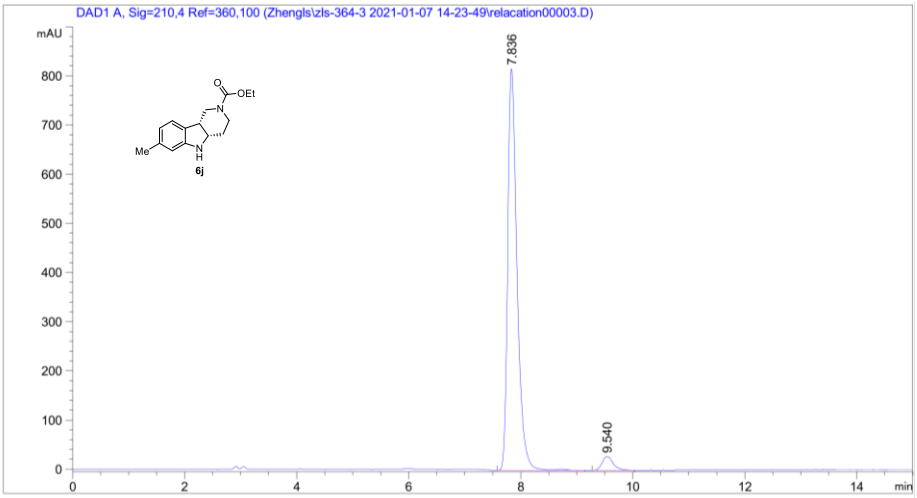


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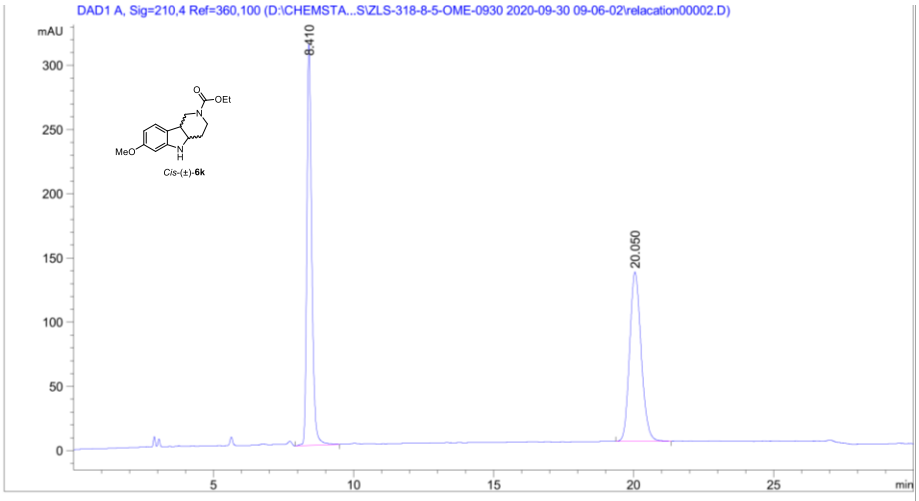
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.836 BV R  0.1740 9413.04492  817.04395  96.0429
   2   9.540 BB    0.2061  387.82751   28.25919   3.9571
```

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=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.410 BB    0.1869 3824.94849  312.24997  50.3719
   2  20.050 BB    0.4436 3768.46826  131.80142  49.6281
```
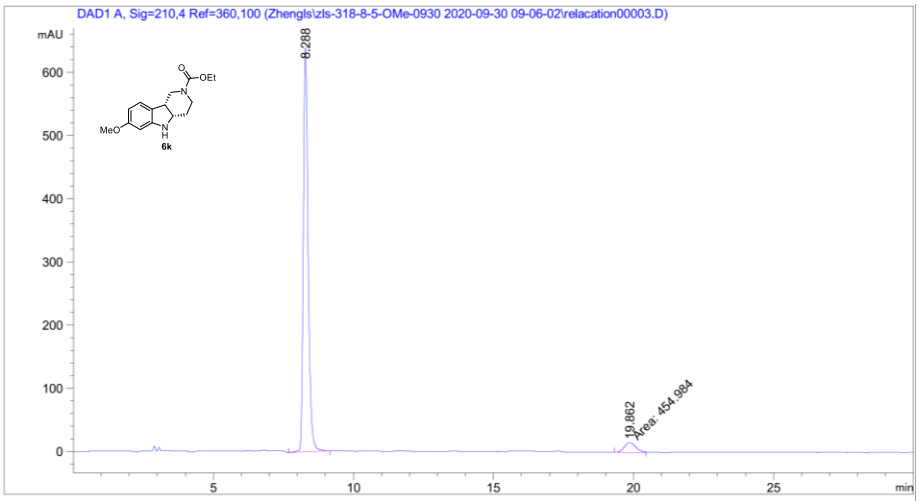
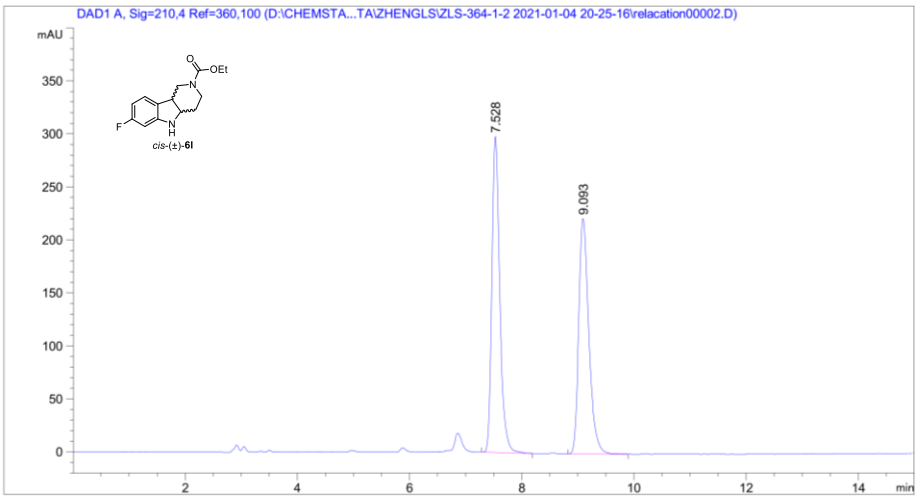
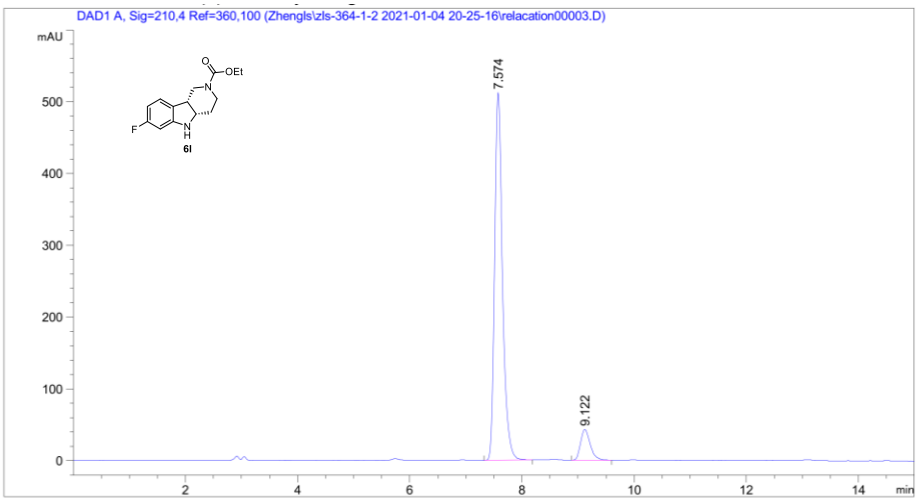




```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.288 BB    0.1831 7621.13818  639.41547  94.3663
   2  19.862 MM    0.4797  454.98428   15.80853   5.6337
```




```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.528 BB    0.1470 2886.17676  298.04651  51.0999
   2   9.093 BB    0.1890 2761.92651  222.24333  48.9001
```

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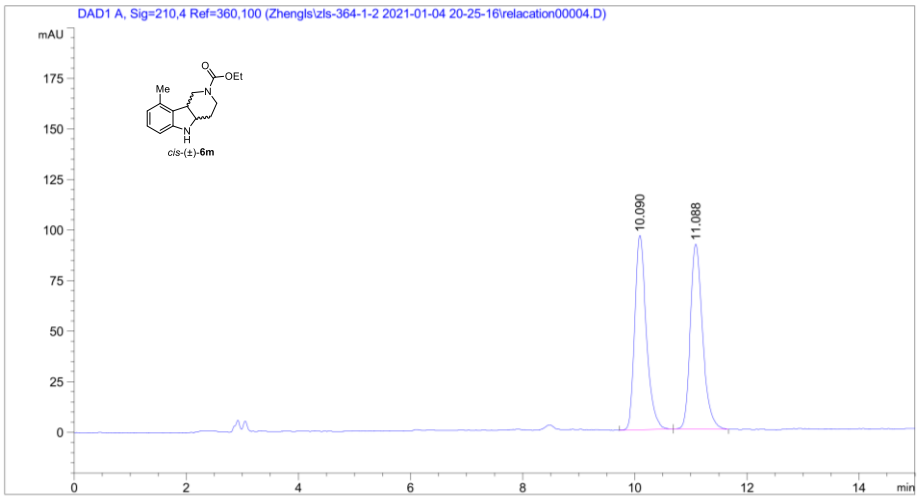
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.574 BB    0.1483 5011.94727  511.79453  90.7561
   2   9.122 BB    0.1811  510.48785   42.80688   9.2439
```

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=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.090 BB    0.2194 1379.77441   96.15178  49.7651
   2  11.088 BB    0.2316 1392.80249   91.51515  50.2349
```

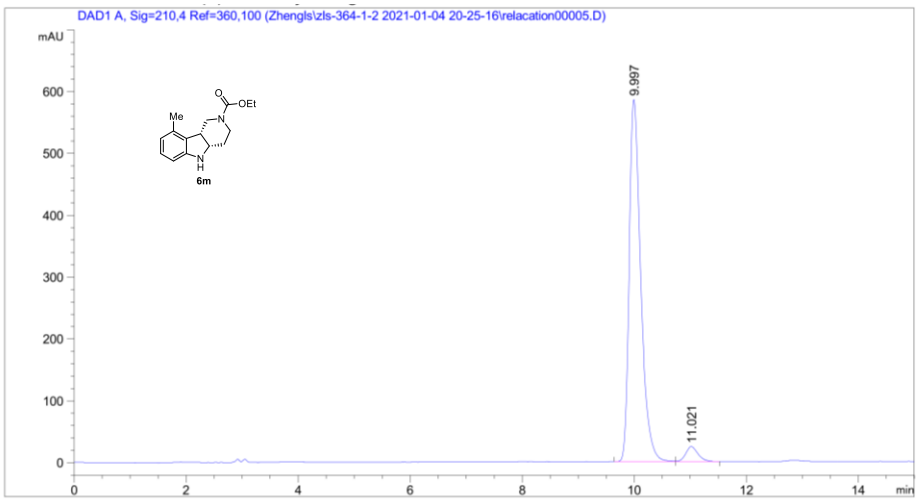


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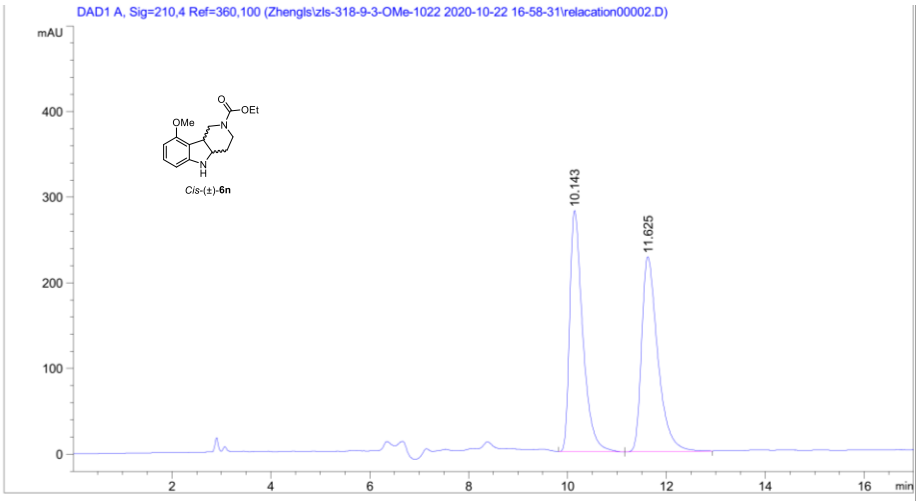
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   9.997 BV    0.2166 8360.83105  585.64514  95.6871
   2  11.021 VB    0.2359  376.84717   24.43579   4.3129
```

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==================================================================
                    Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.143 BB    0.2761 5170.24756  281.67209  50.0186
   2  11.625 BB    0.3406 5166.40137  227.80244  49.9814
```

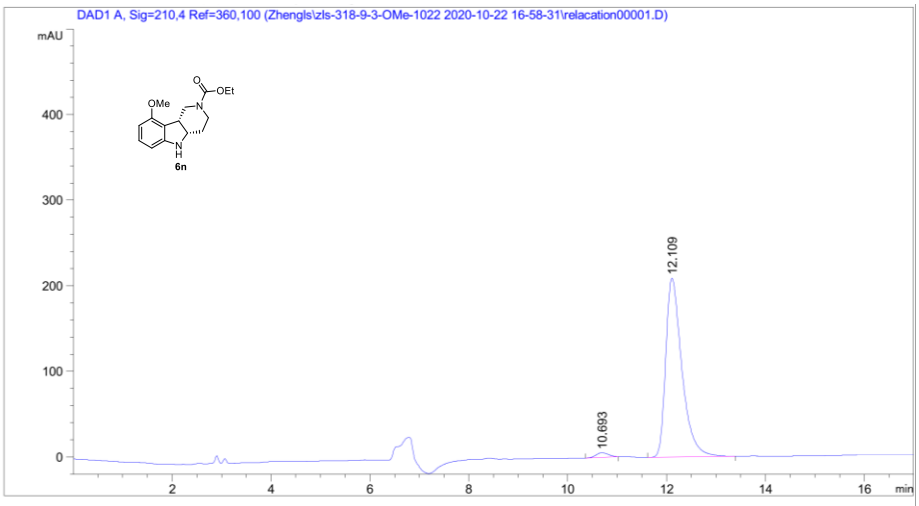


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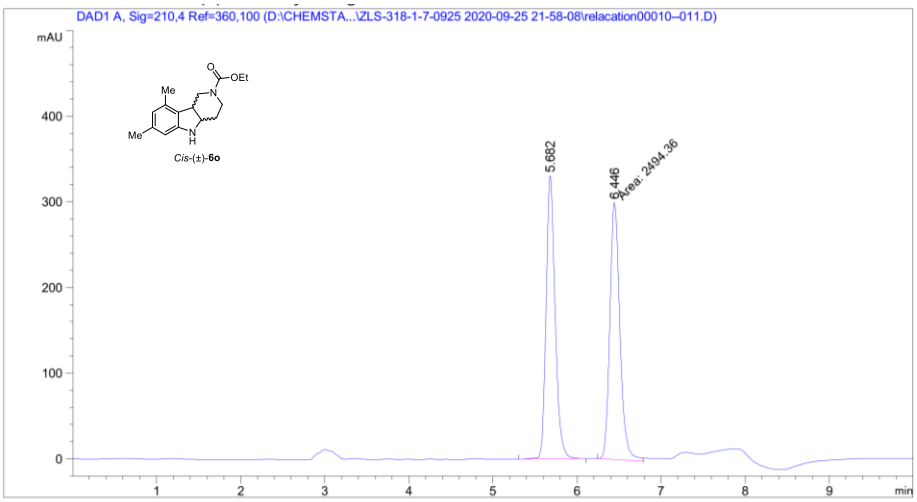
==================================================================
                    Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.693 BB    0.2670   90.52303    5.30674   1.8720
   2  12.109 BB    0.3405 4745.00830  209.25792  98.1280
```

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=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   5.682 BB    0.1147 2457.88428  330.79205  49.6317
   2   6.446 MF    0.1385 2494.35889  300.10770  50.3683
```
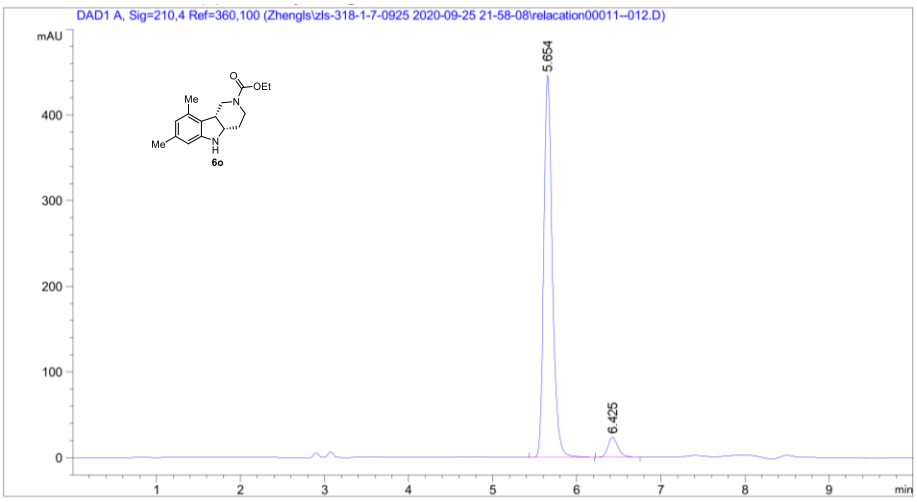
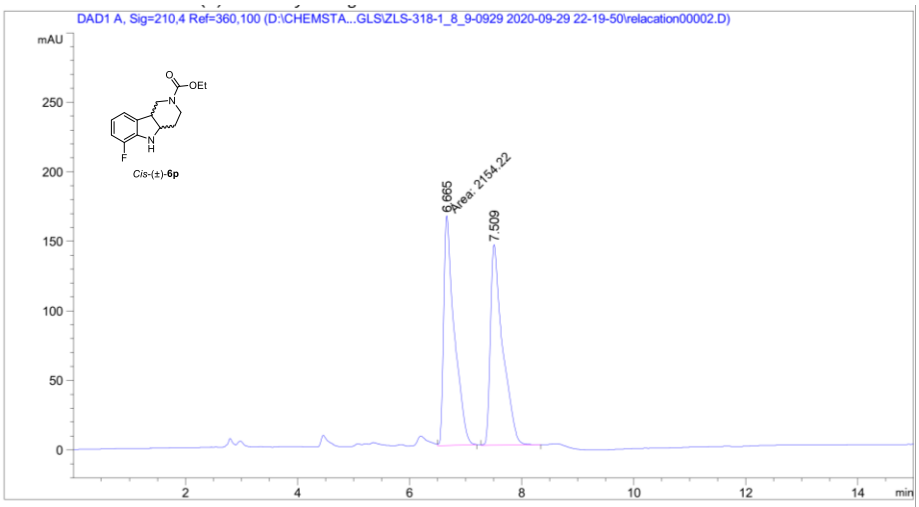




```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   5.654 BB    0.1083 3145.87134  446.07233  94.2446
   2   6.425 BB    0.1258  192.11450   23.38938   5.7554
```

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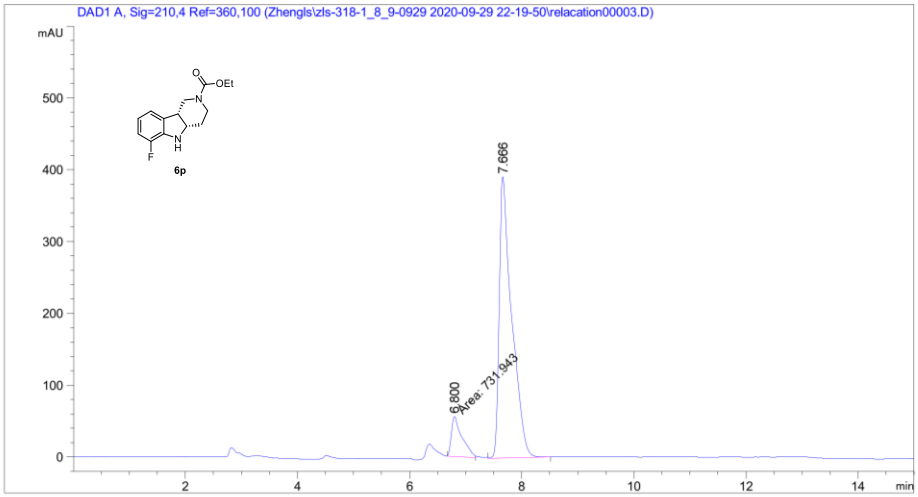
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.665 MM    0.2171 2154.21509  165.37106  49.7189
   2   7.509 VB    0.2104 2178.57349  144.10515  50.2811
```

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=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.800 MM    0.2193  731.94348   55.63153  10.6925
   2   7.666 VB    0.2180 6113.41797  391.89603  89.3075
```

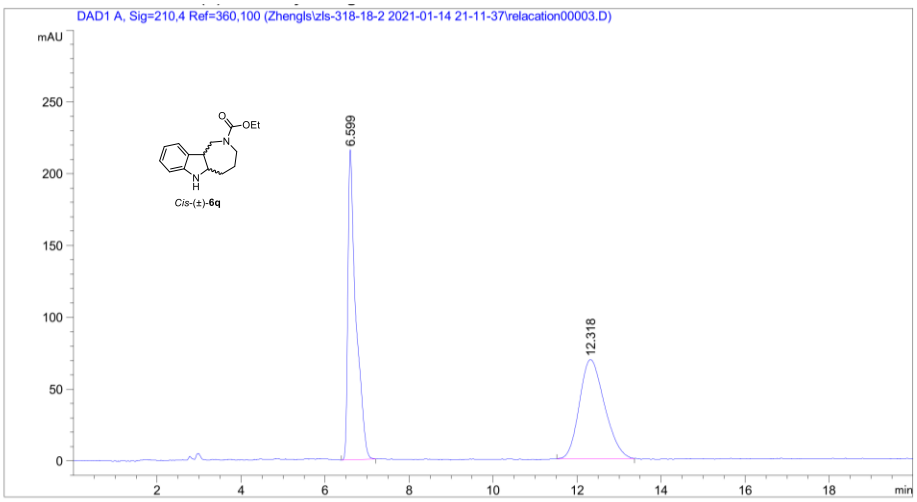


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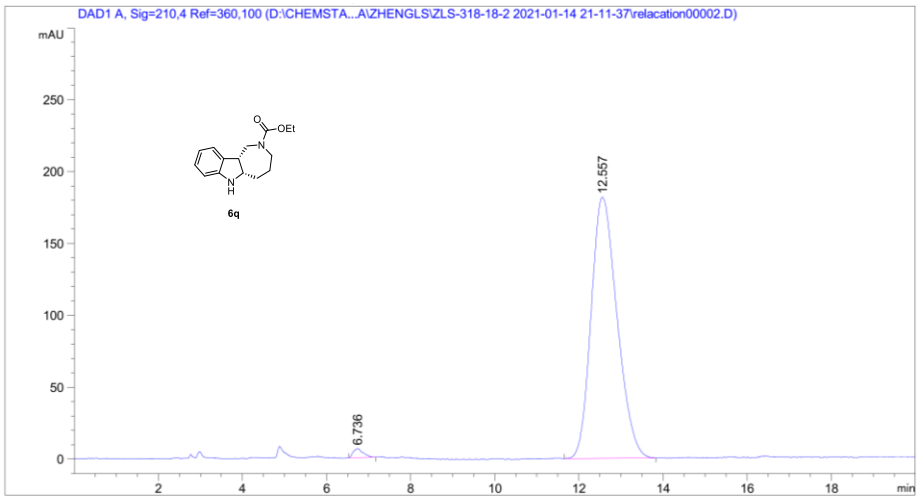
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.599 BB    0.1877 2880.95923  215.87976  50.1722
   2  12.318 BB    0.5760 2861.18213   68.96182  49.8278
```

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=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.736 BV R  0.2166  101.48912    6.34399   1.2892
   2  12.557 BV R  0.6251 7770.65674  181.65631  98.7108
```

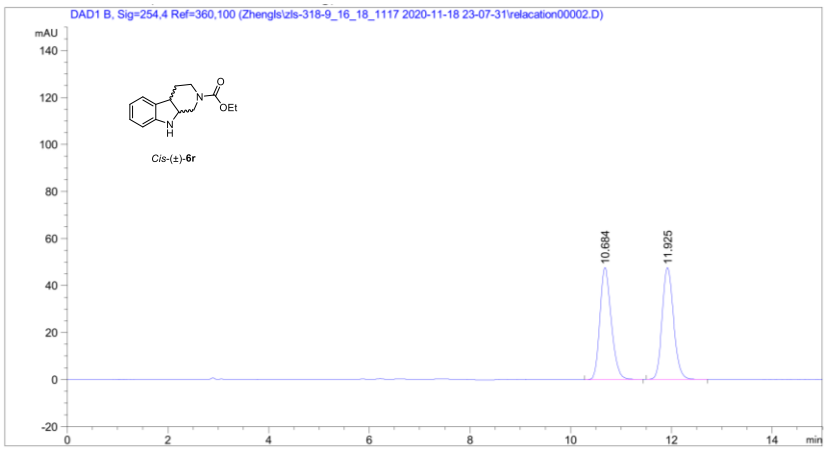


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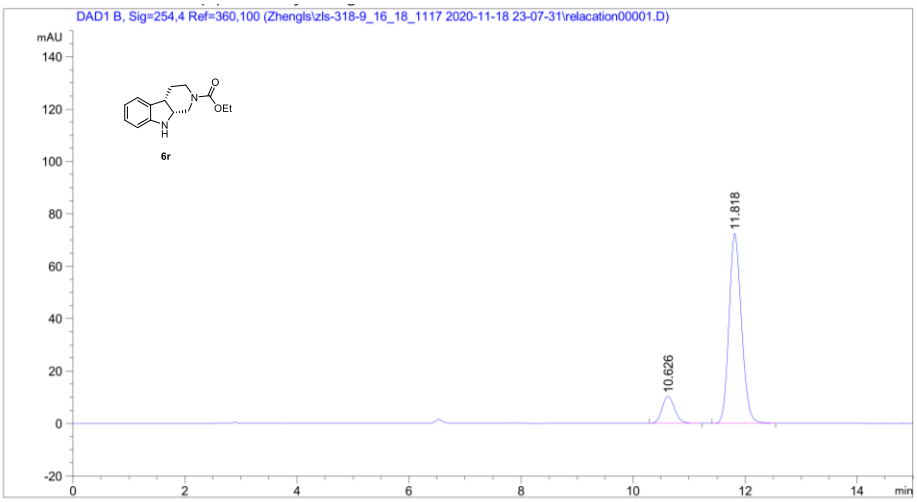
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.684 BB    0.2427  745.30450   47.60540  49.9376
   2  11.925 BB    0.2435  747.16589   47.50566  50.0624
```

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=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.626 BB    0.2370  157.53870   10.27008  12.3351
   2  11.818 BB    0.2404 1119.62085   72.39935  87.6649
```
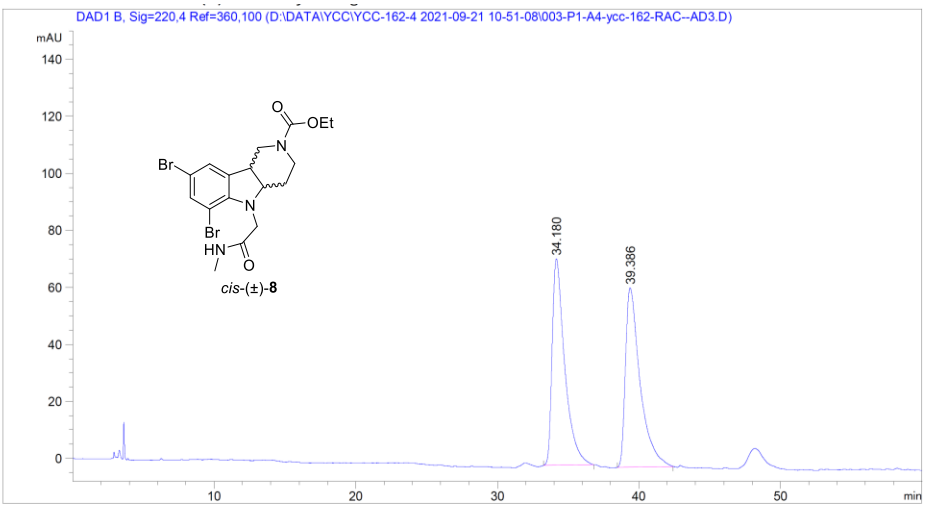
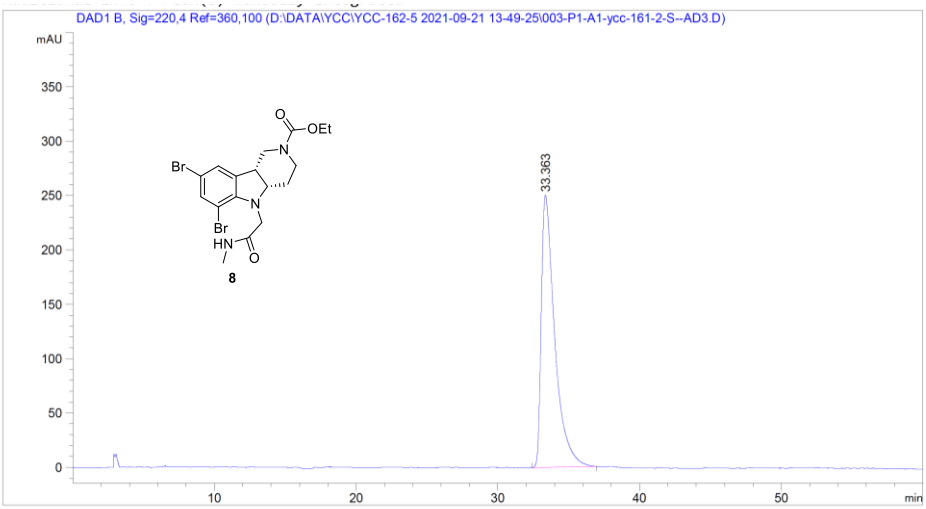




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  34.180 BB    0.7498 4476.57568   72.45246  49.7472
   2  39.386 BB    0.8420 4522.06592   62.91801  50.2528
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=220,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  33.363 BB    0.9014 1.65043e4   250.25591 100.0000
```

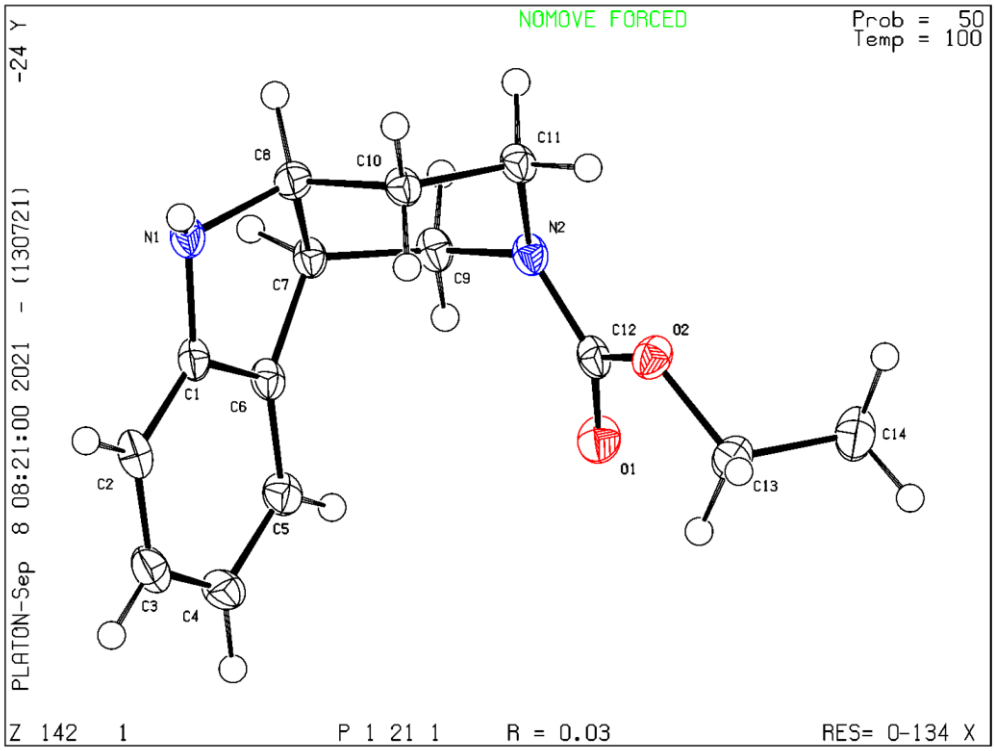
XI. X-Ray Data of Compound 6a (CCDC 2108430)

checkCIF/PLATON report
Structure factors have been supplied for datablock(s) 1
THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR
PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.
No syntax errors found. CIF dictionary Interpreting this report
Datablock: 1
Bond precision: C-C = 0.0028 A Wavelength=1.54178
Cell: a=8.5260(7) b=7.7633(6) c=9.5887(8)
alpha=90 beta=98.910(3) gamma=90
Temperature: 100 K
Calculated Reported
Volume 627.02(9) 627.02(9)
Space group P 21 P 1 21 1
Hall group P 2yb P 2yb
Moiety formula C14 H18 N2 O2 C14 H18 N2 O2
Sum formula C14 H18 N2 O2 C14 H18 N2 O2
Mr 246.30 246.30
Dx,g cm-3 1.305 1.305
Z 2 2
Mu (mm-1) 0.710 0.710
F000 264.0 264.0
F000’ 264.78
h,k,lmax 10,9,11 10,9,11
Nref 2506[1350] 2463
Tmin,Tmax 0.912,0.931 0.469,0.754
Tmin’ 0.912
Correction method= # Reported T Limits: Tmin=0.469 Tmax=0.754
AbsCorr = MULTI-SCAN
Data completeness= 1.82/0.98 Theta(max)= 72.625
R(reflections)= 0.0331(2445) wR2(reflections)=
0.0859(2463)
S = 1.069 Npar= 168
The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.
Alert level G
PLAT791_ALERT_4_G Model has Chirality at C7 (Sohnke SpGr) R Verify
PLAT791_ALERT_4_G Model has Chirality at C8 (Sohnke SpGr) S Verify
PLAT912_ALERT_4_G Missing # of FCF Reflections Above STh/L= 0.600 11 Note
PLAT961_ALERT_5_G Dataset Contains no Negative Intensities ..... Please Check

PLAT978_ALERT_2_G Number C-C Bonds with Positive Residual Density. 6 Info
0 ALERT level A = Most likely a serious problem - resolve or explain
0 ALERT level B = A potentially serious problem, consider carefully
0 ALERT level C = Check. Ensure it is not caused by an omission or oversight
5 ALERT level G = General information/check it is not something unexpected
0 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
1 ALERT type 2 Indicator that the structure model may be wrong or deficient
0 ALERT type 3 Indicator that the structure quality may be low
3 ALERT type 4 Improvement, methodology, query or suggestion
1 ALERT type 5 Informative message, check

PLATON version of 13/07/2021; check.def file version of 13/07/2021

Datablock 1 - ellipsoid plot



XII. References

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