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Oxidative couplings on tryptophan-based diketopiperazines leading to fused and bridged chemotypes

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Abbreviations

Abbreviation used for amino acids and designations of peptides follow the rules of the IUPAC-IUB Commission of Biochemical Nomenclature in J. Biol. Chem. 247, 977-983 (1982). The following additional abbreviations are used: ACN: acetonitrile, Ala: alanine, Asp: aspartic acid, BQ: 1,4-benzoquinone, CD: circular dichroism, DCM: dichloromethane, DDQ: 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone, DIEA: N,N-diisopropylethylamine, DKP: diketopiperazine, DLP: Dilauroyl peroxide, DMF: N,N-dimethylformamide, DMSO: dimethyl sulfoxide, DTBP: Di-*tert*-butyl peroxide, Gly: glycine, HBTU: *o*-benzotriazole-*N,N,N',N'*-tetramethyl-uronium-hexafluoro-phosphate, HPLC-MS: high performance liquid chromatography mass spectrometry, HRMS(ESI): high-resolution mass spectrometry (electrospray ionization), Fmoc: 9H-fluorenylmethyloxycarbonyl, Leu: leucine, Lys: lysine, MW: microwave, NMR: nuclear magnetic resonance, Phe: phenylalanine, PIFA: bis(trifluoroacetoxy)iodobenzene, Pro: proline, TBH: *tert*-Butyl hydroperoxide, TFA: trifluoroacetic acid, Trp: tryptophan, Z: benzyloxylcarbonyl.

General experimental information

Reactions were monitored by HPLC-MS using a HPLC Waters Alliance HT comprising a pump (Edwards RV12) with degasser, an autosampler and a diode array detector. Flow from the column was split to a MS spectrometer. The MS detector was configured with an eletrospray ionization source (micromass ZQ4000) and nitrogen was used as the nebulizer gas. Data acquisition was performed with MassLynx software. Unless otherwise stated, yields are for the isolated pure compound. All microwave reactions were carried out in 10 mL sealed glass tubes in a focused mono-mode microwave oven ("Discover" by CEM Corporation) featured with a surface sensor for internal temperature determination. Cooling was provided by compressed air ventilating the microwave chamber during the reaction. When stated, the final crude was purified via flash column chromatography Combi Flash ISCO RF provided with dual UV detection.

NMR spectra of peptides in DMSO-d_6 were acquired with either a Varian Mercury 400 MHz or a Bruker DMX-500 MHz spectrometer. The spectra were referenced relative to the residual DMSO signal (^{1}H, 2.50 ppm; ^{13}C, 39.5 ppm). Chemical shifts (δ) are reported in ppm. Multiplicities are referred by the following abbreviations: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd: doublet of doublet of doublets, dt = doublet of triplets, td: triplet of doublets, and m = multiplet. HRMS (ESI positive) were obtained with a LTQ-FT Ultra (Thermo Scientific) mass Spectrometer.

CD spectroscopy. Circular dichroism (CD) measurements were performed using a Jasco J-815 spectrophotometer. The spectra were recorded from 300 to 190 nm using a 1.0 mm path-length quartz cuvette at 2 nm bandwidth, 50 nm·min^{-1} scan speed, 0.5 s response time, 0.2 nm data pitch and four-scan accumulations. The background signal of the buffer alone was subtracted for each spectrum. CD spectra were converted from raw ellipticity (θ, mdeg) to molar ellipticity ([θ], deg·cm^{-2}·dmol^{-1}). All the samples were dissolved in MeOH at 0.3 mM final concentration.

Chiral chromatography. The chiral chromatography was performed in a chiral HPLC column (Chiralpak ia, Amylose tris(3,5-dimethylphenylcarbamate) immobilized on 5 µm silica gel, 250 ×

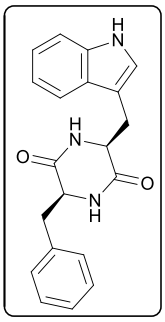
4.6 mm), at a flow rate of 1 mL·min^{-1} and a linear gradient of ACN (+0.036% TFA) into H_2O (+0.045% TFA) from 50% to 70% ACN for 30 min.

Experimental procedures and peptide characterization

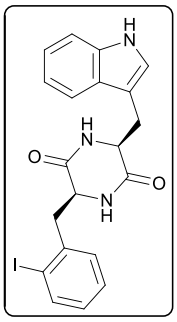
General procedure for the synthesis of 2,5-Diketopiperazines 1a-j

Unless stated otherwise, all DKPs were synthesized using the following procedure. Fmoc-AA-OH (1.0 eq), H-Trp-OMe·HCl (1.0 eq), HBTU (1.0 eq) and DIEA (2.0 eq) were dissolved in DMF and the solution was stirred at r.t. for 24 h followed by evaporation under vacuum. The resulting suspension was dissolved in ethyl acetate and washed with saturated aqueous solution of $NaHCO_3$ (×5). Then, the organic phase was dried over Na_2SO_4, filtered and the solvent was removed under vacuum obtaining the desired dipeptide. The resulting white solid was suspended in 20% piperidine/ACN and stirred for 16 h. The resulting suspension was concentrated under vacuum and washed with diethyl ether (×5). The white solid obtained was dried to yield the corresponding pure product (66-93% isolated yields). Cyclo(Pro-Trp) stereoisomers **1g-i** were prepared according to a previously published procedure on brevianamide arylation disclosed by the group.[1]

Cyclo(Phe-Trp) (1a). Compound **1a** was prepared using Fmoc-Phe-OH (2.32 g, 5.99 mmol, 1.0 eq), following the general procedure for the synthesis of DKPs to obtain the desired product as a white solid (1.86 g, 93%). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 10.87 (s, 1H), 7.89 (d, *J* = 2.7 Hz, 1H), 7.68 (d, *J* = 1.7 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.15 (m, 3H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 2.6 Hz, 1H), 6.69 (dd, *J* = 6.7 Hz, 2H), 3.96 (m, 1H), 3.84 (m, 1H), 2.79 (dd, *J* = 14.5, 4.4 Hz, 1H), 2.53 (m, 1H), 2.43 (d, *J* = 4.6 Hz, 1H), 1.84 (dd, *J* = 13.4, 7.0 Hz, 1H) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6): δ 166.8, 166.2, 136.5, 136.0, 129.7, 128.0, 127.5, 126.4, 124.4, 120.9, 118.8, 118.4, 111.3, 108.8, 55.6, 55.3, 29.7 ppm.

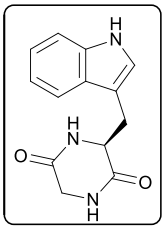


Cyclo(2-I-Phe-Trp) (1b). Compound **1b** was prepared using Fmoc-Phe(2-I)-OH (1.50 g, 2.93 mmol, 1.0 eq), H-Trp-OMe·HCl (730 mg, 2.93 mmol, 98%, 1.0 eq), HBTU (1.10 g, 2.93 mmol, 1.0 eq), DIEA (1.0 mL, 5.86 mmol, 2.0 eq) which were dissolved in DMF (3.3 mL). The pale yellow solution was stirred at r.t. for 24 h. The resulting solution was precipitated over 10 mL of cold water and centrifugated (RPM: 2000, t: 5 min, T= 4 °C). Precipitation cycles in cold water and centrifugation were repeated 8 times obtaining the desired adduct (2.6 g, 89%). The white solid was suspended in 20% piperidine/ACN (15 mL) and stirred for 22 h and the resulting solution was precipitated over 10 mL of cold water and centrifugated (RPM: 2000, t: 5 min, T= 4 °C). Precipitation cycles in cold water and centrifugation were repeated 2 times. The crude was purified by flash chromatography on silica using DCM/MeOH:DCM (1:5) to yield the pure product **1b** as a white solid (1.0 g, 85% yield). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 10.97 (d, *J* = 2.4 Hz, 1H), 8.21 (d, *J* = 2.7 Hz, 1H), 7.66 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.62 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.44 (d, *J* = 3.2 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 2.3 Hz, 1H), 7.13-7.02 (m, 2H), 6.94 (td, *J* = 7.5, 1.3 Hz, 1H), 6.82 (td, *J* = 7.6, 1.7

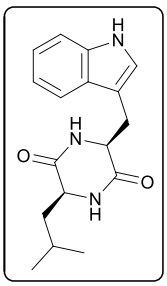


Hz, 1H), 5.56 (dd, *J* = 7.6, 1.7 Hz, 1H), 4.11 (m, 1H), 3.69 (dt, *J* = 9.3, 3.9 Hz, 1H), 3.27 (dd, *J* = 14.4, 3.8 Hz, 1H), 2.97 (dd, *J* = 14.3, 4.6 Hz, 1H), 2.44 (dd, *J* = 13.3, 4.4 Hz, 1H), 1.12 (dd, *J* = 13.4, 9.9 Hz, 1H) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6): δ 166.9, 166.1, 138.9, 138.6, 136.0, 131.8, 128.5, 127.8, 124.9, 121.1, 119.3, 118.6, 111.5, 108.6, 100.6, 55.7, 53.4, 45.2, 29.2 ppm. **HRMS (ESI)**: (M: $C_{20}H_{18}O_2N_3I$) m/z calcd. 460.0516, found 460.0519 $(M+H)^+$.

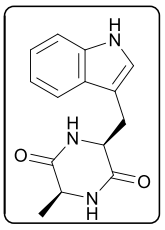
Cyclo(Gly-Trp) (1c). Compound **1c** was prepared using Fmoc-Gly-OH (1.78 g, 5.99 mmol, 1.0 eq), following the general procedure for the synthesis of DKPs to obtain the desired product as a white solid (1.23 g, 85%). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 10.92 (s, 1H), 8.09 (d, *J* = 1.9 Hz, 1H), 7.76 (br s, 1H), 7.54 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.33 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.08 – 7.01 (m, 2H), 6.95 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 4.02 (m, 1H), 3.31 (dd, *J* = 17.2, 2.8 Hz, 1H), 3.24 (dd, *J* = 14.4, 4.7 Hz, 1H), 3.02 (dd, *J* = 14.4, 4.6 Hz, 1H), 2.79 (d, *J* = 17.3 Hz, 1H) ppm.



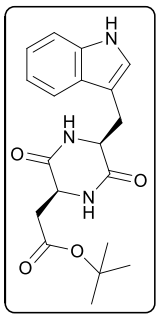
Cyclo(Leu-Trp) (1d). Compound **1d** was prepared using Fmoc-Leu-OH (710 mg, 2.01 mmol, 1.0 eq), following the general procedure for the synthesis of DKPs to obtain the desired product as a white solid (470 mg, 78%). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 10.90 (s, 1H), 8.04 (s, 1H), 7.94 (s, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.02 (m, 2H), 6.92 (t, *J* = 7.4 Hz, 1H), 4.09 (m, 1H), 3.46 – 3.36 (m, 1H), 3.26 (dd, *J* = 14.3, 3.8 Hz, 1H), 2.98 (dd, *J* = 14.3, 4.5 Hz, 1H), 1.19 (m, 1H), 0.64 (m, 1H), 0.53 (d, *J* = 6.5 Hz, 3H), 0.42 (d, *J* = 6.6 Hz, 3H), -0.01 (m, 1H) ppm.



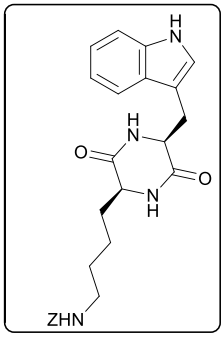
Cyclo(Ala-Trp) (1e). Compound **1e** was prepared using Fmoc-Ala-OH (1.87 g, 6.01 mmol, 1.0 eq), following the general procedure for the synthesis of DKPs to obtain the desired product as a white solid (1.57 g, 83%). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 10.88 (s, 1H), 8.00 (s, 1H), 7.90 (s, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.08 – 6.98 (m, 2H), 6.94 (t, *J* = 7.4 Hz, 1H), 4.10 (m, 1H), 3.59 (q, *J* = 6.5 Hz, 1H), 3.24 (dd, *J* = 14.4, 4.1 Hz, 1H), 3.01 (dd, *J* = 14.4, 4.6 Hz, 1H), 0.42 (d, *J* = 7.0 Hz, 3H) ppm.



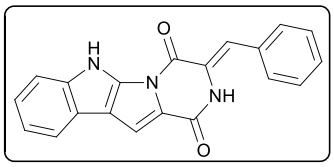
Cyclo[Asp(^{t}Bu)-Trp] (1f). Compound **1f** was prepared using Fmoc-Asp(^{t}Bu)-OH (2.47 g, 6.00 mmol, 1.0 eq), following the general procedure for the synthesis of DKPs to obtain the desired product as a pale yellow solid (2.18 g, 66%). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 10.92 (s, 1H), 7.98 (s, 1H), 7.76 (s, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.10 (d, *J* = 2.3 Hz, 1H), 7.05 (t, *J* = 7.1 Hz, 1H), 6.94 (t, *J* = 7.1 Hz, 1H), 4.16 (t, *J* = 4.2 Hz, 1H), 3.97 (t, *J* = 6.2 Hz, 1H), 3.22 (dd, *J* = 14.5, 4.9 Hz, 1H), 3.08 (dd, *J* = 14.6, 4.5 Hz, 1H), 1.95 (dd, *J* = 16.4, 5.5 Hz, 1H), 1.50 (dd, *J* = 16.4, 6.9 Hz, 1H), 1.32 (s, *J* = 4.3 Hz, 9H) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6): δ 169.1, 167.3, 166.6, 135.9, 127.5, 124.5, 120.9, 118.8, 118.4, 111.2, 108.6, 80.1, 55.1, 51.0, 44.3, 27.7, 23.1 ppm.



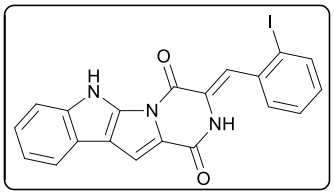
Cyclo[Lys(z)-Trp] (1j). Compound **1j** was prepared using Fmoc-Lys(z)-OH (1.00 g, 1.99 mmol, 1.0 eq), following the general procedure for the synthesis of DKPs to obtain the desired product as a white solid (725 mg, 93%). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 10.85 (s, 1H), 8.02 (d, *J* = 1.5 Hz, 1H), 7.91 (d, *J* = 1.4 Hz, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.41 – 7.26 (m, 6H), 7.09 – 6.98 (m, 3H), 6.92 (t, *J* = 7.4 Hz, 1H), 4.99 (s, 2H), 4.10 (m, 1H), 3.55 – 3.46 (m, 1H), 3.24 (dd, *J* = 14.4, 4.2 Hz, 1H), 3.00 (dd, *J* = 14.4, 4.7 Hz, 1H), 2.71 (q, *J* = 6.9 Hz, 2H), 1.07 – 0.89 (m, 3H), 0.68 – 0.47 (m, 3H) ppm.



(Z)-3-benzylidene-2,3-dihydro-1*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole-1,4(6*H*)-dione (2a). Compound **2a** (150 mg, 0.450 mmol, 1.0 eq) and DDQ (306 mg, 1.35 mmol, 3.0 eq) were dissolved in 100 mL of DMF and the solution was stirred at 120 °C for 24h. Then, the resulting crude was concentrated under vacuum, dissolved in ethyl acetate and washed with saturated aqueous solution of $NaHCO_3$ (3 x 20 mL); the aqueous solution was back-extracted with ethyl acetate. Then, the organic layers were combined, dried over Na_2SO_4, filtered and concentrated under vacuum (17% yield estimated by HPLC-MS conversion). An analytically pure sample was obtained by via flash column chromatography on Celite using H_2O (0.1% formic acid)/ACN (0.1% formic acid). The expected compound was isolated as an orange solid (2.6 mg, 2%). **^{1}H NMR** (500 MHz, DMSO-d_6): δ 12.31 (s, 1H), 9.89 (s, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.68 (d, *J* = 7.4 Hz, 2H), 7.59 – 7.51 (m, *J* = 11.9 Hz, 2H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 7.3 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.18 (t, *J* = 7.3 Hz, 1H), 7.13 (s, 1H) ppm. **HRMS (ESI)**: (M: $C_{20}H_{13}O_2N_3$) m/z calcd 328.10805, found 328.10800 $(M+H)^+$.



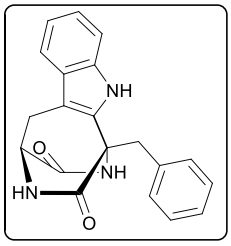
(Z)-3-(2-iodobenzylidene)-2,3-dihydro-1*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole-1,4(6*H*) dione (2b). Compound **2a** (150 mg, 0.327 mmol, 1.0 eq) and DDQ (222 mg, 0.980 mmol, 3.0 eq) were dissolved in 3 mL of DMF and placed in a microwave reactor vessel. The mixture was heated under microwave irradiation (250W) at 120 °C for 20 min. The resulting crude was dissolved in ethyl acetate and washed with saturated aqueous solution of $NaHCO_3$ (4 x 20 mL); the aqueous solution was back-extracted with ethyl acetate. Then, the organic layers were combined, dried over Na_2SO_4, filtered and concentrated under vacuum (24% yield estimated by HPLC-MS conversion). An analytically pure sample was obtained by via flash column chromatography on Celite using H_2O (0.1% formic acid)/ACN (0.1% formic acid). The expected compound was isolated as an orange solid (3.1 mg, 2%). **^{1}H NMR** (500 MHz, DMSO-d_6): δ 12.33 (s, 1H), 10.05 (s, 1H), 7.98 (d, *J* = 7.6 Hz, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.61 (d, *J* = 7.4 Hz, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.54 (s, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.27 (t, *J* = 7.2 Hz, 1H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 6.99 (s, 1H) ppm. **HRMS (ESI)**: (M: $C_{20}H_{12}O_2N_3I$) m/z calcd 454.00470, found 454.00468 $(M+H)^+$.



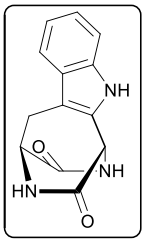
General procedure for the oxidative coupling of DKPs 1a-j

Unless stated otherwise, cyclo(AA-Trp) (0.2 mmol, 1.0 eq) and $Cu(OCOCF_3)_2$ (4.0 eq) were placed in a microwave reactor vessel and dissolved in DMF (1 mL). Afterwards, TFA (4.0 eq) was added to the solution and the mixture was heated under microwave irradiation (250 W) at 120 °C for 30 min. The resulting crude was diluted in ethyl acetate, filtered through Celite and evaporated under vacuum. Then, the crude was dissolved again in ethyl acetate and washed with NaCl (×3); the aqueous solution was back-extracted. Then, all the organic layers were mixed, dried over Mg_2SO_4, filtered and concentrated under vacuum. The crude was purified by flash chromatography on silica using DCM/DCM:MeOH (8:2) to yield the pure products **4a-i**.

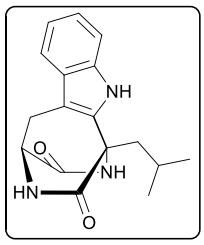
Oxidized cyclo(Phe-Trp) (4a). Compound **4a** was prepared using compound **1a** (67 mg, 0.201 mmol, 1.0 eq), following the general procedure for the synthesis of oxidized DKPs to obtain the pure product **4a** as a yellow solid (30% yield estimated by HPLC-MS conversion). **^{1}H NMR** (500 MHz, DMSO-d_6): δ 11.28 (s, 1H), 8.59 (s, 1H), 8.35 (d, *J* = 4.0 Hz, 1H), 7.55 (d, *J* = 7.1 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.14 (t, *J* = 7.2 Hz, 1H), 7.03 (t, *J* = 7.2 Hz, 1H), 4.02 (m, 1H), 3.91 (d, *J* = 13.7 Hz, 1H), 3.32 (1H), 3.15 (dd, *J* = 17.0, 1.8 Hz, 1H), 2.99 (dd, *J* = 17.0, 3.9 Hz, 1H) ppm. **HRMS (ESI)**: (M: $C_{20}H_{17}O_2N_3$) m/z calcd 332.13935, found 332.13922 $(M+H)^+$.



Oxidized cyclo(Gly-Trp) (4c). Compound **4c** was prepared using compound **1c** (50 mg, 0.206 mmol, 1.0 eq), following the general procedure for the synthesis of oxidized DKPs to obtain the pure product **4c** as a pale brown solid (16.6 mg, 33%). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 11.33 (s, 1H), 9.05 (d, *J* = 4.9 Hz, 1H), 8.43 (d, *J* = 3.9 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.01 (t, *J* = 7.4 Hz, 1H), 4.47 (dd, *J* = 5.1, 1.9 Hz, 1H), 4.11 – 4.05 (m, 1H), 3.14 (dd, *J* = 17.0, 2.5 Hz, 1H), 2.97 (dd, *J* = 17.0, 4.5 Hz, 1H) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6): δ 171.7, 169.3, 134.6, 131.7, 127.7, 121.8, 119.2, 118.0, 111.5, 105.8, 54.5, 52.3, 27.3 ppm. **HRMS (ESI)**: (M: $C_{13}H_{11}O_2N_3$) m/z calcd 242.09240, found 242.09228 $(M+H)^+$.

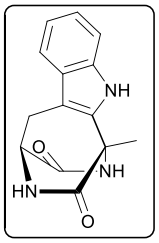


Oxidized cyclo(Leu-Trp) (4d). Compound **1d** (180 mg, 0.601 mmol, 1.0 eq) and $Cu(OCOCF_3)_2$ (6.0 eq) were placed in a microwave reactor vessel and dissolved in DMF (3 mL). Afterwards, TFA (4.0 eq) was added to the solution and the mixture was heated at 200 °C for 18 h. The resulting crude was diluted in ethyl acetate, filtered through Celite and evaporated under vacuum. Then, the crude was dissolved again in ethyl acetate and washed with NaCl (×3) and 5% aqueous LiCl (×3); the aqueous solution was back-extracted. Then, all the organic layers were mixed, dried over Mg_2SO_4, filtered and concentrated under vacuum. The crude was purified by flash chromatography on silica using DCM/DCM:MeOH (8:2) to yield the pure product **4d** as a pale yellow solid (36.4 mg, 20%). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 8.68 (s, 1H), 8.27 (d, *J* = 4.5 Hz, 1H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.99 (t, *J* = 7.5 Hz, 1H), 4.07 (m, 1H), 3.13 (dd, *J* = 17.0, 2.4 Hz, 1H), 2.95 (dd, *J* = 17.1, 4.5 Hz, 1H), 2.41 (dd, *J* = 15.5, 9.4 Hz, 1H), 2.02

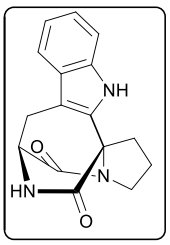


(m, 2H), 1.04 (d, *J* = 6.3 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6): δ 171.9, 169.7, 135.0, 134.6, 127.8, 121.8, 119.2, 117.8, 111.7, 105.7, 57.6, 54.1, 36.2, 27.9, 24.1, 23.9, 23.0 ppm. **HRMS (ESI)**: (M: $C_{17}H_{19}O_2N_3$) m/z calcd 298.1556, found 298.1559 $(M+H)^+$.

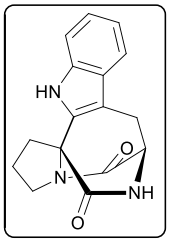
Oxidized cyclo(Ala-Trp) (4e). Compound **4e** was prepared using compound **1f** (73 mg, 0.204 mmol, 1.0 eq), following the general procedure for the synthesis of oxidized DKPs to obtain the pure product **4e** as a brown-orange solid (15.2 mg, 43%). Although formed in a reasonable extent, the isolation of the product **4e** from DKP **1e** was not feasible due to the similarity by HPLC of the different crude compounds. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 8.91 (s, 1H), 8.42 (d, *J* = 5.1 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.1, 1H), 7.12 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.01 (ddd, *J* = 7.9, 7.1, 1.1 Hz, 1H), 4.07 (m, 1H), 3.14 (dd, *J* = 16.9, 2.5 Hz, 1H), 2.97 (dd, *J* = 16.9, 4.6 Hz, 1H), 1.69 (s, 3H) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6): δ 171.8, 170.8, 134.6, 134.3, 127.9, 121.9, 119.2, 117.9, 111.7, 106.2, 54.6, 54.5, 27.5, 17.1 ppm. **HRMS (ESI)**: (M: $C_{14}H_{13}O_2N_3$) m/z calcd 256.1086, found 256.1085 $(M+H)^+$.



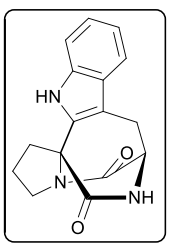
Oxidized cyclo(Pro$_L$-Trp$_L$) (4g). Compound **4g** was prepared using compound **1g** (58 mg, 0.205 mmol, 1.0 eq), following the general procedure for the synthesis of oxidized DKPs to obtain the pure product **4g** as a pale brown solid (34.8 mg, 60%). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 11.20 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 8.1, 1H), 7.13 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.01 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 4.16 (td, *J* = 4.9, 2.3 Hz, 1H), 3.46 – 3.35 (m, 2H), 3.14 (dd, *J* = 17.1, 2.4 Hz, 1H), 3.00 (dd, *J* = 17.1, 4.8 Hz, 1H), 2.80 (ddd, *J* = 13.4, 6.3, 4.2 Hz, 1H), 2.48 – 2.41 (m, 1H), 2.04 – 1.89 (m, 2H) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6): δ 170.8, 167.6, 134.7, 131.7, 128.0, 122.0, 119.2, 117.9, 111.6, 106.9, 64.1, 55.0, 44.5, 28.4, 27.2, 23.0 ppm. $[\alpha]_D^{25}$ +24.6 (c 0.5, MeOH). **HRMS (ESI)**: (M: $C_{16}H_{15}O_2N_3$) m/z calcd 282.1243, found 282.1243 $(M+H)^+$.



Oxidized cyclo(Pro$_D$-Trp$_D$) (4h). Compound **4h** was prepared using compound **1h** (58 mg, 0.205 mmol, 1.0 eq), following the general procedure for the synthesis of oxidized DKPs to obtain the pure product **4h** as a brown-orange solid (41.0 mg, 71%). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 11.20 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.36 (dt, *J* = 8.1, 0.8 Hz, 1H), 7.13 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.01 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 4.16 (td, *J* = 4.9, 2.4 Hz, 1H), 3.46 – 3.35 (m, *J* = 9.7, 8.0, 5.6 Hz, 2H), 3.14 (dd, *J* = 17.1, 2.3 Hz, 1H), 3.00 (dd, *J* = 17.1, 4.8 Hz, 1H), 2.80 (ddd, *J* = 13.6, 6.3, 4.2 Hz, 1H), 2.48 – 2.42 (m, 1H), 2.02 – 1.88 (m, 2H) ppm. $[\alpha]_D^{25}$ -26.0 (c 0.5, MeOH). **HRMS (ESI)**: (M: $C_{16}H_{15}O_2N_3$) m/z calcd 282.1243, found 282.1241 $(M+H)^+$.

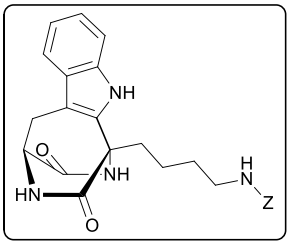


Oxidized cyclo(Pro$_L$-Trp$_D$) (4h). Compound **4h** was prepared using compound **1i** (58 mg, 0.205 mmol, 1.0 eq), following the general procedure for the synthesis of oxidized DKPs to obtain the pure product **4h** as a brown-orange solid (9.6 mg, 17%). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 11.20 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.13 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.01 (ddd, *J* = 7.9, 7.2, 0.9 Hz, 1H), 4.16 (td, *J* = 4.9, 2.3 Hz, 1H), 3.43 – 3.35 (m, 2H), 3.14 (dd, *J* = 17.1, 2.3 Hz, 1H), 3.00 (dd, *J* = 17.1, 4.8 Hz, 1H), 2.80 (ddd, *J* =



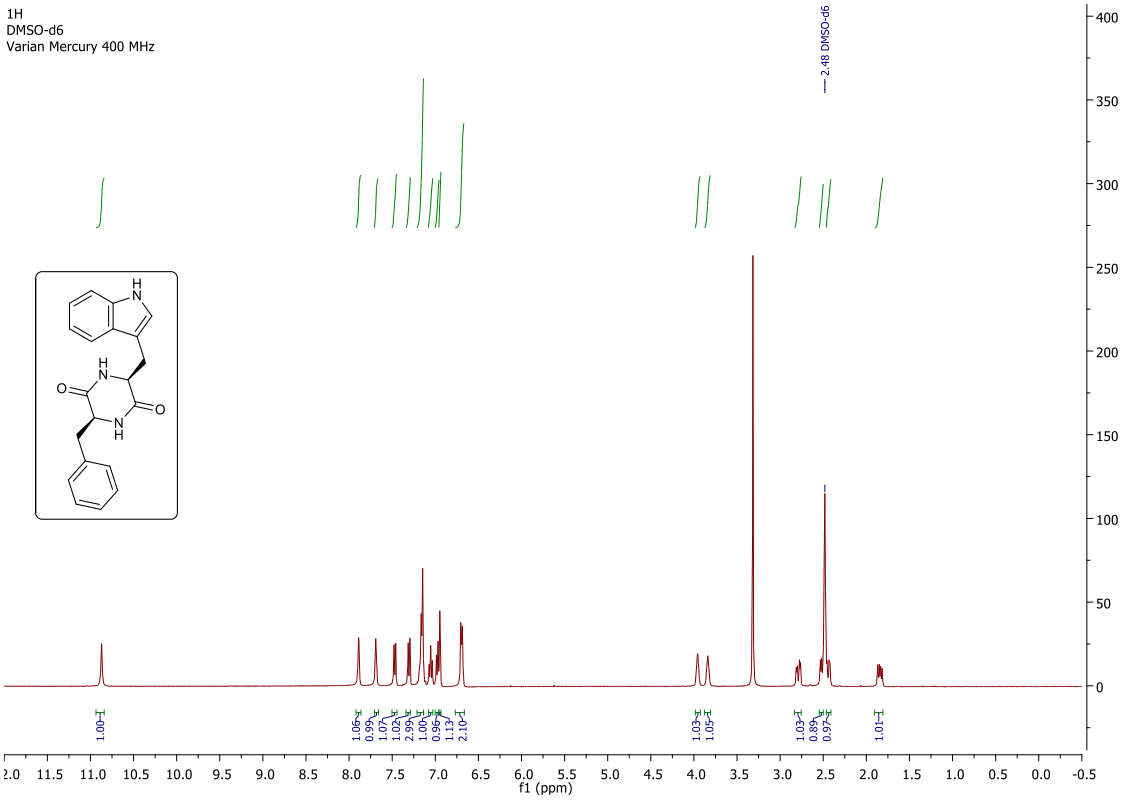
13.4, 6.3, 4.2 Hz, 1H), 2.48 – 2.43 (m, *J* = 8.0, 5.4 Hz, 1H), 2.03 – 1.88 (m, 2H) ppm. **HRMS (ESI)**: (M: $C_{16}H_{15}O_2N_3$) m/z calcd 282.1243, found 282.1242 $(M+H)^+$.

Oxidized cyclo[Lys(z)-Trp] (4i). Compound **4i** was prepared using compound **1j** (90 mg, 0.201 mmol, 1.0 eq) and $Cu(OSO_2CF_3)_2$ (4.0 eq) instead of $Cu(OCOCF_3)_2$, following the general procedure for the synthesis of oxidized DKPs. The crude was purified by flash chromatography on silica using hexane/ethyl acetate to yield the pure product **4i** as a yellow solid (18.5 mg, 20%). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 11.03 (s, 1H), 8.79 (s, 1H), 8.37 (d, *J* = 4.7 Hz, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.39 – 7.26 (m, 7H), 7.11 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.00 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 5.03 (s, 2H), 4.06 (m, 1H), 3.19 – 3.04 (m, 3H), 2.95 (dd, *J* = 17.1, 4.6 Hz, 1H), 2.41 – 2.30 (m, 1H), 2.06 – 1.91 (m, 1H), 1.60 – 1.43 (m, 4H) ppm. **HRMS (ESI)**: (M: $C_{25}H_{26}O_4N_4$) m/z calcd 447.2032, found 447.2036 $(M+H)^+$.

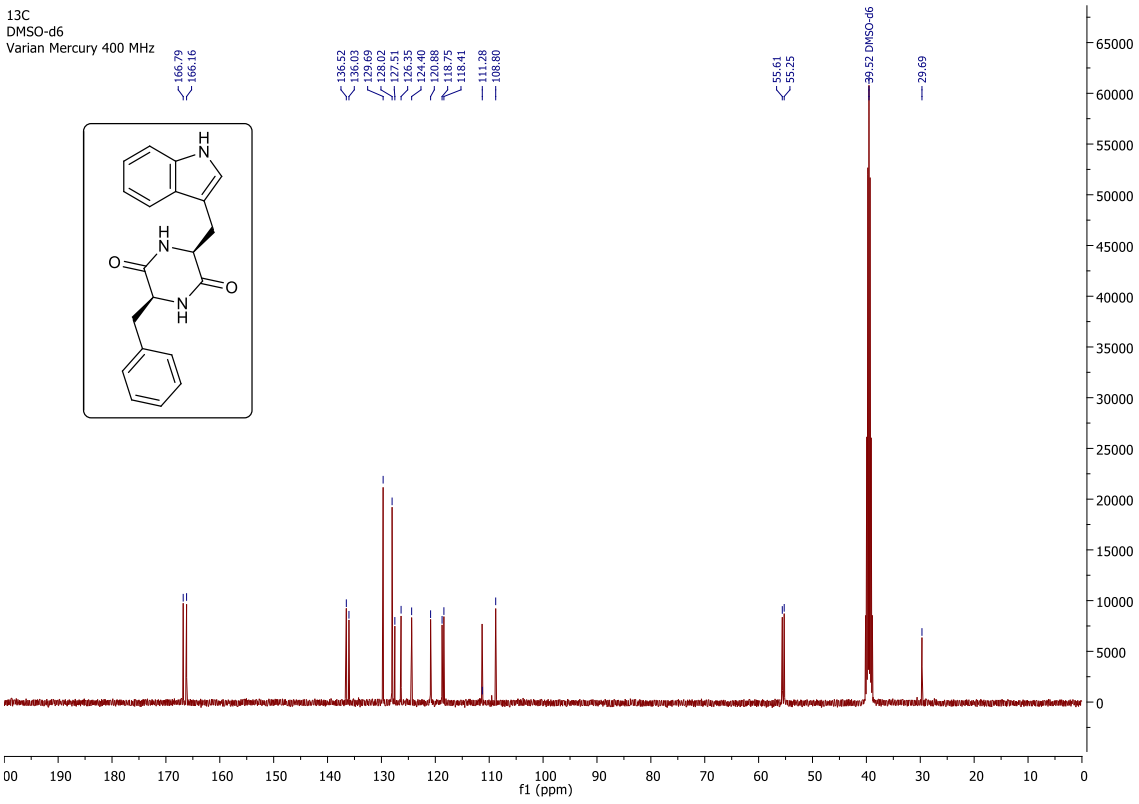


NMR spectra of compounds 1-4

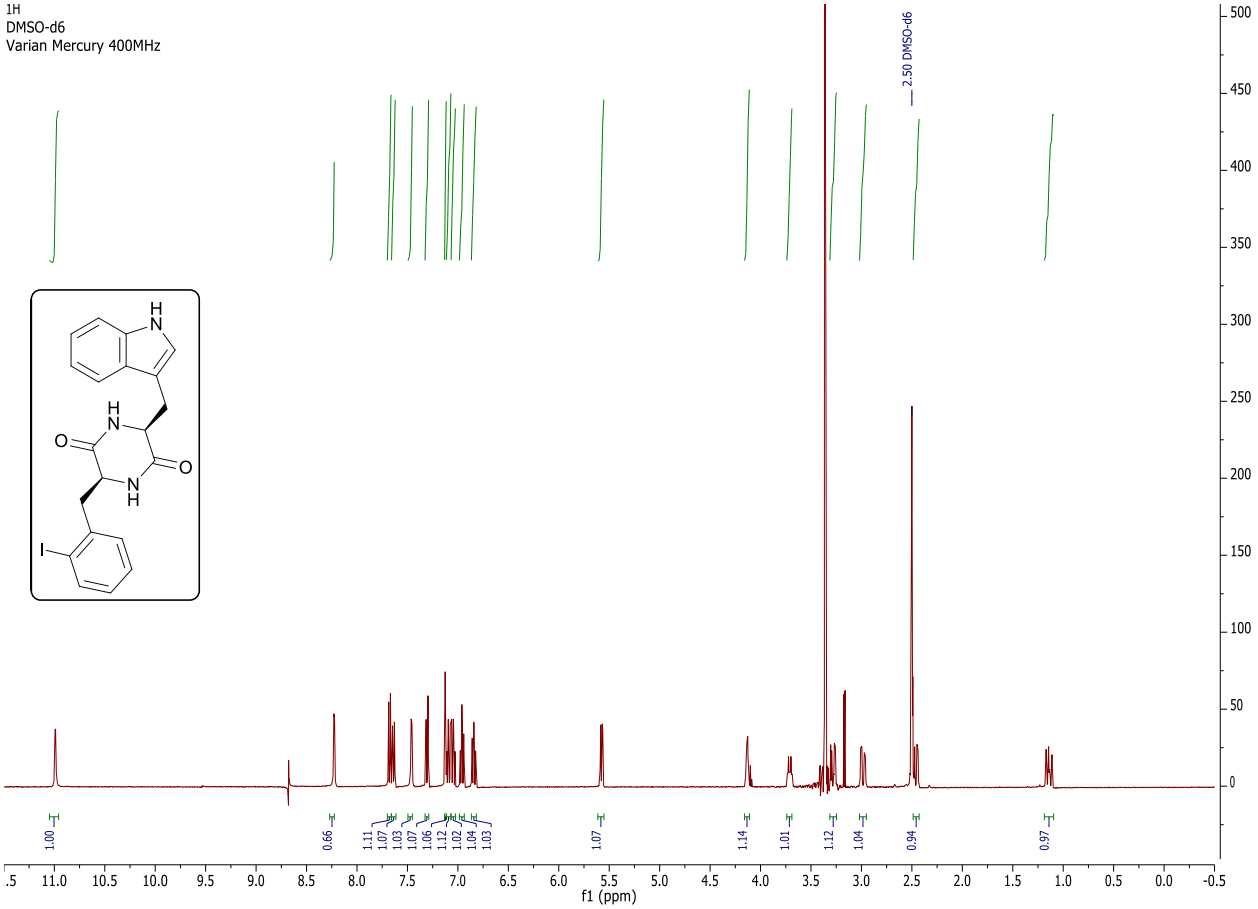
Cyclo(Phe-Trp) (1a) ^{1}H NMR



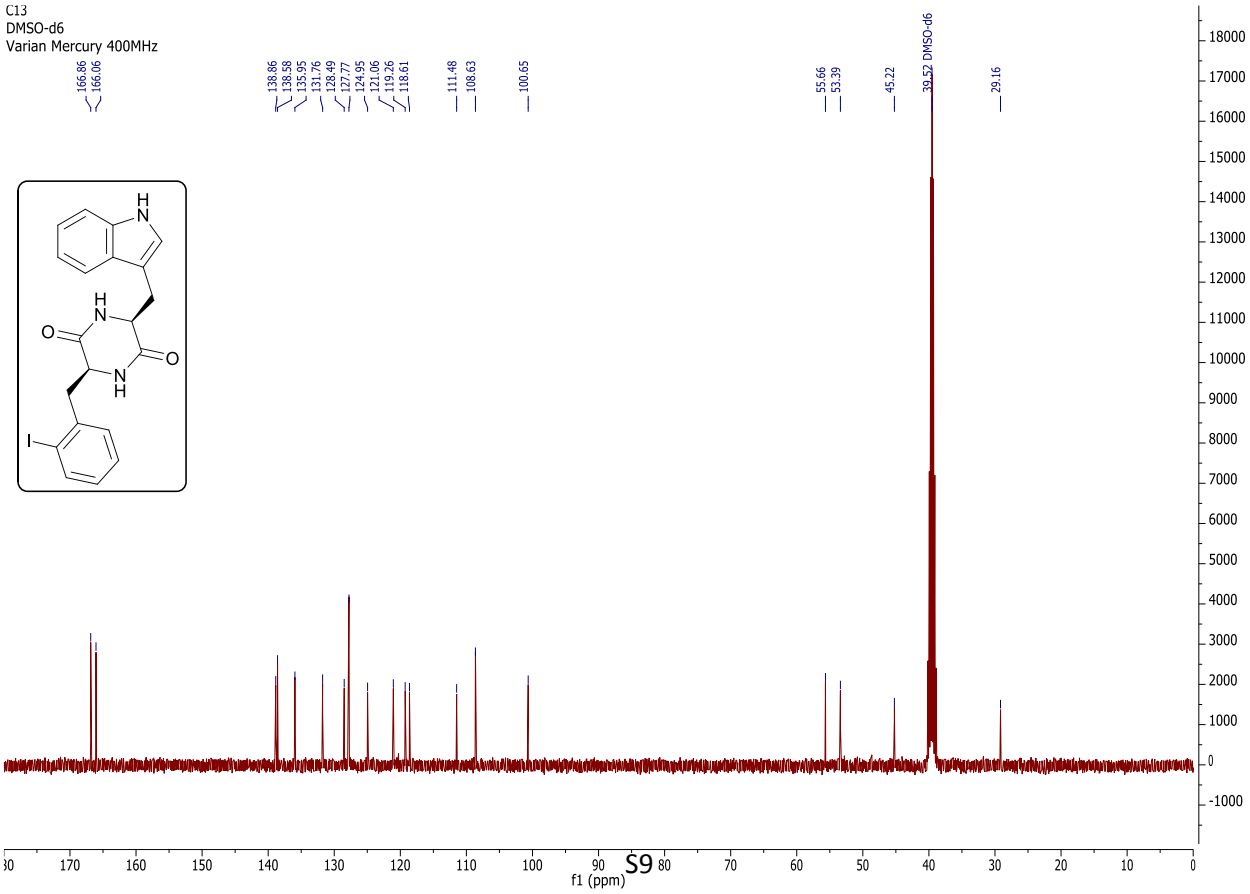
Cyclo(Phe-Trp) (1a) ^{13}C NMR



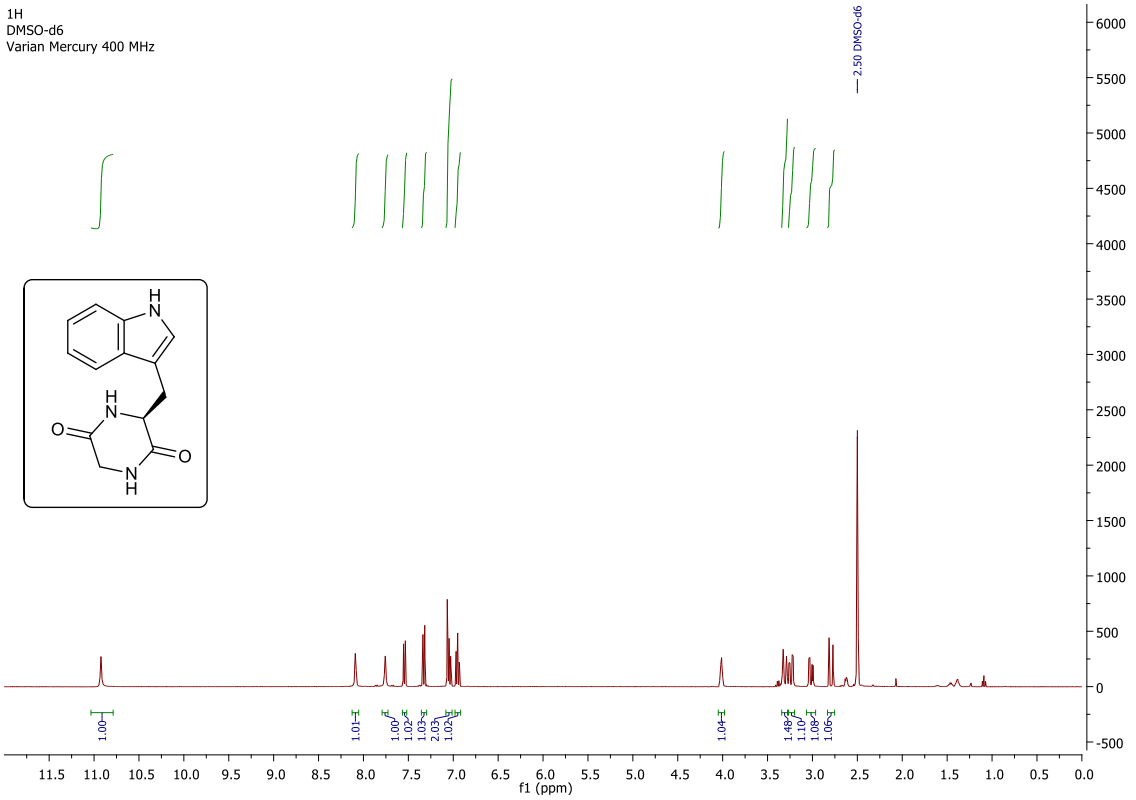
Cyclo(2-I-Phe-Trp) (1b) ^{1}H NMR



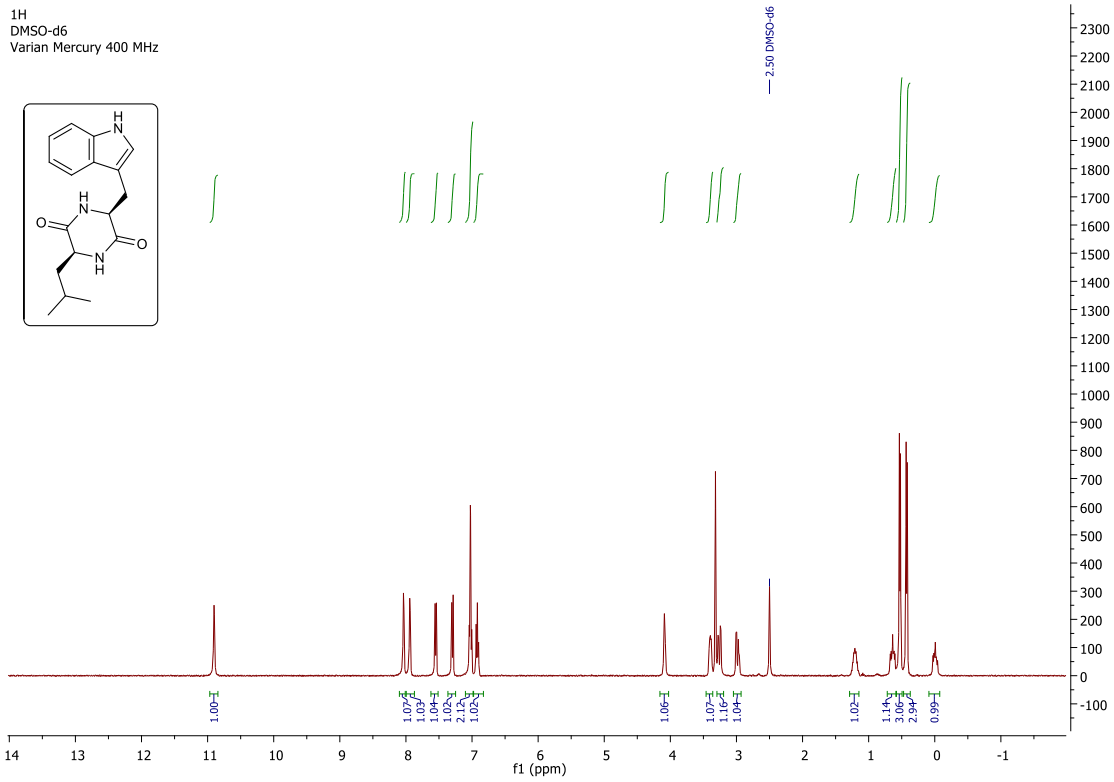
Cyclo(2-I-Phe-Trp) (1b) ^{13}C NMR



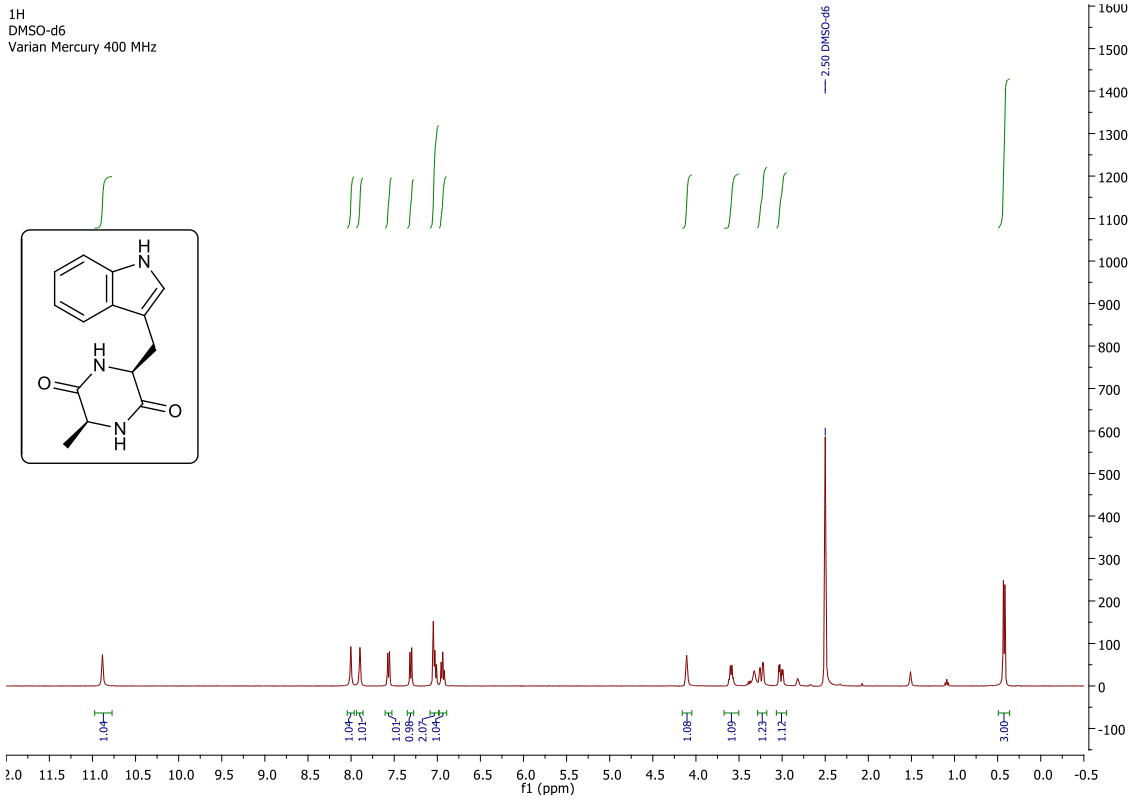
Cyclo(Gly-Trp) (1c) ^{1}H NMR



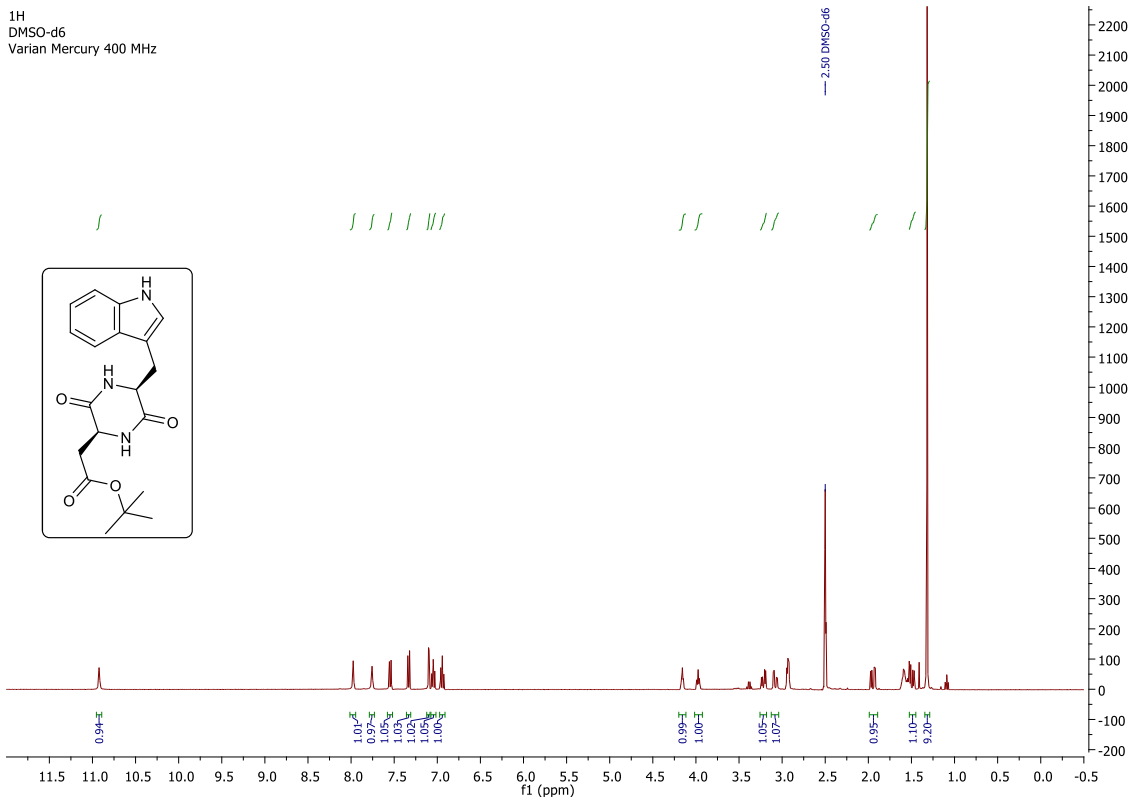
Cyclo(Leu-Trp) (1d) ^{1}H NMR



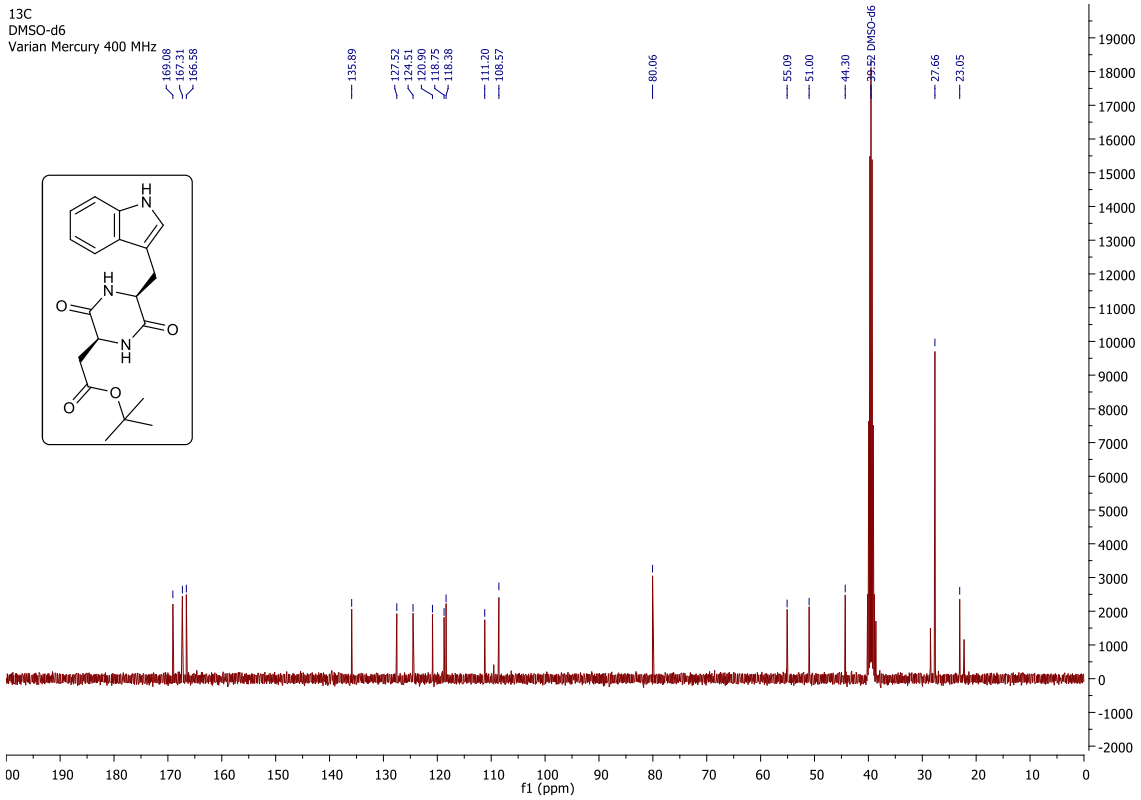
Cyclo(Ala-Trp) (1e) ^{1}H NMR



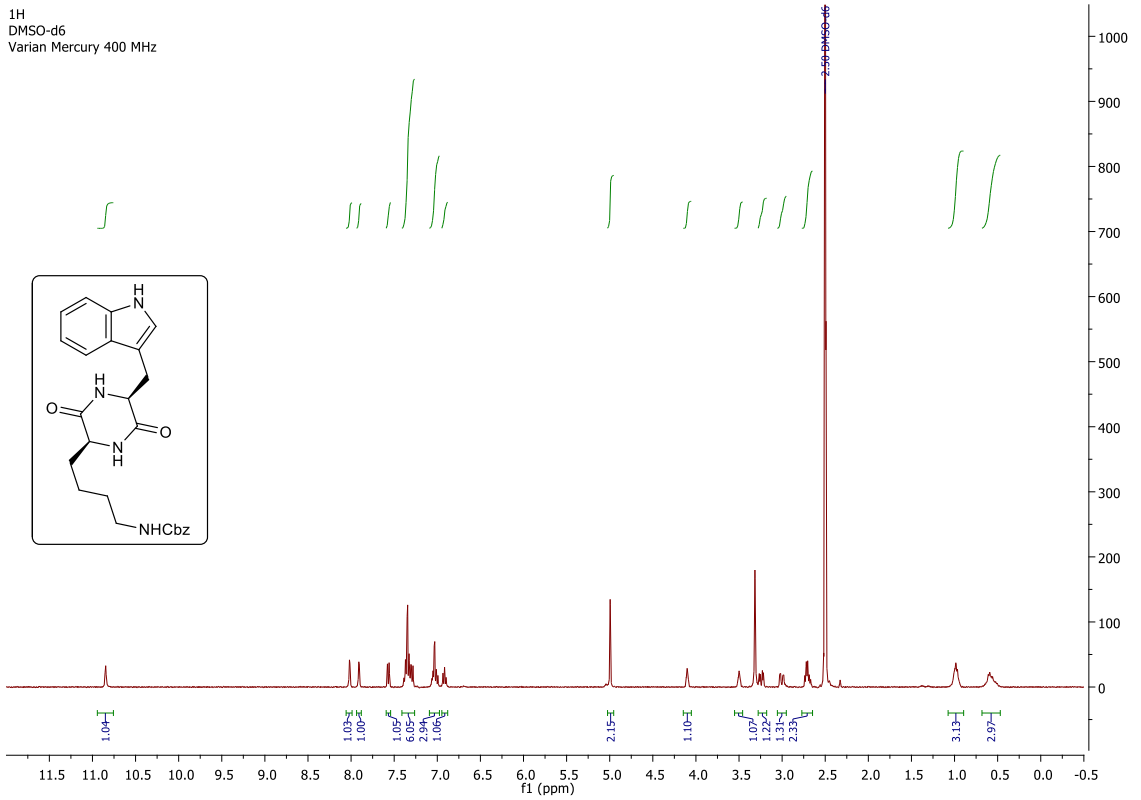
Cyclo[Asp(^{t}Bu)-Trp] (1f) ^{1}H NMR



Cyclo[Asp(ᵗBu)-Trp] (1f) ^{13}C NMR

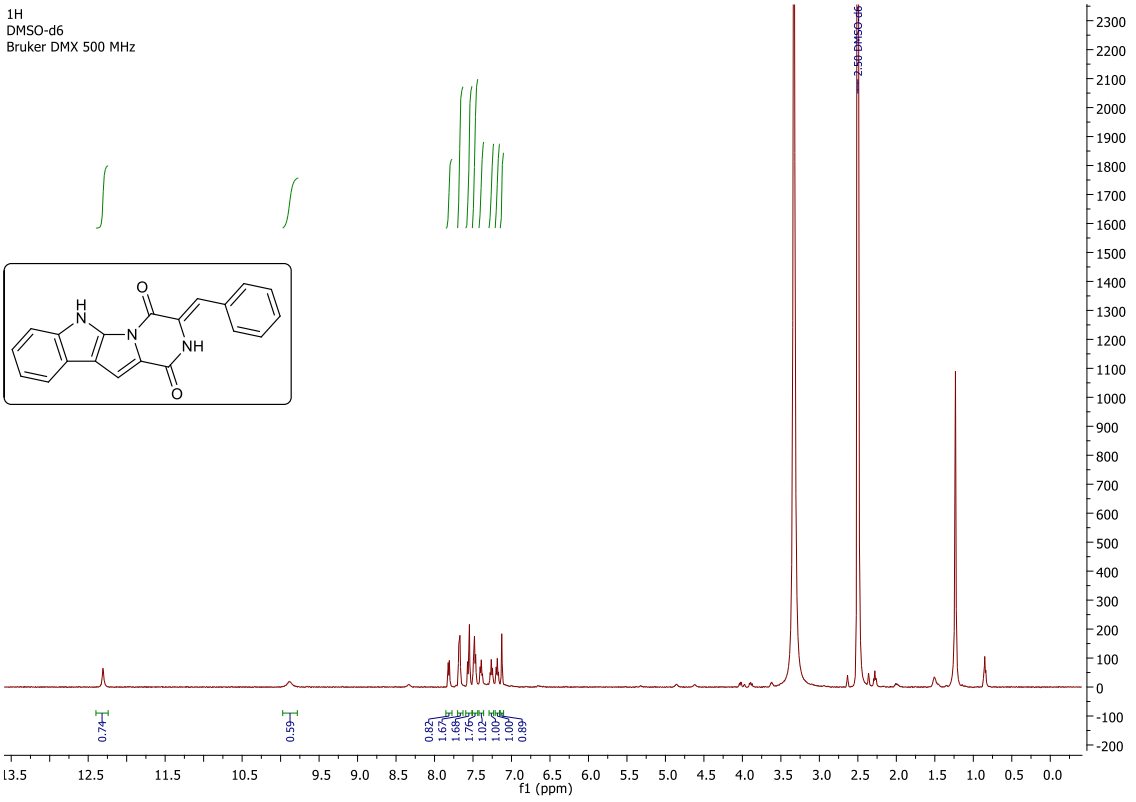


Cyclo[Lys(z)-Trp] (1j) ^{1}H NMR



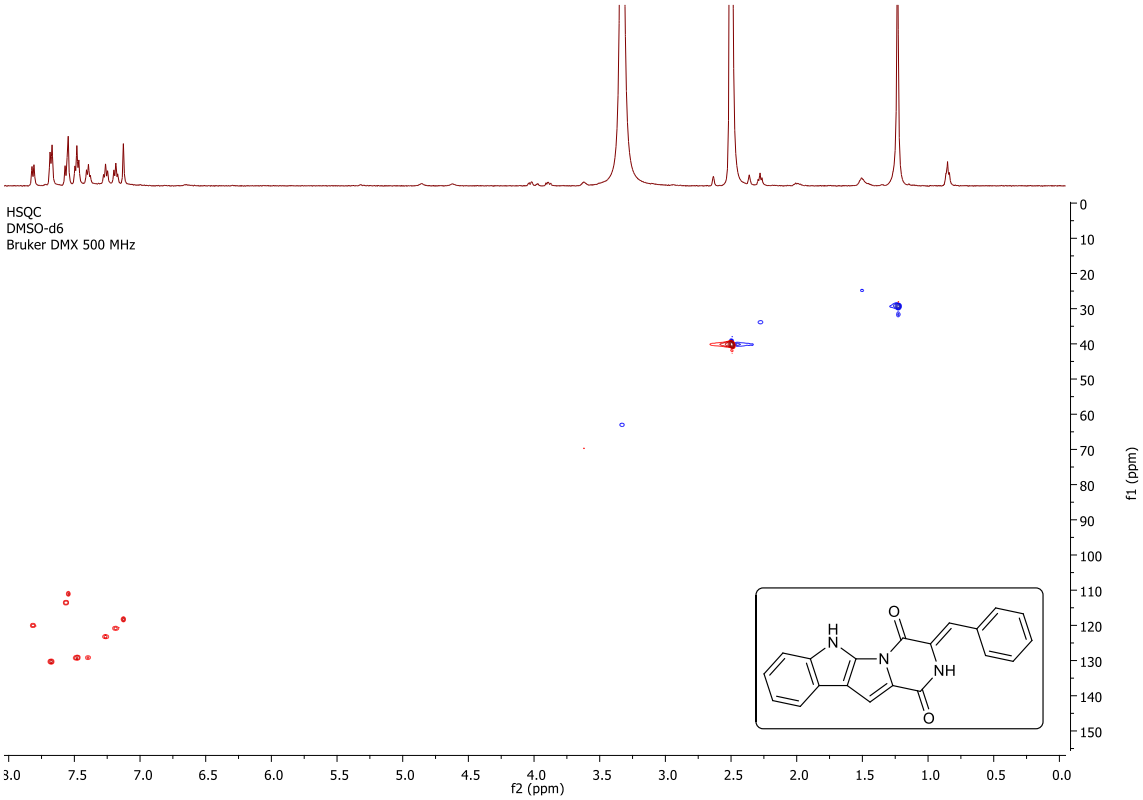
(Z)-3-benzylidene-2,3-dihydro-1*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole-1,4(6*H*)-dione (2a)

^{1}H NMR



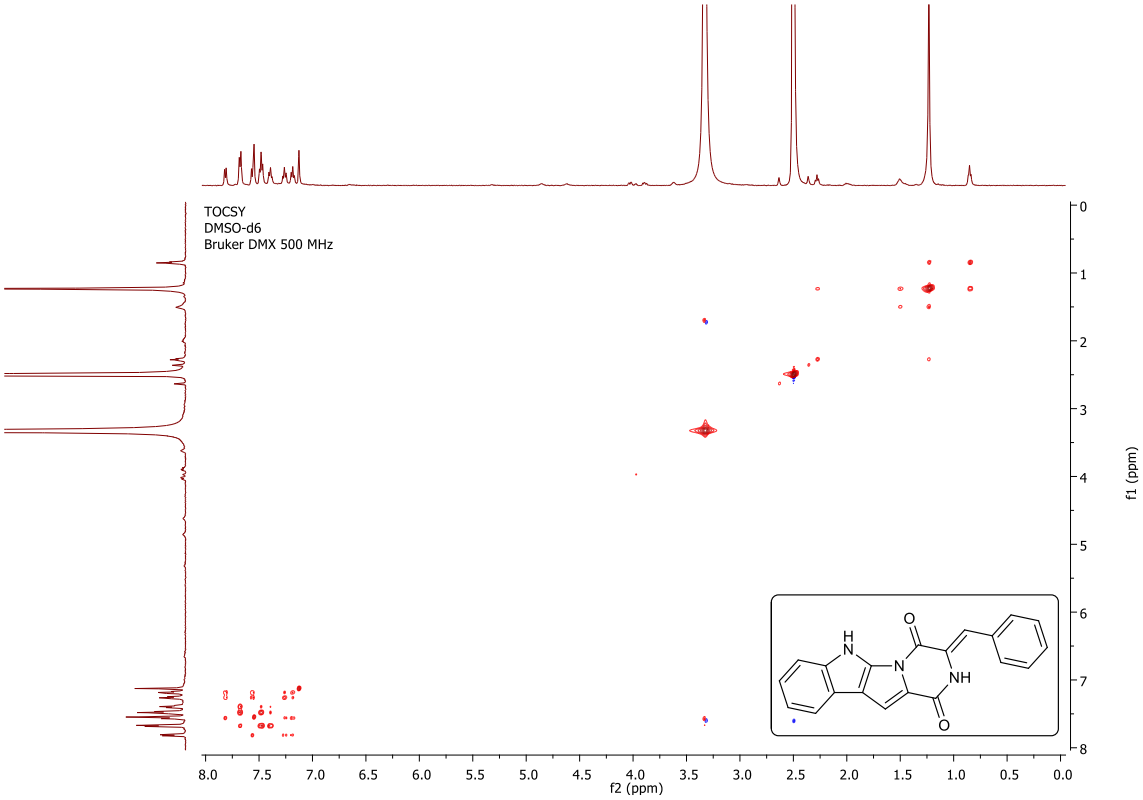
(Z)-3-benzylidene-2,3-dihydro-1*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole-1,4(6*H*)-dione (2a)

^{1}H-^{13}C HSQC NMR



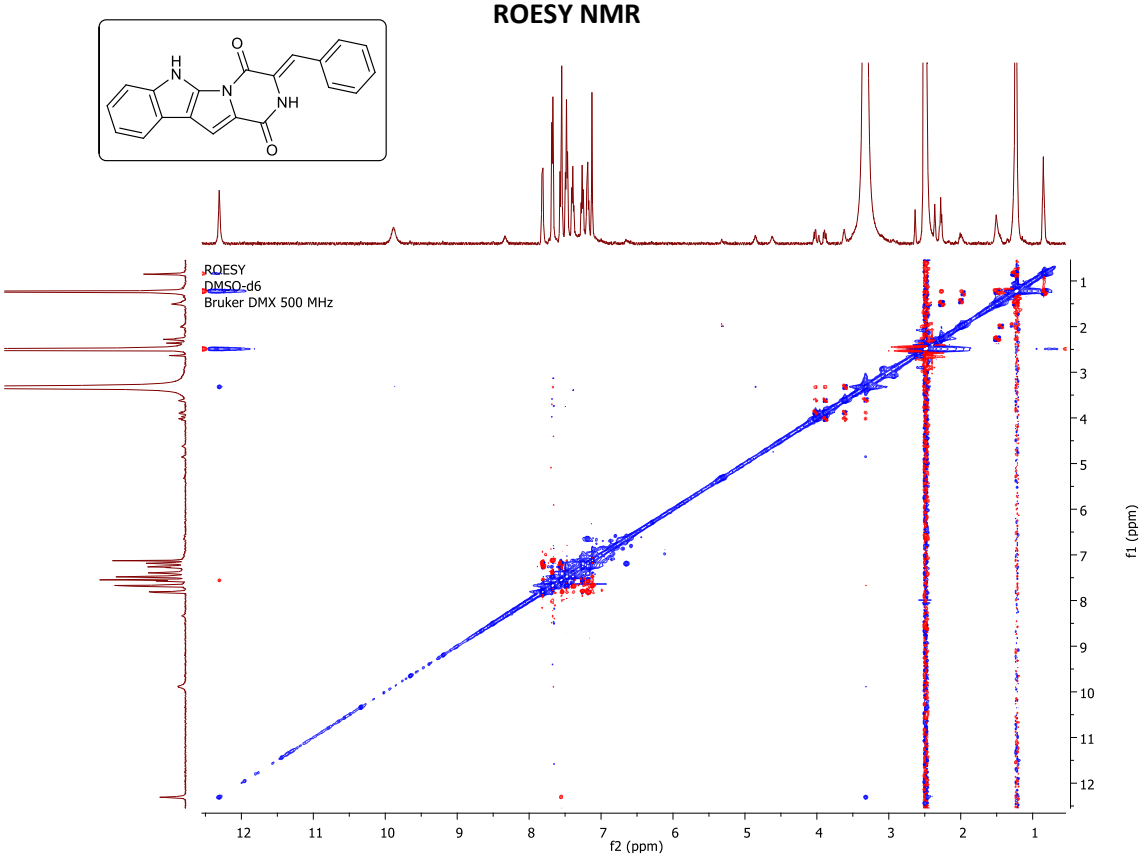
(Z)-3-benzylidene-2,3-dihydro-1*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole-1,4(6*H*)-dione (2a)

TOCSY NMR

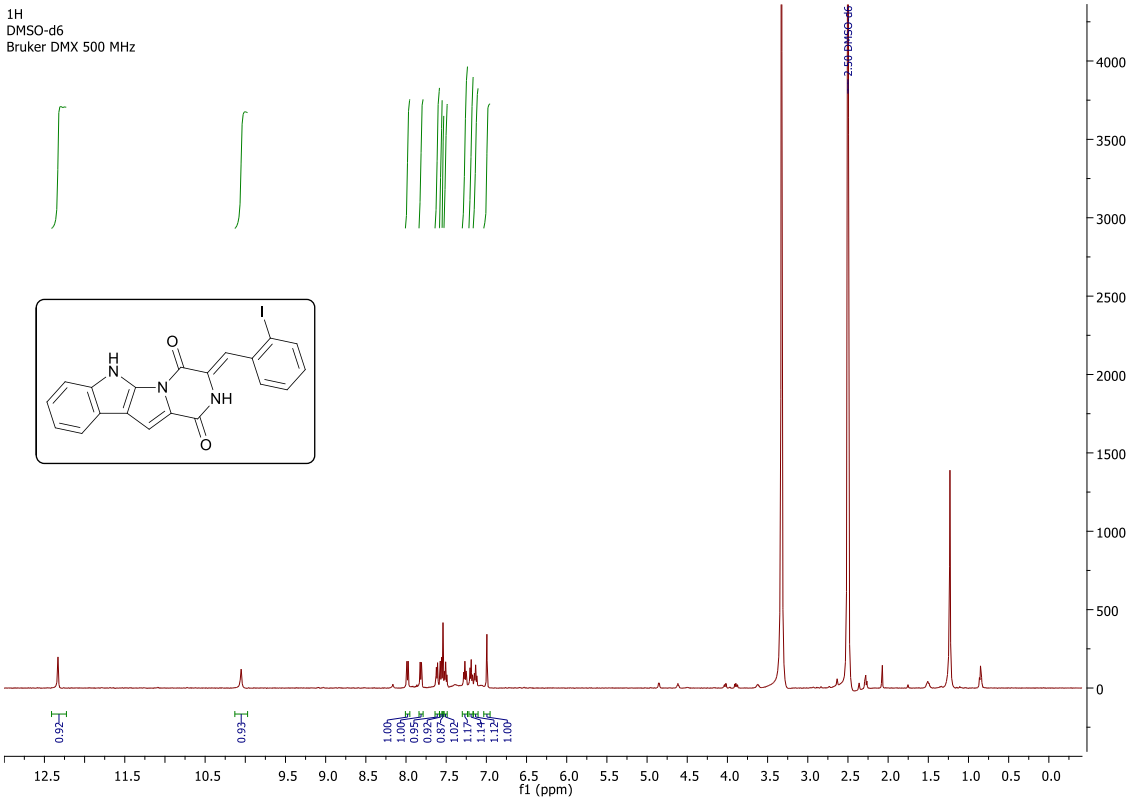


(Z)-3-benzylidene-2,3-dihydro-1*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole-1,4(6*H*)-dione (2a)

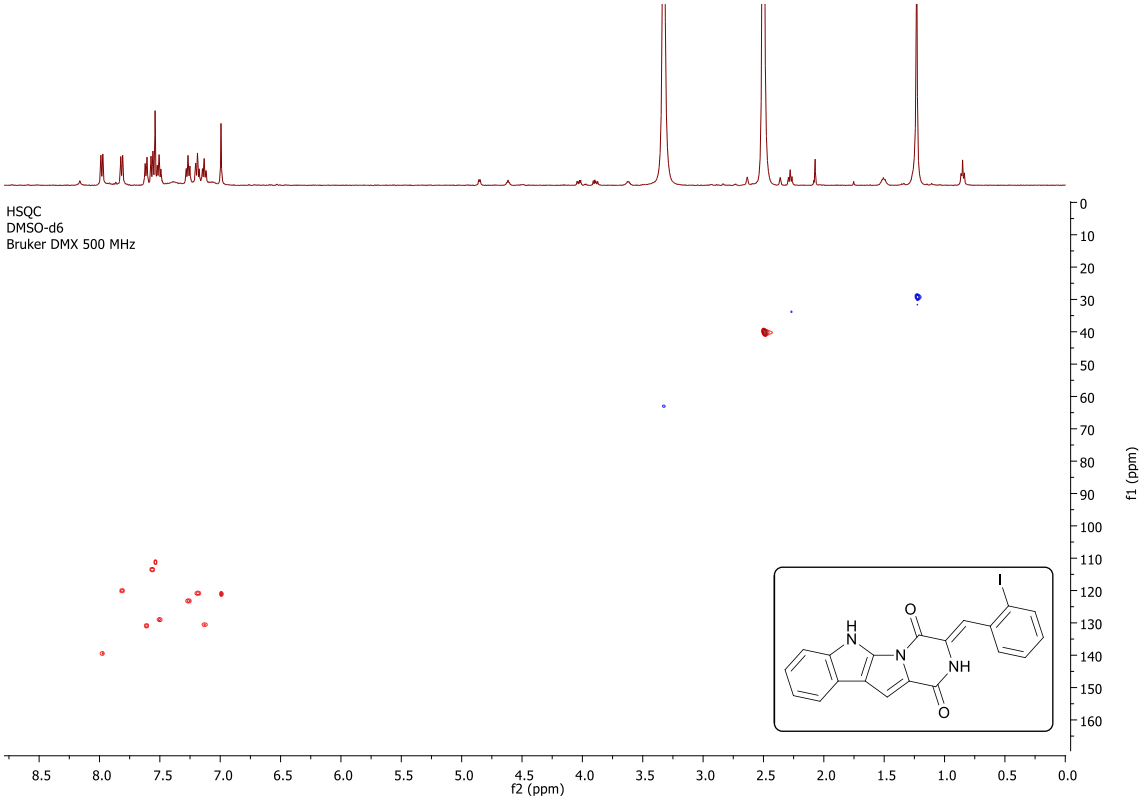
ROESY NMR



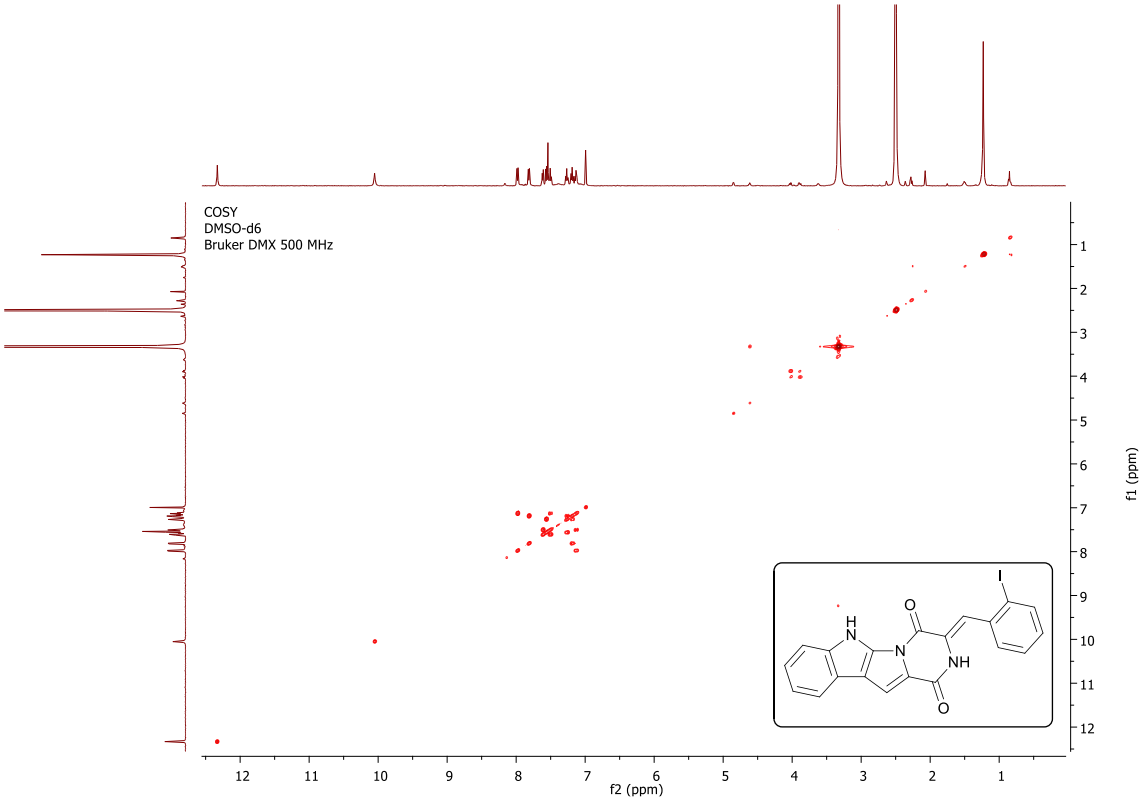
(Z)-3-(2-iodobenzylidene)-2,3-dihydro-1H-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(6H)-dione (2b) ^{1}H NMR



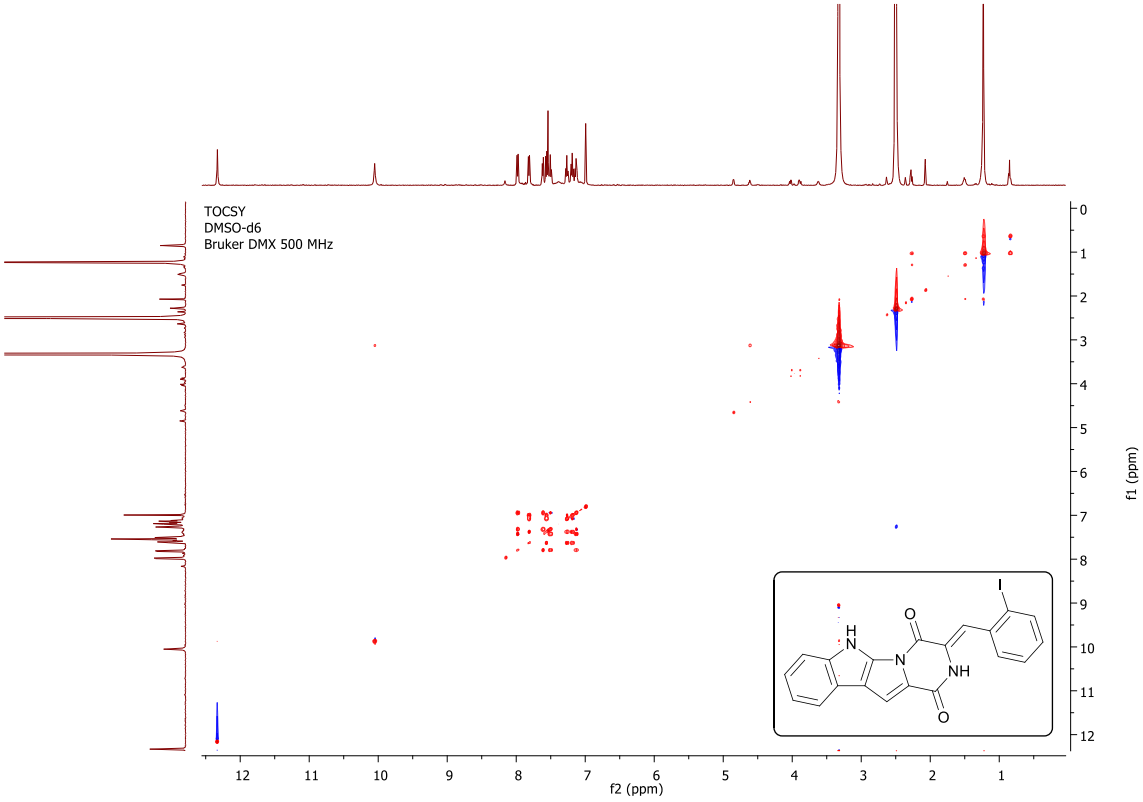
(Z)-3-(2-iodobenzylidene)-2,3-dihydro-1H-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(6H)-dione (2b) ^{1}H-^{13}C HSQC NMR



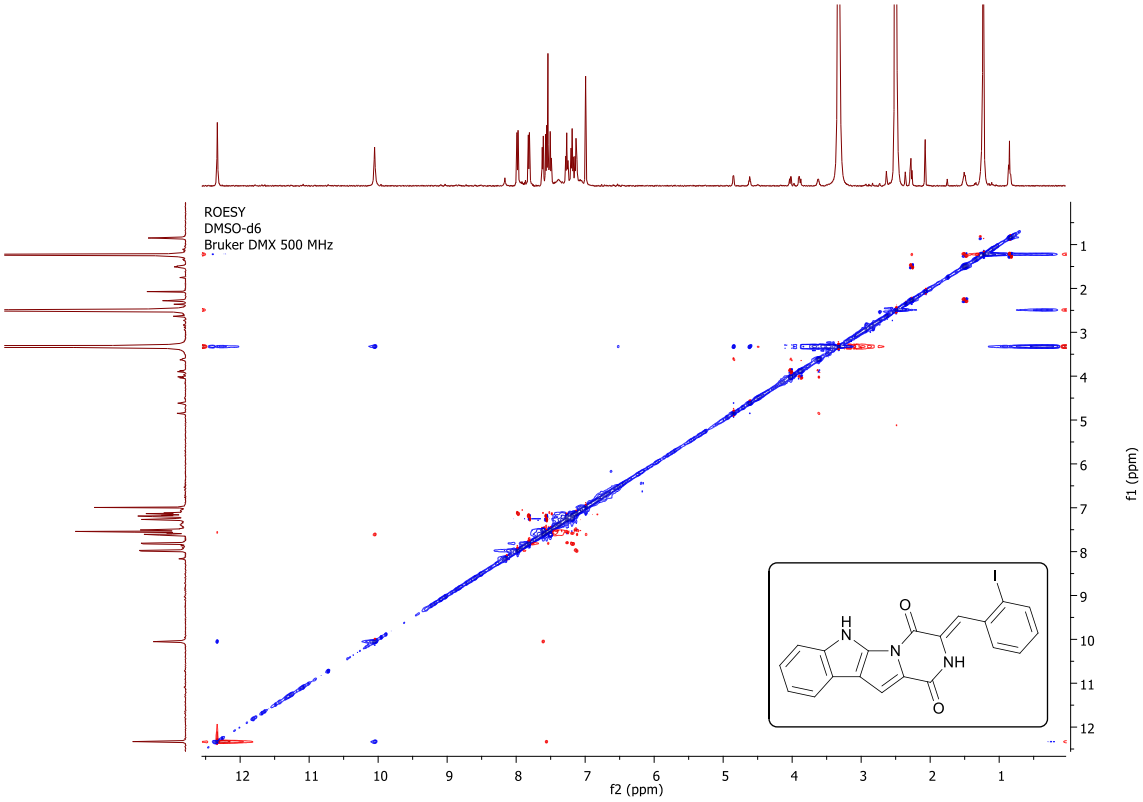
(Z)-3-(2-iodobenzylidene)-2,3-dihydro-1H-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(6H)-dione (2b) COSY NMR



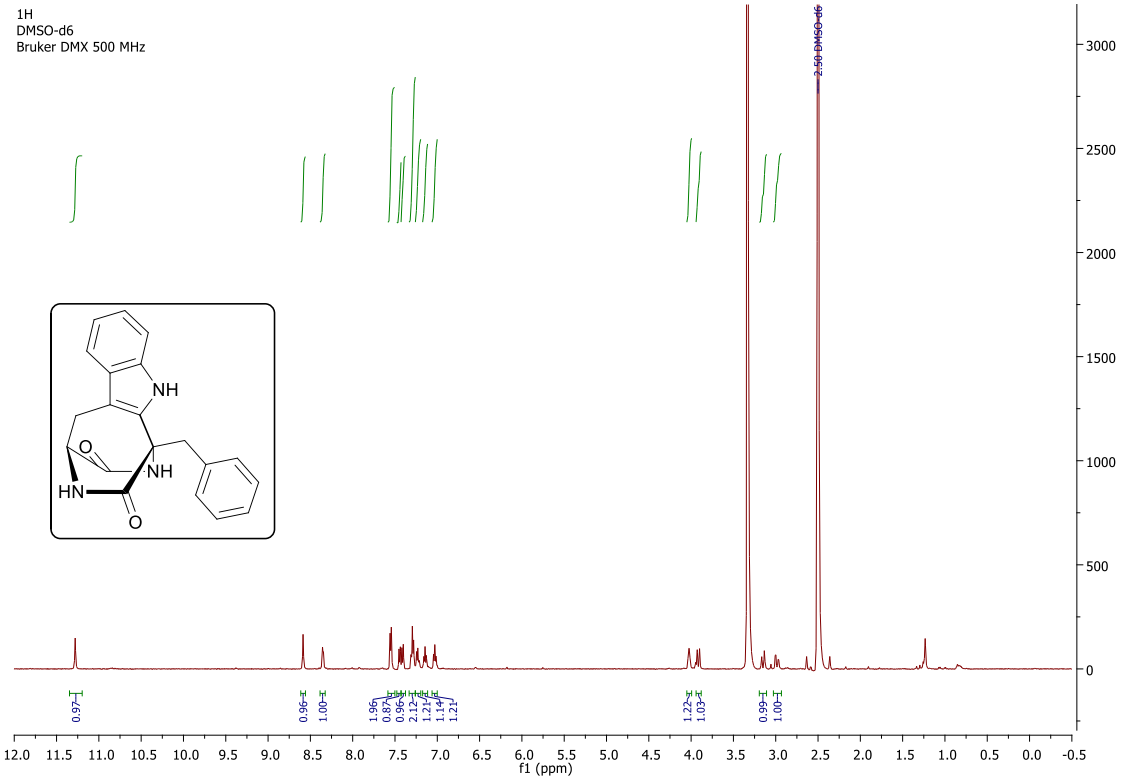
(Z)-3-(2-iodobenzylidene)-2,3-dihydro-1H-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(6H)-dione (2b) TOCSY NMR



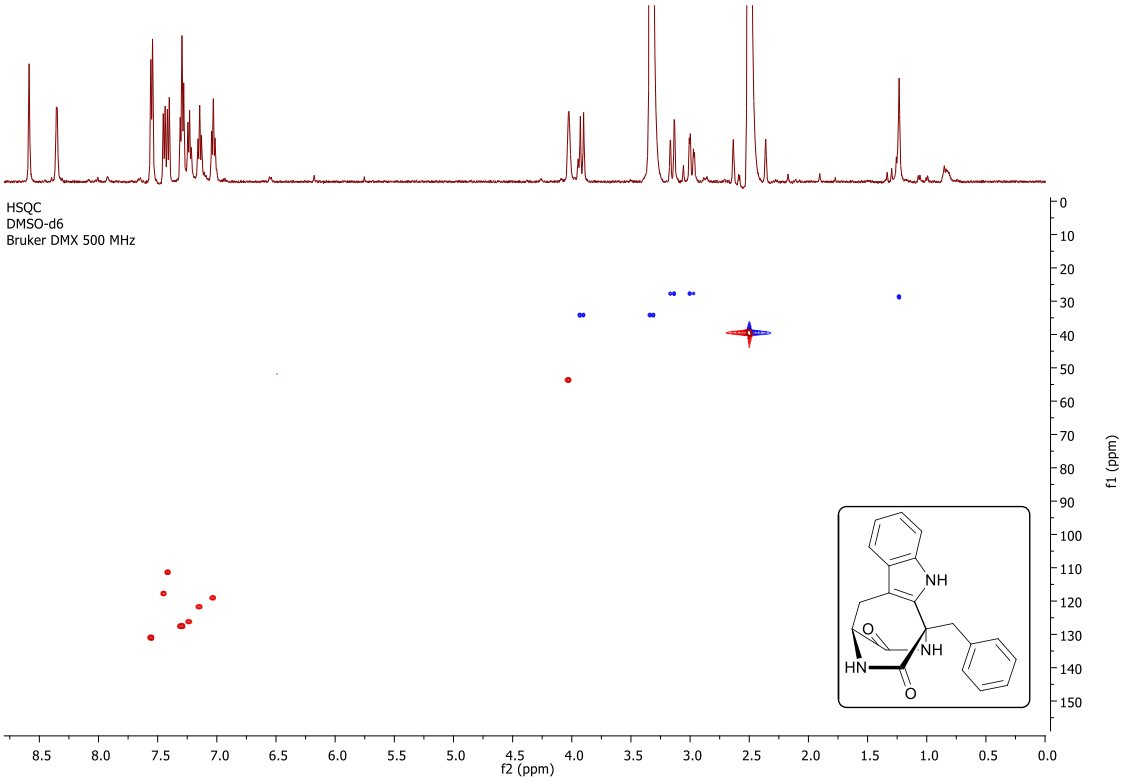
(Z)-3-(2-iodobenzylidene)-2,3-dihydro-1H-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(6H)-dione (2b) ROESY NMR



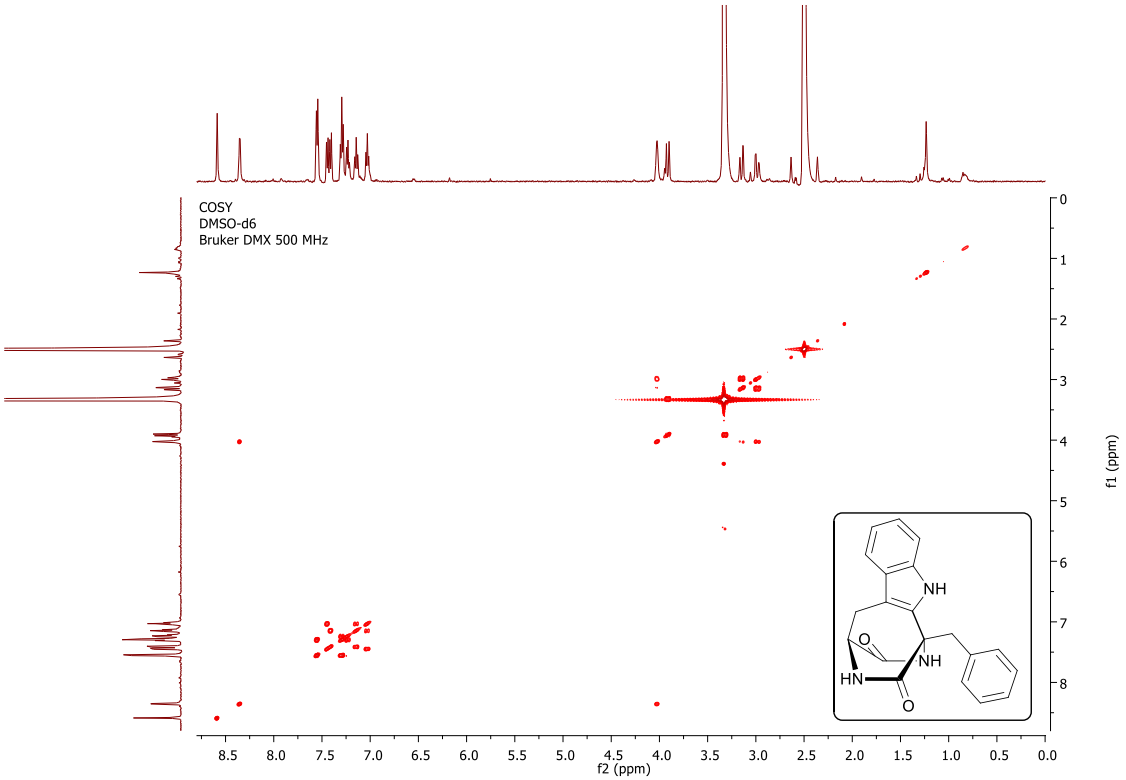
Oxidized cyclo(Phe-Trp) (4a) ^{1}H NMR



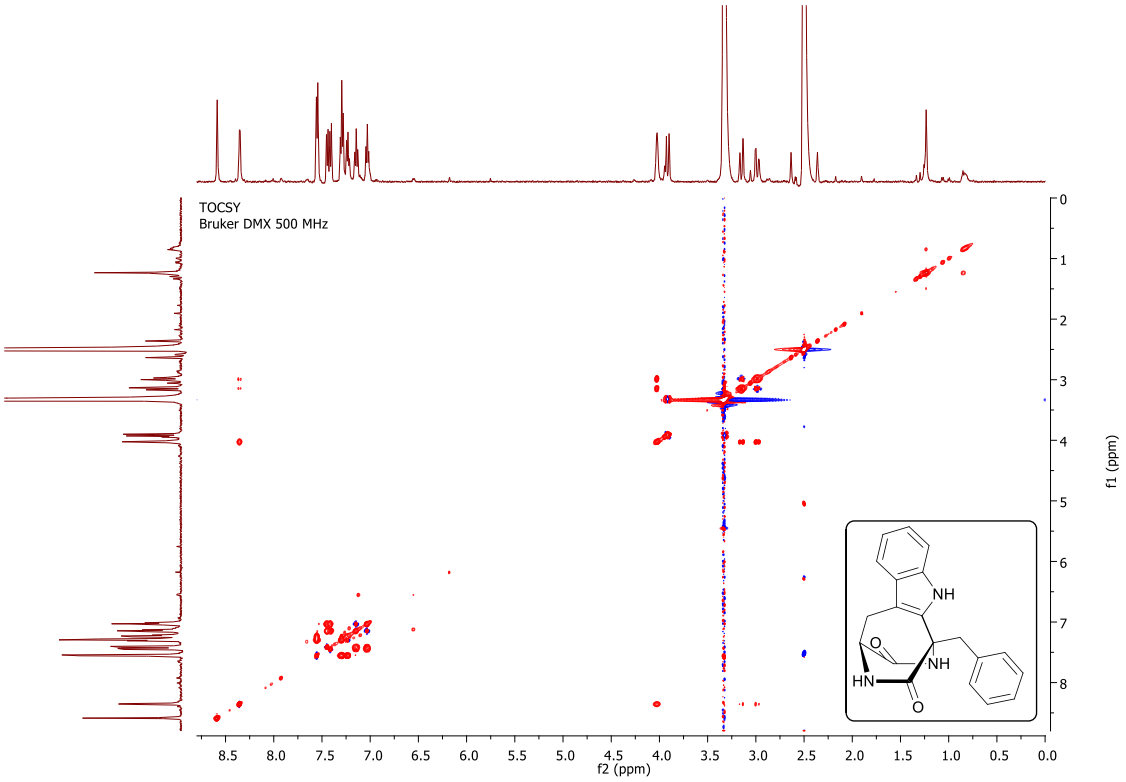
Oxidized cyclo(Phe-Trp) (4a) ^{1}H-^{13}C HSQC NMR



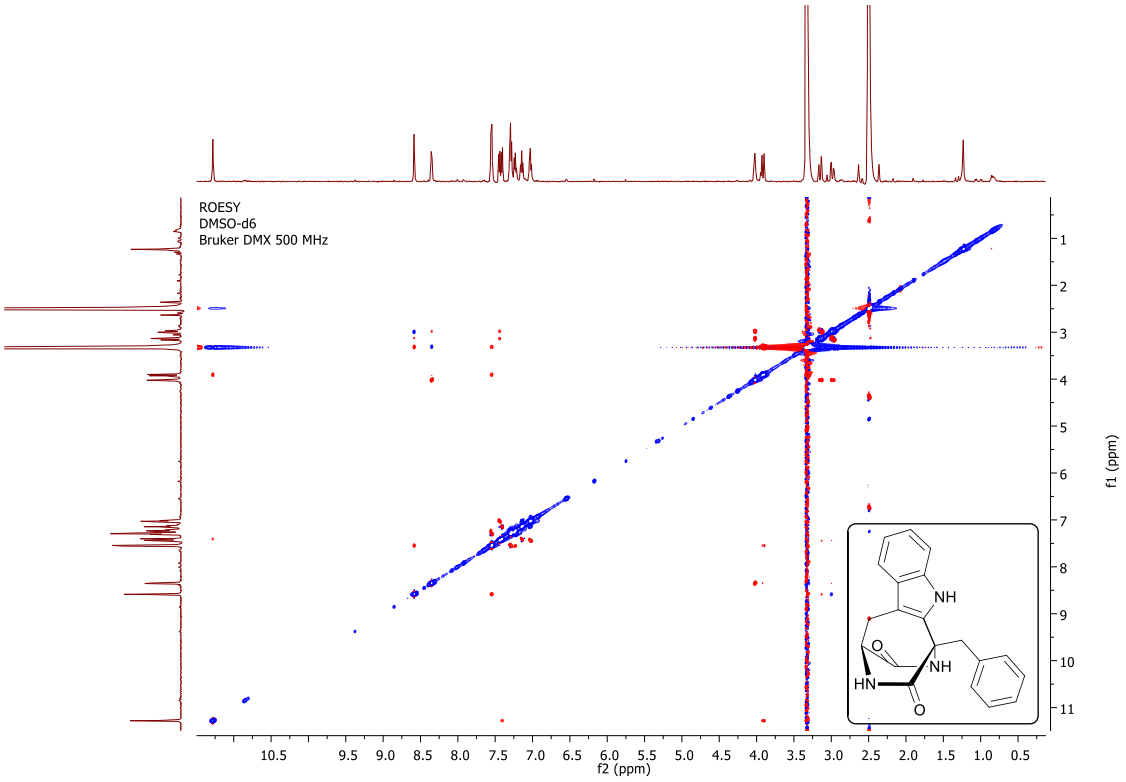
Oxidized cyclo(Phe-Trp) (4a) COSY NMR



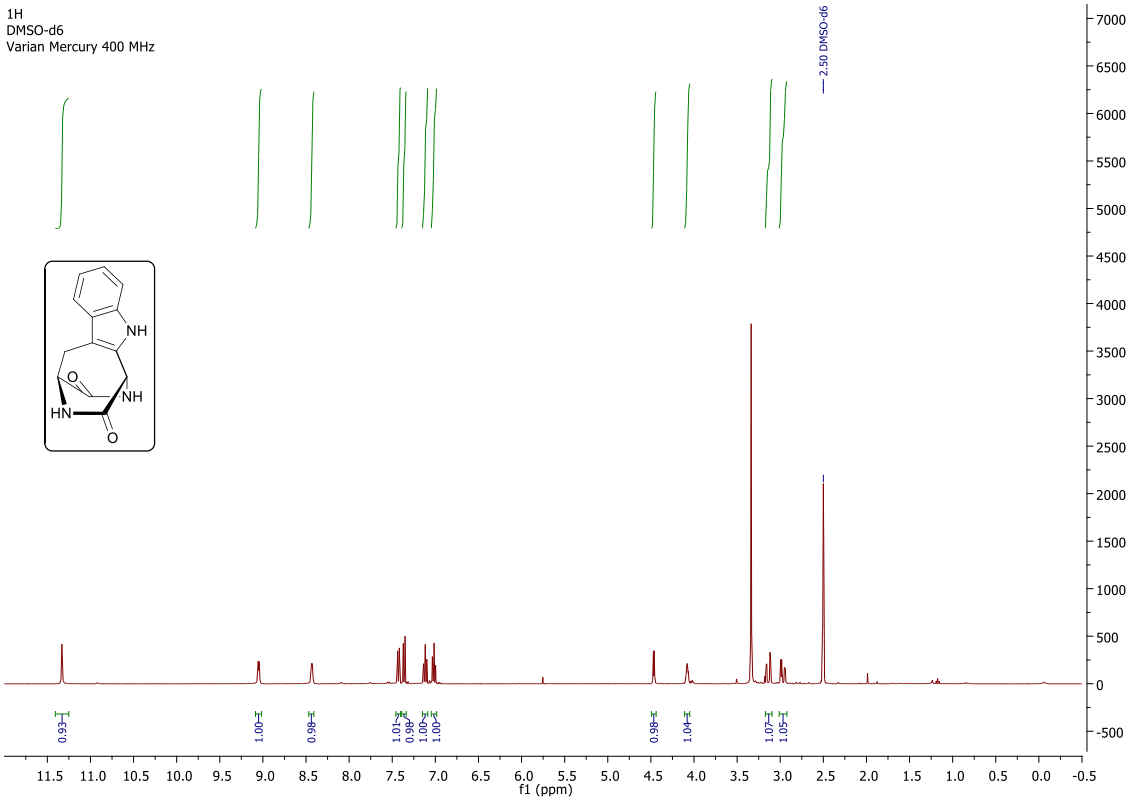
Oxidized cyclo(Phe-Trp) (4a) TOCSY NMR



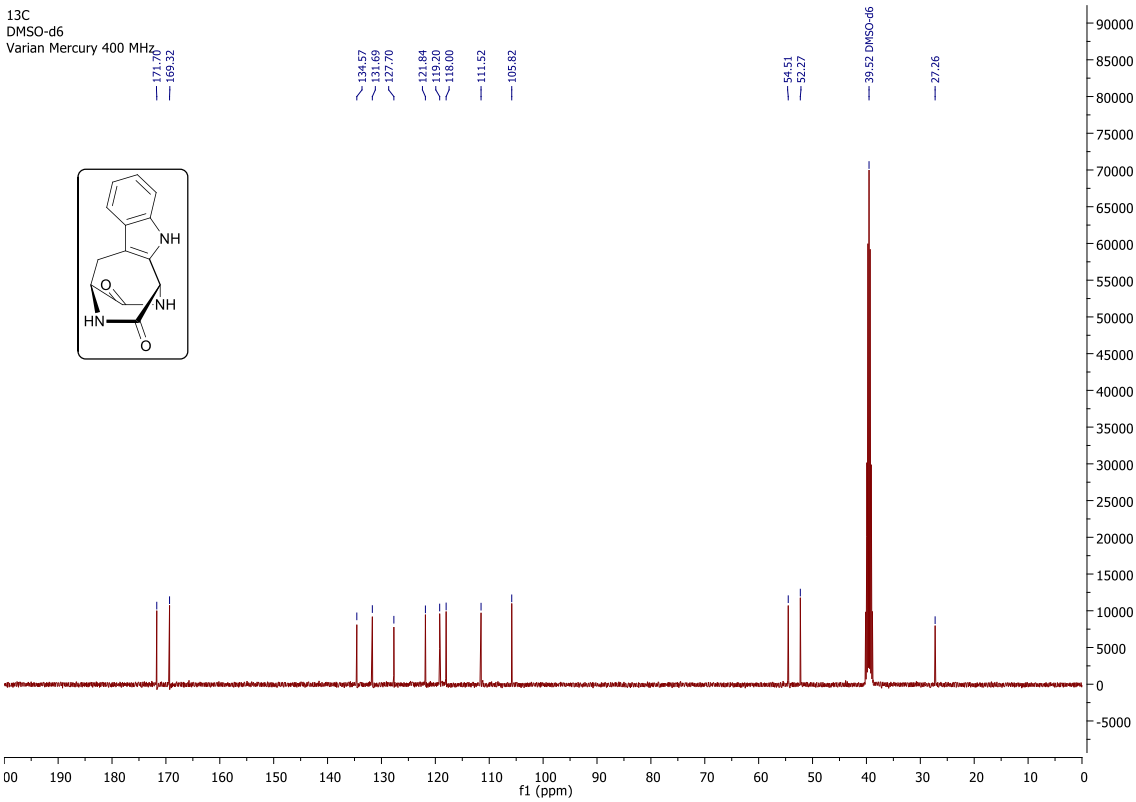
Oxidized cyclo(Phe-Trp) (4a) ROESY NMR



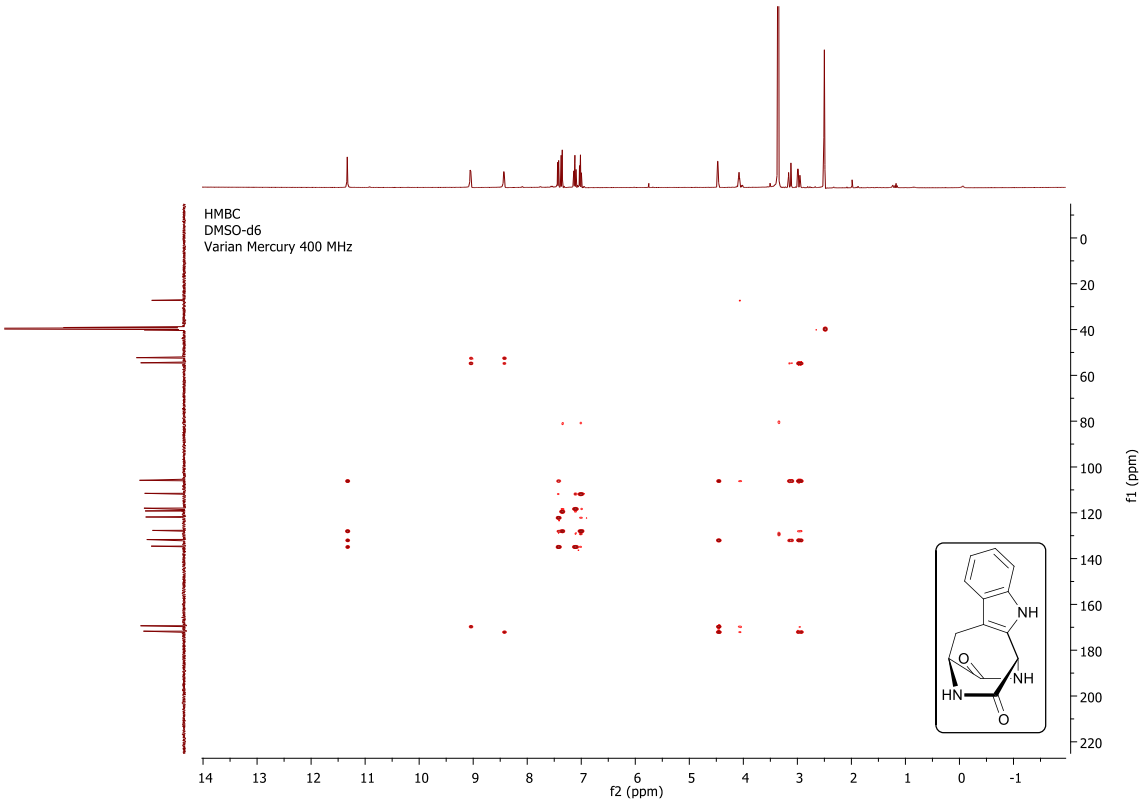
Oxidized cyclo(Gly-Trp) (4c) ^{1}H NMR



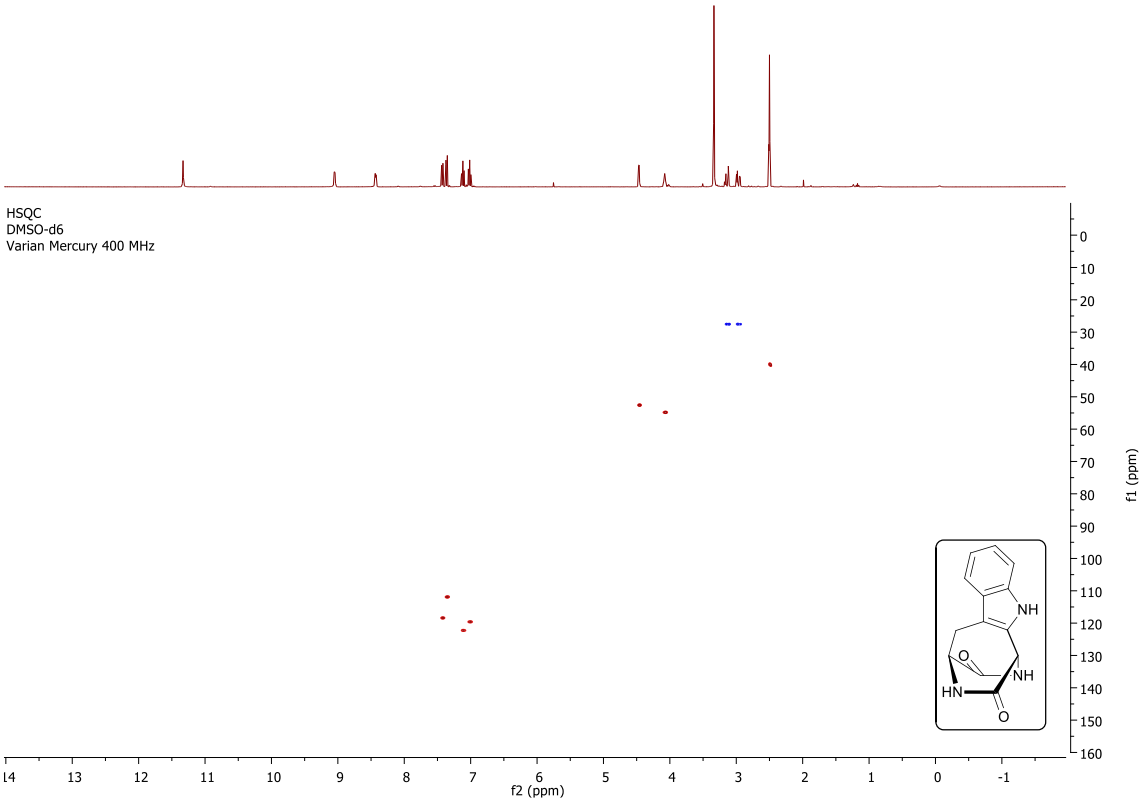
Oxidized cyclo(Gly-Trp) (4c) ^{13}C NMR



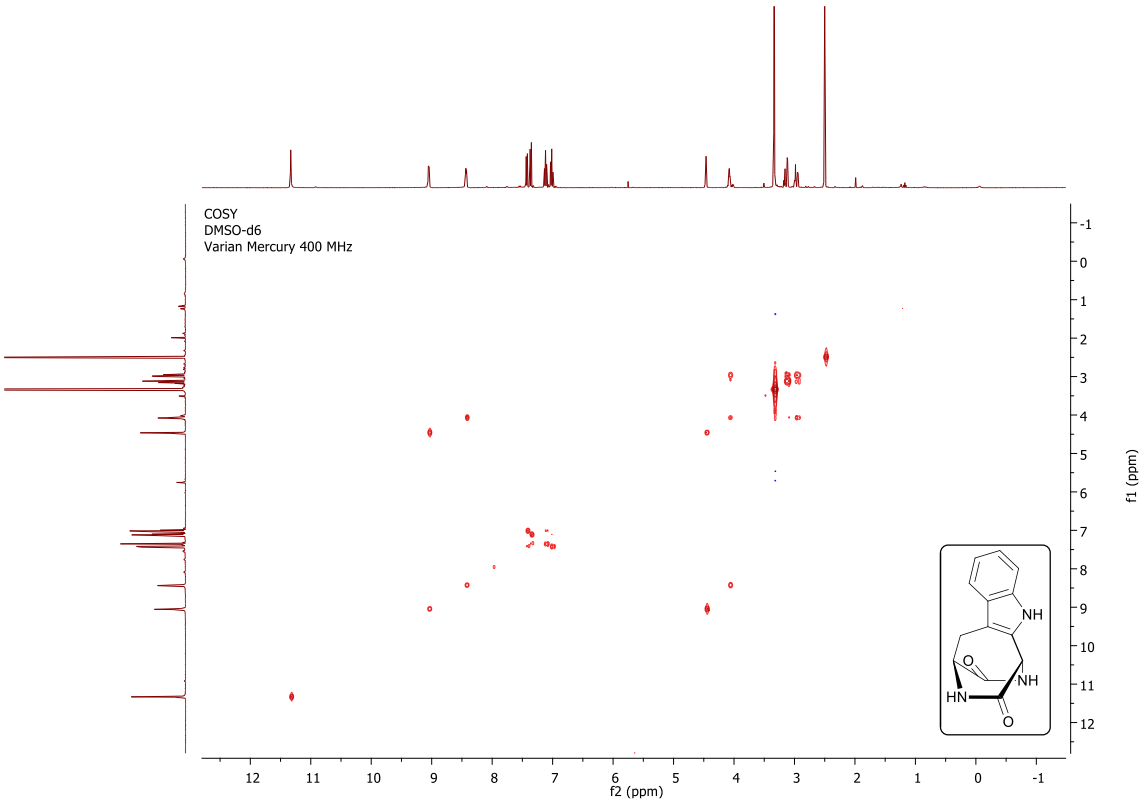
Oxidized cyclo(Gly-Trp) (4c) ^{1}H-^{13}C HMBC NMR



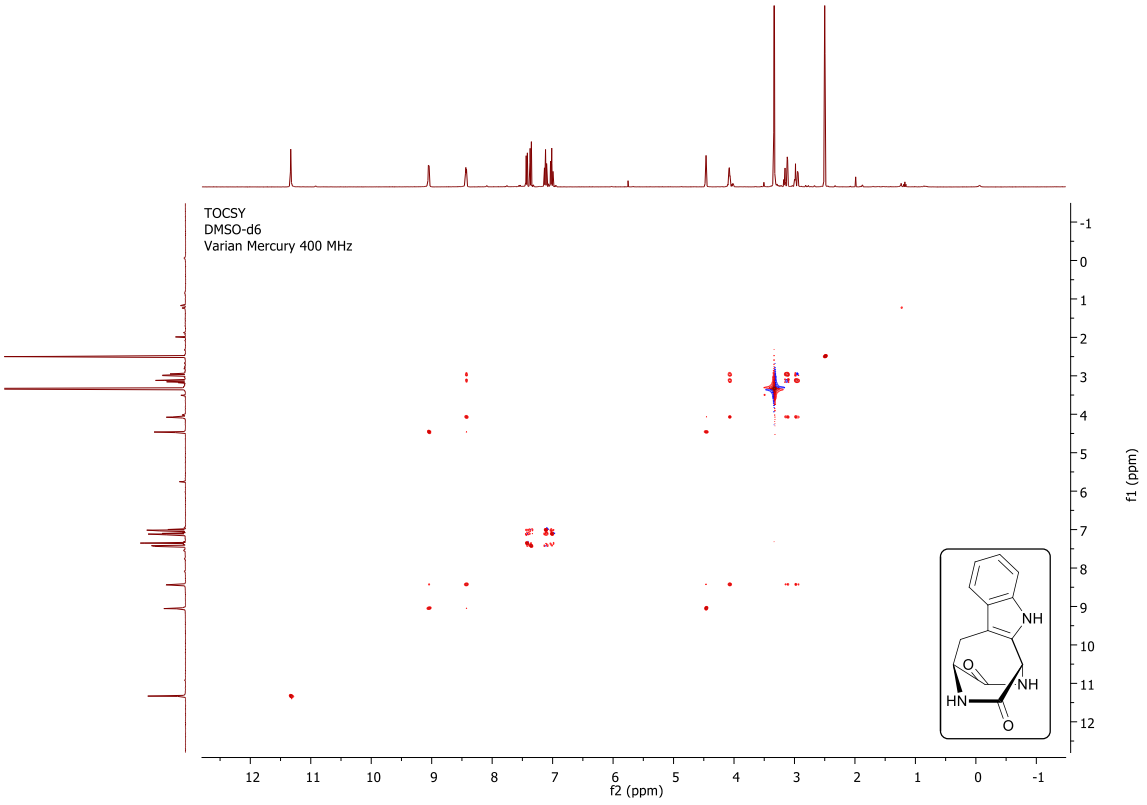
Oxidized cyclo(Gly-Trp) (4c) ^{1}H-^{13}C HSQC NMR



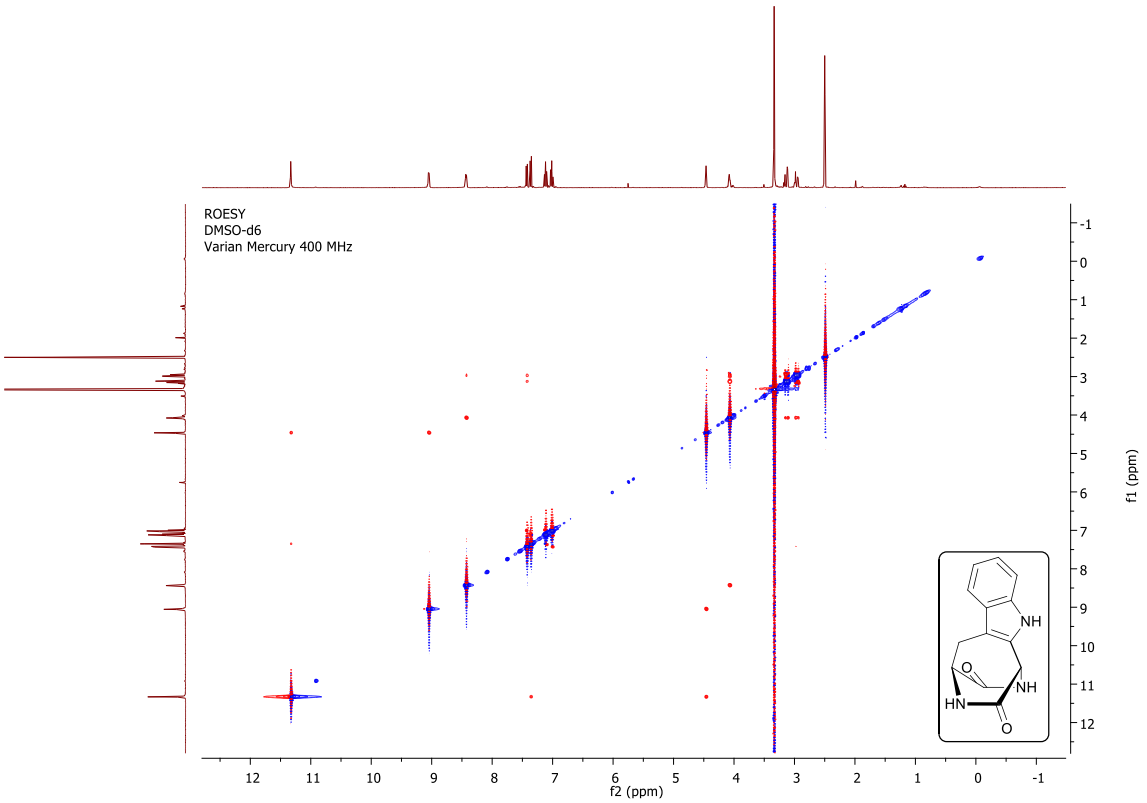
Oxidized cyclo(Gly-Trp) (4c) COSY NMR



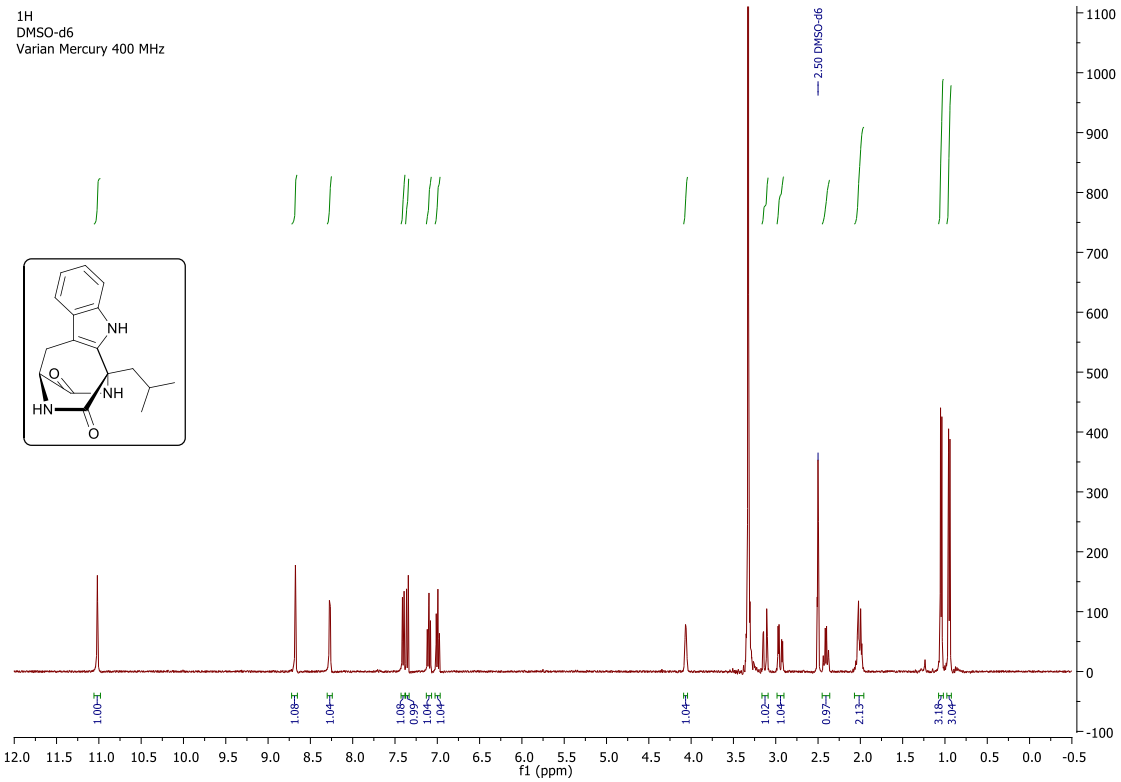
Oxidized cyclo(Gly-Trp) (4c) TOCSY NMR



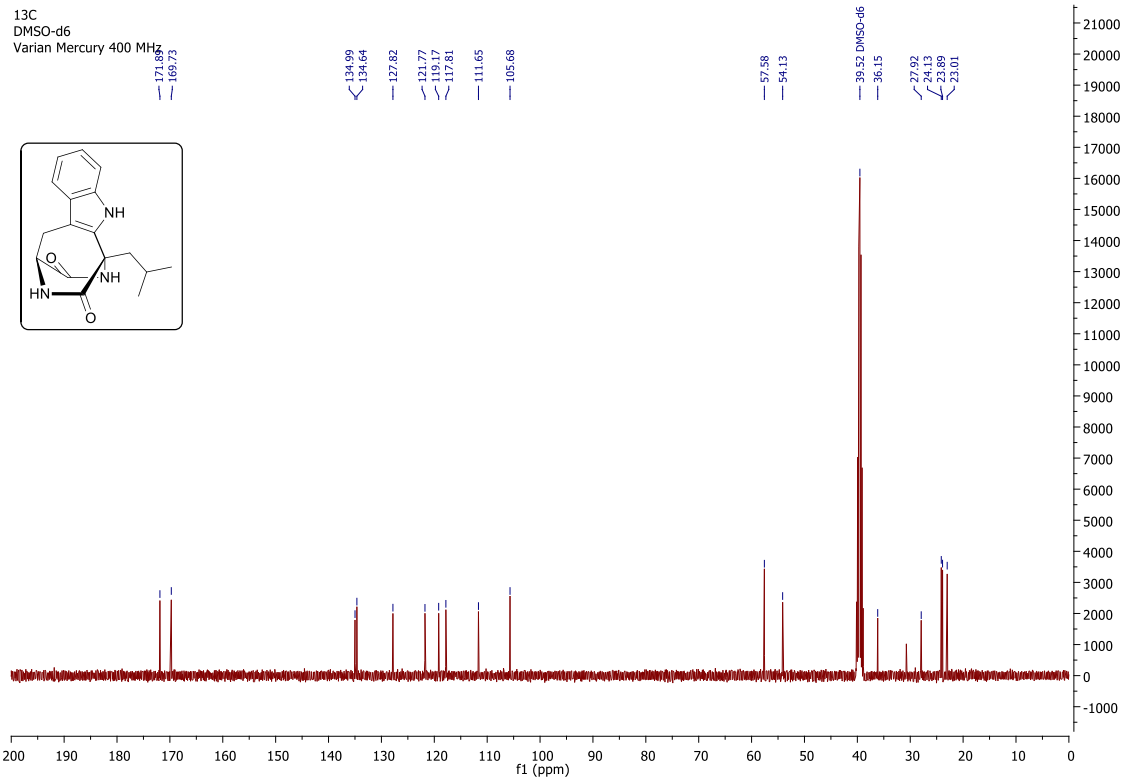
Oxidized cyclo(Gly-Trp) (4c) ROESY NMR



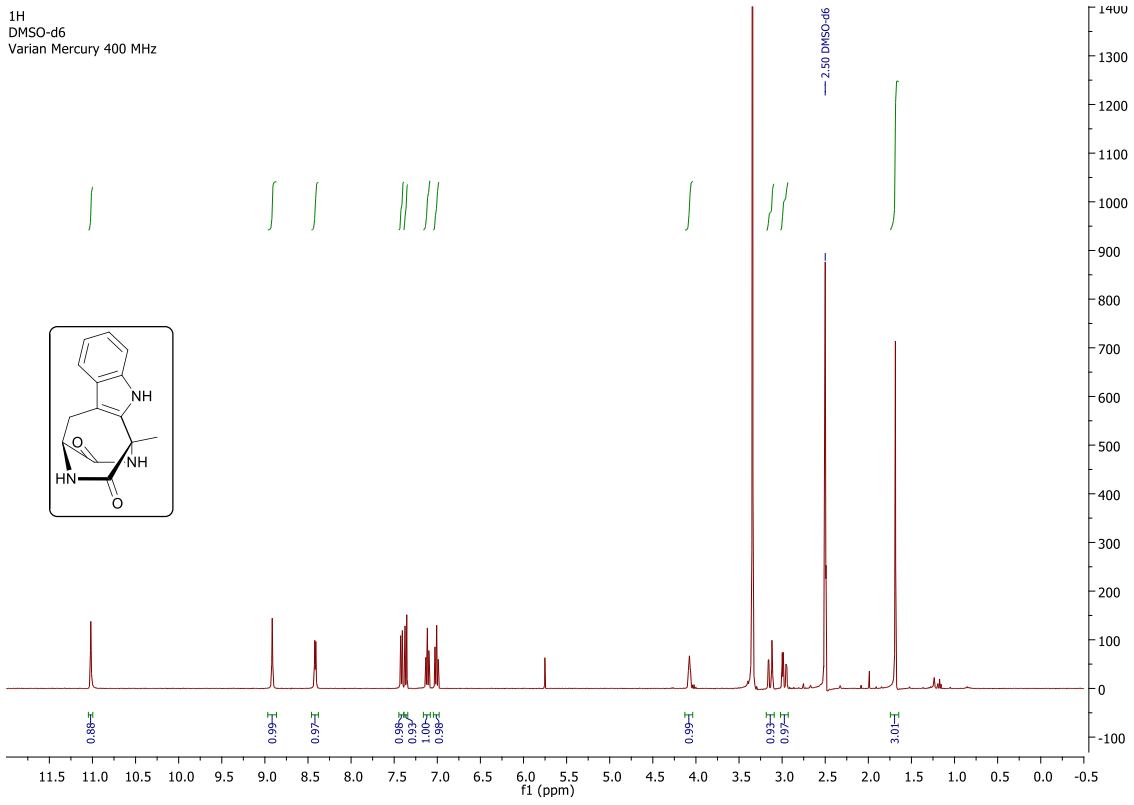
Oxidized cyclo(Leu-Trp) (4d) ^{1}H NMR



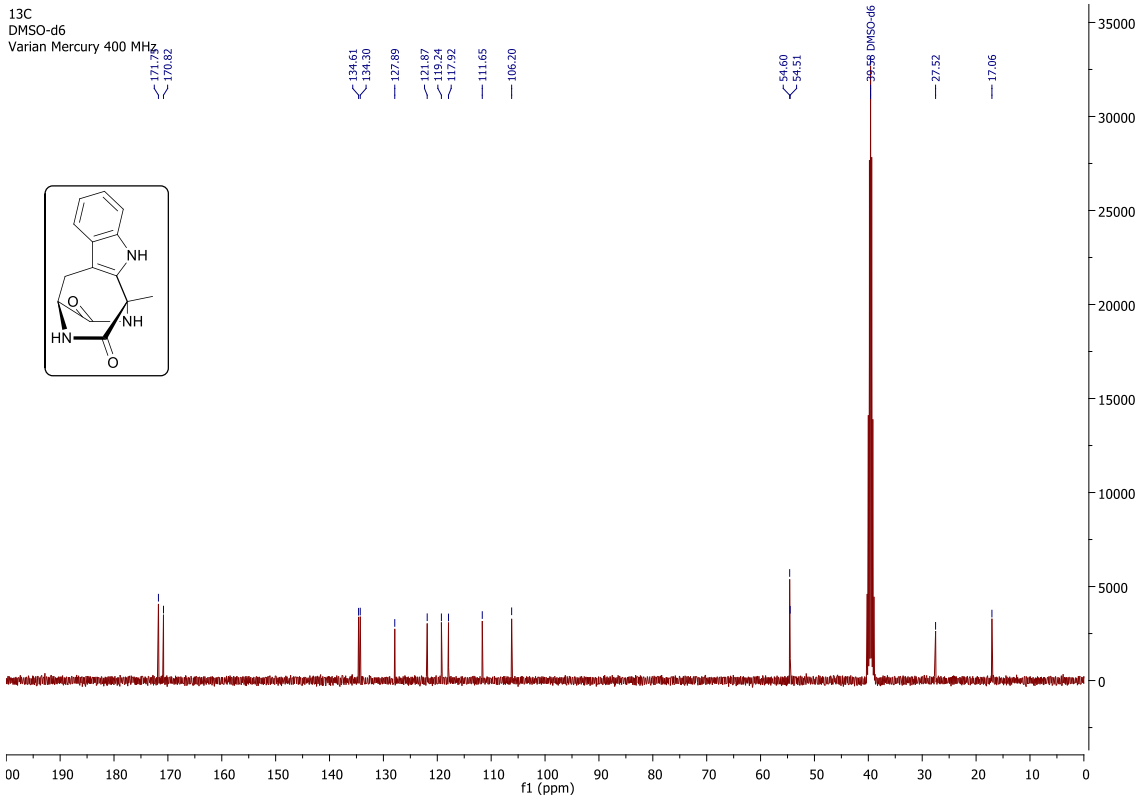
Oxidized cyclo(Leu-Trp) (4d) ^{13}C NMR



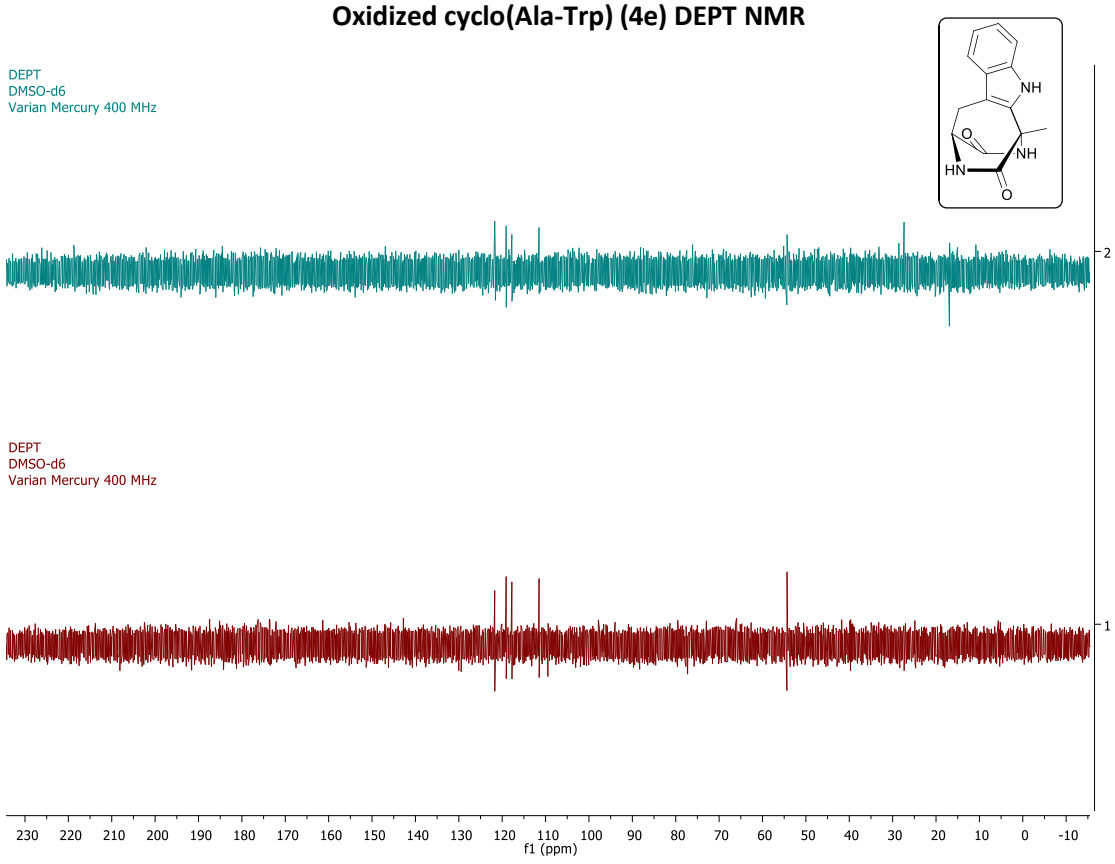
Oxidized cyclo[Ala-Trp) (4e) ^{1}H NMR



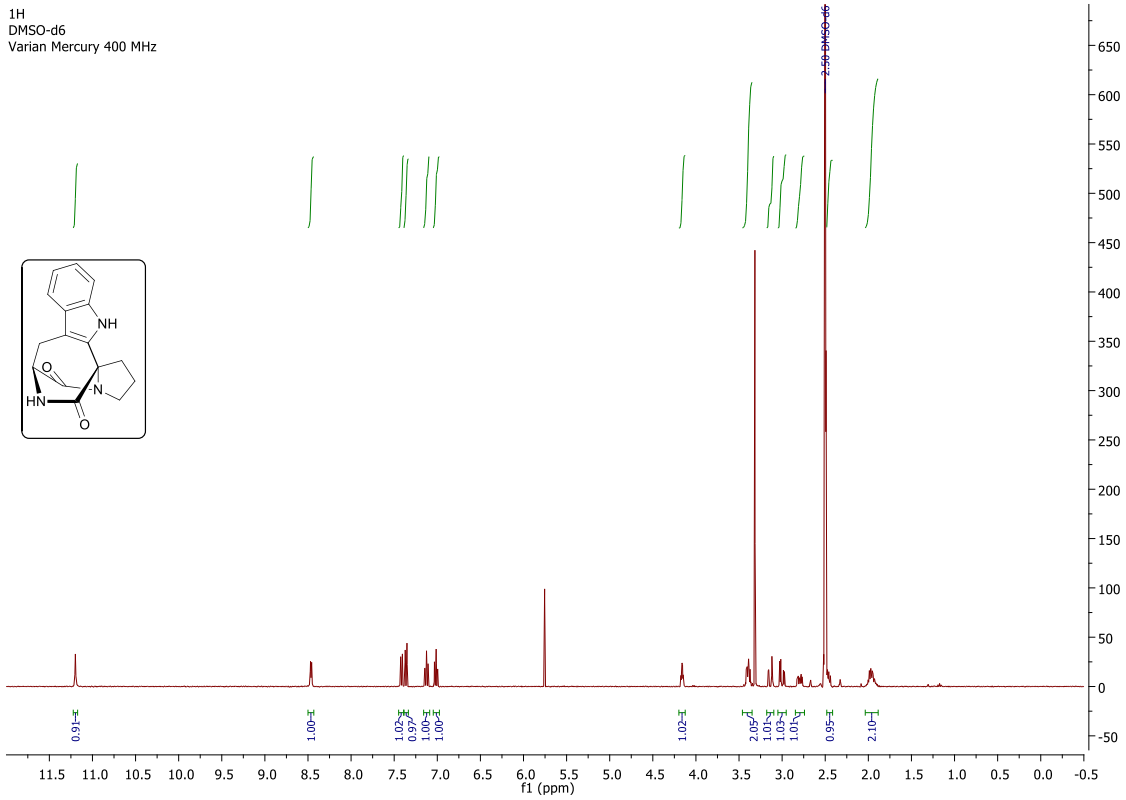
Oxidized cyclo(Ala-Trp) (4e) ^{13}C NMR



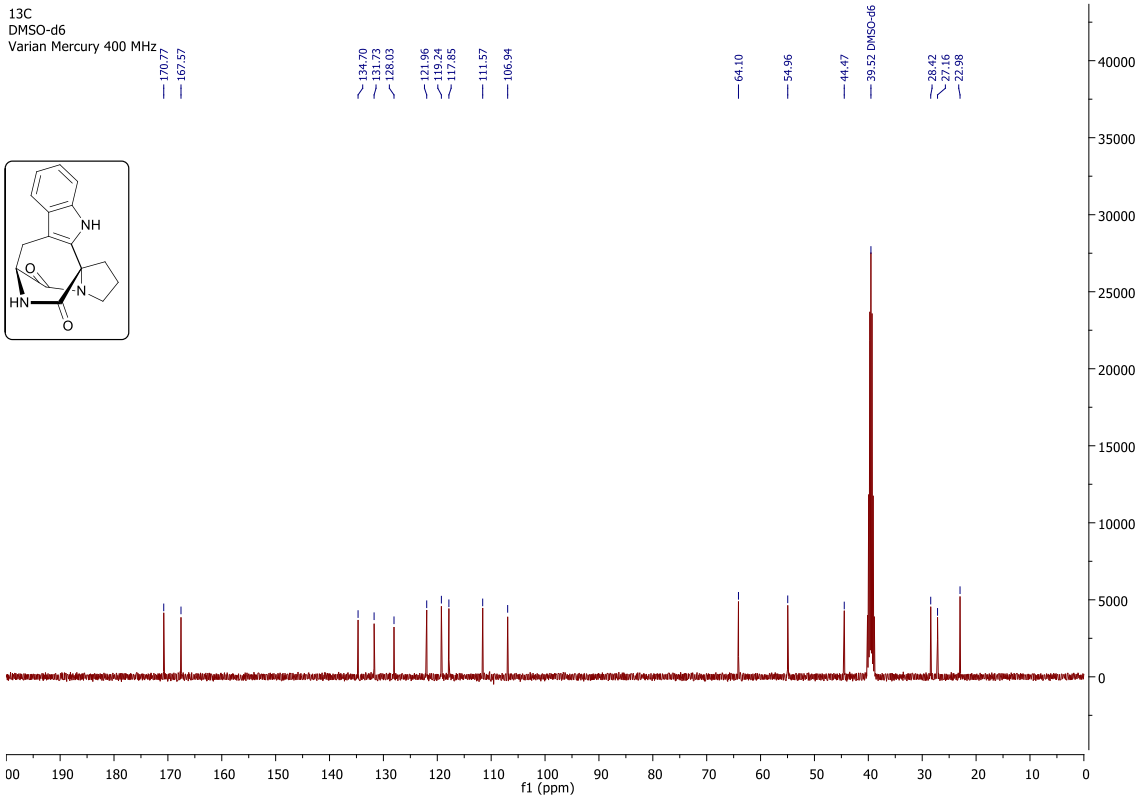
Oxidized cyclo(Ala-Trp) (4e) DEPT NMR



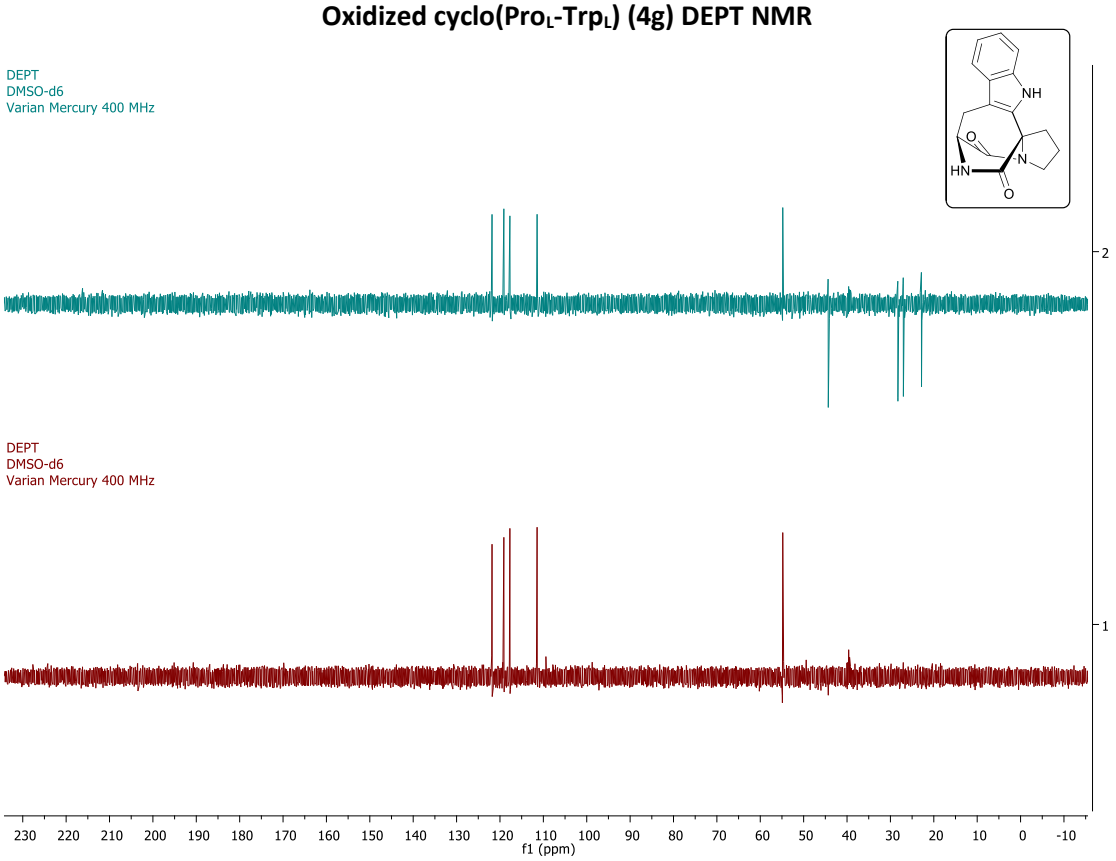
Oxidized cyclo(Pro$_L$-Trp$_L$) (4g) ^{1}H NMR



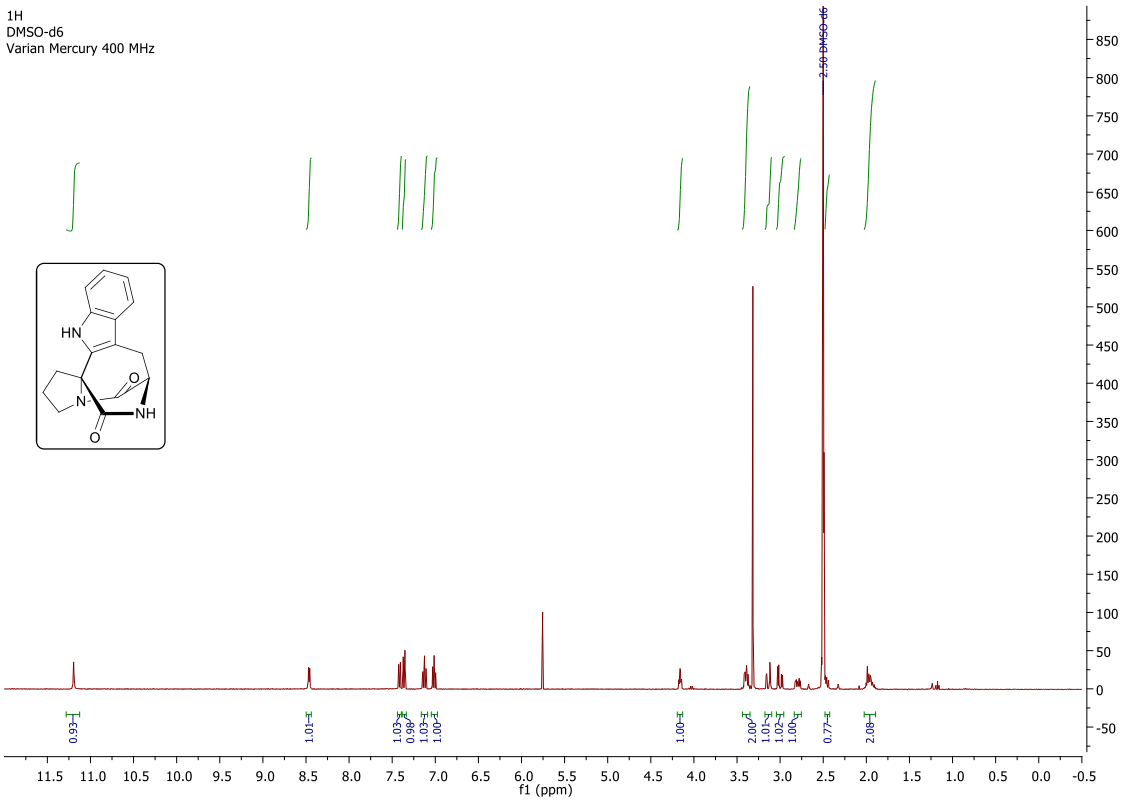
Oxidized cyclo(Pro$_L$-Trp$_L$) (4g) ^{13}C NMR



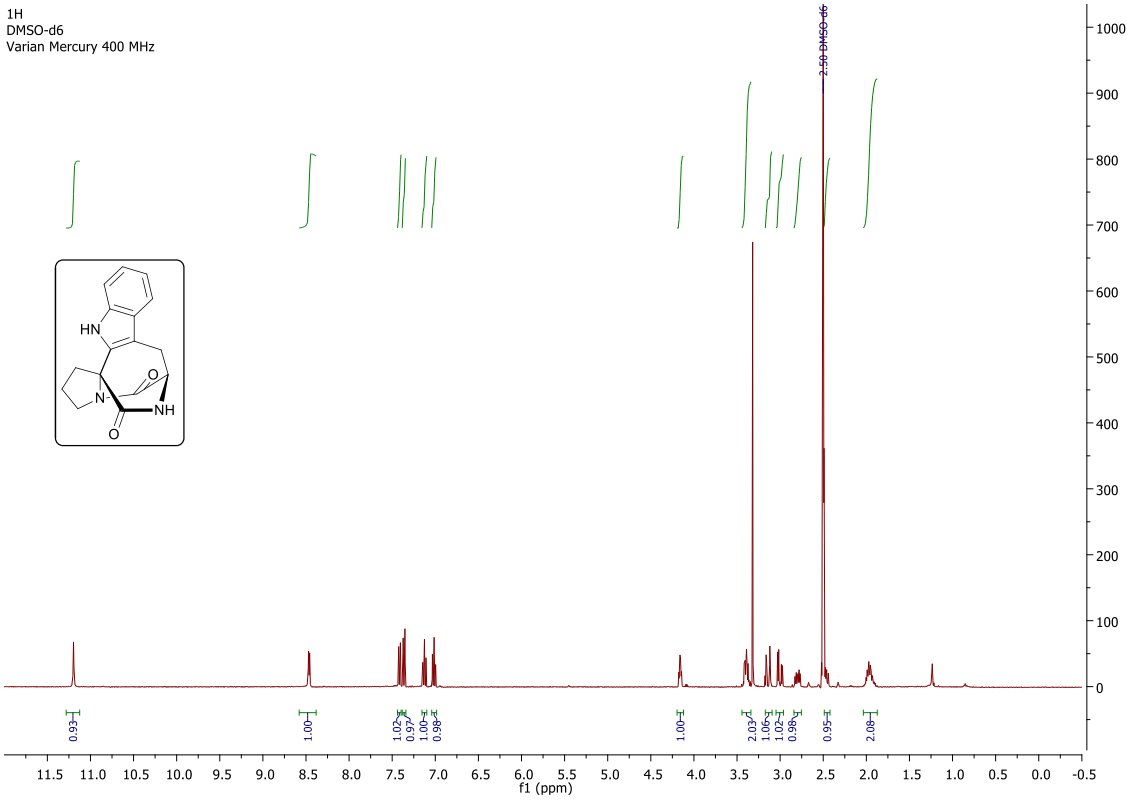
Oxidized cyclo(Pro$_L$-Trp$_L$) (4g) DEPT NMR



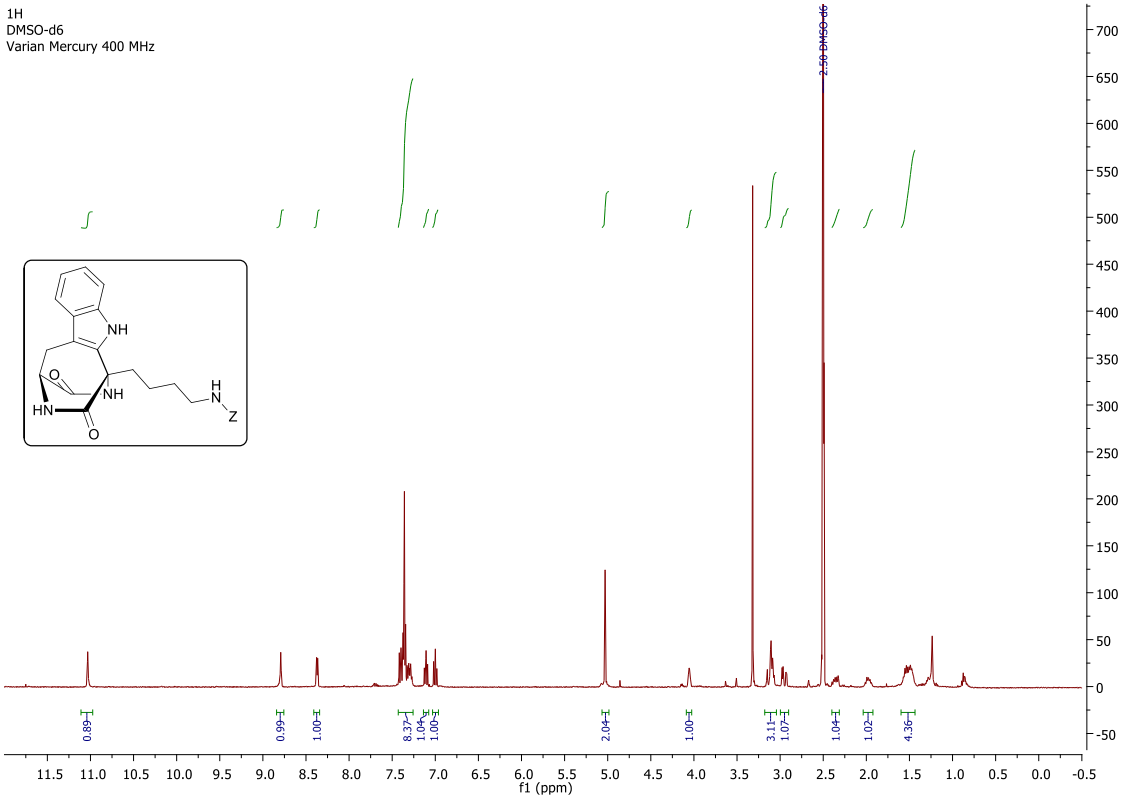
Oxidized cyclo(Pro$_D$-Trp$_D$) (4h) ^{1}H NMR



Oxidized cyclo(Pro$_L$-Trp$_D$) (4h) ^{1}H NMR

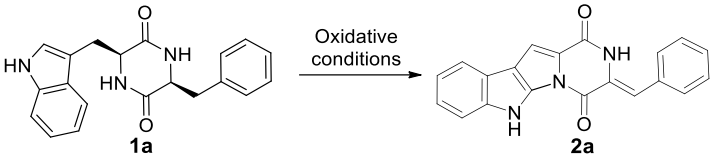


Oxidized cyclo[Lys(z)-Trp] (4i) ^{1}H NMR



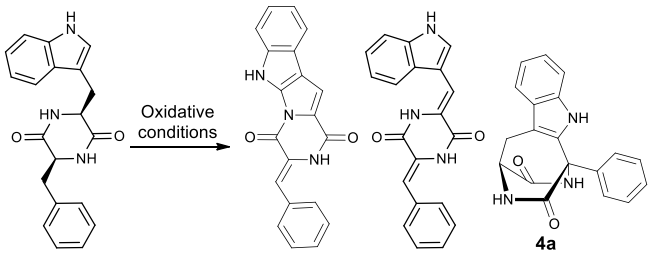
Oxidative screening experiments. Supplementary tables

Table S1. First oxidative screening upon c(Phe-Trp) diketopiperazine **1a**.



T (°C)	Oxidant (eq)	Solvent	Time (h)	**2a** (HPLC-MS conversion %)
120	TBH (3.0)	1-buthanol	26	-
RT	$FeCl_3$(3.0)	CH_2Cl_2	24	-
RT	PIFA (3.0)	DMSO	23	-
120	BQ (3.0)	DMF	25	-
reflux	DLP (3.0)	CH_2Cl_2:H_2O (1:0.2)	30	-
170	DLP (3.0)	DMSO	24	< 5
77	MnO_2 (100)	AcOEt	20	< 5
70	DTBP (3.0)	$CHCl_3$:DMF (1:0.1)	18	-
140	DTBP (4.0)	DMF	48	< 5
140	DTBP:$FeCl_3$ (4.0:0.2)	DMF	24	-
120	DDQ:$FeCl_3$ (3.0:0.1)	DMF	37	16
80	DDQ (3.0)	^{t}BuOH	27	-
120	DDQ (3.0)	DMF	39	25

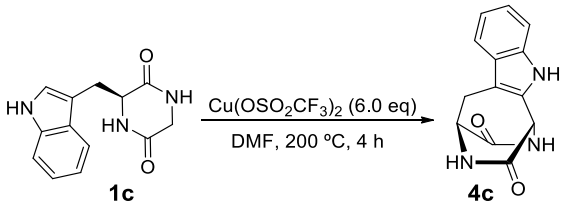
Table S2. Oxidative screening upon c(Phe-Trp) diketopiperazine **1a**.[a]



Entry	Oxidant (eq)	Additive (eq)	Time	**2a**[b]	**3a**	**4a**
1[b]	$PhI(OAc)_2$ (1.1)	-	4 h	-	-	-
2	$PdCl_2$ (3.0)	2,5-lutidine (6.0) Ag_2CO_3 (3.0)	4 h	-	19	5
3	$CuCl_2$ (6.0)	-	4 h	-	-	-
4	$Cu(OAc)_2$ (6.0)	-	4 h	14	59	3
5	$Cu(OCOCF_3)_2$ (6.0)	-	4 h	1	42	28
6	$Cu(OSO_2CF_3)_2$ (6.0)	-	4 h	-	4	71
7	$Cu(OAc)_2$ (6.0)	DDQ (1.0)	4 h	3	45	4
8	$Mn(OAc)_3$ (6.0)	DDQ (1.0)	4 h	-	12	4
9	$Mn(OAc)_3$ (6.0)	$Cu(OAc)_2$ (1.0)	4 h	-	6	20
10	MnO_2 (6.0)	$Cu(OAc)_2$ (1.0)	4 h	-	-	-
11	$Cu(OAc)_2$ (6.0)	TFA (3.0)	4 h	-	32	31
12	$Cu(OAc)_2$ (6.0)	2,5-lutidine (6.0)	4 h	1	44	4

[a] 30 mg of DKP (0.09 mmol), C:0.2-0.3M, DMF, T: 200 °C, [b] T: r.t, HFIP. [b] Values are given in (%).

Table S3. Optimization of Cu(II)-based oxidation upon c(Gly-Trp) diketopiperazine **1c**.[a]



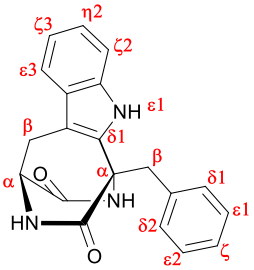
1c **4c**

T (°C)	Oxidant (eq)	Additive (eq)	Solvent	Time	Product (%)[b]
200	$Cu(OCOCF_3)_2$ (6.0)	-	DMF	4 h	90
200	$Cu(OAc)_2$ (6.0)	-	DMF	4 h	75
200	$Cu(OSO_2CF_3)_2$ (6.0)	-	DMF	4 h	40
200	$Cu(OCOCF_3)_2$ (6.0)	-	DMF	2 h	74
200	$Cu(OCOCF_3)_2$ (4.0)	-	DMF	4 h	70
150	$Cu(OCOCF_3)_2$ (6.0)	-	DMF	16 h	68
150 (MW)	$Cu(OCOCF_3)_2$ (6.0)	-	DMF	30 min	49
150 (MW)	$Cu(OCOCF_3)_2$ (2.0)	TFA (4.0)	DMF	30 min	66
150 (MW)	$Cu(OCOCF_3)_2$ (2.0)	-	DMF	30 min	54
120 (MW)	$Cu(OCOCF_3)_2$ (2.0)	TFA (4.0)	DMF	30 min	69
120 (MW)	$Cu(OCOCF_3)_2$ (4.0)	TFA (4.0)	DMF	30 min	92
120 (MW)	$Cu(OCOCF_3)_2$ (4.0)	TFA (2.0)	DMF	30 min	86

[a] 30 mg of DKP (0.12 mmol) , C: 0.2 M. [b] Conversion estimated by HPLC-MS. [c] C: 0.4 M.

Structure elucidation of strained bicyclic products 4a and 4c

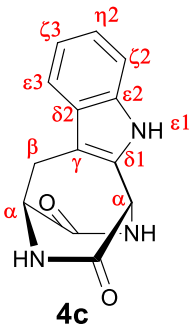
^{1}H and ^{13}C chemical shifts assignments



4a

4a (^{1}H)	δ (ppm)											
AA	**NH**	**α**	**β**	**δ1**	**δ2**	**ε1**	**ε2**	**ζ**	**ζ2**	**η2**	**ζ3**	**ε3**
Phe	8.59	-	3.91/3.32	7.55	7.55	7.29	7.29	7.23	-	-	-	-
Trp	8.35	4.02	3.15/2.99	-	-	11.28	-	-	7.41	7.14	7.03	7.44

4a (^{13}C)	δ (ppm)										
AA	**α**	**β**	**δ1**	**δ2**	**ε1**	**ε2**	**ζ**	**ζ2**	**η2**	**ζ3**	**ε3**
Phe	-	34.3	131.0	131.0	127.7	127.7	126.3	-	-	-	-
Trp	53.9	27.9	-	-	-	-	-	111.4	121.8	119.1	117.8

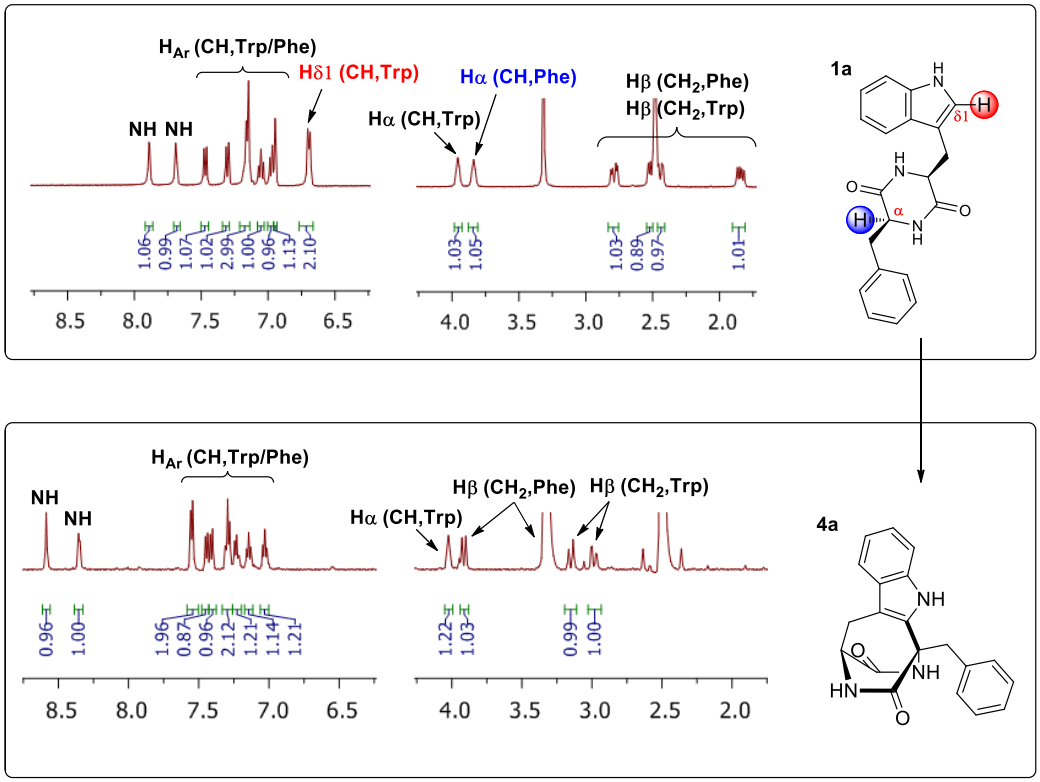


4c

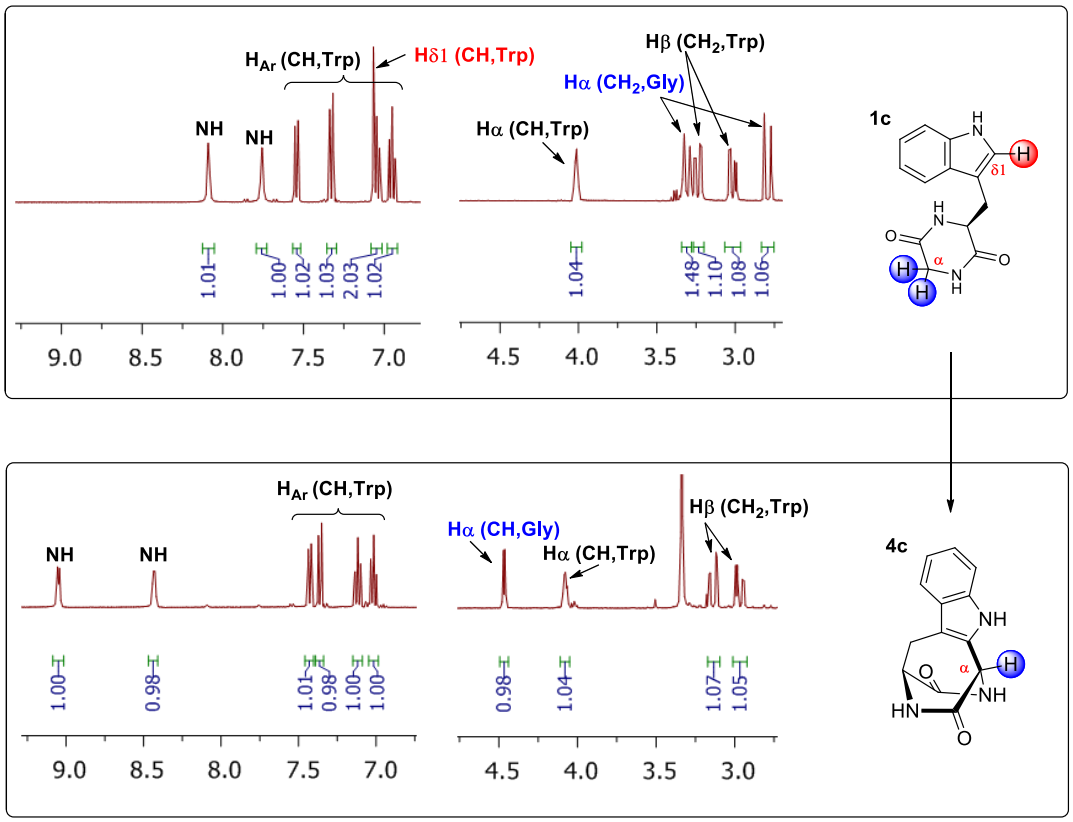
4c (^{1}H)	δ (ppm)							
AA	**NH**	**α**	**β**	**ε1**	**ζ2**	**η2**	**ζ3**	**ε3**
Gly	9.05	4.47	-	-	-	-	-	-
Trp	8.43	4.08	3.14/2.97	11.33	7.36	7.12	7.01	7.43

4c (^{13}C)	δ (ppm)										
AA	**C=O**	**α**	**β**	**δ2**	**γ**	**δ1**	**ε2**	**ζ2**	**η2**	**ζ3**	**ε3**
Gly	171.7	52.3	-	-	-	-	-	-	-	-	-
Trp	169.3	54.5	27.3	134.6	105.8	131.7	127.7	111.5	121.8	119.2	118.0

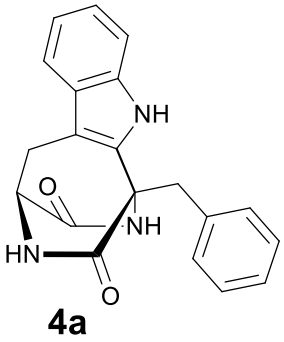
^{1}H NMR comparison between compound 4a and its linear precursor 1a.



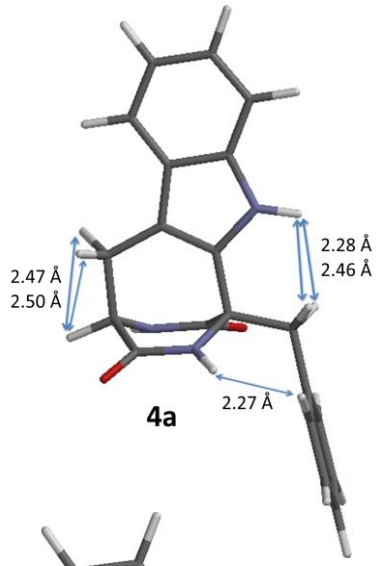
^{1}H NMR comparison between compound 4c and its linear precursor 1c.



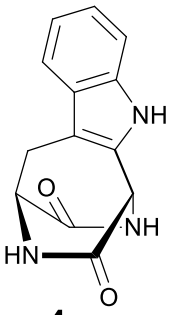
Minimized geometries of compounds 4a and 4b generated by the Spartan '14 suite [Molecular-Mechanics (MMFF) and Semi-Empirical (AM1)] with relevant geometric features



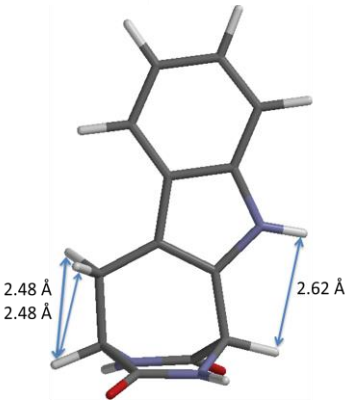
4a



4a

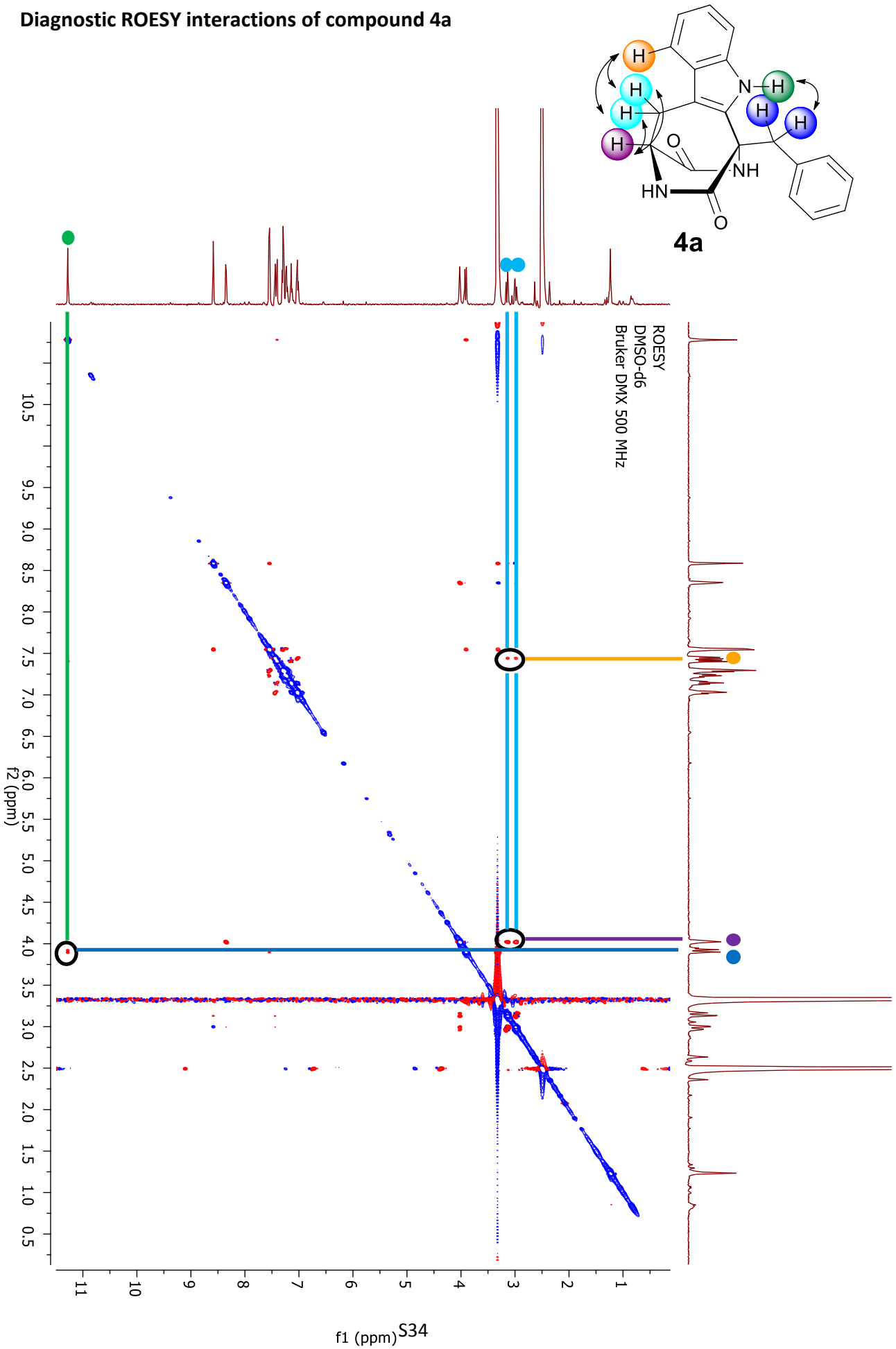


4c

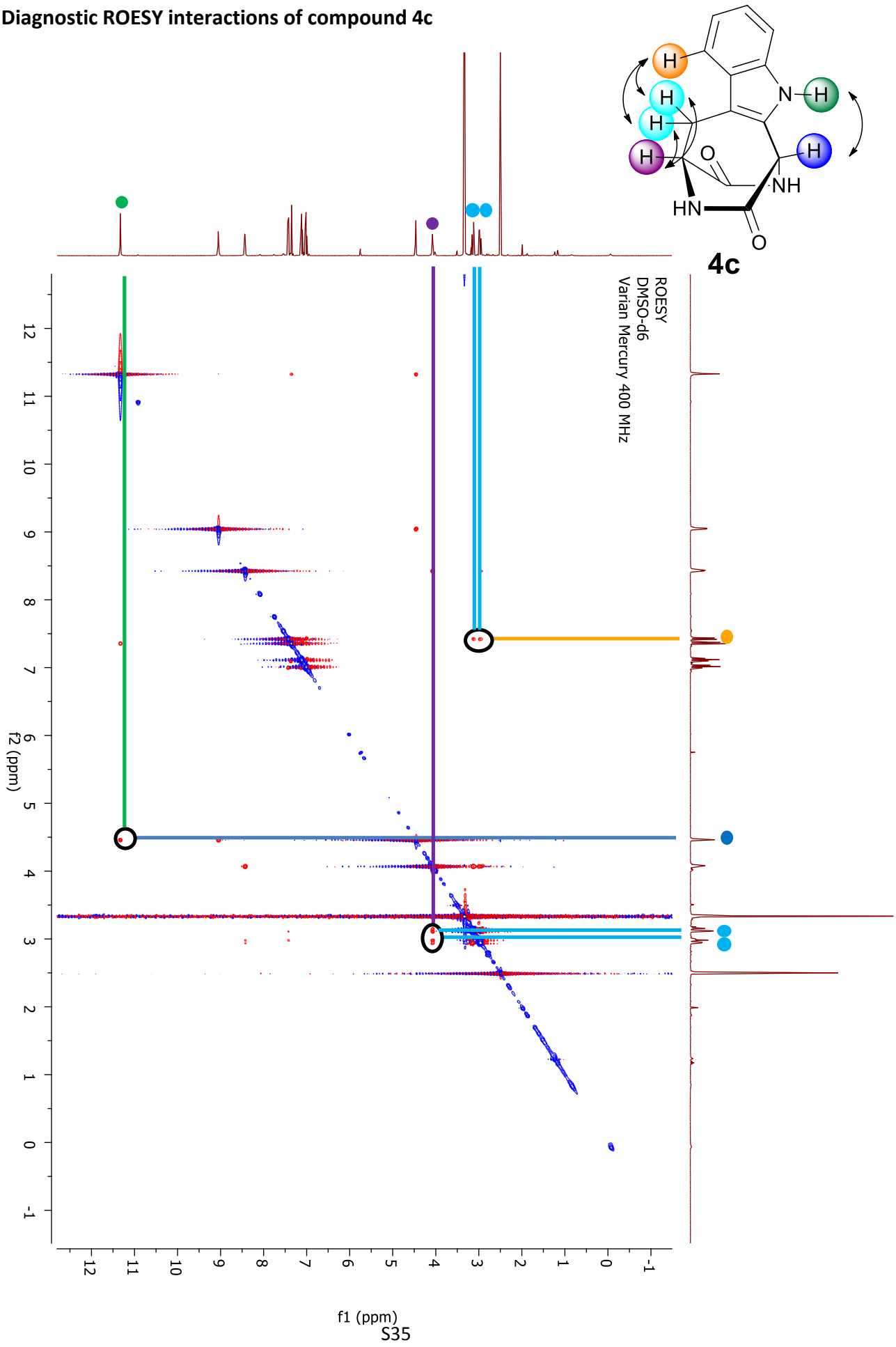


4c

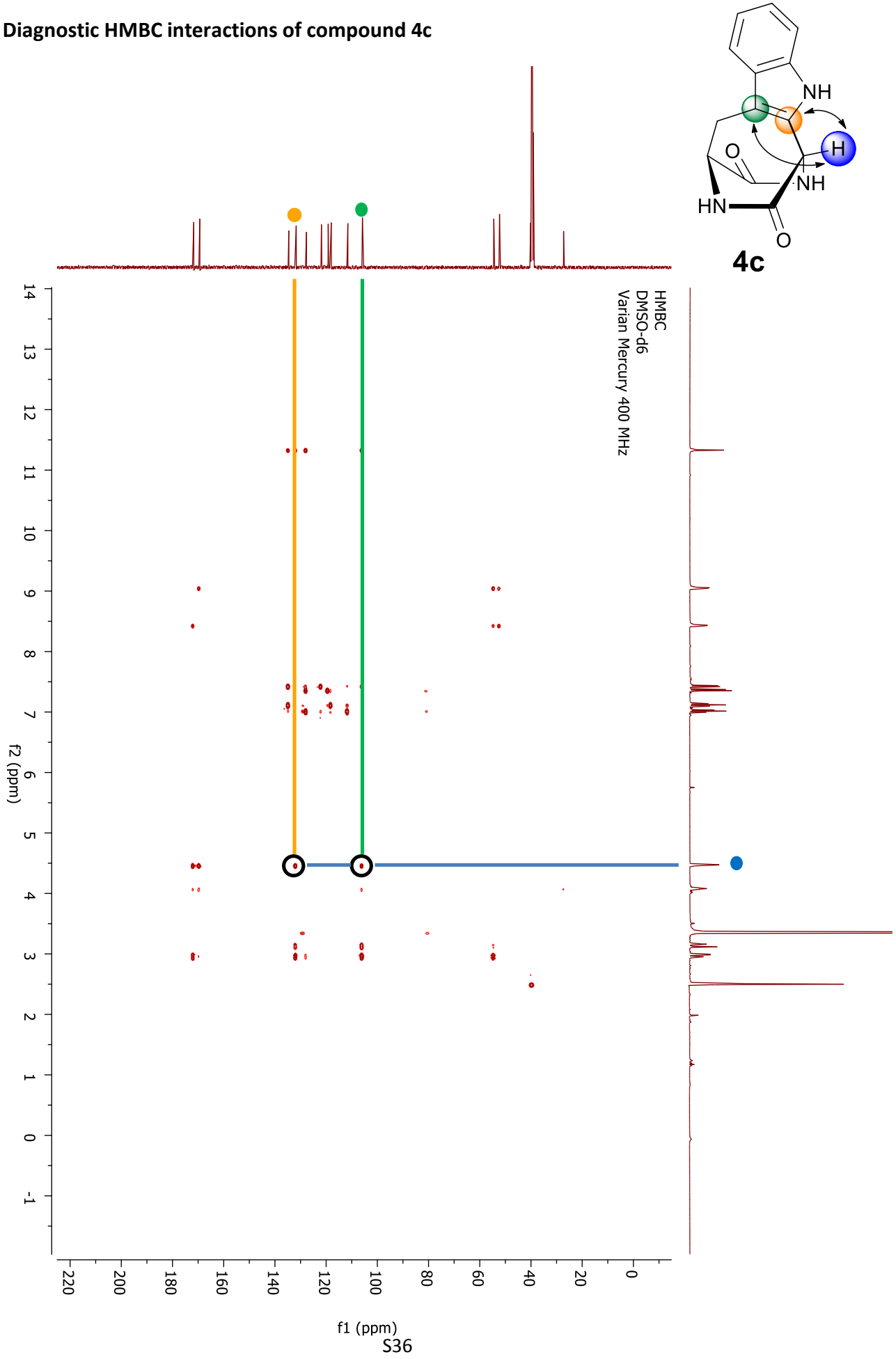
Diagnostic ROESY interactions of compound 4a



Diagnostic ROESY interactions of compound 4c



Diagnostic HMBC interactions of compound 4c



Proposed mechanism for the decarboxylation of Asp-containing DKP

Asp(^{t}Bu)-containing DKP **1f** underwent decarboxylation to yield the oxidized c(Ala-Trp) **4e**. Since no traces of decarboxylated starting DKP **1f** were detected by HPLC-MS analysis, it was proposed a mechanism where the initial DKP undergoes decarboxylation once the dehydrogenative C-C bond is formed to yield compound **4e** (Fig. S2). Incidentally, use of alternative non-acid labile protecting groups for Asp (*i.e.* -Allyl, -Bzl) was detrimental for the outcome of the CDC reaction.

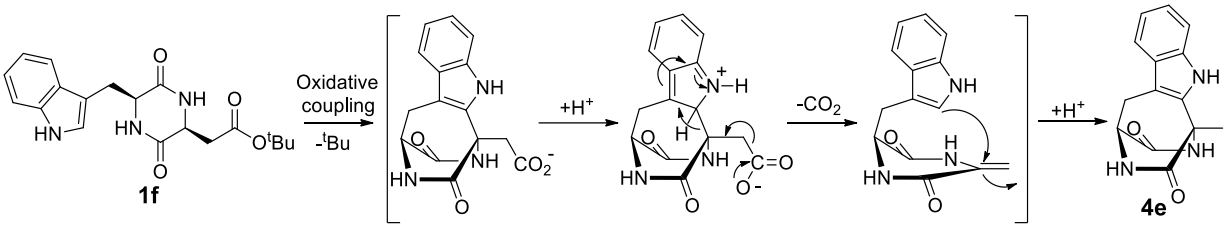


Figure S2. Plausible mechanism for the decarboxylation of compound **4e**.

Proposed 1,4-hydride shift to isomerize iminium ions

The high conversion observed for different DKPs suggests a high α-C selectivity for the C-C bond formation, which is remarkable taking into consideration that two N-iminium intermediates are possible. This may be attributed to a selective oxidation of the right C-H centre due to structural reasons.[2] Alternatively, in the homochiral series (L-L and D-D), an hypothetical *syn*-stereospecific 1,4-hydride shift within the two iminium forms may take place.[3,4] However, this process would lead to inversion of the Trp centre in the heterochiral DKP **1i** (L-Pro-D-Trp) which was not observed. Remarkably, this compound was considerably less reactive than its stereoisomers (see Table 2, entries 6-8). The following mechanism proposal was based on other 1,4-hydride shifts reported in the literature[5–8] as well as hydrogen tunneling and relay mechanisms[9,10] (Fig. S3). Moreover, the cyclization via the nucleophilic attack of the indole ring to the N-iminium of Trp residue would arise a highly strained four-member cycle.

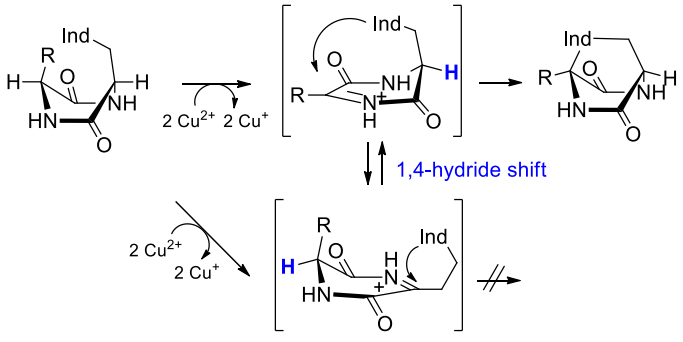
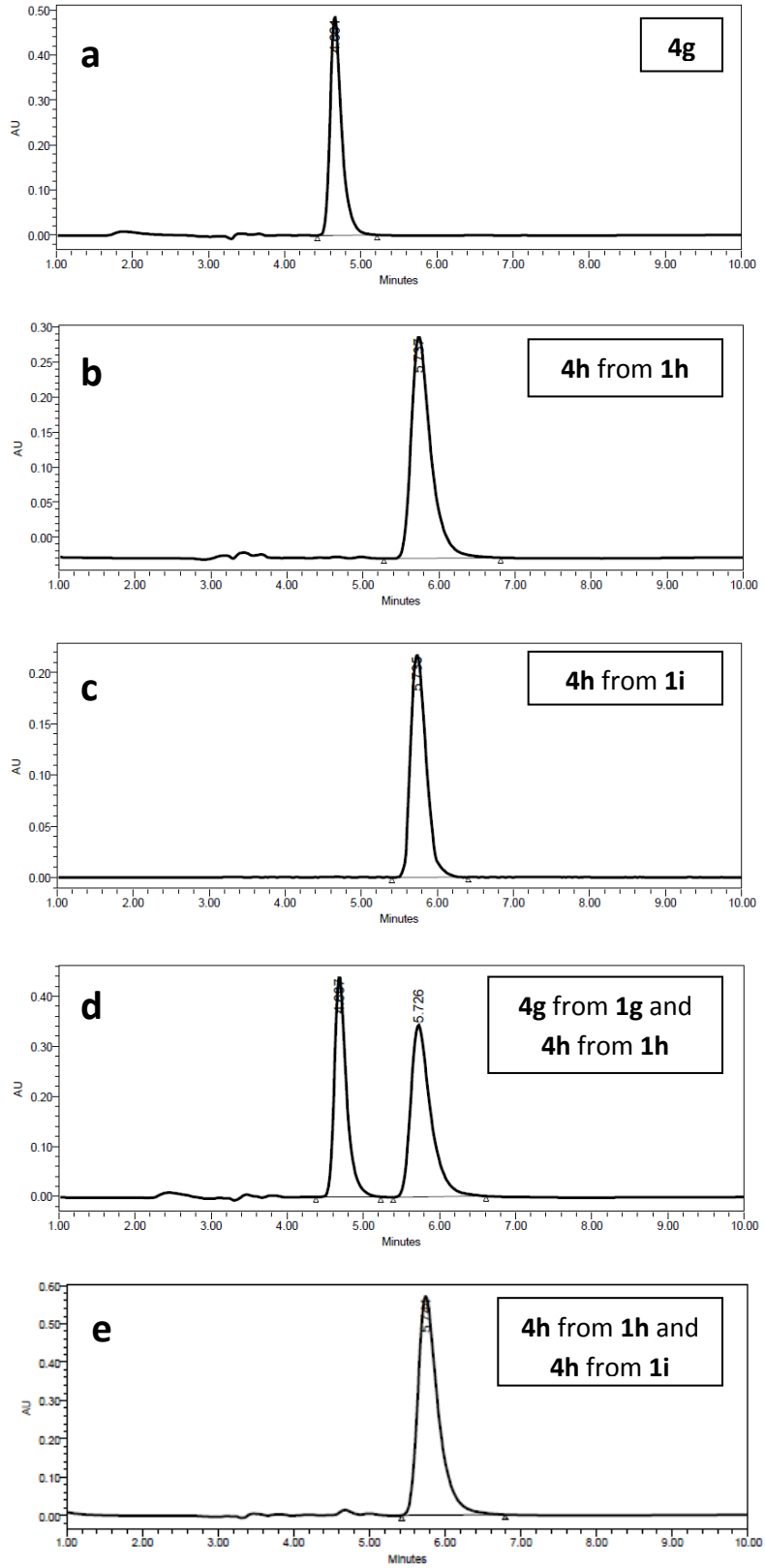
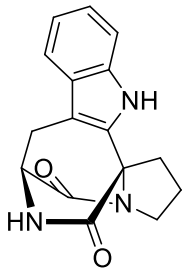


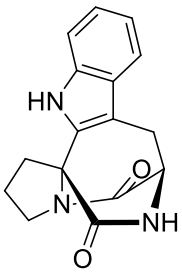
Figure S3. Hypothetical 1,4-hydride shift within iminium intermediates generated during CDC.

Chiral HPLC of oxidized DKPs (4g-h)





4g



4h

Figure S1. Chiral HPLC profiles of a) **4g**, b) **4h** from **1h**, c) **4h** from **1i**, d) co-injection of **4g** from **1g** and **4h** from **1h**, e) co-injection of **4h** from **1h** and **4h** from **1i**. Linear gradient of ACN (+0.036% TFA) into H_2O (+0.045% TFA) from 50% to 70% ACN for 30 min.

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