Electronic Supplementary Information:

Highly stereoselective one-pot construction of trisubstituted tetrahydro-β-carboline-fused diketopiperazines: A synthetic route towards cialis analogues

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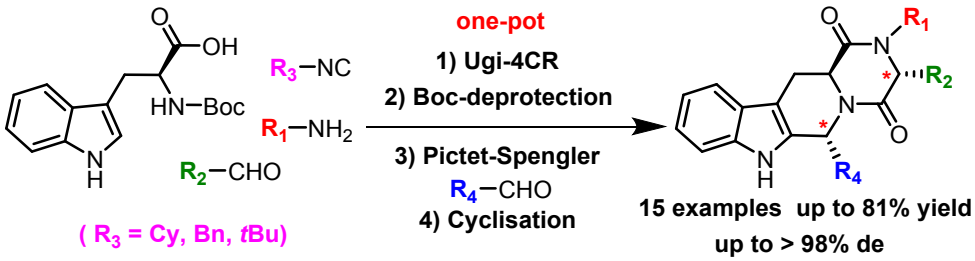
Contents



1. **General information**

^{1}H and ^{13}C NMR spectra (25°C) were recorded at 250 MHz and 63 MHz on a Bruker Avance DRX 250 spectrometer or at 500 MHz and 126 MHz respectively on a Bruker Avance II 500 spectrometer. Chemical shifts are in parts per million (ppm). The assignments were made using one dimensional (1D) ^{1}H and ^{13}C spectra or two-dimensional (2D) HSQC and COSY spectra. HRMS data was recorded with a Micromass QTOF-micro system. Mass spectra were recorded with a LCMS-MS triple-quadrupole system. Analytical HPLC was performed on an Agilent 1100 Series system with a Supelco Discovery BIO Wide Pore RP column (25 cm × 4.6 mm, 5 μm). Flow rates of 1 ml/min were used and detection was done at 215 nm. The solvent system consisted of 0.1% TFA in water (A) and 0.1% TFA in acetonitrile (B). The gradient consisted of a 26 min. run from 3% B to 100% B. Flash chromatography was performed with silica gel 60 (Davisil, 0.040-0.063 mm) from Merck. Glass plates with silica gel 60 F254 (Merck) were used for thin layer chromatography. Visualization of the products on TLC plates was realized using UV light (254 nm), $KMnO_4$ spray. Melting points were determined on a Büchi B-540 apparatus and are uncorrected. Reactions were performed using a Biotage® Initiator^{+} Microwave Synthesizer. All commercial reagents and solvents were used without further purification. Specific rotations were measured on a polarimeter polartronic M Schmidt-Haenschusing a 5 cm cell in standard conditions (20°C / 589.3 nm^{air} / 589.44 nm^{vac}).

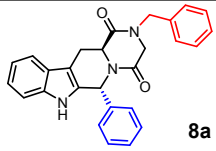
2. General procedure for one-pot tandem Ugi-4CR/Boc-deprotection/Pictet-Spengler/Cyclisation sequence (8a-n).

In a capped 5 mL microwave-vessel containing a stirring bar, the *N*-Boc protected (*L/D*)-tryptophan (0.5 mmol), the aldehyde (0.5 mmol) and the amine (0.5 mmol) were dissolved and mixed in methanol (3 mL). The solution was stirred at room temperature for 30 min. Isocyanide (0.5 mmol) was then added, and the resulting mixture was stirred at room temperature. After 18h, total conversion was determined from LC-MS analysis and the solvent was removed in vacuo. The crude Ugi-4CR product was dissolved in 30% TFA in DCM (3 mL) and the resulting mixture was stirred at room temperature for 3 hours. After completion of the *N*-Boc deprotection step (monitored by HPLC and LC-MS), the solvent was evaporated in vacuo. Next, the crude deprotected Ugi product was dissolved in a mixture of TFA (1.5 mmol) in DCM (3 mL) and the corresponding aldehyde (0.55 mmol) was then added, and the resulting mixture was stirred overnight at room temperature. Total conversion was observed from HPLC and LC-MS analysis and the solvent was removed under reduced pressure.

The crude Ugi Pictet-Spengler product was dissolved in glacial acetic acid (3 mL) and the reaction vessel was capped. The reaction mixtures was heated at 180°C under microwave irradiation for 80 minutes using the Biotage initiator^{+} microwave reactor (average effective ramp time =1 min), the power was set at 400 W and the pressure was set at 30 bar (average effective pressure = 5 bar). After completion of the reaction as indicated by LC-MS, the solvent was evaporated under reduced pressure and the residue was dissolved in EtOAc (20 mL). The organic layer was washed with sat. $NaHCO_3$ (3 X 10 mL), 1*N* HCl (3 X 10 mL), sat. NaCl (3 X 10 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure.The crude products were purified by flash chromatography. The resulting products (**8a-n**) were isolated in good purity and yields as a single diastereomer. Purity (%) was determined by reversed phase HPLC, using UV detection (215 nM).

3. Characterization of compounds (8a-n).

(6R,12aS)-2-benzyl-6-phenyl-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione (8a):

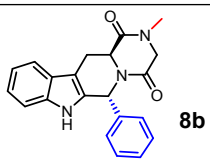


8a

Chemical Formula: $C_{27}H_{23}N_3O_2$
Exact Mass: 421.18

Yield (171 mg, 81%); pale yellow solid; mp= 263-265 °C; $[\alpha]_D$ = -30.0 ° (*c* 0.6, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.92 (br s, 1H, NH), 7.56 (d, *J* = 8.0 Hz, 1H), 7.40-7.14 (m, 13H), 7.04 (s, 1H), 4.87 (d, *J* = 14.75 Hz, 1H), 4.43 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.34 (d, *J* = 14.5 Hz, 1H), 4.00 (d, *J* = 18.25 Hz, 1H), 3.95 (d, *J* = 18.25 Hz, 1H), 3.62 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.99 (dd, *J* = 16.0, 12.0 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.46, 162.07, 137.99, 136.34, 134.74, 129.56, 129.07, 128.96, 128.83, 128.54, 128.33, 126.23, 122.78, 120.13, 118.44, 111.19, 108.95, 52.67, 52.19, 49.45, 48.78, 27.83; TLC: R_f = 0.55 (EtOAc /Hexane 9/1, v/v); rt(HPLC) = 17.20 min; HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{27}H_{23}N_3O_2Na$444.1682; found 444.1660.

(6R,12aS)-2-methyl-6-phenyl-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione (8b):

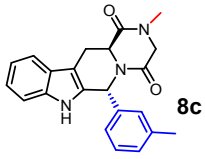


8b

Chemical Formula: $C_{21}H_{19}N_3O_2$
Exact Mass: 345.15

Yield (121 mg, 70%); brown solid; mp= 288-290 °C; $[\alpha]_D$ = -73.3 ° (*c* 0.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 8.14 (br s, 1H, NH), 7.53 (d, *J* = 7.75 Hz, 1H), 7.32-7.12 (m, 8H), 7.06 (s, 1H), 4.32 (dd, *J* = 11.75, 4.5 Hz, 1H), 4.12 (d, *J* = 17.5 Hz, 1H), 3.95 (d, *J* = 17.75 Hz, 1H), 3.55 (dd, *J* = 15.25, 4.5 Hz, 1H), 3.01-2.89 (m, 1H), 2.96 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.46, 161.64, 138.24, 136.36, 129.63, 128.89, 128.78, 126.26, 122.70, 120.06, 118.41, 111.18, 109.07, 52.55, 52.08, 51.42, 33.40, 27.65; TLC: R_f = 0.42 (EtOAc /Hexane 9/1, v/v); rt(HPLC) = 14.22 min; HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{21}H_{20}N_3O_2$ 346.1550; found 346.1558.

(6R,12aS)-2-methyl-6-(m-tolyl)-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione (8c):

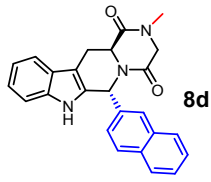


8c

Chemical Formula: $C_{22}H_{21}N_3O_2$
Exact Mass: 359.16

Yield (136 mg, 76%); yellow oil; $[\alpha]_D$ = -176.8 ° (*c* 1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.88 (br s, 1H, NH), 7.55 (d, *J* = 8.0 Hz, 1H), 7.33-7.10 (m, 7H), 7.03 (s, 1H), 4.39 (dd, *J* = 12.5, 4.5 Hz, 1H), 4.15 (d, *J* = 17.5 Hz, 1H), 3.98 (d, *J* = 17.5 Hz, 1H), 3.57 (dd, *J* = 15.0, 4.5 Hz, 1H), 3.04-2.91 (m, 1H), 3.00 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.53, 161.56, 138.83, 138.08, 136.31, 129.84, 129.71, 129.31, 128.81, 125.96, 122.70, 120.08, 118.43, 111.15, 109.12, 52.60, 52.06, 51.48, 33.40, 27.67, 21.38; TLC: R_f = 0.51 (EtOAc /Hexane 9/1, v/v); rt(HPLC) = 14.85 min; HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{22}H_{22}N_3O_2$ 360.1707; found 360.1695.

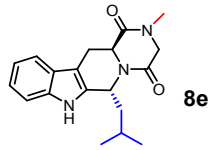
(6R,12aS)-2-methyl-6-(naphthalen-2-yl)-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione (8d):



Chemical Formula: $C_{25}H_{21}N_3O_2$
Exact Mass: 395.16

Yield (141 mg, 71%); brown solid; mp= 165-167 °C; $[\alpha]_D$ = -87.5 ° (*c* 0.7, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.28 (br s, 1H, NH), 7.78-7.70 (m, 1H), 7.62-7.55 (m, 3H), 7.50-7.39 (m, 3H), 7.33-7.15 (m, 5H), 4.34 (dd, *J* = 12.0, 4.5 Hz, 1H), 4.05 (d, *J* = 17.5 Hz, 1H), 3.86 (d, *J* = 17.5 Hz, 1H), 3.57 (dd, *J* = 15.5, 4.5 Hz, 1H), 3.00-2.90 (m, 1H), 2.86 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.40, 161.76, 136.43, 135.73, 133.32, 132.97, 129.73, 128.91, 128.14, 127.95, 127.61, 126.76, 126.63, 126.33, 126.22, 122.68, 120.04, 118.45, 111.31, 109.14, 52.54, 52.24, 51.35, 33.28, 27.69; TLC: R_f = 0.47 (EtOAc /Hexane 8/2, v/v); rt(HPLC) = 15.76 min; HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{25}H_{22}N_3O_2$ 396.1707; found 396.1706.

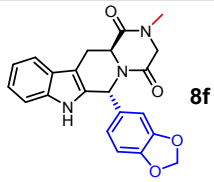
(6R,12aS)-6-isobutyl-2-methyl-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione (8e):



Chemical Formula: $C_{19}H_{23}N_3O_2$
Exact Mass: 325.18

Yield (119 mg, 73%); yellow oil; $[\alpha]_D$ = -29.2 ° (*c* 0.5, $CHCl_3$); ^{1}H NMR (250 MHz, MeOD) δ 7.42 (d, *J* = 8.75 Hz, 1H), 7.29 (d, *J* = 8.75 Hz, 1H), 7.10-6.94 (m, 2H), 6.43 (d, *J* = 16.5 Hz, 1H), 6.21 (dd, *J* = 16.5, 6.75 Hz, 1H), 4.23 (br s, 1H), 3.49-3.11 (m, 5H), 2.58-2.25 (m, 2H), 2.50 (s, 3H), 1.16 (d, *J* = 6.5 Hz, 3H), 1.15 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, MeOD) δ 167.40, 165.77, 137.00, 136.39, 135.25, 128.41, 121.69, 118.65, 118.17, 115.59, 110.00, 105.29, 56.42, 50.01, 32.53, 31.58, 28.69, 21.43; TLC: R_f = 0.32 (EtOAc /Hexane 9/1, v/v); rt(HPLC) = 13.04 min; HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{19}H_{24}N_3O_2$ 326.1863; found 326.1871.

(6R,12aS)-6-(benzo[d][1,3]dioxol-5-yl)-2-methyl-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione {12a-*epi*-Cialis }(8f):

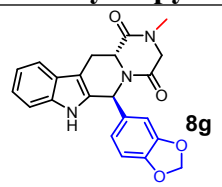


Chemical Formula: $C_{22}H_{19}N_3O_4$
Exact Mass: 389.14

Yield (133 mg, 68%); pale yellow solid; mp= 291-293 °C (lit.[1] mp = 287-289 °C); $[\alpha]_D$ = -297.8 ° (*c* 1, $CHCl_3$) {lit.[2] $[\alpha]_D$ = -293.4 ° (*c* 1.2, $CHCl_3$)}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.00 (br s, 1H, NH), 7.53 (d, *J* = 7.5 Hz, 1H), 7.33-7.12 (m, 3H), 6.97 (s, 1H), 6.81 (s, 1H), 6.70 (s, 2H), 5.92 (s, 2H), 4.34 (dd, *J* = 12.0, 4.5 Hz, 1H), 4.14 (d, *J* = 17.5 Hz, 1H), 3.98 (d, *J* = 17.5 Hz, 1H), 3.55 (dd, *J* = 15.5, 4.5 Hz, 1H), 2.99 (s, 3H), 2.96-2.89 (m, 1H); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.02 (br s, 1H, NH), 7.47 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H),), 6.99 (t, *J* = 7.5 Hz, 1H), 6.85-6.80 (m, 2H), 6.74 (s, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 5.97 (d, *J* = 7.0 Hz, 2H), 4.22 (d, *J* = 18.0 Hz, 1H), 4.05 (dd, *J* = 11.5, 4.0 Hz, 1H), 4.01 (d, *J* = 18.0 Hz, 1H), 3.24 (dd, *J* = 15.5, 4.0 Hz, 1H), 2.93 (dd, *J* = 15.5, 11.5 Hz, 1H), 2.82 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.46, 161.53, 148.15, 148.05, 136.32, 132.05, 129.71, 126.23, 122.77, 122.48, 120.10, 118.45, 111.15, 109.14, 108.31, 101.36, 52.42, 51.81, 51.47, 33.40, 27.60; TLC: R_f = 0.45 (EtOAc /Hexane 8/2, v/v); rt(HPLC) = 14.21 min; HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{22}H_{19}N_3O_4Na$ 412.1268; found 412.1284.

(2) Daugan, A. C. –M. U.S. Patent 5, 859, 006.

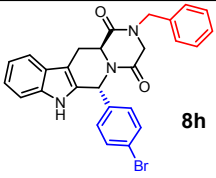
(6S,12aR)-6-(benzo[d][1,3]dioxol-5-yl)-2-methyl-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione{6-*epi*-Cialis } (8g):



Chemical Formula: $C_{22}H_{19}N_3O_4$
Exact Mass: 389.14

Yield (142 mg, 73%); off-white solid; mp= 289-291 °C (lit.[1]mp = 287-288 °C); $[\alpha]_D$ = +288.4 ° (*c* 1, $CHCl_3$) {lit.[20d] $[\alpha]_D^{28}$ = +278 ° (*c* 1.03, $CHCl_3$)};^{1}H NMR (500 MHz, DMSO-d_6) δ 11.02 (br s, 1H, NH), 7.47 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H),), 6.99 (t, *J* = 7.5 Hz, 1H), 6.85-6.81 (m, 2H), 6.75 (s, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 5.97 (d, *J* = 6.0 Hz, 2H), 4.22 (d, *J* = 18.0 Hz, 1H), 4.06 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.01 (d, *J* = 18.0 Hz, 1H), 3.24 (dd, *J* = 15.5, 4.0 Hz, 1H), 2.93 (dd, *J* = 15.5, 12.0 Hz, 1H), 2.82 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.13, 162.74, 148.11, 147.73, 136.75, 133.38, 130.83, 126.39, 122.19, 122.15, 119.36, 118.59, 111.80, 108.83, 108.62, 107.99, 101.73, 52.49, 51.33, 51.15, 33.09, 27.17; TLC: R_f = 0.45 (EtOAc /Hexane 8/2, v/v); rt(HPLC) = 14.20 min; HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{22}H_{19}N_3O_4Na$ 412.1268; found 412.1288.

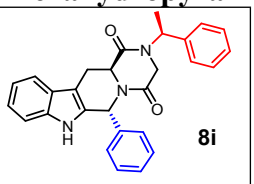
(6R,12aS)-2-benzyl-6-(4-bromophenyl)-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione (8h):



Chemical Formula: $C_{27}H_{22}BrN_3O_2$
Exact Mass: 499.09

Yield (185 mg, 74%); pale yellow oil; $[\alpha]_D$ = -80.0 ° (*c* 0.5, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.23 (br s, 1H, NH), 7.54 (d, *J* = 10.0 Hz, 1H), 7.40-7.21 (m, 8H), 7.13-7.03 (m, 4H), 6.95 (s, 1H), 4.82 (d, *J* = 14.25 Hz, 1H), 4.32 (d, *J* = 14.25 Hz, 1H), 4.31 (dd, *J* = 12.0, 4.5 Hz, 1H), 3.96 (d, *J* = 18.0 Hz, 1H), 3.86 (d, *J* = 18.0 Hz, 1H), 3.59 (dd, *J* = 16.0, 4.5 Hz, 1H), 2.95 (dd, *J* = 16.0, 12.0 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.17, 161.94, 137.22, 136.39, 134.81, 132.04, 130.40, 129.07, 128.52, 128.32, 126.19, 123.05, 122.88, 120.18, 118.49, 111.25, 109.15, 52.65, 51.45, 49.39, 48.78, 27.75; TLC: R_f = 0.56(EtOAc /Hexane 9/1, v/v); rt(HPLC) = 18.33 min; HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{27}H_{23}BrN_3O_2$ 500.0968; found 500.0976.

(6R,12aS)-6-phenyl-2-((S)-1-phenylethyl)-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione (8i):

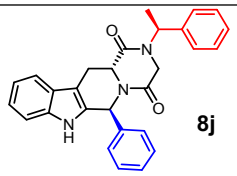


Chemical Formula: $C_{28}H_{25}N_3O_2$
Exact Mass: 435.19

Yield (158 mg, 73%); yellow oil; $[\alpha]_D$ = -184.4 ° (*c* 0.6, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.97 (br s, 1H, NH), 7.55 (d, *J* = 9.0 Hz, 1H), 7.38-7.12 (m, 13H), 7.00 (s, 1H), 6.01 (q, *J* = 7.0 Hz, 1H), 4.44 (dd, *J* = 12.25, 4.5 Hz, 1H), 4.01 (d, *J* = 18.0 Hz, 1H), 3.65 (d, *J* = 18.0 Hz, 1H), 3.62 (dd, *J* = 16.0, 4.5 Hz, 1H), 3.00 (dd, *J* = 16.0, 12.25 Hz, 1H), 1.58 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.49, 162.92, 137.82, 137.38, 136.65, 129.46, 128.99, 128.94, 128.41, 127.82, 127.40, 126.83, 126.21, 122.96, 120.31, 118.47, 111.26, 52.83, 52.39, 50.92, 43.64, 27.59, 15.08; TLC: R_f = 0.35 (EtOAc /Hexane 1/1, v/v); rt(HPLC) = 17.66 min; HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{28}H_{26}N_3O_2$ 436.2020; found 436.2018.

[20d]Vedantham, R.; Shanmugam, S.; Vetukuri, P.V.N.K.V.; Khagga, M.; Bandichhor, R. *Arkivoc***2013**, 22.

(6S,12aR)-6-phenyl-2-((S)-1-phenylethyl)-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione (8j):

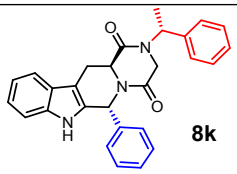


8j

Chemical Formula: $C_{28}H_{25}N_3O_2$
Exact Mass: 435.19

Yield (163 mg, 75%); pale yellow solid; mp= 195-197 °C; $[\alpha]_D$ = +75. 7 ° (*c* 0.6, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.80 (br s, 1H, NH), 7.56 (d, *J* = 7.75 Hz, 1H), 7.39-7.14 (m, 13H), 7.03 (s, 1H), 6.09 (q, *J* = 7.5 Hz, 1H), 4.45 (dd, *J* = 12.0, 3.75 Hz, 1H), 3.90 (d, *J* = 18.0 Hz, 1H), 3.63 (dd, *J* = 15.5, 3.75 Hz, 1H), 3.53 (d, *J* = 18.0 Hz, 1H), 2.94 (dd, *J* = 15.5, 12.0 Hz, 1H), 1.55 (d, *J* = 6.75 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.26, 162.58, 138.08, 136.41, 129.59, 128.93, 128.88, 128.75, 128.28, 127.44, 126.21, 122.78, 120.10, 118.42, 111.17, 108.93, 52.79, 52.18, 50.26, 43.82, 27.72, 14.54; TLC: R_f = 0.47 (EtOAc /Hexane 6/4, v/v); rt(HPLC) = 17.65 min; HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{28}H_{26}N_3O_2$ 436.2020; found 436.2010.

(6R,12aS)-6-phenyl-2-((R)-1-phenylethyl)-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione (8k):

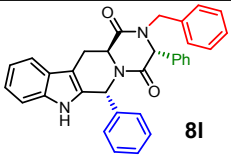


8k

Chemical Formula: $C_{28}H_{25}N_3O_2$
Exact Mass: 435.19

Yield (171mg, 79%); pale yellow solid; mp= 200-203 °C; $[\alpha]_D$ = -82.4 ° (*c* 0.55, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 8.28 (br s, 1H, NH), 7.52 (d, *J* = 7.75 Hz, 1H), 7.40-7.09 (m, 13H), 6.96 (s, 1H), 6.02 (q, *J* = 7.0 Hz, 1H), 4.33 (dd, *J* = 12.5, 4.5 Hz, 1H), 3.81 (d, *J* = 18.0 Hz, 1H), 3.55 (dd, *J* = 15.5, 4.5 Hz, 1H), 3.46 (d, *J* = 18.0 Hz, 1H), 2.86 (dd, *J* = 15.5, 12.5 Hz, 1H), 1.49 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.20, 162.30, 138.27, 136.40, 129.75, 128.98, 128.89, 128.83, 128.21, 127.35, 126.31, 122.64, 120.01, 118.41, 111.19, 108.90, 52.85, 52.07, 50.10, 43.91, 27.76, 14.61; TLC: R_f = 0.48 (EtOAc /Hexane 6/4, v/v); rt(HPLC) = 17.65 min; HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{28}H_{26}N_3O_2$ 436.2020; found 436.2027.

(3R,6R,12aS)-2-benzyl-3,6-diphenyl-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione (8l):

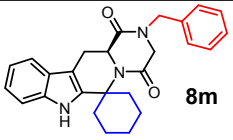


8l

Chemical Formula: $C_{33}H_{27}N_3O_2$
Exact Mass: 497.21

Yield (178 mg, 72%); white solid; mp= 267-269 °C; $[\alpha]_D$ = -26.6 ° (*c* 0.3, $CHCl_3$); ^1H NMR (250 MHz, DMSO-d_6) δ 11.04 (br s, 1H, NH), 7.58 (d, *J* = 7.25 Hz, 1H), 7.35-7.01 (m, 18H), 6.90 (s, 1H), 5.05 (d, *J* = 14.50 Hz, 1H), 5.02 (s, 1H), 4.53 (dd, *J* = 11.25, 4.75 Hz, 1H), 3.59 (dd, *J* = 16.0, 4.75 Hz, 1H), 3.56 (d, *J* = 14.50 Hz, 1H), 3.10 (dd, *J* = 16.0, 11.25 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.70, 163.56, 139.66, 138.02, 136.90, 136.23, 130.42, 129.63, 129.28, 129.05, 128.99, 128.73, 128.16, 128.13, 128.03, 127.86, 126.40, 122.17, 119.42, 118.72, 111.84, 107.38, 63.48, 52.42, 52.07, 47.16, 28.91; TLC: R_f = 0.53 (EtOAc /Hexane 3/7, v/v); rt(HPLC) = 19.25 min; HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{23}H_{27}N_3O_2Na$520.1995; found 520.2089.

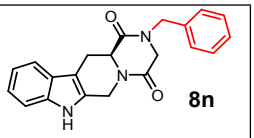
(S)-2'-benzyl-2',3',12',12a'-tetrahydro-4'H-spiro[cyclohexane-1,6'-pyrazino[1',2':1,6]pyrido[3,4-b]indole]-1',4'(7'H)-dione (8m):



Chemical Formula: $C_{26}H_{27}N_3O_2$
Exact Mass: 413.21

Yield (166 mg, 80%); white solid; mp= 281-283 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.83 (br s, 1H, NH), 8.04 (s, 1H); 7.46 (d, *J* = 8.0 Hz, 1H), 7.31-7.22 (m, 4H), 7.05-7.02 (m, 3H), 6.95 (t, *J* = 8.0 Hz, 1H), 6.00 (s, 1H), 4.60 (d, *J* = 15.0 Hz, 1H), 4.10-4.07 (m, 1H); 3.91 (d, *J* = 15. 0 Hz, 1H), 3.31-3.21 (m, 3H), 3.05 (d, *J* = 17.0 Hz, 1H), 2.40-2.35 (m, 2H), 2.20-2.14 (m, 2H), 1.75-1.68 (m, 2H), 1.66-1.59 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.99, 165.07, 139.45, 136.55, 135.65, 130.43, 129.13, 129.04, 128.17, 127.96, 127.85, 121.40, 118.97, 111.17, 104.68, 56.72, 48.92, 48.72, 29.81, 27.96, 25.69, 22.88, 22.00; TLC: R_f = 0.31 (EtOAc /Hexane 8/2, v/v); rt(HPLC) = 15.72 min; HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{26}H_{27}N_3O_2Na$436.1996; found 436.1970.

(S)-2-benzyl-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione (8n):

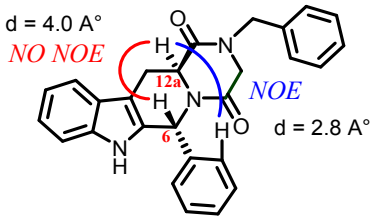


Chemical Formula: $C_{21}H_{19}N_3O_2$
Exact Mass: 345.15

Yield (130 mg, 75%); off-white solid; mp= 185-188 °C;^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (br s, 1H, NH), 7.50 (d, *J* = 7.0 Hz, 1H), 7.41-7.22 (m, 6H), 7.21-7.13 (m, 2H), 5.62 (d, *J* = 17.50 Hz, 1H), 4.74 (d, *J* = 14.0 Hz, 1H), 4.66 (d, *J* = 14. 0 Hz, 1H), 4.45 (d, *J* = 10.50 Hz, 1H), 4.21 (d, *J* = 16.50 Hz, 1H), 4.02 (s, 2H), 3.59 (d, *J* = 15.0 Hz, 1H), 2.96 (t, *J* = 13.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.44, 163.06, 136.22, 134.84, 129.09, 128.53, 128.83, 128.33, 128.02, 126.65, 122.58, 120.20, 118.20, 111.00, 107.44, 56.88, 49.49, 48.68, 40.05, 27.41; TLC: R_f = 0.45 (EtOAc /Hexane 19/1, v/v); rt(HPLC) = 14.95 min; HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{21}H_{20}N_3O_2$346.1550; found 346.1553.

4. NOESY Studies of 8a and 8l

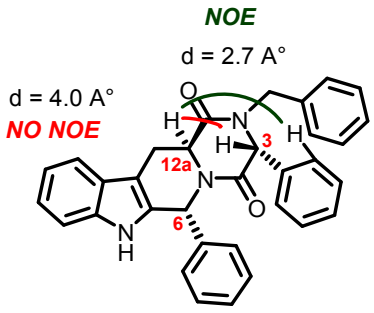
The relative configuration of the THBC-based DKP **8a** was confirmed by NOESY studies. As shown in Figure 3, the configuration of the *trans* isomer **8a** was determined by the presence of a nOe between the proton at position C-12a and the aryl ortho protons at position C-6, thus confirming a *trans*-stereochemistry for **8a**. Since the C-12a configuration was known (L-tryptophan was used as starting material) the absolute configuration of the major isomers corresponds to (6*R*,12a*S*).



THBC-based DKP (**8a**)

Figure 1. Identification of the relative configuration of **8a** by 2D NOESY experiments

The relative configuration of the THBC-based DKP **8l** was confirmed by NOESY studies. As shown in Figure 4, the configuration of the *trans* isomer **8l** was determined by the presence of a nOe between the proton at position C-12a and the aryl ortho protons at position C-3, thus confirming a *trans*-stereochemistry for **8l**. Since the C-12a configuration was known (L-tryptophan was used as starting material) the absolute configuration of the major isomers corresponds to (3*R*, 6*R*,12a*S*).

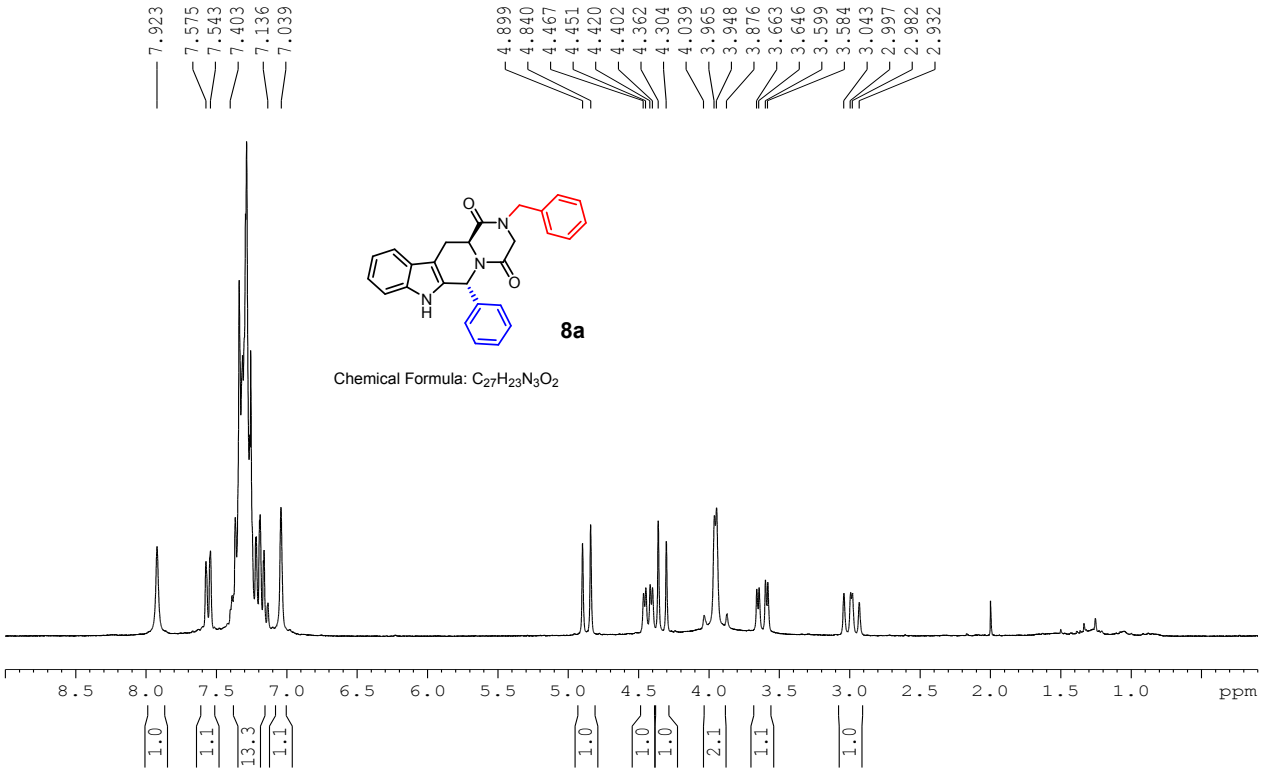


THBC-based DKP (**8l**)

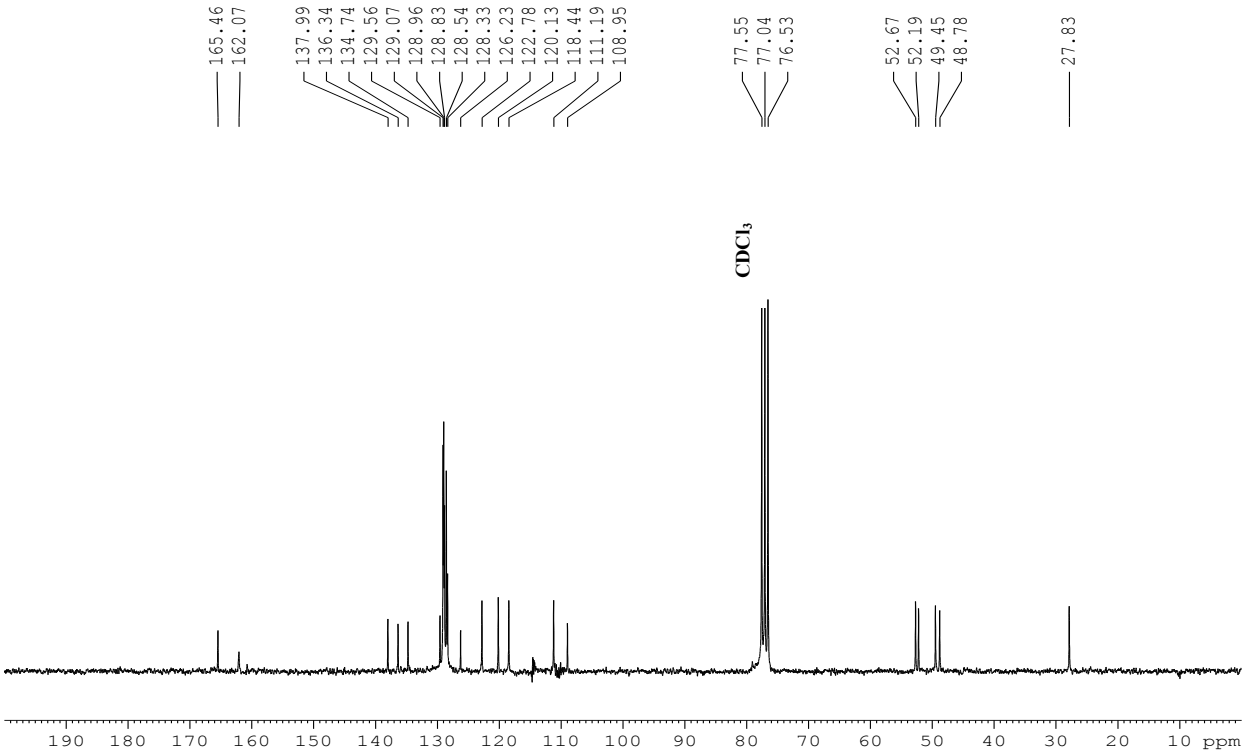
Figure 2. Identification of the relative configuration of **8l** by 2D NOESY experiments

5. NMR Spectra

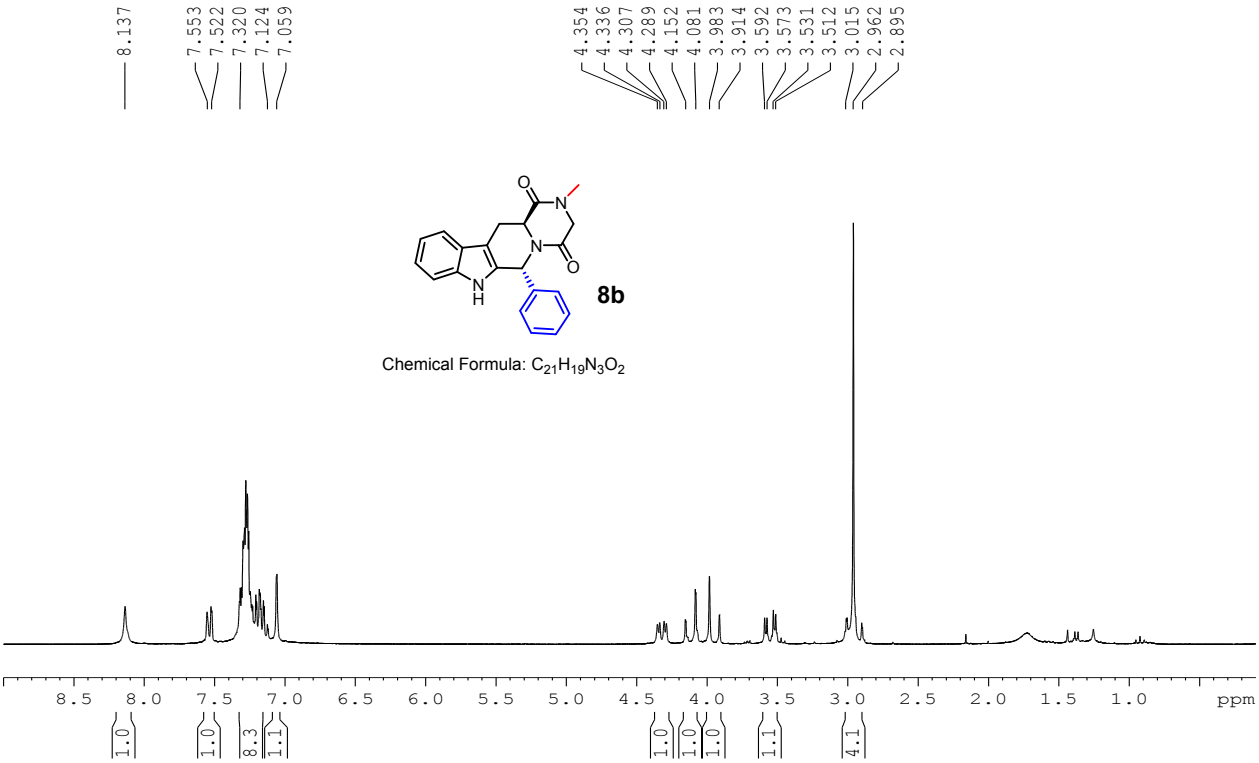
(8a): ^{1}H NMR (250 MHz, $CDCl_3$)



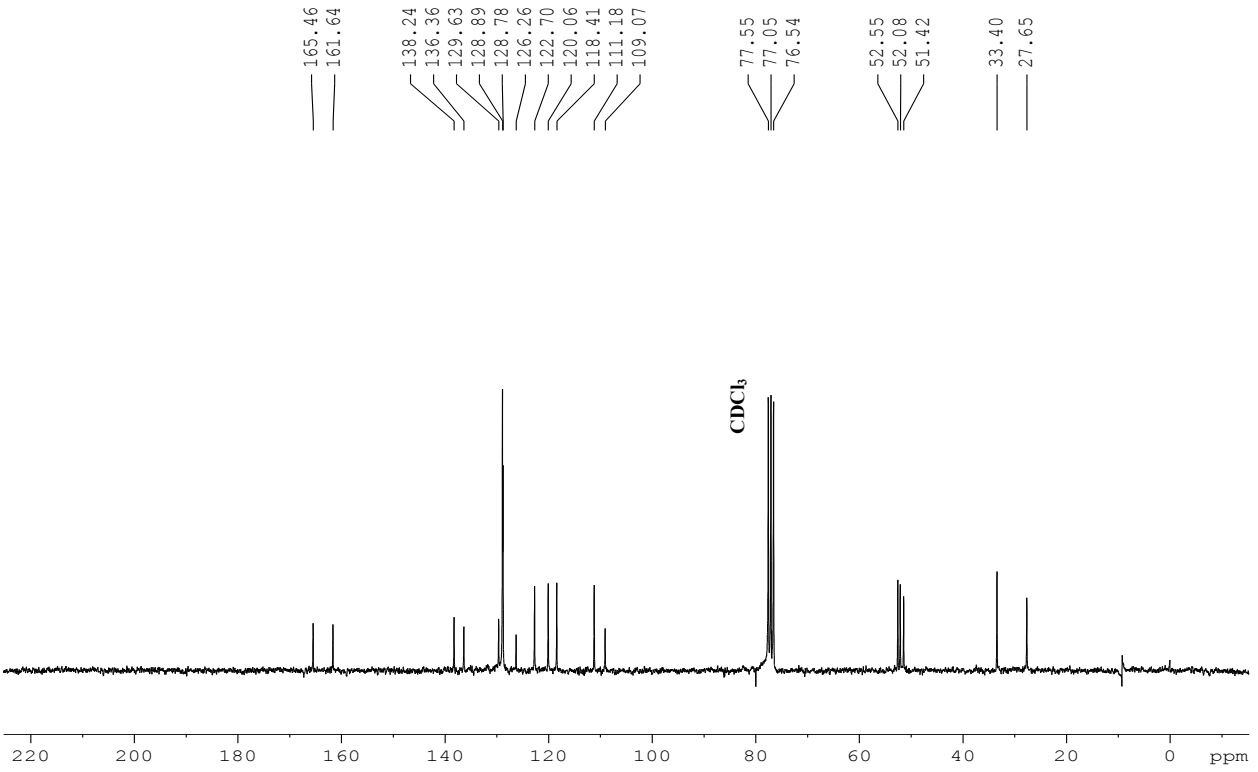
(8a): ^{13}C NMR (63 MHz, $CDCl_3$)



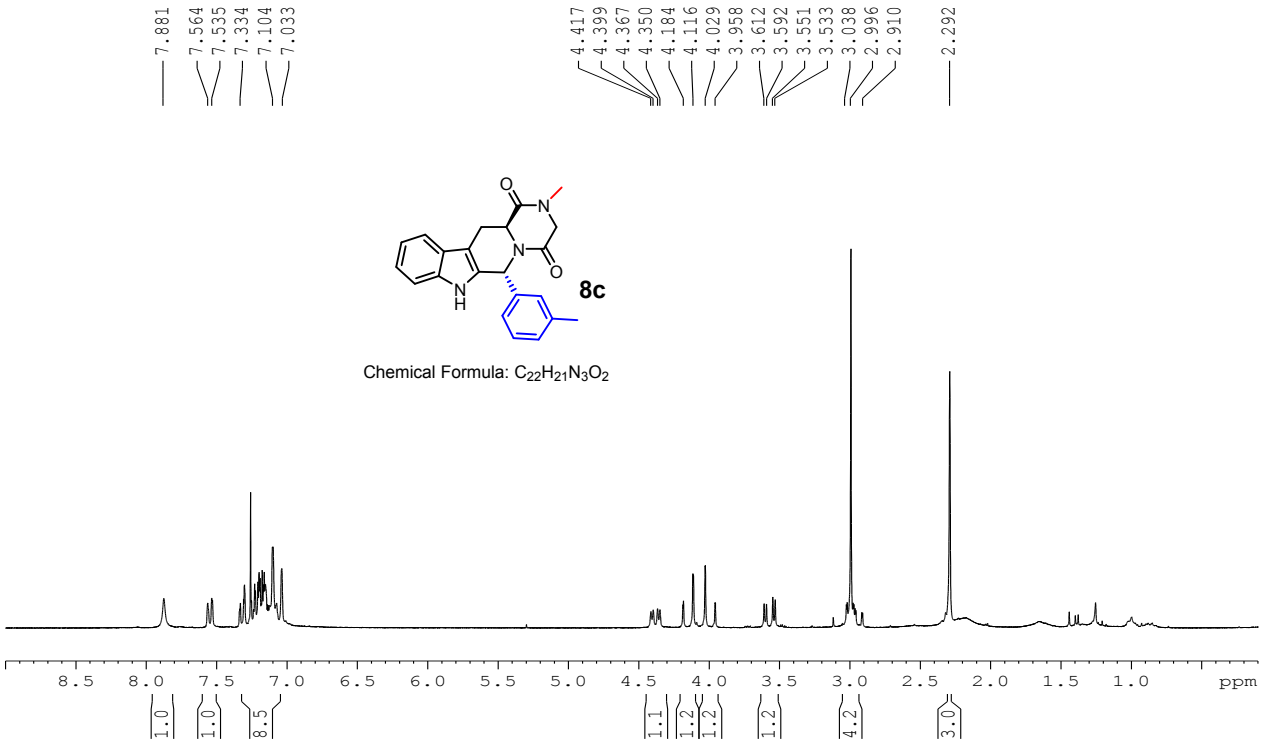
(8b): ^{1}H NMR (250 MHz, $CDCl_3$)



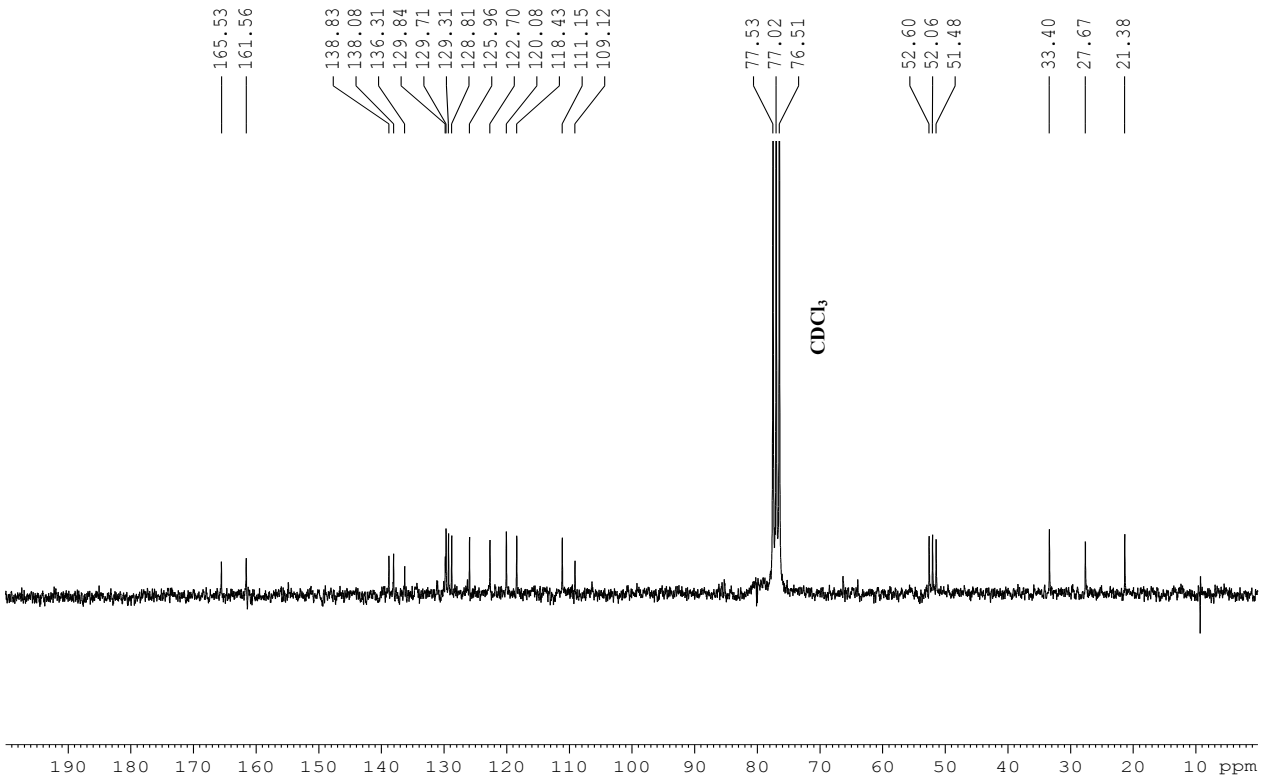
(8b): ^{13}C NMR (63 MHz, $CDCl_3$)



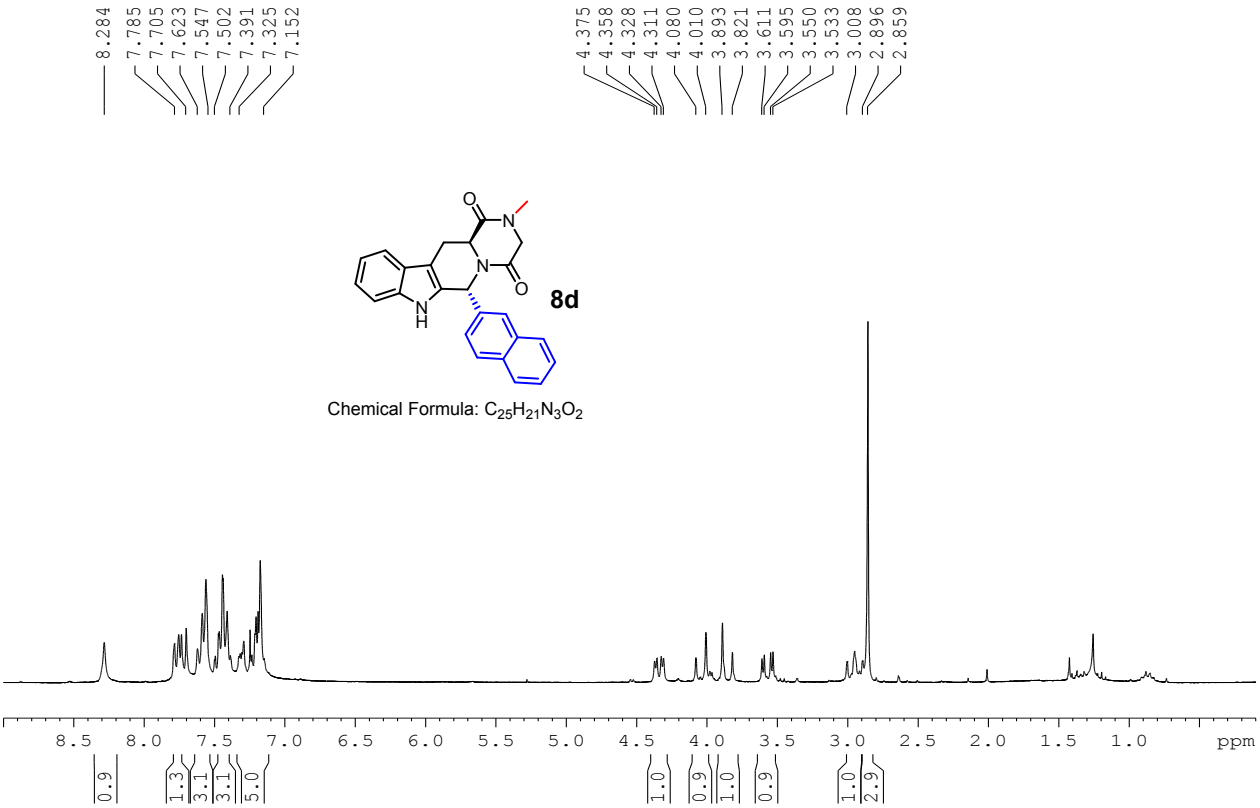
(8c): ^{1}H NMR (250 MHz, $CDCl_3$)



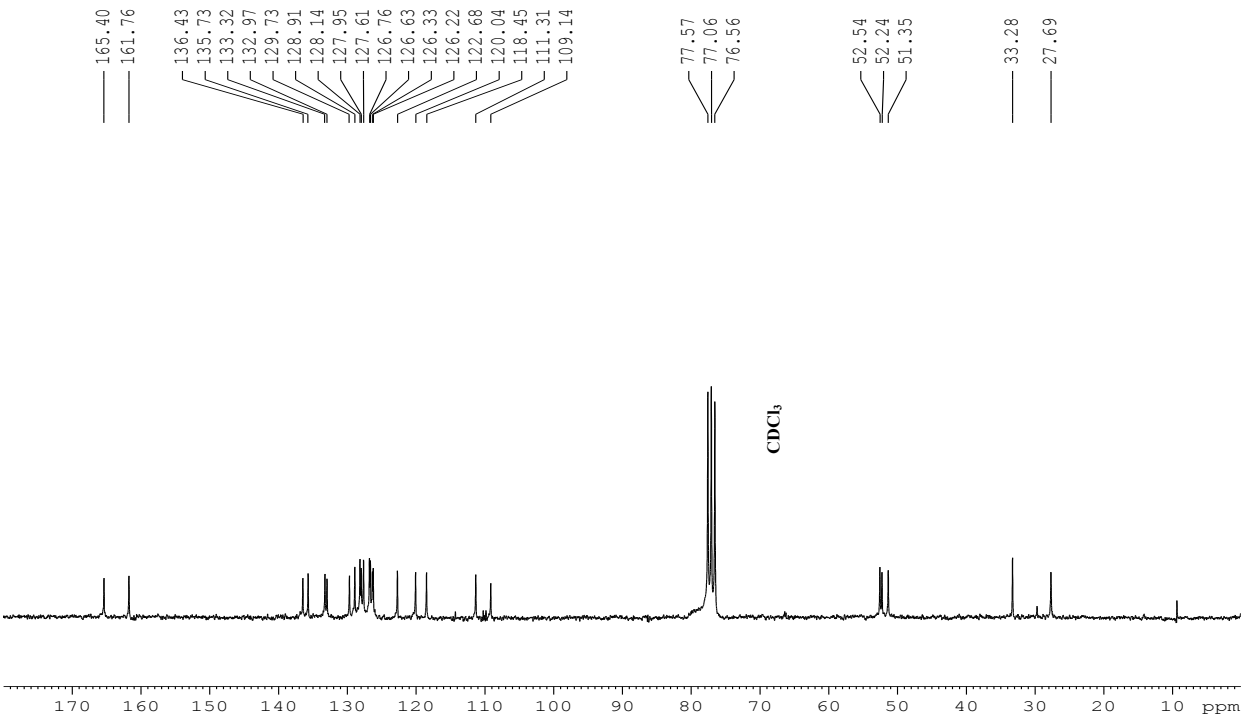
(8c): ^{13}C NMR (63 MHz, $CDCl_3$)



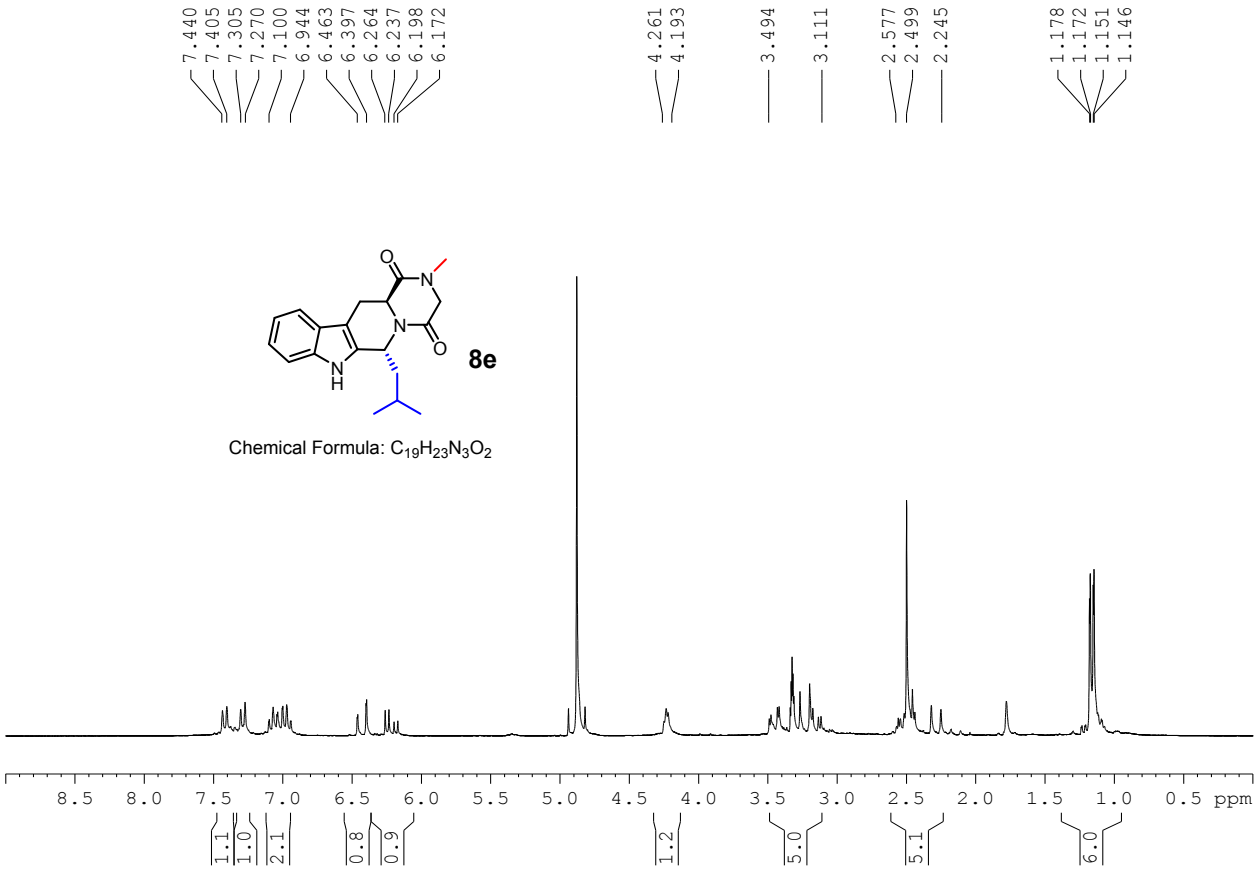
(8d): ^{1}H NMR (250 MHz, $CDCl_3$)



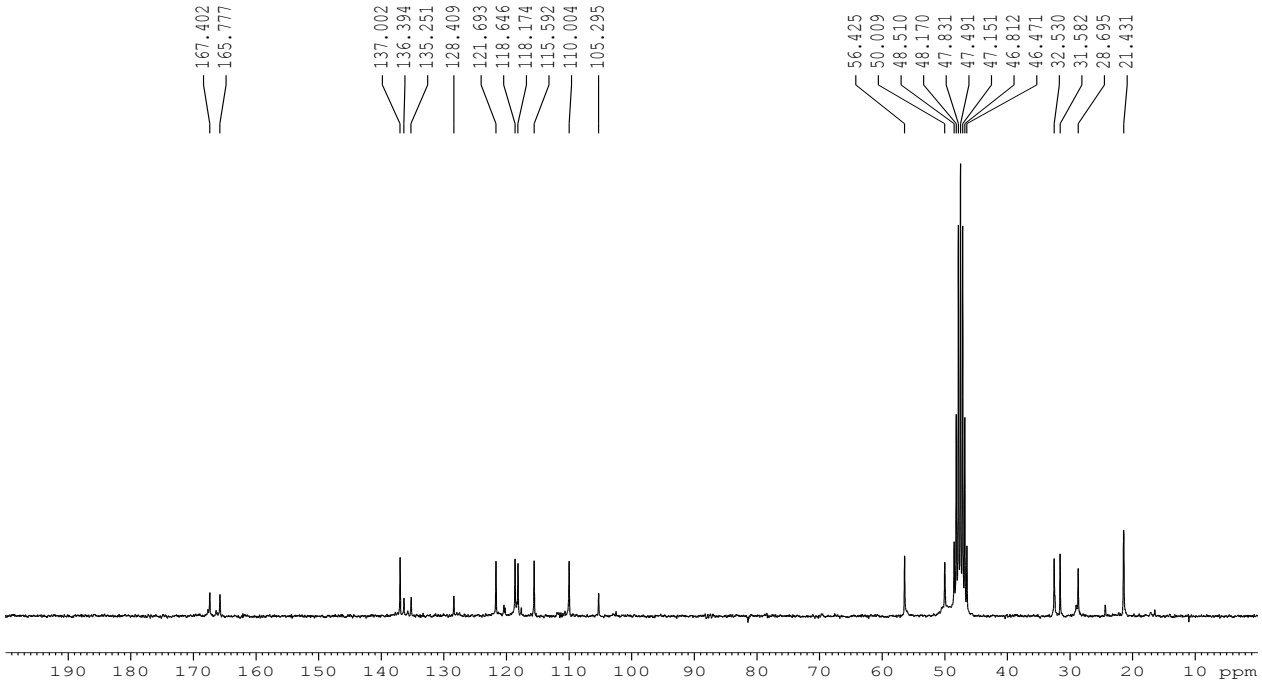
(8d): ^{13}C NMR (63 MHz, $CDCl_3$)



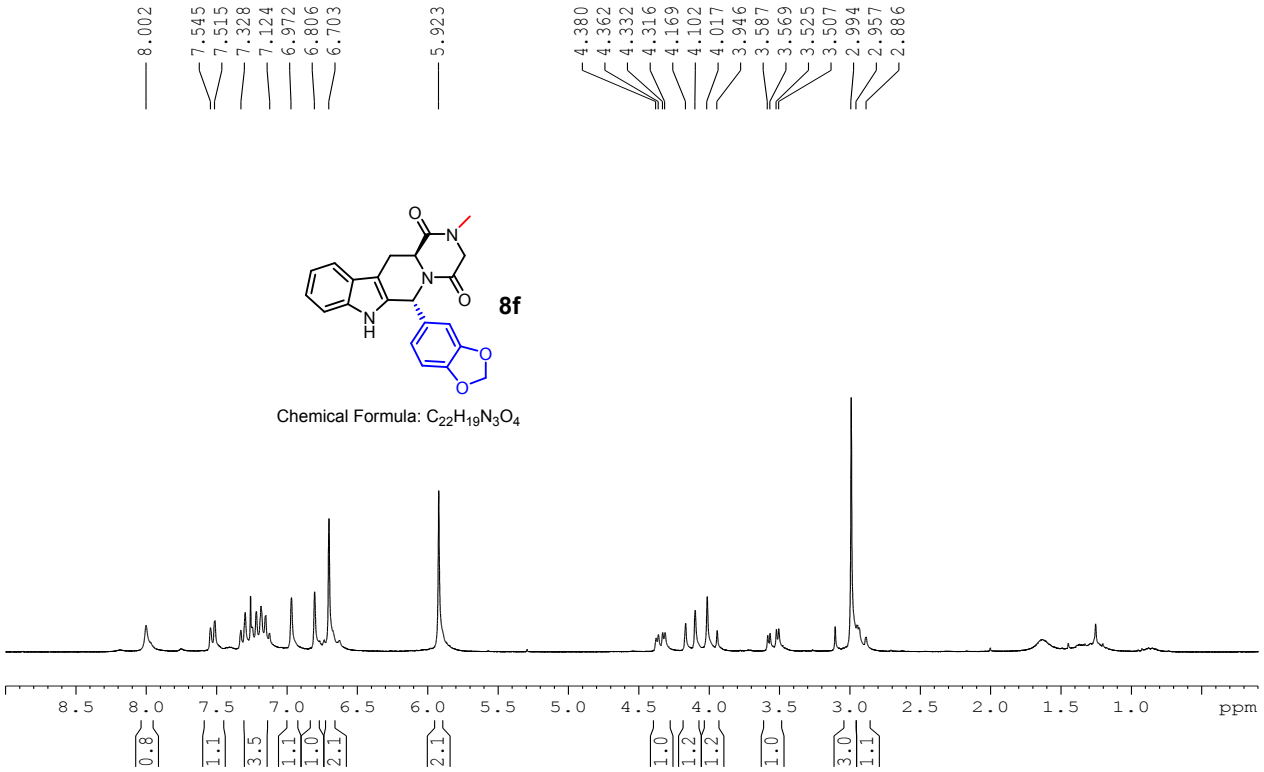
(8e): ^{1}H NMR (250 MHz, MeOD)



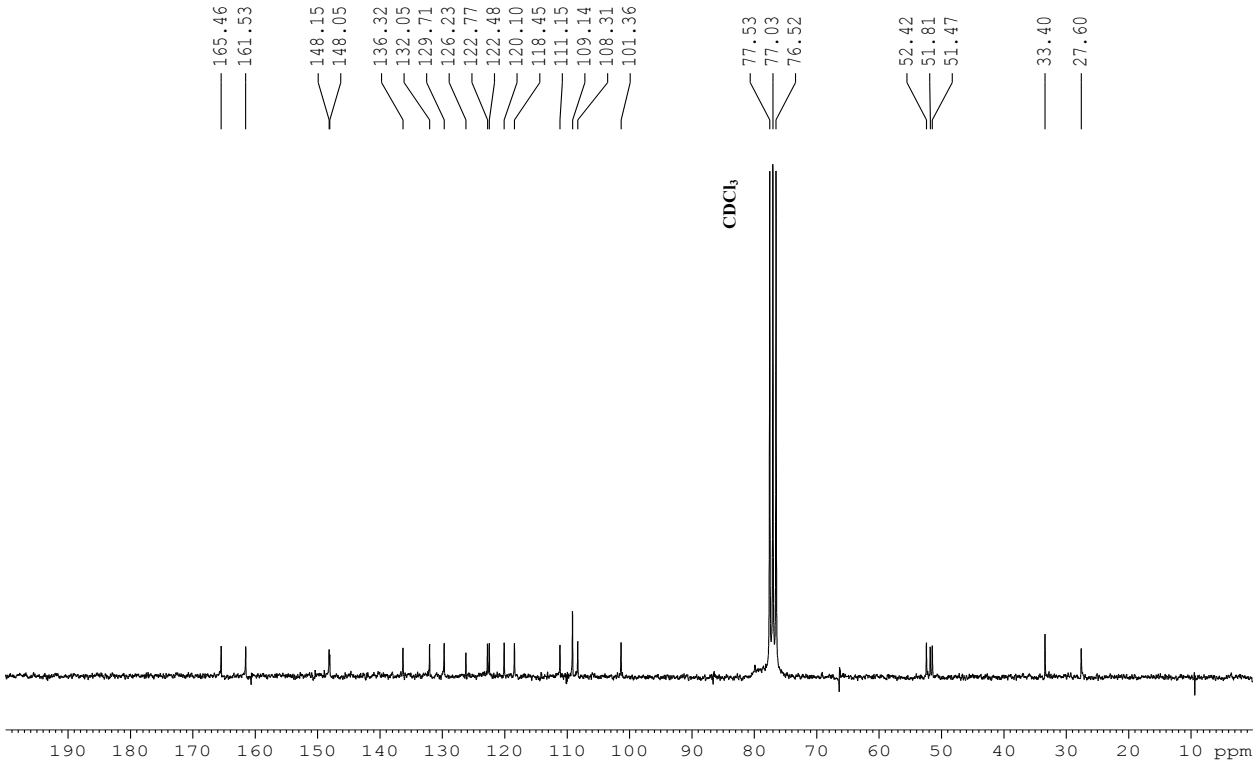
(8e): ^{13}C NMR (63 MHz, MeOD)



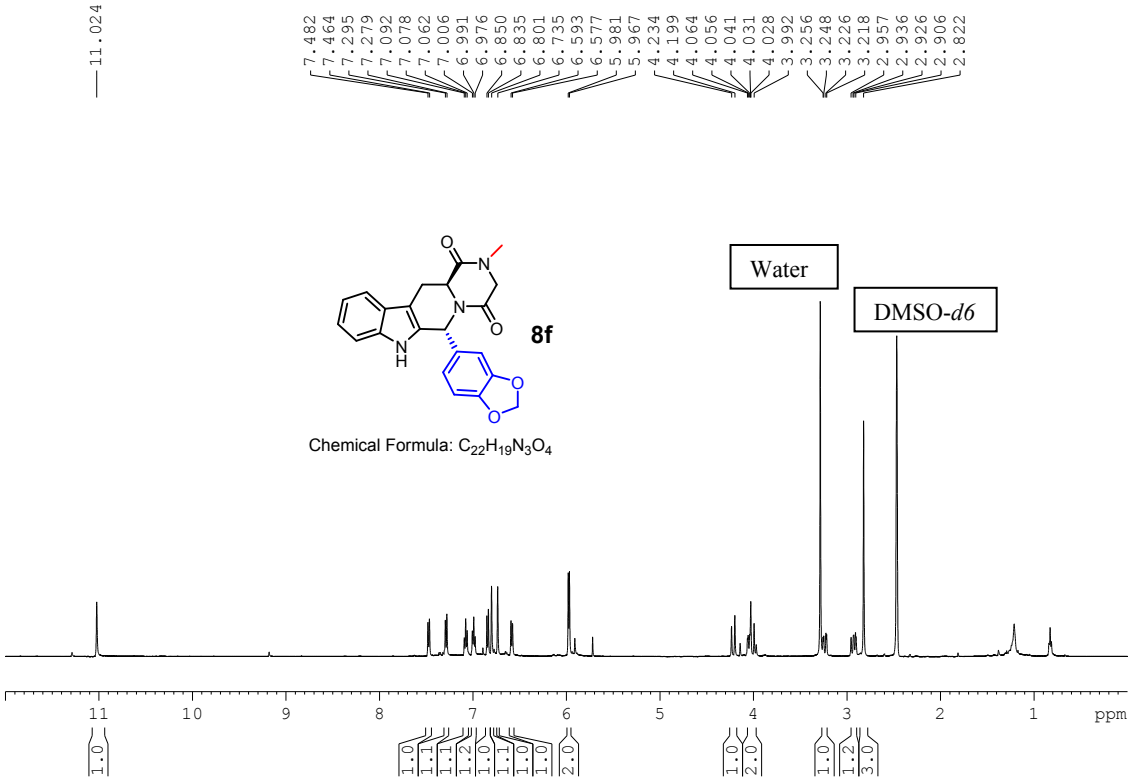
(8f): ^{1}H NMR (250 MHz, $CDCl_3$)



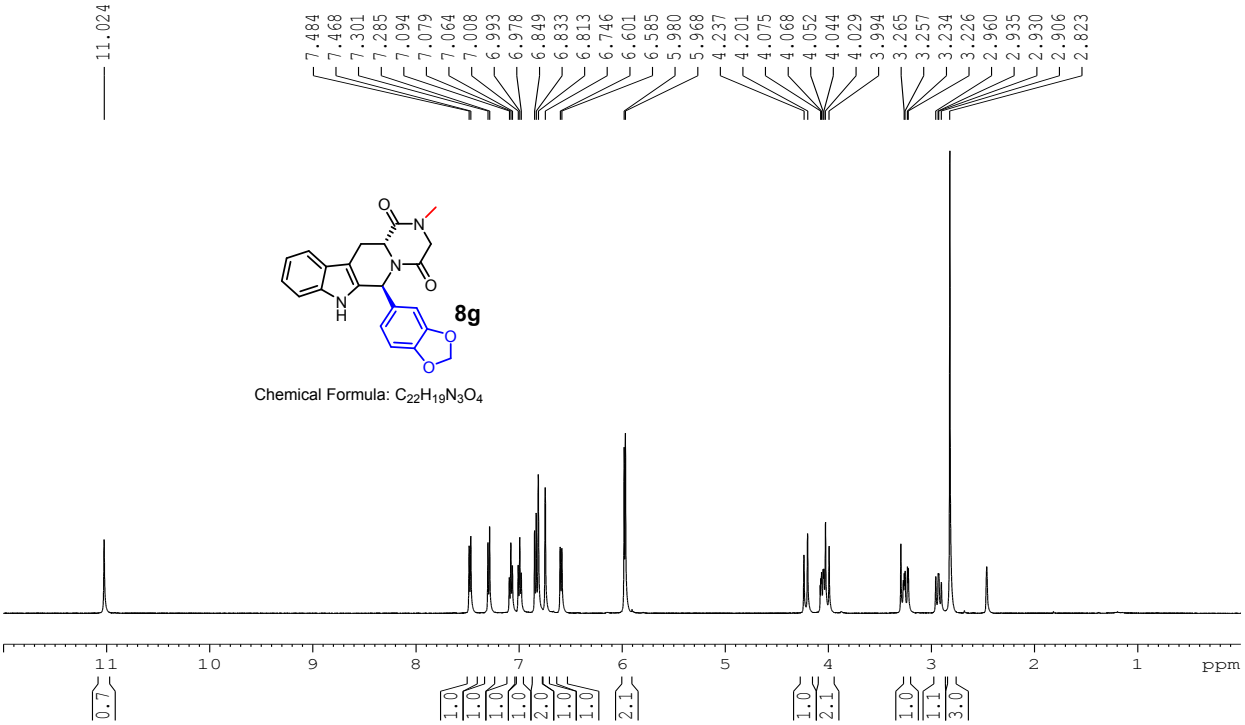
(8f): ^{13}C NMR (63 MHz, $CDCl_3$)



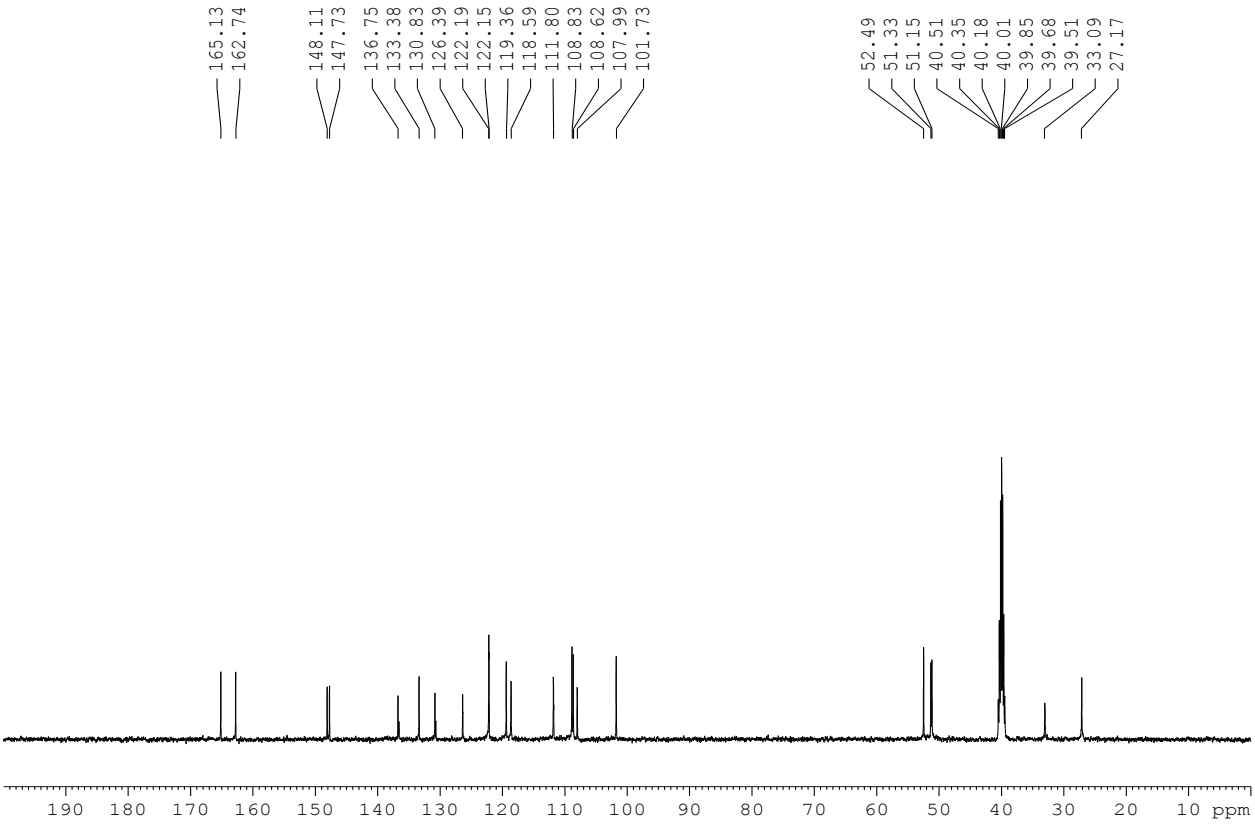
(8f): ^{1}H NMR (500 MHz, $(CD_3)_2SO$)



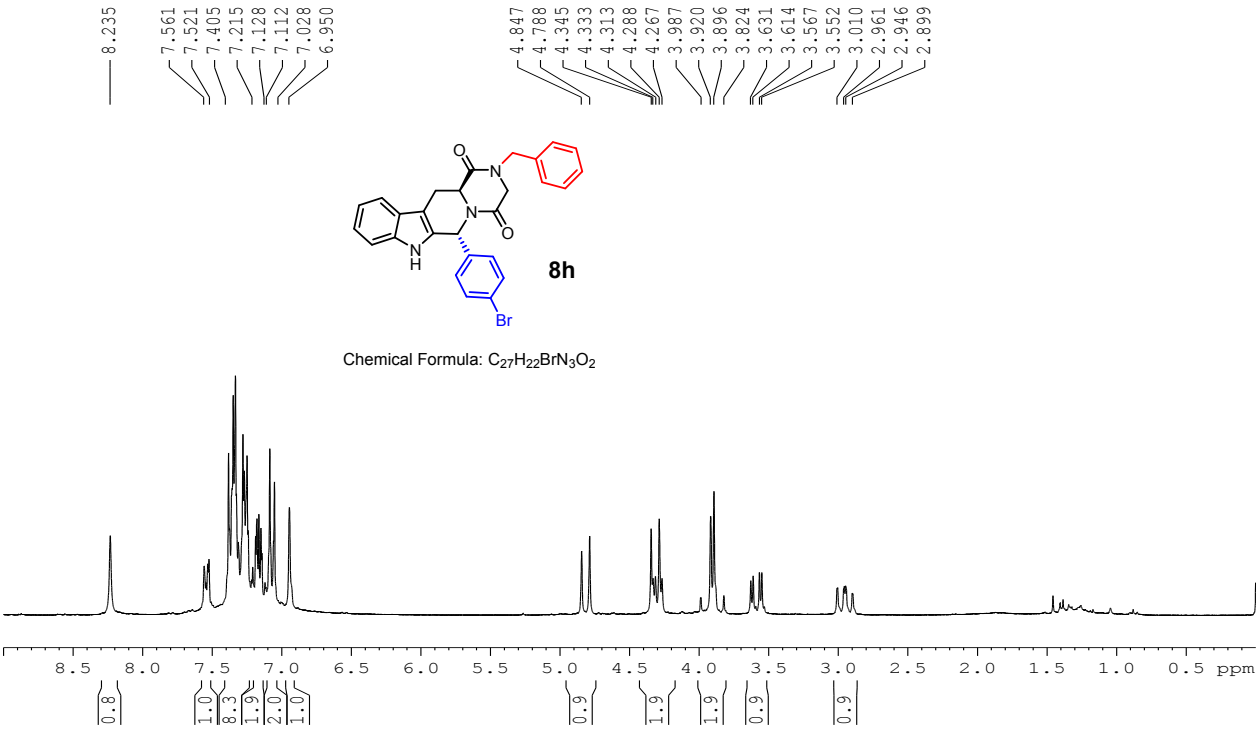
(8g): ^{1}H NMR (500 MHz, $(CD_3)_2SO$)



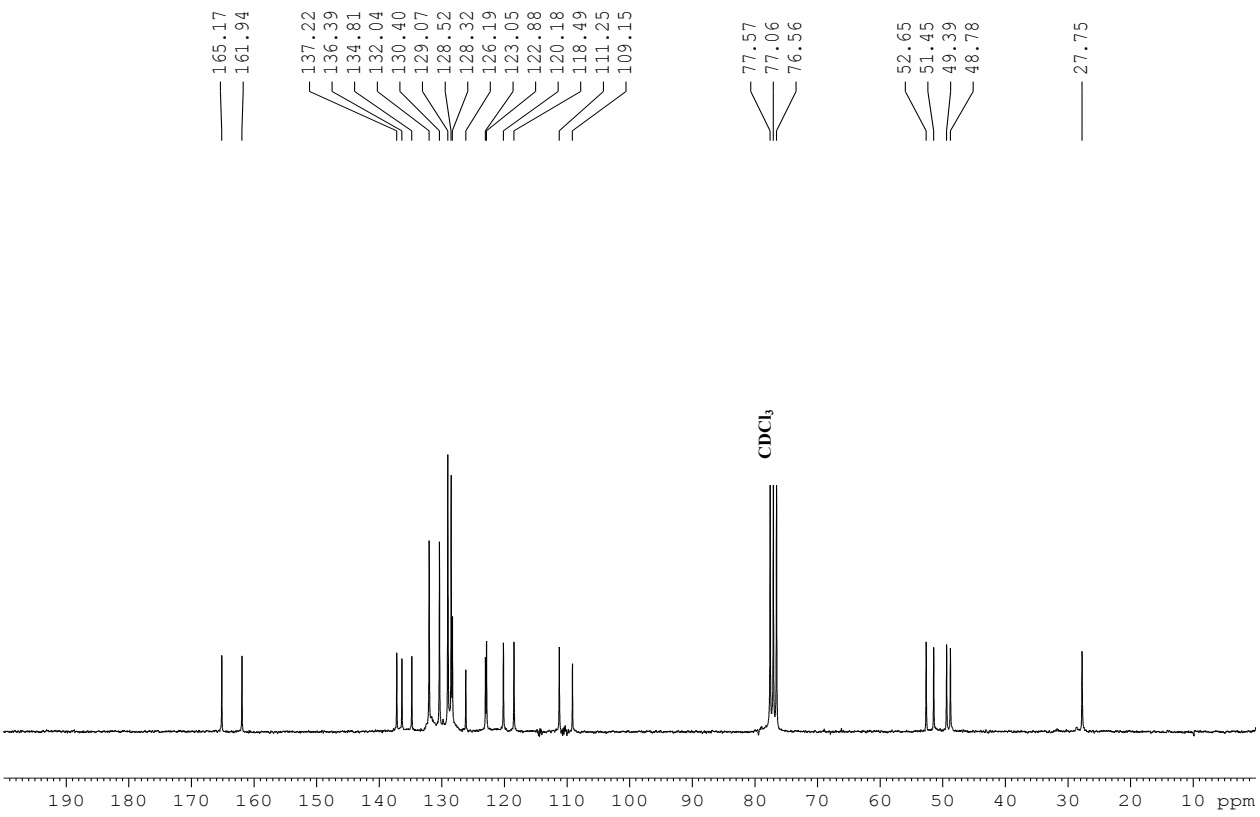
(8g): ^{13}C NMR (126 MHz, $(CD_3)_2SO$)



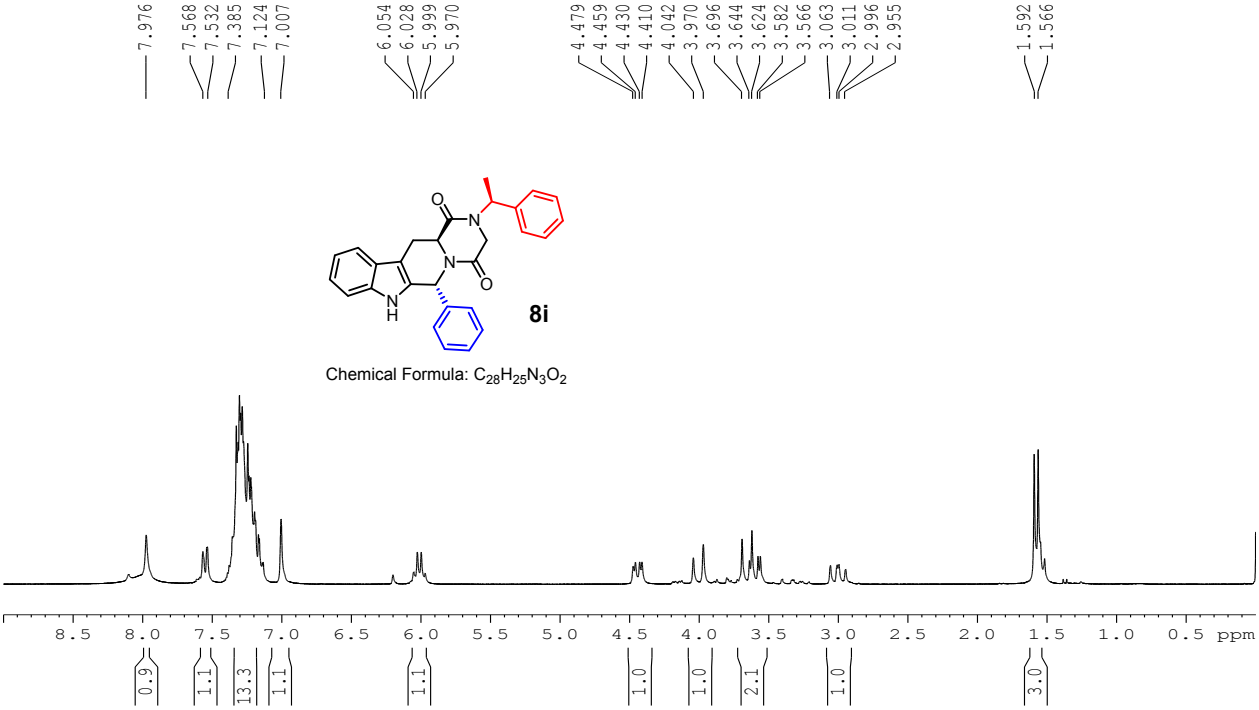
(8h): ^{1}H NMR (250 MHz, $CDCl_3$)



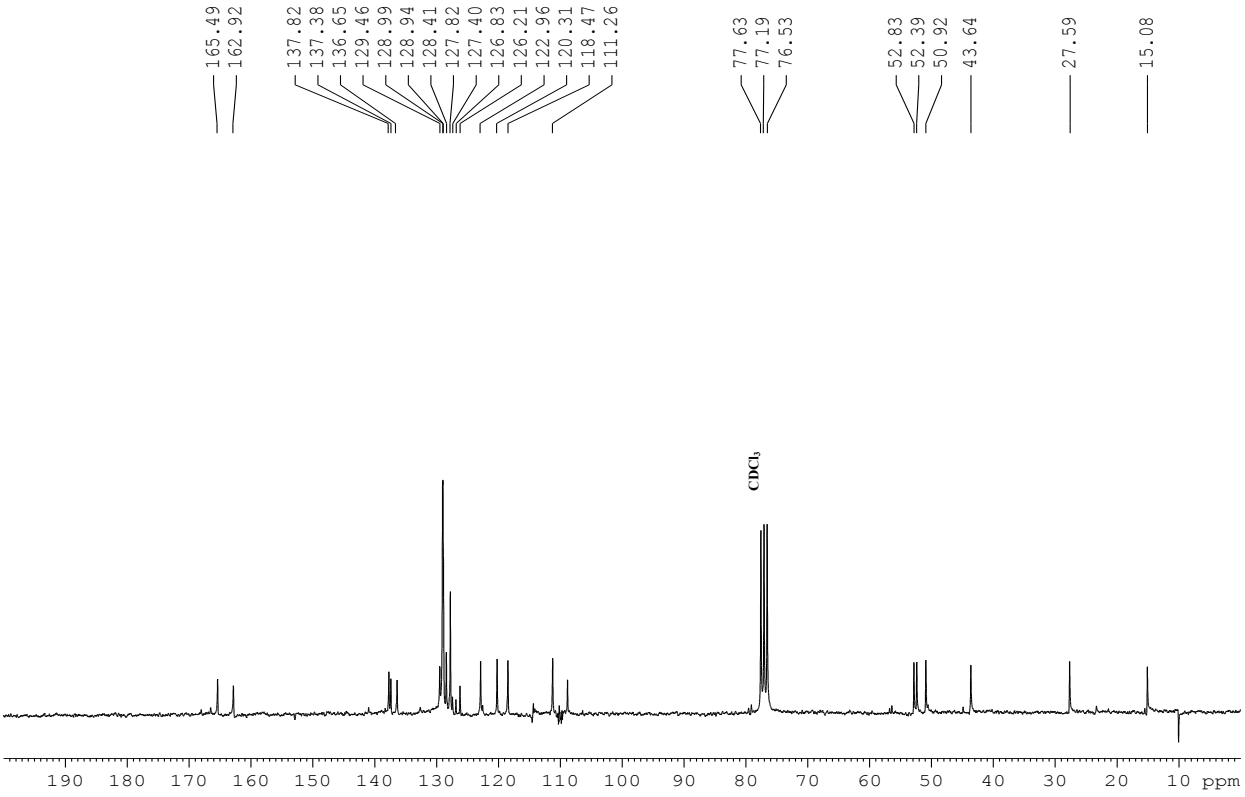
(8h): ^{13}C NMR (63 MHz, $CDCl_3$)



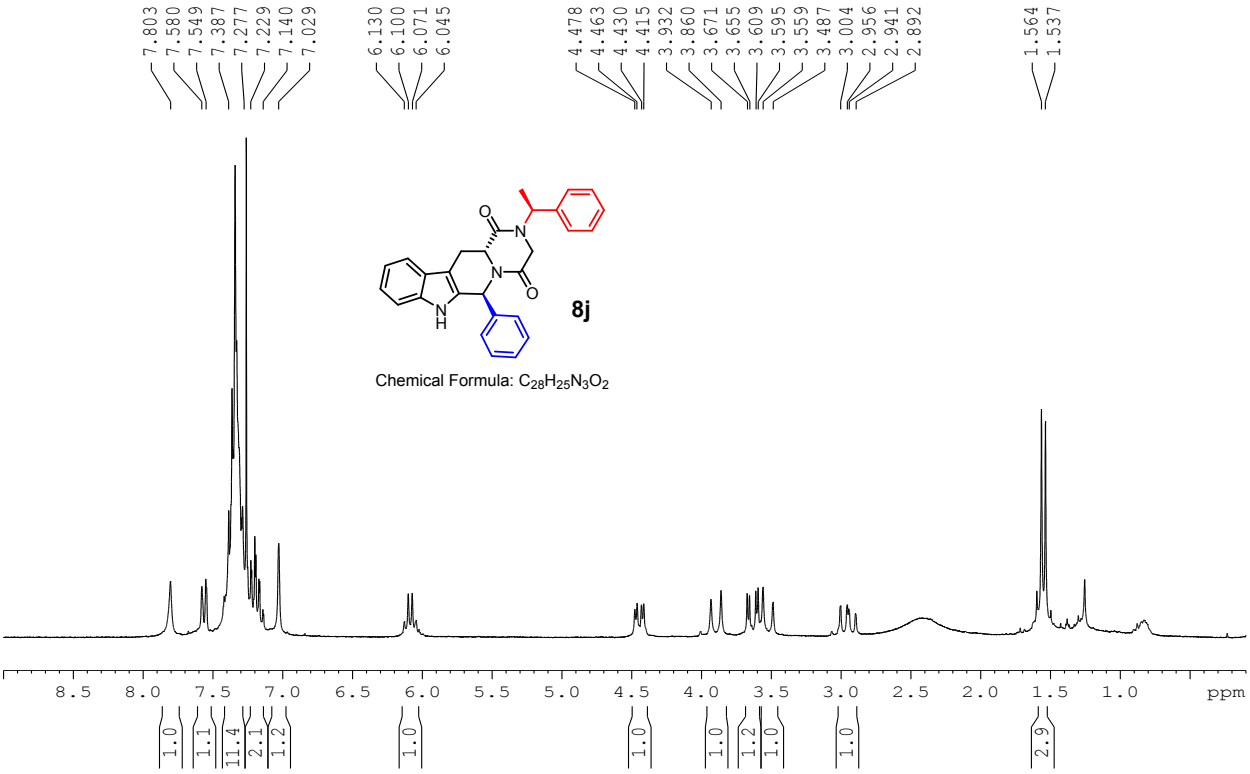
(8i): ^{1}H NMR (250 MHz, $CDCl_3$)



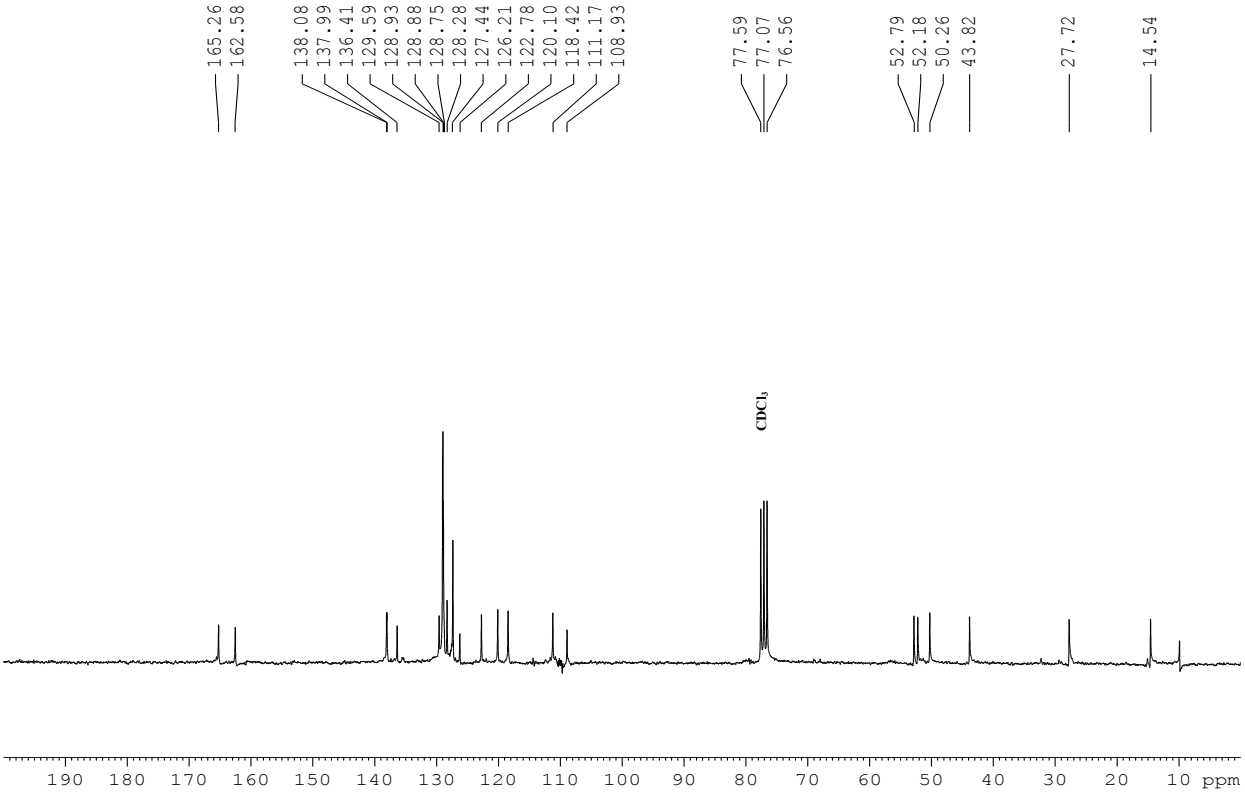
(8i): ^{13}C NMR (63 MHz, $CDCl_3$)



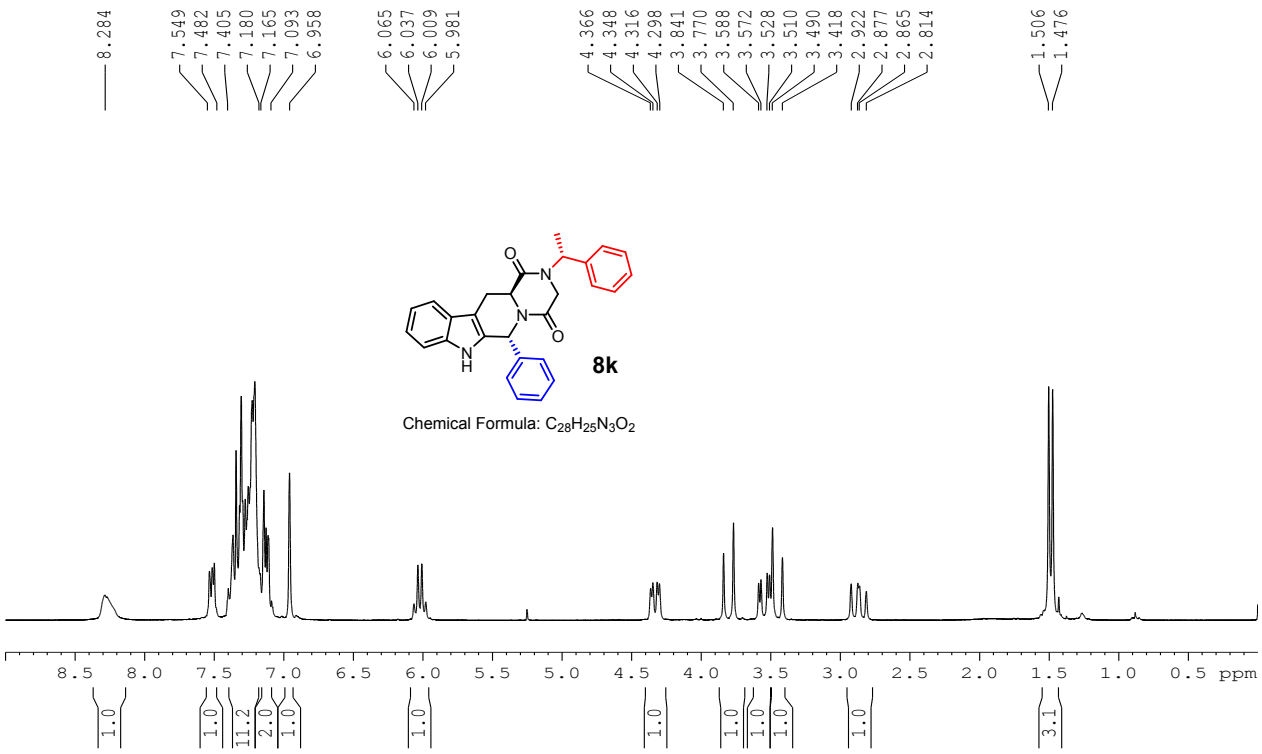
(8j): ^{1}H NMR (250 MHz, $CDCl_3$)



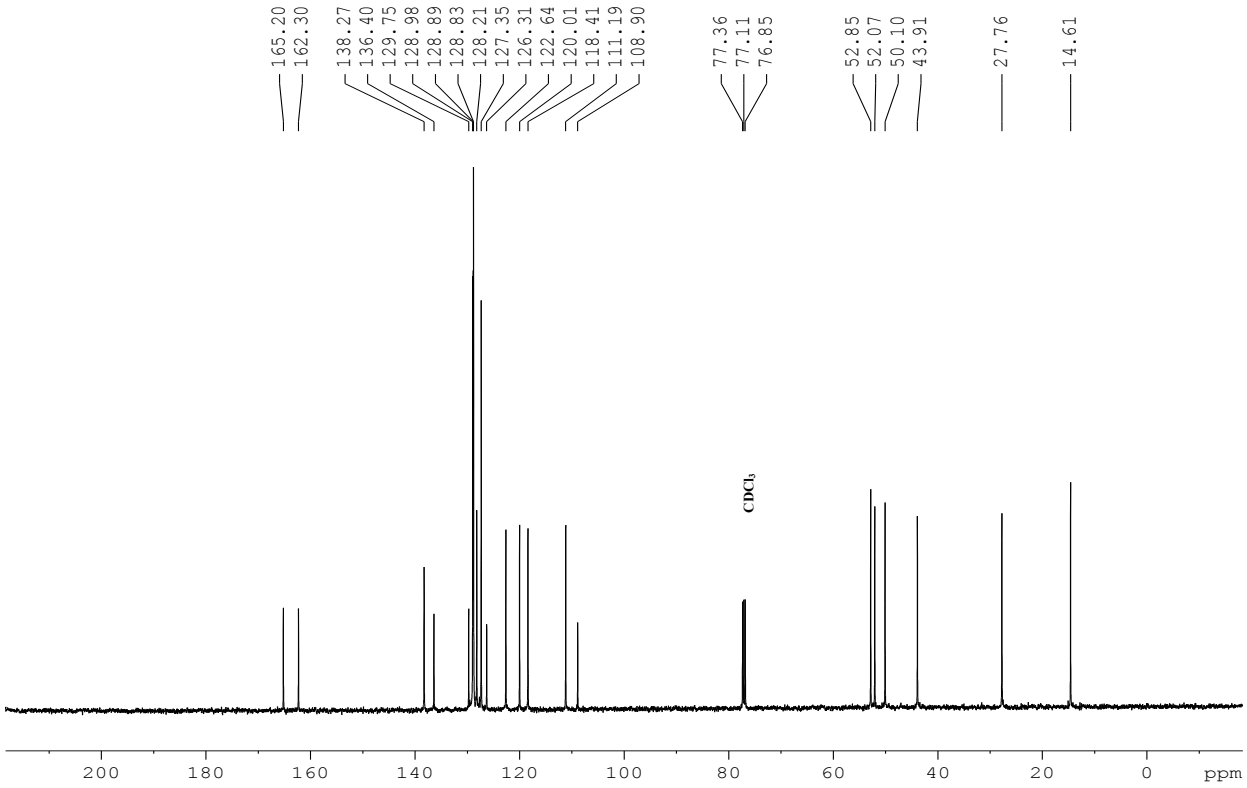
(8j): ^{13}C NMR (63 MHz, $CDCl_3$)



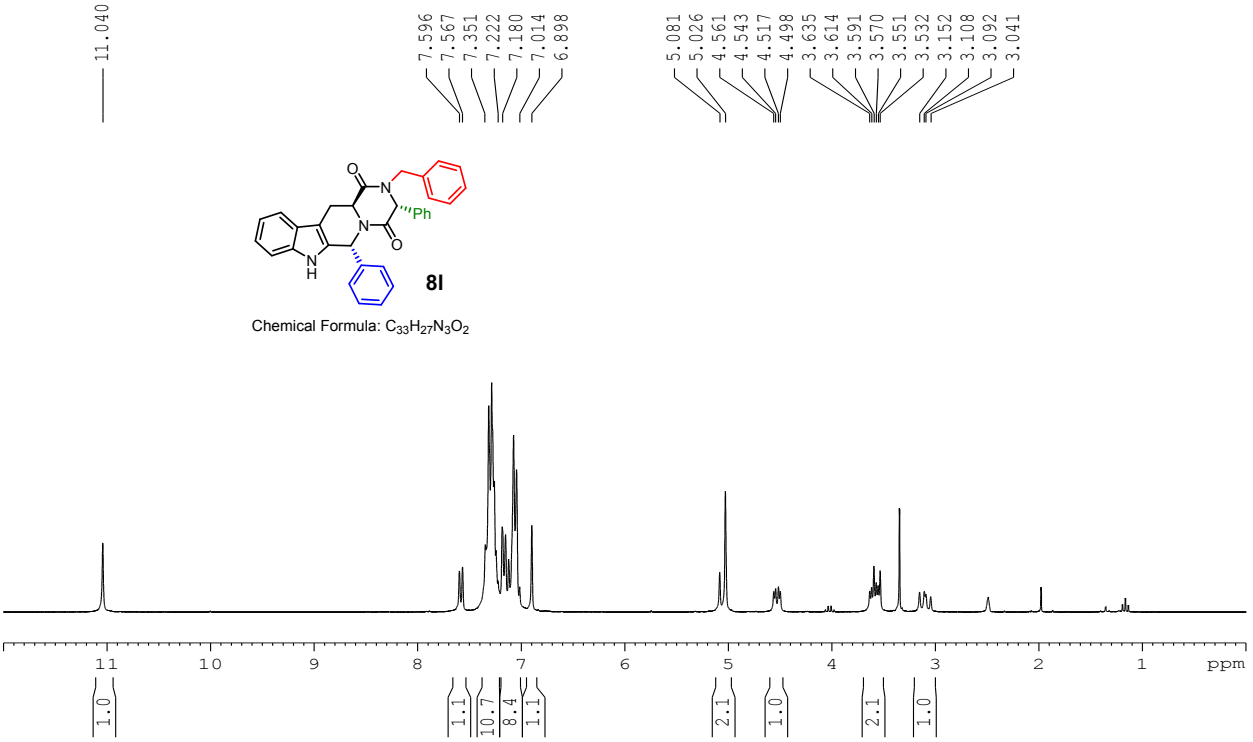
(8k): ^{1}H NMR (250 MHz, $CDCl_3$)



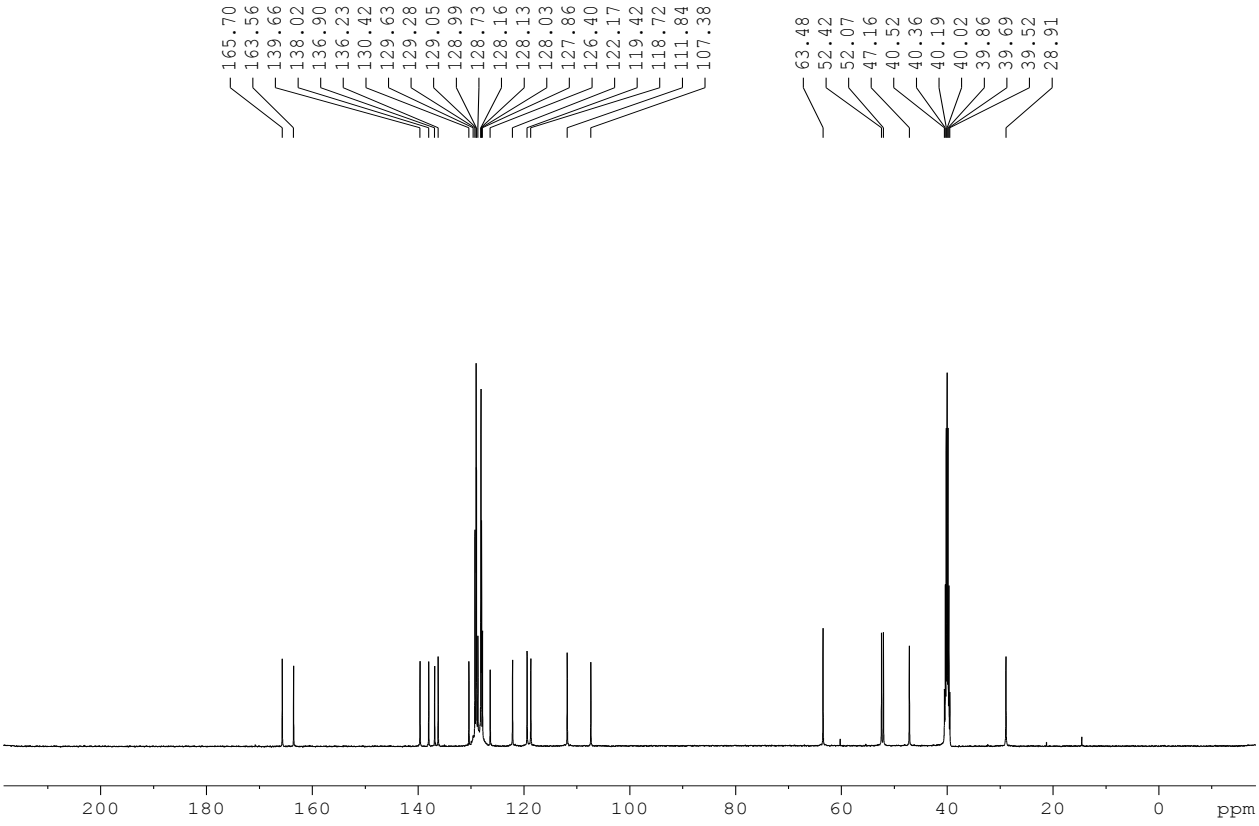
(8k): ^{13}C NMR (126 MHz, $CDCl_3$)



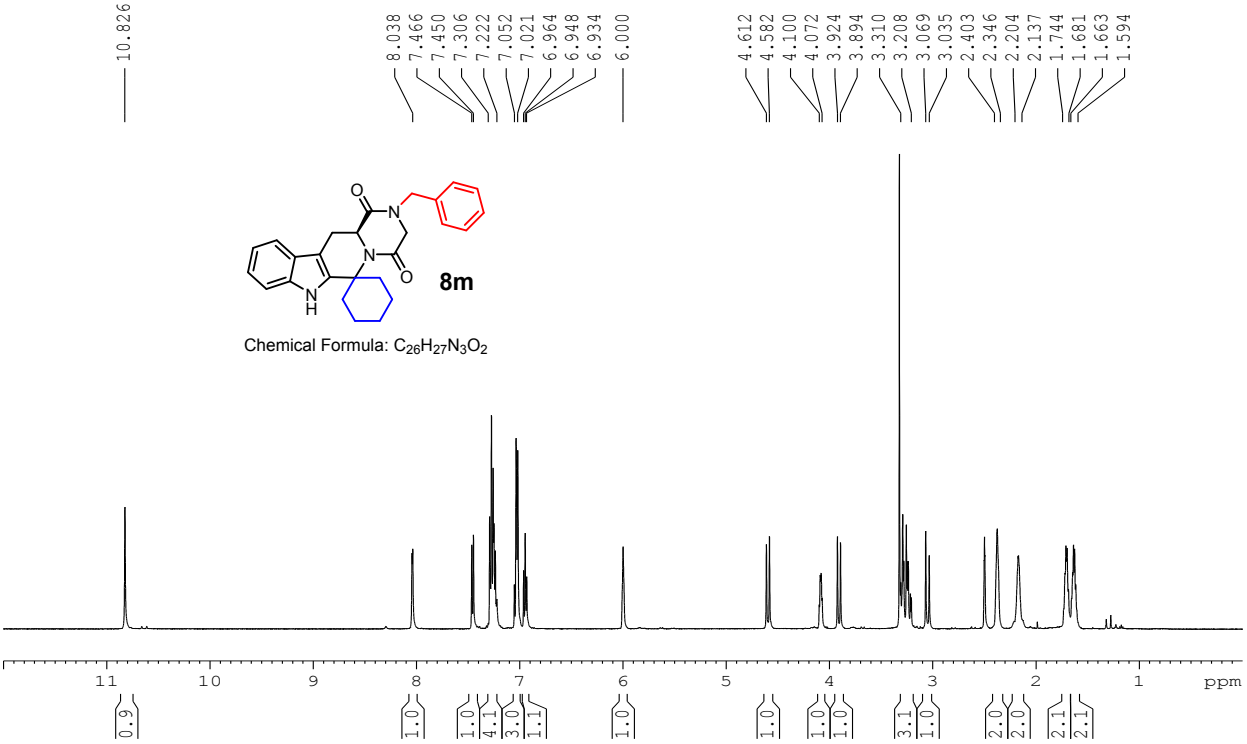
(8l): ^{1}H NMR (250 MHz, $(CD_3)_2SO$)



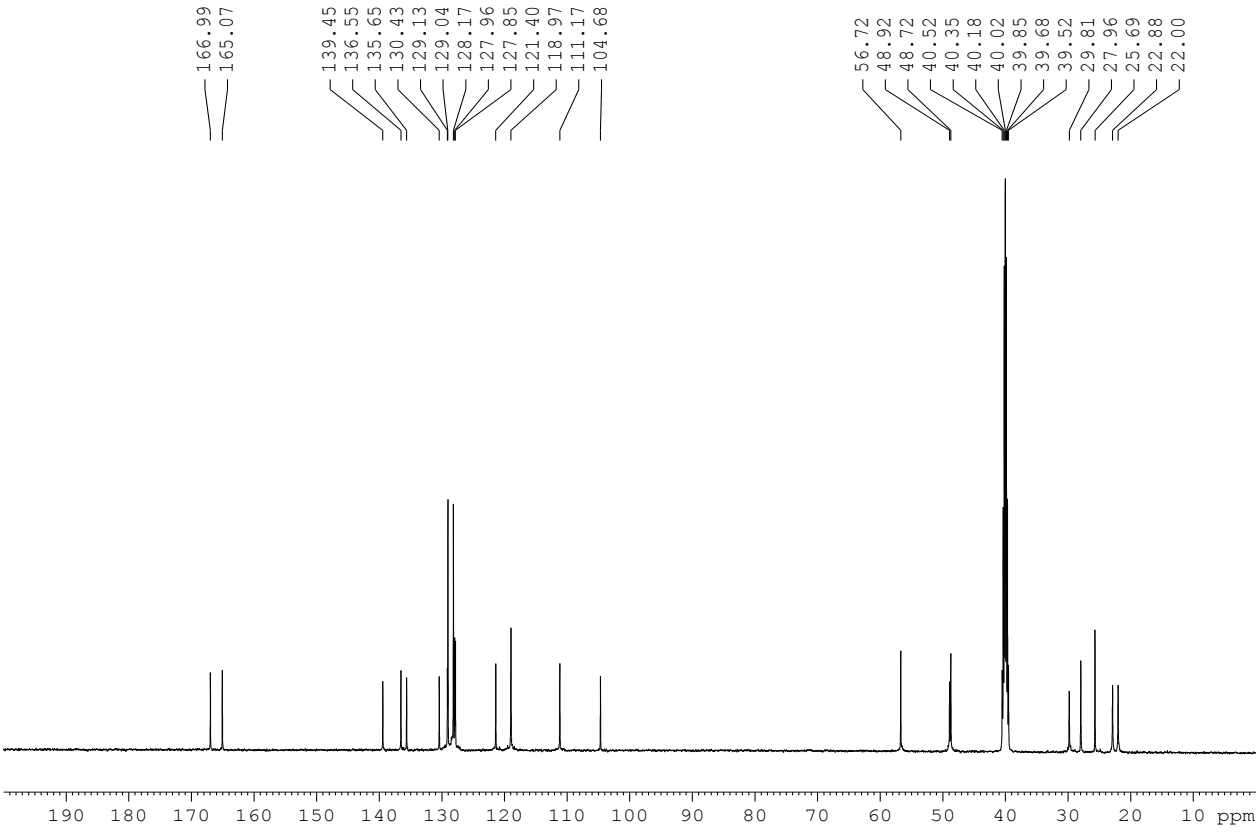
(8l): ^{13}C NMR (126 MHz, $(CD_3)_2SO$)



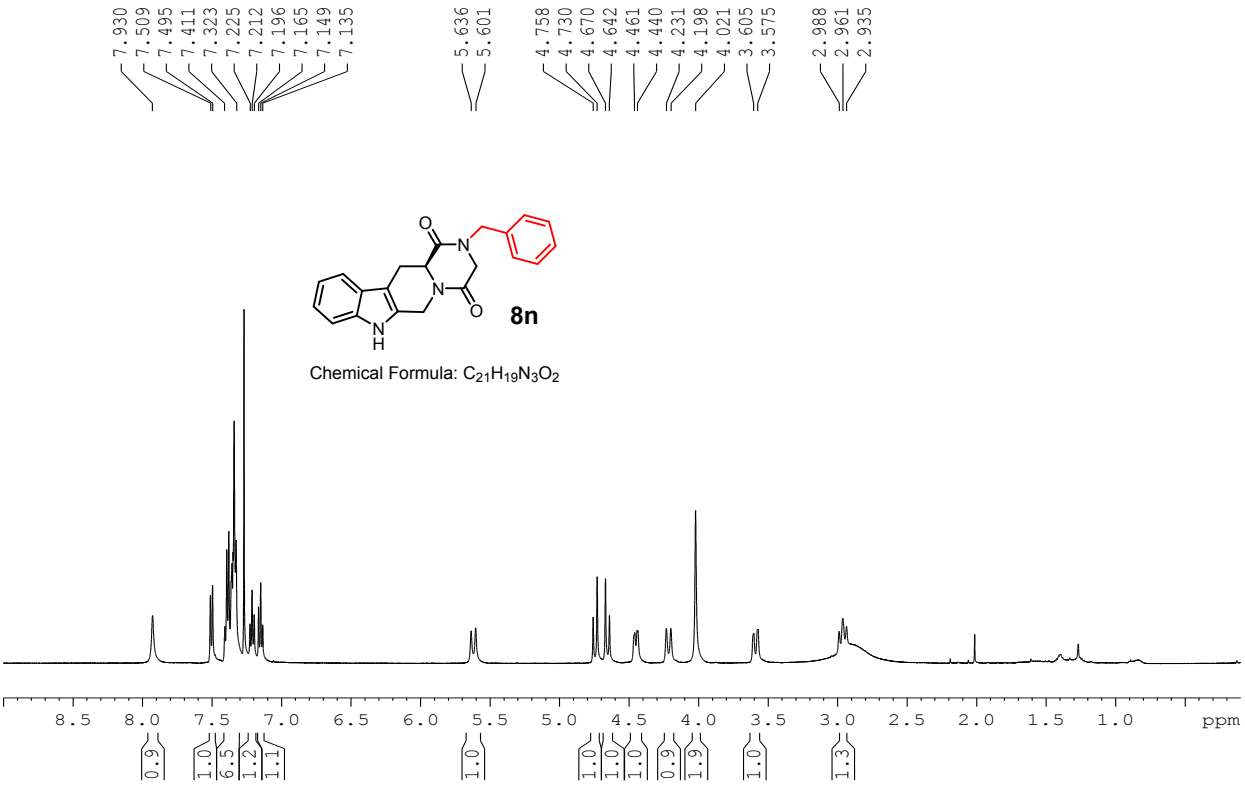
(8m): ^{1}H NMR (500 MHz, $(CD_3)_2SO$)



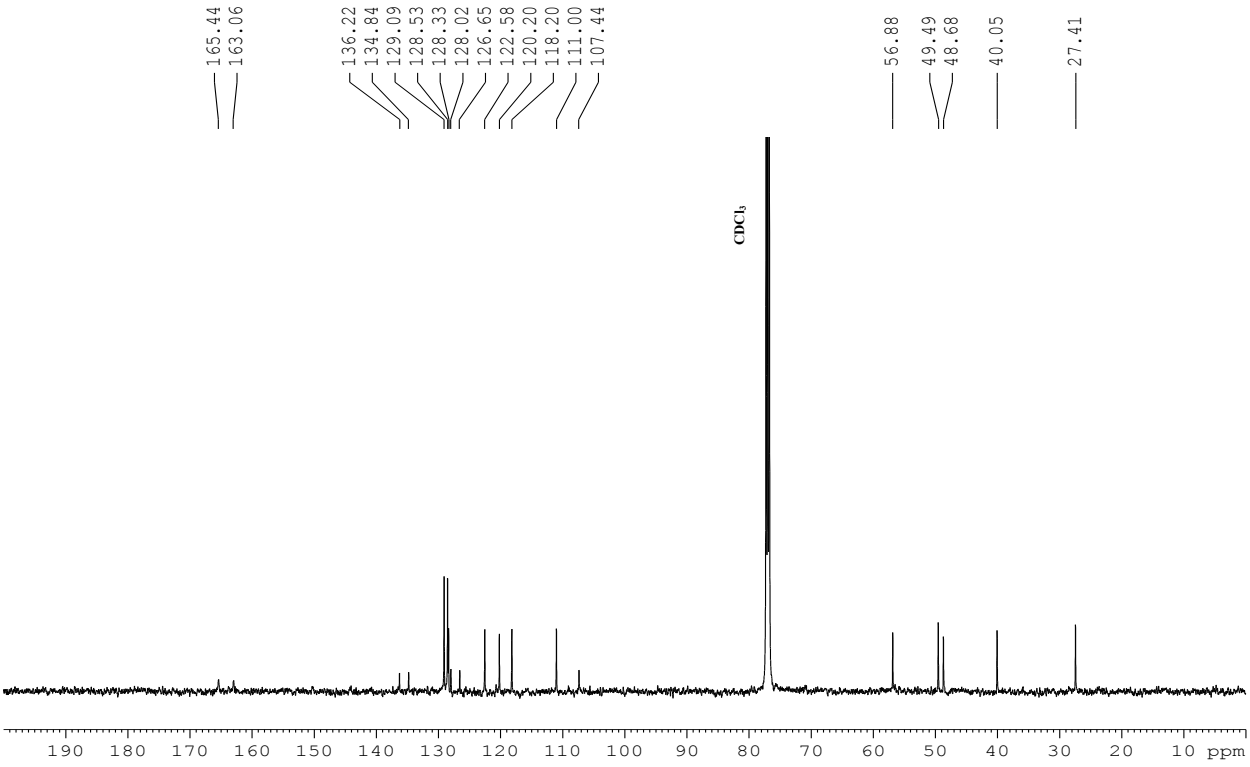
(8m): ^{13}C NMR (126 MHz, $(CD_3)_2SO$)



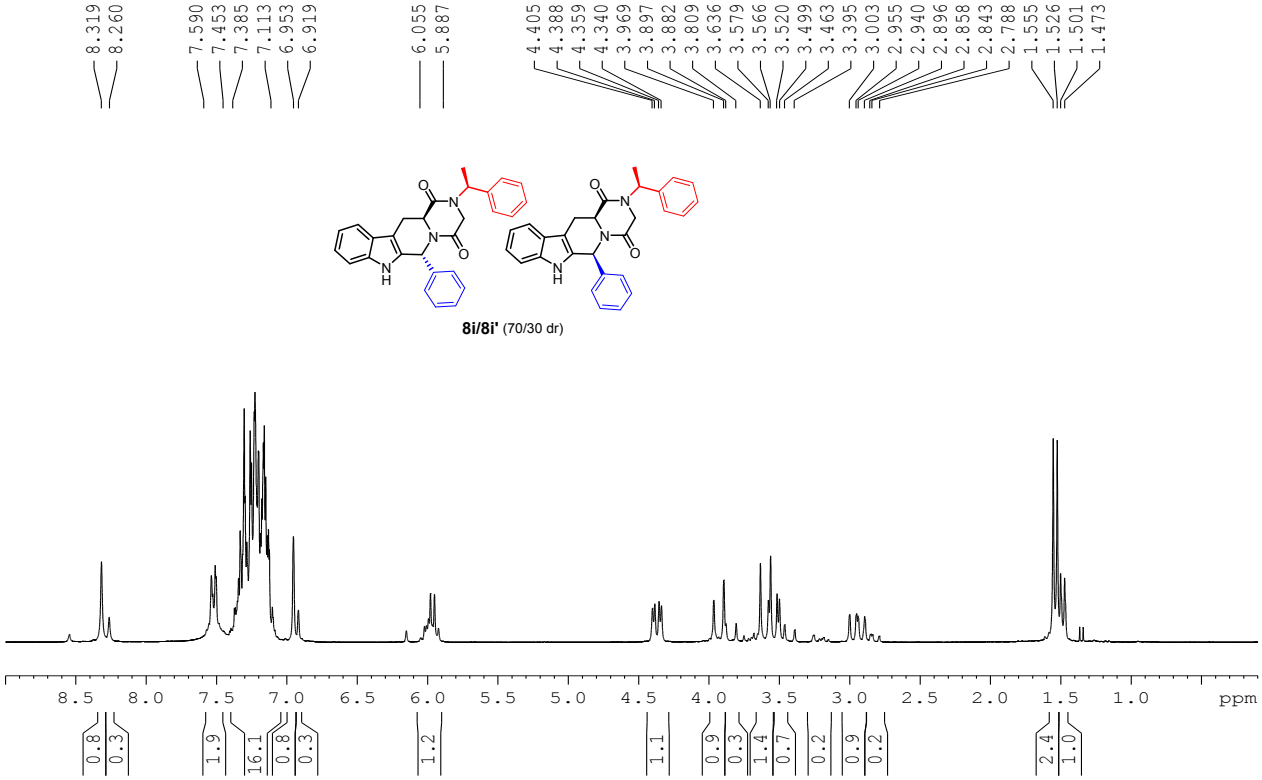
(8n): ^{1}H NMR (500 MHz, $CDCl_3$)



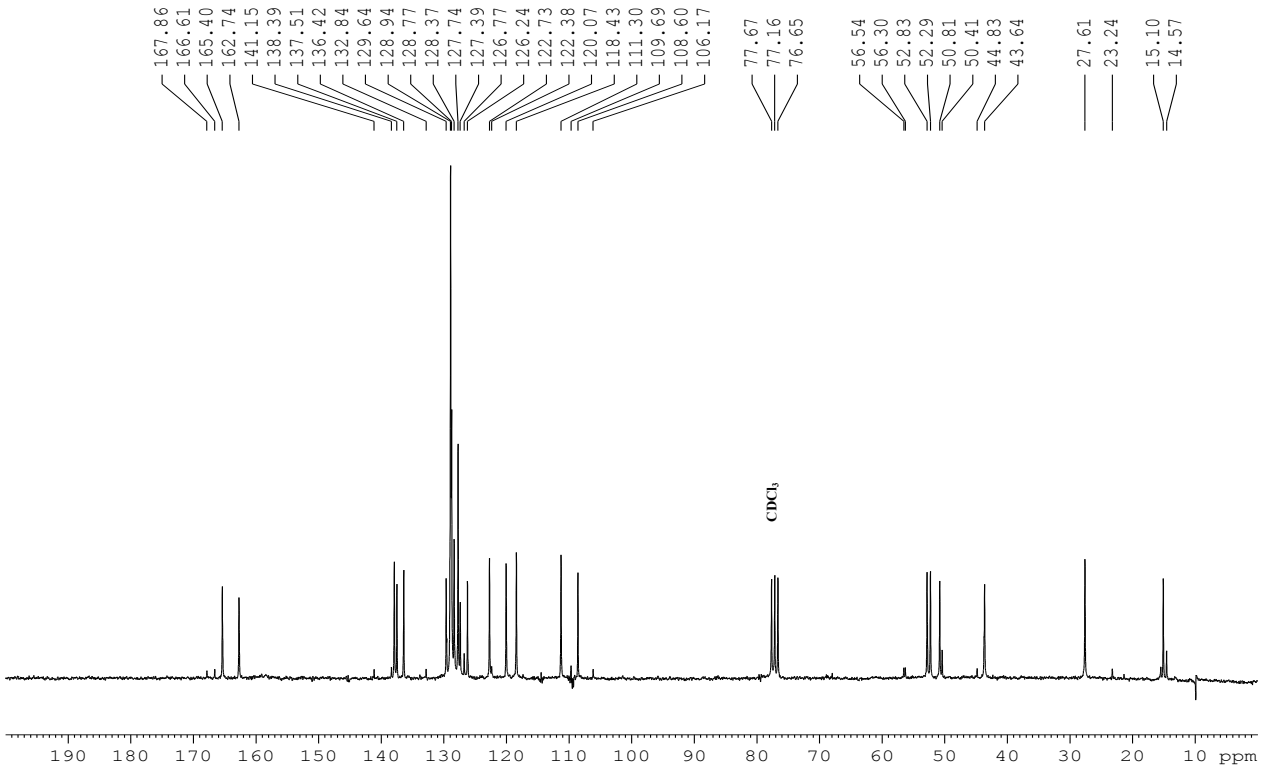
(8n): ^{13}C NMR (126 MHz, $CDCl_3$)



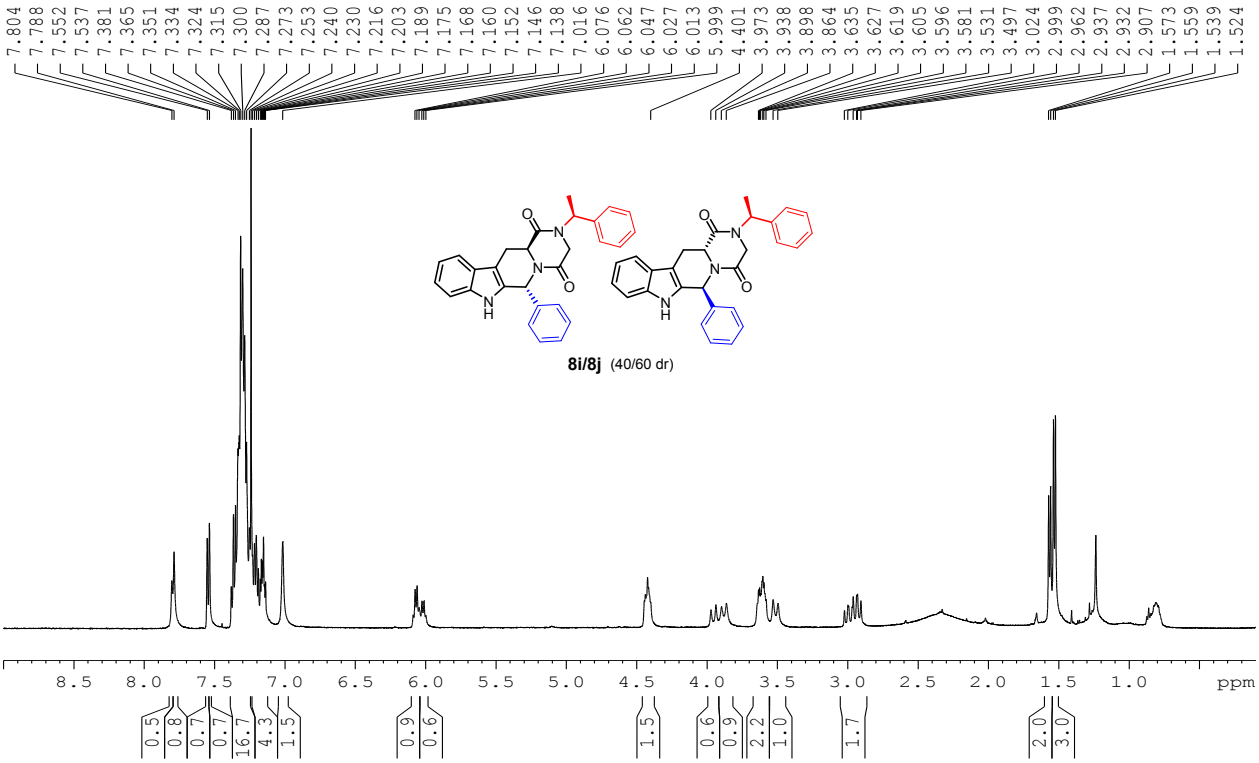
(8i/8i' : 70/30 dr): ^{1}H NMR (250 MHz, $CDCl_3$)



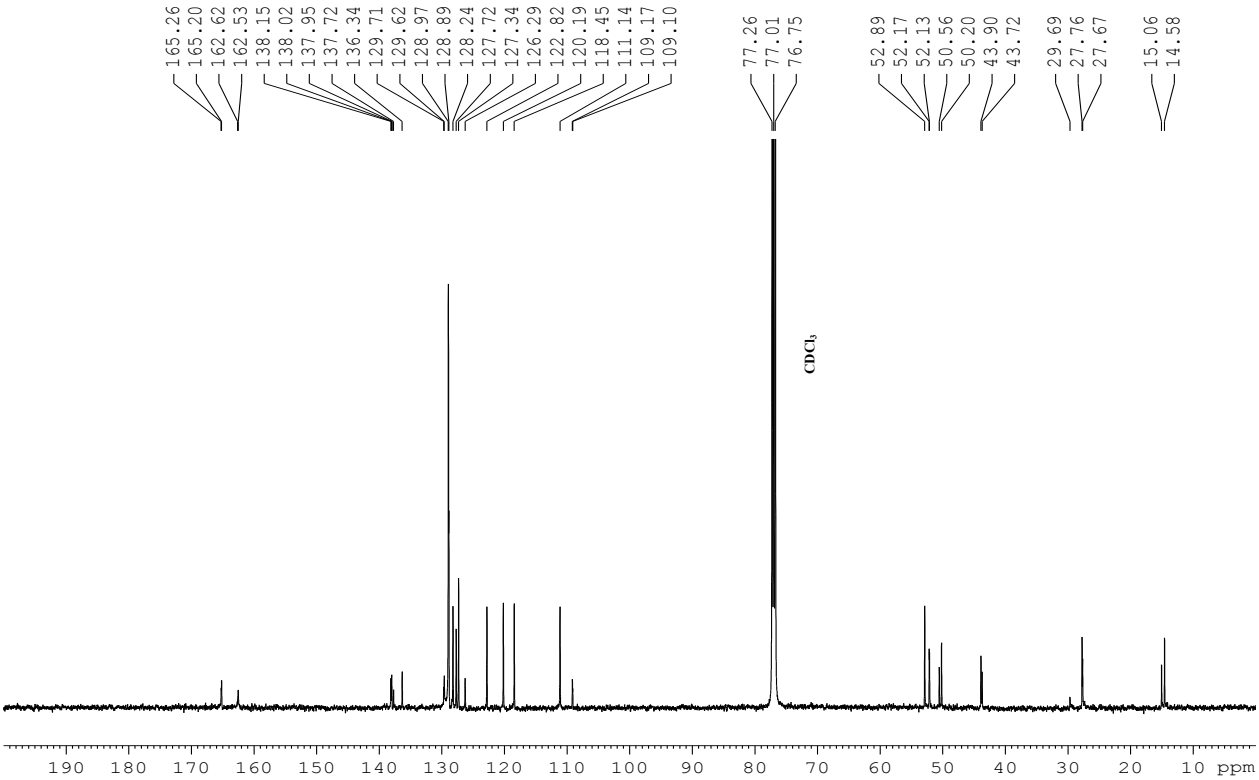
(8i/8i' : 70/30 dr): ^{13}C NMR (63 MHz, $CDCl_3$)



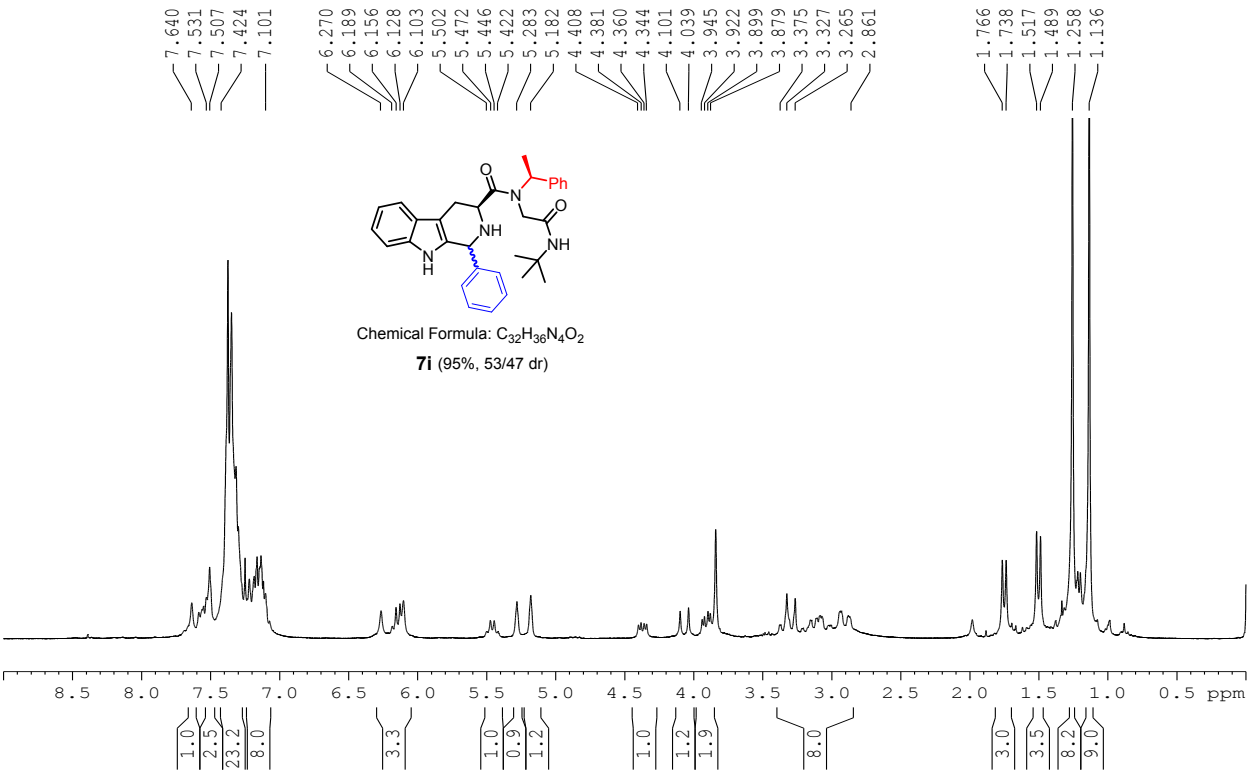
(8i/8j : 40/60 dr): ^{1}H NMR (500 MHz, $CDCl_3$)



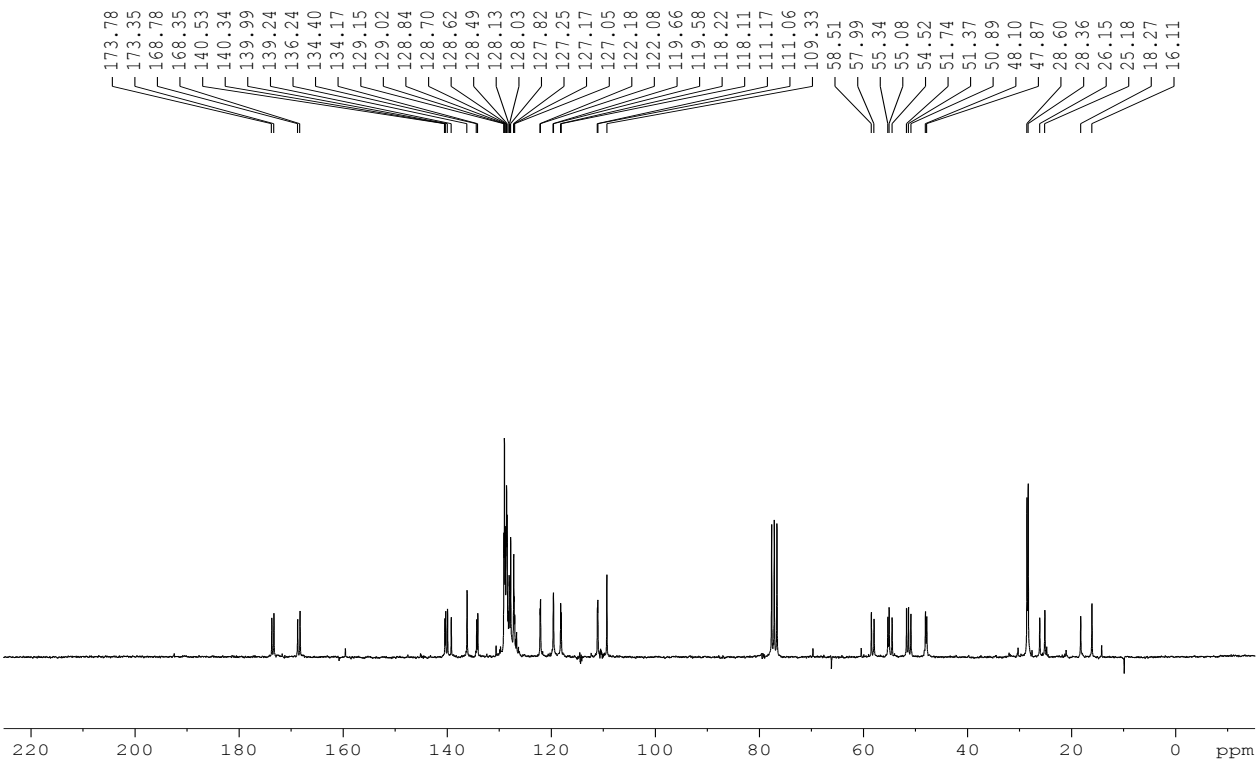
(8i/8j : 40/60 dr): ^{13}C NMR (126 MHz, $CDCl_3$)



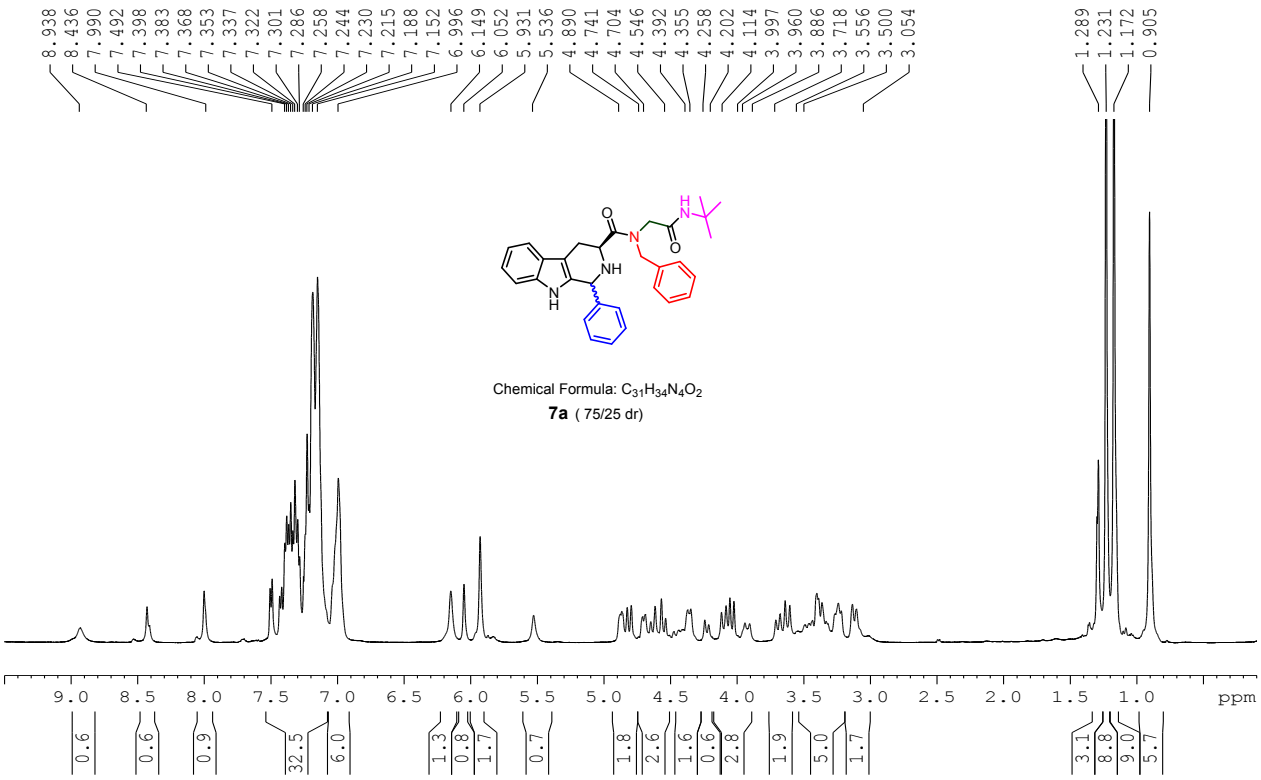
(7i : 53/47 dr): ^{1}H NMR (250 MHz, $CDCl_3$)



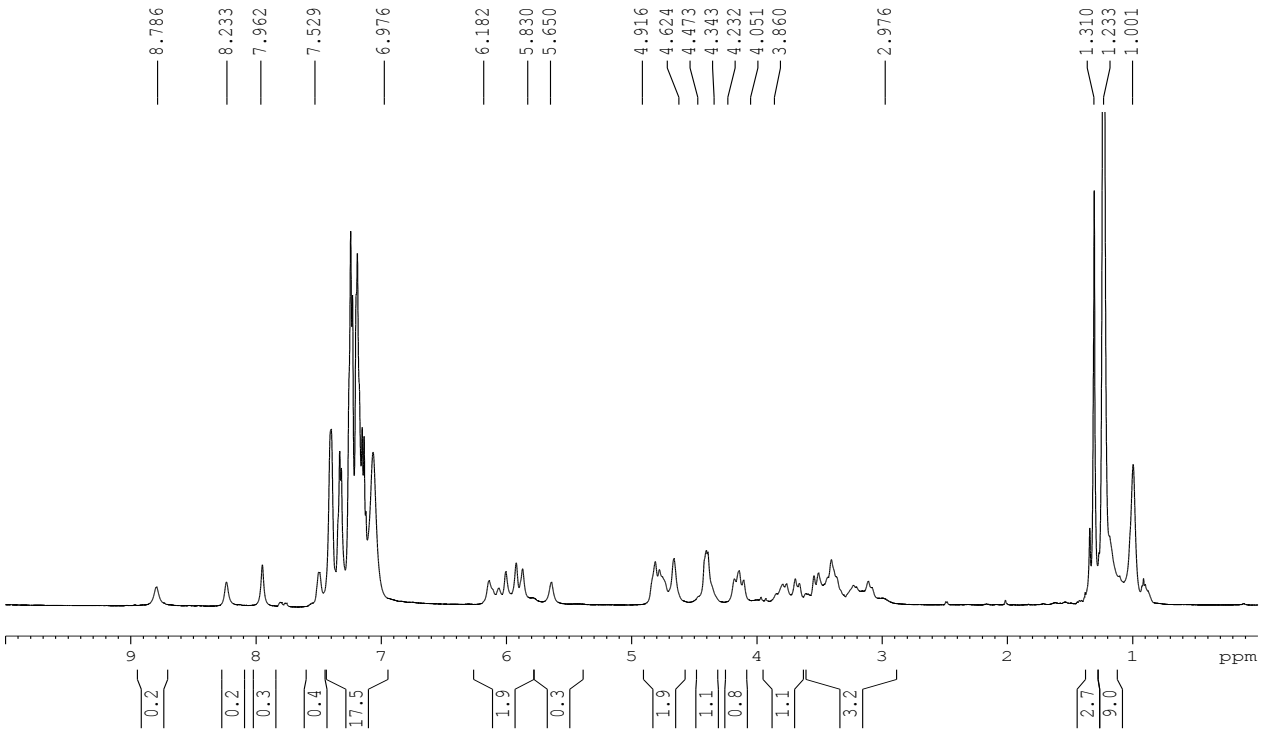
(7i : 53/47 dr):^{13}C NMR (126 MHz, $CDCl_3$)



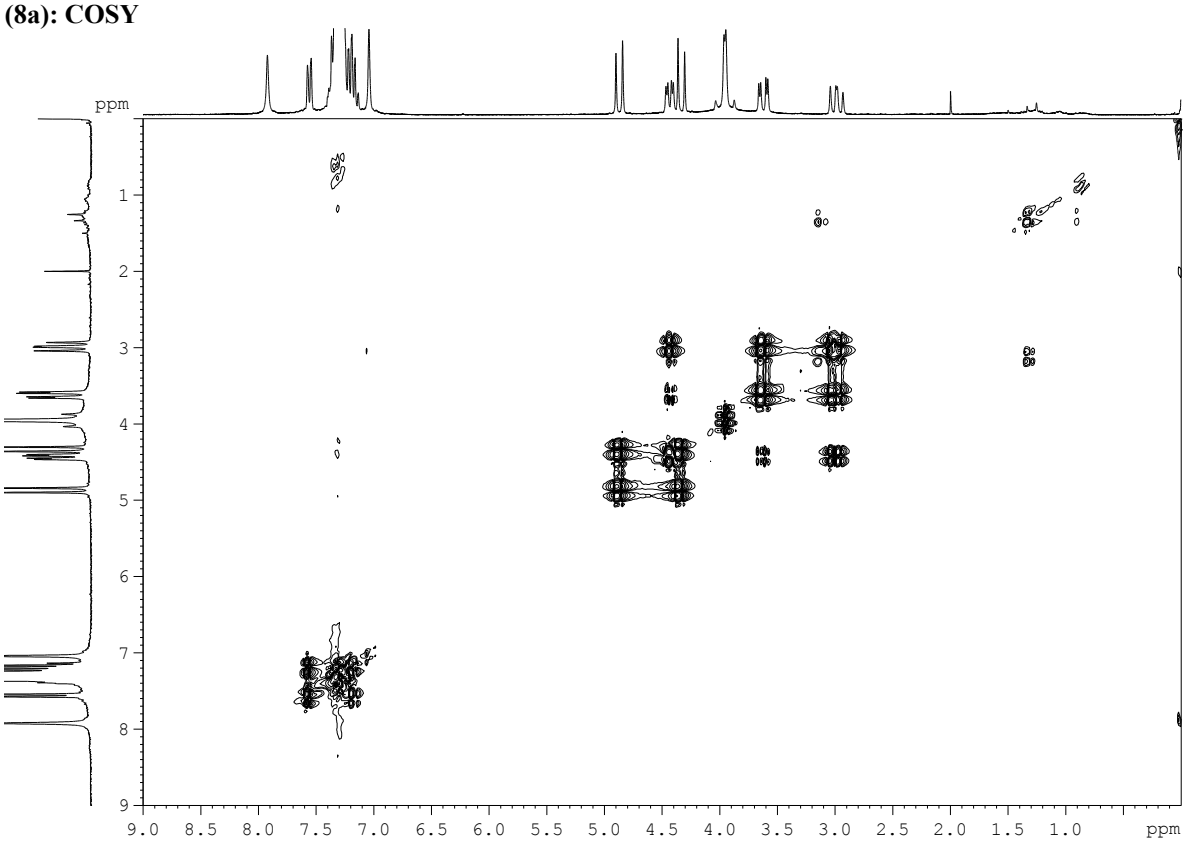
(7a : 75/25 dr): ^{1}H NMR (500 MHz, $CDCl_3$ at 293 K) (4*rotamers* : 34/32/20/14)

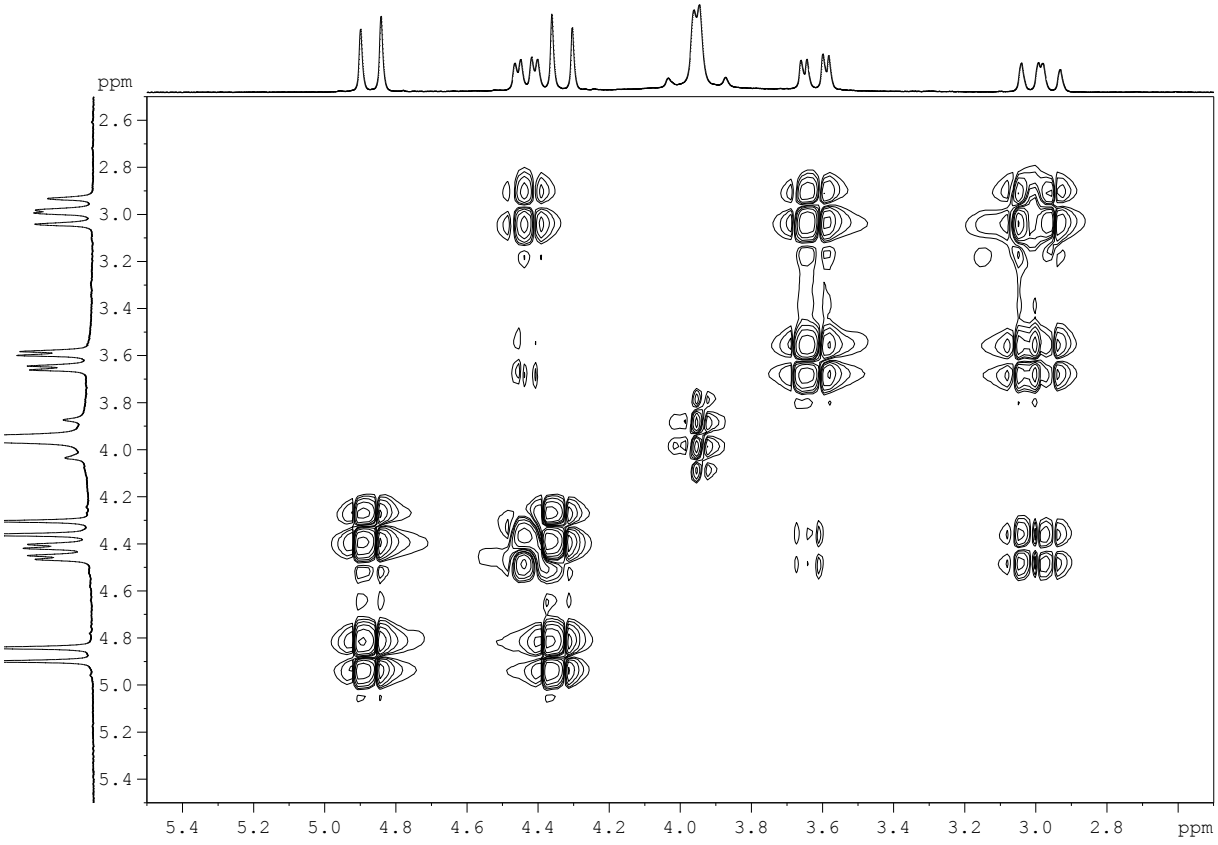


(7a : 75/25 dr): ^{1}H NMR (500 MHz, $CDCl_3$ at 323 K)



(8a): COSY


ppm
1
2
3
4
5
6
7
8
9
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
ppm


ppm
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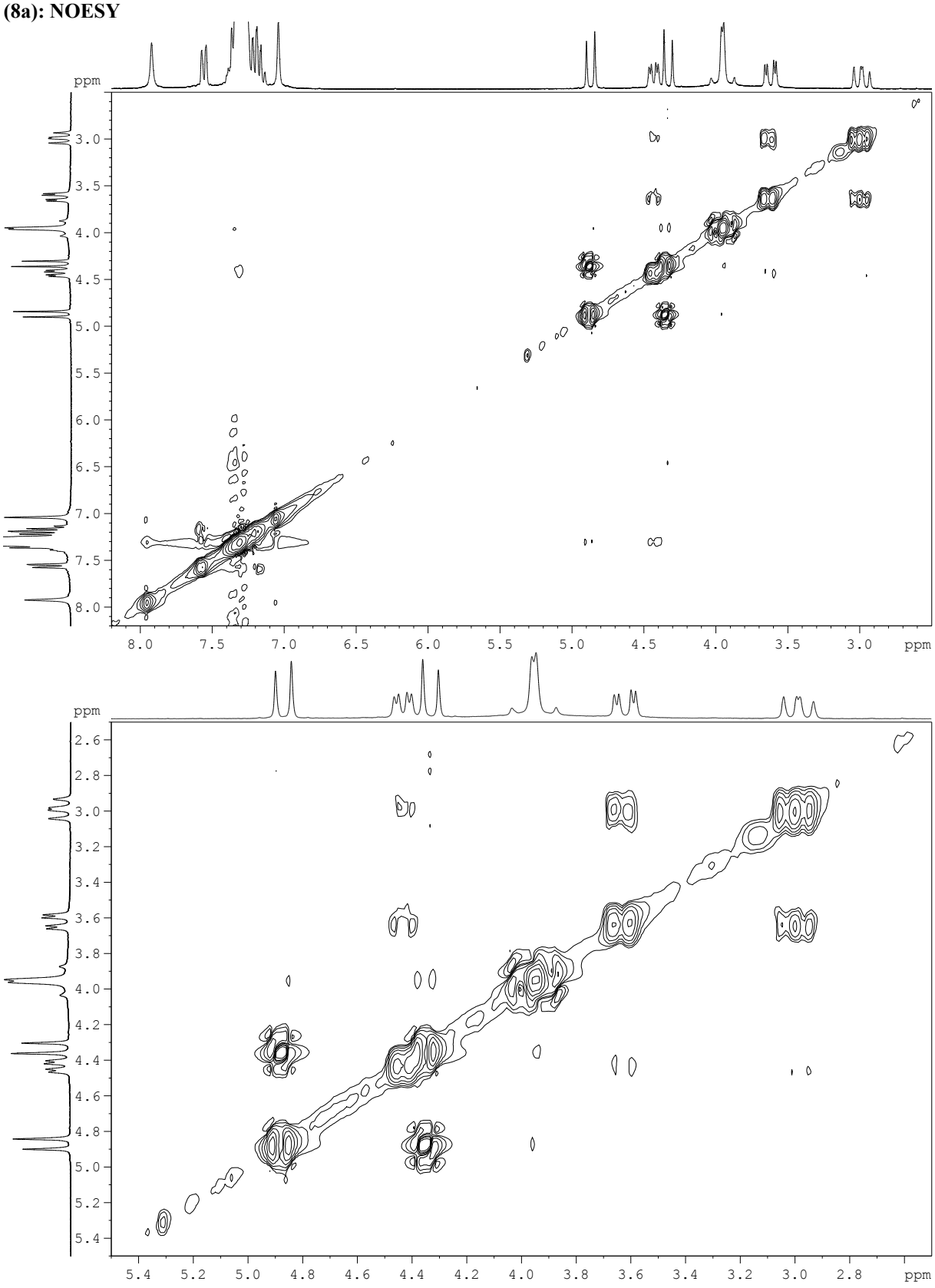
2.8
3.0
3.2
3.4
3.6
3.8
4.0
4.2
4.4
4.6
4.8
5.0
5.2
5.4
5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8
ppm

(8a): NOESY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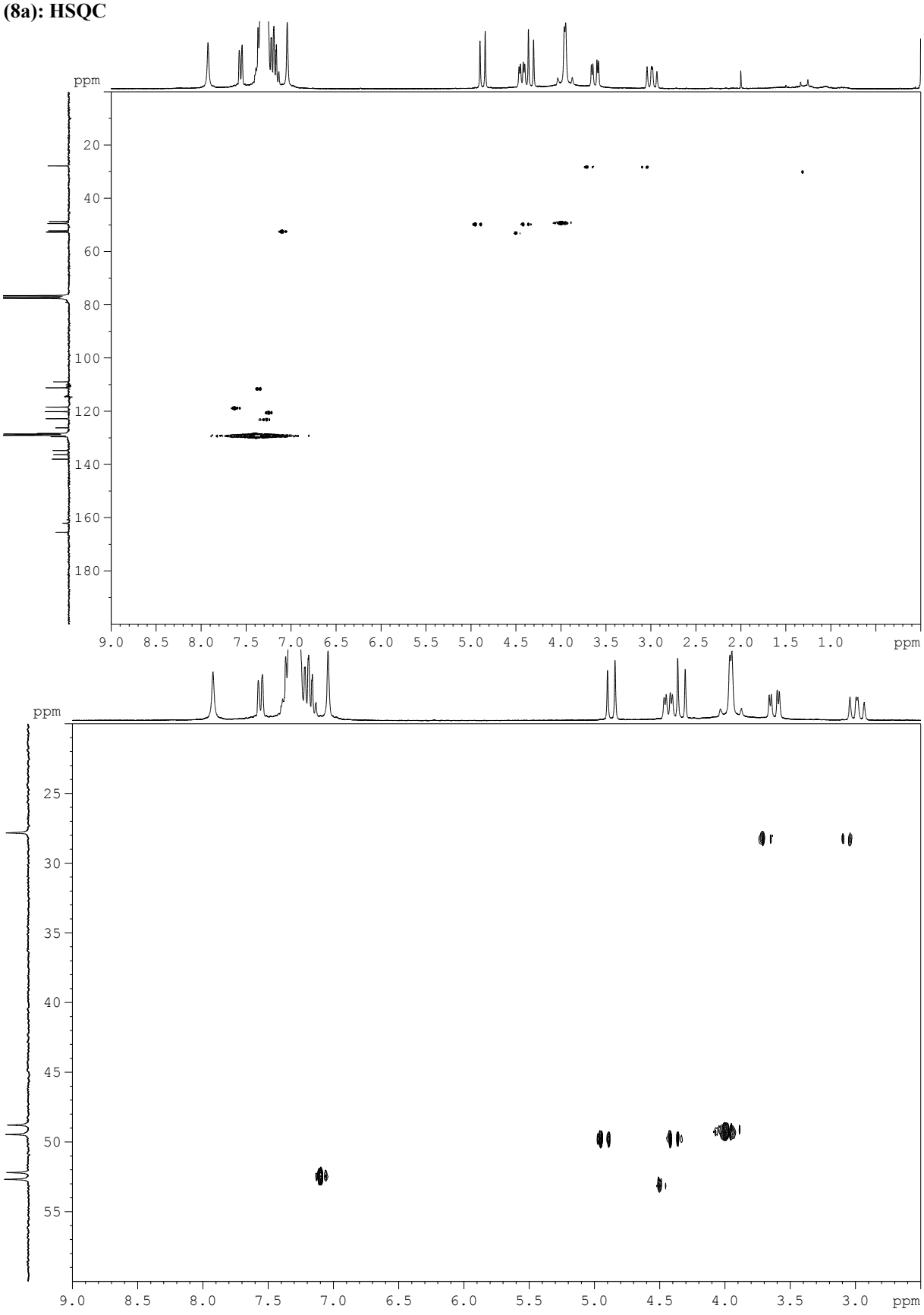
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 ppm
ppm
2.6
2.8
3.0
3.2
3.4
3.6
3.8
4.0
4.2
4.4
4.6
4.8
5.0
5.2
5.4
5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 ppm

(8a): HSQC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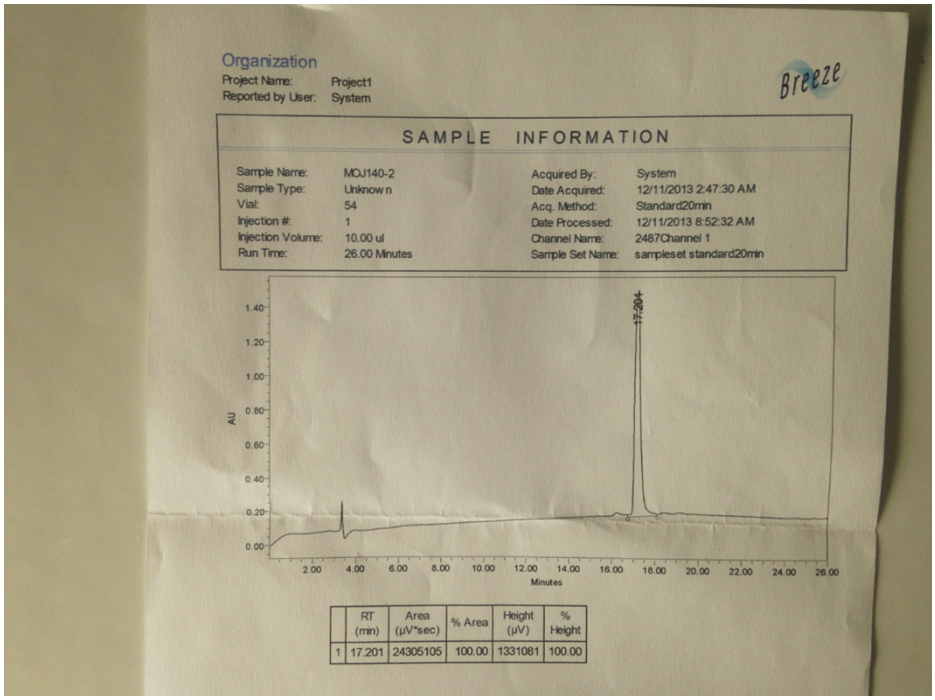
40
60
80
100
120
140
160
180
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm
ppm
25
30
35
40
45
50
55
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0
ppm

(8a): HPLC



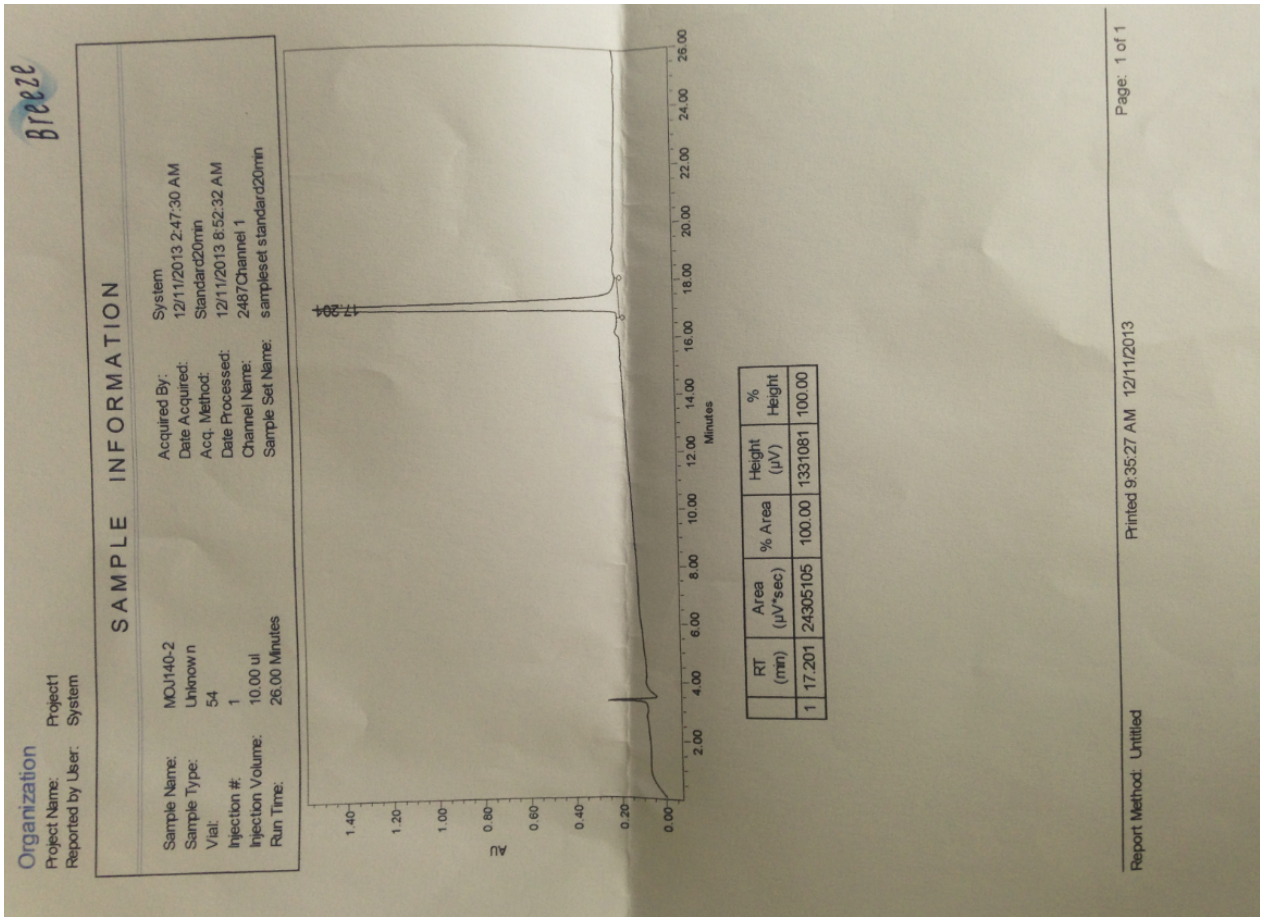
Organization
Project Name: Project1
Reported by User: System

Breeze

SAMPLE INFORMATION

Sample Name:	MOJ140-2	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	12/11/2013 2:47:30 AM
Vial:	54	Acq. Method:	Standard20min
Injection #:	1	Date Processed:	12/11/2013 8:52:32 AM
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	26.00 Minutes	Sample Set Name:	sampleset standard20min

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	17.201	24305105	100.00	1331081	100.00



Organization
Project Name: Project1
Reported by User: System

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SAMPLE INFORMATION

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	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	17.201	24305105	100.00	1331081	100.00

Report Method: Untitled
Printed 9:35:27 AM 12/11/2013
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