SUPPORTING INFORMATION

Continuous Flow Synthesis of the Antiviral Drug Tecovirimat and Related sp^3-rich Scaffolds

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1. Materials and Methods

Unless otherwise stated, all solvents were purchased from Fisher Scientific, Sigma, and Honeywell and used without further purification. Substrates and reagents were purchased from Fluorochem, Alpha Aesar or Sigma and used as received.

^{1}H-NMR spectra were recorded on 400 MHz, 500 MHz and 600 MHz instruments and are reported relative to residual solvent: $CDCl_3$ (δ 7.26 ppm) and DMSO-d_6 (δ 2.50 ppm). ^{13}C-NMR spectra were recorded on the same instruments (100, 125 and 150 MHz) and are reported relative to $CDCl_3$ (δ 77.16 ppm) and DMSO-d_6 (δ 39.52 ppm). ^{19}F-NMR spectra were recorded on a 400 MHz (376 MHz) spectrometer.

Data for ^{1}H-NMR are reported as follows: chemical shift (δ/ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, sext = sextet, sept = septet, m = multiplet. Data for ^{13}C-NMR are reported in terms of chemical shift (δ/ ppm) and multiplicity (C, CH, CH_2 or CH_3). COSY, HSQC and HMBC experiments were used in the structural assignment.

IR spectra were obtained by use of a Bruker Platinum spectrometer (neat, ATR sampling) with the intensities of the characteristic signals being reported as weak (w, <20% of tallest signal), medium (m, 21-70% of tallest signal) or strong (s, >71% of tallest signal).

High-resolution mass spectrometry was performed using the indicated techniques on a micromass LCT orthogonal time-of-flight mass spectrometer with leucine-enkephalin (Tyr-Gly-Phe-Leu) as an internal lock mass.

Thermal continuous flow experiments were performed using a Vapourtec easy-Scholar system, consisting of peristaltic pumps, a 10 mL reactor coil, PFA tubing (internal diameter = 1.59 mm, outer diameter = 3.18 mm). Total injection volume for synthesis of **4** & **4a** = 11.25 mL, total injection volume for the synthesis of **6** = 52.64 mL. Microwave experiments were performed using a CEM Discover 2.0 system.

2. Synthetic Procedures and Spectroscopic Data

2.1 Synthetic Procedures

Batch Procedure for the Synthesis of Polycyclic Scaffolds **4** & **4a**

Prepared according to modified literature procedure.[1] To a solution of maleic anhydride (4.903 g, 50 mmol, 1 equiv.) or maleimide (4.854 g, 50 mmol, 1 equiv.) in xylene (50 mL, 1 M), cycloheptatriene (6.25 mL, 60 mmol, 1.2 equiv.) was added and the reaction was refluxed for 1 h. Solvent was evaporated *in vacuo* and the resulting residue was purified by rinsing with hot diethyl ether.

Flow Procedure for the Synthesis of Polycyclic Scaffolds **4** & **4a**

The flow system was flushed with MeCN prior to adding reagents. A solution of maleic anhydride (0.981 g, 10 mmol, 1 equiv.) or maleimide (0.971 g, 10 mmol, 1 equiv.) and cycloheptatriene (1.25 mL, 12 mmol, 1.2 equiv.) in MeCN (10 mL, 1 M) was injected at the appropriate flow rate (0.222 mL/min, 45 min residence time) under 8 bar pressure. The resulting reaction stream was collected, the solvent was evaporated *in vacuo* and the resulting residue was purified by rinsing with hot diethyl ether.

Microwave Procedure for the Synthesis of Polycyclic Scaffolds **4** & **4a**

To a solution of maleic anhydride (2.452 g, 25 mmol, 1 equiv.) or maleimide (2.427 g, 25 mmol, 1 equiv.) in toluene (25 mL, 1 M), cycloheptatriene (3.11 mL, 30 mmol, 1.2 equiv.) was added and the reaction was heated to 169 ºC, at 250 W, where the temperature was maintained for 15 min. Solvent was evaporated *in vacuo* and the resulting residue was purified by rinsing with hot diethyl ether.

Flow Procedure for the Synthesis of Tecovirimat, **6**

The flow system was flushed with EtOH prior to adding reagents. A solution of scaffold **4** (1 g, 5.26 mmol, 1 equiv.), hydrazide **5** (1.128 g, 5.52 mmol, 1.05 equiv.) and diisopropylethylamine (0.04 mL, 0.2 mmol, 0.04 equiv.) in EtOH (52.6 mL, 0.1 M) was injected at the appropriate flow rate (0.667 mL/min, 15 min residence time) under 7 bar pressure. The resulting reaction stream was collected, the solvent was evaporated *in vacuo* and the resulting residue was purified by hot recrystallisation from EtOH:H_2O (5:1).

Procedure for the Synthesis of Desymmetrised Scaffolds **7** & **8**

Scaffold **4** (2.0 g, 10 mmol, 1 equiv.) was added to a round bottom flask, which was flushed with N_2 and MeOH (50 mL, 0.2 M) was added. The flask was cooled to 0 ºC, and $NaBH_4$ (378 mg, 10 mmol, 1 equiv.) was added. The reaction mixture was stirred at rt for 1 h before being quenched with aq. Sat. NH_4Cl (50 mL). The mixture was extracted with EtOAc and the combined organic layers were washed with brine and dried over Na_2SO_4 and filtered. Solvent was evaporated *in vacuo* and the resulting residue was purified by flash chromatography (EtOAc:hexanes).

Procedure for the Synthesis of Lactone **8** from **7**

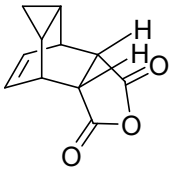
Prepared according to modified literature procedure.[2] Scaffold **8** (1.922 g, 10 mmol, 1 equiv.) was added to a round bottom flask, which was flushed with N_2 and MeOH (50 mL, 0.2 M) was added. The flask was cooled to 0 ºC, and $NaBH_4$ (1.892 g, 50 mmol, 5 equiv.) was added. The reaction mixture was stirred at rt for 1 h before being acidified with a 2.5 M solution of HCl in MeOH (60 mmol, 2.5 M). The reaction was refluxed for 1 h before being quenched with aq. sat. $NaHCO_3$ (150 mL). The mixture was extracted with EtOAc and the combined organic layers were washed with brine and dried over Na_2SO_4 and filtered. Solvent was evaporated *in vacuo* and the resulting residue was purified by flash chromatography (EtOAc:hexanes).

General Procedure for the Synthesis of Hydrazine Derivatives **10** – **11**

To a solution of desymmetrised scaffold **7** (100 mg, 0.52 mmol, 1 equiv.) in MeOH (3.5 mL, 0.15 M), the appropriate phenylhydrazine hydrochloride (0.78 mmol, 1.5 equiv.) (Et_3N (1.5 equiv.) was additionally added if a hydrochloride phenylhydrazine was used) or hydrazine hydrate (0.07 mL of 55% in H_2O, 0.78 mmol, 1.5 equiv.) was added and the mixture was refluxed for 1 h before being quenched with aq. Sat NH_4Cl (5 mL).. The mixture was extracted with EtOAc and the combined organic layers were washed with brine and dried over Na_2SO_4 and filtered. Solvent was evaporated *in vacuo* and the resulting residues of **10a-10d'** were purified by flash chromatography (EtOAc:hexanes). The resulting residue of **11** was rinsed with DCM and used without further purification.

2.2 Spectroscopic Data

Rac-(4*R*,4a*R*,5a*S*,6*S*)-4,4a,5,5a,6,6a-Hexahydro-1*H*-4,6-ethenocyclopropa[*f*]isobenzofuran-1,3(3a*H*)-dione, 4



Chemical Formula: $C_{11}H_{10}O_3$
Exact Mass: 190.0630

Yield: 98% (4.667, 24.5 mmol)

Appearance: White solid

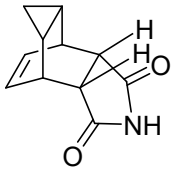
Melting point: 98 – 99 ºC

HR-MS (QTOF) m/z: $[M+H]^+$ Calcd for $C_{11}H_{10}O_3H^+$ 191.0703; Found 191.0703.

^{1}H-NMR (500 MHz, $CDCl_3$) δ/ppm 5.90 – 5.86 (m, 2H), 3.47 – 3.44 (m, 2H), 3.26 – 3.22 (m, 2H), 1.12 (m, 2H), 0.38 – 0.34 (m, 1H), 0.25 (dt, *J* = 5.9, 3.7 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ/ppm 172.5 (2C), 128.6 (2CH), 45.9 (2CH), 33.7 (2CH), 9.6 (2CH), 5.2 (2CH). **IR (neat) ν/cm^{-1}:** 3675 (w), 2987 (m), 2901 (m), 1850 (w), 1762 (m), 1376 (m), 1225 (m), 1072 (s), 909 (s), 600 (m).

This data is consistent with published work.[3]

Rac-(4*R*,4a*R*,5a*S*,6*S*)-4,4a,5,5a,6,6a-Hexahydro-4,6-ethenocyclopropa[*f*]isoindole-1,3(2*H*,3a*H*)-dione, 4a



Chemical Formula: $C_{11}H_{11}NO_2$
Exact Mass: 189.0790

Yield: 96% (4.586 g, 24.0 mmol)

Appearance: White solid

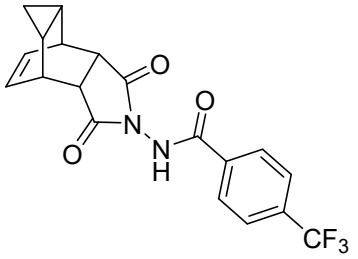
Degradation point: 194 – 196 ºC

HR-MS (QTOF) m/z: $[M+H]^+$ Calcd for $C_{11}H_{11}NO_2H^+$ 190.0863; Found 190.0863.

^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm 10.91 (br s, 1H), 5.73 (dd, *J* = 4.9, 3.3 Hz, 2H), 3.17 – 3.13 (m, 2H), 2.96 – 2.96 (m, 2H), 1.08 – 1.04 (m, 2H), 0.22 (td, *J* = 7.4, 5.3 Hz, 1H), 0.04 (dt, *J* = 5.5, 3.7 Hz, 1H). **^{13}C NMR (101 MHz, DMSO-d_6)** δ/ppm 179.8 (2C), 127.4 (2CH), 46.1 (2CH), 32.7 (2CH), 9.4 (2CH), 4.5 (2CH). **IR (neat) ν/cm^{-1}:** 3675 (m), 3215 (m, br), 2987 (s), 2901 (m), 1755 (m), 1696 (s), 1374 (m), 1177 (s), 1082 (s), 602 (s).

This data is consistent with published work.[4]

Rac-*N*-((4*R*,4a*R*,5a*S*,6*S*)-1,3-Dioxo-3,3a,4,4a,5,5a,6,6a-octahydro-4,6-ethenocyclopropa[*f*]isoindol-2(1*H*)-yl)-4-(trifluoromethyl)benzamide, (tecovirimat) **6**



Chemical Formula: $C_{19}H_{15}F_3N_2O_3$
Exact Mass: 376.1035

Yield: 86% (1.709 g, 4.5 mmol)

Appearance: White solid

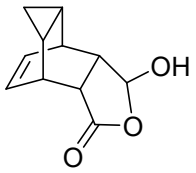
Melting point: 197 – 198 ºC

HR-MS (QTOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{15}F_3N_2O_3H^+$ 377.1108; Found 377.1110.

^{1}H NMR (500 MHz, DMSO-d_6) δ/ppm 11.25 (m, 1H), 8.09 (d, *J* = 7.8 Hz, 2H), 7.93 (d, *J* = 8.3 Hz, 2H), 5.80 (s, 2H), 3.26 (m, 4H), 1.18 (s, 2H), 0.27 (q, *J* = 6.6 Hz, 1H), 0.06 (s, 1H). **^{13}C NMR (126 MHz, DMSO-d_6)** δ/ppm 174.7 (C), 163.5 (C), 163.1 (C), 134.6 (q, *J* = 47 Hz, C), 132.3 (q, *J* = 32 Hz, C), 128.7 (2CH), 127.6 (CH), 127.3 (CH), 125.8 (q, *J* = 3 Hz, 2CH), 123.8 (q, *J* = 273 Hz, CF_3), 43.3 (CH), 42.9 (CH), 33.0 (CH), 32.8 (CH), 9.2 (2CH), 4.1 (CH_2). **^{19}F NMR (470 MHz, DMSO-d_6)** δ/ppm -61.6 (s). **IR (neat) v/cm^{-1}:** 3422 (m, br), 3085 (w), 1790 (m), 1717 (s), 1671 (m), 1558 (m), 1130 (s), 1063 (s), 860 (m), 733 (m).

This data is consistent with published work.[3]

Rac-(4*S*,4a*S*,5a*R*,6*R*)-3-Hydroxy-3,3a,4,4a,5,5a,6,6a-octahydro-1*H*-4,6-ethenocyclopropa[*f*]isobenzofuran-1-one, 7



Chemical Formula: $C_{11}H_{12}O_3$
Exact Mass: 192.0786

Yield: 74% (1.427 g, 7.4 mmol)

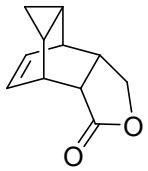
Appearance: White solid

Melting point: 160 – 161 ºC

HR-MS (QTOF) m/z: $[M+H]^+$ Calcd for $C_{11}H_{12}O_3H^+$ 193.0859; Found 193.0860.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm 5.87 – 5.76 (m, 2H), 5.36 (m, 1H), 4.05 (d, *J* = 3.9 Hz, 1H), 3.29 (dtd, *J* = 5.5, 3.5, 1.6 Hz, 1H), 3.13 – 3.10 (m, 1H), 3.07 (dd, *J* = 9.2, 3.7 Hz, 1H), 2.64 (dt, *J* = 9.4, 2.3 Hz, 1H), 1.07 – 0.95 (m, 2H), 0.25 (td, *J* = 7.2, 5.7 Hz, 1H), 0.18 (dt, *J* = 5.9, 3.9 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ/ppm 178.7 (C), 129.6 (CH), 127.9 (CH), 102.2 (CH), 48.8 (CH), 47.0 (CH), 33.7 (CH), 33.2 (CH), 9.6 (CH), 9.4 (CH), 4.4 (CH_2). **IR (neat) v/cm^{-1}:** 3279 (m, br), 3003 (m), 2949 (m), 1721 (s), 1375 (m), 1152 (m), 1077 (m), 920 (s), 839 (s), 673 (s).

Rac-(4*S*,4a*S*,5a*R*,6*R*)-3,3a,4,4a,5,5a,6,6a-Octahydro-1*H*-4,6-ethenocyclopropa-[*f*]isobenzofuran-1-one, 8



Chemical Formula: $C_{11}H_{12}O_2$
Exact Mass: 176.0837

Yield: 87% (792 mg, 4.5 mmol)

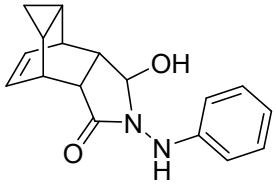
Appearance: White solid

Melting point: 130 – 131 ºC

HR-MS (QTOF) m/z: $[M+H]^+$ Calcd for $C_{11}H_{12}O_2H^+$ 177.0910; Found 177.0910.

^{1}H NMR (500 MHz, $CDCl_3$) δ/ppm 5.88 (t, *J* = 6.8 Hz, 1H), 5.82 (t, *J* = 7.6 Hz, 1H), 4.34 (t, *J* = 9.0 Hz, 1H), 3.86 (dd, *J* = 9.3, 4.4 Hz, 1H), 3.30 – 3.27 (m, 1H), 2.96 – 2.93 (m, 1H), 2.89 (dd, *J* = 10.0, 3.7 Hz, 1H), 2.83 (tt, *J* = 9.8, 3.7 Hz, 1H), 1.03 (tt, *J* = 7.3, 3.9 Hz, 1H), 0.93 (tt, *J* = 7.8, 3.9 Hz, 1H), 0.24 (td, *J* = 7.3, 5.9 Hz, 1H), 0.18 (dt, *J* = 5.9, 3.9 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ/ppm 178.7 (C), 129.9 (CH), 128.0 (CH), 72.0 (CH_2), 46.0 (CH), 39.5 (CH), 34.9 (CH), 33.6 (CH), 9.6 (CH), 9.5 (CH), 4.6 (CH_2). **IR (neat) ν/cm^{-1}:** 3675 (w), 2987 (m), 2901 (m), 1742 (m), 1379 (m), 1185 (m), 1067 (s), 1044 (s), 844 (m), 659 (m).

Rac-(3a*S*,4*S*,4a*S*,5a*R*,6*R*)-3-Hydroxy-2-(phenylamino)-3,3a,4,4a,5,5a,6,6a-octahydro-4,6-ethenocyclopropa[*f*]isoindol-1(2*H*)-one, 10a



Chemical Formula: $C_{17}H_{18}N_2O_2$
Exact Mass: 282.1368

Yield: 84% (122 mg, 0.4 mmol)

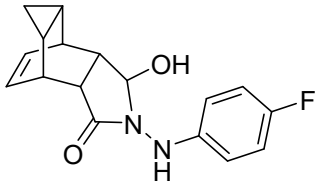
Appearance: White solid

Melting point: 108 – 109 ºC

HR-MS (QTOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{18}N_2O_2H^+$ 283.1441; Found 283.1441.

^{1}H NMR (500 MHz, $CDCl_3$) δ/ppm 7.25 – 7.22 (m, 2H), 6.94 – 6.92 (m, 2H), 6.85 (t, *J* = 7.3 Hz, 1H), 5.91 – 5.88 (m, 1H), 5.85 – 5.82 (m, 1H), 5.44 (s, 1H), 4.96 (dd, *J* = 5.6, 3.7 Hz, 1H), 4.39 (d, *J* = 5.4 Hz, 1H), 3.29 – 3.26 (m, 1H), 3.13 – 3.10 (m, 1H), 3.00 (dd, *J* = 9.3, 3.4 Hz, 1H), 2.68 (dt, *J* = 9.3, 3.4 Hz, 1H), 1.02 – 0.92 (m, 2H), 0.25 (td, *J* = 7.3, 5.6 Hz, 1H), 0.19 (dt, *J* = 5.4, 3.4 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ/ppm 178.3 (C), 148.6 (C), 129.8 (CH), 129.3 (2CH), 128.3 (CH), 120.2 (CH), 113.3 (2CH), 96.7 (CH), 48.0 (CH), 44.4 (CH), 34.0 (CH), 33.6 (CH), 9.6 (CH), 9.4 (CH), 4.7 (CH_2). **IR (neat) ν/cm^{-1}:** 3330 (m), 3289 (m), 3042 (w), 2957 (w), 1733 (s), 1600 (s), 1190 (m), 1168 (m), 747 (s), 717 (s).

Rac-(3a*S*,4*S*,4a*S*,5a*R*,6*R*)-2-((4-Fluorophenyl)amino)-3-hydroxy-3,3a,4,4a,5,5a,6,6a-octahydro-4,6-ethenocyclopropa[*f*]isoindol-1(2*H*)-one, 10b



Chemical Formula: $C_{17}H_{17}FN_2O_2$
Exact Mass: 300.1274

Yield: 89% (139 mg, 0.5 mol)

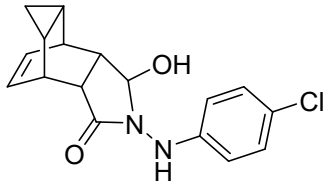
Appearance: White solid

Melting point: 130 – 131 ºC

HR-MS (QTOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{17}FN_2O_2H^+$ 301.1347; Found 301.1347.

^{1}H NMR (500 MHz, $CDCl_3$) δ/ppm 6.95 – 6.91 (m, 2H), 6.88 – 6.85 (m, 2H), 5.90 – 5.87 (m, 1H), 5.84 – 5.81 (m, 1H), 5.43 (s, 1H), 4.93 (dd, *J* = 5.6, 3.7 Hz, 1H), 4.43 (d, *J* = 5.9 Hz, 1H), 3.29 – 3.26 (m, 1H), 3.12 – 3.09 (m, 1H), 3.00 (dd, *J* = 9.5, 3.7 Hz, 1H), 2.64 (dt, *J* = 9.8, 3.4 Hz, 1H), 1.02 – 0.98 (m, 1H), 0.97 – 0.92 (m, 1H), 0.25 (td, *J* = 7.3, 5.6 Hz, 1H), 0.19 (dt, *J* = 5.9, 3.7 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ/ppm 178.2 (C), 157.3 (d, *J* = 238 Hz, CF), 144.8 (C), 129.8 (CH), 128.3 (CH), 115.8 (d, *J* = 23 Hz, 2CH), 114.4 (d, *J* = 8 Hz, 2CH), 96.6 (CH), 47.9 (CH), 44.5 (CH), 34.0 (CH), 33.6 (CH), 9.6 (CH), 9.4 (CH), 4.7 (CH_2). **^{19}F NMR (376 MHz, $CDCl_3$)** δ/ppm -124.8 (m). **IR (neat) ν/cm^{-1}:** 3277 (m), 3043 (w), 3007 (w), 2957 (w), 1736 (s), 1503 (s), 1187 (s), 1094 (m), 829 (s), 714 (s).

Rac-(3a*S*,4*S*,4a*S*,5a*R*,6*R*)-2-((4-Chlorophenyl)amino)-3-hydroxy-3,3a,4,4a,5,5a,6,6a-octahydro-4,6-ethenocyclopropa[*f*]isoindol-1(2*H*)-one, 10c



Chemical Formula: $C_{17}H_{17}ClN_2O_2$
Exact Mass: 316.0979

Yield: 92% (152 mg, 0.5 mmol)

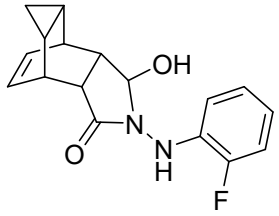
Appearance: White solid

Melting point: 117 – 118 ºC

HR-MS (QTOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{17}ClN_2O_2H^+$ 317.1051; Found 317.1051.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm 7.19 – 7.15 (m, 2H), 6.87 – 6.84 (m, 2H), 5.90 – 5.86 (m, 1H), 5.84 – 5.80 (m, 1H), 5.53 (s, 1H), 4.92 (dd, *J* = 5.9, 3.5 Hz, 1H), 4.44 (d, *J* = 5.9 Hz, 1H), 3.29 – 3.25 (m, 1H), 3.12 – 3.08 (m, 1H), 2.98 (dd, *J* = 9.4, 3.5 Hz, 1H), 2.61 (dt, *J* = 9.4, 3.5 Hz, 1H), 1.02 – 0.92 (m, 2H), 0.27 – 0.22 (m, 1H), 0.19 (dt, *J* = 5.5, 3.5 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ/ppm 178.2 (C), 147.3 (C), 129.8 (CH), 129.2 (2CH), 128.3 (CH), 124.7 (C), 114.5 (2CH), 96.5 (CH), 47.9 (CH), 44.4 (CH), 33.9 (CH), 33.6 (CH), 9.6 (CH), 9.4 (CH), 4.7 (CH_2). **IR (neat) ν/cm^{-1}:** 3367 (m), 3331 (m), 3267 (m), 2926 (m), 1737 (s), 1598 (m), 1487 (s), 1088 (m), 801 (s), 718 (s).

Rac-(3a*S*,4*S*,4a*S*,5a*R*,6*R*)-2-((2-Fluorophenyl)amino)-3-hydroxy-3,3a,4,4a,5,5a,6,6a-octahydro-4,6-ethenocyclopropa[*f*]isoindol-1(2*H*)-one, 10d



Chemical Formula: $C_{17}H_{17}FN_2O_2$
Exact Mass: 300.1274

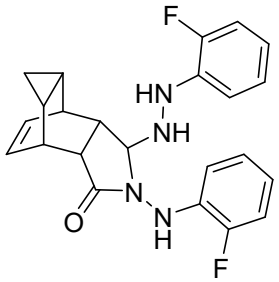
Yield: 72% (112 mg, 0.4 mmol)

Appearance: Pale yellow oil

HR-MS (QTOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{17}FN_2O_2H^+$ 301.1347; Found 301.1348.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm 7.30 -7.26 (m, 1H), 7.08 – 7.04 (m, 1H), 6.98 (ddd, *J* = 11.7, 8.2, 1.4 Hz, 1H), 6.80 – 6.74 (m, 1H), 5.90 (td, *J* = 7.4, 2.0 Hz, 1H), 5.88 – 5.79 (m, 1H), 5.69 (s, 1H), 4.96 (t, *J* = 4.3 Hz, 1H), 4.38 – 4.34 (m, 1H), 3.31 – 3.27 (m, 1H), 3.14 – 3.10 (m, 1H), 3.01 (dd, *J* = 9.8, 3.5 Hz, 1H), 2.67 (dt, *J* = 9.8, 3.5 Hz, 1H), 1.03 – 0.93 (m, 2H), 0.25 (td, *J* = 7.4, 5.9 Hz, 1H), 0.20 (dt, *J* = 5.9, 3.9 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm** 178.0 (C), 150.82 (d, *J* = 240 Hz, CF), 136.8 (d, *J* = 10 Hz, CH), 130.0 (CH), 128.2 (CH), 124.7 (d, *J* = 3 Hz, CH), 119.7 (d, *J* = 7 Hz, CH), 115.1 (CH), 114.9 (d, *J* = 4 Hz, CH), 96.5 (CH), 47.9 (CH), 44.4 (CH), 34.0 (CH), 33.6 (CH), 9.7 (CH), 9.5 (CH), 4.7 (CH_2). **^{19}F NMR (376 MHz, $CDCl_3$)** δ/ppm -134.9 (m). **IR (neat) ν/cm^{-1}:** 3675 (w), 3317 (w), 3259 (w), 2954 (w), 1740 (s), 1618 (m), 1482 (m), 1077 (m), 883 (m), 716 (s).

Rac-(3a*S*,4*S*,4a*S*,5a*R*,6*R*)-2-((2-Fluorophenyl)amino)-3-(2-(2-fluorophenyl)hydrazineyl)-3,3a,4,4a,5,5a,6,6a-octahydro-4,6-ethenocyclopropa[*f*]isoindol-1(2H)-one, 10d'



Chemical Formula: $C_{23}H_{22}F_2N_4O$
Exact Mass: 408.1762

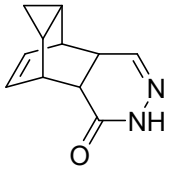
Yield: 18% (38 mg, 0.1 mmol)

Appearance: Pale yellow oil

HR-MS (QTOF) m/z: $[M+Na]^+$ Calcd for $C_{23}H_{22}F_2N_4ONa^+$ 431.1654; Found 431.1655.

^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm 8.01 (s, 1H), 7.33 (td, *J* = 8.6, 1.8 Hz, 1H), 7.11 – 6.97 (m, 5H), 6.73 – 6.61 (m, 3H), 6.06 (t, *J* = 6.8 Hz, 1H), 5.90 (t, *J* = 7.2 Hz, 1H), 5.43 (s, 1H), 4.18 (s, 1H), 3.14 (td, *J* = 4.3, 2.0 Hz, 1H), 3.04 (qt, *J* = 3.9, 2.0 Hz, 1H), 2.61 (dd, *J* = 9.6, 3.3 Hz, 1H), 2.32 (dt, *J* = 9.4, 2.9 Hz, 1H), 1.01 (dq, *J* = 7.8, 3.9 Hz, 1H), 0.90 (dp, *J* = 7.8, 3.7 Hz, 1H), 0.13 (td, *J* = 7.2, 5.3 Hz, 1H), 0.01 (dt, *J* = 5.5, 3.7 Hz, 1H). **^{13}C NMR (101 MHz, DMSO-d_6) δ/ppm** 172.9 (C), 150.0 (d, *J* = 238 Hz, CF), 149.7 (d, *J* = 238 Hz, CF), 138.9 (d, *J* = 10 Hz, C), 134.8 (d, *J* = 11 Hz, C), 129.5 (CH), 128.8 (CH), 124.7 (d, *J* = 3 Hz, CH), 124.5 (d, *J* = 3 Hz, CH), 118.5 (d, *J* = 7 Hz, CH), 117.1 (d, *J* = 7 Hz, CH), 114.9 (d, *J* = 18 Hz, CH), 114.4 (d, *J* = 18 Hz, CH), 114.2 (d, *J* = 4 Hz, CH), 113.7 (d, *J* = 4 Hz, CH), 76.9 (CH), 46.0 (CH), 39.9 (CH), 33.7 (CH), 32.8 (CH), 9.3 (CH), 8.9 (CH), 3.4 (CH_2). **^{19}F NMR (376 MHz, DMSO-d_6)** δ/ppm -133.2 (m), -134.1 (m). **IR (neat) ν/cm^{-1}:** 3677 (w), 3316 (w), 3257 (w), 2954 (m), 1741 (s), 1618 (m), 1481 (m), 1076 (m), 883 (m), 716 (s).

Rac-(5*S*,5a*S*,6a*R*,7*R*)-2,4a,5,5a,6,6a,7,7a-Octahydro-1*H*-5,7-ethenocyclopropa-[*g*]phthalazin-1-one, 11



Chemical Formula: $C_{11}H_{12}N_2O$
Exact Mass: 188.0950

Yield: 97% (95 mg, 0.5 mmol)

Appearance: White solid

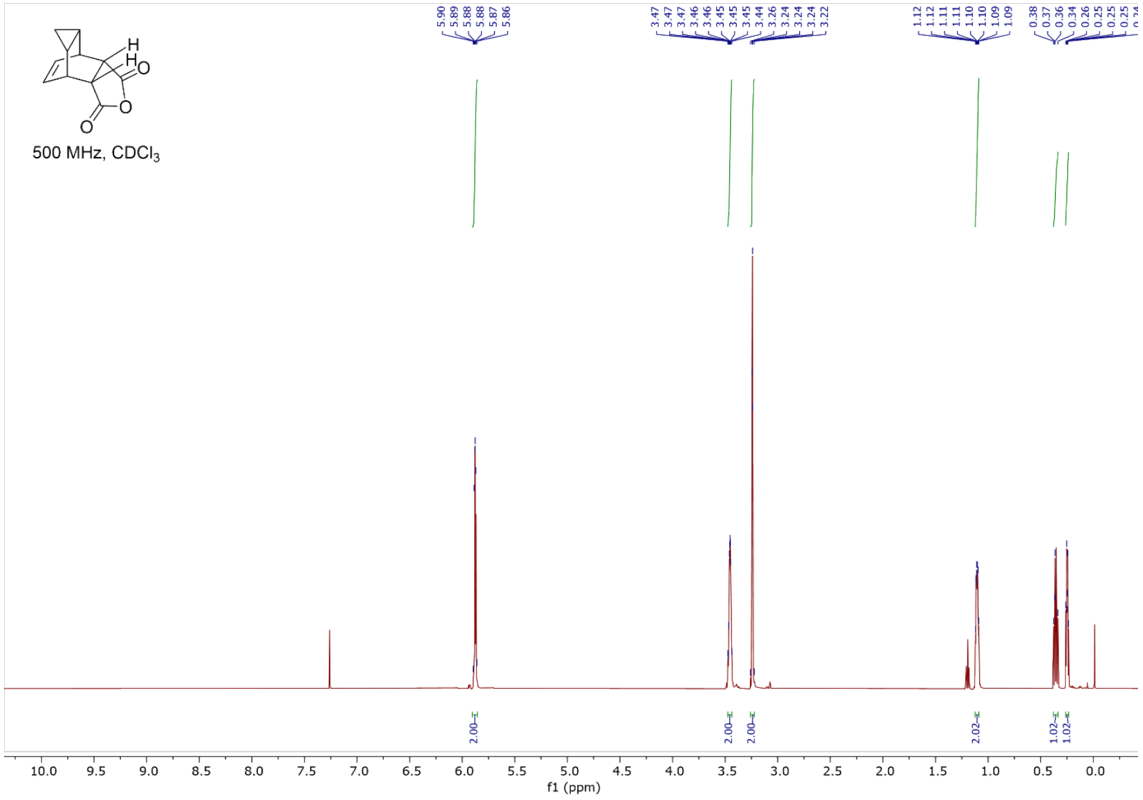
Melting point: 170 – 171 ºC

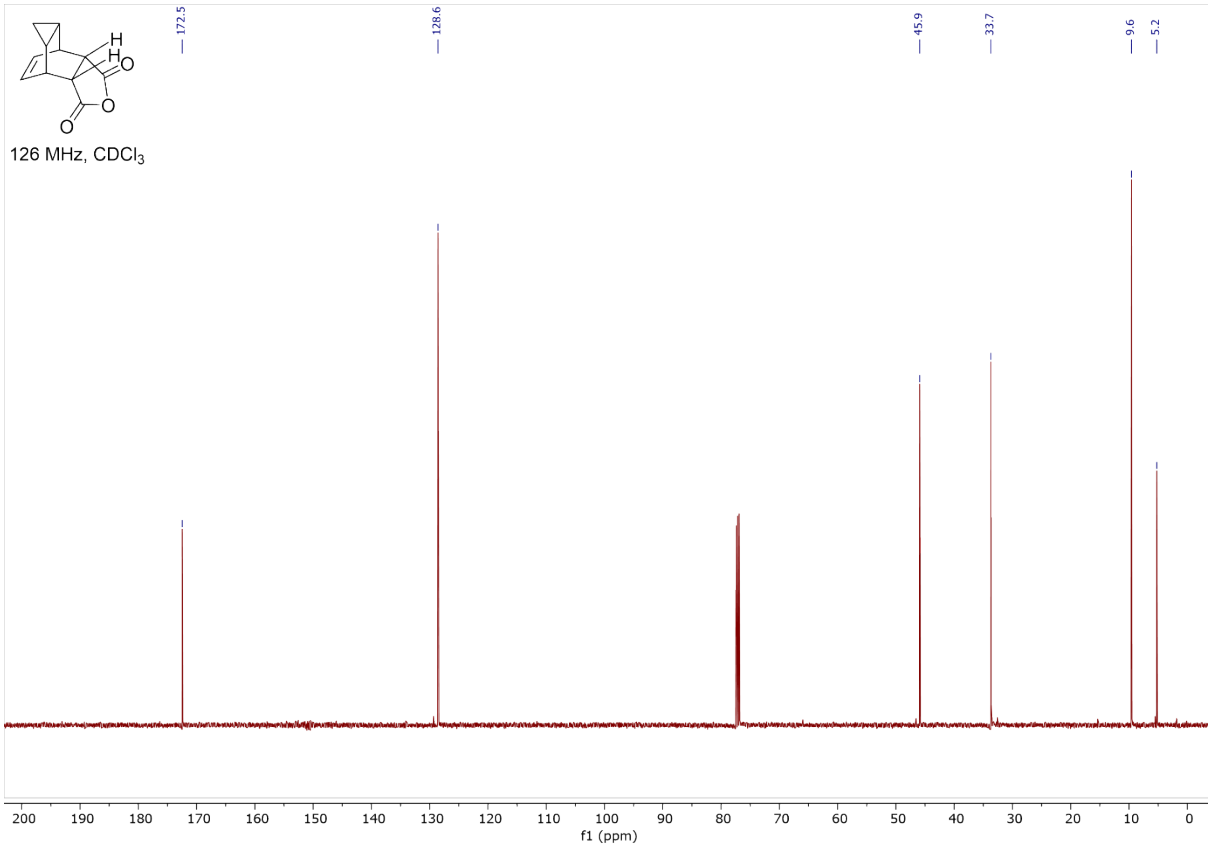
HR-MS (QTOF) m/z: $[M+H]^+$ Calcd for $C_{11}H_{12}N_2OH^+$ 189.1022; Found 189.1024.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm 7.99 (s, 1H), 6.75 (d, *J* = 1.5 Hz, 1H), 5.91 – 5.83 (m, 2H), 3.58 – 3.54 (m, 1H), 3.16 – 3.13 (m, 1H), 2.90 – 2.84 (m, 2H), 1.08 (tt, *J* = 7.6, 3.8 Hz, 1H), 0.96 (tt, *J* = 7.8, 3.8 Hz, 1H), 0.16 (td, *J* = 7.3, 5.7 Hz, 1H), 0.03 (dt, *J* = 5.6, 3.5 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ/ppm 166.8 (C), 145.0 (CH), 129.8 (CH), 129.5 (CH), 42.2 (CH), 41.2 (CH), 34.9 (CH), 34.8 (CH), 9.2 (CH), 8.3 (CH), 1.8 (CH_2). **IR (neat) ν/cm^{-1}:** 3205 (m, br), 3051 (m), 2938 (m), 2897 (m), 1763 (w), 1674 (s), 1183 (w), 1096 (w), 797 (s), 697 (s).

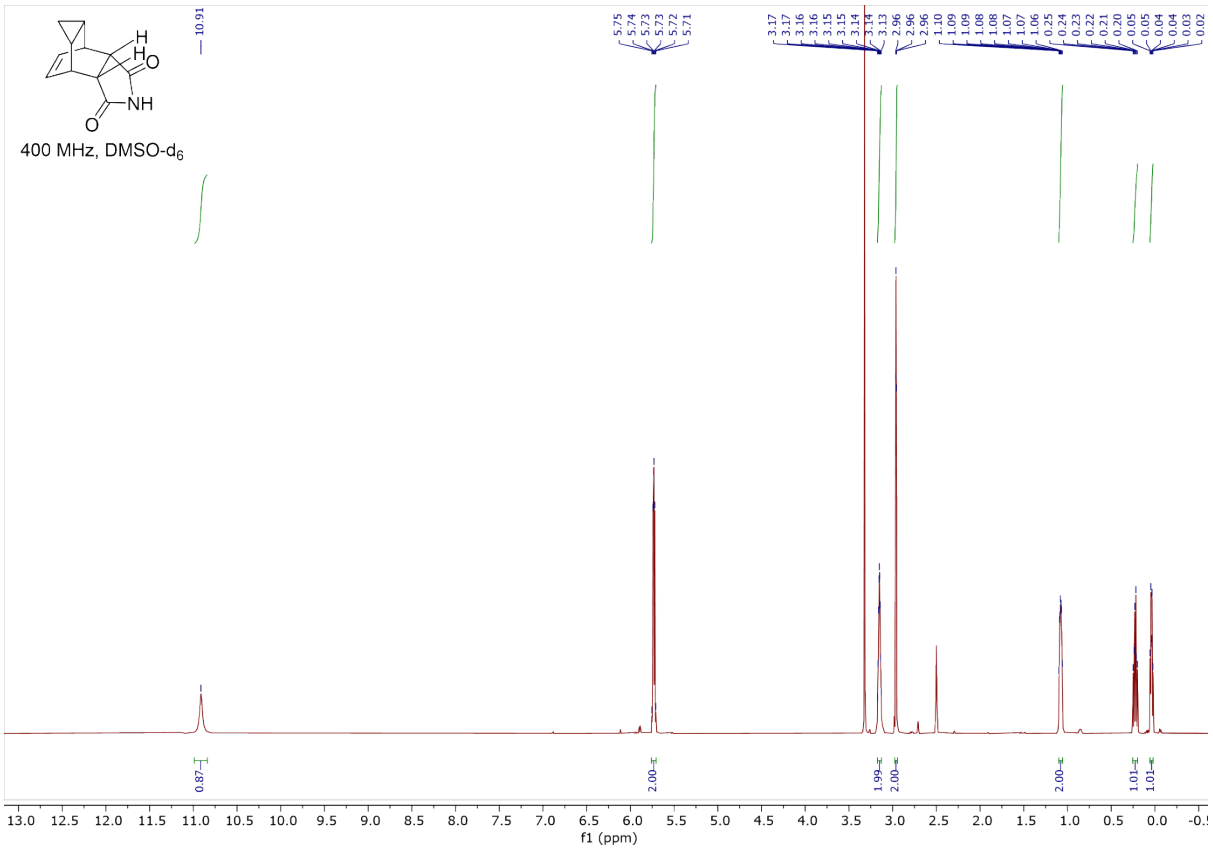
3. Copies of ^{1}H, ^{13}C, and ^{19}F NMR Spectra

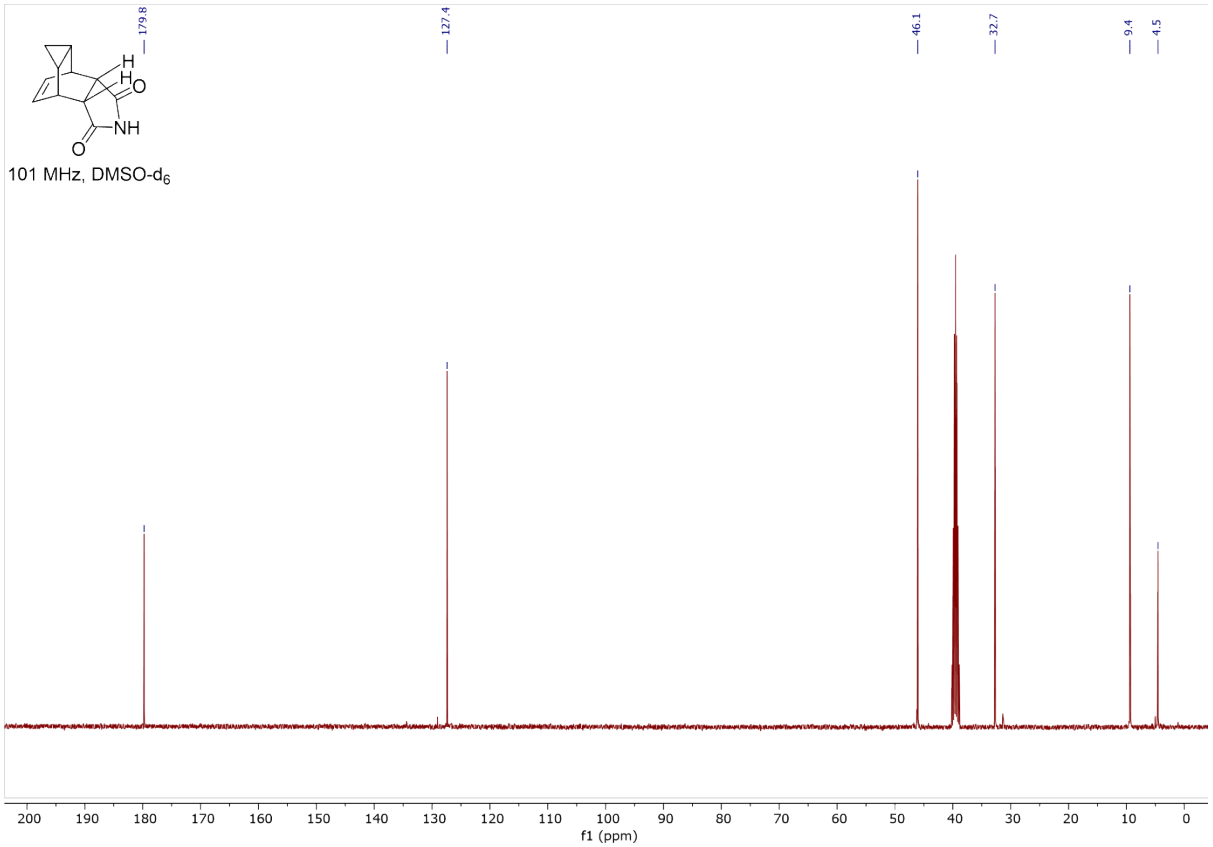
Rac-(4*R*,4a*R*,5a*S*,6*S*)-4,4a,5,5a,6,6a-Hexahydro-1*H*-4,6-ethenocyclopropa-[*f*]isobenzofuran-1,3(3a*H*)-dione, 4



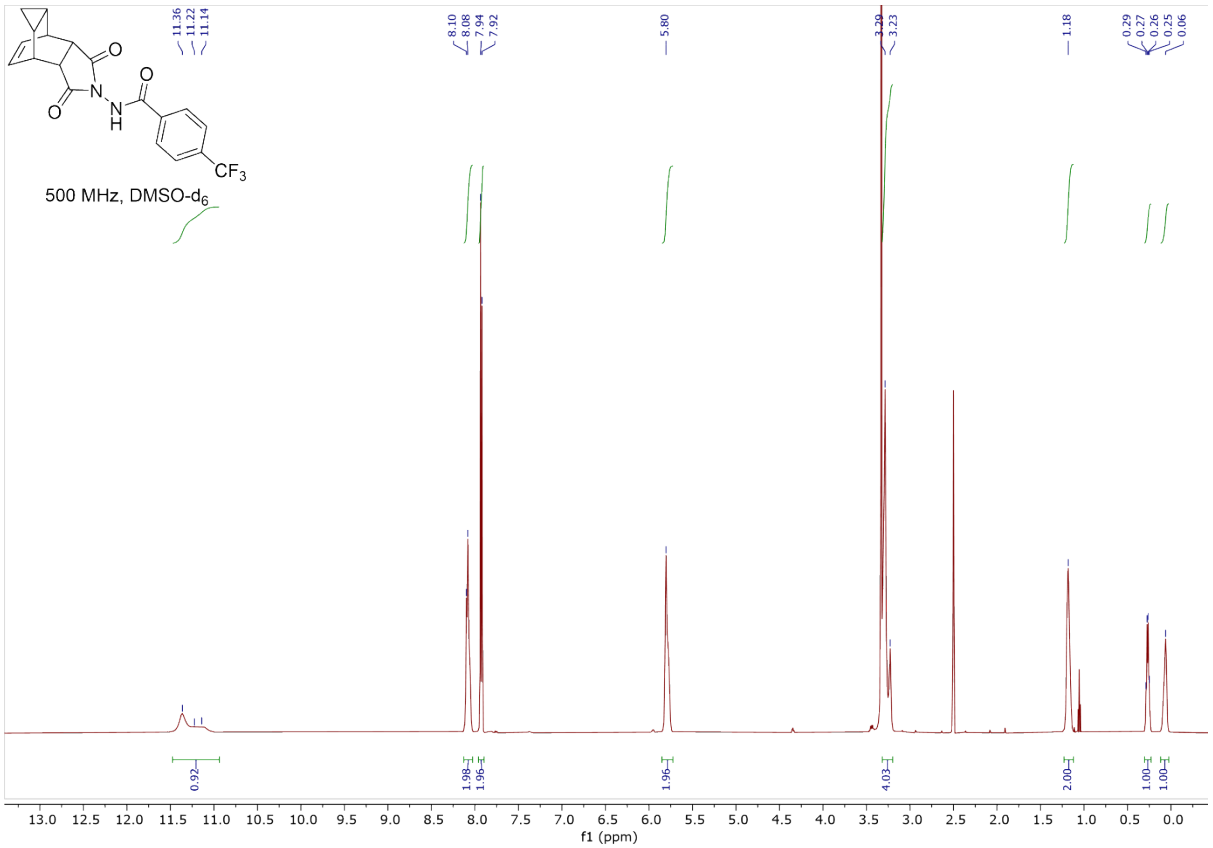


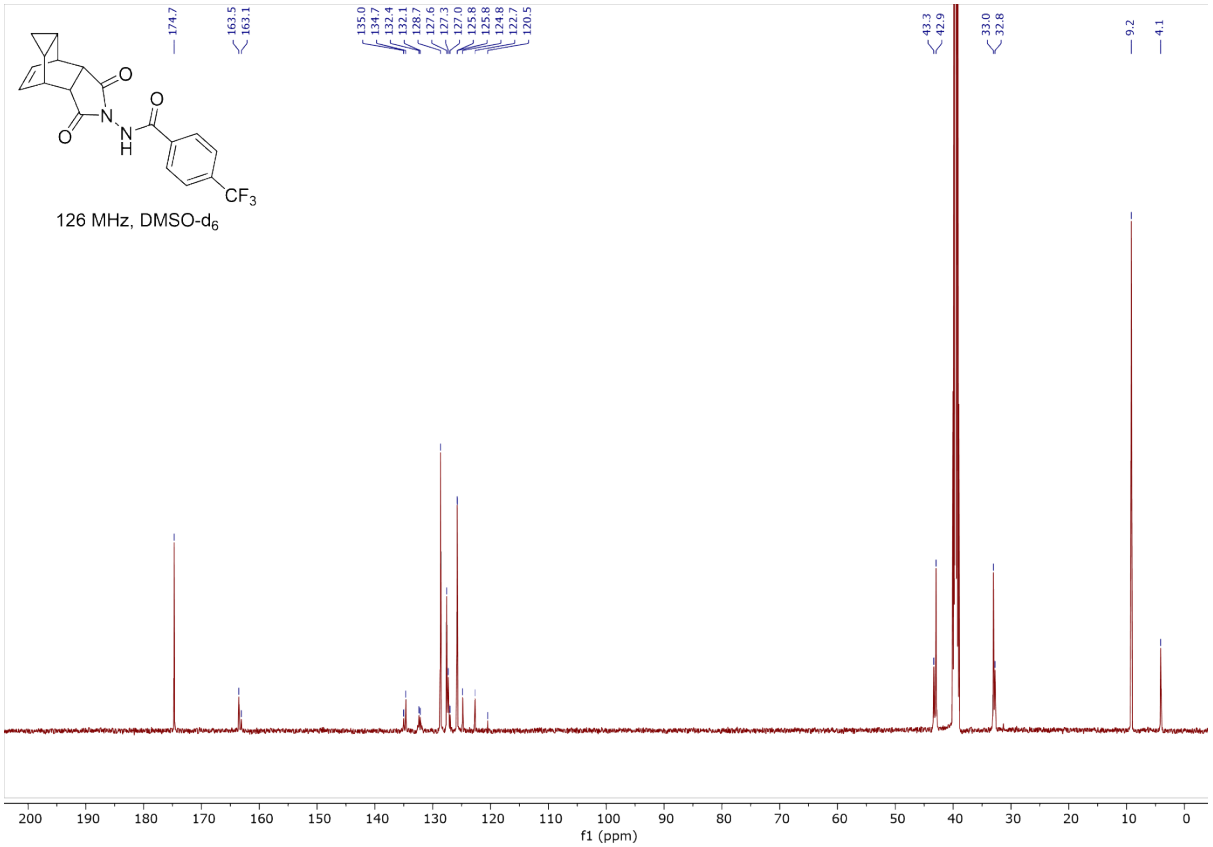
Rac-(4*R*,4a*R*,5a*S*,6*S*)-4,4a,5,5a,6,6a-Hexahydro-4,6-ethenocyclopropa[*f*]isoindole-1,3(2*H*,3a*H*)-dione, 4a

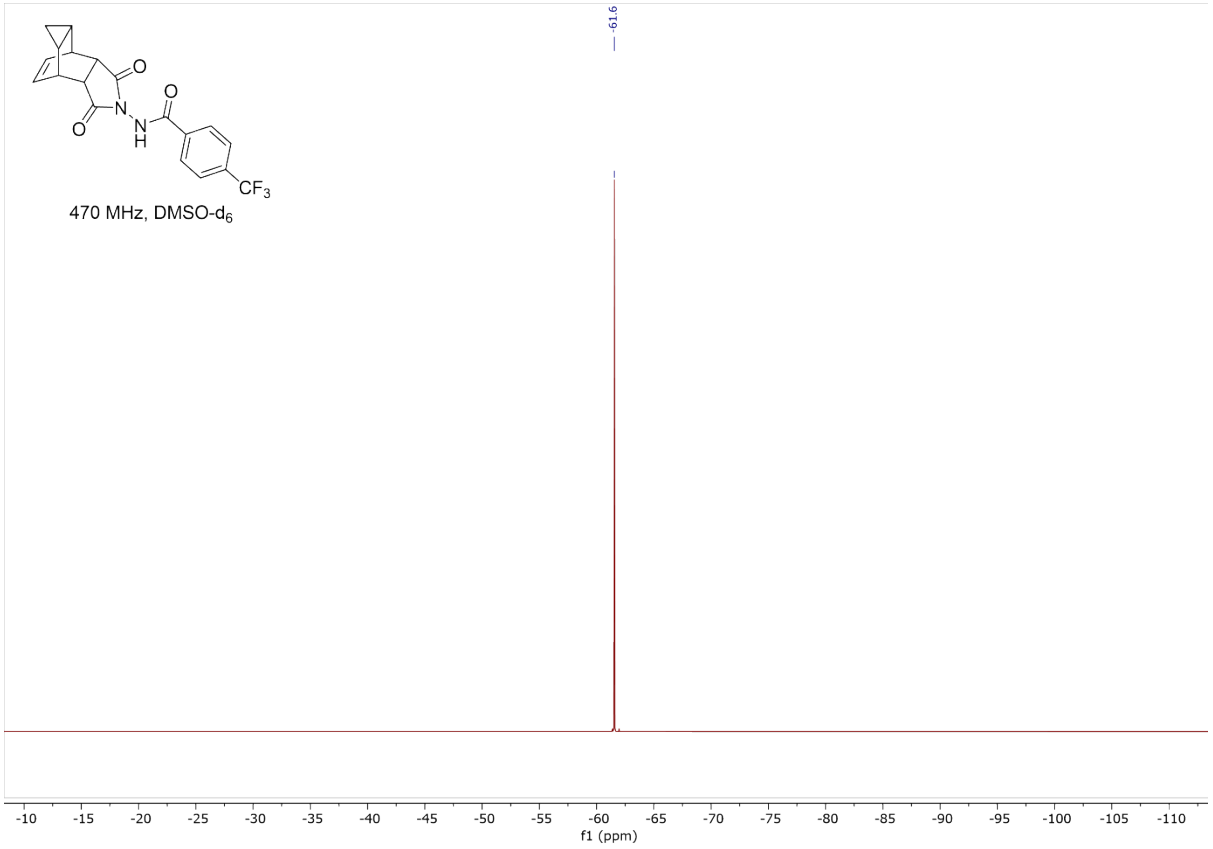




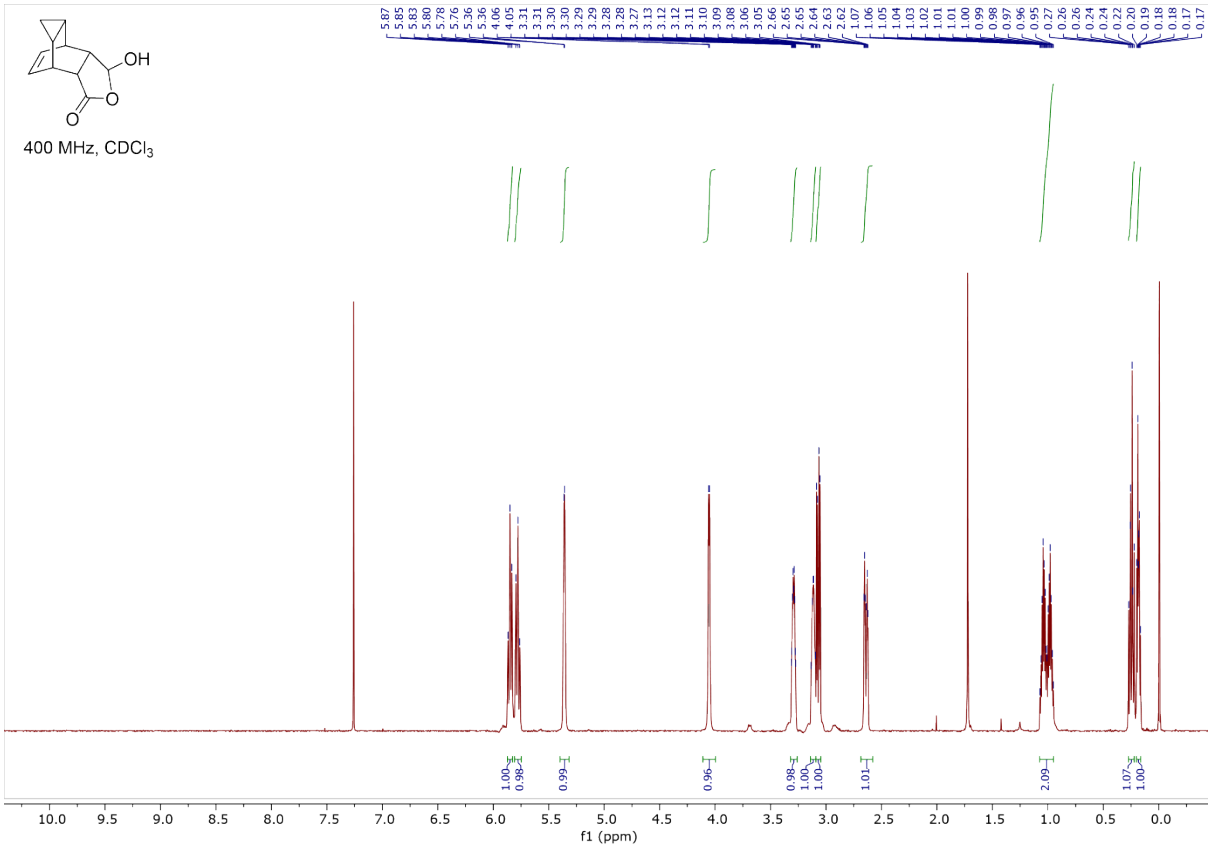
Rac-*N*-((4*R*,4a*R*,5a*S*,6*S*)-1,3-Dioxo-3,3a,4,4a,5,5a,6,6a-octahydro-4,6-ethenocyclopropa[*f*]isoindol-2(1*H*)-yl)-4-(trifluoromethyl)benzamide, 6

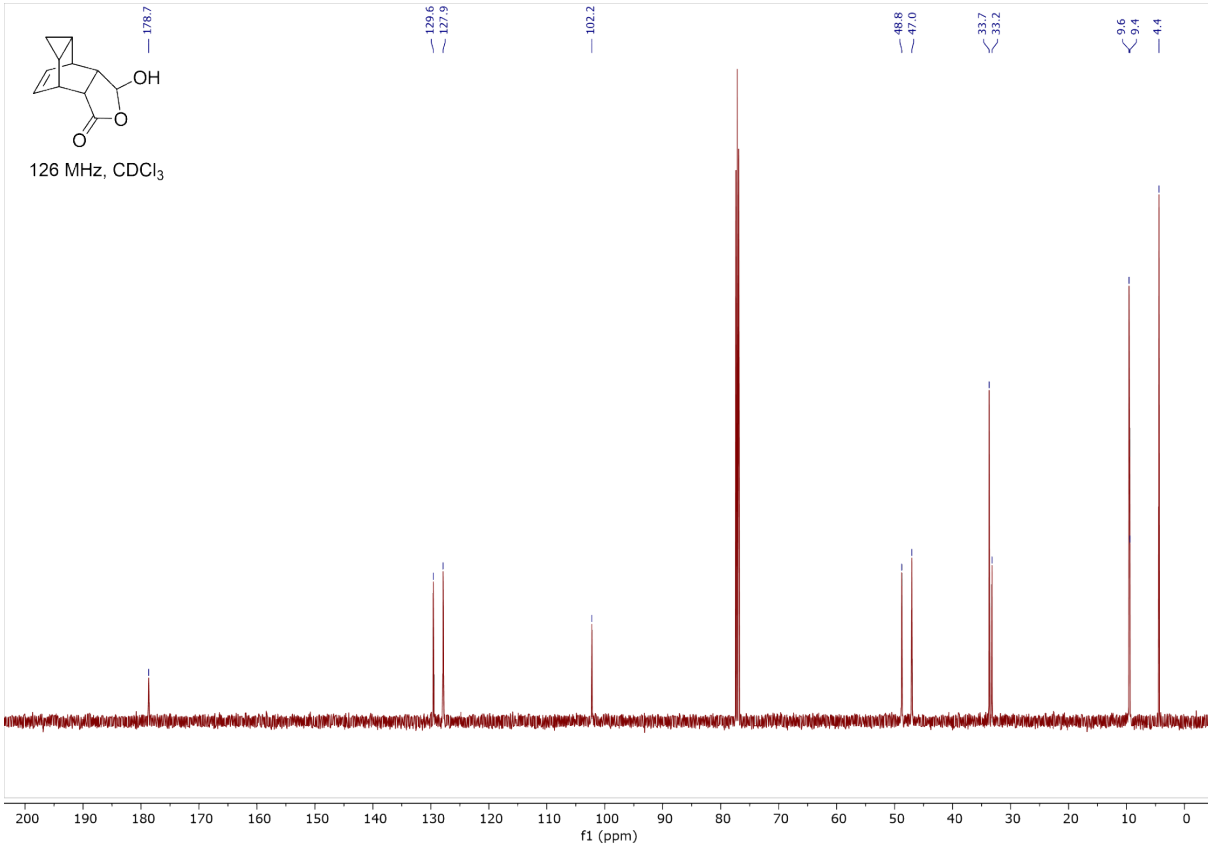




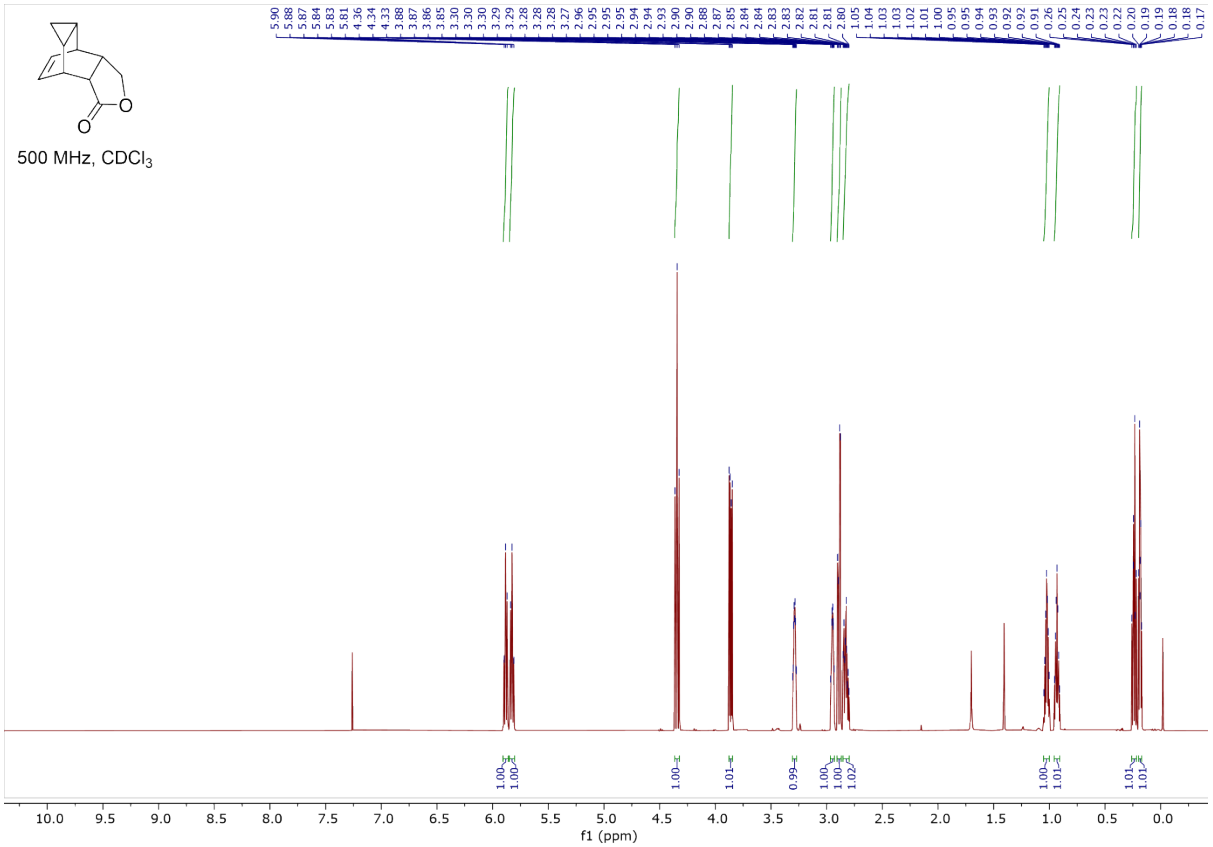


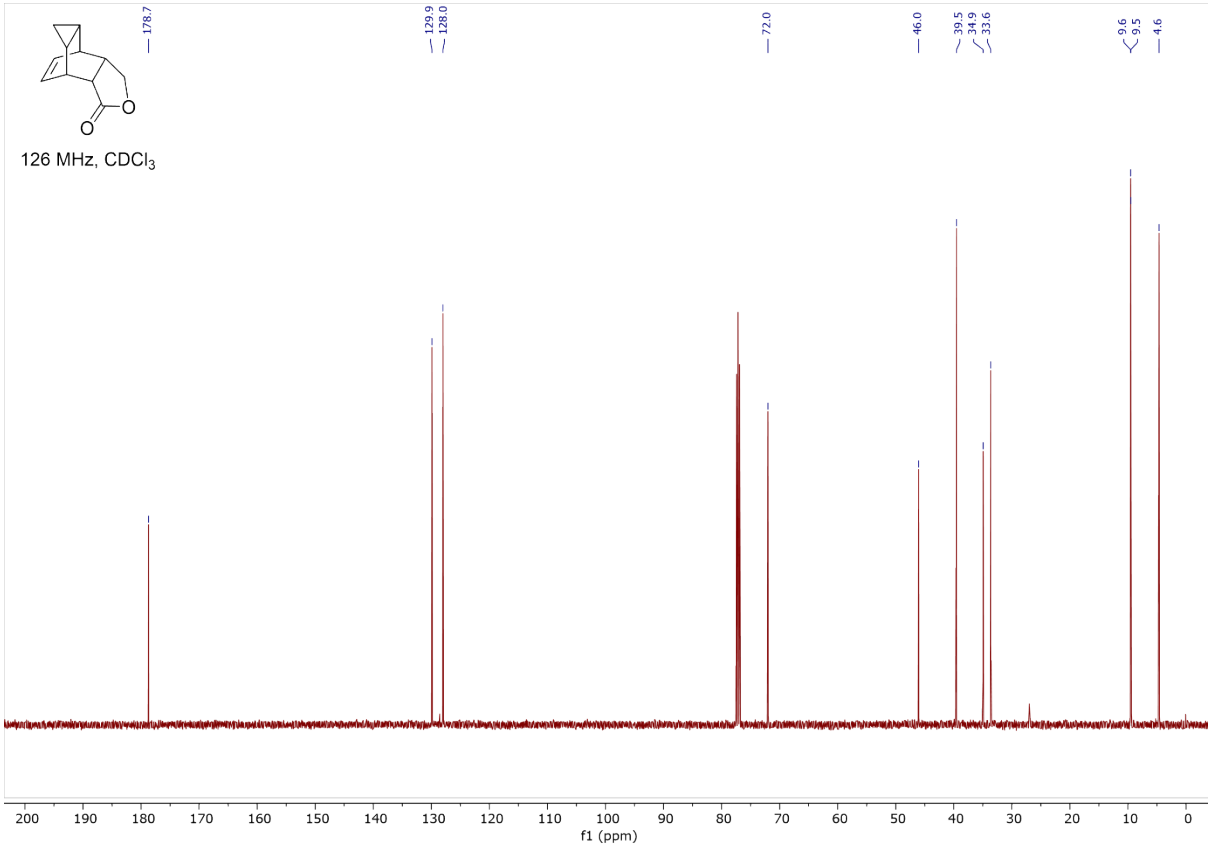
Rac-(4*S*,4a*S*,5a*R*,6*R*)-3-Hydroxy-3,3a,4,4a,5,5a,6,6a-octahydro-1*H*-4,6-ethenocyclopropa[*f*]isobenzofuran-1-one, 7



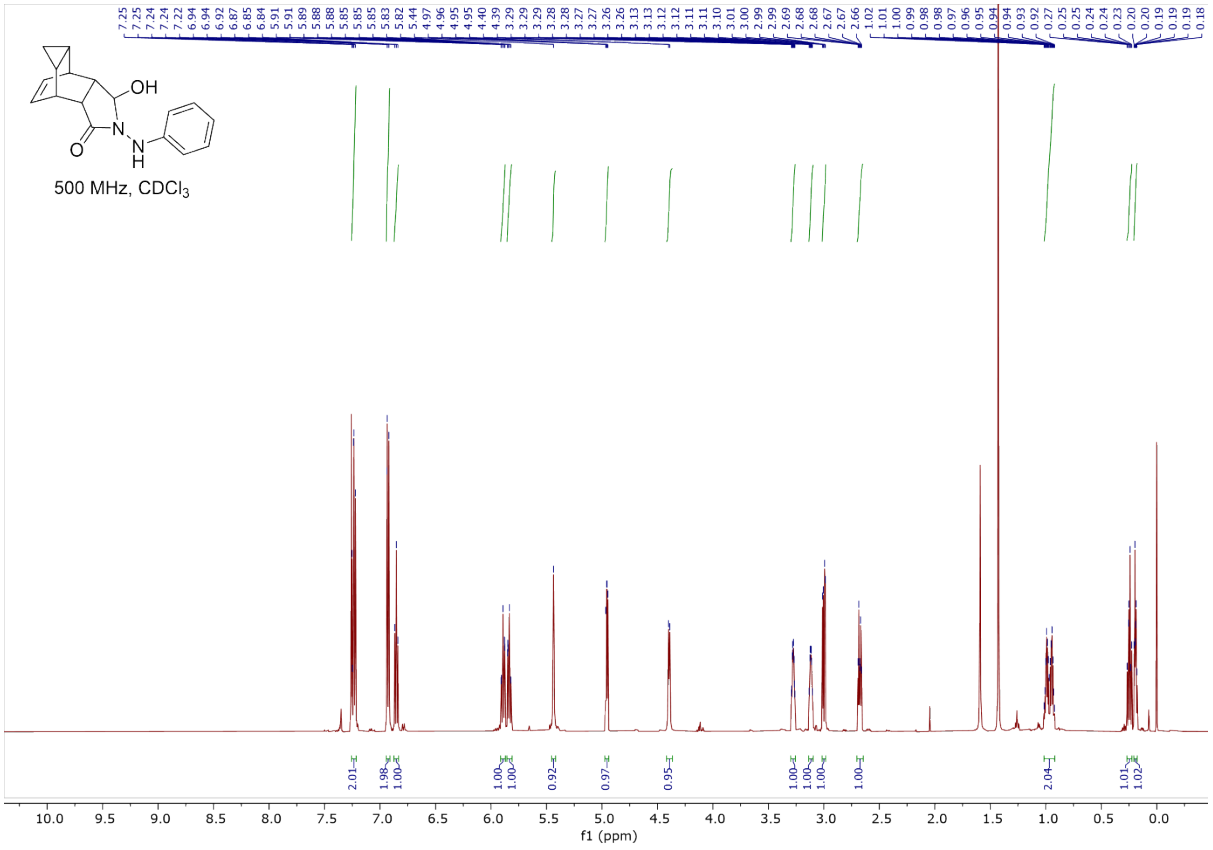


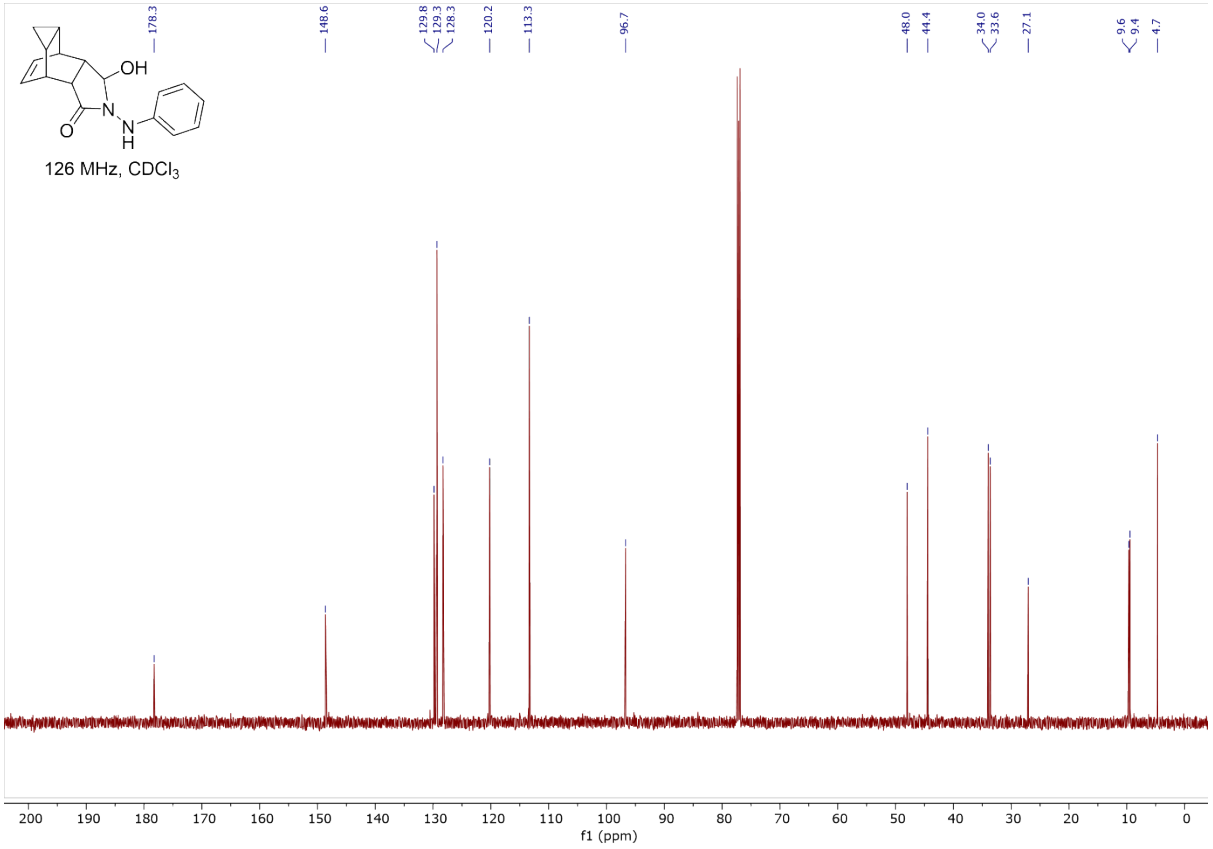
Rac-(4*S*,4a*S*,5a*R*,6*R*)-3,3a,4,4a,5,5a,6,6a-Octahydro-1*H*-4,6-ethenocyclopropa[*f*]iso-benzofuran-1-one, 8



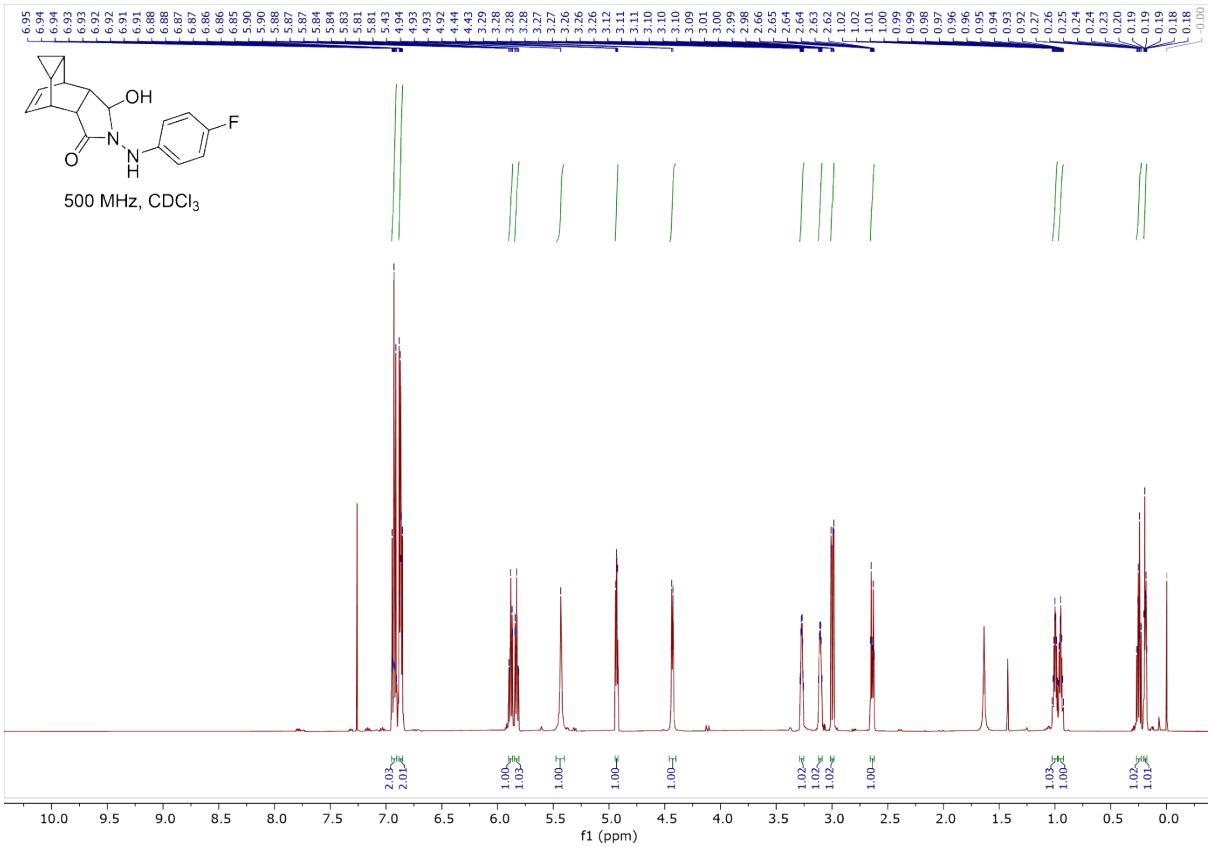


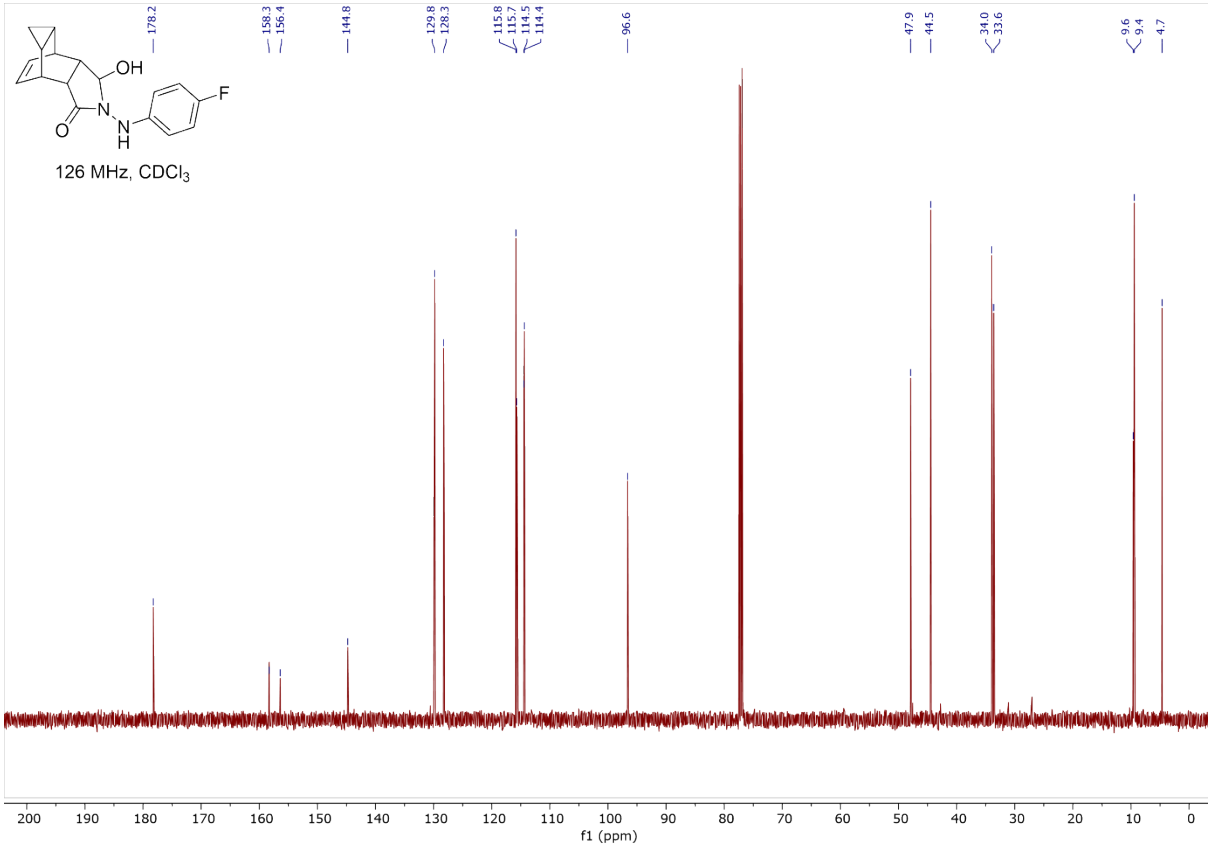
Rac-(3a*S*,4*S*,4a*S*,5a*R*,6*R*)-3-Hydroxy-2-(phenylamino)-3,3a,4,4a,5,5a,6,6a-octahydro-4,6-ethenocyclopropa[*f*]isoindol-1(2*H*)-one, 10a

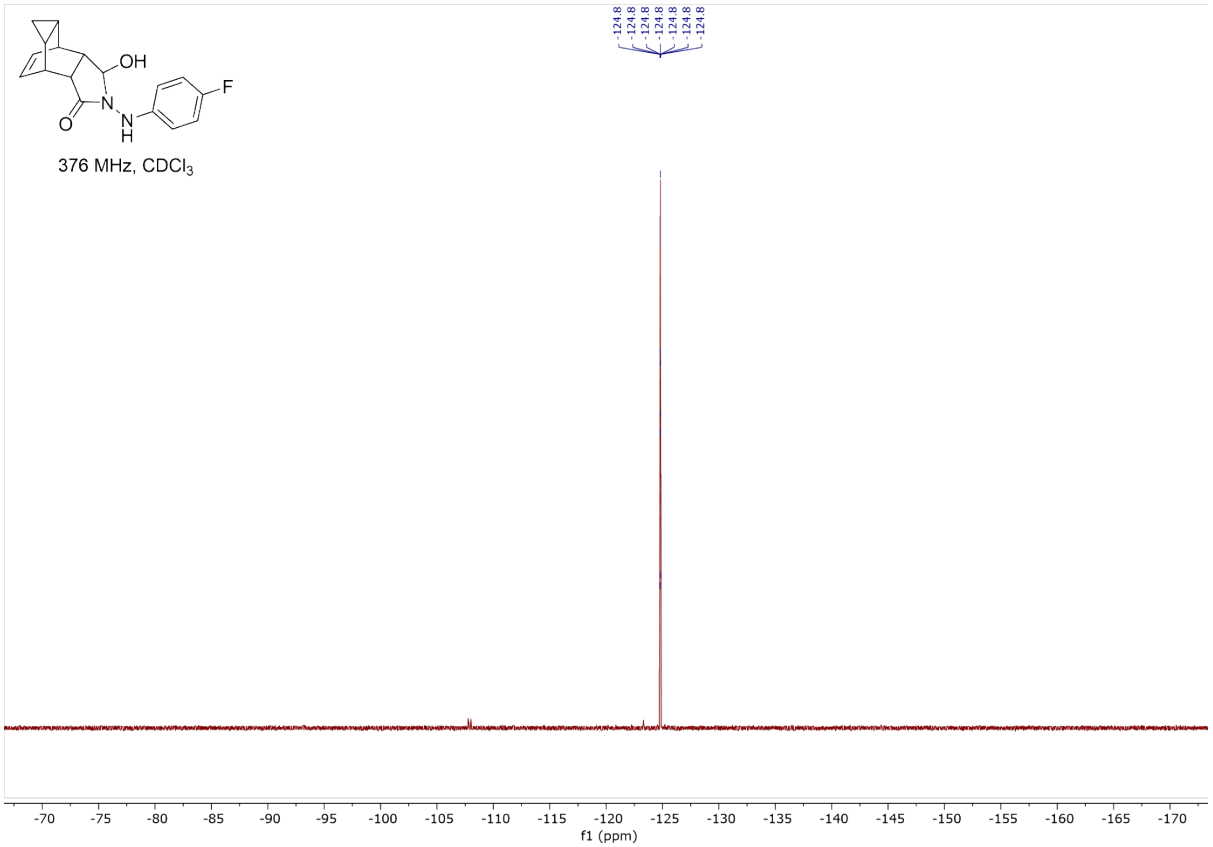




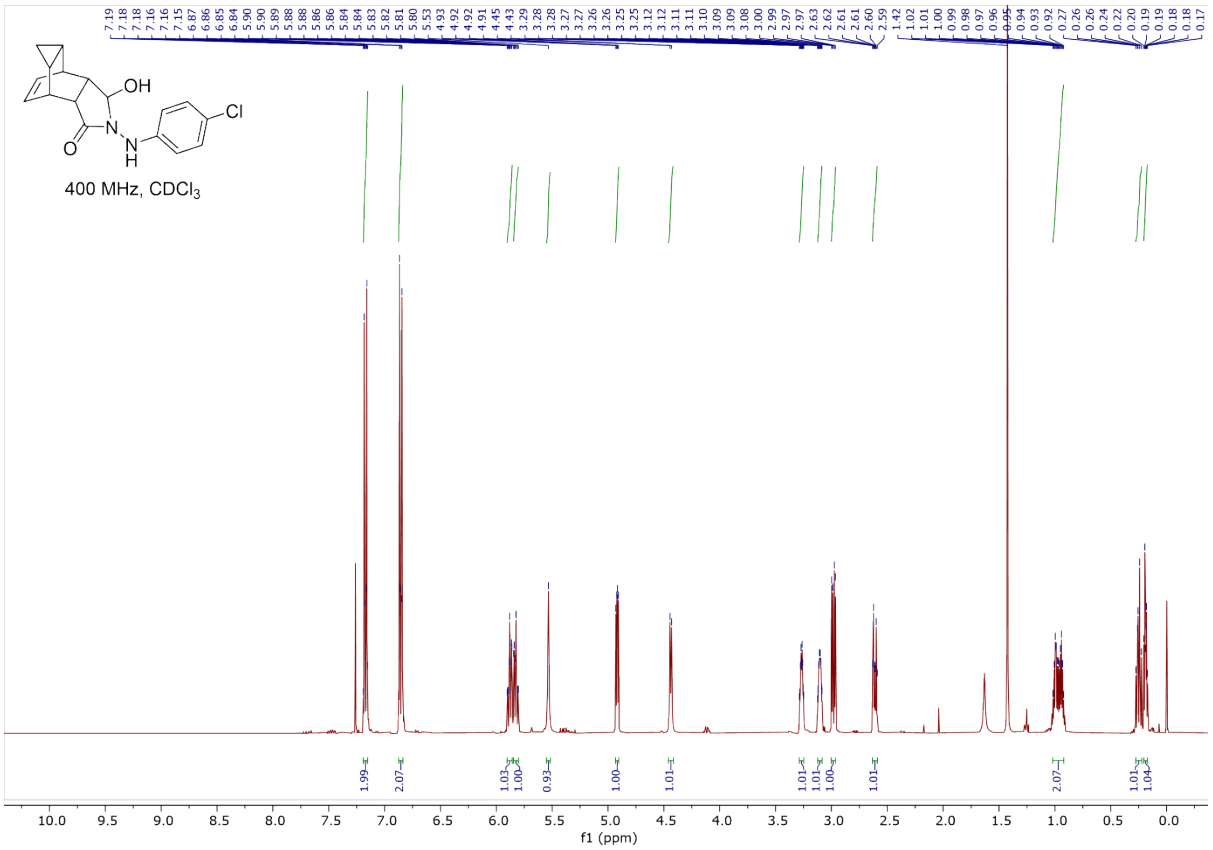
Rac-(3a*S*,4*S*,4a*S*,5a*R*,6*R*)-2-((4-Fluorophenyl)amino)-3-hydroxy-3,3a,4,4a,5,5a,6,6a-octahydro-4,6-ethenocyclopropa[*f*]isoindol-1(2*H*)-one, 10b

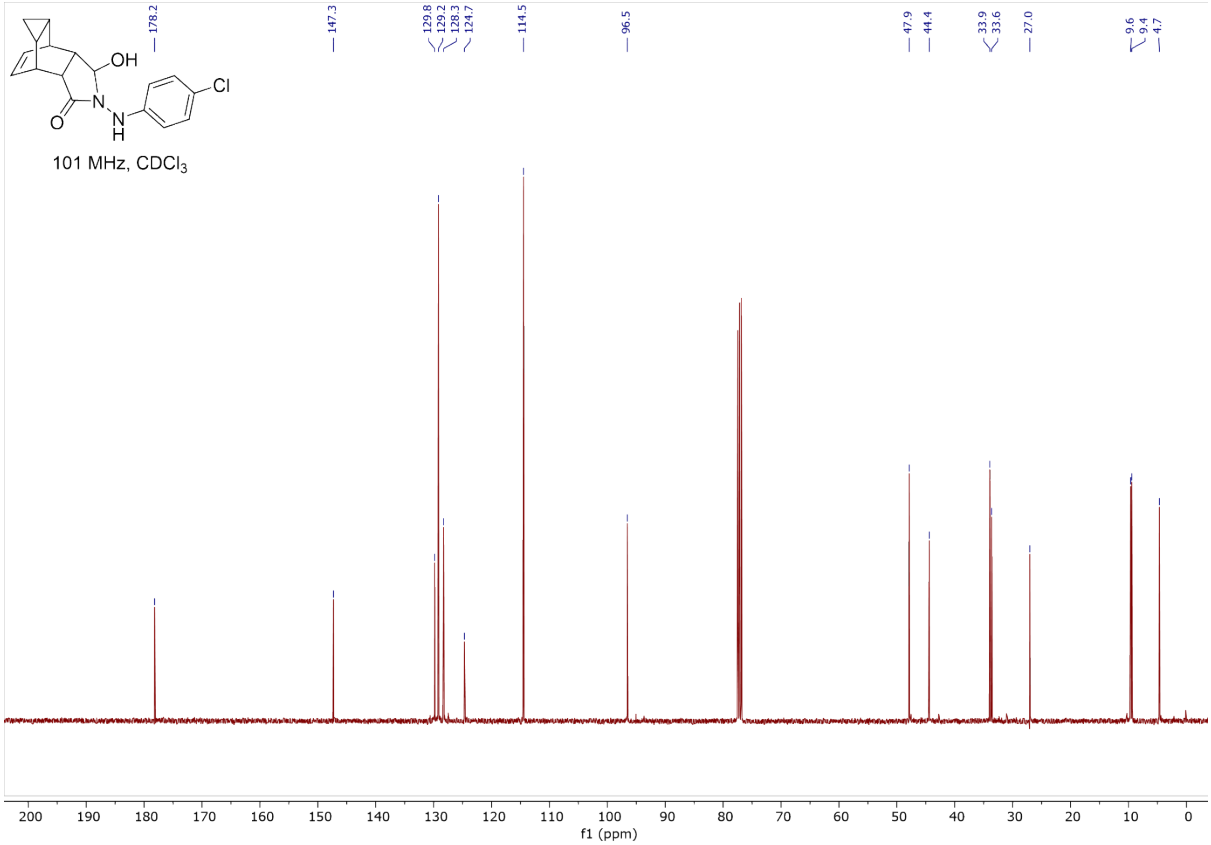

OH
F
O
N
N
H
500 MHz, CDCl3
f1 (ppm)


OH
F
O
N
N
H
126 MHz, CDCl3
f1 (ppm)

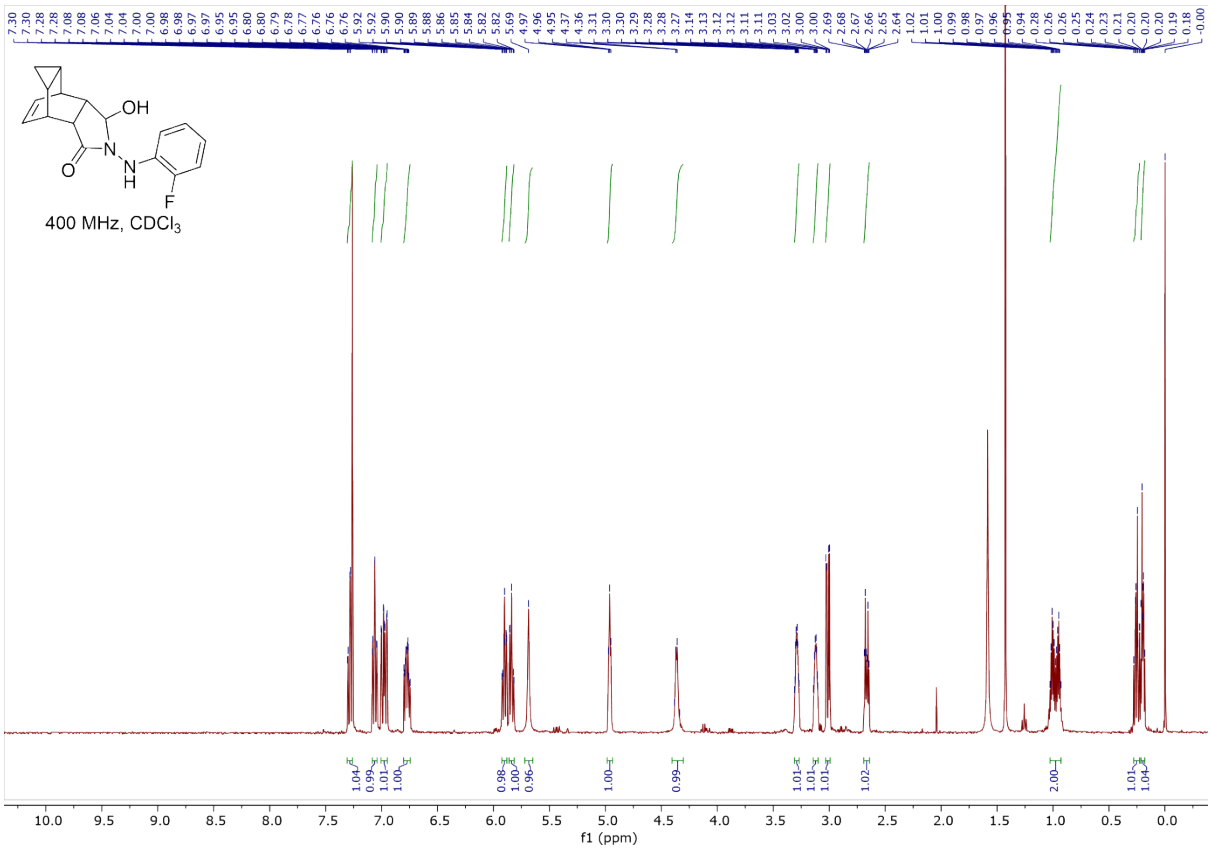


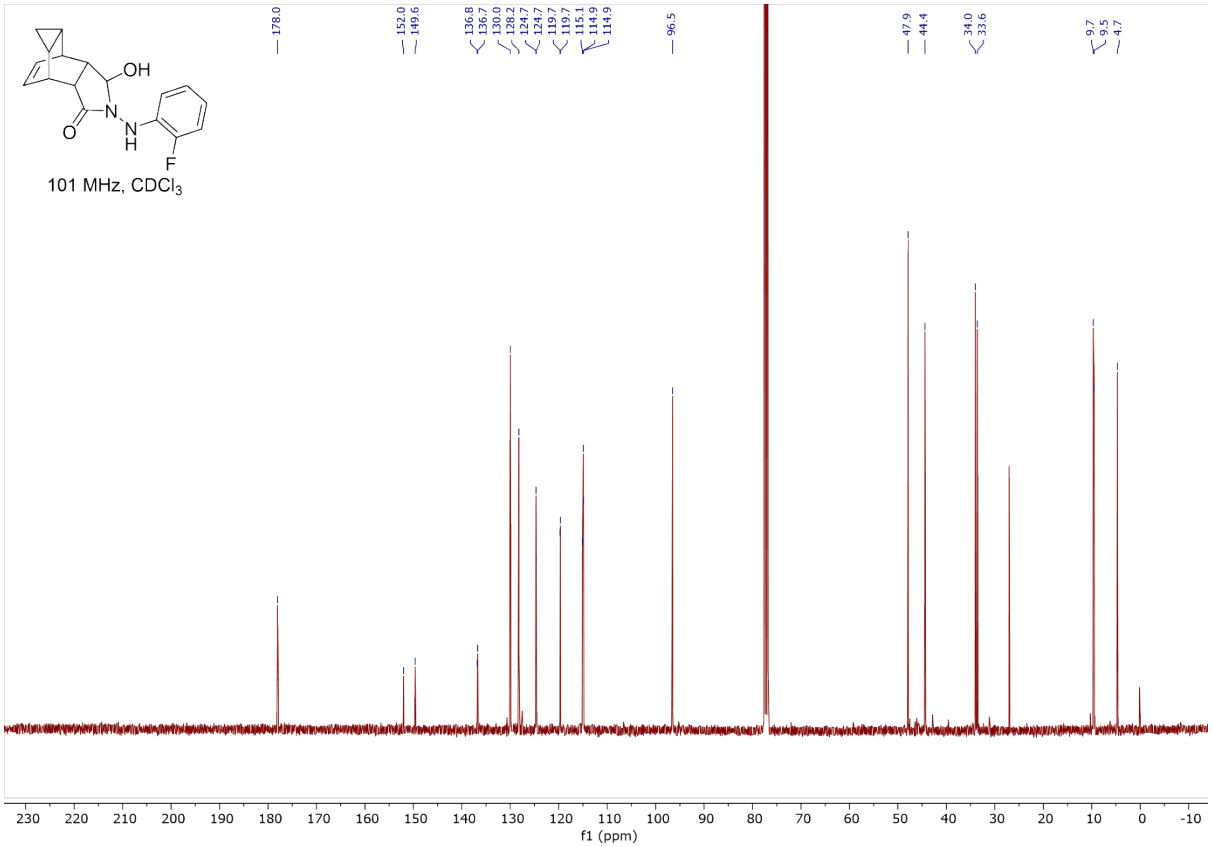
Rac-(3a*S*,4*S*,4a*S*,5a*R*,6*R*)-2-((4-Chlorophenyl)amino)-3-hydroxy-3,3a,4,4a,5,5a,6,6a-octahydro-4,6-ethenocyclopropa[*f*]isoindol-1(2*H*)-one, 10c

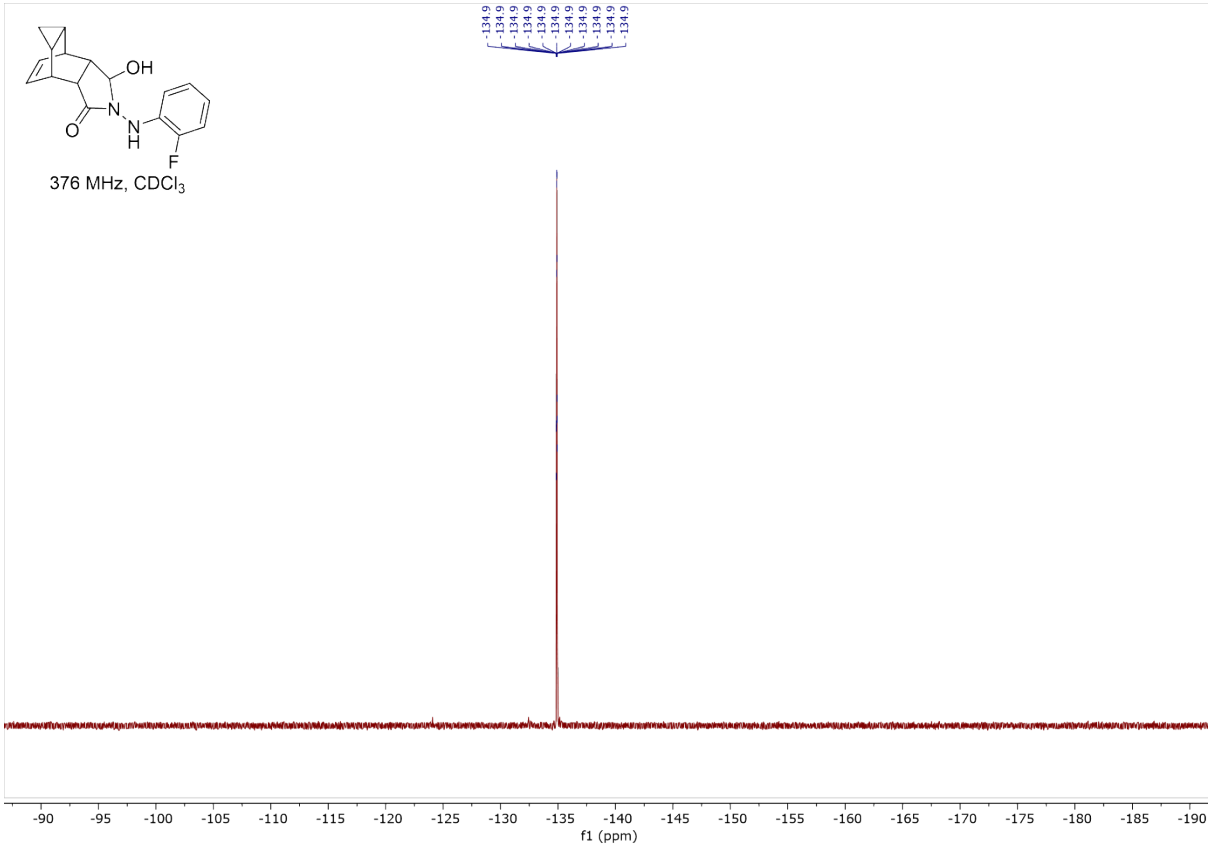




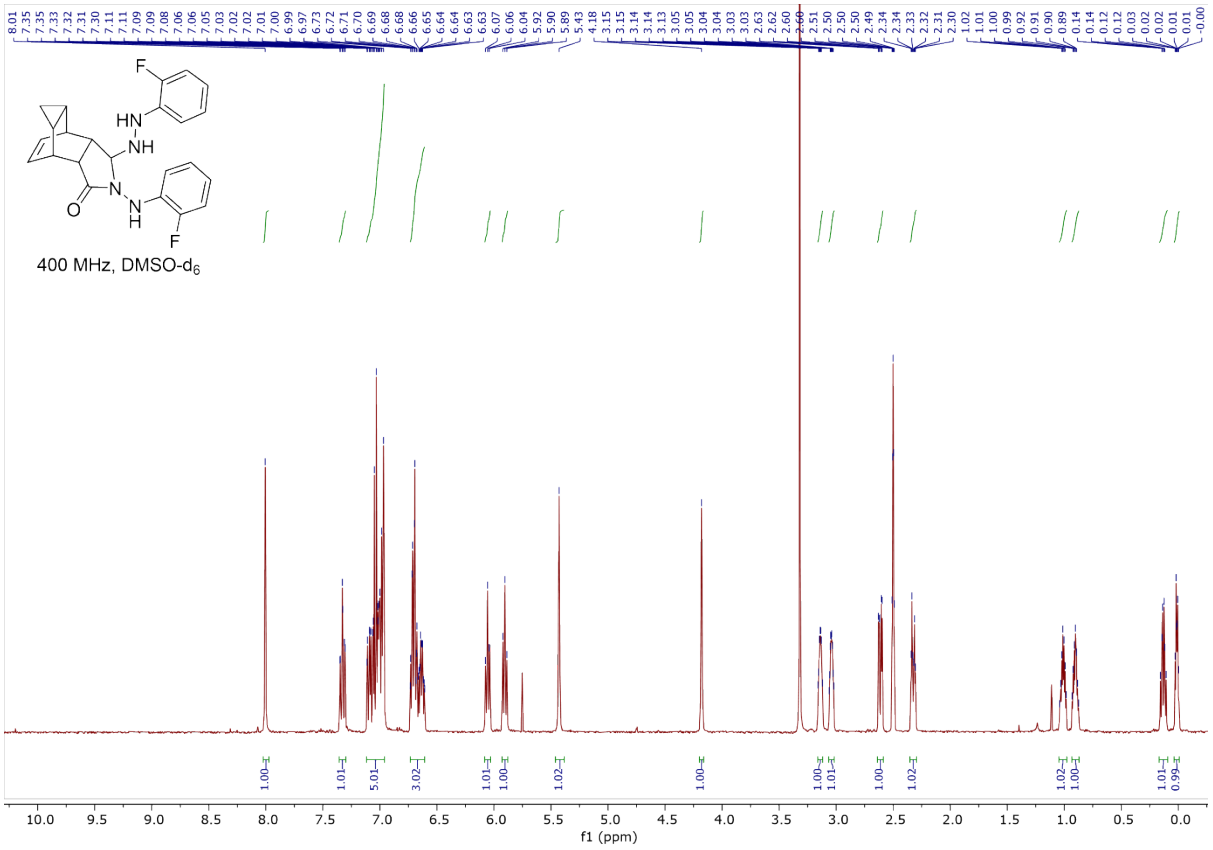
Rac-(3a*S*,4*S*,4a*S*,5a*R*,6*R*)-2-((2-Fluorophenyl)amino)-3-hydroxy-3,3a,4,4a,5,5a,6,6a-octahydro-4,6-ethenocyclopropa[*f*]isoindol-1(2*H*)-one, 10d

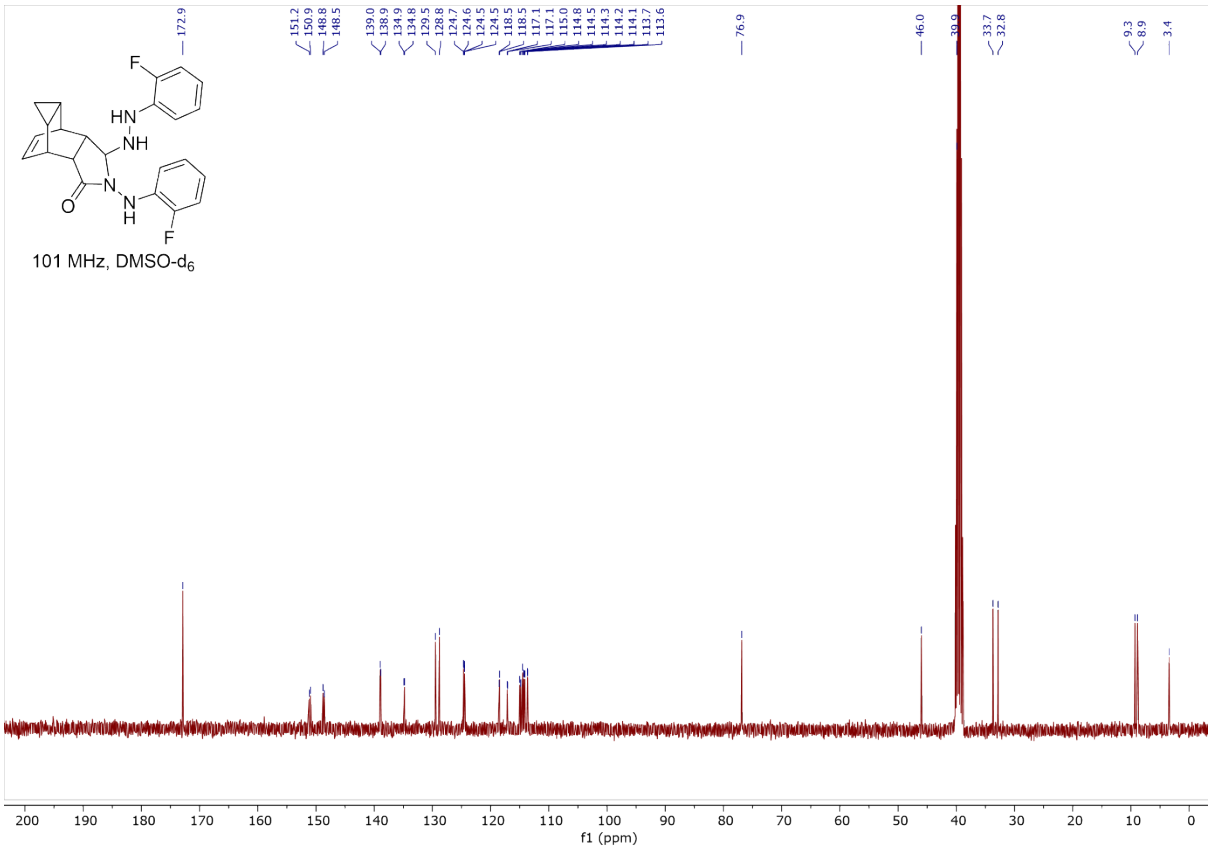


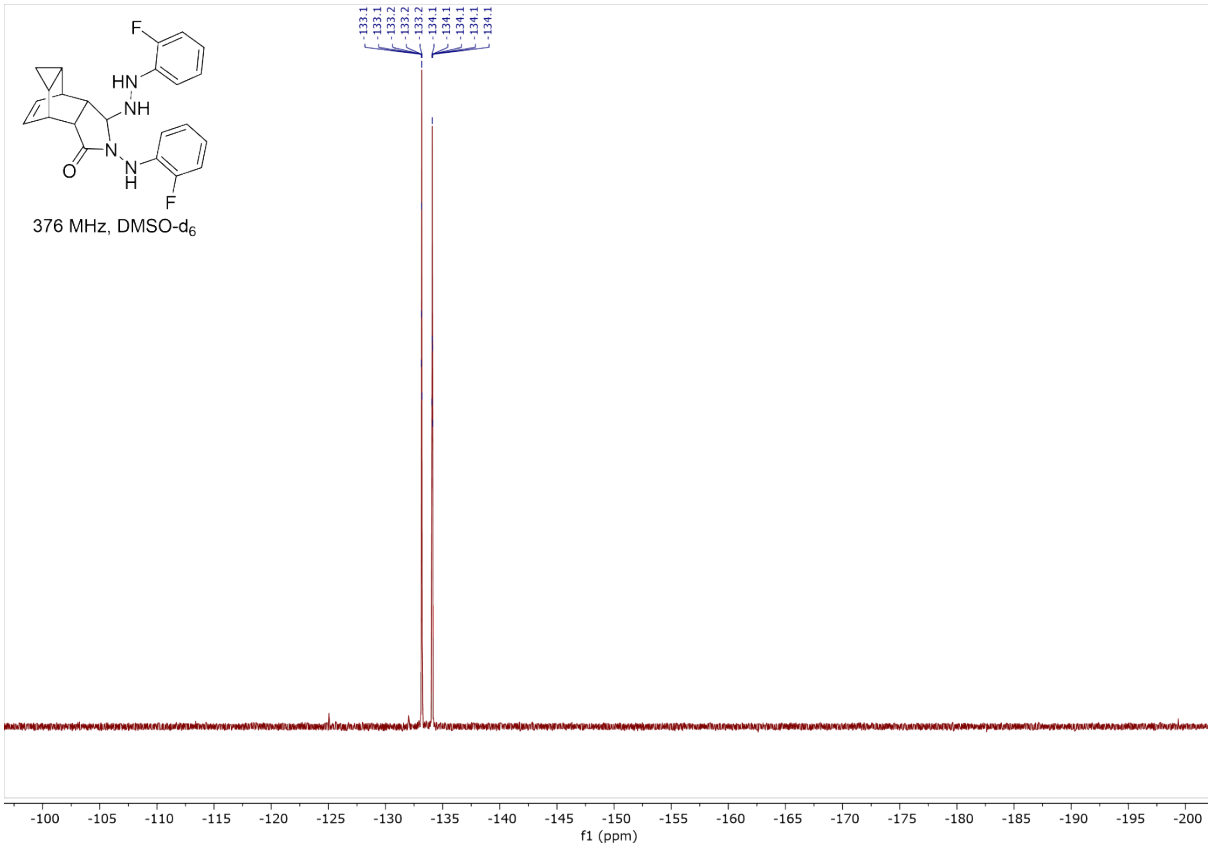

OH
O
N
N
H
F
101 MHz, CDCl3
178.0
152.0
149.6
136.8
136.7
130.0
128.2
124.7
124.7
119.7
119.7
115.1
114.9
114.9
96.5
47.9
44.4
34.0
33.6
9.7
9.5
4.7
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OH
O
N
N
H
F
376 MHz, CDCl3
-134.9
-90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 -180 -185 -190
f1 (ppm)

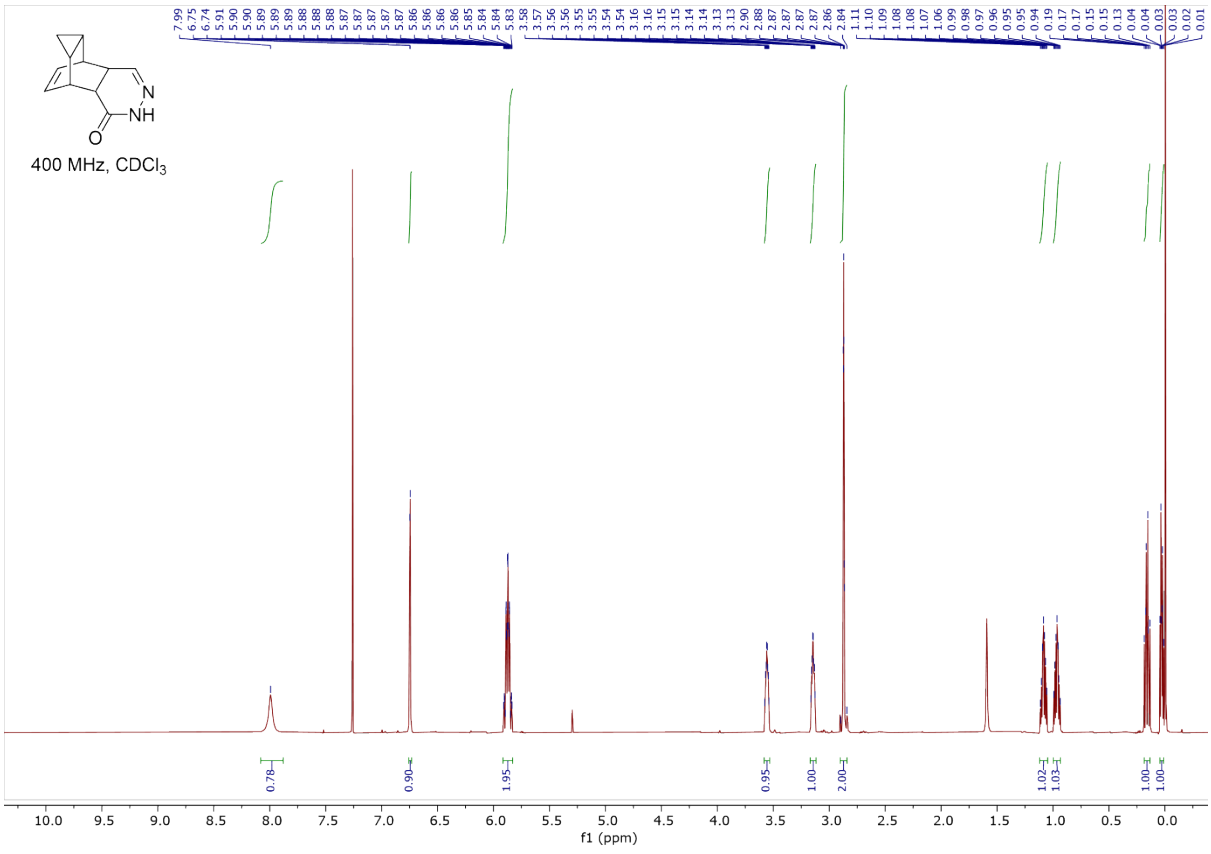
Rac-(3a*S*,4*S*,4a*S*,5a*R*,6*R*)-2-((2-Fluorophenyl)amino)-3-(2-(2-fluorophenyl)hydrazineyl)-3,3a,4,4a,5,5a,6,6a-octahydro-4,6-ethenocyclopropa[*f*]isoindol-1(2H)-one, 10d'

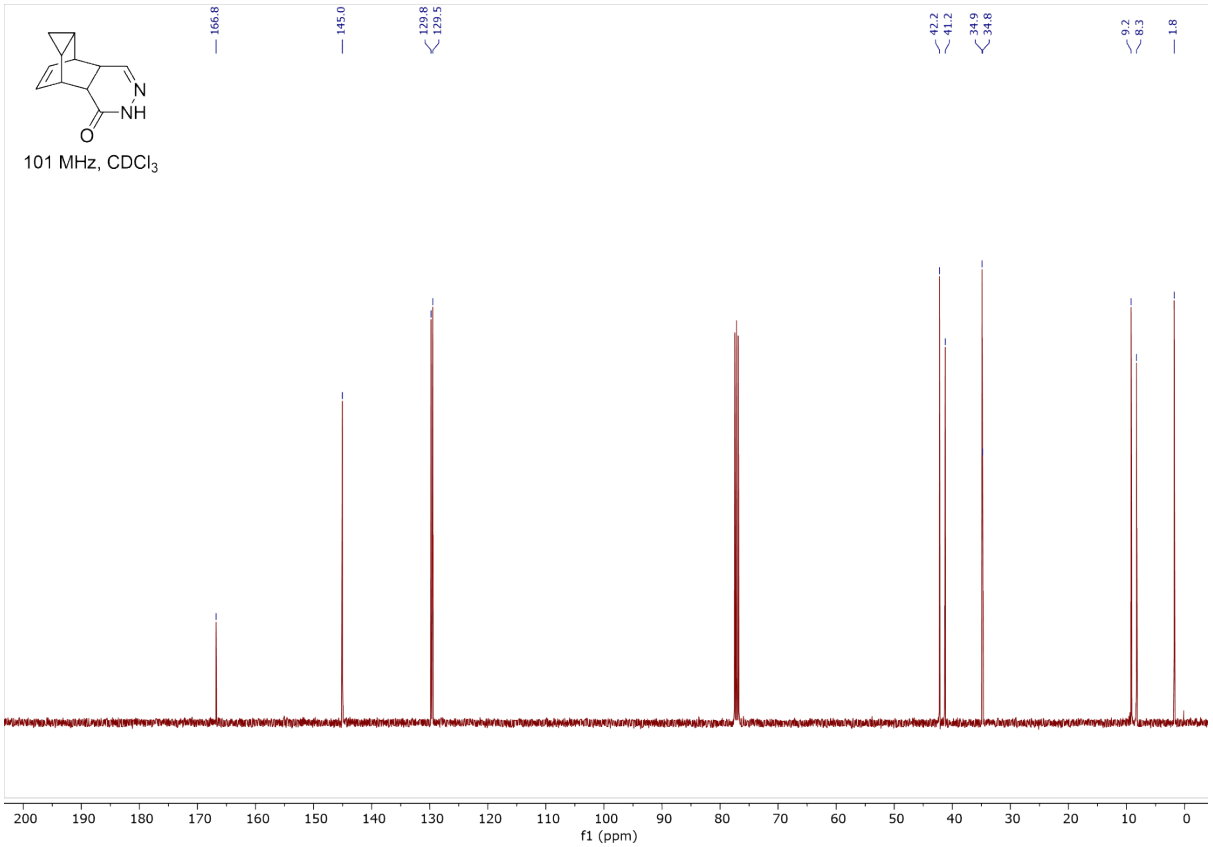






Rac-(5*S*,5a*S*,6a*R*,7*R*)-2,4a,5,5a,6,6a,7,7a-Octahydro-1*H*-5,7-ethenocyclopropa[*g*]-phthalazin-1-one, 11





4. References

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2. V. Hickmann, A. Kondoh, B. Gabor, M. Alcarazo and A. Fürstner, *J. Am. Chem. Soc*., 2011, **133**, 13471 – 13480.

3. E. Mintah Bonku, H. Qin, A. Odilov, F. Yang, X. Xing, X. Wang, S. Desta Guma and J. Shen, *Org. Process Res. Dev*., 2023, **27**, 1984 − 1991.

4. V. P. Arya and S. Shenoy*, Indian Journal of Chemistry*, 1976, **14B**, 780 – 783.