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Supporting Information

Synthesis of sp^3-rich Scaffolds for Molecular Libraries through Complexity-Generating Cascade Reactions

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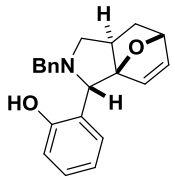
General Methods

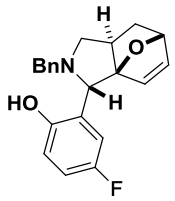
All reagents and solvents were purchased from commercial suppliers and used without further purification. All solvents used were of HPLC-grade, which predominantly were used without further drying. Unless otherwise stated, reactions were run as open-system reactions, using only a loosely-fitted plastic plug in order to avoid contamination of the reaction mixture. Reaction products have been purified using flash column chromatography or preparative high-performance liquid chromatography (prep-HPLC). Reactions were routinely monitored using thin layer chromatography (TLC), ultra-performance liquid-chromatography mass-spectrometry (UPLC-MS) and/or high-performance liquid-chromatography with UV detection (HPLC-UV). Analytical TLC was performed using Merck aluminium sheets covered with silica (C60). The plates were visualized using UV light and/or a $KMnO_4$ staining solution (3 g in water (300 mL), K_2CO_3 (20 g) and 5% aq NaOH (5 mL)) followed by heating. Analytical UPLC-MS (ESI) was performed on a S2 Waters ACQUITY RP-UPLC system equipped with a diode array detector using an ACQUITY UPLC BEH C18 column (*d* 1.7 µm, 2.1 x 50mm; column temp: 65 °C; flow: 0.6 mL/min), as well as a SQD ESI MS detector. Eluents A1 (0.1% HCOOH in H_2O), A2 (0.1% NH_4COOCH_3), B1 (0.1% HCOOH in MeCN) and B2 (0.1% NH_4COOCH_3 in MeCN) were used in a linear gradient 5% B1/B2 to 100% B1/B2 in a total run time of 2.6 min. Analytical LC-HRMS (ESI) analysis was performed on an Agilent 1100 RP-LC system equipped with a diode array detector using a Phenomenex Luna C18 column (*d* 3 µm, 2.1 x 50 mm; column temp: 40 °C; flow: 0.4 mL/min). Eluents A (0.1% HCOOH in H_2O) and B (0.1% HCOOH in MeCN) were used in a linear gradient (20% B to 100% B) in a total run time of 15 min. The LC system was coupled to a Micromass LCT orthogonal time-of-flight mass spectrometer equipped with a Lock Mass probe operating in positive electrospray mode. Flash column chromatography was achieved using a glass column packed with Merck Geduran® 60 silica gel (40-63 µm particles) as stationary phase, and liquid phase as specified in the individual experimental. All purified compounds have been routinely characterized by ^{1}H NMR, ^{13}C NMR, RP-UPLC-MS and RP-HPLC-UV. Novel compounds were further characterized via HRMS. NMR spectra were recorded on a Bruker Ascend spectrometer with a Prodigy cryoprobe (operating at 400 MHz for ^{1}H NMR and at 100 MHz for ^{13}C NMR), and analyzed via the NMR software MestReNova (version 6.2.1-7569) released by Mestrelab Research S.L. The chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (*J*) in Hz. The majority of the spectra have been recorded in $CDCl_3$, and

the signals were adjusted relative to this position (δ 7.26 ppm for ^{1}H NMR and δ 77.2 ppm for ^{13}C NMR). For spectra recorded in DMSO-d_6, the signals were adjusted relative to the DMSO signal (δ 2.5 ppm for ^{1}H NMR and δ 39.5 ppm for ^{13}C NMR). Compounds have been drawn and named through use of the visualization software ChemDraw Ultra 14.0 released by PerkinElmer Informatics. Molecular- and exact masses have been calculated via this program as well.

General procedure 1: Petasis 3-component reaction and Diels-Alder sequence

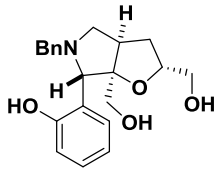


1a. *N*-Allylbenzyl amine (50.0 g, 340 mmol) and salicylaldehyde (41.5 g, 340 mmol) was dissolved in CH_2Cl_2 (650 mL, 0.5 M) and the mixture was cooled to 0 °C. To the mixture was added 2-furanylboronic acid (39.9 g. 357 mmol, 1.05 equiv.) portion wise and the mixture was stirred 30 min at 0 °C and then overnight at rt. Then H_2O (250 mL) and sat. aq. $NaHCO_3$ (250 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2×250 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was taken up in THF (650 mL, 0.5 M) and the mixture was stirred overnight at reflux where after it was concentrated *in vacuo*. The residue was purified by dry column vacuum chromatography (EtOAc:heptane 1:9, R_f = 0.2) to give the title compound as a white amorphous solid (91.7 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.13 (br s, 1H), 7.28 – 7.11 (m, 6H), 7.14 (t, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.76 (t, *J* = 7.5 Hz, 1H), 6.08 (d, *J* = 5.8 Hz, 1H), 5.70 (d, *J* = 5.8 Hz, 1H), 4.94 (d, *J* = 4.3 Hz, 1H), 4.05 (d, *J* = 12.5 Hz, 1H), 3.97 (s, 1H), 3.42 (d, *J* = 12.5 Hz, 1H), 3.14 (dd, *J* = 8.5, 6.3 Hz, 1H), 2.21 – 2.11 (m, 1H), 1.62 (dt, *J* = 11.5, 3.7 Hz, 1H), 1.26 (dd, *J* = 11.5, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 136.9, 135.3, 135.3, 129.6, 129.5, 129.3, 128.7, 127.8, 121.4, 119.6, 117.2, 100.2, 80.1, 70.9, 58.5, 56.7, 43.5, 29.3; HRMS (ESI) calcd for $C_{21}H_{22}NO_2$ [*M*+H$^+$] 320.1645, found 320.1646.

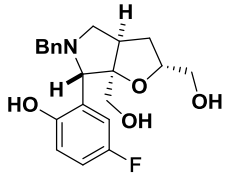


1b. Following **General Procedure I**, using *N*-allylbenzyl amine (16.4 g, 111 mmol), 5-fluorosalicylaldehyde (15.6 g, 111 mmol) and 2-furanylboronic acid (13.1 g, 117 mmol), gave after flash column chromatography (EtOAc:heptane 1:9, R_f = 0.2) the title compound as a yellow solid. The solid was washed with heptane to give a white amorphous solid (34.9 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.95 (br. s, 1H), 7.40 – 7.24 (m, 5H), 6.94 (td, *J* = 8.5, 2.9 Hz, 1H), 6.86 (dd, *J* = 8.8, 4.8 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 1H), 6.22 (d, *J* = 5.8 Hz, 1H), 5.83 (d, *J* = 5.8 Hz, 1H), 5.05 (d, *J* = 4.3 Hz, 1H), 4.11 (d, *J* = 12.5 Hz, 1H), 4.02 (s, 1H), 3.59 (d, *J* = 12.5 Hz, 1H), 3.29 (t, *J* = 7.4 Hz, 1H), 2.29 (dd, *J* = 10.7, 9.2 Hz, 1H), 2.25 – 2.12 (m, 1H), 1.74 (dt, *J* = 11.5, 3.7 Hz, 2H), 1.38 (dd, *J* = 11.5, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3 (d, J_{CF} = 237.1 Hz), 153.8, 136.5, 135.6, 135.0, 129.5, 128.8, 128.0, 122.3 (d, J_{CF} = 6.7 Hz), 118.0 (d, J_{CF} = 7.6 Hz), 115.8 (d, J_{CF} = 23.5 Hz), 100.0, 80.2, 70.6, 70.6, 58.6, 56.9, 43.6, 29.3; HRMS (ESI) calcd for $C_{21}H_{22}FNO_2$ [*M*+H$^+$] 338.1551, found 338.1553.

General procedure 2: Dihydroxylation, oxidative cleavage and reduction sequence



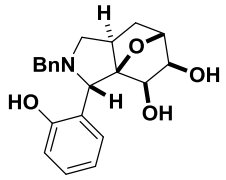
2a. Diels-Alder product **1a** (3.00 g, 9.39 mmol) was dissolved in acetone (27 mL, 0.3 M) and *N*-methyl-morpholin-*N*-oxid (1.43 g, 12.2 mmol) was added. To the solution was then added 2% $K_2OsO_4 \cdot 2H_2O$ (62 mg) in H_2O (3 mL) and the mixture was stirred 2 h at rt. Then H_2O (50 mL) was added and the mixture was filtered and the filter cake was washed with H_2O. The solid was then dispersed in MeOH:H_2O (9:1, 30 mL), $NaIO_4$ (3.0 g, 14.1 mmol) was added and the mixture was stirred at rt. After 2 h water (50 mL) was added along with CH_2Cl_2 (50 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2×50 mL) and the combined organic layers were concentrated *in vacuo*. The residue was dissolved in MeOH (30 mL), cooled to 0 °C and $NaBH_4$ (1.07 g, 28.2 mmol) was added portion wise. After stirring for 30 min at 0 °C the mixture was concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 (50 mL) and sat. aq. $NaHCO_3$ and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2×50 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc:heptane 4:1, R_f = 0.3) to give the title compound as a white amorphous solid (2.93 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.37 (s, 1H), 7.39 – 7.28 (m, 5H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.11 (d, *J* = 7.3 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 1H), 6.84 (d, *J* = 7.3 Hz, 1H), 4.35 (s, 1H), 4.04 (d, *J* = 12.7 Hz, 1H), 3.99 (d, *J* = 11.8 Hz, 1H), 3.76 (s, 1H), 3.61 (d, *J* = 11.8 Hz, 1H), 3.44 (d, *J* = 11.8 Hz, 1H), 3.34 – 3.14 (m, 3H), 3.13 (br. s, 1H), 2.86 (dd, *J* = 17.5, 8.5 Hz, 1H), 2.25 – 2.10 (m, 2H), 1.61 (dd, *J* = 12.5, 5.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2, 136.1, 130.2, 129.7, 129.6, 128.8, 128.0, 119.8, 119.3, 117.0, 95.4, 79.4, 79.3, 66.0, 63.2, 58.4, 56.5, 45.6, 31.3; HRMS (ESI) calcd for $C_{21}H_{26}NO_4$ [*M*+H$^+$] 356.1856, found 356.1854.



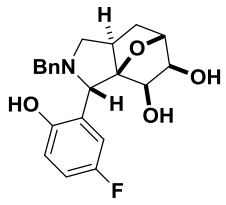
2b. Following **General procedure 2** using Diels-Alder product **1b** (3.00 g, 8.89 mmol), NMO (1.56 g, 13.3 mmol) and 2% $K_2OsO_4 \cdot 2H_2O$ (70 mg), $NaIO_4$ (2.85 g, 13.3 mmol), $NaBH_4$ (1.01 g, 26.7 mmol) gave after flash column chromatography the title compound as a white amorphous solid (2.72 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.13 (s, 1H), 7.37 – 7.17 (m, 5H), 6.87 (td, *J* = 8.6, 3.0 Hz, 1H), 6.79 (dd, *J* = 8.6, 3.0 Hz, 1H), 6.75 (dd, *J* = 8.9, 4.8 Hz, 1H), 4.32 – 4.23 (m, 1H), 3.98 – 3.88 (m, 2H), 3.62 (s, 1H), 3.55 (dd, *J* = 11.8, 2.6 Hz, 1H), 3.36 (d, *J* = 11.8 Hz, 1H), 3.23 – 3.16 (m, 2H), 3.14 (d, *J* = 12.6 Hz, 1H), 2.79 (dd, *J* = 18.4, 8.0 Hz, 1H), 2.17 – 2.03 (m, 2H), 1.55 (dd, *J* = 12.6, 5.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4 (d, J_{CF} = 237.5 Hz), 153.3, 135.9, 129.6, 128.8, 128.0, 120.3 (d, J_{CF} =

6.7 Hz), 117.7 (d, J_{CF} = 7.7 Hz), 116.24 (d, J_{CF} = 22.1 Hz), 116.02 (d, J_{CF} = 22.2 Hz), 95.3, 79.4, 79.1, 65.9, 63.1, 58.4, 56.5, 45.6, 31.3; HRMS (ESI) calcd for $C_{21}H_{25}FNO_4$ [M+H$^+$] 374.1762, found 374.1760.

General procedure 3: Dihydroxylation

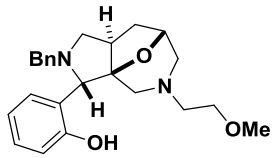


S1. Diels-Alder product **1a** (25 g, 62.6 mmol) was dissolved in THF (150 mL, 0.5 M) and *N*-methyl-morpholin-*N*-oxid (50% in H_2O) (24.3 mL, 117 mmol) was added. To the solution was then added OsO_4 (29.4 mL of 2.5% in tBuOH, 3 mol%, 2.35 mmol) and the mixture was stirred 3 h at rt. The reaction was quenched by slow addition of 20% aq. $NaHSO_4$ (150 mL) and the THF was partially evaporated. Water (300 mL) was added and the mixture was extracted with CH_2Cl_2 (3×300 mL). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4 and concentrated to give the title compound as a brown foam (27.2 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.48 (s, 1H), 7.30 – 7.11 (m, 7H), 6.89 (d, J = 8.2 Hz, 1H), 6.83 (t, J = 7.4 Hz, 1H), 4.27 (d, J = 4.9 Hz, 1H), 4.07 (s, 1H), 3.92 (d, J = 12.6 Hz, 1H), 3.85 (dd, J = 5.9, 3.2 Hz, 1H), 3.82 – 3.77 (m, 1H), 3.35 (d, J = 12.6 Hz, 1H), 3.03 (dd, J = 8.2, 6.4 Hz, 1H), 2.26 – 2.06 (m, 2H), 1.63 – 1.46 (m, 2H), 1.46 – 1.35 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 136.6, 130.6, 130.5, 129.4, 128.8, 127.9, 120.4, 120.0, 118.0, 97.5, 84.8, 75.9, 72.2, 70.7, 57.6, 56.4, 43.3, 30.7; HRMS (ESI) calcd for $C_{21}H_{24}NO_4$ [M+H$^+$] 354.1700, found 354.1699.

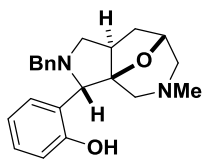


S2. Following **General procedure 3** using Diels-Alder product **1b** (3.33 g, 9.87 mmol), NMO (1.5 g, 12.8 mmol) and 2% $K_2OsO_4 \cdot 2H_2O$ (73 mg) gave after filtration the title compound as a white amorphous solid (3.36 g, 92%). ^{1}H NMR (400 MHz, DMSO) δ 10.21 (br s, 1H), 7.30 (t, J = 7.3 Hz, 2H), 7.24 (d, J = 6.9 Hz, 1H), 7.19 (t, J = 7.7 Hz, 2H), 7.08 (dd, J = 9.7, 3.0 Hz, 1H), 6.88 (td, J = 8.6, 3.1 Hz, 1H), 6.72 (dd, J = 8.8, 4.9 Hz, 1H), 4.98 – 4.87 (m, 1H), 4.18 (s, 1H), 4.08 (d, J = 5.0 Hz, 1H), 3.71 (d, J = 6.2 Hz, 1H), 3.69 (d, J = 13.7 Hz, 1H), 3.53 (d, J = 5.9 Hz, 1H), 3.37 (d, J = 13.2 Hz, 1H), 2.97 (t, J = 7.7 Hz, 1H), 2.33 – 2.17 (m, 1H), 2.14 – 1.95 (m, 1H), 1.49 (dd, J = 12.0, 8.1 Hz, 1H), 1.29 (dt, J = 11.9, 4.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 155.3 (d, J = 232.3 Hz), 152.8, 137.6, 128.7, 128.3, 127.1, 126.4, 116.9 (d, J = 23.3 Hz), 116.1 (d, J = 7.7 Hz), 114.1 (d, J = 22.6 Hz), 97.6, 82.8, 74.2, 71.4, 65.4, 56.6, 56.5, 42.2, 30.2; HRMS (ESI) calcd for $C_{21}H_{23}FNO_4$ [M+H$^+$] 372.1606, found 372.1607.

General procedure 4: Oxidative cleavage and reductive amination

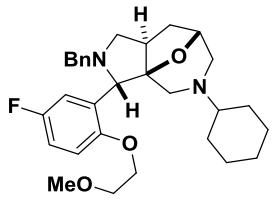


3b. Diol **S1** (22.1 g, 62.6 mmol) was taken up in MeOH/H_2O (9:1, 310 mL, 0.2 M) and $NaIO_4$ (20.1 g, 93.3 mmol) was added and the mixture was stirred at rt. After 2 h water (650 mL) was added along with CH_2Cl_2 (650 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2×650 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude dialdehyde was then dissolved in CH_2Cl_2 (310 mL, 0.2 M), added 2-methoxyethanamine (5.99 mL, 68.9 mmol, 1.1 equiv.) and stirred 5 min at rt. The mixture was then cooled to 0 °C and $NaBH(OAc)_3$ (53.1 g, 250 mmol, 4 equiv.) added portion wise. After stirring for 1 h at 0 °C the cooling was removed and the mixture was stirred overnight at rt. Then the reaction mixture was poured in to sat. aq. $NaHCO_3$ (500 mL) and the pH was adjusted to 7-8 by addition of solid $NaHCO_3$ whereafter the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2×500 mL) and the combined organic layers were washed with brine (300 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc:heptane 2:3, R_f = 0.2) to give the title compound as a colorless oil (25.1 g, >95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.86 (s, 1H), 7.37 – 7.20 (m, 6H), 7.11 (d, J = 7.4Hz, 1H), 6.87 (dd, J = 13.8, 7.5 Hz, 2H), 4.48 (d, J = 6.6 Hz, 1H), 4.01 (d, J = 12.6 Hz, 1H), 3.80 (s, 1H), 3.37 (t, J = 5.5 Hz, 2H), 3.32 (d, J = 12.6 Hz, 1H), 3.27 (s, 3H), 3.20 δ 3.06 (m, 1H), 2.84 (d, J = 7.5 Hz, 1H), 2.58 (d, J = 10.5 Hz, 1H), 2.48 – 2.40 (m, 2H), 2.35 (d, J = 10.9 Hz, 1H), 2.27 (d, J = 10.8 Hz, 1H), 2.15 – 2.07 (m, 1H), 2.04 (d, J = 9.2 Hz, 1H), 1.80 (d, J = 11.2 Hz, 1H), 1.75 – 1.67 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.98, 136.85, 130.32, 129.49, 129.44, 128.63, 127.70, 119.92, 119.31, 116.87, 92.28, 78.58, 77.00, 70.39, 58.76, 58.29, 57.61, 57.04, 46.29, 33.52; HRMS (ESI) calcd for $C_{24}H_{31}N2O_3$ [M+H$^+$] 395.2329, found 395.2325.

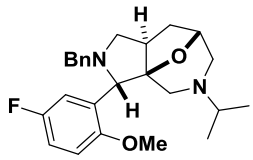


3a. Following **general procedure 4** using diol **S1** (682 mg, 1.94 mmol), $NaIO_4$ (621 mg, 2.91 mmol), $MeNH_2$ (33% in EtOH, 265 µL, 1.1 equiv.) and $NaBH(OAc)_3$ (1.61 g, 7.6 mmol) gave after flash column chromatography (EtOAc:heptane 1:1, R_f = 0.25) the title compound as a colorless oil/solid (585 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.75 (br s, 1H), 7.34 – 7.07 (m, 6H), 7.01 (d, J = 7.3 Hz, 2H), 6.87 – 6.66 (m, 2H), 4.38 (d, J = 6.7 Hz, 1H), 3.90 (d, J = 12.6 Hz, 1H), 3.70 (s, 1H), 3.21 (d, J = 12.6 Hz, 1H), 3.03 (dd, J = 8.6, 7.7 Hz, 1H), 2.77 – 2.66 (m, 1H), 2.38 (d, J = 11.1 Hz, 1H), 2.20 (d, J = 11.3 Hz, 1H), 2.06 (dd, J = 12.0, 2.5 Hz, 1H), 2.01 (s, 3H), 2.00 – 1.91 (m, 2H), 1.66 – 1.61

(m, 1H), 1.58 (d, J = 11.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 136.8, 130.3, 129.5, 129.4, 128.6, 127.7, 119.9, 119.3, 116.9, 92.2, 78.4, 77.0, 60.4, 59.3, 58.3, 57.7, 46.3, 45.5, 33.5; HRMS (ESI) calcd for $C_{22}H_{27}N2O_2$ [M+H$^+$] 351.2067, found 351.2063.

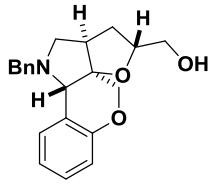


3c. Following **general procedure 4** using diol **S2** (386 mg, 1.04 mmol), $NaIO_4$ (334 mg, 1.56 mmol), cyclohexaneamine (131 μL, 1.14 mmol, 1.1 equiv.) and $NaBH(OAc)_3$ (881 mg, 4.16 mmol) gave after flash column chromatography (EtOAc:heptane 15:85, R_f = 0.2) the title compound as a colorless oil/solid (383 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.57 (s, 1H), 7.34 – 7.09 (m, 5H), 6.83 (td, J = 8.5, 3.0 Hz, 1H), 6.79 – 6.67 (m, 2H), 4.37 (d, J = 6.5 Hz, 1H), 3.87 (d, J = 12.6 Hz, 1H), 3.62 (s, 1H), 3.22 (d, J = 12.6 Hz, 1H), 3.12 – 2.87 (m, 1H), 2.74 – 2.58 (m, 1H), 2.36 (d, J = 10.9 Hz, 1H), 2.28 (dd, J = 10.9, 1.6 Hz, 1H), 2.17 (d, J = 11.1 Hz, 1H), 2.03 – 1.93 (m, 2H), 1.91 – 1.84 (m, 2H), 1.68 – 1.37 (m, 6H), 1.15 – 0.88 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) 156.1 (d, J_{CF} = 236.6 Hz), 154.0 (d, J_{CF} = 1.9 Hz), 136.7, 129.5, 128.7, 127.8, 121.1 (d, J_{CF} = 6.7 Hz), 117.5 (d, J_{CF} = 7.7 Hz), 116.5 (d, J_{CF} = 23.1 Hz), 115.7 (d, J_{CF} = 22.5 Hz), 92.4, 78.9, 76.8, 62.2, 58.4, 57.6, 54.8, 52.7, 46.3, 33.5, 29.5, 28.6, 26.4, 25.5, 25.4; HRMS (ESI) calcd for $C_{27}H_{34}FN_2O_2$ [M+H$^+$] 437.2599, found 437.2602.



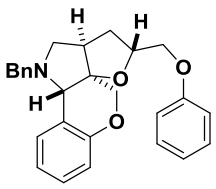
3d. Following **general procedure 4** using diol **S2** (1.43 mg, 3.85 mmol), $NaIO_4$ (1.23 mg, 5.78 mmol), isopropylamine (347 μL, 4.24 mmol, 1.1 equiv.) and $NaBH(OAc)_3$ (3.26 g, 15.4 mmol) gave after flash column chromatography (EtOAc:heptane 3:7, R_f = 0.2) the title compound as a colorless oil/solid (1.37 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.58 (s, 1H), 7.26 – 7.14 (m, 5H), 6.82 (td, J = 8.5, 3.0 Hz, 1H), 6.77 – 6.67 (m, 2H), 4.37 (d, J = 6.6 Hz, 1H), 3.86 (d, J = 12.6 Hz, 1H), 3.62 (s, 1H), 3.22 (d, J = 12.6 Hz, 1H), 3.07 – 2.91 (m, 1H), 2.73 – 2.59 (m, 1H), 2.39 (dt, J = 13.0, 6.5 Hz, 1H), 2.31 (d, J = 10.9 Hz, 1H), 2.24 (dd, J = 11.0, 1.8 Hz, 1H), 2.13 (d, J = 11.1 Hz, 1H), 2.01 (d, J = 9.8 Hz, 1H), 2.04 – 1.95 (m, 1H), 1.87 (dd, J = 11.6, 8.6 Hz, 1H), 1.81 (d, J = 11.1 Hz, 1H), 1.62 – 1.51 (m, 1H), 0.76 (d, J = 6.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0 (d, J_{CF} = 236.6 Hz), 154.0 (d, J_{CF} = 1.9 Hz), 136.7, 129.4, 128.6, 127.7, 121.0 (d, J_{CF} = 6.7 Hz), 117.5 (d, J_{CF} = 7.7 Hz), 116.4 (d, J_{CF} = 23.1 Hz), 115.7 (d, J_{CF} = 22.6 Hz), 92.34, 78.78, 76.74, 58.34, 57.58, 54.52, 53.66, 52.13, 46.30, 33.48, 19.12, 18.03; HRMS (ESI) calcd for $C_{24}H_{30}FN_2O_2$ [M+H$^+$] 397.2286, found 397.2285.

Intramolecular Mitsunobu reaction

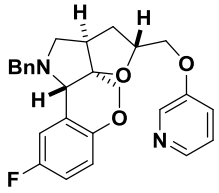


4. Diol **2a** (100 mg, 0.280 mmol) was dissolved in CH_2Cl_2 (3 mL) along with PPh_3 (110 mg, 0.420 mmol) and the mixture was cooled to 10 °C. Then di-*tert*-butyl azodicarboxylate (97 mg, 0.420 mmol) was added portion wise and the mixture was stirred 30 min at 10 °C. The reaction mixture was then concentrated *in vacuo* and the residue was purified by flash column chromatography (EtOAc:heptane 2:3, R_f = 0.2) to give the title compound as an amorphous solid (95 mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.19 (m, 7H), 7.02 – 6.93 (m, 2H), 4.37 (dt, J = 13.2, 5.1 Hz, 1H), 4.24 (d, J = 12.5 Hz, 1H), 4.18 (d, J = 11.2 Hz, 1H), 4.00 (d, J = 11.2 Hz, 1H), 3.81 (dd, J = 12.0, 2.9 Hz, 1H), 3.55 (dd, J = 12.0, 4.8 Hz, 1H), 3.39 (s, 1H), 3.33 (d, J = 12.0 Hz, 1H), 3.07 (t, J = 8.5 Hz, 1H), 2.61 – 2.46 (m, 1H), 2.27 (br. s, 1H), 2.19 – 2.07 (m, 1H), 2.05 – 1.89 (m, 1H), 1.69 (dd, J = 12.5, 5.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4, 138.9, 132.1, 129.0, 128.7, 128.3, 127.0, 121.1, 120.8, 117.4, 88.8, 80.3, 71.0, 65.2, 64.0, 58.1, 57.0, 43.6, 32.2; LCMS (ESI) calcd for $C_{21}H_{23}NO_3$ [M+H+] 338.4, found 338.1.

General procedure 5: Mitsunobu reaction using phenols

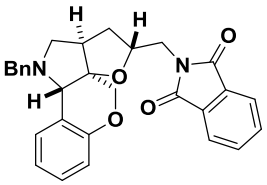


5a. Diol **2a** (350 mg, 0.985 mmol) was dissolved in THF (0.2 M, 5 mL) along with PPh_3 (775 mg, 2.95 mmol) and phenol (278 mg, 2.95 mmol) and the mixture was cooled to 10 °C. Then di-*tert*-butyl azodicarboxylate (680 mg, 2.95 mmol) was added portion wise and the mixture was stirred 30 min at 10 °C followed by 16 h at rt. The reaction mixture was then concentrated *in vacuo* and the residue was taken in EtOAc (100 mL) and washed with 1 M NaOH (2×25 mL) followed by brine (25 mL). The organic layer was then concentrated *in vacuo* and the residue was purified by flash column chromatography to give the title compound as an amorphous solid (407 mg, >95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.07 (m, 9H), 6.93 – 6.75 (m, 5H), 4.59 – 4.48 (m, 1H), 4.12 – 4.04 (m, 2H), 3.96 – 3.88 (m, 3H), 3.41 (s, 1H), 3.27 (d, J = 12.6 Hz, 1H), 3.08 – 2.83 (m, 1H), 2.59 – 2.41 (m, 1H), 2.12 – 2.00 (m, 1H), 1.99 – 1.77 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 155.8, 139.0, 131.8, 129.5, 128.9, 128.7, 128.3, 127.0, 121.7, 121.0, 120.8, 117.5, 114.6, 89.6, 78.4, 71.1, 70.1, 65.8, 57.8, 56.9, 43.7, 34.0; HRMS (ESI) calcd for $C_{27}H_{28}NO_3$ [M+H$^+$] 414.2064, found 414.2060.

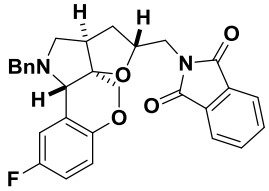


5b. Following **General procedure 5** using diol **2b** (400 mg, 1.07 mmol), PPh_3 (842 mg, 3.21 mmol), 3-hydroxypyridine (305 mg, 3.21 mmol), di-*tert*-butyl azodicarboxylate (740 mg, 3.21 mmol) gave after flash column chromatography (EtOAc:heptane 7:3, R_f = 0.2) the title compound as an yellow amorphous solid (376 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (t, *J* = 1.8 Hz, 1H), 8.13 (t, *J* = 3.0 Hz, 1H), 7.22 – 7.08 (m, 7H), 6.89 – 6.81 (m, 3H), 4.56 (td, *J* = 9.7, 4.7 Hz, 1H), 4.06 (s, 1H), 4.03 (s, 1H), 3.99 (t, *J* = 4.1 Hz, 2H), 3.85 (d, *J* = 11.1 Hz, 1H), 3.42 (s, 1H), 3.31 (d, *J* = 12.6 Hz, 1H), 2.94 (dd, *J* = 9.4, 7.9 Hz, 1H), 2.65 – 2.51 (m, 1H), 2.12 (dd, *J* = 9.5, 7.5 Hz, 1H), 1.99 – 1.90 (m, 1H), 1.85 (ddd, *J* = 12.6, 6.0, 2.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0 (d, J_{CF} = 239.2 Hz), 155.0, 151.9 (d, J_{CF} = 2.0 Hz), 142.5, 138.6, 138.0, 128.6, 128.4, 127.2, 123.9, 123.0 (d, J_{CF} = 7.0 Hz), 121.3, 118.5 (d, J_{CF} = 8.1 Hz), 117.4 (d, J_{CF} = 22.8 Hz), 115.7 (d, J_{CF} = 23.1 Hz), 89.8, 78.1, 71.3, 70.2, 66.0, 66.0, 57.7, 56.8, 43.7, 33.6; HRMS (ESI) calcd for $C_{26}H_{26}FN_2O_3$ [*M*+H$^+$] 433.1922, found 433.1926.

General procedure 6: Mitsunobu reaction using phthalimide

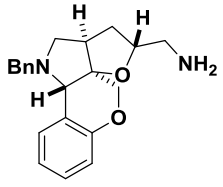


S3. Diol **2a** (1.20 g, 3.38 mmol) was dissolved in CH_2Cl_2 (0.2 M, 17 mL) along with PPh_3 (2.66 g, 6.38 mmol) and phthalimide (646 mg, 4.39 mmol) and the mixture was cooled to 10 °C. Then di-*tert*-butyl azodicarboxylate (2.33 g, 6.38 mmol) was added portion wise and the mixture was stirred 30 min at 10 °C followed by 4 h at rt. The mixture was concentrated *in vacuo* and then treated with TFA:CH_2Cl_2 (1:1, 12 mL) for 30 min. The mixture was then concentrated *in vacuo*, $NaHCO_3$ sat. aq. (50 mL) added and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were concentrated *in vacuo* and the residue was purified by flash column chromatograph (EtOAc:heptane 1:4, R_f = 0.2) to give the title compound as a white amorphous solid (1.42 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.71 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.26 – 7.15 (m, 7H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.95 – 6.88 (m, 1H), 4.59 (p, *J* = 6.4 Hz, 1H), 4.21 – 4.07 (m, 2H), 3.97 (d, *J* = 10.8 Hz, 1H), 3.93 (dd, *J* = 13.6, 6.3 Hz, 1H), 3.76 (dd, *J* = 13.7, 6.1 Hz, 1H), 3.41 (s, 1H), 3.29 (d, *J* = 12.6 Hz, 1H), 2.96 (t, *J* = 8.5 Hz, 1H), 2.66 – 2.56 (m, 1H), 2.09 (t, *J* = 8.4 Hz, 1H), 1.95 – 1.82 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 155.9, 134.3, 134.0, 132.0, 131.6, 128.8, 128.6, 128.2, 126.9, 123.6, 123.4, 120.8, 117.5, 89.7, 76.8, 71.4, 65.8, 57.4, 56.8, 43.8, 41.9, 35.1; HRMS (ESI) calcd for $C_{29}H_{27}N_2O_4$ [*M*+H$^+$] 467.1966, found 467.1964.



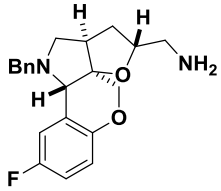
S4. Following **General procedure 6** using diol **2b** (797 mg, 2.13 mmol), PPh_3 (1.68 g, 6.40 mmol), phthalimide (627 mg, 4.26 mmol), di-*tert*-butyl azodicarboxylate (1.47 g, 6.40 mmol) gave after flash column chromatography (EtOAc:heptane 7:3, R_f = 0.2) the title compound as a white amorphous solid (1.03 g, >95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.64 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.24 – 7.09 (m, 5H), 6.88 – 6.75 (m, 3H), 4.61 – 4.43 (m, 1H), 4.02 (dd, *J* = 11.7, 9.3 Hz, 2H), 3.94 – 3.77 (m, 2H), 3.69 (dd, *J* = 13.8, 5.8 Hz, 1H), 3.33 (s, 1H), 3.25 (d, *J* = 12.7 Hz, 1H), 2.89 (t, *J* = 8.6 Hz, 1H), 2.64 – 2.47 (m, 1H), 2.13 – 1.95 (m, 1H), 1.81 (dd, *J* = 7.4, 5.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 157.0 (d, J_{CF} = 239.1 Hz), 152.2, 138.8, 134.2, 132.1, 128.7, 128.4, 127.2, 123.7, 123.5, 118.6 (d, J_{CF} = 7.9 Hz), 117.4 (d, J_{CF} = 22.7 Hz), 115.6 (d, J_{CF} = 23.3 Hz); 90.0, 77.0, 71.8, 66.3, 57.5, 56.9, 44.1, 42.1, 35.1; HRMS (ESI) calcd for $C_{29}H_{26}FN_2O_4$ [*M*+H$^+$] 485.1871, found 485.1872.

General procedure 7: Phthalimide deprotection.



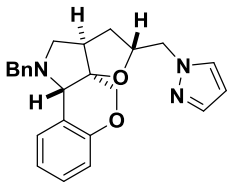
6a. Compound **S3** (851 mg, 1.82 mmol) was taken up in EtOH (9 mL, 0.2 M) and hydrazine monohydrate (265 µL, 5.47 mmol) was added and the mixture was stirred 3 h at reflux. The mixture was then cooled to rt, filtered and the filter cake was washed with EtOH and the filtrate was concentrated *in vacuo*. The residue was resolved in CH_2Cl_2 and the mixture was filtered againg. The filtrate was concentrated *in vacuo* to give the title compound as an off-white solid (610 mg, >95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.09 (m, 4H), 6.92 (d, *J* = 7.9 Hz, 1H), 6.87 (td, *J* = 7.4, 1.0 Hz, 1H), 4.21 – 4.13 (m, 2H), 4.08 (d, *J* = 11.2 Hz, 1H), 3.90 (d, *J* = 11.2 Hz, 1H), 3.27 (s, 1H), 3.21 (d, *J* = 12.5 Hz, 1H), 3.01 – 2.92 (m, 1H), 2.82 (dd, *J* = 13.2, 3.5 Hz, 1H), 2.67 (dd, *J* = 13.2, 6.2 Hz, 1H), 2.44 – 2.34 (m, 1H), 2.05 – 1.94 (m, 1H), 1.80 – 1.59 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6, 139.1, 132.1, 129.0,

128.7, 128.3, 127.0, 121.5, 120.8, 117.5, 88.6, 81.0, 71.2, 65.2, 58.1, 57.1, 45.6, 43.6, 33.9; HRMS (ESI) calcd for $C_{21}H_{24}N_2O_2$ [*M*+H$^+$] 337.1911, found 337.1907.

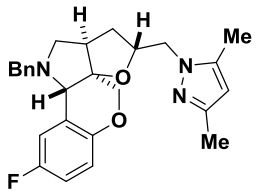


6b. Following **General procedure 7** using compound **S4** (282 mg, 0.582 mmol) and hydrazine hydrate (85 uL, 1.75 mmol) gave after filtration the title compound as an off-white solid (196 mg, >95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.11 (m, 5H), 6.90 – 6.80 (m, 3H), 4.23 – 4.13 (m, 1H), 4.11 (d, *J* = 12.5 Hz, 1H), 4.03 (d, *J* = 11.2 Hz, 1H), 3.85 (d, *J* = 10.7 Hz, 1H), 3.27 (s, 1H), 3.24 (d, *J* = 12.5 Hz, 1H), 2.96 (dd, *J* = 9.2, 8.3 Hz, 1H), 2.83 (dd, *J* = 13.2, 3.7 Hz, 1H), 2.68 (dd, *J* = 13.2, 6.2 Hz, 1H), 2.43 (qd, *J* = 8.2, 1.8 Hz, 1H), 2.03 (dd, *J* = 9.4, 8.0 Hz, 1H), 1.91 (s, 2H), 1.77 – 1.59 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0 (d, J_{CF} = 239.0 Hz), 151.8 (d, J_{CF} = 2.0 Hz), 138.8, 128.7, 128.4, 127.2, 123.0 (d, J_{CF} = 7.0 Hz), 118.5 (d, J_{CF} = 8.1 Hz), 117.7 (d, J_{CF} = 22.8 Hz), 115.8 (d, J_{CF} = 23.1 Hz). 88.7, 81.0, 71.5, 65.6, 58.0, 57.0, 45.6, 43.8, 33.8; HRMS (ESI) calcd for $C_{21}H_{24}FN_2O_2$ [*M*+H$^+$] 355.1817, found 355.1819.

General procedure 8: Mitsunobu reaction using di-*tert*-butyl hydrazine-1,2-dicarboxylate

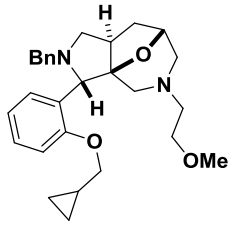


7a. Diol **2a** (258 mg, 0.727 mmol) was dissolved in CH_2Cl_2 (0.2 M, 4 mL) along with PPh_3 (572 mg, 2.18 mmol) and the mixture was cooled to 10 °C. Then di-*tert*-butyl azodicarboxylate (335 mg, 1.45 mmol) was added portion wise and the mixture was stirred 5 min at 10 °C followed by 1 h at rt where upon more di-*tert*-butyl azodicarboxylate (167 mg, 0.727 mmol) was added. The mixture was stirred 16 h at rt and then concentrated *in vacuo*. The residue was taken up in EtOH (5 mL) and 1,1,3,3-tetramethoxypropane (480 uL, 2.91 mmol) was added followed by conc. HCl (0.5 mL) and the mixture was stirred 4 h at reflux. The mixture was then cooled to rt and sat. aq. $NaHCO_3$ was added until pH > 7. The aqueous phase was extracted with CH_2Cl_2 (3× 30 mL) and the combined organic layers were concentrated *in vacuo* and the residue purified by flash column chromatography (EtOAc:heptane 3:7, R_f = 0.1) to give the title compound as a white amorphous solid (234 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 1.9 Hz, 1H), 7.40 (d, *J* = 2.3 Hz, 1H), 7.19 – 7.09 (m, 7H), 6.95 – 6.83 (m, 2H), 6.16 (t, *J* = 2.1 Hz, 1H), 4.49 (td, *J* = 10.0, 4.6 Hz, 1H), 4.31 – 4.18 (m, 2H), 4.09 (d, *J* = 12.5 Hz, 1H), 3.93 (d, *J* = 11.2 Hz, 1H), 3.79 (d, *J* = 11.2 Hz, 1H), 3.29 (d, *J* = 2.6 Hz, 1H), 3.22 (t, *J* = 8.1 Hz, 1H), 2.90 (t, *J* = 8.7 Hz, 1H), 2.36 (q, *J* = 7.6 Hz, 1H), 1.99 (t, *J* = 8.6 Hz, 1H), 1.74 – 1.56 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 139.2, 138.8, 131.8, 130.5, 129.0, 128.6, 128.3, 127.0, 121.6, 120.9, 117.5, 105.7, 89.4, 78.3, 71.1, 65.6, 57.6, 56.9, 54.8, 43.6, 33.5; HRMS (ESI) calcd for $C_{24}H_{26}N_3O_2$ [*M*+H$^+$] 388.2020, found 388.2017.



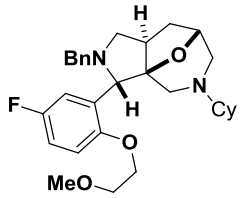
7b. Following **General procedure 8** using diol **2b** (362 mg, 0.969 mmol), PPh_3 (762 g, 2.91 mmol), di-*tert*-butyl azodicarboxylate (670 mg, 2.91 mmol) and acetylacetone (400 uL, 3.88 mmol) gave after flash column chromatography (EtOAc:heptane 7:3, R_f = 0.1) the title compound as a white solid (273 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.18 (m, 5H), 6.93 (m, 3H), 5.79 (s, 1H), 4.57 (dq, *J* = 10.1, 5.1 Hz, 1H), 4.20 – 4.07 (m, 3H), 3.96 (d, *J* = 11.1 Hz, 1H), 3.79 (d, *J* = 11.1 Hz, 1H), 3.39 (s, 1H), 3.33 (d, *J* = 12.6 Hz, 1H), 3.00 (dd, *J* = 9.2, 8.2 Hz, 1H), 2.55 (q, *J* = 7.9 Hz, 1H), 2.25 (s, 3H), 2.23 (s, 3H), 2.19 – 2.10 (m, 1H), 1.98 – 1.87 (m, 1H), 1.84 (ddd, *J* = 13.0, 5.6, 1.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1 (d, J_{CF} = 239.3 Hz), 152.1 (d, J_{CF} = 1.9 Hz), 147.6, 140.2, 138.6, 128.7, 128.4, 127.2, 123.7, 118.5 (d, J_{CF} = 8.1 Hz), 117.5 (d, J_{CF} = 22.9 Hz), 115.7 (d, J_{CF} = 23.0 Hz)., 105.2, 89.8, 79.0, 71.6, 66.3, 57.5, 57.0, 51.9, 43.9, 33.9, 13.6, 11.5; HRMS (ESI) calcd for $C_{26}H_{29}FN_3O_2$ [*M*+H$^+$] 434.2239, found 434.2239.

General procedure 9: Phenol alkylation

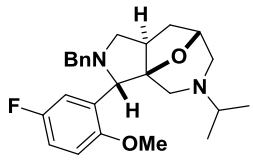


8a. Phenol **3b** (988 mg, 2.50 mmol) was dissolved in DMF (5 mL, 0.5 M) and (bromomethyl)cyclopropane (0.486 µL, 5.01 mmol) and KOH (421 mg, 7.50 mmol) was added and the mixture was stirred overnight at rt. H_2O (50 mL) and EtOAc (50 mL) was added and the layers were separated. The aqueous phase was extracted with EtOAc (2×50 mL) and the combined organic layers were dried using Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc:heptane 3:7, R_f = 0.15) to give the title compound as a colorless oil (934 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.5 Hz, 1H), 7.31 – 7.20 (m, 4H), 7.20 – 7.13 (m, 2H), 6.92 (t, *J* = 7.4 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 4.42 (d, *J* = 6.6 Hz, 1H), 4.16 (s, 1H), 3.92 (dd, *J* = 10.2, 6.5 Hz, 1H), 3.82 (dd, *J* = 10.3, 6.6 Hz, 1H), 3.75 (d, *J* = 13.1 Hz, 1H), 3.26 (t, *J* = 5.9 Hz, 2H), 3.19 (s, 3H), 3.14 (d, *J* = 13.2 Hz, 1H), 3.09 (d, *J* = 7.9 Hz, 1H), 2.70 – 2.59 (m, 1H), 2.47 (d, *J* = 10.7 Hz, 1H), 2.39 – 2.24 (m, 2H), 2.20 (dd, *J* = 10.8, 1.7 Hz, 1H), 2.06 (d, *J* = 9.1 Hz, 1H), 2.01 (d, *J* = 10.7 Hz, 1H), 1.90

(dd, *J* = 11.6, 8.6 Hz, 1H), 1.72 (d, *J* = 11.0 Hz, 1H), 1.69 – 1.56 (m, 1H), 1.40 – 1.20 (m, 1H), 0.63 – 0.49 (m, 2H), 0.46 – 0.32 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 139.8, 128.7, 128.7, 128.2, 127.9, 127.6, 126.8, 120.5, 111.8, 92.7, 78.2, 72.5, 70.4, 68.9, 59.2, 58.8, 58.7, 58.4, 58.0, 57.3, 46.2, 33.2, 10.4, 3.5, 3.3; HRMS (ESI) calcd for $C_{28}H_{37}N_2O_3$ [*M*+H$^+$] 449.2799, found 449.2796.

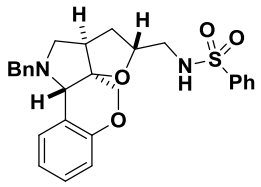


8b. Following **General procedure 9** using phenol **3c** (306 mg, 0.701 mmol), 1-bromo-2-methoxyethane (132 μL, 2 equiv.) and KOH pellets (118 mg, 3 equiv.) gave after flash column chromatography (EtOAc:heptane 1:3, R_f = 0.2) the title compound as a colorless oil (260 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 9.7 Hz, 1H), 7.31 – 7.28 (m, 4H), 7.26 – 7.18 (m, 1H), 6.96 – 6.81 (m, 2H), 4.45 (d, *J* = 6.1 Hz, 1H), 4.22 – 4.07 (m, 3H), 3.90 – 3.69 (m, 3H), 3.48 (s, 3H), 3.19 (d, *J* = 13.1 Hz, 1H), 3.13 (t, *J* = 7.8 Hz, 1H), 2.72 – 2.58 (m, 1H), 2.43 (d, *J* = 10.5 Hz, 1H), 2.33 (d, *J* = 10.5 Hz, 1H), 2.10 – 1.95 (m, 3H), 1.88 (dd, *J* = 17.6, 10.6 Hz, 2H), 1.72 – 1.44 (m, 6H), 1.16 – 0.96 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8 (d, J_{CF} = 237.8 Hz), 154.0, 139.5, 130.5 (d, J_{CF} = 6.6 Hz), 128.7, 128.3, 126.9, 115.5 (d, J_{CF} = 24.4 Hz), 114.0 (d, J_{CF} = 23.2 Hz), 113.6 (d, J_{CF} = 8.1 Hz), 92.8, 78.5, 71.2, 69.1, 68.9, 62.4, 59.5, 58.7, 58.5, 55.1, 53.1, 46.2, 33.2, 29.4, 28.7, 26.4, 25.5, 25.4; HRMS (ESI) calcd for $C_{31}H_{40}FN_2O_3$ [*M*+H$^+$] 495.3018, found 495.3011.

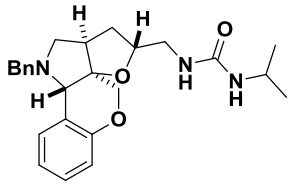


8c. Following **General procedure 9** using phenol **3d** (784 mg, 1.88 mmol), MeI (246 μL, 2 equiv.) and KOH pellets (333 mg, 3 equiv.) gave after flash column chromatography (EtOAc:heptane 1:4, R_f = 0.2) the title compound as a colorless oil (762 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 9.8, 3.2 Hz, 1H), 7.33 – 7.27 (m, 4H), 7.22 (dd, *J* = 8.8, 4.4 Hz, 1H), 6.91 (td, *J* = 8.3, 3.2 Hz, 1H), 6.81 (dd, *J* = 8.9, 4.4 Hz, 1H), 4.48 (d, *J* = 6.6 Hz, 1H), 4.11 (s, 1H), 3.86 (s, 3H), 3.74 (d, *J* = 13.1 Hz, 1H), 3.19 (d, *J* = 13.1 Hz, 1H), 3.13 (t, *J* = 7.9 Hz, 1H), 2.72 – 2.61 (m, 1H), 2.47 – 2.31 (m, 3H), 2.11 – 2.03 (m, 1H), 2.00 (d, *J* = 10.8 Hz, 1H), 1.89 (dd, *J* = 11.5, 8.6 Hz, 1H), 1.79 (d, *J* = 10.9 Hz, 1H), 1.70 – 1.62 (m, 1H), 0.84 (d, *J* = 3.2 Hz, 3H), 0.82 (d, *J* = 3.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5 (d, J_{CF} = 237.2 Hz), 154.7 (d, J_{CF} = 1.9 Hz), 139.4, 129.7 (d, J_{CF} = 6.5 Hz), 128.8, 128.3, 126.9, 115.5 (d, J_{CF} = 24.4 Hz), 113.9 (d, J_{CF} = 23.2 Hz), 111.5 (d, J_{CF} = 8.1 Hz), 92.8, 78.7, 68.6, 58.7, 58.4, 56.4, 54.8, 53.8, 52.5, 46.2, 33.2, 19.1, 18.3; HRMS (ESI) calcd for $C_{25}H_{32}FN_2O_2$ [*M*+H$^+$] 411.2443, found 411.2443.

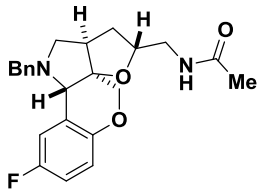
Functionalization of primary amines



9a. Amine **6a** (204 mg, 0.608 mmol) was dissolved in CH_2Cl_2 (3 mL), Et_3N (127 μL,0.912 mmol) was added, and the mixture was cooled to 0 °C. Benzenesulfonyl chloride (93 μL, 0.730 mmol) was then added and the mixture was stirred 1 h at 0 °C. The solvent was removed and the residue was purified by flash column chromatography (EtOAc:heptane 3:7, R_f = 0.2) to give the title compound as a white solid (211 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.72 (m, 2H), 7.54 – 7.46 (m, 1H), 7.45 – 7.37 (m, 2H), 7.20 – 7.11 (m, 7H), 6.91 – 6.83 (m, 2H), 4.88 (t, *J* = 5.8 Hz, 1H), 4.29 – 4.16 (m, 1H), 4.15 (d, *J* = 12.4 Hz, 1H), 4.05 (d, *J* = 11.3 Hz, 1H), 3.86 (d, *J* = 11.3 Hz, 1H), 3.17 (d, *J* = 12.4 Hz, 1H), 3.13 (s, 1H), 3.12 – 3.06 (m, 1H), 2.94 (t, *J* = 8.8 Hz, 1H), 2.93 – 2.78 (m, 1H), 2.33 (q, *J* = 8.2 Hz, 1H), 1.95 – 1.89 (m, 1H), 1.79 (dt, *J* = 12.7, 9.9 Hz, 1H), 1.63 – 1.54 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3, 134.0, 139.0, 132.8, 132.3, 129.2, 129.2, 128.7, 128.4, 127.1, 127.1, 120.9, 120.6, 117.5, 88.4, 77.9, 70.5, 64.5, 58.1, 57.0, 45.9, 43.2, 33.6; HRMS (ESI) calcd for $C_{27}H_{29}N_2O_4S$ [*M*+H$^+$] 477.1843, found 477.1845.

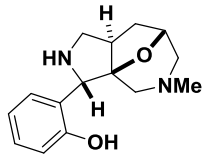


9b. Amine **6a** (251 mg, 0.746 mmol) was dissolved in CH_2Cl_2 (3 mL) and isopropyl isocyanate (89 uL, 0.895 mmol) was added and the mixture was stirred 1 h at rt. The mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography (100% EtOAc, R_f = 0.3) to give the title compound as a white solid (266 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.09 (m, 7H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.86 (dd, *J* = 7.4, 1.1 Hz, 1H), 4.84 (t, *J* = 5.9 Hz, 1H), 4.75 – 4.66 (m, 1H), 4.25 – 4.05 (m, 3H), 3.92 (dd, *J* = 11.2, 0.7 Hz, 1H), 3.73 (dq, *J* = 13.1, 6.5 Hz, 1H), 3.39 (ddd, *J* = 14.3, 6.7, 2.7 Hz, 1H), 3.16 (s, 1H), 3.04 – 2.89 (m, 2H), 2.39 – 2.19 (m, 1H), 2.07 – 1.84 (m, 2H), 1.74 – 1.46 (m, 2H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.98 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 158.2, 155.3, 138.9, 132.4, 129.2, 128.7, 128.3, 127.1, 120.8, 117.4, 88.1, 79.9, 70.7, 64.4, 58.1, 57.1, 43.7, 43.1, 42.1, 33.7, 23.4, 23.4; HRMS (ESI) calcd for $C_{25}H_{32}N_3O_3$ [*M*+H$^+$] 422.2438 found 422.2438.

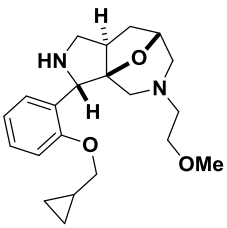


9c. Amine **6b** (173 mg, 0.491 mmol) was dissolved in CH_2Cl_2 (3 mL), Et_3N (102 µL, 0.737 mmol) was added, and the mixture was cooled to 0 °C. Acetyl chloride (39 µL, 0.540 mmol) was then added and the mixture was stirred 30 min at 0 °C. The solvent was removed and the residue was purified by flash column chromatography (EtOAc:heptane 9:1, R_f = 0.2) to give the title compound as a white solid (159 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.20 (m, 5H), 6.98 – 6.92 (m, 3H), 5.86 (t, *J* = 5.1 Hz, 1H), 4.29 (tdd, *J* = 13.3, 8.2, 4.8 Hz, 1H), 4.22 (d, *J* = 12.4 Hz, 1H), 4.13 (d, *J* = 11.2 Hz, 1H), 3.95 (dd, *J* = 11.2, 0.7 Hz, 1H), 3.67 (ddd, *J* = 14.1, 6.7, 3.0 Hz, 1H), 3.29 (d, *J* = 12.1 Hz, 1H), 3.27 (s, 1H), 3.18 (ddd, *J* = 14.1, 6.9, 5.2 Hz, 1H), 3.04 (t, *J* = 8.8 Hz, 1H), 2.46 (q, *J* = 7.8 Hz, 1H), 2.07 (t, *J* = 8.8 Hz, 1H), 1.97 (s, 3H), 1.81 – 1.66 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 157.0 (d, J_{CF} = 239.2 Hz), 151.6, 138.6, 128.7, 128.4, 127.3, 122.4 (d, J_{CF} = 6.5 Hz), 118.6 (d, J_{CF} = 8.2 Hz), 117.9 (d, J_{CF} = 22.8 Hz), 116.0 (d, J_{CF} = 23.1 Hz), 88.5, 78.7, 71.2, 65.1, 58.0, 57.1, 43.4, 42.7, 33.9, 23.4; HRMS (ESI) calcd for $C_{23}H_{26}FN_2O_3$ [*M*+H$^+$] 397.1922, found 397.1918.

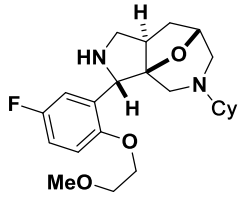
General procedure 10a: Benzyl deprotection in MeOH.



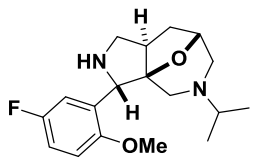
S5. Compound **3a** (507 mg, 1.45 mmol) was dissolved in MeOH (6 mL, 0.3M) and 2.5% Pd/C (38 mg of 10% Pd/C) and $HCOONH_4$ (228 mg, 4.35 mmol, 2.5 equiv.) was added and the mixture was stirred 6 h at reflux. The mixture was then filtered over Celite and the filtrate was concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 (30 mL) and H_2O (30 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2×30 mL) and the combined organic layers were dried using Na_2SO_4 and concentrated *in vacuo* to give the title compound as a colorless oil (369 mg, >95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (t, *J* = 7.7 Hz, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 6.81 – 6.71 (m, 2H), 4.48 (d, *J* = 6.7 Hz, 1H), 4.31 (s, 1H), 3.38 (t, *J* = 8.0 Hz, 1H), 2.92 – 2.80 (m, 1H), 2.65 (dd, *J* = 10.5, 9.1 Hz, 1H), 2.49 (d, *J* = 11.1 Hz, 1H), 2.21 (d, *J* = 11.3 Hz, 1H), 2.15 (dd, *J* = 11.1, 2.0 Hz, 1H), 2.12 – 2.05 (m, 4H), 1.82 – 1.71 (m, 1H), 1.67 (d, *J* = 11.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 129.4, 129.2, 121.2, 119.0, 117.2, 92.2, 78.7, 69.9, 60.4, 59.4, 51.9, 47.6, 45.6, 33.4; HRMS (ESI) calcd for $C_{15}H_{21}N_2O_2$ [*M*+H$^+$] 261.1598, found 261.1598.



S6. Following **General procedure 10a** using **8a** (787 mg, 1.75 mmol), 2.5% Pd/C (47 mg of 10% Pd/C) and $HCOONH_4$ (332 mg, 5.26 mmol) gave after extraction the title compound as a colorless oil (612 mg, >95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.4 Hz, 1H), 7.18 (t, *J* = 8.2 Hz, 1H), 6.90 (t, *J* = 7.4 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 4.52 (s, 1H), 4.48 (d, *J* = 6.7 Hz, 1H), 3.90 – 3.75 (m, 2H), 3.40 (dd, *J* = 10.0, 7.9 Hz, 1H), 3.34 (t, *J* = 5.9 Hz, 3H), 3.25 (s, 3H), 2.82 (ddd, *J* = 11.2, 8.7, 3.3 Hz, 1H), 2.68 (t, *J* = 9.8 Hz, 1H), 2.56 (d, *J* = 10.8 Hz, 1H), 2.49 – 2.33 (m, 3H), 2.30 – 2.20 (m, 2H), 2.07 (dd, *J* = 11.7, 8.5 Hz, 1H), 1.93 (d, *J* = 10.9 Hz, 1H), 1.81 – 1.71 (m, 1H), 1.30 (ddd, *J* = 12.2, 7.4, 5.0 Hz, 1H), 0.63 (d, *J* = 7.9 Hz, 2H), 0.38 (d, *J* = 4.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6, 129.6, 128.2, 120.5, 111.3, 94.2, 78.3, 72.4, 70.3, 65.6, 58.7, 58.2, 58.0, 57.3, 54.3, 48.6, 34.4, 10.2, 3.3, 3.2; HRMS (ESI) calcd for $C_{21}H_{31}N_2O$ [*M*+H$^+$] 359.2329, found 359.2330.

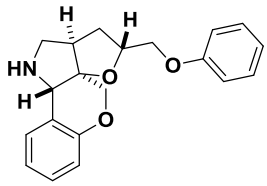


S7. Following **General procedure 10a** using **8b** (226 mg, 0.46 mmol), 5% Pd/C (24 mg of 10% Pd/C) and $HCOONH_4$ (86 mg, 3 equiv.) gave after extraction the title compound as a colorless oil (155 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 9.6 Hz, 1H), 6.91 – 6.83 (m, 1H), 6.82 – 6.75 (m, 1H), 4.52 (s, 1H), 4.47 (d, *J* = 6.3 Hz, 1H), 4.10 (t, *J* = 4.6 Hz, 2H), 3.78 – 3.72 (m, 2H), 3.44 (s, 3H), 3.37 (d, *J* = 6.4 Hz, 1H), 2.76 – 2.63 (m, 2H), 2.60 – 2.51 (m, 1H), 2.46 (d, *J* = 10.8 Hz, 1H), 2.36 (d, *J* = 10.7 Hz, 1H), 2.11 (d, *J* = 10.8 Hz, 1H), 2.04 – 1.95 (m, 3H), 1.72 – 1.48 (m, 6H), 1.17 – 0.97 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5 (d, J_{CF} = 238.3 Hz), 152.8 (d, J_{CF} = 2.0 Hz), 131.0 (d, J_{CF} = 7.0 Hz), 116.2 (d, J_{CF} = 24.1 Hz), 114.1 (d, J_{CF} = 23.1 Hz), 112.8 (d, J_{CF} = 8.1 Hz), 93.8, 78.6, 71.1, 68.4, 64.3, 62.4, 59.4, 54.2, 53.9, 53.2, 48.1, 34.4, 29.4, 28.7, 26.4, 25.5, 25.4 ; HRMS (ESI) calcd for $C_{23}H_{34}FN_2O_3$ [*M*+H$^+$] 405.2548, found 405.2551.

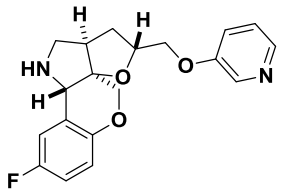


S8. Following **General procedure 10a** using **8c** (700 mg, 1.71 mmol), 5% Pd/C (90 mg of 10% Pd/C) and $HCOONH_4$ (322 mg, 3 equiv.) gave after extraction the title compound as a colorless oil (527 mg, >95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, *J* = 10.1, 3.6 Hz, 1H), 6.93 – 6.81 (m, 1H), 6.76 (dd, *J* = 8.9, 4.4 Hz, 1H), 4.57 (s, 1H), 4.49 (d, *J* = 6.7 Hz, 1H), 3.81 (s, 3H), 3.46 – 3.33 (m, 1H), 2.78 – 2.66 (m, 3H), 2.50 – 2.39 (m, 2H), 2.35 (dd, *J* = 10.9, 2.2 Hz, 1H), 2.08 – 1.89 (m, 3H), 1.71 (ddd, *J* = 11.6, 6.8, 2.9 Hz, 1H), 0.85 (d, *J* = 2.5 Hz, 3H), 0.83 (d, *J* = 2.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3 (d, J_{CF} = 237.8 Hz), 153.5 (d, J_{CF} = 2.0 Hz), 130.5 (d, *J* = 6.5 Hz), 115.8 (d, *J* = 24.2 Hz), 114.0 (d, J_{CF} = 23.0 Hz), 111.2 (d, J_{CF} = 8.1 Hz), 93.6, 78.6, 63.3, 56.1, 53.9, 53.9, 53.8, 52.6, 47.8, 34.4, 19.0, 18.2; HRMS (ESI) calcd for $C_{18}H_{26}FN_2O_2$ [*M*+H$^+$] 321.1973, found 321.1970.

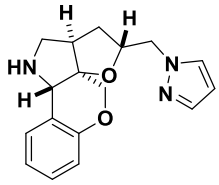
General procedure 10b: Benzyl deprotection in EtOH.



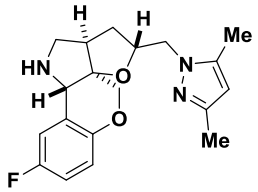
S9. Compound **5a** (141 mg, 0.341 mmol) was dissolved in EtOH (2 mL, 0.2 M) and 5% Pd/C (18 mg of 10% Pd/C) and $HCOONH_4$ (108 mg, 1.7 mmol, 5 equiv.) was added and the mixture was stirred for 6 h at reflux. The mixture was then filtered over Celite and the Celite pad was washed with CH_2Cl_2. The organic layer was washed with sat. $NaHCO_3$ (aq.) and the aqueous phase was extracted with CH_2CL_2 (2×20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as an amorphous solid (100 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.22 – 7.15 (m, 2H), 7.10 – 7.02 (m, 1H), 6.91 – 6.77 (m, 5H), 4.53 (td, *J* = 10.2, 4.6 Hz, 1H), 4.03 (s, 1H), 4.01 (d, *J* = 11.5 Hz, 1H), 3.94 – 3.87 (m, 3H), 3.08 (dd, *J* = 11.3, 8.0 Hz, 1H), 2.75 – 2.57 (m, 2H), 2.09 (s, 1H), 2.01 (ddd, *J* = 12.8, 9.3, 8.4 Hz, 1H), 1.92 (ddd, *J* = 12.8, 6.0, 2.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 154.7, 129.8, 129.5, 128.5, 124.0, 121.8, 121.0, 116.9, 114.6, 90.8, 78.8, 70.1, 69.2, 62.3, 52.2, 46.4, 34.8; HRMS (ESI) calcd for $C_{20}H_{22}NO_3$ [*M*+H$^+$] 324.1594, found 324.1591.



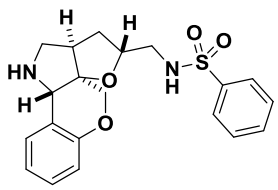
S10. Following **General procedure 10b** using **5b** (169 mg, 0.39 mmol), 5% Pd/C (21 mg of 10% Pd/C) and $HCOONH_4$ (123 mg, 1.95 mmol) gave after extraction the title compound as a colorless oil (134 mg, >95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (t, *J* = 1.8 Hz, 1H), 8.23 (t, *J* = 3.0 Hz, 1H), 7.25 – 7.17 (m, 3H), 6.97 – 6.82 (m, 2H), 4.74 (td, *J* = 9.7, 4.3 Hz, 1H), 4.31 (s, 1H), 4.17 – 4.01 (m, 4H), 3.57 (br. s, 1H), 3.37 (dd, *J* = 11.7, 8.5 Hz, 1H), 2.99 (dd, *J* = 11.7, 6.1 Hz, 1H), 2.88 (dt, *J* = 14.5, 4.1 Hz, 1H), 2.28 – 2.16 (m, 1H), 2.10 (ddd, *J* = 13.0, 6.0, 1.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8 (d, J_{CF} = 240.6 Hz), 155.0, 151.1, 151.1, 142.7, 138.1, 124.0, 121.5, 118.7 (d, J_{CF} = 8.0 Hz), 116.7 (d, J_{CF} = 23.5 Hz), 116.0 (d, J_{CF} = 23.4 Hz). 90.0, 78.9, 69.9, 69.1, 61.8, 51.0, 45.3, 34.0; HRMS (ESI) calcd for $C_{19}H_{20}FN_2O_3$ [*M*+H$^+$] 343.1453, found 343.1455.



S11. Following **General procedure 10b** using **7a** (133 mg, 0.335 mmol), 10% Pd/C (36 mg) and $HCOONH_4$ (105 mg, 1.68 mmol) gave after extraction the title compound as off-white amorphous solid (102 mg, >95%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 2H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.06 (t, *J* = 7.7 Hz, 1H), 6.86 (t, *J* = 5.5 Hz, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.17 – 6.14 (m, 1H), 4.46 (dt, *J* = 9.5, 4.8 Hz, 1H), 4.31 – 4.10 (m, 2H), 3.93 – 3.83 (m, 1H), 3.64 (d, *J* = 11.3 Hz, 1H), 3.22 – 2.90 (m, 1H), 2.68 – 2.54 (m, 1H), 2.44 (d, *J* = 4.2 Hz, 1H), 2.21 (s, 1H), 1.82 – 1.62 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5, 139.1, 130.5, 129.7, 128.5, 123.6, 121.8, 116.9, 105.6, 90.4, 78.7, 69.1, 61.9, 54.8, 51.8, 46.2, 34.4; HRMS (ESI) calcd for $C_{17}H_{20}N_3O_2$ [*M*+H$^+$] 298.1550, found 298.1552.

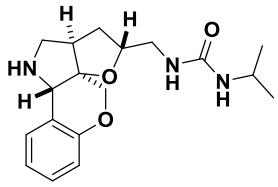


S12. Following **General procedure 10b** using **7b** (194 mg, 0.447 mmol), 10% Pd/C (47 mg) and $HCOONH_4$ (140 mg, 2.34 mmol) gave after extraction the title compound as off-white amorphous solid (155 mg, >95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (dd, *J* = 8.8, 2.7 Hz, 1H), 6.77 – 6.68 (m, 2H), 5.69 (s, 1H), 4.45 (td, *J* = 10.1, 5.0 Hz, 1H), 4.03 (qd, *J* = 14.5, 4.8 Hz, 2H), 3.87 (s, 1H), 3.85 (d, *J* = 10.9 Hz, 1H), 3.61 (d, *J* = 11.3 Hz, 1H), 3.06 (dd, *J* = 11.6, 8.4 Hz, 1H), 2.65 (dd, *J* = 11.6, 6.1 Hz, 1H), 2.49 (dd, *J* = 14.8, 7.3 Hz, 1H), 2.27 (br. s, 1H), 2.16 (s, 3H), 2.12 (s, 3H), 1.95 – 1.76 (m, 2H);^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6 (d, J_{CF} = 239.7 Hz), 150.6 (d, J_{CF} = 1.9 Hz), 147.4, 140.1, 125.1 (d, J_{CF} = 7.1 Hz), 117.9 (d, J_{CF} = 8.1 Hz), 115.5, 115.3, 105.1, 90.3, 79.5, 69.2, 62.2, 51.9 (d, J_{CF} = 5.5 Hz), 46.2, 34.8, 13.5, 11.3; HRMS (ESI) calcd for $C_{19}H_{23}FN_3O_2$ [*M*+H$^+$] 344.1769, found 344.1774.

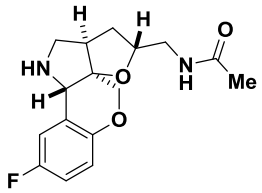


S13. Following **General procedure 10b** using **9a** (134 mg, 0.282 mmol), 10% Pd/C (30 mg) and $HCOONH_4$ (89 mg, 1.41 mmol) gave after extraction the title compound as an amorphous solid (92 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.77 (m, 2H), 7.59 – 7.51 (m, 1H), 7.50 – 7.43 (m, 2H), 7.30 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.25 – 7.11 (m, 2H), 6.94 (td, *J* = 7.5, 1.2 Hz, 1H), 6.85 (dd, *J* = 8.2, 0.9 Hz, 1H), 5.51 (br. s, 1H), 4.26 – 4.17 (m, 1H), 4.01 (dd, *J* = 11.5, 0.8 Hz, 1H), 3.78 (s, 1H), 3.76 (d, *J* = 11.5 Hz, 1H), 3.26 – 3.11 (m, 2H), 2.94 (dd, *J* =

13.1, 5.9 Hz, 1H), 2.64 (dd, *J* = 11.5, 7.0 Hz, 1H), 2.49 (q, *J* = 7.7 Hz, 1H), 2.22 (br. s, 1H), 1.86 (ddd, *J* = 12.8, 10.5, 8.8 Hz, 1H), 1.72 (ddd, *J* = 12.8, 5.2, 0.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 140.1, 132.7, 130.2, 129.2, 128.7, 127.0, 123.0, 121.9, 117.1, 90.2, 78.1, 69.3, 60.8, 51.9, 46.4, 46.0, 34.3; HRMS (ESI) calcd for $C_{20}H_{23}N_2O_4S$ [*M*+H$^+$] 387.1373, found 387.1380.

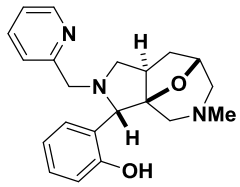


S14. Following **General procedure 10b** using **9b** (165 mg, 0.391 mmol), 5% Pd/C (21 mg of 10% Pd/C) and $HCOONH_4$ (148 mg, 2.34 mmol) gave after extraction the title compound as a yellow oil (108 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.18 – 7.09 (m, 1H), 6.93 (td, *J* = 7.5, 1.1 Hz, 1H), 6.86 (dd, *J* = 8.2, 0.8 Hz, 1H), 5.16 (s, 1H), 4.96 (s, 1H), 4.30 – 4.16 (m, 1H), 4.05 (d, *J* = 11.3 Hz, 1H), 3.85 (s, 1H), 3.79 (d, *J* = 11.5 Hz, 2H), 3.45 (ddd, *J* = 14.2, 6.5, 2.8 Hz, 1H), 3.20 (dd, *J* = 11.4, 8.4 Hz, 1H), 3.07 (dt, *J* = 14.3, 5.8 Hz, 1H), 2.68 (dd, *J* = 11.5, 7.0 Hz, 1H), 2.58 – 2.42 (m, 1H), 2.28 (s, 1H), 1.83 – 1.64 (m, 2H), 1.06 (d, *J* = 6.5 Hz, 3H), 1.04 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3, 154.5, 130.1, 128.6, 123.3, 121.8, 117.0, 90.1, 80.0, 69.5, 61.0, 52.0, 46.5, 43.7, 42.0, 34.3, 23.4, 23.4; HRMS (ESI) calcd for $C_{18}H_{26}N_3O_3$ [*M*+H$^+$] 332.1969, found 332.1971.



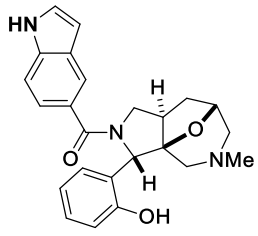
S15. Following **General procedure 10b** using **9c** (151 mg, 0.390 mmol), 10% Pd/C (41 mg) and $HCOONH_4$ (89 mg, 1.95 mmol) gave after extraction the title compound as off-white amorphous solid (102 mg, >95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.85 – 6.79 (m, 2H), 6.20 (t, *J* = 5.3 Hz, 1H), 4.28 – 4.16 (m, 1H), 4.03 (dd, *J* = 11.4, 0.8 Hz, 1H), 3.82 (s, 1H), 3.77 (d, *J* = 11.4 Hz, 1H), 3.66 – 3.54 (m, 1H), 3.21 (dd, *J* = 11.5, 8.4 Hz, 1H), 3.11 (ddd, *J* = 14.0, 6.9, 5.2 Hz, 1H), 2.70 (dd, *J* = 11.5, 6.9 Hz, 1H), 2.51 (q, *J* = 7.2 Hz, 1H), 2.24 (s, 1H), 1.90 (s, 3H), 1.83 – 1.66 (m, 2H);^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 157.6 (d, J_{CF} = 240.0 Hz), 150.5 (d, J_{CF} = 1.9 Hz), 124.6 (d, J_{CF} = 7.3 Hz), 118.1 (d, J_{CF} = 8.1 Hz), 115.8 (d, J_{CF} = 10.6 Hz), 115.52 (d, J_{CF} = 11.2 Hz), 89.9, 78.9, 69.7, 61.2, 52.0, 46.4, 42.8, 34.1, 23.1; HRMS (ESI) calcd for $C_{16}H_{20}FN_2O_3$ [*M*+H$^+$] 307.1453, found 307.1458.

General procedure 11: Reductive alkylation using aldehydes.



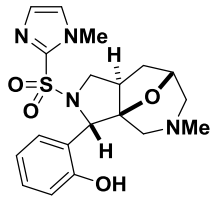
10a. Amine **S5** (45 mg, 0.17 mmol) was taken up in DMF (1 mL) and picolinaldehyde (27 µL, 0.22 mmol, 1.3 equiv.) and $NaBH(OAc)_3$ (56 mg, 2.6 mmol) was added and the mixture was stirred for 16 h at rt. The compound was then purified directly by preparative HPLC to give a colorless oil (24 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 4.7 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 7.8 Hz, 1H), 7.17 – 7.07 (m, 2H), 7.01 (d, *J* = 7.3 Hz, 1H), 6.76 (t, *J* = 8.2 Hz, 2H), 4.39 (d, *J* = 6.7 Hz, 1H), 3.99 (d, *J* = 13.0 Hz, 1H), 3.77 (s, 1H), 3.49 (d, *J* = 13.0 Hz, 1H), 3.18 – 3.07 (m, 1H), 2.83 – 2.68 (m, 1H), 2.41 (d, *J* = 11.1 Hz, 1H), 2.22 (d, *J* = 11.3 Hz, 1H), 2.20 – 2.11 (m, 1H), 2.07 (dd, *J* = 11.1, 1.7 Hz, 1H), 2.02 (s, 3H), 1.96 (t, *J* = 10.3 Hz, 1H), 1.70 – 1.62 (m, 1H), 1.59 (d, *J* = 11.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 156.9, 149.3, 136.8, 130.4, 129.4, 123.7, 122.6, 119.8, 119.4, 117.0, 92.0, 78.4, 60.3, 59.7, 59.2, 58.1, 46.5, 45.5, 33.4; HRMS (ESI) calcd for $C_{21}H_{26}N_3O_2$ [*M*+H$^+$] 352.2020, found 352.2019.

General procedure 12: TBTU mediated amide coupling using carboxylic acids.



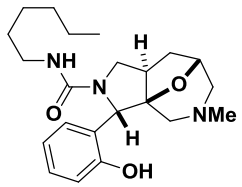
10b. Amine **S5** (44 mg, 0.17 mmol) was dissolved in DMF (0.5 mL). To this solution was added a premixed mixture of indole-5-carboxylic acid (33 mg, 0.20 mmol, 1.2 equiv.), TBTU (71 mg, 0.19 mmol, 1.1 equiv.) and DIPEA (44 µL, 0.26 mmol, 1.5 equiv.) in DMF (0.5 mL), and the mixture was stirred 2 h at rt. The compound was then purified directly by preparative HPLC to give the title compound as a white solid (65 mg, 92%). ^{1}H NMR (400 MHz, DMSO) δ 11.28 (s, 0.5H), 11.17 (s, 0.5H), 9.65 (s, 0.5H), 9.41 (s, 0.5H), 7.77 (s, 0.5H), 7.46 – 7.06 (m, 5.5H), 6.98 – 6.69 (m, 2H), 6.50 (s, 1H), 6.28 (s, 0.5H), 5.96 – 5.81 (m, 0.5H), 5.42 – 5.31 (m, 0.5H), 4.63 – 4.12 (m, 2H), 3.77– 3.63 (m, 0.5H), 3.19 – 2.80 (m, 2H), 2.26 – 1.65 (m, 8H) (two rotamers); ^{13}C NMR (101 MHz, DMSO) δ 172.0, 170.7, 169.7, 154.9, 154.0, 136.4, 136.1, 128.6, 127.7, 126.8, 126.5, 126.2, 120.5, 120.0, 119.5, 118.9, 115.1, 111.0, 110.6, 101.8, 92.4, 90., 75.8, 62.9, 58.4, 57.3, 55.9, 45.0, 43.9, 41.5, 38.1, 37.4, 21.1 (two rotaters); HRMS (ESI) calcd for $C_{25}H_{28}N_3O_3$ [*M*+H$^+$] 418.2125, found 418.2125.

General procedure 13: Sulphonylation using sulphonyl chlorides

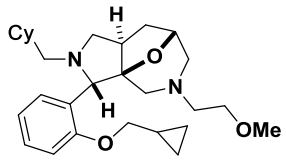


10c. Amine **S5** (37 mg, 0.14 mmol) was taken up in DMF (1 mL), DIPEA (32 µL, 0.18 mmol) was added followed by 1-methyl-1*H*-imidazole-2-sulfonyl chloride (26 mg, 0.14 mmol, 1.0 equiv.) and the mixture was stirred 1 h at rt. The compound was then purified directly by preparative HPLC to give the title compound as a white amorphous solid (36 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (t, *J* = 7.6 Hz, 1H), 7.08 – 7.01 (m, 2H), 6.87 – 6.81 (m, 3H), 5.20 (s, 1H), 4.45 (d, *J* = 4.5 Hz, 1H), 4.17 (t, *J* = 9.4 Hz, 1H), 3.70 (s, 3H), 3.55 – 3.31 (m, 1H), 3.25 (s, 1H), 2.54 (d, *J* = 11.1 Hz, 1H), 2.31 – 2.15 (m, 3H), 2.10 (s, 3H), 1.99 – 1.81 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 154.3, 142.6, 129.6, 127.7, 125.2, 124.8, 121.1, 92.5, 77.2, 76.8, 58.8, 58.3, 57.0, 45.3, 36.5, 35.0, 21.5; HRMS (ESI) calcd for $C_{19}H_{25}N_4O_4S$ [*M*+H$^+$] 405.1591, found 405.1589.

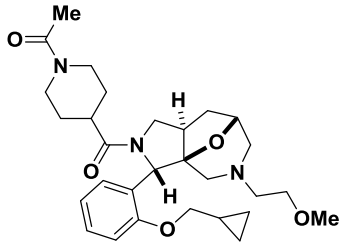
General procedure 14: Urea formation using isocyanates.



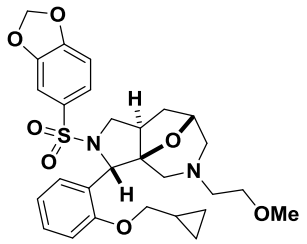
10d. Amine **S5** (32 mg, 0.12 mmol) was taken in DMF (1 mL), hexyl isocyanate (18 µL, 0.13 mmol, 1.1 equiv.) was added and the mixture was stirred 30 min at rt. The compound was then purified directly by preparative HPLC to give a white powder (30 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 8.1 Hz, 1H), 6.83 (t, *J* = 7.4 Hz, 1H), 5.22 (s, 1H), 4.52 (d, *J* = 6.8 Hz, 1H), 4.29 (t, *J* = 4.9 Hz, 1H), 4.09 (t, *J* = 9.9 Hz, 1H), 3.35 – 3.23 (m, 1H), 3.19 – 3.06 (m, 2H), 3.06 – 2.94 (m, 1H), 2.53 (d, *J* = 10.7 Hz, 1H), 2.32 – 2.19 (m, 3H), 2.13 (s, 3H), 2.03 – 1.86 (m, 1H), 1.32 – 0.96 (m, 9H), 0.81 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1, 155.3, 155.1, 129.5, 129.3, 120.1, 116.9, 92.9, 77.2, 59.2, 58 .4, 55.4, 45.5, 43.7, 40.6, 37.4, 31.5, 29.9, 29.7, 26.3, 22.5, 14.0; HRMS (ESI) calcd for $C_{22}H_{34}N_3O_3$ [*M*+H$^+$] 388.2595, found 388.2597.



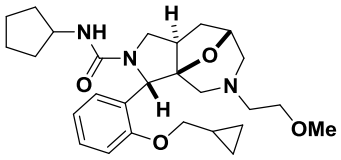
10e. Amine **S6** (30 mg, 0.084 mmol) was reductively alkylated following **General procedure 11** using cyclohexanecarboxaldehyde (15 µL, 0.13 mmol) and $NaBH(OAc)_3$ (27 mg, 0.13 mmol) to give the title compound as a colorless oil (24 mg, 62%) after preparative HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 6.9 Hz, 1H), 7.16 (td, *J* = 8.1, 1.7 Hz, 1H), 6.91 (t, *J* = 7.4 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 4.46 (d, *J* = 6.7 Hz, 1H), 3.98 (s, 1H), 3.93 (dd, *J* = 10.3, 6.4 Hz, 1H), 3.82 (dd, *J* = 10.3, 6.6 Hz, 1H), 3.36 (t, *J* = 7.8 Hz, 1H), 3.31 (t, *J* = 5.9 Hz, 2H), 3.24 (s, 3H), 2.77 – 2.63 (m, 1H), 2.53 (d, *J* = 10.6 Hz, 1H), 2.42 – 2.28 (m, 2H), 2.23 (d, *J* = 11.4 Hz, 1H), 2.17 (d, *J* = 11.1 Hz, 1H), 2.12 – 1.94 (m, 5H), 1.78 – 1.67 (m, 3H), 1.62 (d, *J* = 11.5 Hz, 2H), 1.57 – 1.43 (m, 2H), 1.37 – 1.28 (m, 1H), 1.23 – 1.03 (m, 3H), 0.82 – 0.69 (m, 2H), 0.63 – 0.54 (m, 2H), 0.45 – 0.38 (m, 2H);^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 129.1, 128.2, 127.6, 120.3, 111.6, 92.5, 78.1, 72.4, 70.3, 69.6, 61.5, 59.2, 59.0, 58.8, 58.0, 57.4, 46.4, 36.8, 33.3, 32.2, 31.3, 27.0, 26.4, 26.2, 10.4, 3.5, 3.3; HRMS (ESI) calcd for $C_{28}H_{43}N_2O_3$ [*M*+H$^+$] 455.3268, found 455.3268.



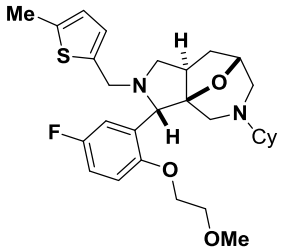
10f. Following **General procedure 12** using **S6** (31.5 mg, 0.088 mmol), 1-acetylpiperidine-4-carboxylic acid (23 mg, 0.132 mmol), TBTU (40 mg, 123 mmol) and DIPEA (17 µL, 0.132 mmol), gave after preparative HPLC the title compound as a yellow solid (25 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.10 (m, 1H), 6.97 (d, *J* = 7.6 Hz, 1H), 6.91 (t, *J* = 7.5 Hz, 1H), 6.84 (dd, *J* = 8.3, 3.3 Hz, 1H), 5.64 (d, *J* = 10.6 Hz, 1H), 4.64 – 4.44 (m, 2H), 4.35 – 4.12 (m, 2H), 3.92 – 3.83 (m, 1H), 3.84 – 3.70 (m, 1H), 3.57 (d, *J* = 13.4 Hz, 0.5H), 3.43 (dd, *J* = 12.8, 7.3 Hz, 1H), 3.37 – 3.27 (m, 2H), 3.18 (s, 3H), 3.06 – 2.84 (m, 1.5H), 2.63 (d, *J* = 11.1 Hz, 1H), 2.53 – 2.40 (m, 3H), 2.39 – 2.22 (m, 3H), 2.15 – 1.88 (m, 6H), 1.84 – 1.40 (m, 3H), 1.37 – 1.25 (m, 1.5H), 0.86 (d, *J* = 12.7 Hz, 0.5H), 0.75 – 0.57 (m, 2H), 0.43 – 0.26 (m, 2H) (two rotamers); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 173.6, 168.9, 164.3, 155.4, 155.2, 129.4, 129.3, 127.7, 127.5, 127.2, 127.1, 121.3, 121.2, 111.2, 93.0, 92.9, 76.9, 76.8, 72.5, 72.4, 70.0, 69.9, 60.8, 58.6, 57.3, 57.3, 57.1, 56.4, 55.7, 45.9, 45.8, 41.8, 41.8, 41.1, 41.0, 40.5, 40.5, 37.8, 28.8, 28.3, 28.1, 27.6, 21.4, 10.3, 3.4, 3.3 (two rotamers); HRMS (ESI) calcd for $C_{29}H_{42}N_3O_5$ [*M*+H$^+$] 512.3119, found 512.3122.



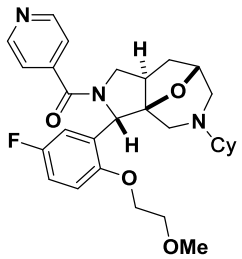
10g. Following **General procedure 13** using amine **S6** (26 mg, 0.073 mmol), benzo[*d*][1,3]dioxole-5-sulfonyl chloride (19 mg, 0.087 mmol) and DIPEA (12 µL, 0.087 mmol) gave after preparative HPLC the title compound as a white powder (25 mg, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 8.2, 1.6 Hz, 0.5H), 7.29 (dd, *J* = 7.6, 1.2 Hz, 0.5H), 7.24 – 7.15 (m, 1H), 7.00 (dd, *J* = 8.2, 1.4 Hz, 0.5H), 6.94 – 6.86 (m, 1H), 6.87 – 6.76 (m, 1.5H), 6.65 (d, *J* = 8.2 Hz, 0.5H), 6.54 (d, *J* = 8.0 Hz, 0.5H), 6.05 (d, *J* = 1.8 Hz, 1H), 5.97 (d, *J* = 2.7 Hz, 1H), 5.30 (s, 0.5H), 4.80 (s, 0.5H), 4.41 (d, *J* = 6.7 Hz, 0.5H), 4.32 (d, *J* = 6.4 Hz, 0.5H), 4.06 – 3.95 (m, 1H), 3.89 (d, *J* = 6.5 Hz, 1H), 3.58 (dd, *J* = 9.5, 7.5 Hz, 0.5H), 3.39 (dd, *J* = 9.3, 7.3 Hz, 0.5H), 3.33 – 3.16 (m, 5H), 2.96 – 2.85 (m, 1H), 2.54 – 2.08 (m, 5H), 2.05 – 1.92 (m, 1H), 1.90 – 1.79 (m, 1H), 1.72 – 1.60 (m, 2H), 1.39 – 1.14 (m, 1H), 0.64 (d, *J* = 8.0 Hz, 2H), 0.47 – 0.24 (m, 2H) (two rotamers); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.8, 155.8, 151.3, 150.5, 148.0, 147.4, 133.1, 133.1, 130.3, 129.9, 128.5, 127.6, 124.4, 123.7, 122.6, 120.7, 120.5, 111.7, 110.9, 108.6, 108.1, 107.8, 107.6, 102.2, 102.0, 93.4, 92.9, 77.1, 77.0, 72.8, 72.5, 70.7, 70.3, 70.3, 62.8, 58.8, 57.6, 57.4, 57.4, 57.2, 57.1, 57.0, 56.3, 45.9, 44.3, 38.0, 35.5, 10.5, 10.0, 3.6, 3.5, 3.3, 3.3 (two rotamers); HRMS (ESI) calcd for $C_{28}H_{35}N_2O_7S$ [*M*+H$^+$] 543.2160, found 543.2163.



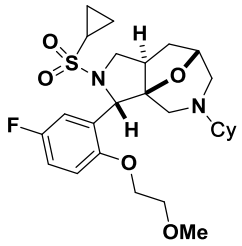
10h. Following **General procedure 14** using amine **S6** (20 mg, 0.056 mmol) and isocyanatocyclopentane (7.5 mg, 0.067 mmol), gave after preparative HPLC the title compound as a white powder (26 mg, >95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (t, *J* = 7.5 Hz, 1H), 7.10 (d, *J* = 7.3 Hz, 1H), 6.91 (t, *J* = 7.4 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 5.30 (s, 1H), 4.50 (d, *J* = 6.7 Hz, 1H), 4.14 (t, *J* = 10.2 Hz, 1H), 4.01 (d, *J* = 7.1 Hz, 1H), 3.93 (dd, *J* = 12.6, 6.1 Hz, 1H), 3.87 (d, *J* = 6.7 Hz, 2H), 3.37 – 3.26 (m, 3H), 3.20 (s, 3H), 2.98 – 2.88 (m, 1H), 2.55 (d, *J* = 10.6 Hz, 1H), 2.44 – 2.19 (m, 5H), 2.12 (d, *J* = 10.6 Hz, 1H), 2.03 (d, *J* = 10.7 Hz, 1H), 1.97 – 1.86 (m, 1H), 1.78 (td, *J* = 13.6, 6.8 Hz, 1H), 1.70 – 1.53 (m, 1H), 1.49 – 1.13 (m, 6H), 0.93 – 0.81 (m, 1H), 0.63 (d, *J* = 7.7 Hz, 2H), 0.36 (d, *J* = 4.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2, 155.9, 129.2, 127.9, 126.9, 121.4, 111.7, 93.4, 77.1, 72.8, 70.3, 59.8, 58.8, 57.6, 57.2, 57.0, 55.3, 52.0, 43.1, 37.0, 33.5, 33.5, 23.4, 23.2, 10.4, 3.5, 3.3; HRMS (ESI) calcd for $C_{27}H_{40}N_3O_4$ [*M*+H$^+$] 470.3014, found 470.3017.



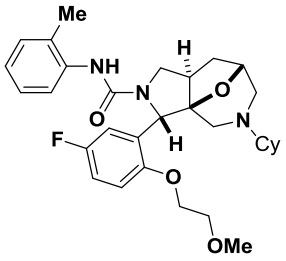
10i. Amine **S7** (23 mg, 0.057 mmol) was reductively alkylated following **General procedure 11** using 5-methylthiophene-2-carbaldehyde (11 µL, 0.085 mmol) and $NaBH(OAc)_3$ (18 mg, 0.085 mmol) to give the title compound as a colorless oil (11 mg, 38%) after preparative HPLC.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 9.8, 3.1 Hz, 1H), 6.94 – 6.87 (m, 1H), 6.88 – 6.82 (m, 1H), 6.61 (d, *J* = 3.2 Hz, 1H), 6.57 – 6.49 (m, 1H), 4.45 (d, *J* = 6.5 Hz, 1H), 4.14 (d, *J* = 5.1 Hz, 1H), 4.12 (d, *J* = 2.8 Hz, 2H), 3.84 – 3.70 (m, 3H), 3.46 (s, 3H), 3.41 (d, *J* = 13.9 Hz, 1H), 3.30 (t, *J* = 7.8 Hz, 1H), 2.75 – 2.66 (m, 1H), 2.54 – 2.48 (m, 1H), 2.44 (s, 3H), 2.36 (d, *J* = 11.0 Hz, 1H), 2.13 (dd, *J* = 10.3, 8.9 Hz, 2H), 2.10 – 2.01 (m, 2H), 1.97 – 1.89 (m, 1H), 1.70 – 1.62 (m, 3H), 1.57 – 1.49 (m, 2H), 1.17 – 0.95 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9 (d, J_{CF} = 238.1 Hz), 153.8, 140.6, 139.1, 129.9, 125.0, 124.4, 115.5 (d, J_{CF} = 24.5 Hz), 114.2 (d, J_{CF} = 23.5 Hz), 113.4 (d, J_{CF} = 8.0 Hz), 92.6, 78.3, 71.2, 69.0, 68.3, 59.5, 58.7, 54.8, 52.9, 52.5, 45.9, 33.0, 29.1, 28.5, 26.3, 25.5, 25.4, 15.5; HRMS (ESI) calcd for $C_{29}H_{40}FN_2O_3S$ [*M*+H$^+$] 515.2738, found 515.2739.



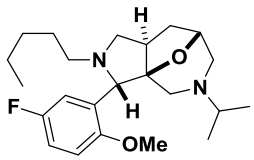
10j. Following **General procedure 12** using amine **S7** (33 mg, 0.082 mmol), iso nicotinic acid (15 mg, 0.12 mmol), TBTU (37 mg, 0.11 mmol) and DIPEA (21 µL, 0.12 mmol), gave after preparative HPLC the title compound as a white powder (28 mg, 66%)., ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.42 (dd, *J* = 4.6, 1.4 Hz, 2H), 7.39 (d, *J* = 3.2 Hz, 1H), 7.00 – 6.61 (m, 4H), 5.29 (s, 1H), 4.58 (d, *J* = 7.4 Hz, 1H), 4.40 – 4.28 (m, 1H), 4.28 – 4.06 (m, 1H), 3.94 – 3.83 (m, 1H), 3.80 – 3.63 (m, 1H), 3.60 – 3.38 (m, 2H), 3.34 (s, 2H), 3.17 – 2.81 (m, 1H), 2.81 – 2.62 (m, 1H), 2.59 – 2.49 (m, 1H), 2.48 – 2.36 (m, 1H), 2.26 – 2.14 (m, 1H), 2.14 – 1.98 (m, 1H), 1.95 – 1.47 (m, 5H), 1.32 – 0.96 (m, 6H) (two rotamers); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 167.2, 165.2, 157.6 (d, J_{CF} = 240.9 Hz), 152.4, 151.5, 150.2, 149.6, 144.5, 129.1, 121.4, 120.8, 115.9 (d, J_{CF} = 22.7 Hz), 113.9 (d, J_{CF} = 23.4 Hz), 112.9 (d, J_{CF} = 7.7 Hz), 92.7, 90.8, 75.9, 71.0, 70.8, 68.3, 63.9, 62.6, 59.3, 55.9, 52.4, 51.9, 42.0, 37.6, 28.8, 28.1, 27.6, 27.3, 25.9, 25.4, 25.4, 25.2 (two rotamers); HRMS (ESI) calcd for $C_{29}H_{37}FN_3O_4$ [*M*+H$^+$] 510.2763, found 510.2757.



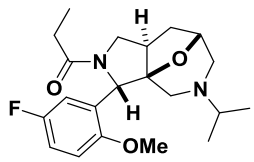
10k. Following **General procedure 13** using amine **S7** (31 mg, 0.077 mmol), cyclopropanesulfonyl chloride (9.4 µL, 0.92 mmol) and DIPEA (17 µL, 0.10 mmol) gave after preparative HPLC the title compound as a white powder (23 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (dd, *J* = 9.2, 3.0 Hz, 1H), 6.94 – 6.87 (m, 1H), 6.83 (dd, *J* = 9.0, 4.5 Hz, 1H), 5.48 (s, 1H), 4.54 (d, *J* = 6.8 Hz, 1H), 4.16 – 4.07 (m, 2H), 4.00 (t, *J* = 9.4 Hz, 1H), 3.83 – 3.67 (m, 2H), 3.44 (s, 3H), 3.31 (t, *J* = 9.1 Hz, 1H), 2.94 (q, *J* = 8.1 Hz, 1H), 2.57 (d, *J* = 10.9 Hz, 1H), 2.45 (d, *J* = 11.2 Hz, 2H), 2.41 – 2.31 (m, 1H), 2.27 (dd, *J* = 11.6, 8.3 Hz, 1H), 2.13 – 2.07 (m, 1H), 2.00 (d, *J* = 11.2 Hz, 1H), 1.86 (ddd, *J* = 11.6, 7.0, 1.7 Hz, 1H), 1.72 – 1.62 (m, 3H), 1.62 – 1.45 (m, 2H), 1.20 – 0.96 (m, 7H), 0.98 – 0.77 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 157.6 (d, J_{CF} = 239.4 Hz), 151.9, 130.3 (d, J_{CF} = 6.6 Hz), 115.1 (d, J_{CF} = 5.6 Hz), 114.9 (d, J_{CF} = 6.8 Hz), 113.8 (d, J_{CF} = 8.1 Hz), 92.9, 71.1, 69.0, 62.8, 59.4, 56.7, 52.4, 52.3, 44.3, 36.2, 29.2, 27.9, 26.8, 26.2, 25.5, 25.4, 4.9, 4.6; HRMS (ESI) calcd for $C_{26}H_{38}FN_2O_5S$ [*M*+H$^+$] 509.2480, found 509.2480.



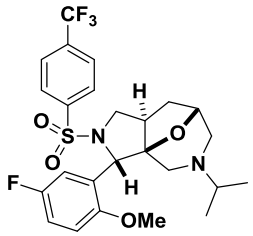
10l. Following **General procedure 14** using amine **S7** (30 mg, 0.074 mmol) and *o*-tolyl isocyanate (11 µL, 0.089 mmol), gave after preparative HPLC the title compound as a white powder (25 mg, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.0 Hz, 1H), 7.10 (t, *J* = 7.7 Hz, 1H), 7.02 – 6.86 (m, 5H), 5.89 (s, 1H), 5.49 (s, 1H), 4.56 (d, *J* = 6.5 Hz, 1H), 4.29 – 4.08 (m, 3H), 3.84 – 3.65 (m, 2H), 3.56 – 3.43 (m, 1H), 3.32 (s, 3H), 2.96 (m, *J* = 6.4 Hz, 1H), 2.60 – 2.39 (m, 4H), 2.32 – 2.19 (m, 1H), 2.08 (s, 1H), 2.03 – 1.90 (m, 2H), 1.75 – 1.62 (m, 6H), 1.55 (s, 2H), 1.20 – 0.97 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9 (d, J_{CF} = 240.8 Hz), 153.8, 152.5, 137.1, 130.1, 128.9 (d, J_{CF} = 8.0 Hz), 128.0, 126.67, 123.6, 122.5, 115.9 (d, J_{CF} = 23.2 Hz), 114.4 (d, J_{CF} = 23.4 Hz), 113.9 (d, J_{CF} = 7.6 Hz), 93.5, 71.1, 69.1, 62.6, 60.7, 59.3, 55.6, 52.6, 42.8, 36.9, 29.4, 28.1, 26.3, 25.6, 25.5, 16.9; HRMS (ESI) calcd for $C_{31}H_{41}FN_3O_4$ [*M*+H$^+$] 538.3076, found 538.3072.



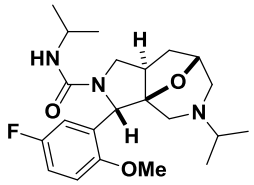
10m. Amine **S8** (25.6 mg, 0.080 mmol) was reductively alkylated following **General procedure 11** using pentanal (13 µL, 0.12 mmol) and $NaBH(OAc)_3$ (25 mg, 0.12 mmol) to give the title compound as a colorless oil (24 mg, 76%) after preparative HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 9.9, 3.2 Hz, 1H), 6.91 – 6.83 (m, 1H), 6.77 (dd, *J* = 8.9, 4.4 Hz, 1H), 4.48 (d, *J* = 6.6 Hz, 1H), 3.92 (s, 1H), 3.82 (s, 3H), 3.37 (t, *J* = 7.8 Hz, 1H), 2.73 – 2.64 (m, 1H), 2.45 – 2.30 (m, 4H), 2.22 – 2.10 (m, 1H), 2.04 (dd, *J* = 10.5, 8.6 Hz, 1H), 1.99 – 1.89 (m, 2H), 1.76 (d, *J* = 10.8 Hz, 1H), 1.73 – 1.65 (m, 1H), 1.45 – 1.36 (m, 2H), 1.29 – 1.15 (m, 4H), 0.89 – 0.74 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5 (d, J_{CF} = 237.0 Hz), 154.5, 130.3, 115.6 (d, J_{CF} = 24.4 Hz), 113.6 (d, J_{CF} = 23.2 Hz), 111.4 (d, J_{CF} = 8.1 Hz), 92.7, 78.5, 69.2, 58.9, 56.4, 54.7, 54.4, 53.9, 52.5, 46.2, 33.3, 29.6, 28.2, 22.7, 19.0, 18.3, 14.2; HRMS (ESI) calcd for $C_{23}H_{36}FN_2O_2$ [*M*+H$^+$] 391.2756, found 391.2752.



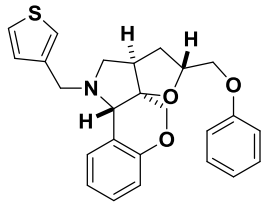
10n. Following **General procedure 12** using amine **S8** (30 mg, 0.093 mmol), propanoic acid (10 µL, 0.14 mmol), TBTU (42 mg, 0.13 mmol) and DIPEA (24 µL, 0.14 mmol), gave after preparative HPLC the title compound as a white powder (16 mg, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (td, *J* = 8.5, 2.9 Hz, 1H), 6.83 (dd, *J* = 9.0, 4.3 Hz, 1H), 6.77 – 6.52 (m, 1H), 5.67 (s, 0.5H), 5.45 (s, 0.5H), 4.52 (d, *J* = 6.5 Hz, 1H), 4.24 – 4.02 (m, 1H), 3.84 (s, 3H), 3.49 – 3.29 (m, 1H), 3.03 – 2.82 (m, 1H), 2.52 – 2.10 (m, 5H), 1.96 – 1.67 (m, 4H), 1.07 (t, *J* = 7.1 Hz, 1H), 0.93 (t, *J* = 7.4 Hz, 2H), 0.90 – 0.72 (m, 6H) (two rotamers); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.25, 172.01, 157.5 (d, J_{CF} = 240.9 Hz), 152.7, 129.6, 115.2 (d, J_{CF} = 22.4 Hz), 113.9 (d, J_{CF} = 25.6 Hz). 112.6, 111.7, 93.5, 61.3, 56.1, 55.7, 53.7, 52.2, 52.0, 42.0, 38.0, 29.8, 27.3, 19.1, 17.6, 9.1, 8.7 (two rotamers); HRMS (ESI) calcd for $C_{21}H_{30}FN_2O_3$ [*M*+H$^+$] 377.2235, found 377.2235.



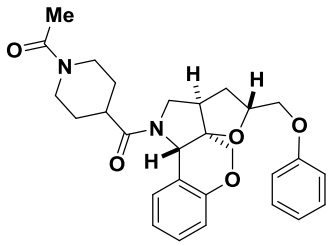
10o. Following **General procedure 13** using amine **S8** (25 mg, 0.078 mmol), 4-(trifluoromethyl)benzenesulfonyl chloride (23 mg, 0.94 mmol) and DIPEA (18 µL, 0.10 mmol) gave after preparative HPLC the title compound as a white powder (34 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.1 Hz, 2H), 7.54 (s, 1H), 7.03 – 6.86 (m, 2H), 5.32 (s, 1H), 4.25 (d, *J* = 6.3 Hz, 1H), 4.05 (t, *J* = 9.1 Hz, 1H), 3.86 (s, 3H), 3.48 – 3.27 (m, 1H), 2.95 (t, *J* = 8.9 Hz, 1H), 2.86 (dd, *J* = 15.8, 7.9 Hz, 1H), 2.46 – 2.36 (m, 1H), 2.31 – 2.27 (m, 1H), 2.18 – 2.07 (m, 1H), 1.83 (d, *J* = 11.1 Hz, 1H), 1.66 – 1.60 (m, 1H), 0.82 – 0.77 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3 (d, J_{CF} = 238.8 Hz), 152.7, 140.7, 129.0, 128.7, 127.5, 126.02 (d, J_{CF} = 3.5 Hz), 125.4, 115.1 (d, J_{CF} = 7.6 Hz), 114.9 (d, J_{CF} = 9.4 Hz), 111.9 (d, J_{CF} = 8.2 Hz). 92.9, 77.4, 63.2, 56.5, 56.3, 53.7, 52.3, 51.7, 44.3, 36.3, 32.0, 22.8, 19.1, 17.5, 14.3; MS (ESI) calcd for [*M*+H$^+$] 529,2, found 529,2.



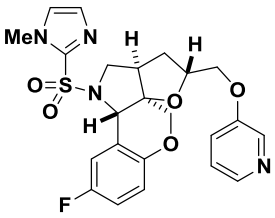
10p. Following **General procedure 14** using amine **S8** (59 mg, 0.18 mmol) and isopropyl isocyanate (22 μL, 0.22 mmol), gave after preparative HPLC the title compound as a white powder (57 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (td, *J* = 8.5, 3.0 Hz, 1H), 6.87 – 6.73 (m, 2H), 5.28 (s, 1H), 4.51 (d, *J* = 6.8 Hz, 1H), 4.05 (t, *J* = 9.9 Hz, 1H), 3.88 (d, *J* = 6.9 Hz, 1H), 3.83 (s, 3H), 3.82 – 3.71 (m, 2H), 3.27 (t, *J* = 9.0 Hz, 1H), 3.01 – 2.86 (m, 1H), 2.53 – 2.36 (m, 3H), 2.31 – 2.17 (m, 2H), 1.98 – 1.81 (m, 2H), 1.01 (d, *J* = 6.4 Hz, 3H), 0.89 – 0.78 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) 157.6 (d, J_{CF} = 239.8 Hz), 155.8, 152.8, 129.2, 115.2 (d, J_{CF} = 22.7 Hz), 114.3 (d, J_{CF} = 24.0 Hz), 111.9 (d, J_{CF} = 7.6 Hz), 93.0, 77.2, 60.2, 56.2, 55.1, 54.0, 52.4, 51.8, 43.3, 42.1, 37.0, 23.6, 23.3, 19.0, 17.5; HRMS (ESI) calcd for $C_{22}H_{33}FN_3O_3$ [*M*+H$^+$] 406.2501, found 406.2500.



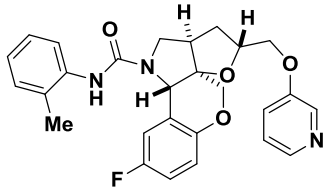
11a. Amine **S9** (21 mg, 0.065 mmol) was reductively alkylated following **General procedure 11** using thiophene-3-carbaldehyde (9 μL, 0.097 mmol) and $NaBH(OAc)_3$ (21 mg, 0.097 mmol) to give the title compound as a white solid (12 mg, 58%) after preparative HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.11 (m, 5H), 7.05 (s, 1H), 6.95 – 6.80 (m, 6H), 4.55 (dq, *J* = 9.6, 4.8 Hz, 1H), 4.10 (d, *J* = 11.1 Hz, 1H), 4.04 – 3.87 (m, 4H), 3.49 (s, 1H), 3.47 (d, *J* = 12.8 Hz, 1H), 3.03 (t, *J* = 8.7 Hz, 1H), 2.63 (dd, *J* = 14.5, 7.0 Hz, 1H), 2.19 (t, *J* = 8.3 Hz, 1H), 2.03 – 1.85 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 155.9, 139.4, 131.7, 129.6, 129.2, 128.4, 125.7, 122.7, 121.7, 121.1, 121.1, 117.7, 114.7, 90.0, 78.4, 71.2, 70.1, 65.8, 57.7, 51.5, 43.8, 33.9; HRMS (ESI) calcd for $C_{25}H_{26}NO_3S$ [*M*+H$^+$] 420.1628, found 420.1628.



11b. Following **General procedure 12** using amine **S9** (24 mg, 0.074 mmol), 1-acetylpiperidine-4-carboxylic acid (19 mg, 0.111 mmol), TBTU (33 mg, 0.104 mmol) and DIPEA (19 μL, 0.111 mmol), gave after preparative HPLC the title compound as a white solid (20 mg, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 17.8, 7.7 Hz, 0.5H), 7.26 – 7.19 (m, 2H), 7.16 (t, *J* = 7.7 Hz, 0.5H), 7.09 (t, *J* = 7.2 Hz, 0.5H), 6.99 (dd, *J* = 7.1, 2.9 Hz, 0.5H), 6.93 – 6.79 (m, 4H), 6.75 (d, *J* = 8.2 Hz, 0.5H), 5.65 (d, *J* = 6.9 Hz, 0.5H), 5.05 (s, 0.5H), 4.71 – 4.32 (m, 2H), 4.12 – 3.74 (m, 5.5H), 3.65 (t, *J* = 10.2 Hz, 0.5H), 3.42 (dd, *J* = 11.2, 4.5 Hz, 0.5H), 3.24 – 2.96 (m, 2H), 2.96 – 2.77 (m, 1.5H), 2.69 – 2.44 (m, 1.5H), 2.32 – 1.51 (m, 8.5H) (two rotamers). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 173.4, 173.0, 169.1, 169.1, 169.0, 158.6, 154.1, 154.1, 153.9, 130.4, 130.2, 129.9, 129.9, 129.6, 129.2, 129.1, 127.7, 127.7, 123.7, 123.5, 122.4, 122.3, 122.0, 121.9, 121.3, 120.3, 120.2, 117.4, 117.4, 116.6, 116.6, 114.7, 114.6, 87.7, 87.6, 87.5, 87.4, 79.2, 79.1, 78.6, 78.5, 69.6, 69.5, 69.4, 69.2, 67.6, 67.5, 67.1, 62.4, 62.3, 60.5, 51.5, 49.4, 49.3, 46.2, 45.9, 45.8, 45.7, 43.5, 42.0, 41.4, 41.1, 41.0, 40.9, 40.2, 40.1, 40.1, 40.1, 34.7, 34.6, 34.5, 34.4, 29.4, 28.8, 28.7, 28.5, 28.1, 28.0, 27.8, 27.7, 21.5 (rotamers); HRMS (ESI) calcd for $C_{28}H_{33}N_2O_5$ [*M*+H$^+$] 477.2384, found 477.2383.

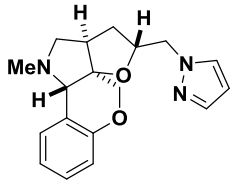


11c. Following **General procedure 13** using **S10** (14 mg, 0.041 mmol), 1-methyl-1*H*-imidazole-2-sulfonyl chloride (9 mg, 0.049 mmol) and DIPEA (9 μL, 0.053 mmol), gave after preparative HPLC the title compound as a white solid (9 mg, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 2.7 Hz, 1H), 8.25 (dd, *J* = 4.6, 1.1 Hz, 1H), 7.49 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.25 – 7.22 (m, 1H), 7.18 (ddd, *J* = 8.5, 2.9, 1.4 Hz, 1H), 7.10 (d, *J* = 0.9 Hz, 1H), 7.02 (d, *J* = 0.7 Hz, 1H), 6.95 – 6.86 (m, 1H), 6.77 (dd, *J* = 9.0, 4.7 Hz, 1H), 5.02 (s, 1H), 4.03 (s, 3H), 4.01 – 3.94 (m, 2H), 3.94 – 3.88 (m, 1H), 3.88 – 3.76 (m, 4H), 3.10 (dd, *J* = 15.5, 6.6 Hz, 1H), 2.19 (ddd, *J* = 13.0, 9.9, 6.6 Hz, 1H), 2.03 (dd, *J* = 13.1, 6.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8 (d, J_{CF} = 240.7 Hz), 154.8, 149.7, 142.5, 142.1, 137.6, 128.9, 125.6, 124.0, 122.8 (d, J_{CF} = 7.4 Hz), 121.5, 117.9 (d, J_{CF} = 8.1 Hz), 116.9 (d, J_{CF} = 23.6 Hz), 116.5 (d, J_{CF} = 24.1 Hz), 88.2, 77.8, 69.4, 67.0, 63.9, 52.8, 43.3, 35.8, 32.1; HRMS (ESI) calcd for $C_{23}H_{24}FN_4O_5S$ [*M*+H$^+$] 487.1446, found 487.1444.

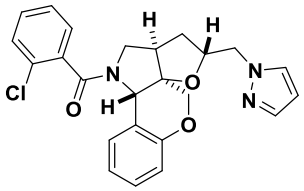


11d. Following **General procedure 14** using amine **S10** (15 mg, 0.044 mmol) and o-tolyl isocyanate (6.5 μL, 0.053 mmol) after preparative HPLC the title compound as white powder (14 mg, 68%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.28 – 8.20 (m, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.49 (dd, *J* = 9.3, 2.9 Hz, 1H), 7.28 – 7.14 (m, 4H), 7.04 (td, *J* = 7.5, 1.0 Hz, 1H), 6.91 – 6.84 (m, 1H), 6.79 (dd, *J* = 9.0, 4.7 Hz, 1H), 6.11 (s, 1H), 5.53 (s, 1H), 4.68 (td, *J* = 9.8, 4.0 Hz, 1H), 4.18 (dd, *J* = 10.2, 3.4 Hz, 1H), 4.07 – 4.00 (m, 2H), 3.95 (d, *J* = 11.4 Hz, 1H), 3.71 (t, *J* = 9.6 Hz, 1H), 3.49 (dd, *J* = 9.9, 5.4 Hz, 1H), 3.23 (dt, *J* = 9.3, 6.0 Hz, 1H), 2.33 (ddd, *J* = 13.0, 10.5, 6.8 Hz, 1H), 2.26 (s, 3H), 2.14 (dd, *J* = 13.1, 5.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0 (d, J_{CF} = 240.1 Hz), 155.0, 154.8, 149.9 (d, J_{CF} = 2.0 Hz), 142.7, 137.9, 136.7, 130.6, 128.7, 127.0, 125.4 (d, J_{CF} = 7.5 Hz), 124.5, 124.1, 122.9, 121.6, 117.8 (d, J_{CF} = 8.1 Hz), 116.4 (d, J_{CF} = 3.9 Hz),

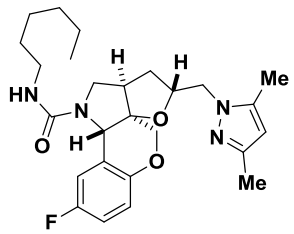
116.2 (d, J_{CF} = 3.7 Hz), 87.9, 78.1, 69.7, 67.6, 61.3, 50.9, 43.5, 33.5, 18.0; HRMS (ESI) calcd for $C_{27}H_{27}FN_3O_4$ [*M*+H$^+$] 476.1980, found 476.1975.



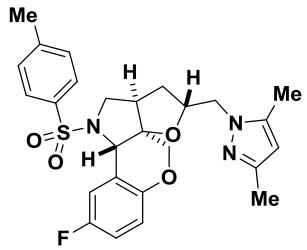
11e. Following **General procedure 11** using **S11** (32.5 mg, 0.109 mmol), 37% formalin in H_2O (12 µL, 0.164 mmol) and $NaBH(OAc)_3$ (27 mg, 0.164 mmol) gave after preparative HPLC the title compound as a white solid (22 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 1.6 Hz, 1H), 7.47 (d, *J* = 2.3 Hz, 1H), 7.24 – 7.15 (m, 2H), 7.00 – 6.92 (m, 2H), 6.23 (t, *J* = 2.1 Hz, 1H), 4.50 (td, *J* = 9.8, 4.7 Hz, 1H), 4.33 (t, *J* = 4.1 Hz, 2H), 3.93 (d, *J* = 11.3 Hz, 1H), 3.82 (dd, *J* = 11.3, 0.4 Hz, 1H), 3.33 – 3.16 (m, 1H), 2.98 (s, 1H), 2.55 (q, *J* = 8.4 Hz, 1H), 2.36 (s, 3H), 2.21 (t, *J* = 9.2 Hz, 1H), 1.81 (dd, *J* = 12.9, 5.4 Hz, 1H), 1.69 (ddd, *J* = 13.0, 10.2, 8.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5, 139.3, 131.2, 130.6, 129.1, 122.2, 121.2, 117.7, 105.8, 90.2, 77.9, 71.5, 67.2, 61.2, 54.8, 44.1, 39.9, 32.9; HRMS (ESI) calcd for $C_{18}H_{22}N_3O_2$ [*M*+H$^+$] 312.1707, found 312.1707.



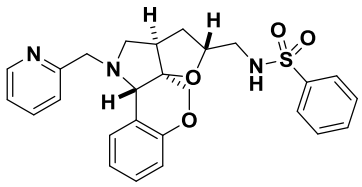
11f. Following **General procedure 12** using **S11** (28 mg, 0.094 mmol), 2-chlorobenzoic acid (22 mg, 0.141 mmol), TBTU (42 mg, 0.132 mmol) and DIPEA (25 µL, 0.141 mmol), gave after preparative HPLC the title compound as a white solid (29 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.7 Hz, 1H), 7.51 (d, *J* = 1.7 Hz, 1H), 7.47 (d, *J* = 2.2 Hz, 1H), 7.41 – 7.27 (m, 3H), 7.22 – 7.14 (m, 1H), 6.98 (t, *J* = 7.2 Hz, 1H), 6.81 (dd, *J* = 8.2, 0.8 Hz, 1H), 6.28 (t, *J* = 2.1 Hz, 1H), 5.83 (s, 1H), 4.82 – 4.52 (m, 1H), 4.40 (dd, *J* = 14.5, 3.9 Hz, 1H), 4.27 (dd, *J* = 14.5, 4.0 Hz, 1H), 3.90 (dd, *J* = 11.3, 6.3 Hz, 1H), 3.63 – 3.42 (m, 2H), 3.05 – 2.82 (m, 2H), 2.06 – 1.76 (m, 3H) (major rotamer); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 153.9, 139.4, 136.4, 130.9, 130.6, 130.5, 130.5, 129.9, 129.7, 129.3, 127.3, 122.3, 116.5, 105.8, 87.9, 78.8, 67.3, 60.4, 54.4, 52.2, 43.1, 34.7 (major rotamer); HRMS (ESI) calcd for $C_{24}H_{22}ClN_3O_3$ [*M*+H$^+$] 436.1423, found 436.1421.



11g. Following **General procedure 14** using **S12** (27 mg, 0.079 mmol) and hexyl isocyanate (14 µL, 0.094 mmol) after preparative HPLC the title compound as a white solid (22 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 9.4, 3.0 Hz, 1H), 6.87 – 6.75 (m, 1H), 6.68 (dd, *J* = 9.0, 4.7 Hz, 1H), 5.79 (s, 1H), 5.35 (s, 1H), 4.50 (td, *J* = 9.2, 4.1 Hz, 1H), 4.28 – 4.21 (m, 1H), 4.19 (d, *J* = 4.0 Hz, 1H), 4.03 (dd, *J* = 14.8, 3.9 Hz, 1H), 3.73 (d, *J* = 11.3 Hz, 1H), 3.46 (t, *J* = 9.6 Hz, 1H), 3.32 (d, *J* = 11.3 Hz, 2H), 3.31 – 3.21 (m, 2H), 3.17 (dd, *J* = 9.7, 5.6 Hz, 1H), 2.98 (dt, *J* = 9.6, 6.0 Hz, 1H), 2.27 – 2.17 (m, 1H), 2.21 (s, 3H), 2.21 (s, 3H), 1.99 (dd, *J* = 13.3, 5.3 Hz, 1H), 1.58 – 1.44 (m, 2H), 1.38 – 1.23 (m, 6H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9 (d, J_{CF} = 239.7 Hz), 157.3, 149.6 (d, J_{CF} = 1.9 Hz), 147.7, 140.7, 125.9 (d, J_{CF} = 7.5 Hz), 117.5 (d, J_{CF} = 8.1 Hz), 116.4 (d, J_{CF} = 23.9 Hz), 115.9 (d, J_{CF} = 23.8 Hz), 105.4, 87.5, 78.9, 67.1, 60.9, 51.2, 50.4, 43.1, 41.1, 34.1, 31.7, 30.4, 26.7, 22.7, 14.1, 13.6, 11.5; HRMS (ESI) calcd for $C_{26}H_{36}FN_4O_3$ [*M*+H$^+$] 471.2766, found 471.2763.

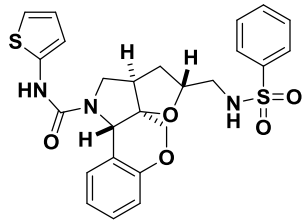


11h. Following **General procedure 13** using **S12** (21.5 mg, 0.063 mmol), *p*-toluenesulfonyl chloride (14 mg, 0.075 mmol) and DIPEA (14 µL, 0.081 mmol), gave after preparative HPLC the title compound as a white solid (22 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.80 (d, *J* = 8.3 Hz, 2H), 7.55 (dd, *J* = 9.3, 2.9 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 6.93 – 6.79 (m, 1H), 6.69 (dd, *J* = 9.0, 4.7 Hz, 1H), 5.80 (s, 1H), 5.11 (s, 1H), 3.86 (qd, *J* = 15.0, 3.7 Hz, 2H), 3.65 (d, *J* = 11.4 Hz, 1H), 3.58 (dd, *J* = 11.3, 9.7 Hz, 1H), 3.27 – 3.18 (m, 1H), 3.15 (d, *J* = 11.4 Hz, 1H), 3.01 (dd, *J* = 11.4, 6.3 Hz, 1H), 2.94 – 2.84 (m, 1H), 2.44 (s, 3H), 2.21 (s, 3H), 2.14 (s, 3H), 2.06 – 1.92 (m, 1H), 1.79 (dd, *J* = 13.4, 5.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 158.0 (d, J_{CF} = 240.2 Hz), 149.6 (d, J_{CF} = 2.0 Hz), 147.6, 143.9, 140.9, 135.6, 129.5, 128.3, 123.9 (d, J_{CF} = 7.5 Hz), 117.7 (d, J_{CF} = 8.1 Hz), 116.9 (d, J_{CF} = 24.1 Hz), 116.6 (d, J_{CF} = 23.8 Hz), 105.6, 88.2, 78.1, 66.7, 64.2, 52.1, 50.6, 43.1, 32.9, 21.7, 13.1, 11.4; HRMS (ESI) calcd for $C_{26}H_{29}FN_3O_4S$ [*M*+H$^+$] 498.1858, found 498.1856.

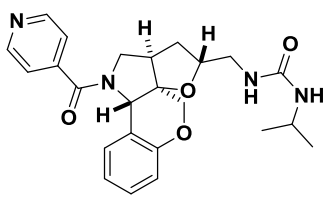


11i. Following **General procedure 11** using **S13** (18.5 mg, 0.040 mmol), picolinaldehyde (6.8 µL, 0.072 mmol) and $NaBH(OAc)_3$ (15 mg, 0.072 mmol) gave after preparative HPLC the title compound as a white solid (11 mg, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 – 8.46 (m, 1H), 7.86 – 7.75 (m, 2H), 7.61 – 7.53 (m, 2H), 7.52 – 7.45 (m, 2H), 7.26 – 7.17 (m, 3H), 7.15 – 7.08 (m, 1H), 6.98 – 6.86 (m, 2H), 4.93 (t, *J* = 6.3 Hz, 1H), 4.35 – 4.22 (m, 2H), 4.14 (d, *J* = 11.3 Hz, 1H), 3.94 (dd, *J* = 11.3, 0.8 Hz, 1H), 3.59 (d, *J* = 13.6 Hz, 1H), 3.29 (s, 1H), 3.20 (ddd, *J* = 13.0, 6.0,

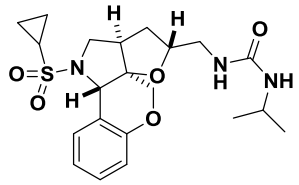
3.3 Hz, 1H), 3.19 – 3.02 (m, 1H), 3.04 – 2.89 (m, 1H), 2.48 (q, *J* = 8.2 Hz, 1H), 2.18 (dd, *J* = 9.4, 8.2 Hz, 1H), 1.90 (dt, *J* = 12.9, 9.8 Hz, 1H), 1.69 (ddd, *J* = 12.9, 5.4, 1.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 155.2, 148.9, 140.0, 136.7, 132.8, 132.2, 129.3, 129.3, 127.1, 123.1, 122.2, 121.0, 120.5, 117.5, 88.4, 77.7, 70.6, 64.3, 58.3, 58.2, 45.8, 43.5, 33.4; HRMS (ESI) calcd for $C_{26}H_{28}N_3O_4S$ [*M*+H$^+$] 478.1795, found 478.1792.



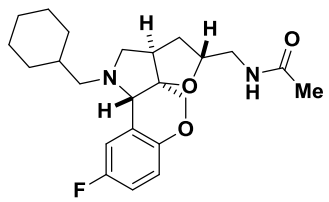
11j. Following **General procedure 14** using **S13** (19.5 mg, 0.050 mmol) and 2-isocyanatothiophene (7.6 mg, 0.061 mmol) after preparative HPLC the title compound as an off-white solid (13 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.57 – 7.49 (m, 3H), 7.21 (s, 1H), 7.19 – 7.12 (m, 1H), 6.95 – 6.87 (m, 1H), 6.82 – 6.76 (m, 3H), 6.58 (dd, *J* = 3.6, 1.4 Hz, 1H), 5.46 (s, 1H), 5.25 (t, *J* = 5.8 Hz, 1H), 4.40 – 4.15 (m, 1H), 3.80 (d, *J* = 1.8 Hz, 2H), 3.56 (t, *J* = 9.9 Hz, 1H), 3.43 (dd, *J* = 10.3, 4.8 Hz, 1H), 3.22 (ddd, *J* = 13.1, 7.4, 3.2 Hz, 1H), 3.11 – 3.03 (m, 1H), 2.96 – 2.83 (m, 1H), 2.05 – 1.86 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7, 153.5, 141.0, 140.0, 133.0, 130.2, 129.4, 129.4, 127.1, 124.2, 123.2, 122.4, 117.4, 116.8, 111.0, 87.8, 78.5, 67.3, 61.4, 50.5, 47.0, 43.4, 34.7; HRMS (ESI) calcd for $C_{25}H_{26}N_3O_5S_2$ [*M*+H$^+$] 512.1309, found 512.1306.



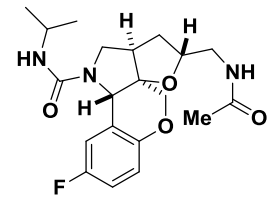
11k. Following **General procedure 12** using **S14** (17 mg, 0.051 mmol), isonicotinic acid (9.5 mg, 0.077 mmol), TBTU (23 mg, 0.072 mmol) and DIPEA (13 µL, 0.077 mmol), gave after preparative HPLC the title compound as a white solid (14 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 4.5 Hz, 2H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 4.5 Hz, 2H), 7.15 (t, *J* = 7.5 Hz, 1H), 6.93 (t, *J* = 7.4 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 5.81 (s, 1H), 5.01 – 4.07 (m, 3H), 3.99 – 3.72 (m, 3H), 3.68 – 3.56 (m, 1H), 3.50 (d, *J* = 13.8 Hz, 1H), 3.34 – 2.81 (m, 3H), 2.04 – 1.68 (m, 3H), 1.10 – 1.04 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 157.7, 154.2, 150.4, 143.5, 129.7, 129.5, 122.6, 122.2, 121.1, 116.9, 87.4, 80.2, 67.8, 60.8, 54.0, 44.0, 43.9, 42.3, 35.0, 23.5; HRMS (ESI) calcd for $C_{24}H_{29}N_4O_4$ [*M*+H$^+$] 437.2184, found 437.2183.



11l. Following **General procedure 13** using **S14** (18 mg, 0.054 mmol), cyclopropanesulfonyl chloride (9 mg, 0.065 mmol) and DIPEA (12 µL, 0.071 mmol), gave after preparative HPLC the title compound as a white solid (9 mg, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.5 Hz, 1H), 7.23 – 7.14 (m, 1H), 6.99 (td, *J* = 7.8, 1.2 Hz, 1H), 6.82 (dd, *J* = 8.2, 1.0 Hz, 1H), 5.15 (s, 1H), 4.74 (s, 1H), 4.62 – 4.45 (m, 1H), 3.92 (s, 2H), 3.84 (dt, *J* = 12.9, 6.4 Hz, 1H), 3.59 – 3.49 (m, 2H), 3.39 (dd, *J* = 11.3, 5.1 Hz, 1H) 3.15 – 3.01 (m, 2H), 2.44 (tt, *J* = 8.0, 4.9 Hz, 1H), 2.10 – 1.94 (m, 3H), 1.34 – 1.25 (m, 1H), 1.21 – 1.15 (m, 1H), 1.14 (d, *J* = 3.3 Hz, 3H), 1.13 (d, *J* = 3.3 Hz, 3H), 1.10 – 1.02 (m, 1H), 1.01 – 0.90 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 154.0, 130.7, 129.5, 122.6, 122.3, 116.8, 88.6, 80.0, 67.8, 64.1, 52.5, 44.9, 44.3, 42.5, 34.4, 29.5, 23.6, 23.6, 5.9, 5.2; HRMS (ESI) calcd for $C_{21}H_{30}N_3O_5S$ [*M*+H$^+$] 436.1901, found 436.1899.



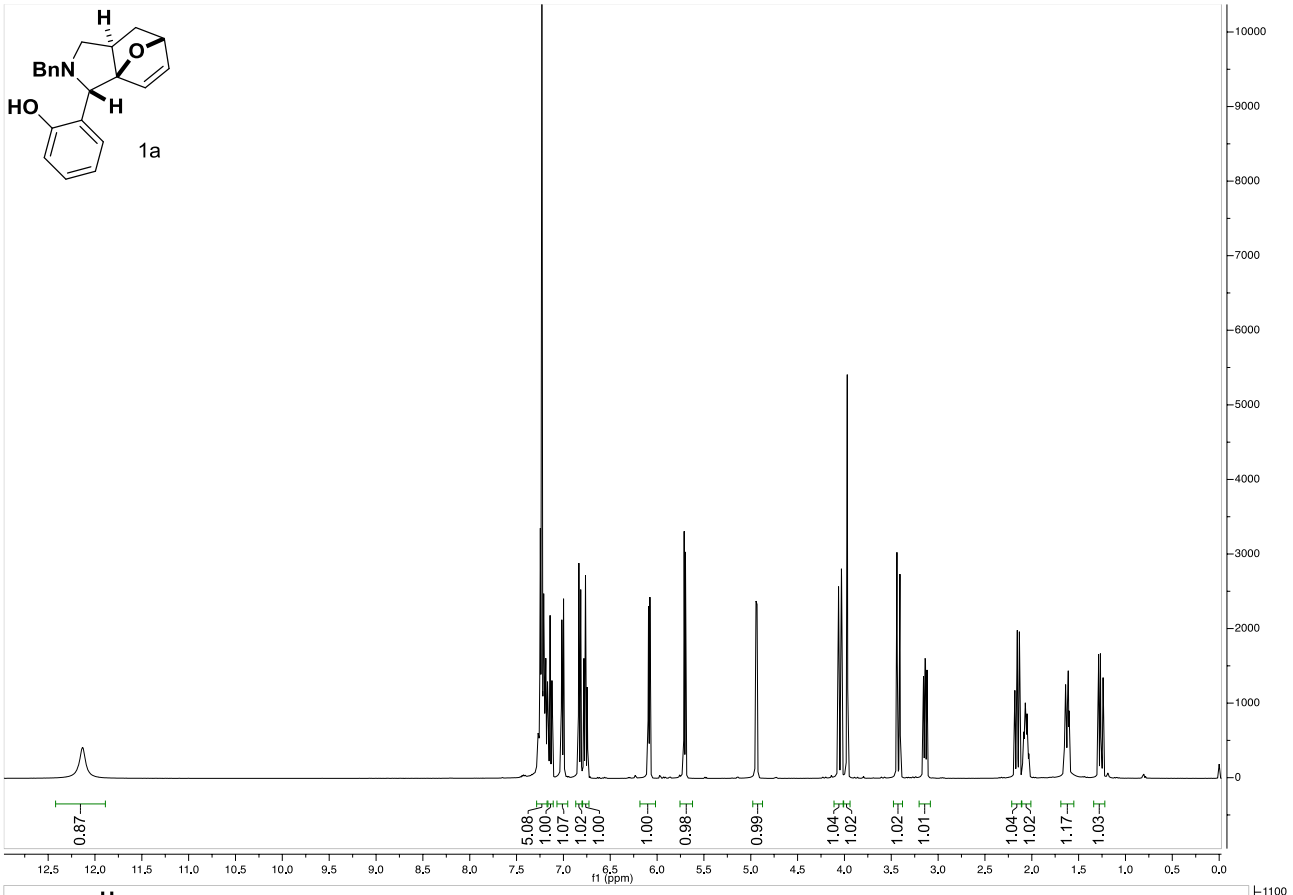
11m. Following **General procedure 11** using **S15** (25 mg, 0.082 mmol), cyclohexanecarbaldehyde (15 µL, 0.122 mmol) and $NaBH(OAc)_3$ (26 mg, 0.122 mmol) gave after preparative HPLC the title compound as a white solid (22 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 – 6.83 (m, 3H), 5.98 (t, *J* = 5.4 Hz, 1H), 4.30 – 4.18 (m, 1H), 4.04 (d, *J* = 11.3 Hz, 1H), 3.91 (dd, *J* = 11.2, 0.7 Hz, 1H), 3.63 (ddd, *J* = 14.1, 6.6, 3.0 Hz, 1H), 3.31 (t, *J* = 8.8 Hz, 1H), 3.16 (ddd, *J* = 11.4, 5.6, 3.9 Hz, 1H), 3.12 (s, 1H), 2.60 (dd, *J* = 11.2, 10.1 Hz, 1H), 2.49 (td, *J* = 9.6, 1.5 Hz, 1H), 2.14 (dd, *J* = 11.5, 4.5 Hz, 1H), 2.14 – 2.04 (m, 1H), 1.95 (s, 3H), 1.84 – 1.53 (m, 7H), 1.48 – 1.32 (m, 1H), 1.26 – 1.04 (m, 3H), 0.94 – 0.81 (m, 1H), 0.70 – 0.52 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 156.8 (d, J_{CF} = 238.9 Hz), 151.3 (d, J_{CF} = 1.9 Hz), 122.3 (d, J_{CF} = 6.9 Hz), 118.3 (d, J_{CF} = 8.1 Hz), 117.9 (d, J_{CF} = 22.8 Hz), 115.9 (d, J_{CF} = 23.2 Hz), 88.2, 78.5, 71.1, 65.3, 59.3, 58.0, 43.4, 42.7, 36.2, 34.0, 32.2, 31.4, 26.8, 26.3, 26.0, 23.3; HRMS (ESI) calcd for $C_{23}H_{32}FN_2O_3$ [*M*+H$^+$] 403.2392, found 403.2393.



11n. Following **General procedure 14** using **S15** (29 mg, 0.095 mmol) and 2-isocyanatopropane (11 µL, 0.114 mmol) after preparative HPLC the title compound as a white solid (21 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 9.4, 2.9 Hz, 1H), 6.88 – 6.79 (m, 1H), 6.73 (dd, *J* = 9.0, 4.7 Hz, 1H), 6.05 (s, 1H), 5.42 (s, 1H), 4.34 – 4.18 (m, 1H), 4.08 – 3.97 (m, 2H), 3.90 (d, *J* = 11.2 Hz, 1H), 3.82 (d, *J* = 11.2 Hz, 1H), 3.68 (ddd, *J* = 14.0, 7.1, 2.9 Hz, 1H), 3.45 (t, *J* = 9.6 Hz, 1H), 3.15 (dd, *J* = 9.8, 5.1 Hz, 1H), 3.10 – 2.98 (m, 2H), 2.02 (s, 3H), 1.98 (dd, *J* = 13.1, 5.1 Hz, 1H), 1.85 (ddd, *J* = 13.1, 10.8, 6.6 Hz, 1H), 1.19 (d, *J* = 3.2 Hz, 3H), 1.18 (d, *J* = 3.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 157.9 (d, J_{CF} = 239.8 Hz), 156.6, 149.7 (d,

J_{CF} = 2.0 Hz), 125.8 (d, J_{CF} = 7.5 Hz), 117.6 (d, J_{CF} = 8.2 Hz), 116.3 (d, J_{CF} = 23.9 Hz), 116.0 (d, J_{CF} = 23.8 Hz), 87.3, 78.9, 67.9, 60.9, 50.5, 43.7, 43.6, 42.9, 35.0, 23.6, 23.4; HRMS (ESI) calcd for $C_{20}H_{27}FN_3O_4$ [M+H^+] 392.1980, found 392.1983.

^{1}H and ^{13}C NMR Spectra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BnN
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HO
H
1a
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1.07
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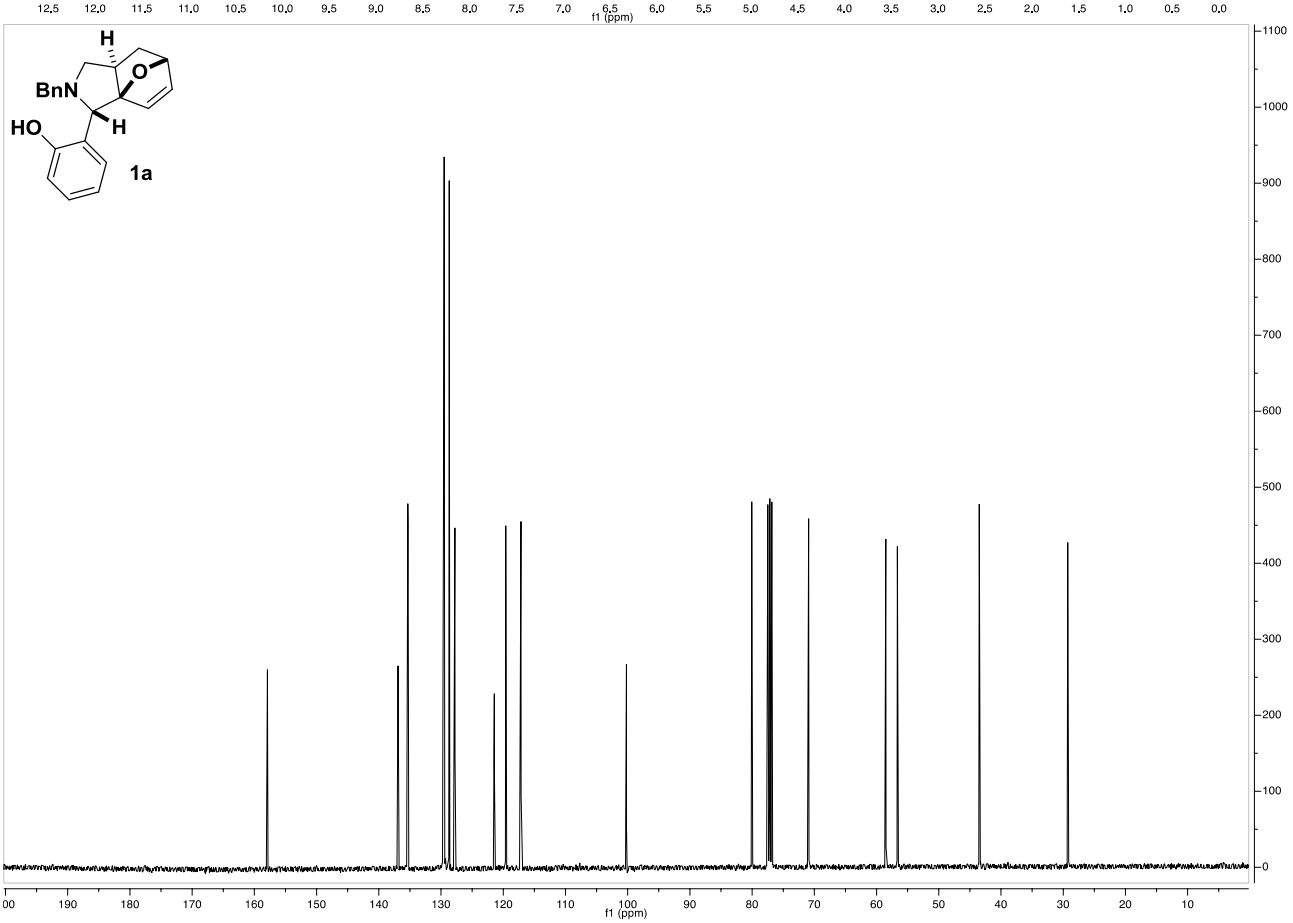
0.99
1.04
1.02
1.02
1.01
1.04
1.02
1.17
1.03
f1 (ppm)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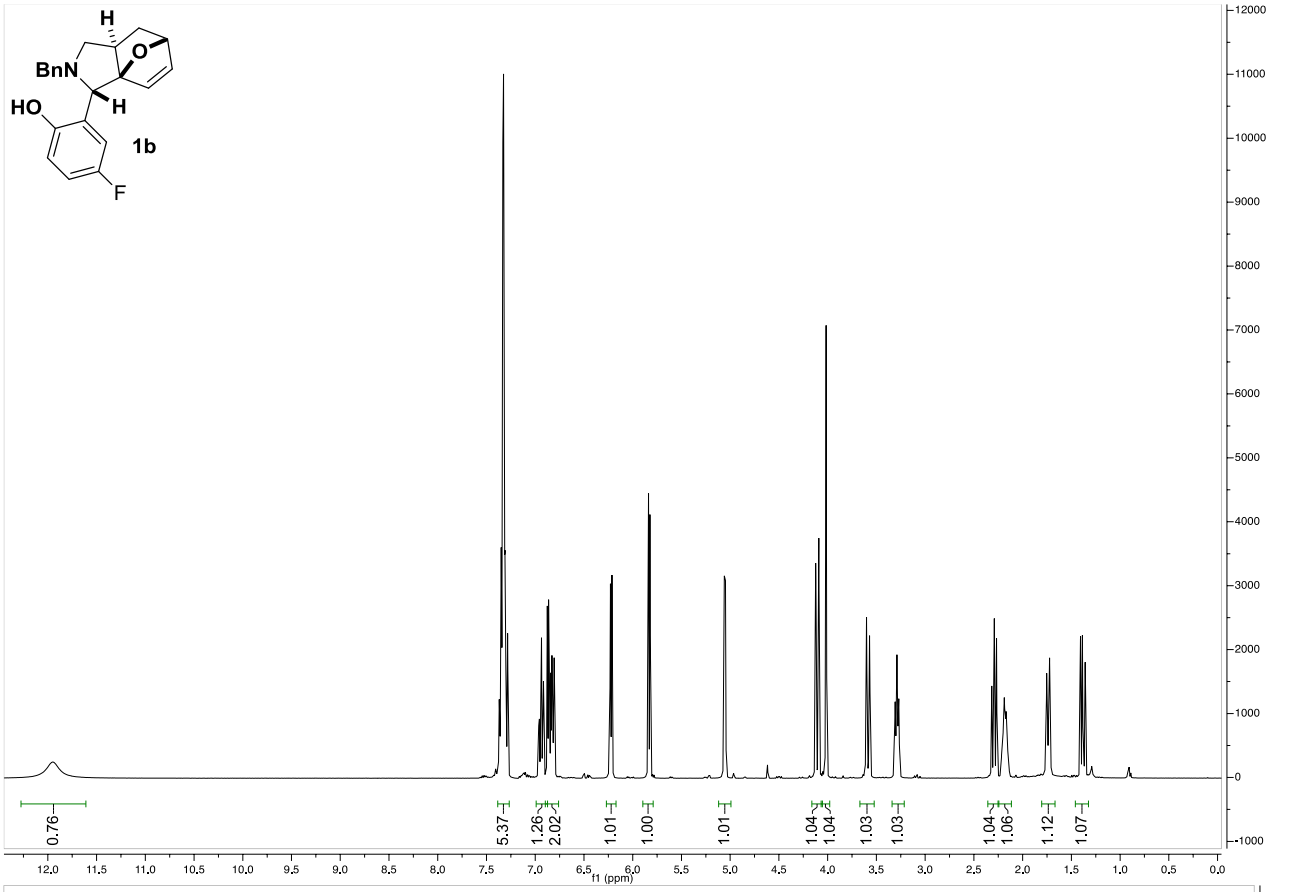
1a
f1 (ppm)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1.06
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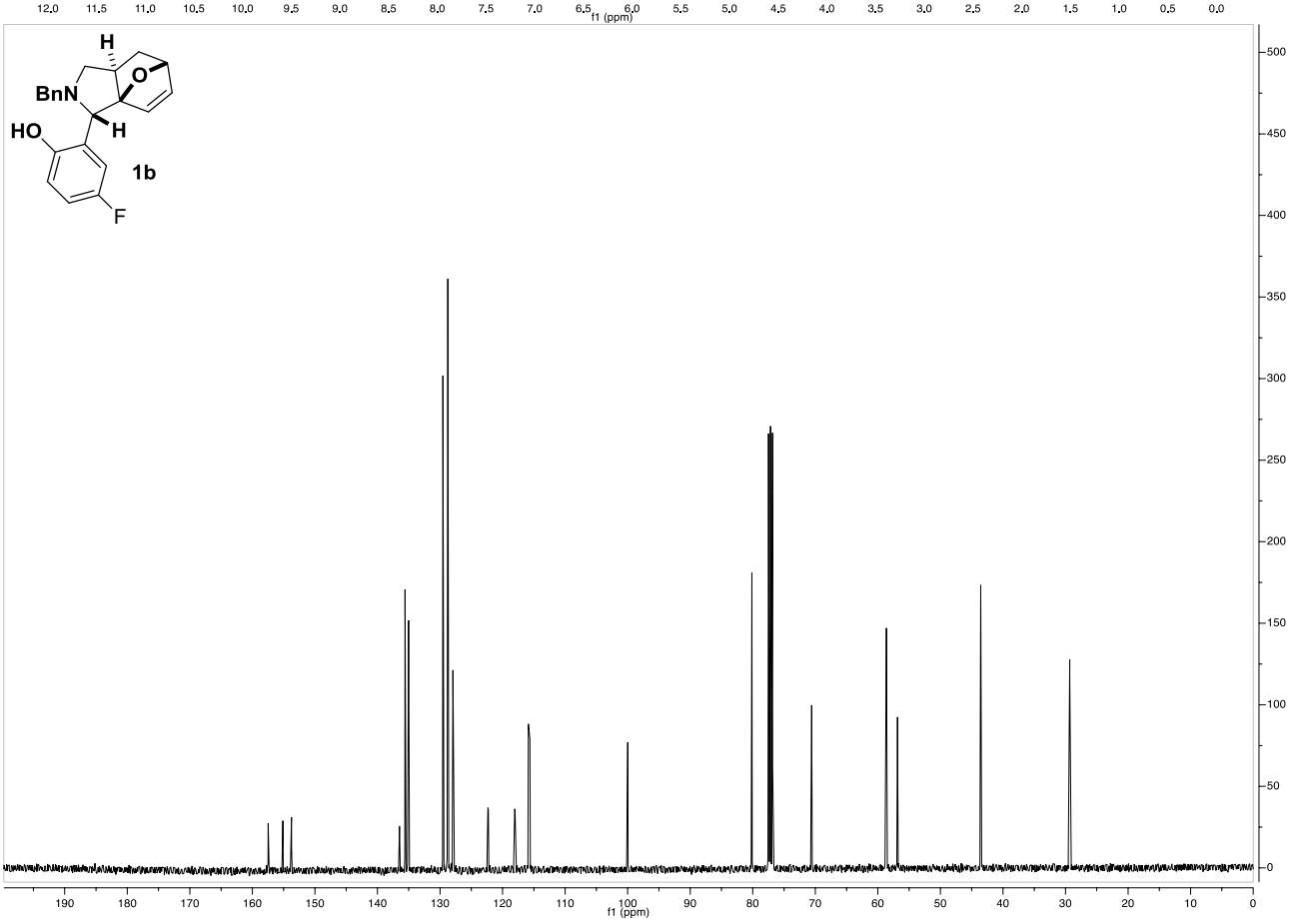
f1 (ppm)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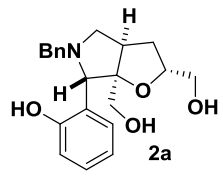
f1 (ppm)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O
OH
HO
OH

2a

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1.00
1.01
1.04
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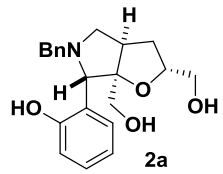
1.37
2.13
1.02
f1 (ppm)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H
O
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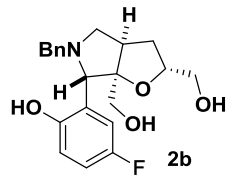
HO
OH

2a

f1 (ppm)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O
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HO
OH
F

2b

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1.00
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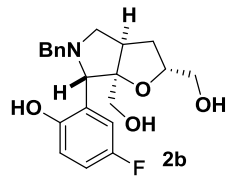
0.97
f1 (ppm)


H
BnN
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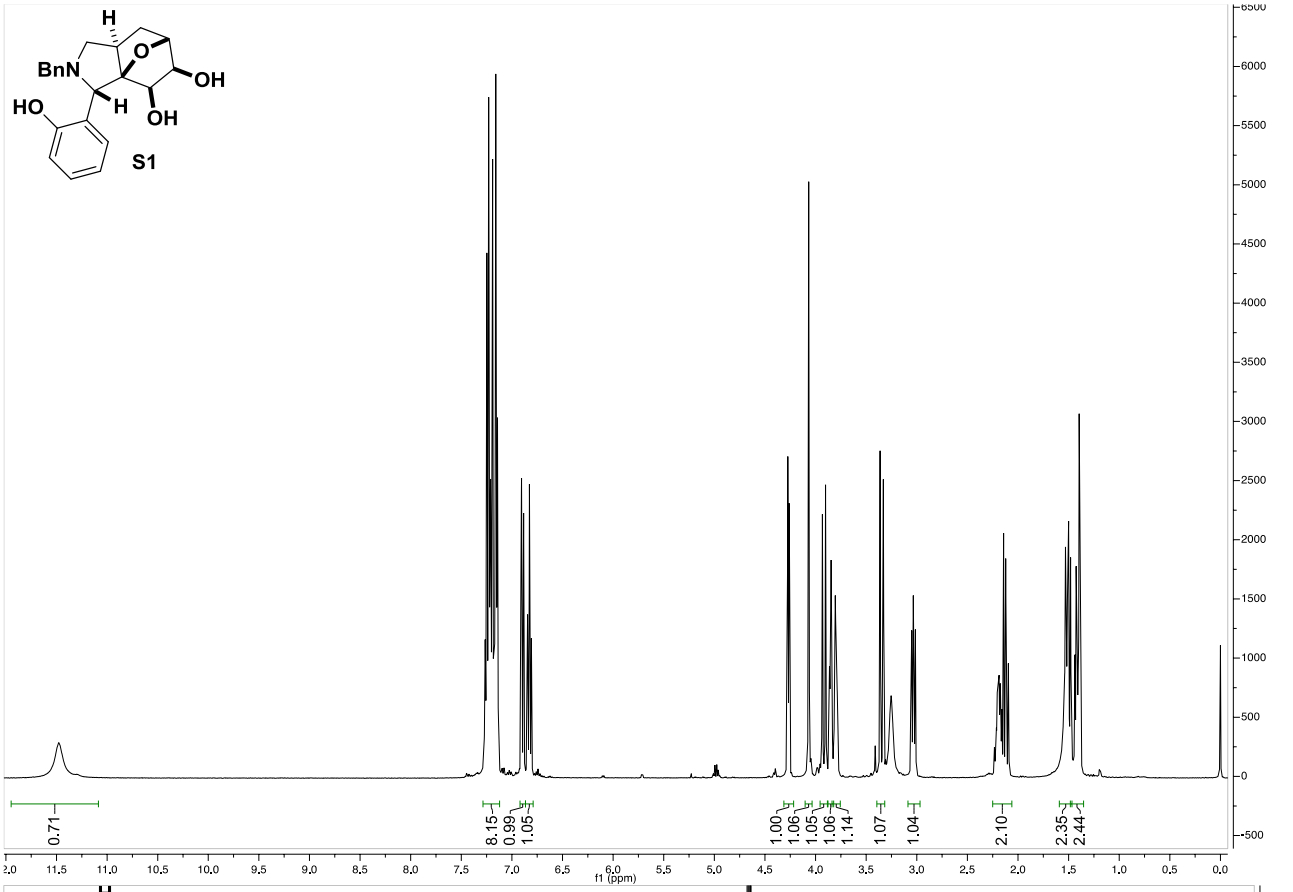
O
OH
HO
OH
F

2b

f1 (ppm)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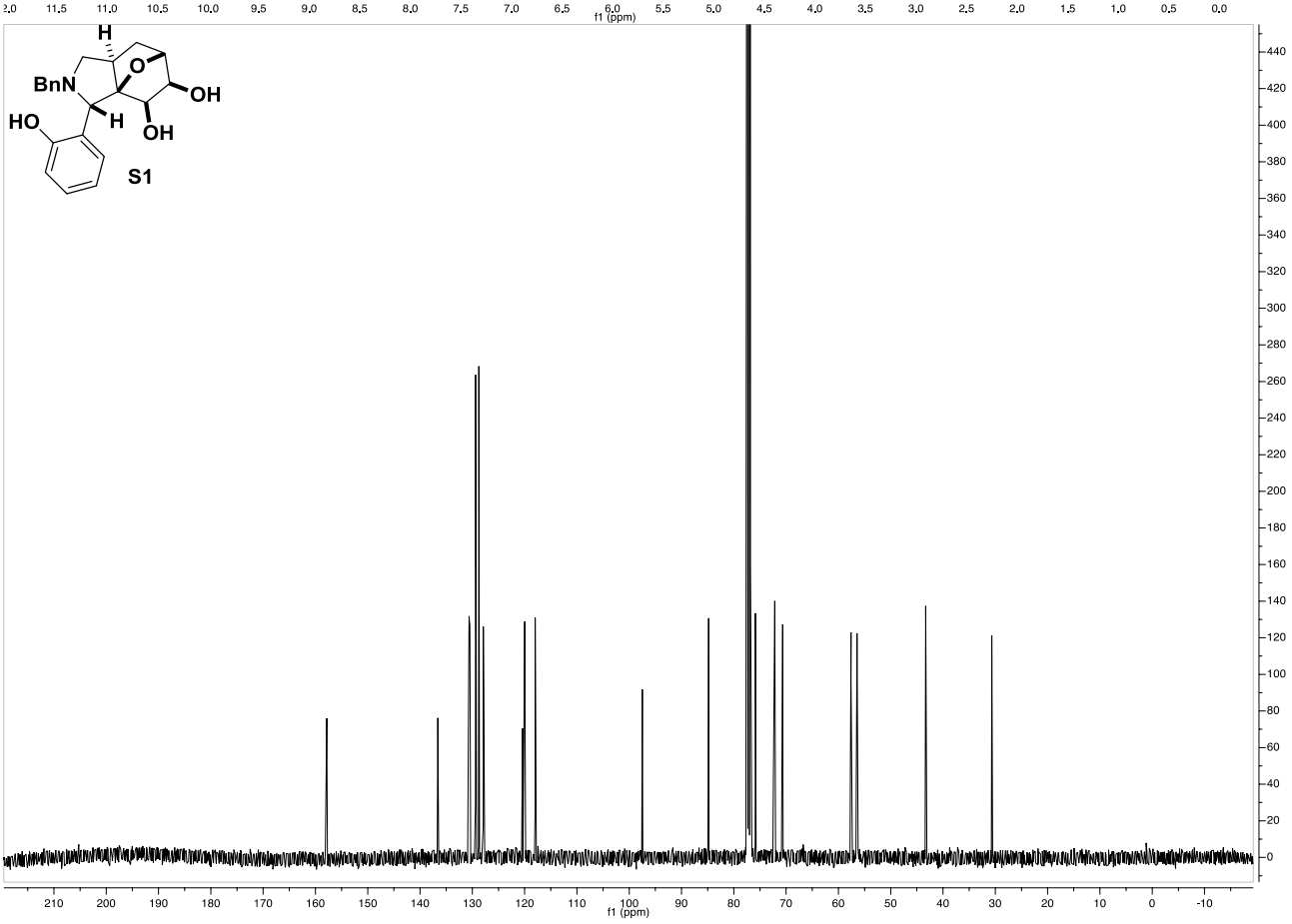
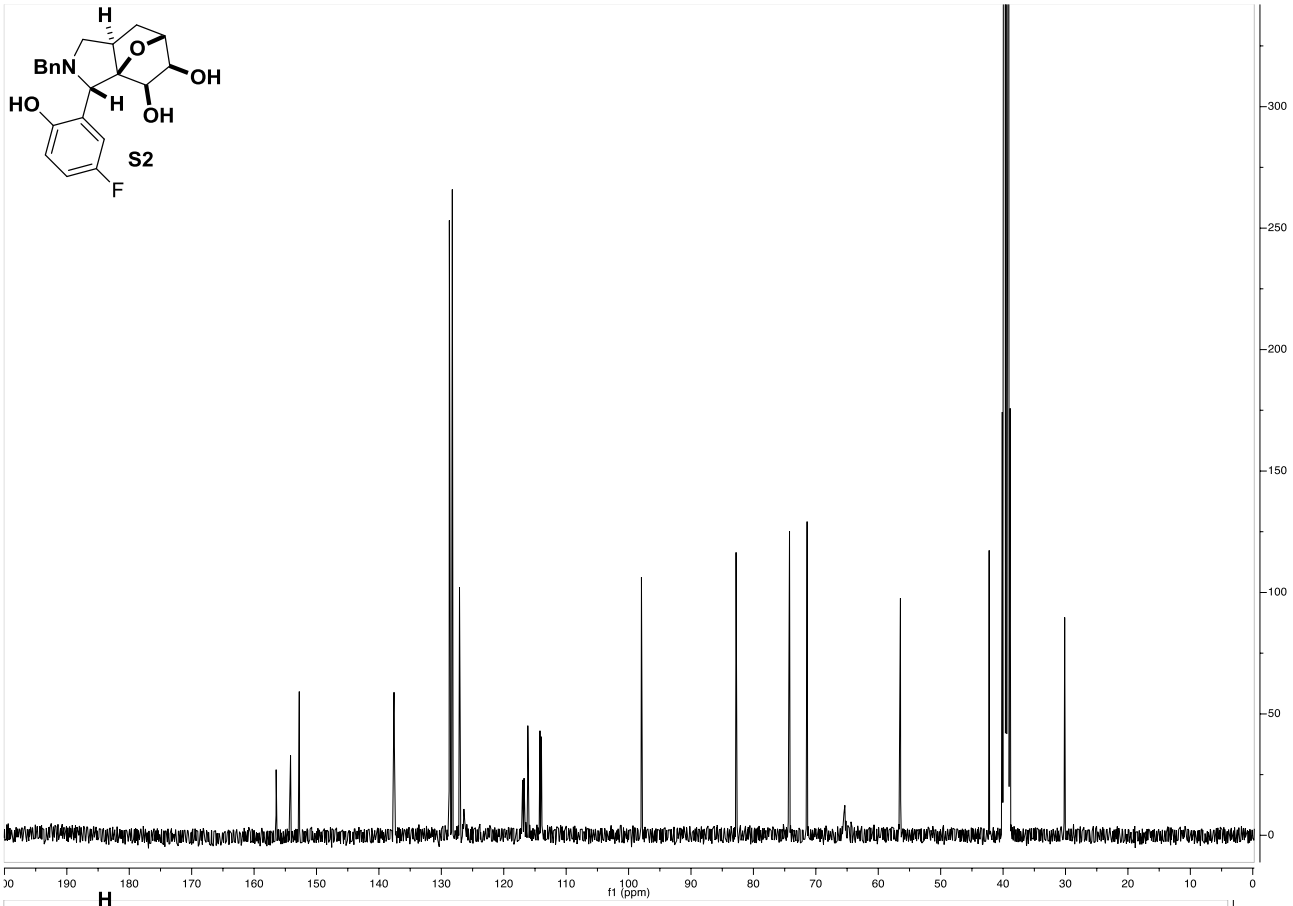
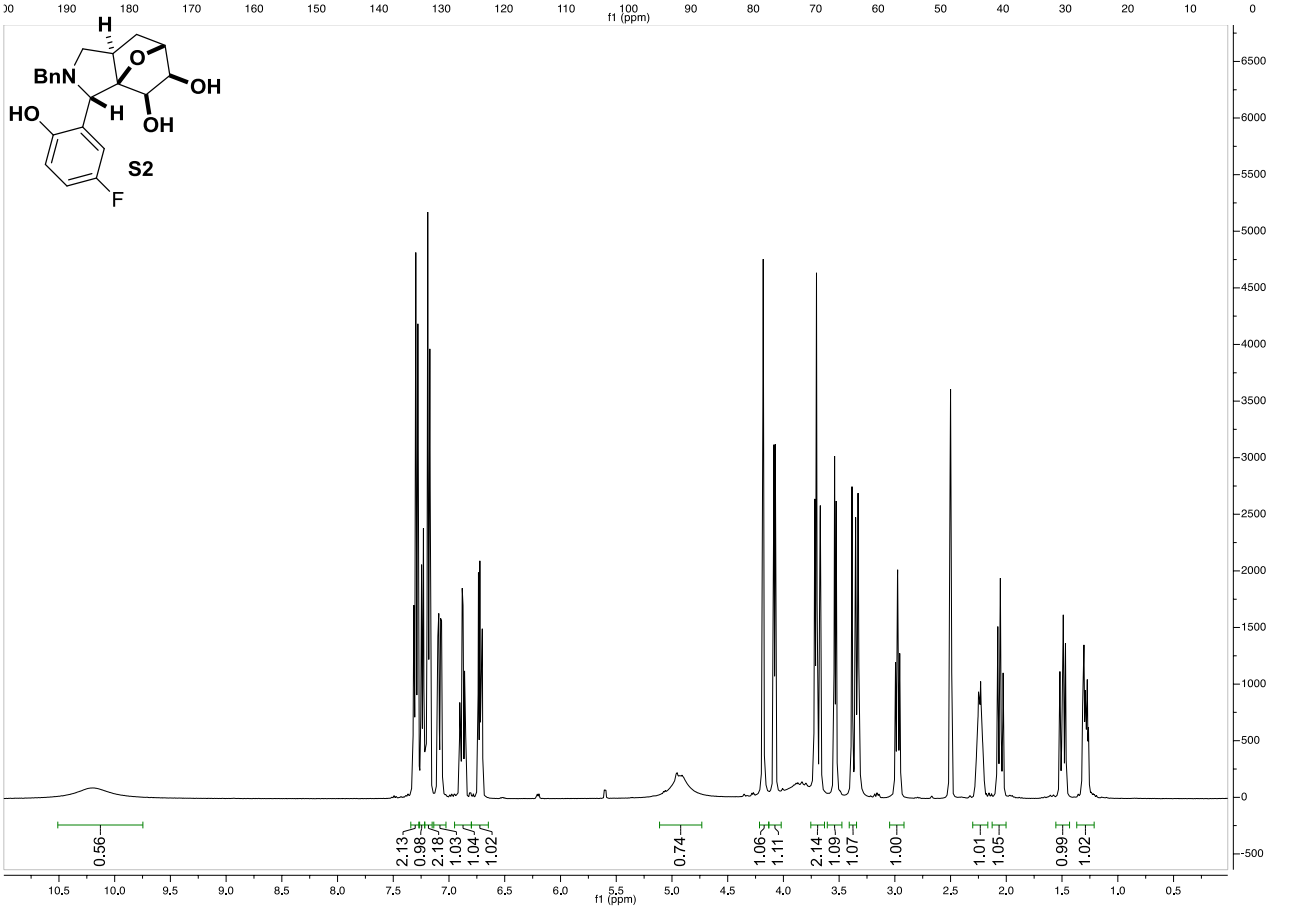
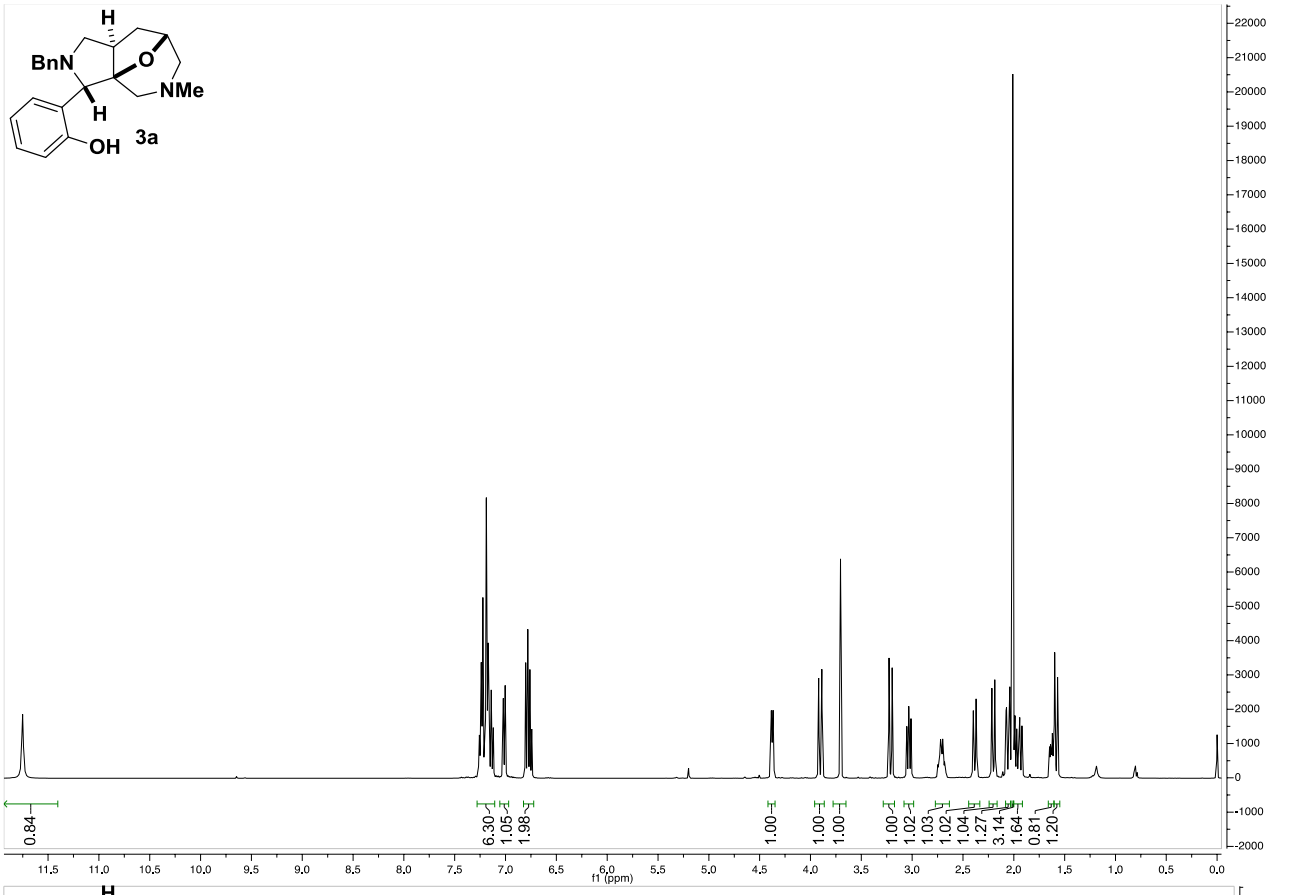
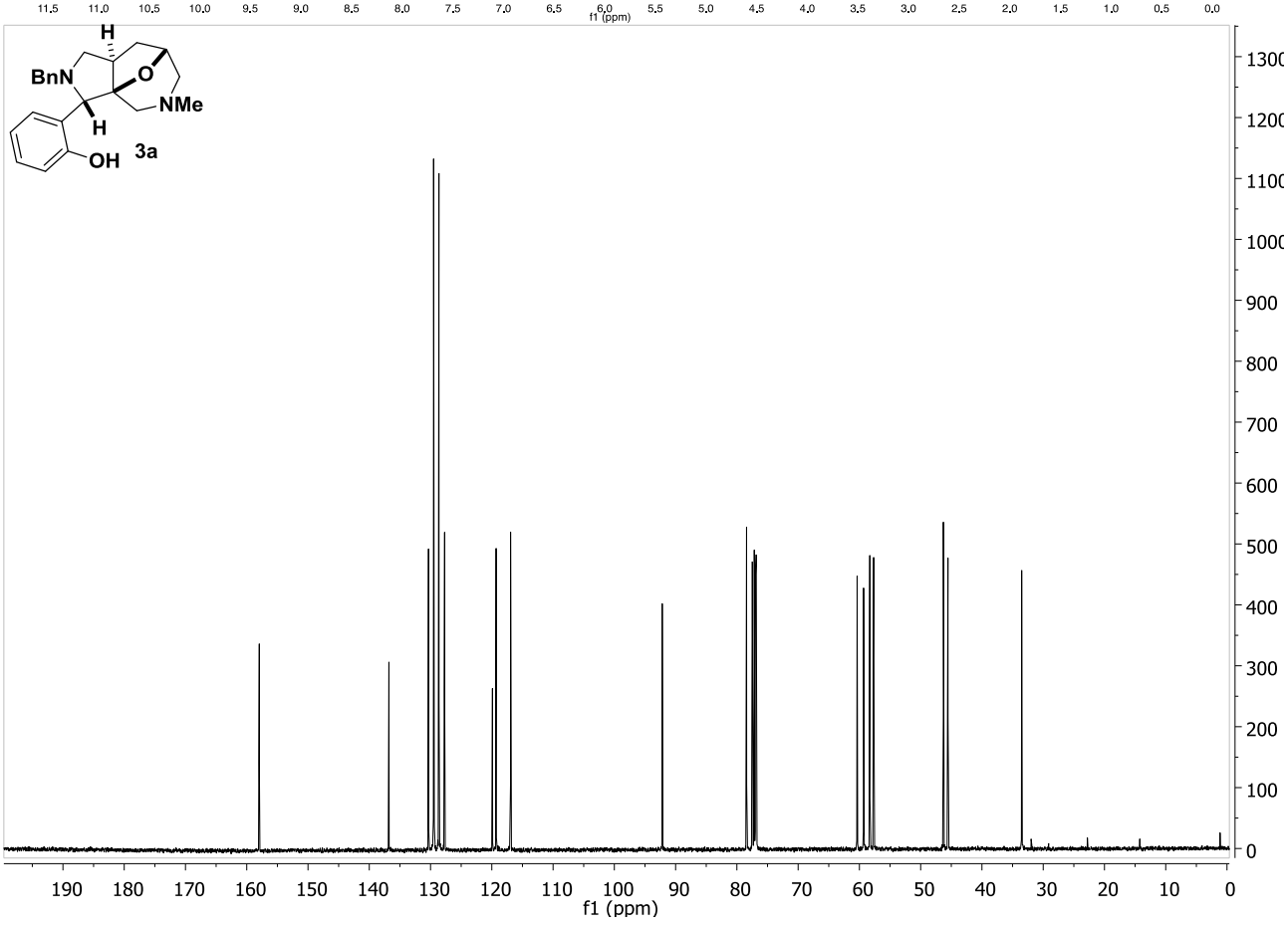
1.06
1.14
1.07
1.04
2.10
2.35
2.44
f1 (ppm)

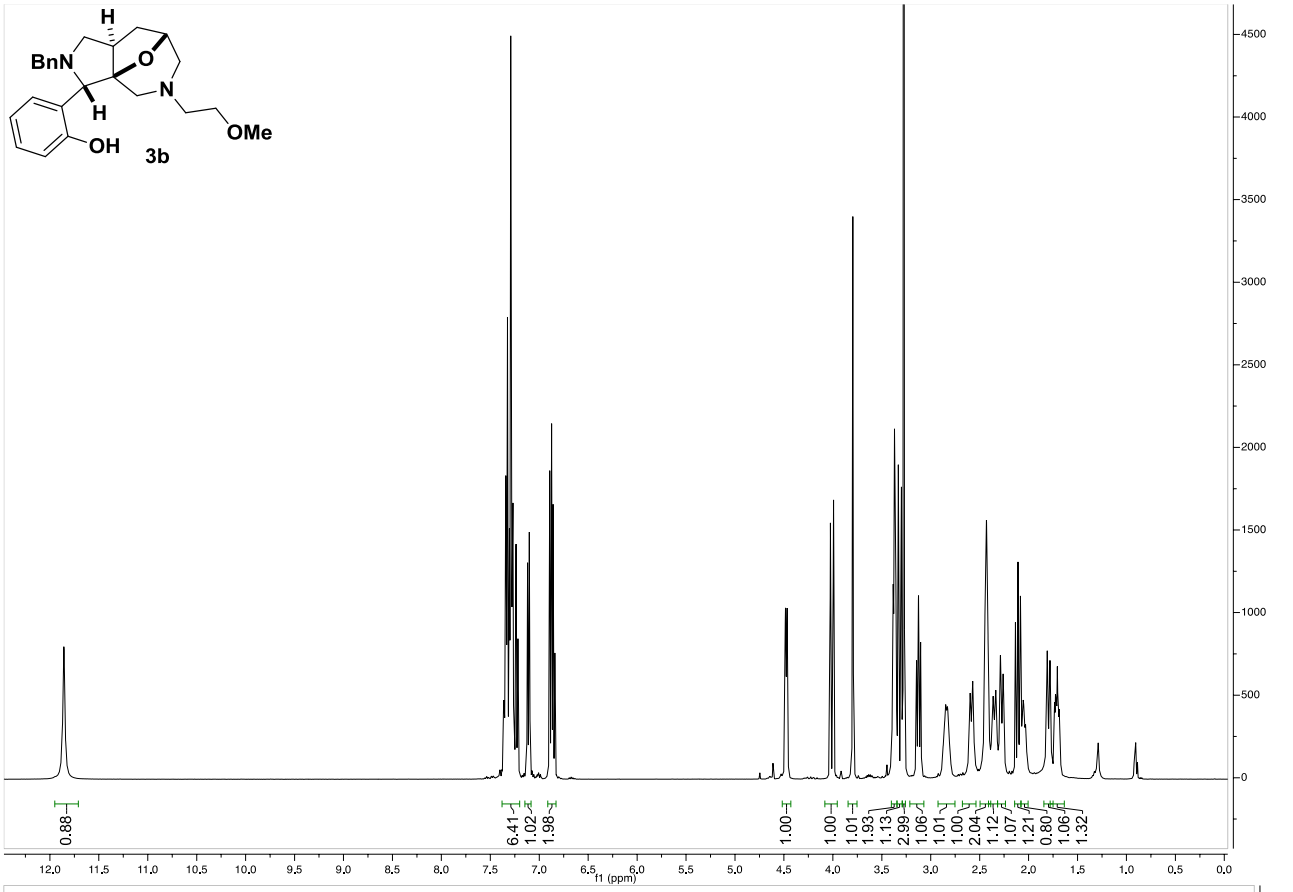

H
BnN
O
OH
HO
H
OH
S1
f1 (ppm)

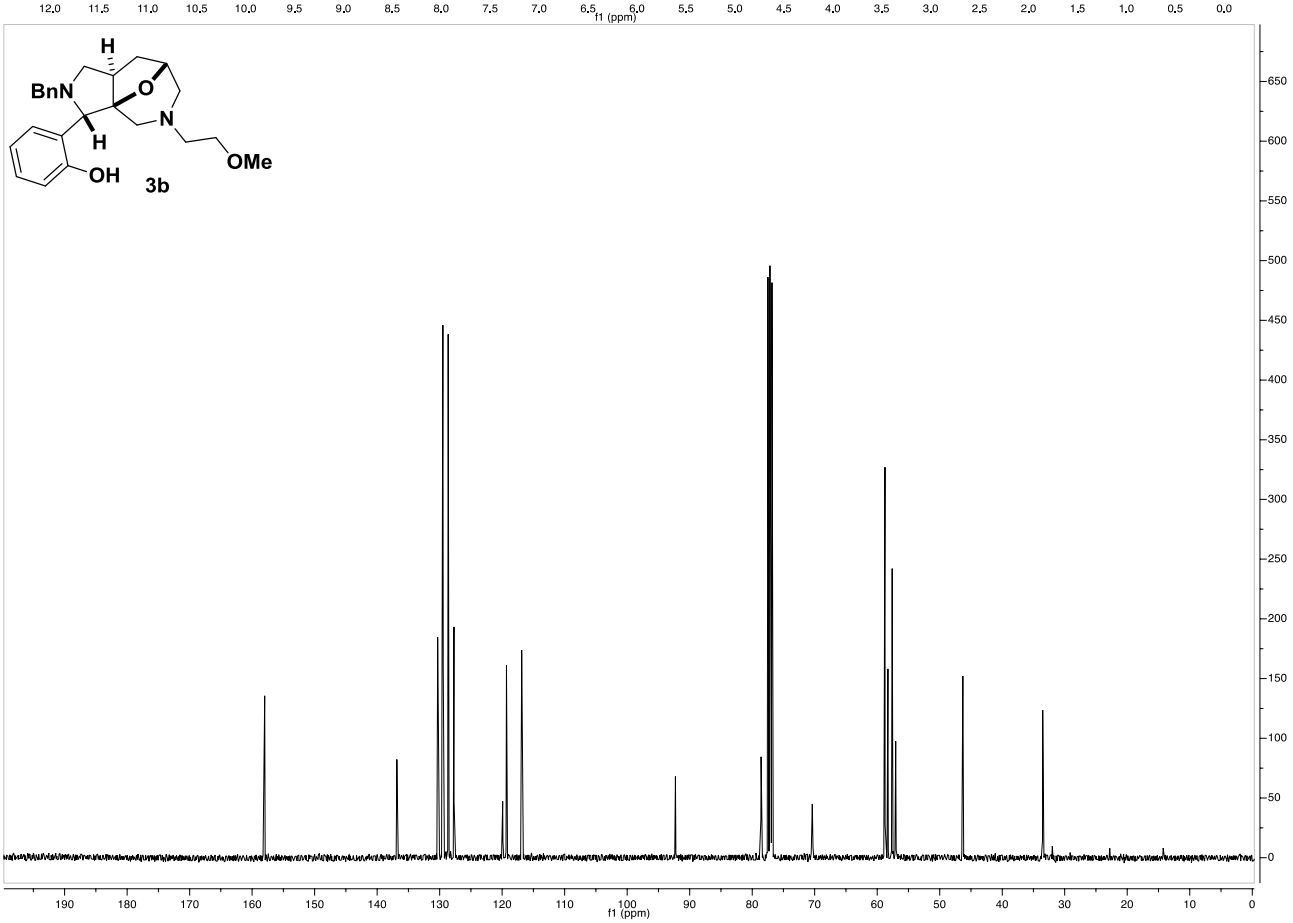

H
O
BnN
OH
HO
H
OH
S2
F
f1 (ppm)

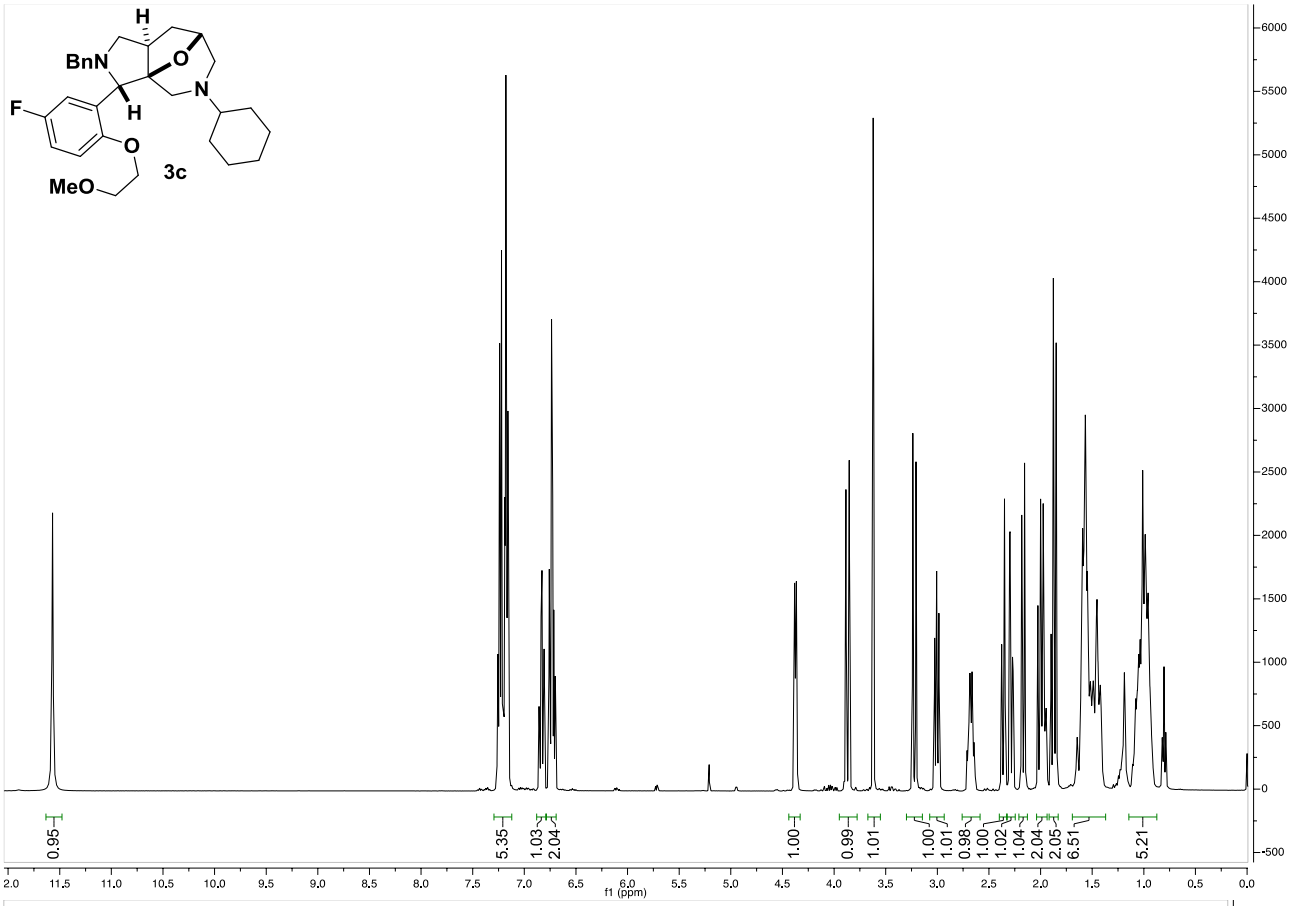

H
O
BnN
OH
HO
H
OH
S2
F
0.56
2.13
0.98
2.18
1.03
1.04
1.02
0.74
1.06
1.11
2.14
1.09
1.07
1.00
1.01
1.05
0.99
1.02
f1 (ppm)

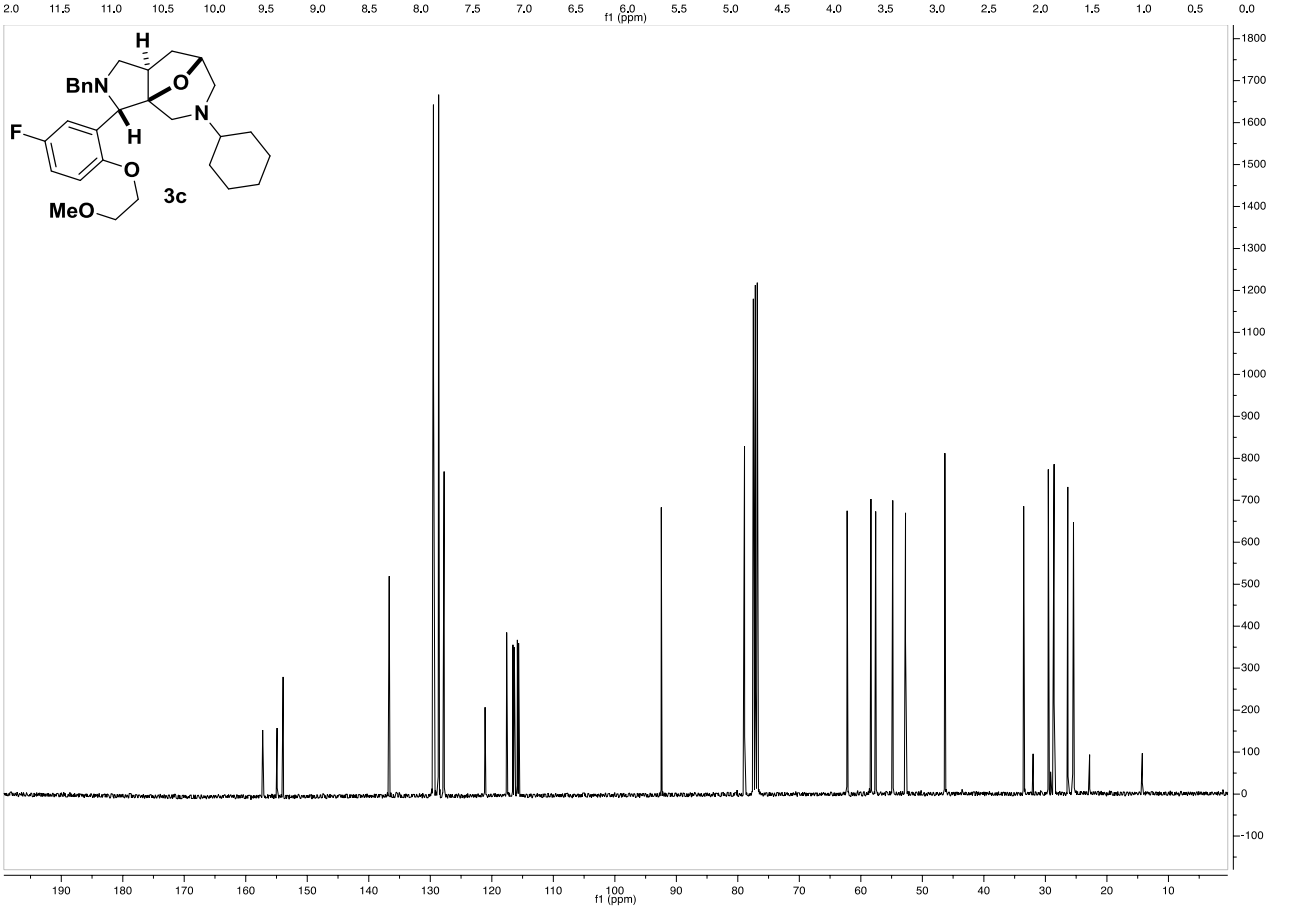

H
BnN
O
NMe
H
OH
3a
0.84
6.30
1.05
1.98
1.00
1.00
1.00
1.00
1.02
1.03
1.02
1.04
1.27
3.14
1.64
0.81
1.20
f1 (ppm)

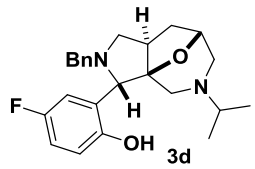

H
BnN
O
NMe
H
OH
3a
f1 (ppm)


H
BnN
O
N
H
OH
OMe
3b
0.88
6.41
1.02
1.98
1.00
1.00
1.01
1.93
1.13
2.99
1.06
1.01
1.00
2.04
1.12
1.07
1.21
0.80
1.06
1.32
f1 (ppm)


H
BnN
O
N
H
OH
OMe
3b
f1 (ppm)

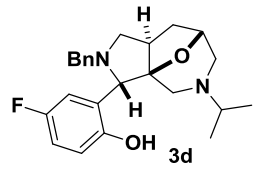

H
BnN
O
N
F
H
O
MeO
3c
0.95
5.35
1.03
2.04
1.00
0.99
1.01
1.00
1.01
0.98
1.00
1.02
1.04
2.04
2.05
6.51
5.21
f1 (ppm)


H
BnN
O
N
F
H
O
MeO
3c
f1 (ppm)


H
BnN
O
N
F
H
OH

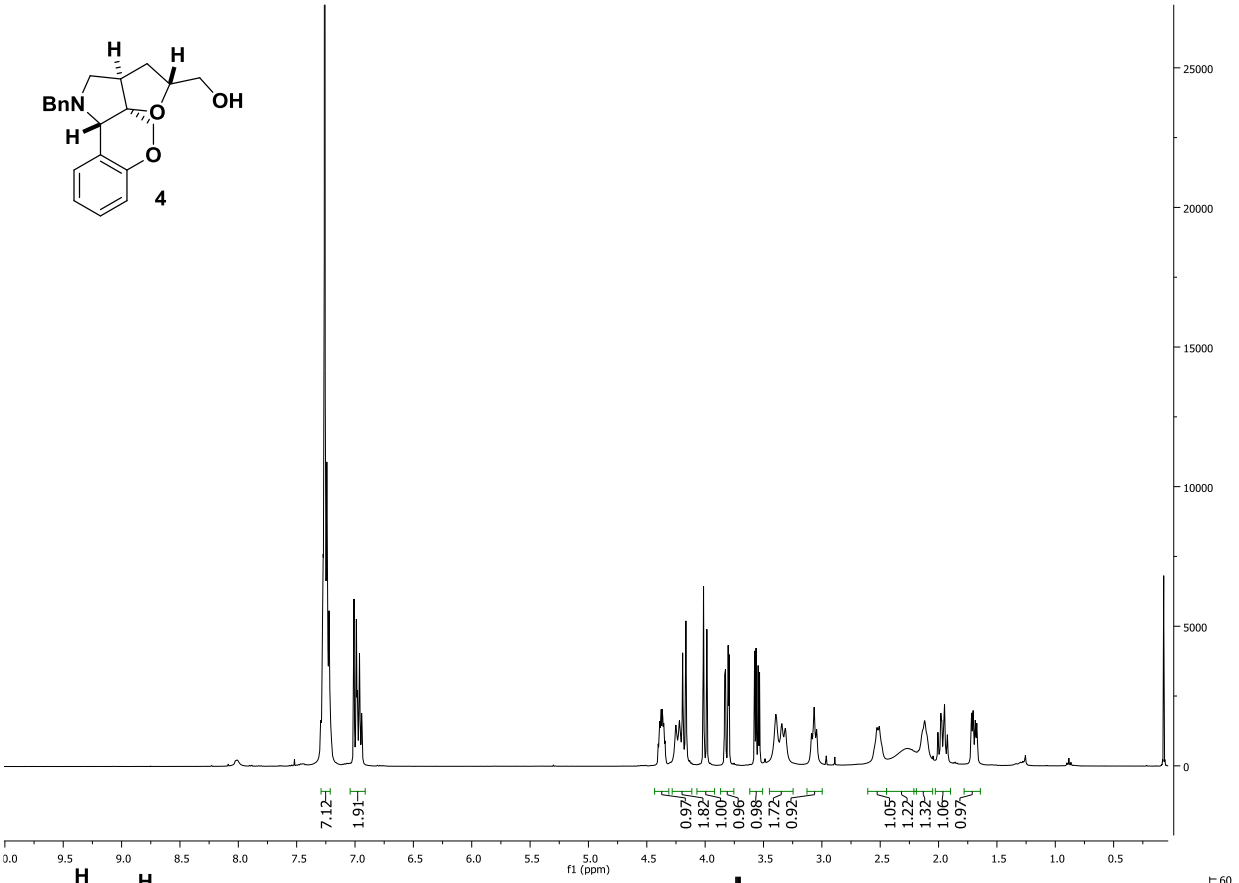
3d

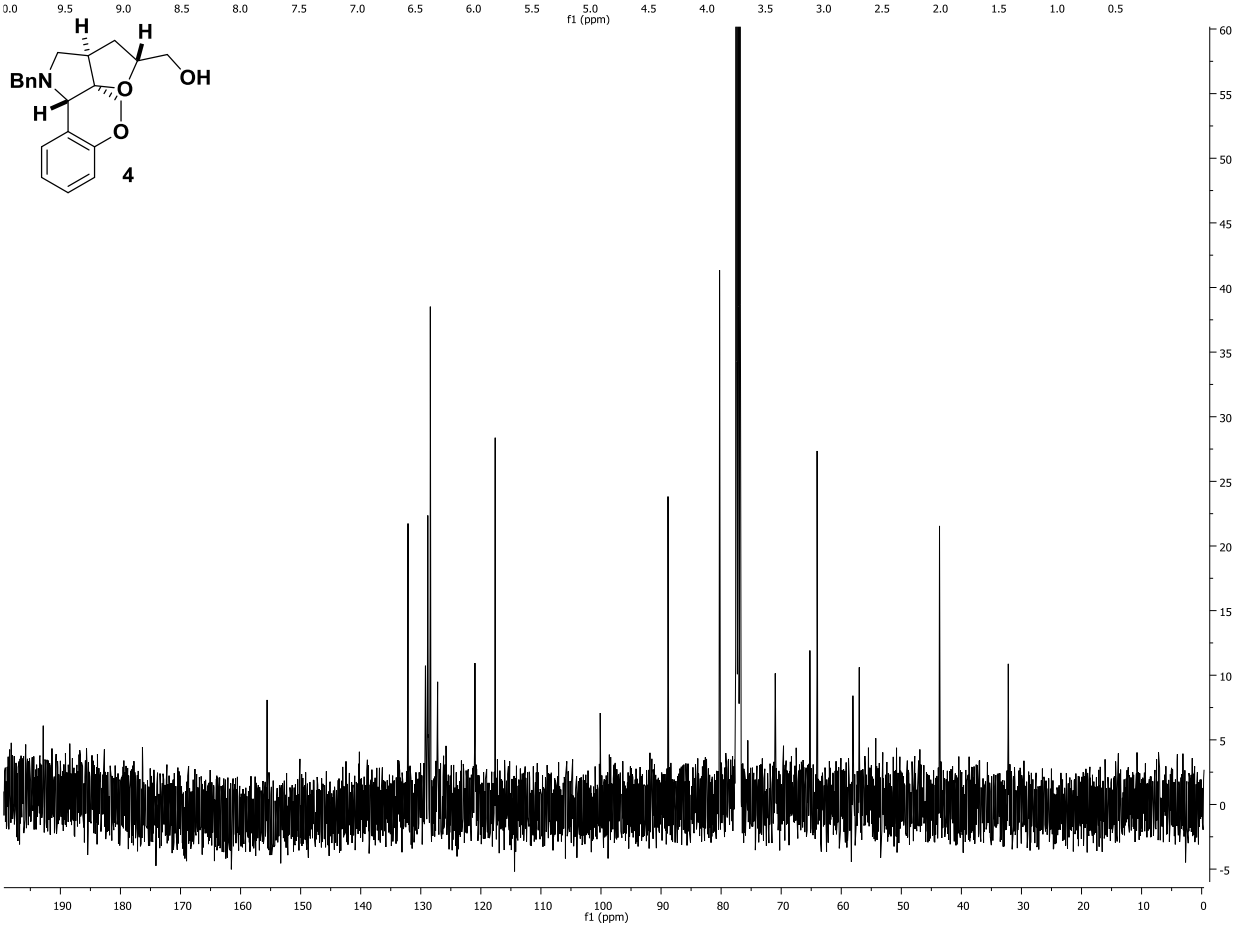
0.94
5.28
1.03
2.07
1.00
1.02
1.01
1.00
1.01
0.99
1.02
1.02
1.01
1.03
1.04
1.02
1.12
1.02
6.16
f1 (ppm)

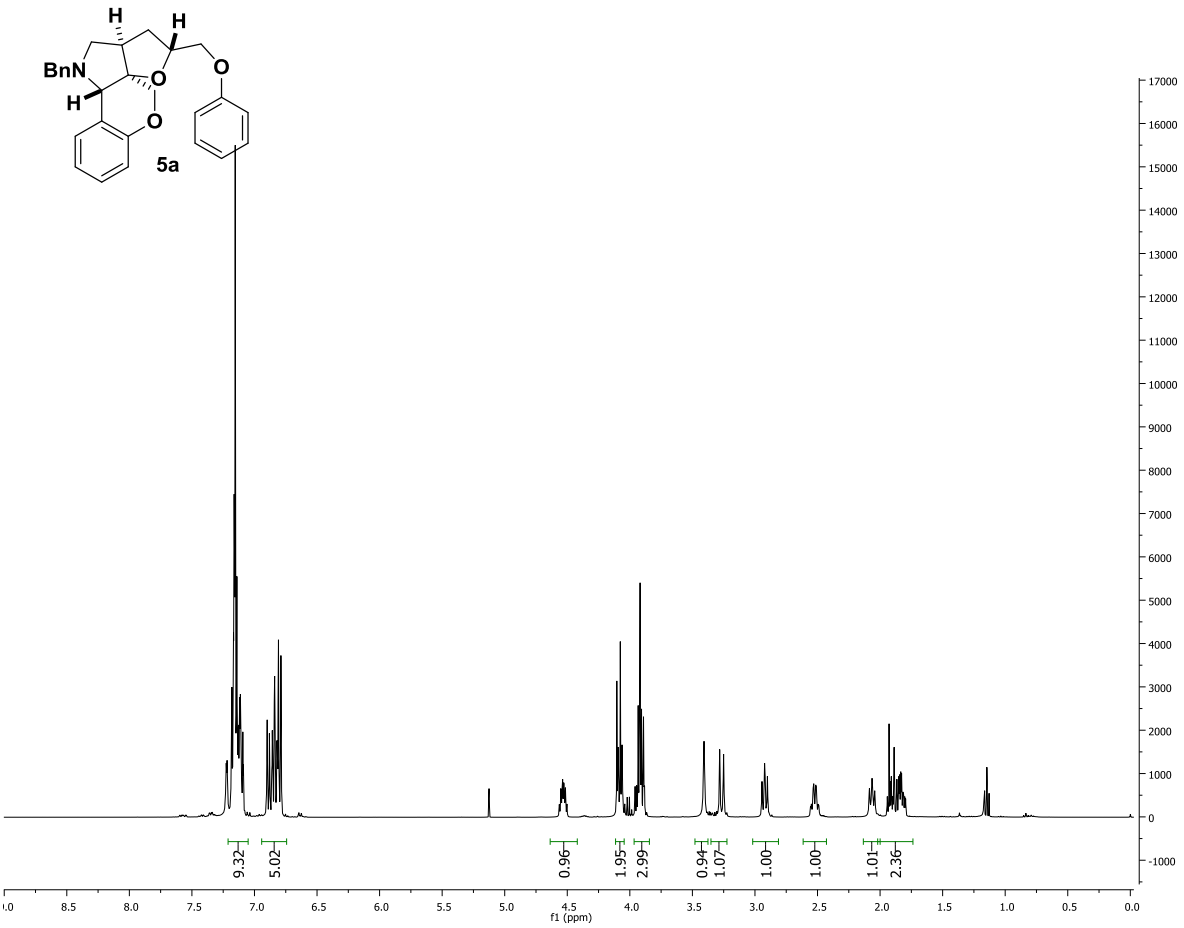

H
BnN
O
N
F
H
OH

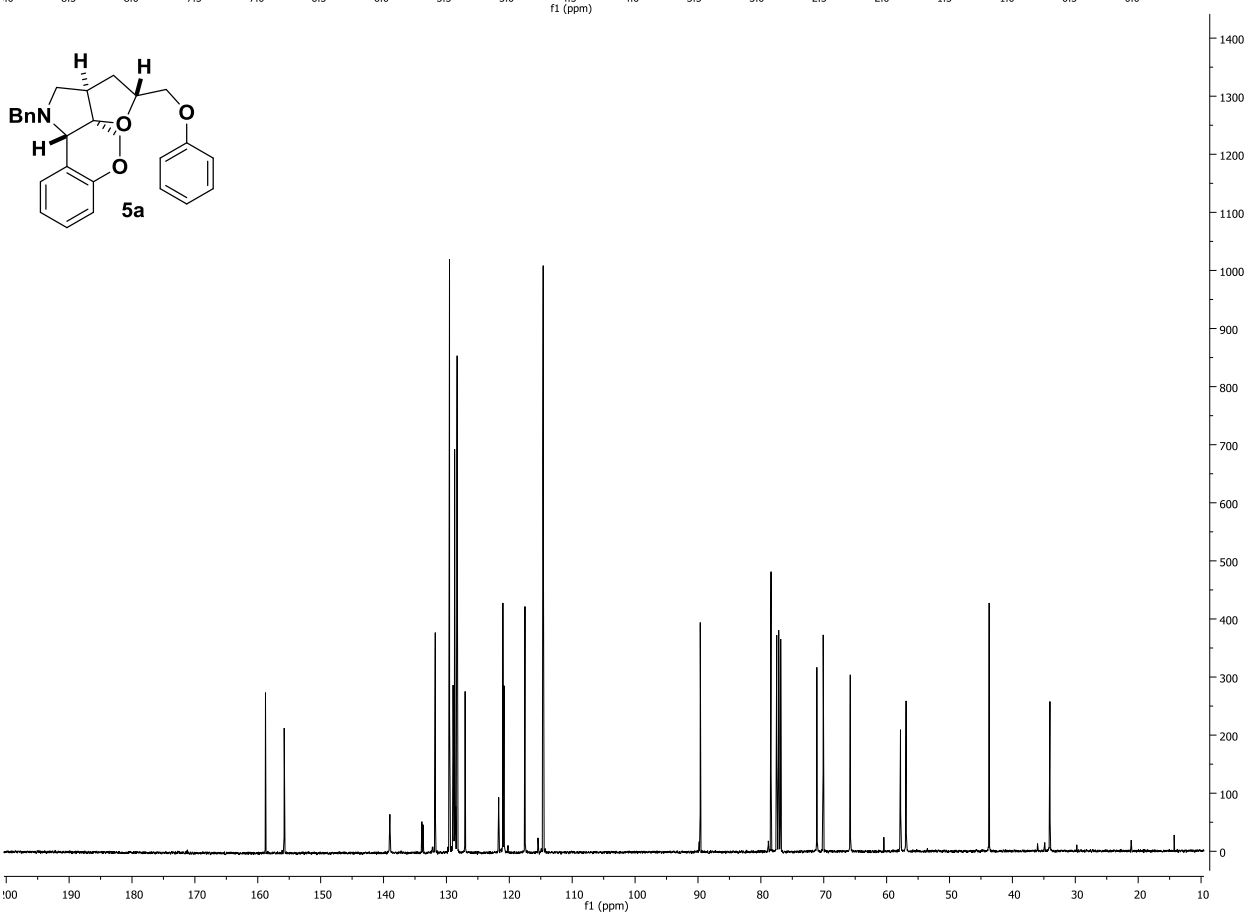
3d

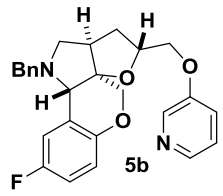
f1 (ppm)


H
H
BnN
O
OH
H
O
4
25000
20000
15000
10000
5000
0
7.12
1.91
0.97
1.82
1.00
0.96
0.98
1.72
0.92
1.05
1.22
1.32
1.06
0.97
f1 (ppm)

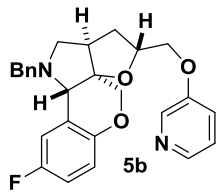

H
H
BnN
O
OH
H
O
4
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
f1 (ppm)


H
H
BnN
O
O
H
O
5a
9.32
5.02
0.96
1.95
2.99
0.94
1.07
1.00
1.00
1.01
2.36
f1 (ppm)

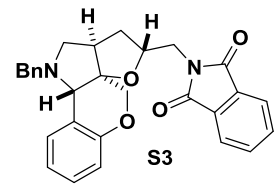

H
H
BnN
O
O
H
O
5a
f1 (ppm)


H
H
BnN
O
O
H
O
N
F
5b

16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
1.01
1.01
7.42
3.13
1.00
0.93
1.24
2.15
1.07
1.02
1.05
1.03
1.16
1.05
1.28
1.03
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

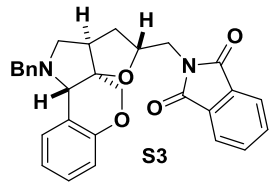

H
H
BnN
O
O
H
O
N
F
5b

1200
1100
1000
900
800
700
600
500
400
300
200
100
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H
H
BnN
O
N
H
O
O
O

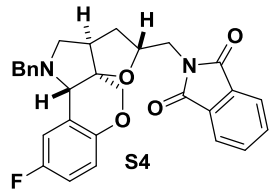
S3

2.27
2.04
7.18
2.12
1.09
2.12
2.19
1.19
0.99
1.03
1.00
0.97
1.00
2.08
f1 (ppm)

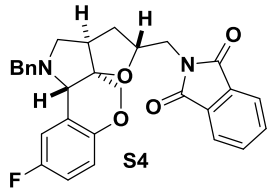

H
H
BnN
O
N
H
O
O
O

S3

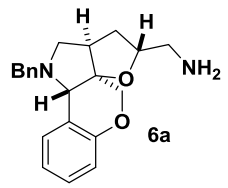
f1 (ppm)


H
H
BnN
O
N
O
H
O
O
S4
F

11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
2.03
2.06
5.50
3.05
1.01
2.03
2.09
1.06
1.01
1.00
0.99
0.99
1.01
2.01
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

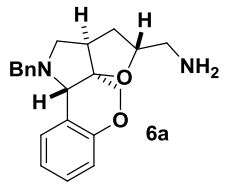

H
H
BnN
O
N
O
H
O
O
S4
F

160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H
H
BnN
O
NH2
H
O

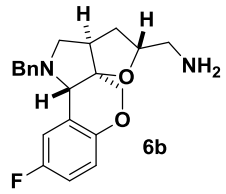
6a

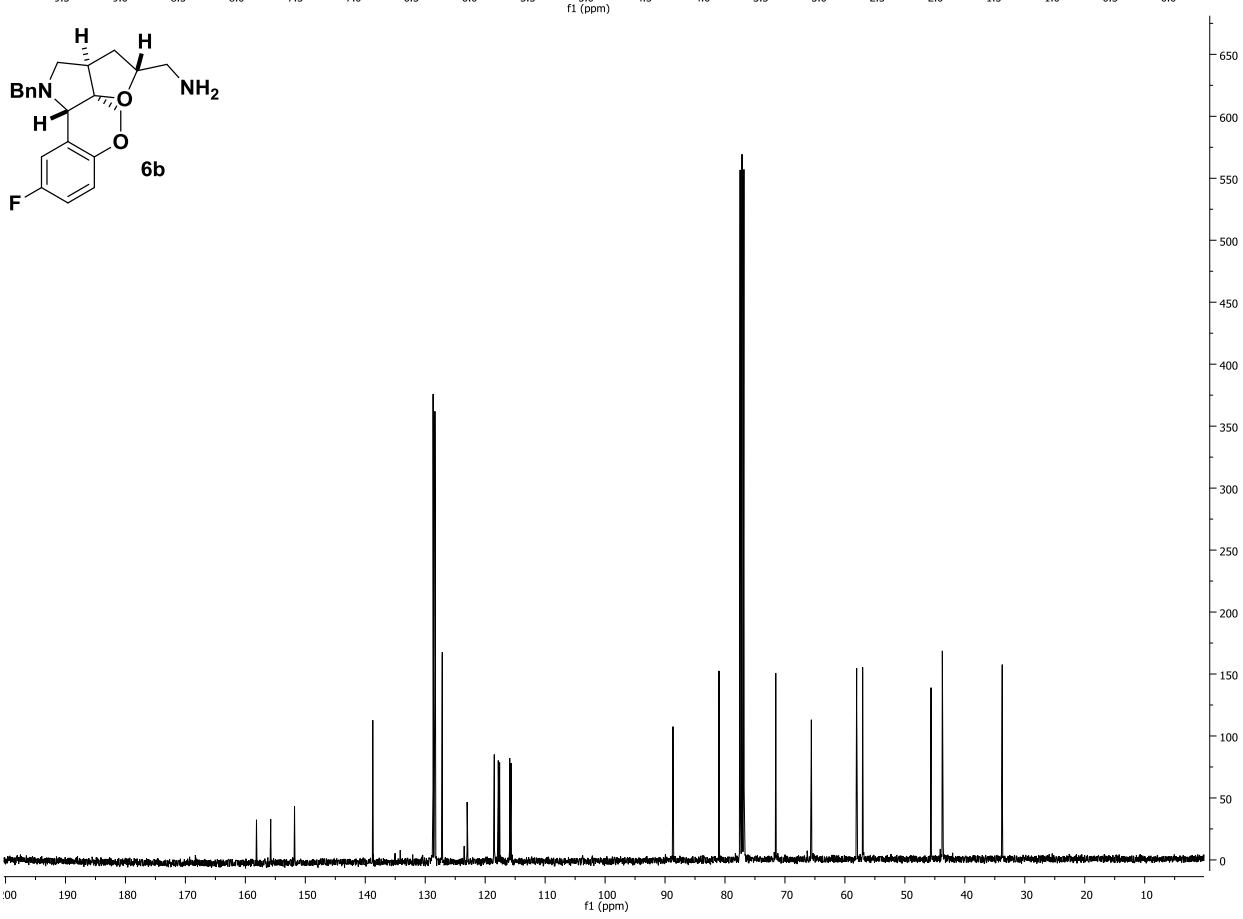
7.15
2.02
1.94
1.09
1.00
0.91
1.09
1.13
0.99
0.99
1.04
1.15
4.47
f1 (ppm)


H
H
BnN
O
NH2
H
O

6a

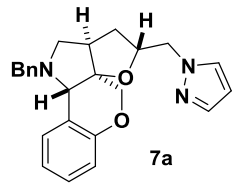
f1 (ppm)


H
H
BnN
O
NH2
H
O
6b
F


5.51
3.16
1.30
0.95
1.06
1.06
0.90
0.95
1.02
0.98
0.94
1.00
1.41
2.30
2.01
f1 (ppm)

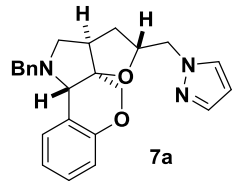
H
H
BnN
O
NH2
H
O
6b
F

f1 (ppm)


H
H
BnN
O
N
N
H
O

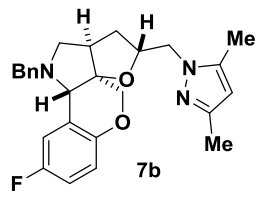
7a

12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
2.03
7.31
2.05
0.97
1.02
2.07
1.00
1.03
1.01
1.04
0.99
1.00
1.00
1.06
2.04
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

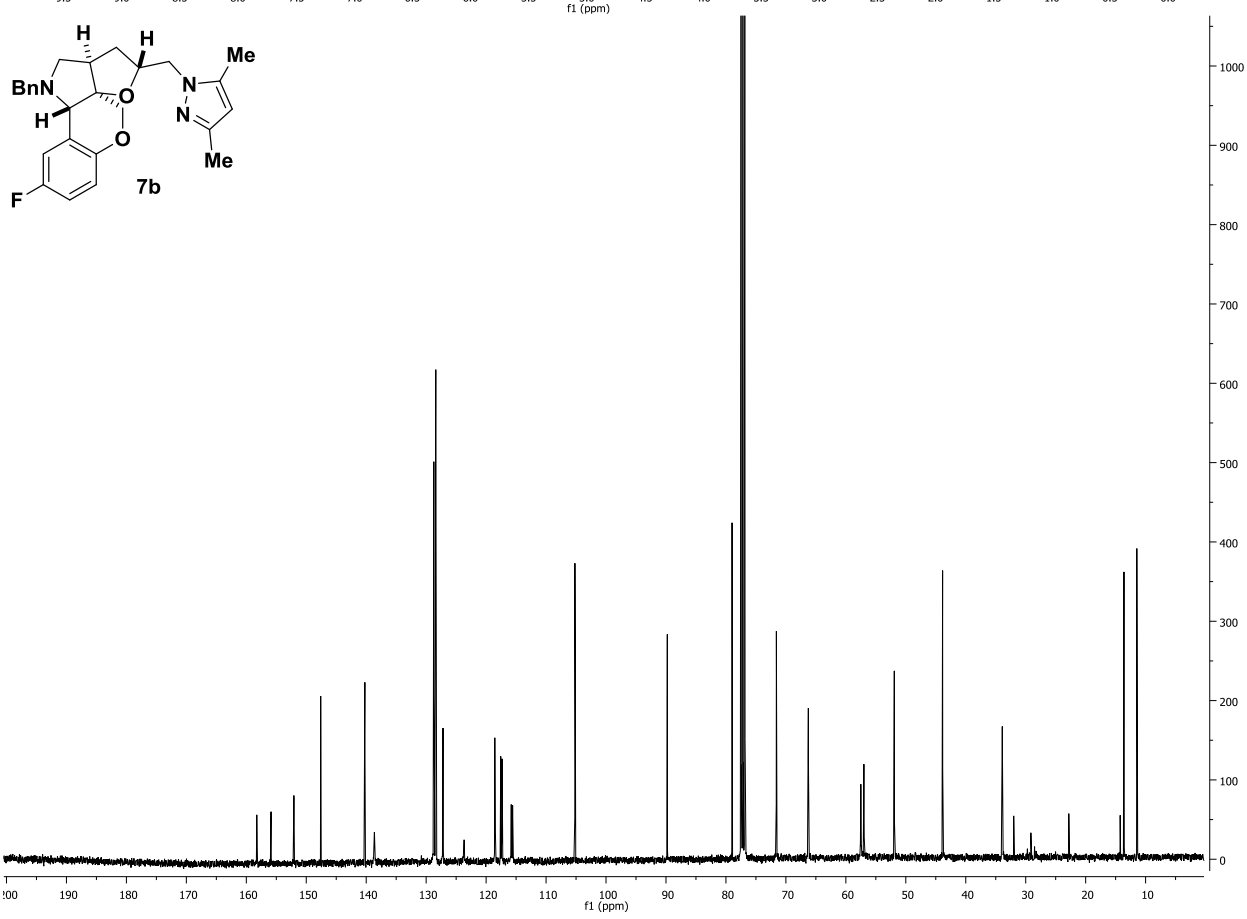

H
H
BnN
O
N
N
H
O

7a

850
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H
H
Me
BnN
N
O
H
N
O
Me
F

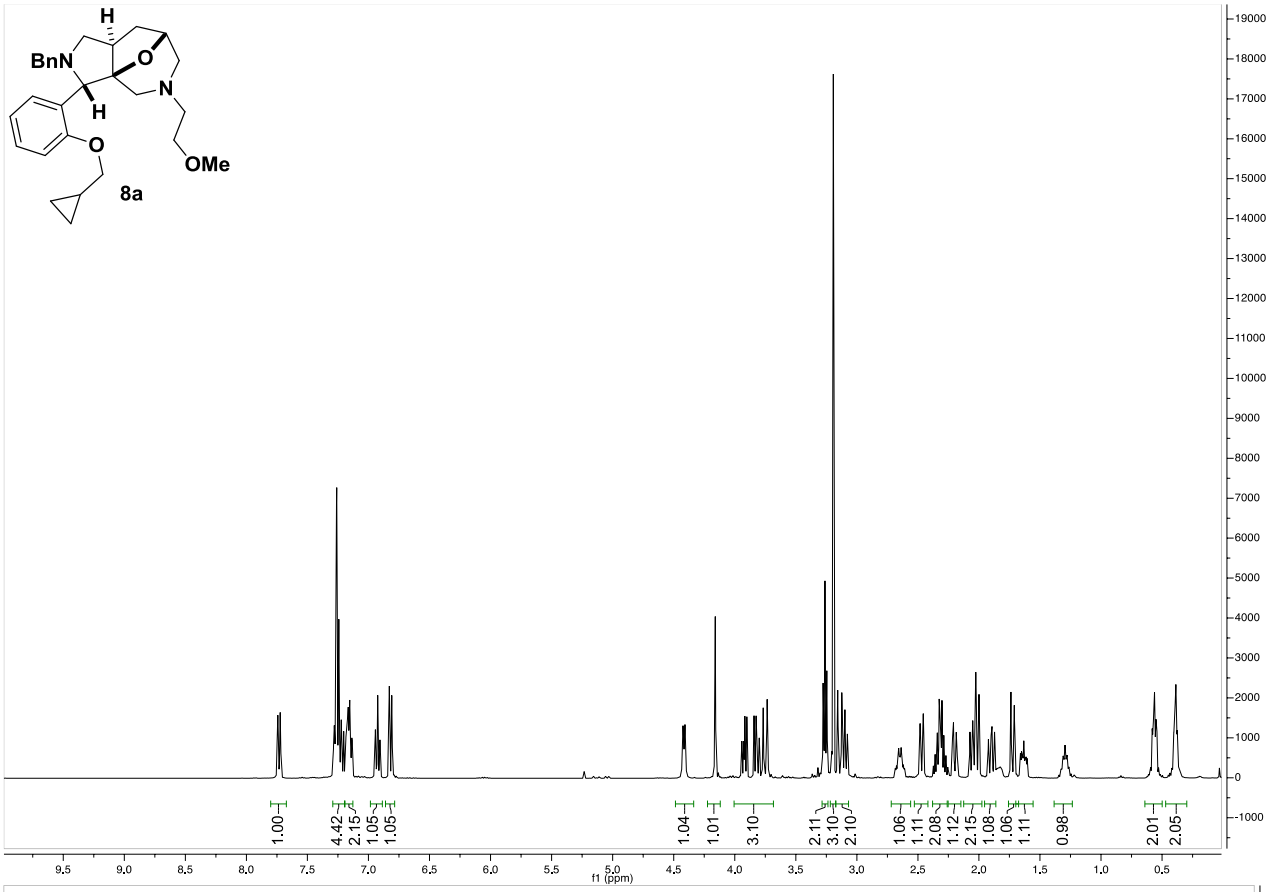
7b

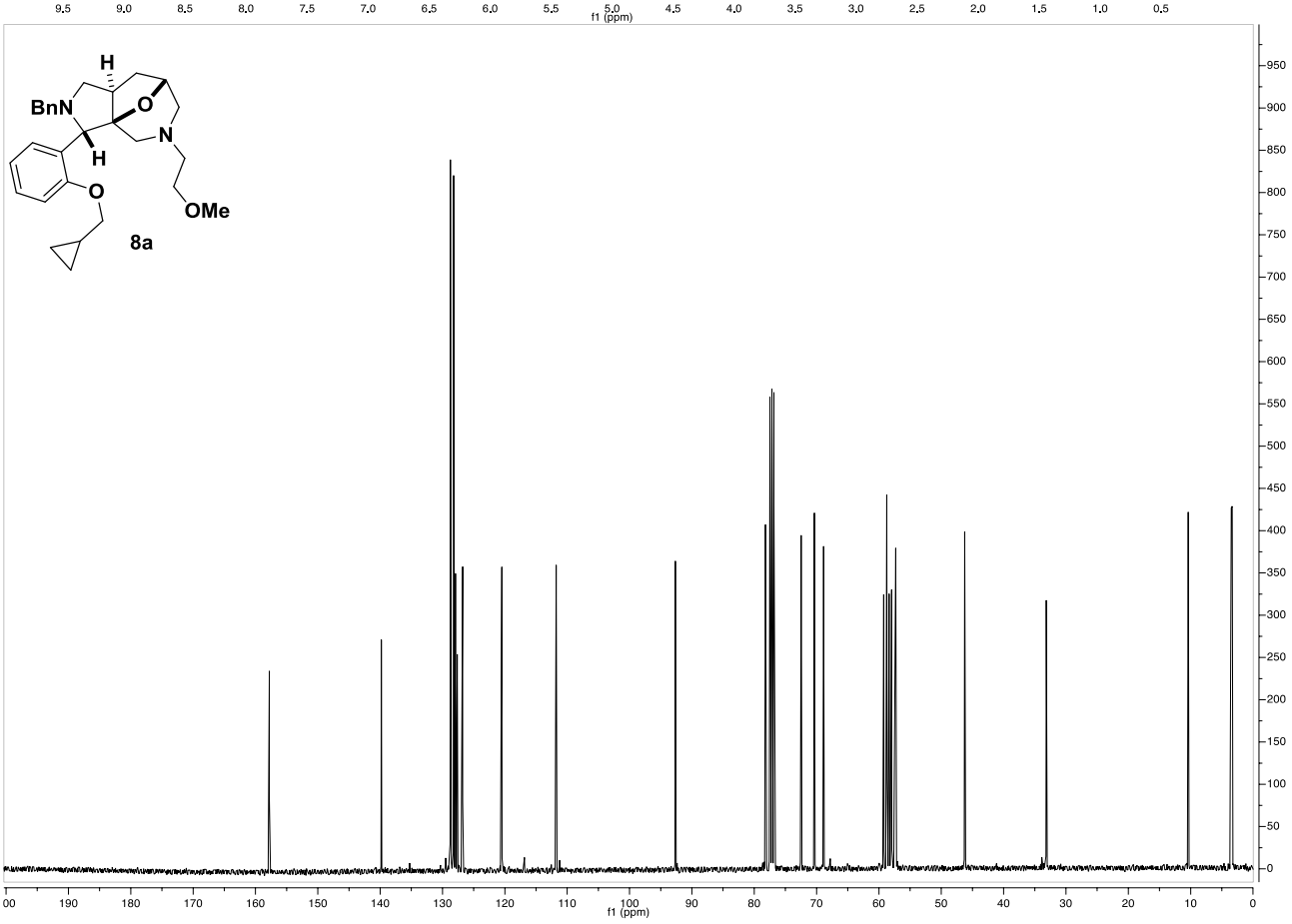

5.64
3.17
0.97
1.01
2.91
1.05
1.03
2.00
1.06
1.09
6.30
1.09
2.25
f1 (ppm)

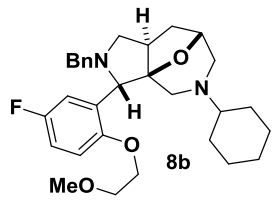
H
H
Me
BnN
N
O
H
N
O
Me
F

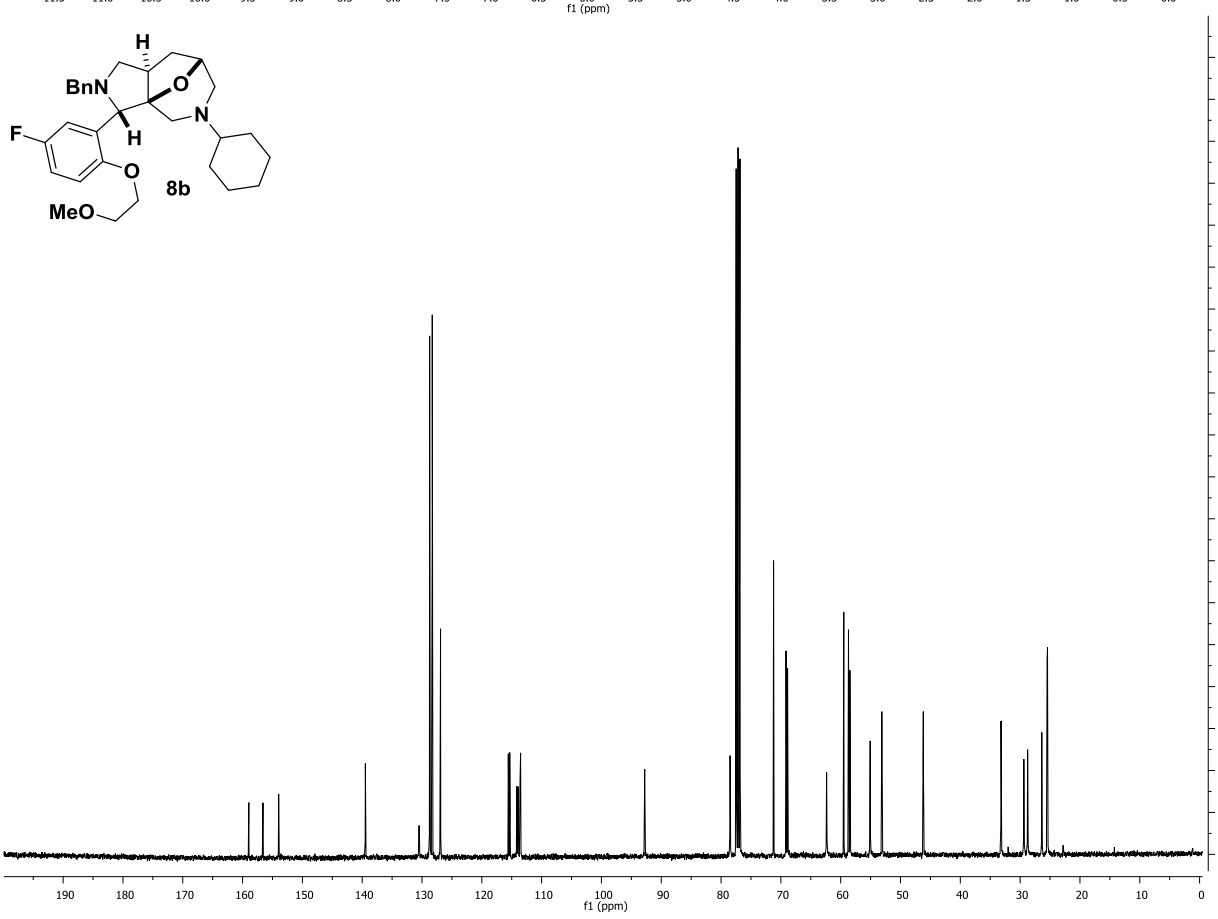
7b

f1 (ppm)


H
BnN
O
N
H
O
OMe
8a
1.00
4.42
2.15
1.05
1.05
1.04
1.01
3.10
2.11
3.10
2.10
1.06
1.11
2.08
1.12
2.15
1.08
1.06
1.11
0.98
2.01
2.05
f1 (ppm)

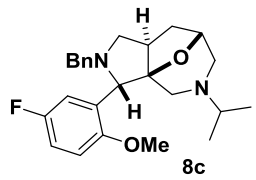

H
BnN
O
N
H
O
OMe
8a
f1 (ppm)


H
BnN
O
N
F
H
O
MeO
8b


1.00
4.10
1.22
2.05
0.99
3.06
2.98
2.99
0.99
1.35
0.96
0.97
1.06
3.47
2.17
6.22
5.10
f1 (ppm)

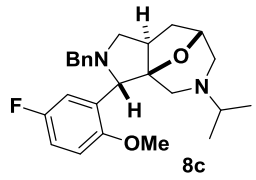
H
BnN
O
N
F
H
O
MeO
8b

f1 (ppm)


H
BnN
O
N
F
H
OMe

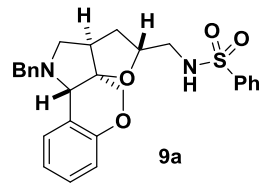
8c

1.00
3.97
1.17
1.01
1.00
0.97
0.98
3.07
1.04
2.00
0.97
3.04
2.05
1.02
1.02
0.74
5.95
f1 (ppm)


H
BnN
O
N
F
H
OMe

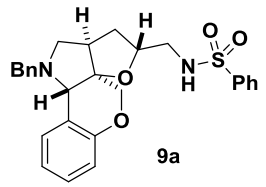
8c

f1 (ppm)


H
H
O
O
BnN
N
S
Ph
H
H
O
O

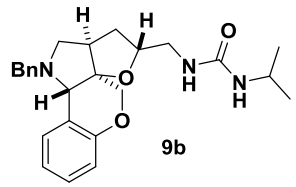
9a

9000
8000
7000
6000
5000
4000
3000
2000
1000
0
2.00
1.11
2.08
7.27
2.00
0.96
1.98
1.05
1.05
3.01
2.14
1.00
1.06
1.08
1.36
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


H
H
O
O
BnN
N
S
Ph
H
H
O
O

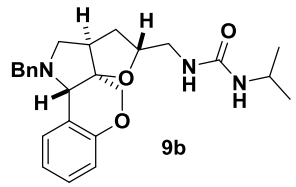
9a

600
550
500
450
400
350
300
250
200
150
100
50
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H
H
BnN
O
N
H
O
N
H
H
O

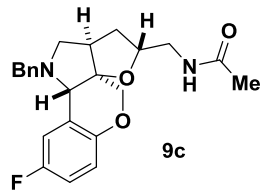
9b

12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
7.34
2.10
0.99
0.90
2.94
1.04
1.00
1.01
1.15
2.03
0.99
2.02
2.03
6.19
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


H
H
BnN
O
N
H
O
N
H
H
O

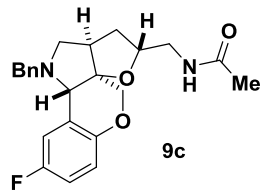
9b

1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H
H
O
BnN
O
N
H
Me
H
O
F

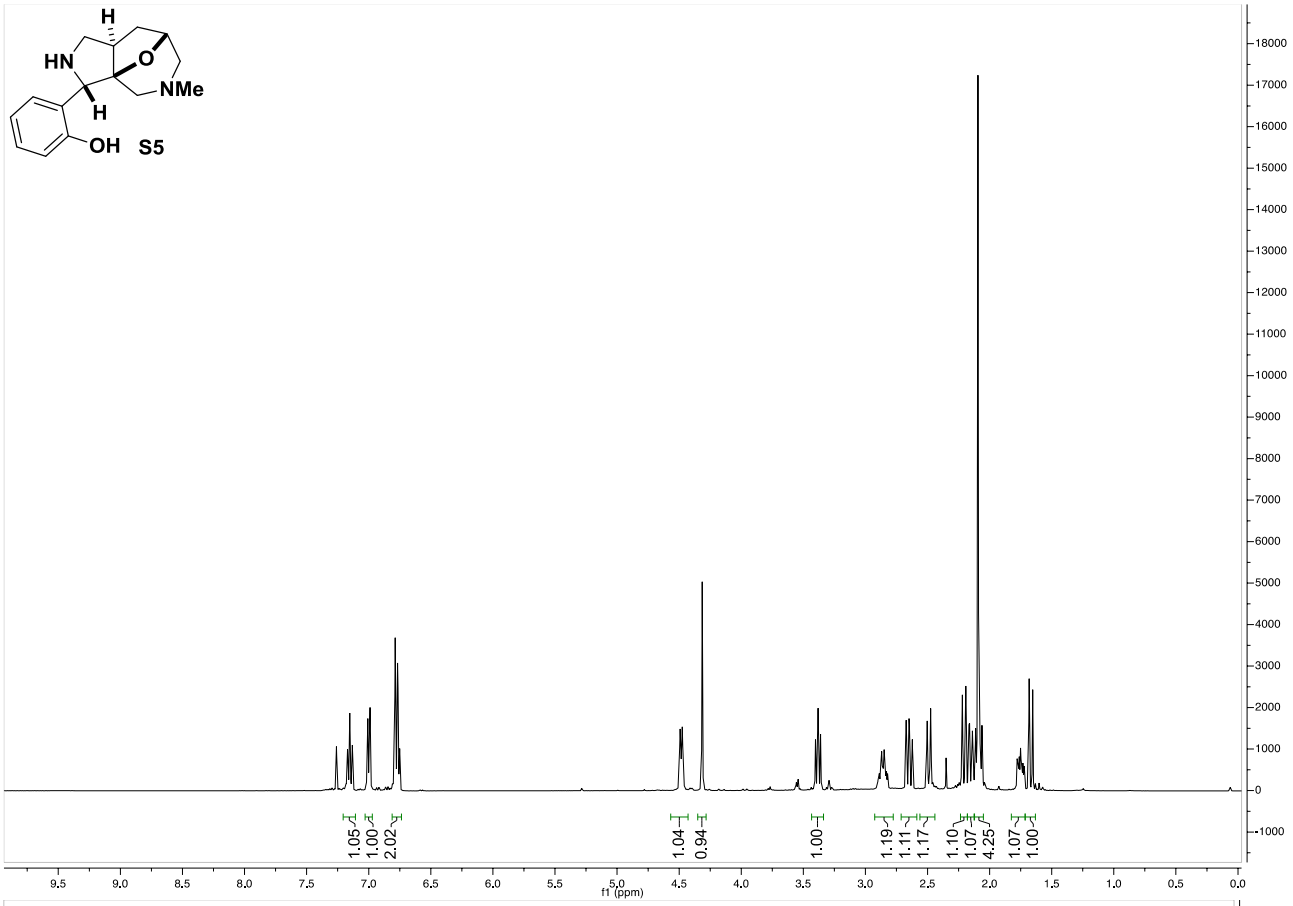
9c

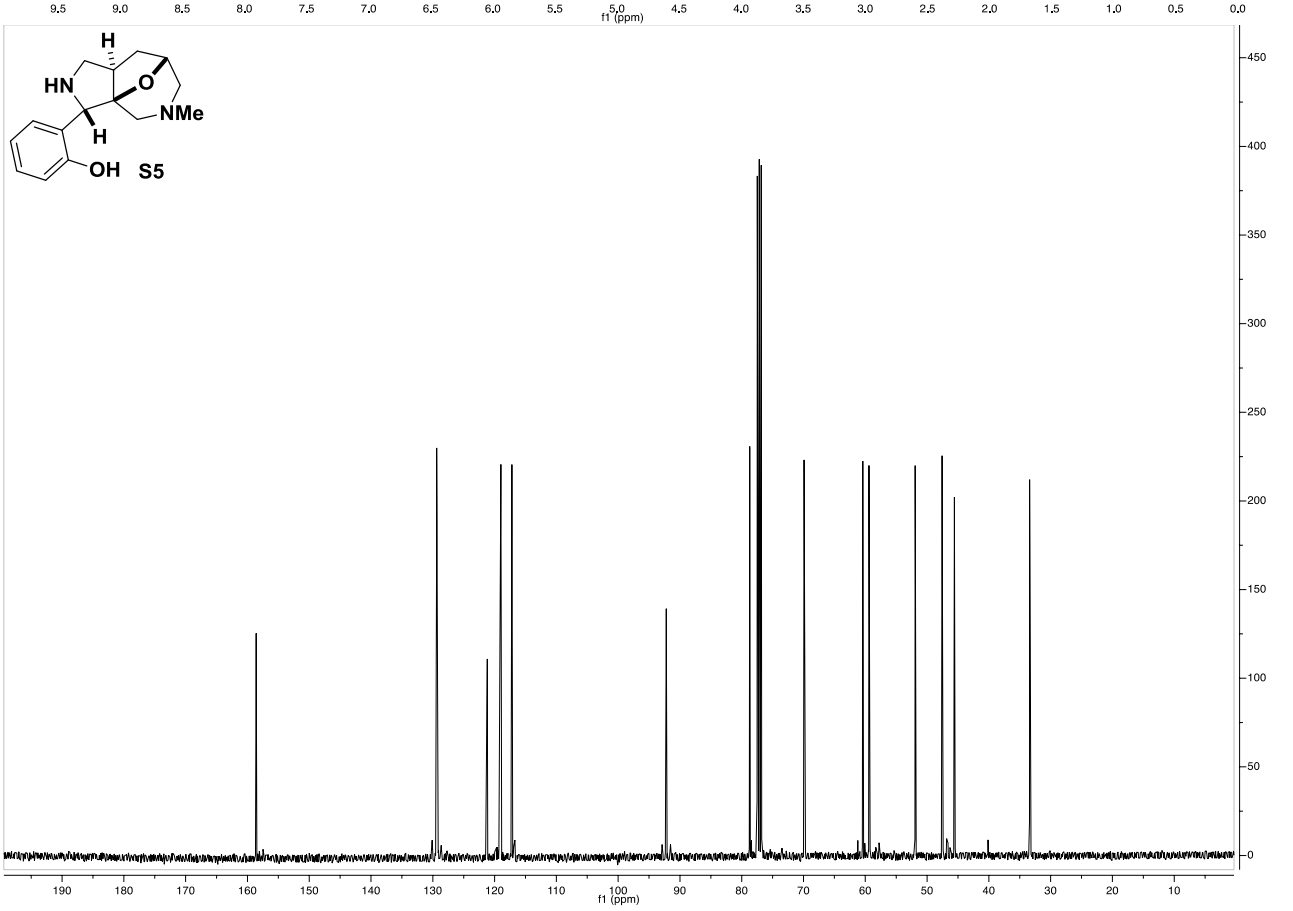
38000
36000
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
5.64
3.15
0.96
1.11
1.04
1.04
1.04
1.03
2.10
1.08
1.03
1.00
1.19
3.07
2.22
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

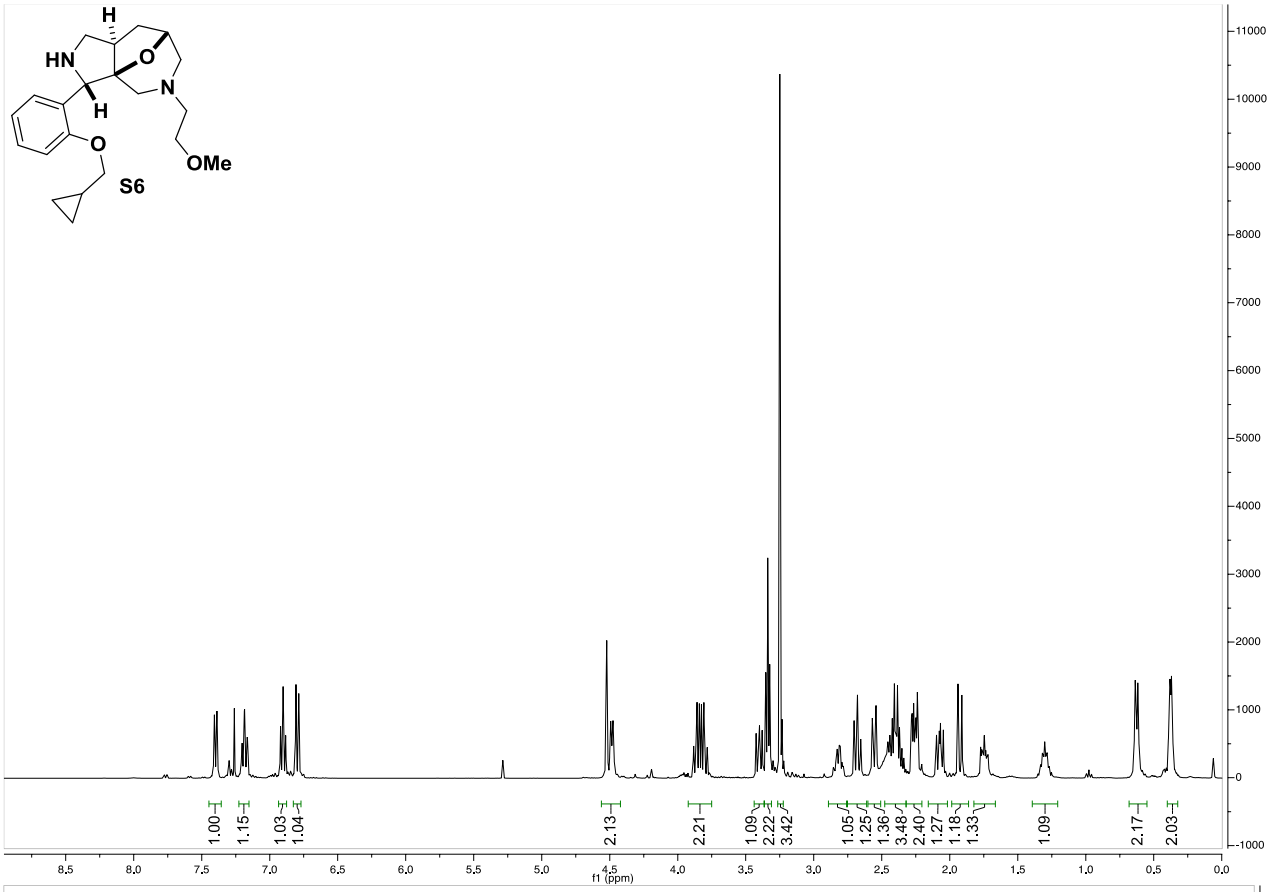

H
H
O
BnN
O
N
H
Me
H
O
F

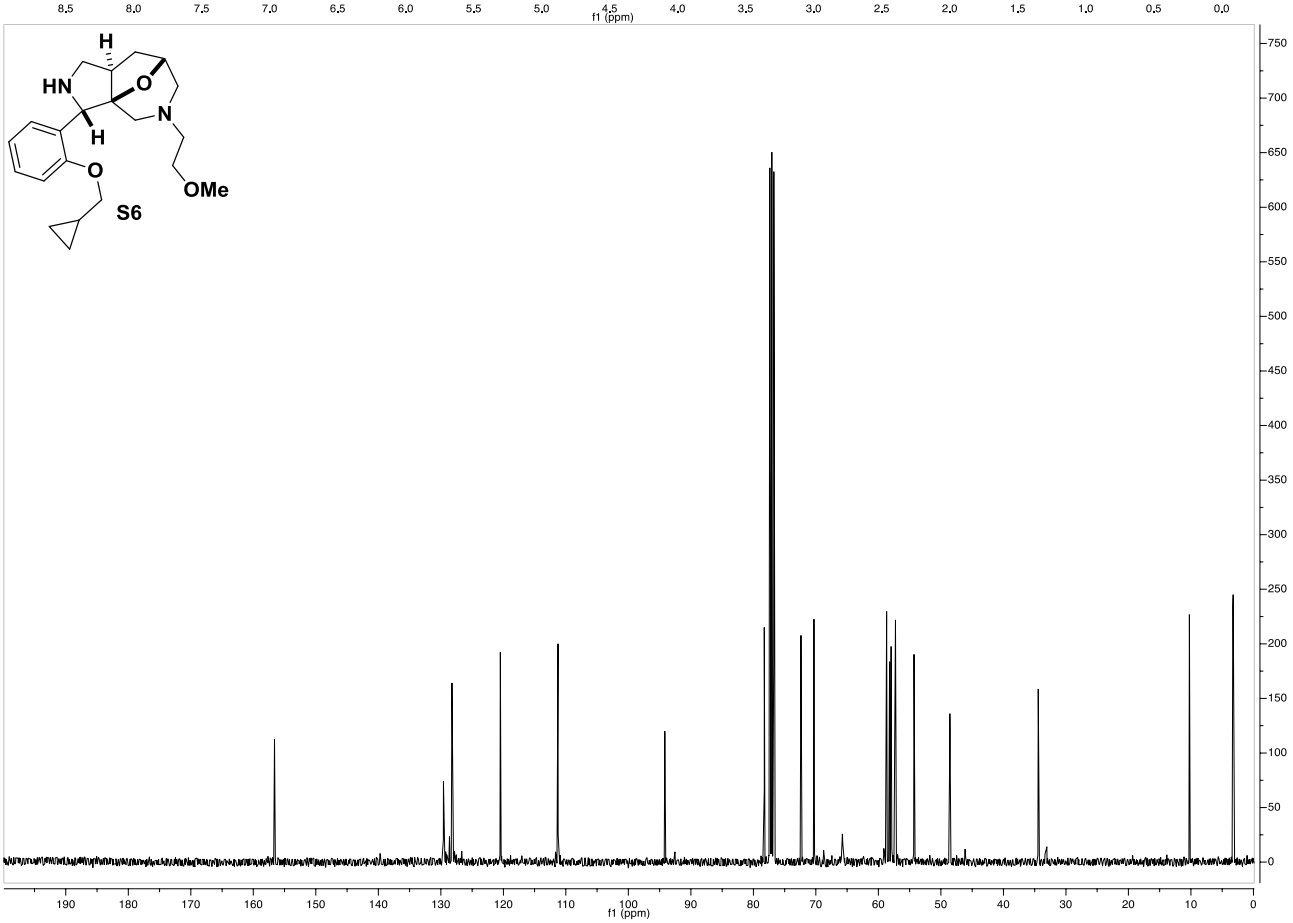
9c

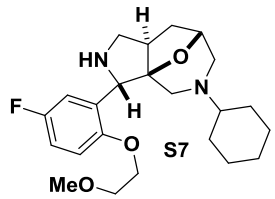
250
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

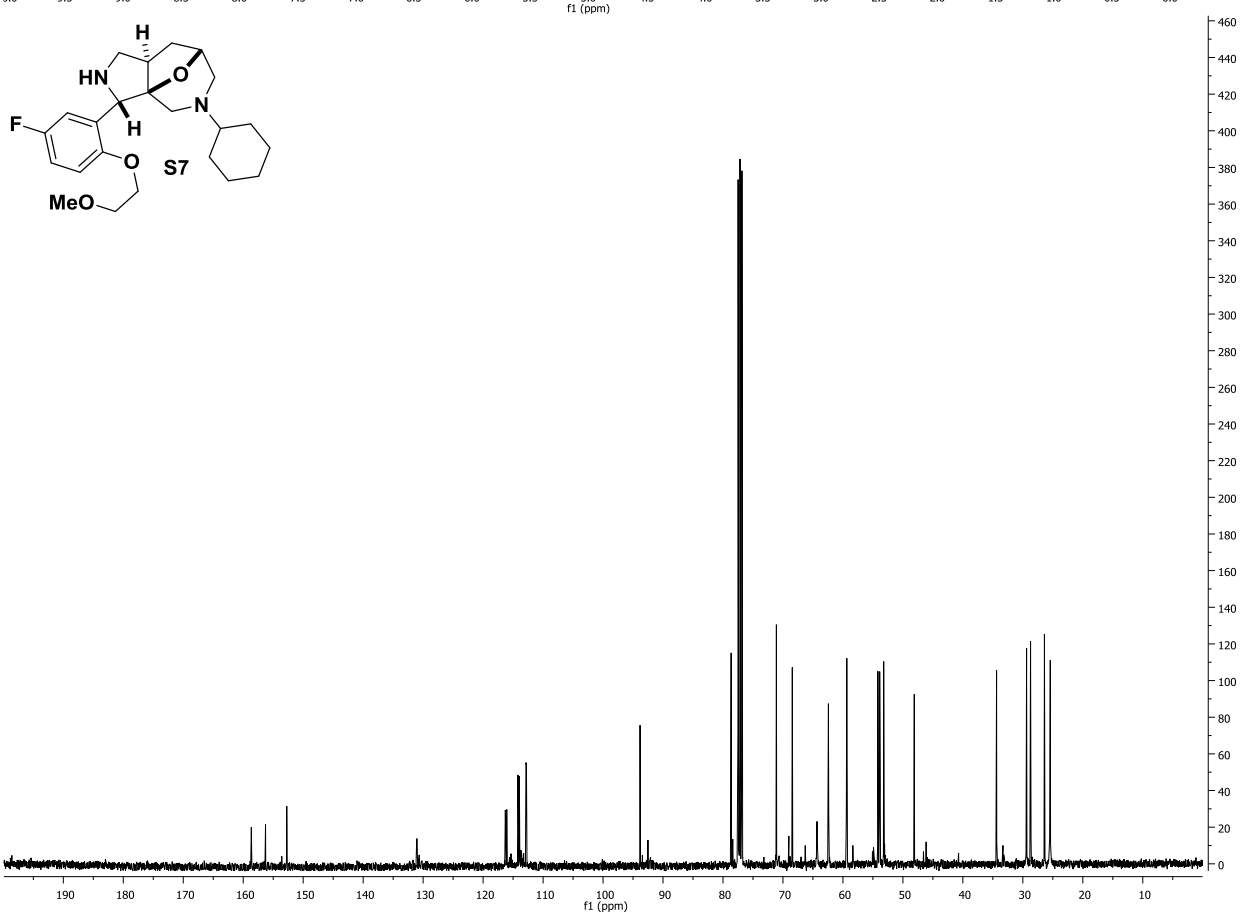

H
HN
O
NMe
H
OH
S5
1.05
1.00
2.02
1.04
0.94
1.00
1.19
1.11
1.17
1.10
1.07
4.25
1.07
1.00
f1 (ppm)


H
HN
O
NMe
H
OH
S5
f1 (ppm)


H
HN
O
N
H
O
OMe
S6
1.00
1.15
1.03
1.04
2.13
2.21
1.09
2.22
3.42
1.05
1.25
1.36
3.48
2.40
1.27
1.18
1.33
1.09
2.17
2.03
f1 (ppm)

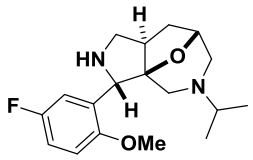

H
HN
O
N
H
O
OMe
S6
f1 (ppm)


H
HN
O
N
F
H
O
S7
MeO


0.91
2.40
0.89
1.00
2.07
2.16
3.04
1.47
2.20
1.22
1.18
1.07
0.89
3.10
6.91
5.79
f1 (ppm)

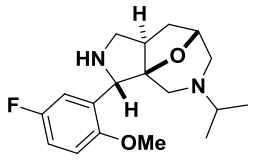
H
HN
O
N
F
H
O
S7
MeO

f1 (ppm)


H
HN
O
N
F
H
OMe

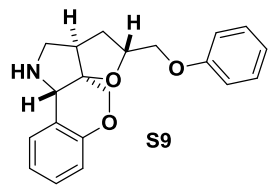
S8

1.11
1.01
1.00
0.95
1.01
3.04
0.90
3.03
2.10
1.12
3.11
1.15
6.27
f1 (ppm)


H
HN
O
N
F
H
OMe

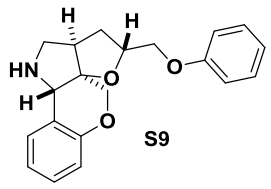
S8

f1 (ppm)


H
H
HN
O
O
H
O

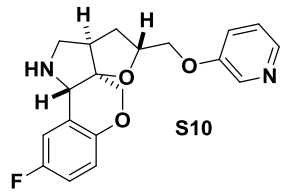
S9

1.03
2.12
1.05
5.09
0.97
1.96
2.95
1.00
2.00
1.33
2.32
f1 (ppm)


H
H
HN
O
O
H
O

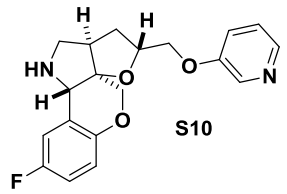
S9

f1 (ppm)


H
H
HN
O
O
H
O
F

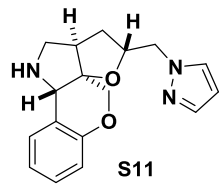
S10

1.02
1.02
3.13
2.16
0.93
0.95
4.23
1.22
1.44
1.10
1.00
1.05
1.02
f1 (ppm)


H
H
HN
O
O
H
O
F

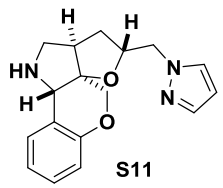
S10

f1 (ppm)


H
H
HN
O
N
N
H
O

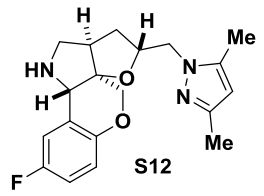
S11

6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
2.00
1.00
1.01
1.00
1.00
0.99
1.02
2.13
1.97
1.04
1.03
1.07
1.05
1.33
2.03
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


H
H
HN
O
N
N
H
O

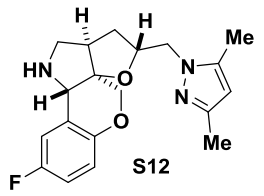
S11

1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H
H
Me
HN
O
N
H
N
O
Me
F

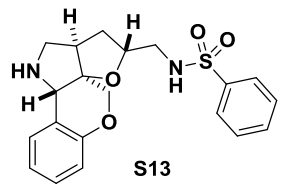
S12

1.07
2.04
0.97
1.00
2.10
2.01
0.97
1.07
1.13
1.25
1.18
3.13
3.38
2.27
f1 (ppm)

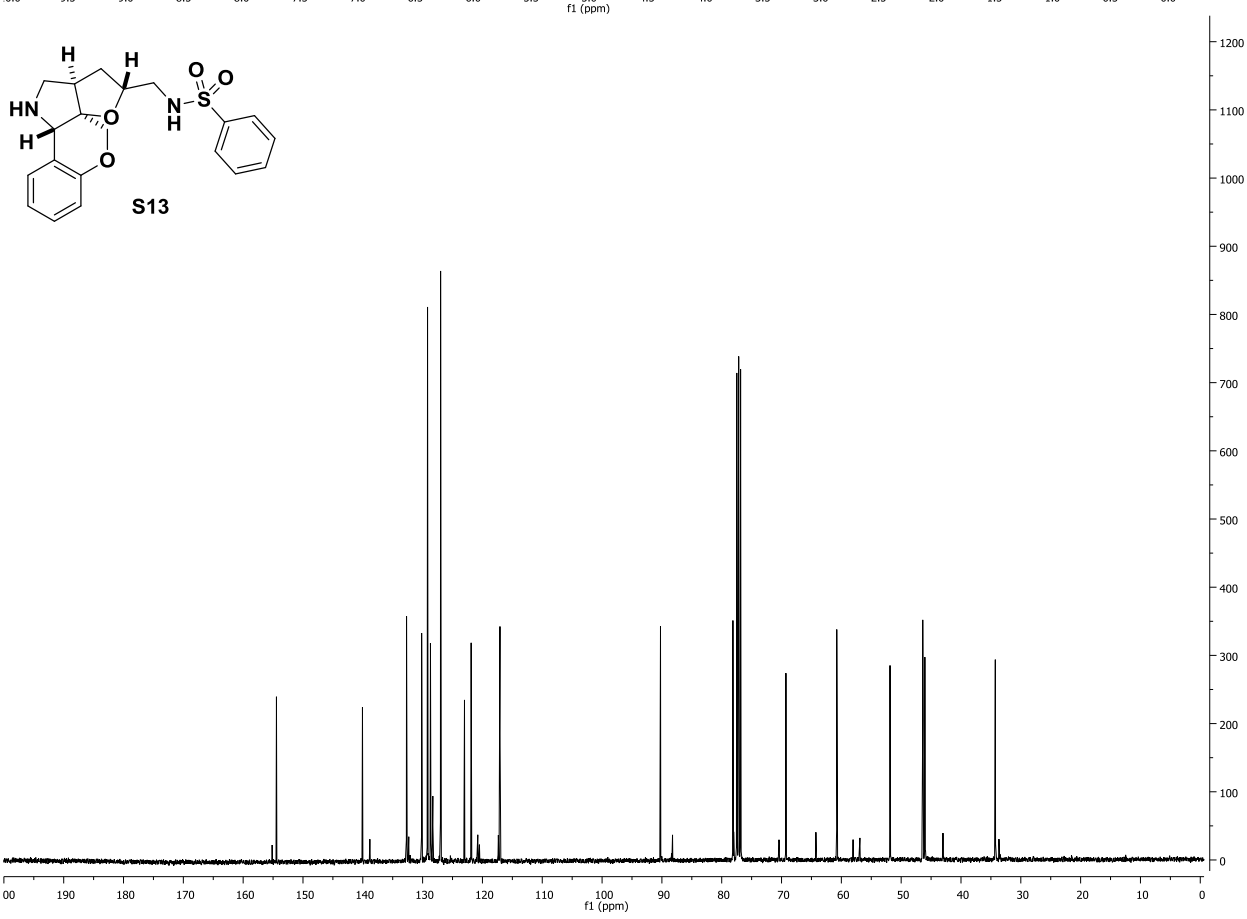

H
H
Me
HN
O
N
H
N
O
Me
F

S12

f1 (ppm)


H
H
HN
H
O
O
N
H
O
O
S

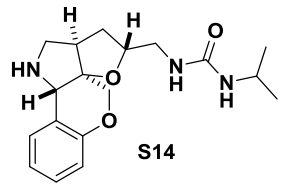
S13


2.21
1.16
2.26
0.98
1.99
1.16
0.99
0.75
1.22
1.00
1.93
2.33
1.17
1.00
1.06
0.77
1.09
1.09
f1 (ppm)

H
H
HN
H
O
O
N
H
O
O
S

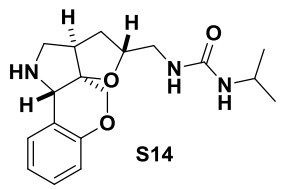
S13

f1 (ppm)


H
H
HN
O
N
H
N
H
H
O
O

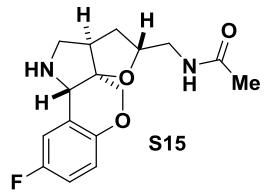
S14

0.98
1.10
1.13
1.00
1.06
1.02
1.06
1.16
0.96
1.74
1.10
1.08
1.08
1.01
1.15
1.44
2.17
3.09
3.34
f1 (ppm)

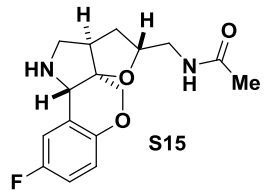

H
H
HN
O
N
H
N
H
H
O
O

S14

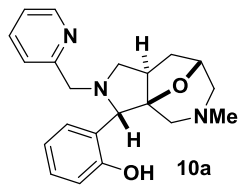
f1 (ppm)


H
H
O
HN
O
N
H
Me
H
O
S15
F

45000
40000
35000
30000
25000
20000
15000
10000
5000
0
0.94
1.90
0.93
1.00
1.01
1.98
1.15
1.01
0.98
0.99
0.99
1.54
2.89
1.98
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

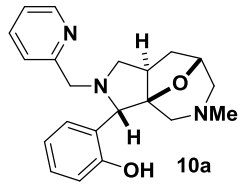

H
H
O
HN
O
N
H
Me
H
O
S15
F

1100
1000
900
800
700
600
500
400
300
200
100
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


N
H
N
O
NMe
H
OH

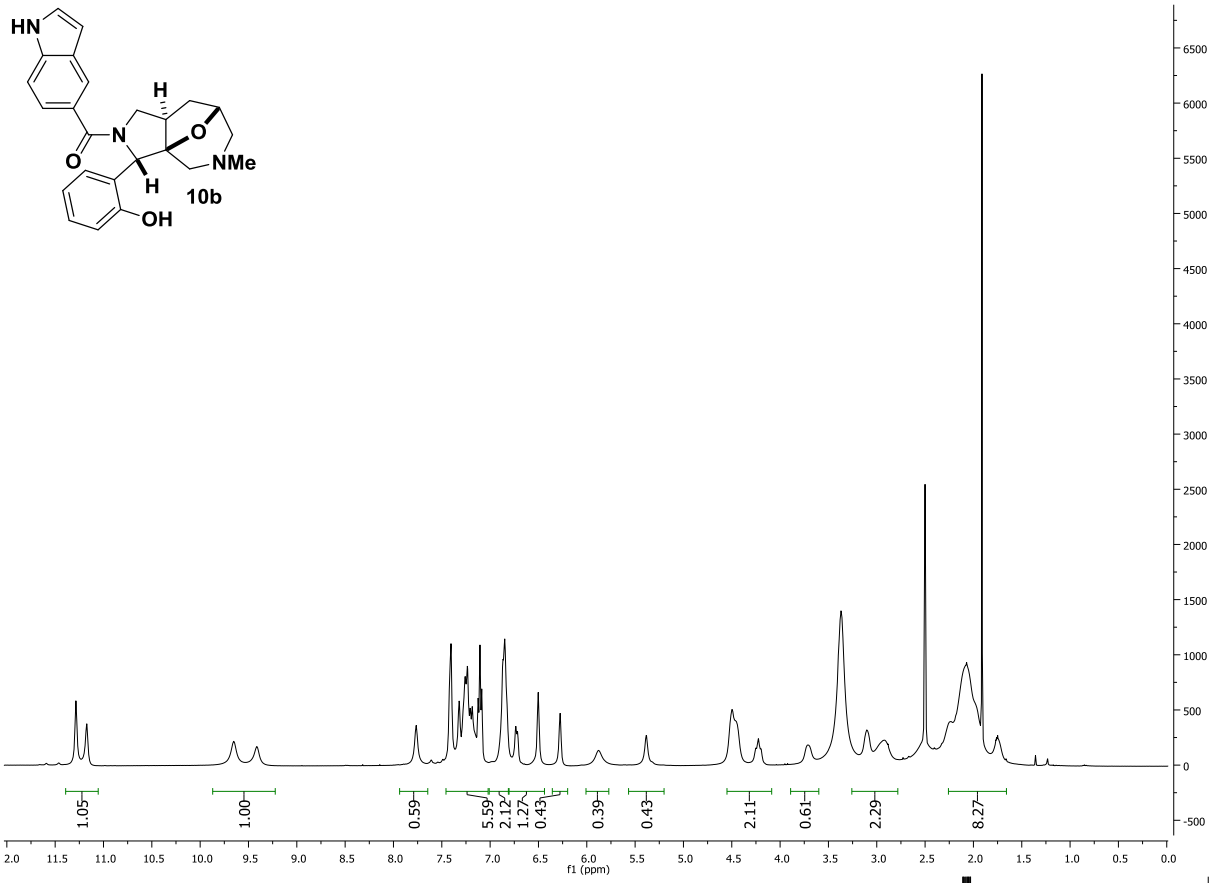
10a

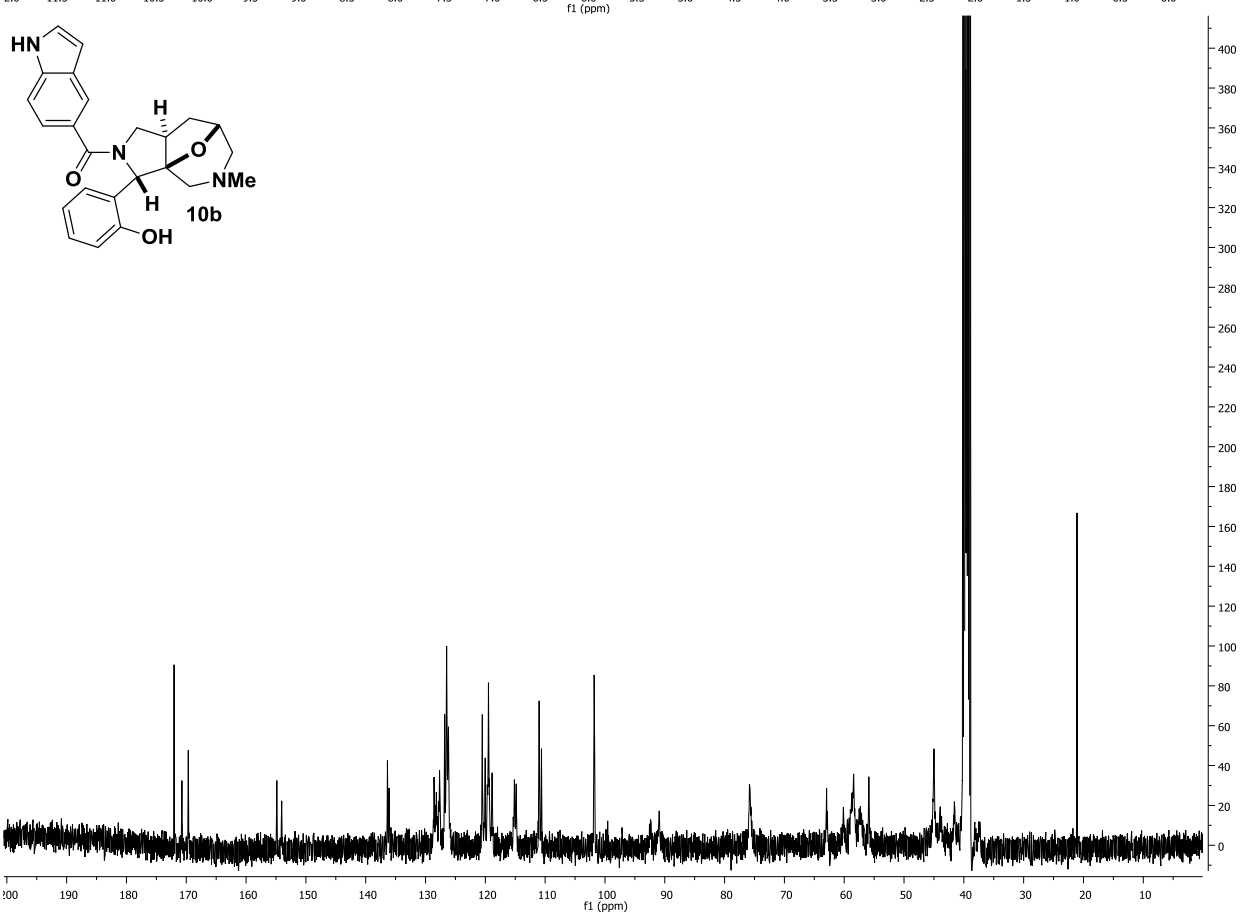
1.00
1.04
1.19
2.10
1.04
2.03
1.06
1.04
1.03
1.07
1.02
1.02
1.05
1.01
1.14
1.10
3.11
1.37
1.06
1.09
f1 (ppm)

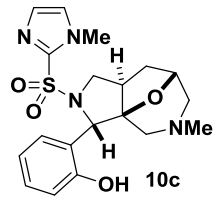

N
H
N
O
NMe
H
OH

10a

f1 (ppm)

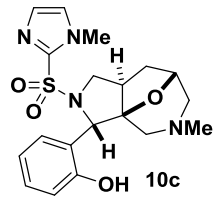

HN
H
N
O
O
NMe
H
OH
10b
1.05
1.00
0.59
5.59
2.12
1.27
0.43
0.39
0.43
2.11
0.61
2.29
8.27
f1 (ppm)


HN
H
N
O
O
NMe
H
OH
10b
f1 (ppm)


N
NMe
H
O
S
O
N
O
NMe
H
OH

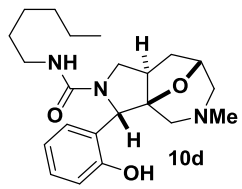
10c

25000
20000
15000
10000
5000
0
1.08
2.07
3.05
0.80
1.36
1.29
3.23
1.16
0.97
1.00
3.00
3.32
1.99
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


N
NMe
H
O
S
O
N
O
NMe
H
OH

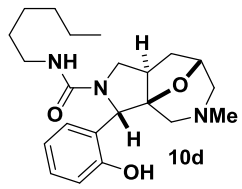
10c

500
450
400
350
300
250
200
150
100
50
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H
NH
O
N
O
NMe
H
OH

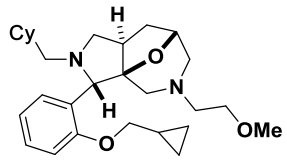
10d

0.58
1.00
1.04
1.04
1.13
0.59
1.05
1.01
1.04
0.98
2.05
1.25
1.10
3.32
3.61
1.36
9.02
3.34
f1 (ppm)


H
NH
O
N
O
NMe
H
OH

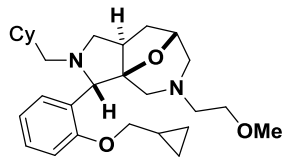
10d

f1 (ppm)


H
Cy
N
O
N
H
OMe
O

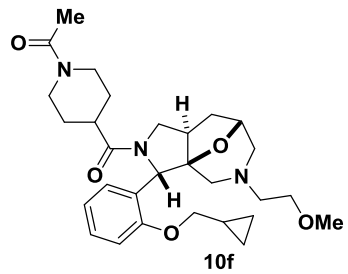
10e

13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
1.00
1.08
1.01
1.06
1.08
0.83
1.10
1.13
0.95
2.05
3.36
1.07
1.13
2.25
1.35
1.24
5.51
3.27
2.19
2.33
1.19
3.02
2.12
2.24
2.25
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


H
Cy
N
O
N
H
OMe
O

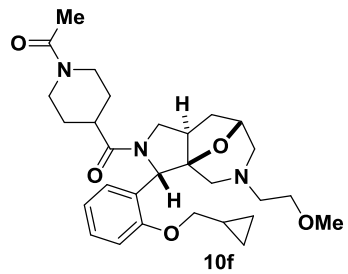
10e

350
300
250
200
150
100
50
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


Me
O
N
H
N
O
O
N
H
O
OMe

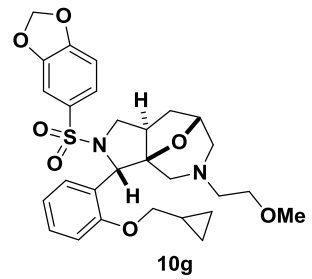
10f

4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
1.00
1.02
1.35
1.24
0.66
2.24
1.90
1.32
1.37
0.51
0.98
2.33
3.24
1.54
1.09
3.14
3.45
6.01
3.21
1.56
0.39
2.61
2.35
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

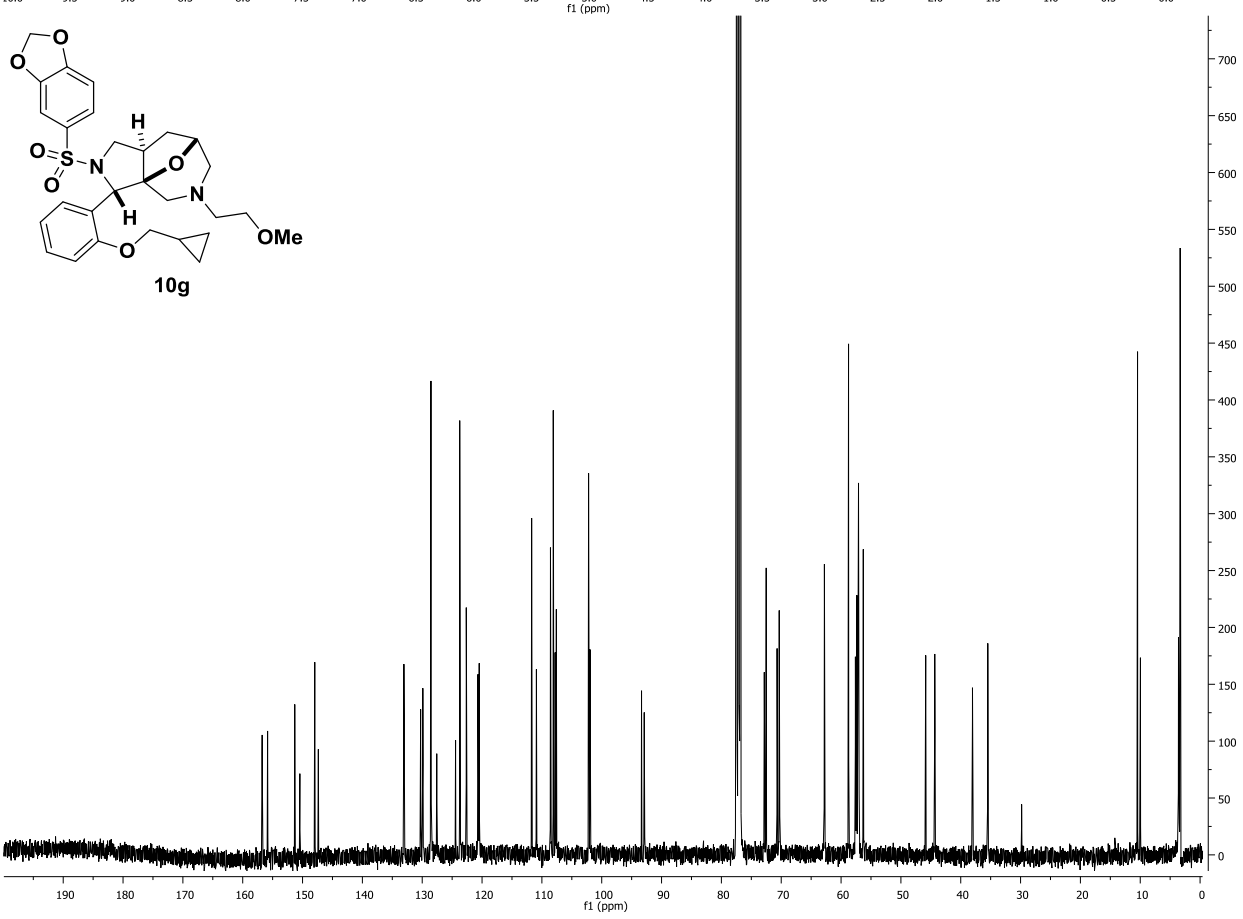

Me
O
N
H
N
O
O
N
H
O
OMe

10f

300
250
200
150
100
50
0
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
H
O
S
N
O
O
N
H
OMe
O

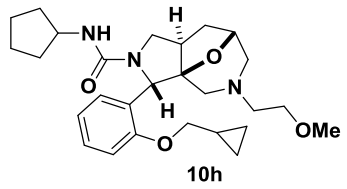
10g


1.38
2.37
4.04
2.17
0.84
1.00
2.47
1.26
5.87
1.39
8.01
2.02
1.58
2.20
2.19
f1 (ppm)

O
O
H
O
S
N
O
O
N
H
OMe
O

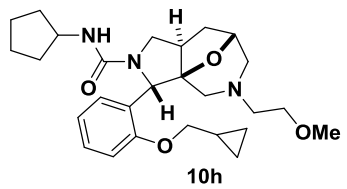
10g

f1 (ppm)


NH
O
N
H
O
N
H
O
OMe

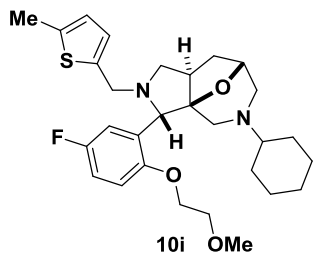
10h

1.09
0.80
1.02
0.83
0.73
1.00
1.02
0.81
2.80
3.10
3.43
0.72
1.01
5.10
1.73
1.25
1.05
1.03
6.15
0.97
2.03
2.02
f1 (ppm)

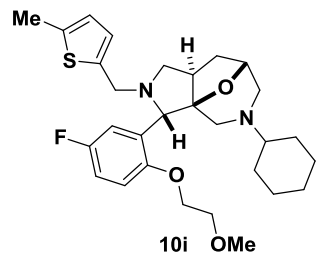

NH
O
N
H
O
N
H
O
OMe

10h

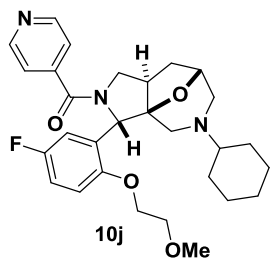
f1 (ppm)


Me
S
H
N
O
N
F
H
O
10i
OMe

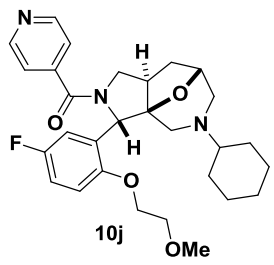
1.00
1.13
1.08
1.05
1.04
1.06
3.04
3.31
3.13
1.48
1.10
1.06
1.52
3.60
1.24
1.33
2.10
1.34
3.80
2.44
5.40
f1 (ppm)


Me
S
H
N
O
N
F
H
O
10i
OMe

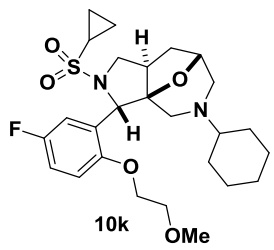
f1 (ppm)


N
H
O
N
O
F
H
O
10j
OMe

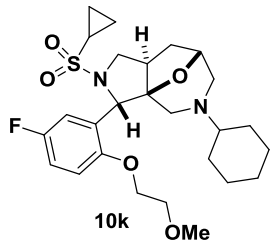
0.75
1.53
0.82
3.28
1.62
0.71
1.34
1.25
1.57
1.17
1.29
4.03
2.82
1.50
1.22
1.96
1.59
0.96
1.62
6.37
6.27
f1 (ppm)


N
H
O
N
O
F
H
O
10j
OMe

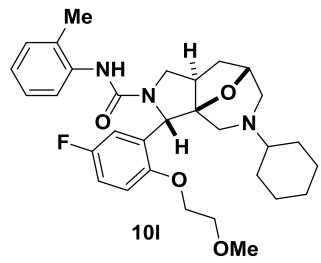
f1 (ppm)


O
O
S
N
H
O
N
F
H
O
10k
OMe

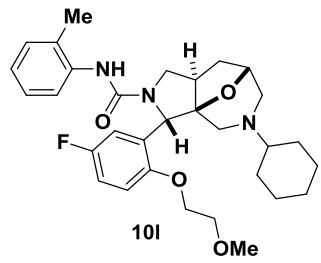
0.79
1.05
0.95
0.78
1.00
2.05
1.10
2.42
3.20
1.24
0.80
0.99
1.83
0.97
1.16
1.47
0.82
1.05
3.12
2.02
7.08
2.07
f1 (ppm)


O
O
S
N
H
O
N
F
H
O
10k
OMe

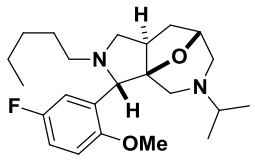
f1 (ppm)


Me
NH
H
N
O
O
N
F
H
O
10l
OMe

1.00
1.09
5.26
0.99
0.85
1.03
3.09
2.10
0.97
3.00
0.83
3.92
1.21
1.34
2.16
6.01
2.36
5.42
f1 (ppm)

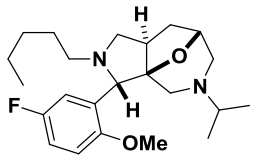

Me
NH
H
N
O
O
N
F
H
O
10l
OMe

f1 (ppm)


H
N
O
N
F
H
OMe

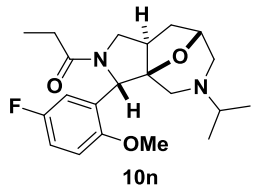
10m

1.00
1.03
1.03
1.01
1.02
3.20
1.02
0.99
4.15
1.10
1.15
2.05
1.34
1.21
2.10
4.32
9.47
f1 (ppm)

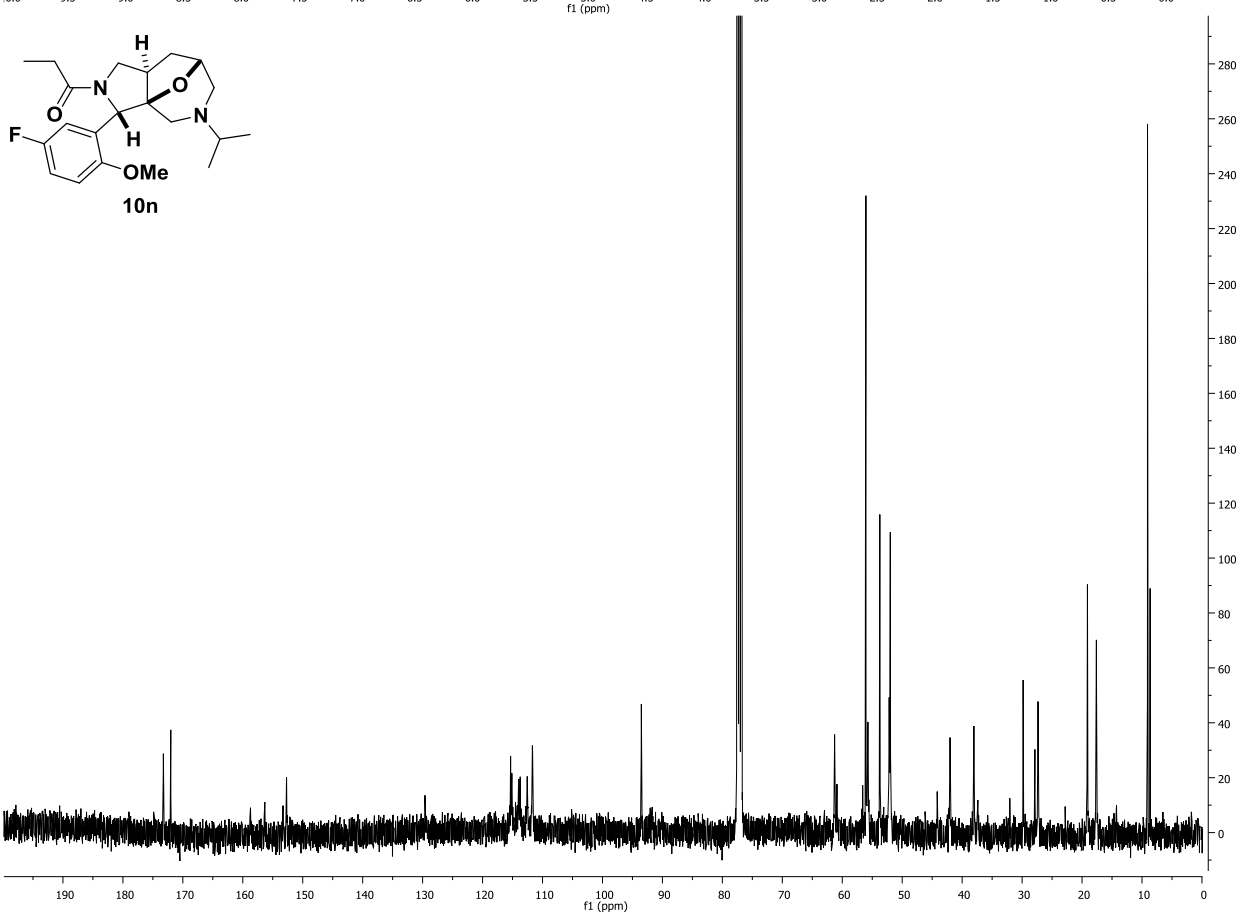

H
N
O
N
F
H
OMe

10m

f1 (ppm)


H
N
O
O
F
H
OMe
N

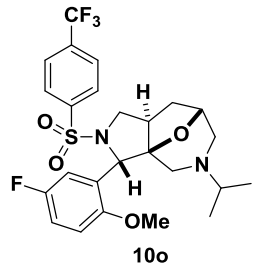
10n


0.74
1.17
0.92
0.73
0.98
1.04
3.08
0.98
0.86
3.32
1.39
0.97
2.00
2.11
1.07
2.43
6.36
f1 (ppm)

H
N
O
O
F
H
OMe
N

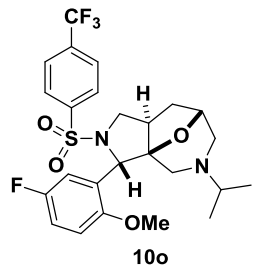
10n

f1 (ppm)


CF3
H
O
S
N
O
O
N
F
H
OMe

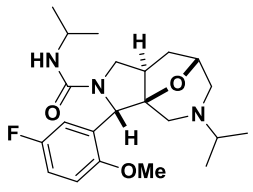
10o

2.11
2.14
1.26
2.44
0.98
1.02
1.19
3.48
0.83
2.04
1.18
2.19
2.52
1.17
0.96
7.04
f1 (ppm)


CF3
H
O
S
N
O
O
N
F
H
OMe

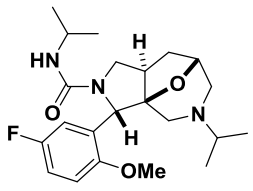
10o

f1 (ppm)


HN
H
N
O
O
F
H
OMe

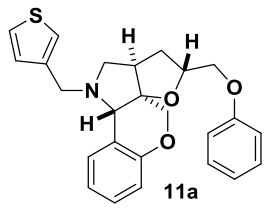
10p

1.14
2.00
0.89
1.07
1.01
0.91
3.12
1.96
1.00
0.94
3.24
2.05
2.00
3.27
9.63
f1 (ppm)


HN
H
N
O
O
F
H
OMe

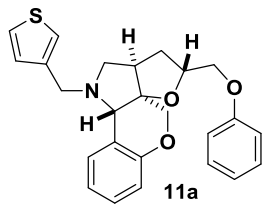
10p

f1 (ppm)


S
H
H
N
O
H
O
O

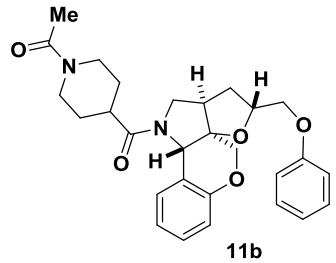
11a

5.45
0.97
6.03
0.98
1.00
3.95
1.89
1.00
1.31
0.97
2.02
f1 (ppm)


S
H
H
N
O
H
O
O

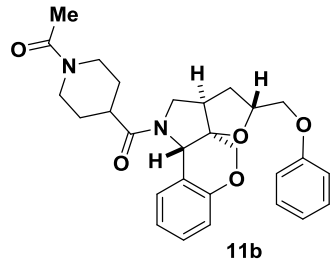
11a

f1 (ppm)


Me
O
N
H
H
N
O
O
H
O
O

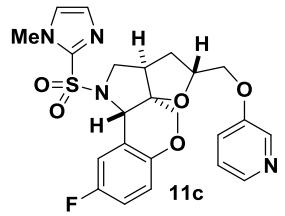
11b

0.50
2.14
0.57
0.57
0.45
4.20
0.51
0.46
0.38
0.65
1.29
5.24
0.51
0.50
2.79
1.53
9.12
f1 (ppm)


Me
O
N
H
H
N
O
O
H
O
O

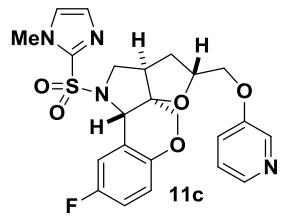
11b

f1 (ppm)


MeN
N
H
H
O
S
N
O
O
H
O
O
N
F

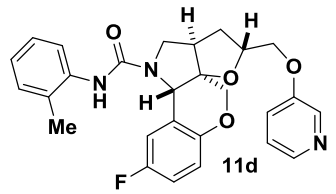
11c

26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
1.00
0.99
1.01
0.69
1.01
1.00
1.01
1.01
1.00
0.99
3.06
2.22
1.04
4.04
1.01
1.60
1.26
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

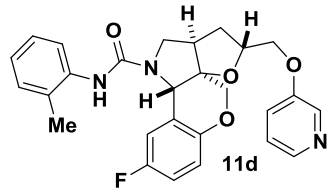

MeN
N
H
H
O
S
N
O
O
H
O
O
N
F

11c

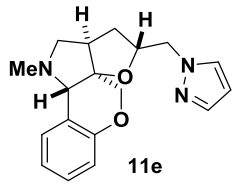
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


H
H
O
N
H
N
O
O
Me
O
N
F
11d

0.95
0.97
0.96
1.00
3.85
1.01
1.00
0.99
0.93
0.97
0.98
1.01
1.98
1.01
1.00
0.99
0.99
1.21
2.99
1.10
f1 (ppm)

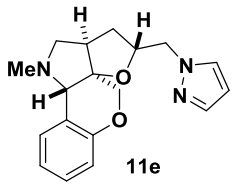

H
H
O
N
H
N
O
O
Me
O
N
F
11d

f1 (ppm)


H
H
MeN
O
N
N
H
O

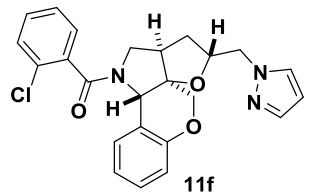
11e

2.12
2.14
2.15
1.03
1.07
2.15
1.06
1.00
1.05
0.99
1.09
3.02
1.37
1.05
1.06
f1 (ppm)


H
H
MeN
O
N
N
H
O

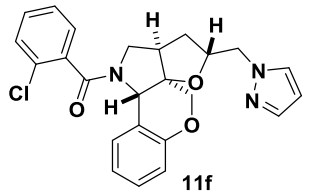
11e

f1 (ppm)


H
H
N
O
H
O
Cl
O
N
N

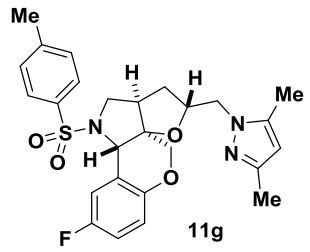
11f

1.03
1.09
1.66
3.29
1.22
1.05
1.02
1.09
1.00
0.85
1.30
1.30
1.26
2.06
2.30
3.27
f1 (ppm)


H
H
N
O
H
O
Cl
O
N
N

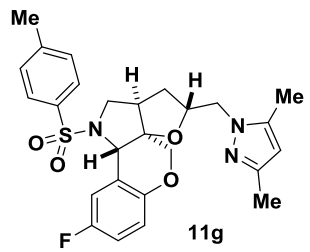
11f

f1 (ppm)


Me
H
H
Me
O
S
N
O
N
O
H
N
O
Me
F

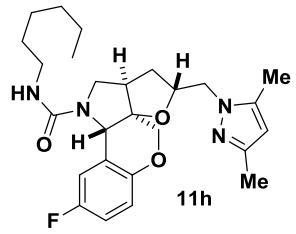
11g

0.76
2.07
1.12
2.04
1.02
1.00
0.93
0.94
2.00
1.00
1.00
1.01
1.05
1.00
1.00
3.01
3.04
3.02
1.27
0.98
f1 (ppm)

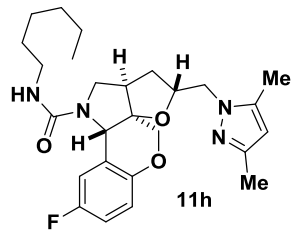

Me
H
H
Me
O
S
N
O
N
O
H
N
O
Me
F

11g

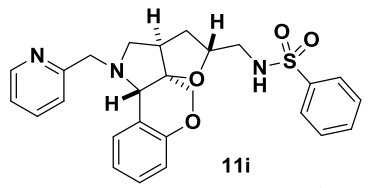
f1 (ppm)


H
H
Me
HN
N
N
O
H
O
N
Me
O
11h
F

0.98
1.00
1.00
0.98
1.00
1.00
2.02
1.01
1.00
1.02
1.11
2.04
1.06
1.02
3.33
3.98
1.26
2.09
6.27
3.09
f1 (ppm)

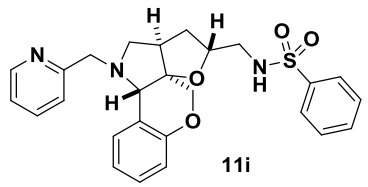

H
H
Me
HN
N
N
O
H
O
N
Me
O
11h
F

f1 (ppm)


H
H
O
O
N
N
S
H
N
H
O
O

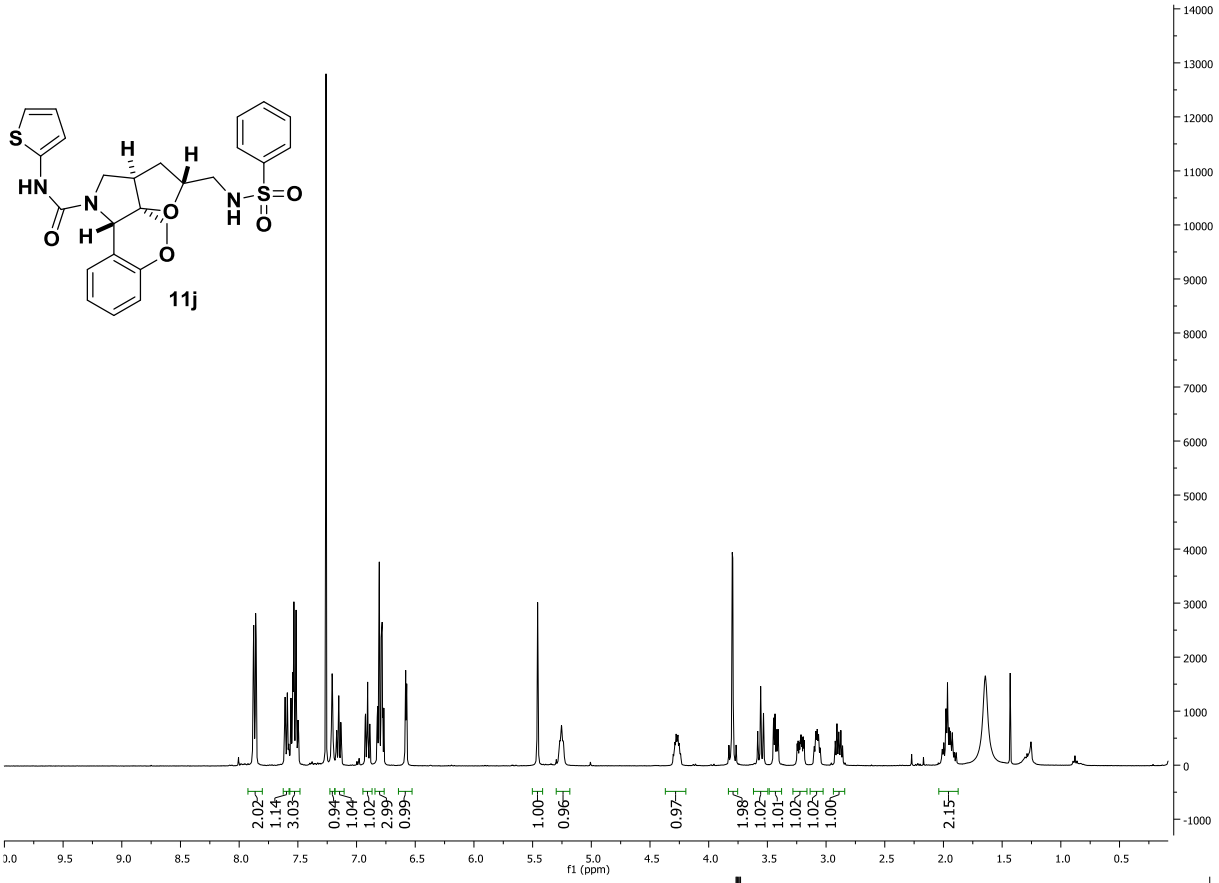
11i

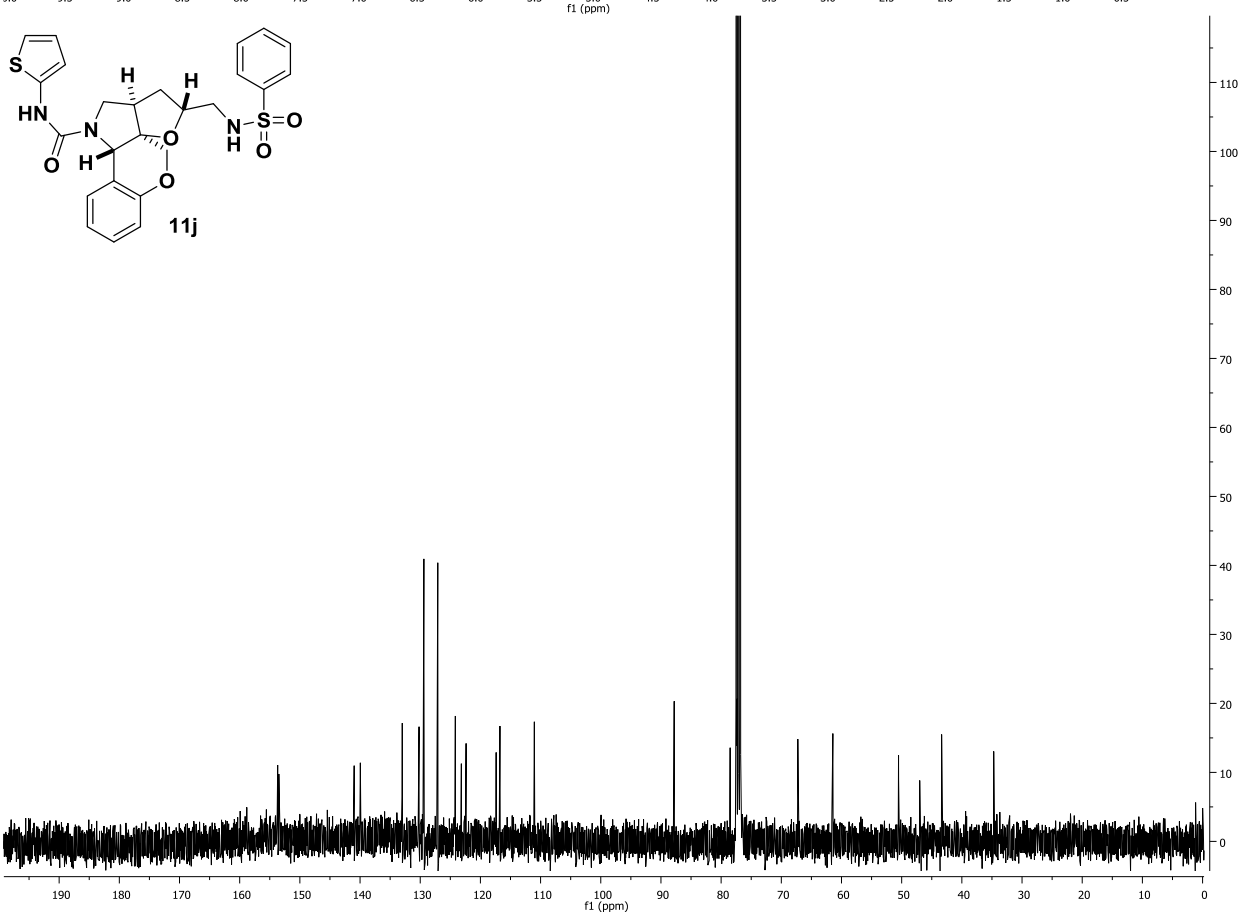
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
0.97
2.04
2.02
2.06
2.04
1.12
1.02
2.06
0.97
2.05
1.02
1.02
1.00
1.02
1.05
1.05
1.05
1.19
1.23
1.08
1.03
f1 (ppm)

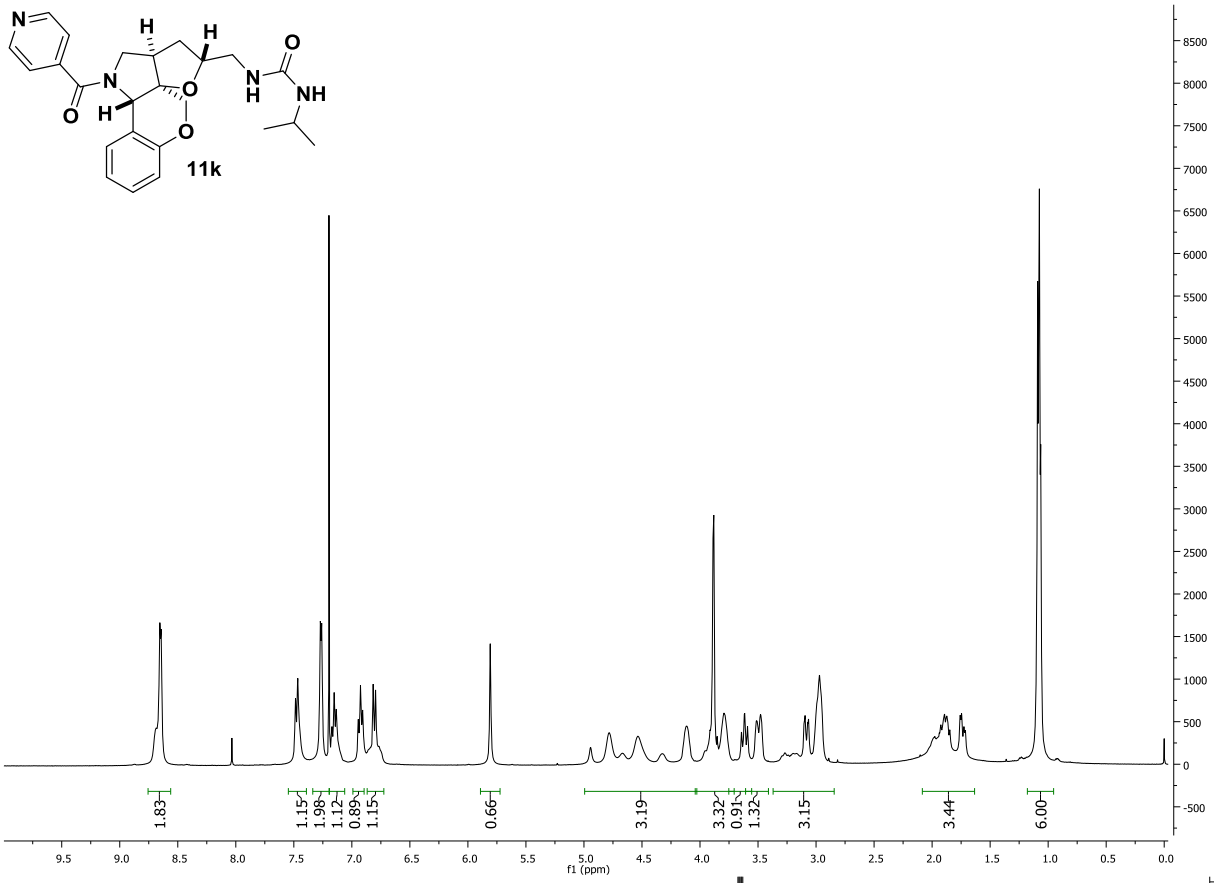

H
H
O
O
N
N
S
H
N
H
O
O

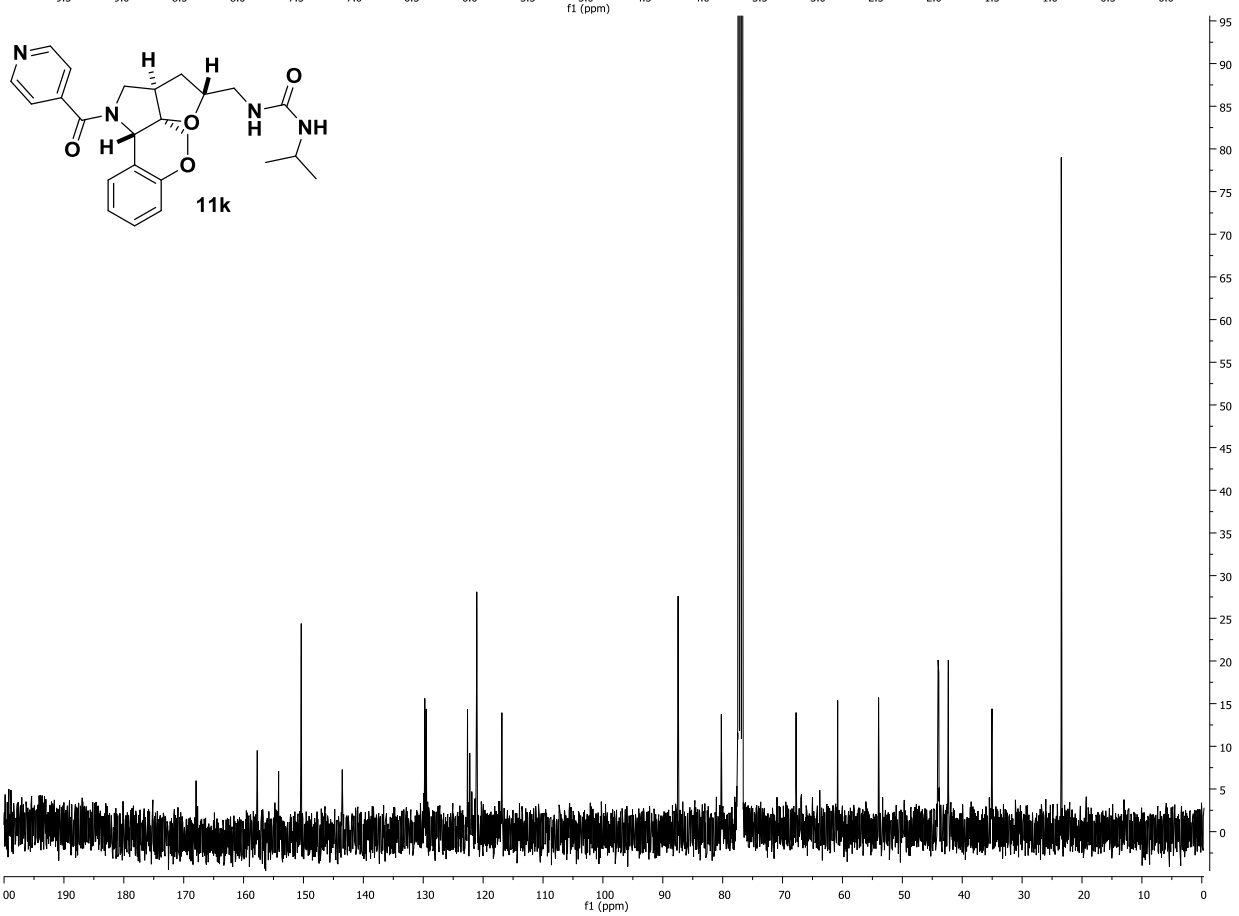
11i

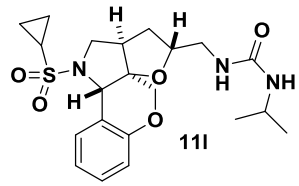
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


11j
2.02
1.14
3.03
0.94
1.04
1.02
2.99
0.99
1.00
0.96
0.97
1.98
1.02
1.01
1.02
1.02
1.00
2.15
f1 (ppm)


11j
f1 (ppm)

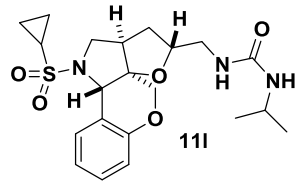

11k
1.83
1.15
1.98
1.12
0.89
1.15
0.66
3.19
3.32
0.91
1.32
3.15
3.44
6.00
f1 (ppm)


11k
f1 (ppm)


H
H
O
O=S
N
N
H
O
NH
H
O

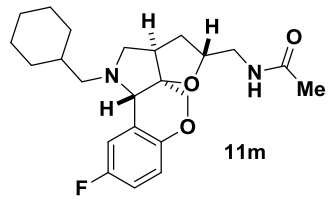
11l

1.00
1.01
1.02
1.00
0.99
0.91
1.68
2.01
1.08
2.04
1.04
2.04
0.99
3.31
1.06
0.78
6.11
1.18
1.11
f1 (ppm)


H
H
O
O=S
N
N
H
O
NH
H
O

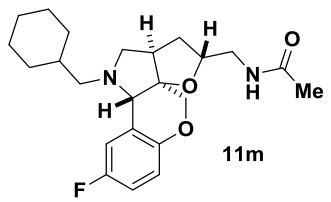
11l

f1 (ppm)


H
H
O
N
H
Me
N
H
O
O
F

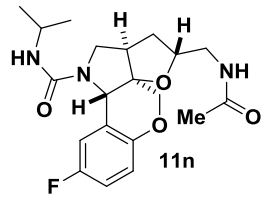
11m

3.00
0.93
1.30
1.09
1.05
1.00
1.02
1.97
1.00
1.00
2.00
2.98
7.29
1.06
3.08
1.03
1.01
f1 (ppm)


H
H
O
N
H
Me
N
H
O
O
F

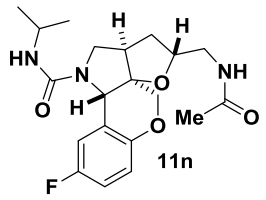
11m

f1 (ppm)


H
H
HN
N
O
H
O
NH
O
Me
O
F

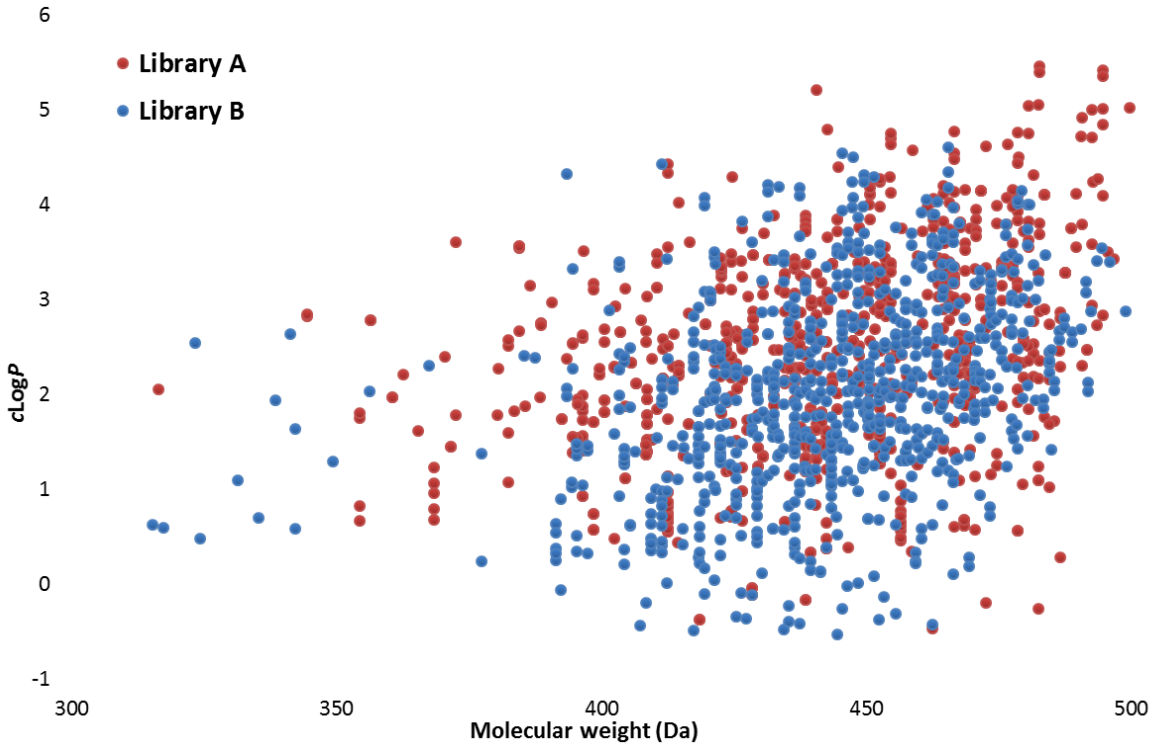
11n

1.00
1.02
0.98
0.96
1.00
1.06
2.06
1.06
1.04
1.02
1.02
1.05
2.04
3.08
1.22
1.36
6.07
f1 (ppm)


H
H
HN
N
O
H
O
NH
O
Me
O
F

11n

f1 (ppm)



Plot of *c*log*P* vs. molecular weight for the compounds produced for the European Lead Factory.