

Intramolecular Buchwald-Hartwig N-Arylation of Bicyclic Hydrazines: Practical Access to Spiro[indoline-2,3'-piperidines]

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List of abbreviations

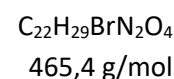
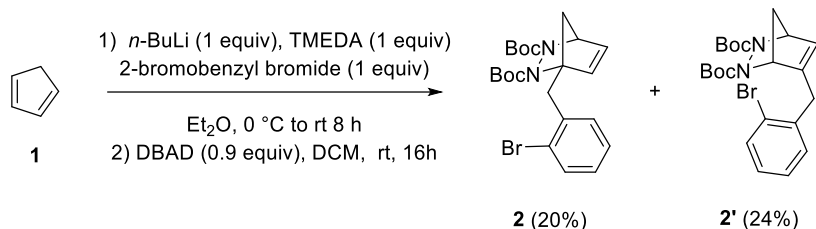
AcOH	Acetic acid
Boc	Tert-Butyl carbamate
Boc ₂ O	Dicarbonate de di-tert-butyle
DABD	di-tert-Butyl azodicarboxylate
DCM	Dichloromethane
DMSO	Dimethyl sulfoxide
ESI	Electrospray ionization
Et ₂ O	Diethyl ether
Et ₃ N	Triethylamine
EtOAc	Ethyl acetate
HPLC	High pressure liquid chromatography
HRMS	High resolution mass spectrometry
IR	Infrared
MeOH	Methanol
NaO ^t Bu	Sodium tert-butoxide
<i>n</i> BuLi	<i>n</i> -Butyllithium
NMO	N-Methylmorpholine N-oxide
NMR	Nuclear magnetic resonance
r.t.	Room temperature
STAB	Sodium triacetoxyborohydride
THF	tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	Tetramethyl ethylenediamine
UV	Ultraviolet

General Remarks

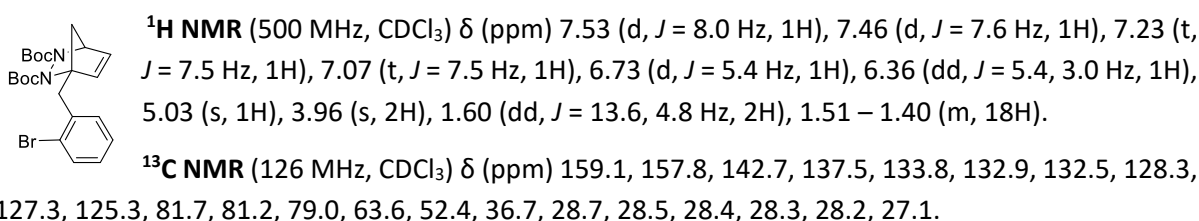
All reactions were carried out under inert atmosphere in oven-dried glassware, using dry solvents unless otherwise specified. Anhydrous solvents were bought from Merck Chemicals. Commercially available chemicals were purchased from Acros, Sigma-Aldrich, Alfa Aesar, VWR, StremChemicals, Enamine or Fluorochem and used as received. Analytical thin layer chromatography (TLC) was performed on silica gel plates (Merck 60F254) visualized with a UV lamp (254 nm) or permanganate, phosphomobyliden and ninhydrin stain solutions, followed by heating. Flash chromatography was performed on silica gel (60-230 mesh) unless otherwise stated. Organic extracts were dried over anhydrous MgSO₄. NMR spectra (¹H and ¹³C{¹H}) were recorded on Bruker Avancell 500 spectrometer, at 500 MHz (H value) in CDCl₃, DMSO-*d*₆, CD₃OD or D₂O. Spectra were referenced to residual non-deuterated solvent signal (chloroform: 7.26 ppm, ¹H; 77.0 ppm, ¹³C{¹H}. DMSO-*d*₆: 2.50 ppm, ¹H; 39.52 ppm, ¹³C{¹H}. CD₃OD: 3.31 ppm, ¹H; 49.00 ppm, ¹³C{¹H}. D₂O: 4.79 ppm, ¹H). Chemical shifts are reported in ppm, multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), and m (multiplet or overlap of nonequivalent resonances), dd (doublet of doublet), td (triplet of doublet), and br (broad signal). Coupling constants, *J*, are reported in hertz (Hz). All NMR spectra were obtained at 300K unless otherwise specified. IR spectra were obtained using a spectrum one FT-IR spectrometer (Perkin Elmer). High Resolution mass spectra were recorded on a ThermoFischer Exactive Orbitrap spectrometer. HPLC analyses were performed on a Shimadzu chromatograph equipped with a diode array UV/VIS detector.

Synthetic procedures and characterization data

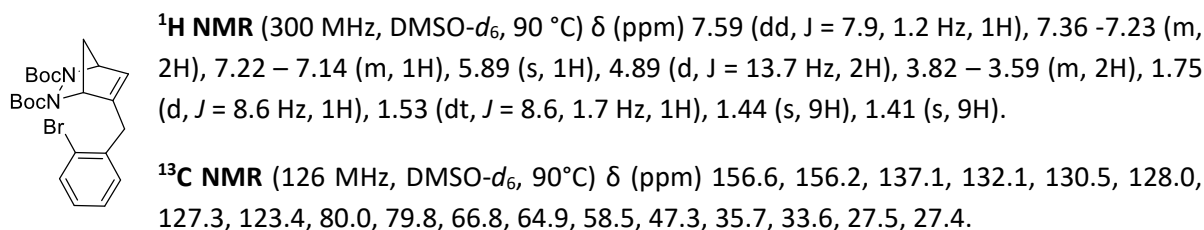
Synthesis of di-tert-Butyl 1-(2-bromobenzyl)-2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate



To a solution of freshly distilled cyclopentadiene (0.05 mL, 0.59 mmol, 1.0 eq.) and TMEDA (0.09 mL, 0.59 mmol, 1.0 eq.) in ether (2 mL) was added dropwise *n*-BuLi (0.28 mL, 0.59 mmol, 1.0 eq, 2.15 M in hexane) at 0 °C. The mixture was stirred for 6h at r.t. then cooled down to 0 °C. 2-Bromobenzyl bromide (152 mg, 0.59 mmol, 1.0 eq.) dissolved in ether (1 mL) was added and the resulting solution was stirred at r.t. for 2h. The reaction mixture was then quenched with a saturated NH₄Cl solution. The aqueous phase was extracted with DCM (3x). The combined organic phases were dried over MgSO₄, filtered, and concentrated under reduced pressure at r.t. The residue was dissolved in DCM (1 mL) and DBAD (119 mg, 0.52 mmol, 0.9 eq.) was added. The resulting mixture was stirred overnight at r.t., and then concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (eluent: cyclohexane/EtOAc, 95/5 to 92/8) to afford **2** (56 mg, 0.12 mmol, 20 %) and **2'** (67 mg, 0.14 mmol, 24 %) as white amorphous solids. This procedure was reproduced several times and successfully scaled up to 5 g of starting material.

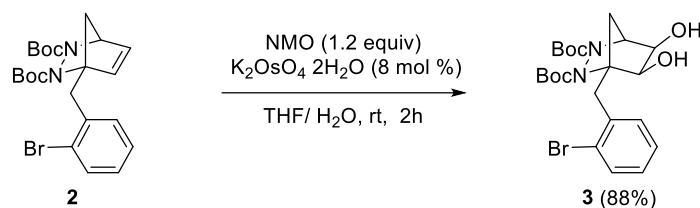


HRMS (ESI+-Orbitrap) *m/z*: [M+H]⁺ Calcd for C₂₂H₃₀N₂O₄Br 465.1383, found 465.1382.



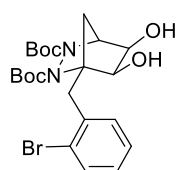
HRMS (ESI+-Orbitrap) *m/z*: [M+H]⁺ Calcd for C₂₂H₃₀N₂O₄Br 465.1383, found 465.1379.

Synthesis of di-tert-Butyl 1-(2-bromobenzyl)-5,6-dihydroxy-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate



$\text{C}_{22}\text{H}_{31}\text{BrN}_2\text{O}_6$
499,4 g/mol

To a solution of **2** (536 mg, 1.15 mmol, 1.0 eq.) in THF (10 mL) were added NMO (162 mg, 1.36 mmol, 1.2 eq.) in water (1 mL), and $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$ (3 mg, 0.001 mmol, 0.008 eq.). The resulting mixture was stirred at r.t. for 2 h. A solution of NaHSO_3 (15 % in water) was then added. The aqueous phase was extracted with ether (3x). The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (eluent: pentane/EtOAc, 8/2 to 7/3) to afford product **3** (500 mg, 1.00 mmol, 87 %) as a white amorphous solid. This procedure was reproduced several times.

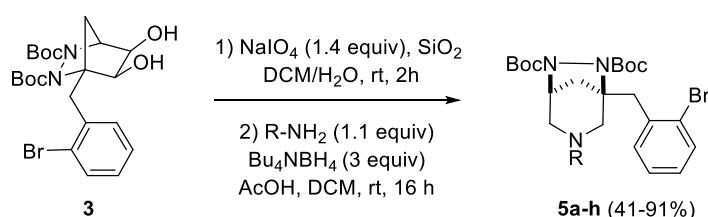


$^1\text{H NMR}$ (500 MHz, CDCl_3) δ (ppm) 7.51 (m, 2H), 7.22 (t, $J = 7.5$ Hz, 1H), 7.07 (t, $J = 7.6$ Hz, 1H), 4.21 – 4.10 (br s, 3H), 4.01 – 3.81 (br s, 1H), 3.70 – 3.61 (br m, 2H), 3.57 (br s, 1H), 2.14 (d, $J = 11.4$ Hz, 1H), 1.53 (s, 9H), 1.31 (s, 9H), 1.12 (d, $J = 11.2$ Hz, 1H).

$^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ (ppm) 157.4 (br s), 156.8 (br s), 137.5, 132.7, 128.1, 127.2, 125.6, 81.8, 75.7 (br s), 72.2, 71.5, 61.6 (br s), 35.6, 32.4, 28.5, 28.0.

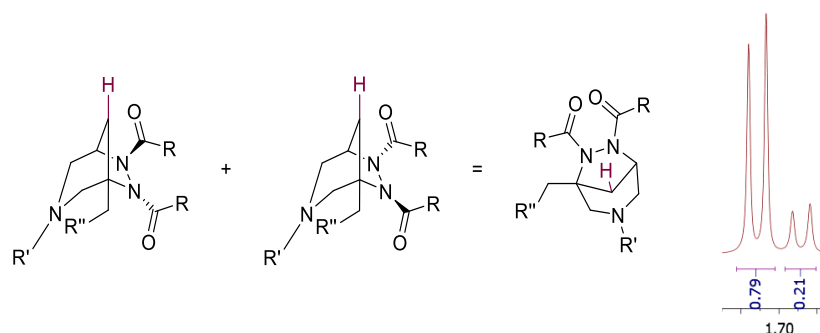
HRMS (ESI+-Orbitrap) m/z : $[\text{M}-\text{H}]^-$ Calcd for $\text{C}_{22}\text{H}_{30}\text{N}_2\text{O}_6\text{Br}$ 497.1293, found 497.1294.

General procedure A: Oxidative cleavage and reductive amination

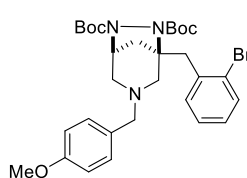


To a vigorously stirred solution of silica (column grade) in DCM (0.03 M), NaIO_4 (0.65 M, 1.4 eq.) in H_2O were added dropwise until formation of a flaky suspension was observed. A solution of diol **3** (1.0 eq.) in DCM (0.03 M) was then added. The mixture was monitored by TLC and kept under stirring until complete consumption of the starting material. The solution was then filtered through a sintered glass funnel packed with Na_2SO_4 and concentrated under reduced pressure. The resulting residue was dissolved in DCM (0.5 M) and the corresponding amine (1.1 eq.) was added followed by the reducing agent (3.0 eq.) and AcOH (1.8 eq.). The mixture was stirred for 16 h at r.t. before being quenched with a saturated aqueous NaHCO_3 solution. The aqueous phase was extracted with DCM (3x). The combined organic layers were dried over MgSO_4 , filtered, and concentrated *in vacuo*. Flash chromatography over silica gel (eluent: cyclohexane/EtOAc) finally afforded the desired product.

Note: Products **5a-h**, obtained after the reductive amination step, have all been isolated as mixture of rotamers or invertomers. Consequently, splitting of the signals are observed in ^1H and ^{13}C NMR spectra.



- *di-tert-Butyl* 1-(2-bromobenzyl)-3-(4-methoxybenzyl)-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate (**5a**)



$\text{C}_{30}\text{H}_{40}\text{BrN}_3\text{O}_5$
602.6 g/mol

Product **5a** was synthesized according to the general procedure A using Silica (1.4 g), NaIO_4 (200 mg, 0.93 mmol, 1.4 eq.), compound **3** (333 mg, 0.67 mmol, 1.0 eq.), 4-methoxybenzylamine (0.1 mL, 0.73 mmol, 1.1 eq.), *tetra*-butylammonium borohydride (515 mg, 2.00 mmol, 3.0 eq.), AcOH (0.1 mL, 1.20 mmol, 1.8 eq.), and DCM (25 mL, 2 mL). Flash chromatography over silica gel (Cyclohexane/EtOAc, 9/1) afforded the title compound (254 mg, 0.42 mmol, 63 %) as a white amorphous solid.

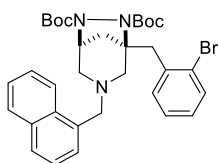
^1H NMR (500 MHz, CDCl_3) δ (ppm) 7.54 – 7.43 (m, 2H), 7.26 – 7.21 (m, 3H), 7.07 (m, 1H), 6.88 – 6.82 (m, 2H), 4.26 (m, 1H), 3.83 – 3.76 (m, 3.7H), 3.74 – 3.63 (m, 1H), 3.61 – 3.55 (m, 1H), 3.48 (m, 1H), 3.38 – 3.33 (m, 0.3H), 3.20 (m, 1H), 3.07 (m, 1H), 2.27 – 2.15 (m, 1H), 2.10 – 2.05 (m, 1H), 1.68 – 1.45 (m, 11H), 1.38 – 1.32 (m, 9H).

^{13}C NMR (126 MHz, CDCl_3) δ (ppm) 158.8, 158.8, 157.8, 155.7, 136.7, 136.4, 133.6, 133.1, 132.5, 132.4, 130.2, 130.1, 129.7, 129.5, 128.3, 128.1, 127.3, 126.2, 126.1, 113.9, 113.6, 81.0, 80.9, 80.8, 80.6, 67.8, 67.7, 61.0, 60.8, 60.5, 58.9, 55.4, 55.1, 54.6, 54.5, 40.4, 39.9, 38.2, 38.0, 28.7, 28.7, 28.2, 28.1, 27.1.

HRMS (ESI+-Orbitrap) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{30}\text{H}_{41}\text{N}_3\text{O}_5\text{Br}$ 602.2224, found 602.2211.

- *di-tert-Butyl* 1-(2-bromobenzyl)-3-(naphthalen-1-ylmethyl)-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate (**5b**)

Product **5b** was synthesized according to the general procedure A using Silica (2.5 g), NaIO_4 (360 mg, 1.68 mmol, 1.4 eq.), compound **3** (600 mg, 1.20 mmol, 1.0 eq.), 1-naphthylmethylamine (0.20 mL, 1.32 mmol, 1.1 eq.), *tetra*-butylammonium borohydride (927 mg, 3.60 mmol, 3.0 eq.), AcOH (0.12 mL, 2.10 mmol, 1.8 eq.), and DCM (40 mL, 4 mL). Flash chromatography over silica gel (eluent: cyclohexane/EtOAc, 9/1) afforded the title compound (588 mg, 0.94 mmol, 79 %) as a white amorphous solid.



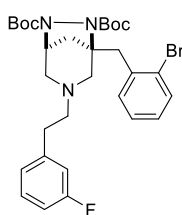
$C_{33}H_{40}BrN_3O_4$
622.6 g/mol

1H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.16 (d, $J = 8.4$ Hz, 0.3H), 8.05 (d, $J = 8.2$ Hz, 0.5H), 7.84 (m, 1.2H), 7.74 (m, 1.5H), 7.57 – 7.42 (m, 5.7H), 7.25 – 7.22 (m, 0.8H), 7.12 – 7.02 (m, 1.2H), 4.58 (m, 0.1H), 4.31 (m, 1H), 4.12 (m, 1H), 3.95 (d, $J = 13.5$ Hz, 0.4H), 3.85 (d, $J = 14.0$ Hz, 0.6H), 3.75 (dd, $J = 10.4$, 1.3 Hz, 0.6H), 3.56 (d, $J = 14.2$ Hz, 0.4H), 3.44 (t, $J = 9.8$ Hz, 0.4H), 3.26 (m, 1.8H), 2.40 (d, $J = 10.5$ Hz, 0.6H), 2.33 (d, $J = 10.6$ Hz, 0.4H), 2.25 (d, $J = 10.9$ Hz, 0.4H), 2.19 – 2.13 (m, 0.6H), 1.71 (d, $J = 11.3$ Hz, 1H), 1.61 – 1.48 (m, 7.0H), 1.42 – 1.24 (m, 12.7H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 159.7, 159.5, 156.9, 138.5, 138.3, 135.8, 135.7, 135.6, 135.4, 134.9, 134.8, 134.4, 134.3, 134.2, 133.9, 133.1, 132.4, 131.8, 131.6, 131.3, 130.7, 130.3, 130.1, 130.0, 129.7, 129.3, 129.2, 129.2, 128.4, 128.1, 128.0, 127.9, 127.6, 127.4, 127.3, 127.2, 126.3, 125.2, 123.6, 82.9, 82.8, 82.7, 82.6, 69.6, 69.1, 63.0, 61.8, 61.2, 59.5, 59.2, 58.0, 57.3, 56.5, 55.6, 42.3, 41.9, 40.1, 39.9, 30.4, 30.3, 30.1, 29.9, 28.9.

HRMS (ESI+-Orbitrap) m/z : $[M+H]^+$ Calcd for $C_{33}H_{41}N_3O_4Br$ 622.2275, found 622.2261.

- *di-tert-Butyl 1-(2-bromobenzyl)-3-(3-Fluorophenethyl)-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate (5c)*



$C_{30}H_{39}BrFN_3O_4$
604.6 g/mol

Product **5c** was synthesized according to the general procedure A using Silica (2.1 g), $NaIO_4$ (300 mg, 1.40 mmol, 1.4 eq.), compound **3** (500 mg, 1.00 mmol, 1.0 eq.), fluorophenethylamine (0.14 mL, 1.10 mmol, 1.1 eq.), STAB (637 mg, 3.00 mmol, 3.0 eq.), AcOH (0.1 mL, 1.80 mmol, 1.8 eq.), and DCM (30 mL, 30 mL, 10 mL). Flash chromatography over silica gel (eluent: cyclohexane/EtOAc, 8/2) afforded the title compound (548 mg, 0.91 mmol, 91 %) as a white amorphous solid.

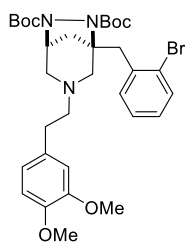
1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.54 – 7.48 (m, 1H), 7.46 (t, $J = 8.0$ Hz, 1H), 7.24 (m, 2H), 7.07 (q, $J = 8.4$ Hz, 1H), 6.93 (d, $J = 7.6$ Hz, 1H), 6.87 (dd, $J = 15.8$, 9.1 Hz, 2H), 4.32 (d, $J = 3.4$ Hz, 1H), 3.78 (d, $J = 14.1$ Hz, 0.6H), 3.64 (d, $J = 10.2$ Hz, 0.6H), 3.60 (d, $J = 14.2$ Hz, 0.4H), 3.43 (d, $J = 10.4$ Hz, 0.4H), 3.27 – 3.18 (m, 1.4H), 3.14 (d, $J = 8.5$ Hz, 0.6H), 2.81 – 2.73 (m, 2H), 2.73 – 2.64 (m, 2H), 2.35 – 2.23 (m, 1.4H), 2.17 (d, $J = 10.4$ Hz, 0.6H), 1.68 (d, $J = 11.4$ Hz, 1H), 1.60 (s, 4H), 1.54 (s, 6H), 1.37 (s, 3H), 1.36 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 163.1 (d, $J = 245.6$ Hz), 158.0, 157.6, 156.9, 155.7, 143.1 (d, $J = 7.3$ Hz), 142.9 (d, $J = 7.2$ Hz), 136.7, 136.4, 133.6, 133.1, 132.6, 132.4, 130.0 (d, $J = 8.3$ Hz), 130.0 (d, $J = 8.4$ Hz), 128.3, 128.1, 127.3, 127.3, 126.2, 126.1, 124.4 (d, $J = 2.7$ Hz), 124.4 (d, $J = 2.7$ Hz), 115.6 (d, $J = 20.9$ Hz), 113.0 (d, $J = 21.1$ Hz), 81.1, 81.0, 80.8, 80.3, 67.7, 67.4, 60.5, 60.4, 58.8, 58.5, 55.8, 55.6, 54.5, 53.7, 40.4, 40.0, 38.2, 38.1, 33.8, 33.5, 28.8, 28.6, 28.2, 28.1.

^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) –113.6.

HRMS (ESI+-Orbitrap) m/z : $[M+H]^+$ Calcd for $C_{30}H_{40}N_3O_4BrF$ 604.2181, found 604.2174.

- *di-tert-Butyl 1-(2-bromobenzyl)-3-(3,4-dimethoxyphenethyl)-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate (5d)*



$C_{32}H_{44}BrN_3O_6$

646.6 g/mol

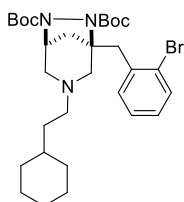
Product **5d** was synthesized according to the general procedure A using Silica (1.4 g), $NaIO_4$ (200 mg, 0.93 mmol, 1.4 eq.), compound **3** (333 mg, 0.67 mmol, 1.0 eq.), 3,4-dimethoxyphenethylamine (0.12 mL, 0.73 mmol, 1.1 eq.), tetrabutylammonium borohydride (515 mg, 2.00 mmol, 3.0 eq.), AcOH (0.1 mL, 1.20 mmol, 1.8 eq.), and DCM (25 mL, 2 mL). Flash chromatography over silica gel (eluent: cyclohexane/EtOAc, 9/1 to 8/2) afforded the title compound (264 mg, 0.40 mmol, 61 %) as a white amorphous solid.

1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.54 – 7.48 (m, 1H), 7.48 – 7.43 (m, 1H), 7.25 – 7.22 (m, 1H), 7.07 (ddd, $J = 9.4, 8.7, 1.7$ Hz, 1H), 6.79 (dd, $J = 6.6, 3.0$ Hz, 1H), 6.69 (ddd, $J = 7.6, 4.6, 1.7$ Hz, 2H), 4.32 (s, 1H), 3.89 – 3.83 (m, 6H), 3.78 (d, $J = 14.1$ Hz, 0.7H), 3.67 – 3.57 (m, 1H), 3.45 (d, $J = 9.3$ Hz, 0.3H), 3.27 – 3.14 (m, 2H), 2.79 – 2.58 (m, 4H), 2.35 – 2.16 (m, 2H), 1.69 (d, $J = 11.3$ Hz, 1H), 1.62 – 1.51 (m, 10H), 1.36 (d, $J = 7.1$ Hz, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 169.9, 158.0, 157.6, 156.8, 155.7, 149.0, 147.4, 136.6, 136.4, 133.6, 133.2, 133.1, 132.5, 132.4, 128.3, 128.1, 127.3, 127.3, 126.1, 120.6, 112.1, 112.0, 111.4, 81.1, 80.9, 80.8, 80.3, 79.3, 67.8, 67.3, 60.3, 59.4, 59.0, 58.5, 56.1, 56.0, 55.5, 54.4, 53.7, 40.4, 39.9, 38.1, 38.0, 33.8, 33.3, 28.7, 28.6, 28.2, 28.1.

HRMS (ESI+-Orbitrap) m/z : $[M+H]^+$ Calcd for $C_{32}H_{45}N_3O_6Br$ 646.2486, found 646.2472.

- *di-tert-Butyl 1-(2-bromobenzyl)-3-(2-cyclohexylethyl)-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate (5e)*



$C_{30}H_{46}N_3O_4Br$

591.6 g/mol

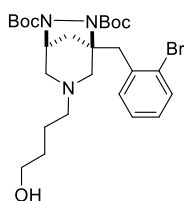
Product **5e** was synthesized according to the general procedure A using Silica (4.2 g), $NaIO_4$ (0.6 g, 2.80 mmol, 1.4 eq.), compound **3** (1.0 g, 2.00 mmol, 1.0 eq.), 2-cyclohexyl-ethylamine (0.31 mL, 2.20 mmol, 1.1 eq.), *tetra*-butylammonium borohydride (1.6 g, 6.00 mmol, 3.0 eq.), AcOH (0.21 mL, 3.60 mmol, 1.8 eq.), and DCM (66 mL, 6 mL). Flash chromatography over silica gel (eluent: cyclohexane/EtOAc, 9/1 to 8/2) afforded the title compound (490 mg, 0.83 mmol, 41 %) as a white amorphous solid.

1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.53 – 7.48 (m, 1H), 7.47 – 7.43 (m, 1H), 7.26 – 7.20 (m, 1H), 7.10 – 7.04 (m, 1H), 4.28 (d, $J = 3.5$ Hz, 1H), 3.76 (d, $J = 14.1$ Hz, 0.7H), 3.61 – 3.50 (m, 1H), 3.35 (dd, $J = 10.5, 1.5$ Hz, 0.3H), 3.25 – 3.14 (m, 1.3H), 3.08 (dd, $J = 10.9, 3.1$ Hz, 0.7H), 2.48 – 2.34 (m, 2H), 2.19 – 2.02 (m, 2H), 1.71 – 1.45 (m, 15H), 1.39 – 1.30 (m, 11H), 1.25 – 1.12 (m, 4H), 0.94 – 0.81 (dd, $J = 22.3, 11.0$ Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 158.0, 157.6, 157.0, 155.6, 136.8, 136.5, 133.6, 133.1, 132.5, 132.3, 128.2, 128.0, 127.3, 127.2, 126.2, 126.1, 80.9, 80.8, 80.7, 80.2, 67.8, 67.3, 60.5, 58.8, 56.0, 55.7, 55.2, 55.0, 54.5, 53.8, 40.5, 40.0, 38.2, 38.0, 36.5, 36.2, 34.7, 34.6, 33.7, 33.7, 33.6, 33.6, 28.7, 28.6, 28.2, 28.1, 27.1, 26.7, 26.4.

HRMS (ESI+-Orbitrap) m/z : $[M+H]^+$ Calcd for $C_{30}H_{47}N_3O_4Br$ 579.2540, found 592.2744.

- *di-tert-Butyl 1-(2-bromobenzyl)-3-(4-hydroxybutyl)-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate (5f)*



$C_{26}H_{40}BrN_3O_5$
554.5 g/mol

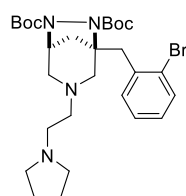
Product **5f** was synthesized according to the general procedure B using Silica (1.5 g), $NaIO_4$ (210 mg, 0.98 mmol, 1.4 eq.), compound **3** (350 mg, 0.70 mmol, 1.0 eq.), butanolamine (0.07 mL, 0.77 mmol, 1.1 eq.), *tetra*-butylammonium borohydride (541 mg, 2.10 mmol, 3.0 eq.), AcOH (0.1 mL, 1.26 mmol, 1.8 eq.), and DCM (25 mL, 2 mL). Flash chromatography over silica gel (eluent: cyclohexane/EtOAc, 7/3) afforded the title compound (304 mg, 0.55 mmol, 78 %) as a white amorphous solid.

1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.54 – 7.47 (m, 1H), 7.44 (m, 1H), 7.25 – 7.21 (m, 1H), 7.10 – 7.03 (m, 1H), 4.29 (s, 1H), 3.77 (d, $J = 14.1$ Hz, 0.7H), 3.65 – 3.54 (m, 3H), 3.33 – 3.07 (m, 4.3H), 2.47 – 2.41 (m, 2H), 2.16 (m, 1H), 2.11 – 2.03 (m, 1H), 1.68 – 1.63 (m, 3H), 1.59 – 1.51 (m, 12H), 1.34 (d, $J = 6.0$ Hz, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 157.8, 155.8, 136.7, 136.4, 133.5, 133.0, 132.5, 132.4, 128.3, 128.1, 127.3, 126.2, 126.1, 81.2, 80.9, 80.9, 80.5, 67.6, 67.5, 63.0, 62.9, 61.2, 60.6, 58.7, 56.9, 56.7, 55.5, 55.1, 54.6, 53.6, 40.4, 40.1, 38.2, 38.0, 30.6, 30.4, 28.8, 28.6, 28.2, 28.1, 23.2, 23.1.

HRMS (ESI+-Orbitrap) m/z : $[M+H]^+$ Calcd for $C_{30}H_{41}N_3O_5Br$ 554.2224, found 554.2211.

- *di-tert-Butyl 1-(2-bromobenzyl)-3-(2-(pyrrolidin-1-yl)ethyl)-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate (5g)*



$C_{28}H_{43}BrN_4O_4$
579.6 g/mol

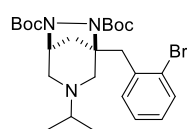
Product **5g** was synthesized according to the general procedure A using Silica (4.2 g), $NaIO_4$ (0.6 g, 2.80 mmol, 1.4 eq.), compound **3** (1.0 g, 2.00 mmol, 1.0 eq.), *N*-(2-aminoethyl)pyrrolidine (0.28 mL, 2.20 mmol, 1.1 eq.), *tetra*butylammonium borohydride (1.55 g, 6.00 mmol, 3.0 eq.), AcOH (0.21 mL, 3.6 mmol, 1.8 eq.), and DCM (66 mL, 8 mL). Flash chromatography over silica gel (eluent: cyclohexane/EtOAc, 8/2 to 7/3) afforded the title compound (499 mg, 0.86 mmol, 43 %) as a white amorphous solid.

1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.51 (t, $J = 8.7$ Hz, 1H), 7.45 – 7.39 (m, 1H), 7.26 – 7.22 (m, 1H), 7.12 – 7.05 (m, 1H), 4.30 (d, $J = 3.5$ Hz, 1H) 3.74 (d, $J = 14.1$ Hz, 0.6H), 3.58 (d, $J = 13.5$ Hz, 1H), 3.40 – 3.05 (m, 4.7H), 2.98 – 2.85 (m, 3.2H), 2.81 – 2.62 (m, 2.4H), 2.37 – 2.29 (m, 1H), 2.28 – 2.09 (m, 3.3H), 1.92 – 1.83 (m, 2H), 1.68 (d, $J = 11.3$ Hz, 1.3H), 1.60 (s, 4.5H), 1.57 – 1.48 (m, 6H), 1.35 (d, $J = 5.1$ Hz, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 169.9, 157.7, 157.5, 156.9, 155.6, 136.4, 136.2, 133.5, 133.0, 132.6, 132.5, 128.3, 128.2, 127.3, 126.2, 126.1, 81.3, 81.1, 81.0, 80.4, 79.3, 67.4, 67.4, 62.4, 62.3, 61.8, 61.7, 61.4, 61.3, 58.6, 56.4, 56.0, 54.6, 53.6, 52.6, 52.1, 40.3, 40.0, 38.1, 37.9, 28.7, 28.6, 28.2, 28.1, 22.9, 22.8, 22.8, 22.7.

HRMS (ESI+-Orbitrap) m/z : $[M+H]^+$ Calcd for $C_{28}H_{44}N_4O_4Br$ 579.2540, found 579.2521.

- *di-tert-Butyl 1-(2-bromobenzyl)-3-isopropyl-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate (5h)*



$C_{25}H_{38}BrN_3O_4$
524.5 g/mol

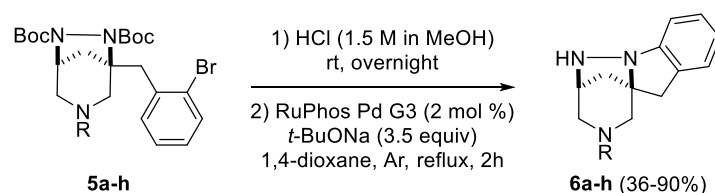
Product **5h** was synthesized according to the general procedure A using Silica (2.5 g), $NaIO_4$ (360 mg, 1.68 mmol, 1.4 eq.), compound **3** (600 mg, 1.20 mmol, 1.0 eq.), isopropyl amine (0.11 mL, 1.32 mmol, 1.1 eq.), tetrabutylammonium borohydride (927 mg, 3.60 mmol, 3.0 eq.), AcOH (0.12 mL, 2.10 mmol, 1.8 eq.), and DCM (40 mL, 4 mL). Flash chromatography over silica gel (eluent: cyclohexane/EtOAc, 95/5 to 9/1) afforded the title compound (269 mg, 0.51 mmol, 43 %) as a white amorphous solid.

1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.53 – 7.42 (m, 2H), 7.26 – 7.21 (m, 1H), 7.10 – 7.03 (m, 1H), 4.30 (t, $J = 3.6$ Hz, 1H), 3.78 (d, $J = 14.1$ Hz, 0.7H), 3.59 (d, $J = 14.2$ Hz, 0.3H), 3.48 (d, $J = 10.4$, 0.7H), 3.27 – 3.14 (m, 1.3H), 3.06 – 3.00 (dd, $J = 10.7$, 3.5 Hz, 1H), 2.86 – 2.73 (m, 1H), 2.41 (d, $J = 10.8$ Hz, 0.3H), 2.36 – 2.28 (m, 1H), 2.24 – 2.15 (m, 0.7H), 1.66 – 1.61 (m, 1H), 1.61 – 1.57 (m, 3H), 1.53 (s, 6H), 1.51 – 1.41 (m, 1H), 1.33 – 1.38 (m, 9H), 1.06 – 0.98 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 157.9, 157.8, 155.6, 136.8, 136.6, 133.6, 133.1, 132.5, 132.3, 128.2, 128.0, 127.3, 127.2, 126.2, 126.1, 81.0, 80.8, 80.7, 80.2, 67.9, 67.5, 55.7, 54.9, 54.6, 53.8, 53.4, 53.2, 40.5, 40.1, 38.3, 38.0, 28.7, 28.6, 28.2, 28.1, 27.1, 19.3, 18.3, 18.1, 18.0.

HRMS (ESI+-Orbitrap) m/z : $[M+H]^+$ Calcd for $C_{25}H_{39}N_3O_4Br$ 524.2118, found 254.2107.

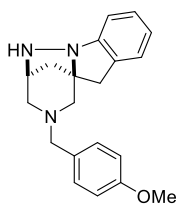
General procedure B: Deprotection and intramolecular Buchwald – Hartwig N-arylation



Substrate **5a-h** (1.0 eq) were dissolved in a 1.5 M solution of HCl in methanol. The resulting mixture was stirred overnight at r.t., and then concentrated under reduced pressure. The residue was dissolved in 1,4-dioxane (0.04 M). NaO^tBu (3.5 eq.) and RuPhos Pd G3 (0.02 eq.) were added, and the resulting solution was stirred for 2h at reflux. The reaction mixture was then cooled back to r.t. and filtered through a pad of Celite® (eluent: DCM/MeOH, 8/2). The filtrate was collected and concentrated *in vacuo*. Flash chromatography over silica gel (eluent: pentane/EtOAc, 9/1 to 8/2) finally afforded products **6a-h**.

- *4-(4-Methoxybenzyl)-2,3,4,5-tetrahydro-1H,6H-2,5a-methano[1,2,5]triazepino[1,7-a]indole (6a)*

Product **6a** was synthesized according to the general procedure B using HCl (1.5 M, 5 mL), compound **5a** (311 mg, 0.52 mmol, 1.0 eq.), 1,4-dioxane (13 mL), NaO^tBu (175 mg, 1.82 mmol, 3.5 eq.), and RuPhos Pd G3 (9 mg, 0.01 mmol, 0.02 eq.). Flash chromatography over silica gel (eluent: pentane/EtOAc, 8/2) afforded the title compound (139 mg, 0.43 mmol, 83 %) as a colorless oil.



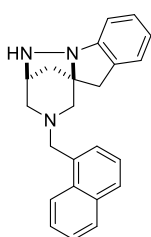
$C_{20}H_{23}N_3O$
321.4 g/mol

1H NMR (500 MHz, $CDCl_3$) δ 7.52 (dd, $J = 8.0, 0.9$ Hz, 1H), 7.46 (dd, $J = 7.7, 1.6$ Hz, 1H), 7.25 – 7.20 (m, 1H), 7.12 (d, $J = 8.5$ Hz, 2H), 7.07 (td, $J = 7.8, 1.6$ Hz, 1H), 6.84 – 6.80 (m, 2H), 4.94 – 4.89 (m, 1H), 3.82 – 3.77 (m, 4H), 3.50 – 3.45 (m, 3H), 2.92 (dd, $J = 11.0, 3.6$ Hz, 1H), 2.85 (dd, $J = 11.1, 1.9$ Hz, 1H), 2.07 (dd, $J = 11.0, 1.0$ Hz, 1H), 1.95 (d, $J = 11.2$ Hz, 1H), 1.36 (ddd, $J = 9.6, 4.9, 3.0$ Hz, 1H), 1.27 – 1.23 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9, 136.4, 132.8, 132.7, 130.1, 129.4, 128.5, 127.7, 125.7, 113.8, 85.2, 78.2, 60.0, 55.4, 53.9, 48.3, 39.4, 38.2.

HRMS (ESI+-Orbitrap) m/z : $[M+H]^+$ Calcd for $C_{20}H_{24}N_3O$ 322.1914, found 322.1905.

- 4-(Naphthalen-1-ylmethyl)-2,3,4,5-tetrahydro-1H,6H-2,5a-methano[1,2,5]triazepino[1,7-a]indole (**6b**)



$C_{23}H_{23}N_3$
341.5 g/mol

Product **6b** was synthesized according to the general procedure B using HCl (1.5 M, 5 mL), compound **5b** (300 mg, 0.48 mmol, 1.0 eq.), 1,4-dioxane (12 mL), NaO^tBu (162 mg, 1.68 mmol, 3.5 eq.), and RuPhos Pd G3 (8 mg, 0.01 mmol, 0.02 eq.). Flash chromatography over silica gel (eluent: pentane/EtOAc, 9/1 to 8/2 to DCM/MeOH 10/0 to 9/1) afforded the title compound (106 mg, 0.31 mmol, 65 %) as a white amorphous.

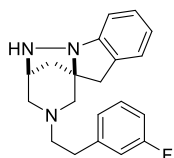
1H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.08 (d, $J = 8.2$ Hz, 1H), 7.82 (d, $J = 8.9$ Hz, 1H), 7.76 (d, $J = 7.7$ Hz, 1H), 7.54 – 7.41 (m, 4H), 7.40 – 7.33 (m, 2H), 7.20 (d, $J = 7.4$ Hz, 1H), 7.06 (td, $J = 7.6, 1.4$ Hz, 1H), 4.90 (t, $J = 4.6$ Hz, 1H), 3.96 (s, 2H), 3.78 (d, $J = 14.2$ Hz, 1H), 3.48 (d, $J = 14.2$ Hz, 1H), 2.97 (dd, $J = 11.2, 3.6$ Hz, 1H), 2.92 (dd, $J = 11.1, 1.7$ Hz, 1H), 2.18 (d, $J = 11.1$ Hz, 1H), 2.05 (d, $J = 11.3$ Hz, 1H), 1.38 (dd, $J = 11.4, 5.5$ Hz, 1H), 1.32 (d, $J = 11.4$ Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 136.4, 133.9, 133.1, 132.8, 132.7, 132.5, 128.5, 128.4, 128.3, 127.7, 127.2, 126.2, 125.9, 125.7, 125.2, 124.5, 85.2, 78.1, 59.1, 54.4, 48.7, 39.4, 38.1.

HRMS (ESI+-Orbitrap) m/z : $[M+H]^+$ Calcd for $C_{23}H_{24}N_3$ 342.1965, found 342.1956.

Note: A diazo derivative (50 mg, 0.12 mmol, 25 %) arising from the oxidation of hydrazine **5b** was isolated as a by-product after the reaction.

- 4-(3-Fluorophenethyl)-2,3,4,5-tetrahydro-1H,6H-2,5a-methano[1,2,5]triazepino[1,7-a]indole (**6c**)



$C_{20}H_{22}FN_3$
323.4 g/mol

Product **6c** was synthesized according to the general procedure B using HCl (1.5 M, 2 mL), compound **5c** (500 mg, 0.83 mmol, 1.0 eq.), 1,4-dioxane (20 mL), NaO^tBu (275 mg, 2.86 mmol, 3.5 eq.), and RuPhos Pd G3 (14 mg, 0.02 mmol, 0.02 eq.). Flash chromatography over silica gel (eluent: pentane/EtOAc, 9/1 to 8/2) afforded the desired product (230 mg, 0.71 mmol, 87 %) as a colorless oil.

1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.54 (dd, $J = 8.0, 1.0$ Hz, 1H), 7.49 (dt, $J = 8.1, 4.1$ Hz, 1H), 7.25 – 7.17 (m, 2H), 7.09 (td, $J = 7.8, 1.7$ Hz, 1H), 6.92 – 6.82 (m, 3H), 4.97 (dd, $J = 10.5, 5.9$ Hz, 1H), 3.81 (d, $J = 14.2$ Hz, 1H), 3.54 (d, $J = 14.0$ Hz, 1H), 3.07 – 2.99 (m, 1H), 2.94 (dd, $J = 11.0, 1.9$ Hz, 1H), 2.72 – 2.62 (m, 2H), 2.64 – 2.54 (m, 2H), 2.12 (dd, $J = 11.0, 1.1$ Hz, 1H), 2.06 – 2.01 (m, 1H), 1.41 (ddd, $J = 21.4, 10.7, 6.6$ Hz, 1H), 1.32 – 1.21 (m, 1H).

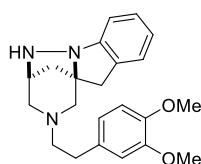
¹³C NMR (126 MHz, CDCl₃) δ (ppm) 163.0 (d, *J* = 245.4 Hz), 142.8 (d, *J* = 7.2 Hz), 136.4, 132.9, 132.7, 129.9 (d, *J* = 8.3 Hz), 128.6, 127.7, 125.7, 124.4, 115.6 (d, *J* = 20.9 Hz), 113.1 (d, *J* = 21.0 Hz), 85.2, 78.1, 58.0, 54.0, 48.5, 39.5, 38.2, 33.0.

¹⁹F NMR (471 MHz, CDCl₃) δ (ppm) –113.7 (dd, *J* = 15.2, 9.1 Hz).

HRMS (ESI+-Orbitrap) *m/z*: [M+H]⁺ Calcd for C₂₀H₂₃N₃F 324.1871, found 324.1862.

- 4-(4-Methoxyphenethyl)-2,3,4,5-tetrahydro-1*H*,6*H*-2,5*a*-methano[1,2,5]triazepino[1,7-*a*]indole (**6d**)

Product **6d** was synthesized according to the general procedure B using HCl (1.5 M, 5 mL), compound **5d** (300 mg, 0.46 mmol, 1.0 eq.), 1,4-dioxane (10 mL), NaO^tBu (148 mg, 1.54 mmol, 3.5 eq.), and RuPhos Pd G3 (7 mg, 0.01 mmol, 0.02 eq.). Flash chromatography over silica gel (eluent: pentane/EtOAc, 9/1 to 8/2 to DCM/MeOH 10/0 to 9/1) afforded the title compound (110 mg, 0.35 mmol, 76 %) as a white amorphous solid.



C₂₂H₂₇N₃O₂
365.5 g/mol

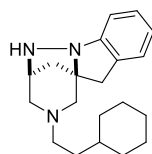
¹H NMR (500 MHz, CD₃OD) δ (ppm) 7.57 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.47 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.31 – 7.26 (m, 1H), 7.14 (td, *J* = 7.8, 1.7 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 6.78 (t, *J* = 2.6 Hz, 1H), 6.68 (dd, *J* = 8.1, 2.0 Hz, 1H), 4.96 (t, *J* = 4.4 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.74 (d, *J* = 14.2 Hz, 1H), 3.56 (d, *J* = 14.2 Hz, 1H), 2.98 (dd, *J* = 10.9, 3.5 Hz, 1H), 2.92 (dd, *J* = 11.2, 1.8 Hz, 1H), 2.65 – 2.54 (m, 4H), 2.16 – 2.11 (m, 1H), 2.08 (d, *J* = 11.3 Hz, 1H), 1.47 – 1.41 (m, 1H), 1.39 (d, *J* = 11.5 Hz, 1H).

¹³C NMR (126 MHz, CD₃OD) δ (ppm) 150.3, 148.8, 137.6, 134.6, 134.0, 133.7, 129.8, 128.6, 126.6, 121.9, 113.8, 113.0, 86.5, 79.4, 59.4, 56.5, 56.4, 54.7, 49.2, 40.3, 39.3, 33.2.

HRMS (ESI+-Orbitrap) *m/z*: [M+H]⁺ Calcd for C₂₂H₂₈N₃O₂ 366.2176, found 366.2165.

Note: A diazo derivative (40 mg, 0.09 mmol, 20 %) arising from the oxidation of hydrazine **5d** was isolated as a by-product after the reaction.

- 4-(2-Cyclohexylethyl)-2,3,4,5-tetrahydro-1*H*,6*H*-2,5*a*-methano[1,2,5]triazepino[1,7-*a*]indole (**6e**)



C₂₀H₂₉N₃
311.5 g/mol

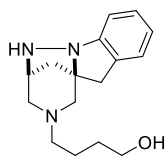
Product **6e** was synthesized according to the general procedure B using HCl (1.5 M, 5 mL), compound **5e** (189 mg, 0.32 mmol, 1.0 eq.), 1,4-dioxane (8 mL), NaO^tBu (107 mg, 1.12 mmol, 3.5 eq.), and RuPhos Pd G3 (5 mg, 0.01 mmol, 0.02 eq.). Flash chromatography over silica gel (eluent: pentane/EtOAc, 9/1 to 7/3) afforded the title compound (73 mg, 0.23 mmol, 73 %) as a white amorphous solid.

¹H NMR (500 MHz, CDCl₃) δ 7.53 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.48 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.07 (td, *J* = 7.8, 1.7 Hz, 1H), 4.92 (t, *J* = 4.6 Hz, 1H), 3.81 (d, *J* = 14.2 Hz, 1H), 3.52 (d, *J* = 14.2 Hz, 1H), 2.97 (dd, *J* = 11.1, 3.9 Hz, 1H), 2.88 (dd, *J* = 11.1, 2.0 Hz, 1H), 2.36 (dd, *J* = 8.7, 6.8 Hz, 2H), 2.00 (dd, *J* = 11.0, 1.1 Hz, 1H), 1.89 (d, *J* = 11.2 Hz, 1H), 1.69 – 1.58 (m, 4H), 1.40 – 1.34 (m, 1H), 1.30 – 1.07 (m, 8H), 0.82 – 0.76 (m 2H).

¹³C NMR (126 MHz, CDCl₃) δ 136.5, 132.8, 132.7, 128.5, 127.7, 125.7, 85.2, 78.2, 54.5, 54.3, 48.6, 39.5, 38.3, 35.9, 33.9, 33.5, 26.7, 26.4.

HRMS (ESI+-Orbitrap) m/z : $[M+H]^+$ Calcd for $C_{20}H_{30}N_3$ 312.2434, found 312.2418.

- 4-(2,3-Dihydro-1H,6H-2,5a-methano[1,2,5]triazepino[1,7-a]indol-4(5H)-yl)butan-1-ol (**6f**)



Product **6f** was synthesized according to the general procedure B using HCl (1.5 M, 6), compound **5f** (151 mg, 0.27 mmol, 1.0 eq.), 1,4-dioxane (7 mL), NaO^tBu (89 mg, 0.93 mmol, 3.5 eq.), and RuPhos Pd G3 (5 mg, 0.01 mmol, 0.02 eq.). Flash chromatography over silica gel (eluent: DCM/MeOH, 100/0 to 92/8) afforded the title compound (36 mg, 0.13 mmol, 50 %) as a colorless oil.

$C_{16}H_{23}N_3O$

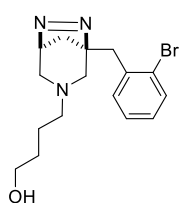
273.4 g/mol

1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.52 (dd, $J = 8.0, 0.9$ Hz, 1H), 7.49 (dd, $J = 7.7, 1.5$ Hz, 1H), 7.25 - 7.20 (m, 1H) 7.08 (td, $J = 7.8, 1.6$ Hz, 1H), 4.99 - 4.94 (m, 1H), 3.83 (d, $J = 14.2$ Hz, 3H), 3.06 - 2.99 (m, 1H), 2.93 (dd, $J = 11.2, 1.9$ Hz, 1H), 2.44 - 2.35 (m, 2H), 2.03 (d, $J = 11.1$ Hz, 1H), 1.94 - 1.86 (m, 1H), 1.58 - 1.45 (m, 4H), 1.39 (dd, $J = 11.5, 5.6$ Hz, 1H), 1.29 (d, $J = 11.5$ Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 136.4, 132.8 (2C), 130.2, 128.5, 125.7, 85.2, 78.0, 62.7, 56.7, 54.2, 48.6, 39.4, 38.1, 31.4, 23.7.

HRMS (ESI+-Orbitrap) m/z : $[M+H]^+$ Calcd for $C_{16}H_{24}N_3O$ 274.1914, found 274.1906.

An inseparable diazo derivative **6'f** (22 mg, 0.06 mmol, 23%) arising from the oxidation of hydrazine **5f** was also obtained as a by-product after the reaction.



1H NMR (500 MHz, $CDCl_3$) δ 7.31 - 7.20 (m, 4H), 4.99 - 4.94 (m, 1H), 3.59 - 3.50 (m, 3H), 3.29 (d, $J = 13.9$ Hz, 1H), 3.06 - 2.99 (m, 1H), 2.87 (dd, $J = 11.3, 1.9$ Hz, 1H), 2.44 - 2.35 (m, 2H), 1.94 - 1.86 (m, 2H), 1.58 - 1.45 (m, 5H), 1.13 (d, $J = 11.3$ Hz, 1H).

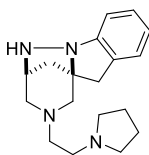
^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 136.2, 129.0, 127.7, 126.8, 85.4, 77.8, 62.7, 56.7, 54.1, 48.6, 40.9, 38.5, 31.4, 23.7.

$C_{16}H_{22}N_3O$

352.3 g/mol

HRMS (ESI+-Orbitrap) m/z : $[M+H]^+$ Calcd for $C_{16}H_{23}N_3OBr$ 352.1019, found 352.1008.

- 4-(2-(Pyrrolidin-1-yl)ethyl)-2,3,4,5-tetrahydro-1H,6H-2,5a-methano[1,2,5]triazepino[1,7-a]indole (**6g**)



Product **6g** was synthesized according to the general procedure B using HCl (1.5 M, 5 mL), compound **5g** (211 mg, 0.36 mmol, 1.0 eq.), 1,4-dioxane (9 mL), NaO^tBu (121 mg, 1.26 mmol, 3.5 eq.), and RuPhos Pd G3 (6 mg, 0.01 mmol, 0.02 eq.). Flash chromatography over silica gel (DCM/MeOH/ NH_4OH , 95/5/0 to 90/5/5) afforded the title compound (139 mg, 0.13 mmol, 36 %) as a colorless oil.

$C_{18}H_{26}N_4$

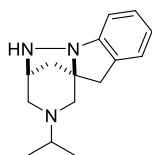
298.7 g/mol

1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.54 (dd, $J = 8.0, 1.0$ Hz, 1H), 7.44 (dd, $J = 7.7, 1.6$ Hz, 1H), 7.24 (td, $J = 7.6, 1.1$ Hz, 1H), 7.10 (td, $J = 7.8, 1.7$ Hz, 1H), 5.01 - 4.94 (m, 1H), 3.82 (d, $J = 14.2$ Hz, 1H), 3.74 (s, 1H) 3.54 (d, $J = 14.2$ Hz, 1H), 3.12 - 2.94 (m, 7H), 2.22 - 2.16 (m, 1H), 2.13 - 2.02 (m, 6H), 1.41 (dd, $J = 11.7, 5.7$ Hz, 2H), 1.33 (d, $J = 11.7$ Hz, 2H).

^{13}C NMR (126 MHz, CDCl_3) δ (ppm) 135.9, 133.0, 132.6, 128.8, 127.8, 125.7, 85.4, 78.0, 54.7, 54.0, 52.0, 51.8, 48.5, 39.3, 37.9, 23.3.

HRMS (ESI+-Orbitrap) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{18}\text{H}_{27}\text{N}_4$ 299.2230, found 299.2214.

- 4-Isopropyl-2,3,4,5-tetrahydro-1H,6H-2,5a-methano[1,2,5]triazepino[1,7-a]indole (**6h**)



Product **6h** was synthesized according to the general procedure B using HCl (1.5 M, 12 mL), compound **5h** (311 mg, 0.59 mmol, 1.0 eq.), 1,4-dioxane (15 mL), NaO^tBu (199 mg, 2.1 mmol, 3.5 eq.), and RuPhos Pd G3 (10 mg, 0.01 mmol, 0.02 eq.). Flash chromatography over silica gel (Pentane/EtOAc, 85/15 to 7/3) afforded the title compound (129 mg, 0.53 mmol, 90 %) as a white amorphous solid.

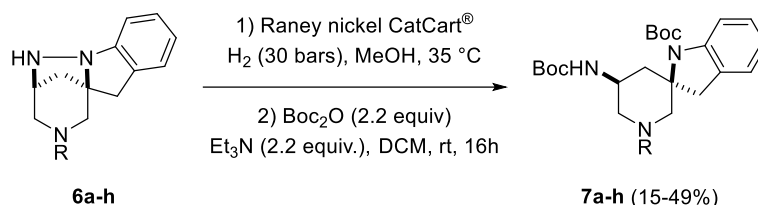
$\text{C}_{15}\text{H}_{21}\text{N}_3$
243.4 g/mol

^1H NMR (500 MHz, CDCl_3) δ (ppm) 7.53 (dd, $J = 8.0, 1.1$ Hz, 1H), 7.48 (dd, $J = 7.7, 1.6$ Hz, 1H), 7.25 – 7.20 (m, 1H), 7.10 – 7.04 (m, 1H), 4.92 (t, $J = 4.4$ Hz, 1H), 3.81 (d, $J = 14.1$ Hz, 1H), 3.51 (d, $J = 14.2$ Hz, 1H), 2.94 – 2.87 (m, 1H), 2.81 (dd, $J = 10.9, 2.0$ Hz, 1H), 2.73 – 2.63 (m, 1H), 2.19 (dd, $J = 10.9, 1.6$ Hz, 1H), 2.12 – 2.07 (m, 1H), 1.39 – 1.30 (m, 1H), 1.30 – 1.19 (m, 1H), 1.00 – 0.91 (m, 6H).

^{13}C NMR (126 MHz, CDCl_3) δ (ppm) 136.6, 132.8, 132.8, 128.5, 127.7 (2C), 85.1, 78.1, 52.9, 50.2, 44.1, 39.6, 38.2, 18.5, 18.2.

HRMS (ESI+-Orbitrap) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{15}\text{H}_{22}\text{N}_3$ 244.1808, found 244.1800.

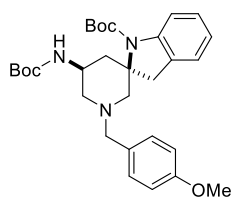
General procedure C: Hydrogenolysis and Boc-protection of the free amino groups



Continuous flow hydrogenolysis was performed using a H-CUBE[®] reactor. Substrates **6a-h** (1.0 eq.) were dissolved in methanol (0.0025M). The resulting solutions were eluted through the reactor which was equipped with Raney nickel CatCart[®] (flow rate: 1 mL/min). The reactions were performed under a H_2 atmosphere (30 bars) at 35 °C. After the hydrogenolysis, the solutions were concentrated. The resulting residues were dissolved in DCM. Boc_2O (2.2 eq.) was added followed by triethylamine (2.2 eq.). The resulting mixtures were stirred overnight at r.t, and then concentrated under reduced pressure. Flash chromatography over silica gel (eluent: pentane/EtOAc) finally afforded the desired product **7a-h**.

- *tert*-Butyl 5'-((*tert*-butoxycarbonyl)amino)-1'-(4-methoxybenzyl)spiro[indoline-2,3'-piperidine]-1-carboxylate (**7a**)

Product **7a** was synthesized according to the general the procedure C using compound **6a** (80 mg, 0.25 mmol, 1.0 eq.), methanol (100 mL), DCM (5 mL), Boc_2O (0.12 mL, 0.55 mmol, 2.2 eq.), and triethylamine (0.08 mL, 0.55 mmol, 2.2 eq.). Flash chromatography over silica gel (eluent: pentane/EtOAc, 9/1 to 8/2) afforded the title compound (45 mg, 0.11 mmol, 45 %) as a white solid.



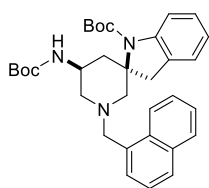
$C_{30}H_{41}N_3O_5$
523.7 g/mol

1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.54 (d, J = 7.9 Hz, 1H), 7.22 – 7.13 (m, 4H), 7.10 – 7.04 (m, 1H), 6.84 (d, J = 8.5 Hz, 2H), 5.16 (s, 1H), 4.86 – 4.84 (br m, 1H), 3.95 (br s, 1H), 3.82 – 3.75 (m, 3H), 3.53 – 3.35 (m, 3H), 3.10 (d, J = 13.7 Hz, 1H), 2.67 – 2.12 (m, 5H), 1.50 (s, 9H), 1.42 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 159.0, 155.4, 154.6, 136.8, 133.0, 130.5, 129.1, 128.3, 127.2, 126.1, 113.8, 79.4, 79.2, 61.9, 60.9, 57.9, 55.7, 55.4, 45.1, 41.2, 35.7, 28.7, 28.6.

HRMS (ESI+-Orbitrap) m/z : $[M+H]^+$ Calcd for $C_{30}H_{42}N_3O_5$ 524.3119, found 524.3110.

- tert-Butyl 5'-((tert-butoxycarbonyl)amino)-1'-(naphthalen-1-ylmethyl)spiro[indoline-2,3'-piperidine]-1-carboxylate (**7b**)



$C_{33}H_{41}N_3O_4$
543.7 g/mol

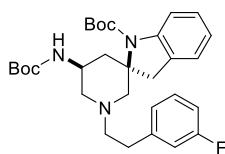
Product **7b** was synthesized according to the general procedure C using compound **6b** (58 mg, 0.17 mmol, 1.0 eq.), methanol (69 mL), DCM (5 mL), Boc_2O (0.08 mL, 0.37 mmol, 2.2 eq.), and triethylamine (0.05 mL, 0.37 mmol, 2.2 eq.). Flash chromatography over silica gel (eluent: pentane/EtOAc, 95/5 to 8/2) afforded the title compound (36 mg, 0.06 mmol, 36 %) as a white solid.

1H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.25 (d, J = 8.2 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.78 (t, J = 8.8 Hz, 1H), 7.55 – 7.45 (m, 3H), 7.39 – 7.35 (m, 1H), 7.31 (d, J = 6.7 Hz, 1H), 7.14 – 6.98 (m, 3H), 5.07 (s, 1H), 4.62 (s, 1H), 4.03 – 3.81 (m, 3H), 3.21 (dd, J = 32.3, 13.7 Hz, 2H), 2.80 – 2.58 (m, 2H), 2.48 – 2.24 (br m, 3H), 1.71 – 1.59 (br s, 1H), 1.45 (s, 9H), 1.34 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 155.4, 154.5, 136.6, 134.2, 133.6, 133.0, 132.4, 130.6, 128.8, 128.5, 128.2, 128.0, 127.1, 126.0, 126.0, 125.8, 125.2, 124.8, 79.2, 79.0, 60.9, 58.4, 55.7, 45.3, 41.3, 35.5, 28.6, 28.5.

HRMS (ESI+-Orbitrap) m/z : $[M+H]^+$ Calcd for $C_{33}H_{42}N_3O_4$ 544.3170, found 544.3160.

- tert-Butyl 5'-((tert-butoxycarbonyl)amino)-1'-(3-fluorophenethyl)spiro[indoline-2,3'-piperidine]-1-carboxylate (**7c**)



$C_{30}H_{40}FN_3O_4$
525.7 g/mol

Product **7c** was synthesized according to the general procedure C using compound (100 mg, 0.31 mmol, 1.0 eq.), methanol (120 mL), DCM (1 mL), Boc_2O (0.15 mL, 0.68 mmol, 2.2 eq.), and triethylamine (0.10 mL, 0.68 mmol, 2.2 eq.). Flash chromatography over silica gel (eluent: pentane/EtOAc, 9/1 to 8/2) afforded the title compound (80 mg, 0.15 mmol, 49 %) as a white solid.

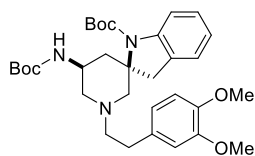
1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.53 (d, J = 8.0 Hz, 1H), 7.24 – 7.19 (m, 3H), 7.12 – 7.06 (m, 1H), 6.94 – 6.77 (m, 3H), 4.54 (s, 1H), 3.98 (s, 1H), 3.44 (d, J = 13.6 Hz, 1H), 3.06 (d, J = 13.8 Hz, 1H), 2.79 (br s, 1H), 2.76 – 2.64 (m, 2H), 2.64 – 2.53 (m, 2H), 2.53 – 2.46 (m, 2H), 2.31 (m, 2H), 1.49 (m, 10H), 1.45 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 163.0 (d, J = 245.6 Hz), 155.4, 154.6, 142.9, 136.7, 133.0, 130.0, 128.3, 127.2, 126.1, 124.5, 115.7 (d, J = 20.9 Hz), 113.1 (d, J = 20.9 Hz), 79.3, 79.3, 61.7, 58.6, 58.2, 55.6, 45.2, 41.0, 35.5, 33.1, 28.6, 28.6.

¹⁹F NMR (471 MHz, CDCl₃) δ (ppm) –113.3 (dd, *J* = 14.7, 8.3 Hz).

HRMS (ESI+-Orbitrap) *m/z*: [M+H]⁺ Calcd for C₃₀H₄₁N₃FO₄ 526.3076, found 526.3077.

- *tert*-Butyl 5'-((*tert*-butoxycarbonyl)amino)-1'-(3,4-dimethoxyphenethyl)spiro[indoline-2,3'-piperidine]-1-carboxylate (**7d**)



C₃₂H₄₅N₃O₆
567.7 g/mol

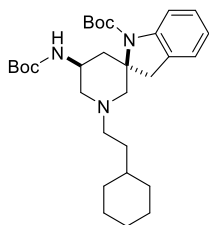
Product **7d** was synthesized according to the general procedure C using compound **6d** (56 mg, 0.15 mmol, 1.0 eq.), methanol (62 mL), DCM (5 mL), Boc₂O (0.07 mL, 0.34 mmol, 2.2 eq.), and triethylamine (0.05 mL, 0.34 mmol, 2.2 eq.). Flash chromatography over silica gel (eluent: pentane/EtOAc, 9/1 to 8/2) afforded the title compound (37 mg, 0.06 mmol, 37 %) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ (ppm) 7.54 (d, *J* = 7.9 Hz, 1H), 7.24 – 7.18 (m, 2H), 7.12 – 7.06 (m, 1H), 6.76 (d, *J* = 8.5 Hz, 1H), 6.68 – 6.64 (m, 2H), 5.18 (br s, 1H), 4.68 (br s, 1H), 4.06 – 3.96 (br s, 1H), 3.85 (dd, *J* = 10.2, 5.7 Hz, 6H), 3.46 (d, *J* = 13.4 Hz, 1H), 3.07 (d, *J* = 13.8 Hz, 1H), 2.79 (br s, 1H), 2.72 – 2.45 (m, 6H), 2.35 – 2.25 (br m, 2H), 1.48 (s, 9H), 1.45 (s, 9H).

¹³C NMR (126 MHz, CDCl₃) δ (ppm) 155.4, 154.6, 149.0, 147.4, 136.7, 133.0, 132.8, 128.2, 127.1, 126.1, 120.7, 111.8, 111.2, 79.3, 61.5, 59.6, 58.6, 56.0, 55.6, 45.2, 41.1, 35.6, 32.9, 29.9, 28.7, 28.6.

HRMS (ESI+-Orbitrap) *m/z*: [M+H]⁺ Calcd for C₃₂H₄₆N₃O₆ 568.3381, found 568.3371.

- *tert*-Butyl 5'-((*tert*-butoxycarbonyl)amino)-1'-(2-cyclohexylethyl)spiro[indoline-2,3'-piperidine]-1-carboxylate (**7e**)



C₃₀H₄₇N₃O₄
513.7 g/mol

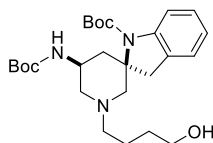
Product **7e** was synthesized according to the general procedure C using compound **6e** (40 mg, 0.13 mmol, 1.0 eq.), methanol (52 mL), DCM (5 mL), Boc₂O (0.06 mL, 0.28 mmol, 2.2 eq.), and triethylamine (0.04 mL, 0.28 mmol, 2.2 eq.). Flash chromatography over silica gel (eluent: pentane/EtOAc, 95/5 to 8/2) afforded the title compound (17 mg, 0.03 mmol, 26 %) as a white solid. Note: Products **7e** was isolated as mixture of rotamers.

¹H NMR (500 MHz, CDCl₃) δ 7.54 – 7.42 (m, 2H), 7.24 (m, 3H), 7.10 – 7.04 (m, 1H), 6.89 – 6.81 (m, 2H), 5.73 (s, 0.3H), 4.26 (d, *J* = 3.2 Hz, 1H), 3.83 – 3.76 (m, 3H), 3.71 (d, *J* = 13.5 Hz, 0.6H), 3.65 (d, *J* = 13.1 Hz, 0.3H), 3.62 – 3.52 (m, 1H), 3.48 (dd, *J* = 13.3, 5.9 Hz, 1H), 3.36 (d, *J* = 10.1 Hz, 0.3H), 3.22 (d, *J* = 14.2 Hz, 0.3H), 3.19 (t, *J* = 11.1 Hz, 0.6H), 3.07 (ddd, *J* = 18.7, 11.0, 2.9 Hz, 1H), 2.24 (d, *J* = 10.6 Hz, 0.3H), 2.18 (d, *J* = 10.5 Hz, 0.6H), 2.10 – 2.03 (m, 1H), 1.64 (dd, *J* = 11.2, 5.7 Hz, 1H), 1.58 (s, 9H), 1.48 (ddd, *J* = 7.0, 4.1, 2.2 Hz, 1H), 1.35 (d, *J* = 3.7 Hz, 9H).

¹³C NMR (126 MHz, CDCl₃) δ 169.7, 158.6, 158.6, 157.6, 155.5, 136.5, 136.3, 133.4, 132.9, 132.4, 132.2, 130.0, 129.9, 129.9, 129.9, 129.9, 129.5, 129.4, 128.1, 127.9, 127.1, 126.0, 125.9, 113.7, 113.5, 113.4 (2C), 80.8, 80.7, 80.7, 80.4, 79.1, 67.6, 67.5, 60.9, 60.7, 60.4, 58.7, 55.2, 54.9, 54.4, 54.3, 53.4, 40.2, 39.7, 38.0, 28.6, 28.5, 28.1, 27.9.

HRMS (ESI+-Orbitrap) *m/z*: [M+H]⁺ Calcd for C₃₀H₄₈N₃O₄ 514.3639, found 514.3777.

- *tert*-Butyl 5'-((*tert*-butoxycarbonyl)amino)-1'-(4-hydroxybutyl)spiro[indoline-2,3'-piperidine]-1-carboxylate (**7f**)



$C_{26}H_{41}N_3O_5$

475.6 g/mol

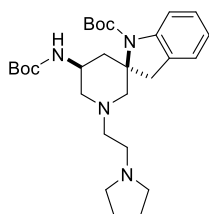
Product **7f** was synthesized according to the general procedure C using compound **6f** (51 mg, 0.12 mmol, 1.0 eq., 63 %), methanol (70 mL), DCM (5 mL), Boc_2O (0.09 mL, 0.40 mmol, 3.5 eq.), and triethylamine (0.06 mL, 0.40 mmol, 3.5 eq.). Flash chromatography over silica gel (eluent: pentane/EtOAc, 9/1 to 8/2) afforded the title compound (12 mg, 0.02 mmol, 17 %) as a white solid.

1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.54 (d, J = 8.0 Hz, 1H), 7.26 – 7.20 (m, 2H), 7.11 – 7.06 (m, 1H), 4.85 (s, 1H), 4.00 (s, 1H), 3.61 (d, J = 5.5 Hz, 2H), 3.42 (d, J = 13.3 Hz, 1H), 3.10 (d, J = 13.8 Hz, 1H), 2.85 – 2.60 (m, 2H), 2.46 (br s, 1H), 2.38 – 2.15 (m, 4H), 1.68 – 1.17 (m, 23H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 155.5, 154.7, 136.7, 133.0, 132.9, 128.3, 127.2, 126.1, 79.5, 79.3, 62.7, 61.7, 58.4, 58.2, 55.6, 45.1, 41.2, 35.7, 31.2, 29.9, 28.7, 28.6, 23.7.

HRMS (ESI+-Orbitrap) m/z : $[M+H]^+$ Calcd for $C_{26}H_{42}N_3O_5$ 476.3119, found 476.3104.

- *tert*-Butyl 5'-((*tert*-butoxycarbonyl)amino)-1'-(2-(pyrrolidin-1-yl)ethyl)spiro[indoline-2,3'-piperidine]-1-carboxylate (**7g**)



$C_{28}H_{44}N_4O_4$

500.7 g/mol

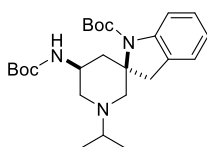
Product **7g** was synthesized according to the general procedure C using compound **6g** (35 mg, 0.12 mmol, 1.0 eq.), methanol (47 mL), DCM (5 mL), Boc_2O (0.06 mL, 0.26 mmol, 2.2 eq.), and triethylamine (0.04 mL, 0.26 mmol, 2.2 eq.). Flash chromatography over silica gel (eluent: DCM/MeOH/ NH_4OH , 95/5/0 to 90/5/5) afforded the title compound (9 mg, 0.02 mmol, 15 %) as a white solid.

1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.53 (d, J = 7.8 Hz, 1H), 7.25 – 7.20 (m, 2H), 7.10 – 7.05 (m, 1H), 5.43 (s, 2H), 3.92 (br s, 1H), 3.41 (br d, J = 13.0 Hz, 1H), 3.10 (d, J = 13.7 Hz, 1H), 2.84 – 2.45 (m, 11H), 2.38 – 2.23 (m, 2H), 1.85 (s, 4H), 1.59 – 1.46 (m, 9H), 1.43 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 155.5, 154.9, 136.7, 133.0, 132.9, 128.2, 127.1, 126.1, 79.1, 60.6, 58.5, 55.7, 54.3, 53.1, 45.6, 41.2, 35.4, 28.7, 28.6, 23.4.

HRMS (ESI+-Orbitrap) m/z : $[M+H]^+$ Calcd for $C_{28}H_{44}N_4O_4$ 501.3435, found 501.3418.

- *tert*-Butyl 5'-((*tert*-butoxycarbonyl)amino)-1'-isopropylspiro[indoline-2,3'-piperidine]-1-carboxylate (**7h**)



$C_{25}H_{39}N_3O_4$

445.6 g/mol

Product **7h** was synthesized according to the general procedure C using compound **6h** (80 mg, 0.33 mmol, 1.0 eq.), methanol (130 mL), DCM (5 mL), Boc_2O (0.15 mL, 0.72 mmol, 2.2 eq.), and triethylamine (0.10 mL, 0.72 mmol, 2.2 eq.). Flash chromatography over silica gel (Pentane/EtOAc, 95/5 to 8/2) afforded the title compound (49 mg, 0.1 mmol, 33 %) as a white solid.

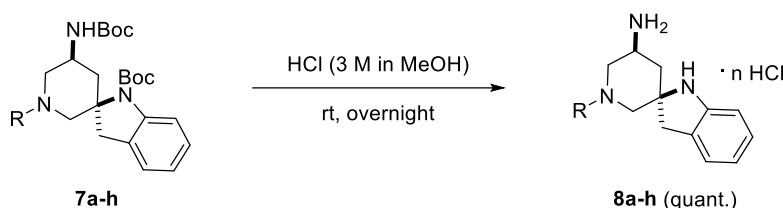
1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.54 (d, J = 7.9 Hz, 1H), 7.29 – 7.24 (m, 1H), 7.22 (t, J = 7.4 Hz, 1H), 7.07 (td, J = 8.0, 1.8 Hz, 1H), 5.21 (s, 1H), 4.88 – 4.59 (m,

1H), 3.97 (s, 1H), 3.47 (d, $J = 13.5$ Hz, 1H), 3.07 (d, $J = 13.8$ Hz, 1H), 2.75 – 2.59 (m, 2H), 2.56 – 2.32 (m, 4H), 1.51 (s, 9H), 1.44 (s, 9H), 0.99 – 0.90 (m, 6H).

^{13}C NMR (126 MHz, CDCl_3) δ (ppm) 155.4, 154.7, 136.9, 133.0, 133.0, 128.2, 127.1, 126.1, 79.2, 57.4, 55.5, 54.6, 54.2, 45.2, 41.2, 36.0, 28.7, 28.6, 18.3, 17.8.

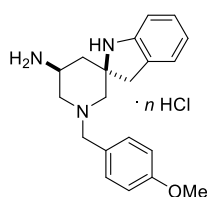
HRMS (ESI+-Orbitrap) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{25}\text{H}_{40}\text{N}_3\text{O}_4$ 446.3013, found 446.3004.

General procedure D: Boc-deprotection



Compound **7a-h** (1.0 eq.) were dissolved in a hydrogen chloride solution (3 M in MeOH). The resulting mixture was stirred at r.t. overnight. Concentration under reduced pressure finally afforded the desired product **8a-h** in quantitative yields.

- **1'-(4-Methoxybenzyl)spiro[indoline-2,3'-piperidin]-5'-amine (8a)**



$\text{C}_{20}\text{H}_{25}\text{N}_3\text{O}$
323.4 g/mol

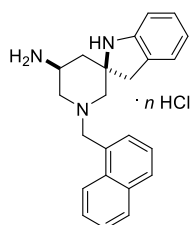
Compound **8a** (28 mg, 0.05 mmol, 1.0 eq.) was synthesized according to the general procedure D, using an HCl solution (1 mL, 1.5 M in MeOH). The title compound (24 mg, 0.05 mmol, quantitative) was isolated as a white powder.

^1H NMR (500 MHz, D_2O) δ (ppm) 7.63 (d, $J = 8.0$ Hz, 1H), 7.36 (d, $J = 8.4$ Hz, 2H), 7.18 (t, $J = 7.7$ Hz, 1H), 7.09 (t, $J = 7.5$ Hz, 1H), 7.02 (d, $J = 8.5$ Hz, 2H), 6.91 (d, $J = 7.5$ Hz, 1H), 3.86 – 3.80 (m, 5H), 3.63 (d, $J = 12.8$ Hz, 1H), 3.38 – 3.33 (m, 1H), 3.32 – 3.25 (m, 2H), 3.07 (d, $J = 11.8$ Hz, 1H), 2.46 (d, $J = 10.5$ Hz, 1H), 2.38 – 2.30 (m, 1H), 2.17 (d, $J = 11.4$ Hz, 1H), 1.73 (t, $J = 12.1$ Hz, 1H).

^{13}C NMR (126 MHz, D_2O) δ (ppm) 159.8, 134.6, 133.7, 133.7, 132.6, 130.9, 128.9, 126.1, 115.1, 61.6, 56.9, 56.6, 56.4, 55.7, 45.5, 39.6, 37.2.

HRMS (ESI+-Orbitrap) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{20}\text{H}_{26}\text{N}_3\text{O}$ 324.2070, found 324.2062.

- **1'-(Naphthalen-1-ylmethyl)spiro[indoline-2,3'-piperidin]-5'-amine (8b)**



$\text{C}_{23}\text{H}_{25}\text{N}_3$
343.5 g/mol

Compound **8b** (32 mg, 0.06 mmol, 1.0 eq.) was synthesized according to the general procedure D, using an HCl solution (1 mL, 1.5 M in MeOH). The title compound (18 mg, 0.06 mmol, quantitative) was isolated as a white powder.

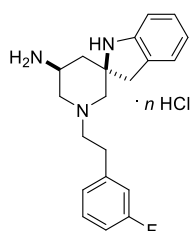
^1H NMR (500 MHz, CD_3OD) δ (ppm) 8.25 (d, $J = 8.4$ Hz, 1H), 7.87 (d, $J = 7.6$ Hz, 1H), 7.85 – 7.82 (m, 1H), 7.52 – 7.47 (m, 1H), 7.47 – 7.42 (m, 1H), 7.37 – 7.30 (m, 2H), 7.03 (t, $J = 7.5$ Hz, 1H), 6.89 – 6.84 (m, 2H), 6.49 – 6.44 (m, 2H), 4.32 (d, $J = 12.6$ Hz, 1H), 3.78 (d, $J = 12.6$ Hz, 1H), 3.70 – 3.61 (m, 1H), 3.44 (dd, $J = 10.6, 4.3$ Hz, 1H), 2.94 (d, $J = 14.3$ Hz, 1H), 2.85 (d, $J = 11.2$ Hz, 1H), 2.75 (d, $J = 14.2$ Hz, 1H), 2.29 –

2.23 (m, 1H), 2.20 (t, $J = 10.8$ Hz, 1H), 1.97 (d, $J = 11.3$ Hz, 1H), 1.65 (t, $J = 12.2$ Hz, 1H).

^{13}C NMR (126 MHz, CD_3OD) δ (ppm) 134.4, 132.7, 132.6, 132.2, 130.1, 128.8, 128.6, 128.4, 128.4, 127.4, 126.0, 125.8, 124.9, 124.4, 59.9, 56.1, 56.0, 54.7, 44.7, 39.0, 37.1.

HRMS (ESI+-Orbitrap) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{23}\text{H}_{25}\text{N}_3$ 344.2121, found 344.2127

- *1'-(3-Fluorophenethyl)spiro[indoline-2,3'-piperidin]-5'-amine (8c)*



$\text{C}_{20}\text{H}_{24}\text{FN}_3$
325.4 g/mol

Compound **8c** (20 mg, 0.04 mmol, 1.0 eq.) was synthesized according to the general procedure D, using an HCl solution (0.5 mL, 1.5 M in MeOH). The title compound (18 mg, 0.04 mmol, quantitative) was isolated as a white powder.

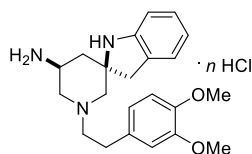
^1H NMR (500 MHz, D_2O) δ (ppm) 7.75 – 7.69 (m, 1H), 7.42 (dd, $J = 14.2, 7.7$ Hz, 1H), 7.33 – 7.27 (m, 2H), 7.22 (d, $J = 7.6$ Hz, 1H), 7.17 (d, $J = 10.0$ Hz, 1H), 7.03 (dd, $J = 11.9, 5.2$ Hz, 1H), 6.79 (d, $J = 3.6$ Hz, 1H), 3.88 (dd, $J = 12.9, 8.9$ Hz, 1H), 3.63 (d, $J = 7.5$ Hz, 1H), 3.25 (s, 2H), 3.07 – 2.91 (m, 5H), 2.51 (d, $J = 9.9$ Hz, 1H), 2.41 (d, $J = 11.7$ Hz, 1H), 2.36 (t, $J = 10.7$ Hz, 1H), 1.79 (t, $J = 12.2$ Hz, 1H).

^{13}C NMR (126 MHz, D_2O) δ (ppm) 163.8 (d, $J = 243.2$ Hz), 143.8 (d, $J = 7.2$ Hz), 134.6, 133.9, 133.8, 131.2 (d, $J = 8.5$ Hz), 131.0, 129.1, 126.0 (d, $J = 4.0$ Hz), 116.7 (d, $J = 20.9$ Hz), 114.1 (d, $J = 20.8$ Hz), 59.0, 58.5, 57.0, 54.5, 45.7, 39.4, 37.0, 32.7.

^{19}F NMR (471 MHz, D_2O) δ (ppm) –114.2.

HRMS (ESI+-Orbitrap) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{20}\text{H}_{25}\text{N}_3\text{F}$ 326.2027, found 326.2021.

- *1'-(3,4-Dimethoxyphenethyl)spiro[indoline-2,3'-piperidin]-5'-amine (8d)*



$\text{C}_{22}\text{H}_{29}\text{N}_3\text{O}_2$
367.5 g/mol

Compound **8d** (23 mg, 0.05 mmol, 1.0 eq.) was synthesized according to the general procedure D, using an HCl solution (1 mL, 1.5 M in MeOH). The title compound (18 mg, 0.05 mmol, quantitative) was isolated as a white powder.

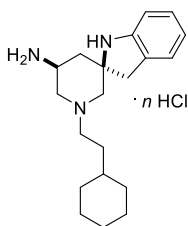
^1H NMR (500 MHz, D_2O) δ (ppm) 7.53 (d, $J = 7.9$ Hz, 1H), 7.11 (t, $J = 7.6$ Hz, 1H), 7.06 (t, $J = 7.4$ Hz, 1H), 6.93 – 6.87 (m, 2H), 6.82 (d, $J = 8.2$ Hz, 1H), 6.48 (d, $J = 6.7$ Hz, 1H), 3.77 – 3.67 (m, 4H), 3.62 (s, 3H), 3.42 (d, $J = 8.0$ Hz, 1H), 3.10 – 3.00 (m, 2H), 2.84 – 2.68 (m, 5H), 2.32 (d, $J = 9.5$ Hz, 1H), 2.24 – 2.14 (m, 2H), 1.59 (t, $J = 12.1$ Hz, 1H).

^{13}C NMR (126 MHz, D_2O) δ (ppm) 149.3, 147.8, 134.9, 134.6, 134.1, 133.9, 131.1, 129.1, 126.2, 123.1, 114.0, 113.3, 59.4, 58.8, 57.2, 56.9, 54.7, 45.9, 39.7, 37.2, 32.8.

HRMS (ESI+-Orbitrap) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{22}\text{H}_{30}\text{N}_3\text{O}_2$ 368.2333, found 368.2322.

- *1'-(2-Cyclohexylethyl)spiro[indoline-2,3'-piperidin]-5'-amine (8e)*

Compound **8d** (42 mg, 0.08 mmol, 1.0 eq.) was synthesized according to the general procedure D, using an HCl solution (1 mL, 1.5 M in MeOH). The title compound (10 mg, 0.03 mmol, quantitative) was isolated as a white powder.



¹H NMR (500 MHz, D₂O) δ (ppm) 7.73 – 7.67 (m, 1H), 7.44 – 7.37 (br m, 1H), 7.35 – 7.31 (br m, 1H), 7.30 – 7.24 (br m, 1H), 3.96 (br s, 1H), 3.48 (br s, 1H), 3.42 – 3.21 (m, 3H), 2.95 (s, 2H), 2.74 (s, 2H), 2.45 – 2.36 (br m, 1H), 1.85 – 1.75 (br m, 1H), 1.70 – 1.47 (m, 8H), 1.31 (s, 1H), 1.24 – 1.06 (m, 4H), 1.00 – 0.85 (m, 2H).

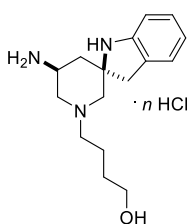
¹³C NMR (126 MHz, D₂O) δ (ppm) 134.8, 133.9, 133.7, 131.1, 129.2, 126.1, 58.2, 57.2, 55.8, 54.5, 45.1, 36.2, 35.2, 33.6, 33.5, 32.6, 27.0, 26.7.

C₂₀H₃₁N₃
313.5 g/mol

HRMS (ESI+-Orbitrap) m/z: [M+H]⁺ Calcd for C₂₀H₃₂N₃ 314.2591, found 314.2578.

- **4-(5'-Aminospiro[indoline-2,3'-piperidin]-1'-yl)butan-1-ol (8f)**

Compound **8f** (6 mg, 0.01 mmol, 1.0 eq.) was synthesized according to the general procedure D, using an HCl solution (1 mL, 1.5 M in MeOH). The title compound (5 mg, 0.01 mmol, quantitative) was isolated as a white powder.



¹H NMR (500 MHz, D₂O) δ (ppm) 7.69 (d, *J* = 8.1 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 7.7 Hz, 1H), 7.27 (t, *J* = 7.7 Hz, 1H), 4.01 – 3.92 (m, 1H), 3.60 (t, *J* = 6.3 Hz, 2H), 3.48 (d, *J* = 8.5 Hz, 1H), 3.40 – 3.24 (m, 3H), 2.91 – 2.85 (m, 2H), 2.65 (d, *J* = 9.2 Hz, 2H), 2.43 (d, *J* = 11.6 Hz, 1H), 1.72 (ddd, *J* = 24.2, 19.9, 10.5 Hz, 3H), 1.61 – 1.54 (m, 2H).

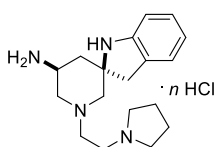
C₁₆H₂₅N₃O
275.4 g/mol

¹³C NMR (126 MHz, D₂O) δ (ppm) 134.8, 133.9, 133.6, 131.2, 129.3, 126.1, 62.1, 58.5, 58.3, 56.2, 54.5, 45.1, 40.4, 35.4, 29.8, 22.2.

HRMS (ESI+-Orbitrap) m/z: [M+H]⁺ Calcd for C₁₆H₂₆N₃O 276.2070, found 276.2062.

- **1'-(2-(pyrrolidin-1-yl)ethyl)spiro[indoline-2,3'-piperidin]-5'-amine (8g)**

Compound **8g** (4 mg, 0.01 mmol, 1.0 eq.) was synthesized according to the general procedure D, using an HCl solution (1 mL, 1.5 M in MeOH). The title compound (4 mg, 0.01 mmol, quantitative) was isolated as a white powder.



¹H NMR (500 MHz, D₂O) δ (ppm) 7.70 (d, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.33 – 7.24 (m, 2H), 4.04 – 3.97 (m, 1H), 3.73 – 3.60 (m, 2H), 3.56 – 3.47 (m, 2H), 3.37 – 3.24 (m, 3H), 3.13 (t, *J* = 10.0 Hz, 3H), 3.00 – 2.93 (m, 1H), 2.87 – 2.80 (m, 1H), 2.44 (d, *J* = 11.5 Hz, 1H), 2.41 – 2.37 (m, 1H), 2.21 (t, *J* = 10.8 Hz, 1H), 2.16 – 2.06 (m, 2H), 2.04 – 1.92 (m, 2H), 1.57 (t, *J* = 12.4 Hz, 1H).

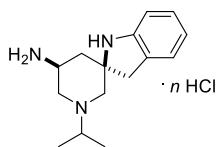
C₁₈H₂₈N₄
300.5 g/mol

¹³C NMR (126 MHz, D₂O) δ (ppm) 134.9, 134.0, 133.7, 131.2, 129.3, 126.2, 60.6, 57.0, 56.0, 54.9, 54.8, 53.4, 52.4, 45.5, 39.6, 35.2, 23.6, 23.5.

HRMS (ESI+-Orbitrap) m/z: [M+H]⁺ Calcd for C₁₈H₂₉N₄ 301.2387, found 301.2380.

- **1'-Isopropylspiro[indoline-2,3'-piperidin]-5'-amine (8h)**

Compound **8h** (40 mg, 0.09 mmol, 1.0 eq.) was synthesized according to the general procedure D, using an HCl solution (1 mL, 1.5 M in MeOH). The title compound (34 mg, 0.09 mmol, quantitative) was isolated as a white powder.



¹H NMR (500 MHz, D₂O) δ (ppm) 7.66 (d, *J* = 7.9 Hz, 1H), 7.36 (t, *J* = 7.0 Hz, 1H), 7.30 (d, *J* = 7.4 Hz, 1H), 7.24 (t, *J* = 7.4 Hz, 1H), 3.96 (s, 1H), 3.53 – 3.17 (m, 5H), 2.90 (s, 2H), 2.37 (d, *J* = 10.8 Hz, 1H), 1.79 (d, *J* = 10.7 Hz, 1H), 1.21 (t, *J* = 6.8 Hz, 6H).

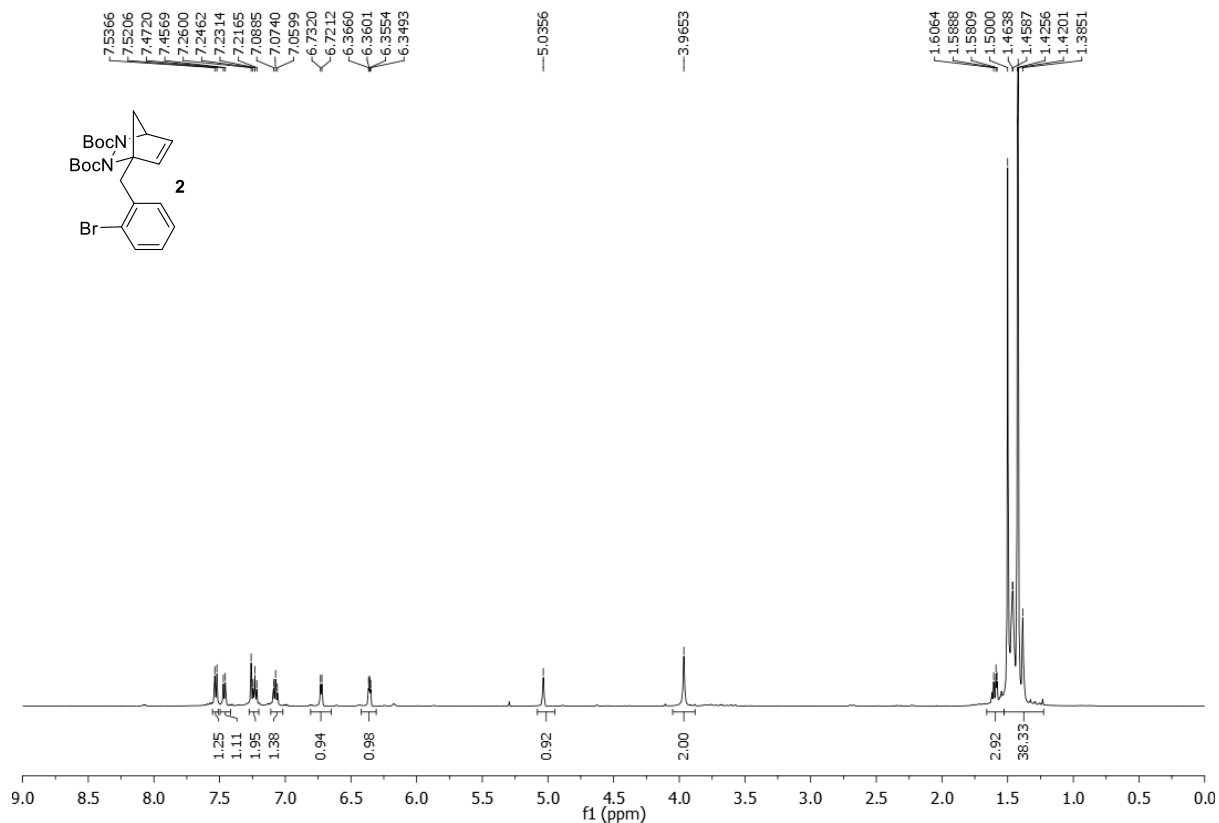
C₁₅H₂₃N₃
245.4 g/mol

¹³C NMR (126 MHz, D₂O) δ (ppm) 134.8, 134.0, 133.7, 131.1, 129.2, 126.2, 59.3, 55.8, 54.4, 50.8, 45.3, 35.0, 17.5, 17.0.

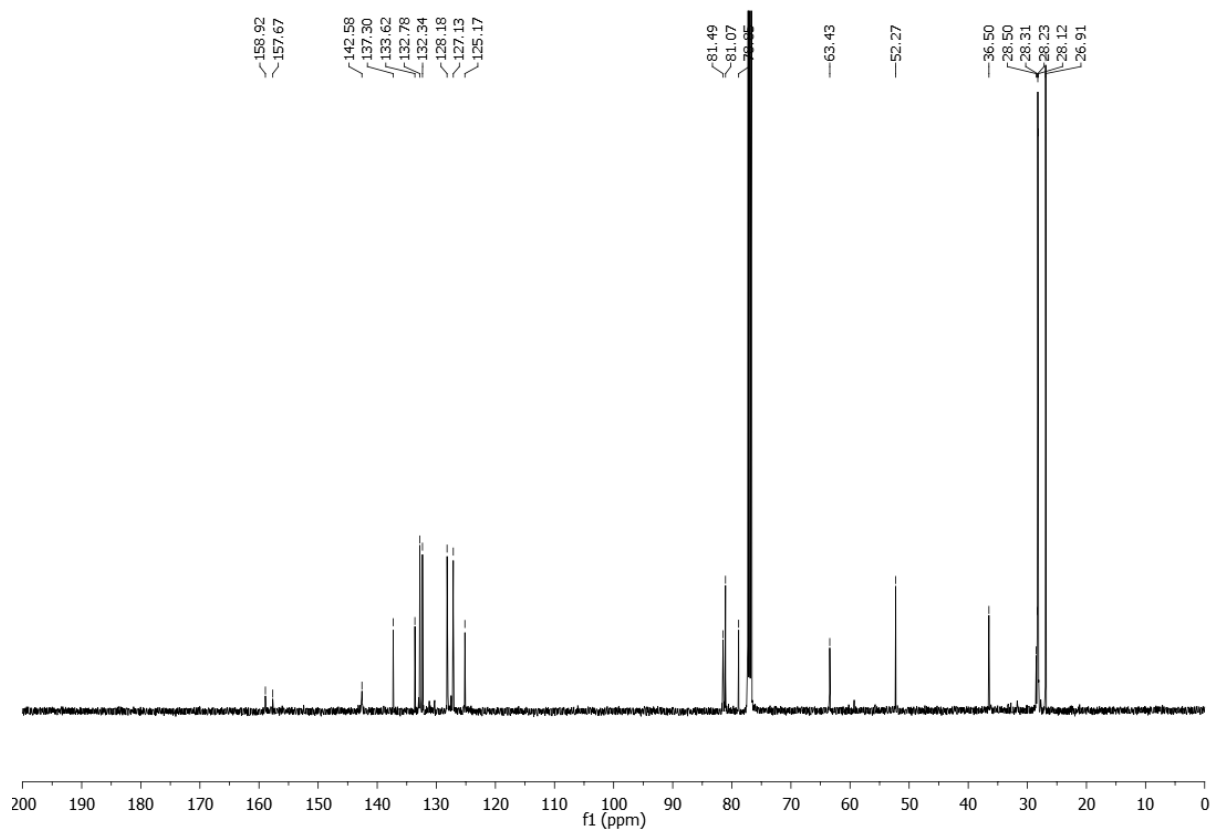
HRMS (ESI+-Orbitrap) *m/z*: [M+H]⁺ Calcd for C₁₅H₂₃N₃ 246.1965, found 246.1954.

Copies of ^1H NMR and ^{13}C NMR spectra

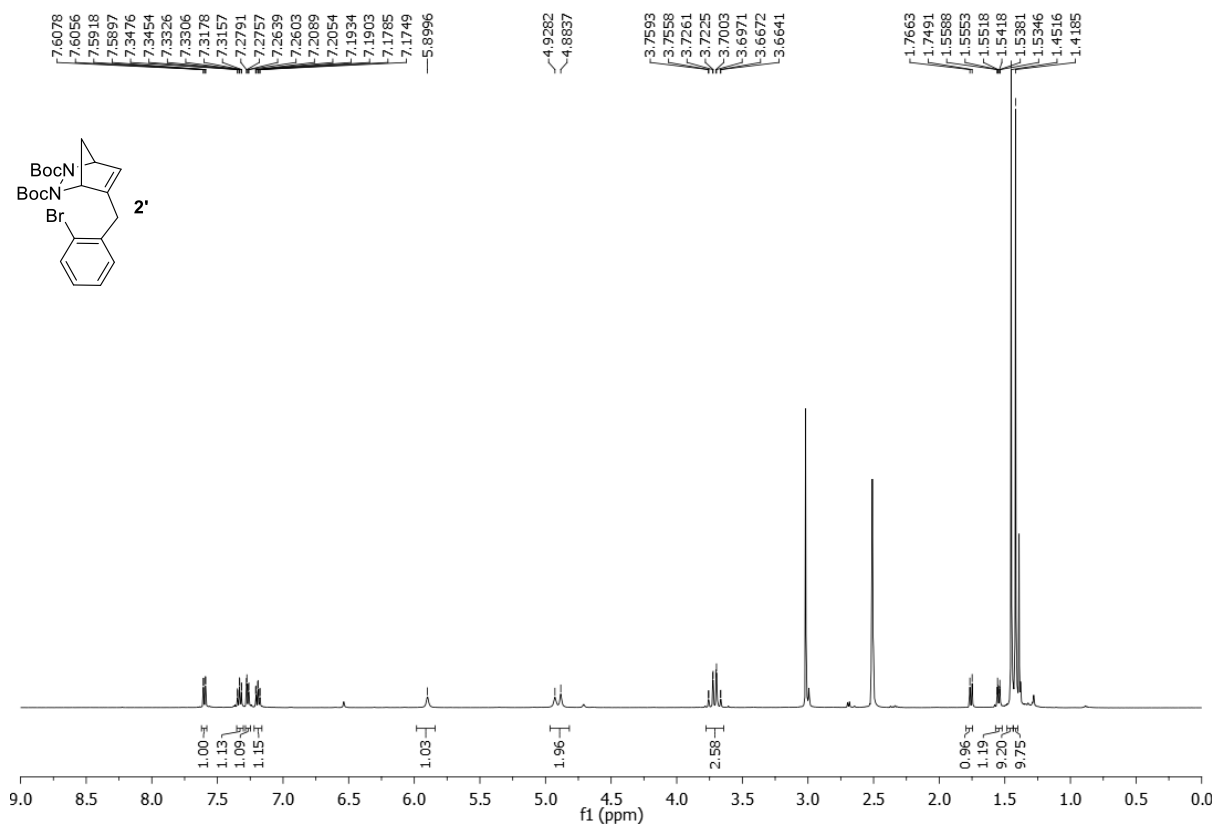
^1H NMR (500 MHz, CDCl_3)



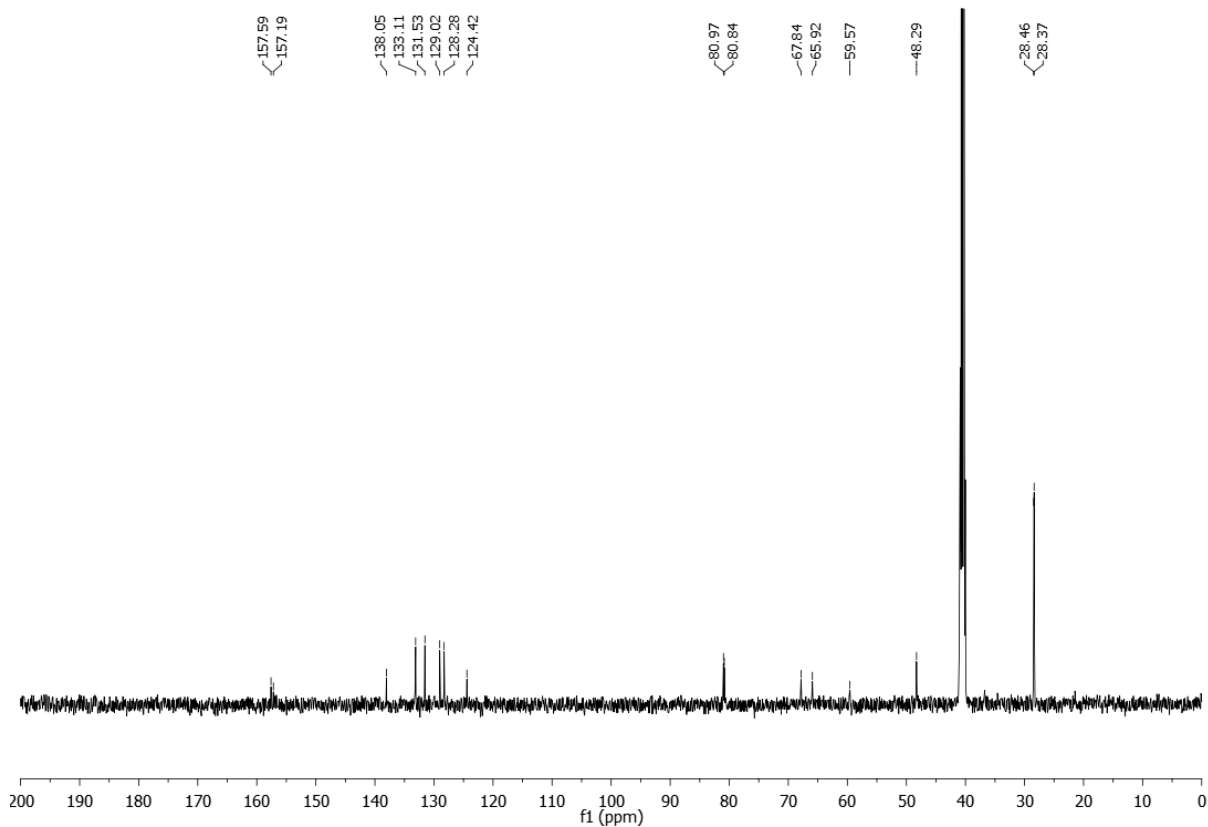
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)



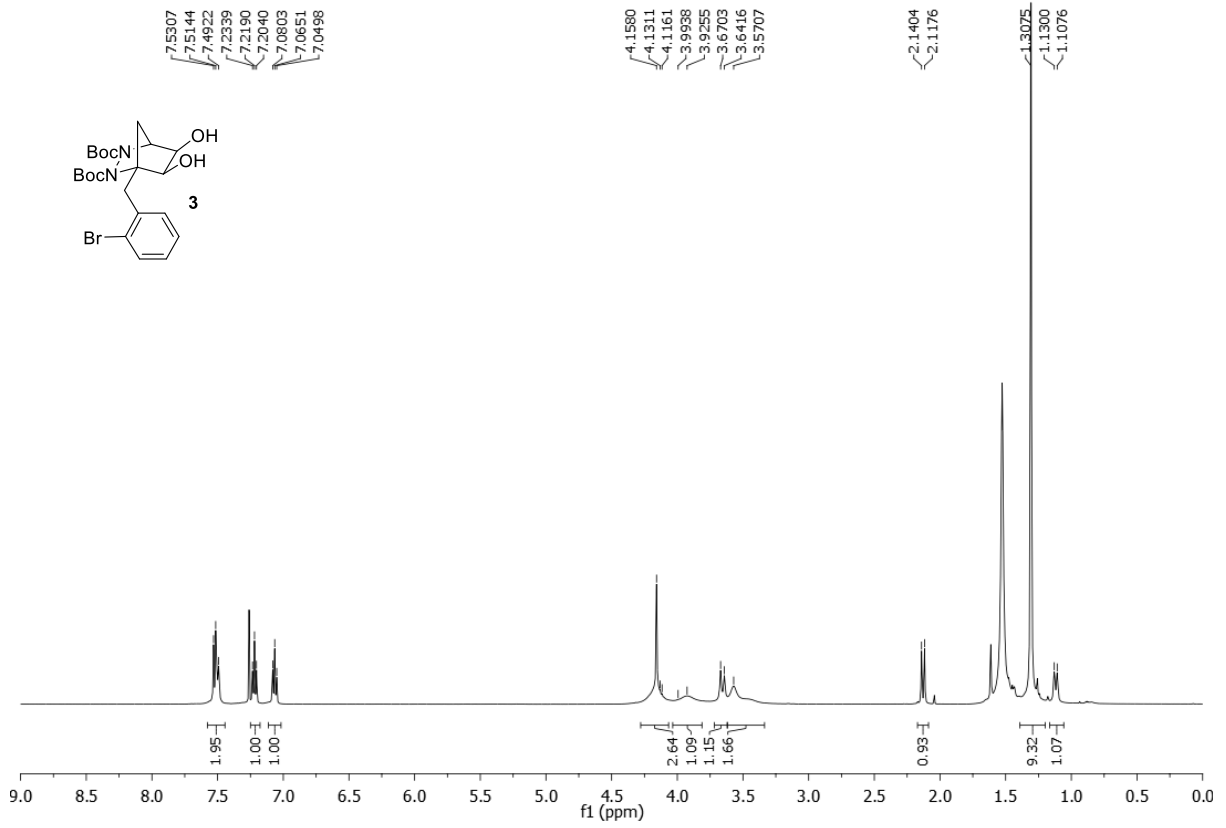
¹H NMR (500 MHz, DMSO-d₆)



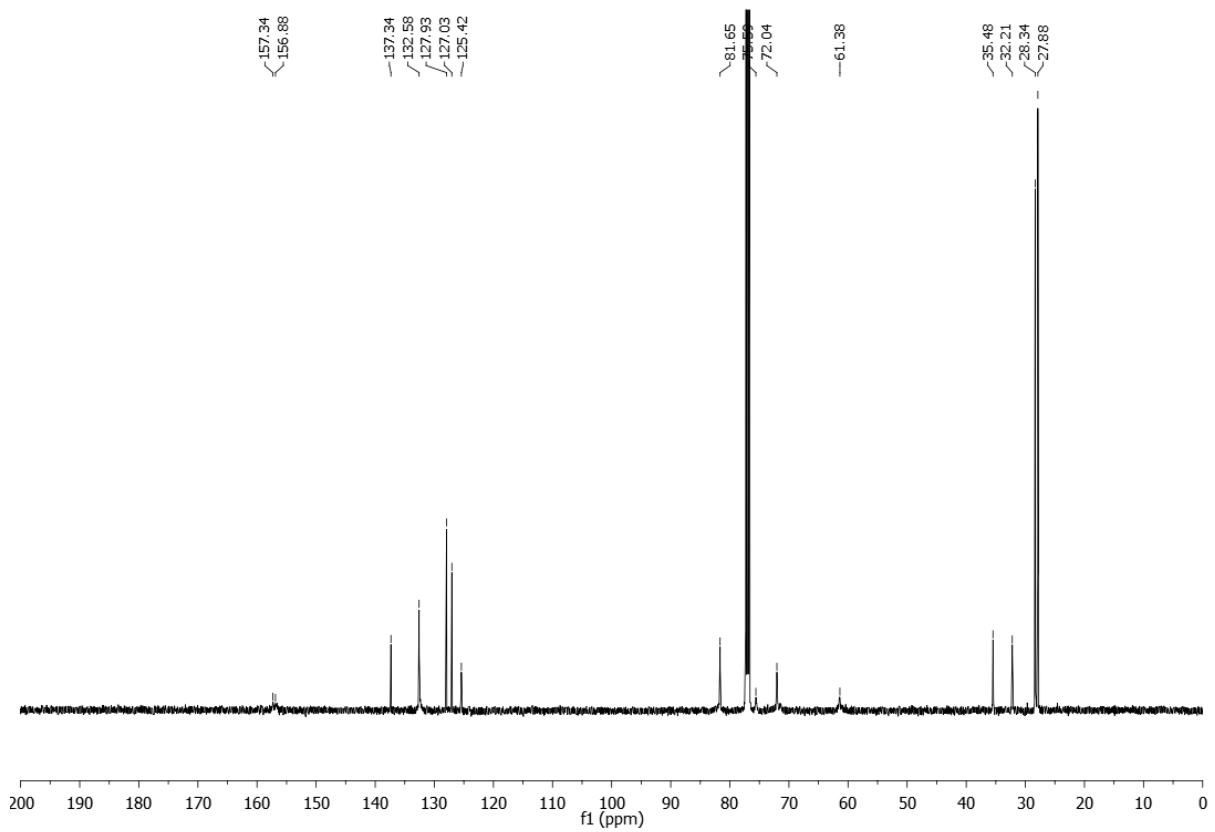
¹³C{¹H} NMR (126 MHz, DMSO-d₆)



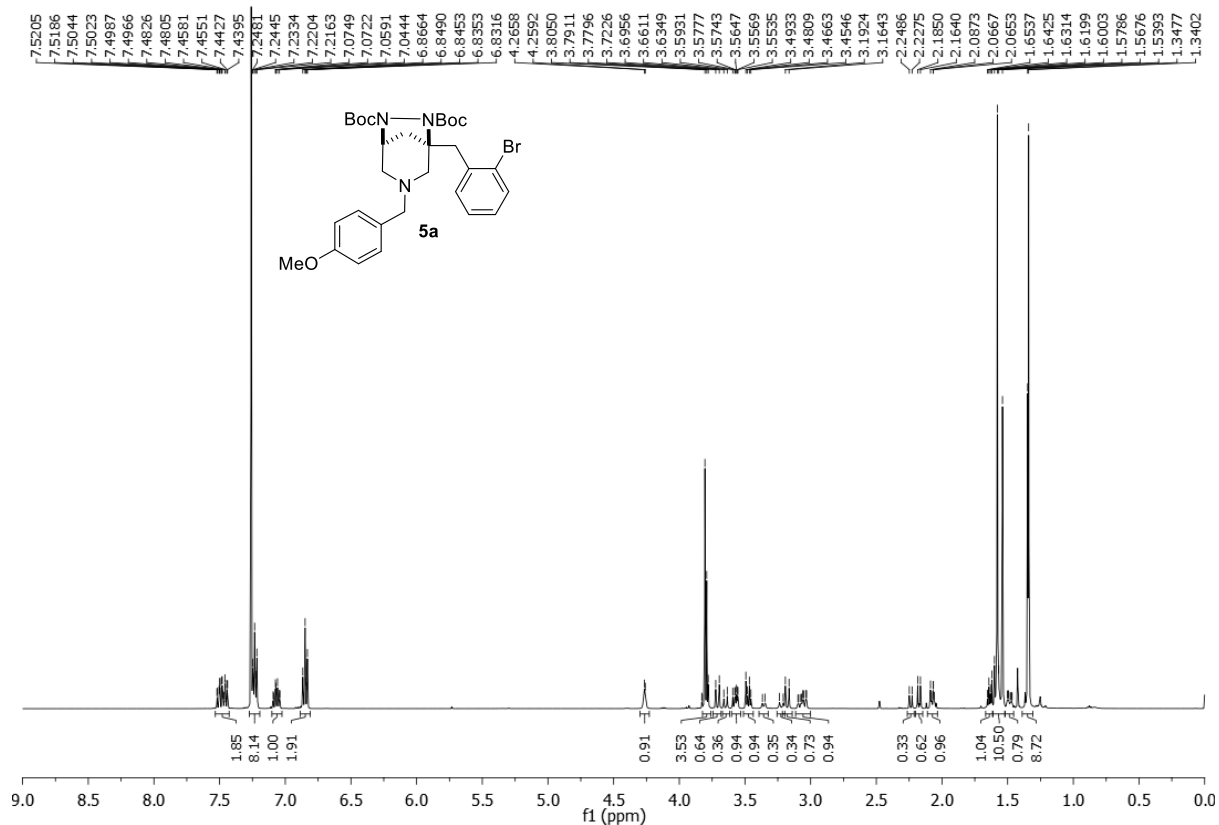
¹H NMR (500 MHz, CDCl₃)



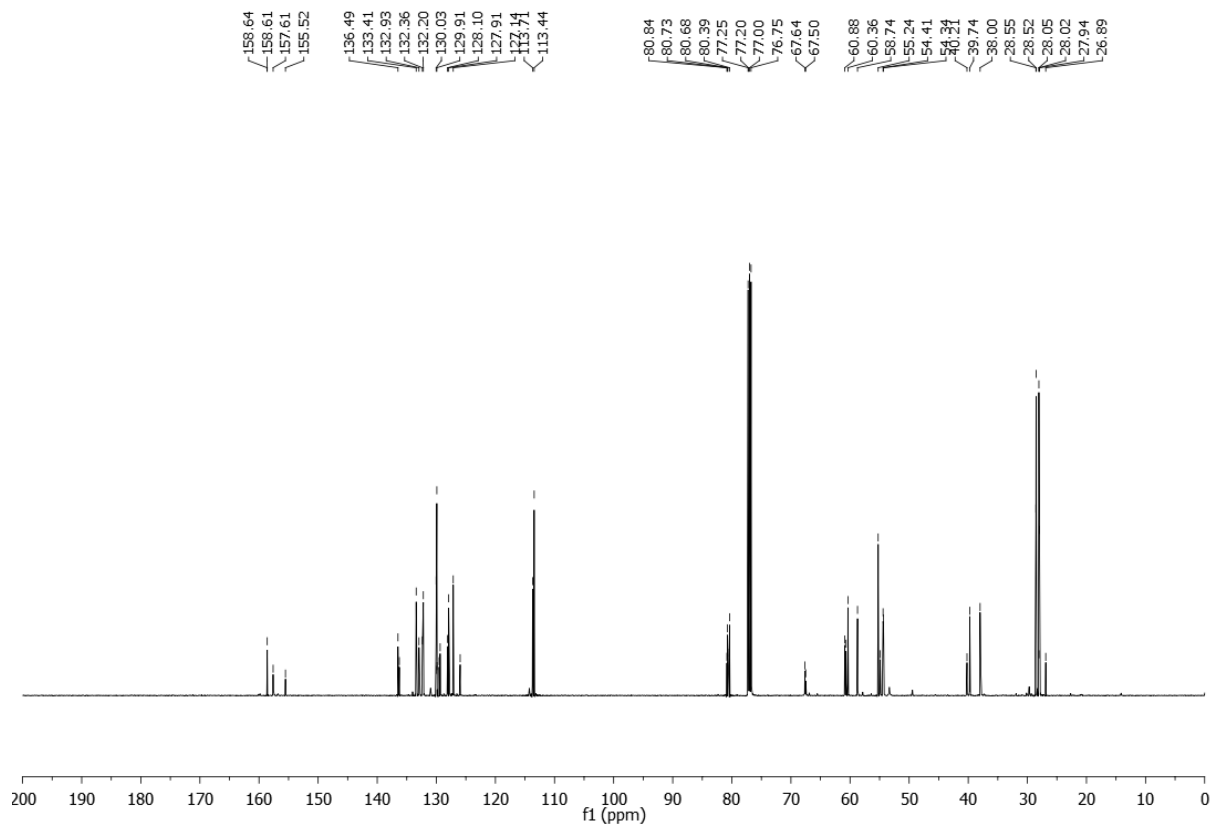
¹³C{¹H} NMR (126 MHz, CDCl₃)



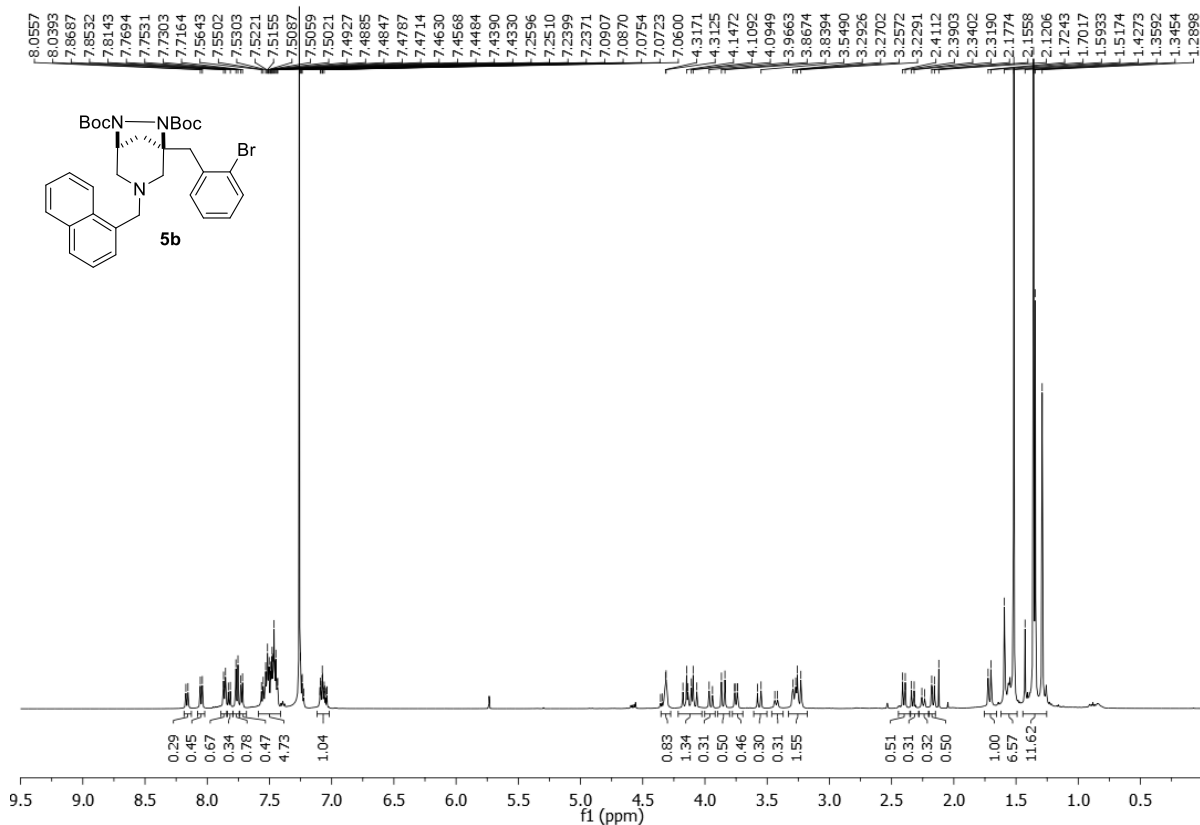
¹H NMR (500 MHz, CDCl₃)



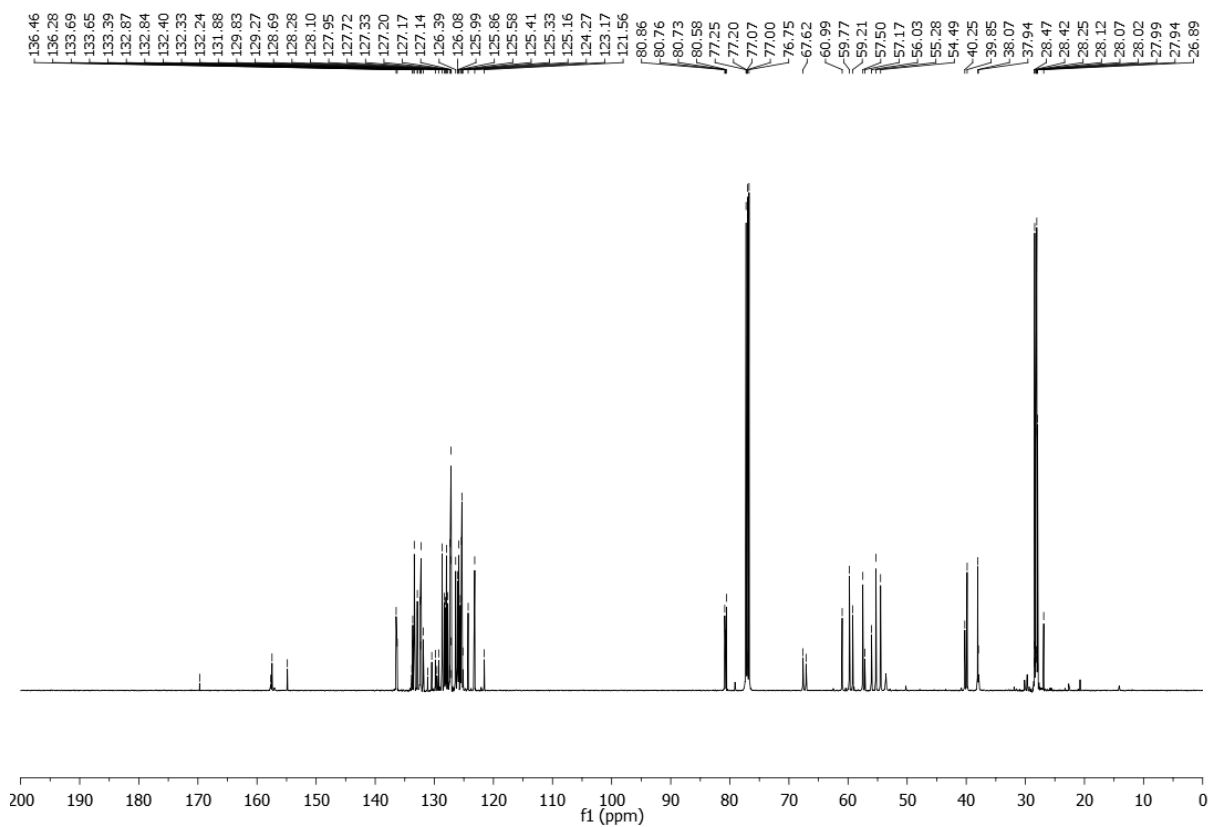
¹³C{¹H} NMR (126 MHz, CDCl₃)



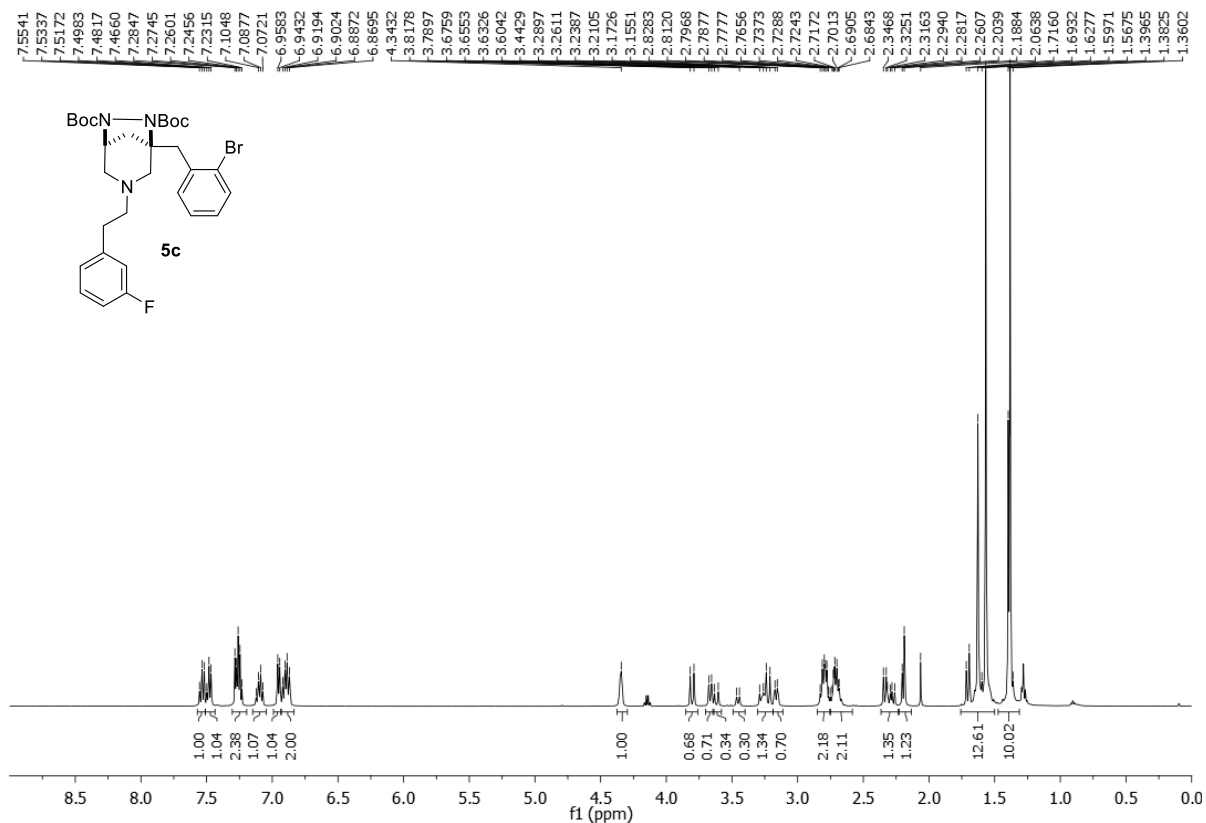
¹H NMR (500 MHz, CDCl₃)



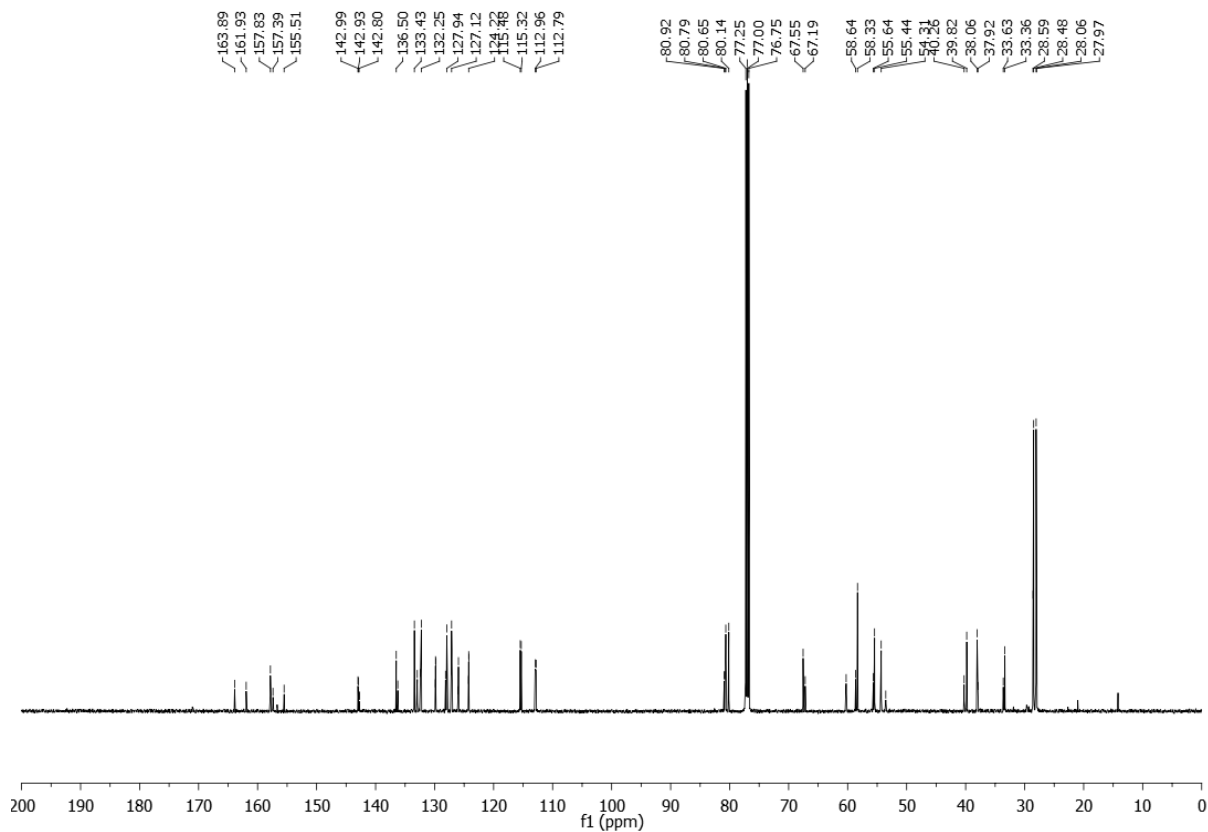
¹³C{¹H} NMR (126 MHz, CDCl₃)



¹H NMR (500 MHz, CDCl₃)

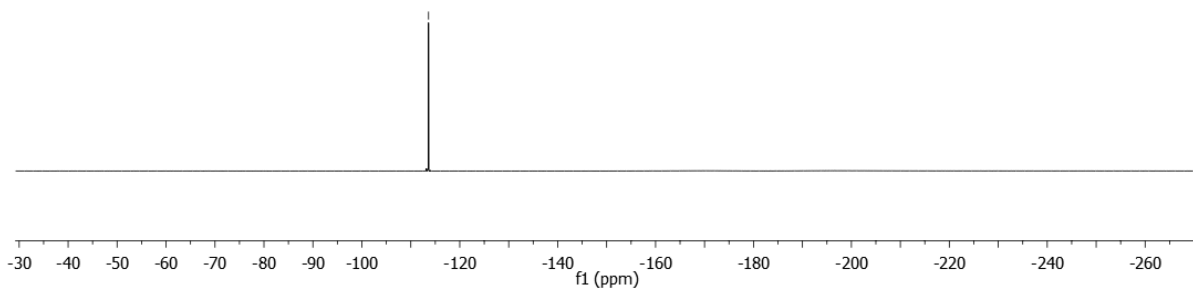
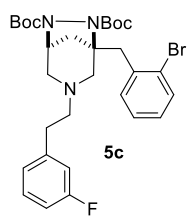


¹³C{¹H} NMR (126 MHz, CDCl₃)

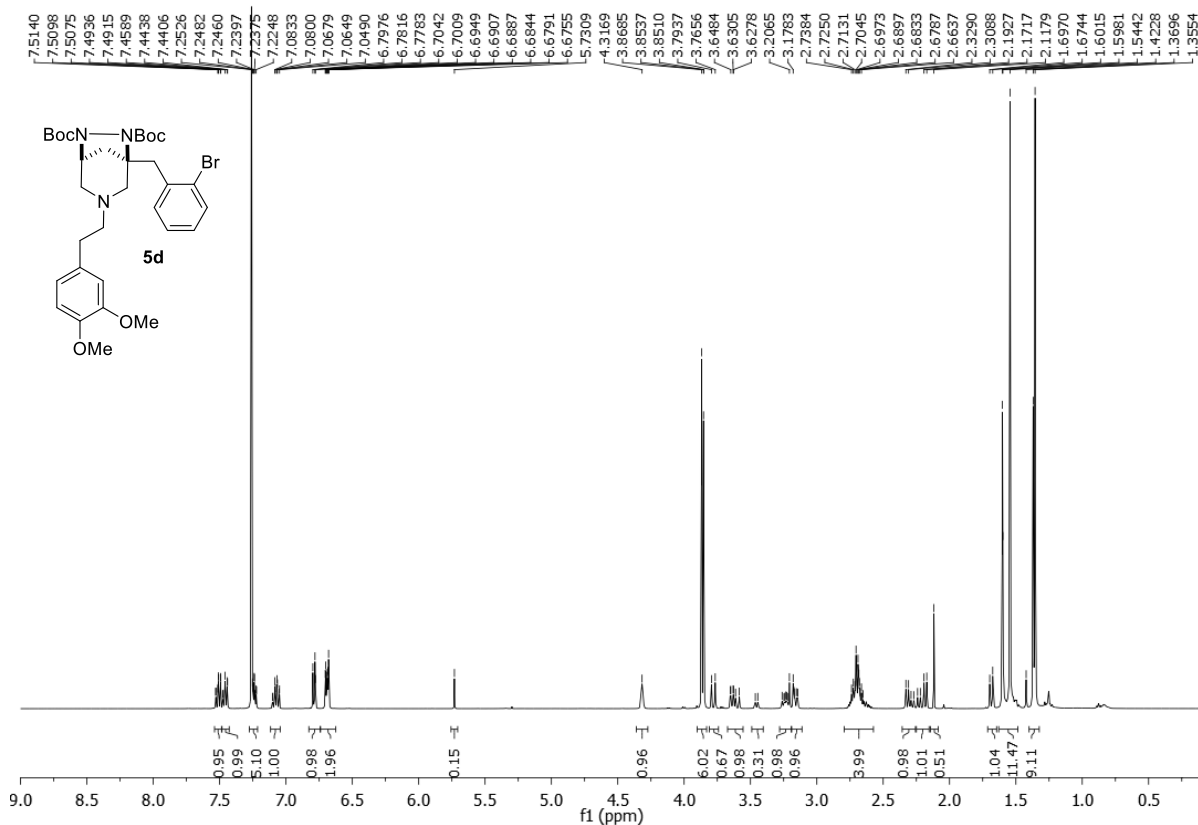


$^{19}\text{F}\{^{13}\text{C}\}$ NMR (471 MHz, CDCl_3)

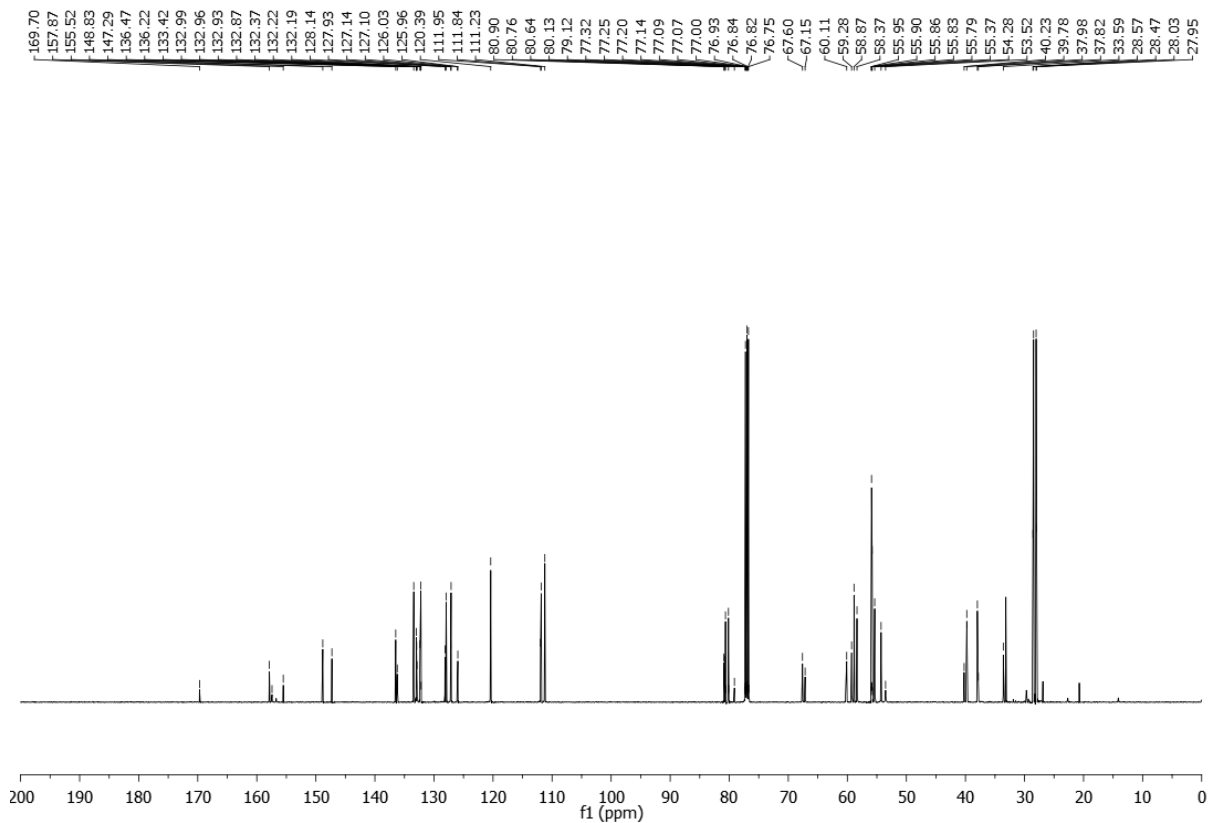
---113.63



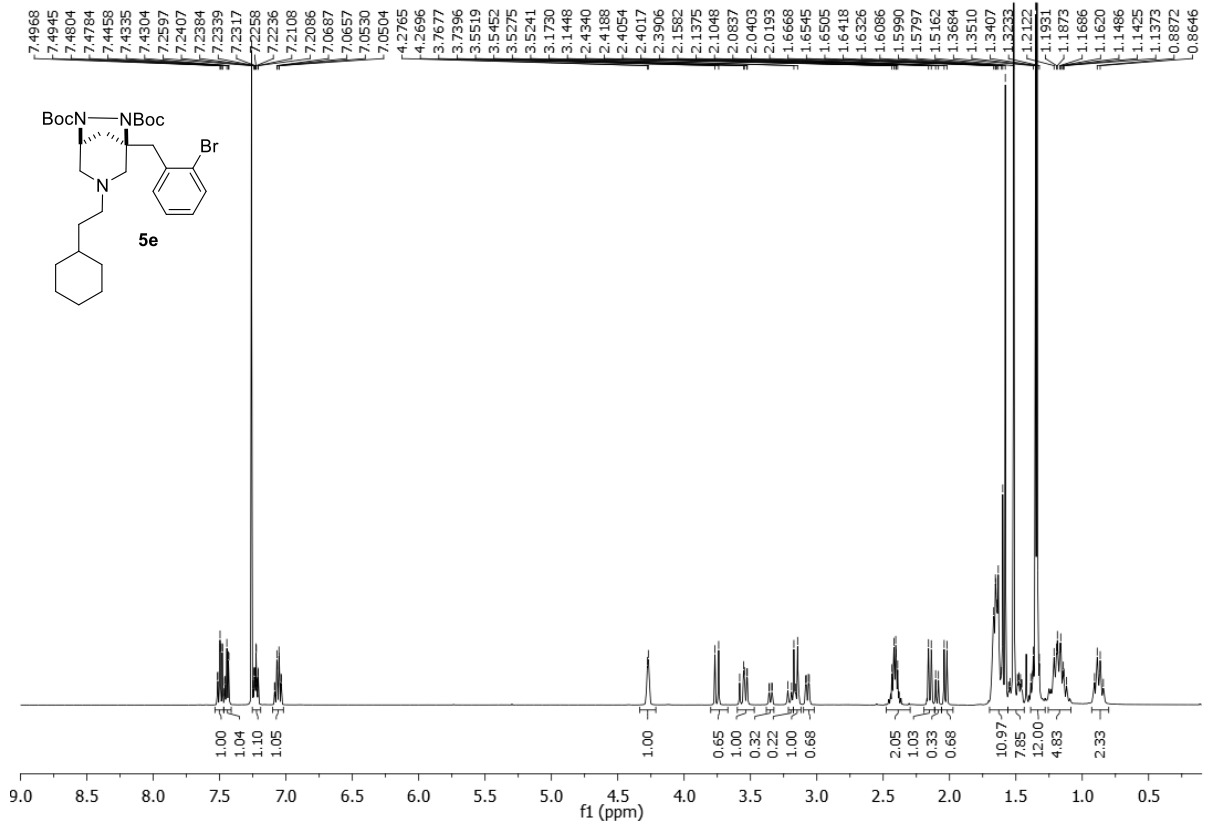
¹H NMR (500 MHz, CDCl₃)



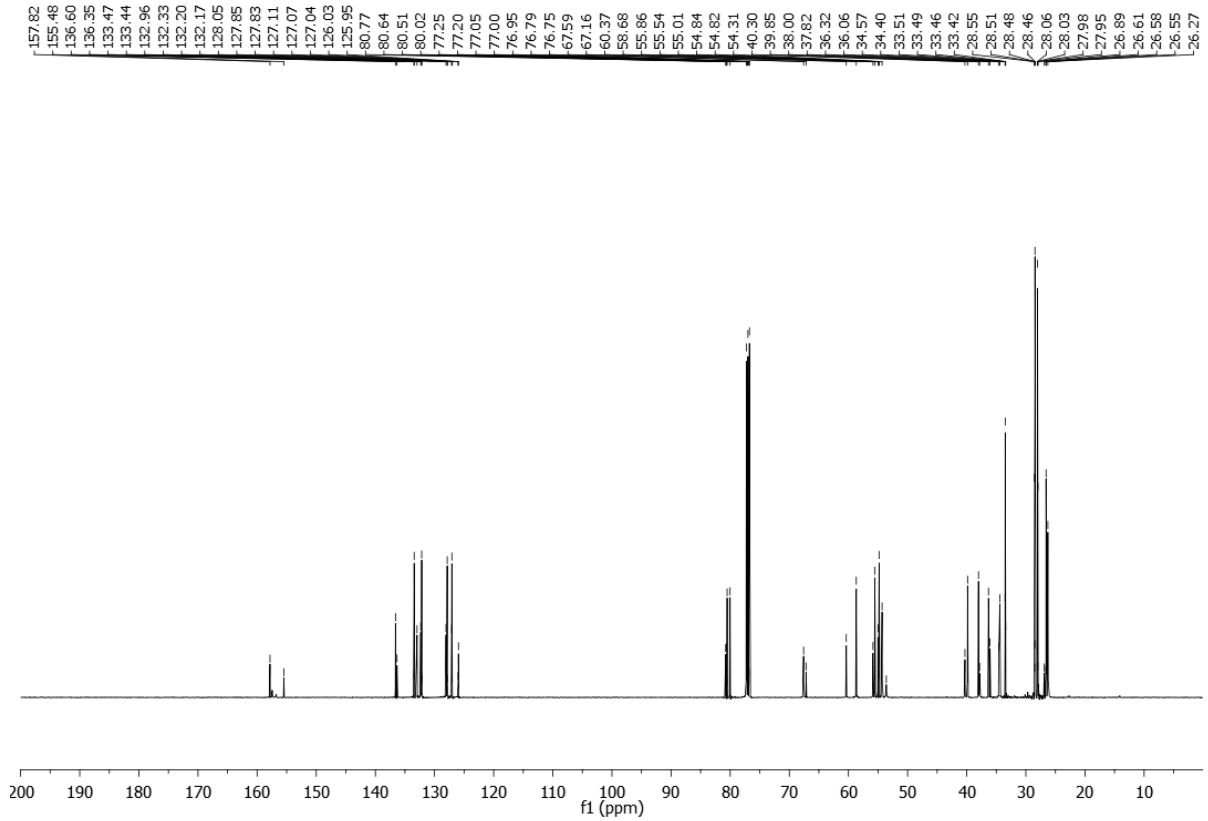
¹³C{¹H} NMR (126 MHz, CDCl₃)



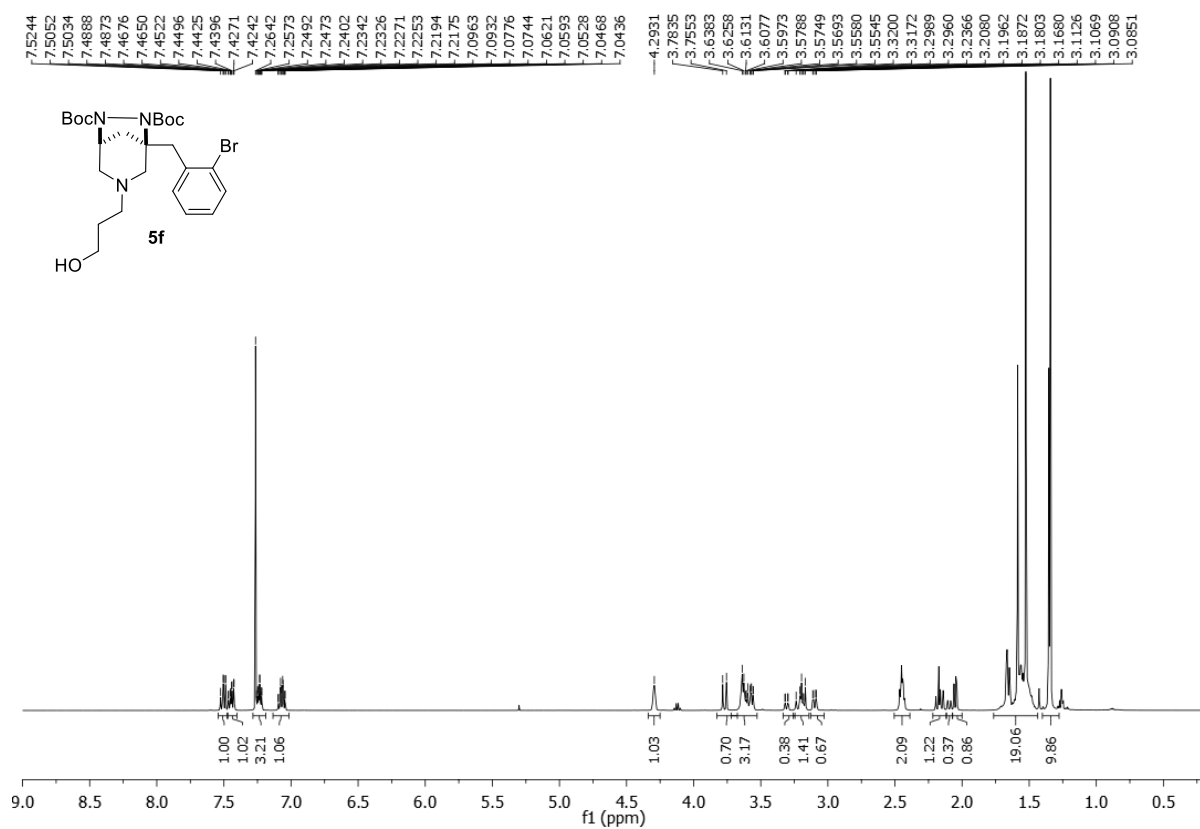
¹H NMR (500 MHz, CDCl₃)



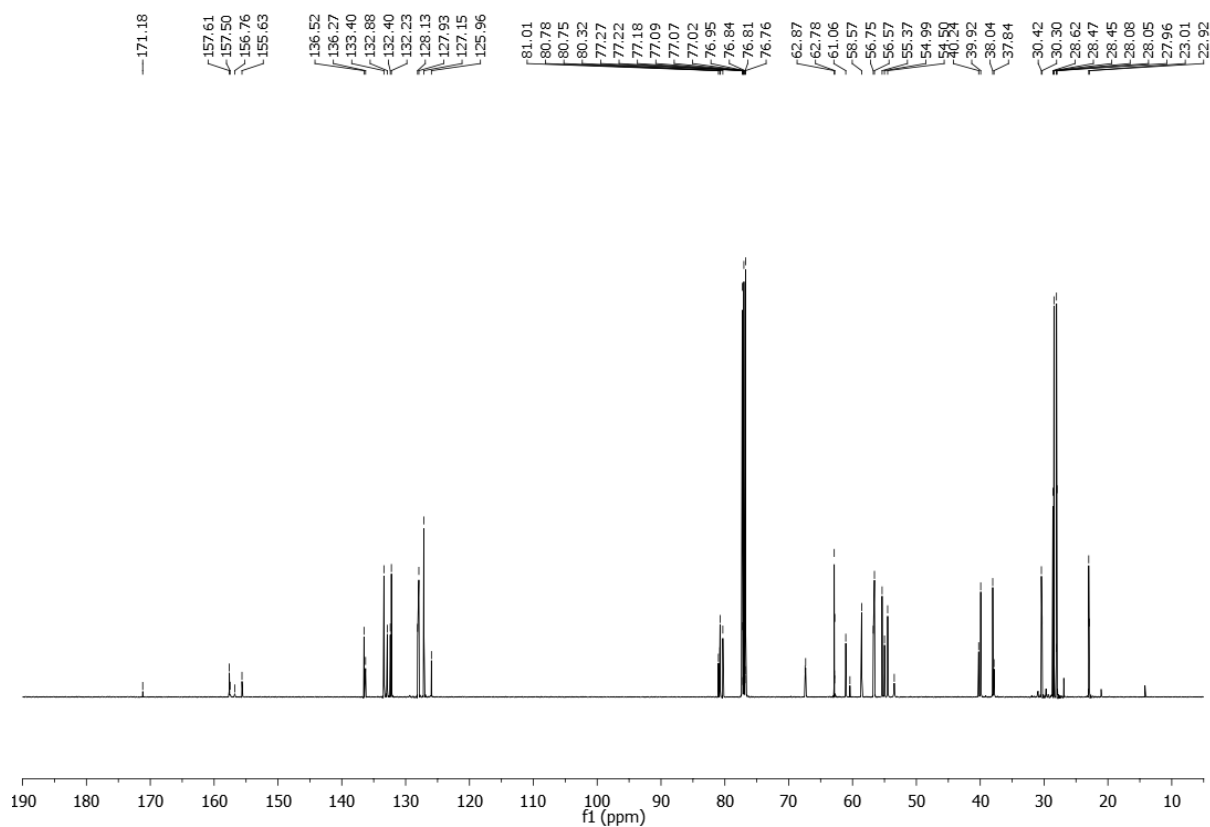
¹³C{¹H} NMR (126 MHz, CDCl₃)



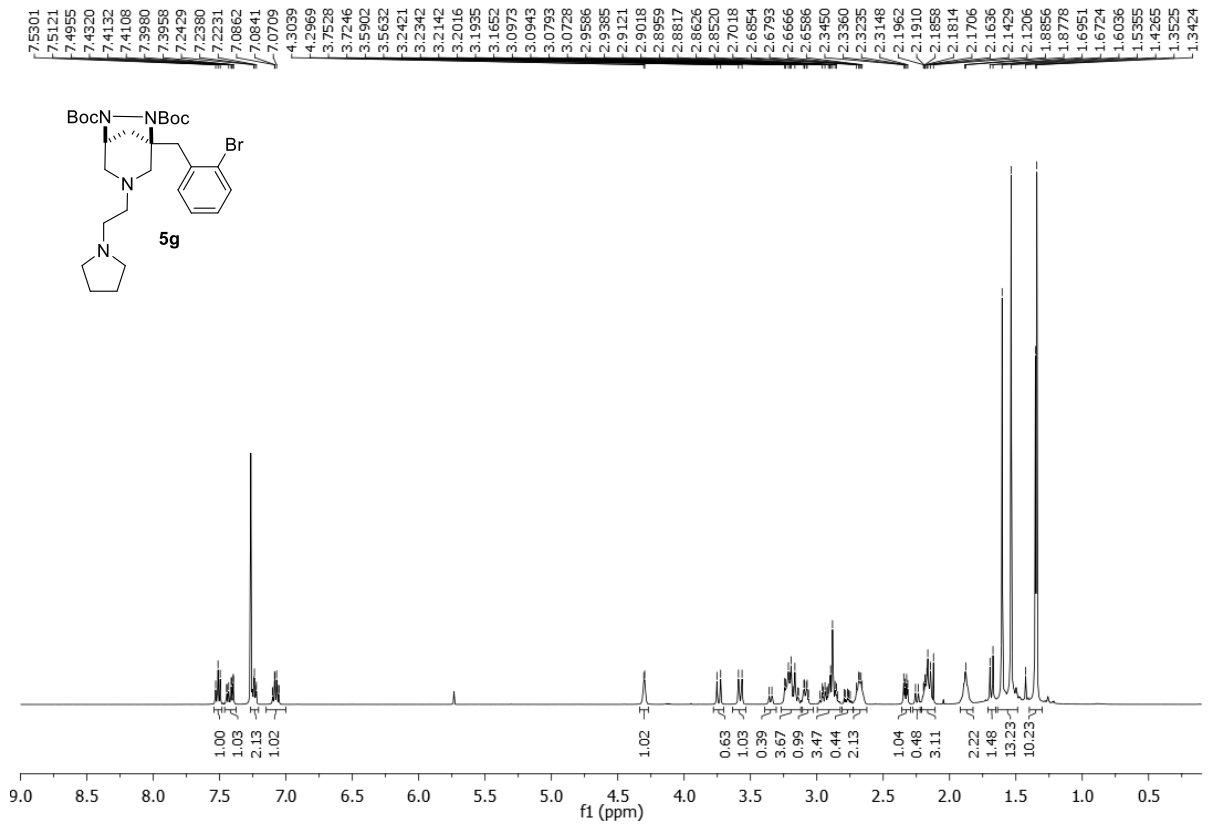
¹H NMR (500 MHz, CDCl₃)



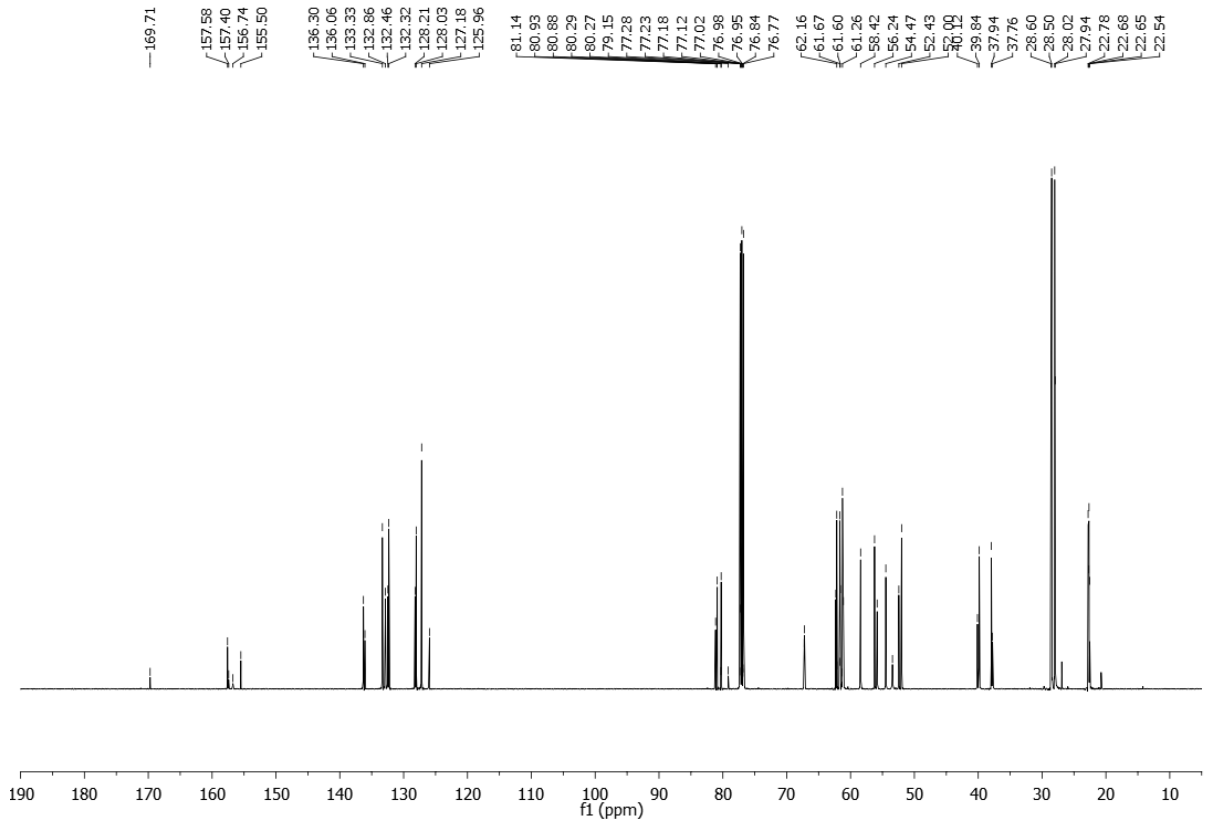
¹³C{¹H} NMR (126 MHz, CDCl₃)



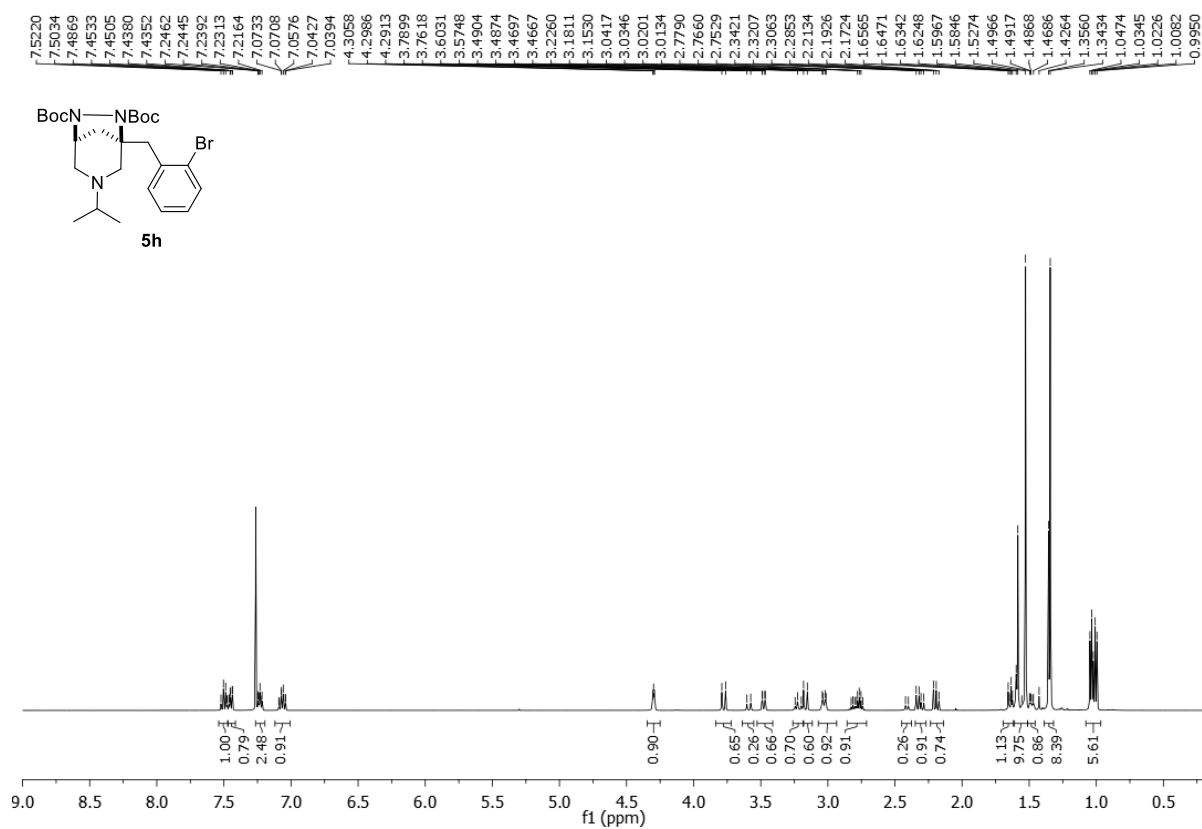
¹H NMR (500 MHz, CDCl₃)



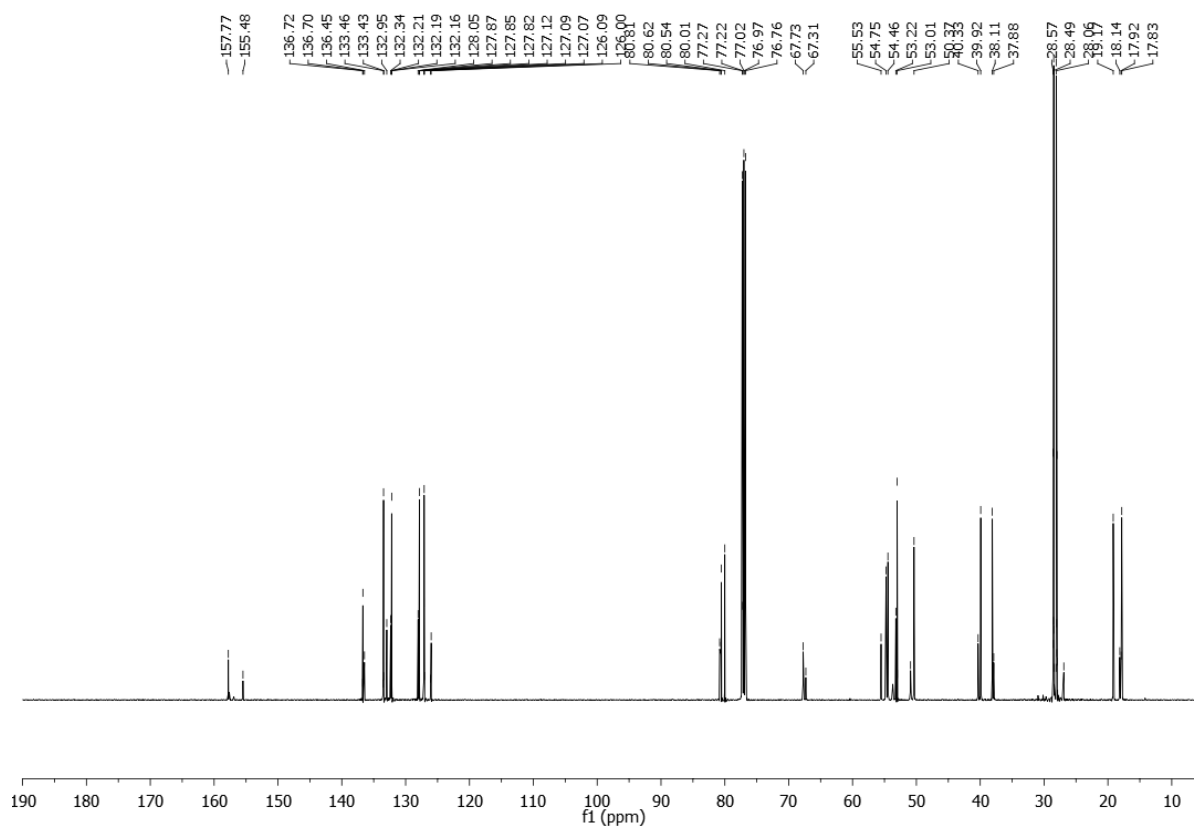
¹³C{¹H} NMR (126 MHz, CDCl₃)



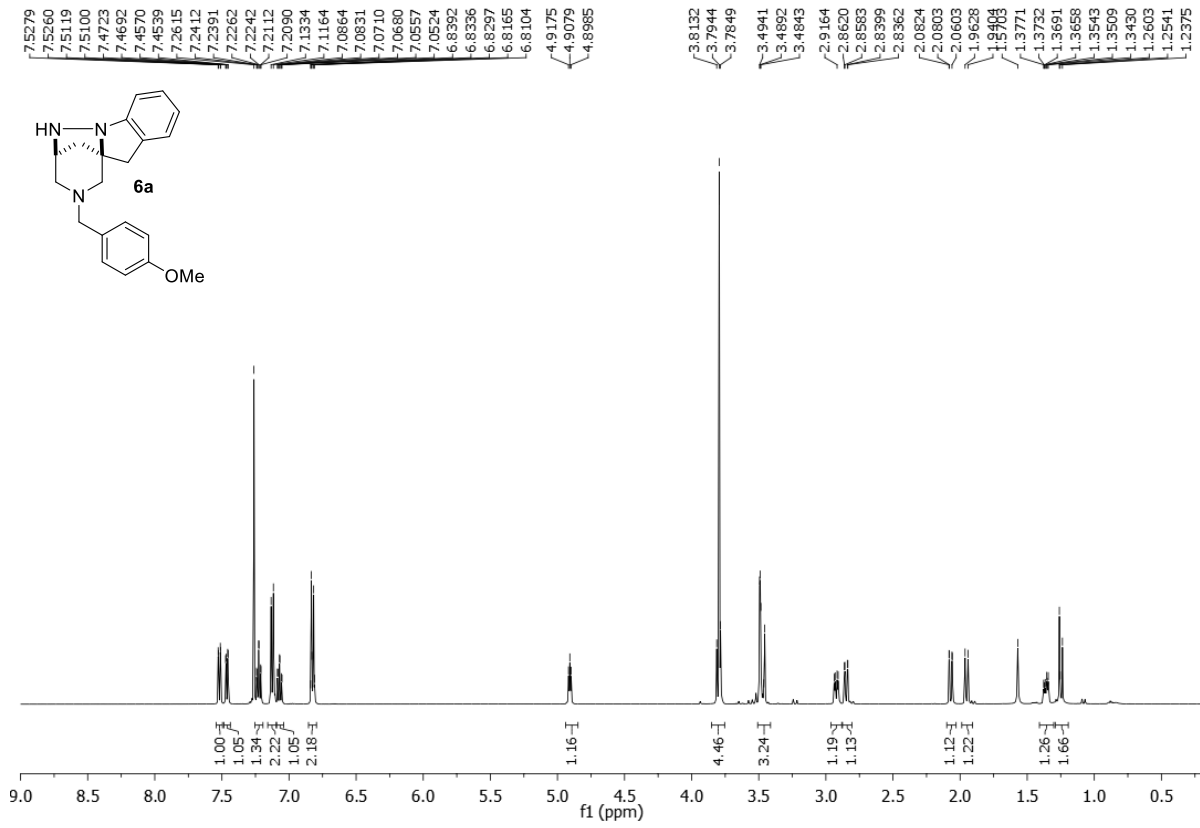
¹H NMR (500 MHz, CDCl₃)



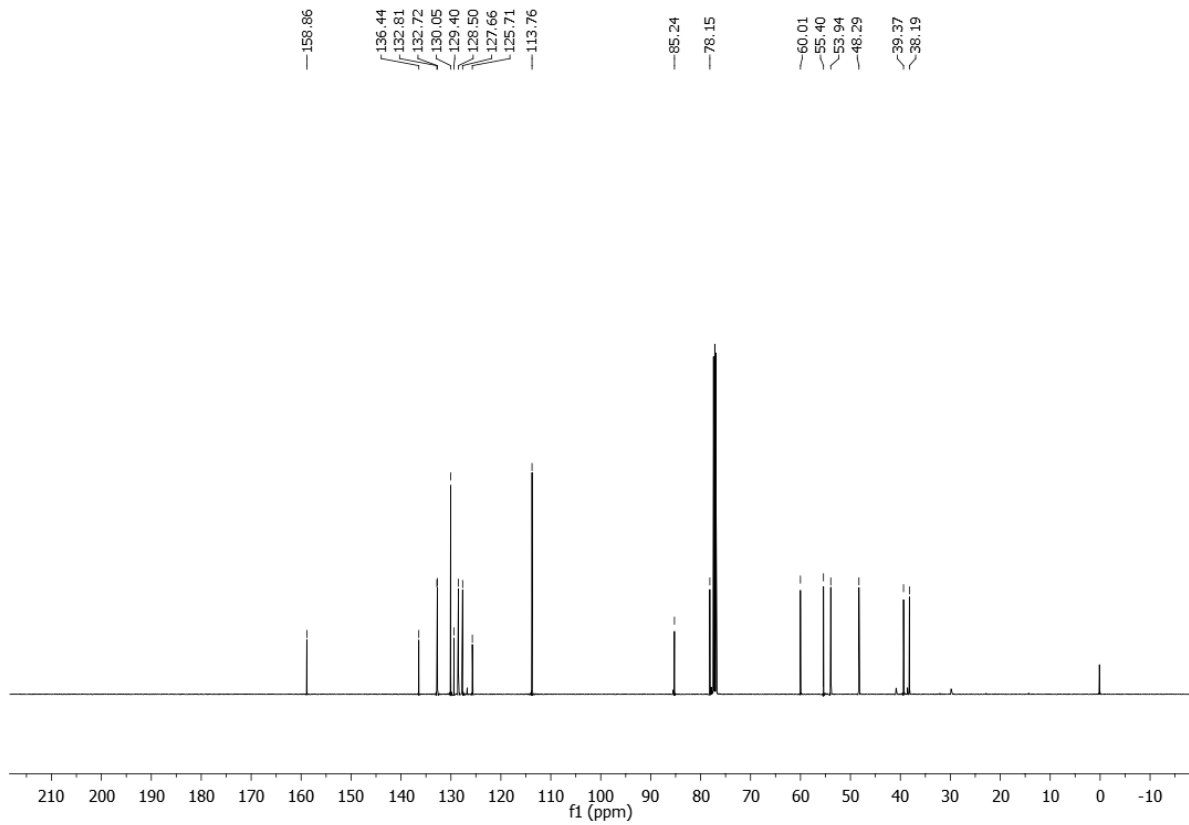
¹³C{¹H} NMR (126 MHz, CDCl₃)



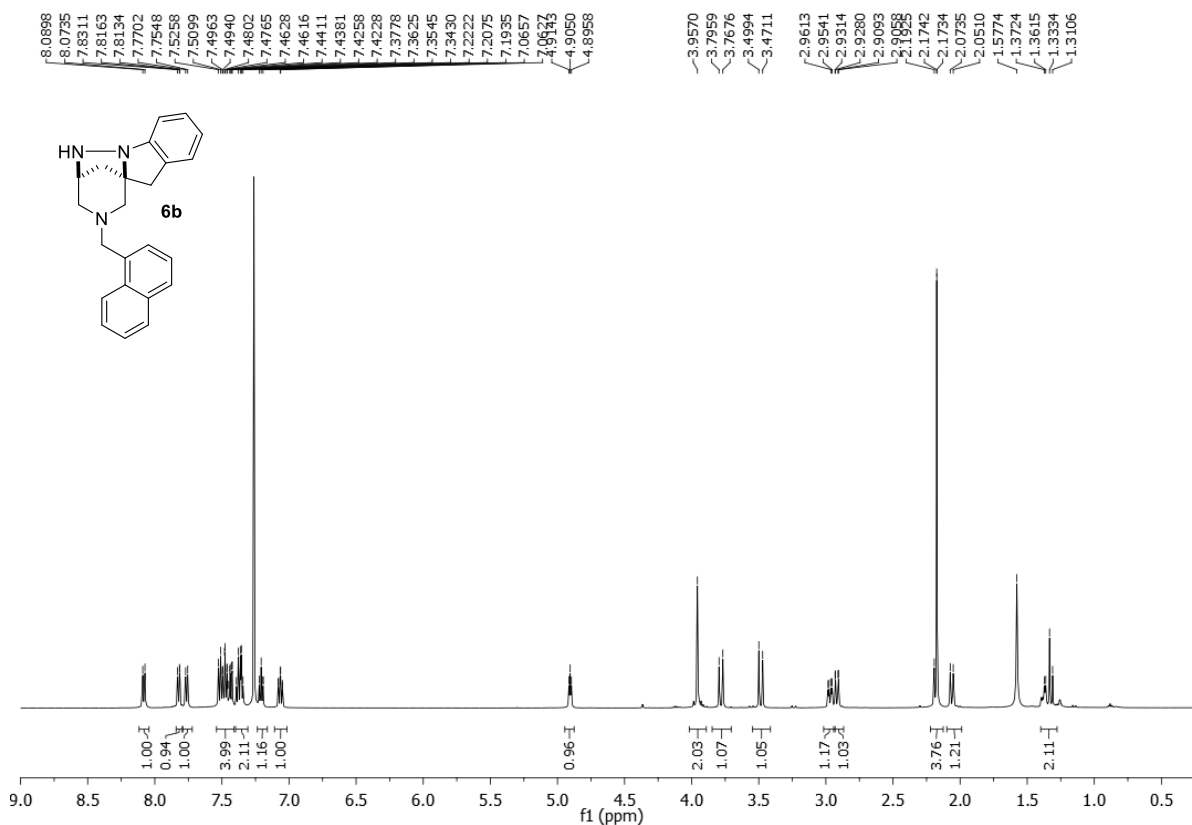
¹H NMR (500 MHz, CDCl₃)



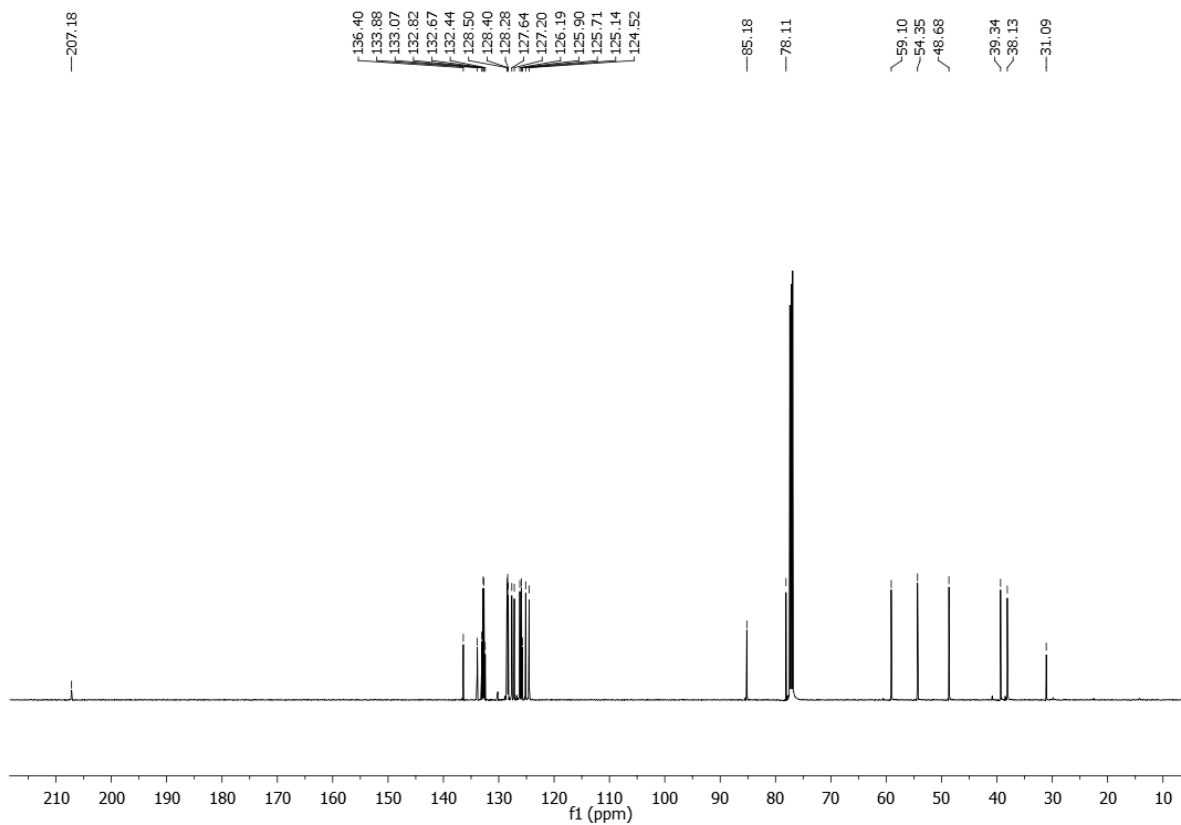
¹³C{¹H} NMR (126 MHz, CDCl₃)



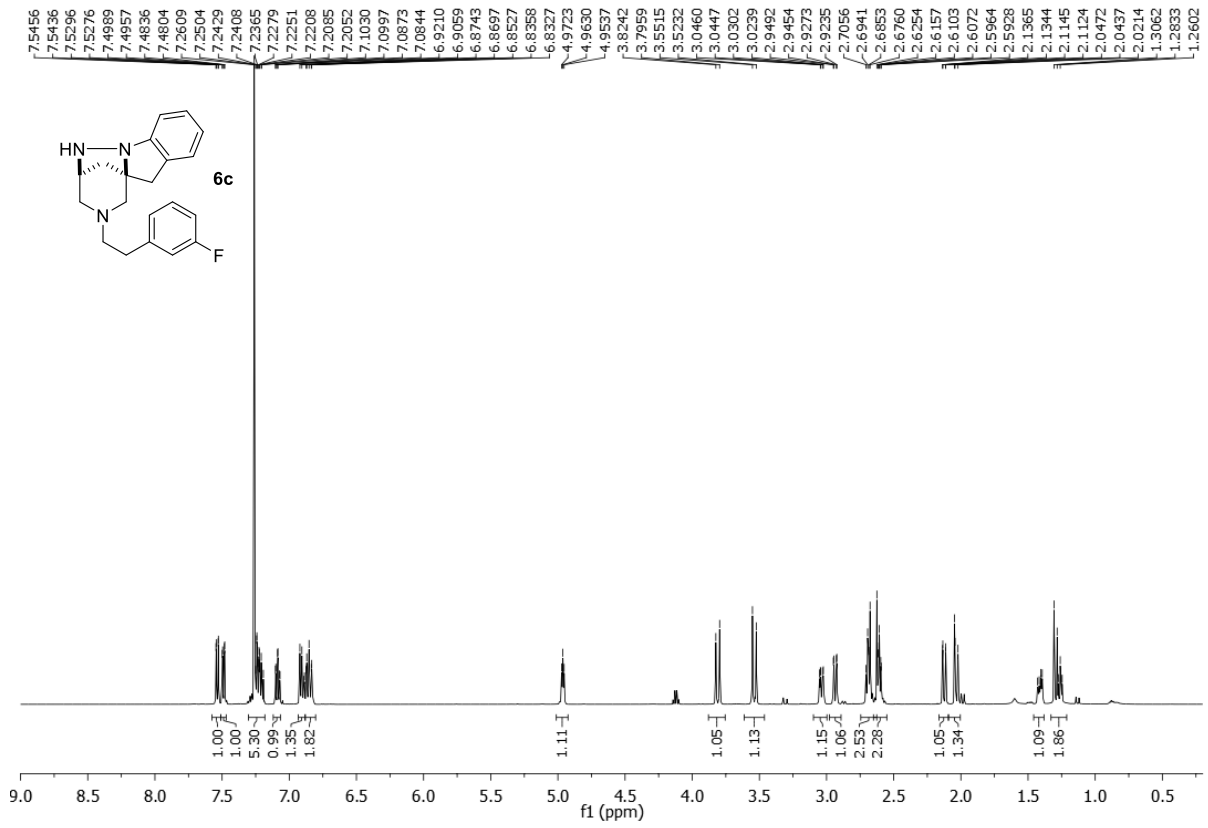
¹H NMR (500 MHz, CDCl₃)



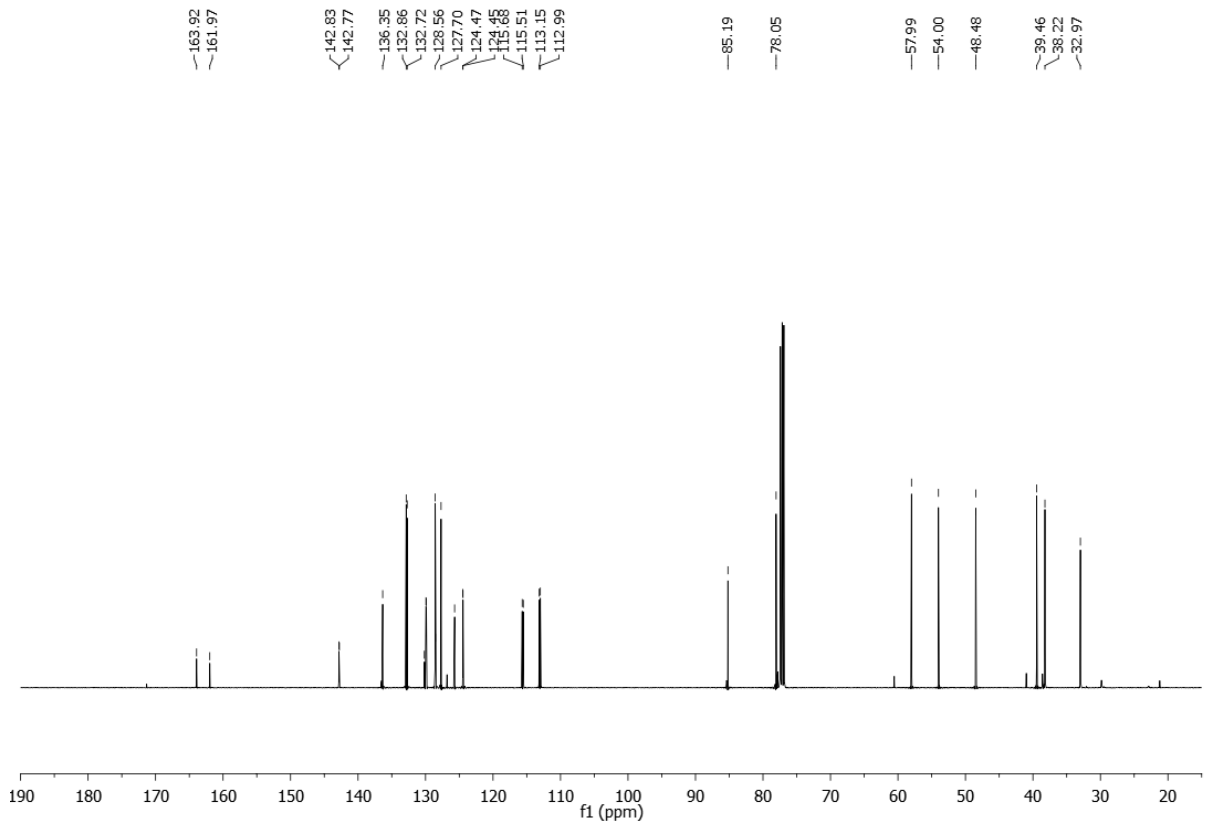
¹³C{¹H} NMR (126 MHz, CDCl₃)



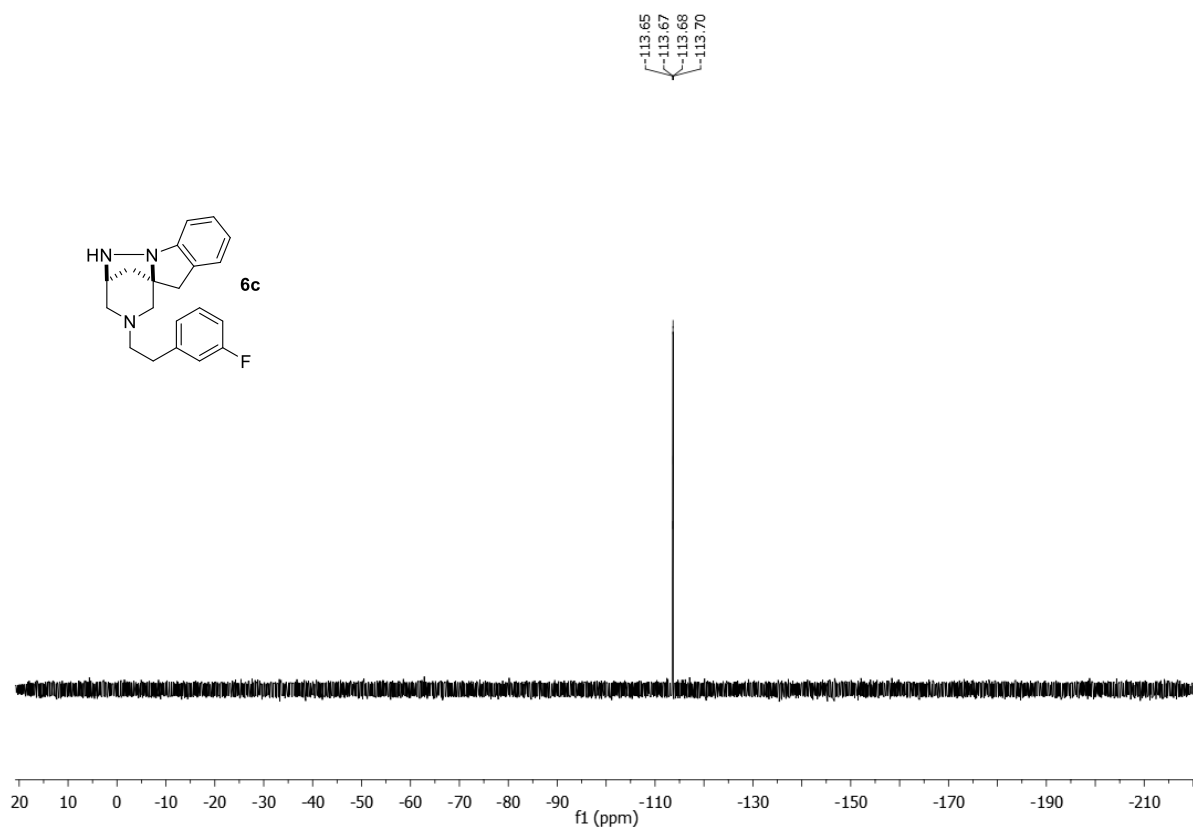
¹H NMR (500 MHz, CDCl₃)



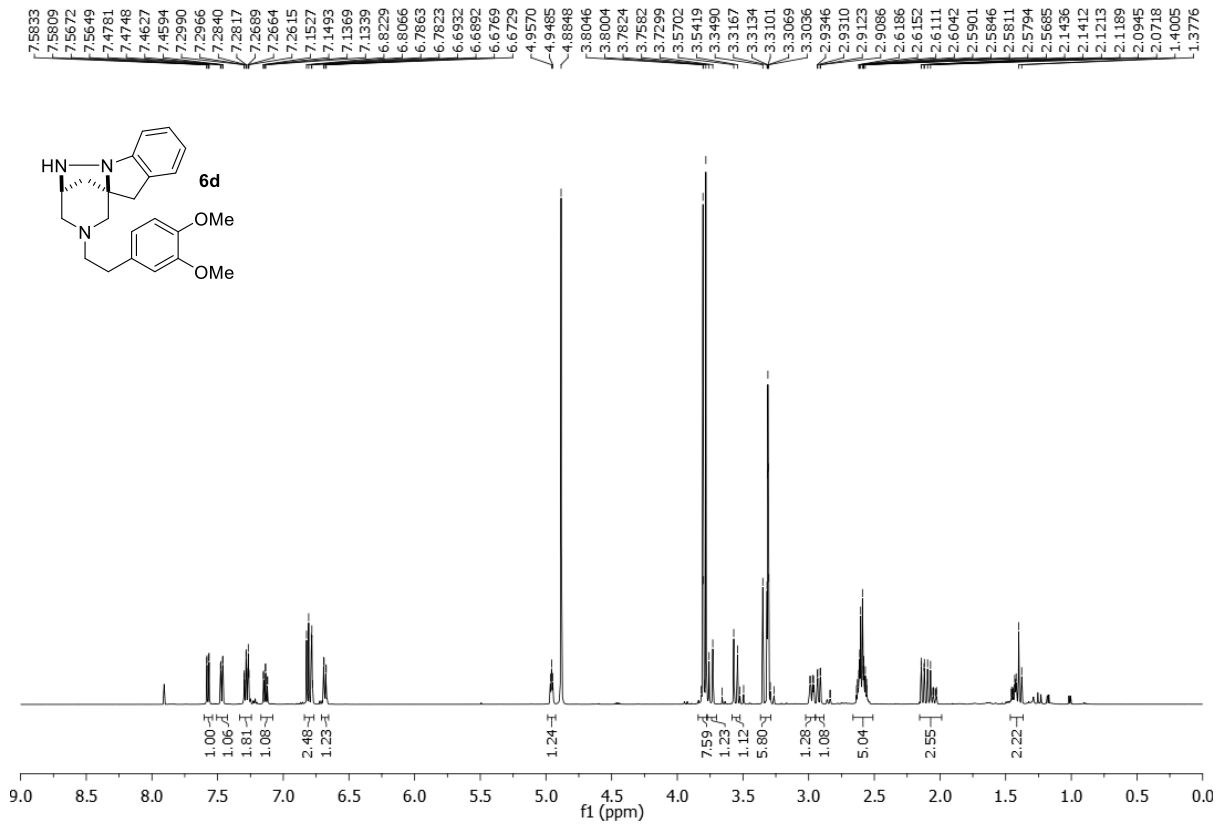
¹³C{¹H} NMR (126 MHz, CDCl₃)



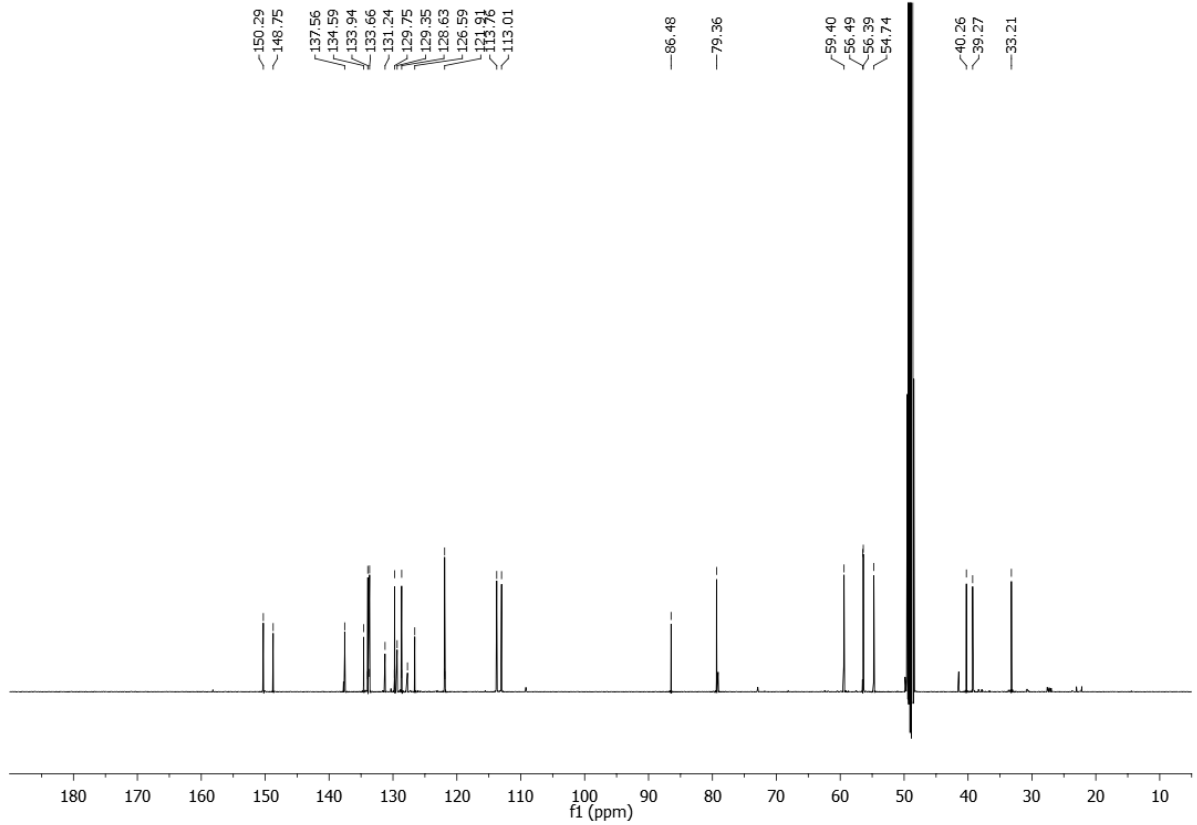
^{19}F NMR (471 MHz, CDCl_3)



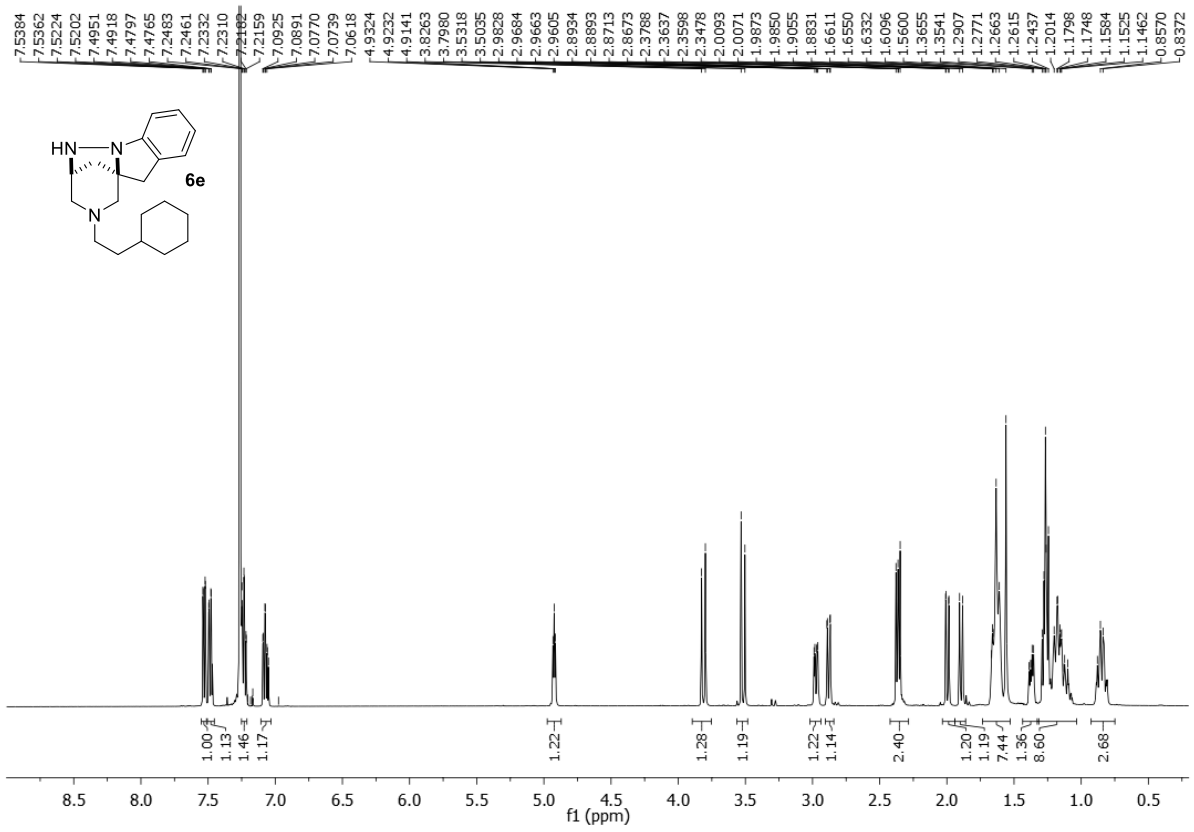
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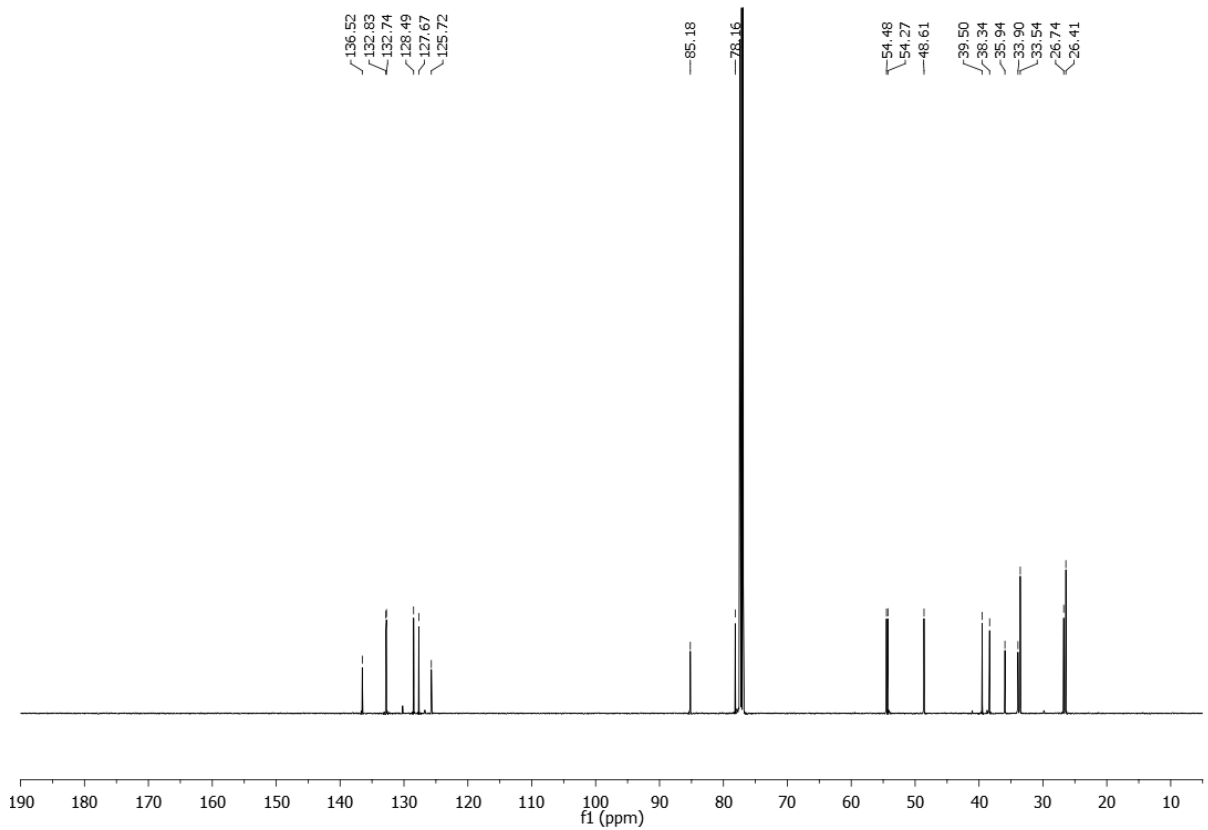
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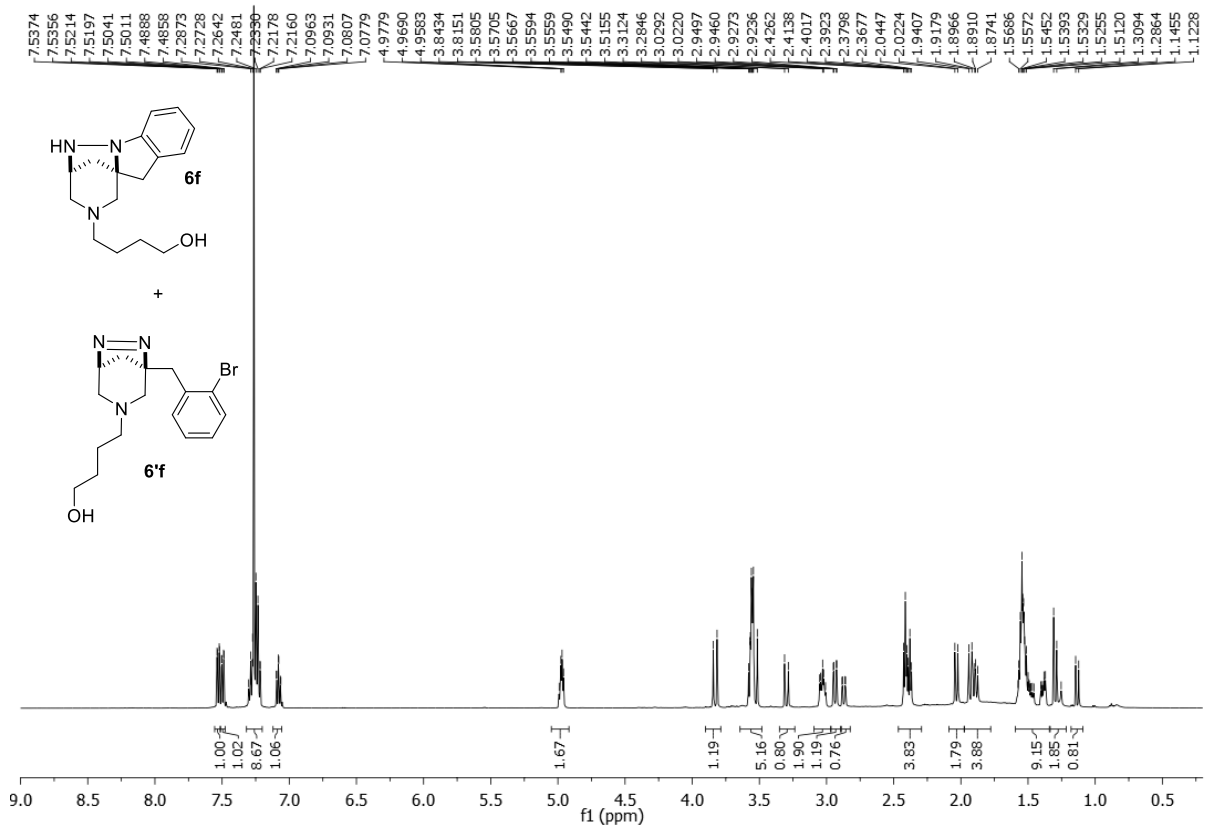
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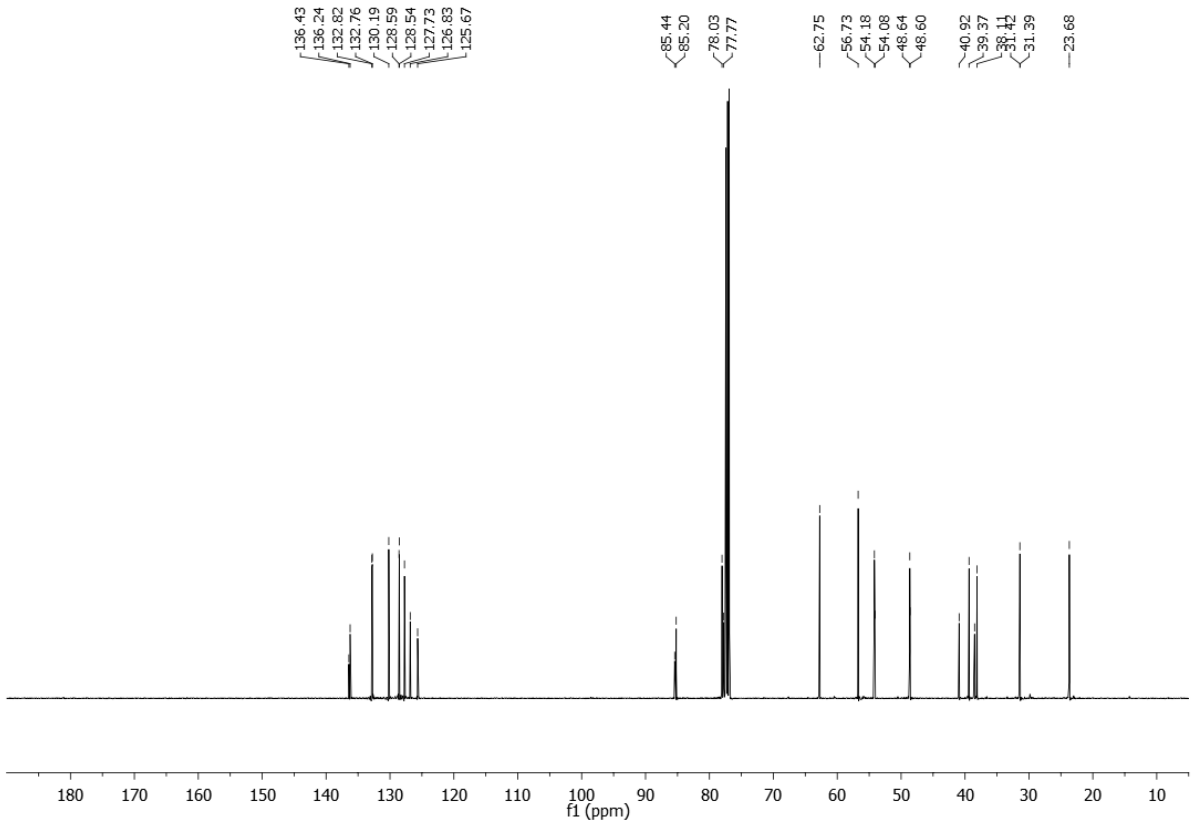
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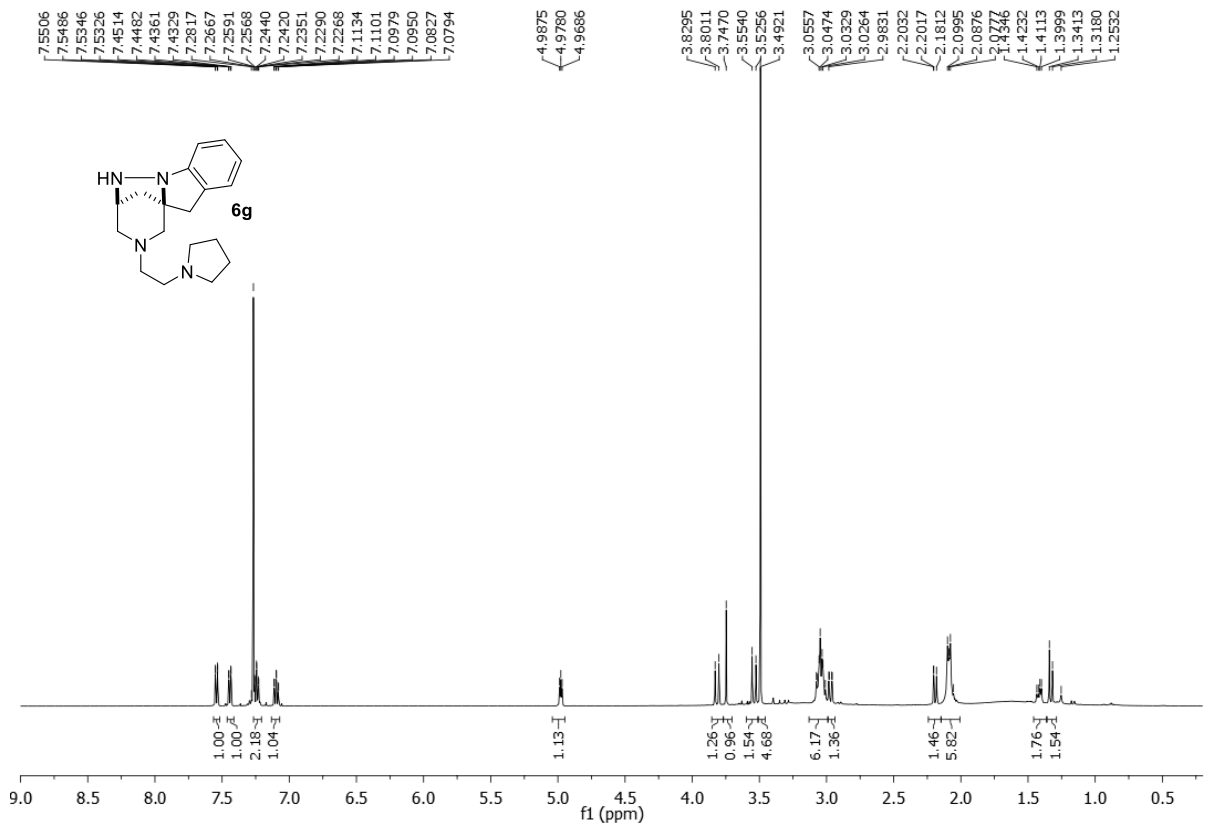
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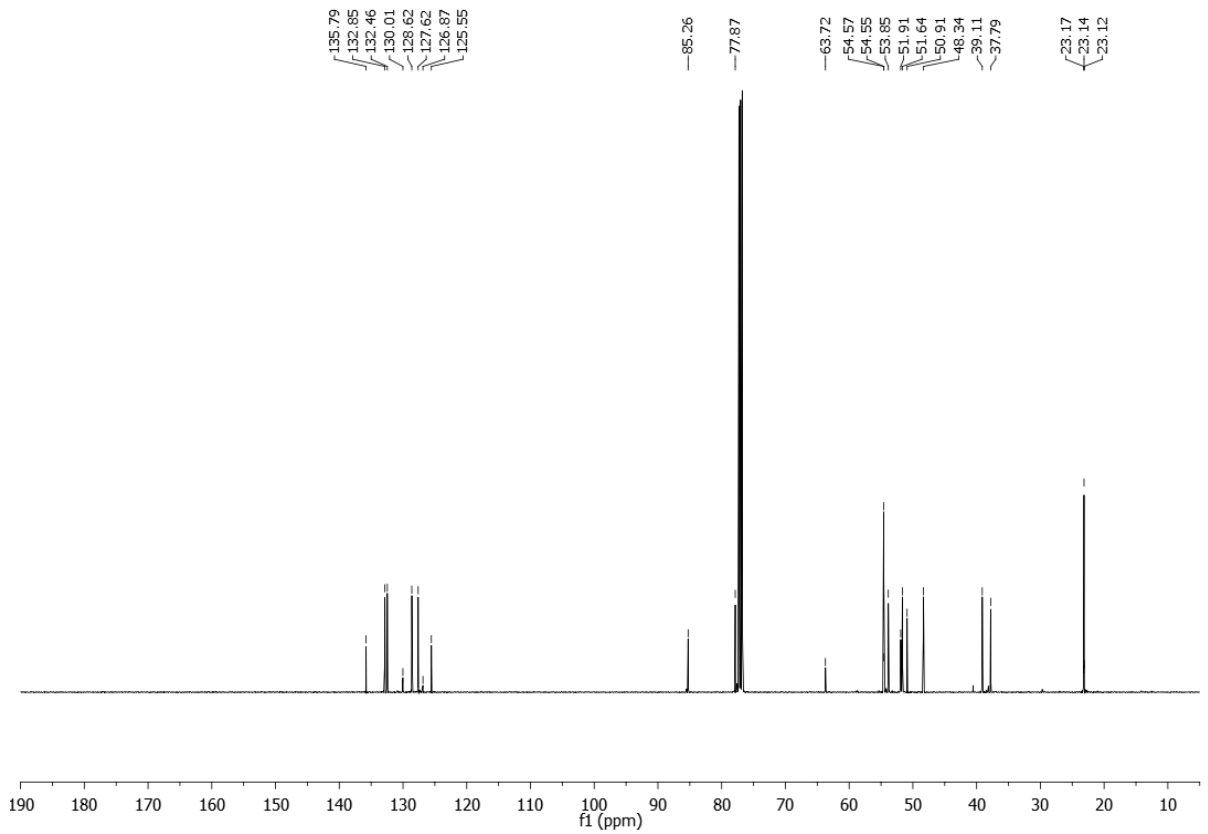
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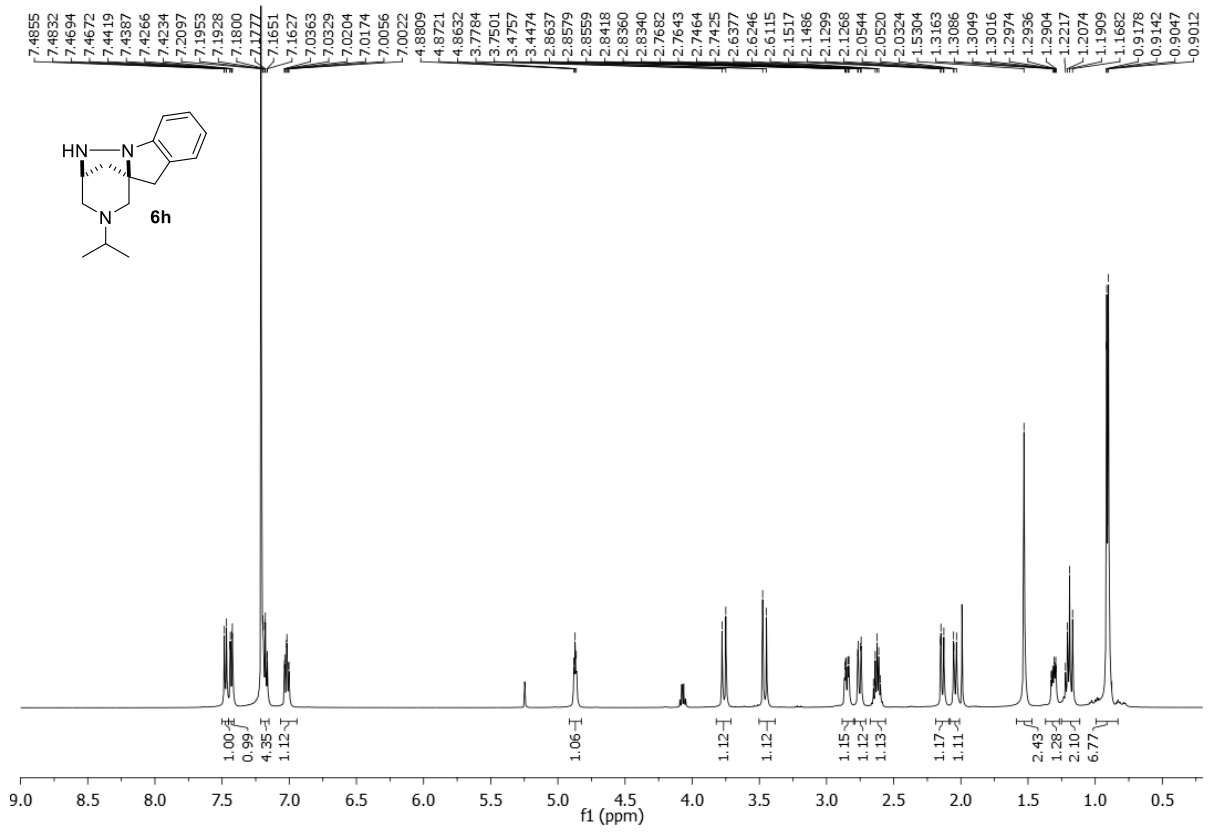
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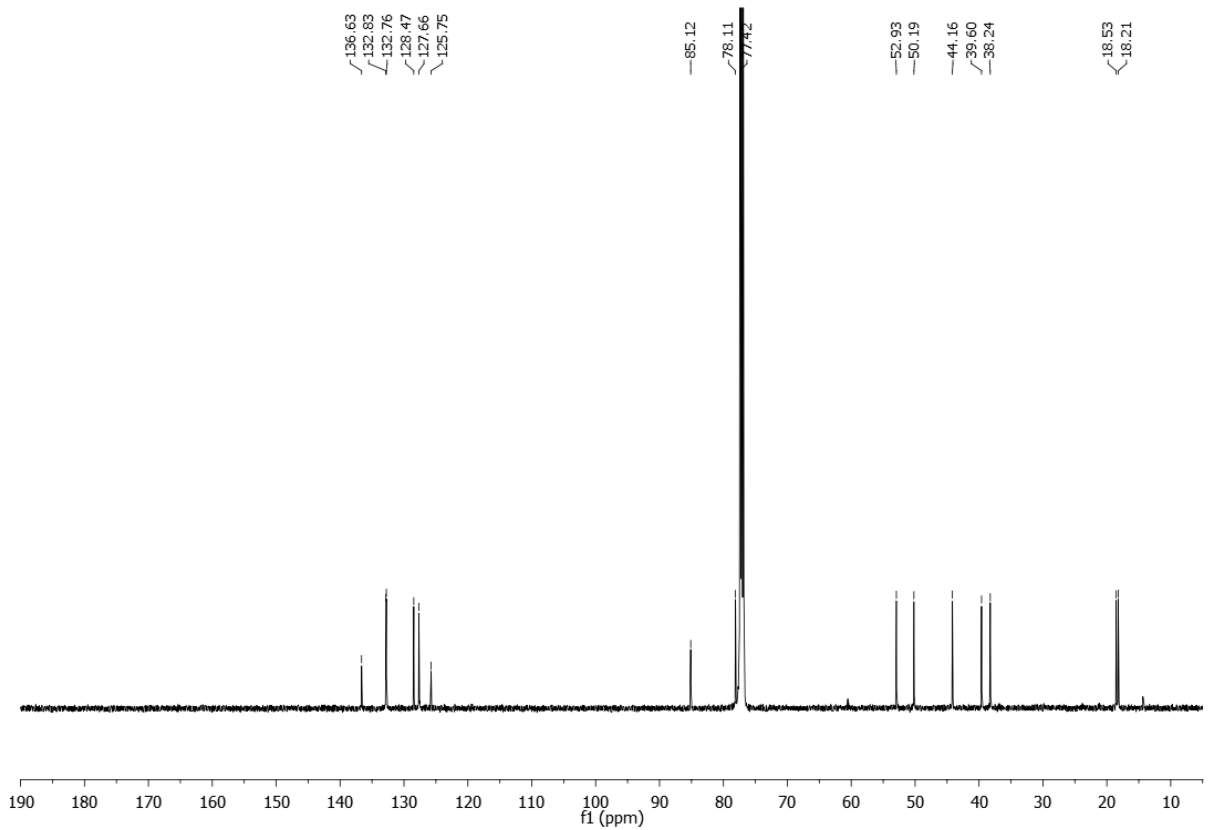
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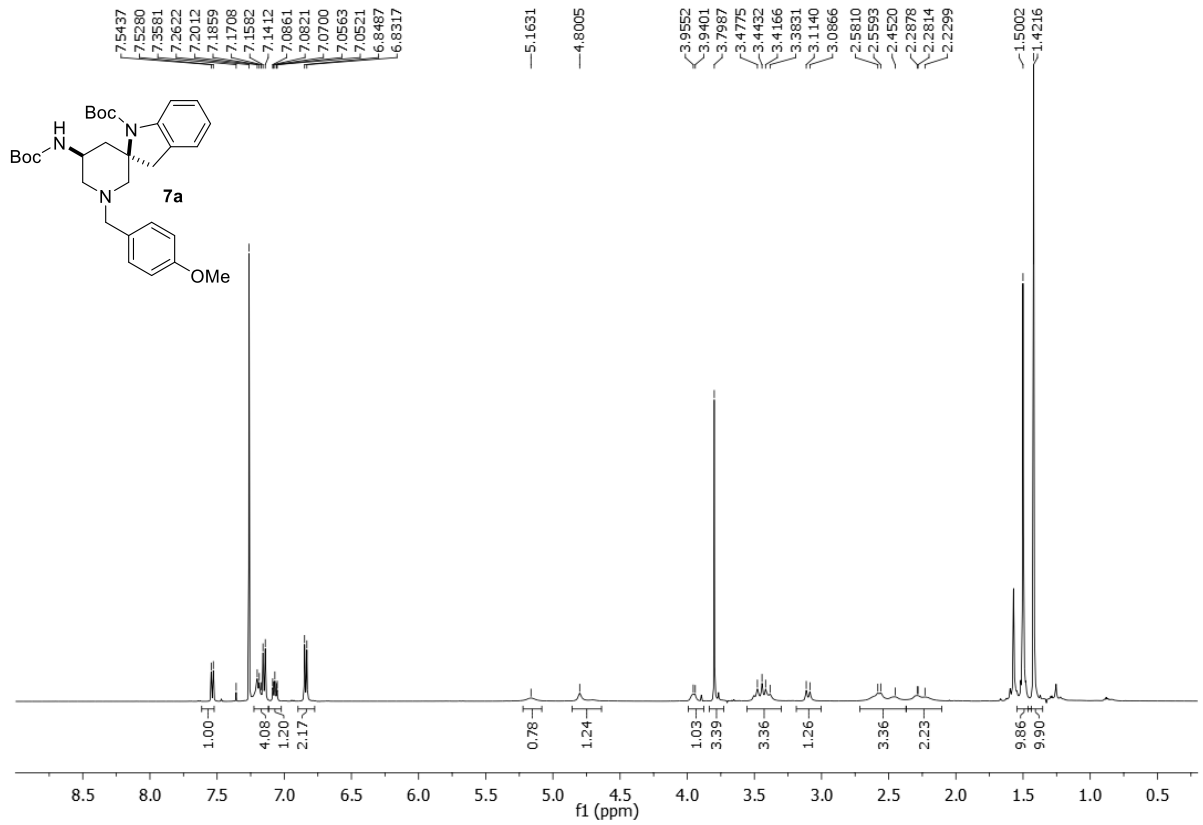
¹H NMR (500 MHz, CDCl₃)



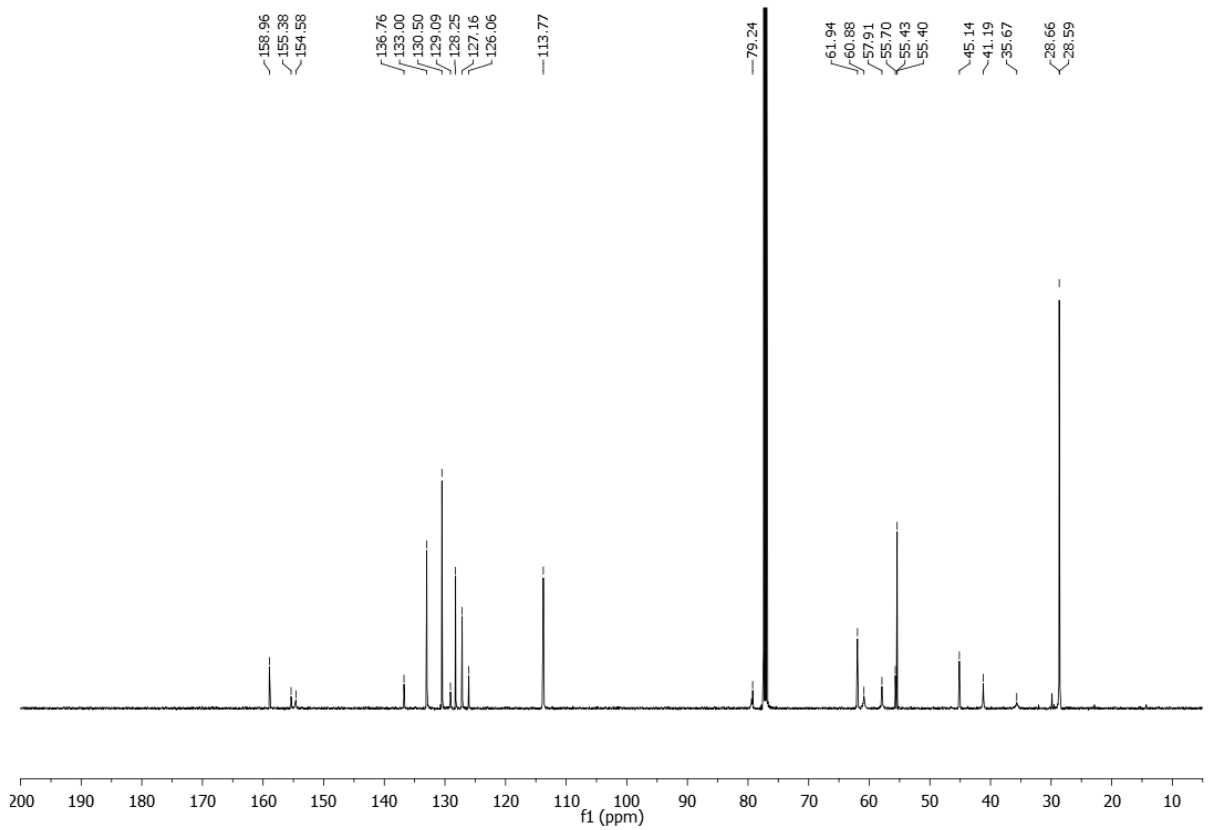
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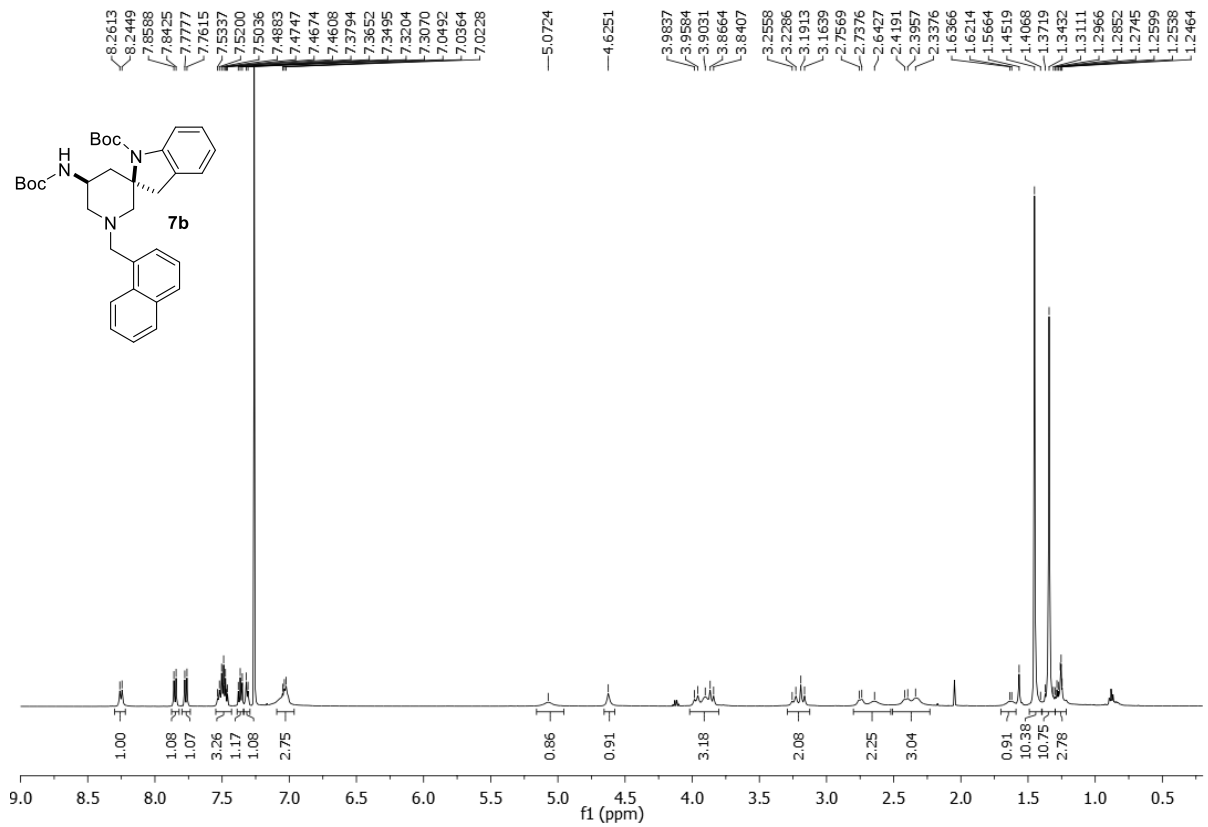
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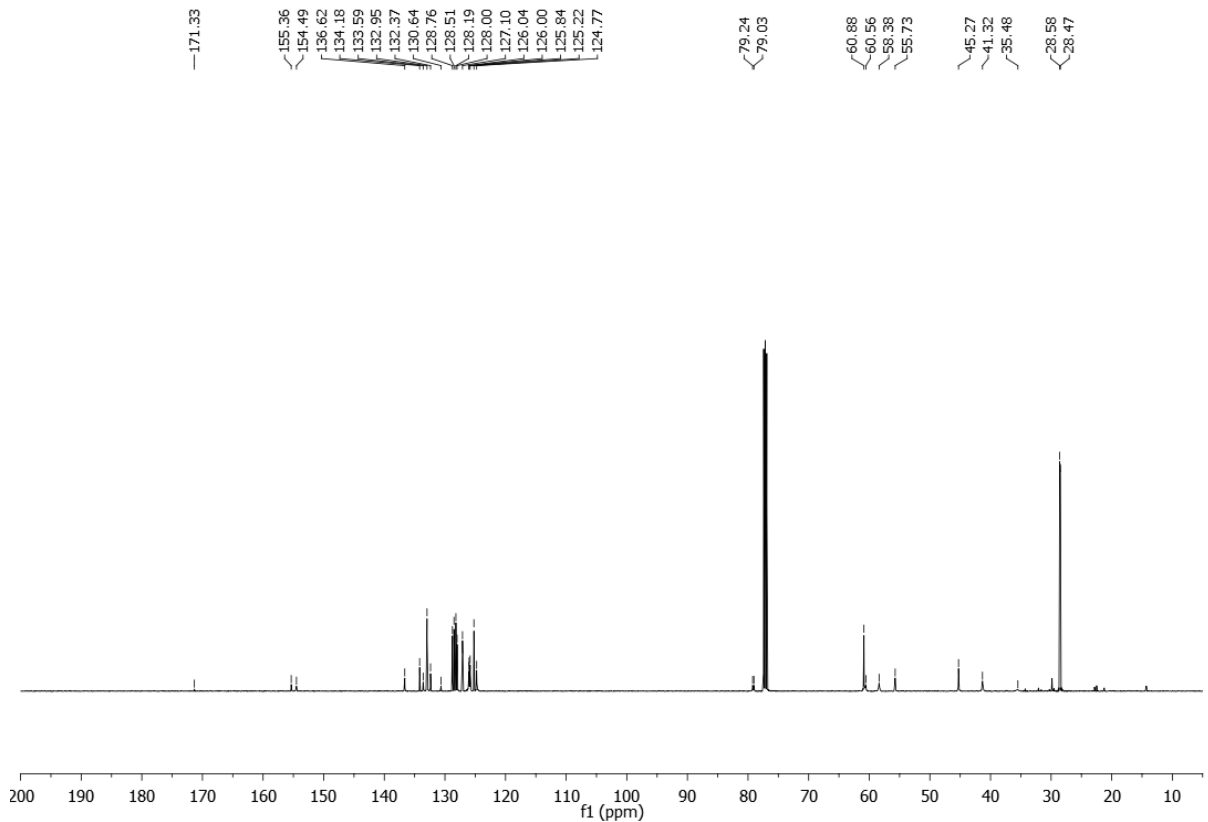
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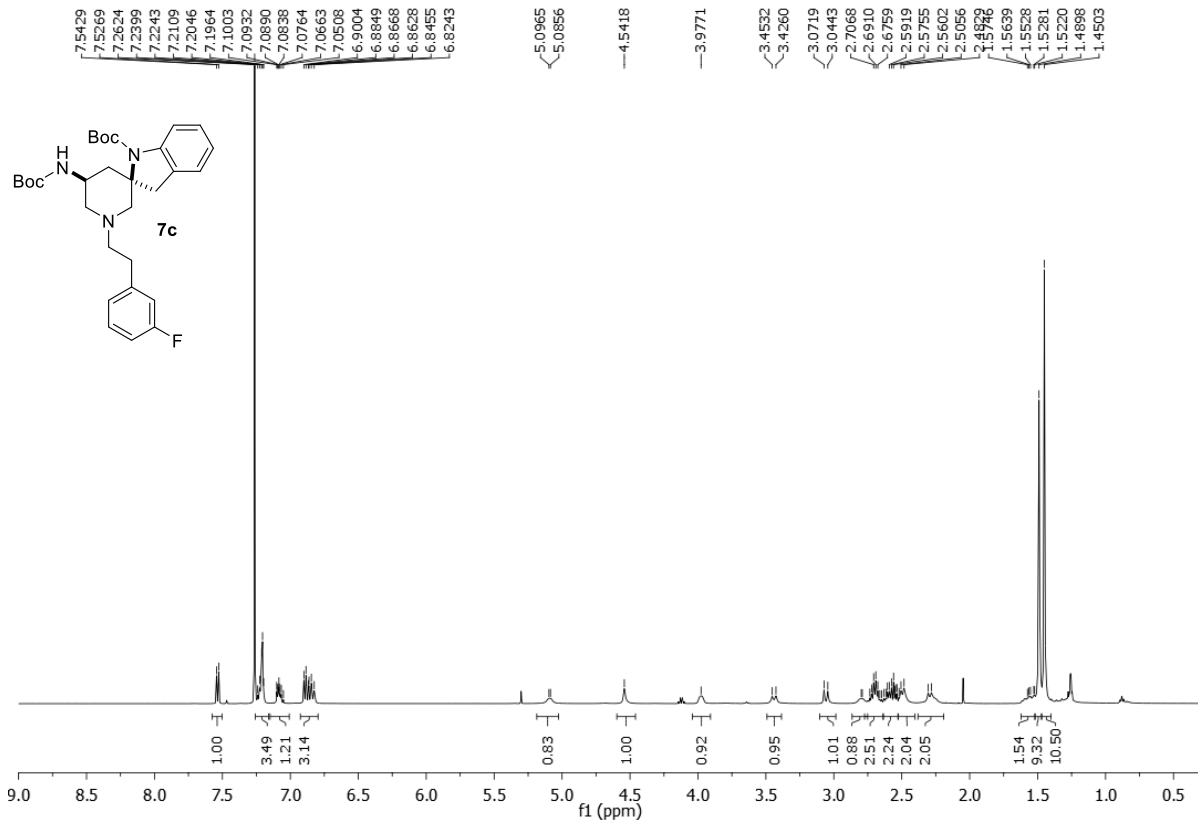
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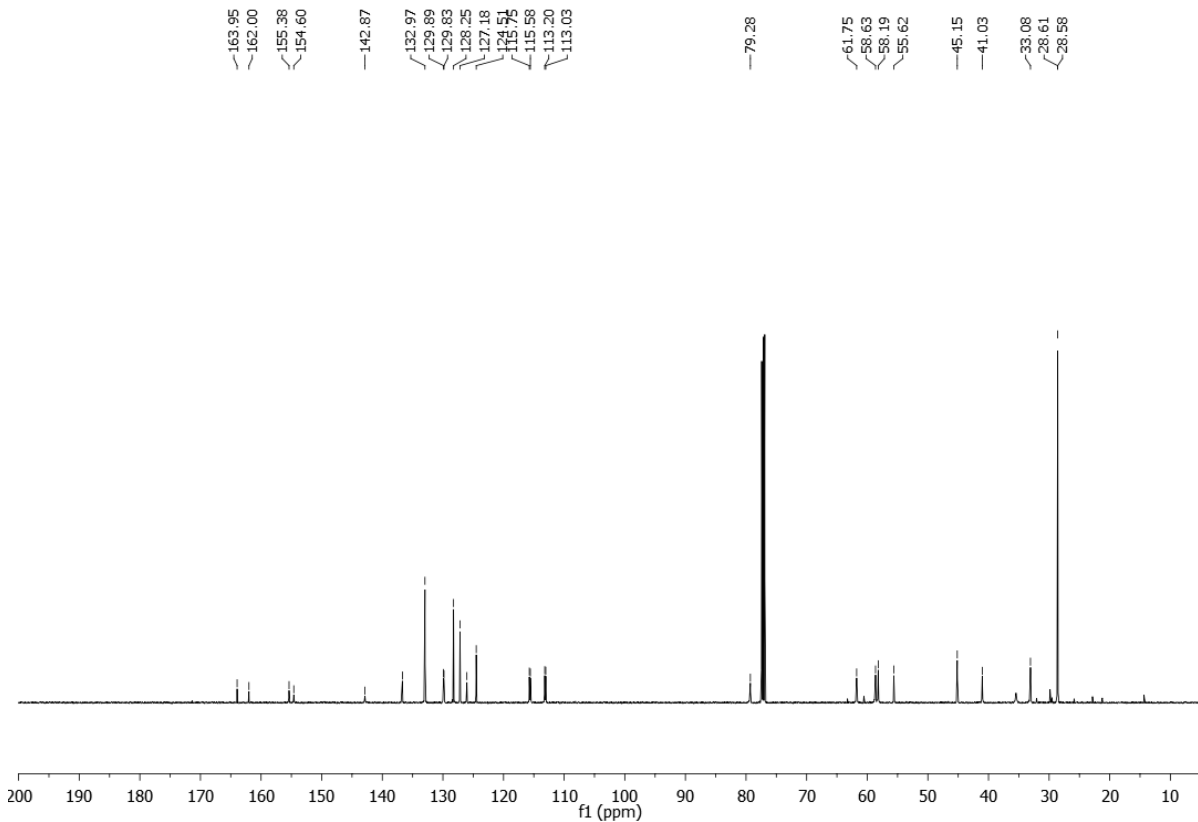
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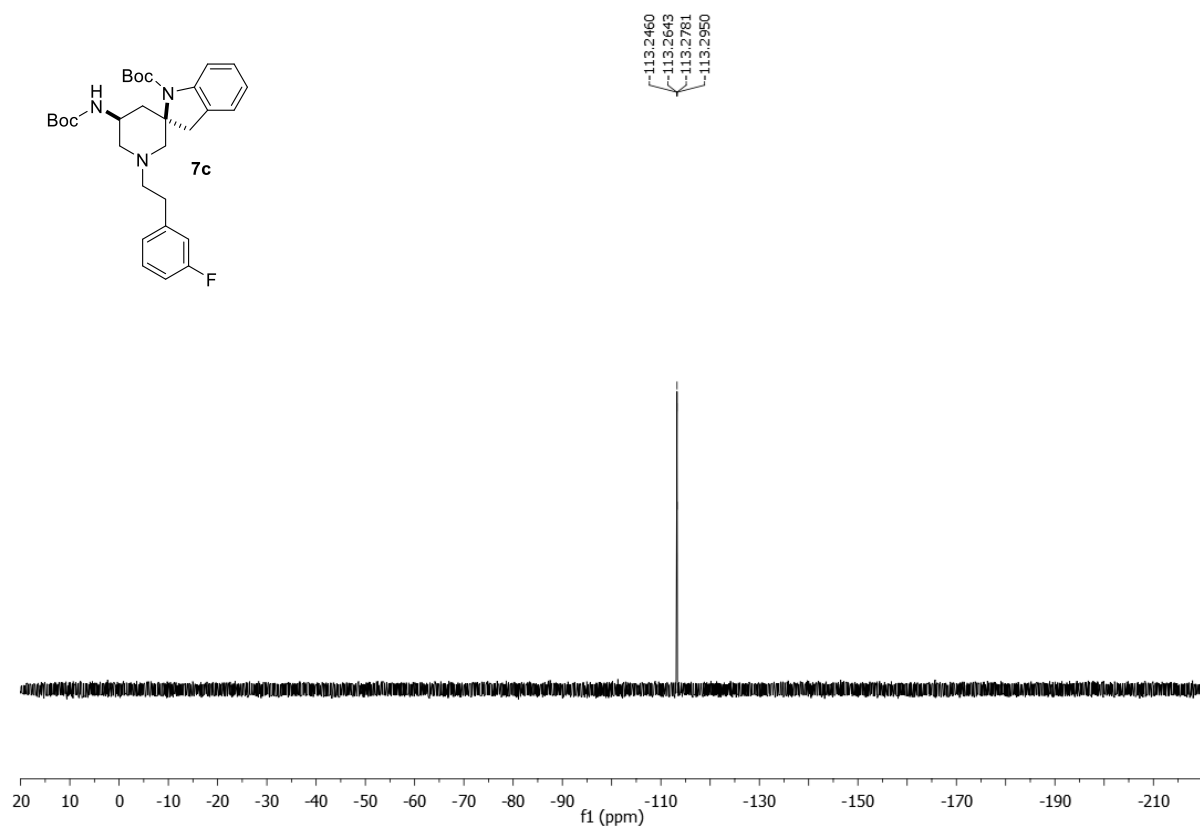
¹H NMR (500 MHz, CDCl₃)



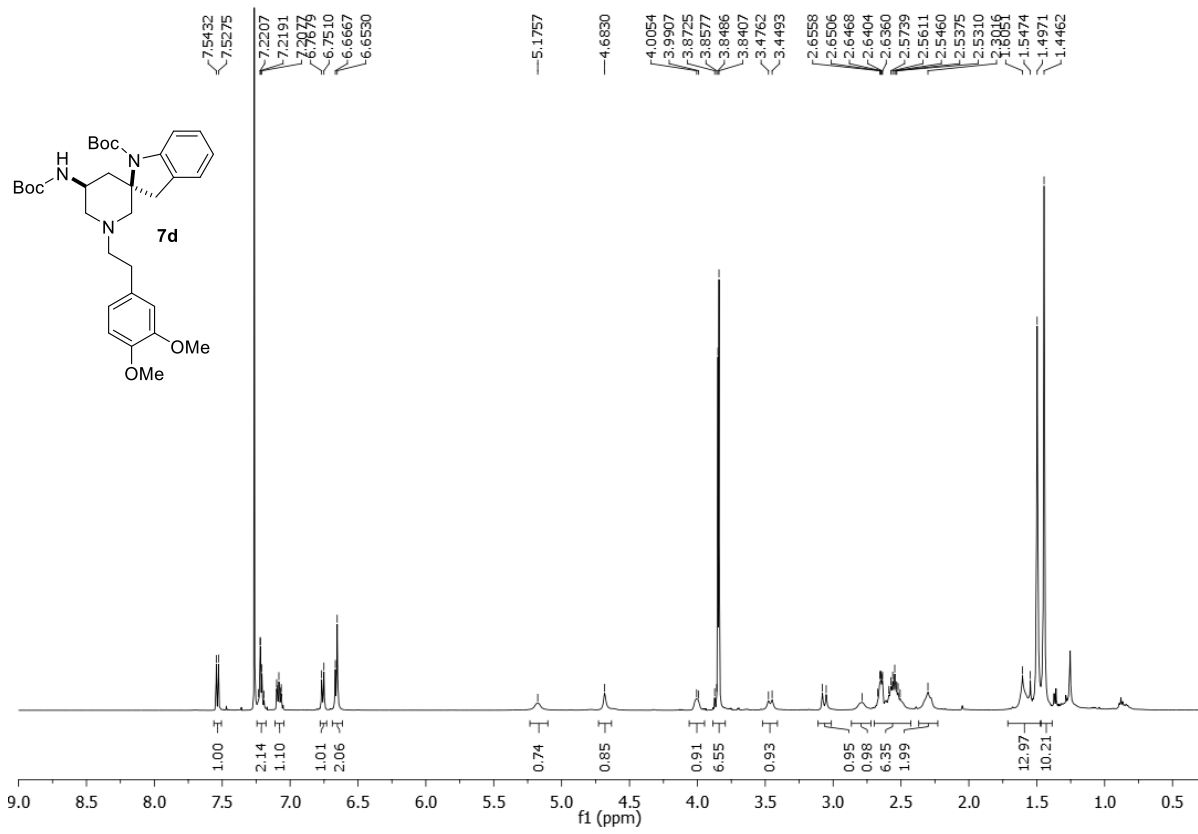
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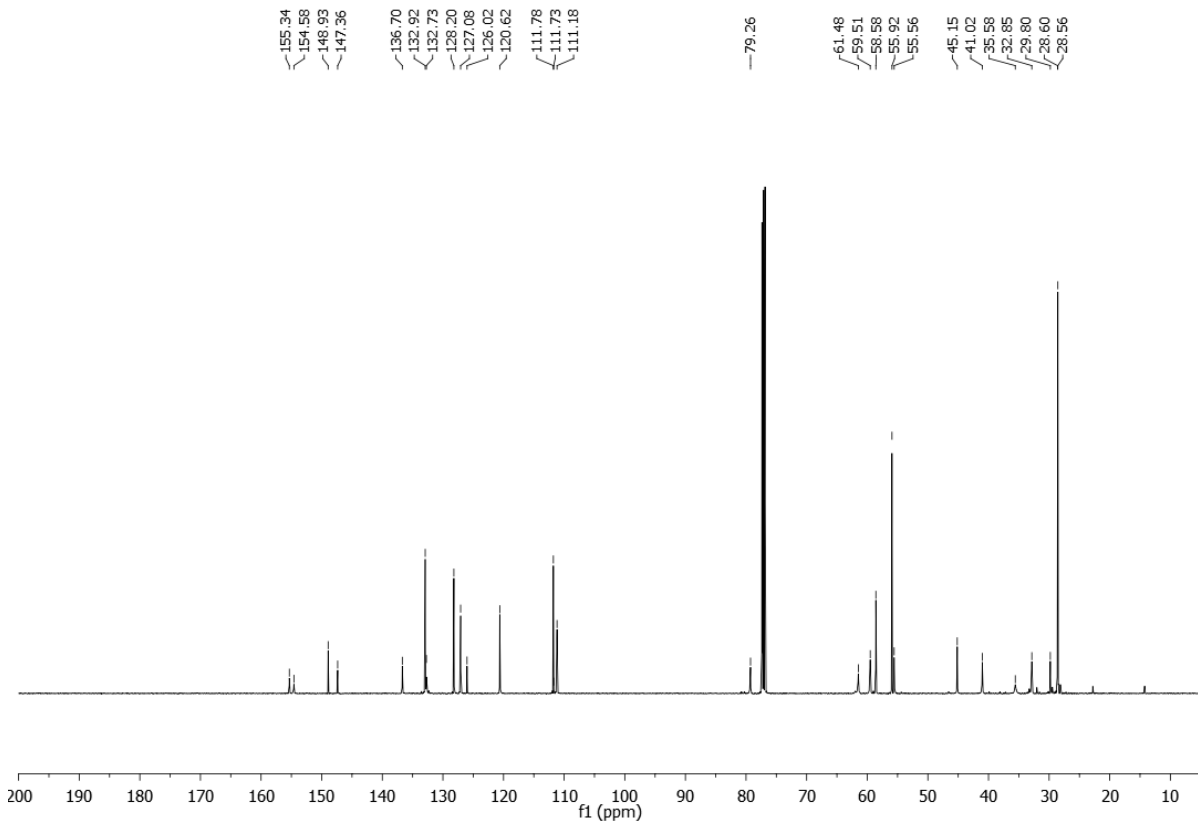
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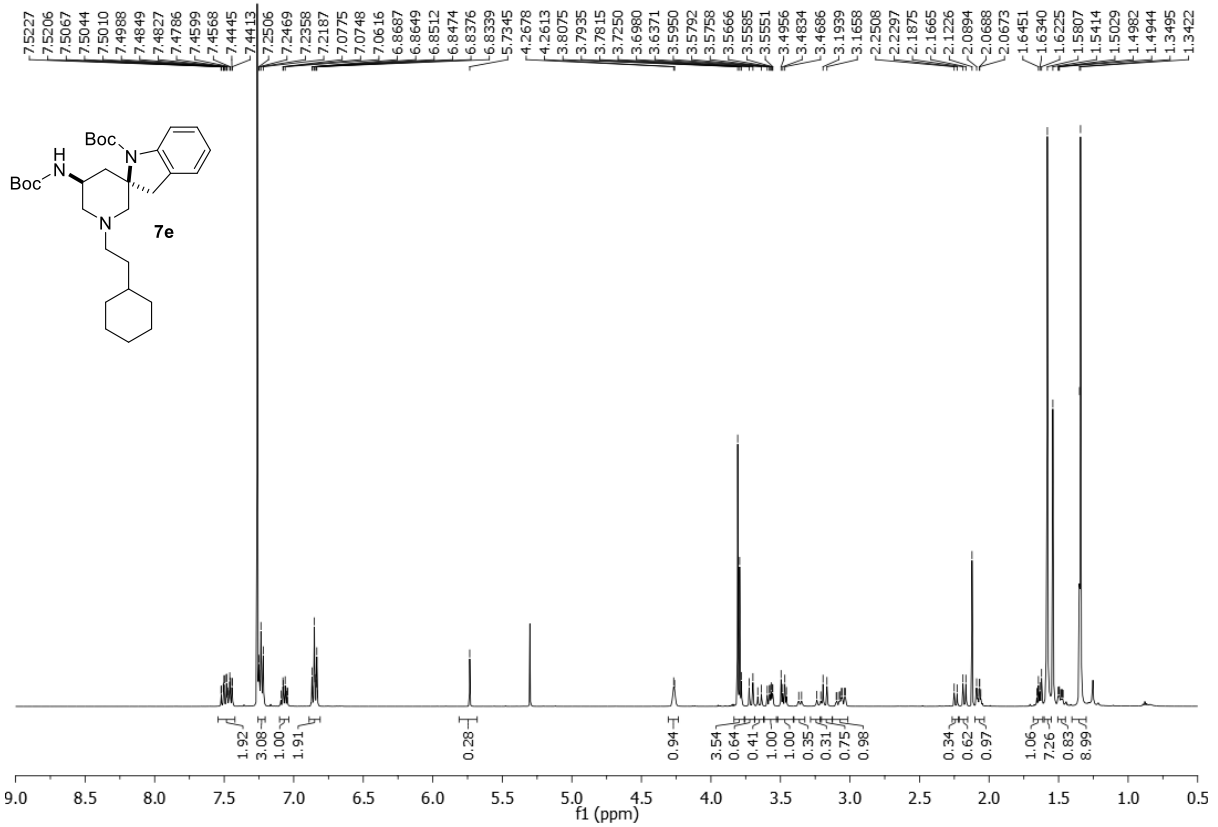
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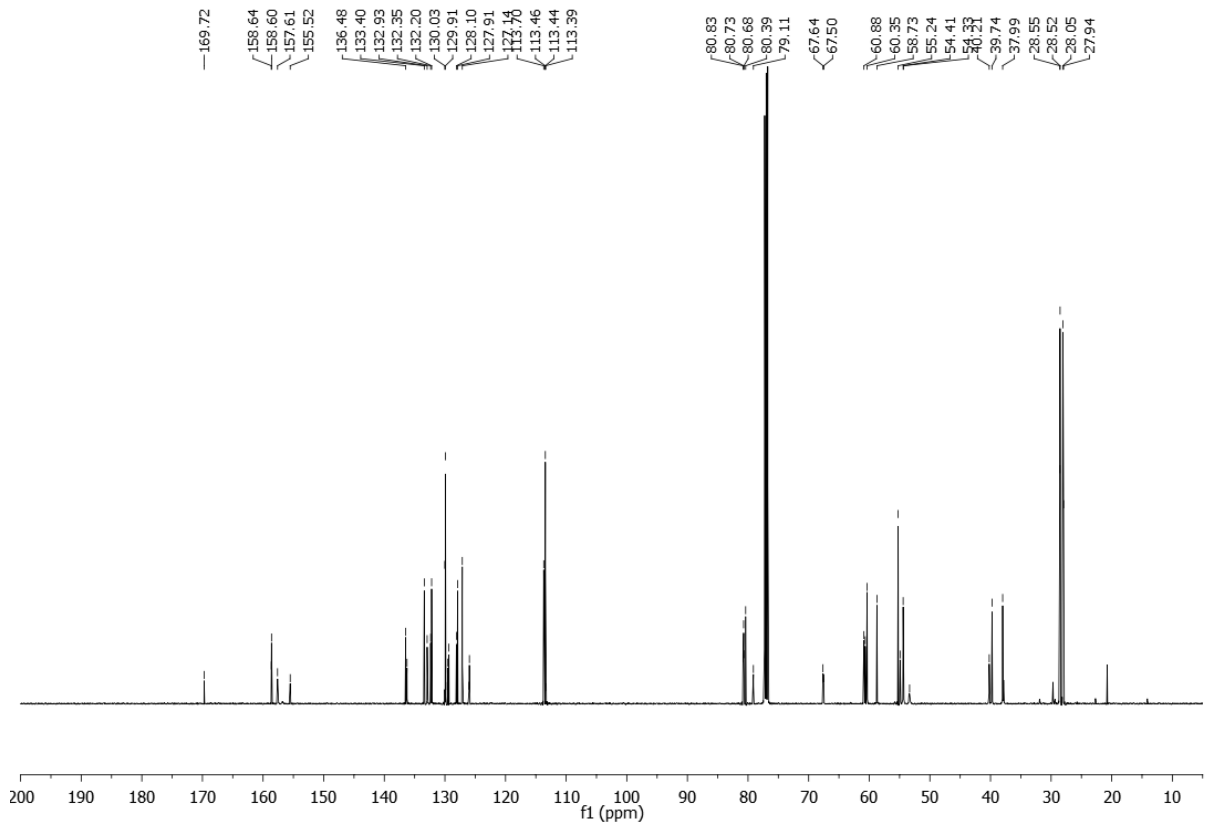
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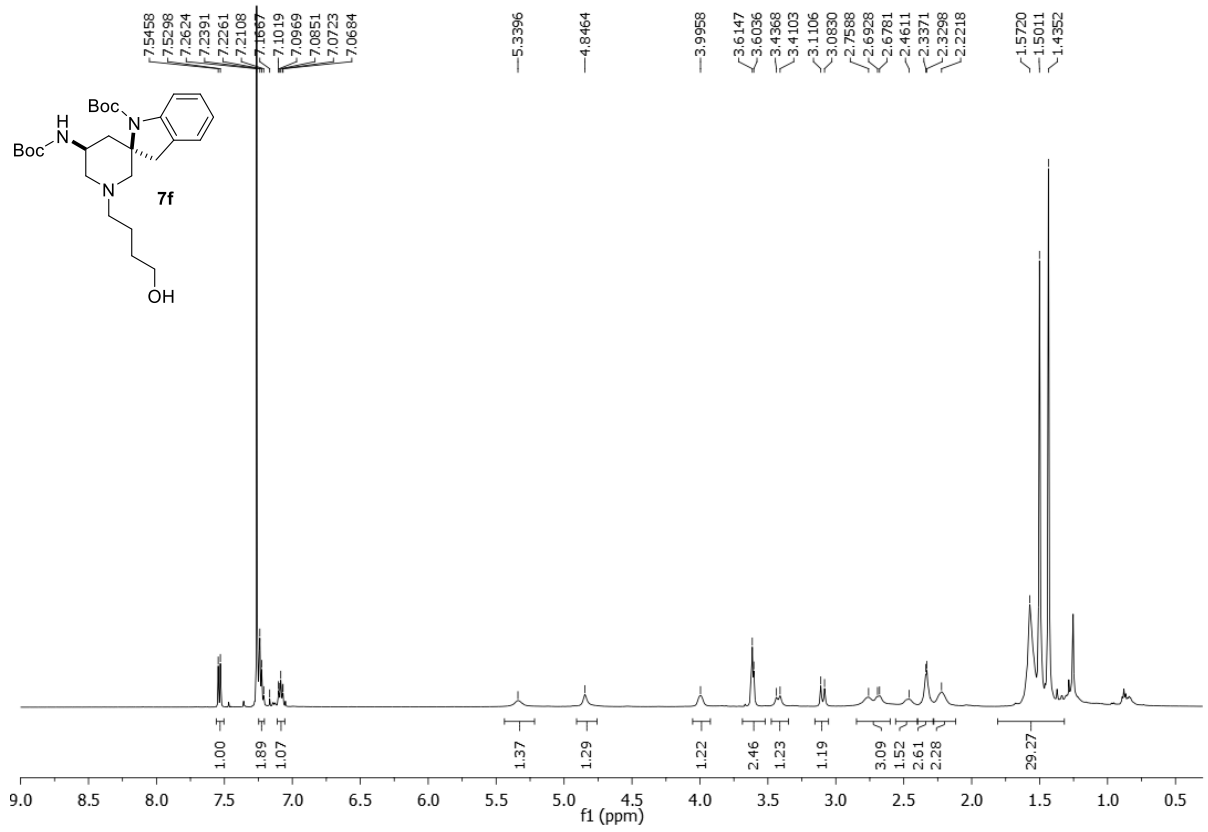
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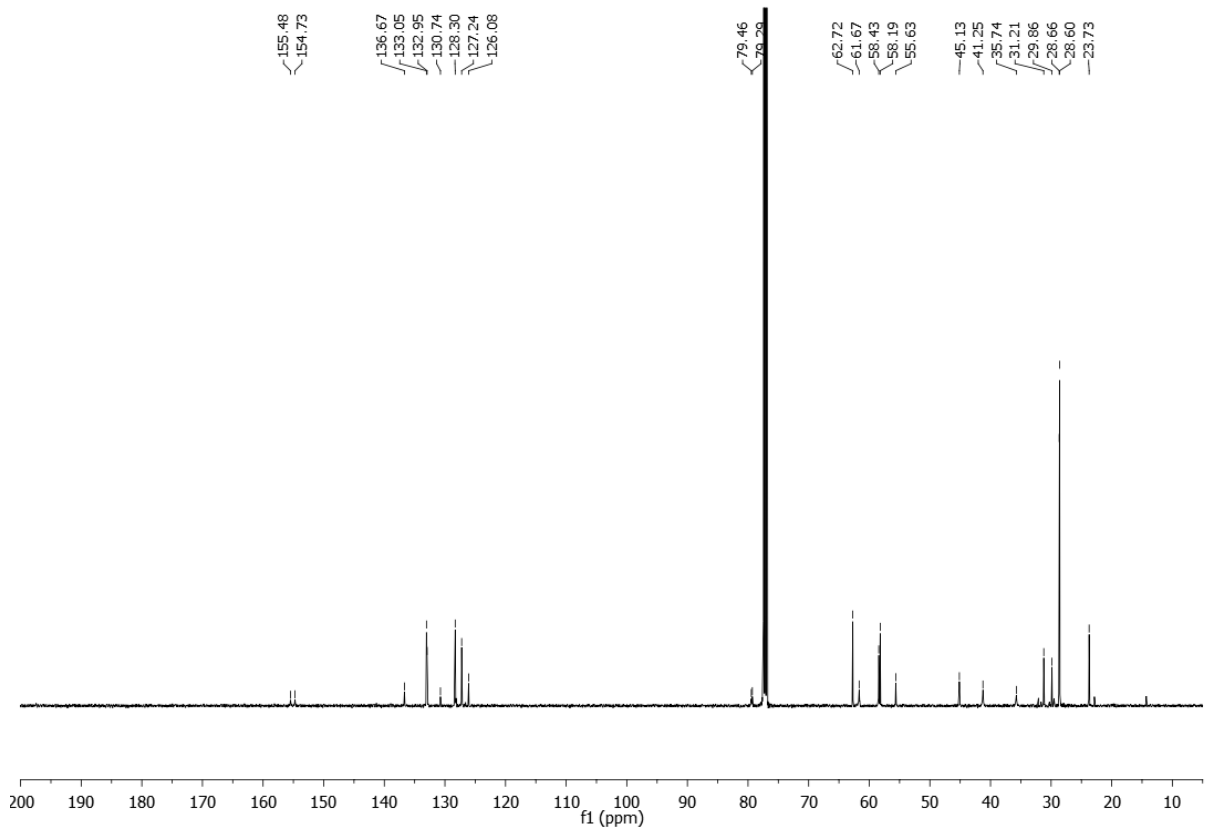
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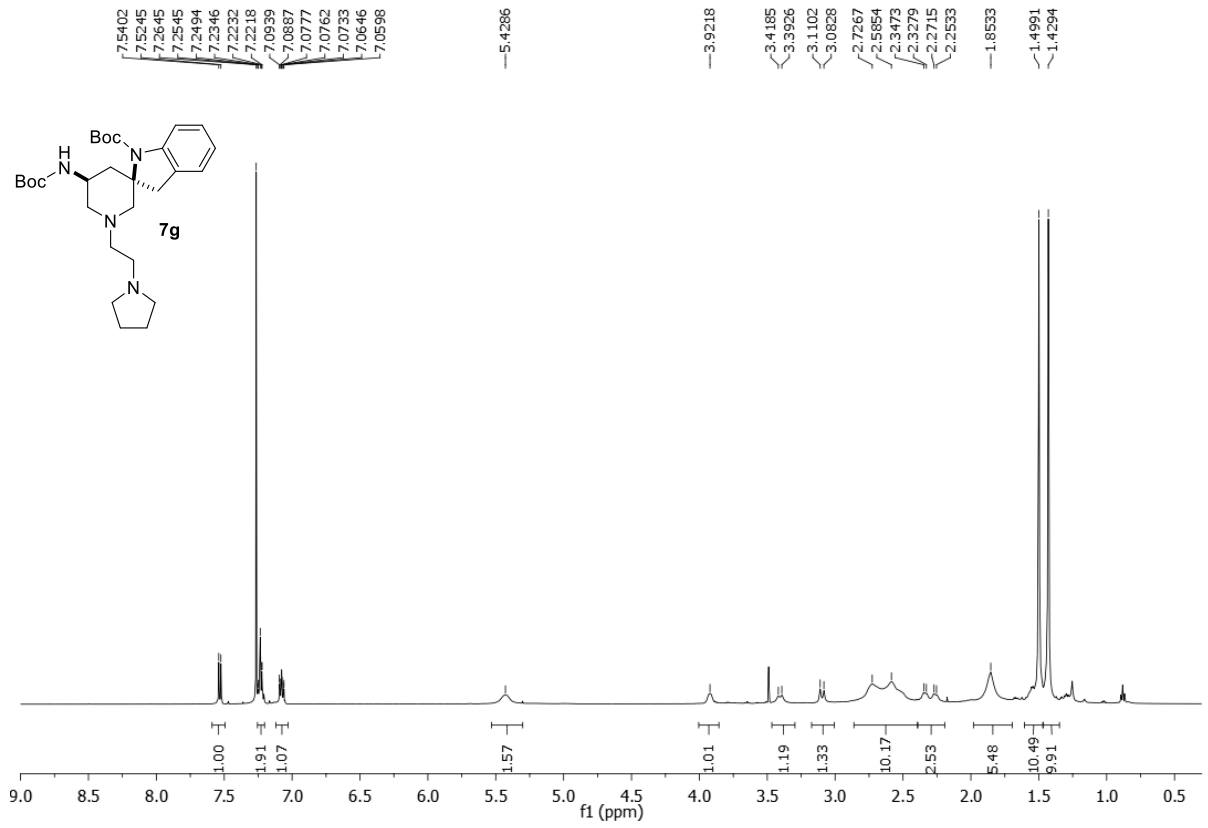
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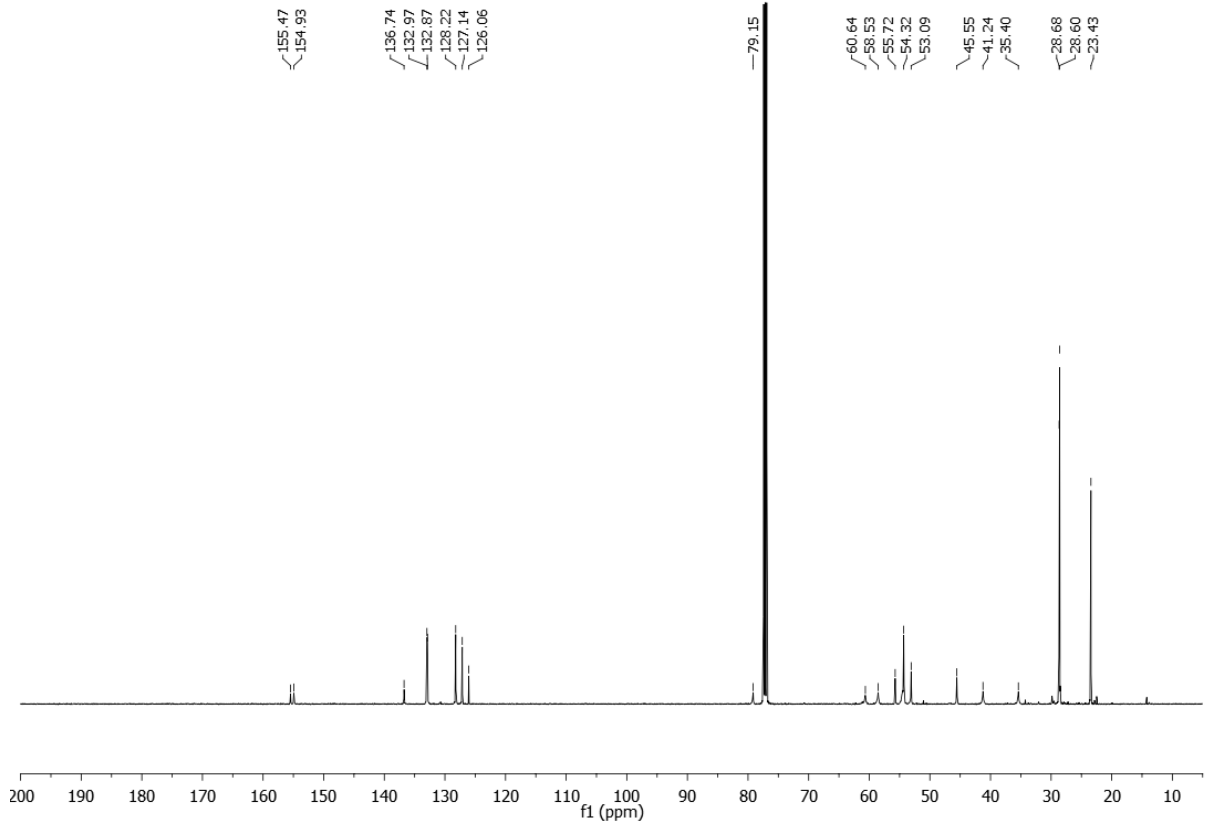
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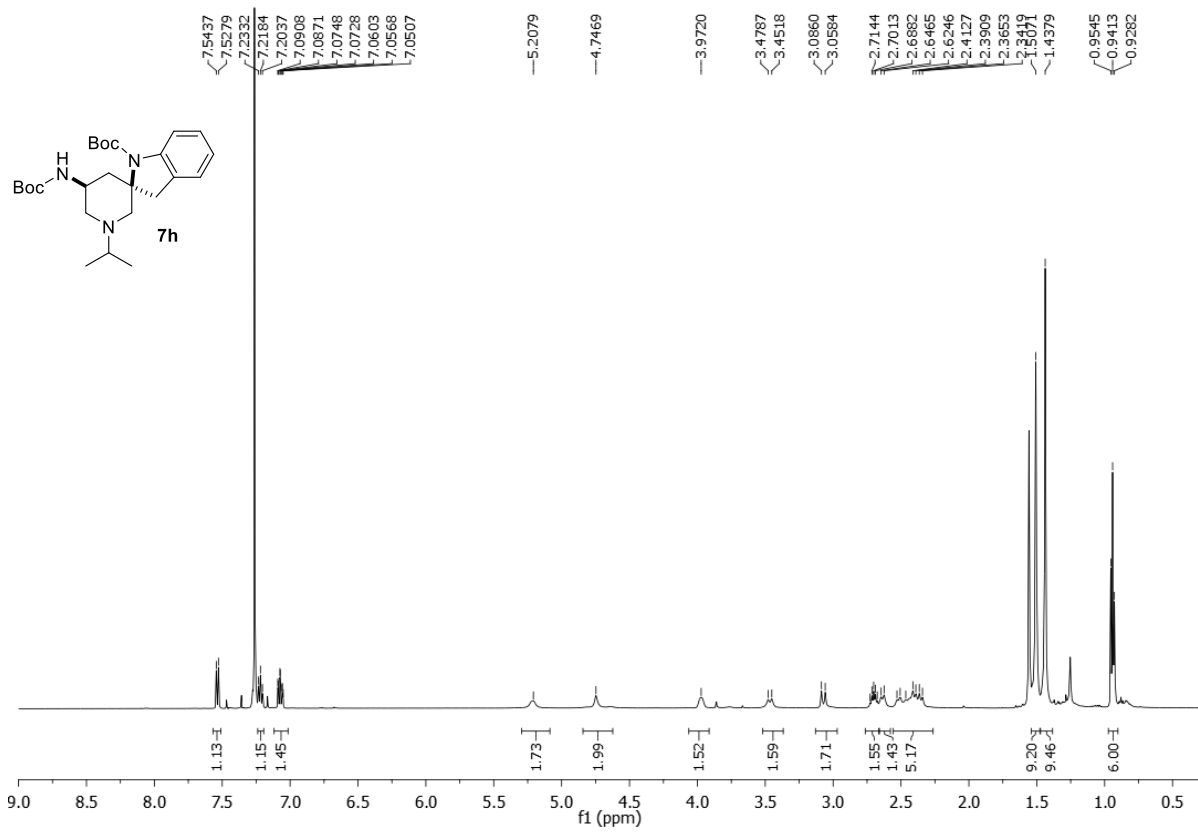
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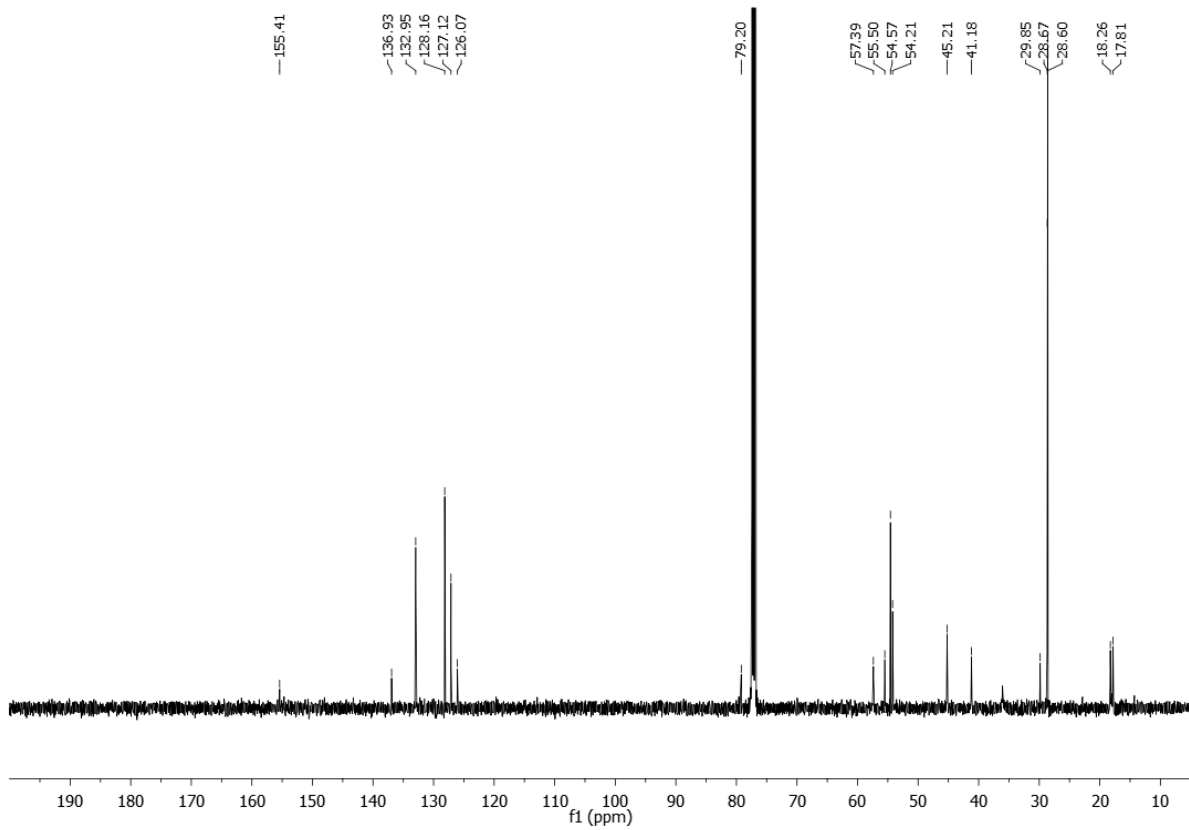
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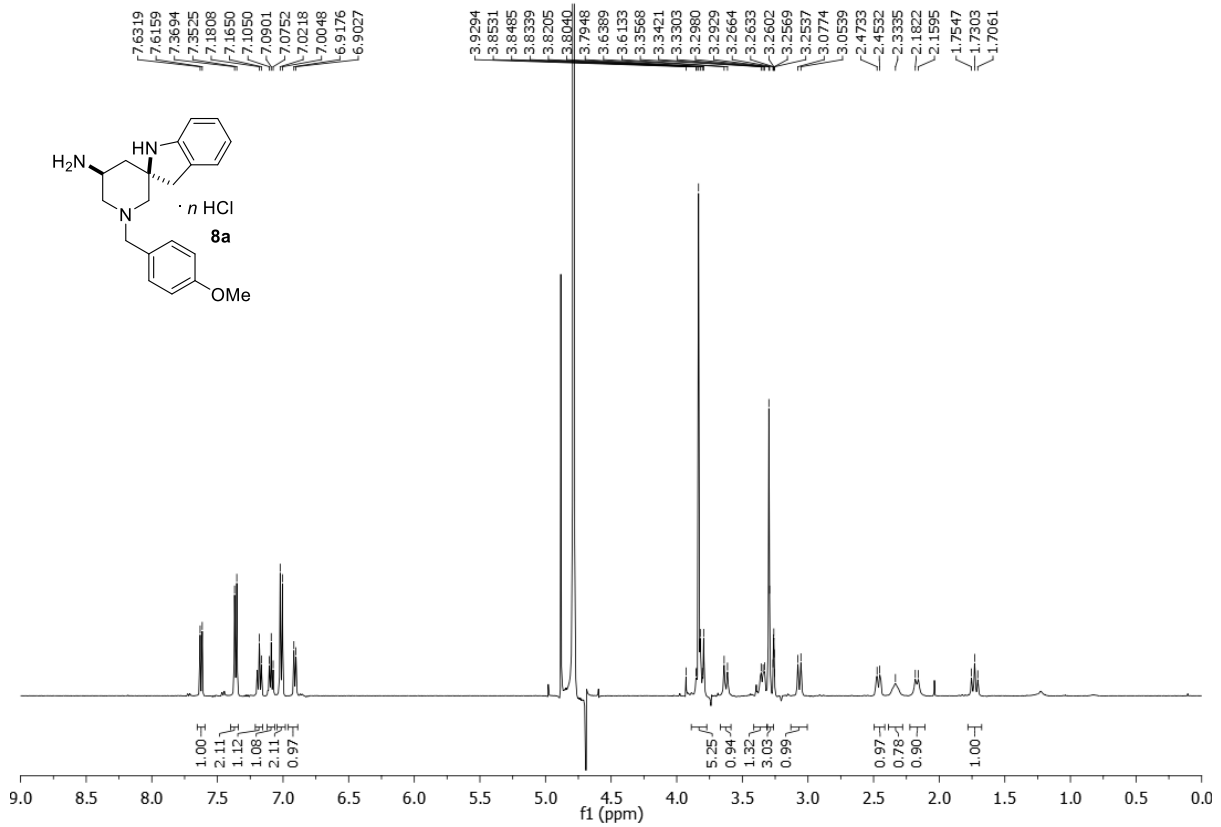
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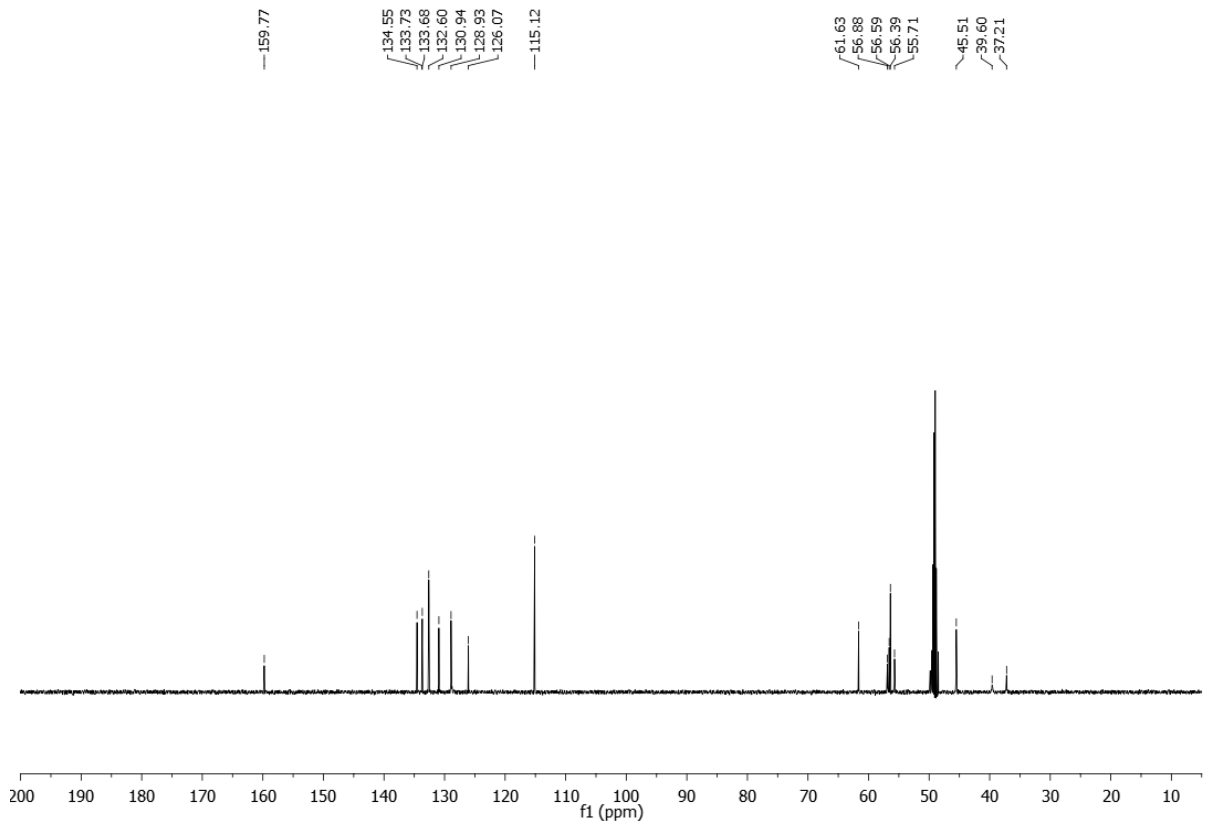
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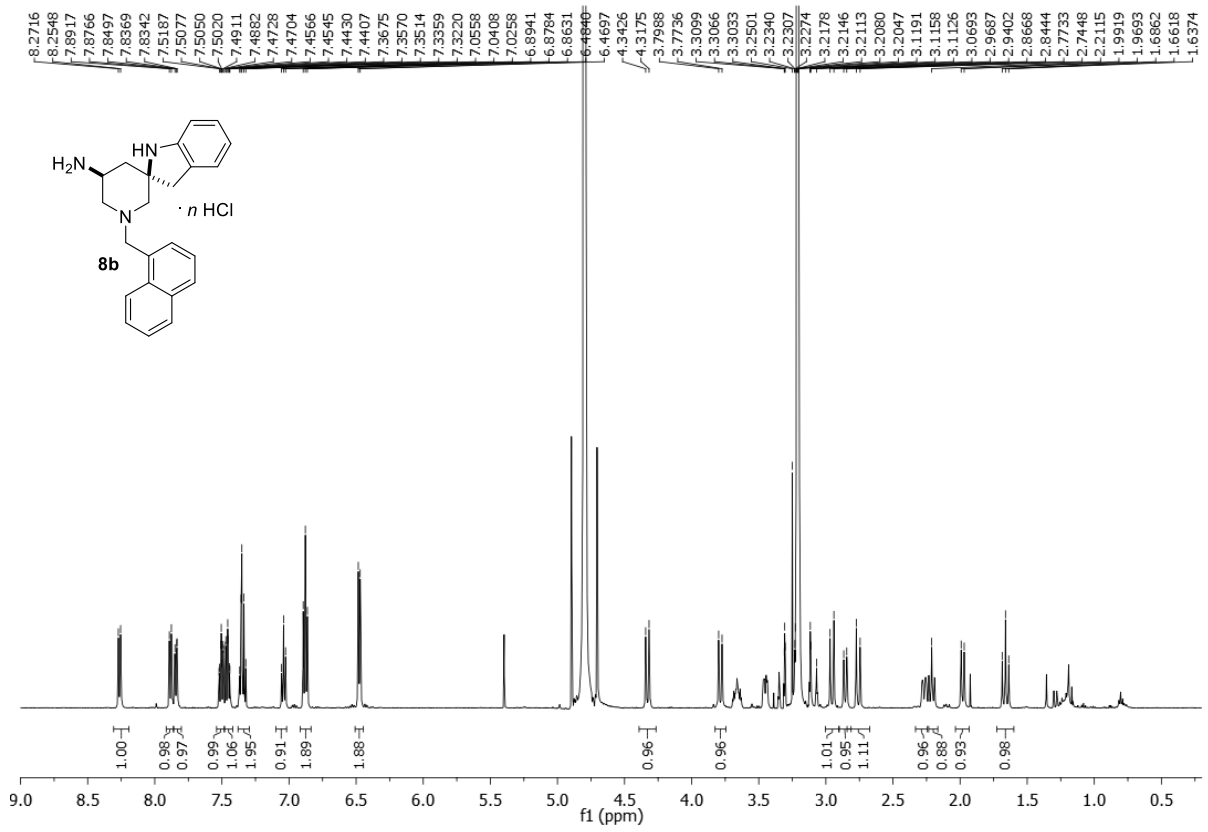
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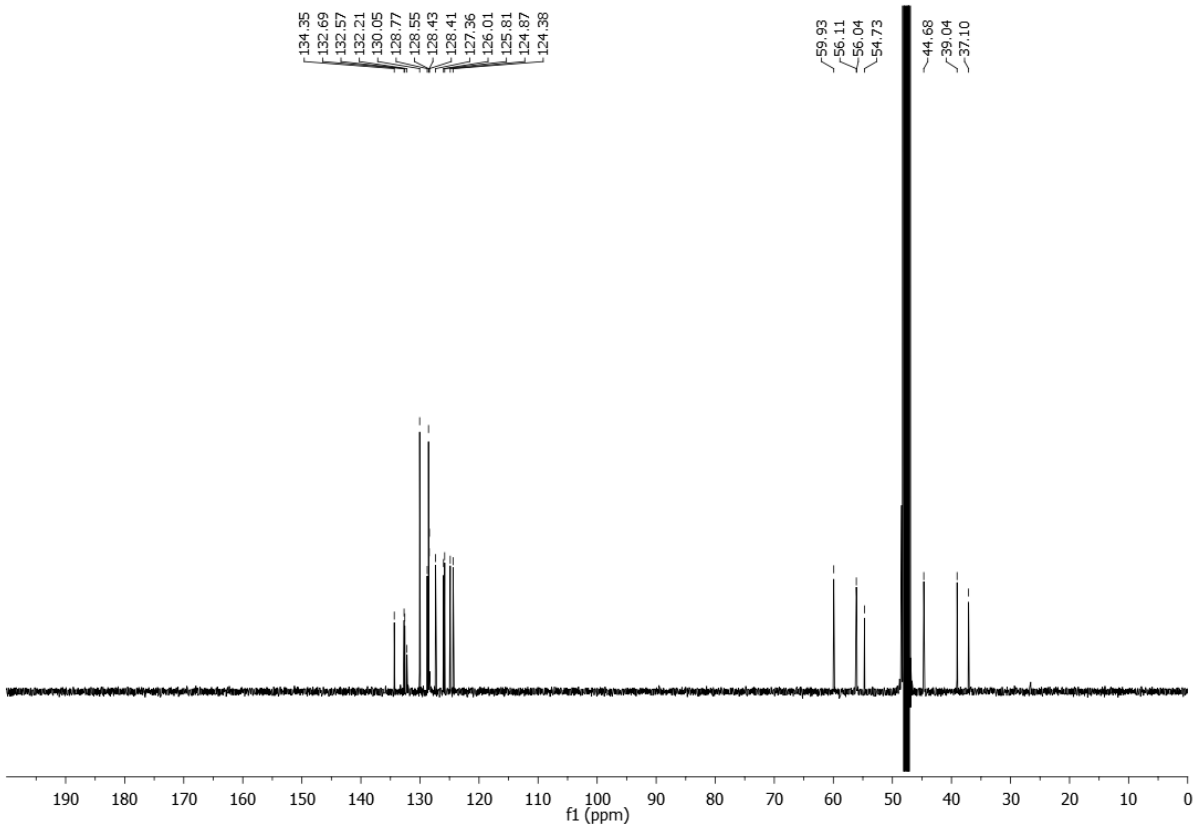
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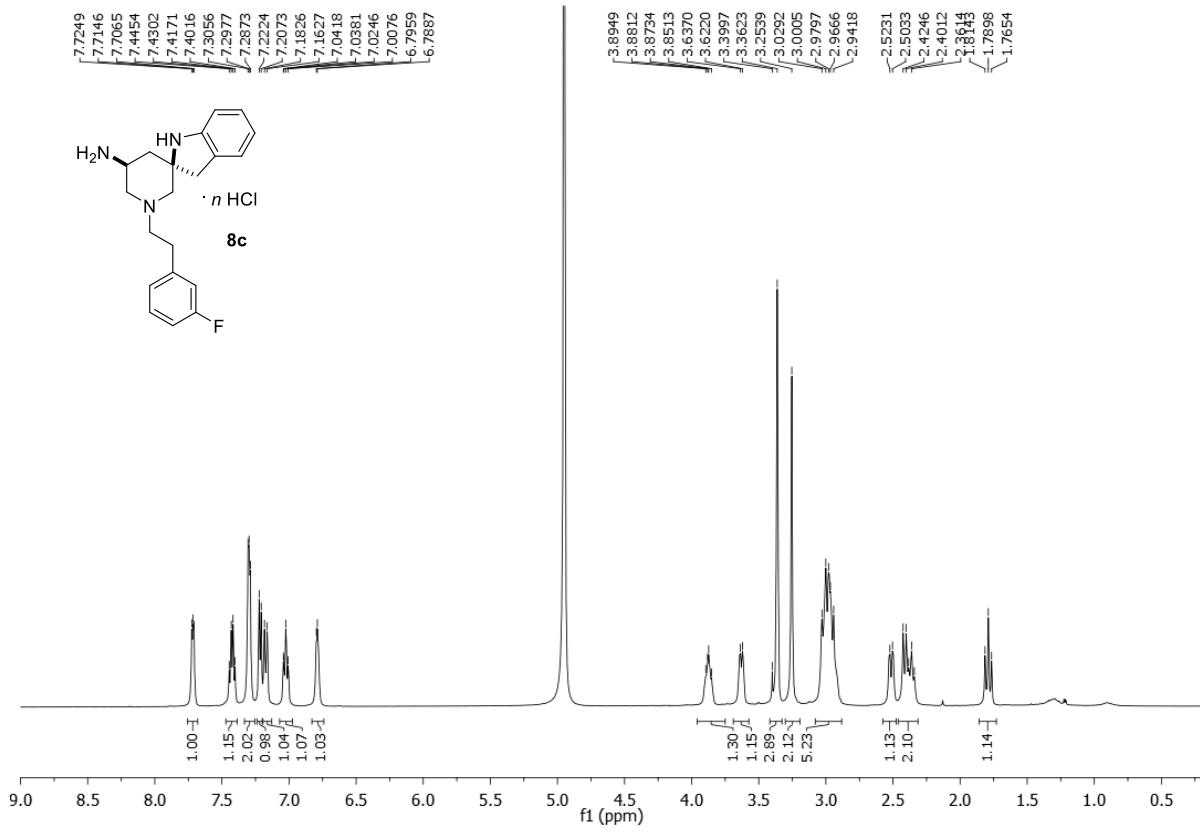
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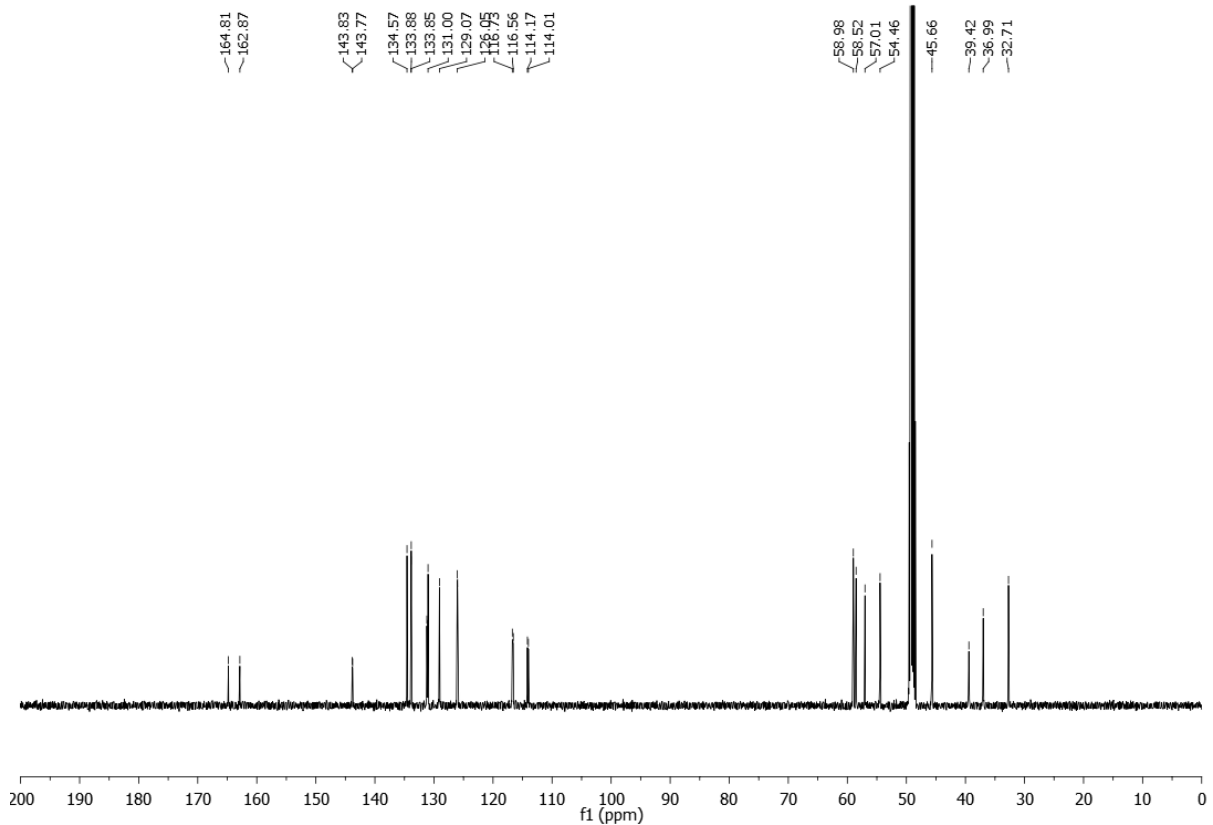
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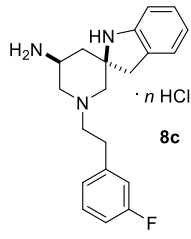
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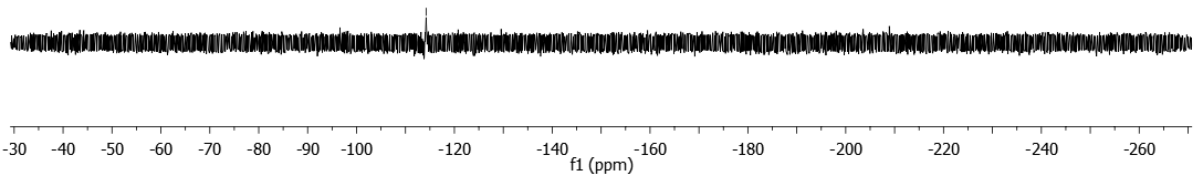
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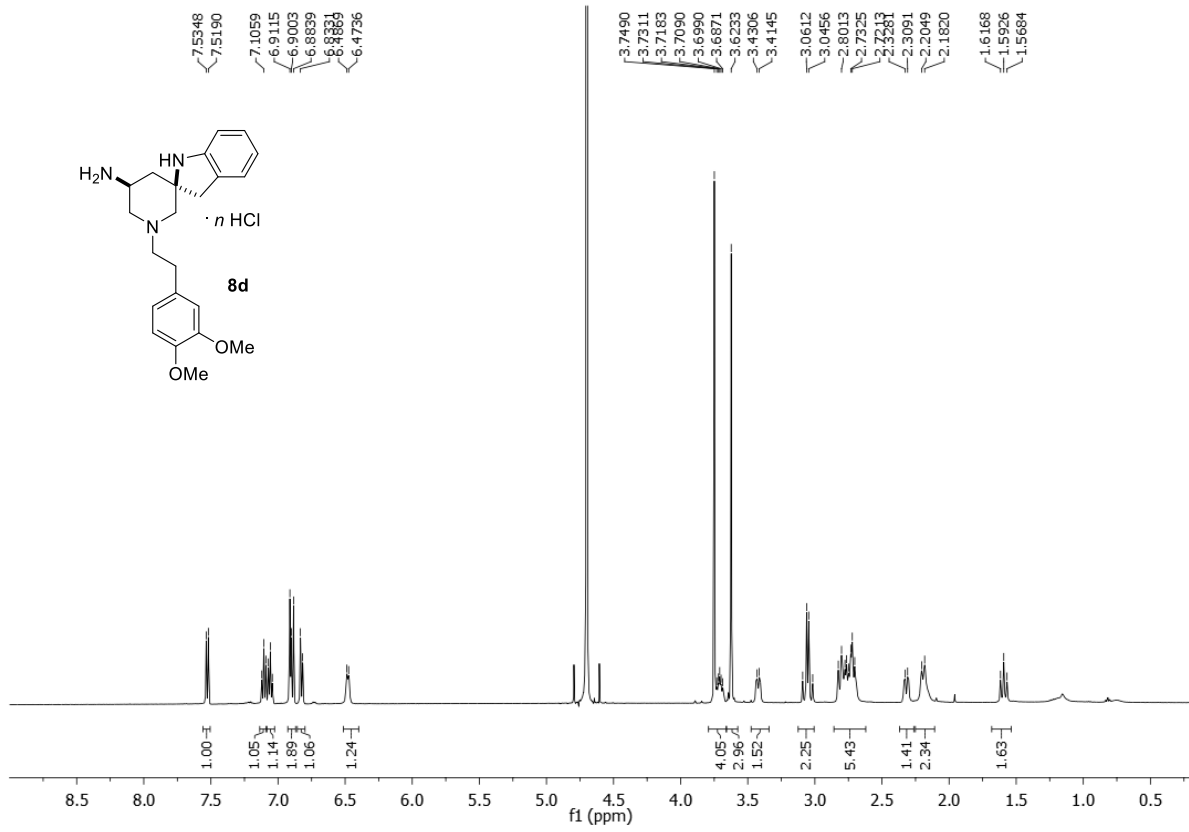
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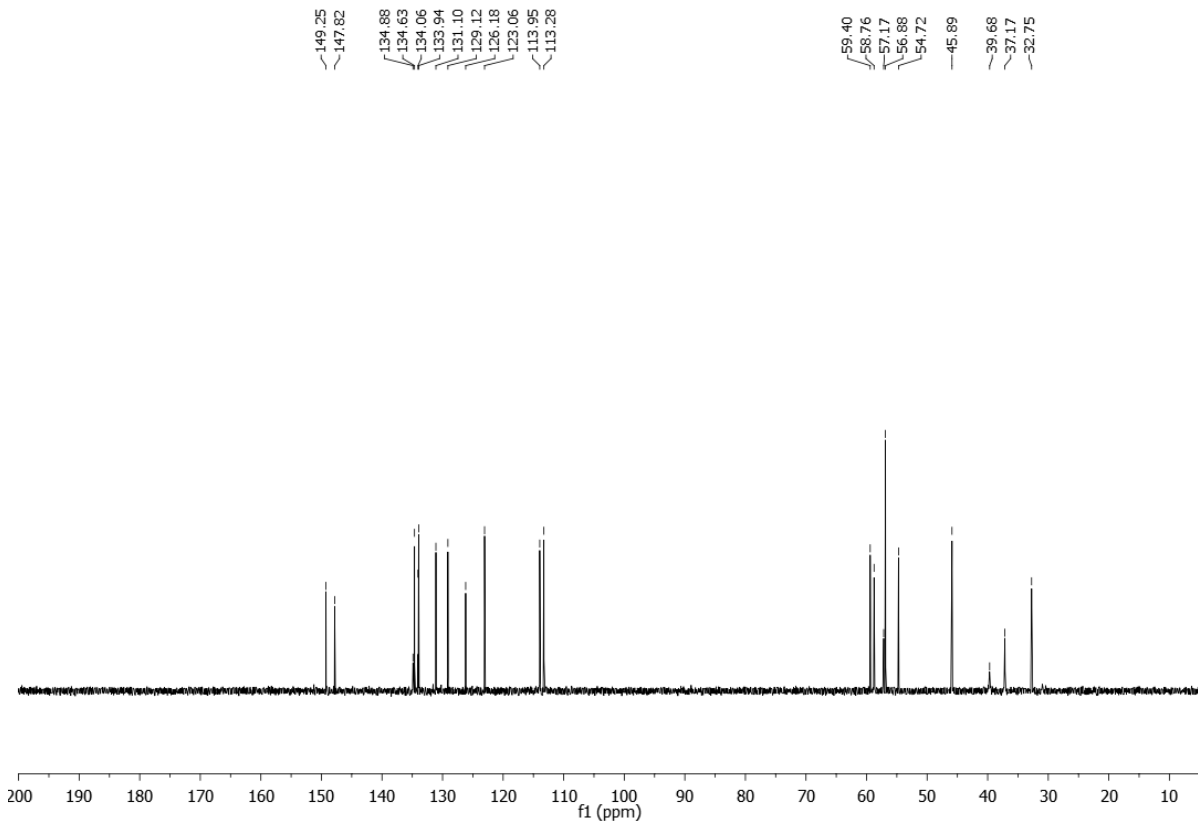
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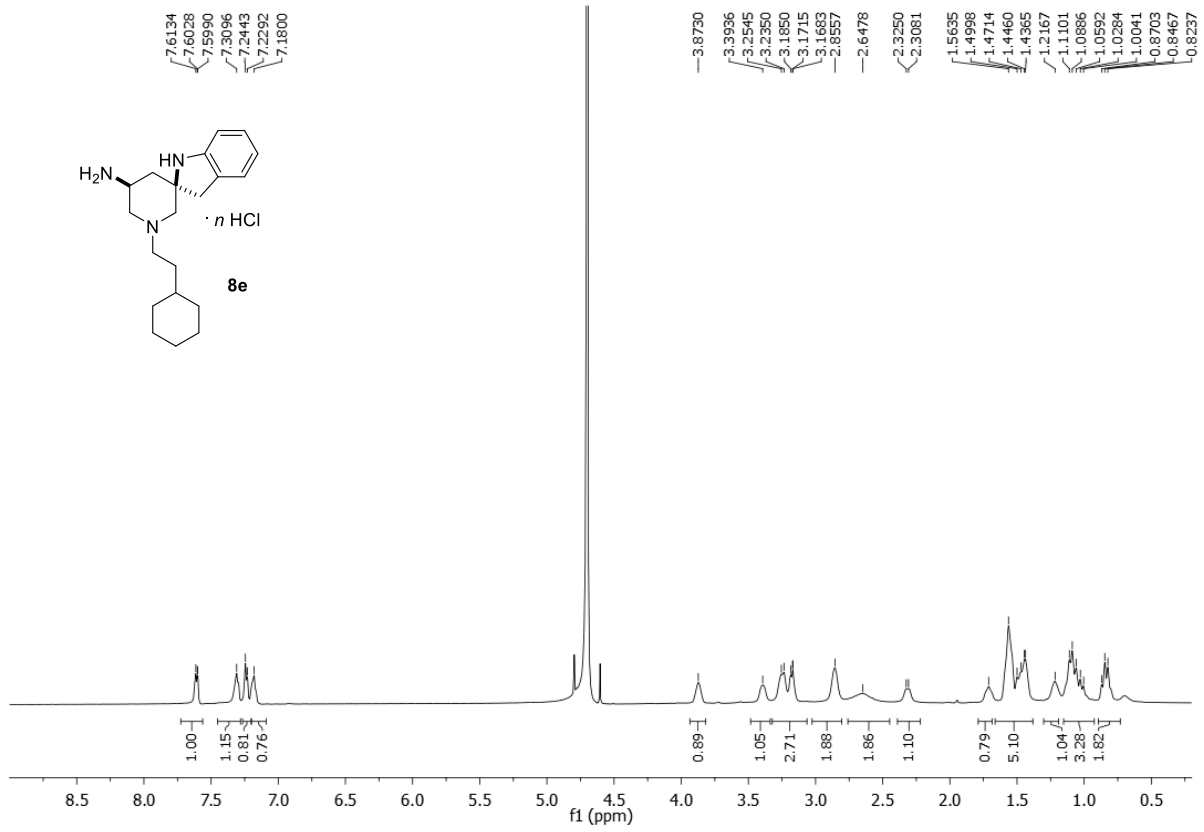
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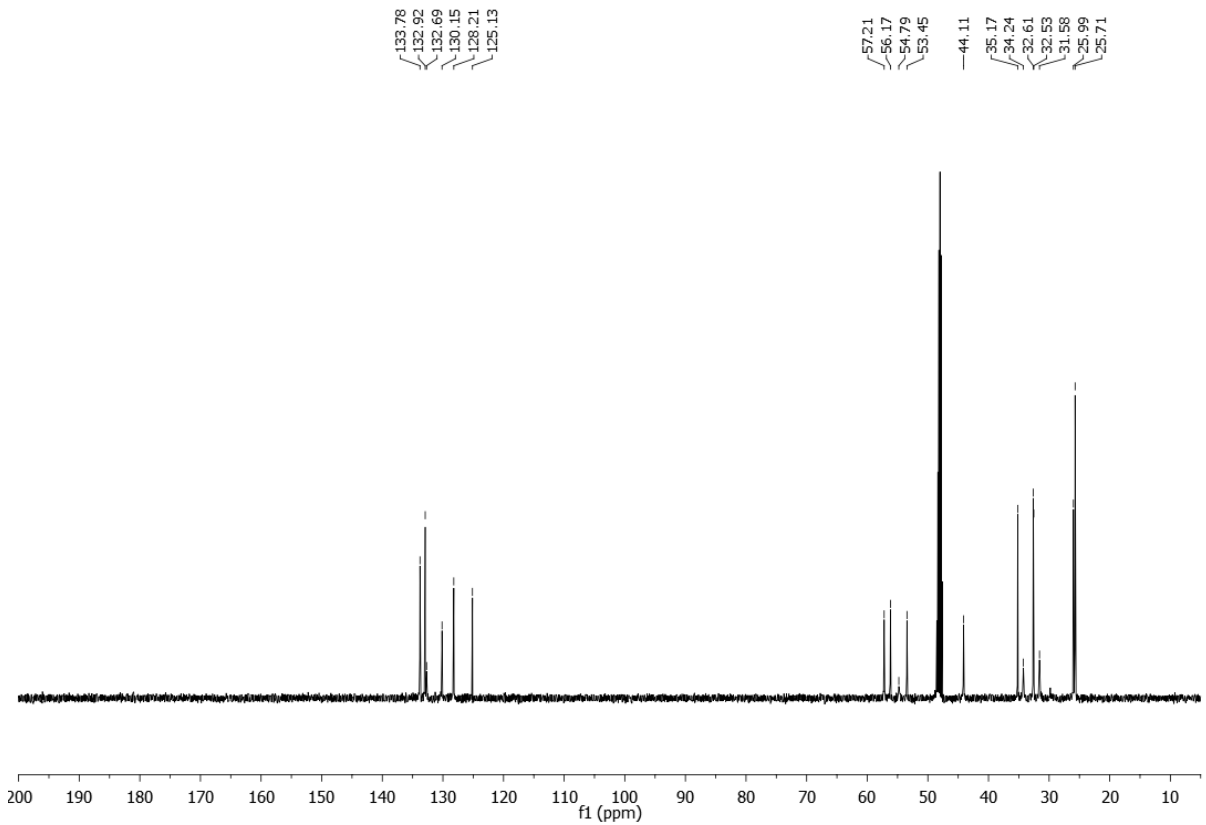
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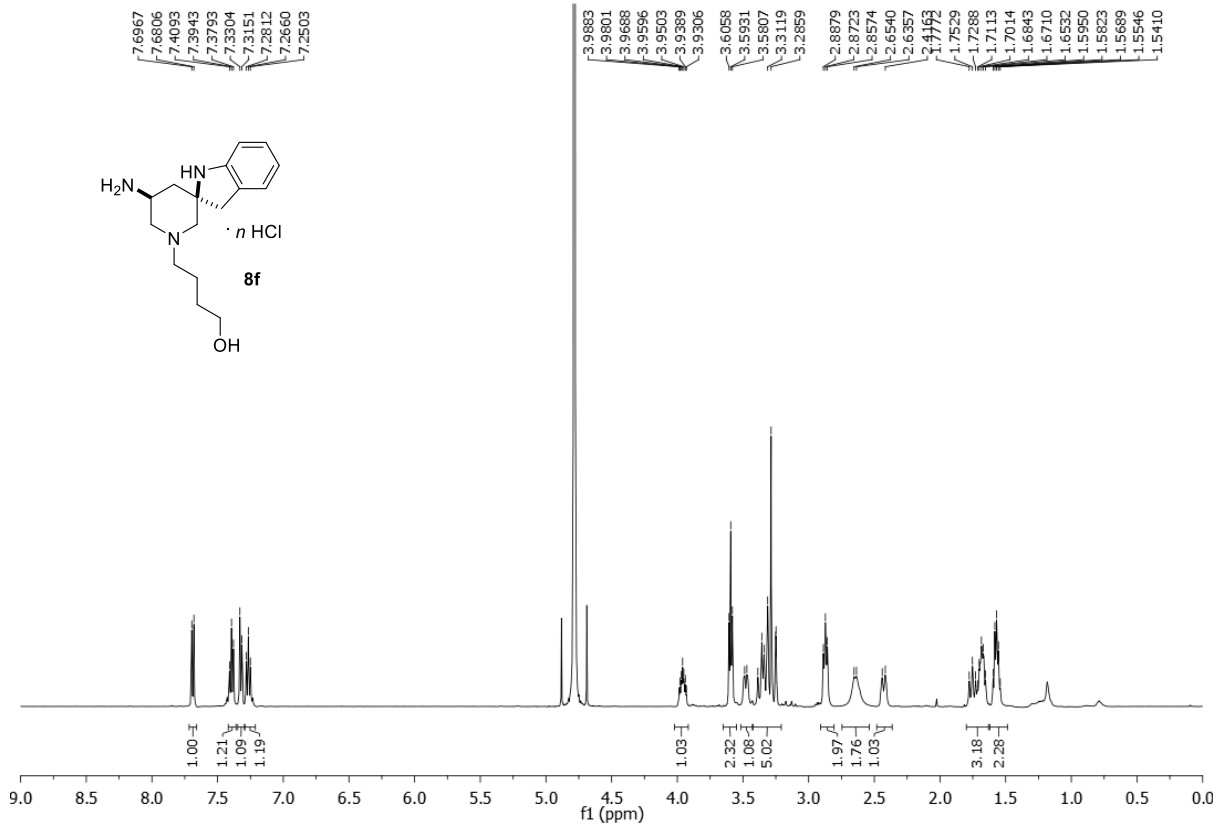
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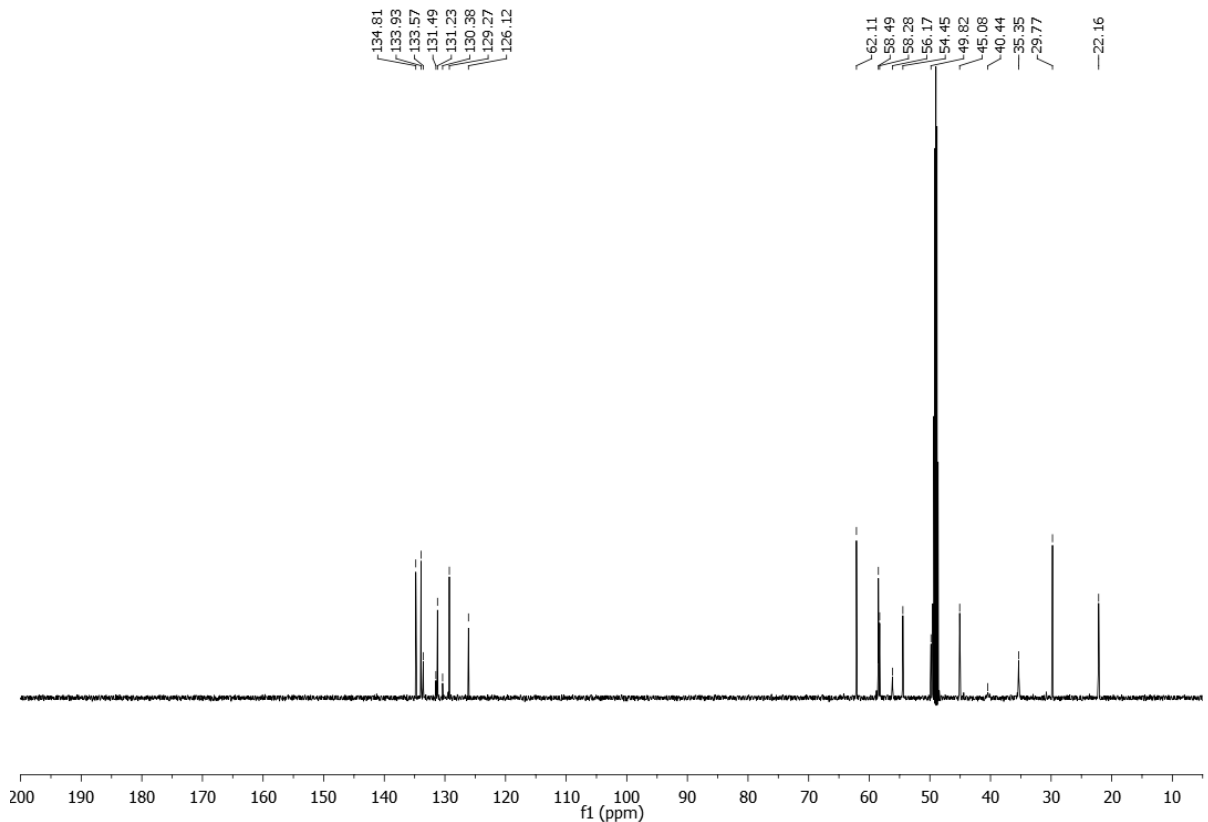
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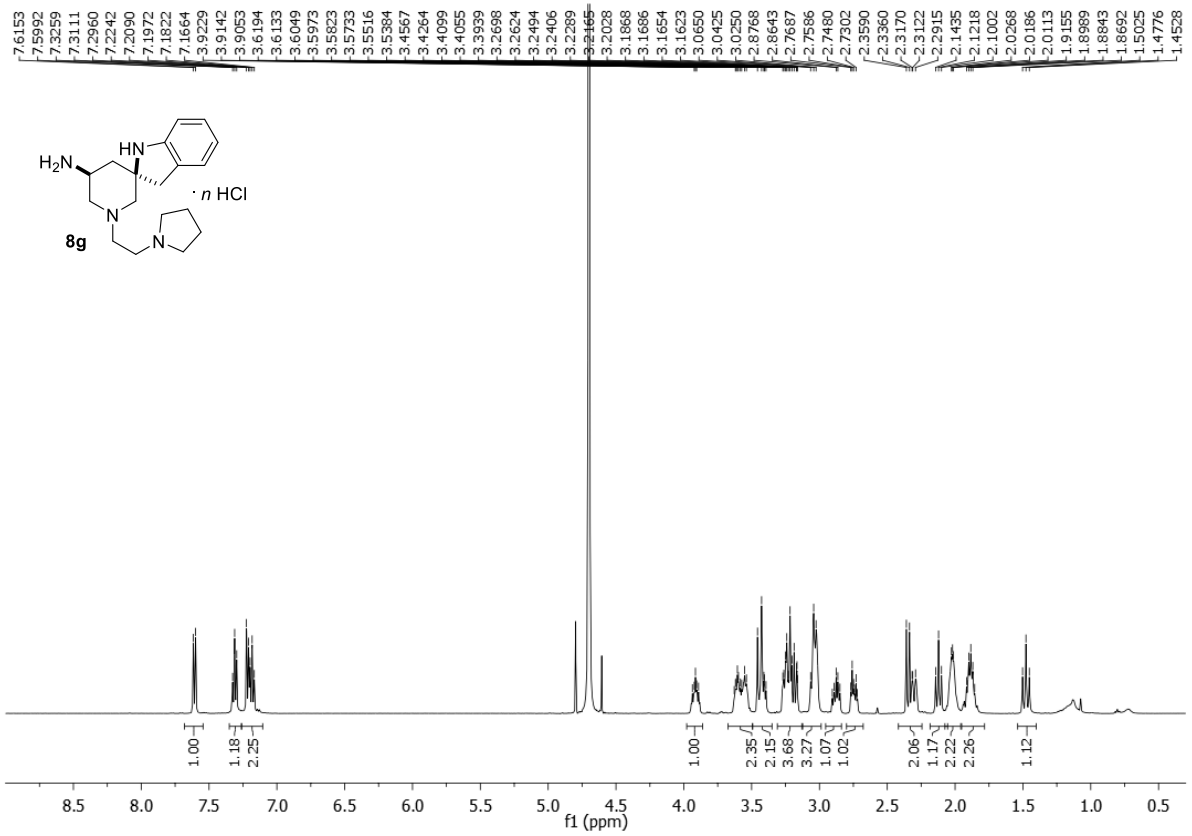
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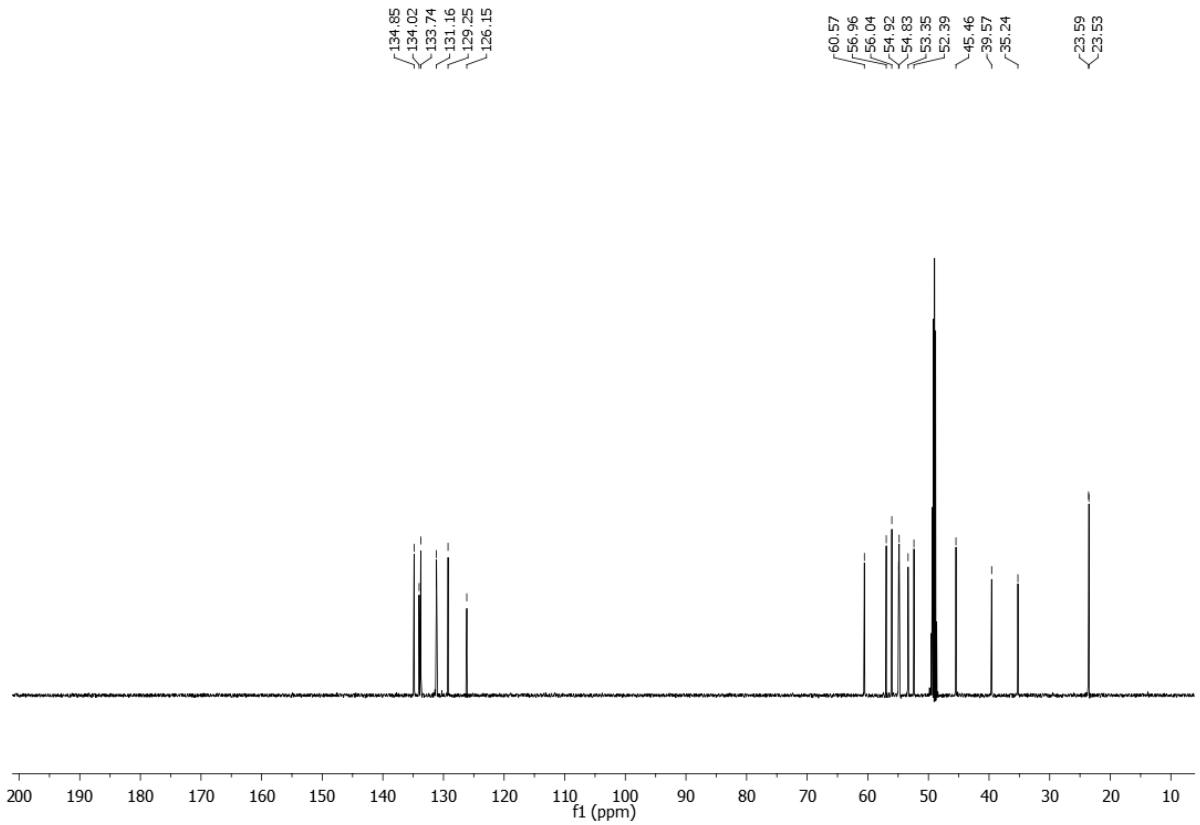
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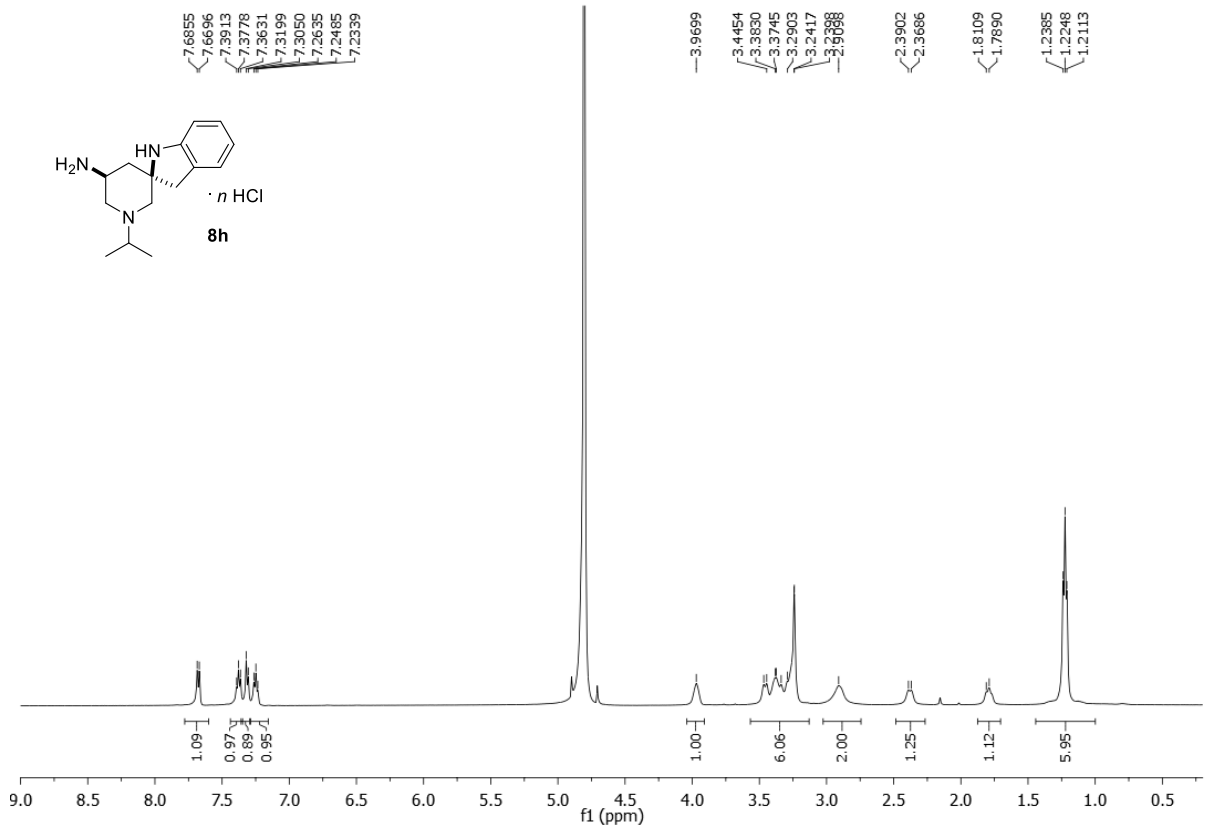
¹H NMR (500 MHz, D₂O)



¹³C{¹H} NMR (126 MHz, D₂O)



¹H NMR (500 MHz, D₂O)



¹³C{¹H} NMR (126 MHz, D₂O)

